STRUCTURE-ACTIVITY RELATIONSHIPS OF SMALL MOLECULE DIRECT INHIBITORS OF KEAP1-NRF2 INTERACTION

by

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And approved by

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ABSTRACT OF THE DISSERTATION

Structure-Activity Relationships of Small Molecule Direct Inhibitors of Keap1-Nrf2 Interaction

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The Keap1–Nrf2–ARE system represents a crucial antioxidant defense mechanism that protects cells against oxidative stress-related diseases and inflammation. Activation of this system leads to elevated expression of a variety of antioxidant defense proteins and enzymes important for protection against oxidative damage, inflammation and tumorigenesis. Targeting Keap1–Nrf2 protein–protein interaction (PPI) has become a promising therapeutic strategy for several oxidative stress conditions and inflammatory diseases including chronic kidney disease, pulmonary fibrosis, chronic obstructive pulmonary disorder (COPD), and cancer chemoprevention. Several PPI inhibitors of Keap1–Nrf2 system have been reported; Tecfidera® is one of these inhibitors that is FDA approved for treatment of patients with relapsing multiple sclerosis. Inhibitors of Keap1–Nrf2 PPI are generally classified into direct and indirect inhibitors. Indirect inhibitors of Keap1–Nrf2 PPI are electrophilic species and can cause off-target side effects. Presently, scientists have been focusing on direct inhibitors of Keap1–Nrf2 PPI. In this work, we are

focusing on the discovery of potent direct inhibitors of Keap1−Nrf2 PPI by performing a comprehensive structure-activity relationship (SAR) study in currently available scaffolds, or by designing new scaffolds. A fluorescence polarization (FP) assay has been used to evaluate the potency of synthesized compounds in vitro and cell-based assays have been used to test the most active compounds, resulting in the discovery of highly potent non-electrophilic Nrf2 activators. One of the best compounds discovered, **65v** (**LH835**), has an IC_{50} of 144 ± 5 nM in the fluorescence polarization assay, and 1.7 ± 0.24 nM in a TR-FRET assay. Furthermore, we have demonstrated that the **65v** (**LH835**) is an efficacious inducer of Nrf2 targeted genes in HepG2 C8 cells, exhibiting activity better than the well-known electrophilic activator, sulforaphane. Our direct inhibitors of Keap1–Nrf2 PPI could potentially be developed into drugs for the treatment of a number of oxidative stress-related diseases and conditions.

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And finally, I would like to give my exceptional thanks to my parents in law for their support and encouragement throughout my academic journey.

DEDICATION

To my wife, my kids, and my parents,

for their encouragement and support.

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INTRODUCTION

The human body is continuously subjected to numerous electrophilic and oxidative chemicals. These chemicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), are produced by living organisms and/or from exogenous sources. These oxidants can cause damage to cellular components and lead to cell death and disease or their damaging effects may be neutralized by the antioxidant defense system in our body.[1,2] Oxidative stress occurs when there is sustained exposure to a high level of these oxidants thereby shifting the balance between the oxidants and antioxidants (Fig.1). Environmental carcinogens, carcinogenic chemicals, and radiation are examples of exogenous sources. Endogenous sources include chemicals involved in intracellular processes that produce oxidative conditions within the body. Examples of ROS are hydrogen peroxide (H_2O_2), superoxide ($\dot{O}_2^-$), hydroxyl radical ($OH^\cdot$), and singlet oxygen ($^1O_2$). Nitric oxide (NO) and peroxynitrate (ONO_2^-) are examples of RNS.[3] All of these reactive species are produced in our body as the result of normal physiological processes (e.g. aerobic respiration in mitochondria), and inflammatory processes (protection against foreign pathogens). Continuous exposure to a high level of these oxidants causes damage to the cellular components; this damaging effect is associated with inflammation and many diseases including diabetes, cancer, hypertension, atherosclerosis, cystic fibrosis, Alzheimer's and Parkinson's diseases.[1,4] The antioxidative and cytoprotective defense mechanisms that up regulate cytoprotective enzyme gene expression have been developed by the human body against different kinds of oxidative stress conditions.[1,5] The antioxidant defense system mitigates the damaging effects of the reactive species (ROS, RNS) by either: a) directly reducing the reactive species through endogenous or dietary antioxidants

or b) using a more efficient catalytic detoxification of reactive species through different antioxidant enzymes. Examples of direct antioxidants are vitamin C, vitamin K, vitamin E, glutathione (GSH), and other polyphenolic compounds. These antioxidants are short-lived, redox-active, and modified or consumed during redox reactions. Therefore, these direct antioxidants have to be regenerated or replenished to perform further antioxidative protection. Examples of antioxidant enzymes that directly sequester reactive species are superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. Other antioxidant enzymes involved in regeneration of direct endogenous antioxidants (e.g. GSH, NAD(P)H) are heme-oxygenase-1(HO-1), NAD(P)H quinone oxidoreductase I (NQO1), glutathione reductase (GSR), and thioredoxin (TRX). These enzymes have long half-lives, are not consumed, and catalyze various detoxification processes (see Fig. 1). Inducible expression of these antioxidant cellular defense enzymes is under the control of the Keap1-Nrf2-ARE transcription pathway.[6,7]

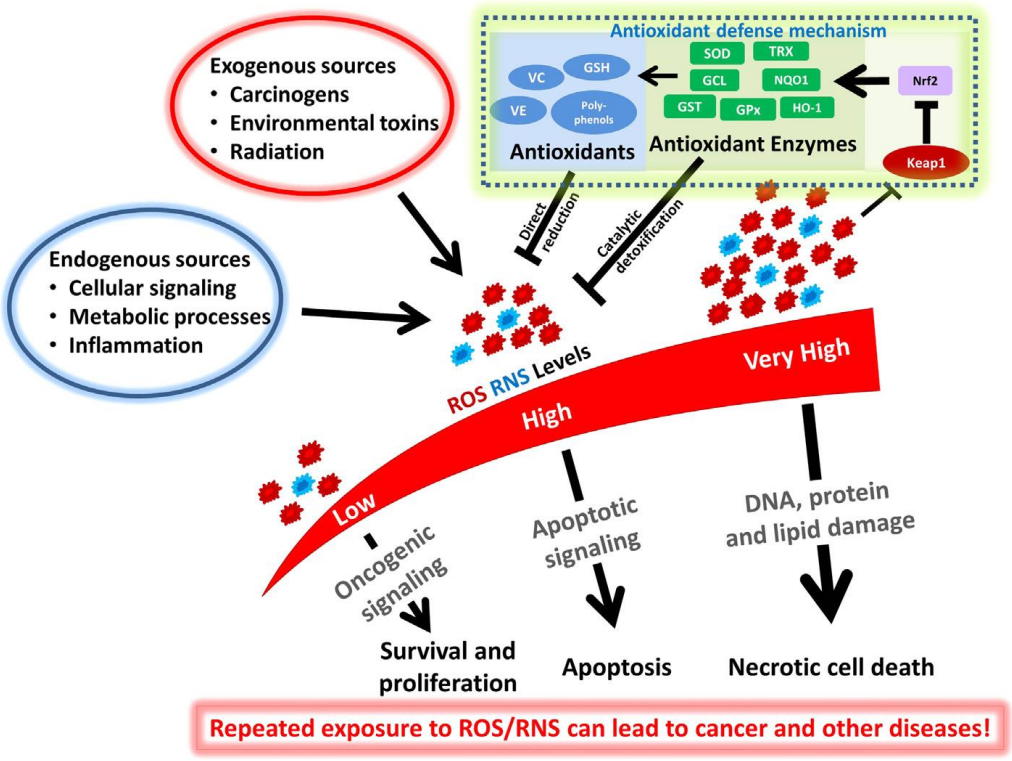


Figure 1. The cellular defense system against electrophilic and/or oxidative stress.[1]

1.1 Keap1-Nrf2-ARE Pathway Components

Continuous exposure of cellular lipids, proteins and DNA to a high level of ROS and RNS causes damage to these components and eventually compromises their activity. Induction of a cellular antioxidant defense system is the main adaptive strategy to detoxify and neutralize these reactive species. The major regulator of these cellular defense enzymes is a Keap1-Nrf2-ARE Pathway. There are three components of this pathway: (1) Kelch-like ECH-associated protein 1 (Keap 1), (2) nuclear factor erythroid 2–related factor 2 (Nrf2), and (3) antioxidant response element (ARE).[1]

1.1.1 Kelch-like ECH-associated protein 1 (Keap1)

Kelch-like ECH-associated protein 1 (Keap1) is a cytoplasmic 69.7-kD actin-binding protein that negatively regulates the activity of Nrf2 protein.[8] As shown in Fig. 2, Keap1 is composed of five functionally distinct domains: (a) an N-terminal region (NTR), (b) a BTB domain, (c) an intervening region (IVR), (d) double glycine repeats (DGR) or Kelch repeats, and (e) a C-terminal region (CTR). Keap1 contains 625 amino acid residues, 27 of which are cysteine residues and most of which are labile for modification by different oxidants and electrophiles.[1,9,10] The BTB domain is a highly conserved domain also found in zinc finger transcription factors and actin-binding proteins. The BTB domain was found to be essential for Keap1 homodimerization which is required for Nrf2 binding. Furthermore, the BTB domain is necessary for the interaction of Keap1 with Cullin3-Rbx1 E3 ubiquitin ligase (Cul3-E3-ligase).[9,11] The IVR is a cysteine rich domain, which is sensitive to oxidation and is necessary for Keap1 activity. In this domain of Keap1, there are four reactive cysteine residues (Cys^{257}, Cys^{273}, Cys^{288} and Cys^{297}) of which Cys^{273} and Cys^{288} are essential for Nrf2 ubiquitination and repression of Nrf2 activity.[12,13] Both IVR and BTB domains were shown to be crucial for Nrf2 degradation. The DGR or Kelch repeats domain is the Nrf2 binding domain. It contains 6 repeating Kelch motifs (KR1–KR6) that form a highly symmetrical 6-bladed β-propeller structure.[14,1]

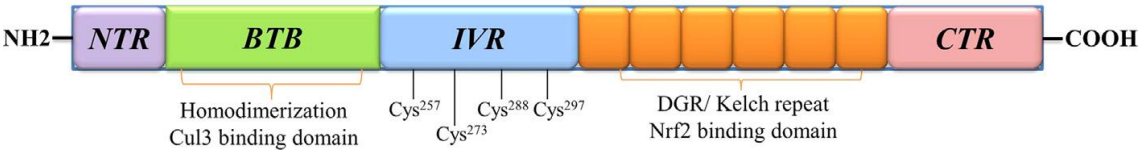


Figure 2. The organization and function of Keap1.[1]

1.1.2 Nuclear factor erythroid2–related factor 2 (Nrf2)

Nrf2 is a transcription factor which is an essential player in the inducible expression of cytoprotective enzymes.[5] It is a 66-kD CNC (cap 'n' collar) transcription factor containing a basic leucine zipper (bZip) motif. There are 6 highly conserved domains called Neh 1-6, (Fig. 3).[1] Neh1, the first domain of Nrf2, contains the bZip motif essential for binding with Maf and DNA. There is also a nuclear localization sequence (NLS, residues 494–511) within the DNA binding domain in Neh1 which is crucial for the nuclear localization of Nrf2.[1] Neh2 is the second domain, a highly conserved domain, which exists at the N-terminal region of the Nrf2. It contains ETGE and DLG motifs that bind Nrf2 to the Keap1 Kelch domain.[15,16] Additionally, there are 7 lysine residues within Neh2 which allow proteasomal degradation of Nrf2 and thereby negatively regulate Nrf2 transcriptional activity. Another important residue in the Neh2 domain is Ser^{40} which was found to be essential for the release of Nrf2 from Keap1. Phosphorylation of Nrf2 at Ser^{40} is necessary for Nrf2-Keap1 dissociation, but it is not required for stabilization and accumulation of Nrf2 in the nucleus. [17,18] The third domain in Nrf2 is Neh3 which belongs to the CNCb ZIP transcription factors. It lies at the C-terminus of Nrf2 and is required for the Nrf2 mediate transactivation of ARE genes. The transactivation domains (Neh4 and Neh5) in Nrf2 cooperatively bind to the transcriptional co-activator, cAMP response element binding (CREB), and trigger transcription. The redox insensitive Neh6 domain is in the middle of Nrf2 and is associated with Keap1 independent degradation of the Nrf2.[19]

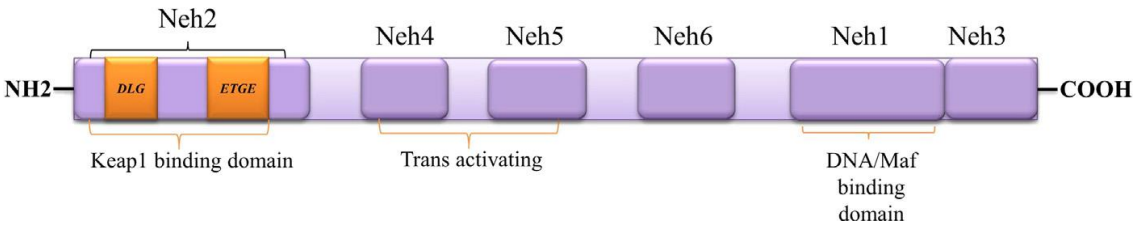


Figure 3. The organization and function of Nrf2.[1]

1.1.3 Antioxidant Response Element

The antioxidant response element (ARE), also known as the electrophile response element (EpRE), is located in the promoter region of numerous genes encoding cytoprotective proteins and detoxification enzymes. [20] Numerous mutagenic analysis studies investigated the ARE nucleotide sequence.[21] The core ARE sequence that was required for basal and inducible activity is a 16 nucleotide sequence of 5'-TGACNNNGC-3'.[22] Bach1 (BTB and CNC homology1) is the ARE transcriptional repressor. In normal physiological conditions, Bach1 dimerizes with Maf protein and thus prevents Nrf2 from binding to DNA. In oxidative stress conditions, Bach1 undergoes proteasomal degradation after nuclear export, Maf and the stabilized Nrf2 heterodimerize and bind to the ARE sites, leading to the activation of ARE-dependent target gene expression.[23]

1.2 Mechanism of Keap1-Nrf2-ARE Pathway Regulation

Based on cellular redox conditions, the major regulator of the Keap1–Nrf2–ARE pathway is Keap1 by controlling the steady state level of Nrf2.[1] Under normal physiological conditions, Nrf2 binds to the Keap1 IVR domain through its high affinity ETGE and DLG motif in the Neh2 domain. Binding of Nrf2 to a Keap1-dimer promotes Nrf2 ubiquitination

and subsequent rapid degradation by the 26S proteasome (Fig.4). This rapid Nrf2 turnover (t1/2 of less than 20 min) prevents the expression of Nrf2 target genes. The ubiquitination of Nrf2 occurs at lysine residues located within the Neh2 domain. Under oxidative stress conditions or in the presence of electrophilic inhibitors, covalent modification at the key cysteine residues in the IVR region causes Cul3 dissociation from Keap1. Subsequently, Nrf2 is not properly oriented for ubiquitination and the Nrf2 is stabilized (t1/2 of up to 200 min) and the newly synthesized Nrf2 can translocate to the nucleus and promote expression of cytoprotective enzyme encoding genes. There are two prevailing mechanistic models of Nrf2 stabilization: 1) Keap1-Cul3 Dissociation Model, and 2) Hinge and Latch Model as shown in Figure 4. In the dissociation model, Keap1 identifies and interacts with Nrf2 through the Keap1 Kelch domain and the Nrf2 ETGE and DLG motifs. Subsequently, this binding will bring Nrf2 into proximity with the Cul3 ubiquitin-conjugating enzyme. Once there, ubiquitin then transfers to the target Nrf2 lysine residues. Under oxidative stress or in the presence of electrophilic inhibitors, conformational changes cause Cul3 dissociation and Nrf2 is not ubiquitinated and a newly formed Nrf2 will translocate to the nucleus.[1] In the hinge and latch model, covalent modification of the sensitive cysteine residues of Keap1 will result in conformational modification of Keap1 and the release of the Nrf2 DLG motif, while continuing to bind to the Nrf2 ETGE motif. Subsequently, Nrf2 swings out from its optimum position for ubiquitination, bypasses degradation by proteasomes, and promotes the expression of targeted genes.[1,24,25]

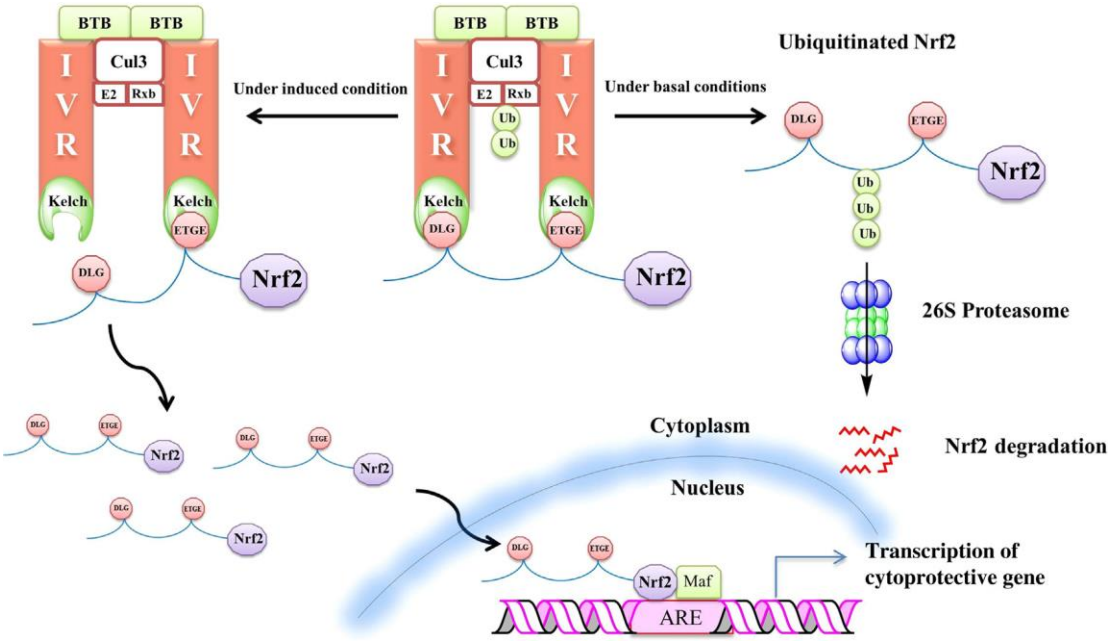


Figure 4. Keap1-Nrf2-ARE pathway regulation mechanism.[1]

Gene expression profiling analysis and chromatin immunoprecipitation (ChIP) analysis have identified several hundred Nrf2 target genes of detoxifying, metabolic, and anti-oxidant enzymes as summarized in Fig. 5.[5] NQO1 is one of the Nrf2 target genes which is a member of the NAD(P)H dehydrogenase family that catalyzes the reduction of quinones to hydroquinones and thus prevents the production of radical species that are produced when there is a one electron reduction of quinones (Fig. 5). Another detoxifying gene is GST which promotes the detoxification of xenobiotics through its ability to catalyze GSH conjugation with xenobiotic substrates. Nrf2 activation induces the expression of antioxidant genes, and the proteins encoded by these genes promote reduction of reactive species. Gpx2 (glutathione peroxidase 2), and Txnrd1 (Thioredoxin reductase 1) are examples of these genes and the proteins encoded by Gpx2 reduce peroxide while the

proteins encoded by Txnrd1 reduce thioredoxins as well as other substrates. Nrf2 activation also promotes the expression of proteins encoded by glucose-6-phosphate dehydrogenase (G6pd) and 1,4-α-glucan branching enzyme 1 (Gbe1); these enzymes are known to have an important role in glucose metabolism. Recent ChIP-sequence and microarray analyses have reported that the binding of Nrf2 in the ARE promoter region of pro-inflammatory cytokine genes (e.g. *IL-6*, *IL-1b*) inhibits the expression of lipopolysaccharide-induced genes (Fig. 5). Consequently, activation of Nrf2 disrupts the RNA polymerase II promoted recruitment of *IL-1b* and *IL-6* loci and thereby relieves inflammation. This process of Nrf2-mediated transcriptional interference does not appear to be correlated to the level of ROS. Although the current hypothesis is that Nrf2 activation mitigates inflammation because of its anti-oxidation function and anti-reactive oxygen species, these analyses propose that the induction of pro-inflammatory cytokine gene transcription is inhibited by Nrf2 activation. Collectively, Nrf2 activation seems to be the major regulator of two important cytoprotective pathways, anti-oxidation and anti-inflammation.[26]

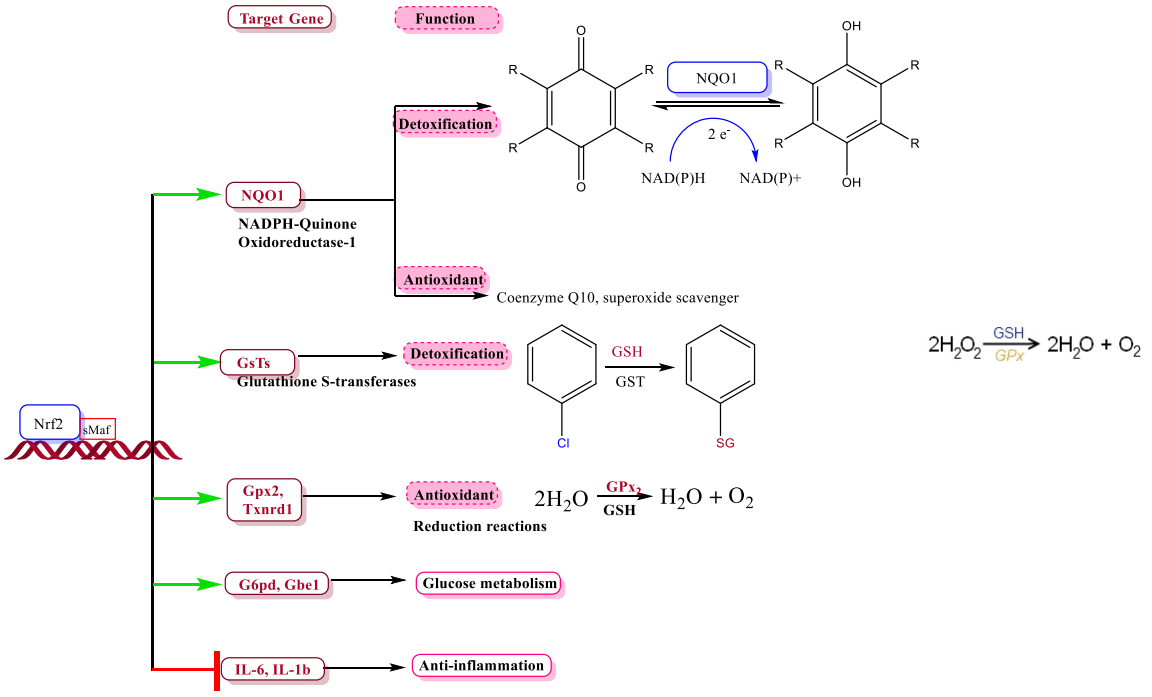


Figure 5. The regulatory role of Nrf2 in cytoprotective pathway.

1.3 Keap1-Nrf2-ARE Pathway and Diseases

Oxidative stress and inflammation play an important role in the pathogenesis of different human diseases and pathological conditions. In the presence of inflammation, our body produces considerable amounts of RNS and ROS which may cause oxidative damage to DNA and other cellular structures including cellular proteins and lipids.[1,27,28] The major defense mechanism employed by our body to neutralize the effects of these reactive species is the Keap1–Nrf2–ARE pathway.[29,30,31] Thus, activation of this pathway can protect many cells and organs. The protective role of this pathway has been evident in different human diseases and age-related diseases including tumors, neurological diseases, cardiovascular diseases, pulmonary disorders, inflammatory bowel disease, diabetes, autoimmune disorders, and aging.[1,32,33] The next section briefly discusses the major diseases and

pathological conditions that involve the Keap1–Nrf2–ARE pathway and the oxidative stress which can be therapeutically targeted by modulators of this pathway.

1.3.1 Cancer

The uncontrolled growth of abnormal cells can lead to a tumor. DNA damage by ROS or electrophilic carcinogens can initiate and eventually lead to cancer. Patients with different types of chronic inflammatory disorders (e.g. ulcerative colitis) are highly vulnerable to developing cancer, which supports the hypothesis that lesions associated with oxidative-stress promote carcinogenesis. Given the interrelation between carcinogenesis and oxidative damage, the Keap1–Nrf2–ARE pathway has been widely considered as a potential therapeutic strategy for chemoprevention. Keap1−Nrf2 PPI inhibitors function as chemopreventive therapeutic agents by preventing carcinogens from interacting with cellular structures and proteins, reaching vital targets, or being activated metabolically.[34, 35] As a result of Nrf2 activation by the inhibitors, the gene encoded Nrf2 is now disrupted. Studies affirm the central importance of Nrf2 in cancer chemoprevention by controlling the expression of cytoprotective enzymes. However, disruption of gene encoded Nrf2 resulted in an increase in the susceptibility to carcinogens due to improper expression of cytoprotective enzymes. In several types of human cancer cells, the elevated level of Nrf2 that resulted from mutations in Nrf2 or Keap1 eventually lead to expression of up-regulated genes.[36,37] The overexpression of Nrf2 seems to exert its effects in both tumor and normal cells which subsequently results in an increased expression of cytoprotective proteins, transporters, and detoxification enzymes. Eventually, cancer cells take advantage of Nrf2 overexpression by enhancing proliferation and developing resistance to chemotherapy.[38]

According to recent studies of the Keap1-Nrf2–ARE pathway, suppression of cancer cell growth and enhancement of the efficacy of chemotherapeutics can be achieved through inhibition of Nrf2.[39,40,41] Accordingly, targeting Nrf2 can be proposed as a promising therapeutic strategy for cancer either by inhibiting Nrf2 activity in existing cancer cells for treatment or inducing Nrf2 activity in normal or premalignant cells for chemoprevention.[42,43]

1.3.2 Neurodegenerative Diseases

The high susceptibility of the central nervous system to oxidative damage is a result of its high level of lipid content, oxygen consumption, and redox-active metals (e.g. Cu and Fe), all of which are capable of catalytic ROS production.[44,45] The onset and progress of neurodegenerative diseases are accompanied by the enhancement of ROS production and subsequent oxidative damage.[46,47] The protective effect of the inhibitors against Keap1–Nrf2 interaction in oxidative stress and neurodegenerative diseases has been reported and Nrf2 activation has been proposed as a potential therapeutic strategy in Parkinson's disease, Alzheimer's disease and other neurological disorders such as multiple sclerosis, Huntington's disease, and traumatic brain injury.[46,48] As a Nrf2 activator, Tecfidera® (dimethyl fumarate) is the first FDA approved drug for treatment of patients with relapsing multiple sclerosis.[49,50]

1.3.3. Diabetic Complications

Diabetes and chronic kidney disease (CKD) are accompanied by an increase in the markers of oxidative stress even in the early stage of the diseases which may be due to dysfunction in the cytoprotective mechanism and overproduction of ROS.[49] Patients with type 2 diabetes may develop chronic kidney disease which is also known as diabetic nephropathy, and the progress of diabetic nephropathy may lead to kidney failure. The Keap1-Nrf2–ARE pathway has been established to serve a vital role in the control of a) inflammation through the production of cytoprotective enzymes and b) blood glucose levels by lowering insulin resistance and inhibition of fat accumulation. Thus, targeting this pathway may have a potential therapeutic advantage for the treatment and prevention of patients with diabetic nephropathy.[1,51,52] In addition to the role of the Keap1-Nrf2-ARE pathway in controlling the pathogenesis and metabolic process for patients with diabetes, the Keap1-Nrf2-ARE pathway appears to have a central role in limiting diabetic complications. Studies have revealed the role of oxidative stress in diabetic complications, including diabetic nephropathy and cardiomyopathy, in which there is an increase in the production of reactive species.[53,54] This may indicate that the increase in glucose levels induces the production of ROS which leads to oxidative damage of the vascular system and eventually diabetic cardiomyopathy. Accordingly, the Keap1-Nrf2-ARE pathway has an important role in protecting our body against glucose-induced oxidative stress and cardiomyopathy. The involvement of the Keap1-Nrf2-ARE pathway in diabetic nephropathy has been demonstrated in several experimental studies. An example of the importance of Nrf2 in diabetic nephropathy is shown in the susceptibility of Nrf2-null mice treated with Streptozotocin (STZ) to renal impairment and oxidative damage as compared to wild type

mice.[1,55] Therefore, the Keap1-Nrf2-ARE pathway could be used to prevent the progress of diabetic nephropathy based on its protective role. Bardoxolonemethyl (CDDO-Me) is a potent inducer of a Nrf2-ARE pathway and was evaluated in clinical trial for the treatment of patients with advanced CKD and type 2 diabetes.[49,56]

1.3.4. Pulmonary Diseases

The airway can be particularly vulnerable to oxidative stress as it is the first point of entry of inhaled oxidants; redox balance in the pulmonary system is repeatedly and continuously disturbed by the accumulation of inhaled oxidants.[57, 58] The Nrf2 expression in the airway is mainly found in the alveolar macrophages and pulmonary epithelium. An aggravation of lung toxicity due to oxidative sources (e.g. cigarette smoke, viral infections, allergens, bacterial endotoxins) has been demonstrated when there is a depletion of Nrf2 expression. An increase in the susceptibility to pulmonary disease (e.g. COPD, asthma, and emphysema) was also reported when there is Nrf2 deficiency.[59,60] Studies indicate that the targeting of the Nrf2 alveolar macrophages appears to be a promising pharmacotherapeutic strategy for the treatment of different pulmonary diseases. Currently, CDDO-Me is under clinical trial for the treatment of pulmonary hypertension.[49]

1.4. Assays for evaluation of inhibitors against Keap1–Nrf2 PPI

Various assays have been developed to meet the need for screening and identification of Keap1–Nrf2 inhibitors. The different types of assays developed include surface plasmon

resonance (SPR)-based solution competition assays, fluorescence polarization (FP) assays, Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) assays, and cell-based Neh2-luciferase assays. For each of these assays, the principles and the advantages are described below (Table 1).

Table 1. Assays for evaluation of inhibitors against Keap1-Nrf2 PPI.

Type of assay	**The principle**	**The evaluated biological effect**
In Vitro assay		
FP assay	luminescence based on molecular size	disruption of Keap1−Nrf2 ETGE peptide interaction
TR-FRET assay	luminescence based on proximity	disruption of Keap1−Nrf2 ETGE peptide interaction
In Vivo assay		
ARE- luciferase reporter gene assay	Luciferase enzymatic activity	Nrf2 transcription activity
Gene expression	mRNA detection by qRT-PCR	mRNA level
Protein expression	protein detection by Antibody-Antigen reaction	protein level

1.4.1. In Vitro Assays

In general, in vitro assays can be used to evaluate Keap1 binding affinity and Keap1−Nrf2 interaction inhibition. Several types of in vitro assays have been used for the evaluation of Keap1−Nrf2 PPI inhibitors; for example, differential scanning fluorimetry (DSF) assays, tracer displacement assays, fluorescence resonance energy transfer (FRET) assays, SPR-based competition assays, fluorescence polarization (FP) assays, isothermal titration calorimetry (ITC), and biolayer interferometry (BLI). The various assays that we used in this project to evaluate our inhibitors of Keap1-Nrf2 PPI will be discussed further in detail.

1.4.1.1. Fluorescence Polarization Assay

A Fluorescence polarization (FP) assay is used to study the biomolecular interactions in solution. This assay can be used for the screening of small molecule inhibitors of Keap1-Nrf2 PPI. Our group successfully used this assay in a high-throughput screening (HTS) for a library of chemicals in order to identify small molecule inhibitors of Keap1–Nrf2 interaction.[61,62] The principle of this assay is that excitation of fluorescently labeled molecules with linear polarized light results in a light that is emitted on different planes (Fig.6).[63] In solution, movement of these fluorescently labeled molecules between excitation and emission give rise to light emission which is governed by the molecular size. In this assay, we used a fluorescently labeled short peptide derived from the protein binding motif (Nrf2 peptides) and the receptor was the binding partner (Keap1). This assay relies on the difference in mass between the bound and the unbound state of the fluorescently labeled short peptide with the target protein.[62,64] The FP assay is the most frequently used assay for the identification of modulators for protein- protein interaction. FP assay

throughput can easily be scaled up, therefore it is commonly used on HTS platforms.[63, 65] However, there are some limitations to an FP assay; the signal has to be measured instantly after excitation and cannot be measured in a time-resolved manner. Furthermore, it is limited to systems in which the partners have a large enough difference in size to create a considerable difference in FP signal. To overcome these limitations, FRET assays may represent an appropriate solution.[63]

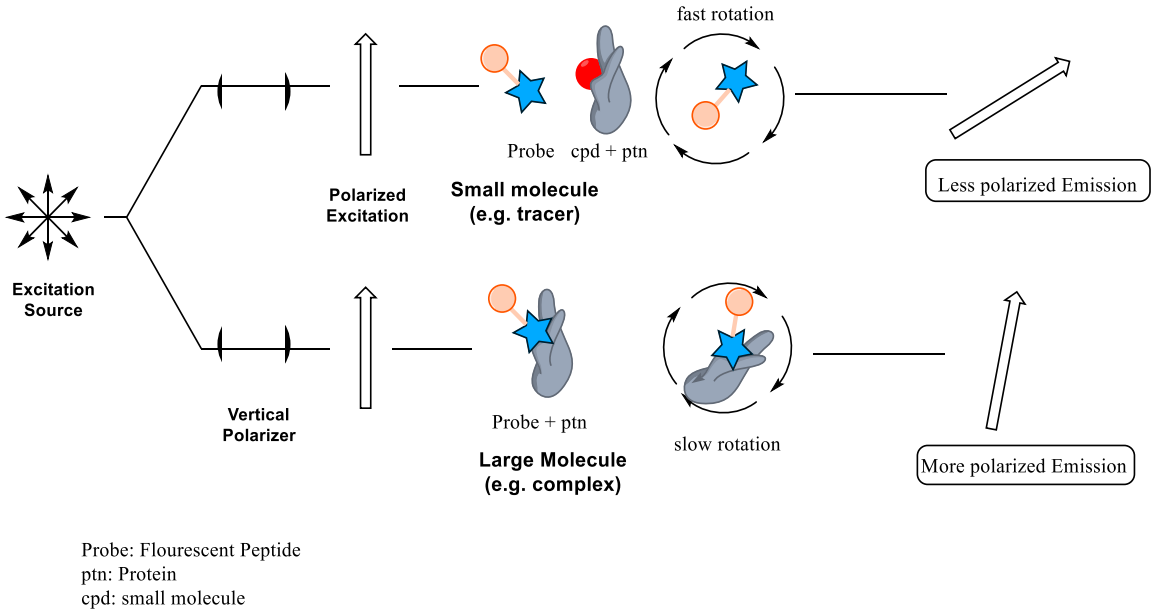


Figure 6. The principle of a Fluorescence Polarization assay.

1.4.1.2. Time-Resolved Fluorescence Resonance Energy Transfer Assay

The basic principle of a TR-FRET assay is a nonradiative transfer of the emission energy from the excited donor fluorophore to the acceptor fluorophore that occurs when the pair of fluorophores are in close proximity and thereby, the acceptor fluorophore can be excited

as shown in Fig.7A.[63] In this assay, the distance between the donor fluorophore and the acceptor fluorophore has to be within a range of 10−100 Å for energy to be transferred, and this occurs when the protein (Keap1 in our assay) brings the two fluorophores in close proximity, within the optimal range, and fluorescence resonance energy transfer occurs. The donor emission arising from resonance energy transfer is technically called luminescence not fluorescence.[66,67] The advantage of a TR-FRET assay over the traditional FRET is the luminescence lifetime of the donor fluorophore which is in milliseconds range whereas the fluorescence lifetime of organic dyes and background fluorescence scattering are within nanosecond range.[66,63] This magnitude of difference in fluorescent lifetime allows the signal due to energy transfer to be detected using time-resolved measurements when the interfering signals from the background or chemicals have decayed (Fig. 7B). Therefore, any overlap that might result from the excitation and emission signals of biological and small molecules or from the background will be excluded. Another advantage of a TR-FRET assay is that the signal in a FRET assay is measured as a ratio of donor /acceptor emission and this minimizes variations between wells, and offsets the interference from a quenching sample. Because the TR-FRET assay is independent of mass differences, different ways of labeling can be used. The TR-FRET assay has broad applications in several fields of Biology (e.g. protein−DNA interaction studies). The good statistical rate and the minimal false positive rate of TR-FRET assays outweigh the higher costs. TR-FRET assays have been used for numerous PPI assays including HTS.[63,68]

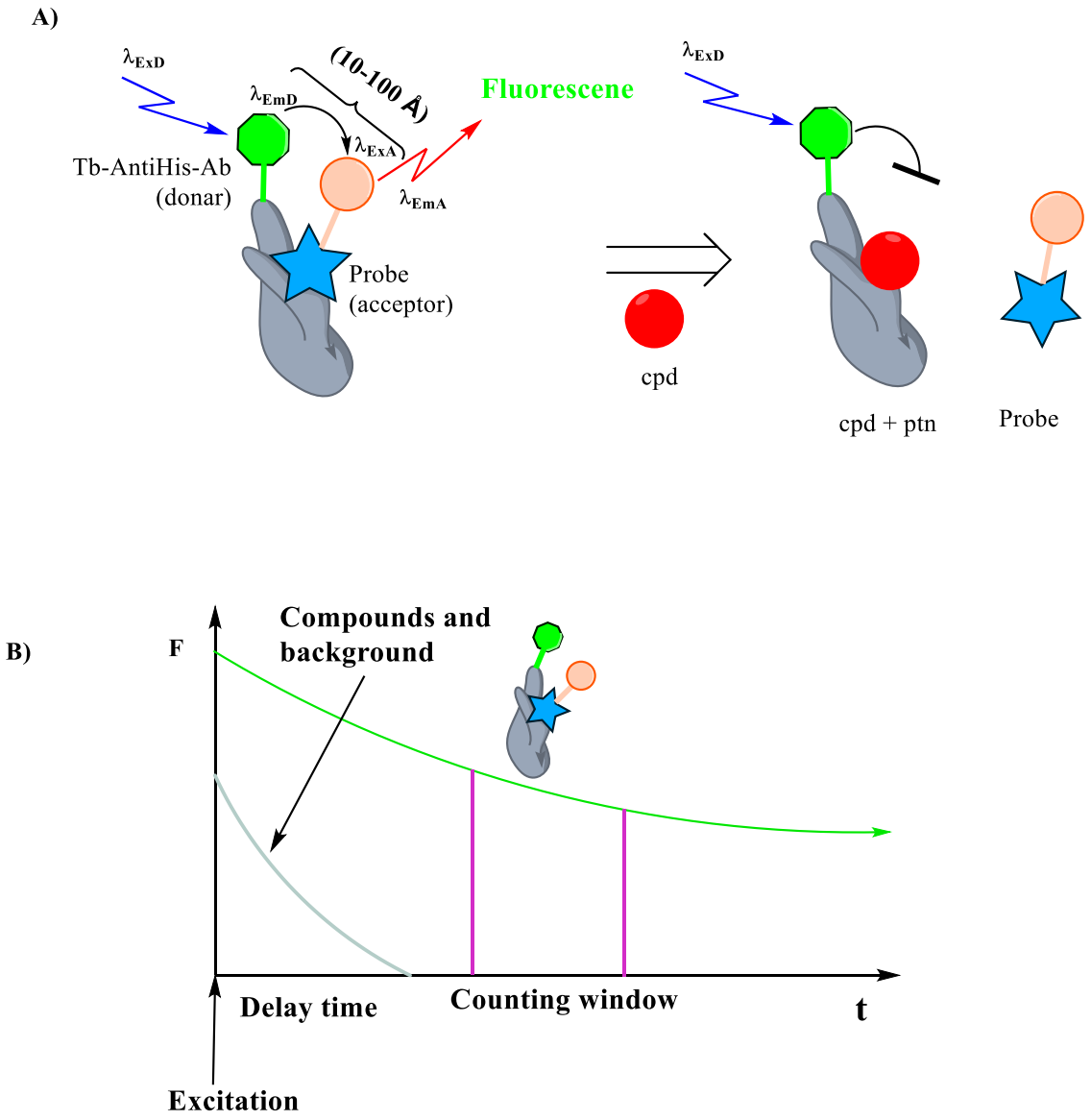


Figure 7. The principle of Time-Resolved Fluorescence Resonance Energy Transfer Assays.

1.4.2. Cell-based Assays

The activity of Keap1-Nrf2 PPI inhibitors can be evaluated qualitatively and quantitatively by measuring the transcriptional Nrf2 activity. The Nrf2−ARE luciferase reporter gene

assay is one of the most direct ways to measure Nrf2 activation. Binding of Nrf2 to promoter regions of ARE induces expression of antioxidant enzymes. The luciferase activity induces easily detected luminescence signals which provide a rapid and appropriate quantification of Nrf2 activation. This type assay can be used in HTS, and it has, in fact, been reported that there are numerous HTS studies are presently using this assay. However, the frequent occurrence of false positives in ARE luciferase reporter gene assays is the main disadvantage. There are several direct methods to validate the Nrf2 activation at the mRNA and protein cellular level including qRT-PCR and Western blot analysis of Nrf2 and downstream genes. The most widely evaluated Nrf2-target genes are heme-oxygenase-1 (HO-1), and NAD(P)H: quinone oxidoreductase-1 (Nqo-1).[49,69]

1.5 Keap1-Nrf2-PPI Inhibitors

Keap1-Nrf2-ARE pathway activation is induced by different cellular stresses (oxidative stress), endogenous chemical inducers (ROS, RNS), and exogenous chemical inducers. Exogenous chemical inducers of the Keap1-Nrf2-ARE system have been identified from both natural and synthetic sources. It has also been shown that toxic chemicals induce the Keap1-Nrf2-ARE pathway by activation of oxidative stress. We can divide the inhibitors of the Keap1-Nrf2-ARE pathway into indirect and direct inhibitors of Keap1–Nrf2 interaction based on their mechanism of action. At present, scientists are focused on the discovery of small molecule direct inhibitors of Keap1–Nrf2 interaction through different approaches including high-throughput screening or structure-based drug design.[8,70,71]

1.5.1 Indirect Inhibitors of the Keap1-Nrf2-PPI

Indirect inhibitors of Keap1–Nrf2 PPI induce Nrf2 activation by forming covalent adducts with the sulfhydryl groups in Keap1.[8] For the majority of indirect inhibitors, electrophilicity is a common property. Nevertheless, not all electrophiles can induce ARE activity. The biological effect of electrophiles depends on both the nature of the electrophile and on the microenvironment of the nucleophilic center in the protein that is the function of both electronic and steric factors mediated mainly through the protein tertiary structure.[8, 72] The mechanism of activation of Nrf2 of these compounds is a covalent reaction of the electrophilic residues with the Keap1 sensor cysteines, particularly Cys 151. There are about ten chemically distinct classes of known indirect inhibitors of Keap1–Nrf2 PPI based on chemical structure and the nature of interaction with sulfhydryl groups of the Keap1 cysteine group. Two of the more well-known electrophilic inhibitors of Keap1–Nrf2 PPI are (Fig.8): a) sulforaphane, an isothiocyanate compound derived from cruciferous vegetables (e.g. broccoli), and b) Dimethyl fumarate, Tecfidera®, an FDA approved drug for treatment of multiple sclerosis.

Although these covalent Nrf2 activators are efficacious, these electrophiles are not selective for Keap1 which may result in off-target toxicity. An example of the lack of selectivity is an electrophilic Nrf2 activator, oleanic triterpenoid bardoxolone imidazole, which has a Michael acceptor for reactive Cys residues on Keap1and thereby induces Nrf2 activation. According to the proteomics study, this compound interacts with at least 577 different cellular proteins. Another example of lack of selectivity of currently known Nrf2 activators is bardoxolone methyl which has entered the phase III clinical trial for treatment of patients with type 2 diabetes and patients with chronic kidney disease. However, development of this chemical was derailed due to its adverse cardiovascular effects.

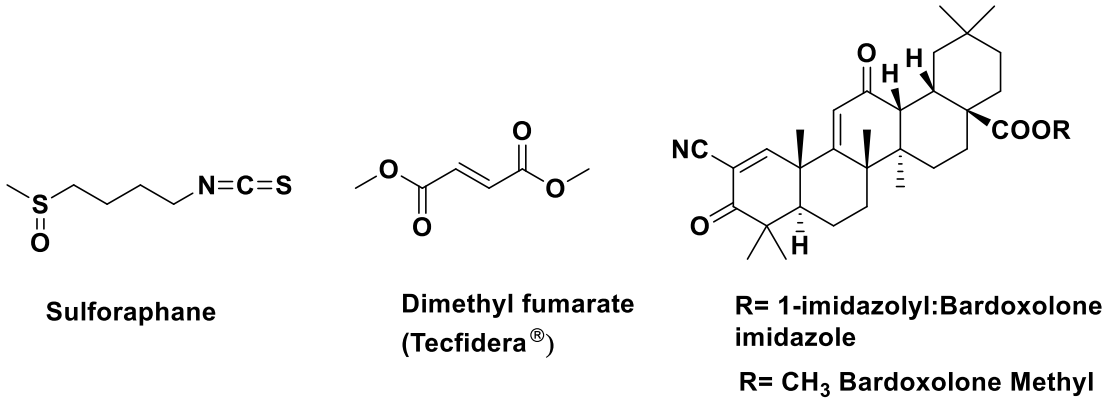


Figure 8. Electrophilic inhibitors of Keap1-Nrf2 interaction.

1.5.2 Direct Inhibitors of the Keap1-Nrf2 PPI

Presently, there is a great interest in developing non-electrophilic direct inhibitors of Keap1-Nrf2 PPI that could be more selective Nrf2 activators and thus have less off-target toxicity. Scientists' efforts focus on the discovery of potent non-covalent Nrf2 activators for eventual therapeutic development.[24] The logical approach in the development of non-electrophilic inhibitors against Keap1-Nrf2 PPI is to inhibit the Nrf2 interaction with Keap1directly. In this approach, binding of an inhibitor with Keap1's Kelch domain where the Nrf2 ETGE motif is bound, which is distal from the Keap1 cysteines binding site of known electrophilic inhibitors, results in Nrf2 activation. HTS using an FP assay developed in our lab for the MLPCN library identified the first-in-class small molecule direct inhibitor of the Keap1-Nrf2 PPI (LH601A, IC_{50} = 3 μM, Fig.9). Other hits, identified by Silvian and colleagues at Biogen through HTS of a library of 267,551 compounds, are a thiopyrimidine derivative **153** (IC_{50} 118 μM) and a naphthalene derivative (compound **1**, IC_{50}= 2.7 μM) (Fig.9). The naphthalene derivative was shown to increase the levels of the Nrf2 target

gene NQO1, in cell-based assays. Binding of the naphthalene derivative directly and specifically to the Keap1 Kelch domain was confirmed using X-ray crystallography and Native mass spectrometry. The diacidic naphthalene derivative compound **2**, a potent inhibitor of the Keap1–Nrf2 interaction derived from compound **1**, was designed by You, Sun and colleagues, and was reported to have an IC_{50}= 29 nM using their FP assay condition (Fig.9). Based on molecular dynamics simulations (MD) and molecular binding determinant studies of Keap1–Nrf2 PPI, the introduction of two acetic acid side chains to compound **1** would provide complementary binding interactions with the Kelch domain of Keap1. [1] An additional hit compound, identified by You and coworkers through HTS from a library of 21,119 compounds, is carbazone **154** (4, 4'-[carbonylbis(2-hydrazinyl-1-ylidene-5,2-furandiyl)]bis- Benzoic acid) (Fig.9). This carbazone compound with two benzoic acids at the ends was reported to have an IC_{50} of 9.8 μM in the FP assay with relatively low activity in a cell-based assay because of its poor cell permeability. In hope of discovering potent direct inhibitors of the Keap1-Nrf2 PPI, molecular modeling and structure-activity relationship studies for some of these scaffolds have been carried out. According to these studies, these non-electrophilic inhibitors behave similarly to the Nrf2 ETGE motif in that they show significant interactions between Arg 415 in the binding pocket and acidic portions of the inhibitors and are also involved in π-stacking and hydrogen bonding.[24]

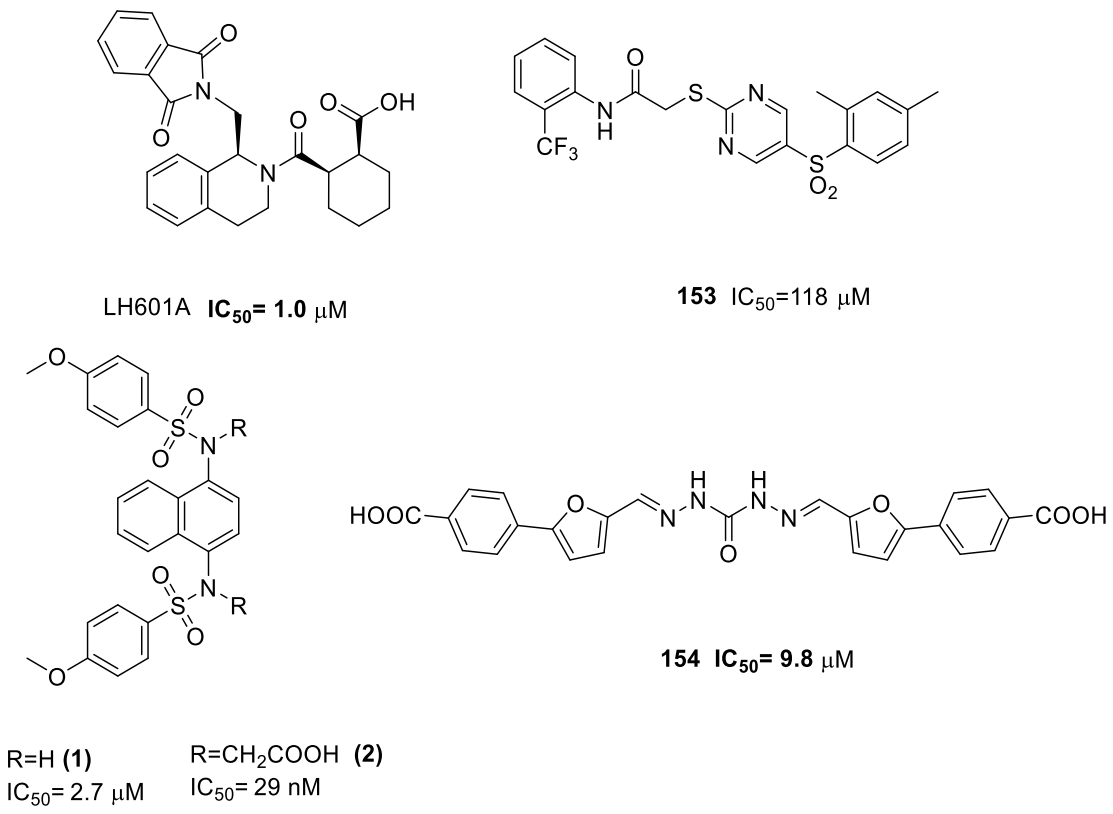


Figure 9. Non-electrophilic inhibitors of Keap1-Nrf2 interactions

1.6 Summary

The major regulator of cellular protective responses for both endogenous and exogenous stresses caused by ROS, RNS, and other electrophiles is the Keap1-Nrf2-ARE pathway. There are three main cellular components involved in the pathway including Keap1, Nrf2, and ARE. To activate this pathway, Nrf2 has to escape ubiquitination and subsequent degradation, translocate to the nucleus, and bind to ARE in the promoter region. Therefore, inhibition of Keap1-Nrf2 interaction can induce expression of ARE-dependent cytoprotective enzymes and proteins which have a critical role in the prevention of oxidative damage, inflammation, and tumourigenesis. Thus, targeting the Keap1-Nrf2-ARE pathway holds great promise for the development of pharmacotherapeutic agents for

a number of oxidative stress-related disorders and inflammatory diseases including cancer, chronic obstructive pulmonary disease (COPD), multiple sclerosis, osteoarthritis and diabetic nephropathy. Based on their mechanisms of action, inhibitors of Keap1-Nrf2 PPI are identified as either indirect or direct. The indirect inhibitors are electrophilic species that react with sulfhydryl groups of Keap1's cysteine residues. There has been great interest in developing indirect inhibitors to activate Nrf2. FDA approved Tecfidera® is an example of an indirect inhibitor developed by Biogen Idec as a first-line treatment of relapsing forms of multiple sclerosis. Although this type of inhibitors is obviously efficacious, off-target side effects, due to the interactions with other cellular protein cysteine residues, offset its efficacy. Another approach to activating Nrf2 is to design molecules that directly inhibit Keap1-Nrf2 PPI which may result in more selective Nrf2 activators. The logical approach to inhibit the Keap1-Nrf2 PPI directly is to design an inhibitor that could occupy the site on Keap1's Kelch domain with which the ETGE motif of Nrf2 is bound. Therefore, when a small molecule binds with the Keap1 Kelch domain, Nrf2 is displaced and activated. The first in-class small molecule direct inhibitor identified by HTS is LH601A, which was reported by our group with an IC_{50} of 3 μM using an FP assay. Since then, several other direct inhibitors have been reported aiming to discover selective and potent therapeutic agents for a variety of inflamatory and oxidative stress related diseases. As we began this project, compound **2** (**LH762**), which is a naphthalene-based compound (Fig. 9), was one of the most potent inhibitors of Keap1-Nrf2 interaction with IC_{50}= 29 nM in their FP assay condition. However, this small molecule has metabolic stability problems and demonstrates limited activity in cell-based assays. With a goal to improve the druggability of compound **2** (**LH762**), we have expanded the SAR around this small molecule. The

work in this dissertation describes the design, synthesis, SAR, and biological evaluation of different small molecule direct inhibitors as analogs of compound **2** (**LH762**).

Results and Discussion

2.1 Synthesis and evaluation of novel disubstituted phenyl analogs as direct inhibitors of Keap1-Nrf2 interaction

Naphthalene-based compound **1** (Fig. 9) has been identified by HTS as a potent inhibitor of Keap1-Nrf2 interaction. As we started this project, compound **2**, which is the analog of compound **1** with two acetic acid side chains, was the most potent inhibitor with IC_{50}= 29 nM in their FP assay condition, and the IC_{50}= 110 ± 7 nM in our FP assay condition. However, this compound has *para*-disubstituted nitrogen which may cause metabolic stability problems. Furthermore, compound **2** showed limited activity in cell-based assays. Therefore, compound **2** served solely as a starting point to begin our investigation of Keap1-Nrf2 PPI inhibitors.

Molecular dissection is one of the approaches to lead optimization that helps to improve lead-like properties of the designed analog with retention of the desired biological action. In this approach, the first step of modification is to remove one phenyl in the naphthalene moiety of the lead molecule and determine the effects of this modification on inhibitory activity. This will help determine the important structural features for activity and improve metabolic stability of designed analogs.

Our design was aimed to improve in vitro activity, enhance cellular Nrf2 activity, and improve metabolic stability. A summary of our designed analogs is shown in Fig. 10.

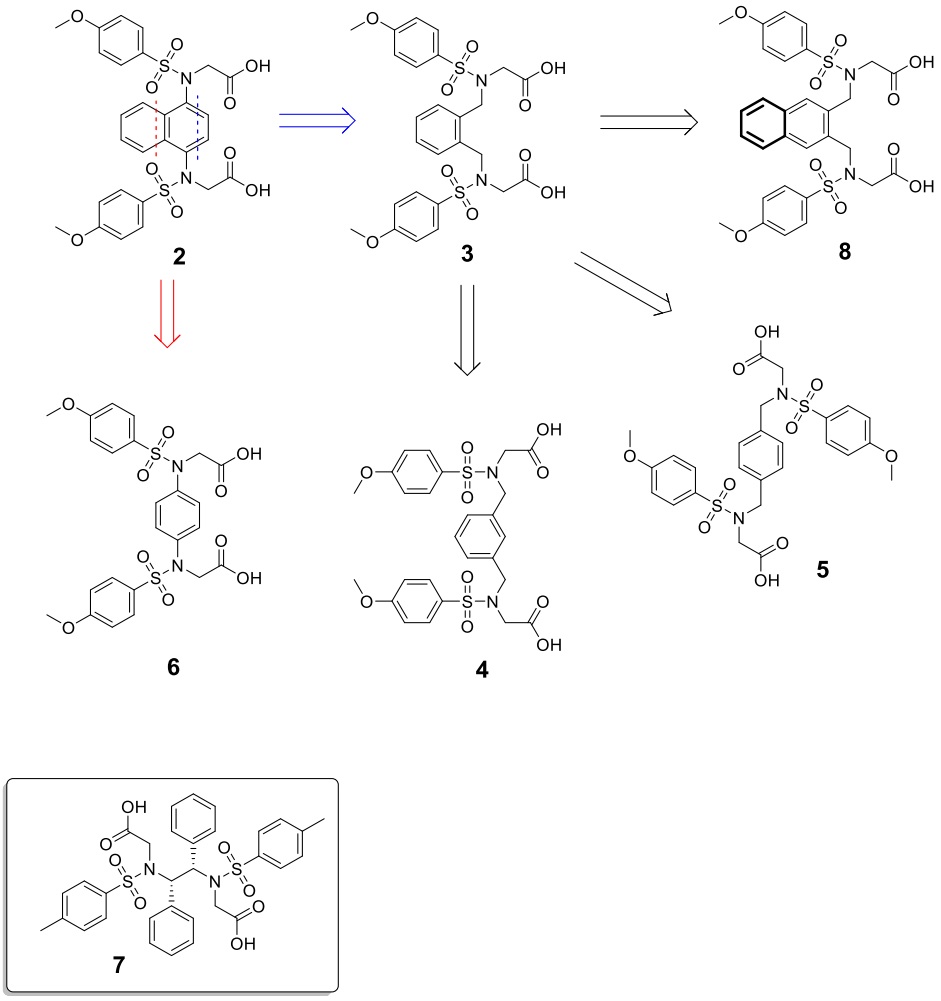
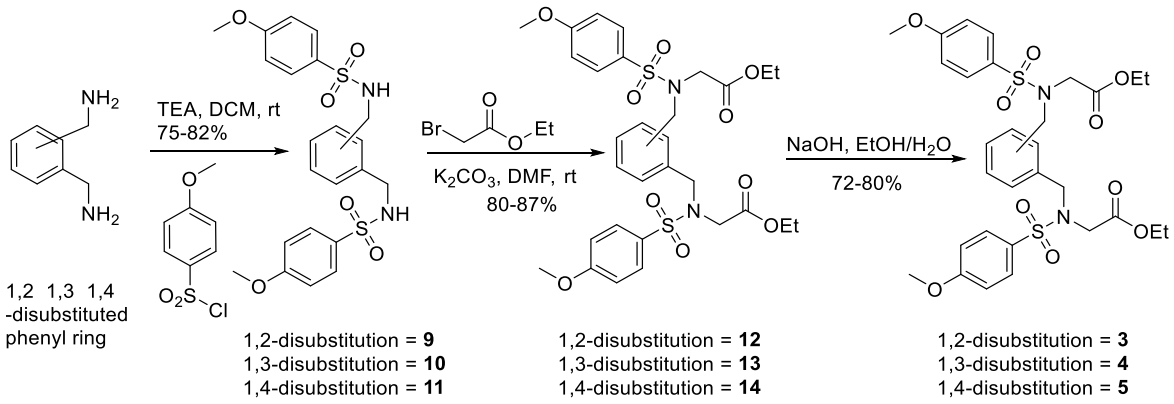


Figure 10. Simplification of Naphthalene analogs of compound **2**.

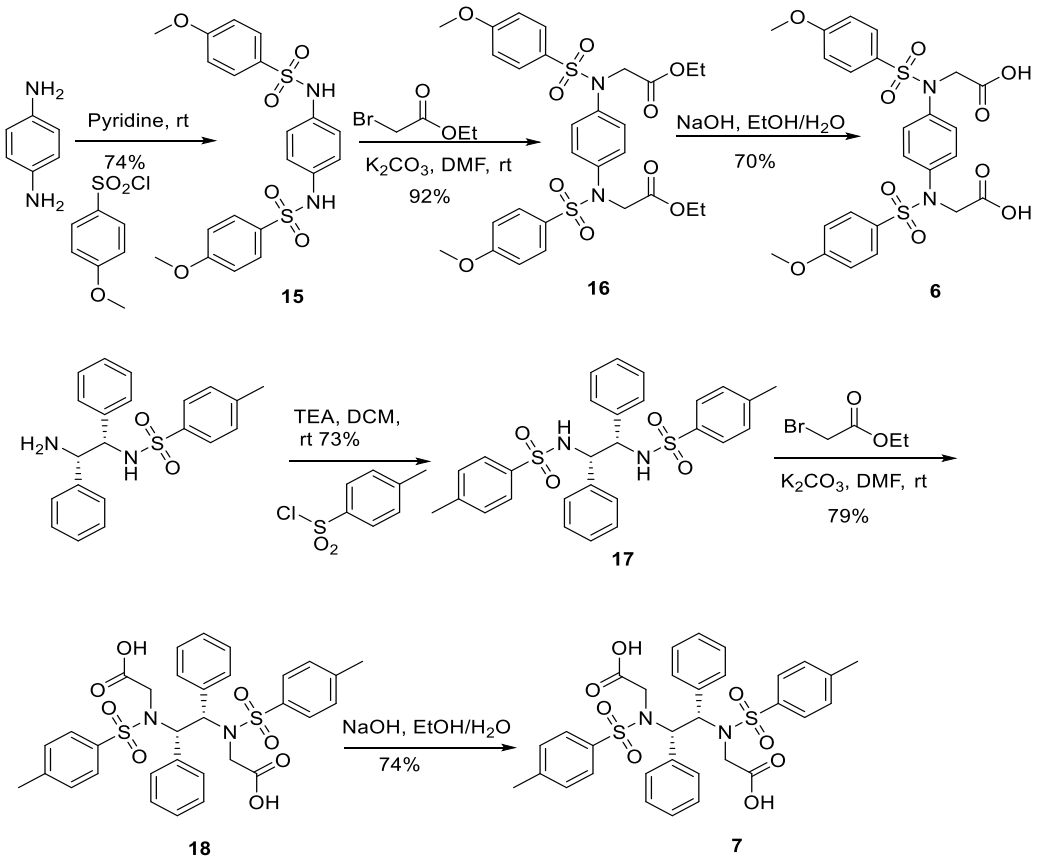
The synthetic route of compounds **3**, **4**, and **5** is shown in Scheme 1. Starting with commercially available diamines, treatment with 4-methoxy benzenesulfonyl chloride and triethylamine in anhydrous dichloromethane at 0 °C then at room temperature produced sulfonamide intermediates (**9-11**) in high yield. Alkylation of the sulfonamide intermediates (**12-14**) with ethyl bromoacetate in DMF at room temperature followed by hydrolysis with 2 N NaOH in ethanol:water (1:1, v/v) gave final compounds (**3-5**) as shown in Scheme 1.



Scheme 1. The synthesis of 1,2- 1,3- 1,4-disubstituted phenyl analogs (compounds **3, 4,** and **5**).

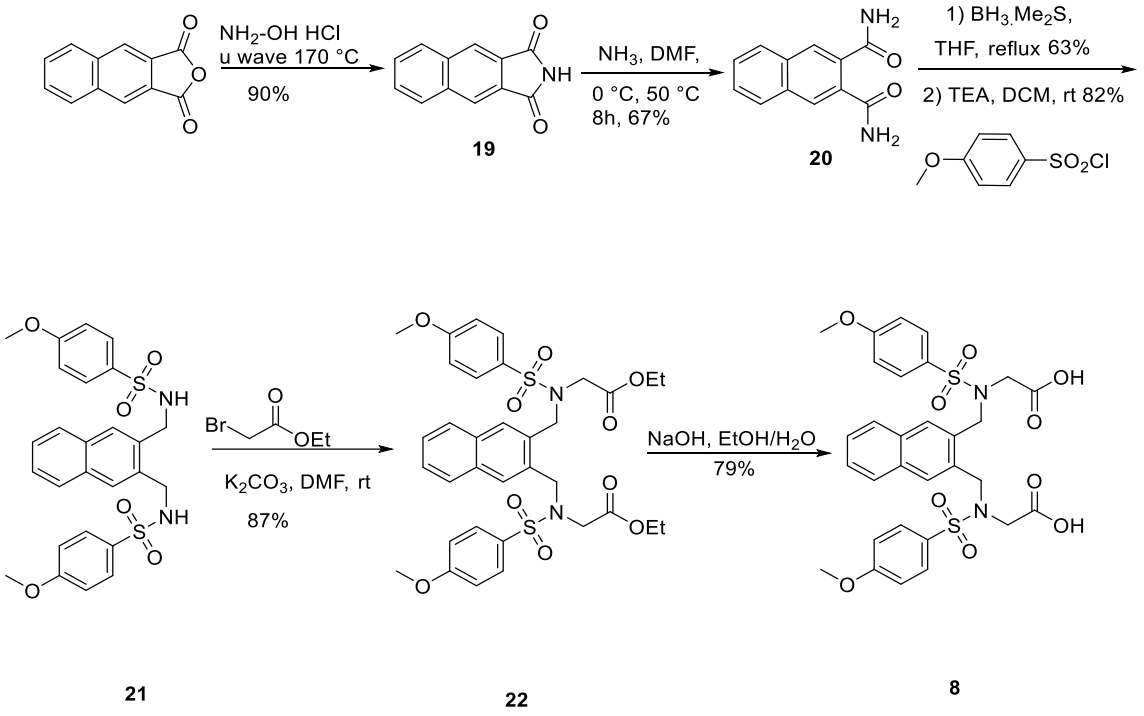
Treatment of *p*-phenylenediamine with 4-methoxy benzenesulfonyl chloride in anhydrous pyridine at 0 °C then at room temperature gave sulfonamide **15**. Treatment of sulfonamide **15** with ethyl bromoacetate in DMF followed by base hydrolysis gave final compound **6** (Scheme 2).

Synthesis of compound **7** is summarized in Scheme **2**. Treatment of (1S,2S)-(+)-N-*p*-tosyl-1,2-diphenylethylenediamine with 4-tosylchloride and triethylamine in anhydrous DCM produced compound **17**. Alkylation of di-sulfonamide compound **17** with ethyl bromoacetate in DMF followed by treatment with 2 N NaOH in ethanol: water gave final compound **7**.



Scheme 2. The synthesis of different disubstituted phenyl analogs (compounds **6** and **7**).

Compound **8** was synthesized using commercially available 2,3-naphthalenedicarboxylic anhydride as starting material (Scheme 3**)**. Treatment of anhydride with hydroxylamine hydrochloride at 150 °C using a microwave reactor gave phthalimide **19** which was then treated with ammonia in DMF at 50 °C to give diamide **20**. Reduction of diamide **20** using $BH_3.H_2S$ in anhydrous THF under reflux gave diamine which was treated with sulfonyl chloride to give compound **21**. Alkylation of sulfonamide **21** with ethyl bromoacetate followed by hydrolysis with 2 N NaOH gave final compound **8**.

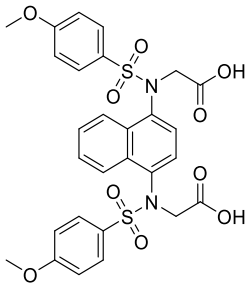
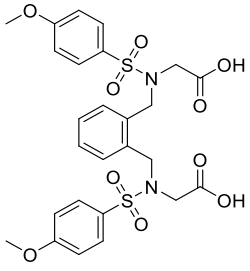


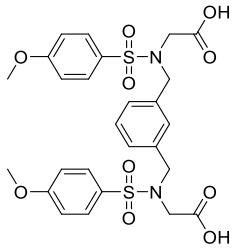
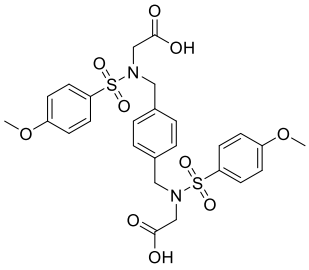
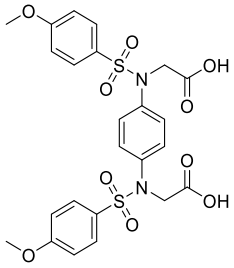
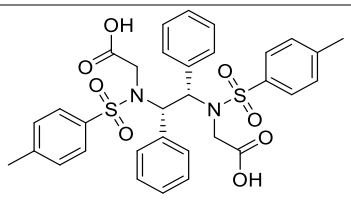
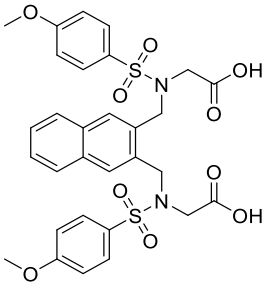
Scheme 3. The synthesis of 1,2-disubstituted naphthalene analog (compound **8**).

The 1,2- 1,3- and 1,4-disubstituted phenyl analogs (compounds **3**-**8**) were then evaluated for their inhibitory activity using an FP assay. Two different concentrations (5 and 50 uM) were used to compare different analogs, and the IC_{50} was measured for the more potent compounds. The results are summarized in Table 2. 1,2-disubstituted phenyl analog compound **3** is the most potent compound in comparison to 1,3- (compound **4**) and 1,4-disubstituted compound **5** with an IC_{50} of 2.3 ± 0.24 uM. Removal of the phenyl ring from the other side of the naphthalene ring produced compound **6** which showed the same inhibitory effects as the 1,2-disubstituted analog **3.** Fusing a phenyl ring to compound **3**, attached to the core-phenyl ring, gave compound **8** which showed a decrease in inhibitory activity compared to compound **3**. This decrease in activity suggest that this substitution is not tolerated. Finally, compound **7** has a phenyl ring attached to the benzylic carbon which gives two chiral centers with S,S stereochemistry. This compound showed no activity

against Keap1-Nrf2 interaction. In comparison to the naphthalene analog compound **2**, 1,2-disubstituted phenyl analogs showed less inhibitory effect which indicates the requirement of a naphthalene core as a key feature for optimum binding with the target protein. The aim of designing the series of derivatives was to get rid of the two nitrogens in the para positions attached directly to the phenyl ring which may cause metabolic stability problems. Therefore, we decided to do a further structure-activity relationship on the 1,2-disubstituted phenyl analog **3** in which the two nitrogen atoms are not directly connected to the phenyl ring. In addition, the moderate activity of analog **3** with an IC_{50} of 2.30 ± 0.24 uM which was considered a good starting point in this series.

Table 2. The inhibitory activities of different disubstituted phenyl analogs (compound **2-8)**.

	Compound structure	**% inhibition FP assay**		**IC_{50} (µM)**
		5 µM	**50 µM**	
2 (LH762)		100	100	0.11 ± 0.007
3 (LH769)		79	100.6	2.30 ± 0.24

4 (LH770)		13.7	19.4	ND
5 (LH771)		5.9	9.7	ND
6 (LH789)		80.6	105.6	ND
7 (LH876)		7.0	9.0	ND
8 (LH791)		24.7	58	ND

We explored the importance of the sulfonamide linker by introducing one carbon atom between sulfonamide and the aryl group as in compound **23** (Figure 11). Sulfonamide with

1,2-disubstitution compound **24** or 1,3-disubstitution compound **25** was also designed and synthesized to determine the requirement of this moiety in these analogs.

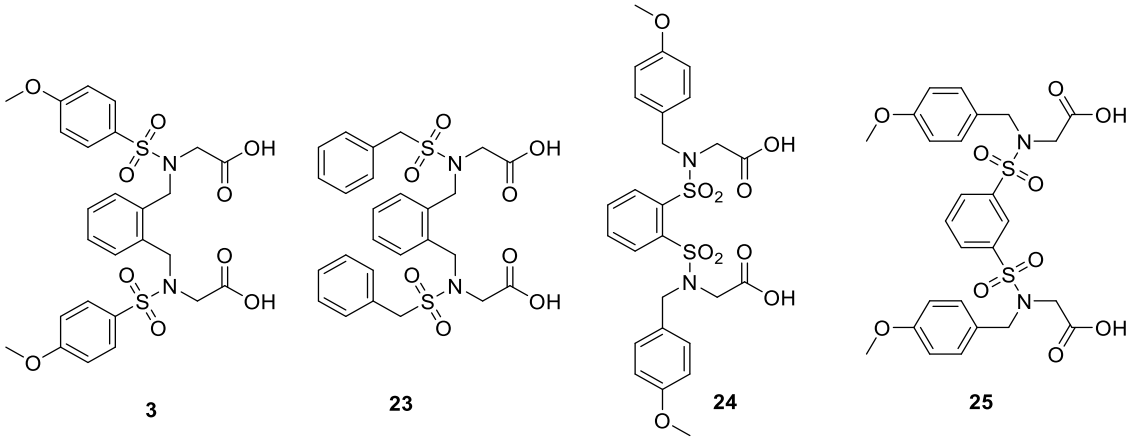
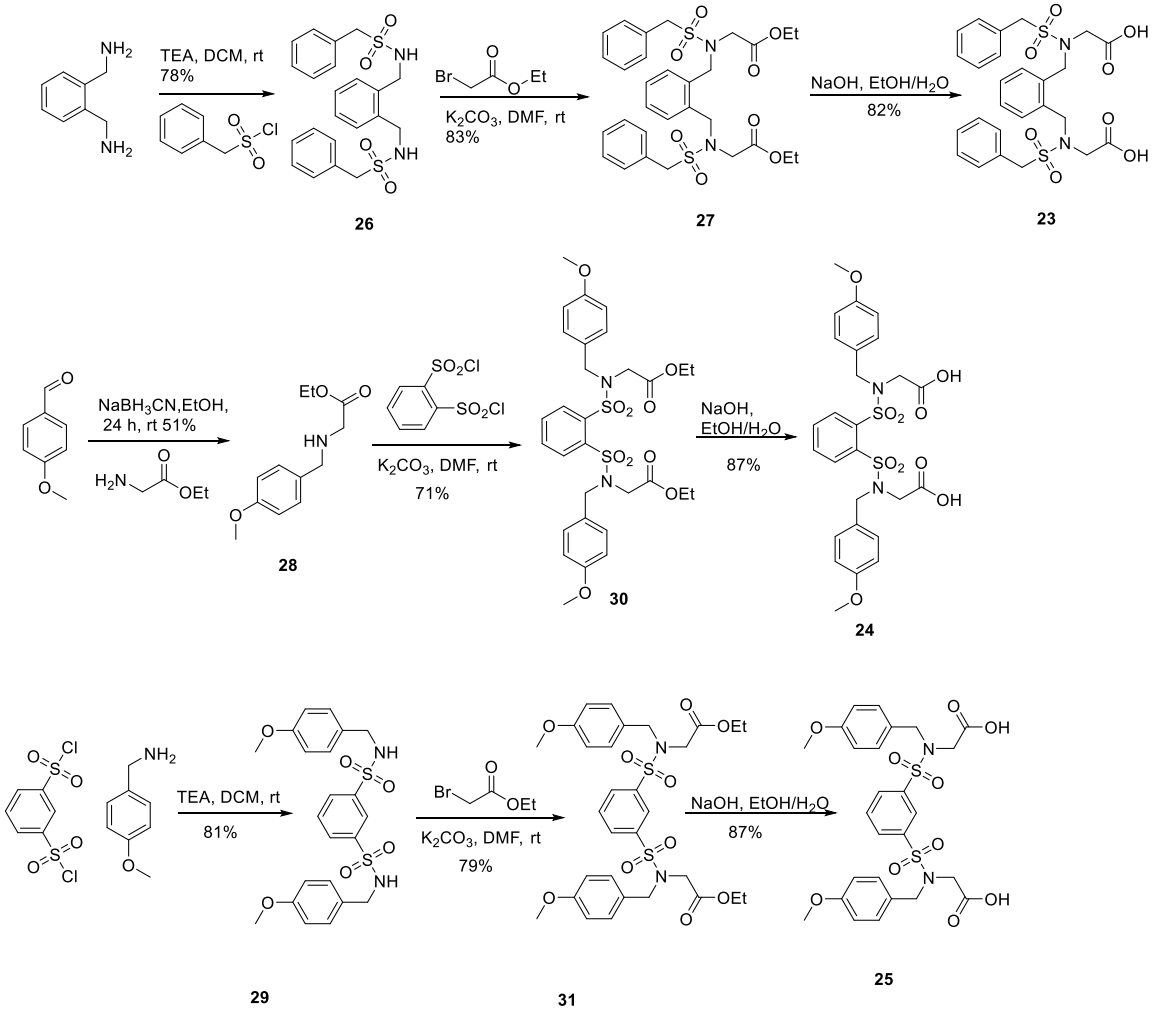


Figure 11. Structure-activity relationship on sulfonamide moieties of compound **3**.

The synthesis of the next group of analogs is outlined in Scheme 4. Treatment of commercially available diamine with sulfonyl chloride in the presence of triethylamine at room temperature gave sulfonamide **26** which was then alkylated and hydrolyzed to give the final compound **23**.

