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DESIGN AND SYNTHESIS OF NOVEL FtsZ-TARGETING ANTIBACTERIAL AGENTS

By

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ABSTRACT OF THE DISSERTATION

DESIGN AND SYNTHESIS OF FtsZ-TARGETING ANTIBACTERIAL AGENTS

By CODY KELLEY

Dissertation Director: Prof. Edmond J. LaVoie, Ph.D.

Bacterial infections pose a major health concern worldwide, and the emergence of multi-drug resistant strains of bacteria has intensified the search for new antibiotic treatments with novel mechanisms of action. Bacterial cell division remains a new, currently untargeted pathway making it highly desirable research area for discovering new ways to kill bacteria. FtsZ is a highly conserved, essential bacterial cell division protein that forms the dynamic Z-ring involved in recruitment of other essential proteins and serving as the constricting force for cell division. Inhibiting the function of this key protein disrupts proper cell division, and has therefore become a key target in the search for new antibiotics. There are many known FtsZ inhibitors spanning from natural products such as sanguinarine and berberine, to synthetic derivatives such as GTP analogs and PC190723. The majority of these known inhibitors, however, lack the proper potency, safety profiles, and physiochemical properties required for clinical development. Initial studies involved modifying the structures of two known FtsZ inhibitors, sanguinarine and berberine, to increase potency and explore the structure-activity relationships. Unfortunately, although successfully obtaining analogs with good antibacterial activity, these compounds lacked desired solubility properties for further advancement. This led

to the second generation of compounds that lacked a constitutive cationic charge while retaining the antibacterial activity seen with the previous analogs. While these compounds had much better solubility, they possessed a new drawback. Compounds from the second generation were found to be highly protein bound resulting in a significant loss of antibacterial activity when administered in the presence of protein. Studies began to design and synthesize analogs that either exhibited much higher potency or much less protein binding. Although initial attempts at this were unsuccessful, continued efforts are being made to find a FtsZ inhibitor with improved potency, physiochemical properties, and a broader spectrum of antibacterial activity.

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DEDICATION

To my parents,

Paul C. Kelley and Virginia R. Kelley

for their never-ending love and support.

You made this possible.

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INTRODUCTION

Bacterial infections have posed a major public health concern around the world for many years. The emerging prevalence of multi-drug resistant (MDR) strains of bacteria as well as the growing concern of bioterrorism has furthered the global threat, and thus, intensified the search for new antibiotic treatments with novel mechanisms of action to combat the ever-developing risk to public health.[1-9] Some of the most common MDR strains of bacteria that represent the biggest therapeutic hurdle include the gram-positive methicillin-resistant *Staphyloccocus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VRE); as well as the gram-negative, extended spectrum β-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae*. Despite the growing urgency for new therapeutic agents, very few new classes of antibiotics have been approved in the past 50 years.[10] Clearly, there is a critical need for the development of novel antibiotics with innovative modes of action to address this serious, worldwide health concern.

The majority of currently approved antibiotics can be classified into four general categories: (1) inhibitors of cell wall synthesis; (2) inhibitors of protein synthesis; (3) inhibitors of nucleic acid synthesis; and (4) inhibitors of folate synthesis.[11] These pathways were originally targeted because they were well understood and known to be

essential for bacterial growth and function. It is these same targeted pathways that bacteria have found ways to adapt resistance mechanisms towards. Simplistically speaking, there are two main components that result in resistance – the use of antibiotics which "select" for resistant microorganisms while killing off susceptible ones, and the genetic resistance determinant itself, which carries on in the resistant "selected for" microorganisms.[1] There are multiple factors that contribute to this including: (1) overuse and/or misuse of antibiotics; (2) rapid bacterial mutations; (3) transference of genes for resistance via plasmids, bacteriophages, naked DNA, and/or transposons; (4) intrinsic mechanisms of defense by formation of biofilms; and (5) efflux pumps in the membrane that actively pump out foreign molecules such as inhibitors.[1,12] As of today, none of the originally targeted antibiotic pathways have escaped resistance mechanisms.[1]

Bacterial cell division, another essential bacterial function, remains a new and currently untargeted mechanism for antibiotics – no clinically approved agents exploit this mode of action as of yet, but many groups are actively investigating the various processes involved with hopes of finding several new targets to focus. One such target that is receiving a lot of attention is the bacterial cell division protein, filamenting temperature-sensitive mutant Z (FtsZ). FtsZ is a particularly attractive target for several reasons: (1) it is essential for multiplication and cell viability; (2) it is highly conserved across bacterial strains; and (3) it is not present in human cells. As such, our research focuses on the identification and synthesis of novel FtsZ-targeting agents with antibacterial activity and the development of potential clinically useful compounds. Based on what is known about FtsZ and bacterial resistance, molecules that disrupt the function of this essential cell division protein should not only be efficacious across

multiple strains of bacteria, but also against bacterial strains that have developed resistance to current available treatments.

1.1 Bacterial Cell Division – An Overview.

There are several reasons why bacterial cell division is a good target for the development of antibacterial agents.[10] The pathway is attractive as a novel mechanism of antibacterial action, therefore bypassing the currently observed resistance mechanisms. In addition to this, cell division and a majority of the proteins involved are essential to multiplication and cell viability making it likely that inhibition of this mechanism would produce bactericidal effects. Not only that, the proteins involved in cell division are highly conserved throughout many bacterial strains making it likely that an inhibitor of cell division processes could be efficacious against many strains of bacteria. At the same time, these proteins are largely absent in human cells; apart from some which have structural homologues in humans but do not appear affected by known specific inhibitors of their bacterial versions. And finally, an additional advantage to inhibiting the proteins involved in cell division is the accessibility and druggability of the targets – many of the proteins involved are located externally allowing for easy access without having to enter the cytoplasm, and many contain known druggable domains that bind ATP and GTP.[10,13]

Bacterial cell division has been studied in great detail – primarily in the rod-shaped bacteria *Escherichia coli* and *Bacillus subtilis*.[10] Following chromosome replication, cell division protein FtsZ localizes to the bacterial mid-cell and forms a dynamic ring-like structure of polymers known as the Z-ring.[14] Formation of the Z-ring initializes cell division and recruits FtsZ-binding proteins that regulate assembly and

disassembly rates of the ring. Once the Z-ring has been established, the remaining proteins that are considered essential to cell division are recruited mid-cell at the division site, using FtsZ as a scaffold, and assemble to form the divisome.[14-16] The Z-ring constricts, and this produces an invagination of the cell membrane and the cell wall of the bacteria forming the septum in the center of the cell.[17,18] Finally, peptidoglycan hydrolases hydrolyze the polymers of amino acids and sugars of the peptidoglycan cross-wall resulting in the separation of the two new cells.[10,19] Gram-positive bacteria contain two layers in their cell wall – a thick layer of peptidoglycan and an inner plasma membrane. Gram-negative bacteria contain three layers in their cell wall – an outer membrane (composed of lipopolysaccharide and protein), a thin layer of peptidoglycan, and an inner plasma membrane. A general schematic of cell division in *E. coli*, *B. subtilis*, and *S. aureus* is shown in Figure 1.[15]

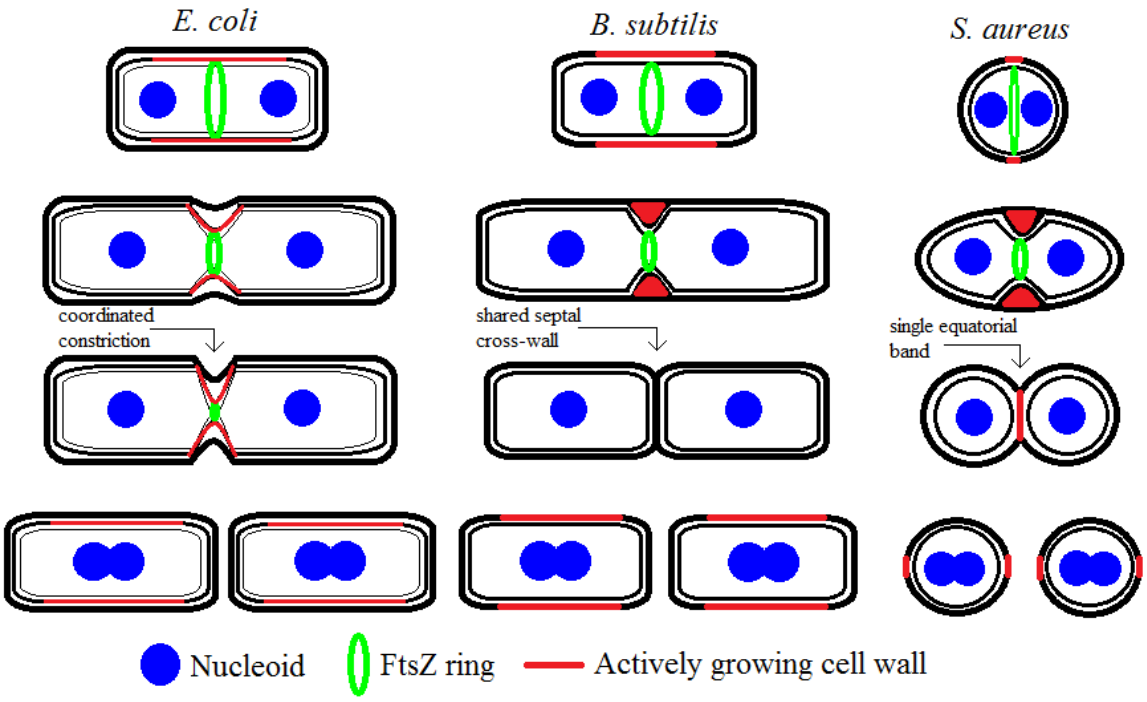


Figure 1. Bacterial cell division overview.[15]

Different strains of bacteria have slightly different cell division mechanics. For example, the gram-negative *E. coli* divide with a coordinated constriction of all three layers (outer membrane, peptidoglycan, and inner plasma membrane), whereas *B. subtilis* synthesize a septal cross wall that is shared between the two new cells before dividing into two distinct daughter cells (Figure 1).[15] Regions of active cell wall growth differ as well. For example, *S. aureus* synthesize a single equatorial band that eventually constricts and generates two new poles, whereas rod-shaped bacteria first insert new cell wall laterally during elongation and then switch to cell wall incorporation only at the septum area during division.[15] In all three of these bacteria, however, the FtsZ ring plays a key role.

1.2 Determination of the Z-ring Location.

During cell division, FtsZ is the first protein to localize directly underneath the plasma membrane of the cell forming the Z-ring.[16,20,21] This localization occurs mid-cell with the guidance of two overlapping processes: (1) nucleoid occlusion, and (2) the MinCDE pathway (Figure 2).[15,19] The first process, nucleoid occlusion, explains the tendency for the Z-ring to form in an area of the cell where there is little to no DNA present.[22-24] This is regulated by two unrelated DNA binding proteins: Noc (*B. subtilis*) and SlmA (*E. coli*).[24] Nucleoid occlusion theoretically limits the position of cell division to either the center or the poles of the dividing cell. The second process, the MinCDE pathway, inhibits cell division at the poles, thereby working with nucleoid occlusion to ensure proper Z-ring formation in mid-cell. If the Min proteins are deleted, cell division occurs at the poles, resulting in mini-cells that are absent of DNA.[25,26] MinC is the protein that interacts and binds directly with FtsZ at the poles, serving as the destabilizing

agent and inhibiting polymerization. This prevents FtsZ ring formation at the poles of the dividing cell. Min D and Min E, on the other hand, are responsible for the localization of MinC to the membrane poles so that it can inhibit Z-ring formation there.[15] The NO and the Min pathway do not require the other to proceed – the absence of one still allows for cell division; but it is the overlapping of the two that results in the correct localization of Z-ring formation.

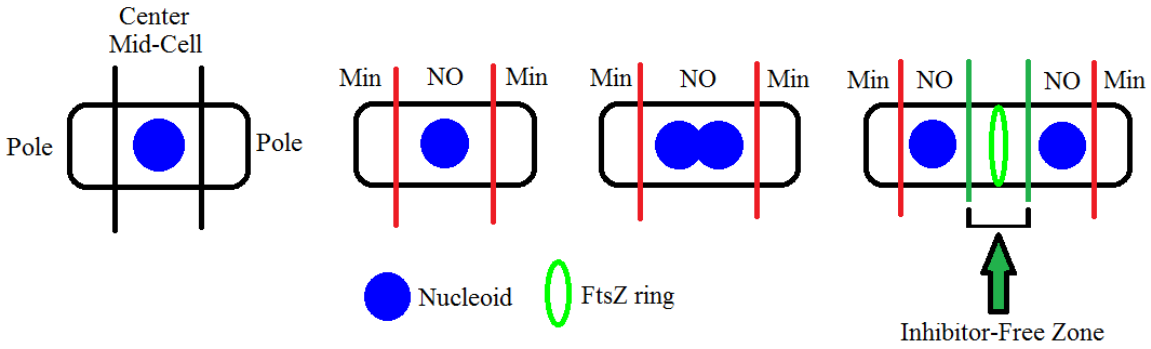


Figure 2. Determination of FtsZ ring location in mid-cell by nucleoid occlusion (NO) and Min.[19]

1.3 Other Cell Division Proteins Associated with FtsZ.

There are numerous other proteins that are involved and associated with FtsZ and cell division. These include cytoplasmic, periplasmic, and membrane-spanning proteins. Many interact directly with FtsZ to regulate the assembly and disassembly rates of the Z-ring. Some of these proteins serve as stabilizing agents such as FtsA, ZipA, ZapA, and SepF, while others serve as destabilizing agents such as MinC, EzrA, SulA, and ClpX.[10,19] In addition to proteins that modulate assembly and disassembly, there are proteins such as FtsK, which is involved with chromosome partitioning; FtsI (PBP3), a member of the penicillin-binding protein (PBP) family, and FtsW, a member of the

SEDS (shape, elongation, division, and sporulation) family, which are involved in peptidoglycan and cell wall synthesis; amidases like AmiC and activating factors like EnvC, which are involved in peptidoglycan hydrolysis; and finally proteins that are less understood but known to be associated with cell division, such as FtsQ, FtsB, FtsL, and FtsN.[10] Table 1 summarizes the specific functions of some of the major cell division proteins.

Table 1. Roles and structural features of the cell division proteins.[15,19]

Protein	Role	Structural Features
FtsZ	Initiates cell division at mid-cell, forms Z-ring, serves as scaffold for additional protein recruitment and formation of divisome.	Self-assembling GTPase structurally related to tubulin, located in cytoplasm.
FtsA	Tethers and stabilizes FtsZ to the membrane, required for Z-ring assembly, organization, and recruitment of additional proteins.	ATPase structurally related to actin, located in cytoplasm.
ZipA	Tethers and stabilizes FtsZ to the membrane and promotes Z-ring formation.	Large globular domain linked to a single N-terminal transmembrane domain by an extended linker.
ZapA	Positive modulator of Z-ring assembly and stability.	Dimer formed by extensive coiled-coil region, located in cytoplasm.
EzrA	Negative regulator of Z-ring assembly, contributes to mid-cell Z ring dynamics, and coordinates cell elongation with division.	Believed to contain 4 coiled-coil regions in C-terminal domain and single N-terminal transmembrane linker.
FtsK	Involved in chromosome partitioning and septal formation.	DNA translocase (ATPase), located in cytoplasmic membrane.
FtsI	Forms cross-links into the septal peptidoglycan.	PBP3 family, transpeptidase located in periplasm, anchored to cytoplasmic membrane.
FtsW	Involved in septal peptidoglycan synthesis.	SEDS family, located in cytoplasmic membrane.

1.4 Structure and Function of FtsZ.

FtsZ is the prokaryotic precursor and structural homologue to tubulin.[27,28] Despite the fact that they only share about 20% sequence similarity, FtsZ and tubulin exhibit a high level of structural similarity.[27] Likewise, FtsZ is a self-activating guanosine triphosphatase (GTPase) – binding to and hydrolyzing GTP resulting in GTP-dependent polymerization and depolymerization.[20,28-31] Despite high structural similarity, it is important to note that there are compounds that have been identified as specific FtsZ-targeting molecules. These molecules show no significant effects on human tubulin, indicating that there are ways to differentiate between the two allowing for selectivity.[10] The nucleotide-binding pocket of FtsZ and tubulin appear to have some subtle differences which may contribute to the ability to achieve selectivity between the two structural homologues. For example, while tubulin has a hydrophobic nucleotide-binding pocket buried inside the protein, FtsZ has a more hydrophilic pocket that is partially filled with water molecules.[32,33] Differences like this appear to be enough to distinguish between the two, as demonstrated by several substituted GTP analogues, which inhibit FtsZ but do not affect tubulin.[34,35]

The FtsZ monomer is globular protein with a relative molecular mass of 40 kDa that consists of an enzymatic N-terminal domain and a long C-terminal extension (~80 residues).[28,36] The enzymatic domain contains two subdomains: an N-terminal and C-terminal subdomain, and these globular subdomains are divided by a central core helix designated H7 helix (Figure 3).[36] The N-terminal subdomain contains the signature tubulin GGGTGTG motif and forms the nucleotide binding pocket, and the C-terminal subdomain is the GTPase-activating subdomain.[36] At the end of the long C-terminal

extension, there is a functional site which is responsible for recognizing all of the accessory proteins that are recruited during the cell division process.[37,38] During polymerization, the T7 loop of the upper subunit inserts itself into the N-terminal subdomain pocket (the nucleotide binding pocket) of the lower subunit, and this interface forms the active site.[39] The active site, not present on the FtsZ monomer, is formed at the interface of two FtsZ monomers, which are joined head to tail.[20,32,40] The catalytic residues of the T7 loop (two highly conserved aspartate residues) position themselves close to the γ-phosphate of GTP allowing for GTP hydrolysis.[32,40] This makes the GTPase activity of the FtsZ protein dependent upon FtsZ polymerization.[40]

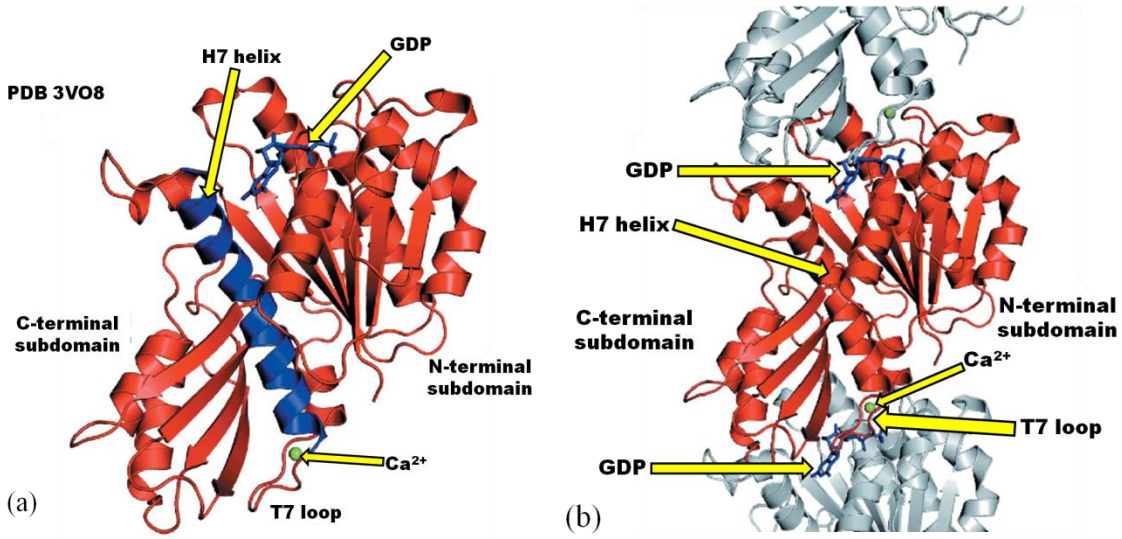


Figure 3. Structures of FtsZ.[36] (a) Structure of GDP-bound form of *S. aureus* FtsZ with H7 helix colored blue (PDB code 3VO8). (b) Crystal packing of *S. aureus* FtsZ. Asymmetric molecule is shown in red, symmetry-related molecules in silver. (*modified from reference 36*)

When GTP is bound, FtsZ polymerizes and assembles to form protofilaments. These linear protofilaments can then bundle laterally into sheets and ribbons.[41] On the

other hand, these protofilaments disassemble by bending and disintegrating when GTP is hydrolyzed to GDP.[19,42] These free FtsZ subunits bound by GDP are then recycled back into FtsZ polymers by exchanging their nucleotide.[43] Interestingly enough, FtsZ polymerization is dependent upon the binding of GTP, not the hydrolysis to GDP, making it likely that the hydrolysis is the rate-limiting step in the cycle.[32,44,45] Because of this, it is likely that, unlike tubulin, FtsZ polymers contain mostly GTP.[46] In any case, the cycle of FtsZ polymerization and depolymerization is a dynamic process, with a subunit half-life of approximately 10 seconds, powered by a repetitive cycle of GTP hydrolysis, and this has been suggested as the driving force behind constriction of the cell membrane during cell division.[47,48]

1.5 FtsZ as a Novel Target for Antibacterial Agents.

There are many proteins involved in the complex cell division process. While many of these may be potentially useful targets for the development of antibacterial agents, not all of them are completely understood. FtsZ is the first known protein to localize mid-cell and assemble the Z-ring, triggering cell division. In addition, it serves as the scaffold for further recruitment of the remaining necessary proteins involved in the cell division process, as well as providing the driving contractile force for constriction of the membrane. Given this, it is not surprising that the majority of studies targeting the inhibition of cell division have been focused around finding ways to specifically inhibit FtsZ.[10] FtsZ is the most characterized of all the cell division proteins, with a wealth of information surrounding its biochemistry and 3-D crystal structure, making it a good candidate for drug screening and development. FtsZ is also essential and highly conserved across most bacterial strains but absent in humans, making it even more

attractive as a drug target. Inhibition of FtsZ should provide antibiotic activity across a broad-spectrum of bacteria while having no detrimental effects on human cells. Most importantly though, FtsZ inhibition is a novel mechanism of action for the treatment of bacterial infections. This makes it promising as an effective approach against the emerging threat of bacteria that have developed resistances to current clinically used agents.

An effective FtsZ inhibitor should disrupt the function of the protein in such a way that it blocks the bacteria's ability to divide. This can be approached in one of two ways: (1) inhibiting FtsZ assembly/destabilizing FtsZ polymers, or (2) enhancing FtsZ assembly/stabilizing FtsZ polymers. Indeed, there have been examples of inhibitors that validate each of these approaches as effective ways to inhibit bacterial cytokinesis. Some examples of these known inhibitors will be discussed in the next section.

1.6 FtsZ Inhibitors.

1.6.1 Natural Product FtsZ Inhibitors.

Natural products have been the source for many pharmaceutical agents, treating a broad range of diseases, for a very long time. Natural products provide a wide variety of diverse chemical scaffolds that often have good biological activity, and they have been particularly useful in the past for identifying compounds with antibacterial activity. A number of natural products have been reported to inhibit FtsZ, and some key examples are shown in Figure 4.

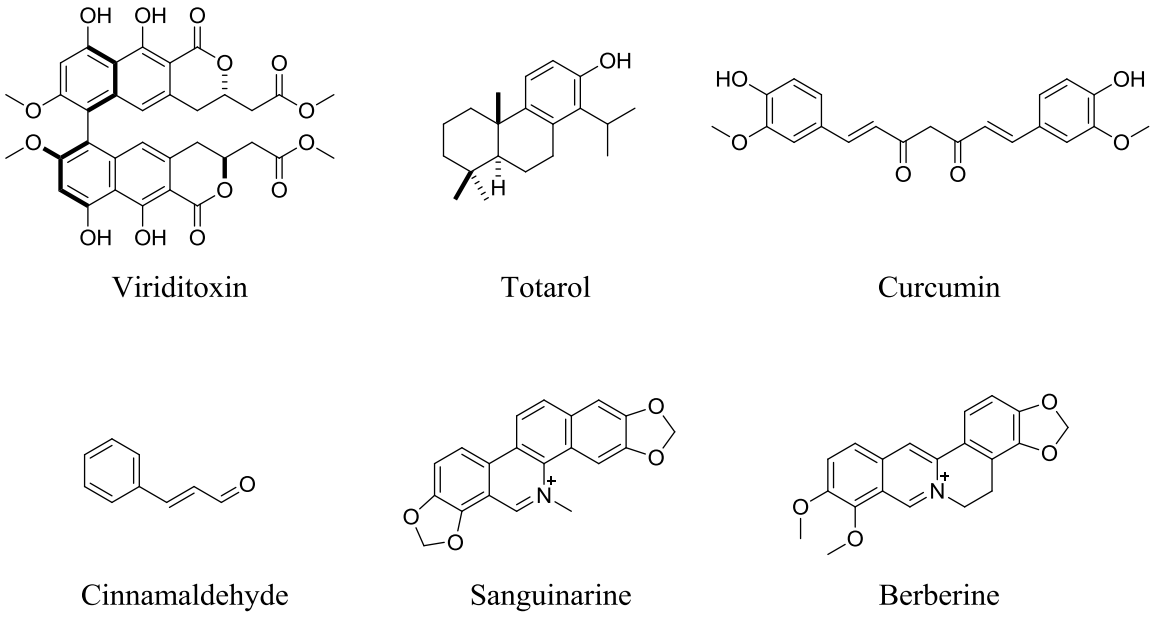


Figure 4. Natural product FtsZ inhibitors.

A high-throughput screening of > 100,000 natural extracts using a florescence-based *in vitro* FtsZ polymerization assay led to the identification of viriditoxin, obtained and originally reported from the fungus *Aspergillus viridinutans* in 1971.[49,50] Viriditoxin inhibits FtsZ polymerization and GTPase activity with an IC_{50} of 8.2 μg/mL and 7.0 μg/mL respectively, and it displays antibiotic activity against a broad-spectrum of both sensitive and resistant gram-positive bacteria including MRSA and VRE with minimum inhibitory concentrations (MIC) between 2-16 μg/mL.[49] Importantly, it was not shown to be toxic to eukaryotic cells.[49]

Totarol is a diterpenoid obtained from the bark of *Podocarpus totara* and has been shown to inhibit the growth of several gram-positive bacteria, such as *B. subtilis* (MIC of 2 μM) and *S. aureus* (MIC of 5.4 μM), by disrupting FtsZ assembly dynamics and decreasing GTPase activity (IC_{50} of 40 μM).[51,52] *In vitro*, totarol has been shown to

bind directly to FtsZ in *Mycobacterium tuberculosis* with modest affinity, a dissociation constant (K_d) of 11 μM.[52] It has also been shown to potentiate the effects of methicillin against MRSA by 256-fold.[53]

Curcumin is a polyphenolic compound from the rhizomes of *Curcuma longa* and has been shown to be effective against many gram-positive and gram-negative bacteria, such as *B. subtilis* (IC_{50} = 17 μM) and *E. coli* (IC_{50} = 58 μM).[54,55] Curcumin has been shown to inhibit assembly of FtsZ with an IC_{50} of 30 μM.[54] In contrast to viriditoxin and totoral, however, it increases the rate of GTP hydrolysis, enhancing the GTPase activity of FtsZ.[54] By increasing the rate of GTP hydrolysis, curcumin destabilizes the FtsZ protofilaments and promotes the disassembly of the GDP-bound polymers into monomers. This, of course, results in disruption of a functional Z-ring formation. Curcumin has also been shown to decrease the rate and the extent to which FtsZ polymerizes *in vitro*, resulting in reduced length and bundling of the protofilaments.[54] It binds to FtsZ with a K_d of 7.3 μM.[54] Development of curcumin as an antibiotic, however, has been hindered by its poor bioavailability.

Cinnamaldehyde is a phenylpropanoid product found in spices like *Cinnamomum cassia* that has been shown to inhibit FtsZ polymerization (IC_{50} = 6.9 μM) and inhibits GTP hydrolysis (IC_{50} of 5.8 μM), disrupting Z-ring formation.[56] It is believed to bind to the T7 loop based on *in silico* docking models.[56]

Sanguinarine is a benzo[*c*]phenanthridine alkaloid from the rhizomes of *Sanguinaria canadensis* and has been shown to strongly induce filamentation, inhibiting cytokinesis in both gram-positive and gram-negative bacteria (*B. subtilis* IC_{50} = 3 μM and

MIC of 10 μM, *E. coli* IC_{50} = 14 μM and MIC 75 μM) without affecting DNA replication or nucleoid segregation.[57] Sanguinarine binds to FtsZ (K_d of 30 μM), disrupts assembly of the Z-ring, and reduces the extent of bundling of FtsZ protofilaments *in vitro*.[57] Sanguinarine, however, has been shown to depolymerize microtubules both *in vitro* and in cancer cells, indicative of possible cytotoxic effects in humans.[58,59] This makes it a potentially difficult and challenging lead compound that is suitable for drug development.

And finally, berberine is a plant alkaloid structurally related to sanguinarine, obtained from *Berberis spp*. and *Hydrastis spp*., and has been shown to destabilize FtsZ protofilaments by disrupting the assembly dynamics (IC_{50} = 10 μM) and inhibiting the GTPase activity (IC_{50} = 16 μM).[60,61] Berberine displays modest antibacterial activity against gram-positive bacteria (MIC range 50-400 μg/mL, gram-negative MIC > 400 μg/mL).[62] Berberine appears to bind to FtsZ at the hydrophobic region of the GTP binding pocket with high affinity (K_d of 0.023 μM) and does not appear to affect tubulin like sanguinarine, making it a more suitable candidate for further development as a FtsZ-targeting antibacterial agent.[59,60] Table 2 summarizes the major natural products that have been identified that target FtsZ.

Table 2. Natural product FtsZ inhibitors.

Compound	Effects on Purified FtsZ	Antibacterial Activity
Viriditoxin	Inhibits FtsZ polymerization (IC_{50} = 8.2 μg/mL) & GTPase activity (IC_{50} = 7.9 μg/mL).	Shown to have broad-spectrum activity against sensitive & resistant gram-positive bacteria (MIC range 2-6 μg/mL).
Totarol	Inhibits assembly & GTPase activity (IC_{50} of 40 μM); binds to *M. tuberculosis* FtsZ with modest affinity (K_d of 11 μM).	Shown to be effective against several gram-positive bacteria: *B. subtilis* MIC 2 μM, *S. aureus* MIC 5.4 μM & shown to potentiate effect of methicillin in MRSA by 256-fold.
Curcumin	Inhibits assembly (IC_{50} = 30 μM) & increases GTPase activity; binds to FtsZ with K_d of 7.3 μM.	Shown to be effective against several gram-positive & gram-negative bacteria: *B. subtilis* IC_{50} = 17 μM, *E. coli* IC_{50} = 56 μM.
Cinnamaldehyde	Inhibits FtsZ polymerization (IC_{50} = 6.9 μM) & GTPase activity (IC_{50} = 5.8 μM).	Displays modest antibiotic effects against *B. subtilis* MIC 500 μg/mL, *E. coli* MIC 1000 μg/mL, MRSA MIC 250 μg/mL.
Sanguinarine	Inhibits assembly & bundling of FtsZ protofilaments; binds to FtsZ with K_d of 30 μM.	Shown to be effective against both gram-positive & gram-negative bacteria: *B. subtilis* IC_{50} = 3 μM (MIC 10 μM), *E. coli* IC_{50} = 14 μM (MIC 75 μM).
Berberine	Inhibits assembly (IC_{50} = 10 μM) & GTPase activity (IC_{50} = 16 μM); binds to FtsZ with K_d = 0.023 μM.	Displays modest effects against gram-positive bacteria: *B. subtilis* MIC 50 μg/mL, *S. aureus* MIC 100 μg/mL, *E. coli* MIC > 400 μg/mL.

1.6.2 Synthetic FtsZ Inhibitors.

As with most drugs, synthetic chemistry has played a huge role in the development of clinically useful antibacterial agents. In addition to the natural products

that have demonstrated FtsZ inhibitory activity, there have been several synthetic FtsZ inhibitors reported in the literature (Figure 5).

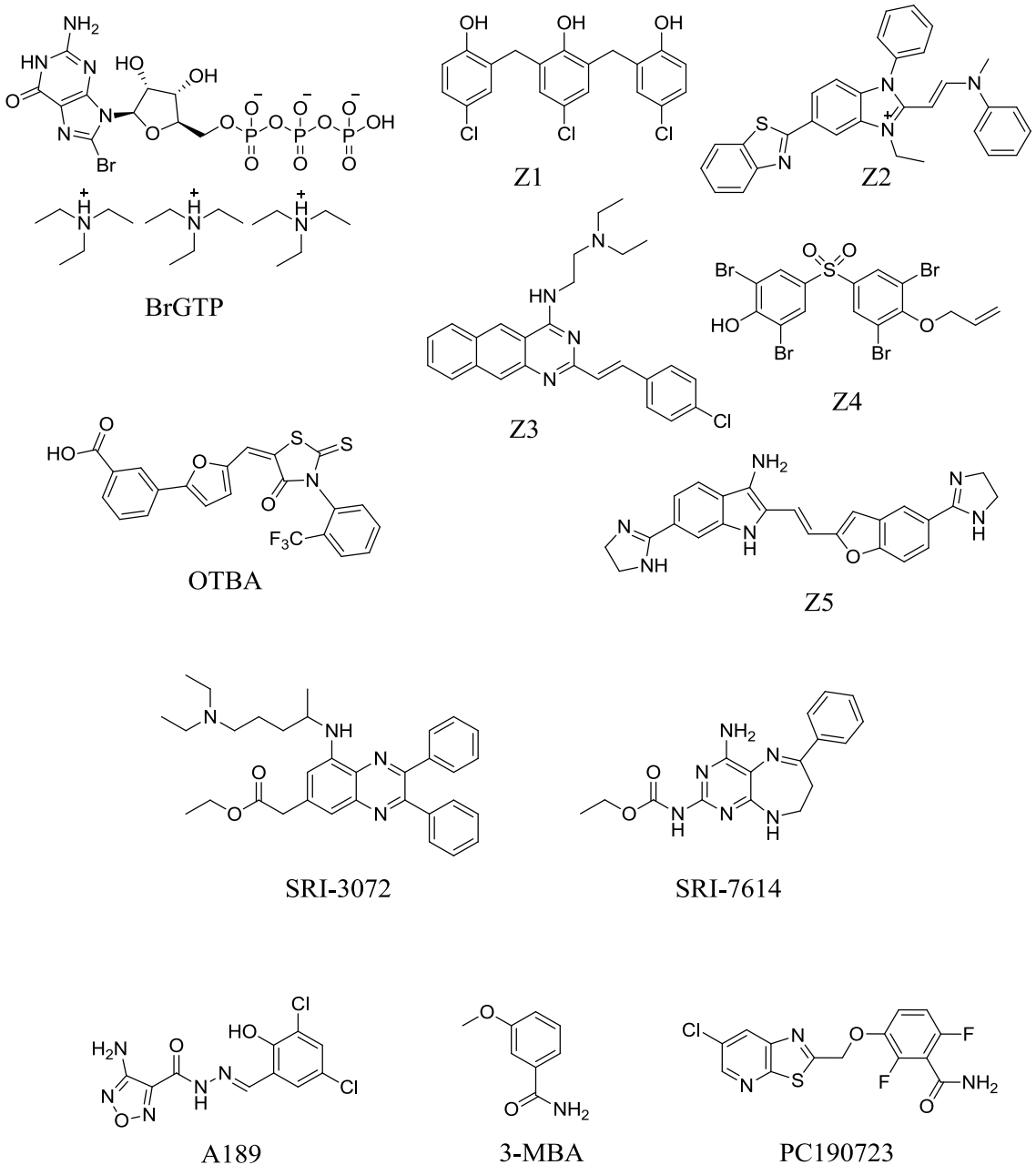


Figure 5. Synthetic FtsZ inhibitors.

Since GTP-binding is essential for FtsZ polymerization, it makes logical sense that GTP analogs could be effective at disrupting FtsZ assembly. 8-Bromoguanosine 5'-triphosphate (BrGTP) has been reported as a selective, competitive inhibitor of FtsZ polymerization (IC_{50} = 37 μM) and GTPase activity (IC_{50} = 60 μM) that does not affect tubulin polymerization.[34,35] These data suggest that there is enough difference in the GTP-binding pocket between FtsZ and tubulin to allow for the development of selective agents. Several other GTP analogs have been prepared and identified through the use of parallel synthesis, leading to compounds that inhibit GTPase activity in *Pseudomonas aeruginosa* (IC_{50} range of 450 μM to 2.6 mM) as well as inhibit *S. aureus* growth.[63]

Five small molecules nick-named zantrins (FtsZ guanosine triphosphate inhibitors) were identified in a high-throughput screening (HTS) of > 18,000 compounds searching for inhibitors of *E. coli* FtsZ with IC_{50} values < 50 μM.[64] The zantrins have been shown to inhibit FtsZ polymerization and disrupt Z-ring assembly by either destabilizing FtsZ polymers (Z1, Z2, and Z4) or stabilizing FtsZ protofilaments (Z3 and Z5).[64] All have been shown to inhibit GTPase activity with an IC_{50} range of 4-25 μM.[64] Z1 and Z2 were demonstrated to have modest antibacterial activity against wild-type *E. coli* with an MIC of 40 and 60 μM, respectively.[64] Z1-Z4 were all effective against both *S. aureus* and MRSA (MIC range 2.5-10 μM), whereas Z5 only demonstrated modest activity against *B. subtilis* (MIC = 40 μM).[64] While none of the zantrins are sufficiently potent or specific enough as is, they could serve as good starting points for lead optimization.

The compound OTBA (3-(5-[4-oxo-2-thioxo-3-{trifluoromethylphenyl}-thiazolidin-5-ylidenemethyl]-furan-2-yl)benzoic acid) was identified in a screening of 81 structurally diverse compounds, and it has been shown to bind to FtsZ (K_d of 15 μM) and, unlike most other inhibitors, promote the assembly of FtsZ causing bundling of protofilaments while preventing the disassembly and decreasing the GTPase activity.[65] OTBA had an MIC of 2 μM in *B. subtilis* with little effect on mammalian cells making it a good candidate for optimization.[65]

In another screening of 200 synthetic alkoxycarbonylpyridine compounds, SRI-3072 and SRI-7614 were identified as inhibitors of FtsZ polymerization and GTPase activity and were effective against both susceptible and resistant strains of *M. tuberculosis*.[66] Additionally, SRI-3072 was demonstrated to be FtsZ specific – having no effect on tubulin polymerization, suggesting it would be a good candidate for further optimization.[66]

In yet another HTS of 95,000 compounds, A189, a 4-aminofurazan derivative, was identified as a potent antibacterial capable of inhibiting FtsZ GTPase activity (IC_{50} = 80 μg/mL) in *E. coli*.[67] A189 inhibits FtsZ ring formation resulting in cell death. It was also equally effective against susceptible and multi-drug resistant strains of *S. aureus* (MIC = 16 μg/mL).[67] A189 has modest antibacterial activity against *E. coli* with an MIC = 64 μg/mL.[67]

And finally, 3-methoxybenzamide (3-MBA) has been shown to have lethal effects on cell division in *B. subtilis*.[68] The lethality of the compound could be suppressed, however, with mutations of FtsZ, indicating this was the targeted protein responsible for

inhibiting cell division.[68] Although not very potent in itself, 3-MBA served as an excellent starting point for the development of new compounds. As such, >500 compounds were synthesized and evaluated, resulting in the identification of PC190723, which displayed inhibitory potency much greater than that of 3-MBA.[69] PC190723 has MICs ranging from 0.5-1.0 μg/mL against *B. subtilis* and a wide variety of staphylococci strains, including MRSA.[69] PC190723 was also reported to be efficacious in a mouse model of infection with a 100% survival rate upon treatment with 30 mg/kg administered intravenously.[69] Interestingly enough, it does not work against other gram-positive bacteria, such as enterococci and streptococci, or any gram-negative bacteria, indicating there must be other important molecular determinants for the resistance seen in other strains. The search for novel chemical entities of FtsZ inhibitors continues, and there are new ones identified in the literature frequently. Table 3 summarizes some of the representative ones discussed here.

Table 3. Synthetic FtsZ inhibitors.

Compound	Effects on Purified FtsZ	Antibacterial Activity
BrGTP (and related analogs)	Selective & competitive inhibitor of FtsZ polymerization (IC_{50} = 37 μM) & GTPase activity (IC_{50} = 60 μM).	Moderate antibacterial activity demonstrated in *S. aureus*; ineffective against *E. coli*.
Zantrins (Z1-Z5)	Z1, Z2 & Z4 destabilize FtsZ assembly; Z3 & Z5 stabilize FtsZ assembly. All inhibit GTPase activity with IC_{50} range of 4 to 25 μM.	Z1-Z4 effective against *S. aureus* & MRSA (MIC range 2.5-10 μM); Z1 & Z2 effective against E. coli (MIC 40 and 80 μM, respectively).
OTBA	Binds to FtsZ (K_d = 15 mM); promotes assembly & stabilization of FtsZ protofilaments; decreases GTPase activity.	Effective against *B. subtilis* with an MIC of 2 μM.
SRI-3072 & SRI-7614	Inhibits FtsZ polymerization & inhibits GTPase activity.	Both effective against *M. tuberculosis* with MIC of 0.28 μM and 19 μM, respectively.
A189	Inhibits FtsZ assembly & inhibits GTPase activity (IC_{50} = 80 μg/mL).	Shown to be equally effective against susceptible & MDR strains of *S. aureus* (MIC = 16 μg/mL); modest activity against *E. coli* (MIC = 128 μg/mL).
PC190723	Inhibits GTPase activity with an IC_{50} of 55 ng/mL.	Effective against *B. subtilis*, *S. aureus* & MRSA (MIC = 1 μg/mL); demonstrated to be effective in an *in vivo* mouse model at 30 mg/kg iv.

1.7 Rationale.

There is a considerable amount of data that supports the idea that inhibition of FtsZ is a promising and effective target for the treatment of resistant-bacterial strains. FtsZ is an essential, highly conserved bacterial cell division protein and, thus far, an untargeted mechanism of action for antibacterial agents. A true understanding and

realization of this will require the development of FtsZ inhibitors that have strong antibacterial activity both *in vitro* and *in vivo*, are effective against resistant strains of bacteria, and display no cytotoxicity in mammalian cells. Our research efforts began with the investigation of chemical modifications to the natural products sanguinarine and berberine, already identified in the literature as FtsZ inhibitors. Initial studies used these two leads as scaffolds for further development. After establishing the SAR, we wanted to remove the constitutive cationic charge that is present in these types of molecules while retaining antibacterial activity. This led to the design of several classes of non-quaternary FtsZ inhibitors containing a basic moiety, which would not contain a constitutive charge, but would likely be protonated to an extent at physiological pH. The development of these types of molecules could improve the physiochemical properties and increase the likelihood that a FtsZ inhibitor might one day find its way to a clinically useful antibiotic.

RESULTS AND DISCUSSION

2.1 Synthesis and Evaluation of 1- and 12-Substituted 5-Methylbenzo[*c*]phenanthridinium Derivatives.

Sanguinarine, **1** (Figure 7) has previously been reported as a FtsZ inhibitor, capable of strongly inducing filamentation and inhibiting cytokinesis, resulting in good antibacterial activity.[57] The structurally related berberine, **2**, has also been identified as a FtsZ inhibitor, capable of binding FtsZ and inhibiting polymerization, resulting in modest antibacterial activity.[60] As we began this research, it was decided early on that these two plant alkaloids could serve as excellent starting points to begin our investigation of FtsZ inhibitors. Sanguinarine is commercially available and exhibits significant antibacterial activity against both the methicillin-sensitive and methicillin-resistant strains of *S. aureus* (MSSA and MRSA, respectively) with an MIC of 2.0 μg/mL for both, when evaluated in our biological studies. It also exhibits modest antibacterial activity against vancomycin-sensitive and vancomycin-resistant *E. faecalis* (VSE and VRE, respectively) with an MIC of 8 and 16 μg/mL, respectively. As such, our early goals for the project included synthesis and evaluation of the following: (1) replacement of the methylenedioxy substitution with functionality that would make the molecule less planar overall; (2) substitution at the 1-position of the benzo[*c*]phenanthridine ring to improve potency; and

(3) substitution at the 12-position of the benzo[*c*]phenanthridine ring to improve potency. We were particularly interested in improving the activity against the resistant strains of bacteria, MRSA and VRE, as these represent a serious health concern.

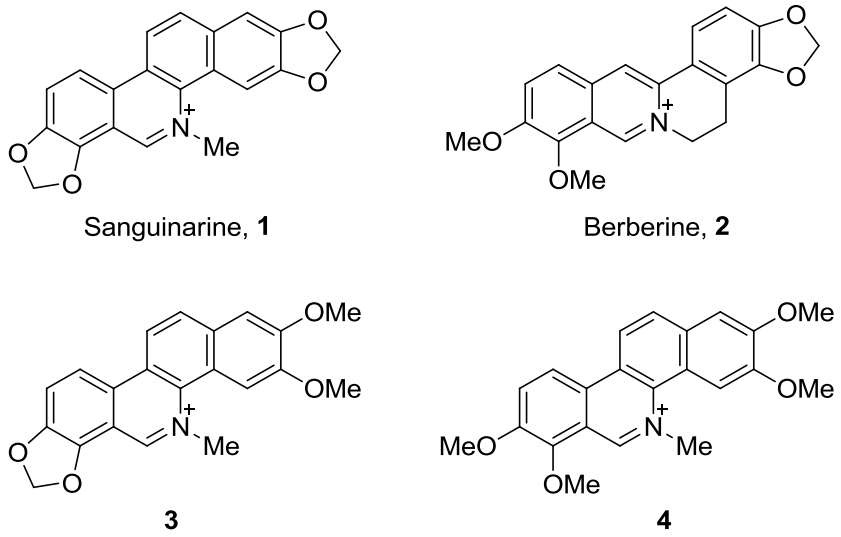
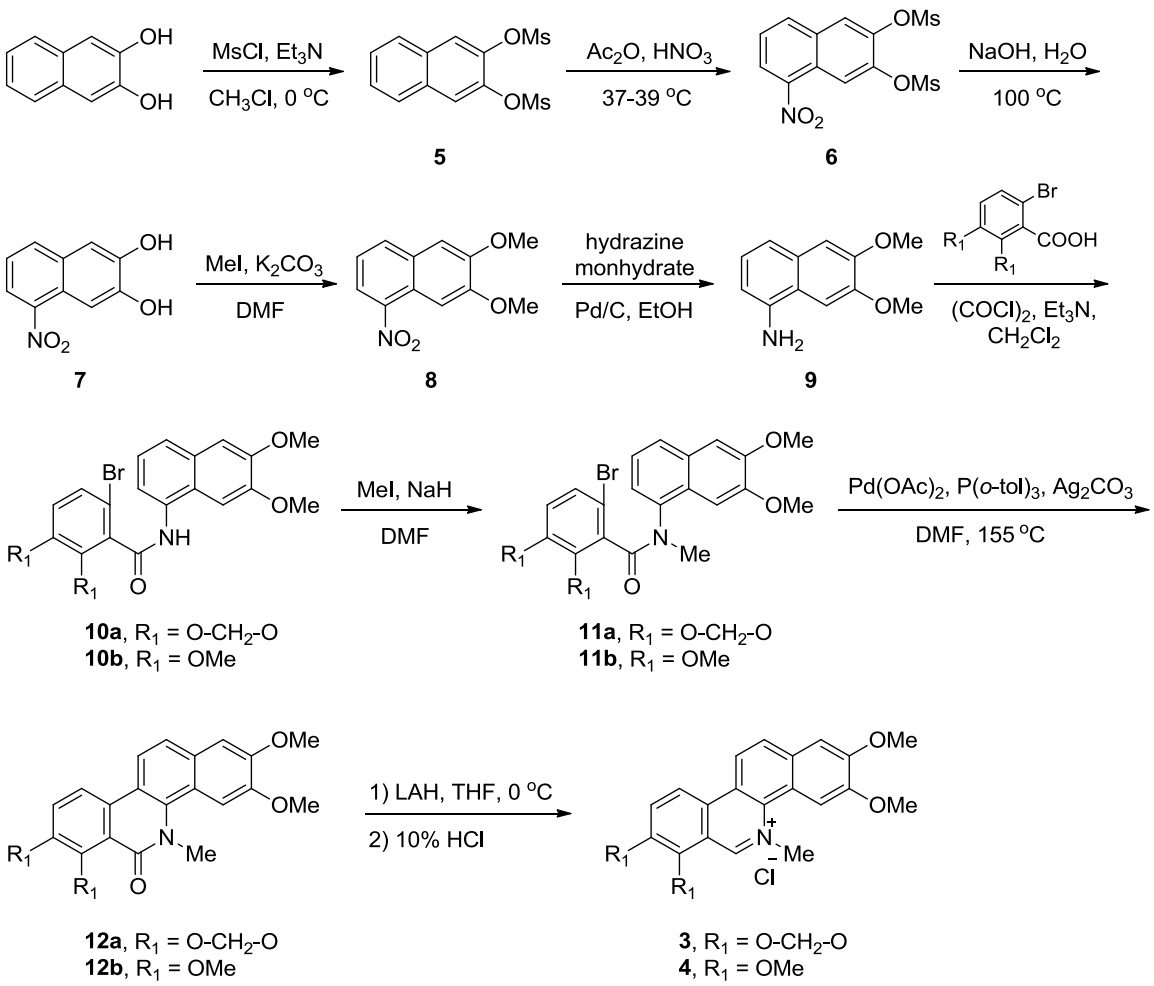


Figure 6. Structure of sanguinarine (**1**), berberine (**2**), and compounds **3** and **4**.

Initial research on this project was done by Dr. Ajit Parhi, who began by investigating the effects of replacing the methylenedioxy substituents on sanguinarine, **1**, with dimethoxyl substituents, compounds **3** and **4**. This replacement is not unlike the substitution pattern found on berberine, **2**. Replacement of the methylenedioxy substituents with dimethoxyls was a reasonable alternative for adding degrees of freedom to the molecule and making it less planar. These types of analogs were considered attractive, as they would be less likely to cause adverse effects on mammalian cells associated with possible intercalation into DNA. The synthetic route for compounds **3** and **4** is shown in Scheme 1.



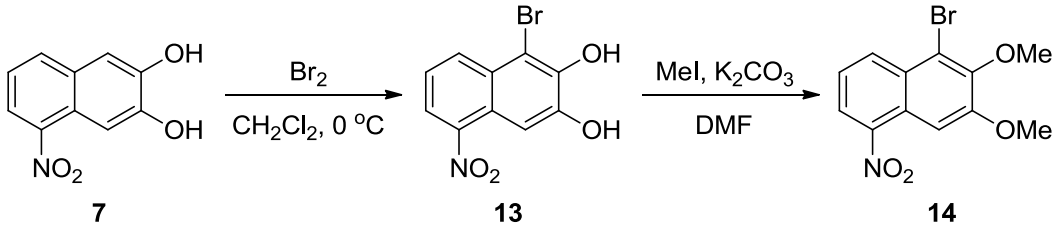
Scheme 1. Synthetic route for compounds **3** and **4**.

Starting with commercially available 2,3-dihydroxynaphthalene, treatment with methanesulfonyl chloride and triethylamine in anhydrous methylene chloride at 0 °C gave the dimesylate, **5** in high yield. The mesyloxy groups were chosen to help direct the nitration in the next step to the unsubstituted ring, as demonstrated in the literature.[70] Compound **5** was treated with nitric acid in acetic anhydride at a temperature of 37-39 °C to give the 5-nitro compound, **6** in reasonable yield.[70] Hydrolysis of the mesyl groups in refluxing NaOH solution yielded the 2,3-dihydroxy-5-nitronaphthalene derivative, **7**

followed by treatment with methyl iodide and potassium carbonate in DMF at 50 ^{o}C to give the 6,7-dimethoxy-1-nitronaphthalene derivative, **8**. The nitro was then reduced to the amine by treatment with hydrazine monohydrate as the hydrogen source and Pd/C (10%) in refluxing ethanol to give **9**. The naphthylamine was then coupled using triethylamine in anhydrous methylene chloride and the appropriate acid chloride formed by treatment of either 6-bromo-2,3-methylenedioxybenzoic acid (for **10a**) or 6-bromo-2,3-dimethoxybenzoic acid (for **10b**) with oxalyl chloride to give the corresponding benzamide derivatives.[71] Compounds **10a** and **10b** were then treated with sodium hydride in anhydrous DMF followed by methyl iodide to provide the tertiary amides (**11a** and **11b**), which were then cyclized under Heck conditions using $Pd(OAc)_2$, tri(*o*-tolyl)phosphine, and Ag_2CO_3 in refluxing DMF to give the substituted 5-methylbenzo[*c*]phenanthridin-6(5*H*)-one derivatives, compounds **12a** and **12b**.[71] Finally, reduction with LAH in anhydrous THF at 0 ^{o}C followed by treatment with 10% HCl provided the desired quarternized compounds **3** and **4**.[71]

In order to place substitution at the 1-position with relative ease, the chemistry had to be altered slightly to accommodate the placement of a bromide (Scheme 2). With the halogen in place, this intermediate could be readily cross-coupled using palladium chemistry to place a wide variety of substitution at that position. Starting with intermediate **7**, bromination with Br_2 at 0 ^{o}C in methylene chloride gave desired 1-bromo-2,3-dihydroxy-5-nitronaphthalene (**13**). Subsequent treatment with methyl iodide and potassium carbonate in DMF gave intermediate **14**, 1-bromo-2,3-dimethoxy-5-nitronaphthalene. Using this key intermediate, all various substitutions could be made

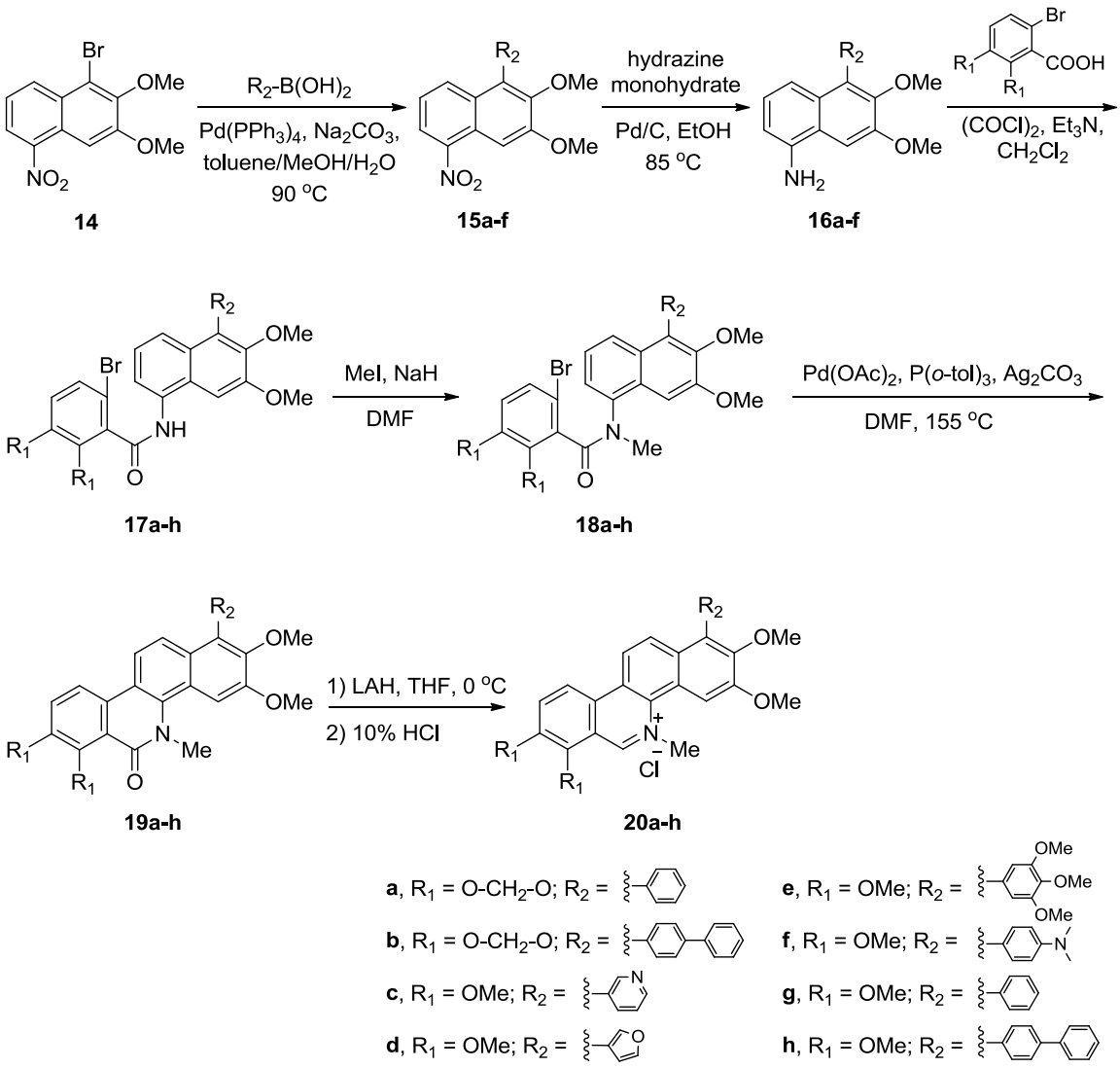
employing palladium-catalyzed cross-coupling reactions with the appropriately substituted boronic acid, pinacol ester, or tributyltin.



7 **13** **14**

Scheme 2. Synthesis of key intermediate **14**.

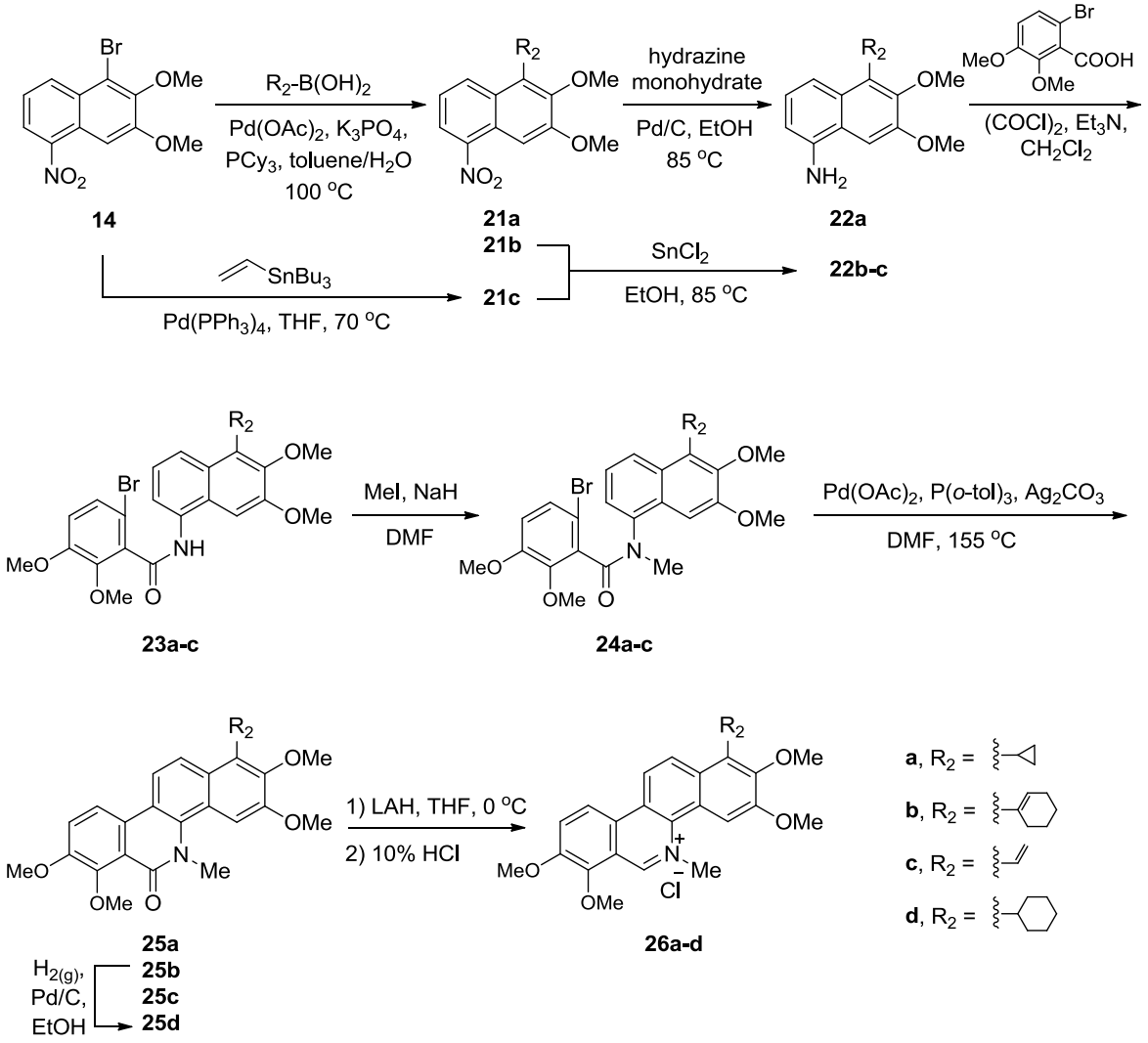
The generalized synthesis for analogs containing an aromatic substituent at the 1-position is summarized in Scheme 3. Using intermediate **14**, a Suzuki coupling with the appropriate boronic acid, tetrakis(triphenylphosphine)palladium(0) as the catalyst/ligand system, and 2M Na_2CO_3 in toluene/methanol (5:1) gave an array of cross-coupled products, **15a-f**, which were then subjected to the same methodology as described for compounds **3** and **4**. **15a-f** were reduced with hydrazine monohydrate to give **16a-f**, which were then coupled with the acid chloride of either 6-bromo-2,3-methylenedioxybenzoic acid (for **17a** and **b**) or 6-bromo-2,3-dimethoxybenzoic acid (for **17c-h**) to give the corresponding benzamide derivatives. *N*-Methylation to give the tertiary amides (**18a-h**) followed by Heck cyclization to give compounds **19a-h**, and lastly, LAH reduction and quaternization yielded the final compounds **20a-h**. The methods for synthesis as outlined in Scheme 3 were developed together with Dr. Ajit Parhi at TAXIS Pharmaceuticals, Inc., and compounds **20c-f** were synthesized by TCRS using the methodology developed in our lab.



Scheme 3. Synthetic route for 1-substituted compounds **20a-h**.

Because of the non-aromaticity and hybridization of the cyclopropyl and cyclohexenyl, the conditions used in the Suzuki coupling to obtain compounds **21a** and **21b** had to be altered (Scheme 4). Instead of using tetrakis(triphenylphosphine)palladium(0) as the catalyst, these compounds required the use of a different catalyst/ligand system. Palladium(II)acetate was used at the catalyst for these two couplings, with tricyclohexylphospine (PCy_3) as a ligand and tribasic

potassium phosphate as the base to give the desired cross-coupled products in high yield.[72]



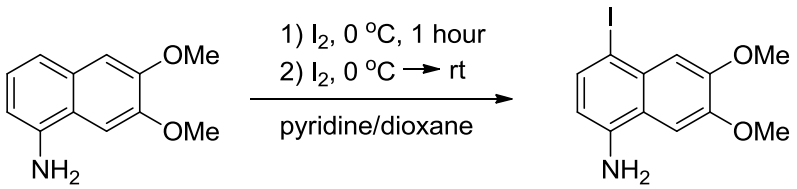
Scheme 4. Synthetic route for 1-substituted compounds **26a-d**.

For the case of **21c**, a Stille coupling with tributyl(vinyl)tin was carried out in place of the Suzuki coupling using tetrakis as the catalyst in refluxing THF. Because of the alkene functionality in compounds **21b** and **21c**, an alternative reduction procedure for the nitro group had to be used to avoid reducing the double bond. In these two cases,

tin(II)chloride in refluxing ethanol was used for the selective reduction of the aromatic nitro group, while leaving the cyclohexenyl and vinyl functionality untouched. Once the amines **22a-c** were obtained, amidation with the acid chloride of 6-bromo-2,3-dimethoxybenzoic acid gave compounds **23a-c**, followed by *N*-methylation to give compounds **24a-c**, and subsequent Heck cyclization gave compounds **25a-c**. At this point, compound **25d** was made directly from compound **25b** by hydrogenation using $H_{2(g)}$ and Pd/C (10%) in ethanol following the Heck cyclization to yield the cyclohexyl substituted analog. Lastly, the Heck cyclization products were reduced with LAH and quaternized to give the desired target compounds **26a-d**.

Substitution at the 12-position required a different intermediate for the palladium-catalyzed cross-couplings. Scheme 3 details the synthetic route employed for these derivatives. Intermediate **9** was used as the starting material in this synthesis. Initial attempts at selective iodination at the 4-position on the naphthalene ring involved first treating **9** with 3 equivalents of iodine at 0 ^{o}C in a 50/50 mix of anhydrous pyridine and dioxane for 1 hour, followed by the addition of 2.5 more equivalents of iodine and continuous stirring at room temperature for 3 more hours. Under these reaction conditions, a mixture of iodination products was obtained, with only 34% yield of desired product (Figure 8). The second set of conditions used involved lowering the amount of iodine added in the second step of the reaction (from 2.5 eq. to 1.5 eq.) and decreasing the reaction time at room temperature (from 3 hours to 1.5 hours). This set of conditions resulted in an improvement of yield from 34% to 47%. Finally, the conditions that gave the best overall yield of the desired product were treatment of the naphthylamine with iodine (3 eq.) in a 50/50 mix of anhydrous pyridine and dioxane at 0 ^{o}C for 1 hour,

followed by the addition of 1.34 eq. of iodine and warming to room temperature over a period of 1.5 hours. This improved the yield up to 63%, which we found sufficient for obtaining enough material to carry out the rest of the synthesis.



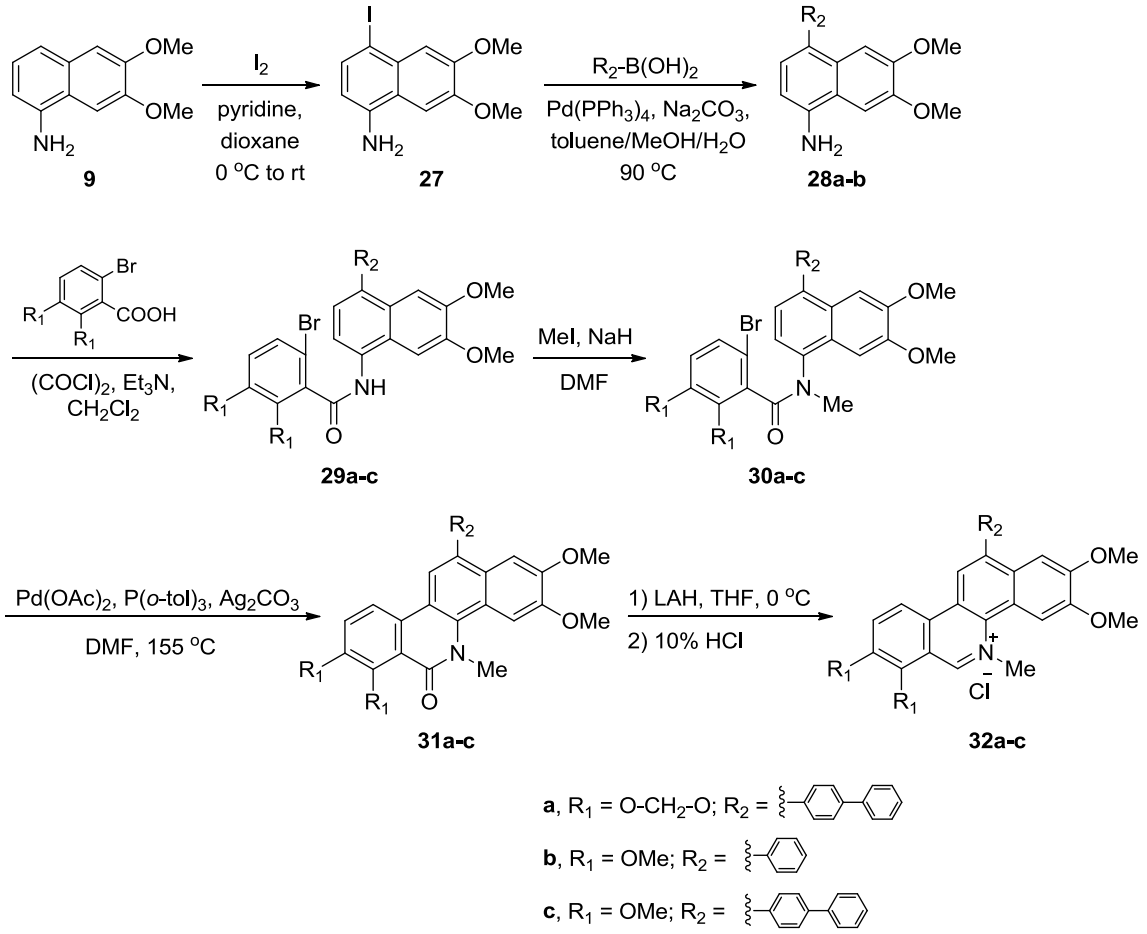
9 **27**

		Best yield of desired iodination product:
First condition:	1) 3 eq. I_2, 0 °C, 1 hour 2) 2.5 eq. I_2, 0 °C → rt, 3 hours	34%
Second condition:	1) 3 eq. I_2, 0 °C, 1 hour 2) 1.5 eq. I_2, 0 °C → rt, 1.5 hours	47%
Third condition:	1) 3 eq. I_2, 0 °C, 1 hour 2) 1.34 eq. I_2, 0 °C → rt, 1.5 hours	**63%**

Figure 7. Variations of iodination reaction. Each condition was carried out at least two separate times to determine best reaction conditions.

Following iodination, primary intermediate **27** was then used in several standard Suzuki couplings with either phenyl or 4-biphenylboronic acid with tetrakis as the catalyst and 2M sodium carbonate as the base in a mixture of toluene and methanol (5:1) at 90 °C to give **28a** and **28b**. Then, as per previous schemes, these naphthylamines were subjected to amidation with the acid chloride of either 6-bromo-2,3-methylenedioxybenzoic acid (**29a**) or 6-bromo-2,3-dimethoxybenzoic acid (**29b** and **29c**) to yield the benzamide. Subsequent *N*-methylation with sodium hydride and methyl

iodide, Heck cyclization using previous conditions, and LAH reduction and quaternization gave desired final products **32a-c**. Compound **32a** was prepared by Dr. Ajit Parhi at TAXIS Pharmaceuticals.



Scheme 5. Synthetic route for 12-substituted compounds **32a-c**.

The relative antibiotic activity of the synthesized analogs was then evaluated in 4 strains of bacteria. The values are reported as minimum inhibitory concentrations (MIC), which is defined as the minimum concentration of compound required to inhibit growth by ≥ 90%. Synthesized compounds were evaluated against both methicillin-sensitive and methicillin-resistant *S. aureus* (MSSA and MRSA, respectively), as well as vancomycin-

sensitive and vancomycin-resistant *E. faecalis* (VSE and VRE, respectively), and clinically relevant antibiotics oxacillin, vancomycin, erythromycin, tetracycline, and clindamycin (Figure 8) were used as reference standards.

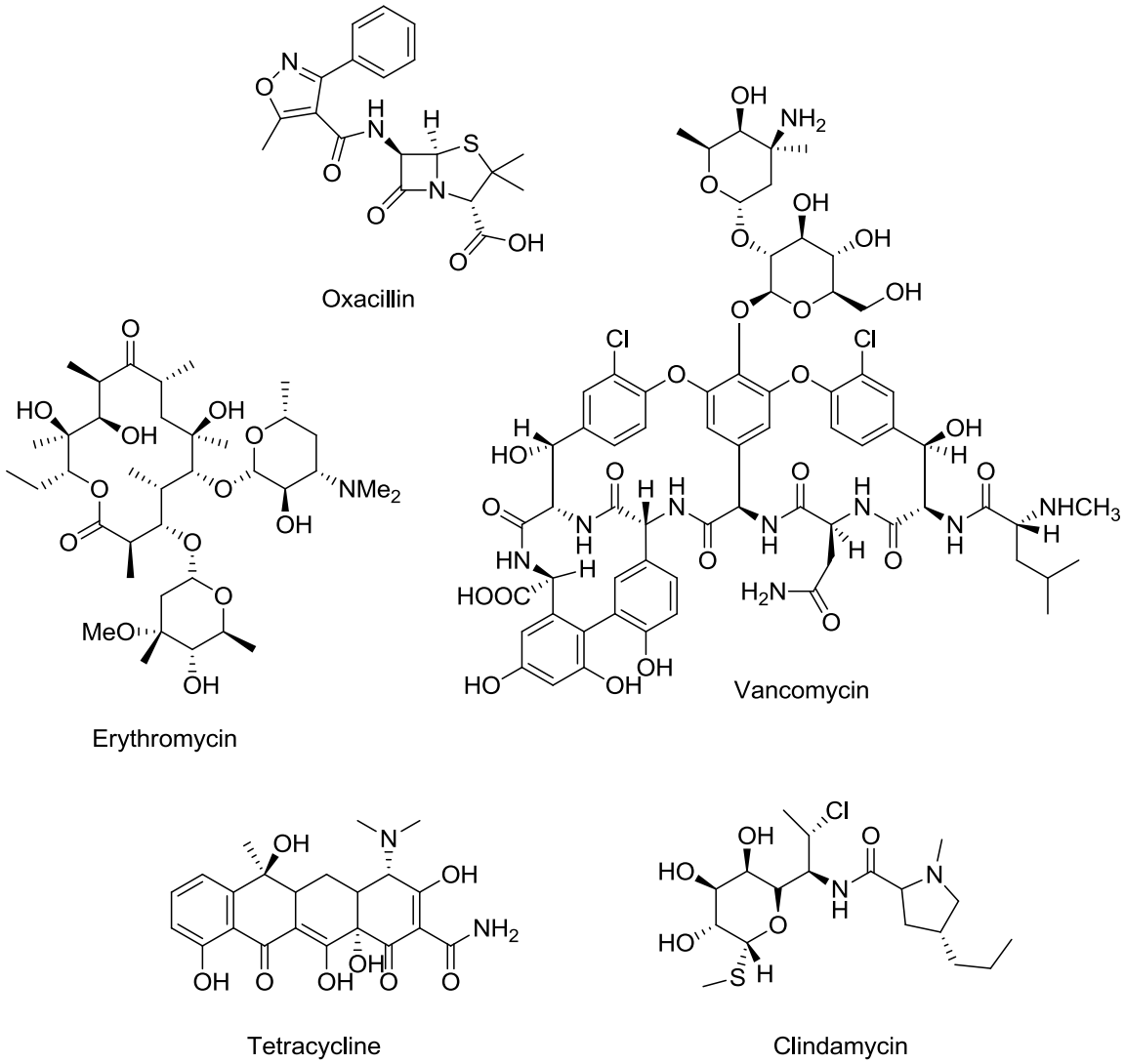


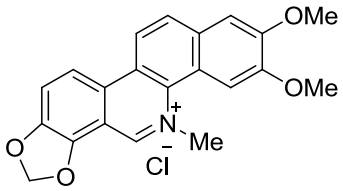
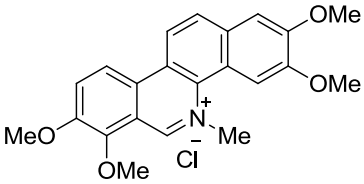
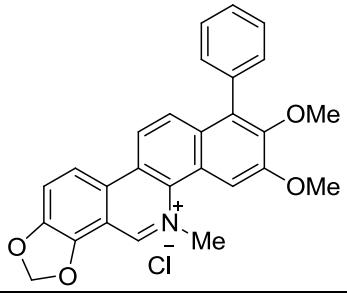
Figure 8. Structure of the clinical antibiotics used as reference standards.

