



Original article

Antimicrobial activity of various 4- and 5-substituted 1-phenylnaphthalenes

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ABSTRACT

Bacterial cell division occurs in conjunction with the formation of a cytokinetic Z-ring structure comprised of FtsZ subunits. Agents that can disrupt Z-ring formation have the potential, through this unique mechanism, to be effective against several of the newly emerging multi-drug resistant strains of infectious bacteria. 1- and 12-Aryl substituted benzo[c]phenanthridines have been identified as antibacterial agents that could exert their activity by disruption of Z-ring formation. Substituted 4- and 5-amino-1-phenylnaphthalenes represent substructures within the pharmacophore of these benzo[c]phenanthridines. Several 4- and 5-substituted 1-phenylnaphthalenes were synthesized and evaluated for antibacterial activity against *Staphylococcus aureus* and *Enterococcus faecalis*. The impact of select compounds on the polymerization dynamics of *S. aureus* FtsZ was also assessed.

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1. Introduction

Nosocomial infections associated with multi-drug resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) represent a major health concern. Bacterial resistance to conventional antibiotics has created a critical need for the identification of novel therapeutic antibacterial targets [1,2]. FtsZ is an essential and highly conserved bacterial protein involved in cytokinesis [3–8]. Cell division in bacteria occurs at the site of formation of a cytokinetic Z-ring polymeric structure comprised of FtsZ subunits [3]. Several recent reviews have discussed the potential of antibacterial agents that target FtsZ, as well as recent advances in the discovery of small molecules that perturb processes in which FtsZ is involved [9–13]. FtsZ-targeting antibacterial agents can exert their disruptive effects on the Z-ring by either enhancing or inhibiting FtsZ self-polymerization [14–21].

Sanguinarine (**a**) (Fig. 1) is a plant alkaloid that has been identified as a small molecule that alters FtsZ Z-ring formation and has modest antibacterial activity [15]. Studies in our laboratory have also shown

that chelerythrine (**b**) has similar effects on *S. aureus* and *Bacillus subtilis*. In addition, the presence of hydrophobic functionality at either the 12- or 1-position of benzo[c]phenanthridines, as in the case of (**c**) and (**d**), significantly enhanced antibacterial activity relative to either (**a**) or (**b**) [22,23]. These compounds (**a–d**) have a constitutive cationic charge that can adversely affect their desired pharmacokinetic properties. 4- and 5-Substituted 1-phenylnaphthalenes represent a truncated form within the core structure of these alkaloids. Similar results were observed within a series of substituted dibenzo [a,g]quinolizinium derivatives [24]. In the present study, we examined the relative structure–activity relationships associated with the potential antibacterial activity of several 4- and 5-substituted 1-phenylnaphthalene derivatives (Fig. 1). Unlike sanguinarine and chelerythrine, the 4- and 5-substituted 1-phenylnaphthalene derivatives selected for synthesis and evaluation did not possess a constitutive cationic charge. Instead, they contained functionality at the site in proximity to that of the iminium cation of compounds (**a–d**), which would to some extent be protonated at physiological pH. Using aminomethyl, alkylamidinomethyl, or alkyl guanidinomethyl derivatives, the functionality of different base strengths was assessed. Increasing the alkyl linkage to two carbons from the naphthyl-ring further increases basic properties and the degree to which these derivatives will be protonated under physiological conditions.

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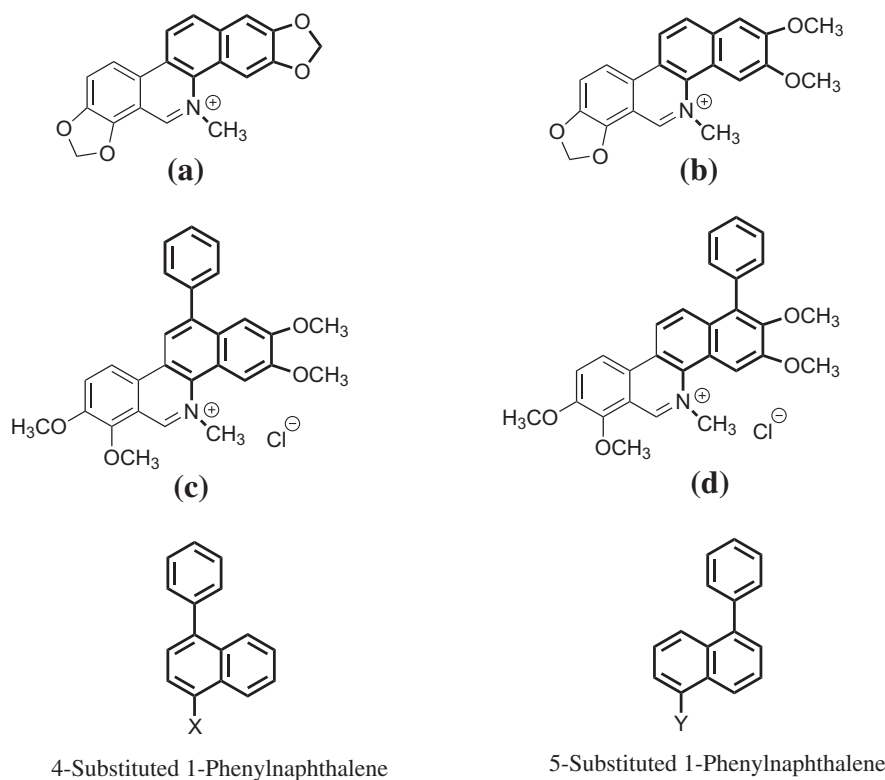


Fig. 1. The structure of sanguinarine (a), chelerythrine (b), 2,3,7,8-tetramethoxy-5-methyl-12-phenylbenzo[c]phenathridin-5-ium chloride (c), and 2,3,7,8-tetramethoxy-5-methyl-1-phenylbenzo[c]phenathridin-5-ium chloride (d).

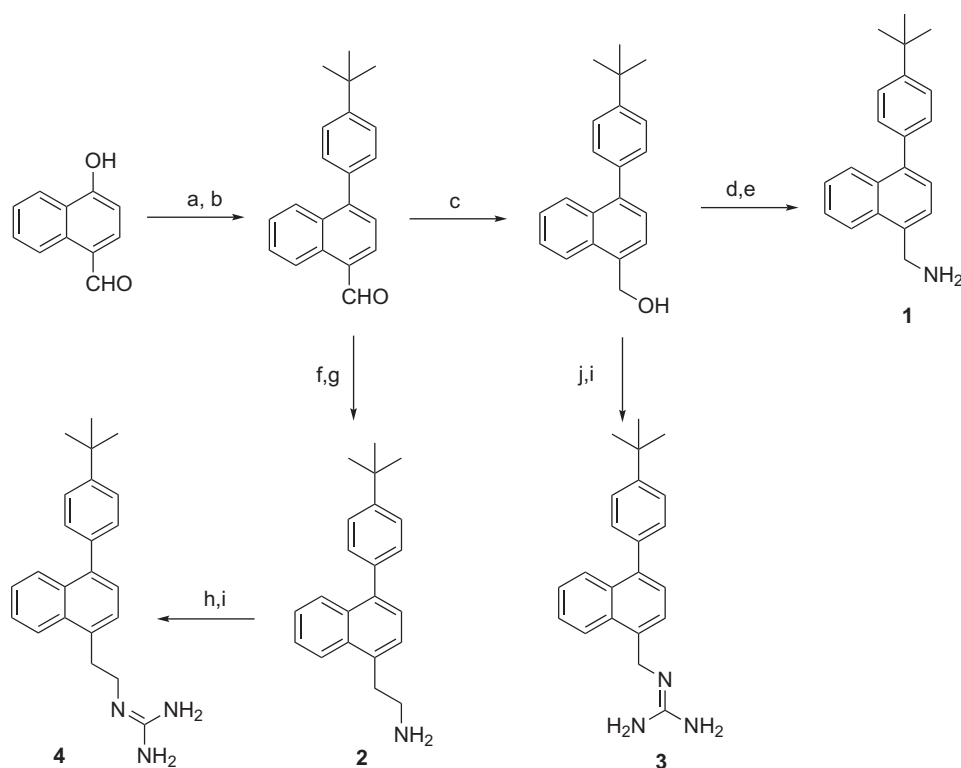
2. Chemistry

The methods used for preparation of the 4-substituted-1-phenylnaphthalenes listed in Table 1 are outlined in Scheme 1. Treatment of 4-hydroxy-1-naphthaldehyde with triflic anhydride followed by Suzuki coupling with 4-(*t*-butyl)phenylboronic acid provided 4-(4-(*t*-butyl)phenyl)-1-naphthaldehyde. This intermediate was reduced with NaBH₄ to its hydroxymethyl derivative, which was converted to its azidomethyl derivative allowing for reduction with PPh₃ to give **1**. Alternatively, this benzyl alcohol intermediate was treated under Mitsunobu conditions to provide the bis-*N*-Boc protected guanidinomethyl intermediate, which was treated with trifluoroacetic acid to yield **3**. Condensation of 4-(4-(*t*-butyl)phenyl)-1-naphthaldehyde with nitromethane provided the 2-nitroethylene intermediate, which was reduced with LAH to give **2**. Treatment of **2** with 1,3-di-Boc-2-(trifluoromethylsulfonyl) guanidine followed by treatment with TFA provided the 2-guanidinoethyl derivative, **4**.

The 5-substituted-1-phenylnaphthalenes listed in Table 1 were synthesized as outlined in Schemes 2–4. 1-Naphthaldehyde was converted to 5-bromo-1-naphthaldehyde as previously described [25]. 5-Bromo-1-naphthaldehyde was subjected to a Suzuki coupling reaction to form the appropriate 5-phenyl-1-naphthaldehyde, which was then reduced to its hydroxymethyl derivative with NaBH₄. These 5-phenyl-1-hydroxymethylnaphthalenes were then treated under Mitsunobu conditions with 1,3-bis(*t*-butoxycarbonyl) guanidine followed by treatment with TFA to provide the guanidinomethyl derivatives, **8** and **14**. Alternatively, 5-bromo-1-hydroxymethylnaphthalene was converted first to its bis-(*N*-Boc) guanidinomethyl derivative and subsequently subjected to a Suzuki coupling followed by treatment with TFA to provide the

Table 1
4- and 5-substituted 1-phenylnaphthalenes.

