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OPTIMIZATION OF DIRECT SMALL MOLECULE INHIBITORS OF KEAP1-NRF2 PROTEIN-PROTEIN INTERACTION

by

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ABSTRACT OF THE DISSERTATION

OPTIMIZATION OF DIRECT SMALL MOLECULE INHIBITORS

OF KEAP1-NRF2 PROTEIN-PROTEIN INTERACTION

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The Keap1-Nrf2-ARE signaling system that regulates the transcription and subsequent expression of cellular cytoprotective proteins and enzymes plays a crucial role in preventing pathological conditions exacerbated by the overproduction of oxidative stress. Thus, a noncovalent inhibitor that directly interrupts the Keap1-Nrf2 protein-protein interaction (PPI) and eventually leads to stimulation of related antioxidant responses has attracted a great deal of attention as a preventive and therapeutic agent for the treatment of oxidative stress-related diseases. Considering that the cellular potency or drug-like properties of direct inhibitors have remained as significant factors to be overcome, we have focused on discovering diverse classes of potent small molecule inhibitors based on known

compounds via two different rational approaches. In this study, we found a series of 1,4-diamino phenyl and naphthalene scaffolds containing an oxygen-linked substituent that could be modified, contributing to greater structural diversity of the core moiety. The SAR studies revealed that *O*-linked derivatives displayed potent inhibitory activity in the submicromolar or nanomolar range. Among them, compound **120** is the most promising noncovalent inhibitor, with 64.5 nM in the fluorescent polarization (FP) assay and 14.2 nM in a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. In addition, we designed three different scaffolds as direct inhibitors of Keap1-Nrf2 PPI via a molecular hybridization strategy, and identified THIQ and *N*-phenylglycine analogs which exhibited good potency for a preliminary SAR study. As a result, THIQ analog **139c** was found to be the most potent with an IC_{50} value of 0.37 μM among a series of THIQ compounds developed by our group and other groups. Among the *N*-phenylglycine derivatives, compound **191b** is the most active with an IC_{50} value of 183.4 nM in the FP assay and 107.5 nM in a TR-FRET assay. The optimized new scaffolds may serve as a promising starting point for further biological evaluation and rational optimization as a Nrf2 activator.

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DEDICATION

To my family,

For their love and support.

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INTRODUCTION

1.1 Oxidative stress and antioxidant response

All organisms are frequently exposed to endogenous and exogenous sources during their lifetime, some of which cause deleterious reactive oxidants and electrophiles. The oxidants are generated in the body as a result of natural physiological processes, including various types of cytosolic enzyme systems as well as normal intracellular metabolism in peroxisomes and mitochondria.[1] In addition, many environmental stimuli including ultraviolet light (UV) radiation, ionizing radiation, chemotherapeutics, inflammatory cytokines, and environmental toxins can trigger high levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that can perturb the normal redox balance between the reactive species and antioxidants and shift cells into a state of oxidative stress.[1] While ROS include a variety of chemical species including superoxide anions, hydroxyl radicals, singlet oxygen, and hydrogen peroxide, RNS encompass peroxynitrate and nitric oxide. A rise in the levels of such species results in impaired physiological function, one of which is random oxidative damage to cellular proteins, DNA, and lipids, leading to cell death (Figure 1).[1,2] Repeated exposure to oxidative stress accelerates a pathologic condition, ultimately leading to a wide range of diseases that include neurodegenerative disorders, inflammatory conditions, respiratory diseases, and cancer. [1,2]

The major biological response to oxidative stress is the antioxidant defense system. Cells are equipped with elaborate defense systems, which induce the expression of enzymes that can detoxify the oxidative and electrophilic chemicals.[3] The first response involves the expression of phase I and II metabolizing enzymes, such as cytochrome P450 enzymes,

glutathione S-transferase (GST), NAD(P)H:quinone oxidoreductase I (NQO1), heme-oxygenase-1 (HO-1), and glutamate-cysteine ligase (GCL). The sophisticated phase II detoxification enzymes change the structure of large hydrophobic organic molecules to increase their polarity, and give functionality to allow the conjugation of solubilizing moieties, thereby providing high clearance. Once specific signaling pathways involved in the regulation of an antioxidant response are activated, antioxidant cytoprotective proteins including NAD(P)H, NAD(P)H quinone oxidoreductase I (NQO1), heme-oxygenase-1 (HO-1), glutamate-cysteine ligase (GCL), and thioredoxin (TRX) are also expressed, which counteract and regulate overall ROS levels to maintain physiological homeostasis (Figure 1).[1,2] These enzymes are not consumed during the antioxidant process, have relatively long half-lives, and activate chemical detoxification reactions. Some of them are also involved in the production of small molecule antioxidants.[2,4]

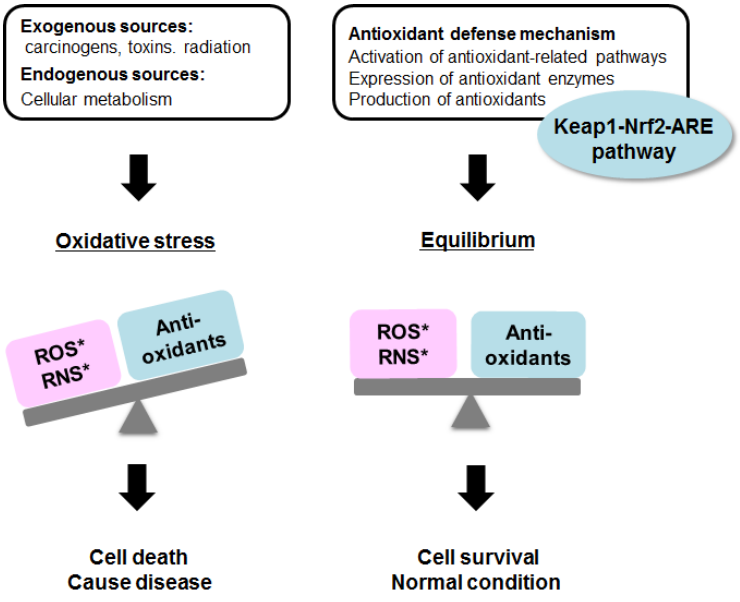


Figure 1. Oxidative stress and antioxidant response

In addition, other non-enzymatic antioxidants are important in directly reducing a high level of ROS or RNS. These low molecular mass molecules are short-lived, redox-active, and consumed during scavenging ROS, requesting to be replenished for further protection. They include ascorbate, pyruvate, flavonoids, tocophenols (vitamin E), vitamin K, lipoid acid, ubiquinol, carotenoids, and more importantly, glutathione. Consequently, the balance between ROS production and antioxidant defense contributes to redox homeostasis, eventually leading to cell survival (Figure 1).[1,2,4]

1.2 Regulation of Keap1-Nrf2-ARE pathway

The Keap1-Nrf2-ARE pathway is the major regulator of cytoprotective responses that determine the sensitivity of cells to oxidative stress by controlling the inducible expression of detoxification and antioxidant enzymes.[5] The pathway consists of three cellular components, namely Kelch-like ECH-associated protein 1 (Keap1), nuclear factor erythroid 2-related factor 2 (Nrf2) and antioxidant response element (ARE).

1.2.1 Kelch-like ECH-Associated protein 1 (Keap1)

Keap1 acts as a sensor of chemical and oxidative stresses and a negative regulator of Nrf2 to control Nrf2 level. With the inhibitory Neh2 domain of Nrf2, Keap1 was identified as a Nrf2-binding protein from yeast two-hybrid screening.[6] The complete amino acid sequences of Keap1 from eight species including mouse, pig, and human have been reported, and the four mammalian proteins exhibit a high degree of homology. Keap1 belongs to the superfamily of BTB-Kelch proteins that occur in the Metazoa.[3] Human Keap1, a 69-kDa protein, contains 627 amino acid residues and consists of five distinct

domains: the N-terminal region (NTR), the broad complex, tramtrack, and bric-a-brac (BTB) domain, the intervening region (IVR), double glycine repeats (DGR) or Kelch domain, and the C-terminal region (CTR) (Figure 2).[2,7] The BTB domain, an evolutionary conserved domain, mediates homo-dimerization and is responsible for the binding of Keap1 to Cullin 3 (Cul3), a scaffold protein of Nrf2 ubiquitin ligase (E3). The DGR domain comprises six repetitive Kelch motifs (KR1-KR6) which form a six-bladed β-propeller structure. The DGR and CTR domains, together named as the DC domain, mediate binding of Keap1 with Nrf2 Neh2.[7-10] The IVR or linker region (LR) domain located between the BTB and the DGR has a large number of highly reactive cysteine residues that are sensitive to oxidation stress. These residues act as regulators of Keap1 conformation as well as redox stress sensors. More specifically, seven reactive cysteine residues have been confirmed to be involved in Keap1-mediated repression of Nrf2 activity and Keap1-dependent ubiquitination of Nrf2: Cys151, Cys257, Cys273, Cys288, Cys297, Cys434, and Cys613.[7,11-13]

1.2.2 Nuclear factor erythroid 2-related factor 2 (Nrf2) and small Mafs

Nrf2 is a key transcription factor that is critical for cellular homeostasis.[14] In fact, Nrf2 KO mice have a tendency to develop autoimmune lesions and are sensitive to a wide variety of toxicity and disease conditions.[15,16] The cloning of Nrf2 cDNA was identified by expression cloning with tandem NFE2-binding motifs as a screening probe.[17] Nrf2 has a distinctive CNC bZip domain in the C terminal region that serves as DNA binding as well as hetero-dimerization with a small Maf. The CNC (cap ‘n’ collar) protein, named after the *Drosophila* segmentation protein CNC, shares a high homology among the CNC bZip

proteins.[18] Human Nrf2, containing 605 amino acid residues, consists of six conserved Neh (Nrf2-ECH homology) domains, namely Neh1 to Neh6 (Figure 2).[2,19] While Neh1 contains the bZip motif at the C-terminal region, the Neh2 domain at the N-terminus includes DLG and ETGE that are essential for the interaction between Nrf2 and its suppressor Keap1, which negatively regulates the transcriptional activity of Nrf2.[20,21] The Neh3 domain located at the C-terminus is crucial for the transactivation of ARE-dependent genes.[22,23] The Neh4 and Neh5 domains cooperatively bind to the CH3 motif of the CREB-binding protein (CBP), a transcriptional co-activator that regulates Nrf2 transcriptional activity. Neh6, which has a large number of serine residues in the middle of Nrf2, is involved in redox-insensitive degradation of the Nrf2 in a Keap1-independent manner.[2,24]

Small Maf (musculoaponeurotic fibrosarcoma) protein contains a basic leucine zipper (bZip) domain for dimerization and DNA binding. There are three small Maf proteins, MafF, MafG, and MafK, that lack a transcriptional activation domain. The sMaf proteins form heterodimers with large CNC bZip proteins of Nrf2, and bind to the GC dinucleotide of ARE which is classified as a CNC-sMaf-binding element (CsMBE).[18]

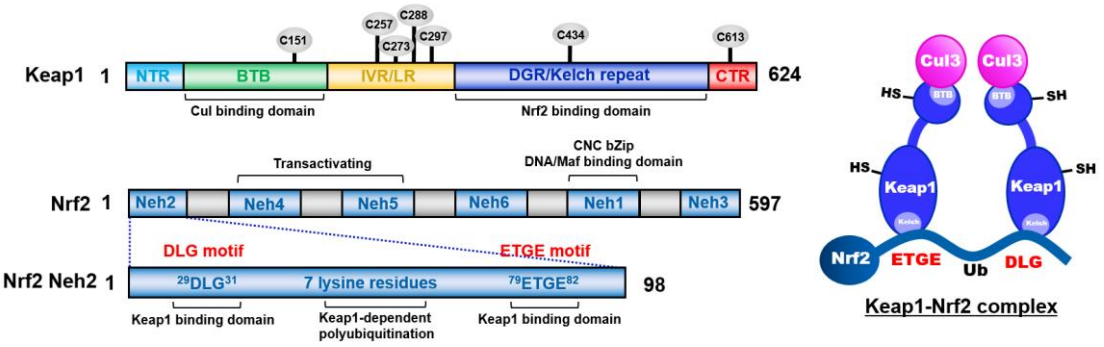


Figure 2. Structures of Keap1, Nrf2 and small Maf

1.2.3 Antioxidant response elements (ARE)

ARE is a *cis*-regulatory element located in the enhancer region of many genes which are encoding detoxification enzymes and cytoprotective proteins.[25] A transfection experiment identified a 41 base pair enhancer sequence upstream of the rat *Gsta2* gene for the induction of a reporter gene.[18,26] ARE also mediates the induction of mouse *Gsta1* and human *NQO1* genes by antioxidants and electrophiles.[18,27] ARE contains a core sequence, 5'-TGACnnnGC-3' (n = any base) that is later expanded into a 16 base pair sequence, 5'-TMAnnRTGAYnnnGCR-3' (M = A or C, R = A, Y = C or T, W = A or T).[28,29] Under basal conditions, Bach1 (BTB and CNC homology1), a transcriptional repressor of ARE, forms a heterodimer with a sMaf protein, which blocks Nrf2 from binding to DNA. Once oxidative stress occurs, the Nrf2 translocates into the nucleus, and the Bach1 is degraded by a proteasome. The Nrf2 is capable of forming a heterodimer with sMaf and binding to the ARE, eventually activating the expression of downstream ARE-dependent target genes.[2,30]

1.2.4 Mechanism of Keap1-Nrf2-ARE pathway

In terms of mechanics, Nrf2 has two different processes of activation: suppression of Nrf2 under basal conditions and activation of Nrf2 by inducers. Under unstressed conditions, a Keap1 homodimer forms a complex with a Nrf2 and two Cul3, where its DGR domain binds to the Neh2 domain of Nrf2 and its BTB domain binds to the Cul3 N-terminal region.[5,31] Neh2 interacts with Keap1 DC domains (DC = DGR + CTR) with a ratio of 1:2 through its ETGE and DLG motifs. The ETGE motif has a higher binding affinity than the DLG motif due to more electrostatic interactions occurring between DC and ETGE as

compared to DC and DLG.[32,33] Keap1 recruits the Cul3-RBX1 E3 ubiquitin ligase complex and serves as a substrate adaptor to bring Nrf2 into close proximity with the E3 complex. The consequent ubiquitination of Nrf2 marks it for proteasomal degradation by the 26S proteasome. Nrf2 is rapidly degraded with a half-life of less than 20 min, resulting in a low level of Nrf2 in many types of cells and thereby maintaining cellular homeostasis (Figure 3).[18,34-36]

Under conditions of oxidative or electrophilic stress, inducers modify cysteine thiols of Keap1 and Nrf2, presumably altering the structure of the Keap1-Nr2-Cul3 complex to inhibit Nrf2 ubiquitination. Evidence for binding of inducers to Keap1 cysteine thiols was provided using label inducers, stoichiometry, ultraviolet spectroscopy, and mutational studies.[37,38] As a result, free Nrf2 is stabilized with a half-life of up to 200 min, and then translocated into the nucleus where it activates the expression of antioxidant genes regulated by ARE (Figure 3).[31,32] The exact mechanism of Nrf2 activation by cysteine modification is not known, but there are two representative models that have been proposed: the “Keap1-Cul3 dissociation model” and the “hinge and latch model”.[39]

In the Keap1-Cul3 dissociation model, the binding of Keap1 and Cul3 plays a significant role in the stabilization of Nrf2. Inducers, such as electrophiles, cause thiol modification of cysteine residues in the Keap1, leading to disruption of the binding between Keap1 and Cul3 and dissociation of Cul3 from Keap1. As a result, Nrf2 escapes from the ubiquitination system. In this model, it has been reported that Cys151 serves as a key factor, suggesting that substitution of serine for Cys151 in the BTB domain prevents Keap1 from dissociating with Nrf2 even under the condition of oxidative stress.[2,40,41] According to the hinge and latch model, modification of Keap1 cysteine residues, located in the IVR of

Keap1, leads to conformational changes in Keap1 resulting in the misalignment with the lysine residues in Nrf2. The Nrf2 DLG motif that has lower affinity than ETGE is dissociated from Keap1, which makes Nrf2 no longer poly-ubiquitinylated. Through one of the two suggested models, free or newly synthesized Nrf2 proteins consequently translocate into the nucleus and bind to ARE providing the expression of Nrf2 target genes, such as HMOX1, GCL and GSTs.[33,42,43]

More recently, additional studies have suggested a new conformation cycling model. Under normal conditions, a Keap1-Nrf2 complex exists in two distinct forms, as an open or a closed conformation, depending on the binding of Nrf2 DLG motif. The closed conformation is only involved in the ubiquitination process of Nrf2. Under oxidative stress, the accumulation of the closed conformations is observed because covalent modification of Keap1 by inducers results in conformational changes of Keap1, and thus the degradation

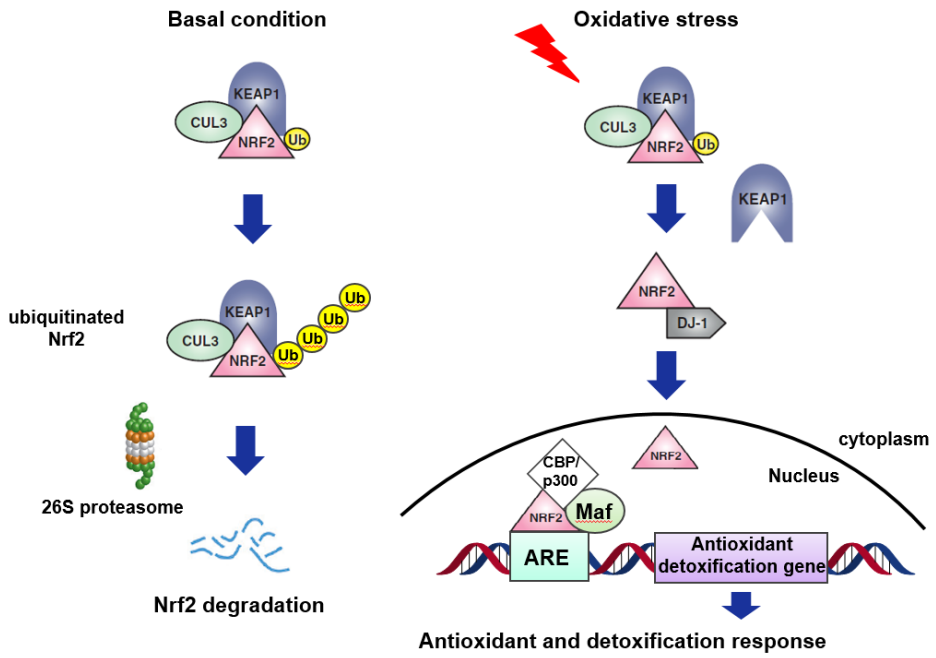


Figure 3. The Keap1-Nrf2-ARE signaling in basal and oxidative stress conditions

process of Nrf2 is suppressed. Ultimately, newly synthesized Nrf2 proteins activate an antioxidant response system.[44]

1.3 Therapeutic function of Keap1-Nrf2-ARE pathway

The continuous exposure to oxidative stress contributes to the development of various diseases, including cancer, neurodegenerative disease, chronic obstructive pulmonary disease (COPD), inflammatory disease, and aging.[45] The Keap1-Nrf2-ARE pathway plays a crucial role in regulating the antioxidant defense system against oxidative stress-mediated disease.

The role of Nrf2 in regard to cancer is complex in that dysregulation of the Keap1-Nrf2 signaling pathway shows different modalities depending on the type and stage of the disease.[46,47] Nrf2 plays a part in protecting the body from DNA-damaging and carcinogenic effects of ROS. Therefore, the induction of an endogenous antioxidant response can be chemopreventative.[48] Nrf2 KO mice are more susceptible to the carcinogenic effect of several carcinogens in animal models, and tumor formation is associated with reduced expression of ARE genes. Conversely, the inhibition of tumorigenesis in wild-type mice has a correlation with the increased expression of cytoprotective genes through chemoprevention.[18] Interestingly, electrophilic small molecule activators show broad anti-cancer activity in cellular and animal models, such as vinyl carbamate-induced lung cancer and aflatoxin-induced liver cancer.[49-52] The most potent inducers of ARE genes are the synthesized derivatives of oleanolic triterpenoids which react with Keap1 cysteine thiols.[52] In contrast, cells in some tumors can act as cellular machinery, resulting in the persistent activation of Nrf2 and the expression of ARE genes. As a result, they are protected against

apoptosis from endogenous exposure to high levels of ROS or anticancer drugs, and promote tumor growth.[39,53] However, activation of Nrf2 in tumors is likely to be an outcome of selection during cancer development, rather than a cancer-initiating event. This supports the fact that Keap1 KO mice with activated Nrf2 functions did not develop spontaneous cancer over a 2-year period.[54] Based on these findings, it is expected that specific inhibitors of Nrf2 may be developed for anticancer therapy.

Neurodegenerative disease, including Huntington's disease (HD), Parkinson's disease (PD), multiple sclerosis, as well as amyotrophic lateral sclerosis (ALS), can be developed by a high level of oxidative stress, which contributes to neuronal cell death.[55,56] Modification of genes that trigger ROS formation in neurons is related to PD. In addition, several studies prove that Nrf2 has a protective role against neurodegenerative disease. An ALS mouse model shows that the overexpression of Nrf2 delays in the onset of ALS, leading to extended survival of the mice with ALS.[57] Nrf2-knockout mice are much more susceptible to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced PD-like lesion formation in the brain of the mice, which is also relieved by overexpression of Nrf2 in astrocytes.[3,58] Functional decline of Nrf2 exacerbates disease in an experimental autoimmune encephalomyelitis (EAE) mouse model for multiple sclerosis.[59]

Several mechanisms such as oxidative stress, alveolar cell apoptosis and chronic inflammation contribute to chronic obstructive pulmonary disease **(**COPD) development.[60] Moreover, environmental factors like air pollutants, infections and occupational dust are likely to debilitate respiratory conditions and produce oxidative stress that might maintain inflammation and aggravate COPD.[60] Nrf2, a transcription factor expressed in alveolar macrophages, has a key protective role in the lungs with the activation of ARE-dependent

antioxidant and cytoprotective genes. Several animal models and human studies support an essential role of Nrf2 and several Nrf2 target genes as a protective system against COPD disease. Nrf2 KO mice exposed to cigarette smoke (CS) are highly sensitive to emphysema with earlier onset and more severe pathology when compared with wild-type mice. The mice exhibited elevated oxidative genotoxic stress, increased apoptosis, inflammation, as well as decreased function.[61-63] Loss of Nrf2 is also shown in lungs of COPD patients.[64] Therefore, the activation of the Nrf2-ARE signaling pathway might be a promising strategy to recover antioxidant and detoxifying enzymes, counteracting CS effects.

In addition to the three representative diseases described above, Nrf2 has been implicated in a wide range of toxicities and chronic diseases, including diabetes,[65] cardiovascular,[66] gastrointestinal,[67] liver, and autoimmune diseases,[68-70] all of which are characteristically associated with oxidative stress.[2] In regard to disease development, oxidative damage exacerbates physiological conditions. Therefore, Nrf2 can participate in multiple protective effects against toxicity and chronic diseases by regulating oxidant levels and oxidant signaling. Thus, the Keap1-Nrf2-ARE pathway is shown to be extensively involved in a variety of diseases and biological mechanisms, leading to interest in the pathway as a promising drug target for prevention and treatment.

1.4 Indirect inhibitors of Keap1-Nrf2 interaction

Based on the mechanism of action in the Keap1-Nrf2 system, Nrf2 activators are divided into two categories: indirect and direct small-molecule inhibitors. Most Nrf2 activators are indirect inhibitors bearing electrophilic functionality which can covalently bind with sulfhydryl groups of cysteine residues on Keap1. Cysteine thiolate ions, formed at neutral

pH, are highly reactive with ROS, RNS, and other electrophiles, resulting in changes in Keap1 protein conformation and thus disrupting the Keap1-Nrf2 interaction. Unfortunately, this has the possibility of reacting with other off-target proteins, which may then cause unpredictable side effects. The covalent cysteine modifiers are further classified into five distinct scaffolds based on their chemical structure.[4]

Isothiocyanates and related derivatives, including sulforaphane (SFN) and phenyl isothiocyanate (PEITC), show cancer chemopreventative activity (Figure 4). The electrophiles react with the cysteines of Keap1, prevent the protein from interacting with Nrf2, and stabilize Nrf2. Biological data shows that a high level of ARE by isothiocyanates activates enzymes like GST in rodent tissues, and in mammalian cells.[71]

Fumarates are characterized by a Michael acceptor with α,β-unsaturated systems, enabling reaction with cysteine thiols of Keap1. The representative material is the salt mixture of monoethyl fumarate and dimethyl fumarate (Fumaderm®), and dimethyl fumarate (Tecfidera®) for the treatment of psoriasis and relapsing multiple sclerosis (MS), respectively (Figure 4).[72,73] These electrophilic modulators mainly have an interaction with Cys151, which consequently inhibits Nrf2 ubiquitination and induces the expression of ARE-mediated antioxidative and cytoprotective enzymes.

The main chemical structure of chalcones consists of two phenyl rings and a three-carbon α,β-unsaturated system (Figure 4). Chalcones found in plants also act as Michael acceptors to activate Nrf2 involved in the expression of downstream antioxidant genes, indicating a broad range of biological properties including anti-proliferation, anti-infective, and anti-inflammatory activities.[74,75] The electrophiles are identified as a potent activator of Nrf2 that upregulates glutamate-cysteine ligase modifier subunit (GCLM) and NQO1 in human

lung epithelial cells and in mice.[76] In addition to chalcones, vinyl sulfones have been shown to mediate Keap1-Nrf2 activity, resulting in the Nrf2-dependent expression of NQO1, heme-oxygenase 1 (HO-1), glutamate-cysteine ligase catalytic subunit (GCLC) and GCLM in dopaminergic neuronal cells.[77]

Quinones, one class of Michael acceptors, covalently bind with cysteines on Keap1, activating Nrf2. For instance, 1,4-naphthoquinone has cellular anti-inflammatory activity (Figure 4),[78] and polyphenols can effectively act as ARE-inducers. In the presence of sufficient oxygen and copper II or other transition metals, catechol and hydroquinone are oxidized to generate electrophilic quinones which contain Michael acceptors, activing ARE-mediated transcription.[79] In addition, catechols undergo cytochrome P450-mediated oxidation, and thus alter redox states in cells or their environment, which can, in turn, upregulate Nrf2. Examples of oxidizable polyphenols contain *tert*-butylhydroquinone and epigallocatechin gallate.[80-82]

Based on natural oleanane triterpenoids which have antitumor and anti-inflammatory effects, CDDO, known as Bardoxolone, was developed as a potent Nrf2 inducer, by introducing highly active α,β-unsaturated α-cyano ketone to A and C rings of an oleanolic acid scaffold.[83] The crystal structure of CDDO, in a fragment of the BTB domain of Keap1, showed that Cys151 is a key factor as a target for these electrophilic covalent modulators.[84] Interestingly, a proteomic study on the CDDO analogue showed that only two proteins were altered in Nrf2 KO mice, while 43 proteins indicated altered expression in WT animals, meaning high selectivity for the Keap1-Nrf2 pathway.[85] The triterpenoid CDDO-methyl ester is also a potent Nrf2 inducer.[84] It first entered in phase II clinical trial to study the efficacy for the treatment of type 2 diabetes mellitus and chronic kidney disease (CKD).

Unfortunately, its further study in phase III was withdrawn due to cardiac adverse effects. It was shown that nonspecific interactions of covalent cysteine modifiers contributed to unexpected safety issues.[86,87]

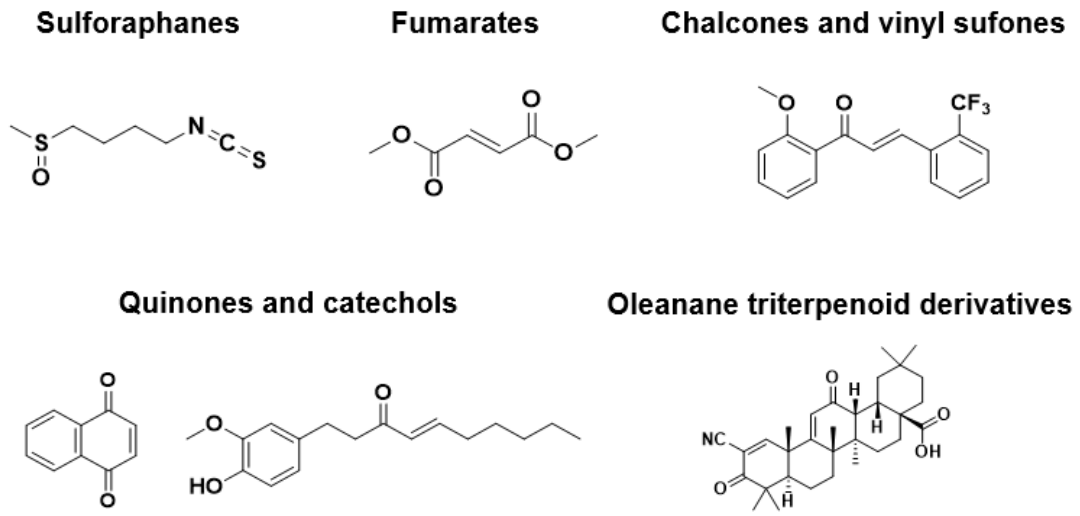


Figure 4. Structures of indirect Keap1-Nrf2 PPI inhibitors

1.5 Discovery of direct inhibitors of Keap1-Nrf2 interaction

1.5.1 Targeting protein-protein interactions (PPI)

The discovery of small-molecule PPI inhibitors has been considered a challenging task, although PPI offers a rich source of novel drug targets. PPI interfaces are generally flat, large, and complex, which prevents small molecules from effectively disrupting interactions.[88,89] Furthermore, inhibitors are more likely to face pharmacokinetic issues as an orally available drug, including large molecular weight and poor solubility. However, several potent inhibitors have been successfully developed, and studied in clinical trials through novel biological and chemical technologies and strategies.[88,90]

1.5.2 Characteristics of Keap1-Nrf2 PPI as a drug target of direct inhibitors

As mentioned previously, a Keap1 homodimer forms an interaction with a Nrf2 through two binding sites, the ETGE and DLG motifs, located in the Neh2 domain of Nrf2. More specificially, the ETGE motif has stronger binding affinity to Keap1 than the DLG motif, which led to the development of ETGE-containing Nrf2 peptide inhibitors. Furthermore, X-ray co-crystal structures of the Keap1 Kelch domain along with Nrf2 peptides have provided a deep understanding of protein-protein interactions. The crystallographic data revealed that the Kelch domain forms a symmetric 6-bladed β-propeller structure, and the 16mer Nrf2 peptide has two antiparallel β-strands (β-hairpin conformation) that bind to the top face of the β-propeller (Figure. 5A).[2,10] The conformation of a Nrf2 peptide is stabilized by the intramolecular hydrogen bonds of Asp77 and Thr80. The peptide-domain-mediated PPI was primarily formed by multiple electrostatic interactions between six residues in Keap1 (Ser363, Asn382, Arg380, Arg415, Arg483, and Ser508) and carboxylate oxygen atoms of Glu79 and Glu82 in Nrf2 peptides (Figure 5B).[2] Conversely, the peptide-binding site of the Kelch domain is a positively charged region because of the highly conserved Arg residues.[2]

Based on the structural analysis of the co-crystal structure of the Keap-Nrf2 ETGE motif (PDB ID: 1X2R), You et al. investigated multiple substrates binding determinants of Keap1 using molecular dynamics (MD) simulations combined with mechanics-generalized Born surface area (MM-GBSA) free energy calculations.[91,92] The computational analysis suggested that the ligand-binding site of the Keap1 Kelch domain is mainly divided into five subpockets (P1-P5), namely five “hot spots”, where different distinct residues are involved in forming significant interactions for high binding affinity (Figure 5c). While P1

and P2 contain polar residues that play an important role in forming electrostatic interactions, P4 and P5 are the non-polar parts that are associated with hydrophobic interactions, and P3 is the central part in the cavity of the Kelch domain.[91,93] Consequently, these structural analysis results enabled a discovery of direct inhibitors of Keap1-Nrf2 PPI via structure-based design approaches.

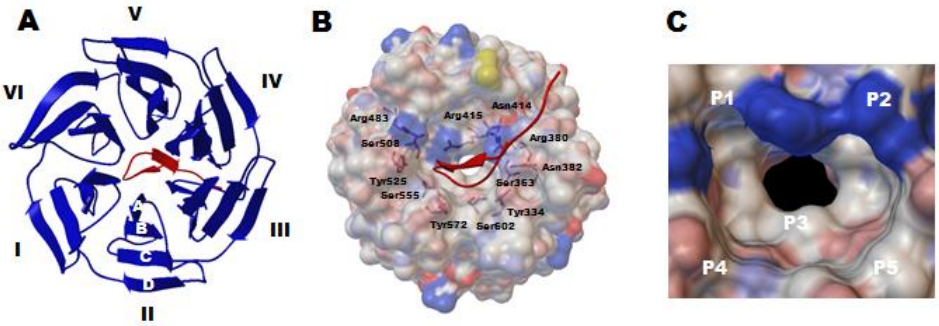


Figure 5. X-ray crystal structures of the Keap1 Kelch domain and Nrf2 ETGE motif

1.5.3 Assay development for evaluation of Keap1-Nrf2 PPI inhibitors

At the early drug discovery stage, well-established bioassays play an important role in discovering novel hits through the screening of chemical libraries and in evaluating an inhibitory effect of Keap1-Nrf2 interaction for hit-to-lead optimization. Generally, *in vitro* assays can be divided into two types, Keap1 binding assay and Keap1-Nrf2 inhibition assay, based on the purpose of the assay methods. The binding assay employs a thermodynamic (e.g. isothermal titration calorimetry assay) or kinetic method (e.g. surface plasmon resonance) to determine an equilibrium dissociation constant K_d reflecting binding strength. The advantages of these assays include label-free detection, real-time monitoring of binding interactions, and quantitative evaluation of binding strength.[94,95]

The inhibition assay reflecting the potency of compounds includes a fluorescence polarization (FP) assay and a time-resolved fluorescence resonance energy transfer (TR-FRET) assay. The FP assay is a powerful tool that exhibits substantial tolerance and has been successfully applied for HTS. In 2012, our group first established the FP assay by developing the novel fluorescently-labeled Nrf2 peptide containing the ETGE motif, FITC-9mer Nrf2 peptide amide, as a probe that competitively binds to Keap1 Kelch domain with other inhibitors.[96] As illustrated in Figure 6, the FP assay is measuring the change of polarization depending on the size of the fluorescent molecule. When a probe binds to a Keap1 protein, the large complex has slow rotation, leading to high polarization. Once an inhibitor binds to the protein, the free probe is rapidly rotated, leading to low polarization. Each polarization is determined by measuring the parallel and perpendicular fluorescence intensities, and the competitive activity of a test compound is obtained through the difference of polarization.

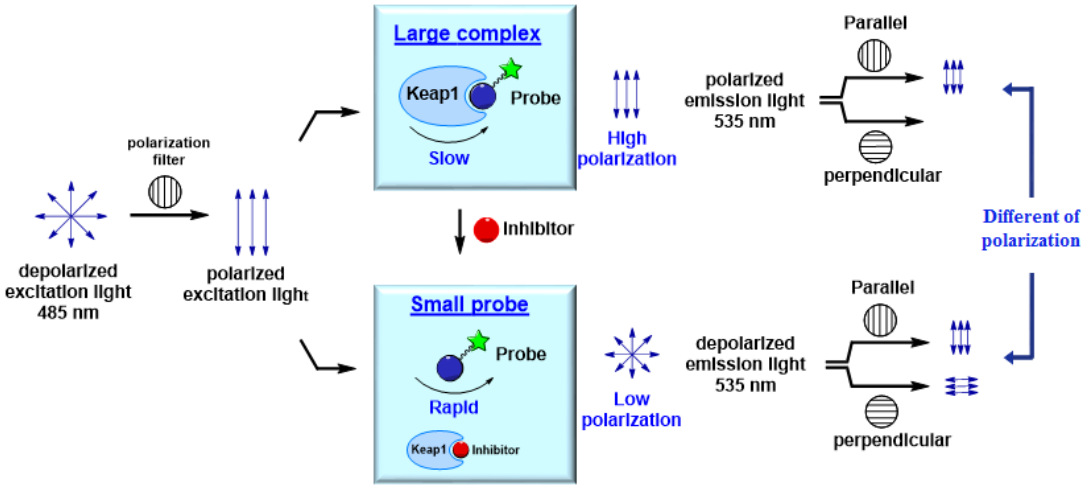


Figure 6. Principle of a fluorescence polarization assay

The TR-FRET assay is a proximity-based method that uses a distance-dependent energy transfer of excited state energy from a donor to an acceptor fluorophore. As outlined in Figure 7, the terbium labeled anti-His antibody forms a complex with the His-tagged Kelch domain of the Keap1. When a probe binds to the complex, the distance between donor and acceptor becomes closer which causes the activation of the acceptor by the transfer of donor emission energy. Once an inhibitor binds to the complex, there is no longer energy transfer due to the long distance. By measuring fluorescence intensity at 520 nm and 495 nm, competitive activity of a test compound was determined. Our group selected a fluorescein-labeled 9-mer Nrf2 peptide amide derived from Nrf2 ETGE motif (FITC-LDEETGEFL-NH_2) as a probe in the assay.

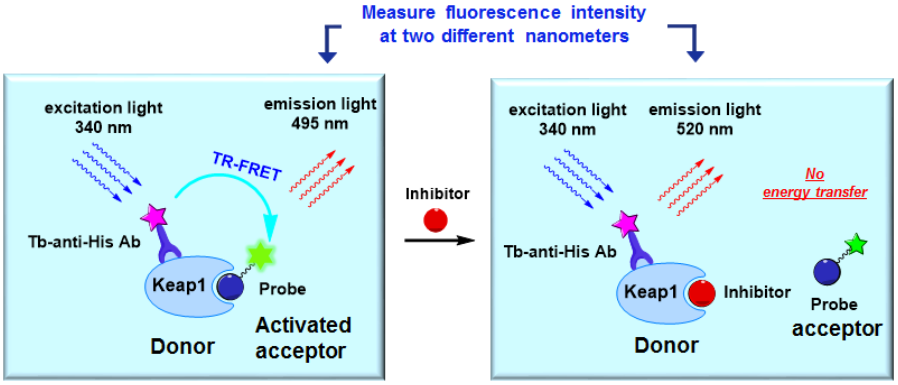


Figure 7. Principle of a time-resolved fluorescence resonance energy transfer assay

Cellular and *in vivo* assays are divided into two categories; assays for Keap1-Nrf2 PPI inhibition and Nrf2 activation. First, a cell-based luciferase enzyme fragment complementation (EFC) assay is used to evaluate inhibitory activity using the Nrf2 protein with an N-terminal luciferase fragment and the Keap1 protein with a C-terminal luciferase fragment. To estimate the potency of Nrf2 activation, a Nrf2-ARE luciferase reporter gene

assay is widely used in HTS becase a luciferase gene, under the control of ARE promoters, can reflect Nrf2 activation. In addition, western blot and qRT-PCR analysis of Nrf2 and its downstream genes is a direct method to validate the activation of Nrf2 and its function at the cellular level.[94]

1.5.4 Small molecule inhibitors of Keap1-Nrf2 PPI

The direct and noncovalent activators of Nrf2 have certain advantages over electrophilic compounds in terms of target selectivity. A Keap1 homodimer forms an interaction with a Nrf2 through two binding sites, ETGE and DLG motifs, located in the Neh2 domain of Nrf2.[32,33] The binding of non-electrophilic small molecules to the Keap1 Kelch domain contributes to selectively disrupting the interaction between Keap1 and Nrf2. Recently, several small molecule inhibitors have been discovered (Figure 5) via various drug design strategies including high-throughput screening (HTS) and fragment-based drug discovery (FBDD).[97] In 2013, our group reported the first small molecule inhibitor of Keap1-Nrf2 bearing 1,2,3,4-tetrahydrohydroquinoline scaffold via high-throughput screening (HTS) from the NIH MLPCN library.[98] The initial hit involving predominantly one pair of enantiomers exhibited the inhibitory potency with IC_{50} value of 3.0 μM in a fluorescence polarization (FP) assay, while a K_d of the most active (*SRS)*-isomer was 1.0 μM in a surface plasmon resonance (SPR) assay. Cell-based functional assays indicated that the one isomer exhibited ARE-inducing activation in HepG2 cells with an EC_{50} value of 18 μM and the stimulation of Nrf2 nuclear translocation with an EC_{50} of 12 μM. Furthermore, compound **1** was found to upregulate a subset of Nrf2 target genes including HO-1, NQO1 and TRX1, as well as enhance HO-1 (3.5 fold) and TRX1 (2-4 fold) protein expression in cultured

human kidney cells (HEK293) at the concentrations of 50 and 100 μM.[99] These biological studies suggested the need for improving both *in vitro* inhibition activity and cellular potency.

The symmetric 1,4-diaminonaphthalene scaffold is another series of inhibitors identified from a high-throughput screen of a 267,551-compound library using an FA assay. Through further computational analysis, compound **2** was rationally designed by introducing symmetric acetic acid groups onto sulfonamide groups, and shown to potently inhibit the Keap1-Nrf2 interactions with an IC_{50} value of 28.6 nM in an FP assay. Cell-based functional assays revealed that compound **2** served to activate Nrf2, up-regulate Nrf2-dependent gene expression and increase the protein level of Nrf2 targeted genes containing HO-1, NQO1, and GCLM.[92,100] In addition, this compound dramatically reduced the levels of pro-inflammatory cytokines in a lipopolysaccharide-challenged mouse model. A naphthyl-pyrrolidine-3-carboxylic acid, compound **3**, was discovered as a Keap1-Nrf2 interaction inhibitor by Winkel *et al*. in 2015.[101] It was reported that the compound, namely RA839, inhibited the protein-protein interaction with an IC_{50} of 0.14 μM, and a lead compound significantly increased the hepatic mRNA levels of the Nrf2 target genes, GCLC and NQO1 in a mouse model, when it was administered to mice together with a cytochrome P450 inhibitor.

In 2016, Astex Pharmaceuticals and GlaxoSmithKline Pharmaceuticals reported a 3-phenylpropanoic acid scaffold, which was identified through the fragment-based drug design (FBDD) approach.[102] In the initial stage, a fragment-growing approach was applied, designing compound **4** which had improved activity with an IC_{50} value of 0.27 μM in the enzyme-based FP assay. Through further modification, its derivative, with the cyclic

sulfonamide, showed the most inhibitory potency with an IC_{50} value of 15 nM and served as the activator of the Keap1-Nrf2 antioxidant response in cell-based assays and activated the Nrf2 pathway *in vivo* using chronic obstructive pulmonary disease (COPD) models.[102,103]

In 2014, a systematic target-based virtual screening approach was developed by Xing et al., which contributed to the discovery of three classes of inhibitors. Through SAR study, lead compounds, **6** and **7** displayed moderate inhibitory activities against Keap1-Nrf2 interactions, with K_D values of 2.9 μM and 10.4 μM, respectively. Several biological experiments including Nrf2 nuclear translocation, the up-regulation of Nrf2 downstream genes and cellular protective effect supported that compound **6** was involved in Nrf2 activation as a true Keap1-Nrf2 inhibitor.[104] Furthermore, Compound **8,** which had a similar structure to **6**, was discovered as a Nrf2 activator with a K_D value of 1.7 μM by our group in 2013.[105]

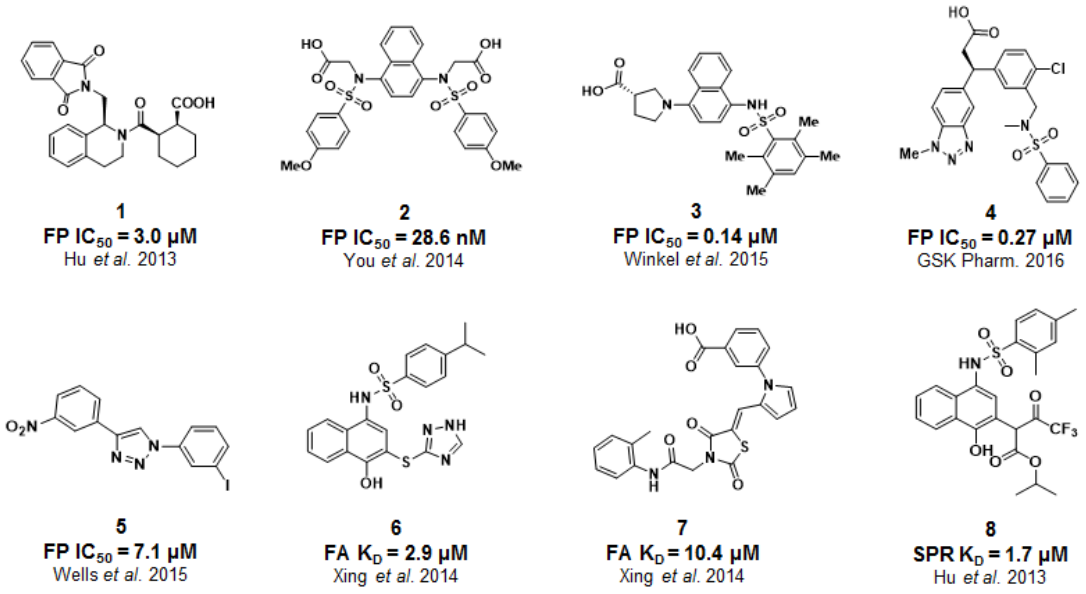


Figure 8. Structures of direct Keap1-Nrf2 PPI inhibitors

RESULTS AND DISCUSSION

2.1 Design of novel biphenyl and *O*-linked analogs

Considering that key residues located in subpockets are essential for high binding affinity, a substrate, which fully occupies the five subpockets of the Nrf2-binding site, is more likely to result in potent PPI inhibition, which is validated by the nanomolar activity of compound **10**, as shown in Figure 9C.[106] However, compound **9** bearing a phenyl core moiety exhibited dramatically reduced potency with an IC_{50} value of 1448 nM relative to **2**, despite full occupation of the five subpockets (Figure 9B).[100,107] According to the previously reported literature, replacement of the phenyl ring leads to weakening of the hydrophobic interactions as well as the π-cation interaction with Arg415 in the P3 subpocket. Accordingly, to improve structural diversity of the core moiety without losing activity, we were interested in replacing one phenyl ring on the naphthalene ring with diverse aromatic ring fragments, including *O*-linked aryl rings (Figure 9A). Moreover, the binding mode of compound **6** indicated that its *p*-cumenesulfonamide is inserted deeply into the pore of the P3 pocket through a cation- π interaction with Arg415, supporting the hypothesis that there is enough chemical space to introduce an additional fragment at the back of P3 pocket (Figure 9D).[104]

Although 1,4-diaminonaphthalene analogs possess strong binding activities, cell-based potency and drug-like properties remain as significant factors to be overcome for the development of preventive and therapeutic agents. However, previous SAR studies demonstrated that this scaffold had the disadvantage of limited structural modification. Therefore, we focused our optimization effort on the *O*-linked phenyl and naphthalene

scaffolds by exploring and expanding the chemical space in the P3 sub-pocket, in order to increase the diversity of analogs

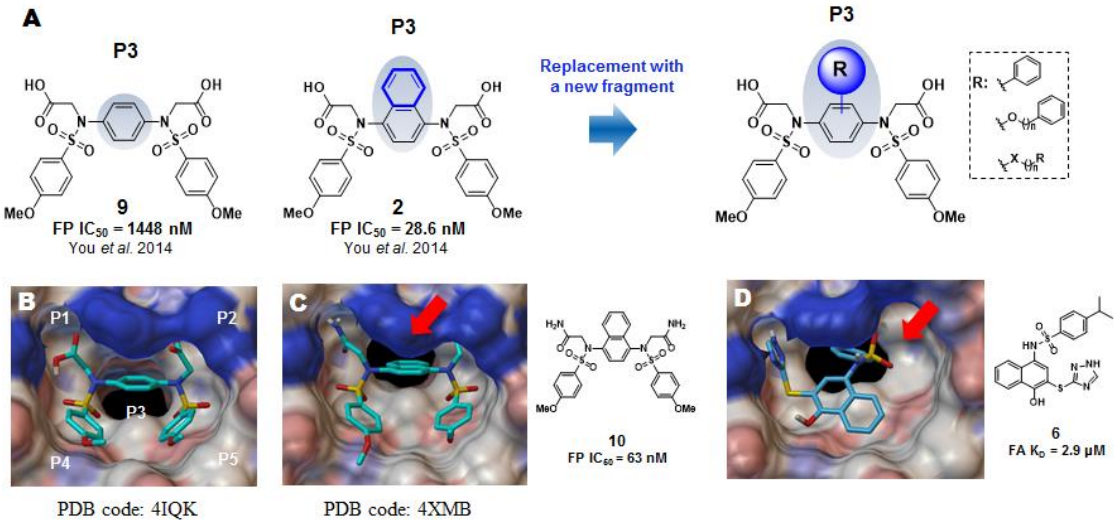
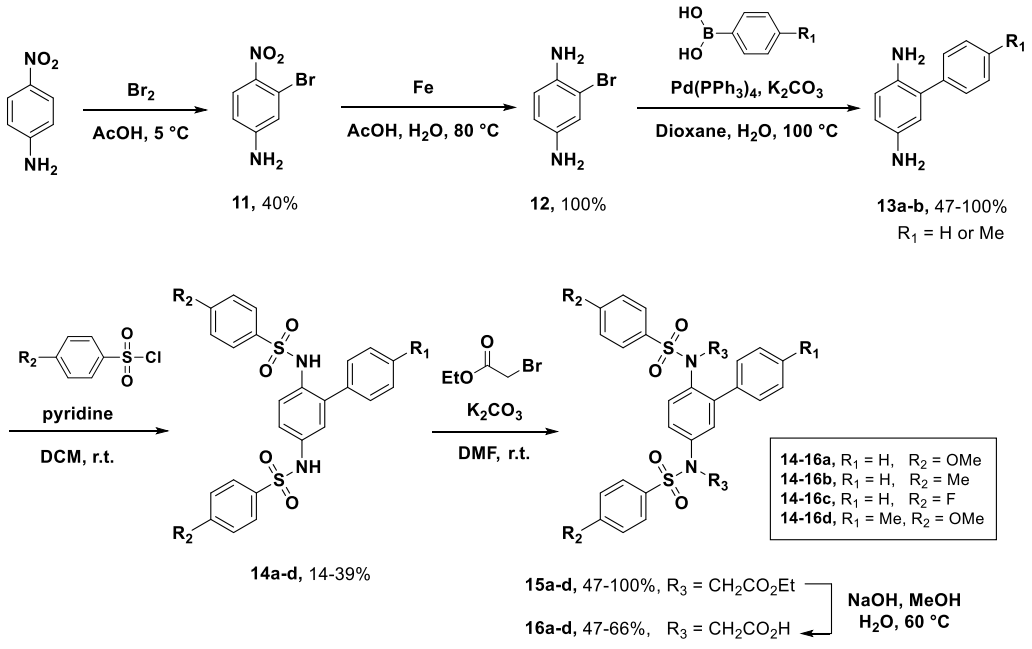


Figure 9. Design strategy of 1,4-diaminophenyl analog with various fragments

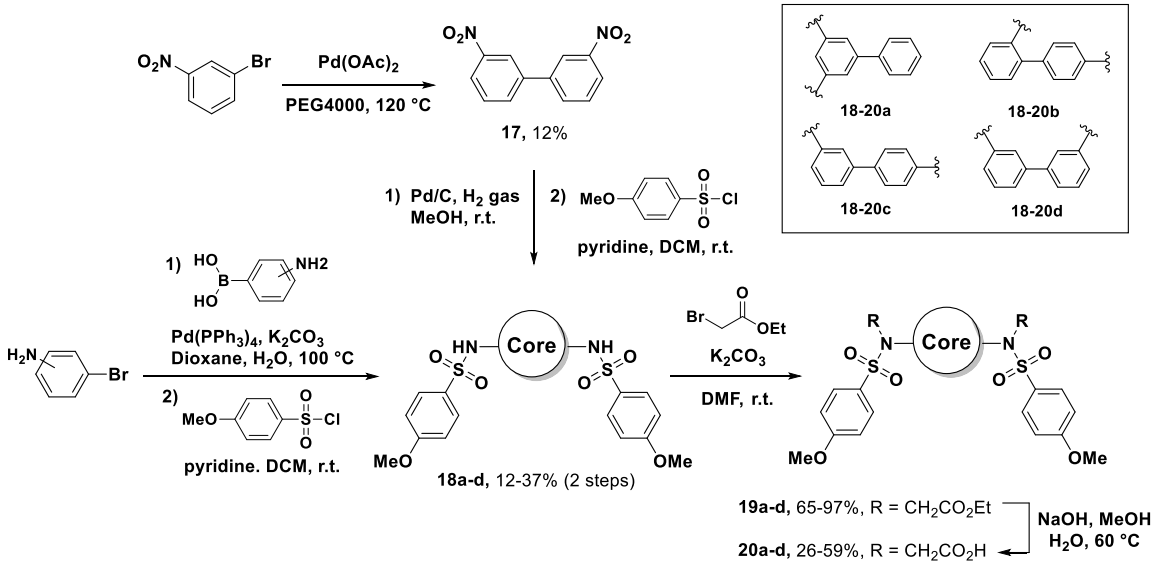
2.2 Synthesis and evaluation of biphenyl derivatives

As shown in Scheme 1, biphenyl analogs **16a-d** were synthesized to evaluate their inhibitory activity. Starting with commercially available 4-nitroaniline, reaction with bromine in acetic acid at 5 ℃ gave 3-bromo-4-nitroaniline, **11**. Diamine **12**, obtained by an iron-catalyzed nitro reduction, was subsequently used with phenylboronic acid under Suzuki coupling conditions using $Pd(PPh_3)_4$ and K_2CO_3 in the solvent mixture of dioxane and water at 100 ℃ to provide compounds **13a-b**. Treatment with 4-substituted benzenesulfonyl chloride and pyridine in dichloromethane at room temperature produced compounds **14a-d**. Alkylation of **14a-d** with ethyl 2-bromoactate in DMF at room

temperature, followed by base hydrolysis of the two ethyl esters of **15a-d** with NaOH in water and methanol at 60 °C, afforded the desired products **16a-d**.



Scheme 1. Synthesis of compounds **16a-d**

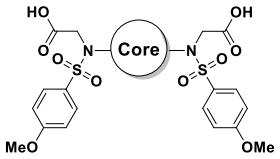


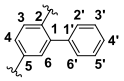
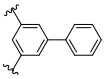
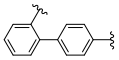
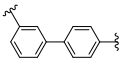
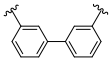
Scheme 2. Synthesis of compounds **20a-d**

Synthesis of compounds **20a-d** is summarized in Scheme 2. Biphenyl intermediates **18a-d** bearing two 4-methoxybenzenesulfonamides were prepared by two different synthetic routes. First, Suzuki-coupling reaction with *p*-substituted phenylboronic acid followed by sulfonylation with 4-methoxybenzenesulfonyl chloride afforded compounds **18a-c**. Another intermediate **18d** was synthesized in three steps, including a palladium-catalyzed homocoupling reaction in polyethylene glycol 4000, nitro reduction,[108] and sulfonamide formation. Addition of two acetate groups and subsequent saponification gave target compounds **20a-d**.

Inhibitory activity of the biphenyl analogs (**16a** and **20a-d**) was evaluated using the FP assay (Table 1).[96] Initially, percent inhibition of a test compound was measured at three concentrations of 50, 5 and 0.5 μM. If the compound had more than 50% inhibition at 5 μM, an IC_{50} value was determined for SAR study. Compound **16a** displayed moderate activity with an IC_{50} value of 3.47 μM while other biphenyl derivatives **20a-d** bearing two sub-moieties at different positions were less active than **16a**. The results indicated that 2,5-position of the core moiety is preferred for biological activity against Keap1-Nrf2 PPI. Accordingly, compound **16a** was further optimized by modifications of the *O*-benzyl ring fragment or 4-methoxy groups of the benzenesulfonamide moieties. 4-Methylbenzyl alcohol fragment (**16d**) and 4-methyl substituent (**16b**) retained potency, whereas 4-fluoro groups on the sulfonamide parts (**16c**) led to reduced activity with 42% at 5 μM (Table 2 and 3).

Table 1. Inhibitory activity of compounds **16a** and **20a-d**



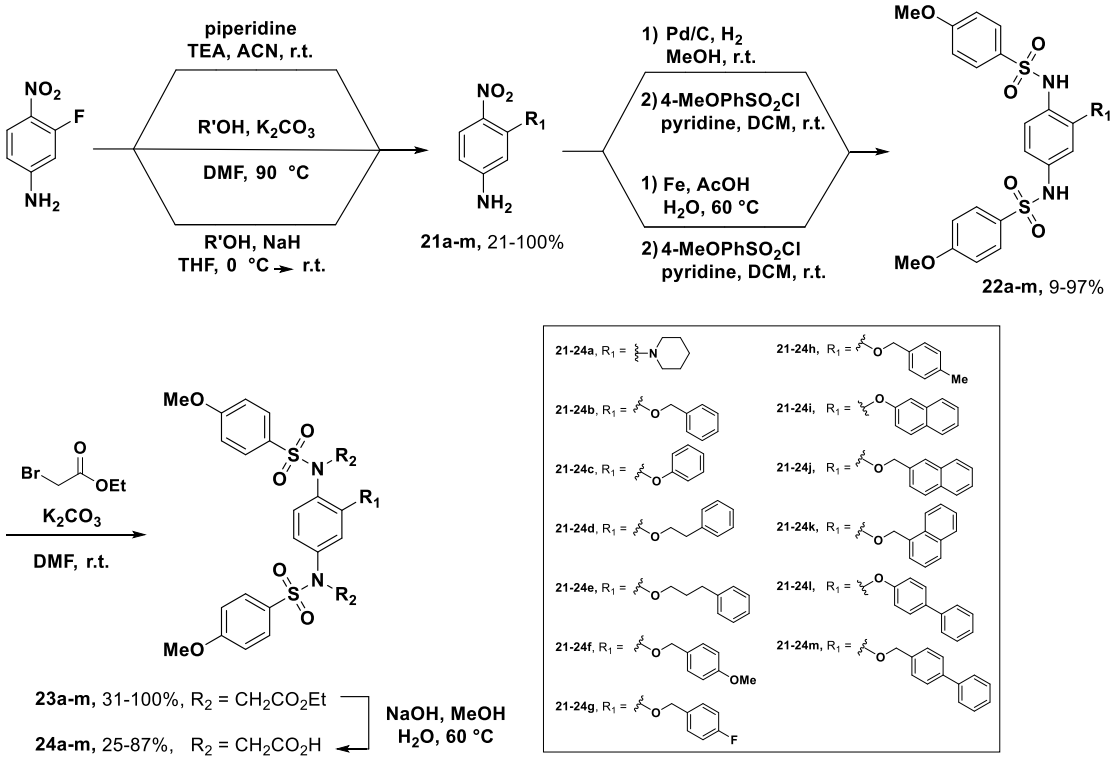
compd	core	% inhibition (FP assay)			IC_{50} (μM)
		50 μM	5 μM	0.5 μM	
16a		98	75	30	3.47 ± 1.24
20a		80	30	ND	ND
20b		42	24	ND	ND
20c		65	31	ND	ND
20d		88	23	ND	ND

2.3 Synthesis and evaluation of a phenyl scaffold with *O*-linked fragments

2.3.1 Exploration on an *O*-linked phenyl fragment

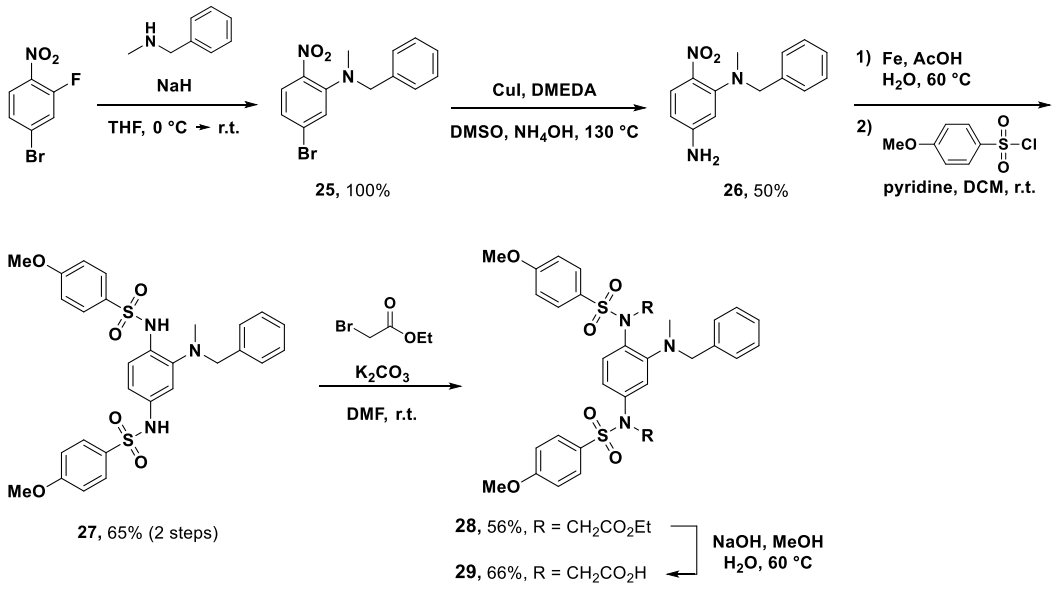
To reduce the rigidity of the biphenyl scaffold, we introduced an *O*-linker between the phenyl rings designing an *O*-linked phenyl scaffold. First, we aimed to explore the *O*-linked aromatic fragment. Beside, compound **24a** was synthesized by replacing the benzene ring with piperidine to identify aryl-protein interactions. Compounds **24a-m** containing various linker fragments were prepared according to Scheme 3. To add different fragments on the core moiety (**21a-m**), the fluorine of 2-fluoro-4-nitroaniline was displaced by piperidine, aryl or aliphatic alcohols using three different bases, TEA, K_2CO_3 and NaH. Iron or palladium-catalyzed nitro reduction of **21a-m** yielded the desired 1,4-benzenediamine intermediates, which were then treated with 4-methoxybenzene sulfonyl chloride to give

22a-m. Alkylation of the sulfonamides with ethyl 2-bromoactate followed by hydrolysis of the ester groups with NaOH provided compounds **24a-m**.



Scheme 3. Synthesis of compounds **24a-m**

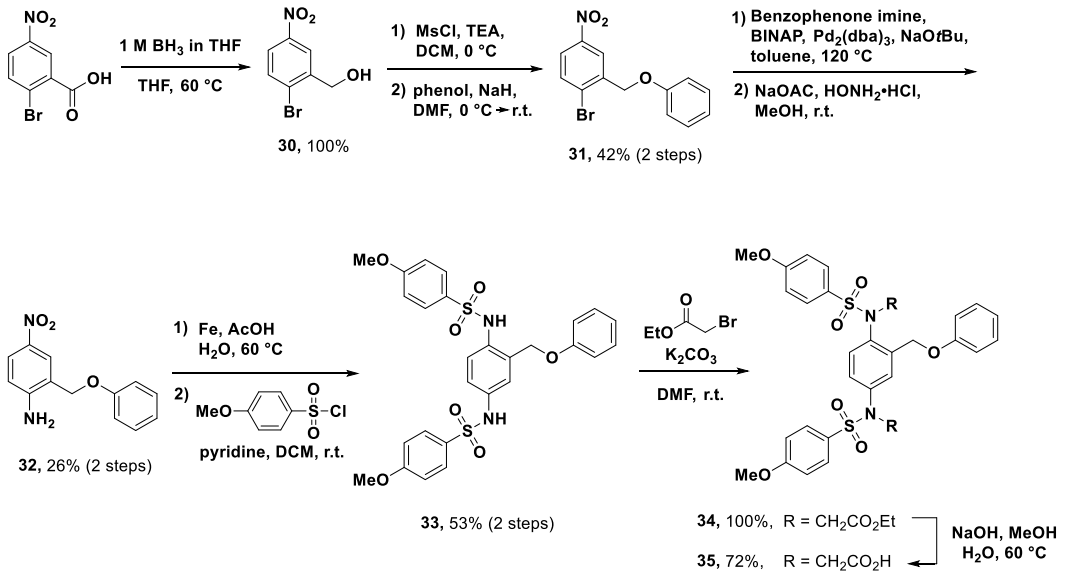
As outlined in Scheme 4, compound **29** with an *N*-benzyl linker was prepared in order to study the inhibitory effect of the nitrogen through a bioisoteric replacement strategy. Starting with 4-bromo-2-fluoro-1-nitrobenzene, treatment with sodium hydride and *N*-benzyl methylamine in THF gave **25**. The bromine of **25** was displaced with copper(I) iodide and *N,N'*-dimethylethyleneamine in ammonium hydroxide solution to form aniline analogue **26**.[109] Reduction of the nitro group followed by sulfonamide formation provided disulfonamide derivative **27**. After alkylation with ethyl 2-bromoacetate, two ethyl esters of **28** were hydrolyzed under basic conditions to afford target compound **29.**



Scheme 4. Synthesis of compound **29**

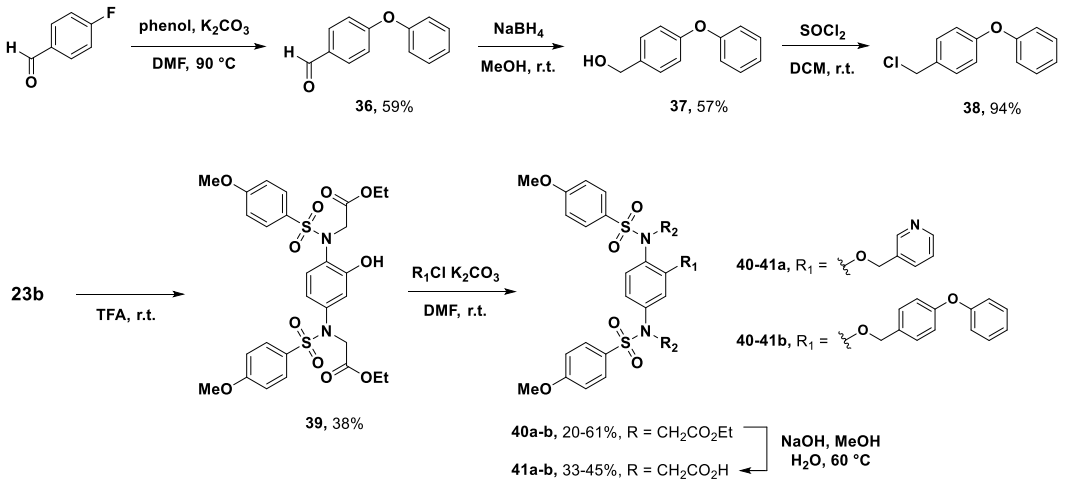
The synthesis of **35** bearing a reversed *O*-linker was performed as indicated in Scheme 5. 2-Bromo-5-nitrobenzoic acid was reduced with borane tetrahydrofuran complex solution at 60 °C to give compound **30** in quantitative yield. Mesylation of the primary alcohol followed by substitution with a phenol produced the ether derivative **31** over 2 steps. Palladium-catalyzed coupling reaction with benzophenone imine and BINAP ligand gave an imine intermediate, which was reduced under acidic conditions with sodium acetate and hydroxylamine to afford aniline analog **32**.[110] After reducing the nitro group, the diamine intermediate was treated with 4-methoxybenzenesulfonyl chloride to produce compound **33**. Nucleophilic substitution with ethyl 2-bromoactate followed by saponification of **34** yielded the final product **35**.

Analogs possessing pyridine (**41a**) or 4-phenoxybenzene (**41b**) were prepared by different routes outlined in Scheme 6. 1-(Chloromethyl)-4-phenoxybenzene **38**, used as a building block for nucleophilic substitution, was prepared starting from 4-fluoro-benzaldehyde via



Scheme 5. Synthesis of compound **35**

three steps including aromatic nucleophilic substitution with phenol, reduction of the aldehyde **36**, and chlorination of **37**. Cleavage of the benzyl protecting group of **23b** gave key intermediate **39**, which was alkylated with either 3-(chloromethyl)pyridine hydrochloride or **38** followed by saponification to form compounds **41a-b**.



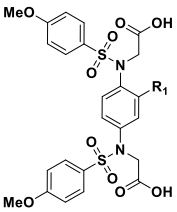
Scheme 6. Synthesis of compound **41a-b**

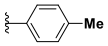
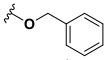
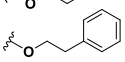
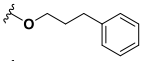
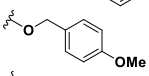
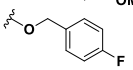
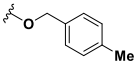
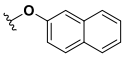
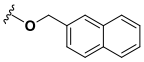
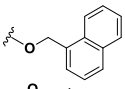
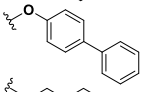
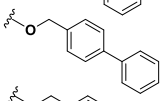
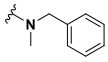
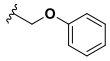
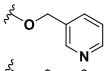
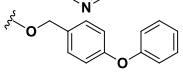
To evaluate Keap1-Nrf2 PPI inhibitory activity of small molecules, an FP assay was carried out according to the procedure developed by our group.[96] We first focused our studies on exploring R_1 fragment on the core phenyl ring, as shown in Table 2. Piperidine **24a** reached only about 50% inhibition, indicating a preference for aromatic rings over the saturated ring. In an effort to offer greater flexibility to the core moiety, benzylic analogs were prepared by increasing a linker length. Interestingly, the *N*-benzyl fragment (**29**) did not afford additional potency, whereas the *O*-benzyl one (**24b**) achieved potency enhancement by 4-fold as compared to the biphenyl scaffold **16a**. Thus, we fixed the *O*-benzyl linker as a fragment, and its length was then changed from 0- to 3-carbon atoms. As a result, **24b-e** exhibited comparable potency in a range of 0.79 to 1.37 μM, suggesting the existence of chemical space at the back of P3 subpocket. The reversed *O*-benzylic linker **35** resulted in a 3-fold decrease in activity relative to **24b**, meaning the position of the oxygen between the two phenyl rings is important for inhibitory potency. On the other hand, a variety of substituents (**24f-h**) at the 4-position of the benzyl fragment or replacement of the phenyl ring with pyridine (**41a**) were well tolerated with similar activity (IC_{50} = 0.62-0.91 μM) in comparison to **24b**. The SAR results revealed that a series of benzyl phenyl ether derivatives did not provide a significant improvement in potency.

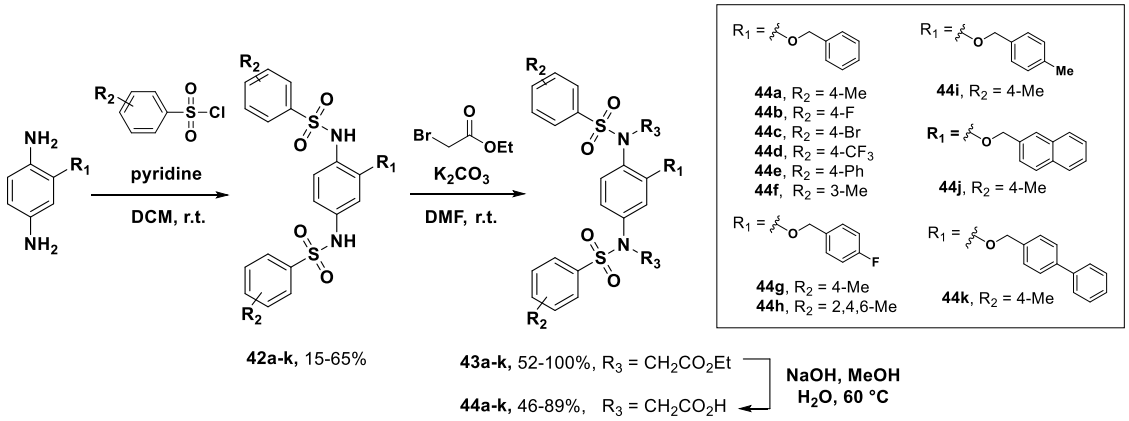
We attempted to replace the benzyl group with two ring system possessing biphenyl or naphthalene ring, as outlined in Table 2. The naphthalene **24j** retained activity (IC_{50} = 0.48 μM), while the biphenyl compound **24m** displayed a 2-fold increase in potency when compared to **24b**, given with the same liner length. In a series of naphthalene derivatives, 1-substituted analog **24k** and compound **24i** bearing a short linker maintained PPI inhibitory potency (IC_{50} = 0.79-0.89 μM). However, in the case of biphenyl series, the

reduced linker length (**24l**) or introduction of an oxygen between two phenyl rings (**41b**) led to 3- or 2-fold reduction in activity relative to **24m**.

Table 2. Inhibitory activity of phenyl ring scaffolds with various *O*-linked fragments



compd	R_1	% inhibition (FP assay)			IC_{50} (μM)
		50 μM	5 μM	0.5 μM	
16a		98	75	30	3.47 ± 1.24
16d		90	73	19	1.99 ± 0.27
24a		89	51	ND	ND
24b		96	97	56	0.79 ± 0.08
24c		95	93	31	1.37 ± 0.19
24d		109	90	41	1.02 ± 0.09
24e		103	99	48	0.95 ± 0.16
24f		91	93	55	0.77 ± 0.12
24g		105	88	57	0.91 ± 0.10
24h		98	92	40	0.62 ± 0.09
24i		102	92	39	0.89 ± 0.12
24j		99	101	63	0.48 ± 0.06
24k		98	79	41	0.79 ± 0.12
24l		94	76	40	1.19 ± 0.15
24m		98	92	51	0.39 ± 0.06
29		101	74	14	6.17 ± 2.70
35		97	96	35	2.62 ± 0.55
41a		98	96	48	0.76 ± 0.15
41b		99	98	40	0.83 ± 0.20



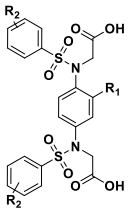
Scheme 7. Synthesis of compounds **44a-k**

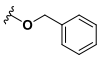
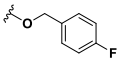
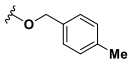
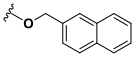
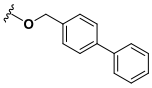
Based on the previous biological results, we selected active compounds, and then carried out SAR study on 4-substituents of the two benzenes connected to the sulfonamide. For substituent modification, compounds **44a-k** were obtained by following the optimized synthetic procedures, as seen in Scheme 7. Treatment of diamine intermediates with appropriate benzenesulfonyl chloride reagents gave sulfonamide analogs **42a-k**, which were reacted with ethyl 2-bromoaceate, followed by base hydrolysis of the ester groups to produce compounds **44a-k** in three overall steps.

As shown in Table 3, we turned our attention toward R_2 modification on the benzenesulfonyl moieties. Among analogs involving a benzyl fragment, the electron-donating groups, such as 4-methyl and 4-phenyl substituents (**44a** and **44e**), exhibited better activities (IC_{50} = 0.45-0.75 μM). However, the electron-withdrawing groups, involving 4-fluoro and 4-trifluoromethyl substituents (**44b** and **44d**), were less potent than 4-methoxy group by 3- and 2-fold, with the exception of 4-bromo substituent (**44c**). Additionally, we observed that the para position of substituents (**44a**) was preferred for PPI inhibition than the meta position (**44f**). From the previous SAR data, 4-methoxy

substituents on the sulfonamide moieties of the phenyl derivatives possessing 4-fluorobenzyl (**24g**), 4-methylbenzyl (**24h**), naphthalene (**24j**), or biphenyl fragment (**24m**), which showed good affinity for Keap1, were replaced with 4-methyl group. Consequently, only 4-fluorobenzyl compound **44g** resulted in an improvment in activity by approximately 2-fold, whereas the potency values of the others (**44i**, **44j** and **44k**) were very similar within 2-fold (IC_{50} = 0.38-0.64 μM) as compared to the corresponding derivatives with 4-methoxy groups. Steric factor at the ortho position may be responsible for reduced activity observed for the 2,4,6-trimethyl group (**44h**) in comparison to **44g**.

Table 3. Inhibitory activity of compounds **16b-c** and **44a-k**



compd	R_1	R_2	% inhibition (FP assay)			IC_{50} (μM)
			50 μM	5 μM	0.5 μM	
16b		4-Me	100	75	27	5.93 ± 2.64
16c		4-F	87	42	5	ND
44a		4-Me	97	102	58	0.45 ± 0.05
44b		4-F	103	87	41	2.41 ± 0.46
44c		4-Br	87	91	54	0.59 ± 0.10
44d		4-CF_3	90	89	32	1.76 ± 0.30
44e		4-Ph	99	97	47	0.75 ± 0.07
44f		3-Me	93	89	43	1.00 ± 0.16
44g		4-Me	106	109	76	0.45 ± 0.04
44h		2,4,6-Me	104	74	29	3.73 ± 0.96
44i		4-Me	103	91	ND	0.64 ± 0.13
44j		4-Me	109	107	68	0.38 ± 0.06
44k		4-Me	104	102	70	0.44 ± 0.04

2.3.2 SAR study of compound 44g

Among the phenyl ring analogues with *O*-liked aromatic fragments, compound **44g** was one of potent inhibitors against Keap1-Nrf2 PPI in the fluorescent polarization assay. Before further optimization of the core moiety, we performed SAR study of compound **44g** by modifying four different parts, as seen in Figure 10.

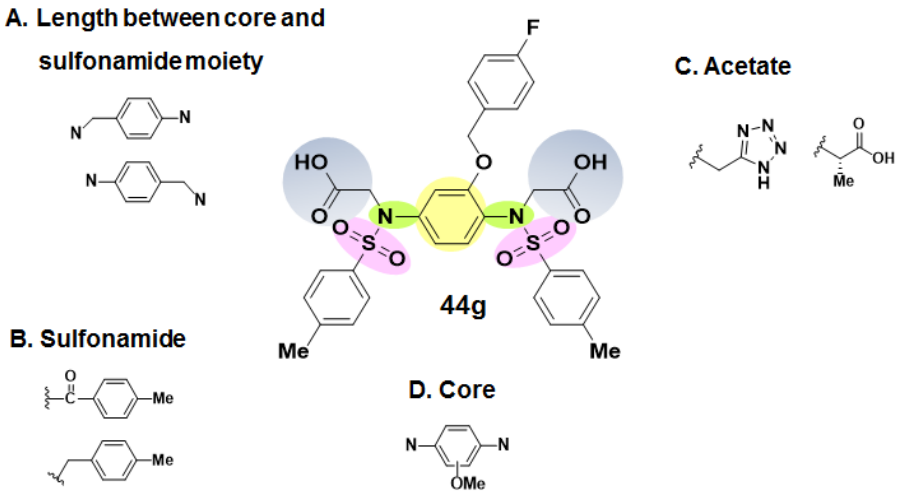
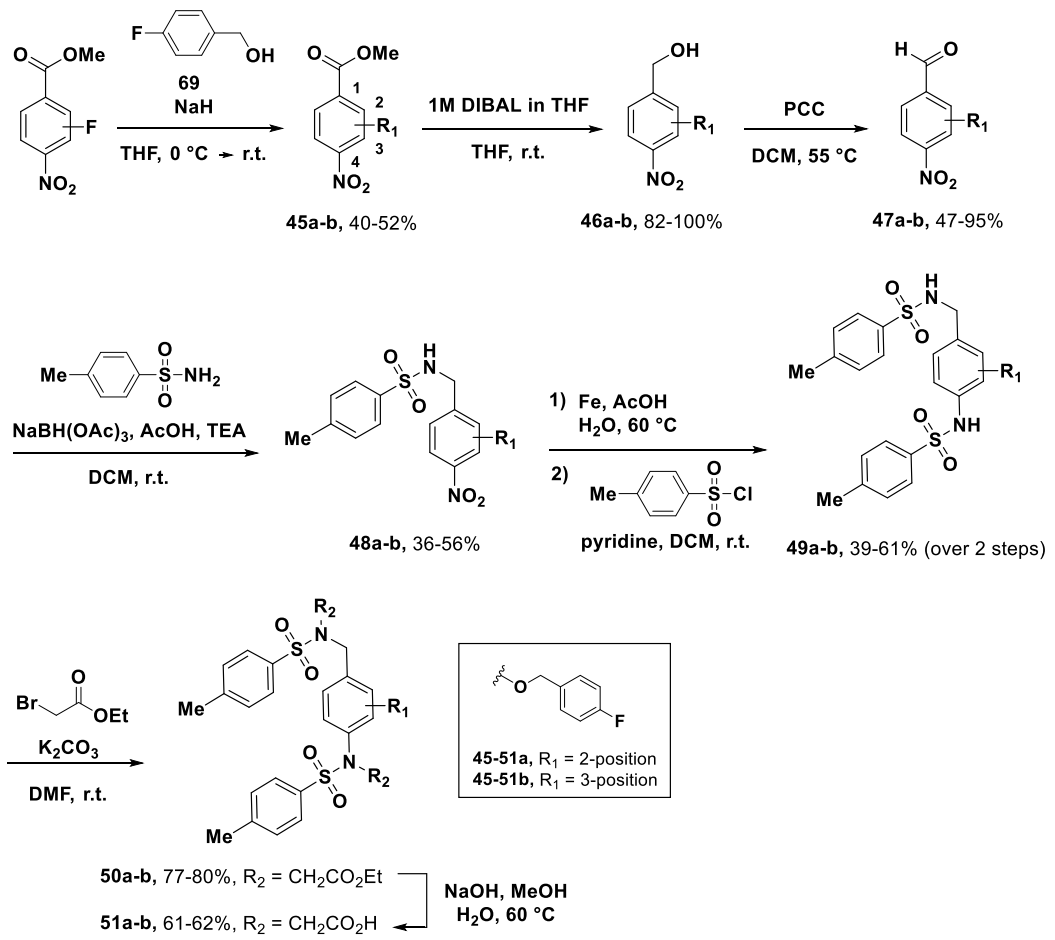


Figure 10. SAR study of compound **44g**

Initially, the linker length between the core phenyl ring and the sulfonamide moiety was changed in order to confirm an optimal distance for potency. Thus, compounds **51a-b** were designed, and prepared according to Scheme 8. Starting with commercially available 2- or 3-fluoro-4-nitrobenzoic acid, treatment with 4-fluorobenzyl alcohol followed by reduction of a methyl ester gave primary alcohol analogs **46a-b**, which were selectively oxidized to aldehydes using PCC reagent. Benzyl-type sulfonamides (**48a-b**) were formed via a reductive amination of **47a-b**, while aryl-type sulfonamide moiety was introduced by an iron-catalyzed nitro reduction and subsequent treatment with 4-toluenesulfonyl chloride.

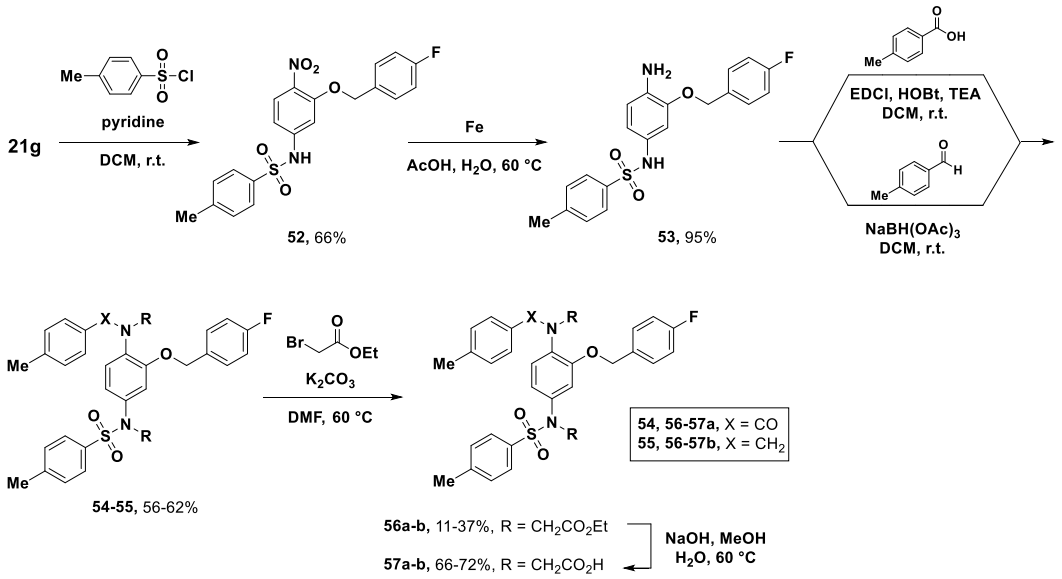


Scheme 8. Synthesis of compounds **51a-b**

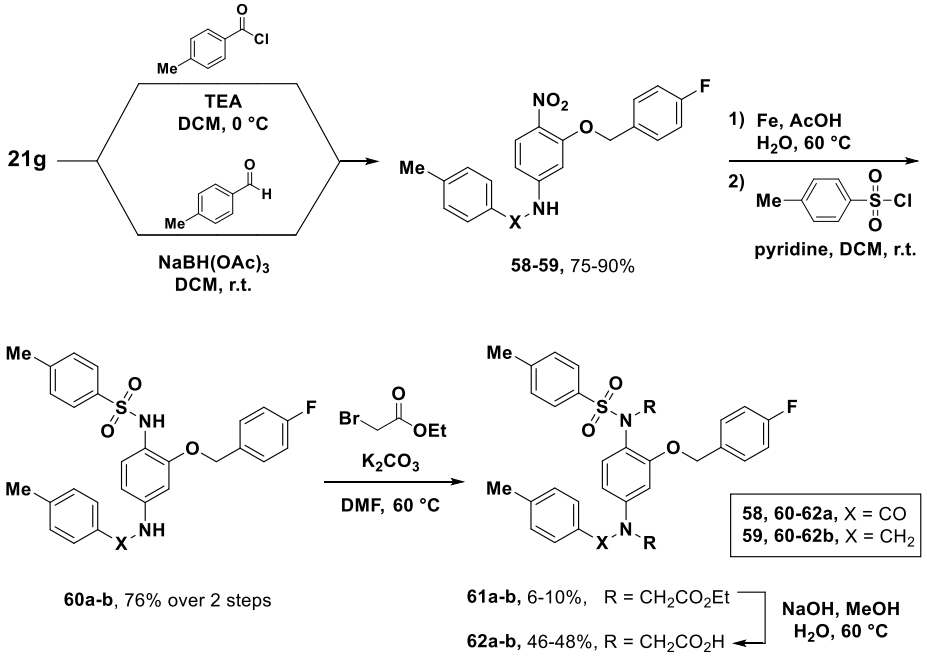
The resulting compounds **49a-b** were alkylated with ethyl bromoacetate, and then hydrolyzed under basic conditions to afford the final products **51a-b.**

Next, two sulfonamide functional linkers were modified by replacing with an amide (**57a** and **62a**) or removing the sulfonyl group (**57b** and **62b**). The synthesis of compounds **57a-b** was accomplished in five steps from the intermediate **21g**, as outlined in Scheme 9. Reaction with 4-methylbenzenesulfonyl chloride gave sulfonamide analog **52**, which was then reduced in the presence of iron powder to provide key intermediate **53**. The amino group was subjected to an EDC-mediated amide coupling with 4-methylbenzoic acid or a reductive amination with 4-methylbenzaldehyde to afford **54** and **55**, respectively.

