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SYNTHESIS AND BIOLOGICAL EVALUATION OF INHIBITORS OF BOTULINUM NEUROTOXIN METALLOPROTEASE[Ω]

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Abstract – Based on the lead therapeutic agent NSC 240898, a new series of heterocyclic inhibitors of the BoNT serotype A metalloprotease has been generated. Highlights of the synthetic sequences include Sonogashira couplings of polysubstituted building blocks and gold-catalyzed indole formations. Preliminary structure-activity relationship studies afford detailed insights into the steric and electrostatic properties of the pharmacophore of this molecular scaffold.

INTRODUCTION

Botulinum neurotoxins (BoNTs), produced by bacteria *Clostridium botulinum* are the deadliest of biological toxins.[1,2] Among the seven BoNT serotypes (A-G), BoNT A has been used for the treatment of muscle hyperactivity and spasticity disorders, as well as cosmetic applications,[2] raising the concern of overdosing. Furthermore, BoNTs have been recognized as potential biological weapons.[3] Consequently, they are listed as category A biowarfare agents, and there is an urgent need for therapeutic strategies to counter BoNT intoxication.

BoNT proteins consist of a 100 kDa heavy chain (HC) and a 50 kDa light chain (LC) linked by a disulfide bridge.[4] The HC mediates the binding of BoNTs to the cell membrane at the nerve terminus and delivers the light chain LC into the cytosol. LC acts as a metalloprotease and cleaves components of the SNARE

[Ω]This paper is dedicated to the memory of Dr. John Daly.

(soluble NSF-attachment protein receptors) complex.[5,6] SNARE is critical for the release of acetylcholine into neuromuscular synapses. This process is blocked by the LC, resulting in the paralysis associated with botulism.

Inhibitors of both BoNT HC and LC functions have been identified.[7] For example, a variety of antibiotic and antimalaria agents have been found to inhibit the translocation of BoNTs into the cytosol.[8-11] In 2003, several small molecules were identified as inhibitors of the LC metalloprotease activity. Screening of the National Cancer Institute (NCI) Diversity Set and a series of 4-aminoquinolines led to the identification of the first reported small molecule inhibitors (michellamine B, Q2-15 and NSC 357756; Figure 1) of the BoNT serotype A LC.[12a] Zinc-coordinating hydroxamic acids represent another class of LC inhibitors; however these compounds possess poor efficacy in cells and animals;[12b] 2,4-dichlorocinnamic hydroxamic acid is an example from this class.[12c] More recently, an indole bis-amidine, NSC 240898 (Figure 2), was identified as a potent inhibitor of the BoNT A LC (IC_{50} = 3.0 μM; 75% inhibition at 20 μM concentration) that is active in neurons with no toxicity – thereby constituting a lead for potential therapeutic development.[13a]