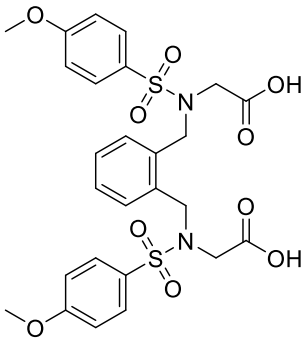
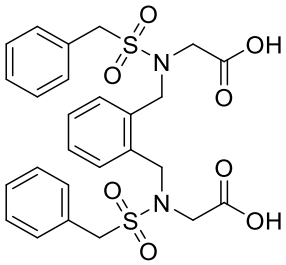
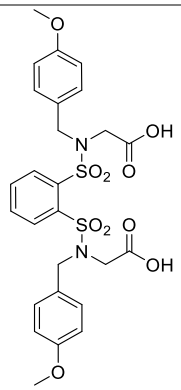
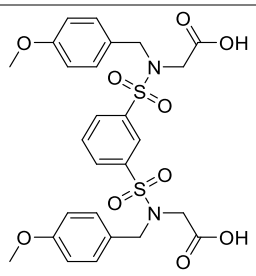
Intermediate compound **28** was synthesized using reductive amination. A solution of the 4-anisaldehyde, ethyl glycinate hydrochloride and $NaBH_3CN$ in EtOH was stirred at room temperature for 24 h to give compound **28**.[73] Treatment of benzene-1,2-disulfonyl chloride with compound **28** using K_2CO_3 in DMF produced compound **30** which was treated with base in EtOH:H_2O mixture to obtain the final product, compound **24**. For synthesis of meta substituted reverse amide compound **25**, benzene-1,3-disulfonyl chloride was treated with 4-methoxybenzylamine to produce compound **29**. Alkylation of compound **29** with ethyl bromoacetate followed by base hydrolysis gave the final compound **25**.



Scheme 4. The synthesis of compound **23** and **24**.

Then, these analogs were tested for their inhibitory effect against Keap1-Nrf2 interactions using an FP assay (Table 3). Introducing a methylene group between aryl and sulfonamide moiety as in compound **23** resulted in loss of activity. Analogs **24** and **25** showed no activity up to 50 uM. These modifications indicate the importance of a sulfonamide linker in this arrangement. Therefore, we decided to keep the arrangement of this moiety in the next analogs.

Table 3. The inhibitory activities of disubstituted phenyl analogs (compound **23-25)**.

Compound structure		% inhibition FP assay	
		5 µM	**50 µM**
3 (LH769)		79	100.6
23 (LH784)		0	12.7
24 (LH787)		13.7	15.1
25 (LH788)		9.4	11.6

Another important area to be explored is the alkyl group attached to sulfonamide moiety. Replacement of a hydrogen atom at the alpha carbon with an alkyl substituent results in a stereogenic center which might improve Keap1 binding. Different analogs were designed as described in Figure 12.

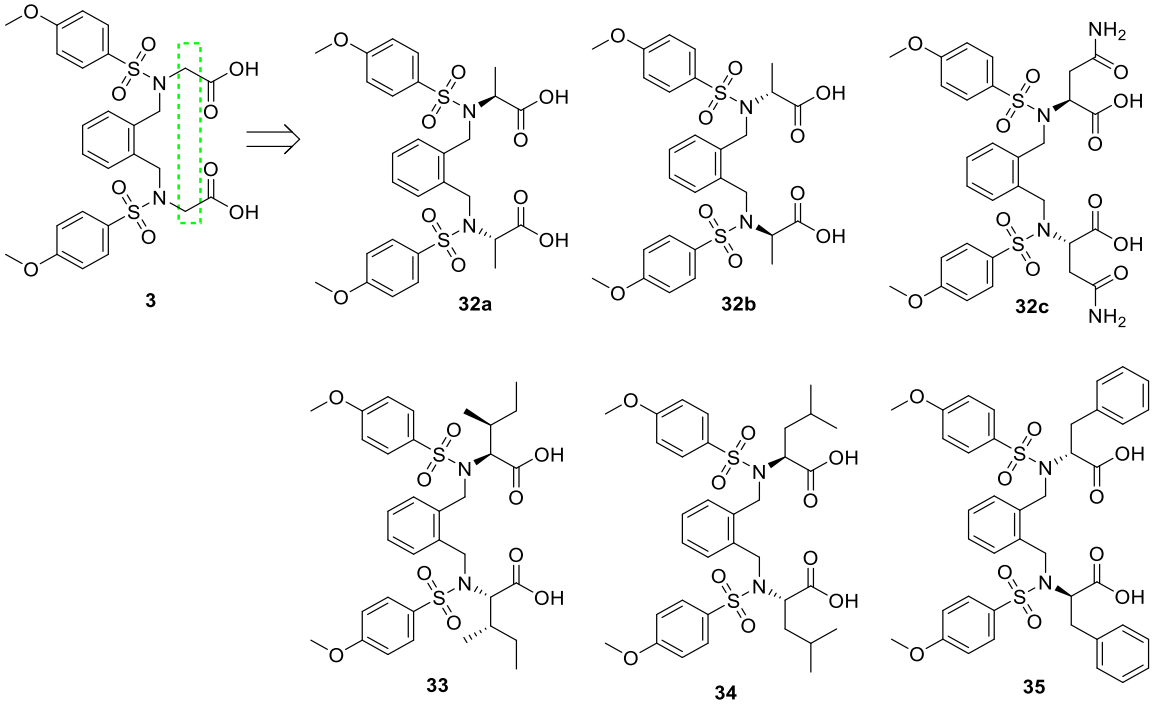
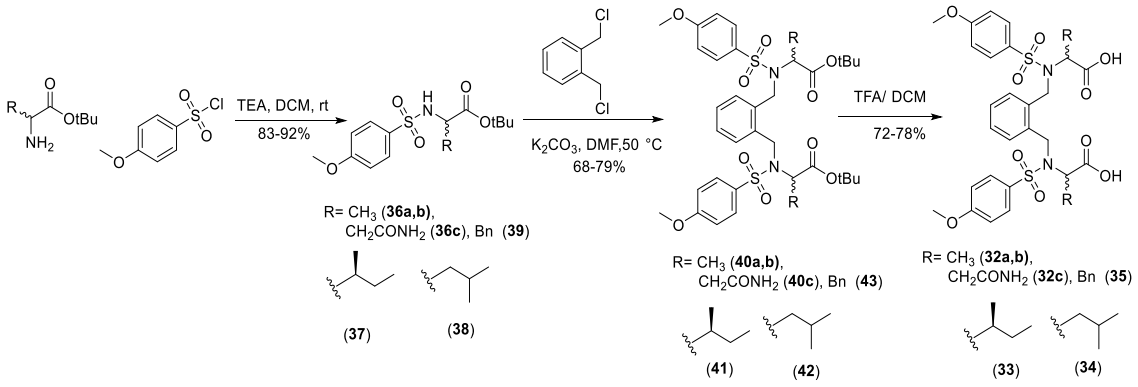


Figure 12. Structural modifications of alkyl side chain of compound **3**.

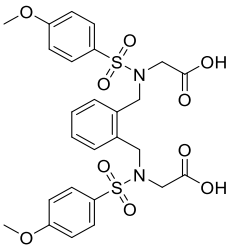
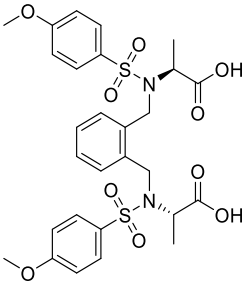
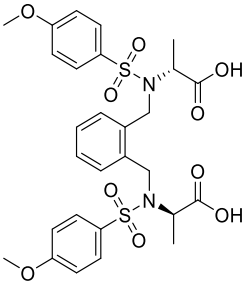
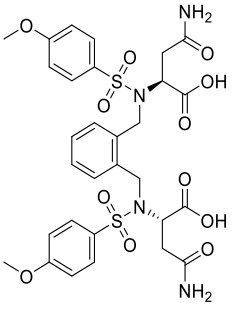
For synthesis of these analogs, commercially available R or S amino acid was treated with 4-methoxybenzenesulfonyl chloride and triethyl amine in DCM at room temperature to produce a sulfonamide intermediate. Treatment of sulfonamide with *o*-xylylene dichloride at 50 °C using K_2CO_3 as a base and DMF as a solvent gave alkylated sulfonamide. Removal of the *t*-butyl protecting group was done by using TFA/DCM 1:3 mixture at room temperature to get the final compounds (Scheme 5).

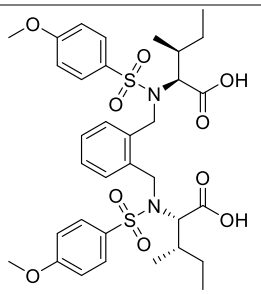
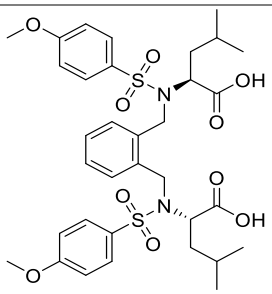
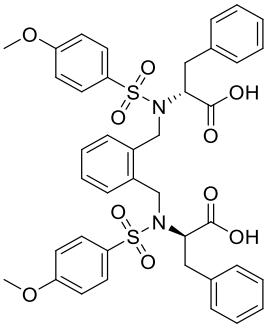


Scheme 5. Synthetic route for compounds **32-35**.

The inhibitory activity of amino acid derived analogs on Keap-Nrf2 protein-protein interaction was evaluated using an FP assay (Table 4). Introducing a methyl group with S,S stereochemistry resulted in an improvement in the activity by approximately 15 fold in comparing compound **32a** with compound **3** based on their IC_{50} (Table 4) while the analog **32b** with R,R stereochemistry is less potent in comparison to compound **32a**. Subsequently, we increased the number of carbon atoms and maintained S,S stereochemistry as in compounds **33** and **34**. As we can see in Table 4, this modification resulted in a decrease in activity of our analogs. Compound **32c**, which has amide moieties with S, S stereochemistry, is less potent in comparison to compound **3**. Analog **35** with R, R stereochemistry is less potent as compared to compound **3**. The important point in this SAR is that introducing stereocenters resulted in a more potent compound **32a** which may be due to the proper orientation of carboxylic acid moieties in the binding site.

Table 4. The inhibitory activities of disubstituted phenyl analogs (compound **32-34)**.

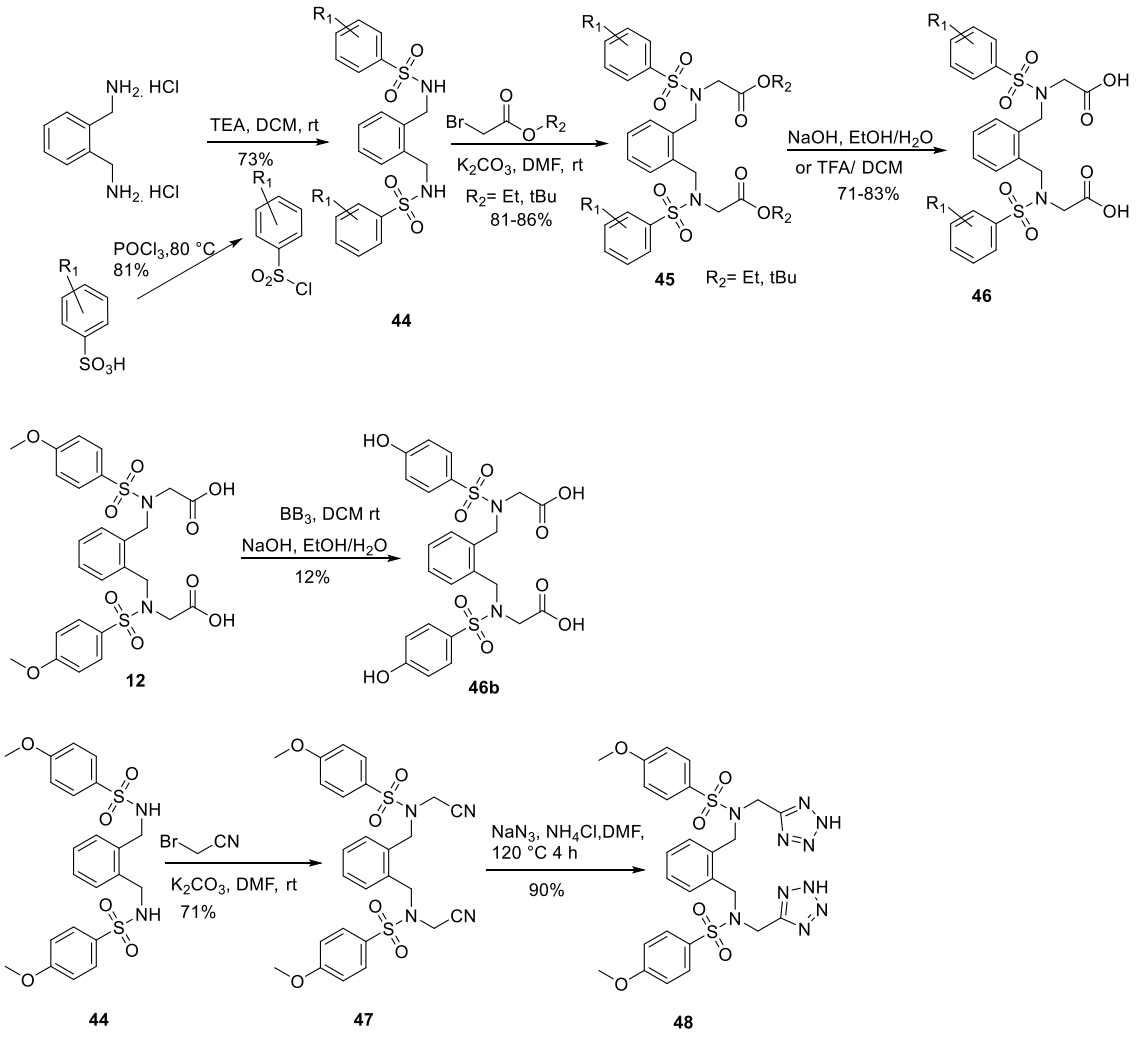
	Compound structures	% inhibition FP assay			IC_{50} (μM)
		5 μM	5 μM	50 μM	
3 (LH769)		ND	79	100.6	2.30 ± 0.24
32a (LH945)		101.4	103.9	109.9	0.15 ± 0.016
32b (LH967)		44.1	91.7	104.5	ND
32c (LH968)		ND	5.4	19.0	ND

33 (LH946)		ND	37.1	86.8	ND
34 (LH947)		ND	16.5	20.6	ND
35 (LH887)		ND	16.4	69.5	ND

The next area we explored is the 4-methoxyphenyl moiety and the bioisosteric replacement of acid moiety by tetrazole. Structure-activity relationships on this moiety might improve not only the activity, but also the physicochemical properties such as lipophilicity and ultimately improve cell-based activity.

Different electron-donating and/or electron-withdrawing groups were introduced at different positions on the phenyl ring linked with sulfonamide moiety. Scheme 6 outlines synthesis of the next group of analogs. O-xylylenediamine dihydrochloride was treated with different benzenesulfonyl chlorides using triethylamine as a base in anhydrous dichloromethane or acetonitrile at room temperature to give sulfonamide intermediate **44**.

Alkylation of a sulfonamide intermediate with different alkyl bromoacetates in DMF at room temperature followed by removal of an ester protecting group using acid or base gave final compound **46**. In order to get a tetrazole analog, sulfonamide intermediate **44** was treated with bromoacetonitrile in DMF at room temperature, and then the alkylated sulfonamide **47** was treated with NaN_3 in presence of NH_4Cl in DMF at 85 °C to get the tetrazole analog **48**.

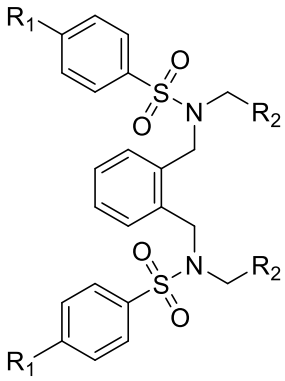


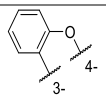
Scheme 6. Synthetic route for different substituted aryl sulfonamide analogs.

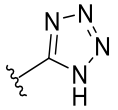
Then, the synthesized analogs were evaluated for their inhibitory activity against Keap-Nrf2 protein-protein interaction using an FP assay (Table 5). Removal of a methoxy or

methyl group resulted in reduction in the %-inhibition at 5uM to less than 40% suggesting the importance of the substitution in the phenyl ring. Replacement of a methoxy group with a nitro, amino, or fluoro group reduced the activity by about 25% or more at 5uM. Introducing hydrophobic moiety in the *para*-position of aryl sulfonamide moiety as in compounds **46k** and **46l** resulted in an improvement in the activity which may be due to π interactions with receptor binding site. We were interested in di-substitution on the phenyl ring and different dimethoxy and difluoro analogs were designed and synthesized. Only 2,6-difluoro analog **46j** showed an improvement in activity with IC_{50} of 1.78 ± 0.4 uM. Bioisosteric replacement of carboxylic acid moiety in compound 3 with tetrazole, **48**, resulted in improvement in activity with IC_{50} of 1.17 ± 0.5 uM.

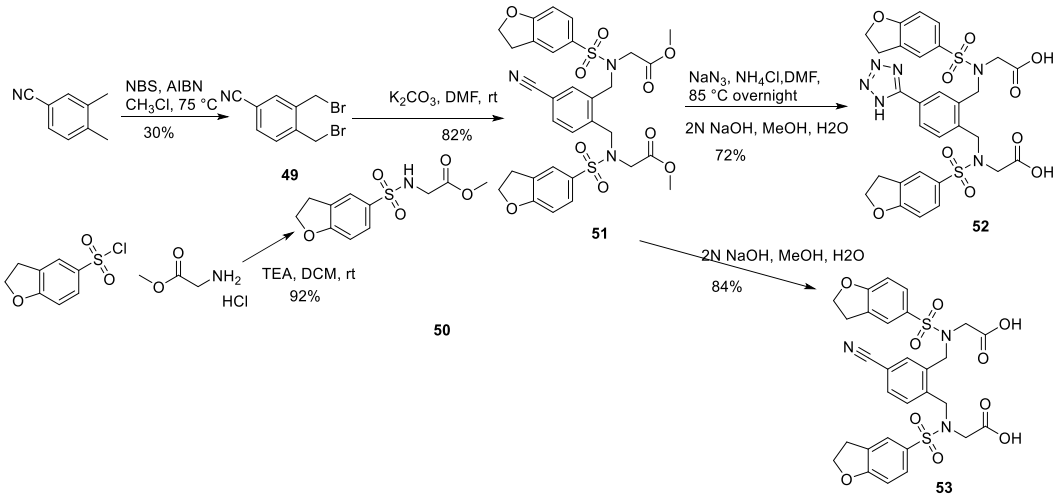
Table 5. The inhibitory activities of different substituted aryl sulfonamide analogs (compound **46**-**48**).



	R_1	R_2	% inhibition FP assay		IC_{50} (μM)
			5 μM	50 μM	
3 (LH769)	4-OCH_3	COOH	79	100.6	2.30 ± 0.24
46a (LH786)	4-H	COOH	38	75.7	ND
46b (LH813)	4-OH	COOH	36.1	83.5	ND
46c (LH790)	4-NO_2	COOH	62.5	95.8	ND
46d (LH792)	4-NH_2	COOH	61.3	99.2	ND
46e (LH811)	4-F	COOH	51.1	84.4	ND
46f (LH810)	3-F	COOH	38.5	87.2	ND
46g (LH805)	2,4-diOCH_3	COOH	57.8	95.6	ND
46h (LH807)	2,4-diF	COOH	68.8	91.8	ND
46i (LH809)	3,4-diF	COOH	37.9	93.6	ND
46j (LH806)	2,6-diF	COOH	86.8	98	1.78 ± 0.4
46k (LH886)	4-OBn	COOH	81.9	93.5	0.57 ± 0.04
46l (LH883)		COOH	96.2	98.1	0.42 ±0.03
47 (LH783)	4-OCH_3	CN	6.5	18.4	ND

48 (LH785)	4-OCH_3		68.1	83.1	1.17 ± 0.5

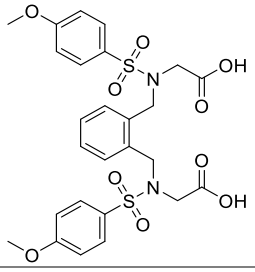
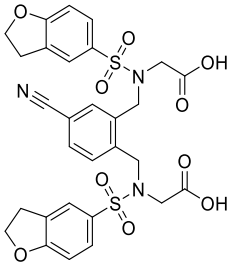
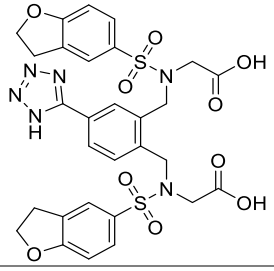
The next area being explored is the position 4 in the core-phenyl moiety. The effect of introducing moieties capable of hydrogen bonding and hydrophobic interactions of compound **3** with the receptor binding site was evaluated. As a result, analogs with tetrazole moiety **52** or cyano moiety **53** were designed and synthesized. Synthesis of these analogs is summarized in Scheme 7. Bromination of commercially available o-xylene with NBS/AIBN in chloroform as a solvent at 80 °C using a sealed tube gave brominated intermediate **49**. Treatment of glycine with 4-methoxybenzenesulfonyl chloride gave sulfonamide **50** which was then treated with compound **49** using K_2CO_3 in DMF at room temperature to give compound **51.** Base hydrolysis with 2 N NaOH gave final compound **53**. Treatment of intermediate **51** with sodium azide at 80 °C followed by base hydrolysis gave compound **52**.



Scheme 7. Synthetic route for 4-substituted analogs (compounds **52** and **53**).

The activity of synthesized analogs was evaluated using an FP assay (Table 6). As we can see from assay data, analogs with substitution on position 3 with either cyano or tetrazole moiety reduces activity by more than 50% at 5 μM as compared to compound **3**. This indicates that these substitutions are not appropriate for binding to the Keap1 Klech domain.

Table 6. The inhibitory activities of different substituted aryl sulfonamide analogs (compounds **52-53**).

	Compound structure	**% inhibition FP assay**	
		5 μM	50 μM
3 (LH769)		79	100.6
52 (LH884)		34.8	86
53 (LH885)		24.9	57

2.2 Synthesis and evaluation of naphthalene-based direct inhibitors of Keap1-Nrf2 interaction

Replacement of the naphthalene core region in compound **2** (% inhibition =100 at 5 μM) with a phenyl ring as seen in compound **3** (% inhibition =79 at 5 μM), and **6** (% inhibition =80.6 at 5 μM) resulted in less potent analogs (Table 2). This confirms the necessity of the naphthalene ring as a key feature for protein binding and the next set of analogs with a naphthalene core was designed with specific goals: (1) improve in vitro activity, and (2) enhance cellular activity. To achieve these goals, we had to design a new set of analogs.

We focused our SAR studies around three regions of compound **2**: Region I the sulfonamide linker, region II the methoxyphenyl region, and region III the naphthalene core region (Fig. 13).

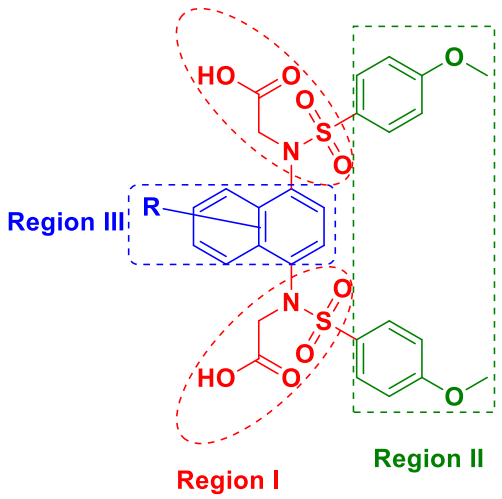


Figure 13. Regions of Structure-activity relationship on compound **2**.

2.2.1 Synthesis and evaluation of different analogs of compound 2 with modification on linkers between naphthalene ring and aryl moiety

Analogs with different sulfonamide linkers were designed to explore the importance of the sulfonamide linker between the naphthalene moiety and the flanking aryl moiety through extension by a 1 carbon or carbonyl group (Fig. 14).

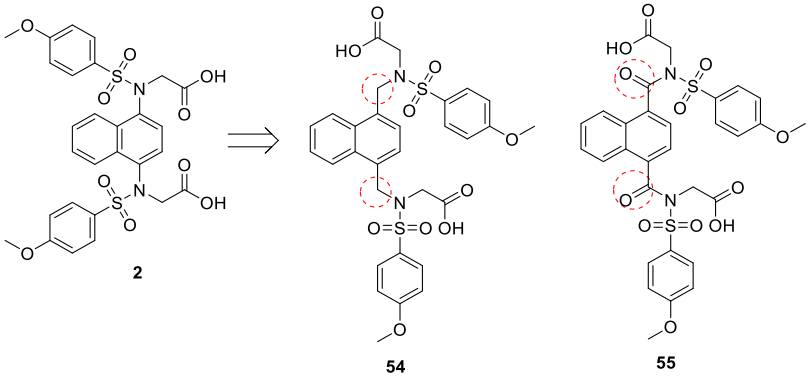
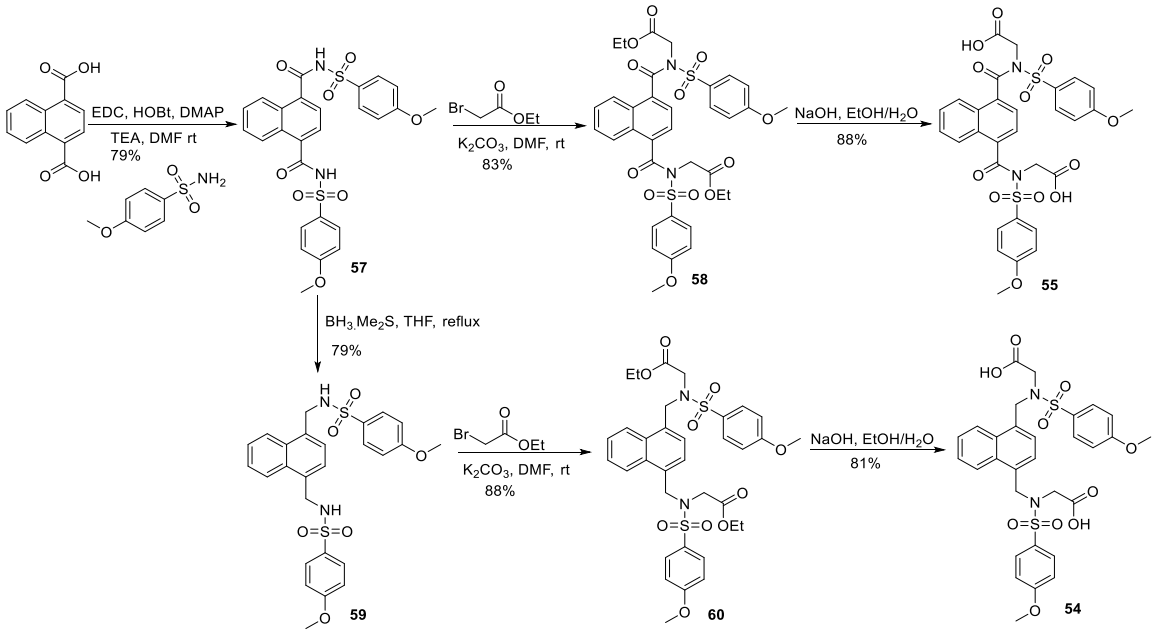


Figure 14. Modification on sulfonamide moieties of compound **2**.

Synthesis of this set of series is summarized in Scheme 8. According to Scheme 8, commercially available 1,4-naphthalenedicarboxylic acid was coupled with a commercially available sulfonamide in the presence of EDC, HOBt, DMAP, and TEA in DMF at room temperature under nitrogen atmosphere to give compound **57** in a good yield. Treatment of acyl sulfonamide intermediate **57** with ethyl bromoacetate in DMF at room temperature gave compound **58**. Base hydrolysis with 2N NaOH in EtOH: H_2O 1:1 at room temperature of compound **58** gave the final compound **55**.

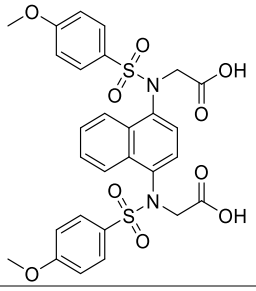
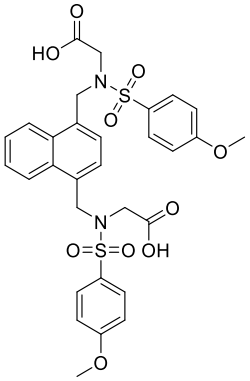
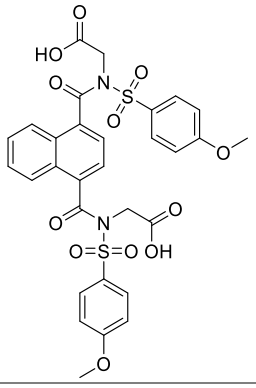
To get compound **54**, acyl sulfonamide group in intermediate **57** was reduced to sulfonamide using $BH_3.Me_2S$ in anhydrous THF under reflux. Alkylation of the sulfonamide **59** intermediate followed by base hydrolysis gave compound **54**.



Scheme 8. Synthesis of different disubstituted naphthalene analogs (compounds **54** and **55**).

Results from an FP assay of these analogs are summarized in Table 7. As we can see from the data, all of these modifications resulted in completely inactive analogs against Keap1 Nrf2 interaction. This indicates the necessity of this sulfonamide functional group to maintain the activity of this set of analogs.

Table 7. The inhibitory activities of different disubstituted naphthalene analogs (compound **54-56**).

	Compound structure	**% inhibition FP assay**	
		5 µM	**50 µM**
2 (LH762)		100	100
54 (LH844)		0	2.5
55 (LH845)		4	3.4

2.2.2 Synthesis and evaluation of different aryl sulfonamide analogs of compound 2

Based on our results from the SAR studies of compound **2**, a naphthalene core and a sulfonamide linker have a crucial role in maintaining protein binding of compound **2** with the Keap1 Klech domain.

We had aimed to design analogs containing these moieties while studying the SAR of flanking aryl moiety (region II, Fig. 15) to improve physicochemical properties and activity of the designed analog.

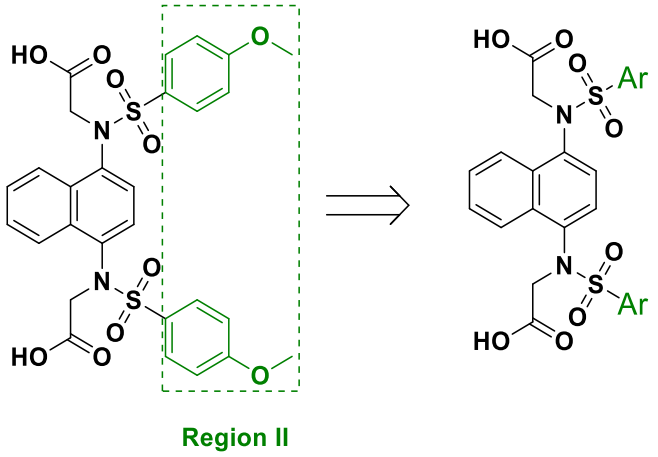
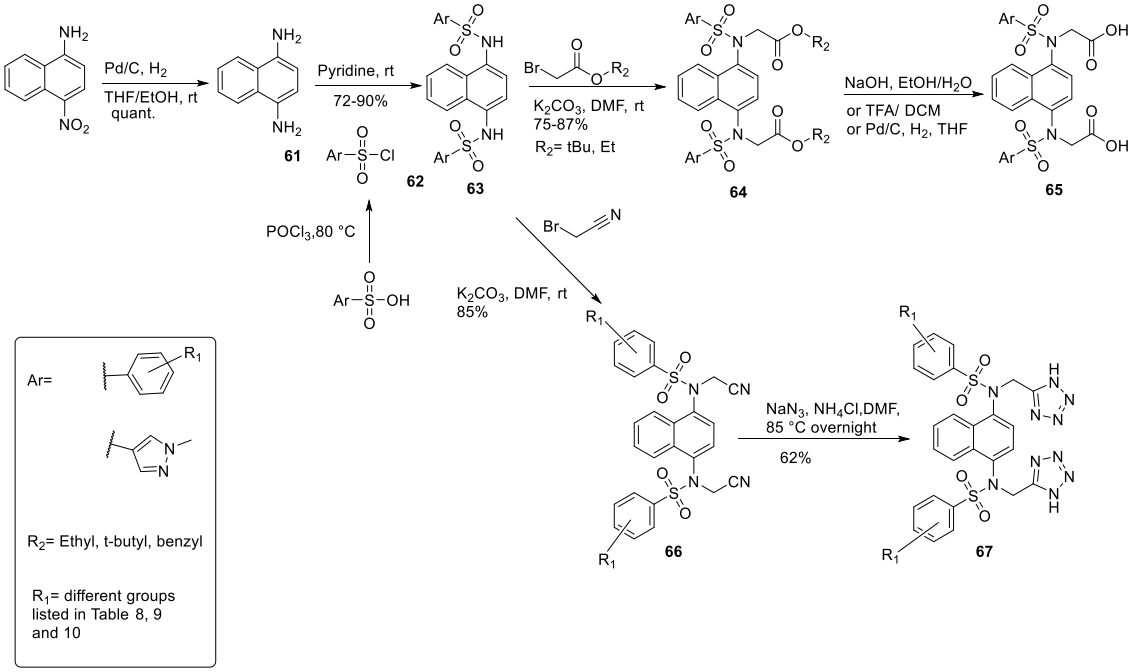


Figure 15. Structure-activity relationship on region II of compound **2**.

Scheme 9 outlines the synthesis of the naphthalene sulfonamide derivatives. For these derivatives, 4-nitro-1-naphthylamine was the starting material. Reduction of a nitro-group with H_2(g) and Pd/C (10%) in EtOH: THF 1:1 at room temperature produced diamine compound **61** in high yield. Sulfonic acids were converted to the corresponding sulfonyl chloride, represented by **62** using phosphorus oxychloride. Subsequently, diamine

intermediate was treated with appropriate arylsulfonyl chloride in pyridine at room temperature to get sulfonamide intermediate **63**. Alkylation of sulfonamide **63** with alkyl bromoacetate in the presence of K_2CO_3 at room temperature followed by removal of the carboxylic acid protecting group gave the final compound **65**. For analogs with tetrazole moieties, sulfonamide **63** was alkylated with bromoacetonitrile and K_2CO_3 in DMF followed by treatment with NaN_3 in DMF at 85 °C to produce the final compound **67**.



Scheme 9. Synthesis of different disubstituted naphthalene analogs (compounds **65** and **67**).

Using an FP assay, inhibitory activity of synthesized analogs against Keap1-Nrf2 protein-protein interaction was evaluated (Table 8). At the *para*-position, replacement of a methoxy group with trifluoromethyl resulted in a three-fold reduction in activity ($IC_{50=}$ 384 ± 19 nM), while replacement with a bromo-group resulted in about a two-fold reduction. Replacement of a methoxy group by either a trifluoroacetamide, a biphenyl, or a phthalimide group retained activity, while replacement with methanesulfonamide resulted

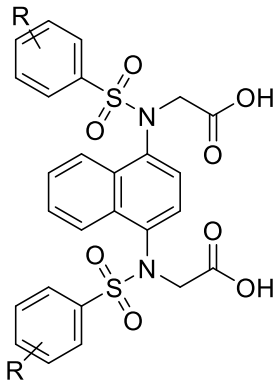
in less active analogs with IC_{50} 194 ± 18 nM. These results indicate that a trifluoroacetamide, a biphenyl, or a phthalimide group might be an optimum substitution for a 4-methoxy group depending on cell-based activity.

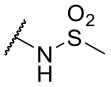
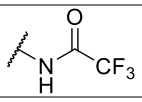
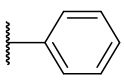
Replacement of a 4-methoxy group with either a 2-chloro or a 2-trifluoromethyl group resulted in less active analogs. Therefore, mono-substitution at the *ortho*-position generally resulted in less potent derivatives.

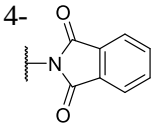
For disubstituted analogs, compounds with a 2-Br and a 4-OCH_3 group on a flanking phenyl ring were slightly less active with IC_{50} 184 ± 7 nM. A reduction in activity was observed in analogs with a 2-OCH_3 and a 4-Br group and a further reduction in activity was observed when a 2-OCF_3 and a 4-Br group replaced a 4-OCH_3 group.

The next pattern of substitution we explored is meta and para di-substitution. Analog with an electron withdrawing group (3-CN, 4-OCH_3) is less active in comparison with compound **2** (% inhibition at 5 uM = 66.5). Replacement of a 4-OCH_3 group with a 4-F with introduction of either an electron withdrawing group (3-CN) or an electron donating group (3-CH_3) resulted also in less analogs with% inhibition at 5 uM of (48.9, and 67.6) respectively. The 2,6-diF analog was the most potent analog in the *ortho*-disubstituted phenyl analog **46k** (Table 5) while the naphthalene analog **65j** showed a slight decrease in activity with IC_{50} 224 ± 50 nM.

Table 8. The inhibitory activities of different substituted aryl sulfonamide analogs (compounds **65a-o)**.



	R	% inhibition FP assay			IC_{50} (nM)
		0.5 µM	**5 µM**	**50 µM**	
2 (LH762)	4-OCH_3	100	100	100	110 ± 7
65a (LH818)	4-CF_3	ND	100	100	384 ± 19
65b (LH832)	4-Br	87.5	100.7	92	235 ± 37
65c (LH829)	2-Cl	79.4	97.9	93.4	ND
65d (LH820)	2-CF_3	12.9	23.9	52.5	ND
65e (LH825)	2-Br , 4-OCH_3	88.2	99.3	95.3	184 ± 7
65f (LH821)	2-OCH_3, 4-Br	56.1	95.2	94.6	ND
65g (LH822)	2-OCF_3, 4-Br	15.4	56.2	86.3	ND
65h (LH824)	3-CN, 4-OCH_3	66.5	100.7	98	ND
65i (LH828)	3-CN , 4-F	48.9	95.2	98	ND
65j (LH834)	3-CH_3 , 4-F	67.6	96.1	103	ND
65k (LH812)	2,6-diF	ND	101	101	224 ± 50
65l (LH921)	4- 	68.3	85.0	91.2	194 ± 18
65m (LH926)	4- 	76.1	92.1	100.6	126 ± 13
65n (LH922)	4- 	91.5	95.9	100.2	70 ± 6

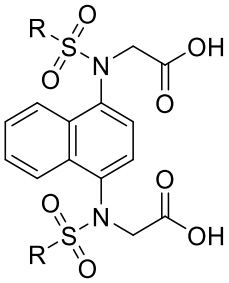
65o (LH923)	4- 	84.8	96.0	100.7	82 ± 7

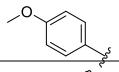
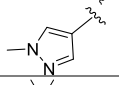
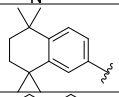
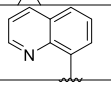
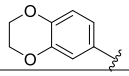
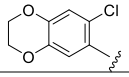
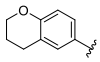
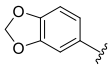
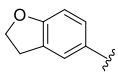
The next set of analogs we had aimed to study was those with possible bioisosteric replacement of phenyl moiety (Table 9). This included a variety of heterocycles such as pyrazole, quinoline, 2,3-dihydrobenzofuran, or 2,3-di-hydro-4H-benzopyran.

Naphthalene, tetrahydronaphthalene, 1,3-benzodioxole, 2,3-dihydrobenzo[b][1,4]dioxin moieties are the other replacements that were designed and synthesized. Unfortunately, these heterocyclic compounds that contain a pyrazole or quinoline moiety did not provide any desired inhibitory activity. 4-Bromonaphthalene analog **65t** retained some activity with an IC_{50} of 331 ± 69 nM while the naphthalene analog **65s** and the tetrahydronaphthalene analog **65q** were less active in comparison to compound **2**.

2,3-Dihydro-benzofuran, 2,3-dihydro-4H-benzopyran, 1,3-benzodioxole, and 2,3-dihydrobenzo[b][1,4] dioxin analogs were as active as 4-methoxyphenyl compound in our FP assay condition. For these analogs, we need to do a cell-based assay to better differentiate between them.

Table 9. The inhibitory activities of different substituted aryl sulfonamide analogs (compound **65p**-**y**).



R		% inhibition FP assay			IC_{50} (nM)
		0.5 µM	5 µM	50 µM	
2 (LH762)		97	100	100	110 ± 7
65p (LH823)		21.6	71.5	96.2	ND
65q (LH827)		8.7	37.2	83.4	ND
65r (LH830)		25.1	75	98.2	ND
65s (LH831)		57	92.2	83.9	ND
65t (LH833)		89.9	103	87.4	331 ± 69
65u (LH837)		96	100.7	101.4	120 ± 11
65v (LH835)		99.6	97.4	98.5	144 ± 5
65w (LH838)		109.6	102.1	105.2	146 ± 9
65x (LH843)		85.6	96.6	98	149 ± 13
65y (LH839)		85.4	100.8	100.7	164 ± 18

For potent analogs of compound **2,** we had aimed to study the effect of isosteric replacement of carboxylic acid moiety with tetrazole moiety on inhibitory activity (Fig. 16).

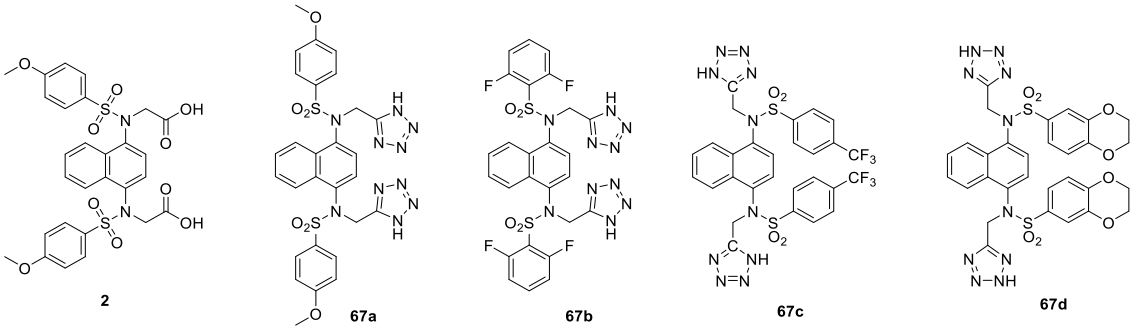
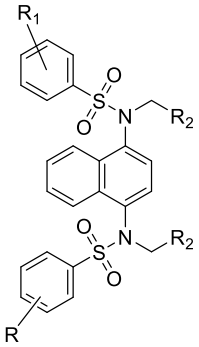
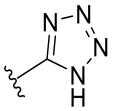
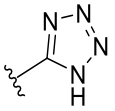
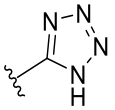
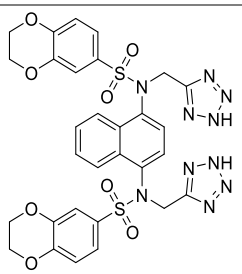


Figure 16. Different tetrazole analogs of compound **2**.

Based on the FP assay, except for the di-fluoro analogs **67b** and **67c**, tetrazole analogs were as active as when the compounds contained the acid moieties and further cell-based assays may differentiate between these compounds (Table 10).

Table 10. The inhibitory activities of different tetrazole analogs (compounds **67a-d**).



	R1	R2	% inhibition FP assay			IC_{50} nM
			0.5 μM	5 μM	50 μM	
2 (LH762)	4-OCH_3	COOH	ND	100	100	110 ± 7
67a (LH715)	4-OCH_3		ND	93.3	94.1	96.7± 6
67b (LH814)	2,6-di-F		ND	68.1	83.1	418 ± 59
67c (LH819)	4-CF_3		80	96.3	103.4	302 ± 35
67d (LH841)			104.2	98.5	96.4	93.5 ± 6

2.2.3 Synthesis and evaluation of substituted naphthalene analogs of compound 2

The third region we had aimed to explore in compound **2** is the substitution on naphthalene core moiety (region III, Fig.17). To do this, we designed, and synthesized another series of analogs to improve in vitro and in vivo activity of our designed compounds.

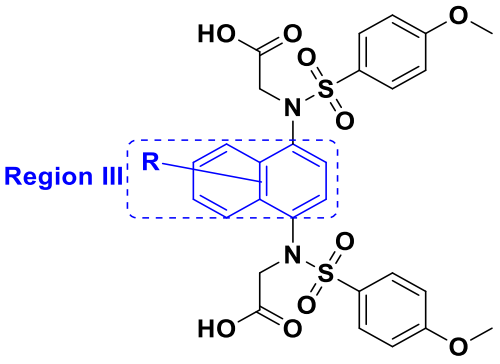
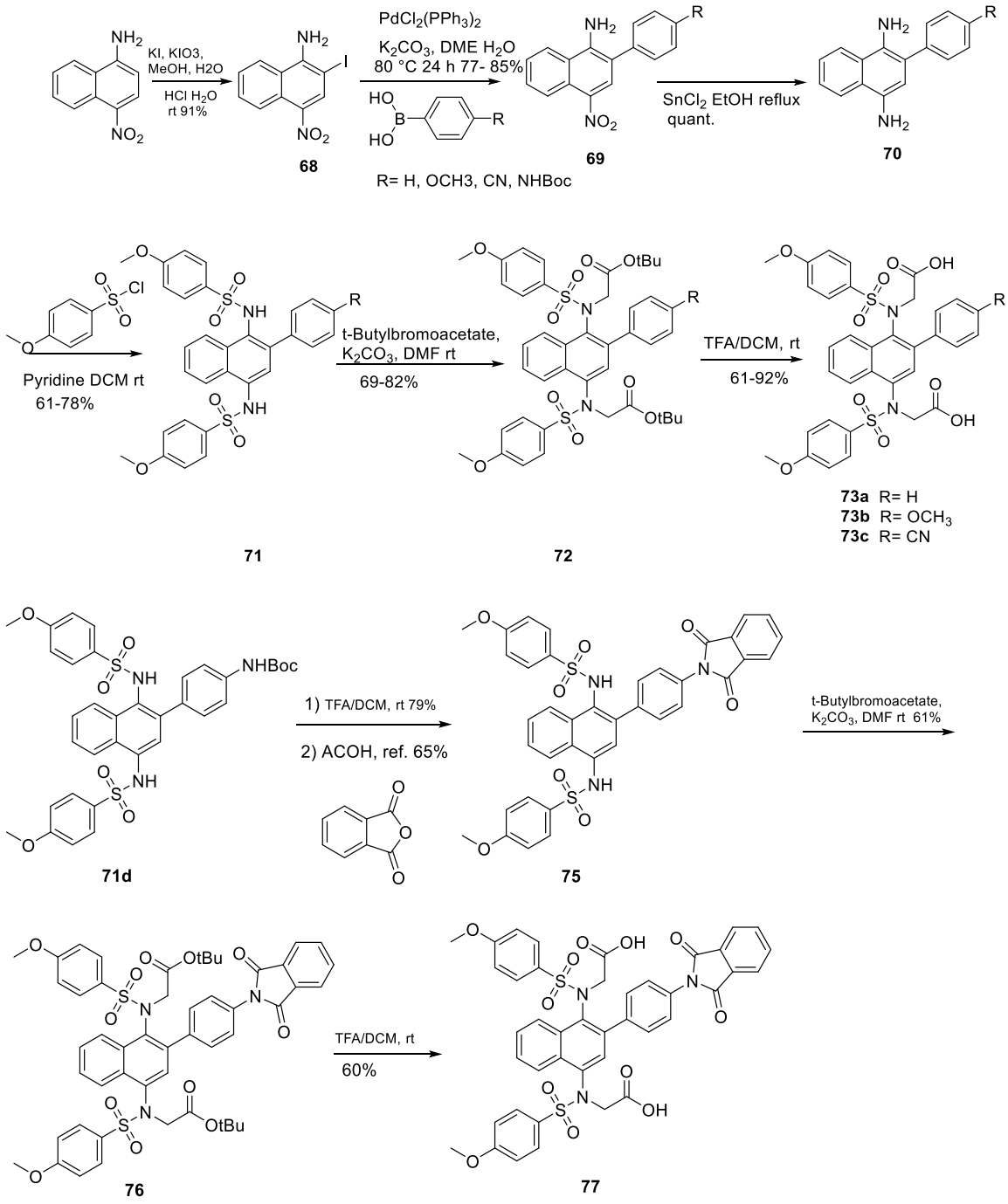


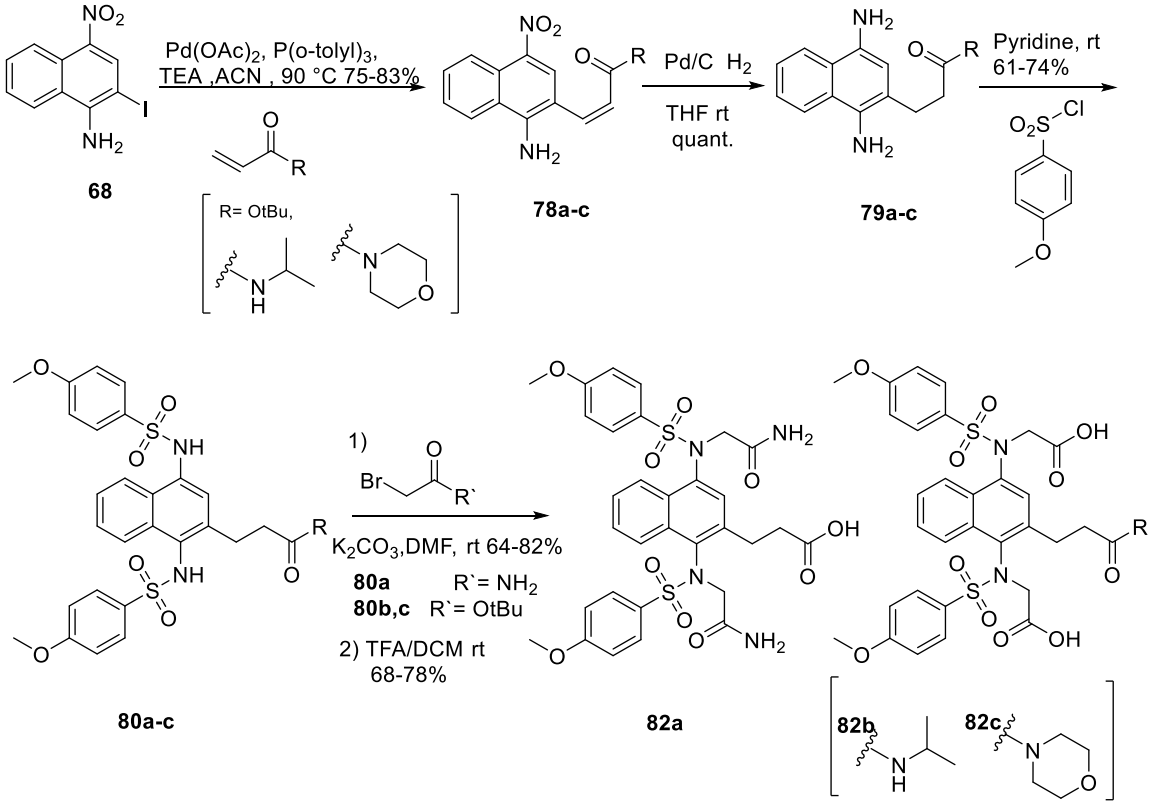
Figure 17. Substitution on naphthalene ring of compound **2**.

Synthesis of this series of analogs is summarized in Scheme 10. Treatment of 4-nitro-1-naphthylamine with KIO_3/KI /HCl gave the 2-iodo-intermediate **68** in high yield.[74] Intermediate **68** was then subjected to Suzuki cross-coupling to give 2-aryl intermediate **69**. The general procedure for the Suzuki coupling involved $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base in DME/H_2O (2:1) at 80 °C.[75] Subsequently, the nitro group was reduced using tin chloride in DMF at room temperature to get diamine intermediate **70** in good yields. Treatment of diamine **70** with *p*-methoxybenzenesulfonyl chloride in pyridine at room temperature gave the sulfonamide intermediate **71**. Alkylation of sulfonamide intermediates was done using *t*-butyl-bromoacetate as an alkylating agent, K_2CO_3 as a base, and DMF as a solvent. Removal of the *t*-butyl group was done using TFA: DCM mixture in a 1:3 ratio at room temperature to generate the final compound **73**. Treatment of **71d** with TFA/DCM 1:3 at room temperature followed by treatment with phthalic anhydride in acetic acid under reflux gave compound **75**. Alkylation of compound **75** with *t*-butyl bromoacetate followed by treatment with acid to remove the *t*-butyl protecting group gave compound **77**.



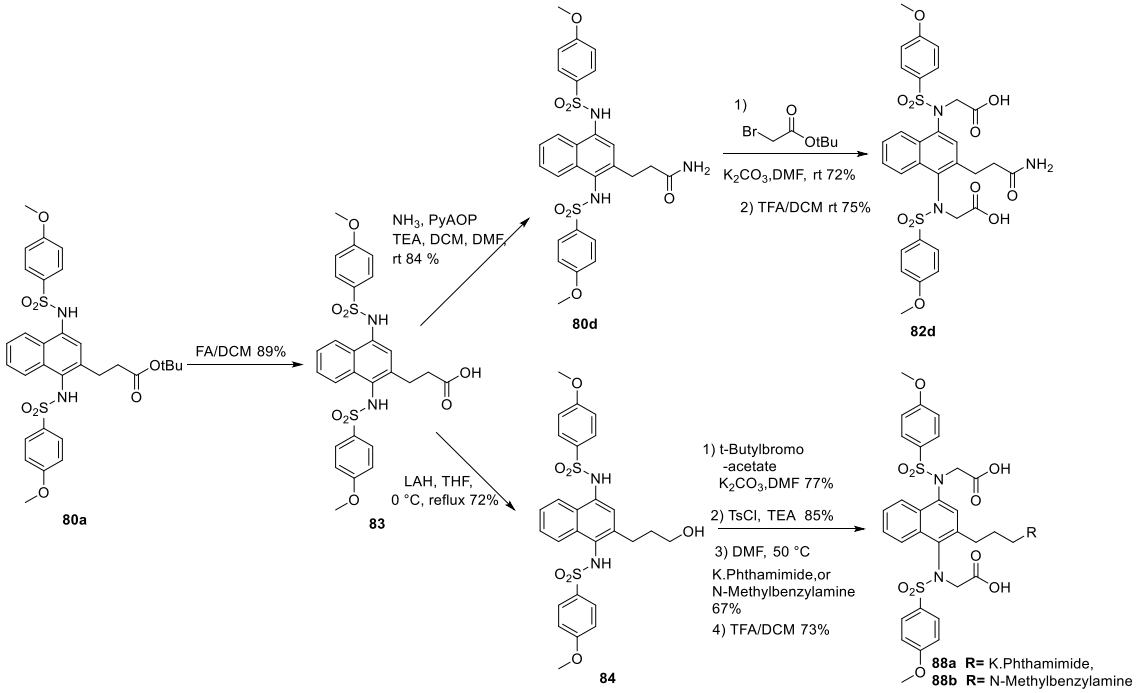
Scheme 10. Synthesis of different 2-substituted naphthalene analogs **(**compounds **73** and **77**).

The key intermediate **82** was used to synthesize 2-alkyl substituted naphthalene derivatives. The 2-iodo intermediate **82** was subjected to Heck-couplings to give 2-substituted alkene intermediate **78**. The general procedure for the Heck-coupling involved using $Pd(OAc)_2$, tri(o-tolyl)phosphine, and TEA in ACN at 90 °C. [76] Subsequently, the alkene double bond and nitro group were reduced using H_2(g) and Pd/C (10%) in THF to get compound **79**. Sulfonamide intermediates **80** was synthesized using the appropriate arylsulfonyl chloride in pyridine as a base followed by alkylation of sulfonamide intermediate using *t*-butyl-bromoacetate as an alkylating agent, K_2CO_3 as a base in DMF at room temperature. Treatment of alkylated intermediate **81** with TFA: DCM mixture at room temperature gave diacid final compound **82**.



Scheme 11. Synthesis of different 2-substituted naphthalene analogs **(**compound **82a, 82b,** and **82c**).

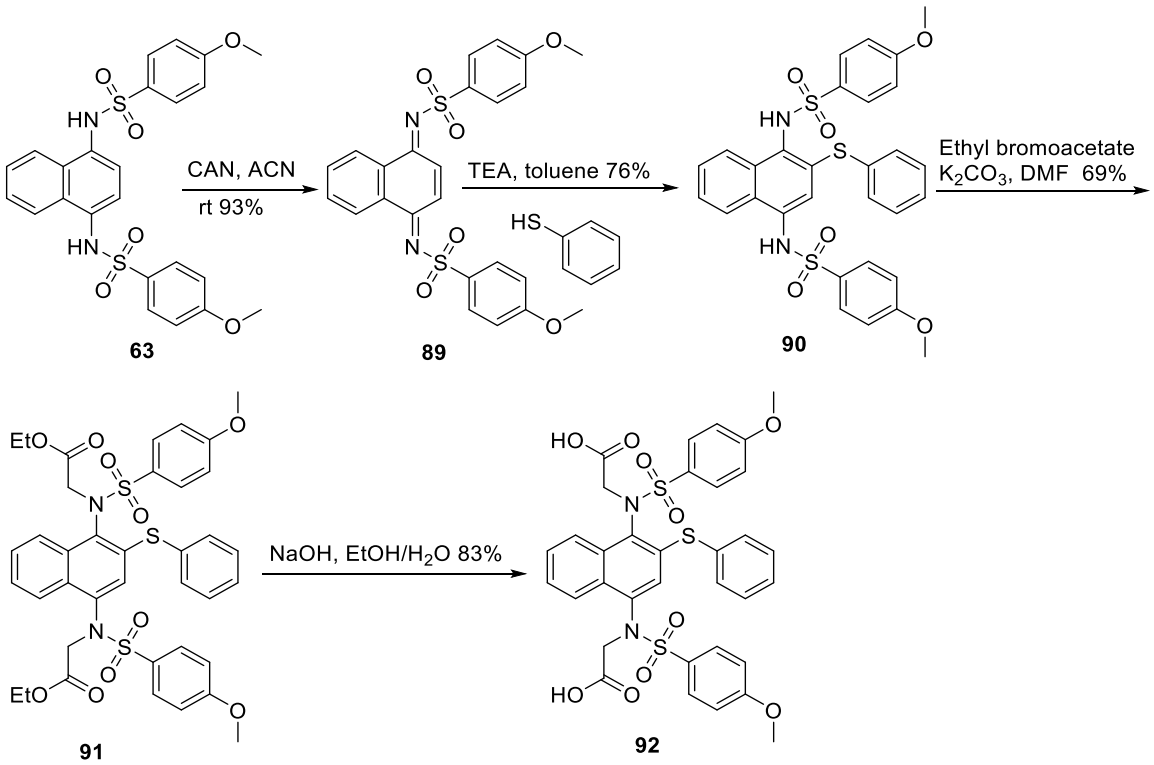
Compound **88** was synthesized using intermediate **80a**. Removal of the t-butyl group under acidic condition followed by treatment with LAH in anhydrous THF under reflux gave the alcohol intermediate **84**. Alkylation of the sulfonamide group of compound **84** followed by treatment with tosyl chloride gave intermediate **86.** Treatment of the tosylated intermediate with phthalimide or N-methylbenzyl amine in DMF at 50 °C followed by acid catalyzed removal of the t-butyl group gave final compounds **88a** and **88b**.



Scheme 12. Synthesis of different 2-substituted naphthalene analogs (compound **82d** and **88a,** and **88b**).

Synthesis of analog **92** is summarized in Scheme 13. Sulfonamide intermediate **63** was used as a starting material for synthesis of this analog. Treatment of bis-*p*-methoxybenzenesulfonamide **63** with ceric ammonium nitrate in acetonitrile gave intermediate **89**.[77] Then, treatment of compound **89** with benzenethiol via a Michael-type

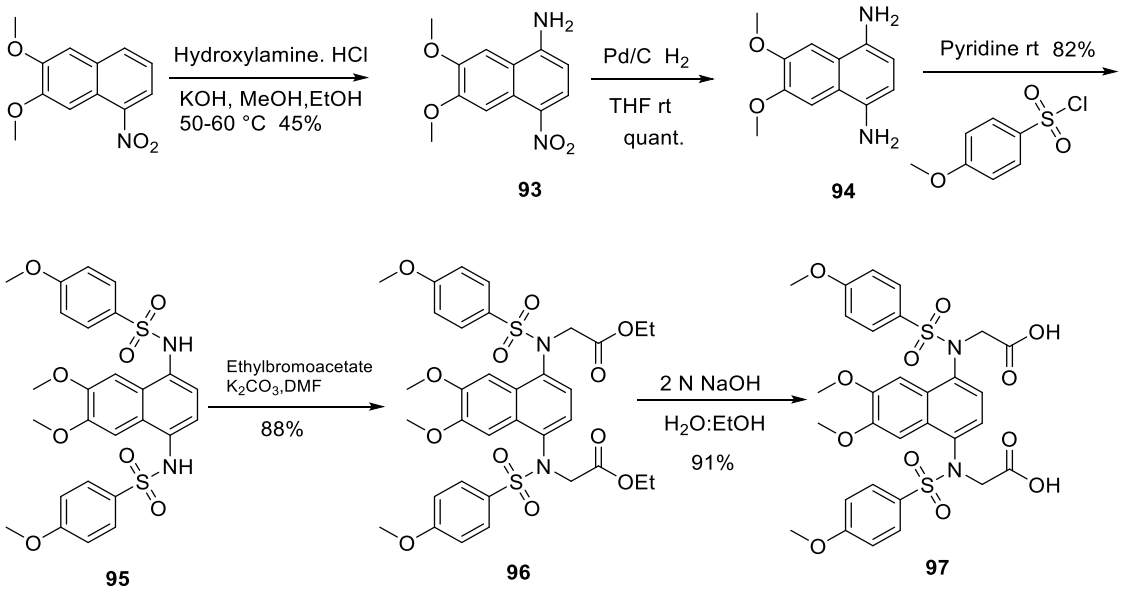
reaction gave intermediate **90**. Alkylation of intermediate **90** with ethyl bromoacetate in DMF at room temperature followed by the removal of the ethyl protecting groups from compound **91** under basic condition gave final compound **92**.



Scheme 13. Synthesis of different 2-substituted naphthalene analog (compound **92**).

Synthesis of 6,7 dimethoxy-naphthalene analog **97** is summarized in Scheme 14. Treatment of nitronaphthalene with hydroxylamine under basic condition at 50-60 °C gave 4-nitro-1-naphthylamine intermediate **93**. Reduction of the nitro group in compound **93** using H_2(g) and Pd/C (10%) in THF at room temperature gave diamine intermediate **94** in high yield. Diamine **94** was treated with 4-methoxybenzenesulfonyl chloride in pyridine to give compound **95**. Alkylation of compound **95** using ethyl bromoacetate as an alkylating agent

and K_2CO_3 as a base in DMF at room temperature followed by the removal of the ethyl group under basic condition gave compound **97**.



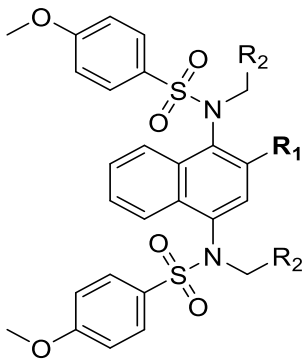
Scheme 14. Synthesis of different 6,7-disubstituted naphthalene analog (compound **97**).

The activity of analogs with the substitution on naphthalene core moiety was evaluated initially using an FP assay. The results from the assay are summarized in Table 11 and 12. Except the analog with basic tertiary amine, **88b**, all analogs with substitution at the 2-position are as potent as compound **2**. Conversely, the 6,7-dimethoxy-naphthalene **97** was less potent than compound **2** (17% inhibition at 0.5 uM concentration) and this indicates that this pattern of substitution is not optimum for this series (Table 13).

With the FP assay condition used to evaluate the potency of our compounds, we were unable to differentiate compounds with IC_{50} less than 100 nM concentration. As reported in other literature the IC_{50} of compound **2** using FP assay is in nanomolar range (IC_{50}= 29 nM).[78,79] Therefore, a more sensitive time-resolved fluorescence energy transfer (TR-FRET) assay was used to differentiate between these potent compounds.

In a TR-FRET assay, the fluorescence energy transfer signal is measured as a ratio of the donor and the acceptor emission. The TR-FRET ratio-metric nature is useful to lower inter well variations and counteract the effect of the quenching sample. However, the high cost of reagents used in this assay is one of the drawbacks of a TR-FRET assay. We did assay optimization using different concentrations of Probe, Keap1, antibody, and DMSO. The optimum condition used to evaluate our analogs was 0.5 nM Tb-anti-his-antibody, 5 nM Keap1, 25 nM Probe, and 1% DMSO. The results from the TR-FRET assay are summarized in Table 11. Based on the results from the TR-FRET assay, all compounds with 2-substitution maintain the potency except compound **88b** which has a basic center. The most potent compound is this series is **88a** with IC_{50} 2.5 ± 0.18 nM. The important points in this series are a) substitution at position 2 in the naphthalene ring is tolerated and b) there is an increase in potency for some analogs. Based on these results, we may assume that removal of the substitution on position 4 while maintaining 1,3 substitutions could result in potent compounds while improving the metabolic stability.

Table 11. The inhibitory activities of different 2-substituted naphthalene analogs (compounds **82a-d**, **88a**, and **88b**).



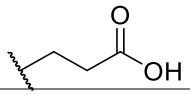
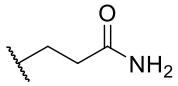
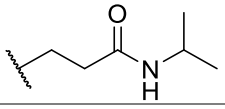
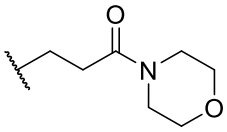
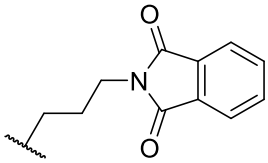
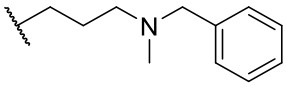
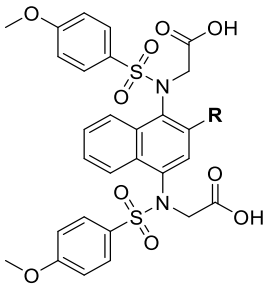
	R_1	R_2	FP assay IC_{50} (nM)	TR-REET IC_{50} (nM)
2 (LH762)	H	COOH	110 ± 7	7.5 ± 0.39
82a (LH914)		$CONH_2$	162 ± 10	22.7 ± 1.8
82b (LH927)		COOH	108 ± 7	11.7 ± 0.68
82c (LH915)		COOH	102 ± 7	12.6 ± 0.18
82d (LH916)		COOH	87 ± 6	6.9 ± 0.55
88a (LH918)		COOH	77 ± 5	2.5 ± 0.18
88b (LH919)		COOH	276 ± 17	73.6 ± 16.6

Table 12. The inhibitory activities of different 2-substituted naphthalene analogs (compounds **73a-c**, **77**, and **92**).



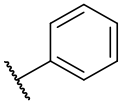
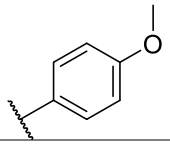
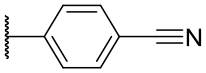
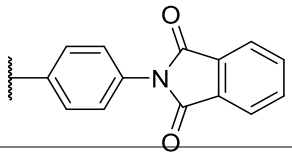
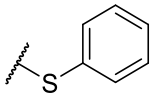
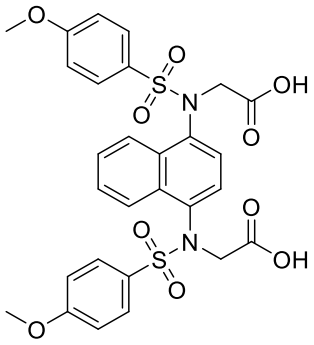
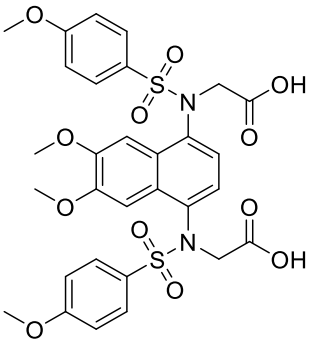
	R	**FP assay IC_{50} (nM)**	**TR-REET IC_{50} (nM)**
2 (LH762)	H	110 ± 7	7.5 ± 0.39
73a (LH890)		96 ± 6	7.7 ± 0.13
73b (LH924)		85 ± 6	13.1 ± 0.9
73c (LH935)		117 ± 7	9.2 ± 0.32
77 (LH936)		90 ± 6	7.1 ± 0.57
92 (LH913)		85 ± 5	5.8 ± 0.28

Table 13. The inhibitory activities of different 6,7-disubstituted naphthalene analog (compound **97**).



2



97

	% inhibition FP assay			FP assay IC_{50} (nM)
	0.5 μM	5 μM	50 μM	
2 (LH762)	100	100	100	110 ± 7
97 (LH925)	17.3	66.6	100	ND

2.3 **Synthesis and evaluation of novel heterocyclic-based direct inhibitors of Keap1-Nrf2 interaction**

Our next approach was the design and synthesis of multiple new scaffolds as novel direct small molecule non-electrophilic Nrf2 activators to overcome the metabolic stability problems associated with *para*-disubstituted naphthalene analogs. Our first attempt was the synthesis of different disubstituted heterocyclic compounds to determine the effect of substituents on protein binding affinity.

Based on our structure-activity relationship studies on naphthalene and phenyl analogs, alkylated sulfonamide has been used as a substituent on heterocyclic ring since it has been

shown to be an optimum substituent for direct inhibition of Keap1-Nrf2 interaction. A Fluorescence polarization (FP) assay was used to compare the activity of different heterocyclic compounds. At first, different disubstituted indole analogs were synthesized (Fig. 18) to find the optimum substitution pattern.

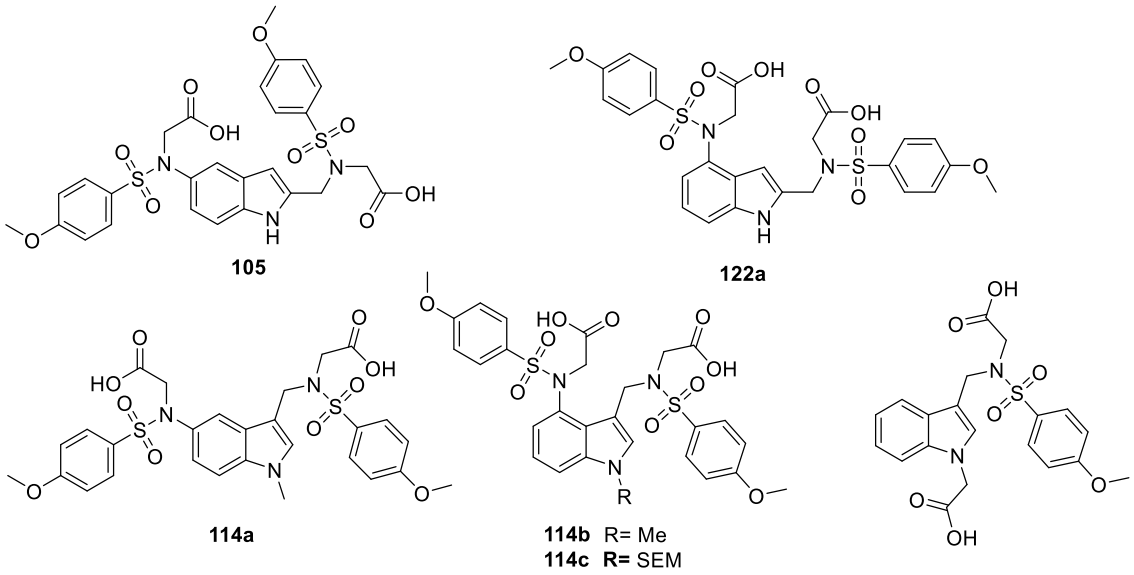
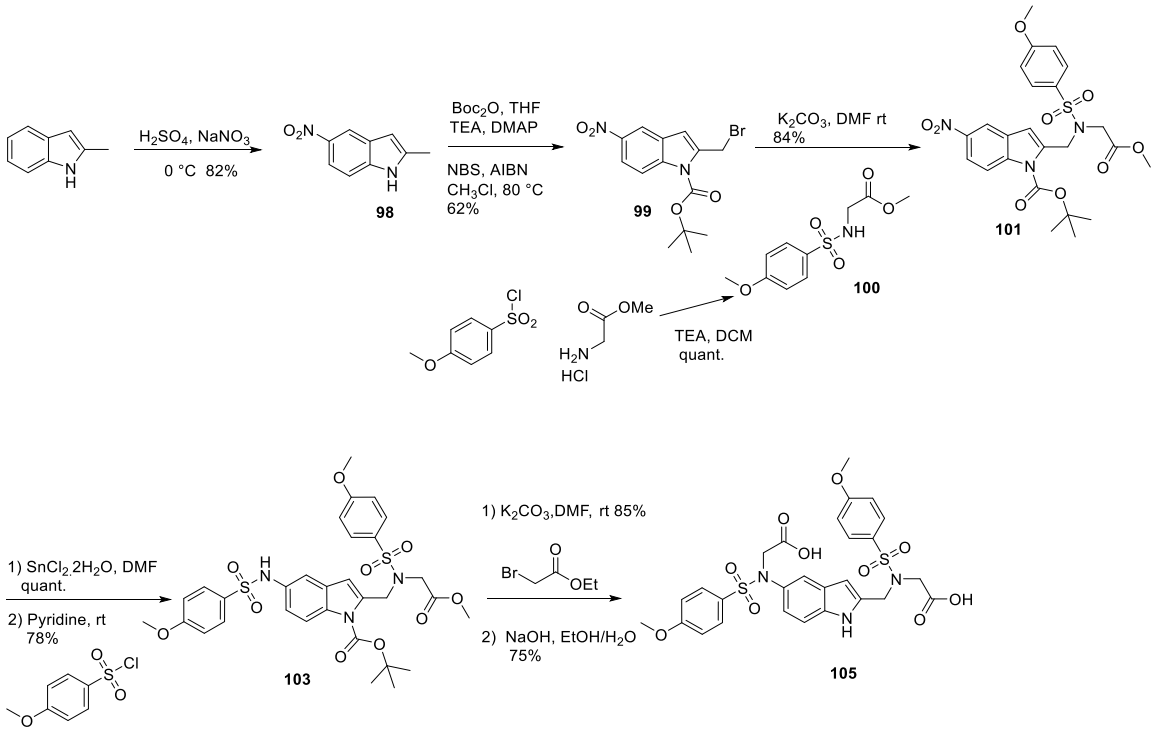


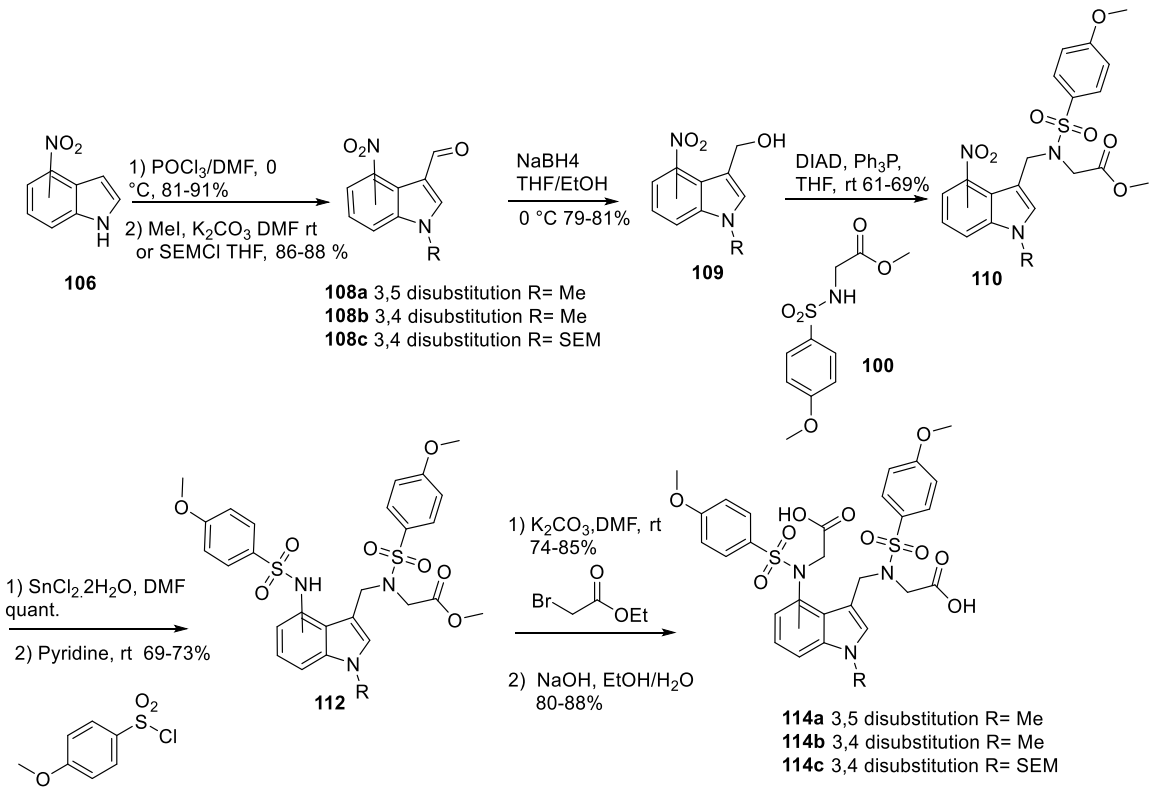
Figure 18. Different disubstituted indole analogs.