Addition of acetate groups to the sulfonamide followed by saponification yielded the final products **57a-b.**

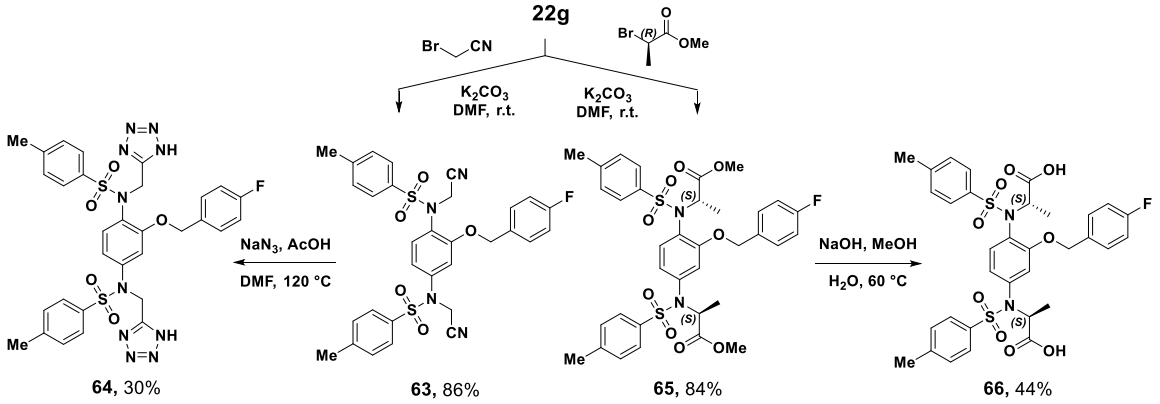


Scheme 9. Synthesis of compounds **57a-b**



Scheme 10. Synthesis of compounds **62a-b**

Other analogs **62a-b** were prepared via an analogous sequence starting from **21g**, as summarized in Scheme 10. Reaction of the amino group of **21g** with 4-methylbenzoyl chloride or 4-methylbenzaldehyde afforded compounds **58** and **59**, which were further converted to the sulfonamide derivatives **60a-b** through a nitro reduction and subsequent sulfonamide formation. Alkylation with ethyl 2-bromoacetate in the presence of K_2CO_3, followed by the removal of the ethyl protective groups of **61a-b** with NaOH, gave target compounds **62a-b**.

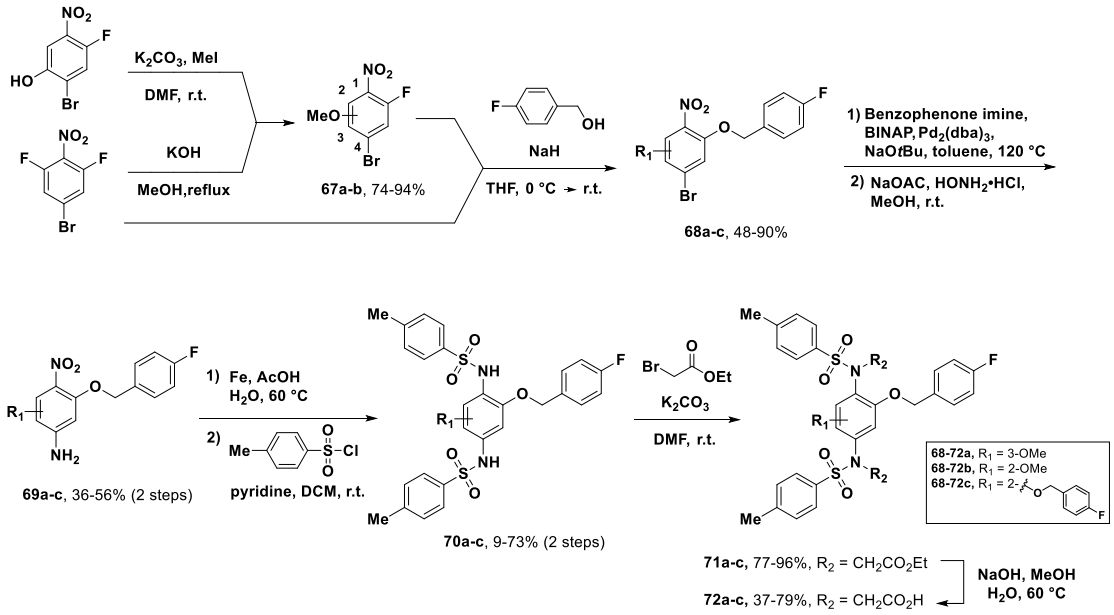


Scheme 11. Synthesis of compounds **64** and **66**

To explore the acetate moieites of **44g**, tetrazole **64** and *(S)*-methylated **66** were prepared from intermediate **22g** by following the synthetic route shown in Scheme 11. Alkylation with bromoacetonitrile followed by tetrazole formation with NaN_3 yielded the derised product **64**. Another compound **66** was synthesized by alkylation with methyl *(R)*-2-bromopropanoate followed by hydrolysis of the esters of **65** under basic conditions.

Final optimization of **44g** was the introduction of 4-fluorobenzyloxy (**72c**) or methoxy groups (**72a-b**) to the core phenyl ring in order to explore additional binding interactions with keap1 protein in the P3 subpocket. Preparation of **72a-c** was achieved using the

synthetic route in Scheme 12. First, 2 or 3-methoxybenzene analogs **67a-b** were synthesized from either methylation of 2-bromo-4-fluoro-5-nitrophenol[111] or nucleophilic aromatic substitution of 5-bromo-1,3-difluoro-2-nitrobenzene in methanol. Addition of 4-fluorobenzyl alcohol fragment produced 4-bromobenzene derivatives **68a-c**, which were converted to the anilines **69a-c** by Buchwald-Hartwig amination and subsequent imine hydrolysis.[110] Nitro reduction of the intermediates **69a-c** followed by sulfonamide formation gave **70a-c**, which were reacted with ethyl 2-bromoacetate and then hydrolyzed under basic conditions to obtain diacetate derivatives **72a-c**.

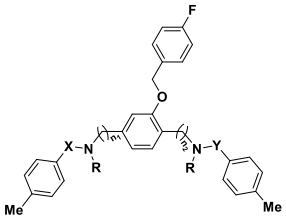


Scheme 12. Synthesis of compounds **72a-c**

The SAR results of **44g** were summarized in Tables 4 and 5. Increasing the linker length (n_1 or n_2 = 1) between the phenyl core and the sulfonamide moiety (**51a-b**) resulted in a 4-fold reduction in potency relative to **44g** (n_1 and n_2 = 0), meaning the benzene-1,4-diamine structure plays a crucial role in forming an appropriate conformation in the cavity of Kelch domain. Replacement of sulfonamides with amides (**57a** and **62a**) or *N*-benzyl linkers (**57b**

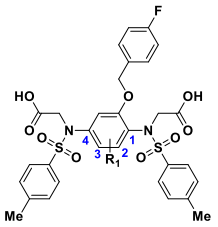
and **62b**) led to significantly decreased activity since the phenyl rings connected to sulfonamide groups lose π-π interactions or hydrophobic interactions with nonpolar residues. Bioisosteric replacement of two acetate groups with tetrazoles (**64**) and addition of *(S)*-methyl groups to α-carbon of the acetate groups (**66**) resulted in a significant loss in potency with 8- and 3-fold reduction. As shown in Table 5, the presence of a methoxy (**72a-b**) or 4-fluorobenzyloxy group (**72c**) at the 2- or 3-positions of the core phenyl ring led to a dramatic drop-off in potency, presumably due to the polarity of the oxygen. Collectively, the SAR studies demonstrates that **44g** is the most potent among its analogs and four moieties, including the benzene-1,4-diamine fragment, acetate groups, sulfonamide linkers, and no additional substituent on the core part of **44g**, play important roles in maintaining activity.

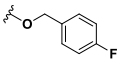
Table 4. Inhibitory activity of compounds **51a-b, 57a-b, 62a-b, 64,** and **65**



compd	n_1	n_2	X	Y	R	% inhibition (FP assay)			IC_{50} (μM)
						50 μM	5 μM	0.5 μM	
44g	0	0	SO_2	SO_2		106	109	76	0.45 ± 0.04
51a	0	1	SO_2	SO_2		110	95	34	1.75 ± 0.42
51b	1	0	SO_2	SO_2		109	73	23	1.81 ± 0.31
57a	0	0	SO_2	CO		59	15	-4	ND
57b	0	0	SO_2	CH_2		-1	-13	ND	ND
62a	0	0	CO	SO_2		52	-6	ND	ND
62b	0	0	CH_2	SO_2		54	19	6	ND
64	0	0	SO_2	SO_2		95	60	16	3.92 ± 0.58
66	0	0	SO_2	SO_2		98	78	ND	1.27 ± 0.22

Table 5. Inhibitory activity of compounds **72a-c**



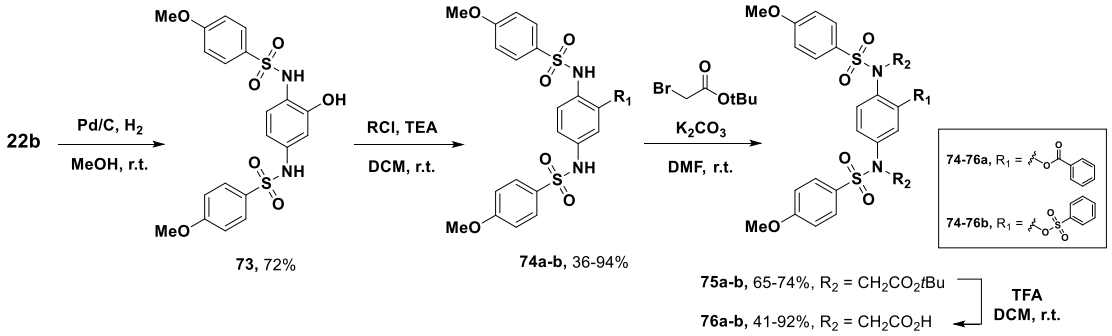
compd	position	R_1	% inhibition (FP assay)			IC_{50} (μM)
			50 μM	5 μM	0.5 μM	
44g	-	H	106	109	76	0.45 ± 0.04
72a	3-	OMe	74	41	26	ND
72b	2-	OMe	75	45	7	ND
72c	2-		58	19	10	ND

2.3.3 *O*-linker modification.

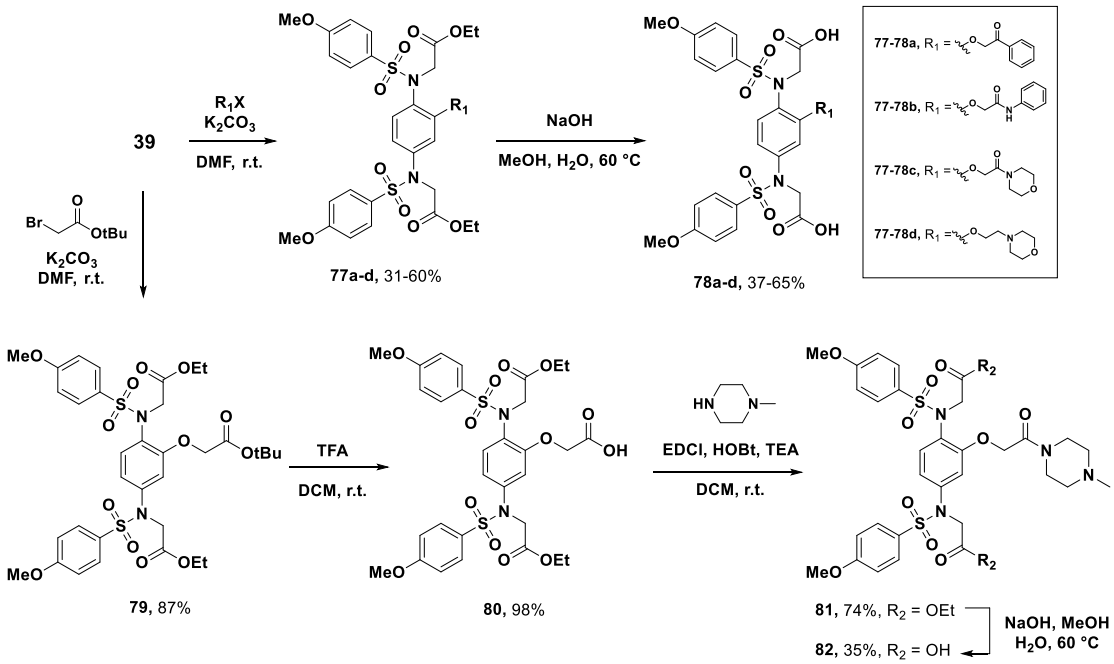
In an attempt to improve activity, we modified the ether linker on the core moiety with two different approaches. The methyleneoxy linker between the two benzene rings was first replaced by a sulfonic acid, an ester, or a carbonyl-containing ether. The linker was further extended in efforts to improve potency. The ester **76a** and sulfonic acid **76b** were prepared according to the synthetic procedure, seen in Scheme 13. Palladium-mediated removal of the benzyl protecting group followed by substitution of the phenolic alcohol with benzoyl chloride or benzenesulfonyl chloride gave acetate analogues **74a-b**, which were alkylated with *tert*-butyl 2-bromoacetate, and then hydrolyzed under acidic conditions to yield target compounds 7**6a-b**.

Additionally, the linker-modified analogs, **78a-d**, were prepared from the ethyl acetate analogue **39**, as outlined in Scheme 14. The phenolic alcohol of **39** was subjected to nucleophilic substitution with various aliphatic halides, followed by saponification to produce target compounds **78a-d**. Methylpiperazine **82** was also prepared from the key

intermediate **39**. Addition of *tert*-butyl acetate provided **79**, followed by acid hydrolysis with TFA to enable an amide coupling reaction with 1-methylpiperazine under a general procedure using EDCI and HOBt. The base hydrolysis of **81** in the presence of NaOH yielded compound **82**.

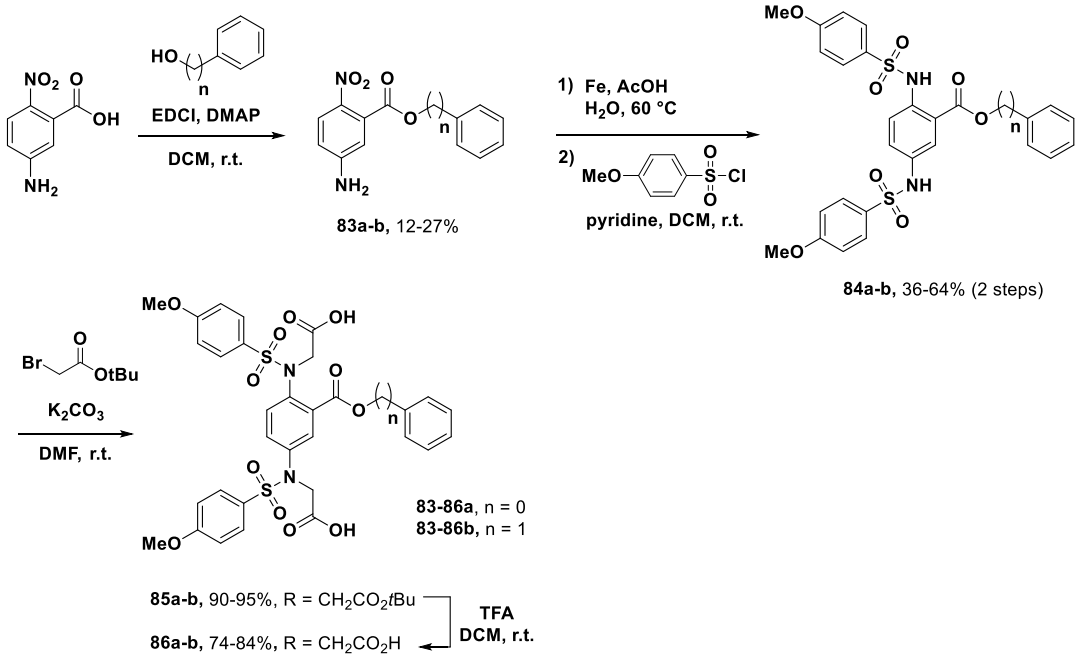


Scheme 13. Synthesis of compounds **76a-b**



Scheme 14. Synthesis of compounds **78a-d** and **82**

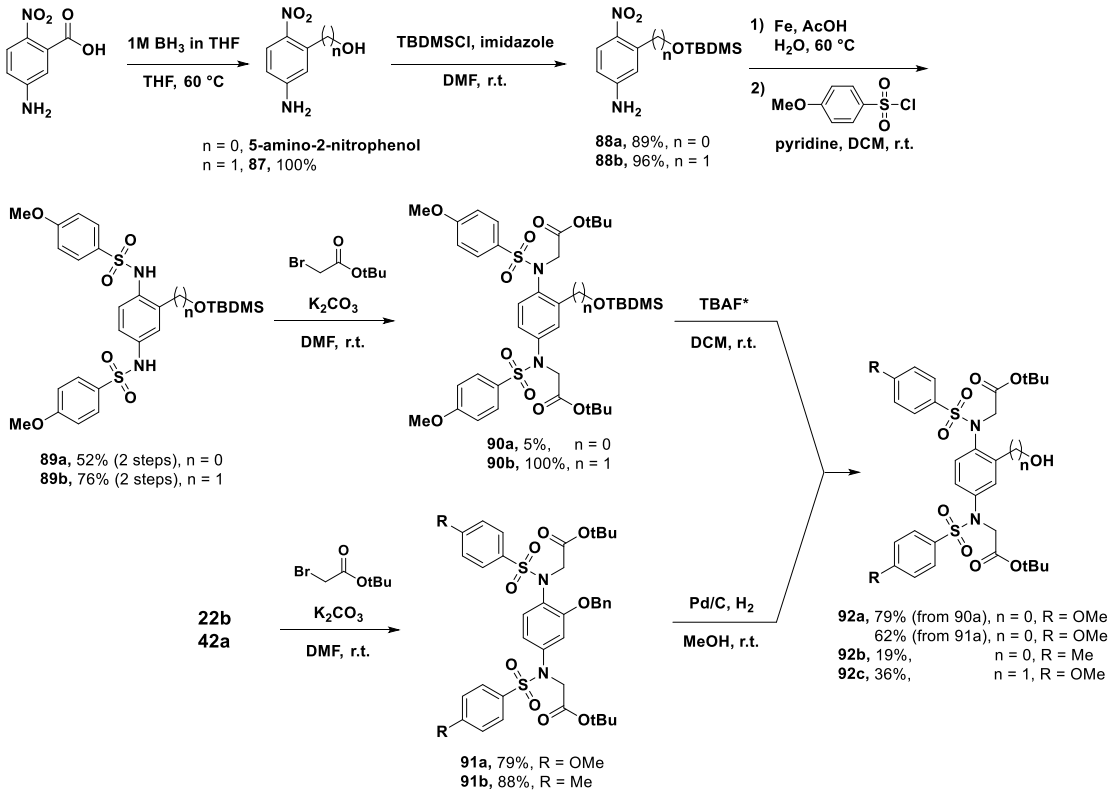
A general procedure for the preparation of a series of reverse ester analogues, **86a-b**, is summarized in Scheme 15. Under ester coupling conditions using EDCI and DMAP, 5-amino-2-nitrobenzoic acid was treated with phenol or benzyl alcohol to form ester compounds **83a-b**, respectively. Nitro reduction and subsequent sulfonamide formation provided sulfonamide derivatives **84a-b**, which underwent alkylation with *tert*-butyl bromoacetate followed by acid hydrolysis to afford the desired products **86a-b**.



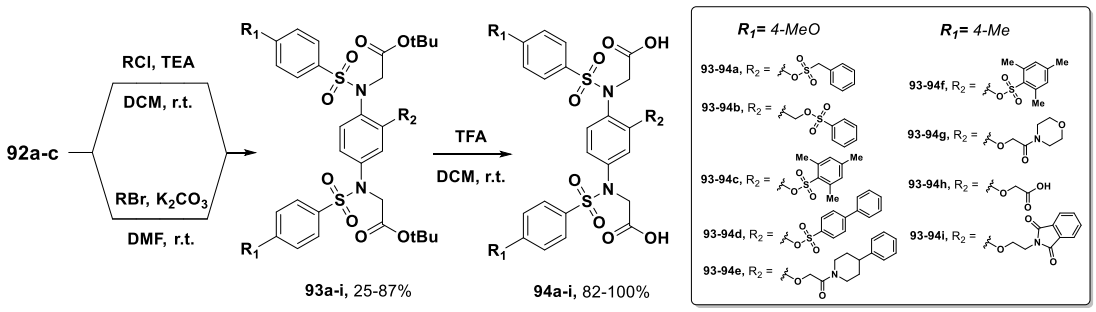
Scheme 15. Synthesis of compounds **86a-b**

As indicated in Scheme 16, key intermediates **92a-c** were prepared by two different synthetic routes. The first method is that phenolic or aliphatic alcohols were protected with a TBDMS group starting from commercially available 5-amino-2-nitrobenzoic acid or 5-amino-2-nitrophenol to provide **88a-b**. Iron-catalyzed nitro reduction followed by *N*-sulfonylation produced **89a-b**, which were converted to the acetate analgos **90a-b** by alkylation with *tert*-butyl 2-bromoacetate. Removal of the TBDMS protecting group with

tetra-butylammonium fluoride gave the desired key intermediates **92a and 92c**. Alternatively, key intermediates **92a-b** were prepared by alkylation of **22b** or **42a** with *tert*-butyl 2-bromoacetate, followed by debenzylation of **91a-b.**

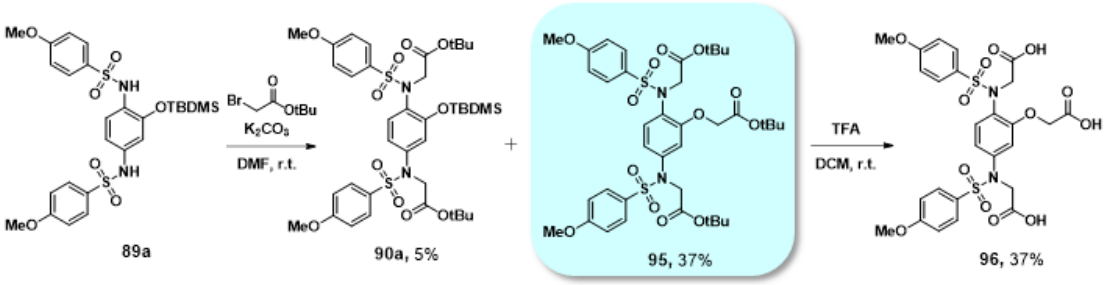


Scheme 16. Synthesis of key intermediates **92a-c**



Scheme 17. Synthesis of compounds **94a-i**

With the key intermediates **92a-c**, *O*-linker-modified analogs **94a-i** were prepared in two steps, as illustrated in Scheme 17. Compounds **93a-i** were formed by substitution of the intermediates **92a-c** with the corresponding sulfonyl chloride reagents or alkyl bromides using TEA or K_2CO_3 as a base. Removal of *tert*-butyl groups of **93a-i** under acidic conditions afforded the desired products **94a-i**.



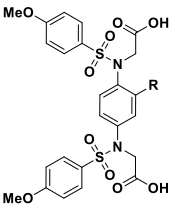
Scheme 18. Synthesis of compound **96**

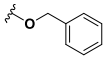
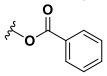
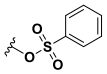
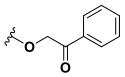
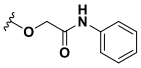
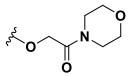
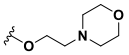
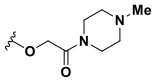
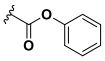
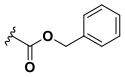
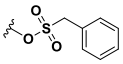
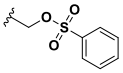
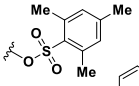
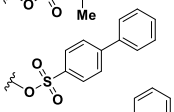
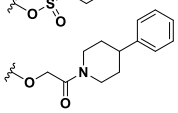
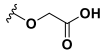
In the alkylation of **89a**, the TBDMS protecting group was unexpectedly removed, and the resulting *tert*-butyl 2-bromoacetate was subsequently reacted with a phenolic alcohol to produce the undesired product, **95**, as shown Scheme 18. It was expected that the bromine generated from reaction led to removing the TBDMS protecting group. Fortunately, acetate analogue **96** was prepared from compound **95** by a TFA-mediated acid hydrolysis.

As illustrated in Table 6, linker R modification was performed in order to examine whether it contributed to improving potency against Keap1-Nrf2 interaction. Both the ester (**76a**) linker and reversed ester linkers (**86a-b**) resulted in a drop in biological activity by 2- to 5-fold compared to ether linker (**24b**). Surprisingly, introduction of the carbonyl group next to benzene (**78a**) and sulfonic acid linker (7**6b**) retained good potency, which were further optimized to improve activity. It seemed that the position of the carbonyl group and the

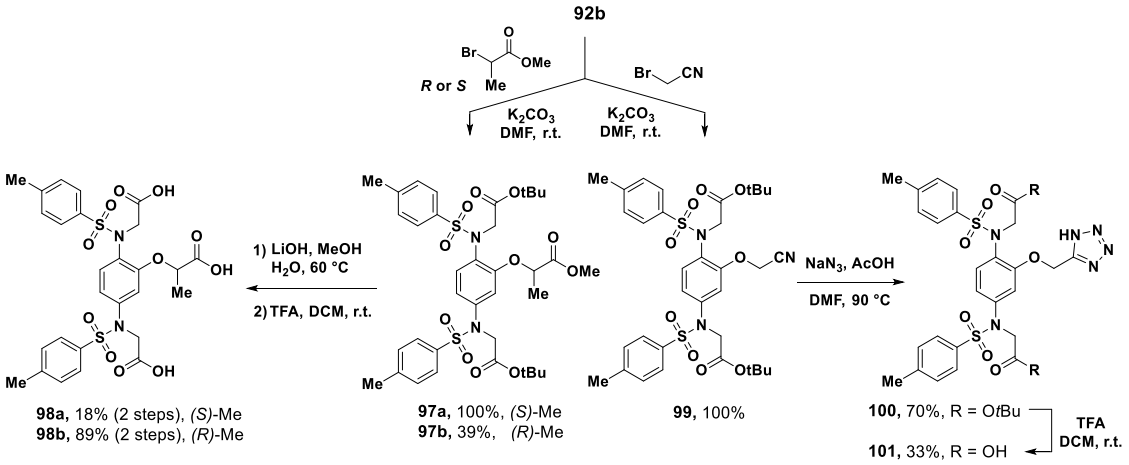
oxygen on the linker (7**6a, 78a,** and **86a-b**) played important roles in binding with Keap1 protein residues.

Table 6. Inhibitory activity of phenyl ring scaffolds with various *O*-linked fragments



compd	R	% inhibition (FP assay)			IC_{50} (μM)
		50 μM	5 μM	0.5 μM	
24b		96	97	56	0.79 ± 0.08
76a		86	80	26	1.78 ± 0.26
76b		99	89	58	0.44 ± 0.04
78a		98	92	50	0.59 ± 0.05
78b		101	79	33	7.68 ± 4.35
78c		93	94	66	0.40 ± 0.03
78d		104	99	44	2.50 ± 0.64
82		98	83	47	2.26 ± 0.26
86a		107	72	22	3.85 ± 0.97
86b		102	82	ND	1.61 ± 0.23
94a		104	96	66	0.48 ± 0.06
94b		103	46	22	ND
94c		102	96	66	0.32 ± 0.04
94d		99	90	58	0.46 ± 0.06
94e		103	94	47	0.76 ± 0.08
96		100	91	77	0.22 ± 0.26

For a series of sulfonic acid analogues, 2,4,6-trimethyl or 4-phenyl substituents (**94c-d**) as well as benzyl ring (**94a**) were well tolerated, with the exception of the increased *O*-linker (**94b**). On the other hand, the replacement of ketone with amide (**78b**) led to a dramatic loss of activity by 13-fold, whereas the amide analogue **78c** possessing morpholine exhibited comparable potency to **78a**. On the basis of this observation, compound **78c** was further modified by the removal of morpholine (**96)** or a carbonyl group (**78d**), the replacement of 1-methylpiperazine (**82**), and the introduction of a lipophilic phenyl ring (**94e**). Intriguingly, the carboxylic acid derivative **96** only maintained activity (IC_{50} = 0.22 μM), while the others resulted in 2- and 6-fold decrease in potency as compared to **78c**.

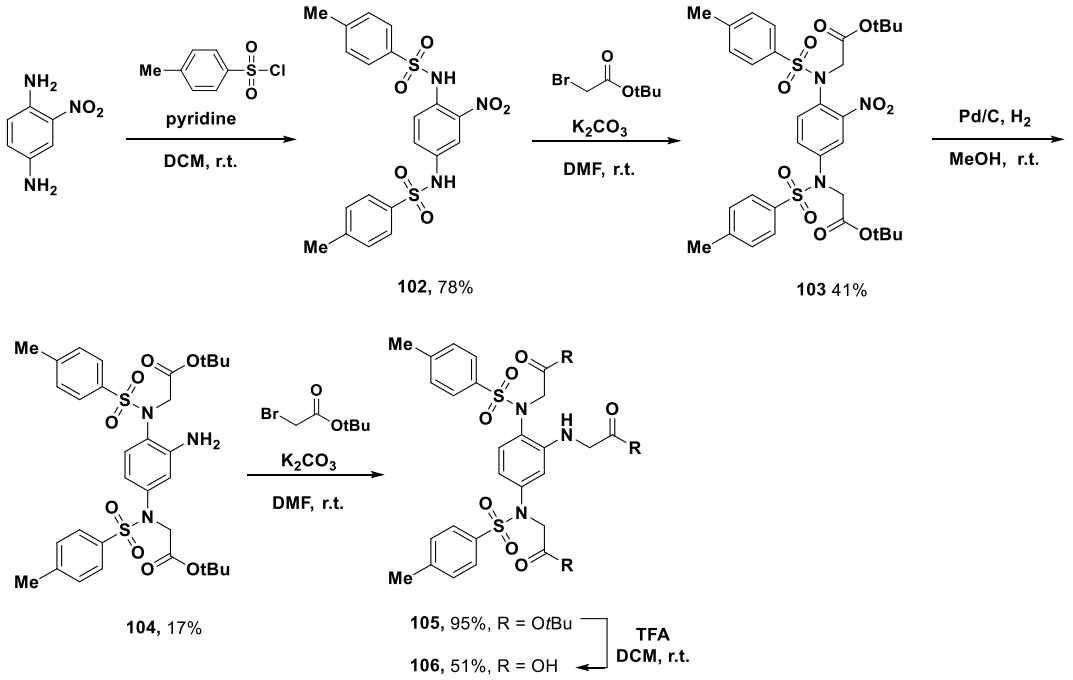


Scheme 19. Synthesis of compounds **98a-b** and **101**

In an effort to optimize an acetate fragment, *(S)*- or *(R)*-methylated acetate derivatives **98a-b** and tetrazole **101** were prepared as presented in Scheme 19. The intermediate **92b** was alkylated with methyl *(R)* or *(S)*-2-bromopropionate to yield *(S)* and *(R)*-methylated analogs (**97a-b**) by inversion of configuration. Hydrolysis both the methyl and two *tert*-butyl esters afforded target compounds **98a-b**. In a similar manner, compound **99** was

prepared by nucleophilic substitution of **92b** using bromoacetonitrile, which was then subjected to tetrazole formation with NaN_3, followed by acid hydrolysis to give compound **101**.

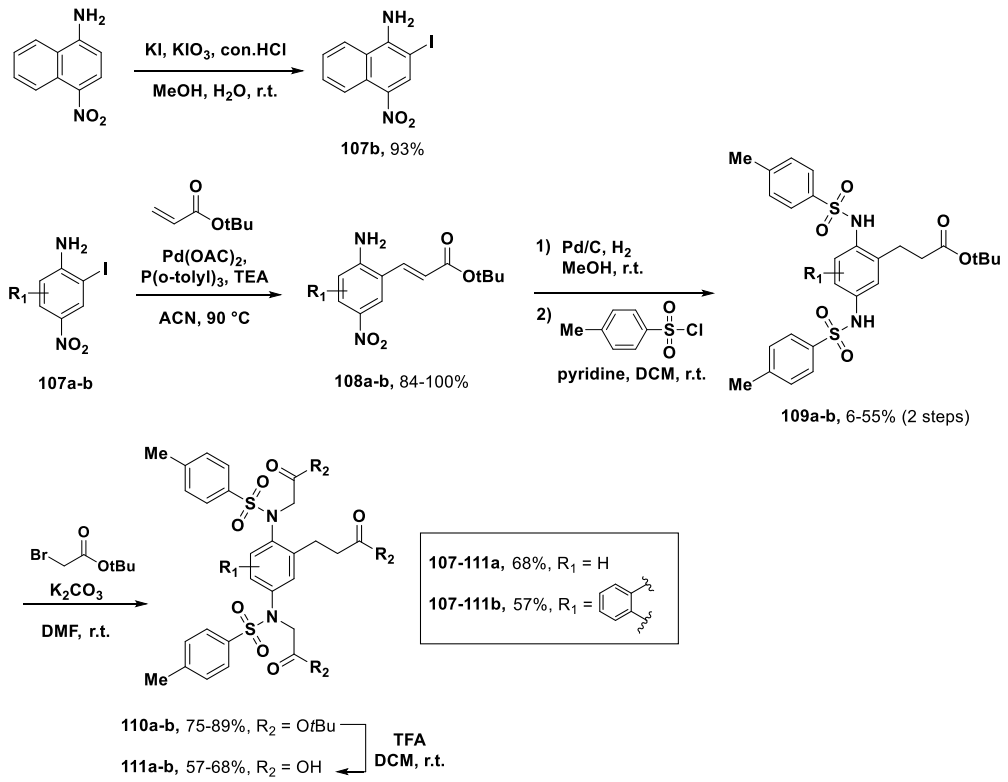
Compound **106** with a nitrogen-containing linker was readily synthesized as depicted in Scheme 20. Treatment of 2-nitrobenzene-1,4-diamine with 4-toluenebenzenesulfonyl chloride followed by alkylation with *tert*-butyl 2-bromoacetate produced **103**. Reduction of the nitro group of **103** allowed for introduction with an extra *tert*-butyl 2-bromoacetate to provide **105**. Formation of **106** was carried out by the cleavage of three *tert*-butyl groups with TFA.



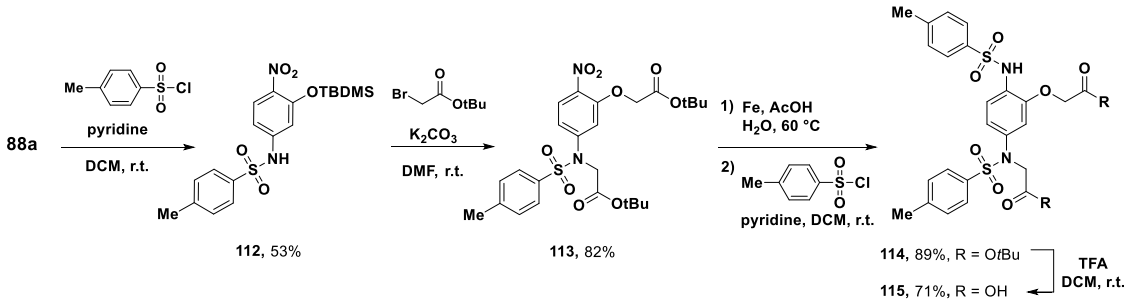
Scheme 20. Synthesis of compound **106**

A general procedure for the preparation of compounds **111a-b** containing an alkyl linker instead of an ether group is summarized in Scheme 21. 2-Iodonaphthalene **107a** was first synthesized from commercially-available 4-nitronaphthalen-1-amine in the presence of potassium iodide and potassium iodate.[112] Heck coupling of 2-iodo substituted compounds

along with *tert*-butyl acrylate in the presence of $Pd(OAc)_2$ and $P(O\text{-tolyl})_3$ provided **108a-b**.[113] Reduction of both the alkene double bond and the nitro group with Pd/C afforded diamine intermediates, which were subsequently treated with 4-methylbenzenesulfonyl chloride to give **109a-b**. Nucleophilic substitution with *tert*-butyl 2-bromoacetate followed by removal of three *tert*-butyl groups with TFA yielded carboxylate analogs **111a-b.**



Scheme 21. Synthesis of compounds **111a-b**

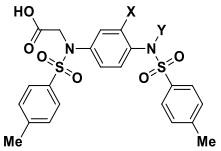


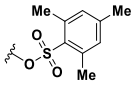
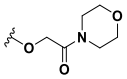
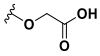
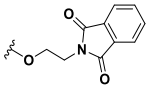
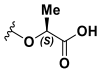
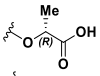
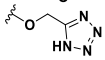
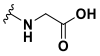
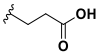
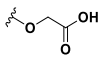
Scheme 22. Synthesis of compound **115**

As shown in Scheme 22, we also sought to prepare compound **115** that includes only one acetate moiety. Starting from intermediate **88a**, treatment of 4-methylbenzenesulfonyl chloride yielded sulfonamide **112**, which was subsequently alkylated with *tert*-butyl 2-bromoacetate to afford compound **113**. Interestingly, the TBDMS protective group was removed under basic conditions with K_2CO_3, and then an extra *tert*-butyl 2-bromoacetate was added to the phenolic alcohol. After reducing a nitro group, *N*-sulfonylation with 4-methyl-benzenesulfonyl chloride provided **114**, which was converted to target compound **115** by acid hydrolysis. From the previous SAR study, we observed a preference for a methyl group over a methoxy substituent at the 4-position of the benzene rings on the sulfonamide moiety. Therefore, the methoxy groups of active compounds (**94c**, **78c** and **96**), selected from *O*-linker modified derivatives, were replaced by methyl substituents (Table 7). The results revealed that the sulfonic acid (**94c** and **94f**) or morpholine analogs (**78c** and **94g**) showed a small difference in activity within 2-fold, while the carboxylic acid analogue, **94h** with 4-methyl groups displayed 2-fold greater potency than **96** with methoxy groups. Accordingly, we focused our attention on optimizing the most potent compound **94h**, as shown in Table 7. Replacement of the oxygen with divalent bioisosteres, nitrogen and carbon atoms (**106** and **111a**), led to significantly decreased potency by 16- and 5-fold, suggesting that the change of bond angle, conformation or electronegativity affects with biological activity. Additionally, introduction of tetrazole as a bioisosteric substituent (**101**) or phthalimide (**94i**) also resulted in 4- and 2-fold less activities as compared to **94h**. Removal of one acetic group connected to the sulfonamide analog (**115**) provided significantly decreased activity (IC_{50} = 1.24 μM), indicating that the two acetic groups are essential for maintaining excellent potency by occupying the P1 and P2 subpockets.

Enantioselective compound **98a**, which contains a *(S)*-methyl group at the α-position of acetic acid connected to the core moiety, maintained PPI inhibition activity with an IC_{50} of 0.14 μM, in comparison to **94h**. To gain better understanding in the inhibitory effect of **94h** and **98a** against Keap1-Nrf2 interaction, they were further evaluated using the TR-FRET assay. Consistent with the SAR analysis in the FP assay, they were found to be equally potent (IC_{50} = 54.3-72.2 nM). The potency of another enantiomer **98b** bearing a *(R)*-methyl group was also almost equivalent to that of **94h** and **98a**, indicating that the methyl group was not associated with binding to the protein residues.

Table 7. Inhibitory activity of phenyl ring scaffolds with various *O*-linked fragments



compd	X	Y	FP	TR-FRET
			IC_{50} (μM)	IC_{50} (nM)
94f			0.41 ± 0.11	ND
94g			0.64 ± 0.10	ND
94h			0.11 ± 0.01	54.3 ± 5.6
94i			0.23 ± 0.05	ND
98a			0.14 ± 0.02	72.2 ± 4.0
98b			ND	92.0 ± 12.3
101			0.41 ± 0.04	ND
106			1.78 ± 0.31	ND
111a			0.57 ± 0.20	ND
115		H	1.24 ± 0.26	ND

2.4 Synthesis and evaluation of a naphthalene scaffold with *O*-linked fragments

The most active compound **94h** among phenyl ring scaffolds had an IC_{50} value of 0.11 μM, while naphthalene analogue **2** displayed nanomolar activity (IC_{50} = 63.1 nM) obtained by our group. Therefore, the phenyl core part was replaced with a naphthalene scaffold to identify the PPI inhibitory effect of two ring system, as shown in Figure 11.

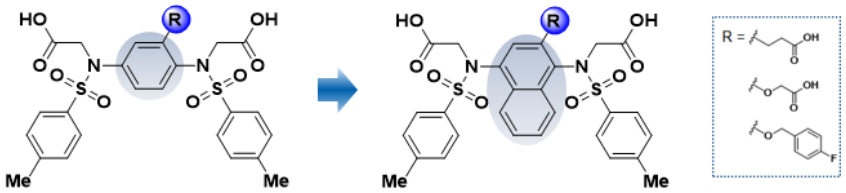
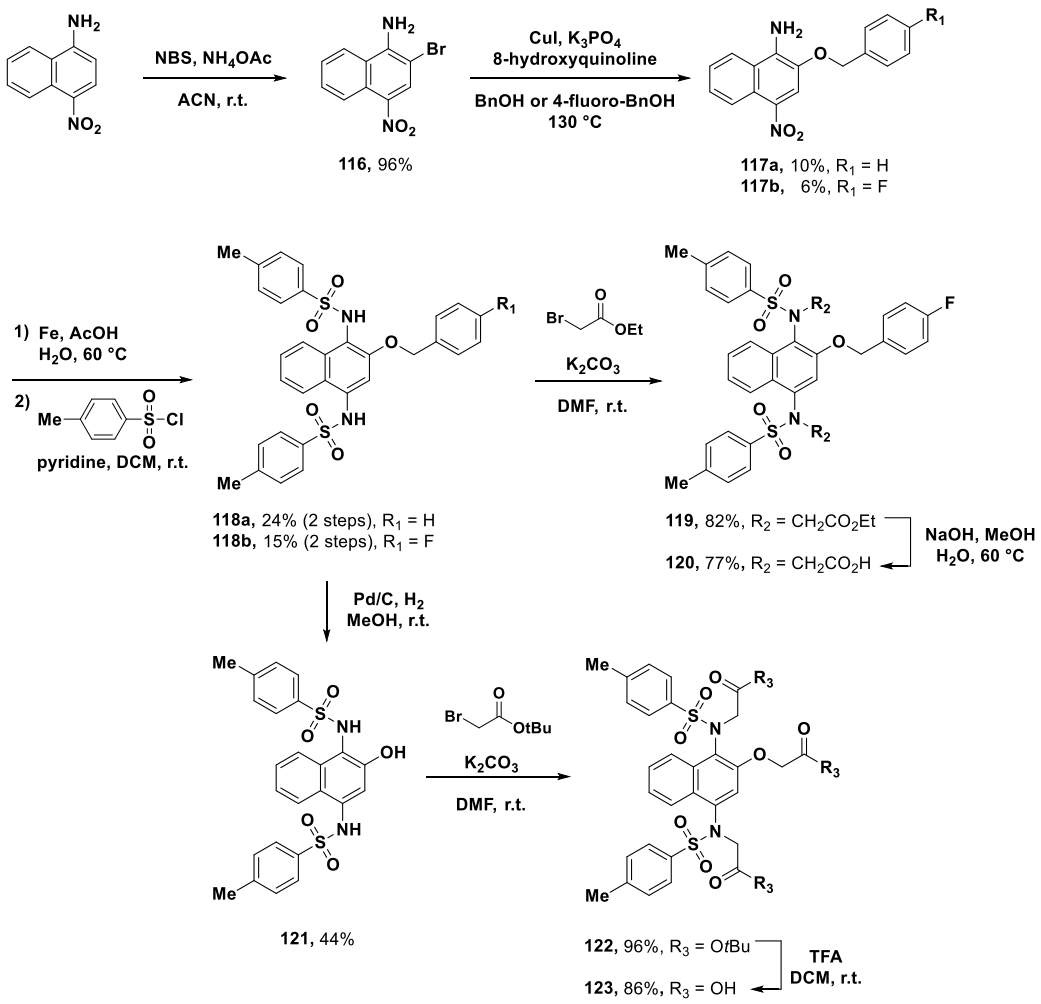


Figure 11. Replacement of a phenyl ring on core moiety with a naphthalene

Synthesis of naphthalene derivatives **120** and **123** with oxygen-containing linkers is summarized in Scheme 23. 2-Bromo naphthalene **116,** synthesized via selective bromination of 4-nitronaphthalen-1-amine with NBS,[114] had a coupling reaction in the presence of a catalytic amount of copper (I) iodide with 4-fluorobenzyl or benzyl alcohols to give benzyl-protected derivatives **117a-b**.[115] Iron-catalyzed nitro reduction and subsequent *N*-sulfonylation afforded disulfonamide derivatives **118a-b.** Compound **120** containing a 4-fluorobenzyl alcohol fragment was formed by a nucleophilic substitution reaction of **118b** and followed by saponification. Another intermediate **118a** was debenzylated by a palladium catalyst in order to introduce an *O*-linked acetate group. The phenolic alcohol **121** was converted to the acetate derivative **123** by alkylation and TFA-mediated acid hydrolysis.

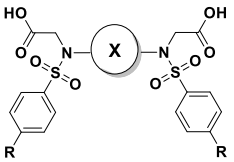


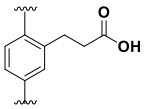
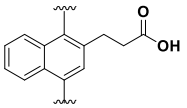
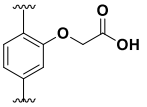
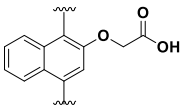
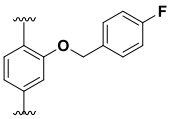
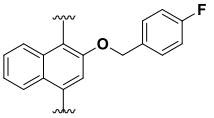
Scheme 23. Synthesis of compounds **120** and **123**

As depicted in Table 8, biological activity of naphthalene scaffolds with diverse *O*-linked fragments (X) against Keap1-Nrf2 PPI was evaluated using the FP assay. Interestingly, all three compounds (**111b**, **120**, and **123**) displayed excellent inhibitory potency with IC_{50} values in the nanomolar range (64.5-88.6 nM), similar to reference **2** without a X fragment (IC_{50} = 63.1 nM). Moreover, we performed a TR-FRET assay with the naphthalene analogs which had less than 0.2 μM in the FP assay. As a result, compound **120** had 2-fold greater potency with an IC_{50} value of 14.2 nM than **2** (IC_{50} = 28.5 nM) and was more active than

other naphthalene analogs, **111b** and **123** (IC_{50} = 19.0-22.3 nM). The SAR studies revealed two interesting facts. First, it proved that the naphthalene system was superior in potency to the phenyl ring scaffold. Importantly, the naphthalene analogs (**111b**, **120**, and **123**) showed comparable activities in both FP and TR-FRET assays regardless of the structure of X fragment, while the phenyl ring derivatives (**44g**, **94h**, and **111a**) displayed big differences in potency depending on the X fragment (IC_{50} = 0.11-0.57 μM in the FP assay).

Table 8. Inhibitory activity of compounds **111b, 120** and **123**



compd	X	R	FP	TR-FRET
			IC_{50} (nM)	IC_{50} (nM)
2	H	OMe	63.1 ± 7.7	28.5 ± 2.4
111a		Me	565.1 ± 203.6	ND
111b			69.3 ± 4.2	22.3 ± 2.0
94h		Me	110.7 ± 9.2	54.3 ± 5.6
123			88.6 ± 17.8	19.0 ± 2.9
44g		Me	448.9 ± 43.7	ND
120			64.5 ± 3.8	14.2 ± 0.6

2.5 Molecular docking analysis of *O*-linked phenyl and naphthalene scaffolds

In order to fully understand the role of the *O*-linked fragments of core moiety in the Kelch domain binding site, we selected active compounds **2, 44g, 94h, 120** and **123,** and performed molecular docking studies based on the co-crystal structure of compound **10** bound to the Kelch domain of Keap1 protein (PDB code: 4XMB).[106] Similar to reference **2** (Figure 12A), the other *O*-linked derivatives occupy all subpockets of the Keap1 cavity. As we expected, the binding mode of **44g** reveals that the 4-fluorobenzyl alcohol fragment is inserted deeply into the central solvent-exposed channel (Figure 12B). Introduction of the fragment appears to make hydrophobic contacts at the back of P3 subpocket because compound **44g** shows an improvement in activity relative to known compound **9**. Interestingly, the acetate fragment on the core phenyl ring (**94h**) is oriented toward the polar P2 subpocket, and forms hydrogen bonds with the side chains of key residues Arg415 and Arg380 (Figure 12D). Their contrasting binding modes are likely due to the strong polar interactions of the acetate group. Moreover, unlike compound **44g,** the acetate moiety of **94h**, located in the P1 subpocket, also makes a hydrogen bond with the side chain of Arg483. Consequently, it seems that these favorable polar interactions in the Keap1 cavity lead to a 4-fold increase in potency. On the other hand, naphthalene analogs indicate a similar spatial orientation in the P3 central pocket, although they contain different *O*-linked fragments, 4-fluorobenzyloxy (**120**) and acetate groups (**123**). It is likely that the preference for hydrophobic contact and π-cation interactions of the naphthalene in the Arg415 pocket make the fragments oriented forward. In addition, we hypothesize that nanomolar potency of the naphthalene derivatives might be attributed to high binding affinities through these hydrophobic interactions, whereas the phenyl ring scaffold, compound **44g**, loses a cation-

π stacking interaction with Arg415. Surprisingly, the 4-flourobenzyl group of **120** results in a 2-fold increase in potency relative to **123**, which suggests that hydrophobic contacts of the benzyl ring along with 4-methylbenzenesulfonamide in the P5 region might contribute to higher inhibitory effect than the polar acetate fragment of **123**.

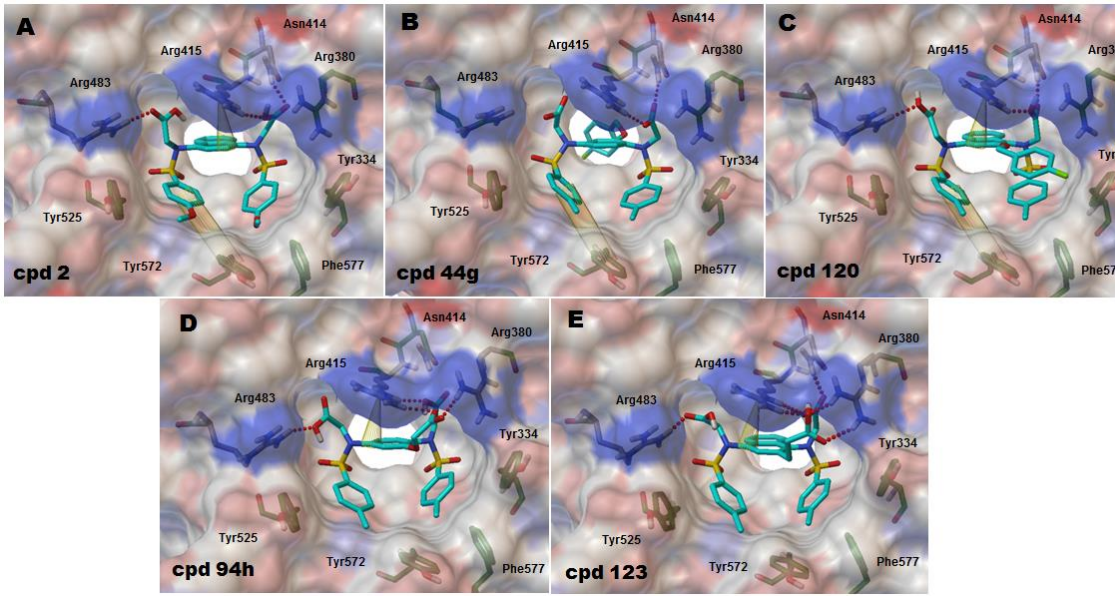


Figure 12. Binding modes of compounds **2**, **44g**, **94h**, **120** and **123**

3.1 Optimization of new scaffolds via a molecular hybridization strategy

Molecular hybridization is a strategy of rational drug design based on the combination of pharmacophore moieties of different bioactive substances, leading to a new hybrid compound with improved potency. Considering that known template substances were already evaluated concerning the physicochemical and pharmacological profiles, mechanism of action, and toxicity, new optimized ligands have a high possibility of being successfully developed as a drug candidate. Recently, this approach has widely been used

for discovering new innovative drugs for the treatment of inflammation, infectious diseases and cancer.[116]

Interactions with key polar residues, located in five subpockets of Keap1 Kelch domain, are determinants for potent Keap1-Nrf2 PPI inhibition. The co-crystal structure of the Kelch domain in complex with compound **10** (PDB code: 4XMB) showed that it fulfilled five subpockets in the Keap1 protein, leading to predominant inhibitory activity (IC_{50} = 63 nM).[106] However, some direct inhibitors partially occupy the five hotspots that might be associated with low or moderate activity in the micromolar range. Accordingly, we focused on designing new hybrid ligands that may occupy all of the five subpockets in the Keap1 protein through an adequate fusion between bioactive regions of known inhibitors.

3.2 Optimization of an *O*-linked phenylpyrrolidine-3-carboxylic acid scaffold

The X-ray co-crystal structure of **3** bound to the Kelch domain revealed that it occupied P1, P3 and P5 subpockets (PDB code: 5CGJ).[101] The naphthalene ring system posed in the P3 subpocket by forming a cation-π stacking interaction with Arg415. While the sulfonamide moiety, located into the hydrophobic P5 pocket, formed two hydrogen bonds with Ser363 and Ser602 as well as a π-π stacking interaction with Tyr334, the carboxylic group on pyrrolidine had key hydrogen bonding interactions with Arg483 and Ser508. Although **3** only occupied in three subpockets, it exhibited good potency with an IC_{50} of 0.14 μM in the FP assay, probably due to strong binding interactions of the carboxylic acid and sulfonamide in the P1 and P5 subpockets, respectively. Accordingly, we attempted to combine two active fragments with the morpholine-containing core moiety of **78c** designing new compounds **126a-b**, as outlined in Figure 12. Additionally, the addition of

an acetic group to the sulfonamide (**130**) was predicted to have polar interactions with key residues in the P2 subpocket.

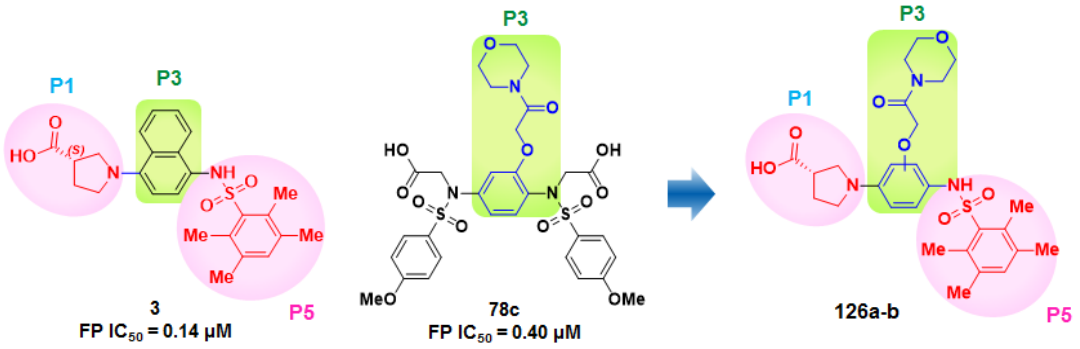
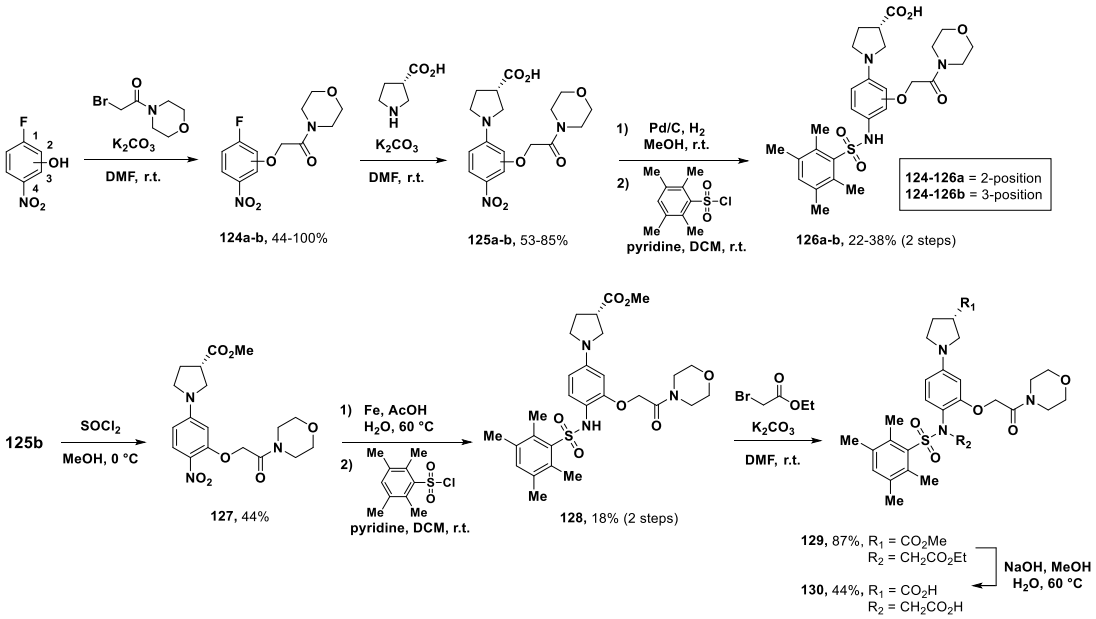


Figure 13. Design of 1-phenylpyrrolidine scaffold via a molecular hybridization

Synthesis of 1-phenylpyrrolidine analogs was accomplished, as shown in Scheme 24. Starting with 2-fluoro-5-nitrophenol or 5-fluoro-2-nitrophenol, treatment with 2-bromo-1-morpholinoethan-1-one gave **124a-b**, which were converted to **125a-b** by nucleophilic substitution with *(S)*-pyrrolidine-3-carboxylic acid. Aniline intermediates, generated by a palladium-catalyzed hydrogenation, were easily reacted with 2,3,5,6-tetramethyl-benzenesulfonyl chloride to yield target compounds **126a-b**. In the case of acetate derivative **130**, the carboxylic acid was first protected with a methyl group giving compound **127**. Reduction of a nitro group and ensuing sulfonamide formation gave **128**, which was then alkylated with ethyl 2-bromoacetate to provide **129**. The final product **130** was obtained by removing both the methyl and ethyl protective groups.

The biological activity of **126a-b** and **130** is summarized in Table 9. Unfortunately, all compounds displayed low activities with less than 50% inhibition at 5 μM, suggesting the importance of the naphthalene core moiety for good activity.



Scheme 24. Synthesis of compounds **126a-b** and **130**

Table 9. Inhibitory activity of compounds **126a-b** and **130**

compd	% inhibition (FP assay)		
	50 μM	5 μM	0.5 μM
126a	-4	-7	ND
126b	40	7	ND
130	61	14	0

See Scheme 24 for the chemical structure
ND: not determined.

3.3 Optimization of a 1,2,3,4-Tetrahydroisoquinoline (THIQ) scaffold

3.3.1 Design strategy

Based on a detailed understanding of the binding mode of compound **1**or **2** bound to the Keap1 Kelch domain through the above mentioned five hotspots, we identified the interesting relationship between the number of occupied subpockets and the activity of a direct inhibitor. The 1,4-dimainonaphthalene **2**, which exhibited potent activity with an

IC_{50} value of 63.1 nM in FP assay, occupied all of the subpockets (Figure 14A),[92] whereas the THIQ analogue **1** only posed in P2, P3, and the middle point of nonpolar subpockets P4 and P5 (Figure 14B),[117] by showing lower inhibitory activity with an IC_{50} value of 3.0 μM in the same *in vitro* assay.[98] Our hypothesis for the observed weaker potency of **1** was due to the absence of fragments located in P1 or P4 hotspots, which encouraged us to employ a molecular hybridization strategy. We attempted to combine the 4-methoxybenzenesulfonamide of **2** with compound **1** by connecting the sulfonamide moiety to the 8-position of the THIQ system core of **1**, leading to the hybrid compound **139a** that was predicted to occupy P4 subpocket as well as three hotspots (P2, P3 and P5). The docking analysis of the designed product **139a** indicates that the overall conformation is similar to that of **1,** and 4-methoxybenzenesulfonamide occupies the P4 subpocket, as we expected (Figure 14C). Considering the introduced sulfonamide fragment forms hydrophobic interactions including a π-π stacking interaction with Tyr525 in the P4 subpocket, the designed compound **139a** might have greater potency than **1**.

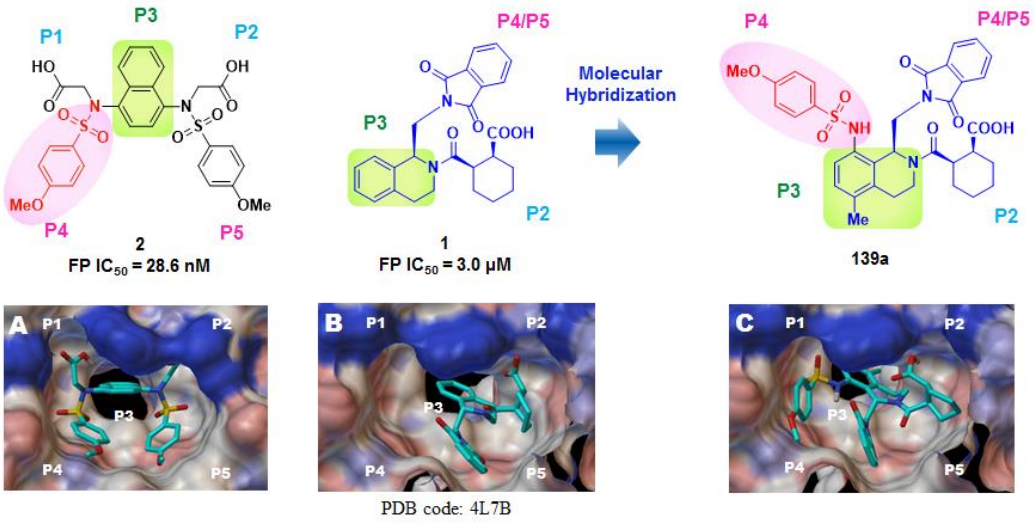
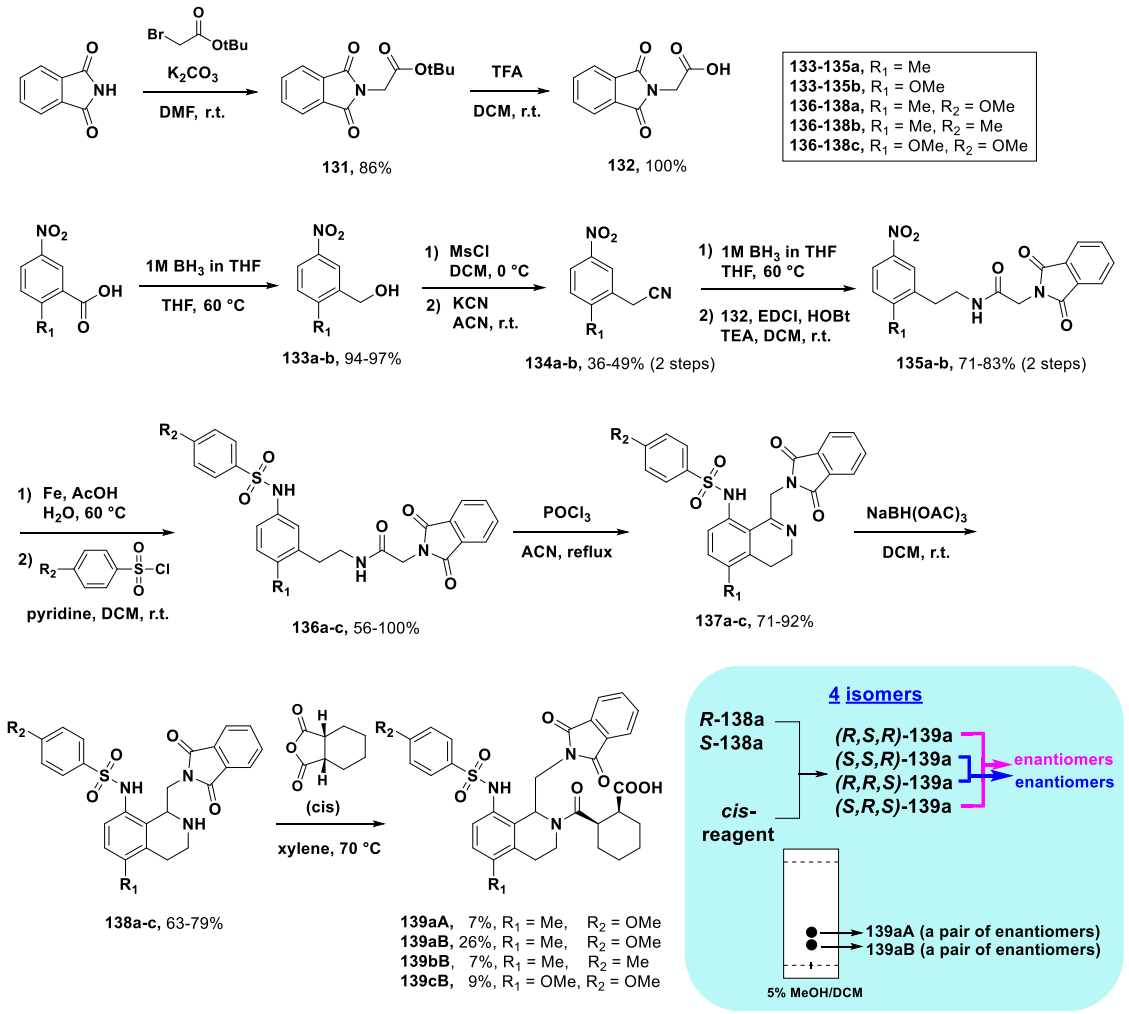


Figure 14. Design of a THIQ scaffold via a molecular hybridization strategy

3.3.2 Synthesis and evaluation

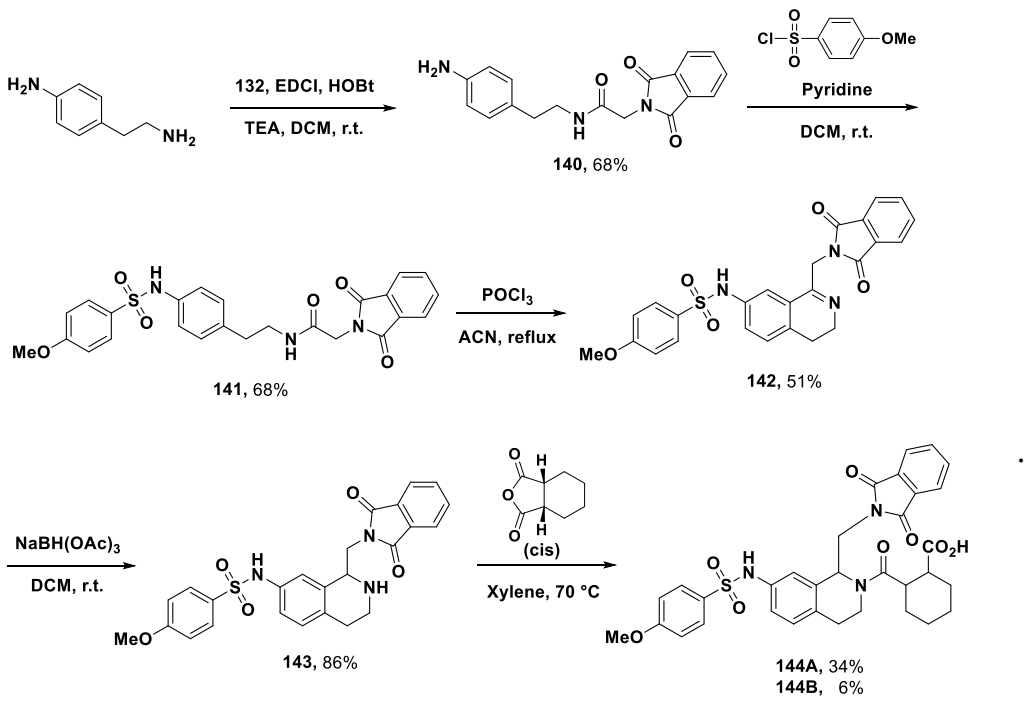
The designed THIQ analogs, **139aA-B**, **139bB** and **139cB**, were prepared, as outlined in Scheme 25. Phthalimide intermediate **132** was first synthesized in two steps by alkylation of the phthalimide with *tert*-butyl 2-bromoacetate and subsequent acid hydrolysis using TFA. The counterparts, required for amide coupling reaction, were obtained through four steps starting from 2-methyl or methoxy-5-nitro benzoic acid. Reduction of a carboxylic acid to a primary alcohol and mesylation of **133a-b** allowed for facile displacement with potassium cyanide to give nitrile compounds **134a-b**. Primary amine derivatives, synthesized by nitrile reduction in the presence of borane tetrahydrofuran complex, were assembled with **132** under general EDC-mediated amide coupling conditions to afford **135a-b**. Iron-catalyzed nitro reduction followed by introduction of the sulfonamide part yielded intermediates **136a-c**, which were further cyclized via Bischler-Napieralski reaction using $POCl_3$ to give THIQ compounds **137a-c** in good yield.[118] Reduction of the imine groups with sodium triacetoxyborohydride provided **138a-c** as a racemic mixture, followed by coupling reaction with cis-1,2-cyclohexanecarboxylic anhydride to give compounds **139a-c** which consist of 4 stereoisomers. Two pairs of the enantiomers were readily separated by flash silica gel chromatography to obtain compounds **139aA** and **139aB** containing one set of enantiomers, respectively. To distinguish two substances, we labelled the upper spot with a higher retention factor (Rf) value on TLC as A and a lower one as B. In the case of **139b-c**, only B was prepared in a similar method (**139bB** and **139cB**) for evaluation of biological activity in the FP assay.



Scheme 25. Synthesis of compounds **139aA-B, 139bB** and **139cB**

To determine the best position of the sulfonamide moiety on the THIQ core part, 7-substituted THIQ compounds **144A** and **B** were prepared using the similar synthetic route as for **139aA-B**, as shown in Scheme 26. EDC-mediated amide coupling reaction of 4-(2-aminoethyl)aniline with **132** afforded phthalimide derivative **140**, which was treated with 4-methoxy benzenesulfonyl chloride to yield **141**. Through three further steps, including Bischler-Napieralski cyclization,[118] reduction of the imine group, and coupling with cis-1,2-cyclohexanecarboxylic anhydride, the target compound **144AB** with 4 stereoisomers

was generated, and then separated using flash silica gel chromatography to give compounds **144A** and **B** containing two enantiomers, respectively.

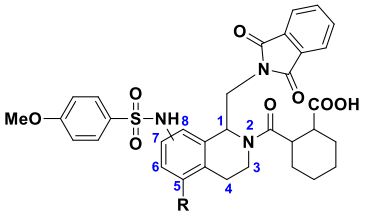


Scheme 26. Synthesis of compounds **144A-B**

Competitive inhibition by the designed THIQ analogs against Keap1-Nrf2 PPI was assessed utilizing the FP assay as outlined in Table 10. Interestingly, only **139aB** displayed potent activity with an IC_{50} value of 0.97 μM, whereas another compound **139aA** was almost inactive (33% inhibition at 50 μM), indicating that the most active stereoisomer was included in the **139aB**. When compared to compound **1**, the result demonstrated that the 4-methoxy benzenesulfonamide moiety actually contributed to increased binding affinity via hydrophobic interactions with nonpolar residues in the P4 subpocket. When compared to **139aB**, the 7-position of the sulfonamide moiety (**144B**) led to a dramatic reduction in activity with 46% inhibition at 5 μM, suggesting a preference for the 8-position over the 7-position. Consistent with a loss of activity observed with **139aA**, another separated

compound **144A** exhibited lower potency with 16% inhibition at 50 μM than **144B**. Based on the potency trend, only B purified from THIQ derivatives was tested for SAR study.

Table 10. Inhibitory activity of compounds **139aA-B** and **144A-B**

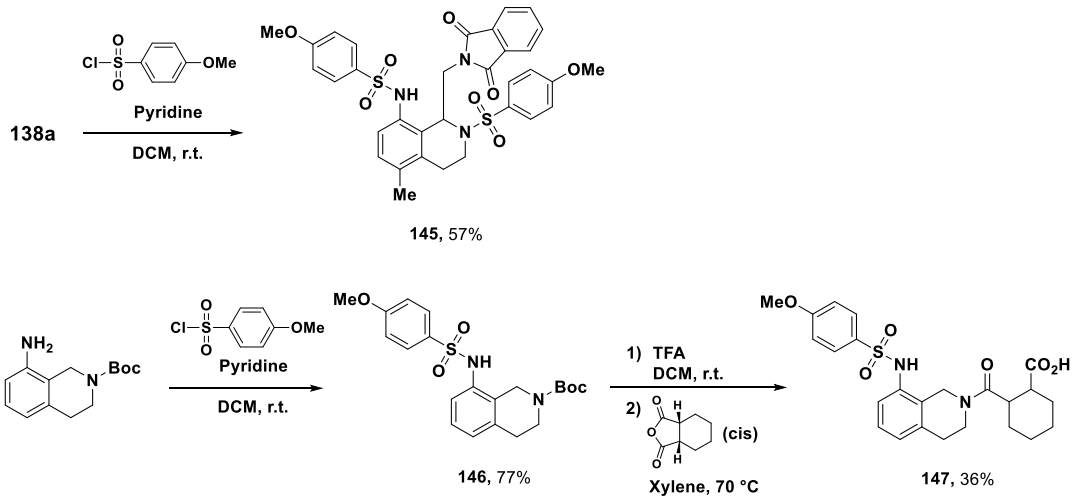


compd	position	R	% inhibition (FP assay)			IC_{50} (μM)
			50 μM	5 μM	0.5 μM	
(±)-**139aA**	8-	Me	32	2	ND	ND
(±)-**139aB**			97	82	26	0.97 ± 0.20
(±)-**144A**	7-	H	16	10	ND	ND
(±)-**144B**			86	46	3	ND

We performed a preliminary SAR study of **139aB** by mainly modifying four moieties, including cyclohexane, phthalimide, sulfonamide and THIQ core part. As outlined in Scheme 27, compound **145**, bearing an extra sulfonamide instead of cyclohexane, was readily prepared from intermediate **138a**. For the synthesis of **147** without a phthalimide, *tert*-butyl 8-amino-3,4-dihydroisoquinoline-2(1*H*)-carboxylate was treated with 4-methoxybenzenesulfonyl chloride to give sulfonamide **146**. Removal of the Boc protective group allowed for a coupling reaction with cis-1,2-cyclohexanecarboxylic anhydride to afford target compound **147**.

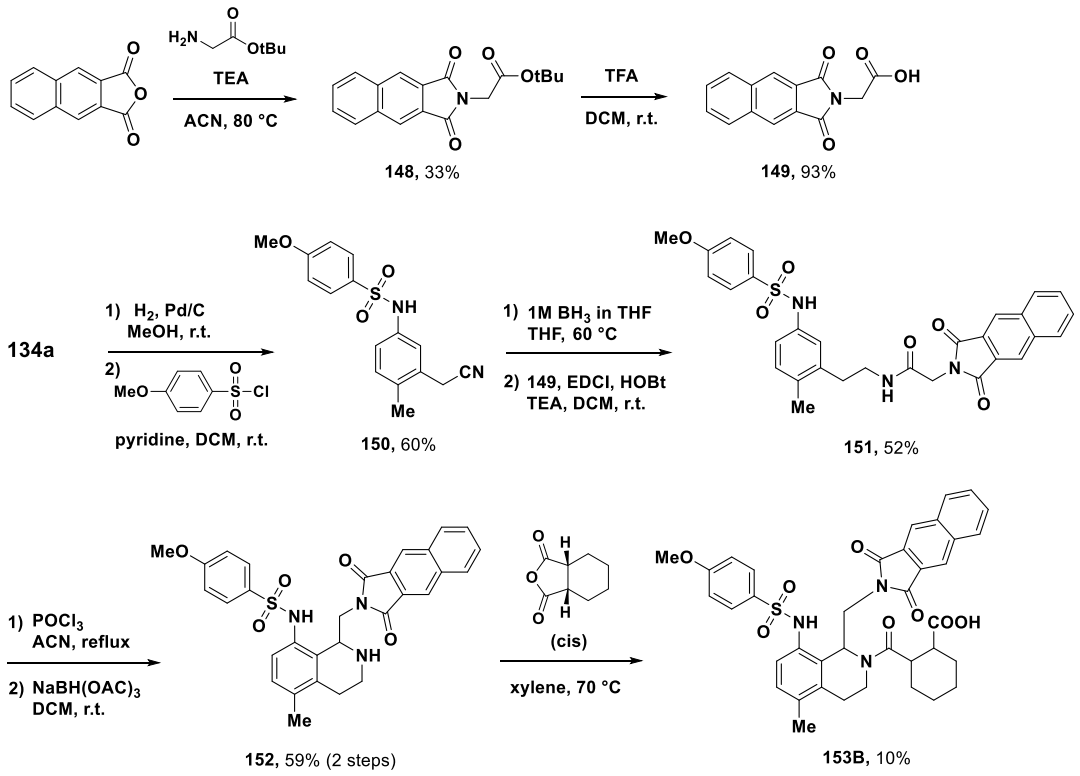
The benzo[*f*]isoindole analog **153B** was prepared according to Scheme 28. Treatment of 2,3-naphthalic anhydride with *tert*-butyl glycinate followed by acid hydrolysis of the *tert*-

butyl ester group provided the carboxylic acid analog **149** needed for an amine coupling reaction. Starting from the intermediate **134a**, a primary amine counterpart was synthesized in 3 steps; palladium-catalyzed nitro reduction, *N*-sulfonylation with 4-methoxybenzene-sulfonyl chloride, and nitrile reduction. Amide formation with **149** followed by Bischler-Napieralski cyclization using $POCl_3$ gave the THIQ derivative,[118] which was further reduced from the imine group to a secondary amine giving compound **152.** Coupling reaction with cis-1,2-cyclohexanecarboxylic anhydride afforded compound **153B** after separation by column chromatography.



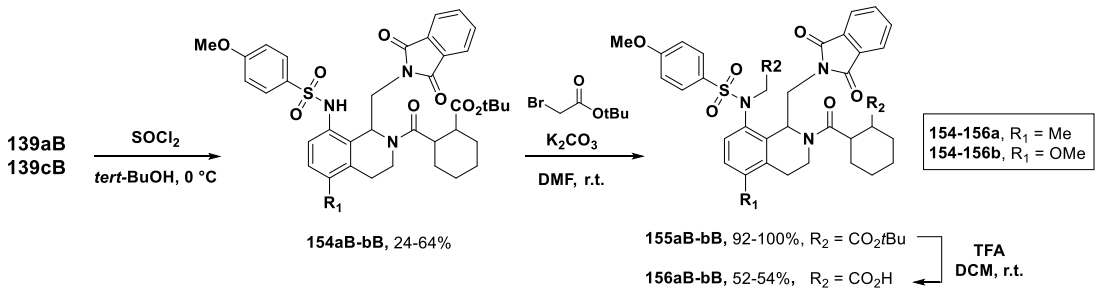
Scheme 27. Synthesis of compounds **145** and **147**

As shown in Scheme 29, the introduction of an acetate group onto the sulfonamide (**156aB** and **156bB**) was achieved starting from **139aB** and **139cB**. Protection of the carboxylic acid with *tert*-butyl group of these intermediates followed by alkylation with *tert*-butyl 2-bromoacetate gave **155aB** and **155bB**, which were subsequently hydrolyzed under acid conditions in the presence of TFA to obtain compounds **156aB** and **156bB** after purification using silica gel chromatography.

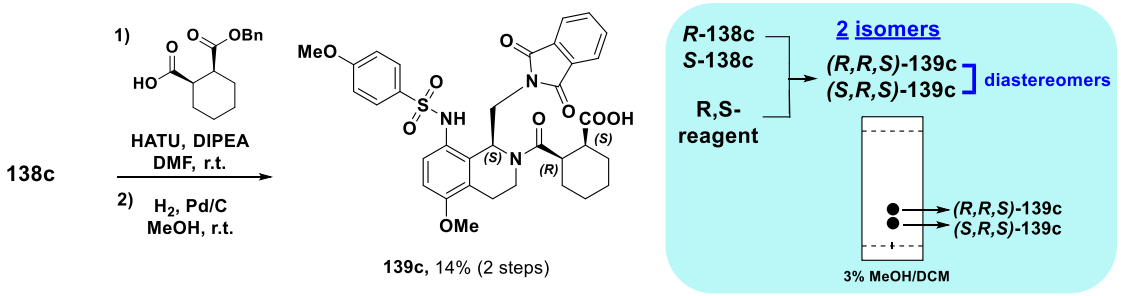


Scheme 28. Synthesis of compound **153B**

Enantioselective compound **139c** was prepared from intermediate **138c** by following an alternative synthetic pathway, as seen in Scheme 30. (*1R*,*2S*)-2-((Benzyloxy)carbonyl)-cyclohexane-1-carboxylic acid was enantiomerically prepared by a quinidine-mediated nucleophilic ring opening of cis-1,2-cyclohexanedicarboxylic anhydride with benzyl alcohol as previously described.[119] A HATU-mediated amide coupling reaction of intermediate **138c** with the cyclohexane-1-carboxylic acid derivative followed by a palladium-catalyzed debenzylation afforded the enantioselective final compound **139c** after purification of two diastereomers by silica gel column chromatography.



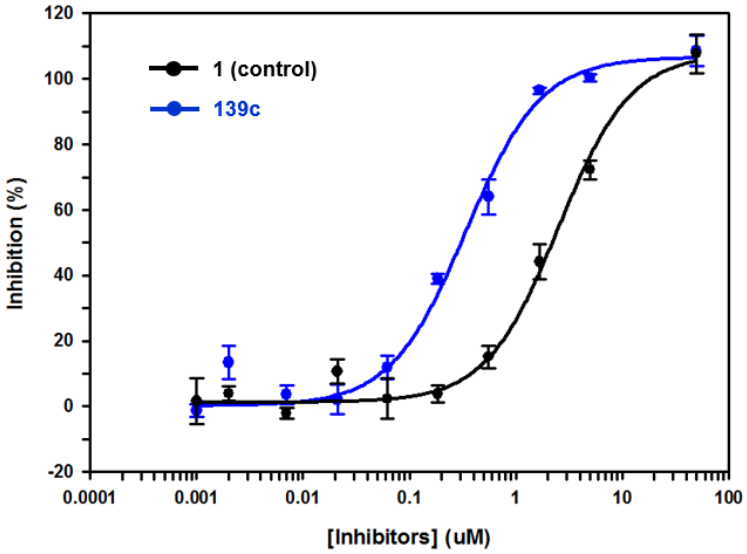
Scheme 29. Synthesis of compounds **156aB** and **156bB**



Scheme 30. Synthesis of compound **139c**

The initial SAR study on a series of THIQ compounds was accomplished using FP assay, and is summarized in Table 11 and 12. Removal (**138a**) or replacement (**145**) of the cyclohexane moiety resulted in a complete loss of activity. To confirm an inhibition effect on the phthalimide moiety of **139aB,** the phthalimide was removed to give compound **147**, which also displayed dramatically reduced activity. Accordingly, we fixed the cyclohexane and phthalimide parts as an essential bioactive fragment. Addition of a phenyl ring to the phthalimide (**153B**) maintained potency with an IC_{50} value of 1.00 μM, which is comparable to that of **139aB** (IC_{50} = 0.97 μM). As shown in Table 12, the methyl substituent (R_2) at the 4-positon of the benzenesulfonamide group (**139bB**) retained a good level of potency with an IC_{50} value of 0.80 μM. On the other hand, an investigation of the THIQ core structure revealed that electron-donating groups, methyl and methoxy

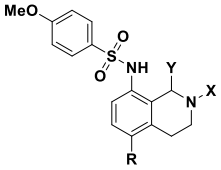
substituents at the 5-position (**139aB** and **139cB**), showed similar activity. According to the previous docking study of compound **2**, two acetic acid groups resulted in strong binding affinity via polar interactions, such as hydrogen bonds, in the polar P1 and P2 subpockets. Therefore, one acetic group was connected to the sulfonamide group of **139aB** or **139cB** to provide compounds **156aB** and **156bB** because we expected that the carboxylic acid fragment would occupy in the P1 subpocket by forming hydrogen bonds with Arg483 and Arg415. However, the acetate did not afford improved potency (IC_{50} = 0.65 and 1.04 μM), demonstrating that the carboxylic acid was less likely to be involved in making a hydrogen bonding interaction. In an attempt to evaluate the ability of the most active isomer for inhibiting Keap1-Nrf2 PPI, we selected **139cB** which is one of the most potent compounds among THIQ derivatives on the basis of previous SAR results. As a result, (*S*,*R*,*S*)-**139c** displayed improved potency with an IC_{50} value of 0.37 μM, which was 8-fold more active than the reference **1** (IC_{50} = 2.79), as illustrated in Figure 15.



compd	FP assay IC_{50} (μM)
(*S*,*R*,*S*)-**1**	2.79±0.45
(*S*,*R*,*S*)-**139c**	0.37±0.07

Figure 15. Concentration-response curves of **1** and **139c** in the FP assay

Table 11. Inhibitory activity of compounds **138a, 145, 147** and **153B**



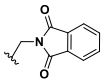
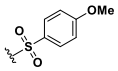
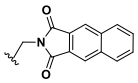
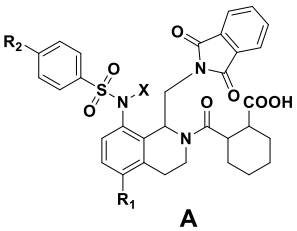
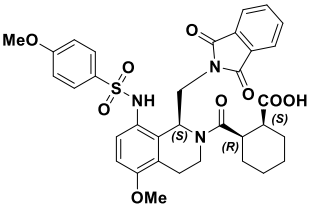
compd	X	Y	R	% inhibition (FP assay)			IC_{50} (μM)
				50 μM	5 μM	0.5 μM	
(±)-**139aB**			Me	97	82	26	0.97 ± 0.20
(±)-**138a**	H		Me	-3.3	0.4	ND	ND
(±)-**145**			Me	1.5	-7.4	ND	ND
(±)-**147**		H	H	10	8	ND	ND
(±)-**153B**			Me	98	87	ND	1.00 ± 0.13

Table 12. Inhibitory activity of compounds **139bB, 139cB, 156aB, 156Bb** and **139c**



A



(*S,R,S*)-**139c**
IC_{50} = 0.37 μM

compd	series	R_1	R_2	X	% inhibition (FP assay)			IC_{50} (μM)
					50 μM	5 μM	0.5 μM	
(±)-**139aB**	A	Me	OMe	H	97	82	26	0.97 ± 0.20
(±)-**139bB**	A	Me	Me	H	79	89	27	0.80 ± 0.29
(±)-**139cB**	A	OMe	OMe	H	103	105	64	0.64 ± 0.10
(±)-**156aB**	A	Me	OMe		105	85	ND	0.65 ± 0.10
(±)-**156bB**	A	OMe	OMe		98	91	ND	1.04 ± 0.24

3.3.3 Molecular docking analysis

Based on the co-crystal structure of compound **1** bound to the Kelch domain of Keap1 protein (PDB code: 4L7B),[117] we carried out the molecular docking study of active compound **139c**. Compared to reference **1**, the hybrid compound shows a similar binding pose, as shown in Figures 16A and B. The phthalimide, located in the middle between P4 and P5 subpockets, still forms a hydrogen bond with Ser602 as well as a π-π stacking interaction with Tyr572. Interestingly, the sulfonamide moiety of **139c** occupies P4 subpocket, resulting in higher binding affinity to the Keap1 cavity through π-π stacking interaction with the phenolic group of Tyr525. Moreover, introduction of the sulfonamide fragment makes positive conformational changes, especially the cyclohexane part, which leads to strong hydrogen bonding interactions with the side chains of Arg415 and Asn414 in the polar P2 subpocket. Consequently, the analysis of docking simulation of **139c** suggests that these additional interactions may be associated with improved inhibitory activity, compared to **1**.