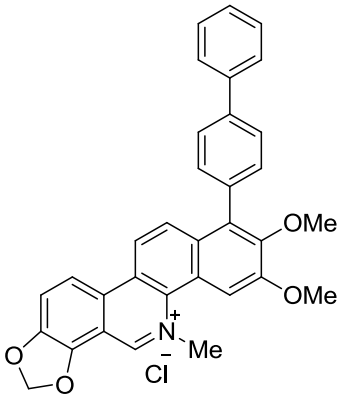
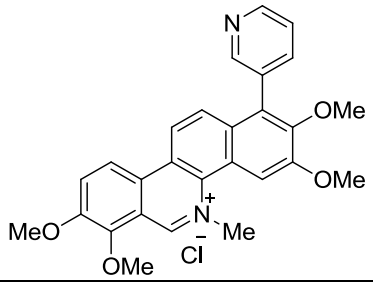
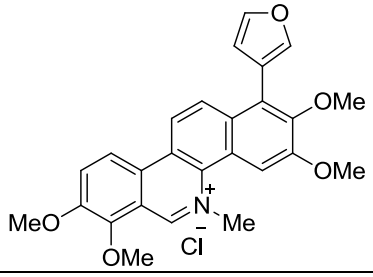
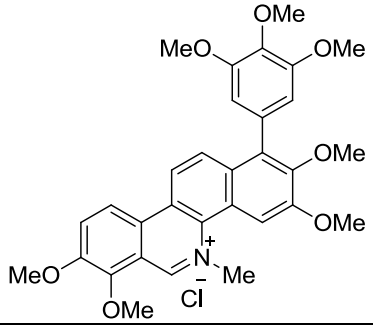
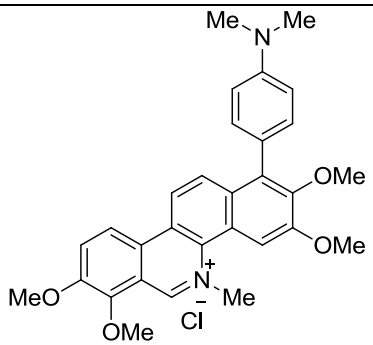
Table 4 summarizes the results of these studies. The replacement of either one or both of the methylene dioxy substituents of sanguinarine led to an overall decrease in antibiotic activity. Recall that sanguinarine has an MIC of 2 μg/mL in MSSA and

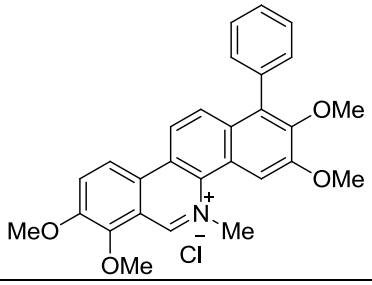
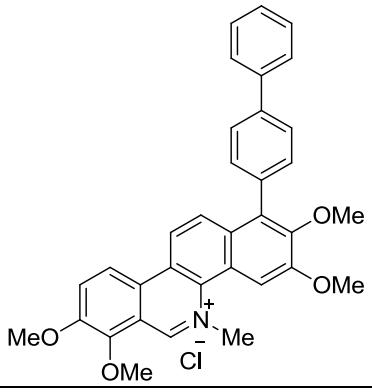
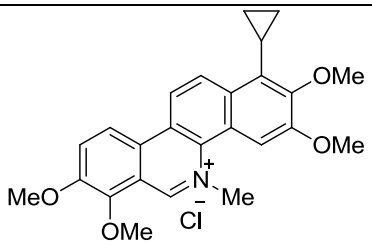
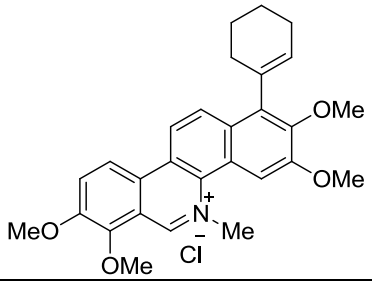
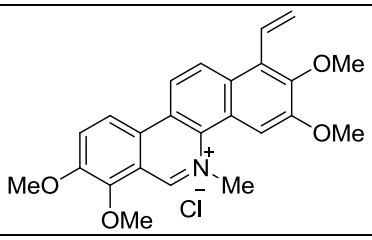
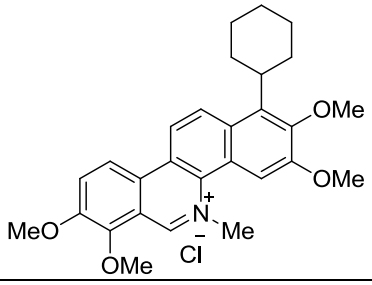
MRSA, and an MIC of 8 and 16 μg/mL for VSE and VRE, respectively. Compound **3** and **4** were significantly less active, dropping to an MIC of 32 μg/mL against both MSSA and MRSA and demonstrating no appreciable activity against VSE and VRE (MIC > 64 μg/mL). The antibacterial activity, however, was dramatically increased with the addition of either a single phenyl or biphenyl substitution at the 1-position of these compounds, as demonstrated in **20a**, **20b**, **20g**, and **20h**. This was also the trend seen in the 12-substituted analogs. Addition of either a phenyl or biphenyl at the 12-position, **32a-c**, dramatically increased the activity when compared to the unsubstituted compound. The tetramethoxy 1-biphenyl (**20h**) and 12-biphenyl (**32c**) were particularly active against MRSA (MICs of 0.5 μg/mL). Additionally, several other 1-substituted analogs were synthesized and evaluated for their activity. When compared to a simple phenyl substitution (**20g**), the 3-pyridyl (**20c**), 3,4,5-trimethoxyphenyl (**20e**), and 1-cyclohexenyl (**26b**) derivatives were all less potent against all 4 strains of bacteria. The presence of a 3-furanyl (**20d**), *p*-(dimethylamino)phenyl (**20f**), cyclopropyl (**26a**), vinyl (**26c**), and cyclohexyl (**26d**) were associated with comparable, but not improved, activity to **20g** against MSSA and MRSA but all had decreased antibacterial activity relative to **20g** against VSE and VRE. Regardless, when compared to clinically relevant antibiotics, many of these substituted derivatives have MICs comparable or even lower than that of vancomycin against MRSA. Although more modest of an effect, all of the substituted analogs also have greater antibacterial activity against VRE compared to all the clinically relevant standards tested. These data indicate that 1- and 12-substituted 5-methylbenzo[*c*]phenanthridines have significant antibacterial activity against MDR strains of *S. aureus* and *E. faecalis*. All MIC and biochemical data presented here and in

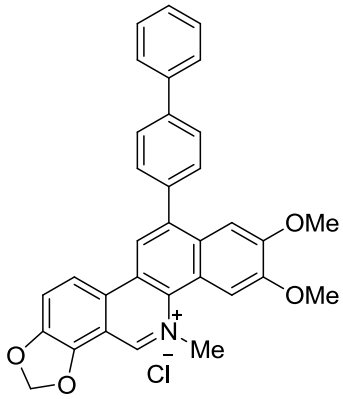
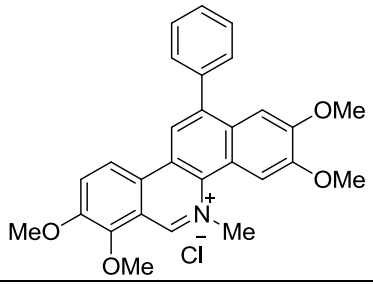
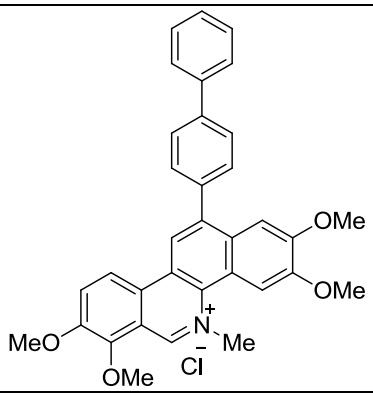
the subsequent pages was done by Dr. Malvika Kaul and Dr. Daniel S. Pilch in the Department of Pharmacology at Rutgers-UMDNJ, unless otherwise noted.

Table 4. Biological activity of 1- and 12-substituted 5-methylbenzo[*c*]phenanthridines.

	Compound Structure	**[a]MIC (μg/mL)**			
		***S. aureus* 8325-4 (MSSA)**	***S. aureus* ATCC 33591 (MRSA)**	***E. faecalis* ATCC 19433 (VSE)**	***E. faecalis* ATCC 51575 (VRE)**
1	Sanguinarine	2	2	8	16
3		32	32	64	>64
4		32	32	>64	>64
20a		1	2	8	8

20b		2	2	8	8
20c		8	32	32	32
20d		1	1	16	16
20e		4	4	32	32
20f		1	1	8	8

20g		1	1	4	4
20h		0.5	0.5	4	8
26a		1	2	8	8
26b		2	4	16	32
26c		1	2	8	8
26d		1	2	8	8

32a		2	2	4	8
32b		1	2	8	16
32c		0.5	0.5	16	16
	Oxacillin	**0.06**	**>64**	**8**	**64**
	Vancomycin	**1**	**2**	**1**	**>64**
	Erythromycin	**0.13**	**>64**	**1**	**>64**
	Tetracycline	**0.06**	**64**	**0.5**	**>64**
	Clindamycin	**0.3**	**>64**	**2**	**>64**

[a]Minimum inhibitory concentration (MIC) assays were conducted in accordance with Clinical Laboratory Standards Institute (CLSI) guidelines for broth microdilution.[73] MIC is defined as the lowest compound concentration at which bacterial growth is ≥90% inhibited.

Although we were able to synthesize a collection of analogs that displayed good antibacterial activity, these compounds suffered from some undesirable pharmacological properties – primarily that they were extremely difficult to formulate. This prevented us

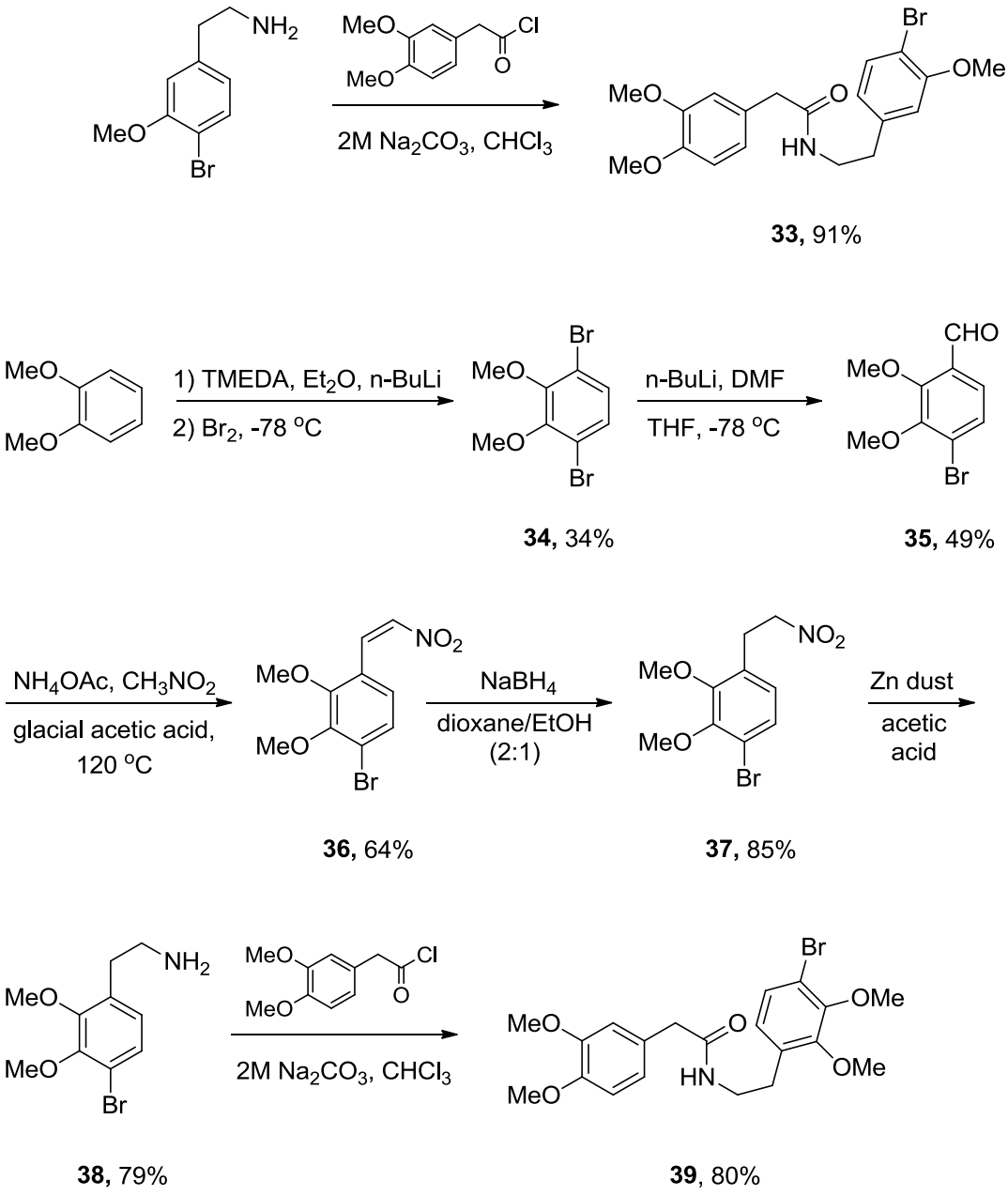
from being able to find a suitable formulation to take these compounds forward properly into *in vivo* mouse model studies. It also made it difficult to perform some of the biochemical assays we sought to evaluate. For example, these compounds gave inconclusive results when evaluated in the FtsZ GTPase assay because they would crash FtsZ out of solution. At first glance, these compounds appeared to inhibit GTPase activity, but because they were also causing FtsZ to crash out, the results are difficult to interpret. As such, we set these compounds aside and began putting more efforts into our second identified series.

2.2 Synthesis and Evaluation of 2- and 12-Substituted Dibenzo[*a,g*]quinolizin-7-ium Derivatives.

The next set of derivatives we had aimed to look at was those bearing a structure similar to berberine, **2**. Although capable of inhibiting both FtsZ polymer assembly and GTPase activity, berberine itself only exhibits weak antibacterial activity, with MICs typically in the range of 50-400 μg/mL for gram-positive bacteria and > 500 μg/mL for gram-negative bacteria.[61,74,75] As such, similar to our goals with the sanguinarine analogs, we sought to increase the relative potency by exploring the effects of adding substitution to the 2- and 12-position of a series of dibenzo[*a,g*]quinolizin-7-ium and 8-methyldibenzo[*a,g*]quinolizin-7-ium derivatives, which are structurally related to berberine.

Two key intermediates were used in the synthesis of the various 2-substituted derivatives: *N*-(4-bromo-3-methoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide, **33**, and *N*-(4-bromo-2,3-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide, **39**. The

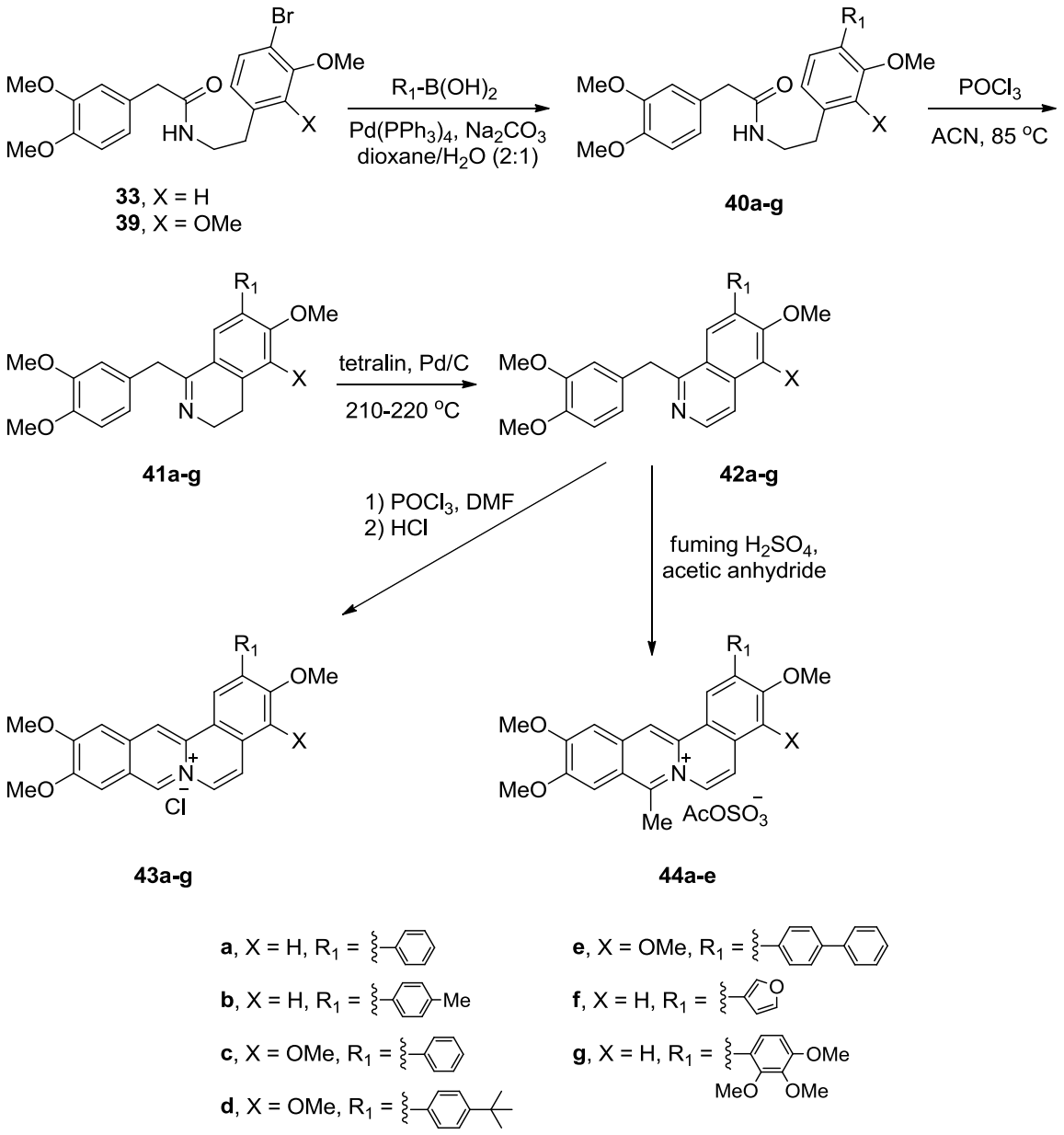
synthetic route to **33** and **39** is shown in Scheme 6. Intermediate **33** could be easily scaled up in large quantities by treating commercially available 2-(4-bromo-3-methoxyphenyl)ethanamine with 2-(3,4-dimethoxyphenyl)acetyl chloride and 2M Na_2CO_3 in chloroform. Intermediate **39** was made by treating 1,2-dimethoxybenzene with *n*-butyllithium (1.6M in hexanes) and tetramethylethylenediamine to promote the double lititation on the ring followed by quenching with bromine at -78 ^oC to give the dibrominated compound **34**. Formylation of **34** was performed using *n*-BuLi and DMF to give **35**, which was then treated with nitromethane and ammonium acetate in refluxing glacial acetic acid to give **36**. Conversion to the ethylamine required two successive reductions, the first to reduce the double bond using sodium borohydride in a 2:1 dioxane/ethanol solution and the second to reduce the nitro group using zinc dust in acetic acid to give **38**. Then, as with the preparation of **33**, coupling with 2-(3,4-dimethoxyphenyl)acetyl chloride and 2M Na_2CO_3 in chloroform gave the desired tetramethoxy amide, **39**.



Scheme 6. Synthesis of key intermediates **33** and **39**.

A series of 3,10,11-trimethoxy- and 3,4,10,11-tetramethoxydibenzo[*a*,*g*]quinolizin-7-ium derivatives were synthesized using intermediate **33** and **39**, respectively, as outlined in Scheme 7. Key intermediates were subjected to various Suzuki cross-couplings to functionalize at the 2-position to give **40a-g**. The general procedure for the Suzuki involved $Pd(PPh_3)_4$ as the catalyst and Na_2CO_3

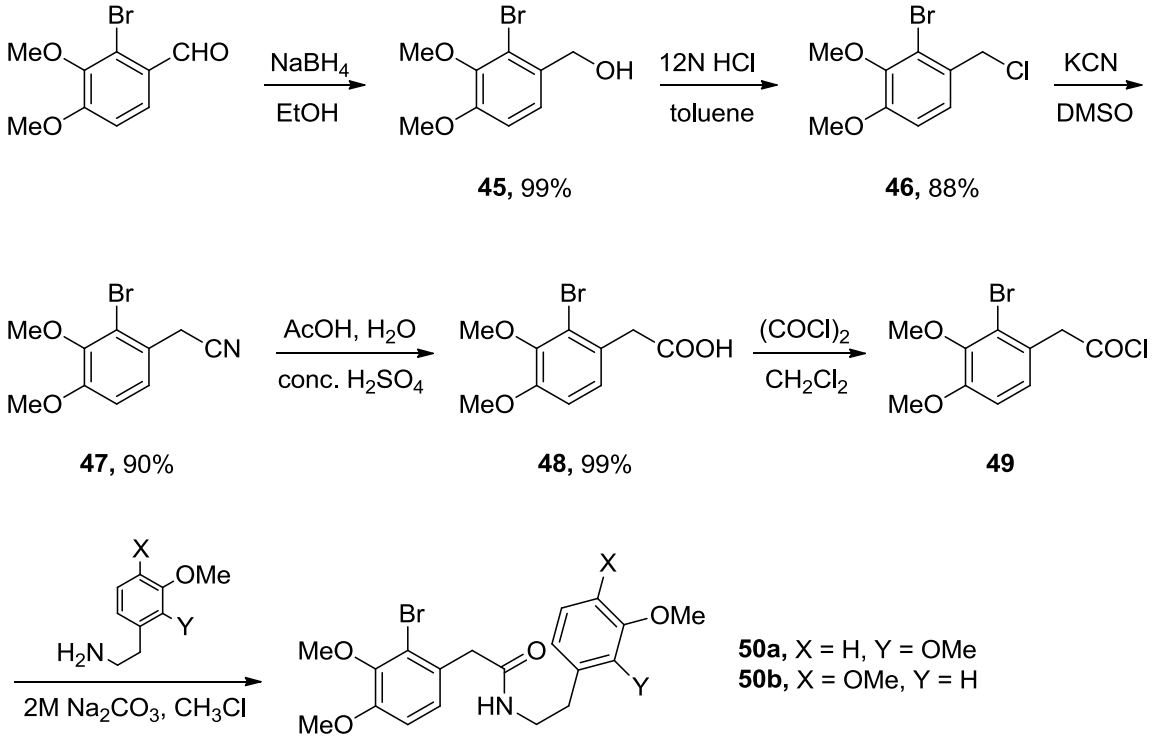
as the base in refluxing dioxane/H_2O (2:1). These Suzuki conditions had to be altered slightly for the 3-furanyl derivative, **40f**, which did not give the desired product under these general conditions. Instead, cross-coupling was performed using $Pd(PPh_3)_2Cl_2$ as the catalyst and ligand cesium carbonate as the base. Subsequent refluxing in dioxane/H_2O (2:1) overnight or irradiating with a microwave at 120 ^oC for 10 minutes resulted in good yields (62%) of the desired product, **40f**. Intermediates **40a-g** were then cyclized with phosphorus(V)oxychloride in refluxing acetonitrile followed by aromatization with refluxing tetralin and Pd/C (10%) to give **42a-g**. Intermediates **42a-g** could then be reacted with either $POCl_3$ in DMF and then treatment with HCl to give the desired compounds **43a-g**, or 20% fuming sulfuric acid and acetic anhydride to give the 8-methyl analogs **44a-e**. This series was a joint effort between several chemists. Compounds **43a**&**c**, **44a&c**, and **44e** were synthesized by Dr. Ajit Parhi, and compounds **43d**, **43e,** and **44d** were synthesized by Songfeng Lu, both at TAXIS Pharmaceuticals, Inc.



Scheme 7. Synthetic route for 2-substituted dibenzo[*a*,*g*]quinolizin-7-ium derivatives.

Additionally, several 12-substituted tetramethoxy analogs were synthesized. This substitution pattern required scaling up a different key intermediates **50a-b** (Scheme 8). 2-Bromo-3,4-dimethoxybenzaldehyde was reduced to the hydroxymethyl derivative with sodium borohydride to give **45** quantitatively. Treatment with 12N HCl in toluene to give the chloro (**46**) and subsequent displacement with potassium cyanide in

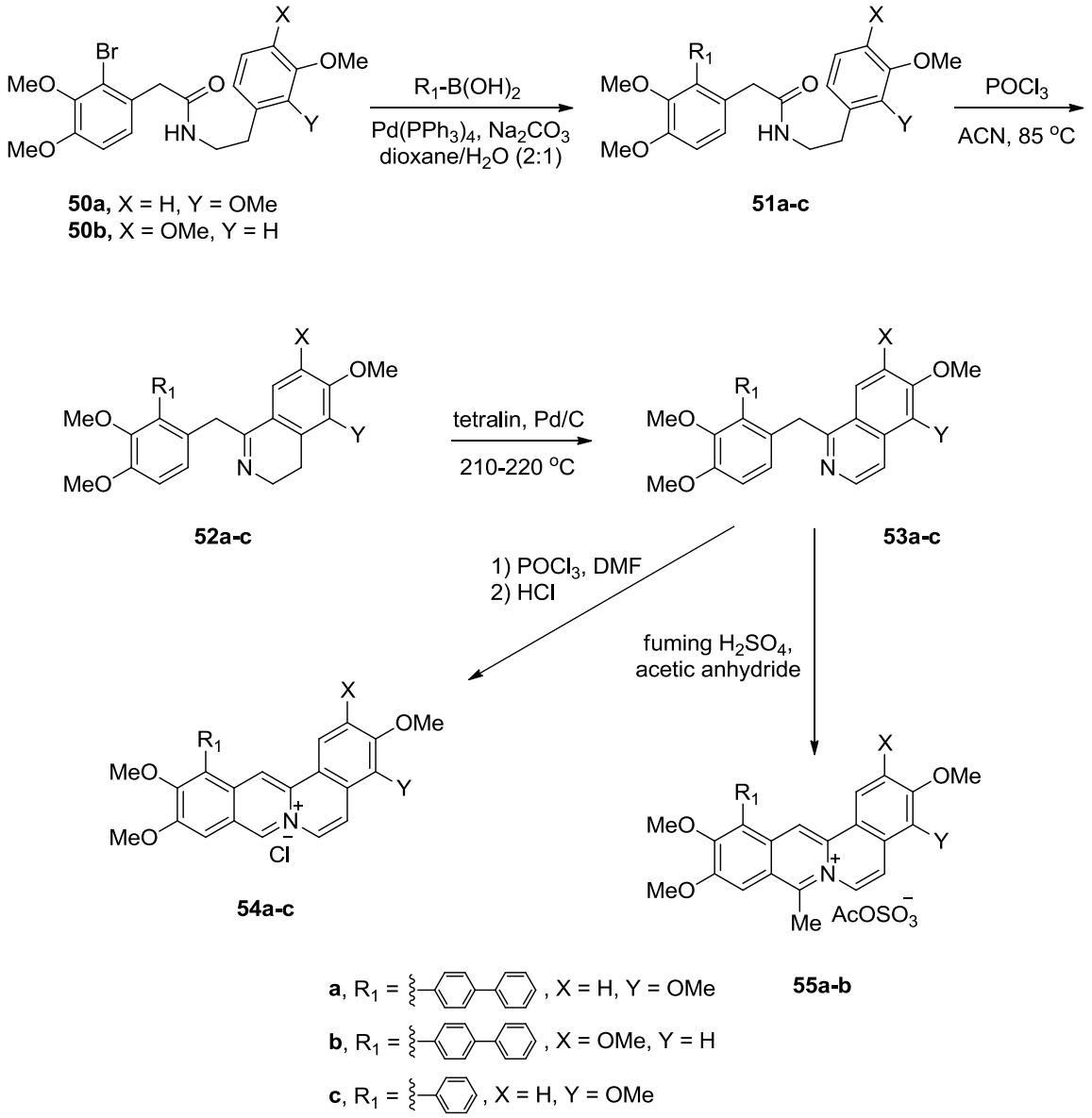
dimethylsulfoxide gave the nitrile compound **47** in high yield. The nitrile was then hydrolyzed down with acetic acid in water with a catalytic amount of sulfuric acid to the carboxylic acid (**48**), which was then converted to the acid chloride (**49**) with oxalyl chloride and coupled with either 2-(2,3-dimethoxyphenyl)ethanamine or 2-(3,4-dimethoxyphenyl)ethanamine to give key intermediate **50** in overall good yield.



Scheme 8. Synthesis of key intermediates **50a** and **50b**.

From **50a-b**, similar chemistry as seen with the 2-substitituted analogs was carried out as outlined in Scheme 9 to give the desired final compounds. A Suzuki coupling followed by cyclization and aromatization to give intermediates **51a-c**, and then subsequent treatment with either $POCl_3$ in DMF or fuming H_2SO_4 and acetic anhydride gave final compounds **54a-c** and **55a-b**, respectively. Compounds **54a** and **54b** were

synthesized by Dr. Ajit Parhi, and compounds **55a** and **55b** were synthesized by Songfeng Lu.



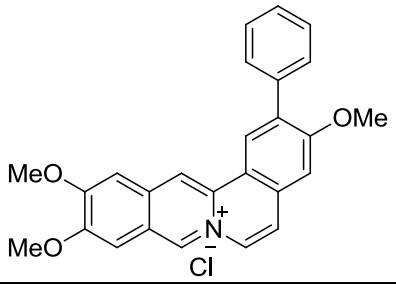
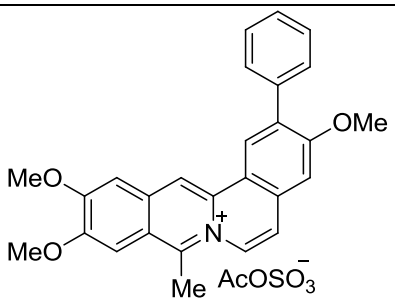
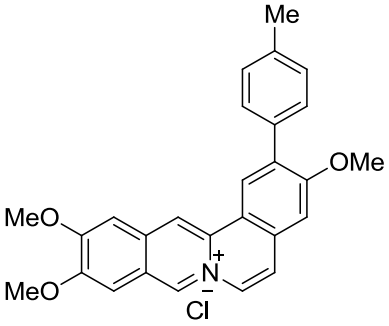
Scheme 9. Synthetic route for 12-substituted dibenzo[*a*,*g*]quinolizin-7-ium derivatives.

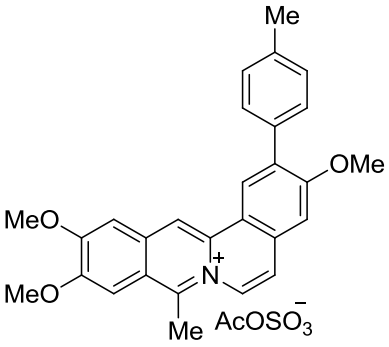
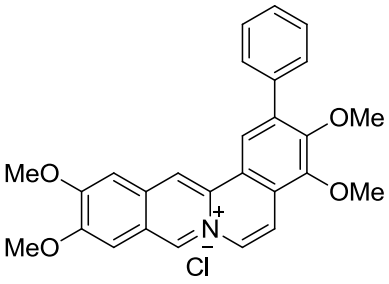
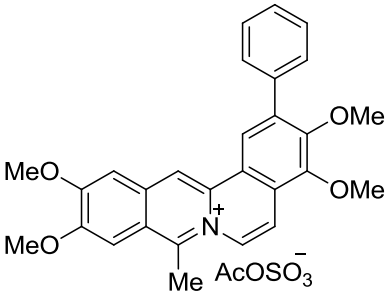
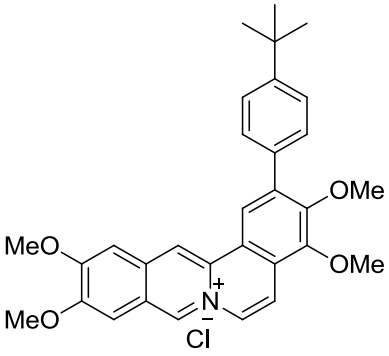
The relative antibacterial activity of the synthesized analogs was then evaluated in the 4 strains of bacteria (MSSA, MRSA, VSE, and VRE). Table 5 summarizes the results. Berberine (**2**), in line with previous reports, did not exhibit any appreciable

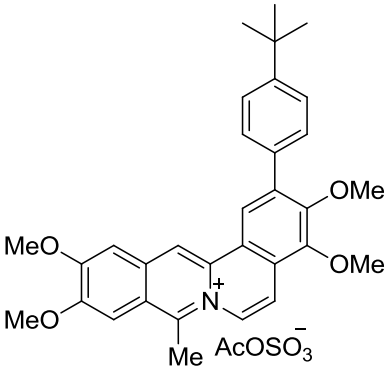
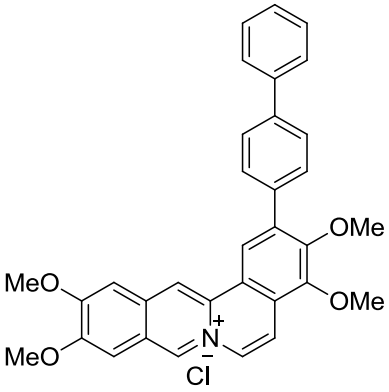
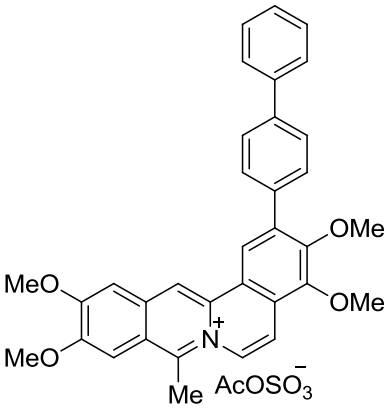
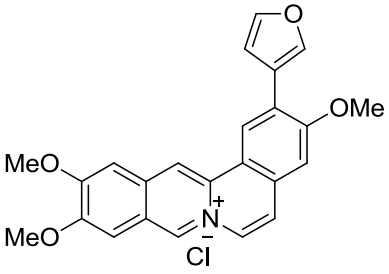
antibacterial activity against any of the 4 strains of bacteria (MIC > 64 μg/mL for all) evaluated in these studies. Looking first at the 2-substituted 3,10,11-trimethoxydibenzo[*a,g*]quinolizin-7-ium compounds, **43a**, **43b**, **44a**, and **44b** showed significantly improved activity against MSSA, with the 2-(4-tolyl) derivatives (**43b** and **44b**) displaying more activity than the 2-phenyl derivatives (**43a** and **44a**) versus both strains of *S. aureus* and VSE. The 2-(3-furanyl) derivative (**43f**) and 2-(2,3,4-trimethoxyphenyl) derivative (**43g**) displayed no appreciable activity against MSSA (MIC > 64 μg/mL), similar to that of berberine, indicating these groups were not well tolerated at this position. The presence or absence of an 8-methyl substituent on these 2-substituted 3,10,11-trimethoxydibenzo[*a,g*]quinolizin-7-ium analogs appears to have only a modest effect, if any, on antibacterial activity, with this effect being variable and typically in the range of a 2-fold shift in MIC values.

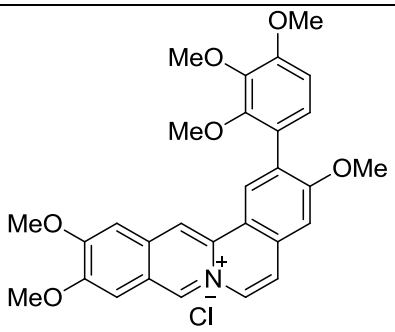
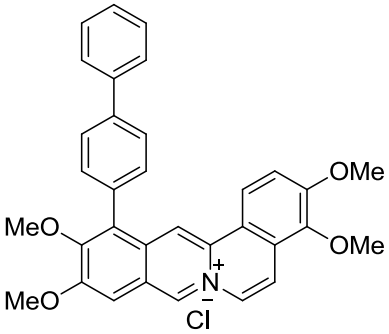
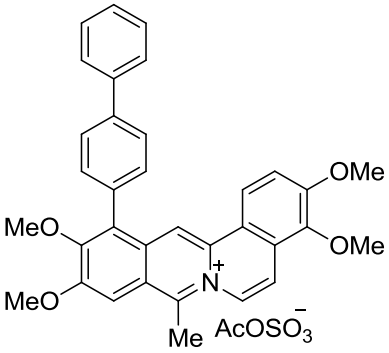
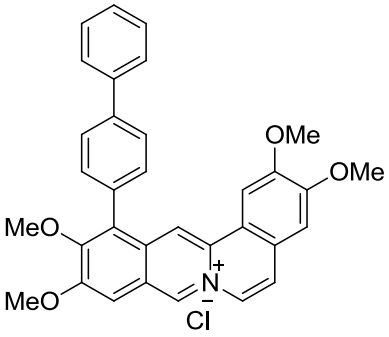
The 2-substituted 3,4,10,11-tetramethoxydibenzo[*a,g*]quinolizin-7-ium derivatives (**43c-e** and **44c-e**) also displayed significantly improved antibacterial activity (MIC range 1-4 μg/mL) compared to berberine. The presence of an 8-methyl substituent results in, once again, only a modest effect on antibacterial activity, with a general tendency for slightly greater antibacterial activity. As seen with the 2-substituted 3,10,11-trimethoxy analogs, the extension of another group, either a *t*-butyl (**43d** and **44d**) or a second phenyl (**43e** and **44e**), from the single 2-phenyl substitution in **43c** and **44c**, resulted in greater antibacterial activity.

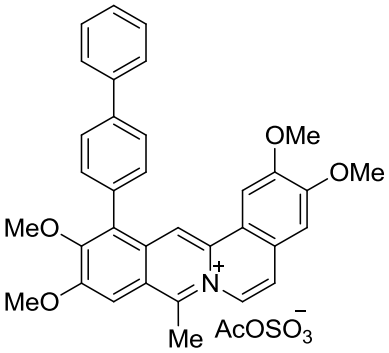
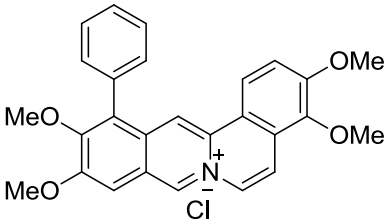
Table 5. Biological activity of 2- and 12-substituted dibenzo[*a*,*g*]quinolizin-7-ium derivatives.

	Compound Structure	**[a]MIC (μg/mL)**			
		***S. aureus* 8325-4 (MSSA)**	***S. aureus* ATCC 33591 (MRSA)**	***E. faecalis* ATCC 19433 (VSE)**	***E. faecalis* ATCC 51575 (VRE)**
2	Berberine	>64	>64	>64	>64
43a		8	32	32	64
44a		8	>64	>64	>64
43b		2	8	16	>64

44b		4	8	8	>64
43c		4	8	16	32
44c		2	8	8	16
43d		4	4	4	8

44d		1	2	4	4
43e		2	2	8	4
44e		1	2	4	8
43f		>64	ND	ND	ND

43g		>64	ND	ND	ND
54a		2	8	8	16
55a		1	4	16	16
54b		2	4	8	32

55b		1	4	4	32
54c		2	ND	ND	ND
	Oxacillin	**0.06**	**>64**	**8**	**64**
	Vancomycin	**1**	**2**	**1**	**>64**
	Erythromycin	**0.13**	**>64**	**1**	**>64**
	Tetracycline	**0.06**	**64**	**0.5**	**>64**
	Clindamycin	**0.3**	**>64**	**2**	**>64**

[a]Minimum inhibitory concentration (MIC) assays were conducted in accordance with Clinical Laboratory Standards Institute (CLSI) guidelines for broth microdilution.[73] MIC is defined as the lowest compound concentration at which bacterial growth is ≥90% inhibited.

There was a notable difference between the 3,10,11-trimethoxy- and 3,4,10,11-tetramethoxydibenzo[*a*,*g*]quinolizin-7-ium derivatives with regard to their activity versus *E. faecalis*. None of the trimethoxy derivatives have an MIC < 64 μg/mL versus the vancomycin-resistant strain (VRE), whereas several of the 2-aryl substituted tetramethoxy derivatives have greatly enhanced activity versus both strains. This suggests that the tetramethoxy-substitution is better for antibacterial activity. When comparing 2-aryl substitution versus 12-aryl substitution, the antibacterial activity seems to be similar, with the 12-substituted derivatives generally being slightly less potent than the 2-substituted derivatives. For example, when comparing the 2-biphenyl-3,4,10,11-

tetramethoxydibenzo[*a*,*g*]quinolizin-7-ium derivatives **43e** and **44e** with the 12-biphenyl-3,4,10,11-tetramethoxydibenzo[*a*,*g*]quinolizin-7-ium derivatives **54a** and **55a**, the 2-biphenyl analogs display better overall potency against all the strains than do the 12-biphenyl analogs.

Using the already identified FtsZ inhibitor, berberine, and its chemical structure, we were able to successfully design and synthesize analogs which displayed significantly improved potency and antibacterial activity against 4 different strains of bacteria. However, similar to the problems we encountered with the benzo[*c*]phenanthridines, these compounds were extremely difficult to formulate, thus preventing them from *in vivo* mouse model evaluation. Without a suitable formulation, these compounds were extremely difficult to administer, which precluded them from further investigation. At this point, we had to take a step back and examine some new scaffolds that might have better pharmacological properties that would allow us to further their biological assessment.

2.3 Synthesis and Evaluation of 3-Phenylisoquinoline and 3-Phenylisoquinolinium Derivatives.

Taking a look at what we already knew, the natural products sanguinarine (**1**), the dimethoxy analog chelerythrine (**56**), and the structurally related berberine (**2**) all possess antibacterial activity, albeit to varying degrees. The presence of a hydrophobic moiety at either the 1-position of the benzo[*c*]phenanthridine ring, as seen in compound **20g**, or the 2-position of the dibenzo[*a*,*g*]quinolizin-7-ium ring, as seen in compound **43d**, significantly enhanced antibacterial activity (Figure 9).

3-Phenylisoquinoline represents a flexible subunit found within the scaffold associated with the core structure of each of these compounds, as illustrated in Figure 9. As such, we turned our attention towards synthesizing a series of substituted 3-phenylisoquinoline and 3-phenylisoquinolinium derivatives to evaluate their antibacterial activity.

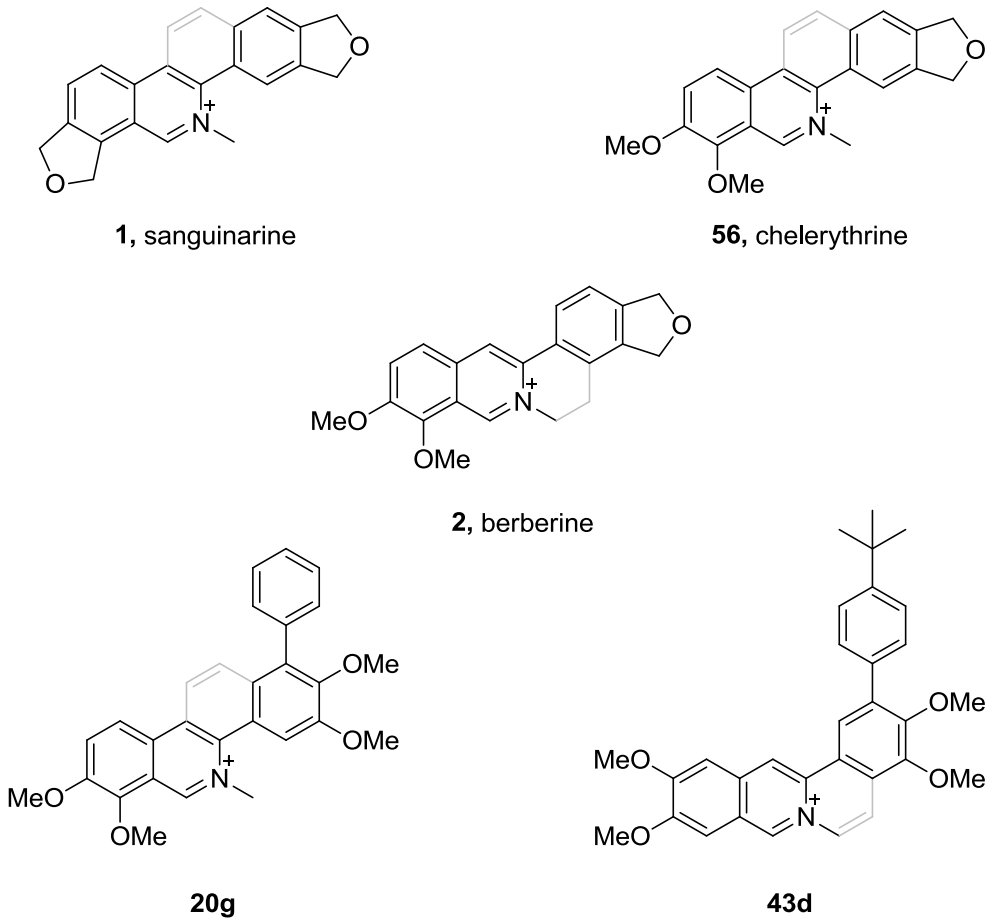
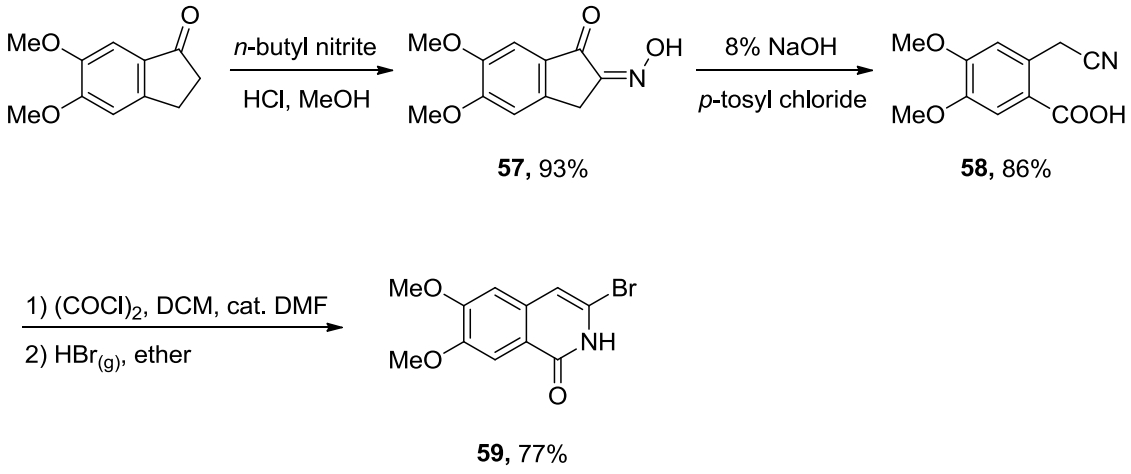


Figure 9. Chemical structures of sanguinarine (**1**), chelerythrine (**56**), berberine (**2**), and synthetic analogs **20g** and **43d**.

In addition to evaluating the flexible 3-phenylisoquinoline scaffold for its ability to produce antibacterial effects, we were also interested in modifying the structure in such

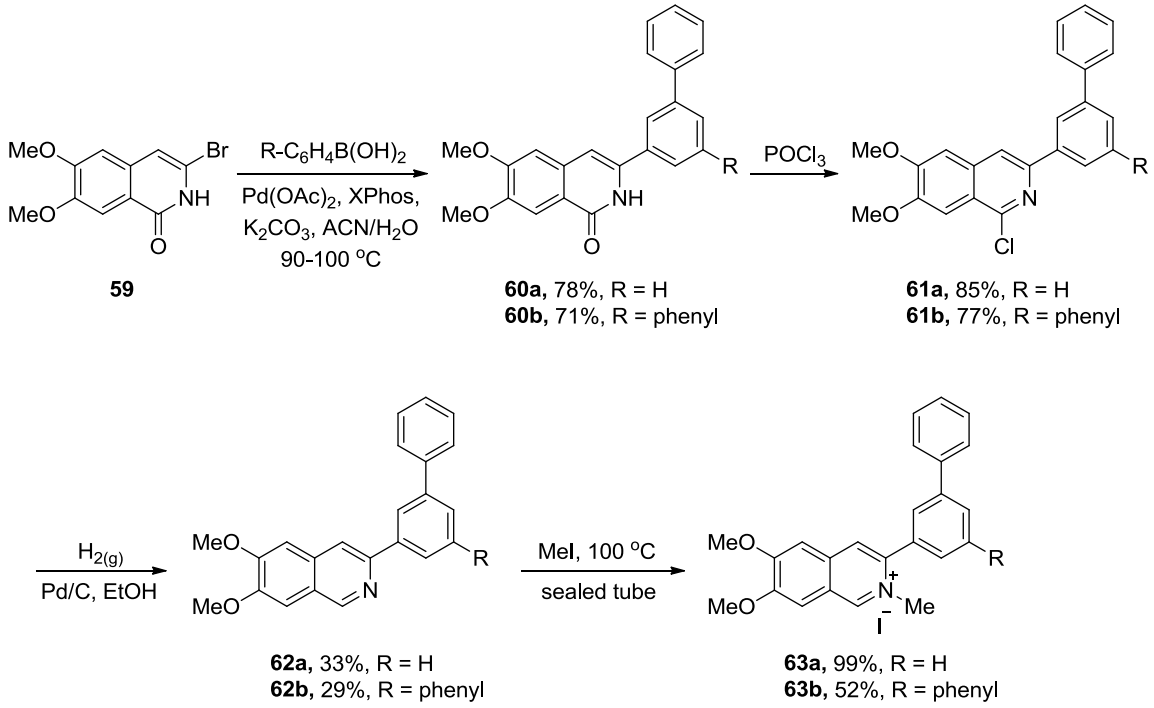
a way that might improve its pharmacological properties such as solubility and ultimately improve formulation. Adding flexibility to the molecule might be one way to achieve this. Another way to improve solubility properties might be to synthesize isoquinoline analogs that did not contain a constitutive cationic charge. As we quickly learned, the quaternary isoquinolinium derivatives consistently led to increased antibacterial activity when compared to their non-charged precursors. As such, we decided to explore the effects of various basic functional groups at the 1-position of the isoquinoline ring. These types of compounds would not bear a constitutive positive charge, but would likely be protonated to some extent at physiological pH. To explore the structure-activity relationships (SAR) of these non-charged compounds, we sought to evaluate the effects of basicity by attaching a basic functionality at the 1-position either directly, extended by a 1 carbon linker, or extended by a 2 carbon linker.



Scheme 10. Synthetic route to key intermediate **59**.

Scheme 10 details the synthesis of the first major intermediate used in this series.[76] Intermediate **59** would readily allow for easy substitution at the targeted 1- and

3-positions. Starting with commercially available 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one in methanol, treatment with concentrated hydrochloric acid followed by addition of *n*-butyl nitrite gave the oxime, **57**, in high yield. Subsequent treatment of the oxime with 8% NaOH followed by addition of *p*-toluenesulfonylchloride gave the benzoic acid, **58**, in 85% yield. Conversion of the carboxylic acid to its acid chloride with oxalyl chloride in dichloromethane followed by treatment with a continuous flow of $HBr_{(g)}$ in ether gave the cyclized 3-bromo-6,7-dimethoxyisoquinolin-1(2*H*)-one intermediate **59** in good yield.



59

60a, 78%, R = H
60b, 71%, R = phenyl

61a, 85%, R = H
61b, 77%, R = phenyl

62a, 33%, R = H
62b, 29%, R = phenyl

63a, 99%, R = H
63b, 52%, R = phenyl

Scheme 11. Synthetic route to compounds **63a-b**.

From intermediate **59**, the first few compounds were synthesized as outlined in Scheme 11. Palladium-catalyzed Suzuki reaction with the appropriate boronic acid (3-biphenylboronic acid for **a** and [1,1':3',1"-terphenyl]-5'-ylboronic acid for **b**), $Pd(OAc)_2$, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), and potassium carbonate

in acetonitrile and water mix (2:1) gave the cross-coupled products **60a** and **60b**. Since we learned from the first two series that the presence of a hydrophobic moiety gives the best compounds, it was decided to start out this series with a biphenyl and terphenyl attached at the 3-position of the isoquinoline ring. Conversion to the chloride was accomplished by refluxing in phosphorus(V)oxychloride to give **61a** and **61b** followed by dechlorination with $H_{2(g)}$ and Pd/C to give **62a** and **62b**. Finally, quaternization with methyl iodide at 100 ^{o}C in a sealed tube gave the final compounds **63a** and **63b**.

We then wanted to use the chloro intermediates **61a** and **61b** to synthesize several non-quaternized analogs, with different functionality attached at the 1-position. Initial attempts at displacement of the chloro by simply heating in a sealed tube with excess nucleophile only worked, in low yield, for the nitrile (**64**) and ethylenediamine (**65**) derivatives (Figure 10). Heating of **61a** and **61b** with dimethylamine, methylamine, and guanidine gave no desired product. Compounds **66a**, **66b**, **68**, **69a**, and **69b** required different conditions and the use of a special Buchwald palladacycle precatalyst, chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]PdII (*t*-BuXPhos precatalyst) to form the carbon-nitrogen bond.[77] Palladacycle precatalysts like this were developed by Buchwald's group for cases as this; in which a highly active palladium complex is required for difficult cross-coupling reactions – particularly useful for unactivated aryl chloride groups to undergo facile oxidative addition.[77] Treatment of the chloro intermediates, **61a** and **61b**, with the appropriate amine, a base (either LHMDS or NaH), and the *t*-BuXPhos precatalyst gave the desired products in high yield in the case of the dimethyl- and methylamine derivatives (**66a**, **66b**, and **68**) and in moderate

yield for the guanidine derivatives (**69a** and **69b**). Compound **66a** was also taken one step further to the quaternized version, **67** for direct comparison.

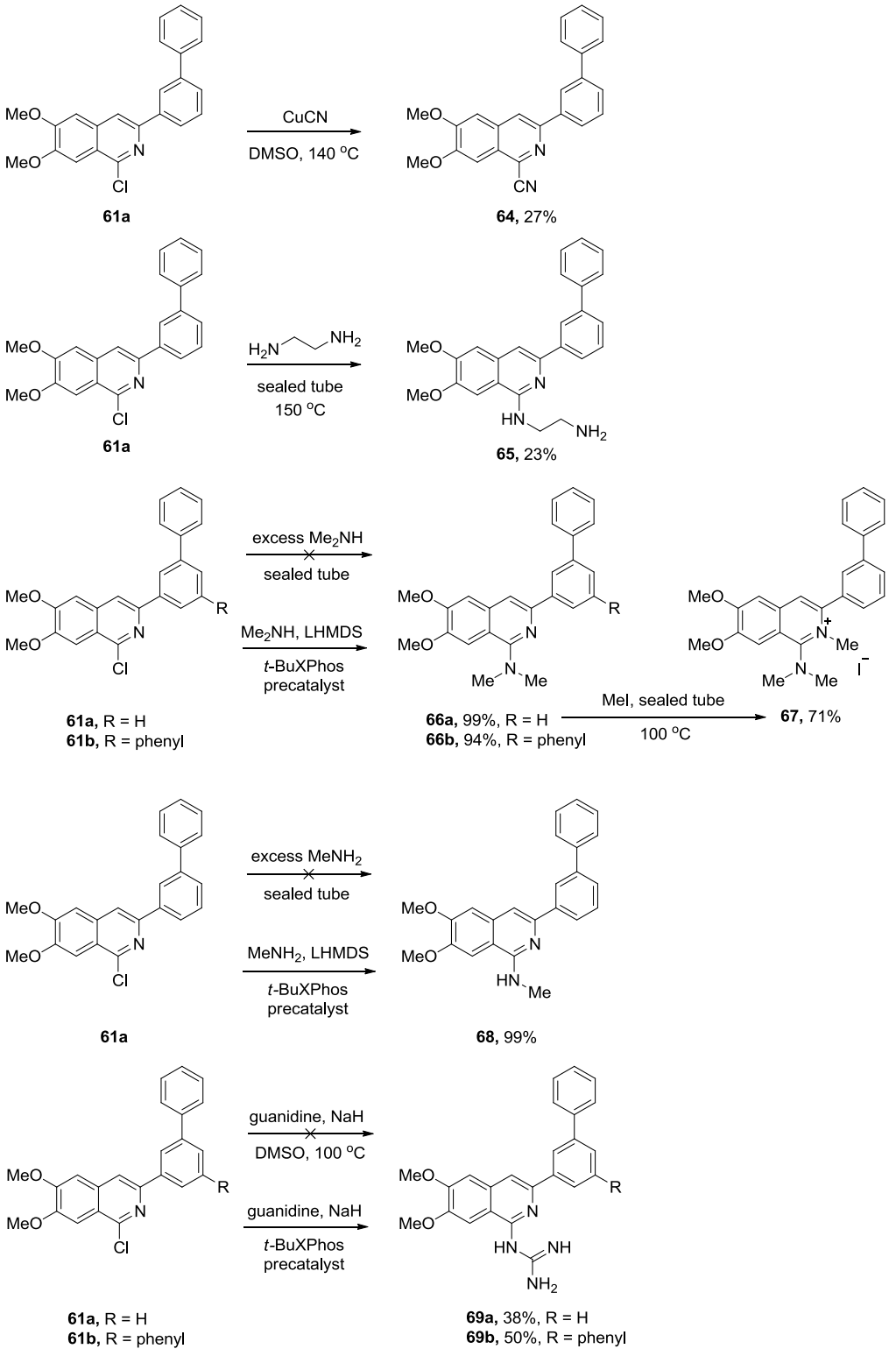
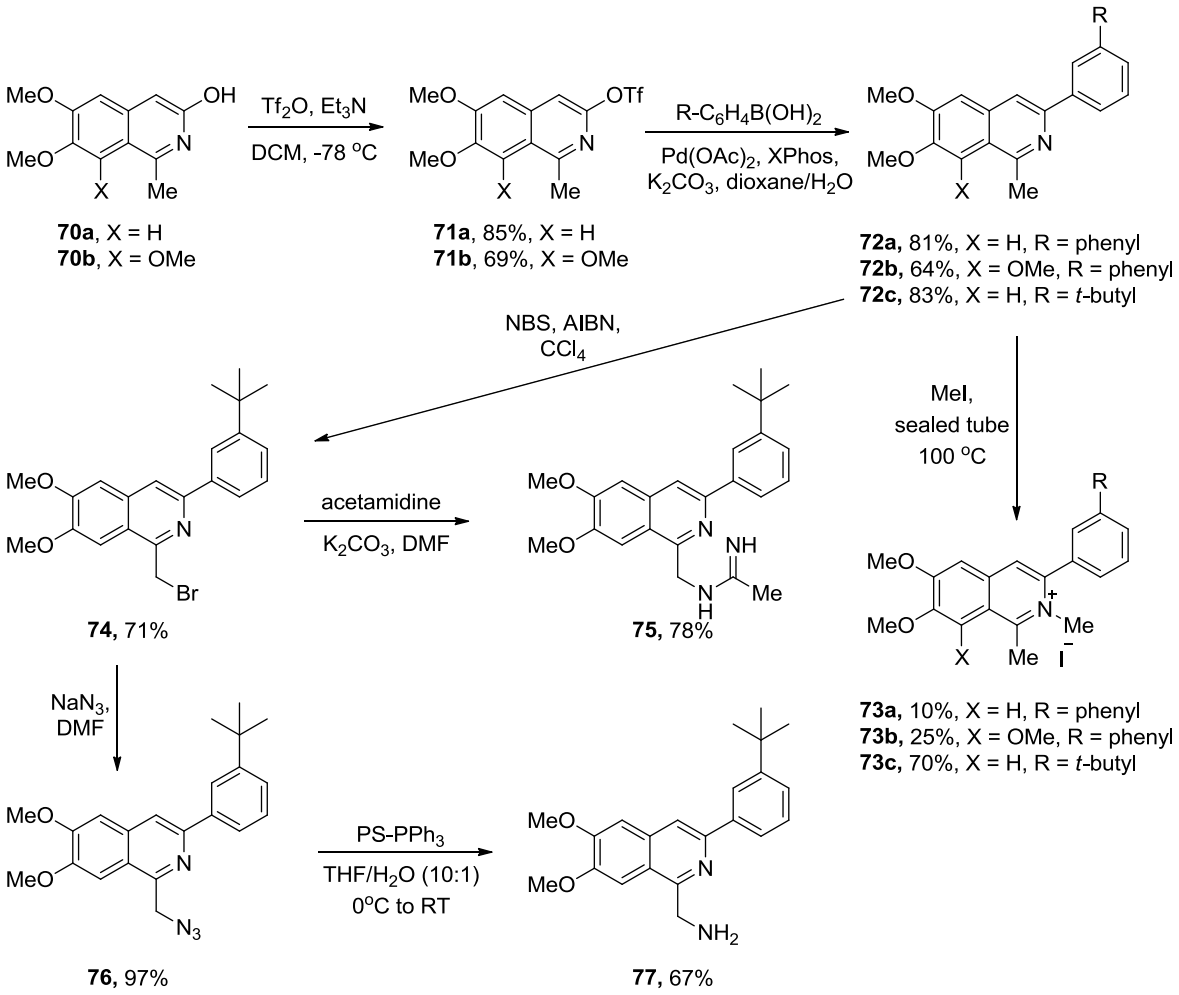


Figure 10. Reaction conditions for compounds **64-65**, **66a-b**, **67-68**, and **69a-b**.

The synthesis of the next group of analogs is outlined in Scheme 12. 6,7-Dimethoxy-1-methylisoquinolin-3-ol (**70a**) and 6,7,8-trimethoxy-1-methylisoquinolin-3-ol (**70b**) were prepared in high yield from either 3,4-dimethoxyphenyl acetic acid or 3,4,5-trimethoxyphenyl acetic acid as described in the literature.[78]

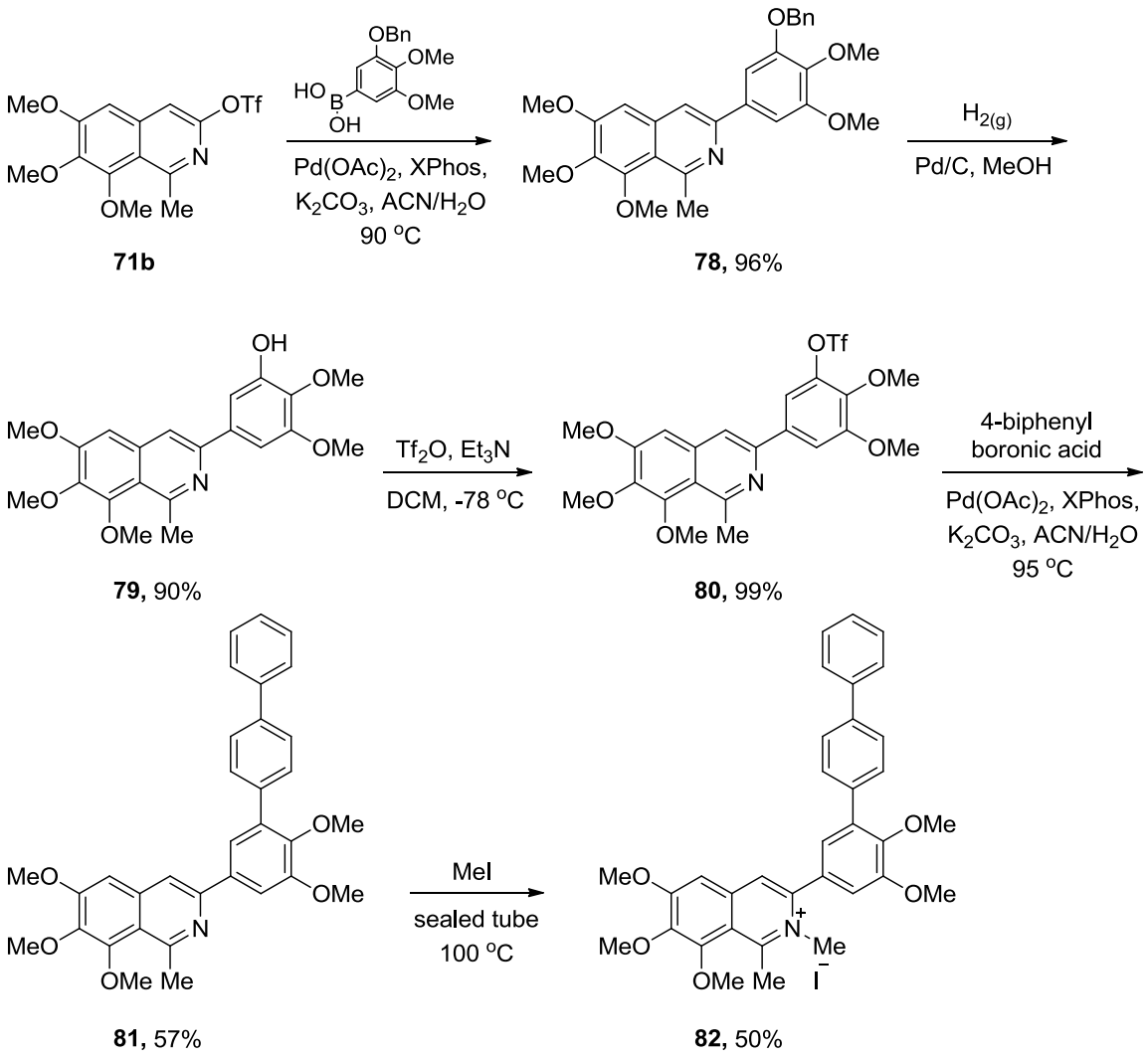


Scheme 12. Synthetic route for compounds **72a-c**, **73a-c**, **75**, and **77**.

These intermediates were then treated with triflic anhydride and triethylamine in dichloromethane at -78 ^{o}C to give the corresponding triflates, **71a** and **71b**. Subsequent palladium-catalyzed Suzuki reaction with either 3-biphenyl boronic acid (for **72a** and **72b**) or 3-*t*-butylphenylboronic acid (for **72c**), $Pd(OAc)_2$ and XPhos as the catalyst/ligand system, and potassium carbonate as the base in a refluxing mix of either acetonitrile/water or dioxane/water afforded the cross-coupled products in good yield. **72a-c** were then heated to 100 ^{o}C in a sealed tube with excess methyl iodide to give the quaternized analogs, **73a-c**. The *t*-butylphenyl analog, **72c**, was also brominated with *N*-bromosuccinimide in carbon tetrachloride using azobisisobutyronitrile (AIBN) as the radical initiator to give **74** in good yield. This bromomethyl derivative was then used to make two final compounds. **74** was either reacted with acetamidine HCl and potassium carbonate in DMF to form the acetamide derivative, **75**, or reacted with sodium azide in DMF, followed by reduction to the methanamine with polymer-supported triphenylphosphine to give compound **77**.

Intermediates from Scheme 12 were then used to make a variety of other analogs, which are outlined in the next few schemes. A palladium-catalyzed Suzuki coupling using triflate **71b** with (3-(benzyloxy)-4,5-dimethoxyphenyl)boronic acid, $Pd(OAc)_2$, XPhos, and potassium carbonate in acetonitrile and water (2:1) was heated for 4 hours at 90 ^{o}C to give the cross-coupled product, **78**, in high yield. Cleavage of the benzyl group with hydrogen gas and Pd/C (10%) as the catalyst in methanol gave the deprotected product, **79**, in high yield. Treatment of the phenol with triflic anhydride and triethylamine in dichloromethane at -78 ^{o}C gave the triflated product, **80**, quantitatively. A second Suzuki coupling with 4-biphenylboronic acid, $Pd(OAc)_2$, XPhos, and potassium

carbonate in acetonitrile and water (2:1) yielded compound **81**, which was then quaternized by heating with excess methyl iodide in a sealed tube to give desired compound **82** (Scheme 13).



Scheme 13. Synthetic route for compounds **81** and **82**.

Triflate **71a** was subjected to a Suzuki coupling with 3-hydroxyphenylboronic acid with $Pd(OAc)_2$, XPhos, and cesium carbonate in acetonitrile and water (3:1) to give the cross-coupled intermediate **83** in moderate yield. This phenol was then triflated with

triflic anhydride and triethylamine at -78 ^{o}C to give **84** in high yield. This triflate was then subjected to a second Suzuki coupling with either 4-biphenylboronic acid (for **85a**), 4-*t*-butylphenylboronic acid (for **85b**), or 3-*t*-butylboronic acid (for **85c**) using standard coupling conditions. **85a** and **85b** were quaternized by heating with excess methyl iodide in a sealed tube to give **86a** and **86b** for comparison. **85b** and **85c**, the *t*-butylphenyl derivatives, were also used to make compounds **90a** and **90b**, respectively. 1-Methyl derivatives, **85b** and **85c**, were oxidized to the aldehyde by refluxing with selenium dioxide in anhydrous dioxane to give **87a** and **87b** in reasonable yield. Reduction of the aldehyde by treatment with sodium borohydride in ethanol gave the corresponding alcohol, compound **88a** and **88b**. Under Mitsunobu conditions (Figure 11),[79-82] intermediates **88a-b** were converted to the bis-Boc guanidine compounds, **89a** and **89b**, which were then taken crude and deprotected with trifluoroacetic acid and dichloromethane (1:1) to give desired final compounds **90a** and **90b** (Scheme 14).