Compound **105** was synthesized starting from commercially available 2-methylindole as shown in scheme 15. Nitration of 2-methyl indole [80] followed by Boc-protection of indole NH and then bromination of methyl group with NBS using AIBN as the radical initiator was performed resulting in compound **99**. Treatment of brominated compound **99** with alkylated sulfonamide **100** gave compound **101**. Reduction of the nitro group in compound **101** with tin chloride in DMF at room temperature followed by treatment with 4-methoxybenzenesulfonyl chloride gave compound **103**. Alkylation of compound **104** with ethyl bromoacetate followed by base hydrolysis produced final compound **105**.



Scheme 15. The synthesis of 2,5-disubstituted indole analog (compound **105**).

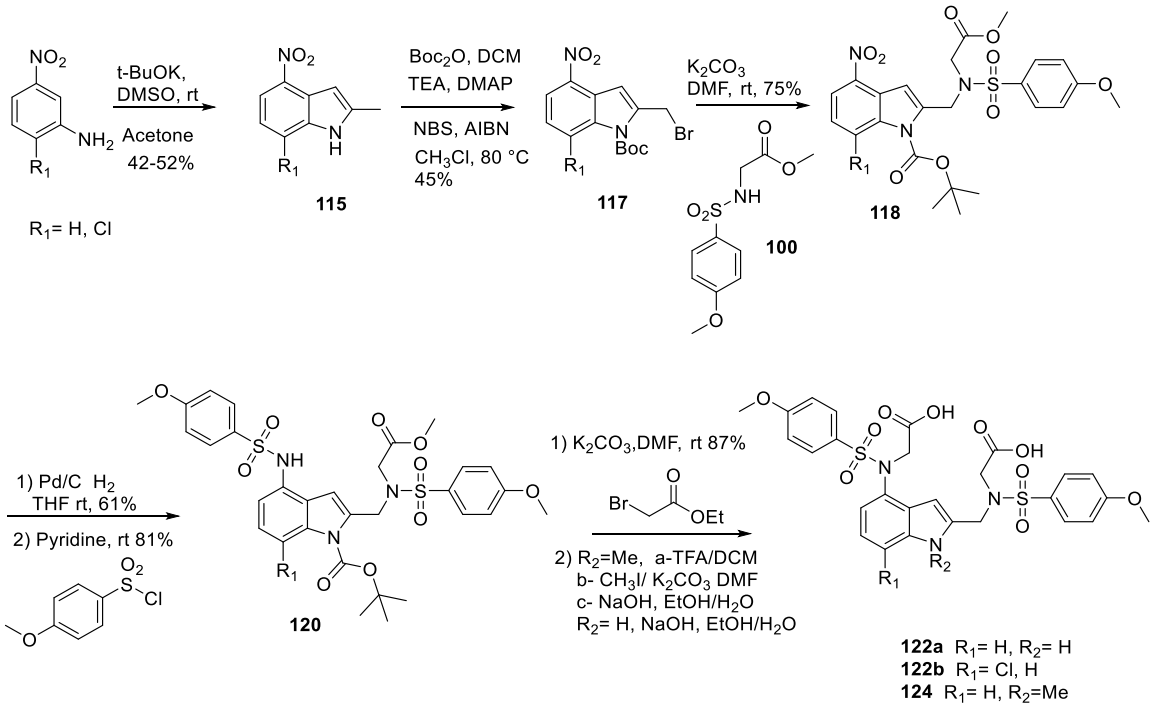
Synthesis of 3,4 and 3,5-disubstituted indole analogs is summarized in Scheme 16. Formylation of commercially available nitroindole gave a 3 formyl nitroindole compound **108**.[81,82] Initially, we used a different protecting group at indole NH but the final compound showed stability problems after deprotection. Therefore, a methyl group was introduced for this series by treatment with methyl iodide under basic conditions, and the activity of a 3,4 disubstituted compound with SEM protecting group was evaluated as well. Reduction of an aldehyde group followed by Mitsunobou reaction with compound **100** gave compound **110**.[83] Reduction of the nitro group with tin chloride in DMF at room temperature followed by treatment with sulfonyl chloride gave compound **112**. Alkylation of compound **112** with ethyl bromoacetate followed by base hydrolysis gave final compound **114** as shown in Scheme 16.



Scheme 16. The synthesis of 3,4 and 3,5-disubstituted indole analog (compound **113**).

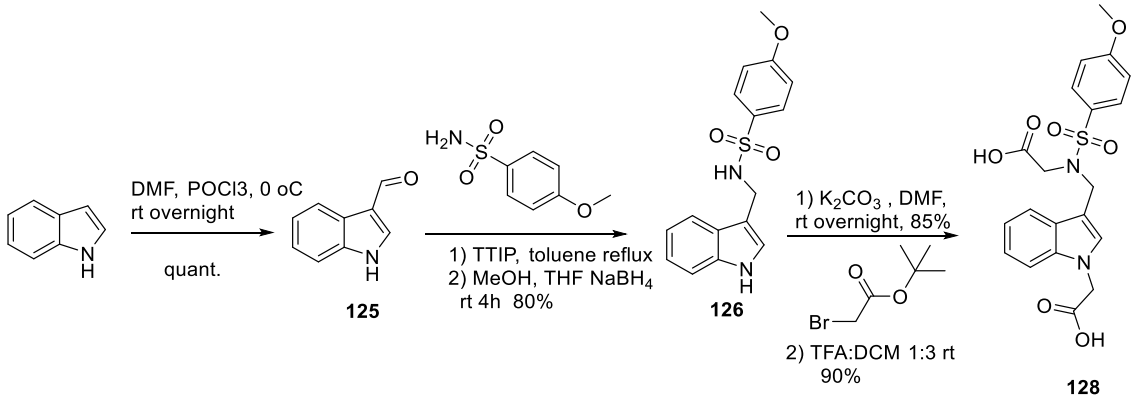
Synthesis of 2,4-disubstituted indole analogs using commercially available nitroaniline which was treated with acetone in the presence of t-BuOK using DMSO as a solvent at room temperature gave 2-methyl nitroindole, compounds **115a** and **115b**.[6] Protection of indole NH by treatment with Boc-anhydride and then bromination with NBS of the methyl group followed by alkylation with sulfonamide **100** gave compound **118**. Reduction of the nitro group of compound **118** with tin chloride in DMF at room temperature followed by treatment with 4-methoxybenzenesulfonyl chloride produced compound **120**. Alkylation of compound **120** with ethyl bromoacetate followed by base hydrolysis gave final compound **122.** Treatment of compound **121** with TFA: DCM 1:3 at room temperature and

then with methyl iodide in K_2CO_3 followed by base hydrolysis of the ester groups gave compound **124** as shown in Scheme 17.



Scheme 17. The synthesis of 2,4-disubstituted indole analogs (compound **122a**, **122b**, and **124**).

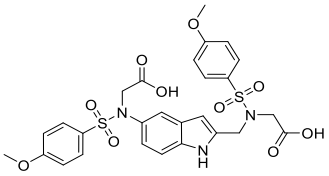
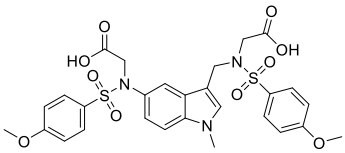
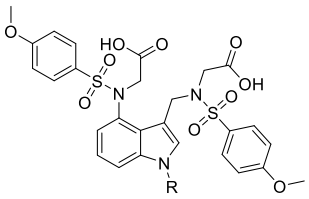
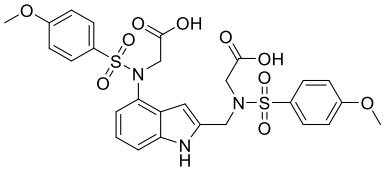
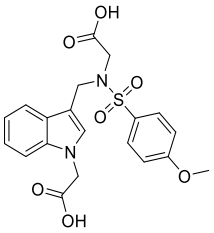
The synthesis of 1,3 disubstituted indole analogs is summarized in Scheme 18. Vilsmeier–Haack reaction of commercially-available indole with $POCl_3$ in DMF gave indole-3-aldehyde **125** in high yield.[84] Compound **125** was then treated with 4-methoxybenzenesulfonamide in the presence of titanium(IV) ethoxide in toluene under reflux, followed by treatment of the reaction mixture with $NaBH_4$ in THF: MeOH mixture at room temperature to give compound **126**.[85] Indole NH and sulfonamide moieties were then alkylated with t-butyl bromoacetate followed by treatment with TFA: DCM mixture to produce the final compound **128**.



Scheme 18. The synthesis of 1,3-disubstituted indole analog (compound **128**).

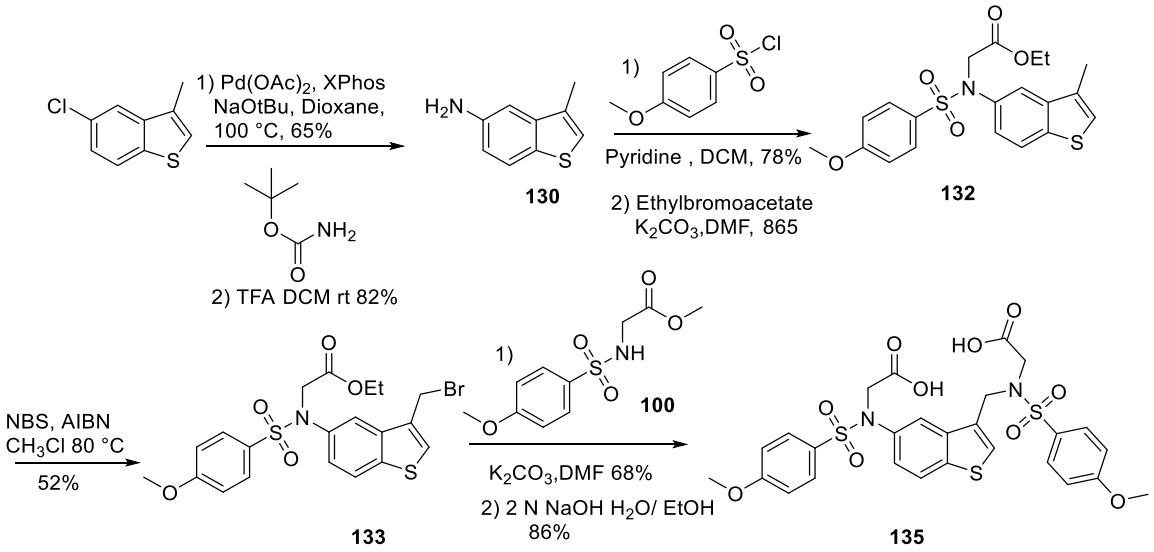
Disubstituted indole analogs were evaluated for their activity using an FP assay. Two different concentrations (5 and 50 μM) have been used to compare between different analogs as you can see in Table 14. 3,5 and 3,4-disubstituted indole analogs have a methyl group in position 1 due to instability of an unsubstituted one. Among these analogs, 2,4-disubstituted is the most potent compound with 77% inhibition at 5 μM.

Table 14. The inhibitory activities of different disubstituted indole analogs.

	Position	Chemical Structure	% inhibition FP assay		
			0.5 µM	5 µM	50 µM
105 (LH938)	2,5		ND	28	78
114a (LH941)	3,5		ND	25	80
114b (LH940)	3,4	 **114b** R= Me **114c** R= SEM	ND	03	16
114c (LH939)			ND	02	09
122 (LH933)	2,4		ND	77.1	100
128 (LH850)	1,3		ND	8.7	11.4

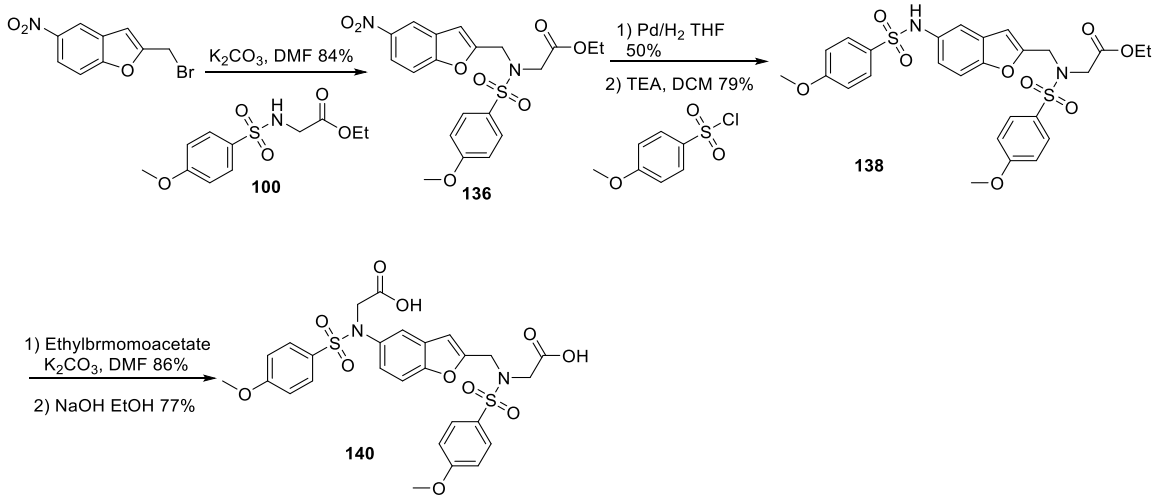
To compare the effects of different heteroatoms in indole, benzothiophene, and benzofuran, disubstituted benzofuran and disubstituted benzothiophene derivatives were designed and synthesized.

5-Amino-3-methylbenzothiophene, compound **135**, was synthesized starting from commercially available 5-chloro-3-methyl-1H-benzothiophene. Buchwald–Hartwig amination of the 5-chloro-3-methyl-1H-benzothiophene followed by treatment with TFA gave compound **130**. [86] Treatment with sulfonyl chloride followed by alkylation with ethyl bromoacetate gave compound **132**. Bromination of compound **132** then treatment of the brominated compound with N-alkylated sulfonamide **100** followed by base hydrolysis gave the final compound **135** as shown in Scheme 19.



Scheme 19. The synthesis of 3,5-disubstituted benzothiophene analog (compound **135**).

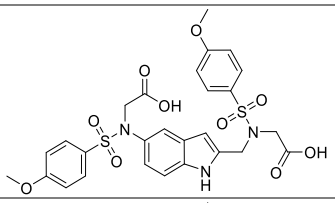
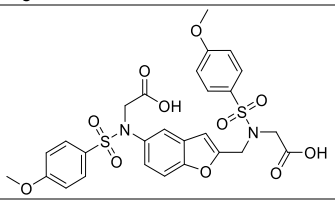
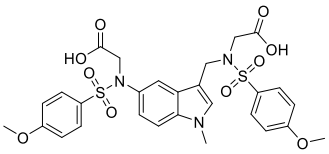
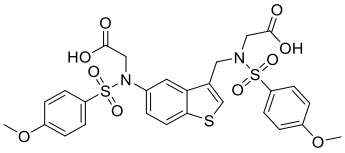
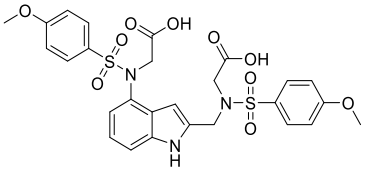
The synthesis of 2,5 disubstituted benzofuran is summarized in scheme 20. Alkylation of commercially available 2-(bromomethyl)-5-nitro-1-benzofuran with compound **100** gave compound **136**. Reduction of the nitro group in compound **136** by hydrogenation using hydrogen gas and Pd/C (10%) in THF followed by treatment with 4-methoxybenzenesulfonyl chloride and then alkylation with ethyl bromoacetate gave compound **139**. Base hydrolysis of compound **139** gave final compound **140**.



Scheme 20. The synthesis of 2,5 disubstituted benzofuran analog (compound **140**).

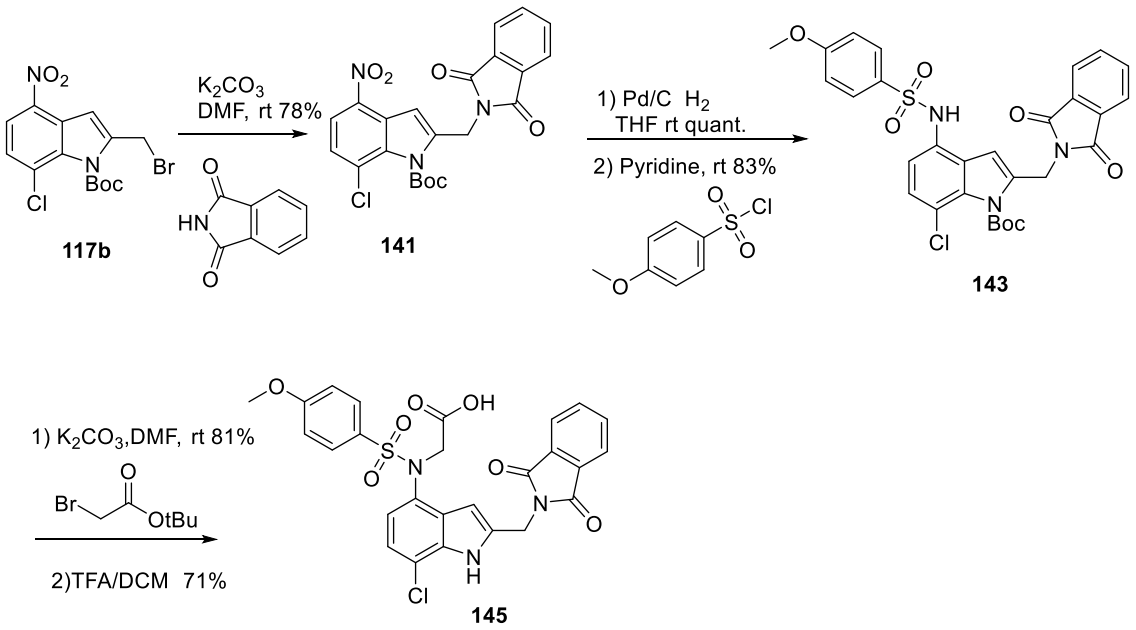
Inhibitory activities of the benzofuran and benzothiophene analog are summarized in Table 15. 2,5 Disubstituted benzofuran and indole showed no difference in binding affinity. Because the 3,5 disubstituted indole was methylated at the 1-position, we cannot fully conclude that benzothiophene is better than indole as a core structure. Out of these different heterocyclic analogs, 2,4 disubstituted indole and 3,5 disubstituted benzothiophene were the more active analogs, as is shown in Table 14. From the above structure-activity relationship, we decided to further optimize the 2,4 disubstituted indole because it showed good inhibitory activity and flexibility introducing different functional groups to the core structure.

Table 15. The inhibitory activities of different heterocyclic analogs.

	Position	Chemical Structure	% inhibition FP assay		
			0.5 μM	5 μM	50 μM
105 (LH938)	2,5		-	28	78
140 (LH882)	2,5		-	25	70
114a (LH941)	3,5		-	25	80
135 (LH920)	3,5		45.7	84.8	107.8
122 (LH933)	2,4		29	77	100

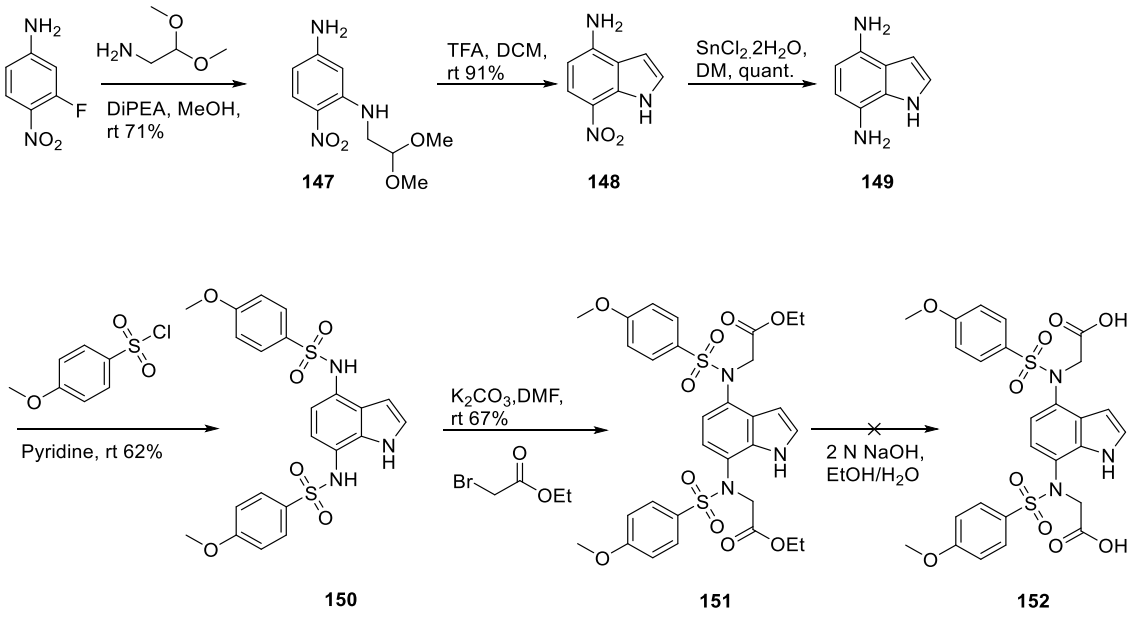
To enhance potency of the 2,4 disubstituted indole analog, different substituents have been introduced to improve the inhibitory activity. Synthesis of these analogs is similar to that of the 2,4 disubstituted indole analogs summarized in Schemes 17 and 20. To synthesize analog **145**, intermediate **117b** was used. Alkylation of **117b** with phthalimide in DMF at room temperature gave compound **141**. Reduction of a nitro group using 10% Pd/C followed by treatment with 4-methoxybenzenesulfonyl chloride gave compound **143**.

Alkylation of compound **143** with t-butyl bromoacetate followed by treatment with TFA: DCM at room temperature gave compound **145**.



Scheme 21. The synthesis of 2,4-disubstituted indole analog (compound **145**).

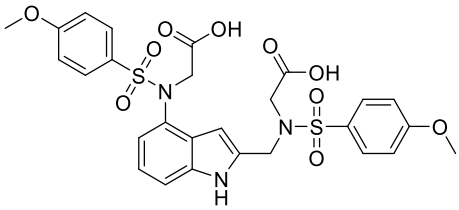
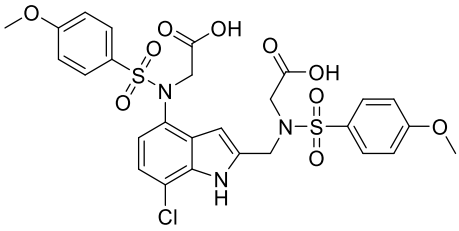
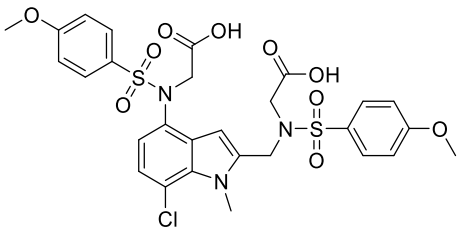
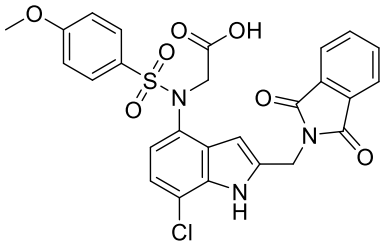
Compound **152** with two substitutions at the 4,7-positions of the indole ring was designed. This compound is an analog to the naphthalene compound **2** with indole as a core structure. Starting with commercially-available nitroaniline treated with 2-aminoacetaldehyde dimethyl acetal in presence of DiPEA at room temperature and followed by treatment with TFA gave indole intermediate **148**. Reduction of the nitro group of compound **148** followed by sulfonation and then alkylation gave intermediate **151**. Hydrolysis of compound **151** under basic condition resulted in the decomposition of this compound (the color changed to a dark solution which may indicate an oxidation problem).



Scheme 22. The synthesis of 4,7-disubstituted indole analog (compound **152**).

The inhibitory activity of these analogs is summarized in Table 16. Compound **122b** with a chloro substituent on position 7 showed an increase in binding affinity. Indole with a methyl group at the 1-position (compound **124**) was then designed and synthesized. Modification at this position was aimed to improve activity and simplify synthetic route. However, 1-Methylindole analog **124** showed less activity compared to the analog without the methyl group. This may indicate that substitution at this position has a detrimental effect on inhibitory activity. Finally, replacement of sulfonamide moiety with phthalimide at position 2 was aimed to improve physicochemical properties and activity of the designed analog. This modification resulted in a decrease of inhibitory activity as we can see with analog **145**. Based on these results, heterocyclic analogs proved to be successful inhibitors of Keap1-Nrf2 interaction and they are suitable for further investigation and further SAR studies are being conducted to improve the potency within a single digit nanomolar range.

Table 16. The inhibitory activities of different 2,4-disubstituted indole analogs.

	Chemical Structure	% inhibition FP assay			IC_{50} (μM)
		0.5 μM	5 μM	50 μM	
122a (LH933)		29	77	100	ND
122b (LH917)		87.3	100	100	0.26 ± 0.02
124 (LH937)		51.1	77.1	100.3	ND
145 (LH934)		ND	09	41.4	ND

2.4 Biological activities of direct inhibitors on cellular Nrf2 signaling Pathway

The cellular activities of our potent compounds were further evaluated using the ARE-luciferase reporter assay. The aim of this assay is to evaluate the ability of potent compounds to activate cellular Nrf2 signaling. In the beginning, the effect of our compounds on cell viability was evaluated to make sure our compounds are non-toxic in the effective concentration range. In this assay, two different cell lines were used which are namely human HepG2 C8 hepatoma cells and mouse brain microglia cells. Eight compounds (Fig. 19) were tested in three different concentrations 1 μM, 10 μM, and 50 μM. The results from this assay are summarized in Fig. 20. All screened compounds showed no effect on cell viability up to 50 μM in both cell lines. Eights compounds were then evaluated for their ability to activate cellular Nrf2 in human HepG2 C8 hepatoma cell lines. From the results (Fig. 21), compounds **2** (**LH762**), **65v** (**LH835**), **65u** (**LH837**), and **65x** (**LH843**) showed significant activation. In addition, the ARE luciferase reporter assay indicated that **65x** (**LH835**) has the best cellular Nrf2-inducing activity. Further cell-based assays are being conducted with these analogs.

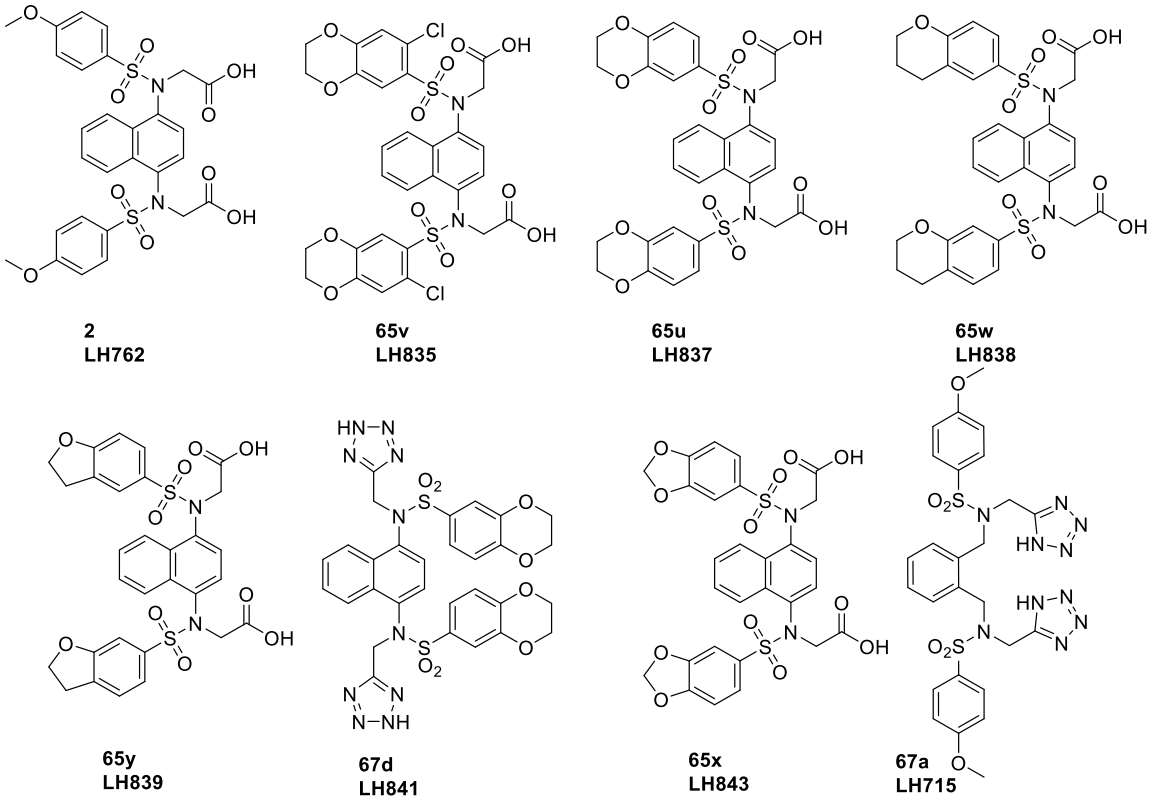


Figure 19. List of compounds evaluated in cell-based assays.

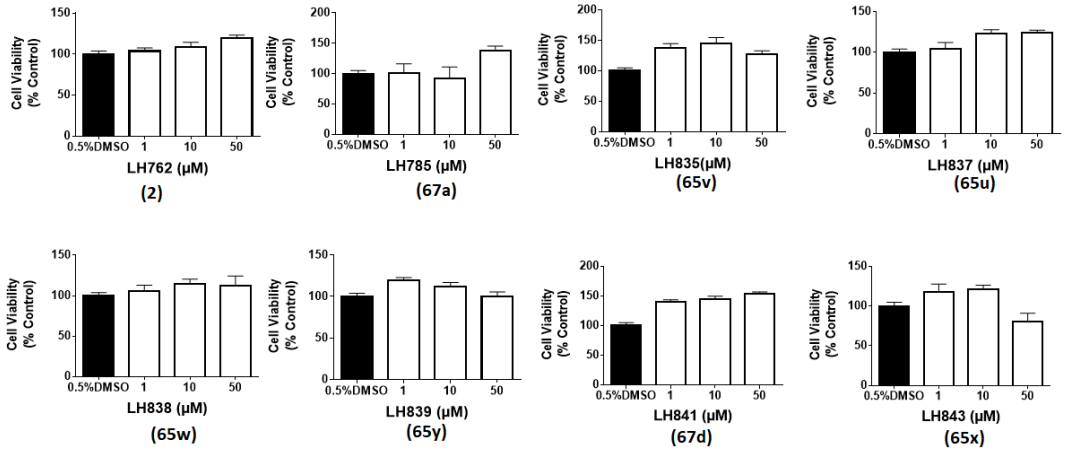


Figure 20. Effect of direct inhibitors of Keap1-Nrf2 PPI on human HepG2 C8 hepatoma cell viability.

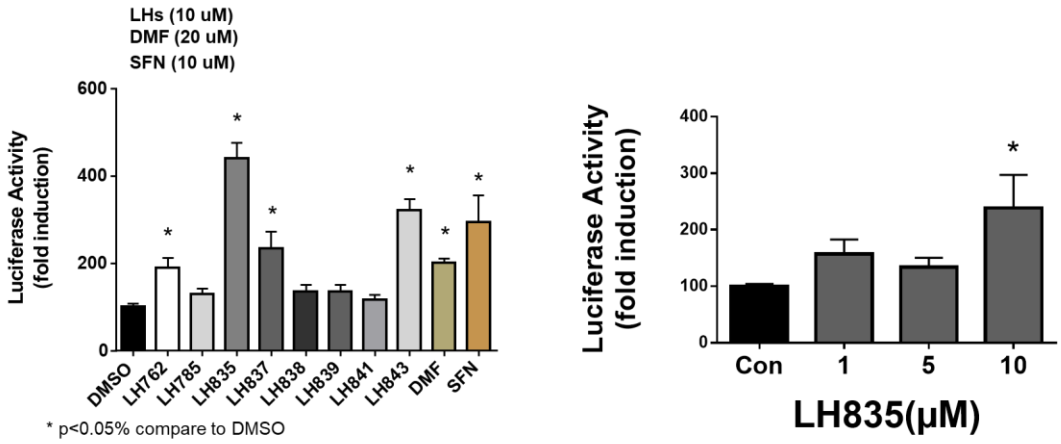


Figure 21. Effect of screened compounds on activation of the ARE-luciferase gene in HepG2 C8 cells.

SUMMARY

There have been a number of Keap1-Nrf2 PPI inhibitors identified in the literature including both direct and indirect inhibitors. However, most of these inhibitors have different features which would impede them from further development including potency, metabolic stability, and toxicity. Therefore, there is a need to further improve the current scaffolds, or design new scaffolds as potent inhibitors for the Keap1-Nrf2 PPI. Naphthalene-based hit compound **2** (Fig. 9) is a potent inhibitor of the Keap1-Nrf2 interaction with IC_{50}= 29 nM in their FP assay condition, and the IC_{50}= 110 ± 7 nM in our FP assay condition. However, metabolic instability and limited activity in cell-based assays represent the main drawbacks of this compound. Therefore, compound **2** served as the starting point to begin our studies of Keap1-Nrf2 PPI inhibitors.

Initially, our research efforts focused on studying the chemical modifications on a naphthalene core structure, which is already identified in the literature as a potent Keap1-Nrf2 PPI inhibitor. Replacement of a naphthalene ring with a phenyl ring resulted in less potent compounds which indicated the importance of this core structure as a key feature for Keap1 binding. However, the aim of this study was to improve the metabolic stability, and thus, further SAR studies on the phenyl core structure were performed. These SAR studies revealed several interesting facts. When making a substitution on the phenyl core structure, 1,2-disubstitution was revealed to be the optimum pattern of substitution and substitution with cyano or tetrazole on position number 4 resulted in a decrease in activity. These studies also showed that sulfonamide moieties are required for optimum activity,

and when a substitution was made on the flanking aryl sulfonamide moieties, the hydrophobic substituents on the *para*-position and the 2,6-difluoro resulted in an improvement in the activity. Lastly, when a substitution was made on the alkyl side chain, activity was maintained when the carboxylic acid moieties were replaced with tetrazole moieties and introduction of a chiral center on the alkyl side chain resulted in a promising increase in activity with IC_{50}= 154 ± 16 nM using our FP assay condition.

In the second part of the SAR studies, the naphthalene core was maintained, and further investigation was performed to improve the potency and study the structural requirements. Once again, several interesting facts were discovered through the SAR studies we conducted. Sulfonamide moieties were shown to be important for optimum activity and when a substitution was made on the flanking aryl sulfonamide moieties, an improvement in the activity in both an FP assay and cell-based assay was obtained as compared to compound **2**. These studies also showed that the activity was maintained with isosteric replacement of carboxylic acid moieties with tetrazole moieties and substitution on position number 2 on naphthalene ring resulted in potent analogs, except the one with a basic center while substitution with 6,7-dimethoxy resulted in a less potent analog.

In the last part, new scaffolds were designed and synthesized, namely indole, benzofuran, and benzothiophene. The most potent scaffolds found were indole and benzothiophene. Indole was selected for further SAR studies because it represented a flexible scaffold which could help to improve the potency in these compounds. From this series of compounds, a potent analog, compound **122b**, with IC_{50}= 0.26 ± 0.02 uM in the FP assay was identified, and further SAR studies are being conducted to improve the potency of this scaffold.

In closing, design, synthesis, structure-activity relationship, and biological evaluation of different Keap1-Nrf2 PPI inhibitors with good activity have been described in this work. Ongoing studies of the heterocyclic and naphthalene analogs are continuing with the aim of further improvement in potency and stability.

EXPERIMENTAL

General Methods

Reagents purchased were ACS grade and used without further purification. Solvents purchased were either HPLC grade or ACS reagent grade. All reactions were monitored and followed-up by a thin-layer chromatography (TLC) using aluminum backed Silica G TLC plates and visualized with ultraviolet light, a Shimadzu 2010 LC-MS system, and/or Agilent 1200 LC-MS system. Flash column chromatography was done on a Teledyne ISCO CombiFlash Companion using ethyl acetate, dichloromethane, hexane, and methanol as a mobile phase with prepacked silica gel columns as a stationary phase. Lyophilization of the final compound was performed on a VirTis freezemobile freeze dryer. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on Bruker 400 MHz Multinuclear NMR spectrometers using $CDCl_3$, acetone-d6, methanol-d4, and DMSO-d6. For NMR spectra at 100 °C, ^{1}H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were recorded on Bruker 500 MHz Multinuclear NMR spectrometers using DMSO-d6 as a solvent. NMR Data is reported in parts per million (ppm) relative to the residual nondeuterated solvent signals. High-resolution mass spectra (HRMS) experiments were conducted by Center for Integrative Proteomics Research (CIPR) at Rutgers University.

General procedure for synthesis of sulfonamides

Method A1

To a mixture of Xylylenediamine dihydrochloride or the free base form (1 mmol) and triethylamine (5 mmol) in DCM (5 mL) at 0 °C under nitrogen atmosphere, a solution of 4-methoxybenzenesulfonyl chloride (2.2 mmol) in DCM (5 mL) was added slowly. Then, the reaction was stirred at room temperature overnight and monitored by TLC and LCMS. Upon completion, reaction mixture was diluted with DCM, washed with 1 N HCl, water, brine, and dried over Na_2SO_4, and concentrated under reduced pressure to get the crude products, which were purified by a flash column chromatography using 0 - 100% EtOAc in hexane.

Method A2

To a solution of 1,4-diaminobenzene (1 mmol) in 5 ml pyridine at 0 °C under N_2 (g), 4-methoxybenzenesulfonyl chloride (2.2 mmol) was added and the reaction mixture was stirred at room tempreture for 8 h and monitored by TLC and LCMS. Upon completion, the reaction mixture was diluted with DCM and washed with 1 N HCl, water, and brine. Then, the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure followed by purification by a flash column chromatography using 0 - 100% EtOAc in hexanes.

General procedure for synthesis of alkylated sulfonamides (Method B)

To a solution of sulfonamide (1 mmol) in DMF (3 ml), K_2CO_3 (10 mmol) and alkyl bromoacetate (5 mmol) were added. Then, the reaction was stirred at room temperature overnight and monitored by TLC and LCMS. On completion, reaction mixture was diluted with ethyl acetate, washed with 1 N HCl, water, and brine. Then, organic layer was dried

over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified by flash column chromatography using 0 - 50% EtOAc/hexane.

General procedure for hydrolysis of ethyl ester to get di-acidic compounds

Method C1: basic hydrolysis

To a solution of alkylated sulfonamide in EtOH (2 ml), 4 N NaOH in water (2 ml) was added and reaction mixture was stirred at room temperature and monitored by TLC and LCMS. Upon completion, reaction mixture was diluted with ethyl acetate, washed with 1 N HCl, water, and brine. Then, organic layer dried over Na_2SO_4 and concentrated under reduced pressure to yield crude product, which was recrystallized using ethyl acetate/hexane, and washed with petroleum ether to afforded pure final product.

Method C2: removal of acid sensitive protecting group

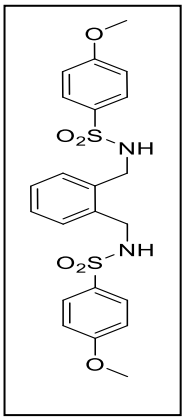
To solution of alkylated sulfonamide in DCM (0.5ml) was cooled to 0 °C, a solution of TFA: DCM (1:2) was added dropwise (1.5 ml). Then reaction mixture was stirred at room temperature for 1 hour. Upon completion, reaction mixture was concentrated under reduced pressure to yield crude product, which was recrystallized using ethyl acetate hexane or ethyl ether to afford pure final product.

Method C3: removal of benzyl protecting group

A solution of starting material in EtOH: THF (1:1) was degassed with N_2 three times. A catalytic amount of 10% Pd/C was added to the solution and the mixture was purged with H_2. The reaction was stirred under H_2 (g) for 3 h and then filtered through a celite bed to

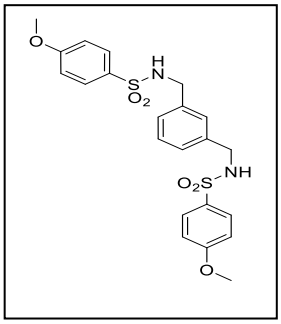
remove the catalyst. The filtrate was concentrated under vacuum to get the desired product which was recrystallized using ethyl acetate hexane or ethyl ether to afford pure final product.

N,N'-(1,2-Phenylenebis(methylene))bis(4-methoxybenzenesulfonamide) (**9**)



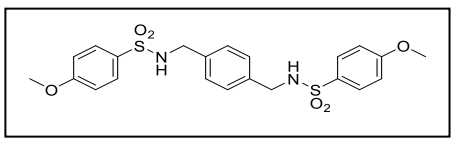
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid (391 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, 4H, *J*=8.8 Hz), 7.15 (s, 4H), 6.92 (d, 4H, *J*=8.8 Hz), 5.17 (t, 2H, *J*=7.0 Hz), 4.06 (d, 4H, *J*=7.0 Hz), 3.84 (s, 6H); ^{13}C NMR (100 MHz), $CDCl_3$): δ 163.1, 134.8, 131.2, 130.3, 129.4, 128.6, 114.5, 55.8, 44.9.

N,N'-(1,3-Phenylenebis(methylene))bis(4-methoxybenzenesulfonamide) (**10**)



Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid (377 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, 4H, *J*=8.8 Hz), 7.22 (t, 2H *J*= 7.6 Hz), 7.11 (d, 2H *J*= 8.0 Hz), 6.98 (d, 4H *J*= 8.8 Hz), 4.57 (t, 2H *J*=6.4), 4.05 (d, 4H *J*=6.4 *Hz*), 3.89 (s, 6H).

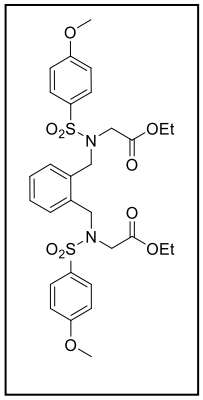
N,N'-(1,4-Phenylenebis(methylene))bis(4-methoxybenzenesulfonamide) (**11**)



Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid (358 mg, 75% yield). 1H NMR (400 MHz, DMSO): δ 7.97 (t, 2H, *J*=5.6 Hz), 7.74 (d, 4H *J*= 8.0Hz), 7.16 (s, 4H),

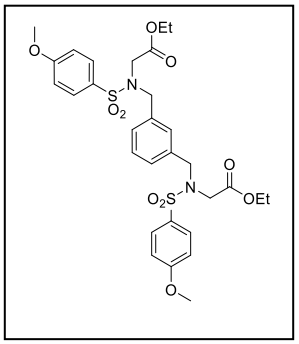
7.10 (d, 4H *J*= 8.0Hz), 3.89 (d, 2H *J*=8.0), 3.83 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.14, 136.67, 132.34, 128.71, 127.51, 114.35, 55.66, 45.87.

Diethyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (**12**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (Method B) to get the title compound as an oily product (208 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, 4H, *J*=8.8 Hz), 7.36-7.33 (m, 2H), 7.28-7.25 (m, 2H), 6.98 (d, 4H, *J*=8.8 Hz), 4.57 (s, 4H), 3.94 (q, 4H, *J*=7.2 Hz), 3.87 (s, 6H), 3.84 (s, 4H) , 1.1 (t, 6H, *J*= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.59, 163.05, 134.02, 130.81, 129.68, 129.63, 128.39, 114.19, 61.21, 55.61, 49.12, 47.72, 13.92.

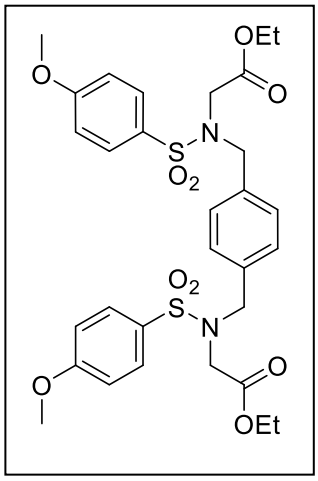
Diethyl 2,2'-((1,3-phenylenebis(methylene)) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (**13**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (Method B) to get the title compound as an oily product (226 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, 4H, *J*=8.8 Hz), 7.28-7.25 (m, 3H), 7.14 (s, 1H), 7.01 (d, 4H, *J*=8.8 Hz), 4.46 (s, 4H), 4.04 (q, 4H, *J*=7.2 Hz), 3.91 (s, 6H), 3.90 (s, 4H) , 1.18 (t, 6H, *J*= 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.44,

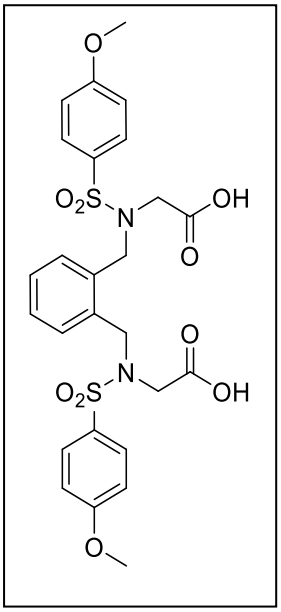
162.80, 135.59, 131.11, 129.39, 128.93, 128.38, 128.09, 113.92, 60.97, 55.40, 50.89, 46.64, 13.80.

Diethyl 2,2'-((1,4-phenylenebis (methylene)) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (**14**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (Method B) to get the title compound as oily product; (219 mg, 84% yield) a as oily product. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.84 (d, 4H, *J*=9.0 Hz), 7.25 (s, 4H), 7.12 (d, 4H, *J*=9.0 Hz), 4.47 (s, 4H), 3.97 (q, 4H, *J*=7.0 Hz), 3.92 (s, 6H), 3.90 (s, 4H), 1.11 (t, 6H, *J*= 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.59, 163.05, 134.02, 130.81, 129.68, 129.63, 128.39, 114.19, 61.21, 55.61, 49.12, 47.72, 13.92.

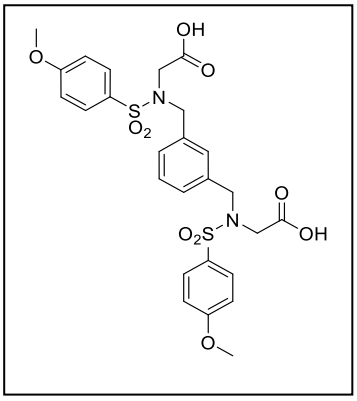
2,2'-((1,2-Phenylenebis(methylene))bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (**3**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid (39 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.64 (s, 2H)7.77 (d, 4H, *J*=8.8 Hz), 7.29 (s, 2H), 7.25 (s, 2H), 7.11 (d, 4H, *J*=8.8 Hz), 4.45 (s, 4H), 3.86 (s, 6H), 3.78 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.84, 162.60, 134.36, 130.56, 129.44, 128.68, 127.58, 114.40,

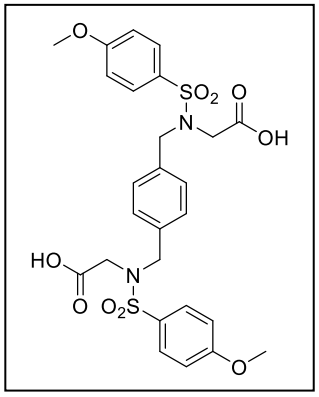
55.73, 49.09, 48.26. HRMS (ESI) Calcd for $C_{26}H_{29}N_2O_{10}S_2$ $(M+H)^+$ 593.1185, found 593.1258.

2,2'-((1,3-Phenylenebis(methylene))bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (**4**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid (36 mg, 72% yield). ^{1}H NMR (400 MHz, MeOH-d4): δ 7.80 (d, 4H, *J*=9.0 Hz), 7.24 (t, 1H *J*=8.0 Hz), 7.15 (d, 2H *J*=8.0 Hz), 7.10 (d, 4H, *J*=9.0 Hz), 6.96 (s, 1H), 4.39 (s, 4H), 3.88 (s, 6H), 3.84 (s, 4H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.75, 162.50, 136.01, 131.26, 129.30, 128.59, 128.03,127.57, 114.33, 55.69, 50.89, 47.35. HRMS (ESI) Calcd for $C_{26}H_{28}N_2O_{10}S_2$ $(M+H)^+$ 593.1258, found 593.1254

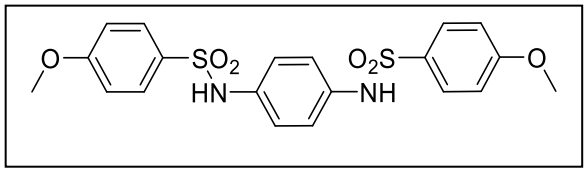
2,2'-((1,4-Phenylenebis(methylene))bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (**5**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid (36 mg, 72% yield). ^{1}H NMR (400 MHz, MeOH-d4): δ 7.79 (d, 4H, *J*=9.0 Hz), 7.12 (s, 4H), 7.06 (d, 4H, *J*=9.0 Hz), 4.36 (s, 4H), 3.84 (s, 6H), 3.64 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

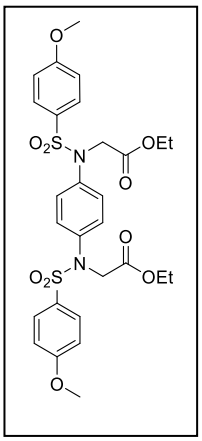
169.75, 162.47, 135.56, 131.39, 129.47, 128.54, 114.35, 55.81, 50.60, 48.16; HRMS (ESI) Calcd for $C_{26}H_{28}N_2O_{10}S_2$ $(M+H)^+$ 593.1258, found 593.1252.

N,N'-(1,4-Phenylene)bis(4-methoxybenzenesulfonamide) (**15**)



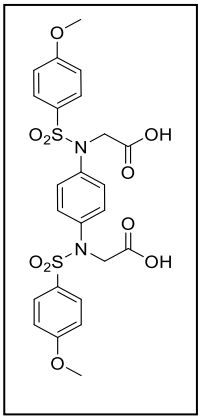
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound (332 mg, 74% yield) as a light pink powder; ^{1}H-NMR (400 MHz, DMSO-d6): δ 9.93 (s, 2H), 7.58 (d, 4H *J*= 8.8 Hz), 7.01 (d, 4H *J*= 8.8 Hz), 6.89 (s, 4H), 3.79 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d6): δ 163.31, 134.02, 130.97, 128.79, 121.40, 114.20, 55.56.

Diethyl 2,2'-(1,4-phenylenebis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetate (**16**)



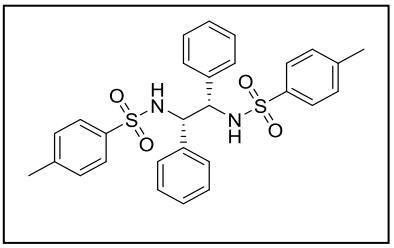
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product ; (153 mg, 92% yield). ^{1}H-NMR (400 MHz, DMSO): δ 753 (d, 4H, *J*=8.8 Hz) 7.09 (s, 4H), 7.06 (d, 4H, *J*=8.8 Hz), 4.46 (s, 4H), 4.05 (q, 4H, *J* = 7.2 Hz), 3.84 (s, 6H), 1.12(t, 6H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, DMSO): δ 169.52, 162.87, 138.64, 129.65, 129.57, 127.90, 114.39, 60.96, 55.78, 51.92, 13.92.

2,2′-(1,4-Phenylenebis(((4-methoxyphenyl)sulfonyl)azanediyl))-diacetic Acid (**6**)



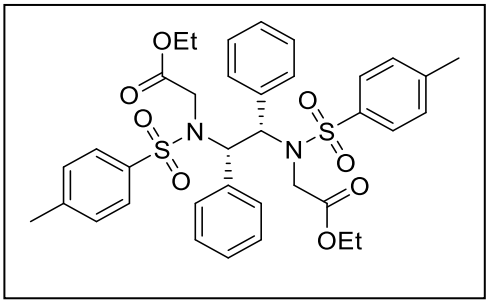
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a yellow solid; (32 mg, 70% yield). ^{1}H NMR (400 MHz, DMSO): δ 12.85 (br, 2H), 7.53 (d, 4H, *J* = 8.4 Hz), 7.09−7.05 (m, 8H), 4.36 (s, 4H), 3.84 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ 169.84, 162.73, 138.62, 129.79, 129.47, 127.71, 114.29, 55.70, 51.74. HRMS (ESI) Calcd for $C_{24}H_{24}N_2O_{10}S_2$ $(M+H)^+$ 565.0945, found 565.0939

N,N'-((1S,2S)-1,2-Diphenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) (17)



Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; (381 mg, 73% yield). ^{1}H NMR (400 MHz, DMSO): δ 8.18 (s, 2 H), 7.18 (d, 4 H, *J* = 7.6 Hz), 4.51 (s, 2H), 2.21 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ 141.57, 38.30, 137.91, 128.73, 127.31, 126.48, 126.02, 62.38, 20.78.

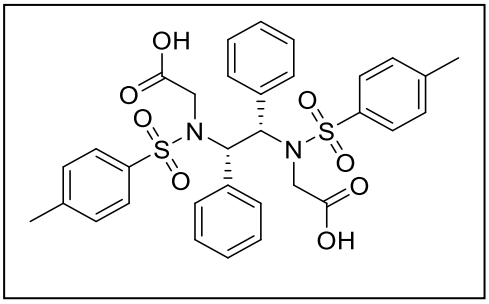
Diethyl 2,2'-(((1S,2S)-1,2-diphenylethane-1,2-diyl) bis(tosylazanediyl)) diacetate (18)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (274 mg, 79% yield) as a pale yellow oily product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, 4H, *J* = 8.0 Hz), 7.25-7.23 (m, 4H), 6.98-6.78 (m, 10H), 5.59 (s, 2H), 4.57-4.53 (m, 2H), 4.29-4.19 (m, 2H), 3.64 (s, 4H), 2.37 (s, 6H), 0.95-.82 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.16,

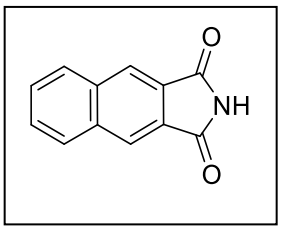
143.35, 137.88, 135.08, 129.13, 128.97, 128.63, 128.33, 127.94, 127.82, 60.83, 21.50, 13.82.

2,2'-(((1S,2S)-1,2-Diphenylethane-1,2-diyl) bis(tosylazanediyl)) diacetic acid (7)



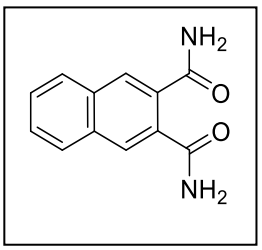
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; (47 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 4H), 7.28-7.26 (m, 4H), 6.94-6.92 (m, 4H), 6.81-6.79 (m, 6H), 5.51 (s, 2H), 4.28 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.96, 142.61, 138.02, 135.33, 129.19, 128.7, 128.48, 127.96, 127.27, 126.99, 60.54, 46.27, 20.96. HRMS (ESI) Calcd for $C_{32}H_{32}N_2O_8S_2$ $(M+H_2O)^+$ 654.1706, found 654.1737.

1*H*-Benzo[f]isoindole-1,3(2H)-dione (19)



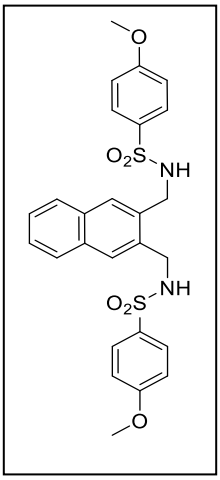
A mixture of 2,3-Naphthalene dicarboxylic anhydride (218 mg, 1.1 mmole) and urea (140 mg, 2 mmole) was heated at 170 °C for 2 hours. Then, the mixture was triturated with 5 ml water and the resulting solid was collected by filtration. of this reaction. (195 mg, 90% yield), as a white solid. ^{1}H NMR (400 MHz, DMSO): δ 11.50 (br, 1H), 8.44 (s, 2H), 8.26-8.25 (m, 2H), 7.77-7.74 (m, 2H). ^{13}C NMR (100 MHz, DMSO): δ 168.97, 135.03, 130.17, 129.02, 128.67, 124.12.

Naphthalene-2,3-dicarboxamide (20)



Phthalimide **19** (190 mg, 0.97 mmole) in anhydrous DMF (2 ml) in sealed tube was cooled to -78 °C using dry ice/ acetone bath. Then, NH_3 (g) was bubbled into the reaction mixture for 15 min., followed by gradual heating of the reaction mixture to room temperature and then heating at 50 °C for 8 hours (reaction done with protective shield inside the hood because of high pressure). Upon reaction completion, cool down to 0 °C to allow NH_3 (g) to be removed and the mixture was purified by a flash column chromatography using 0 - 20% MeOH/DCM afforded the desired product as a white solid (140 mg, 67%). ^{1}H NMR (400 MHz, DMSO): δ 8.04 (s, 2H), 8.00-7.98 (m, 2H), 7.88 (br, 2H), 7.63-7.60 (m, 2H), 7.36 (br, 2H). ^{13}C NMR (100 MHz, DMSO): δ 170.10, 134.01, 132.24, 128.03, 127.47, 127.16.

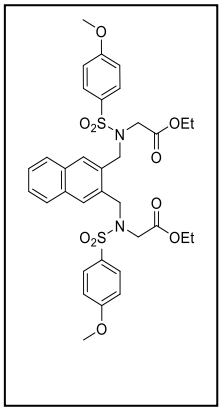
N,N'-(Naphthalene-2,3-diylbis(methylene))bis(4-methoxybenzenesulfonamide) (21)



To a suspension of 2,3-dicarboxamide (**20**) (120 mg, 0.56 mmole) in 5 ml anhydrous THF, 1.3 ml of $BH_3.Me_2S$ was added at room temperature and the reaction mixture was heated to reflux for 2 days. The, reaction checked using LCMS for completion. Then, reaction mixture was cooled to 0 °C and quench with MeOH. Basified the mixture with 4 N NaOH and extracted with ethyl acetate, wash with water, brine, and dried over Na_2SO_4. The product used for next step without further purification. The total amount of crude solid product yield (65 mg, 63% yield). Then, synthesis of sulfonamide intermediate was done using the general procedure for synthesis of sulfonamide (method A1) to get intermediate (**21)** 115 mg, 82% yield). ^{1}H NMR (400 MHz, DMSO): δ 7.78 (d, 4H *J*= 9.0 Hz), 7.73-7.70 (m, 2H), 7.61 (s, 2H), 7.48-7.46 (m,

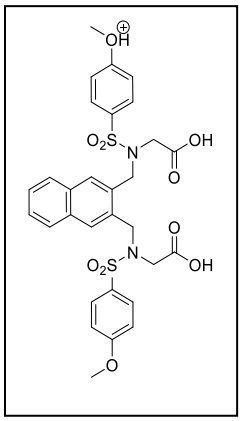
2H), 6.93 (d, 4H *J*= 9.0 Hz),4.80 (t, 2H *J*= 6.0 Hz), 4.30 (t, 4H *J*= 6.0 Hz), 3.85 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ 163.02, 132.83, 132.10, 131.14, 129.53, 129.34, 127.46, 126.72, 114.33, 55.62, 45.50.

Diethyl 2,2'-((naphthalene-2,3-diylbis(methylene)) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (22)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; using 100 mg, 0.19 mmole of intermediate (**21**). (115 mg, 87% yield) as an oily product. ^{1}H NMR (400 MHz, DMSO): δ 7.83 (d, 4H *J*= 9.0 Hz), 7.77-7.75 (m, 4H), 7.75 (s, 1H), 7.74 (s, 1H), 6.98 (d, 4H *J*= 9.0 Hz), 4.74 (s, 4H), 3.94-3.87 (m, 14H), 1.06 (t, 6H, *J*=7 Hz). ^{13}C NMR (100 MHz, DMSO): δ 168.78, 163.25, 133.01, 131.66, 130.94, 129.93, 129.18, 127.72, 126.75, 114.37, 61.36, 55.77, 50.06, 48.17, 14.04.

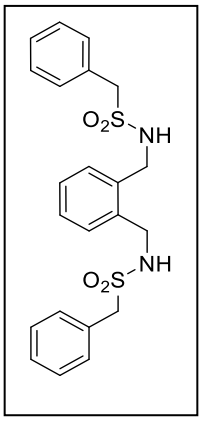
2,2'-((Naphthalene-2,3-diylbis(methylene)) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (8)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a yellow solid; using 70 mg, 0.1 mmole of intermediate (**22**). (51 mg, 79% yield) as an oily product. ^{1}H NMR (400 MHz, DMSO): δ 7.80 (d, 4H *J*= 9.0 Hz), 7.74-7.72 (m, 4H), 7.47-7.44 (m, 2H), 7.02 (d, 4H *J*= 9.0 Hz), 4.86 (s, 4H), 3.89 (s, 4H), 3.85 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ 164.71, 134.20, 133.26, 132.08, 130.87, 130.05,

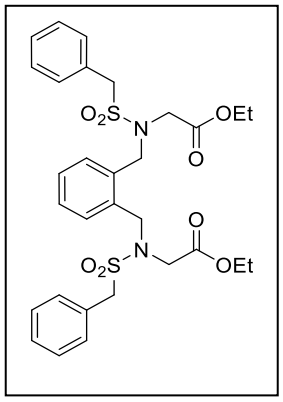
128.56, 127.44, 115.34, 56.19, 51.50. HRMS (ESI) Calcd for Calcd for $C_{30}H_{30}N_2O_{10}S_2$ $(M+H)^+$ 643.1415, found 643.1401.

N,N'-(Naphthalene-2,3-diylbis(methylene))bis(4-methoxybenzenesulfonamide) (26)



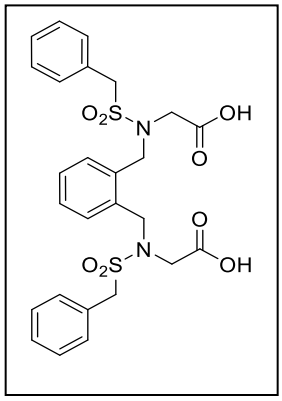
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; **(**347 mg, 78% yield). ^{1}H NMR (400 MHz, $(CD_3)_2$ CO): δ 7.46-7.29 (m, 14H), 6.42 (t, 2H *J*= 6.0 Hz), 4.54 (d, 4H *J*= 4.0 Hz), 4.34 (s, 4H). ^{13}C NMR (100 MHz, $(CD_3)_2$ CO): δ 137.05, 131.78, 131.29, 130.33, 129.30, 129.00, 128.67, 59.01, 45.03, 44.92.

Diethyl 2,2'-((1,2-phenylenebis(methylene))bis((benzylsulfonyl)azanediyl))diacetate (27)



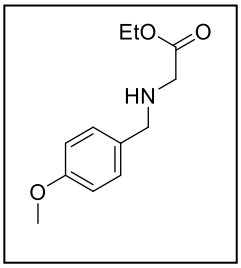
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; **(**358 mg, 83% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.58-7.50 (m, 4H), 7.45-7.13 (m, 10H), 4.48 (s, 4H), 4.39 (s, 4H), 4.17 (q, 4H, *J*=7.2 Hz), 3.82 (s, 4H), 1.24 (t, 6H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.56, 133.97, 131.24, 130.06, 129.04, 128.87, 128.77, 128.7661.67, 59.28, 48.96, 48.00, 14.22.

2,2'-((1,2-Phenylenebis(methylene))bis((benzylsulfonyl)azanediyl))diacetic acid (**23**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; (46 mg, 82% yield). ^{1}H NMR (400 MHz) ($(CD_3)_2$ CO) δ 7.53-7.52 (m, 4H), 7.48-7.45 (m, 2H), 7.41-7.33 (m, 8H), 4.62 (s, 4H), 4.56 (s, 4H), 3.94 (s, 4H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 171.09, 135.59, 132.05, 130.75, 130.32, 129.29, 129.09, 128.95, 59.00, 49.78, 48.74. HRMS (ESI) Calcd for $C_{26}H_{28}N_2O_8S_2$ $(M+H)^+$ 561.1360, found 561.1343.

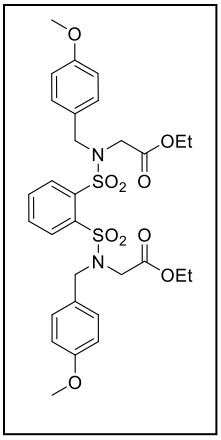
Ethyl (4-methoxybenzyl) glycinate (28)



A solution of 4-anisaldehyde (486 uL, 4 mmol), ethyl glycinate hydrochloride (1.68 g, 12 mmol) and $NaBH_3CN$ (252 mg, 4 mmol) in EtOH (10 mL) was stirred at room temperature for overnight and checked using TLC and LCMS. Then, the organic solvent was remover under reduced pressure and the residue was dissolved in HCl (2 M, 5 mL) and washed with Et2O. Then, neutralize the aqueous phase with sat. aq K_2CO_3 and extracted with ethyl acetate and the organic layer dried over anhydrous sodium sulfate, evaporated under reduced pressure and the crude product purified by ISCO to get the desired compound as oily product (455 mg, 51%). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.28 (d 2H *J*= 8.8 Hz), 6.89 (d 2H *J*= 8.8 Hz), 4.21 (d, 2H *J*= 7.2 Hz), 3.82 (s, 3H) , 3.77 (s, 2H) , 3.42

(s, 2H), 1.30 (t, 3H *J*= 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.60, 158.98, 131.78, 129.64, 114.01, 60.86, 55.42, 52.84, 50.16, 14.38.

Diethyl 2,2'-((1,2-phenylenedisulfonyl) bis((4-methoxybenzyl) azanediyl)) diacetate (30)

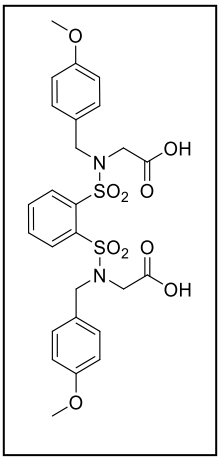


To a stirred solution of ethyl (4-methoxybenzyl) glycinate (**28**) (223 mg, 1 mmole) and K_2CO_3 (552 mg, 4 mmole) in 3 ml DMF at room temperature, benzene-1,2-disulfonyl chloride (125 mg, 0.45 mmole) was added and reaction magnetically stirred at room temperature till reaction completion. Then, reaction diluted with ethyl acetate and washed with 1N HCl, water, brine, and dried over magnesium sulfate and purified with a flash column chromatography using 0 - 50% EtOAc in hexane afforded desired oily product (**30) (**208 mg, 71% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.37-7.34 (m, 2H), 7.69-7.68 (m, 2H), 7.12 (d, 4H *J*= 8.8 Hz), 6.81 (d, 4H *J*= 8.8 Hz), 4.50 (s, 4H), 4.08-4.07 (m, 8H), 3.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.33, 159.65, 139.04, 132.78, 132.70, 130.14, 126.78, 114.29, 61.27, 55.42, 51.15, 47.28, 29.84, 14.19.

2,2'-((1,2-Phenylenedisulfonyl) bis((4-methoxybenzyl) azanediyl)) diacetic acid (24)

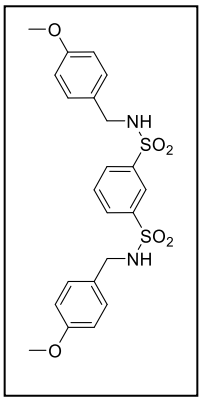
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a beige solid; (11

mg, 87% yield). ^{1}H NMR (400 MHz, (MeOH-d4)): δ 8.34-8.31 (m, 2H), 7.75-7.73 (m, 2H), 7.09 (d, 4H *J*= 8.8 Hz), 6.38 (d, 4H *J*= 8.8 Hz), 4.52 (s, 4H), 4.05 (s, 4H), 3.75 (s, 6H). ^{13}C NMR (100 MHz, MeOH-d4): δ 172.36, 161.10, 140.19, 133.99, 133.41, 131.19, 128.20, 115.11, 55.71, 52.07. HRMS (ESI) Calcd for $C_{26}H_{28}N_2O_{10}S_2$ $(M+H)^+$ 591.1258, found 593.1254.



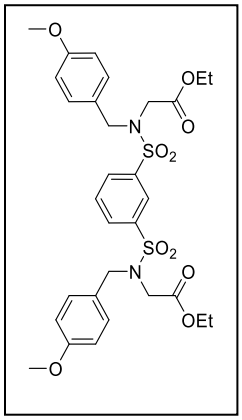
N1, N3-Bis(4-methoxybenzyl)benzene-1,3-disulfonamide (29)

Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a beige solid; **(**385 mg, 81% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.98-7.96 (m, 2H), 7.61-7.57 (m, 2H), 7.09 (d, 4H *J*= 8.8 Hz), 6.79 (d, 4H *J*= 8.8 Hz), 4.89 (t, 2H *J*= 5.6 Hz), 4.12 (d, 4H *J*= 5.6 Hz), 3.76 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.60, 142.07, 130.84, 130.10, 129.52, 127.79, 125.83, 114.37, 55.45, 47.10.

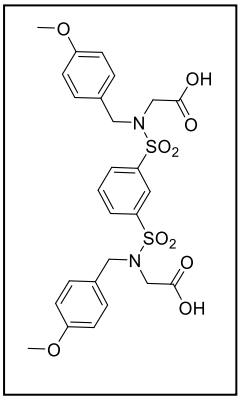


Diethyl 2,2'-((1,3-phenylenedisulfonyl)bis((4-methoxybenzyl)azanediyl))diacetate (31)

Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; **(**262 mg, 79% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 8.38 (t, 1H *J*= 1.6 Hz), 8.10 (dd, 2H *J*= 1.6 Hz, 7.6 Hz), 7.69 (t, 1H *J*= 7.6 Hz), 7.16 (d, 4H *J*= 8.8 Hz), 6.83 (d, 4H *J*= 8.8 Hz), 4.44 (s, 4H), 3.99 (q, 4H *J*= 7.2 Hz), 3.78 (s, 6H), 1.14 (t 6H *J*= 7.2 Hz).

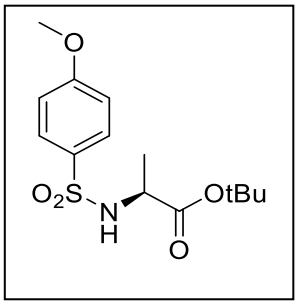


2,2'-((1,3-Phenylenedisulfonyl)bis((4-methoxybenzyl)azanediyl))diacetic acid (25)



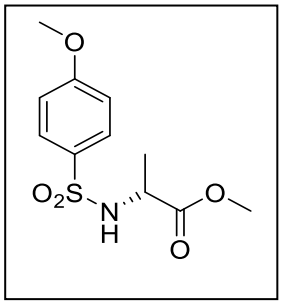
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as an off-white solid; (14 mg, 87% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 8.24 (s, 1H), 8.14 (d, 2H *J*= 8.0 Hz), 7.80 (t, 1H *J*= 8.0 Hz), 7.13 (d, 4H *J*= 8.0 Hz), 6.86 (d, 4H *J*= 8.0 Hz), 4.35 (s, 4H), 3.87 (s, 4H), 3.72 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ 169.65, 158.96, 140.85, 131.16, 130.52, 129.87, 126.87, 125.30, 113.92, 55.04, 50.60, 47.11. HRMS (ESI) Calcd for $C_{26}H_{28}N_2O_{10}S_2$ $(M+H)^+$ 593.1258, found 593.1253

***tert*-Butyl ((4-methoxyphenyl) sulfonyl)-L-alaninate (36a)**



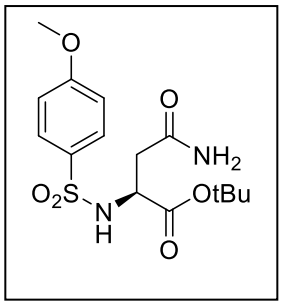
The synthesis of sulfonamide intermediate **36** was done using the general procedure (method A1) using L-alanine *tert*-butyl ester hydrochloride as the amine starting material to get intermediate (**36) (**261 mg, 83% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 8.02 (d, 1 H *J*= 8.0 Hz), 7.69 (d, 2H *J*= 8.0 Hz), 7.07 (d, 2H *J*= 8.4 Hz), 3.80 (s, 3 H), 3.66 (t, 1H *J*= 7.2 Hz), 1.24 (s, 9 H), 1.12 (d, 3H *J*= 6.8 Hz). ^{13}C NMR (100 MHz, DMSO): δ 170.74, 161.98, 132.77, 128.50, 114.02, 80.43, 55.44, 51.55, 27.18, 18.33.

Methyl ((4-methoxyphenyl) sulfonyl)-D-alaninate (36b)



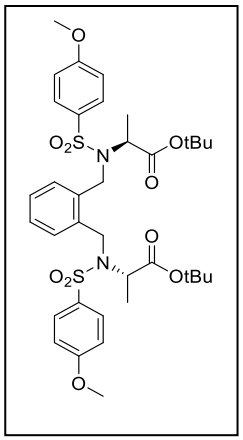
The synthesis of sulfonamide intermediate **36** bwas done using the general procedure (method A1) using D-alanine methyl ester hydrochloride as the amine starting material to get intermediate (**36b) (**246 mg, 91% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.75 (d, 2H *J*= 8.8 Hz), 6.93 (d, 2H *J*= 8.8 Hz), 5.38 (d, 1H *J*= 8.8 Hz), 3.98-3.91 (m, 1 H), 3.52 (s, 3 H), 1.34 (d, 3H *J*= 8.8 Hz). ^{13}C NMR (100 MHz, DMSO): δ 172.66, 163.00, 131.39, 129.34, 114.18, 55.62, 52.55, 51.41, 19.67.

***tert*-Butyl ((4-methoxyphenyl) sulfonyl)-L-asparaginate (36c)**



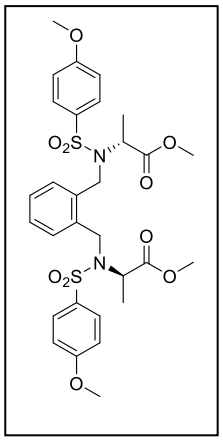
The synthesis of sulfonamide intermediate **36** was done using the general procedure (method A1) using L-Alanine *tert*-butyl ester hydrochloride as the amine starting material to get intermediate (**36c) (**261 mg, 83% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.94 (d, 1 H *J*= 8.8 Hz), 7.71 (d, 2H *J*= 8.8 Hz), 7.33 (br, 1 H), 7.07 (d, 2H *J*= 8.8 Hz), 6.88 (br, 1 H), 4.04-3.98 (m, 1H), 3.81 (s, 3 H),2.50-2.41 (m, 2 H), 2.29-2.23 (m, 2 H), 1.22 (s, 9 H).^{13}C NMR (100 MHz, DMSO): δ 170.15, 169.36, 161.93, 132.76, 128.53, 113.92, 80.45, 55.42, 52.88, 27.09.

Di-*tert*-butyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl))(2S,2'S)-dipropionate (**40a**)



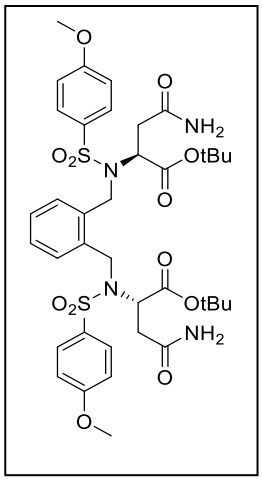
The synthesis of alkylated sulfonamide intermediate **40a** was done using the general procedure (method B) to get intermediate (**40a)** (131 mg, 71% yield). ^{1}H NMR (400 MHz, $(CD_3)_2$ CO): δ 7.79 (d, 4H *J*= 9.0 Hz), 7.52-7.50 (m, 2H), 7.23-7.21 (m, 2H), 7.07 (d, 4H *J*= 9.0 Hz), 4.70-4.58 (m, 4H), 4.44 (q, 2H *J*= 7.2 Hz), 3.89 (s, 6H), 1.33 (s, 18H), 1.25 (d, 6H *J*= 7.2 Hz). ^{13}C NMR (100 MHz, $(CD_3)_2$ CO): δ 206.29, 170.98, 163.98, 136.56, 133.08, 130.57, 129.14, 127.74, 115.11, 82.06, 57.05, 56.17, 46.99, 16.90.

Dimethyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl))(2R,2'R)-dipropionate (**40b**)



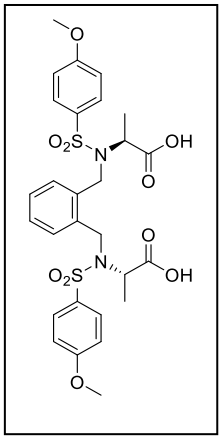
The synthesis of alkylated sulfonamide intermediate **40b** was done using the general procedure (method B) to get intermediate (**40b)** (211 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77(d, 4H *J*= 8.8 Hz), 7.42-7.39 (m, 2H), 7.21-7.19 (m, 2H), 6.96 (d, 4H *J*= 8.8 Hz), 4.65-4.54 (m, 4H), 4.50 (q, 2H *J*= 7.2 Hz), 3.85 (s, 6H), 3.39 (s, 6 H), 1.17 (d, 6H *J*= 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.48, 163.06, 134.98, 131.44, 129.71, 129.05, 127.73, 114.26, 55.69, 55.05, 52.22, 46.95, 15.40.