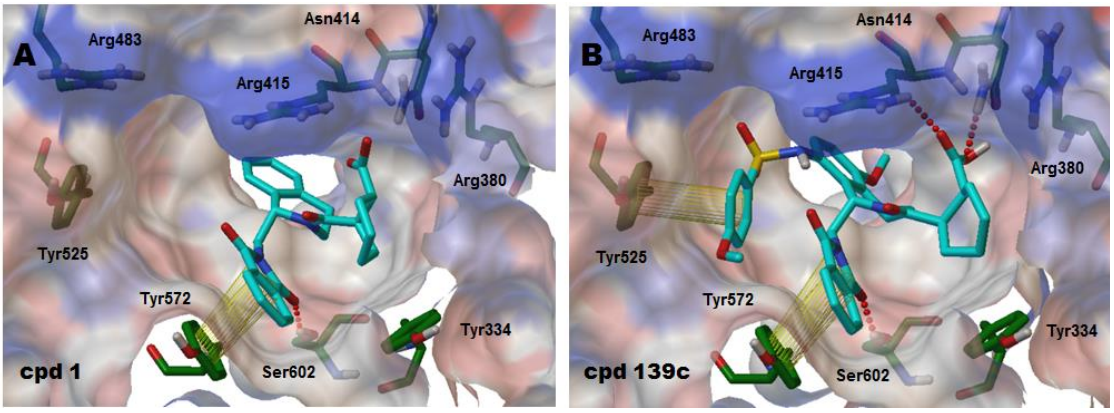


Figure 16. Binding modes of compounds **1** and **139c**

3.4 Optimization of an *N*-Phenylglycine scaffold

3.4.1 Design strategy

In an effort to design a new scaffold utilizing a molecular hybridization strategy, we first sought to analyze binding modes of potent compounds **2** and **4** based on five hotspots of the binding cavity in Keap1 Kelch domain. As seen in Figure 17A, active compound **2** with an IC_{50} value of 63.1 nM occupy fully five subpockets.[92] The naphthalene core moiety is located in the P3, and two acetate groups occupy the polar subpockets P1 and P2. Two benzenesulfonamide moieties poses in the hydrophobic P4 and P5. In the case of **4** with an IC_{50} value of 0.27 μM,[102] it occupies four subpockets except for P2 (Figure 17B). Similar to the binding mode of **2**, one acetate group and *N*-methyl sulfonamide fragment occupy the P1 and P5, respectively. The core 4-chlorophenyl ring poses in the P3, and the benzotriazole is located in the hydrophobic P4. Based on their binding modes, we fixed the 4-substituted benzene as a core moiety, and then rationally combined an active fragment located in each subpocket (P1, P2, P4 and P5) designing new hybrid compounds **164a**, **171**, and **181a-b**. As shown in Figure 17, compound **164a** was formed by replacing the naphthalene of **2** with the 4-chlorobenzene core part of **4**. Compound **171** consisted of *N*-[(4-methoxyphenyl)sulfonyl]glycine (derived from **2**, red color), *N*-methylated sulfonamide, and 4-chlorobenzene (derived from **4**, blue color). Compound **181a** was designed by combining *N*-[(4-methoxyphenyl)sulfonyl]glycine of **2** (red color) with fragments of **4**, which consisted of acetate, benzotriazole, and 4-methylbenzene (blue color). Last, the chemical structure of **181b** was almost similar to that of **4**, with the exception of a nitrogen next to the benzotriazole. As we predicted. the docking analysis of the designed compounds showed that the acetate analogs **164a** and **181a** occupy five

subpockets (Figure 17C and E), while *N*-methyl derivative **171** occupies four subpockets except for the polar P2 pocket (Figure 17D).

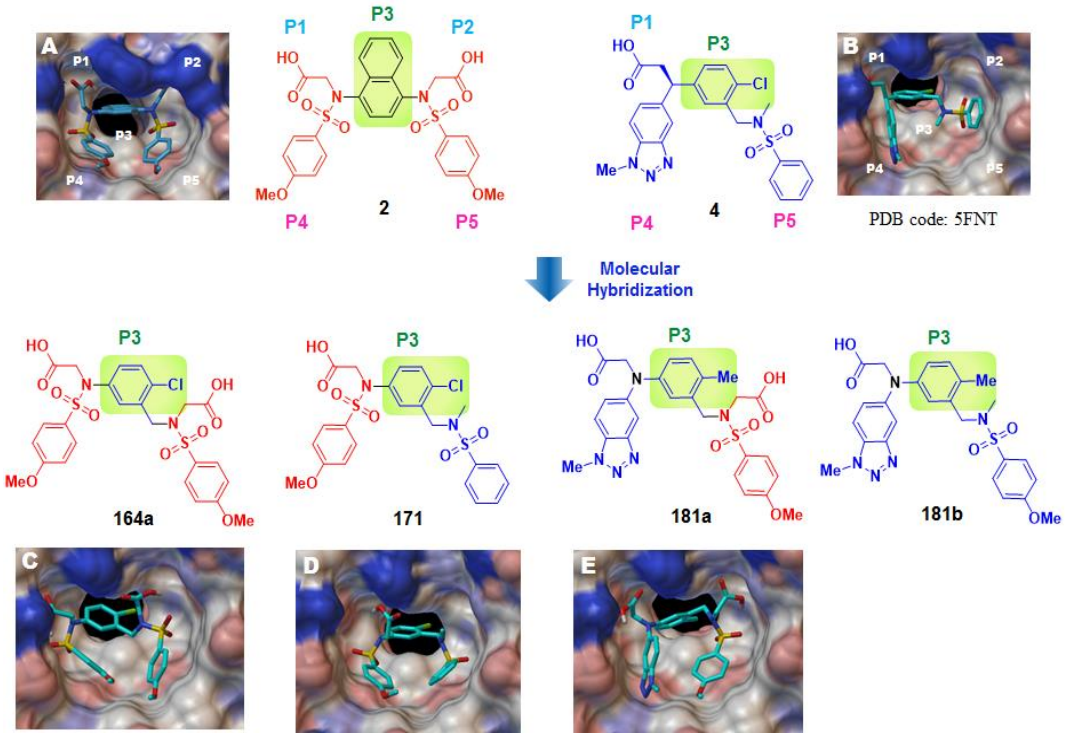
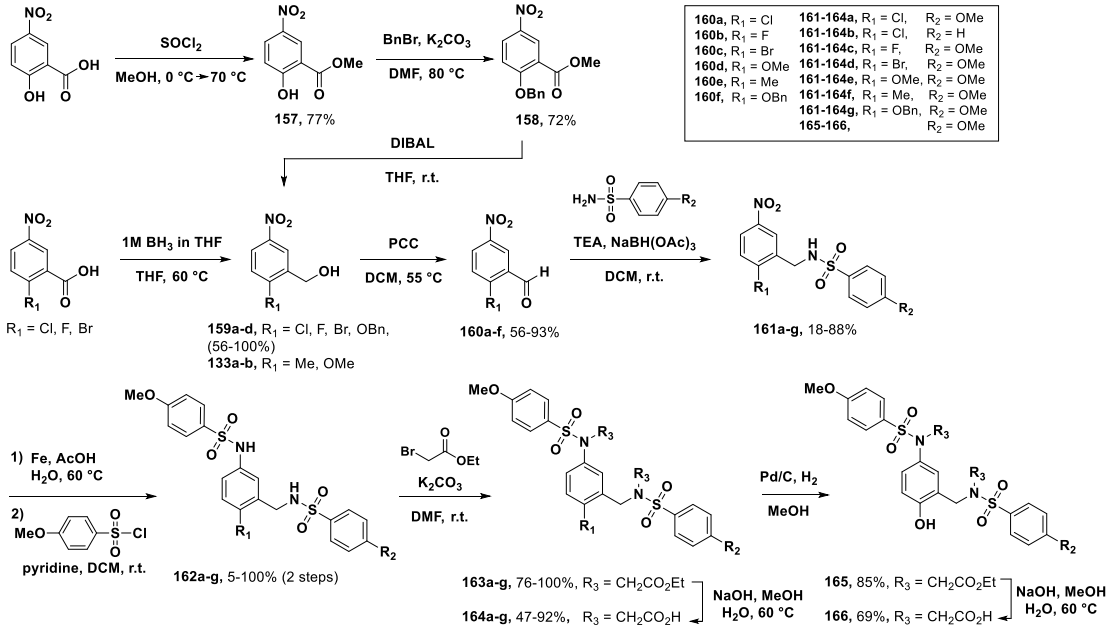


Figure 17. Design of an *N*-phenylglycine scaffold via a molecular hybridization

3.4.2 Synthesis and evaluation

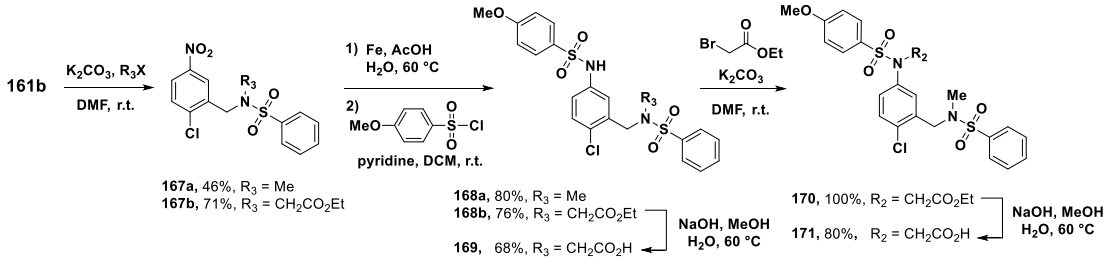
Synthesis of *N*-phenylglycine analogs **164a-g** and **166** containing a methylamine linker was performed as shown in Scheme 31. Primary alcohol intermediates **159a-d** were prepared by two different synthetic routes. 4-Hydroxyl substituent **159d** was synthesized in 3 steps, including methyl esterification of 2-hydroxy-5-nitrobenzoic acid, benzylation of **157**, and reduction of a methyl ester to a primary alcohol, while the other groups **159a-c** were obtained from reduction of benzoic acid reagents using borane tetrahydrofuran complex. The selective oxidation of alcohols to aldehyde, such as analogs **160a-f**, allowed for reductive amination with 4-substituted benzenesulfonamide to give **161a-g**. Nitro

reduction in the presence of an iron catalyst and *N*-sulfonylation with 4-methoxybenzenesulfonyl chloride provided disulfonamides analogues **162a-g**. Alkylation with ethyl 2-bromoacetate followed by saponification afforded desired products **164a-g**. In the case of **166** bearing a hydroxyl group**,** the benzyl protecting group of **163g** was removed by a palladium catalyst, and then two ethyl ester groups of **165** were hydrolyzed to yield the target product **166**.



Scheme 31. Synthesis of compounds **164a-g** and **166**

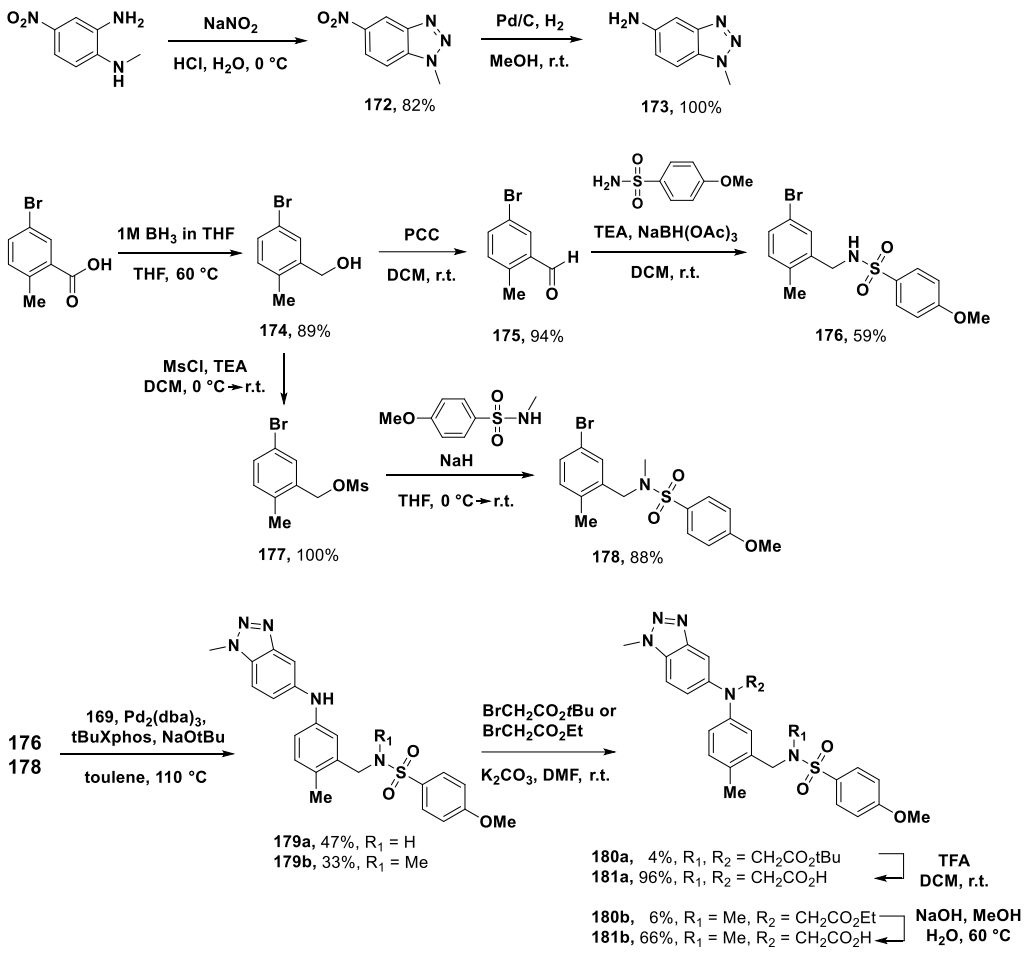
As outlined in Scheme 32, 4-chlorobenzene analogs **169** and **171** were prepared from intermediate **161b** using an optimized synthetic procedure similar to that of **164a**. Nucleophilic substitution with methyl iodide or ethyl 2-bromoacetate gave **167a-b**, which were then reduced by an iron catalyst, and treacted with 4-methoxybenzenesulfonyl chloride to afford disulfonamides **168a-b**. Compound **169** was directly synthesized by saponification, while another target compound **171** was obtained in two steps, including alkylation with ethyl 2-bromoacetate and saponification.



Scheme 32. Synthesis of compounds **169** and **171**

Benzotriazole derivatives **181a-b** were synthesized according to Scheme 33. The amine component **173** for palladium-mediated amination was readily generated by an intramolecular cyclization reaction of N^1-ethyl-4-nitro-1,2-phenylenediamine,[120] followed by a nitro reduction of **172**. The corresponding 1-bromobenzene analogues **176** and **178** were synthesized using two different synthetic pathways, starting from compound **174** generated after reduction of 5-bromo-2-methylbenzoic acid. While selective oxidation of **174** with PCC followed by reductive amination afforded **176**, mesylation of **174** and subsequent nucleophilic substitution with 4-methoxy-*N*-methylbenzenesulfonamide gave *N*-methylated **178**. Buchwald-Hartwig cross coupling reaction of **176** or **178** with the intermediate **173** gave benzotriazole derivatives **179a-b**, which led to alkylation with *tert*-butyl or ethyl 2-bromoacetates, followed by acid or base hydrolysis to afford compounds **181a-b**.

To determine the ability of small molecules to disrupt the PPI interaction of Keap1-Nrf2, the FP assay was carried. As described in Table 13, biological results revealed that analog **164a** bearing acetates and 4-methoxybenzenesulfonamides exhibited good potency with an IC_{50} value of 1.91 μM, while the others (**171** and **181a-b**) were almost inactive by showing less than 50% inhibition at 5 μM. Therefore, we selected compound **164a** as a good starting point for a preliminary SAR study.



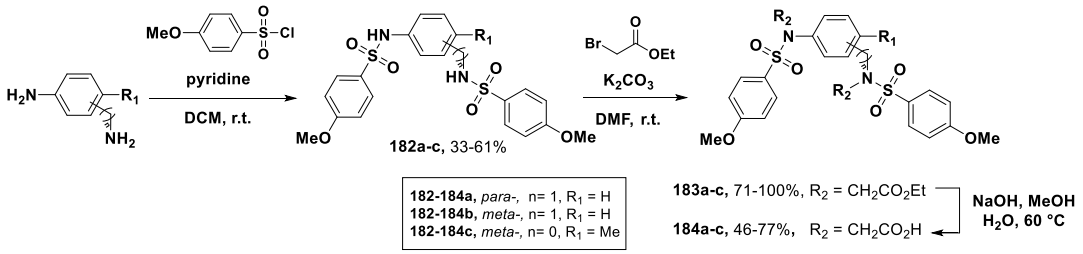
Scheme 33. Synthesis of compounds **181a-b**

Table 13. Inhibitory activity of compounds **164a, 171** and **181a-b**

compd	% inhibition (FP assay)			IC_{50} (μM)
	50 μM	5 μM	0.5 μM	
164a	96	68	ND	1.91 ± 0.50
171	53	15	ND	ND
181a	48	13	ND	ND
181b	86	33	ND	ND

See Scheme 31-33 for the chemical structure
ND: not determined.

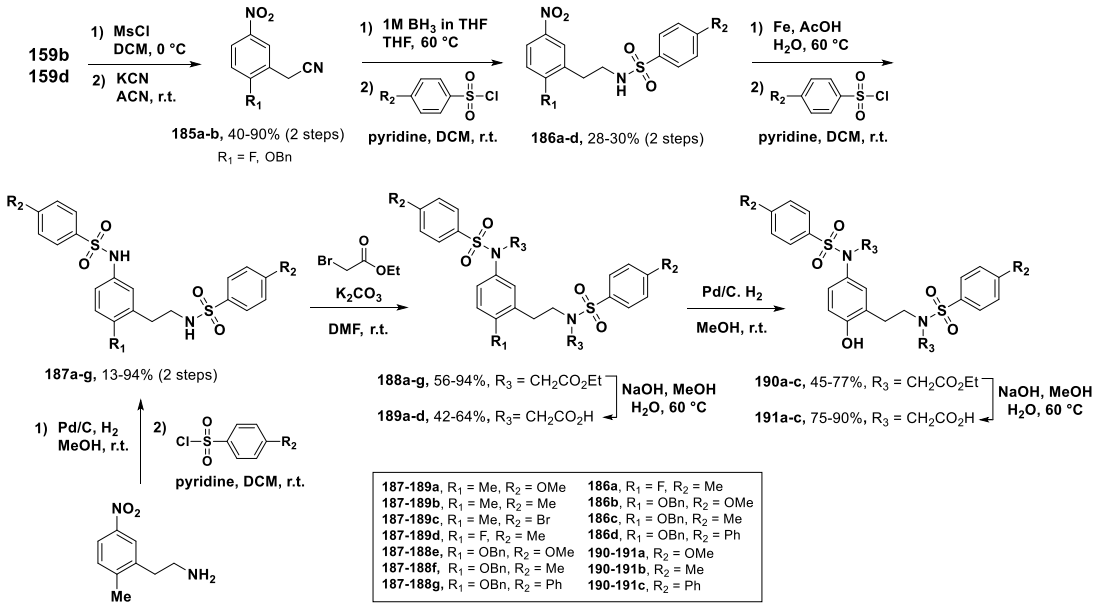
Next, we focused on optimizing compound **164a** through six different modifications; removal of two acetate groups, change of linker position, modification of chlorine substituent or phenyl ring on the core moiety, linker modification, and replacement of 4-methoxy groups on benzenesulfonamide moieties. As shown in Scheme 34, compounds **184a-c** were prepared in more concise manner by diamine derivatives. Treatment with 4-methoxy benzenesulfonyl chloride followed by alkylation of **182a-c** with ethyl 2-bromoacetae gave the corresponding **183a-c**, which were converted to compounds **184a-c** by saponification.



Scheme 34. Synthesis of compounds **184a-c**

Analogs **189a-d** and **191a-c** involving an ethylamine linker were prepared via two different synthetic pathways, as depicted in Scheme 35. First, the synthesis of **189d** with 4-fluoro group or **191a-c** with 4-hydroxy group was conducted starting from primary alcohol intermediates **159b** or **159d**. Mesylation of the hydroxyl group and subsequent displacement with KCN afforded **185a-b** which had an increased linker length by one carbon. Each sulfonamide part was formed in sequence via four steps, involving nitrile reduction of **185a-b**, sulfonamide formation with R_2-substituted benzenesulfonyl chloride, iron-catalyzed nitro reduction, and additional sulfonamide formation, giving disulfonamide derivatives **187d-g.** Alternatively, **187a-c** with 4-methyl substituent were obtained in a straightforward manner through nitro reduction of 2-(2-methyl-5-nitrophenyl)-ethan-1-

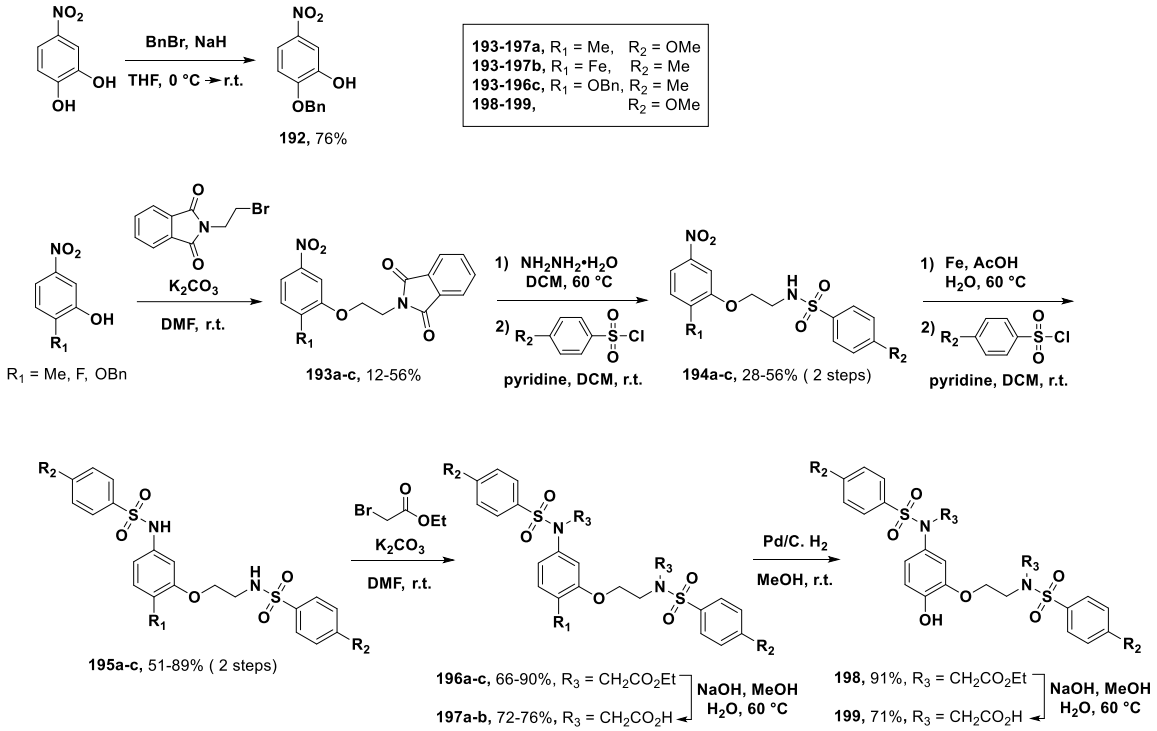
amine and subsequent *N*-sulfonylation. Two acetate groups were introduced to the resulting **187a-g**, some of which were further hydrolyzed under basic conditions to afford **189a-d**. Additionally, the benzylation of **188e-g** followed by saponification gave target compounds **191a-c**.



Scheme 35. Synthesis of compounds **189a-d** and **191a-c**

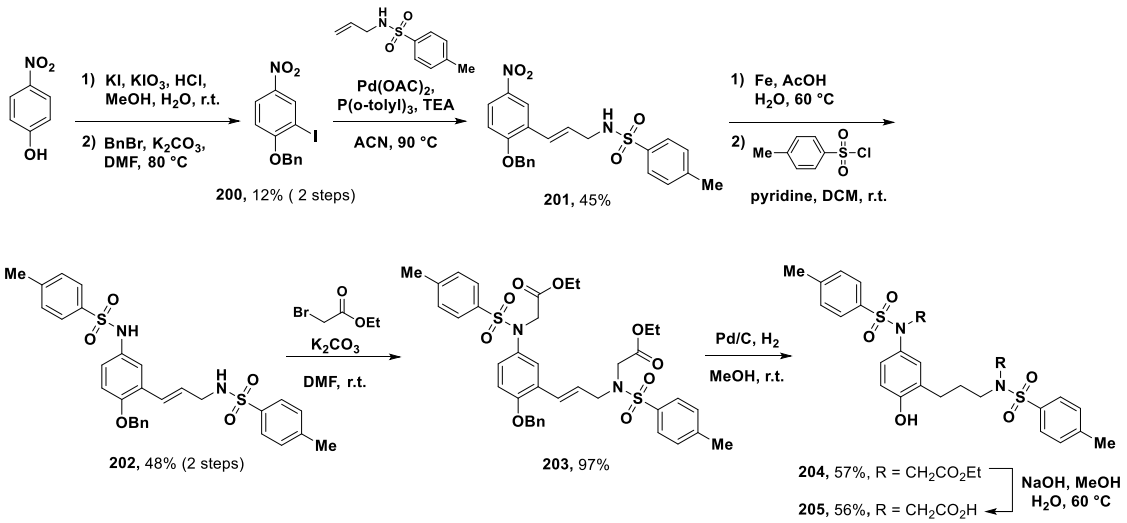
Preparation of ethanolamine analogs **197a-b** and **199** was achieved, as presented in Scheme 36. The phthalimide-protected intermediates **193a-c** were synthesized by treatment of 2-substituted-5-nitrophenol derivatives with 2-(2-bromoethyl)isoindoline-1,3-dione. One of phenol analogues, **192**, was selectively produced by benzylation of 4-nitrobenzene-1,2-diol in the presence of 1.0 equivalent of sodium hydride, according to the procedure previously reported by Bolchi's group.[121] Deprotection of phthalimide derivatives **193a-c** using hydrazine followed by *N*-sulfonylation provided **194a-c**, which were converted to acetate derivatives **196a-c** via three further steps, involving iron-mediated reduction, additional sulfonamide formation with R_2-substituted benzenesulfonyl chloride, and alkylation of

195a-c with ethyl bromoacetate. While **197a-b** were obtained after saponification of **196a-b**, compound **199** was generated by debenzylation of **196c** and saponification.



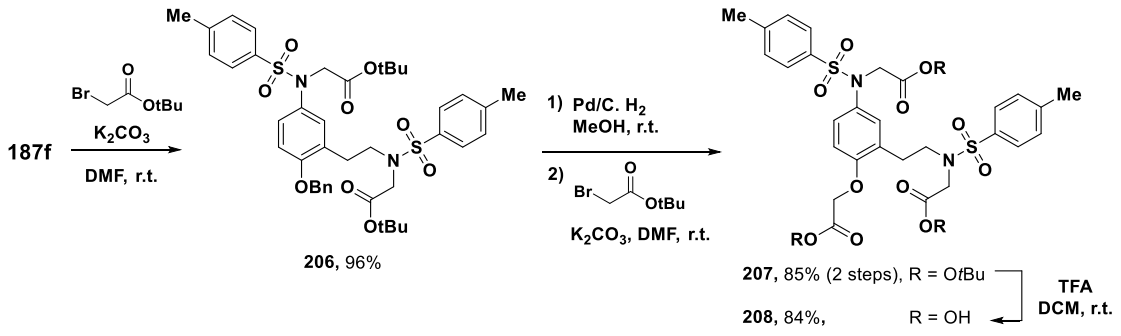
Scheme 36. Synthesis of compounds **197a-b** and **199**

Synthesis of propylamine analog **205** was accomplished according to Scheme 37. 1-(Benzyloxy)-2-iodo-4-nitrobenzene **200** was synthesized by selective addition of an iodide at the 2-position[112] and subsequent benzylation. Heck coupling of the 2-iodo substituted compound **200** along with *N*-allyl-*p*-toluenesulfonamide in the presence of $Pd(OAc)_2$ and $P(O\text{-tolyl})_3$ provided alkene derivative **201**.[113] A two-step process, involving iron-mediated nitro reduction and treatment with 4-methoxybenzenesulfonyl chloride, yielded compound **202**, which then had nucleophilic substitution with ethyl bromoacetate to yield acetate derivative **203**. The *O*-benzyl group was cleaved by hydrogenolysis, and then saponification of the resulting **204** produced compound **205**.



Scheme 37. Synthesis of compound **205**

Starting from **187f**, compound **208** containing an extra acetate group was prepared in four further steps, as depicted in Scheme 38. Addition of acetate groups to sulfonamides provided **206**, which was followed by removal of the benzyl protective group via a palladium-catalyzed hydrogenation, and introduction of an additional acetate to the hydroxyl group giving the acetate analog **207**. Deprotection of three esters using TFA gave compound **208**.

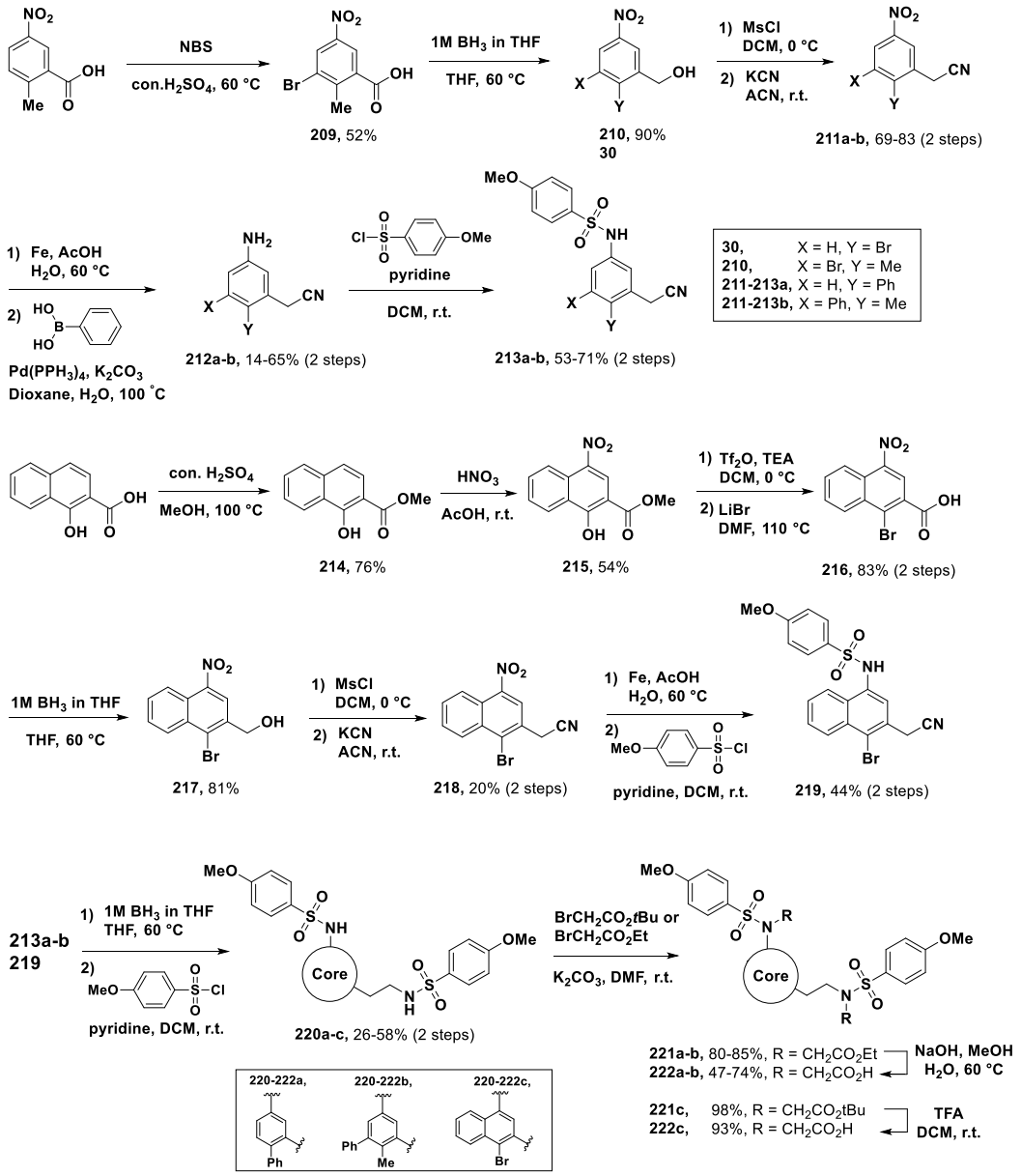


Scheme 38. Synthesis of compound **208**

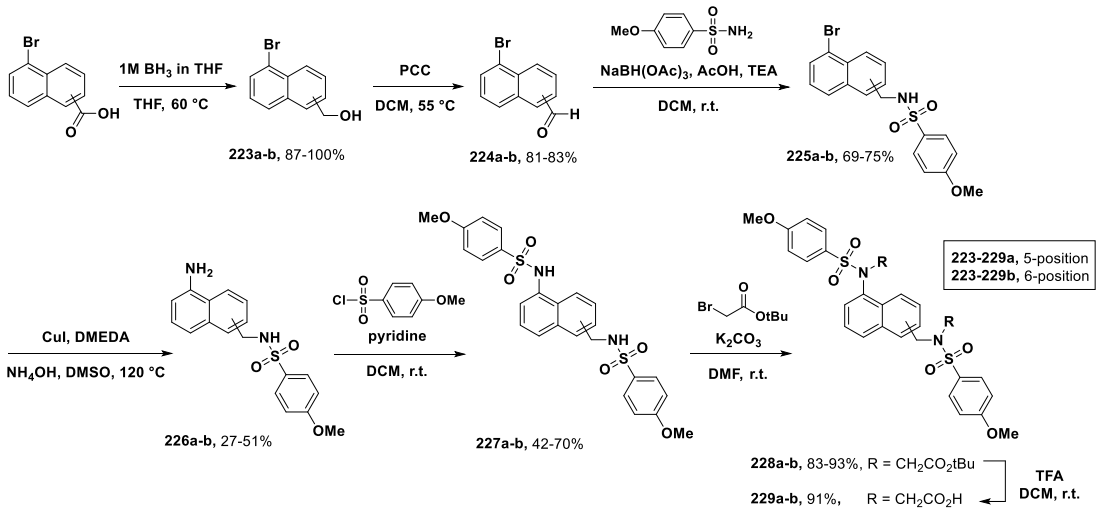
Biphenyl scaffolds **222a-b** and naphthalene **222c** were synthesized according to Scheme 39. Alcohol intermediate **210** was first obtained by selective bromination of 2-methyl-5-nitrobenzoic acid and reduction of the carboxylate group of **209** to a primary alcohol. Mesylation of **30** or **210** followed by displacement with KCN gave the bromo-substituted nitrile derivatives **211a-b**, which were converted to the biphenyl compounds **212a-b** in two steps involving nitro reduction and Suzuki coupling reaction. Treatment of **212a-b** with 4-methoxybenzene-sulfonyl chloride gave the sulfonamide intermediates **213a-b**. On the other hand, sulfonamide intermediate **219** containing a naphthalene scaffold was synthesized by a different synthetic route. A nitro group was selectively introduced to the 4-position of **214** containing a methyl ester in the presence of nitric acid and acetic acid. The hydroxyl group of **215** was successfully converted to the corresponding bromine (**216**) by tosylation and subsequent nucleophilic aromatic substitution with lithium bromide.[122] By following a synthetic route similar to **213a-b**, intermediate **219** was obtained in five further steps, which included reduction of a carboxylic acid to a primary alcohol, mesylation, nucleophilic substitution with KCN, iron-catalyzed nitro reduction, and *N*-sulfonylation. Next, the introduction of another sulfonamide moiety to **213a-b** or **219** was achieved by reduction of a nitrile group to a primary amine and subsequent treatment of 4-methoxy-benzenesulfonyl chloride leading to compounds **220a-c**. After alkylation with *tert*-butyl or ethyl bromoacetate, **221a-c** were hydrolyzed under acidic or basic conditions to give the target products **222a-c**.

The general synthesis of naphthalene analogs **229a-b** with a methylamine linker is summarized in Scheme 40. Reduction of 5-bromo-2-naphthoic acid or 5-bromo-1-naphthoic acid followed by selective oxidation in the presence of PCC provided **224a-b,**

which underwent a reductive amination reaction with 4-methoxybenzenesulfonamide to yield **225a-b**. Conversion of a bromine into an amine was accomplished by using copper (I) iodide and *N,N'*-dimethylethylenediamine in ammonium hydroxide solution,[111] which was subjected to *N*-sulfonylation. The resulting compounds **227a-b** were alkylated, and then deprotected under acidic conditions to give compounds **229a-b**.



Scheme 39. Synthesis of compounds **222a-c**

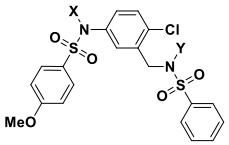


Scheme 40. Synthesis of compounds **229a-b**

First, we confirmed an inhibition effect of the carboxylic acid moiety by removing an acetate group (X or Y), as presented in Table 14. Compound **164b** possessing two acetate groups displayed moderate potency with an IC_{50} value of 4.10 μM, whereas the removal of one acetate fragment (**169** and **171**) led to a loss of activity. As illustrated in Table 15, we focused our optimization effort on the chloro substituent (R) at the 4-position of the benzene ring as well as the position of two sulfonamide moieties. Considering that 1,3-position (**164a**) was favorable for good activity rather than 1,4-position (**184**), the *meta*-position appeared to play an important role in forming an appropriate conformation in the Kelch domain. The absence of a substituent (**184b**) resulted in lower potency than 4-chloro group (**164a**). Similar to **184b**, electron-donating groups (**164e-f**) also displayed decreased inhibitory activity. The presence of the bulky benzyl group (**164g**) led to a significant drop-off in potency. Interestingly, 4-fluoro group (**164c**) retained potency in comparison to 4-chloro group. (IC_{50} = 1.54 μM), whereas larger 4-bromo group (**164d**) was not preferred over small-sized halogen substituents, 4-chloro and 4-fluoro groups (**164a** and **164d**). In the R modification, a hydroxyl group (**166**) was found to be the best activity with an IC_{50}

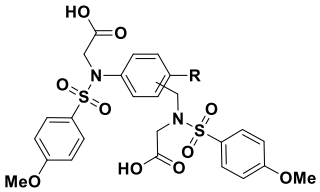
value of 1.08 μM, which suggested that the hydroxyl group might be associated with polar interactions with key residues.

Table 14. Inhibitory activity of compounds **164b, 169** and **171**



compd	X	Y	% inhibition (FP assay)			IC_{50} (μM)
			50 μM	5 μM	0.5 μM	
164b	$-CH_2CO_2H$	$-CH_2CO_2H$	83	73	ND	4.10 ± 1.12
169	H	$-CH_2CO_2H$	36	12	ND	ND
171	$-CH_2CO_2H$	Me	53	15	ND	ND

Table 15. Inhibitory activity of compounds **164a, 184a-b, 164c-g** and **166**

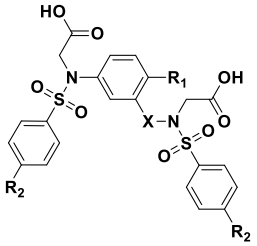


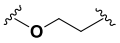
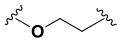
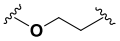
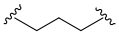
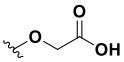
compd	position	R	% inhibition (FP assay)			IC_{50} (μM)
			50 μM	5 μM	0.5 μM	
164a	1,3-	Cl	96	68	ND	1.91 ± 0.50
184a	1,4-	-	100	50	ND	6.40 ± 0.96
164c	1,3-	F	111	82	28	1.54 ± 0.27
164d	1,3-	Br	85	46	4	ND
164e	1,3-	OMe	78	39	8	ND
164f	1,3-	Me	91	42	11	10.03 ± 3.45
164g	1,3-	OBn	64	16	13	ND
166	1,3-	OH	109	78	28	1.08 ± 0.40
184b	1,3-	H	85	41	ND	ND

On the basis of these SAR results, a linker (X) and a substituent (R_2) at the 4-position of the benzenesulfonamide moieties were explored as shown in Table 16. The linker length, which was predicted to play an important role in forming the optimal conformation, was first modified. With respect to the analogs containing a methyl group at the R_1 position, compounds with a longer linker (**189a** and **197a**) tended to display better activity than those with a shorter linker (**184c** and **164f**). For instance, direct amine linker (**184c)** had 25% inhibition at 5 μM, while the longest ethanolamine linker (**197a**) resulted in a 2-fold increased activity (IC_{50} = 4.29 μM) compared to methylamine one (**164f**). Contrary to the SAR results observed for the 4-methyl group on the core phenyl ring, increasing the linker length of analogues containing 4-fluoro group (**164c, 189d** and **197b**) led to a significant reduction in potency (IC_{50} = 1.54 to 10.85 μM). In series of analogs containing a hydroxyl group on the core part, an ethylamine linker was the optimal length in terms of activity. Compound **191a** had 2-fold greater potency than the shorter linker (**166**), while another ethylamine linker (**191b**) exhibited 8-and 5-fold increase in activity compared to the longer linkers such as ethanolamine (**199**) and propylamine (**205**). Next, we explored a R_2 region on sulfonamide moieties of compounds **189a** and **191a** possessing an ethylamine linker. Different R_2 substituents of the 4-methyl phenyl core moiety (**189a-c**), such as methoxy, methyl and bromo groups, were tolerated, whereas a methyl group of the 4-hydroxy phenyl core part (**191b**) displayed greater potency than methoxy (**191a**) or phenyl substituents (**191c**). Our last task in the core modification was the addition of an acetate group to the phenyl core moiety (**208**), which showed an unfavorable result with 47% inhibition at 5 μM. The biological results of the core modifications are summarized in Table 17. Introducing a bulky phenyl ring to the core moiety (**222a-b**) led to dramatically reduced

activity, presumably due to the unfavorable binding mode. Replacement of the phenyl ring with a naphthalene (**222c**) resulted in a retention of potency relative to phenyl ring scaffolds. In addition, other naphthalene analogs **229a-b**, designed by an incorporation of the linker into a cyclic structure as a ring cyclization strategy, were found to be almost inactive against Keap1-Nrf2 PPI.

Table 16. Inhibitory activity of *N*-phenylglycine analogs with various linkers



compd	R_1	X	R_2	% inhibition (FP assay)			IC_{50} (μM)
				50 μM	5 μM	0.5 μM	
184c	Me		OMe	80	25	ND	ND
189a	Me		OMe	99	61	28	7.68 ± 2.73
189b	Me		Me	90	57	25	5.22 ± 1.19
189c	Me		Br	93	50	7	ND
189d	F		Me	94	49	ND	6.13 ± 1.61
191a	OH		OMe	112	107	83	0.44 ± 0.13
191b	OH		Me	107	93	101	0.18 ± 0.03
191c	OH		Ph	109	87	ND	1.13 ± 0.27
197a	Me		OMe	98	61	ND	4.29 ± 1.39
197b	F		Me	90	41	ND	10.85 ± 7.05
199	OH		Me	87	71	ND	1.39 ± 0.15
205	OH		Me	104	89	ND	0.96 ± 0.28
208			Me	10	47	29	ND

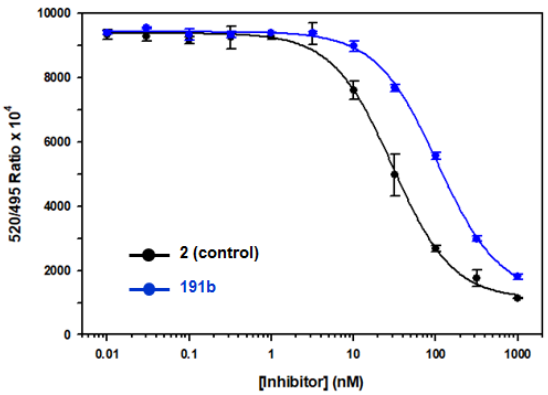
The key observations of SARs on the *N*-phenylglycine scaffold is summarized as follows: generally, two acetate groups and the 1,3-position between two sulfonamide moieties were essential for potency. The core phenyl ring moiety, 4-methyl groups on the sulfonamide

parts, the ethylamine linker, and the 4-hydroxy group on the core moiety are optimal for effective inhibitory activity in the FP assay. In a new series of *N*-phenylglycine analogues, compound **191b** was the most active with an IC_{50} value of 0.18 μM. As it was less than 0.2 μM, we additionally conducted a confirmatory TR-FRET assay. As a result, the 4-hydroxy phenyl ring analog **191b** exhibited a similar IC_{50} value (107.5 nM) in comparison to the FP assay result (183.4 nM), as presented in Figure 18.

Table 17. Inhibitory activity of compounds **222a-c** and **229a-b**

compd	% inhibition (FP assay)		
	50 μM	5 μM	0.5 μM
222a	37	17	ND
222b	65	23	ND
222c	89	60	22
229a	43	15	ND
229b	31	13	ND

See Scheme 39-40 for the chemical structure
ND: not determined.



compd	TR-FRET assay IC_{50} (nM)
2	25.5±2.4
191b	107.5±6.9

Figure 18. Concentration-response curves of **191b** in the TR-FRET assay

3.4.3 Molecular docking analysis

To investigate the binding mode of hybrid compounds **164a** and **191b**, we performed molecular docking studies with the co-crystal structure of compound **4** bound to the Kelch domain of Keap1 protein (PDB code: 5FNT).[102] As we expected, a series of *N*-phenylglycine analogs occupy all subpockets (P1-P5), as seen in Figure 17. Analysis of the binding mode of compound **164a** containing an *N*-methylamine linker suggests that one acetate forms hydrogen bonds with polar residues Arg483 and Ser508 in the P1 subpocket of Keap1, while another carboxylate group makes a hydrogen bond with Arg415 (Figure 17a). It seems that the moderate activity of **3** (IC_{50} = 1.91 μM) is associated with too short distance for binding interactions between the acetate moiety and polar residues in the P2 subpocket. Interestingly, the docking simulation of compound **191b** bearing an *N*-ethylamine linker reveals that the acetate group occupied in the P2 subpocket forms strong polar interactions such as hydrogen bonds and electrostatic interactions with the side chains of Asn414 and Asn382 due to the increased length of the linker. Besides, the phenyl ring connected to the sulfonamide makes a π-π stacking interaction with Tyr525 in the P4 subpocket. The high binding affinity of **191b** bound to the Keap1 Kelch domain results in a 11-fold increase in potency relative to **164a**.

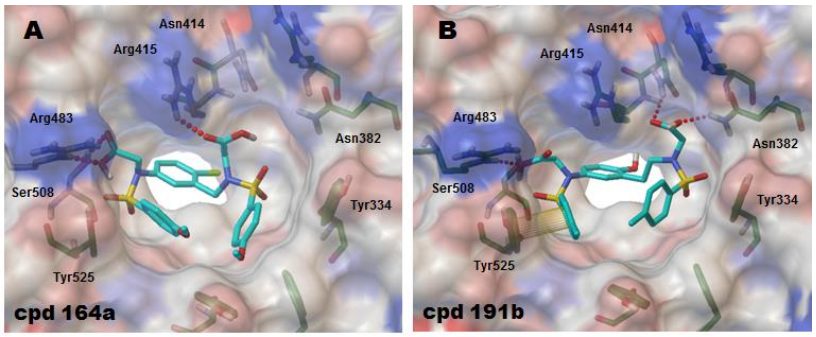


Figure 19. Binding modes of compounds **164a** and **191b**.

SUMMARY

The Keap1-Nrf2-ARE signaling system is an attractive therapeutic target for the prevention and treatment of oxidative stress related diseases including cancer and COPD, through the induction of the expression of cellular cytoprotective proteins. However, targeting protein-protein interactions is considered more challenging than targeting classical drug targets such as enzymes. Direct inhibitors of Keap1-Nrf2 PPI have also shown related issues involving cellular potency and PK properties. In this regard, it is necessary to discover diverse types of inhibitors, which can increase the success rate of drug development. In this study, we aimed to find a new series of direct inhibitors via two strategies. First, a series of 1,4-diamino phenyl ring or naphthalene derivatives containing an oxygen-containing linker were designed based on the analysis of co-crystal structure of a non-electrophilic inhibitor bound to the Kelch domain of Keap1 protein. The structure-activity relationship studies on exploring *O*-linked fragments of the core part revealed that *O*-linked phenyl ring **94h** and naphthalene **120** displayed promising Keap1-Nrf2 PPI inhibitory activity in either FP or TR-FRET assays. In addition, we observed interesting results through *in vitro* assays and computational modeling studies. Generally, the core naphthalene system was favorable for inhibitory activities in both FP and TR-FRET assays, compared to the phenyl ring moiety. It is likely that high hydrophobic interactions of the naphthalene (**123**) in the P3 subpocket might result in improved activities (2-fold in FP assay and 4-fold in TR-FRET assay) relative to **94h**. Importantly, the phenyl ring scaffold indicated big differences in potency depending on the structure of *O*-linked fragments, while the naphthalene ring scaffold retained activity regardless of the fragment. In the phenyl ring core moiety, a polar interaction of the acetate group (**49h**) in the Arg415 pocket

contributed to 4-fold greater inhibitory potency than the 4-fluorobenzyloxy fragment (**44g**). Moreover, we employed a molecular hybridation strategy with known direct inhibitors, and designed new scaffolds such as THIQ and *N*-phenylglycine analogs. In the case of the THIQ scaffold, the SAR results of **139aB** suggested that **139cB** with 5-methoxy group on the THIQ core moiety was the most active among THIQ analogues developed by our group and others. Accordingly, we synthesized one stereoisomer **139c** that exhibited improved potency with an IC_{50} value of 0.37 μM. The analysis of the docking mode of **139c** and its comparisons with that of **1**, provided that π-π stacking interaction of the sulfonamide moiety with Tyr525 in the P4 subpocket, as well as polar interactions of the carboxylic group with Arg415 and Asn414 in the P2 subpocket, leads to higher binding affinity and greater inhibitory activity in FP assays. In a series of *N*-phenylglycine analogues, compound **191b**, containing an ethylamine linker, displayed the best inhibitory activity in both FP and TR-FRET assays. The docking simulation and biological results of **164a** and **191b** suggested that the linker length plays a crucial role in potency. The methylamine linker of **164a** is too short for binding interactions with polar residues in the P2 subpocket, where the increased ethylamine linker of **191b** makes strong hydrogen bond interactions with the chains of Asn414 and Asn382. Although further studies such as optimization and cell-based potency are needed, the direct inhibitors would provide the advantage of structural diversity that is a key factor for appropriate structural modifications of small molecules in the early drug discovery process. Furthermore, the new scaffolds optimized through the rational structure-based design approach can be an attractive starting point for the development of Keap1-Nrf2 PPI inhibitors.

EXPERIMENTAL

General Chemistry.

All solvents and reagents were purchased from commercial sources and used as received unless specified otherwise. All moisture sensitive reactions were carried out using dry solvents under nitrogen atmosphere. Analytical thin layer chromatography was carried out using aluminum-backed Silica G TLC plates coated with DC Kieselgel 60 F254 (Merk or Sigma-Aldrich). Plates were visualized using ultraviolet light (254 nm) and/or by staining with potassium permanganate followed by heating. Flash chromatography was carried out on a Teledyne ISCO Combiflash Companion system with prepacked Teledyne ISCO RediSep normal phase silica cartridges (230-400 mesh), eluting with a 0−100% ethyl acetate/ hexane or 0-20% methanol/dichloromethane gradient. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz at ambient temperature, using a Bruker Avance III 400 Multinuclear NMR spectrometer**.** Chemical shifts (δ) are expressed in parts per million (ppm) relative to a solvent signal as an internal reference ($CDCl_3$, methanol-d4, or DMSO-d6). In the NMR tabulation, spin multiplicities are indicated as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and brs (broad singlet). Coupling constants (*J*) are reported in hertz (Hz). Analytical liquid chromatography/mass spectrometry (LC/MS) were performed on an Agilent 1200 Infinity high-performance LC (HPLC) system coupled to an Agilent 6410 quadrupole mass spectrometer operating an electrospray ionization (ESI) source, with an Inertsil ODS-3 C18 column (3 mm × 33 mm, 3 μM) at a temperature of 40 °C. The mobile phases A and B were water with 0.1% formic acid and methanol with 0.1% formic acid, respectively. The ratio of mobile phase B was increased linearly from 5% to 90% over 5 minutes, at a flow

rate of 0.8 mL/min, monitoring UV absorbance at 280 nm. High-resolution mass spectra (HRMS) experiments were conducted by Center for Integrative Proteomics Research (CIPR) at Rutgers University. 1 μg/mL solutions were directly infused using the Thermo LTQ Orbitrap Velos ETD with Dionex UltiMate 3000 nano-flow 2D LC.

2-Bromo-4-nitroaniline (11). To a solution of 4-nitroaniline (500 mg, 3.62 mmol) in acetic acid (5 mL) was added bromine (607 mg, 3.80 mmol) at 5 °C. The reaction mixture was stirred at 5 °C for 30 minutes. After the reaction was completed, the precipitate was filtered, dissolved with ethyl acetate, and then washed with sat. $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-40% ethyl acetate/hexane) to give the product as a yellow solid (310 mg, 40%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, *J* = 2.4 Hz, 1H), 7.97 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.84 (s, 2H, NH), 6.82 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.4, 136.2, 128.8, 125.0, 113.4, 105.0; LC/MS (ESI) *m/z* 216.9 [M(^{79}Br) + H]$^+$, 218.9 [M(^{81}Br) + H]$^+$.

2-Bromobenzene-1,4-diamine (12). To a solution of **11** (300 mg, 1.38 mmol) in acetic acid (3 mL) and water (1 mL) was added iron powder (772 mg, 13.82 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 30 minutes. The crude mixture was cooled to room temperature, added to sat. $NaHCO_3$, and then extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the product as a dark brown solid (269 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.69 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.42 (dd, *J* =

8.4, 2.4 Hz, 1H), 4.42 (brs, 4H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.5, 135.8, 117.4, 116.8, 115.4, 108.8; LC/MS (ESI) *m/z* 161.2 [M(^{79}Br) + H]$^+$, 163.2 [M(^{81}Br) + H]$^+$.

[1,1'-Biphenyl]-2,5-diamine (13a). To a solution of **12** (269 mg, 1.44 mmol) in dioxane (4.5 mL) and water (1.5 mL) were added phenylboronic acid (351 mg, 2.88 mmol), $Pd(PPh_3)_4$ (166 mg, 0.14 mmol) and potassium carbonate (398 mg, 2.88 mmol) at room temperature. The reaction mixture was stirred at 100 °C for overnight. After the reaction was completed, the crude mixture was cooled to room temperature, filtered off through celite, and then concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-70% ethyl acetate/hexane) to give the product as a brown oil (125 mg, 47%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44-7.39 (m, 4H), 7.32-7.28 (m, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.43 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 4.17 (brs, 4H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.4., 139.8, 135.2, 128.6, 128.5, 127.2, 126.5, 117.0, 116.3, 115.2; LC/MS (ESI) *m/z* 185.2 [M + H]$^+$.

***N,N'*-([1,1'-Biphenyl]-2,5-diyl)bis(4-methoxybenzenesulfonamide) (14a).** To a solution of **13a** (49 mg, 0.27 mmol) in dichloromethane (2 mL) were added pyridine (63 mg, 0.80 mmol) and 4-methoxybenzenesulfonyl chloride (166 mg, 0.80 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to 1N HCl, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-40% ethyl acetate/hexane) to give the product as a colorless oil (54 mg, 39%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.26-7.20 (m, 2H), 6.97 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.77-6.72 (m, 3H),

6.66 (d, J = 7.6 Hz, 2H), 6.49 (s, 1H), 3.78 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 136.5, 135.6, 133.9, 131.0, 130.5, 130.4, 129.6, 129.3, 129.1, 128.7, 128.4, 123.5, 123.3, 121.8, 114.3, 114.2, 55.72, 55.70; LC/MS (ESI) *m/z* 525.1 $[M + H]^+$.

***N,N'*-([1,1'-Biphenyl]-2,5-diyl)bis(4-methylbenzenesulfonamide) (14b).** Prepared as described in the experimental procedure of **14a** from intermediate **13a** and 4-methylbenzenesulfonyl chloride to obtain the title compound as a colorless oil (125 mg, 30%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.45 (brs, 1H, NH), 7.37 (d, J = 8.4 Hz, 2H), 7.33-7.27 (m, 3H), 7.23 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.04 (dd, J = 8.8, 2.8 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.71 (dd, J = 8.0, 1.6 Hz, 2H), 6.58 (brs, 1H, NH), 2.42 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 136.5, 136.2, 135.6, 133.9, 130.9, 129.7, 129.6, 129.1, 128.7, 128.3, 127.4, 127.2, 123.5, 123.3, 121.8, 21.6; LC/MS (ESI) *m/z* 495.1 $[M + H]^+$.

***N,N'*-([1,1'-Biphenyl]-2,5-diyl)bis(4-fluorobenzenesulfonamide) (14c).** Prepared as described in the experimental procedure of **14a** from intermediate **13a** and 4-fluorobenzenesulfonyl chloride to obtain the title compound as a colorless oil (81 mg, 24%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 8.8, 5.2 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.45 (dd, J = 8.8, 5.2 Hz, 2H), 7.38-7.29 (m, 3H), 7.14-7.10 (m, 3H), 7.06-6.99 (m, 3H), 6.85 (d, J = 2.4 Hz, 1H), 6.73 (dd, J = 7.6, 1.6 Hz, 2H), 6.61 (brs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.73, 166.69, 164.18, 164.15, 136.2 ($J_{C,F}$ = 10 Hz), 134.4 ($J_{C,F}$ = 20 Hz), 130.9, 130.3 ($J_{C,F}$ = 9 Hz), 130.0 ($J_{C,F}$ = 9 Hz), 129.4, 128.7, 128.6, 123.9, 123.6, 122.0, 116.5 ($J_{C,F}$ = 17 Hz), 116.3 ($J_{C,F}$ = 18 Hz); LC/MS (ESI) *m/z* 501.1 $[M + H]^+$.

***N,N'*-(4'-Methyl-[1,1'-biphenyl]-2,5-diyl)bis(4-methoxybenzenesulfonamide) (14d).** Prepared as described in the experimental procedure of **13a** from i**12** and 4-

methylphenylboronic acid to obtain the product, **13b**, as a black oil. The resulting compound was used for the next reaction. Prepared as described in the experimental procedure of **14a** from **13b** to obtain the title compound as a pale yellow solid (47 mg, 14% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 9.2 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 9.2 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.88 (d, *J* = 9.2 Hz, 2H), 6.83 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 2H), 6.49 (brs, 1H, NH), 3.85 (s, 3H), 3.85 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 138.5, 135.3, 133.4, 131.6, 130.7, 130.6, 130.0, 129.6, 129.5, 128.7, 124.0, 122.5, 122.1, 114.3, 114.2, 55.79, 55.76, 22.8; LC/MS (ESI) *m/z* 539.2 $[M + H]^+$.

Diethyl 2,2'-([1,1'-biphenyl]-2,5-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetate (15a). To a solution of **14a** (54 mg, 0.10 mmol) in *N*,*N*-dimethylformamide (0.5 mL) were added potassium carbonate (43 mg, 0.31 mmol) and ethyl 2-bromoacetate (52 mg, 0.31 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to water, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-40% ethyl acetate/hexane) to give the product as a colorless oil (34 mg, 47%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.37-7.36 (m, 3H), 7.28-7.18 (m, 4H), 7.10-7.03 (m, 5H), 4.54 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.91 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.7, 168.1, 162.9, 162.8, 141.4, 139.5, 137.8, 136.0, 130.7, 130.6, 129.9, 129.7, 129.6, 128.6, 128.2, 127.7, 126.8, 114.4, 114.3, 60.9, 60.8, 55.8, 52.0, 51.9, 13.9, 13.7; LC/MS (ESI) *m/z* 697.3 $[M + H]^+$.

Diethyl 2,2'-([1,1'-biphenyl]-2,5-diylbis(tosylazanediyl))diacetate (15b). Prepared as described in the procedure of **15a** from **14b** to obtain the title compound as a colorless oil (150 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.30-7.28 (m, 3H), 7.24-7.19 (m, 7H), 7.09 (d, *J* = 2.8 Hz, 1H), 7.07-7.06 (m, 1H), 4.32 (s, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.94-3.89 (m, 4H), 2.39 (s, 3H), 2.36 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 144.0, 143.9, 142.2, 139.9, 137.7, 136.9, 136.0, 131.4, 131.3, 129.6, 128.9, 128.5, 128.1, 128.0, 127.8, 61.6, 61.3, 52.6, 52.0, 21.7, 21.6, 14.1, 14.0; LC/MS (ESI) *m/z* 665.3 $[M + H]^+$.

Diethyl 2,2'-([1,1'-biphenyl]-2,5-diylbis(((4-fluorophenyl)sulfonyl)azanediyl))diacetate (15c). Prepared as described in the experimental procedure of **15a** from **14c** to obtain the title compound as a colorless oil (53 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.72 (m, 4H), 7.38-7.37 (m, 3H), 7.31-7.28 (m, 3H), 7.19 (d, *J* = 2.8 Hz, 1H), 7.16-7.11 (m, 5H), 4.41 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.02-3.96 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.6, 166.7, 166.6, 164.2, 164.1, 142.7, 139.9, 137.4, 136.9, 136.7 ($J_{C,F}$ = 4 Hz), 135.1 ($J_{C,F}$ = 4 Hz), 131.5 ($J_{C,F}$ = 9 Hz), 130.9 ($J_{C,F}$ = 5 Hz), 130.8, 130.7, 128.8, 128.7, 128.3, 127.8, 116.2 ($J_{C,F}$ = 23 Hz), 61.8, 61.5, 52.7, 52.2, 14.1, 14.0; LC/MS (ESI) *m/z* 691.2 $[M + H + H_2O]^+$.

Diethyl 2,2'-((4'-methyl-[1,1'-biphenyl]-2,5-diyl)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (15d). Prepared as described in the experimental procedure of **15a** from intermediate **14d** to obtain the title compound as a colorless oil (31 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 9.2 Hz, 2H), 7.64 (d, *J* = 9.2 Hz, 4H), 7.28-7.26 (m, 1H), 7.21-7.11 (m, 6H), 6.94 (d, *J* = 9.6 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.37 (s, 2H), 4.18-4.09 (m, 6H), 3.89 (s, 3H), 3.86 (s, 3H), 2.38 (s, 3H), 1.27-1.20 (m, 6H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 168.9, 163.34, 163.26, 142.3, 140.0, 137.9, 136.9, 134.8, 132.4, 131.30, 131.25, 130.5, 130.3, 130.2, 129.3, 128.8, 127.6, 114.12, 114.07, 61.7, 61.3, 55.8, 52.6, 52.0, 21.3, 21.2, 14.3, 14.1; LC/MS (ESI) *m/z* 711.2 $[M + H]^+$.

2,2'-([1,1'-Biphenyl]-2,5-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (16a). To a solution of **15a** (34 mg, 0.05 mmol) in methanol (0.3 mL) was added sodium hydroxide (10 mg, 0.24 mmol) in water (0.1 mL) at room temperature. The reaction mixture was stirred at 60 °C for overnight. After the reaction was completed, the crude mixture was concentrated under reduced pressure, dissolved with water, and then washed with dichloromethane. The aqueous solution was acidified with 6 N HCl until the pH reached around 1 and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting solid was dissolved with the minimum amount of dichloromethane, solidified from hexane, and then filtered to give the product as a white solid (21 mg, 67%); ^{1}H NMR (400 MHz, MeOD) δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.40-7.32 (m, 4H), 7.22-7.16 (m, 3H), 7.06-6.99 (m, 5H), 4.43 (s, 2H), 3.90 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.1, 171.7, 165.0, 164.9, 143.6, 141.4, 139.6, 138.0, 133.0, 132.7, 132.2, 131.23, 131.19, 130.0, 129.3, 129.1, 128.9, 128.6, 115.3, 115.2, 115.0, 56.30, 56.27, 53.12, 53.06; LC/MS (ESI) *m/z* 639.0 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_2O_{10}S_2$ $[M - H]^-$ 639.1113; found 639.1118.

2,2'-([1,1'-Biphenyl]-2,5-diylbis(tosylazanediyl))diacetic acid (16b). Prepared as described in the experimental procedure of **16a** from intermediate **15b** to obtain the title compound as a white solid (71 mg, 52%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (brs, 2H, CO_2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H),

7.35-7.30 (m, 6H), 7.20-7.16 (m, 3H), 6.97 (d, *J* = 2.4 Hz, 1H), 4.44 (s, 2H), 3.91 (s, 2H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 169.4, 143.7, 143.5, 141.2, 139.4, 137.8, 136.6, 135.8, 135.5, 130.8, 129.6, 129.5, 128.5, 128.1, 127.6, 127.4, 127.3, 126.7, 51.8, 20.99, 20.95; LC/MS (ESI) *m/z* 607.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_2O_8S_2$ [M - H]$^-$ 607.1214; found 607.1220.

2,2'-([1,1'-Biphenyl]-2,5-diylbis(((4-fluorophenyl)sulfonyl)azanediyl))diacetic acid (16c). Prepared as described in the experimental procedure of **15a** from intermediate **14c** to obtain the title compound as a white solid (23 mg, 48%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78-7.75 (m, 2H), 7.69-7.64 (m, 2H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.44 (dd, *J* = 8.8, 8.8 Hz, 2H), 7.37-7.33 (m, 5H), 7.25-7.21 (m, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 2.8 Hz, 1H), 4.48 (s, 2H), 3.84 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 169.5, 141.5, 139.4, 137.7, 135.9, 134.8, 131.1, 130.6, 130.5, 129.9, 129.6, 128.5, 128.2, 127.7, 127.1, 116.4 ($J_{C,F}$ = 23 Hz), 116.1, 114.4, 114.2, 55.7, 52.1, 51.9; LC/MS (ESI) *m/z* 615.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{28}H_{22}F_2N_2O_8S_2$ [M - H]$^-$ 615.0713; found 615.0720.

2,2'-((4'-Methyl-[1,1'-biphenyl]-2,5-diyl)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (16d). Prepared as described in the procedure of **15a** from **14d** to obtain the title compound as a white solid (19 mg, 66%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (brs, 2H, CO_2H), 7.60 (d, *J* = 9.2 Hz, 2H), 7.53 (d, *J* = 9.2 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.17-7.13 (m, 3H), 7.11-7.07 (m, 4H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 2.8 Hz, 1H), 4.41 (s, 4H), 3.86 (s, 3H), 3.84 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.0, 169.6, 162.8, 162.7, 141.1, 139.5, 137.0, 135.9, 135.0, 131.3, 130.9, 129.9, 129.7, 129.6, 128.8, 128.4, 126.4, 114.4, 114.1, 55.74, 55.70, 51.8, 20.7; LC/MS (ESI) *m/z* 653.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_{10}S_2$ [M - H]$^-$ 653.1269; found 653.1277.

3,3'-Dinitro-1,1'-biphenyl (17). To a solution of 1-bromo-3-nitrobenzene (300 mg, 1.50 mmol) in polyethylene glycol 4000 (1.5 g) were added palladium (II) acetate (7 mg, 0.03 mmol) and potassium carbonate (207 mg, 1.50 mmol) at room temperature. The reaction mixture was stirred at 100 °C for overnight. After the reaction was completed, the crude mixture was cooled to room temperature, added to water, and then extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-10% ethyl acetate/hexane) to give the product as a white solid (42 mg, 12%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 2H), 8.31-8.27 (m, 4H), 7.82 (dd, *J* = 7.8, 7.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.5, 139.5, 133.7, 130.7, 123.2, 121.8; LC/MS (ESI) *m/z* 244.1 $[M]^-$.

***N,N'*-([1,1'-Biphenyl]-3,5-diyl)bis(4-methoxybenzenesulfonamide) (18a).** To a solution of crude 5-bromobenzene-1,3-diamine (170 mg, 1.44 mmol) in dioxane (3 mL) and water (1 mL) were added phenylboronic acid (222 mg, 2.88 mmol), $Pd(PPh_3)_4$ (105 mg, 0.14 mmol) and potassium carbonate (251 mg, 2.88 mmol) at room temperature. The reaction mixture was stirred for 4 hours at 100 °C. After the reaction was completed, the crude mixture was cooled to room temperature, filtered off through celite, and then concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-60% ethyl acetate/hexane) to give [1,1'-biphenyl]-3,5-diamine as a pale pink solid (105 mg, 47% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.37 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.12 (d, *J* = 1.6 Hz, 2H), 5.89 (s, 1H), 4.91 (brs, 4H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 131.5, 131.4, 128.7, 128.6, 128.5, 126.7, 126.2, 102.2; LC/MS (ESI) *m/z* 185.2 $[M + H]^+$. To a solution of [1,1'-biphenyl]-3,5-diamine (52 mg, 0.28 mmol) in dichloromethane (2 mL) were added pyridine (67 mg, 0.85 mmol) and

4-methoxybenzenesulfonyl chloride (175 mg, 0.85 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The crude mixture was added to 1N HCl, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-40% ethyl acetate/hexane) to give the product as a colorless oil (35 mg, 24%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 9.2 Hz, 4H), 7.36-7.26 (m, 5H), 7.06-7.05 (m, 1H), 7.03-7.02 (m, 2H), 6.80 (d, *J* = 9.2 Hz, 4H), 3.72 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 143.4, 139.4, 138.4, 130.3, 129.7, 128.9, 128.1, 127.0, 115.1, 114.4, 110.6, 55.6; LC/MS (ESI) *m/z* 525.2 $[M + H]^+$.

***N,N'*-([1,1'-Biphenyl]-2,4'-diyl)bis(4-methoxybenzenesulfonamide) (18b).** Prepared as described in the procedure of **18a** from 2-bromoaniline and 4-aminophenylboronic acid to obtain the title compound as a colorless oil (93 mg, 27% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 9.2 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 (brs, 1H, NH), 7.34 (d, *J* = 8.8 Hz, 2H), 7.28-7.22 (m, 1H), 7.10-7.08 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.48 (brs, 1H, NH), 3.78 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 163.3, 136.9, 134.0, 133.79, 133.76, 130.6, 130.5, 130.3, 130.0, 129.6, 129.3, 128.8, 125.3, 122.4, 121.5, 114.5, 114.2, 55.8; LC/MS (ESI) *m/z* 525.1 $[M + H]^+$

***N,N'*-([1,1'-Biphenyl]-3,4'-diyl)bis(4-methoxybenzenesulfonamide) (18c).** Prepared as described in the experimental procedure of **18a** from 3-bromoaniline and 4-aminophenylboronic acid to obtain [1,1'-biphenyl]-2,5-diamine as a brown oil (133 mg, 62%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (d, *J* = 8.0 Hz, 2H), 7.01 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.74 (s, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 7.6 Hz,

1H), 5.13 (brs, 2H, NH), 5.00 (brs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.8., 148.0, 141.4, 129.1, 128.4, 126.9, 114.1, 113.4, 111.7, 111.1; LC/MS (ESI) *m/z* 185.2 [M + H]$^+$. Prepared as described in the experimental procedure of **18a** from [1,1'-biphenyl]-2,5-diamine to obtain the title compound as a colorless oil (64 mg, 45%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (brs, 2H, NH), 7.73 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 9.2 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.27-7.17 (m, 6H), 7.06 (d, *J* = 9.2 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.43, 162.41, 140.2, 138.5, 137.6, 134.9, 131.2, 131.1, 129.6, 128.9, 128.8, 127.2, 121.9, 120.0, 118.5, 117.5, 114.40, 114.35, 55.6; LC/MS (ESI) *m/z* 525.2 [M + H]$^+$.

***N,N'*-([1,1'-Biphenyl]-3,3'-diyl)bis(4-methoxybenzenesulfonamide) (18d).** To a solution of **17** (42 mg, 0.17 mmol) in methanol (10 mL) was added Pd/C (10% wt.) (4 mg) at room temperature under N_2. The reaction mixture was stirred at room temperature for 2 hours under H_2. After the reaction was completed, the crude mixture was filtered off through celite, and then concentrated under reduced pressure to give the product, [1,1'-biphenyl]-3,3'-diamine, as a pale brown solid. The resulting crude compound was used for the next reaction without further purification. To a solution of [1,1'-biphenyl]-3,3'-diamine (80 mg, 0.43 mmol) in dichloromethane (2 mL) were added pyridine (103 mg, 1.30 mmol) and 4-methoxybenzenesulfonyl chloride (224 mg, 1.09 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to 1N HCl, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-40% ethyl acetate/hexane) to give the product as a colorless oil (84 mg, 37% over 2 steps); ^{1}H NMR

(400 MHz, DMSO-d_6) δ 10.33 (brs, 2H, NH), 7.74 (d, *J* = 9.2 Hz, 4H), 7.31-7.27 (m, 4H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 6H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 140.5, 138.6, 131.0, 129.8, 128.9, 122.0, 118.9, 117.5, 114.4, 55.6; LC/MS (ESI) *m/z* 525.2 $[M + H]^+$.

Diethyl 2,2'-([1,1'-biphenyl]-3,5-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetate (19a). Prepared as described in the experimental procedure of **15a** from intermediate **18a** to obtain the title compound as a pale yellow oil (45 mg, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 9.2 Hz, 4H), 7.41 (d, *J* = 2.0 Hz, 2H), 7.39-7.34 (m, 5H), 7.01 (dd, *J* = 2.0, 2.0 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 4H), 4.32 (s, 4H), 4.14 (q, *J* = 7.2 Hz, 4H), 3.86 (s, 6H), 1.22 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 163.4, 143.0, 141.2, 139.0, 130.3, 130.2, 129.0, 128.3, 127.2, 127.1, 126.7, 114.3, 61.7, 55.8, 52.6, 14.2; LC/MS (ESI) *m/*z 697.2 $[M + H]^+$.

Diethyl 2,2'-([1,1'-biphenyl]-2,4'-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetate (19b). Prepared as described in the experimental procedure of **15a** from intermediate **18b** to obtain the title compound as a colorless oil (101 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.35-7.33 (m, 1H), 7.30-7.28 (m, 2H), 7.27-7.25 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 4H), 4.44 (s, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.04-3.97 (m, 4H), 3.89 (s, 3H), 3.86 (s, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.8, 163.4, 163.3, 140.6, 139.6, 138.6, 137.5, 132.2, 131.6, 130.4, 130.2, 130.1, 130.0, 128.8, 128.3, 123.2, 114.5, 114.14, 114.08, 61.7, 61.4, 55.8, 55.7, 52.7, 52.3, 14.3, 14.1; LC/MS (ESI) *m/z* 697.2 $[M + H]^+$.

Diethyl 2,2'-([1,1'-biphenyl]-3,4'-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetate (19c). Prepared as described in the experimental procedure of **15a** from intermediate **18c** to obtain the title compound as a pale yellow oil (56 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.47-7.32 (m, 5H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.15-7.12 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.41 (s, 4H), 4.19-4.12 (m, 4H), 3.86 (s, 3H), 3.85 (s, 3H), 1.25-1.19 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.89, 168.87, 163.30, 163.27, 141.2, 140.7, 139.7, 139.6, 130.61, 130.58, 130.2, 130.1, 129.7, 129.0, 127.9, 127.8, 127.6, 126.8, 114.13, 114.09, 61.6, 55.74, 55.72, 52.8, 52.7, 14.2; LC/MS (ESI) *m/z* 697.3 $[M + H]^+$.

Diethyl 2,2'-([1,1'-biphenyl]-3,3'-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetate (19d). Prepared as described in the experimental procedure of **15a** from intermediate **18d** to obtain the title compound as a colorless oil (72 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.8 Hz, 4H), 7.39-7.37 (m, 2H), 7.34-7.30 (m, 4H), 7.15-7.12 (m, 2H), 6.94 (d, *J* = 9.2 Hz, 4H), 4.41 (s, 4H), 4.18-4.11 (m, 4H), 3.87 (s, 6H), 1.27-1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 163.4, 141.3, 140.7, 130.6, 130.2, 129.7, 127.8, 127.7, 126.9, 114.2, 61.6, 55.8, 52.8, 14.2; LC/MS (ESI) *m/z* 697.2 $[M + H]^+$.

2,2'-([1,1'-Biphenyl]-3,5-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (20a). Prepared as described in the experimental procedure of **16a** from **19a** to obtain the title compound as a white solid (8 mg, 30%); ^{1}H NMR (400 MHz, MeOD) δ 7.58 (d, *J* = 8.8 Hz, 4H), 7.43-7.40 (m, 6H), 7.38-7.35 (m, 1H), 7.02 (d, *J* = 9.2 Hz, 4H), 6.91-6.90 (m, 1H), 4.34 (s, 4H), 3.86 (s, 6H); ^{13}C NMR (100 MHz, MeOD) δ 172.0, 165.0, 143.9, 142.5, 140.4, 131.1, 130.0, 129.2, 128.1, 127.9, 127.2, 115.3, 56.3, 53.1; LC/MS (ESI) *m/z* 639.0 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_2O_{10}S_2$ $[M - H]^-$ 639.1113; found 639.1120.

2,2'-([1,1'-Biphenyl]-2,4'-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (20b). Prepared as described in the experimental procedure of **16a** from intermediate **19b** to obtain the title compound as a white solid (21 mg, 59%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58-7.55 (m, 4H), 7.42-7.36 (m, 2H), 7.35-7.28 (m, 4H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 9.2 Hz, 2H), 7.06 (d, *J* = 9.2 Hz, 2H), 4.43 (s, 2H), 4.19 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.0, 169.5, 162.8, 162.7, 140.0, 139.1, 137.7, 137.2, 131.3, 131.0, 130.1, 129.8, 129.61, 129.57, 129.2, 128.4, 128.1, 126.9, 114.3, 114.2, 55.7, 55.6, 51.8; LC/MS (ESI) *m/z* 639.0 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_2O_{10}S_2$ [M - H]$^-$ 639.1113; found 639.1119.

2,2'-([1,1'-Biphenyl]-3,4'-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (20c). Prepared as described in the experimental procedure of **16a** from intermediate **19a** to obtain the title compound as a white solid (26 mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.47-7.44 (m, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.32 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.01-6.99 (m, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.46 (s, 2H), 4.42 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 163.48, 163.45, 141.2, 140.4, 139.8, 139.3, 130.4, 130.2, 130.12, 130.07, 129.8, 129.2, 128.2, 128.1, 127.0, 114.30, 114.27, 55.82, 55.81, 52.3; LC/MS (ESI) *m/z* 639.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_2O_{10}S_2$ [M - H]$^-$ 639.1113; found 639.1121.

2,2'-([1,1'-Biphenyl]-3,3'-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (20d). Prepared as described in the experimental procedure of **16a** from intermediate **19a** to obtain the title compound as a white solid (17 mg, 26%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (brs, 2H, CO_2H), 7.62 (d, *J* = 8.4 Hz, 4H), 7.45-7.39 (m, 4H), 7.31 (s, 2H), 7.16

(d, *J* = 6.8 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 4H), 4.44 (s, 4H), 3.83 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 162.8, 140.6, 139.9, 130.0, 129.6, 126.9, 126.1, 125.8, 114.4, 55.7, 51.9; LC/MS (ESI) *m/z* 639.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_2O_{10}S_2$ [M - H]$^-$ 639.1113; found 639.1120.

4-Nitro-3-(piperidin-1-yl)aniline (21a). To a solution of piperidine (218 mg, 2.56 mmol) in acetonitrile (6 mL) were added triethylamine (259 mg, 2.56 mmol) and 3-fluoro-4-nitroaniline (200 mg, 1.28 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to water, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-20% ethyl acetate/hexane) to give the product as a yellow oil (301 mg, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, *J* = 9.2 Hz, 1H), 6.42 (brs, 2H, NH), 6.19-6.16 (m, 2H), 2.88-2.86 (m, 4H), 1.63-1.61 (m, 4H), 1.54-1.53 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.3, 151.2, 130.0, 129.4, 106.6, 102.0, 52.7, 25.5, 23.7; LC/MS (ESI) m/z 222.2 [M + H]$^+$.

3-(Benzyloxy)-4-nitroaniline (21b). To a solution of benzyl alcohol (1.7 g, 15.37 mmol) in tetrahydrofuran (60 mL) was added sodium hydride (60% dispersion in mineral oil, 769 mg, 19.22 mmol) at 0 °C. After stirring at 0 °C for 15 minutes, 3-fluoro-4-nitroaniline (2.0 g, 12.81 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 6 hours. After the reaction was completed, the crude mixture was added to water and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-60% ethyl acetate/hexane) to give the product as a yellow solid (1.7 g,

54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.41-7.37 (m, 2H), 7.34-7.31 (m, 1H), 6.24 (d, *J* = 2.4 Hz, 1H), 6.21 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.18 (s, 2H), 4.27 (brs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 155.5, 136.3, 128.9, 128.4, 127.8, 127.1, 105.8, 97.2, 69.7; LC/MS (ESI) *m/z* 245.1 $[M + H]^+$.

4-Nitro-3-phenoxyaniline (21c). Prepared as described in the experimental procedure of **21b** from 3-fluoro-4-nitroaniline and phenol to obtain the title compound as a colorless oil (440 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, *J* = 9.2 Hz, 1H), 7.44-7.40 (m, 2H), 7.20-7.16 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.68 (brs, 2H, NH), 6.40 (d, *J* = 9.2 Hz, 1H), 6.07 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 155.7, 153.6, 130.1, 129.0, 128.1, 124.0, 118.7, 108.6, 102.6; LC/MS (ESI) *m/z* 231.1 $[M + H]^+$.

4-Nitro-3-phenethoxyaniline (21d). Prepared as described in the procedure of **21b** from 3-fluoro-4-nitroaniline and 2-phenylethan-1-ol to obtain the title compound as a colorless oil (100 mg, 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 9.2 Hz, 1H), 7.30-7.22 (m, 4H), 7.21-7.16 (m, 1H), 6.08-6.06 (m, 2H), 4.43 (brs, 2H, NH), 4.12 (t, *J* = 6.8 Hz, 2H), 3.08 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 153.7, 137.9, 129.6, 129.3, 129.2, 128.5, 126.7, 106.2, 98.2, 70.2, 35.6; LC/MS (ESI) *m/z* 259.1 $[M + H]^+$.

4-Nitro-3-(3-phenylpropoxy)aniline (21e). Prepared as described in the experimental procedure of **21b** from 3-fluoro-4-nitroaniline and 3-phenylpropan-1-ol to obtain the title compound as a colorless oil (241 mg, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.8 Hz, 1H), 7.26-7.22 (m, 2H), 7.17-7.14 (m, 3H), 6.13 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 4.37 (s, 2H, NH), 3.95 (t, *J* = 6.4 Hz, 2H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.14-2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 153.5, 141.3, 130.0, 129.3, 128.7, 128.5, 126.1, 106.1, 98.3, 68.0, 31.9, 30.5; LC/MS (ESI) *m/z* 273.2 $[M + H]^+$.

3-((4-Methoxybenzyl)oxy)-4-nitroaniline (21f). Prepared as described in the experimental procedure of **21b** from 3-fluoro-4-nitroaniline and 4-methoxybenzyl alcohol to obtain the title compound as a yellow solid (70 mg, 57%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, *J* = 9.2 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.57 (brs, 2H, NH), 6.37 (d, *J* = 2.0 Hz, 1H), 6.21 (dd, *J* = 9.2, 2.0 Hz, 1H), 5.09 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.0, 156.1, 155.6, 129.0, 128.9, 128.1, 127.1, 113.8, 105.8, 97.2, 69.7, 55.1; LC/MS (ESI) *m/z* 275.1 $[M + H]^+$.

3-((4-Fluorobenzyl)oxy)-4-nitroaniline (21g). Prepared as described in the experimental procedure of **21b** from 3-fluoro-4-nitroaniline and 4-fluorobenzyl alcohol to obtain the title compound as a yellow solid (182 mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 9.2 Hz, 1H), 7.46 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.07 (dd, *J* = 8.8, 8.8 Hz, 2H), 6.23-6.21 (m, 2H), 5.12 (s, 2H), 4.31 (brs, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 ($J_{C,F}$ = 245 Hz), 155.3, 153.0, 131.6, 129.3, 128.7 ($J_{C,F}$ = 8 Hz), 115.6 ($J_{C,F}$ = 21 Hz), 106.5, 99.2, 70.4; LC/MS (ESI) *m/z* 261.0 $[M - H]^-$.

3-((4-Methylbenzyl)oxy)-4-nitroaniline (21h). Prepared as described in the experimental procedure of **21b** from 3-fluoro-4-nitroaniline and 4-methylbenzyl alcohol to obtain the title compound as a yellow solid (144 mg, 58%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.59 (brs, 2H, NH), 6.35 (d, *J* = 1.6 Hz, 1H), 7.94 (dd, *J* = 8.8, 1.6 Hz, 1H), 5.12 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 155.6, 137.1, 133.3, 129.0, 127.2, 127.0, 105.8, 97.2, 69.7, 20.8; LC/MS (ESI) *m/z* 259.1 $[M + H]^+$.

3-(Naphthalen-2-yloxy)-4-nitroaniline (21i). Prepared as described in the procedure of **21b** from 3-fluoro-4-nitroaniline and 2-naphthol to obtain the title compound as a yellow

solid (238 mg, 88%); ^{1}H NMR (400 MHz, DMSO-d_6) 7.99 (dd, *J* = 9.2, 9.2 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.54-7.45 (m, 3H), 7.34 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.69 (brs, 2H, NH), 6.43 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.13 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.3, 153.6, 153.5, 133.9, 130.2, 130.1, 129.1, 128.0, 127.7, 127.2, 126.8, 125.1, 119.8, 114.1, 108.7, 102.9; LC/MS (ESI) *m/z* 281.1 $[M + H]^+$.

3-(Naphthalen-2-ylmethoxy)-4-nitroaniline (21j). Prepared as described in the experimental procedure of **21b** from 3-fluoro-4-nitroaniline and 2-naphthalenemethanol to obtain the title compound as a yellow solid (121 mg, 21%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 1H), 7.98-7.91 (m, 3H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.55-7.53 (m, 2H), 6.60 (brs, 2H, NH), 6.42 (d, *J* = 1.6 Hz, 1H), 6.23 (dd, *J* = 8.8, 1.6 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 155.6, 133.9, 132.7, 132.5, 129.0, 128.0, 127.7, 127.6, 127.0, 126.3, 126.1, 125.8, 125.2, 105.9, 97.3, 70.0; LC/MS (ESI) *m/z* 295.1 $[M + H]^+$.