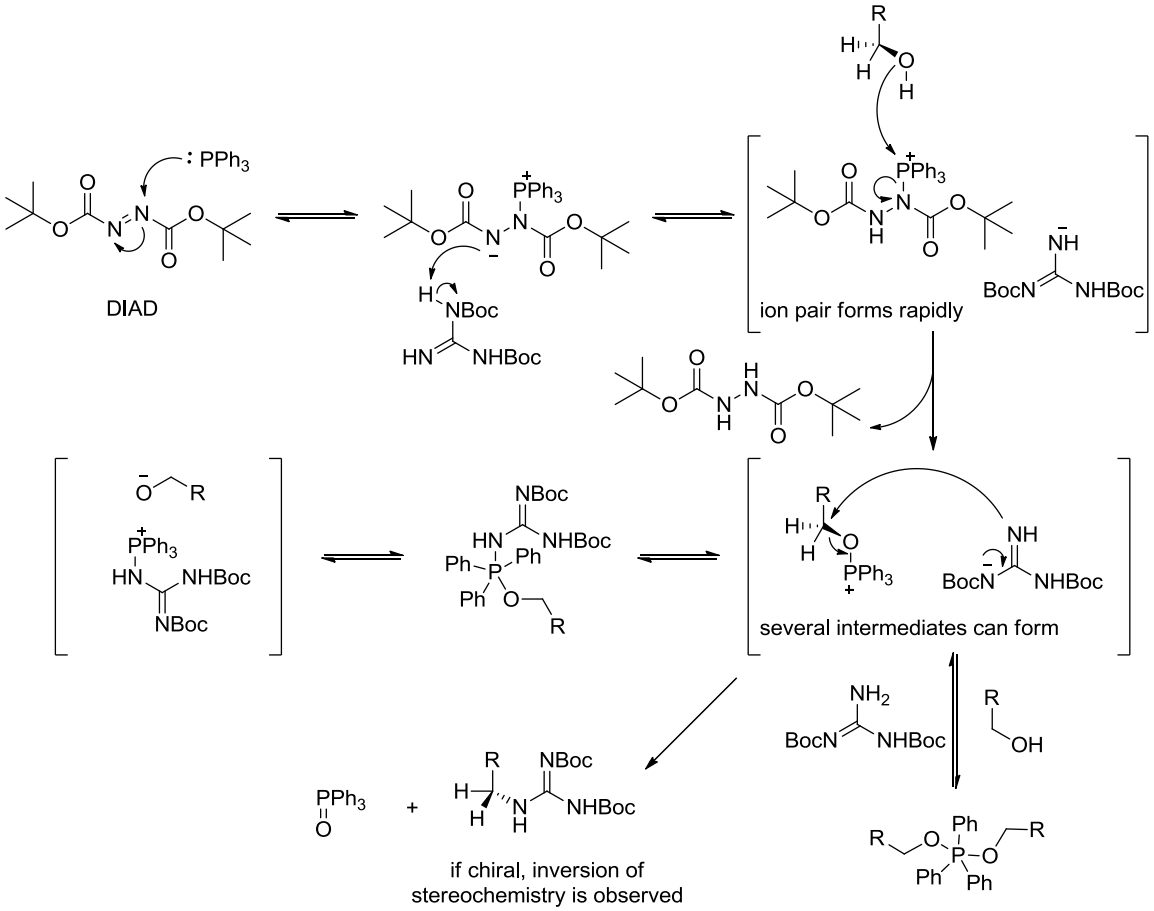
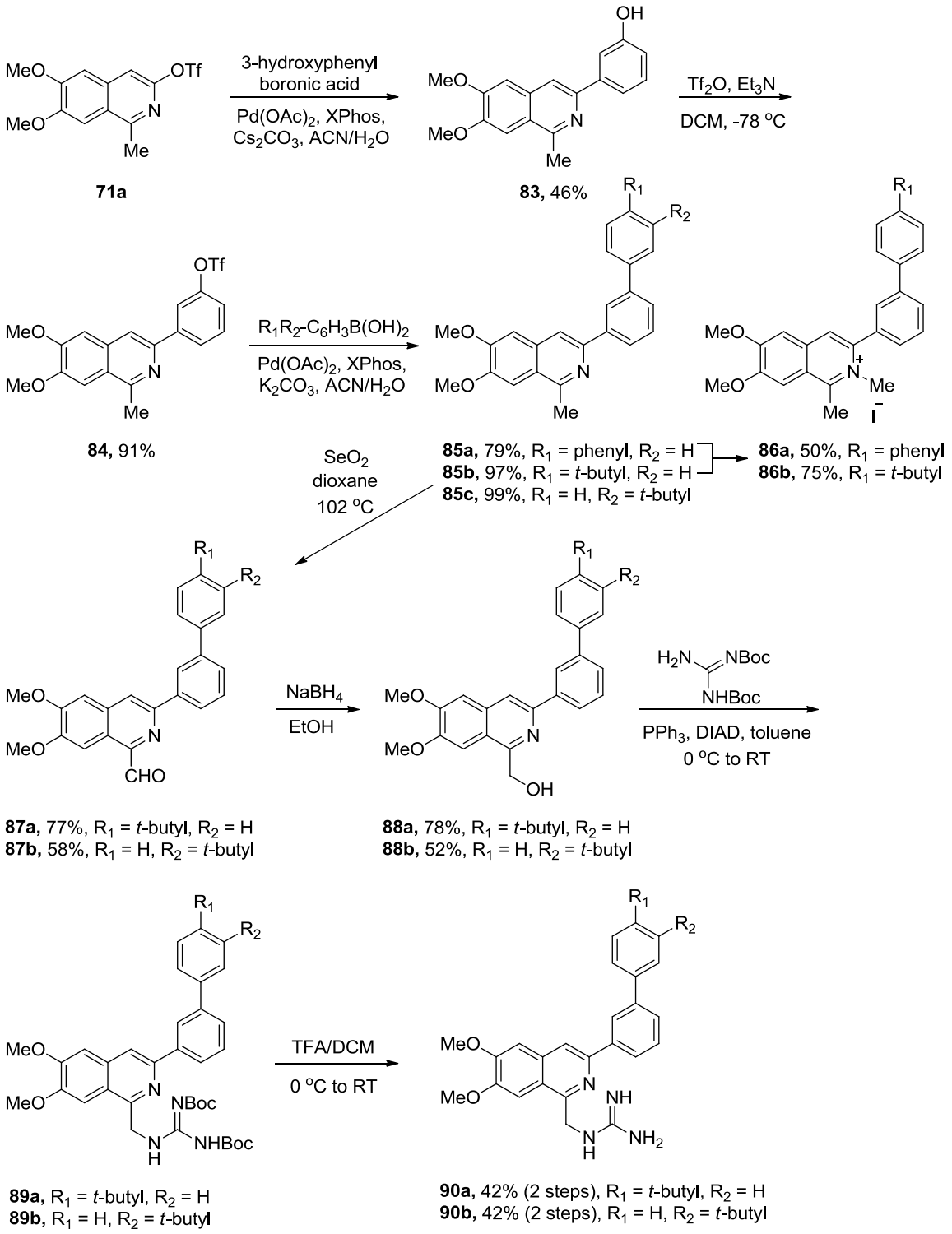
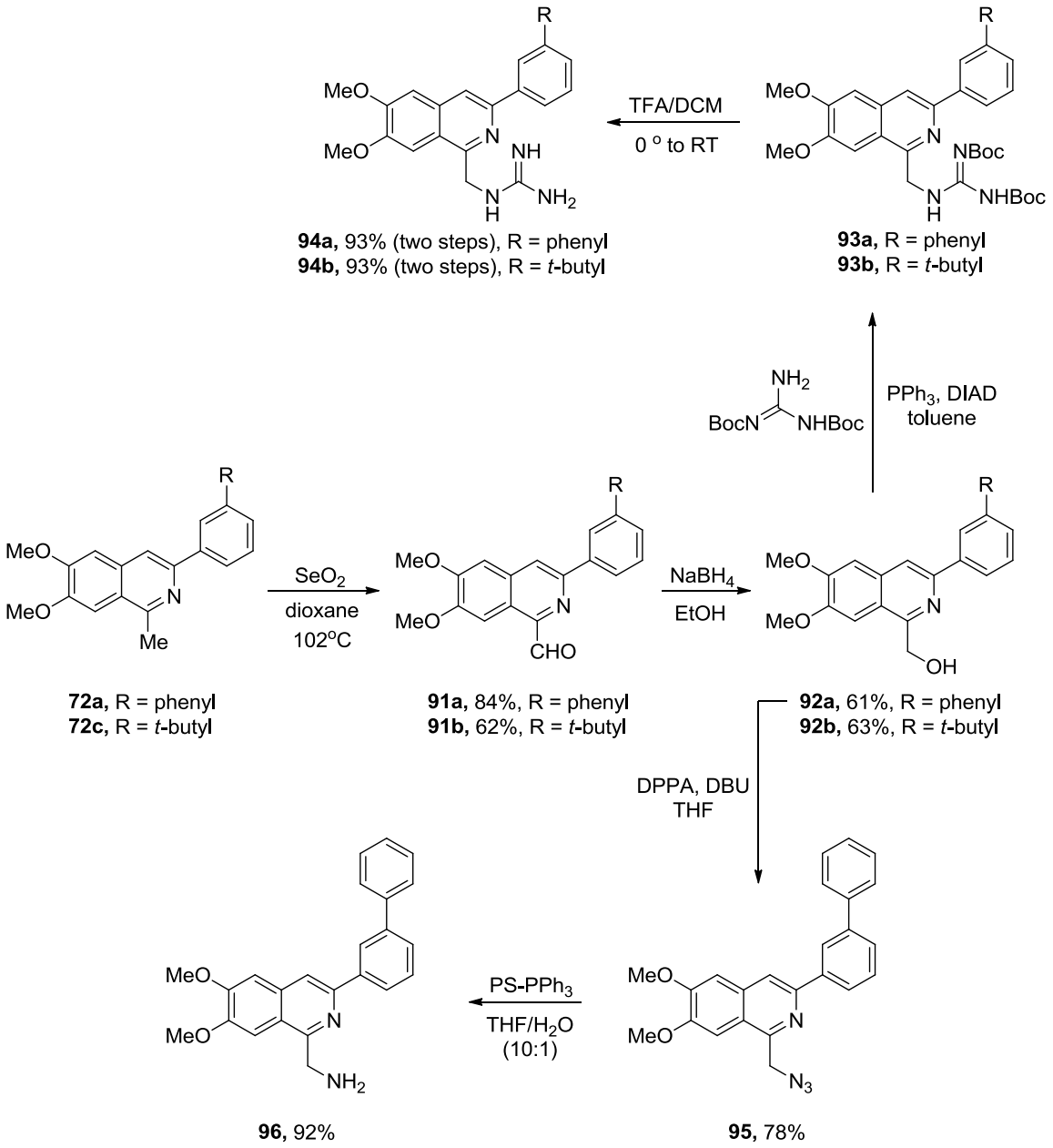


Figure 11. Mechanism for the Mitsunobu reaction.



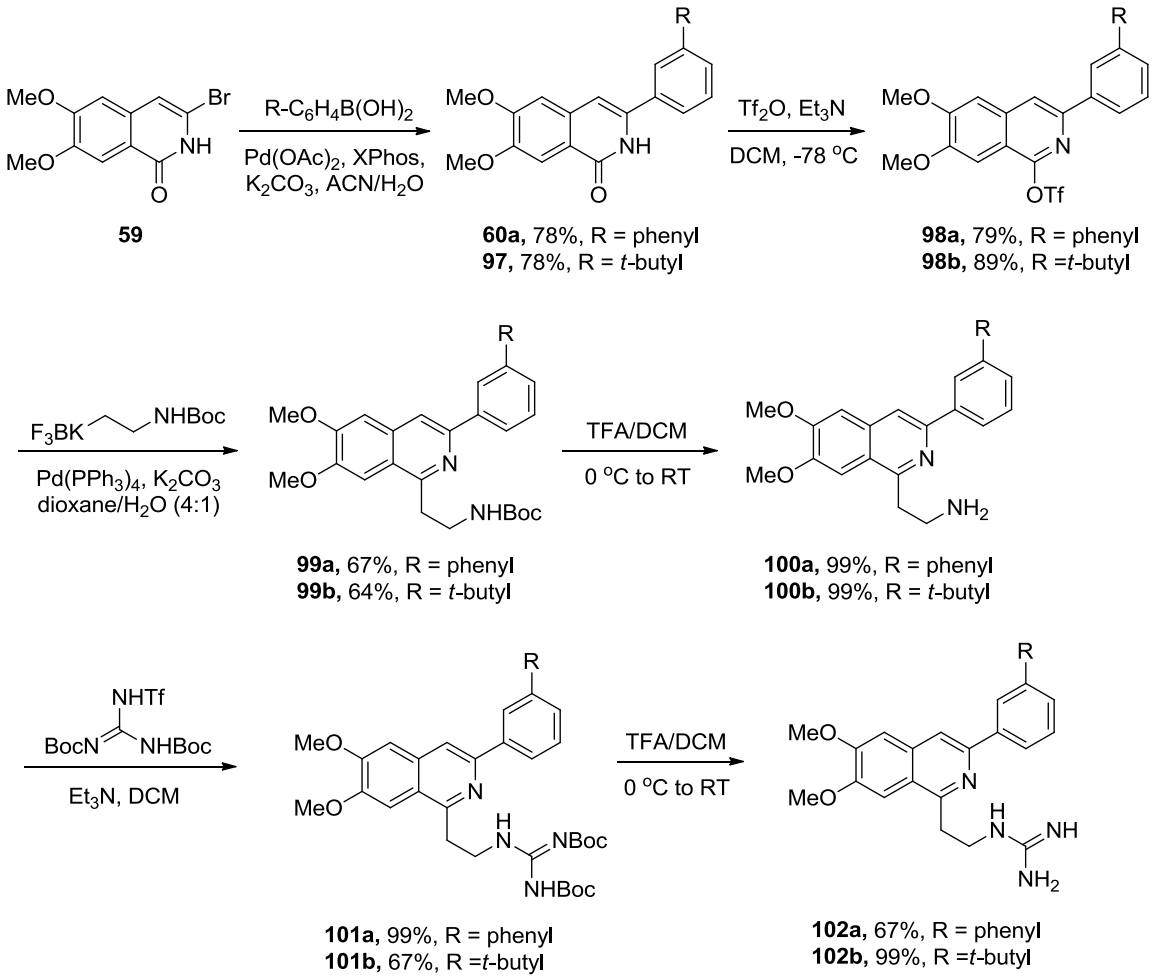
Scheme 14. Synthetic route to compounds **85a-c**, **86a-b**, and **90a-b**.

The cross-coupled intermediates **72a** and **72c**, were used to synthesize the methanamine and methylguanidine derivatives as outlined in Scheme 15. Following the same chemistry from the previous scheme, the 1-methyl was oxidized to the aldehyde (**91a** and **91b**) by refluxing selenium dioxide in anhydrous dioxane. The aldehyde was then reduced with sodium borohydride to give the hydroxymethyl derivatives **92a** and **92b**. From this intermediate, several compounds were made. First, both **92a** and **92b** were subjected to a Mitsunobu with the bis-Boc guanidine, triphenylphospine, and diisopropyl azidodicarboxylate (DIAD) which was taken crude and deprotected with trifluoroacetic acid and dichloromethane (1:1) to give the desired methylguanidine compounds **94a** and **94b** in high yield. The biphenyl intermediate **92a** was also reacted with diphenylphosphorylazide (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in anhydrous THF to give the azidomethyl compound **95**. Reduction with polymer-supported triphenylphosphine in a mixture of THF and water (10:1) gave the desired methanamine compound **96** in high yield.



Scheme 15. Synthetic route to compounds **94a-b**, and **96**.

To synthesize the analogs containing a 2 carbon linker to the basic moiety at the 1-position, the 3-bromo-6,7-dimethoxyisoquinolin-1(2*H*)-one intermediate, **59**, was used (Scheme 16).



Scheme 16. Synthetic route to the 2 carbon linkers.

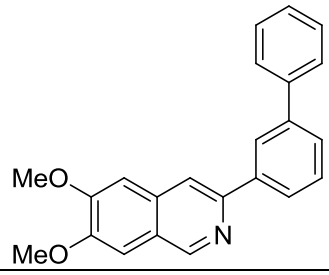
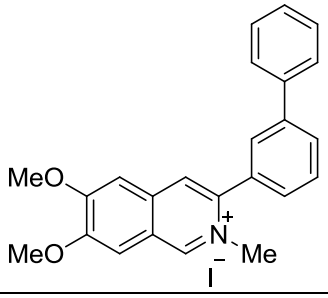
Suzuki coupling with either 3-biphenylboronic acid or 3-*t*-butylphenylboronic acid, $Pd(OAc)_2$, XPhos, and K_2CO_3 in acetonitrile and water (3:1) at 100 ^oC for 2 hours gave the cross-coupled products **60a** and **97** in good yield. Triflation with triflic anhydride and triethylamine in dichloromethane at -78 ^oC gave compounds **98a** and **98b** in good yield. A palladium-catalyzed Suzuki coupling utilizing Molander's trifluoroborate salt[83,84] gave desired cross-coupled products **99a** and **99b**, which were then deprotected to give final ethanamine products **100a** and **100b**. Reaction of these

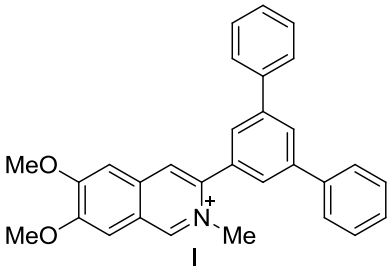
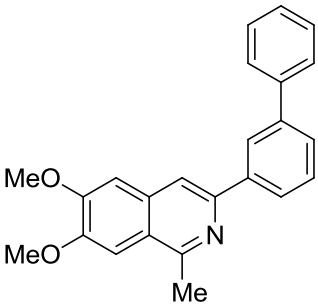
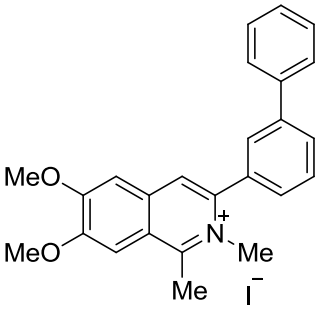
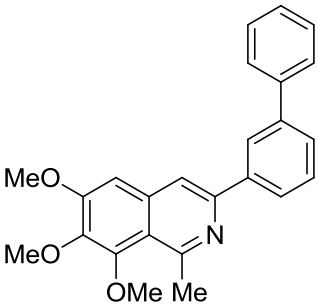
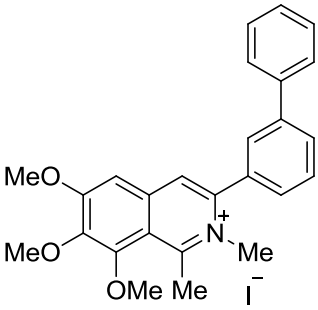
ethanamines with 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethylsulfonyl)guanidine and triethylamine in dichloromethane gave the protected guanidine products **101a** and **101b**, which were then deprotected with trifluoroacetic acid and dichloromethane to give desired 2 carbon chain guanidine compounds **102a** and **102b**. I would like to acknowledge Yongzheng Zhang at TAXIS Pharmaceuticals who was responsible for preparing key starting materials **70a** and **70b** in large quantities, as well as doing scale-ups of several compounds for additional biochemical/*in vivo* studies, and contributing to the SAR by synthesizing many other isoquinoline and isoquinolinium derivatives (not shown) in this series.

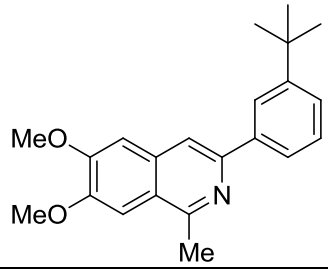
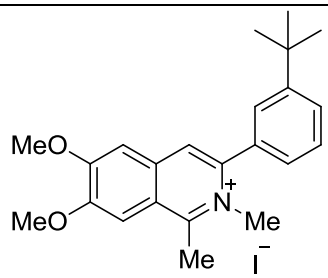
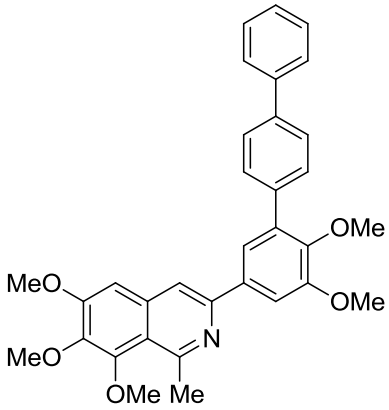
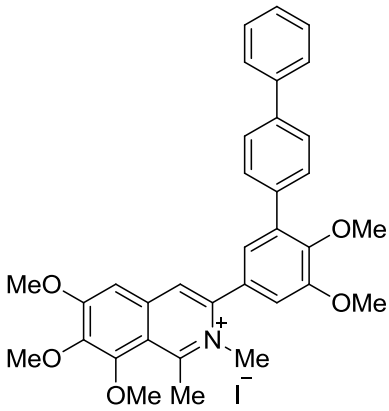
The relative antibacterial activity of these synthesized analogs was then evaluated in the 4 strains of bacteria (MSSA, MRSA, VSE, and VRE), as seen previously. Table 6 summarizes the results. No significant antibacterial activity was observed for the non-quaternary isoquinoline derivatives **62a**, **72a-c**, **81**, and **85a-b** against either *S. aureus* or *E. faecalis* (MICs > 64 μg/mL). Their *N*-methyl quaternary ammonium counterparts, however, did display antibacterial activity versus *S. aureus*, both sensitive and resistant strains, as seen with compounds **63a-b**, **73a-c**, **82**, and **86a-b**. With the exception of **63a**, **86a**, and **63b** (which was not determined), there were relatively minor differences between the MICs observed with MSSA and MRSA – several of them being equipotent against both. When looking at *E. faecalis*, the MICs for all compounds were greater than that observed with *S. aureus*. Against VRE in particular, only 3 of the quaternary ammonium compounds displayed activity within the 4-8 μg/mL range: **82**, **86a**, and **86b**. Interestingly enough, these are the 3 compounds that have an extended, 3 unit 1,1':4',1''-terphenyl or 4-(*t*-butyl)-1,1'-biphenyl attached at the 3-position.

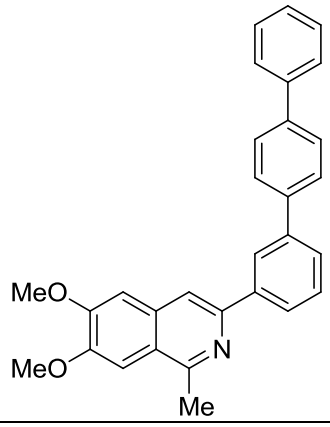
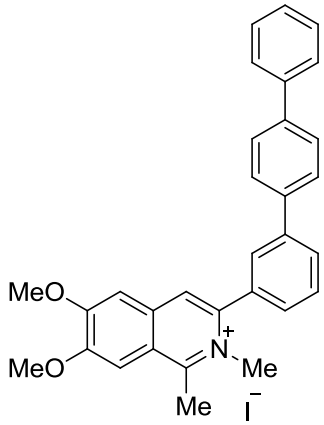
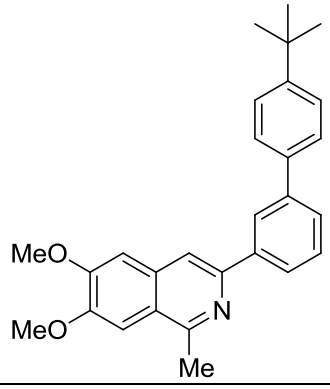
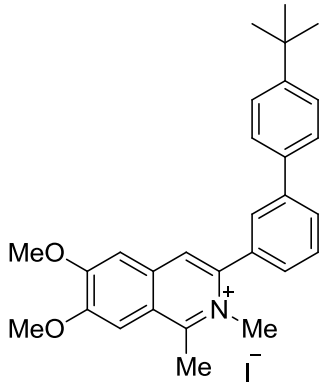
Based on these results, it became clear that the constitutively charged quaternary isoquinolinium derivatives uniformly displayed significantly enhanced antibacterial activity relative to their non-quaternary isoquinoline counterparts. Because one of our goals was to eliminate the constitutive cationic charge with hopes of retaining antibacterial activity, we decided to look at the effects of substituting basic moieties at the 1-position of the isoquinoline ring. While not bearing a constitutive positive charge, it was intended that these types of molecules would likely contain a charge at physiological pH. As already mentioned, this SAR was explored by synthesizing a collection of analogs containing various basic functional groups attached either directly, extended by 1 carbon, or extended by 2 carbons off of the 1-position.

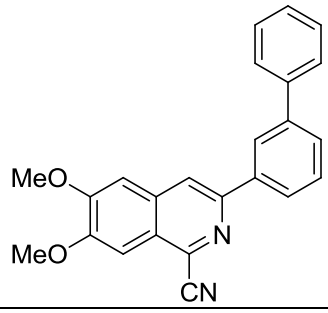
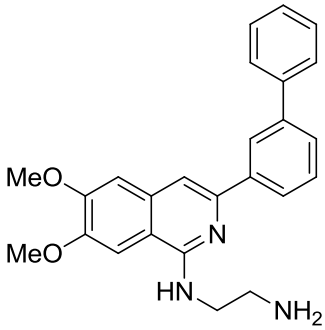
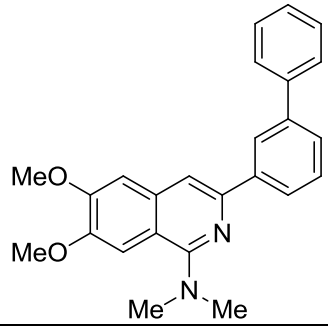
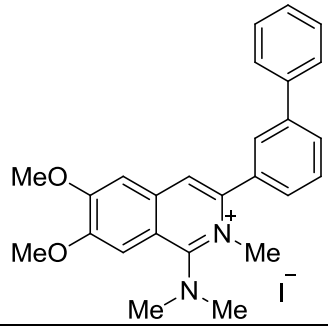
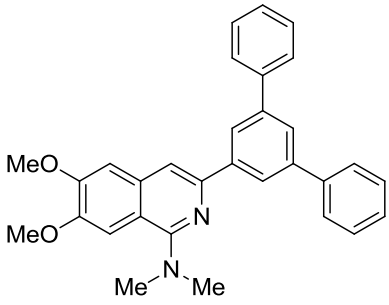
Table 6. Biological activity of 3-phenylisoquinoline and 3-phenylisoquinolinium derivatives.

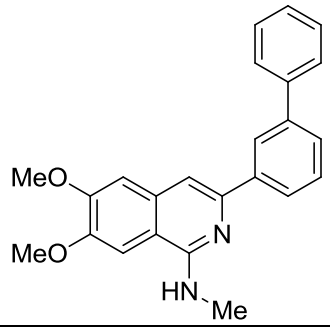
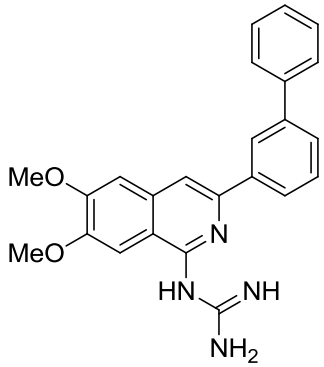
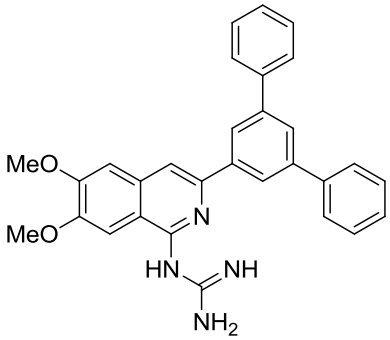
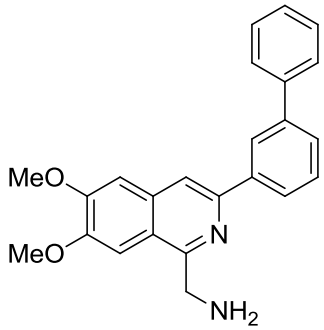
	Compound Structure	**[a]MIC (μg/mL)**			
		***S. aureus* 8325-4 (MSSA)**	***S. aureus* ATCC 33591 (MRSA)**	***E. faecalis* ATCC 19433 (VSE)**	***E. faecalis* ATCC 51575 (VRE)**
62a		>64	>64	>64	>64
63a		16	64	>64	>64

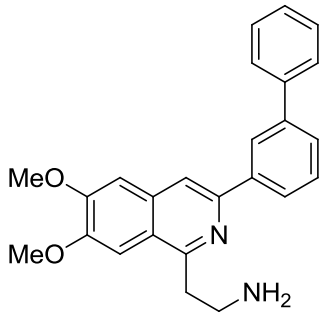
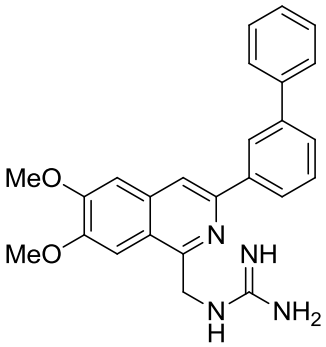
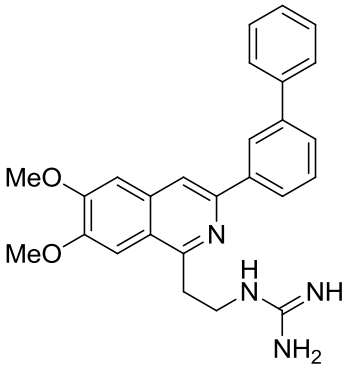
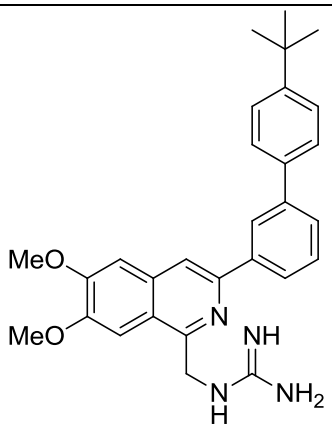
63b		4	ND	ND	ND
72a		>64	>64	>64	>64
73a		16	32	>64	>64
72b		>64	>64	>64	>64
73b		8	8	32	32

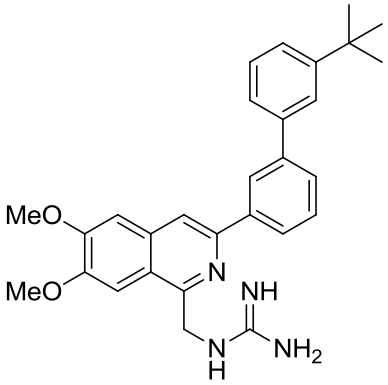
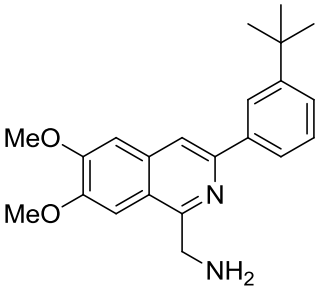
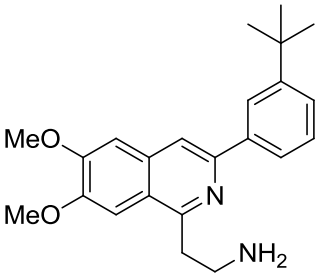
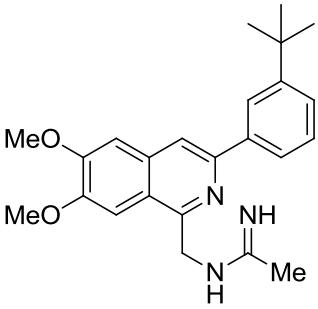
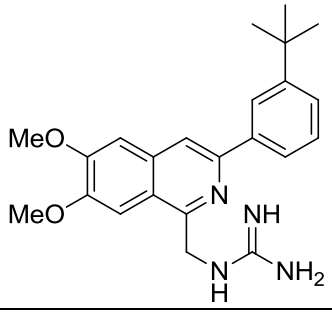
72c		>64	>64	>64	>64
73c		16	16	64	64
81		>64	>64	>64	>64
82		1	1	4	4

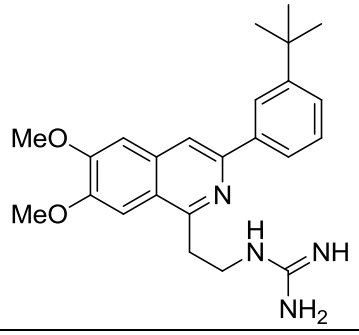
85a		>64	>64	>64	>64
86a		1	2	4	8
85b		>64	>64	>64	>64
86b		1	8	8	8

64		>64	>64	>64	>64
65		4	ND	ND	ND
66a		>64	>64	>64	>64
67		8	32	64	64
66b		>64	ND	ND	ND

68		>64	>64	>64	>64
69a		8	4	8	8
69b		32	ND	ND	ND
96		8	16	>64	>64

100a		4	4	16	>64
94a		2	2	8	8
102a		2	2	8	8
90a		4	4	8	16

90b		4	ND	ND	ND
77		4	8	32	32
100b		16	16	16	16
75		8	8	16	16
94b		4	8	16	16

102b		4	4	16	16
	Sanguinarine	**2**	**2**	**8**	**16**
	Chelerythrine	**4**	**4**	**32**	**32**
	Berberine	**>64**	**>64**	**>64**	**>64**
	Oxacillin	**0.06**	**>64**	**8**	**64**
	Vancomycin	**1**	**2**	**1**	**>64**
	Erythromycin	**0.13**	**>64**	**1**	**>64**
	Tetracycline	**0.06**	**64**	**0.5**	**>64**
	Clindamycin	**0.3**	**>64**	**2**	**>64**

[a]Minimum inhibitory concentration (MIC) assays were conducted in accordance with Clinical Laboratory Standards Institute (CLSI) guidelines for broth microdilution.[73] MIC is defined as the lowest compound concentration at which bacterial growth is ≥90% inhibited.

. A series of 3-(3'-phenyl)phenylisoquinoline derivatives with varying substituents at the 1-position were evaluated and compared for their antibacterial activity. Among the 1-amino-3-(3'-phenyl)phenylisoquinolines **66a**, **67**, and **68**, only the quaternary ammonium derivative, **67**, exhibited modest antibacterial activity against *S. aureus* with an MIC of 8 μg/mL for MSSA and 32 μg/mL for MRSA. It was not, however, significantly active against *E. faecalis*. The 1-guanidino derivative, **69a** was active against the sensitive and resistant strains of both *S. aureus* and *E. faecalis* suggesting that the presence of a basic moiety that would be protonated to some extent at physiological pH would still be associated with the antibacterial activity we observed with the constitutively charged analogs. This SAR is further substantiated by the observation that the 1-nitrile derivative, **64** was completely inactive, while its reduced product, the aminomethyl derivative **96** was active against both sensitive and resistant *S. aureus*. The

1-ethylenediamine derivative, **65** was active against MSSA with an MIC of 4 μg/mL. The 1-guanidinomethyl and 1-(2-guanidinoethyl) derivatives **94a** and **102a** were active against both strains of S. aureus and E. faecalis, while the less basic 1-(2-aminoethyl) derivative **100a** was active against both strains of *S. aureus* but less active against both strains of *E. faecalis*.

Compounds **66b** and **69b** are analogous to **66a** and **69a**, having an additional phenyl attached at the 5'-position. They follow the same trend observed with **66a** and **69a** – the 1-dimethylamino being inactive but the 1-guanidino displaying activity, albeit less potently, with an MIC of 32 μg/mL versus the MIC of 8 μg/mL observed with **69a**. Compounds **90a** and **90b** are analogous to **94a**, having a *t*-butyl attached at the 4"- and 3"-position, respectively. Overall, the addition of the *t*-butyl group resulted in slightly less antibacterial activity than what was observed with compound **94a**.

A series of 3-(3'-*t*-butyl)phenylisoquinoline derivatives with varying substituents at the 1-position were also evaluated and compared for their antibacterial activity. In this series of compounds, the results indicate that, unlike the 3-(3'-phenyl)isoquinolines, the 1-aminomethyl derivative, **77** was more active than the 1-(2-aminoethyl) derivative, **100b**. The more basic amidinomethyl derivative **75** and guanidinomethyl derivative **94b** were modestly more active than **77** against both strains of *E. faecalis* with an MIC of 16 μg/mL for both, compared to an MIC of 32 μg/mL observed with **77**, and the guanidinomethyl displayed comparable activity to **77** against both strains of *S. aureus*. The 1-(2-guanidinoethyl) derivative **102b** was the most active of the 3-(3'-*t*-butylphenyl) analogs versus MRSA with an MIC of 4 μg/mL. When comparing the 3-(3'-

phenyl)phenyl derivatives to the 3-(3'-*t*-butyl)phenyl derivatives, the 3-(3'-phenyl)phenyl derivatives were generally more active than the 3-(3'-*t*-butyl)phenyl counterparts. The exception was the 1-aminomethyl derivative, in which case, the *t*-butyl analog was slightly more potent.

Overall, these data indicate that various 3-phenylisoquinoline and 3-phenylisoquinolinium derivatives can exhibit significant antibacterial activity against both methicillin-sensitive and methicillin-resistant *S. aureus*. The presence of a basic substituent at the 1-position of the 3-phenylisoquinolines is associated with increased antibacterial activity. Few of these compounds, however, exhibit good activity versus the vancomycin-resistant *E. faecalis*, however, compounds **69a**, **94a**, and **102a** have MICs of 8 μg/mL, which is significantly lower than any of the clinical standards (MICs ≥ 64 μg/mL).

Several additional biochemical assays were performed on representative compounds from this series to determine whether the antibacterial activity might reflect their ability to target bacterial FtsZ. The first step was to evaluate the ability of these compounds to bind to purified *S. aureus* FtsZ (SaFtsZ). To do this, the intrinsic fluorescence of the compounds was monitored as a function of added SaFtsZ. Figure 12 shows representative results for **86a** and **86b**, two of the more active compounds. What these data show is that as the concentration of SaFtsZ is increased, the fluorescence emission intensities of both **86a** and **86b** increase, while also blue-shifting the maximum spectral wavelength by 4-6 nm (Fig. 12A and B). These FtsZ-induced changes in the compounds' fluorescence are indicative of the compounds binding to the target protein.

The compound-FtsZ dissociation constants (K_d) were determined by analyzing the FtsZ-induced changes in compound fluorescence using the following 1:1 binding formalism:

$$I = I_0 + \frac{I_\infty - I_0}{2}\left[([C]_{tot} + [P]_{tot} + K_d) - \sqrt{([C]_{tot} + [P]_{tot} + K_d)^2 - 4[C]_{tot}[P]_{tot}}\right] \quad \textbf{Eq. 1}$$

The I and I_0 are the fluorescence emission intensities of the compounds in either the presence or absence of FtsZ, respectively. I_∞ is the fluorescence emission intensity of the compounds at infinite FtsZ concentrations, and $[C]_{tot}$ and $[P]_{tot}$ are the total concentrations of the compounds and FtsZ, respectively. This 1:1 binding formalism gave an excellent fit (R^2>0.99) of the fluorescence intensity profiles for compounds **86a** and **86b**, which can be seen as the solid lines in Fig. 12C and D. The K_d values obtained by this fit were 2.0 ± 0.7 μM for **86a** and 5.4 ± 1.5 μM for **86b**. Significantly, the K_d values are similar in magnitude to their corresponding MIC values against MSSA (MIC = 1 μg/mL = 2.2 μM for **86a** and 2.3 μM for **86b**).

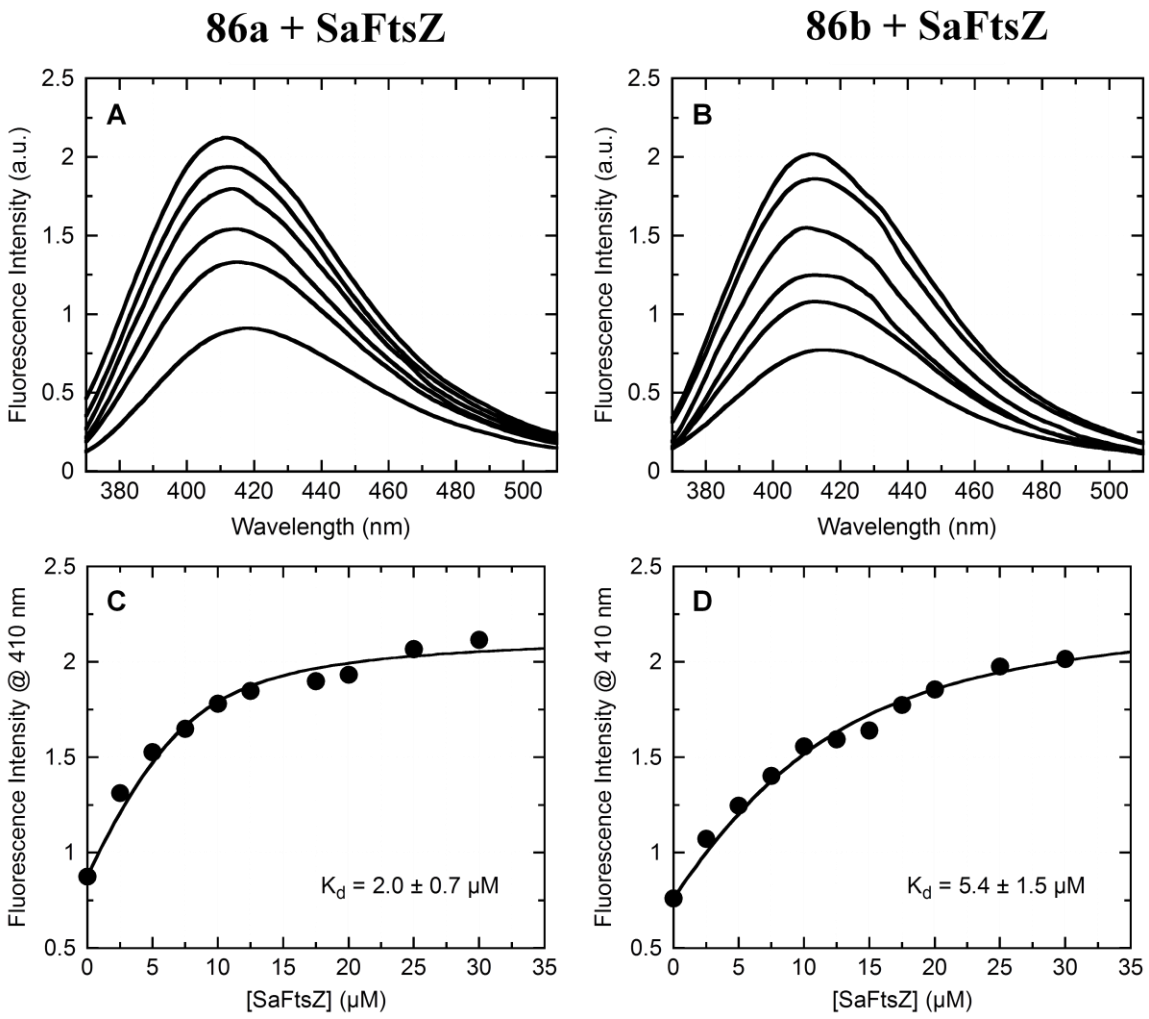


Figure 12. (A and B) Fluorescence emission spectra of 7 μM of **86a** (A) and 10 μM **86b** (B) acquired in the absence and presence of purified SaFtsZ at concentrations ranging from 2.5 to 30 μM. From bottom to top curve, the SaFtsZ concentrations correspond to 0, 2.5. 5, 10, 20, and 30 μM. **(C and D)** Fluorescence profiles of emission intensity at 410 nm for the titration of SaFtsZ into a solution of **86a** (C) and **86b** (D). The solid line represents fits of the experimental data with Eq. 1 yielding the indicated K_d values.

The next biochemical assay conducted was to evaluate the series' ability to impact self-polymerization activity of FtsZ. To do this, a microtiter plate-based light scattering

(turbidity) assay was used. In this assay, FtsZ polymerization is detected in solution by a time-dependent increase in light scattering, as reflected by a corresponding increase in solution absorbance at 340 nm (A_{340}). A representative set of active compounds in the series with MIC values ≤ 16 μg/mL were evaluated in this assay at 40 μg/mL. All compounds were found to stimulate SaFtsZ polymerization in a time-dependent manner. The A_{340} profiles were acquired in the presence of DMSO and the seven active compounds (**86a**, **86b**, **102a**, **100b**, **75**, **94b**, and **102b**) as illustrative examples shown in Figure 13A. In striking contrast to the active compounds, the inactive isoquinolines **72c** and **85b** (MIC > 64 μg/mL) did not significantly impact FtsZ polymerization at all. This stimulatory behavior seen with the active compounds is similar to that of the previously reported benzamide FtsZ inhibitor, PC190723[48,69] which was used as a positive control (Fig. 13B). The non-FtsZ-targeting drug, vancomycin, was used as the negative control, and as expected, had no impact on SaFtsZ polymerization (Fig. 13B), similar to the inactive isoquinolines **72c** and **85b** that were tested. Based on these results, the SAR of the isoquinolines with regard to their anti-staphylococcal activity appears to correlate well with their ability to stimulate SaFtsZ polymerization. As an additional comparator, berberine (**2**), which is inactive against *S. aureus* at concentrations < 64 μg/mL, was included. Similar to the inactive isoquinolines **72c** and **85b**, berberine did not significantly affect SaFtsZ polymerization at an equivalent concentration of 40 μg/mL (Fig. 13B).

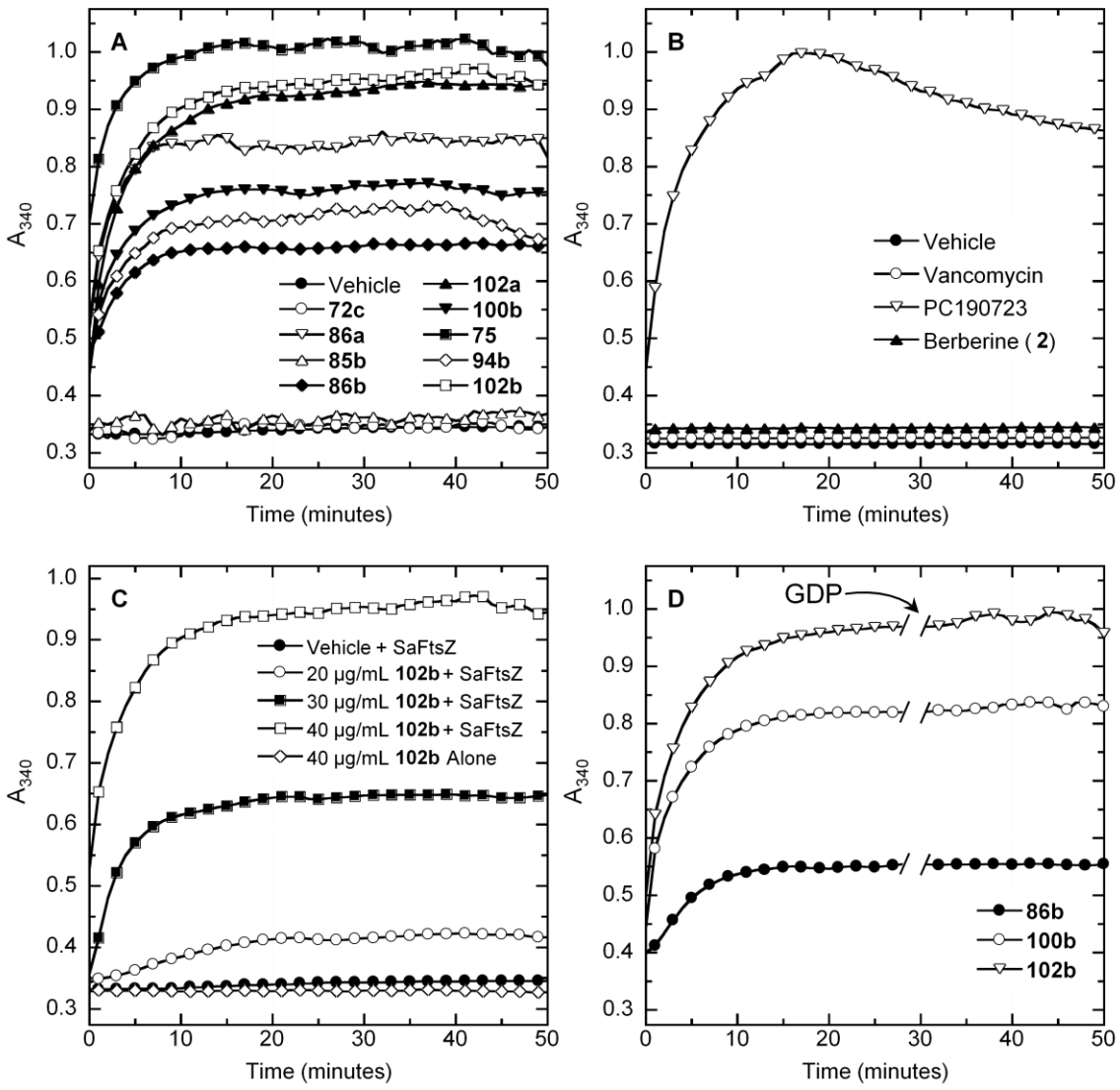


Figure 13. Impact of isoquinolines on SaFtsZ (10 μM) polymerization in the presence of 1 mM GTP, as determined by time-dependent changes in absorbance at 340 nm. **(A and B)** A_{340} profiles of SaFtZ in the presence of DMSO vehicle or 40 μM of compound/comparator. **(C)** A_{340} profiles of SaFtsZ in the presence of DMSO vehicle or **102b** at 20, 30, or 40 μg/mL. As a comparator, 40 mg/mL of **102b** without protein is also included as a control. (D) A_{340} profiles of SaFtsZ in the presence of 40 mg/mL of **86b**, **100b**, and **102b**. GDP (1 mM) was added at the time indicated by the arrows.

The stimulatory impact of the isoquinolines on SaFtsZ was further investigated by evaluating whether this phenomenon was dependent upon compound concentration. Figure 13C illustrates the A_{340} results for either DMSO vehicle or compound **102b** at varying concentrations of 20, 30, and 40 μg/mL. These results show that increasing compound concentration also increases the extent to which **102b** enhances SaFtsZ polymerization. Similar results were observed with other isoquinolines from this series, but this is an illustrative example. Also included in this study was a non-protein control of **102b** alone at 40 μg/mL. The lack of SaFtsZ polymerization confirms that the enhanced light scattering induced by the varying concentrations of **102b** in the presence of SaFtsZ reflects a corresponding stimulation of self-polymerization – not just a non-specific compound aggregation or precipitation.

The stability of the SaFtsZ polymers induced by the isoquinolines was then examined. In the absence of a polymer-stabilizing agent, the addition of GDP has been demonstrated in the literature to depolymerize FtsZ polymers that were formed in the presence of GTP.[48] To evaluate the impact, if any, of adding GDP to the polymers formed in the presence of 40 μg/mL of the active isoquinolines and 1 mM of GTP, 1 mM of GDP was added. Figure 13D shows the results from these studies with compounds **86a**, **100b**, and **102b** as illustrative examples. The addition of GDP did not exert a significant effect on the A_{340} signal, indicating that SaFtsZ polymerization was unaffected by the addition and that the polymers induced by the presence of the isoquinolines are stable to depolymerization. These results are similar to that observed with PC190723 and the *B. subtilis* FtsZ.[48] Taken as a whole, these data indicate that the antibacterial activity

observed with the isoquinolines is related, at least in part, to their ability to stimulate and stabilize FtsZ polymerization.

The next thing to investigate was the impact, if any, of the isoquinoline compounds on GTPase activity. Table 7 summarizes the results for 40 mg/mL of the same seven active compounds evaluated in the SaFtsZ profiling study (**86a**, **86b**, **102a**, **100b**, **75**, **94b**, and **102b**). These isoquinoline compounds inhibited the GTPase activity of SaFtsZ by as much as 85%, in stark contrast to the non-FtsZ-targeting vancomycin, which had no significant impact. This inhibitory activity is consistent with what was previously reported for PC190723.[48,69,85]

Table 7. Impact of selected isoquinoline compounds on SaFtsZ GTPase activity.

Compound or Control Agent[a]	Percent GTPase activity[b]
Vehicle (DMSO)	100.0 ± 3.3
86a	30.2 ± 0.3
86b	14.9 ± 1.7
102a	56.0 ± 1.7
100b	59.7 ± 1.0
75	64.8 ± 0.1
94b	60.4 ± 1.9
102b	66.5 ± 1.7
Vancomycin	99.7 ± 12.2

[a]Vancomycin and all isoquinoline compounds were used at a concentration of 40 μg/mL.
[b]Percent GTPase activity reflects the percentage of the GTPase activity observed in the presence of vehicle (DMSO) alone. Each value represents the mean of two independent assessments, with the indicated uncertainty reflecting the standard deviation from the mean.

A more in-depth analysis of the concentration dependence of compounds **102a** and **75** and inhibition of GTPase activity reveals that both of these compounds stimulate GTPase activity at lower concentrations followed by an inhibition of GTPase activity at higher concentrations (Figure 14). This pattern was also seen with PC190723 and *B. subtilis* FtsZ.[48] It has been suggested that the increase in GTPase activity seen with low concentrations of compound may simply reflect a polymerization-induced enhancement of GTPase activity relative to that associated with FtsZ polymerization in the absence of compound.[48]

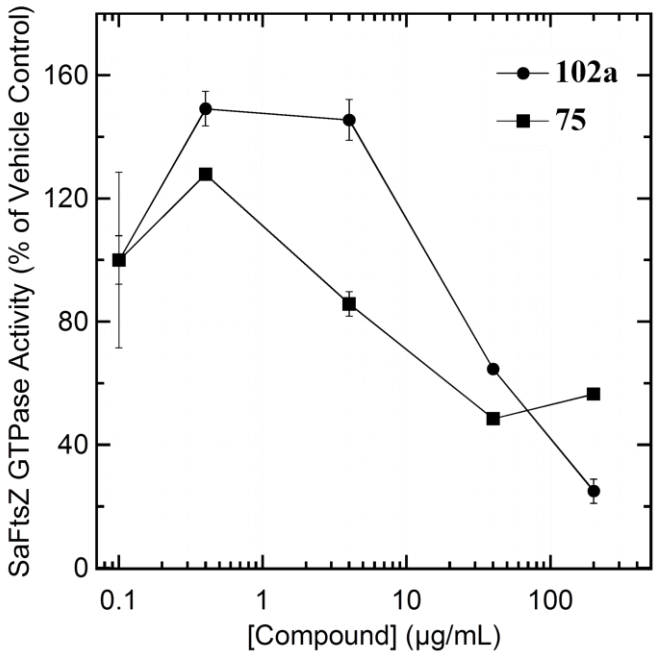


Figure 14. Concentration dependence of compounds **102a** and **75** on SaFtsZ (10 μM) GTPase activity in the presence of 1 mM GTP. GTPase activity reflects % of control GTPase activity observed in the presence of DMSO vehicle alone. Each data point is the mean of two independent assessments.

Another important evaluation for an FtsZ inhibitor is to investigate whether or not the compounds have an impact on mammalian tubulin, which would be indicative of toxicity. As mentioned earlier, tubulin is the closest mammalian functional homologue to bacterial FtsZ. Compounds **86b** and **94b** were monitored for their effect on porcine β-tubulin polymerization using an assay similar to that described for FtsZ polymerization. Two positive controls were used in this assay: paclitaxel (taxol), which is a known stimulator of tubulin polymerization, and nocodazole, which is a known inhibitor of tubulin polymerization.[86-88] Figure 15 shows the A_{340} profiles of porcine b-tubulin in the absence and presence of **86b** and **94b** (40 μg/mL), taxol (25 μg/mL), and nocodazole (10 μg/mL). As expected, both taxol and nocodazole produce their respective impacts on tubulin polymerization, whereas compounds **86b** and **94b** display no significant impact. These data indicate that the isoquinoline compounds, which greatly stimulate bacterial polymerization, do not appear to cross-react with the mammalian structural homologue tubulin.

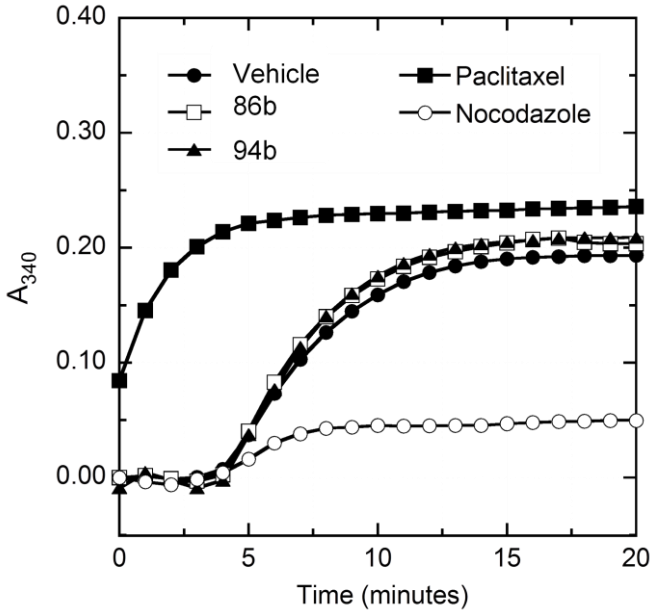


Figure 15. Time-dependent impact of **86b** and **94b** on polymerization of microtubule-associated protein (MAP)-rich porcine β-tubulin (70% tubulin, 20% MAPs) as determined by changes in absorbance at 340 nm (A_{340}).

The non-quaternized isoquinoline derivatives that displayed significant antibacterial activity did tend to have better solubility properties than did the quaternary ammonium compounds. This was one of the goals when initially designing these analogs. As a result, it would be expected that these non-quaternized isoquinoline derivatives would be more efficiently absorbed and distributed. To this end, several of the isoquinoline compounds were evaluated for cytotoxicity in mammalian cells. Among those that were evaluated were compounds **69a**, **77**, **90a**, **94a**, **94b**, **96**, **100b**, **102a**, and **102b**. For compounds **77**, **90a**, **94a**, **94b**, **102a**, and **102b**, no significant human cell toxicity was detected at the highest concentration tested (10 μM) in human embryonic kidney (HEK293) cells. There was modest human cell cytotoxicity observed with compound **96**, which had an IC_{50} of 3.0 μM in HEK239 cells, but displayed less toxicity

in canine MDCK cells with an IC_{50} of 7.0 μM. Compounds **69a** and **100b** were among the more toxic of the compounds evaluated, with IC_{50} values ranging from 2.2 to 3.5 μM in these cells. The results of these cytotoxicity studies reveal that there is no clear correlation between the observed antibacterial activity, as reflected by their MICs (IC_{90} values) and any observed mammalian cytotoxicity, as reflected by their IC_{50} values. Once again, the biochemical studies were conducted by Dr. Malvika Kaul and Dr. Daniel S. Pilch at Rutgers-UMDNJ, aside from the cytotoxicity assay, which was conducted by. Angela Liu in the Department of Pharmacology at Rutgers-UMDNJ.

After obtaining a general biochemical profile of this series and better solubility (while maintaining antibacterial activity), it was time to evaluate some of the compounds in an *in vivo* mouse model. Mouse *in vivo* studies were conducted by Lilly Mark at TAXIS Pharmaceuticals. Although we were able to find suitable formulations for these compounds, preliminary *in vivo* studies did not display any efficacy at any of the doses tested. After further investigation and re-evaluation of the MIC values with mouse serum present, it became clear that the lack of efficacy observed *in vivo* was likely due to plasma protein binding of the compounds. Given that the MIC values generally shifted several orders of magnitude higher when evaluated in the presence of protein, we now had a new challenge to face in our quest for *in vivo* efficacy.

2.4 Synthesis and Evaluation of 4- and 5-Substituted 1- and 2-Phenylnaphthalene Derivatives.

Based on the results from the previous 3-phenylisoquinoline and 3-phenylisoquinolinium series, this project now had a new primary goal: either (1) decrease

the amount of protein binding of the compounds, or (2) increase the potency of the compounds so that even with the observed protein binding, the MIC values would still be low enough to observe efficacy *in vivo*. To do this, once again we had to design, synthesize, and evaluate a new series of compounds.

4- and 5-Substituted 1-phenylnaphthalenes represent a truncated form of the 5-methylbenzo[*c*]phenanthridine series. This series, of course, contains a constitutive cationic charge, which we already knew could have adverse effects on the desired pharmacological properties of the molecules. Based on what we learned from the 3-phenylisoquinoline series, we decided to once again evaluate basic groups that would not bear a constitutive positive charge, but would likely be protonated to some extent at physiological pH. Placement at the 4- and 5-position of the 1-phenylnaphthalene ring would put these groups in close proximity to where the iminium cation group is located on the 5-methylbenzo[*c*]phenanthridine series as illustrated in Figure 16. As such, similar to what was done in the isoquinoline series, various aminoalkyl, amidinoalkyl, and guanidinoalkyl derivatives were synthesized and evaluated for their antibacterial activity.

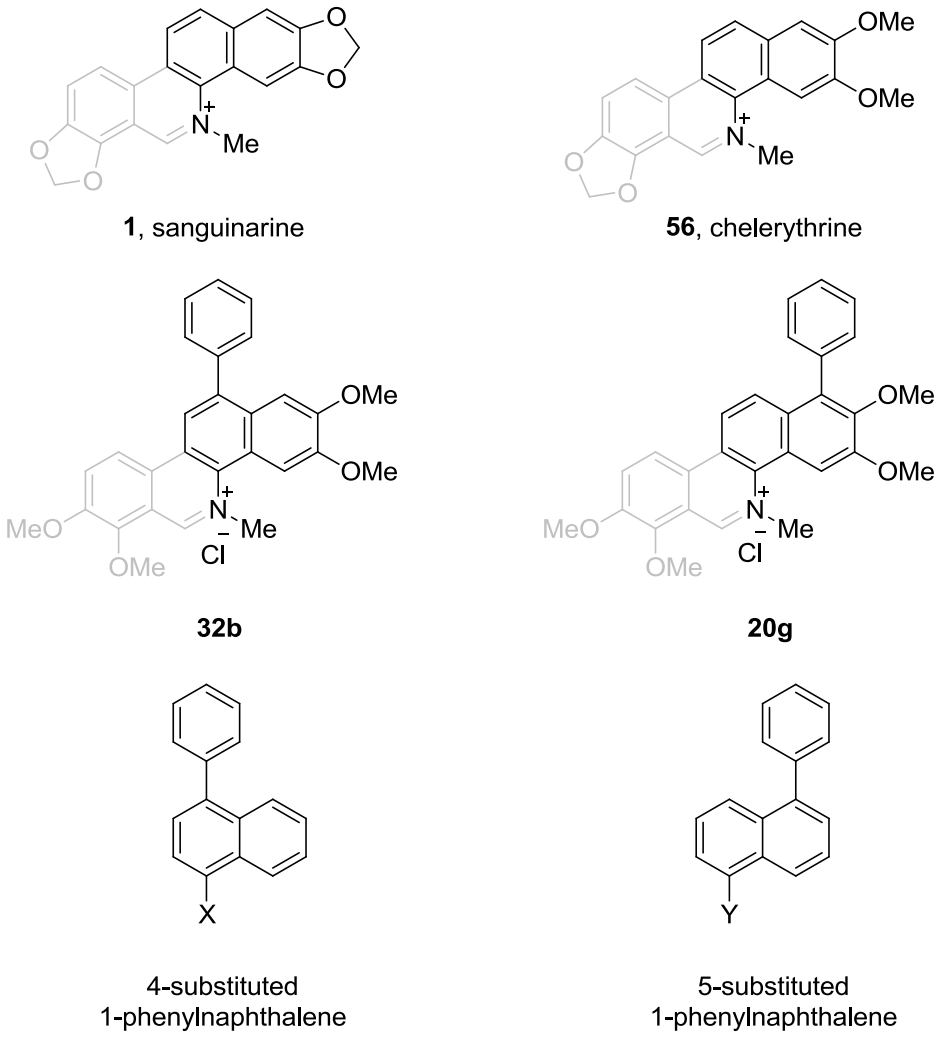
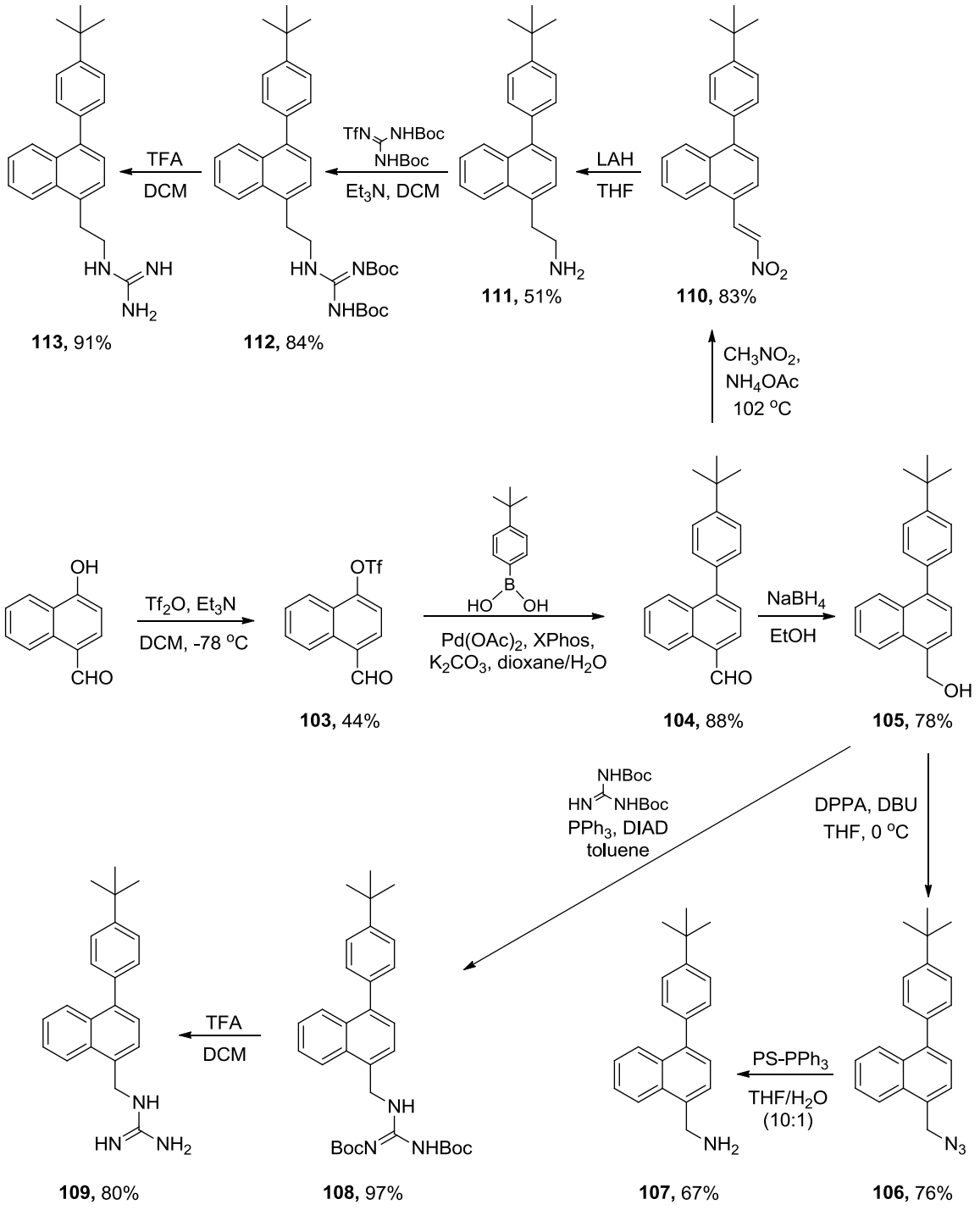


Figure 16. Chemical structures of sanguinarine (**1**), chelerythrine (**56**), synthetic analogs **20g** and **32b**, and proposed new 4- and 5-substituted 1-phenylnaphthalene derivatives.

Scheme 17 outlines the synthesis of the 4-substituted 1-phenylnaphthalene derivatives. For these derivatives, a 1-(4-*t*-butylphenyl) substitution was chosen for all analogs. Starting with commercially available 4-hydroxynaphthaldehyde, treatment with triflic anhydride and triethylamine in dichloromethane at -78 ^{o}C gave the triflate derivative **103**, which was then Suzuki coupled with 4-*t*-butylphenylboronic acid, $Pd(OAc)_2$, XPhos, and potassium carbonate in refluxing dioxane/water (2:1) to give **104**

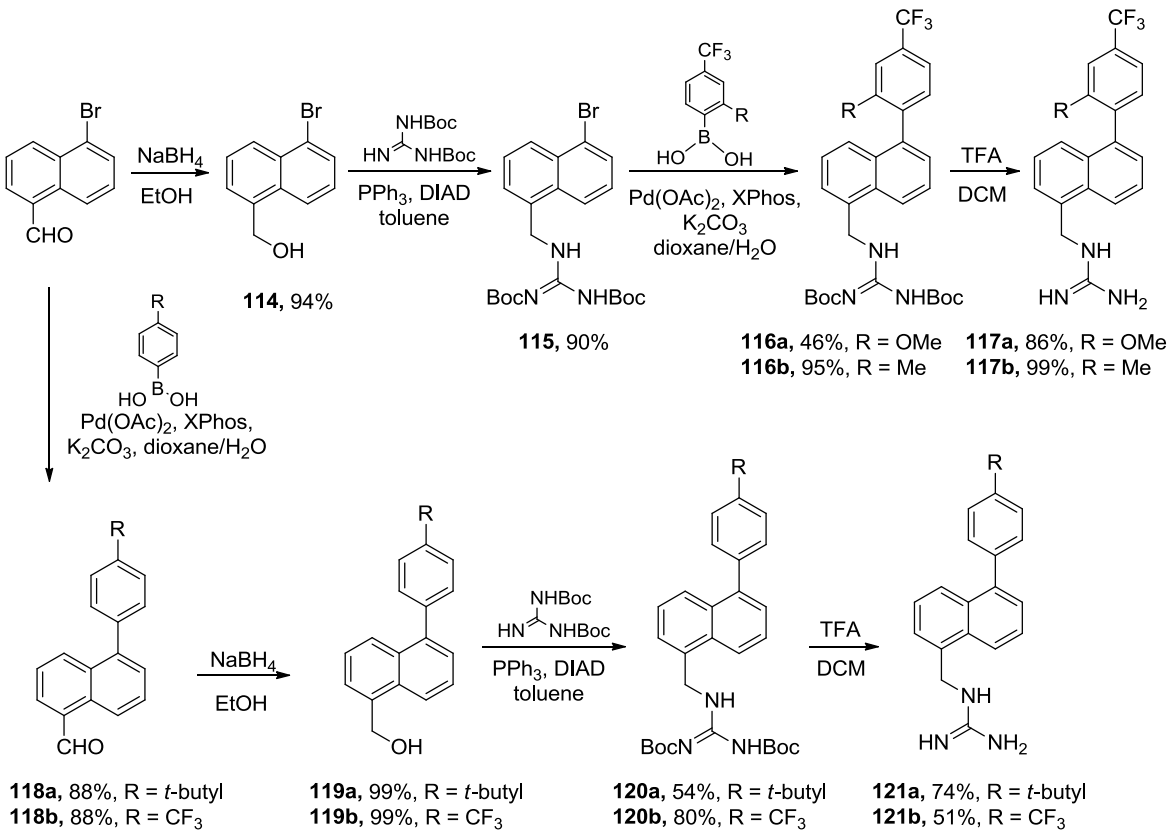
in good yield. Reduction of the aldehyde with sodium borohydride in ethanol gave the hydroxymethyl derivative **105**, which was then used to make two separate final compounds. Treatment of **105** with diphenylphosphorylazide (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in anhydrous THF gave the azide, **106**, which was then reduced with polymer-supported triphenylphosphine to give final aminomethyl compound **107**. Alternatively, **107** was subjected to Mitsunobu conditions with 1,3-(*t*-butoxycarbonyl)guanidine to give **108** in high yield. Subsequent deprotection with trifluoroacetic acid and dichloromethane gave final guanidinomethyl compound **109**.



Scheme 17. Synthetic route to 4-substituted 1-(4-*t*-butylphenyl)naphthalene derivatives.

To make the 2 carbon linker analogs, the aldehyde intermediate **104** was condensed with nitromethane by refluxing with ammonium acetate to give the 2-

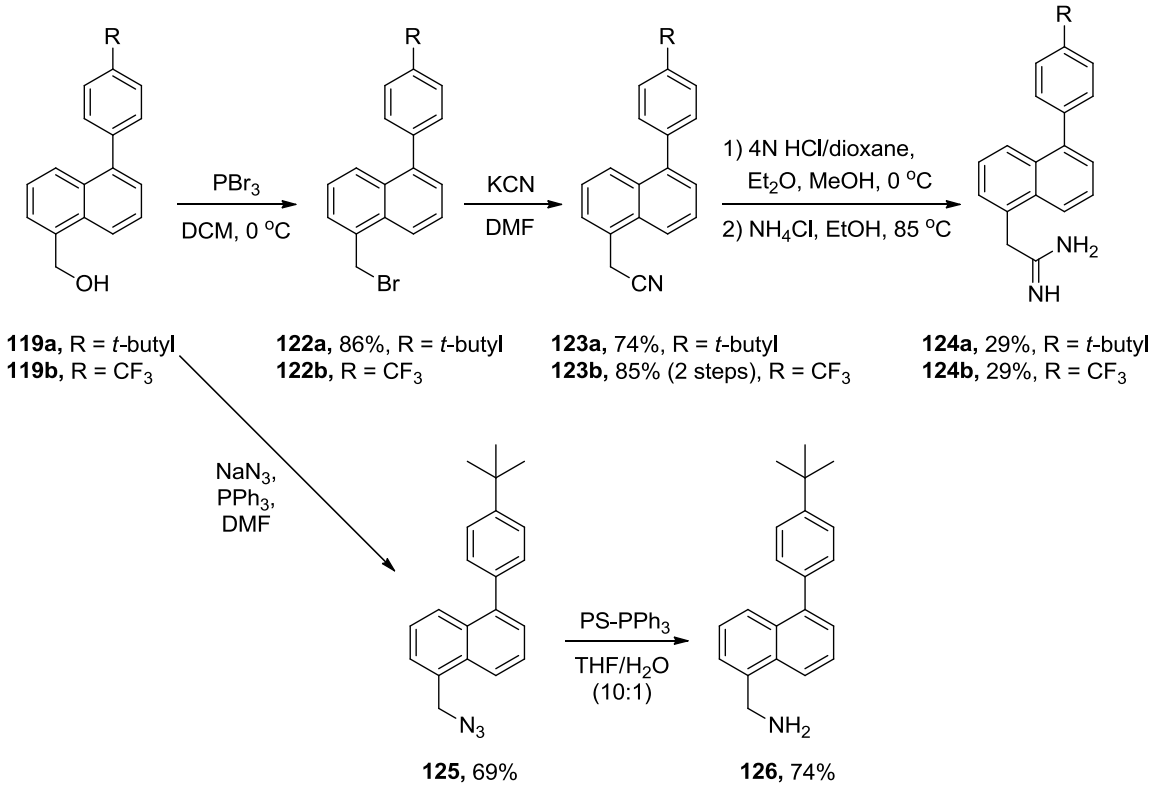
nitroethylene derivative **110** in good yield. Reduction of the alkene and nitro group was achieved with LAH in anhydrous THF to give the 2-aminoethyl, **111** in reasonable yield. Treatment of **111** with 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethanesulfonyl)guanidine and triethylamine gave **112** followed by removal of the Boc groups to give final guanidinoethyl compound **113** in good yield. Compound **113** was synthesized by Songfeng Lu at TAXIS Pharmaceuticals.



Scheme 18. Synthetic route to compounds **117a-b**, and **121a-b**.

Several 1-phenylnaphthalene derivatives substituted with a 5-methylguanidine were prepared as outlined in Scheme 18. 5-Bromo-1-naphthaldehyde was prepared in quantity following literature procedures.[89] Reduction of the aldehyde to the

hydroxymethyl with sodium borohydride gave **114** in high yield. Conversion of **114** under Mitsunobu conditions gave intermediate **115** in good yield. Subsequent Suzuki coupling with (2-methoxy-4-(trifluoromethyl)phenyl)boronic acid (for **116a**) or (2-methyl-4-(trifluoromethyl)phenyl)boronic acid (for **116b**) using $Pd(OAc)_2$, XPhos, and K_2CO_3 in refluxing dioxane and water (3:1) gave the cross-coupled products. Removal of the Boc groups with trifluoroacetic acid and dichloromethane gave the desired final compounds, **117a** and **117b** in good yield. Alternatively, 5-bromo-1-naphthaldehyde was first Suzuki coupled with either 4-*t*-butylphenyl or 4-trifluoromethylphenylboronic acid to give **118a** and **118b** in good yield. Reduction of the aldehyde with sodium borohydride gave **119a** and **119b** quantitatively. Conversion to **120a** and **120b** under Mitsunobu conditions followed by removal of the Boc groups gave the desired final guanidinomethyl compounds **121a** and **121b**.



Scheme 19. Synthetic route to compounds **124a**, **124b**, and **126**.

Cross-coupled intermediates **119a** and **119b** were also used for the synthesis of the amidinomethyl analogs, **124a** and **124b**, and the aminomethyl analog, **126** as shown in Scheme 19. Conversion of the hydroxymethyl to the bromomethyl intermediates, **122a** and **122b**, with phosphorus tribromide followed by displacement with potassium cyanide in DMF gave the nitrile intermediates **123a** and **123b** in good yield. The final amidino compounds were made by a series of nucleophilic additions known as the Pinner reaction (Figure 17).[90] Treatment with 4N HCl in dioxane, ether, and methanol at 0 °C followed by treatment with ammonium chloride in refluxing ethanol gave final compounds **124a** and **124b** in modest yield.[91] Intermediate **119a** was also taken and converted to the

azidomethyl compound **125**, which was reduced with polymer-supported triphenylphosphine to give the aminomethyl compound **126**.