	X	Y	R ₁	R ₂
1	CH ₂ NH ₂	H	H	<i>t</i> -butyl
2	CH ₂ CH ₂ NH ₂	H	H	<i>t</i> -butyl
3	CH ₂ NC(NH ₂) ₂	H	H	<i>t</i> -butyl
4	CH ₂ CH ₂ NC(NH ₂) ₂	H	H	<i>t</i> -butyl
5	H	CH ₂ NH ₂	H	<i>t</i> -butyl
6	H	CH ₂ CH ₂ NH ₂	H	<i>t</i> -butyl
7	H	CH ₂ CN(NH ₂)	H	<i>t</i> -butyl
8	H	CH ₂ NC(NH ₂) ₂	H	<i>t</i> -butyl
9	H	CH ₂ CH ₂ NC(NH ₂) ₂	H	<i>t</i> -butyl
10	H	CH ₂ NC(NH ₂) ₂	H	cyclopropyl
11	H	CH ₂ NC(NH ₂) ₂	H	Cl
12	H	CH ₂ NC(NH ₂) ₂	H	Br
13	H	CH ₂ CN(NH ₂)	H	CF ₃
14	H	CH ₂ NC(NH ₂) ₂	H	CF ₃
15	H	CH ₂ CH ₂ NC(NH ₂) ₂	H	CF ₃
16	H	CH ₂ CH ₂ NH ₂	OCH ₃	CF ₃
17	H	CH ₂ CH ₂ NH ₂	OH	CF ₃
18	H	CH ₂ NC(NH ₂) ₂	OCH ₃	CF ₃
19	H	CH ₂ CH ₂ NC(NH ₂) ₂	OCH ₃	CF ₃



Scheme 1. Preparation of 1-(4-*t*-butylphenyl)-4-naphthalene derivatives. Reagents and conditions: (a) TiF_4 , Et_3N , DCM, -78°C ; (b) 4-*t*-butylphenylboronic acid, $\text{Pd}(\text{OAc})_2$, XPhos, K_2CO_3 , $\text{ACN}/\text{H}_2\text{O}$, 90°C ; (c) NaBH_4 , EtOH , rt; (d) DPPA, DBU, THF, 0°C to rt; (e) PPh_3 polymer bound, THF/ H_2O , rt; (f) CH_3NO_2 , NH_4OAc , reflux; (g) LAH, THF, rt; (h) 1,3-di-Boc-2-(trifluoromethylsulfonyl)guanidine, Et_3N , CH_2Cl_2 , rt; (i) TFA, CH_2Cl_2 , 0°C to rt; (j) 1,3-bis(*t*-butoxycarbonyl)guanidine, PPh_3 , DIAD, toluene, 0°C to rt.

1-guanidinomethyl-5-phenyl substituted naphthalene, **18**. In the case of 5-(4-*t*-butylphenyl)-1-hydroxymethylnaphthalene, formation of its mesylate followed by treatment with sodium azide and reduction with triphenylphosphine provided the 1-aminomethyl derivative, **5**.

The 5-[(4-trifluoromethyl)phenyl]- and 5-[(4-*t*-butyl)phenyl]-1-aminomethylnaphthalenes, **7** and **13**, were synthesized from their respective bromomethylnaphthalenes, which were synthesized by treatment of their 1-hydroxymethylnaphthalene derivatives with PBr_3 .

The 1-(2-aminoethyl)-5-phenylnaphthalenes, **6** and **16**, were prepared as outlined in Scheme 3. In one instance, the 1-naphthaldehyde intermediates could be condensed with nitromethane and then reduced with LAH. Alternatively, the 1-hydroxymethyl intermediates could be converted to their mesylates, reacted with NaCN and then reduced with LAH. Treatment of the requisite 2-aminoethyl derivative with 1,3-di-Boc-2-(trifluoromethylsulfonyl)guanidine followed by TFA provided the 2-guanidinoethyl derivatives, **9**, **15** and **19**.

Preparation of **10** was accomplished by coupling 5-(4-bromophenyl)-1-naphthaldehyde with cyclopropylboronic acid, yielding an aldehyde that was reduced to its hydroxymethyl derivative, which was converted to the *bis*-(*N*-Boc)guanidinomethyl derivative and then treated with TFA. The preparation of **11** and **12** was accomplished by conversion of 5-bromo-1-naphthaldehyde to its borane ester, which was Suzuki-coupled with either 1-bromo-4-chlorobenzene or 1-bromo-4-iodobenzene. The resulting 5-(4-chlorophenyl)-1-naphthaldehyde and 5-(4-bromophenyl)-1-naphthaldehyde were reduced to their hydroxymethyl derivatives, treated under Mitsunobu conditions and subsequently treated with TFA.

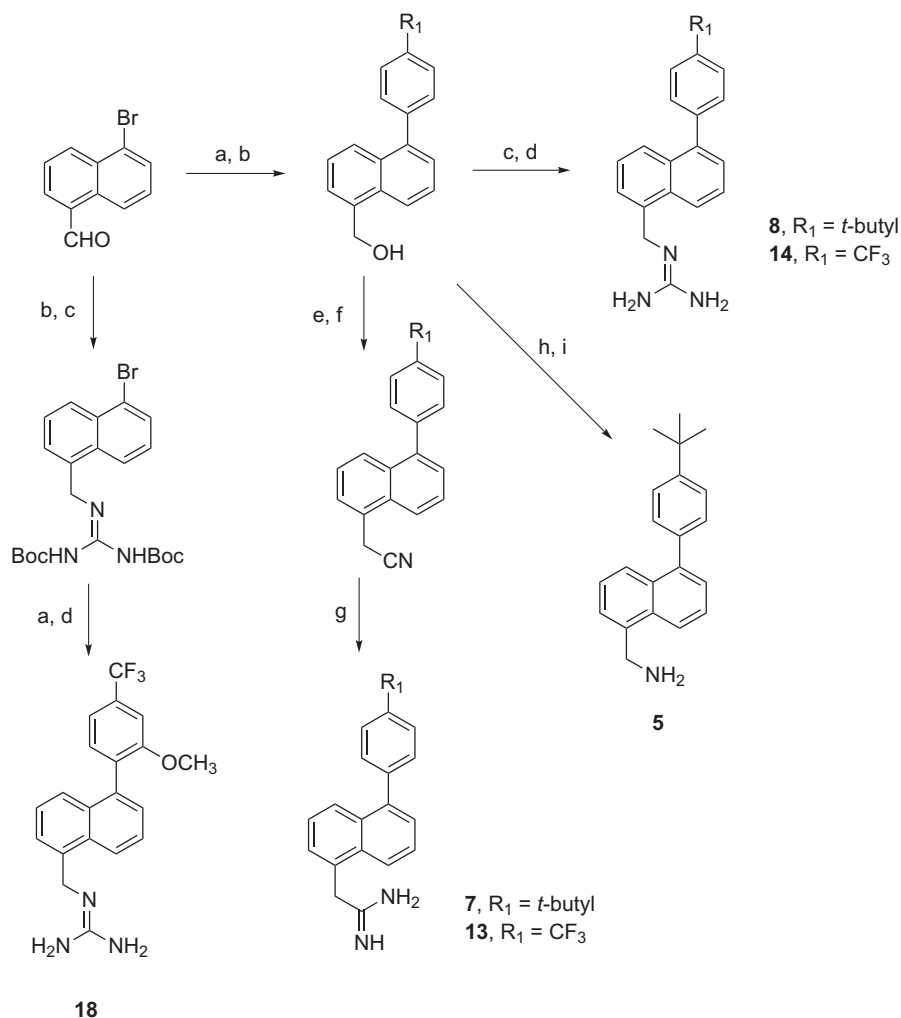
3. Results and discussion

3.1. In vitro antibacterial activity

The antibiotic activities of several 4- and 5-substituted 1-phenylnaphthalenes are provided in Table 2.

The data in Table 2 include the relative activities of (4-*t*-butyl) phenylnaphthalenes with identical substituents at either the 4- or 5-position (**1–9**). Among the pairs of similarly substituted derivatives are the aminomethyl derivatives, **1** and **5**; 2-aminoethyl derivatives, **2** and **6**; guanidinomethyl derivatives, **3** and **8** and; 2-guanidinoethyl derivatives, **4** and **9**. The only notable difference in activity is that the 5-substituted guanidinoalkyl derivatives, **8** and **9**, tend to be slightly more active than their comparable 4-substituted isomers, **3** and **4**, in *S. aureus*. The data suggest that, at either the 4- or 5-position, the more basic guanidine derivatives (**3**, **8** and **4**, **9**) have a tendency to be more potent than their corresponding aminomethyl (**1**, **5**) and 2-aminoethyl (**2**, **6**) derivatives. While less active than the 5-guanidinomethyl derivative, **8**, the 5-aminomethyl derivative, **7**, exhibited antibacterial activity comparable to **5** and **6**.