3-(Naphthalen-1-ylmethoxy)-4-nitroaniline (21k). Prepared as described in the experimental procedure of **21b** from 3-fluoro-4-nitroaniline and 1-naphthalenemethanol to obtain the title compound as a yellow solid (78 mg, 28%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.61-7.53 (m, 3H), 6.61 (brs, 2H, NH), 6.55 (s, 1H), 6.24 (d, *J* = 8.8 Hz, 1H), 5.64 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 155.6, 133.2, 131.7, 130.6, 129.0, 128.9, 128.6, 128.5, 126.4, 126.0, 125.9, 125.4, 123.6, 105.9, 97.3, 68.4; LC/MS (ESI) *m/z* 295.1 $[M + H]^+$.

3-([1,1'-Biphenyl]-4-yloxy)-4-nitroaniline (21l). Prepared as described in the experimental procedure of **21b** from 3-fluoro-4-nitroaniline and 4-phenylphenol to obtain

the title compound as a yellow solid (144 mg, 73%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, *J* = 9.2 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.49-7.46 (m, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.72 (brs, 2H, NH), 6.42 (dd, *J* = 9.2, 2.0 Hz, 1H), 6.15 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.3, 155.4, 153.4, 139.4, 135.9, 129.03, 128.95, 128.4, 127.3, 126.5, 119.0, 115.7, 108.8, 102.9; LC/MS (ESI) *m/z* 307.1 $[M + H]^+$.

3-([1,1'-Biphenyl]-4-ylmethoxy)-4-nitroaniline (21m). Prepared as described in the experimental procedure of **21b** from 3-fluoro-4-nitroaniline and [1,1'-biphenyl]-4-ylmethanol to obtain the title compound as a yellow solid (193 mg, 63%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, *J* = 8.8 Hz, 1H), 7.72-7.68 (m, 4H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 6.60 (brs, 2H, NH), 6.39 (d, *J* = 2.0 Hz, 1H), 6.23 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.23 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 155.6, 139.8, 139.7, 135.5, 129.0, 128.9, 127.7, 127.5, 127.0, 126.72, 126.67, 105.9, 97.1, 69.5; LC/MS (ESI) *m/z* 321.2 $[M + H]^+$.

***N,N'*-(2-(Piperidin-1-yl)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22a).** Prepared as described in the procedure of **18d** from **21a** to obtain the title compound as a pale yellow solid (120 mg, 50% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (brs, 1H, NH), 8.41 (brs, 1H, NH), 7.62 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 9.2 Hz, 1H), 7.02 (d, *J* = 9.2 Hz, 2H), 7.01 (d, *J* = 9.2 Hz, 2H), 6.74-6.72 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.29-2.27 (m, 4H), 2.53-2.51 (m, 4H), 1.44-1.42 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 162.4, 146.2, 135.0, 131.6, 130.8, 128.9, 128.7, 128.2, 122.2, 116.7, 114.2, 114.0, 55.7, 55.6, 53.1, 25.7, 23.4; LC/MS (ESI) *m/z* 532.2 $[M + H]^+$.

***N,N'*-(2-(Benzyloxy)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22b).** To a solution of **21b** (61 mg, 0.25 mmol) in acetic acid (0.4 mL) and water (0.4 mL) was added iron powder (140 mg, 2.51 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 30 minutes. The crude mixture was cooled to room temperature, added to sat. $NaHCO_3$, and then extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the product, 2-(benzyloxy)-benzene-1,4-diamine, as a pale yellow solid. The resulting crude compound was used for the next reaction without further purification. To a solution of 2-(benzyloxy)benzene-1,4-diamine (53 mg, 0.25 mmol) in dichloromethane (2 mL) were added pyridine (59 mg, 0.74 mmol) and 4-methoxybenzenesulfonyl chloride (153 mg, 0.74 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to 1N HCl, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-40% ethyl acetate/hexane) to give the product as a white solid (65 mg, 47% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (brs, 1H, NH), 9.24 (brs, 1H, NH), 7.54 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.34-7.32 (m, 3H), 7.21-7.19 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.75 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 162.1, 151.9, 136.3, 132.2, 130.9, 128.8, 128.6, 128.1, 127.6, 127.0, 126.8, 114.2, 113.8, 111.7, 104.6, 69.3, 55.6, 55.5; LC/MS (ESI) *m/z* 555.2 $[M + H]^+$.

***N,N'*-(2-Phenoxy-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22c).** Prepared as described in the experimental procedure of **22b** from intermediate **21c** to obtain the title

compound as a beige solid (64 mg, 54% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (brs, 1H, NH), 9.59 (brs, 1H, NH), 7.51 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.27 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.78 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 2H), 6.37 (d, *J* = 2.0 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 162.3, 155.3, 150.5, 136.3, 131.8, 130.5, 129.6, 128.8, 127.4, 123.7, 118.6, 115.4, 115.1, 114.3, 114.0, 109.4, 55.6, 55.5; LC/MS (ESI) *m/z* 541.2 $[M + H]^+$.

***N,N'*-(2-Phenethoxy-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22d).** Prepared as described in the experimental procedure of **22b** from intermediate **21d** to obtain the title compound as a colorless oil (64 mg, 29% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (brs, 1H, NH), 9.03 (brs, 1H, NH), 7.62 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.35-7.32 (m, 2H), 7.27-7.24 (m, 3H), 7.09 (d, *J* = 9.2 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.60-6.58 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.2, 151.7, 137.8, 136.5, 131.9, 130.9, 128.9, 128.8, 128.4, 126.4, 126.2, 121.5, 114.2, 113.8, 112.2, 104.8, 68.9, 55.6, 55.5, 34.3; LC/MS (ESI) m/z 569.2 $[M + H]^+$.

***N,N'*-(2-(3-Phenylpropoxy)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22e).** Prepared as described in the experimental procedure of **22b** from intermediate **21e** to obtain the title compound as a colorless oil (63 mg, 17% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (brs, 1H, NH), 9.10 (brs, 1H, NH), 7.63 (d, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.32-7.28 (m, 2H), 7.22-7.20 (m, 1H), 7.15 (d, *J* = 6.8 Hz, 2H), 7.08 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.92 (d, *J* = 7.2 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.54 (s, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.49 (t, *J* = 5.6 Hz, 2H), 2.55 (t, *J* = 7.2 Hz,

2H), 1.72-1.69 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 162.4, 162.1, 152.2, 141.4, 136.7, 132.3, 130.9, 128.9, 128.6, 128.3, 128.2, 126.9, 125.8, 121.1, 114.2, 113.8, 111.6, 104.1, 67.0, 55.6, 55.5, 31.1, 29.7; LC/MS (ESI) *m/z* 583.2 [M + H]$^+$.

***N,N'*-(2-((4-Methoxybenzyl)oxy)-1,4-phenylene)bis(4-methoxybenzenesulfonami-de) (22f).** Prepared as described in the experimental procedure of **22b** from intermediate **21f** to obtain the title compound as a pale yellow solid (79 mg, 52% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.07 (brs, 1H, NH), 9.20 (brs, 1H, NH), 7.55 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 4H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.69 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 162.4, 162.1, 158.8, 151.8, 136.5, 132.2, 130.9, 128.9, 128.74, 128.66, 128.2, 126.5, 121.3, 114.2, 113.8, 113.5, 111.5, 104.6, 69.0, 55.6, 55.5, 55.1; LC/MS (ESI) *m/z* 585.2 [M + H]$^+$.

***N,N'*-(2-((4-Fluorobenzyl)oxy)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22g).** Prepared as described in the procedure of **22b** from **21g** to obtain the title compound as a pale yellow solid (105 mg, 33% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.08 (brs, 1H, NH), 9.25 (brs, 1H, NH), 7.56 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.28-7.25 (m, 2H), 7.19-7.14 (m, 2H),7.05 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.55 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.72 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 162.4, 162.1, 151.8, 136.6, 132.51, 132.48, 132.2, 130.9, 129.2 ($J_{C,F}$ = 9 Hz), 128.9, 128.6, 127.0, 121.3, 114.9 ($J_{C,F}$ = 22 Hz), 114.2, 113.8, 111.8, 104.6, 68.5, 55.6, 55.5; LC/MS (ESI) *m/z* 573.2 [M + H]$^+$.

***N,N'*-(2-((4-Methylbenzyl)oxy)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22h).** Prepared as described in the procedure of **22b** from **21h** to obtain the title compound

as a white solid (29 mg, 9% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (brs, 1H, NH), 9.16 (brs, 1H, NH), 7.55 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 1.6 Hz, 1H), 6.54 (dd, *J* = 8.8, 1.6 Hz, 1H), 4.71 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 162.1, 151.8, 136.8, 136.5, 133.2, 132.5, 130.9, 128.8, 128.64, 128.61, 127.1, 126.5, 121.3, 114.2, 113.8, 111.7, 104.7, 69.2, 55.5, 55.4, 20.7; LC/MS (ESI) *m/z* 569.2 $[M + H]^+$.

***N,N'*-(2-(Naphthalen-2-yloxy)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22i).** Prepared as described in the procedure of **18d** from intermediate **21i** to obtain 2-(naphthalen-2-yloxy)benzene-1,4-diamine as a pale pink solid (191 mg, 97%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.47-7.43 (m, 1H), 7.40-7.36 (m, 1H), 7.27 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.32 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.23 (d, *J* = 2.4 Hz, 1H), 4.44 (brs, 2H, NH), 4.09 (brs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.5, 142.6, 140.3, 133.9, 130.2, 129.7, 129.3, 127.6, 126.8, 126.5, 124.2, 119.0, 117.5, 111.8, 110.9, 107.2; LC/MS (ESI) *m/z* 251.1 $[M + H]^+$. Prepared as described in the procedure of **18d** from 2-(naphthalen-2-yloxy)benzene-1,4-diamine to obtain the title compound as a pale purple solid (71 mg, 30%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (brs, 1H, NH), 9.69 (brs, 1H, NH), 7.92 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.54-7.45 (m, 6H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.87-6.83 (m, 3H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.74 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 162.3, 153.2, 150.6, 136.5,

133.5, 131.8, 130.6, 129.9, 129.7, 128.8, 127.68, 127.65, 127.0, 126.7, 125.0, 123.2, 119.6, 115.1, 114.3, 114.0, 113.9, 109.6, 55.7, 55.4; LC/MS (ESI) *m/z* 591.2 $[M + H]^+$.

***N,N'*-(2-(Naphthalen-2-ylmethoxy)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22j).** Prepared as described in the experimental procedure of **22b** from intermediate **21j** to obtain the title compound as a white solid (77 mg, 26% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (brs, 1H, NH), 9.32 (brs, 1H, NH), 7.96-7.94 (m, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.87-7.85 (m, 1H), 7.79 (s, 1H), 7.56-7.53 (m, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.41-7.37 (m, 3H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.77-6.75 (m, 3H), 6.51 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.94 (s, 2H), 3.72 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 162.1, 151.9, 136.6, 134.1, 132.7, 132.5, 132.3, 130.8, 128.8, 128.7, 127.8, 127.7, 127.6, 126.9, 126.3, 126.0, 125.6, 125.1, 121.3, 114.0, 113.8, 111.6, 104.4, 69.4, 55.5, 55.4; LC/MS (ESI) *m/z* 605.2 $[M + H]^+$.

***N,N'*-(2-(Naphthalen-1-ylmethoxy)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (22k).** Prepared as described in the experimental procedure of **22b** from intermediate **21k** to obtain the title compound as a white solid (99 mg, 62% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (brs, 1H, NH), 9.29 (brs, 1H, NH), 8.00-7.99 (m, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.62-7.57 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.48-7.42 (m, 3H), 7.30 (d, *J* = 6.8 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.79-6.77 (m, 3H), 6.57 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.21 (s, 2H), 3.78 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.0, 152.0, 136.5, 133.1, 132.1, 131.7, 130.9, 130.3, 128.8, 128.7, 128.5, 128.2, 126.4, 126.3, 125.9, 125.3, 125.2, 123.4, 121.6, 114.2, 113.8, 112.0, 105.2, 68.2, 55.6, 55.4; LC/MS (ESI) *m/z* 605.2 $[M + H]^+$.

***N,N'*-(2-([1,1'-Biphenyl]-4-yloxy)-1,4-phenylene)bis(4-methoxybenzenesulfonami-de) (22l).** Prepared as described in the experimental procedure of **18d** from intermediate **21l** to obtain 2-([1,1'-biphenyl]-4-yloxy)benzene-1,4-diamine as a pale pink solid (126 mg, 97%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, *J* = 8.0 Hz, 4H), 7.44 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.31 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 4.44 (brs, 2H, NH), 4.07 (brs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.4, 142.5, 140.3, 139.7, 134.1, 130.2, 128.9, 127.9, 126.9, 126.3, 117.4, 117.0, 111.8, 107.2; LC/MS (ESI) *m/z* 277.1 $[M + H]^+$. Prepared as described in the procedure of **18d** from 2-([1,1'-biphenyl]-4-yloxy)benzene-1,4-diamine to obtain the title compound as a pale yellow solid (71 mg, 32%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (brs, 1H, NH), 9.62 (brs, 1H, NH), 7.65 (d, *J* = 7.2 Hz, 2H), 7.54-7.47 (m, 8H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.83 (dd, *J* = 8.4, 2.4 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 6.42 (d, *J* = 2.4 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 162.3, 155.2, 150.1, 139.3, 136.4, 135.4, 131.8, 130.5, 129.0, 128.9, 128.8, 127.8, 127.5, 127.2, 126.4, 123.6, 118.6, 115.8, 114.3, 114.0, 110.2, 55.6, 55.5; LC/MS (ESI) *m/z* 617.2 $[M + H]^+$.

***N,N'*-(2-([1,1'-Biphenyl]-4-ylmethoxy)-1,4-phenylene)bis(4-methoxybenzenesulfo-namide) (22m).** Prepared as described in the experimental procedure of **22b** from intermediate **21k** to obtain the title compound as a white solid (72 mg, 24% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (brs, 1H, NH), 9.30 (brs, 1H, NH), 7.70 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.54-7.47 (m, 6H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.73 (s, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 4.83 (s, 2H), 3.75 (s, 3H), 3.71 (s, 3H); ^{13}C NMR

(100 MHz, DMSO-d_6) δ 162.3, 162.1, 151.8, 139.7, 139.4, 136.6, 135.6, 132.2, 130.9, 128.9, 128.8, 128.7, 127.6, 127.5, 126.7, 126.6, 126.4, 121.3, 114.2, 113.8, 111.6, 104.4, 68.9, 55.5; LC/MS (ESI) *m/z* 631.2 $[M + H]^+$.

Diethyl 2,2'-((2-(piperidin-1-yl)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23a). Prepared as described in the experimental procedure of **15a** from intermediate **22a** to obtain the title compound as a colorless oil (149 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 9.2 Hz, 2H), 6.94 (s, 1H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 1H), 4.73 (s, 2H), 4.34 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 2.82-2.80 (m, 4H), 1.62-1.57 (m, 4H), 1.51-1.55 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.1, 163.3, 150.8, 140.1, 133.1, 131.4, 130.7, 130.2, 130.1, 122.4, 122.1, 114.2, 114.0, 61.6, 61.2, 55.8, 55.7, 53.2, 52.8, 49.5, 26.7, 24.3, 14.3, 14.1; LC/MS (ESI) *m/z* 704.3 $[M + H]^+$.

Diethyl 2,2'-((2-(benzyloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23b). Prepared as described in the experimental procedure of **15a** from intermediate **22b** to obtain the title compound as a colorless oil (26 mg, 31%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.32-7.31 (m, 3H), 7.09-7.07 (m, 2H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 7.11 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.70 (s, 2H), 4.35 (s, 2H), 4.34 (s, 2H), 4.18-4.11 (m, 4H), 3.86 (s, 3H), 3.76 (s, 3H), 1.23 (t, *J* = 6.8 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.9, 163.4, 162.9, 155.1, 141.5, 135.7, 134.3, 131.9, 130.3, 130.2, 129.6, 128.6, 128.2, 127.1, 126.8, 119.3, 114.1, 113.8, 70.3, 61.7, 61.4, 55.7, 55.6, 52.6, 51.0, 14.2; LC/MS (ESI) *m/z* 727.2 $[M + H]^+$.

Diethyl 2,2'-((2-phenoxy-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23c). Prepared as described in the experimental procedure of **15a** from **22c** to obtain the title compound as a colorless oil (189 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.24-7.22 (m, 2H), 7.11 (t, *J* = 7.2 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.84-6.80 (m, 3H), 6.64 (d, *J* = 2.0 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 2H), 4.46 (s, 2H), 4.29 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 6.8 Hz, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 1.25 (t, *J* = 6.8 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.7, 163.3, 163.2, 154.9, 154.4, 141.2, 134.4, 131.8, 130.4, 130.1, 129.90, 129.88, 128.2, 124.5, 121.7, 119.4, 117.6, 114.2, 114.0, 61.7, 61.5, 55.8, 55.7, 52.4, 51.6, 14.3, 14.2; LC/MS (ESI) *m/z* 713.3 $[M + H]^+$.

Diethyl 2,2'-((2-phenethoxy-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23d). Prepared as described in the procedure of **15a** from **22d** to obtain the title compound as a colorless oil (96 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 9.2 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.32-7.28 (m, 2H), 7.25-7.21 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 2.4 Hz, 1H), 6.54 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.33 (s, 2H), 4.17-4.08 (m, 6H), 3.84 (s, 3H), 3.82 (s, 3H), 3.78 (t, *J* = 6.8 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.8, 163.3, 163.0, 155.0, 141.3, 137.4, 134.2, 132.2, 130.3, 130.1, 129.7, 128.9, 128.7, 126.9, 126.5, 119.1, 114.1, 113.79, 113.75, 68.9, 61.6, 61.2, 55.71, 55.69, 52.5, 50.7, 35.2, 14.2; LC/MS (ESI) *m/z* 741.2 $[M + H]^+$.

Diethyl 2,2'-((2-(3-phenylpropoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23e). Prepared as described in the experimental procedure of **15a** from **22e** to obtain the title compound as a colorless oil (31 mg, 57%); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.62 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.33-7.29 (m, 2H), 7.23-7.20 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.92-6.90 (m, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.54 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.35 (s, 4H), 4.19-4.12 (m, 4H), 3.85 (s, 3H), 3.75 (s, 3H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.54 (t, *J* = 7.6 Hz, 2H), 1.74-1.69 (m, 2H), 1.25-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.9, 163.4, 163.0, 155.4, 141.4, 141.2, 134.1, 132.2, 130.4, 130.2, 129.7, 128.7, 128.4, 126.6, 126.3, 118.9, 114.1, 113.9, 113.8, 67.6, 61.7, 61.4, 55.8, 55.6, 52.6, 50.9, 32.2, 30.6, 14.2; LC/MS (ESI) *m/z* 755.2 $[M + H]^+$.

Diethyl 2,2'-((2-((4-methoxybenzyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23f). Prepared as described in the experimental procedure of **15a** from intermediate **22f** to obtain the title compound as a colorless oil (107 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.43-7.38 (m, 3H), 6.95-6.93 (m, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.56 (s, 2H), 4.29 (s, 2H), 4.23 (s, 2H), 4.12-4.01 (m, 4H), 3.78 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 1.19-1.13 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.8, 163.3, 162.8, 159.5, 155.0, 141.3, 134.1, 131.7, 130.2, 130.0, 129.5, 128.8, 127.6, 126.7, 119.1, 114.0, 113.91, 113.85, 113.7, 70.0, 61.5, 61.2, 55.6, 55.5, 55.3, 52.5, 50.8, 14.1; LC/MS (ESI) *m/z* 757.2 $[M + H]^+$.

Diethyl 2,2'-((2-((4-fluorobenzyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23g). Prepared as described in the experimental procedure of **15a** from intermediate **22g** to obtain the title compound as a colorless oil (138 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 6.8 Hz, 1H), 7.07-6.99 (m, 5H), 6.92 (d, *J* = 7.2 Hz, 2H), 6.73 (d, *J* = 7.2 Hz, 2H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.70 (s, 2H), 4.35 (s, 2H), 4.31 (s, 2H), 4.16-4.13 (m,

4H), 3.86 (s, 3H), 3.78 (s, 3H), 1.23-1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.9, 163.4, 163.0, 155.1, 141.5, 134.3, 131.9, 131.6, 130.3, 130.1, 129.6, 129.1 ($J_{C,F}$ = 8 Hz), 126.9, 119.3, 115.5 ($J_{C,F}$ = 22 Hz), 114.3, 114.1, 113.8, 69.7, 61.7, 61.4, 55.8, 55.6, 52.6, 51.0, 50.9, 14.2; LC/MS (ESI) *m/z* 745.3 $[M + H]^+$.

Diethyl 2,2'-((2-((4-methylbenzyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23h). Prepared as described in the experimental procedure of **15a** from intermediate **22h** to obtain the title compound as a colorless oil (36 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 9.2 Hz, 2H), 7.51-7.47 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.58 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.66 (s, 2H), 4.35 (s, 2H), 4.33 (s, 2H), 4.19-4.12 (m, 4H), 3.86 (s, 3H), 3.78 (s, 3H), 2.37 (s, 3H), 1.25-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.9, 163.4, 162.9, 155.2, 141.4, 137.9, 134.3, 132.7, 131.9, 130.4, 130.2, 129.6, 129.2, 127.3, 126.8, 119.2, 114.1, 113.8, 70.3, 61.7, 61.4, 55.8, 55.6, 52.6, 50.9, 21.3, 14.2; LC/MS (ESI) *m/z* 741.3 $[M + H]^+$.

Diethyl 2,2'-((2-(naphthalen-2-yloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23i). Prepared as described in the experimental procedure of **15a** from intermediate **22i** to obtain the title compound as a colorless oil (129 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.66-7.60 (m, 4H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.50-7.42 (m, 3H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.78-6.71 (m, 5H), 4.51 (s, 2H), 4.28 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 3.62 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.6, 163.3, 163.1, 154.2, 152.7, 141.3, 134.5, 134.1, 131.7, 130.7, 130.5, 130.0, 129.9, 129.8, 128.2, 127.9,

127.4, 126.9, 125.4, 121.8, 119.6, 117.8, 115.1, 114.1, 114.0, 61.6, 61.5, 55.7, 55.5, 52.3, 51.8, 14.2, 14.0; LC/MS (ESI) *m/z* 761.2 $[M - H]^-$.

Diethyl 2,2'-((2-(naphthalen-2-ylmethoxy)-1,4-phenylene)bis(((4-methoxyphenyl) sulfonyl)azanediyl))diacetate (23j). Prepared as described in the experimental procedure of **15a** from intermediate **22j** to obtain the title compound as a white solid (89 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (m, 3H), 7.61-7.58 (m, 3H), 7.53-7.49 (m, 5H), 7.21 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.63-6.59 (m, 3H), 4.88 (s, 2H), 4.38 (s, 2H), 4.37 (s, 2H), 4.17-4.11 (m, 4H), 3.84 (s, 3H), 3.56 (s, 3H), 1.24-1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.9, 163.4, 162.9, 155.1, 141.5, 134.4, 133.22, 133.19, 133.1, 131.9, 130.4, 130.2, 129.6, 128.4, 128.2, 127.9, 126.9, 126.5, 126.4, 126.3, 124.9, 119.2, 114.2, 114.1, 113.8, 70.4, 61.7, 61.4, 55.7, 55.4, 52.6, 51.1, 14.23, 14.21; LC/MS (ESI) *m/z* 777.3 $[M + H]^+$.

Diethyl 2,2'-((2-(naphthalen-1-ylmethoxy)-1,4-phenylene)bis(((4-methoxyphenyl) sulfonyl)azanediyl))diacetate (23k). Prepared as described in the experimental procedure of **15a** from intermediate **22k** to obtain the title compound as a colorless oil (110 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.88 (m, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.80-7.78 (m, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.54-7.51 (m, 3H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 6.8 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.64 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.58 (d, *J* = 8.8 Hz, 2H), 5.13 (s, 2H), 4.38 (s, 2H), 4.26 (s, 2H), 4.19-4.08 (m, 4H), 3.83 (s, 3H), 3.64 (s, 3H), 1.26-1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.9, 163.4, 162.8, 155.2, 141.5, 134.4, 133.7, 131.7, 131.0, 130.9, 130.4, 130.2, 129.5, 129.0, 128.9, 126.9, 126.7, 126.1, 126.0, 125.3, 123.2, 119.5, 114.2, 114.1, 113.7, 68.7, 61.7, 61.3, 55.7, 55.4, 52.6, 51.1, 14.2; LC/MS (ESI) *m/z* 777.3 $[M + H]^+$.

Diethyl 2,2'-((2-([1,1'-biphenyl]-4-yloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23l). Prepared as described in the experimental procedure of **15a** from **22l** to obtain the title compound as a colorless oil (99 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.59-7.55 (m, 5H), 7.47-7.43 (m, 4H), 7.35 (t, *J* = 7.2 Hz, 1H), 6.89-6.86 (m, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.71 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 2H), 4.47 (s, 2H), 4.30 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 168.7, 163.3, 163.2, 154.4, 154.2, 141.2, 140.2, 137.5, 134.5, 131.7, 130.4, 130.1, 129.8, 129.0, 128.5, 128.4, 127.5, 127.0, 122.1, 119.4, 117.8, 114.2, 114.0, 61.7, 61.5, 55.7, 55.6, 52.4, 51.7, 14.2, 14.1; LC/MS (ESI) *m/z* 789.3 $[M + H]^+$.

Diethyl 2,2'-((2-([1,1'-biphenyl]-4-ylmethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (23m). Prepared as described in the experimental procedure of **15a** from intermediate **22m** to obtain the title compound as a white solid (86 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.61 (m, 4H), 7.57-7.45 (m, 7H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 6.59 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.77 (s, 2H), 4.37 (s, 4H), 4.19-4.13 (m, 4H), 3.85 (s, 3H), 3.72 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.9, 163.4, 163.0, 155.2, 141.5, 141.1, 140.7, 134.7, 134.4, 132.0, 130.4, 130.2, 129.7, 129.0, 127.7, 127.6, 127.3, 127.2, 126.9, 119.3, 114.20, 114.15, 113.8, 70.1, 61.7, 61.4, 55.8, 55.6, 52.6, 51.1, 14.2; LC/MS (ESI) *m/z* 803.3 $[M + H]^+$.

2,2'-((4'-Methyl-[1,1'-biphenyl]-2,5-diyl)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (24a). Prepared as described in the experimental procedure of **16a** from intermediate **23a** to obtain the title compound as a white solid (19 mg, 25%); ^{1}H NMR (400

MHz, DMSO-d_6) δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 9.2 Hz, 2H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.85 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 4.53 (s, 2H), 4.35 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 2.58-2.54 (m, 4H), 1.48-1.41 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 169.9, 162.8, 162.6, 149.7, 139.7, 132.2, 132.1, 131.1, 130.1, 129.6, 121.9, 120.3, 114.32, 114.27, 55.7, 52.5, 52.0, 49.3, 25.9, 23.6; LC/MS (ESI) *m/z* 646.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{29}H_{33}N_3O_{10}S_2$ [M - H]$^-$ 646.1535; found 646.1541.

2,2'-((2-(Benzyloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetic acid (24b). Prepared as described in the procedure of **16a** from **23b** to obtain the title compound as a white solid (21 mg, 46%); ^{1}H NMR (400 MHz, MeOD) δ 7.60 (d, *J* = 9.2 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.33-7.31 (m, 3H), 7.10-7.07 (m, 2H), 7.03 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 2.4 Hz, 1H), 6.82-6.78 (m, 3H), 4.59 (s, 2H), 4.41 (s, 2H), 4.31 (s, 2H), 3.87 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.7, 172.3, 165.0, 164.6, 156.3, 142.9, 137.3, 135.2, 132.8, 131.3, 130.5, 129.5, 129.1, 128.3, 127.7, 120.9, 115.2, 115.0, 114.4, 71.3, 56.3, 56.1, 30.7; LC/MS (ESI) *m/z* 669.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_{11}S_2$ [M - H]$^-$ 669.1218; found 669.1224.

2,2'-((2-Phenoxy-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diace-tic acid (24c). Prepared as described in the experimental procedure of **16a** from intermediate **23c** to obtain the title compound as a white solid (61 mg, 55%); ^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.25 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.99-6.96 (m, 3H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.51 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 2.0 Hz, 1H), 4.43 (s, 2H), 4.31 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.5, 172.0, 164.9, 164.8, 155.8, 155.5, 142.6,

135.5, 132.7, 131.2, 131.0, 130.9, 130.8, 128.9, 125.6, 122.9, 120.5, 117.5, 115.3, 115.2, 56.3, 56.2, 52.9, 52.4; LC/MS (ESI) *m/z* 655.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_2O_{11}S_2$ [M - H]$^-$ 655.1062; found 655.1068.

2,2'-((2-(Benzyloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetic acid (24d). Prepared as described in the procedure of **16a** from **23d** to obtain the title compound as a white solid (60 mg, 68%); ^{1}H NMR (400 MHz, MeOD) δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.30-7.26 (m, 3H), 7.21-7.20 (m, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 9.2 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 6.78 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 4.41 (s, 2H), 4.05 (s, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.62 (t, *J* = 6.8 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, MeOD) δ 172.7, 172.2, 164.9, 164.6, 156.1, 142.7, 138.9, 135.1, 133.0, 131.2, 130.7, 129.9, 129.6, 127.7, 127.4, 120.9, 115.2, 115.0, 113.9, 69.8, 56.31, 56.28, 53.2, 51.7, 35.9; LC/MS (ESI) *m/z* 683.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{32}N_2O_{11}S_2$ [M - H]$^-$ 683.1375; found 683.1382.

2,2'-((2-(3-Phenylpropoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azane diyl))diacetic acid (24e). Prepared as described in the procedure of **16a** from **23e** to obtain the title compound as a white solid (15 mg, 52%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (brs, 2H, CO_2H), 7.61 (d, *J* = 9.2 Hz, 2H), 7.49 (d, *J* = 9.2 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.32-7.28 (m, 2H), 7.22-7.18 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 9.2 Hz, 2H), 7.00 (d, *J* = 9.2 Hz, 2H), 6.81 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.58 (d, *J* = 2.0 Hz, 1H), 4.40 (s, 2H), 4.22 (s, 2H), 3.82 (s, 3H), 3.73 (s, 3H), 3.42-3.40 (m, 2H), 2.41 (t, *J* = 7.8 Hz, 2H), 1.52-1.47 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 170.0, 162.8, 162.5, 154.5, 141.2, 140.9, 133.4, 131.5, 129.9, 129.6, 129.1, 128.3, 128.2, 125.8, 125.3, 118.9, 114.3,

114.0, 111.3, 66.9, 55.7, 55.5, 51.8, 50.5, 31.3, 29.9; LC/MS (ESI) *m/z* 697.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{33}H_{34}N_2O_{11}S_2$ [M - H]$^-$ 697.1531; found 697.1525.

2,2'-((2-((4-Methoxybenzyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetic acid (24f). Prepared as described in the experimental procedure of **16a** from intermediate **23f** to obtain the title compound as a white solid (66 mg, 67%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.78 (brs, 2H, CO_2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 9.2 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 9.2 Hz, 2H), 6.83 (dd, *J* = 8.4, 2.4 Hz, 2H), 6.77 (d, *J* = 2.4 Hz, 1H), 4.51 (s, 2H), 4.41 (s, 2H), 4.16 (s, 2H), 3.84 (s, 3H), 3.80 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 170.2, 169.9, 162.8, 162.4, 158.9, 154.4, 140.9, 133.2, 131.2, 129.9, 129.6, 129.0, 128.7, 127.7, 125.6, 119.1, 114.3, 113.9, 113.6, 111.9, 69.3, 55.7, 55.5, 55.0, 51.8, 50.4; LC/MS (ESI) *m/z* 699.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{32}N_2O_{12}S_2$ [M - H]$^-$ 699.1324; found 699.1329.

2,2'-((2-((4-Fluorobenzyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)az-anediyl))diacetic acid (24g). Prepared as described in the experimental procedure of **16a** from intermediate **23g** to obtain the title compound as a white solid (56 mg, 44%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.82 (brs, 2H, CO_2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.17-7.08 (m, 6H), 6.86-6.83 (m, 3H), 6.78 (d, *J* = 2.0 Hz, 1H), 4.58 (s, 2H), 4.41 (s, 2H), 4.19 (s, 2H), 3.84 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 170.3, 170.0, 162.8, 162.4, 154.3, 141.0, 133.4, 132.1, 131.2, 129.9, 129.7, 129.1 ($J_{C,F}$ = 8 Hz), 129.0, 125.7, 119.3, 115.0 ($J_{C,F}$ = 21 Hz), 114.3, 113.9, 111.9, 68.8, 55.7, 55.5, 51.8, 50.6; LC/MS (ESI) *m/z* 689.2 [M + H]$^+$; HRMS (ESI) *m/z* calcd for $C_{31}H_{29}FN_2O_{11}S_2$ [M + H]$^+$ 689.1270; found 689.1281.

2,2'-((2-((4-Methylbenzyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)az-anediyl))diacetic acid (24h). Prepared as described in the experimental procedure of **16a** from intermediate **23h** to obtain the title compound as a white solid (29 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 9.2 Hz, 2H), 7.47-7.43 (m, 3H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.98-6.95 (m, 3H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.59 (dd, *J* = 8.4, 2.4 Hz, 2H), 4.62 (s, 2H), 4.33 (s, 2H), 4.28 (s, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 163.4, 163.1, 155.1, 141.4, 138.1, 134.0, 132.5, 131.3, 130.2, 129.7, 129.3, 127.5, 127.4, 126.6, 119.3, 114.2, 113.9, 113.8, 70.4, 55.8, 55.6, 52.2, 51.0, 21.3; LC/MS (ESI) *m/z* 683.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{32}N_2O_{11}S_2$ [M - H]$^-$ 683.1375; found 683.1381.

2,2'-((2-(Naphthalen-2-yloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)aza-nediyl))diacetic acid (24i). Prepared as described in the experimental procedure of **16a** from intermediate **23h** to obtain the title compound as a white solid (32 mg, 27%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (brs, 2H, CO_2H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.57-7.48 (m, 3H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 2.4 Hz, 1H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.76 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 4.38 (s, 2H), 4.31 (s, 2H), 3.75 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 169.9, 162.64, 162.57, 153.4, 151.9, 140.8, 133.9, 133.5, 131.1, 130.2, 129.9, 129.8, 129.3, 127.7, 127.1, 126.9, 126.8, 125.3, 120.9, 119.5, 115.3, 115.0, 114.2, 114.1, 55.7, 55.5, 51.6, 51.3; LC/MS (ESI) *m/z* 705.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{34}H_{30}N_2O_{11}S_2$ [M - H]$^-$ 705.1218; found 705.1224.

2,2'-((2-(Naphthalen-2-ylmethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetic acid (24j). Prepared as described in the experimental procedure of **16a** from intermediate **23j** to obtain the title compound as a white solid (59 mg, 67%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95-7.92 (m, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.57-7.53 (m, 3H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 9.2 Hz, 1H), 7.21 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.05 (d, *J* = 9.2 Hz, 2H), 6.87-6.85 (m, 2H), 6.76 (d, *J* = 9.2 Hz, 2H), 4.77 (s, 2H), 4.43 (s, 2H), 4.26 (s, 2H), 3.82 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 170.0, 162.8, 162.3, 154.5, 141.0, 133.5, 132.6, 132.5, 131.3, 129.9, 129.7, 129.0, 127.9, 127.6, 126.3, 126.2, 125.7, 125.5, 124.9, 114.3, 113.9, 111.9, 69.6, 55.8, 55.3, 51.8, 50.6; LC/MS (ESI) *m/z* 719.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{35}H_{32}N_2O_{11}S_2$ [M - H]$^-$ 719.1375; found 719.1382.

2,2'-((2-(Naphthalen-1-ylmethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetic acid (24k). Prepared as described in the experimental procedure of **16a** from **23k** to obtain the title compound as a white solid (84 mg, 82%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (brs, 2H, CO_2H), 7.99-7.97 (m, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.79-7.77 (m, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.58-7.55 (m, 2H), 7.47-7.43 (m, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.95-6.93 (m, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 5.03 (s, 2H), 4.46 (s, 2H), 4.15 (s, 2H), 3.80 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 169.9, 162.8, 162.3, 154.5, 141.0, 133.3, 133.0, 131.22, 131.15, 130.1, 129.9, 129.7, 128.9, 128.5, 128.2, 126.3, 125.9, 125.8, 125.2, 125.0, 123.1, 120.1, 114.3, 113.8, 112.1, 67.8, 55.7, 55.3, 51.8, 50.6; LC/MS (ESI) *m/z* 719.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{35}H_{32}N_2O_{11}S_2$ [M - H]$^-$ 719.1375; found 719.1382.

2,2'-((2-([1,1'-Biphenyl]-4-yloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)-azanediyl))diacetic acid (24l). Prepared as described in the experimental procedure of **16a** from intermediate **23l** to obtain the title compound as a white solid (68 mg, 74%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (brs, 2H, CO_2H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.58-7.47 (m, 9H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.03-7.01 (m, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 2H), 6.45 (d, *J* = 2.0 Hz, 1H), 4.34 (s, 2H), 4.33 (s, 2H), 3.75 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 169.9, 162.7, 162.6, 153.8, 153.2, 140.7, 139.2, 136.0, 133.8, 131.1, 129.8, 129.4, 129.2, 129.0, 127.9, 127.3, 127.2, 126.4, 121.7, 119.2, 115.6, 114.4, 114.2, 55.60, 55.57, 51.7, 51.3; LC/MS (ESI) *m/z* 731.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{36}H_{32}N_2O_{11}S_2$ [M - H]$^-$ 731.1375; found 731.1381.

2,2'-((2-([1,1'-Biphenyl]-4-ylmethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulf-onyl)azanediyl))diacetic acid (24m). Prepared as described in the experimental procedure of **16a** from intermediate **23m** to obtain the title compound as a white solid (65 mg, 81%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (d, *J* = 7.6 Hz, 2H), 7.63-7.61 (m, 4H), 7.51-7.37 (m, 6H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.87-6.84 (m, 3H), 6.81 (d, *J* = 2.4 Hz, 1H), 4.65 (s, 2H), 4.42 (s, 2H), 4.23 (s, 2H), 3.82 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 170.0, 162.8, 162.4, 154.4, 141.0, 139.7, 139.5, 135.0, 133.4, 131.2, 129.9, 129.7, 129.0, 127.5, 127.4, 126.6, 126.5, 125.6, 119.3, 114.3, 114.0, 111.9, 69.2, 55.7, 55.4, 51.8, 50.6; LC/MS (ESI) *m/z* 745.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{37}H_{34}N_2O_{11}S_2$ [M - H]$^-$ 745.1531; found 745.1538.

***N*-Benzyl-5-bromo-*N*-methyl-2-nitroaniline (25).** Prepared as described in the procedure of **21b** from 4-bromo-2-fluoro-1-nitrobenzene and *N*-benzylmethylamine to obtain the title compound as a yellow solid (458 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d,

J = 8.4 Hz, 1H), 7.36 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.37 (s, 2H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 136.5, 128.9, 127.94, 127.89, 127.8, 127.7, 122.9, 122.0, 58.6, 40.3; LC/MS (ESI) *m/z* 321.1 [M(^{79}Br) + H]$^+$, 323.0 [M(^{81}Br) + H]$^+$.

***N*-Benzyl-*N*-methyl-6-nitrobenzene-1,3-diamine (26).** To a solution of **25** (400 mg, 1.25 mmol) in ammonium hydroxide solution (1.9 mL) and dimethyl sulfoxide (0.7 mL) were added copper(I) iodide (24 mg, 0.12 mmol) and *N,N'*-dimethylethyleneamine (17 mg, 0.19 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was stirred at 130 ℃ for 3 hours. After the reaction was completed the crude mixture was cooled to room temperature, added to water and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a pale yellow solid (160 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 1H), 7.28-7.26 (m, 2H), 7.23-7.20 (m, 3H), 6.11-6.08 (m, 2H), 4.28 (s, 2H), 4.14 (brs, 2H, NH), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 149.8, 137.6, 131.7, 130.3, 128.7, 127.9, 127.4, 106.4, 103.1, 59.0, 40.4; LC/MS (ESI) *m/z* 258.2 [M + H]$^+$.

***N,N'*-(2-(Benzyl(methyl)amino)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (27).** Prepared as described in the experimental procedure of **22b** from intermediate **26** to obtain the title compound as a pale yellow solid (120 mg, 65% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (brs, 1H, NH), 7.65(d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.30-7.25 (m, 3H), 7.18-7.13 (m, 3H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.70 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.81 (s, 3H),

3.80 (s, 3H), 3.67 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.21, 163.16, 142.8, 137.1, 132.8, 131.2, 131.0, 130.4, 129.5, 129.3, 128.8, 128.6, 127.6, 120.1, 118.6, 117.6, 114.2, 114.1, 61.1, 55.6, 42.7; LC/MS (ESI) *m/z* 568.2 $[M + H]^+$.

Diethyl 2,2'-((2-(benzyl(methyl)amino)-1,4-phenylene)bis(((4-methoxyphenyl) sulfonyl)azanediyl))diacetate (28). Prepared as described in the experimental procedure of **15a** from intermediate **27** to obtain the title compound as a colorless oil (87 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.34-7.25 (m, 3H), 7.22-7.20 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.89-6.86 (m, 3H), 6.74 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.71 (s, 2H), 4.33 (s, 2H), 4.19-7.12 (m, 2H), 4.11 (s, 2H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.56 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.9, 163.2, 162.6, 150.1, 140.1, 137.6, 132.6, 132.3, 131.2, 130.7, 130.2, 130.1, 128.9, 128.4, 127.3, 122.3, 121.8, 114.04, 113.95, 61.5, 61.2, 59.9, 55.7, 53.5, 52.7, 40.1, 14.2, 14.0; LC/MS (ESI) *m/z* 740.2 $[M + H]^+$.

2,2'-((2-(Benzyl(methyl)amino)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)a-zanediyl))diacetic acid (29). Prepared as described in the procedure of **16a** from **28** to obtain the title compound as a white solid (53 mg, 66%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (brs, 2H, CO_2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.34-7.28 (m, 3H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.72 (s, 1H), 4.53 (s, 2H), 4.33 (s, 2H), 4.02 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 173.4, 171.9, 165.3, 165.0, 147.3, 142.8, 134.9, 134.1, 131.9, 131.5, 131.3, 131.1, 131.0, 129.8, 127.0, 123.8, 115.5, 115.3, 114.4, 62.8, 56.33, 56.31, 53.2, 52.8, 42.1; LC/MS (ESI) m/z 682.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{33}N_3O_{10}S_2$ $[M - H]^-$ 682.1535; found 682.1525.

(2-Bromo-5-nitrophenyl)methanol (30). To a solution of 2-bromo-5-nitrobenzoic acid (500 mg, 2.03 mmol) in tetrahydrofuran (5 mL) was added borane tetrahydrofuran complex solution (1.0 M in THF, 4 ml, 4.06 mmol) at room temperature. The reaction mixture was stirred at 60 ℃ for 1 hour. After the reaction was completed, the crude mixture was added to methanol and water, and then concentrated under reduced pressure. The aqueous solution was acidified with 6 N HCl until the pH reached around 1 and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the product as a pale yellow solid (478 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 2.8 Hz, 1H), 8.02 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 4.83 (d, *J* = 5.6 Hz, 2H), 2.14 (t, *J* = 5.6 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 142.1, 133.5, 128.9, 123.5, 123.1, 64.2.

1-Bromo-4-nitro-2-(phenoxymethyl)benzene (31). To a solution of **30** (478 mg, 2.06 mmol) in dichloromethane (10 mL) was added triethylamine (250 mg, 2.47 mmol) at room temperature, and methanesulfonyl chloride (248 mg, 2.16 mmol) was added at 0 ℃. The reaction mixture was stirred at 0 ℃ for 5 minutes. Tthe crude mixture was added to water and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2-bromo-5-nitrobenzyl methanesulfonate as a pale yellow oil. The resulting compound was used for the next reaction without further purification. To a solution of phenol (233 mg, 2.47 mmol) in *N*,*N*-dimethylformamide (3 mL) was added sodium hydride (60% dispersion in mineral oil, 124 mg, 3.09 mmol) at 0 ℃. After stirring at 0 ℃ for 5 minutes, 2-bromo-5-nitrobenzyl methanesulfonate (639 mg, 2.06 mmol) was added at 0 ℃. The reaction mixture was stirred at room temperature for 5 hours. After the reaction was completed, the crude mixture was added to water and

extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-40% ethyl acetate/hexane) to give the product as a pale yellow solid (267 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.8 Hz, 1H), 8.05 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.34 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.05-7.02 (m, 3H).

4-Nitro-2-(phenoxymethyl)aniline (32). To a solution of **31** (88 mg, 0.29 mmol) in toluene (1 mL) were added diphenylmethanimine (124 mg, 0.69 mmol), Tris(dibenzyl-ideneacetone)dipalladium(0) (1 mg, 0.0014 mmol), 2,2`-bis (diphenylphosphino)-1,1`-binaphthalene (3 mg, 0.0043 mmol) and sodium *tert*-butoxide (77 mg, 0.80 mmol) at room temperature. The reaction mixture was stirred at 80 ℃ for overnight. After the reaction was completed, the crude mixture was cooled to room temperature, filtered off through celite, and then concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-20% ethyl acetate/hexane) to give *N*-(4-nitro-2-(phenoxymethyl) phenyl)-1,1-diphenylmethanimine as a pale yellow solid. The resulting compound was used for the next reaction. To a solution of *N*-(4-nitro-2-(phenoxymethyl) phenyl)-1,1-diphenylmethanimine (109 mg, 0.27 mmol) in methanol (1.3 mL) were added sodium acetate (37 mg, 0.45 mmol) and hydroxylamine hydrochloride (32 mg, 0.45 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was concentrated under reduced pressure, added to sat. $NaHCO_3$, and then extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-50% ethyl acetate/hexane) to give the product as a yellow solid (18 mg, 26%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.4 Hz, 1H), 8.08 (dd, *J* =

8.8, 2.4 Hz, 1H), 7.35-7.30 (m, 2H), 7.04-6.98 (m, 3H), 6.68 (d, *J* = 8.8 Hz, 1H), 5.08 (s, 2H), 4.87 (brs, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 152.4, 138.9, 129.9, 126.7, 126.4, 122.1, 120.0, 115.2, 114.9, 68.8; LC/MS (ESI) *m/z* 245.1 $[M + H]^+$.

***N,N'*-(2-(Phenoxymethyl)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (33).** Prepared as described in the experimental procedure of **22b** from intermediate **32** to obtain the title compound as a pale yellow solid (52 mg, 53% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (brs, 1H, NH), 9.49 (brs, 1H, NH), 7.55 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.27 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.98-6.93 (m, 3H), 6.87 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.75-6.73 (m, 3H), 4.84 (s, 2H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.43, 162.37, 157.8, 136.6, 135.1, 131.4, 130.9, 129.5, 129.2, 128.9, 128.8, 127.9, 120.8, 119.0, 118.4, 114.5, 114.28, 114.26, 64.8, 55.6; LC/MS (ESI) *m/z* 553.1 $[M - H]^-$.

Diethyl 2,2'-((2-(phenoxymethyl)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetate (34). Prepared as described in the experimental procedure of **15a** from intermediate **33** to obtain the title compound as a colorless oil (66 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.34 (s, 1H), 7.30-7.26 (m, 2H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.98-6.91 (m, 5H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.46-5.41 (m, 1H), 5.14-5.09 (m, 1H), 4.35 (s, 4H), 4.16-4.07 (m, 4H), 3.87 (s, 3H), 3.81 (s, 3H), 1.27-1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 168.4, 163.6, 163.3, 158.6, 140.8, 140.5, 137.0, 130.4, 130.3, 130.1, 129.6, 129.43, 129.35, 128.6, 127.7, 121.1, 115.0, 114.2, 114.1, 66.0, 61.70, 61.65, 55.8, 55.7, 53.3, 52.5, 14.2, 14.1; LC/MS (ESI) *m/z* 727.3 $[M + H]^+$.

2,2'-((2-(Phenoxymethyl)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanedi-yl))diacetic acid (35). Prepared as described in the experimental procedure of **16a** from intermediate **34** to obtain the title compound as a white solid (44 mg, 72%); ^{1}H NMR (400 MHz, MeOD) δ 7.53 (d, *J* = 8.8 Hz, 4H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.26 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.09 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.95-6.91 (m, 5H), 6.77 (d, *J* = 8.8 Hz, 1H), 5.51-5.48 (m, 1H), 5.16-5.13 (m, 1H), 4.44-4.40 (m, 1H), 4.37 (s, 2H), 4.16-4.12 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.1, 171.7, 165.1, 164.8, 160.0, 142.1, 141.6, 138.1, 131.4, 131.2, 131.1, 130.5, 130.4, 128.6, 128.2, 122.0, 116.0, 115.9, 115.4, 115.2, 67.1, 56.29, 56.25, 54.1, 53.1; LC/MS (ESI) *m/z* 699.1 [M - H]$^{-}$; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_{11}S_2$ [M - H]$^{-}$ 669.1218; found 669.1225.

4-Phenoxybenzaldehyde (36). To a solution of phenol (1.1 g, 12.09 mmol) in *N*,*N*-dimethylformamide (12 mL) were added potassium carbonate (2.2 g, 16.11 mmol) and 4-fluorobenzaldehyde (1.0 g, 8.06 mmol) at room temperature. The reaction mixture was stirred at 90 ºC for 6 hours. After the reaction was completed, the crude mixture was cooled to room temperature, added to water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-10% ethyl acetate/hexane) to give the product as a colorless oil (945 mg, 59%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.44-7.40 (m, 2H), 7.25-7.20 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 163.4, 155.3, 132.1, 131.4, 130.3, 125.1, 120.6, 117.7; LC/MS (ESI) *m/z* 199.1 [M + H]$^{+}$.

(4-Phenoxyphenyl)methanol (37). To a solution of **36** (945 mg, 4.77 mmol) in methanol (20 mL) was added sodium borohydride (180 mg, 4.77 mmol) at 0 ºC. After stirring at 0 ºC

for 10 minutes, the reaction mixture was warmed to room temperature and stirred for 1 hour. After the reaction was completed, the crude mixture was added to water and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the product as a white solid. (539 mg, 57%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39-7.32 (m, 4H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.99-6.96 (m, 4H), 5.19 (t, *J* = 5.6 Hz, 1H, OH), 4.48 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.0, 155.2, 137.8, 130.0, 128.2, 123.2, 118.5, 118.2, 62.4.

1-(Chloromethyl)-4-phenoxybenzene (38). To a solution of **37** (302 mg, 1.51 mmol) in dichloromethane (6 mL) was added thionyl chloride (1.8 g, 15.08 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 hours. The crude mixture was added to sat. $NaHCO_3$ until the pH reached around 7 and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-10% ethyl acetate/hexane) to give the product as a white solid (309 mg, 94%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.40 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 2H), 4.75 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.8, 156.2, 132.5, 130.7, 130.1, 123.7, 118.9, 118.4, 45.8.

Diethyl 2,2'-((2-hydroxy-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (39). Intermediate **23b** (861 mg, 1.18 mmol) was added TFA (5 mL) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30%

ethyl acetate/hexane) to give the product as a beige solid (285 mg, 38%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (brs, 1H, OH), 7.64 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 4H), 6.76 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.70-6.69 (m, 2H), 4.33 (s, 4H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 168.8, 163.7, 163.3, 156.2, 142.4, 130.4, 130.24, 130.16, 130.1, 129.7, 125.6, 120.2, 116.2, 114.3, 114.1, 62.9, 61.7, 55.8, 55.7, 53.3, 52.4, 14.2, 14.1; LC/MS (ESI) *m/z* 637.2 $[M + H]^+$.

Diethyl 2,2'-((2-(pyridin-3-ylmethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (40a). Prepared as described in the experimental procedure of **16a** from intermediate **39** and 3-(chloromethyl)pyridine hydrochloride to obtain the title compound as a pale yellow solid (30 mg, 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 9.2 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.47-7.45 (m, 2H), 7.31-7.26 (m, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.95-6.90 (m, 3H), 6.73 (d, *J* = 9.2 Hz, 2H), 6.59 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.75 (s, 2H), 4.36 (s, 2H), 4.31 (s, 2H), 4.28-4.11 (m, 4H), 3.87 (s, 3H), 3.79 (s, 3H), 1.26-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.9, 163.4, 163.0, 154.9, 149.7, 148.6, 141.6, 138.3, 135.0, 134.4, 131.9, 130.9, 130.2, 129.6, 127.0, 119.6, 114.5, 114.3, 114.2, 113.8, 68.0, 61.7, 61.5, 55.8, 55.7, 52.5, 51.0, 14.2; LC/MS (ESI) *m/z* 728.2 $[M + H]^+$.

Diethyl 2,2'-((2-((4-phenoxybenzyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (40b). To a solution of **39** (60 mg, 0.09 mmol) in *N*,*N*-dimethylformamide (0.5 mL) were added potassium carbonate (26 mg, 0.19 mmol) and **38** (41 mg, 0.19 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added

to water, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-50% ethyl acetate/hexane) to give the product as a colorless oil (47 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.06-7.03 (m, 5H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.57 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.69 (s, 2H), 4.36 (s, 2H), 4.32 (s, 2H), 4.19-4.11 (m, 4H), 3.86 (s, 3H), 3.76 (s, 3H), 1.26-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.9, 163.3, 162.9, 157.4, 156.9, 155.0, 141.4, 134.3, 131.9, 130.3, 130.2, 130.1, 130.0, 129.6, 128.8, 126.8, 123.7, 119.3, 119.1, 118.6, 114.2, 114.1, 113.8, 69.9, 61.7, 61.4, 55.7, 55.6, 52.5, 50.9, 14.2; LC/MS (ESI) *m/z* 819.2 $[M + H]^+$.

2,2'-((2-(Pyridin-3-ylmethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)az-anediyl))diacetic acid (41a). Prepared as described in the experimental procedure of **16a** from intermediate **40a** to obtain the title compound as a white solid (7 mg, 45%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (brs, 2H, CO_2H), 8.54 (d, *J* = 4.4 Hz, 1H), 8.33 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.40-7.35 (m, 4H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.87-6.80 (m, 4H), 4.67 (s, 2H), 4.43 (s, 2H), 4.21 (s, 2H), 3.85 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 169.8, 162.8, 162.3, 154.3, 149.0, 148.2, 141.0, 134.7, 133.3, 131.4, 131.1, 129.9, 129.6, 128.9, 125.7, 123.3, 119.3, 114.3, 113.8, 111.9, 67.2, 55.7, 55.4, 51.7, 50.6; LC/MS (ESI) *m/z* 670.0 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{29}N_3O_{11}S_2$ $[M - H]^-$ 670.1171; found 670.1167.

2,2'-((2-((4-Phenoxybenzyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetic acid (41b). Prepared as described in the experimental procedure of

16a from intermediate **40b** to obtain the title compound as a white solid (15 mg, 33%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.40-7.34 (m, 3H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.02-7.00 (m, 2H), 6.94-6.92(m, 5H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 7.6 Hz, 1H), 4.65 (s, 2H), 4.42 (s, 2H), 4.39 (s, 2H), 3.86 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 164.5, 158.7, 158.5, 156.3, 142.9, 135.2, 132.8, 132.1, 131.3, 131.0, 130.6, 130.1, 127.8, 124.6, 120.7, 120.1, 120.0, 119.5, 115.2, 115.0, 114.5, 70.8, 56.3, 56.1, 53.2, 51.9; LC/MS (ESI) *m/z* 761.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{38}H_{36}N_2O_{12}S_2$ [M - H]$^-$ 761.1480; found 761.1476.

***N,N'*-(2-(Benzyloxy)-1,4-phenylene)bis(4-methylbenzenesulfonamide) (42a).** Prepared as described in the experimental procedure of **14a** from 2-(benzyloxy)benzene -1,4-diamine and 4-methylbenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (29 mg, 24%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (brs, 1H, NH), 9.30 (brs, 1H, NH), 7.49 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.35-7.32 (m, 3H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.19-7.14 (m, 4H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.54-6.52 (m, 1H), 4.71 (s, 2H), 2.34 (s, 3H), 3.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.0, 143.2, 142.6, 137.7, 136.5, 136.4, 136.3, 129.5, 129.1, 128.1, 127.6, 127.0, 126.9, 126.7, 126.5, 121.2, 111.8, 104.7, 69.3, 20.9; LC/MS (ESI) *m/z* 523.1 [M + H]$^+$..

***N,N'*-(2-(Benzyloxy)-1,4-phenylene)bis(4-fluorobenzenesulfonamide) (42b).** Prepared as described in the experimental procedure of **14a** from 2-(benzyloxy)benzene -1,4-diamine and 4-fluorobenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (67 mg, 53%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (brs, 1H, NH), 9.54 (brs, 1H, NH), 7.65 (dd, *J* = 8.0, 6.0 Hz, 2H), 7.59 (dd, *J* = 8.0, 6.0 Hz, 2H), 7.35-7.30 (m, 5H), 7.20-7.15 (m, 4H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.57 (dd, *J* = 8.8, 2.4 Hz,

1H), 6.75 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.4 ($J_{C,F}$ = 21 Hz), 162.9 ($J_{C,F}$ = 19 Hz), 152.2, 136.9, 136.6, 136.2, 135.5, 129.8 ($J_{C,F}$ = 10 Hz), 129.5 ($J_{C,F}$ = 10 Hz), 128.2, 127.7, 126.9, 121.1, 116.4 ($J_{C,F}$ = 23 Hz), 115.8 ($J_{C,F}$ = 24 Hz), 112.1, 104.8, 69.2; LC/MS (ESI) *m/z* 531.2 [M + H]$^+$.

***N,N'*-(2-(Benzyloxy)-1,4-phenylene)bis(4-bromobenzenesulfonamide) (42c).** Prepared as described in the procedure of **14a** from 2-(benzyloxy)benzene -1,4-diamine and 4-bromobenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (51 mg, 15%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (brs, 1H, NH), 9.63 (brs, 1H, NH), 7.71 (d, *J* = 6.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.34-7.30 (m, 3H), 7.15-7.10 (m, 3H), 6.66 (s, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.3, 139.8, 138.4, 136.6, 136.2, 132.3, 131.8, 128.6, 128.5, 128.2, 127.9, 127.7, 126.93, 126.85, 126.3, 121.0, 112.2, 104.9, 69.3; LC/MS (ESI) *m/z* 652.9 [M(2^{79}Br,) + H]$^+$, 654.9 [M(^{79}Br, ^{81}Br) + H]$^+$, 656.9 [M(2^{81}Br) + H]$^+$.

***N,N'*-(2-(Benzyloxy)-1,4-phenylene)bis(4-(trifluoromethyl)benzenesulfonamide) (42d).** Prepared as described in the procedure of **14a** from 2-(benzyloxy)benzene -1,4-diamine and 4-trifluoromethylbenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (61 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.36-7.33 (m, 3H), 7.10-7.07 (m, 3H), 7.00 (s, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 6.50 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 142.7, 142.3, 135.2, 134.3, 129.1, 128.9, 128.8, 127.8, 127.7, 127.6, 126.33, 126.29, 126.1, 126.0, 123.7, 123.0, 114.3, 106.3, 70.9; LC/MS (ESI) *m/z* 631.3 [M + H]$^+$.

***N,N'*-(2-(Benzyloxy)-1,4-phenylene)bis(([1,1'-biphenyl]-4-sulfonamide)) (42e).** Prepared as described in the experimental procedure of **14a** from 2-(benzyloxy)benzene -1,4-diamine and biphenyl-4-sulfonyl chloride to obtain the title compound as a white solid (55 mg, 21%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (brs, 1H, NH), 9.52 (brs, 1H, NH), 7.78 (d, *J* = 7.2 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.60-7.58 (m, 4H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.50-7.41 (m, 6H), 7.27-7.23 (m, 3H), 7.17-7.11 (m, 3H), 6.71 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 4.71 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.3, 144.2, 143.8, 139.3, 138.4, 138.2, 138.0, 136.7, 136.2, 129.1, 129.0, 128.6, 128.4, 128.1, 127.5, 127.3, 127.2, 127.1, 127.0, 126.93, 126.87, 126.8, 121.1, 112.0, 104.8, 69.3; LC/MS (ESI) *m/z* 647.2 $[M + H]^+$.

***N,N'*-(2-(Benzyloxy)-1,4-phenylene)bis(3-methylbenzenesulfonamide) (42f).** Prepared as described in the experimental procedure of **14a** from 2-(benzyloxy)benzene -1,4-diamine and 3-methylbenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (49 mg, 33%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.42 (s, 1H), 7.39-7.33 (m, 4H), 7.31-7.27 (m, 5H), 7.22-7.18 (m, 1H), 7.09-7.07 (m, 2H), 6.67 (d, *J* = 2.4 Hz, 1H), 6.56 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.72 (s, 2H), 2.33 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 141.3, 140.8, 140.5, 140.3, 138.0, 137.7, 134.6, 134.4, 129.9, 129.6, 128.9, 128.42, 128.38, 128.1, 127.6, 125.4, 125.3, 123.5, 114.2, 106.8, 71.2, 21.33, 21.29; LC/MS (ESI) *m/z* 523.2 $[M + H]^+$.

***N,N'*-(2-((4-Fluorobenzyl)oxy)-1,4-phenylene)bis(4-methylbenzenesulfonamide) (42g).** Prepared as described in the procedure of **14a** from 2-((4-fluorobenzyl)-oxy)benzene-1,4-diamine and 4-methylbenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (96 mg, 27%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13

(brs, 1H, NH), 9.31 (brs, 1H, NH), 7.51 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.26-7.23 (m, 2H), 7.19-7.13 (m, 4H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.54 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.68 (s, 2H), 2.34 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6 ($J_{C,F}$ = 242 Hz), 151.9, 143.2, 142.6, 137.6, 136.6, 136.4, 132.5 ($J_{C,F}$ = 3 Hz), 129.5, 129.2 ($J_{C,F}$ = 8 Hz), 129.1, 127.1, 126.7, 126.5, 121.2, 114.9 ($J_{C,F}$ = 21 Hz), 111.9, 104.7, 68.5, 20.92, 20.90; LC/MS (ESI) *m/z* 541.2 $[M + H]^+$.

***N,N'*-(2-((4-Fluorobenzyl)oxy)-1,4-phenylene)bis(2,4,6-trimethylbenzenesulfonamide) (42h).** Prepared as described in the experimental procedure of **14a** from 2-((4-fluorobenzyl)-oxy)benzene-1,4-diamine and 2,4,6-trimethylbenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (116 mg, 50%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (brs, 1H, NH), 9.14 (brs, 1H, NH), 7.19-7.14 (m, 4H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.97 (s, 2H), 6.69 (s, 2H), 6.48 (dd, *J* = 8.4, 2.0 Hz, 2H), 6.44 (d, *J* = 2.0 Hz, 1H), 4.50 (s, 2H), 2.45 (s, 6H), 2.24 (s, 3H), 2.18 (s, 3H), 2.12 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 153.1, 142.0, 141.1, 138.7, 138.6, 136.9, 134.7, 133.4, 132.3, 131.7, 131.1, 129.2 ($J_{C,F}$ = 9 Hz), 128.9, 120.2, 114.8 ($J_{C,F}$ = 21 Hz), 111.4, 104.2, 68.6, 22.5, 22.4, 20.39, 20.35; LC/MS (ESI) *m/z* 597.3 $[M + H]^+$.

***N,N'*-(2-((4-Methylbenzyl)oxy)-1,4-phenylene)bis(4-methylbenzenesulfonamide) (42i).** Prepared as described in the experimental procedure of **14a** from 2-((4-methylbenzyl)oxy)benzene-1,4-diamine and 4-methylbenzenesulfonyl chloride to obtain the title compound as a pale brown solid (57 mg, 61%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (brs, 1H, NH), 9.29 (brs, 1H, NH), 7.50 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.67 (s, 1H), 6.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.67 (s, 2H),

2.34 (s, 3H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.9, 143.2, 142.6, 137.7, 136.8, 136.5, 136.4, 133.2, 129.5, 129.1, 128.7, 127.1, 126.69, 126.66, 126.5, 121.3, 111.7, 104.7, 69.2, 20.9, 20.8; LC/MS (ESI) *m/z* 537.3 $[M + H]^+$.

***N,N'*-(2-(Naphthalen-2-ylmethoxy)-1,4-phenylene)bis(4-methylbenzenesulfonam-ide) (42j).** Prepared as described in the experimental procedure of **14a** from 2-(naphthalen-2-ylmethoxy)benzene-1,4-diamine and 4-methylbenzenesulfonyl chloride to obtain the title compound as a white solid (273 mg, 65%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (brs, 1H, NH), 9.40 (brs, 1H, NH), 7.97-7.95 (m, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.87-7.84 (m, 1H), 7.76 (s, 1H), 7.57-7.54 (m, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.12-7.04 (m, 5H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.89 (s, 2H), 2.25 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.0, 143.1, 142.5, 137.7, 136.6, 136.3, 134.0, 132.7, 132.5, 129.4, 129.1, 127.74, 127.67, 127.6, 127.1, 126.6, 126.5, 126.2, 126.0, 125.6, 125.0, 121.3, 111.7, 104.6, 69.4, 20.9; LC/MS (ESI) *m/z* 573.2 $[M + H]^+$.

***N,N'*-(2-([1,1'-Biphenyl]-4-ylmethoxy)-1,4-phenylene)bis(4-methylbenzenesulfon-amide) (42k).** Prepared as described in the experimental procedure of **14a** from 2-([1,1'-biphenyl]-4-ylmethoxy)benzene-1,4-diamine and 4-methylbenzenesulfonyl chloride to obtain the title compound as a white solid (108 mg, 39%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (brs, 1H, NH), 9.39 (brs, 1H, NH), 7.70 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.51-7.47 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.77 (s, 2H), 2.30 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.9, 143.2, 142.6, 139.8, 139.5, 137.7, 136.6, 136.4,

135.6, 129.5, 129.2, 129.0, 127.7, 127.5, 127.0, 126.7, 126.62, 126.55, 126.4, 121.2, 111.7, 104.6, 68.9, 21.0, 20.9; LC/MS (ESI) *m/z* 599.2 $[M + H]^+$.

Diethyl 2,2'-((2-(benzyloxy)-1,4-phenylene)bis(tosylazanediyl))diacetate (43a). Prepared as described in the experimental procedure of **15a** from intermediate **42a** to obtain the title compound as a colorless oil (31 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.33-7.31 (m, 3H), 7.26 (d, *J* = 6.4 Hz, 2H), 7.06-7.04 (m, 5H), 6.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.69 (s, 2H), 4.36 (s, 4H), 4.19-4.12 (m, 4H), 2.43 (s, 3H), 2.31 (s, 3H), 1.23 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.8, 155.1, 144.1, 143.4, 141.4, 137.3, 135.8, 135.7, 134.4, 129.6, 129.3, 128.5, 128.2, 128.0, 127.5, 127.1, 126.8, 119.2, 114.3, 70.3, 61.7, 61.4, 52.6, 51.0, 21.7, 21.6, 14.2; LC/MS (ESI) *m/z* 695.3 $[M + H]^+$.

Diethyl 2,2'-((2-(benzyloxy)-1,4-phenylene)bis(((4-fluorophenyl)sulfonyl)azanediyl))diacetate (43b). Prepared as described in the experimental procedure of **15a** from intermediate **42b** to obtain the title compound as a colorless oil (64 mg, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.56 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.35-7.34 (m, 3H), 7.14-7.09 (m, 4H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 8.8 Hz, 2H), 6.63 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.70 (s, 2H), 4.37 (s, 2H), 4.34 (s, 2H), 4.19-4.08 (m, 4H), 1.26-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.8, 166.5 ($J_{C,F}$ = 32 Hz), 164.1 ($J_{C,F}$ = 31 Hz), 155.2, 141.3, 136.1, 135.4, 135.0, 134.5, 130.8 ($J_{C,F}$ = 9 Hz), 130.2 ($J_{C,F}$ = 9 Hz), 128.7, 128.5, 127.4, 126.7, 119.6, 116.2 ($J_{C,F}$ = 22 Hz), 115.8 ($J_{C,F}$ = 22 Hz), 114.1, 70.5, 61.8, 61.6, 52.7, 51.1, 14.2; LC/MS (ESI) *m/z* 703.0 $[M + H]^+$.

Diethyl 2,2'-((2-(benzyloxy)-1,4-phenylene)bis(((4-bromophenyl)sulfonyl)azanediyl))diacetate (43c). Prepared as described in the procedure of **15a** from **42c** to obtain the

title compound as a colorless oil (60 mg, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.41-7.35 (m, 7H), 7.11-7.09 (m, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.67 (s, 2H), 4.38 (s, 2H), 4.34 (s, 2H), 4.20-4.13 (m, 4H), 1.27-1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.8, 155.2, 141.3, 139.1, 137.9, 135.3, 134.5, 132.3, 132.0, 129.6, 129.0, 128.8, 128.5, 128.4, 127.8, 127.4, 126.7, 119.7, 114.1, 70.6, 61.9, 61.6, 52.8, 51.2, 14.3; LC/MS (ESI) *m/z* 823.2 [M(2^{79}Br,) + H]$^{+}$, 825.0 [M(^{79}Br, ^{81}Br) + H]$^{+}$, 827.0 [M(2^{81}Br) + H]$^{+}$.

Diethyl 2,2'-((2-(benzyloxy)-1,4-phenylene)bis(((4-(trifluoromethyl)phenyl)sulfonyl)azanediyl))diacetate (43d). Prepared as described in the experimental procedure of **15a** from intermediate **42d** to obtain the title compound as a colorless oil (42 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 9.2 Hz, 2H), 7.64 (d, *J* = 9.2 Hz, 2H), 7.46-7.42 (m, 3H), 7.28-7.26 (m, 3H), 7.00-6.98 (m, 2H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.60 (s, 2H), 4.34 (s, 2H), 4.30 (s, 2H), 4.13-4.06 (m, 4H), 1.19-1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.7, 155.2, 142.6, 141.2, 135.1, 134.5, 128.8, 128.59, 128.55, 128.0, 127.3, 126.8, 126.1, 125.83, 125.79, 119.9, 114.3, 70.6, 62.0, 61.7, 53.0, 51.3, 14.2; LC/MS (ESI) *m/z* 803.3 [M + H]$^{+}$.

Diethyl 2,2'-((2-(benzyloxy)-1,4-phenylene)bis(([1,1'-biphenyl]-4-ylsulfonyl)azanediyl))diacetate 43e). Prepared as described in the experimental procedure of **15a** from intermediate **42e** to obtain the title compound as a colorless oil (31 mg, 52%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 6.8 Hz, 2H), 7.59-7.56 (m, 4H), 7.48-7.41 (m, 9H), 7.23-7.18 (m, 3H), 7.04 (s, 1H), 6.99 (d, *J* = 7.6 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.65 (s, 2H), 4.41 (s, 2H), 4.40 (s, 2H), 4.20-4.09 (m, 4H), 1.27-1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.8, 155.1, 146.1, 145.4,

141.4, 139.2, 139.1, 138.7, 137.3, 135.5, 134.5, 129.2, 129.1, 128.8, 128.6, 128.2, 128.0, 127.5, 127.4, 127.3, 127.2, 127.1, 126.8, 119.6, 114.2, 70.3, 61.8, 61.5, 52.7, 51.1, 14.2; LC/MS (ESI) *m/z* 819.2 $[M + H]^+$.

Diethyl 2,2'-((2-(benzyloxy)-1,4-phenylene)bis((m-tolylsulfonyl)azanediyl))diacet-ate (43f). Prepared as described in the procedure of **15a** from **42f** to obtain the title compound as a colorless oil (39 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 1H), 7.48-7.46 (m, 2H), 7.42-7.30 (m, 7H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.17-7.13 (m, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 7.04-7.02 (m, 2H), 6.56 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.66 (s, 2H), 4.36 (s, 4H), 4.18-4.11 (m, 4H), 2.39 (s, 3H), 2.22 (s, 3H), 1.27-1.21(m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.6, 155.1, 141.3, 140.0, 139.3, 138.9, 138.6, 135.6, 134.4, 134.0, 133.5, 128.9, 128.6, 128.5, 128.22, 128.15, 127.7, 127.0, 126.8, 124.9, 124.6, 119.3, 114.5, 70.3, 61.7, 61.4, 52.6, 51.0, 21.5, 21.3, 14.3 14.2; LC/MS (ESI) *m/z* 695.2 $[M + H]^+$.

Diethyl 2,2'-((2-((4-fluorobenzyl)oxy)-1,4-phenylene)bis(tosylazanediyl))diacetate (43g). Prepared as described in the experimental procedure of **15a** from intermediate **42g** to obtain the title compound as a colorless oil (102 mg, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.07-6.95 (m, 7H), 6.52 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.66 (s, 2H), 4.33 (s, 2H), 4.30 (s, 2H), 4.16-4.08 (m, 4H), 2.40 (s, 3H), 2.31 (s, 3H), 1.22-1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.7, 162.5 ($J_{C,F}$ = 245 Hz), 154.9, 144.1, 143.4, 141.3, 137.3, 135.7, 134.2, 131.5 ($J_{C,F}$ = 3 Hz), 129.6, 129.2, 129.0 ($J_{C,F}$ = 9 Hz), 127.8, 127.5, 126.8, 119.3, 115.4 ($J_{C,F}$ = 21 Hz), 114.4, 69.5, 61.6, 61.4, 52.5, 50.9, 25.7, 21.6, 21.5, 14.1; LC/MS (ESI) *m/z* 713.2 $[M + H]^+$.

Di-*tert*-butyl 2,2'-((2-((4-fluorobenzyl)oxy)-1,4-phenylene)bis((mesitylsulfonyl)azanediyl))diacetate (43h). Prepared as described in the experimental procedure of **15a** from intermediate **42h** to obtain the title compound as a colorless oil (102 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.8 Hz, 1H), 7.11-7.07 (m, 2H), 7.03-6.98 (m, 2H), 6.84 (s, 2H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.68 (s, 2H), 6.63 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.56 (s, 2H), 4.33 (s, 4H), 2.37 (s, 6H), 2.25 (s, 3H), 2.23 (s, 3H), 2.17 (s, 6H), 1.38 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.7, 162.6 ($J_{C,F}$ = 245 Hz), 155.3, 142.9, 141.9, 141.0, 140.5, 140.1, 134.3, 134.1, 132.7, 131.9, 131.6, 131.5 ($J_{C,F}$ = 3 Hz), 129.5 ($J_{C,F}$ = 8 Hz), 126.2, 120.1, 115.4 ($J_{C,F}$ = 21 Hz), 113.7, 82.3, 82.1, 69.6, 52.5, 51.6, 28.0, 27.9, 23.2, 23.0, 21.0, 20.9; LC/MS (ESI) *m/z* 713.2 $[M + H - C_8H_{16}]^+$.

Diethyl 2,2'-((2-((4-methylbenzyl)oxy)-1,4-phenylene)bis(tosylazanediyl))dacetate (43i). Prepared as described in the experimental procedure of **15a** from intermediate **42i** to obtain the title compound as a pale yellow oil (53 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.07-7.04 (m, 3H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.54 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.63 (s, 2H), 4.35 (s, 2H), 4.33 (s, 2H), 4.18-4.11 (m, 4H), 2.43 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H), 1.23 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.8, 155.1, 144.1, 143.3, 141.3, 137.9, 137.3, 135.8, 134.3, 132.7, 129.6, 129.3, 129.2, 128.0, 127.5, 127.3, 126.8, 119.2, 114.3, 70.2, 61.7, 61.4, 52.6, 51.0, 21.7, 21.6, 21.3, 14.2; LC/MS (ESI) *m/z* 709.3 $[M + H]^+$.

Diethyl 2,2'-((2-(naphthalen-2-ylmethoxy)-1,4-phenylene)bis(tosylazanediyl))diacetate (43j). Prepared as described in the experimental procedure of **15a** from **42j** to obtain the title compound as a white solid (138 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.86-7.84 (m, 1H), 7.82-7.78 (m, 2H), 7.56-7.49 (m, 6H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.57 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.86 (s, 2H), 4.39 (s, 2H), 4.36 (s, 2H), 4.17-4.10 (m, 4H), 2.40 (s, 3H), 2.14 (s, 3H), 1.24-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.7, 155.1, 144.1, 143.4, 141.4, 137.2, 135.8, 134.3, 133.2, 133.14, 133.08, 129.6, 129.2, 128.3, 128.1, 127.9, 127.8, 127.4, 126.8, 126.5, 126.4, 126.1, 124.8, 119.2, 114.3, 70.4, 61.6, 61.4, 52.6, 51.0, 25.7, 21.6, 21.4, 14.2; LC/MS (ESI) *m/z* 745.3 $[M + H]^+$.

Diethyl 2,2'-((2-([1,1'-biphenyl]-4-ylmethoxy)-1,4-phenylene)bis(tosylazanediyl)) diacetate (43k). Prepared as described in the experimental procedure of **15a** from intermediate **42k** to obtain the title compound as a colorless oil (97 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.47 (m, 11H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.29-7.27 (m, 2H), 7.14-7.08 (m, 5H), 6.58 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.76 (s, 2H), 4.40 (s, 2H), 4.39 (s, 2H), 4.20-4.12 (m, 4H), 2.44 (s, 3H), 2.31 (s, 3H), 1.33-1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.7, 155.0, 144.1, 143.4, 141.3, 141.1, 140.6, 137.3, 135.8, 134.7, 134.3, 129.6, 129.3, 129.0, 127.9, 127.6, 127.50, 127.47, 127.2, 127.1, 126.8, 119.2, 114.3, 70.0, 61.6, 61.4, 52.6, 51.0, 21.7, 21.6, 14.2; LC/MS (ESI) *m/z* 771.3 $[M + H]^+$.

2,2'-((2-(Benzyloxy)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (44a). Prepared as described in the experimental procedure of **16a** from intermediate **43a** to obtain the title compound as a white solid (20 mg, 70%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (brs, 2H, CO_2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.39-7.36 (m, 5H), 7.33-7.32 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.02-7.00 (m, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.77 (s, 1H), 4.54 (s, 2H), 4.42 (s, 2H), 4.22 (s, 2H), 2.40 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 169.8, 154.3, 143.6, 143.0, 140.8, 136.7, 135.8, 135.5, 133.2, 129.6, 129.2, 128.1, 127.7,

127.3, 126.8, 125.5, 119.3, 112.0, 69.4, 51.8, 50.6, 21.0, 20.9; LC/MS (ESI) m/z 637.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_9S_2$ [M - H]$^-$ 637.1320; found 637.1326.

2,2'-((2-(Benzyloxy)-1,4-phenylene)bis(((4-fluorophenyl)sulfonyl)azanediyl))diac-etic acid (44b). Prepared as described in the experimental procedure of **16a** from intermediate **43b** to obtain the title compound as a white solid (32 mg, 54%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.79 (brs, 2H, CO_2H), 7.76 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.56 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.45-7.37 (m, 3H), 7.34-7.32 (m, 2H), 7.15-7.08 (m, 2H), 7.06-7.04 (m, 2H), 6.88 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 4.61 (s, 2H), 4.46 (s, 2H), 4.25 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 170.1, 169.8, 163.3 ($J_{C,F}$ = 30 Hz), 154.4, 140.8, 135.9, 135.7, 134.7, 133.4, 130.5 ($J_{C,F}$ = 10 Hz), 129.8 ($J_{C,F}$ = 10 Hz), 129.6, 128.2, 127.8, 126.9, 126.0, 119.7, 116.4 ($J_{C,F}$ = 22 Hz), 115.9 ($J_{C,F}$ = 23 Hz), 114.3, 112.1, 69.6, 52.0, 50.7; LC/MS (ESI) *m/z* 645.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{29}H_{24}F_2N_2O_9S_2$ [M - H]$^-$ 645.0819; found 645.0826.

,2'-((2-(Benzyloxy)-1,4-phenylene)bis(((4-bromophenyl)sulfonyl)azanediyl))diace-tic acid (44c). Prepared as described in the experimental procedure of **16a** from intermediate **43c** to obtain the title compound as a white solid (31 mg, 56%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.88 (brs, 2H, CO_2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.43-7.39 (m, 3H), 7.36-7.34 (m, 3H), 7.07-7.02 (m, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 4.54 (s, 2H), 4.46 (s, 2H), 4.25 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 170.1, 169.8, 154.4, 140.7, 138.7, 137.5, 135.6, 135.5, 132.3, 131.9, 129.4, 128.7, 128.3, 127.8, 127.3, 126.94, 126.85, 125.6, 120.1, 112.2, 69.6, 52.0, 50.7; LC/MS (ESI) m/z 767.0 [M(2^{79}Br,) + H]$^+$, 769.0 [M(^{79}Br, ^{81}Br) + H]$^+$, 771.0 [M(2^{81}Br) + H]$^+$;

HRMS (ESI) *m/z* calcd for $C_{29}H_{24}Br_2N_2O_9S_2$ [M(2^{79}Br,) + H]$^+$ 766.9324, [M(^{79}Br, ^{81}Br) + H]$^+$ 768.9303 and [M(2^{81}Br) + H]$^+$ 770.9283; found 766.9380, 768.9356 and 770.9332.

2,2'-((2-(Benzyloxy)-1,4-phenylene)bis(((4-(trifluoromethyl)phenyl)sulfonyl)azanediyl))diacetic acid (44d). Prepared as described in the experimental procedure of **16a** from intermediate **43d** to obtain the title compound as a white solid (25 mg, 64%); ^{1}H NMR (400 MHz, MeOD) δ 7.87-7.85 (m, 4H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.31-7.29 (m, 3H), 7.04-7.01 (m, 2H), 6.91-6.87 (m, 2H), 4.54 (s, 2H), 4.49 (s, 2H), 4.37 (s, 2H); ^{13}C NMR (100 MHz, MeOD) δ 172.2, 171.9, 156.3, 145.0, 143.9, 142.6, 136.9, 135.7, 135.4, 129.8, 129.5, 129.23, 129.17, 128.4, 127.7, 127.2, 127.0, 121.6, 114.7, 71.3, 53.5, 52.2; LC/MS (ESI) *m/z* 745.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{31}H_{24}F_6N_2O_9S_2$ [M - H]$^-$ 745.0755; found 745.0764.

2,2'-((2-(Benzyloxy)-1,4-phenylene)bis(([1,1'-biphenyl]-4-ylsulfonyl)azanediyl))diacetic acid (44e). Prepared as described in the experimental procedure of **16a** from intermediate **43e** to obtain the title compound as a white solid (25 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.56-7.53 (m, 5H), 7.44-7.35 (m, 10H), 7.19-7.11 (m, 3H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.92 (d, *J* = 6.4 Hz, 2H), 6.69 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.56 (s, 2H), 4.34 (s, 2H), 4.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.6, 155.0, 146.1, 145.4, 141.3, 139.1, 139.0, 138.3, 137.1, 135.4, 134.4, 129.2, 129.0, 128.7, 128.50, 128.46, 128.4, 128.1, 127.9, 127.5, 127.3, 127.2, 127.10, 127.06, 126.5, 119.6, 113.8, 70.2, 52.4, 50.9; LC/MS (ESI) *m/z* 761.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{41}H_{34}N_2O_9S_2$ [M - H]$^-$ 761.1633; found 761.1628.

2,2'-((2-(Benzyloxy)-1,4-phenylene)bis((m-tolylsulfonyl)azanediyl))diacetic acid (44f).

Prepared as described in the experimental procedure of **16a** from intermediate **43f** to obtain the title compound as a white solid (29 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.8 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.37-7.27 (m, 7H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.00-6.98 (m, 3H), 6.55 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.59 (s, 2H), 4.31 (s, 2H), 4.29 (s, 2H), 2.35 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.5, 155.0, 141.3, 139.7, 139.3, 139.0, 138.3, 135.6, 134.3, 134.0, 133.5, 128.9, 128.54, 128.48, 128.13, 128.10, 127.6, 127.0, 126.6, 124.9, 124.5, 119.3, 114.1, 70.2, 52.4, 50.9, 21.3, 21.2; LC/MS (ESI) *m/z* 637.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_9S_2$ [M - H]$^-$ 637.1320; found 637.1311.

2,2'-((2-((4-Fluorobenzyl)oxy)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (44g). Prepared as described in the procedure of **16a** from **43g** to obtain the title compound as a white solid (66 mg, 70%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (brs, 2H, CO_2H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.40-7.35 (m, 5H), 7.18-7.14 (m, 4H), 7.08-7.05 (m, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.78 (s, 1H), 4.55 (s, 2H), 4.43 (s, 2H), 4.20 (s, 2H), 2.40 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 169.9, 160.5, 154.3, 143.7, 143.1, 140.9, 136.7, 135.5, 133.3, 132.1 ($J_{C,F}$ = 3 Hz), 129.6, 129.3, 129.1 ($J_{C,F}$ = 8 Hz), 127.4, 126.8, 125.6, 119.3, 115.0 ($J_{C,F}$ = 22 Hz), 112.0, 68.8, 51.8, 50.6, 21.0, 20.9; LC/MS (ESI) *m/z* 655.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{31}H_{29}FN_2O_9S_2$ [M - H]$^-$ 655.1226; found 655.1221.

2,2'-((2-((4-Fluorobenzyl)oxy)-1,4-phenylene)bis((mesitylsulfonyl)azanediyl))diacetic acid (44h). Prepared as described in the experimental procedure of **16a** from **43h** to obtain the title compound as a pale yellow solid (79 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (brs, 2H, CO_2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.08-7.00 (m, 4H), 6.87 (s, 2H), 6.72 (s, 2H), 6.64-6.61 (m, 2H), 4.56 (s, 6H), 2.36 (s, 6H), 2.30 (s, 3H), 2.28 (s, 3H), 2.18 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 175.6, 162.8 ($J_{C,F}$ = 246 Hz) 155.4, 143.4, 142.3, 140.7, 140.4, 134.5, 133.6, 132.1, 131.9, 131.8, 131.3, 129.5 ($J_{C,F}$ = 8 Hz), 125.8, 121.4, 115.7 ($J_{C,F}$ = 21 Hz), 112.6, 69.9, 50.8, 50.2, 23.3, 23.0, 21.2, 21.1; LC/MS (ESI) *m/z* 711.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{35}H_{37}FN_2O_9S_2$ [M - H]$^-$ 711.1852; found 711.1847.

2,2'-((2-((4-Methylbenzyl)oxy)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (44i). Prepared as described in the experimental procedure of **16a** from intermediate **43i** to obtain the title compound as a white solid (34 mg, 62%); ^{1}H NMR (400 MHz, MeOD) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.40 (s, 2H), 4.31 (s, 2H), 4.19 (s, 2H), 2.32 (s, 3H), 2.25 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.6, 172.2, 156.3, 145.6, 144.9, 142.8, 139.0, 138.2, 136.9, 135.2, 134.2, 130.6, 130.4, 130.0, 129.0, 128.42, 128.40, 127.7, 120.7, 114.5, 71.1, 53.3, 52.0, 21.57, 21.56, 21.2; LC/MS (ESI) *m/z* 651.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{32}N_2O_9S_2$ [M - H]$^-$ 651.1476; found 651.1484.