***tert*-Butyl N2-(2-(((N-((R)-4-amino-1-(*tert*-butoxy)-1,4-dioxobutan-2-yl)-4-di-*tert*-butyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl)azanediyl)) (2S,2'S)-bis(4-amino-4-oxobutanoate)** (**40c**)



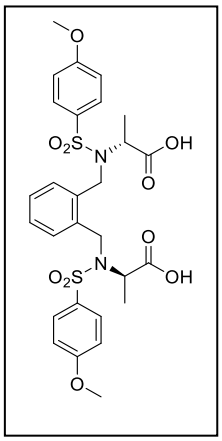
The synthesis of alkylated sulfonamide intermediate **40c** was done using the general procedure (method B) to get intermediate (**40c)** as oily product **(**131 mg, 71% yield). ^{1}H NMR (400 MHz, (CD_3CN): δ 7.79 (d, 4H *J*= 8.8 Hz), 7.37-7.35 (m, 2H), 7.23-7.21 (m, 2H), 7.03 (d, 4H *J*= 8.8 Hz), 6.08 (br, 2 H), 5.63 (br, 2 H), 4.60-4.57 (m, 4H), 4.45 (s, 4 H), 3.85 (s, 6H), 2.78-2.72 (m, 2 H), 2.31-2.27 (m, 2 H), 1.28 (s, 18 H). ^{13}C NMR (100 MHz, (CD_3CN): δ 172.28, 169.64, 163.96, 135.62, 132.25, 130.55, 129.52, 128.20, 118.04, 115.10, 82.63, 58.18, 56.32, 48.09, 36.66, 27.83.

(2S,2'S)-2,2'-((1,2-Phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl)) dipropionic acid (**32a**)



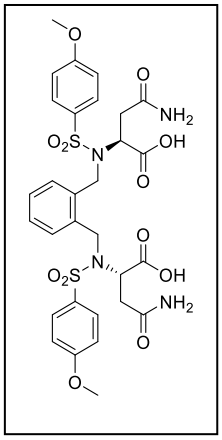
The synthesis of diacid final compound **32** was done using the general procedure (method C2) to get compound (**32)** as a white solid **(**23 mg, 74% yield). ^{1}H NMR (400 MHz, $(CD_3)_2$ CO): δ 7.82 (d, 4H *J*= 9.0 Hz), 7.53-7.51 (m, 2H), 7.23-7.21 (m, 2H), 7.05 (d, 4H *J*= 9.0 Hz), 4.61 (s, 4H), 4.52 (q, 4H *J*= 7.2 Hz), 3.89 (s, 6H), 1.31 (d, 6H *J*= 7.2 Hz). ^{13}C NMR (100 MHz, $(CD_3)_2$ CO): δ 206.25, 172.47, 163.73, 136.12, 132.65, 130.42, 129.20, 127.65, 114.77, 55.91, 55.87, 47.10, 16.26. HRMS (ESI) Calcd for $C_{28}H_{32}N_2O_{10}S_2$ $(M+H)^+$ 621.1498, found 621.1567.

(2R,2'R)-2,2'-((1,2-Phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl)) dipropionic acid (**32b**)



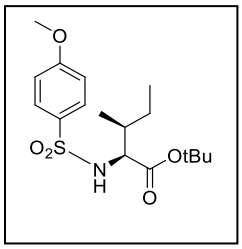
The synthesis of diacid final compound **32b** was done using the general procedure (method C1) to get compound (**32b)** as a white solid (31 mg, 79% yield). ^{1}H NMR (400 MHz, CD_3CN): δ 7.76-7.73 (m, 4H), 7.41-7.38 (m, 2H), 7.22-7.19 (m, 2H), 7.02-6.99 (m, 4H), 4.59-4.39 (m, 6H), 3.85 (s, 6H), 1.22 (d, 6H *J*= 7.2 Hz). ^{13}C NMR (100 MHz, CD_3CN): δ. 172.59, 163.86, 135.91, 132.08, 130.40, 129.25, 127.94, 114.91, 56.24, 55.92, 47.44, 15.88. HRMS (ESI) Calcd for $C_{28}H_{32}N_2O_{10}S_2$ $(M+H)^+$ 621.1571, found 621.1577.

(2S,2'S)-2,2'-((1,2-Phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl)) bis(4-amino-4-oxobutanoic acid) (**32c**)



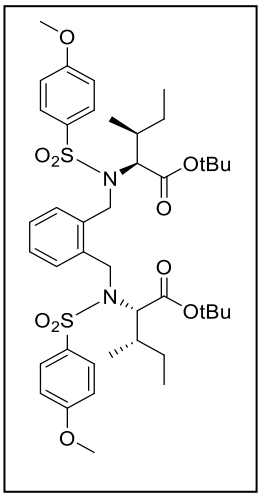
The synthesis of diacid final compound **32** was done using the general procedure (method C2) to get compound (**32)** as a white solid (33 mg, 77% yield). ^{1}H NMR (400 MHz, DMSO): δ 7.77 (d, 4H *J*= 8.4 Hz), 7.30-7.28 (m, 4H), 7.17-7.14 (m, 2H), 7.06 (d, 4H *J*= 8.8 Hz), 6.85 (br, 2 H), 4.54-4.51 (m, 2 H), 4.48-4.24 (m, 4 H), 3.84 (s, 4H), 2.80-2.73 (m, 2 H), 2.21-2.16 (m, 2 H). ^{13}C NMR (100 MHz, DMSO): δ 171.09, 170.53, 162.53, 134.37, 130.86, 129.61, 128.49, 127.14, 114.21, 56.05, 55.62, 46.95, 35.07. HRMS (ESI) Calcd for $C_{30}H_{34}N_4O_{12}S_2$ $(M+H)^+$ 707.1687, found 707.1663.

tert-Butyl ((4-methoxyphenyl)sulfonyl)-L-isoleucinate (37)



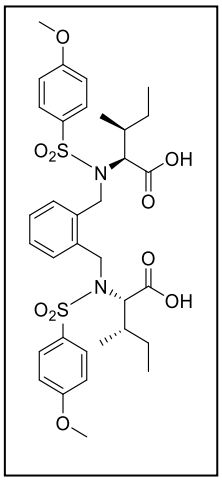
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound; using L-isoleucine *tert*-butyl ester hydrochloride as the amine starting material to get intermediate (**37)** white solid (329 mg, 92% yield). ^{1}H NMR (400 MHz, $(CD_3)_2$ CO): δ 7.76 (d, 2H, *J*= 8.8 Hz), 7.07 (d, 2H, *J*= 8.8 Hz), 6.43 (d, 1H, *J*= 9.8 Hz), 3.87 (s, 3H), 3.65-3.61 (dd, 1H, *J*= 9.8 Hz, 5.8 Hz), 1.77-1.72 (m, 1H), 1.51-1.46 (m, 1H), 1.25 (s, 9H), 1.21-1.13 (m, 1H), 0.91 (d, 3H, *J*=6.8 Hz), 0.86 (t, 3H, *J*=7.4 Hz). ^{13}C NMR (100 MHz, $(CD_3)_2$ CO): δ170.63, 163.56, 133.68, 129.91, 114.76, 81.82, 61.45, 55.90, 39.01, 27.74, 25.39, 15.66, 11.37.

Di-_tert_-butyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl)) (2S,2'S,3S,3'S)-bis(3-methylpentanoate) (**41**)



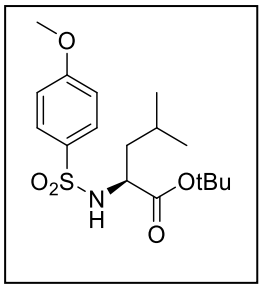
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as a white solid product; (129 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, 4H *J*= 8.8 Hz), 7.44-7.42 (m, 2H), 7.02-6.99 (m, 2H), 6.85 (d, 4H *J*= 8.8 Hz), 4.91-4.80 (m, 4H), 4.20 (d, 2H *J*= 10.0 Hz), 3.83 (s, 6H), 1.71-1.67 (m, 2H), 1.59-1.52 (m, 2H), 1.29 (s, 18H), 1.05-0.97 (m, 2H), 0.81 (d, 6H, *J*= 6.8), 0.61 (t, 6H, *J*= 7.6).

(2S,2'S,3S,3'S)-2,2'-((1,2-Phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl))bis(3-methylpentanoic acid) (**33**)



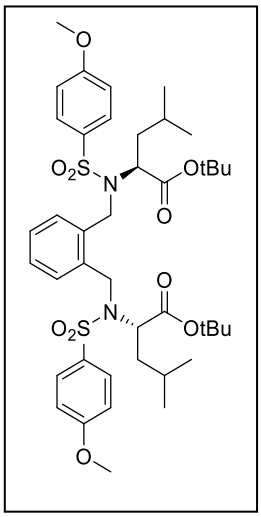
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; **(**32 mg, 72% yield). ^{1}H NMR (400 MHz, $(CD_3)_2$ CO): δ 7.74 (d, 4H *J*= 8.8 Hz), 7.56-7.53 (m, 2H), 7.14-7.12 (m, 2H), 6.98 (d, 4H *J*= 8.8 Hz), 4.90 (d, 2H *J*= 16.8 Hz), 4.74 (d, 2H *J*= 16.8 Hz), 4.22 (d, 2H *J*= 10.0 Hz), 3.87 (s, 6H), 1.65-1.58 (m, 4H), 0.96-0.88 (m, 2H), 0.82 (d, 6H, *J*= 6.8), 0.57 (t, 6H, *J*= 7.6). ^{13}C NMR (100 MHz, $(CD_3)_2$ CO): δ 171.92, 163.86, 136.41, 132.87, 130.57, 129.51, 127.32, 114.82, 65.47, 56.07, 45.78, 35.42, 26.88, 15.99, 11.03. HRMS (ESI) Calcd for $C_{34}H_{44}N_2O_{10}S_2$ $(M+H)^+$ 705.2510, found 705.2510.

***tert*-Butyl ((4-methoxyphenyl) sulfonyl)-L-leucinate (38)**



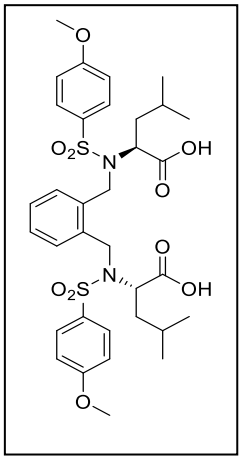
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; using L-Leucine *tert*-butyl ester hydrochloride as the amine starting material to get intermediate (**37) (**268 mg, 75% yield). ^{1}H NMR (400 MHz, $(CDCl_3)$): δ 7.76 (d, 2H, *J*= 8.8 Hz), 6.93 (d, 2H, *J*= 8.8 Hz), 5.07 (d, 1H, *J*= 10.0 Hz), 3.83 (s, 3H), 3.78-3.71 (m, 1H), 1.86-1.80 (m, 1H), 1.42 (t, 2H, *J*= 7.2 Hz), 1.22 (s, 9H), 0.90 (d, 6H, *J*= 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ171.57, 162.98, 131.53, 129.51, 114.16, 82.08, 55.61, 54.66, 42.66, 27.62, 24.34, 22.84, 21.46.

Di-*tert*-butyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl))(2S,2'S)-bis(4-methylpentanoate) (**42**)



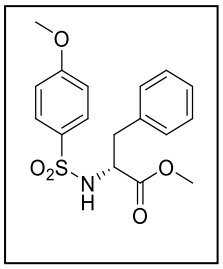
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (119 mg, 73% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.73 (d, 4H, *J*= 8.8 Hz), 7.49-7.47 (m, 2H), 7.16-7.13 (m, 2H), 6.90 (d, 2H, *J*= 8.8 Hz), 4.73-4.63 (m, 4H), 4.42 (t, 2H, *J*= 6.4 Hz), 3.84 (s, 6H), 1.60-1.32 (m, 6H), 1.30 (s, 18H), 0.86 (d, 6H, *J*= 6.4 Hz), 0.68 (d, 6H, *J*= 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.31, 162.67, 134.94, 132.07, 129.61, 129.45, 128.25, 126.87, 113.95, 81.54, 58.88, 55.48, 45.58, 45.58, 39.62, 27.74, 27.62, 24.99, 22.05.

(2S,2'S)-2,2'-((1,2-Phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl))bis(4-methylpentanoic acid) (**34**)



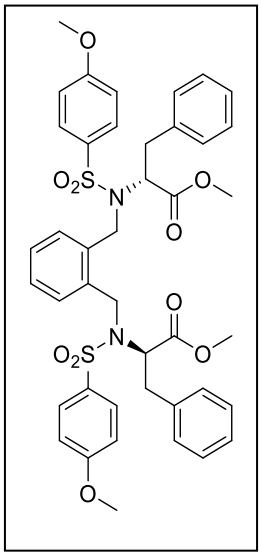
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; (15 mg, 72% yield). ^{1}H NMR (400 MHz, $(CD_3)_2$ CO): δ 7.86 (d, 4H, *J*= 8.8 Hz), 7.67-7.64 (m, 2H), 7.32-7.29 (m, 2H), 7.11 (d, 2H, *J*= 8.8 Hz), 4.79-4.61 (m, 4H), 4.62-4.59 (m, 2H), 3.96 (s, 6H), 1.76-1.60 (m, 4H), 1.52-1.45 (m, 2H), 0.95 (d, 6H, *J*= 6.4 Hz), 0.75 (d, 6H, *J*= 6.4 Hz). ^{13}C NMR (100 MHz, $(CD_3)_2$ CO): δ 172.58, 163.94, 136.56, 132.71, 130.61, 129.39, 127.64, 114.95, 58.92, 56.13, 46.70, 40.22, 25.65, 22.62, 22.24. HRMS (ESI) Calcd for $C_{34}H_{44}N_2O_{10}S_2$ $(M+H)^+$ 705.2510, found 705.2505.

Methyl ((4-methoxyphenyl)sulfonyl)-D-phenylalaninate (39)



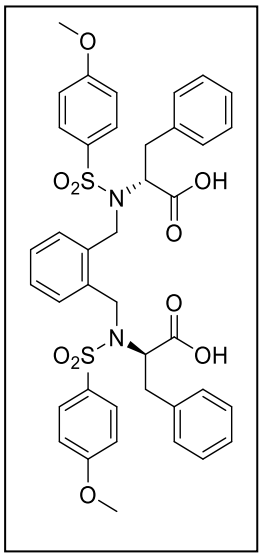
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; using D-Phenylalanine methyl ester hydrochloride as the amine starting material to get intermediate (**39) (**298 mg, 85% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 8.33 (d, 1H *J*= 8.8), 7.53 (d, 2H *J*= 8.8 Hz), 7.24-7.16 (m, 3H), 7.11-7.09 (m, 2H), 6.98 (d, 2H *J*= 8.8 Hz), 3.94-3.88 (m, 1H), 3.81 (s, 3H), 3.34 (s, 3H), 2.92-2.87 (m, 1H), 2.78-2.74 (m, 1H). ^{13}C NMR (100 MHz, DMSO): δ 171.21, 162.04, 136.27, 132.33, 126.66, 114.03, 57.31, 57.31, 55.60, 51.72, 37.70.

Dimethyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl))(2R,2'R)-bis(3-phenylpropanoate) (**43**)



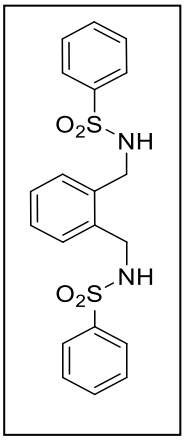
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (109 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, 4H *J*= 8.8 Hz), 7.38-7.23 (m, 10H), 7.13-7.09 (m, 4H), 7.03 (d, 4H *J*= 8.8 Hz), 4.78-4.60 (m, 6H), 3.89 (s, 6H), 3.78 (s, 6H), 3.16-3.09 (m, 2H), 2.82-2.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.27, 163.14, 137.06, 134.75, 131.50, 129.96, 129.57, 129.44, 129.40, 128.48, 127.79, 126.81, 114.25, 60.91, 55.71, 52.06, 47.27, 36.50.

(2R,2'R)-2,2'-((1,2-Phenylenebis(methylene))bis(((4-methoxyphenyl)sulfonyl) azanediyl))bis(3-phenylpropanoic acid) (**35**)



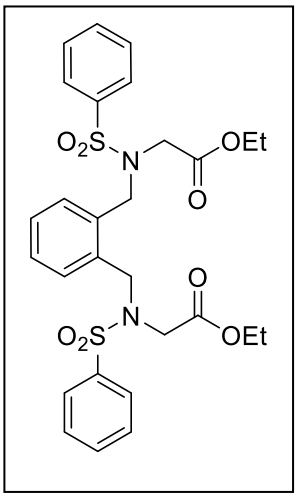
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; **(**19 mg, 78% yield). ^{1}H NMR (400 MHz, DMSO): δ 7.84 (m, 4H), 7.25-7.21 (m, 9H), 7.13-7.06 (m, 9H), 4.62-4.44 (m, 6H), 3.83-3.79 (m, 6H), 3.09-3.01 (m, 2H), 2.69-2.59 (m, 2H). ^{13}C NMR (100 MHz, DMSO): δ 170.75, 162.67, 137.13, 134.70, 130.96, 129.65, 129.59, 129.16, 129.02, 128.95, 128.46, 128.23, 128.12, 127.96, 126.67, 126.48, 114.35, 114.31, 113.95, 60.75, 55.65, 55.62, 55.54, 45.89, 45.75, 36.01, 35.67. HRMS (ESI) Calcd for $C_{40}H_{40}N_2O_{10}S_2$ $(M+H)^+$ 773.2197, found 773.2190.

N,N'-(1,2-Phenylenebis(methylene)) dibenzenesulfonamide (44a)



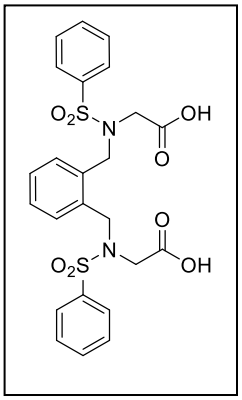
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; (305 mg, 73% yield). ^{1}H NMR (400 MHz, (MeOH-d4)): δ 7.85-7.82 (m, 4H), 7.85-7.82 (m, 4H), 7.61-7.52 (m, 6H), 7.20-7.16 (m, 4H), 4.08 (s, 4 H), ^{13}C NMR (100 MHz, MeOH-d4): δ 141.75, 136.45, 133.61, 130.42, 130.22, 128.92, 128.02, 45.16.

Diethyl 2,2'-((1,2-phenylenebis(methylene))bis((phenylsulfonyl)azanediyl))diacetate (45a)



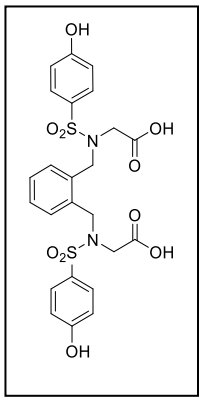
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; **(**98 mg, 83% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.79 (d, 4H *J*= 7.2 Hz), 7.53-7.49 (m, 2H), 7.47-7.43 (m, 4H), 7.27-7.25 (m, 2H), 7.21-7.18 (m, 2H), 4.54 (s, 4 H), 3.85 (t, 4H *J*= 7.2 Hz), 3.79 (s, 4H), 0.99 (t, 6H *J*= 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.38, 139.21, 133.87, 132.80, 129.69, 129.03, 128.49, 127.47, 61.24, 49.13, 47.67, 29.68, 22.67, 13.87.

2,2'-((1,2-Phenylenebis(methylene))bis((phenylsulfonyl)azanediyl))diacetic acid (**46a**)



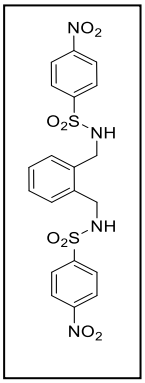
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; (19 mg, 72% yield). ^{1}H NMR (400 MHz, (MeOH-d_4)): δ 7.86-7.84 (m, 4H), 7.63-7.53 (m, 6H), 7.30-7.22 (m, 4H), 4.58 (s, 4 H), 3.84 (s, 4 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 171.89, 140.63, 135.61, 134.04, 130.94, 130.25, 129.29, 128.62, 50.63, 48.83. HRMS (ESI) Calcd for $C_{24}H_{24}N_2O_8S_2$ $(M+H)^+$ 533.1047, found 533.1031.

2,2'-((1,2-Phenylenebis(methylene))bis(((4-hydroxyphenyl) sulfonyl) azanediyl)) diacetic acid (**46b**)



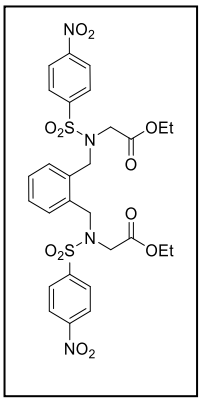
To a suspension of compound (**2**) (65 mg, 0.1 mmole) in dry DCM (1 ml), 1 ml solution of BBr3 (1M, in DCM) was added and reaction stirred at room temperature overnight. Then, reaction quenched with water and diluted with DCM and washed with water, brine, and dried over sodium sulfate. The crude product purified on an ISCO silica gel (0-20% MeOH/DCM). The total amount of pure product was (6.8 mg, 12% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.69 (d, 4H *J*= 8.8 Hz), 7.23 (s, 4H), 7.86 (d, 4H *J*= 8.8 Hz), 4.47 (s, 4 H), 3.52 (s, 4 H). ^{13}C NMR (100 MHz, DMSO): δ 169.97, 161.69, 134.56, 129.59, 128.80, 128.65, 127.57, 115.75, 49.14, 48.35. HRMS (ESI) Calcd for $C_{24}H_{24}N_2O_{10}S_2$ $(M+H)^+$ 565.0945, found 565.0936.

N,N'-(1,2-Phenylenebis(methylene))bis(4-nitrobenzenesulfonamide) (44c)



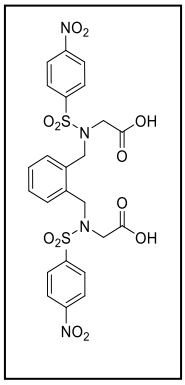
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a yellow solid; (324 mg, 64% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 8.41 (t, 2H *J*= 6.0 Hz), 8.37 (d, 2H *J*= 8.4 Hz), 8.00 (d, 2H *J*= 8.4 Hz), 7.17 (s, 4 H), 4.06 (d, 4H *J*= 6.0 Hz), ^{13}C NMR (100 MHz, DMSO): δ 149.42, 146.11, 134.74, 128.68, 128.00, 127.45, 124.44, 43.23.

Diethyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-nitrophenyl) sulfonyl) azanediyl)) diacetate (**45c**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (103 mg, 76% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 8.36 (d, 4H *J*= 8.8 Hz), 8.05 (d, 4H *J*= 8.8 Hz), 7.34-7.29 (m, 4H), 4.67 (s, 4 H), 3.98 (q, 4H *J*= 7.2 Hz), 3.95 (s, 4H), 1.12 (t, 6H *J*= 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.19, 150.34, 145.02, 133.36, 130.03, 129.15, 128.95, 124.37, 61.74, 49.16, 47.54, 29.85, 14.12.

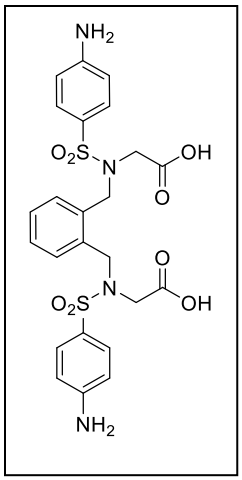
2,2'-((1,2-Phenylenebis(methylene)) bis (((4-nitrophenyl)sulfonyl) azanediyl)) diacetic acid (**46c**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a yellow solid; (23 mg, 79% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 8.35 (d, 4H *J*= 8.8 Hz), 8.08 (d, 4H *J*= 8.8 Hz), 7.26 (s, 4H), 4.52 (s, 4H), 3.79 (s, 4H). ^{13}C NMR (100 MHz, DMSO): δ 169.56, 149.76, 144.53, 133.80, 128.27, 128.58, 127.88, 124.39, 49.05, 48.33. HRMS (ESI) Calcd for $C_{24}H_{22}N_4O_{12}S_2$ $(M+H)^+$ 623.0748, found 623.0743

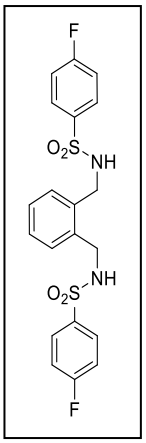
2,2'-((1,2-Phenylenebis(methylene))bis(((4-aminophenyl)sulfonyl)azanediyl))diacetic acid (**46d**)

A solution of compound (**46c**) (13 mg, 0.02 mmole) in EtOH 5 ml was degassed with N_2 three times. A catalytic amount of 10% Pd/C (5 mg) was added to the solution and the reaction was purged with H_2. The reaction was stirred under H_2 for 3 h and then filtered through a celite bed to remove the catalyst. The filtrate was concentrated under vacuum to give an off-white solid (11 mg, 94% yield). ^{1}H NMR (400 MHz, (MeOH-d_4)): δ 7.52 (d, 4H *J*= 8.8 Hz), 7.25-7.19 (m, 4H), 6.56 (d, 4H *J*= 8.8 Hz),5.86 (s, 4H), 4.47 (s, 4H), 3.38 (s, 4H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 172.44, 154.38, 135.95, 130.85, 130.68, 128.96, 126.01, 114.51, 50.74. HRMS (ESI) Calcd for $C_{24}H_{26}N_4O_8S_2$ $(M+H)^+$ 563.1265, found 563.1254.

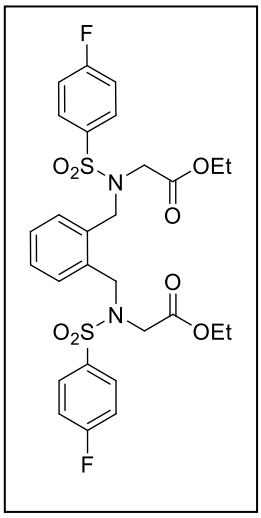


N,N'-(1,2-Phenylenebis(methylene))bis(4-fluorobenzenesulfonamide) (44e)

Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; **(**321 mg, 71% yield). ^{1}H NMR (400 MHz, (MeOH-d_4)): δ 7.89-7.85 (m, 4H), 7.28-7.24 (m, 4H), 7.21-7.16 (m, 4H), 4.09 (s, 4 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 167.60, 165.09, 138.02, 136.35, 131.02, 130.93, 130.43, 128.97, 117.30, 117.07, 45.19. ^{19}F NMR (377 MHz, MeOH-d_4): δ – 108.51 (s, 2F).

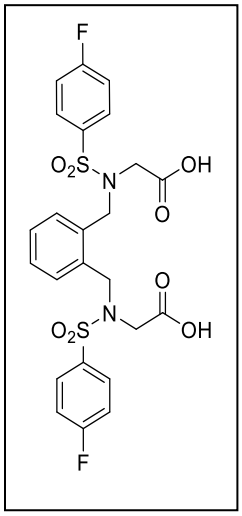


Diethyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-fluorophenyl)sulfonyl)azanediyl)) diacetate (**45e**)



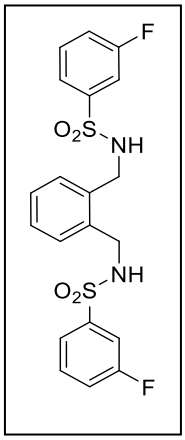
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (43 mg, 69% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.90-7.87 (m, 4H), 7.32-7.26 (m, 4H), 7.22-7.18 (m, 4H), 4.60 (s, 4 H), 3.96 (q, *J*= 7.2 Hz, 4H), 3.88 (s, 4H), 1.12 (t, *J*= 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.45, 166.60, 164.07, 135.34, 133.77, 130.41, 130.32, 129.81, 128.75, 116.46, 116.23, 61.45, 49.13, 47.60, 14.04.

2,2'-((1,2-Phenylenebis(methylene))bis(((4-fluorophenyl)sulfonyl)azanediyl))diacetic acid (**46e**)



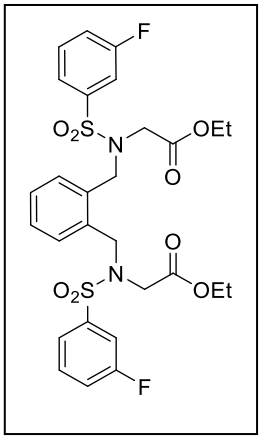
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; (11 mg, 76% yield). ^{1}H NMR (400 MHz, (MeOH-d_4)): δ 7.93-7.89 (m, 4H), 7.33-7.25 (m, 8H), 4.59 (s, 4 H), 3.87 (s, 4 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 171.80, 167.93, 165.48, 136.95, 135.54, 131.69, 131.60, 130.89, 129.37, 117.31, 117.08, 50.47, 48.38. ^{19}F NMR (377 MHz, MeOH-d_4): δ – 107.92 (s, 2F). HRMS (ESI) Calcd for $C_{24}H_{22}F_2N_2O_8S_2$ $(M+H)^+$ 569.0858, found 569.0851.

N,N'-(1,2-Phenylenebis(methylene))bis(3-fluorobenzenesulfonamide) (44f)



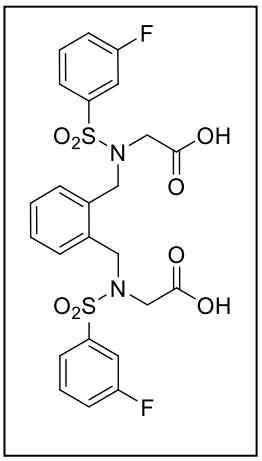
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; (335 mg, 74% yield). n^{1}H NMR (400 MHz, (MeOH-d_4)): δ 7.66-7.64 (m, 2H), 7.59-7.51 (m, 4H), 7.38-7.33 (m, 2H), 7.21-7.16 (m, 4H), 4.11 (s, 4 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 165.08, 162.60, 144.08, 144.01, 136.30, 132.37, 132.29, 130.46, 129.01, 124.01, 123.98, 120.65, 120.44, 115.18, 114.93, 45.13. ^{19}F NMR (377 MHz, MeOH-d_4): δ – 112.30 (s, 2F).

Diethyl 2,2'-((1,2-phenylenebis(methylene))bis(((2,6-difluorophenyl) sulfonyl) azanediyl)) diacetate (**45f**)



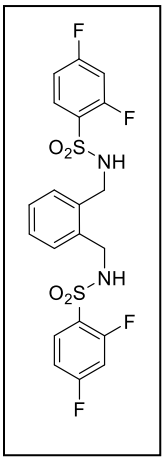
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (101 mg, 76% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.67-7.65 (m, 2H), 7.56-7.49 (m, 4H), 7.33-7.27 (m, 6H), 4.62 (s, 4 H), 3.95 (q, 4 H *J*= 7.2 Hz), 3.89 (s, 4 H), 1.09 (t, 6 H *J*= 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.29, 163.70, 161.21, 141.26, 141.19, 133.66, 130.99, 130.91, 129.85, 128.79, 123.37, 123.34, 120.22, 120.01, 115.04, 114.79, 61.48, 49.11, 47.62, 13.98.

2,2'-((1,2-Phenylenebis(methylene))bis(((3-fluorophenyl)sulfonyl)azanediyl))diacetic acid (**46f**)



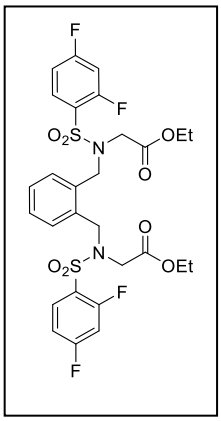
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; (13 mg, 70% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 12.68 (br, 2H), 7.68-7.60 (m, 6H), 7.56-7.53 (m, 2H), 7.23-7.22 (m, 4H), 4.51 (s, 4 H), 3.98-3.86 (m, 4 H). ^{13}C NMR (100 MHz, DMSO): δ 169.71, 168.76, 163.01, 160.55, 141.07, 141.00, 134.04, 133.93, 131.66, 131.54, 131.46, 128.78, 128.56, 127.77, 127.67, 123.40, 120.36, 120.19, 119.98, 114.36, 114.12, 51.76, 49.17, 49.17, 49.09, 48.52, 48.36. HRMS (ESI) Calcd for $C_{24}H_{22}F_2N_2O_8S_2$ $(M+H)^+$ 569.0858, found 569.0852.

N,N'-(1,2-Phenylenebis(methylene))bis(2,4-difluorobenzenesulfonamide) (44h)



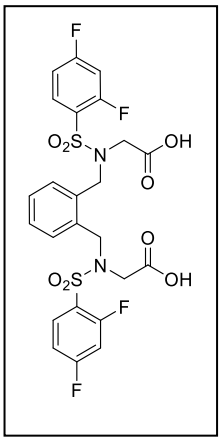
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; (371 mg, 76% yield). ^{1}H NMR (400 MHz, (MeOH-d_4)): δ 7.82-7.79 (m, 2H), 7.19-7.01 (m, 8H), 4.18 (s, 4 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 168.38, 168.27,m 135.85, 165.73, 162.23, 162.10, 159.68, 159.55, 136.09, 133.19, 133.18, 133.18, 133.08, 130.51, 128.93, 126.69, 126.65, 126.55, 126.51, 112.87, 112.84, 112.65, 112.61, 106.69, 106.43, 106.17, 44.74. ^{19}F NMR (377 MHz, MeOH-d_4): δ – 103.97 (d, J = 12 Hz, 1F), – 106.31 (d, J = 12 Hz, 1F).

Diethyl 2,2'-((1,2-phenylenebis(methylene))bis(((2,4-difluorophenyl) sulfonyl) azanediyl)) diacetate (**45h**)



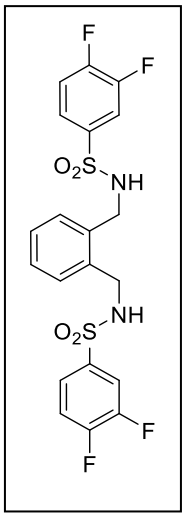
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (109 mg, 83% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.88-7.82 (m, 2H), 7.34-7.28 (m, 4H), 6.98-6.92 (m, 4H), 4.68 (s, 4 H), 4.01 (q, *J*= 7.2 Hz, 4H), 3.97 (s, 4 H), 1.14 (t, *J*= 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.41, 167.25, 167.13, 164.69, 164.58, 161.47, 161.34, 158.91, 158.78, 133.77, 132.46, 132.36, 129.78, 128.78, 124.67, 124.53, 124.49, 111.81, 111.78, 111.59, 111.56, 106.01, 105.76, 105.50, 61.55, 48.82, 48.79, 47.59, 14.06. ^{19}F NMR (377 MHz, $CDCl_3$): δ – 100.67 (d, J = 12 Hz, 1F), – 102.01 (d, J = 12 Hz, 1F).

2,2'-((1,2-Phenylenebis(methylene))bis(((2,4-difluorophenyl) sulfonyl) azanediyl)) diacetic acid (**46h**)



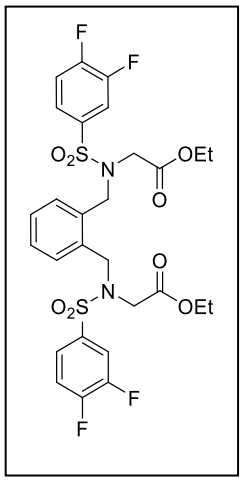
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; **(**16 mg, 72% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.85-7.79 (m, 2H), 7.29-7.24 (m, 4H), 7.19-7.14 (m, 2H), 7.06-7.02 (m, 2H), 4.65 (s, 4 H), 3.95 (s, 4 H). ^{13}C NMR (100 MHz, DMSO): δ 171.79, 168.61, 168.49, 166.07, 165.95, 162.76, 162.61, 160.19, 160.05, 135.43, 133.57, 133.46, 130.87, 129.44, 129.35, 126.15, 126.11, 126.00, 125.97, 112.79, 112.76, 112.57, 112.53, 106.90, 106.63, 106.37, 65.77, 48.80. ^{19}F NMR (377 MHz, $CDCl_3$): δ – 103.55 (d, J = 12 Hz, 1F), – 103.74 (d, J = 12 Hz, 1F). HRMS (ESI) Calcd for $C_{24}H_{20}F_4N_2O_8S_2$ $(M+H)^+$ 605.0670, found 605.0661.

N,N'-(1,2-Phenylenebis(methylene))bis(3,4-difluorobenzenesulfonamide) (44i)



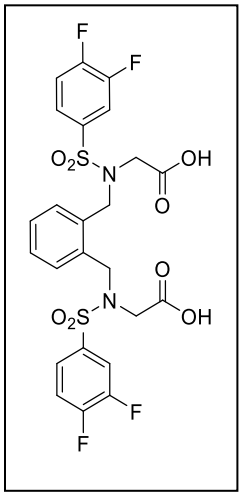
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; **(**386 mg, 79% yield). ^{1}H NMR (400 MHz, (MeOH-d_4)): δ 7.72-7.65 (m, 4H), 7.47-7.41 (m, 2H), 7.22-7.18 (m, 4H), 4.12 (s, 4 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 155.42, 155.29, 152.89, 152.77, 152.62, 152.49, 150.12, 149.99, 139.12, 139.07, 139.03, 136.25, 130.51, 129.05, 125.65, 125.62, 125.58, 125.54, 119.40, 119.21, 117.91, 117.71, 45.16. ^{19}F NMR (377 MHz, MeOH-d_4): δ – 133.69 (d, 2F *J*= 2Hz), – 137.16 (d, 2F *J*= 2Hz).

Diethyl 2,2'-((1,2-phenylenebis(methylene))bis(((3,4-difluorophenyl) sulfonyl) azanediyl)) diacetate (**45i**)



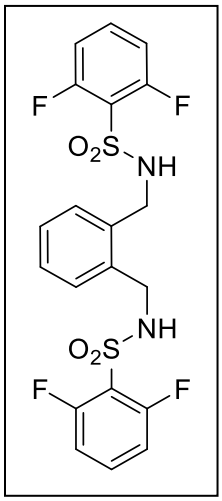
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; **(**48 mg, 73% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.72-7.65 (m, 4 H), 7.35-31 (m, 6 H), 4.59 (s, 4 H), 4.00 (q, *J*= 6.8 Hz, 4H), 3.89 (s, 4 H), 1.14 (t, *J*= 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.36, 136.13, 133.56, 129.96, 129.88, 128.96, 124.80, 118.33, 118.15, 117.71, 117.52, 117.38, 61.62, 61.49, 49.08, 48.95, 47.56, 14.08.

2,2'-((1,2-Phenylenebis(methylene))bis(((3,4-difluorophenyl) sulfonyl) azanediyl)) diacetic acid (**46i**)



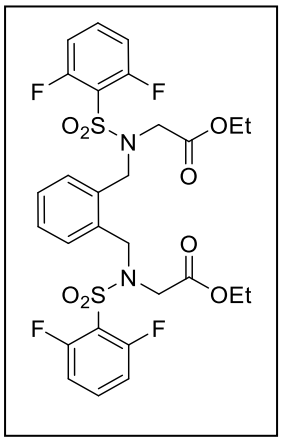
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; **(**9 mg, 65% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.67-59 (m, 6H), 7.55-7.51 (m, 2H), 7.23 (s, 4H), 4.49 (s, 4 H), 3.98 (s, 1 H), 3.84 (s, 3 H). ^{13}C NMR (100 MHz, DMSO): δ 169.60, 168.65, 162.98, 162.89, 160.51, 160.42, 141.07, 141.00, 140.64, 140.58, 140.48, 133.95, 133.89, 133.86, 133.79, 131.55, 131.47, 131.40, 131.32, 128.67, 128.46, 127.71, 127.65, 127.54, 123.29, 120.26, 120.03, 119.82, 114.26, 114.01, 51.65, 49.20, 49.06, 48.98, 48.85, 48.42, 48.32, 48.24. HRMS (ESI) Calcd for $C_{24}H_{20}F_4N_2O_8S_2$ $(M+H)^+$ 605.0670, found 605.0700.

N,N'-(1,2-Phenylenebis(methylene))bis(2,6-difluorobenzenesulfonamide) (44j)



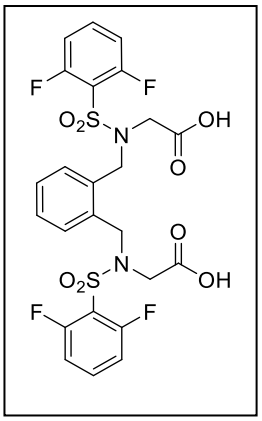
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a yellow solid; **(**317 mg, 66% yield). ^{1}H NMR (400 MHz, (MeOH-d_4)): δ 7.55-7.51 (m, 2H), 7.21-7.19 (m, 2H), 7.09-6.99 (m, 6H), 4.31 (s, 4 H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 161.88 (d, *J*= 16 Hz), 159.33 (d, *J*= 20 Hz), 135.81 (dd, *J*= 64 Hz, *J*= 16 Hz), 130.70, 129.02, 119.85 (d, 64), 114.18, 113.94 (d, *J*= 16 Hz). ^{19}F NMR (377 MHz, MeOH-d_4): δ – 109.55 (s, 2F).

Diethyl 2,2'-((1,2-phenylenebis(methylene))bis(((2,6-difluorophenyl) sulfonyl) azanediyl)) diacetate (**45j**)



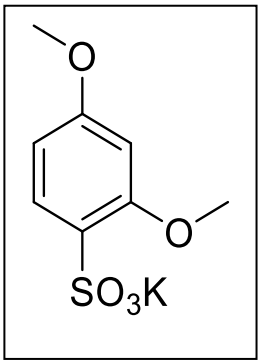
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; **(**101 mg, 76% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.54-7.47 (m, 2H), 7.37-7.34 (m, 2H), 7.31-7.26 (m, 2H), 7.03-6.98 (m, 4H), 4.72 (s, 4 H), 4.05 (s, 4 H), 4.01 (q, *J*= 6.8 Hz, 4H), 1.12 (t, *J*= 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.37, 161.21 (d, *J*= 16 Hz), 158.63 (d, *J*= 16 Hz), 134.60 (t, *J*= 44 Hz), 133.63, 129.93, 128.84, 118.04, 113.15 (dd, *J*= 96 Hz, *J*= 20 Hz), 61.60, 48.66, 47.86, 14.03. ^{19}F NMR (377 MHz, $CDCl_3$): δ) – 105.15 (s, 2F).

2,2'-((1,2-Phenylenebis(methylene))bis(((2,6-difluorophenyl) sulfonyl) azanediyl)) diacetic acid (**46j**)



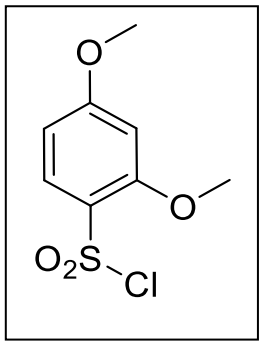
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as an off-white solid; (16 mg, 72% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.75-7.67 (m, 2H), 7.27-7.23 (m, 8H), 4.63 (s, 4 H), 3.97 (s, 4 H). ^{13}C NMR (100 MHz, (DMSO)): δ 169.96, 161.91, 159.34, 137.54, 137.45, 136.78, 136.67, 136.55, 133.62, 128.96, 128.76, 128.21, 128.04, 124.86, 124.78, 114.25, 114.02, 55.37. HRMS (ESI) Calcd for $C_{24}H_{20}F_4N_2O_8S_2$ $(M+H)^+$ 605.0670, found 605.0669.

Potassium 2,4-dimethoxybenzenesulfonate (**44ga**)



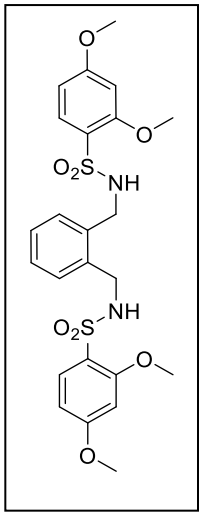
1,3 Dimethoxy benzene (0.638 ml, 5 mmole) was mixed with conc. H_2SO_4 (ml, 7.5 mmole) and the reaction stirred for 2h at room temperature. Then, a saturated solution of potassium carbonate was added slowly (~ 20 ml) and filter the mixture. The solid washed with isopropanol (~ 5 ml) and desired product was dried under vacuum to give compound (**44ga) (**832 mg, 65% yield). ^{1}H NMR (400 MHz, (D_2O)): δ 7.69 (d, 1H, *J*= 8.8 Hz), 6.60 (d, 1H, *J*= 2.4 Hz), 6.54 (dd, 1H, *J*= 8.8 Hz), 3.88 (s, 3 H), 3.79 (s, 3 H). ^{13}C NMR (100 MHz, D_2O): δ 163.05, 157.69, 129.63, 122.92, 104.52, 99.20, 55.78, 55.62.

2,4-Dimethoxybenzenepotassium sulfonate (**44gb**)



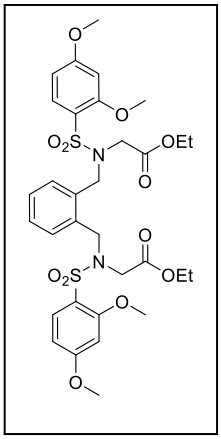
2,4-Dimethoxybenzenepotassium sulfonate (**44ga**) (765 mg, 3 mmole) was suspended in $POCl_3$ and reaction mixture was stirred at 110 °C for 1.5 hours. Then, reaction checked by TLC for completion and quenched with crushed ice and extracted with ether. Organic layer then dried over sodium sulfate, and organic solvent removed to get compound (**44gb) (**554 mg, 78% yield). ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.84 (d, 1H, *J*= 8.8 Hz), 6.55 (d, 1H, *J*= 2.4 Hz), 6.54 (dd, 1H, *J*= 8.8 Hz), 4.00 (s, 3 H), 3.89 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.07, 159.30, 131.92, 124.40, 105.02, 99.67, 56.66, 56.13.

N,N'-(1,2-Phenylenebis(methylene))bis(2,4-dimethoxybenzenesulfonamide) (44g)



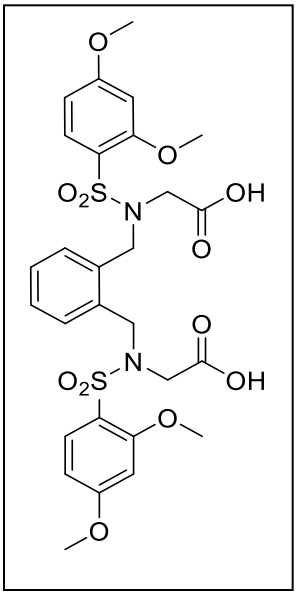
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; (369 mg, 69% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.80 (d, 2H *J*= 8.8 Hz), 7.15 (d, 4H *J*= 2.4 Hz), 6.55 (dd, 2H *J*= 8.8, *J*= 2.4 Hz), 6.49 (d, 2H, *J*= 2.4), 5.25 (t, 2H *J*= 6.4 Hz), 4.02 (d, 4H *J*= 6.4 Hz), 3.89 (s, 3 H), 3.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.93, 157.66, 135.08, 132.11, 129.98, 128.28, 119.15, 104.62, 99.47, 56.42, 55.77, 44.90.

Diethyl 2,2'-((1,2-phenylenebis(methylene)) bis(((2,4-dimethoxyphenyl) sulfonyl) azanediyl)) diacetate (**45g**)



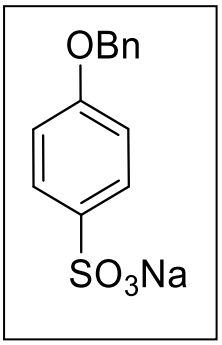
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (115 mg, 81% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.81 (d, 2H *J*= 8.8 Hz), 7.35- 7.33 (m, 2H), 7.26- 7.23 (m, 2H), 6.50-6.46 (m, 4H), 4.69 (s, 4H), 3.96-3.93 (m, 8H), 3.91 (s, 6 H), 3.86 (s, 6 H), 1.09 (t, 6 H *J*= 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.15, 164.94, 158.77, 134.84, 132.91, 129.85, 128.25, 120.58, 104.16, 99.48, 61.09, 56.22, 55.82, 49.36, 48.00, 13.97.

2,2'-((1,2-Phenylenebis(methylene))bis(((2,4-dimethoxyphenyl) sulfonyl) azanediyl)) diacetic acid (**46g**)



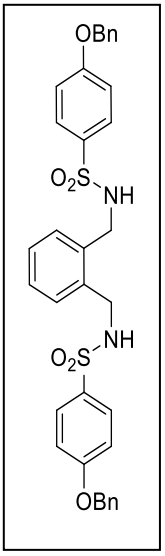
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; **(**13 mg, 81% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 12.53 (s, 2H), 7.60 (d, 2H *J*= 8.8 Hz), 7.17 (s, 4H), 6.67 (d, 4H *J*= 2.0 Hz), 6.55 (dd, 2H, *J*= 8.8 Hz, *J*= 2.0 Hz), 4.46 (s, 4H), 3.86 (s, 4H), 3.83 (s, 6H), 3.81 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ 170.06, 164.32, 158.19, 134.48, 131.69, 128.47, 127.31, 119.87, 104.61, 99.30, 56.03, 55.72, 48.34, 47.94. HRMS (ESI) Calcd for $C_{28}H_{32}N_2O_{12}S_2$ $(M+H)^+$ 653.1469 found 653.1460.

Sodium 4-(benzyloxy) benzenesulfonate (44ka)



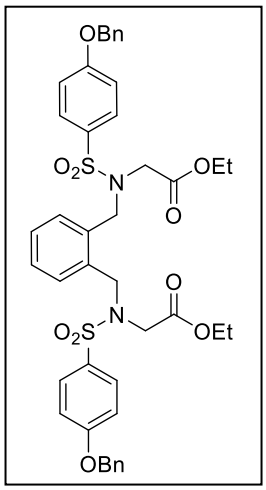
To a solution of sulfonic acid 65%w/v in H_2O (1.88 ml, 7 mmole), a solution of NaOH (840 mg, 21 mmole) in 5 ml water was added and stirred at room temperature. Then, place the reaction mixture in NaCl ice bath and a solution of benzyl bromide (1.02 ml, 8.4 mmole) in 7 ml EtOH was added. Reaction mixture then stirred at 110 C for 2 days. Then, reaction cooled and filtered. The precipitate washed with 2X water, i-PrOH to get colorless crystal (**44ka) (**800 mg, 75% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.55 (d, 2H *J*= 8.8 Hz), 7.45-7.32 (m, 5H), 6.95 (d, 2H *J*= 8.8 Hz), 5.11 (s, 2H). ^{13}C NMR (100 MHz, DMSO): δ 158.34, 140.95, 136.96, 128.39, 127.78, 127.60, 127.07, 113.69, 69.22.

N,N'-(1,2-Phenylenebis(methylene))bis(4-(benzyloxy)benzenesulfonamide) (44k)



To sodium 4-(benzyloxy) benzenesulfonate (**44ka**) (500 mg, 1.7 mmole) in DCM (10 ml), PCl5 (545 mg, 2.6 mmole) was added at room temperature and reaction stirred at 40 C for 24 hours. Upon completion, DCM was removed, and toluene was added and filter the mixture through celite, rotovap to get off-white solid 4-(benzyloxy) benzenesulfonyl chloride which used directly for next step (345 mg, 71%). The synthesis of sulfonamide intermediate **44k** was done using Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a beige solid; 87 mg, 69% yield). ^{1}H NMR (400 MHz, (Acetone-d_6)): δ 7.83-7.80 (m, 4H), 7.52-7.50 (m, 4H), 7.44-7.36 (m, 7H), 7.27-7.24 (m, 2H), 7.19-7.17 (m, 5H), 6.65 (t, 2H *J*= 6.4 Hz), 5.23 (s, 4 H), 4.15 (d, 4H *J*= 6.4 Hz). ^{13}C NMR (100 MHz, Acetone-d_6): δ 162.78, 137.60, 136.36, 133.68, 130.13, 130.00, 129.98, 129.41, 128.92, 128.61, 128.49, 115.92, 70.90, 44.99, 44.90.

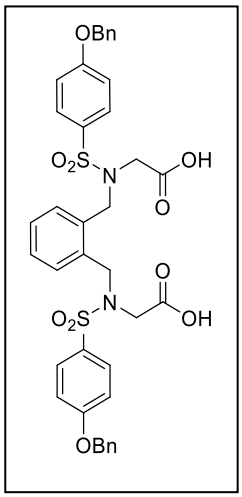
Diethyl 2,2'-((1,2-phenylenebis(methylene))bis(((4-(benzyloxy)phenyl) sulfonyl) azanediyl)) diacetate (**45k**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (113 mg, 71% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.73 (d, 4H *J*= 8.8 Hz), 7.37- 7.26 (m, 12H), 7.19- 7.17 (m, 2H), 6.99 (d, 4H *J*= 8.8 Hz), 5.05 (s, 4H), 4.50 (s, 4H), 3.85 (t, 4H, *J*= 7.2 Hz), 3.77 (s, 4 H), 1.01 (t, 6 H *J*= 7.2 Hz). ^{13}C NMR (100

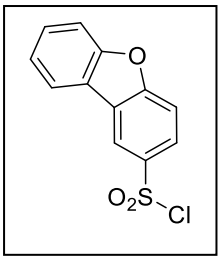
MHz, $CDCl_3$): δ 168.73, 162.30, 136.03, 134.13, 131.19, 129.83, 129.78, 128.87, 128.55, 128.47, 127.67, 115.17, 61.36, 49.27, 47.85, 14.07.

2,2'-((1,2-Phenylenebis(methylene))bis(((4-(benzyloxy) phenyl) sulfonyl) azanediyl)) diacetic acid (**46k**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as an off-white solid; (17 mg, 76% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.76 (d, 4H *J*= 9.2 Hz), 7.48-7.46 (m, 4H), 7.42-7.35 (m, 6H), 7.28-7.25 (m, 2H), 7.21-7.16 (m, 6H), 5.19 (s, 4H), 4.44 (s, 4H), 3.75 (s, 4H). ^{13}C NMR (100 MHz, DMSO): δ 169.86, 161.62, 136.29, 134.29, 130.82, 129.38, 128.60, 128.51, 128.09, 127.89, 127.48, 115.06, 69.71, 48.96, 48.31. HRMS (ESI) Calcd for $C_{38}H_{36}N_2O_{10}S_2$ $(M+H)^+$ 745.1884, found 745.1872.

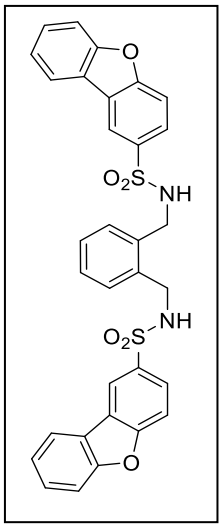
Dibenzo[*b,d*]furan-2-sulfonyl chloride (**46la**)



To a commercially available sodium dibenzo[*b,d*]furan-2-sulfonate (810 mg, 3 mmole), $POCl_3$ (3 ml) was added at room temperature and reaction mixture was stirred at 80 °C for 18 hours. Then, reaction checked by TLC for completion and quenched with crushed ice and extracted with chloroform. Organic layer separated and then dried over sodium sulfate, and organic solvent removed to get dibenzo[*b,d*]furan-2-sulfonyl chloride (729 mg, 91% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 8.62 (d, 2H *J*= 2.4 Hz), 8.14 (dd, 1H *J*= 8.8, 2.4 Hz), 7.99 (d, 2H *J*= 7.6 Hz),7.71 (d, 1H *J*= 8.8 Hz),

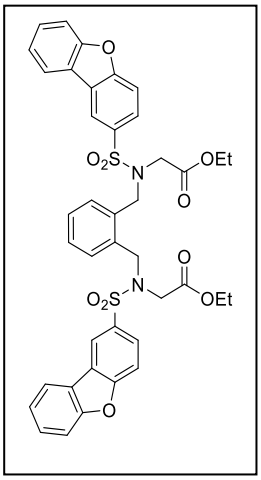
7.64-7.56 (m, 2 H), 7.47-7.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.30, 157.39, 139.10, 129.38, 126.20, 125.46, 124.25, 122.65, 121.46, 120.93, 112.96, 112.38.

N,N'-(1,2-Phenylenebis(methylene))bis(dibenzo[b,d]furan-2-sulfonamide) (44l)



Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a beige solid; **(**373 mg, 62% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 8.58 (d, 2H *J*= 1.2 Hz), 8.27 (d, 2H *J*= 3.8 Hz), 8.02 (t, 2H *J*= 6.4 Hz), 7.93-7.91 (m, 2H), 7.83 (d, 2H *J*= 8.8 Hz), 7.77 (d, 2H *J*= 8.4 Hz), 7.60 (t, 2H *J*= 7.6 Hz), 7.45 (t, 2H *J*= 7.6 Hz), 7.22-7.19 (m, 2H), 7.31-7.09 (m, 2H), 4.07 (d, 4H *J*= 6.4 Hz). ^{13}C NMR (100 MHz, DMSO): δ 156.97, 156.21, 135.59, 135.19, 128.63, 128.58, 127.17, 125.98, 123.91, 123.71, 122.71, 121.82, 120.44, 112.30, 111.91, 43.38.

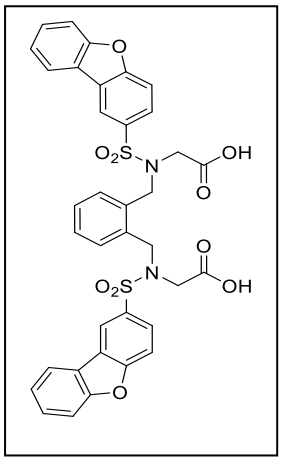
Diethyl 2,2'-((1,2-phenylenebis(methylene))bis((dibenzo[*b,d*]furan-2-ylsulfonyl) azanediyl)) diacetate (**45l**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (125 mg, 81% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 8.49 (d, 2H *J*= 1.4 Hz), 8.03-7.97 (m, 4H), 7.67-7.60 (m, 4H), 7.55-7.51 (m, 2H), 7.41-7.35 (m, 4H), 7.34-7.25 (m, 2H), 4.71 (s,4H), 3.94 (s,4H), 3.87 (q, 4H *J*= 6.8 Hz), 1.03-0.99 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.82, 168.62, 134.08, 133.93, 129.87,

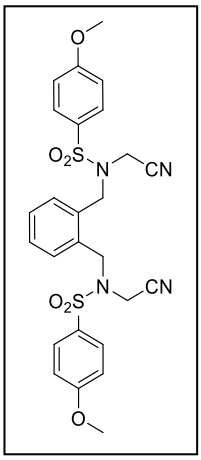
128.62, 128.54, 126.73, 124.97, 123.71, 123.33, 121.44, 121.19, 112.31, 112.10, 61.35, 49.42, 49.71, 13.97.

2,2'-((1,2-Phenylenebis(methylene))bis((dibenzo[b,d]furan-2-ylsulfonyl)azanediyl)) diacetic acid (**46l**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a beige solid; (14 mg, 78% yield). ^{1}H NMR (400 MHz, (Acetone-d_6)): δ 8.65 (d, 2H *J*= 1.2 Hz), 8.25 (d, 2H *J*= 8.0 Hz), 8.05 (dd, 2H *J*= 2.0 Hz, *J*= 8.8 Hz), 7.77 (d, 2H *J*= 8.8 Hz), 7.70 (d, 2H *J*= 8.8 Hz), 7.62-7.58 (m, 2H), 7.46-7.42 (m, 2H), 7.40-7.38 (m, 2H), 7.24-7.23 (m, 2H), 4.74 (s, 4H), 4.02 (s, 4H). ^{13}C NMR (100 MHz, Acetone-d_6): δ 170.17, 158.86, 157.76, 135.54, 135.49, 130.28, 129.43, 128.76, 127.84, 125.52, 124.54, 124.19, 122.67, 122.15, 112.92, 112.65, 50.29, 48.73. HRMS (ESI) Calcd for $C_{36}H_{28}N_2O_{10}S_2$ $(M+H)^+$ 713.1258, found 713.1252.

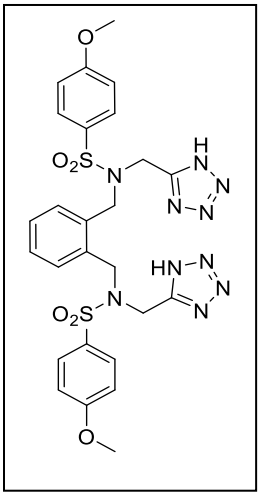
N,N'-(1,2-Phenylenebis(methylene))bis(N-(cyanomethyl)-4-methoxybenzene-sulfonamide) (**47**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (119 mg, 71% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.86 (d, 4H *J*= 8.8 Hz), 7.45-7.38 (m, 4H), 7.08 (d, 2H *J*= 8.8 Hz), 4.51 (s,4H), 4.03 (s,4H), 3.89 (s,4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.01, 132.78, 130.29,

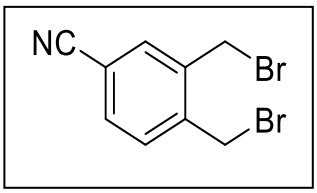
130.10, 129.44, 127.77, 55.70, 48.57, 34.90. HRMS (ESI) Calcd for $C_{26}H_{26}N_4O_6S_2$ $(M+H)^+$ 555.1294, found 555.1362.

N-((1H-Tetrazol-5-yl)methyl)-N-(2-(((N-((1H-tetrazol-5-yl)methyl)-4-methoxyphenyl) sulfonamido)methyl)benzyl)-4-methoxybenzenesulfonamide (**48**), **General procedure for synthesis of tetrazole (Method D)**



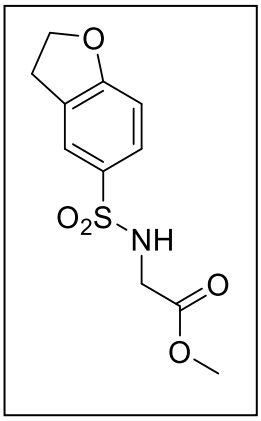
N,N'-(1,2-Phenylenebis(methylene))bis(N-(cyanomethyl)-4-methoxy- benzenesulfonamide) (**46n**) (50 mg, 0.09 mmole) dissolved in DMF (1.5 ml) and triethyl ammonium chloride (37 mg, 0.27 mmole) and sodium azide (35 mg, 0.45 mmole) were added at room temperature and the reaction mixture stirred at 120 °C for 4 hr and then checked by TLC and LCMS. Then, acidify reaction mixture with 1 N HCl, and extract with ethyl acetate, washed with water, brine, and dried over sodium sulfate. Purification was done with a flash column chromatography using 0 -20% MeOH/ DCM to get compound (**48) (**52 mg, 90% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.73 (d, 4H *J*= 8.8 Hz), 7.30-7.28 (m, 2H), 7.17-7.16 (m, 2H), 7.06 (d, 4H *J*= 8.8 Hz), 4.50 (s,4H), 3.84 (s,4H). ^{13}C NMR (100 MHz, DMSO): δ 163.86, 153.23, 132.88, 129.81, 129.43, 128.84, 55.84, 41.38, 29.75. HRMS (ESI) Calcd for $C_{26}H_{28}N_{10}O_6S_2$ $(M+H)^+$ 640.1707, found 641.1687.

3,4-Bis(bromomethyl)benzonitrile (**49**)



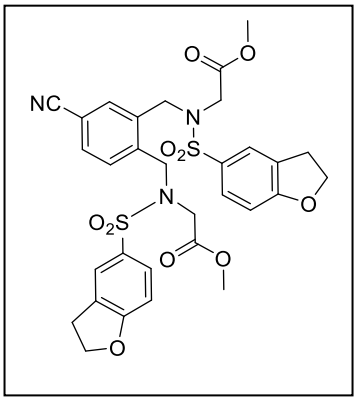
To a solution of 3,4-dimethyl benzonitrile (**49**) (300 mg, 2.3 mmole) dissolved in CH_3Cl (10 ml), NBS (897 mg, 5 mmole) and AIBN (75 mg, 0.45 mmole) were added at room temperature and the reaction mixture stirred at 75 °C for overnight and then checked by TLC. Then, dilute the reaction mixture with DCM and filter through celite followed by purification by ISCO using 0 - 50% EtOAc in hexane to get compound (**49**) as a white solid (560 mg, 84% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.67 (d, 1H, *J*= 1.6 Hz), 7.59 (dd, 2H, *J*= 1.6 Hz, *J*= 8.0 Hz), 7.49 (d, 1H, *J*= 8.0 Hz), 4.62 (s,2H), 4.61 (s,2H),^{13}C NMR (100 MHz, DMSO): δ 141.68, 138.10, 134.47, 132.80, 131.92, 117.78, 113.37, 28.11, 27.95.

Methyl ((2,3-dihydrobenzofuran-5-yl) sulfonyl) glycinate (50)



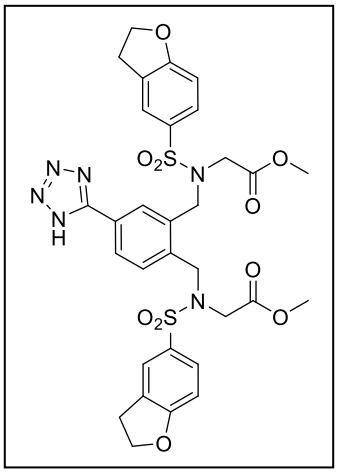
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; **(**651 mg, 80% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.68-7.63 (m, 2H), 6.83 (d, 1H *J*= 8.4 Hz), 4.95 (br,1H), 4.68 (t, 2H *J*= 8.8 Hz), 3.76 (d, 2H *J*= 5.2 Hz), 3.67 (s,3H), 3.26 (t, 2H *J*= 8.8 Hz). ^{13}C NMR (100 MHz, DMSO): δ 169.52, 164.10, 130.67, 128.91, 128.60, 124.63, 109.49, 72.42, 52.62, 44.13, 29.09.

Dimethyl 2,2'-(((4-cyano-1,2-phenylene)bis(methylene))bis(((2,3-dihydrobenzofuran-5-yl) sulfonyl)azanediyl))diacetate (**51**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; (536 mg, 82% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 7.62-7.51 (m, 7H), 6.81-6.78 (m, 2H), 4.67-4.63 (m, 4H), 4.57 (s,2H), 4.48 (s,2H), 4.06-3.73 (m, 4H), 3.48 (s,3H), 3.47 (s,3H), 3.24 (t, 4H *J*= 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.10, 168.79, 164.36, 164.30, 140.39, 135.55, 132.81, 131.92, 129.99, 129.74, 129.69, 129.16, 128.92, 128.78, 128.72, 128.48, 124.86, 124.74, 124.56, 118.17, 112.07, 109.55, 72.43, 72.31, 60.36, 52.16, 49.59, 49.42, 48.53, 48.23, 44.02, 29.07, 21.01, 14.19.

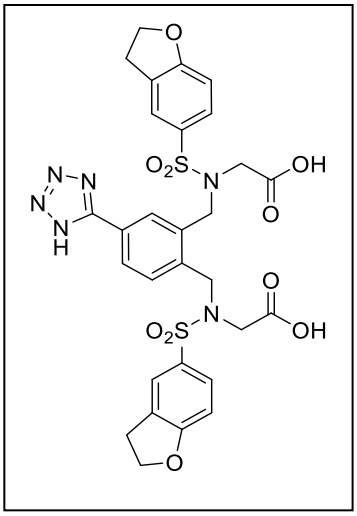
Methyl N-((2,3-dihydrobenzofuran-5-yl)sulfonyl)-N-(2-(((N-(2-methoxy-2-oxoethyl)-2,3-dihydrobenzofuran)-5-sulfonamido)methyl)-4-(1H-tetrazol-5-yl)benzyl)glycinate (**51a**)



Intermediate (**51**) (60 mg, 0.09 mmole) dissolved in DMF (1.5 ml) and triethyl ammonium chloride (37 mg, 0.14 mmole) and sodium azide (35 mg, 0.27 mmole) were added at room temperature and the reaction mixture stirred at 85 °C for overnight and then checked by TLC and LCMS. Then, acidify reaction mixture with 1 N HCl, and extract with ethyl acetate, washed with water, brine, and dried over sodium sulfate. Purification done using silica gel on a ISCO with maximum ratio of 20% MeOH/ DCM to

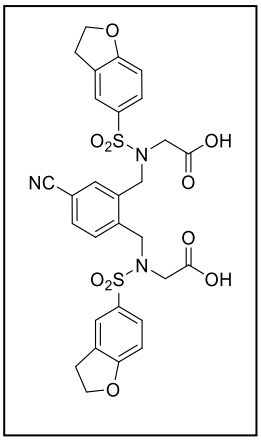
get compound (**51a) (**46 mg, 72% yield). ^{1}H NMR (400 MHz, ($CDCl_3$)): δ 8.39 (s,1H), 8.02 (dd, 1H *J*= 1.6 Hz , *J*= 7.8 Hz), 7.72 (d, 1H *J*= 1.6 Hz), 7.72-7.61 (m, 3H), 7.42 (d, 1H *J*= 8.0 Hz), 6.86 (dd, 2H *J*= 2.8 Hz , *J*= 8.8 Hz), 4.71-4.65 (m, 6H *J*= 1.6 Hz), 4.55 (s,2H), 3.84 (s,2H), 3.79 (s,2H), 3.59 (s,3H), 3.48 (s,3H), 3.30 (t, 4H *J*= 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.95, 164.47, 164.37, 136.60, 130.91, 129.35, 129.15, 128.78, 127.74, 126.96, 124.90, 124.80, 109.64, 109.61, 72.52, 72.45, 52.63, 52.21, 50.55, 50.20, 49.65, 48.01, 29.08, 29.05.

N-(2-(((N-(Carboxymethyl)-2,3-dihydrobenzofuran)-5-sulfonamido)methyl)-4-(1H-tetrazol-5-yl) benzyl)-N-((2,3-dihydrobenzofuran-5-yl)sulfonyl)glycine (**52**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a yellow solid; (14 mg, 78% yield). ^{1}H NMR (400 MHz, (acetone-d_6)): δ 7.97 (d, 1H *J*= 1.2 Hz), 7.91 (dd, 1H *J*= 1.6 Hz, *J*= 8.0 Hz), 7.67-7.58 (m, 5H), 6.84 (d, 1H *J*= 8.8 Hz), 6.77 (d, 1H *J*= 8.8 Hz), 4.66-4.59 (m, 8H), 3.99 (s, 2H), 3.88 (s, 2H), 3.26-3.24 (m, 4H). ^{13}C NMR (100 MHz, Acetone-d_6): δ 172.32, 172.11, 165.64, 165.56, 139.60, 137.58, 131.83, 131.73, 131.48, 130.42, 130.38, 130.26, 130.17, 129.22, 127.50, 126.13, 125.97, 125.14, 110.29, 110.18, 73.62, 73.57, 51.11, 29.94. HRMS (ESI) Calcd for $C_{29}H_{28}N_6O_{10}S_2$ $(M+H)^+$ 685.1381, found 685.1370.

2,2'-(((4-Cyano-1,2-phenylene)bis(methylene))bis(((2,3-dihydrobenzofuran-5-yl)sulfonyl)azanediyl))diacetic acid (**53**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a beige solid; **(**16 mg, 84% yield). ^{1}H NMR (400 MHz, (DMSO)): δ 7.71-7.66 (m, 4H), 7.58-7.54 (m, 3H), 6.90-6.87 (m, 2H), 4.64 (t, 4H *J*= 8.8 Hz), 4.47 (s, 2H), 4.45 (s, 2H), 3.83 (s, 2H), 3.79 (s, 2H), 3.24 (t, 4H *J*= 8.8 Hz). ^{13}C NMR (100 MHz, DMSO): δ 170.14, 169.89, 163.50, 163.47, 140.61, 136.48, 131.66, 130.89, 129.90, 129.81, 129.30, 129.05, 128.93, 128.67, 128.64, 124.67, 124.60, 118.69, 109.94, 109.07, 72.27, 49.61, 49.48, 49.31, 49.19, 28.44. HRMS (ESI) Calcd for $C_{29}H_{27}N_3O_{10}S_2$ $(M+H)^+$ 642.1211, found 642.1211.

General procedure for reduction of nitro group

(Method E1):

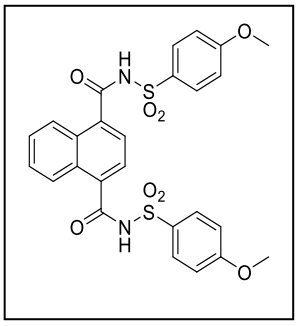
A solution of 4-nitronaphthalen-1-amine (1 mmol) in THF: EtOH (1:1) was degassed with N_2 three times. Then, a catalytic amount of 10% Pd/C (5 mg) was added to the solution and the reaction was purged with H_2. The reaction was stirred under H_2 for 8 h and then filtered through a celite bed to remove the catalyst. The filtrate was concentrated under reduced pressure to give the desired product. The crude product was used without further purification.

(Method E2):

To a solution of the nitro containing starting material (1 equiv.) in DMF (1 ml), $SnCl_2.H_2O$ (5 equiv.) was slowly added while reaction mixture stirring at room temperature. Then, stir

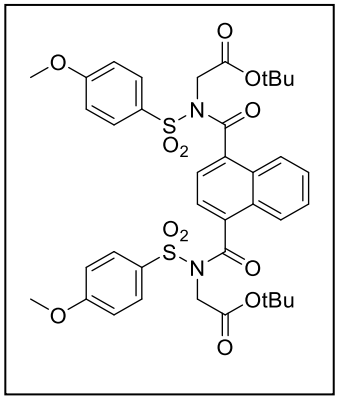
the reaction mixture at room temperature for overnight. Upon completion, dilute the mixture with ethyl acetate and extract with saturated solution of sodium bicarbonate, dried over sodium sulfate and concentrated under reduced pressure. The crude product used without further purification.

N1,N4-bis((4-Methoxyphenyl)sulfonyl)naphthalene-1,4-dicarboxamide (**57**)



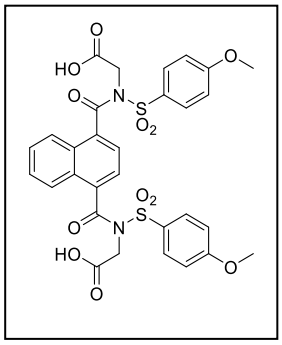
A suspension of naphthalene 1,4 -dicarboxylic acid (432 mg, 2 mmol) in DCM (10 ml), EDC.HCl (920 mg, 4.8 mmol), DMAP (59 mg, 0.48 mmol) were added and reaction mixture stirred at room temperature under N_2 for 5 min., and then 4-methoxybenzenesulfonamide (899 mg, 4.8 mmol) was added and the mixture stirred at room temperature for overnight. Then, the mixture was dilute with DCM (100 ml) and washed with 1 N HCl, water, and brine. Dried over sodium sulfate and concentrated under reduced pressure followed by purification using silica gel on an ISCO using hexane/ ethyl acetate. The yield (877 mg, 79% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.09 (s, 2 H), 8.15 (d, 4 H, J= 8.4 Hz), 7.06 (d, 6 H, J= 4.8 Hz), 6.85 (s, 2 H), 6.58 (s, 2 H), 3.91 (s, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 166.29, 164.34, 132.47, 131.36, 129.93, 128.86, 128.68, 127.67, 124.49, 124.28, 114.44, 114.35, 56.02.

Di-*tert*-butyl 2,2'-((naphthalene-1,4-dicarbonyl)bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (**58**)



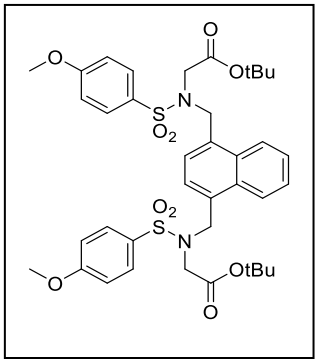
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as a pale yellow oily product, the yield (63 mg, 80%). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.54 (s, 6 H), 7.37 (s, 2 H), 7.31-7.29 (m, 2H), 6.65 (s, 4 H), 4.63 (s, 4 H), 3.73 (s, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.11, 167.31, 163.84, 134.40, 131.34, 129.46, 129.11, 127.55, 125.13, 123.86, 113.95, 82.97, 55.69, 47.77, 28.12.

2,2'-((Naphthalene-1,4-dicarbonyl)bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (**55**)



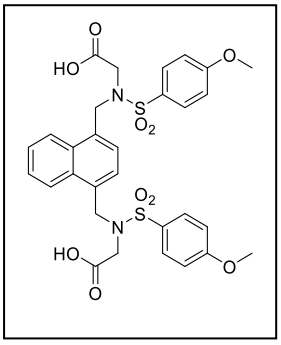
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as an off-white solid; (19 mg, 76% yield). ^{1}H NMR (400 MHz) (DMSO) δ 7.65 (d, 4 H, J= 6.8 Hz), 7.51 (s, 2 H), 7.43 (s, 2 H), 7.31 (s, 2 H), 6.92 (d, 4 H, J= 8.4 Hz), 4.60 (s, 4 H), 3.79 (s, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.30, 168.53, 163.52, 134.09, 130.65, 129.20, 128.85, 127.44, 124.74, 123.37, 114.13, 55.80, 47.82. HRMS (ESI) Calcd for $C_{30}H_{26}N_2O_{12}S_2$ $(M+H)^+$ 671.0994, found 671.0998.

Di-*tert*-butyl 2,2'-((naphthalene-1,4-diylbis(methylene)) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (**60**)



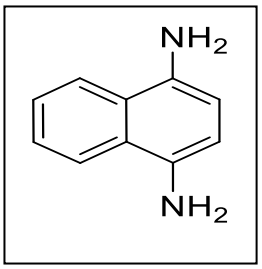
Intermediate (**57**) (100 mg, 0.18 mmol) dissolved in 5 ml anhydrous THF and then $BH_3.Me_2S$ (277 uL, 2.88 mmol) was added at room temperature and the reaction mixture refluxed for 2 hours. Then, diluted with ethyl acetate and washed with 1 N HCl, water, and brine. Dried over sodium sulfate, and organic layer removed under reduced pressure to get 63mg, 66%) which was dissolved in 5 ml DCM using general procedure for synthesis of sulfonamides (method A1) to get the title compound as a pale yellow oily product, the yield 61 mg, 80%). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.22-8.19 (m, 2H), 7.85 (d, 4 H, J= 8.8 Hz), 7.56-7.54 (m, 2H),7.25 (s, 2 H), 7.01 (d, 4 H, J= 8.8 Hz), 4.97 (s, 4 H), 3.89 (s, 6 H), 3.71 (s, 4 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 167.84, 163.03, 132.32, 131.49, 131.28, 129.72, 127.12, 126.95, 124.31, 114.13, 81.81, 55.62, 49.00, 47.16, 27.82.