Compound **8** was most active against MSSA of the 1-(4-*t*-butylphenyl)naphthalenes (**1–9**), with an MIC of $0.5\ \mu\text{g}/\text{mL}$. Compounds **1–9** are significantly less active against MRSA, VSE and VRE. These data prompted further assessment of various 1-phenyl-5-guanidinomethylnaphthalene derivatives wherein the phenyl moiety had in place of the *p*-(*t*-butyl) substituent a cyclopropyl (**10**), chloro (**11**), bromo (**12**), or trifluoromethyl group (**14–19**). 5-Aminomethyl-1-(4-trifluoromethyl)phenylnaphthalene (**13**) is 8-fold less active against MSSA and 4-fold less active against MRSA than **8**. 5-(2-Guanidinoethyl)-1-(4-trifluoromethyl)



Scheme 2. Methods used in the preparation of 5-substituted 1-(4-*t*-butylphenyl)naphthalenes, **5**, **7**, and **8**, and 1-(4-trifluoromethylphenyl)naphthalene derivatives, **13**, **14**, and **18**. Reagents and conditions: (a) R₁R₂-phenylboronic acid, Pd(OAc)₂, XPhos, K₂CO₃, ACN/H₂O, 90 °C; (b) NaBH₄, EtOH, rt; (c) 1,3-bis(*t*-butoxycarbonyl)guanidine, PPh₃, DIAD, toluene, 0 °C to rt; (d) TFA/CH₂Cl₂, 0 °C to rt; (e) PBr₃, CH₂Cl₂, 0 °C to rt; (f) KCN, DMF, rt; (g) (i) 4 N HCl/dioxane, Et₂O, MeOH, 0 °C; (ii) NH₄Cl, EtOH, 85 °C [26]; (h) NaN₃, PPh₃, DMF/CCl₄, 90 °C; (i) polymer-bound PPh₃, THF/H₂O, rt.

phenylnaphthalene (**15**) had comparable activity to **9** against MSSA, but is less active against MRSA, VSE and VRE. The addition of an *o*-methoxyl group to the 1-phenyl substituent did slightly improve the activity of **18** relative to **14** against *Enterococcus faecalis*, but slightly decreased the potency of **19** relative to **15** against *S. aureus*. As anticipated from the previous structure–activity studies, the 5-(2-aminoethyl) derivatives, **16** and **17**, are less active than similarly substituted 5-(guanidinoalkyl)-1-(4-trifluoromethyl)phenylnaphthalenes (**15** and **19**).

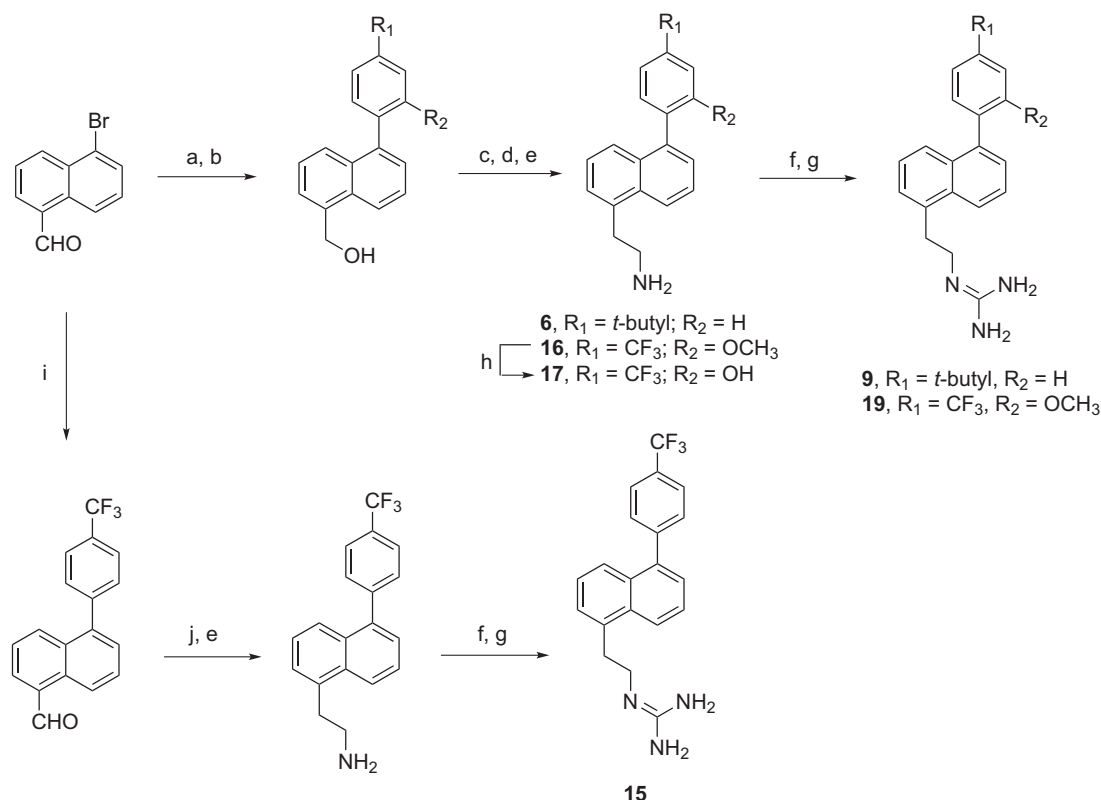
All of these compounds were more active than chelerythrine against both *E. faecalis* strains and only in the case of the vancomycin-sensitive *E. faecalis* did one compound, **17**, exhibit less active antibacterial activity than sanguinarine. Several of these compounds (**8**–**10**, and **15**) were more active against methicillin-sensitive *S. aureus* than either sanguinarine or chelerythrine. When evaluated for their antibacterial activity against methicillin-resistant *S. aureus*, the more potent 1-phenylnaphthalene derivatives had comparable or slightly reduced potency relative to sanguinarine.

The various 4- and 5-substituted 1-phenylnaphthalenes did not exhibit pronounce cross-resistance between MSSA and MRSA, as well as between VSE and VRE, strains of bacteria. This is particularly apparent among the various 1-(*t*-butylphenyl)naphthalene

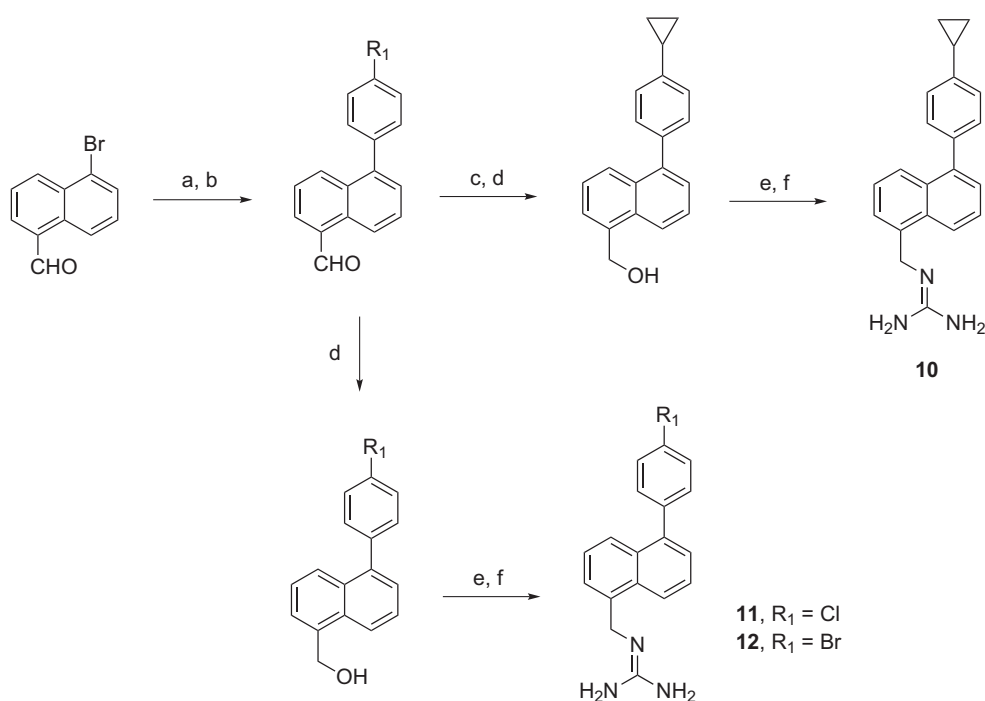
derivatives (**1**–**9**) wherein each instance there is less than a one well difference in potency between pairs of sensitive and resistant bacterial strains. The potency of these compounds against resistant bacteria is clearly evident in a comparison of their activity to that observed with the five known antibiotics used as control agents in this study. Compounds **3**, **8**, and **9** had comparable MICs to vancomycin against MRSA. Compounds **1**–**9** all had lower MIC values (2.0–8.0 µg/mL) against VRE than the clinical antibiotics evaluated in this study.

3.2. FtsZ polymerization assays

The selection of various 4- and 5-substituted 1-phenylnaphthalenes evaluated in this study was based upon the reported activity of sanguinarine to alter FtsZ Z-ring formation, as well as the observation that chelerythrine has a similar effect in *S. aureus* and *B. subtilis* [15,22]. It has been speculated that agents that alter or perturb the formation of FtsZ Z-ring could be effective against bacteria that have shown multi-drug resistance, such as MRSA and VRE [6–9]. Recent studies have shown that agents that stimulate FtsZ polymerization can cause an inhibition of FtsZ Z-ring formation [14,17,18]. To determine whether this mechanism of antibacterial activity may be associated with the antibacterial activity observed for these 4- and 5-substituted



Scheme 3. Methods used in the preparation of 5-substituted 1-(4-*t*-butylphenyl)naphthalenes, **6** and **9**, and 1-(4-trifluoromethylphenyl)naphthalene derivatives, **15–17** and **19**. Reagents and conditions: (a) R₁R₂-phenylboronic acid, Pd(OAc)₂, XPhos, K₂CO₃, ACN/H₂O, 90 °C; (b) NaBH₄, EtOH, rt; (c) MsCl, Et₃N, CH₂Cl₂, 0 °C to rt; (d) KCN, DMF, rt; (e) LAH, ether; (f) 1,3-di-Boc-2-(trifluoromethylsulfonyl)-guanidine, Et₃N, CH₂Cl₂, rt; (g) TFA/CH₂Cl₂; (h) BBr₃, CH₂Cl₂, 0 °C to rt; (i) 4-trifluoromethylphenylboronic acid, Pd(OAc)₂, XPhos, K₂CO₃, ACN/H₂O, 90 °C; (j) nitromethane, NH₄OAc, 100 °C.



Scheme 4. Methods used in the preparation of 5-substituted 1-phenylnaphthalenes, **10–12**. Reagents and conditions: (a) borane ester, Pd(OAc)₂, KOAc, DMF, 80 °C; (b) 4-bromo-X-benzene [X = Cl or I], Pd(PPh₃)₄, K₂CO₃, dioxane/H₂O, 100 °C; (c) cyclopropylboronic acid, Pd(OAc)₂, Pcy₃, K₃PO₄, toluene/H₂O, 100 °C; (d) NaBH₄, EtOH, rt; (e) 1,3-bis(*t*-butoxycarbonyl)guanidine, PPh₃, DIAD, toluene, 0 °C to rt; (f) TFA/CH₂Cl₂, 0 °C to rt.