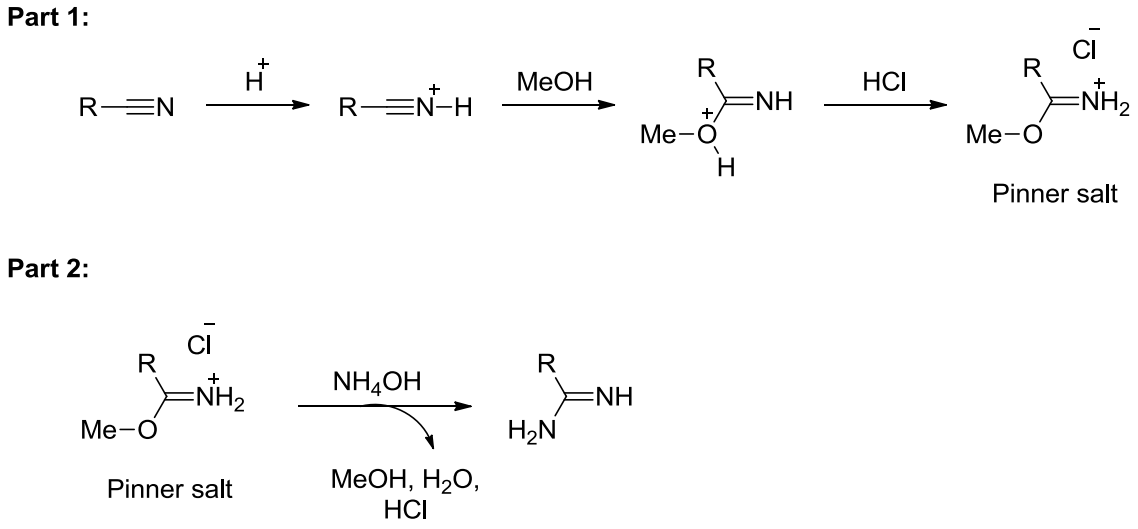
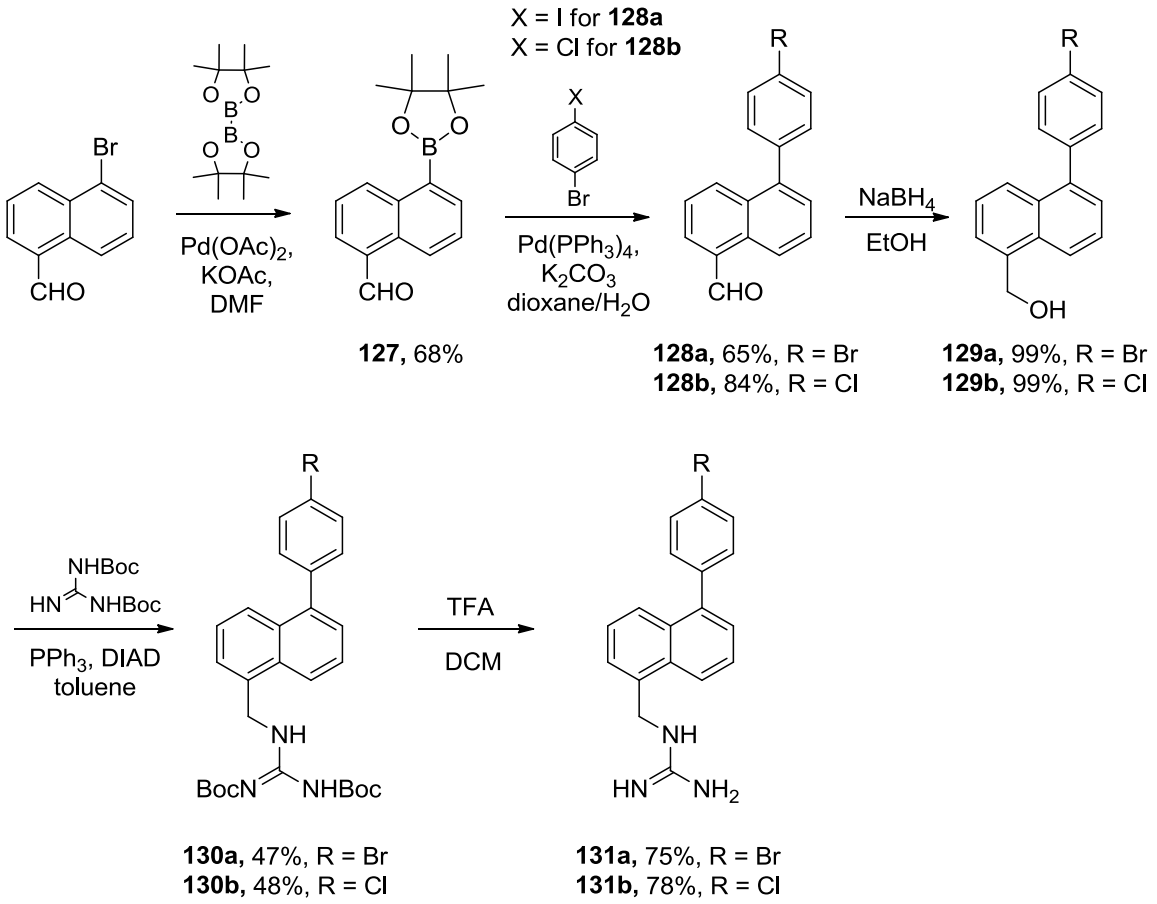


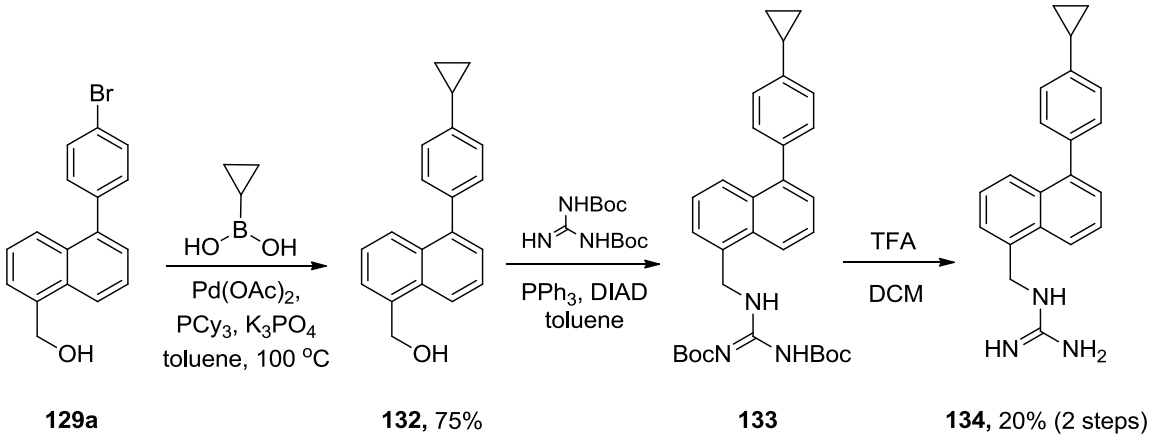
Figure 17. Mechanism of the Pinner reaction.

Several other guanidinomethyl derivatives were made with slightly different chemistry (Scheme 20). For the case of compounds **131a** and **131b**, 5-bromo-1-naphthaldehyde was first converted to its boronic acid pinacol borane (**127**) with bis(pinacolato)diborane, $Pd(OAc)_2$, and potassium acetate in DMF at 80 ^{o}C. Suzuki cross-coupling with either 1-bromo-4-iodobenzene or 1-bromo-4-chlorobenzene gave **128a** and **128b**, respectively. Reduction of the aldehyde with sodium borohydride in ethanol gave the hydroxymethyl derivatives **129a** and **129b** quantitatively. The Mitsunobu reaction with these intermediates were performed with 1,3-bis-(*t*-butoxycarbonyl)guanidine, followed by removal of the Boc groups to provide final compounds **131a** and **131b**.



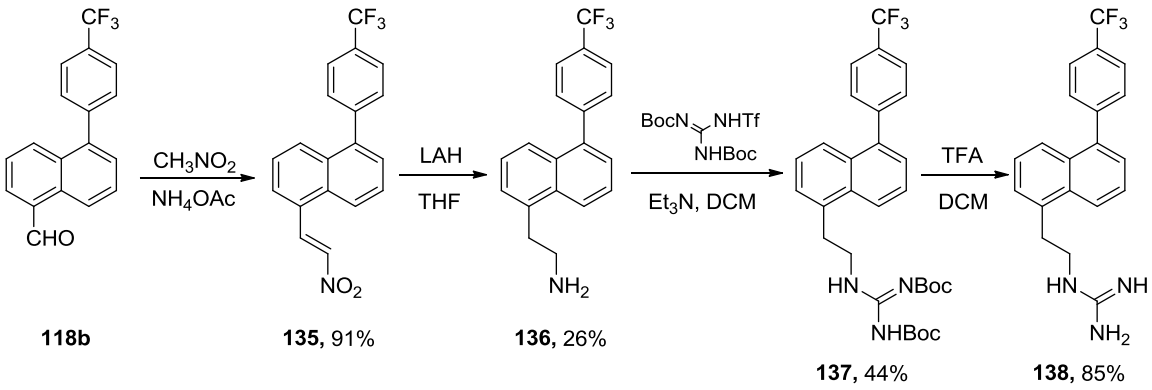
Scheme 20. Synthetic route for compounds **131a** and **131b**.

Intermediate **129a** was also used to synthesize a 4-cyclopropylphenyl derivative (Scheme 21) by doing an additional Suzuki coupling with cyclopropylboronic acid and using the conditions worked out previously in the benzo[*c*]phenanthridine series: $Pd(OAc)_2$, PCy_3, and K_3PO_4 in toluene at 100 ^oC to provide **132**. This followed by the Mitsunobu reaction and removal of the Boc groups to give compound **134**.



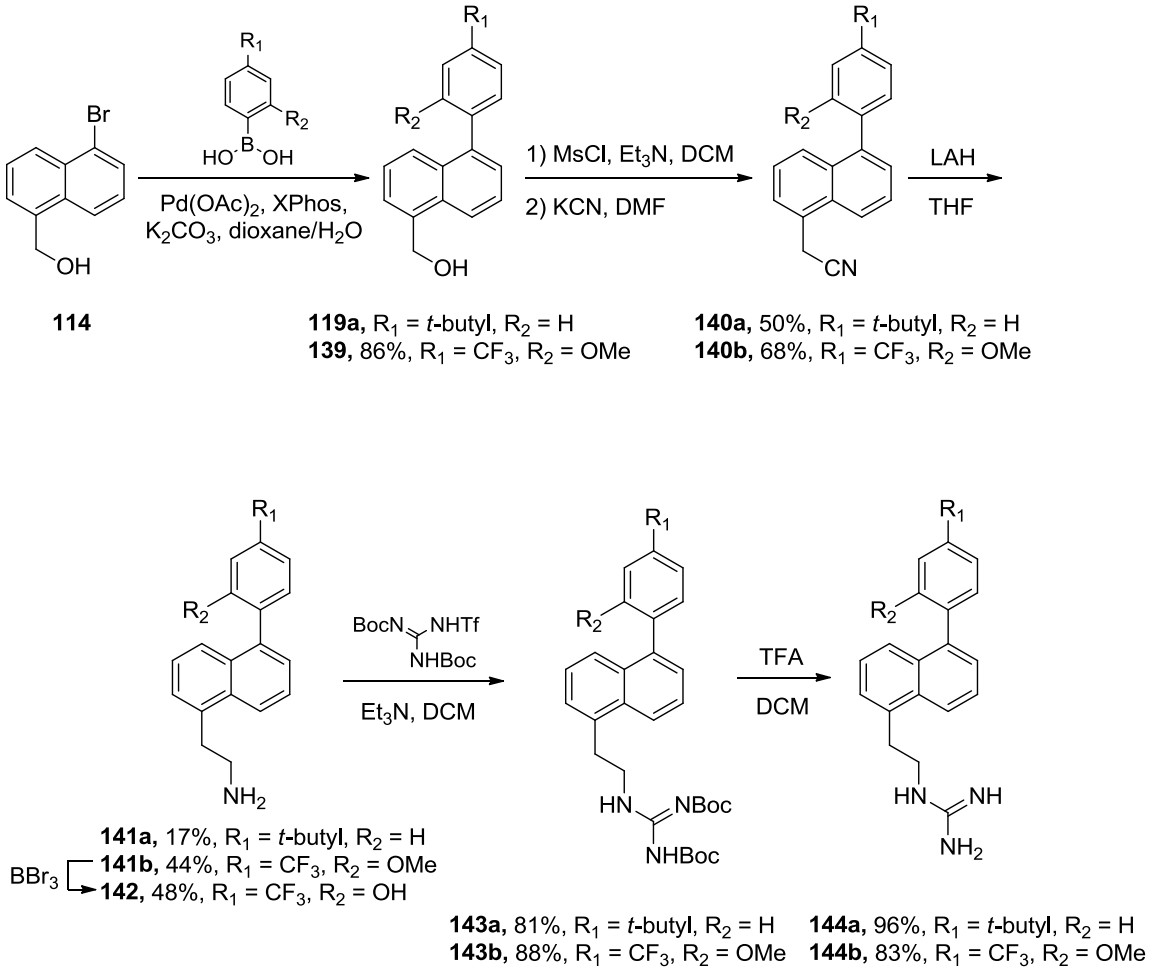
Scheme 21. Synthetic route to compound **134**.

The 2 carbon linker analogs were prepared as shown in Scheme 22 and Scheme 23. Compound **138** was prepared starting from intermediate **118b**. Condensation with nitromethane and ammonium acetate at reflux gave **135**, which was reduced with LAH to give the 2-aminoethyl, **136**. Addition of the protected guanidine with 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethylsulfonyl)guanidine and triethylamine followed by removal of the Boc groups gave the final guanidinoethyl compound, **138**.



Scheme 22. Synthetic route to compound **138**.

Compounds **141a-b**, **142**, and **144a-b** were made as outlined below. Starting from intermediate **114**, Suzuki coupling with the appropriate boronic acid gave the cross-coupled products **119a** (already described previously) and **139**. Treatment with methanesulfonylchloride and triethylamine in dichloromethane followed by potassium cyanide in DMF gave the nitrile derivatives **140a** and **140b**. The nitrile intermediates were reduced with LAH to give the final 2-aminoethyl compounds **141a** and **141b**. For the case of **141b**, treatment with boron tribromide (1.0M in DCM) cleaved the methoxyl group to give the hydroxyl compound **142**. Finally, as seen previously, addition of the protected guanidine with 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethylsulfonyl)guanidine and triethylamine followed by removal of the Boc groups gave the desired guanidinoethyl compounds **144a** and **144b** in good yields. Intermediate **118a** and compound **121a** was prepared by Dr. Ajit Parhi, and intermediate **136** and compounds **124a**, **131a-b**, and **144a** were prepared by Songfeng Lu, both at TAXIS Pharmaceuticals, Inc.



Scheme 23. Synthetic route to compounds **141a-b**, **142**, and **144a-b**.

The relative antibacterial activity of these varied phenylnaphthalenes was evaluated in the 4 strains of bacteria (MSSA, MRSA, VSE, and VRE) as seen previously. The results are summarized in Table 8. The various 4-*t*-butylphenylnaphthalene analogs with identical substituents at either the 4- or 5-position are listed first for comparison (**107**, **109**, **111**, **113**, **121a**, **124a**, **126**, **141a**, and **144a**). The pairs of similarly substituted analogs are the aminomethyl derivatives **107** and **126**; the 2-aminoethyl derivatives, **111** and **141a**; the guanidinomethyl derivatives, **109** and **121a**; and the 2-guanidinoethyl derivatives, **113** and **144a**. When comparing these pairs, there was little notable

difference between the 4- and 5-substitution patterns other than the guanidinoalkyl derivatives, in which case, the 5-substituted analogs **141a** and **144a** displayed slightly greater potency (MICs of 0.5 and 2 μg/mL, respectively) than the 4-substituted analogs **109** and **113** (MICs of 2 μg/mL for both) in MSSA. As seen with the 3-phenylisoquinoline series, the results of the 1-phenylnaphthalene series suggest that the more basic guanidinoalkyl derivatives (**109**, **113**, **141a**, and **144a**) had a tendency to be more active than their corresponding aminoalkyl derivatives (**107**, **111**, **126**, and **141a**) for both the 4- and 5-substituted analogs. The amidinomethyl analog, **124a**, was less active than the guanidomethyl compound **141a**, but displayed comparable activity to the aminoalkyl derivatives **126** and **144a**. Overall, the most active compound was the 5-guanidinomethyl compound **141a** with an MIC of 0.5 μg/mL with MSSA.

Most of the 4-*t*-butylphenylnaphthalene analogs had a tendency to be slightly less active against MRSA and both strains of *E. faecalis*, prompting the investigation of different substitutions on the phenyl ring. In place of the *p*-(*t*-butyl), we evaluated bromine (**131a**), chlorine (**131b**), cyclopropyl (**134**), and trifluoromethyl (**117a**, **117b**, **121b**, **124b**, **138**, **141b**, **142**, and **144b**). The bromine, chlorine, and cyclopropyl analogs displayed comparable activity to the *p*-(*t*-butyl) analogs against MSSA but were only as active as the least potent *p*-(*t*-butyl) analogs when looking at MRSA, VSE, and VRE (MICs of 8 μg/mL for all). No significant improvement in activity was seen with the trifluoromethyl analogs. The addition of a methoxyl or methyl group *meta* to the trifluoromethyl (compounds **117a** and **117b**, respectively) did not significantly alter the antibacterial activity relative to **121b**. As expected based on previous SAR studies, the 2-

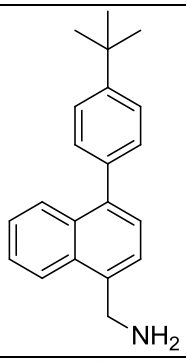
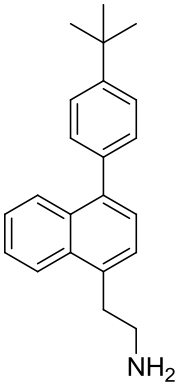
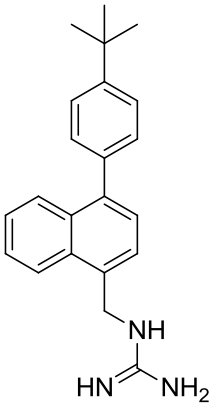
aminoethyl derivatives **141b** and **142** were less active than the similarly substituted 2-guanidinoethyl derivatives **138** and **144b**.

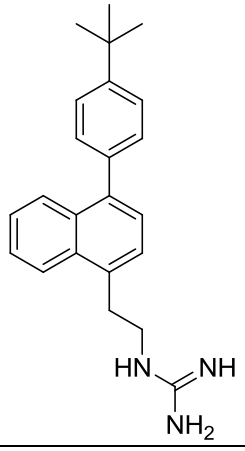
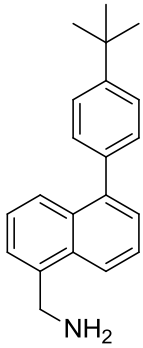
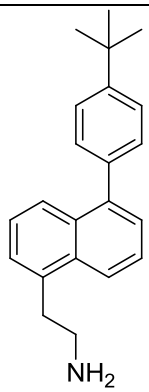
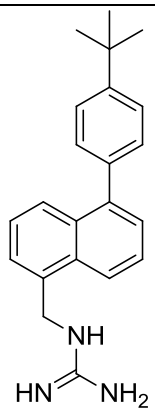
All of the evaluated compounds exhibited higher potency than chelerythrine in both strains of *E. faecalis*, and except for compound **142**, all tested compounds were more active against VSE than sanguinarine. Most of the compounds had activity comparable to sanguinarine against MSSA, with several (**121a**, **134**, **138**, and **144a**) exhibiting improved activity. When comparing relative activity against MRSA, the majority of compounds displayed slightly less potent antibacterial activity than sanguinarine, with only a few exhibiting comparable activity (**109**, **121a**, and **144a**).

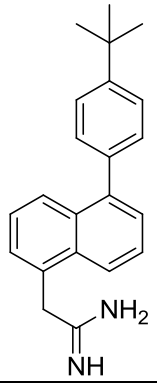
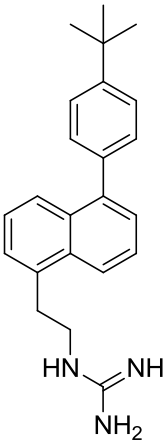
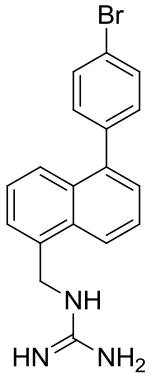
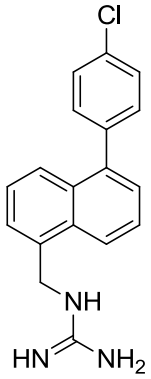
An important feature to note, is that these 4- and 5-substituted 1-phenylnaphthalenes did not have pronounced cross-resistance between the respective methicillin/vancomycin-sensitive strains and the methicillin/vancomycin-resistant strains. This is best visualized by comparing the 4-*t*-butylphenylnaphthalene analogs (**107**, **109**, **111**, **113**, **121a**, **124a**, **126**, **141a**, and **144a**) where there is less than a one-well difference in MIC values between the sensitive and resistant strains of each respective bacteria. The potency of these compounds against the resistant strains becomes clearly obvious when comparing their MIC values to the clinical standards used in this study. Other than vancomycin, which has an MIC of 2 μg/mL versus MRSA, all other clinical antibiotics (oxacillin, erythromycin, tetracycline, and clindamycin) have MIC values ≥ 64 μg/mL. Compounds **109**, **121a**, and **144a** had MICs comparable to that of vancomycin versus MRSA, and all compounds evaluated had significantly lower MICs than the other 4 clinical controls. When looking at VRE, all 5 clinical compounds have MICs ≥ 64 μg/mL, whereas all synthesized analogs that were tested displayed MIC values of ≤ 8

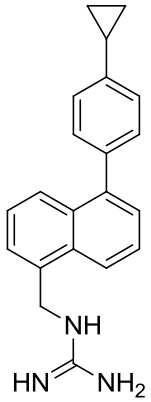
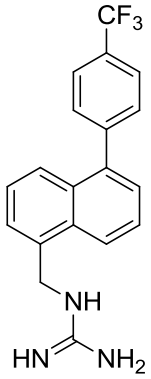
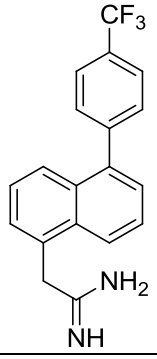
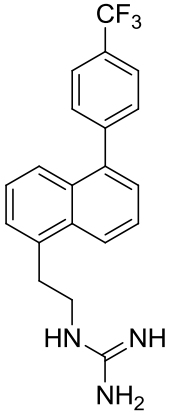
μg/mL, except for **124b** and **142**, which have MICs of 16 μg/mL (but still significantly lower than clinical test standards).

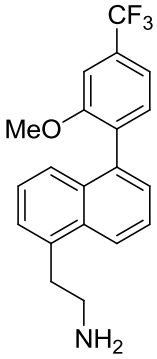
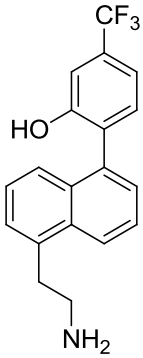
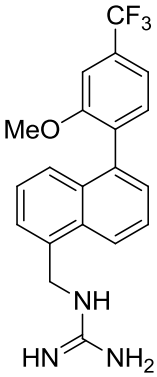
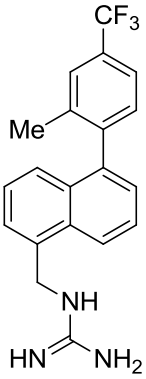
Table 8. Biological activity of 4- and 5-substituted 1-phenylnaphthalene derivatives.

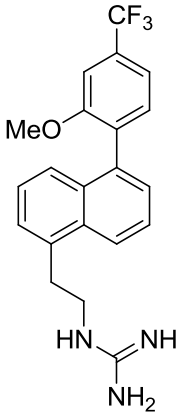
	Compound Structure	**[a]MIC (μg/mL)**			
		***S. aureus* 8325-4 (MSSA)**	***S. aureus* ATCC 33591 (MRSA)**	***E. faecalis* ATCC 19433 (VSE)**	***E. faecalis* ATCC 51575 (VRE)**
107		4	8	8	8
111		4	4	4	4
109		2	2	2	2

113		2	4	2	4
126		4	4	8	8
141a		2	4	2	4
121a		0.5	2	2	4

124a		4	4	4	8
144a		1	2	2	2
131a		2	8	8	8
131b		2	8	8	8

134		1	8	8	8
121b		4	8	4	8
124b		2	8	8	16
138		1	4	4	4

141b		8	16	8	8
142		8	16	16	16
117a		2	8	4	4
117b		2	ND	ND	ND

144b		2	8	4	4
	Sanguinarine	**2**	**2**	**8**	**16**
	Chelerythrine	**4**	**4**	**32**	**32**
	Oxacillin	**0.06**	**>64**	**8**	**64**
	Vancomycin	**1**	**2**	**1**	**>64**
	Erythromycin	**0.13**	**>64**	**1**	**>64**
	Tetracycline	**0.06**	**64**	**0.5**	**>64**
	Clindamycin	**0.3**	**>64**	**2**	**>64**

[a]Minimum inhibitory concentration (MIC) assays were conducted in accordance with Clinical Laboratory Standards Institute (CLSI) guidelines for broth microdilution.[73] MIC is defined as the lowest compound concentration at which bacterial growth is ≥90% inhibited.

To determine whether these 1-phenylnaphthalenes produce their observed antibiotic effects by altering FtsZ dynamics, select compounds from this series were evaluated in the SaFtsZ self-polymerization turbidity assay described earlier with the isoquinolines. Figure 18 shows the time-dependent A_{340} profiles of compounds **141a** and **121a** at 40 μg/mL, as illustrative examples with DMSO as the vehicle and the non-FtsZ-targeting vancomycin as a standard comparator. As expected, vancomycin had no significant effect on SaFtsZ polymerization, in stark contrast to compounds **141a** and **121a**, which profoundly increased both the kinetics and the extent of SaFtsZ polymerization. These polymerization results are similar to that seen with the 3-phenylisoquinoline series and support the idea that the 1-phenylnaphthalenes may also exert their antibiotic effects, at least in part, by stimulating FtsZ polymerization.

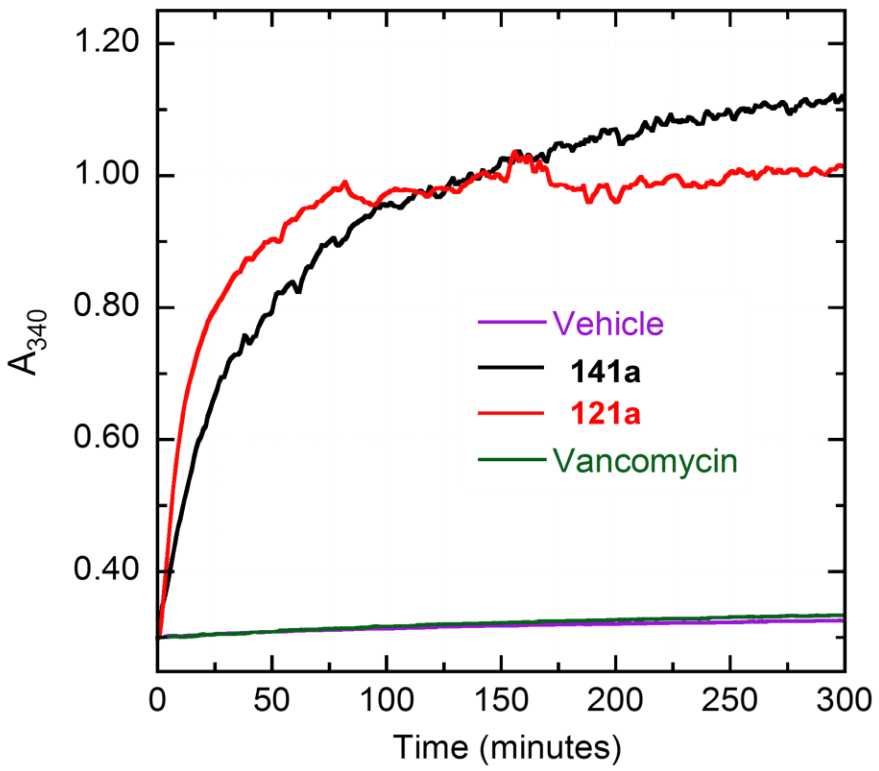


Figure 18. Impact of **141a** and **121a** (40 μg/mL) on SaFtsZ (10 μM) polymerization as determined by monitoring time-dependent changes in absorbance at 340 nm (A_{340}).

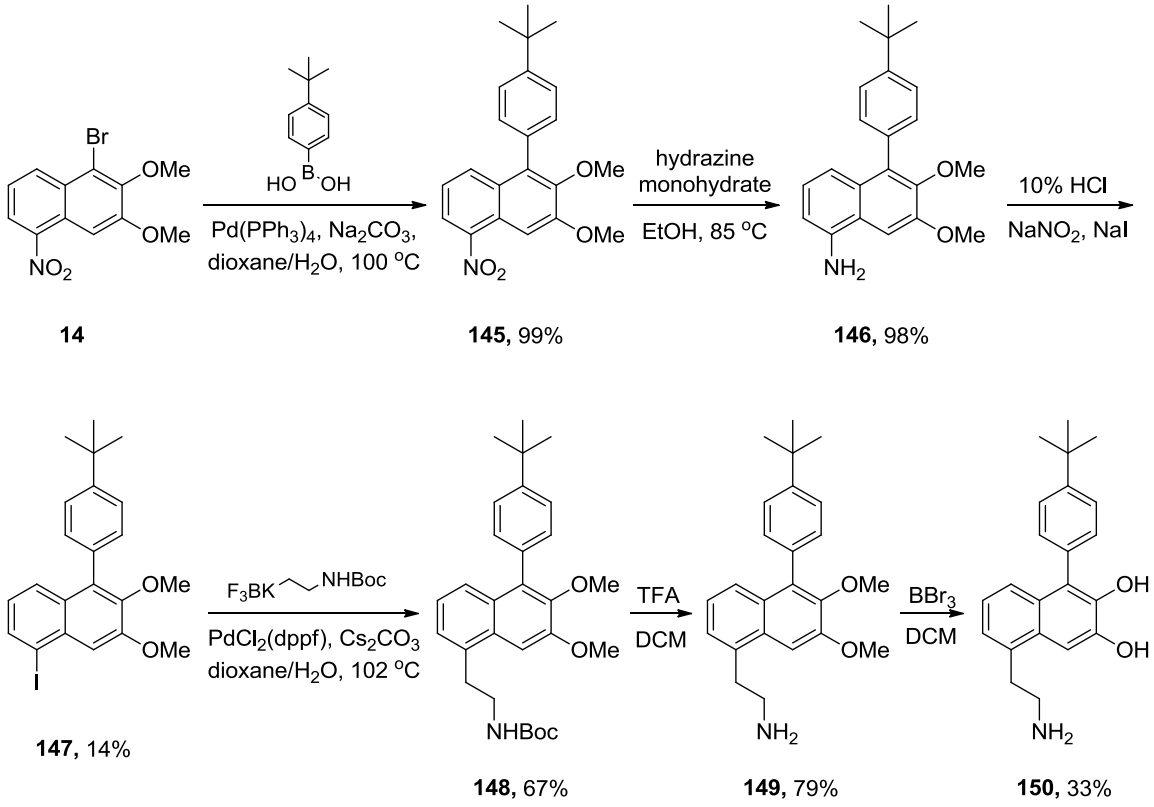
At this point, we were now in a similar situation to that of the 3-phenylisoquinolines. We had a series of compounds that displayed antibacterial activity and could be easily formulated for *in vivo* testing. We now had to determine whether the protein binding of these compounds would preclude them from giving us efficacy *in vivo* the way it did for the 3-phenylisoquinolines. Because we were unable to significantly increase the potency observed for the 1-phenylnaphthalenes from the 3-phenylisoquinolines, we had to rely strictly on the inherent ability of our compounds to either bind or not bind to protein. Unfortunately, as seen with the previous series, both the 4- and 5-substituted 1-phenylnaphthalenes experience at least a 2-well shift higher in

MIC values when evaluated in the presence of serum. Given that neither the potency of these compounds was increased nor, alternatively, the protein binding decreased, none of the 4- and 5-substituted 1-phenylnaphthalenes that were synthesized were viewed as suitable for *in vivo* efficacy studies.

To this extent, a couple more 1-phenylnaphthalene analogs containing a 2,3-substitution pattern were made to see if antibacterial activity could be improved (or protein binding decreased). Likewise, some 5-substituted 2-phenylnaphthalenes were synthesized to evaluate if movement of the phenyl substitution on the naphthalene ring would improve activity or decrease protein binding. For these analogs, MIC studies were not conducted against every strain of bacteria as seen with most compounds previously. The primary parameter was focused on the difference in MIC values against MSSA in the presence or absence of serum protein.

The 2,3-substituted 1-phenylnaphthalenes were prepared as outlined in Scheme 23. Starting with intermediate **14** from the benzo[*c*]phenanthridine series, a Suzuki coupling with 4-*t*-butylphenylboronic acid, tetrakis, and sodium carbonate in a refluxing mixture of dioxane and water (4:1) gave the cross-coupled product, **145** quantitatively. Reduction of the nitro group with hydrazine monohydrate in refluxing ethanol gave the amine, **146**. Conversion of the amine to the iodo via the Sandmeyer reaction resulted in compound **147**, albeit, in poor yield.[92] The Suzuki coupling with Molander's trifluoroborate salt was conducted using the same conditions as previous (tetrakis and K_3PO_4) but did not work in this case. Instead, the catalyst/ligand system and base were switched to [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane - $PdCl_2$(dppf) and cesium carbonate to give the cross-coupled product

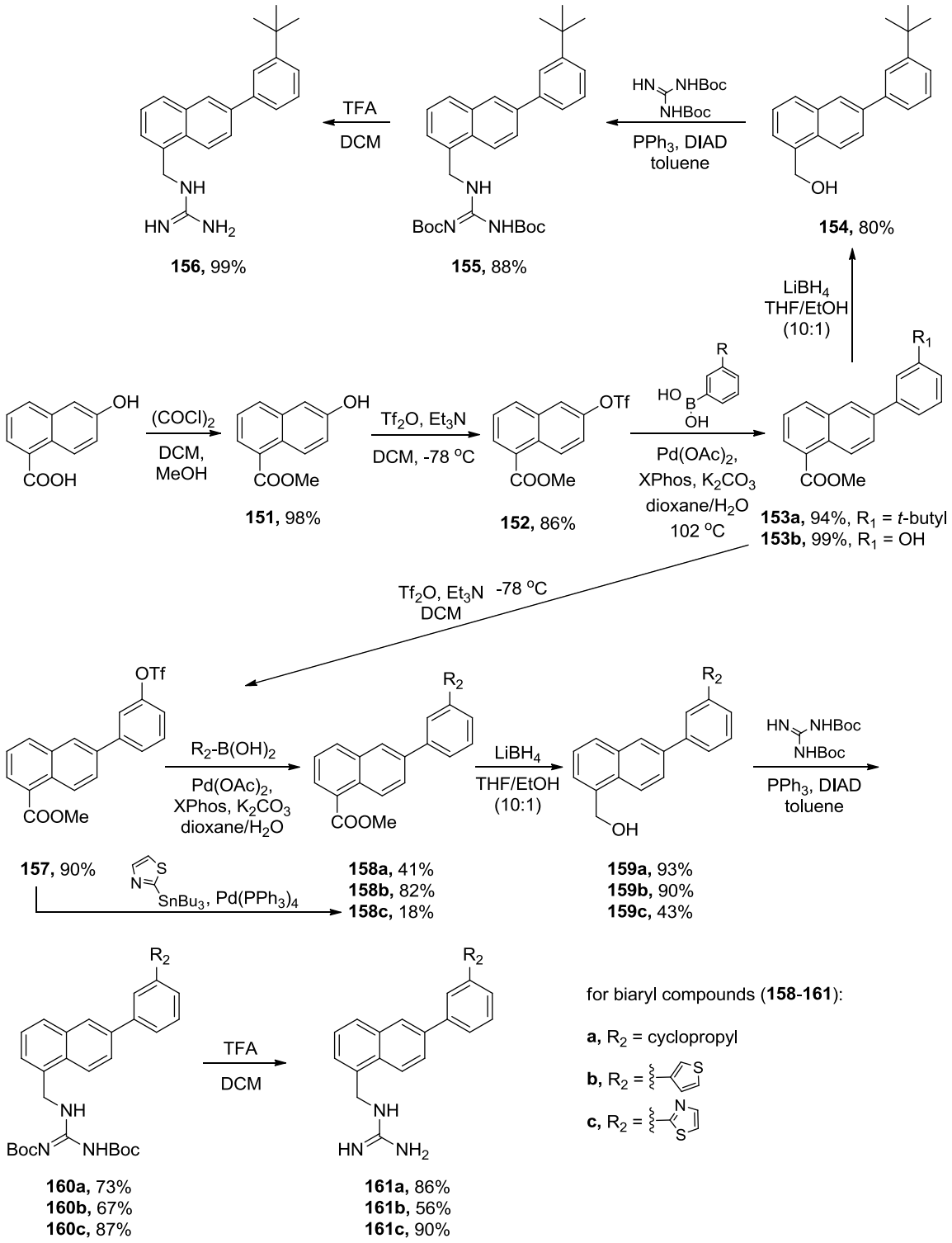
148.[83,84] Removal of the Boc group with trifluoroacetic acid gave the 2-aminoethyl compound **149**, and subsequent cleavage of the methyl group from the methoxyls with boron tribromide gave the dihydroxy compound **150**.



Scheme 24. Synthetic route to compounds **146**, **149**, and **150**.

The 2-phenylnaphthalene analogs were prepared as outlined in Scheme 25. Commercially available 6-hydroxy-1-naphthoic acid was converted to its methyl ester by treatment with oxalyl chloride and methanol to give **151** in high yield.[93] Triflation of the hydroxyl group with triflic anhydride and triethylamine at -78 °C gave intermediate **152**, which was then used for two separate Suzuki cross-couplings with either 3-*t*-butylphenylboronic acid (for **153a**) or 3-hydroxyphenylboronic acid (for **153b**) to evaluate different 3-substituted phenyl groups at that position. Reduction of the methyl

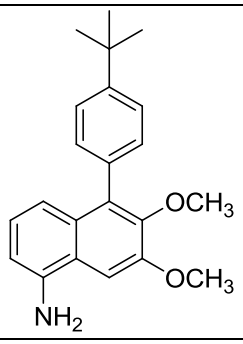
ester of **153a** gave **154** in good yield followed by a Mitsunobu reaction using 1,3-bis-(*t*-butoxycarbonyl)guanidine to give **155**. Removal of the Boc groups with trifluoroacetic acid gave final guanidinomethyl compound **156**. Intermediate **153b** was subjected to another triflation to give intermediate **157**, which was then used in several palladium-catalyzed cross-couplings with either cyclopropylboronic acid (for **158a**), 3-thienylboronic acid (for **158b**), or 2-(tributylstannyl)thiazole (for **158c**). Then, similar to what was done with the 3-*t*-butyl analog, reduction of the methyl ester followed by a Mitsunobu reaction using 1,3-bis-(*t*-butoxycarbonyl)guanidine and a removal of the Boc groups gave compounds **161a**, **161b**, and **161c**.

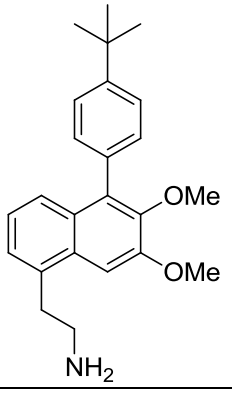
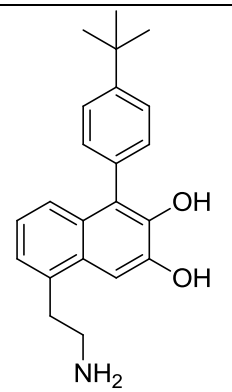
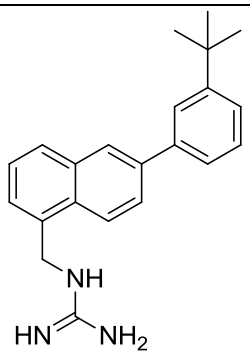
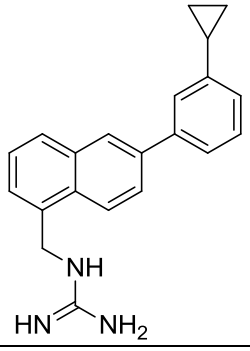


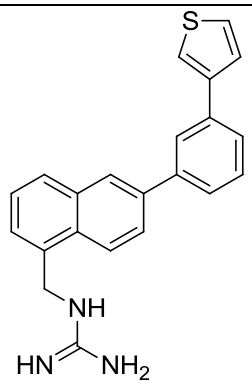
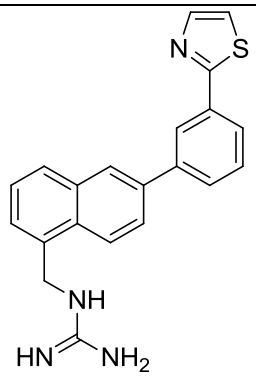
Scheme 25. Synthetic route for 5-guanidinomethyl 2-phenylnaphthalene derivatives.

This subset of compounds was then evaluated for antibacterial activity against MSSA, in the absence and presence of mouse serum. The results are summarized in Table 9. As expected, compound **146** exhibited no significant activity against MSSA alone, but extending the amino group (increasing basicity) as in compounds **149** and **150**, resulted in much improved potency. In the presence of serum protein, however, the MIC values went up 3-wells to 16 μg/mL. The same held true for the 2-phenylnaphthalene derivatives (**161a-c**), which exhibited antibacterial activity when evaluated alone against MSSA, but dropped significantly in potency in the presence of serum. Based upon these results, it was concluded that the entire series of phenylnaphthalenes would be insufficient for achieving *in vivo* efficacy.

Table 9. Biological activity against MSSA in the absence and presence of serum for 2,3-disubstituted 5-guanidinomethyl 1-phenylnaphthalene and 5-guanidinomethyl 2-phenylnaphthalene derivatives.

	Compound Structure	**MIC vs MSSA (μg/mL)**	**MIC vs MSSA 50% Mouse Serum (μg/mL)**
146		>64.0	>64.0

149		4	32
150		4	32
156		1	16
161a		2	16

161b		1	64
161c		2	16

2.6 Synthesis and Evaluation of 2-Phenylquinolines and 3-Methoxybenzamide Bioisosteres.

Our group decided to split up efforts to design and synthesize multiple new scaffolds in attempt to overcome the protein binding problem associated with the isoquinoline and naphthalene derivatives. One such attempt was to evaluate the movement of the nitrogen in the isoquinoline series to a quinoline series to see whether this would affect either protein binding or potency. Initially, there were two proposed ring closure procedures that could give the desired intermediate (Figure 19). Condensation of methyl propiolate with 3-aminocyclohex-2-enone followed by aromatization of the ring could give the desired quinolone intermediate. Alternatively,

condensation of 3-aminobenzoic acid with the acid chloride of ethyl 3-ethoxyacrylate could also give a quinolone intermediate.

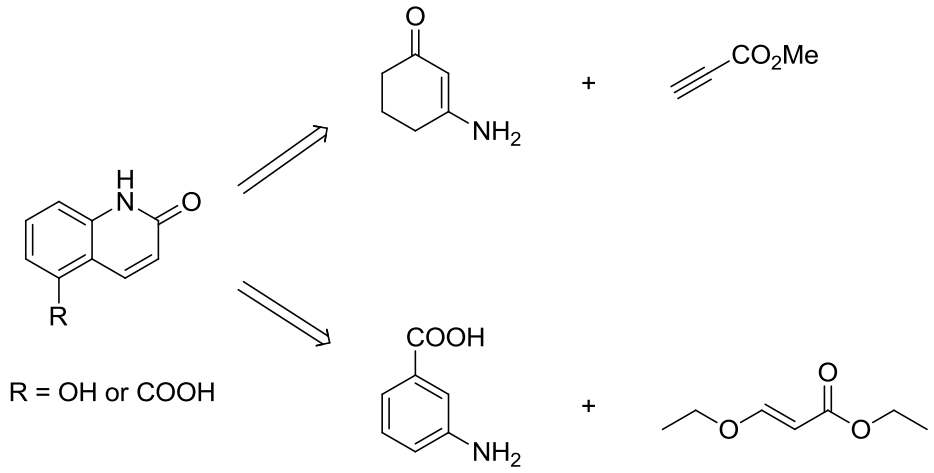
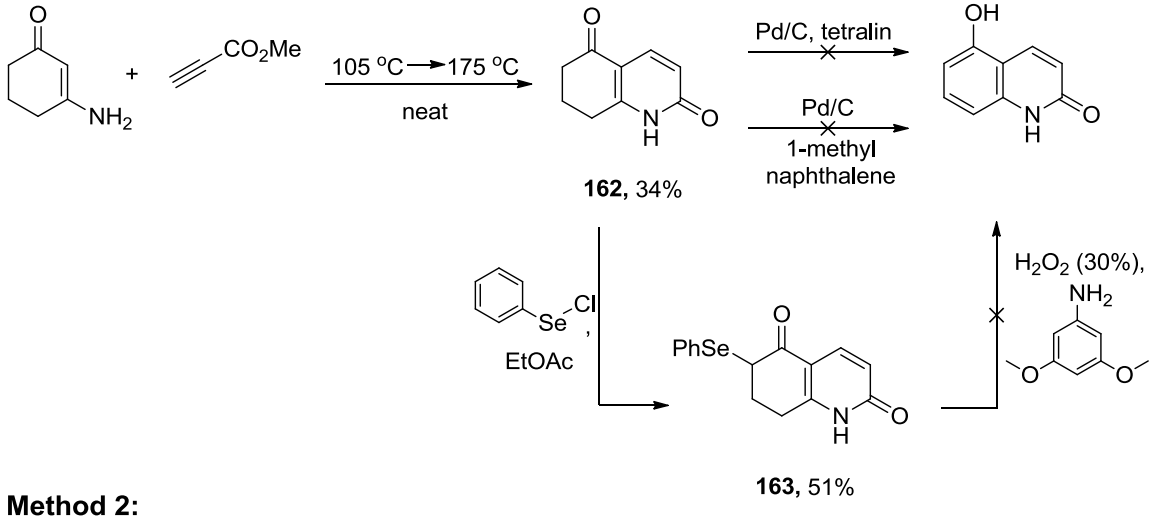


Figure 19. Proposed retrosynthesis for key quinolone intermediate.

The condensation of methyl propiolate with 3-aminocyclohex-2-enone proceeded in modest yield to give compound **162**.[94] However, multiple attempts at aromatization to the phenol were unsuccessful (Figure 20). Treatment with Pd/C (10 wt.) and tetralin, as done in the dibenzo[*a*,*g*]quinolizin-7-ium series, resulted in almost no detectable product. Refluxing with Pd/C (10 wt.) in 1-methylnaphthalene also proved unsuccessful. Following a literature procedure for the preparation of phenols from polycyclic aromatic ketones, α-phenylselenation of the cyclohexenone with phenylselenium chloride resulted in compound **163** in moderate yield.[95] Unfortunately, subsequent attempts at oxidation with hydrogen peroxide to give the desired product were unsuccessful. The alternative cyclization procedure,[96] Method B, was also unsuccessful.

Method 1:



Method 2:

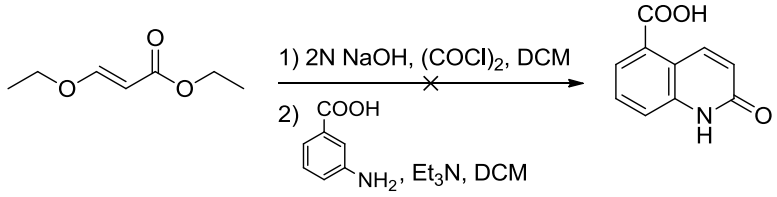
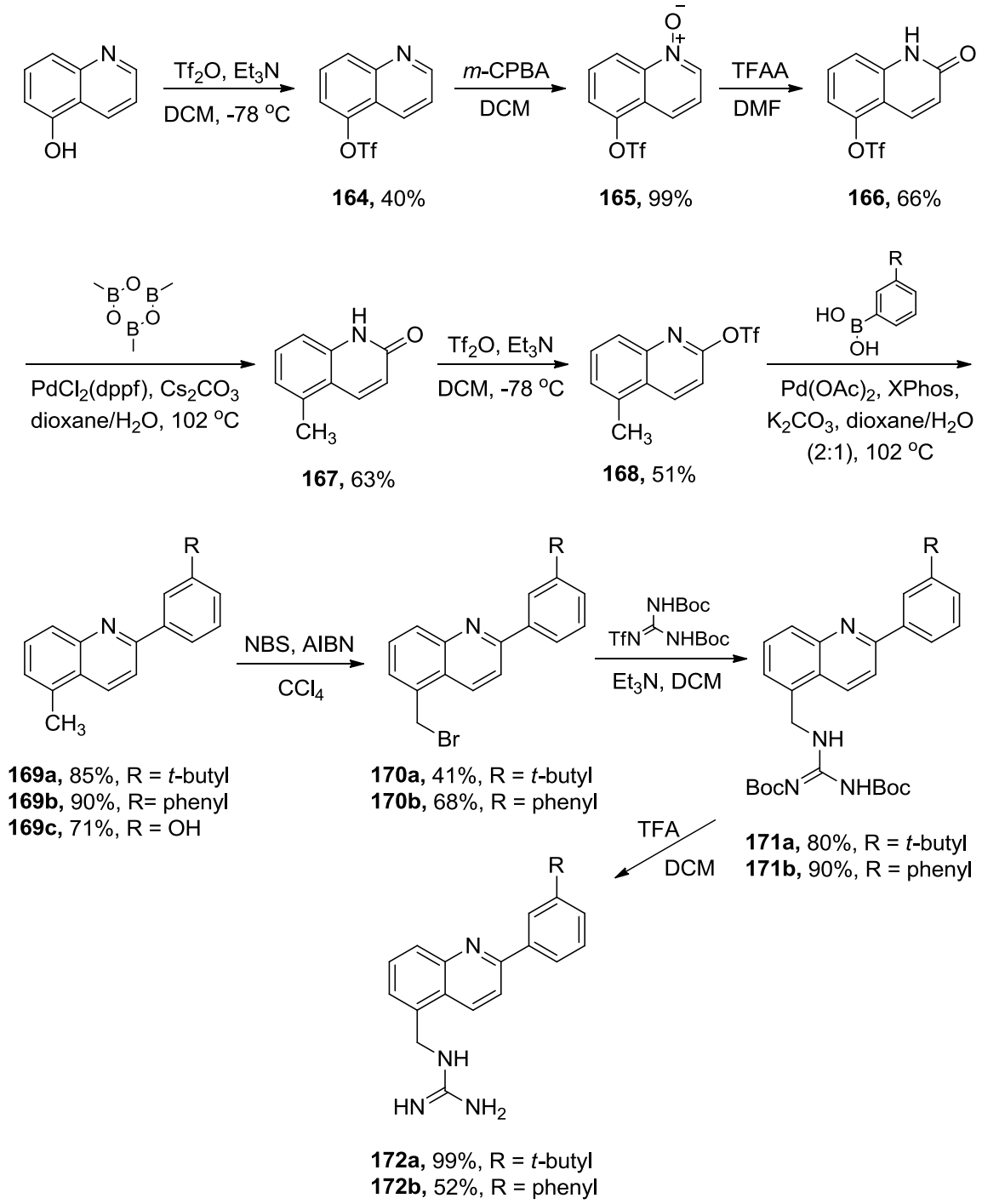


Figure 20. Attempts at obtaining key quinolone intermediate.

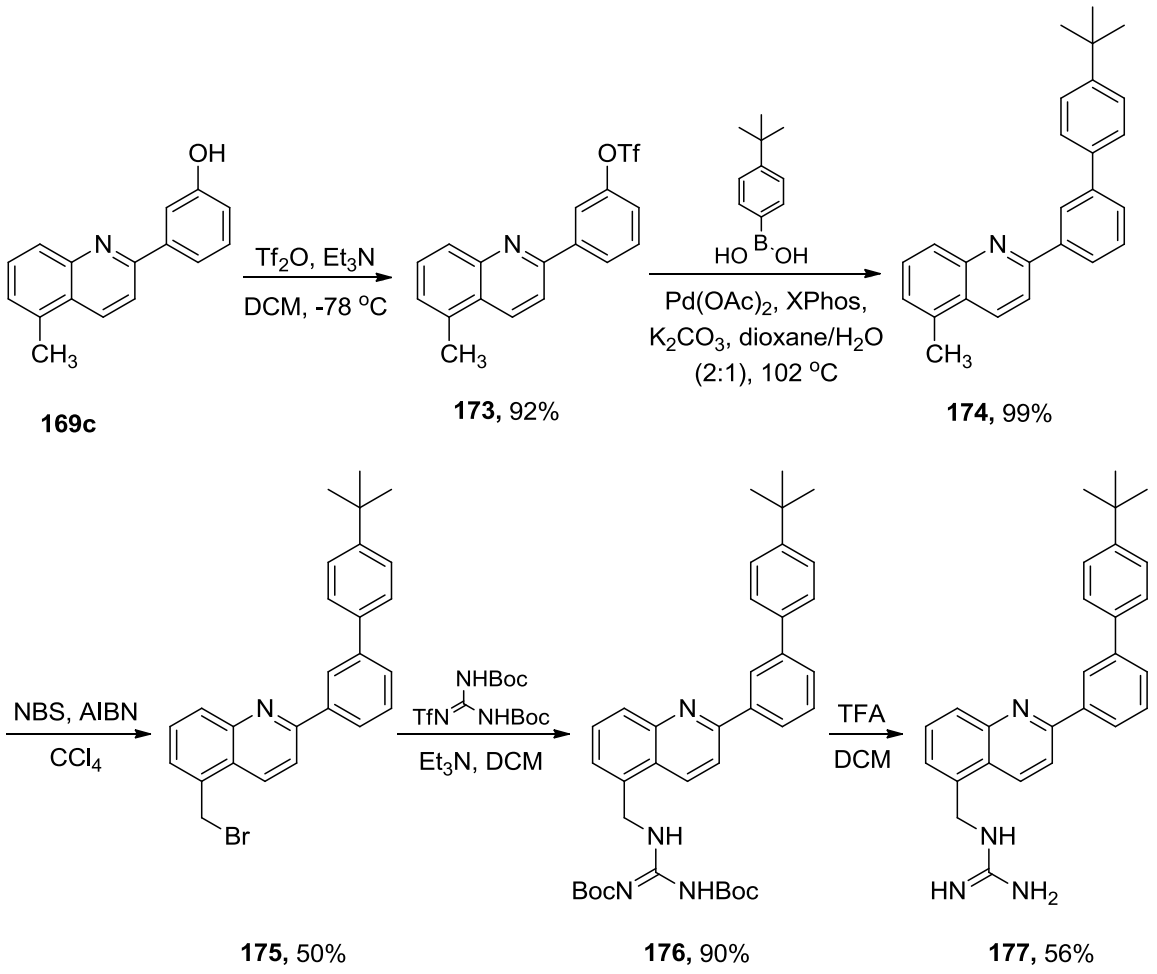
The procedure that eventually led to the desired products is outlined in Scheme 26. Quinolin-5-ol was triflated with triflic anhydride and triethylamine in anhydrous DCM at -78 ^{o}C to give **164** in moderate yield. Treatment with *m*-CPBA gave the *N*-oxide intermediate **165** quantitatively, which was then treated with trifluoroacetic anhydride to finally give the desired quinolone intermediate **166**. A Suzuki coupling with trimethylboroxine, $PdCl_2$(dppf), and cesium carbonate in refluxing dioxane and water (2:1) gave the cross-coupled product **167**. A second triflation gave key intermediate **168**, which was then used to make several derivatives.



Scheme 26. Synthetic route for compounds **172a** and **172b**.

Suzuki couplings with the appropriate boronic acids (3-*t*-butylphenylboronic acid for **169a**, 3-biphenylboronic acid for **169b**, and 3-hydroxyphenylboronic acid for **169c**)

gave the respective cross-coupled products **169a-c**. Radical bromination of the methyl group of **169a** and **169b** with *N*-bromosuccinimide in carbon tetrachloride using azobisisobutyronitrile as the radical initiator gave the bromomethyl derivatives **170a** and **170b**. Displacement of the bromide with 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethanesulfonyl)guanidine gave the protected guanidomethyl derivatives **171a** and **171b**, followed by removal of the Boc groups with trifluoroacetic acid in dichloromethane to give final compounds **172a** and **172b**.



169c

173, 92%

174, 99%

175, 50%

176, 90%

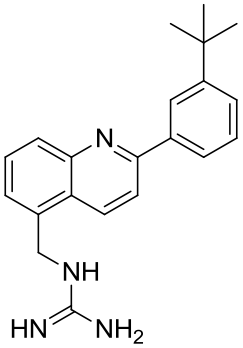
177, 56%

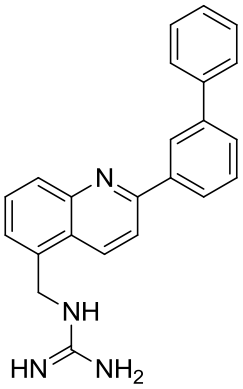
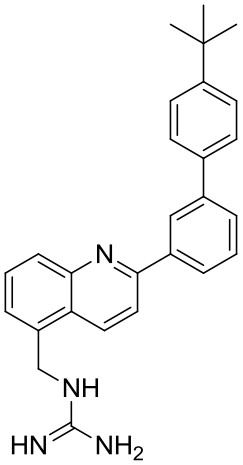
Scheme 27. Synthetic route to compound **177**.

Intermediate **169c** was subjected to an additional triflation to give compound **173**, which was then Suzuki coupled with 4-*t*-butylphenylboronic acid to give **174** (Scheme 27). **174** was then brominated with NBS and AIBN to give the bromomethyl derivative **175**. Displacement of the bromide with 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethanesulfonyl)guanidine gave the protected guanidomethyl derivative **176**, followed by removal of the Boc groups with trifluoroacetic acid in dichloromethane to give compound **177**.

These three quinoline derivatives were then evaluated for their biological activity against MSSA with and without protein present to see if there were any improvements. The results are summarized in Table 10. Although **171a**, **171b**, and **177** all demonstrate respectable antibiotic activity in the absence of protein, the MIC values dramatically increase in the presence of protein. These data were enough of an indication for us to drop any further efforts to develop in this series.

Table 10. Biological activity of 5-guanidinomethyl 2-phenylquinoline derivatives.

	Compound Structure	**MIC vs MSSA (μg/mL)**	**MIC vs MSSA 50% Mouse Serum (μg/mL)**
171a		4	64

171b		2	32
177		2	64

In addition to these 2-phenylquinolines, many 3-phenylquinoliniums, biaryls, diazanaphthalenes, and 1,6-diphenylnaphthalenes were synthesized and evaluated by various members of TAXIS Pharmaceuticals (not shown). Although these efforts resulted in many active compounds, none could overcome the issue of protein binding and serve as suitable candidates for *in vivo* testing. As a result, we shifted completely away from using sanguinarine and berberine as a lead and moved to a new chemical scaffold. 3-Methoxybenzamide (3-MBA) has been shown to be an inhibitor of FtsZ, and the synthetic analog derived from 3-MBA, PC190723, has been reported to be extremely potent and efficacious *in vivo*.[68,69] Our in-house data show that 3-MBA has an MIC of 1024 μg/mL against MSSA (Figure 21). 2,6-Difluoro-3-methoxybenzamide, the

truncated 3-MBA portion of PC190723, is more active than 3-MBA, with an MIC of 256 μg/mL against MSSA.

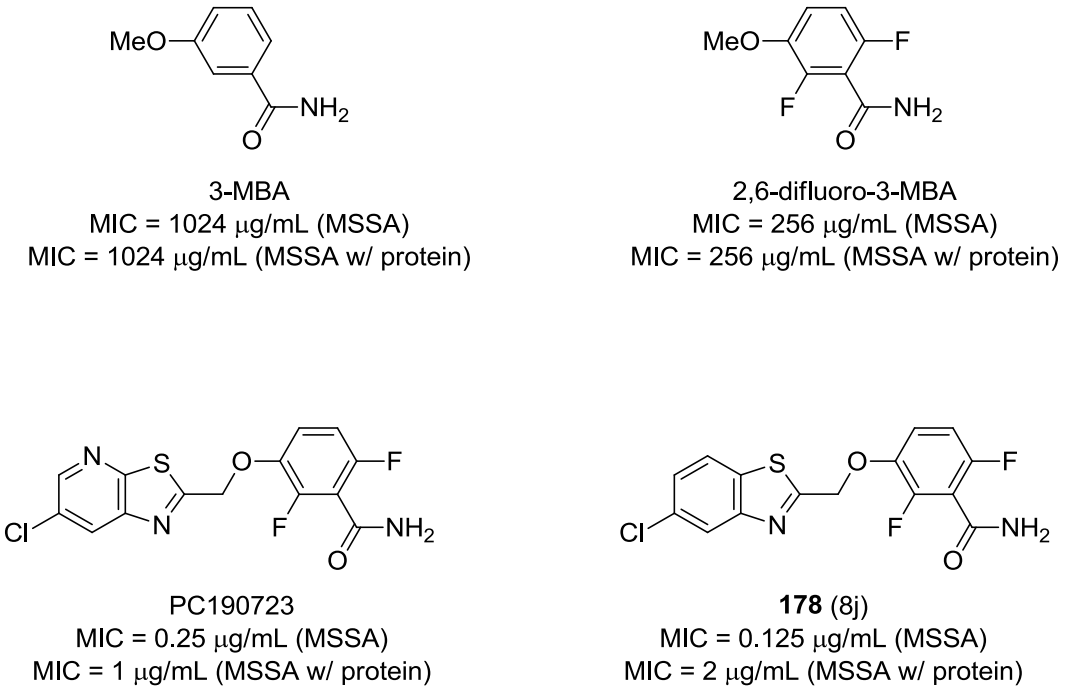


Figure 21. Chemical structures and MIC values of 3-methoxybenzamide, 2,6-difluoro3-methoxybenzamide, PC190723, and **178** (8j).

PC190723 is >1000-fold more active than 2,6-difluoro-3-MBA (MIC = 0.25 μg/mL), but similar to what we had seen with our synthesized analogs, PC190723 displays a large shift in its MIC value when evaluated in the presence of protein. Despite this huge decrease in potency, PC190723 is still extremely active (MIC = 1 μg/mL). Compound **178** (8j) with a similar structure to PC190723, synthesized by the same group, has a very similar profile to that of PC190723.[97] Even though these compounds are just as affected by protein binding as the analogs synthesized and evaluated in our previous series, the overall activity is so potent that their MIC values in the presence of protein are

still comparable to some of our best compounds in the absence of protein. This potency observed with PC190723 and **178** was more than enough reason to investigate these types of compounds more closely.

We began this area of work by synthesizing and evaluating some cyclic bioisosteres of the amide functionality in 3-MBA with hopes of increasing potency. The most commonly employed bioisosteres of amides are azole heterocycles.[98,99] As such, several azole heterocycles were prepared as outlined in Figure 22. Starting with readily available 3-methoxybenzoic acid, treatment with oxalyl chloride in anhydrous dichloromethane and a catalytic amount of DMF gave the acid chloride, followed by the addition of freshly prepared sodium hydrogen cyanamide to give the iminomethyleneamide intermediate, which was taken crude and reacted with hydroxylamine hydrochloride in pyridine to give **179**.[100] Alternatively, treatment of the same starting material with thiosemicarbazole and phosphorus(V)oxychloride gave **180** in good yield.[100] Compounds **181** and **182** were synthesized by Dr. Kurt Saionz, and compound **183** was synthesized by Yongzheng Zhang, both at TAXIS Pharmaceuticals.

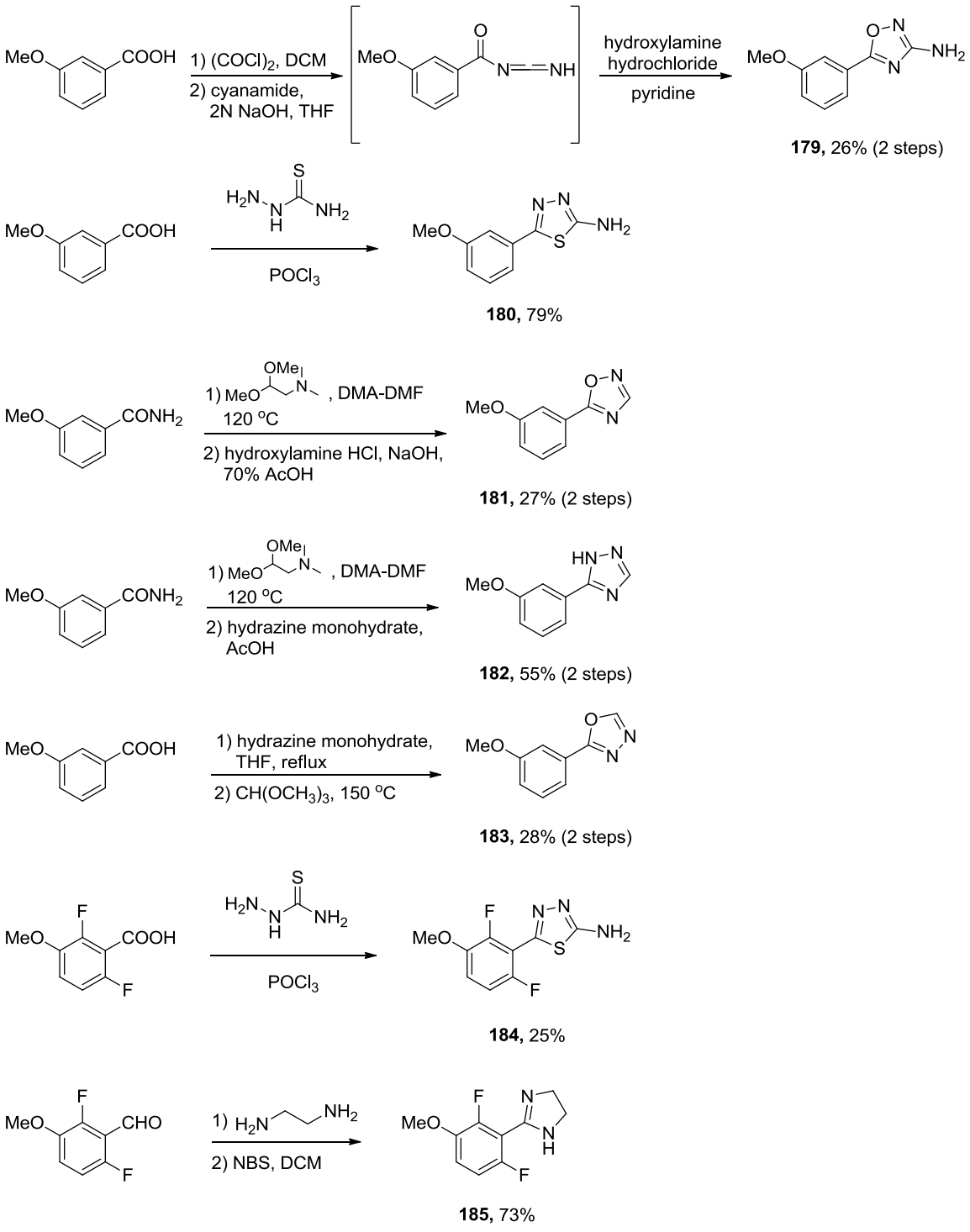
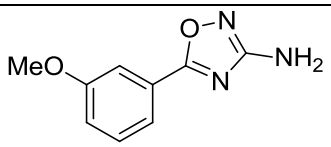
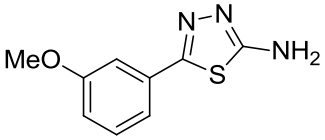
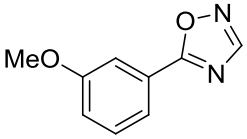
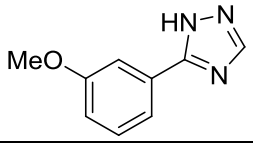


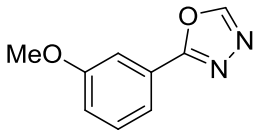
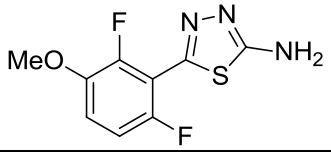
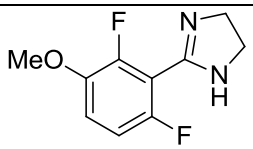
Figure 22. Preparation of various 3-heterocyclic anisole derivatives.

In addition to **179-183**, a couple 2,6-difluoro analogs were also made. Treatment of 2,6-difluoro-3-methoxybenzoic acid with thiosemicarbazide and phosphorus(V)oxychloride gave **184**. Compound **185** was made from 2,6-difluoro-3-methoxybenzaldehyde by first treating with ethylenediamine and then *N*-bromosuccinimide.[101]

These seven compounds were then evaluated for their antibacterial activity against MSSA in the absence and presence of protein. The results are summarized in Table 11. Although we did not expect to see extremely potent activity with any of these compounds, we wanted to evaluate them in case we could see an early hint of activity from which we could build off of. None of them, however, displayed promising activity.

Table 11. Biological activity for the 3-heterocyclic anisole derivatives.

	Compound Structure	**MIC vs MSSA (μg/mL)**	**MIC vs MSSA 50% Mouse Serum (μg/mL)**
179		>512	>512
180		>512	>512
181		>512	>512
182		>512	>512

183		>512	>512
184		>512	>512
185		>512	>512

Nonetheless, several of these compounds were taken a couple steps further to evaluate their activity when attached to the 5-chlorobenzo[*d*]thiazole, as in compound **178**. The methoxyl was cleaved to the phenol with boron tribromide to give compounds **186-190**, and the ether linkage was formed by stirring these phenols in DMF with potassium carbonate and 2-(bromomethyl)-5-chlorobenzo[*d*]thiazole to give compounds **191-195** (Figure 23).

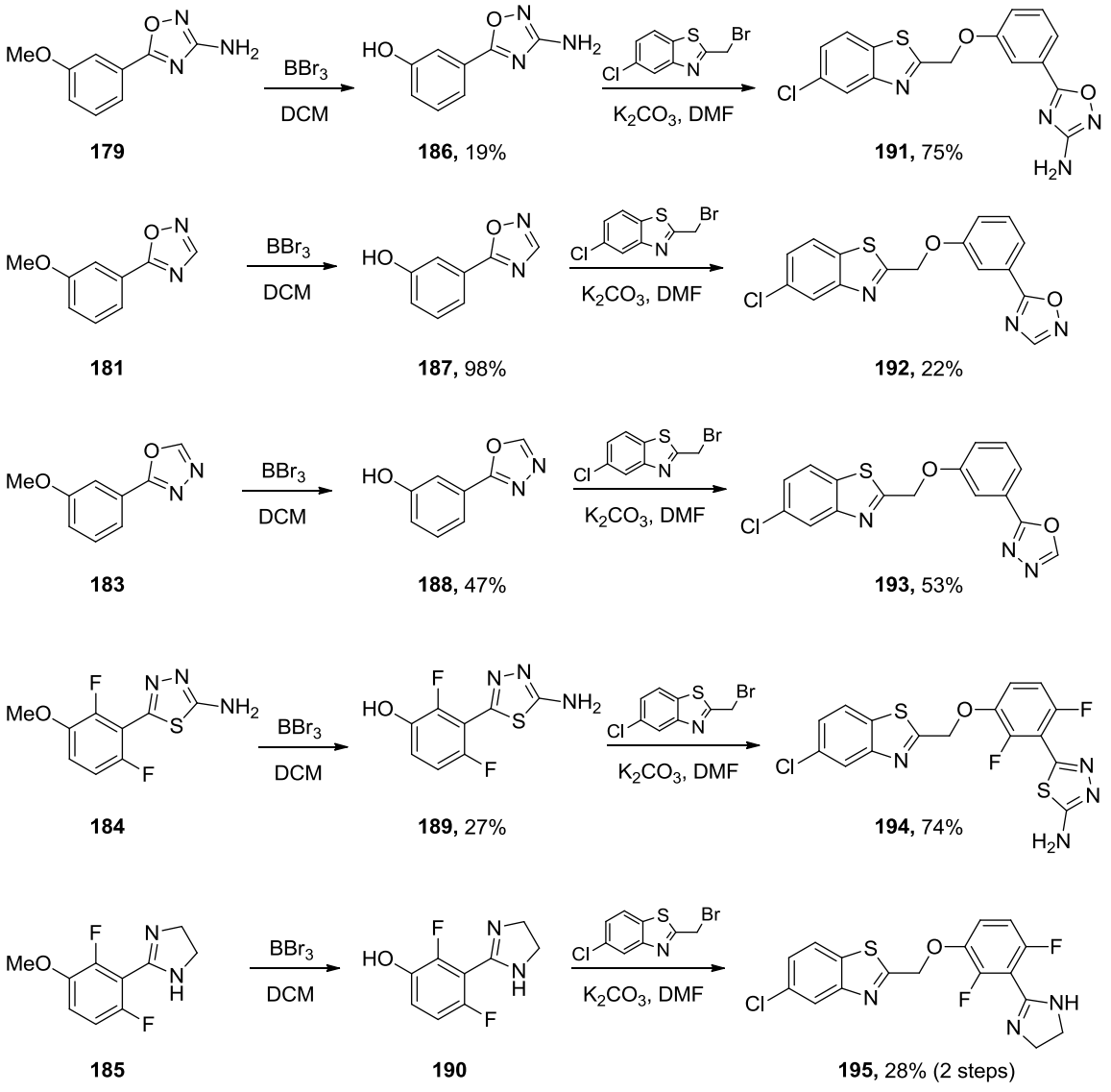
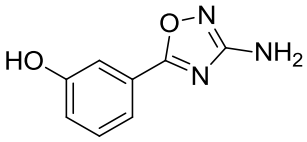
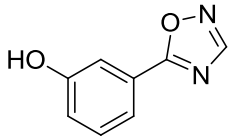
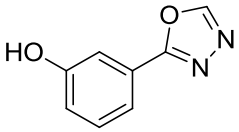
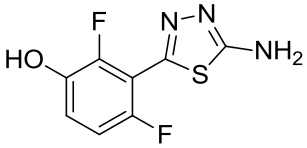
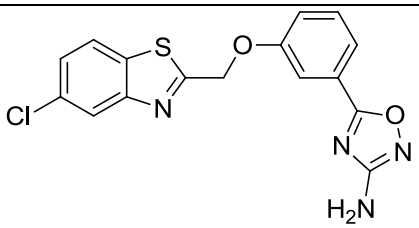
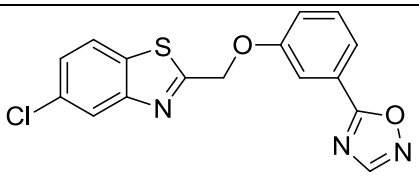
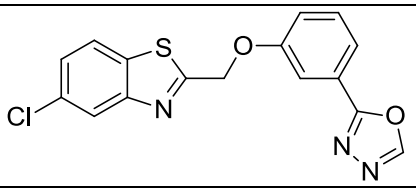


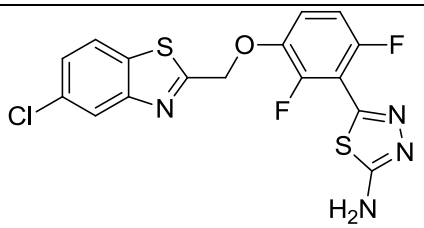
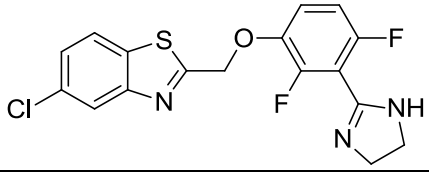
Figure 23. Preparation of compounds **186-195**.