2,2'-((2-(Naphthalen-2-ylmethoxy)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (44j). Prepared as described in the experimental procedure of **16a** from intermediate **43j** to obtain the title compound as a white solid (59 mg, 46%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (brs, 2H, CO_2H), 7.96-7.93 (m, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.56-7.54 (m, 5H), 7.41-7.37 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.87-6.85 (m, 2H), 4.74(s, 2H), 4.44 (s, 2H), 4.27 (s, 2H), 2.37 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 169.9, 154.4, 143.7, 143.0, 140.9, 136.7, 135.5, 133.5, 133.4, 132.6, 132.5, 129.6, 129.2, 127.84, 127.81, 127.6, 127.4, 126.8, 126.3, 126.1,

125.7, 125.5, 124.9, 119.3, 112.0, 69.6, 51.9, 50.6, 21.0, 20.8; LC/MS (ESI) *m/z* 687.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{35}H_{32}N_2O_9S_2$ [M - H]$^-$ 687.1476; found 687.1473.

2,2'-((2-([1,1'-Biphenyl]-4-ylmethoxy)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (44k). Prepared as described in the experimental procedure of **16a** from intermediate **43k** to obtain the title compound as a white solid (52 mg, 58%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (brs, 2H, CO_2H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.50 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.41-7.38 (m, 6H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.85 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 4.61 (s, 2H), 4.44 (s, 2H), 4.25 (s, 2H), 2.38 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 169.9, 154.4, 143.7, 143.1, 140.9, 139.7, 139.5, 136.7, 135.5, 135.0, 133.3, 129.6, 129.3, 129.0, 127.5, 127.42, 127.35, 126.8, 126.6, 126.4, 125.6, 119.3, 112.0, 69.2, 51.8, 50.6, 21.0; LC/MS (ESI) *m/z* 713.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{37}H_{34}N_2O_9S_2$ [M - H]$^-$ 713.1633; found 713.1630.

Methyl 2-((4-fluorobenzyl)oxy)-4-nitrobenzoate (45a). Prepared as described in the experimental procedure of **21b** from methyl 2-fluoro-4-nitrobenzoate and 4-fluorobenzyl alcohol to obtain the title compound as a yellow solid (303 mg, 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.89-7.86 (m, 2H), 7.50-7.47 (m, 2H), 7.13-7.08 (m, 2H), 5.23 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 162.8 ($J_{C,F}$ = 245 Hz), 158.2, 150.8, 132.5, 131.3 ($J_{C,F}$ = 4 Hz), 129.1 ($J_{C,F}$ = 8 Hz), 126.7, 116.0, 115.7 ($J_{C,F}$ = 20 Hz), 108.6, 70.7, 52.8.

Methyl 3-((4-fluorobenzyl)oxy)-4-nitrobenzoate (45b). Prepared as described in the experimental procedure of **21b** from methyl 3-fluoro-4-nitrobenzoate and 4-fluorobenzyl alcohol to obtain the title compound as a yellow solid (395 mg, 52%); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.69 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.45-7.41 (m, 2H), 7.09-7.04 (m, 2H), 5.22 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.8 ($J_{C,F}$ = 246 Hz), 151.3, 142.9, 134.9, 130.9 ($J_{C,F}$ = 3 Hz), 129.2 ($J_{C,F}$ = 8 Hz), 125.5, 122.0, 116.0 ($J_{C,F}$ = 25 Hz), 115.7, 70.9, 52.9.

(2-((4-Fluorobenzyl)oxy)-4-nitrophenyl)methanol (46a). To a solution of **45a** (280 mg, 0.92 mmol) in tetrahydrofuran (5 mL) was added diisobutylaluminum hydride (1.0 M in THF, 2.8 ml, 2.75 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to 6 N HCl, filtered off through celite, and then extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-50% ethyl acetate/hexane) to give the product as a pale yellow oil (261 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.43-7.39 (m, 2H), 7.12-7.08 (m, 2H), 5.14 (s, 2H), 4.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 ($J_{C,F}$ = 246 Hz), 156.0, 148.3, 137.2, 131.4, 129.6 ($J_{C,F}$ = 8 Hz), 128.1, 116.5, 116.0 ($J_{C,F}$ = 21 Hz), 106.3, 70.1, 60.7.

(3-((4-Fluorobenzyl)oxy)-4-nitrophenyl)methanol (46b). Prepared as described in the procedure of **46a** from **45b** to obtain the title compound as a pale yellow oil (293 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 1H), 7.47-7.44 (m, 2H), 7.20 (s, 1H), 7.11-7.06 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.21 (s, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 148.0, 129.0, 128.9, 126.0, 118.3, 115.8, 115.6, 112.7, 70.6, 64.1.

2-((4-Fluorobenzyl)oxy)-4-nitrobenzaldehyde (47a). To a solution of **46a** (240 mg, 0.87 mmol) in dichloromethane (5 mL) was added pyridinium chlorochromate (280 mg, 1.30

mmol) at room temperature. The reaction mixture was stirred at 55 °C for 1 hour. The crude mixture was filtered off through celite, added water, and then extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-20% ethyl acetate/hexane) to give the product as a pale yellow solid (113 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.90 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.47-7.44 (m, 2H), 7.15-7.11 (m, 2H), 5.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 163.1 ($J_{C,F}$ = 246 Hz), 160.8, 152.2, 130.6, 129.8 ($J_{C,F}$ = 10 Hz), 129.1, 116.3 ($J_{C,F}$ = 21 Hz), 116.1, 108.5, 70.9; LC/MS (ESI) *m/z* 275.0 $[M]^-$.

3-((4-Fluorobenzyl)oxy)-4-nitrobenzaldehyde (47b). Prepared as described in the experimental procedure of **47a** from intermediate **46b** to obtain the title compound as a pale yellow solid (410 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 1.2 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.45-7.42 (m, 2H), 7.11-7.06 (m, 2H), 5.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 162.9 ($J_{C,F}$ = 246 Hz), 151.9, 143.9, 139.7, 130.7 ($J_{C,F}$ = 3 Hz), 129.2 ($J_{C,F}$ = 8 Hz), 126.1, 123.2, 116.0 ($J_{C,F}$ = 21 Hz), 114.0, 71.0; LC/MS (ESI) *m/z* 275.0 $[M]^-$.

***N*-(2-((4-Fluorobenzyl)oxy)-4-nitrobenzyl)-4-methylbenzenesulfonamide (48a).** To a solution of **47a** (113 mg, 0.41 mmol) in dichloromethane (2 mL) were added sodium triacetoxyborohydride (174 mg, 0.82 mmol), 4-methyl benzenesulfonamide (77 mg, 0.45 mmol), acetic acid (3 drops) and triethylamine (287 mg, 0.82 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a pale yellow solid (98 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64 (d, *J* = 1.6 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.37-7.33 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.10-7.06 (m, 2H), 5.31 (t, *J* = 6.4 Hz, 1H, NH), 5.04 (s, 2H), 4.20 (d, *J* = 6.4 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 ($J_{C,F}$ = 246 Hz), 156.3, 148.4, 143.7, 132.4, 130.0, 129.6 ($J_{C,F}$ = 9 Hz), 129.55, 129.2, 126.9, 116.1, 115.9 ($J_{C,F}$ = 21 Hz), 106.4, 70.2, 42.9, 21.4; LC/MS (ESI) *m/z* 431.1 $[M + H]^+$.

***N*-(3-((4-Fluorobenzyl)oxy)-4-nitrobenzyl)-4-methylbenzenesulfonamide (48b).** Prepared as described in the experimental procedure of **48a** from intermediate **47b** to obtain the title compound as a pale yellow solid (221 mg, 36%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (brs, 1H, NH), 7.79 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.52-7.49 (m, 2H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.27-7.23 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.15 (s, 2H), 4.08 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9 ($J_{C,F}$ = 243 Hz), 150.7, 145.0, 142.7, 138.3, 137.7, 132.0, 129.7 ($J_{C,F}$ = 9 Hz), 129.4 ($J_{C,F}$ = 26 Hz), 126.5, 119.7, 115.3 ($J_{C,F}$ = 22 Hz), 114.2, 69.7, 45.6, 20.9; LC/MS (ESI) *m/z* 429.0 $[M - H]^-$.

***N*-(3-((4-Fluorobenzyl)oxy)-4-(((4-methylphenyl)sulfonamido)methyl)phenyl)-4-methylbenzenesulfonamide (49a).** Prepared as described in the experimental procedure of **22b** from intermediate **48a** to obtain the title compound as a white solid (47 mg, 39% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (brs, 1H, NH), 7.75 (t, *J* = 6.0 Hz, 1H, NH), 7.61 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.41-7.38 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 4H), 7.21-7.16 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 4.93 (s, 2H), 3.81 (d, *J* = 6.0 Hz, 2H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7 ($J_{C,F}$ = 242 Hz), 155.7, 143.3, 142.5, 138.2, 137.6, 136.6, 132.9

($J_{C,F}$ = 3 Hz), 129.7, 129.4 ($J_{C,F}$ = 9 Hz), 126.7, 126.5, 121.1, 115.2 ($J_{C,F}$ = 21Hz), 111.3, 103.8, 68.5, 48.62, 21.0, 20.9; LC/MS (ESI) *m/z* 553.1 $[M - H]^-$.

***N*-(2-((4-Fluorobenzyl)oxy)-4-(((4-methylphenyl)sulfonamido)methyl)phenyl)-4-methylbenzenesulfonamide (49b).** Prepared as described in the experimental procedure of **22b** from intermediate **48b** to obtain the title compound as a pale yellow solid (158 mg, 61% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (brs, 1H, NH), 7.99 (t, *J* = 6.0 Hz, 1H, NH), 7.71 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.37-7.32 (m, 4H), 7.21-7.12 (m, 4H), 6.80 (d, *J* = 1.2 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.73 (s, 2H), 3.88 (d, *J* = 6.0 Hz, 1H), 2.35 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7 ($J_{C,F}$ = 242 Hz), 151.1, 142.6, 142.5, 137.8, 136.2, 132.7, 129.5 ($J_{C,F}$ = 3 Hz), 129.4, 129.2 ($J_{C,F}$ = 6 Hz), 126.5, 125.6, 125.5, 124.4, 119.7, 114.8 ($J_{C,F}$ = 22 Hz), 112.0, 68.6, 45.8, 20.9; LC/MS (ESI) *m/z* 553.1 $[M - H]^-$.

Ethyl *N*-(4-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-((4-fluoro benzyl)oxy)benzyl)-*N*-tosylglycinate (50a). Prepared as described in the experimental procedure of **15a** from **49a** to obtain the title compound as a colorless oil (43 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.04 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.33-7.26 (m, 7H), 7.08-7.04 (m, 3H), 6.58 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.92 (s, 2H), 4.51 (s, 2H), 4.37 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 2H), 3.88 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 2.44 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.8, 162.7 ($J_{C,F}$ = 245 Hz), 156.9, 144.0, 143.5, 140.9, 137.3, 136.0, 132.1, 130.9, 129.6 ($J_{C,F}$ = 9 Hz), 128.0, 127.5, 124.4, 120.0, 115.6 ($J_{C,F}$ = 21 Hz), 113.7, 69.8, 61.6, 61.2, 52.8, 48.0, 46.0, 21.71, 21.66, 14.2, 14.0; LC/MS (ESI) *m/z* 726.1 $[M]^-$.

Ethyl *N*-(4-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)-3-((4-fluoro benzyl)oxy)benzyl)-*N*-tosylglycinate (50b). Prepared as described in the experimental procedure of **15a** from intermediate **49b** to obtain the title compound as a colorless oil (160 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.49-7.46 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.08-7.03 (m, 4H), 7.00-6.96 (m, 2H), 6.92 (d, *J* = 1.2 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.68 (s, 2H), 4.42 (s, 2H), 4.31 (s, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 2H), 3.39 (s, 3H), 3.30 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.6, 162.5 ($J_{C,F}$ = 245 Hz), 155.1, 143.8, 143.3, 137.5, 137.4, 136.8, 133.9, 131.8 ($J_{C,F}$ = 3 Hz), 129.7, 129.2, 129.0 ($J_{C,F}$ = 8 Hz), 127.5, 127.0, 120.9, 115.3 ($J_{C,F}$ = 22 Hz), 112.5, 69.3, 61.3, 51.3, 51.0, 47.1, 21.52, 21.46, 14.1, 14.0; LC/MS (ESI) *m/z* 727.2 $[M + H]^+$.

***N*-(4-((*N*-(Carboxymethyl)-4-methylphenyl)sulfonamido)-2-((4-fluorobenzyl)ox-y)benzyl)-*N*-tosylglycine (51a).** Prepared as described in the experimental procedure of **16a** from intermediate **50a** to obtain the title compound as a yellow solid (24 mg, 61%); ^{1}H NMR (400 MHz, MeOD) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.34-7.27 (m, 6H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.09-7.04 (m, 2H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.66 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.83 (s, 2H), 4.46 (s, 2H), 4.38 (s, 2H), 3.85 (s, 2H), 2.40 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.3, 172.1, 165.2, 158.2, 145.4, 144.8, 142.4, 138.7, 137.1, 133.8, 132.2, 131.0 ($J_{C,F}$ = 8 Hz), 130.6, 130.5, 128.9, 128.3, 125.4, 121.2, 116.3 ($J_{C,F}$ = 21 Hz), 114.2, 70.7, 53.4, 47.8, 21.49, 21.45; LC/MS (ESI) *m/z* 669.0 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{31}FN_2O_9S_2$ $[M - H]^-$ 669.1382; found 669.1391.

***N*-(4-((*N*-(Carboxymethyl)-4-methylphenyl)sulfonamido)-3-((4-fluorobenzyl)ox-y)benzyl)-*N*-tosylglycine (51b).** Prepared as described in the experimental procedure of

16a from intermediate **50b** to obtain the title compound as a pale yellow solid (92 mg, 62%); ^{1}H NMR (400 MHz, MeOD) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.12-7.02 (m, 6H), 6.86 (d, *J* = 1.2 Hz, 1H), 6.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.56 (s, 2H), 4.47 (s, 2H), 4.29 (s, 2H), 3.90 (s, 2H), 2.37 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.7, 172.0, 163.8 ($J_{C,F}$ = 243 Hz), 156.2, 145.1, 144.8, 139.4, 138.50, 138.45, 135.1, 133.6, 133.6, 130.8, 130.43, 130.4 ($J_{C,F}$ = 2 Hz), 128.5 ($J_{C,F}$ = 14 Hz), 127.9, 121.7, 116.1 ($J_{C,F}$ = 22 Hz), 113.8, 70.2, 52.7, 52.0, 21.52, 21.49; LC/MS (ESI) *m/z* 669.1 [M - H]$^{-}$; HRMS (ESI) *m/z* calcd for $C_{32}H_{31}FN_2O_9S_2$ [M - H]$^{-}$ 669.1382; found 669.1390.

***N*-(3-((4-Fluorobenzyl)oxy)-4-nitrophenyl)-4-methylbenzenesulfonamide (52).** To a solution of **21g** (500 mg, 1.91 mmol) in pyridine (5 mL) was added 4-methylbenzenesulfonyl chloride (727 mg, 3.81 mmol) at room temperature. The reaction mixture was stirred at 60 °C for overnight. The crude mixture was added to 1N HCl, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a yellow solid (527 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.44-7.40 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.07-7.03 (m, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.63 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.14 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 ($J_{C,F}$ = 245 Hz), 153.5, 145.2, 142.8, 135.7, 135.4, 131.1, 130.2, 129.1 ($J_{C,F}$ = 8 Hz), 127.9, 127.2, 115.8 ($J_{C,F}$ = 22 Hz), 110.6, 104.9, 70.6, 21.7; LC/MS (ESI) *m/z* 416.1 [M]$^{-}$.

***N*-(4-Amino-3-((4-fluorobenzyl)oxy)phenyl)-4-methylbenzenesulfonamide (53).** Prepared as described in the experimental procedure of **21** from intermediate **52** to obtain

the title compound as a dark brown oil (465 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.34-7.31 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.04-6.99 (m, 2H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.30 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.90 (s, 2H), 2.77 (s, 4H, NH), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 146.3, 143.5, 136.1, 134.5, 132.5, 129.6 ($J_{C,F}$ = 8 Hz), 129.4, 127.5, 127.3, 127.1, 115.5 ($J_{C,F}$ = 22 Hz), 115.1, 109.1, 69.8, 21.5; LC/MS (ESI) *m/z* 387.1 $[M + H]^+$.

***N*-(2-((4-Fluorobenzyl)oxy)-4-((4-methylphenyl)sulfonamido)phenyl)-4-methyl benzamide (54).** To a solution of **53** (240 mg, 0.62 mmol) in dichloromethane (3 mL) were added 4-methylbenzoic acid (102 mg, 0.75 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (143 mg, 0.75 mmol), 1-hydroxybenzotiazole (101 mg, 0.75 mmol) and trimethylamine (189 mg, 1.86 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a pale yellow solid (174 mg, 56%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (brs, 1H, NH), 9.35 (brs, 1H, NH), 7.79 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.53-7.49 (m, 2H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.22-7.18 (m, 2H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.63 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.06 (s, 2H), 2.36 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 161.7 ($J_{C,F}$ = 242 Hz), 151.1, 143.2, 141.5, 136.5, 135.6, 132.9 ($J_{C,F}$ = 3 Hz), 131.7, 129.6, 129.4 ($J_{C,F}$ = 8 Hz), 129.0, 127.4, 126.7, 125.6, 123.4, 115.2 ($J_{C,F}$ = 21 Hz), 111.9, 105.3, 69.0, 21.0; LC/MS (ESI) *m/z* 505.2 $[M + H]^+$.

***N*-(3-((4-Fluorobenzyl)oxy)-4-((4-methylbenzyl)amino)phenyl)-4-methylbenzene sulfonamide (55).** To a solution of **53** (225 mg, 0.58 mmol) in dichloromethane (3 mL) were added sodium triacetoxyborohydride (247 mg, 1.16 mmol) and 4-methyl benzaldehyde (84 mg, 0.70 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 hours. The crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a pale yellow solid (178 mg, 62%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (brs, 1H, NH), 7.51-7.46 (m, 4H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.23-7.19 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 2.0 Hz, 1H), 6.29 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.21 (d, *J* = 8.4 Hz, 1H), 5.37 (t, *J* = 6.4 Hz, 1H, NH), 4.97 (s, 2H), 4.19 (d, *J* = 6.4 Hz, 2H), 2.32 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7 ($J_{C,F}$ = 242 Hz), 144.8, 142.6, 137.0, 136.9, 135.9, 135.5, 133.1, 129.7 ($J_{C,F}$ = 8 Hz), 129.3, 128.8, 126.9, 126.7, 125.7, 115.8, 115.1 ($J_{C,F}$ = 21 Hz), 109.6, 107.7, 68.8, 46.1, 20.9, 20.6; LC/MS (ESI) *m/z* 491.2 $[M + H]^+$.

Ethyl *N*-(4-(*N*-(2-ethoxy-2-oxoethyl)-4-methylbenzamido)-3-((4-fluorobenzyl)oxy) phenyl)-*N*-tosylglycinate (56a). Prepared as described in the experimental procedure of **15a** from intermediate **54** to obtain the title compound as a colorless oil (81 mg, 37%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45-7.41 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.30-7.226 (m, 4H), 7.05-7.02 (m, 4H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.01-4.98 (m, 1H), 4.87-4.84 (m, 1H), 4.63-4.59 (m, 1H), 4.44 (s, 2H), 4.13-4.11 (m, 1H), 4.10-4.00 (m, 4H), 2.38 (s, 3H), 2.27 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 169.3, 168.5, 162.7 ($J_{C,F}$ = 246 Hz),

153.0, 143.9, 140.2, 140.0, 135.1, 132.3, 132.2, 131.7, 131.0, 129.5 ($J_{C,F}$ = 8 Hz), 129.3, 128.5, 128.3, 127.8, 119.4, 115.7 ($J_{C,F}$ = 21 Hz), 114.8, 69.8, 61.6, 61.2, 50.7, 50.4, 21.6, 21.5, 14.2, 14.1; LC/MS (ESI) *m/z* 677.3 $[M + H]^+$.

Ethyl *N*-(4-((2-ethoxy-2-oxoethyl)(4-methylbenzyl)amino)-3-((4-fluorobenzyl)oxy) phenyl)-*N*-tosylglycinate (56b). Prepared as described in the experimental procedure of **15a** from intermediate **55** to obtain the title compound as a colorless oil (25 mg, 11%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8. 4 Hz, 2H), 7.37-7.33 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.08-7.01 (m, 4H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.94 (s, 2H), 4.45 (s, 2H), 4.32 (s, 2H), 4.13 (q, *J* = 7.2 Hz, 2H),), 4.01 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 2H), 2.40 (s, 3H), 2.33 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.1, 162.6 ($J_{C,F}$ = 243 Hz), 150.7, 143.6, 140.3, 136.9, 136.2, 135.1, 133.4, 132.6, 129.8 ($J_{C,F}$ = 8 Hz), 129.4, 129.2, 128.3, 128.1, 121.2, 120.2, 115.7, 115.5 ($J_{C,F}$ = 22 Hz), 70.4, 61.5, 60.5, 55.8, 53.2, 52.1, 21.7, 21.2, 14.3, 14.2; LC/MS (ESI) *m/z* 663.3 $[M + H]^+$.

***N*-(4-(*N*-(Carboxymethyl)-4-methylbenzamido)-3-((4-fluorobenzyl)oxy)phenyl)-*N*-tosylglycine (57a).** Prepared as described in the experimental procedure of **16a** from intermediate **56a** to obtain the title compound as a pale yellow solid (49 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (brs, 2H, CO_2H), 7.37-7.33 (m, 2H), 7.26-7.24 (m, 1H), 7.12-7.03 (m, 8H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.16 (d, *J* = 8.0 Hz, 1H), 6.17-6.15 (m, 1H), 4.98 (s, 2H), 4.93-4.89 (m, 1H), 4.44-4.40 (m, 1H), 4.19-4.07 (m, 2H), 2.37 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 173.5, 171.8, 162.8 ($J_{C,F}$ = 245 Hz), 153.0, 144.2, 140.8, 139.9, 134.7, 131.7, 131.5, 131.2, 129.7 ($J_{C,F}$ = 8 Hz), 129.5, 128.7, 128.5, 127.8, 119.1, 115.8 ($J_{C,F}$ = 21 Hz), 114.8, 70.0, 51.8, 50.1, 21.7, 21.6;

LC/MS (ESI) *m/z* 621.2 [M + H]$^+$; HRMS (ESI) *m/z* calcd for $C_{32}H_{29}FN_2O_8S$ [M + H]$^+$ 621.1701; found 621.1713.

***N*-(4-((Carboxymethyl)(4-methylbenzyl)amino)-3-((4-fluorobenzyl)oxy)phenyl)-*N*-tosylglycine (57b).** Prepared as described in the experimental procedure of **16a** from intermediate **56b** to obtain the title compound as a pale yellow solid (17 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.31-7.28 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.12-7.08 (m, 4H), 7.02-6.98 (m, 2H), 6.92-6.89 (m, 2H), 6.52 (s, 1H), 4.92 (s, 2H), 4.36 (s, 4H), 3.94 (s, 2H), 2.41 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 170.0, 161.8 ($J_{C,F}$ = 243 Hz), 149.7, 143.3, 139.0, 135.9, 135.1, 132.9 ($J_{C,F}$ = 3 Hz), 132.8, 129.9 ($J_{C,F}$ = 8 Hz), 129.5, 128.8, 128.7, 128.0, 127.3, 121.0, 119.5, 115.4 ($J_{C,F}$ = 27 Hz), 114.3, 69.6, 54.9, 52.4, 52.1, 21.0, 20.6; LC/MS (ESI) *m/z* 605.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{31}FN_2O_7S$ [M - H]$^-$ 605.1763; found 605.1772.

***N*-(3-((4-Fluorobenzyl)oxy)-4-nitrophenyl)-4-methylbenzamide (58).** To a solution of **21g** (300 mg, 1.14 mmol) in dichloromethane (6 mL) were added triethylamine (174 mg, 1.72 mmol) and 4-methylbenzoyl chloride (195 mg, 1.26 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a yellow solid (325 mg, 75%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H, NH), 8.03-8.00 (m, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.59-7.55 (m, 3H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.29-7.24 (m, 2H), 5.27 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-

d_6) δ 166.0, 161.9 ($J_{C,F}$ = 243 Hz), 152.6, 145.4, 142.4, 133.9, 132.1 ($J_{C,F}$ = 3 Hz), 131.3, 129.7 ($J_{C,F}$ = 9 Hz), 129.1, 127.9, 126.8, 115.3 ($J_{C,F}$ = 21 Hz), 111.6, 105.5, 69.7, 21.0.

3-((4-Fluorobenzyl)oxy)-*N*-(4-methylbenzyl)-4-nitroaniline (59). Prepared as described in the experimental procedure of **55** from intermediate **21g** to obtain the title compound as a yellow solid (251 mg, 90%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, *J* = 9.2 Hz, 1H), 7.64 (t, *J* = 6.0 Hz, 1H, NH), 7.52-7.48 (m, 2H), 7.24-7.19 (m, 4H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.38 (s, 1H), 6.29 (dd, *J* = 9.2, 1.6 Hz, 1H), 5.17 (s, 2H), 4.35 (d, *J* = 6.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 ($J_{C,F}$ = 244 Hz), 155.7, 153.8, 137.8, 134.4, 131.8 ($J_{C,F}$ = 3 Hz), 129.7, 129.4, 128.8, 128.7, 127.4, 115.7 ($J_{C,F}$ = 22 Hz), 105.1, 97.1, 70.4, 47.6, 21.2; LC/MS (ESI) *m/z* 367.2 $[M + H]^+$.

***N*-(3-((4-Fluorobenzyl)oxy)-4-((4-methylphenyl)sulfonamido)phenyl)-4-methyl-benzamide (60a).** Prepared as described in the experimental procedure of **22b** from intermediate **58** to obtain *N*-(4-amino-3-((4-fluorobenzyl)oxy) phenyl)-4-methylbenzamide as a dark brown oil (277 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (brs, 1H, NH), 7.84 (d, *J* = 8.0 Hz, 2H), 7.58-7.55 (m, 2H), 7.29 (d, *J* = 1.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.25-7.20 (m, 2H), 7.10 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 5.05 (s, 2H), 4.61 (brs, 2H, NH), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 161.7 ($J_{C,F}$ = 242 Hz), 144.7, 141.0, 134.3, 133.54, 133.51, 132.4, 129.6 ($J_{C,F}$ = 8 Hz), 128.8 ($J_{C,F}$ = 8 Hz), 127.4, 115.1 ($J_{C,F}$ = 22 Hz), 114.1, 113.6, 106.5, 68.8, 21.0.

Prepared as described in the experimental procedure of **22b** from *N*-(4-amino-3-((4-fluorobenzyl)oxy)phenyl)-4-methylbenzamide and 4-methylbenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (304 mg, 76%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (brs, 1H, NH), 9.38 (brs, 1H, NH), 7.83 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J*

= 2.04 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.35-7.29 (m, 5H), 7.21-7.15 (m, 5H), 4.79 (s, 2H), 2.38 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3, 161.7 ($J_{C,F}$ = 241 Hz), 151.8, 142.6, 141.6, 138.3, 137.8, 132.7, 131.9, 129.3 ($J_{C,F}$ = 8 Hz), 129.1, 128.9, 127.6, 126.8, 126.6, 120.5, 114.9 ($J_{C,F}$ = 22 Hz), 112.3, 105.0, 68.6, 21.0, 20.9; LC/MS (ESI) *m/z* 505.3 [M + H]$^+$.

***N*-(2-((4-Fluorobenzyl)oxy)-4-((4-methylbenzyl)amino)phenyl)-4-methylbenzene sulfonamide (60b).** Prepared as described in the experimental procedure of **22b** from intermediate **59** to obtain the title compound as a pale yellow solid (264 mg, 76% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.91-6.88 (m, 5H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 6.29 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.52 (s, 2H), 4.48 (s, 2H), 2.34 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 ($J_{C,F}$ = 248 Hz), 148.5, 143.7, 137.2, 136.3, 136.2, 135.3, 132.7, 131.3 ($J_{C,F}$ = 3 Hz), 129.4 ($J_{C,F}$ = 10 Hz), 129.3, 129.0, 128.6, 127.7, 127.1, 125.7, 121.4, 120.6, 115.6 ($J_{C,F}$ = 21 Hz), 114.5, 70.0, 54.4, 21.6; LC/MS (ESI) *m/z* 491.2 [M + H]$^+$..

Ethyl *N*-(4-(*N*-(2-ethoxy-2-oxoethyl)-4-methylbenzamido)-2-((4-fluorobenzyl)oxy) phenyl)-*N*-tosylglycinate (61a). Prepared as described in the experimental procedure of **15a** from intermediate **60a** to obtain the title compound as a colorless oil (41 mg, 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.03-7.00 (m, 4H), 6.97-6.92 (m, 2H), 6.88-6.85 (m, 2H), 6.82 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.55 (d, *J* = 2.0 Hz, 1H), 4.54 (s, 2H), 4.36 (s, 2H), 4.29 (s, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 2.30 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.22, 169.15, 162.5

($J_{C,F}$ = 246 Hz), 154.8, 145.3, 143.3, 140.5, 137.3, 134.5, 132.1, 131.3 ($J_{C,F}$ = 3 Hz), 129.1 ($J_{C,F}$ = 12 Hz), 128.7, 128.6, 128.5, 127.4, 125.5, 119.1, 115.4 ($J_{C,F}$ = 21 Hz), 113.3, 69.5, 61.5, 61.4, 52.2, 51.0, 21.59, 21.56, 14.3, 14.2; LC/MS (ESI) *m/z* 677.3 $[M + H]^+$.

Ethyl *N*-(4-((2-ethoxy-2-oxoethyl)(4-methylbenzyl)amino)-2-((4-fluorobenzyl)oxy) phenyl)-*N*-tosylglycinate (61b). Prepared as described in the experimental procedure of **15a** from intermediate **60b** to obtain the title compound as a colorless oil (22 mg, 6%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.14-7.08 (m, 6H), 7.00-6.92 (m, 4H), 6.19 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.08 (d, *J* = 2.4 Hz, 1H), 4.59 (s, 2H), 4.54 (s, 2H), 4.26 (s, 2H), 4.24-4.10 (m, 4H), 4.00 (s, 2H), 2.35 (s, 3H), 2.32 (s, 3H), 1.31-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.8, 169.7, 162.4 ($J_{C,F}$ = 244 Hz), 155.8, 150.3, 142.9, 138.0, 137.1, 134.8, 134.2, 132.4, 129.6, 129.1, 128.6 ($J_{C,F}$ = 8 Hz), 127.8, 126.9, 117.1, 115.4 ($J_{C,F}$ = 22 Hz), 104.9, 97.6, 69.1, 61.3, 61.2, 55.7, 52.7, 51.7, 21.6, 21.2, 14.4, 14.2 ; LC/MS (ESI) *m/z* 663.3 $[M + H]^+$.

***N*-(4-(*N*-(Carboxymethyl)-4-methylbenzamido)-2-((4-fluorobenzyl)oxy)phenyl)-*N*-tosylglycine (62a).** Prepared as described in the experimental procedure of **16a** from intermediate **61a** to obtain the title compound as a pale yellow solid (18 mg, 48%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (brs, 2H, CO_2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.95-6.91(m, 2H), 6.87-6.83 (m, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.50 (s, 1H), 4.58 (s, 2H), 4.35 (s, 4H), 2.33 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 161.4, 154.9, 144.9, 143.5, 141.0, 136.8, 134.6, 131.6, 131.2, 129.3, 129.2, 128.8, 128.7 ($J_{C,F}$ = 5 Hz), 127.5, 125.4, 119.6, 115.5 ($J_{C,F}$ = 22 Hz), 113.1, 69.7, 53.6, 21.7; LC/MS (ESI) *m/z* 621.2 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{32}H_{29}FN_2O_8S$ $[M + H]^+$ 621.1701; found 621.1711.

***N*-(4-((Carboxymethyl)(4-methylbenzyl)amino)-2-((4-fluorobenzyl)oxy)phenyl)-*N*-tosylglycine (62b).** Prepared as described in the experimental procedure of **16a** from intermediate **61b** to obtain the title compound as a pale yellow solid (9 mg, 46%); ^{1}H NMR (400 MHz, MeOD) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.12-7.10(m, 6H), 7.00-6.97 (m, 4H), 6.22 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.13 (d, *J* = 2.4 Hz, 1H), 4.55 (s, 2H), 4.52 (s, 2H), 4.27 (s, 2H), 4.12 (s, 2H), 2.31 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 174.6, 173.1, 162.5, 156.8, 151.6, 144.5, 138.8, 137.8, 136.6, 135.2, 134.1 ($J_{C,F}$ = 3 Hz), 130.3 ($J_{C,F}$ = 9 Hz), 130.0, 129.9, 128.6, 127.8, 117.5, 116.0 ($J_{C,F}$ = 21 Hz), 105.5, 98.7, 69.9, 56.6, 53.6, 52.7, 21.5, 21.1; LC/MS (ESI) *m/z* 605.2 [M - H]$^{-}$; HRMS (ESI) *m/z* calcd for $C_{32}H_{31}FN_2O_7S$ [M - H]$^{-}$ 605.1763; found 605.1771.

***N,N'*-(2-((4-Fluorobenzyl)oxy)-1,4-phenylene)bis(*N*-(cyanomethyl)-4-methyl benzenesulfonamide) (63).** Prepared as described in the experimental procedure of **15a** from intermediate **22g** and 2-bromoacetonitrile to obtain the title compound as a pale yellow solid (98 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 4H), 7.31-7.28 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.13-7.09 (m, 2H), 7.05 (s, 1H), 7.03-7.00 (m, 2H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.76 (s, 2H), 4.54 (s, 2H), 4.51 (s, 2H), 2.44 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 155.8, 145.3, 144.6, 140.8, 136.0, 134.0, 133.3, 130.9, 130.0, 129.8, 129.5 ($J_{C,F}$ = 9 Hz), 128.1, 127.7, 126.4, 119.5, 118.7 ($J_{C,F}$ = 22 Hz), 115.0, 114.8, 114.0, 70.2, 39.3, 38.3, 21.8, 21.7; LC/MS (ESI) *m/z* 619.2 [M + H]$^{+}$.

***N*-((1*H*-Tetrazol-5-yl)methyl)-*N*-(4-((*N*-((1*H*-tetrazol-5-yl)methyl)-4-methyl phenyl)sulfonamido)-2-((4-fluorobenzyl)oxy)phenyl)-4-methylbenzenesulfon-amide (64).** To a solution of **63** (40 mg, 0.06 mmol) in *N*,*N*-dimethylformamide (1 mL) were added sodium azide (25 mg, 0.39 mmol) and acetic acid (3 drops) at room temperature.

The reaction mixture was stirred at 120 °C for 6 hours. The crude mixture was added to water, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-10% methanol/ dichloromethane) to give the product as a white solid (14 mg, 30%); ^{1}H NMR (400 MHz, MeOD) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.36-7.33 (m, 4H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.13-7.03 (m, 4H), 6.76 (d, *J* = 2.4 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.12 (s, 2H), 5.10 (s, 2H), 4.50 (s, 2H), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 162.8, 156.6, 155.6, 146.1, 145.4, 142.1, 137.3, 135.2, 134.7, 133.1, 130.9, 130.7 ($J_{C,F}$ = 4 Hz), 130.6, 129.1, 128.6, 127.2, 121.4, 116.2 ($J_{C,F}$ = 22 Hz), 114.8, 70.8, 45.5, 44.2, 21.62, 21.58; LC/MS (ESI) *m/z* 705.2 [M + H]$^+$; HRMS (ESI) *m/z* calcd for $C_{31}H_{29}FN_{10}O_5S_2$ [M + H]$^+$ 705.1821; found 705.1822.

Dimethyl 2,2'-((2-((4-fluorobenzyl)oxy)-1,4-phenylene)bis(tosylazanediyl)) *(2S,2'S)* -dipropionate (65). Prepared as described in the experimental procedure of **15a** from intermediate **22g** and methyl *(R)*-2-bromopropanoate to obtain the title compound as a colorless oil (165 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 4H), 7.14-7.12 (m, 2H), 7.05-7.01 (m, 2H), 6.97-6.93 (m, 1H), 6.72-6.68 (m, 1H), 5.04 (q, *J* = 7.2 Hz, 1H), 4.78-4.64 (m, 3H), 3.67 (d, *J* = 5.2 Hz, 3H), 3.58 (d, *J* = 2.4 Hz, 3H), 2.41 (s, 3H), 2.38 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.22 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 163.8, 157.3, 143.7, 143.3, 138.1, 137.8, 136.9, 134.3, 131.8, 129.24, 129.15, 129.1, 128.2, 127.9, 125.8, 123.9, 117.1, 115.6, 115.4, 69.9, 57.5, 57.3, 52.4, 52.2, 21.7, 21.6, 17.1, 16.1; LC/MS (ESI) *m/z* 713.3 [M + H]$^+$.

***(2S,2'S)*-2,2'-((2-((4-Fluorobenzyl)oxy)-1,4-phenylene)bis(tosylazanediyl))dipropionic acid (66).** Prepared as described in the experimental procedure of **16a** from intermediate **65** to obtain the title compound as a white solid (28 mg, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.6 Hz, 2H), 7.47-7.45 (m, 1H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 2H), 7.16-7.12 (m, 6H), 6.90-6.80 (m, 2H), 4.77-4.74 (m, 1H), 4.57-4.46 (m, 3H), 2.36 (s, 3H), 2.30 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 163.7, 161.2, 156.7, 143.7, 143.2, 138.2, 137.3, 136.8, 134.6, 131.6, 129.2, 129.1, 129.0, 127.9, 127.7, 123.9, 116.6, 115.4, 115.1, 69.5, 57.8, 57.7, 21.4, 21.3, 16.9, 15.9; LC/MS (ESI) *m/z* 683.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{33}H_{33}FN_2O_9S_2$ $[M - H]^-$ 683.1539; found 683.1545.

1-Bromo-5-fluoro-2-methoxy-4-nitrobenzene (67a). Prepared as described in the experimental procedure of **40b** from 2-bromo-4-fluoro-5-nitrophenol and iodomethane to obtain the title compound as a pale yellow solid (993 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 2.4 Hz, 1H), 7.54 (d, *J* = 6.4 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6 ($J_{C,F}$ = 3 Hz), 149.5 ($J_{C,F}$ = 261 Hz), 136.2, 123.3 ($J_{C,F}$ = 24 Hz), 119.5 ($J_{C,F}$ = 8 Hz), 107.7 ($J_{C,F}$ = 3 Hz), 57.3.

5-Bromo-1-fluoro-3-methoxy-2-nitrobenzene (67b). To a solution of 5-bromo-1,3-difluoro-2-nitrobenzene (1.0 g, 4.20 mmol) in methanol (20 mL) was added potassium hydroxide (248 mg, 4.41 mmol) at room temperature. The reaction mixture was stirred at 90 °C for overnight. After the reaction was completed, the crude mixture was concentrated under reduced pressure, added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-20% ethyl acetate/hexane) to give

the product as a white solide (782 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05-7.00 (m, 2H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 ($J_{C,F}$ = 259 Hz), 153.0 ($J_{C,F}$ = 3 Hz), 130.1, 125.5 ($J_{C,F}$ = 11 Hz), 112.5 ($J_{C,F}$ = 23 Hz), 112.3 ($J_{C,F}$ = 4 Hz), 57.3; LC/MS (ESI) *m/z* 266.0 [M(^{79}Br) - H + H_2O]$^-$, 268.0 [M(^{81}Br) - H + H_2O]$^-$.

1-Bromo-5-((4-fluorobenzyl)oxy)-2-methoxy-4-nitrobenzene (68a). Prepared as described in the procedure of **21b** from **67a** and 4-fluorolbenzyl alcohol to obtain the title compound as a pale yellow solid (842 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.43-7.41 (m, 2H), 7.38 (s, 1H), 7.10-7.06 (m, 2H), 5.12 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 ($J_{C,F}$ = 246 Hz), 150.4, 146.3, 139.2, 131.2 ($J_{C,F}$ = 3 Hz), 129.3 ($J_{C,F}$ = 9 Hz), 121.6, 118.4, 115.8 ($J_{C,F}$ = 21 Hz), 108.7, 72.1, 57.2.

5-Bromo-1-((4-fluorobenzyl)oxy)-3-methoxy-2-nitrobenzene (68b). Prepared as described in the experimental procedure of **21b** from intermediate **67b** and 4-fluorolbenzyl alcohol to obtain the title compound as a pale yellow solid (478 mg, 48%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.40 (m, 2H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.26-7.21 (m, 2H), 7.18 (d, *J* = 1.6 Hz, 1H), 5.27 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 ($J_{C,F}$ = 243 Hz), 151.6, 150.3, 131.7 ($J_{C,F}$ = 3 Hz), 130.8, 129.9 ($J_{C,F}$ = 8 Hz), 124.7, 115.4 ($J_{C,F}$ = 21 Hz), 110.1, 109.2, 70.2, 57.3.

4,4'-(((5-Bromo-2-nitro-1,3-phenylene)bis(oxy))bis(methylene))bis(fluorobenzene) (68c). Prepared as described in the experimental procedure of **21b** from 5-bromo-1,3-difluoro-2-nitrobenzene and 4-fluorolbenzyl alcohol to obtain the title compound as a yellow solid (850 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.32 (m, 4H), 7.09-7.05 (m, 4H), 6.84 (s, 2H), 5.09 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 ($J_{C,F}$ = 246 Hz), 151.4, 130.8 ($J_{C,F}$ = 3 Hz), 129.3 ($J_{C,F}$ = 9 Hz), 124.9, 115.9 ($J_{C,F}$ = 22 Hz), 110.4, 71.0.

5-((4-Fluorobenzyl)oxy)-2-methoxy-4-nitroaniline (69a). Prepared as described in the experimental procedure of **32** from intermediate **68a** to obtain the title compound as a orange solid (275 mg, 56% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.55-7.52 (m, 2H), 7.45 (s, 1H), 7.26-7.21 (m, 2H), 6.47 (s, 1H), 6.41 (brs, 2H, NH), 5.12 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 161.7 ($J_{C,F}$ = 242 Hz), 150.9, 146.7, 139.1, 132.7 ($J_{C,F}$ = 3 Hz), 129.3 ($J_{C,F}$ = 8 Hz), 125.3, 117.2 ($J_{C,F}$ = 22 Hz), 107.8, 97.6, 69.7, 55.9; LC/MS (ESI) *m/z* 293.1 [M + H]$^+$.

3-((4-Fluorobenzyl)oxy)-5-methoxy-4-nitroaniline (69b). Prepared as described in the experimental procedure of **32** from intermediate **68b** to obtain the title compound as a yellow solid (199 mg, 52% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.44-7.41 (m, 2H), 7.24-7.20 (m, 2H), 5.99 (d, *J* = 1.6 Hz, 1H), 5.96 (brs, 2H, NH), 5.93 (d, *J* = 1.6 Hz, 1H), 5.07 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 161.8 ($J_{C,F}$ = 242 Hz), 153.6, 152.5, 152.4, 132.5 ($J_{C,F}$ = 3 Hz), 129.4 ($J_{C,F}$ = 8 Hz), 122.0, 115.3 ($J_{C,F}$ = 21 Hz), 90.4, 89.4, 69.1, 55.9; LC/MS (ESI) *m/z* 293.0 [M + H]$^+$.

3,5-Bis((4-fluorobenzyl)oxy)-4-nitroaniline (69c). Prepared as described in the experimental procedure of **32** from intermediate **68c** to obtain the title compound as a yellow solid (238 mg, 36% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.45-7.42 (m, 4H), 7.25-7.21 (m, 4H), 6.01 (s, 2H), 5.96 (brs, 2H, NH), 5.08 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 161.8 ($J_{C,F}$ = 242 Hz), 152.4, 132.5 ($J_{C,F}$ = 3 Hz), 129.4 ($J_{C,F}$ = 8 Hz), 122.3, 115.3 ($J_{C,F}$ = 22 Hz), 90.7, 69.1; LC/MS (ESI) *m/z* 387.1 [M + H]$^+$.

***N,N'*-(2-((4-Fluorobenzyl)oxy)-5-methoxy-1,4-phenylene)bis(4-methylbenzene sulfonamide) (70a).** Prepared as described in the experimental procedure of **22b** from intermediate **69a** to obtain the title compound as a pale blue solid (25 mg, 9% over 2 steps);

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.40 (brs, 1H, NH), 7.48 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.26-7.23 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.18-7.14 (m, 2H), 6.78 (s, 1H), 6.75 (s, 1H), 4.69 (s, 2H), 3.35 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 161.7 ($J_{C,F}$ = 241 Hz), 145.9, 144.7, 143.02, 142.99, 137.5, 137.2, 132.9, 129.3 ($J_{C,F}$ = 7 Hz), 129.2, 126.74, 126.69, 123.4, 114.9 ($J_{C,F}$ = 21 Hz), 110.4, 110.0, 69.4, 56.1, 21.0; LC/MS (ESI) *m/z* 569.1 [M - H]$^-$.

***N,N'*-(2-((4-Fluorobenzyl)oxy)-6-methoxy-1,4-phenylene)bis(4-methylbenzenesulfonamide) (70b).** Prepared as described in the experimental procedure of **22b** from intermediate **69b** to obtain the title compound as a white solid (161 mg, 57% over 2 steps); ^{1}H NMR (400 MHz) (CDCl$_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.27-7.23 (m, 2H), 7.26 (brs, 1H, NH), 7.18 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.01-6.97 (m, 2H), 6.35 (d, *J* = 2.0 Hz, 1H), 6.18 (d, *J* = 2.0 Hz, 1H), 6.14 (brs, 1H, NH), 4.80 (s, 2H), 3.41 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz) (CDCl$_3$) δ 161.8 ($J_{C,F}$ = 242 Hz), 155.9, 154.8, 144.2, 143.2, 138.2, 136.8, 136.0, 132.0, 129.8, 129.3 ($J_{C,F}$ = 8 Hz), 129.0, 127.41, 127.37, 115.5 ($J_{C,F}$ = 21 Hz), 111.3, 99.0, 97.7, 70.1, 55.8, 21.7, 21.6; LC/MS (ESI): m/z 569.1 [M-H]$^-$.

***N,N'*-(2,6-Bis((4-fluorobenzyl)oxy)-1,4-phenylene)bis(4-methylbenzenesulfonami-de) (70c).** Prepared as described in the experimental procedure of **22b** from intermediate **69c** to obtain the title compound as a pale yellow solid (189 mg, 73% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.25 (brs, 1H, NH), 8.77 (brs, 1H, NH), 7.52 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.35-7.32 (m, 4H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.18-7.14 (m, 4H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.38 (s, 2H), 4.75 (s, 4H), 2.34 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 161.6 ($J_{C,F}$ = 242 Hz), 156.3, 143.3, 141.7, 139.7, 138.1, 136.4,

132.7 ($J_{C,F}$ = 2 Hz), 129.6, 129.1 ($J_{C,F}$ = 8 Hz), 128.6, 126.7, 126.3, 114.9 ($J_{C,F}$ = 21 Hz), 109.5, 96.9, 68.7, 20.9, 20.8; LC/MS (ESI) *m/z* 665.3 $[M + H]^+$.

Diethyl 2,2'-((2-((4-fluorobenzyl)oxy)-5-methoxy-1,4-phenylene)bis (tosylazanediyl))diacetate (71a). Prepared as described in the experimental procedure of **15a** from **70a** to obtain the title compound as a pale orange oil (22 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.25-7.23 (m, 3H), 7.09-7.07 (m, 3H), 6.98 (d, *J* = 6.8 Hz, 4H), 4.65 (s, 2H), 4.36 (s, 2H), 4.32 (s, 2H), 4.18-4.13 (m, 4H), 3.32 (s, 3H), 2.41 (s, 3H), 2.31 (s, 3H), 1.26-1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.4, 162.5 ($J_{C,F}$ = 245 Hz), 149.5, 148.1, 143.5, 137.3, 137.1, 131.9 ($J_{C,F}$ = 3 Hz), 129.3, 129.2, 128.9 ($J_{C,F}$ = 8 Hz), 127.9, 127.7, 127.6, 118.4, 117.6, 115.4 ($J_{C,F}$ = 21 Hz), 69.8, 61.43, 61.38, 55.6, 51.04, 51.00, 21.6, 14.3; LC/MS (ESI) *m/z* 743.3 $[M + H]^+$.

Diethyl 2,2'-((2-((4-fluorobenzyl)oxy)-6-methoxy-1,4-phenylene)bis (tosylazanediyl))diacetate (71b). Prepared as described in the procedure of **15a** from **70b** to obtain the title compound as a colorless oil (102 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 6.8 Hz, 2H), 7.59 (d, *J* = 6.8 Hz, 2H), 7.30-7.24 (m, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 7.02-6.98 (m, 2H), 6.49 (s, 1H), 6.38 (s, 1H), 4.84-4.75 (m, 2H), 4.36 (s, 2H), 4.19 (s, 2H), 4.17-4.14 (m, 2H), 4.02-3.97 (m, 2H), 3.46 (s, 3H), 2.40 (s, 3H), 2.34 (s, 3H), 1.25-1.22 (m, 3H), 1.11-1.07 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.6, 162.5 ($J_{C,F}$ = 244 Hz), 158.5, 157.5, 144.0, 143.2, 141.4, 137.4, 135.9, 132.0 ($J_{C,F}$ = 3 Hz), 129.5, 129.1 ($J_{C,F}$ = 8 Hz), 129.0, 128.1, 128.0, 116.9, 115.3 ($J_{C,F}$ = 21 Hz), 106.4, 105.4, 70.1, 61.7, 61.0, 55.8, 52.7, 51.2, 21.6, 21.5, 14.2, 14.0; LC/MS (ESI) *m/z* 743.3 $[M + H]^+$.

Diethyl 2,2'-((2,6-bis((4-fluorobenzyl)oxy)-1,4-phenylene)bis(tosylazanediyl))diacetate (71c). Prepared as described in the experimental procedure of **15a** from

intermediate **70c** to obtain the title compound as a colorless oil (121 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.58 (m, 4H), 7.27-7.24 (m, 6H), 7.03-6.96 (m, 6H), 6.53 (s, 2H), 4.84-4.74 (m, 4H), 4.36 (s, 2H), 4.19-4.14 (m, 4H), 3.98-3.94 (m, 2H), 2.41 (s, 3H), 2.28 (s, 3H), 1.26-1.23 (m, 3H), 1.07-1.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.4, 162.5 ($J_{C,F}$ = 244 Hz), 157.6, 144.0, 143.2, 141.4, 137.2, 136.0, 131.9 ($J_{C,F}$ = 3 Hz), 129.5, 129.2 ($J_{C,F}$ = 8 Hz), 129.0, 128.1, 128.0, 117.2, 115.3 ($J_{C,F}$ = 22 Hz), 106.5, 70.1, 61.7, 61.0, 52.7, 51.2, 21.6, 21.5, 14.2, 14.0; LC/MS (ESI) *m/z* 837.3 $[M + H]^+$.

2,2'-((2-((4-Fluorobenzyl)oxy)-5-methoxy-1,4-phenylene)bis(tosylazanediyl))diac-etic acid (72a). Prepared as described in the experimental procedure of **16a** from intermediate **71a** to obtain the title compound as a beige solid (16 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.28-7.24 (m, 2H), 7.15 (s, 1H), 7.12-7.08 (m, 2H), 7.01 (s, 1H), 6.97 (d, *J* = 7.2 Hz, 4H), 4.62 (s, 2H), 4.41 (s, 2H), 4.38 (s, 2H), 3.29 (s, 3H), 2.42 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.19, 170.15, 161.7 ($J_{C,F}$ = 241 Hz), 149.1, 147.8, 143.34, 143.25, 136.5, 132.4 ($J_{C,F}$ = 3 Hz), 129.30, 129.25, 129.2 ($J_{C,F}$ = 9 Hz), 127.7, 127.2, 127.0, 117.7, 116.8, 114.9 ($J_{C,F}$ = 21 Hz), 69.2, 55.6, 51.0, 21.0, 20.9; LC/MS (ESI) *m/z* 685.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{31}FN_2O_{10}S_2$ $[M - H]^-$ 685.1331; found 685.1338.

2,2'-((2-((4-Fluorobenzyl)oxy)-6-methoxy-1,4-phenylene)bis(tosylazanediyl))diac-etic acid (72b). Prepared as described in the experimental procedure of **16a** from intermediate **71b** to obtain the title compound as a white solid (35 mg, 37%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.229-7.19 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.04-7.00 (m, 2H), 6.56 (s, 1H), 6.41 (s, 1H), 4.85-4.76 (m, 2H), 4.43 (s, 2H), 4.21-4.10 (m, 2H), 3.51 (s, 3H), 2.44 (s, 3H), 2.36 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 172.6, 170.4, 162.8 ($J_{C,F}$ = 247 Hz), 157.7, 156.7, 144.6, 144.4, 142.3, 135.9, 135.5, 130.9 ($J_{C,F}$ = 2 Hz), 129.8, 129.6, 129.5, 128.1, 128.0, 116.2, 115.7 ($J_{C,F}$ = 21 Hz), 106.5, 105.4, 70.7, 56.4, 53.6, 52.1, 21.71, 21.66; LC/MS (ESI) *m/z* 685.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{31}FN_2O_{10}S_2$ $[M - H]^-$ 685.1331; found 685.1327.

***N*-(3,5-Bis((4-fluorobenzyl)oxy)-4-((*N*-(2-methoxy-2-oxoethyl)-4-methylphenyl) sulfonamido)phenyl)-*N*-tosylglycine (72c).** Prepared as described in the procedure of **16a** from **71c** to obtain the title compound as a white solid (25 mg, 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.29-7.26 (m, 2H), 7.21-7.18 (m, 4H), 7.04-6.99 (m, 6H), 6.56 (s, 2H), 4.84-4.75 (m, 4H), 4.41 (s, 2H), 4.15 (s, 2H), 2.43 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 162.9 ($J_{C,F}$ = 246 Hz), 156.8, 144.6, 144.5, 142.3, 135.7, 135.5, 130.7, 129.8, 129.6 ($J_{C,F}$ = 8 Hz), 128.1, 116.5, 115.8 ($J_{C,F}$ = 21 Hz), 106.5, 70.8, 52.2, 52.0, 21.8, 21.7; LC/MS (ESI) *m/z* 779.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{38}H_{34}F_2N_2O_{10}S_2$ $[M - H]^-$ 779.1550; found 779.1545.

***N,N'*-(2-Hydroxy-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (73).** To a solution of **22b** (800 mg, 1.44 mmol) in methanol (30 mL) was added Pd/C (10% wt.) (80 mg) at room temperature under N_2. The reaction mixture was stirred at room temperature for 4 hours under H_2. After the reaction was completed, the crude mixture was filtered off through celite, and then concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-70% ethyl acetate/hexane) to give the product as a white solid (483 mg, 72%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (brs, 1H, NH), 9.48 (brs, 1H, NH), 8.89 (brs, 1H, OH), 7.63 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.43 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)

δ 162.3, 162.1, 151.0, 136.0, 132.2, 131.1, 128.80, 128.76, 125.7, 120.2, 114.2, 113.8, 110.6, 107.3, 55.6, 55.5; LC/MS (ESI) *m/z* 465.1 $[M + H]^+$.

2,5-Bis((4-methoxyphenyl)sulfonamido)phenyl benzoate (74a). To a solution of **73** (70 mg, 0.15 mmol) in dichloromethane (1 mL) were added triethylamine (18 mg, 0.18 mmol) and benzoyl chloride (21 mg, 0.15 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. The crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (27 mg, 36%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.70-7.66 (m, 3H), 7.53-7.47 (m, 5H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 162.9, 162.7, 136.6, 133.6, 131.0, 130.4, 129.9, 129.6, 129.0, 128.6, 128.3, 128.2, 124.3, 118.0, 115.0, 113.8, 113.7, 55.1; LC/MS (ESI) *m/z* 569.1 $[M + H]^+$.

2,5-Bis((4-methoxyphenyl)sulfonamido)phenyl benzenesulfonate (74b). Prepared as described in the procedure of **74a** from **73** and benzenesulfonyl chloride to obtain the title compound as a white solid (86 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.62-7.53 (m, 6H), 7.38 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.86-6.79 (m, 4H), 3.83 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 163.5, 141.0, 135.3, 134.8, 134.5, 130.6, 130.1, 129.8, 129.57, 129.55, 128.5, 126.9, 125.0, 120.6, 115.9, 114.5, 114.3, 55.8, 55.7; LC/MS (ESI) *m/z* 605.1 $[M + H]^+$.

Di-*tert*-butyl 2,2'-((2-(benzoyloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetate (75a). To a solution of **74a** (27 mg, 0.05 mmol) in *N,N*-

dimethylformamide (0.5 mL) were added potassium carbonate (16 mg, 0.12 mmol) and *tert*-butyl 2-bromoacetate (28 mg, 0.14 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to water, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a colorless oil (28 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.58-7.52 (m, 3H), 6.45 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.10 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 4.28 (s, 2H), 4.17 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 1.42 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 167.6, 163.7, 163.3, 163.1, 148.3, 141.1, 134.0, 133.7, 131.5, 130.8, 130.3, 130.2, 129.7, 128.6, 125.4, 123.3, 114.2, 114.1, 82.7, 82.4, 55.7, 55.6, 53.2, 52.7, 28.09, 28.06; LC/MS (ESI) *m/z* 815.3 $[M + H + H_2O]^+$.

Di-*tert*-butyl 2,2'-((2-((phenylsulfonyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl) sulfonyl)azanediyl))diacetate (75b). Prepared as described in the procedure of **75a** from **74b** to obtain the title compound as a colorless oil (77 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.61-7.53 (m, 5H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.07 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.22 (s, 2H), 4.16 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 167.4, 163.4, 163.2, 146.9, 141.4, 136.0, 134.6, 134.2, 131.4, 131.0, 130.1, 129.92, 129.89, 129.5, 128.3, 125.7, 121.0, 114.3, 114.0, 82.7, 82.2, 55.7, 55.6, 52.9, 52.8, 28.03, 27.98; LC/MS (ESI) *m/z* 849.1 $[M - H + H_2O]^-$.

2,2'-((2-(Benzoyloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetic acid (76a). To a solution of **75a** (28 mg, 0.12 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.2 mL) at room temperature. The reaction mixture was stirred at room temperature for 4 hours. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting solid was dissolved with the minimum amount of dichloromethane, solidified from hexane, and then filtered to give the product as a white solid (22 mg, 92%); ^{1}H NMR (400 MHz, MeOD) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.70-7.64 (m, 3H), 7.53-7.48 (m, 5H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.43 (s, 2H), 4.31 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.1, 165.2, 165.0, 164.8, 149.5, 142.5, 135.1, 134.5, 132.4, 132.0, 131.3, 131.1, 130.7, 130.0, 129.7, 126.6, 124.5, 115.3, 56.3, 56.2, 53.0; LC/MS (ESI) *m/z* 683.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{31}H_{28}N_2O_{12}S_2$ $[M - H]^-$ 683.1011; found 683.1017.

2,2'-((2-((Phenylsulfonyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)aza-nediyl))diacetic acid (76b). Prepared as described in the experimental procedure of **76a** from intermediate **75b** to obtain the title compound as a white solid (27 mg, 41%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.63-7.55 (m, 6H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.04 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.41 (s, 2H), 4.36 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 163.0, 162.7, 146.1, 141.0, 135.3, 134.7, 133.7, 130.5, 129.9, 129.5, 129.4, 127.8, 124.4, 119.5, 114.5, 114.1, 55.8, 55.6, 51.6, 51.5;

LC/MS (ESI) *m/z* 719.0 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_2O_{13}S_3$ [M - H]$^-$ 719.0681; found 719.0688.

Diethyl 2,2'-((2-(2-oxo-2-phenylethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (77a). Prepared as described in the experimental procedure of **40b** from intermediate **39** and 2-chloroacetophenone to obtain the title compound as a yellow oil (27 mg, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 9.2 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 9.2 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.59 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.84 (s, 2H), 4.52 (s, 2H), 4.32 (s, 2H), 4.17-4.09 (m, 4H), 3.83 (s, 3H), 3.66 (s, 3H), 1.26-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 168.8, 163.4, 162.9, 162.7, 154.4, 141.3, 134.5, 134.2, 131.8, 130.1, 129.9, 129.1, 127.9, 127.2, 120.0, 114.1, 113.7, 70.1, 61.7, 61.3, 55.7, 55.5, 52.5, 51.2, 14.24, 14.18; LC/MS (ESI) *m/z* 755.2 [M + H]$^+$.

Diethyl 2,2'-((2-(2-oxo-2-(phenylamino)ethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (77b). Prepared as described in the experimental procedure of **40b** from intermediate **39** and 2-bromo-*N*-phenylacetamide to obtain the title compound as a yellow oil (29 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H, NH), 7.76 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.33 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.76 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.51 (s, 2H), 4.36 (s, 4H), 4.17-4.07 (m, 4H), 3.84 (s, 3H), 3.83 (s, 3H), 1.25-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.8, 165.4, 163.53, 163.48, 155.1, 142.3, 137.9, 132.4,

130.5, 130.3, 130.2, 129.0, 127.5, 124.6, 121.2, 120.4, 114.20, 114.15, 112.5, 67.3, 61.8, 61.7, 55.79, 55.75, 52.4, 51.8, 14.22, 14.17; LC/MS (ESI) *m/z* 770.2 $[M + H]^+$.

Diethyl 2,2'-((2-(2-morpholino-2-oxoethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (77c). Prepared as described in the procedure of **40b** from **39** and 2-bromo-1-morpholinoethan-1-one to obtain the title compound as a pale yellow oil (29 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.92-6.88 (m, 5H), 6.54 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.47 (s, 2H), 4.42 (s, 2H), 4.32 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.85 (s, 3H), 3.70-3.68 (m, 4H), 3.59-3.57 (m, 2H), 3.46-3.44 (m, 2H), 1.24-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.8, 165.2, 163.4, 163.0, 154.9, 141.4, 133.5, 131.9, 130.2, 130.1, 130.0, 127.3, 119.9, 114.1, 114.0, 113.8, 66.8, 61.7, 61.3, 55.74, 55.71, 52.5, 51.1, 45.5, 42.4, 14.2; LC/MS (ESI) *m/z* 764.2 $[M + H]^+$.

Diethyl 2,2'-((2-(2-morpholinoethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (77d). Prepared as described in the experimental procedure of **40b** from intermediate **39** and 4-(2-chloroethyl)morpholine hydrochloride to obtain the title compound as a pale yellow oil (29 mg, 31%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 6.93-6.87 (m, 5H), 6.52 (d, *J* = 8.4 Hz, 1H), 4.39 (s, 2H), 4.33 (s, 2H), 4.18-4.12 (m, 4H), 3.86 (s, 6H), 3.75-3.74 (m, 2H), 3.72-3.68 (m, 4H), 2.42-2.41 (m, 4H), 2.36-2.35 (m, 2H), 1.25-1.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.8, 163.4, 163.0, 155.2, 141.4, 134.0, 132.2, 130.3, 130.1, 129.8, 126.8, 119.1, 114.1, 113.8, 67.0, 65.7, 61.7, 61.3, 57.0, 55.8, 54.0, 52.5, 50.8, 14.2; LC/MS (ESI) *m/z* 750.3 $[M + H]^+$.

2,2'-((2-(2-Oxo-2-phenylethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetic acid (78a). Prepared as described in the experimental procedure of **16a** from intermediate **77a** to obtain the title compound as a yellow solid (14 mg, 56%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.60-7.53 (m, 4H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.92-6.88 (m, 3H), 6.66 (s, 1H), 4.96 (s, 2H), 4.37 (s, 2H), 4.35 (s, 2H), 3.77 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.8, 170.4, 169.7, 162.7, 162.3, 153.7, 140.8, 134.0, 133.9, 133.2, 131.2, 129.7, 129.5, 129.3, 128.8, 127.6, 125.7, 120.4, 114.2, 113.8, 111.7, 70.1, 55.6, 55.3, 51.7, 50.6; LC/MS (ESI) *m/z* 697.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{30}N_2O_{12}S_2$ [M - H]$^-$ 697.1167; found 697.1174.

2,2'-((2-(2-Oxo-2-(phenylamino)ethoxy)-1,4-phenylene)bis(((4-methoxyphenyl) sulfonyl)azanediyl))diacetic acid (78b). Prepared as described in the experimental procedure of **16a** from **77b** to obtain the title compound as a white solid (15 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H, NH), 7.68-7.66 (m, 4H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.31 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.88-6.84 (m, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.79 (s, 2H), 4.53 (s, 2H), 4.37 (s, 2H), 3.84 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.9, 165.4, 162.8, 162.6, 154.1, 141.1, 138.1, 132.6, 130.9, 129.8, 129.6, 129.3, 128.8, 126.0, 123.8, 119.6, 114.3, 114.0, 111.6, 66.8, 55.7, 55.5, 51.7, 51.1; LC/MS (ESI) *m/z* 712.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{31}N_3O_{12}S_2$ [M - H]$^-$ 712.1276; found 712.1284.

2,2'-((2-(2-Morpholino-2-oxoethoxy)-1,4-phenylene)bis(((4-methoxyphenyl) sulfonyl)azanediyl))diacetic acid (78c). Prepared as described in the experimental procedure of **16a** from intermediate **77c** to obtain the title compound as a white solid (10

mg, 37%); ^{1}H NMR (400 MHz, MeOD) δ 7.61-7.48 (m, 4H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.03-6.94 (m, 4H), 6.82 (d, *J* = 6.8 Hz, 1H), 6.74-6.65 (m, 1H), 4.45 (s, 2H), 3.88-3.87 (m, 2H), 3.98 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.68-7.65 (m, 4H), 3.54-3.52 (m, 2H), 3.42-3.40 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ 164.9, 164.7, 164.6, 155.9, 142.9, 134.7, 132.8, 131.19, 131.17, 130.94, 130.88, 128.1, 121.0, 115.22, 115.18, 115.0, 114.9, 67.6, 67.0, 56.29, 56.26, 56.2, 53.4, 52.3, 46.4, 43.4; LC/MS (ESI) *m/z* 708.2 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{30}H_{33}N_3O_{13}S_2$ $[M + H]^+$ 708.1528; found 708.1539.

2,2'-((2-(2-Morpholinoethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetic acid (78d). Prepared as described in the experimental procedure of **16a** from intermediate **77d** to obtain the title compound as a white solid (18 mg, 65%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.85-6.81 (m, 1H), 6.63 (s, 1H), 4.40 (s, 2H), 4.26 (s, 2H), 3.84 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.61-3.57 (m, 10H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.5, 169.9, 162.9, 162.7, 154.2, 141.1, 132.4, 131.3, 129.9, 129.7, 129.5, 126.1, 119.6, 114.5, 114.2, 112.0, 69.8, 63.3, 63.0, 55.9, 55.8, 54.8, 51.8, 51.1; LC/MS (ESI) *m/z* 692.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{30}H_{35}N_3O_{12}S_2$ $[M - H]^-$ 692.1589; found 692.1598.

Diethyl 2,2'-((2-(2-(*tert*-butoxy)-2-oxoethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (79). Prepared as described in the experimental procedure of **40b** from intermediate **39** and *tert*-butyl 2-bromoacetate to obtain the title compound as a white solid (103 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.75 (s, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 4.41 (s, 2H), 4.28 (s, 2H), 4.13-

4.07 (m, 2H), 4.01 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 1.42 (s, 9H), 1.20-1.16 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.7, 166.3, 163.3, 162.9, 154.0, 141.2, 134.3, 131.7, 130.1, 130.0, 129.8, 126.8, 119.6, 114.0, 113.6, 113.4, 82.7, 65.2, 61.5, 61.1, 55.64, 55.58, 52.4, 50.9, 28.0, 14.1; LC/MS (ESI) *m/z* 695.2 $[M + H - C_4H_8]^+$.

2-(2,5-Bis((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)phenoxy) acetic acid (80). Prepared as described in the experimental procedure of **76a** from intermediate **79** to obtain the title compound as a pale yellow solid (93 mg, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.2 Hz, 2H), 7.62 (d, *J* = 9.2 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.72 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.39-4.38 (m, 6H), 4.21-4.14 (m, 4H), 3.89 (s, 3H), 3.88 (s, 3H), 1.28-1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.9, 168.8, 163.6, 163.5, 154.4, 141.9, 133.3, 130.6, 130.3, 130.2, 130.1, 127.5, 121.2, 114.3, 114.1, 113.3, 65.2, 61.9, 61.8, 55.8, 52.5, 51.7, 14.2; LC/MS (ESI) *m/z* 695.3 $[M - H]^-$.

Diethyl 2,2'-((2-(2-(4-methylpiperazin-1-yl)-2-oxoethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (81). Prepared as described in the experimental procedure of **54** from intermediate **80** and 1-methylpiperazine to obtain the title compound as a pale yellow oil (88 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.93-6.87 (m, 5H), 6.55 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.49 (s, 2H), 4.39 (s, 2H), 4.33 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 6H), 3.64-3.60 (m, 2H), 3.46-3.42 (m, 2H), 2.48-2.40 (m, 4H), 2.33 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.7, 164.7, 163.3, 162.9, 154.7, 141.2, 133.6, 131.8, 130.1, 130.0, 129.9,

127.1, 119.7, 114.0, 113.8, 113.7, 66.4, 61.5, 61.2, 55.64, 55.61, 55.0, 54.4, 52.4, 51.0, 46.0, 44.7, 41.9, 14.1; LC/MS (ESI) *m/z* 777.3 $[M + H]^+$.

2,2'-((2-(2-(4-Methylpiperazin-1-yl)-2-oxoethoxy)-1,4-phenylene)bis(((4-methoxy-phenyl)sulfonyl)azanediyl))diacetic acid (82). Prepared as described in the experimental procedure of **16a** from intermediate **81** to obtain the title compound as a pale yellow solid (13 mg, 35%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.9 (brs, 2H, CO_2H), 7.55 (d, *J* = 8.8 Hz, 4H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 9.2 Hz, 2H), 7.01 (d, *J* = 9.2 Hz, 2H), 6.74-6.72 (m, 2H), 4.75-4.55 (m, 6H), 4.38-4.37 (m, 4H), 3.85 (s, 3H), 3.84 (s, 3H), 2.77-2.75 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.8, 170.1, 165.5, 163.0, 162.7, 154.2, 141.0, 133.1, 131.4, 129.84, 129.78, 129.6, 127.3, 126.0, 119.2, 114.5, 114.2, 65.4, 56.0, 55.9, 52.5, 52.4, 51.9, 50.7, 42.6, 41.3, 41.1; LC/MS (ESI) *m/z* 719.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{31}H_{36}N_4O_{12}S_2$ $[M - H]^-$ 719.1698; found 719.1707.

Phenyl 5-amino-2-nitrobenzoate (83a). To a solution of 5-amino-2-nitrobenzoic acid (250 mg, 1.37 mmol) in dichloromethane (7 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (316 mg, 1.65 mmol), 4-(dimethylamino)pyridine (17 mg, 0.14 mmol) and phenol (155 mg, 1.65 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-40% ethyl acetate/hexane) to give the product as a yellow solid (97 mg, 27%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.8 Hz, 1H), 7.44-7.40 (m, 2H), 7.30-7.26 (m, 3H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.62 (dd, *J* = 8.8,

2.4 Hz, 1H), 4.75 (s, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 152.6, 150.6, 131.7, 129.7, 127.5, 126.5, 121.4, 114.6, 113.1; LC/MS (ESI) *m/z* 259.1 $[M + H]^+$.

Benzyl 5-amino-2-nitrobenzoate (83b). Prepared as described in the experimental procedure of **83a** from 5-amino-2-nitrobenzoic acid and benzyl alcohol to obtain the title compound as a yellow solid (37 mg, 12%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.6 Hz, 1H), 7.41-7.32 (m, 5H), 6.62-6.59 (m, 2H), 5.34 (s, 2H), 4.61 (s, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 152.1, 136.5, 135.1, 132.3, 128.74, 128.66, 127.4, 113.4, 113.1, 63.4; LC/MS (ESI) *m/z* 291.1 $[M + H + H_2O]^+$.

Phenyl 2,5-bis((4-methoxyphenyl)sulfonamido)benzoate (84a). Prepared as described in the experimental procedure of **22b** from intermediate **83a** to obtain the title compound as a pale yellow solid (76 mg, 36% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (brs, 1H, NH), 7.79 (d, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.39-7.35 (m, 2H), 7.24-7.21 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 4H), 3.77 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 163.44, 163.41, 150.0, 138.5, 132.1, 130.6, 130.2, 129.7, 129.63, 129.56, 129.1, 126.6, 125.0, 121.5, 120.8, 116.2, 114.42, 114.36, 55.72, 55.70; LC/MS (ESI) *m/z* 569.1 $[M + H]^+$.

Benzyl 2,5-bis((4-methoxyphenyl)sulfonamido)benzoate (84b). Prepared as described in the experimental procedure of **22b** from intermediate **83b** to obtain the title compound as a pale yellow solid (30 mg, 64% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (brs, 1H, NH), 7.68 (d, *J* = 8.8 Hz, 2H), 7.62-7.55 (m, 4H), 7.40-7.35 (m, 5H), 7.15 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.25 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 163.4, 163.3, 138.1, 135.1, 131.9, 130.8,

130.2, 129.6, 129.5, 128.9, 128.8, 128.5, 128.3, 124.4, 120.7, 117.0, 114.4, 114.3, 67.5, 55.7; LC/MS (ESI) *m/z* 583.2 $[M + H]^+$.

Di-*tert*-butyl 2,2'-((2-(phenoxycarbonyl)-1,4-phenylene)bis(((4-methoxyphenyl) sulfonyl)azanediyl))diacetate (85a). Prepared as described in the procedure of **75a** from **84a** to obtain the title compound as a colorless oil (96 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.4 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.44-7.37 (m, 3H), 7.30-7.28 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.35 (s, 4H), 3.84 (s, 6H), 1.45 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.4, 163.5, 163.3, 163.0, 150.6, 140.8, 138.0, 134.6, 131.99, 131.96, 131.6, 130.6, 130.1, 130.0, 129.5, 126.2, 121.6, 114.3, 113.9, 82.8, 82.1, 55.7, 55.6, 54.1, 52.9, 28.1, 28.0; LC/MS (ESI) *m/z* 685.1 $[M + H - C_8H_{16}]^+$.

Di-*tert*-butyl 2,2'-((2-((benzyloxy)carbonyl)-1,4-phenylene)bis(((4-methoxyphenyl) sulfonyl)azanediyl))diacetate (85b). Prepared as described in the experimental procedure of **75a** from intermediate **84b** to obtain the title compound as a colorless oil (40 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.4 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.38-7.35 (m, 5H), 7.28 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.09 (s, 2H), 4.27 (s, 4H), 3.82 (s, 3H), 3.79 (s, 3H), 1.41 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 167.4, 164.6, 163.4, 163.0, 140.7, 137.6, 135.4, 134.4, 132.4, 131.8, 131.4, 130.2, 130.1, 130.0, 128.7, 128.6, 128.5, 114.2, 113.8, 82.7, 82.1, 67.4, 55.7, 55.6, 54.3, 52.9, 28.1, 28.0; LC/MS (ESI) *m/z* 699.2 $[M + H - C_8H_{16}]^+$.

2,2'-((2-((Phenylsulfonyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetic acid (86a). Prepared as described in the experimental procedure of

76a from **85a** to obtain the title compound as a white solid (65 mg, 78%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.89 (brs, 2H, CO_2H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.49-7.45 (m, 4H), 7.42 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 9.2 Hz, 2H), 7.03 (d, *J* = 9.2 Hz, 2H), 4.49 (s, 4H), 3.82 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 169.8, 162.9, 162.8, 162.7, 150.3, 140.2, 137.0, 133.2, 131.2, 130.8, 130.6, 129.9, 129.64, 129.55, 129.5, 129.4, 126.0, 121.5, 114.5, 114.1, 55.7, 55.6, 52.8, 51.5; LC/MS (ESI) *m/z* 683.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{31}H_{28}N_2O_{12}S_2$ [M - H]$^-$ 683.1011; found 683.1017.

2,2'-((2-((Benzyloxy)carbonyl)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetic acid (86b). Prepared as described in the experimental procedure of **76a** from intermediate **85b** to obtain the title compound as a white solid (29 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-7.97 (m, 3H), 7.66 (d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.43-7.33 (m, 6H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.29 (s, 2H), 4.41 (s, 2H), 4.26 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 171.3, 166.7, 163.9, 163.7, 140.5, 137.9, 134.9, 132.8, 132.2, 130.3, 130.1, 129.7, 128.88, 128.85, 128.6, 128.3, 114.50, 114.46, 68.5, 55.9, 55.8, 53.3, 51.8; LC/MS (ESI) *m/z* 697.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{30}N_2O_{12}S_2$ [M - H]$^-$ 697.1167; found 697.1174.

(5-Amino-2-nitrophenyl)methanol (87). Prepared as described in the experimental procedure of **30** from 5-amino-2-nitrobenzoic acid to obtain the title compound as a pale yellow solid (910 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, *J* = 82.8 Hz, 1H), 7.00 (d, *J* = 1.2 Hz, 1H), 6.69 (s, 2H, NH), 6.50 (dd, *J* = 8.8, 1.2 Hz, 1H), 5.38 (t, *J* = 5.2 Hz, 1H, OH), 4.81 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.1, 143.3, 133.8, 128.3, 110.8, 110.4, 60.9 LC/MS (ESI) *m/z* 169.1 [M + H]$^+$.

3-((*tert*-Butyldimethylsilyl)oxy)-4-nitroaniline (88a). To a solution of 5-amino-2-nitrophenol (1.0 g, 6.49 mmol) in *N*,*N*-dimethylformamide (10 mL) were added imidazole (1.1 g, 16.22 mmol) and *tert*-butyldimethylsilyl chloride (1.1 g, 7.14 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to water, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-10% ethyl acetate/hexane) to give the product as a yellow solid (1.6 g, 89%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.13 (s, 2H, NH), 0.97 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.9, 139.9, 135.5, 120.1, 113.1, 112.1, 25.7, 18.1, -4.4; LC/MS (ESI) *m/z* 269.1 $[M + H]^+$.

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-nitroaniline (88b). Prepared as described in the experimental procedure of **88a** from intermediate **87** to obtain the title compound as a white solid (880 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 1H), 7.08 (s, 1H), 6.52 (d, *J* = 8.8 Hz, 1H), 5.09 (s, 2H), 4.40 (s, 2H, NH), 0.98 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 142.5, 137.0, 128.4, 111.8, 62.9, 26.1, 18.6, -5.22; LC/MS (ESI) *m/z* 283.2 $[M + H]^+$.

***N*,*N'*-(2-((*tert*-Butyldimethylsilyl)oxy)-1,4-phenylene)bis(4-methoxybenzenesulfo-namide) (89a).** Prepared as described in the experimental procedure of **22b** from intermediate **88a** to obtain the title compound as a pale yellow solid (1.7 g, 52% over steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.29 (brs, 1H, NH), 6.85 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.68 (brs, 1H, NH), 6.62 (d, *J* = 2.4 Hz, 1H), 6.54 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.81 (s, 3H), 3.80

(s, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.29, 163.26, 146.3, 133.8, 130.8, 130.4, 129.5, 129.3, 125.5, 121.7, 115.1, 114.3, 114.2, 111.8, 55.7, 25.8, 18.2, -4.5; LC/MS (ESI) *m/z* 577.0 $[M - H]^-$.

***N,N'*-(2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1,4-phenylene)bis(4-methoxybenzenesulfonamide) (89b).** Prepared as described in the experimental procedure of **18d** from intermediate **88b** to obtain the title compound as a pale yellow solid (823 mg, 81%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (brs, 1H, NH), 9.19 (brs, 1H, NH), 7.63 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.14 (s, 1H), 7.03-7.00 (m, 4H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.31 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 0.85 (s, 9H), -0.07 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 138.9, 136.4, 131.8, 131.2, 128.7, 128.6, 128.2, 127.6, 118.4, 117.7, 114.2, 60.1, 55.6, 25.7, 17.9, -5.7; LC/MS (ESI) *m/z* 591.2 $[M - H]^-$.

Di-*tert*-butyl 2,2'-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (90a). Prepared as described in the experimental procedure of **75a** from intermediate **89a** to obtain the title compound as a pale yellow oil (105 mg, 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.63 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.24 (s, 4H), 3.83 (s, 3H), 3.83 (s, 3H), 1.40 (s, 9H), 1.35 (s, 9H), 0.90 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.8, 163.2, 162.9, 153.1, 140.8, 132.9, 132.7, 130.4, 130.1, 129.8, 129.1, 119.6, 119.3, 114.03, 113.97, 82.4, 82.0, 55.7, 53.2, 51.8, 50.9, 28.1, 25.9, 18.2, -4.3; LC/MS (ESI) *m/z* 825.3 $[M + H + H_2O]^+$.

Di-*tert*-butyl 2,2'-((2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (90b). Prepared as described in the

experimental procedure of **75a** from intermediate **89b** to obtain the title compound as a colorless oil (551 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.12 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.93-4.77 (m, 2H), 4.26 (s, 2H), 4.13 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 1.39 (s, 9H), 1.35 (s, 9H), 0.88 (s, 9H), -0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.2, 163.4. 163.2, 144.3, 140.6, 135.9, 130.4, 130.3, 130.1, 129.9, 129.0, 127.4, 126.2, 114.13, 114.09, 82.38, 82.36, 61.1, 55.8, 55.7, 54.0, 53.1, 28.09, 28.05, 26.1, 18.4, -5.25; LC/MS (ESI) *m/z* 839.3 $[M + H + H_2O]^+$.

Di-*tert*-butyl 2,2'-((2-(benzyloxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetate (91a). Prepared as described in the experimental procedure of **75a** from intermediate **22b** to obtain the title compound as a colorless oil (628 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 9.2 Hz, 2H), 7.49-7.47 (m, 3H), 7.33-7.31 (m, 3H), 7.10-7.08 (m, 2H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.57 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.69 (s, 2H), 4.25 (s, 2H), 4.24 (s, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 1.41 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.7, 163.3, 162.8, 155.0, 141.4, 135.8, 134.2, 132.0, 130.2, 130.1, 129.5, 128.6, 128.1, 127.1, 126.7, 118.8, 114.1, 113.8, 113.7, 82.5, 82.1, 70.2, 55.7, 55.6, 53.2, 51.8, 28.14, 28.09; LC/MS (ESI) *m/z* 671.2 $[M + H - C_8H_{16}]^+$.

Di-*tert*-butyl 2,2'-((2-(benzyloxy)-1,4-phenylene)bis(tosylazanediyl))diacetate (91b). Prepared as described in the experimental procedure of **75a** from intermediate **42a** to obtain the title compound as a colorless oil (1.3 g, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.32-7.31 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.063-7.02 (m, 5H), 6.55 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.68 (s, 2H), 4.26

(s, 4H), 2.42 (s, 3H), 2.30 (s, 3H), 1.41 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 167.6, 155.1, 144.0, 143.3, 141.4, 137.4, 135.82, 135.79, 134.2, 129.6, 129.3, 128.5, 128.2, 127.9, 127.5, 127.1, 126.8, 118.8, 114.0, 82.5, 82.1, 70.3, 53.3, 51.9, 28.14, 28.09, 21.7, 21.6; LC/MS (ESI) *m/z* 769.3 $[M + H + H_2O]^+$.

Di-*tert*-butyl 2,2'-((2-hydroxy-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (92a). Method A: To a solution of **90a** (105 mg, 0.13 mmol) in tetrahydrofuran (1 mL) was added tetrabutylammonium fluoride solution (1.0 M in THF, 0.14 ml, 0.14 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-40% ethyl acetate/hexane) to give the product as a pale yellow oil (71 mg, 79%). Method B: Prepared as described in the experimental procedure of **73** from intermediate **91a** to obtain the title compound as a white solid (311 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (brs, 1H, OH), 7.64 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.76-6.68 (m, 3H), 4.23 (s, 4H), 3.87 (s, 3H), 3.86 (s, 3H), 1.49 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 167.7, 163.6, 163.3, 156.3, 142.4, 130.5, 130.2, 130.1, 130.0, 125.5, 119.9, 113.0, 114.2, 114.1, 84.4, 82.5, 55.8, 55.7, 54.0, 53.0, 28.1; LC/MS (ESI) *m/z* 581.2 $[M + H - C_8H_{16}]^+$.

Di-*tert*-butyl 2,2'-((2-hydroxy-1,4-phenylene)bis(tosylazanediyl))diacetate (92b). Prepared as described in the experimental procedure of **73** from intermediate **90b** to obtain the title compound as a white solid (213 mg, 19%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (brs, 1H, OH), 7.55 (d, *J* = 8.4 Hz, 2H), 7.51(d, *J* = 8.4 Hz, 2H), 7.23-7.21 (m, 4H), 6.70

(dd, *J* = 8.4, 2.4 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.21 (s, 4H), 2.40 (s, 3H), 2.39 (s, 3H), 1.46 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 167.6, 156.3, 144.5, 143.9, 142.4, 136.1, 135.6, 130.1, 129.7, 128.1, 127.9, 125.6, 120.0, 116.3, 84.4, 82.5, 54.2, 53.1, 28.1, 21.8, 21.7; LC/MS (ESI) *m/z* 679.3 $[M + H + H_2O]^+$.

Di-*tert*-butyl 2,2'-((2-(hydroxymethyl)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (92c). Prepared as described in the procedure (method B) of **92a** from **91b** to obtain the title compound as a pale yellow oil (118 mg, 36%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.09-7.07 (m, 4H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 5.17 (t, *J* = 5.2 Hz, 1H, OH), 4.70 (s, 1H), 4.51 (s, 1H), 4.35 (s, 2H), 4.20 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 1.31 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.31, 167.25, 162.9, 162.8, 144.1, 139.8, 135.2, 129.9, 129.8, 129.6, 129.2, 128.7, 126.4, 124.8, 114.3, 81.53, 81.47, 58.6, 55.7, 53.5, 52.6, 27.5; LC/MS (ESI) *m/z* 725.3 $[M + H + H_2O]^+$.

Di-*tert*-butyl 2,2'-((2-((benzylsulfonyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (93a). Prepared as described in the experimental procedure of **74a** from intermediate **92a** and phenylmethanesulfonyl chloride to obtain the title compound as a white solid (63 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.2 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.46-7.38 (m, 6H), 7.18 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 2H), 4.57 (s, 2H), 4.20 (s, 2H), 4.17 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 1.39 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.4, 163.40, 163.37, 146.8, 141.5, 133.0, 131.3, 131.2, 131.1, 130.3, 130.1, 129.8, 129.5, 129.1, 126.9, 126.6, 121.0, 114.4, 114.1, 82.8, 82.3, 57.9, 55.74, 55.70, 52.9, 52.8, 28.1, 28.0; LC/MS (ESI) *m/z* 865.3 $[M + H + H_2O]^+$.

Di-*tert*-butyl 2,2'-((2-(((phenylsulfonyl)oxy)methyl)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (93b). Prepared as described in the experimental procedure of **74a** from intermediate **92c** and benzenesulfonyl chloride to obtain the title compound as a pale yellow solid (58 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.61-7.59 (m, 4H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.21-7.18 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.50-5.47 (m, 1H), 5.13-5.09 (m, 1H), 4.25-4.22 (m, 2H), 4.15-4.11 (m, 1H), 3.97-3.93 (m, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 1.40 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.0, 163.6, 163.5, 141.0, 137.03, 136.93, 136.0, 134.0, 130.3, 130.1, 129.5, 129.30, 129.27, 129.1, 128.1, 127.5, 114.4, 114.2, 82.6, 68.1, 55.8, 53.8, 53.0, 28.1, 28.0; LC/MS (ESI) *m/z* 865.3 $[M + H + H_2O]^+$.