Table 2
Antistaphylococcal and antienterococcal activities of 4- and 5-substituted 1-phenylnaphthalenes.

Compound	^a MIC (μg/mL)			
	<i>S. aureus</i> 8325-4 (MSSA)	<i>S. aureus</i> ATCC 33591 (MRSA)	<i>E. faecalis</i> ATCC 19433 (VSE)	<i>E. faecalis</i> ATCC 51575 (VRE)
1	4.0	8.0	8.0	8.0
2	4.0	4.0	4.0	4.0
3	2.0	2.0	2.0	2.0
4	2.0	4.0	2.0	4.0
5	4.0	4.0	8.0	8.0
6	2.0	4.0	2.0	4.0
7	4.0	4.0	4.0	8.0
8	0.5	2.0	2.0	4.0
9	1.0	2.0	2.0	2.0
10	1.0	8.0	8.0	8.0
11	2.0	8.0	8.0	8.0
12	2.0	8.0	8.0	8.0
13	4.0	8.0	4.0	8.0
14	2.0	8.0	8.0	16
15	1.0	4.0	4.0	4.0
16	8.0	16	8.0	8
17	8.0	16	16	16
18	2.0	8.0	4.0	4.0
19	2.0	8.0	4.0	4.0
Sanguinarine	2.0	2.0	8.0	16
Chelerythrine	4.0	4.0	32	32
Oxacillin	0.06	>64	8.0	>64
Vancomycin	1.0	2.0	1.0	>64
Erythromycin	0.13	>64	1.0	>64
Tetracycline	0.06	64	0.5	>64
Clindamycin	0.03	>64	2.0	>64

MIC is defined as the lowest compound concentration at which bacterial growth is $\geq 90\%$ inhibited.

^a Minimum inhibitory concentration (MIC) assays were conducted in accordance with Clinical Laboratory Standards Institute (CLSI) guidelines for broth micro-dilution [27].

1-phenylnaphthalenes, we examined the effects of select compounds on the dynamics of FtsZ self-polymerization. To this end, we used a turbidity assay to monitor the self-polymerization of purified *S. aureus* FtsZ (SaFtsZ). In this assay, FtsZ polymerization is detected in solution by a time-dependent increase in solution turbidity, as reflected by a corresponding increase in solution absorbance at 340 nm (A_{340}).

As illustrative examples, Fig. 2 shows the time-dependent A_{340} profiles of SaFtsZ in the absence and presence of **6**, **8**, or the non-FtsZ-targeting control antibiotic vancomycin at a concentration of 40 μg/mL. As expected, vancomycin exerts a negligible impact on SaFtsZ polymerization since its antibacterial target is the bacterial cell wall. In striking contrast to vancomycin, compounds **6** and **8** markedly increase both the kinetics and extent of SaFtsZ polymerization. Stimulation of FtsZ polymerization has been shown to be the antibacterial mechanism of action for agents such as the substituted benzamide class of compounds (e.g., PC190723) [14,17,18]. Our polymerization results suggest that the antibacterial activity of the phenylnaphthalenes is associated with the stimulatory impact of the compounds on the dynamics of FtsZ polymerization.

4. Conclusions

The antistaphylococcal activities of several 4- and 5-substituted 1-phenylnaphthalenes, as measured by their MIC values, are significant. Particularly noteworthy are the antibacterial activities observed against methicillin-resistant *S. aureus*, which in several instances ranged between 2.0 and 4.0 μg/mL. These values are comparable to that observed with vancomycin and are well below the MICs observed with several clinical antibiotics evaluated in this study. Similar activity against MRSA was observed for sanguinarine or chelerythrine. As these alkaloids have a constitutive cationic charge, the physico-chemical properties of several of these 1-phenylnaphthalenes, would be expected to favor their in vivo absorption and distribution. In addition, the relative MIC values for several of these 1-phenylnaphthalenes against vancomycin-resistant *E. faecalis* (VRE) are lower than the clinical antibiotics or the two alkaloids evaluated in this study. Our studies with FtsZ polymerization suggest that the antibacterial activity of the phenylnaphthalenes is associated with the stimulatory impact of the compounds on the dynamics of FtsZ polymerization. These data suggest that compounds that interfere with FtsZ polymerization may prove to be useful in the development of antibiotics against multi-drug resistant bacteria.

5. Experimental

5.1. Chemistry: general methods

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 on a Combi Flash Rf Teledyne ISCO using hexane, ethyl acetate, dichloromethane, and methanol. The ^1H (400 MHz or 300 MHz) and ^{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 or a Varian Unity INOVA (300 MHz) NMR Spectrometer. Data is expressed in parts per million relative to the residual nondeuterated solvent signals, spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (doublet of triplets), q (quartet), m (multiplet), bs (broad singlet), and bt (broad triplet), and coupling constants (J) are reported in Hertz. Melting points were determined using Mel-temp II apparatus and are uncorrected. HRMS

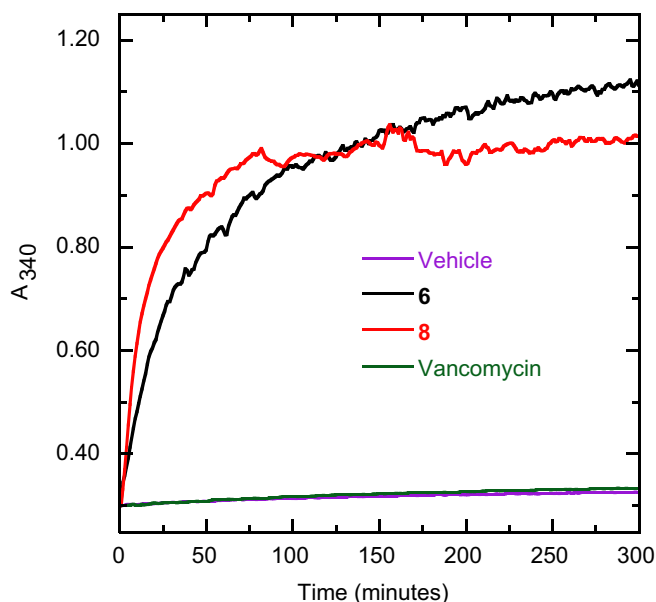


Fig. 2. Impact of select phenylnaphthalenes on the polymerization of *S. aureus* FtsZ (SaFtsZ), as determined by monitoring time-dependent changes in absorbance at 340 nm (A_{340}). Polymerization profiles of SaFtsZ (10 μM) in the presence of DMSO vehicle (violet) or 40 μg/mL of either **6** (black), **8** (red), or the non-FtsZ-targeting comparator antibiotic vancomycin (green) are depicted.

experiments were conducted by Washington University Resource for Biomedical and Bioorganic Mass Spectrometry Department of Chemistry. All compounds tested for biological activity were analyzed for purity using a Shimadzu LC-20AT Prominence chromatograph equipped with an SPD-20A UV–VIS detector monitoring absorbances at both 254 and 280 nm. Compounds were analyzed using a Princeton SPHER-100 5 μ M C18 reverse-phase column (150 mm \times 4.6 mm), using gradients of 0.1% TFA in water with increasing percentages of 0.1% TFA in acetonitrile. Under these solvent conditions, compounds eluted within 12 min using a flow rate of 1.0 mL/min and a gradient from 10 to 100% of acetonitrile containing 0.1% TFA.

5.2. General procedure for the synthesis of compound (1)

5.2.1. 4-Formylnaphthalen-1-yl trifluoromethanesulfonate

4-Hydroxy-1-naphthaldehyde (250 mg, 1.45 mmol) and Et₃N (0.4 mL, 2.9 mmol) in anhydrous DCM (20 mL) were cooled to -78°C . Tf₂O (0.3 mL, 1.74 mmol) was slowly added to the mixture and was stirred for 30 min at -78°C . Reaction was then quickly diluted with additional DCM and washed with saturated NaHCO₃. Organic layer was dried over sodium sulfate and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a brown oil (192 mg, 44% yield); ¹H NMR (400 MHz) (CDCl₃) 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); ¹³C NMR (100 MHz) (CDCl₃) 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.

5.2.2. 4-(4-(*t*-Butyl)phenyl)-1-naphthaldehyde

4-Formylnaphthalen-1-yl trifluoromethanesulfonate (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 K₂CO₃ (259 mg, 1.875 mmol) in dioxane (6 mL) and H₂O (3 mL) were combined in a flask and degassed. Reaction was refluxed at 100°C for 1 h. Reaction was then cooled to RT, diluted with EtOAc, and washed with saturated NaHCO₃. Organic layer was collected, dried over sodium sulfate, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a sticky golden oil (158 mg, 88% yield); ¹H NMR (400 MHz) (CDCl₃) 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); ¹³C NMR (100 MHz) (CDCl₃) 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 C₂₁H₂₁O (M + H)⁺ 289.1587, found 289.1582.

5.2.3. 4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol

NaBH₄ (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 h then quenched with acetone (5 drops), filtered, and concentrated. Chromatography using ISCO max gradient 40% EtOAc/hexane yielded product as a glassy white solid (95 mg, 78% yield); mp 114 – 115°C ; ¹H NMR (400 MHz) (CDCl₃) 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); ¹³C NMR (100 MHz) (CDCl₃) 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 C₂₁H₂₂NaO (M + Na)⁺ 313.1563, found 313.1560.

5.2.4. 1-(Azidomethyl)-4-(4-(*t*-butyl)phenyl)naphthalene

4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol (95 mg, 0.328 mmol) in anhydrous THF (3 mL) was cooled to 0°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

0.5 N HCl and extracted with EtOAc. Organic layer was collected, dried over sodium sulfate, and concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane yielded product as a white solid (78 mg, 76% yield); mp 80 – 81°C ; ¹H NMR (400 MHz) (CDCl₃) 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); ¹³C NMR (100 MHz) (CDCl₃) 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.