2,2'-((Naphthalene-1,4-diylbis(methylene)) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (**54**)



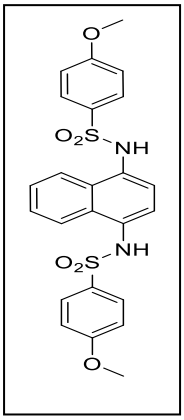
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a beige solid; the yield (12 mg, 78% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.16-8.14 (m, 2H), 7.81 (d, 4 H, J= 8.4 Hz), 7.81 (d, 2 H, J= 6 Hz), 7.29 (s, 2 H), 7.09 (d, 4 H, J= 8.4 Hz), 4.85 (s, 4 H), 3.85 (s, 6 H), 3.69 (s, 4 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.74, 162.53, 131.60, 131.35, 130.62, 129.43, 126.79, 126.29, 124.10, 114.26, 55.66, 49.27, 47.23. HRMS (ESI) Calcd for $C_{30}H_{30}N_2O_{10}S_2$ $(M+H)^+$ 643.1415, found 643.1413.

Naphthalene-1,4-diamine (**61**)



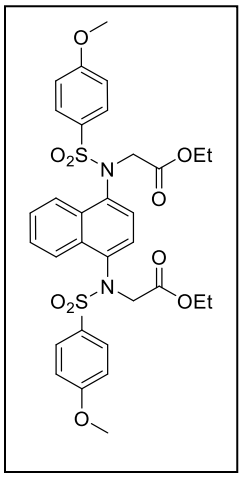
Prepared as described in the general procedure for reduction of nitro group (method E1) to get the title compound as a dark pink solid, the yield (1.52 g (96% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.86-7.84 (m, 2 H), 7.48-7.46 (m, 2 H), 6.65 (s, 2 H), 3.77 (br, 4 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 134.63, 124.86, 121.62, 110.79.

N,N'-(Naphthalene-1,4-diyl)bis(4-methoxybenzenesulfonamide) (**2a**)



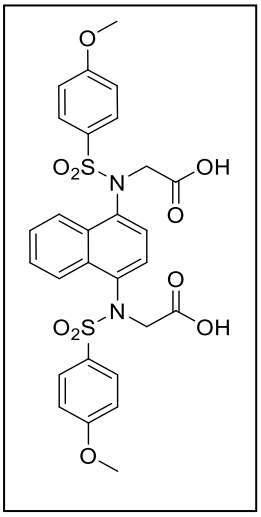
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a pink solid, the yield (758 mg, 76% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.05 (s, 2 H), 7.97-7.95 (m, 2 H), 7.56 (d, 4 H, *J*= 8.8 Hz), 7.41-7.38 (m, 2 H), 7.02 (s, 2 H), 6.98 (d, 4 H, *J*= 8.8 Hz), 3.77 (s, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 162.30, 131.42, 131.03, 130.02, 128.86, 126.06, 123.33, 122.67, 114.17, 55.56.

Diethyl 2,2'-(naphthalene-1,4-diylbis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (**2b**)



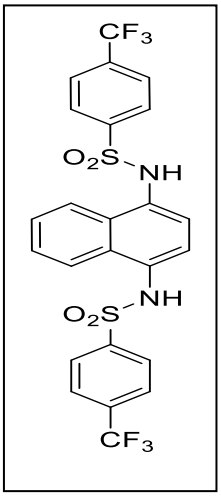
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as a light pink solid, the yield (113 mg, 84% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.11-8.09 (m, 1 H), 8.07-8.04 (m, 1 H), 7.66-7.62 (m, 4 H), 7.55-7.52 (m, 1 H), 7.50-7.48 (m, 1 H), 7.18 (s, 1 H), 7.15 (s, 1 H), 6.93-6.89 (m, 4 H), 4.70-4.58 (m, 2 H), 4.28-4.23 (m, 2 H), 4.15-4.07 (m, 4 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 1.18 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.90, 163.40, 163.37, 137.40, 137.28, 133.25, 133.14, 130.81, 130.40, 130.30, 127.88, 127.69, 127.63, 127.45, 124.38, 124.33, 114.11, 61.56, 55.73, 53.27, 53.19, 14.12.

2,2'-(Naphthalene-1,4-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (2)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a light pink solid; (30 mg, 69% yield). ^{1}H NMR (400 MHz) (DMSO) δ 12.84 (BR, 2 H), 8.31-8.29 (m, 1 H), 8.18-8.16 (m, 1 H), 7.60-7.56 (m, 6 H), 7.14-7.12 (m, 3 H), 7.05 (d, 2 H, J= 8.8 Hz), 6.88 (s, 1 H)4.47-4.32 (m, 4 H), 3.89 (s, 3 H), 3.84 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.53, 162.57, 136.80, 136.73, 132.64, 132.49, 129.78, 129.55, 129.22, 128.69, 126.40, 126.25, 125.98, 124.34, 124.16, 114.00, 113.95, 55.41, 52.89, 52.74. HRMS (ESI) Calcd for $C_{28}H_{26}N_2O_{10}S_2$ $(M+H)^+$ 615.1102, found 615.1113.

N,N'-(Naphthalene-1,4-diyl)bis(4-(trifluoromethyl)benzenesulfonamide) (**63a**)



Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a pink solid, the yield (419 mg, 72% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.47 (s, 2 H), 7.86-7.80 (m, 10 H), 7.34-7.32 (m, 2 H), 7.07 (s, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 143.71, 132.87, 132.54, 132.22, 131.89, 130.86, 130.15, 127.62, 127.41, 126.25, 126.17, 124.70, 123.46, 123.11, 121.99. ^{19}F NMR (377 MHz, DMSO): δ – 61.76 (s, 3F), – 61.78 (s, 3F)

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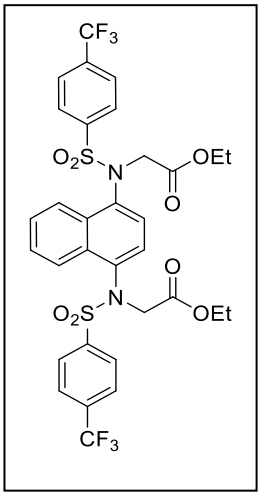
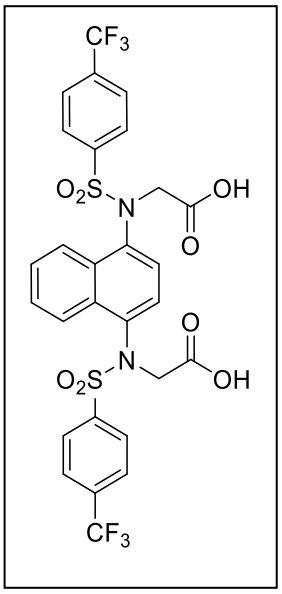
Diethyl 2,2'-(naphthalene-1,4-diylbis(((4-(trifluoromethyl) phenyl)sulfonyl) azanediyl)) diacetate (**64a**)



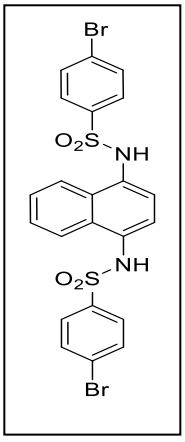
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as a light pink solid, the yield (103 mg, 69% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.02-7.86 (m, 6 H), 7.75-7.71 (m, 4 H), 7.60-7.50 (m, 2 H), 7.25-7.24 (m, 2 H), 4.88-4.75 (m, 2 H), 4.25-4.07 (m, 6 H), 1.23-1.15 (m, 6 H).^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.64, 142.98, 137.11, 136.97, 133.02, 132.90, 128.80, 128.72, 128.38, 128.19, 128.11, 128.02, 126.11, 124.07, 123.98, 61.87, 53.22, 14.14. ^{19}F NMR (377 MHz, DMSO): δ – 63.13 (s, 3F), – 63.16 (s, 3F) .

2,2'-(Naphthalene-1,4-diylbis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (**65a**)



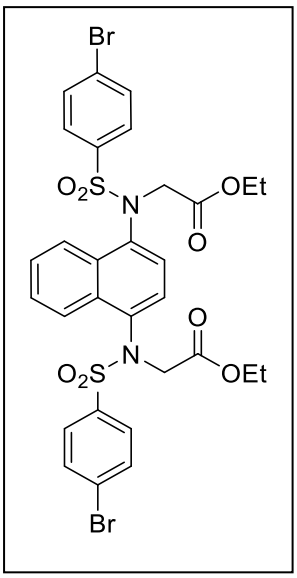
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a beige solid; the yield (42 mg, 69% yield). ^{1}H NMR (400 MHz) (MeOH-d4) δ 8.03-8.00 (m, 1 H), 7.98-7.96 (m, 1 H), 7.92-7.79 (m, 8 H), 7.49-7.45 (m, 2 H), 7.39 (s, 1 H), 7.27 (s,1 H), 4.81-4.71 (m, 2 H), 4.37-4.30 (m, 2 H). ^{13}C NMR (100 MHz) (MeOH-d4) δ 171.81, 144.15, 143.93, 138.39, 138.34, 134.17, 130.04, 129.88, 129.42, 129.30, 128.34, 127.20, 125.28, 125.24, 123.52, 54.17. ^{19}F NMR (377 MHz, MeOH-d4): δ – 64.59 (s, 3F), – 64.60 (s, 3F). HRMS (ESI) Calcd for $C_{28}H_{20}F_6N_2O_8S_2$ $(M+H)^+$ 691.0638, found 691.0639.

4-Bromo-N-(4-((4-hydroxyphenyl) sulfonamido) naphthalen-1-yl) benzenesulfonamide (**63b**)



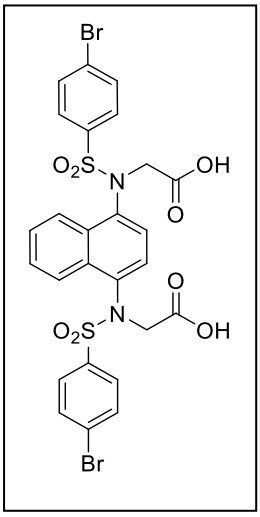
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a pink solid, the yield (416 mg, 78% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.46 (s, 2 H), 8.15-8.12 (m, 2 H), 7.82-7.80 (m, 2 H), 7.49-7.42 (m, 6 H), 7.07 (s, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 138.85, 135.42, 134.29, 131.24, 130.67, 130.25, 128.09, 126.35, 123.36, 122.77, 119.35.

Diethyl 2,2'-(naphthalene-1,4-diylbis (((4-bromophenyl) sulfonyl) azanediyl)) diacetate (**64b**)



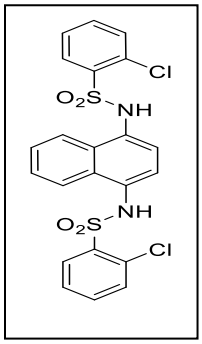
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as a light pink solid, the yield (109 mg, 71% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.07-8.01 (m, 2 H), 7.64-7.57 (m, 10 H), 7.22 (s, 1 H), 7.19 (s, 1 H), 4.81-4.68 (m, 2 H), 4.24-4.08 (m, 6 H), 1.22-1.16 (m, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.69, 138.40, 138.03, 137.17, 137.06, 133.08, 133.00, 132.25, 129.80, 129.71, 128.40, 128.34, 128.13, 128.03, 127.93, 124.17, 61.77, 53.26, 53.19, 14.32, 14.14.

2,2'-(Naphthalene-1,4-diylbis(((4-bromophenyl)sulfonyl)azanediyl))diacetic acid (65c)



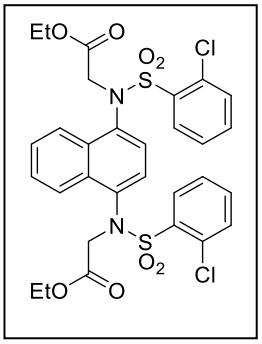
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a yellow solid; the yield (9 mg, 67% yield). ^{1}H NMR (400 MHz) (DMSO) δ 8.22 (s, 1 H), 8.15 (s, 1 H), 7.81-7.72 (m, 3 H), 7.60-7.52 (m, 5 H), 7.23 (s, 1 H), 6.89 (s, 1 H), 4.46-4.09 (m, 4 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.54, 138.02, 137.38, 136.88, 136.66, 132.83, 132.06, 131.95, 130.58, 129.91, 129.62, 127.74, 126.97, 126.57, 126.40, 124.62, 54.44. HRMS (ESI) Calcd for $C_{26}H_{20}Br_2N_2O_8S_2$ $(M+H)^+$ 710.9101, found 710.9105.

N,N'-(Naphthalene-1,4-diyl)bis(2-chlorobenzenesulfonamide) (63c)



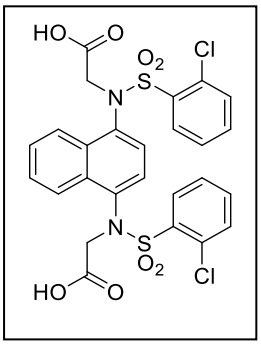
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a pink solid; the yield (401 mg, 79% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.49 (s, 2 H), 8.10-8.09 (m, 2 H), 7.76-7.73 (m, 2 H), 7.62-7.60 (m, 2 H), 7.62-7.36 (m, 8 H), 7.05 (s, 2 H), ^{13}C NMR (100 MHz) (DMSO) δ 136.77, 133.95, 131.41, 130.52, 130.39, 130.25, 129.85, 127.17, 125.97, 122.82, 122.47.

Diethyl 2,2'-(naphthalene-1,4-diylbis(((2-chlorophenyl)sulfonyl)azanediyl))diacetate (64c)



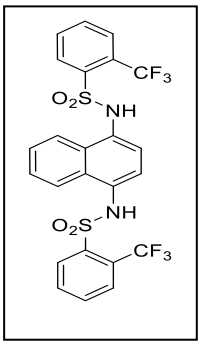
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (98 mg, 72% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.01-7.95 (m, 2 H), 7.78-7.72 (m, 2 H),7.60-7.37 (m, 8 H), 7.22-7.18 (m, 2 H), 5.07-4.98 (m, 2 H),4.37-4.30 (m, 2 H), 4.19-4.09 (m, 4 H), 1.28-1.19 (m, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.97, 168.87, 137.54, 137.15, 136.44, 136.22, 134.02, 132.54, 132.45, 132.35, 132.18, 129.58, 129.42, 127.57, 127.41, 127.11, 123.63, 123.51, 61.69, 54.06, 53.89, 14.18.

2,2'-(Naphthalene-1,4-diylbis(((2-chlorophenyl)sulfonyl)azanediyl))diacetic acid (65c)



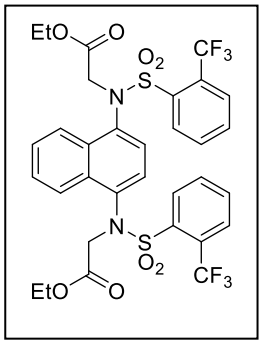
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as an off-white solid; the yield (21 mg, 72% yield). ^{1}H NMR (400 MHz) (DMSO) δ 12.98 (s ,2 H), 7.98-7.96 (m, 2 H), 7.73-7.54 (m, 8 H), 7.42-7.36 (m, 4 H), 4.86-4.76 (m, 2 H), 4.46-4.37 (m, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.03, 169.90, 162.29, 136.41, 136.04, 135.96, 135.82, 134.74, 132.11, 131.89, 131.07, 128.83, 127.72, 127.60, 126.87, 126.73, 123.42, 53.67. HRMS (ESI) Calcd for $C_{26}H_{20}Cl_2N_2O_8S_2$ $(M+H)^+$ 623.0111, found 623.0108.

N,N'-(Naphthalene-1,4-diyl)bis(2-(trifluoromethyl)benzenesulfonamide) (**63d**)



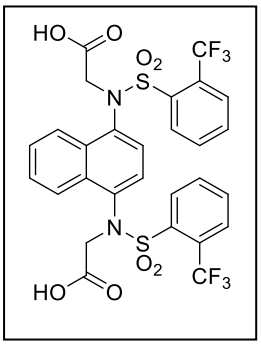
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a beige solid; the yield (766 mg, 81% yield). ^{1}H NMR (400 MHz) (MeOH-d4) δ 7.91-7.85 (m, 4 H), 7.80 (d, 2 H, J= 8.0 Hz), 7.68 (t, 2 H, J= 7.6 Hz), 7.53 (t, 2 H, J= 7.6 Hz), 7.34-7.31 (m, 2 H), 7.19 (s, 2 H). ^{13}C NMR (100 MHz) (MeOH-d4) δ 140.13, 134.14, 133.49, 132.95, 132.47, 132.18, 129.35, 129.28, 127.58, 125.19, 124.02. ^{19}F NMR (377 MHz, MeOH-d4): δ – 58.62 (s, 6F).

Diethyl 2,2'-(naphthalene-1,4-diylbis(((2-(trifluoromethyl) phenyl) sulfonyl) azanediyl)) diacetate (**64d**)



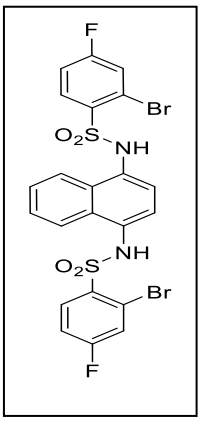
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (110 mg, 73% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.87-7.76 (m, 5 H), 7.69 (s, 1 H), 7.63-7.60 (m, 4 H), 7.47-7.39 (m, 3 H), 7.29-7.28 (m, 1 H), 5.05-4.96 (m, 2 H), 4.20-4.09 (m, 6 H), 1.25-1.20 (m, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.98, 138.89, 138.38, 136.67, 136.26, 133.05, 132.88, 132.57, 132.35, 132.20, 130.06, 129.43, 128.17, 127.76, 127.49, 123.43, 123.10, 121.29, 61.78, 53.42, 53.32, 14.20. ^{19}F NMR (377 MHz, MeOH-d4): δ – 57.17 (s, 3F), – 57.28 (s, 3F).

N-(4-((N-(Carboxymethyl)-2-(trifluoromethyl)phenyl)sulfonamido)naphthalen-1-yl)-N-((2-(trifluoromethyl)phenyl)sulfonyl)glycine (**65d**)



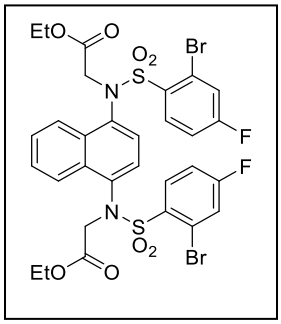
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a light yellow solid; the yield (19 mg, 76% yield). ^{1}H NMR (400 MHz) (DMSO) δ 8.02-7.31 (m, 14 H), 4.76-4.69 (m, 2 H), 4.37-4.23 (m, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.91, 137.32, 135.74, 133.83, 132.98, 132.37, 131.71, 129.14, 128.05, 126.77, 122.93, 53.16. ^{19}F NMR (377 MHz, DMSO): δ – 55.97 (s, 6F). HRMS (ESI) Calcd for $C_{28}H_{20}F_6N_2O_8S_2$ $(M+H)^+$ 691.0638, found 691.0628.

N,N'-(Naphthalene-1,4-diyl)bis(2-bromo-4-fluorobenzenesulfonamide) (**63e**)



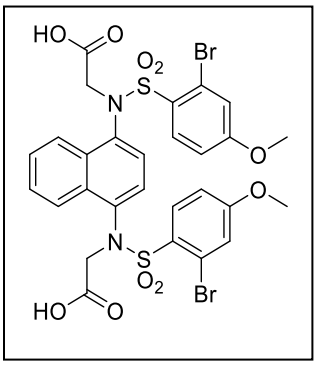
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a beige solid; the yield (411 mg, 65% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.52 (s, 2 H), 8.12-8.10 (m, 2 H), 7.85-7.78 (m, 4 H), 7.49-7.47 (m, 2 H), 7.31-7.27 (m, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 164.61, 162.06, 135.34, 135.31, 133.46, 133.37, 130.48, 130.19, 126.29, 123.21, 122.91, 122.68, 122.43, 120.77, 120.66, 115.12, 114.91. ^{19}F NMR (377 MHz, DMSO): δ – 104.85 (s, 2F).

Diethyl 2,2'-(naphthalene-1,4-diylbis(((2-bromo-4-fluorophenyl)sulfonyl)azanediyl)) diacetate (**64e**)



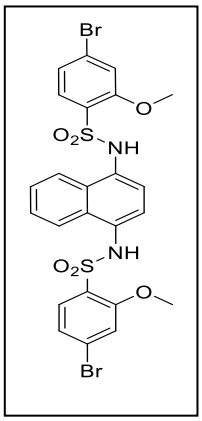
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (109 mg, 68% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.00-7.93 (m, 2 H), 7.84-7.78 (m, 2 H), 7.69 (s, 1 H), 7.63 (s, 1 H), 7.48-7.41 (m, 4 H), 6.96-6.93 (m, 2 H), 5.11-5.04(m, 2 H), 4.33 (s, 3 H), 4.29 (s, 3 H), 4.20-4.13 (m, 4 H), 1.24-1.21 (m, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.91, 168.84, 165.57, 162.98, 136.40, 136.21, 135.56, 135.37, 134.80, 134.77, 134.71, 134.67, 132.46, 132.33, 129.84, 129.56, 127.72, 127.59, 123.60, 123.46, 123.20, 122.95, 121.91, 121.81, 121.77, 115.00, 114.87, 114.78, 114.66, 61.79, 54.22, 54.14, 14.20. ^{19}F NMR (377 MHz, $CDCl_3$): δ – 103.46 (s, 1F), – 103.60 (s, 1F).

2,2'-(Naphthalene-1,4-diylbis(((2-bromo-4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (**65 e**)



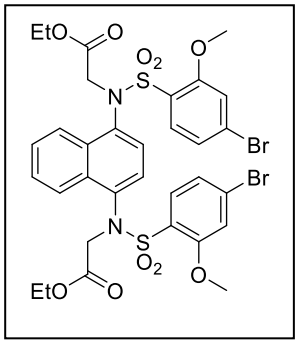
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a beige solid; the yield (17 mg, 75% yield). ^{1}H NMR (400 MHz) (DMSO) δ 8.00-7.94 (m, 2 H), 7.69-7.61 (m, 4 H), 7.40-733 (m, 4 H), 6.89 (d, 2 H, *J*= 8.4 Hz), 4.75-4.63 (m, 2 H), 4.22-4.11 (m, 2 H), 3.80 (s, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 162.35, 135.81, 133.56, 131.88, 130.48, 129.23, 126.16, 123.62, 120.89, 120.55, 112.97, 56.10, 55.02. HRMS (ESI) Calcd for $C_{28}H_{24}Br_2N_2O_{10}S_2$ $(M+H)^+$ 770.9312, found 770.9335.

N,N'-(Naphthalene-1,4-diyl)bis(4-bromo-2-methoxybenzenesulfonamide) (**63f**)



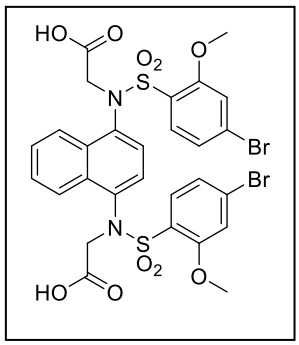
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a white solid; the yield (518 mg, 79% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.19 (s, 2 H), 8.09-8.07 (m, 2 H), 7.72-7.69 (m, 2 H), 7.61 (d, 2 H, *J*= 2.4 Hz), 7.48-7.46 (m, 2 H), 7.18 (s, 2 H), 7.18-7.09 (m, 2 H), 3.67 (s, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 156.07, 137.74, 131.67, 131.31, 130.54, 129.48, 126.71, 123.56, 123.51, 115.59, 111.15, 56.42.

Diethyl 2,2'-(naphthalene-1,4-diylbis(((4-bromo-2-methoxyphenyl) sulfonyl) azanediyl)) diacetate (**64f**)



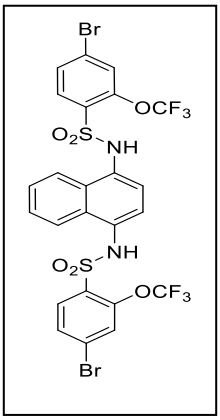
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (108 mg, 65% yield). ^{1}H NMR (400 MHz) (MeOH-d4) δ 7.82-7.79 (m,1 H), 7.71-7.68 (m,1 H), 7.56 (d, 1 H, *J*= 2.4 Hz), 7.46 (d, 2 H, *J*= 2.4 Hz), 7.41-7.37 (m, 3 H), 7.30 (s, 1 H), 7.26-7.20 (m, 2 H), 6.79 (d, 1 H, *J*= 8.8 Hz), 6.72 (d, 1 H, *J*= 8.8 Hz),4.67-4.62 (m, 2 H), 4.23-4.12 (m, 2 H), 3.92-3.87 (m, 5 H), 3.67 (s, 3 H), 3.42 (s, 3 H)1.00-0.95 (m, 6 H).

2,2'-(Naphthalene-1,4-diylbis(((4-bromo-2-methoxyphenyl) sulfonyl)azanediyl)) diacetic acid (**65f**)



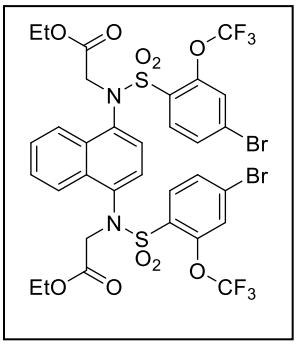
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; (19 mg, 64% yield). ^{1}H NMR (400 MHz) (DMSO) δ 12.77 (br, 2 H), 8.02-7.98 (m, 2 H), 7.78 (d, 2 H, *J*= 8.8 Hz), 7.56 (d, 2 H, *J*= 8.8 Hz), 7.51 (s, 4 H), 7.24-7.20 (m, 2 H), 4.74-4.67 (m, 2 H), 4.45-4.35 (m, 2 H), 3.80 (s, 3 H), 3.71 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.16, 155.85, 137.65, 136.27, 132.06, 131.98, 131.94, 128.76, 128.39, 126.75, 123.76, 123.67, 115.51, 115.46, 110.94, 56.28, 56.10, 53.50. HRMS (ESI) Calcd for $C_{28}H_{24}Br_2N_2O_{10}S_2$ $(M+H)^+$ 770.9312, found 770.1224.

N,N'-(Naphthalene-1,4-diyl)bis(4-bromo-2-(trifluoromethoxy)benzenesulfonamide) (**63g**)



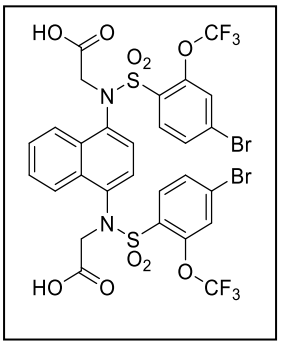
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a light yellow solid; the yield (589 mg, 77% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.01-7.99 (m, 2 H), 7.69 (d, 2 H, *J*= 8.8 Hz), 7.58-7.56 (m, 2 H), 7.52 (t, 2 H, *J*= 1.5 Hz), 7.44 (dd, 2 H, *J*= 8.8, 1.5 Hz), 7.12 (s, 2 H), 7.01 (br, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 146.27, 132.47, 130.51, 130.18, 130.03, 129.87, 129.87, 128.98, 127.78, 123.59, 123.57, 122.24, 121.55, 118.97. ^{19}F NMR (377 MHz, $CDCl_3$): δ – 56.24 (s, 6F).

Diethyl 2,2'-(naphthalene-1,4-diylbis(((4-bromo-2-(trifluoromethoxy) phenyl) sulfonyl) azanediyl)) diacetate (**64g**)



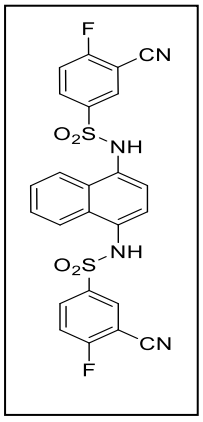
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (109 mg, 66% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.02-7.93 (m, 2 H), 7.66-7.42 (m, 10 H), 5.02-4.91 (m, 2 H), 4.27-4.07 (m, 6 H), 1.22 (t, 6 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.68, 146.46, 136.50, 132.92, 132.68, 132.59, 131.41, 129.85, 128.95, 128.71, 128.02, 127.85, 123.58, 123.48, 61.70, 53.42, 53.18. ^{19}F NMR (377 MHz, $CDCl_3$): δ – 56.26 (s, 3F), – 56.47 (s, 3F).

2,2'-(Naphthalene-1,4-diylbis(((4-bromo-2-(trifluoromethoxy) phenyl) sulfonyl) azanediyl)) diacetic acid (**65g**)



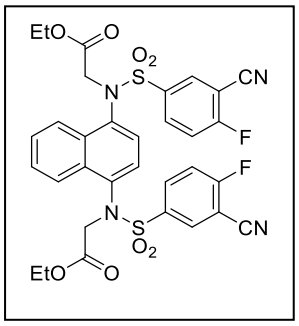
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a beige solid; the yield (17 mg, 63% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.06-8.00 (m, 2 H), 7.85 (s, 1 H), 7.77-7.69 (m, 4 H), 7.61-7.58 (m, 3 H), 7.48 (s, 1 H), 7.39 (s, 1 H), 4.74-4.63 (m, 2 H), 4.41-4.02 (m, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.62, 169.52, 145.33, 136.09, 132.83, 132.73, 132.16, 132.01, 130.82, 130.61, 130.49, 128.18, 128.10, 128.01, 127.18, 124.32, 123.85, 123.67, 123.56, 52.99. HRMS (ESI) Calcd for $C_{28}H_{18}Br_2F_6N_2O_{10}S_2$ $(M+H)^+$ 878.8747, found 878.8773.

N,N'-(Naphthalene-1,4-diyl)bis(3-cyano-4-fluorobenzenesulfonamide) (**63h**)



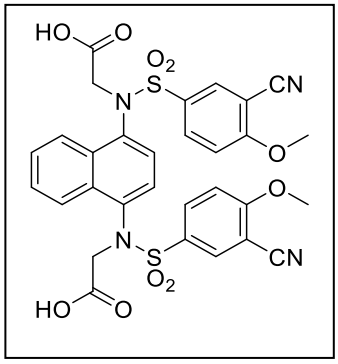
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a beige solid; the yield (415 mg, 79% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.44 (s, 2 H), 8.18-8.16 (m, 2 H), 8.00-7.95 (m, 4 H), 7.65 (t, 2 H, *J*= 8.8 Hz), 7.50-7.47 (m, 2 H), 7.00 (s, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 165.57, 162.96, 137.02, 134.44, 134.34, 132.57, 130.61, 130.22, 126.44, 123.41, 123.16, 117.83, 117.62, 112.47, 101.49, 101.32. ^{19}F NMR (377 MHz, $CDCl_3$): δ – 101.54 (s, 2F).

Diethyl 2,2'-(naphthalene-1,4-diylbis(((3-cyano-4-fluorophenyl)sulfonyl)azanediyl)) diacetate (**64h**)



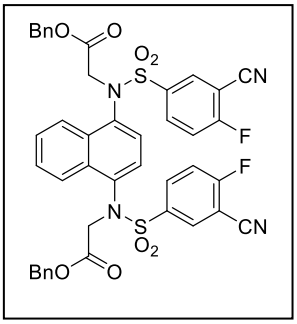
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (102 mg, 71% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.44-8.42 (m, 1 H), 8.26-8.16 (m, 3 H), 8.03-7.91 (m, 2 H), 7.71-7.56 (m, 4 H), 7.19 (s, 1 H), 7.12 (s, 1 H), 4.74-4.52 (m, 4 H), 4.11-3.98 (m, 4 H), 1.14-1.05 (m, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 168.25, 168.17, 166.23, 166.13, 163.61, 163.51, 136.61, 136.56, 135.60, 135.50, 135.31, 135.27, 135.23, 135.09, 135.06, 133.95, 133.80, 132.64, 132.53, 127.15, 126.78, 124.17, 124.07, 117.52, 117.31, 112.49, 112.29, 101.92, 101.81, 101.76, 101.64, 60.99, 60.92, 53.19, 13.42, 13.35. ^{19}F NMR (377 MHz, $CDCl_3$): δ – 101.11 (s, 1F), – 101.24 (s, 1F).

2,2'-(Naphthalene-1,4-diylbis(((3-cyano-4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (**65h**)



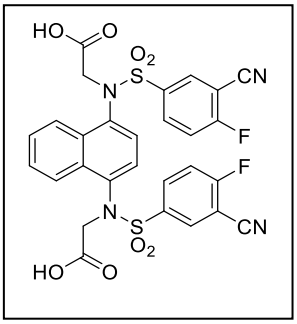
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a light yellow solid; yield (21 mg, 69% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.25-8.16 (m, 4 H), 7.95-7.89 (m, 1 H), 7.77 (d, 1 H, *J*= 8.8 Hz), 7.61-7.59 (m, 2 H), 7.41 (d, 1 H, *J*= 9.2Hz), 7.31 (d, 1 H, *J*= 8.8 Hz), 7.19 (s, 1 H), 7.11 (s, 1 H), 4.57-4.32 (m, 4 H), 4.03 (s, 3 H), 3.99 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.98, 164.04, 137.02, 134.99, 134.76, 133.94, 133.71, 132.95, 130.90, 130.64, 126.93, 124.56, 112.79, 101.25, 57.34, 53.65. HRMS (ESI) Calcd for $C_{30}H_{24}N_4O_{10}S_2$ $(M+H)^+$ 665.1007, found 665.0997.

Dibenzyl 2,2'-(naphthalene-1,4-diylbis (((3-cyano-4-fluorophenyl) sulfonyl) azanediyl)) diacetate (**64i**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (122 mg, 74% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.09-7.95 (m, 5 H), 7.65-7.61 (m, 2 H), 7.42-7.22 (m, 15 H), 5.23-4.93 (m, 6 H), 4.31-4.17 (m, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.63, 168.59, 137.06, 137.03, 136.81, 135.23, 135.11, 135.01, 134.81, 134.73, 134.22, 132.92, 128.92, 128.87, 128.83, 128.65, 128.62, 128.54, 128.08, 128.01, 123.88, 117.56, 117.44, 117.35, 117.23, 112.44, 112.27, 102.67, 102.50, 67.89, 67.76, 53.33, 53.26.

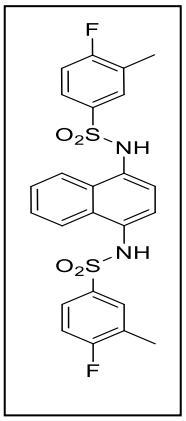
2,2'-(Naphthalene-1,4-diylbis(((3-cyano-4-fluorophenyl)sulfonyl)azanediyl))diacetic acid (**65i**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C3) to get the title compound as a yellow solid; the yield (21 mg, 69% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.51-8.49 (m, 1 H), 8.43-8.41 (m, 1 H), 8.25-8.23 (m, 1 H), 8.18-8.16 (m, 1 H), 8.02-7.98 (m, 1 H), 7.89-7.86 (m, 1 H), 7.75 (t, 1 H, *J*= 8.8 Hz), 7.65-7.61 (m, 1 H), 7.22 (s, 1 H), 7.11 (s, 1 H), 4.66-4.45 (m, 4 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.98, 136.83, 136.00, 135.76, 135.38, 134.28, 134.13, 132.83, 132.66, 127.41, 127.08, 126.98, 124.46, 117.63, 117.44,

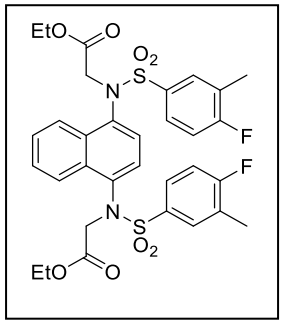
112.97, 112.80, 101.86, 101.69, 53.72. ^{19}F NMR (377 MHz, $CDCl_3$): δ – 101.31 (s, 1 F), – 101.42 (s, 1 F). HRMS (ESI) Calcd for $C_{28}H_{18}F_2N_4O_8S_2$ $(M+H)^+$ 641.0607, found 641.0599.

N,N'-(Naphthalene-1,4-diyl)bis(4-fluoro-3-methylbenzenesulfonamide) (**63j**)



Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a white solid; the yield (397 mg, 79% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.17 (s, 2 H), 7.98-7.95 (m, 2 H), 7.60-7.57 (m, 2 H), 7.52-7.50 (m, 2 H), 7.44-7.42 (m, 2 H), 7.25 (t, 2 H, *J*= 8.8 Hz), 7.03 (s, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 164.01, 161.52, 135.84, 135.80, 130.98, 130.38, 130.31, 130.18, 126.99, 126.90, 126.19, 125.78, 125.59, 123.31, 123.03, 115.87, 115.63, 48.56, 13.93, 13.90. ^{19}F NMR (377 MHz, DMSO): δ – 110.52 (s, 2F).

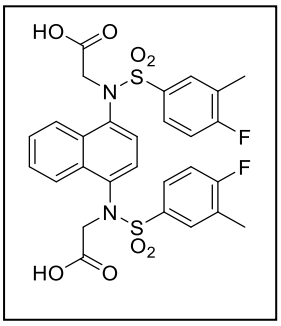
Diethyl 2,2'-(naphthalene-1,4-diylbis(((4-fluoro-3-methylphenyl)sulfonyl)azanediyl)) diacetate (**64j**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (97 mg, 72% yield). ^{1}H NMR (400 MHz) (DMSO) δ 8.20-8.16 (m, 2 H), 7.73-7.72 (m, 2 H), 7.59-7.57 (m, 3 H), 7.52-7.48 (m, 2 H), 7.37-7.27 (m, 2 H), 7.10 (s, 1 H), 7.07 (s,1 H), 4.62-4.53 (m, 4 H), 4.07-4.00 (m, 4H), 2.30 (s,1 H), 2.23 (s,1 H), 1.10-1.03 (m, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 168.38, 168.35, 164.55, 162.09, 162.05, 136.82, 133.49, 132.71, 131.44, 128.16, 128.07, 127.94, 127.84, 126.88, 126.78, 126.71, 126.17, 126.06,

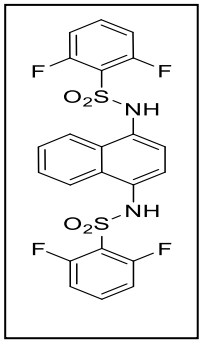
125.99, 125.87, 124.35, 115.97, 115.86, 115.73, 115.62, 60.89, 53.25, 13.98, 13.95, 13.86, 13.75. ^{19}F NMR (377 MHz, DMSO): δ – 109.48 (s, 1F) – 109.53 (s, 1F).

2,2'-(Naphthalene-1,4-diylbis(((4-fluoro-3-methylphenyl)sulfonyl)azanediyl))diacetic acid (**65j**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; the yield (26 mg, 79% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.20-8.16 (m, 2 H), 7.74-7.72 (m, 1 H), 7.59-7.56 (m, 3 H), 7.53-7.49 (m, 2 H), 7.37-7.28 (m, 2 H), 7.15 (s, 1 H), 7.13 (s, 1 H), 4.55-4.39 (m, 4 H), 2.30 (s, 3 H), 2.24 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.88, 164.52, 162.06, 136.92, 136.87, 133.74, 132.73, 131.51, 131.47, 128.16, 128.06, 127.94, 127.85, 127.05, 126.96, 126.72, 126.08, 126.01, 125.89, 125.82, 124.41, 115.95, 115.82, 115.72, 115.58, 53.19, 14.03, 13.94, 13.92. ^{19}F NMR (377 MHz, DMSO): δ – 109.67 (s, 1 F), – 109.69 (s, 1 F). HRMS (ESI) Calcd for $C_{28}H_{24}F_2N_2O_8S_2$ $(M+H)^+$ 619.1015, found 619.1009.

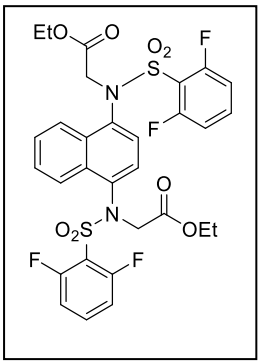
N,N'-(Naphthalene-1,4-diyl)bis(2,6-difluorobenzenesulfonamide) (**63k**)



Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a yellow product; the yield (399 mg, 78% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.17 (s, 2 H), 7.98-7.95 (m, 2 H), 7.60-7.57 (m, 2 H), 7.52-7.50 (m, 2 H), 7.44-

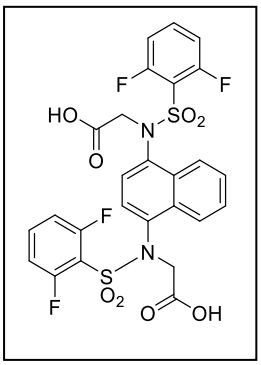
7.42 (m, 2 H), 7.25 (t, 2 H, *J*= 8.8 Hz), 7.03 (s, 2 H). ^{19}F NMR (377 MHz, DMSO): δ – 104.90 (s, 2F), – 105.35 (s, 2F).

Diethyl 2,2'-(naphthalene-1,4-diylbis(((2,6-difluorophenyl) sulfonyl) azanediyl)) diacetate (**64k**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; yield (86 mg, 63% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.08-8.03 (m, 2 H), 7.59-7.49 (m, 6 H), 7.01-6.92 (m, 4 H), 5.10-4.94 (m, 2 H), 4.39-4.04 (m, 6H), 1.25-1.18 (m, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.78, 164.20, 160.65, 136.93, 136.83, 135.52, 135.11, 132.73, 128.15, 128.07, 127.87, 124.07, 113.95, 113.82, 53.68. ^{19}F NMR (377 MHz, $CDCl_3$): δ – 104.25 (s, 2F) – 104.29 (s, 2F).

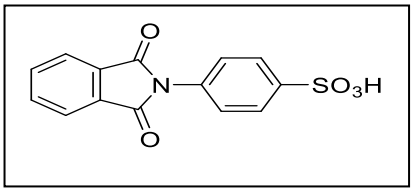
2,2'-(Naphthalene-1,4-diylbis(((2,6-difluorophenyl)sulfonyl)azanediyl))diacetic acid (**65k**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as an off-white solid, the yield (9 mg, 61% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.19-8.17 (m, 1 H), 8.10-8.08 (m, 1 H), 7.75-7.59 (m, 3 H), 7.50 (s, 1 H), 7.35 (s, 1 H), 7.29-7.12 (m, 4 H), 4.73-4.58 (m, 2 H), 4.38-4.32 (m, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 168.78, 168.60, 158.65, 136.49, 136.13, 135.13, 135.02,

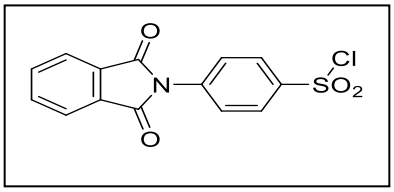
132.78, 128.33, 128.05, 127.77, 123.69, 113.34, 113.11, 61.74, 53.57, 53.23.^{19}F NMR (377 MHz, DMSO): δ – 104.90 (s, 2F), – 105.35 (s, 2F). HRMS (ESI) Calcd for $C_{26}H_{18}F_4N_2O_8S_2$ $(M+H)^+$ 627.0513, found 627.0512.

4-(1,3-Dioxoisoindolin-2-yl)benzenesulfonic acid (**63al**)



To a mixture of sulfanilic acid (540 mg, 3.13 mmol) and Phthalic anhydride (463 mg, 3.13 mmol), DMF (15 ml) and pyridine (0.25 ml) were added. Then, the mixture was heated to 100 °C with stirring for 20 min. (majority of the solid material dissolved). Then, the reaction mixture was poured into 100 ml acetone and kept at 0 °C for 20 min. Then, the suspension filtered and washed with diethyl ether to get a white solid which was taken in glacial acetic acid (20 ml) and refluxed for 2 hours. Upon completion, the mixture was cooled to room temperature and the solution was filtered to (remove insoluble solid). Then, add diethyl ether (50 ml) was added and filter the suspension followed by washing of the solid with diethyl ether to get beige color solid (503 mg, 53% yield). ^{1}H NMR (400 MHz) (DMSO) δ 7.88-7.84 (m, 4 H), 7.69 (d, 2 H, *J*= 8.0 Hz), 7.47 (s, 1 H), 7.36 (d, 2 H, *J*= 8.0 Hz). ^{13}C NMR (100 MHz) (DMSO) δ 166.96, 147.62, 146.00, 142.50, 134.79, 132.01, 131.53, 126.77, 126.10, 123.47.

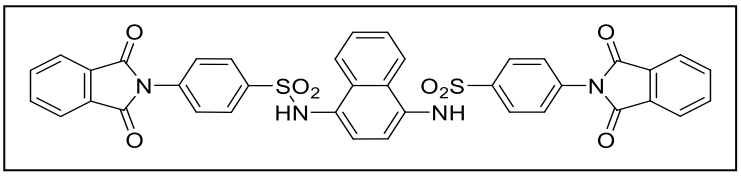
4-(1,3-Dioxoisoindolin-2-yl)benzenesulfonyl chloride (**63bl**)



To a solution of **63al** (455 mg, 1.5 mmol) in DMF (3 ml), thionyl chloride (0.15 ml) was added. Then, the mixture was stirred at room temperature for 2 hours and then

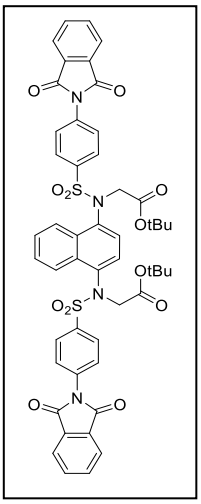
checked by TLC. After completion, the reaction mixture was extracted with ice water: DCM. Wash the organic layer with brine and dried over sodium sulfate and remove the organic solvent by rotovap to get a yellow solid (371 mg, 77% yield). ^{1}H NMR (400 MHz) (DMSO) δ 7.94-7.86 (m, 2 H), 7.72 (d, 1 H, *J*= 8.4 Hz), 7.69 (d, 1 H, *J*= 8.4 Hz), 7.64-7.53 (m, 2 H), 7.39 (d, 1 H, *J*= 8.4 Hz), 7.30 (d, 1 H, *J*= 8.4 Hz).^{13}C NMR (100 MHz) (DMSO) δ 167.00, 147.58, 135.82, 130.84, 128.39, 126.83, 126.13, 123.52.

N,N'-(Naphthalene-1,4-diyl)bis(4-(1,3-dioxoisoindolin-2-yl)benzenesulfonamide) (63l)



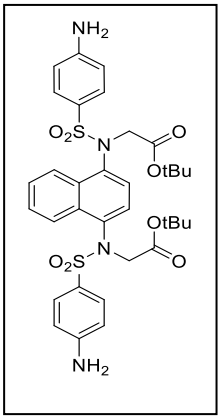
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a yellow solid; the yield (215 mg, 59% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.40 (s, 2 H), 8.04-8.01 (m, 2 H), 7.89-7.83 (m, 12 H), 7.64 (d, 4 H, *J*= 8.8 Hz), 7.46-7.44 (m, 2 H), 7.13 (s, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 166.42, 138.69, 135.65, 134.83, 131.32, 131.03, 130.17, 127.47, 127.33, 126.41, 123.51, 123.38, 122.86.

***tert*-Butyl N-(4-((4-(1,3-dioxoisoindolin-2-yl)-N-(2-ethoxy-2-oxoethyl)phenyl) sulfonamido) naphthalen-1-yl)-N-((4-(1,3-dioxoisoindolin-2-yl)phenyl)sulfonyl) glycinate (64l)**



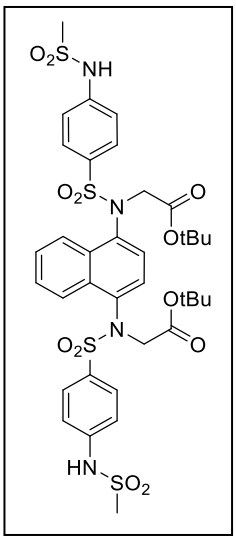
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (71 mg, 76% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.09-8.04 (m, 2 H), 7.98-7.96 (m, 2 H), 7.87-7.77 (m, 10 H), 7.72-7.64 (m, 4 H), 7.57-7.52 (m, 2 H), 7.33 (s, 1 H), 4.65-4.55 (m, 2 H), 4.23-4.10 (m, 2H), 1.38 (s, 9 H), 1.34 (s, 9 H). ^{13}C NMR (100 MHz) (($CDCl_3$) δ 167.44, 167.35, 166.48, 137.75, 137.42, 137.19, 137.04, 136.14, 134.85, 134.70, 133.08, 132.98, 131.50, 131.42, 128.89, 128.80, 127.71, 127.62, 127.53, 126.10, 126.01, 124.25, 124.18, 124.04, 123.95, 82.65, 82.51, 54.05, 53.93, 27.95.

***tert*-Butyl N-(4-((4-amino-N-(2-ethoxy-2-oxoethyl)phenyl)sulfonamido)naphthalen-1-yl)-N-((4-aminophenyl)sulfonyl)glycinate** (**65al**)



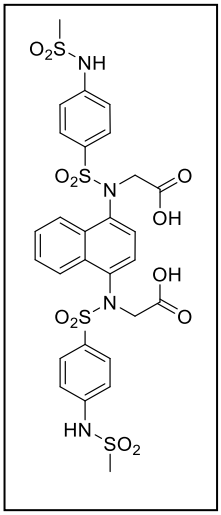
To a stirred solution of **64l** (60 mg, 0.06 mmol) in mixture of DCM: MeOH (1: 1), hydrazine monohydrate was added (40 uL) and the reaction stirred at room temperature for 1 hour. Upon completion, the organic solvent removed under reduced pressure and then purify the crude product using a silica gel ISCO column ethyl acetate/ hexane to get the desired product as a beige solid, the yield (36 mg, 89% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.36-8.34 (m, 1 H), 8.24-8.22 (m, 1 H), 7.59-7.56 (m, 2 H), 7.25-7.22 (m, 4 H), 7.03 (s, 1 H), 6.82 (s, 1 H), 6.65 (d, 2 H, *J*= 8.4 Hz), 6.55 (d, 2 H, *J*= 8.4 Hz), 6.13-6.11 (br, 4 H), 4.38-4.02 (m, 4 H), 1.25 (s, 9 H), 1.20 (s, 9 H). ^{13}C NMR (100 MHz) (($CDCl_3$) δ 167.31, 153.32, 137.23, 137.14, 133.06, 132.96, 129.81, 129.61, 126.28, 125.75, 125.48, 124.84, 124.67, 121.94, 121.48, 112.50, 81.26, 81.18, 54.15, 53.90, 27.39.

***tert*-Butyl N-(4-((N-(2-ethoxy-2-oxoethyl)-4-(methylsulfonamido) phenyl) sulfonamido) naphthalen-1-yl)-N-((4-(methylsulfonamido)phenyl)sulfonyl)glycinate (65bl)**



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (18 mg, 82% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.26-8.24 (m, 1 H), 8.18-8.16 (m, 1 H), 7.87 (br, 2 H), 7.69-7.49 (m, 8 H), 7.28 (s, 1 H), 7.26-7.22 (m, 1 H), 7.14 (s, 1 H), 6.86 (s, 1 H), 4.63-4.49 (m, 2 H), 4.22-4.09 (m, 2 H), 3.07 (s, 6 H), 1.33 (s, 18 H). ^{13}C NMR (100 MHz) (($CDCl_3$) δ 167.61, 141.82, 136.99, 133.30, 132.94, 130.33, 130.06, 127.70, 127.55, 127.26, 124.45, 124.34, 118.12, 117.80, 82.56, 54.26, 40.10, 27.91.

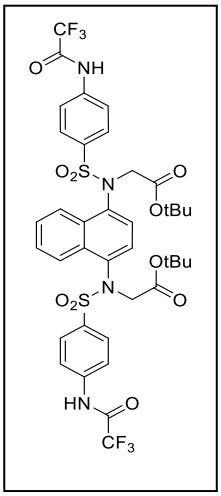
2,2'-(Naphthalene-1,4-diylbis(((4-(methylsulfonamido) phenyl) sulfonyl) azanediyl)) diacetic acid (65l)



Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a white solid; the yield (9 mg, 58% yield). ^{1}H NMR (400 MHz) (MeOH-d4) δ 8.05-8.01 (m, 2 H), 7.64 (d, 2 H, J= 8.8 Hz), 7.61 (d, 2 H, J= 8.8 Hz), 7.47-7.45 (m, 2 H), 7.33 (dd, 4 H, J= 2.8 Hz, 8.8 Hz), 7.26 (d, 2 H, *J*= 8.8 Hz), 4.69-4.60 (m, 2 H), 4.36-4.30 (m, 2 H), 3.06 (s, 3 H), 3.04 (s, 3 H). ^{13}C NMR (100 MHz) (MeOH-d4) δ 172.07,

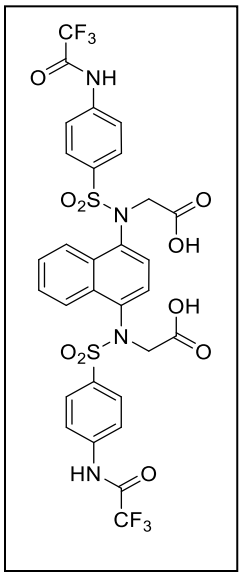
144.54, 138.64, 134.60, 134.39, 134.30, 130.91, 130.80, 129.20, 128.03, 125.49, 119.25, 54.13, 54.05, 40.07, 39.97. HRMS (ESI) Calcd for $C_{28}H_{28}N_4O_{12}S_4$ $(M+H)^+$ 741.0659, found 741.0671.

Di-*tert*-butyl 2,2'-(naphthalene-1,4-diylbis(((4-(2,2,2-trifluoroacetamido) phenyl) sulfonyl) azanediyl))diacetate (**65am**)



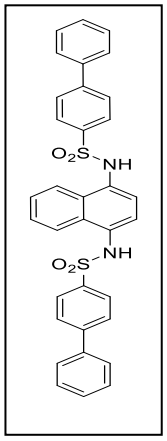
To a stirred solution of 65al (16 mg, 0.026 mmol) in 1 ml pyridine at 0 °C, TFAA (7.8 uL, 0.06 mmol) was added and the reaction stirred at 0 °C for 1 hour. Upon completion, reaction quenched with ice water and extracted with ethyl acetate, washed the organic layer with water, brine, and dried over sodium sulfate. The organic solvent removed under reduced pressure and then purify the crude product using a silica gel ISCO column ethyl acetate/ hexane to get the desired product, the yield (21 mg, 82% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.83 (br, 2 H), 8.30-8.29 (m, 2 H), 7.75 (d, 2 H, J= 8.8 Hz), 7.73-7.59 (m, 6 H), 6.79 (s, 2 H), 4.64-4.50 (m, 2 H), 4.20-4.13 (m, 2 H), 1.33 (s, 18 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 167.65, 139.60, 137.12, 135.11, 133.62, 129.92, 129.71, 127.91, 127.49, 127.03, 124.57, 120.46, 120.20, 82.77, 54.48, 28.01.

2,2'-(Naphthalene-1,4-diylbis(((4-(2,2,2-trifluoroacetamido) phenyl) sulfonyl) azanediyl)) diacetic acid (**65m**)



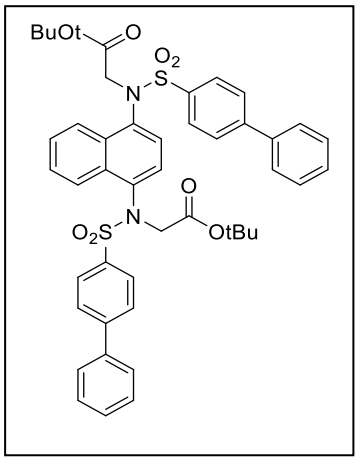
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a white solid; the yield (8 mg, 62% yield). ^{1}H NMR (400 MHz) (DMSO) δ 12.84 (br, 2 H), 11.59 (br, 2 H), 8.27-8.16 (m, 2 H), 7.92-7.85 (m, 4 H), 7.72-7.69 (m, 4 H), 7.58-7.55 (m, 2 H), 7.16 (s, 1 H), 7.01 (s, 1 H), 4.54-4.38 (m, 4 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.77, 169.74, 155.12, 154.75, 140.75, 140.69, 136.97, 136.90, 134.38, 133.92, 132.83, 132.74, 129.07, 128.90, 126.96, 126.75, 126.59, 124.50, 124.39, 120.80, 120.73, 116.95, 114.08, 59.72. HRMS (ESI) Calcd for $C_{30}H_{22}F_6N_4O_{10}S_2$ $(M+H)^+$ 777.0754, found 777.0759.

N,N'-(Naphthalene-1,4-diyl)bis(([1,1'-biphenyl]-4-sulfonamide)) (**63n**)



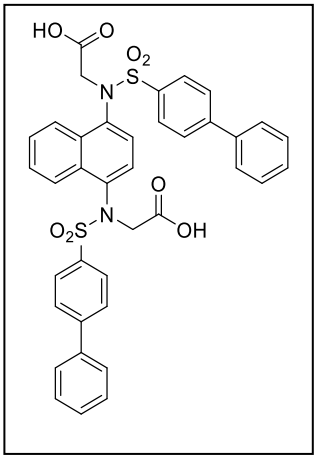
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a light yellow solid; the yield (485 mg, 82% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.27 (s, 2 H), 7.96-7.94 (m, 2 H), 7.76-7.62 (m, 12 H), 7.46-7.34 (m, 8 H), 7.12 (s, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ. 144.06, 138.58, 138.19, 131.02, 130.09, 129.07, 128.90, 128.51, 127.50, 127.34, 127.13, 126.92, 126.69, 126.14, 125.97, 123.30, 123.01.

Di-*tert*-butyl 2,2'-(naphthalene-1,4-diylbis(([1,1'-biphenyl]-4-ylsulfonyl) azanediyl)) diacetate (**64n**)



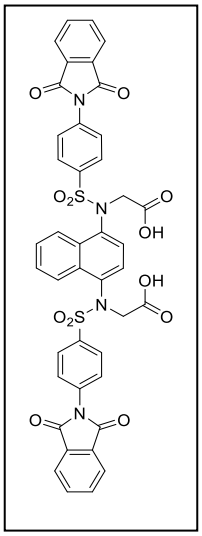
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (116 mg, 71% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.16-8.14 (m, 1 H), 8.04-8.02 (m, 1 H), 7.78 (d, 4 H, *J*= 8.4 Hz), 7.65-7.63 (m, 4 H), 7.60-7.54 (m, 5 H), 7.50-7.42 (m, 7 H), 7.29-7.25 (m, 2 H), 4.65-4.56 (m, 2 H), 4.25-4.15 (m, 2 H), 1.37 (s, 18 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 167.60, 167.54, 145.92, 145.87, 139.23, 139.17, 137.49, 137.27, 137.13, 133.22, 132.99, 129.12, 129.08, 128.64, 128.61, 128.57, 127.81, 127.60, 127.45, 127.33, 124.40, 124.22, 82.50, 54.01, 53.91, 27.93.

2,2'-(Naphthalene-1,4-diylbis(([1,1'-biphenyl]-4-ylsulfonyl)azanediyl))diacetic acid (65n)



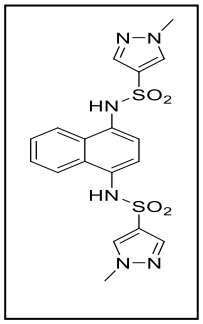
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a light yellow solid; the yield (24 mg, 84% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 7.99-7.97 (m, 2 H), 7.73-7.70 (m, 4 H), 7.63-7.50 (m, 8 H), 7.45-7.35 (m, 8 H), 7.32 (s, 1 H), 7.26 (s, 1 H), 4.70-4.61 (m, 2 H), 4.28-4.18 (m, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.82, 170.78, 146.22, 139.33, 139.21, 137.56, 137.36, 137.27, 137.19, 133.15, 133.10, 129.28, 129.21, 128.75, 128.63, 128.35, 128.27, 127.64, 127.56, 127.45, 127.40, 124.33, 124.27, 53.20. HRMS (ESI) Calcd for $C_{38}H_{30}N_2O_8S_2$ $(M+H)^+$ 707.1516, found 707.1529.

2,2'-(Naphthalene-1,4-diylbis(((4-(1,3-dioxoisoindolin-2-yl)phenyl) sulfonyl) azanediyl)) diacetic acid (**65o**)



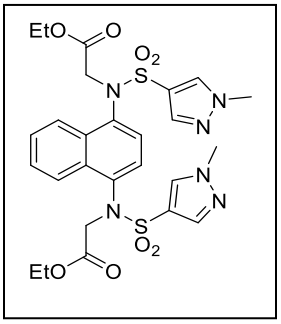
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a light yellow solid; the yield (9 mg, 59% yield). ^{1}H NMR (400 MHz) (DMSO) δ 12.94 (br, 2 H), 8.37-8.35 (m, 1 H), 8.10-8.08 (m, 1 H), 7.99-7.54 (m, 18 H), 7.33 (s, 1 H), 6.93 (s, 1 H), 4.68-4.41 (m, 4H). ^{13}C NMR (100 MHz) ((DMSO) δ 169.93, 166.45, 137.27, 136.97, 136.30, 136.24, 136.11, 134.97, 134.92, 133.09, 132.67, 131.50, 131.39, 128.74, 128.37, 127.38, 127.08, 126.98, 126.89, 126.50, 124.75, 124.34, 123.67, 123.53, 53.50. HRMS (ESI) Calcd for $C_{42}H_{28}N_4O_{12}S_2$ $(M+H)^+$ 845.1218, found 845.1230.

1-Methyl-N-(4-((1-methyl-1H-pyrazole)-4-sulfonamido)naphthalen-1-yl)-1H-pyrazole-4-sulfonamide (**63p**)



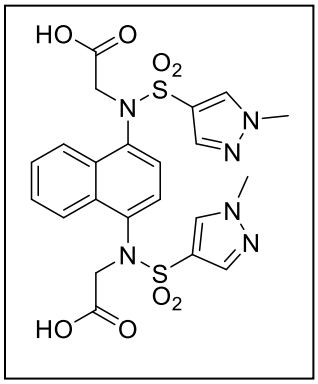
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; the yield (275 mg, 62% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.01 (s, 2 H), 8.11 (s, 2 H), 8.09-8.06 (m, 2 H), 7.60 (s, 2 H), 7.50-7.48 (m, 2 H), 7.16 (s, 2 H), 3.80 (s, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 137.84, 132.66, 131.12, 130.14, 126.13, 123.49, 122.49, 121.43.

Ethyl N-(4-((N-(2-ethoxy-2-oxoethyl)-1-methyl-1H-pyrazole)-4-sulfonamido) naphthalen-1-yl)-N-((1-methyl-1H-pyrazol-4-yl)sulfonyl)glycinate (**64p**)



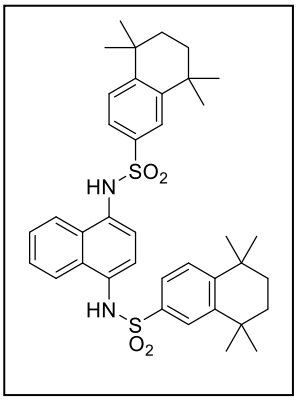
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (81 mg, 61% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.29-8.27 (m, 2 H), 8.12 (s, 1 H), 8.05 (s, 1 H), 7.62 (s, 1 H), 7.54 (m, 3 H), 7.15 (s, 1 H), 7.02 (s, 1 H), 4.42-4.37 (m, 4 H), 3.99-3.94 (m, 4 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 1.10- 1.06 (t, 3 H, *J*= 7.2 Hz), 1.04-1.00 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) (DMSO) δ 169.48, 169.36, 139.64, 139.48, 138.38, 134.27, 134.18, 134.12, 127.56, 127.06, 126.75, 125.48, 125.42, 120.21, 119.88, 61.81, 61.75, 56.15, 54.02, 53.96, 14.13, 14.06.

N-(4-((N-(Carboxymethyl)-1-methyl-1H-pyrazole)-4-sulfonamido)naphthalen-1-yl)-N-((1-methyl-1H-pyrazol-4-yl)sulfonyl)glycine (**65p**)



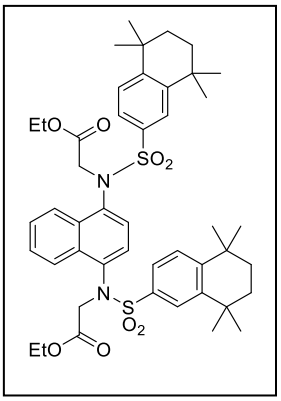
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; the yield (17 mg, 51% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.39-8.31 (m, 3 H), 8.27 (s, 1 H), 7.72 (s, 1 H), 7.65 (s, 1 H), 7.62-7.60 (m, 2 H), 7.18 (s, 1 H), 7.01 (s, 1 H), 4.45-4.29 (m, 4 H), 3.92 (s, 3 H), 3.87 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.86, 138.82, 138.65, 137.41, 133.80, 133.54, 133.24, 133.10, 126.56, 126.13, 125.68, 124.69, 118.92, 118.39, 53.30. HRMS (ESI) Calcd for $C_{22}H_{22}N_6O_8S_2$ $(M+H)^+$ 563.1013, found 563.1004.

N,N'-(Naphthalene-1,4-diyl)bis(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-sulfonamide) (**63q**)



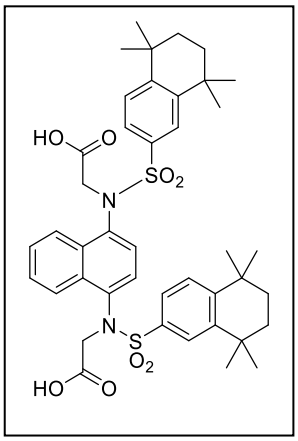
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as an off-white solid; the yield (515 mg, 78% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.63-7.61 (m, 2 H), 7.42-7.37 (m, 4 H), 7.29-7.19 (m, 5 H), 1.57-1.52 (m, 8 H), 7.161.17 (s, 12 H), 0.94 (s, 12 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 150.52, 145.99, 136.15, 131.05, 130.33, 127.39, 126.18, 125.62, 123.64, 123.54, 122.56, 34.53, 34.49, 31.47, 31.21.

Diethyl 2,2'-(naphthalene-1,4-diylbis(((5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl) sulfonyl) azanediyl))diacetate (**64q**)



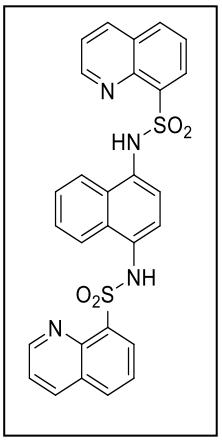
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (68 mg, 82% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.80-7.77 (m, 2 H), 7.56-7.52 (m, 2 H), 7.49 (s, 1 H), 7.44-7.33 (m, 7 H), 4.68-4.56 (m, 2 H), 4.23-4.08 (m, 6 H), 1.67-1.60 (m, 8 H), 1.30-1.13 (m, 24 H), 1.00-1.88 (m, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.75, 150.91, 150.86, 146.38, 146.07, 137.17, 135.90, 135.76, 132.98, 128.60, 128.55, 127.54, 127.18, 126.98, 126.73, 124.54, 124.44, 124.12, 61.52, 53.30, 53.16, 34.83, 34.80, 34.72, 34.55, 31.87, 31.82, 31.72, 31.69, 31.26, 14.20, 14.14.

2,2'-(Naphthalene-1,4-diylbis(((5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)sulfonyl)azanediyl))diacetic acid (**65q**)



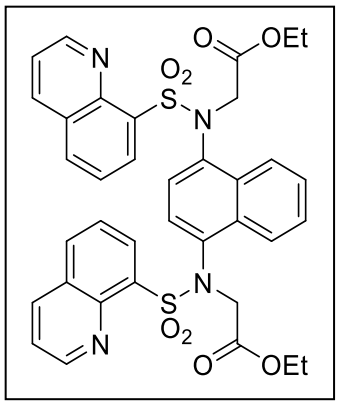
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; the yield (28 mg, 85% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 12.50 (br, 2 H), 7.74-7.72 (m, 2 H), 7.56-7.52 (m, 4 H), 7.38-7.26 (m, 5 H), 7.17 (s, 1 H), 4.57-4.51 (m, 2 H), 4.26-4.21 (m, 2 H), 1.63-1.53 (m, 8 H), 1.28-1.22 (m, 15 H), 1.18 (s, 3 H), 1.17 (s, 3 H), 1.04 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.96, 169.87, 150.22, 145.54, 145.31, 136.63, 136.50, 135.39, 135.04, 132.29, 132.22, 127.87, 127.63, 126.32, 125.74, 124.03, 123.91, 123.85, 52.86, 34.32, 34.26, 33.97, 33.93, 33.86, 31.38, 31.33, 31.25, 31.13, 30.97, 30.74, 30.64. HRMS (ESI) Calcd for $C_{42}H_{50}N_2O_8S_2$ $(M+H)^+$ 775.3081, found 775.3059.

N,N'-(Naphthalene-1,4-diyl)bis(quinoline-8-sulfonamide) (**63r**)



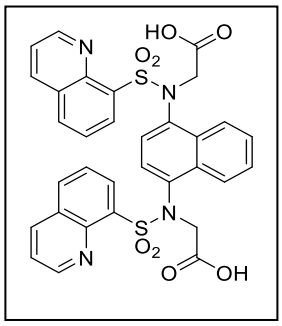
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a light yellow solid; the yield (379 mg, 70% yield). ^{1}H NMR (400 MHz) (MeOH-d4) δ 9.27 (s, 2 H), 9.26 (d, 1 H, *J*= 4.0 Hz), 9.05 (dd, 2 H, *J*= 2.0 Hz, 4.0 Hz), 8.50 (dd, 1 H, *J*= 1.6 Hz, 4.4 Hz), 8.37 (dd, 1 H, *J*= 1.2 Hz, 7.2 Hz), 8.30 (d, 1 H, *J*= 7.6 Hz), 8.21 (dd, 1 H, *J*= 1.2 Hz, 8.0 Hz), 8.07 (dd, 1 H, *J*= 1.2 Hz, 7.2 Hz), 7.95 (dd, 1 H, *J*= 1.6 Hz, 6.4 Hz), 7.88-7.84 (m, 2 H), 7.86 (t, 1 H, *J*= 7.6 Hz), 7.71-7.68 (m, 2 H), 7.58 (t, 2 H, *J*= 7.6 Hz), 7.18-7.15 (m, 1 H), 6.75 (s, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 151.03, 142.48, 136.71, 135.66, 133.68, 130.90, 130.84, 130.41, 129.79, 128.52, 128.14, 125.32, 125.26, 123.14, 122.27, 121.75, 121.66

Diethyl 2,2'-(naphthalene-1,4-diylbis((quinolin-8-ylsulfonyl)azanediyl))diacetate (64r)



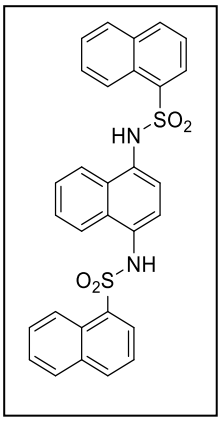
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (113 mg, 79% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 9.15-9.14 (m, 2 H), 8.34-8.27 (m, 3 H), 8.19-8.13 (m, 2 H), 8.07-7.99 (m, 2 H), 7.87-7.85 (m, 1 H), 7.76-7.75 (m, 1 H), 7.63-758 (m, 2 H), 7.51-7.39 (m, 2 H), 7.21 (s, 1 H), 7.13-7.11 (m, 1 H), 7.04-7.03 (m, 1 H), 5.48-5.42 (m, 2 H), 4.81-4.71 (m, 2 H), 4.09-4.00 (m, 4 H), 1.16 (s, 3 H), 1.14 (s, 3 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.97, 151.26, 144.28, 137.97, 136.92, 133.75, 133.51, 133.31, 129.12, 126.84, 126.66, 125.78, 124.02, 123.91, 122.22, 61.20, 54.88, 54.71, 14.34, 14.19.

2,2'-(Naphthalene-1,4-diylbis((quinolin-8-ylsulfonyl)azanediyl))diacetic acid (65r)



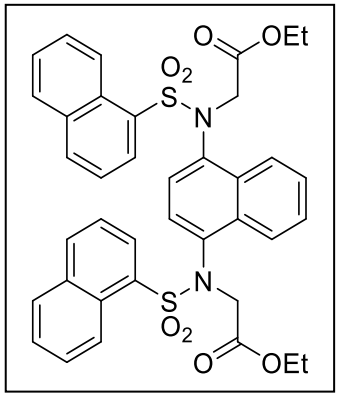
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a beige solid; the yield (18 mg, 74% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 9.18-9.13 (m, 2 H), 8.58 (d, 2 H, J= 8.0 Hz), 8.29-8.22 (m, 2 H), 7.98 (d, 2 H, J= 7.2 Hz), 7.78-7.51 (m, 6 H),7.22-7.06 (m, 4 H), 5.27-5.05 (m, 2 H), 4.80-4.71 (m, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.80, 151.50, 143.13, 137.17, 136.92, 136.66, 136.49, 134.28, 132.41, 128.72, 128.39, 126.08, 125.57, 123.60, 122.62, 54.23. HRMS (ESI) Calcd for $C_{32}H_{24}N_4O_8S_2$ $(M+H)^+$ 657.1108, found 657.1092.

N,N'-(Naphthalene-1,4-diyl)bis(quinoline-8-sulfonamide) (63s)



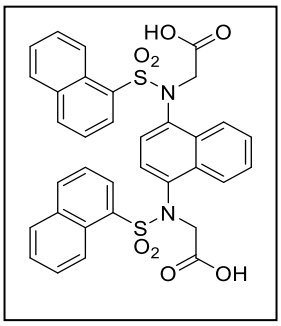
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as an off-white solid; the yield (414 mg, 77% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.49 (br, 2 H), 8.72-8.70 (m, 2 H), 8.14 (d, 3 H, *J*= 8.0 Hz), 8.03-8.01 (m, 2 H), 7.92 (d, 2 H, *J*= 7.2 Hz), 7.78-7.75 (m, 3 H), 7.62-7.60 (m, 4 H), 7.48 (t, 2 H, *J*= 8.0 Hz), 7.11-7.09 (m, 2 H), 6.93 (s, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 134.94, 134.13, 133.63, 130.67, 129.73, 129.21, 128.90, 127.77, 127.48, 126.78, 125.83, 124.46, 124.30, 122.93, 122.39.

Diethyl 2,2'-(naphthalene-1,4-diylbis((naphthalen-1-ylsulfonyl)azanediyl))diacetate (64s)



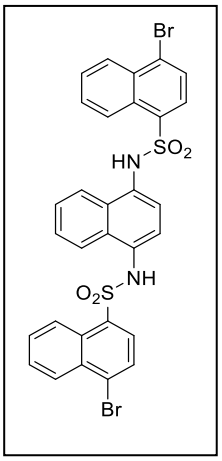
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (90 mg, 63% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.43 (d, 1 H, *J*= 8.8 Hz), 8.35 (d, 1 H, *J*= 8.8 Hz), 8.18-8.13 (m, 2 H), 8.06 (d, 1 H, *J*= 8.0 Hz), 8.00 (d, 1 H, *J*= 8.0 Hz), 7.90 (d, 1 H, *J*= 8.0 Hz), 7.84-7.78 (m, 2 H), 7.72-7.69 (m, 1 H), 7.55-7.40 (m, 5 H), 7.33-7.28 (m, 2 H), 7.23 (s, 2 H), 7.15-7.12 (m, 1 H), 4.79-4.69 (m, 2 H), 4.29-4.21 (m, 2 H), 4.14-3.89 (m, 4 H), 1.11-1.04 (m, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.69, 168.58, 137.01, 136.94, 134.86, 134.82, 134.44, 134.35, 132.86, 132.74, 130.82, 129.08, 128.90, 128.84, 128.67, 128.24, 127.81, 127.30, 127.09, 127.06, 126.86, 125.66, 125.58, 124.21, 124.15, 124.03, 123.92, 61.62, 61.56, 53.34, 53.19, 14.05, 14.02.

2,2'-(Naphthalene-1,4-diylbis((naphthalen-1-ylsulfonyl)azanediyl))diacetic acid (65s)



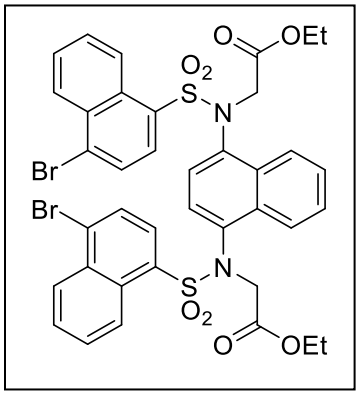
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; the yield (27 mg, 78% yield). ^{1}H NMR (400 MHz) (MeOH-d4) δ) 8.38-8.36 (m, 1 H), 8.14-7.94 (m, 5 H), 8.00-7.95 (m, 1 H),7.94-7.82 (m, 1 H), 7.60-7.37 (m, 8 H), 7.29-7.27 (m, 2 H), 7.00-6.96 (m, 2H), 4.79-4.67 (m, 2 H), 4.34-4.20 (m, 2 H). ^{13}C NMR (100 MHz) (MeOH-d4) δ 171.96, 170.94, 138.12, 138.02, 136.01, 135.89, 135.68, 133.76, 131.95, 131.85, 131.60, 131.49, 130.16, 130.00, 129.96, 129.75, 129.07, 128.59, 128.00, 127.77, 127.66, 127.53, 126.53, 126.48, 126.19, 125.27, 124.90, 124.80, 54.28, 53.94. HRMS (ESI) Calcd for $C_{34}H_{26}N_2O_8S_2$ $(M+H)^+$ 654.1203, found 655.1194.