Compounds **191-195**, along with the phenol intermediates, **186-189**, were then evaluated in the biological assay against MSSA in the absence and presence of protein. The results are summarized in Table 12. Although we were hoping to get some better activity with the linked compounds **191-195**, they did not exhibit signs of improved antibacterial activity. Based on these results, it was clear that these heterocyclic analogs were not suitable for further investigation. Although these analogs proved unsuccessful,

ongoing studies are being continued to investigate improved solubility of these types of analogs, as well as a broader spectrum of activity.

Table 12. Biological activity of compounds **186-189** and **191-195**.

	Compound Structure	**MIC vs MSSA (μg/mL)**	**MIC vs MSSA 50% Mouse Serum (μg/mL)**
186		>64	>64
187		>64	>64
188		>64	>64
189		>64	>64
191		>64	>64
192		>64	>64
193		>64	>64

194		>64	>64
195		>64	>64

SUMMARY

Bacterial infections and the emerging prevalence of multi-drug resistant strains of bacteria have intensified the search for new antibiotics with novel mechanisms of action. FtsZ, an essential and highly conserved bacterial cell division protein, represents a novel and promising therapeutic target. FtsZ is a GTPase, structurally similar to tubulin, and it is the first protein to localize to mid-cell at the onset of cell division. FtsZ is responsible for polymerizing and forming the dynamic Z-ring, which serves as a scaffold for the recruitment of the remaining essential cell division proteins and provides the constricting force for the cell wall and cell membrane. FtsZ therefore plays a crucial role in the entire cell division process, making it a key target for inhibiting bacterial growth.

There have been quite a few FtsZ inhibitors identified in the literature. These include natural products as well as synthetic analogs, which provide good proof of concept and validate FtsZ as a potential clinically useful target. The majority of these compounds, however, possess various features which would preclude them from clinical use, at least in their current form. The primary feature that limits further development is potency, but there are other limitations relating to their druggability, such as solubility

and toxicity, which also hold these compounds back. There is clearly a need to further refine the current scaffolds, or design completely new ones, before a true clinically useful FtsZ inhibitor is identified.

Our research efforts in this field began with modifying the chemical structures of two plant alkaloids reported to be FtsZ inhibitors: sanguinarine and berberine. Focused on sanguinarine first, a variety of 1- and 12-substituted 5-methylbenzo[*c*]phenanthridines were synthesized and evaluated for their antibacterial activity against methicillin-sensitive and methicillin-resistant *S. aureus* (MSSA and MRSA, respectively) and vancomycin-sensitive and vancomycin-resistant *E. faecalis* (VSE and VRE, respectively). These SAR studies revealed that the presence of a hydrophobic moiety, particularly a phenyl or biphenyl, at either the 1- or the 12-position of the benzo[*c*]phenanthridine ring resulted overall in improved activity against all 4 strains of bacteria tested when compared to the unsubstituted ring. This same general trend held true in the SAR studies with the dibenzo[*a,g*]quinolizin-7-iums, the second series of compounds that were synthesized as berberine derivatives. Unlike sanguinarine, berberine itself has only modest antibacterial activity. The addition of a phenyl or biphenyl substituent at either the 2- or 12-position of the structurally related dibenzo[*a,g*]quinolizin-7-ium core drastically improved the antibacterial activity against all 4 strains tested. The activity against *E. faecalis* was generally higher in the case of the 3,4,10,11-tetramethoxy derivatives than was seen in the 3,10,11-trimethoxy derivatives, suggesting that the tetramethoxy substitution was preferred for this strain. Despite many of the compounds from these two series displaying good MIC values (0.5 to 2 μg/mL), they all proved extremely difficult to formulate. This severely limited further evaluation

in other biological assays, particularly the *in vivo* testing. Research efforts then shifted towards modifying the scaffold in such a way that could address the solubility issue.

3-Phenylisoquinoline represents a flexible scaffold within the core structures of both the benzo[*c*]phenanthridin-5-ium and dibenzo[*a,g*]quinoliz-7-ium rings. More flexibility could help improve some of the solubility issues we experienced with the previous two series. In addition to this, efforts were made to remove the constitutive cationic charge found in the benzo[*c*]phenanthridin-5-ium and dibenzo[*a,g*]quinoliz-7-ium rings. SAR studies of various 3-phenylisoquinoline and 3-phenylisoquinolinium derivatives quickly revealed that the quaternary derivatives consistently lead to increased antibacterial activity when compared directly to their non-charged precursors. As such, we decided to explore the effects of basicity at the 1-position of the 3-phenylisoquinoline ring. These types of compounds would lack a constitutive cationic charge but would likely be protonated to some extent at physiological pH. Evaluation of various basic groups was consistent with the previous SAR, in that more basic functionality had a tendency to lead to increased antibacterial activity. This was best seen in the 1-substituted 3-biphenylisoquinoline group, where the presence of a 1-guanidino led to an MIC of 8 μg/mL (MSSA) while a nitrile, *N,N*-dimethylamino, and *N*-methylamino directly attached at the 1-position all had MIC values > 64 μg/mL. Extension of the amine with a 1 carbon linker by reduction of the nitrile group improved the potency from >64 μg/mL to 8 μg/mL. The SAR was further substantiated by the extension of the amine with a 2 carbon linker at the 1-position leading to an MIC of 4 μg/mL, and the extension of the guanidine group to the guanidinomethyl and 2-guanidinoethyl derivatives leading to MIC values of 2 μg/mL.

With compounds from this series showing some comparable activity to those in the previous series, along with improved solubility, we were able to conduct numerous more biological tests with the 3-phenylisoquinolines and 3-phenylisoquinoliniums. Representative compounds were shown to bind to SaFtsZ, stimulate FtsZ polymerization, and inhibit the GTPase activity of SaFtsZ. They were also evaluated for potential toxicity and were demonstrated to have no effect on mammalian tubulin and little cytotoxicity. Unfortunately, these compounds were unable to demonstrate efficacy *in vivo* – most likely due to their high protein binding.

To address the protein binding issue, we then sought to synthesize new compounds that either (1) did not protein bind or (2) had improved activity so that even if they protein bind, they might still be potent enough to produce a response *in vivo*. We then turned to a series of 4- and 5-substituted 1-phenylnapthalenes, which represent another truncated scaffold contained within the benzo[*c*]phenanthridine core structure. Applying the SAR results from the 3-phenylisoquinoline series, a number of analogs containing either a 4- or 5-substituted basic moiety were synthesized and evaluated. The SAR studies from this series were consistent with the results from the 3-phenylisoquinoline series in that more basic substitutions typically led to increased potency. These compounds were also shown to stimulate SaFtsZ polymerization. Unfortunately, they were also highly protein bound, and given that they showed comparable but not improved potency to the 3-phenylisoquinolines, were also insufficient for *in vivo* evaluation. Additional naphthalene derivatives were synthesized containing either a 2,3-dimethoxy substitution pattern or a 2-phenyl instead of a 1-phenyl, but none of these were able to address the protein binding either.

Several 2-phenylquinoline analogs were synthesized to evaluate the effect of moving the nitrogen over from the isoquinoline to the quinoline. While exhibiting antibacterial activity on their own, these analogs were not able to overcome the protein binding issue either. Numerous 3-phenylquinoliniums, biaryls, diazanaphthalenes, and 1,6-diphenylnaphthalenes were synthesized and evaluated by various members of TAXIS Pharmaceuticals, but still no compounds were suitable candidates for *in vivo* testing.

Unable to overcome the issue of protein binding, we then shifted away completely from the sanguinarine and berberine leads towards 3-methoxybenzamide, which has been reported to be a FtsZ inhibitor with weak antibacterial activity. Early studies were to investigate possible bioisosteric replacements for the amide functionality. This included a variety of azole-containing heterocycles such as oxadiazoles, thiadiazoles, triazoles, and imidazoles. Unfortunately, these heterocyclic compounds did not give us any desired antibacterial activity. Even when linked up to 5-chlorobenzo[*d*]thiazole connected through an ether linkage similar to that of the reported PC190723, these heterocycles proved to be inadequate replacements for the amide in the methoxybenzamide scaffold.

Overall, the work in this dissertation describes the synthesis, SAR, and biological evaluation of numerous, novel scaffolds of FtsZ inhibitors with good antibacterial activity. Despite the lack of activity associated with the last set of analogs, ongoing studies are continuing with this type of 3-MBA scaffold. Several compounds with improved activity and protein binding profiles have been synthesized and evaluated *in vivo*. Compounds to improve physiochemical properties such as solubility and pharmacokinetics, as well as broadening the bacterial spectrum, are also being prepared.

EXPERIMENTAL

This section details the intermediates and target compounds prepared by Cody Kelley as part of her dissertation in fulfillment of her requirements for a Ph.D. in medicinal chemistry. All reactions, unless otherwise stated, were done under nitrogen atmosphere. Reaction monitoring and follow-up were done using aluminum backed Silica G TLC plates (UV254 - Sorbent Technologies), visualizing with ultraviolet light. Flash column chromatography was done using 230-400 mesh silica gel (Dynamics Adsorbants, Inc.), with the chromatotron using a silica gel GF 2000m pre-scraped rotor (Analtech, Newark, DE), or on a Combi Flash Rf Teledyne ISCO using hexane, ethyl acetate, dichloromethane, and methanol as indicated. The proton, ^{1}H (400 MHz) and carbon, ^{13}C (100 MHz) NMR spectra were done in $CDCl_3$, Methanol-d_4, and DMSO-d_6 and recorded on a Bruker Avance III (400 MHz) Multinuclear NMR Spectrometer. Deuterated solvents were purchased from Cambridge Isotopes Laboratory (Cambridge, MA). Data is expressed in parts per million (δ) relative to the residual nondeuterated solvent signals, spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), dt (doublet of triplets), td

(triplet of doublets), q (quartet), m (multiplet), bs (broad singlet), and bt (broad triplet), and coupling constants (*J*) are reported in Hertz (Hz). Melting points were determined using Mel-temp II apparatus and are uncorrected. Infrared spectra was obtained using a Thermo-Nicolet Avatar 360 Fourier transform spectrophotometer and reported in cm^{-1}. High-resolution mass spectra (HRMS) experiments were conducted by Washington University Resource for Biomedical and Bioorganic Mass Spectrometry within the Department of Chemistry at Washington University, St. Louis, MO.

6,7-Dimethoxynaphthalen-1-amine (9).

6,7-Dimethoxy-1-nitronaphthalene (**8**) (2 g, 8.58 mmol) was suspended in ethanol (75 mL) followed by addition of Pd/C (10% wt.) (400 mg) and excess hydrazine monohydrate (4 mL). Reaction mixture was heated at 85 ^{o}C for 1.5 hours then cooled to RT. Catalyst was removed by gravity filtration through filter paper and filtrate was concentrated. Chromatography using flash column max gradient 2% MeOH/DCM afforded product as a pink solid (1.6 g, 92% yield); mp 111-112 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.24-7.17 (m, 2H), 7.13 (s, 1H), 7.08 (s, 1H), 6.74-6.72 (m, 1H), 4.04 (s, 3H), 4.02 (s, 3H), 4.00 (bs, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 149.4, 148.9, 140.9, 130.3, 124.7, 119.1, 118.0, 109.3, 107.2, 100.2, 55.9, 55.8.

1-Bromo-5-nitronaphthalene-2,3-diol (13).

A solution of Br_2 (1.9 mL) in anhydrous DCM (37 mL) was added to a solution of 5-nitronaphthalene-2,3-diol (**7**) (6.1 g, 29.8 mmol) in anhydrous DCM (90 mL) at 0 ^oC. Reaction was stirred for 10 minutes at RT then solvents were evaporated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as a brown solid (7.87 g, 93% yield); mp 209-211 ^oC; ^1H NMR (400 MHz) (CD_3OD) δ 8.40 (d, *J* = 8.5 Hz, 1H), 8.05 (dd, *J* = 7.6 Hz, *J* = 0.9 Hz, 1H), 7.85 (s, 1H), 7.45 (t, *J* = 8.1 Hz, 1H); ^{13}C NMR (100 MHz) (CD_3OD) δ 150.6, 147.4, 132.6, 130.5, 123.6, 122.9, 122.8, 104.8.

1-Bromo-2,3-dimethoxy-5-nitronaphthalene (14).

To a flask containing **13** (3 g, 10.7 mmol) and K_2CO_3 (3.9 g, 28.3 mmol) in DMF (33 mL) was added MeI (5.2 mL). Solution was heated at 50 ^oC overnight then cooled to RT and diluted with EtOAc. Solution was washed with H_2O and extracted with EtOAc. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 10% EtOAc/hexane afforded product as a yellow solid (2.7 g, 81% yield); mp 100-102 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.54 (d, *J* = 8.5 Hz, 1H), 8.23 (dd, *J* = 7.7 Hz, *J* = 1.1 Hz, 1H), 8.01 (s, 1H), 7.52 (t, *J* = 8.1 Hz, 1H), 4.07 (s, 3H), 4.01 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 155.1, 133.4, 129.2, 124.2, 124.0, 123.3, 117.1, 102.4, 60.8, 56.2.

2,3-Dimethoxy-5-nitro-1-phenylnaphthalene (15g).

14 (350 mg, 1.12 mmol), 4-phenylboronic acid (273 mg, 2.24 mmol), $Pd(PPh_3)_4$ (129 mg, 0.112 mmol), and aqueous 2M Na_2CO_3 (1.12 mL) in toluene/MeOH (5:1) were combined in a flask and degassed. Reaction mixture was heated to 90 ^oC overnight. Solution was then cooled to RT, diluted with EtOAc, and filtered through a pad of celite and silica gel. Filtrate was concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as a yellow oil (310 mg, 90% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.07 (dd, *J* = 7.7 Hz, *J* = 1.1 Hz, 1H), 7.98 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.45-7.36 (m, 3H), 7.26-7.24 (m, 2H), 7.18-7.14 (m, 1H), 3.99 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 155.0, 147.5, 145.5, 135.2, 132.8, 132.5, 130.5, 128.4, 127.8, 123.6, 123.5, 122.0, 102.4, 61.0, 55.9.

6,7-Dimethoxy-5-phenylnaphthalen-1-amine (16g).

15g (310 mg, 1.0 mmol) was suspended in ethanol (14 mL) followed by addition of Pd/C (10% wt.) (70 mg) and excess hydrazine monohydrate (0.85 mL). Reaction mixture was heated at 85 ^oC for 1.5 hours then cooled to RT. Catalyst was removed by gravity filtration through filter paper and filtrate was concentrated. Chromatography using flash column max gradient 2% MeOH/DCM afforded product as beige fluffy solid (280 mg, quantitative); mp 136-138 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.56-7.43 (m, 5H), 7.22 (s, 1H), 7.13-7.10 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 4.07 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 151.7, 146.6, 141.0, 136.6, 132.9, 130.6, 129.9, 128.1, 127.2, 124.4, 121.4, 117.6, 110.1, 100.7, 61.0, 55.8.

6-Bromo-*N*-(6,7-dimethoxy-5-phenylnaphthalen-1-yl)-2,3-dimethoxybenzamide (17g).

Oxalyl chloride (0.41 mL, 4.76 mmol) was added to a solution of 6-bromo-2,3-dimethoxybenzoic acid (621 mg, 2.38 mmol) in anhydrous DCM (6 mL). This solution was then refluxed at 45 ^{o}C for 2 hours. Solvents were evaporated and flask was placed on vacuum pump for 30 minutes. Residue was taken back up in anhydrous DCM (5 mL) and **16g** (332 mg, 1.19 mmol) in anhydrous DCM (10 mL) was added to the flask followed by addition of Et_3N (0.5 mL, 3.57 mmol). Reaction was stirred at RT overnight. Additional DCM was added and solution was washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 5% MeOH/DCM afforded product as a beige fluffy solid (575 mg, 93% yield); mp 121-124 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.89 (s, 1H), 7.77 (s, 1H), 7.51-7.38 (m, 5H), 7.33-7.31 (m, 2H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.9 Hz, 1H), 4.16 (s, 3H), 3.79 (s, 3H), 3.61 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 164.8, 152.9, 152.4, 147.2, 146.8, 136.0, 134.2, 132.6, 130.7, 130.6, 129.9, 128.4, 128.1, 127.4, 127.4, 125.6, 123.5, 123.3, 114.5, 109.6, 102.1, 62.4, 60.9, 56.1, 55.9.

6-Bromo-*N*-(6,7-dimethoxy-5-phenylnaphthalen-1-yl)-2,3-dimethoxy-*N*-methylbenzamide (18g).

To a solution of **17g** (535 mg, 1.02 mmol) in anhydrous DMF (10 mL) was quickly added NaH (241 mg, 6.0 mmol) followed by excess MeI (0.8 mL). Reaction was stirred at RT

overnight then diluted with EtOAc and washed with 10% HCl solution followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as a tan fluffy solid (350 mg, 64% yield); mp 84-88 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.32-6.46 (m, 11H), 4.02-3.21 (m, 15H).

2,3,7,8-Tetramethoxy-5-methyl-1-phenylbenzo[*c*]phenanthridin-6(5H)-one (19g).

A flask containing **18g** (80 mg, 0.15 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), P(*o*-tol)$_3$ (18 mg, 0.06 mmol), and Ag_2CO_3 (83 mg, 0.3 mmol) was degassed and anhydrous DMF (7 mL) was added. Reaction mixture was refluxed at 160 ^oC overnight. Solution was then filtered through filter paper to remove catalyst. Filtrate was diluted with EtOAc and washed with brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using chromatotron max gradient 2% MeOH/$CHCl_3$ afforded product as a clear oil (29 mg, 43% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 7.94 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 9.1 Hz, 1H), 7.58 (s, 1H), 7.55-7.47 (m, 3H), 7.42-7.40 (m, 2H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 4.10 (s, 3H), 4.06 (s, 3H), 4.00 (s, 3H), 3.98 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 162.9, 152.8, 151.0, 150.3, 146.6, 135.9, 134.8, 132.5, 130.6, 129.7, 128.9, 128.2, 127.5, 122.2, 122.0, 119.9, 117.9, 117.8, 117.4, 105.6, 61.8, 61.0, 56.6, 55.8, 40.8.

2,3,7,8-Tetramethoxy-5-methyl-1-phenylbenzo[*c*]phenanthridin-5-ium chloride (20g).

A small flask containing **19g** (29 mg, 0.064 mmol) in anhydrous THF (3 mL) was cooled to 0 ^{o}C. LAH (7.3 mg, 0.192 mmol) was then quickly added and flask was removed from ice bath. Reaction was stirred for 30 minutes at RT. Flask was then put back in ice bath and H_2O (9 drops) was carefully added. Solution was filtered through filter paper and solvents evaporated. Residue was then treated with 10% HCl to afford product as a bright yellow solid (30 mg, quantitative); mp 169-172 ^{o}C; ^{1}H NMR (400 MHz) (DMSO-d_6) δ 10.10 (s, 1H), 8.74 (d, *J* = 9.3 Hz, 1H), 8.66 (d, *J* = 9.3 Hz, 1H), 8.27-8.24 (m, 2H), 7.71-7.55 (m, 4H), 7.40-7.38 (m, 2H), 5.07 (s, 3H), 4.19 (s, 3H), 4.16 (s, 3H), 4.09 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 152.0, 150.8, 147.5, 145.6, 134.7, 132.8, 131.2, 130.3, 129.0, 128.5, 128.1, 127.7, 126.2, 125.7, 121.4, 119.5, 119.3, 118.1, 108.3, 62.2, 60.7, 57.0, 56.2, 52.1; HRMS (ESI) Calcd for $C_{28}H_{26}ClNO_4$ $(M\text{-}Cl)^+$ 440.1862, found 440.1854.

1-Cyclopropyl-2,3-dimethoxy-5-nitronaphthalene (21a).

14 (250 mg, 0.8 mmol), cyclopropylboronic acid (138 mg, 1.6 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), Pcy3 (22 mg, 0.08 mmol), and K_3PO_4 (594 mg, 2.8 mmol) were combined in a flask and degassed. A toluene/H_2O solution (20:1, 5.25 mL) was then added and reaction was refluxed at 100 ^{o}C for 3 hours. Reaction was then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 20%

EtOAc/hexane afforded product as a yellow waxy solid (215 mg, 99% yield); mp 82-85 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.62 (d, *J* = 8.4 Hz, 1H), 8.05-8.03 (m, 1H), 7.78 (s, 1H), 7.32 (t, *J* = 8.1 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 1.95-1.88 (m, 1H), 1.16-1.11 (m, 2H), 0.78-0.74 (m, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 155.0, 150.3, 145.8, 131.8, 131.4, 130.3, 123.4, 123.2, 121.8, 101.3, 61.3, 55.8, 9.0, 8.0.

1-(Cyclohex-1-en-1-yl)-2,3-dimethoxy-5-nitronaphthalene (21b).

14 (500 mg, 1.60 mmol), cyclohexenyl boronic acid pinacol ester (0.67 mL, 3.2 mmol), $Pd(OAc)_2$ (18 mg, 0.08 mmol), Pcy3 (45 mg, 0.16 mmol), and K_3PO_4 (1.19 g, 5.6 mmol) were combined in a flask and degassed. A toluene/H_2O solution (20:1, 21 mL) was then added and reaction was refluxed at 100 ^{o}C for 3 hours. Reaction was cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 15% EtOAc/hexane afforded product as a yellow solid (483 mg, 96% yield); mp 115-118 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.19-8.17 (m, 2H), 7.97 (s, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 5.72-5.70 (m, 1H), 4.05 (s, 3H), 3.91 (s, 3H), 2.45-2.40 (m, 1H), 2.32 (m, 2H), 2.16-2.12 (m, 1H), 1.93-1.82 (m, 4H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 155.1, 146.7, 135.3, 133.2, 132.1, 129.9, 128.7, 123.7, 123.5, 121.8, 101.5, 61.4, 55.8, 30.2, 25.5, 23.1, 22.1.

2,3-Dimethoxy-5-nitro-1-vinylnaphthalene (21c).

14 (100 mg, 0.32 mmol), tributyl(vinyl)tin (0.47 mL, 1.6 mmol), and $Pd(PPh_3)_4$ (19 mg, 0.016 mmol) were combined in a flask and degassed. Anhydrous THF was then added and reaction was heated at 70 ^oC for 48 hours. Reaction was cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 30% DCM/hexane afforded product as a yellow solid (59 mg, 71% yield); mp 70-73 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.40 (d, *J* = 8.5 Hz, 1H), 8.19 (dd, *J* = 7.7, *J* = 1.0 Hz, 1H), 7.98 (s, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 17.9 Hz, *J* = 11.6 Hz, 1H), 5.85 (dd, *J* = 11.6 Hz, *J* = 1.8 Hz, 1H), 5.70 (dd, *J* = 17.9 Hz, *J* = 1.8 Hz, 1H), 4.06 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.8, 147.4, 145.7, 131.4, 129.7, 129.2, 129.1, 123.8, 123.6, 122.9, 122.1, 102.0, 60.7, 55.9.

5-Cyclopropyl-6,7-dimethoxynaphthalen-1-amine (22a).

21a (215 mg, 0.79 mmol) was suspended in ethanol (10 mL) followed by addition of Pd/C (10% wt.) (60 mg) and excess hydrazine monohydrate (1 mL). Reaction mixture was heated at 85 ^oC for 1.5 hours then cooled to RT. Catalyst was removed by gravity filtration through filter paper and filtrate was concentrated. Chromatography using flash column max gradient 2% MeOH/DCM afforded product as an off-white solid (172 mg, 90% yield); mp 83-85 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 1H), 7.26 (dd, *J* = 8.4 Hz, *J* = 7.4 Hz, 1H), 7.06 (s, 1H), 6.79 (dd, *J* = 7.4 Hz, *J* = 0.7 Hz, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 2.05-1.98 (m, 1H), 1.23-1.18 (m, 2H), 0.93-0.89 (m, 2H); ^{13}C NMR

(100 MHz) ($CDCl_3$) δ 151.7, 149.4, 141.2, 131.2, 130.3, 124.1, 121.1, 116.7, 110.0, 99.6, 61.2, 55.7, 9.1, 7.8.

5-(Cyclohex-1-en-1-yl)-6,7-dimethoxynaphthalen-1-amine (22b).

21b (480 mg, 1.53 mmol) and $SnCl_2$ dihydrate (1.73 g, 7.65 mmol) in EtOH (20 mL) were refluxed at 85 ^oC for 2 hours. Reaction was cooled to RT then basified with saturated $NaHCO_3$. Solids were filtered out and filtrate was extracted with $CHCl_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as maroon crystals (369 mg, 85% yield); mp 131 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 1H), 7.16-7.12 (m, 1H), 7.03 (s, 1H), 6.73 (dd, *J* = 7.3 Hz, *J* = 0.9 Hz, 1H), 5.67-5.65 (m, 1H), 3.98 (s, 3H), 3.85 (s, 3H), 2.40-2.15 (m, 4H), 1.86-1.76 (m, 4H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 151.7, 145.8, 140.9, 135.4, 134.0, 129.2, 127.3, 124.3, 121.5, 117.1, 110.0, 99.6, 61.4, 55.7, 30.1, 25.5, 23.2, 22.3.

6,7-Dimethoxy-5-vinylnaphthalen-1-amine (22c).

21c (55 mg, 0.22 mmol) was combined with tin(II)chloride (248 mg, 1.1 mmol) in ethanol (3 mL) and refluxed for 30 minutes at 85 ^oC. Reaction was then cooled to RT and basified with saturated $NaHCO_3$. Solid precipitate was filtered off and filtrate was concentrated. Chromatography achieved using flash column max gradient 2% MeOH/DCM afforded product as a dark oil (29 mg, 58% yield); ^1H NMR (400 MHz)

($CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.98-6.94 (m, 2H), 6.71 (d, *J* = 8.0 Hz), 5.65-5.63 (m, 2H), 3.98 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 151.5, 146.8, 140.7, 130.5, 128.8, 128.6, 124.4, 121.6, 121.5, 116.7, 110.5, 100.3, 60.5, 55.7.

6-Bromo-*N*-(5-cyclopropyl-6,7-dimethoxynaphthalen-1-yl)-2,3-dimethoxybenzamide (23a).

Oxalyl chloride (0.25 mL, 2.84 mmol) was added to a solution of 6-bromo-2,3-dimethoxybenzoic acid (371 mg, 1.42 mmol) in anhydrous DCM (5 mL). This solution was then refluxed at 45 ^oC for 2 hours. Solvents were evaporated and flask was placed on vacuum pump for 30 minutes. Residue was taken back up in anhydrous DCM (5 mL) and **22a** (172 mg, 0.71 mmol) in anhydrous DCM (7 mL) was added to the flask followed by addition of Et_3N (0.3 mL, 2.13 mmol). Reaction was stirred at RT overnight. Additional DCM was added and solution was washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 5% MeOH/DCM afforded product as a white solid (200 mg, 58% yield); mp 208-210 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.37 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.47-7.41 (m, 3H), 7.35 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 2.04-1.97 (m, 1H), 1.21-1.16 (m, 2H), 0.88-0.84 (m, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 164.7, 152.9, 149.7, 147.2, 134.2, 131.3, 130.8, 130.2, 128.4, 127.1, 124.6, 123.3, 123.0, 114.4, 109.7, 100.9, 62.4, 61.2, 56.1, 55.9, 8.9, 7.8.

6-Bromo-*N*-(5-(cyclohex-1-en-1-yl)-6,7-dimethoxynaphthalen-1-yl)-2,3-dimethoxybenzamide (23b).

Oxalyl chloride (0.24 mL, 2.74 mmol) was added to a solution of 6-bromo-2,3-dimethoxybenzoic acid (358 mg, 1.37 mmol) in anhydrous DCM (8 mL). This solution was then refluxed at 45 ^{o}C for 2 hours. Solvents were evaporated and flask was placed on vacuum pump for 30 minutes. Residue was taken back up in anhydrous DCM (5 mL) and **22b** (194 mg, 0.69 mmol) in anhydrous DCM (7 mL) was added to the flask followed by addition of Et_3N (0.29 mL, 2.06 mmol). Reaction was stirred at RT overnight. Additional DCM was added and solution was washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 2% MeOH/DCM afforded product as a tan solid (171 mg, 58% yield); mp 268-270 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.47 (s, 1H), 7.38-7.32 (m, 2H), 6.86 (d, *J* = 8.8 Hz, 1H), 5.70-5.68 (m, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 2.44-2.40 (m, 1H), 2.32-2.31 (m, 2H), 2.20-2.15 (m, 1H), 1.90-1.81 (m, 4H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 164.7, 152.9, 152.4, 147.1, 146.0, 135.2, 134.3, 133.6, 130.7, 129.3, 128.4, 127.8, 127.5, 125.0, 123.3, 123.1, 114.4, 109.7, 101.1, 62.4, 61.4, 56.1, 56.0, 30.1, 25.6, 23.2, 22.3.

6-Bromo-*N*-(6,7-dimethoxy-5-vinylnaphthalen-1-yl)-2,3-dimethoxybenzamide (23c).

Oxalyl chloride (0.09 mL, 1 mmol) was added to a solution of 6-bromo-2,3-dimethoxybenzoic acid (131 mg, 0.5 mmol) in anhydrous DCM (3 mL). This solution was then refluxed at 45 ^{o}C for 2 hours. Solvents were evaporated and flask was placed on vacuum pump for 30 minutes. Residue was taken back up in anhydrous DCM (4 mL) and **22c** (57 mg, 0.25 mmol) in anhydrous DCM (4 mL) was added to the flask followed by addition of Et_3N (0.1 mL, 0.75 mmol). Reaction was stirred at RT overnight. Additional DCM was added and solution was washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 2% MeOH/DCM afforded product as an off-white solid (77 mg, 65% yield); mp 191-193 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 2H), 7.50 (s, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 5.81-5.71 (m, 2H), 4.01 (s, 3H), 3.97 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 164.7, 152.7, 152.4, 147.2, 146.9, 134.2, 130.8, 130.2, 128.8, 128.6, 128.4, 127.6, 124.5, 123.6, 123.3, 121.8, 114.4, 109.6, 101.8, 62.43, 60.6, 56.1, 55.9.

6-Bromo-*N*-(5-cyclopropyl-6,7-dimethoxynaphthalen-1-yl)-2,3-dimethoxy-*N*-methylbenzamide (24a).

To a solution of **23a** (200 mg, 0.41 mmol) in anhydrous DMF (10 mL) was quickly added NaH (90 mg, 2.25 mmol) followed by excess MeI (0.3 mL). Reaction was stirred at RT overnight then diluted with EtOAc and washed with 10% HCl solution followed by brine.

Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as a white fluffy solid (189 mg, 92% yield); mp 75-76 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.42-8.40 (m, 1H), 7.44-6.39 (5H), 3.95-3.15 (m, 15H), 1.93-1.85 (m, 1H), 1.12-1.04 (m, 2H), 0.84-0.73 (m, 2H).

6-Bromo-*N*-(5-(cyclohex-1-en-1-yl)-6,7-dimethoxynaphthalen-1-yl)-2,3-dimethoxy-*N*-methylbenzamide (24b).

To a solution of **23b** (171 mg, 0.33 mmol) in anhydrous DMF (13 mL) was quickly added NaH (78 mg, 2 mmol) followed by excess MeI (0.26 mL). Reaction was stirred at RT overnight then diluted with EtOAc and washed with 10% HCl solution followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as a tan fluffy solid (146 mg, 82% yield); mp 88-90 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.80-6.43 (m, 6H), 5.62-5.55 (m, 1H), 3.92-3.14 (m, 15H), 2.35-2.06 (m, 4H), 1.81-1.70 (m, 4H).

6-Bromo-*N*-(6,7-dimethoxy-5-vinylnaphthalen-1-yl)-2,3-dimethoxy-*N*-methylbenzamide (24c).

To a solution of **23c** (55 mg, 0.12 mmol) in anhydrous DMF (4 mL) was quickly added NaH (25 mg, 0.6 mmol) followed by excess MeI (0.08 mL). Reaction was stirred at RT

overnight then diluted with EtOAc and washed with 10% HCl solution followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as a fluffy off-white solid (60 mg, quantitative); mp 61-64 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.05-6.80 (m, 7H), 5.72-5.61 (m, 2H), 4.04-3.48 (m, 15H).

1-Cyclopropyl-2,3,7,8-tetramethoxy-5-methylbenzo[*c*]phenanthridin-6(5*H*)-one (25a).

A flask containing **24a** (156 mg, 0.31 mmol), $Pd(OAc)_2$ (14 mg, 0.062 mmol), P(*o*-tol)$_3$ (38 mg, 0.12 mmol), and Ag_2CO_3 (172 mg, 0.62 mmol) was degassed and anhydrous DMF (12 mL) was added. Reaction mixture was refluxed at 160 ^oC overnight. Solution was then filtered through filter paper to remove catalyst. Filtrate was diluted with EtOAc and washed with brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using chromatotron max gradient 2% MeOH/$CHCl_3$ afforded product as a tan oil (40 mg, 31% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.20 (d, *J* = 9.0 Hz, 1H), 7.96 (dd, *J* = 9.1 Hz, *J* = 1.9 Hz, 2H), 7.33 (t, *J* = 4.5 Hz, 2H), 4.02 (s, 3H), 3.92-3.91 (m, 9H), 3.85 (s, 3H), 1.99-1.92 (m, 1H), 1.18-1.11 (m, 2H), 0.82-0.78 (m, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 162.9, 152.8, 151.0, 149.4, 135.1, 131.2, 130.2, 129.0, 122.0, 121.1, 119.9, 117.9, 117.6, 117.3, 104.6, 61.8, 61.2, 56.6, 55.7, 40.8, 9.0, 7.8.

1-(Cyclohex-1-en-1-yl)-2,3,7,8-tetramethoxy-5-methylbenzo[*c*]phenanthridin-6(5*H*)-one (25b).

A flask containing **24b** (146 mg, 0.27 mmol), $Pd(OAc)_2$ (12 mg, 0.054 mmol), P(*o*-tol)$_3$ (33 mg, 0.108 mmol), and Ag_2CO_3 (149 mg, 0.54 mmol) was degassed and anhydrous DMF (12 mL) was added. Reaction mixture was refluxed at 160 ^oC overnight. Solution was then filtered through filter paper to remove catalyst. Filtrate was diluted with EtOAc and washed with brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using chromatotron max gradient 2% MeOH/$CHCl_3$ afforded product as a golden oil (57 mg, 46% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 7.93-7.88 (m, 2H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.37 (s, 1H), 7.31 (d, *J* = 8.9 Hz, 1H), 5.66-5.64 (m, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 2.24-2.07 (m, 4H), 1.83-1.74 (m, 4H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 162.9, 151.1, 143.5, 133.6, 132.9, 132.8, 132.0, 131.9, 131.8, 131.7, 128.1, 125.5, 125.4, 122.3, 121.5, 117.9, 117.7, 117.4, 104.7, 61.8, 61.4, 56.6, 55.7, 40.7, 30.2, 25.6, 23.2, 22.3.

2,3,7,8-Tetramethoxy-5-methyl-1-vinylbenzo[*c*]phenanthridin-6(5*H*)-one (25c).

A flask containing **24c** (60 mg, 0.12 mmol), $Pd(OAc)_2$ (10 mg, 0.048 mmol), P(*o*-tol)$_3$ (29 mg, 0.09 mmol), and Ag_2CO_3 (133 mg, 0.44 mmol) was degassed and anhydrous DMF (5 mL) was added. Reaction mixture was refluxed at 160 ^oC overnight. Solution was then filtered through filter paper to remove catalyst. Filtrate was diluted with EtOAc and washed with brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using chromatotron max gradient 2% MeOH/$CHCl_3$

afforded product as a golden oil (19 mg, 39% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.93 (d, *J* = 9.0 Hz, 1H), 7.91 (s, 2H), 7.38 (s, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.03 (dd, *J* = 17.9 Hz, *J* = 11.6 Hz, 1H), 5.76-5.71 (m, 2H), 4.02 (s, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 152.1, 150.8, 143.6, 143.5, 132.8, 132.1, 130.1, 128.8, 128.5, 122.5, 122.2, 121.1, 119.9, 118.1, 118.0, 117.9, 117.5, 105.4, 61.8, 60.7, 56.6, 55.6, 40.8.

1-Cyclohexyl-2,3,7,8-tetramethoxy-5-methylbenzo[*c*]phenanthridin-6(5*H*)-one (25d).

A small flask containing **25b** (27 mg, 0.05 mmol), Pd/C (10% wt.) (10 mg) in EtOH (5 mL) was degassed and a balloon containing $H_{2(g)}$ was inserted. Reaction was stirred at RT overnight then catalyst was filtered out over filter paper and solvent evaporated. Chromatography using chromatotron max gradient 2% MeOH/$CHCl_3$ afforded product as a golden oil (18 mg, 67% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.94-7.88 (m, 2H), 7.37-7.29 (m, 2H), 7.19 (s, 1H), 4.08-3.79 (m, 15H), 2.42-2.13 (m, 2H), 1.88-1.74 (m, 3H), 1.53-1.33 (m, 3H), 1.18-1.15 (m, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.0, 152.8, 143.8, 143.5, 135.3, 133.0, 132.8, 132.0, 131.9, 131.3, 130.3, 129.0, 125.5, 120.0, 117.8, 117.2, 104.5, 61.8, 61.2, 56.6, 55.5, 40.9, 31.7, 27.7, 26.4, 22.0.

1-Cyclopropyl-2,3,7,8-tetramethoxy-5-methylbenzo[*c*]phenanthridin-5-ium chloride (26a).

A small flask containing **25a** (40 mg, 0.095 mmol) in anhydrous THF (4 mL) was cooled to 0 ^{o}C. LAH (10.9 mg, 0.286 mmol) was then quickly added and flask was removed from ice bath. Reaction was stirred for 30 minutes at RT. Flask was then put back in ice bath and H_2O (9 drops) was carefully added. Solution was filtered through filter paper and solvents evaporated. Residue was then treated with 10% HCl to afford product as a bright yellow solid (28 mg, 67% yield); mp 134-135 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 9.91 (s, 1H), 8.85 (d, *J* = 9.2 Hz, 1H), 8.63 (d, *J* = 9.2 Hz, 1H), 8.58 (d, *J* = 9.4 Hz, 1H), 8.14 (d, *J* = 9.2 Hz, 1H), 7.92 (s, 1H), 4.94 (s, 3H), 4.20 (s, 3H), 4.05 (s, 3H), 4.04 (s, 3H), 3.93 (s, 3H), 2.11-2.04 (m, 1H), 1.25-1.21 (m, 2H), 0.73-0.69 (m, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 154.2, 152.5, 152.2, 151.5, 147.6, 133.3, 133.2, 133.0, 130.2, 130.0, 127.4, 122.9, 121.2, 120.0, 118.5, 108.1, 62.8, 61.7, 57.6, 56.7, 52.8, 10.0, 8.8; HRMS (ESI) Calcd for $C_{25}H_{26}ClNO_4$ $(M\text{-}Cl)^+$ 404.1862, found 404.1855.

1-(Cyclohex-1-en-1-yl)-2,3,7,8-tetramethoxy-5-methylbenzo[*c*]phenanthridin-5-ium chloride (26b).

A small flask containing **25b** (29 mg, 0.064 mmol) in anhydrous THF (3 mL) was cooled to 0 ^{o}C. LAH (7.2 mg, 0.19 mmol) was then quickly added and flask was removed from ice bath. Reaction was stirred for 30 minutes at RT. Flask was then put back in ice bath and H_2O (9 drops) was carefully added. Solution was filtered through filter paper and solvents evaporated. Residue was then treated with 10% HCl to afford product as a

bright yellow solid (28 mg, quantitative); mp 173-174 ^{o}C; ^{1}H NMR (400 MHz) (DMSO-d_6) δ 10.17 (s, 1H), 8.83 (m, 2H), 8.33 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 8.14 (s, 1H), 5.36 (m, 1H), 5.07 (s, 3H), 4.20 (s, 3H), 4.13 (s, 3H), 4.12 (s, 3H), 3.89 (s, 3H), 2.39-2.18 (m, 4H), 1.85-1.80 (m, 4H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 152.0, 150.8, 150.5, 147.0, 145.5, 135.1, 132.7, 131.3, 128.6, 128.5, 127.8, 126.2, 125.7, 121.4, 119.5, 119.4, 118.1, 107.7, 62.3, 61.0, 57.1, 56.2, 52.2, 30.1, 25.0, 22.6, 21.7; HRMS (ESI) Calcd for $C_{28}H_{30}ClNO_4$ $(M\text{-}Cl)^+$ 444.2175, found 444.2167.

2,3,7,8-Tetramethoxy-5-methyl-1-vinylbenzo[*c*]phenanthridin-5-ium chloride (26c).

A small flask containing **26c** (19 mg, 0.047 mmol) in anhydrous THF (3 mL) was cooled to 0 ^{o}C. LAH (5 mg, 0.14 mmol) was then quickly added and flask was removed from ice bath. Reaction was stirred for 30 minutes at RT. Flask was then put back in ice bath and H_2O (8 drops) was carefully added. Solution was filtered through filter paper and solvents evaporated. Residue was then treated with 10% HCl to afford product as a bright yellow solid (17 mg, 85% yield); mp 160-161 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 9.92 (s, 1H), 8.60-8.46 (m, 3H), 8.12 (d, *J* = 9.1 Hz, 1H), 7.97 (s, 1H), 5.81 (d, *J* = 11.6 Hz, 1H), 5.62 (d, *J* = 17.8 Hz, 1H), 4.95, (s, 3H), 4.21 (s, 3H), 4.07 (s, 3H), 4.05 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz) (CD_3OD) δ 153.9, 152.3, 151.7, 149.7, 147.7, 133.2, 131.3, 130.9, 130.2, 130.1, 129.8, 127.7, 127.5, 124.0, 123.3, 121.3, 120.0, 118.9, 109.0, 62.9, 61.2, 57.6, 56.9, 52.8; HRMS Calcd for $C_{24}H_{24}NClO_4$ $(M\text{-}Cl)^+$ 390.1700, found 390.1690.

1-Cyclohexyl-2,3,7,8-tetramethoxy-5-methylbenzo[*c*]phenanthridin-5-ium chloride (26d).

A small flask containing **25d** (18 mg, 0.04 mmol) in anhydrous THF (3 mL) was cooled to 0 ^{o}C. LAH (4.6 mg, 0.12 mmol) was then quickly added and flask was removed from ice bath. Reaction was stirred for 30 minutes at RT. Flask was then put back in ice bath and H_2O (9 drops) was carefully added. Solution was filtered through filter paper and solvents evaporated. Residue was then treated with 10% HCl to afford product as a bright yellow solid (20 mg, quantitative); mp 169-171 ^{o}C; ^{1}H NMR (400 MHz) (DMSO-d_6) δ 10.25 (s, 1H), 8.95 (d, *J* = 8.0 Hz, 1H), 8.87 (d, *J* = 8.0 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 8.23 (s, 1H), 5.15 (s, 3H), 4.35 (s, 3H), 4.20 (s, 3H), 4.16 (s, 3H), 3.89 (s, 3H), 2.01-1.77 (m, 7H), 1.67-1.52 (m, 4H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 150.8, 150.5, 132.1, 128.5, 127.5, 126.2, 119.5, 119.3, 107.5, 62.3, 60.9, 57.1, 56.1, 52.1, 31.2, 29.2, 26.9; HRMS (ESI) Calcd for $C_{28}H_{30}ClNO_4$ $(M\text{-}Cl)^+$ 446.2331, found 446.2324.

4-Iodo-6,7-dimethoxynaphthalen-1-amine (27).

Iodine (2.17 g, 17.1 mmol), pyridine (32.5 mL), and dioxane (32.5 mL) were added to a flask containing 6,7-dimethoxynaphthalen-1-amine (1.18 g, 5.7 mmol) at 0 ^{o}C and stirred for 1 hour. Additional iodine (970 mg, 7.64 mmol) was then added and solution was taken off ice bath and stirred at RT for 1.5 hours. Mixture was then diluted with saturated sodium thiosulfate and extracted with $CHCl_3$. Organic layer was dried over Na_2SO_4 and concentrated. Chromatography using silica column max gradient 50%

hexane/DCM afforded product as a brown solid (1.18 g, 63% yield); mp 46-48 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.39 (s, 1H), 7.26 (s, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 4.05 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 150.7, 149.3, 141.9, 135.6, 130.7, 119.6, 112.1, 110.8, 100.6, 84.7, 56.1, 56.0.

6,7-Dimethoxy-4-phenylnaphthalen-1-amine (28b).

27 (300 mg, 0.912 mmol), 4-phenylboronic acid (223 mg, 1.824 mmol), $Pd(PPh_3)_4$ (105 mg, 0.0.912 mmol), and Na_2CO_3 (338 mg, 3.192 mmol) in dioxane (6 mL) and H_2O (3 mL) were combined in a flask and degassed. Reaction mixture was heated to 100 ^{o}C for 1.5 hours. Solution was then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 2% MeOH/DCM afforded product as a brown oil (200 mg, 78% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.41-7.35 (m, 4H), 7.27 (tt, *J* = 8.7 Hz, *J* = 2.0 Hz, 1H), 7.18 (s, 1H), 7.05-7.02 (m, 2H), 6.67 (d, *J* = 7.6 Hz, 1H), 3.93 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 149.4, 148.8, 141.7, 140.4, 130.8, 130.1, 128.3, 128.11, 126.6, 126.0, 119.4, 109.2, 105.8, 100.5, 55.9, 55.7.

4-([1,1'-Biphenyl]-4-yl)-6,7-dimethoxynaphthalen-1-amine (28c).

27 (300 mg, 0.91 mmol), 4-biphenylboronic acid (361 mg, 1.824 mmol), $Pd(PPh_3)_4$ (105 mg, 0.0.912 mmol), and Na_2CO_3 (338 mg, 3.192 mmol) in dioxane (6 mL) and H_2O (3 mL) were combined in a flask and degassed. Reaction mixture was heated to 100 ^{o}C for

1.5 hours. Solution was then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 2% MeOH/DCM afforded product as a purplish solid (200 mg, 62% yield); mp 191-192 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.64-7.60 (m, 4H), 7.51-7.47 (m, 2H), 7.42-7.38 (m, 2H), 7.31-7.27 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.06 (s, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 3.96 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 149.5, 148.8, 140.9, 140.7, 140.4, 139.4, 130.5, 130.3, 128.8, 128.1, 127.3, 127.1, 127.0, 126.1, 119.4, 109.3, 105.8, 100.5, 55.9, 55.8.

6-Bromo-*N*-(6,7-dimethoxy-4-phenylnaphthalen-1-yl)-2,3-dimethoxybenzamide (29b).

Oxalyl chloride (0.3 mL, 3.44 mmol) was added to a solution of 6-bromo-2,3-dimethoxybenzoic acid (449 mg, 1.72 mmol) in anhydrous DCM (10 mL). This solution was then refluxed at 45 ^oC for 2 hours. Solvents were evaporated and flask was placed on vacuum pump for 30 minutes. Residue was taken back up in anhydrous DCM (5 mL) and **28b** (240 mg, 0.86 mmol) in anhydrous DCM (10 mL) was added to the flask followed by addition of Et_3N (0.36 mL, 2.58 mmol). Reaction was stirred at RT overnight. Additional DCM was added and solution was washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 2% MeOH/DCM afforded product as a tan solid (105 mg, 23% yield); mp 169-170 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.69-7.66 (m, 2H), 7.55 (s, 1H), 7.52-7.51 (m, 4H), 7.47-7.44 (m, 1H), 7.36-7.33 (m, 2H), 7.25

(s, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 4.05 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 164.8, 152.4, 149.9, 149.7, 147.2, 141.0, 138.3, 134.2, 130.1, 129.9, 128.4, 128.3, 127.3, 125.5, 125.2, 121.7, 114.4, 109.7, 105.5, 101.9, 62.4, 56.1, 56.0, 55.7.

_N_-(4-([1,1'-Biphenyl]-4-yl)-6,7-dimethoxynaphthalen-1-yl)-6-bromo-2,3-dimethoxybenzamide. (29c)

Oxalyl chloride (0.2 mL, 2.25 mmol) was added to a solution of 6-bromo-2,3-dimethoxybenzoic acid (276 mg, 1.13 mmol) in anhydrous DCM (8 mL). This solution was then refluxed at 45 ^{o}C for 2 hours. Solvents were evaporated and flask was placed on vacuum pump for 30 minutes. Residue was taken back up in anhydrous DCM (5 mL) and **28c** (200 mg, 0.56 mmol) in anhydrous DCM (8 mL) was added to the flask followed by addition of Et_3N (0.23 mL, 1.69 mmol). Reaction was stirred at RT overnight. Additional DCM was added and solution was washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 2% MeOH/DCM afforded product as a white solid (140 mg, 42% yield); mp 274-275 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.68-7.61 (m, 5H), 7.52-7.51 (m, 3H), 7.47 (s, 1H), 7.44-7.40 (m, 2H), 7.33-7.28 (m, 3H), 7.24 (s, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.85 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 164.8, 152.5, 150.0, 149.8, 147.3, 140.7, 140.1, 140.0, 137.9, 134.2, 130.3, 130.1, 128.9, 128.5, 128.3, 127.4, 127.1, 127.0, 125.6, 125.3, 121.8, 114.5, 109.7, 105.5, 101.8, 62.5, 56.1, 55.8.

6-Bromo-*N*-(6,7-dimethoxy-4-phenylnaphthalen-1-yl)-2,3-dimethoxy-*N*-methylbenzamide (30b).

To a solution of **29b** (105 mg, 0.2 mmol) in anhydrous DMF (3 mL) was quickly added NaH (50 mg, 1.3 mmol) followed by excess MeI (0.3 mL). Reaction was stirred at RT overnight then diluted with EtOAc and washed with 10% HCl solution followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as an off-white solid (100 mg, 93% yield); mp 189-191 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.31-6.45 (m, 11H), 4.01-3.31 (m, 15H).

***N*-(4-([1,1'-Biphenyl]-4-yl)-6,7-dimethoxynaphthalen-1-yl)-6-bromo-2,3-dimethoxy-*N*-methylbenzamide. (30c)**

To a solution of **29c** (140 mg, 0.23 mmol) in anhydrous DMF (3 mL) was quickly added NaH (60 mg, 1.5 mmol) followed by excess MeI (0.3 mL). Reaction was stirred at RT overnight then diluted with EtOAc and washed with 10% HCl solution followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as a tan fluffy solid (135 mg, 96% yield); mp 129-131 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.68-6.81 (m, 15H), 4.02-3.21 (m, 15H).

2,3,7,8-Tetramethoxy-5-methyl-12-phenylbenzo[*c*]phenanthridin-6(5*H*)-one (31b).

A flask containing **30b** (30 mg, 0.056 mmol), $Pd(OAc)_2$ (5 mg, 0.011 mmol), P(*o*-tol)$_3$ (10 mg, 0.022 mmol), and Ag_2CO_3 (46 mg, 0.11 mmol) was degassed and anhydrous DMF (4 mL) was added. Reaction mixture was refluxed at 160 ^oC overnight. Solution was then filtered through filter paper to remove catalyst. Filtrate was diluted with EtOAc and washed with brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using chromatotron max gradient 2% MeOH/$CHCl_3$ afforded product as a tan oil (12 mg, 46% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 7.90 (d, *J* = 9.1 Hz, 1H), 7.85 (s), 7.48-7.46 (m, 5H), 7.41-7.37 (m, 1H), 7.28 (d, *J* = 9.0, 1H), 7.15 (s, 1H), 4.02 (s, 3H), 3.97 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 162.8, 152.7, 150.3, 149.3, 148.1, 135.0, 134.4, 129.9, 129.0, 128.6, 128.5, 127.5, 120.3, 119.9, 119.3, 117.9, 117.8, 116.4, 105.7, 105.4, 61.8, 56.6, 55.9, 40.7.

12-([1,1'-Biphenyl]-4-yl)-2,3,7,8-tetramethoxy-5-methylbenzo[*c*]phenanthridin-6(5*H*)-one. (31c)

A flask containing **30c** (287 mg, 0.47 mmol), $Pd(OAc)_2$ (31 mg, 0.14 mmol), P(*o*-tol)$_3$ (85 mg, 0.28 mmol), and Ag_2CO_3 (387 mg, 1.4 mmol) was degassed and anhydrous DMF (20 mL) was added. Reaction mixture was refluxed at 160 ^oC overnight. Solution was then filtered through filter paper to remove catalyst. Filtrate was diluted with EtOAc and washed with brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using chromatotron max gradient 2% MeOH/$CHCl_3$ afforded product as

a tan oil (139 mg, 57% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.94-7.91 (m, 23H), 7.72-7.70 (m, 2H), 7.66-7.64 (m, 2H), 7.58-7.56 (m, 2H), 7.48 (s, 1H), 7.45-7.41 (m, 2H), 7.35-7.29 (m, 2H), 7.23 (s, 1H).

2,3,7,8-Tetramethoxy-5-methyl-12-phenylbenzo[*c*]phenanthridin-5-ium chloride (32b).

A small flask containing **31b** (12 mg, 0.026 mmol) in anhydrous THF (1.5 mL) was cooled to 0 ^{o}C. LAH (3 mg, 0.078 mmol) was then quickly added and flask was removed from ice bath. Reaction was stirred for 30 minutes at RT. Flask was then put back in ice bath and H_2O (9 drops) was carefully added. Solution was filtered through filter paper and solvents evaporated. Residue was then treated with 10% HCl to afford product as a bright orange solid (10 mg, 83% yield); mp 145-147 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 9.88 (s, 1H), 8.54 (d, *J* = 9.2 Hz, 1H), 8.38 (s, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 8.02 (s, 1H), 7.51 (m, 5H), 7.31 (s, 1H), 4.97 (s, 3H), 4.20 (s, 3H), 4.04 (s, 3H), 4.01 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz) (CD_3OD) δ 152.4, 152.0, 151.2, 151.1, 147.5, 144.4, 140.5, 131.0, 130.9, 129.8, 127.4, 126.4, 121.1, 121.0, 119.9, 119.8, 108.8, 108.2, 62.9, 57.5, 57.0, 56.2, 52.8; HRMS Calcd for $C_{28}H_{26}NClO_4$ $(M\text{-}Cl)^{+}$ 440.1862, found 440.1855.

12-([1,1'-Biphenyl]-4-yl)-2,3,7,8-tetramethoxy-5-methylbenzo[*c*]phenanthridin-5-ium chloride. (32c)

A small flask containing **31c** (98 mg, 0.19 mmol) in anhydrous THF (5 mL) was cooled to 0 ^{o}C. LAH (22 mg, 0.57 mmol) was then quickly added and flask was removed from ice bath. Reaction was stirred for 30 minutes at RT. Flask was then put back in ice bath and H_2O (9 drops) was carefully added. Solution was filtered through filter paper and solvents evaporated. Residue was then treated with 10% HCl to afford product as a bright orange solid (90 mg, 86% yield); mp 140-141 ^{o}C; ^{1}H NMR (400 MHz) (DMSO-d_6) δ 10.07 (s, 1H), 8.89 (d, *J* = 9.4 Hz, 1H), 8.67 (s, 1H), 8.18-8.13 (m, 2H), 7.89-7.84 (m, 2H), 7.75-7.71 (m, 4H), 7.48-7.32 (m, 4H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 150.6, 150.3, 150.1, 149.0, 145.4, 141.4, 140.1, 139.4, 137.6, 132.1, 131.0, 130.7, 130.4, 129.1, 128.5, 127.8, 127.0, 126.7, 125.9, 124.6, 119.6, 119.4, 118.9, 108.1, 106.4, 62.3, 57.0, 56.2, 55.5, 52.1; HRMS Calcd for $C_{34}H_{30}ClNO_4$ $(M\text{-}Cl)^+$ 516.2175, found 516.2196.

***N*-(4-Bromo-3-methoxyphenethyl)-2-(3,4-dimethoxyphenyl)acetamide (33).**

To a solution of 2-(3-methoxy-4-bromophenyl)ethylamine hydrochloride (530 mg, 2.0 mmol) and 2M Na_2CO_3 (3 mL) in $CHCl_3$ (4 mL) was slowly added a solution of 3,4-dimethoxyphenyl acetyl chloride (430 mg, 2.0 mmol) in $CHCl_3$ (4 mL) at 0 ^{o}C. Reaction was stirred for 1 hour at 0 ^{o}C then diluted with additional $CHCl_3$ and H_2O. Organic layer was separated then washed with 0.1% NaOH followed by 0.1N HCl and then brine. Organic layer was collected, dried over Na_2CO_3, and concentrated. Chromatography

achieved using flash column max gradient 70% EtOAc/hexane yielding product as a white solid (740 mg, 91% yield); mp 119-120 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.69-6.64 (m, 3H), 6.50 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 1H), 5.46 (bs, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.48-3.44 (m, 4H), 2.72 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 171.1, 156.0, 149.3, 148.4, 139.6, 133.2, 127.1, 122.0, 121.5, 112.5, 112.4, 111.6, 110.0, 56.1, 56.0, 55.9, 43.5, 40.3, 35.3.

2-(3,4-Dimethoxyphenyl)-*N*-(2-(2-methoxy-4'-methyl-[1,1'-biphenyl]-4-yl)ethyl)acetamide (40b).

33 (400 mg, 0.98 mmol), 4-methylphenylboronic acid (200 mg, 1.47 mmol), $Pd(PPh_3)_4$ (113 mg, 0.098 mmol), and Na_2CO_3 (312 mg, 2.94 mmol) in dioxane/H_2O (6 mL/3 mL) were degassed and refluxed at 100 ^{o}C overnight. Reaction was cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$ followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as a pinkish-brown solid (315 mg, 77% yield); mp 123-124 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.43 (d, *J* = 8.1 Hz, 2H), 7.24 (d *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.74-6.70 (m, 4H), 5.58 (bs, 1H), 3.85 (s, 6H), 3.78 (s, 3H), 3.57-3.52 (m, 4H), 2.80 (t, *J* = 6.9 Hz, 2H); 2.42 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 171.4, 156.7, 149.3, 148.4, 139.1, 136.6, 135.7, 135.3, 130.8, 129.3, 129.0, 128.8, 128.6, 127.2, 121.6, 121.0, 112.6, 111.6, 111.5, 55.9, 55.8, 55.6, 43.5, 40.6, 35.5, 21.2.

2-(3,4-Dimethoxyphenyl)-*N*-(4-(furan-3-yl)-3-methoxyphenethyl)acetamide (40f).

33 (150 mg, 0.37 mmol), $Pd(PPh_3)_2Cl_2$ (15 mg, 0.02 mmol), 3-furanylboronic acid (83 mg, 0.74 mmol), and Cs_2CO_3 (362 mg, 1.1 mmol) in dioxane (3 mL) were microwaved at 120 ^oC for 10 minutes. Solution was then cooled and passed through a pad of celite. Filtrate was then collected, dried over Na_2SO_4, and concentrated. Chromatography achieved using flash column, max gradient 10% MeOH/DCM yielding product as a pale tan solid (90 mg, 62% yield); mp 118 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.89 (s, 1H), 7.38 (t, *J* = 1.7 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 6.71-6.70 (m, 2H), 6.61-6.58 (m, 4H), 5.35 (bs, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.44-3.40 (m, 4H), 2.68 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 171.2, 156.6, 149.3, 148.4, 142.3, 141.4, 138.4, 127.9, 127.2, 121.6, 121.4, 121.0, 119.6, 112.5, 111.6, 111.4, 109.3, 55.8, 55.4, 43.5, 40.5, 35.4.

2-(3,4-Dimethoxyphenyl)-*N*-(2-(2,2',3',4'-tetramethoxy-[1,1'-biphenyl]-4-yl)ethyl)acetamide (40g).

A flask containing **33** (200 mg, 0.49 mmol), 2,3,4-trimethoxyphenylboronic acid (208 mg, 0.98 mmol), $Pd(PPh_3)_4$ (57 mg, 0.05 mmol), and 2M Na_2CO_3 (1 mL) in toluene/MeOH (5:1) (7 mL) was degassed and then heated overnight at 100 ^oC. Reaction mixture was cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$ solution followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane

afforded product as a clear oil (82 mg, 34% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.62-7.38 (m, 5H), 6.99 (d, *J* = 7.1 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 5.54 (bs, 1H), 3.82 (s, 3H), 3.76 (s, 6H), 3.65 (s, 6H), 3.63 (s, 6H), 3.45-3.42 (m, 4H), 2.70 (s, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 171.2, 157.1, 153.1, 151.8, 149.3, 148.4, 142.1, 139.3, 132.0, 131.9, 131.5, 128.5, 125.8, 125.2, 121.6, 120.5, 112.6, 111.7, 106.9, 60.8, 60.7, 56.0, 55.9, 55.9, 55.5, 43.5, 40.7, 35.7.

1-(3,4-Dimethoxybenzyl)-6-methoxy-7-(*p*-tolyl)-3,4-dihydroisoquinoline (41b).

40b (67 mg, 0.16 mmol) was dissolved in anhydrous ACN (3 mL) and $POCl_3$ (0.06 mL, 0.62 mmol) was added. Solution was refluxed at 85 ^{o}C for 1.5 hours then cooled to RT. Reaction was then basified using 10% NH_4OH to a pH of 9-10, and this solution was extracted with DCM. Extract was washed with H_2O, dried over Na_2SO_4, and concentrated. Crude product was carried directly to next step.

1-(3,4-Dimethoxybenzyl)-7-(furan-3-yl)-6-methoxy-3,4-dihydroisoquinoline (41f).

40f (159 mg, 0.4 mmol) was dissolved in anhydrous ACN (4 mL) and $POCl_3$ (0.15 mL, 1.6 mmol) was added. Solution was refluxed at 85 ^{o}C for 1.5 hours then cooled to RT. Reaction was then basified using 10% NH_4OH to a pH of 9-10, and this solution was extracted with DCM. Extract was washed with H_2O, dried over Na_2SO_4, and concentrated. Crude product was carried directly to next step.

1-(3,4-Dimethoxybenzyl)-6-methoxy-7-(2,3,4-trimethoxyphenyl)-3,4-dihydroisoquinoline (41g).

40g (80 mg, 0.16 mmol) was dissolved in anhydrous ACN (4 mL) and $POCl_3$ (0.06 mL, 0.64 mmol) was added. Solution was refluxed at 85 ^oC for 1.5 hours then cooled to RT. Reaction was then basified using 10% NH_4OH to a pH of 9-10, and this solution was extracted with DCM. Extract was washed with H_2O, dried over Na_2SO_4, and concentrated. Crude product was carried directly to next step.

1-(3,4-Dimethoxybenzyl)-6-methoxy-7-(*p*-tolyl)isoquinoline (42b).

Crude **41b** (67 mg) was dissolved in tetralin (3 mL) and Pd/C (10% wt.) (40 mg) was added. Solution was refluxed at 215 ^oC for 2.5 hours. Reaction mixture was cooled to RT and catalyst was filtered out. Solvent was then evaporated using Kugelrohr. Chromatography using flash column max gradient 5% MeOH/DCM afforded product as golden oil (41 mg, 64% yield over two steps); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.34 (d, *J* = 5.8 Hz, 1H), 8.02 (s, 1H), 7.40 (d, *J* = 5.8 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.17 (s, 1H), 7.16 (s, 1H), 7.05 (s, 1H), 6.80 (d, *J* = 1.8 Hz, 1H), 6.73-6.67 (m, 2H), 4.47 (2H), 3.86 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 159.8, 158.2, 149.0, 147.5, 142.5, 137.9, 137.5, 134.9, 133.4, 132.2, 129.6, 128.9, 128.0, 122.8, 120.7, 118.7, 112.2, 111.4, 104.7, 55.9, 55.8, 55.7, 41.7, 21.2.

1-(3,4-Dimethoxybenzyl)-7-(furan-3-yl)-6-methoxyisoquinoline (42f).

Crude **41f** (159 mg) was dissolved in tetralin (5 mL) and Pd/C (10% wt.) (75 mg) was added. Solution was refluxed at 215 ^{o}C for 2.5 hours. Reaction mixture was cooled to RT and catalyst was filtered out. Solvent was then evaporated using Kugelrohr. Chromatography using flash column max gradient 5% MeOH/DCM afforded product as tan oil (45 mg, 30% yield over two steps); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.51 (d, *J* = 5.6 Hz, 1H), 8.29 (s, 1H), 8.06 (s, 1H), 7.75 (d, *J* = 1.9 Hz, 1H), 7.69 (d, *J* = 5.6 Hz, 1H), 7.48 (t, *J* = 1.7 Hz, 1H), 7.43 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 7.24 (s, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.84 (m, 1H), 4.51 (s, 2H), 4.10 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 159.6, 158.0, 149.1, 147.7, 142.6, 142.3, 142.2, 137.3, 132.4, 125.1, 124.1, 122.8, 121.4, 120.6, 118.7, 112.1, 111.5, 109.6, 104.8, 55.9, 55.8, 55.6, 42.0.

1-(3,4-Dimethoxybenzyl)-6-methoxy-7-(2,3,4-trimethoxyphenyl)isoquinoline (42g).

Crude **41g** (80 mg) was dissolved in tetralin (4 mL) and Pd/C (10% wt.) (40 mg) was added. Solution was refluxed at 215 ^{o}C for 2.5 hours. Reaction mixture was cooled to RT and catalyst was filtered out. Solvent was then evaporated using Kugelrohr. Chromatography using flash column max gradient 5% MeOH/DCM afforded product as golden oil (55 mg, 72% yield over two steps); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.34 (d, *J* = 5.8 Hz, 1H), 7.96 (s, 1H), 7.41 (d, *J* = 5.2 Hz, 1H), 7.04 (s, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 1H), 6.69-6.64 (m, 3H), 4.46 (s, 2H), 3.84 (s, 6H), 3.83 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 159.7, 158.8, 153.7,

152.0, 148.9, 147.5, 138.1, 131.9, 131.8, 130.6, 128.5, 125.3, 124.7, 122.6, 120.7, 118.8, 112.2, 111.3, 106.9, 104.3, 60.8, 60.7, 56.0, 55.9, 55.8, 55.7, 41.4.

3,10,11-Trimethoxy-2-(*p*-tolyl)isoquinolino[3,2-*a*]isoquinolin-7-ium chloride (43b).

A solution of anhydrous DMF (1 mL) and $POCl_3$ (0.2 mL) was chilled to 0 ^oC and stirred for 15 minutes. **42b** (20 mg, 0.05 mmol) in anhydrous DMF (1 mL) was then added to the chilled solution and mixture was stirred for an another hour at 0 ^oC. Reaction was then heated for 1 hour at 100 ^oC and allowed to cool to RT. Solution was poured into a test tube containing 0.5 mL 6N HCl and an ice cube, and test tube was placed in the fridge to chill overnight. Solid that formed was then filtered off, washed with a small amount of MeOH followed by Et_2O, and dried to afford product as a yellow solid (11 mg, 50% yield); mp 230-233 ^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 9.95 (s, 1H), 9.69 (s, 1H), 8.80 (d, *J* = 7.6 Hz, 1H), 8.77 (s, 1H), 7.99 (d, *J* = 7.4 Hz, 1H), 7.75 (s, 1H), 7.70 (s, 1H), 7.66 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 4.08 (s, 3H), 4.04 (s, 3H), 4.00 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 159.1, 157.2, 152.9, 138.0, 137.4, 135.0, 134.9, 133.7, 133.6, 130.3, 129.9, 129.6, 129.0, 128.8, 126.1, 122.5, 120.5, 118.4, 116.8, 108.7, 104.4, 56.6, 56.4, 56.3, 20.8; HRMS (ESI) Calcd for $C_{27}H_{24}ClNO_3$ $(M\text{-}Cl)^+$ 410.1751, found 410.1749.

2-(Furan-3-yl)-3,10,11-trimethoxyisoquinolino[3,2-*a*]isoquinolin-7-ium chloride (43f).

A solution of anhydrous DMF (0.4 mL) and $POCl_3$ (0.15 mL) was chilled to 0 ^oC and stirred for 15 minutes. **42f** (9 mg, 0.02 mmol) in anhydrous DMF (0.6 mL) was then added to the chilled solution and mixture was stirred for an another hour at 0 ^oC. Reaction was then heated for 1 hour at 100 ^oC and allowed to cool to RT. Solution was poured into a test tube containing 0.5 mL 6N HCl and an ice cube, and test tube was placed in the fridge to chill overnight. Solid that formed was then filtered off, washed with a small amount of MeOH followed by Et_2O, and dried to afford product as a yellow solid (7 mg, 87% yield); mp 223-226 ^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 10.07 (s, 1H), 9.79 (s, 1H), 9.66 (s, 1H), 9.08 (s, 1H), 8.90 (d, *J* = 8.0 Hz, 1H), 8.26 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.65 (s, 1H), 7.12 (s, 1H), 4.12 (s, 3H), 4.06 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 159.9, 158.7, 152.7, 150.1, 147.3, 146.9, 144.3, 140.1, 139.8, 136.9, 132.0, 129.1, 128.7, 128.6, 127.4, 125.1, 124.8, 119.1, 115.6, 114.2, 108.4, 56.6, 56.4, 56.2.

3,10,11-Trimethoxy-2-(2,3,4-trimethoxyphenyl)isoquinolino[3,2-*a*]isoquinolin-7-ium chloride (43g).

A solution of anhydrous DMF (1 mL) and $POCl_3$ (0.38 mL) was chilled to 0 ^oC and stirred for 15 minutes. **42g** (23 mg, 0.05 mmol) in anhydrous DMF (1 mL) was then added to the chilled solution and mixture was stirred for an another hour at 0 ^oC. Reaction was then heated for 1 hour at 100 ^oC and allowed to cool to RT. Solution was

poured into a test tube containing 0.5 mL 6N HCl and an ice cube, and test tube was placed in the fridge to chill overnight. Solid that formed was then filtered off, washed with a small amount of MeOH followed by Et_2O, and dried to afford product as a yellow solid (15 mg, 60% yield); mp 237-240 ^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 9.99 (s, 1H), 9.73 (s, 1H), 8.85 (d, *J* = 5.5 Hz, 1H), 8.72 (s, 1H), 8.03 (d, *J* = 6.1 Hz, 1H), 7.75-7.69 (m, 3H), 7.06-6.95 (m, 2H), 4.07 (s, 3H), 4.06 (s, 3H), 3.98 (s, 3H), 3.90 (s, 3H), 3.83 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 159.9, 157.2, 153.8, 152.9, 151.3, 141.7, 138.0, 135.1, 131.7, 130.3, 130.2, 130.0, 127.0, 125.2, 123.6, 122.6, 120.7, 118.1, 116.8, 108.0, 107.7, 104.5, 104.4, 60.6, 60.4, 56.6, 56.4, 56.1, 54.8; HRMS (ESI) Calcd for $C_{29}H_{28}ClNO_6$ $(M\text{-}Cl)^+$ 486.1917, found 486.1906.

3,10,11-Trimethoxy-8-methyl-2-(*p*-tolyl)isoquinolino[3,2-*a*]isoquinolin-7-ium (44b).

Fuming sulfuric acid (20%) (0.1 mL) was added to freshly distilled acetic anhydride (1 mL) resulting in a vigorous exothermic reaction and a red-wine color. This mixture was heated at 90 ^oC for 10 minutes. A solution of 1-(3,4-dimethoxybenzyl)-6-methoxy-7-(*p*-tolyl)isoquinoline (20 mg, 0.05 mmol) in acetic anhydride (1 mL) was added to the red-wine mixture and reaction was heated at 90 ^oC for an additional hour. Solution is then cooled to RT and MeOH (0.5 mL) was added and stirred for 15 minutes. Solution was then chilled over ice and ether was added to crash precipitate out of solution. This precipitate was filtered off and washed with a small amount of MeOH to give product as a brown solid (17 mg, 61% yield); mp 212-216 ^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 9.63 (s, 1H), 8.90 (d, *J* = 7.9 Hz, 1H), 8.77 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.77 (s, 1H),

7.73 (s, 1H), 7.66 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.09 (s, 3H), 4.06 (s, 3H), 3.98 (s, 3H), 2.51 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 158.9, 156.4, 146.2, 137.4, 134.0, 129.6, 129.1, 128.8, 126.5, 121.9, 120.6, 108.2, 105.1, 104.3, 57.0, 56.5, 56.3, 20.8, 17.3; HRMS (ESI) Calcd for $C_{28}H_{26}NO_3^+$ $(M)^+$ 424.1907, found 424.1907.

2-(5,6-Dimethoxy-[1,1'-biphenyl]-2-yl)-*N*-(2,3-dimethoxyphenethyl)acetamide (51c).