5.2.5. 4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanamine (1)

1-(Azidomethyl)-4-(4-(*t*-butyl)phenyl)naphthalene (70 mg, 0.222 mmol) was combined in a flask with polymer supported (3 mmol/g loading) PPh₃ (111 mg, 0.333 mmol), THF (5 mL), and H₂O (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 yielded product as a golden oil (43 mg, 67% yield); ¹H NMR (400 MHz) (CD₃OD) 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); ¹³C NMR (100 MHz) (CD₃OD) 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 C₂₁H₂₄N (M + H)⁺ 290.1903, found 290.1903.

5.3. General procedure for the synthesis of compound (2)

5.3.1. 1-(4-(*t*-Butyl)phenyl)-4-(2-nitrovinyl)naphthalene

4-(4-(*t*-Butyl)phenyl)-1-naphthaldehyde (5.2.2) (168 mg, 0.583 mmol) and NH₄OAc (52 mg, 0.67 mmol) in nitromethane (4 mL) were refluxed at 102°C for 2 h. Solvents were then evaporated. Chromatography using ISCO max gradient 10% EtOAc/hexane yielded product as a yellow solid (160 mg, 83% yield); mp 151°C ; ¹H NMR (400 MHz) (CDCl₃) 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); ¹³C NMR (100 MHz) (CDCl₃) 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 C₂₂H₂₁NO₂ (M)⁺ 331.1572, found 331.1569.

5.3.2. 2-(4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)ethanamine (2)

To a cooled solution of 1-(4-(*t*-butyl)phenyl)-4-(2-nitrovinyl)naphthalene (160 mg, 0.483 mmol) in anhydrous THF (5 mL) was carefully added LAH (55 mg, 1.45 mmol) at 0°C . Reaction was then stirred at RT overnight and quenched with H₂O over an ice bath. Reaction mixture was then diluted with EtOAc and washed with 1 N NaOH solution. Organic layer was collected, dried over sodium sulfate, and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM/0.1% NH₄OH yielded product as a tan solid (75 mg, 51% yield); mp 101 – 102°C ; ¹H NMR (400 MHz) (CD₃OD) 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 = 16.0 Hz, 2H), 3.07–3.03 (m, 2H), 1.41 (s, 9H); ¹³C NMR (100 MHz) (CD₃OD) 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 C₂₂H₂₆N (M + H)⁺ 304.2060, found 304.2052.

5.4. General procedure for the synthesis of compound (3)

5.4.1. 1,3-Di-Boc-2-((4-(4-(*t*-butyl)phenyl)naphthalen-1-yl)methyl)guanidine

4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol (5.2.3) (40 mg, 0.14 mmol), PPh₃ (60 mg, 0.23 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (70 mg, 0.27 mmol) in anhydrous toluene (3 mL) at 0°C was added diisopropylazodicarboxylate (0.04 mL,

0.20 mmol) drop-wise over 15 min. Reaction was stirred at RT overnight then concentrated to an oil residue. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a white fluffy solid (70 mg, 97% yield); mp 88–90 °C; ^1H 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 $\text{C}_{32}\text{H}_{42}\text{N}_3\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 532.3175, found 532.3185.

5.4.2. 2-((4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methyl)guanidine (**3**)

To a cooled solution of 1,3-di-Boc-2-((4-(4-(*t*-butyl)phenyl)naphthalen-1-yl)methyl)guanidine (70 mg, 0.13 mmol) in anhydrous DCM (0.5 mL) was slowly added TFA (0.5 mL). Reaction was stirred at RT overnight then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM/0.1% NH_4OH yielded product as a white solid (35 mg, 80% yield); mp 85–87 °C; ^1H 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 $\text{C}_{22}\text{H}_{26}\text{N}_3$ ($\text{M} + \text{H}$) $^+$ 332.2121, found 332.2137.

5.5. General procedure for the synthesis of compound (**4**)

5.5.1. 1,3-Di-Boc-2-(2-(4-(4-(*t*-butyl)phenyl)naphthalen-1-yl)ethyl)guanidine

2-(4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)ethanamine (**2**) (25 mg, 0.08 mmol), 1,3-di-Boc-2-(trifluoromethylsulfonyl)-guanidine (40 mg, 0.1 mmol), and Et_3N (0.03 mL, 0.22 mol) in anhydrous DCM (4 mL) were stirred at RT overnight then concentrated to an oil residue. Chromatography using ISCO max gradient 10% EtOAc/hexane yielded product as a white solid (38 mg, 84% yield); ^1H NMR (300 MHz) (CDCl_3) δ 8.50 (m, 1H), 8.35 (d, J = 9.0 Hz, 1H), 8.18 (d, J = 6.0 Hz, 1H), 7.56–7.34 (m, 7H), 3.82 (m, 2H), 3.42 (t, J = 6.0 Hz, 2H), 1.55 (s, 9H), 1.49 (s, 9H), 1.42 (s, 9H).

5.5.2. 2-(2-(4-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)ethyl)guanidine (**4**)

To a cooled solution of 1,3-di-Boc-2-(2-(4-(4-(*t*-butyl)phenyl)naphthalen-1-yl)ethyl)guanidine (36 mg, 0.07 mmol) in anhydrous DCM (0.8 mL) was slowly added TFA (0.8 mL). Reaction was stirred at RT overnight then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM/0.1% NH_4OH yielded product as a white solid (21 mg, 91% yield); mp 115–116 °C; ^1H NMR (300 MHz) (CD_3OD) δ 8.16 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 6.0 Hz, 1H), 7.57 (m, 3H), 7.47 (m, 2H), 7.38 (m, 3H), 3.66 (t, J = 6.0 Hz, 2H), 3.44 (t, J = 6.0 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.7, 151.5, 141.2, 139.2, 134.6, 133.6, 133.5, 130.8, 128.1, 127.7, 127.6, 127.2, 126.8, 126.3, 124.6, 43.1, 35.5, 33.0, 31.9; HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{28}\text{N}_3$ ($\text{M} + \text{H}$) $^+$ 346.2278, found 346.2284.

5.6. General procedure for the synthesis of compound (**5**)

5.6.1. 5-(4-(*t*-Butyl)phenyl)-1-naphthaldehyde

5-Bromo-1-naphthaldehyde (500 mg, 2.1 mmol), 4-*t*-butylphenylboronic acid (470 mg, 2.6 mmol), and K_2CO_3 (880 mg, 6.4 mmol) in dioxane (15 mL) and H_2O (3 mL) were degassed and $\text{Pd}(\text{PPh}_3)_4$ (73 mg, 0.06 mmol) was quickly added. Reaction was then refluxed at 100 °C for 5 h then cooled to RT. Solution was dried over magnesium sulfate, filtered, and concentrated.

Chromatography using ISCO max gradient 50% EtOAc/hexane yielded product as a glassy white residue (490 mg, 88% yield); ^1H NMR (300 MHz) (CDCl_3) δ 10.45 (s, 1H), 9.29 (d, J = 6.0 Hz, 1H), 8.24 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.76–7.70 (m, 1H), 7.60–7.51 (m, 4H), 7.42–7.39 (m, 2H), 1.42 (s, 9H); HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{20}\text{NaO}$ ($\text{M} + \text{Na}$) $^+$ 311.1412, found 311.1406.

5.6.2. (5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol

A mixture of 5-(4-(*t*-butyl)phenyl)-1-naphthaldehyde (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 h. 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 °C; ^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 $\text{C}_{21}\text{H}_{22}\text{NaO}$ ($\text{M} + \text{Na}$) $^+$ 313.1568, found 313.1565.

5.6.3. 1-(Azidomethyl)-5-(4-(*t*-butyl)phenyl)naphthalene

(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol (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 °C overnight. Solvents were then evaporated without further purification yielded 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.

5.6.4. (5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanamine (**5**)

1-(Azidomethyl)-5-(4-(*t*-butyl)phenyl)naphthalene (50 mg, crude material) 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 yielded 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 $\text{C}_{21}\text{H}_{23}\text{N}$ ($\text{M} + \text{H}$) $^+$ 290.1903, found 290.1891.

5.7. General procedure for the synthesis of compound (**6**)

5.7.1. 2-(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)acetonitrile

To a solution of (5-(4-(*t*-butyl)phenyl)naphthalen-1-yl)methanol (**5.6.2**) (1.0 g, 3.4 mmol) and Et_3N (0.8 mL, 5.8 mmol) in DCM (25 mL) at 0 °C was slowly added MsCl (0.33 mL, 4.3 mmol). The reaction was stirred at 0 °C for 30 min 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); ^1H 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 $\text{C}_{22}\text{H}_{21}\text{N}$ (M) $^+$ 299.1674, found 299.1672.

5.7.2. 2-(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)ethanamine (**6**)

LAH (1.0M/THF, 0.9 mL) was added drop-wise to a cooled 0 °C solution of 2-(5-(4-(*t*-butyl)phenyl)naphthalen-1-yl)acetonitrile (85 mg, 0.28 mmol) in anhydrous THF (5 mL). The resultant mixture was then refluxed for 7 h. Reaction was cooled to 0 °C 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% $\text{NH}_4\text{OH}/\text{MeOH}/\text{DCM}$ solution yielded product as a pale oil (15 mg, 17% yield); ^1H 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 $\text{C}_{22}\text{H}_{25}\text{N}$ ($\text{M} + \text{H}$) $^+$ 304.2060, found 304.2046.

5.8. General procedure for the synthesis of compound (**7**)

5.8.1. 1-(Bromomethyl)-5-(4-(*t*-butyl)phenyl)naphthalene

(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol (5.6.2) (600 mg, 2.0 mmol) in anhydrous DCM (15 mL) was cooled to 0 °C and PBr_3 (0.4 mL) was added drop-wise. The reaction was stirred at 0 °C for 1 h then quenched with saturated NaHCO_3 and extracted with DCM. Organic layer was collected, dried over magnesium sulfate, and concentrated to yield product as a pale oil (670 mg, 86% yield); ^1H NMR (300 MHz) (CDCl_3) δ 8.21 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.69 (m, 2H), 7.60–7.50 (m, 3H), 7.46–7.36 (m, 3H), 5.06 (s, 2H), 1.45 (s, 9H).