N,N'-(Naphthalene-1,4-diyl)bis(4-bromonaphthalene-1-sulfonamide) (**63t**)



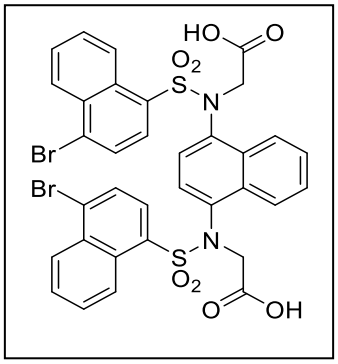
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a yellow solid; the yield (468 mg, 67% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.65 (s, 2 H), 8.77 (d, 2 H, *J*= 8.4 Hz), 8.25 (d, 2 H, *J*= 8.4 Hz), 7.92-7.69 (m, 10 H), 7.13 (dd, 2 H, *J*= 2.8 Hz, 6.0 Hz), 6.99 (s, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 135.39, 131.60, 130.66, 129.87, 129.52, 128.79, 128.77, 128.69, 128.61, 128.43, 127.50, 126.02, 125.29, 122.92, 122.85.

Diethyl 2,2'-(naphthalene-1,4-diylbis(((4-bromonaphthalen-1-yl)sulfonyl)azanediyl)) diacetate (**64t**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (111 mg, 64% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.42-8.28 (m, 2 H), 8.30 (d, 1 H, *J*= 8.4 Hz), 8.04-7.98 (m, 2 H), 7.84-7.81 (m, 2 H), 7.76 (d, 1 H, *J*= 8.0 Hz), 7.72-7.69 (m, 1 H), 7.63 (t, 1 H, *J*= 8.4 Hz), 7.57 (t, 1 H, *J*= 8.4 Hz), 7.45 (t, 1 H, *J*= 7.6 Hz), 7.37 (s, 1 H), 7.34-7.28 (m, 2 H), 7.20-7.17 (m, 1 H), 4.80-4.70 (m, 2 H), 4.28-4.18 (m, 2 H), 4.10-3.86 (m, 4 H), 1.13-1.05 (m, 6 H)..^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.50, 168.41, 136.86, 136.81, 134.88, 134.70, 132.73, 132.68, 132.63, 130.63, 130.59, 130.45, 130.40, 129.92, 128.96, 128.88, 128.69, 128.56, 128.52, 128.47, 128.23, 128.16, 128.12, 127.50, 127.29, 126.09, 126.02, 123.91, 123.81, 61.71, 61.63, 53.27, 53.12, 14.03, 13.99.

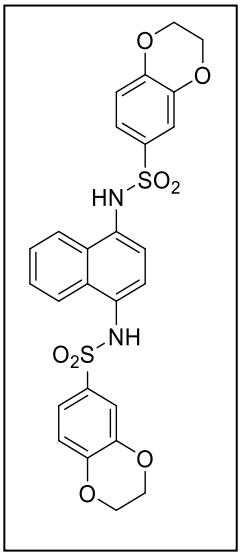
2,2'-(Naphthalene-1,4-diylbis(((4-bromonaphthalen-1-yl)sulfonyl)azanediyl))diacetic acid (**65t**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as yellow solid; the yield (14 mg, 71% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.32 (t, 2 H, *J*= 8.0 Hz), 8.20 (d, 1 H, *J*= 8.4 Hz), 8.11-8.00 (m, 4 H), 7.94 (d, 1 H, *J*= 8.0 Hz), 7.90-7.87 (m, 1 H), 7.77 (t, 1 H, *J*=

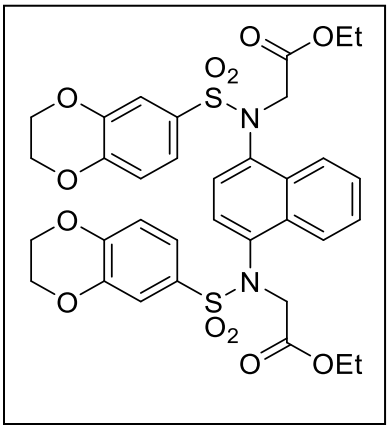
7.6 Hz), 7.72-7.70 (m, 1 H), 7.62 (t, 1 H, *J*= 8.0 Hz), 7.50 (t, 1 H, *J*= 8.0 Hz), 7.38 (s, 1 H), 7.31-7.27 (m, 2 H), 7.19-7.16 (m, 1 H), 7.10 (s, 1 H), 4.69-4.61 (m, 2 H), 4.40-4.27 (m, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 171.88, 169.61, 136.29, 134.35, 134.01, 132.28, 132.05, 131.76, 131.54, 130.77, 130.52, 129.22, 129.17, 129.07, 129.01, 128.90, 128.67, 128.48, 128.33, 128.20, 127.88, 127.42, 127.13, 126.49, 125.60, 125.46, 123.90, 123.63, 55.08, 52.75. HRMS (ESI) Calcd for $C_{34}H_{24}Br_2N_2O_8S_2$ $(M+H)^+$ 810.9414, found 810.9452

N,N'-(Naphthalene-1,4-diyl)bis(2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonamide) (63u)



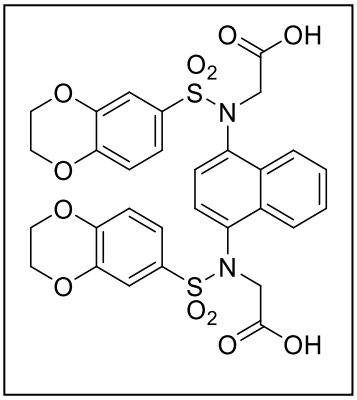
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as an off-white solid; the yield (439 mg, 79% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.26 (s, 2 H), 8.19-8.16 (m, 2 H), 7.65-7.62 (m, 2 H), 7.32 (d, 2 H, *J*= 2.0 Hz), 7.28 (d, 1 H, *J*= 2.0 Hz), 7.26-7.25 (m, 3 H), 7.12 (s, 1 H), 7.10 (s, 1 ah), 4.48-4.44 (m, 8 H). ^{13}C NMR (100 MHz) (DMSO) δ 147.03, 143.15, 132.16, 131.02, 130.02, 126.09, 123.30, 122.62, 120.30, 117.35, 115.68, 64.33, 63.98.

Diethyl 2,2'-(naphthalene-1,4-diylbis(((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl) azanediyl))diacetate (64u)



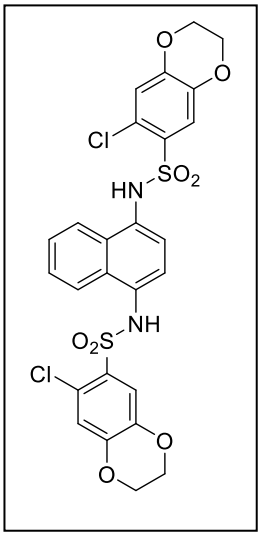
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (94 mg, 65% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.13-8.10 (m, 2 H), 7.57-7.52 (m, 2 H),, 7.29-7.14 (m, 6 H), 6.90 (t, 2 H, *J*= 8.4 Hz), 74.70-4.56 (m, 2 H), 4.33-4.26 (m, 10 H), 4.15-4.09 (m, 4 H), 41.27-1.17 (m, 6 H).^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.73, 168.66, 147.79, 147.75, 143.41, 143.39, 137.26, 137.11, 133.11, 133.04, 131.36, 130.65, 127.57, 127.43, 127.24, 124.25, 121.97, 121.76, 117.69, 117.62, 117.50, 117.45, 64.56, 64.12, 61.44, 53.22, 53.10, 13.99.

2,2'-(Naphthalene-1,4-diylbis(((2,3-dihydrobenzo[b][1,4] dioxin-6-yl) sulfonyl) azanediyl)) diacetic acid (**65u**)



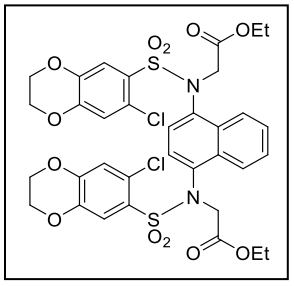
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a beige solid; the yield (21 mg, 76% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.26-8.13 (m, 2 H), 7.58-7.56 (m, 2 H), 7.20-7.15 (m, 3 H), 7.06-6.96 (m, 5 H), 4.50-4.30 (m, 12 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.82, 147.66, 143.33, 137.01, 132.86, 132.74, 130.20, 129.66, 126.79, 126.53, 126.36, 124.54, 124.41, 121.60, 121.36, 117.44, 117.31, 116.75, 116.62, 64.49, 64.05, 53.10. HRMS (ESI) Calcd for $C_{30}H_{26}N_2O_{12}S_2$ $(M+H)^+$ 671.1000, found 671.0994.

N,N'-(Naphthalene-1,4-diyl)bis(7-chloro-2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonamide) (**63v**)



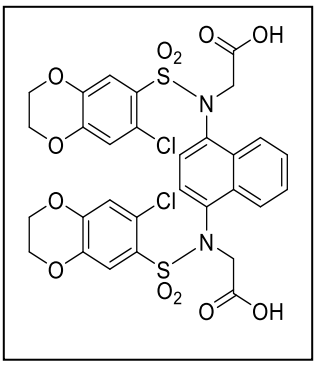
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a pink solid; the yield (368 mg, 59% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.35 (s, 2 H), 8.15 (dd, 2 H, *J*= 3.2 Hz, 6.4 Hz), 7.50 (dd, 2 H, *J*= 3.2 Hz, 6.4 Hz), 7.25 (s, 2 H), 7.12 (d, 2 H, *J*= 3.2 Hz), 4.29 (t, 4 H, *J*= 2.8 Hz), 4.24 (t, 4 H, *J*= 3.2 Hz). ^{13}C NMR (100 MHz) (DMSO) δ 147.36, 141.76, 130.23, 129.57, 126.31, 1213.34, 122.70, 122.66, 119.73, 119.36, 64.52, 63.99, 59.70, 20.71, 14.05.

D**iethyl 2,2'-(naphthalene-1,4-diylbis(((7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl) azanediyl))diacetate** (**64v**)



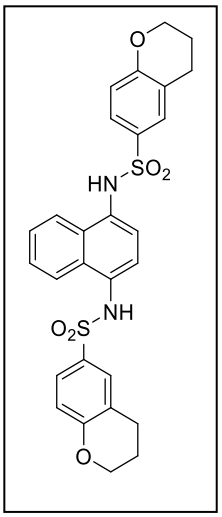
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (97 mg, 61% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.08-8.06 (m, 2 H), 7.53-7.47 (m, 4 H), 7.18-7.14 (m, 4 H), 4.82-4.73 (m, 2 H), 4.55-4.49 (m, 2 H), 4.33-4.24 (m, 8 H), 4.06-4.02 (m, 4 H), 1.12-1.06 (m, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 168.58, 168.37, 147.79, 141.87, 136.09, 132.15, 128.26, 127.89, 126.76, 123.73, 123.18, 120.34, 120.03, 119.90, 64.65, 64.00, 60.94, 53.63, 13.79.

2,2'-(Naphthalene-1,4-diylbis(((7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl) azanediyl))diacetic acid (**65v**)



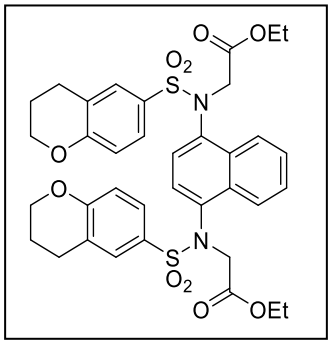
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a pink solid; the yield (26 mg, 75% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 12.92 (s, 2 H), 8.05-8.03 (m, 2 H), 7.56 (s, 1 H), 7.50-7.13 (m, 3 H), 7.17 (s, 2 H), 7.15 (s, 1 H), 7.13 (s, 1 H), 4.77-4.67 (m, 2 H), 4.44-4.39 (m, 2 H), 4.34-4.28 (m, 4 H), 4.28-4.23 (m, 4 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.08, 169.92, 147.74, 141.90, 136.16, 132.18, 128.53, 128.26, 126.88, 126.71, 123.75, 123.22, 120.35, 120.16, 120.02, 119.92, 64.70, 64.06, 53.68. HRMS (ESI) Calcd for $C_{30}H_{24}Cl_2N_2O_{12}S_2$ $(M+H)^+$ 739.0220, found 739.0238.

N,N'-(Naphthalene-1,4-diyl)bis(chromane-6-sulfonamide) (**63w**)



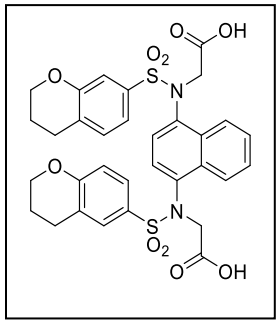
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a beige solid; the yield (452 mg, 81% yield). ^{1}H NMR (400 MHz) (DMSO) δ 9.97 (s, 2 H), 7.97 (dd, 2 H, *J*= 3.2 Hz, 6.4 Hz), 7.42 (dd, 2 H, *J*= 3.2 Hz, 6.4 Hz), 7.36-7.32 (m, 4 H), 7.04 (s, 2 H), 6.77 (d, 2 H, *J*= 8.4 Hz), 4.17 (t, 4 H, *J*= 4.8 Hz), 2.64 (t, 4 H, *J*= 6.0 Hz), 1.88-1.86 (m, 4 H). ^{13}C NMR (100 MHz) (DMSO) δ 157.86, 131.12, 130.79, 130.04, 128.86, 126.12, 125.94, 123.36, 122.82, 122.56, 116.67, 66.49, 23.96, 21.05.

Diethyl 2,2'-(naphthalene-1,4-diylbis((chroman-6-ylsulfonyl)azanediyl))diacetate (**64w**)



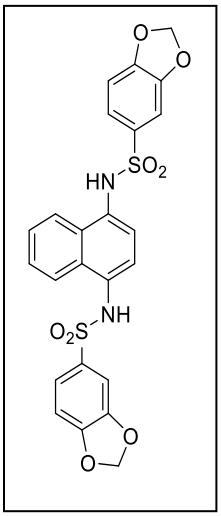
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (88 mg, 61% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.09 (dd, 1 H, *J*= 3.2 Hz, 6.4 Hz), 8.00 (dd, 1 H, *J*= 3.2 Hz, 6.4 Hz), 7.52 (dd, 2 H, *J*= 3.2 Hz, 6.4 Hz), 7.47-7.22 (m, 6 H), 6.82-6.78 (m, 3 H), 4.65-4.54 (m, 2 H), 4.29-4.28 (m, 2 H), 4.25-4.21 (m, 4 H), 4.13-4.07 (m, 4 H), 2.72-2.68 (m, 4 H), 2.00-1.98 (m, 4 H), 1.17 (t, 6 H, *J*= 7.2 Hz).^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.84, 168.75, 158.99, 158.95, 137.31, 137.19, 133.15, 132.99, 130.38, 130.27, 129.63, 129.26, 127.87, 127.57, 127.47, 127.08, 124.35, 124.19, 122.63, 122.56, 117.14, 66.98, 61.41, 53.07, 24.70, 21.66, 14.02.

N-(4-(N-(Carboxymethyl)chromane-6-sulfonamido)naphthalen-1-yl)-N-(chroman-7-ylsulfonyl) glycine (**65w**)



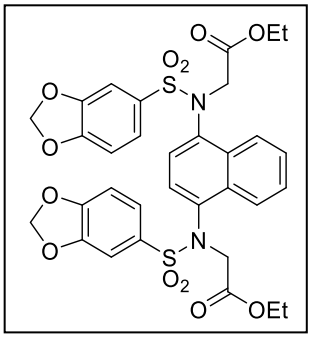
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as an off-white solid; the yield (19 mg, 77% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.21-8.20 (m, 2 H), 7.57-7.55 (m, 2 H), 7.42 (s, 1 H), 7.32-7.27 (m, 3 H), 7.12 (s, 1 H), 7.09 (s, 1 H), 6.88-6.83 (m, 2 H), 4.41 (s, 2 H), 4.39 (s, 2 H), 4.23 (t, 4 H, *J*= 6.8 Hz), 2.76-2.69 (m, 4 H), 1.95-1.94 (m, 4 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.93, 158.49, 137.13, 137.07, 132.84, 129.99, 128.44, 127.26, 127.05, 126.71, 126.44, 124.55, 123.16, 116.78, 116.63, 66.70, 53.09, 24.09, 23.96, 21.11. HRMS (ESI) Calcd for $C_{32}H_{30}N_2O_{10}S_2$ $(M+H)^+$ 667.1415, found 667.1410.

N,N'-(Naphthalene-1,4-diyl)bis(benzo[d][1,3]dioxole-5-sulfonamide) (**63x**)



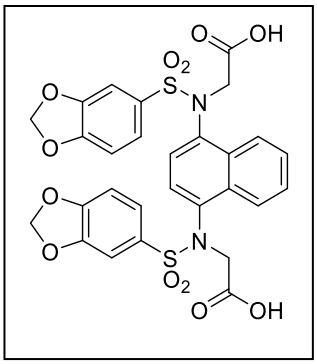
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a light pink solid; the yield (401 mg, 74% yield). ^{1}H NMR (400 MHz) (DMSO) δ 10.15 (s, 2 H), 8.05-8.03 (m, 2 H), 7.50-7.48 (m, 2 H), 7.18 (d, 1 H, *J*= 2.0 Hz), 7.16 (s, 3 H), 7.09 (s, 2 H), 6.99 (d, 2 H, *J*= 8.8 Hz), 6.16 (s, 4 H). ^{13}C NMR (100 MHz) (DMSO) δ 150.93, 147.73, 133.04, 131.10, 130.19, 126.24, 123.41, 122.88, 122.50, 108.15, 106.57, 102.49.

Diethyl 2,2'-(naphthalene-1,4-diylbis((benzo[d][1,3]dioxol-5-ylsulfonyl) azanediyl)) diacetate (**64x**)



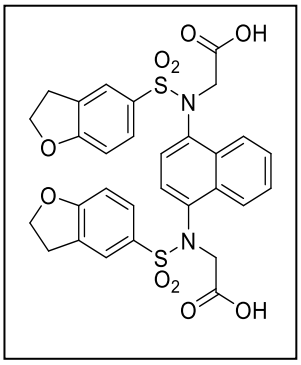
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (106 mg, 76% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.36 (dd, 1 H, *J*= 2.8 Hz, 6.0 Hz), 8.23 (dd, 1 H, *J*= 3.2 Hz, 6.0 Hz), 7.64-7.62 (m, 2 H), 7.24-7.16 (m, 5 H), 7.17 (d, 1 H, *J*= 8.4 Hz), 7.02-6.99 (m, 2 H), 6.21 (d, 2 H, *J*= 2.0 Hz), 6.16 (d, 2 H, *J*= 6.0 Hz), 4.64-4.47 (m, 4 H), 4.07-3.97 (m, 4 H), 1.10-1.04 (m, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 168.15, 151.29, 151.22, 147.63, 136.70, 132.67, 132.49, 130.52, 129.89, 126.50, 126.40, 125.96, 124.33, 124.11, 123.66, 123.35, 107.85, 107.28, 107.18, 102.37, 60.60, 53.02, 52.92, 13.42.

2,2'-(Naphthalene-1,4-diylbis((benzo[d][1,3]dioxol-5-ylsulfonyl) azanediyl)) diacetic acid (**65x**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a pink solid; the yield (17 mg, 62% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.29 (s, 1 H), 8.17 (s, 1 H), 7.58 (s, 2 H), 7.19-7.00 (m, 8 H), 6.21-6.17 (m, 4 H), 4.48-4.35 (m, 4 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.88, 151.48, 151.42, 147.90, 147.86, 137.00, 132.92, 132.75, 131.07, 130.41, 126.88, 126.67, 126.57, 126.34, 124.63, 124.43, 123.89, 123.62, 108.12, 107.58, 107.48, 102.63, 53.23, 53.12. HRMS (ESI) Calcd for $C_{28}H_{22}N_2O_8S_2$ $(M+H)^+$ 643.0687, found 643.0683.

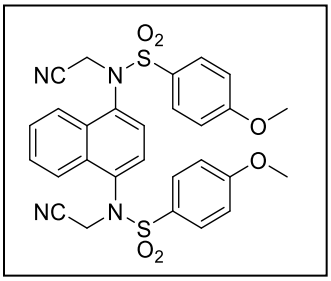
2,2'-(Naphthalene-1,4-diylbis(((2,3-dihydrobenzofuran-5-yl)sulfonyl) azanediyl)) diacetic acid (**65x**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as light-pink solid; the yield (21 mg, 72% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 12.75 (s, 1 H), 8.27-8.22 (m, 2 H), 7.59-7.56 (m, 3 H), 7.48 (s, 1 H), 7.37 (d, 1 H, *J*= 8.4 Hz), 7.33 (d, 1 H, *J*= 8.4 Hz), 7.11 (s, 1 H), 7.05 (s, 1 H), 6.90 (d, 1 H, *J*= 8.8 Hz), 6.86 (d, 1 H, *J*= 8.8 Hz), 4.71-4.63 (m, 4 H), 4.42 (s, 2 H), 4.40 (s, 2 H), 3.28-3.19 (m, 4 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.43, 163.21, 136.68, 132.41, 128.89, 132.41,

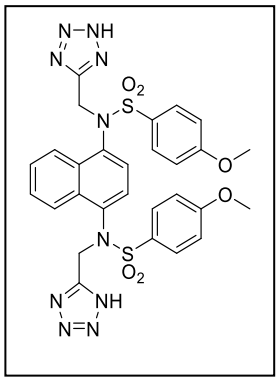
128.89, 128.65, 128.44, 126.21, 126.02, 124.65, 124.11, 108.48, 108.33, 71.87, 52.65, 27.95. HRMS (ESI) Calcd for $C_{30}H_{26}N_2O_{10}S_2$ $(M+H)^+$ 639.1102, found 639.1115.

N,N'-(Naphthalene-1,4-diyl)bis(N-(cyanomethyl)-4-methoxybenzenesulfonamide) (**66a**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (128 mg, 74% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) 8.09-8.08 (m, 2 H), 8.19-8.09 (m, 2 H), 7.75-6.36 (m, 6 H), 7.05-7.00 (m, 6 H), 5.11-4.93 (m, 2H), 4.32-4.25 (m, 2H), 3.93 (s, 3 H), 3.89 (s, 3 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 164.14, 136.77, 133.47, 130.61, 130.46, 129.16, 129.00, 126.81, 126.48, 123.86, 114.84, 114.81, 114.63, 55.90, 40.07, 39.98.

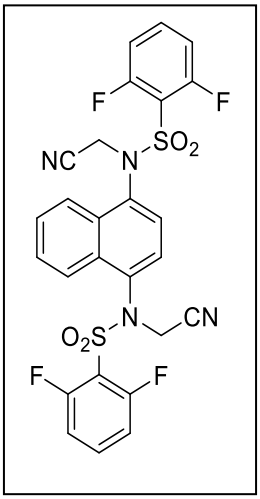
N-((1*H*-Tetrazol-5-yl)methyl)-N-(4-((N-((2*H*-tetrazol-5-yl)methyl)-4-methoxyphenyl) sulfonamido)naphthalen-1-yl)-4-methoxybenzenesulfonamide (**67a**)



Prepared as described in the general procedure for synthesis of tetrazole (Method D) to get the title compound as a white solid; the yield (23 mg, 77% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.15-8.13 (m, 1 H), 8.05-8.02 (m, 1 H), 7.60-7.49 (m, 6 H), 7.17 (d, 2 H, *J*= 8.8 Hz), 7.07 (d, 2 H, *J*= 8.8 Hz), 6.79 (s, 1 H), 6.75 (s, 1 H), 5.35-5.23 (m, 2 H), 5.12-4.97 (m, 2 H), 3.91 (s, 3 H), 3.86 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 163.19, 163.12, 162.36, 136.55, 136.00, 133.08, 132.88, 130.28, 130.10, 123.10, 128.01, 126.96, 126.33, 125.95, 124.09, 123.97, 114.52, 114.47,

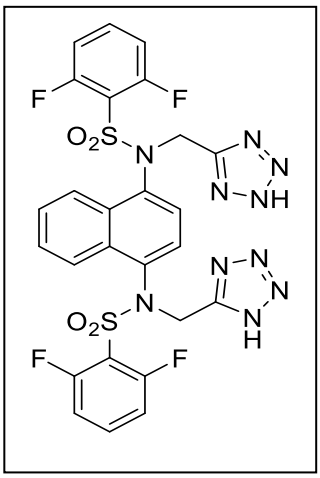
55.85, 55.78, 45.38, 44.82. HRMS (ESI) Calcd for $C_{28}H_{26}N_{10}O_6S_2$ $(M+H)^+$ 663.1551, found 663.1538.

N,N'-(Naphthalene-1,4-diyl)bis(N-(cyanomethyl)-2,6-difluorobenzenesulfonamide) (**66b**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (128 mg, 73% yield). ^{1}H NMR (400 MHz) (DMSO) δ 8.17-8.15 (m, 1 H), 8.09-8.08 (m, 1 H), 7.95- 7.83 (m, 2 H), 7.79-7.76 (m, 2 H), 7.41-7.35 (m, 5 H), 7.27 (s, 1 H) 5.22-5.08 (m, 4H). ^{13}C NMR (100 MHz) (DMSO) δ 162.31, 160.18, 157.71, 157.60, 137.39, 135.43, 135.37, 132.65, 132.45, 128.28, 128.23, 126.93, 126.38, 123.55, 123.49, 115.80, 115.69, 115.13, 114.56, 114.42, 114.11, 113.99, 113.87, 113.75, 38.87. ^{19}F NMR (377 MHz, DMSO): δ – 105.27 (s, 1F) – 104.29 (s, 1F).

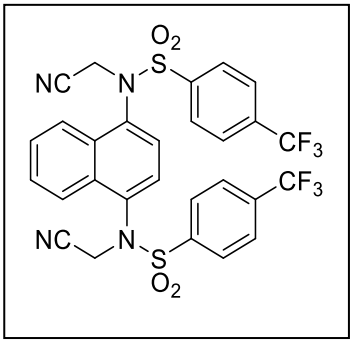
N-((1*H*-Tetrazol-5-yl)methyl)-N-(4-((N-((2*H*-tetrazol-5-yl)methyl)-2,6-difluorophenyl) sulfonamido)naphthalen-1-yl)-2,6-difluorobenzenesulfonamide (**67b**)



Prepared as described in the general procedure for synthesis of tetrazole (Method D) to get the title compound as a beige solid; the yield (19 mg, 72% yield). ^{1}H NMR (400 MHz) (MeOH-d4) δ) 7.94-7.91 (m, 1 H), 7.85-7.83 (m, 1 H), 7.71-7.66 (m, 3 H), 7.48-7.41 (m, 2 H), 7.21 (s, 1 H), 7.17-7.08 (m, 4 H), 5.50- 5.33 (m, 4 H). ^{13}C NMR (100 MHz) (MeOH-d4) δ 162.50, 155.48, 137.56, 137.22, 136.97, 134.51, 134.30, 129.15, 128.78, 128.56,

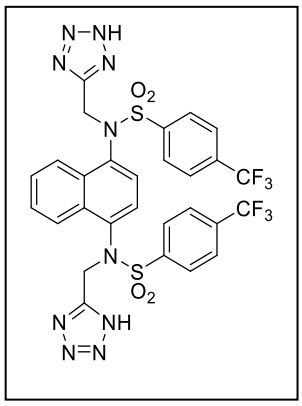
124.90, 124.81, 114.78, 114.56, 61.54, ^{19}F NMR (377 MHz, MeOH-d4): δ – 106.04 (s, 2F), – 106.21 (s, 2F). HRMS (ESI) Calcd for $C_{26}H_{18}F_4N_{10}O_4S_2$ $(M+H)^+$ 675.0963, found 675.0954.

N,N'-(Naphthalene-1,4-diyl)bis(N-(cyanomethyl)-4-(trifluoromethyl) benzenesulfonamide) (**66c**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (17 mg, 69% yield). ^{1}H NMR (400 MHz) (DMSO) 8.14-7.99 (m, 10 H), 7.78-7.72 (m, 2 H), 7.23 s, 1 H), 6.95 (s, 1 H), 5.14- 5.00 (m, 4H). ^{13}C NMR (100 MHz) (DMSO) δ 141.05, 140.30, 136.17, 135.94, 133.85, 133.72, 133.53, 133.39, 132.82, 132.71, 129.04, 128.75, 128.20, 126.87, 126.75, 126.47, 124.65, 123.61, 121.94, 116.04, 115.92, 114.53. ^{19}F NMR (377 MHz, DMSO): δ – 61.72 (s, 3F), – 61.89 (s, 3F).

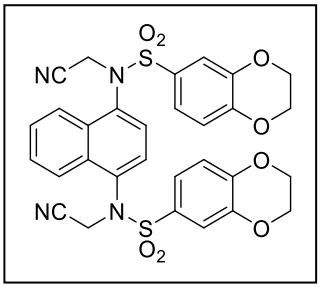
N-((1H-Tetrazol-5-yl)methyl)-N-(4-((N-((2H-tetrazol-5-yl)methyl)-4-(trifluoromethyl) phenyl)sulfonamido)naphthalen-1-yl)-4-(trifluoromethyl)benzenesulfonamide (**67c**)



Prepared as described in the general procedure for synthesis of tetrazole (Method D) to get the title compound as a light yellow solid; the yield (23 mg, 77% yield). ^{1}H NMR (400 MHz) (MeOH-d4) δ) 7.95-7.79 (m, 10 H), 7.44-7.38 (m, 2 H), 6.83 (s, 1 H), 6.80 (s, 1 H), 5.33-5.19 (m, 2 H), 5.12-4.97 (m, 2 H), 3.91 (s, 3 H), 3.86 (s, 3 H). ^{13}C NMR (100 MHz) (MeOH-d4) δ 156.16, 143.35, 142.79, 137.71, 137.26, 135.94, 135.61, 134.74, 134.57, 130.10, 130.02, 128.52, 128.45,

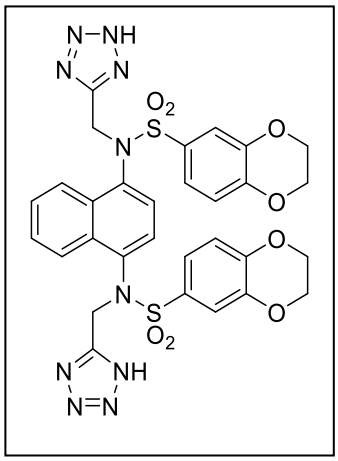
128.42, 128.34, 127.51, 127.47, 126.19, 125.00, 124.97, 123.48. 46.64. ^{19}F NMR (377 MHz, MeOH-d4): δ – 64.56 (s, 3F), – 64.60 (s, 3F). HRMS (ESI) Calcd for $C_{28}H_{20}F_6N_{10}O_4S_2$ $(M+H)^+$ 739.1087, found 739.1070.

N,N'-(Naphthalene-1,4-diyl)bis(N-(cyanomethyl)-2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonamide) (**66d**)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (148 mg, 78% yield). ^{1}H NMR (400 MHz) (DMSO) 8.15-8.12 (m, 1 H), 8.08-8.6 (m, 1 H), 7.77-7.74 (m, 2 H), 7.35-7.33 (m, 2 H), 7.23-7.18 (m, 3 H), 7.14-7.08 (m, 3 H), 5.06-5.00 (m, 4 H), 4.41-4.33 (m, 8 H). ^{13}C NMR (100 MHz) (DMSO) δ 162.28, 148.32, 148.24, 143.68, 136.47, 136.32, 132.93, 132.87, 129.32, 128.66, 127.94, 126.47, 126.15, 123.69, 121.78, 121.50, 117.91, 117.80, 116.89, 116.76, 116.34, 116.24, 64.58, 64.09, 64.05, 38.90.

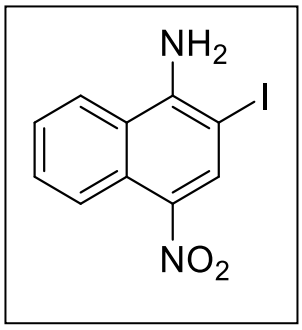
N-((1H-Tetrazol-5-yl)methyl)-N-(4-((N-((2H-tetrazol-5-yl)methyl)-2,3-dihydrobenzo [b] b [1,4]dioxine)-6-sulfonamido)naphthalen-1-yl)-2,3-dihydrobenzo[b][1,4]dioxine-6-sulfonamide (**67d**)



Prepared as described in the general procedure for synthesis of tetrazole (Method D) to get the title compound as a light yellow solid; the yield (35 mg, 75% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.13-8.10 (m, 1 H), 8.04-8.02 (m, 1 H), 7.56-7.54 (m, 2 H), 7.26 (s, 1 H), 7.22 (s, 1 H), 7.09-6.88 (m, 6 H), 5.35-5.25 (m, 2 H), 5.14-5.01 (m, 2 H), 4.41-4.34 (m, 8

H). ^{13}C NMR (100 MHz) (DMSO) δ 147.96, 147.87, 143.52, 136.55, 136.14, 132.98,132.82, 128.80, 128.53, 126.90, 126.33, 125.92, 124.00, 123.91, 121.79, 121.67, 117.47, 116.85, 116.69, 64.52, 64.07, 48.57. HRMS (ESI) Calcd for $C_{30}H_{26}N_{10}O_8S_2$ $(M+H)^+$ 719.1449, found 719.1440.

2-Iodo-4-nitronaphthalen-1-amine (68)



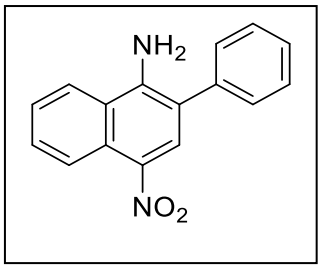
To a stirred solution of 4-nitronaphthalene-1-amine (2.0 g, 10.6 mmol) in methanol/water (10 mL/60 mL), potassium iodide (1.17 g, 7.1 mmol) and potassium iodate (0.76 g, 3.05 mmol) were added and the mixture was stirred for 10 min. Then, dilute HCl (1.2 mL diluted to10 mL) was added during a period of 1 hour, and the reaction stirred overnight at room temperature. Upon completion, the reaction mixture filtered, and the yellow solid washed with water, dilute sodium thiosulfate solution and dried to get the desired product as a yellow solid 3.06 g yield: (91%). ^1H NMR (400 MHz) ($CDCl_3$) δ) 8.90 (d, 1 H, *J*= 8.8 Hz), 8.75 (s, 1 H), 7.83 (d, 1 H, *J*= 8.8 Hz), 7.76-7.72 (m, 1 H), 7.60-7.56 (m, 1 H), 5.44 (br, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 149.25, 136.78, 130.10, 127.06, 125.10, 121.60, 120.94.

General procedure for Suzuki coupling: (Method F)

To a Schlenk tube under argon atmosphere was added 2-iodo-4-nitronaphthalen-1-amine (1 equiv.), phenylboronic acid (1.2 equiv.), $PdCl_2(PPh_3)_2$ (0.02 equiv.), DME: H_2O (1:1), and K_2CO_3 (2 equiv.). and then the flask was degassed with argon three times. The reaction mixture was stirred at 80 °C for overnight. After completion of the reaction, the mixture was diluted with water, and extracted with EtOAc. The organic layer washed with brine,

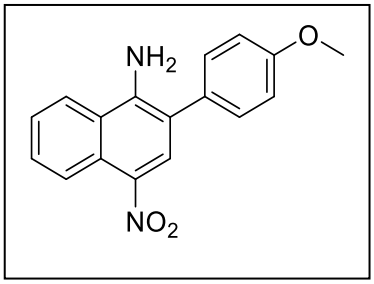
dried over anhydrous Na_2SO_4 and concentrated under reduced pressure followed by purification on an ISCO using silica gel and hexane/ ethyl acetate.

4-Nitro-2-phenylnaphthalen-1-amine (69a)



Prepared as described in the general procedure for Suzuki coupling (Method F) to get the title compound as a yellow solid; 449 mg, yield 85. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 9.00 (d, 1 H, *J*= 8.8 Hz), 8.99 (s, 1 H), 7.90 (d, 1 H, *J*= 8.8 Hz), 7.76-7.72 (m, 1 H), 7.61-7.43 (m, 6 H), 5.11 (br, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 146.33, 137.54, 136.35, 130.01, 129.88, 129.61, 129.60, 128.42, 127.09, 126.41, 124.88, 122.25, 121.55, 119.52.

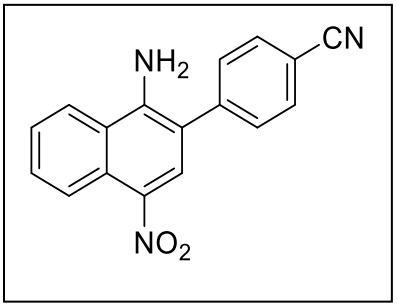
2-(4-Methoxyphenyl)-4-nitronaphthalen-1-amine (69b)



Prepared as described in the general procedure for Suzuki coupling (Method F) to get the title compound as a yellow solid; 232 mg, yield 79%. ^{1}H NMR (400 MHz) (DMSO) δ) 8.90 (d, 1 H, *J*= 8.8 Hz), 8.47 (d, 1 H, *J*= 8.4 Hz), 8.23 (s, 1 H), 7.76-7.72 (m, 1 H), 7.56 (t, 1 H, *J*= 8.0 Hz), 7.42 (d, 2 H, *J*= 8.0 Hz), 7.07 (d, 2 H, *J*= 8.8 Hz), 7.00 (br, 2 H), 3.81 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 158.78, 149.71,

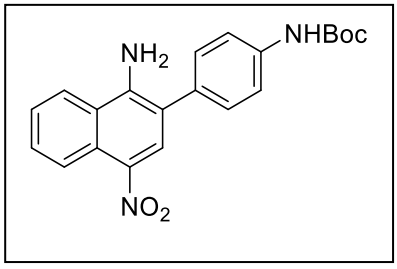
132.26, 130.82, 130.50, 130.02, 129.57, 126.79, 125.39, 123.90, 123.31, 121.28, 117.38, 114.63, 55.12.

4-(1-Amino-4-nitronaphthalen-2-yl) benzonitrile (69c)



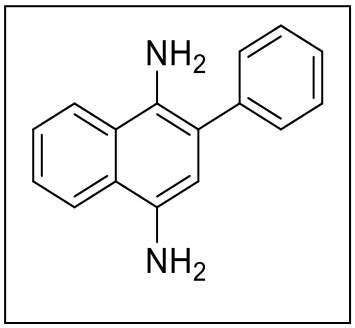
Prepared as described in the general procedure for Suzuki coupling (Method F) to get the title compound as dark brown solid; 453 mg, yield 77%. ^{1}H NMR (400 MHz) (DMSO) δ) 8.86 (d, 1 H, *J*= 8.8 Hz), 8.49 (d, 1 H, *J*= 8.8 Hz), 8.23 (s, 1 H), 7.97 (d, 2 H, *J*= 8.4 Hz), 7.81-7.77 (m, 1 H), 7.72 (d, 2 H, *J*= 8.4 Hz), 7.61-7.57 (m, 1 H), 7.22 (br, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 149.32, 142.47, 132.73, 130.26, 130.22, 126.76, 125.41, 123.70, 123.03, 121.22, 118.56, 115.27, 109.93.

***tert*-Butyl (4-(1-amino-4-nitronaphthalen-2-yl) phenyl) carbamate (69d)**



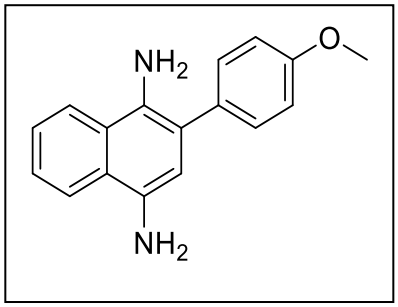
Prepared as described in the general procedure for Suzuki coupling (Method F) to get the title compound as a yellow solid; 585 mg, yield 77%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.97 (d, 1 H, *J*= 8.8 Hz), 8.36 (s, 1 H), 7.88 (d, 1 H, *J*= 8.8 Hz), 7.71-7.67 (m, 1 H), 7.56-7.50 (m, 3 H), 7.39 (d, 1 H, *J*= 8.4 Hz), 6.71 (s, 1 H), 5.15 (br, 2 H), 1.54 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 152.93, 146.72, 138.52, 136.02, 131.91, 130.16, 130.04, 129.79, 127.00, 126.29, 124.72, 122.14, 121.65, 119.58, 118.96, 81.07, 28.46.

2-Phenylnaphthalene-1,4-diamine (70a)



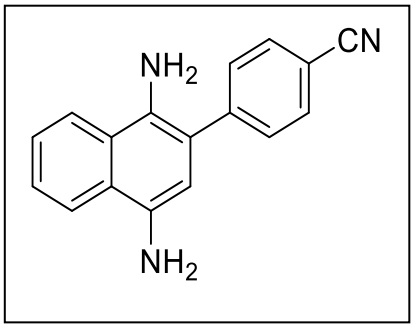
Prepared as described in the general procedure for nitro group reduction (Method E2) to get the title compound as dark yellow solid; 344 mg, quantitative. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.94-7.89 (m, 2 H), 7.52-7.47 (m, 6 H), 7.40-7.36 (m, 1 H), 6.72 (s, 1 H), 3.82 (br, 4 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ. 129.72, 129.01, 127.25, 125.67, 125.22, 122.28, 121.90.

2-(4-Methoxyphenyl)naphthalene-1,4-diamine (70b)



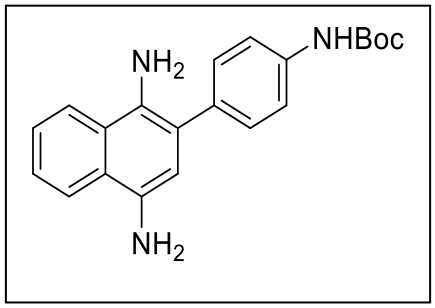
Prepared as described in the general procedure for nitro group reduction (Method E2) to get the title compound as a yellow solid; 261 mg, quantitative. ^{1}H NMR (400 MHz) (DMSO) δ) 7.90-7.85 (m, 2 H), 7.53-7.46 (m, 3 H), 7.41 (d, 2 H, *J*= 8.8 Hz), 7.00 (d, 2 H, *J*= 8.8 Hz), 3.85 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 158.78, 149.71, 132.26, 130.82, 130.50, 130.02, 129.57, 126.79, 125.39, 123.90, 123.31, 121.28, 117.38, 114.63, 55.12.

4-(1,4-Diaminonaphthalen-2-yl) benzonitrile (70c)



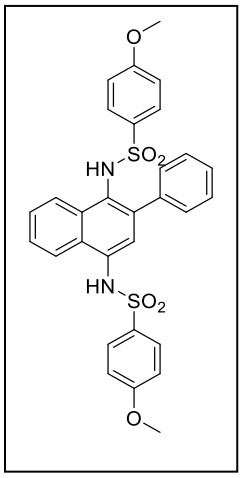
Prepared as described in the general procedure for nitro group reduction (Method E2) to get the title compound as dark solid; 378 mg, quantitative. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.92-7.87 (m, 2 H), 7.74 (d, 2 H, *J*= 8.4 Hz), 7.64 (d, 2 H, *J*= 8.4 Hz), 7.55-7.52 (m, 2 H), 6.23 (s, 1 H), 3.87 (br, 4 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ. 159.09, 143.72, 131.08, 130.99, 130.76, 125.80, 125.30, 125.24, 123.37, 122.43, 122.08, 121.59, 114.77, 114.65, 55.73.

tert-Butyl (4-(1,4-diaminonaphthalen-2-yl) phenyl) carbamate (70d)



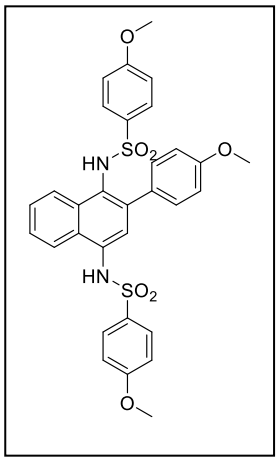
Prepared as described in the general procedure for nitro group reduction (Method E2) to get the title compound as an off-white solid; 519 mg, yield quantitative. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.92-7.86 (m, 2 H), 7.53-7.40 (m, 6 H), 3.86 (br, 4 H), 1.55 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ. 153.75, 137.23, 134.73, 134.12, 131.36, 129.99, 125.34, 125.04, 124.83, 124.48, 122.68, 121.96, 121.60, 118.90, 113.26, 80.54, 28.25.

N,N'-(2-Phenylnaphthalene-1,4-diyl)bis(4-methoxybenzenesulfonamide) (71a)



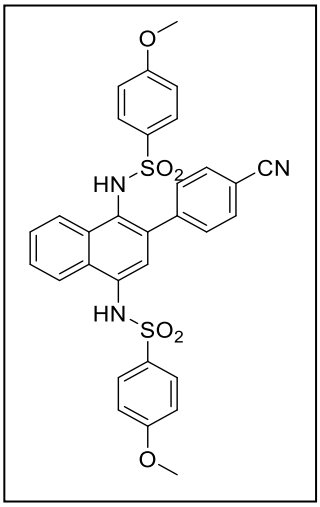
Using general procedure (method A2), 489 mg, yield 85%. ^{1}H NMR (400 MHz) (DMSO) δ) 10.16 (s, 1 H), 9.76 (s, 1 H), 8.14-8.11 (m, 2 H), 7.64 (d, 2 H, J= 8.8 Hz), 7.52-7.50 (m, 2 H), 7.24-7.18 (m, 2 H), 7.09-7.03 (m, 2 H), 6.89 (s, 1 H), 6.70 (d, 2 H, J= 8.8 Hz), 3.82 (s, 3 H), 3.80 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ. 162.53, 161.76, 138.80, 138.68, 133.86, 132.51, 132.41, 131.06, 129.38, 129.15, 129.02, 128.04, 127.75, 126.92, 126.64, 126.58, 126.10, 125.27, 125.17, 123.21, 114.30, 113.82, 55.67, 55.47.

N,N'-(2-(4-Methoxyphenyl)naphthalene-1,4-diyl)bis(4-methoxybenzenesulfonamide) (71b)



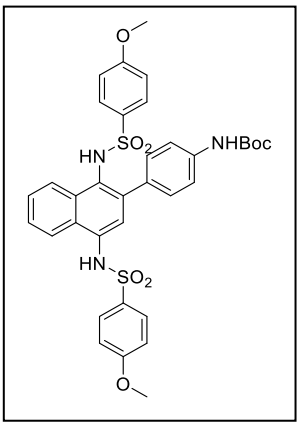
Using general procedure (method A2), Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a beige solid; 472 mg, yield 78%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.50 (d, 1H, J= 8.4 Hz), 7.68-7.66 (m, 2 H), 7.55 (t, 1H, J= 7.2 Hz), 7.48-7.44 (m, 1 H), 7.24 (s, 1 H), 7.07-7.05 (m, 3 H), 6.98 (s, 1 H), 6.84-6.82 (m, 2 H), 6.77-6.70 (m, 4 H), 6.61 (d, 2H, J= 8.8 Hz), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.79 (s, 3 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 163.25, 162.80, 158.92, 136.82, 133.01, 131.36, 130.80, 130.59, 130.39, 129.80, 129.56.29.04, 128.38, 127.06, 126.94, 126.81, 126.49, 124.06, 120.93, 114.15, 114.07, 113.82, 55.61, 55.58, 55.32.

N,N'-(2-(4-Cyanophenyl)naphthalene-1,4-diyl)bis(4-methoxybenzenesulfonamide) (71c)



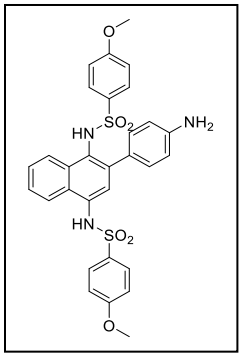
Using general procedure (method A2), Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a yellow solid; 408 mg, yield 68%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.30-8.28 (m, 1 H), 7.84-7.81 (m, 1 H), 7.69 (d, 2 H, *J*= 8.8 Hz), 7.52-7.45 (m, 5 H), 7.29 (s, 1 H), 7.16-7.14 (m, 4 H), 6.95 (br, 1 H), 6.83 (d, 2 H, *J*= 9.2 Hz), 6.64 (d, 2 H, *J*= 8.8 Hz), 3.87 (s, 3 H), 3.79 (s, 3 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ. 163.55, 163.38, 163.25, 162.83, 143.52, 136.64, 133.40, 132.91, 132.56, 1310.16, 130.64, 130.32, 130.09, 129.86, 129.69, 129.64, 129.10, 128.80, 127.81, 127.75, 126.79, 125.76, 122.81, 121.43, 118.69, 114.41, 114.30, 114.19, 114.12, 111.29, 55.85, 55.79,

tert-Butyl (4-(1,4-bis((4-methoxyphenyl) sulfonamido) naphthalen-2-yl) phenyl) carbamate (71d)



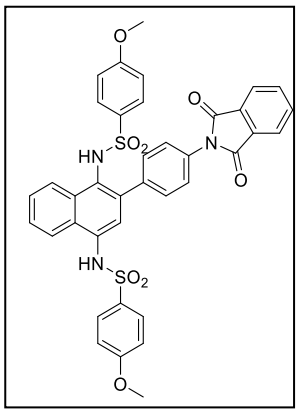
Using general procedure (method A2), Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as an off-white solid; 421 mg, yield 62%. ^{1}H NMR (400 MHz) (MeOH-d_4) δ) 8.31 (d, 1 H, *J*= 8.4 Hz), 8.04 (d, 1 H, *J*= 8.4 Hz), 7.75 (d, 1 H, *J*= 8.8 Hz), 7.64 (s, 1 H), 7.62 (d, 1 H, *J*= 8.8 Hz), 7.51-7.41 (m, 2 H), 7.18 (d, 1 H, *J*= 8.8 Hz), 7.11-7.09 (m, 2 H), 7.00 (s, 1 H), 6.89 (d, 4 H, *J*= 9.2 Hz), 6.61 (d, 2 H, *J*= 9.2 Hz), 3.82 (s, 3 H), 3.81 (s, 3 H), 1.55 (s, 9 H). ^{13}C NMR (100 MHz) (MeOH-d_4) δ.162.93, 162.37, 137.88, 132.82, 132.19, 131.56, 130.83, 129.30, 129.20, 128.42, 126.58, 126.47, 126.13, 125.26, 124.94, 122.19, 117.95, 113.81, 113.48, 80.10, 55.22, 55.11, 27.94.

tert-Butyl (4-(1,4-bis((4-methoxyphenyl) sulfonamido) naphthalen-2-yl) phenyl) carbamate (74)



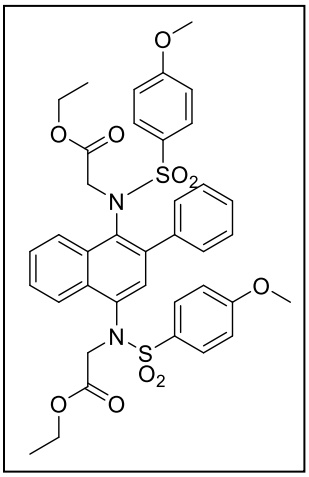
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as an off-white solid; 270 mg, yield 79%. ^{1}H NMR (400 MHz) (MeOH-d_4) δ) 8.01-8.00 (m, 1 H), 7.93-7.91 (m, 1 H), 7.63 (d, 2 H, *J*= 9.2 Hz), 7.45 (s, 1 H), 7.41-7.34 (m, 2 H), 7.16-7.12 (m, 4 H), 7.08 (d, 2 H, *J*= 8.4 Hz), 6.85 (d, 2 H, *J*= 8.8 Hz), 6.66 (d, 2 H, *J*= 8.8 Hz), 3.81 (s, 3 H), 3.79 (s, 3 H).

N,N'-(2-(4-(1,3-Dioxoisoindolin-2-yl)phenyl)naphthalene-1,4-diyl)bis(4-methoxybenzene-sulfonamide) (75)



Intermediate compound (**74**) (197 mg, 0.33 mmol) and phthalic anhydride (50 mg, 0.33 mmol) were taken in acetic acid 3 ml and the mixture refluxed for overnight. After completion, acetic acid removed, and the product purified by ISCO chromatography using ethyl acetate/ hexane to get 154 mg, yield 65%. ^{1}H NMR (400 MHz) (DMSO) δ) 10.21 (s, 1 H), 9.84 (s, 1 H), 8.21-8.16 (m, 2 H), 8.02-8.01 (m, 2 H), 7.94-7.93 (m, 2 H), 7.66 (d, 2 H, *J*= 8.8 Hz), 7.55-7.52 (m, 2 H), 7.37 (d, 2 H, *J*= 8.0 Hz), 7.19 37 (d, 2 H, *J*= 8.0 Hz), 7.08 37 (d, 4 H, *J*= 8.8 Hz), 6.95 (s, 1 H), 6.80 37 (d, 2 H, *J*= 8.8 Hz), 3.81 (s, 3 H), 3.74 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ. 167.05, 162.60, 162.01, 138.48, 138.04, 134.80, 133.83, 132.70, 131.89, 131.54, 131.05, 130.97, 130.87, 129.60, 129.46, 129.27, 128.27, 126.79, 126.72, 126.57, 126.33, 125.35, 125.10, 123.51, 123.33, 114.34, 114.05, 55.72, 55.41.

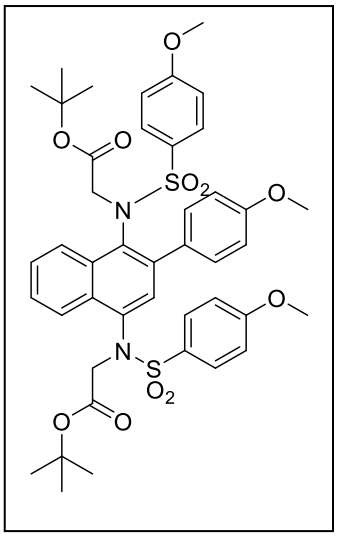
Diethyl 2,2'-((2-phenylnaphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (72a)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; 127mg, yield 82%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.24 (t, 1 H, J= 8.0 Hz), 8.15 (t, 1 H, J= 8.4 Hz), 7.72 (d, 1 H, J= 8.8 Hz), 7.63 (t, 2 H, J= 8.8 Hz), 7.55-7.50 (m, 2 H), 7.40-7.29 (m, 6 H), 7.08-7.02 (m, 1 H), 6.95- 6.85 (m, 4 H), 4.39-4.32 (m, 3 H), 4.16-3.94 (m, 5 H), 3.93-3.86 (m, 6 H), 1.18-1.14 (m, 3 H), 1.09-1.02 (m, 3 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ. 168.87, 168.81, 163.44, 163.37,

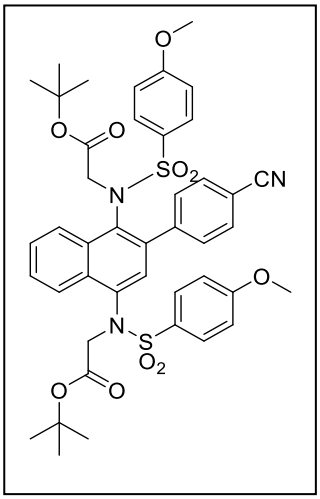
139.64, 138.57, 136.73, 136.31, 134.02, 132.61, 132.20, 131.57, 131.35, 130.77, 130.72, 130.57, 129.49, 128.30, 128.14, 128.10, 127.92, 127.37, 126.94, 126.84, 126.43, 124.22, 124.13, 114.08, 113.82, 61.61, 61.40, 55.76, 54.39, 53.67, 53.33, 14.32, 14.10, 13.97.

Di-*tert*-butyl 2,2'-((2-(4-methoxyphenyl) naphthalene-1,4-diyl) bis (((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (72b)



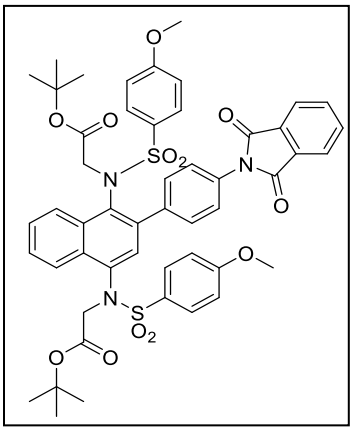
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; 123 mg, yield 74%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.22-8.17 (m, 2 H), 7.74-7.69 (m, 1 H), 7.65-7.63 (m, 2 H), 7.61-7.47 (m, 2 H), 7.36 (t, 1H, J= 8.0 Hz), 7.30 (d, 1H, J= 8.4 Hz), 7.23 (d, 1H, J= 8.4 Hz), 7.08-7.05 (m, 1 H), 6.94-6.85 (m, 6 H), 4.49-4.20 (m, 3 H), 3.89-3.81 (m, 9 H), 3.77-3.60 (m, 1 H), 1.33 (s, 9 H), 1.23-1.22 (m, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 167.76, 167.63, 167.58, 163.36, 163.31, 163.22, 163.14, 162.61, 159.41, 159.28, 139.90, 139.17, 136.83, 136.78, 136.09, 135.93, 134.22, 134.12, 132.47, 132.42, 132.33, 132.23, 131.51, 131.43, 131.26, 130.96, 130.64, 130.47, 130.32, 129.95, 127.05, 126.95, 126.81, 126.70, 124.17, 114.06, 113.81, 113.68, 82.44, 82.17, 77.47, 77.16, 76.84, 55.73, 55.36, 55.21, 54.48, 54.24, 54.19, 27.99, 27.86.

Di-*tert*-butyl 2,2'-((2-(4-cyanophenyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (72c)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; 118 mg, yield 71%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.16-8.05 (m, 2 H), 7.69-7.63 (m, 4 H), 7.57-7.38 (m, 6 H), 7.14-7.08 (m, 1 H), 6.91-6.83 (m, 4 H), 4.57-4.48 (m, 1 H), 4.29-4.12 (m, 2 H), 3.92-3.84 (m, 6 H), 3.80-3.76 (m, 1 H), 1.34-1.33 (m, 9 H), 1.24 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 167.65, 167.07, 167.00, 163.47, 163.44, 143.93, 143.67, 138.82, 138.23, 137.32, 136.04, 135.81, 133.91, 133.77, 133.02, 132.90, 131.94, 131.83, 131.62, 131.41, 130.65, 130.56, 130.48, 130.42, 130.08, 127.85, 127.69, 127.45, 126.82, 126.38, 124.31, 118.84, 114.09, 113.90, 111.89, 111.73, 82.58, 82.50, 55.82, 55.79, 55.29, 54.77, 54.04, 53.90, 28.02, 27.87.

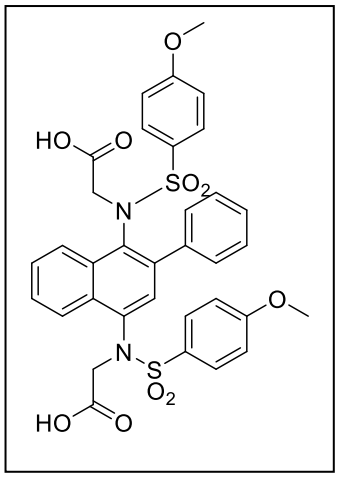
Di-*tert*-butyl 2,2'-((2-(4-(1,3-dioxoisoindolin-2-yl) phenyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (76)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; 58 mg, yield 61%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.32-8.29 (m, 2 H), 8.01-7.99 (m, 2 H), 7.85-7.82 (m, 2 H), 7.70 (d, 1 H, J= 8.8 Hz), 7.65 (d, 1 H, J= 8.8 Hz), 7.56 (d, 2 H, J= 8.8 Hz), 7.51-7.39 (m, 6 H), 7.06-6.89 (m, 5 H), 4.48-4.26 (m, 3 H), 3.90-3.85 (m, 6 H), 3.78-3.75 (m, 1 H), 1.34-1.33 (m, 9 H), 1.24 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 167.54, 167.29, 167.25, 163.45, 163.34,

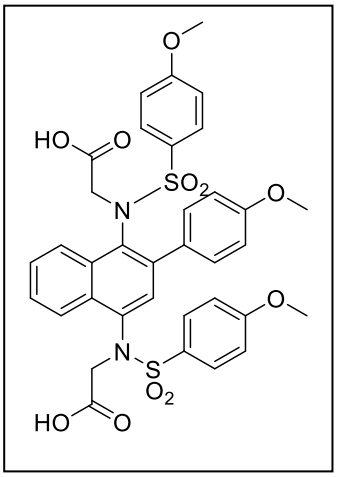
138.90, 138.45, 137.16, 134.65, 134.17, 132.99, 131.87, 131.77, 131.57, 130.83, 130.72, 130.53, 130.25, 130.17, 127.41, 127.22, 127.00, 125.98, 125.89, 124.49, 123.94, 114.14, 114.01, 82.51, 82.27, 55.81, 55.74, 28.01, 27.88.

2,2'-((2-Phenylnaphthalene-1,4-diyl)bis(((4-methoxyphenyl)sulfonyl)azanediyl))diacetic acid (73a)



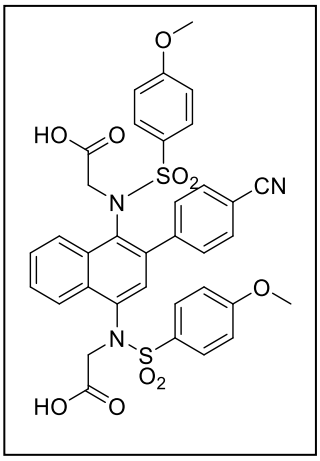
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (basic hydrolysis) to get the title compound as a white solid; 32 mg, yield 92%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.27(d, 2 H, *J*= 7.6 Hz), 7.62 (d, 2 H, *J*= 7.2 Hz), 7.55-749 (m, 3 H), 7.42-7.27 (m, 6 H), 7.05 (d, 2 H, *J*= 7.2 Hz), 6.95 (s, 1 H), 6.87-6.86 (m, 1 H), 6.70-6.69 (m, 1 H), 4.43-4.4.24 (m, 2H), 3.90(s, 3 H), 3.87 (s, 2 H), 3.85 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.99, 169.95, 169.68, 169.55, 162.91, 162.81, 162.66, 139.64, 138.79, 138.58, 138.36, 136.55, 136.47, 135.41, 134.91, 133.68, 133.45, 132.34, 131.34, 130.99, 130.73, 130.22, 130.09, 129.87, 129.15, 128.99, 128.94, 127.83, 127.60, 127.44, 126.60, 126.47, 126.21, 124.37, 124.13, 114.26, 114.00, 55.74, 53.27, 53.04. HRMS (ESI) Calcd for $C_{34}H_{30}N_2O_{10}S_2$ $(M+H)^+$ 691.1415, found 691.1414.

2,2'-((2-(4-Methoxyphenyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (73b)



Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a yellow solid; 17 mg, yield 71%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.30 (br, 1 H), 8.24 (d, 1 H, *J*= 6.8 Hz), 7.62 (d, 2 H, *J*= 7.2 Hz), 7.54-7.51 (m, 3 H), 7.40 (t, 1 H, *J*= 6.0 Hz), 7.17 (s, 2 H), 7.05 (d, 2 H, *J*= 7.6 Hz), 6.99 (d, 2 H, *J*= 6.4 Hz), 6.96 (s, 1 H), 6.87 (d, 2 H, *J*= 6.8 Hz), 4.44 -3.89 (m, 4 H), 3.85 (s, 3 H), 3.83 (s, 3 H). ^{13}C NMR (125 MHz, 100 °C) (DMSO) δ 168.98, 168.53, 162.57, 162.38, 158.44, 135.93, 134.74, 133.22, 131.47, 131.18, 130.60, 130.42, 129.73, 129.48, 129.43, 129.37, 125.94, 125.66, 125.56, 123.47, 113.79, 113.49, 112.91, 55.22, 55.20, 54.67, 52.72. HRMS (ESI) Calcd for $C_{35}H_{32}N_2O_{11}S_2$ $(M+H)^+$ 721.1520, found 721.1532.

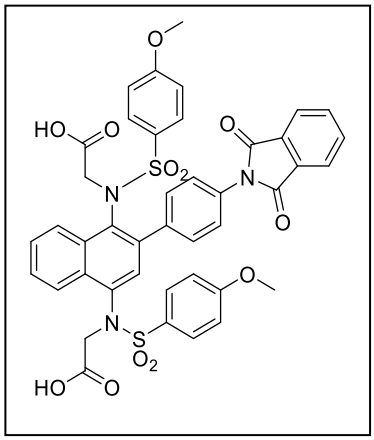
2,2'-((2-(4-Cyanophenyl)naphthalene-1,4-diyl)bis(((4-methoxyphenyl)sulfonyl) azanediyl)) diacetic acid (73c)



Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as brown solid; 13 mg, yield 61%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.30 (d, 1 H, *J*= 8.5 Hz), 8.22 (d, 1 H, *J*= 8.5 Hz), 7.74 (d, 2 H, *J*= 8.0 Hz), 7.62-7.56 (m, 3 H), 7.47-7.44 (m, 5 H), 7.05 (d, 2 H, *J*= 7.0 Hz), 6.96 (d, 3 H, *J*= 9.0 Hz),4.45-4.30 (m, 4 H), 3.90 (s, 3 H), 3.85 (s, 3 H). ^{13}C NMR (125 MHz, 100 °C) (DMSO) δ 168.79, 168.19, 162.46, 162.37, 142.93, 137.72, 136.33,

134.49, 132.66, 131.96, 130.69, 130.48, 129.65, 129.36, 129.26, 128.96, 126.06, 125.97, 125.32, 123.70, 117.74, 113.63, 113.37, 109.97, 55.10, 55.08, 52.51. HRMS (ESI) Calcd for $C_{35}H_{29}N_3O_{10}S_2$ $(M+H)^+$ 716.1367, found 716.1373.

2,2'-((2-(4-(1,3-Dioxoisoindolin-2-yl) phenyl) naphthalene-1,4-diyl) bis (((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (77)



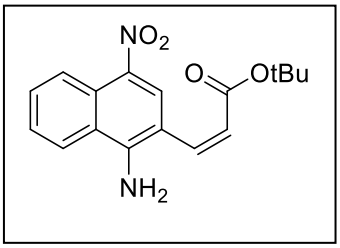
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a yellow solid;15 mg, yield 60%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.34 (d, 2 H, *J*= 8.0 Hz), 8.03-8.01 (m, 2 H), 7.96-7.94 (m, 2 H), 7.63 (d, 2 H, *J*= 8.5 Hz), 7.58 (t, 1 H, *J*= 7.0 Hz), 7.48-7.43 (m, 7 H), 7.08 (d, 2 H, *J*= 8.5 Hz), 7.08 (d, 2 H, *J*= 8.5 Hz), 7.00 (s, 1 H), 4.47-4.33 (m, 4 H), 3.87 (s, 3 H), 3.86 (s, 3 H). ^{13}C NMR (125 MHz, 100 °C) (DMSO) δ 169.08, 168.48, 166.33, 162.71, 162.59, 137.88, 136.34, 134.67, 134.23, 133.12, 132.02, 131.17, 130.73, 130.16, 129.62, 129.60, 129.17, 125.97, 125.85, 125.66, 123.92, 122.92, 113.92, 113.75, 55.36, 55.23, 52.90. HRMS (ESI) Calcd for $C_{42}H_{33}N_3O_{12}S_2$ $(M+H)^+$ 836.1578, found 836.1587.

General procedure for synthesis of (method G)

To a Schlenk tube equipped with a magnetic stir bar under argon atmosphere was added 2-iodo-4-nitronaphthalen-1-amine (1 equiv.), acrylate (1.4 equiv.), $Pd(OAc)_2$ (0.06 equiv.), P(o-tolyl) (0.12 equiv.), TEA (1.4 equiv.), in CH_3CN, and then the tube was degassed with argon three times and refluxed for 24 hours. Upon completion, the mixture diluted with EtOAc and extracted with water, brine, dried over Na_2SO_4, and organic layer removed

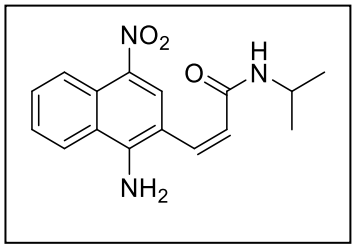
under reduced pressure. The crude product purified by ISCO using ethyl acetate/ hexane to get the desired product.

***tert*-Butyl (Z)-3-(1-amino-4-nitronaphthalen-2-yl) acrylate (78a)**



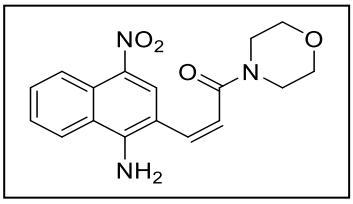
Prepared as described in the general procedure for Heck coupling (Method G) to get the title compound as brown solid; 521 mg, yield 83%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.88 (d, 1 H, J= 8.8 Hz), 8.54 (s, 1 H), 7.88 (d, 1 H, J= 8.4 Hz), 7.80 (d, 1 H, J= 15.6 Hz), 7.74-7.70 (m, 1 H), 7.60-7.56 (m, 1 H), 6.45 (d, 1 H, J= 15.6 Hz), 5.35 (br, 2 H), 1.56 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 166.22, 147.37, 137.07, 136.47, 130.56, 127.55, 126.89, 126.51, 124.99, 122.63, 122.35, 121.61, 111.47, 81.24, 28.35.

(Z)-3-(1-Amino-4-nitronaphthalen-2-yl)-N-isopropylacrylamide (78b)



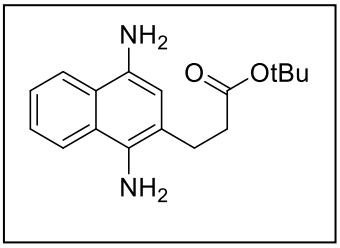
Prepared as described in the general procedure for Heck coupling (Method G) to get the title compound as a beige solid; 468 mg, yield 78%. ^{1}H NMR (400 MHz) (DMSO) δ) 8.80 (d, 1 H, J= 8.0 Hz), 8.59 (s, 1 H), 8.46 (d, 1 H, J= 8.8 Hz), 7.99 (d, 1 H, J= 7.6 Hz), 7.86 (d, 1 H, J= 15.6 Hz), 7.76-7.73 (m, 3 H), 7.58-7.54 (m, 1 H), 6.64 (d, 1 H, J= 15.6 Hz), 3.99-3.97 (m, 1 H), 1.13 (d, 6 H, J= 6.8 Hz). ^{13}C NMR (100 MHz) (DMSO) δ) 164.05, 150.70, 132.87, 132.47, 130.45, 127.11, 126.69, 125.88, 123.97, 123.50, 122.74, 122.00, 110.27, 22.48.

(Z)-3-(1-Amino-4-nitronaphthalen-2-yl)-1-morpholinoprop-2-en-1-one (78c)



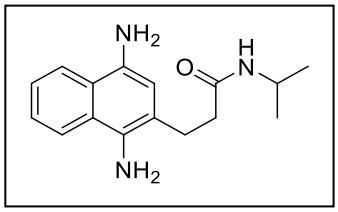
Prepared as described in the general procedure for Heck coupling (Method G) to get the title compound as an off-white solid; 504 mg, yield 77%. ^{1}H NMR (400 MHz) (DMSO) δ) 8.72-7.70 (m, 2 H), 8.46 (d, 1 H, J= 8.8 Hz), 7.96 (d, 1 H, J= 15.2 Hz), 7.74 (t, 1 H, J= 8.0 Hz), 7.69 (br, 2 H), 7.56 (t, 1 H, J= 8.0 Hz), 3.74 (br, 2 H), 3.61 (br, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ) 164.74, 150.38, 135.83, 133.37, 130.25, 127.00, 126.91, 125.76, 123.84, 123.22, 121.88, 117.90, 110.30, 66.34, 45.59, 41.96.

tert-Butyl 3-(1,4-diaminonaphthalen-2-yl) propanoate (79a)



Prepared as described in the general procedure for nitro group reduction (Method E1) to get the title compound as an off-white solid; 409 mg, quantitative. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.86-7.81 (m, 2 H), 7.48-7.41 (m, 2 H), 6.60 (s, 1 H), 3.94 (br, 2 H), 3.76 (br, 2 H), 2.93 (t, 2 H, J= 8.0 Hz), 2.59 (t, 2 H, J= 7.6 Hz), 1.44 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 172.83, 134.27, 131.85, 125.21, 125.16, 124.34, 124.07, 121.67, 121.47, 120.65, 113.14, 80.56, 35.44, 28.12, 26.98.

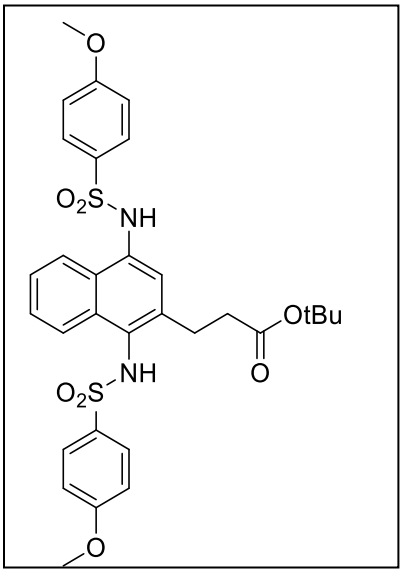
3-(1,4-Diaminonaphthalen-2-yl)-N-isopropyl propanamide (79b)



Prepared as described in the general procedure for nitro group reduction (Method E1) to get the title compound as a beige solid; 4.07 mg, quantitative. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.81-7.78 (m, 2 H), 7.45-7.40 (m, 2 H), 6.52 (s, 1 H), 5.37 (br, 1 H), 4.03-3.96 (br, 2 H),

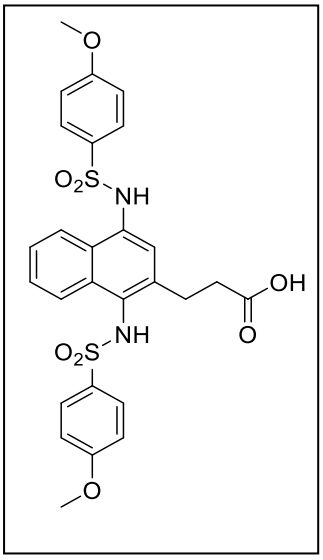
3.75 (br, 2 H), 2.95 (t, 2 H, J= 7.6 Hz), 2.43 (t, 2 H, J= 7.6 Hz), 0.98 (d, 6 H, J= 6.4 Hz),^{13}C NMR (100 MHz) ($CDCl_3$) δ) 171.77, 134.27, 132.12, 125.28, 124.45, 124.17, 121.74, 121.57, 120.91, 113.44, 41.46, 36.95, 27.53, 22.69.

tert-Butyl 3-(1,4-bis((4-methoxyphenyl) sulfonamido) naphthalen-2-yl) propanoate (80a)



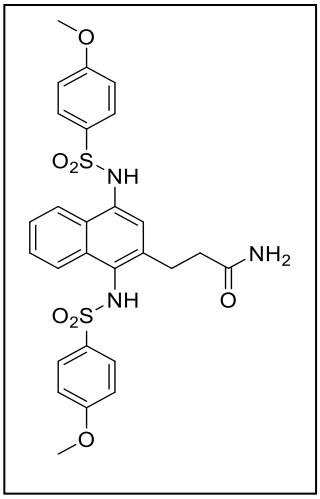
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as an off-white solid; 464 mg, yield 74%. ^{1}H NMR (400 MHz) (DMSO) δ) 10.03 (s, 1 H), 9.69 (s, 1 H), 7.96 (d, 1 H, J= 8.4 Hz), 7.66 (d, 1 H, J= 7.6 Hz), 7.60 (d, 2 H, J= 8.8 Hz), 7.47 (d, 2 H, J= 8.4 Hz), 7.33 (t, 1 H, J= 8.0 Hz), 7.23 (t, 1 H, J= 7.6 Hz), 7.02 (d, 2 H, J= 8.0 Hz), 6.98 (d, 2 H, J= 8.8 Hz), 6.94 (s, 1 H). 3.80 (s, 3 H), 3.78 (s, 3 H), 2.69 (br, 2 H), 2.14 (br, 2 H), 1.39 (s, 9 H). ^{13}C NMR (100 MHz) (DMSO) δ) 171.17, 162.42, 162.39, 137.50, 132.55, 132.49, 132.17, 131.29, 129.04, 128.86, 128.63, 127.89, 125.89, 125.30, 124.29, 124.20, 123.05, 114.26, 114.18, 79.70, 55.61, 35.19, 27.69, 26.47.