2-(2-Bromo-3,4-dimethoxyphenyl)-*N*-(2,3-dimethoxyphenethyl)acetamide (**50**) (300 mg, 0.69 mmol), phenylboronic acid (167 mg, 1.37 mmol), and K_2CO_3 (293 mg, 2.12 mmol) in dioxane/H_2O (10 mL/1 mL) were degassed and $Pd(PPh_3)_4$ (80 mg, 0.07 mmol) was added. Reaction was refluxed at 100 ^oC for 2 hours then cooled to RT and diluted with EtOAc, washed with $NaHCO_3$ followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using flash column max gradient 70% EtOAc/hexane afforded product as a golden oil (296 mg, 99% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.38-7.32 (m, 3H), 7.12-7.10 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.98-6.91 (m, 2H), 6.81 (dd, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H), 6.63 (dd, *J* = 7.6 Hz, *J* = 1.4 Hz, 1H), 5.52 (bs, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 3.76 (s, 3H), 3.53 (s, 3H), 3.36 (q, *J* = 6.3 Hz, 2H), 3.25 (s, 2H), 2.72 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 171.3, 152.8, 152.0, 147.2, 147.0, 136.5, 132.7, 129.7, 128.1, 127.2, 126.4, 125.4, 124.0, 122.4, 122.2, 111.9, 111.0, 60.5, 56.2, 55.9, 55.8, 40.8, 40.4, 29.6.

1-((5,6-Dimethoxy-[1,1'-biphenyl]-2-yl)methyl)-5,6-dimethoxy-3,4-dihydroisoquinoline (52c).

51c (269 mg, 0.62 mmol) was dissolved in anhydrous ACN (8 mL) and $POCl_3$ (0.23 mL, 2.5 mmol) was added. Solution was refluxed at 85 ^oC for 1.5 hours then cooled to RT. Reaction was then basified using 10% NH_4OH to a pH of 9-10, and this solution was extracted with DCM. Extract was washed with H_2O, dried over Na_2SO_4, and concentrated. Crude product was carried directly to next step.

1-((5,6-Dimethoxy-[1,1'-biphenyl]-2-yl)methyl)-5,6-dimethoxyisoquinoline (53c).

Crude **52c** (269 mg) was dissolved in tetralin (7 mL) and Pd/C (10% wt.) (100 mg) was added. Solution was refluxed at 215 ^oC for 2.5 hours. Reaction mixture was cooled to RT and catalyst was filtered out. Solvent was then evaporated using Kugelrohr. Chromatography using flash column max gradient 5% MeOH/DCM afforded product as clear oil (117 mg, 46% yield over two steps); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.41 (d, J = 6.0 Hz, 1H), 7.78 (d, J = 6.0 Hz, 1H), 7.48-7.42 (m, 3H), 7.40-7.36 (m, 3H), 7.16 (d, J = 9.2 Hz, 1H), 6.79-6.71 (m, 2H), 4.36 (s, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.56 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 160.4, 151.2, 150.9, 146.6, 142.3, 141.8, 137.1, 136.2, 132.4, 130.9, 129.9, 128.2, 127.1, 124.5, 123.1, 122.7, 115.0, 113.2, 111.6, 61.1, 60.5, 56.4, 55.8, 39.1.

3,4,10,11-Tetramethoxy-12-phenylisoquinolino[3,2-*a*]isoquinolin-7-ium chloride (54c).

A solution of anhydrous DMF (1 mL) and $POCl_3$ (0.4 mL) was chilled to 0 ^oC and stirred for 15 minutes. **53c** (66 mg, 0.16 mmol) in anhydrous DMF (1 mL) was then added to the chilled solution and mixture was stirred for an another hour at 0 ^oC. Reaction was then heated for 1 hour at 100 ^oC and allowed to cool to RT. Solution was poured into a test tube containing 0.5 mL 6N HCl and an ice cube, and test tube was placed in the fridge to chill overnight. Solid that formed was then filtered off, washed with a small amount of MeOH followed by Et_2O, and dried to afford product as a brown solid (35 mg, 48% yield); mp 264-267 ^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 10.33-10.21 (m, 1H), 8.91-8.84 (m, 1H), 8.63 (d, *J* = 11.1 Hz, 1H), 8.22-7.97 (m, 3H), 7.75-7.69 (m, 4H), 7.54 (s, 2H), 4.21 (s, 3H), 4.17 (s, 3H), 4.01 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 155.5, 154.0, 153.8, 143.0, 134.6, 133.9, 133.7, 130.4, 130.2, 129.6, 129.4, 128.9, 124.0, 123.4, 120.4, 118.1, 117.3, 116.9, 115.5, 106.1, 105.3, 61.5, 61.4, 56.8, 56.5; HRMS (ESI) Calcd for $C_{27}H_{24}ClNO_4$ $(M\text{-}Cl)^+$ 426.1700, found 426.1704.

2-(Hydroxyimino)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (57).

To a solution of 5,6-dimethoxy-1-indanone (2 g, 10.4 mmol) in MeOH (40 mL) was added concentrated HCl (1.04 mL). Butyl nitrite (1.34 mL, 11.5 mmol) in MeOH (10 mL) was then added at 40 ^oC and reaction mixture was allowed to stir for 2.5 hours. Reaction mixture was then cooled to RT and precipitate was filtered out and dried to afford product as a pale yellow solid (2.14 g, 93% yield); mp 221-223 ^oC; ^1H NMR (400

MHz) (DMSO-d_6) δ 12.44 (s, 1H), 7.18 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.66 (s, 2H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 187.5, 156.0, 154.7, 149.3, 142.5, 130.5, 108.6, 104.5, 55.9, 55.7, 27.8.

2-(Cyanomethyl)-4,5-dimethoxybenzoic acid (58).

57 (2.14 g, 9.7 mmol) was added to a solution of 8% NaOH (20 mL) and heated to 50^{o}C. *p*-Toluenesulfonyl chloride (2.46 g, 12.9 mmol) was then added in portions. Reaction mixture was heated to 80 ^{o}C for 15 minutes then cooled to RT. Precipitate was filtered off and filtrate was collected and acidified with concentrated HCl to a pH of 3-4. Resulting precipitate was collected and dried to afford product as a tan solid (1.84 g, 86% yield); mp 153-156 ^{o}C; ^{1}H NMR (400 MHz) (DMSO-d_6) δ 13.05 (s, 1H), 7.51 (s, 1H), 7.15 (s, 1H), 4.19 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 167.1, 151.9, 147.7, 126.4, 121.4, 119.1, 114.1, 113.9, 56.8, 56.2, 22.0.

3-Bromo-6,7-dimethoxyisoquinolin-1(2*H*)-one (59).

58 (500 mg, 2.36 mmol) was added to a 3-neck flask with a stir bar under N_2 and dissolved in anhydrous DCM (7 mL). Oxalyl chloride (0.79 mL, 9.05 mmol) was then added followed by catalytic amount of anhydrous DMF. Reaction was allowed to stir for 2 hours at RT then solvents were evaporated and placed on vacuum pump for 30 minutes. Crude product was then taken back up in anhydrous ether (30 mL) and $HBr_{(g)}$ was bubbled through the solution for 2 hours. Reaction mixture was diluted with $CHCl_3$ and

washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. DCM was then added to precipitate product out. Precipitate was then filtered and dried to afford product as a brown solid (498 mg, 78% yield); mp 249-253 ^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 12.03 (s, 1H), 7.50 (s, 1H), 7.14 (s, 1H), 6.79 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 161.5, 153.4, 148.8, 133.4, 128.9, 128.2, 107.7, 106.6, 106.3, 55.8, 55.5.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1(2*H*)-one (60a).

59 (550 mg, 1.94 mmol) was combined with 3-biphenyl boronic acid (768 mg, 3.88 mmol), $Pd(OAc)_2$ (43.5 mg, 0.194 mmol), XPhos (185 mg, 0.388 mmol), and K_2CO_3 (1.07 g, 7.76 mmol) in a flask and degassed. ACN (15 mL) and H_2O (7.5 mL) were then added and solution was heated at 100 ^oC for 1.5 hours. Reaction mixture was cooled to RT then diluted with EtOAc and washed with $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 70% EtOAc/hexane afforded product as a white solid (540 mg, 78% yield); mp 229-231 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.98 (bs, 1H), 7.97 (m, 1H), 7.78 (s, 1H), 7.75-7.67 (m, 4H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.50-7.46 (m, 2H), 7.43-7.39 (m, 1H), 7.01 (s, 1H), 6.81 (s, 1H), 4.05 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.5, 153.9, 149.3, 142.0, 140.4, 138.5, 135.1, 133.9, 129.5, 128.9, 127.8, 127.8, 127.2, 125.1, 125.0, 119.0, 107.4, 106.6, 104.2, 56.1, 56.1; HRMS (ESI) Calcd for $C_{23}H_{20}NO_3$ $(M+H)^+$ 358.1438, found 358.1432.

3-([1,1':3',1''-Terphenyl]-5'-yl)-6,7-dimethoxyisoquinolin-1(2*H*)-one (60b).

59 (100 mg, 0.35 mmol) was combined with [1,1':3',1"-terphenyl]-5'-ylboronic acid (193 mg, 0.7 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol), XPhos (33.5 mg, 0.07 mmol), and K_2CO_3 (194 mg, 1.06 mmol) in a flask and degassed. ACN (6 mL) and H_2O (3 mL) were then added and solution was heated at 100 ^oC for 1.5 hours. Reaction mixture was cooled to RT then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 70% EtOAc/hexane afforded product as a white solid (108 mg, 71% yield); mp 256-260 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 11.20 (s, 1H), 7.91 (d, *J* = 4.0 Hz, 2H), 7.84 (t, *J* = 2.0 Hz, 1H), 7.74-7.72 (m, 4H), 7.65 (s, 1H), 7.41-7.38 (m, 4H), 7.34- 7.30 (m, 2H), 6.93 (s, 1H), 6.80 (s, 1H), 3.95 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.6, 154.0, 149.3, 142.7, 140.5, 138.5, 135.6, 133.9, 129.0, 127.9, 127.3, 126.8, 124.0, 119.0, 107.4, 106.6, 104.5, 56.1, 53.4.

3-([1,1'-Biphenyl]-3-yl)-1-chloro-6,7-dimethoxyisoquinoline (61a).

60a (130 mg, 0.36 mmol) was refluxed at 110 ^oC in $POCl_3$ (3 mL) for 3 hours. $POCl_3$ was then removed under vacuum. Chromatography achieved using ISCO max gradient 70% EtOAc/hexane yielding product as a beige solid (117 mg, 85% yield); mp 143-144 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.32 (t, *J* = 2.0 Hz, 1H), 8.10-8.07 (m, 1H), 7.96 (s, 1H), 7.73-7.71 (m, 2H), 7.66-7.64 (m, 1H), 7.57 (t, *J* = 6.0 Hz, 2H), 7.52-7.48 (m, 1H), 7.18 (s, 1H), 4.11 (s, 3H), 4.08 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 8.32 (t, *J* = 2.0 Hz, 1H), 8.10-8.07 (m, 1H), 7.96 (s, 1H), 7.73-7.71 (m, 2H), 7.66-7.64 (m, 1H), 7.57 (t, *J*

= 6.0 Hz, 2H), 7.52-7.48 (m, 2H), 7.42-7.38 (m, 1H), 7.18 (s, 1H), 4.11 (s, 3H), 4.08 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.7, 151.1, 149.2, 149.1, 141.8, 141.2, 138.9, 135.3, 129.2, 128.8, 127.5, 127.4, 127.3, 125.6, 125.6, 121.8, 115.4, 105.4, 104.6, 56.2; HRMS (ESI) Calcd for $C_{23}H_{19}ClNO_2$ $(M+H)^+$ 376.1099, found 376.1087.

3-([1,1':3',1''-Terphenyl]-5'-yl)-1-chloro-6,7-dimethoxyisoquinoline (61b).

60b (105 mg, 0.24 mmol) was refluxed at 110^{o}C in $POCl_3$ (3 mL) for 3 hours. $POCl_3$ was then removed under vacuum. Chromatography using ISCO max gradient 70% EtOAc/hexane afforded product as a beige solid (84 mg, 77% yield); mp 183-184 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.29 (d, *J* = 4.0 Hz, 2H), 8.01 (s, 1H), 7.86 (t, *J* = 2.0 Hz, 1H), 7.79- 7.76 (m, 4H), 7.57 (s, 1H), 7.54-7.50 (m, 4H), 7.45-7.41 (m, 2H), 7.18 (s, 1H), 4.11 (s, 3H), 4.08 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.8, 151.2, 149.2, 142.4, 141.2, 139.4, 135.3, 128.8, 127.5, 127.4, 126.5, 124.6, 121.8, 115.6, 105.5, 104.6, 56.2.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinoline (62a).

61a (60 mg, 0.16 mmol) was dissolved in EtOH (5 mL) and Pd/C (10% wt.) (20 mg) was added. Flask was then degassed to remove air and reaction was then stirred under an $H_{2(g)}$ atmosphere overnight at RT. Catalyst was then filtered out and solvent evaporated. Chromatography using ISCO max gradient 70% EtOAc/hexane afforded product as a beige oil (18 mg, 33% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.09 (s, 1H), 8.25 (t, *J* = 4.0 Hz, 1H), 8.00-7.98 (m, 1H), 7.93 (s, 1H), 7.66-7.64 (m, 2H), 7.57-7.55 (m, 1H), 7.49

(t, *J* = 6.0 Hz, 1H), 7.42-7.38 (m, 2H), 7.32-7.28 (m, 1H), 7.17 (s, 1H), 7.07 (s, 1H), 3.98 (s, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.3, 150.4, 150.2, 149.9, 141.8, 141.3, 140.4, 133.4, 129.2, 128.8, 128.7, 127.3, 127.0, 125.8, 125.8, 123.9, 115.7, 105.3, 105.0, 56.1, 56.1; HRMS (ESI) Calcd for $C_{23}H_{20}NO_2$ $(M+H)^+$ 342.1489, found 342.1485.

3-([1,1':3',1''-Terphenyl]-5'-yl)-6,7-dimethoxyisoquinoline (62b).

61b (37 mg, 0.82 mmol) was dissolved in EtOH (5 mL) and Pd/C (10% wt.) (35 mg) was added. Flask was then degassed to remove air and reaction was then stirred under an $H_{2(g)}$ atmosphere overnight at RT. Catalyst was then filtered out and solvent evaporated. Chromatography using ISCO max gradient 60% EtOAc/hexane afforded product as a clear oil (10 mg, 29% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.10 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 2H), 7.99 (s, 1H), 7.77 (t, *J* = 4.0 Hz, 1H), 7.71-7.69 (m, 4H), 7.44-7.40 (m, 4H), 7.34-7.30 (m, 2H), 7.19 (s, 1H), 7.09 (s, 1H), 3.99 (s, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.3, 150.5, 150.2, 149.9, 142.3, 141.3, 141.0, 133.4, 128.8, 127.5, 127.4, 126.0, 124.8, 124.0, 115.8, 105.4, 105.0, 56.1; HRMS (ESI) Calcd for $C_{29}H_{23}NO_2$ $(M+H)^+$ 418.1816, found 418.1794.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxy-2-methylisoquinolin-2-ium iodide (63a).

62a (9 mg, 0.026 mmol) and MeI (1 mL) were heated in a sealed tube overnight at 100 ^{o}C. Solvent was then evaporated and residue was taken back up in DCM. Ether was then used to crash out solid which was filtered and dried to afford product as a tan solid (13

mg, quantitative); mp 205-208 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.90 (s, 1H), 8.21 (s, 1H), 7.92 (s, 1H), 7.86-7.84 (m, 1H), 7.69-7.62 (m, 4H), 7.51-7.41 (m, 4H), 7.25 (s, 1H), 4.40 (s, 3H), 4.16 (s, 3H), 4.13 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.6, 150.5, 150.2, 141.4, 140.2, 139.2, 129.3, 129.2, 129.0, 128.4, 128.0, 127.8, 127.2, 126.9, 107.8, 56.7, 53.1, 46.0; HRMS (ESI) calculated for $C_{24}H_{22}INO_2$ $(M\text{-}I)^+$ 356.1651, found 356.1647.

3-([1,1':3',1''-Terphenyl]-5'-yl)-6,7-dimethoxy-2-methylisoquinolin-2-ium iodide (63b).

62b (10 mg, 0.024 mmol) and MeI (1 mL) were heated in a sealed tube overnight at 100 ^{o}C. Solvent was then evaporated and residue was taken back up in DCM. Ether was then used to crash out solid which was filtered and dried to afford product as a off-white solid (7 mg, quantitative); mp 185-186 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.74 (s, 1H), 8.11 (s, 1H), 7.96 (t, *J* = 4.0 Hz, 1H), 7.95 (s, 1H), 7.63-7.61 (m, 6H), 7.45-7.42 (m, 4H), 7.39-7.35 (m, 2H), 7.19 (s, 1H), 4.38 (s, 3H), 4.06 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 159.9, 153.3, 147.7, 143.3, 139.3, 133.0, 129.2, 128.5, 128.3, 127.3, 126.7, 124.3, 124.2, 107.9, 104.5 57.4, 57.1, 46.8; HRMS (ESI) Calcd for $C_{30}H_{26}INO_2$ $(M\text{-}I)^+$ 432.1958, found 432.1961.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinoline-1-carbonitrile (64).

61a (50 mg, 0.13 mmol) and CuCN (24 mg, 0.27 mmol) in DMSO (2 mL) were heated at 140 ^{o}C for 3 hours. Reaction mixture was then cooled to RT, diluted with EtOAc, and washed with H_2O. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a beige solid (13 mg, 27% yield); mp 171-174 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.25 (t, *J* = 2.0 Hz, 1H), 8.10 (s, 1H), 8.00-7.98 (m, 1 H), 7.64-7.62 (m, 2H), 7.60-7.57 (m, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.43-7.39 (m, 3H), 7.34-7.30 (m, 1H), 7.11 (s, 1H), 4.03 (s, 3H), 4.00 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.3, 152.6, 150.7, 142.0, 141.0, 138.5, 134.1, 131.6, 129.3, 128.8, 127.9, 127.5, 127.3, 125.7, 125.6, 125.5, 118.9, 116.6, 105.2, 102.7, 56.5, 56.3; HRMS (ESI) Calcd for $C_{24}H_{19}N_2O_2$ $(M+H)^+$ 367.1441, found 367.1435.

***N*^{1}-(3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)ethane-1,2-diamine (65).**

61a (50 mg, 0.13 mmol) in ethylenediamine (0.5 mL) was heated at 150 ^{o}C in a sealed tube overnight. Solution was then cooled to RT and concentrated. Chromatography using flash column max gradient 10% MeOH/DCM/1% NH_4OH afforded product as a beige oil (12 mg, 23% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.26 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.42-7.38 (m, 2H), 7.34 (s, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 4.0 Hz, 2H), 5.50 (bs, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.75 (q, *J* = 5.3 Hz, 2H), 3.08 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.0, 152.2, 149.1, 147.7, 141.7, 141.4, 140.9, 134.2,

128.9, 128.7, 127.3, 127.2, 126.7, 125.5, 125.4, 112.1, 106.7, 106.5, 101.3, 56.2, 55.9, 44.3, 41.4; HRMS (ESI) Calcd for $C_{25}H_{26}N_3O_2$ $(M+H)^+$ 400.2020, found 400.2017.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxy-*N*,*N*-dimethylisoquinolin-1-amine (66a).

61a (20 mg, 0.053 mmol) and chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]PdII) (*t*-buXPhos precatalyst) (4 mg, 0.0053 mmol) were combined in a flask and air was evacuated and replaced with N_2. Dimethylamine (2M in THF) (2 mL) followed by LHMDS (1M in THF) (0.02 mL, 0.08 mmol) was then added, and reaction was allowed to stir overnight at RT. Reaction mixture was then diluted with EtOAc and washed with NH_4Cl. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a tan oil (20 mg, quantitative); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.30 (t, *J* = 2.0 Hz, 1H), 8.05 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.64-7.62 (m, 2H), 7.58 (s, 1H), 7.52-7.49 (m, 1H), 7.47-7.44 (m, 1H), 7.42-7.38 (m, 2H), 7.36 (s, 1H), 7.32-7.28 (m, 1H), 7.03 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.06 (s, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 152.2, 148.9, 147.2, 145.9, 141.7, 141.5, 140.7, 135.6, 128.9, 128.7, 127.3, 127.2, 126.8, 125.5, 125.43, 115.9, 110.4, 106.1, 105.0, 56.0, 55.9, 43.0; HRMS (ESI) Calcd for $C_{25}H_{25}N_2O_2$ $(M+H)^+$ 385.1911, found 385.1903.

3-([1,1':3',1''-Terphenyl]-5'-yl)-6,7-dimethoxy-*N*,*N*-dimethylisoquinolin-1-amine (66b).

61b (25 mg, 0.06 mmol) and chloro(2-di-t-butylphosphino-2', 4', 6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]PdII) (4 mg, 0.006 mmol) were combined in a flask and air was evacuated and replaced with N_2. Dimethylamine (2M in THF) (2 mL) followed by LHMDS (1M in THF) (0.02 mL, 0.01 mmol) was then added, and reaction was allowed to stir overnight at RT. Reaction mixture was then diluted with EtOAc and washed with saturated NH_4Cl. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a tan solid (24 mg, 94% yield); mp 102-104 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.28 (m, 2H), 7.72 (m, 1H), 7.69-7.67 (m, 4H), 7.63 (s, 1H), 7.44-7.40 (m, 4H), 7.37 (s, 1H), 7.34-7.30 (m, 2H), 7.18 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.08 (s, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 160.5, 152.2, 148.9, 147.2, 142.1, 141.6, 141.3, 135.5, 128.8, 127.4, 127.4, 125.8, 124.6, 115.9, 106.1, 105.0, 56.0, 55.9, 43.0; HRMS (ESI) Calcd for $C_{31}H_{28}N_2O_2$ $(M+H)^+$ 461.2184, found 461.2212.

3-([1,1'-Biphenyl]-3-yl)-1-(dimethylamino)-6,7-dimethoxy-2-methylisoquinolin-2-ium iodide (67).

66a (28 mg, 0.073 mmol) was heated in MeI (0.5 mL) in a sealed tube overnight at 100 ^oC. Solvent was then evaporated and residue was taken back up in DCM. Ether was then used to crash out solid which was filtered and dried to afford product as a tan solid (20 mg, 71% yield); mp 158-161 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.87 (t, J = 2.0 Hz, 1H),

7.79-7.77 (m, 1H), 7.75 (s, 1H), 7.73-7.69 (m, 3H), 7.67-7.63 (m, 1H), 7.56 (s, 1H), 7.52-7.48 (m, 2H), 7.44-7.42 (m, 1H), 7.39 (s, 1H), 4.15 (s, 3H), 4.12 (s, 3H), 3.97 (s, 3H), 3.63 (s, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 158.7, 156.9, 151.9, 144.9, 142.5, 139.6, 136.9, 134.2, 130.0, 129.1, 129.0, 128.2, 127.6, 127.3, 120.1, 119.4, 106.9, 106.6, 57.1, 45.6, 45.2, 34.5; HRMS (ESI) Calcd for $C_{26}H_{27}IN_2O_2$ $(M-I)^+$ 399.2073, found 399.2071.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxy-*N*-methylisoquinolin-1-amine (68).

61a (20 mg, 0.053 mmol) and chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]PdII) (*t*-buXPhos precatalyst) (4 mg, 0.0053 mmol) were combined in a flask and air was evacuated and replaced with N_2. Methylamine (2M in THF) (2 mL) followed by LHMDS (1M in THF) (0.02 mL, 0.08 mmol) was then added, and reaction was allowed to stir overnight at RT. Reaction mixture was then diluted with EtOAc and washed with saturated NH_4Cl. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 50% EtOAc/hexane afforded product as a clear oil (20 mg, quantitative); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.31 (t, *J* = 2.0 Hz, 1H), 8.06 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.64-7.62 (m, 2H), 7.51-7.49 (m, 1H), 7.46-7.43 (m, 1H), 7.41-7.37 (m, 2H), 7.34 (s, 1H), 7.31-7.27 (m, 1H), 6.99 (s, 1H), 6.91 (s, 1H), 4.92 (bs, 1H), 3.93 (s, 6H), 3.21 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.5, 152.2, 149.1, 141.7, 141.4, 141.0, 134.1, 128.9, 128.7, 127.2, 126.7, 125.5, 125.5, 112.1, 106.6, 106.6, 101.2, 56.1, 55.9, 29.0; HRMS (ESI) calculated for $C_{24}H_{23}N_2O_2$ $(M+H)^+$ 371.1754, found 371.1746.

2-(3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)guanidine (69a).

Guanidine HCl (38 mg, 0.4 mmol) was added to a suspension of NaH (10 mg, 0.24 mmol) in anhydrous DMSO (5 mL). Reaction was heated at 60 ^{o}C for 30 minutes then **61a** (50 mg, 0.13 mmol) and chloro(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]PdII) (*t*-buXPhos precatalyst) (9 mg, 0.013 mmol) were then quickly added, and the reaction was heated at 100 ^{o}C overnight. Reaction mixture was cooled to RT, diluted with EtOAc, and washed with H_2O. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 5% MeOH/DCM afforded product as a tan solid (20 mg, 38% yield); mp 255-257 ^{o}C; ^{1}H NMR (400 MHz) (DMSO-d_6) δ 11.36 (bs, 1H), 8.26-8.19 (m, 3H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.81-7.74 (m, 3H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.55-7.50 (m, 3H), 7.43 (t, *J* = 6.0 Hz, 1H), 4.05 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 156.3, 153.4, 150.6, 145.0, 141.0, 140.0, 139.0, 135.1, 129.7, 129.0, 127.7, 126.9, 125.2, 124.5, 113.4, 113.2, 106.6, 102.9, 56.9, 55.8; HRMS (ESI) Calcd for $C_{24}H_{23}N_4O_2$ $(M+H)^+$ 399.1816, found 398.1823.

2-(3-([1,1':3',1''-Terphenyl]-5'-yl)-6,7-dimethoxyisoquinolin-1-yl)guanidine (69b).

Guanidine HCl (13 mg, 0.13 mmol) was added to a suspension of NaH (6 mg, 0.08 mmol) in anhydrous DMSO (2 mL). Reaction was heated at 60^{o}C for 30 minutes then **61b** (20 mg, 0.04 mmol) and chloro(2-di-t-butylphosphino-2', 4', 6'-tri-i-propyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl]PdII) (5 mg, 0.004 mmol) were then quickly added, and the reaction was heated at 100 ^{o}C overnight. Reaction mixture was cooled to RT,

diluted with EtOAc, and washed with H_2O. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 5% MeOH/DCM afforded product as a brown solid (10.5 mg, 50% yield); mp 293-296^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 8.28 (s, 1H), 8.28 (m, 2H), 8.11 (s, 1H), 7.97 (s, 1H), 7.90 (d, *J* = 12.0 Hz, 4H), 7.56 (t, *J* = 6.0 Hz, 4H), 7.51-7.44 (m, 3H), 4.04 (s, 3H), 3.99 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 156.0, 153.4, 145.0, 141.7, 140.0, 139.7, 129.0, 127.9, 127.1, 125.5, 123.7, 106.6, 56.6, 55.9, 54.8; HRMS (ESI) Calcd for $C_{30}H_{26}N_4O_2$ $(M+H)^+$ 475.2128, found 475.2120.

6,7-Dimethoxy-1-methylisoquinolin-3-yl trifluoromethanesulfonate (71a).

6,7-Dimethoxy-1-methylisoquinolin-3-ol (**70a**) (540 mg, 2.47 mmol) and Et_3N (0.7 mL, 4.94 mmol) in DCM were cooled to -78 ^oC. Tf_2O (0.5 mL, 2.96 mmol) was slowly added to the mixture and was stirred for 30 minutes at -78 ^oC. Reaction was then quickly diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a white solid (737 mg, 85% yield); mp 142-142 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.28 (m, 2H), 7.10 (s, 1H), 4.06 (m, 6H), 2.88 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.5, 153.8, 150.7, 150.6, 135.5, 123.3, 107.6, 105.4, 103.7, 56.2, 56.1, 22.0; HRMS (ESI) Calcd for $C_{13}H_{13}F_3NO_5S$ $(M+H)^+$ 352.0461, found 352.0459.

6,7,8-Trimethoxy-1-methylisoquinolin-3-yl trifluoromethanesulfonate (71b).

6,7,8-Trimethoxy-1-methylisoquinolin-3-ol (**70b**) (200 mg, 0.80 mmol) and Et_3N (0.22 mL, 1.60 mmol) in anhydrous DCM (15 mL) were cooled to -70 ^oC and Tf_2O (0.15 mL, 0.88 mmol) was slowly added. The reaction mixture was stirred at -70 to - 40 ^oC for 30 minutes then diluted with DCM and washed with saturated $NaHCO_3$ followed by brine. Organic layer was collected, dried over $MgSO_4$, and concentrated. Chromatography using ISCO max gradient 100% DCM afforded product as a white solid (210 mg, 69% yield); mp 46-47 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.13 (s, 1H), 6.83 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H), 2.96 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 158.4, 157.3, 151.1, 151.0, 143.1, 137.7, 120.4, 119.3-117.2 (m), 107.2, 102.0, 61.3, 61.1, 56.1, 26.5; HRMS (ESI) Calcd for $C_{14}H_{15}F_3NO_6S$ $(M+H)^+$ 382.0567, found 382.0560.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxy-1-methylisoquinoline (72a).

71a (575 mg, 1.64 mmol), 3-biphenylboronic acid (390 mg, 1.968 mmol), $Pd(OAc)_2$ (37 mg, 0.16 mmol), XPhos (156 mg, 0.33), and K_2CO_3 (792 mg, 5.74 mmol) were combined in a flask with ACN (9 mL) and H_2O (3 mL) and degassed. Reaction mixture was then refluxed at 100 ^oC for 5 hours. Solution was cooled to RT then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography achieved using ISCO max gradient 30% EtOAc/hexane yielding product as white solid (473 mg, 81% yield); mp 106-108 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.36 (m, 1H), 8.11-8.09 (m, 1H), 7.89 (s, 1H), 7.75-7.73 (m, 2H), 7.64-7.62 (m, 1H), 7.58 (t, *J* = 6.0 Hz, 2H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 6.0 Hz, 1H),

7.33 (s, 1H), 7.16 (s, 1H), 4.09 (s, 3H), 4.08 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.0, 152.7, 149.9, 149.2, 141.6, 141.5, 140.7, 133.5, 129.1, 128.7, 127.3, 127.3, 126.8, 125.8, 122.4, 114.5, 105.7, 104.0, 56.0, 30.9, 22.8; HRMS (ESI) Calcd for $C_{24}H_{22}NO_2$ $(M+H)^+$ 356.1645, found 356.1638.

3-([1,1'-Biphenyl]-3-yl)-6,7,8-trimethoxy-1-methylisoquinoline (72b).

71b (100 mg, 0.26 mmol), [1,1'-biphenyl]-3-ylboronic acid (78 mg, 0.39 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol), XPhos (12 mg, 0.03 mmol), and K_2CO_3 (90 mg, 0.65 mmol) were combined in a flask with ACN (6 mL) and H_2O (3 mL) and degassed. Reaction mixture was then refluxed at 100 ^oC for 5 hours. The reaction mixture was cooled to room temperature then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 50% EtOAc/hexane afforded product as white solid (65 mg, 64% yield); mp 45-46 ^oC; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.36-8.34 (m, 1H), 8.12-8.10 (m, 1H), 7.83 (s, 1H), 7.75-7.72 (m, 2H), 7.66-7.63 (m, 1H), 7.60-7.55 (m, 1H), 7.52-7.48 (m, 2H), 7.42-7.37 (m, 1H), 6.99 (s, 1H), 4.07 (s, 3H), 4.06 (s, 3H), 4.00 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.9, 156.4, 151.1, 149.1, 142.6, 141.7, 141.4, 139.7, 136.1, 129.1, 128.7, 127.3, 127.3, 127.2, 125.9, 125.9, 118.1, 114.7, 102.3, 61.3, 61.1, 56.0, 26.9; HRMS (ESI) Calcd for $C_{25}H_{24}NO_3$ $(M+H)^+$ 386.1751, found 386.1746.

3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxy-1-methylisoquinoline (72c).

71a (300 mg, 0.85 mmol), 3-*t*-butylphenylboronic acid (183 mg, 1.02 mmol), $Pd(OAc)_2$ (19 mg, 0.09 mmol), XPhos (81 mg, 0.17 mmol), and K_2CO_3 (354 mg, 2.55 mmol) were combined in a flask with dioxane (9 mL) and H_2O (3 mL) and degassed. Reaction mixture was then refluxed at 100 ^oC for 2 hours. Solution was cooled to RT then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a clear oil (245 mg, 83% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.14 (s, 1H), 7.92-7.89 (m, 1H), 7.81 (s, 1H), 7.45-7.44 (m, 2H), 7.31 (s, 1H), 7.15 (s, 1H), 4.08 (s, 3H), 4.07 (s, 3H), 3.00 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 155.9, 152.6, 151.4, 149.9, 149.7, 134.0, 133.5, 128.4, 125.1, 124.2, 123.9, 122.2, 114.5, 105.7, 103.9, 56.0, 56.0, 34.9, 31.5, 22.8; HRMS (ESI) Calcd for $C_{22}H_{26}NO_2$ $(M+H)^+$ 336.1958, found 336.1954.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxy-1,2-dimethylisoquinolin-2-ium iodide (73a).

72a (35 mg, 0.099 mmol) and MeI (1.5 mL) were heated in a sealed tube for 3 hours. Solvent was then evaporated. Ether was then used to crash out solid which was filtered and dried to afford product as a pale yellow solid (5 mg, 10% yield); mp 224-225 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.88 (s, 1H), 7.60 (s, 1H), 7.44-7.30 (m, 4H), 7.28 (m, 1H), 7.24 (s, 1H), 7.15-7.02 (m, 4H), 4.50 (s, 3H), 4.05 (s, 3H), 4.02 (s, 3H), 3.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.4, 155.5, 152.7, 145.4, 141.4, 138.9, 135.4, 133.9, 129.5, 129.0,

128.7, 128.3, 128.1, 128.1, 127.2, 123.5, 123.4, 106.4, 104.9, 58.0, 56.6, 44.5, 20.0; HRMS (ESI) Calcd for $C_{25}H_{24}INO_2$ $(M-I)^+$ 370.1807, found 370.1793.

3-([1,1'-Biphenyl]-3-yl)-6,7,8-trimethoxy-1,2-dimethylisoquinolin-2-ium iodide (73b).

72b (30 mg, 0.08 mmol) in MeI (1.5 mL) was stirred in a sealed vial at 70 ^oC overnight. After cooling to RT, acetone (5 mL) was added and solids were collected by filtration yielding product as an off-white solid (10 mg, 25% yield); mp 179-180 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.91 (s, 2H), 7.82-7.78 (m, 2H), 7.72-7.69 (m, 2H), 7.65-7.60 (m, 1H), 7.52-7.48 (m, 2H), 7.43-7.39 (m, 1H), 7.18 (s, 1H), 4.28 (s, 3H), 4.15 (s, 3H), 4.10 (s, 3H), 4.05 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 161.1, 158.7, 146.1, 145.6, 142.1, 139.3, 136.2, 133.9, 129.6, 129.0, 128.8, 128.8, 128.1, 128.1, 127.3, 123.9, 119.4, 103.4, 62.4, 61.5, 57.5, 44.5, 21.8; HRMS (ESI) Calcd for $C_{26}H_{26}INO_3$ $(M-I)^+$ 400.1913, found 400.1899.

3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxy-1,2-dimethylisoquinolin-2-ium iodide (73c).

72c (23.5 mg, 0.07 mmol) was heated in MeI (0.5 mL) in a sealed tube overnight at 100 ^oC. Solvent was then evaporated and residue was taken back up in DCM. Ether was then used to crash out solid which was filtered and dried to afford product as an off-white solid (23 mg, 70% yield); mp 209-211 ^oC; ^1H NMR (400 MHz) (CD_3OD) δ 8.04 (s, 1H), 7.81 (s, 1H), 7.74-7.71 (m, 1H), 7.69 (t, J = 2.0 Hz, 1H), 7.61-7.57 (m, 2H), 7.45-7.43

(m, 1H), 4.15 (s, 3H), 4.12 (s, 6H), 3.28 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.4, 157.6, 154.6, 153.9, 147.6, 136.9, 135.3, 130.2, 128.6, 127.8, 124.7, 124.6, 107.1, 106.6, 57.5, 57.2, 43.9, 35.9, 31.7, 18.2; HRMS (ESI) Calcd for $C_{23}H_{28}INO_2$ $(M-I)^+$ 350.2115, found 350.2107.

1-(Bromomethyl)-3-(3-(*t*-butyl)phenyl)-6,7-dimethoxyisoquinoline (74).

72c (400 mg, 1.19 mmol), NBS (223 mg, 1.25 mmol), and AIBN (20 mg, 0.119 mmol) in CCl_4 (7 mL) were heated at 85 ^{o}C for 2 hours. Reaction mixture was then cooled to RT and diluted with hexane. Solid precipitate was filtered off and filtrate was concentrated. Chromatography using ISCO max gradient 15% EtOAc/hexane afforded product as a white solid (350 mg, 71% yield); mp 167-170 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.15-8.14 (m, 1H), 7.94-7.91 (m, 2 H), 7.48-7.45 (m, 3H), 7.18 (s, 1H), 5.10 (s, 2H), 4.11 (s, 3H), 4.07 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.0, 152.9, 151.5, 150.1, 150.0, 139.2, 134.6, 128.5, 125.5, 124.2, 123.9, 121.5, 116.6, 105.8, 103.6, 56.2, 56.1, 34.9, 33.0, 31.5; HRMS (ESI) Calcd for $C_{22}H_{25}BrNO_2$ $(M+H)^+$ 414.1063, found 414.1057.

***N*'-((3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl)methyl)acetimidamide (75).**

74 (25 mg, 0.06 mmol), acetamidine HCl (7 mg, 0.072 mmol), and K_2CO_3 (17 mg, 0.12 mmol) in anhydrous DMF (2 mL) were heated at 50 ^{o}C for 2 hours. Reaction mixture was then cooled to RT, diluted with EtOAc, and washed with 10% LiCl solution.

Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as an off-white solid (18 mg, 78% yield); mp 137-140 ^oC; ^1H NMR (400 MHz) (CD_3OD) δ 8.22 (t, *J* = 2.0 Hz, 1H), 8.13 (s, 1H), 7.94-7.72 (m, 1H), 7.50 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.46-7.43 (m, 2H), 7.40 (s, 1H), 5.16 (s, 2H), 4.08 (s, 3H), 4.04 (s, 3H), 2.44 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 167.3, 155.0, 152.8, 152.4, 150.7, 150.1, 140.3, 136.1, 129.6, 126.5, 124.8, 124.6, 122.2, 117.1, 107.3, 103.2, 56.7, 56.6, 46.3, 35.8, 31.9, 19.3; HRMS (ESI) Calcd for $C_{24}H_{30}N_3O_2$ $(M+H)^+$ 392.2333, found 392.2328.

1-(Azidomethyl)-3-(3-(*t*-butyl)phenyl)-6,7-dimethoxyisoquinoline (76).

74 (130 mg, 0.31 mmol) and sodium azide (25 mg, 0.38 mmol) were combined in anhydrous DMF (3 mL) and stirred at RT overnight. Reaction was then diluted with EtOAc and washed with saturated $NaHCO_3$ followed by 10% LiCl solution. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 25% EtOAc/hexane afforded product as a clear oil (114 mg, 97% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.24 (s, 1H), 7.96 (s, 2H), 7.48-7.46 (m, 2H), 7.30 (s, 1H), 7.20 (s, 1H), 4.91 (s, 2H), 4.08 (s, 6H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.0, 152.1, 151.6, 150.4, 149.7, 139.1, 134.5, 128.5, 125.5, 124.0, 121.3, 116.0, 105.8, 102.7, 56.1, 53.8, 34.9, 31.5; IR (thin film NaCl) 2099 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{25}N_4O_2$ $(M+H)^+$ 377.1972, found 377.1966.

(3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl)methanamine (77).

76 (110 mg, 0.29 mmol) was combined in a flask with polymer supported (3 mmol/g loading) PPh_3 (145 mg, 0.44 mmol), THF (5 mL), and H_2O (0.5 mL). Reaction was stirred overnight at RT. Resin was then filtered off and filtrate concentrated. Chromatography using silica column max gradient 10% MeOH/DCM/0.1% NH_4OH afforded product as a white solid (68 mg, 67% yield); mp 173-174 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.08 (s, 1H), 7.87-7.84 (m, 1H), 7.74 (s, 1H), 7.36-7.35 (m, 2H), 7.12 (s, 1H), 7.06 (s, 1H), 4.10 (s, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.1, 152.7, 151.5, 150.0, 149.0, 139.5, 133.8, 128.5, 125.4, 124.0, 123.6, 120.6, 114.8, 105.8, 102.2, 56.1, 56.0, 44.0, 34.9, 31.5; HRMS (ESI) Calcd for $C_{22}H_{27}N_2O_2$ $(M+H)^+$ 351.2067, found 351.2069.

3-(3-(Benzyloxy)-4,5-dimethoxyphenyl)-6,7,8-trimethoxy-1-methylisoquinoline (78).

A flask containing **71b** (1.7 g, 4.46 mmol), (3-(benzyloxy)-4,5-dimethoxyphenyl)boronic acid (1.54 g, 5.35 mmol), K_2CO_3 (1.54 mg, 11.2 mmol), and XPhos (212 mg, 0.45 mmol) in ACN (20 mL) and H_2O (10 mL) was degassed and then $Pd(OAc)_2$ (50 mg, 0.22 mmol) was added. The resulting solution was carefully degassed again. Reaction was then heated at 90 ^oC for 4 hours. After cooling to RT, the reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane yielding product as a light yellow oil (2.03 g, 96% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 7.66 (s, 1H), 7.73-7.55 (m, 2H), 7.44-7.39 (m, 4H), 7.37-

7.33 (m, 1H), 6.95 (s, 1H), 5.28 (s, 2H), 4.05 (s, 3H), 4.04 (s, 3H), 4.02 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 3.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.6, 156.1, 153.7, 152.7, 150.9, 149.1, 142.4, 139.5, 137.4, 135.9, 135.3, 128.5, 127.9, 127.5, 117.9, 113.8, 106.6, 104.6, 102.2, 71.4, 61.2, 61.0, 60.9, 56.3, 55.9, 27.3; HRMS (ESI) Calcd for $C_{28}H_{30}NO_6$ $(M+H)^+$ 476.2073, found 476.2078.

2,3-Dimethoxy-5-(6,7,8-trimethoxy-1-methylisoquinolin-3-yl)phenol (79).

78 (2.3 g, 4.84 mmol) was suspended in MeOH (250 mL) followed by addition of Pd/C (10% wt.) (200 mg). The reaction flask was sealed with septum and purged with N_2 (3x) followed by H_2 (3x). Reaction mixture was then stirred at RT under H_2 balloon for 3 hours. Reaction was monitored by TLC and stopped once the starting material was consumed. Reaction mixture was then passed through a pad of Celite and washed with MeOH. The filtrate was concentrated yielding the crude product as a grey foam which was taken forward without further purification required (1.67 g, 90% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.69 (s, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 7.31 (d, *J* = 2.0 Hz, 1H), 6.94 (s, 1H), 5.83 (s, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 3.97 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.6, 156.1, 152.6, 150.9, 149.4, 149.0, 142.4, 136.0, 135.9, 135.8, 118.0, 113.9, 106.5, 103.2, 102.2, 61.2, 61.0, 56.0, 55.9, 27.2; HRMS (ESI) Calcd for $C_{21}H_{24}NO_6$ $(M+H)^+$ 386.1604, found 386.1606.

2,3-Dimethoxy-5-(6,7,8-trimethoxy-1-methylisoquinolin-3-yl)phenyl trifluoromethanesulfonate (80).

79 (1.66 g, 4.31 mmol) in DCM (100 mL) and triethylamine (1.20 mL, 8.62 mmol) was cooled to -70 ^{o}C and triflic anhydride (0.80 mL, 4.74 mmol) was added slowly. The resulting reaction mixture was stirred at -70 -to -30 ^{o}C for 30 minutes. Reaction was then diluted with DCM and washed with saturated $NaHCO_3$ followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a clear golden oil (2.21 g, 99% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.72 (d, *J* = 1.9 Hz, 1H), 7.59 (s, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 6.89 (s, 1H), 3.96 (s, 6H), 3.95 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 157.1, 156.3, 153.9, 151.0, 147.2, 142.9, 142.8, 141.5, 135.8, 135.7, 118.3, 114.0, 112.3, 110.8, 102.3, 61.4, 61.2, 61.1, 56.4, 56.0, 27.2; HRMS (ESI) Calcd for $C_{22}H_{23}F_3NO_8S$ $(M+H)^+$ 518.1096, found 518.1091.

3-(5,6-Dimethoxy-[1,1':4',1''-terphenyl]-3-yl)-6,7,8-trimethoxy-1-methylisoquinoline (81).

80 (100 mg, 0.19 mmol), [1,1'-biphenyl]-4-ylboronic acid (58 mg, 0.29 mmol), K_2CO_3 (66 mg, 0.48 mmol), and XPhos (10 mg, 0.02 mmol) in ACN (4 mL) and H_2O (2 mL) were degassed then $Pd(OAc)_2$ (3.0 mg, 0.065 mmol) was added and solution was carefully degassed again. The reaction mixture was warmed to 100 ^{o}C and stirred for 1 hour. After cooling to RT, the reaction mixture was diluted with EtOAc and washed with saturated $NaHCO_3$ followed by brine. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane

afforded product as a clear oil (56 mg, 57% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.82 (d, *J* = 2.0 Hz, 1H), 7.78-7.69 (m, 8H), 7.52-7.47 (m, 2H), 7.41-7.37 (m, 1H), 6.96 (s, 1H), 4.09 (s, 3H), 4.06 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H), 3.71 (s, 3H), 3.17 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.7, 156.1, 153.4, 151.0, 149.1, 147.1, 142.4, 141.0, 139.9, 137.6, 136.0, 135.8, 135.4, 129.8, 128.8, 127.3, 127.1, 126.8, 121.1, 118.0, 113.9, 110.5, 102.2, 61.2, 61.1, 60.8, 56.1, 55.9, 27.3; HRMS (ESI) Calcd for $C_{33}H_{32}NO_5$ $(M+H)^+$ 522.2280, found 522.2288.

3-(5,6-Dimethoxy-[1,1':4',1''-terphenyl]-3-yl)-6,7,8-trimethoxy-1,2-dimethylisoquinolin-2-ium iodide (82).

A solution of **81** (50 mg, 0.096 mmol) in MeI (1.5 mL) was stirred in a sealed vial at 70 ^{o}C overnight. After cooling to RT, acetone (5 mL) was added and solids were collected by filtration to afford product as a white solid (32 mg, 50% yield); mp 222-224 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.88 (s, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.78-7.64 (m, 6H), 7.51-7.46 (m, 2H), 7.41-7.38 (m, 1H), 7.12 (s, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 4.35 (s, 3H), 4.14 (s, 3H), 4.11 (s, 3H), 4.09 (s, 3H), 4.05 (s, 3H), 3.78 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 161.7, 157.9, 153.8, 148.4, 145.6, 140.6, 140.5, 136.0, 135.9, 129.6, 128.8, 127.5, 127.1, 127.0, 125.1, 122.9, 119.5, 114.1, 102.5, 63.2, 61.5, 60.9, 59.7, 57.4, 57.2, 44.5; HRMS (ESI) Calcd for $C_{34}H_{34}INO_5$ $(M-I)^+$ 536.2437, found 536.2418.

3-(6,7-Dimethoxy-1-methylisoquinolin-3-yl)phenol (83).

71a (200 mg, 0.57 mmol), 3-hydroxyphenylboronic acid (157 mg, 1.14 mmol), $Pd(OAc)_2$ (13 mg, 0.057 mmol), XPhos (54 mg, 0.114 mmol), and Cs_2CO_3 (650 mg, 1.995 mmol) were combined in a flask with ACN (9 mL) and H_2O (3 mL) and degassed. Reaction mixture was then refluxed at 100 ^oC for 5 hours. Solution was cooled to RT then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 50% EtOAc/hexane afforded product as white solid (78 mg, 46% yield); mp 111-113 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.66-7.63 (m, 2H), 7.38 (d, *J* = 4.0 Hz, 1H), 7.20 (t, *J* = 4.0 Hz, 1H), 7.17 (s, 1H), 7.00 (s, 1H), 6.73-6.71 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.7, 156.1, 152.9, 149.9, 149.2, 141.5, 133.6, 129.9, 122.4, 118.7, 115.5, 115.3, 114.6, 105.7, 103.9, 56.1, 56.0, 22.2; HRMS (ESI) Calcd for $C_{18}H_{18}NO_3$ $(M+H)^+$ 296.1281, found 296.1274.

3-(6,7-Dimethoxy-1-methylisoquinolin-3-yl)phenyl trifluoromethanesulfonate (84).

83 (175 mg, 0.59 mmol) and Et_3N (0.16 mL, 1.18 mmol) in DCM were cooled to -78 ^oC. Tf_2O (0.12 mL, 0.708 mmol) was slowly added to the mixture and was stirred for 30 minutes at -78 ^oC. Reaction was then quickly diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a white solid (230 mg, 91% yield); mp 81-82 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.14 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 1H), 7.82 (s, 1H), 7.56 (t, *J* = 8.0 Hz, 1H),

7.31 (s, 1H), 7.29 (dd, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H), 7.15 (s, 1H), 4.08 (s, 3H), 4.07 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.3, 152.9, 150.3, 150.2, 146.6, 143.0, 133.2, 130.3, 126.3, 122.8, 120.3, 119.6-117.2 (m), 114.8, 105.8, 103.9, 56.1, 56.0, 22.7; HRMS (ESI) Calcd for $C_{19}H_{17}F_3NO_5S$ $(M+H)^+$ 428.0774, found 428.0762.

3-([1,1':4',1''-Terphenyl]-3-yl)-6,7-dimethoxy-1-methylisoquinoline (85a).

84 (80 mg, 0.19 mmol), [1,1'-biphenyl]-4-ylboronic acid (56 mg, 0.28 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), XPhos (9 mg, 0.02 mmol), and K_2CO_3 (65 mg, 0.47mmol) were combined in a flask with ACN (6 mL) and H_2O (3 mL) and degassed. Reaction mixture was then refluxed at 100 ^oC for 5 hours. Solution was cooled to room temperature then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as white solid (64 mg, 79% yield); mp 150-153 ^oC; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.40 (m, 1H), 8.12-8.10 (m, 1H), 7.90 (s, 1H), 7.84-7.82 (m, 2H), 7.75-7.64 (m, 5H), 7.59 (t, *J* = 3.9 Hz, 1H), 7.52-7.47 (m, 2H), 7.41-7.38 (m, 1H), 7.34 (s, 1H), 7.18 (s, 1H), 4.09 (s, 3H), 4.08 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.0, 152.7, 149.9, 149.1, 141.1, 140.8, 140.8, 140.4, 140.1, 133.5, 129.2, 128.8, 127.7, 127.5, 127.3, 127.1, 126.7, 125.9, 125.7, 122.4, 114.6, 105.7, 104.0, 56.0, 56.0, 22.8; HRMS (ESI) Calcd for $C_{30}H_{26}NO_2$ $(M+H)^+$ 432.1958, found 432.1950.

3-(4'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxy-1-methylisoquinoline (85b).

84 (130 mg, 0.3 mmol), 4-*t*-butylphenylboronic acid (108 mg, 0.6 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), XPhos (29 mg, 0.06 mmol), and K_2CO_3 (147 mg, 1.05 mmol) in ACN (3 mL) and H_2O (1.5 mL) were combined in a flask and degassed. Reaction mixture was heated to 95 ^oC for 2 hours. Solution was then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a white solid (121 mg, 97% yield); mp 185-187 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.35-8.34 (m, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.33 (s, 1H), 7.16 (s, 1H), 4.09 (s, 3H), 4.08 (s, 3H), 3.00 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.0, 152.7, 150.3, 149.8, 149.3, 141.5, 140.6, 138.6, 133.5, 129.0, 127.0, 126.7, 125.7, 125.7, 125.5, 122.3, 114.5, 105.7, 104.0, 56.0, 34.6, 31.4, 22.7; HRMS (ESI) Calcd for $C_{28}H_{30}NO_2$ $(M+H)^+$ 412.2271, found 412.2259.

3-(3'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxy-1-methylisoquinoline (85c).

84 (100 mg, 0.23 mmol), 3-*t*-butylphenylboronic acid (50 mg, 0.28 mmol), $Pd(OAc)_2$ (5 mg, 0.023), XPhos (22 mg, 0.047), and K_2CO_3 (390 mg, 0.82 mmol) in ACN (4 mL) and H_2O (2 mL) were combined in a flask and degassed. Reaction mixture was heated to 95 ^oC for 2 hours. Solution was then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a

pearly oil (97 mg, quantitative); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.33 (m, 1H), 8.12-8.10 (m, 1H), 7.89 (s, 1H), 7.74 (s, 1H), 7.65-7.53 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.56-7.54 (m, 1H), 7.45-7.44 (m, 2H), 7.33 (s, 1H), 7.16 (s, 1H), 4.09 (s, 3H), 4.08 (s, 3H), 3.01 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.0, 152.7, 151.6, 149.9, 149.3, 142.4, 141.3, 140.7, 133.5, 129.0, 129.0, 128.2, 127.1, 125.9, 125.7, 124.6, 124.5, 124.3, 122.3, 114.5, 105.7, 104.0, 56.0, 54.0, 34.9, 31.5, 22.8.

3-(5,6-Dimethoxy-[1,1':4',1''-terphenyl]-3-yl)-6,7,8-trimethoxy-1,2-dimethylisoquinolin-2-ium iodide (86a).

A solution of **85a** (50 mg, 0.096 mmol) in MeI (1.5 mL) was stirred in a sealed vial at 70 ^{o}C overnight. After cooling to RT, acetone (5 mL) was added and solids were collected by filtration to afford product as a white solid (32 mg, 50% yield); mp 222-224 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.88 (s, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.78-7.64 (m, 6H), 7.51-7.46 (m, 2H), 7.41-7.38 (m, 1H), 7.12 (s, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 4.35 (s, 3H), 4.14 (s, 3H), 4.11 (s, 3H), 4.09 (s, 3H), 4.05 (s, 3H), 3.78 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 161.7, 157.9, 153.8, 148.4, 145.6, 140.6, 140.5, 136.0, 135.9, 129.6, 128.8, 127.5, 127.1, 127.0, 125.1, 122.9, 119.5, 114.1, 102.5, 63.2, 61.5, 60.9, 59.7, 57.4, 57.2, 44.5; HRMS (ESI) Calcd for $C_{34}H_{34}INO_5$ $(M\text{-}I)^{+}$ 536.2437, found 536.2418.

3-(4'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxy-1,2-dimethylisoquinolin-2-ium iodide (86b).

85b (15 mg, 0.036 mmol) was heated in MeI (0.5 mL) in a sealed tube overnight at 100 ^{o}C. Solvent was then evaporated and residue was taken back up in DCM. Ether was then used to crash out solid which was filtered and dried to afford product as a tan solid (15 mg, 75% yield); mp 202-204 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.21 (s, 1H), 7.86 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.70-7.68 (m, 3H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.53-7.48 (m, 3H), 7.38 (s, 1H), 4.24 (s, 3H), 4.09 (s, 3H), 3.99 (s, 3H), 3.36 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 157.5, 152.7, 151.4, 145.6, 136.0, 135.4, 133.9, 129.5, 128.4, 128.2, 127.9, 126.8, 126.0, 123.5, 106.3, 105.1, 57.8, 56.6, 44.5, 34.6, 31.3, 20.1; HRMS (ESI) Calcd for $C_{28}H_{32}INO_2$ $(M-I)^+$ 426.2433, found 426.2431.

3-(4'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinoline-1-carbaldehyde (87a).

85b (100 mg, 0.24 mmol) and SeO_2 (32 mg, 0.29 mmol) in anhydrous dioxane (5 mL) were refluxed at 102 ^{o}C for 3 hours. Solution was then cooled to RT and filtered to remove precipitate. Resulting filtrate was concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a yellow solid (80 mg, 77% yield); mp 165-168 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.40 (s, 1H), 8.68 (s, 1H), 8.34 (m, 1H), 8.14 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 3H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.13 (s, 1H), 4.05 (s, 3H), 4.00 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 196.8, 153.3, 152.8, 149.8, 141.8, 139.2, 138.3, 135.4, 129.3,

127.4, 127.0, 125.8, 125.6, 125.4, 122.2, 120.0, 105.0, 103.6, 56.3, 56.0, 34.6, 31.4; HRMS (ESI) Calcd for $C_{28}H_{28}NO_3$ $(M+H)^+$ 426.2064, found 426.2041.

3-(3'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinoline-1-carbaldehyde (87b).

85c (92 mg, 0.22 mmol) and SeO_2 (25 mg, 0.27 mmol) in anhydrous dioxane (5 mL) were refluxed at 102^{o}C for 3 hours. Solution was then cooled to RT and filtered to remove precipitate. Resulting filtrate was concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a yellow oil (55 mg, 58% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.39 (s, 1H), 8.66 (s, 1H), 8.31 (s, 1H), 8.12 (s, 1H), 8.07 (d, *J* = 4.0 Hz, 1H), 7.63 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 6.0 Hz, 1H), 7.46-7.44 (m, 1H), 7.36-7.35 (m, 2H), 7.11 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 196.9, 153.3, 152.8, 151.7, 149.7, 147.0, 142.7, 141.0, 139.2, 135.4, 129.3, 128.5, 127.8, 125.8, 125.5, 124.6, 124.5, 124.5, 122.2, 120.1, 105.0, 103.5, 56.3, 56.1, 34.9, 31.5.

(3-(4'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methanol (88a).

87a (76 mg, 0.18 mmol) in methanol (5 mL) was treated slowly with $NaBH_4$ (20 mg, 0.53 mmol) at RT. Reaction was stirred for 1 hour then acetone(2 mL) was added and solution was filtered through filter paper. Filtrate was concentrated then re-dissolved in DCM and washed with H_2O. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 50% EtOAc/hexane afforded

product as a pearly, gold solid (59 mg, 78% yield); mp 104-106 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.25-8.24 (m, 1H), 7.99-7.97 (m, 1H), 7.85 (s, 1H), 7.57-7.54 (m, 3H), 7.47 (t, *J* = 6.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.08 (s, 1H), 6.96 (s, 1H), 5.22 (t, *J* = 6.0 Hz, 1H), 5.10 (d, *J* = 4.0 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.6, 153.2, 150.5, 150.4, 147.7, 141.7, 139.6, 138.3, 133.8, 129.1, 127.1, 126.9, 125.8, 125.4, 125.3, 119.8, 115.3, 105.9, 101.3, 61.4, 56.1, 56.1, 34.6, 31.4; HRMS (ESI) Calcd for $C_{28}H_{30}NO_3$ $(M+H)^+$ 428.2220, found 428.2213.

(3-(3'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methanol (88b).

87b (52 mg, 0.122 mmol) in ethanol (4 mL) was treated slowly with $NaBH_4$ (14 mg, 0.366) at RT. Reaction was stirred for 1 hour then acetone (2 mL) was added and solution was filtered through filter paper. Filtrate was concentrated then re-dissolved in DCM and washed with H_2O. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 50% EtOAc/hexane afforded product as a yellow oil (27 mg, 52% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.24 (t, *J* = 2.0 Hz, 1H), 8.03-8.01 (m, 1H), 7.88 (s, 1H), 7.62 (m, 1H), 7.57-7.55 (m, 1H), 7.51 (t, *J* = 6.0 Hz, 1H), 7.45-7.42 (m, 1H), 7.36-7.35 (m, 2H), 7.12 (s, 1H), 6.98 (s, 1H), 5.39 (bs, 1H), 5.12 (s, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.6, 153.2, 151.7, 150.4, 147.6, 142.5, 141.1, 139.6, 133.8, 129.1, 128.6, 127.5, 125.7, 125.5, 124.6, 124.5, 124.5, 119.8, 115.4, 105.9, 101.2, 61.4, 56.1, 34.9, 31.5.

1,3-bis-(*t*-Butoxycarbonyl)-2-((3-(4'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methyl)guanidine (89a).

To a solution of **88a** (39 mg, 0.091 mmol), PPh_3 (35 mg, 0.14 mmol), and 1,3-bis-(*t*-butoxycarbonyl)guanidine (47 mg, 0.18 mmol) in anhydrous toluene (3 mL) at 0 ^oC was added diisopropylazodicarboxylate (0.03 mL, 0.14 mmol) drop wise over 15 minutes. Reaction was stirred for 3 hours at RT then 2 drops H_2O were added, and the solution was concentrated. Solid was then dissolved in DCM and passed through silica column and resulting crude product was taken to the next step.

1,3-bis-(*t*-Butoxycarbonyl)-2-((3-(3'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methyl)guanidine (89b).

88b (27 mg), PPh_3 (25 mg, 1.5 eq.), and 1,3-bis(*t*-butoxycarbonyl)guanidine (33 mg, 2 eq.) in 3 mL toluene at 0^oC was added diisopropylazodicarboxylate (0.02 mL, 1.5 eq.) drop wise over 15 minutes. Reaction was stirred for 3 hours at RT then 2 drops H_2O were added, and the solution was concentrated. Solid was then re-dissolved in DCM and passed through silica column and resulting crude product was taken to next step.

2-((3-(4'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methyl)guanidine (90a).

To a cooled solution of crude **89a** in anhydrous DCM (1.5 mL) was added TFA (1.5 mL) at 0 ^oC. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were

evaporated. Solid was then taken back up in DCM and precipitate was filtered off to afford product as a grayish white solid (22 mg, 42% yield over 2 steps); mp 119-122 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.25 (m, 1H), 8.08 (s, 1H), 8.04 (d, *J* = 4.0 Hz, 1H), 7.58-7.56 (m, 3H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.33 (s, 1H), 7.29 (s, 1H), 4.95 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 160.1, 159.6, 155.1, 152.5, 151.9, 151.7, 149.5, 142.9, 141.1, 139.5, 130.3, 128.0, 127.8, 126.8, 126.6, 126.1, 122.1, 117.3, 107.4, 103.2, 56.7, 56.6, 45.1, 35.4, 31.8; HRMS (ESI) Calcd for $C_{29}H_{33}N_4O_2$ $(M+H)^+$ 469.2598, found 469.2599.

2-((3-(3'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methyl)guanidine (90b).

To a cooled solution of crude **89b** in anhydrous DCM (1.5 mL) was added TFA (1.5 mL) at 0 ^{o}C. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Solid was then taken back up in DCM and precipitate was filtered off to afford product as a tan solid (21 mg, 55% yield over 2 steps); mp 129-133 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.21 (m, 1H), 8.11-8.07 (m, 2H), 7.61 (m, 1H), 7.55-7.47 (m, 2H), 7.43-7.41 (m, 1H), 7.36-7.30 (m, 3H), 7.27 (s, 1H), 4.92 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.5, 155.0, 153.0, 152.4, 151.7, 149.5, 143.8, 142.4, 141.2, 135.9, 130.3, 129.7, 128.3, 126.7, 126.3, 125.6, 125.2, 122.0, 117.2, 107.3, 103.1, 55.6, 56.5, 45.1, 35.7, 31.9; HRMS (ESI) Calcd for $C_{29}H_{33}N_4O_2$ $(M+H)^+$ 469.2598, found 469.2585.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinoline-1-carbaldehyde (91a).

72a (200 mg, 0.56 mmol) and SeO_2 (75 mg, 0.68 mmol) in anhydrous dioxane (10.5 mL) were refluxed at 102 ^oC for 3 hours. Solution was then cooled to RT and filtered to remove precipitate. Resulting filtrate was concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a yellow solid (175 mg, 84% yield); mp 153-154 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 10.50 (s, 1H), 8.77 (s, 1H), 8.44 (s, 1H), 8.23-8.18 (m, 2H), 7.75-7.66 (m, 3H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.44-7.42 (m, 1H), 7.22 (s, 1H), 4.14 (s, 3H), 4.09 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 196.8, 153.3, 152.8, 149.6, 147.1, 142.0, 141.2, 139.3, 135.4, 129.3, 128.8, 127.6, 127.5, 127.3, 125.7, 125.6, 122.2, 120.0, 105.0, 103.6, 56.3, 56.1; HRMS (ESI) Calcd for $C_{24}H_{20}NO_3$ $(M+H)^+$ 370.1438, found 370.1431.

3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinoline-1-carbaldehyde (91b).

72c (153 mg, 0.46 mmol) and SeO_2 (61 mg, 0.55 mmol) in anhydrous dioxane (5 mL) were refluxed at 102 ^oC for 3 hours. Solution was then cooled to RT and filtered to remove precipitate. Resulting filtrate was concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a yellow solid (97 mg, 62% yield); mp 178-179 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 10.40 (s, 1H), 8.67 (s, 1H), 8.14 (s, 1H), 8.08 (s, 1H), 7.90 (dt, *J* = 4.0 Hz, *J* = 2.0 Hz, 1H), 7.42-7.40 (m, 2H), 7.13 (s, 1H), 4.04 (s, 3H), 4.00 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 197.0, 153.2, 152.7, 151.8, 150.4, 147.0, 138.5, 135.4, 128.7, 125.9, 124.1, 123.8, 122.1, 120.1, 105.0, 103.5,

56.3, 56.1, 35.0, 31.5; HRMS (ESI) Calcd for $C_{22}H_{24}NO_3$ $(M+H)^+$ 350.1751, found 350.1746.

(3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methanol (92a).

91a (160 mg, 0.43 mmol) in ethanol (7 mL) was treated slowly with $NaBH_4$ (50 mg, 1.302 mmol)) at RT. Reaction was stirred for 1 hour then acetone (2 mL) was added and solution was filtered through filter paper. Filtrate was concentrated then re-dissolved in DCM and washed with H_2O. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 50% EtOAc/hexane afforded product as a yellow solid (98 mg, 61% yield); mp 164-165 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.36-8.35 (m, 1H), 8.13-8.11 (m, 1H), 7.98 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.68-7.66 (m, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 6.0 Hz, 1H), 7.22 (s, 1H), 7.09 (s, 1H), 5.35 (bs, 1H), 5.32 (s, 2H), 4.08 (s, 3H), 4.07 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.7, 141.8, 141.2, 129.2, 128.8, 127.4, 127.3, 127.3, 125.6, 125.5, 119.8, 115.4, 105.9, 101.3, 61.4, 56.2, 56.1; HRMS (ESI) Calcd for $C_{24}H_{22}NO_3$ $(M+H)^+$ 372.1594, found 372.1587.

(3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl)methanol (92b).

91b (97 mg, 0.23 mmol) in ethanol (5 mL) was treated slowly with $NaBH_4$ (26 mg, 0.68 mmol) at RT. Reaction was stirred for 1 hour then acetone (2 mL) was added and solution was filtered through filter paper. Filtrate was concentrated then re-dissolved in

DCM and washed with H_2O. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography achieved using ISCO max gradient 50% EtOAc/hexane yielding product as a pale yellow solid (50 mg, 63% yield); mp 181-182 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.07 (m, 1H), 7.86-7.83 (m, 1H), 7.82 (s, 1H), 7.39-7.37 (m, 2H), 7.13 (s, 1H), 6.98 (s, 1H), 5.12 (s, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.5, 153.1, 151.6, 150.3, 148.2, 138.9, 133.9, 128.5, 125.6, 124.0, 123.7, 119.6, 115.3, 105.8, 101.2, 61.3, 56.1, 56.1, 34.9, 31.5; HRMS (ESI) Calcd for $C_{22}H_{26}NO_3$ $(M+H)^+$ 352.1907, found 352.1905.

1,3-bis-(*t*-Butoxycarbonyl)-2-((3-([1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methyl)guanidine trifluoroacetate (93a).

92a (30 mg, 0.081 mmol), PPh_3 (32 mg, 0.12 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (42 mg, 0.162 mmol) in anhydrous toluene (3 mL) at 0 ^oC was added diisopropylazodicarboxylate (0.024 mL, 0.12 mmol) drop wise over 15 minutes. Reaction was stirred for 3 hours at RT then 2 drops H_2O were added, and the solution was concentrated. Solid was then dissolved in DCM and passed through silica column and resulting crude product was taken forward to next step.

2-((3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl)methyl)guanidine (93b).

92b (50 mg, 0.14 mmol), PPh_3 (56 mg, 0.21 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (74 mg, 0.28 mmol) in anhydrous toluene (4 mL) at 0 ^oC was

added diisopropylazodicarboxylate (0.04 mL, 0.21 mmol) drop wise over 15 minutes. Reaction was stirred for 3 hours at RT then 2 drops H_2O were added, and the solution was concentrated. Solid was then dissolved in DCM and passed through silica column and resulting crude product was taken forward to next step.

2-((3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methyl)guanidine trifluoroacetate (94a).

To a cooled solution of crude **93a** in anhydrous DCM (1.5 mL) was added TFA (1.5 mL). Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Solid was then taken back up in DCM and precipitate was filtered off to afford product as a white solid (40 mg, 93% yield over 2 steps); mp 210-213 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.40 (m, 1H), 8.22 (s, 1H), 8.20 (m, 1H), 7.76-7.74 (m, 2H), 7.68 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.53-7.49 (m, 2H), 7.46 (s, 1H), 7.42-7.38 (m, 2H), 5.07 (s, 2H), 4.07 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.6, 155.0, 152.4, 151.8, 149.4, 143.1, 142.5, 141.3, 135.9, 130.3, 130.0, 128.5, 128.2, 128.1, 126.8, 122.1, 117.2, 107.4, 103.2, 56.7, 56.6, 45.1; HRMS (ESI) Calcd for $C_{25}H_{25}N_4O_2$ $(M+H)^+$ 413.1972, found 413.1973.

2-((3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl)methyl)guanidine (94b).

To a cooled solution of crude **93b** in anhydrous DCM (1.5 mL) was added TFA (1.5 mL) at 0 ^{o}C. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were

evaporated. Chromatography achieved using ISCO max gradient 10% MeOH/DCM to afford product as an off-white solid (52 mg, 93% yield over two steps); mp 194-196 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.69 (bs, 1H), 7.96 (s, 1H), 7.93 (s, 1H), 7.76-7.75 (m, 1H), 7.47-7.42 (m, 3H), 7.18 (s, 1H), 4.87 (d, *J* = 4.0 Hz, 2H), 4.10 (s, 3H), 4.07 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 159.1, 154.1, 151.9, 151.8, 151.4, 148.2, 137.7, 135.3, 128.8, 126.0, 123.9, 123.5, 121.5, 117.1, 105.6, 102.6, 56.3, 56.2, 44.7, 34.8, 31.3; HRMS (ESI) Calcd for $C_{23}H_{29}N_4O_2$ $(M+H)^+$ 393.2285, found 393.2287.

3-([1,1'-Biphenyl]-3-yl)-1-(azidomethyl)-6,7-dimethoxyisoquinoline (95).

92a (90 mg, 0.24 mmol) in anhydrous THF (5 mL) was cooled to 0 ^{o}C. Diphenylphosphorylazide (0.21 mL, 0.97 mmol) was then added followed by drop wise addition of DBU (0.15 mL, 0.97 mmol). Reaction was kept stirring at 0 ^{o}C for 4 hours then allowed to warm to RT overnight. Reaction mixture was then poured into 0.5 N HCl and extracted with EtOAc. Organic layer was washed with brine then collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a clear oil (75 mg, 78% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.43 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.02 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.43-7.39 (m, 1H), 7.32 (s, 1H), 7.20 (s, 1H), 4.92 (s, 2H), 4.08 (s, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.1, 152.2, 150.5, 149.0, 141.7, 141.3, 139.9, 134.4, 129.2, 127.4, 127.3, 127.1, 125.7, 125.7, 125.6, 121.5, 116.1, 105.9, 102.8, 56.2, 56.1, 53.9; IR (thin film NaCl) 2099 cm^{-1}; HRMS (ESI) Calcd for $C_{24}H_{21}N_4O_2$ $(M+H)^+$ 397.1659, found 397.1650.

(3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)methanamine (96).

95 (70 mg, 0.18 mmol) was combined in a flask with polymer supported (3 mmol/g loading) PPh_3 (88.5 mg, 0.26 mmol), THF (3 mL), and H_2O (0.3 mL). Reaction was stirred overnight at RT. Resin was then filtered off and filtrate concentrated. Chromatography using flash column max gradient 10% MeOH/DCM/0.1% NH_4OH afforded product as a tan oil (60 mg, 92% yield); ^{1}H NMR (400 MHz) (DMSO-d_6) δ 8.58 (s, 1H), 8.43 (s, 1H), 8.34 (d, *J* = 4.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 4.0 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 6.0 Hz, 2H), 7.54 (s, 1H), 7.54-7.46 (m, 2H), 4.66 (s, 2H), 4.04 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 152.8, 150.1, 146.6, 140.6, 140.2, 139.6, 129.3, 128.9, 127.6, 126.9, 126.6, 125.4, 124.5, 120.3, 115.1, 106.1, 102.9, 55.9, 55.7, 48.6; HRMS (ESI) Calcd for $C_{24}H_{23}N_2O_2$ $(M+H)^+$ 371.1754, found 371.1748.

3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinolin-1(2H)-one (97).

59 (300 mg, 1.06 mmol) was combined with 3-*t*-butylphenyl boronic acid (226 mg, 1.27 mmol), $Pd(OAc)_2$ (24 mg, 0.11 mmol), XPhos (100 mg, 0.21 mmol), and K_2CO_3 (437 mg, 3.17 mmol) in a flask and degassed. ACN (9 mL) and H_2O (3 mL) were then added and solution was heated at 100 ^{o}C for 2 hours. Reaction mixture was cooled to RT then diluted with EtOAc and washed with $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 70% EtOAc/hexane afforded product as a white solid (276 mg, 78% yield); mp 211-214 ^{o}C;

^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.14 (bs, 1H), 7.81 (s, 1H), 7.67-7.66 (m, 1H), 7.53-7.50 (m, 1H), 7.47-7.45 (m, 2H), 7.00 (s, 1H), 6.73 (s, 1H), 4.05 (s, 6H), 1.42 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.1, 153.9, 152.3, 149.2, 138.8, 134.3, 134.0, 129.0, 126.5, 123.3, 123.0, 118.8, 107.3, 106.5, 104.0, 56.2, 56.1, 35.0, 31.4; HRMS (ESI) Calcd for $C_{21}H_{24}NO_3$ $(M+H)^+$ 338.1751, found 338.1744.

3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl trifluoromethanesulfonate (98a).