5.8.2. 2-(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)acetonitrile

1-(Bromomethyl)-5-(4-(*t*-butyl)phenyl)naphthalene (200 mg, 0.57 mmol) and KCN (55 mg, 0.85 mmol) in DMSO (6 mL) 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 pale oil (120 mg, 74% yield); ^1H 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 $\text{C}_{22}\text{H}_{21}\text{N}$ (M) $^+$ 299.1674, found 299.1672.

5.8.3. 2-(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)acetimidamide (**7**)

A solution of 2-(5-(4-(*t*-butyl)phenyl)naphthalen-1-yl)acetonitrile (120 mg, 0.4 mmol) in anhydrous Et_2O (2 mL) was cooled to 0 °C and treated with 4 N HCl/dioxane solution (2 mL). Reaction was stirred at 0 °C for 4 h. The mixture was then placed in the refrigerator overnight. The precipitated solids were filtered out then treated with $\text{NH}_4\text{OH}/\text{EtOH}$ (6 mL) and heated to reflux for 6 h. Solvents were then evaporated. Chromatography using ISCO max gradient 20% 3% $\text{NH}_4\text{OH}/\text{MeOH}/\text{DCM}$ solution yielded product as pale solid (37 mg, 29% yield); mp 266–269 °C; ^1H NMR (300 MHz) (CD_3OD) δ 7.96 (m, 2H), 7.68 (m, 1H), 7.59–7.57 (m, 3H), 7.52–7.45 (m, 3H), 7.40 (m, 1H), 4.41 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 171.8, 151.8, 142.9, 139.0, 133.7,

133.5, 130.8, 129.6, 129.5, 128.4, 127.6, 127.4, 126.7, 126.3, 123.2, 54.8, 35.5, 31.8; HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 317.2012, found 317.2019.

5.9. General procedure for the synthesis of compound (**8**)

5.9.1. 1,3-Di-Boc-2-((5-(4-(*t*-butyl)phenyl)naphthalen-1-yl)methyl)guanidine

(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methanol (5.6.2) (106 mg, 0.364 mmol), PPh_3 (100 mg, 0.38 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (132 mg, 0.52 mmol) in anhydrous toluene (3 mL) at 0 °C was added diisopropylazodicarboxylate (0.1 mL, 0.52 mmol) drop-wise over 15 min. Reaction was stirred at RT overnight then 2 drops H_2O were added, and the solution was concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a yellow solid (104 mg, 54% yield); ^1H NMR (400 MHz) (CDCl_3) δ 9.55 (bs, 1H), 9.50 (bs, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.59–7.51 (m, 3H), 7.47–7.43 (m, 2H), 7.39–7.37 (m, 2H), 7.18 (d, J = 4.0 Hz, 1H), 5.77 (s, 2H), 1.46 (s, 9H), 1.43 (s, 9H), 1.20 (s, 9H).

5.9.2. 2-((5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)methyl)guanidine (**8**)

1,3-Di-Boc-2-((5-(4-(*t*-butyl)phenyl)naphthalen-1-yl)methyl)guanidine (20 mg, 0.07 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% $\text{NH}_4\text{OH}/\text{MeOH}/\text{DCM}$ solution yielded product as a white solid (17 mg, 74% yield); mp 160–163 °C; ^1H NMR (400 MHz) (CD_3OD) δ 8.00–7.60 (m, 5H), 7.56–7.36 (m, 5H), 4.89 (s, 2H), 1.41 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.8, 151.7, 142.7, 139.1, 133.6, 132.9, 132.8, 130.8, 128.3, 128.2, 127.3, 126.7, 126.4, 126.3, 126.3, 44.7, 35.5, 31.8; HRMS (ESI): calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3$ ($\text{M} + \text{H}$) $^+$ 332.2121, found 332.2104.

5.10. General procedure for the synthesis of compound (**9**)

5.10.1. 1,3-Di-Boc-2-(2-(5-(4-(*t*-butyl)phenyl)naphthalen-1-yl)ethyl)guanidine

2-(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)ethanamine (5.7.2) (35 mg, 0.12 mmol), 1,3-di-Boc-2-(trifluoromethylsulfonyl)guanidine (55 mg, 0.14 mmol), and Et_3N (0.04 mL, 0.29 mmol) in anhydrous DCM (6 mL) were stirred at RT overnight. Solvents were then evaporated. Chromatography using ISCO max gradient 20% EtOAc/hexane yielded product as a white solid (51 mg, 81% yield); ^1H NMR (300 MHz) (CDCl_3) δ 8.50 (t, J = 3.0 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 7.87 (dd, J = 6.0 Hz, J = 3.0 Hz, 1H), 7.62–7.50 (m, 3H), 7.46–7.33 (m, 4H), 3.80 (m, 2H), 3.43 (t, J = 6.0 Hz, 2H), 1.56 (s, 9H), 1.43 (s, 9H), 1.41 (s, 9H).

5.10.2. 2-(2-(5-(4-(*t*-Butyl)phenyl)naphthalen-1-yl)ethyl)guanidine (**9**)

1,3-Di-Boc-2-(2-(5-(4-(*t*-butyl)phenyl)naphthalen-1-yl)ethyl)guanidine (40 mg, 0.09 mmol) was stirred at RT in a mixture of anhydrous DCM (0.8 mL) and TFA (0.8 mL) overnight. Solvents were then evaporated. Chromatography using ISCO max gradient 15% 3% $\text{NH}_4\text{OH}/\text{MeOH}/\text{DCM}$ solution yielded product as a white solid (29 mg, 96% yield); mp 185 °C; ^1H NMR (300 MHz) (CD_3OD) δ 8.13 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.65–7.55 (m, 3H), 7.45–7.36 (m, 5H), 3.66 (t, J = 6.0 Hz, 2H), 3.46 (t, J = 6.0 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.7, 151.6, 142.6, 139.4, 135.5, 133.7, 133.6, 130.8, 128.1, 127.9, 126.8, 126.7, 126.5, 126.3, 123.7, 43.2, 35.5, 33.3, 31.9; HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{28}\text{N}_3$ ($\text{M} + \text{H}$) $^+$ 346.2278, found 346.2281.

5.11. General procedure for the synthesis of compound (**10**)

5.11.1. 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthaldehyde

To a stirred mixture of 5-bromo-naphthaldehyde (500 mg, 2.21 mmol), diborane (810 mg, 3.19 mmol), and KOAc (800 mg, 6.3 mmol) in anhydrous DMF (10 mL) was added Pd(OAc)₂ (20 mg, 0.09 mmol). Reaction mixture was degassed then heated at 80 °C for 6 h. Reaction was cooled to RT and diluted with EtOAc and washed with brine. Organic layer was collected, dried over magnesium sulfate, and concentrated. Chromatography using ISCO max gradient 15% EtOAc/hexane yielded product as a clear oil (410 mg, 68% yield); ¹H NMR (400 MHz) (CDCl₃) δ 10.40 (s, 1H), 9.42 (d, *J* = 8.0 Hz, 1H), 9.12 (d, *J* = 8.0 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.73–7.69 (m, 2H), 1.46 (s, 12H).

5.11.2. 5-(4-Bromophenyl)-1-naphthaldehyde

A flask containing 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthaldehyde (209 mg, 0.7 mmol), 4-bromiodobenzene (230 mg, 0.8 mmol), and K₂CO₃ (200 mg, 1.4 mmol) in dioxane (8 mL) and H₂O (1.5 mL) was purged with N₂. Pd(PPh₃)₄ (40 mg, 0.03 mmol) was then quickly added and resultant mixture was heated at 100 °C for 5 h. Reaction was cooled to RT, dried over magnesium sulfate, and concentrated. Chromatography using ISCO max gradient 50% EtOAc/hexane yielded product as a light yellow solid (142 mg, 65% yield); ¹H NMR (300 MHz) (CDCl₃) δ 10.50 (s, 1H), 8.15 (d, *J* = 9.0 Hz, 1H), 8.05 (d, *J* = 9.0 Hz, 1H), 7.76 (m, 2H), 7.69–7.60 (m, 3H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.39–7.36 (m, 2H).

5.11.3. (5-(4-Bromophenyl)naphthalen-1-yl)methanol

5-(4-Bromophenyl)-1-naphthaldehyde (140 mg, 0.45 mmol) and NaBH₄ (12 mg, 0.32 mmol) in 95% EtOH/MeOH (8 mL) were stirred at RT for 2 h. Reaction mixture was then filtered and filtrate concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a clear oil (140 mg, quantitative); ¹H NMR (300 MHz) (CDCl₃) δ 8.11 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.56–7.47 (m, 4H), 7.36–7.26 (m, 4H), 5.14 (s, 2H).

5.11.4. (5-(4-Cyclopropylphenyl)naphthalen-1-yl)methanol

(5-(4-Bromophenyl)naphthalen-1-yl)methanol (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 K₃PO₄ (308 mg, 1.45 mmol) were combined in a flask with toluene (3 mL) and H₂O (1 mL) and degassed. Reaction mixture was then refluxed at 100 °C for 3 h. Solution was cooled to RT then diluted with EtOAc and washed with saturated NaHCO₃. Organic layer was dried over sodium sulfate and concentrated. Chromatography using ISCO max gradient 35% EtOAc/hexane yielded product as a brown oil (86 mg, 75% yield); ¹H NMR (400 MHz) (CDCl₃) 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); ¹³C NMR (100 MHz) (CDCl₃) 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 C₂₀H₁₈NaO (M + Na)⁺ 297.1250, found 297.1251.

5.11.5. 2-((5-(4-Cyclopropylphenyl)naphthalen-1-yl)methyl)guanidine (**10**)

To a solution of (5-(4-cyclopropylphenyl)naphthalen-1-yl)methanol (80 mg, 0.292 mmol), PPh₃ (115 mg, 0.584 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (151 mg, 0.438 mmol) in anhydrous toluene (3 mL) at 0 °C was added diisopropylazodicarboxylate (0.09 mL, 0.438 mmol) drop-wise over 15 min. Reaction was stirred for 3 h at RT then 2 drops H₂O were added,

and the solution was concentrated. Solid was then dissolved in DCM and passed through silica column and resulting crude product was then re-dissolved in anhydrous DCM (1.5 mL) and cooled to 0 °C. TFA (1.5 mL) was then added. Reaction was taken off ice bath and stirred at RT for 2 h then solvents were evaporated. Solid was then taken back up in DCM and precipitate was filtered off yielded product as a gummy tan solid (18 mg, 20% yield over 2 steps); ¹H NMR (400 MHz) (CD₃OD) 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); ¹³C NMR (100 MHz) (CD₃OD) 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 C₂₁H₂₂N (M + H)⁺ 316.1808, found 316.1805.