Di-*tert*-butyl 2,2'-((2-((mesitylsulfonyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (93c) Prepared as described in the experimental procedure of **74a** from intermediate **92a** and 2,4,6-trimethylbenzenesulfonyl chloride to obtain the title compound as a white solid (16 mg, 25%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 4H), 7.05 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.99 (s, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 2.4 Hz, 1H), 4.29 (s, 2H), 4.14 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.46 (s, 6H), 2.35 (s, 3H), 1.44 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.2, 163.2, 162.9, 147.1, 144.3, 141.3, 139.9, 134.6, 132.0, 131.6, 131.5, 131.3, 130.0, 129.8, 129.7, 125.6, 121.0, 114.1, 113.8, 82.5, 82.1, 55.6, 55.5, 53.2, 52.7, 28.0, 27.9, 22.6, 21.2.

Di-*tert*-butyl 2,2'-((2-(([1,1'-biphenyl]-4-ylsulfonyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (93d) Prepared as described in the

experimental procedure of **74a** from intermediate **92a** and biphenyl-4-sulfonyl chloride to obtain the title compound as a white solid (35 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.56-7.43 (m, 4H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.26 (s, 2H), 4.20 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 167.4, 163.4, 163.2, 147.7, 146.9, 141.4, 138.9, 134.34, 134.28, 131.5, 131.1, 130.2, 130.0, 129.3, 129.1, 128.9, 128.0, 127.5, 125.8, 121.1, 114.3, 114.0, 82.7, 82.3, 55.7, 55.6, 52.9, 28.1, 28.0; LC/MS (ESI) *m/z* 909.4 $[M + H]^+$.

Di-*tert*-butyl 2,2'-((2-(2-oxo-2-(4-phenylpiperidin-1-yl)ethoxy)-1,4-phenylene)bis (((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (93e). Prepared as described in the experimental procedure of **40b** from **92a** and 2-bromo-1-(4-phenylpiperidin-1-yl)ethan-1-one to obtain the title compound as a pale yellow solid (32 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.35-7.30 (m, 3H), 7.23-7.20 (m, 3H), 6.92-6.87 (m, 5H), 6.55 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.70-4.68 (m, 1H), 4.40 (s, 2H), 4.39 (s, 2H), 4.24 (s, 2H), 3.84 (s, 3H), 3.84 (s, 3H), 3.80-3.76 (m, 1H), 3.20-3.14 (m, 1H), 2.78-2.70 (m, 2H), 1.93-1.89 (m, 2H), 1.72-1.66 (m, 2H), 1.40 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.7, 164.7, 163.3, 162.9, 154.9, 145.1, 141.4, 133.6, 132.2, 130.2, 130.1, 130.0, 128.7, 127.2, 126.9, 126.7, 119.3, 114.1, 113.8, 82.4, 81.9, 66.8, 55.7, 53.1, 52.0, 45.7, 42.8, 33.9, 32.9, 28.14, 28.08; LC/MS (ESI) *m/z* 894.3 $[M + H]^+$.

Di-*tert*-butyl 2,2'-((2-((mesitylsulfonyl)oxy)-1,4-phenylene)bis(tosylazanediyl))di-acetate (93f). Prepared as described in the experimental procedure of **74a** from **92b** and 2,4,6-trimethylbenzenesulfonyl chloride to obtain the title compound as a white solid (42

mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.02 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.99 (s, 2H), 6.77 (d, *J* = 2.4 Hz, 1H), 4.30 (s, 2H), 4.15 (s, 2H), 2.46 (s, 6H), 2.42 (s, 3H), 2.38 (s, 3H), 2.36 (s, 3H), 1.44 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 167.2, 147.2, 144.4, 144.1, 143.5, 141.4, 140.1, 137.2, 135.5, 134.7, 132.1, 131.7, 131.5, 129.7, 129.4, 127.9, 127.8, 125.7, 121.5, 82.7, 82.2, 53.3, 52.9, 28.2, 28.0, 22.6, 21.73, 21.68, 21.3; LC/MS (ESI) *m/z* 861.4 $[M + H + H_2O]^+$.

Di-*tert*-butyl 2,2'-((2-(2-morpholino-2-oxoethoxy)-1,4-phenylene)bis(tosylazanediyl))diacetate (93g). Prepared as described in the experimental procedure of **40b** from **92b** and and 2-bromo-1-morpholinoethan-1-one to obtain the title compound as a white solid (44 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.23-7.20 (m, 5H), 6.93 (s, 1H), 6.52 (d, *J* = 8.4 Hz, 1H), 4.40 (s, 2H), 4.34 (s, 2H), 4.22 (s, 2H), 3.70-3.68 (m, 4H), 3.59-3.57 (m, 2H), 3.49-3.47 (m, 2H), 2.40 (s, 6H), 1.38 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.5, 165.2, 154.9, 144.0, 143.4, 141.4, 137.5, 135.6, 133.1, 129.5, 129.3, 127.8, 127.2, 119.5, 113.8, 82.5, 82.0, 67.1, 66.8, 53.1, 51.9, 45.6, 42.4, 28.1, 28.0, 21.6; LC/MS (ESI) *m/z* 788.3 $[M + H]^+$.

Di-*tert*-butyl 2,2'-((2-(2-(*tert*-butoxy)-2-oxoethoxy)-1,4-phenylene) bis(tosylazanediyl))diacetate (93h). Prepared as described in the experimental procedure of **40b** from intermediate **92b** and and *tert*-butyl 2-bromoacetate to obtain the title compound as a colorless oil (42 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.48-4.46 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.51 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.36 (s, 2H), 4.22 (s, 2H), 3.98 (s, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 1.46 (s, 9H), 1.41 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 168.5, 167.5, 166.4, 154.0, 144.0, 143.2, 141.2, 137.2, 135.6, 134.3, 129.6, 129.1, 127.9, 127.7, 126.8, 119.2, 113.5, 82.7, 82.5, 81.9, 65.2, 53.1, 51.8, 28.2, 28.13, 28.05, 21.7, 21.6; LC/MS (ESI) *m/z* 607.2 $[M + H - C_{12}H_{24}]^+$.

Di-*tert*-Butyl 2,2'-((2-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)-1,4-phenylene)bis(tosylazanediyl))diacetate (93i). Prepared as described in the procedure of **40b** from **92b** and and *N*-(2-bromoethyl)phthalimide to obtain the title compound as a white solid (28 mg, 28%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.86 (m, 2H), 7.75-7.72 (m, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 2.4 Hz, 1H), 6.53 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.23 (s, 2H), 4.18 (s, 2H), 3.74-3.70 (m, 2H), 3.68-3.66 (m, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 1.39 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.0, 167.5, 154.7, 144.0, 143.3, 141.3, 137.5, 135.7, 134.3, 132.1, 129.6, 129.1, 127.9, 127.7, 126.5, 123.6, 119.3, 113.3, 82.5, 81.8, 64.9, 53.2, 51.8, 36.6, 28.14, 28.06, 21.7, 21.6; LC/MS (ESI) *m/z* 833.3 $[M]^-$.

2,2'-((2-((Benzylsulfonyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (94a). Prepared as described in the experimental procedure of **76a** from intermediate **93a** to obtain the title compound as a white solid (8 mg, quantitative); ^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.39-7.38 (m, 5H), 7.17 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 2.4 Hz, 1H), 4.66 (s, 2H), 4.32 (s, 2H), 4.22 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.6, 163.7, 146.8, 141.1, 133.1, 131.2, 130.7, 130.5, 130.3, 130.0, 129.6, 129.4, 129.2, 126.9, 126.7, 121.2, 114.6, 114.3, 58.0, 55.84, 55.80, 51.8; LC/MS (ESI) *m/z* 735.1 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_{13}S_3$ $[M + H]^+$ 735.0983; found 735.0997.

2,2'-((2-(((Phenylsulfonyl)oxy)methyl)-1,4-phenylene)bis(((4-methoxyphenyl)sulf-onyl)azanediyl))diacetic acid (94b). Prepared as described in the experimental procedure of **76a** from **93b** to obtain the title compound as a white solid (41 mg, 82%); ^{1}H NMR (400 MHz, MeOD) δ 7.94 (d, *J* = 7.6 Hz, 2H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.64 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 1H), 5.57-5.54 (m, 1H), 5.16-5.13 (m, 1H), 4.41-4.41 (m, 1H), 4.37-4.34 (m, 2H), 4.03-3.99 (m, 1H), 3.88 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 171.9, 171.3, 165.2, 165.1, 142.1, 138.2, 137.2, 135.3, 131.3, 131.2, 131.0, 130.7, 130.3, 130.0, 129.8, 129.3, 129.1, 128.7, 115.4, 115.2, 69.1, 56.3, 53.9, 52.9; LC/MS (ESI) *m/z* 733.0 [M - H]$^{-}$; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_{13}S_3$ [M - H]$^{-}$ 733.0837; found 733.0847.

2,2'-((2-((Mesitylsulfonyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl) azanediyl))diacetic acid (94c). Prepared as described in the experimental procedure of **76a** from **93c** to obtain the title compound as a white solid (14 mg, quantitative); ^{1}H NMR (400 MHz, MeOD) δ 7.74 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.22 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05 (s, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.20 (d, *J* = 2.4 Hz, 1H), 4.42 (s, 2H), 4.15 (s, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 2.38 (s, 3H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, MeOD) δ 172.4, 171.3, 165.0, 164.8, 148.5, 146.3, 142.9, 141.1, 136.1, 133.3, 132.52, 132.46, 132.3, 131.1, 130.9, 130.4, 127.6, 121.0, 115.3, 115.2, 56.4, 56.3, 53.5, 52.4, 22.8, 21.3; LC/MS (ESI) *m/z* 761.1 [M - H]$^{-}$; HRMS (ESI) *m/z* calcd for $C_{33}H_{34}N_2O_{13}S_3$ [M - H]$^{-}$ 761.1150; found 761.1159.

2,2'-((2-(([1,1'-Biphenyl]-4-ylsulfonyl)oxy)-1,4-phenylene)bis(((4-methoxyphenyl) sulfonyl)azanediyl))diacetic acid (94d). Prepared as described in the experimental

procedure of **76a** from intermediate **93d** to obtain the title compound as a white solid (26 mg, 86%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (brs, 2H, CO_2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.63-7.58 (m, 3H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.52-7.48 (m, 3H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.15 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.43 (s, 2H), 4.10 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 163.0, 162.7, 146.7, 146.1, 141.0, 137.9, 133.7, 133.3, 130.6, 129.5, 129.4, 129.2, 129.1, 128.5, 128.0, 127.3, 124.4, 119.5, 114.5, 114.1, 55.8, 55.6, 51.6, 51.5; LC/MS (ESI) *m/z* 795.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{36}H_{32}N_2O_{13}S_3$ [M - H]$^-$ 795.0994; found 795.1002.

2,2'-((2-(2-Oxo-2-(4-phenylpiperidin-1-yl)ethoxy)-1,4-phenylene)bis(((4-methoxy phenyl)sulfonyl)azanediyl))diacetic acid (94e). Prepared as described in the experimental procedure of **76a** from intermediate **93e** to obtain the title compound as a pale yellow solid (26 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.33-7.29 (m, 2H), 7.23-7.17 (m, 4H), 6.91-6.87 (m, 4H), 6.80 (s, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 4.65-4.61 (m, 1H), 4.42 (s, 4H), 4.34 (s, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.74-3.71 (m, 1H), 3.20-3.14 (m, 1H), 2.78-2.70 (m, 2H), 1.95-1.88 (m, 2H), 1.73-1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.3, 163.5, 163.2, 154.9, 144.8, 141.1, 133.4, 131.4, 130.1, 129.9, 128.8, 127.2, 126.9, 126.8, 120.4, 114.5, 114.3, 114.0, 66.5, 55.81, 55.80, 52.0, 51.0, 45.8, 43.5, 42.6, 33.6, 32.8, 22.8; LC/MS (ESI) *m/z* 780.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{37}H_{39}N_3O_{12}S_2$ [M - H]$^-$ 780.1902; found 780.1913.

2,2'-((2-((Mesitylsulfonyl)oxy)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (94f). Prepared as described in the experimental procedure of **76a** from intermediate **93f** to obtain the title compound as a white solid (38 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6)

δ 12.97 (brs, 2H, CO_2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.19 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.13 (s, 2H), 6.34 (d, *J* = 8.8 Hz, 1H), 4.28 (s, 2H), 4.22 (s, 2H), 2.50 (s, 3H), 2.44 (s, 3H), 2.36 (s, 3H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 169.3, 146.3, 144.6, 144.1, 143.5, 140.9, 139.1, 136.3, 134.6, 134.4, 131.9, 130.6, 129.7, 129.4, 127.1, 127.0, 125.2, 118.8, 51.9, 51.2, 22.0, 21.6, 21.1, 21.0; LC/MS (ESI) *m/z* 729.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{33}H_{34}N_2O_{11}S_3$ $[M - H]^-$ 729.1252; found 729.1263.

2,2'-((2-(2-Morpholino-2-oxoethoxy)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (94g). Prepared as described in the experimental procedure of **76a** from intermediate **93g** to obtain the title compound as a white solid (39 mg, quantitative); ^1H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.32-7.29 (m, 3H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.68 (s, 1H), 4.39 (s, 2H), 4.38 (s, 4H), 3.56-3.54 (m, 4H), 3.39-3.37 (m, 2H), 3.29-3.27 (m, 2H), 2.50 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.4, 169.7, 164.9, 154.0, 143.7, 143.1, 140.7, 136.8, 135.5, 132.9, 129.6, 129.2, 127.3, 127.1, 125.6, 119.1, 111.6, 65.9, 65.2, 51.7, 50.5, 44.4, 41.5, 21.03, 21.00; LC/MS (ESI) *m/z* 676.3 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{30}H_{33}N_3O_{11}S_2$ $[M + H]^+$ 676.1629; found 676.1643.

2,2'-((2-(Carboxymethoxy)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (94h). Prepared as described in the procedure of **76a** from **93h** to obtain the title compound as a white solid (29 mg, 87%); ^1H NMR (400 MHz, DMSO-d_6) δ 12.88 (brs, 2H, CO_2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.36-7.34 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.85 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 4.37 (s, 2H), 4.31 (s, 2H), 4.00 (s, 2H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)

δ 170.3, 169.8, 168.9, 153.5, 143.7, 143.1, 140.8, 136.6, 135.4, 133.2, 129.6, 129.2, 127.3, 127.0, 125.5, 120.0, 111.5, 64.3, 51.7, 50.5, 20.98, 20.96; LC/MS (ESI) *m/z* 605.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{26}N_2O_{11}S_2$ $[M - H]^-$ 605.0905; found 605.0915.

2,2'-((2-(2-(1,3-Dioxoisoindolin-2-yl)ethoxy)-1,4-phenylene)bis(tosylazanediyl))di-acetic acid (94i). Prepared as described in the experimental procedure of **76a** from **93a** to obtain the title compound as a pale yellow solid (20 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2H), 7.73-7.70 (m, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.78 (s, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 4.29 (s, 2H), 4.24 (s, 2H), 3.73-3.71 (m, 2H), 3.66-3.65 (m, 2H), 2.38 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.6, 169.9, 167.7, 154.0, 143.8, 143.2, 140.8, 136.6, 135.3, 134.5, 133.2, 131.7, 129.6, 129.0, 127.4, 126.9, 125.2, 123.1, 119.8, 111.4, 64.6, 51.9, 50.7, 36.3, 21.0; LC/MS (ESI) *m/z* 722.3 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{34}H_{31}N_3O_{11}S_2$ $[M + H]^+$ 722.1473; found 722.1479.

Di-*tert*-butyl 2,2'-((2-(2-(*tert*-butoxy)-2-oxoethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (95). Prepared as described in the procedure of **75a** from **89a** to obtain the title compound as a pale yellow oil (860 mg, 37%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.8 Hz, 4H), 7.48 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.56 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.36 (s, 2H), 4.24 (s, 2H), 4.06 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 1.48 (s, 9H), 1.43 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.6, 166.4, 163.3, 162.9, 154.0, 141.3, 134.3, 132.0, 130.13, 130.05, 129.8, 126.8, 119.2, 114.1, 113.6, 113.3, 82.7, 82.4, 81.8, 65.3, 55.7, 55.6, 53.1, 51.8, 28.13, 28.05; LC/MS (ESI) *m/z* 639.1 $[M + H - C_{12}H_{24}]^+$.

2,2'-((2-(Carboxymethoxy)-1,4-phenylene)bis(((4-methoxyphenyl)sulfonyl)azane-diyl))diacetic acid (96). Prepared as described in the experimental procedure of **76a** from intermediate **95** to obtain the title compound as a white solid (42 mg, 71%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.83 (brs, 2H, CO_2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.60 (s, 1H), 4.36 (s, 2H), 4.31 (s, 2H), 4.09 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.4, 169.8, 168.9, 162.8, 162.5, 153.5, 140.9, 133.2, 131.1, 129.8, 129.5, 129.2, 125.6, 119.9, 114.3, 113.8, 111.3, 64.4, 55.7, 55.6, 51.7, 50.5; LC/MS (ESI) *m/z* 637.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{26}N_2O_{13}S_2$ $[M - H]^-$ 637.0804; found 637.0813.

Methyl *(S)*-2-(2,5-bis((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl)sulfonamido)phenoxy)propanoate (97a). Prepared as described in the experimental procedure of **40b** from **92b** and methyl *(R)*-2-bromopropanoate to obtain the title compound as a colorless oil (54 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.47-7.45 (m, 3H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.48 (q, *J* = 6.8 Hz, 1H), 4.40-4.35 (m, 1H), 4.27-4.20 (m, 3H), 3.70 (s, 3H), 2.39 (s, 3H), 2.39 (s, 3H), 1.42 (s, 9H), 1.38 (s, 9H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 168.6, 167.5, 153.5, 143.9, 143.2, 141.0, 137.6, 135.6, 134.3, 129.5, 129.3, 127.8, 127.7, 127.0, 118.8, 113.9, 82.4, 81.9, 72.0, 53.1, 52.5, 51.7, 28.1, 28.0, 21.64, 21.55, 17.8; LC/MS (ESI) *m/z* 764.4 $[M + H + H_2O]^+$.

Methyl *(R)*-2-(2,5-bis((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl)sulfonamido)phenoxy)propanoate (97b). Prepared as described in the experimental procedure of **40b** from intermediate **92b** and methyl *(S)*-2-bromopropanoate to obtain the title compound

as a colorless oil (35 mg, 39%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.48-7.46 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.80 (s, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 4.49-4.47 (m, 1H), 4.40-4.36 (m, 1H), 4.27-4.16 (m, 3H), 3.70 (s, 3H), 2.40 (s, 3H), 2.39 (s, 3H), 1.42 (s, 9H), 1.38 (s, 9H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 168.6, 167.5, 153.5, 143.9, 143.2, 141.0, 137.7, 135.7, 134.4, 129.6, 129.3, 127.8, 127.7, 127.0, 118.9, 113.9, 82.4, 81.9, 72.0, 53.1, 52.5, 51.8, 28.2, 28.1, 21.7, 21.6, 17.8; LC/MS (ESI) *m/z* 635.3 $[M + H - C_8H_{16}]^+$.

***(S)*-2-(2,5-Bis((*N*-(carboxymethyl)-4-methylphenyl)sulfonamido)phenoxy)propa-noic acid (98a).** To a solution of **97a** (54 mg, 0.072 mmol) in methanol (0.3 mL) was added sodium hydroxide (4 mg, 0.11 mmol) in water (0.1 mL) at room temperature. The reaction mixture was stirred at 60 °C for 4 hours. After the reaction was completed, the crude mixture was concentrated under reduced pressure, dissolved with water, and then washed with dichloromethane. The aqueous solution was acidified with 6 N HCl until the pH reached around 1 and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-10% methanol/dichloromethane) to give *(S)*-2-(2,5-bis((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl)sulfonamido)-phenoxy)propanoic acid as a colorless oil (18 mg, 34%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.28-7.20 (m, 5H), 6.78 (s, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 4.54-4.53 (m, 1H), 4.39-4.34 (m, 1H), 4.27-4.17 (m, 3H), 2.40 (s, 3H), 2.40 (s, 3H), 1.40 (s, 9H), 1.38 (s, 9H), 1.31 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.6, 153.9, 144.2, 143.7, 141.4, 136.9, 135.6, 133.5, 129.7, 129.4, 127.9, 127.8, 127.2, 119.8, 113.2, 82.6, 82.3, 72.3, 53.1, 52.1, 28.12, 28.05, 21.7, 21.6, 17.8; LC/MS (ESI) *m/z* 731.3 $[M - H]^-$.

Prepared as described in the experimental procedure of **76a** from *(S)*-2-(2,5-bis((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl)sulfon-amido)phenoxy)propanoic acid to obtain the title compound as a pale yellow solid (8 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (brs, 2H, CO_2H), 8.68 (brs, 1H, CO_2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.50-7.47 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.28-7.26 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 12.4 Hz, 1H), 6.43-6.39 (m, 1H), 4.56-4.44 (m, 2H), 4.40-4.39 (m, 1H), 4.10-4.01 (m, 1H), 3.70-3.60 (m, 1H), 2.42 (s, 6H), 1.17 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 174.8, 173.8, 153.2, 144.5, 143.9, 140.6, 136.8, 135.4, 134.8, 129.9, 129.5, 127.69, 127.65, 126.6, 120.0, 114.7, 71.3, 52.1, 50.1, 21.72, 21.66, 17.7; LC/MS (ESI) *m/z* 619.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{27}H_{28}N_2O_{11}S_2$ $[M - H]^-$ 619.1062; found 619.1070.

***(R)*-2-(2,5-Bis((*N*-(carboxymethyl)-4-methylphenyl)sulfonamido)phenoxy)propanoic acid (98b).** To a solution of **97b** (35 mg, 0.047 mmol) in methanol (0.3 mL) was added lithium hydroxide (1.7 mg, 0.070 mmol) in water (0.1 mL) at room temperature. The reaction mixture was stirred at 50 ℃ for 4 hours. The crude mixture was concentrated under reduced pressure, dissolved with water, and then washed with dichloromethane. The aqueous solution was acidified with 6 N HCl until the pH reached around 1 and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give *(R)*-2-(2,5-bis((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl)sulfon-amido)phenoxy)-propanoic acid as a pale yellow solid. The resulting crude compound was used for the next reaction without further purification. Prepared as described in the experimental procedure of **76a** from *(R)*-2-(2,5-bis((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl)sulfonamido)phenoxy)pro-panoic acid to obtain the title compound as a white solid (26 mg, 89% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.52 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.28-7.22 (m, 4H), 6.74 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 4.48 (s, 2H), 4.42-4.33 (m, 1H), 4.10-4.06 (m, 1H), 3.67-3.64 (m, 1H), 2.41 (s, 6H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 174.8, 173.6, 153.3, 144.5, 144.0, 140.6, 136.6, 135.3, 134.5, 129.9, 129.6, 127.73, 127.67, 126.6, 120.0, 114.6, 71.7, 52.2, 50.4, 21.7, 21.6, 17.6; LC/MS (ESI) *m/z* 619.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{27}H_{28}N_2O_{11}S_2$ [M - H]$^-$ 619.1062; found 619.1069.

***N*-(4-((*N*-(2-(*tert*-Butoxy)-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-(cyanomethoxy)phenyl)-*N*-tosylglycine (99).** Prepared as described in the experimental procedure of **40b** from intermediate **92b** and 2-bromoacetonitrile to obtain the title compound as a colorless oil (55 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 4H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.71 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.36 (s, 2H), 4.26 (s, 2H), 420 (s, 2H), 2.41 (s, 3H), 2.40 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 167.5, 153.3, 144.3, 143.9, 141.7, 137.0, 135.6, 134.4, 129.7, 129.6, 127.8, 127.5, 127.4, 121.2, 114.0, 113.8, 82.7, 82.3, 53.6, 53.1, 52.1, 28.1, 28.0, 21.7, 21.6.

***tert*-Butyl *N*-(2-((1*H*-tetrazol-5-yl)methoxy)-4-((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl)sulfonamido)phenyl)-*N*-tosylglycinate (100).** Prepared as described in the experimental procedure of **64** from intermediate **99** to obtain the title compound as a pale yellow oil (45 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.20-7.18 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.94 (s, 1H), 6.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.06 (s, 2H), 4.19 (s, 2H), 4.16 (s, 2H), 2.36 (s, 3H), 2.30 (s, 3H), 1.33 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.6, 154.5, 144.4, 144.3, 141.7, 136.1,

135.3, 133.1, 129.6, 129.3, 127.7, 127.5, 127.4, 120.7, 113.6, 82.9, 82.8, 60.5, 53.0, 52.3, 27.8, 21.5, 21.4; LC/MS (ESI) *m/z* 743.3 $[M + H]^+$.

***N*-(2-((1*H*-tetrazol-5-yl)methoxy)-4-((*N*-(carboxymethyl)-4-methylphenyl)sulfon-amido)phenyl)-*N*-tosylglycine (101).** Prepared as described in the experimental procedure of **76a** from intermediate **100** to obtain the title compound as a white solid (12 mg, 33%); ^{1}H NMR (400 MHz, MeOD) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.93 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.48 (s, 2H), 4.33 (s, 4H), 2.43 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 163.3, 156.0, 145.6, 145.1, 143.0, 137.9, 135.9, 135.0, 130.6, 130.2, 128.9, 128.4, 128.0, 121.4, 119.7, 116.8, 114.2, 62.1, 54.8, 21.6, 21.5; LC/MS (ESI) *m/z* 629.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{26}N_6O_9S_2$ $[M - H]^-$ 629.1130; found 629.1140.

***N,N'*-(2-Nitro-1,4-phenylene)bis(4-methylbenzenesulfonamide) (102).** Prepared as described in the experimental procedure of **14a** from 2-nitrobenzene-1,4-diamine and 4-methylbenzenesulfonyl chloride to obtain the title compound as a yellow oil (468 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (brs, 1H, NH), 7.76 (brs, 1H, NH), 7.69 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 4H), 7.57 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.24-7.20 (m, 4H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 144.6, 137.6, 135.7, 135.5, 133.8, 130.1, 130.0, 128.3, 127.3, 122.8, 117.4, 21.7; LC/MS (ESI) *m/z* 462.1 $[M + H]^+$.

Di-*tert*-butyl 2,2'-((2-nitro-1,4-phenylene)bis(tosylazanediyl))diacetate (103). Prepared as described in the procedure of **75a** from **102** to obtain the title compound as a pale yellow oil (183 mg, 41%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 5.6 Hz, 1H), 7.67 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.46-4.42 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.41 (s, 2H), 4.31 (s, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 1.44 (s, 9H), 1.40 (s, 9H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 168.3, 167.1, 149.0, 144.8, 144.3, 141.6, 136.3, 135.7, 135.4, 131.8, 131.2, 130.0, 129.7, 127.9, 127.8, 123.6, 83.2, 82.7, 54.0, 52.7, 28.2, 28.1, 21.7.

Di-*tert*-butyl 2,2'-((2-amino-1,4-phenylene)bis(tosylazanediyl))diacetate (104). To a solution of **103** (183 mg, 0.27 mmol) in methanol (20 mL) was added Pd/C (10% wt.) (20 mg) at room temperature under N_2. The reaction mixture was stirred at room temperature for overnight under H_2. After the reaction was completed, the crude mixture was filtered off through celite, and then concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-20% ethyl acetate/hexane) to give the product as a colorless oil (30 mg, 17%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 6.27 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.50 (brs, 1H, NH), 4.38-4.33 (m, 1H), 4.20 (s, 2H), 3.85-3.81 (m, 1H), 2.42 (s, 3H), 2.40 (s, 3H), 1.43 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.7, 147.4, 144.1, 143.7, 141.3, 136.1, 135.6, 130.2, 129.5, 129.4, 128.2, 127.9, 124.5, 116.6, 116.0, 82.6, 82.3, 53.7, 53.2, 28.07, 28.05, 21.70, 21.66; LC/MS (ESI) m/z 660.3 $[M + H]^+$.

Di-*tert*-butyl 2,2'-((2-((2-(*tert*-butoxy)-2-oxoethyl)amino)-1,4-phenylene)bis(tosyl-azanediyl))diacetate (105). Prepared as described in the experimental procedure of **40b** from intermediate **104** and *tert*-butyl 2-bromoacetate to obtain the title compound as a pale yellow solid (34 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.22 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.53 (brs, 1H, 1NH), 4.25-4.21 (m, 1H), 4.21 (s, 2H), 4.07-4.03 (m, 1H), 3.66-3.51 (m, 2H), 2.41 (s, 6H), 1.47 (s, 9H), 1.41 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.5, 167.7, 146.6, 143.9,

143.7, 141.7, 136.1, 135.9, 130.8, 129.4, 128.3, 128.0, 124.6, 115.3, 111.7, 82.4, 82.2, 81.9, 53.3, 53.2, 46.0, 28.2, 28.1, 21.7, 21.6; LC/MS (ESI) *m/z* 774.4 $[M + H]^+$.

2,2'-((2-((Carboxymethyl)amino)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (106). Prepared as described in the procedure of **76** from **105** to obtain the title compound as a pale yellow solid (29 mg, 51%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.08 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 4.43 (s, 2H), 4.41 (s, 2H), 3.45 (s, 2H), 2.40 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.7, 168.3, 163.8, 144.7, 143.9, 139.8, 135.4, 135.0, 132.9, 129.7, 129.5, 127.6, 127.3, 126.6, 124.4, 122.7, 114.6, 51.8, 49.0, 43.3, 21.0, 20.9; LC/MS (ESI) *m/z* 604.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{27}N_3O_{10}S_2$ $[M - H]^-$ 604.1065; found 604.1075.

2-Iodo-4-nitronaphthalen-1-amine (107). To a solution of 4-nitronaphthalen-1-amine (2.0 g, 10.63 mmol) in methanol (10 mL) and water (60 mL) were added potassium iodide (1.2 g, 7.05 mmol) and potassium iodate (760 mg, 3.55 mmol) at room temperature. After stirring at 0 ℃ for 10 minutes, con. HCl (1.2 mL) in water (10 mL) was slowly added at room temperature during 1 hour. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude precipiate was filtered to give the product as a yellow solid (3.1 g, 93%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, *J* = 8.4 Hz, 1H), 8.69 (s, 1H), 8.44 (d, *J* = 6.8 Hz, 1H), 7.78-7.75 (m, 1H), 7.60-7.57 (m, 1H), 7.34 (brs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.2, 137.9, 133.5, 130.3, 126.6, 126.2, 123.8, 123.5, 120.0, 72.0; LC/MS (ESI) *m/z* 315.0 $[M + H]^+$.

***tert*-Butyl *(E)*-3-(2-amino-5-nitrophenyl)acrylate (108a).** To a solution of 2-iodo-4-nitroaniline (500 mg, 1.89 mmol) in acetonitrile (10 mL) were added *tert*-butyl acrylate

(340 mg, 2.65 mmol), palladium (II) acetate (26 mg, 0.11 mmol), tri(o-tolyl)phosphine (69 mg, 0.23 mmol) and triethylamine (268 mg, 2.65 mmol) at room temperature. The reaction mixture was stirred at 90 °C for overnight. The crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-20% ethyl acetate/hexane) to give the product as a yellow solid (498 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 2.4 Hz, 1H), 8.02 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.59 (d, *J* = 15.6 Hz, 1H), 6.68 (d, *J* = 9.2 Hz, 1H), 6.39 (d, *J* = 15.6 Hz, 1H), 4.74 (brs, 1H, NH), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 150.8, 139.4, 136.5, 126.7, 124.7, 123.5, 119.0, 115.4, 81.3, 28.3; LC/MS (ESI) *m/z* 263.1 $[M + H]^+$.

***tert*-Butyl *(E)*-3-(1-amino-4-nitronaphthalen-2-yl)acrylate (108b).** Prepared as described in the experimental procedure of **108a** from intermediate **107** to obtain the title compound as a yellow solid (420 mg, 84%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (d, *J* = 8.8 Hz, 1H), 8.58 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 15.6 Hz, 1H), 7.81 (brs, 2H, NH), 7.78-7.74 (m, 1H), 7.60-7.56 (m, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.7, 150.9, 138.0, 133.5, 130.7, 127.2, 126.9, 126.0, 124.1, 123.4, 122.1, 119.1, 109.1, 79.7, 27.9; LC/MS (ESI) *m/z* 313.0 $[M - H]^-$.

***tert*-Butyl 3-(2,5-bis((4-methylphenyl)sulfonamido)phenyl)propanoate (109a).** Prepared as described in the experimental procedure of **18d** from intermediate **108a** to obtain the title compound as a pale yellow solid (515 mg, 55% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (brs, 1H, NH), 9.38 (brs, 1H, NH), 7.58 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.36

(s, 3H), 2.34 (s, 3H), 2.07 (t, *J* = 7.6 Hz, 2H), 1.37 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.2, 143.2, 142.9, 138.6, 137.3, 136.5, 136.2, 130.3, 129.52, 129.45, 127.7, 126.7, 126.6, 121.0, 118.3, 79.7, 34.8, 27.7, 25.5, 20.94, 20.89; LC/MS (ESI) *m/z* 543.2 $[M + H]^+$.

***tert*-Butyl 3-(1,4-bis((4-methylphenyl)sulfonamido)naphthalen-2-yl)propanoate (109b).** Prepared as described in the experimental procedure of **18d** from **108b** to obtain the title compound as a pale yellow solid (47 mg, 6% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.4 Hz, 1H), 8.13 (brs, 1H, NH), 7.65 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.45-7.43 (m, 1H), 7.42-7.38 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.12 (s, 1H), 6.75 (brs, 1H, NH), 2.42 (s, 3H), 2.35 (s, 3H), 2.33-2.32 (m, 2H), 2.26-2.24 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 144.2, 143.7, 137.0, 136.3, 136.2, 133.3, 131.6, 129.7, 128.9, 128.4, 127.5, 126.7, 126.5, 123.5, 120.9, 81.7, 36.2, 28.1, 25.4, 21.7, 21.6; LC/MS (ESI) *m/z* 593.2 $[M - H]^-$.

Di-*tert*-butyl 2,2'-((2-(3-(tert-butoxy)-3-oxopropyl)-1,4-phenylene)bis(tosylazane-diyl))diacetate (110a). Prepared as described in the procedure of **75a** from **109a** to obtain the title compound as a colorless oil (160 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 4H), 7.00 (s, 1H), 6.96-6.94 (m, 2H), 4.35 (d, *J* = 17.6 Hz, 1H), 4.23 (d, *J* = 3.6 Hz, 21H), 4.00 (d, *J* = 17.6 Hz, 1H), 2.92-2.78 (m, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 2.35-2.30 (m, 2H), 1.44 (s, 9H), 1.39 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 167.53, 167.48, 144.0, 143.0, 140.5, 137.7, 136.1, 135.8, 130.9, 129.6, 129.5, 129.0, 128.3, 128.0, 126.5, 82.5, 82.4, 80.5, 54.0, 53.2, 35.6, 28.3, 28.1, 25.7, 21.72, 21.69; LC/MS (ESI) *m/z* 605.3 $[M + H - C_{12}H_{24}]^+$.

Di-*tert*-butyl 2,2'-((2-(3-(*tert*-butoxy)-3-oxopropyl)naphthalene-1,4-diyl)bis(tosyl-azanediyl))diacetate (110b). Prepared as described in the experimental procedure of **75a**

from intermediate **109b** to obtain the title compound as a colorless oil (58 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.4 Hz, 1H), 7.85-7.66 (m, 1H), 7.62-7.57 (m, 4H), 7.48-7.39 (m, 1H), 7.37-7.33 (m, 1H), 7.31-7.27 (m, 2H), 7.24-7.20 (m, 2H), 7.02-7.00 (m, 1H), 4.53-4.43 (m, 1H), 4.36-4.27 (m, 2H), 4.22-4.16 (m, 1H), 3.12-2.96 (m, 1H), 2.88-2.63 (m, 1H), 2.46-2.41 (m, 6H), 2.26-2.10 (m, 2H), 1.47-1.35 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.7, 167.7, 167.6, 144.1, 144.0, 140.1, 139.9, 137.4, 136.5, 136.4, 135.9, 135.52, 135.45, 133.4, 133.1, 132.1, 132.0, 129.6, 129.3, 129.1, 128.42, 128.38, 128.35, 128.3, 127.2, 127.1, 126.7, 126.5, 125.4, 125.1, 124.50, 124.47, 82.5, 82.4, 82.34, 82.30, 80.4, 55.0, 54.8, 54.2, 54.1, 36.3, 35.9, 28.3, 28.2, 28.1, 28.0, 27.1, 26.9, 21.8, 21.72, 21.69; LC/MS (ESI) *m/z* 655.3 $[M + H - C_{12}H_{24}]^{+}$.

2,2'-((2-(2-Carboxyethyl)-1,4-phenylene)bis(tosylazanediyl))diacetic acid (111a). Prepared as described in the experimental procedure of **76a** from intermediate **110b** to obtain the title compound as a white solid (43 mg, 68%); ^{1}H NMR (400 MHz, MeOD) δ 7.50 (d, *J* = 8.4 Hz, 4H), 7.35-7.33 (m, 4H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.99 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 4.40 (s, 2H), 4.31 (s, 2H), 3.02-2.94 (m, 1H), 2.79-2.71 (m, 1H), 2.44 (s, 3H), 2.43 (s, 3H), 2.40-2.23 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ 176.5, 172.1, 171.7, 145.7, 145.6, 144.4, 141.7, 138.9, 136.9, 136.7, 131.6, 130.7, 130.1, 129.2, 128.9, 127.8, 54.2, 53.3, 35.0, 26.5, 21.6, 21.5; LC/MS (ESI) *m/z* 603.2 $[M - H]^{-}$; HRMS (ESI) *m/z* calcd for $C_{27}H_{28}N_2O_{10}S_2$ $[M - H]^{-}$ 603.1113; found 603.1120.

2,2'-((2-(2-Carboxyethyl)naphthalene-1,4-diyl)bis(tosylazanediyl))diacetic acid (111b). Prepared as described in the experimental procedure of **76a** from **110a** to obtain the title compound as a white solid (26 mg, 57%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (brs, 2H, CO_2H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.06-7.73 (m, 1H), 7.55-7.46 (m, 6H), 7.43-7.30

(m, 4H), 6.89-6.82 (m, 1H), 4.52-4.31 (m, 4H), 2.95-2.87 (m, 1H), 2.43-2.38 (m, 6H), 2.33-2.22 (m, 1H), 2.06-1.88 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.5, 173.4, 170.0, 169.9, 144.0, 143.9, 139.7, 139.0, 137.2, 137.1, 135.8, 135.7, 134.5, 134.3, 132.8, 132.4, 131.8, 131.7, 129.8, 129.7, 128.2, 127.9, 127.6, 126.4, 125.8, 125.7, 125.2, 125.0, 124.7, 124.6, 53.5, 53.3, 33.9, 33.4, 26.2, 25.9, 21.1, 21.04, 21.02; LC/MS (ESI) *m/z* 655.3 [M + H]$^+$; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_{10}S_2$ [M + H]$^+$ 655.1415; found 655.1420.

***N*-(3-((*tert*-Butyldimethylsilyl)oxy)-4-nitrophenyl)-4-methylbenzenesulfonamide (112).** Prepared as described in the experimental procedure of **52** from intermediate **88a** and 4-methylbenzenesulfonyl chloride to obtain the title compound as a yellow soild (413 mg, 53%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (brs, 1H, NH), 7.75 (d, *J* = 8.0 Hz, 2H), 7.63 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.54 (d, *J* = 2.8 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 2.34 (s, 3H), 0.83 (s, 9H), -0.05 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.3, 143.6, 143.4, 137.1, 132.2, 129.7, 126.8, 120.0, 115.0, 109.5, 25.8, 21.0, 17.8, -3.20; LC/MS (ESI) *m/z* 423.2 [M + H]$^+$.

***tert*-Butyl *N*-(3-(2-(*tert*-butoxy)-2-oxoethoxy)-4-nitrophenyl)-*N*-tosylglycinate (113).** Prepared as described in the experimental procedure of **40b**from intermediate **112** and *tert*-butyl 2-bromoacetate to obtain the title compound as a pale yellow oil (424 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 2.4 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.39 (s, 2H), 4.22 (s, 2H), 2.40 (s, 3H), 1.46 (s, 9H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.0, 154.3, 148.1, 143.8, 137.1, 134.8, 133.7, 129.4, 127.7, 116.6, 107.4, 83.5, 82.4, 65.6, 51.5, 28.1, 21.7; LC/MS (ESI) *m/z* 554.3 [M + H + H_2O]$^+$.

***tert*-Butyl *N*-(3-(2-(*tert*-butoxy)-2-oxoethoxy)-4-((4-methylphenyl)sulfonamido)p-henyl)-*N*-tosylglycinate (114).** Prepared as described in the procedure of **22b** from **113** to obtain the title compound as a colorless oil (218 mg, 89% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (brs, 1H, NH), 7.65 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.51 (d, *J* = 2.0 Hz, 1H), 4.18 (s, 2H), 4.04 (s, 2H), 2.35 (s, 3H), 2.34 (s, 3H), 1.36 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.9, 166.6, 153.9, 143.5, 143.2, 139.2, 136.6, 136.5, 133.7, 129.7, 129.3, 127.1, 126.8, 122.0, 111.2, 103.5, 81.9, 81.2, 64.6, 51.4, 27.64, 27.57, 21.03, 21.01; LC/MS (ESI) *m/z* 659.3 [M - H]$^-$.

***N*-(3-(Carboxymethoxy)-4-((4-methylphenyl)sulfonamido)phenyl)-*N*-tosylglycine (115).** Prepared as described in the experimental procedure of **76a** from intermediate **114** to obtain the title compound as a white solid (59 mg, 71%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (brs, 1H, NH), 7.67 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 1H), 6.63 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 4.22 (s, 2H), 4.05 (s, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.5, 169.1, 154.2, 143.7, 143.2, 139.2, 136.7, 136.6, 134.0, 129.9, 129.3, 127.1, 126.9, 122.0, 111.0, 103.3, 64.3, 50.7, 21.09, 21.06; LC/MS (ESI) *m/z* 547.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{24}H_{24}N_2O_9S_2$ [M - H]$^-$ 547.0850; found 547.0856.

2-Bromo-4-nitronaphthalen-1-amine (116). To a solution of 4-nitronaphthalen-1-amine (1.0 g, 5.31 mmol) in acetonitrile (17 mL) were added ammonium acetate (41 mg, 0.53 mmol) and *N*-bromosuccinimide (993 mg, 5.58 mmol) at room temperature. The reaction mixture was stirred at room temperature for 10 minutes. After the reaction was completed, the crude mixture was concentrated under reduced pressure, added to water, and then

extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting solid was dissolved with the minimum amount of dichloromethane, solidified from hexane, and then filtered to give the product as a yellow solid (1.4 g, 96%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, *J* = 8.8 Hz, 1H), 8.54 (s, 1H), 8.45 (d, *J* = 8.8 Hz, 1H), 7.79-7.75 (m, 1H), 7.62-7.58 (m, 1H), 7.51 (brs, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.5, 132.8, 131.9, 130.3, 126.24, 126.21, 123.7, 123.5, 121.0, 97.6; LC/MS (ESI) *m/z* 267.9 [M(^{79}Br) + H]$^+$, 269.6 [M(^{81}Br) + H]$^+$.

2-(Benzyloxy)-4-nitronaphthalen-1-amine (117a). To a solution of **116** (3 g, 11.23 mmol) in benzyl alcohol (12mL) were added copper (I) iodide (64 mg, 0.34 mmol), 8-hydroxyquinoline (98 mg, 0.67 mmol) and potassium phosphate tribasic (4.8 g, 22.47 mmol) at room temperature. The reaction mixture was stirred at 130 °C for overnight. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-15% dichloromethane/hexane) to give the product as a orange solid (320 mg, 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 8.8 Hz, 1H), 8.28 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.54-7.48 (m, 1H), 7.41-7.39 (m, 1H), 7.38 (s, 2H, NH), 7.35-7.16 (m, 5H), 5.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 138.3, 136.1, 128.8, 128.7, 128.5, 128.4, 128.0, 127.4, 126.9, 125.6, 124.5, 121.2, 114.8, 71.8; LC/MS (ESI) *m/z* 295.1 [M + H]$^+$.

2-((4-Fluorobenzyl)oxy)-4-nitronaphthalen-1-amine (117b). Prepared as described in the experimental procedure of **117a** from intermediate **116** and 4-fluorobenzyl alcohol to obtain the title compound as a orange solid (206 mg, 6%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (d, *J* = 8.8 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 8.35 (s, 1H), 7.67-7.60 (m, 4H), 7.28

(s, 2H, NH), 7.25-7.20 (m, 2H), 5.33 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 161.8 ($J_{C,F}$ = 243 Hz), 143.2, 136.9, 133.0 ($J_{C,F}$ = 3 Hz), 130.4, 130.0 ($J_{C,F}$ = 8 Hz), 129.0, 124.9, 124.1, 123.4, 123.2, 120.3, 115.4, 115.2 ($J_{C,F}$ = 21 Hz), 70.0; LC/MS (ESI) *m/z* 313.1 [M + H]$^+$.

***N,N'*-(2-(Benzyloxy)naphthalene-1,4-diyl)bis(4-methylbenzenesulfonamide) (118a).** Prepared as described in the experimental procedure of **22b** from **117a** to obtain the title compound as a beige solid (118 mg, 24% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.27 (brs, 1H, NH), 9.53 (brs, 1H, NH), 8.07 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.47-7.44 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.33-7.28 (m, 6H), 7.15-7.13 (m, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.90 (s, 1H), 4.50 (d, *J* = 10.4 Hz, 2H), 2.32 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 151.5, 143.2, 142.3, 138.5, 136.8, 136.4, 133.6, 133.3, 129.6, 128.9, 128.1, 127.6, 126.9, 126.72, 126.66, 126.6, 124.7, 123.94, 123.86, 122.9, 116.2, 111.0, 67.8, 20.96, 20.95; LC/MS (ESI) *m/z* 571.1 [M - H]$^-$.

***N,N'*-(2-((4-Fluorobenzyl)oxy)naphthalene-1,4-diyl)bis(4-methylbenzenesulfon-amide) (118b).** Prepared as described in the experimental procedure of **22b** from intermediate **117b** to obtain the title compound as a white solid (57 mg, 15% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.27 (brs, 1H, NH), 9.50 (brs, 1H, NH), 8.07 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.45-7.44 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.34-7.28 (m, 3H), 7.20-7.14 (m, 4H), 7.10-7.08 (m, 2H), 6.91 (s, 1H), 2.32 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 161.6 ($J_{C,F}$ = 245 Hz), 151.3, 143.2, 142.3, 138.6, 136.8, 133.6, 133.3, 132.5 ($J_{C,F}$ = 2 Hz), 129.5, 128.9, 128.8, 126.8, 126.7, 126.6, 124.6, 123.92, 123.87, 122.9, 116.2, 114.9 ($J_{C,F}$ = 22 Hz), 110.9, 69.1, 20.9; LC/MS (ESI) *m/z* 589.2 [M - H]$^-$.

Diethyl 2,2'-((2-((4-fluorobenzyl)oxy)naphthalene-1,4-diyl)bis(tosylazanediyl)) diacetate (119). Prepared as described in the experimental procedure of **15a** from intermediate **118b** to obtain the title compound as a white solid (53 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54-8.50 (m, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.42-7.26 (m, 5H), 7.17-7.13 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.96-6.87 (m, 5H), 4.73-4.51 (m, 3H), 4.45-4.25 (m, 1H), 4.11-3.89 (m, 6H), 2.30-2.18 (m, 6H), 1.14-1.01 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.2, 169.1, 162.6 ($J_{C,F}$ = 245 Hz), 152.0, 151.8, 144.0, 143.6, 143.5, 137.7, 137.6, 136.9, 136.8, 136.7, 136.5, 135.5, 135.4, 131.6, 129.6, 129.3, 129.1 ($J_{C,F}$ = 8 Hz), 129.0 ($J_{C,F}$ = 7 Hz), 128.3, 128.1, 127.5, 127.3, 127.2, 126.5, 126.4, 125.6, 123.5, 123.4, 122.5, 122.3, 118.5, 118.1, 115.50 ($J_{C,F}$ = 21 Hz), 115.46 ($J_{C,F}$ = 22 Hz), 70.1, 70.0, 61.63, 61.58, 61.5, 52.8, 52.7, 21.73, 21.68, 21.6, 14.24, 14.19, 14.15, 14.1; LC/MS (ESI) *m/z* 763.4 $[M + H]^+$.

2,2'-((2-((4-Fluorobenzyl)oxy)naphthalene-1,4-diyl)bis(tosylazanediyl))diacetic acid (120). Prepared as described in the experimental procedure of **16a** from intermediate **119** to obtain the title compound as a white solid (38 mg, 77%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (brs, 2H, CO_2H), 8.74-8.66 (m, 1H), 8.31-8.21 (m, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.47-7.41 (m, 1H), 7.37-7.33 (m, 3H), 7.20-7.14 (m, 4H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.03-6.99 (m, 1H), 6.97-6.69 (m, 1H), 6.96-6.93 (m, 1H), 4.56-3.79 (m, 4H), 4.40-4.35 (m, 1H), 4.19-4.08 (m, 1H), 2.33-2.25 (m, 6H); ^{13}C NMR (100 MHz, MeOD) δ 172.5, 172.0, 163.9 ($J_{C,F}$ = 243 Hz), 153.2, 153.0, 145.6, 145.5, 145.0, 139.4, 139.3, 137.8, 137.6, 137.2, 137.2, 136.7, 136.6, 133.2 ($J_{C,F}$ = 4 Hz), 130.6, 130.5 ($J_{C,F}$ = 10 Hz), 130.3 ($J_{C,F}$ = 9 Hz), 129.5, 129.2, 128.9, 127.9, 127.50, 127.45, 126.0, 125.9, 124.3, 118.5, 118.4, 116.2 ($J_{C,F}$ = 22 Hz), 116.1 ($J_{C,F}$ = 22 Hz), 70.9,

70.8, 54.1, 53.7, 21.7, 21.64, 21.57, 21.5; LC/MS (ESI) *m/z* 707.3 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{35}H_{31}FN_2O_9S_2$ $[M + H]^+$ 707.1528; found 707.1540.

***N,N'*-(2-Hydroxynaphthalene-1,4-diyl)bis(4-methylbenzenesulfonamide) (121).** Prepared as described in the procedure of **73** from **118a** to obtain the title compound as a pale red solid (41 mg, 44%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (brs, 1H, NH), 9.56 (brs, 1H, NH), 9.20 (brs, 1H, OH), 7.98-7.69 (m, 1H), 7.89-7.85 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.53-7.50 (m, 2H), 7.40-7.35 (m, 1H), 7.32-7.25 (m, 4H), 7.18-7.15 (m, 1H), 6.98-6.88 (m, 1H), 2.36 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.5, 143.2, 143.1, 142.3, 141.9, 141.5, 138.9, 137.1, 132.8, 129.8, 129.7, 129.6, 129.4, 129.0, 126.9, 126.8, 125.7, 122.7, 114.2, 21.03, 20.96; LC/MS (ESI) *m/z* 481.0 $[M - H]^-$.

Di-*tert*-butyl 2,2'-((2-(2-(*tert*-butoxy)-2-oxoethoxy)naphthalene-1,4-diyl)bis(tosylazanediyl))diacetate (122). Prepared as described in the experimental procedure of **75a** from intermediate **121** to obtain the title compound as a colorless oil (54 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84-8.79 (m, 1H), 7.64-7.47 (m, 6H), 7.34-7.28 (m, 1H), 7.26-7.13 (m, 4H), 6.96 (s, 1H), 4.76-4.61 (m, 2H), 4.16-4.01 (m, 2H), 3.91-3.65 (m, 1H), 3.46-3.42 (m, 1H), 2.47-2.44 (m, 3H), 2.40 (s, 3H), 1.50-1.40 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.4, 167.89, 167.86, 166.5, 166.4, 150.80, 150.75, 143.9, 143.3, 137.6, 136.7, 136.6, 129.6, 129.5, 129.1, 128.3, 128.0, 127.4, 127.33, 127.26, 126.9, 125.7, 125.6, 123.4, 122.4, 117.2, 117.0, 82.8, 82.3, 82.0, 81.9, 65.4, 65.2, 54.3, 54.0, 53.6, 53.5, 28.2, 28.1, 21.7, 21.6; LC/MS (ESI) *m/z* 842.5 $[M + H + H_2O]^+$.

2,2'-((2-(Carboxymethoxy)naphthalene-1,4-diyl)bis(tosylazanediyl))diacetic acid (123). Prepared as described in the experimental procedure of **76a** from intermediate **122** to obtain the title compound as a white solid (37 mg, 86%); ^{1}H NMR (400 MHz, DMSO-

d_6) δ 12.98 (brs, 3H, CO_2H), 8.73-8.66 (m, 1H), 8.36-8.23 (m, 1H), 7.60-7.58 (m, 3H), 7.53-7.38 (m, 6H), 7.28-7.26 (m, 1H), 6.85-6.34 (m, 1H), 4.64-4.52 (m, 1H), 4.39 (s, 1H), 4.31-4.16 (m, 2H), 4.07-3.86 (m, 1H), 3.77-3.02 (m, 1H), 2.45 (s, 3H), 2.38-2.36 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.6, 170.4, 169.7, 169.1, 168.5, 150.8, 150.1, 144.0, 143.3, 138.5, 138.2, 135.9, 134.7, 134.5, 134.1, 129.8, 129.6, 129.3, 129.2, 128.4, 128.1, 127.7, 127.5, 126.6, 125.7, 125.5, 124.4, 124.3, 122.2, 121.9, 115.0, 114.5, 64.0, 53.6, 53.0, 52.2, 21.0; LC/MS (ESI) *m/z* 657.2 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{30}H_{28}N_2O_{11}S_2$ $[M + H]^+$ 657.1207; found 657.1220.

2-(2-Fluoro-5-nitrophenoxy)-1-morpholinoethan-1-one (124a). Prepared as described in the procedure of **40b** from 2-fluoro-5-nitrophenol and 2-bromo-1-morpholinoethan-1-one to obtain the title compound as a colorless oil (601 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H), 7.30-7.24 (m, 1H), 4.91 (s, 2H), 3.75-3.73 (m, 4H), 3.68-3.67 (m, 2H), 3.60-3.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 156.5 ($J_{C,F}$ = 257 Hz), 146.4 ($J_{C,F}$ = 11 Hz), 144.4, 118.3 ($J_{C,F}$ = 9 Hz), 116.8 ($J_{C,F}$ = 21 Hz), 111.0 ($J_{C,F}$ = 3 Hz), 67.9, 66.9, 66.7, 45.8, 42.5; LC/MS (ESI) *m/z* 285.1 $[M + H]^+$.

2-(5-Fluoro-2-nitrophenoxy)-1-morpholinoethan-1-one (124b). Prepared as described in the experimental procedure of **40b** from 5-fluoro-2-nitrophenol and 2-bromo-1-morpholinoethan-1-one to obtain the title compound as a white solid (236 mg, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 9.2, 6.0 Hz, 1H), 6.90 (dd, *J* = 10.0, 2.4 Hz, 1H), 6.79-6.75 (m, 1H), 4.83 (s, 2H), 3.68-3.61 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 ($J_{C,F}$ = 256 Hz), 164.8, 153.3 ($J_{C,F}$ = 11 Hz), 136.3 128.3 ($J_{C,F}$ = 11 Hz), 108.7 ($J_{C,F}$ = 23 Hz), 103.0 ($J_{C,F}$ = 27 Hz), 68.8, 66.84, 66.78, 46.1, 42.7; LC/MS (ESI) *m/z* 285.1 $[M+ H]^+$.

***(S)*-1-(2-(2-Morpholino-2-oxoethoxy)-4-nitrophenyl)pyrrolidine-3-carboxylic acid (125a).** Prepared as described in the experimental procedure of **36** from intermediate **124a** and *(S)*-pyrrolidine-3-carboxylic acid to obtain the title compound as a yellow solid (71 mg, 53%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, *J* = 8.8 Hz, 1H), 7.64 (s, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 4.94 (s, 2H), 3.85-3.80 (m, 4H), 3.79-3.76 (m, 4H), 3.61-3.57 (m, 8H), 3.15-3.10 (m, 1H), 2.17-2.07 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.5, 165.6, 145.5, 144.8, 136.4, 119.6, 112.5, 108.3, 66.7, 66.1, 52.8, 49.9, 44.7, 42.4, 41.7, 28.1; LC/MS (ESI) *m/z* 380.2 $[M + H]^+$.

***(S)*-1-(3-(2-Morpholino-2-oxoethoxy)-4-nitrophenyl)pyrrolidine-3-carboxylic acid (125b).** Prepared as described in the experimental procedure of **36** from intermediate **124b** and *(S)*-pyrrolidine-3-carboxylic acid to obtain the title compound as a yellow solid (170 mg, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, *J* = 9.6 Hz, 1H), 6.24 (dd, *J* = 9.6, 2.0 Hz, 1H), 6.05 (d, *J* = 2.0 Hz, 1H), 5.02 (s, 2H), 3.54-3.50 (m, 4H), 3.45-3.42 (m, 4H), 3.41-3.37 (m, 3H), 3.27-3.12 (m, 2H), 2.29-2.13 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.5, 165.5, 154.8, 152.1, 128.6, 127.2, 104.6, 96.1, 66.8, 66.2, 50.0, 47.2, 45.2, 42.4, 41.9, 28.2; LC/MS (ESI) *m/z* 380.2 $[M + H]^+$.

***(S)*-1-(2-(2-Morpholino-2-oxoethoxy)-4-((2,3,5,6-tetramethylphenyl)sulfonamido) phenyl)pyrrolidine-3-carboxylic acid (126a).** Prepared as described in the experimental procedure of **18d** from intermediate **125a** and 2,3,5,6-tetramethylbenzenesulfonyl chloride to obtain the title compound as a white solid (20 mg, 22% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.71 (brs, 1H, NH), 6.60 (d, *J* = 2.0 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.46 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.55 (s, 2H), 3.65-3.64 (m, 4H), 3.60-3.56 (m, 3H), 3.51-3.47 (m, 2H), 3.39-3.32 (m, 2H), 3.25-3.17 (m, 1H), 3.15-3.10 (m, 1H), 2.48 (s, 6H),

2.24 (s, 6H), 2.21-2.20 (m, 2H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 166.3, 149.2, 137.9, 136.9, 136.1, 136.0, 135.5, 129.3, 117.3, 116.7, 109.9, 67.5, 66.9, 66.7, 53.2, 49.8, 45.83, 45.80, 42.5, 28.1, 21.2, 18.1; LC/MS (ESI) *m/z* 544.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{27}H_{35}N_3O_7S$ [M - H]$^-$ 544.2123; found 544.2127.

***(S)*-1-(3-(2-Morpholino-2-oxoethoxy)-4-((2,3,5,6-tetramethylphenyl)sulfonamido) phenyl)pyrrolidine-3-carboxylic acid (126b).** Prepared as described in the experimental procedure of **18d** from intermediate **125b** and 2,3,5,6-tetramethylbenzenesulfonyl chloride to obtain the title compound as a white solid (82 mg, 38% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 1H), 6.05 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.98 (d, *J* = 2.4 Hz, 1H), 4.42 (s, 2H), 3.65-3.61 (m, 4H), 3.59-3.58 (m, 2H), 3.43-3.41 (m, 2H), 3.38-3.36 (m, 2H), 3.31-3.27 (m, 1H), 3.24-3.18 (m, 1H), 3.17-3.09 (m, 1H), 2.39 (s, 6H), 2.25-2.21 (m, 2H), 2.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 167.2, 152.8, 146.9, 138.9, 135.8, 135.7, 135.6, 127.0, 115.9, 106.2, 99.0, 69.1, 66.8, 66.7, 50.2, 47.4, 45.5, 42.8, 42.6, 28.5, 21.2, 18.2; LC/MS (ESI) *m/z* 544.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{27}H_{35}N_3O_7S$ [M - H]$^-$ 544.2123; found 544.2128.

Methyl *(S)*-1-(3-(2-morpholino-2-oxoethoxy)-4-nitrophenyl)pyrrolidine-3-carboxylate (127). To a solution of **125b** (457 mg, 1.20 mmol) in methanol (6.5 mL) was added thionyl chloride (1.4 g, 12.05 mmol) at 0 °C. The reaction mixture was stirred 0 °C for 1 hour. After the reaction was completed, the crude mixture was added to sat. $NaHCO_3$ until the pH reached around 7 and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the product as a yellow solid (208 mg, 44%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, *J* = 9.2 Hz, 1H), 6.25 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 5.04 (s, 2H), 3.66 (s, 3H), 3.64-

3.59 (m, 4H), 3.58-3.53 (m, 4H), 3.52-3.50 (m, 3H), 3.36-3.34 (m, 2H), 2.32-2.18 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.2, 165.3, 154.7, 152.0, 128.5, 127.2, 104.5, 96.1, 66.7, 66.2, 52.0, 49.8, 47.1, 45.1, 42.0, 41.8, 28.0; LC/MS (ESI) *m/z* 394.2 $[M + H]^+$.

Methyl *(S)*-1-(3-(2-morpholino-2-oxoethoxy)-4-((2,3,5,6-tetramethylphenyl)sulfonamido)phenyl)pyrrolidine-3-carboxylate (128). Prepared as described in the experimental procedure of **22b** from intermediate **127** and 2,3,5,6-tetramethylbenzenesulfonyl chloride to obtain the title compound as a white solid (50 mg, 18% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (brs, 1H, NH), 7.14 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.13-6.11 (m, 1H), 6.11 (s, 1H), 4.51 (s, 2H), 3.63 (s, 3H), 3.58-3.50 (m, 8H), 3.28-3.15 (m, 5H), 2.30 (s, 6H), 2.24-2.19 (m, 1H), 2.16 (s, 6H), 2.13-2.07 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.7, 166.9, 154.1, 146.9, 139.4, 135.0, 134.9, 134.8, 128.0, 114.8, 105.4, 99.8, 68.8, 65.9, 51.8, 49.8, 47.0, 44.5, 42.1, 41.7, 28.0, 20.5, 17.8; LC/MS (ESI) *m/z* 558.2 $[M - H]^-$.

Methyl *(S)*-1-(4-((*N*-(2-ethoxy-2-oxoethyl)-2,3,5,6-tetramethylphenyl)sulfonamido) -3-(2-morpholino-2-oxoethoxy)phenyl)pyrrolidine-3-carboxylate (129). Prepared as described in the experimental procedure of **115a** from intermediate **128** to obtain the title compound as a colorless oil (46 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 7.05 (d, *J* = 8.8 Hz, 1H), 6.05 (d, *J* = 2.4 Hz, 1H), 5.97 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.57 (s, 2H), 4.40 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 1H), 3.70 (s, 3H), 3.68-3.66 (m, 4H), 3.64-3.62 (m, 4H), 3.48-3.44 (m, 2H), 3.36-3.33 (m, 1H), 3.29-3.21 (m, 1H), 3.19-3.13 (m, 1H), 2.26 (s, 6H), 2.24-2.22 (m, 2H), 2.19 (s, 6H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 169.5, 166.9, 156.8, 148.9, 138.2, 136.7, 135.7, 135.4, 134.6, 114.6, 104.8, 96.9, 68.7, 67.2, 66.8, 61.1, 52.2, 50.6, 50.2, 47.3, 46.0, 43.0, 42.5, 28.7, 21.1, 18.2, 14.2.

***(S)*-1-(4-((*N*-(Carboxymethyl)-2,3,5,6-tetramethylphenyl)sulfonamido)-3-(2-morpholino-2-oxoethoxy)phenyl)pyrrolidine-3-carboxylic acid (130).** Prepared as described in the experimental procedure of **16a** from intermediate **129** to obtain the title compound as a dark gray solid (19 mg, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 7.09-7.06 (m, 1H), 6.14 (s, 1H), 6.14-6.02 (m, 1H), 4.59 (s, 2H), 4.46 (s, 2H), 3.67-3.66 (m, 4H), 3.61-3.58 (m, 4H), 3.51-3.49 (m, 2H), 3.29-3.19 (m, 3H), 2.52-2.49 (m, 1H), 2.37-2.34 (m, 1H), 2.26 (s, 6H), 2.20 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.8, 170.8, 165.7, 155.7, 148.6, 138.5, 135.8, 135.1, 135.0, 134.1, 113.8, 103.7, 96.3, 66.1, 65.3, 50.8, 49.9, 47.0, 44.6, 42.4, 41.6, 28.1, 20.6, 17.8; LC/MS (ESI) *m/z* 602.3 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{29}H_{37}N_3O_9S$ $[M - H]^-$ 602.2178; found 602.2185.

***tert*-Butyl 2-(1,3-dioxoisoindolin-2-yl)acetate (131).** Prepared as described in the experimental procedure of **40b** from phthalimide and *tert*-butyl 2-bromoacetate to obtain the title compound as a white solide (7.6 g, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.85 (m, 2H), 7.73-7.71 (m, 2H), 4.32 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 166.4, 134.3, 132.2, 123.6, 82.9, 39.8, 28.1.

2-(1,3-Dioxoisoindolin-2-yl)acetic acid (132). Prepared as described in the experimental procedure of **76a** from intermediate **131** to obtain the title compound as a white solid (2.4 g, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.25 (brs, 1H, CO_2H), 7.95-7.86 (m, 4H), 4.32 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9, 167.2, 134.8, 131.4, 123.4, 38.9; LC/MS (ESI) *m/z* 206.1 $[M + H]^+$.

(2-Methyl-5-nitrophenyl)methanol (133a). Prepared as described in the experimental procedure of **30** from 2-methyl-5-nitrobenzoic acid to obtain the title compound as a white solid (871 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.4 Hz, 1H), 8.06 (dd, *J*

= 8.4, 2.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 4.78 (d, *J* = 5.6 Hz, 2H), 2.42 (s, 3H), 1.82 (t, *J* = 5.6 Hz, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 140.5, 131.1, 122.6, 122.0, 62.6, 19.0; LC/MS (ESI) *m/z* 166.1 $[M - H]^-$.

(2-Methoxy-5-nitrophenyl)methanol (133b). Prepared as described in the experimental procedure of **30** from 2-methoxy-5-nitrobenzoic acid to obtain the title compound as a white solid (451 mg, 97%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, *J* = 2.0 Hz, 1H), 8.15 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 5.43 (t, *J* = 5.2 Hz, 1H, OH), 4.52 (d, *J* = 5.2 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 140.7, 132.0, 124.1, 121.7, 110.5, 57.3, 56.3; LC/MS (ESI) *m/z* 184.1 $[M + H]^+$.

2-(2-Methyl-5-nitrophenyl)acetonitrile (134a). To a solution of **133a** (100 mg, 0.60 mmol) in dichloromethane (3 mL) were added triethylamine (73 mg, 0.72 mmol) and methanesulfonyl chloride (72 mg, 0.63 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2-methyl-5-nitrobenzyl methanesulfonate as a pale yellow oil (143 mg, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 2.4 Hz, 1H), 8.12 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.29 (s, 2H), 3.06 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 145.1, 133.4, 131.7, 124.34, 124.30, 68.9, 38.2, 19.2. To a solution of 2-methyl-5-nitrobenzyl methanesulfonate (103 mg, 0.42 mmol) in acetonitrile (2.1 mL) was added potassium cyanide (82 mg, 1.26 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

The residue was purified by flash column chromatograph (0-20% ethyl acetate/hexane) to give the product as a pale yellow solid (38 mg, 37%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 2.4 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 3.77 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 144.2, 131.7, 130.4, 123.8, 123.5, 116.4, 22.0, 19.7; LC/MS (ESI) *m/z* 175.1 $[M - H]^-$.

2-(2-Methoxy-5-nitrophenyl)acetonitrile (134b). Prepared as described in the experimental procedure of **134a** from intermediate **133b** to obtain the title compound as a white solid (184 mg, 49% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30-8.27 (m, 2H), 7.30 (d, *J* = 9.2 Hz, 1H), 4.00 (s, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 140.5, 125.9, 125.0, 120.7, 118.0, 111.6, 56.9, 18.0.

2-(1,3-Dioxoisoindolin-2-yl)-*N*-(2-methyl-5-nitrophenethyl)acetamide (135a). To a solution of **134a** (430 mg, 2.44 mmol) in tetrahydrofuran (5 mL) was added borane tetrahydrofuran complex solution (1.0 M in THF, 4.9 ml, 4.88 mmol) at room temperature. The reaction mixture was stirred at 60 ℃ for 1 hour. After the reaction was completed, the crude mixture was added to methanol and water, and then concentrated under reduced pressure. The aqueous solution was acidified with 6 N HCl until the pH reached around 1 and stirred at 70 ℃ for 1 hour. After cooling to room temperature, the solution was basified with sat. $NaHCO_3$ until the pH reached around 10, and then extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2-(2-methyl-5-nitrophenyl)ethan-1-amine as a pale yellow oil (440 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.4 Hz, 1H), 7.97 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 144.5, 140.0, 131.1, 124.1, 121.5, 42.1, 37.3,

19.9; LC/MS (ESI) *m/z* 181.1 [M + H]$^+$. Prepared as described in the experimental procedure of **54** from intermediate **132** and 2-(2-methyl-5-nitrophenyl)ethan-1-amine to obtain the title compound as a white solid (1.3 g, 83%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.37 (t, *J* = 5.6 Hz, 1H, NH), 8.00-7.96 (m, 2H), 7.90-7.85 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 1H), 4.15 (s, 2H), 3.34-3.29 (m, 4H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 167.4, 166.1, 145.8, 145.0, 139.3, 134.5, 131.7, 131.1, 123.9, 123.1, 121.2, 40.1, 38.6, 32.3, 19.1; LC/MS (ESI) *m/z* 368.1 [M + H]$^+$.

2-(1,3-Dioxoisoindolin-2-yl)-*N*-(2-methoxy-5-nitrophenethyl)acetamide (135b). Prepared as described in the procedure of **135a** from **134b** to obtain the title compound as a white solid (256 mg, 71% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.29 (t, *J* = 5.6 Hz, 1H, NH), 8.15 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.02 (d, *J* = 2.8 Hz, 1H), 7.90-7.85 (m, 4H), 7.18 (d, *J* = 8.8 Hz, 1H), 4.12 (s, 2H), 3.93 (s, 3H), 3.33-3.28 (m, 2H), 2.78 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 167.4, 165.9, 162.6, 140.4, 134.5, 131.7, 128.4, 125.5, 124.2, 123.1, 110.9, 56.4, 40.0, 38.1, 29.5; LC/MS (ESI) *m/z* 384.1 [M + H]$^+$.

***N,N'*-([1,1'-Biphenyl]-2,5-diyl)bis(4-methoxybenzenesulfonamide) (136a).** To a solution of **135a** (500 mg, 1.36 mmol) in methanol (50 mL) was added Pd/C (10% wt.) (50 mg) at room temperature under N_2. The reaction mixture was stirred at room temperature for 1 hour under H_2. The crude mixture was filtered off through celite, and then concentrated under reduced pressure to give *N*-(5-amino-2-methylphenethyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide as a white solid (460 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.39 (t, *J* = 5.6 Hz, 1H, NH), 7.93-7.87 (m, 4H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 6.32 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.75 (brs, 2H, NH), 4.19 (s, 2H), 3.18-3.13 (m, 2H), 2.54 (t, *J* = 8.0 Hz, 2H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$)

δ 167.6, 165.9, 146.6, 137.4, 134.6, 131.8, 130.4, 123.2, 122.5, 115.1, 112.2, 33.1, 17.9; LC/MS (ESI) *m/z* 338.2 $[M + H]^+$. Prepared as described in the experimental procedure of **52** from *N*-(5-amino-2-methylphenethyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide to obtain the title compound as a white solid (390 mg, 56%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (brs, 1H, NH), 8.38 (brs, 1H, NH), 7.93-7.86 (m, 4H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.85-6.81 (m, 2H), 4.19 (s, 2H), 3.77 (s, 3H), 3.11-3.09 (m, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 166.0, 162.3, 138.0, 135.7, 134.6, 131.8, 131.6, 131.2, 130.6, 128.9, 123.2, 121.1, 118.4, 114.3, 55.6, 32.9, 18.1; LC/MS (ESI) *m/z* 508.2 $[M + H]^+$.

2-(1,3-Dioxoisoindolin-2-yl)-*N*-(2-methyl-5-((4-methylphenyl)sulfonamido)phenethyl)acetamide (136b). Prepared as described in the experimental procedure of **52** from 4-methylbenzene-sulfonyl chloride and *N*-(5-amino-2-methylphenethyl)-2-(1,3-dioxoisoindolin-2-yl)-acetamide to obtain the title compound as a white solid (350 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (brs, 1H, NH), 8.37 (t, *J* = 5.2 Hz, 1H, NH), 7.93-7.86 (m, 4H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.19 (s, 2H), 3.12-3.07 (m, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 166.0, 143.0, 138.0, 136.7, 135.6, 134.5, 131.8, 131.7, 130.6, 129.6, 126.7, 123.2, 121.1, 118.4, 32.9, 20.9, 18.1; LC/MS (ESI) *m/z* 492.2 $[M + H]^+$.

2-(1,3-Dioxoisoindolin-2-yl)-*N*-(2-methoxy-5-((4-methoxyphenyl)sulfonamido)phenethyl)acetamide (136c). Prepared as described in the experimental procedure of **12** from intermediate **135b** to obtain *N*-(5-amino-2-methoxyphenethyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide as a white solid (205 mg, 90%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (brs,

1H, NH), 7.92-7.86 (m, 4H), 6.66 (d, *J* = 9.2 Hz, 1H), 6.42-6.39 (m, 2H), 4.53 (brs, 2H, NH), 4.18 (s, 2H), 3.64 (s, 3H), 3.21-3.17 (m, 2H), 2.56 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 165.7, 148.7, 142.1, 134.4, 131.8, 127.4, 123.1, 116.4, 112.6, 112.2, 55.9, 29.9; LC/MS (ESI) *m/z* 354.2 $[M + H]^+$. Prepared as described in the experimental procedure of **52** from *N*-(5-amino-2-methoxyphenethyl)-2-(1,3-dioxo-isoindolin-2-yl)acetamide to obtain the title compound a white solid (253 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.87 (m, 2H), 7.75-7.73 (m, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.16 (brs, 1H, NH), 7.06 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 1H), 5.96 (brs, 1H, NH), 4.22 (s, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 3.37-3.33 (m, 2H), 2.67 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.3, 163.0, 155.6, 134.5, 132.0, 130.9, 129.5, 129.3, 127.9, 126.7, 123.8, 123.4, 114.2, 111.0, 55.72, 55.69, 40.9, 39.7, 29.3; LC/MS (ESI) *m/z* 542.2 $[M + H]^+$.

***N*-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-5-methyl-3,4-dihydroisoquinolin-8-yl)-4-methoxybenzenesulfonamide (137a).** To a solution of **136a** (304 mg, 0.60 mmol) in acetonitrile (12 mL) was added phosphorus(V) oxychloride (531 mg, 3.84 mmol) at room temperature. The reaction mixture was stirred at 85 °C for 4 hours. After the reaction was completed, the crude mixture was cooled to room temperature, added to to sat. $NaHCO_3$, and then extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-50% ethyl acetate/hexane to 0-5% methanol/dichloromethane) to give the product as a white solid (270 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (brs, 1H, NH), 7.87-7.84 (m, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.72-7.70 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.95-6.91 (m, 3H), 4.89 (s, 2H), 3.84 (s, 3H), 3.39 (t, *J* = 6.8 Hz, 2H), 2.43 (t, *J* = 6.8

Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.4, 161.5, 140.2, 134.0, 132.9, 132.7, 132.6, 131.4, 131.3, 129.7, 124.6, 123.7, 123.2, 114.4, 55.8, 46.5, 42.9, 24.2, 19.1; LC/MS (ESI) *m/z* 490.2 $[M + H]^+$.

***N*-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-5-methyl-3,4-dihydroisoquinolin-8-yl)-4-methylbenzenesulfonamide (137b).** Prepared as described in the experimental procedure of **137a** from **136b** to obtain the title compound as a white solid (285 mg, 90%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (brs, 1H, NH), 7.91-7.85 (m, 4H), 7.48-7.34 (m, 5H), 6.92 (s, 1H), 5.38 (s, 2H), 3.57-3.54 (m, 2H), 2.91-2.88 (m, 2H), 2.36 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.3, 143.9, 139.4, 137.3, 135.2, 134.9, 134.6, 134.4, 132.0, 129.6, 127.0, 125.1, 123.8, 123.3, 41.5, 23.5, 21.0, 18.6; LC/MS (ESI) *m/z* 474.1 $[M + H]^+$.

***N*-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-5-methoxy-3,4-dihydroisoquinolin-8-yl)-4-methoxybenzenesulfonamide (137c).** Prepared as described in the procedure of **137a** from **136c** to obtain the title compound as a pale yellow solid (167 mg, 71%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (brs, 1H, NH), 7.90-7.87 (m, 4H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 1H), 4.98 (s, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.12-3.10 (m, 2H), 2.38-2.36 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.2, 162.9, 160.9, 154.7, 134.9, 132.1, 131.0, 129.5, 129.3, 128.5, 127.4, 126.0, 123.5, 114.6, 113.2, 56.1, 56.0, 45.6, 43.9, 20.0; LC/MS (ESI) *m/z* 506.1 $[M + H]^+$.

***N*-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-5-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-methoxybenzenesulfonamide (138a).** To a solution of **137a** (80 mg, 0.16 mmol) in dichloromethane (2 mL) was added sodium triacetoxyborohydride (69 mg, 0.33 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. The crude mixture was added to water, and extracted with dichloromethane. The organic layer

was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-50% ethyl acetate/hexane to 0-5% methanol/dichloromethane) to give the product as a pale yellow solid (63 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.81 (m, 2H), 7.74-7.69 (m, 4H), 7.24 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 4.28-4.25 (m, 1H), 4.10-4.05 (m, 1H), 3.74 (s, 3H), 3.39-3.32 (m, 2H), 3.17-3.13 (m, 1H), 2.58-2.55 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 168.8, 162.9, 134.2, 134.0, 133.4, 132.0, 131.8, 131.7, 129.4, 126.4, 123.6, 120.9, 114.0, 55.5, 50.0, 38.8, 35.6, 25.3, 18.9; LC/MS (ESI) *m/z* 490.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{25}N_3O_5S$ $[M - H]^-$ 490.1442; found 490.1446.

***N*-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-5-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-methylbenzenesulfonamide (138b).** Prepared as described in the experimental procedure of **138a** from **137b** to obtain the title compound as a white solid (155 mg, 63%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93-7.85 (m, 4H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 4.72-4.69 (m, 1H), 3.78-3.76 (m, 2H), 3.19-3.12 (m, 2H), 2.85-2.80 (m, 2H), 2.38 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 168.0, 142.8, 137.9, 135.2, 134.2, 131.9, 129.5, 127.7, 127.1, 122.9, 48.7, 35.8, 25.9, 21.03, 20.97, 18.7; LC/MS (ESI) *m/z* 476.2 $[M + H]^+$.

***N*-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-5-methoxy-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-methoxybenzenesulfonamide (138c).** Prepared as described in the experimental procedure of **138a** from **137c** to obtain the title compound as a pale yellow solid (106 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 5.2, 2.8 Hz, 2H), 7.77-7.74 (m, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 1H), 4.12-4.06 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.74-3.71 (m, 1H), 3.29-3.16 (m,

2H), 3.06-3.01 (m, 1H), 2.70-2.65 (m, 1H), 2.48-2.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.9, 155.3, 134.4, 132.2, 131.9, 130.1, 129.5, 126.3, 124.6, 123.9, 123.2, 114.0, 108.8, 55.64, 55.55, 50.9, 39.7, 36.0, 22.6; LC/MS (ESI) *m/z* 508.2 $[M + H]^+$.

2-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-8-((4-methoxyphenyl)sulfonamido)-5-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid (139aA and 139aB). To a solution of **138a** (50 mg, 0.10 mmol) in xylene (1 mL) was added cis-1,2-cyclohexanecarboxylic anhydride (19 mg, 0.20 mmol) at room temperature. The reaction mixture was stirred at 70 °C for overnight. After the reaction was completed, the crude mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-3% methanol /dichloromethane) to give two diastereomers (A: white solid, 5 mg, 7%, B: pale orange solid, 17 mg, 26%); **139aA**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (brs, 1H, NH), 7.92-7.90 (m, 2H), 7.79-7.76 (m, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 5.69-5.67 (m, 1H), 4.12-4.06 (m, 1H), 3.88-3.84 (m, 1H), 3.74 (s, 3H), 3.47-3.43 (m, 1H), 2.91-2.83 (m, 2H), 2.78-2.69 (m, 1H), 2.45-2.44 (m, 1H), 2.33-2.27 (m, 1H), 2.22 (s, 3H), 1.63-1.49 (m, 3H), 1.30-1.25 (m, 4H), 0.94-0.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 169.2, 163.0, 134.6, 134.4, 133.5, 132.4, 131.8, 131.2, 129.8, 129.4, 124.9, 123.7, 122.0, 114.1, 55.5, 47.8, 42.0, 39.6, 39.1, 27.8, 26.9, 26.4, 24.7, 23.8, 22.4, 19.0; LC/MS (ESI) *m/z* 644.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{34}H_{35}N_3O_8S$ $[M - H]^-$ 644.2072; found 644.2079; **139aB**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (brs, 1H, NH), 7.88-7.87 (m, 2H), 7.75-7.71 (m, 4H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 2H), 5.80-5.77 (m, 1H), 4.03-3.97 (m, 1H), 3.86-3.81 (m, 1H), 3.74 (s, 3H), 3.40-3.36 (m, 1H), 2.90-2.88 (m, 1H), 2.79-2.74 (m, 2H), 2.46-

2.44 (m, 1H), 2.19 (s, 3H), 2.17-2.10 (m, 1H), 1.56-1.45 (m, 3H), 1.27-1.25 (m, 4H), 0.95-0.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.2, 168.9, 162.7, 134.6, 133.4, 132.5, 132.2, 131.9, 131.7, 130.0, 129.5, 124.4, 123.9, 122.0, 114.4, 55.8, 47.4, 42.8, 39.9, 39.2, 29.8, 27.6, 26.7, 26.3, 24.2, 23.1, 19.2; LC/MS (ESI) *m/z* 644.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{34}H_{35}N_3O_8S$ [M - H]$^-$ 644.2072; found 644.2078.

2-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-8-((4-methylphenyl)sulfonamido)-5-meth-yl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid (139bB). Prepared as described in the experimental procedure of **139aA** and **B** from intermediate **138b** to obtain the title compound as a white solid (12 mg, 7%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.73-7.70 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.04-6.01 (m, 1H), 3.95-3.88 (m, 1H), 3.85-3.82 (m, 1H), 3.77-3.69 (m, 1H), 3.54-3.50 (m, 1H), 3.05-3.04 (m, 1H), 2.79-2.76 (m, 2H), 2.31 (s, 3H), 2.14 (s, 3H), 2.02-2.00 (m, 1H), 1.53-1.45 (m, 3H), 1.27-1.23 (m, 2H), 1.16-1.08 (m, 2H), 0.85-0.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 174.3, 168.8, 143.7, 137.1, 134.5, 132.9, 132.8, 132.3, 131.9, 129.9, 129.7, 127.5, 123.8, 120.3, 51.8, 47.3, 43.0, 42.5, 39.6, 39.4, 26.8, 26.3, 23.8, 23.3, 21.6, 19.1; LC/MS (ESI) *m/z* 628.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{34}H_{35}N_3O_7S$ [M - H]$^-$ 628.2123; found 628.2130.

2-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-5-methoxy-8-((4-methoxyphenyl) sulfona-mido)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid (139cB). Prepared as described in the procedure of **139aA** and **B** from **138c** to obtain the title compound as a white solid (6 mg, 9%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H), 7.73-7.70 (m, 4H), 7.40 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 5.87-5.85 (m, 1H), 3.95-3.88 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.68-3.61 (m,

1H), 3.49-3.45 (m, 1H), 3.00-2.98 (m, 1H), 2.88-2.84 (m, 1H), 2.74-2.65 (m, 2H), 2.35-2.32 (m, 1H), 2.03-1.99 (m, 1H), 1.57-1.52 (m, 1H), 1.48-1.43 (m, 2H), 1.25-1.21 (m, 2H), 1.17-1.10 (m, 2H), 0.84-0.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 175.0, 168.8, 162.8, 154.6, 134.4, 131.9, 131.7, 129.5, 127.4, 126.6, 123.7, 123.5, 123.3, 114.3, 109.3, 55.7, 55.6, 46.9, 42.9, 39.5, 38.9, 29.8, 26.9, 26.1, 23.8, 22.9, 22.8; LC/MS (ESI) *m/z* 660.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{34}H_{35}N_3O_9S$ [M - H]$^-$ 660.2021; found 660.2029.

(*1S*,*2R*)-2-((*S*)-1-((1,3-Dioxoisoindolin-2-yl)methyl)-5-methoxy-8-((4-methoxyphenyl) sulfonamido)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid (139c). To a solution of **138c** (100 mg, 0.20 mmol) in DMF (1 mL) were added (*1R*,*2S*)-2-((benzyloxy)carbonyl)cyclohexane-1-carboxylic acid (78 mg, 0.30 mmol), HATU (135 mg, 0.35 mmol) and *N*,*N*-diisopropylethylamine (76 mg, 0.59 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-50% ethyl acetate/hexane) to give the product as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.79 (m, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.52-7.50 (m, 2H), 7.37-7.30 (m, 3H), 7.10 (d, *J* = 6.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 5.87-5.84 (m, 1H), 4.45-4.42 (m, 1H), 4.24-4.21 (m, 1H), 4.12-4.06 (m, 1H), 3.92-3.84 (m, 1H), 3.81 (s, 3H), 3.77-3.73 (m, 1H), 3.69 (s, 3H), 3.28-3.23 (m, 1H), 3.11-3.10 (m, 1H), 2.90-2.85 (m, 1H), 2.64-2.52 (m, 1H), 2.28-2.24 (m, 1H), 2.20-1.85 (m, 1H), 1.79-1.75 (m, 2H), 1.65-1.62 (m, 1H), 1.48-1.41 (m, 1H), 1.32-1.29 (m, 1H), 1.21-1.13 (m, 1H), 1.07-1.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 172.8, 169.9, 162.9, 154.5, 136.8, 133.6, 132.5, 131.3, 129.6, 128.4, 127.8, 127.5,

127.0, 126.9, 123.8, 123.0, 122.8, 114.2, 109.1, 64.9, 55.6, 55.4, 46.3, 42.7, 40.0, 39.2, 37.5, 27.2, 25.4, 24.2, 23.5, 22.8; LC/MS (ESI) *m/z* 750.2 $[M - H]^-$. To a solution of benzyl (*1S*,*2R*)-2-((*S*)-1-((1,3-dioxoisoindolin-2-yl)methyl)-5-methoxy-8-((4-methoxyphenyl)-sulfonamido)-1,2,3,4-tetrahydroisoquinol-ine-2-carbonyl)cyclo-hexane-1-carboxylate (63 mg, 0.08 mmol) in methanol (9 mL) and water (1 mL) was added Pd/C (10% wt.) (7 mg) at room temperature under N_2. The reaction mixture was stirred at room temperature for overnight under H_2. After the reaction was completed, the crude mixture was filtered off through celite, and then concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-3% methanol/dichloromethane) to give the product as a white solid (18 mg, 14% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.79 (m, 2H), 7.68-7.66 (m, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 2H), 5.64-5.61 (m, 1H), 3.95-3.89 (m, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.64-3.55 (m, 1H), 3.37-3.34 (m, 1H), 2.86-2.78 (m, 2H), 2.69-2.60 (m, 1H), 2.38-2.36 (m, 1H), 2.10-2.08 (m, 1H), 1.49-1.44 (m, 1H), 1.39-1.36 (m, 2H), 1.25-1.18 (m, 4H), 0.82-0.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 174.3, 168.8, 162.7, 154.7, 134.5, 131.9, 131.6, 130.1, 129.5, 126.6, 124.5, 123.8, 123.0, 114.3, 109.5, 55.74, 55.66, 47.5, 42.8, 39.9, 39.0, 29.8, 27.5, 26.7, 24.2, 23.2, 22.8; LC/MS (ESI) *m/z* 660.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{34}H_{35}N_3O_9S$ $[M - H]^-$ 660.2021; found 660.2012.