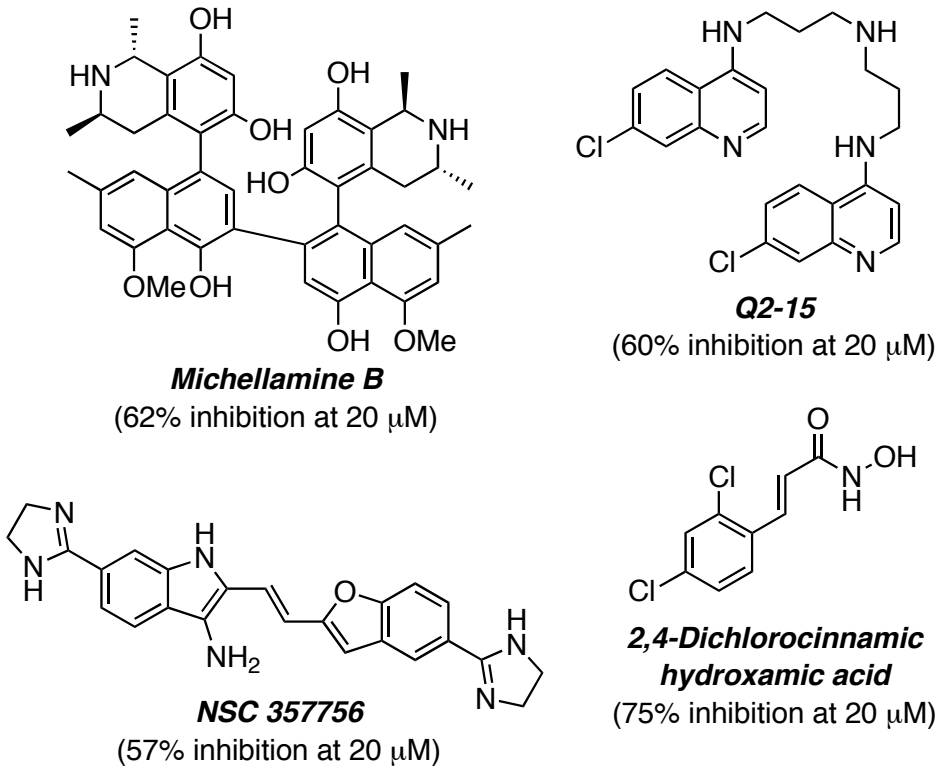


Figure 1. Small molecule inhibitors of the BoNT/A LC.

NSC 240898 and NSC 377363 exhibit a 70-75% inhibition of BoNT/A LC inhibitory activity at 20 μM concentration. We hypothesized that it would be possible to improve this activity further by modifications of the aromatic backbone and the distance between the two amidine functions. Here, we describe the synthesis of a series of NSC 240898 analogues that provide preliminary structure-activity relationships

(SAR) to guide rational design efforts. The scaffold modifications performed during this study are summarized in Figure 3. Specifically, we were interested in benzimidazole analogues of the indole (**A**), substitutions on the benzene rings (**B**, **C**, and **D**), and the incorporation of heteroarenes (**E**). We also planned the replacement of the biaryl ether with a thioether (**F**) to study the interaction of the biaryl hinge region with the binding site.

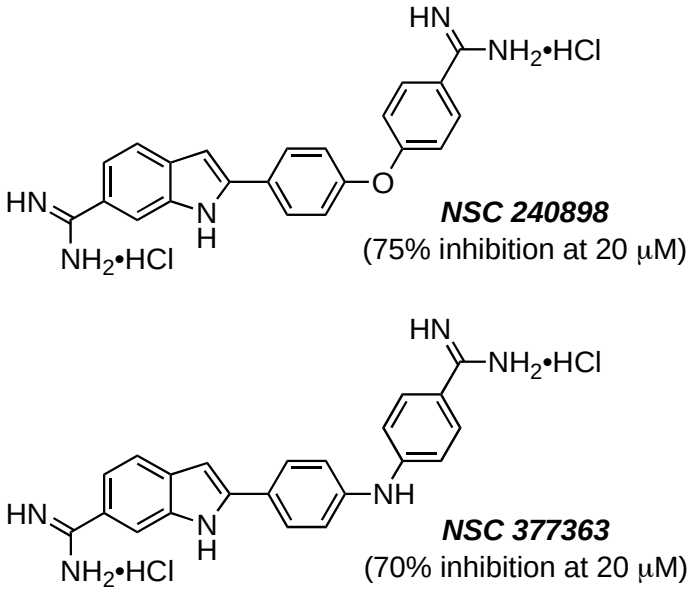


Figure 2. BoNT/A LC inhibitor NSC 240898 and congener NSC 377363.