5.12. General procedure for the synthesis of compound (**11**)

5.12.1. 5-(4-Chlorophenyl)-1-naphthaldehyde

A flask containing 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthaldehyde (200 mg, 0.7 mmol), 4-chlorobromobenzene (160 mg, 0.8 mmol), and K₂CO₃ (200 mg, 1.4 mmol) in dioxane (6 mL) and H₂O (1.5 mL) was purged with N₂. Pd(PPh₃)₄ (40 mg, 0.03 mmol) was then quickly added and resultant mixture was heated at 100 °C for 5 h. Reaction was cooled to RT, dried over magnesium sulfate, and concentrated. Chromatography using ISCO max gradient 15% EtOAc/hexane yielded product as a pale solid (160 mg, 84% yield); ¹H NMR (300 MHz) (CDCl₃) δ 10.50 (s, 1H), 8.15 (d, *J* = 9.0 Hz, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.77 (m, 1H), 7.63 (m, 1H), 7.56–7.50 (m, 4H), 7.44–7.14 (m, 2H).

5.12.2. (5-(4-Chlorophenyl)naphthalen-1-yl)methanol

5-(4-Chlorophenyl)-1-naphthaldehyde (160 mg, 0.6 mmol) and NaBH₄ (16 mg, 0.42 mmol) in 95% EtOH/MeOH (10 mL) were stirred at RT for 1 h. Reaction mixture was then filtered and filtrate concentrated. Residue was then taken back up in DCM and washed with saturated NaHCO₃ 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 clear oil (160 mg, quantitative); ¹H NMR (300 MHz) (CDCl₃) δ 8.21 (d, *J* = 9.0 Hz, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.66–7.58 (m, 2H), 7.52–7.48 (m, 6H), 5.23 (s, 2H); ¹³C NMR (100 MHz) (CDCl₃) δ 139.7, 139.4, 136.6, 133.4, 131.9, 131.6, 131.4, 128.5, 127.0, 126.3, 125.8, 125.7, 125.4, 123.6, 63.8; HRMS (ESI): calcd for C₁₇H₁₄ClO (M + H)⁺ 291.0547, found 291.0541.

5.12.3. 1,3-Di-Boc-2-((5-(4-chlorophenyl)naphthalen-1-yl)methyl)guanidine

To a solution of (5-(4-chlorophenyl)naphthalen-1-yl)methanol (50 mg, 0.186 mmol), PPh₃ (73 mg, 0.278 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (96 mg, 0.37 mmol) in anhydrous toluene (3 mL) at 0 °C was added diisopropylazodicarboxylate (0.06 mL, 0.31 mmol) drop-wise over 15 min. Reaction was stirred at RT overnight, and the solution was then concentrated to an oil residue. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a pale solid (46 mg, 48% yield); ¹H NMR (300 MHz) (CDCl₃) δ 8.06 (d, *J* = 9.0 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.61–7.37 (m, 7H), 7.21 (d, *J* = 6.0 Hz, 1H), 5.80 (s, 2H), 1.47 (s, 9H), 1.21 (s, 9H).

5.12.4. 2-((5-(4-Chlorophenyl)naphthalen-1-yl)methyl)guanidine (**11**)

1,3-Di-Boc-2-((5-(4-chlorophenyl)naphthalen-1-yl)methyl)guanidine (46 mg, 0.09 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% NH₄OH/MeOH/DCM solution yielded product as a white solid

(27 mg, 78% yield); mp 106–109 °C; ^1H NMR (300 MHz) (DMSO- d_6) δ 8.08 (m, 2H), 7.75–7.59 (m, 4H), 7.53–7.46 (m, 4H), 4.89 (d, J = 3.0 Hz, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.9, 141.3, 140.7, 134.7, 133.3, 132.8, 132.6, 129.6, 128.4, 127.6, 127.3, 126.8, 123.9, 44.6; HRMS (ESI): calcd $\text{C}_{18}\text{H}_{17}\text{ClN}_3$ ($\text{M} + \text{H}$) $^+$ 310.1106, found 310.1110.

5.13. General procedure for the synthesis of compound (12)

5.13.1. 1,3-Di-Boc-2-((5-(4-bromophenyl)naphthalen-1-yl)methyl)guanidine

To a solution of (5-(4-bromophenyl)naphthalen-1-yl)methanol (5.11.3) (40 mg, 0.128 mmol), PPh_3 (60 mg, 0.23 mmol), and 1,3-bis(*t*-butoxycarbonyl)guanidine (66 mg, 0.26 mmol) in anhydrous toluene (3 mL) at 0 °C was added diisopropylazodicarboxylate (0.04 mL, 0.20 mmol) drop-wise over 15 min. Reaction was stirred at RT overnight, and the solution was then concentrated to an oil residue. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a pale solid (46 mg, 47% yield); ^1H NMR (300 MHz) (CDCl_3) δ 9.60 (bs, 1H), 9.50 (bs, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.66–7.37 (m, 7H), 7.21 (d, J = 6.0 Hz, 1H), 5.78 (s, 2H), 1.47 (s, 9H), 1.22 (s, 9H).

5.13.2. 2-((5-(4-Bromophenyl)naphthalen-1-yl)methyl)guanidine (12)

1,3-Di-Boc-2-((5-(4-bromophenyl)naphthalen-1-yl)methyl)guanidine (34 mg, 0.06 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% $\text{NH}_4\text{OH}/\text{MeOH}/\text{DCM}$ solution yielded product as a white solid (18 mg, 75% yield); mp 124–127 °C; ^1H NMR (300 MHz) (DMSO- d_6) δ 8.02 (m, 2H), 7.75–7.67 (m, 2H), 7.52 (m, 2H), 7.12 (m, 4H), 4.90 (s, 2H); ^{13}C NMR (100 MHz) (CD_3OD) δ 158.9, 141.3, 141.2, 133.2, 133.1, 132.9, 132.8, 132.6, 131.0, 128.3, 127.6, 127.3, 126.8, 124.0, 122.7, 44.6; HRMS (ESI): calcd for $\text{C}_{18}\text{H}_{17}\text{BrN}_3$ ($\text{M} + \text{H}$) $^+$ 354.0600, found 354.0599.

5.14. General procedure for the synthesis of compound (13)

5.14.1. 5-(4-(Trifluoromethyl)phenyl)-1-naphthaldehyde

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 $\text{Pd}(\text{PPh}_3)_4$ (73 mg, 0.06 mmol) was quickly added. Reaction was then refluxed at 100 °C for 5 h then cooled to RT. Solution was dried over magnesium sulfate, filtered, and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a pale solid (560 mg, 88% yield); mp 78–80 °C; ^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.

5.14.2. (5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)methanol

A mixture of 5-(4-(trifluoromethyl)phenyl)-1-naphthaldehyde (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 h. 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 (350 mg, quantitative); mp 98 °C; ^1H NMR (400 MHz) (CDCl_3) δ 8.23 (d, J = 8.5 Hz, 1H), 7.79 (t, J = 15.0, 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.

5.14.3. 2-(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)acetonitrile

(5-(4-(Trifluoromethyl)naphthalen-1-yl)methanol (300 mg, 0.99 mmol) in anhydrous DCM (10 mL) was cooled to 0 °C and PBr_3 (0.14 mL) was added drop-wise. The reaction was stirred at 0 °C for 1 h 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 °C; ^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) δ 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 $\text{C}_{19}\text{H}_{12}\text{F}_3\text{NNa}$ ($\text{M} + \text{Na}$) $^+$ 334.0820, found 334.0823.

5.14.4. 2-(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)acetimidamide (13)

A solution of 2-(5-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)acetonitrile (100 mg, 0.32 mmol) in anhydrous Et_2O (2 mL) was cooled to 0 °C and treated with 4 N HCl/dioxane solution (2 mL). Reaction was stirred at 0 °C for 4 h. The mixture was then placed in the refrigerator overnight. The precipitated solids were filtered out then treated with $\text{NH}_4\text{OH}/\text{EtOH}$ (5 mL) and heated to reflux for 6 h. Solvents were then evaporated. Chromatography using ISCO max gradient 20% 3% $\text{NH}_4\text{OH}/\text{MeOH}/\text{DCM}$ solution yielded product as a pale gummy solid (37 mg, 29% yield); mp ^1H NMR (300 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 $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_2$ ($\text{M} + \text{H}$) $^+$ 329.1260, found 329.1244.

5.15. General procedure for the synthesis of compound (14)

5.15.1. 1,3-Di-Boc-2-((5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine

To a solution of (5-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)methanol (5.14.2) (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 °C was added diisopropylazodicarboxylate (0.04 mL, 0.20 mmol) drop-wise over 15 min. Reaction was stirred at RT overnight, and the solution was then concentrated to an oil residue. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded 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 $\text{C}_{29}\text{H}_{33}\text{F}_3\text{N}_3\text{O}_4$ ($\text{M} + \text{H}$) $^+$ 544.2423, found 544.2431.

5.15.2. 2-((5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (**14**)

1,3-Di-Boc-2-((5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (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% NH₄OH/MeOH/DCM solution yielded product as a white solid (20 mg, 51% yield); mp 198–200 °C; ¹H NMR (400 MHz) (CD₃OD) 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); ¹³C NMR (100 MHz) (CD₃OD) 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 C₁₉H₁₇F₃N₃ (M + H)⁺ 344.1369, found 344.1352.