***N*-(4-Aaminophenethyl)-2-(1,3-dioxoisoindolin-2-yl)acetamide (140).** Prepared as described in the experimental procedure of **54** from intermediate **132** and 4-(2-aminoethyl)aniline to obtain the title compound as a white solid (984 mg, 68%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (t, *J* = 5.6 Hz, 1H, NH), 7.93-7.86 (m, 4H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 8.4 Hz, 2H), 4.84 (brs, 2H, NH), 4.17 (s, 2H), 3.20-3.15 (m, 2H),

3.54-3.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 167.5, 165.8, 146.8, 134.5, 131.8, 129.0, 126.1, 123.2, 114.0, 41.0, 34.3; LC/MS (ESI) *m/z* 324.2 [M + H]$^+$.

2-(1,3-Dioxoisoindolin-2-yl)-*N*-(4-((4-methoxyphenyl)sulfonamido)phenethyl)acetamide (141). Prepared as described in the experimental procedure of **52** from **140** to obtain the title compound as a white solid (833 mg, 56%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.05 (brs, 1H, NH), 8.28 (t, *J* = 5.6 Hz, 1H, NH), 7.92-7.85 (m, 4H), 7.68 (d, *J* = 9.2 Hz, 2H), 7.07-7.01 (m, 6H), 4.15 (s, 2H), 3.78 (s, 3H), 3.23-3.18 (m, 2H), 2.59 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 167.5, 165.9, 162.3, 136.0, 134.8, 134.5, 131.8, 131.3, 129.3, 128.8, 123.1, 120.1, 114.3, 55.6, 54.9, 34.2; LC/MS (ESI) *m/z* 494.2 [M + H]$^+$.

***N*-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-3,4-dihydroisoquinolin-7-yl)-4-methoxybenzenesulfonamide (142).** Prepared as described in the experimental procedure of **137a** from intermediate **141** to obtain the title compound as a white solid (403 mg, 51%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.28 (brs, 1H, NH), 7.95-7.89 (m, 4H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.38 (s, 1H), 7.20-7.14 (m, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 4.73 (s, 2H), 3.83 (s, 3H), 3.45-3.42 (m, 2H), 2.52-2.50 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 167.6, 162.5, 157.8, 136.8, 134.6, 132.8, 131.8, 130.9, 129.0, 128.5, 127.1, 123.2, 122.8, 116.1, 114.4, 55.6, 46.1, 40.5, 23.4; LC/MS (ESI) *m/z* 476.2 [M + H]$^+$.

***N*-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-7-yl)-4-methoxybenzenesulfonamide (143).** Prepared as described in the experimental procedure of **138a** from intermediate **142** to obtain the title compound as a pale yellow solid (258 mg, 86%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85-7.83 (m, 2H), 7.72-7.68 (m, 4H), 6.98 (s, 3H), 6.89-6.86 (m, 3H), 5.17 (s, 1H, NH), 4.31-4.28 (m, 1H), 3.98-3.92 (m, 1H), 3.79 (s, 3H), 3.71-3.66 (m, 1H), 3.31-3.24 (m, 1H), 2.99-2.93 (m, 1H), 2.76-2.66 (m, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 168.8, 163.2, 136.1, 134.9, 134.2, 132.4, 132.2, 130.9, 130.5, 129.6, 123.5, 121.0, 120.3, 114.3, 55.7, 53.9, 42.2, 38.6, 28.5; LC/MS (ESI) *m/z* 478.2 $[M + H]^+$.

2-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-7-((4-methoxyphenyl) sulfonamido)-1,2,3, 4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid (144A and 144B). Prepared as described in the experimental procedure of **139aA and B** from intermediate **143** to obtain two diastereomers (A: white solid, 45 mg, 34%, B: white solid, 6 mg, 5%); **144A**: ^{1}H NMR (400 MHz, MeOD) δ 7.87-7.61 (m, 6H), 7.06-6.95 (m, 5H), 5.78-5.76 (m, 1H), 4.10-3.91 (m, 2H), 3.77 (s, 3H), 3.68-3.63 (m, 1H), 3.01-2.71 (m, 3H), 2.37-2.32 (m, 1H), 1.97-1.89 (m, 1H), 1.60-1.27 (m, 7H), 0.95-0.89 (m, 1H); ^{13}C NMR (100 MHz, MeOD) δ 176.3, 176.1, 169.9, 164.6, 137.5, 135.8, 135.2, 133.4, 132.4, 132.0, 130.8, 130.5, 124.3, 122.0, 121.3, 115.2, 56.2, 52.7, 42.2, 42.0, 40.9, 37.3, 29.5, 28.0, 27.2, 24.8, 24.0; LC/MS (ESI) *m/z* 630.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{33}H_{33}N_3O_8S$ $[M - H]^-$ 630.1916; found 630.1922; **144B**: ^{1}H NMR (400 MHz, CDCl3) δ 7.84-7.81 (m, 2H), 7.73-7.71 (m, 4H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.93-6.89 (m, 3H), 5.90-5.86 (m, 1H), 3.97-3.91 (m, 1H), 3.82 (s, 3H), 3.77-3.67 (m, 2H), 2.95-2.88 (m, 2H), 2.83-2.79 (m, 1H), 2.50-2.47 (m, 1H), 2.16-2.12 (m, 1H), 1.52-1.47 (m, 2H), 1.40-1.38 (m, 1H), 1.28-1.25 (m, 2H), 1.15-1.10 (m, 2H), 0.89-0.83 (m, 1H); ^{13}C NMR (100 MHz, MeOD) δ 177.4, 175.9, 169.3, 164.2, 137.0, 135.2, 135.1, 133.0, 132.04, 131.97, 130.7, 130.2, 124.1, 121.5, 120.8, 115.0, 56.0, 51.3, 44.0, 41.7, 40.5, 38.1, 29.1, 28.2, 25.6, 25.3, 22.2; LC/MS (ESI) *m/z* 630.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{33}H_{33}N_3O_8S$ $[M - H]^-$ 630.1916; found 630.1921.

***N*-(1-((1,3-Dioxoisoindolin-2-yl)methyl)-2-((4-methoxyphenyl)sulfonyl)-5-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-methoxybenzenesulfonamide (145).** Prepared as

described in the experimental procedure of **52** from intermediate **138a** to obtain the title compound as a pale yellow solid (31 mg, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (brs, 1H, NH), 7.91-7.85 (m, 4H), 7.73-7.71 (m, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.45 (d, *J* = 8.8 Hz, 2H), 5.22-5.20 (m, 1H), 4.09-4.03 (m, 1H), 3.99-3.93 (m, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 340-3.36 (m, 1H), 2.47-2.41 (m, 1H), 2.30-2.21 (m, 2H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 163.1, 162.5, 134.2, 133.4, 132.7, 132.0, 131.9, 131.7, 129.7, 128.7, 123.8, 123.3, 119.7, 114.4, 113.8, 55.6, 55.4, 51.0, 39.7, 37.2, 24.4, 18.9; LC/MS (ESI) *m/z* 660.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{33}H_{31}N_3O_8S_2$ [M - H]$^-$ 660.1480; found 660.1489.

***tert*-Butyl 8-((4-methoxyphenyl)sulfonamido)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (146).** Prepared as described in the experimental procedure of **52** from *tert*-butyl 8-amino-3,4-dihydroisoquinoline-2(1*H*)-carboxylate to obtain the title compound as a pale yellow oil (260 mg, 77%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (brs, 1H, NH), 7.61 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.04-7.02 (m, 2H), 6.60 (dd, *J* = 6.4, 2.4 Hz, 1H), 4.45 (s, 2H), 3.82 (s, 3H), 3.44 (t, *J* = 5.6 Hz, 2H), 2.51-2.50 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 154.0, 136.1, 133.2, 132.0, 131.2, 128.8, 127.1, 126.4, 124.0, 114.3, 78.9, 55.6, 42.6, 42.1, 28.4, 28.1; LC/MS (ESI) *m/z* 417.2 [M - H]$^-$.

2-(8-((4-Methoxyphenyl)sulfonamido)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl) cyclohexane-1-carboxylic acid (147). Prepared as described in the procedure of **76a** from **146** to obtain 4-methoxy-*N*-(1,2,3,4-tetrahydroisoquinolin-8-yl)benzenesulfonamide as a colorless oil (62 mg, qunatitative). The resulting crude compound was used for the next reaction without further purification. Prepared as described in the experimental procedure of **139aA** and **B** from 4-methoxy-*N*-(1,2,3,4-tetrahydroisoquinolin-8-yl)benzenesulfon-

amide to obtain the title compound as a pale yellow solid (16 mg, 36%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (brs, 1H, CO_2H), 9.56 (brs, 1H, NH), 7.65-7.59 (m, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.02-7.00 (m, 2H), 6.82-6.57 (m, 1H), 4.72-4.41 (m, 2H), 3.82-3.80 (m, 3H), 3.64-3.59 (m, 1H), 3.08-2.83 (m, 1H), 2.68-2.65 (m, 1H), 2.42-2.36 (m, 1H), 2.17-2.13 (m, 1H), 1.82-1.68 (m, 4H), 1.56-1.38 (m, 3H), 1.26-1.23 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.0, 172.6, 172.2, 162.4, 136.2, 135.8, 133.6, 133.1, 132.0, 131.1, 129.9, 128.8, 128.7, 127.1, 126.8, 126.7, 126.2, 124.1, 123.5, 114.3, 55.6, 44.0, 42.5, 42.2, 42.0, 37.8, 37.6, 29.3, 29.0, 28.1, 27.0, 26.7, 24.7, 24.2, 21.8; LC/MS (ESI) *m/z* 471.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}N_2O_6S$ [M - H]$^-$ 471.1595; found 471.1598.

***tert*-Butyl 2-(1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)acetate (148).** To a solution of 2,3-naphthalic anhydride (1.0 g, 5.05 mmol) in acetonirtile (20 mL) were added *tert*-butyl glycinate (846 mg, 5.05 mmol) and triethylamine (562 mg, 5.55 mmol) at room temperature. The reaction mixture was stirred at 80 °C for overnight. After the reaction was completed, the crude mixture was cooled to room temperature, added to water and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-20% ethyl acetate/hexane) to give the product as a pale yellow oil (522 mg, 33%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 2H), 8.29-8.27 (m, 2H), 7.81-7.79 (m, 2H), 4.36 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 166.4, 135.1, 130.4, 129.5, 127.0, 124.9, 82.1, 27.6; LC/MS (ESI) *m/z* 328.1 [M - H + H_2O]$^-$.

2-(1,3-Dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)acetic acid (149). Prepared as described in the experimental procedure of **76a** from **148** to obtain the title compound as a white solid (380 mg, 93%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (brs, 1H, CO_2H), 8.50

(s, 2H), 8.24-8.21 (m, 2H), 7.77-7.75 (m, 2H), 4.36 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.8, 166.8, 135.0, 130.3, 129.4, 127.0, 124.8; LC/MS (ESI) *m/z* 256.1 $[M + H]^+$.

***N*-(3-(Cyanomethyl)-4-methylphenyl)-4-methoxybenzenesulfonamide (150).** Prepared as described in the experimental procedure of **18d** from intermediate **134a** to obtain 2-(5-amino-2-methylphenyl)acetonitrile as a yellow solid (422 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.0 Hz, 1H), 6.72 (s, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 3.64 (brs, 2H, NH), 3.57 (s, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 131.5, 129.2, 125.5, 117.9, 115.3, 115.0, 21.9, 18.3; LC/MS (ESI) *m/z* 147.2 $[M + H]^+$. Prepared as described in the experimental procedure of **18d** from 2-(5-amino-2-methylphenyl)acetonitrile to obtain the title compound as a pale yellow solid (536 mg, 60%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (brs, 1H, NH), 7.69 (d, *J* = 8.8 Hz, 2H), 7.14 (s, 1H), 7.08-7.04 (m, 3H), 6.94 (d, *J* = 8.0 Hz, 1H), 3.19 (s, 2H), 3.78 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 136.2, 131.6, 131.1, 130.9, 130.5, 128.9, 120.0, 119.4, 118.5, 114.3, 55.6, 20.8, 18.0; LC/MS (ESI) *m/z* 317.1 $[M + H]^+$.

2-(1,3-Dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)-*N*-(5-((4-methoxyphenyl)sulfon-amido)-2-methylphenethyl)acetamide (151). Prepared as described in the experimental procedure of **135a** from intermediate **150** to obtain *N*-(3-(2-aminoethyl)-4-methylphenyl)-4-methoxybenzenesulfonamide as a white solid (254 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.79 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.78 (s, 3H), 2.62-2.60 (m, 2H), 2.55-2.51 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 138.7, 136.0, 131.5, 131.3, 130.5, 128.8, 121.2, 118.2, 114.2, 55.6, 41.9, 36.5, 18.2; LC/MS (ESI) *m/z* 321.2 $[M + H]^+$. Prepared as described in the experimental procedure of **54** from

intermediate **149** and *N*-(3-(2-aminoethyl)-4-methylphenyl)-4-methoxybenzenesulfonamide to obtain the title compound as a white solid (272 mg, 52%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.41 (s, 1H, NH), 8.57 (s, 2H), 8.41 (t, *J* = 5.6 Hz, 1H, NH), 8.30-8.28 (m, 2H), 7.81-7.79 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.85-6.81 (m, 2H), 4.25 (s, 2H), 3.77 (s, 3H), 3.14-3.08 (m, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 167.1, 165.9, 162.3, 138.0, 135.8,135.0, 131.6, 131.3, 130.6, 130.3, 129.3, 128.8, 127.6, 124.6, 121.1, 118.3, 114.2, 55.6, 40.4, 32.9, 18.1; LC/MS (ESI) *m/z* 558.2 [M + H]$^{+}$.

***N*-(1-((1,3-Dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)methyl)-5-methyl-1,2,3,4-tetrahydroisoquinolin-8-yl)-4-methoxybenzenesulfonamide (152).** Prepared as described in the experimental procedure of **137a** from **151** to obtain *N*-(1-((1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)methyl)-5-methyl-3,4-dihydroisoquin-olin-8-yl)-4-methoxybenzenesulfonamide as a white solid (213 mg, 88%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.89 (brs, 1H, NH), 8.55 (s, 2H), 8.29-8.28 (m, 2H), 7.81-7.78 (m, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.12-7.07 (m, 3H), 6.42 (d, *J* = 7.6 Hz, 1H), 5.03 (s, 2H), 3.82 (s, 3H), 3.33-3.31 (m, 2H), 2.41-2.39 (m, 2H), 2.20 (s, 3H); LC/MS (ESI) *m/z* 540.2 [M + H]$^{+}$.Prepared as described in the experimental procedure of **138a** from *N*-(1-((1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)methyl)-5-methyl-3,4-dihydroisoquinolin-8-yl)-4-methoxybenzene-sulfonamide to obtain the title compound as a white solid (137 mg, 67%); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.55 (s, 2H), 8.31-8.28 (m, 2H), 7.80-7.78 (m, 2H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 4.73-4.70 (m, 1H), 3.89-3.86 (m, 2H), 3.82 (s, 3H), 3.24-3.17 (m, 2H), 2.89-2.83 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 167.7, 162.2, 135.2, 135.0, 132.3, 130.2, 129.2,

129.1, 127.9, 127.8, 124.2, 122.8, 114.2, 55.6, 48.8, 35.8, 25.9, 21.0, 18.7; LC/MS (ESI) *m/z* 542.2 $[M + H]^+$.

2-(1-((1,3-Dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)methyl)-8-((4-methoxy-phenyl)sulfonamido)-5-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylic acid (153B). Prepared as described in the experimental procedure of **139aA** and **B** from intermediate **152** to obtain the title compound as a white solid (10 mg, 10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 2H), 8.08-8.06 (m, 2H), 7.74-7.71 (m, 4H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 2H), 5.87-5.84 (m, 1H), 4.15-4.08(m, 1H), 3.84-3.80 (m, 1H), 3.73 (s, 3H), 3.50-3.46 (m, 1H), 2.91-2.89 (m, 1H), 2.81-2.76 (m, 2H), 2.44-2.42 (m, 1H), 2.20 (s, 3H), 2.15-2.10 (m, 1H), 1.63-1.60 (m, 1H), 1.48-1.40 (m, 2H), 1.29-1.25 (m, 4H), 0.89-0.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 174.6, 168.6, 162.7, 135.6, 133.3, 132.5, 132.3, 131.8, 130.7, 129.9, 129.6, 129.5, 127.4, 125.8, 125.6, 124.5, 121.9, 114.4, 55.7, 47.5, 42.8, 40.1, 39.1, 29.8, 27.4, 26.8, 26.3, 24.1, 23.2, 19.2; LC/MS (ESI) *m/z* 694.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{38}H_{37}N_3O_8S$ $[M - H]^-$ 694.2229; found 694.2235.

***tert*-Butyl 2-(1-((1,3-dioxoisoindolin-2-yl)methyl)-8-((4-methoxyphenyl) sulfonamido)-5-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylate (154aB).** To a solution of **139aB** (20 mg, 0.031 mmol) in *tert*-butanol (06.5 mL) was added thionyl chloride (37 mg, 0.31 mmol) at 0 ℃. The reaction mixture was stirred 0 ℃ for 1 hour. The crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-50% ethyl acetate/hexane) to give the product as a pale yellow solid (14 mg, 64%); ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.33 (brs, 1H, NH), 7.92-7.87 (m, 4H), 7.74-7.71 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.08-6.05 (m, 1H), 4.14-4.03 (m, 1H), 4.00-3.92 (m, 1H), 3.78 (s, 3H), 3.72-3.71 (m, 1H), 3.52-3.48 (m, 1H), 3.07-3.05 (m, 1H), 2.77-2.73 (m, 2H), 2.25-2.22 (m, 1H), 2.12 (s, 3H), 1.92-1.85 (m, 1H), 1.76-1.73 (m, 1H), 1.64-1.61 (m, 1H), 1.53-1.51 (m, 1H), 1.43-1.37 (m, 1H), 1.27-1.13 (m, 1H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 172.9, 168.9, 163.1, 134.2, 133.2, 132.9, 132.1, 131.9, 131.8, 129.7, 129.6, 123.9, 122.8, 117.6, 114.3, 79.8, 55.6, 46.2, 43.5, 38.9, 38.5, 38.2, 27.6, 27.1, 26.8, 25.1, 24.3, 22.4, 19.0; LC/MS (ESI) m/z 702.4 $[M + H]^+$.

***tert*-Butyl 2-(1-((1,3-dioxoisoindolin-2-yl)methyl)-5-methoxy-8-((4-methoxyphenyl) sulfonamido)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxyl-ate (154bB).** Prepared as described in the experimental procedure of **154aB** from intermediate **139cB** to obtain the title compound as a pale yellow solid (29 mg, 24%); ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (brs, 1H, NH), 7.90-7.84 (m, 4H), 7.74-7.70 (m, 2H), 7.67-7.63 (m, 1H), 6.86-6.82 (m, 2H), 6.72-6.69 (m, 1H), 6.03-5.97 (m, 1H), 4.07-3.97 (m, 1H), 3.91-3.86 (m, 1H), 3.80-3.79 (m, 3H), 3.77 (s, 3H), 3.69-3.62 (m, 1H), 3.48-3.42 (m, 1H), 3.18-3.01 (m, 1H), 2.85-2.82 (m, 1H), 2.74-2.59 (m, 1H), 2.29-2.22 (m, 1H), 1.99-1.84 (m, 1H), 1.80-1.69 (m, 2H), 1.55-1.46 (m, 1H), 1.44-1.37 (m, 1H), 1.23-1.15 (m, 3H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 173.2, 172.9, 172.7, 169.1, 168.9, 162.9, 154.4, 154.3, 134.0, 133.6, 132.7, 132.5, 131.2, 129.6, 126.8, 123.7, 123.0, 122.4, 122.1, 114.2, 108.9, 78.6, 55.5, 46.4, 46.1, 42.5, 39.3, 39.1, 37.4, 28.7, 27.8, 26.8, 26.0, 24.0, 23.5, 23.0, 19.3; LC/MS (ESI) *m/z* 718.4 $[M + H]^+$.

***tert*-Butyl 2-(8-((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methoxyphenyl) sulfonamido)-1-((1,3-dioxoisoindolin-2-yl)methyl)-5-methyl-1,2,3,4-tetrahydro isoquinoline-2-ca-**

rbonyl)cyclohexane-1-carboxylate (155aB). Prepared as described in the experimental procedure of **40b** from intermediate **154aB** and *tert*-butyl 2-bromoacetate to obtain the title compound as a colorless oil (15 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.78 (m, 4H), 7.67-7.65 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.30-6.22 (m, 1H), 5.30-5.25 (m, 1H), 4.64-4.60 (m, 1H), 4.10-4.01 (m, 3H), 3.87 (s, 3H), 3.86-3.83 (m, 1H), 3.15-3.13 (m, 1H), 2.92-2.89 (m, 2H), 2.20 (s, 3H), 2.18-2.14 (m, 1H), 2.02-1.94 (m, 2H), 1.91-1.77 (m, 1H), 1.69-1.58 (m, 2H), 1.38-1.32 (m, 3H), 1.31 (s, 9H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.5, 173.1, 168.2, 163.1, 137.2, 136.1, 134.9, 133.8, 133.7, 133.3, 132.4, 131.0, 129.2, 129.1, 123.4, 113.8, 81.6, 79.6, 55.7, 53.0, 46.3, 43.8, 39.5, 39.2, 37.7, 29.8, 28.1, 27.8, 27.6, 26.4, 25.0, 24.6, 19.5; LC/MS (ESI) *m/z* 816.5 $[M + H]^+$.

***tert*-Butyl 2-(8-((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methoxyphenyl)sulfonamido)-1-((1,3-dioxoisoindolin-2-yl)methyl)-5-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)cyclohexane-1-carboxylate (155bB).** Prepared as described in the experimental procedure of **40b** from intermediate **154bB** and *tert*-butyl 2-bromoacetate to obtain the title compound as a colorless oil (36 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.78 (m, 4H), 7.67-7.65 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.66-6.63 (m, 1H), 6.33-6.17 (m, 1H), 5.32-5.27 (m, 1H), 4.65-4.60 (m, 1H), 4.14-3.99 (m, 3H), 3.87 (s, 3H), 3.80-3.79 (m, 3H), 3.76-3.72 (m, 1H), 3.20-3.14 (m, 1H), 2.92-2.89 (m, 2H), 2.25-2.15 (m, 1H), 2.01-1.89 (m, 1H), 1.76-1.74 (m, 1H), 1.68-1.60 (m, 3H), 1.38-1.35 (m, 3H), 1.33 (s, 9H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 168.3, 168.2, 163.0, 157.0, 133.7, 133.3, 132.3, 130.9, 130.1, 125.1, 123.3, 113.7, 108.3, 81.6, 79.5, 55.6, 55.5, 52.7, 46.4, 43.0, 39.2, 28.4, 28.0, 27.8, 27.5, 24.6, 23.3, 21.0; LC/MS (ESI) m/z 832.5 $[M + H]^+$.

2-(8-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-1-((1,3-dioxo isoindoli-n-2-yl)methyl)-5-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl) cyclohexane-1-carboxylic acid (156aB). Prepared as described in the experimental procedure of **76a** from intermediate **155aB** to obtain the title compound as a white solid (7 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.66 (m, 6H), 7.05-6.95 (m, 3H), 6.77-6.36 (m, 1H), 4.74-4.65 (m, 1H), 4.17-4.14 (m, 1H), 3.90-3.89 (m, 1H), 3.86 (s, 3H), 3.76-3.73 (m, 2H), 3.62-3.59 (m, 1H), 3.04-3.01 (m, 2H), 2.27 (s, 3H), 1.58-1.50 (m, 2H), 1.26-1.19 (m, 6H), 0.88-0.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7, 178.7, 169.5, 163.6, 138.4, 134.5, 134.2, 132.1, 131.7, 131.6, 131.2, 129.9, 123.7, 123.4, 114.4, 114.1, 55.9, 53.1, 48.6, 43.3, 40.8, 35.7, 30.3, 29.8, 28.3, 26.0, 25.8, 25.5, 19.7, 19.5; LC/MS (ESI) *m/z* 702.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{36}H_{37}N_3O_{10}S$ $[M - H]^-$ 702.2127; found 702.2134.

2-(8-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-1-((1,3-dioxoiso-indol-in-2-yl)methyl)-5-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-cyclohexa-ne-1-carboxylic acid (156bB). Prepared as described in the experimental procedure of **76a** from **155bB** to obtain the title compound as a white solid (16 mg, 52%); ^{1}H NMR (400 MHz, CDCl3) δ 7.82-7.68 (m, 6H), 7.05-6.97 (m, 2H), 6.72-6.63 (m, 1H), 6.49-6.37 (m, 1H), 4.83-4.45 (m, 1H), 4.16-4.14 (m, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.73-3.69 (m, 1H), 3.62-3.59 (m, 1H), 3.40-3.31 (m, 2H), 3.18-3.12 (m, 2H), 1.63-1.60 (m, 1H), 1.37-1.33 (m, 1H), 1.25-1.19 (m, 6H), 0.87-0.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 176.4, 169.5, 163.5, 156.2, 137.3, 134.4, 132.2, 131.8, 130.8, 126.7, 125.1, 123.4, 114.4, 110.3, 55.8, 55.7, 49.5, 48.3, 42.0, 40.5, 32.0, 29.7, 29.4, 26.3, 21.4, 21.1, 14.1; LC/MS (ESI) *m/z* 718.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{36}H_{37}N_3O_{11}S$ $[M - H]^-$ 718.2076; found 718.2086.

Methyl 2-hydroxy-5-nitrobenzoate (157). To a solution of 2-hydroxy-5-nitrobenzoic acid (2.0 g, 10.92 mmol) in methanol (25 mL) was added thionyl chloride (13.0 g, 109.22 mmol) at 0 ℃. The reaction mixture was stirred at 70 ℃ for overnight. After the reaction was completed, the crude mixture was cooled to room temperature, added to sat. $NaHCO_3$, and then extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-60% ethyl acetate/hexane) to give the product as a yellow solid (1.7 g, 77%);^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 6.42 (d, *J* = 9.2 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.0, 166.8, 130.7, 130.0, 128.2, 122.9, 115.0, 51.2; LC/MS (ESI) *m/z* 196.1 $[M - H]^-$.

Methyl 2-(benzyloxy)-5-nitrobenzoate (158). Prepared as described in the experimental procedure of **36** from intermediate **157** and benzyl bromide to obtain the title compound as a yellow solid (523 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.8 Hz, 1H), 8.31 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.43-7.32 (m, 3H), 7.10 (d, *J* = 9.2 Hz, 1H), 5.30 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.7, 140.9, 135.3, 128.92, 128.87, 128.5, 128.0, 126.9, 121.1, 113.6, 71.3, 52.7.

(2-Chloro-5-nitrophenyl)methanol (159a). Prepared as described in the experimental procedure of **30** from 2-chloro-5-nitrobenzoic acid to obtain the title compound as a white solid (1.4 g, 98%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, *J* = 2.8 Hz, 1H), 8.17 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 5.79 (t, *J* = 5.6 Hz, 1H, OH), 4.62 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.5. 141.9. 137.5. 130.2. 123.0. 122.1. 59.7; LC/MS (ESI) *m/z* 186.1 $[M - H]^-$.

(2-Fluoro-5-nitrophenyl)methanol (159b). Prepared as described in the experimental procedure of **30** from 2-fluoro-5-nitrobenzoic acid to obtain the title compound as a pale yellow oil (404 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-8.38 (m, 1H), 8.18-8.14 (m, 1H), 7.20-7.15 (m, 1H), 4.83 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 ($J_{C,F}$ = 256 Hz), 144.5, 130.0 ($J_{C,F}$ = 17 Hz), 125.1 ($J_{C,F}$ = 10 Hz), 124.8 ($J_{C,F}$ = 6 Hz), 116.3 ($J_{C,F}$ = 24 Hz), 58.4 ($J_{C,F}$ = 4 Hz).

(5-Bromo-2-chlorophenyl)methanol (159c). Prepared as described in the experimental procedure of **30** from 2-bromo-5-nitrobenzoic acid to obtain the title compound as a pale yellow solid (1.8 g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 2.4 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 4.73 (s, 2H), 2.26 (brs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 131.7, 131.3, 130.8, 120.9, 62.2.

(2-(Benzyloxy)-5-nitrophenyl)methanol (159d). Prepared as described in the experimental procedure of **46a** from intermediate **158** to obtain the title compound as a yellow solid (454 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 2.4 Hz, 1H), 8.15 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.43-7.39 (m, 2H), 7.36-7.34 (m, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 5.47 (brs, 1H, OH), 5.29 (s, 2H), 4.59 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 140.9, 136.2, 132.4, 128.6, 128.1, 127.4, 124.0, 121.8, 111.8, 70.0, 57.4; LC/MS (ESI) *m/z* 260.1 $[M + H]^+$.

2-Chloro-5-nitrobenzaldehyde (160a). Prepared as described in the experimental procedure of **47a** from intermediate **159a** to obtain the title compound as a white solid (1.2 g, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.75 (d, *J* = 2.8 Hz, 1H), 8.38 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5, 147.2, 143.7, 133.3, 132.2, 129.0, 124.6.

2-Fluoro-5-nitrobenzaldehyde (160b). Prepared as described in the experimental procedure of **47a** from intermediate **159b** to obtain the title compound as a white solid (275 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.74-8.72 (m, 1H), 8.51-8.47 (m, 1H), 7.43-7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9 ($J_{C,F}$ = 5 Hz), 167.3 ($J_{C,F}$ = 267 Hz), 144.9, 131.1 ($J_{C,F}$ = 11Hz), 124.9 ($J_{C,F}$ = 4 Hz), 124.6 ($J_{C,F}$ = 11 Hz), 118.3 ($J_{C,F}$ = 23 Hz); LC/MS (ESI) *m/z* 168.9 $[M]^-$.

2-Bromo-5-nitrobenzaldehyde (160c). Prepared as described in the procedure of **47a** from **159c** to obtain the title compound as a white solid (300 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.72 (d, *J* = 2.8 Hz, 1H), 8.29 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 135.4, 134.5, 133.1, 128.9, 124.8.

2-Methoxy-5-nitrobenzaldehyde (160d). Prepared as described in the experimental procedure of **47a** from intermediate **133b** to obtain the title compound as a white solid (314 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.67 (d, *J* = 2.8 Hz, 1H), 8.42 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.13 (d, *J* = 9.2 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 165.7, 141.7, 130.8, 124.7, 112.4, 56.9.

2-Methyl-5-nitrobenzaldehyde (160e). Prepared as described in the experimental procedure of **47a** from **133a** to obtain the title compound as a pale yellow solid (154 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.63 (d, *J* = 2.4 Hz, 1H), 8.30 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 147.7, 146.8, 134.7, 133.2, 127.6, 126.6, 19.9; LC/MS (ESI) *m/z* 166.1 $[M + H]^+$.

2-(Benzyloxy)-5-nitrobenzaldehyde (160f). Prepared as described in the experimental procedure of **47a** from **159d** to obtain the title compound as a yellow solid (268 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.71 (d, *J* = 2.8 Hz, 1H), 8.40 (dd, *J* = 9.2,

2.8 Hz, 1H), 7.45-7.39 (m, 5H), 7.19 (d, *J* = 9.2 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 164.8, 141.9, 134.7, 130.7, 129.1, 129.0, 127.6, 125.1, 124.8, 113.6, 71.7.

***N*-(2-Chloro-5-nitrobenzyl)-4-methoxybenzenesulfonamide (161a).** Prepared as described in the experimental procedure of **48a** from intermediate **160a** and 4-methyl benzenesulfonamide to obtain the title compound as a pale yellow solid (272 mg, 71%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (brs, 1H, NH), 8.19 (s, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.71-7.67 (m, 3H), 7.05 (d, *J* = 8.4 Hz, 2H), 4.17 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 146.2, 138.9, 137.2, 132.0, 130.6, 128.6, 124.1, 123.6, 114.3, 55.6, 43.2; LC/MS (ESI) *m/z* 357.1 $[M + H]^+$.

***N*-(2-Chloro-5-nitrobenzyl)benzenesulfonamide (161b).** Prepared as described in the experimental procedure of **48a** from intermediate **160a** and benzenesulfonamide to obtain the title compound as a pale yellow solid (483 mg, 46%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (brs, 1H, NH), 8.21 (d, *J* = 2.4 Hz, 1H), 8.09 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.62-7.58 (m, 1H), 7.54-7.52 (m, 2H), 4.22 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.2, 140.4, 138.9, 137.1, 132.5, 130.6, 129.2, 126.4, 124.1, 123.7, 43.2; LC/MS (ESI) *m/z* 325.0 $[M - H]^-$.

***N*-(2-Fluoro-5-nitrobenzyl)-4-methoxybenzenesulfonamide (161c).** Prepared as described in the experimental procedure of **48a** from intermediate **160b** to obtain the title compound as a pale yellow solid (245 mg, 49%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (t, *J* = 6.0 Hz, 1H, NH), 8.17-8.16 (m, 1H), 7.54-7.52 (m, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.42-7.38 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.13 (d, *J* = 6.0 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3 ($J_{C,F}$ = 254 Hz), 162.2, 143.7, 132.1, 128.6, 126.7

($J_{C,F}$ = 17 Hz), 125.7 ($J_{C,F}$ = 6 Hz), 125.2 ($J_{C,F}$ = 11 Hz), 116.7 ($J_{C,F}$ = 24 Hz), 114.3, 55.6; LC/MS (ESI) *m/z* 341.0 $[M + H]^+$.

***N*-(2-Bromo-5-nitrobenzyl)-4-methoxybenzenesulfonamide (161d).** Prepared as described in the experimental procedure of **48a** from intermediate **160c** to obtain the title compound as a white solid (206 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.4 Hz, 1H), 7.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.53 (t, *J* = 6.4 Hz, 1H, NH), 4.22 (d, *J* = 6.4 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 147.1, 138.5, 133.6, 131.5, 130.1, 129.1, 124.3, 123.4, 114.3, 55.6, 46.6; LC/MS (ESI) *m/z* 401.1 $[M(^{79}Br) + H]^+$, 403.0 $[M(^{81}Br) + H]^+$.

***N*-(2-Methoxy-5-nitrobenzyl)-4-methoxybenzenesulfonamide (161e).** Prepared as described in the experimental procedure of **48a** from intermediate **160d** to obtain the title compound as a yellow solid (513 mg, 88%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11-8.08 (m, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.22 (s, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 4.00 (d, *J* = 6.4 Hz, 2H), 3.86 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 140.3, 132.2, 128.6, 126.8, 124.8, 123.7, 114.2, 110.9, 56.5, 55.6, 40.4.

***N*-(2-Methyl-5-nitrobenzyl)-4-methoxybenzenesulfonamide (161f).** Prepared as described in the experimental procedure of **48a** from intermediate **160e** to obtain the title compound as a white solid (57 mg, 18%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (t, *J* = 6.0 Hz, 1H, NH), 8.04 (d, *J* = 2.4 Hz, 1H), 7.99 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 6.4 Hz, 2H), 4.06 (d, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 145.6, 144.5, 137.6, 132.2, 131.2, 128.6, 122.6, 122.0, 114.3, 55.6, 43.4, 18.7; LC/MS (ESI) *m/z* 337.1 $[M + H]^+$.

***N*-(2-(Benzyloxy)-5-nitrobenzyl)-4-methoxybenzenesulfonamide (161g).** Prepared as described in the experimental procedure of **48a** from intermediate **160f** to obtain the title compound as a pale yellow solid (249 mg, 60%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15-8.09 (m, 3H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.46-7.35 (m, 5H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 5.27 (s, 2H), 4.07 (d, *J* = 6.0 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 160.5, 140.5, 136.0, 132.1, 128.6, 128.5, 128.1, 127.4, 127.3, 124.6, 123.9, 114.2, 112.2, 70.2, 55.6, 40.3; LC/MS (ESI) *m/z* 429.1 $[M + H]^+$.

***N*-(4-Chloro-3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-4-methoxybenzenesulfonamide (162a).** Prepared as described in the procedure of **22b** from intermediate **161a** to obtain *N*-(5-amino-2-chlorobenzyl)-4-methoxybenzenesulfonamide as a pale brown oil (108 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.61 (s, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 5.39 (brs, 1H, NH), 4.07 (d, *J* = 5.6 Hz, 2H), 3.83 (s, 3H), 2.85 (brs, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 145.7, 134.5, 131.6, 130.0, 129.3, 121.9, 116.6, 115.7, 114.3, 55.7, 45.1; LC/MS (ESI) *m/z* 327.1 $[M + H]^+$. Prepared as described in the experimental procedure of **22b** from *N*-(5-amino-2-chlorobenzyl)-4-methoxybenzenesulfonamide to obtain the title compound as a pale yellow solid (125 mg, 77%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (brs, 1H, NH), 8.07 (t, *J* = 6.4 Hz, 1H, NH), 7.73 (d, *J* = 8.8 Hz, 4H), 7.33 (d, *J* = 2.8 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.98 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.86 (d, *J* = 6.4 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 162.2, 137.1, 135.9, 131.9, 130.9, 129.6, 129.0, 128.7, 126.6, 120.5, 119.5, 114.5, 114.4, 55.6, 43.4; LC/MS (ESI) *m/z* 497.1 $[M + H]^+$.

***N*-(4-Chloro-3-(phenylsulfonamidomethyl)phenyl)-4-methoxybenzenesulfonami-de (162b).** Prepared as described in the experimental procedure of **22b** from intermediate **161b** to obtain give *N*-(5-amino-2-chlorobenzyl)benzenesulfonamide as a pale brown oil (108 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.47-7.43 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 6.44 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.50 (brs, 1H, NH), 4.10 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 140.0, 134.4, 132.7, 130.0, 129.1, 127.1, 121.8, 116.6, 115.8, 45.1; LC/MS (ESI) *m/z* 297.1 $[M + H]^+$. Prepared as described in the experimental procedure of **22b** from *N*-(5-amino-2-chlorobenzyl)benzenesulfonamide to obtain the title compound as a pale yellow solid (127 mg, 75%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (brs, 1H, NH), 8.25 (t, *J* = 6.0 Hz, 1H, NH), 7.80 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.66-7.55 (m, 3H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.99 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.91 (d, *J* = 6.0 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.5, 140.3, 137.1, 135.8, 132.5, 130.9, 129.7, 129.2, 129.0, 126.6, 126.5, 120.5, 119.6, 114.5, 55.6, 43.5; LC/MS (ESI) *m/z* 467.1 $[M + H]^+$.

***N*-(4-Fluoro-3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-4-methoxybenz-enesulfonamide (162c).** Prepared as described in the procedure of **22b** from intermediate **161c** to obtain *N*-(5-amino-2-fluorobenzyl)-4-methoxybenzenesulfonamide as a pale pink solid (137 mg, 75%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (brs, 1H, NH), 7.74 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.78-6.73 (m, 1H), 6.57-6.55 (m, 1H), 6.43-6.40 (m, 1H), 4.96 (s, 2H, NH), 3.84 (s, 3H), 3.78 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 151.8 ($J_{C,F}$ = 230 Hz), 145.0, 132.1, 128.7, 124.2 ($J_{C,F}$ = 15 Hz), 115.1, 114.9, 114.4 ($J_{C,F}$ = 17 Hz), 113.6 ($J_{C,F}$ = 7 Hz), 55.6; LC/MS (ESI) *m/z* 311.1 $[M + H]^+$. Prepared as

described in the experimental procedure of **22b** from *N*-(5-amino-2-fluorobenzyl)-4-methoxybenzenesulfonamide to obtain the title compound as a pale yellow solid (183 mg, 93%); H NMR (400 MHz, DMSO-d_6) δ 10.13 (brs, 1H, NH), 8.03 (t, *J* = 5.6 Hz, 1H, NH), 7.72-7.68 (m, 4H), 7.22-7.20 (m, 1H), 7.07-7.04 (m, 4H), 6.99-6.96 (m, 2H), 3.86 (d, *J* = 5.6 Hz, 2H), 3.83 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.2, 156.5 ($J_{C,F}$ = 241 Hz), 134.0, 131.9, 131.0, 128.9, 128.7, 125.4 ($J_{C,F}$ = 16 Hz), 122.2, 121.0 ($J_{C,F}$ = 8 Hz), 115.6 ($J_{C,F}$ = 22 Hz), 114.4, 114.3, 55.6; LC/MS (ESI) *m/z* 481.1 $[M + H]^+$.

***N*-(4-Bromo-3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-4-methoxybenzenesulfonamide (162d).** Prepared as described in the procedure of **22b** from **161d** to obtain *N*-(5-amino-2-bromobenzyl)-4-methoxybenzenesulfonamide as a black solid (70 mg, 37%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (brs, 1H, NH), 7.77 (d, *J* = 8.4 Hz, 2H), 7.14-7.10 (m, 3H), 6.73 (s, 1H), 6.40 (d, *J* = 8.8 Hz, 1H), 5.33 (s, 2H, NH), 3.84 (s, 3H), 3.78 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 148.4, 136.3, 132.3, 132.0, 128.7, 114.8, 114.6, 114.4, 106.5, 55.6, 46.1; LC/MS (ESI) *m/z* 371.0 $[M(^{79}Br) + H]^+$, 373.0 $[M(^{81}Br) + H]^+$. Prepared as described in the experimental procedure of **22b** from *N*-(5-amino-2-bromobenzyl)-4-methoxybenzenesulfonamide to obtain the title compound as a white solid (13 mg, 13%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (brs, 1H, NH), 7.70 (d, *J* = 9.2 Hz, 2H), 7.69 (d, *J* = 9.2 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 2.8 Hz, 1H), 6.91-6.83 (m, 3H), 5.99 (t, *J* = 6.4 Hz, 1H, NH), 4.02 (d, *J* = 6.4 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 163.0, 137.1, 136.9, 133.3, 131.4, 130.6, 129.5, 129.2, 121.7, 120.9, 117.9, 114.4, 114.3, 55.7, 55.6, 46.9; LC/MS (ESI) *m/z* 541.0 $[M(^{79}Br) + H]^+$, 543.0 $[M(^{81}Br) + H]^+$.

***N*-(4-Methoxy-3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-4-methoxybenzenesulfonamide (162e).** Prepared as described in the procedure of **22b** from **161e** to obtain *N*-(5-amino-2-methoxybenzyl)-4-methoxybenzenesulfonamide as a beige solid (328 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.8 Hz, 2H), δ 6.87 (d, *J* = 8.8 Hz, 2H), 6.53-6.51 (m, 2H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.37 (s, 1H, NH), 4.00 (s, 2H, NH), 3.82 (s, 3H), 3.62 (s, 3H), 3.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 150.4, 139.6, 131.9, 129.6, 125.2, 117.5, 115.4, 114.0, 111.4, 55.7, 43.7; LC/MS (ESI) *m/z* 321.1 $[M + H]^+$. Prepared as described in the procedure of **22b** from *N*-(5-amino-2-methoxybenzyl)-4-methoxy-benzenesulfonamide to obtain the title compound as a pale yellow solid (399 mg, 96%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (brs, 1H, NH), 7.86 (t, *J* = 5.6 Hz, 1H, NH), 7.75-7.70 (m, 4H), 7.21 (s, 1H), 7.08-7.03 (m, 4H), 6.93 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 3.81 (s, 5H), 3.77 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.1, 153.5, 132.2, 131.4, 130.3, 129.0, 128.8, 126.1, 122.4, 121.4, 114.28, 114.25, 110.8, 55.59, 55.57, 55.4, 40.9; LC/MS (ESI) *m/z* 493.2 $[M + H]^+$.

***N*-(4-Methyl-3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-4-methoxybenzenesulfonamide (162f).** Prepared as described in the experimental procedure of **22b** from intermediate **161f** to obtain the title compound as a colorless oil (90 mg, quantitative over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (brs, 1H, NH), 7.82 (t, *J* = 6.0 Hz, 1H, NH), 7.73 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.11-7.07 (m, 3H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.74 (d, *J* = 6.0 Hz, 2H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 162.1, 136.2, 135.7, 132.0, 131.4, 131.3, 130.5, 128.9, 128.7, 120.5, 118.7, 114.3, 55.61, 55.57, 44.1, 17.7; LC/MS (ESI) *m/z* 477.2 $[M + H]^+$.

***N*-(4-(Benzyloxy)-3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-4-methoxy-benzenesulfonamide (162g).** Prepared as described in the experimental procedure of **22b** from **161g** to obtain *N*-(5-amino-2-(benzyloxy)benzyl)-4-methoxy-benzenesulfonamide as a dark brown oil (176 mg, 95%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.68 (t, *J* = 6.0 Hz, 1H, NH), 7.36-7.29 (m, 5H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.40 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.88 (s, 2H), 4.70 (s, 2H, NH), 3.83 (s, 3H), 3.82-3.80 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 146.8, 142.6, 137.7, 132.0, 128.7, 128.2, 127.5, 127.2, 126.4, 114.8, 114.2, 114.1, 113.2, 70.4, 55.6, 41.0; LC/MS (ESI) *m/z* 399.2 $[M + H]^+$. Prepared as described in the experimental procedure of **22b** from *N*-(5-amino-2-(benzyloxy)benzyl)-4-methoxybenzenesulfonamide to obtain the title compound as a pale yellow solid (114 mg, 44%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (brs, 1H, NH), 7.82 (t, *J* = 6.0 Hz, 1H, NH), 7.70 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 9.2 Hz, 2H), 7.36-7.30 (m, 5H), 7.17 (s, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 9.2 Hz, 2H), 6.86-6.85 (m, 2H), 3.82 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 162.1, 152.4, 137.0, 131.9, 131.3, 130.6, 128.9, 128.7, 128.3, 127.7, 127.2, 126.5, 122.3, 121.1, 114.3, 114.2, 112.4, 69.5, 55.59, 55.57, 40.6; LC/MS (ESI) *m/z* 569.2 $[M + H]^+$.

Ethyl *N*-(4-chloro-3-(((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido) methyl)phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (163a). Prepared as described in the experimental procedure of **15a** from **162a** to obtain the title compound as a colorless oil (119 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.28-7.27 (m, 2H), 7.18 (s, 1H), 7.00-6.95 (m, 4H), 4.50 (s, 2H), 4.36 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 6H), 3.83 (s, 2H), 1.24 (t, *J* =

7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.6, 163.4, 163.2, 139.3, 134.4, 133.2, 131.2, 130.4, 130.2, 130.0, 129.7, 129.2, 114.4, 114.3, 61.7, 61.5, 55.7, 52.5, 50.9, 48.7, 47.8, 14.2, 14.1; LC/MS (ESI) *m/z* 669.2 $[M + H]^+$.

Ethyl *N*-(4-chloro-3-((*N*-(2-ethoxy-2-oxoethyl)phenylsulfonamido)methyl)phenyl) -*N*-((4-methoxyphenyl)sulfonyl)glycinate (163b). Prepared as described in the procedure of **15a** from **162b** to obtain the title compound as a colorless oil (128 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.60-7.59 (m, 1H), 7.54-7.50 (m, 2H), 7.29 (s, 2H), 7.19 (s, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.54 (s, 2H), 4.36 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.3, 163.4, 139.5, 139.3, 134.1, 133.2, 133.0, 130.3, 130.2, 130.1, 129.9, 129.2, 129.1, 127.4, 114.3, 61.6, 61.4, 55.7, 52.4, 48.7, 47.7, 14.1, 14.0; LC/MS (ESI) *m/z* 639.2 $[M + H]^+$.

Ethyl *N*-(4-fluoro-3-(((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido) methyl)phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (163c). Prepared as described in the experimental procedure of **15a** from **162c** to obtain the title compound as a colorless oil (146 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.31-7.27 (m, 1H), 7.10-7.08 (m, 1H), 6.97-6.93 (m, 5H), 4.41 (s, 2H), 4.36 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 3.86 (s, 3H), 3.82 (s, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.6, 163.3, 163.2, 160.4 ($J_{C,F}$ = 248 Hz), 136.4, 131.6 ($J_{C,F}$ = 8 Hz), 131.2, 130.7 ($J_{C,F}$ = 5 Hz), 130.3, 130.0, 129.7, 123.7 ($J_{C,F}$ = 15 Hz), 116.3 ($J_{C,F}$ = 23 Hz), 114.31, 114.25, 61.6, 61.4, 55.7, 52.7, 47.6, 44.7, 14.2, 14.1; LC/MS (ESI) *m/z* 653.2 $[M + H]^+$.

Ethyl *N*-(4-bromo-3-(((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido) methyl)phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (163d). Prepared as described in the experimental procedure of **15a** from **162d** to obtain the title compound as a colorless oil (27 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.21-7.16 (m, 2H), 6.98-6.94 (m, 4H), 4.47 (s, 2H), 4.34 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 2H), 3.86 (s, 6H), 1.25-1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.6, 163.4, 163.2, 140.0, 136.1, 133.7, 131.2, 130.4, 130.2, 130.0, 129.7, 129.0, 122.9, 114.4, 114.3, 61.7, 61.5, 55.7, 52.4, 51.2, 47.9, 14.2, 14.1; LC/MS (ESI) *m/z* 713.1 [M(^{79}Br) + H]$^{+}$, 715.1 [M(^{81}Br) + H]$^{+}$.

Ethyl *N*-(4-methoxy-3-(((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido) methyl)phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (163e). Prepared as described in the experimental procedure of **15a** from intermediate **162e** to obtain the title compound as a colorless oil (220 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.21 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.90-6.87 (m, 5H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.31 (s, 2H), 4.24 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 2H), 3.63 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 168.7, 163.0, 162.8, 157.1, 132.4, 131.6, 130.9, 130.5, 129.7, 129.4, 124.3, 114.0, 113.9, 110.6, 61.3, 61.0, 55.5, 55.3, 52.8, 47.6, 45.7, 14.0, 13.9; LC/MS (ESI) *m/z* 665.2 [M + H]$^{+}$.

Ethyl *N*-(4-methyl-3-(((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido) methyl)phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (163f). Prepared as described in the experimental procedure of **15a** from **162f** to obtain the title compound as a colorless oil (89 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 9.2

Hz, 2H), 7.07-7.06 (m, 2H), 7.00-6.97 (m, 3H), 6.91 (d, *J* = 8.8 Hz, 2H), 4.42 (s, 2H), 4.30 (s, 2H), 4.13-4.11 (m, 2H), 3.98-3.96 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.70 (s, 2H), 2.27 (s, 3H), 1.27-1.21 (m, 3H), 1.19-1.12 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.7, 163.2, 138.1, 138.0, 133.9, 131.6, 131.0, 130.7, 130.0, 129.8, 129.5, 128.7, 114.3, 114.1, 61.5, 61.4, 55.8, 55.7, 52.7, 49.3, 46.9, 18.9, 14.2, 14.1; LC/MS (ESI) *m/z* 649.1 $[M + H]^+$.

Ethyl *N*-(4-(benzyloxy)-3-(((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)methyl)phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (163g). Prepared as described in the experimental procedure of **15a** from intermediate **162g** to obtain the title compound as a colorless oil (119 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.37-7.26 (m, 6H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 1H), 4.97 (s, 2H), 4.42 (s, 2H), 4.31 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.81 (s, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 163.2, 162.9, 156.5, 136.3, 133.0, 131.8, 131.2, 130.7, 130.1, 130.0, 129.6, 128.7, 128.3, 127.5, 125.1, 114.2, 114.1, 112.2, 70.5, 61.5, 61.2, 55.68, 55.66, 52.9, 48.0, 46.0, 14.2, 14.0; LC/MS (ESI) *m/z* 741.2 $[M + H]^+$.

***N*-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-chlorobenzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (164a).** Prepared as described in the experimental procedure of **16a** from intermediate **163a** to obtain the title compound as a pale yellow solid (84 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.35 (brs, 2H, CO_2H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.12 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.40 (s, 2H), 4.34 (s, 2H), 3.86 (s, 3H),3.85 (s, 3H), 3.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5,

163.53, 163.47, 138.9, 134.1, 133.4, 130.4, 130.2, 130.1, 130.0, 129.8, 129.7, 114.6, 114.5, 55.84, 55.81, 52.2, 49.7, 48.5; LC/MS (ESI) *m/z* 613.1 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}ClN_2O_{10}S_2$ $[M + H]^+$ 613.0712; found 613.0723.

***N*-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-chlorobenzyl)-*N*-(phenylsulfonyl)glycine (164b).** Prepared as described in the experimental procedure of **16a** from intermediate **163b** to obtain the title compound as a pale yellow solid (78 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (brs, 2H, CO_2H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.60-7.55 (m, 3H), 7.51-7.48 (m, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.13 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.44 (s, 2H), 4.33 (s, 2H), 3.84 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 173.3, 163.5, 138.9, 138.8, 133.9, 133.5, 133.4, 130.5, 130.2, 130.0, 129.7, 129.4, 127.5, 114.5, 55.8, 52.2, 49.6, 48.3; LC/MS (ESI) *m/z* 581.0 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}ClN_2O_9S_2$ $[M - H]^-$ 581.0461; found 581.0466.

***N*-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-fluorobenzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (164c).** Prepared as described in the experimental procedure of **16a** from **163c** to obtain the title compound as a white solid (84 mg, 92%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (brs, 2H, CO_2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.16-7.15 (m, 2H), 6.98-6.89 (m, 5H), 4.34 (s, 2H), 4.33 (s, 2H), 3.86 (s, 3H),3.85 (s, 3H), 3.81 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.9, 163.53, 163.48, 159.1, 136.0, 131.6, 131.24, 131.15, 130.3, 130.0, 129.8 ($J_{C,F}$ = 5 Hz), 123.5 ($J_{C,F}$ = 16 Hz), 116.4 ($J_{C,F}$ = 23 Hz), 114.6, 114.5, 55.84, 55.82, 52.4, 48.1, 45.7; LC/MS (ESI) *m/z* 595.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}FN_2O_{10}S_2$ $[M - H]^-$ 595.0862; found 595.0867.

***N*-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-bromobenzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (164d).** Prepared as described in the experimental

procedure of **16a** from intermediate **163d** to obtain the title compound as a white solid (12 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.38 (s, 2H), 4.36 (s, 2H), 3.88 (s, 3H),3.86 (s, 3H), 3.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 163.6, 139.7, 135.7, 133.8, 130.2, 130.0, 129.9, 129.8, 123.1, 114.6, 114.5, 55.9, 55.8, 52.3, 52.0, 49.6; LC/MS (ESI) *m/z* 657.1 [M(^{79}Br) + H]$^{+}$, 659.1 [M(^{81}Br) + H]$^{+}$; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}BrN_2O_{10}S_2$ [M(^{79}Br) + H]$^{+}$ 657.0168 and [M(^{81}Br) + H]$^{+}$ 659.0147; found 657.0219 and 659.0195.

***N*-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-methoxybenzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (164e).** Prepared as described in the experimental procedure of **16a** from intermediate **163e** to obtain the title compound as a white solid (76 mg, 83%); ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.22 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 4.37 (s, 2H), 4.26 (s, 2H), 3.87 (s, 3H),3.86 (s, 3H), 3.81 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.1, 164.8, 164.5, 158.7, 133.8, 133.2, 132.0, 131.6, 131.1, 131.0, 130.5, 125.6, 115.3, 115.2, 111.8, 56.23, 56.21, 56.0, 53.8, 47.3; LC/MS (ESI) *m/z* 607.1 [M + H]$^{+}$; HRMS (ESI) *m/z* calcd for $C_{26}H_{28}N_2O_{11}S_2$ [M - H]$^{-}$ 607.1062; found 607.1067.

***N*-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-methylbenzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (164f).** Prepared as described in the procedure of **16a** from **163f** to obtain the title compound as a white solid (61 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (brs, 2H, CO_2H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.08 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.91-6.86 (m, 3H), 4.34 (s, 2H),

4.30 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.68 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.24, 174.15, 163.5, 163.4, 138.8, 137.5, 133.4, 131.6, 131.3, 130.1, 130.0, 129.9, 129.8, 127.9, 114.5, 114.3, 55.9, 55.8, 52.2, 50.3, 47.0, 18.8; LC/MS (ESI) *m/z* 591.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{28}N_2O_{10}S_2$ [M - H]$^-$ 591.1113; found 591.1116.

***N*-(4-(Benzyloxy)-3-(((*N*-(carboxymethyl)-4-methoxyphenyl)sulfonamido)methyl)-phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (164g).** Prepared as described in the experimental procedure of **16a** from intermediate **163g** to obtain the title compound as a pale yellow solid (16 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.34-7.32 (m, 5H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.03 (s, 1H), 6.93-6.90 (m, 4H), 6.79 (d, *J* = 8.4 Hz, 1H), 4.96 (s, 2H), 4.34 (s, 2H), 4.29 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 163.4, 163.3, 156.6, 136.3, 132.7, 131.2, 130.9, 130.8, 130.3, 130.0, 129.8, 128.8, 128.4, 127.6, 124.5, 114.41, 114.36, 112.4, 70.6, 55.8, 52.7, 48.4, 47.0; LC/MS (ESI) *m/z* 683.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{32}N_2O_{11}S_2$ [M - H]$^-$ 683.1375; found 683.1382.

Ethyl *N*-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)-2-hydroxy benzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (165). Prepared as described in the experimental procedure of **73** from intermediate **163g** to 173.4, 163.5, obtain the title compound as a pale yellow solid (62 mg, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (brs, 1H, OH), 7.68 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.09-7.05 (m, 4H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.71-6.69 (m, 2H), 4.25 (s, 4H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.94 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 6H), 3.77 (s, 2H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.6, 168.5, 162.7, 162.5, 155.2, 131.1, 130.8, 130.1,

129.8, 129.5, 129.3, 129.2, 122.1, 115.3, 114.4, 114.3, 60.9, 60.7, 55.70, 55.67, 52.7, 47.7, 45.7, 13.9, 13.8; LC/MS (ESI) *m/z* 651.2 $[M + H]^+$.

***N*-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-hydroxybenzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (166).** Prepared as described in the procedure of **16a** from **165** to obtain the title compound as a pale yellow solid (39 mg, 69%); ^{1}H NMR (400 MHz, MeOD) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 9.2 Hz, 2H), 7.07 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.03 (d, *J* = 9.2 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 4.36 (s, 2H), 4.27 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 2H); ^{13}C NMR (100 MHz, MeOD) δ 172.5, 172.3, 164.8, 164.5, 157.0, 133.0, 132.7, 132.0, 131.6, 131.3, 131.0, 130.5, 123.8, 116.3, 115.3, 115.2, 56.23, 56.19, 53.8; LC/MS (ESI) *m/z* 595.1 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{25}H_{26}N_2O_{11}S_2$ $[M + H]^+$ 595.1051; found 595.1063.

***N*-(2-Chloro-5-nitrobenzyl)-*N*-methylbenzenesulfonamide (167a).** Prepared as described in the experimental procedure of **40b** from intermediate **161b** and methyl iodide to obtain the title compound as a pale yellow solid (88 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.4 Hz, 1H), 8.09 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.88-7.85 (m, 2H), 7.68-7.64 (m, 1H), 7.61-7.57 (m, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 4.37 (s, 2H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 140.1, 137.2, 136.0, 133.3, 130.7, 129.5, 127.5, 124.4, 123.9, 51.3, 35.8; LC/MS (ESI) *m/z* 341.1 $[M + H]^+$.

Ethyl *N*-(2-chloro-5-nitrobenzyl)-*N*-(phenylsulfonyl)glycinate (167b). Prepared as described in the procedure of **40b** from **161b** and ethyl 2-bromoacetate to obtain the title compound as a colorless oil (132 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.04 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.61-7.57 (m, 1H), 7.52-7.46 (m, 3H), 4.66 (s, 2H), 4.03 (s, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 1.12 (t, *J* = 7.2 Hz,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 146.9, 140.1, 139.0, 135.6, 133.3, 130.6, 129.2, 127.4, 124.8, 123.9, 61.6, 49.2, 48.8, 14.0; LC/MS (ESI) *m/z* 413.1 $[M + H]^+$.

***N*-(2-Chloro-5-((4-methoxyphenyl)sulfonamido)benzyl)-*N*-methylbenzenesulfonamide (168a).** Prepared as described in the experimental procedure of **22b** from intermediate **167a** to obtain *N*-(5-amino-2-chlorobenzyl)-*N*-methylbenzenesulfonamide as a pale yellow oil (63 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.2 Hz, 2H), 7.64-7.55 (m, 3H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.22 (s, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 137.6, 133.9, 132.9, 130.1, 129.3, 127.5, 122.2, 115.9, 115.8, 51.0, 35.1; LC/MS (ESI) *m/z* 311.1 $[M + H]^+$. Prepared as described in the experimental procedure of **22b** from *N*-(5-amino-2-chlorobenzyl)-*N*-methylbenzenesulfonamide to obtain the title compound as a white solid (71 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.65-7.55 (m, 3H), 7.20-7.18 (m, 2H), 7.11 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.18 (s, 2H), 3.80 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 137.3, 136.5, 134.4, 133.1, 130.4, 130.3, 129.7, 129.4, 129.3, 127.5, 121.8, 121.6, 114.4, 55.7, 51.1, 35.1; LC/MS (ESI) *m/z* 481.1 $[M + H]^+$.

Ethyl *N*-(2-chloro-5-((4-methoxyphenyl)sulfonamido)benzyl)-*N*-(phenylsulfonyl) glycinate (168b). Prepared as described in the experimental procedure of **22b** from intermediate **167b** to obtain ethyl *N*-(5-amino-2-chlorobenzyl)-*N*-(phenylsulfonyl)-glycinate as a pale yellow oil (113 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.59-7.55 (m, 1H), 7.51-7.48 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 2.8 Hz, 1H), 6.51 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.53 (s, 2H), 3.99 (s, 2H), 3.97 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 146.0, 139.8, 133.2,

132.8, 130.1, 129.0, 127.4, 122.4, 116.4, 116.1, 61.3, 48.6, 47.6, 14.0; LC/MS (ESI) *m/z* 383.1 $[M + H]^+$. Prepared as described in the experimental procedure of **22b** from ethyl *N*-(5-amino-2-chlorobenzyl)-*N*-(phenylsulfonyl)glycinate to obtain the title compound as a pale yellow solid (136 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.62 (brs, 1H, NH), 7.57 (t, *J* = 7.6 Hz, 1H), 7.51-7.47 (m, 2H), 7.19-7.08 (m, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.53 (s, 2H), 3.96 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 2H), 3.80 (s, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 163.3, 139.6, 136.6, 134.0, 133.0, 130.4, 130.3, 129.7, 129.5, 129.1, 127.5, 122.2, 121.8, 114.4, 61.5, 55.7, 48.7, 47.7, 14.0; LC/MS (ESI) *m/z* 553.1 $[M + H]^+$.

***N*-(2-Chloro-5-((4-methoxyphenyl)sulfonamido)benzyl)-*N*-(phenylsulfonyl)glyci-ne (169).** Prepared as described in the experimental procedure of **16b** from intermediate **168b** to obtain the title compound as a pale yellow solid (82 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.48-7.44 (m, 2H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.47 (s, 2H), 3.88 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 163.4, 138.9, 136.3, 133.7, 133.2, 130.5, 130.1, 129.9, 129.7, 129.3, 127.5, 123.1, 122.0, 114.5, 55.8, 49.5, 48.2; LC/MS (ESI) *m/z* 523.0 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{22}H_{21}ClN_2O_7S_2$ $[M - H]^-$ 523.0406; found 523.0411.

Ethyl *N*-(4-chloro-3-((*N*-methylphenylsulfonamido)methyl)phenyl)-*N*-((4-metho-xyphenyl)sulfonyl)glycinate (170). Prepared as described in the experimental procedure of **40b** from intermediate **168a** and ethyl 2-bromoacetate to obtain the title compound as a colorless oil (71 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.63-7.52 (m, 5H), 7.28-7.27 (m, 1H), 7.23-7.17 (m, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.34 (s,

2H), 4.15 (s, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 2.53 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 163.3, 139.2, 137.1, 134.4, 132.98, 132.96, 130.3, 130.0, 129.8, 129.3, 128.9, 127.4, 114.3, 612, 55.7, 52.5, 51.0, 35.0, 14.1; LC/MS (ESI) *m/z* 567.1 $[M + H]^+$.

***N*-(4-Chloro-3-((*N*-methylphenylsulfonamido)methyl)phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (171).** Prepared as described in the experimental procedure of **16b** from intermediate **170** to obtain the title compound as a pale yellow solid (54 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.66-7.56 (m, 5H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.27-7.24 (m, 1H), 7.20 (s, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 4.41 (s, 2H), 4.19 (s, 2H), 3.88 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 163.5, 139.1, 137.2, 134.6, 133.3, 133.1, 130.6, 130.1, 130.0, 129.9, 129.4, 129.1, 127.5, 114.5, 55.8, 52.3, 51.1, 35.2; LC/MS (ESI) *m/z* 539.1 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{23}H_{23}ClN_2O_7S_2$ $[M + H]^+$ 539.0708; found 539.0721.

1-Methyl-5-nitro-1*H*-benzo[*d*][1,2,3]triazole (172). To a solution of *N*^{1}-ethyl-4-nitro-1,2-phenylenediamine (200 mg, 1.20 mmol) in con. HCl (1 mL) and water (4 mL) was added sodium nitrite (104 mg, 1.51 mmol) in water (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours. After the reaction was completed, the crude mixture was warmed to room temperature and basified with sat. NaOH until the pH reached around 7. The resulting solid was filtered to give the product as a dark brown solid (175 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.42 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 4.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 144.9, 136.2, 122.7, 117.5, 109.9, 34.8; LC/MS (ESI) *m/z* 179.1 $[M + H]^+$.

1-Methyl-1*H*-benzo[*d*][1,2,3]triazol-5-amine (173). To a solution of **172** (355 mg, 0.47 mmol) in methanol (20 mL) was added Pd/C (10% wt.) (36 mg) at room temperature under N_2. The reaction mixture was stirred at room temperature for 1 hour under H_2. The crude mixture was filtered off through celite, and then concentrated under reduced pressure to give the product as a brown solid (311 mg, quantitative); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.91 (s, 1H), 5.22 (s, 1H, NH), 4.16 (s, 3H), 3.36 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.9, 145.8, 129.2, 119.0, 110.1, 97.5, 33.9; LC/MS (ESI) *m/z* 149.2 $[M + H]^+$.

(5-Bromo-2-methylphenyl)methanol (174). Prepared as described in the experimental procedure of **30** from 5-bromo-2-methylbenzoic acid to obtain the title compound as a pale yellow solid (830 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.31 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 4.63 (s, 2H), 3.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 134.7, 132.0, 130.5, 130.0, 119.7, 62.8, 18.3.

5-Bromo-2-methylbenzaldehyde (175). Prepared as described in the experimental procedure of **47a** from intermediate **174** to obtain the title compound as a colorless oil (473 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.56 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 139.4, 136.5, 135.6, 134.2, 133.6, 120.2, 19.0.

***N*-(5-Bromo-2-methylbenzyl)-4-methoxybenzenesulfonamide (176).** Prepared as described in the experimental procedure of **48a** from intermediate **175** to obtain the title compound as a white solid (154 mg, 59%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.23 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 6.98-6.95 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.05 (d, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 163.2, 136.3, 135.6, 132.3, 131.6, 131.3, 131.1, 129.4, 119.7, 114.5, 55.8, 45.0, 18.5; LC/MS (ESI) *m/z* 370.1 [M(^{79}Br) + H]$^+$, 372.0 [M(^{81}Br) + H]$^+$.

5-Bromo-2-methylbenzyl methanesulfonate (177). To a solution of **174** (325 mg, 1.62 mmol) in dichloromethane (8 mL) were added triethylamine (196 mg, 1.94 mmol) and methanesulfonyl chloride (194 mg, 1.70 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 minutes. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the product as a pale yellow oil (456 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 2.0 Hz, 1H), 7.30 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.09 (s, 2H), 2.87 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 133.6, 132.4, 132.3, 131.6, 119.5, 68.7, 38.0, 18.3.

***N*-(5-Bromo-2-methylbenzyl)-4-methoxy-*N*-methylbenzenesulfonamide (178).** Prepared as described in the experimental procedure of **21b** from intermediate **177** and 4-methoxy-*N*-methylbenzenesulfonamide to obtain the title compound as a white solid (486 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.32-7.28 (m, 2H), 7.05-7.02 (m, 3H), 4.05 (s, 2H), 3.89 (s, 3H), 2.53 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 136.6, 135.6, 132.5, 132.2, 131.1, 129.8, 128.3, 119.6, 114.5, 55.8, 52.2, 34.5, 18.8; LC/MS (ESI) *m/z* 384.1 [M(^{79}Br) + H]$^+$, 386.1 [M(^{81}Br) + H]$^+$.

4-Methoxy-*N*-(2-methyl-5-((1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)amino)benz-yl)benzenesulfonamide (179a). To a solution of **176** (281 mg, 0.76 mmol) in toluene (3.6 mL) were added intermediate **169** (107 mg, 0.72 mmol), Tris(dibenzylideneacetone)-dipalladium(0) (66 mg, 0.07 mmol), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (61 mg, 0.14 mmol) and sodium *tert*-butoxide (104 mg, 1.08 mmol) at room temperature.

The reaction mixture was stirred at 80 °C for overnight. The crude mixture was cooled to room temperature, filtered off through celite, and then concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-60% ethyl acetate/hexane) to give the product as a pale yellow solid (156 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.16 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.94-6.90 (m, 4H), 5.93 (brs, 1H, NH), 4.24 (s, 3H), 4.04 (d, *J* = 6.0 Hz, 2H), 3.83 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 147.3, 141.5, 140.5, 135.4, 131.6, 131.5, 129.7, 129.4, 129.3, 121.9, 118.6, 117.6, 114.4, 110.0, 104.8, 55.8, 45.4, 34.4, 18.2; LC/MS (ESI) *m/z* 438.2 $[M + H]^+$.

4-Methoxy-*N*-methyl-*N*-(2-methyl-5-((1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5yl)amino)benzyl)benzenesulfonamide (179b). Prepared as described in the experimental procedure of **179a** from intermediates **178** and **169** to obtain the title compound as a dark yellow solid (120 mg, 33%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.18 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.99-6.95 (m, 2H), 5.93 (brs, 1H, NH), 4.23 (s, 3H), 4.04 (s, 2H), 3.87 (s, 3H), 2.54 (s, 3H), 2.3 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 147.3, 141.3, 140.6, 134.3, 131.8, 130.4, 129.8, 129.6, 128.4, 121.9, 119.4, 117.7, 114.4, 110.0, 104.5, 55.7, 52.5, 34.5, 34.4, 18.5; LC/MS (ESI) *m/z* 452.2 $[M + H]^+$.

***tert*-Butyl *N*-(5-((2-(*tert*-butoxy)-2-oxoethyl)(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)amino)-2-methylbenzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (180a).** Prepared as described in the experimental procedure of **75a** from intermediates **179a** to obtain the title compound as a colorless oil (10 mg, 4%); %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.21 (dd, *J* = 8.8, 2.0

Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.84 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 4.24 (s, 2H), 4.24 (s, 2H), 4.24 (s, 3H), 3.83 (s, 3H), 4.24 (s, 2H), 4.24 (s, 3H), 4.24 (s, 9H), 2.17 (s, 9H); LC/MS (ESI) *m/z* 667.3 $[M + H]^+$.

Ethyl *N*-(3-(((4-methoxy-*N*-methylphenyl)sulfonamido)methyl)-4-methyl phenyl)-*N*-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)glycinate (180b). Prepared as described in the procedure of **140b** from **179b** and ethyl 2-bromoacetate to obtain the title compound as a white solid (8 mg, 6%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 7.20 (dd, *J* = 9.2, 1.6 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.87 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 4.45 (s, 2H), 4.25 (s, 3H), 4.18 (q, *J* = 8.0 Hz, 2H), 4.01 (s, 2H), 3.87 (s, 3H), 2.49 (s, 3H), 2.33 (s, 3H), 1.24 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 163.1, 147.3, 145.8, 144.8, 134.2, 131.9, 131.4, 130.0, 129.8, 128.3, 124.0, 122.1, 120.3, 114.4, 109.6, 108.9, 82.1, 55.7, 55.6, 52.7, 34.4, 34.3, 28.2, 18.5; LC/MS (ESI) *m/z* 566.3 $[M + H]^+$.

***N*-(5-((Carboxymethyl)(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)amino)-2-methyl-benzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (181a).** Prepared as described in the experimental procedure of **76a** from intermediates **180a** to obtain the title compound as a pale yellow solid (7 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.74 (m, 2H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.40-7.37 (m, 1H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.19-7.16 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.95-6.93 (m, 1H), 6.92-6.89 (m, 2H), 4.43 (s, 1H), 4.23 (s, 3H), 3.90 (s, 2H), 3.83 (s, 1H), 3.81 (s, 3H), 3.31 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 163.1, 146.7, 133.0, 132.2, 131.0, 129.8, 129.7, 129.6, 124.5, 123.0, 120.9, 114.4, 114.2, 110.2, 77.4, 55.9, 55.7, 49.8, 40.5, 18.3; LC/MS (ESI) *m/z* 554.2 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{26}H_{27}N_5O_7S$ $[M + H]^+$ 554.1704; found 554.1714.

***N*-(3-(((4-Methoxy-*N*-methylphenyl)sulfonamido)methyl)-4-methylphenyl)-*N*-(1-methyl-1*H*-benzo[*d*][1,2,3]triazol-5-yl)glycine (181b).** Prepared as described in the procedure of **16a** from **180b** to obtain the title compound as a white solid (5 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.52 (s, 1H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.14-7.11 (m, 2H), 6.99-6.97 (m, 3H), 6.89 (s, 1H), 4.49 (s, 2H), 3.82 (s, 3H), 4.49 (s, 2H), 3.82 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 131.8, 129.9, 129.8, 114.53, 114.47, 114.4, 109.8, 55.8, 34.5, 29.8, 18.6; LC/MS (ESI) *m/z* 508.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{25}H_{27}N_5O_5S$ [M - H]$^-$ 508.1660; found 508.1650.

4-Methoxy-*N*-(4-((4-methoxyphenyl)sulfonamido)benzyl)benzenesulfonamide (182a). Prepared as described in the experimental procedure of **52** from 4-(aminomethyl)aniline to obtain the title compound as a pale yellow solid (238 mg, 63%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (brs, 1H, NH), 7.86 (t, *J* = 6.4 Hz, 1H, NH), 7.70 (d, *J* = 9.2 Hz, 2H), 7.68 (d, *J* = 9.2 Hz, 2H), 7.08-7.05 (m, 5H), 7.03-6.98 (m, 3H), 3.83 (s, 3H), 3.81 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.1, 136.9, 133.1, 132.2, 131.2, 128.8, 128.6, 128.4, 119.7, 114.33, 114.26, 55.6, 45.5; LC/MS (ESI) *m/z* 461.1 [M - H]$^-$.

4-Methoxy-*N*-(3-((4-methoxyphenyl)sulfonamido)benzyl)benzenesulfonamide (182b). Prepared as described in the procedure of **52** from 3-(aminomethyl)aniline to obtain the title compound as a pale yellow solid (230 mg, 61%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (brs, 1H, NH), 7.95 (t, *J* = 6.4 Hz, 1H, NH), 7.70 (d, *J* = 8.8 Hz, 4H), 7.12-7.03 (m, 6H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.2 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.1, 138.9, 138.0, 132.2, 131.2, 128.9, 128.6, 122.9, 118.8, 118.2, 114.33, 114.26, 55.6, 45.9; LC/MS (ESI) *m/z* 461.1 [M - H]$^-$.

***N,N'*-(4-Methyl-1,3-phenylene)bis(4-methoxybenzenesulfonamide) (182c).** Prepared as described in the experimental procedure of **52** from 4-methylbenzene-1,3-diamine to obtain the title compound as a white solid (100 mg, 33%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (brs, 1H, NH), 9.36 (brs, 1H, NH), 7.61 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.05-7.00 (m, 5H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.77 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.3, 136.1, 135.5, 132.1, 131.00, 130.95, 128.9, 128.6, 128.5, 117.6, 117.3, 114.23, 114.18, 55.63, 55.59, 16.9; LC/MS (ESI) *m/z* 463.1 $[M + H]^+$.

Ethyl *N*-(4-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)benzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (183a). Prepared as described in the experimental procedure of **15a** from **182a** to obtain the title compound as a colorless oil (142 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.15-7.08 (m, 4H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.38 (s, 2H), 4.30 (s, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.94 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 168.6, 163.1, 163.0, 139.7, 135.2, 131.2, 130.3, 129.8, 129.5, 129.2, 128.8, 114.1, 114.0, 61.4, 61.2, 55.58, 55.55, 52.5, 50.8, 46.9, 14.0, 13.9; LC/MS (ESI) *m/z* 635.2 $[M + H]^+$.

Ethyl *N*-(3-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)benzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (183b). Prepared as described in the experimental procedure of **15a** from intermediate **182b** to obtain the title compound as a colorless oil (138 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.31-7.25 (m, 1H), 7.22-7.18 (m, 2H), 7.05 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.41 (s, 2H), 4.36 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.02 (q, *J* =

7.2 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.5, 163.2, 163.0, 140.4, 136.6, 131.2, 130.2, 129.8, 129.51, 129.45, 128.3, 128.2, 128.1, 114.2, 114.0, 61.4, 61.2, 55.61, 55.59, 52.4, 50.8, 46.8, 14.02, 13.96; LC/MS (ESI) *m/z* 635.2 $[M + H]^+$.

Diethyl 2,2'-((4-methyl-1,3-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetate (183c). Prepared as described in the experimental procedure of **15a** from **182c** to obtain the title compound as a white solid (98 mg, 71%); ^{1}H NMR (400 MHz, MeOD) δ 7.55 (d, *J* = 8.8Hz, 2H), 7.54 (d, *J* = 8.8, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.11 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 2.4 Hz, 1H), 4.19 (s, 2H), 4.16 (s, 2H), 4.15-4.07 (m, 4H), 3.89 (s, 3H), 3.86 (s, 3H), 2.32 (s, 3H), 1.29-1.15 (m, 6H); ^{13}C NMR (100 MHz, MeOD) δ 170.2, 169.9, 164.94, 164.85, 141.2, 140.5, 139.5, 132.6, 131.39, 131.38, 131.2, 131.0, 130.2, 129.9, 115.4, 115.3, 62.53, 62.48, 56.30, 56.27, 53.8, 53.5, 18.3, 14.41, 14.37; LC/MS (ESI) *m/z* 635.3 $[M + H]^+$.

***N*-(4-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)benzyl)-*N*-((4-metho-xyphenyl)sulfonyl)glycine (184a).** Prepared as described in the experimental procedure of **16a** from intermediate **183a** to obtain the title compound as a white solid (100 mg, 77%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.78 (brs, 2H, CO_2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.11-7.05 (m, 6H), 4.36 (s, 2H), 4.35 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.81 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 169.8, 162.7, 162.5, 139.2, 135.4, 131.1, 130.0, 129.5, 129.3, 128.6, 127.6, 114.3, 55.67, 55.66, 51.9, 50.7, 47.7; LC/MS (ESI) *m/z* 577.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{25}H_{26}N_2O_{10}S_2$ $[M - H]^-$ 577.0956; found 577.0961.

***N*-(3-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)benzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (184b).** Prepared as described in the experimental procedure of **16a** from intermediate **183b** to obtain the title compound as a white solid (80 mg, 64%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.80 (brs, 2H, CO_2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.14-7.13 (m, 2H), 7.08-7.05 (m, 4H), 6.90 (s, 2H), 4.33 (s, 2H), 4.27 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.69 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.8, 169.7, 162.7, 162.5, 140.1, 136.9, 131.2, 129.8, 129.5, 129.2, 129.0, 127.4, 126.8, 114.32, 114.29, 55.6, 54.9, 51.9, 50.5, 47.2; LC/MS (ESI) *m/z* 577.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{25}H_{26}N_2O_{10}S_2$ [M - H]$^-$ 577.0956; found 577.0960.

2,2'-((4-Methyl-1,3-phenylene)bis(((4-methoxyphenyl)sulfonyl)azanediyl)) diacetic acid (184c). Prepared as described in the experimental procedure of **16a** from intermediate **183c** to obtain the title compound as a white solid (41 mg, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (brs, 2H, CO_2H), 7.54 (d, *J* = 8.4 Hz, 4H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.05 (s, 1H), 6.971-6.93 (m, 5H), 4.44-4.33 (m, 2H), 4.21-4.17 (m, 2H), 4.07-4.03 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 163.47, 163.45, 139.6, 138.5, 137.5, 131.8, 130.5, 130.3, 130.0, 129.9, 129.8, 128.3, 114.5, 114.4, 55.8, 51.7, 51.6, 17.9; LC/MS (ESI) *m/z* 577.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{25}H_{26}N_2O_{10}S_2$ [M - H]$^-$ 577.0956; found 577.0960.

2-(2-Fluoro-5-nitrophenyl)acetonitrile (185a). Prepared as described in the experimental procedure of **134a** from intermediate **159b** to obtain 2-fluoro-5-nitrobenzyl methanesulfonate as a pale yellow solid (637 mg, 49%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.38 (m, 1H), 8.33-8.30 (m, 1H), 7.32-7.26 (m, 1H), 5.34 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 ($J_{C,F}$ = 259 Hz), 144.5, 127.1 ($J_{C,F}$ = 10 Hz), 126.6 ($J_{C,F}$

= 5 Hz), 123.1 ($J_{C,F}$ = 17 Hz), 117.1 ($J_{C,F}$ = 24 Hz), 63.4 ($J_{C,F}$ = 4 Hz), 38.2. Prepared as described in the experimental procedure of **134a** from 2-fluoro-5-nitrobenzyl methanesulfonate to obtain the title compound as a pale yellow solid (363 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.35 (m, 1H), 8.30-8.24 (m, 1H), 7.33-7.26 (m, 1H), 3.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8 ($J_{C,F}$ = 257 Hz), 144.6, 126.4 ($J_{C,F}$ = 10 Hz), 126.0 ($J_{C,F}$ = 4 Hz), 119.7 ($J_{C,F}$ = 17 Hz), 117.0 ($J_{C,F}$ = 23 Hz), 115.6, 17.8.

2-(2-(Benzyloxy)-5-nitrophenyl)acetonitrile (185b). Prepared as described in the procedure of **134a** from **159d** to obtain 2-(benzyloxy)-5-nitrobenzyl methanesulfonate as a pale yellow solid (1.6 g, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.8 Hz, 1H), 8.25 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.43-7.42 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 5.31 (s, 2H), 5.23 (s, 2H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 141.6, 135.0, 129.1, 128.9, 127.7, 126.8, 125.8, 123.6, 111.9, 71.4, 65.8, 37.8. Prepared as described in the procedure of **134a** from 2-(benzyloxy)-5-nitrobenzyl methanesulfonate to obtain the title compound as a pale yellow solid (1.1 g, 90%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, *J* = 2.8 Hz, 1H), 8.26 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 2H), 7.42 (d, *J* = 7.2, 7.2 Hz, 2H), 7.37-7.34 (m, 2H), 4.27 (s, 2H), 4.27 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 140.6, 135.7, 128.5, 128.2, 127.5, 125.8, 125.2, 121.0, 118.0, 112.6, 70.6, 18.2.

***N*-(2-Fluoro-5-nitrophenethyl)-4-methylbenzenesulfonamide (186a).** To a solution of **185a** (804 mg, 4.46 mmol) in tetrahydrofuran (8 mL) was added borane tetrahydrofuran complex solution (1.0 M in THF, 8.9 ml, 8.93 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 1 hour. After the reaction was completed, the crude mixture was added to methanol and water, and then concentrated under reduced pressure. The aqueous solution was acidified with 6 N HCl until the pH reached around 1 and stirred at

80 °C for 30 minutes. After cooling to room temperature, the solution was basified with sat. $NaHCO_3$ until the pH reached around 10, and then extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2-(2-fluoro-5-nitrophenyl)ethan-1-amine as a pale yellow oil. The resulting crude compound was used for the next reaction without further purification. To a solution of 2-(2-fluoro-5-nitrophenyl)ethan-1-amine (300 mg, 1.63 mmol) in dichloromethane (8 mL) were added pyridine (193 mg, 2.44 mmol) and 4-methylbenzenesulfonyl chloride (466 mg, 2.44 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to 1N HCl, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-35% ethyl acetate/hexane) to give the product as a pale yellow solid (227 mg, 28% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.03 (m, 1H), 7.95-7.93 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.10-7.06 (m, 1H), 4.78 (t, *J* = 6.4 Hz, 1H, NH), 3.26-3.21 (m, 2H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8 ($J_{C,F}$ = 255 Hz), 144.3 ($J_{C,F}$ = 4 Hz), 143.9, 137.0, 130.2, 129.9, 127.2 ($J_{C,F}$ = 17 Hz), 127.1, 124.7 ($J_{C,F}$ = 10 Hz), 116.5 ($J_{C,F}$ = 25 Hz), 42.6, 29.8, 21.6; LC/MS (ESI) *m/z* 339.1 $[M + H]^+$.

***N*-(2-(Benzyloxy)-5-nitrophenethyl)-4-methoxybenzenesulfonamide (186b).** Prepared as described in the experimental procedure of **186a** from intermediate **185b** to obtain 2-(2-(benzyloxy)-5-nitrophenyl)ethan-1-amine as a pale yellow oil (1.1 g, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-8.07 (m, 2H), 7.41-7.40 (m, 5H), 6.95 (d, *J* = 8.8 Hz, 1H), 5.18 (s, 2H), 2.99 (t, *J* = 6.8 Hz, 2H), 2.86 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 161.8, 141.4, 135.8, 129.8, 128.9, 128.5, 127.3, 126.1, 124.1, 111.3, 70.8, 41.6, 34.6; LC/MS (ESI) *m/z* 273.2 $[M + H]^+$. Prepared as described in the experimental procedure of **186a** from 2-(2-(benzyloxy)-5-nitrophenyl)ethan-1-amine to obtain the title compound as a pale yellow solid (258 mg, 29%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.87 (d, *J* = 2.8 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.44-7.37 (m, 5H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.14 (s, 2H), 4.72 (t, *J* = 6.4 Hz, 1H, NH), 3.84 (s, 3H), 3.28-3.23 (m, 2H), 2.83 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 161.7, 141.3, 135.5, 131.6, 129.1, 128.9, 128.6, 128.0, 127.5, 126.3, 124.5, 114.3, 111.4, 70.9, 55.6, 42.4, 30.8; LC/MS (ESI) *m/z* 443.1 $[M + H]^+$.