60a (234 mg, 0.66 mmol) and Et_3N (0.182 mL, 1.31 mmol) in anhydrous DCM (20 mL) were cooled to -78 ^{o}C. Tf_2O (0.132 mL, 0.79 mmol) was slowly added to the mixture and was stirred for 30 minutes at -78 ^{o}C. Reaction was then quickly diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 50% EtOAc/hexane afforded product as a white solid (255 mg, 79% yield); mp 127-129 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.15 (t, *J* = 2.0 Hz, 1H), 7.87 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.84 (s, 1H), 7.58-7.52 (m, 2H), 7.51-7.49 (m, 1H), 7.42-7.36 (m, 3H), 7.31-7.26 (m, 1H), 7.12 (s, 1H), 7.02 (s, 1H), 3.91 (s, 6H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.4, 151.6, 151.4, 147.0, 141.7, 140.9, 137.8, 137.4, 129.3, 128.9, 127.7, 127.5, 127.1, 125.3, 125.2, 117.3, 115.9, 114.4, 105.4, 100.6, 56.3, 56.2; HRMS (ESI) Calcd for $C_{24}H_{19}F_3NO_5S$ $(M+H)^+$ 490.0931, found 490.0910.

3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl trifluoromethanesulfonate (98a).

97 (125 mg, 0.37 mmol) and Et_3N (0.1 mL, 0.45 mmol) in anhydrous DCM (15 mL) were cooled to -78 ^oC. Tf_2O (0.07 mL, 0.74 mmol) was slowly added to the mixture and was stirred for 30 minutes at -78 ^oC. Reaction was then quickly diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a white solid (155 mg, 89% yield); mp 131-134 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.20 (s, 1H), 7.98 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.49-7.41 (m, 2H), 7.30 (s, 1H), 7.20 (s, 1H), 4.07 (s, 6H), 1.44 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.3, 151.8, 154.5, 154.5, 147.8, 137.5, 137.1, 128.5, 126.1, 123.8, 123.5, 117.3, 115.8, 114.3, 105.4, 100.6, 56.3, 56.2, 34.9, 31.3; HRMS (ESI) Calcd for $C_{22}H_{23}F_3NO_5S$ $(M+H)^+$ 470.1244, found 470.1234.

***t*-Butyl (2-(3-([1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)ethyl)carbamate (99a).**

98a (250 mg, 0.51 mmol), potassium *t*-butyl *N*-[2-(trifluoroboranuidyl)ethyl]carbamate (256 mg, 1.02 mmol), $Pd(PPh_3)_4$ (59 mg, 0.051 mmol), and K_2CO_3 (246 mg, 1.785 mmol) were combined in a flask with dioxane (8 mL) and H_2O (2 mL) and degassed. Reaction mixture was then refluxed at 102 ^oC overnight. Solution was cooled to RT then diluted with EtOAc and washed with saturated NH_4Cl. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30%

EtOAc/hexane afforded product as a white fluffy solid (166 mg, 67% yield); mp 66-69 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.37-8.36 (m, 1H), 8.14 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.94 (s, 1H), 7.75-7.72 (m, 2H), 7.65 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.60 (t, *J* = 6.0 Hz, 1H), 7.53-7.49 (m, 2H), 7.44-7.39 (m, 2H), 7.17 (s, 1H), 5.63 (bs, 1H), 4.10 (s, 3H), 4.08 (s, 3H), 3.90 (q, *J* = 5.3 Hz, 2H), 3.49 (t, *J* = 6.0 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 152.8, 150.2, 141.7, 141.4, 140.5, 129.2, 128.8, 127.4, 127.3, 127.0, 125.6, 125.5, 122.4, 114.6, 105.8, 103.3, 56.2, 56.1, 38.5, 34.7, 28.5; HRMS (ESI) Calcd for $C_{30}H_{33}N_2O_4$ $(M+H)^+$ 485.2435, found 485.2428.

_t_-Butyl (2-(3-(3-(_t_-butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl)ethyl)carbamate (99b).

98b (155 mg, 0.33 mmol), potassium *t*-butyl *N*-[2-(trifluoroboranuidyl)ethyl]carbamate (166 mg, 0.66 mmol), $Pd(PPh_3)_4$ (38 mg, 0.033 mmol), and K_2CO_3 (159 mg, 1.16 mmol) were combined in a flask with dioxane (5 mL) and H_2O (2.5 mL) and degassed. Reaction mixture was then refluxed at 102 ^{o}C overnight. Solution was cooled to RT then diluted with EtOAc and washed with saturated NH_4Cl. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a clear oil (99 mg, 64% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.22 (s, 1H), 7.94-7.92 (m, 1H), 7.87 (s, 1H), 7.47-7.45 (m, 2H), 7.39 (s, 1H), 7.16 (s, 1H), 5.75 (bs, 1H), 4.08 (s, 3H), 4.07 (s, 3H), 3.92 (q, *J* = 5.3 Hz, 2H), 3.48 (t, *J* = 6.0 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.3, 152.7, 151.5, 150.0, 139.6, 133.7, 128.5, 125.2, 123.8, 123.7, 122.2, 114.3, 105.8, 103.2, 79.0, 56.1, 56.0,

38.2, 34.9, 34.5, 31.5, 28.5; HRMS (ESI) Calcd for $C_{28}H_{37}N_2O_4$ $(M+H)^+$ 465.2748, found 465.2738.

2-(3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)ethanamine (100a).

To a cooled solution of **99a** (166 mg, 0.34 mmol) in anhydrous DCM (1.5 mL) was added trifluoroacetic acid (1.5 mL) at 0 ^oC. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a tan fluffy solid (131 mg, quantitative); mp 187-189 ^oC; ^1H NMR (400 MHz) (CD_3OD) δ 8.19 (t, *J* = 2.0 Hz, 1H), 8.08 (s, 1H), 7.93 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.64-7.59 (m, 3H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.40-7.35 (m, 4H), 7.31-7.27 (m, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.62-3.55 (m, 4H); ^{13}C NMR (100 MHz) (CD_3OD) δ 155.8, 154.9, 152.8, 143.3, 142.3, 136.4, 130.5, 130.0, 128.7, 128.5, 128.2, 126.9, 126.7, 123.3, 117.8, 107.4, 104.0, 56.7, 39.0, 31.1; HRMS (ESI) Calcd for $C_{25}H_{25}N_2O_2$ $(M+H)^+$ 385.1911, found 385.1912.

2-(3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl)ethanamine (100b).

To a cooled solution of **99b** (99 mg, 0.21 mmol) in anhydrous DCM (2 mL) was added trifluoroacetic acid (2 mL) at 0 ^oC. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Chromatography using ISCO max gradient 5% MeOH/DCM afforded product as a tan fluffy solid (78 mg, quantitative); mp 97-100 ^oC; ^1H NMR (400 MHz) (CD_3OD) δ 8.13 (s, 1H), 8.07 (t, *J* = 2.0 Hz, 1H), 7.84 (dt, *J* = 8.0

Hz, *J* = 2.0 Hz, 1H), 7.57-7.55 (m, 1H), 7.51-7.47 (m, 3H), 4.08 (s, 3H), 4.06 (s, 3H), 3.76 (t, *J* = 6.0 Hz, 2H), 3.69-3.65 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 156.2, 154.6, 153.2, 153.0, 148.8, 136.9, 129.8, 127.2, 125.5, 125.2, 123.1, 118.2, 107.4, 104.1, 56.9, 56.8, 39.2, 35.8, 31.8, 30.8; HRMS (ESI) Calcd for $C_{23}H_{29}N_2O_2$ $(M+H)^+$ 365.2224, found 365.2226.

1,3-bis-(*t*-Butoxycarbonyl)-2-(2-(3-([1,1'-biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)ethyl)guanidine (101a).

100a (50 mg, 0.13 mmol), 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethylsulfonyl)-guanidine (61 mg, 0.156 mmol), and Et_3N (0.02 mL, 0.156 mol) in anhydrous DCM (3 mL) were stirred for 1 hour at 37 ^oC. Reaction mixture was then diluted with DCM and washed with $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a white fluffy solid (80 mg, 99% yield); mp 69-72 ^oC; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.03 (bs, 1H), 8.78 (bs, 1H), 8.25-8.24 (m, 1H), 8.07 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.82 (s, 1H), 7.64-7.61 (m, 2H), 7.55-7.52 (m, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.41-7.37 (m, 2H), 7.31-7.26 (m, 2H), 7.06 (s, 1H), 4.04-4.01 (m, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.50 (t, *J* = 6.0 Hz, 2H), 1.42 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.5, 156.3, 155.9, 152.8, 152.8, 151.9, 150.1, 149.1, 141.5, 140.4, 133.8, 129.0, 128.8, 127.3, 126.9, 126.1, 125.9, 122.2, 121.0, 115.1, 105.8, 103.2, 86.0, 82.9, 56.2, 56.0, 53.4, 39.2, 34.0, 28.3, 27.9; HRMS (ESI) Calcd for $C_{36}H_{43}N_4O_6$ $(M+H)^+$ 627.3177, found 627.3164.

1,3-bis-(*t*-Butoxycarbonyl)-2-(2-(3-(3-(*t*-butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl)ethyl)guanidine (101b).

100b (67 mg, 0.18 mmol), 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethylsulfonyl)-guanidine (86 mg, 0.22 mmol), and Et_3N (0.03 mL, 0.22 mmol) in anhydrous DCM (5 mL) were stirred for 1 hour at 37 ^oC. Reaction mixture was then diluted with DCM and washed with $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a clear oil (75 mg, 67% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 11.48 (bs, 1H), 9.04 (t, *J* = 6.0 Hz, 1H), 8.15 (s, 1H), 8.04-8.02 (m, 1H), 7.85 (s, 1H), 7.44-7.43 (m, 2H), 7.35 (s, 1H), 7.16 (s, 1H), 4.20-4.15 (m, 2H), 4.08 (s, 3H), 4.07 (s, 3H), 3.57 (t, *J* = 8.0 Hz, 2H), 1.54 (s, 9H), 1.43 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 156.3, 155.7, 152.7, 152.6, 151.2, 149.9, 149.7, 139.7, 133.7, 128.3, 125.1, 124.4, 123.8, 122.0, 114.6, 105.8, 103.1, 82.7, 79.1, 56.1, 56.0, 38.9, 34.9, 34.2, 31.5, 28.4, 28.0; HRMS (ESI) Calcd for $C_{34}H_{47}N_4O_6$ $(M+H)^+$ 607.3490, found 607.3485.

2-(2-(3-([1,1'-Biphenyl]-3-yl)-6,7-dimethoxyisoquinolin-1-yl)ethyl)guanidine (102a).

To a cooled solution of **101a** (80 mg, 0.12 mmol) in anhydrous DCM (2 mL) was added trifluoroacetic acid (2 mL) at 0 ^oC. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a white solid (36 mg, 67% yield); mp 239-241 ^oC; ^1H NMR (400 MHz) (CD_3OD) δ 8.18 (s, 1H), 8.15 (t, *J* = 2.0 Hz, 1H), 7.88-7.86 (m, 1H),

7.71-7.69 (m, 1H), 7.66-7.64 (m, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.46 (s, 2H), 7.42-7.38 (m, 2H), 7.32-7.28 (m, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.79 (t, *J* = 6.0 Hz, 2H), 3.64 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.8, 155.4, 153.5, 143.5, 141.9, 137.6, 130.7, 130.1, 129.2, 127.5, 127.2, 123.6, 119.3, 107.5, 104.7, 57.0, 56.8, 41.3, 33.0; HRMS (ESI) Calcd for $C_{26}H_{27}N_4O_2$ $(M+H)^+$ 427.2129, found 427.2132.

2-(2-(3-(3-(*t*-Butyl)phenyl)-6,7-dimethoxyisoquinolin-1-yl)ethyl)guanidine (102b).

To a cooled solution of **101b** (53 mg, 0.087 mmol) in anhydrous DCM (1 mL) was added trifluoroacetic acid (1 mL) at 0 ^oC. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a tan fluffy solid (36 mg, quantitative); mp 91-94 ^oC; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.30 (s, 1H), 7.94 (t, *J* = 2.0 Hz, 1H), 7.74-7.69 (m, 2H), 7.67 (s, 1H), 7.63 (s, 1H), 7.60-7.56 (m, 1H), 4.13 (s, 6H), 3.85 (s, 4H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.1, 158.8, 154.5, 154.5, 153.8, 145.3, 139.1, 130.2, 128.8, 126.5, 126.2, 123.5, 121.3, 107.5, 105.0, 57.3, 57.0, 41.7, 35.9, 31.9, 31.7; HRMS (ESI) Calcd for $C_{24}H_{31}N_4O_2$ $(M+H)^+$ 407.2442, found 407.2443.

4-Formylnaphthalen-1-yl trifluoromethanesulfonate (103).

4-Hydroxy-1-naphthaldehyde (250 mg, 1.45 mmol) and Et_3N (0.4 mL, 2.9 mmol) in anhydrous DCM (20 mL) were cooled to -78 ^oC. Tf_2O (0.3 mL, 1.74 mmol) was slowly added to the mixture and was stirred for 30 minutes at -78 ^oC. Reaction was then quickly

diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a brown oil (192 mg, 44% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.28 (s, 1H), 9.18 (d, *J* = 8.0 Hz, 1H), 8.06-8.04 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71-7.61 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 191.8, 149.5, 135.6, 132.2, 131.2, 130.4, 128.7, 126.5, 125.2, 121.2, 120.2-117.1 (m), 116.8.

4-(4-(*t*-Butyl)phenyl)-1-naphthaldehyde (104).

103 (190 mg, 0.625 mmol), 4-*t*-butylphenylboronic acid (134 mg, 0.75 mmol), $Pd(OAc)_2$ (14 mg, 0.0625 mmol), XPhos (60 mg, 0.125 mmol), and K_2CO_3 (259 mg, 1.875 mmol) in dioxane (6 mL) and H_2O (3 mL) were combined in a flask and degassed. Reaction was refluxed at 100 ^{o}C for 1 hour. Reaction was then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a sticky golden oil (158 mg, 88% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.45 (s, 1H), 9.41 (d, *J* = 8.0 Hz, 1H), 8.08-8.05 (m, 2H), 7.75-7.72 (m, 1H), 7.63-7.55 (m, 4H), 7.47 (d, *J* = 8.0 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 193.3, 151.2, 147.6, 136.9, 136.3, 132.1, 131.2, 130.5, 129.6, 128.8, 127.0, 126.9, 126.1, 125.4, 125.1, 34.8, 31.4; HRMS (ESI) Calcd for $C_{21}H_{21}O$ $(M+H)^+$ 289.1587, found 289.1582.

(4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol (105).

$NaBH_4$ (48 mg, 1.26 mmol) was carefully added to a solution of 4-(4-(*t*-butyl)phenyl)-1-naphthaldehyde (120 mg, 0.42 mmol) in EtOH (5 mL). Reaction was stirred at RT for 1 hour then quenched with acetone (5 drops), filtered, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a glassy white solid (95 mg, 78% yield); mp 114-115 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.23 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.62-7.38 (m, 8H), 5.22 (s, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 150.2, 140.9, 137.7, 135.5, 132.2, 131.6, 129.8, 127.1, 126.5, 126.2, 125.9, 125.2, 125.1, 123.9, 63.8, 34.7, 31.5; HRMS (ESI) Calcd for $C_{21}H_{22}NaO$ $(M+Na)^+$ 313.1563, found 313.1560.

1-(Azidomethyl)-4-(4-(*t*-butyl)phenyl)naphthalene (106).

105 (95 mg, 0.328 mmol) in anhydrous THF (3 mL) was cooled to 0 ^{o}C. DPPA (0.14 mL, 0.656 mmol) was then added drop-wise followed by DBU (0.1 mL, 0.656 mmol). Reaction was kept stirring over ice and was warmed to RT overnight. Reaction mixture was then poured into 0.5N HCl and extracted with EtOAc. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a white solid (78 mg, 76% yield); mp 80-81 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.13 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.65-7.61 (m, 1H), 7.58-7.50 (m, 4H), 7.49-7.44 (m, 3H), 4.85 (s, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 150.4, 141.7, 137.4, 132.3, 131.7, 130.2, 129.7, 127.3, 127.0, 126.6, 126.2, 126.1, 125.3, 123.7, 53.3, 34.7, 31.5; IR (thin film NaCl) 2099 cm^{-1}.

(4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanamine (107).

106 (70 mg, 0.222 mmol) was combined in a flask with polymer supported (3 mmol/g loading) PPh_3 (111 mg, 0.333 mmol), THF (5 mL), and H_2O (0.5 mL). Reaction was stirred overnight at RT. Resin was then filtered off and filtrate concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a golden oil (43 mg, 67% yield); ^{1}H NMR (400 MHz) (CD_3OD) δ 8.12 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.56-7.49 (m, 4H), 7.42-7.38 (m, 1H), 7.34-7.32 (m, 3H), 4.30 (s, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 151.4, 141.2, 139.2, 138.1, 133.4, 132.8, 130.8, 128.0, 127.6, 127.2, 126.7, 126.3, 125.5, 124.4, 43.9, 35.5, 31.9; HRMS (ESI) Calcd for $C_{21}H_{24}N$ $(M+H)^+$ 290.1903, found 290.1903.

1,3-bis-(*t*-Butoxycarbonyl)-2-((4-(4-(*t*-butyl)phenyl)naphthalen-1-yl)methyl)guanidine (108).

105 (40 mg, 0.14 mmol), PPh_3 (60 mg, 0.23 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (70 mg, 0.27 mmol) in anhydrous toluene (3 mL) at 0 ^{o}C was added diisopropylazodicarboxylate (0.04 mL, 0.20 mmol) drop wise over 15 minutes. Reaction was stirred at RT overnight then concentrated to an oil residue. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a white fluffy solid (70 mg, 97% yield); mp 88-90 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.46 (bs, 1H), 9.39 (bs, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.46-7.41 (m,

3H), 7.37-7.28 (m, 3H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 5.67 (s, 2H), 1.37 (s, 9H), 1.33 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 161.0, 155.2, 150.1, 139.2, 137.8, 133.7, 131.8, 131.0, 129.8, 127.0, 126.3, 125.7, 125.5, 125.1, 123.1, 121.6, 84.1, 79.0, 45.3, 34.6, 31.5, 28.3, 27.6; HRMS (ESI) Calcd for $C_{32}H_{42}N_3O_4$ $(M+H)^+$ 532.3175, found 532.3185.

2-((4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methyl)guanidine (109).

To a cooled solution of **108** (70 mg, 0.13 mmol) in anhydrous DCM (0.5 mL) was slowly added TFA (0.5 mL) at 0 ^{o}C. Reaction was stirred at RT overnight then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM/0.1% NH_4OH afforded product as a white solid (35 mg, 80% yield); mp 85-87 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.65-7.61 (m, 1H), 7.57-7.48 (m, 4H), 7.43-7.37 (m, 3H), 4.93 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.9, 151.7, 142.6, 138.9, 133.6, 132.8, 131.9, 130.8, 128.1, 127.7, 127.4, 127.2, 126.4, 126.3, 124.3, 44.5, 35.5, 31.9; HRMS (ESI) Calcd for $C_{22}H_{26}N_3$ $(M+H)^+$ 332.2121, found 332.2137.

1-(4-(*t*-Butyl)phenyl)-4-(2-nitrovinyl)naphthalene (110).

104 (168 mg, 0.583 mmol) and NH_4OAc (52 mg, 0.67 mmol) in nitromethane (4 mL) were refluxed at 102 ^{o}C for 2 hours. Solvents were then evaporated. Chromatography using ISCO max gradient 10% EtOAc/hexane afforded product as a yellow solid (160

mg, 83% yield); mp 151 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.84 (d, *J* = 12.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 4.0 Hz, 1H), 7.61 (d, *J* = 4.0 Hz, 1H), 7.60-7.56 (m, 1H), 7.48-7.44 (m, 3H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.37-7.34 (m, 2H), 1.34 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 151.1, 145.1, 138.3, 136.8, 136.3, 132.2, 132.1, 129.6, 127.5, 126.7, 126.6, 126.2, 126.0, 124.4, 123.2, 34.7, 31.4; HRMS (ESI) Calcd for $C_{22}H_{21}NO_2$ $(M)^+$ 331.1572, found 331.1569.

2-(4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)ethanamine (111).

To a cooled solution of **110** (160 mg, 0.483 mmol) in anhydrous THF (5 mL) was carefully added LAH (55 mg, 1.45 mmol) at 0 ^{o}C. Reaction was then stirred at RT overnight and quenched with H_2O over an ice bath. Reaction mixture was then diluted with EtOAc and washed with 1N NaOH solution. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM/0.1% NH_4OH afforded product as a tan solid (75 mg, 51% yield); mp 101-102 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.18 (d, *J* = 12.0 Hz, 1H), 7.90-7.88 (m, 1H), 7.55-7.50 (m, 3H), 7.43-7.39 (m, 2H), 7.37-7.34 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 3.30 (t, *J* = 8.0 Hz, 2H), 3.07-3.03 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 151.3, 140.6, 139.4, 136.1, 133.6, 130.8, 127.9, 127.5, 127.4, 126.9, 126.6, 126.2, 125.0, 43.4, 37.1, 35.5, 31.9; HRMS (ESI) Calcd for $C_{22}H_{26}N$ $(M+H)^+$ 304.2060, found 304.2052.

(5-Bromonaphthalen-1-yl)methanol (114).

To a solution of 5-bromo-1-naphthaldehyde (500 mg, 2.13 mmol) in EtOH (20 mL) was slowly added $NaBH_4$ (243 mg, 6.39 mmol) and reaction was stirred at RT for 30 minutes. Acetone (2 mL) was then added and solution was filtered through filter paper. Filtrate was concentrated then re-dissolved in DCM and washed with H_2O. Organic layer was collected, dried over Na_2SO_4, and concentrated to afford pure product as a white solid (473 mg, 94% yield); mp 100-101 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.19-8.17 (m, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.75-7.73 (m, 1H), 7.51-7.46 (m, 2H), 7.33-7.29 (m, 1H), 5.08 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 136.7, 132.6, 132.4, 130.1, 127.8, 126.8, 126.6, 126.2, 123.6, 63.6.

1,3-bis-(*t*-Butoxycarbonyl)-2-((5-bromonaphthalen-1-yl)methyl)guanidine (115).

114 (275 mg, 1.16 mmol), PPh_3 (456 mg, 1.74 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (601 mg, 2.32 mmol) in anhydrous toluene (5 mL) at 0 ^oC was added diisopropylazodicarboxylate (0.34 mL, 1.74 mmol) drop wise over 15 minutes. Reaction was stirred for 3 hours at RT then 2 drops H_2O were added, and the solution was concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a white solid (493 mg, 90% yield); mp 164-165 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.47 (bs, 2H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 5.62 (s, 2H), 1.36 (s, 9H), 1.07 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 160.8,

155.0, 135.0, 132.0, 129.9, 126.7, 126.3, 126.2, 123.7, 122.9, 122.7, 84.2, 79.0, 45.1, 28.2, 27.6; HRMS (ESI) Calcd for $C_{22}H_{29}BrN_3O_4$ $(M+H)^+$ 478.1336, found 478.1344.

1,3,-bis-(*t*-Butoxycarbonyl)-2-((5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (116a).

115 (100 mg, 0.21 mmol), 2-methoxy-4-trifluromethylphenylboronic acid (55 mg, 0.252 mmol), $Pd(OAc)_2$ (5 mg, 0.021 mmol), XPhos (20 mg, 0.042 mmol), and K_2CO_3 (87 mg, 0.63 mmol) were combined in a flask with dioxane (3 mL) and H_2O (1 mL) and degassed. Reaction mixture was then refluxed at 100 ^oC for 2 hours. Solution was cooled to RT then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 15% EtOAc/hexane afforded product as a clear oil (55 mg, 46% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 9.55 (bs, 1H), 9.48 (bs, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.61-7.57 (m, 1H), 7.42-7.33 (m, 5H), 7.27 (s, 1H), 7.19 (d, *J* = 4.0 Hz, 1H), 5.86-5.70 (m, 2H), 3.75 (s, 3H), 1.47 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 160.9, 157.4, 155.1, 136.2, 134.7, 132.2, 131.9, 127.0, 125.3, 125.0, 123.0, 121.9, 84.0, 79.0, 55.8, 45.4, 28.3, 27.6; HRMS (ESI) Calcd for $C_{30}H_{35}F_3N_3O_5$ $(M+H)^+$ 574.2523, found 574.2541.

1,3,-bis-(*t*-Butoxycarbonyl)-2-((5-(2-methyl-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (116b).

115 (165 mg, 0.35 mmol), 2-methyl-4-trifluromethylphenylboronic acid (85 mg, 0.41 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol), and K_2CO_3 (169 mg, 1.2 mmol) were combined in a flask with dioxane (5 mL) and H_2O (2.5 mL) and degassed. Reaction mixture was then refluxed at 100^oC overnight. Solution was cooled to RT then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a clear oil (208 mg, 95% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 9.55 (bs, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.62-7.57 (m, 3H), 7.41-7.22 (m, 5H), 5.84-5.74 (m, 2H), 2.06 (s, 3H), 1.48 (s, 9H), 1.17 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 161.0, 155.0, 139.0, 137.8, 135.1, 131.6, 130.9, 130.7, 126.6, 126.2, 125.7, 125.4, 124.6, 122.9, 122.5, 122.2, 84.0, 79.0, 45.2, 28.3, 27.6, 19.9.

2-((5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (117a).

To a cooled solution of **116a** (55 mg, 0.1 mmol) in anhydrous DCM (1.5 mL) was added TFA (1.5 mL) at 0 ^oC. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a tan gummy solid (31 mg, 86% yield); ^1H NMR (400 MHz) (CD_3OD) δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.59-7.55 (m, 1H), 7.43-7.36 (m, 2H), 7.34-7.28 (m, 5H), 4.84-4.82 (m, 2H), 3.62 (s, 3H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.1, 158.8,

138.1, 135.0, 133.7, 133.2, 132.9, 132.4, 128.6, 128.0, 127.3, 127.0, 126.8, 126.5, 124.1, 118.5, 118.4, 108.9, 56.3, 44.8; HRMS (ESI) Calcd for $C_{20}H_{19}F_3N_3O$ $(M+H)^+$ 374.1475, found 374.1470.

2-((5-(2-Methyl-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (117b).

To a cooled solution of **116b** (80 mg, 0.14 mmol) DCM (1 mL) was added trifluoroacetic acid (1 mL) at 0 ^oC. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Chromatography achieved using ISCO max gradient 10% MeOH/DCM yielding product as a clear oil (50 mg, quantitative); ^1H NMR (400 MHz) (CD_3OD) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.74-7.69 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.57-7.55 (m, 1H), 7.47-7.37 (m, 4H), 4.96 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.9, 145.6, 140.6, 139.3, 133.3, 132.6, 132.0, 128.0, 127.6, 127.4, 127.4, 127.1, 126.9, 124.2, 123.7, 123.6, 44.6, 20.1; HRMS (ESI) Calcd for $C_{20}H_{18}F_3N_3$ $(M+H)^+$ 358.1526, found 358.1527.

5-(4-(Trifluoromethyl)phenyl)-1-naphthaldehyde (118b).

5-Bromo-1-naphthaldehyde (500 mg, 2.1 mmol), 4-trifluoromethylphenylboronic acid (620 mg, 3.2 mmol), and K_2CO_3 (880 mg, 6.4 mmol) in dioxane (15 mL) and H_2O (3 mL) were degassed and $Pd(PPh_3)_4$ (73 mg, 0.06 mmol) was quickly added. Reaction was then refluxed at 100 ^oC for 5 hours then cooled to RT. Solution was collected, dried over

Mg_2SO_4, filtered, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a pale solid (560 mg, 88% yield); mp 78-80 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 10.45 (s, 1H), 9.35 (d, *J* = 8.0 Hz, 1H), 8.08-8.01 (m, 2H), 7.78-7.73 (m, 3H), 7.62-7.58 (m, 3H), 7.52 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 193.4, 144.1, 139.3, 136.6, 132.7, 131.7, 131.0, 130.5, 128.4, 128.0, 125.4, 125.3, 125.2, 125.1, 124.9, 120.3.

(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol (119a).

A mixture of 5-(4-(*t*-butyl)phenyl)-1-naphthaldehyde (**118a**) (750 mg, 2.6 mmol) and $NaBH_4$ (70 mg, 1.85 mmol) in 95% EtOH/MeOH (20 mL) was stirred at RT for 1 hour. Reaction was then filtered and filtrate was concentrated. Residue was taken back up in EtOAc and washed with saturated $NaHCO_3$ solution followed by brine. Organic layer was collected, dried over magnesium sulfate, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a white solid (740 mg, 99% yield); mp 81-83 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.6 Hz, 1H), 7.64-7.60 (m, 1H), 7.57-7.52 (m, 3H), 7.49 (dd, *J* = 7.0 Hz, *J* = 1.2 Hz, 1H), 7.46-7.40 (m, 3H), 5.22 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 150.2, 141.0, 137.9, 136.4, 132.2, 131.6, 129.8, 128.6, 127.0, 126.9, 125.9, 125.4, 125.2, 123.0, 64.0, 34.6, 31.5; HRMS (ESI) Calcd for $C_{21}H_{22}NaO$ $(M+Na)^+$ 313.1568, found 313.1565.

(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)methanol (119b).

A mixture of **118b** (350 mg, 1.16 mmol) and $NaBH_4$ (31 mg, 0.82 mmol) in 95% EtOH/MeOH (15 mL) was stirred at RT for 1 hour. Reaction was then filtered and filtrate was concentrated. Residue was taken back up in EtOAc and washed with saturated $NaHCO_3$ solution followed by brine. Organic layer was collected, dried over Mg_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a white solid (350 mg, quantitative); mp 98 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.23 (d, *J* = 8.5 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 3H), 7.66-7.58 (m, 4H), 7.48-7.43 (m, 2H), 5.22 (s, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 144.7, 139.5, 136.7, 131.7-131.6 (m), 130.4, 129.8, 129.4, 127.0, 126.2, 125.9, 125.8, 125.5, 125.3-125.2 (m), 124.0, 123.0, 63.9.

1,3-bis-(*t*-Butoxycarbonyl)-2-((5-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (120b).

To a solution of **119b** (40 mg, 0.13 mmol), PPh_3 (55 mg, 0.21 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (70 mg, 0.27 mmol) in anhydrous toluene (3 mL) at 0 ^oC was added diisopropylazodicarboxylate (0.04 mL, 0.20 mmol) drop wise over 15 minutes. Reaction was stirred at RT overnight, and the solution was then concentrated to an oil residue. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a white glassy residue (56 mg, 80% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ

9.44 (bs, 2H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.53-7.48 (m, 3H), 7.35-7.28 (m, 2H), 7.12 (d, *J* = 4.0 Hz, 1H), 5.68 (s, 2H), 1.37 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 160.9, 155.1, 144.8, 139.4, 134.4, 131.4, 131.0, 130.5, 129.7, 126.8, 125.7, 125.6, 125.3, 125.2-125.1 (m), 124.6, 123.1, 122.1, 84.1, 79.0, 45.4, 28.2, 27.7; HRMS (ESI) Calcd for $C_{29}H_{33}F_3N_3O_4$ $(M+H)^+$ 544.2423, found 544.2431.

2-((5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (121b).

120b (56 mg, 0.1 mmol) in a mixture of anhydrous DCM (0.8 mL) and TFA (0.8 mL) was stirred at RT overnight. Solvents were then evaporated. Chromatography using ISCO max gradient 20% 3% NH_4OH/MeOH/DCM solution afforded product as a white solid (20 mg, 51% yield); mp 198-200 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.10 (d, *J* = 8.6 Hz, 1H), 7.85-7.79 (m, 3H), 7.73-7.69 (m, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.58-7.47 (m, 3H), 4.96 (s, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.9, 146.2, 141.0, 133.2, 133.1, 132.8, 131.8, 130.9, 128.5, 127.4, 127.3, 127.0, 126.9, 126.4-126.3 (m), 124.5, 124.4, 44.6; HRMS (ESI) Calcd for $C_{19}H_{17}F_3N_3$ $(M+H)^+$ 344.1369, found 344.1352.

2-(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)acetonitrile (123b).

119b (300 mg, 0.99 mmol) in anhydrous DCM (10 mL) was cooled to 0 ^{o}C and PBr_3 (0.14 mL) was added drop-wise. The reaction was stirred at 0 ^{o}C for 1 hour then quenched with saturated $NaHCO_3$ and extracted with DCM. Organic layer was collected,

dried over magnesium sulfate, and concentrated to yield crude product as a pale gum which was taken forward without further purification. This crude 1-(bromomethyl)-5-(4-(trifluoromethyl)phenyl)naphthalene (300 mg, 0.82 mmol) and KCN (100 mg, 1.5 mmol) in DMSO were stirred at RT overnight. Reaction was then diluted with H_2O and extracted with ether. Organic layer was collected, dried over magnesium sulfate, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane yielded product as a white solid (260 mg, 85% yield over two steps); mp 44-45 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.87 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.69-7.68 (m, 2H), 7.62-7.58 (m, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.52-7.51 (m, 2H), 7.43-7.34 (m, 2H), 4.12 (s, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) □ 144.2, 140.0, 131.8, 131.2, 130.4, 130.0, 129.7, 127.5, 126.8, 126.7, 126.5, 126.3, 125.9, 125.3, 122.7, 117.5, 22.1; HRMS (ESI): calcd for $C_{19}H_{12}F_3NNa$ $(M+Na)^+$ 334.0820, found 334.0823.

2-(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)acetimidamide (124b).

123b (100 mg, 0.32 mmol) in anhydrous Et_2O (2 mL) was cooled to 0 ^oC and treated with 4N HCl/dioxane solution (2 mL). Reaction was stirred at 0 ^oC for 4 hours. The mixture was then placed in the refrigerator overnight. The precipitated solids were filtered out then treated with NH_4OH/EtOH (5 mL) and heated to reflux for 6 hours. Solvents were then evaporated. Chromatography using ISCO max gradient 20% 3% NH_4OH/MeOH/DCM solution yielded product as a pale gummy solid (37 mg, 29% yield); mp ^1H NMR (400 MHz) ($CDCl_3$) δ 8.06 (d, *J* = 6.0 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 2H), 7.76-7.67 (m, 3H), 7.62-7.50 (m, 4H), 4.44 (s, 2H); ^{13}C NMR (100 MHz)

(CD_3OD) δ 171.7, 141.2, 133.5, 133.2, 131.8, 130.2, 130.0, 129.8, 129.4, 128.6, 127.8, 127.6, 127.4, 127.3, 126.4-126.3 (m), 124.2, 37.2; HRMS (ESI) Calcd for $C_{19}H_{16}F_3N_2$ $(M+H)^+$ 329.1260, found 329.1244.

1-(Azidomethyl)-5-(4-(*t*-butyl)phenyl)naphthalene (125).

119a (66 mg, 0.23 mmol), NaN_3 (18 mg, 0.27 mmol), and PPh_3 (125 mg, 0.48 mmol) in DMF (4 mL) and CCl_4 (1 mL) were heated to 90 ^oC overnight. Solvents were then evaporated without further purification afforded product as a clear oil (50 mg, 69% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.54-7.50 (m, 1H), 7.44-7.38 (m, 4H), 7.35-7.28 (m, 3H), 4.72 (s, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 150.3, 141.2, 137.7, 132.3, 131.8, 131.1, 129.8, 127.8, 127.3, 127.2, 126.2, 125.2, 125.1, 122.8, 53.4, 34.7, 31.5; IR (thin film NaCl) 2099 cm^{-1}.

(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanamine (126).

125 (50 mg, 0.16 mmol) was combined in a flask with polymer supported (3 mmol/g loading) PPh_3 (300 mg), THF (5 mL), and H_2O (0.5 mL). Reaction was stirred overnight at RT. Resin was then filtered off and filtrate concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as an oily residue (34 mg, 74% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.51 (m, 1H), 7.44-7.29 (m, 7H), 4.31 (s, 2H), 1.58 (bs, 2H), 1.34 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 151.5, 142.5, 139.5, 138.6, 133.5, 132.9, 130.8, 127.9, 127.0, 126.8,

126.5, 126.2, 126.1, 123.5, 44.0, 35.5, 31.9; HRMS (ESI) Calcd for $C_{21}H_{23}N$ $(M+H)^+$ 290.1903, found 290.1891.

(5-(4-Cyclopropylphenyl)naphthalen-1-yl)methanol (132).

5-(4-Bromophenyl)naphthalen-1-yl)methanol (**129a**) (130 mg, 0.415 mmol), cyclopropylboronic acid (71 mg, 0.83 mmol), $Pd(OAc)_2$ (5 mg, 0.021 mmol), tricyclohexylphosphine (12 mg, 0.0415 mmol), and K_3PO_4 (308 mg, 1.45 mmol) were combined in a flask with toluene (3 mL) and H_2O (1 mL) and degassed. Reaction mixture was then refluxed at 100 ^oC for 3 hours. Solution was cooled to RT then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 35% EtOAc/hexane afforded product as a brown oil (86 mg, 75% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.17-8.15 (m, 1H), 7.96-7.94 (m, 1H), 7.61 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 7.56-7.53 (m, 2H), 7.49-7.47 (m, 1H), 7.43-7.40 (m, 2H), 7.25-7.23 (m, 2H), 5.19 (s, 2H), 2.08-2.01 (m, 1H), 1.11-1.06 (m, 2H), 0.87-0.83 (m, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 143.2, 138.0, 136.5, 132.2, 131.6, 130.1, 130.1, 138.3, 126.8, 125.8, 125.6, 125.4, 125.3, 123.0, 63.9, 15.3, 9.4; HRMS (ESI) Calcd for $C_{20}H_{18}NaO$ $(M+Na)^+$ 297.1250, found 297.1251.

1,3-bis-(*t*-Butoxycarbonyl)-2-((5-(4-cyclopropylphenyl)naphthalen-1-yl)methyl)guanidine (133).

To a solution of **132** (80 mg, 0.292 mmol), PPh_3 (115 mg, 0.584 mmol), and 1,3-bis-(*t*-butoxycarbonyl)guanidine (151 mg, 0.438 mmol) in anhydrous toluene (3 mL) at 0 ^oC was added diisopropylazodicarboxylate (0.09 mL, 0.438 mmol) drop wise over 15 minutes. Reaction was stirred for 3 hours at RT then 2 drops H_2O were added, and the solution was concentrated. Solid was then dissolved in DCM and passed through silica column and resulting crude product was taken forward to the next step.

2-((5-(4-Cyclopropylphenyl)naphthalen-1-yl)methyl)guanidine (134).

Crude **133** was dissolved in anhydrous DCM (1.5 mL) and cooled to 0 ^oC. TFA (1.5 mL) was then added. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Solid was then taken back up in DCM and precipitate was filtered off afforded product as a sticky, gummy tan solid (18 mg, 20% yield over 2 steps); ^1H NMR (400 MHz) (CD_3OD) δ 8.02-8.00 (m, 1H), 7.90-7.88 (m, 1H), 7.67-7.63 (m, 1H), 7.54-7.50 (m, 2H), 7.47-7.42 (m, 1H), 7.33-7.31 (m, 2H), 7.24-7.22 (m, 2H), 4.93 (s, 2H), 2.06-1.99 (m, 1H), 1.06-1.02 (m, 2H), 0.79-0.76 (m, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.9, 144.9, 142.7, 139.1, 133.6, 132.8, 131.0, 129.4, 128.2, 128.1, 127.3, 126.7, 126.6, 126.4, 123.3, 44.7, 16.0, 9.7; HRMS (ESI) Calcd for $C_{21}H_{22}N$ $(M+H)^+$ 316.1808, found 316.1805.

1,3,-bis-(*t*-Butoxycarbonyl)-2-(2-(5-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine (137).

2-(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)ethanamine (**136**) (25 mg, 0.08 mmol), 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethylsulfonyl)-guanidine (40 mg, 0.1 mmol), and Et_3N (0.03 mL, 0.22 mmol) in anhydrous DCM (6 mL) were stirred at RT overnight. Solvents were then evaporated. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a white solid (20 mg, 44% yield); mp 134-137 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.50-8.40 (m, 1H), 7.78-7.60 (m, 6H), 7.44-7.35 (m, 3H), 3.81 (m, 2H), 3.44 (t, *J* = 6.0 Hz, 2H), 1.56 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.7, 156.2, 153.2, 144.9, 139.4, 135.2, 132.4, 131.8, 130.5, 131.8, 127.0, 126.9, 125.9, 125.7, 125.5, 125.2-125.1 (m), 124.9, 124.5, 83.1, 79.1, 41.8, 33.0, 28.4, 28.1; HRMS (ESI) Calcd for $C_{30}H_{35}F_3N_3O_4$ $(M+H)^+$ 558.2580, found 558.2590.

2-(2-(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine (138).

137 (20 mg, 0.036 mmol) was stirred at RT in a mixture of anhydrous DCM (0.5 mL) and TFA (0.5 mL) overnight. Solvents were then evaporated. Chromatography using ISCO max gradient 20% 3% NH_4OH/MeOH/DCM solution yielded product as a white solid (11 mg, 85% yield); mp 240 ^oC; ^1H NMR (400 MHz) (CD_3OD) δ 8.21 (d, *J* = 6.0 Hz, 1H), 7.84 (d, *J* = 6.0 Hz, 2H), 7.73-7.64 (m, 4H), 7.51-7.43 (m, 3H), 3.66 (t, *J* = 6.0 Hz, 2H), 3.46 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.7, 146.4, 140.9, 135.9, 133.5, 133.1, 131.7, 128.4, 128.1, 127.1, 126.8, 126.3, 126.2, 126.1, 124.8, 124.5, 43.1, 33.2; HRMS (ESI): calcd for $C_{20}H_{19}F_3N_3$ $(M+H)^+$ 358.1526, found 358.1535.

(5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methanol (139).

114 (150 mg, 0.63 mmol), 2-methoxy-4-trifluromethylphenylboronic acid (167 mg, 0.76 mmol), $Pd(OAc)_2$ (14 mg, 0.063 mmol), XPhos (60 mg, 0.13 mmol), and K_2CO_3 (262 mg, 1.9 mmol) were combined in a flask with dioxane (5 mL) and H_2O (1.6 mL) and degassed. Reaction mixture was then refluxed at 100 ^oC for 2 hours. Solution was cooled to RT then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 35% EtOAc/hexane afforded product as a clear oil (180 mg, 86% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.24-8.22 (m, 1H), 7.64 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.45-7.37 (m, 4H), 7.29 (s, 1H), 5.22 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 157.5, 136.5, 136.3, 133.5, 132.2, 132.2, 131.5, 131.3, 131.2, 127.3, 126.6, 125.8, 125.5-125.4 (m), 123.9, 122.8, 117.5-117.4 (m), 107.7, 66.0, 55.8; HRMS (ESI) Calcd for $C_{19}H_{15}F_3NaO_2$ $(M+Na)^+$ 355.0916, found 355.0919.

2-(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)acetonitrile (140a).

119a (1.0 g, 3.4 mmol) and Et_3N (0.8 mL, 5.8 mmol) in DCM (25 mL) at 0 ^oC was slowly added MsCl (0.33 mL, 4.3 mmol). The reaction was stirred at 0 ^oC for 30 minutes then quenched with saturated $NaHCO_3$ and extracted with EtOAc. Organic layer was collected, dried over magnesium sulfate, and concentrated to an oil. To this oil residue was added KCN (310 mg, 4.8 mmol) in DMSO (10 mL). The reaction was stirred at RT

overnight then diluted with H_2O and extracted with EtOAc. Extract was then washed with additional H_2O followed by brine. Organic layer was collected, dried over magnesium sulfate, and concentrated. Chromatography using ISCO max gradient 50% EtOAc/hexane yielded product as a pale oil (510 mg, 50% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.70-7.63 (m, 2H), 7.57-7.53 (m, 3H), 7.46-7.42 (m, 3H), 4.21 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 150.5, 141.5, 137.5, 132.2, 131.2, 129.8, 127.5, 127.4, 126.6, 126.4, 125.9, 125.4, 125.2, 121.7, 117.7, 34.7, 31.4, 22.1; HRMS (ESI) Calcd for $C_{22}H_{21}N$ $(M)^+$ 299.1674, found 299.1672.

2-(5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)acetonitrile (140b).

To a solution of **139** (180 mg, 0.54 mmol) and Et_3N (0.15 mL, 1.08 mmol) in DCM (5 mL) was added MsCl (0.06 mL, 0.81 mmol), and the reaction mixture was stirred at RT overnight. Reaction was then diluted with DCM and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated without further purification. This crude (5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methyl methanesulfonate (150 mg, 0.37 mmol) was combined with KCN (48 mg, 0.73 mmol) in anhydrous DMF (3 mL) and stirred at RT overnight. Reaction mixture was then diluted with EtOAc and washed with 10% LiCl solution. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as clear oil (125 mg, 68% yield over two steps); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.97 (d, *J* = 12.0 Hz, 1H), 7.72-7.68 (m, 1H), 7.63

(d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 4.0 Hz, 1H), 7.44-7.40 (m, 3H), 7.30 (s, 1H), 4.21 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 157.4, 136.8, 133.0, 132.2, 132.2, 130.9, 127.8, 127.2, 126.6, 126.5, 126.1, 125.5, 122.6, 117.7, 117.5, 117.4, 107.8, 107.7, 55.8, 22.0; HRMS (ESI) Calcd for $C_{20}H_{14}F_3NO$ $(M)^+$ 341.1022, found 341.1019.

2-(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)ethanamine (141a).

LAH (1.0M/THF, 0.9 mL) was added drop-wise to a cooled 0 ^oC solution of **140a** (85 mg, 0.28 mmol) in anhydrous THF (5 mL). The resultant mixture was then refluxed for 7 hours. Reaction was cooled to 0 ^oC and carefully treated with aqueous NaOH solution and extracted with EtOAc. Organic layer was collected, dried over magnesium sulfate, and concentrated. Chromatography using ISCO max gradient 20% 1.5% NH_4OH/MeOH/DCM solution yielded product as a pale oil (15 mg, 17% yield); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 8.99 (d, *J* = 6.0 Hz, 1H), 7.77 (d, *J* = 6.0 Hz, 1H), 7.50-7.41 (m, 3H), 7.34 (m, 3H), 7.29 (m, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 3.08 (t, *J* = 6.0 Hz, 2H), 1.92 (bs, 2H), 1.34 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 151.3, 140.6, 139.4, 136.1, 133.6, 130.8, 127.9, 127.5, 127.4, 126.9, 126.2, 125.0, 43.5, 37.1, 35.5, 31.9; HRMS (ESI) Calcd for $C_{22}H_{25}N$ $(M+H)^+$ 304.2060, found 304.2046.

2-(5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethanamine (141b).

A flask was charged with LAH (15.6 mg, 0.41 mmol) in anhydrous ether (3 mL). To the suspension was added **140b** (70 mg, 0.21 mmol) in anhydrous ether (2 mL) drop-wise. Reaction was stirred at RT for 30 minutes then placed on an ice bath. H_2O (10 drops) was carefully added in to quench remaining LAH then 1M NaOH was added to increase pH > 9. Solution was then diluted with additional ether and organic layer was extracted from aqueous layer. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as clear oil (31 mg, 44% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.62-7.58 (m, 1H), 7.43-7.32 (m, 6H), 7.28 (s, 1H), 3.77 (s, 3H), 3.33-3.29 (m, 2H), 3.19 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 157.5, 136.3, 135.9, 133.7, 132.3, 132.2, 132.0, 127.0, 126.8, 125.5, 125.2, 125.0, 123.9, 117.4, 117.3, 107.7, 55.8, 42.9, 37.5; HRMS (ESI) Calcd for $C_{20}H_{19}F_3NO$ $(M+H)^+$ 346.1413, found 346.1415.

2-(5-(2-Aminoethyl)naphthalen-1-yl)-5-(trifluoromethyl)phenol (142).

To a cooled solution of **141b** (28 mg, 0.081 mmol) in anhydrous DCM (4 mL) was added BBr_3 (1.0 M in DCM, 0.41 mL) dropwise. The solution was then stirred at RT for 3 hours and reaction was placed back over ice. H_2O was slowly dripped into the flask to quench the remaining BBr_3 and mixture was then diluted with additional DCM and washed with $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM to afford product as a clear oil (13 mg, 48% yield); ^{1}H NMR (400 MHz) (CD_3OD) δ 8.05 (d, *J* =

8.0 Hz, 1H), 7.48 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.29-7.26 (m, 2H), 7.24-7.20 (m, 2H), 7.12-7.10 (m, 2H), 3.20 (t, *J* = 6.0 Hz, 2H), 2.96 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 157.0, 138.1, 136.5, 133.8, 133.6, 133.5, 133.4, 132.3, 132.0, 128.3, 127.9, 127.0, 126.6, 126.4, 124.8, 116.8, 113.4-113.3 (m), 43.2, 36.5; HRMS (ESI) Calcd for $C_{19}H_{17}F_3NO$ $(M+H)^+$ 332.1257, found 332.1259.

1,3-bis-(*t*-Butoxycarbonyl)-2-(2-(5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine (143b).

141b (25 mg, 0.073 mmol), 1,3-bis-(*t*-butoxycarbonyl)-2-(trifluoromethylsulfonyl)-guanidine (34 mg, 0.087 mmol), and Et_3N (0.01 mL, 0.087 mmol) in anhydrous DCM (2.5 mL) were stirred at RT overnight. Reaction mixture was then diluted with DCM and washed with $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a clear oil (37 mg, 88% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 11.50 (bs, 1H), 8.50 (bt, *J* = 6.0 Hz, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 7.62 (dd, *J* = 8.0 Hz, *J* = 8.0 Hz, 1H), 7.43-7.36 (m, 5H), 7.35-7.31 (m, 1H), 7.27 (s, 1H), 3.85-3.79 (m, 2H), 3.76 (s, 3H), 3.50-3.37 (m, 2H), 1.57 (s, 9H), 1.51 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.7, 157.5, 156.1, 153.2, 136.2, 135.0, 133.8, 132.2, 132.1, 127.1, 126.8, 125.5, 125.4, 125.3, 124.3, 117.3, 83.0, 79.1, 55.8, 41.8, 33.0, 28.4, 28.1; HRMS (ESI) Calcd for $C_{31}H_{37}F_3N_3O_5$ $(M+H)^+$ 588.2680, found 588.2698.

2-(2-(5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine (144b).

To a cooled solution of **143b** (35 mg, 0.06 mmol) in anhydrous DCM (1 mL) was added TFA (1 mL). Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a clear oil (19 mg, 83% yield); ^{1}H NMR (400 MHz) (CD_3OD) δ 8.16 (d, *J* = 8.6 Hz, 1H), 7.66-7.62 (m, 1H), 7.44-7.34 (m, 7H), 3.74 (s, 3H), 3.65 (t, *J* = 8.0 Hz, 2H), 3.46-3.42 (m, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.1, 158.7, 138.0, 135.5, 135.3, 133.7, 133.3, 133.2, 128.3, 128.1, 127.0, 126.8, 126.7, 126.6, 124.5, 118.4, 118.3, 108.8, 56.2, 43.2, 33.1; HRMS (ESI) Calcd for $C_{21}H_{21}F_3N_3O$ $(M+H)^+$ 388.1631, found 388.1630.

1-(4-(*t*-Butyl)phenyl)-2,3-dimethoxy-5-nitronaphthalene (145).

14 (1 g, 3.2 mmol), 4-*t*-butylphenylboronic acid (685 mg, 3.8 mmol), $Pd(PPh_3)_4$ (370 mg, 0.32), and Na_2CO_3 (680 mg, 6.4 mmol) were combined in a flask with dioxane (20 mL) and H_2O (5 mL) and degassed. Reaction mixture was then refluxed at 100^{o}C overnight. Solution was cooled to RT then diluted with EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a yellow solid (1.16 g, 99% yield); mp 179 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.18 (dd, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H), 8.08 (s, 1H), 7.79-7.77 (m, 1H), 7.54 (dt, *J* = 8.0 Hz, *J* = 2.0 Hz, 2H), 7.30 (t, *J* = 2.0 Hz, 1H), 7.28-7.27 (m, 2H), 3.99 (s, 3H), 3.58 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz)

($CDCl_3$) δ 155.01, 150.7, 147.5, 145.4, 132.9, 132.7, 132.0, 130.7, 130.1, 125.3, 123.6, 123.5, 121.9, 102.2, 61.1, 55.9, 34.7, 31.4.

5-(4-(*t*-Butyl)phenyl)-6,7-dimethoxynaphthalen-1-amine (146).

145 (1.16 g, 3.2 mmol) was combined with hydrazine monohydrate (3 mL) and Pd/C (10% wt.) (200 mg) in ethanol (35 mL) and refluxed at 85 ^oC for 1.5 hours. Pd/C was then filtered out and filtrate concentrated to afford product as a pinkish-white solid (1.03 g, 97% yield); mp 181-182 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.41-7.39 (m, 2H), 7.22-7.20 (m, 2H), 7.07 (s, 1H), 7.00-6.96 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.67-6.65 (m, 1H), 3.94 (s, 3H), 3.54 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 151.7, 149.9, 146.7, 133.3, 132.9, 130.1, 130.01, 124.9, 124.2, 121.3, 117.9, 110.1, 100.4, 61.0, 55.8, 34.6, 31.6.

1-(4-(*t*-Butyl)phenyl)-5-iodo-2,3-dimethoxynaphthalene (147).

146 (1 g, 3 mmol) was dissolved in 10% HCl (40 mL) solution and cooled to 0^oC. A solution of $NaNO_2$ (223 mg, 3.2 mmol) in H_2O (10 mL) was rapidly added to the mixture and reaction was stirred for 20 minutes at 0 ^oC. A cooled solution of NaI (905 mg, 6 mmol) in H_2O (10 mL) was then rapidly added and reaction was stirred for an additional 3 hours, keeping the temperature at 0 ^oC. Reaction mixture was then poured into a mixture of ether and H_2O (250 mL/100 mL) and filtered through filter paper. Filtrate was then extracted and organic layer was collected, dried over Na_2SO_4, and concentrated.

Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a white solid (189 mg, 14% yield); mp 127-129 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.90-7.89 (m, 1H), 7.45-7.37 (m, 4H), 7.19-7.18 (m, 2H), 6.85-6.81 (m, 1H), 4.01 (s, 3H), 3.55 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.6, 150.3, 136.7, 132.2, 130.1, 129.3, 127.1, 125.1, 124.6, 111.7, 98.1, 60.1, 55.8, 34.7, 31.5.

_t_-Butyl (2-(5-(4-(_t_-butyl)phenyl)-6,7-dimethoxynaphthalen-1-yl)ethyl)carbamate (148).

147 (155 mg, 0.35 mmol), potassium *t*-butyl *N*-[2-(trifluoroboranuidyl)ethyl]carbamate (132 mg, 0.52 mmol), $PdCl_2$(dppf) (29 mg, 0.035), and Cs_2CO_3 (342 mg, 1.05 mmol) were combined in a flask with dioxane (6 mL) and H_2O (2 mL) and degassed. Reaction mixture was then refluxed at 102 ^{o}C overnight. Solution was cooled to RT then diluted with EtOAc and washed with saturated NH_4Cl. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a tan solid (108 mg, 67% yield); mp 113-115 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.40 (s, 1H), 7.35-7.33 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.14-7.12 (m, 2H), 7.08-7.06 (m, 1H), 7.02-6.98 (m, 1H), 4.54 (bs, 1H), 3.92 (s, 3H), 3.47 (s, 3H), 3.39 (q, *J* = 6.7 Hz, 2H), 3.10 (t, *J* = 8.0 Hz, 2H), 1.30 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.0, 152.4, 150.0, 146.5, 133.4, 133.1, 130.1, 129.8, 129.5, 126.0, 125.3, 125.0, 123.4, 103.2, 61.0, 55.9, 34.6, 34.3, 31.5, 28.4.

2-(5-(4-(t-Butyl)phenyl)-6,7-dimethoxynaphthalen-1-yl)ethanamine (149).

To a cooled solution of **148** (100 mg, 0.22 mmol) in DCM (2 mL) was added trifluoroacetic acid (2 mL) at 0 ^{o}C. Reaction was taken off ice bath and stirred at RT for 2 hours then solvents were evaporated. Chromatography using ISCO max gradient 5% MeOH/DCM afforded product as a white solid (80 mg, 79% yield); mp 181-183 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 7.56-7.53 (m, 2H), 7.45 (s, 1H), 7.35-7.32 (m, 2H), 7.24-7.17 (m, 3H), 4.09 (s, 3H), 3.63 (s, 3H), 3.48 (m, 2H), 3.36-3.33 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 154.1, 151.6, 147.7, 134.5, 132.4, 131.3, 131.0, 130.8, 127.6, 127.0, 126.1, 124.7, 103.6, 61.4, 56.4, 41.1, 35.5, 32.2, 31.9; HRMS (ESI) Calcd for $C_{24}H_{30}NO_2$ $(M+H)^+$ 364.2271, found 364.2269.

5-(2-Aminoethyl)-1-(4-(*t*-butyl)phenyl)naphthalene-2,3-diol (150).

To a cooled solution of **149** (52 mg, 0.14 mmol) in anhydrous DCM (5 mL) was added BBr_3 (1.0 M in DCM) (1.12 mL, 1.4 mmol) dropwise at 0 ^{o}C. The solution was then stirred at RT for 3 hours and reaction was placed back over ice. H_2O was slowly dripped into the flask to quench the remaining BBr_3 and mixture was then diluted with additional DCM and washed with $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a rusty brown solid (16 mg, 33% yield); mp 180 ^{o}C (decomposes to black sticky tar); ^{1}H NMR (400 MHz) (CD_3OD) δ 7.57-7.55 (m, 2H), 7.39 (s, 1H), 7.28-7.25 (m, 3H), 7.19 (d, *J* = 4.0 Hz, 1H), 7.11-7.07 (m, 1H), 3.39-3.37 (m, 2H), 3.34-3.32 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 151.4, 147.9, 134.6, 131.8, 131.5,

131.0, 128.7, 126.4, 126.1, 125.7, 125.1, 123.9, 105.5, 41.1, 35.5, 32.3, 31.9; HRMS (ESI) Calcd for $C_{22}H_{25}NO_2$ $(M+H)^+$ 336.1958, found 336.1956.

Methyl 6-hydroxy-1-naphthoate (151).

6-Hydroxy-1-naphthoic acid (1 g, 5.32 mmol) was suspended in anhydrous DCM (20 mL) and oxalyl chloride (0.93 mL, 10.64 mmol) was added followed by 15 drops of catalytic anhydrous DMF. Reaction was stirred at RT for 1 hour then solvents were evaporated. Residue was then redissolved in methanol (10 mL) and stirred at RT for 2 hours. Solvent was then evaporated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a white solid (1.05 g, 98% yield); mp 94-95 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.86 (d, *J* = 9.2 Hz, 1H), 8.05 (dd, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.28-7.44 (m, 1H), 7.26-7.22 (m, 2H), 5.37 (s, 1H), 4.02 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.2, 153.5, 135.4, 131.8, 128.0, 127.9, 127.1, 126.7, 125.2, 119.5, 110.1, 52.2.

Methyl 6-(((trifluoromethyl)sulfonyl)oxy)-1-naphthoate (152).

151 (1.03 g, 5.1 mmol) in anhydrous DCM (30 mL) was cooled to -78 ^oC. Triflic anhydride (1.03 mL, 6.12 mmol) was then added followed by Et_3N (1.42 mL, 10.2 mmol) and reaction was stirred for 30 minutes at -78 ^oC. Mixture was then diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20%

EtOAc/hexane afforded product as a white solid (1.46 g, 86% yield); mp 51 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.02 (d, *J* = 9.5 Hz, 1H), 8.19 (dd, *J* = 7.3 Hz, *J* = 1.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.41 (dd, *J* = 9.6 Hz, *J* = 2.7 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 167.3, 147.2, 134.2, 133.3, 131.4, 130.4, 129.2, 127.3, 126.4, 121.1, 120.4, 119.6-117.2 (m), 52.4.

Methyl 6-(3-(*t*-butyl)phenyl)-1-naphthoate (153a).

152 (250 mg, 0.75 mmol), 3-*t*-butylphenylboronic acid (163 mg, 0.9 mmol), $Pd(OAc)_2$ (17 mg, 0.075 mmol), XPhos (71 mg, 0.15 mmol), and K_2CO_3 (311 mg, 2.25 mmol) in dioxane/H_2O (6 mL/2 mL) were degassed then refluxed at 102 ^{o}C for 2 hours. Reaction was cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a clear oil (225 mg, 94% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.03 (d, *J* = 9.0 Hz, 1H), 8.22 (dd, *J* = 7.3 Hz, *J* = 1.2 Hz, 1H), 8.13-8.10 (m, 2H), 7.93 (dd, *J* = 9.0 Hz, *J* = 2.0 Hz, 1H), 7.78 (s, 1H), 7.59-7.54 (m, 2H), 7.49-7.47 (m, 2H), 4.06 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.0, 151.8, 140.3, 139.5, 134.2, 133.6, 130.5, 130.1, 128.7, 127.7, 127.0, 126.4, 126.2, 124.9, 124.7, 124.6, 124.5, 52.1, 34.9, 31.5.

Methyl 6-(3-hydroxyphenyl)-1-naphthoate (153b).

152 (500 mg, 1.5 mmol), 3-hydroxyphenylboronic acid (311 mg, 2.25 mmol), $Pd(OAc)_2$ (34 mg, 0.15 mmol), XPhos (143 mg, 0.3 mmol), and K_2CO_3 (621 mg, 4.5 mmol) in dioxane/H_2O (9 mL/3 mL) were degassed and refluxed at 102 ^oC for 2 hours then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a clear oil (415 mg, quantitative); ^1H NMR (400 MHz) ($CDCl_3$) δ 9.00 (d, *J* = 9.0 Hz, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 8.09-8.07 (m, 2H), 7.87 (dd, *J* = 9.0 Hz, *J* = 1.8 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.32-7.20 (m, 1H), 7.23 (t, *J* = 1.8 Hz, 1H), 6.88 (dt, *J* = 7.9 Hz, *J* = 1.2 Hz, 1H), 5.61 (s, 2H), 4.05 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.0, 156.3, 142.2, 138.4, 134.2, 133.7, 130.7, 130.3, 130.1, 127.3, 127.0, 126.4, 126.2, 124.9, 119.7, 114.7, 114.4, 52.2.

(6-(3-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol (154).

To a cooled solution of **153a** (210 mg, 0.66 mmol) in anhydrous THF/EtOH (5 mL/0.5 mL) was added $LiBH_4$ (44 mg, 1.98 mmol). Solution was stirred at RT overnight. Reaction was then quenched with ice over an ice bath, diluted with EtOAc, and washed with water. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a clear oil (153 mg, 80% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.23 (d, *J* = 8.8 Hz, 1H), 8.10 (d, *J* = 1.7 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.85 (dd, *J* = 8.8 Hz, *J* = 1.9 Hz, 1H),

7.78 (m, 1H), 7.58-7.51 (m, 3H), 7.49-7.46 (m, 2H), 5.21-5.20 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 151.8, 140.7, 139.3, 136.3, 134.2, 130.4, 128.9, 128.6, 126.5, 126.3, 125.8, 125.3, 124.7, 124.5, 124.2, 63.7, 34.9, 31.5.

1,3-bis-(*t*-Butoxycarbonyl)-2-((6-(3-(*t*-butyl)phenyl)naphthalen-1-yl)methyl)guanidine (155).

154 (150 mg, 0.52 mmol), 1,3-bis(*t*-butoxycarbonyl)guanidine (268 mg, 1.03 mmol), and PPh_3 (203 mg, 0.78 mmol) in anhydrous toluene (4 mL) were cooled to 0 ^{o}C and DIAD (0.15 mL, 0.78 mmol) was added dropwise. Reaction was stirred at RT overnight then quenched with 5 drops of H_2O and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a white fluffy solid (243 mg, 88% yield); mp 66-68 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.46 (bs, 1H), 9.39 (bs, 1H), 8.01-7.98 (m, 2H), 7.73-7.70 (m, 2H), 7.67 (d, *J* = 0.7 Hz, 1H), 7.48-7.46 (m, 1H), 7.38-7.34 (m, 3H), 7.09 (dd, *J* = 7.1 Hz, *J* = 0.7 Hz, 1H), 5.66 (s, 2H), 1.37 (s, 9H), 1.34 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 161.0, 155.1, 151.8, 140.6, 138.8, 134.5, 133.9, 129.9, 128.6, 127.3, 126.5, 125.8, 125.7, 124.6, 124.5, 124.4, 123.4, 122.0, 84.1, 79.0, 45.2, 34.9, 31.5, 28.7, 27.6.

2-((6-(3-(*t*-Butyl)phenyl)naphthalen-1-yl)methyl)guanidine (156).

155 (240 mg) in anhydrous DCM (2 mL) was cooled to 0 ^{o}C and TFA (2 mL) was added. Reaction was stirred at RT for 1 hour then solvents were evaporated. Chromatography

using ISCO max gradient 10% MeOH/DCM afforded product as a tan fluffy solid (170 mg, quantitative); mp 74-76 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.15 (d, *J* = 1.8 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 8.00 (dd, *J* = 7.2 Hz, *J* = 2.0 Hz, 1H), 7.91 (dd, *J* = 8.8 Hz, *J* = 1.9 Hz, 1H), 7.79 (t, *J* = 1.6 Hz, 1H), 7.59-7.51 (m, 3H), 7.49-7.42 (m, 2H), 4.92 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.9, 153.1, 141.6, 140.8, 135.9, 132.6, 131.5, 130.5, 129.8, 127.5, 127.4, 126.9, 126.7, 125.8, 125.6, 125.3, 124.6, 44.4, 35.7, 31.9; HRMS (ESI) Calcd for $C_{22}H_{26}N_3$ $(M+H)^+$ 332.2121, found 332.2114.

Methyl 6-(3-(((trifluoromethyl)sulfonyl)oxy)phenyl)-1-naphthoate (157).

153b (415 mg, 1.5 mmol) in anhydrous DCM (20 mL) was cooled to -78 ^{o}C. Triflic anhydride (0.3 mL, 1.8 mmol) was then added followed by Et_3N (0.42 mL, 3 mmol) and reaction was stirred for 30 minutes at -78 ^{o}C. Mixture was then diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a clear oil (556 mg, 90% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.96 (d, *J* = 9.0 Hz, 1H), 8.15 (dd, *J* = 7.3 Hz, *J* = 1.1 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 1.9 Hz, 1H), 7.73 (dd, *J* = 9.0 Hz, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.54-7.53 (m, 1H), 7.50-7.45 (m, 2H), 7.22 (dd, *J* = 8.2 Hz, *J* = 2.4 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 167.7, 150.1, 143.3, 136.5, 134.1, 133.7, 131.0, 130.8, 130.7, 127.3, 127.1, 127.0, 126.8, 126.6, 125.4, 120.4, 120.2-120.1 (m), 117.2, 52.2.

Methyl 6-(3-cyclopropylphenyl)-1-naphthoate (158a).

157 (160 mg, 0.39 mmol), cyclopropylboronic acid (40 mg, 0.47 mmol), $Pd(OAc)_2$ (9 mg, 0.039 mmol), XPhos (37 mg, 0.078 mmol), and K_2CO_3 (162 mg, 1.17 mmol) in dioxane/H_2O (3 mL/1 mL) were degassed and refluxed at 102 ^oC overnight. Reaction was cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a clear oil (48 mg, 41% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.90 (d, *J* = 9.0 Hz, 1H), 8.12-8.10 (m, 1H), 8.00-7.97 (m, 2H), 7.79 (dd, *J* = 9.0 Hz, *J* = 1.9 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 1.6 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 3.94 (s, 3H), 1.96-1.89 (m, 1H), 0.97-0.92 (m, 2H), 0.73-0.72 (m, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.0, 144.7, 140.5, 139.0, 134.2, 133.6, 130.6, 130.1, 128.9, 127.5, 127.0, 126.4, 126.2, 125.1, 124.9, 124.8, 124.6, 52.1, 15.5, 9.2.

Methyl 6-(3-(thiophen-3-yl)phenyl)-1-naphthoate (158b).

157 (370 mg, 0.9 mmol), 3-thienylboronic acid (138 mg, 1.08 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), XPhos (86 mg, 0.18 mmol), and K_2CO_3 (373 mg, 2.7 mmol) in dioxane/H_2O (6 mL/3 mL) were degassed refluxed at 102 ^oC overnight. Reaction was then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$ solution. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a golden oil (253 mg, 82% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.92 (d, *J* = 9.0 Hz, 1H), 8.10 (dd, *J* = 7.3 Hz, *J* = 1.2 Hz,

1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.84-7.80 (m, 2H), 7.56-7.50 (m, 2H), 7.45-7.36 (m, 4H), 7.33-7.31 (m, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.0, 142.3, 141.1, 138.7, 136.6, 134.2, 133.7, 130.7, 130.3, 129.4, 127.4, 127.0, 126.6, 126.5, 126.4, 126.3, 126.2, 125.8, 125.6, 125.0, 120.7, 52.2.

Methyl 6-(3-(thiazol-2-yl)phenyl)-1-naphthoate (158c).

157 (164 mg, 0.4 mmol) and 2-(tributylstannyl)thiazole (299 mg, 0.8 mmol) in dioxane were degassed followed by quick addition of $Pd(PPh_3)_4$ (46 mg, 0.04 mmol). Reaction was then refluxed at 102 ^{o}C overnight then cooled to RT, diluted with EtOAc, and washed with saturated NH_4Cl solution. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a clear oil (25 mg, 18% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.05 (d, *J* = 9.0 Hz, 1H), 8.39 (t, *J* = 1.7 Hz, 1H), 8.24 (dd, *J* = 7.3 Hz, *J* = 1.3 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.01-7.94 (m, 3H), 7.81 (m, 1H), 7.62-7.55 (m, 2H), 7.40 (d, *J* = 3.2 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.3, 168.0, 143.9, 143.8, 141.4, 137.9, 134.3, 134.2, 133.7, 130.4, 129.6, 129.0, 127.2, 127.0, 126.6, 126.5, 125.9, 125.4, 125.1, 119.0, 52.2.

(6-(3-Cyclopropylphenyl)naphthalen-1-yl)methanol (159a).

To a cooled solution of **158a** (45 mg, 0.15 mmol) in anhydrous THF/EtOH (2 mL/0.2 mL) was added $LiBH_4$ (10 mg, 0.45 mmol). Solution was stirred at RT overnight.

Reaction was then quenched with ice over an ice bath, diluted with EtOAc, and washed with water. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a clear oil (38 mg, 93% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.22 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 1.8 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 8.8 Hz, *J* = 1.9 Hz, 1H), 7.56-7.47 (m, 4H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.13-7.11 (m, 1H), 5.21 (s, 2H), 2.07-2.00 (m, 1H), 1.07-1.03 (m, 2H), 0.84-0.80 (m, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 144.6, 140.9, 138.8, 136.3, 134.1, 130.4, 128.9, 128.8, 126.5, 126.1, 125.8, 125.3, 125.1, 124.7, 124.6, 124.2, 63.7, 15.5, 9.2.

(6-(3-(Thiophen-3-yl)phenyl)naphthalen-1-yl)methanol (159b).

To a cooled solution of **158b** (210 mg, 0.61 mmol) in anhydrous THF/EtOH (5 mL/0.5 mL) was added $LiBH_4$ (40 mg, 1.83 mmol). Solution was stirred for 3 hours at RT. Reaction was then quenched with ice over an ice bath, diluted with EtOAc, and washed with water. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a white solid (173 mg, 90% yield); mp 137 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.15 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.86 (t, *J* = 1.7 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.77 (dd, *J* = 8.8 Hz, *J* = 1.9 Hz, 1H), 7.58-7.53 (m, 2H), 7.47-7.39 (m, 5H), 7.36-7.34 (m, 1H), 5.11 (s, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 142.3, 141.5, 138.5, 136.6, 136.3, 134.1, 130.5, 129.4, 128.9, 126.6, 126.5, 126.4, 126.3, 126.0, 125.9, 125.6, 125.5, 124.4, 120.7, 63.7.

(6-(3-(Thiazol-2-yl)phenyl)naphthalen-1-yl)methanol (159c).

To a cooled solution of **158c** (25 mg, 0.073 mmol) in anhydrous THF/EtOH (3 mL/0.3 mL) was added $LiBH_4$ (5 mg, 0.22 mmol). Solution was stirred at RT overnight. Reaction was then quenched with ice over an ice bath, diluted with EtOAc, and washed with water. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a clear oil (10 mg, 43% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.38 (t, *J* = 1.8 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 8.18 (d, *J* = 1.8 Hz, 1H), 8.00-7.97 (m, 1H), 7.95-7.88 (m, 3H), 7.82-7.80 (m, 1H), 7.61-7.50 (m, 3H), 7.40 (d, *J* = 3.2 Hz, 1H), 5.23-5.22 (m, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 143.8, 141.8, 136.3, 134.1, 129.6, 129.0, 126.7, 126.0, 125.9, 125.8, 125.6, 125.4, 124.5, 119.0, 63.7.

1,3-bis-(*t*-Butoxycarbonyl)-2-((6-(3-cyclopropylphenyl)naphthalen-1-yl)methyl)guanidine (160a).

159a (35 mg, 0.13 mmol), 1,3-bis(*t*-butoxycarbonyl)guanidine (66 mg, 0.26 mmol), and PPh_3 (50 mg, 0.19 mmol) in anhydrous toluene (3 mL) were cooled to 0 ^{o}C and DIAD (0.04 mL, 0.19 mmol) was added dropwise. Reaction was stirred at RT overnight then quenched with 5 drops of H_2O and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a clear oil (48 mg, 73% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.53 (bs, 2H), 8.10-8.07 (m, 2H), 7.82-7.78 (m, 2H), 7.55-7.38 (m,

4H), 7.20 (d, *J* = 7.0 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 5.75 (s, 2H), 2.07-2.00 (m, 1H), 1.47 (s, 9H), 1.19 (s, 9H), 1.07-1.02 (m, 2H), 0.84-0.81 (m, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 161.0, 155.1, 144.6, 140.8, 138.4, 134.5, 133.9, 129.9, 128.8, 127.3, 126.4, 125.7, 125.6, 125.0, 124.7, 124.5, 123.4, 122.0, 80.1, 79.0, 45.1, 28.3, 27.6, 15.5, 9.2.

1,3-bis-(*t*-Butoxycarbonyl)-2-((6-(3-(thiophen-3-yl)phenyl)naphthalen-1-yl)methyl)guanidine (160b).