5.16. General procedure for the synthesis of compound (**15**)

5.16.1. 1-(2-Nitrovinyl)-5-(4-(trifluoromethyl)phenyl)naphthalene

5-(4-(Trifluoromethyl)phenyl)-1-naphthaldehyde (200 mg, 0.67 mmol) and NH₄OAc (60 mg, 0.78 mmol) in nitromethane (3 mL) were heated to reflux for 6 h. Solvents were then evaporated. Chromatography using ISCO max gradient 10% EtOAc/hexane yielded product as a yellow solid (210 mg, 91% yield); ¹H NMR (400 MHz) (CDCl₃) δ 8.82 (d, *J* = 13.4 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 3H), 7.66–7.58 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.42–7.40 (m, 2H); ¹³C NMR (100 MHz) (CDCl₃) δ 143.9, 139.9, 138.9, 136.3, 131.9, 131.8, 130.4, 130.1, 127.9, 127.6, 127.1, 126.5, 125.8, 125.4, 125.3, 123.3.

5.16.2. 2-(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)ethanamine

LAH (1.0M/THF, 2 mL) was added drop-wise to a cooled 0 °C solution of 1-(2-nitrovinyl)-5-(4-(trifluoromethyl)phenyl)naphthalene (210 mg, 0.62 mmol) in anhydrous THF (10 mL). The resultant mixture was then refluxed for 7 h. Reaction was cooled to 0 °C and carefully treated with aqueous NaOH solution and diluted with EtOAc. Solids were filtered off and filtrate washed with 6 N HCl to extract out amine. 6 N HCl solution was then basified with 4 N NaOH solution back to pH 9 and extracted with CHCl₃. Organic layer was then washed with brine, collected, dried over magnesium sulfate, and concentrated yielded product as a pale solid requiring no further purification (50 mg, 26% yield); ¹H NMR (300 MHz) (CDCl₃) δ 8.16 (d, *J* = 9.0 Hz, 1H), 7.80–7.71 (m, 3H), 7.63–7.57 (m, 3H), 7.44–7.37 (m, 3H), 3.36 (m, 2H), 3.23 (m, 2H).

5.16.3. 1,3-Di-Boc-2-(2-(5-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine

2-(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)ethanamine (25 mg, 0.08 mmol), 1,3-di-Boc-2-(trifluoromethylsulfonyl)-guanidine (40 mg, 0.1 mmol), and Et₃N (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 °C; ¹H NMR (300 MHz) (CDCl₃) 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); ¹³C NMR (100 MHz) (CDCl₃) 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 C₃₀H₃₅F₃N₃O₄ (M + H)⁺ 558.2580, found 558.2590.

5.16.4. 2-(2-(5-(4-(Trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine (**15**)

1,3-Di-Boc-2-(2-(5-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine (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% NH₄OH/MeOH/DCM solution yielded product as a white solid (11 mg, 85% yield); mp 240 °C; ¹H NMR (300 MHz) (CD₃OD) 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); ¹³C NMR (100 MHz) (CD₃OD) 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 C₂₀H₁₉F₃N₃ (M + H)⁺ 358.1526, found 358.1535.

5.17. General procedure for the synthesis of compound (**16**)

5.17.1. (5-Bromonaphthalen-1-yl)methanol

To a solution of 5-bromo-1-naphthaldehyde (500 mg, 2.13 mmol) in EtOH (20 mL) was slowly added NaBH₄ (243 mg, 6.39 mmol) and reaction was stirred at RT for 30 min. Acetone (2 mL) was then added and solution was filtered through filter paper. Filtrate was concentrated then re-dissolved in DCM and washed with H₂O. Organic layer was dried over sodium sulfate and concentrated to yield pure product as a white solid (473 mg, 94% yield); mp 100–101 °C; ¹H NMR (400 MHz) (CDCl₃) 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); ¹³C NMR (100 MHz) (CDCl₃) δ 136.7, 132.6, 132.4, 130.1, 127.8, 126.8, 126.6, 126.2, 123.6, 63.6.

5.17.2. (5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methanol

(5-Bromonaphthalen-1-yl)methanol (150 mg, 0.63 mmol), 2-methoxy-4-trifluoromethylphenylboronic acid (167 mg, 0.76 mmol), Pd(OAc)₂ (14 mg, 0.063 mmol), XPhos (60 mg, 0.13 mmol), and K₂CO₃ (262 mg, 1.9 mmol) were combined in a flask with dioxane (5 mL) and H₂O (1.6 mL) and degassed. Reaction mixture was then refluxed at 100 °C for 2 h. Solution was cooled to RT then diluted with EtOAc and washed with saturated NaHCO₃. Organic layer was dried over sodium sulfate and concentrated. Chromatography using ISCO max gradient 35% EtOAc/hexane yielded product as a clear oil (180 mg, 86% yield); ¹H NMR (400 MHz) (CDCl₃) 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); ¹³C NMR (100 MHz) (CDCl₃) 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 C₁₉H₁₅F₃NaO₂ (M + Na)⁺ 355.0916, found 355.0919.

5.17.3. 2-(5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)acetonitrile

To a solution of (5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methanol (180 mg, 0.54 mmol) and Et₃N (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 NaHCO₃. Organic layer was dried over sodium sulfate 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 dried over sodium sulfate and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as clear oil (125 mg, 68% yield over two steps); ¹H NMR (400 MHz) (CDCl₃) 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 $\text{C}_{20}\text{H}_{14}\text{F}_3\text{NO}$ (M^+)⁺ 341.1022, found 341.1019.

5.17.4. 2-(5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethanamine (**16**)

A flask was charged with LAH (15.6 mg, 0.41 mmol) in anhydrous ether (3 mL). To the suspension was added 2-(5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)acetonitrile (70 mg, 0.21 mmol) in anhydrous ether (2 mL) drop-wise. Reaction was stirred at RT for 30 min then placed on an ice bath. H_2O (10 drops) was carefully added in to quench remaining LAH then 1 M 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 dried over sodium sulfate and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM yielded product as clear oil (31 mg, 44% yield); ^1H 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 = 12.0 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 $\text{C}_{20}\text{H}_{19}\text{F}_3\text{NO}$ ($\text{M} + \text{H}^+$)⁺ 346.1413, found 346.1415.

5.18. General procedure for the synthesis of 2-(5-(2-aminoethyl)naphthalen-1-yl)-5-(trifluoromethyl)phenol (**17**)

To a cooled solution of 2-(5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethanamine (28 mg, 0.081 mmol) in anhydrous DCM (4 mL) was added BBr_3 (1.0 M in DCM, 0.41 mL) drop-wise. The solution was then stirred at RT for 3 h 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 dried over sodium sulfate and concentrated. Chromatography using ISCO max gradient 10% MeOH/DCM to yield product as a clear oil (13 mg, 48% yield); ^1H 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 = 12.0 Hz, 2H), 2.96 (t, J = 12.0 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 $\text{C}_{19}\text{H}_{17}\text{F}_3\text{NO}$ ($\text{M} + \text{H}^+$)⁺ 332.1257, found 332.1259.

5.19. General procedure for the synthesis of compound (**18**)

5.19.1. 1,3-Di-Boc-2-((5-bromonaphthalen-1-yl)methyl)guanidine

(5-Bromonaphthalen-1-yl)methanol (**5.17.1**) (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 °C was added diisopropylazodicarboxylate (0.34 mL, 1.74 mmol) drop-wise over 15 min. Reaction was stirred for 3 h at RT then 2 drops H_2O were added, and the solution was concentrated. Chromatography using ISCO max gradient 20% EtOAc/hexane yielded product as a white solid (493 mg, 90% yield); mp 164–165 °C; ^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 = 16.0 Hz, 1H), 7.28 (t, J = 16.0 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 $\text{C}_{22}\text{H}_{29}\text{BrN}_3\text{O}_4$ ($\text{M} + \text{H}^+$)⁺ 478.1336, found 478.1344.

5.19.2. 1,3-Di-Boc-2-((5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine

1,3-Di-Boc-2-((5-bromonaphthalen-1-yl)methyl)guanidine (100 mg, 0.21 mmol), 2-methoxy-4-trifluoromethylphenylboronic acid (55 mg, 0.252 mmol), $\text{Pd}(\text{OAc})_2$ (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 °C for 2 h. Solution was cooled to RT then diluted with EtOAc and washed with saturated NaHCO_3 . Organic layer was dried over sodium sulfate and concentrated. Chromatography using ISCO max gradient 15% EtOAc/hexane yielded 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 $\text{C}_{30}\text{H}_{35}\text{F}_3\text{N}_3\text{O}_5$ ($\text{M} + \text{H}^+$)⁺ 574.2523, found 574.2541.

5.19.3. 2-((5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (**18**)

To a cooled solution of 1,3-di-Boc-2-((5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)methyl)guanidine (55 mg, 0.1 mmol) in anhydrous DCM (1.5 mL) was added TFA (1.5 mL). Reaction was taken off ice bath and stirred at RT for 2 h then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM yielded 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 $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_3\text{O}$ ($\text{M} + \text{H}^+$)⁺ 374.1475, found 374.1470.

5.20. General procedure for the synthesis of compound (**19**)

5.20.1. 1,3-Di-Boc-2-(2-(5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine

2-(5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethanamine (25 mg, 0.073 mmol), 1,3-di-Boc-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 dried over sodium sulfate and concentrated. Chromatography using ISCO max gradient 30% EtOAc/hexane yielded product as a clear oil (37 mg, 88% yield); ^1H NMR (400 MHz) (CDCl_3) δ 11.50 (bs, 1H), 8.50 (bt, J = 12.0 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 $\text{C}_{31}\text{H}_{37}\text{F}_3\text{N}_3\text{O}_5$ ($\text{M} + \text{H}^+$)⁺ 588.2680, found 588.2698.

5.20.2. 2-(2-(5-(2-Methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine (**19**)

To a cooled solution of 1,3-di-Boc-2-(2-(5-(2-methoxy-4-(trifluoromethyl)phenyl)naphthalen-1-yl)ethyl)guanidine (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 h then solvents were evaporated. Chromatography using ISCO max gradient 10% MeOH/DCM yielded product as a clear oil (19 mg, 83% yield); ^1H NMR (400 MHz) (CD_3OD) δ 8.16 (d, J = 8.6 Hz, 1H), 7.66–

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