***N*-(2-(Benzyloxy)-5-nitrophenethyl)-4-methylbenzenesulfonamide (186c).** Prepared as described in the experimental procedure of **52** from 2-(2-(benzyloxy)-5-nitrophenyl)ethan-1-amine and 4-methylbenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (256 mg, 30%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, *J* = 8.8 Hz, 1H), 7.99 (s, 1H), 7.65 (t, *J* = 5.2 Hz, 1H, NH), 7.56 (d, *J* = 8.0 Hz, 2H), 7.44-7.36 (m, 5H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 1H), 5.24 (s, 2H), 3.34 (s, 2H), 3.07-3.02 (m, 2H), 2.77 (t, *J* = 6.8 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5, 142.4, 140.4, 137.6, 136.0, 129.5, 128.5, 128.1, 127.4, 126.3, 125.9, 124.2, 112.1, 70.1, 41.5, 30.0, 20.9; LC/MS (ESI) *m/z* 427.2 $[M + H]^+$.

***N*-(2-(Benzyloxy)-5-nitrophenethyl)-[1,1'-biphenyl]-4-sulfonamide (186d).** Prepared as described in the experimental procedure of **52** from 2-(2-(benzyloxy)-5-nitrophenyl)ethan-1-amine and 4-biphenylsulfonyl chloride to obtain the title compound as a pale yellow solid (229 mg, 25%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.80-7.73 (m, 4H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.53-

7.49 (m, 2H), 7.45-7.33 (m, 6H), 7.19 (d, *J* = 8.8 Hz, 1H), 5.24 (s, 2H), 3.11-3.10 (m, 2H), 2.82-2.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6, 143.8, 140.5, 139.2, 138.6, 136.1, 129.1, 128.6, 128.5, 128.1, 128.0, 127.50, 127.45, 127.3, 127.0, 126.0, 124.2, 112.1, 70.1, 41.6, 30.1; LC/MS (ESI) *m/z* 489.3 $[M + H]^+$.

4-Methoxy-*N*-(5-((4-methoxyphenyl)sulfonamido)-2-methylphenethyl)benzene sulfonamide (187a). Prepared as described in the procedure of **18d** from 2-(2-methyl-5-nitrophenyl)ethan-1-amine to obtain 3-(2-aminoethyl)-4-methylaniline as a pale yellow oil (394 mg, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 7.6 Hz, 1H), 6.48-6.45 (m, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 138.6, 131.0, 126.0, 116.5, 113.3, 42.2, 37.5, 18.4. Prepared as described in the procedure of **18d** from 3-(2-aminoethyl)-4-methylaniline to obtain the title compound as a white solid (41 mg, 18%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.69 (m, 4H), 7.30 (brs, 1H, NH), 6.93-6.90 (m, 3H), 6.87-6.84 (m, 3H), 6.81 (s, 1H), 4.98 (t, *J* = 6.0 Hz, 1H, NH), 3.83 (s, 3H), 3.78 (s, 3H), 3.08-3.03 (m, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 163.0, 137.3, 134.8, 133.4, 131.4, 131.3, 130.6, 129.6, 129.3, 122.8, 120.2, 114.4, 114.3, 55.8, 55.7, 42.8, 33.2, 18.7; LC/MS (ESI) *m/z* 491.1 $[M + H]^+$.

4-Methyl-*N*-(5-((4-methylphenyl)sulfonamido)-2-methylphenethyl)benzenesulfon-amide (187b). Prepared as described in the experimental procedure of **52** from 3-(2-aminoethyl)-4-methylaniline and 4-methylbenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (14 mg, 13%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.99 (brs, 1H, NH), 6.94 (d, *J* = 8.4 Hz, 1H), 6.84 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 4.78 (t, *J* = 6.0 Hz, 1H, NH), 3.11-3.06 (m, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.41

(s, 3H), 2.35 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 143.6, 137.2, 137.1, 136.3, 134.7, 133.6, 131.4, 130.0, 129.8, 127.4, 127.2, 123.0, 120.4, 42.9, 33.3, 21.6, 18.8; LC/MS (ESI) *m/z* 459.2 $[M + H]^+$.

4-Bromo-*N*-(5-((4-bromophenyl)sulfonamido)-2-methylphenethyl)benzenesulfonamide (187c). Prepared as described in the experimental procedure of **52** from 3-(2-aminoethyl)-4-methylaniline and 4-bromobenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (509 mg, 32%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.54 (m, 8H), 7.12 (brs, 1H, NH), 6.97 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.98 (t, *J* = 6.0 Hz, 1H, NH), 3.15-3.10 (m, 2H), 2.71 (t, *J* = 6.8 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 138.1, 137.3, 134.2, 132.6, 132.5, 131.6, 129.0, 128.7, 128.2, 127.8, 123.5, 120.7, 42.8, 33.4, 18.8; LC/MS (ESI) *m/z* 587.0 $[M(2^{79}Br,) + H]^+$, 589.0 $[M(^{79}Br, {}^{81}Br) + H]^+$, 590.9 $[M(2^{81}Br) + H]^+$.

***N*-(4-Fluoro-3-(2-((4-methylphenyl)sulfonamido)ethyl)phenyl)-4-methylbenzene sulfonamide (187d).** Prepared as described in the experimental procedure of **22b** from **186a** to obtain the title compound as a pale yellow oil (189 mg, 65% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.94-6.90 (m, 1H), 6.88-6.85 (m, 1H), 6.83-6.79 (m, 1H), 3.12 (t, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.41 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9 ($J_{C,F}$ = 242 Hz), 144.2, 143.7, 136.9, 135.9, 132.7 ($J_{C,F}$ = 3 Hz), 129.89, 129.85, 129.8 ($J_{C,F}$ = 6 Hz), 127.4, 127.1, 126.0 ($J_{C,F}$ = 17 Hz), 125.4 ($J_{C,F}$ = 5 Hz), 116.2 ($J_{C,F}$ = 23 Hz), 42.8, 29.5, 21.7; LC/MS (ESI) *m/z* 463.2 $[M + H]^+$.

***N*-(4-(Benzyloxy)-3-(2-((4-methoxyphenyl)sulfonamido)ethyl)phenyl)-4-methoxybenzenesulfonamide (187e).** Prepared as described in the experimental procedure of **22b**

from intermediate **186b** to obtain the title compound as a white solid (282 mg, 94% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (brs, 1H, NH), 7.64 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.51 (t, *J* = 6.0 Hz, 1H, NH), 7.36-7.30 (m, 5H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.88-6.83 (m, 3H), 3.81 (s, 2H), 3.78 (s, 3H), 2.84-2.79 (m, 2H), 2.56 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 162.0, 153.2, 137.0, 132.0, 131.2, 130.4, 128.8, 128.6, 128.3, 127.7, 127.3, 124.0, 120.9, 114.19, 114.15, 112.4, 69.3, 55.5, 42.3, 30.4; LC/MS (ESI) *m/z* 583.2 $[M + H]^+$.

***N*-(4-(Benzyloxy)-3-(2-((4-methylphenyl)sulfonamido)ethyl)phenyl)-4-methyl-benzenesulfonamide (187f).** Prepared as described in the procedure of **22b** from **186c** to obtain the title compound as a white solid (175 mg, 57%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (brs, 1H, NH), 7.59 (brs, 1H, NH), 7.59 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.36-7.28 (m, 9H), 6.87-6.80 (m, 3H), 4.96 (s, 2H), 2.83-2.78 (m, 2H), 2.57-2.50 (m, 2H), 2.36 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.2, 142.9, 142.4, 137.5, 137.0, 136.6, 130.2, 129.5, 129.4, 128.3, 127.7, 127.3, 127.2, 126.7, 126.4, 124.0, 121.0, 112.4, 69.3, 42.3, 30.4, 20.90, 20.87; LC/MS (ESI) *m/z* 551.2 $[M + H]^+$.

***N*-(5-([1,1'-Biphenyl]-4-sulfonamido)-2-(benzyloxy)phenethyl)-[1,1'-biphenyl]-4-sulfonamide (187g).** Prepared as described in the procedure of **22b** from **186d** to obtain the title compound as a white solid (201 mg, 67% over 2 stpes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.56-7.54 (m, 4H), 7.48-7.38 (m, 9H), 7.35-7.31 (m, 4H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.92 (s, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 4.90 (s, 2H), 3.21 (dd, *J* = 12.4, 6.4 Hz, 1H), 7.59 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 145.8, 145.4, 139.4, 139.2, 138.6, 137.7, 136.6, 129.4,

129.2, 129.1, 128.8, 128.7, 128.60, 128.56, 128.3, 128.0, 127.74, 127.69, 127.63, 127.55, 127.42, 127.39, 126.5, 123.4, 112.4, 70.4, 42.9, 30.7; LC/MS (ESI) *m/z* 675.3 $[M + H]^+$.

Ethyl *N*-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)-2-methyl phenethyl) -*N*-((4-methoxyphenyl)sulfonyl)glycinate (188a). Prepared as described in the procedure of **15a** from **187a** to obtain the title compound as a colorless oil (32 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.8Hz, 2H), 7.60 (d, *J* = 8.8, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.93-6.90 (m, 4H), 4.33 (s, 2H), 4.15-4.07 (m, 4H), 3.99 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.30 (t, *J* = 8.0 Hz, 2H), 2.80 (t, *J* = 8.0 Hz, 2H), 2.24 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 169.0, 163.2, 163.1, 138.0, 137.6, 136.7, 131.5, 131.3, 130.8, 130.1, 129.9, 129.7, 127.0, 114.3, 114.0, 61.5, 55.7, 52.8, 48.78, 48.76, 32.7, 19.0, 14.2; LC/MS (ESI) *m/z* 663.3 $[M + H]^+$.

Ethyl *N*-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-methyl phenethyl) -*N*-((4-methylphenyl)sulfonyl)glycinate (188b). Prepared as described in the experimental procedure of **15a** from intermediate **187b** to obtain the title compound as a colorless oil (18 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.0, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.33 (s, 2H), 4.15-4.05 (m, 4H), 3.99 (s, 2H), 3.31 (t, *J* = 8.0 Hz, 2H), 2.81 (t, *J* = 8.0 Hz, 2H), 2.41 (s, 3H), 2.40 (s, 3H), 2.25 (s, 3H), 1.22-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.9, 143.8, 143.7, 137.9, 137.5, 136.8, 136.1, 131.2, 129.9, 129.7, 129.5, 127.9, 127.5, 127.0, 61.5, 52.8, 48.8, 32.7, 21.7, 19.0, 14.2; LC/MS (ESI) *m/z* 631.2 $[M + H]^+$.

Ethyl *N*-(3-(2-((4-bromo-*N*-(2-ethoxy-2-oxoethyl)phenyl)sulfonamido)ethyl)meth-ylphenyl)-*N*-((4-bromophenyl)sulfonyl)glycinate (188c). Prepared as described in the

experimental procedure of **15a** from intermediate **187c** to obtain the title compound as a colorless oil (355 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.64-7.53 (m, 6H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.36 (s, 2H), 4.16-4.07 (m, 4H), 4.01 (s, 2H), 3.34 (t, *J* = 7.6 Hz, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.27 (s, 3H), 1.27-1.19 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 168.7, 139.0, 138.4, 137.6, 137.2, 132.4, 132.1, 131.5, 130.2, 129.5, 129.1, 128.0, 127.9, 126.9, 61.7, 53.0, 48.74, 48.69, 32.6, 19.0, 14.2; LC/MS (ESI) *m/z* 759.0 [M(2^{79}Br,) + H]$^{+}$, 761.0 [M(^{79}Br, ^{81}Br) + H]$^{+}$, 763.0 [M(2^{81}Br) + H]$^{+}$.

Ethyl *N*-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-fluorophenethyl)-*N*-tosylglycinate (188d). Prepared as described in the experimental procedure of **15a** from **187d** to obtain the title compound as a colorless oil (169 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.25-7.22 (m, 4H), 7.03-6.98 (m, 2H), 6.88-6.84 (m, 1H), 4.31 (s, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.94 (s, 2H), 3.37 (t, *J* = 7.6 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.38 (s, 3H), 2.37 (s, 3H), 1.23-1.13 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.7, 160.6 ($J_{C,F}$ = 246 Hz), 144.1, 143.6, 136.7, 135.75 ($J_{C,F}$ = 3 Hz), 135.71, 132.0 ($J_{C,F}$ = 5 Hz), 129.7, 129.6, 129.4 ($J_{C,F}$ = 8 Hz), 127.8, 127.4, 126.2 ($J_{C,F}$ = 17 Hz), 116.1 ($J_{C,F}$ = 24 Hz), 61.6, 61.4, 52.8, 50.7, 48.6, 28.6, 21.60, 21.57, 14.11, 14.05; LC/MS (ESI) *m/z* 635.3 [M + H]$^{+}$.

Ethyl *N*-(4-(benzyloxy)-3-(2-((N-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)ethyl)phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (188e). Prepared as described in the experimental procedure of **15a** from **187e** to obtain the title compound as a colorless oil (311 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.39-7.30 (m, 5H), 7.07 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.93 (d, *J* = 8.4 Hz,

2H), 6.89-6.87 (m, 3H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.98 (s, 2H), 4.33 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.02 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.38 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 169.0, 163.2, 162.9, 156.5, 136.6, 132.6, 131.7, 131.2, 130.7, 130.1, 129.5, 129.3, 128.7, 128.2, 127.7, 127.4, 114.1, 114.0, 111.9, 70.3, 61.4, 61.3, 55.7, 55.6, 53.0, 48.4, 48.0, 30.0, 14.2, 14.1; LC/MS (ESI) *m/z* 755.3 $[M + H]^+$.

Ethyl *N*-(4-(benzyloxy)-3-(2-((N-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)ethyl)phenyl)-*N*-((4-methylphenyl)sulfonyl)glycinate (188f). Prepared as described in the procedure of **15a** from **187f** to obtain the title compound as a colorless oil (41 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.39-7.30 (m, 5H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.06 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.88 (d, *J* = 2.4 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 4.98 (s, 2H), 4.33 (s, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 2H), 3.40 (t, *J* = 7.6 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.9, 156.5, 143.8, 143.3, 137.1, 136.6, 136.2, 132.5, 131.3, 129.54, 129.48, 129.2, 128.7, 128.2, 127.9, 127.6, 127.4, 111.9, 70.3, 61.5, 61.2, 53.0, 48.4, 48.0, 30.0, 21.65, 21.63, 14.2, 14.1; LC/MS (ESI) *m/z* 723.2 $[M + H]^+$.

Ethyl *N*-([1,1'-biphenyl]-4-ylsulfonyl)-*N*-(4-(benzyloxy)-3-(2-(*N*-(2-ethoxy-2-oxoethyl)-[1,1'-biphenyl]-4-sulfonamido)ethyl)phenyl)glycinate (188g). Prepared as described in the experimental procedure of **15a** from intermediate **187g** to obtain the title compound as a white solid (152 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (m, 4H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.64-7.56 (m, 6H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.42-7.38 (m, 6H), 7.36-7.32 (m, 1H), 7.12 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05 (d, *J* =

2.4 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 4.99 (s, 2H), 4.41 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.95 (s, 2H), 3.51 (t, *J* = 7.6 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 156.6, 145.7, 145.3, 139.4, 139.3, 138.6, 137.8, 136.5, 132.4, 131.4, 129.2, 129.1, 128.7, 128.53, 128.46, 128.4, 128.2, 127.9, 127.7, 127.5, 127.42, 127.40, 127.3, 111.9, 70.3, 61.5, 61.3, 53.1, 48.4, 48.0, 30.0, 14.2, 14.0; LC/MS (ESI) *m/z* 847.4 $[M + H]^+$.

***N*-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-methylphenethyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (189a).** Prepared as described in the experimental procedure of **16a** from intermediate **188a** to obtain the title compound as a white solid (12 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (brs, 2H, CO_2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.01-6.99 (m, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.76 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.34 (s, 2H), 3.94 (s, 2H), 3.83 (s, 6H), 3.30 (t, *J* = 7.6 Hz, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 163.30, 163.25, 137.8, 137.6, 137.0, 131.3, 131.0, 130.4, 130.2, 130.0, 129.6, 126.3, 114.4, 114.2, 55.8, 52.6, 49.0, 32.6, 29.8, 19.1; LC/MS (ESI) *m/z* 605.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_2O_{10}S_2$ $[M - H]^-$ 605.1269; found 605.1274.

***N*-(5-((*N*-(Carboxymethyl)-4-methylphenyl)sulfonamido)-2-methylphenethyl)-*N*-((4-methylphenyl)sulfonyl)glycine (189b).** Prepared as described in the experimental procedure of **16a** from intermediate **188b** to obtain the title compound as a pale yellow solid (10 mg, 61%); ^{1}H NMR (400 MHz, MeOD) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.81 (s, 1H), 4.34 (s, 2H), 3.97 (s, 2H), 3.28-3.26 (m, 2H), 2.74 (t, *J* = 8.0 Hz, 2H), 2.43 (s, 3H), 2.39 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz,

DMSO-d_6) δ 170.4, 169.8, 143.5, 143.1, 137.5, 137.1, 136.8, 135.60, 135.57, 130.5, 129.7, 129.5, 128.6, 127.3, 126.9, 126.2, 52.2, 48.4, 48.3, 31.6, 21.0, 18.2; LC/MS (ESI) *m/z* 573.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_2O_8S_2$ [M - H]$^-$ 573.1371; found 573.1376.

***N*-(3-(2-((4-Bromo-*N*-(carboxymethyl)phenyl)sulfonamido)ethyl)-4-methylphenyl)-*N*-((4-bromophenyl)sulfonyl)glycine (189c).** Prepared as described in the experimental procedure of **16a** from **188c** to obtain the title compound as a pale yellow solid (172 mg, 54%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (brs, 2H, CO_2H), 7.76-7.70 (m, 6H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 1.6 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.35 (s, 2H), 4.05 (s, 2H), 3.23 (t, *J* = 8.0 Hz, 2H), 2.76 (t, *J* = 8.0 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 169.7, 138.8, 137.8, 137.24, 137.18, 136.0, 132.23, 132.16, 130.6, 129.2, 129.0, 128.9, 127.0, 126.7, 126.2, 52.3, 48.4, 48.3, 32.7, 18.2; LC/MS (ESI) *m/z* 703.0 [M(2^{79}Br) + H]$^+$, 705.0 [M(^{79}Br, ^{81}Br) + H]$^+$, 707.0 [M(2^{81}Br) + H]$^+$; HRMS (ESI) *m/z* calcd for $C_{25}H_{24}Br_2N_2O_8S_2$ [M(2^{79}Br) + H]$^+$ 702.9374, [M(^{79}Br, ^{81}Br) + H]$^+$ 704.9354 and [M(2^{81}Br) + H]$^+$ 706.9333; found 702.9421, 704.9400 and 706.9375.

***N*-(5-((*N*-(Carboxymethyl)-4-methylphenyl)sulfonamido)-2-fluorophenethyl)-*N*-tosylglycine (189d).** Prepared as described in the experimental procedure of **16a** from intermediate **188d** to obtain the title compound as a white solid (50 mg, 64%); ^{1}H NMR (400 MHz, MeOD) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 4H), 7.12-7.08 (m, 1H), 6.98-6.96 (m, 1H), 6.94-6.90 (m, 1H), 4.37 (s, 2H), 3.97 (s, 2H), 3.40 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.2Hz, 2H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.3, 172.1, 161.7 ($J_{C,F}$ = 245 Hz), 145.6, 145.1, 138.3, 137.2 ($J_{C,F}$ = 4 Hz), 137.0, 132.9 ($J_{C,F}$ = 6 Hz), 130.8, 130.7, 130.6, 128.9, 128.4, 127.4 ($J_{C,F}$ = 17 Hz),

116.8 ($J_{C,F}$ = 23 Hz), 53.6, 49.3, 28.9, 21.53, 21.49; LC/MS (ESI) *m/z* 577.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{27}FN_2O_8S_2$ [M - H]$^-$ 577.1120; found 577.1126.

Ethyl *N*-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)-2-hydroxy benzyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (190a). Prepared as described in the procedure of **73** from **188e** to obtain the title compound as a colorless oil (96 mg, 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.89-6.86 (m, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 4.30 (s, 2H), 4.15-4.06 (m, 4H), 3.97 (s, 2H), 3.84 (s, 6H), 3.34 (t, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 1.22-1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.2, 163.2, 163.1, 154.7, 131.9, 131.5, 131.0, 130.6, 130.1, 129.7, 129.1, 125.2, 116.4, 114.3, 114.0, 61.6, 61.5, 55.7, 49.2, 48.6, 31.7, 30.2, 22.7, 14.2, 14.1; LC/MS (ESI) *m/z* 665.3 [M + H]$^+$.

Ethyl *N*-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-hydroxybe-nzyl)-*N*-((4-methylphenyl)sulfonyl)glycinate (190b). Prepared as described in the experimental procedure of **73** from intermediate **188f** to obtain the title compound as a colorless oil (122 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.90-6.86 (m, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.51 (brs, 1H, OH), 4.32 (s, 2H), 4.16-4.07 (m, 4H), 3.99 (s, 2H), 3.35 (t, *J* = 7.6 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 6H), 1.24-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.1, 154.7, 143.8, 136.4, 136.1, 132.0, 131.7, 129.8, 129.5, 129.1, 127.9, 127.5, 125.0, 116.5, 61.7, 61.5, 53.1, 49.3, 48.8, 30.4, 21.7, 21.6, 14.2, 14.1; LC/MS (ESI) *m/z* 633.3 [M + H]$^+$.

Ethyl *N*-([1,1'-biphenyl]-4-ylsulfonyl)-*N*-(5-(*N*-(2-ethoxy-2-oxoethyl)-[1,1'-biphe-nyl]-4-sulfonamido)-2-hydroxyphenethyl)glycinate (190c). Prepared as described in the

experimental procedure of **73** from **188g** to obtain the title compound as a white solid (22 mg, 16%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.68-7.65 (m, 3H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.48-7.44 (m, 4H), 7.43-7.37 (m, 3H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.92 (dd, *J* = 8.4, 2.4 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 1H), 4.37 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 1H), 4.03 (s, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.1, 154.7, 145.9, 145.8, 139.4, 137.9, 137.8, 132.2, 132.0, 129.2, 129.1, 128.8, 128.6, 128.5, 128.1, 127.8, 127.48, 127.45, 125.1, 116.7, 61.7, 61.6, 53.3, 49.5, 49.0, 29.8, 14.23, 14.15; LC/MS (ESI) m/z 757.3 $[M + H]^+$.

***N*-(4-Hydroxy-3-(2-((4-methoxy-*N*-(2-methoxy-2-oxoethyl)phenyl)sulfonamido) ethyl)phenyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (191a).** Prepared as described in the experimental procedure of **16a** from intermediate **190a** to obtain the title compound as a pale yellow solid (79 mg, 90%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (brs, 2H, CO_2H), 9.64 (brs, 1H, OH), 7.69 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 9.2 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.80 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 4.22 (s, 2H), 3.84 (s, 2H), 3.82 (s, 6H), 3.25 (t, *J* = 7.6 Hz, 2H), 2.57-2.50 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 170.0, 162.5, 162.3, 154.8, 131.4, 130.7, 130.4, 130.2, 129.5, 129.0, 128.1, 124.7, 114.9, 114.3, 114.1, 55.6, 52.5, 47.9, 47.4, 30.9, 28.7; LC/MS (ESI) *m/z* 607.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{28}N_2O_{11}S_2$ $[M - H]^-$ 607.1062; found 607.1068.

***N*-(4-Hydroxy-3-(2-((4-methyl-*N*-(2-methoxy-2-oxoethyl)phenyl)sulfonamido) ethyl)phenyl)-*N*-((4-methylphenyl)sulfonyl)glycine (191b).** Prepared as described in the experimental procedure of **16a** from intermediate **190b** to obtain the title compound as a

pale yellow solid (83 mg, 75%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (brs, 2H, CO_2H), 9.67 (brs, 1H, OH), 7.64 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.81 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.34 (d, *J* = 8.8 Hz, 1H), 4.23 (s, 2H), 3.92 (s, 2H), 3.24 (t, *J* = 7.6 Hz, 2H), 2.56-2.50 (m, 2H), 2.38 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.3, 169.9, 154.9, 143.3, 143.0, 137.0, 135.7, 130.5, 130.3, 129.6, 129.4, 128.2, 127.3, 126.8, 124.7, 114.9, 52.5, 47.9, 47.5, 28.6, 20.9; LC/MS (ESI) *m/z* 575.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{28}N_2O_9S_2$ [M - H]$^-$ 575.1163; found 575.1169.

***N*-([1,1'-Biphenyl]-4-ylsulfonyl)-*N*-(4-hydroxy-3-(2-(*N*-(2-methoxy-2-oxoethyl)-[1,1'-biphenyl]-4-sulfonamido)ethyl)phenyl)glycine (191c).** Prepared as described in the experimental procedure of **16a** from intermediate **190c** to obtain the title compound as a white solid (10 mg, 50%); ^{1}H NMR (400 MHz, MeOD) δ 7.78-7.75 (m, 6H), 7.69-7.67 (m, 5H), 7.47-7.44 (m, 5H), 7.42-7.38 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.83 (s, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 4.37 (s, 2H), 3.98 (s, 2H), 3.50 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, MeOD) δ 172.60, 172.55, 156.7, 147.1, 146.6, 140.6, 140.5, 140.1, 139.0, 132.4, 130.12, 130.10, 129.54, 129.50, 128.9, 128.5, 128.41, 128.36, 128.3, 126.8, 116.2, 54.1, 30.4; LC/MS (ESI) *m/z* 699.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{36}H_{32}N_2O_9S_2$ [M - H]$^-$ 699.1476; found 699.1487.

2-(Benzyloxy)-5-nitrophenol (192). To a solution of 4-nitrobenzene-1,2-diol (2.0 g, 12.89 mmol) in tetrahydrofuran (3 mL) was added sodium hydride (60% dispersion in mineral oil, 516 mg, 12.89 mmol) at 0 °C. After stirring at 0 °C for 5 minutes, benzyl bromide (2.2 g, 12.89 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to water and

extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-15% ethyl acetate/hexane) to give the product as a pale yellow solid (2.4 g, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (m, 2H), 7.41-7.37 (m, 5H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 146.2, 142.1, 135.0, 128.9, 128.8, 127.9, 116.6, 111.1, 110.6, 71.5; LC/MS (ESI) *m/z* 244.1 $[M - H]^-$.

2-(2-(2-Methyl-5-nitrophenoxy)ethyl)isoindoline-1,3-dione (193a). Prepared as described in the experimental procedure of **40b** from 2-methyl-5-nitrophenol and and *N*-(2-bromoethyl)phthalimide to obtain the title compound as a white solid (126 mg, 12%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.89 (m, 2H), 7.87-7.84 (m, 2H), 7.74 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 4.36 (t, *J* = 5.6 Hz, 2H), 4.05 (t, *J* = 5.6 Hz, 2H), 2.12 (s, 3H); LC/MS (ESI) *m/z* 327.0 $[M + H]^+$.

2-(2-(2-Fluoro-5-nitrophenoxy)ethyl)isoindoline-1,3-dione (193b). Prepared as described in the experimental procedure of **40b** from 2-fluoro-5-nitrophenol and and *N*-(2-bromoethyl)phthalimide to obtain the title compound as a white solid (178 mg, 17%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01-7.99 (m, 1H), 7.89-7.83 (m, 5H), 7.49-7.44 (m, 1H), 4.45 (t, *J* = 5.6 Hz, 2H), 4.01 (t, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.6, 155.7 ($J_{C,F}$ = 254 Hz), 146.3 ($J_{C,F}$ = 12 Hz), 144.1, 134.5, 131.5, 123.1, 117.5 ($J_{C,F}$ = 9 Hz), 116.8 ($J_{C,F}$ = 21 Hz), 110.3 ($J_{C,F}$ = 4 Hz), 66.4; LC/MS (ESI) *m/z* 330.0 $[M]^-$.

2-(2-(2-(Benzyloxy)-5-nitrophenoxy)ethyl)isoindoline-1,3-dione (193c). Prepared as described in the experimental procedure of **40b** from intermediate **190** and and *N*-(2-bromoethyl)phthalimide to obtain the title compound as a white solid (467 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.77 (m, 4H), 7.74-7.69 (m, 2H), 7.38-7.35 (m, 5H), 6.90

(d, J = 8.8 Hz, 1H), 5.13 (s, 2H), 4.37-4.35 (m, 2H), 4.20-4.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 154.3, 148.2, 141.6, 135.8, 134.2, 132.2, 128.8, 128.3, 127.1, 123.5, 118.5, 112.5, 109.1, 71.1, 66.2, 37.1; LC/MS (ESI) *m/z* 419.2 $[M + H]^+$.

4-Methoxy-*N*-(2-(2-methyl-5-nitrophenoxy)ethyl)benzenesulfonamide (194a). To a solution of **193a** (126 mg, 0.39 mmol) in methanol (5 mL) and dichloromethane (3 mL) was added hydrazine monohydrate (58 mg, 1.16 mmol) at room temperature. The reaction mixture was stirred at 60 ℃ for overnight. The crude mixture was cooled to room temperature, added to sat. $NaHCO_3$, and then extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give 2-(2-methyl-5-nitrophenoxy)ethan-1-amine as a pale yellow oil (113 mg, quantitative); ^{1}H NMR (400 MHz, MeOD) δ 7.75 (dd, J = 8.0, 2.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 4.16 (t, J = 5.2 Hz, 2H), 3.15 (t, J = 5.2 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 158.4, 136.4, 131.8, 126.8, 116.8, 106.6, 70.4, 41.4, 16.6; LC/MS (ESI) *m/z* 197.1 $[M + H]^+$. To a solution of 2-(2-methyl-5-nitrophenoxy)ethan-1-amine (113 mg, 0.58 mmol) in dichloromethane (3 mL) were added pyridine (68 mg, 0.86mmol) and 4-methoxybenzenesulfonyl chloride (179 mg, 0.86 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. After the reaction was completed, the crude mixture was added to 1N HCl, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (60 mg, 28%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2H), 7.73 (dd, J = 8.4, 2.0 Hz, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 5.37 (s, 1H, NH), 4.03 (t, J =

5.2 Hz, 2H), 3.86 (s, 3H), 3.46-3.39 (m, 2H), 2.27 (s, 3H), 3.08-3.03 (m, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 156.4, 147.1, 135.2, 131.6, 130.8, 129.2, 116.3, 114.5, 105.6, 67.0, 55.7, 42.4, 16.7; LC/MS (ESI) *m/z* 367.1 $[M + H]^+$.

***N*-(2-(2-Fluoro-5-nitrophenoxy)ethyl)-4-methylbenzenesulfonamide (194b).** Prepared as described in the experimental procedure of **194a** from intermediate **193b** to obtain the title compound as a pale yellow solid (182 mg, 47% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91-7.86 (m, 2H), 7.88 (brs, 1H, NH), 7.69 (d, *J* = 8.4 Hz, 2H), 7.53-7.48 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.17 (t, *J* = 5.6 Hz, 2H), 3.18-3.16 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.6 ($J_{C,F}$ = 254 Hz), 146.4 ($J_{C,F}$ = 12 Hz), 144.1, 142.6, 137.6, 129.5, 126.4, 117.4 ($J_{C,F}$ = 8 Hz), 116.8 ($J_{C,F}$ = 20 Hz), 110.2 ($J_{C,F}$ = 3 Hz), 68.2, 41.6, 20.9; LC/MS (ESI) *m/z* 355.1 $[M + H]^+$.

***N*-(2-(2-(Benzyloxy)-5-nitrophenoxy)ethyl)-4-methylbenzenesulfonamide (194c).** Prepared as described in the experimental procedure of **194a** from intermediate **193c** to obtain 2-(2-(benzyloxy)-5-nitrophenoxy)ethan-1-amine as a pale yellow oil (351 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.77 (d, *J* = 2.8 Hz, 1H), 7.43-7.31 (m, 5H), 6.94 (d, *J* = 8.8 Hz, 1H), 5.21 (s, 2H), 4.10 (t, *J* = 5.2 Hz, 2H), 3.13 (t, *J* = 5.2 Hz, 2H), 1.69 (brs, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 148.8, 141.7, 135.9, 128.9, 128.5, 127.3, 118.0, 112.4, 108.9, 72.0, 71.2, 41.4; LC/MS (ESI) *m/z* 289.2 $[M + H]^+$. Prepared as described in the experimental procedure of **194a** from 2-(2-(benzyloxy)-5-nitrophenoxy)ethan-1-amine and 4-methylbenzenesulfonyl chloride to obtain the title compound as a pale yellow solid (288 mg, 56%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90-7.87 (m, 2H), 7.71 (brs, 1H, NH), 7.69 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.43-7.39 (m, 2H), 3.37-7.34 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.25 (dd, *J* =

9.2, 1.6 Hz, 1H), 5.28 (s, 2H), 4.10 (t, *J* = 5.2 Hz, 2H), 3.15-3.11 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.0, 147.7, 142.6, 140.7, 137.5, 136.1, 129.6, 128.5, 128.1, 127.6, 126.5, 118.1, 113.0, 108.8, 70.3, 67.9, 41.7, 20.9.

4-Methoxy-*N*-(2-(5-((4-methoxyphenyl)sulfonamido)-2-methylphenoxy)ethyl) benzenesulfonamide (195a). Prepared as described in the experimental procedure of **22b** from intermediate **194a** to obtain the title compound as a pale yellow solid (45 mg, 51% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.03 (s, 1H, NH), 6.95 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.56 (s, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.09 (t, *J* = 5.6 Hz, 1H, NH), 3.91-3.84 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.33-3.29 (m, 2H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.23, 163.16, 156.6, 135.5, 131.5, 131.1, 130.7, 129.6, 129.3, 124.0, 114.5, 114.3, 105.8, 66.6, 55.8, 55.7, 42.6, 15.8; LC/MS (ESI) *m/z* 507.2 $[M + H]^+$.

***N*-(4-Fluoro-3-(2-((4-methylphenyl)sulfonamido)ethoxy)phenyl)-4-methylbenzene-sulfonamide (195b).** Prepared as described in the experimental procedure of **22b** from intermediate **194b** to obtain the title compound as a pale yellow solid (203 mg, 87% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (brs, 1H, NH), 7.85 (t, *J* = 5.6 Hz, 1H, NH), 7.69 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.36-7.32 (m, 4H), 7.04 (dd, *J* = 11.2, 8.8 Hz, 1H), 6.78 (dd, *J* = 7.6, 2.4 Hz, 1H), 6.59-6.55 (m, 1H), 3.89 (t, *J* = 5.6 Hz, 2H), 3.11-3.07 (m, 2H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.6 ($J_{C,F}$ = 239 Hz), 145.9 ($J_{C,F}$ = 12 Hz), 143.3, 142.6, 137.5, 136.3, 134.3 ($J_{C,F}$ = 3 Hz), 129.64, 129.56, 126.7, 126.5, 116.2 ($J_{C,F}$ = 19 Hz), 113.0 ($J_{C,F}$ = 7 Hz), 107.8, 67.6, 41.7, 20.9; LC/MS (ESI) *m/z* 479.2 $[M + H]^+$.

***N*-(4-(Benzyloxy)-3-(2-((4-methylphenyl)sulfonamido)ethoxy)phenyl)-4-methyl benzenesulfonamide (195c).** Prepared as described in the experimental procedure of **22b** from **194c** to obtain the title compound as a pale yellow solid (317 mg, 89% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (brs, 1H, NH), 7.81 (brs, 1H, NH), 7691 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.39-7.30 (m, 9H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.53 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.98 (s, 2H), 3.84 (t, *J* = 5.6 Hz, 1H, NH), 3.07-3.03 (m, 2H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.2, 145.3, 143.1, 142.7, 137.5, 137.1, 136.6, 131.3, 129.6, 129.5, 128.3, 127.7, 127.6, 126.7, 126.5, 115.2, 114.1, 108.5, 70.4, 67.6, 41.8, 20.9; LC/MS (ESI) *m/z* 567.3 $[M + H]^+$.

Ethyl *N*-(2-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)-2-methyl phenoxy)ethyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (196a). Prepared as described in the experimental procedure of **15a** from intermediate **195a** to obtain the title compound as a colorless oil (40 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 6.99-6.92 (m, 5H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.62 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.34 (s, 2H), 4.24 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.05-3.99 (m, 4H), 3.86 (s, 3H), 3.85 (s, 3H), 3.63 (t, *J* = 5.2 Hz, 2H), 2.10 (s, 3H), 1.22 (t, *J* = 6.8 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 169.0, 163.23, 163.17, 156.5, 138.7, 131.5, 130.8, 130.7, 130.2, 129.6, 126.9, 120.7, 114.3, 114.0, 112.0, 67.7, 61.6, 61.4, 55.8, 55.7, 53.0, 49.9, 47.6, 16.2, 14.2, 14.1; LC/MS (ESI) *m/z* 679.2 $[M + H]^+$.

Ethyl *N*-(2-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-fluoro-phenoxy)ethyl)-*N*-tosylglycinate (196b). Prepared as described in the experimental procedure of **15a** from intermediate **195b** to obtain the title compound as a colorless oil (183 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4

Hz, 2H), 7.31-7.27 (m, 4H), 7.04 (dd, *J* = 10.8, 8.8 Hz, 1H), 6.83 (dd, *J* = 7.6, 2.4 Hz, 1H), 6.72-6.68 (m, 1H), 4.35 (s, 2H), 4.25 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.10 (t, *J* = 5.2 Hz, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.65 (t, *J* = 5.2 Hz, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.8, 152.1 ($J_{C,F}$ = 247 Hz), 146.5 ($J_{C,F}$ = 11 Hz), 144.2, 143.8, 136.8, 136.1 ($J_{C,F}$ = 4 Hz), 135.8, 129.8, 129.6, 128.0, 127.5, 122.0 ($J_{C,F}$ = 7 Hz), 116.2 ($J_{C,F}$ = 19 Hz), 116.1 ($J_{C,F}$ = 2 Hz), 69.3, 61.7, 61.4, 53.0, 50.1, 47.6, 21.7, 21.6, 14.2, 14.1; LC/MS (ESI) *m/z* 651.3 $[M + H]^+$.

Ethyl *N*-(4-(benzyloxy)-3-(2-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamide)ethoxy)phenyl)-*N*-tosylglycinate (196c). Prepared as described in the experimental procedure of **15a** from **195c** to obtain the title compound as a colorless oil (171 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.40-7.31 (m, 5H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.73 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 5.02 (s, 2H), 4.34 (s, 2H), 4.26 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 4.03 (t, *J* = 5.2 Hz, 2H), 3.94 (q, *J* = 7.2 Hz, 2H), 3.62 (t, *J* = 5.2 Hz, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 169.0, 148.6, 148.2, 143.9, 143.6, 136.9, 136.6, 136.0, 132.8, 129.7, 129.5, 128.7, 128.1, 128.0, 127.6, 127.4, 122.3, 114.6, 113.2, 71.0, 69.2, 61.5, 61.2, 53.1, 50.0, 47.5, 21.7, 21.6, 14.2, 14.1; LC/MS (ESI) *m/z* 739.3 $[M + H]^+$.

***N*-(2-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-methylphenoxy) ethyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (197a).** Prepared as described in the experimental procedure of **16a** from intermediate **196a** to obtain the title compound as a pale yellow solid (28 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (brs, 2H, CO_2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 6.95-6.89 (m, 5H), 6.30 (s, 1H), 6.53 (d, *J* =

7.6 Hz, 1H), 4.44 (s, 2H), 4.28 (s, 2H), 4.03-4.00 (m, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.59-3.56 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 173.9, 163.28, 163.25, 156.3, 138.4, 130.89, 130.86, 130.2, 130.0, 129.5, 127.2, 120.7, 114.5, 114.1, 112.3, 67.2, 55.8, 52.7, 50.0, 48.1, 16.0; LC/MS (ESI) *m/z* 621.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_2O_{11}S_2$ $[M - H]^-$ 621.1218; found 621.1223.

***N*-(2-(5-((*N*-(Carboxymethyl)-4-methylphenyl)sulfonamido)-2-fluorophenoxy) ethyl)-*N*-tosylglycine (197b).** Prepared as described in the experimental procedure of **16a** from **196b** to obtain the title compound as a white solid (69 mg, 72%); ^{1}H NMR (400 MHz, MeOD) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.02-6.97 (m, 1H), 6.80-6.75 (m, 2H), 4.38 (s, 2H), 4.17 (s, 2H), 4.02 (t, *J* = 5.4 Hz, 2H), 3.63 (t, *J* = 5.4 Hz, 2H), 2.43 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.4, 172.1, 153.2 ($J_{C,F}$ = 246 Hz), 147.6 ($J_{C,F}$ = 10 Hz), 145.7, 145.1, 138.3, 137.4 ($J_{C,F}$ = 3 Hz), 137.0, 130.8, 130.7, 129.0, 128.3, 123.3 ($J_{C,F}$ = 7 Hz), 116.95 ($J_{C,F}$ = 3 Hz), 116.90 ($J_{C,F}$ = 20 Hz), 69.6, 53.6, 50.9, 21.54, 21.48; LC/MS (ESI) *m/z* 595.2 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{26}H_{27}FN_2O_9S_2$ $[M + H]^+$ 595.1215; found 595.1218.

Ethyl *N*-(2-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-hydroxy phenoxy)ethyl)-*N*-tosylglycinate (198). Prepared as described in the experimental procedure of **73** from intermediate **196c** to obtain the title compound as a white solid (137 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.64 (brs, 1H, OH), 6.47 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.32 (s, 2H), 4.16-4.05 (m, 8H), 3.62 (t, *J* = 4.8 Hz, 2H), 2.41 (s, 3H), 2.41 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 169.0, 146.6, 145.5, 144.1, 143.8,

136.2, 136.0, 131.5, 129.9, 129.4, 128.0, 127.6, 122.2, 115.0, 114.6, 66.6, 61.9, 61.5, 53.2, 49.5, 47.8, 21.7, 14.2, 14.1; LC/MS (ESI) *m/z* 649.3 $[M + H]^+$.

***N*-(4-Hydroxy-3-(2-((*N*-(2-methoxy-2-oxoethyl)-4-methylphenyl)sulfonamido) ethoxy)phenyl)-*N*-tosylglycine (199).** Prepared as described in the experimental procedure of **16a** from **198** to obtain the title compound as a white solid (39 mg, 71%); ^{1}H NMR (400 MHz, MeOD) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 4H), 6.69-6.60 (m, 3H), 5.49 (bss, 1H, OH), 4.33 (s, 2H), 4.19 (s, 2H), 3.98 (t, *J* = 5.4 Hz, 2H), 3.60 (t, *J* = 5.4 Hz, 2H), 2.42 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 172.6, 172.3, 148.3, 147.3, 145.4, 145.1, 138.2, 137.2, 132.6, 130.8, 130.6, 129.0, 128.4, 123.9, 116.2, 115.7, 68.9, 53.9, 50.6, 21.53, 21.48; LC/MS (ESI) *m/z* 591.2 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{26}H_{28}N_2O_{10}S_2$ $[M - H]^-$ 591.1113; found 591.1121.

1-(Benzyloxy)-2-iodo-4-nitrobenzene (200). Prepared as described in the experimental procedure of **107a** from 4-nitrophenol to obtain 2-iodo-4-nitrophenol as a pale yellow solid. The resulting crude compound was used for the next reaction without further purification. Prepared as described in the experimental procedure of **36** from 2-iodo-4-nitrophenol and benzyl bromide to obtain the title compound as a pale yellow solid (604 mg, 12% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 2.8 Hz, 1H), 8.28 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.43 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.39-7.34 (m, 1H), 7.28 (d, *J* = 9.2 Hz, 1H), 5.36 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 141.5, 135.7, 134.1, 128.6, 128.1, 127.4, 125.8, 112.3, 86.8, 71.1.

***(E)*-*N*-(3-(2-(Benzyloxy)-5-nitrophenyl)allyl)-4-methylbenzenesulfonamide (201).** Prepared as described in the experimental procedure of **108a** from intermediate **200** and *N*-allyl-*p*-toluenesulfonamide to obtain the title compound as a pale yellow solid (162 mg,

45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.44-7.36 (m, 5H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 1H), 6.80 (d, *J* = 15.6 Hz, 1H), 6.16-6.09 (m, 1H), 5.19 (s, 2H), 4.66 (t, *J* = 6.0 Hz, 1H, NH), 3.81-3.78 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 143.9, 141.7, 137.4, 135.5, 129.9, 129.0, 128.7, 128.2, 127.5, 127.4, 126.6, 126.0, 124.8, 122.7, 112.1, 71.2, 45.7, 21.6; LC/MS (ESI) *m/z* 437.1 $[M - H]^-$.

***(E)-N*-(4-(Benzyloxy)-3-(3-((4-methylphenyl)sulfonamido)prop-1-en-1-yl)phenyl)-4-methylbenzenesulfonamide (202).** Prepared as described in the experimental procedure of **22b** from intermediate **201** to obtain the title compound as a pale yellow solid (113 mg, 48% over 2 steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (brs, 1H, NH), 7.77 (t, *J* = 6.0 Hz, 1H, NH), 7.67 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.41-7.37 (m, 4H), 7.35-7.31 (m, 5H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.63 (d, *J* = 16.0 Hz, 1H), 5.91-5.84 (m, 1H), 5.03 (s, 2H), 3.54-3.51 (m, 2H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.4, 143.1, 142.6, 137.8, 136.9, 136.6, 130.6, 129,9, 129.6, 128.4, 127.8, 127.4, 126.9, 126.7, 126.5, 125.6, 125.4, 122.0, 119.9, 113.4, 69.7, 44.8, 20.9; LC/MS (ESI) *m/z* 563.3 $[M + H]^+$.

Ethyl *(E)-N*-(4-(benzyloxy)-3-(3-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)prop-1-en-1-yl)phenyl)-*N*-tosylglycinate (203). Prepared as described in the experimental procedure of **15a** from intermediate **202** to obtain the title compound as a pale yellow oil (136 mg, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.34-7.33 (m, 5H), 7.26-7.22 (m, 4H), 7.07 (d, *J* = 2.8 Hz, 1H), 7.03 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.69 (d, *J* = 16.0 Hz, 1H), 5.88-5.81 (m, 1H), 5.00 (s, 2H), 4.30 (s, 2H), 4.13-4.06 (m, 4H), 3.99-3.96 (m, 4H), 2.40 (s, 3H),

2.38 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.8, 155.6, 144.0, 143.6, 137.1, 136.6, 136.2, 132.8, 130.1, 129.7, 129.5, 128.8, 128.7, 128.2, 128.0, 127.8, 127.5, 127.4, 126.3, 125.3, 112.8, 70.6, 61.5, 61.3, 53.0, 50.6, 47.1, 21.63, 21.58, 14.2, 14.1; LC/MS (ESI) *m/z* 735.3 $[M + H]^+$.

Ethyl *N*-(3-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-hydroxyphenyl)propyl)-*N*-tosylglycinate (204). Prepared as described in the experimental procedure of **73** from intermediate **203** to obtain the title compound as a pale yellow solid (68 mg, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.38 (brs, 1H, OH), 4.32 (s, 2H), 4.15-4.09 (m, 4H), 3.96 (s, 2H), 3.23 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.40 (s, 6H), 1.73-1.70 (m, 2H), 1.22-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.1, 154.2, 143.7, 136.4, 136.2, 132.0, 131.2, 129.8, 129.5, 128.4, 128.1, 128.0, 127.5, 116.2, 61.8, 61.5, 53.2, 49.0, 48.9, 28.3, 27.3, 21.7, 14.2, 14.1; LC/MS (ESI) *m/z* 647.3 $[M + H]^+$.

***N*-(3-(5-((*N*-(Carboxymethyl)-4-methylphenyl)sulfonamido)-2-hydroxyphenyl) propyl)-*N*-tosylglycine (205).** Prepared as described in the experimental procedure of **16a** from intermediate **204** to obtain the title compound as a white solid (35 mg, 56%); ^{1}H NMR (400 MHz, MeOD) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.35-7.31 (m, 4H), 6.87 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 1H), 4.31 (s, 2H), 3.99 (s, 2H), 3.19 (d, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 2.41 (s, 3H), 2.39-2.37 (m, 2H), 1.72-1.65 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ 172.5, 172.4, 156.4, 145.2, 144.9, 138.2, 137.2, 132.3, 131.6, 130.7, 130.5, 129.52, 129.47, 129.0, 128.4, 116.0, 54.0, 28.6, 28.0,

21.52, 21.47; LC/MS (ESI) *m/z* 589.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_2O_9S_2$ [M - H]$^-$ 589.1320; found 589.1326.

***tert*-Butyl *N*-(4-(benzyloxy)-3-(2-((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl) sulfonamido)ethyl)phenyl)-*N*-tosylglycinate (206).** Prepared as described in the experimental procedure of **40b** from intermediate **187f** and *tert*-butyl 2-bromoacetate to obtain the title compound as a colorless oil (385 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.40-7.30 (m, 5H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.07 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.87 (d, *J* = 2.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 4.99 (s, 2H), 4.22 (s, 2H), 3.80 (s, 2H), 3.39 (t, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 1.39 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 167.9, 156.4, 143.7, 143.2, 137.4, 136.7, 136.2, 132.7, 131.1, 129.6, 129.5, 129.2, 128.8, 128.2, 127.9, 127.7, 127.42, 127.37, 111.8, 82.2, 82.0, 70.3, 53.7, 49.2, 48.1, 30.2, 28.1, 28.0, 21.7, 21.6 ; LC/MS (ESI) *m/z* 796.5 [M + H + H_2O]$^+$.

***tert*-Butyl *N*-(4-(2-(*tert*-butoxy)-2-oxoethoxy)-3-(2-((*N*-(2-(*tert*-butoxy)-2-oxoethyl) -4-methylphenyl)sulfonamido)ethyl)phenyl)-*N*-tosylglycinate (207).** Prepared as described in the experimental procedure of **73** from intermediate **206** to obtain *tert*-butyl *N*-(5-((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-hydroxyphenethyl) -*N*-tosylglycinate as a white solid (306 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.58 (brs, 1H, OH), 4.20 (s, 2H), 3.89 (s, 2H), 3.33 (t, *J* = 7.6 Hz, 2H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.40 (s, 6H), 1.39 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 168.0, 154.7, 143.7, 143.6, 136.6, 136.1, 132.0, 131.4, 129.7, 129.5, 128.9, 127.9, 127.5, 125.0, 116.4,

82.5, 82.2, 53.8, 50.0, 48.8, 30.5, 28.1, 28.0, 21.63, 21.59; LC/MS (ESI) *m/z* 577.3 [M + H - C_8H_{16}]$^+$. Prepared as described in the experimental procedure of **40b** from *tert*-butyl *N*-(5-((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methylphenyl)sulfonamido)-2-hydroxyphenethyl) -*N*-tosylglycinate and *tert*-butyl 2-bromoacetate to obtain the title compound as a colorless oil (93 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 4H), 7.08 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 4.44 (s, 2H), 4.21 (s, 2H), 3.90 (s, 2H), 3.44 (t, *J* = 7.6 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 2.40 (s, 3H), 1.44 (s, 9H), 1.39 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 167.9, 167.5, 155.6, 143.8, 143.2, 137.5, 136.1, 133.2, 131.2, 129.6, 129.5, 129.2, 128.0, 127.9, 127.5, 111.3, 82.5, 82.2, 81.9, 65.7, 53.7, 49.2, 48.1, 30.3, 28.2, 28.11, 28.06, 21.7, 21.6; LC/MS (ESI) *m/z* 635.3 [M + H - $C_{12}H_{24}$]$^+$.

***N*-(4-(Carboxymethoxy)-3-(2-((*N*-(carboxymethyl)-4-methylphenyl)sulfonamido) ethyl)phenyl)-*N*-tosylglycine (208).** Prepared as described in the experimental procedure of **76a** from intermediate **207** to obtain the title compound as a white solid (62 mg, 84%); ^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.04 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 4.58 (s, 2H), 4.33 (s, 2H), 3.97 (s, 2H), 3.46 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.42 (s, 6H); ^{13}C NMR (100 MHz, MeOD) δ 172.29, 172.27, 172.25, 157.0, 145.4, 144.9, 138.6, 137.2, 134.2, 132.4, 130.7, 130.6, 130.0, 129.0, 128.9, 128.5, 112.6, 66.0, 53.8, 53.7, 30.5, 21.54, 21.49; LC/MS (ESI) *m/z* 633.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{28}H_{30}N_2O_{11}S_2$ [M - H]$^-$ 633.1218; found 633.1227.

3-Bromo-2-methyl-5-nitrobenzoic acid (209). To a solution of 2-methyl-5-nitrobenzoic acid (1.5 g, 8.28 mmol) in con. H_2SO_4 (8 mL) was added *N*-bromosuccinimide (1.9 g, 9.94

mmol) at 60 °C for 30 minutes. The reaction mixture was stirred at 60 °C for overnight. The crude mixture was cooled to room temperature. The precipitate was washed with water and hexande, and then filtered to give the product as a dark yellow solid (1.1 g, 52%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, *J* = 2.4 Hz, 1H), 8.44 (d, *J* = 2.4 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 145.5, 145.1, 134.4, 129.1, 126.5, 123.3, 20.7; LC/MS (ESI) *m/z* 257.9 [M(^{79}Br) - H]$^{-}$, 259.9 [M(^{81}Br) - H]$^{-}$.

(3-Bromo-2-methyl-5-nitrophenyl)methanol (210). Prepared as described in the procedure of **30** from **209** to obtain the title compound as a pale yellow oil (850 mg, 90%); ^{1}H NMR (400 MHz, MeOD) δ 8.25 (s, 1H), 8.23 (s, 1H), 5.65 (t, *J* = 5.2 Hz, 1H, OH), 4.61 (d, *J* = 5.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 145.9, 144.5, 142.3, 124.8, 124.5, 119.6, 60.7, 18.0; LC/MS (ESI) m/z 246.1 [M(^{79}Br) + H]$^{+}$, 248.1 [M(^{81}Br) + H]$^{+}$.

2-(2-Bromo-5-nitrophenyl)acetonitrile (211a). Prepared as described in the procedure of **134a** from **30** to obtain the title compound as a pale yellow solid (407 mg, 83% over 2 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.11 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 134.4, 132.2, 131.0, 125.1, 124.7, 115.7, 25.2; LC/MS (ESI) *m/z* 238.9 [M(^{79}Br) - H]$^{-}$, 240.9 [M(^{81}Br) - H]$^{-}$.

2-(3-Bromo-2-methyl-5-nitrophenyl)acetonitrile (211b). Prepared as described in the experimental procedure of **134a** from intermediate **210** to obtain the title compound as a pale yellow solid (610 mg, 69% over 2 steps); ^{1}H NMR (400 MHz, MeOD) δ 8.44 (d, *J* = 2.4 Hz, 1H), 8.29 (d, *J* = 2.43.30 (s, 2H), 2.55 (s, 3H) Hz, 1H),; ^{13}C NMR (100 MHz, MeOD) δ 147.8, 145.4, 134.6, 128.2, 127.0, 123.8, 118.1, 19.9; LC/MS (ESI) *m/z* 253.0 [M(^{79}Br) - H]$^{-}$, 255.0 [M(^{81}Br) - H]$^{-}$.

2-(4-Amino-[1,1'-biphenyl]-2-yl)acetonitrile (212a). Prepared as described in the experimental procedure of **22b** from **211a** to obtain the title compound as a pale yellow solid (27 mg, 15%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.17-7.16 (m, 2H), 7.05 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.60 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 140.2, 131.6, 129.4, 128.6, 127.3, 117.9, 115.0, 114.8, 114.6, 114.3, 22.1; LC/MS (ESI) *m/z* 209.2 $[M + H]^+$.

2-(5-Amino-2-methyl-[1,1'-biphenyl]-3-yl)acetonitrile (212b). Prepared as described in the experimental procedure of **22b** from **211b** to obtain 2-(5-amino-3-bromo-2-methylphenyl)acetonitrile as a pale brown solid (152 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.4 Hz, 1H), 6.67 (d, *J* = 2.4 Hz, 1H), 3.73 (s, 2H, NH), 3.62 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 130.6, 126.8, 124.9, 118.9, 117.5, 114.9, 23.2, 18.2. Prepared as described in the experimental procedure of **22b** from 2-(5-amino-3-bromo-2-methylphenyl)acetonitrile to obtain the title compound as a pale yellow solid (106 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.34 (m, 3H), 7.28-7.26 (m, 2H), 6.77 (d, *J* = 2.4 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 3.65 (s, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.4, 114.3, 141.9, 130.0, 129.2, 128.2, 127.1, 123.2, 118.0, 116.8, 114.7, 22.6, 15.7; LC/MS (ESI) *m/z* 223.2 $[M + H]^+$.

***N*-(2-(Cyanomethyl)-[1,1'-biphenyl]-4-yl)-4-methoxybenzenesulfonamide (213a).** Prepared as described in the experimental procedure of **52** from intermediate **212a** to obtain the title compound as a pale yellow oil (26 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 9.2 Hz, 2H), 7.44-7.36 (m, 3H), 7.23-7.20 (m, 3H), 7.17 (s, 2H), 6.95 (d, *J* = 9.2 Hz, 2H), 3.84 (s, 3H), 3.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 139.2, 138.5, 137.0,

131.6, 130.7, 129.7, 129.1, 128.9, 128.0, 121.0, 120.6, 118.0, 114.6, 55.8, 22.2; LC/MS (ESI) *m/z* 379.1 $[M + H]^+$.

***N*-(5-(Cyanomethyl)-6-methyl-[1,1'-biphenyl]-3-yl)-4-methoxybenzenesulfon-amide (213b).** Prepared as described in the experimental procedure of **52** from intermediate **212b** to obtain the title compound as a pale yellow solid (132 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.8 Hz, 2H), 7.37-7.31 (m, 3H), 7.14-7.12 (m, 3H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 3.70 (s, 2H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 144.3, 140.7, 135.0, 130.5, 130.4, 130.3, 129.6, 129.1, 128.2, 127.4, 122.6, 120.6, 117.5, 114.3, 55.6, 22.6, 16.2; LC/MS (ESI) *m/z* 393.2 $[M + H]^+$.

Methyl 1-hydroxy-2-naphthoate (214). To a solution of 1-hydroxy-2-naphthoic acid (1.0 g, 5.31 mmol) in methanol (30 mL) was added con. H_2SO_4 (0.5 mL) at room temperature for 30 minutes. The reaction mixture was stirred at 100 ℃ for overnight. After the reaction was completed, the crude mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-30% ethyl acetate/hexane) to give the product as a white solid (811 mg, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.88 (s, 1H, OH), 8.31 (d, *J* = 7.6 Hz, 1H), 7.65-7.63 (m, 2H), 7.48 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.40 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 161.0, 137.3, 129.5, 127.6, 125.8, 124.9, 124.3, 124.0, 118.7, 105.7, 52.4; LC/MS (ESI) *m/z* 203.1 $[M + H]^+$.

Methyl 1-hydroxy-4-nitro-2-naphthoate (215). To a solution of **214** (950 mg, 4.70 mmol) in acetic acid (3.2 mL) was added nitric acid (70% in H_2O, 0.3 mL, 5.17 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. After the reaction was completed, the precipitate was filtered to give the product as a yellow solid

(623 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, 1H, OH), 8.79 (s, 1H), 8.74 (d, *J* = 8.8 Hz, 1H), 8.51 (d, *J* = 8.8 Hz, 1H), 7.87-7.82 (m, 1H), 7.68-7.64 (m, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 165.2, 138.1, 132.8, 129.2, 127.4, 125.7, 125.3, 124.7, 123.9, 104.1, 53.2; LC/MS (ESI) *m/z* 246.1 $[M - H]^-$.

1-Bromo-4-nitro-2-naphthoic acid (216). To a solution of **215** (455 mg, 1.84 mmol) in dichloromethane (9 mL) were added triethylamine (261 mg, 2.58 mmol) and trifluoromethanesulfonic anhydride (623 mg, 2.21 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 minutes. After the reaction was completed, the crude mixture was added to water, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatograph (0-10% ethyl acetate/hexane) to give methyl 4-nitro-1-(((trifluoromethyl)sulfonyl)oxy)-2-naphthoate as a pale yellow solid (655 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.60 (d, *J* = 8.8 Hz, 1H), 8.32 (d, *J* = 8.8 Hz, 1H), 7.96-7.92 (m, 1H), 7.88-7.84 (m, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 147.6, 132.5, 129.8, 128.1, 127.8, 124.7, 123.8, 123.2, 120.7, 53.5. To a solution of methyl 4-nitro-1-(((trifluoromethyl)sulfonyl)oxy)-2-naphthoate (655 mg, 1.73 mmol) in *N*,*N*-dimethylformamide (2 mL) was added lithium bromide (900 mg, 10.36 mmol) at room temperature. The reaction mixture was stirred at 115 °C for overnight. The crude mixture was cooled to room temperature. The aqueous solution was acidified with 6 N HCl until the pH reached around 1 and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the product as a beige solid (449 mg, 88%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.10 (brs, 1H, CO_2H), 8.57-8.54 (m, 1H), 8.47 (s, 2H), 8.38-8.36 (m, 1H), 7.98-7.94 (m, 2H); ^{13}C NMR

(100 MHz, DMSO-d_6) δ 166.5, 145.9, 132.3, 132.3, 131.3, 130.1, 128.7, 126.6, 124.9, 123.0, 122.8; LC/MS (ESI) *m/z* 294.0 [M(^{79}Br) - H]$^-$, 296.0 [M(^{81}Br) - H]$^-$.

(1-Bromo-4-nitronaphthalen-2-yl)methanol (217). Prepared as described in the experimental procedure of **30** from intermediate **216** to obtain the title compound as a pale yellow oil (346 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52-8.42 (m, 2H), 8.41 (s, 1H), 7.77-7.70 (m, 2H), 5.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 133.0, 129.8, 129.0, 128.0, 127.7, 125.3, 123.5, 122.9, 64.9.

2-(1-Bromo-4-nitronaphthalen-2-yl)acetonitrile (218). Prepared as described in the experimental procedure of **134a** from intermediate **217** to obtain (1-bromo-4-nitronaphthalen-2-yl)methyl methanesulfonate as a pale yellow solid (226 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53-8.49 (m, 2H), 8.28 (s, 1H), 7.83-7.76 (m, 2H), 5.30 (s, 2H), 3.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 130.9, 130.8, 130.5, 130.2, 129.6, 128.3, 125.8, 123.7, 123.4, 69.8, 38.3. Prepared as described in the experimental procedure of **134a** from (1-bromo-4-nitronaphthalen-2-yl)methyl methanesulfonate to obtain the title compound as a pale yellow solid (41 mg, 22%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54-8.43 (m, 3H), 8.30 (s, 1H), 7.83-7.78 (m, 1H), 4.15 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 130.7, 129.8, 129.0, 128.4, 127.5, 125.4, 123.7, 123.5, 122.9, 116.0, 26.2; LC/MS (ESI) *m/z* 291.0 [M(^{79}Br) + H]$^+$, 293.0 [M(^{81}Br) + H]$^+$.

***N*-(4-Bromo-3-(cyanomethyl)naphthalen-1-yl)-4-methoxybenzenesulfonamide (219).** Prepared as described in the experimental procedure of **22b** from intermediate **218** to obtain the title compound as a pale yellow solid (27 mg, 44% over 2 steps); ^{1}H NMR (400 MHz, MeOD) δ 8.28 (d, *J* = 8.8 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.64-7.58 (m, 3H), 7.53-7.47 (m, 1H), 7.25 (s, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.92 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100

MHz, MeOD) δ 133.0, 130.5, 130.0, 129.1, 129.0, 128.4, 128.1, 124.9, 124.8, 115.3, 115.2, 56.2, 26.0; LC/MS (ESI) *m/z* 431.0 [M(^{79}Br) + H]$^+$, 433.0 [M(^{81}Br) + H]$^+$.

4-Methoxy-*N*-(2-(4-((4-methoxyphenyl)sulfonamido)-[1,1'-biphenyl]-2-yl)ethyl) benzenesulfonamide (220a). Prepared as described in the experimental procedure of **186a** from intermediate **213a** to obtain the title compound as a white solid (25 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.32-7.31 (m, 4H), 7.08-7.06 (m, 2H), 7.03-7.01 (m, 2H), 6.98 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.88 (t, *J* = 6.8 Hz, 2H), 2.66 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 163.0, 140.5, 139.1, 136.7, 136.3, 131.42, 131.39, 130.8, 129.7, 129.3, 129.2, 128.4, 127.3, 122.3, 119.3, 114.5, 114.4, 55.8, 43.4, 33.1; LC/MS (ESI) *m/z* 553.2 [M + H]$^+$.

4-Methoxy-*N*-(2-(5-((4-methoxyphenyl)sulfonamido)-2-methyl-[1,1'-biphenyl]-3-yl)ethyl)benzenesulfonamide (220b). Prepared as described in the experimental procedure of **186a** from intermediate **213b** to obtain *N*-(5-(2-aminoethyl)-6-methyl-[1,1'-biphenyl]-3-yl)-4-methoxybenzenesulf-onamide as a brown oil (113 mg, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.42-7.38 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 3.79 (s, 3H), 2.66-2.61 (m, 4H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2, 142.4, 141.7, 139.6, 135.8, 131.8, 128.9, 128.8, 128.1, 126.9, 120.3, 119.5, 114.2, 55.6, 42.0, 37.4, 15.6; LC/MS (ESI) *m/z* 397.2 [M + H]$^+$. Prepared as described in the experimental procedure of **186a** from *N*-(5-(2-aminoethyl)-6-methyl-[1,1'-biphenyl]-3-yl)-4-methoxybenzene sulfonamide to obtain the title compound as a white solid (46 mg, 30%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.8 Hz, 4H), 7.36-7.30 (m, 4H), 7.17 (brs,

1H, NH), 7.09 (d, *J* = 8.0 Hz, 2H), 6.94-6.88 (m, 5H), 6.81 (d, *J* = 2.4 Hz, 1H), 4.95 (t, *J* = 6.0 Hz, 1H, NH), 3.83 (s, 3H), 3.80 (s, 3H), 3.16-3.11 (m, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 163.0, 144.0, 141.5, 138.0, 134.2, 131.5, 130.9, 130.6, 129.8, 129.3, 129.2, 128.2, 127.1, 121.8, 121.7, 114.43, 114.38, 55.7, 42.8, 34.0, 16.1; LC/MS (ESI) *m/z* 567.2 $[M + H]^+$.

***N*-(4-Bromo-3-(2-((4-methoxyphenyl)sulfonamido)ethyl)naphthalen-1-yl)-4-methoxybenzenesulfonamide (220c).** Prepared as described in the experimental procedure of **186a** from intermediate **219** to obtain the title compound as a pale yellow solid (18 mg, 36%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (brs, 1H, NH), 8.13 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.69-7.58 (m, 6H), 7.51-7.47 (m, 1H), 7.08 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 4H), 3.76 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4, 162.0, 135.9, 132.5, 132.1, 131.1, 129.0, 128.6, 128.1, 126.6, 125.2, 123.7, 114.2, 114.2, 55.6, 55.5, 54.9, 36.8; LC/MS (ESI) *m/z* 605.0 $[M(^{79}Br) + H]^+$, 607.0 $[M(^{81}Br) + H]^+$.

Ethyl *N*-(2-(4-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)-[1,1'-bi-phenyl]-2-yl)ethyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (221a). Prepared as described in the experimental procedure of **15a** from **220a** to obtain the title compound as a colorless oil (28 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.40-7.34 (m, 3H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.15-7.10 (m, 2H), 7.06 (d, *J* = 1.6 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.41 (s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.62 (s, 2H), 3.10 (t, *J* = 8.0 Hz, 2H), 2.76 (t, *J* = 8.0 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.94, 168.85, 163.3, 163.0, 142.0, 140.4, 139.5,

136.8, 131.6, 131.1, 130.8, 130.1, 129.9, 129.5, 129.1, 128.4, 127.5, 127.0, 114.2, 61.6, 61.3, 55.8, 55.7, 52.8, 49.0, 48.1, 32.4, 14.22, 14.16; LC/MS (ESI) *m/z* 725.2 $[M + H]^+$.

Ehyl *N*-(2-(5-((*N*-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl)sulfonamido)-2-methyl-[1,1'-biphenyl]-3-yl)ethyl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (221b). Prepared as described in the experimental procedure of **15a** from intermediate **220b** to obtain the title compound as a colorless oil (48 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.37-7.30 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 2.4 Hz, 1H), 4.33 (s, 2H), 4.14-4.07 (m, 4H), 4.04 (s, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 3.36 (t, *J* = 8.0 Hz, 2H), 2.91-2.89 (m, 2H), 2.11 (s, 3H), 1.24-1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.9, 163.2, 163.1, 143.9, 141.3, 138.2, 137.4, 134.2, 131.5, 130.6, 130.1, 129.6, 129.2, 129.1, 128.3, 128.2, 127.2, 114.2, 114.0, 61.5, 55.7, 52.7, 48.8, 33.3, 16.4, 14.2; LC/MS (ESI) *m/z* 739.2 $[M + H]^+$.

***tert*-Butyl *N*-(4-bromo-3-(2-((N-(2-(*tert*-butoxy)-2-oxoethyl)-4-methoxyphenyl) sulfonamido)ethyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (221c).** Prepared as described in the procedure of **75a** from **220c** to obtain the title compound as a colorless oil (14 mg, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.61-7.54 (m, 2H), 7.13 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.51-4.47 (m, 1H), 4.22-4.19 (m, 1H), 4.04-3.99 (m, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.48-3.44 (m, 2H), 3.18-3.11 (m, 1H), 3.06-3.01 (m, 1H), 1.41 (s, 9H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 167.7, 163.5, 162.9, 136.7, 135.5, 133.6, 132.2, 131.8, 130.4, 130.1, 129.6, 128.3,

127.6, 127.3, 125.4, 124.7, 114.3, 114.2, 82.4, 82.3, 55.8, 55.7, 54.1, 49.3, 48.0, 36.5, 28.13, 28.07; LC/MS (ESI) *m/z* 721.0 [M(^{79}Br) + H-C_8H_{16}]$^+$, 723.1 [M(^{81}Br) + H- C_8H_{16}]$^+$.

***N*-(2-(4-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-[1,1'-biphenyl]-2-yl)ethyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (222a).** Prepared as described in the experimental procedure of **16a** from intermediate **221a** to obtain the title compound as a white solid (19 mg, 74%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (brs, 2H, CO_2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.45-7.39 (m, 3H), 7.23-7.21 (m, 2H), 7.11-7.06 (m, 5H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.39 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.72 (s, 2H), 3.06 (t, *J* = 8.0 Hz, 2H), 2.68-2.64 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 169.9, 162.7, 162.3, 140.7, 139.8, 139.1, 136.3, 131.2, 130.3, 130.1, 129.5, 128.9, 128.7, 128.6, 128.3, 127.3, 125.9, 114.3, 114.2, 55.6, 51.9, 48.9, 48.0, 31.3; LC/MS (ESI) *m/z* 667.1 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{32}H_{32}N_2O_{10}S_2$ [M - H]$^-$ 667.1426; found 667.1432.

***N*-(2-(5-((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-2-methyl-[1,1'-biphenyl]-3-yl)ethyl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (222b).** Prepared as described in the experimental procedure of **16a** from **221b** to obtain the title compound as a white solid (21 mg, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.38-7.32 (m, 3H), 7.11-7.09 (m, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 2.0 Hz, 1H), 4.35 (s, 2H), 4.06 (s, 2H), 3.85 (s, 6H), 3.39 (t, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 163.4, 163.3, 144.1, 141.3, 138.4, 137.0, 134.7, 131.2, 130.1, 130.0, 129.7, 129.3, 128.3, 127.6, 127.3, 114.5, 114.3, 55.8, 52.5, 49.1, 48.9, 33.4, 16.6; LC/MS (ESI) *m/z* 681.2 [M - H]$^-$; HRMS (ESI) *m/z* calcd for $C_{33}H_{34}N_2O_{10}S_2$ [M - H]$^-$ 681.1582; found 681.1589.

***N*-(4-Bromo-3-(2-((*N*-(carboxymethyl)-4-methoxyphenyl)sulfonamido)ethyl) naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (222c).** Prepared as described in the experimental procedure of **76a** from intermediate **221c** to obtain the title compound as a pale yellow solid (12 mg, 93%); ^{1}H NMR (400 MHz, MeOD) δ 8.20 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.62-7.50 (m, 4H), 7.17 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 4.64-4.59 (m, 1H), 4.33-4.29 (m, 1H), 4.08-4.07 (m, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 3.60-3.56 (m, 1H), 3.51-3.46 (m, 1H), 3.10-2.99 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ 164.9, 164.2, 137.5, 136.9, 134.6, 133.4, 133.1, 132.4, 132.3, 131.7, 131.3, 130.3, 129.8, 129.0, 128.3, 127.9, 125.9, 125.6, 115.2, 115.0, 56.2, 56.0, 54.0, 36.4; LC/MS (ESI) *m/z* 721.0 [M(^{79}Br) + H]$^{+}$, 723.0 [M(^{81}Br) + H]$^{+}$; HRMS (ESI) *m/z* calcd for $C_{30}H_{29}BrN_2O_{10}S_2$ [M(^{79}Br) + H]$^{+}$ 721.0481 and [M(^{81}Br) + H]$^{+}$ 723.0460; found 721.0531 and 723.0506.

(5-Bromonaphthalen-1-yl)methanol (223a). Prepared as described in the experimental procedure of **30** from 5-bromo-1-naphthoic acid to obtain the title compound as a white solid (327 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (m, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.55-7.51 (m, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 5.10 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 132.7, 132.4, 130.2, 127.8, 126.9, 126.7, 126.2, 123.72, 123.70, 63.6.

(5-Bromonaphthalen-2-yl)methanol (223b). Prepared as described in the experimental procedure of **30** from 5-bromo-2-naphthoic acid to obtain the title compound as a white solid (766 mg, quantitative); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.71-7.70 (m, 2H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H),

4.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 134.6, 131.4, 129.8, 127.9, 127.5, 126.5, 126.4, 125.6, 122.7, 64.7.

5-Bromo-1-naphthaldehyde (224a). Prepared as described in the experimental procedure of **47a** from intermediate **223a** to obtain the title compound as a white solid (247 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 9.92 (d, *J* = 8.4 Hz, 1H), 8.58 (d, *J* = 8.8 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8.4, 7.2 Hz, 1H), 7.52 (d, *J* = 8.8, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 137.3, 134.4, 132.4, 132.1, 131.8, 131.4, 129.5, 126.4, 124.9, 123.5.

5-Bromo-2-naphthaldehyde (224b). Prepared as described in the experimental procedure of **47a** from intermediate **223b** to obtain the title compound as a white solid (618 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.08-8.05 (m, 2H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.72-7.69 (m, 2H), 7.20 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 134.6, 134.4, 134.0, 133.8, 132.8, 129.4, 128.2, 127.3, 124.1, 122.8.

***N*-((5-Bromonaphthalen-1-yl)methyl)-4-methoxybenzenesulfonamide (225a).** Prepared as described in the experimental procedure of **48a** from intermediate **224a** to obtain the title compound as a white solid (268 mg, 69%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H, NH), 8.10-8.08 (m, 2H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.58 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.52 (d, *J* = 6.8 Hz, 1H), 7.47-7.43 (m, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.40 (d, *J* = 6.0 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.1, 133.7, 132.3, 132.0, 131.3, 130.0, 128.7, 127.8, 127.1, 126.8, 126.6, 124.0, 122.4, 114.2, 55.6, 44.4; LC/MS (ESI) *m/z* 406.0 $[M(^{79}Br) + H]^+$, 408.0 $[M(^{81}Br) + H]^+$.

***N*-((5-Bromonaphthalen-2-yl)methyl)-4-methoxybenzenesulfonamide (225b).** Prepared as described in the experimental procedure of **48a** from intermediate **224b** to

obtain the title compound as a white solid (805 mg, 75%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H, NH), 8.02 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 4.16 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.0, 136.5, 134.0, 132.3, 130.3, 129.8, 128.7, 128.0, 127.8, 126.9, 126.6, 126.3, 121.5, 114.2, 55.5, 46.0; LC/MS (ESI) *m/z* 406.0 [M(^{79}Br) + H]$^{+}$, 408.0 [M(^{81}Br) + H]$^{+}$.

***N*-((5-Aminonaphthalen-1-yl)methyl)-4-methoxybenzenesulfonamide (226a).** Prepared as described in the experimental procedure of **26** from intermediate **225a** to obtain the title compound as a pale yellow solid (46 mg, 27%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.8 Hz, 2H), 7.65-7.63 (m, 1H), 6.96-6.92 (m, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.68-6.66 (m, 1H), 4.38 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 142.9, 132.2, 131.9, 131.3, 129.5, 127.3, 127.0, 124.2, 123.9, 121.8, 114.3, 114.0, 110.1, 55.7, 45.8; LC/MS (ESI) *m/z* 341.0 [M - H]$^{-}$.

***N*-((5-Aminonaphthalen-2-yl)methyl)-4-methoxybenzenesulfonamide (226b).** Prepared as described in the experimental procedure of **26** from intermediate **225b** to obtain the title compound as a pale yellow solid (28 mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.53 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.96-6.92 (m, 3H), 6.76 (d, *J* = 7.2 Hz, 1H), 4.90 (brs, 2H, NH), 4.25 (d, *J* = 6.4 Hz, 2H), 4.15 (brs, 1H, NH), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 142.2, 134.3, 133.8, 129.5, 128.7, 127.5, 127.1, 124.7, 121.7, 118.9, 114.39, 114.35, 110.2, 55.7, 47.5; LC/MS (ESI) *m/z* 343.1 [M + H]$^{+}$.

4-Methoxy-*N*-(5-(((4-methoxyphenyl)sulfonamido)methyl)naphthalen-1-yl)benzene-sulfonamide (227a). Prepared as described in the experimental procedure of **52** from

intermediate **226a** to obtain the title compound as a pale yellow solid (48 mg, 70%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (brs, 1H, NH), 8.02 (d, *J* = 8.0 Hz, 1H), 7.97 (t, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.44-7.36 (m, 3H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.31 (d, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 3.16 (brs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.3, 162.1, 133.1, 132.8, 132.0, 131.7, 131.6, 129.8, 128.9, 128.7, 126.8, 125.6, 125.2, 123.5, 123.0 ,122.3, 114.3, 114.2, 55.60, 55.56, 44.6; LC/MS (ESI) *m/z* 511.1 $[M - H]^-$.

4-Methoxy-*N*-(6-(((4-methoxyphenyl)sulfonamido)methyl)naphthalen-1-yl)benzene sulfonamide (227b). Prepared as described in the experimental procedure of **52** from intermediate **226b** to obtain the title compound as a pale yellow solid (23 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.59-7.56 (m, 2H), 7.53 (brs, 1H, NH), 7.29-7.23 (m, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.88 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 1H), 4.14 (brs, 1H, NH), 3.82 (s, 3H), 3.79 (s, 3H), 3.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 162.8, 162.6, 134.6, 134.1, 129.2, 129.0, 128.1, 126.8, 126.7, 126.1, 125.7, 123.2, 123.0, 114.1, 114.0, 113.9, 55.4, 46.8; LC/MS (ESI) *m/z* 513.1 $[M + H]^+$.

***tert*-Butyl *N*-(5-(((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methoxyphenyl)sulfonamido) methyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (228a).** Prepared as described in the experimental procedure of **75b** from **227a** to obtain the title compound as a pale yellow oil (54 mg, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.25 (m, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.44-7.33 (m, 3H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.03-44.94 (m, 2H), 4.48-4.44 (m, 1H), 4.24-4.19 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.88-3.86 (m, 2H), 1.32 (s, 9H), 1.27 (s, 9H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 167.9, 167.7, 163.3, 163.2, 137.2, 133.5, 133.0, 131.3, 130.6, 130.41, 130.36, 129.8, 128.8, 127.8, 126.11, 126.05, 125.7, 125.3, 114.3, 114.0, 82.3, 81.9, 55.7, 54.4, 49.4, 47.1, 28.0, 27.9; LC/MS (ESI) *m/z* 759.3 $[M + H + H_2O]^+$.

***tert*-Butyl *N*-(6-(((*N*-(2-(*tert*-butoxy)-2-oxoethyl)-4-methoxyphenyl)sulfonamido) methyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycinate (228b).** Prepared as described in the procedure of **75b** from **227b** to obtain the title compound as a colorless oil (25 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.63 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.32-7.26 (m, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 9.2 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 2H), 4.65-4.56 (m, 2H), 4.44-4.40 (m, 1H), 4.16-4.12 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.77 (s, 2H), 1.28 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 167.8, 163.3, 163.1, 162.7, 136.7, 134.7, 133.7, 132.0, 130.5, 130.4, 129.8, 129.2, 128.1, 127.8, 127.3, 125.8, 125.1, 114.3, 114.1, 82.3, 82.1, 55.8, 54.2, 51.1, 47.4, 28.1; LC/MS (ESI) *m/z* 759.3 $[M + H + H_2O]^+$.

***N*-(5-(((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)methyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (229a).** Prepared as described in the experimental procedure of **76b** from **228a** to obtain the title compound as a white solid (42 mg, 91%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (brs, 2H, CO_2H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.48-7.14 (m, 3H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 4.95-4.83 (m, 2H), 4.47-4.43 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.75 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9, 169.7, 162.8, 162.6, 137.0, 132.4, 132.3, 130.9, 130.6, 129.9, 129.7, 129.5, 127.7, 127.4, 125.7, 125.6, 124.9, 124.5, 114.33, 114.29, 55.72, 55.70, 55.2, 49.4, 47.3; LC/MS (ESI) *m/z* 627.1 $[M - H]^-$; HRMS (ESI) *m/z* calcd for $C_{29}H_{28}N_2O_{10}S_2$ $[M - H]^-$ 627.1113; found 627.1119.

***N*-(6-(((*N*-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)methyl)naphthalen-1-yl)-*N*-((4-methoxyphenyl)sulfonyl)glycine (229b).** Prepared as described in the experimental procedure of **76b** from intermediate **228b** to obtain the title compound as a white solid (21 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.63 (m, 1H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.61-7.59 (m, 2H), 7.53 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.31-7.29 (m, 1H), 7.12-7.10 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.65-4.61 (m, 1H), 4.46-4.40 (m, 3H), 3.91 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 163.5, 163.4, 134.6, 132.2, 131.0, 130.4, 129.8, 129.5, 129.0, 128.1, 127.8, 127.6, 125.8, 114.5, 114.3, 55.8, 53.4, 52.4, 46.1; LC/MS (ESI) *m/z* 629.2 $[M + H]^+$; HRMS (ESI) *m/z* calcd for $C_{29}H_{28}N_2O_{10}S_2$ $[M + H]^+$ 629.1258; found 629.1271.

Fluorescence Polarization Competition Assay.[96]

To determine the inhibitory potency of the Keap1-Nrf2 interaction, the FP assay was performed in a 384-well non-bonding surface (NBS) black plate (Corning, 3575). All FP assay data were recorded using a PerkinElmer Wallac Victor 3V microplate reader equipped with excitation (485 nm) and emission (535 nm) filters appropriate for the label detected. The assay buffer solution was 10 mM HEPES pH 7.4 buffer containing 3.4 mM EDTA, 150 mM NaCl, and 0.005% Tween-20. The fluorescent probe used for the FP assay was 9-mer Nrf2 ETGE motif derived peptide, FITC-LDEETGEFL-NH2. In each well, 10 μL of test compounds in 20 % DMSO/HEPES buffer were incubated with 10 μL of 400 nM Keap1 Kelch domain (final concentration, 100 nM) in HEPES assay buffer for 30 minutes at room temperature. Then 20 μL of 20 nM FITC- 9mer Nrf2 amide (final concentration, 10 nM) in the assay buffer was dispensed to each well and incubated again

for 1 hour at room temperature. For an evaluation of % inhibition at a single concentration of 50, 5, 0.5 μM, 200, 20, 2 μM of samples in 20 % DMSO/HEPES buffer were prepared, respectively. For determination of IC_{50} value, compounds were prepared in a ten-point dilution with 20 % DMSO/HEPES buffer. All experiments were performed in triplicates, and all plates were centrifuged at 2500 rpm for 2 minutes at room temperature before and after incubation. Subsequently, the fluorescence polarization was determined by measuring the parallel and perpendicular fluorescence intensity ($F_{\parallel}$ and $F_{\perp}$) with respect to the linearly polarized excitation light. The % inhibition at each concentration of compounds was calculated according to the method previously reported by our group. The IC_{50} values were determined by fitting the % inhibition data to a four-parameter logistic fit using Sigma Plot 12.3 software.

Time-Resolved Fluorescence Resonance Energy Transfer Assay.

TR-FRET assay was performed in a 384-well non-bonding surface (NBS) white plate (Corning, 3574). All TR-FRET assay data were recorded on a PerkinElmer Wallac Victor 3V microplate reader using an excitation wavelength of 340 nm with filters detecting the fluorescent emission signals of terbium at 495 nm and fluorescein at 520 nm. The assay buffer solution was 10 mM HEPES pH 7.4 buffer containing 0.5 mM EDTA, 150 mM NaCl, and 0.005% Tween-20. Terbium labeled-anti-His antibody was purchased from Thermo Fisher Scientific. The fluorescent probe used for the TR-FRET assay was 9-mer Nrf2 ETGE motif derived peptide, FITC-LDEETGEFL-NH2. Initially, test compounds were prepared in a semi-log dilution from 100 μM to 1 nM, with DMSO. 20 nM His-tagged Keap1 Kelch domain and 2 nM Terbium-anti-His antibody diluted with the assay buffer

were mixed with a ratio of 1:1, and then pre-incubated for 30 minutes at room temperature. 10 μL of a mixture of the protein (final concentration, 5 nM) and the antibody (final concentration, 0.5 nM) were dispensed to each well where 0.2 μL of each compound concentration (final concentration, 1 μM to 0.01 nM) in DMSO was added in advance. After incubation for 30 minutes at room temperature, 9.8 μL of 51 nM FITC-9mer Nrf2 peptide amide (final concentration, 25 nM) in the assay buffer was added and incubated again for 1 hour at room temperature. All experiments were performed in triplicates, and all plates were centrifuged at 2500 rpm for 2 minutes at room temperature before and after incubation. Subsequently, the TR-FRET fluorescence emission intensities at two different nanometers were measured using the microplate reader, and then their ratio was calculated according to the following equation: (intensity of 520nm)/(intensity of 495 nm) x 10,000. The IC_{50} values were determined by fitting the 520 nm/495 nm ratio data to a four-parameter logistic fit using Sigma Plot 12.3 software.

Molecular docking simulation.

To analyze the interactions of designed compounds with the active site of Keap1 Kelch domain, molecular docking simulation was performed using the Autodock 4.0 software.[123] The co-crystal structure of a small molecule bound to Keap1 protein was obtained from the RCSB protein data bank (4XMB, 4L7B, and 5FNT).[102,106,117] For protein preparation, all water molecules were removed from the structure file, missing hydrogen atoms were added, and Kollman charges were calculated using Autodock tool. The ligand structures were built in MOE and prepared for docking using Autodock. The docking grid was centered on the observed binding pocket of the ligand, and the number of grid points in each direction was

set to X, Y, Z = 44 or 40, 40, 40 with spacing of 0.375 Å resolution. The prepared ligands were docked into the binding sites of the Kelch protein. For a docking parameter file, Lamarckian genetic algorithm was used,[124] the number of GA runs was 100, and all other parameters were set to default values. The results of the docking experiments were reported in kcal/mol, and the docked conformations were ranked according to their binding energy. To validate the docking method, the prepared ligand was re-docked using the same method, and then compared with the corresponding X-ray crystal structure. As a result, the top-scoring docked pose was similar to the crystal structure of the ligand with a low RMSD value of 0.94 Å (for 4XMB), 0.89 Å (for 4L7B), or 0.6 Å (for 5FNT). This demonstrated that the docking method was reliable protocol that could be used for docking simulation of other compounds with the Keap1 Kelch domain.

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