3-(1,4-Bis((4-methoxyphenyl) sulfonamido) naphthalen-2-yl) propanoic acid (83)



Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as an off-white solid; 102 mg, yield 89%. ^{1}H NMR (400 MHz) (MeOH-d_4) δ) 7.96 (d, 1 H, J= 8.4 Hz), 7.75 (d, 1 H, J= 8.4 Hz), 7.60 (d, 2 H, J= 8.8 Hz), 7.49 (d, 2 H, J= 9.2 Hz), 7.33-7.29 (m, 1 H), 7.24-7.20 (m, 1 H), 7.03 (s, 1 H), 6.95-6.90 (m, 4 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 2.80 (br, 2 H), 2.36 (t, 2 H, J= 8.0 Hz). ^{13}C NMR (100 MHz) (MeOH-d_4) δ) 176.57, 164.67, 164.63, 139.05, 134.25, 133.88, 133.38, 132.28, 130.74, 130.61, 130.29, 129.58, 127.18, 126.59, 125.86, 125.64, 124.04, 115.24, 115.10, 56.16, 56.14, 35.36, 27.63.

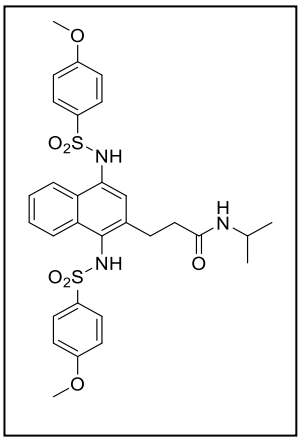
3-(1,4-Bis((4-methoxyphenyl) sulfonamido) naphthalen-2-yl) propanamide (80d)



To a stirred solution of (**83**) (96 mg, 0.128 mmol) in DCM (2 ml): DMF (0.2 ml), PyAOP (93 mg, 0.18 mmol), TEA (95 uL, 0.7 mmol) were added at 0 °C under nitrogen. Then, NH_3/ DCM (1.5 N, 100 uL) was added and reaction stirred at 0 °C for 10 min. and then room temperature for 3 hours Upon completion, the reaction diluted with ethyl acetate and washed with 1 N HCl, brine, dried over Na_2SO_4, and the organic layer removed under reduced pressure. The crude product purified by ISCO using ethyl acetate hexane to get the desired product as a beige solid 63 mg, yield 84%. ^{1}H NMR (400 MHz) (DMSO) δ) 10.38 (s, 1 H), 10.01 (s, 1 H), 8.28 (d, 1 H, J= 8.0 Hz), 8.07 (d, 1 H, J= 8.4 Hz), 7.95 (d, 2 H, J=

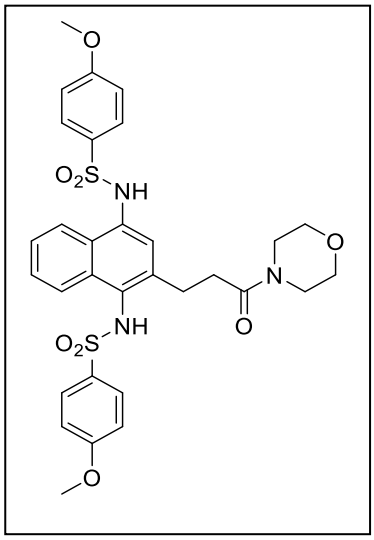
8.8 Hz), 7.79 (d, 2 H, J= 8.8 Hz), 7.67-7.56 (m, 3 H), 7.36-7.30 (m, 5 H), 7.17 (s, 1 H), 4.14 (s, 3 H), 4.10 (s, 3 H), 3.67 (br, 3 H), 2.83 (br, 1 H). ^{13}C NMR (100 MHz) (DMSO) δ) 173.61, 162.42, 162.39, 138.06, 132.40, 132.17, 132.05, 131.39, 128.99, 128.68, 128.60, 127.78, 125.79, 125.22, 124.52, 124.10, 122.85, 114.25, 114.19, 55.62, 55.58, 35.64, 26.35.

3-(1,4-Bis((4-methoxyphenyl) sulfonamido) naphthalen-2-yl)-N-isopropylpropanamide (80b)



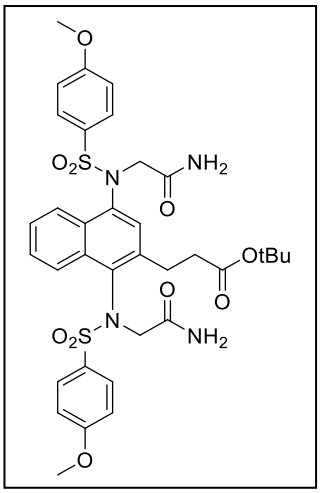
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a beige solid; 416 mg, yield 68%. ^{1}H NMR (400 MHz) (DMSO) δ) 7.93 (d, 1 H, J= 8.4 Hz), 7.74 (d, 1 H, J= 8.4 Hz), 7.64-7.59 (m, 3 H), 7.47-7.44 (m, 2 H), 7.33-7.23 (m, 2 H), 7.04-6.97 (m, 5 H), 3.80 (s, 4 H), 3.77 (s, 3 H), 2.60 (br, 2 H), 2.13 (t, 2 H, J= 7.6 Hz), 1.01 (d, 6 H, J= 6.8 Hz). ^{13}C NMR (100 MHz) (DMSO) δ) 170.34, 162.42, 162.39, 138.06, 132.46, 132.22, 132.05, 131.45, 128.98, 128.69, 128.62, 127.78, 125.80, 125.22, 124.54, 124.27, 122.86, 114.25, 114.19, 55.62, 55.60, 36.11, 26.68, 22.32.

N,N'-(2-(3-Morpholino-3-oxopropyl)naphthalene-1,4-diyl)bis(4-methoxybenzene-sulfonamide) (80c)



Using general procedure (method E1) intermediate **(78d)** to get the diamine (440 mg, quantitative) which was dissolved in pyridine using general procedure (method A2) to get the title compound, 317 mg, yield 65%. ^{1}H NMR (400 MHz) (DMSO) δ) 10.06 (s, 1 H), 9.75 (s, 1 H), 7.99 (d, 1 H, J= 8.4 Hz), 7.75 (d, 1 H, J= 8.4 Hz), 7.65 (d, 2 H, J= 8.8 Hz), 7.48 (d, 2 H, J= 8.8 Hz), 7.37-7.33 (m, 1 H), 7.29-7.27 (m, 1 H), 7.04-6.98 (m, 5 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.53-3.52 (m, 4 H), 3.43-3.32 (m, 4 H), 2.65 (br, 2 H), 2.31 (t, 2 H, J= 7.6 Hz). ^{13}C NMR (100 MHz) (DMSO) δ)170.07, 162.46, 162.43, 137.97, 132.55, 132.32, 132.21, 131.45, 129.12, 128.79, 128.74, 127.96, 125.93, 125.35, 124.53, 124.23, 123.05, 114.33, 114.23, 66.02, 55.68, 55.65, 45.28, 41.55, 33.24, 26.56.

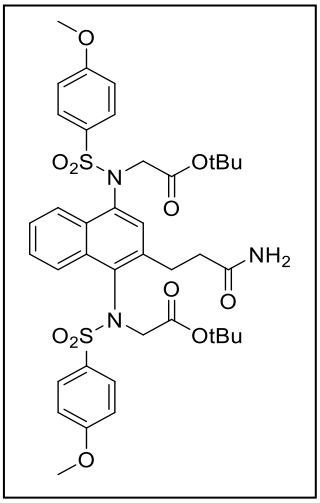
***tert*-Butyl 3-(1,4-bis((N-(2-amino-2-oxoethyl)-4-methoxyphenyl) sulfonamido) naphthalen-2-yl) propanoate (81a)**



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; 61 mg, yield 82%.%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.08-7.95 (m, 1 H), 7.66-7.59 (m, 4 H), 7.37-7.30 (m, 1 H), 7.16-7.15 (m, 2 H), 6.99-6.55 (m, 7 H), 5.97-5.88 (m, 2 H), 4.48-4.20 (m, 4 H), 3.88-3.84 (m, 6 H), 3.21-2.82 (2 H), 2.55-2.26 (m, 2 H), 1.46 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 171.92, 171.76, 170.46, 170.31, 170.16, 163.72, 162.55, 140.61, 137.77, 137.64, 134.76, 134.69,

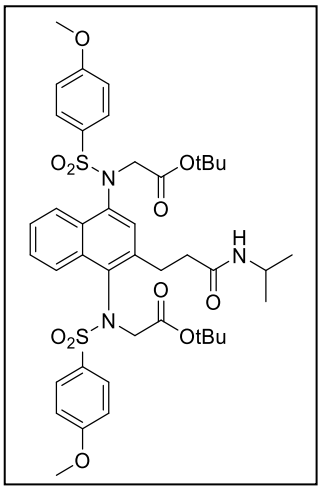
132.08, 132.02, 131.95, 131.78, 130.62, 130.50, 130.37, 130.30, 130.13, 129.94, 128.55, 128.35, 128.31, 127.15, 126.63, 124.25, 114.44, 114.37, 114.25, 80.72, 80.63, 55.72, 36.44, 36.30, 35.90, 31.55, 31.41, 28.11.

Di-*tert*-butyl 2,2'-((2-(3-amino-3-oxopropyl) naphthalene-1,4-diyl) bis (((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (81d)



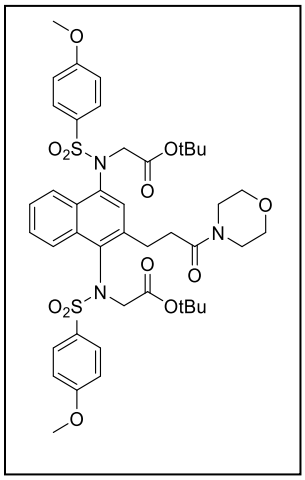
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; 29 mg, yield 72%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.49-8.45 (m, 1 H), 7.84 (d, 2 H, J= 8.8 Hz), 7.80-7.77 (m, 2 H), 7.67-7.59 (m, 1 H), 7.45-7.44 (m, 2 H), 7.39-7.32 (m, 1 H), 7.17-7.14 (m, 2 H), 7.07-7.04 (m, 2 H), 4.81-4.55 (m, 2 H), 4.41-4.29 (m, 2 H), 4.09 (s, 3 H), 4.03 (s, 3 H), 3.81-3.73 (m, 1 H), 3.13-3.04 (m, 1 H), 2.47-2.42 (m, 2 H), 1.64-1.59 (m, 9 H), 1.53-1.51 (m, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 174.91, 174.83, 168.77, 168.40, 167.56, 167.42, 163.65, 140.91, 140.72, 138.03, 137.96, 134.93, 132.69, 132.42, 130.81, 130.50, 130.44, 130.35, 129.95, 129.79, 128.85, 128.77, 127.38, 127.20, 126.66, 126.42, 125.40, 124.8, 123.88, 114.36, 114.29, 55.86, 55.83, 54.44, 54.08, 38.17, 37.71, 28.20, 28.13, 28.04.

Di-*tert*-butyl 2,2'-((2-(3-(isopropylamino)-3-oxopropyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (81b)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; 60 mg, yield 71%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.32 (d, 1 H, J= 8.4 Hz), 7.67-7.60 (m, 3 H), 7.52-7.18 (m, 4 H), 7.04-6.86 (m, 5 H), 6.38-6.30 (m, 1 H), 4.72-4.4.02 (m, 5 H), 3.91 (s, 1 H), 3.84 (s, 3 H), 3.47-3.40 (m, 1 H), 2.77-2.70 (m, 1 H), 2.20-2.07 (m, 2 H), 1.47-1.33 (m, 18 H), 1.17-1.11 (m, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 171.39, 168.79, 167.37, 163.64, 163.52, 140.70, 138.01, 134.97, 132.69, 131.01, 130.40, 130.34, 129.95, 128.77, 127.45, 126.64, 125.37, 124.20, 114.35, 114.27, 114.21, 82.71, 82.59, 82.40, 55.87, 55.72, 54.49, 54.05, 41.24, 39.16, 29.49, 28.13, 28.08, 28.01, 22.89, 22.82, 22.73.

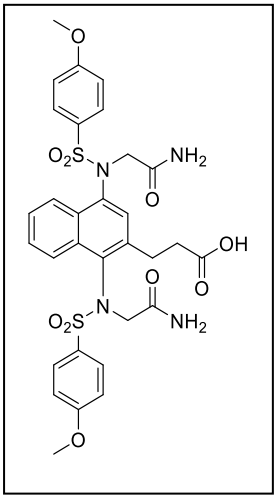
di-*tert*-butyl 2,2'-((2-(3-morpholino-3-oxopropyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl))diacetate (81c)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; 60 mg, yield 71%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.18-8.13 (m, 1 H), 7.67-7.60 (m, 4 H), 7.42-7.36 (m, 2 H), 7.26-7.11 (m, 2 H), 6.95-6.86 (m, 4 H), 4.46-4.14 (m, 4 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.75-3.01 (m, 10 H), 2.72-2.25 (m, 2 H), 1.40-1.32 (m, 18 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 170.94, 170.77,

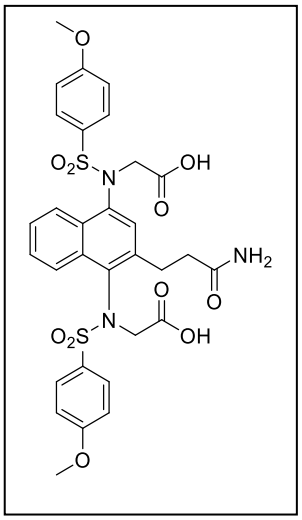
167.45, 167.35, 167.30, 163.27, 163.17, 163.14, 162.35, 140.65, 140.49, 137.42, 137.39, 135.28, 135.18, 132.43, 132.16, 132.00, 131.91, 130.63, 130.52, 130.21, 130.06, 130.00, 129.82, 129.06, 128.97, 126.82, 126.72, 126.26, 126.15, 124.62, 124.46, 124.10, 113.97, 113.93, 82.07, 82.04, 66.89, 66.75, 55.54, 54.41, 54.29, 53.80, 53.76, 46.05, 45.95, 41.90, 34.01, 33.91, 27.81, 27.74, 20.88.

3-(1,4-Bis((N-(2-amino-2-oxoethyl)-4-methoxyphenyl) sulfonamido) naphthalen-2-yl) propanoic acid (82a)



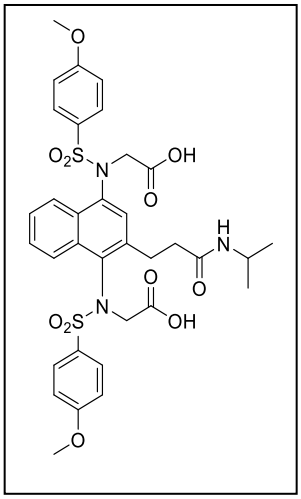
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a yellow solid; 18 mg, yield 78%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.18 (d, 1 H, *J*= 6.4 Hz), 7.86-7.83 (m, 1 H), 7.64-7.59 (m, 4 H), 7.44-7.41 (m, 1 H), 7.32-7.29 (m, 1 H), 7.08-7.06 (m, 3 H), 7.01 (d, 1 H, *J*= 6.8 Hz), 6.84 (br, 4 H), 4.35-4.23 (m, 4 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.96-2.90 (br, 1 H), 2.75 (br, 1 H), 2.26 (br, 2 H). ^{13}C NMR (125 MHz, 100 °C) (DMSO) δ 172.73, 168.48, 168.35, 162.64, 162.62, 139.27, 136.77, 134.39, 132.28, 131.28, 130.89, 129.64, 129.51, 129.43, 129.37, 129.34, 128.07, 125.68, 125.61, 125.10, 125.03, 124.53, 124.04, 113.99, 113.93, 113.85, 113.83, 55.31, 55.26, 53.90, 53.77, 33.69, 26.12. HRMS (ESI) Calcd for $C_{31}H_{32}N_4O_{10}S_2$ $(M+H)^+$ 685.1633, found 685.1628.

2,2'-((2-(3-Amino-3-oxopropyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (82d)



Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as an off-white solid; 21 mg, yield 75%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.18 (d, 1 H, *J*= 6.8 Hz), 7.90 (d, 1 H, *J*= 6.8 Hz), 7.62-7.59 (m, 4 H), 7.44 (t, 1 H, *J*= 6.0 Hz), 7.34 (t, 1 H, *J*= 6.0 Hz), 7.15 (s, 1 H), 7.10 (d, 2 H, *J*= 6.8 Hz), 7.03 (d, 2 H, *J*= 6.8 Hz), 6.63 (br, 2 H), 4.40 (s, 4 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 2.99-2.95 (m, 2 H), 2.74-2.68 (m, 2 H), 2.23(br, 2 H). ^{13}C NMR (125 MHz, 100 °C) (DMSO) δ 172.59, 169.02, 168.90, 162.66, 162.62, 139.86, 136.80, 134.18, 132.30, 131.05, 130.35, 129.41, 129.39, 129.34, 128.22, 125.68, 125.00, 124.35, 123.87, 113.92, 113.88, 55.28, 55.26, 52.98, 52.69, 35.17, 26.51. HRMS (ESI) Calcd for $C_{31}H_{31}N_3O_{11}S_2$ $(M+H)^+$ 686.1473, found 686.1471.

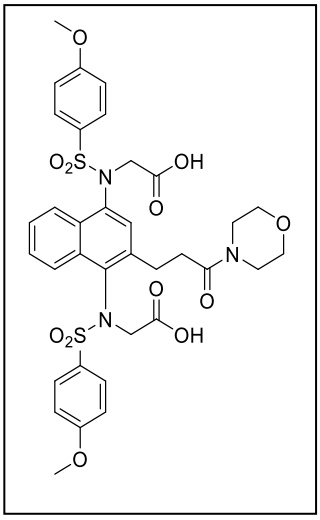
2,2'-((2-(3-(Isopropylamino)-3-oxopropyl) naphthalene-1,4-diyl) bis (((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (82b)



Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as an off-white solid; 19 mg, yield 71%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.18 (d, 1 H, *J*= 8.5 Hz), 7.94 (d, 1 H, *J*= 9.0 Hz), 7.61-7.59 (m, 4 H), 7.43 (t, 1 H, *J*= 7.0 Hz), 7.36-7.33 (m, 1 H), 7.13 (s, 1 H), 7.09-7.08 (m, 3 H), 7.03 (d, 2 H, *J*= 9.0 Hz), 4.39-4.38 (m, 4 H), 3.87-3.86 (m, 6 H), 2.93-2.87 (m, 1 H), 2.71-2.65 (m, 1 H), 2.19 (br, 2 H), 1.09-1.06 (m, 6 H). ^{13}C NMR (125 MHz, 100 °C) (DMSO) δ 169.68, 169.10, 162.74, 162.72, 139.88, 136.90, 134.32, 132.47, 131.14, 130.46, 129.51,

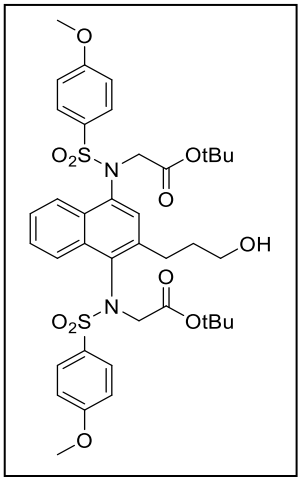
129.43, 128.33, 125.79, 125.10, 124.51, 123.97, 114.01, 113.96, 55.34, 53.08, 52.78, 35.70, 26.74, 21.84. HRMS (ESI) Calcd for $C_{34}H_{37}N_3O_{11}S_2$ $(M+H)^+$ 728.1942, found 728.1928.

2,2'-((2-(3-Morpholino-3-oxopropyl)naphthalene-1,4-diyl)bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (82c)



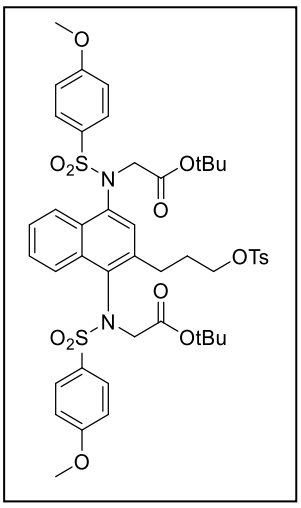
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a pink solid; 17 mg, yield 68%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 12.37 (br, 2 H), 8.18 (d, 1 H, *J*= 6.8 Hz), 7.83 (d, 1 H, *J*= 6.8 Hz), 7.62-7.58 (m, 4 H), 7.43 (t, 1 H, *J*= 5.6 Hz), 7.32 (t, 1 H, *J*= 5.6 Hz), 7.14 (s, 1 H), 7.07 (d, 2 H, *J*= 5.6 Hz), 7.02 (d, 2 H, *J*= 7.2 Hz), 4.43- 4.34 (m, 4 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.58 (t, 4 H, *J*= 4.0 Hz), 3.43 (t, 4 H, *J*= 3.6 Hz), 2.94-2.92 (m, 1 H), 2.83-2.77 (m, 1 H), 2.40 (br, 2 H). ^{13}C NMR (125 MHz, 100 °C) (DMSO) δ 169.41, 168.83, 162.57, 162.45, 139.62, 136.68, 134.12, 132.09, 130.99, 130.24, 129.38, 129.35, 129.25, 128.10, 125.59, 124.93, 124.18, 123.84, 113.80, 113.73, 65.48, 55.18, 55.17, 52.84, 52.60, 31.96, 26.24. HRMS (ESI) Calcd for $C_{35}H_{37}N_3O_{12}S_2$ $(M+H)^+$ 756.1891, found 756.1877.

Di-*tert*-butyl 2,2'-((2-(3-hydroxypropyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (85)



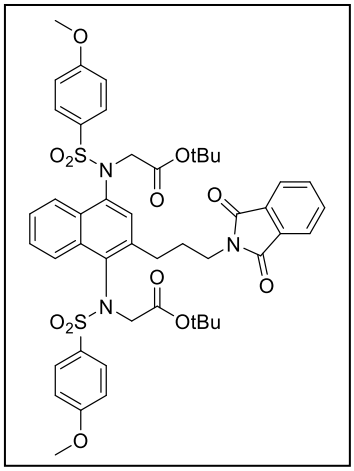
To a stirred solution of (**83**) (100 mg, 0.18 mmol) in anhydrous THF (2 ml) under nitrogen at 0 °C, LAH (20 mg, 0.53 mmol) was added at room temperature and the mixture refluxed for 8 hours. Upon completion, the reaction quenched with methanol and diluted with ethyl acetate, washed with bine, dried over anhydrous Na_2SO_4, and the organic lyer removed and the crude product then diluted with DMF and using general procedure (method B) to give the desired product as oily product 71 mg, yield 51%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.18-8.10 (m, 1 H), 7.70-7.66 (m, 2 H), 7.64-7.61 (m, 2 H), 7.54-7.37 (m, 2 H), 7.32-7.21 (m, 1 H), 7.19-7.14 (m, 1 H), 6.96-6.93 (m, 2 H), 6.90-6.86 (m, 2 H), 4.56-4.43 (m, 2 H), 4.31-4.17 (m, 2 H), 3.87-3.85 (m, 6 H), 3.62-3.56 (m, 2 H), 3.29-3.21 (m, 1 H), 2.59-2.52 (m, 1 H), 1.87-1.58 (m, 2 H), 1.43-1.34 (m, 18 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 168.21, 168.03, 167.81, 167.69, 163.47, 163.35, 141.54, 141.43, 137.35, 137.30, 135.41, 135.36, 132.98, 132.84, 132.03, 131.81, 131.13, 131.02, 130.54, 130.52, 130.46, 130.42, 130.31, 129.64, 129.31, 127.12, 126.90, 126.46, 126.28, 124.74, 124.71, 124.59, 124.52, 114.13, 82.59, 82.42, 82.40, 62.21, 55.76, 54.61, 54.05, 33.31, 33.07, 31.67, 28.09, 28.04, 28.02, 22.73.

Di-*tert*-butyl 2,2'-((2-(3-(tosyloxy) propyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl)azanediyl)) diacetate (86)



Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as brown solid; 67 mg, yield 91%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.22-8.14 (m, 1 H), 7.78 (d, 2 H, J= 8.4 Hz), 7.68-7.52 (m, 4 H), 7.46-719 (m, 5 H), 7.07-6.84 (m, 5 H), 4.50-4.38 (m, 2 H), 4.28-4.01 (m, 4 H), 3.89-3.85 (m, 6 H), 3.56-2.47 (m, 4 H), 2.44 (s, 3 H), 1.40-1.34 (m, 18 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 167.72, 167.54, 163.46, 144.77, 140.67, 137.61, 135.15, 135.06, 133.16, 132.71, 132.24, 130.98, 130.38, 130.30, 130.25, 129.97, 129.65, 129.24, 128.83, 127.96, 127.75, 127.16, 126.99, 126.52, 126.36, 124.91, 124.71, 124.50, 114.16, 82.19, 70.39, 55.85, 55.74, 54.34, 54.04, 30.14, 28.04, 27.98, 27.62, 21.70.

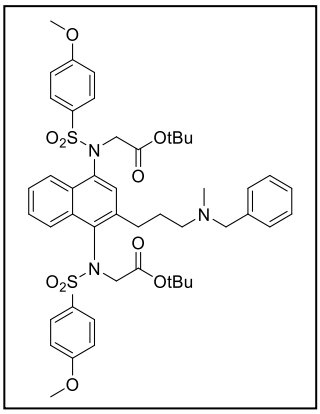
Di-*tert*-butyl 2,2'-((2-(3-(1,3-dioxoisoindolin-2-yl) propyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (87a)



To a stirred solution of (**86**) (30 mg, 0.03 mmol) in 1 ml DMF, Phthalimide potassium salt (9 mg, 0.045mmol) and K_2CO_3 (12 mg, 0.06 mmol) were added and the eaction mixture stirred at room tempreture for 3 hours. Then, the mixture diluted with ethyl acetate and washed with brine, dried over anhydrous Na_2SO_4. The organic layer removed under reduced pressure and the crude mixture purified by ISCO using ethyl acetate hexane to get the desired product 24 mg, yield 84%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.22-8.16 (m, 1 H), 7.87-7.32 (m, 11 H), 7.08-7.05 (m, 1 H), 6.93-6.87 (m, 4 H), 4.51-4.16 (m, 4 H), 3.87-3.73 (m, 6 H), 3.72-3.62 (m, 2 H), 3.08-3.00 (m, 1 H), 2.85-2.81 (m, 1 H), 2.49-

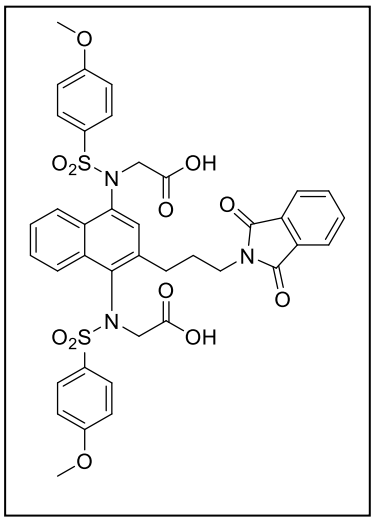
2.41 (m, 1 H), 1.74-1.66 (m, 1 H), 1.39-1.32 (m, 18 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 171.20, 168.33, 168.27, 167.78, 167.70, 167.64, 167.57, 163.36, 140.59, 137.57, 135.43, 135.28, 134.48, 133.88, 133.70, 133.28, 132.41, 132.17, 132.01, 131.16, 130.43, 130.34, 130.01, 129.07, 128.88, 127.24, 127.02, 126.55, 126.33, 125.08, 124.76, 123.24, 123.06, 114.17, 113.96, 82.09, 55.72, 55.63, 54.71, 54.50, 54.26, 54.15, 38.07, 32.02, 22.79, 21.13.

Di-*tert*-butyl 2,2'-((2-(3-(benzyl(methyl) amino) propyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (87b)



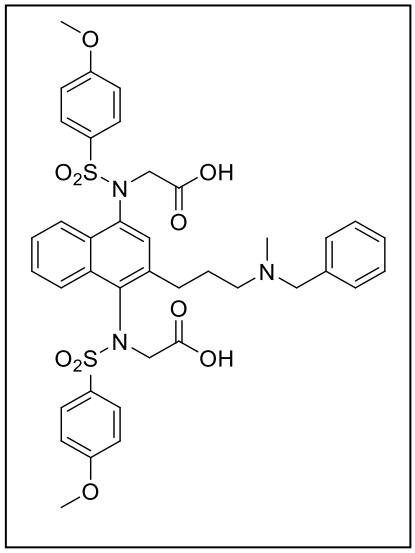
To a stirred solution of (**86**) (30 mg, 0.03 mmol) in 1 ml DMF, N-Benzylmethylamine (5 uL, 0.045mmol) and K_2CO_3 (12 mg, 0.06 mmol) were added and the eaction mixture stirred at room tempreture for 1 hour. Then, the mixture diluted with ethyl acetate and washed with brine, dried over anhydrous Na_2SO_4. The organic layer removed under reduced pressure and the crude mixture purified by ISCO using ethyl acetate hexane to get the desired product 18 mg, yield 69%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.15 (d, 1 H, J= 8.8 Hz), 7.66 (d, 2 H, J= 8.8 Hz), 7.61 (d, 2 H, J= 8.8 Hz), 7.46-7.28 (m, 7 H), 724-7.17 (m, 2 H), 7.00-6.92 (m, 2 H), 6.88-6.85 (m, 2 H), 4.47-4.12 (m, 4 H), 3.85-3.81 (m, 6 H), 3.56-3.51 (m, 2 H), 2.85-2.79 (m, 2 H), 2.59-2.39 (m, 2 H), 2.27-2.07 (m, 2 H), 1.60 (s, 3 H), 1.42-1.35 (m, 18 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 167.31, 167.20, 167.09, 162.83, 162.77, 129.79, 128.98, 128.68, 128.01, 126.47, 125.89, 125.69, 124.07, 113.56, 81.75, 55.14, 54.06, 53.50, 27.51, 27.44.

2,2'-((2-(3-(1,3-Dioxoisoindolin-2-yl) propyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (88a)



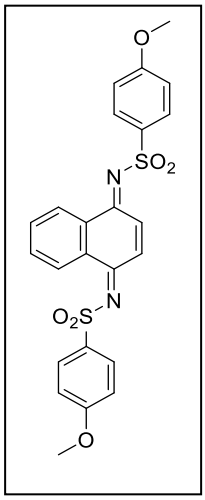
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C2) to get the title compound as a pink solid; 17 mg, yield 68%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.22 (d, 1 H, *J*= 6.8 Hz), 7.93 (d, 1 H, *J*= 6.8 Hz), 7.90-7.84 (m, 4 H), 7.58 (d, 2 H, *J*= 7.2 Hz), 7.56 (d, 2 H, *J*= 7.2 Hz), 7.46-7.43 (m, 1 H), 7.37-7.34 (m, 1 H), 7.08 (s, 1 H), 7.01 (d, 4 H, *J*= 6.8 Hz), 4.41 (s, 2 H), 4.33 (s, 2 H), 3.86 (s, 3 H), 3.76 (s, 3 H), 3.57 (t, 2 H, *J*= 6.0 Hz), 2.76 (t, 2 H, *J*= 6.0 Hz), 1.72 (t, 2 H, *J*= 6.0 Hz). ^{13}C NMR (125 MHz, 100 °C) (DMSO) δ 168.82, 168.76, 167.08, 162.54, 162.47, 139.37, 136.74, 134.08, 133.55, 132.29, 131.20, 131.02, 130.21, 129.31, 129.23, 129.19, 127.91, 125.63, 124.94, 124.32, 123.85, 122.25, 113.77, 113.68, 55.15, 55.13, 55.02, 55.00, 52.80, 52.66, 36.99, 27.90. HRMS (ESI) Calcd for $C_{39}H_{35}N_3O_{12}S_2$ $(M+H)^+$ 802.1735, found 802.1733.

2,2'-((2-(3-(Benzyl (methyl) amino) propyl) naphthalene-1,4-diyl) bis (((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (88b)



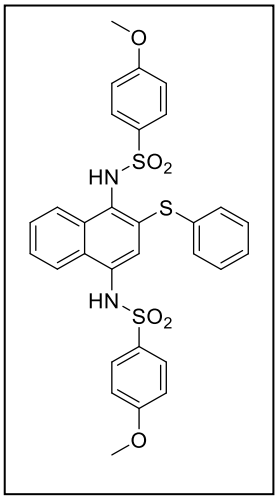
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C2) to get the title compound as a yellow solid; 17 mg, yield 68%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.03 (d, 1 H, *J*= 6.8 Hz), 7.61 (d, 2 H, *J*= 7.2 Hz), 7.56-7.52 (m, 5 H), 7.47-7.45 (m, 3 H), 7.38 (t, 1 H, *J*= 6.0 Hz), 7.32 (s, 1 H), 7.26 (t, 1 H, *J*= 6.4 Hz), 7.06 (d, 2 H, *J*= 7.2 Hz), 6.99 (d, 2 H, *J*= 7.2 Hz), 4.49-4.46 (m, 1 H), 4.28-4.26 (m, 3 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 3.09-3.07 (m, 2 H), 3.01-2.94 (m, 1 H), 2.69-2.68 (m, 1 H), 2.67 (s, 3 H), 1.94-1.90 (m, 2 H). ^{13}C NMR (125 MHz 100 °C) (DMSO) δ 168.83, 168.69, 162.48, 162.30, 139.06, 136.58, 133.97, 131.55, 130.73, 130.19, 129.97, 129.48, 129.28, 129.13, 128.74, 128.19, 128.04, 125.64, 124.93, 123.57, 113.70, 113.63, 58.20, 55.06, 55.01, 54.38, 52.77, 52.27, 27.63, 23.27.HRMS (ESI) Calcd for $C_{39}H_{41}N_3O_{10}S_2$ $(M+H)^+$ 776.2306, found 776.2308.

2,2'-((2-(3-(Benzyl(methyl) amino) propyl) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (89)



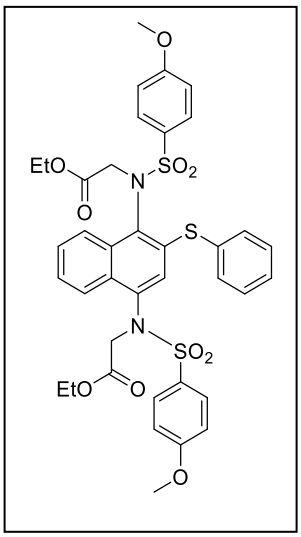
Ceric ammonium nitrate (219 mg, 0.4 mmol,) was added to a solution of (**2c**) (99 mg, 0.2 mmol) in acetonitrile (20 mL). Then, the reaction mixture was stirred at room temperature and checked by TLC and LCMS; upon completion, the reaction mixture was filtered and the yellow solid product was collected and washed with diethyl ether to get the pure product yellow solid (99 mg, quantitative). ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.34 (s, 2 H), 8.20-8.18 (m, 2 H), 8.00 (d, 4 H, J= 8.8 Hz), 7.61-7.58 (m, 2 H), 7.05 (d, 2 H, J= 8.8 Hz), 3.90 (s, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 163.77, 161.44, 133.30, 132.93, 132.40, 130.60, 129.93, 126.97, 114.51, 55.87.

N,N'-(2-(Phenylthio)naphthalene-1,4-diyl)bis(4-methoxybenzenesulfonamide) (90)



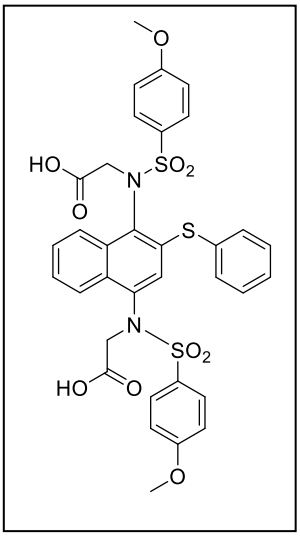
To a suspension of (**88b**) (40 mg, 0.08 mmol) in toluene (1 mL), thiophenol (11 uL, 0.1 mmol) and DiPEA (29 uL, 0.1 mmol) were added; The reaction mixture was stirred at room temperature and checked by TLC and LCMS. Then, the reaction mixture was filtered and the crude product purified by ISCO using ethyl acetate:hexane to get the title compound as a pink solid 33 mg, yield 68%. ^{1}H NMR (400 MHz) (DMSO) δ 9.01 (s, 1 H), 9.95 (s, 1 H), 8.00 (d, 1 H, J= 8.0 Hz), 7.70 (d, 1 H, J= 8.4 Hz), 7.57 (d, 2 H, J= 8.8 Hz), 7.41-7.3 (m, 7 H), 7.12-7.10 (m, 2 H), 6.98 (d, 2 H, J= 8.8 Hz), 6.91 (d, 2 H, J= 8.8 Hz), 6.77 (s, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ) 162.46, 162.32, 135.56, 133.45, 132.99, 132.79, 132.29, 131.41, 129.52, 128.99, 128.89, 128.62, 128.14, 127.99, 127.83, 126.80, 125.89, 124.23, 123.22, 122.11, 114.30, 114.15, 55.63.

Diethyl 2,2'-((2-(phenylthio) naphthalene-1,4-diyl) bis(((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (91)



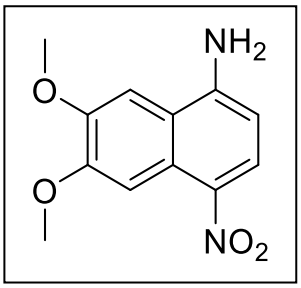
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; 27 mg, yield 69%. ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.47-8.38 (m, 1 H), 8.08-7.95 (m, 1 H), 7.72-7.68 (m, 2 H), 7.55-7.45 (m, 4 H), 7.31-7.27 (m, 3 H), 7.14-7.13 (m, 2 H), 7.12 (s, 1 H), 6.92-6.89 (m, 2 H), 6.83 (d, 1 H, J= 8.8 Hz), 6.67 (d, 1 H, J= 8.8 Hz), 4.89-4.83 (m, 1 H), 4.58-4.35 (m, 1 H), 4.22-3.99 (m, 6 H), 3.88-3.81 (m, 6 H), 1.25-1.09 (m, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ) 169.14, 168.50, 163.64, 163.32, 163.16, 138.25, 137.91, 137.55, 135.22, 134.94, 134.03, 132.15, 131.34, 131.09, 130.93, 130.81, 130.74, 130.52, 130.29, 130.05, 129.61, 129.53, 128.01, 127.82, 127.70, 127.66, 127.58, 127.45, 126.78, 126.44, 123.87, 114.20, 114.16, 114.11, 61.68, 61.61, 61.56, 61.49, 55.81, 55.71, 53.30, 53.15, 52.90, 14.20, 14.10.

2,2'-((2-(Phenylthio) naphthalene-1,4-diyl) bis (((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (92b)



Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a yellow solid; 19 mg, yield 68%. ^{1}H NMR (500 MHz, 100 °C) (DMSO) δ) 8.49 (d, 1 H, *J*= 6.4 Hz), 8.09 (d, 1 H, *J*= 6.4 Hz), 7.66 (d, 2 H, *J*= 6.8 Hz), 7.58-7.46 (m, 5 H), 7.35-7.34 (m, 3 H), 7.16-7.15 (m, 2 H), 7.06 (d, 2 H, *J*= 7.2 Hz), 6.93-6.92 (m, 2 H), 4.71-4.17 (m, 4 H), 3.87 (s, 6 H). ^{13}C NMR (125 MHz, 100 °C) (DMSO) δ 169.01, 168.67, 162.96, 162.58, 137.45, 133.95, 131.23, 130.83, 129.81, 129.24, 129.08, 127.48, 126.23, 126.17, 126.00, 123.54, 113.98, 55.44, 55.40, 52.57, 52.28. HRMS (ESI) Calcd for $C_{34}H_{30}N_2O_{10}S_3$ $(M+H)^+$ 723.1135, found 723.1133.

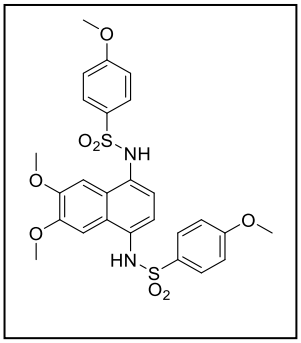
6,7-Dimethoxy-4-nitronaphthalen-1-amine (93)



Commercially available 6,7-dimethoxy-1-nitronaphthalene 2 g (1.2 g, 5.1 mmol) and (2.22 g, 32 mmol) of powdered hydroxylamine hydrochloride are dissolved in 150 ml. of 95% ethanol heated in a bath maintained at 50-60°C. A filtered solution of (4.4 g, 79 mmol) of potassium hydroxide in 30 ml of ethanol is added slowly with stirring over 1 hour. Stirring is continued for overnight, and the warm solution is poured slowly into 0.5 l. of ice water. Then, filter the solid and washed thoroughly with water and recrystallized from acetonitrile. The greenish colored solid, 575 mg, yield 45%. ^{1}H NMR (400 MHz) (DMSO) δ) 8.57 (s, 1 H), 8.31 (d, 1 H, *J*= 8.8 Hz), 7.80 (d, 2 H, *J*= 1.6 Hz), 7.45 (s, 1 H), 6.58 (d, 2 H, *J*= 9.2 Hz), 3.99 (s, 3 H), 3.98 (s, 3 H).

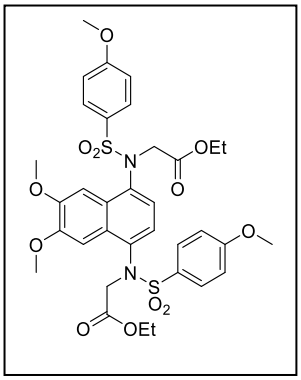
^{13}C NMR (100 MHz) (DMSO) δ 152.51, 152.26, 147.97, 133.30, 128.61, 124.31, 115.73, 105.04, 103.60, 103.41, 55.83, 55.29.

N,N'-(6,7-Dimethoxynaphthalene-1,4-diyl)bis(4-methoxybenzenesulfonamide) (95)



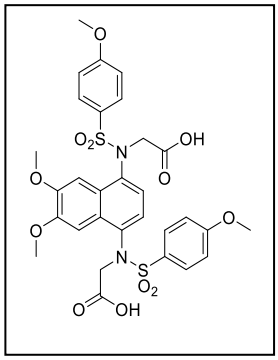
Reduction of intermediate (93) using general procedure (E1) gave the diamine intermediate which was taken directly after removal of organic solvent to the next step. The sulfonamide intermediate (95) prepared using general procedure (method A2), off-white solid, the yield (458 mg, 82% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 9.94 (s, 2 H), 7.53-7.50 (m, 4 H), 7.10-7.07 (m, 4 H), 6.95 (d, 2 H, *J*= 8.4 Hz), 3.74 (s, 6 H), 3.67 (s, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 162.25, 148.94, 131.78, 129.55, 128.78, 125.27, 121.62, 114.16, 102.42, 55.57, 55.20.

Diethyl 2,2'-((6,7-dimethoxynaphthalene-1,4-diyl)bis(((4-methoxyphenyl)sulfonyl) azanediyl)) diacetate (96)



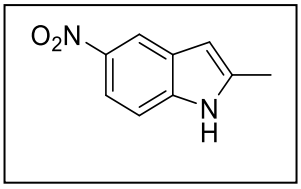
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product, the yield 129 mg, 88% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 7.64-7.61 (m, 4 H), 7.46 (d, 2 H, *J*= 5.2 Hz), 6.99 (s, 1 H), 6.95 (s, 1 H), 6.91-6.86 (m, 4 H), 4.41-4.36 (m, 4 H), 4.15-4.09 (m, 4 H), 3.90 (s, 6 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 1.21-1.14 (m, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 168.92, 168.87, 163.26, 163.22, 150.72, 150.63, 135.99, 135.86, 130.67, 130.33, 130.28, 130.19, 129.37, 129.32, 125.79, 125.67, 113.98, 113.95, 103.22, 103.17, 61.45, 61.42, 55.96, 55.64, 55.61, 53.22, 14.08.

2,2'-((6,7-Dimethoxynaphthalene-1,4-diyl) bis (((4-methoxyphenyl) sulfonyl) azanediyl)) diacetic acid (**97**)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (base hydrolysis) to get the title compound as an off-white solid; the yield (32 mg, 91% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 12.90 (s, 2 H), 7.60 (d, 4 H, *J*= 8.4 Hz), 7.55 (s, 1 H), 7.37 (s, 1 H), 7.09 (d, 2 H, *J*= 8.4 Hz), 7.07 (s, 1 H), 7.04 (d, 2 H, *J*= 8.4 Hz), 6.83 (s, 1 H), 4.44-4.27 (m, 4 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.71 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.36, 170.32, 162.83, 162.80, 149.76, 149.76, 135.57, 135.53, 130.36, 129.94, 129.82, 129.76, 128.85, 128.59, 125.79, 125.30, 114.39, 114.30, 103.59, 103.41, 55.75, 55.26, 55.14, 53.24, 53.09. HRMS (ESI) Calcd for $C_{30}H_{30}N_2O_{12}S_2$ $(M+H)^+$ 675.1313, found 675.1313.

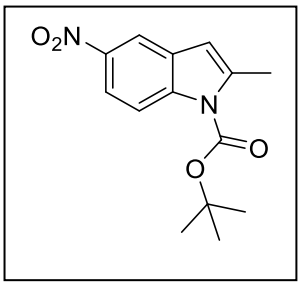
2-Methyl-5-nitro-1*H*-indole (98)



To a vigorously stirred solution of commercially available 2-methyl-indole (262 mg, 2 mmol) in H_2SO_4 (2 mL) at 0 °C, A solution of $NaNO_3$ (187 mg, 2.2 mmol) in H_2SO_4 (2 mL) was added dropwise. Then, the reaction was stirred for another 10 minutes, and then poured into 8 mL of ice-water, precipitating a yellow product. The product was isolated via filtration and washed with cold water. 335 mg of yellow solid (96%). ^{1}H NMR (400 MHz) (DMSO) δ) 11.68 (s, 1 H), 8.38 (s, 1 H), 7.90 (d, 1 H, *J*= 8.8 Hz), 7.40 (d, 1 H, *J*= 8.8 Hz),

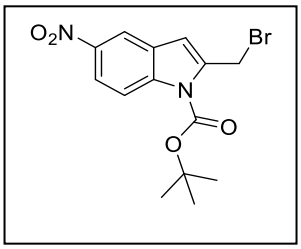
6.37 (s, 1 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ140.48, 139.90, 139.42, 127.96, 115.81, 115.61, 110.63, 101.58, 13.32.

tert-Butyl 2-methyl-5-nitro-1_H_-indole-1-carboxylate (99a)



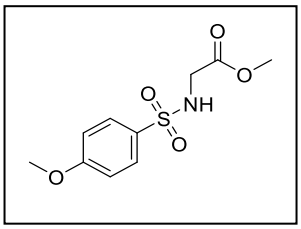
Prepared as described in the general procedure (method B) to get the title compound as brown oily product; the yield 449 mg, quantitative). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.32 (d, 1 H, *J*= 2.4 Hz), 8.20 (d, 1 H, *J*= 9.2 Hz), 8.11 (dd, 1 H, *J*= 2.4 Hz, 9.2 Hz), 6.45 (s, 1 H) 2.62 (s, 3 H), 1.70 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ149.91, 143.59, 141.15, 139.82, 129.18, 118.41, 115.59, 115.49, 108.34, 85.22, 28.23, 17.26.

tert-Butyl 2-(bromomethyl)-5-nitro-1_H_-indole-1-carboxylate (99)



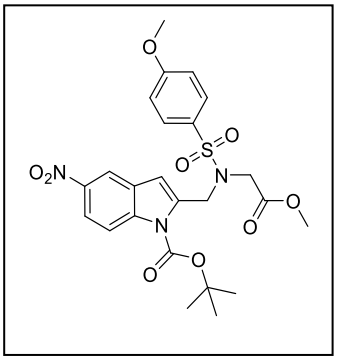
Intermediate (**99a**) (415 mg, 1.5 mmol), NBS (320 mg, 1.8 mmol), and AIBN (50 mg, 0.3 mmol) were taken in DCM (7 ml) in sealed tube and the reaction mixture stirred at 80 °C for 8 hours and checked for reaction completion using TLC. Then, filter and the organic layer removed under reduced pressure to get the crude product which was purified using ISCO (Ethyl acetate: Hexane), the yield (329 mg, 62% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.42 (d, 1 H, *J*= 2.4 Hz), 8.28 (d, 1 H, *J*= 9.2 Hz), 8.20 (dd, 1 H, *J*= 2.4 Hz, 9.2 Hz), 6.84 (s, 1 H), 4.90 (s, 2 H), 1.75 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ149.14, 144.05, 140.63, 139.31, 128.07, 120.35, 117.13, 116.24, 111.78, 86.54, 28.11, 26.26.

Methyl ((4-methoxyphenyl) sulfonyl) glycinate (100)



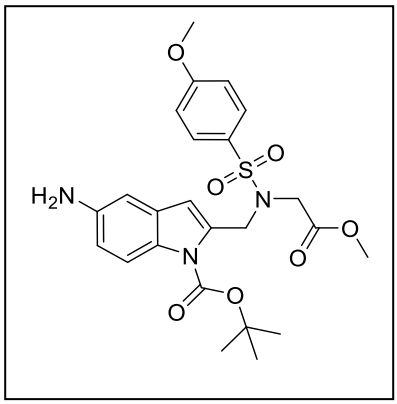
Prepared as described in the general procedure for synthesis of sulfonamides (method A1) to get the title compound as a white solid; the yield 129 mg, 88% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.05 (s, 1 H), 7.71 (d, 2 H, *J*= 8.8 Hz), 7.08 (d, 2 H, *J*= 8.8 Hz), 3.82 (s, 3 H), 3.65 (s, 2 H), 3.52 (s, 3 H), 3.37 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.22, 161.99, 131.93, 128.46, 114.01, 55.41, 51.58, 43.51.

tert-Butyl 2-(((4-methoxy-N-(2-methoxy-2-oxoethyl)phenyl)sulfonamido)methyl)-5-nitro-1*H*-indole-1-carboxylate (101)



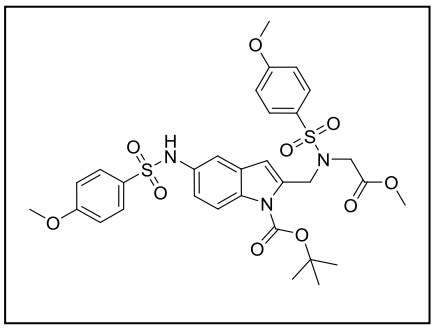
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (129 mg, 88% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.51 (s, 1 H), 8.14 (s, 2 H), 7.77 (d, 2 H, *J*= 8.8 Hz), 7.08 (d, 2 H, *J*= 8.8 Hz), 6.88 (s, 1 H), 4.79 (s, 2 H), 4.21 (s, 2 H), 3.83 (s, 3 H), 3.52 (s, 3 H), 1.61 (s, 9 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.20, 168.94, 162.50, 148.66, 142.91, 140.18, 139.19, 132.00, 130.26, 129.14, 128.44, 128.21, 118.69, 116.25, 115.18, 114.15, 114.00, 108.33, 85.67, 55.49, 55.42, 51.63, 51.57, 48.83, 47.60, 43.51, 27.31.

tert-Butyl 5-amino-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1*H*-indole-1-carboxylate (102)



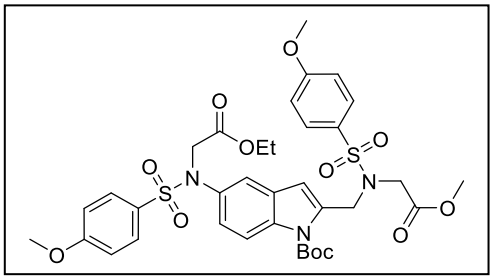
Prepared as described in the general procedure for nitro group reduction (Method E2) to get the title compound as a beige solid; the yield (129 mg, 88% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.76 (m, 3 H), 6.86 (d, 2 H, *J*= 9.2 Hz), 6.70 (d, 1 H, *J*= 2.0 Hz), 6.60 (dd, 2 H, *J*= 2.4 Hz, 8.8 Hz), 6.41 (s, 1 H), 4.85 (s, 2 H), 4.16 (s, 2 H), 3.79 (s, 3 H), 3.57 (s, 3 H), 1.60 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.50, 162.55, 150.22, 142.25, 136.17, 131.55, 130.64, 129.87, 129.47, 116.03, 113.92, 113.39, 109.00, 105.47, 83.98, 55.55, 52.08, 48.63, 47.77, 28.19.

***tert*-Butyl 2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-5-((4-methoxyphenyl) sulfonamido)-1*H*-indole-1-carboxylate (103)**



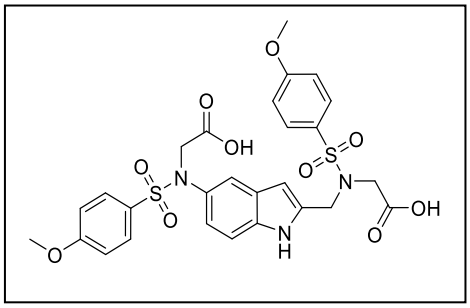
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a beige solid; the yield (129 mg, 88% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.80 (d, 1 H, *J*= 8.8 Hz), 7.76 (d, 2 H, *J*= 9.2 Hz), 7.12 (d, 1 H, *J*= 1.6 Hz), 7.08 (s, 1 H), 6.95 (dd, 1 H, *J*= 2.4 Hz, 8.8 Hz), 6.89 (d, 2 H, *J*= 8.8 Hz), 6.82 (d, 2 H, *J*= 8.8 Hz), 6.51 (s, 1 H), 4.87 (s, 2 H), 4.18 (s, 2 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.58 (s, 3 H), 1.62 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.46, 163.09, 163.04, 150.04, 137.33, 134.69, 131.79, 131.40, 130.69, 129.62, 129.48, 129.37, 119.54, 116.04, 114.38, 114.21, 114.10, 108.94, 84.89, 55.69, 55.62, 52.25, 48.78, 47.98, 28.25.

***tert*-Butyl 5-((N-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl) sulfonamido)-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1*H*-indole-1-carboxylate (104)**



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (129 mg, 88% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.88 (d, 1 H, *J*= 8.8 Hz), 7.75 (d, 2 H, *J*= 8.8 Hz), 7.60 (d, 2 H, *J*= 8.8 Hz), 7.27 (d, 1 H, *J*= 2.0 Hz), 7.13 (dd, 1 H, *J*= 2.0 Hz, 8.8 Hz), 6.92-6.89 (m, 4 H), 6.57 (s, 1 H), 4.88 (s, 2 H), 4.42 (s, 2 H), 4.17-4.11 (m, 4 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.60 (s, 3 H), 1.63 (s, 9 H), 1.22 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.40, 168.99, 163.07, 150.00, 137.48, 136.06, 134.95, 131.37, 130.68, 130.03, 129.57, 129.26, 125.12, 120.89, 116.00, 114.08, 113.98, 109.16, 85.05, 61.46, 55.68, 55.66, 53.25, 52.21, 48.68, 47.86, 28.22, 14.17.

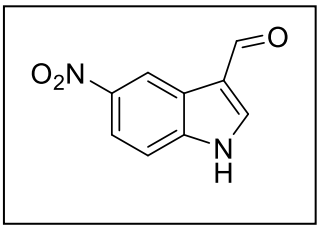
N-((5-((N-(Carboxymethyl)-4-methoxyphenyl) sulfonamido)-1*H*-indol-2-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycine (105)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (base hydrolysis) to get the title compound as an off-white solid; the yield (129 mg, 88% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 12.73 (br, 2 H), 11.13 (s, 1 H), 7.77 (d, 2 H, *J*= 8.8 Hz), 7.56 (d, 2 H, *J*= 8.8 Hz), 7.26-7.22 (m, 2 H), 7.08-7.05 (m, 4 H), 6.78 (dd, 1 H, *J*= 2.0 Hz, 8.8 Hz), 6.20 (s, 1 H), 4.53 (s, 2 H),

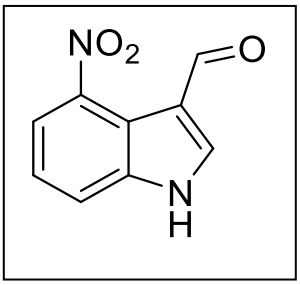
4.34 (s, 2 H), 3.89 (s, 2 H), 3.84 (s, 6 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.18, 169.85, 162.51, 162.46, 135.54, 134.85, 131.37, 130.93, 130.65, 129.49, 129.30, 127.49, 121.86, 120.53, 114.26, 114.14, 111.40, 101.88, 55.66, 53.16, 47.58, 44.87. HRMS (ESI) Calcd for $C_{27}H_{27}N_3O_{10}S_2$ $(M+H)^+$ 618.1211, found 618.1217.

5-Nitro-1*H*-indole-3-carbaldehyde (107a)



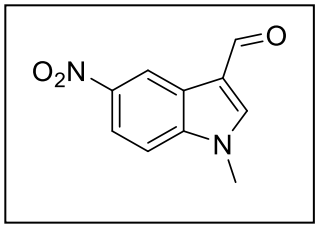
To a stirred solution of commercially available 5-nitroindole (486 mg, 3 mmol) in anhydrous DMF under nitrogen, phosphorus chloride oxide (0.834 ml, 9 mmol) was added at 0 °C. The reaction mixture stirred at room temperature for 1h and then poured into cold saturated aqueous $NaHCO_3$ solution and stirred for 0.5 h and extracted by EtOAc (3 X). The organic layer washed with brine, dried over anhydrous Na_2SO_4, and the organic layer removed using rotovap. The crude product purified by ISCO to get the desired product, 519 mg, yield 91%. ^{1}H NMR (400 MHz) (DMSO) δ) 12.68 (s, 1H) 10.02 (s, 1H) 8.43 (s, 1H) 8.92 (d, J = 2.0 Hz, 1H) 8.56 (s, 1 H), 7.96 (dd, J = 2.4 Hz, 8.8 Hz, 1H) 7.71 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz) (DMSO) δ 185.48, 123.50, 119.04, 118.75, 117.03, 113.19.

4-Nitro-1*H*-indole-3-carbaldehyde (107b)



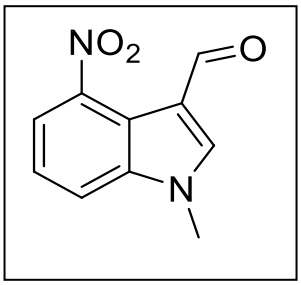
To a stirred solution of commercially available 4-nitroindole (486 mg, 3 mmol) in anhydrous DMF under nitrogen, phosphorus chloride oxide (0.834 ml, 9 mmol) was added at 0 °C. The reaction mixture stirred at room temperature for 1h and then poured into cold saturated aqueous $NaHCO_3$ solution and stirred for 0.5 h and extracted by EtOAc (3 X). The organic layer washed with brine, dried over anhydrous Na_2SO_4, and the organic layer removed using rotovap. The crude product purified by ISCO to get the desired product, 461 mg, yield 81% ^{1}H NMR (400 MHz) (DMSO) δ) 12.86 (s, 1H) 10.12 (s, 1H) 8.50 (s, 1H), 7.92-7.86 (m, 2 H), 7.42 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz) (DMSO) δ 185.02, 142.29, 138.92, 138.11, 122.23, 118.33, 117.90, 116.30, 115.49.

1-Methyl-5-nitro-1*H*-indole-3-carbaldehyde (108a)



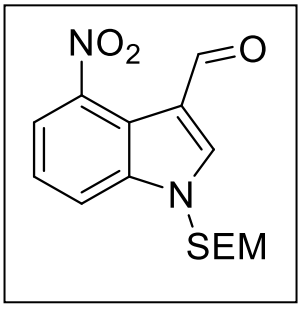
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (351 mg, 86% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 9.94 (s, 1 H), 8.81 (d, J = 2.4 Hz, 1H) 8.48 (s, 1 H), 8.12 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 3.94 (s, 1 H). ^{13}C NMR (100 MHz) (DMSO) δ 184.84, 144.29, 142.95, 140.39, 123.69, 118.51, 117.84, 116.92, 111.69, 33.75.

1-Methyl-4-nitro-1*H*-indole-3-carbaldehyde (108b)



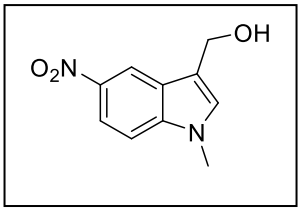
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield 343 mg, 86% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 10.07 (s, 1H) 8.51 (s, 1H), 8.03-7.92 (m, 2 H), 7.49 (s, 1H), 3.97 (s, 3 H); ^{13}C NMR (100 MHz) (DMSO) δ 184.95, 142.54, 141.72, 139.64, 122.52, 118.58, 117.32, 116.23, 115.27, 33.83.

4-Nitro-1-((2-(trimethylsilyl) ethoxy) methyl)-1*H*-indole-3-carbaldehyde (108c)



Prepared as described in the general procedure (method A2) to get the title compound as a yellow solid; the yield 129 mg, 88% yield). ^{1}H NMR (400 MHz) (acetone-d_6) δ) 10.25 (s, 1H) 8.50 (s, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 5.86 (s, 2 H), 3.64 (t, *J* = 8.0 Hz, 2H), 2.82 (s, 6 H), 0.93 (t, *J* = 8.0 Hz, 2H), -0.06 (s, 9 H); ^{13}C NMR (100 MHz) (acetone-d_6) δ 186.18, 140.27, 140.19, 123.73, 120.03, 118.59, 118.55, 117.81, 77.65, 67.19, 18.24, -1.35

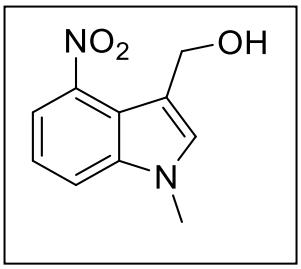
(1-Methyl-5-nitro-1*H*-indol-3-yl) methanol (109a)



To a stirred solution of (306 mg, 1.5 mmol) in EtOH: THF (1:1) (10 ml) at 0 °C, NaBH4 (121 mg, 3 mmol) was added and the reaction stirred at 0 °C for 2 h and monitor the reaction by TLC. Then, reaction mixture diluted with ethyl acetate and washed with 1N HCl, brine, dried over anhydrous Na_2SO_4, and the organic layer concentrated under reduced pressure to get the desired product, the yield 251 mg, 81% yield). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 8.65 (d, J = 2.0 Hz, 1H), 8.07 (dd, J = 2.4 Hz, 5.2 Hz, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.42 (s, 1 H), 4.85 (d, J = 5.2 Hz, 2H), 4.11 (t, J = 5.2 Hz, 1H), 3.90 (s, 1 H). ^{13}C NMR (100

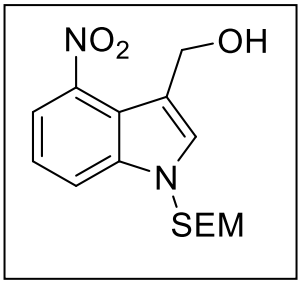
MHz) (Acetone-d_6) δ 142.00, 141.00, 131.77, 127.48, 119.60, 117.49, 117.30, 110.59, 56.49, 33.24.

(1-Methyl-4-nitro-1*H*-indol-3-yl) methanol (109b)



To a stirred solution of (306 mg, 1.5 mmol) in EtOH: THF (1:1) (10 ml) at 0 °C, NaBH4 (121 mg, 3 mmol) was added and the reaction stirred at 0 °C for 2 h and monitor the reaction by TLC. Then, reaction mixture diluted with ethyl acetate and washed with 1N HCl, brine, dried over anhydrous Na_2SO_4, and the organic layer concentrated under reduced pressure to get the desired product, the yield 244 mg, 79% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.93 (d, 1 H, *J*= 8.0 Hz), 7.53 (d, 1 H, *J*= 8.4 Hz), 7.22-7.18 (m, 2 H), 4.82 (s, 2 H), 3.76 (s, 3 H), 2.39 (s, 1 H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 142.46, 140.10, 133.73, 120.69, 119.18, 118.19, 116.09, 114.94, 58.46, 33.25.

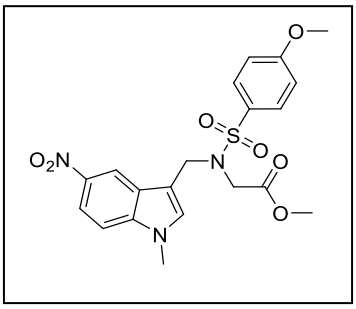
(4-Nitro-1-((2-(trimethylsilyl) ethoxy) methyl)-1*H*-indol-3-yl) methanol (109c)



To a stirred solution of (485 mg, 1.5 mmol) in EtOH: THF (1:1) (10 ml) at 0 °C, NaBH4 (121 mg, 3 mmol) was added and the reaction stirred at 0 °C for 2 h and monitor the reaction by TLC. Then, reaction mixture diluted with ethyl acetate and washed with 1N HCl, brine, dried over anhydrous Na_2SO_4, and the organic layer concentrated under reduced pressure to get the desired product, the yield 387 mg, 80% yield). ^{1}H NMR (400 MHz) (acetone-d_6) δ) 8.01 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.77 (s, 1 H), 7.41 (t, *J* = 8.0 Hz, 1H), 5.74 (s, 2 H), 4.95 (s, 2 H), 3.97 (br, 1 H), 3.63 (t, *J* = 8.0 Hz, 2H), 0.00

(s, 9 H); ^{13}C NMR (100 MHz) (acetone-d_6) δ 143.56, 140.27, 132.58, 121.48, 120.02, 118.04, 117.36, 116.83, 76.40, 66.47, 58.67, 18.13, -1.33.

Methyl N-((4-methoxyphenyl) sulfonyl)-N-((1-methyl-5-nitro-1*H*-indol-3-yl) methyl) glycinate (110a)

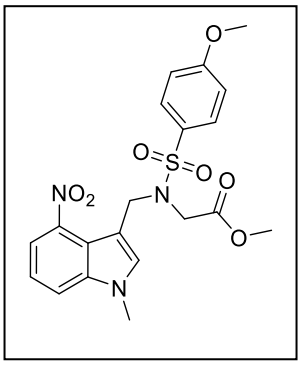


A mixture of (**109 a**) (206 mg, 1 mmol), PPh_3 (314 mg, 1.2 mmol), DIAD (242 mg, 1.2 mmol), in anhydrous THF (5 ml) under nitrogen atmosphere was stirred at room temperature overnight till reaction completion. Then the organic layer concentrated under reduced pressure and the crude mixture purified by ISCO using ethyl acetate: hexane to get the desired product, the yield (308 mg, 69% yield). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 8.57 (d, J = 6.4 Hz, 1H), 8.06 (dd, J = 2.0 Hz, 8.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 9.2 Hz, 1H), 7.43 (s, 1 H), 7.10 (d, J = 8.8 Hz, 1H), 4.69 (s, 2H), 3.96 (s, 2 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.46 (s, 3 H). ^{13}C NMR (100 MHz) (Acetone-d_6) δ 170.02, 164.01, 142.42, 141.04, 134.46, 132.63, 130.36, 127.55, 117.32, 117.19, 115.03, 111.77, 110.87, 56.13, 52.06, 47.64, 43.43, 33.44.

Methyl N-((4-methoxyphenyl)sulfonyl)-N-((1-methyl-4-nitro-1*H*-indol-3-yl)methyl)glycinate (110b)

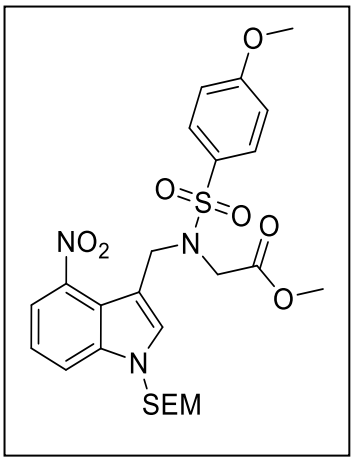
A mixture of (**109 b**) (206 mg, 1 mmol), PPh3 (314 mg, 1.2 mmol), DIAD (242 mg, 1.2 mmol), in anhydrous THF (5 ml) under nitrogen atmosphere was stirred at room temperature overnight till reaction completion. Then the organic layer concentrated under reduced pressure and the crude mixture purified by ISCO using ethyl acetate: hexane to get

the desired product, the yield 273 mg, 61% yield). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 7.65 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.47 (s, 1 H), 7.22 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 7.2 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 5.46 (s, 2H), 4.71 (s, 2 H), 4.03 (s, 3 H), 3.87 (s, 3 H), 3.55 (s, 3 H).

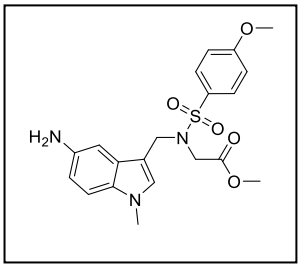


Methyl N-((4-methoxyphenyl) sulfonyl)-N-((4-nitro-1-((2-(trimethylsilyl) ethoxy) methyl)-1*H*-indol-3-yl) methyl)glycinate (110c)

A mixture of (**109 c**) (323 mg, 1 mmol), PPh3 (314 mg, 1.2 mmol), DIAD (242 mg, 1.2 mmol), in anhydrous THF (5 ml) under nitrogen atmosphere was stirred at room temperature overnight till reaction completion. Then the organic layer concentrated under reduced pressure and the crude mixture purified by ISCO using ethyl acetate: hexane to get the desired product, the yield (361 mg, 64% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.89 (d, 1 H, *J*= 8.0 Hz), 7.78 (d, 1 H, *J*= 8.4 Hz), 7.71-7.69 (m, 3 H), 7.31-7.26 (m, 1 H), 6.87 (d, 2 H, *J*= 8.8 Hz), 5.54 (s, 2 H), 4.80 (s, 2 H), 4.12 (s, 2 H), 3.86 (s, 3 H), 3.66 (s, 3 H), 3.55 (t, 2 H, *J*= 8.0 Hz), 0.94 (t, 2 H, *J*= 8.8 Hz), 0.00 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.70, 162.63, 142.44, 139.12, 133.56, 131.38, 129.25, 120.99, 119.85, 118.36, 113.78, 109.95, 76.17, 66.39, 55.52, 52.07, 49.23, 46.62, 17.69, -1.44.

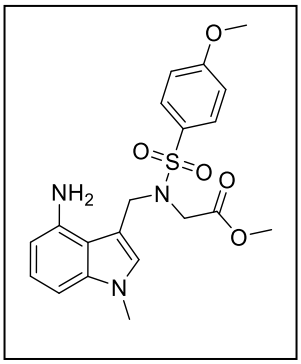


Methyl N-((5-amino-1-methyl-1*H*-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycinate (111a)



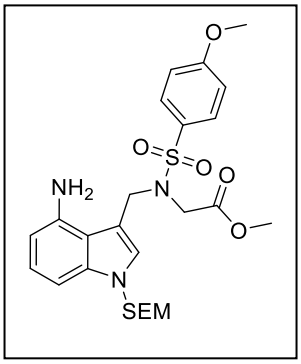
Prepared as described in the general procedure for nitro group reduction (Method E2) to get the title compound as a light pink solid; the yield 245 mg, quantitative). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 7.60 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 6.61 (s, 1 H), 6.56 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 2.0 Hz, 8.4 Hz, 1H), 4.34 (s, 2H), 3.68 (s, 3 H), 3.66 (s, 2 H), 3.45 (s, 3 H), 3.27 (s, 3 H). ^{13}C NMR (100 MHz) (Acetone-d_6) δ 170.02, 162.50, 142.30, 138.50, 134.10, 132.00, 130.90, 128.92, 127.00, 117.00, 113.54, 109.50, 108.06, 55.03, 54.91, 47.10, 43.05, 33.07.

Methyl N-((4-amino-1-methyl-1*H*-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycinate (111b)



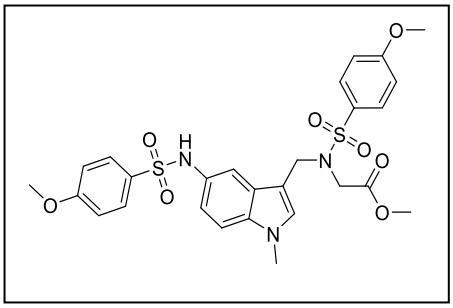
Prepared as described in the general procedure for nitro group reduction (Method E2) to get the title compound as a yellow solid; the yield 201 mg, quantitative). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.70 (d, 2 H, *J*= 8.8 Hz), 6.92-6.89 (m, 3 H), 6.56-6.54 (m, 2 H), 6.24 (d, 1 H, *J*= 7.6 Hz), 4.54 (s, 2 H), 3.81 (s, 2 H), 3.78 (s, 3 H), 3.52 (s, 3 H), 3.26 (s, 3 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.53, 163.28, 145.13, 141.81, 139.60, 130.00, 128.73, 123.89, 115.95, 114.25, 106.68, 105.00, 99.69, 55.74, 51.82, 46.55, 44.77, 31.53.

Methyl N-((4-amino-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)methyl)-N-((4-methoxyphenyl)sulfonyl)glycinate (111c)



Prepared as described in the general procedure for nitro group reduction (Method E2) to get the title compound as a yellow solid; the yield 245 mg, quantitative). ^{1}H NMR (400 MHz) (DMSO) δ) 7.81 (d, 2 H, *J*= 8.8 Hz), 7.01-6.99 (m, 3 H), 6.82-6.78 (m, 2 H), 6.36 (d, 2 H, *J*= 7.6 Hz), 5.30 (s, 2 H), 4.63 (s, 2 H), 3.90-3.87 (m, 5), 3.40 (t, 2 H, *J*= 8.0 Hz), 3.34 (s, 3 H), 0.84 (t, 2 H, *J*= 8.0 Hz), -0.09 (s, 9 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.37, 166.34, 141.82, 139.29, 130.03, 127.85, 124.45, 122.22, 116.30, 114.28, 111.89, 108.25, 105.82, 100.38, 75.64, 65.92, 55.74, 51.82, 46.69, 44.78, 17.84, -1.35.

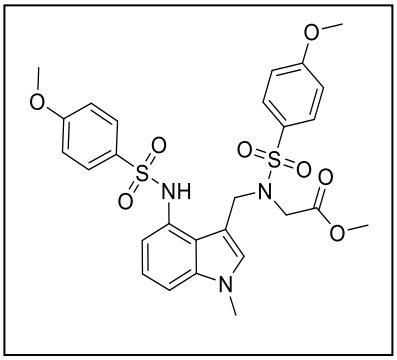
Methyl N-((5-((4-methoxyphenyl) sulfonamido)-1-methyl-1*H*-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycinate (112a)



Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a yellow solid; the yield (215 mg, 73% yield). ^{1}H NMR (400 MHz) (acetone-d_6) δ) 8.63 (s, 1 H), 7.81 (d, 2 H, *J*= 8.8 Hz), 7.70 (d, 2 H, *J*= 8.8 Hz), 7.36 (d, 1 H, *J*= 2.0 Hz), 7.25 (d, 1 H, *J*= 8.8 Hz), 7.11-7.08 (m, 4 H), 6.98 (d, 2 H, *J*= 8.8 Hz), 4.55 (s, 2 H), 3.92 (s, 3 H), 3.83 (s, 3 H), 3.79 (s, 2 H), 3.72 (s, 3 H), 3.41 (s, 3 H). ^{13}C NMR (100 MHz) (acetone-d_6) δ 169.96, 163.89, 163.65, 136.16, 132.76, 132.72, 131.83,

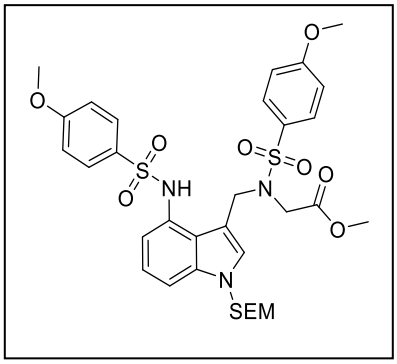
131.05, 130.37, 130.27, 128.52, 119.12, 114.98, 114.79, 114.00, 110.73, 108.32, 56.14, 55.98, 51.97, 47.07, 43.41, 32.95.

Methyl N-((4-((4-methoxyphenyl) sulfonamido)-1-methyl-1*H*-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycinate (112b)



Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a yellow solid; the yield (203 mg, 69% yield). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 8.19 (s, 1 H), 7.82 (d, 2 H, *J*= 8.8 Hz), 7.72 (d, 2 H, *J*= 8.8 Hz), 7.21 (d, 1 H, *J*= 8.0 Hz), 7.12-7.06 (m, 4 H), 7.00 (t, 3 H, *J*= 8.4 Hz), 4.42 (s, 2 H), 3.92 (s, 3 H), 3.88 (s, 2 H), 3.85 (s, 3 H), 3.72 (s, 3 H), 3.31 (s, 3 H). ^{13}C NMR (100 MHz) (Acetone-d_6) δ 169.89, 164.21, 163.89, 139.87, 133.44, 132.14, 131.12, 130.79, 130.49, 130.31, 122.87, 122.66, 117.25, 115.07, 114.75, 108.68, 107.56, 56.20, 56.09, 51.97, 48.66, 45.72, 33.08.