159b (155 mg, 0.49 mmol), 1,3-bis(*t*-butoxycarbonyl)guanidine (254 mg, 0.98 mmol), and PPh_3 (193 mg, 0.74 mmol) in anhydrous toluene (10 mL) were cooled to 0 ^{o}C and DIAD (0.15 mL, 0.74 mmol) was added dropwise. Reaction was stirred at RT overnight then quenched with 5 drops of H_2O and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a white fluffy solid (182 mg, 67% yield); mp 80-82 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.59 (bs, 2H), 8.13-8.10 (m, 2H), 7.97 (t, *J* = 1.7 Hz, 1H), 7.86-7.82 (m, 2H), 7.69 (dt, *J* = 7.6 Hz, *J* = 1.4 Hz, 1H), 7.64 (dt, *J* = 7.7 Hz, *J* = 1.9 Hz, 1H), 7.58-7.45 (m, 5H), 7.22-7.21 (m, 1H), 5.76 (s, 2H), 1.48 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 161.0, 155.1, 142.3, 141.4, 138.0, 136.6., 134.5, 133.8, 130.0, 129.3, 127.4, 126.6, 126.5, 126.3, 126.2, 125.8, 125.6, 125.5, 123.5, 122.2, 120.6, 84.1, 79.0, 45.1, 28.3, 27.6.

1,3-bis-(*t*-Butoxycarbonyl)-2-((6-(3-(thiazol-2-yl)phenyl)naphthalen-1-yl)methyl)guanidine (160c).

159c (22 mg, 0.07 mmol), 1,3-bis(*t*-butoxycarbonyl)guanidine (36 mg, 0.14 mmol), and PPh_3 (27 mg, 0.1 mmol) in anhydrous toluene (3 mL) were cooled to 0 ^oC and DIAD (0.02 mL, 0.1 mmol) was added dropwise. Reaction was stirred at RT overnight then quenched with 5 drops of H_2O and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a white solid (33 mg, 87% yield); mp 134-137 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.61 (bs, 1H), 9.48 (bs, 1H), 8.38 (t, *J* = 1.6 Hz, 1H), 8.17 (d, *J* = 1.7 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.99-7.97 (m, 1H), 7.94 (d, *J* = 3.3 Hz, 1H), 7.88-7.81 (m, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 3.2 Hz, 1H), 7.27-7.17 (m, 2H), 5.76 (s, 2H), 1.47 (s, 9H), 1.17 (s, 1H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 168.3, 163.8, 161.0, 158.3, 155.1, 143.8, 141.7, 137.3, 134.6, 134.2, 130.1, 129.0, 128.9, 128.2, 127.4, 126.4, 125.9, 125.7, 125.4, 125.3, 122.3, 119.0, 84.1, 79.0, 45.1, 34.7, 31.6.

2-((6-(3-Cyclopropylphenyl)naphthalen-1-yl)methyl)guanidine (161a).

160a (48 mg) in anhydrous DCM (1 mL) was cooled to 0 ^oC and TFA (1 mL) was added. Reaction was stirred at RT for 1 hour then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a tan sticky residue (25 mg, 86% yield); mp 66-68 ^oC; ^1H NMR (400 MHz) (CD_3OD) δ 8.17 (d, *J* = 1.8 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.99 (dd, *J* = 7.3 Hz, *J* = 2.1 Hz, 1H), 7.92-7.89 (m, 1H), 7.56-7.51 (m, 3H), 7.50-7.49 (m, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.11-7.10 (m, 1H), 4.91 (s,

2H), 2.07-2.00 (m, 1H), 1.06-1.01 (m, 2H), 0.81-0.77 (m, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.9, 146.2, 141.8, 140.3, 135.8, 132.6, 131.6, 130.5, 130.0, 127.5, 127.4, 126.9, 126.7, 125.8, 125.7, 125.4, 124.6, 44.4, 16.3, 9.6; HRMS (ESI) Calcd for $C_{21}H_{21}N_3$ $(M+H)^+$ 316.1808, found 316.1813.

2-((6-(3-(Thiophen-3-yl)phenyl)naphthalen-1-yl)methyl)guanidine (161b).

160b (180 mg) in anhydrous DCM (1.5 mL) was cooled to 0 ^oC and TFA (1.5 mL) was added. Reaction was stirred at RT for 1 hour then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a white solid (64 mg, 56% yield); mp 138-140 ^oC; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.26 (d, *J* = 1.7 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 8.05 (t, *J* = 1.6 Hz, 1H), 8.02-7.96 (m, 2H), 7.75-7.74 (m, 1H), 7.70 (dd, *J* = 7.6 Hz, *J* = 1.7 Hz, 2H), 7.58-7.52 (m, 5H), 4.92 (s, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.8, 143.4, 142.4, 140.0. 138.0, 135.8, 132.6, 131.7, 130.6, 130.5, 127.7, 127.5, 127.3, 127.2, 127.0, 126.8, 126.7, 126.2, 124.7, 121.8, 119.7, 44.4; HRMS (ESI) Calcd for $C_{22}H_{20}N_3S$ $(M+H)^+$ 358.1399, found 358.1386.

2-((6-(3-(Thiazol-2-yl)phenyl)naphthalen-1-yl)methyl)guanidine (161c).

160c (33 mg) in anhydrous DCM (1.5 mL) was cooled to 0 ^oC and TFA (1.5 mL) was added. Reaction was stirred at RT for 1 hour then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a tan sticky residue (19 mg, 90% yield); mp 85-88 ^oC; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.40

(s, 1H), 8.30 (d, *J* = 1.8 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 8.05-7.95 (m, 4H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 3.1 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.59-7.55 (m, 2H), 4.93 (s, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.8, 144.5, 142.9, 139.1, 135.8, 135.3, 132.7, 131.8, 131.0, 130.6, 130.2, 127.9, 127.2, 127.1, 127.0, 126.9, 126.1, 124.9, 121.3, 44.3; HRMS (ESI) Calcd for $C_{21}H_{18}N_4S$ $(M+H)^+$ 359.1325, found 359.1326.

7,8-Dihydroquinoline-2,5(1*H*,6*H*)-dione (162).

Methyl propiolate (1.95 mL, 23.4 mmol) was added to a flask containing 3-amino-2-cyclohexen-1-one (2 g, 18 mmol) and solids were heated to 105 ^{o}C. Upon warming, the solids melted to a homogenous solution. Heating continued for 1 hour then condenser was removed, and mixture was heated to 175 ^{o}C for 20 minutes to remove excess methyl propiolate and promote cyclization to desired product. Reaction was then removed from heat and treated with 2 portions of warmed DCM and solids were crashed out with acetone to afford product as a pale yellow solid (1.01 g, 34% yield); mp 191-193 ^{o}C; ^{1}H NMR (400 MHz) (DMSO-d_6) δ 7.76 (d, *J* = 9.5 Hz, 1H), 6.24 (d, *J* = 9.5 Hz, 1H), 2.79 (t, *J* = 6.2 Hz, 2H), 2.43 (t, *J* = 6.3 Hz, 2H), 2.03-1.97 (m, 2H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 193.4, 162.7, 157.6, 136.9, 117.8, 112.5, 36.5, 26.4, 20.8

6-(Phenylselanyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (163).

162 (720 mg, 4.42 mmol) was combined in a flask with phenylselenyl chloride (1.27 g, 6.63 mmol) in EtOAc (30 mL) and stirred for 48 hours at RT. Reaction was then diluted

with additional EtOAc, washed with saturated NaHCO3, followed by H2O and brine. Organic layer was collected, dried over Na2SO4, and concentrated. Chromatography using ISCO max gradient 2% MeOH/DCM afforded product as a pale yellow solid (710 mg, 51% yield); mp 185-187 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 12.99 (bs, 1H), 8.05 (d, *J* = 9.5 Hz, 1H), 7.64-7.62 (m, 2H), 7.37-7.30 (m, 3H), 6.49 (d, *J* = 9.5 Hz, 1H), 3.33-3.25 (m, 1H), 2.91-2.84 (m, 1H), 2.56-2.48 (m, 1H), 2.34-2.28 (m, 1H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 165.7, 154.6, 139.5, 135.7, 129.3, 128.7, 118.4, 113.5, 46.3, 27.2, 24.6.

Quinolin-5-yl trifluoromethanesulfonate (164).

5-Quinolinol (1 g, 6.9 mmol) in anhydrous DCM (20 mL) was cooled to -78 ^{o}C. Triflic anhydride (1.4 mL, 8.28 mmol) was then added followed by Et_3N (1.9 mL, 13.8 mmol) and reaction was stirred for 30 minutes at -78 ^{o}C. Mixture was then diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a golden oil (757 mg, 40% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.00 (dd, *J* = 4.2 Hz, *J* = 1.6 Hz, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 7.72 (t, *J* = 8.2 Hz, 1H), 7.55-7.52 (m, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 151.7, 148.9, 144.5, 130.2, 128.3, 128.4, 122.5, 122.0, 120.3, 118.4-117.1 (m).

5-(((Trifluoromethyl)sulfonyl)oxy)quinoline 1-oxide (165).

m-CPBA (384 mg, 2.22 mmol) was added to a flask containing **164** (560 mg, 2.02 mmol) in anhydrous DCM (10 mL) at 0 ^{o}C. Reaction was stirred overnight at RT then quenched with saturated $NaHCO_3$. Additional DCM was added and organic layer was extracted, dried over Na_2SO_4, and concentrated to afford product as an orange oil (587 mg, 99% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.82 (d, *J* = 8.9 Hz, 1H), 8.61 (d, *J* = 6.1 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.81 (t, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.49-7.45 (m, 1H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 144.9, 142.8, 136.4, 129.3, 124.9, 122.7, 120.9, 120.5, 120.3, 118.3-117.1 (m).

2-Oxo-1,2-dihydroquinolin-5-yl trifluoromethanesulfonate (166).

Trifluoroacetic anhydride (3 mL) was added to a solution of **165** (587 mg) in anhydrous DMF (3 mL) at 0 ^{o}C. Reaction was stirred overnight at RT then quenched with saturated $NaHCO_3$ solution and extracted with EtOAc, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as an orange solid (386 mg, 66% yield); mp 192-194 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 12.69 (bs, 1H), 8.06 (d, *J* = 9.8 Hz, 1H), 7.59 (t, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 9.8 Hz, 1H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.9, 145.5, 140.1, 133.6, 131.0, 123.5, 120.3, 117.1-116.3 (m), 115.0, 113.4.

5-Methylquinolin-2(1*H*)-one (167).

166 (380 mg, 1.3 mmol), $PdCl_2$(dppf) (106 mg, 0.13 mmol), and Cs_2CO_3 (1.48 g, 4.55 mmol) in dioxane/H_2O (6 mL/3 mL) were degassed and trimethylboroxine (0.36 mL, 2.6 mmol) was added. Mixture was refluxed at 102 ^oC overnight. Reaction was cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 80% EtOAc/hexane afforded product as a yellow solid (130 mg, 63% yield); mp 176-178 ^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 11.72 (bs, 1H), 8.02 (d, *J* = 9.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 9.7 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 161.6, 139.2, 136.9, 135.3, 130.1, 122.9, 121.3, 117.7, 113.4, 18.2.

5-Methylquinolin-2-yl trifluoromethanesulfonate (168).

167 (130 mg, 0.82 mmol) and Et_3N (0.23 mL, 1.64 mmol) in anhydrous DCM (10 mL) were cooled to -78 ^oC and Tf_2O (0.17 mL, 0.98 mmol) was added. Reaction was stirred for 30 minutes at -78 ^oC then diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a clear oil (122 mg, 51% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.52 (d, *J* = 9.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.72-7.68 (m, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.28 (d, *J* = 8.9 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 153.5, 146.4, 138.5, 135.0, 131.1, 128.3, 127.8, 127.2 (m), 120.3, 117.1, 112.6, 18.8.

2-(3-(*t*-Butyl)phenyl)-5-methylquinoline (169a).

168 (120 mg, 0.41 mmol), 3-*t*-butylphenylboronic acid (89 mg, 0.49 mmol), $Pd(OAc)_2$ (10 mg, 0.041 mmol), XPhos (39 mg, 0.082 mmol), and K_2CO_3 (170 mg, 1.23 mmol) in dioxane/H_2O (4 mL/2 mL) were degassed then refluxed at 102 ^oC for 30 minutes. Reaction was cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a clear oil (96 mg, 85% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.26 (dd, *J* = 8.8 Hz, *J* = 0.6 Hz, 1H), 8.12 (t, *J* = 1.8 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.84 (dt, *J* = 7.4 Hz, *J* = 1.6 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.52-7.49 (m, 1H), 7.43-7.35 (m, 2H), 7.25-7.23 (m, 1H), 2.60 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 157.5, 151.7, 148.6, 139.5, 134.3, 133.1, 129.3, 128.6, 128.2, 126.7, 126.5, 126.4, 124.9, 124.6, 118.8, 35.0, 31.5, 18.6.

2-([1,1'-Biphenyl]-3-yl)-5-methylquinoline (169b).

168 (166 mg, 0.57 mmol), 3-biphenylboronic acid (134 mg, 0.68 mmol), and Na_2CO_3 (180 mg, 1.7 mmol) in dioxane/H_2O (3 mL/1 mL) were degassed followed by the addition of $Pd(PPh_3)_4$ (65 mg, 0.057 mmol). Mixture was refluxed at 102 ^oC for 2 hours then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a clear oil (151 mg, 90% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.31 (t, *J* = 1.7 Hz, 1H), 8.24 (dd, *J* = 8.8 Hz, *J* = 0.7 Hz,

1H), 8.01 (dt, *J* = 7.7 Hz, *J* = 1.5 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.61-7.59 (m, 1H), 7.58-7.56 (m, 1H), 7.51-7.45 (m, 2H), 7.38-7.35 (m, 2H), 7.26 (tt, *J* = 7.4 Hz, *J* = 1.3 Hz, 1H), 7.23-7.21 (m, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.7, 148.7, 141.9, 141.2, 140.3, 134.4, 133.3, 129.4, 129.3, 128.8, 128.2, 128.1, 127.5, 127.4, 126.9, 126.6, 126.5, 118.6, 18.6.

3-(5-Methylquinolin-2-yl)phenol (169c).

168 (658 mg, 2.26 mmol), 3-hydroxyphenylboronic acid (374 mg, 2.71 mmol), and Na_2CO_3 (719 mg, 6.78 mmol) in dioxane/H_2O (6 mL/3 mL) were degassed followed by the addition of $Pd(PPh_3)_4$ (261 mg, 0.23 mmol). Mixture was refluxed at 102 ^{o}C for 2 hours then cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane afforded product as a off-white fluffy solid (375 mg, 71% yield); mp 78-80 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.42 (dd, *J* = 8.8 Hz, *J* = 0.6 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.62-7.55 (m, 2H), 7.52-7.49 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 2H), 6.95-6.93 (m, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 159.1, 158.6, 149.4, 142.1, 136.1, 135.1, 131.0, 130.8, 128.0, 127.9, 127.8, 120.2, 120.1, 117.6, 115.6, 18.6.

5-(Bromomethyl)-2-(3-(*t*-butyl)phenyl)quinoline (170a).

169a (90 mg, 0.33 mmol), AIBN (5 mg, 0.033 mmol), and NBS (61 mg, 0.34 mmol) in CCl_4 (3 mL) were combined and heated to 85 ^oC for 2 hours. Reaction was cooled to RT and hexane was added. Precipitate was filtered off and filtrate was concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a clear oil (48 mg, 41% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.46 (d, *J* = 8.9 Hz, 1H), 8.12-8.09 (m, 2H), 7.91-7.85 (m, 2H), 7.58-7.37 (m, 4H), 4.86 (s, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 158.2, 151.8, 148.9, 139.1, 133.5, 132.7, 131.5, 129.0, 128.6, 127.6, 126.7, 125.2, 124.9, 124.6, 119.5, 35.0, 31.4, 30.3.

2-([1,1'-Biphenyl]-3-yl)-5-(bromomethyl)quinoline (170b).

169b (145 mg, 0.49 mmol), AIBN (8 mg, 0.049 mmol), and NBS (92 mg, 0.51 mmol) in CCl_4 (4 mL) were heated to 85 ^oC for 2 hours. Reaction was cooled to RT and hexane was added. Precipitate was filtered off and filtrate was concentrated. Chromatography using ISCO max gradient 10% EtOAc/hexane afforded product as a sticky yellow oil (125 mg, 68% yield); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.57 (d, *J* = 8.8 Hz, 1H), 8.46 (t, *J* = 1.7 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.77-7.74 (m, 3H), 7.70-7.62 (m, 2H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.55-7.52 (m, 2H), 7.46-7.42 (m, 1H), 4.96 (s, 2H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 157.4, 148.9, 142.0, 141.1, 139.8, 133.5, 132.9, 131.5, 129.4, 129.2, 128.9, 128.4, 127.8, 127.5, 127.4, 126.5, 125.3, 119.3, 30.4.

1,3-bis-(*t*-Butoxycarbonyl)-2-((2-(3-(*t*-butyl)phenyl)quinolin-5-yl)methyl)guanidine (171a).

170a (45 mg, 0.13 mmol), 1,3-bis-(*t*-butoxycarbonyl)guanidine (66 mg, 0.25 mmol), and K_2CO_3 (35 mg, 0.25 mmol) in DMF (2 mL) were stirred overnight at RT. Solution was then diluted with EtOAc, washed with saturated $NaHCO_3$, and then 10% LiCl solution. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% EtOAc/hexane afforded product as a white solid (54 mg, 80% yield); mp 160-161 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.59 (bs, 1H), 9.44 (bs, 1H), 8.46 (d, *J* = 8.9 Hz, 1H), 8.26 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.55-7.47 (m, 2H), 7.29 (s, 1H), 5.73 (s, 2H), 1.49 (s, 9H), 1.46 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 160.9, 157.4, 154.9, 151.7, 148.4, 139.2, 134.9, 132.0, 129.0, 128.9, 128.6, 126.6, 124.8, 124.7, 124.5, 122.7, 118.8, 84.3, 79.1, 44.5, 34.9, 31.4, 28.3, 27.5.

1,3-bis-(*t*-Butoxycarbonyl)-2-((2-([1,1'-biphenyl]-3-yl)quinolin-5-yl)methyl)guanidine (171b).

170b (75 mg, 0.2 mmol), 1,3-bis-(*t*-butoxycarbonyl)guanidine (104 mg, 0.4 mmol), and K_2CO_3 (55 mg, 0.4 mmol) in DMF (3 mL) were stirred overnight at RT. Solution was then diluted with EtOAc, washed with saturated $NaHCO_3$, and then 10% LiCl solution. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% EtOAc/hexane afforded product as a sticky off-white solid

(100 mg, 90% yield); mp 81-82 ^{o}C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.61 (bs, 1H), 9.43 (bs, 1H), 8.50-8.45 (m, 2H), 8.18 (dt, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 1H), 7.76-7.68 (m, 4H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.53-7.50 (m, 2H), 7.42 (tt, *J* = 7.7 Hz, *J* = 1.4 Hz, 1H), 7.30-7.28 (m, 1H), 5.74 (s, 2H), 1.50 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 160.8, 156.8, 154.9, 148.4, 141.9, 141.1, 139.9, 135.0, 132.2, 129.3, 129.2, 128.9, 128.8, 128.2, 127.5, 127.3, 126.4, 124.8, 122.8, 118.7, 84.3, 79.1, 44.5, 28.3, 27.7.

2-((2-(3-(*t*-Butyl)phenyl)quinolin-5-yl)methyl)guanidine (172a).

171a (50 mg) in anhydrous DCM (1 mL) was cooled to 0 ^{o}C and TFA (1 mL) was added. Reaction was stirred at RT for 1 hour then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a tan solid (30 mg, quantitative); mp 129-131 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.70 (d, *J* = 9.0 Hz, 1H), 8.22-8.15 (m, 3H), 7.95-7.93 (m, 1H), 7.89-7.85 (m, 1H), 7.67-7.65 (m, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 4.98 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.4, 153.4, 139.0, 135.5, 134.0, 131.5, 129.9, 129.3, 128.5, 127.0, 126.6, 126.3, 126.0, 121.4, 43.5, 35.9, 31.8; HRMS (ESI) Calcd for $C_{21}H_{24}N_4$ $(M+H)^+$ 333.2074, found 333.2070.

2-((2-([1,1'-Biphenyl]-3-yl)quinolin-5-yl)methyl)guanidine (172b).

171b (100 mg) in anhydrous DCM (1.5 mL) was cooled to 0 ^{o}C and TFA (1.5 mL) was added. Reaction was stirred at RT for 1 hour then solvents were evaporated.

Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a sticky wet solid (33 mg, 52% yield); mp 66-67 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.58 (d, *J* = 8.9 Hz, 1H), 8.43 (t, *J* = 1.7 Hz, 1H), 8.19-8.16 (m, 2H), 8.14 (dt, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H), 7.83-7.76 (m, 4H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.61 (dd, *J* = 7.0 Hz, *J* = 0.5 Hz, 1H), 7.53-7.49 (m, 2H), 7.41 (tt, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H), 4.95 (s, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.0, 149.8, 143.3, 142.1, 140.9, 134.3, 133.7, 130.8, 130.7, 130.6, 130.0, 129.5, 128.7, 128.2, 127.7, 127.4, 126.8, 126.6, 120.9, 105.2, 43.6; HRMS (ESI) Calcd for $C_{23}H_{20}N_4$ $(M+H)^+$ 353.1761, found 353.1763.

3-(5-Methylquinolin-2-yl)phenyl trifluoromethanesulfonate (173).

169c (373 mg, 1.59 mmol) and Et_3N (0.44 mL, 3.18 mmol) in anhydrous DCM (15 mL) were cooled to -78 ^{o}C and Tf_2O (0.32 mL, 1.91 mmol) was added. Reaction was stirred for 30 minutes at -78 ^{o}C then diluted with additional DCM and washed with saturated $NaHCO_3$. Organic layer collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a clear oil (537 mg, 92% yield); ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.30 (dd, *J* = 8.8 Hz, *J* = 0.5 Hz, 1H), 8.09-8.07 (m, 2H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.56-7.53 (m, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.30-7.25 (m, 2H), 2.61 (s, 3H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 154.2, 150.2, 148.5, 142.4, 134.5, 133.7, 130.5, 129.9, 129.8, 128.2, 127.4, 127.2, 126.9, 121.7, 120.4, 118.0-117.2 (m), 18.6.

2-(4'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)-5-methylquinoline (174).

173 (195 mg, 0.53 mmol), 4-*t*-butylphenylboronic acid (113 mg, 0.64 mmol), $Pd(OAc)_2$ (12 mg, 0.053 mmol), XPhos (51 mg, 0.011 mmol), and K_2CO_3 (147 mg, 1.06 mmol) in dioxane/H_2O (6 mL/3 mL) were degassed then refluxed at 102 ^oC for 30 minutes. Reaction was cooled to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane afforded product as a clear oil (186 mg, quantitative); ^1H NMR (400 MHz) ($CDCl_3$) δ 8.30 (t, *J* = 1.7 Hz, 1H), 8.24 (dd, *J* = 8.8 Hz, *J* = 0.4 Hz, 1H), 8.01 (dt, *J* = 7.7 Hz, *J* = 1.4 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.59-7.54 (m, 3H), 7.52-7.46 (m, 2H), 7.41-7.39 (m, 2H), 7.23-7.21 (m, 1H), 2.57 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 156.9, 150.5, 148.7, 141.7, 140.2, 138.3, 134.4, 133.3, 129.4, 129.3, 128.2, 128.0, 127.0, 126.9, 126.6, 126.4, 126.3, 125.8, 118.6, 34.6, 31.5, 18.7.

5-(Bromomethyl)-2-(4'-(*t*-butyl)-[1,1'-biphenyl]-3-yl)quinoline (175).

174 (185 mg, 0.53 mmol), AIBN (9 mg, 0.053 mmol), and NBS (99 mg, 0.55 mmol) in CCl_4 (5 mL) were heated to 85 ^oC for 2 hours. Reaction was cooled to RT and hexane was added. Precipitate was filtered off and filtrate was concentrated. Chromatography using ISCO max gradient 10% EtOAc/hexane afforded product as a white solid (113 mg, 50% yield); mp 119 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.58 (d, *J* = 8.8 Hz, 1H), 8.45 (t, *J* = 1.7 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.17-8.15 (m, 1H), 8.05 (d, *J* = 8.9 Hz, 1H), 7.76-7.56 (m, 8H), 4.96 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 157.5,

150.6, 148.9, 141.8, 139.8, 138.2, 133.5, 132.9, 131.5, 129.3, 129.2, 128.3, 127.7, 127.0, 126.4, 126.3, 125.8, 125.3, 119.3, 34.6, 31.5, 30.4.

1,3-bis-(*t*-Butoxycarbonyl)-2-((2-(4'-(*t*-butyl)-[1,1'-biphenyl]-3-yl)quinolin-5-yl)methyl)guanidine (176).

174 (110 mg, 0.26 mmol), 1,3-bis-(*t*-butoxycarbonyl)guanidine (133 mg, 0.51 mmol), and K_2CO_3 (71 mg, 0.51 mmol) in DMF (5 mL) were stirred overnight at RT. Solution was then diluted with EtOAc, washed with saturated $NaHCO_3$, and then 10% LiCl solution. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane afforded product as a fluffy white solid (146 mg, 94% yield); mp 114-117 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.62 (bs, 1H), 9.45 (bs, 1H), 8.50-8.45 (m, 2H), 8.18-8.10 (m, 2H), 7.98 (d, *J* = 8.9 Hz, 1H), 7.74-7.60 (m, 5H), 7.56-7.54 (m, 2H), 7.29 (d, *J* = 5.7 Hz, 1H), 5.74 (s, 2H), 1.50 (s, 9H), 1.42 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 163.8, 160.9, 156.8, 154.9, 150.5, 148.4, 141.7, 139.9, 138.2, 135.0, 132.2, 129.3, 129.1, 128.9, 128.1, 127.0, 126.3, 126.2, 125.8, 124.8, 122.7, 118.7, 84.3, 79.1, 44.5, 34.6, 31.4, 28.3, 27.7.

2-((2-(4'-(*t*-Butyl)-[1,1'-biphenyl]-3-yl)quinolin-5-yl)methyl)guanidine (177).

176 (140 mg) in anhydrous DCM (1.5 mL) was cooled to 0 ^oC and TFA (1.5 mL) was added. Reaction was stirred at RT for 1 hour then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a tan

fluffy solid (55 mg, 56% yield); mp 94-97 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 8.46 (dd, *J* = 8.8 Hz, *J* = 0.5 Hz, 1H), 8.29 (t, *J* = 1.7 Hz, 1H), 8.04 (d, *J* = 8.9 Hz, 2H), 8.00-7.97 (m, 1H), 7.70-7.65 (m, 2H), 7.60-7.56 (m, 2H), 7.53-7.48 (m, 2H), 7.44-7.43 (m, 2H), 4.83 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 159.1, 158.9, 151.9, 149.8, 143.1, 140.8, 139.1, 134.2, 133.7, 130.8, 130.7, 130.5, 129.3, 127.8, 127.4, 127.2, 126.9, 126.8, 126.6, 121.0, 43.6, 35.4, 31.8; HRMS (ESI) Calcd for $C_{27}H_{29}N_4$ $(M+H)^+$ 409.2387, found 409.2403.

5-(3-Methoxyphenyl)-1,2,4-oxadiazol-3-amine (179).

Oxalyl chloride (0.57 mL, 6.58 mmol) was added to a solution of 3-methoxybenzoic acid (500 mg, 3.29 mmol) in anhydrous DCM (20 mL). A catalytic amount of DMF (10 drops) was then added and solution stirred for 1 hour at RT. Solvents were then evaporated and crude residue placed on vacuum pump. Sodium hydrogen cyanamide was prepared by treatment of cyanamide (276 mg, 6.58 mmol) with 2N NaOH (3.3 mL). This solution was then added to a flask containing the acid chloride in THF (15 mL) and reaction was stirred for 16 hours at RT. Mixture was then diluted with EtOAc and washed with 10% HCl. Organic layer was collected, dried over Na_2SO_4, and concentrated. Crude material was then taken back up in pyridine (7 mL) and hydroxylamine hydrochloride (525 mg, 7.5 mmol) was added. Reaction was heated at 60 ^{o}C for 16 hours. Reaction was allowed to cool to RT, diluted with EtOAc, and washed with saturated $NaHCO_3$ (3x) to remove excess pyridine. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a white solid (165 mg, 26% yield);

mp 117 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 7.64-7.62 (m, 1H), 7.58-7.57 (m, 1H), 7.45 (t, *J* = 8.2 Hz, 1H), 7.21-7.18 (m, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz) (CD_3OD) δ 175.5, 170.6, 161.6, 131.4, 126.8, 121.0, 119.8, 113.7, 56.0; HRMS (ESI) Calcd for $C_9H_9N_3O_2$ $(M+H)^+$ 214.0587, found 214.0592.

5-(3-Methoxyphenyl)-1,3,4-thiadiazol-2-amine (180).

To an ice-cooled mixture of 3-methoxybenzoic acid (500 mg, 3.29 mmol) and thiosemicarbazide (360 mg, 3.95 mmol) was slowly added $POCl_3$ (2 mL) with vigorous stirring. Reaction was then removed from the ice bath and heated to 70 ^{o}C for 2 hours. Reaction was allowed to cool to room temperature and was placed back over an ice bath. Ice water was slowly added to quench reaction until the evolution of gas ceased. Solution was then basified with 2N NaOH to a pH of 6. Solid material was filtered out and air dried. Chromatography using ISCO max gradient 10% MeOH/DCM/0.1% NH_4OH afforded product as an off-white solid (551 mg, 79% yield); mp 144-146 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 7.36-7.35 (m, 2H), 7.31-7.28 (m, 1H), 7.03-7.00 (m, 1H), 4.89 (s, 3H); ^{13}C NMR (100 MHz) (CD_3OD) δ 171.2, 161.6, 159.8, 133.2, 131.3, 120.4, 117.1, 112.5, 55.9; HRMS (ESI) Calcd for $C_9H_9N_3OS$ $(M+H)^+$ 208.0539, found 208.0548.

5-(2,6-Difluoro-3-methoxyphenyl)-1,3,4-thiadiazol-2-amine (184).

To an ice-cooled mixture of 2,6-difluoro-3-methoxybenzoic acid (250 mg, 1.33 mmol) and thiosemicarbazide (145 mg, 1.6 mmol) was slowly added $POCl_3$ (1.5 mL) with

vigorous stirring. Reaction was then removed from the ice bath and heated to 70 ^{o}C for 2 hours. Reaction was allowed to cool to room temperature and was placed back over an ice bath. Ice water was slowly added to quench reaction until the evolution of gas ceased. Solution was then basified with 2N NaOH to a pH of 6. Solid material was filtered out and air dried. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a white solid (80 mg, 25% yield); mp 154-155 ^{o}C; ^{1}H NMR (400 MHz) (DMSO-d_6) δ 7.54 (bs, 2H), 7.36-7.30 (m, 1H), 7.21 (td, *J* = 9.6 Hz, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 170.3, 153.6, 151.2, 149.7, 147.2, 144.4-144.3 (m), 142.8, 115.1-115.0 (m), 111.3-111.0 (m), 56.7; HRMS (ESI) Calcd for $C_9H_7F_2N_3OS$ $(M+H)^+$ 244.0351, found 244.0350.

2-(2,6-Difluoro-3-methoxyphenyl)-4,5-dihydro-1*H*-imidazole (185).

2,6-Difluoro-3-methoxybenzaldehyde (500 mg, 2.91 mmol) and ethylenediamine (0.2 mL, 3.06 mmol) in DCM (5 mL) were stirred for 20 minutes at 0 ^{o}C. NBS (544 mg, 3.06 mmol) was then added and reaction was stirred and allowed to warm to RT overnight. Solvents were then evaporated and residue was taken back up in EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as an off-white solid (450 mg, 73% yield); mp 128-130 ^{o}C; ^{1}H NMR (400 MHz) (CD_3OD) δ 7.24-7.18 (m, 1H), 6.99 (td, *J* = 9.2 Hz, *J* = 2.1 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 4H); ^{13}C NMR (100 MHz) (CD_3OD) δ 156.2, 153.8, 152.5, 150.0, 146.1-145.9 (m), 116.6-116.5 (m),

111.9-111.6 (m); HRMS (ESI) Calcd for $C_{10}H_{10}F_2N_2O$ $(M+H)^+$ 213.0834, found 213.0838.

3-(3-Amino-1,2,4-oxadiazol-5-yl)phenol (186).

To an ice-cooled solution of **179** (150 mg, 0.79 mmol) in anhydrous DCM (10 mL) was slowly added BBr_3 (1.6 mL, 1.58 mmol). Reaction was taken off ice-bath and allowed to stir overnight at RT. Solvents were then evaporated and residue was taken back up in EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a white solid (27 mg, 19% yield); mp 210-211 ^oC; ^1H NMR (400 MHz) (CD_3OD) δ 7.40 (dt, *J* = 7.7 Hz, *J* = 1.2 Hz, 1H), 7.34-7.33 (m, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 6.92 (ddd, *J* = 8.2 Hz, *J* = 2.5 Hz, *J* = 0.9 Hz, 1H); ^{13}C NMR (100 MHz) (CD_3OD) δ 175.7, 170.6, 159.3, 131.4, 126.7, 120.9, 119.9, 115.2.

3-(5-Amino-1,3,4-thiadiazol-2-yl)-2,4-difluorophenol (189).

To an ice-cooled solution of **184** (58 mg, 0.24 mmol) in anhydrous DCM (5 mL) was slowly added BBr_3 (0.5 mL, 0.48 mmol). Reaction was taken off ice-bath and allowed to stir overnight at RT. Solvents were then evaporated and residue was taken back up in EtOAc and washed with saturated $NaHCO_3$. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a white solid (15 mg, 27% yield); mp 185-187 ^oC; ^1H

NMR (400 MHz) (CD_3OD) δ 6.97-6.91 (m, 1H), 6.84 (td, *J* = 9.5 Hz, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz) (CD_3OD) δ 172.7, 155.0, 152.6, 151.0, 148.5, 143.5-143.4 (m), 120.2-120.1 (m), 112.4-112.1 (m); HRMS (ESI) Calcd for $C_8H_5F_2N_3OS$ $(M+H)^+$ 230.0194, found 230.0197.

3-(4,5-Dihydro-1*H*-imidazol-2-yl)-2,4-difluorophenol (190).

To an ice-cooled solution of **185** (265 mg, 1.25 mmol) in anhydrous DCM (10 mL) was slowly added BBr_3 (2.5 mL, 2.5 mmol). Reaction was taken off ice-bath and allowed to stir overnight at RT. Solvents were then evaporated and crude residue was taken forward directly to the next step.

5-(3-((5-Chlorobenzo[*d*]thiazol-2-yl)methoxy)phenyl)-1,2,4-oxadiazol-3-amine (191).

186 (20 mg, 0.11 mmol), 2-(bromomethyl)-5-chlorobenzo[*d*]thiazole (31 mg, 0.12 mmol), and potassium carbonate (23 mg, 0.17 mmol) in anhydrous DMF (1.5 mL) were combined and stirred overnight at RT. H_2O was then used to crash out solid, which was filtered out, washed with MeOH, and air dried to afford product as a tan solid (30 mg, 75% yield); mp 215-217 ^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 8.18 (d, *J* = 8.6 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.66-7.64 (m, 2H), 7.59-7.52 (m, 2H), 7.42-7.39 (m, 1H), 6.41 (bs, 2H), 5.75 (s, 2H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 172.6, 170.5, 169.0, 157.8, 153.5, 133.2, 131.2, 130.9, 125.6, 125.4, 124.0, 122.2, 120.8, 119.6, 113.3, 67.3; HRMS (ESI) Calcd for $C_{16}H_{12}ClN_4O_2S$ $(M+H)^+$ 359.0364, found 359.0358.

5-(3-((5-Chlorobenzo[d]thiazol-2-yl)methoxy)-2,6-difluorophenyl)-1,3,4-thiadiazol-2-amine (194).

189 (12 mg, 0.05 mmol), 2-(bromomethyl)-5-chlorobenzo[*d*]thiazole (14 mg, 0.06 mmol), and potassium carbonate (11 mg, 0.08 mmol) in anhydrous DMF (1 mL) were combined and stirred overnight at RT. H_2O was then used to crash out solid, which was filtered out, washed with MeOH, and air dried to afford product as a brown solid (16 mg, 74% yield); mp 228-230 ^oC; ^1H NMR (400 MHz) (DMSO-d_6) δ 8.19 (d, *J* = 8.6 Hz, 1H), 8.13 (m, 1H), 7.55-7.50 (m, 4H), 7.28-7.22 (m, 1H); ^{13}C NMR (100 MHz) (DMSO-d_6) δ 170.4, 170.0, 153.4, 152.0, 142.6-142.4 (m), 133.3, 131.2, 125.6, 124.0, 122.3, 117.3-117.2 (m), 111.6-111.3 (m), 109.6, 68.7; HRMS (ESI) Calcd for $C_{16}H_9ClF_2N_4O_2S_2$ $(M+H)^+$ 410.9947, found 410.9944.

5-Chloro-2-((3-(4,5-dihydro-1H-imidazol-2-yl)-2,4-difluorophenoxy)methyl)benzo[*d*]thiazole (195).

Crude **190** (50 mg, 0.25 mmol), 2-(bromomethyl)-5-chlorobenzo[*d*]thiazole (69 mg, 0.26 mmol), and potassium carbonate (52 mg, 0.38 mmol) in anhydrous DMF (3 mL) were combined and stirred overnight at RT. Reaction was then diluted with EtOAc and washed with saturated $NaHCO_3$ followed by 10% LiCl solution. Organic layer was collected, dried over Na_2SO_4, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM afforded product as a tan solid (27 mg, 28% yield over two steps); mp 170-171 ^oC; ^1H NMR (400 MHz) ($CDCl_3$) δ 8.00 (t, *J* = 1.9 Hz, 1H), 7.82 (dd,

J = 8.6 Hz, *J* = 2.0 Hz, 1H), 7.40 (dt, *J* = 8.6 Hz, *J* = 2.1 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.19-7.13 (m, 1H), 6.92-6.87 (m, 1H), 5.50 (m, 2H), 3.84 (m, 4H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ 169.2, 156.4-156.3 (m), 154.0-153.9 (m), 152.6, 152.4-152.3 (m), 149.9-149.8 (m), 142.7-142.6 (m), 133.3, 132.5, 126.1, 123.0, 122.6, 118.7-118.6 (m), 111.5-111.2 (m), 69.9, 50.4, 50.2; HRMS (ESI) Calcd for $C_{17}H_{13}ClF_2N_3OS$ $(M+H)^+$ 380.0430, found 380.0423.

Minimum Inhibitory Concentration (MIC) Assays.

MIC assays were conducted in accordance with Clinical Laboratory Standards Institute (CLSI) guidelines for broth microdilution. The assays included the following bacterial strains: *S. aureus* 8325-4 (MSSA), *S. aureus* ATCC 33591 (MRSA), *E. faecalis* ATCC 19433 (VSE), and *E. faecalis* ATCC 51575 (VRE). Log-phase bacteria were added to 96-well microtiter plates (at 10^5 CFU/mL) containing two-fold serial dilutions of compound or comparator drug (at concentrations ranging from 64 to 0.031 μg/mL) in cation-adjusted Mueller-Hinton (CAMH) broth (for the *S. aureus* assays) or brain-heart infusion (BHI) broth (for the *E. faecalis* assays). In the MRSA assays, the CAMH broth was supplemented with 2% NaCl. The final volume in each well was 0.1 mL, and the microtiter plates were incubated aerobically for 24 hours at 37 °C. Bacterial growth was then monitored by measuring OD_{600} using a VersaMax® plate reader (Molecular Devices, Inc.), with the MIC being defined as the lowest compound concentration at which growth was ≥90% inhibited.

Expression and Purification of *S. aureus* FtsZ (SaFtsZ).

The *FtsZ* gene from *S. aureus* was amplified by polymerase chain reaction (PCR) from the *S. aureus* genome obtained from ATCC (ATCC 33591-D). The amplified gene product was then ligated into the pET-22b(+) cloning vector (Novagen-EMD Chemicals, Inc.), with the sequence of the final recombinant plasmid (pETSAftsZ) being verified by sequence analysis and used to transform *E. coli* BL21 (DE3) cells. A single colony of pETSAFtsZ-transformed *E. coli* cells was used to inoculate Luria Bertani media containing 100μg/mL of ampicillin (LB-amp) and grown overnight at 37 °C. 20 mL of the culture was diluted into 4 L of LB-amp and grown until an optical density at 600 nm (OD_{600}) of 0.4, at which point FtsZ production was induced by addition of isopropyl β-D-1-thiogalactopyranoside (IPTG) to a final concentration of 1 mM. Following addition of IPTG, the cultures were incubated for an additional 3 hours at 37 °C. Cells were then harvested by centrifugation at 4 °C and 4000 × g in a swinging bucket Sorvall RC-3BP+ centrifuge with rotor H-6000 for 20 minutes. The bacterial cell pellet was washed with ice cold 50 mM Tris•HCl (pH 8.0), 0.5 M NaCl and re-pelleted by centrifugation as described above. The washed bacterial pellet was stored at -20 °C. The dialyzed material was loaded onto a MonoQ 10/100 anion exchange column at 1 ml/min and washed with 5 column volumes of TKEGE buffer at 1 ml/min. The column was eluted at 4° C with a 0-60% (v/v) linear gradient (120 mL total volume) of the following two buffers: (i) TKEGE (containing 50 mM KCl) and (ii) TKEGE containing 1 M KCl instead of 50 mM KCl. The rate of elution was maintained at 1 ml/min. Fractions were assayed for FtsZ by SDS-PAGE analysis on a 10%-15% Tris•HCl polyacrylamide gel. FtsZ elutes at 250-350 mM KCl. The FtsZ containing fractions were pooled and dialyzed

against 2 L of TKEGE buffer. The dialyzed fractions were concentrated, if necessary, to 5 mL and loaded onto a Superdex-200 size exclusion column, with TKEGE buffer as the running buffer at 0.25 mL/min. SaFtsZ-containing fractions were detected by SDS-PAGE as above. Peak fractions containing the pure SaFtsZ were pooled and concentrated using Amicon® Ultra centrifugal filters (Millipore Corp.). Quantitation was performed spectrophotometrically at 595 nm using a colorimetric protein assay kit (Bio-Rad) and bovine serum albumin as the standard. The final FtsZ concentration was ~8 mg/ml and the protein was ~90% pure as determined by SDS-PAGE analysis.

FtsZ Binding Assays.

The binding of compounds to SaFtsZ was assayed by monitoring protein-induced changes in the intrinsic fluorescence of the compounds. In these experiments, aliquots (1.5 to 3 µL) of a 250 µM SaFtsZ stock solution were sequentially added to a buffered solution (150 µL) containing compound (7 or 10 µM). After each protein addition, the reaction was allowed to equilibrate for 3 minutes, and the emission spectrum was then acquired from 510 to 370 nm in 1-nm increments. Each spectrum acquired in this manner was corrected by subtraction of the corresponding background spectrum resulting from the titration of protein into buffer alone. The excitation wavelength was set at 265 nm, the bandwidth was set at 5 nm in both the excitation and emission directions, and the time constant was set at 1 second. All measurements were acquired at 25 °C using an AVIV model ATF 105 spectrofluorimeter (AVIV Biomedical, Inc.) equipped with a thermoelectrically controlled cell holder. A quartz ultra-micro cuvette was used in each

experiment, with the pathlength being 10 mm in the excitation direction and 2 mm in the emission direction. Buffer conditions were 50 mM Tris•HCl (pH 7.4), 50 mM KCl, and 2 mM magnesium acetate.

FtsZ Polymerization Assays.

Polymerization of SaFtsZ was monitored using a microtiter plate-based turbidity assay. Experiments were conducted at 25 °C in solution containing 50 mM Tris•HCl (pH 7.4), 50 mM KCl, 2 mM magnesium acetate and 1 mM GTP. GTP was combined with vehicle, compound, or control drug and the reactions were initiated by addition of the protein at a final concentration of 10 μM. The reactions (100 μL total volume) were assembled in half-volume, flat-bottom 96-well microtiter plates and their absorbances at 340 nm were continuously monitored using a VersaMax® plate reader over a time period of 300 minutes.

FtsZ GTPase Assays.

The impact of the synthesized compounds on the GTPase activity of SaFtsZ was assayed by measuring the inorganic phosphate (P_i) released upon GTP hydrolysis by FtsZ in the absence or presence of compound via an end-point malachite green colorimetric assay. This assay is based on the spectrophotometric detection of the green complex formed between malachite green molybdate and P_i under acidic conditions. Duplicate reactions of 20 μL were assembled in 96-well plates containing 10 μM FtsZ and either DMSO

vehicle or compound (at concentrations ranging from 0.1 to 200 µg/mL) in buffer containing 50 mM Tris•HCl (pH 7.4), 50 mM KCl, and 2 mM magnesium acetate, and 5 mM $CaCl_2$. The reactions were pre-equilibrated for 10 minutes at room temperature, whereupon the GTPase activity was then initiated by the addition of 250 µM GTP (Roche Diagnostics GmbH, Mannheim, Germany) and shifting the plates to 37 °C. The GTPase reactions were allowed to proceed for 2 hours, and terminated by the addition of 80 µL of a malachite green (Sigma, St. Louis, MO) reagent, which had been previously prepared by mixing a solution of 0.045% (w/v) malachite green (made in water) with a solution of 4.2% (w/v) ammonium molybdate (made in 4 M HCl) at ratio of 3 to 1, and filtering through a 0.22-µm filter. After addition of the malachite green reagent to the 96-well plates, the plates were incubated at room temperature for one minute, and the absorbance at 620 nm was recorded using a VersaMax® plate reader. The concentration of P_i released in each reaction was determined by using a phosphate standard curve, which was obtained by diluting a 200 µM KH_2PO_4 stock solution to achieve final phosphate concentrations ranging from 0 to 60 µM. The P_i released in the presence of each compound is reported as a percentage of P_i released in the presence of vehicle (DMSO) alone.

Tubulin Polymerization Assays.

Polymerization of microtubule-associated protein (MAP)-rich porcine β-tubulin containing 70% β-tubulin and 30% MAPs (Cytoskeleton, Inc.) was monitored using a microtiter plate-based light scattering (turbidity) assay similar to that described above for

FtsZ polymerization. Test compound or comparator drug was combined with 1 mM GTP and 2 mg/mL porcine β-tubulin in 100 μL of reaction solution containing 80 mM PIPES•NaOH (pH 7.0), 2 mM $MgCl_2$, and 1 mM EGTA. Reactions were assembled in half-volume, flat-bottom, 96-well microtiter plates, and polymerization was continuously monitored at 37 °C by measuring A_{340} in a VersaMax® plate reader over a time period of 60 minutes.

Cytotoxicity Studies.

Cytotoxicity was determined using the MTT-microtiter plate tetrazolinium cytotoxicity assay. The human embryonic kidney 293 (HEK293) cell line was provided by Dr. Zue Hung Hsu (formerly at Columbia University, presently at Beijing National academy). The Madin-Darby Canine Kidney (MDCK) epithelial cells were obtained from Professor Patrick Sinko (Rutgers University). The cytotoxicity assay was performed using 96-well microtiterplates. Cells were grown in suspension at 37 ^{o}C in 5% CO2 and maintained by regular passage in DMEM media. For determination of IC_{50}, cells were exposed continuously for four days to varying concentrations of drug in triplicate wells, each seeded with 1500 cells. Each assay was performed with a control that did not contain any drug. The MTT assays were performed at the end of the fourth day.

APPENDIX

List of Compounds Evaluated for Antibacterial Activity and Their Corresponding CK Codes

Final Compound Number	Corresponding CK Code
20g	CK-1-12
26a	CK-1-74
26b	CK-1-83
26c	CK-1-85
26d	CK-1-108
32b	CK-1-43
32c	CK-1-57
43b	CK-1-153
43f	CK-1-140
43g	CK-1-173
44b	CK-1-154
54c	CK-1-182
62a	CK-4-78
63a	CK-2-67
63b	CK-2-76
64	CK-2-94

65	**CK-2-137**
66a	**CK-2-28**
66b	**CK-2-16**
67	**CK-2-69**
68	**CK-2-31**
69a	**CK-2-63**
69b	**CK-2-22**
72a	**CK-2-103**
72b	**CK-4-174**
72c	**CK-2-144**
73a	**CK-4-126**
73b	**CK-4-175**
73c	**CK-4-70**
75	**CK-3-81**
77	**CK-3-51**
81	**CK-4-181**
82	**CK-4-182**
85a	**CK-4-176**
85b	**CK-2-142**
86a	**CK-4-177**
86b	**CK-2-145**

90a	**CK-2-154**
90b	**CK-2-164**
94a	**CK-2-128**
94b	**CK-2-17**
96	**CK-2-111**
100a	**CK-2-165**
100b	**CK-3-181**
102a	**CK-3-29**
102b	**CK-3-183**
107	**CK-4-173**
109	**CK-4-157**
111	**CK-4-106**
117a	**CK-3-93**
117b	**CK-3-109**
121b	**CK-4-137**
124b	**CK-4-142**
126	**CK-4-147**
134	**CK-3-88**
138	**CK-4-158**
141a	**CK-4-151**
141b	**CK-3-106**

142	**CK-3-114**
144b	**CK-3-110**
146	**CK-2-182**
149	**CK-3-134**
150	**CK-3-137**
156	**CK-3-154**
161a	**CK-3-162**
161b	**CK-4-16**
161c	**CK-3-175**
172a	**CK-4-22**
172b	**CK-4-48**
177	**CK-4-61**
178	**CK-5-7**
180	**CK-5-2**
184	**CK-5-5**
185	**CK-5-37**
186	**CK-5-10**
189	**CK-5-11**
191	**CK-5-13**
194	**CK-5-12**
195	**CK-5-60**

REFERENCES

1. Levy, S. B.; Marshall, B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat. Med.* **2004**, *10*, S122-S129.

2. Aries, C. A.; Murray, B. E. Antibiotic-resistant bugs in the 21st century – a clinical super-challenge. *New Engl. J. Med.* **2009**, *360*, 439-443.

3. Cornaglia, G. Fighting infections due to multidrug-resistant gram-positive pathogens. *Clin. Microbiol. Infect.* **2009**, *15*, 209-211.

4. Cornaglia, G.; Rossolini, G. M. Forthcoming therapeutic perspectives for infections due to multidrug-resistant gram-positive pathogens. *Clin. Microbiol. Infect.* **2009**, *15*, 218-223.

5. Rasko, D. A.; Sperandio, V. Anti-virulence strategies to combat bacteria-mediated disease. *Nat. Rev. Drug Discovery* **2010**, *9*, 117-128.

6. Gould, I. M.; David, M. Z.; Esposito, S.; Garau, J.; Lina, G.; Mazzei, T.; Peters, G. New insights into meticillin-resistant *Staphylococcus aureus* (MRSA) pathogenesis, treatment and resistance. *Int. J. Antimicrob. Agents* **2012**, *39*, 96-104.

7. Klevens, R. M.; Morrison, M. A.; Nadle, J.; Petit, S.; Gershman, K.; Ray, S.; Harrison, L. H.; Lynfield, R.; Dumyati, G.; Townes, J. M.; Craig, A. S.; Zell, E. R.; Foshiem, G. E.; McDougal, L. K.; Carey, R. B.; Fridkin, S. K. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *J. Am. Med. Assoc.* **2007**, *298*, 1763-1771.

8. Snitkin, E. S.; Zelazny, A. M.; Thomas, P. J.; Stock, F.; Hendersin, D. K.; Palmore, T. N.; Segre, J. A. Tracking a hospital outbreak of carbapenem-resistant Klebsiella pneumoniae with whole-genome sequencing. *Sci. Transl. Med.* **2012**, *4*, 148ra116.

9. Leclercq, R. Epidemiological and resistance issues in multidrug-resistant gram-positive pathogens. *Clin. Microbiol. Infect.* **2009**, *15*, 224-231.

10. Lock, R. L.; Harry, E. J. Cell-division inhibitors: new insights for future antibiotics. *Nat. Rev. Drug Discovery* **2008**, *7*, 324-338.

11. Walsh, C. Where will new antibiotics come from? *Nature Rev. Microbiol.* **2003**, *1*, 65-70.

12. Projan, S. J.; Youngman, P. J. Antimicrobials: new solutions badly needed. *Curr. Opin. Microbiol.* **2002**, *5*, 463-465.

13. Hopkins, A. L.; Groom, C. R. The druggable genome. *Nature Rev. Drug Discov.* **2002**, *1*, 727-730.

14. Errington, J.; Daniel, R. A.; Scheffers, D. J. Cytokinesis in bacteria. *Microbiol. Mol. Biol. Rev.* **2003**, *67*, 52-65.

15. Goehring, N. W.; Beckwith, J. Diverse paths to midcell: assembly of the bacterial cell division machinery. *Curr. Biol.* **2005**, *15*, R514-R526.

16. Buddelmeijer, N.; Beckwith, J. Assembly of cell division proteins at the *E. coli* cell center. *Curr. Opin. Microbiol.* **2002**, *5*, 553-557.

17. Harry, E.; Monahan, L.; Thompson, L. Bacterial cell division: the mechanism and its precision. *Int. Rev. Cytol.* **2006**, *253*, 27-94.

18. Vicente, M.; Rico, A. I.; Martinez-Arteaga, R.; Mingorance, J. Septum enlightenment: assembly of bacterial division proteins. *J. Bacteriol.* **2006**, *188*, 19-27.

19. Adams, D. W.; Errington, J. Bacterial cell division: assembly, maintenance and disassembly of the Z ring. *Nature Rev. Microbiol.* **2009**, *7*, 642-653.

20. Mingorance, J.; Rivas, G.; Vélez, M.; Gómez-Puertas, P.; Vicente, M. Strong FtsZ is with the force: mechanisms to constrict bacteria. *Trends in Microbiol.* **2010**, *18*, 348-356.

21. Bi, E.; Dai, K.; Subbarao, S.; Beall, B.; Lutkenhaus, J. FtsZ and cell division. *Res. Microbiol.* **1991**, *142*, 249-252.

22. Woldringh, C. L.; Mulder, E.; Huls, P. G.; Vischer, N. Toporegulation of bacterial division according to the nucleoid occlusion model. *Res. Microbiol.* **1991**, *142*, 309-320.

23. Sun, Q.; Margolin, W. Effects of perturbing nucleoid structure on nucleoid occlusion-mediated toporegulation of FtsZ-ring assembly. *J. Bacteriol.* **2004**, *186*, 3951–3959.

24. Wu, L. J.; Errington, J. Coordination of cell division and chromosome segregation by a nucleoid occlusion protein in *Bacillus subtilis*. *Cell* **2004**, *117*, 915-925.

25. Lee, S.; Price, C. W. The minCD locus of *Bacillus subtilis* lacks the minE determinant that provides topological specificity to cell division. *Mol. Microbiol.* **1993**, *7*, 601-610.

26. de Boer, P. A.; Crossley, R. E.; Rothfield, L. I. A division inhibitor and a topological specificity factor coded for by the mini-cell locus determine proper placement of the division septum in *E. coli*. *Cell* **1989**, *56*, 641-649.

27. Lowe, J.; Amos, L. A. Crystal structure of the bacterial cell division protein FtsZ. *Nature* **1998**, *391*, 203-206.

28. Nogales, E.; Downing, K. H.; Amos, L. A.; Lowe, J. Tubulin and FtsZ form a distinct family of GTPases. *Nat. Struct. Mol. Biol.* **1998**, *5*, 451-458.

29. Romberg, L.; Levin, P. A. Assembly dynamics of the bacterial cell division protein FtsZ: poised at the edge of stability. *Annu. Rev. Microbiol.* **2003**, *57*, 124-154.

30. de Boer, P.; Crossley, R.; Rothfield, L. The essential bacterial cell-division protein FtsZ is a GTPase. *Nature* **1992**, *359*, 254-256.

31. Mukherjee, A.; Lutkenhaus, J. Dynamic assembly of FtsZ regulated by GTP hydrolysis. *EMBO J.* **1998**, *17*, 462-469.

32. Oliva, M. A.; Cordell, S. C.; Lowe, J. Structural insights into FtsZ protofilament formation. *Nat. Struct. Mol. Biol.* **2004**, *11*, 1243-1250.

33. Singh, P.; Panda, D. FtsZ inhibition: a promising approach for anti-staphylococcal therapy. *Drug News & Perspect.* **2010**, *23*, 295-304.

34. Lappchen, T.; Hartog, A. F.; Pinas, V. A.; Koomen, G. J.; den Blaauwen, T. GTP analogue inhibits polymerization and GTPase activity of the bacterial protein FtsZ without affecting its eukaryotic homologue tubulin. *Biochemistry* **2005**, *44*, 7879-7884.

35. Lappchen, T.; Pinas, V. A.; Hartog, A. F.; Koomen, G. J.; Schaffner-Barbero, C.; Andreu, J. M.; Trambaiolo, D.; Lowe, J.; Juhem, A.; Popov, A. V.; den Blaauwen, T. Probing FtsZ and tubulin with C-8 substituted GTP analogs reveals differences in their nucleotide binding sites. *Chem. Biol.* **2008**, *15*, 189-199.

36. Matsui, T.; Yamane, J.; Mogi, N.; Yamaguchi, H.; Takemoto, H.; Yao, M.; Tanaka, I. Structural reorganization of bacterial cell-division protein FtsZ from *Staphylococcus aureus*. *Acta Crystallogr., Sec. D: Biol. Crystallogr.* **2012**, *68*, 1175-1188.

37. Mosyak, L.; Zhang, Y.; Glasfeld, E.; Haney, S.; Stahl, M.; Seehra, J.; Somers, W. S. The bacterial cell-division protein ZipA and its interaction with an FtsZ fragment revealed by X-ray crystallography. *EMBO J.* **2000**, *19*, 3179-3191.

38. Yan, K.; Pearce, K. H.; Payne, D. J. A conserved residue at the extreme C-terminus of FtsZ is critical for the FtsA-FtsZ interaction in *Staphylococcus aureus*. *Biochem. Biophys. Res. Commun.* **2000**, *270*, 387-392.

39. Lowe, J.; Amos, L. A. Helical tubes of FtsZ from *Methanococcus jannaschii*. *Biol. Chem.* **2000**, *381*, 993-999.

40. Scheffers, D. J.; de Wit, J. G.; den Blaauwen, T.; Driessen, A. J. M. GTP hydrolysis of cell division protein FtsZ: evidence that the active site is formed by the association of monomers. *Biochemistry* **2002**, *41*, 521-529.

41. Kirkpatrick, C. L.; Viollier, P. H. New(s) to the (Z-)ring. *Curr. Opin. Microbiol.* **2011**, *14*, 691-697.

42. Lu, C. L.; Reedy, M.; Erickson, H. P. Straight and curved formations of FtsZ are regulated by GTP hydrolysis. *J. Bacteriol.* **2000**, *182*, 164-170.

43. Chen, Y. D.; Erickson, H. P. Rapid *in vitro* assembly dynamics and subunit turnover of FtsZ demonstrated by fluorescence resonance energy transfer. *J. Biol. Chem.* **2005**, *280*, 22549-22554.

44. Mukherjee, A.; Lutkenhaus, J. Guanosine nucleotide-dependent assembly of FtsZ into filaments. *J. Bacteriol.* **1994**, *176*, 2754-2758.

45. Romberg, L.; Mitchison, T. J. Rate-limiting guanosine 5'-triphosphate hydrolysis during nucleotide turnover by FtsZ, a prokaryotic tubulin homologue involved in bacteria cell division. *Biochemistry* **2004**, *43*, 282-288.

46. Mingorance, J.; Rueda, S.; Gomez-Puertas, P.; Valencia, A.; Vicente, M. *Escherichia coli* FtsZ polymers contain mostly GTP and have a high nucleotide turnover. *Mol. Microbiol.* **2001**, *41*, 83-91.

47. Li, Z.; Trimble, M. J.; Brun, Y. V.; Jensen, G. J. The structure of FtsZ filaments in vivo suggests a force-generating role in cell division. *EMBO J.* **2007**, *26*, 4694-4708.

48. Andreu, J. M.; Schaffner-Barbero, C.; Huecas, S.; Alonso, D.; Lopez-Rodriguez, M. L.; Ruiz-Aliva, L. B.; Nunez-Ramirez, R.; Llorca, O.; Martin-Galiano, J. The antibacterial cell division inhibitor PC190723 is an FtsZ polymer-stabilizing agent that induces filament assembly and condensation. *J. Biol. Chem.* **2010**, *285*, 14239-14246.

49. Wang, J.; Galgoci, A.; Kodali, S.; Herath, K. B.; Jayasuriya, H.; Dorso, K.; Vicente, F.; Gonza´lez, A.; Cully, D.; Bramhill, D.; and Singh, S. Discovery of a small molecule that inhibits cell division by blocking FtsZ, a novel therapeutic target of antibiotics. *J. Biol. Chem.* **2003**, *45*, 44424–44428.

50. Weisleder, D.; Lillehoj, E. B. Structure of viriditoxin, a toxic metabolite of *Aspergillus viridinutans*. *Tetrahedron Lett.* **1971**, *48*, 4705-4706.

51. Kubo, I.; Muroi, H.; Himejima, M. Antibacterial activity of totarol and its potentiation. *J. Nat. Prod.* **1992**, *55*, 1436-1440.

52. Jaiswal, R.; Beuria, T. K.; Mohan, R.; Mahajan, S. K.; Panda, D. Totarol inhibits bacterial cytokinesis by perturbing the assembly dynamics of FtsZ. *Biochemistry* **2007**, *46*, 4211-4220.

53. Nicolson, K.; Evans, G.; O'Toole, P. W. Potentiation of methicillin-resistant *Staphylococcus aureus* by diterpenes. *FEMS Microbiol. Lett.* **1999**, *179*, 233-239.

54. Rai, D.; Singh, J. K.; Roy, N.; Panda, D. Curcumin inhibits FtsZ assembly: an attractive mechanism for its antibacterial activity. *Biochem. J.* **2008**, *410*, 147-155.

55. Mishra, S.; Narain, U.; Mishra, R.; Misra, K. Design, development and synthesis of mixed bioconjugates of piperic acid–glycine, curcumin–glycine/alanine and curcumin–glycine–piperic acid and their antibacterial and antifungal properties. *Bioorg. Med. Chem.* **2005**, *13*, 1477-1486.

56. Domadia, P.; Swarup, S.; Bhunia, A.; Sivaraman, J.; Dasgupta, D. Inhibition of bacterial cell division protein FtsZ by cinnamaldehyde. *Biochem. Pharm.* **2007**, *74*, 831-840.

57. Beuria, T. K.; Santra, M. K.; Panda, D. Sanguinarine blocks cytokinesis by inhibiting FtsZ assembly and bundling. *Biochemistry* **2005**, *44*, 16584-16593.

58. Wolff, J.; Knipling, L. Antimicrotubule properties of benzophenanthridine alkaloids. *Biochemistry* **1993**, *32*, 13334-13339.

59. Slaninova, I.; Taborska, E.; Bochorakova, H.; Slanina, J. Interaction of benzo[*c*]phenanthridine and protoberberine alkaloids with animal and yeast cells. *Cell Biol. Toxicol.* **2001**, *17*, 51-63.

60. Domadia, P. N.; Bhunia, A.; Sivaraman, J.; Swarup, S.; Dasgupta, D. Berberine targets assembly of *Escherichia coli* cell division protein FtsZ. *Biochemistry* **2008**, *47*, 3225-3234.

61. Boberek, J. M.; Stach, J.; Good, L. Genetic evidence for inhibition of bacterial division protein FtsZ by berberine. *PLoS One* **2010**, *5*, e13745.

62. Kim, S.; Shin, D.; Oh, M.; Chung, S.; Lee, J.; Oh, K. Inhibition of bacterial surface protein anchoring transpeptidase sortase by isoquinoline alkaloids. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 421-424.

63. Paradis-Bleau, C.; Beaumont, M.; Sanschagrin, F.; Voyer, N.; Levesque, R. C. Parallel solid synthesis of inhibitors of the essential cell division FtsZ enzyme as a new potential class of antibiotics. *Bioorg. Med. Chem.* **2007**, *15*, 1330-1340.

64. Margalit, D. N.; Romberg, L.; Mets, R. B.; Hebert, A. M.; Mitchison, T. J.; Kirschner, M. W.; RayChaudhuri, D. Targeting cell division: small molecule inhibitors of FtsZ GTPase perturb cytokinetic ring assembly and induce bacterial lethality. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11821-11826.

65. Beuria, T. K.; Singh, P.; Surolia, A.; Panda, D. Promoting assembly and bundling of FtsZ as a strategy to inhibit bacterial cell division: a new approach for developing novel antibacterial drugs. *Biochem. J.* **2009**, *423*, 61-69.

66. White, E. L.; Suling, W. J.; Ross, L. J.; Seitz, L. E.; Reynolds, R. C. 2-Alkoxycarbonylaminopyridines: inhibitors of *Mycobacterium tuberculosis* FtsZ. *J. Antimicrob. Chemother.* **2002**, *50*, 111-114.

67. Ito, H.; Ura, A.; Oyamada, Y.; Tanitame, A.; Yoshida, H.; Yamada, S.; Wachi, M.; Yamagishi, J. A 4-aminofuranzan derivative - A189 - inhibits assembly of bacterial cell division protein *in vitro* and *in vivo*. *Microbiol. Immunol.* **2006**, *50*, 759-764.

68. Ohashi, Y.; Chijiwa, Y.; Suzuki, K.; Takahashi, K.; Nanamiya, H.; Sato, T.; Hosoya, Y.; Ochi, K.; Kawamura, F. The lethal effect of a benzamide derivative, 3-methoxybenzamide, can be suppressed by mutations within a cell division gene, ftsZ, in *Bacillus subtilis*. *J. Bacteriol.* **1999**, *181*, 1348-1351.

69. Haydon, D. J.; Stokes, N. R.; Ure, R.; Galbraith, G.; Bennett, J. M.; Brown, D. R.; Baker, P. J.; Barynin, V. V.; Rice, D. W.; Sedelnikova, S. E.; Heal, J. R.; Sheridan, J. M.; Aiwale, S. T.; Chauhan, P. K.; Srivastava, A.; Taneja, A.; Collins, I.; Errington, J.; Czaplewski, L. G. An inhibitor of FtsZ with potent and selective anti-staphylococcal activity. *Science* **2008**, *321*, 1673-1675.

70. Stermitz, F. R.; Gillespie, J. P.; Amoros, L. G.; Romero, R.; Stermitz, T. A. Synthesis and biological activity of some antitumor benzophenanthridinium salts. *J. Med. Chem.* **1975**, *18*, 708-713.

71. Harayama, T.; Akiyama, T.; Akamatsu, H.; Kawano, K.; Abe, H.; Takeuchi, Y. Total synthesis of benzo[*c*]phenanthridine alkaloids, chelerythrine and 12-methoxydihydrochelerythrine, by a palladium-assisted internal biaryl coupling reaction. *Synthesis* **2001**, *3*, 444-450.

72. Wallace, D. J.; Chen, C. Cyclopropylboronic acid: synthesis and Suzuki cross-coupling reactions. *Tetrahedron Lett.* **2002**, *43*, 6987-6990.

73. CLSI *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, approved standard - eighth edition.* Clinical Laboratory Standards Institute: Wayne, PA, 2009.

74. Ball, A. R.; Casadei, G.; Samsorn, S.; Bremner, J. B.; Ausubel, F. M.; Moy, T. I.; Lewis, K. Conjugating berberine to a multidrug resistance pump inhibitor creates an effective antimicrobial. *ACS Chem. Biol.* **2006**, *1*, 594-600.

75. Iwasa, K.; Kamigauchi, M.; Ueki, M.; Taniguchi, M. Antibacterial activity and structure-activity relationships of berberine analogs. *Eur. J. Med. Chem.* **1996**, *31*, 469-478.

76. Simchen, G.; Kramer, W. Reactions with hydrogen halide adducts of nitriles. I. New isoquinoline synthesis. *Chem. Ber.* **1969**, *102*, 3656-3665.

77. Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. A new class of easily activated palladium precatalysts for facile C-N cross-coupling reactions and the low temperature oxidative addition of aryl chlorides. *J. Am. Chem. Soc.* **2008**, *130*, 6686–6687.

78. Kanojia, R. M.; Press, J. B.; Lever, O. W., Jr.; Williams, L.; McNally, J. J.; Tobia, A. J.; Falotico, R.; Moore, J. B., Jr. Cardiotonic agents. Synthesis and inotopic activity of a series of isoquinolin-3-ol derivatives. *J. Med. Chem.* **1988**, *31*, 1363-1368.

79. Camp, D.; Jenkins, I. D. Mechanism of the Mitsunobu esterification reaction. 1. The involvement of phosphoranes and oxyphosphonium salts. *J. Org. Chem.* **1989**, *54*, 3045-3049.

80. Camp, D.; Jenkins, I. D. Mechanism of the Mitsunobu esterification reaction. 2. The involvement of (acyloxy)alkoxyphosphoranes. *J. Org. Chem.* **1989**, *54*, 3049-3054.

81. Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. A mechanistic study of the Mitsunobu esterification reaction. *J. Am. Chem. Soc.* **1988**, *110*, 6487-6491.

82. Mitsunobu, O. The use of diethylazidocarboxylate and triphenylphosphine in synthesis and transformation of natural products. *Synthesis* **1981**, *1*, 1-28.

83. Molander, G. A.; Vargas, F. B-Aminoethyltrifluoroborates: efficient aminoethylations via Suzuki-Miyaura cross-coupling. *Org. Lett.* **2007**, *9*, 203-206.

84. Molander, G. A.; Jean-Gerard, L. Scope of the Suzuki-Miyaura aminoethylation reaction using organotrifluoroborates. *J. Org. Chem.* **2007**, *72*, 8422-8426.

85. Stokes, N. R.; Sievers, J.; Barker, S.; Bennett, J. M.; Brown, D. R.; Collins, I.; Errington, V. M.; Foulger, D.; Hall, M.; Halsey, R.; Johnson, H.; Rose, V.; Thomaides, H. B.; Haydon, D. J.; Czaplewski, L. G.; Errington, J. Novel inhibitors of bacterial cytokinesis. *J. Biol. Chem.* **2005**, *280*, 39709-39715.

86. Lin, C. M.; Hamel, E. Effects of inhibitors of tubulin polymerization on GTP hydrolysis. *J. Biol. Chem.* **1981**, *256*, 9242-9245.

87. Carlier, M. F.; Pantaloni, D. Taxol effect on tubulin polymerization and associated guanosine 5'-triphosphate hydrolysis. *Biochemistry* **1983**, *22*, 4814-4822.

88. Kumar, N. J. Taxol-induced polymerization of purified tubulin. Mechanism of action. *J. Biol. Chem.* **1981**, *256*, 10435-10441.

89. Ruggli, P.; Preuss, R. Naphthaldehyde. III. Derivatives of 1-naphthaldehyde and 5-bromo-1-naphthaldehyde. *Helv. Chem. Acta* **1941**, *24*, 1345-1359.

90. Roger, R.; Neilson, D. G. The chemistry of imidates. *Chem. Rev.* **1961**, *61*, 179-211.

91. Kotian, P. L.; Krishnan, R.; Rowland, S.; El-Kattan, Y.; Saini, S. K.; Upshaw, R.; Bantia, S.; Arnold, S.; Babu, Y. S.; Chand, P. Design, parallel synthesis, and crystal structures of biphenyl antithrombotics as selective inhibitors of tissue factor FVIIa complex. Part 1. Exploration of S2 pocket pharmacophore. *Bioorg. Med. Chem.* **2009**, *17*, 3934–3958.

92. O'Meara, J. A.; Yoakim, C.; Bonneau, P. R.; Boes, M.; Cordingley, M. G.; Deziel, R.; Doyon, L.; Duan, J.; Garneau, M.; Guse, I.; Landry, S.; Malenfont, E.; Naud, J.; Ogilvie, W. W.; Thavonekham, B.; Simoneau, B. Novel 8-substituted dipyridodiazepinone inhibitors with a broad-spectrum of activity against HIV-1 strains resistant to non-nucleoside reverse transcriptase inhibitors. *J. Med. Chem.* **2005**, *48*, 5580–5588.

93. Bernstein, P. R.; Aharony, D.; Albert, J. S.; Andisik, D.; Barthlow, H. G.; Bialecki, R.; Davenport, T.; Dedinas, R. F.; Dembofsky, B. T.; Koether, G.; Kosmider, B. J.; Kirkland, K.; Ohnmacht, C. J.; Potts, W.; Rumsey, W. L.; Shen, L.; Shenvi, A.; Sherwood, S.; Stollman, D.; Russell, K. Discovery of novel, orally active dual NK1/NK2 antagonists. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2769-2773.

94. Pettit, G. R.; Fleming, W. C.; Paull, K. D. Synthesis of the 6- and 7-hydroxy-5,8-dioxocarbostyrils. *J. Org. Chem.* **1968**, *33*, 1089-1092.

95. Rice, J. E.; Beresis, R. A mild procedure for the prepartion of phenols from polycyclic aromatic ketones. *Polycyclic Aromat. Compd.* **1992**, *2*, 235-243.

96. Csuk, R.; von Scholz, Y. Synthesis of racemic carbocyclic cyclopropanoid nucleoside analogues. *Tetrahedron* **1995**, *51*, 7193-7206.

97. Haydon, D. J.; Bennett, J. M.; Brown, D.; Collins, I.; Galbraith, G.; Lancett, P.; Macdonald, R.; Stokes, N. R.; Chauhan, P. K.; Sutariya, J. K.; Nayal, N.; Srivastava, A.; Beanland, J.; Hall, R.; Henstock, V.; Noula, C.; Rockley, C.; Czaplewski, L. Creating an antibacterial with in vivo efficacy: synthesis and characterization of potent inhibitors of the bacterial cell division protein FtsZ with improved pharmaceutical properties. *J. Med. Chem.* **2010**, *53*, 3927–3936.

98. Patani, G. A.; LaVoie, E. J. Bioisosterism: A rational approach in drug design. *Chem. Rev.* **1996**, *96*, 3147-3176.

99. Meanwell, N. A. Synopsis of some recent tactical application of bioisosteres in drug design. *J. Med. Chem.* **2011**, *54*, 2529–2591.

100. Polozov, A. M.; Hategan, G.; Cao, H.; Kiselyov, A. S.; Zeller, W.; Singh, J. A general approach to indole-7-yl derivatives of isoxazole, oxadiazole, thiadiazole and pyrazole. *Tetrahedron Lett.* **2010**, *51*, 575–578.

101. Fujioka, H.; Murai, K.; Ohba, Y.; Hiramatsu, A.; Kita, Y. A mild and efficient one-pot synthesis of 2-dihydroimidazoles from aldehydes. *Tetrahedron Lett.* **2005**, *46*, 2197-2199.