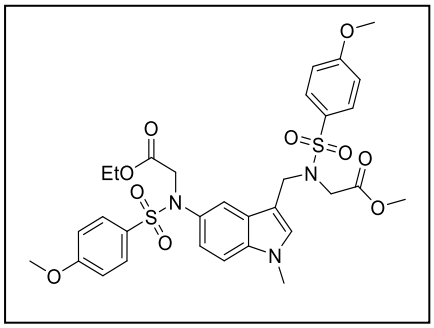
Methyl N-((4-((4-methoxyphenyl) sulfonamido)-1-((2-(trimethylsilyl) ethoxy) methyl)-1*H*-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycinate (112c)



Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a yellow solid; the yield (249 mg, 71% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.94 (s, 1 H), 7.82-7.79 (m, 4 H), 7.25-7.13 (m, 3 H), 6.95 (d, 2 H, *J*= 8.8 Hz), 6.91 (s, 1 H), 6.86 (d, 2 H, *J*= 8.8 Hz), 5.33 (s, 2 H),

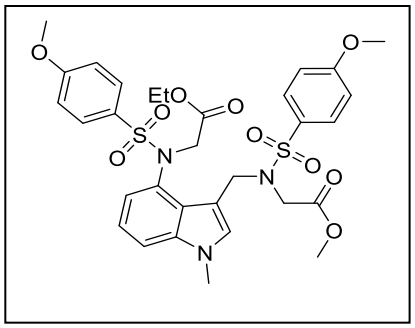
4.35 (s, 2 H), 3.86 (s, 3 H), 3.81 (s, 5 H), 3.40 (t, 2 H, *J*= 8.0 Hz), 3.29 (s, 3 H), 0.85 (t, 2 H, *J*= 8.0 Hz), -0.08 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.31, 163.36, 162.86, 138.46, 132.50, 130.19, 129.91, 129.60, 129.40, 123.39, 121.56, 116.51, 114.24, 113.93, 108.04, 107.49, 75.80, 66.15, 55.75, 55.64, 51.96, 47.73, 44.61, 17.79, -1.36.

Ethyl N-(3-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1-methyl-1*H*-indol-5-yl)-N-((4-methoxyphenyl) sulfonyl) glycinate (113a)



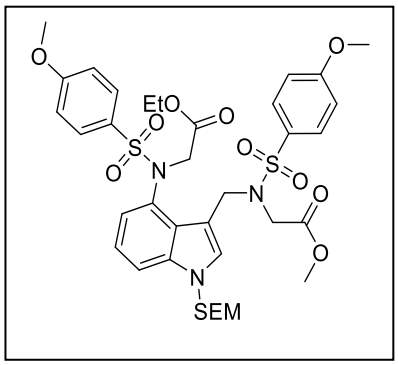
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (114 mg, 85% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.80 (d, 2 H, *J*= 8.8 Hz), 7.63 (d, 2 H, *J*= 8.8 Hz), 7.26 (d, 1 H, *J*= 2.0 Hz), 7.17 (d, 2 H, *J*= 1.2 Hz), 7.00 (d, 2 H, *J*= 8.8 Hz), 6.96 (s, 1 H), 6.93 (d, 1 H, *J*= 8.8 Hz), 4.50 (s, 2 H), 4.39 (s, 2 H), 4.13 (q, 2 H, *J*= 7.2 Hz), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.84 (s, 2 H), 3.70 (s, 3 H), 3.51 (s, 3 H), 1.22 t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.61, 169.07, 163.02, 163.00, 136.57, 132.35, 131.32, 130.91, 130.56, 129.94, 129.64, 127.44, 124.17, 119.69, 114.17, 114.03, 109.80, 108.34, 61.30, 55.67, 55.62, 53.55, 51.91, 46.36, 42.68, 33.00, 14.13.

Ethyl N-(3-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1-methyl-1*H*-indol-4-yl)-N-((4-methoxyphenyl) sulfonyl) glycinate (96)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (109 mg, 81% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.92 (d, 2 H, *J*= 9.2 Hz), 7.53 (d, 2 H, *J*= 9.2 Hz), 7.39 (s, 1 H), 7.24 (d, 1 H, *J*= 7.6 Hz), 7.01 (d, 2 H, *J*= 9.2 Hz), 6.95 (d, 1 H, *J*= 7.4 Hz), 6.91 (d, 2 H, *J*= 8.8 Hz), 6.32 (d, 1 H, *J*= 7.2 Hz), 5.02 (q, 2 H, *J*= 8.0 Hz), 4.43-4.26 (m, 2 H), 4.13 (d, 2 H, *J*= 5.2 Hz), 4.02 (q, 2 H, *J*= 7.2 Hz), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.77 (s, 3 H), 3.55 (s, 3 H), 1.09 (t, 1 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.93, 168.39, 163.27, 162.96, 138.95, 132.36, 131.54, 130.73, 130.58, 129.98, 129.73, 126.63, 120.95, 119.27, 114.17, 113.83, 110.57, 110.41, 61.29, 55.71, 55.69, 53.74, 51.95, 48.48, 45.41, 33.19, 14.10.

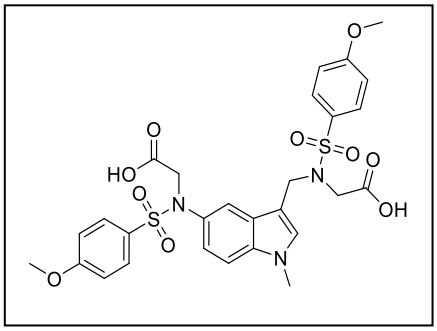
Ethyl N-(3-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1-((2-(trimethylsilyl) ethoxy) methyl)-1*H*-indol-4-yl)-N-((4-methoxyphenyl) sulfonyl) glycinate (113c)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (117 mg, 74% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.92 (d, 2 H, *J*= 8.8 Hz), 7.51-7.48 (m, 3 H), 7.42 (d, 1 H, *J*= 8.4 Hz), 7.01 (d, 2 H, *J*= 6.8 Hz), 6.97-6.89 (m, 3 H), 6.32 (d, 1 H, *J*= 7.6 Hz), 5.43 (q, 2 H, *J*= 8.8 Hz), 5.02 (q, 2 H, *J*= 8.4 Hz), 4.44-4.22 (m, 2 H), 4.10 (d, 2 H, *J*= 2.4 Hz), 4.05-3.98 (m, 2 H),

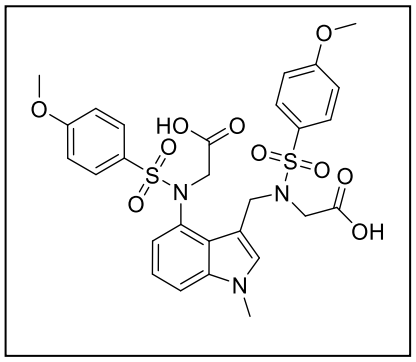
3.87 (s, 3 H), 3.86 (s, 3 H), 3.54 (s, 3 H), 3.50 (t, 2 H, *J*= 8.0 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.78, 168.22, 163.24, 162.90, 138.45, 132.39, 131.21, 130.63, 129.89, 129.60, 129.33, 127.44, 121.53, 119.93, 114.11, 113.78, 111.81, 111.26, 76.09, 66.10, 61.21, 55.65, 55.62, 53.69, 51.90, 48.48, 45.38, 17.77, 14.00, -1.37.

N-((5-((N-(Carboxymethyl)-4-methoxyphenyl) sulfonamido)-1-methyl-1*H*-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycine (114a)



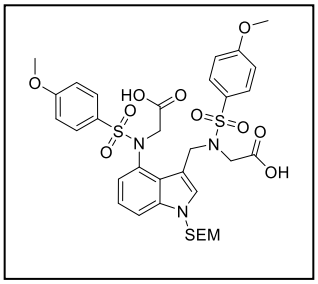
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (base hydrolysis) to get the title compound as a yellow solid; the yield (14 mg, 80% yield). ^{1}H NMR (400 MHz) (acetone-d_6) δ) 7.65 (d, 2 H, *J*= 8.8 Hz), 7.51 (d, 2 H, *J*= 8.8 Hz), 7.17 (d, 1 H, *J*= 8.8 Hz), 7.13 (d, 2 H, *J*= 1.6 Hz), 7.06 (d, 2 H, *J*= 2.0 Hz), 7.04 (s, 1 H), 6.96-6.92 (m, 4 H), 4.42 (s, 2 H), 4.29 (s, 2 H), 3.79 (s, 6 H), 3.73 (s, 2 H), 3.65 (s, 3 H). ^{13}C NMR (100 MHz) (acetone-d_6) δ 170.60, 170.45, 164.04, 163.82, 137.49, 133.44, 133.11, 132.12, 131.95, 130.75, 130.39, 128.25, 124.92, 120.06, 114.95, 114.91, 110.52, 109.20, 56.12, 53.94, 46.99, 43.27, 33.03. HRMS (ESI) Calcd for $C_{28}H_{29}N_3O_{10}S_2$ $(M+H)^+$ 632.1367, found 632.1364.

N-((4-((N-(Carboxymethyl)-4-methoxyphenyl) sulfonamido)-1-methyl-1*H*-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycine (114b)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (base hydrolysis) to get the title compound as a yellow solid; the yield (15 mg, 84% yield). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 7.92 (d, 2 H, *J*= 8.8 Hz), 7.55 (d, 2 H, *J*= 8.8 Hz), 7.34 (d, 1 H, *J*= 8.0 Hz), 7.28 (s, 1 H), 7.13 (d, 2 H, *J*= 8.8 Hz), 7.06 (d, 2 H, *J*= 8.8 Hz), 6.96 (t, 1 H, *J*= 8.0 Hz), 6.49 (d, 1 H, *J*= 7.6 Hz), 5.14-4.90 (m, 2 H), 4.59-4.34 (m, 2 H), 4.00 (d, 2 H, *J*= 6.8 Hz), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.78 (s, 3 H). ^{13}C NMR (100 MHz) (Acetone-d_6) δ 170.77, 170.08, 164.19, 163.91, 139.84, 133.42, 132.25, 131.30, 131.05, 130.85, 130.75, 127.52, 121.61, 120.18, 114.99, 114.71, 111.15, 111.10, 56.16, 56.11, 54.01, 49.23, 46.99, 33.12. HRMS (ESI) Calcd for $C_{28}H_{29}N_3O_{10}S_2$ $(M+H)^+$ 632.1367, found 632.1360.

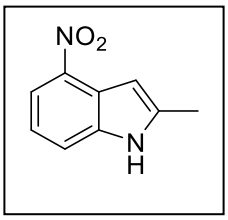
N-((4-((N-(Carboxymethyl)-4-methoxyphenyl) sulfonamido)-1-((2-(trimethylsilyl) ethoxy) methyl)-1*H*-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycine (114c)



Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (base hydrolysis) to get the title compound as light brown solid; the yield (25 mg, 88% yield). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 7.94 (d, 2 H, *J*= 8.4 Hz), 7.55 (d, 2 H, *J*= 8.8 Hz), 7.50 (d, 1 H, *J*= 8.0 Hz), 7.45 (s, 1 H), 7.13 (d, 2 H, *J*= 8.8 Hz), 7.06 (d, 2 H, *J*= 8.8 Hz), 7.00 (t, 1 H, *J*= 8.0 Hz), 6.52 (d, 1 H, *J*=

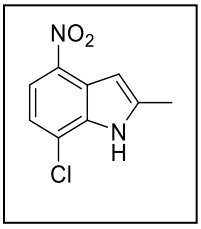
7.2 Hz), 5.53 (s, 2 H), 5.18-4.95 (m, 2 H), 4.62-4.33 (m, 2 H), 4.00 (d, 2 H, *J*= 8.4 Hz), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.55 (t, 2 H, *J*= 7.6 Hz), 0.87 (d, 2 H, *J*= 8.0 Hz), -0.06 (s, 9 H).^{13}C NMR (100 MHz) (Acetone-d_6) δ 164.22, 163.90, 139.43, 133.67, 132.20, 131.32, 310.75, 130.14, 128.36, 122.17, 120.88, 115.01, 114.73, 112.56, 111.93, 76.44, 66.42, 56.17, 56.11, 54.06, 49.28, 46.94, 18.24, -1.24. HRMS (ESI) Calcd for $C_{33}H_{41}N_3O_{11}S_2$ Si_2 $(M+H)^+$ 748.2025, found 748.2022.

2-Methyl-4-nitro-1*H*-indole (115a)



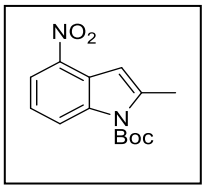
In open flask under air, to a stirred solution of 3-nitroaniline (690 mg, 5 mmol) and acetone (0.882 ml, 7 mmol) in DMSO (15 mL) at 15 °C, t-BuOK (1.34 g, 12 mmol) was added in one portion results in red-violet colored reaction mixture which indicate the reaction progress. The reaction kept at room temperature overnight and then diluted with ethyl acetate (150 mL) and washed with aqueous NH4Cl (60 mL), brine, dried over Na_2SO_4, and the organic layer concentrated under vacuum to get the crude product. The crude product purified by ISCO using hexane–toluene as a mobile phase to get the desired product as a yellow solid (the yield (461 mg, 52% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 11.86 (s, 1 H), 8.00 (d, 1 H, *J*= 8.4 Hz), 7.75 (d, 1 H, *J*= 8.0 Hz), 7.20 (t, 1 H, *J*= 8.0 Hz), 6.81 (s, 1 H). ^{13}C NMR (100 MHz) (DMSO) δ 142.30, 138.46, 138.04, 122.61, 119.13, 117.97, 116.51, 99.80, 13.42.

7-Chloro-2-methyl-4-nitro-1*H*-indole (115b)



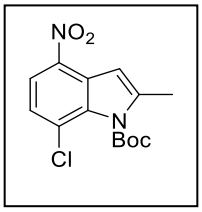
In open flask under air, to a stirred solution of 2-chloro-5-nitroaniline (860 mg, 5 mmol) and acetone (0.882 ml, 7 mmol) in DMSO (15 mL) at 15 °C, t-BuOK (1.34 g, 12 mmol) was added in one portion results in red-violet colored reaction mixture which indicate the reaction progress. The reaction kept at room temperature overnight and then diluted with ethyl acetate (150 mL) and washed with aqueous NH4Cl (60 mL), brine, dried over Na_2SO_4, and the organic layer concentrated under vacuum to get the crude product. The crude product purified by ISCO using hexane–toluene as a mobile phase to get the desired product as a yellow solid (the yield (441 mg, 42% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 12.11 (br, 1 H), 7.94 (d, 1 H, *J*= 8.4 Hz), 7.23 (d, 1 H, *J*= 8.4 Hz), 6.82 (s, 1 H), 2.49 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 143.88, 136.93, 134.80, 123.86, 122.41, 118.91, 117.62, 101.12, 13.34.

tert-Butyl 2-methyl-4-nitro-1*H*-indole-1-carboxylate (116a)



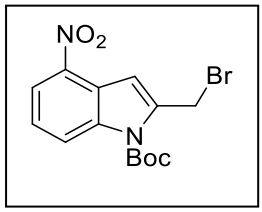
To a stirred solution of (**115a**) (345 mg, 2 mmole) in DCM (10 ml), $(Boc)_2O$ (872 mg, 4 mmol), TEA (0.415 ml, 3 mmol), DMAP (25 mg, 0.2 mmol) were added and the reaction mixture stirred under nitrogen for 3 hours then diluted with DCM (100 mL) and washed with aqueous NH_4Cl (20 mL), brine, dried over Na_2SO_4, and the organic layer concentrated under vacuum to get the crude product. The crude product purified by ISCO using hexane–DCM as a mobile phase to get the desired product as oily product. The yield (547 mg, quantitative). ^{1}H NMR (400 MHz) (DMSO) δ) 8.43 (d, 1 H, *J*= 8.4 Hz), 8.09-8.07 (m, 1 H), 7.27-7.25 (m, 1 H), 7.07 (s, 1 H), 2.64 (d, 3 H, *J*= 0.8 Hz), 1.69 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 149.91, 142.74, 139.27, 138.50, 12419, 122.27, 121.57, 119.43, 107.39, 85.21, 28.23, 17.40.

***tert*-Butyl 7-chloro-2-methyl-4-nitro-1*H*-indole-1-carboxylate (116b)**



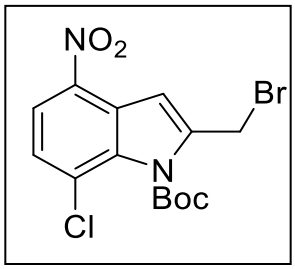
To a stirred solution of (**115b**) (420 mg, 2 mmole) in DCM (10 ml), $(Boc)_2O$ (872 mg, 4 mmol), TEA (0.415 ml, 3 mmol), DMAP (25 mg, 0.2 mmol) were added and the reaction mixture stirred under nitrogen for 3 hours then diluted with DCM (100 mL) and washed with aqueous NH_4Cl (20 mL), brine, dried over Na_2SO_4, and the organic layer concentrated under vacuum to get the crude product. The crude product purified by ISCO using hexane–DCM as a mobile phase to get the desired product as oily product. The yield (615 mg, quantitative). ^{1}H NMR (400 MHz) (CDCl3) δ) 8.22 (d, 1 H, *J*= 8.4 Hz), 7.41 (d, 1 H, *J*= 8.4 Hz), 7.26 (s, 1 H), 2.71 (s, 3 H), 1.82 (s, 9 H). ^{13}C NMR (100 MHz) (DMSO) δ 149.00, 143.39, 138.24, 134.43, 126.50, 125.65, 123.39, 119.94, 105.29, 86.26, 27.82, 14.87.

***tert*-Butyl 2-(bromomethyl)-4-nitro-1*H*-indole-1-carboxylate (117a)**



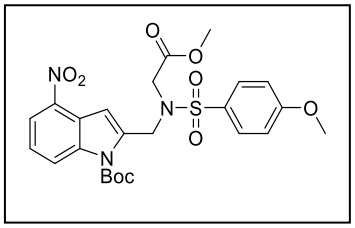
Intermediate (**116a**) (415 mg, 1.5 mmol), NBS (320 mg, 1.8 mmol), and AIBN (50 mg, 0.3 mmol) were taken in DCM (7 ml) in sealed tube and the reaction mixture stirred at 80 °C for 8 hours and checked for reaction completion using TLC. Then, filter and the organic layer removed under reduced pressure to get the crude product which was purified using ISCO (Ethyl acetate: hexane), the yield (239 mg, 45% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.59 (d, 1 H, *J*= 8.4 Hz), 8.20 (d, 1 H, *J*= 8.0 Hz), 7.50 (s, 1 H), 7.44 (t, 1 H, *J*= 8.4 Hz), 4.95 (s, 2 H), 1.78 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 148.90, 140.09, 139.96, 138.99, 124.23, 122.03, 119.81, 110.27, 86.25, 27.82, 25.85.

***tert*-Butyl 2-(bromomethyl)-7-chloro-4-nitro-1*H*-indole-1-carboxylate (117b)**



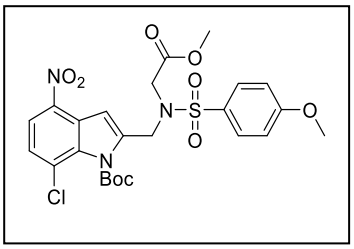
Intermediate (**116b**) (465 mg, 1.5 mmol), NBS (320 mg, 1.8 mmol), and AIBN (50 mg, 0.3 mmol) were taken in DCM (7 ml) in sealed tube and the reaction mixture stirred at 80 °C for 8 hours and checked for reaction completion using TLC. Then, filter and the organic layer removed under reduced pressure to get the crude product which was purified using ISCO (Ethyl acetate: hexane), the yield (233 mg, 40% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.12 (d, 1 H, *J*= 8.8 Hz), 7.46 (s, 1 H), 7.39 (d, 1 H, *J*= 8.8 Hz), 4.82 (s, 2 H), 1.71 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 148.08, 141.27, 139.21, 134.90, 126.55, 125.50, 125.32, 120.44, 108.20, 87.48, 27.83, 22.97.

***tert*-Butyl 2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-4-nitro-1*H*-indole-1-carboxylate (118a)**



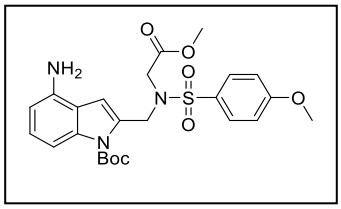
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (234 mg, 88% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.39 (d, 1 H, *J*= 8.4 Hz), 8.14 (d, 1 H, *J*= 8.0 Hz), 7.78 (d, 1 H, *J*= 8.8 Hz), 7.34 (t, 1 H, *J*= 8.0 Hz), 7.18 (s, 1 H), 6.92 (d, 1 H, *J*= 8.8 Hz), 5.00 (s, 2 H), 4.20 (s, 2 H), 3.84 (s, 3 H), 3.65 (s, 3 H), 1.69 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.45, 163.31, 149.53, 140.92, 140.07, 138.74, 131.34, 129.66, 123.51, 123.42, 121.66, 119.80, 114.28, 107.89, 86.32, 55.73, 52.36, 48.92, 47.94, 28.26.

***tert*-Butyl 7-chloro-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-4-nitro-1*H*-indole-1-carboxylate (118b)**



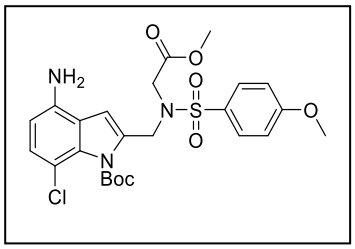
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (234 mg, 88% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.07 (d, 1 H, *J*= 8.8 Hz), 7.77 (d, 2 H, *J*= 9.2 Hz), 7.33 (d, 1 H, *J*= 8.8 Hz), 7.12 (s, 1 H), 6.95 (d, 2 H, *J*= 9.2 Hz), 4.86 (s, 2 H), 4.13 (s, 2 H), 3.85 (s, 3 H), 3.61 (s, 3 H), 1.65 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.20, 163.44, 148.44, 140.81, 138.85, 134.82, 130.80, 129.98, 129.75, 126.26, 125.65, 124.68, 120.27, 114.34, 114.10, 107.03, 87.51, 55.75, 52.33, 48.47, 45.57, 27.75.

tert-Butyl 4-amino-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1*H*-indole-1-carboxylate (119a)



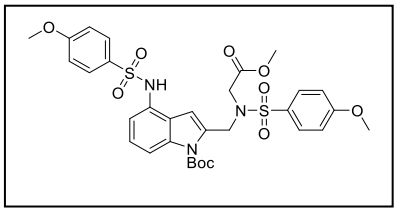
Prepared as described in the general procedure for nitro group reduction (Method E1) to get the title compound as a yellow solid; the yield (61 mg, 61% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.75 (d, 1 H, *J*= 8.8 Hz), 7.39 (d, 1 H, *J*= 8.4 Hz), 7.03 (t, 1 H, *J*= 8.0 Hz), 6.89 (d, 1 H, *J*= 8.8 Hz), 6.54 (s, 1 H), 6.49 (d, 1 H, *J*= 8.0 Hz), 4.90 (s, 2 H), 4.19 (s, 2 H), 3.82 (s, 3 H), 3.61 (s, 3 H), 1.63 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.66, 163.04, 150.57, 139.08, 137.97, 134.09, 131.82, 129.67, 125.39, 117.39, 114.45, 114.07, 108.04, 106.53, 105.85, 84.47, 55.70, 52.25, 48.90, 48.00, 28.34.

tert-Butyl 4-amino-7-chloro-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1*H*-indole-1-carboxylate (119b)



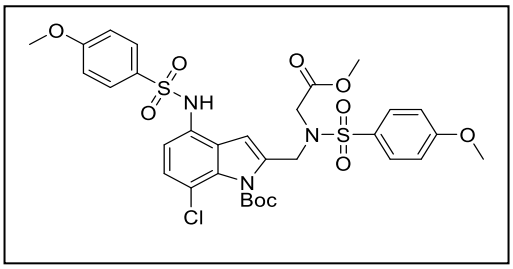
Prepared as described in the general procedure for nitro group reduction (Method E1) to get the title compound as a yellow solid; the yield (58 mg, 54% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.72 (d, 2 H, *J*= 8.4 Hz), 7.00 (d, 1 H, *J*= 8.4 Hz), 6.89 (d, 2 H, *J*= 8.8 Hz), 6.46 (s, 1 H), 6.39 (d, 1 H, *J*= 8.4 Hz), 4.75 (s, 2 H), 4.13 (s, 2 H), 3.82 (s, 3 H), 3.57 (s, 3 H), 1.58 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.47, 163.04, 149.58, 138.15, 134.14, 133.99, 131.27, 129.62, 126.49, 119.95, 114.06, 109.10, 108.27, 104.76, 85.58, 55.66, 52.15, 48.41, 45.93, 27.71.

tert-Butyl 2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-4-((4-methoxyphenyl) sulfonamido)-1*H*-indole-1-carboxylate (120a)



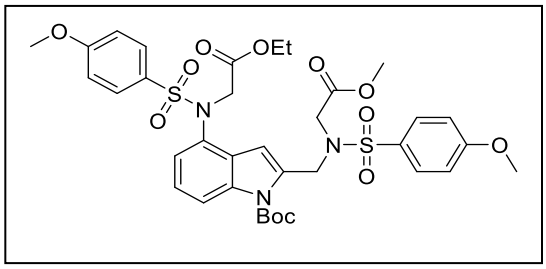
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a yellow solid; the yield (44 mg, 81% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 10.14 (s, 1 H), 7.74-7.70 (m, 5 H), 7.15-7.09 (m, 2 H), 7.05-7.01 (m, 4 H), 6.93 (s, 1 H), 4.73 (s, 2 H), 4.17 (s, 2 H), 3.84 (s, 2 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 3.54 (s, 2 H), 3.52 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.00, 162.55, 162.31, 149.35, 136.97, 135.68, 131.61, 130.92, 129.25, 129.16, 128.85, 128.66, 124.18, 122.72, 115.94, 114.24, 114.22, 114.18, 111.78, 106.06, 84.65, 55.64, 55.51, 51.79, 48.37, 47.25, 43.73, 27.58.

tert-Butyl 7-chloro-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-4-((4-methoxyphenyl) sulfonamido)-1*H*-indole-1-carboxylate (120b)



Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as brwon solid; the yield (44 mg, 78% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.80 (d, 2 H, *J*= 8.8 Hz), 7.55 (d, 2 H, *J*= 8.8 Hz), 7.38 (s, 1 H), 7.10 (d, 2 H, *J*= 8.4 Hz), 6.93 (d, 2 H, *J*= 8.8 Hz), 6.64 (s, 1 H), 6.58 (d, 2 H, *J*= 8.8 Hz), 4.74 (s, 2 H), 4.18 (s, 2 H), 3.85 (s, 3 H), 3.58 (s, 3 H), 1.53 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.45, 163.25, 163.14, 148.96, 136.94, 133.91, 131.03, 130.64, 129.91, 129.53, 127.63, 125.89, 125.79, 116.87, 116.70, 114.25, 114.19, 104.09, 86.22, 55.72, 55.56, 52.22, 48.34, 45.86, 27.72.

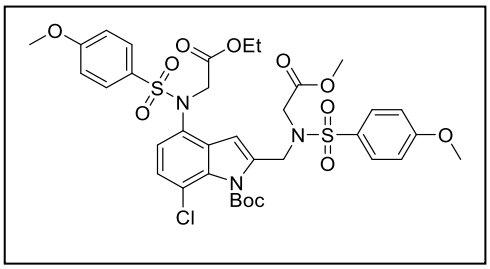
tert-Butyl 4-((N-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl) sulfonamido)-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1*H*-indole-1-carboxylate (121a)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (30 mg, 79% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.99 (d, 1 H, *J*= 8.4 Hz), 7.80 (d, 2 H, *J*= 9.2 Hz), 7.66 (d, 2 H, *J*= 8.8 Hz), 7.16 (t, 1 H, *J*= 8.0 Hz), 7.05 (d, 1 H, *J*= 8.0 Hz), 6.97-6.93 (m, 4 H), 6.48 (s, 1 H), 4.93 (s, 2 H), 4.40 (s, 2 H), 4.15 (q, 2 H, *J*= 7.2 Hz), 4.11 (s, 2 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.66 (s, 3 H), 1.67 (s, 9 H), 1.24 (d, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.57, 168.97, 163.19, 163.10, 149.98, 138.10, 137.04, 131.61, 131.52, 131.17,

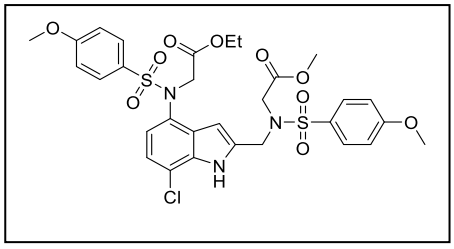
130.08, 129.69, 128.51, 124.56, 124.26, 116.09, 114.24, 114.13, 107.08, 85.12, 61.53, 55.69, 52.84, 52.28, 48.60, 47.67, 28.30, 14.25.

tert-Butyl 7-chloro-4-((N-(2-ethoxy-2-oxoethyl)-4-methoxyphenyl) sulfonamido)-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1*H*-indole-1-carboxylate (121b)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (43 mg, 87% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.75 (d, 2 H, *J*= 8.8 Hz), 7.62 (d, 2 H, *J*= 8.8 Hz), 7.10 (d, 2 H, *J*= 8.0 Hz), 6.96 (d, 2 H, *J*= 8.8 Hz), 6.90 (d, 2 H, *J*= 8.8 Hz), 6.88 (d, 1 H, *J*= 8.0 Hz), 6.42 (s, 1 H), 4.77 (s, 2 H), 4.33 (s, 2 H), 4.11 (q, 2 H, *J*= 7.2 Hz), 4.03 (s, 2 H), 3.85 (s, 3 H), 3.54 (s, 3 H), 3.60 (s, 3 H), 1.62 (s, 9 H), 1.19 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.29, 168.77, 163.22, 163.19, 148.90, 137.10, 134.21, 131.18, 131.01, 130.74, 130.50, 130.04, 129.70, 125.57, 124.67, 120.04, 114.25, 114.12, 106.08, 86.29, 61.53, 55.68, 55.67, 52.68, 52.24, 48.08, 45.62, 27.74, 14.16.

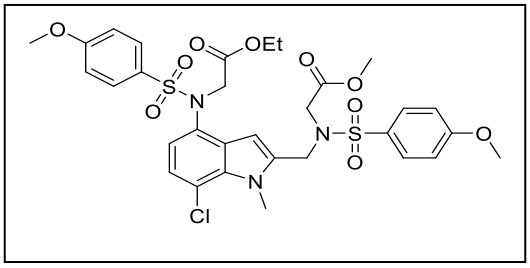
Ethyl N-(7-chloro-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl)-1*H*-indol-4-yl)-N-((4-methoxyphenyl) sulfonyl) glycinate (123a)



Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as dark brown solid; the

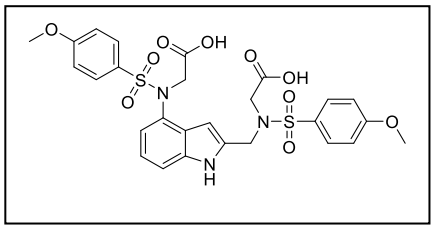
yield (17 mg, quantitative). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.75 (d, 2 H, *J*= 8.8 Hz), 7.64 (d, 2 H, *J*= 8.8 Hz), 7.02 (d, 1 H, *J*= 8.0 Hz), 6.92-6.88 (m, 4 H), 6.74 (d, 1 H, *J*= 2.0 Hz), 4.44 (s, 2 H), 4.41 (s, 2 H), 4.11 (q, 2 H, *J*= 7.2 Hz), 4.08 (s, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.70 (s, 3 H),1.19 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 170.12, 169.27, 163.42, 163.25, 135.14, 134.12, 130.74, 130.58, 130.43, 130.19, 129.72, 128.45, 121.93, 121.74, 117.28, 114.38, 114.03, 102.94, 66.15, 61.63, 55.74, 55.71, 52.65, 52.65, 48.14, 45.70, 14.15.

N-(7-Chloro-2-(((4-methoxy-N-(2-methoxy-2-oxoethyl)phenyl)sulfonamido)methyl)-1-methyl-1*H*-indol-4-yl)-N-((4-methoxyphenyl)sulfonyl)glycine (123b)



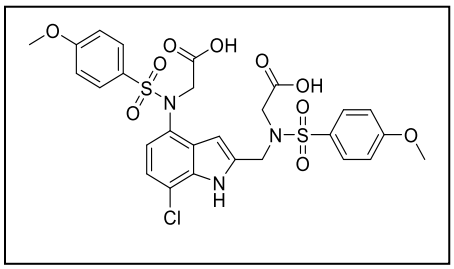
Prepared using general procedure (method B), oily product, the yield (11 mg, 62% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.79 (d, 2 H, *J*= 9.2 Hz), 7.63 (d, 2 H, *J*= 9.2 Hz), 7.02 (d, 2 H, *J*= 9.2 Hz), 6.98 (d, 1 H, *J*= 8.0 Hz), 6.89 (d, 2 H, *J*= 8.8 Hz), 6.64 (d, 1 H, *J*= 8.0 Hz), 6.42 (s, 1 H), 4.61 (s, 2 H), 4.35 (s, 2 H), 4.13 (s, 3 H), 4.08 (q, 2 H, *J*= 7.2 Hz), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.48 (s, 3 H), 1.17 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.96, 168.83, 163.46, 163.19, 134.87, 134.68, 130.99, 130.81, 130.22, 130.18, 129.79, 129.50, 124.06, 121.42, 117.72, 114.46, 113.98, 104.15, 61.43, 55.81, 55.71, 52.62, 52.23, 46.90, 44.48, 32.97, 14.19.

N-((4-((N-(Carboxymethyl)-4-methoxyphenyl) sulfonamido)-1*H*-indol-2-yl)methyl)-N-((4-methoxyphenyl)sulfonyl)glycine (122a)



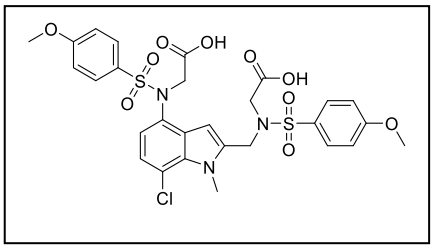
Prepared using general procedure (method C1), yellow product, the yield (14 mg, 75% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 11.21 (s, 1 H), 7.70 (d, 2 H, *J*= 8.8 Hz), 7.55 (d, 2 H, *J*= 8.8 Hz), 7.26 (d, 2 H, *J*= 8.0 Hz), 7.03-6.96 (m, 5 H), 6.89 (d, 1 H, *J*= 7.6 Hz), 5.58 (s, 1 H), 4.50 (s, 2 H), 4.25 (s, 2 H), 3.81 (s, 8 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.09, 169.98, 162.48, 162.40, 137.49, 134.30, 131.26, 131.19, 130.53, 129.38, 129.13, 125.65, 121.21, 120.77, 114.17, 114.09, 111.60, 98.66, 55.58, 51.76, 47.53, 44.56. HRMS (ESI) Calcd for $C_{27}H_{27}N_3O_{10}S_2$ $(M+H)^+$ 618.1211, found 618.1221.

N-((4-((N-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)-7-chloro-1*H*-indol-2-yl)methyl)-N-((4-methoxyphenyl)sulfonyl)glycine (122b)



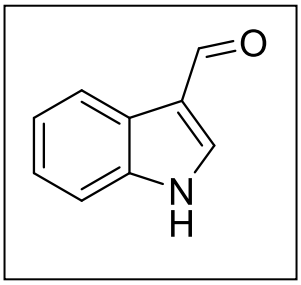
Prepared using general procedure (method C1), light brown product, the yield (11 mg, 71% yield). ^{1}H NMR (400 MHz) (MeOH-d_4) δ) 7.59-7.56 (m, 4 H), 7.01 (s, 1 H), 6.94 (d, 2 , *J*= 9.2 Hz), 6.83 (d, 2 H, *J*= 8.8 Hz), 5.81 (s, 1 H), 4.56 (s, 2 H), 4.37 (s, 2 H), 4.04 (s, 2 H), 3.84 (s, 3 H), 3.77 (s, 3 H). ^{13}C NMR (100 MHz) (MeOH-d_4) δ 172.62, 172.08, 164.47, 164.15, 136.57, 135.64, 132.39, 132.03, 130.96, 130.64, 130.12, 129.97, 128.65, 123.65, 121.54, 117.52, 114.90, 114.75, 101.66, 61.24, 55.94, 55.87, 46.32. HRMS (ESI) Calcd for $C_{27}H_{26}ClN_3O_{10}S_2$ $(M+H)^+$ 652.0821, found 652.0830.

N-((4-((N-(Carboxymethyl)-4-methoxyphenyl) sulfonamido)-7-chloro-1-methyl-1*H*-indol-2-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycine (124)



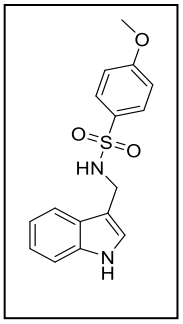
Prepared using general procedure (method B), brown solid, the yield (129 mg, 88% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.78 (d, 2 H, *J*= 9.2 Hz), 7.54 (d, 2 H, *J*= 8.8 Hz), 7.01 (d, 2 H, *J*= 8.8 Hz), 6.94 (d, 1 H, *J*= 8.0 Hz), 6.89 (d, 2 H, *J*= 8.8 Hz), 6.63 (s, 1 H), 6.31 (d, 1 H, *J*= 8.4 Hz), 4.53 (s, 2 H), 4.27 (s, 2 H), 4.11 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.76 (s, 2 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 174.45, 173.68, 163.57, 163.39, 134.68, 134.41, 131.04, 130.38, 130.03, 129.85, 129.74, 129.71, 124.08, 119.54, 117.86, 114.65, 114.26, 105.74, 55.84, 55.78, 52.80, 46.88, 44.71, 32.88. HRMS (ESI) Calcd for $C_{28}H_{28}ClN_3O_{10}S_2$ $(M+H)^+$ 666.0977, found 666.0990.

1*H*-Indole-3-carbaldehyde (125)



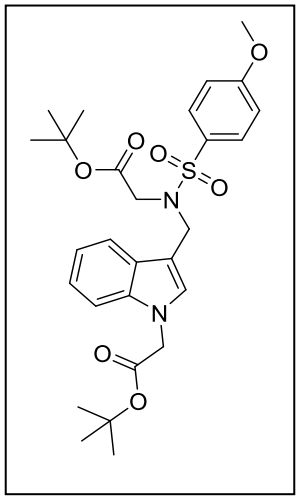
To a stirred solution of commercially available indole (351 mg, 3 mmol) in anhydrous DMF under nitrogen, phosphorus chloride oxide (0.834 ml, 9 mmol) was added at 0 °C. The reaction mixture stirred at room temperature for 1h and then poured into cold saturated aqueous $NaHCO_3$ solution and stirred for 0.5 h and extracted by EtOAc (3 X). The organic layer washed with brine, dried over anhydrous Na_2SO_4, and the organic layer removed using rotovap. The crude product purified by ISCO to get the desired product, 435 mg, (quantitative). ^{1}H NMR (400 MHz) (DMSO) δ) 9.95 (s, 1 H), 8.28 (s, 1 H), 8.12 (d, 1 H, *J*= 7.2 Hz), 7.54 (d, 1 H, *J*= 8.0 Hz), 7.28-7.20 (m, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 184.56, 138.14, 136.85, 123.83, 123.01, 121.69, 120.44, 117.79, 112.15.

N-((1*H*-Indol-3-yl) methyl)-4-methoxybenzenesulfonamide (126)



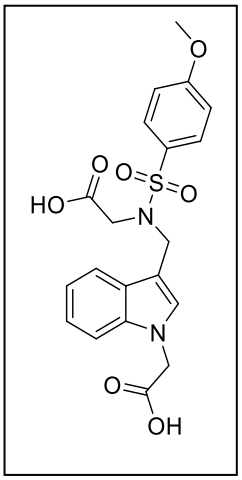
To a solution of indole carboxaldehyde (**125**) (1 mmol) in toluene (5 mL), commercially available 4-methoxybenzenesulfonamide (282 mg, 1.5 mmol) and titanium(IV) isopropoxide (588 uL, 2 mmol) were added at room temperature. Then, the reaction mixture refluxed and checked for completion using TLC (4 h). Then, the mixture cooled to room temperature and the solvent was evaporated, and the residue dissolved in MeOH (5 mL) and THF (5 mL) and cooled to 0 °C. $NaBH_4$ (190 mg, 5 mmol) was added slowly at 0 °C and the mixture stirred at room temperature for 4 hours Upon completion, water (250 uL) was added at 0 °C and the organic solvents removed under reduced pressure to get the crude product which was purified using ISCO to get the desired pure product as a beige solid, the yield (253 mg, 80% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 10.91 (s, 1 H), 7.79 (d, 2 H, *J*= 8.8 Hz), 7.70 (t, 1 H, *J*= 6.0 Hz), 7.50 (d, 1 H, *J*= 8.0 Hz), 7.35 (d, 1 H, *J*= 8.0 Hz), 7.17 (d, 1 H, *J*= 2.0 Hz), 7.11-7.07 (m, 3 H), 6.98 (t, 1 H, *J*= 8.0 Hz), 4.10 (d, 2 H, *J*= 5.6 Hz), 3.85 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 161.64, 135.93, 132.05, 128.35, 126.02, 123.74, 120.84, 118.20, 118.18, 113.82, 111.03, 109.98, 55.24, 38.05.

tert-Butyl N-((1-(2-(_tert_-butoxy)-2-oxoethyl)-1_H_-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycinate (127)



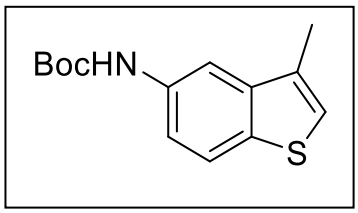
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (93 mg, 85% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.85 (d, 2 H, *J*= 8.8 Hz), 7.56 (d, 1 H, *J*= 8.0 Hz), 7.26-7.19 (m, 2 H), 7.12-7.08 (m, 1 H), 7.00-6.97 (m, 3 H), 4.71 (s, 2 H), 4.67 (s, 2 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 1.43 (s, 9 H), 1.33 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.44, 167.43, 162.90, 137.14, 132.24, 129.69, 129.14, 127.82, 122.62, 120.22, 119.58, 114.16, 109.30, 109.19, 82.72, 81.66, 55.68, 48.64, 46.74, 42.36, 28.08, 27.98.

N-((1-(Carboxymethyl)-1*H*-indol-3-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycine (128)



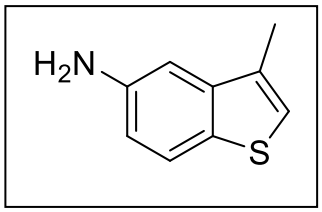
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as an off-white solid; the yield 21 mg, 90% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 12.78 (br, 2 H), 7.79 (d, 2 H, *J*= 8.8 Hz), 7.40 (d, 1 H, *J*= 8.0 Hz), 7.34 (d, 1 H, *J*= 8.4 Hz), 7.21 (s, 1 H), 7.14-7.10 (m, 1 H), 7.07 (d, 2 H, *J*= 8.8 Hz), 6.99 (t, 1 H, *J*= 7.2 Hz), 4.95 (s, 2 H), 4.58 (s, 2 H), 3.83 (s, 3 H), 3.74 (s, 2 H). ^{13}C NMR (100 MHz) (DMSO) δ 170.25, 169.95, 162.41, 136.94, 131.67, 130.15, 129.26, 127.03, 121.70, 119.28, 118.61, 114.24, 109.98, 107.73, 55.65, 47.00, 45.85, 42.20. HRMS (ESI) Calcd for $C_{20}H_{20}N_2O_7S$ $(M+H_2O)^+$ 450.1064, found 450.1074.

***tert*-Butyl (3-methylbenzo[b]thiophen-5-yl)carbamate** (**129**)



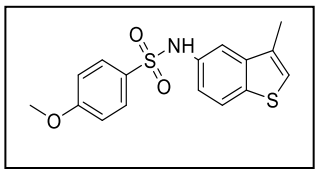
To a Schlenk tube equipped with a magnetic stir bar under argon atmosphere was added commercially available 5-chloro-3-methyl-1-benzothiophene (183 mg, 1 1 mmol), t-butyl carbamate (165 mg, 1.4 mmol), Pd(OAc)2 (15 mg, 0.06 mmol), XPhos (57 mg, 0.12 mmol), sodium *tert*-butoxide (134 mg, 1.4 mmol), dioxane (5 ml), and then the tube was degassed with argon three times and refluxed for 24 hours. Upon completion, the mixture diluted with EtOAc and extracted with water, brine, dried over Na_2SO_4, and organic layer removed under reduced pressure. The crude product purified by ISCO using ethyl acetate/ hexane to get the desired product., the yield (170 mg, 65% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.89 (s, 1 H), 7.71 (d, 1 H, *J*= 8.8 Hz), 7.26-7.21 (m, 1 H), 7.06 (s, 1 H), 6.80 (s, 1 H), 2.39 (s, 3 H), 1.57 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.13, 140.40, 135.18, 134.94, 132.12, 122.93, 122.57, 116.73, 111.42, 80.48, 28.45, 13.95.

3-Methylbenzo[b]thiophen-5-amine (**130**)



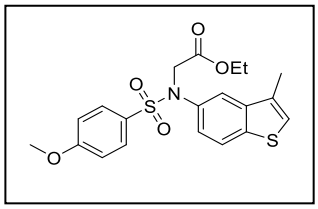
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a white solid; the yield (76 mg, 82% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 9.42 (s, 2 H), 8.01 (d, 1 H, *J*= 8.4 Hz), 7.64 (s, 1 H), 7.49 (s, 1 H), 7.28 (d, 1 H, *J*= 8.0 Hz), 2.37 (s, 3 H). ^{13}C NMR (100 MHz) (DMSO) δ 139.90, 136.93, 131.30, 131.17, 124.38, 123.82, 118.28, 114.06, 13.22.

4-Methoxy-N-(3-methylbenzo[b]thiophen-5-yl) benzenesulfonamide (**131**)



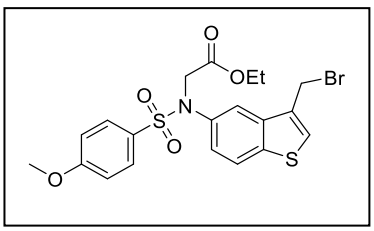
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a beige solid; the yield (112 mg, 78% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.75 (d, 2 H, *J*= 8.8 Hz), 7.65 (d, 1 H, *J*= 8.4 Hz), 7.47 (d, 1 H, *J*= 2.0 Hz), 7.37 (s, 1 H), 7.08 (d, 1 H, *J*= 2.4 Hz), 7.06 (d, 1 H, *J*= 1.2 Hz), 6.85 (d, 2 H, *J*= 9.2 Hz), 3.78 (s, 3 H), 2.34 (d, 3 H, *J*= 2.0 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.20, 140.52, 137.54, 133.32, 132.22, 130.62, 129.64, 123.47, 123.16, 119.56, 115.53, 114.28, 55.64, 13.93.

Ethyl N-((4-methoxyphenyl)sulfonyl)-N-(3-methylbenzo[b]thiophen-5-yl)glycinate (132)



Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (108 mg, 86% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.71 (d, 1 H, *J*= 8.4 Hz), 7.62 (d, 2 H, *J*= 8.8 Hz), 7.56 (d, 1 H, *J*= 2.0 Hz),7.12-7.08 (m, 2 H), 6.89 (d, 2 H, *J*= 8.8 Hz), 4.45 (s, 2 H), 4.14 (q, 2 H, *J*= 7.2 Hz), 3.84 (s, 3 H), 2.33 (d, 3 H, *J*= 0.8 Hz), 1.21 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.98, 163.16, 140.40, 140.16, 136.39, 132.39, 130.76, 130.20, 124.74, 123.36, 123.15, 122.93, 113.93, 61.48, 55.66, 53.32, 14.16, 13.87.

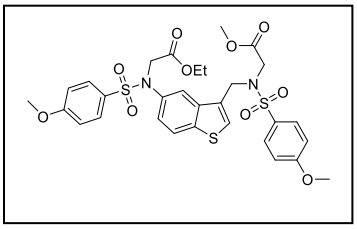
Ethyl N-(3-(bromomethyl) benzo[b]thiophen-5-yl)-N-((4-methoxyphenyl) sulfonyl) glycinate (133)



Intermediate (**132**) (63 mg, 0.15 mmol), NBS (32 mg, 0.18 mmol), and AIBN (5 mg, 0.03 mmol) were taken in DCM (5 ml) in sealed tube and the reaction mixture stirred at 80

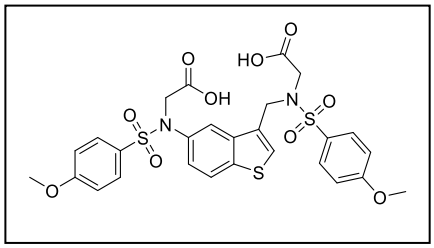
°C for 8 hours and checked for reaction completion using TLC. Then, filter and the organic layer removed under reduced pressure to get the crude product which was purified using ISCO (Ethyl acetate: hexane), the yield (39 mg, 52% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.78 (d, 1 H, *J*= 8.8 Hz), 7.64 (d, 2 H, *J*= 8.4 Hz), 7.52 (s, 1 H), 7.31 (dd, 1 H, *J*= 2.0 Hz, 8.4 Hz), 6.91 (d, 2 H, *J*= 9.2 Hz), 4.61 (s, 2 H), 4.47 (s, 2 H), 4.15 (q, 2 H, *J*= 7.2 Hz), 3.84 (s, 3 H), 1.23 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.84, 163.10, 140.25, 137.80, 136.87, 132.08, 130.42, 130.04, 129.56, 127.81, 126.14, 123.64, 123.56, 122.38, 114.23, 114.18, 114.07, 61.51, 55.57, 53.14, 25.38, 14.08.

Ethyl N-(3-(((4-methoxy-N-(2-methoxy-2-oxoethyl) phenyl) sulfonamido) methyl) benzo[b]thiophen-5-yl)-N-((4-methoxyphenyl)sulfonyl)glycinate (**134**)



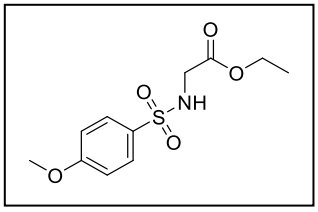
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (36 mg, 68% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.78 (d, 2 H, *J*= 9.2 Hz), 7.75 (d, 1 H, *J*= 8.8 Hz), 7.63-7.61 (m, 2 H), 6.99 (d, 2 H, *J*= 8.8 Hz), 6.93 (d, 2 H, *J*= 8.8 Hz), 4.56 (s, 2 H), 4.44 (s, 2 H), 4.14 (q, 2 H, *J*= 7.2 Hz), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.84 (s, 2 H), 3.49 (s, 3 H), 1.21 (t, 1 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.79, 168.38, 162.79, 162.78, 139.80, 138.00, 136.77, 130.37, 130.27, 129.97, 129.71, 129.58, 129.43, 129.31, 127.57, 125.89, 122.87, 121.45, 113.86, 113.76, 113.67, 61.05, 55.26, 55.21, 52.61, 51.62, 46.64, 45.07, 13.71.

N-((5-((N-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)benzo[b]thiophen-3-yl)methyl)-N-((4-methoxyphenyl)sulfonyl)glycine (**135**)



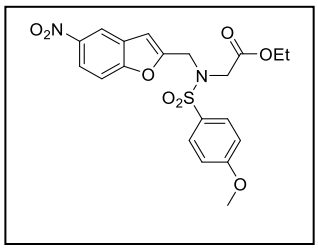
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (base hydrolysis) to get the title compound as a beige solid; the yield (14 mg, 86% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 7.93 (d, 1 H, *J*= 8.8 Hz), 7.71 (d, 2 H, *J*= 8.8 Hz), 7.64 (s, 1 H), 7.60 (d, 2 H, *J*= 8.8 Hz), 7.54 (d, 1 H, *J*= 1.6 Hz), 7.26 (dd, 1 H, *J*= 1.6 Hz, 8.4 Hz), 7.09 (d, 2 H, *J*= 8.8 Hz), 7.05 (d, 2 H, *J*= 8.8 Hz), 4.51 (s, 2 H), 4.38 (s, 2 H), 3.84 (s, 8 H). ^{13}C NMR (100 MHz) (DMSO) δ 169.55, 169.47, 162.42, 162.12, 138.74, 137.64, 136.49, 130.39, 129.92, 129.53, 129.24, 128.91, 127.67, 125.34, 122.74, 120.67, 114.05, 113.98, 113.85, 55.30, 52.13, 47.59, 45.25. HRMS (ESI) Calcd for $C_{27}H_{26}N_2O_{10}S_3$ $(M+H)^+$ 635.0822, found 635.0827.

Ethyl ((4-methoxyphenyl) sulfonyl) glycinate (146)



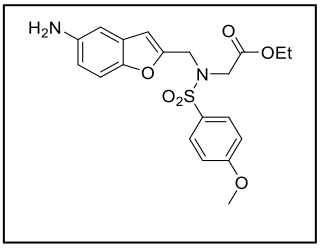
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a white solid; the yield (712 mg, 87% yield). ^{1}H NMR (400 MHz) (DMSO) δ) 8.01 (s, 1 H), 7.70 (d, 2 H, *J*= 8.8 Hz), 7.06 (d, 2 H, *J*= 8.8 Hz), 3.94 (d, 2 H, *J*= 7.2 Hz), 3.79 (s, 3 H), 3.62 (s, 2 H), 1.06 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) (DMSO) δ 168.69, 162.00, 132.05, 128.48, 113.96, 60.40, 55.37, 43.65, 13.63.

Ethyl N-((4-methoxyphenyl)sulfonyl)-N-((5-nitrobenzofuran-2-yl)methyl)glycinate (136)



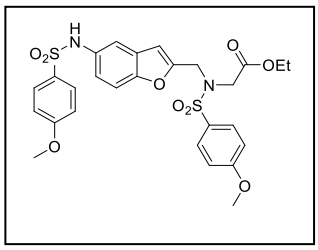
Prepared using general procedure (method B) using commercially available 2-(bromomethyl)-5-nitrobenzofuran, the yield (461 mg, 84% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.44 (d, 1 H, *J*= 2.0 Hz), 8.20 (dd, 1 H, *J*= 2.0 Hz, 8.8 Hz), 7.79 (d, 2 H, *J*= 8.8 Hz), 7.44 (d, 1 H, *J*= 9.2 Hz), 6.93 (d, 2 H, *J*= 8.8 Hz), 6.77 (s, 1 H), 4.71 (s, 2 H), 4.11-4.06 (m, 4 H), 3.85 (s, 3 H), 1.19 (d, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.67, 163.34, 157.95, 156.02, 144.47, 131.22, 129.77, 128.48, 120.58, 117.74, 114.27, 111.70, 107.02, 61.66, 55.77, 48.08, 44.89, 14.19.

Ethyl N-((5-aminobenzofuran-2-yl)methyl)-N-((4-methoxyphenyl)sulfonyl)glycinate (**137**)



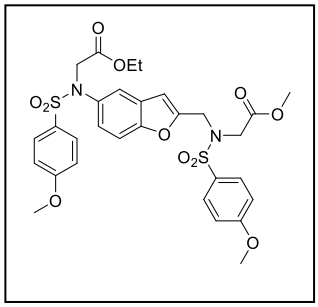
Prepared as described in the general procedure for nitro group reduction (Method E1) to get the title compound as a yellow solid; the yield (173 mg, 50%). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.78 (d, 2 H, *J*= 8.8 Hz), 7.09 (d, 2 H, *J*= 8.4 Hz), 6.97-6.90 (m, 2 H), 6.74 (d, 1 H, *J*= 2.0 Hz), 6.61 (dd, 1 H, *J*= 2.4 Hz, 8.8 Hz), 6.41 (s, 1 H), 4.62 (s, 2 H), 4.12-4.03 (m, 4 H), 3.83 (s, 3 H), 1.17 (t, 3 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.88, 163.23, 163.08, 152.23, 149.76, 142.34, 131.51, 129.69, 129.52, 128.80, 114.38, 114.10, 113.85, 111.47, 106.27, 105.88, 61.95, 61.42, 55.72, 55.68, 47.69, 44.85, 44.27, 14.12, 14.09.

Ethyl N-((5-((4-methoxyphenyl) sulfonamido) benzofuran-2-yl) methyl)-N-((4-methoxyphenyl) sulfonyl) glycinate (**138**)



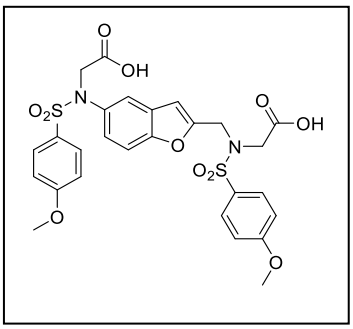
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as a beige solid; the yield (92 mg, 79% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.78 (d, 2 H, *J*= 8.8 Hz), 7.62 (d, 2 H, *J*= 8.8 Hz), 7.19 (d, 1 H, *J*= 8.8 Hz), 6.93-6.86 (m, 5 H), 6.53 (s, 1 H), 6.45 (s, 1 H), 4.64 (s, 2 H), 4.09-4.04 (m, 4 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 1.17 (t, 2 H, *J*= 7.2 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) 168.81, 163.24, 153.61, 153.38, 131.77, 131.41, 131.03, 130.70, 129.76, 129.58, 128.75, 120.94, 116.34, 114.30, 114.21, 111.77, 106.55, 61.56, 55.76, 55.72, 47.85, 44.86, 14.18.

Ethyl N-(2-(((4-methoxy-N-(2-methoxy-2-oxoethyl)phenyl) sulfonamido) methyl) benzofuran-5-yl)-N-((4-methoxyphenyl) sulfonyl) glycinate (**139**)



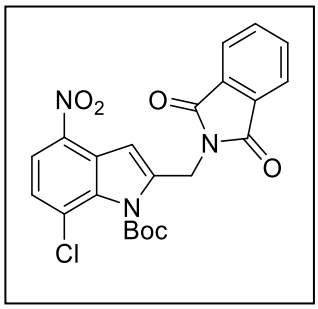
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (77 mg, 86% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.78 (d, 2 H, *J*= 8.8 Hz), 7.60 (d, 2 H, *J*= 8.8 Hz), 7.41 (d, 1 H, *J*= 2.4 Hz), 7.23 (d, 1 H, *J*= 8.8 Hz), 7.03 (dd, 1 H, *J*= 2.0 Hz, 8.8 Hz), 6.93 (d, 2 H, *J*= 8.8 Hz), 6.90 (d, 2 H, *J*= 8.8 Hz), 6.54 (s, 1 H), 4.65 (s, 2 H), 4.40 (s, 2 H), 4.16-4.03 (m, 6 H), 1.25-1.16 (m, 6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) 169.04, 168.75, 163.21, 163.17, 154.42, 153.52, 135.18, 131.36, 130.74, 130.11, 129.72, 128.57, 125.76, 122.62, 114.19, 114.02, 111.71, 106.77, 61.53.55.70, 53.39, 47.69, 44.76, 14.20, 14.15.

N-((5-((N-(Carboxymethyl)-4-methoxyphenyl)sulfonamido)benzofuran-2-yl)methyl)-N-((4-methoxyphenyl)sulfonyl)glycine (**140**)



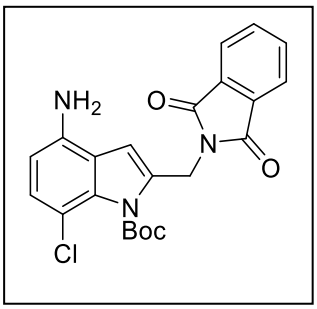
Prepared as described in the general procedure for hydrolysis of ethyl ester to get di-acidic compounds (Method C1) (base hydrolysis) to get the title compound as a beige solid; the yield (19 mg, 77% yield). ^{1}H NMR (400 MHz) (CD_3CN) δ) 7.71(d, 2 H, *J*= 9.2 Hz), 7.60 (d, 2 H, *J*= 9.2 Hz), 7.31 (d, 1 H, *J*= 2.0 Hz), 7.21 (d, 1 H, *J*= 8.8 Hz), 7.00 (dd, 1 H, *J*= 2.0 Hz, 8.8 Hz), 6.97-6.92 (m, 4 H), 6.57 (s, 1 H), 4.56 (s, 2 H), 4.35 (s, 2 H), 3.97 (s, 2 H), 3.82 (s, 3 H), 3.78 (s, 3 H). ^{13}C NMR (100 MHz) (CD_3CN)) 170.50, 170.35, 164.28, 164.13, 154.99, 154.83, 136.23, 132.27, 131.34, 130.75, 130.42, 129.34, 126.48, 123.02, 118.26, 115.09, 112.13, 107.48, 60.96, 56.51, 53.64, 48.72, 45.72. HRMS (ESI) Calcd for $C_{27}H_{26}N_2O_{11}S_2$ $(M+H)^+$ 619.1051, found 619.1047.

***tert*-Butyl 7-chloro-2-((1,3-dioxoisoindolin-2-yl)methyl)-4-nitro-1*H*-indole-1-carboxylate** (**141**)



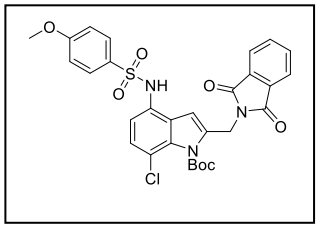
Prepared as described in the general procedure for alkylation (method B) to get the title compound as oily product; the yield (117 mg, 78% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.07 (d, 1 H, *J*= 8.4 Hz), 7.94-7.92 (m, 2 H), 7.80-7.78 (m, 2 H), 7.33 (d, 1 H, *J*= 8.8 Hz), 7.03 (t, 1 H, *J*= 1.2 Hz), 5.16 (d, 2 H, *J*= 1.2 Hz), 1.70 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 167.85, 167.59, 167.33, 148.50, 141.46, 138.70, 134.83, 134.60, 132.02, 126.71, 126.20, 124.71, 123.96, 120.45, 104.82, 87.32, 35.85, 27.89.

***tert*-Butyl 4-amino-7-chloro-2-((1,3-dioxoisoindolin-2-yl)methyl)-1*H*-indole-1-carboxylate** (**142**)



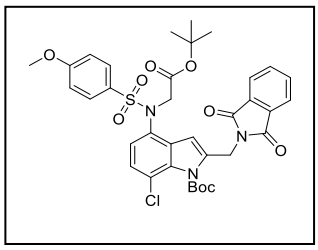
Prepared as described in the general procedure for nitro group reduction (Method E1) to get the title compound as a yellow solid; the yield (94 mg, 79% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.93-7.91 (m, 2 H), 7.79-7.76 (m, 2 H), 7.03 (d, 1 H, *J*= 8.0 Hz), 6.38 (d, 1 H, *J*= 8.4 Hz), 6.15 (s, 1 H), 5.14 (s, 2 H), 1.70 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 167.73, 149.65, 137.84, 134.68, 134.37, 133.85, 132.20, 126.45, 123.73, 123.49, 120.37, 109.68, 108.63, 101.90, 85.68, 36.04, 27.95.

tert-Butyl 7-chloro-2-((1,3-dioxoisoindolin-2-yl)methyl)-4-((4-methoxyphenyl) sulfonamido)-1*H*-indole-1-carboxylate (**143**)



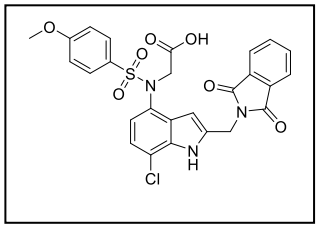
Prepared as described in the general procedure for synthesis of sulfonamides (method A2) to get the title compound as an off-white solid; the yield (75 mg, 86% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.89-7.88 (m, 2 H), 7.77-7.75 (m, 2 H), 7.51 (d, 2 H, *J*= 9.2 Hz), 7.11 (d, 1 H, *J*= 8.4 Hz), 7.03 (d, 1 H, *J*= 8.4 Hz), 6.85 (s, 1 H), 6.69 (d, 2 H, *J*= 8.8 Hz), 5.03 (d, 1 H, *J*= 1.2 Hz), 3.81 (s, 3 H), 1.66 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 167.83, 167.64, 163.26, 163.13, 149.03, 136.99, 134.51, 133.71, 132.01, 130.62, 129.37, 127.15, 126.13, 126.02, 123.84, 117.51, 117.25, 114.24, 101.57, 86.30, 55.67, 36.03, 27.95.

tert-Butyl 4-((N-(2-(_tert_-butoxy)-2-oxoethyl)-4-methoxyphenyl)sulfonamido)-7-chloro-2-((1,3-dioxoisoindolin-2-yl)methyl)-1*H*-indole-1-carboxylate (**144**)



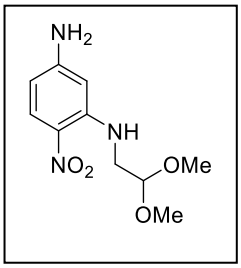
Prepared as described in the general procedure for synthesis of alkylated sulfonamides (method B) to get the title compound as oily product; the yield (75 mg, 81% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 7.95-7.93 (m, 2 H), 7.82-7.80 (m, 2 H), 7.50 (d, 2 H, *J*= 8.8 Hz), 7.15 (d, 2 H, *J*= 8.4 Hz), 7.03 (d, 1 H, *J*= 8.0 Hz), 6.85 (s, 1 H), 6.75 (d, 2 H, *J*= 8.8 Hz), 5.05 (s, 2 H), 4.14 (s, 2 H), 3.89 (s, 3 H), 1.66 (s, 9 H), 1.32 (s, 9 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 167.59, 167.23, 162.83, 148.85, 137.29, 134.14, 133.90, 131.83, 130.90, 130.60, 130.26, 129.66, 125.35, 123.61, 123.35, 120.07, 113.68, 102.96, 85.97, 81.98, 55.41, 53.24, 35.77, 27.78, 27.70.

N-(7-Chloro-2-((1,3-dioxoisoindolin-2-yl)methyl)-1*H*-indol-4-yl)-N-((4-methoxyphenyl) sulfonyl) glycine (**145**)



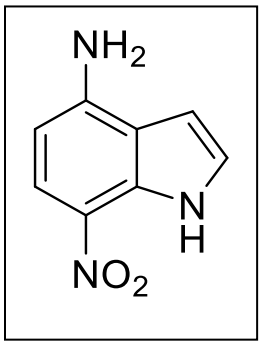
Prepared as described in the general procedure for removal of acid sensitive protecting group (Method C2) to get the title compound as a beige solid; the yield (21 mg, 71% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 9.03 (s, 1 H), 8.63 (br, 2 H), 7.88-7.86 (m, 2 H), 7.75-7.73 (m, 2 H), 7.58 (d, 2 H, *J*= 8.8 Hz), 7.05 (d, 2 H, *J*= 8.4 Hz), 6.87-6.84 (m, 3 H), 6.35 (s, 1 H), 4.92 (s, 2 H), 4.45 (s, 2 H), 3.85 (s, 3 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.40, 163.38, 134.82, 134.71, 134.56, 131.89, 130.48, 130.38, 130.10, 127.85, 123.86, 122.86, 122.01, 117.40, 114.14, 102.11, 55.71, 52.44, 34.69. HRMS (ESI) Calcd for $C_{26}H_{20}ClN_3O_7S$ $(M+H)^+$ 554.0783, found 554.0795.

N1-(2,2-Dimethoxyethyl)-6-nitrobenzene-1,3-diamine (**147**)



to a solution of 3-fluoro-4-nitroaniline (780 mg, 5 mmol) in 20 mL methanol, diisopropylethylamine (0.870 ml, 5 mmol) then 2-aminoacetaldehyde dimethyl acetal (0.653 ml, 6 mmol) were added and the reaction mixture stirred at room temperature for 10 hours. Then, dilute the mixture diluted with ethyl acetate and washed with water, brine, and dried over Na_2SO_4 followed by removal of organic layer under reduced pressure to get the crude product which was purified by ISCO to give the title compound as an orange colored solid 856 mg, 71% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 8.44 (br, 1 H), 8.04 (d, 1 H, *J*= 8.8 Hz), 5.97 (dd, 1 H, *J*= 2.4 Hz, 9.2 Hz), 5.85 (d, 1 H, *J*= 2.4 Hz), 4.63 (t, 1 H, *J*= 5.6 Hz), 4.36 (br, 2 H), 3.44 (s, 6 H), 3.63 (d, 2 H, *J*= 5.6 Hz). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.52, 147.53, 129.45, 124.81, 104.96, 101.88, 93.76, 53.82, 44.47.

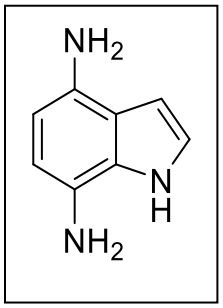
7-Nitro-1*H*-indol-4-amine (**148**)



To a solution of intermediate (**147**) (341 mg, 1.5 mmol) in DCM (5 mL) was added TFA (0.6 ml) and the mixture was stirred at room temperature and monitored using TLC and LCMs. Upon completion, the organic solvent under reduced pressure to get the title compound as dark brown solid 242 mg, 91% yield). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 10.98 (s, 1 H), 87.96 (d, 1 H, *J*= 8.8 Hz), 7.31-7.30 (m, 1 H), 6.83-6.82 (m, 1 H), 6.52 (br, 2 H), 6.40 (d, 1 H, *J*= 8.8 Hz). ^{13}C NMR (100 MHz) (Acetone-d_6) δ 151.00, 132.27, 129.81, 124.70, 124.41, 116.85, 104.34, 101.78.

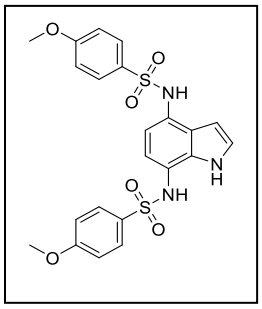
1*H*-Indole-4,7-diamine (**149**)

Prepared as described in the general procedure for nitro group reduction (Method E2) to get the title compound as dark solid 147 mg, quantitative). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 7.34-7.21 (m, 2 H), 6.83-6.68 (m, 2 H), 6.50-6.39 (m, 1 H), 4.37 (br, 4 H).



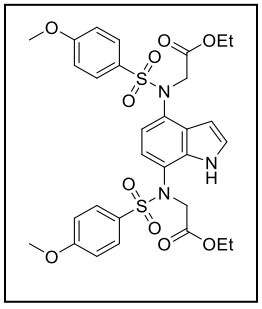
N,N'-(1*H*-Indole-4,7-diyl)bis(4-methoxybenzenesulfonamide) (**150**)

Prepared as described in the general procedure for sulfonamide synthesis (Method A2) to get the title compound as a yellow solid 212 mg, 52% yield). ^{1}H NMR (400 MHz) (Acetone-d_6) δ) 8.67 (br, 2 H), 7.68 (d, 2 H, *J*= 8.8 Hz), 7.59 (d, 2 H, *J*= 8.8 Hz), 7.26-7.25 (m, 1 H), 6.98-6.88 (m, 5 H), 6.66-6.62 (m, 2 H), 3.84 (s, 3 H), 3.81 (s, 3 H). ^{13}C NMR (100 MHz) (Acetone-d_6) δ 163.01, 132.86, 132.51, 132.13, 131.09, 129.20, 127.95, 127.89, 125.01, 118.88, 118.85, 117.65, 117.56, 113.87, 113.81, 112.52, 99.79, 99.77, 55.17, 55.11.



Diethyl 2,2'-((1*H*-indole-4,7-diyl) bis (((4-methoxyphenyl) sulfonyl) azanediyl)) diacetate (**151**)

Prepared as described in the general procedure for alkylation of sulfonamide (Method b) to get the title compound as oily product 133 mg, 67% yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ) 9.66 (s, 1 H), 7.63-7.56 (m, 4 H), 7.14 (t, 1 H, *J*= 1.4 Hz), 6.88-6.85 (m, 4 H), 6.82 (d, 1 H, *J*= 3.6 Hz), 6.53 (t, 1 H, *J*= 3.6 Hz), 6.22 (t, 1 H, *J*= 2.4 Hz), 4.45 (s, 2 H), 4.35 (s, 2 H), 4.21 (q, 2 H, *J*= 7.2 Hz), 4.13 (q, 2 H, *J*= 7.2 Hz), 3.85



(s, 3 H), 3.84 (s, 3 H), 1.27-1.20 (m ,6 H). ^{13}C NMR (100 MHz) ($CDCl_3$) δ 170.79, 169.08, 163.27, 163.01, 136.15, 132.24, 132.17, 131.18, 130.17, 129.98, 129.97, 128.38, 125.97, 124.52, 121.77, 121.67, 121.51, 121.41, 113.95, 113.81, 100.83, 61.97, 61.30, 55.61, 55.56, 53.59, 52.28, 14.06, 14.04.

Fluorescence Polarization (FP) Assay for Determination of the Inhibitory Potency of Designed Analogs

Fluorescence polarization assay was performed on a Wallac Victor 3V multi-label counter/plate reader (PerkinElmer, Shelton, CT) using 484 nm excitation and 535 nm emission filters for the fluorophore used in the binding experiment. The plate used for the FP measurement was Corning 3575 384-well plate, loaded with 40 µL of assay solution per well. The buffer used in FP assays is 10 mM HEPES buffer, pH 7.4, containing 150 mM NaCl, 50 mM EDTA, and 0.005% Tween-20. Deionized water from a Millipore water purification used to prepare all aqueous solutions in FP assay. The fluorescent probe used in this assay is 9-mer Nrf2 ETGE motif derived peptide, FITC-LDEETGEFL-NH_2. In each well, the final volume is 40 µL that consisted of 10 µL of 400 nM Keap1 Kelch domain protein, and 20 µL of 20 nM FITC-9mer Nrf2 peptide amide, and 10 µL of an inhibitor compound of different concentrations. The experiments were done in triplicates, with initial concentration of the inhibitor typically 5 µM and 50 µM. Then, the plate was centrifuged for 2 min. to ensure thorough mixing and get rid of any air bubbles in the solution. The plate was covered and shacked for 30 min at room temperature and then centrifuged for 2 min. prior to FP measurements.

The determination of FP is by measuring the parallel and perpendicular fluorescence intensity ($F_{\parallel}$ and $F_{\perp}$) with respect to the linearly polarized excitation light. The measurement of IC_{50} of the inhibitors was determined from the plot of% inhibition against concentration of the inhibitor analyzed by Sigma Plot 12.3 software.

Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) assay

TR-FRET assay was performed on a Wallac Victor 3V multi-label counter/plate reader (PerkinElmer, Shelton, CT). The plate used for the FP measurement was 384-well plates (Corning® 384 Well Low Flange White Flat Bottom Polystyrene NBS™ Microplate).
, loaded with 20 µL of assay solution per well. The buffer used in FP assays is TR-FRET dilution buffer from ThermoFisher (PV3574). The fluorescent probe used in this assay is 9-mer Nrf2 ETGE motif derived peptide, FITC-LDEETGEFL-NH_2. In each well, the final volume is 20 µL containing 5 nM of Keap1, 25 nM of FITC-Nrf2-9mer-NH_2 and 0.5 nM of Terbium labeled anti-HIS antibody + inhibitor compound of different concentrations in DMSO or DMSO alone (1% final concentration) in assay buffer in triplicate. Then, the plate was centrifuged for 2 min. to ensure thorough mixing and get rid of any air bubbles in the solution. The plate was covered and shacked for 60 min at room temperature and then centrifuged for 2 min. and TR-FRET was measured on a Victor 3V microplate reader. After excitation at 340 nm, well fluorescence was monitored at 495 nm and 520 nm. The measurement of IC_{50} of the inhibitors was determined from the plot of% inhibition against concentration of the inhibitor analyzed by Sigma Plot 12.3 software.

Cell Culture:

The human hepatocellular carcinoma cells HepG2-C8 cells cell line was provided by Dr. Tony Kongs (Rutgers University, Piscataway, NJ). The HepG2-C8 cells were transfected with pARE-TI-luciferase construct containing a single copy of 41-base pair mouse ARE (obtained from Professor William Fahl; University of Wisconsin). In detail, Human hepatoma HepG2-C8 were cultured in DMEM media at 37 °C in 5% CO_2 and maintained by regular passage in DMEM media supplemented with 5% penicillin-streptomycin (Life Technologies Grand Island, NY, USA) and 10% FBS (Atlanta Biologicals, Lawrenceville, GA). HepG2-C8 cells were used in experiment when they reached 80 to 90% confluence.

Cytotoxicity studies (AlamarBlue Assay):

The cell viability study performed using alamarBlue assay; the principle of this assay is based on the reduction potential of metabolically active cells. Using 96-well plates, HepG2-C8 cells were seeded at a density of 8,000 cells/well and kept overnight; then, HepG2-C8 cells were exposed to varying concentrations of LH-762, 785, 835, 837, 838, 839, 841, and 843 (0, 1, 10 and 50 µM), in triplicate wells, for 24 hours. Then, AlamarBlue® reagent (100 µl) (Sigma, USA) was added to the wells and incubated (3 h at 37 °C). DMSO (10%) was used as a positive control. Plate reader (Spectramax M5, Sunnyvale, CA, USA) was used to measure the fluorescence at wavelengths 570 nm excitation and 585 nm emission at room temperature. Results were represented as the percent of viable cells versus the control.

ARE-Luciferase Assay:

Using 12-well plates, HepG2-C8 cells were seeded at a density of 1.5 x 105 cells/well. After 24 h, HepG2-C8 cells were treated with LH-762, 785, 835, 837, 838, 839, 841, and 843 (10 µM). Using the protocol provided by the manufacturer (Promega Corp., Madison, WI), the luciferase activity was determined. Then after 24 h of treatment with the chemicals, cells washed with PBS and covered by RLB and scraped the attached cells from the dish. Then, cells transferred to a microcentrifuge tube and the cell lysates were centrifuged for 1 min at room temperature at 12,000 x g and 10 µl supernatant was collected. The luciferase activity measured using a TD-20/20 luminometer (Turner Designs, Sunnyvale,CA). The ARE-Luciferase activity was normalized to protein concentration.

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