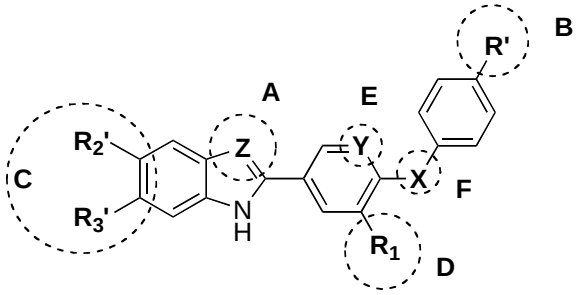
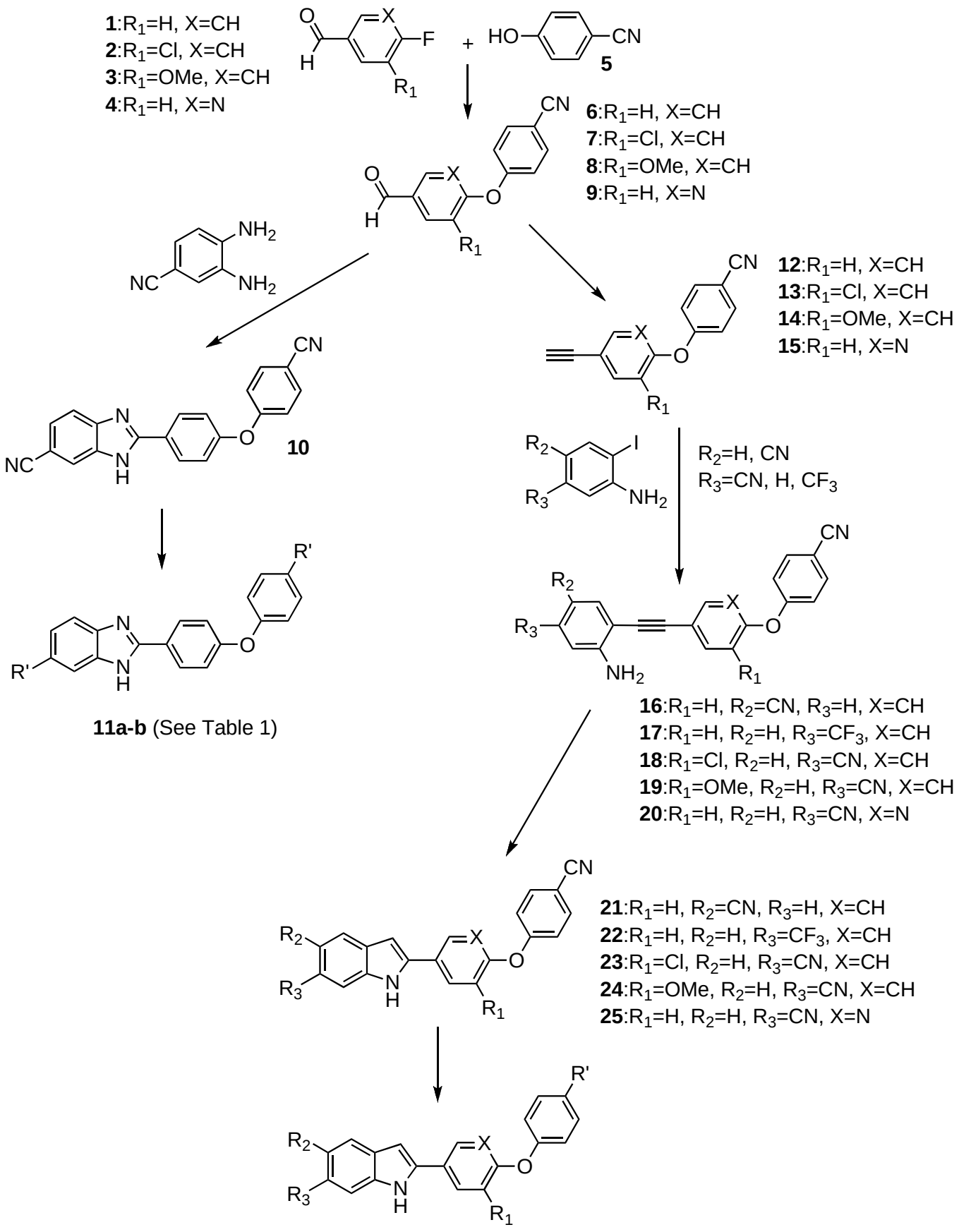


Figure 3. Sites of planned synthetic modifications of the NSC 240898 scaffold.

RESULTS AND DISCUSSION

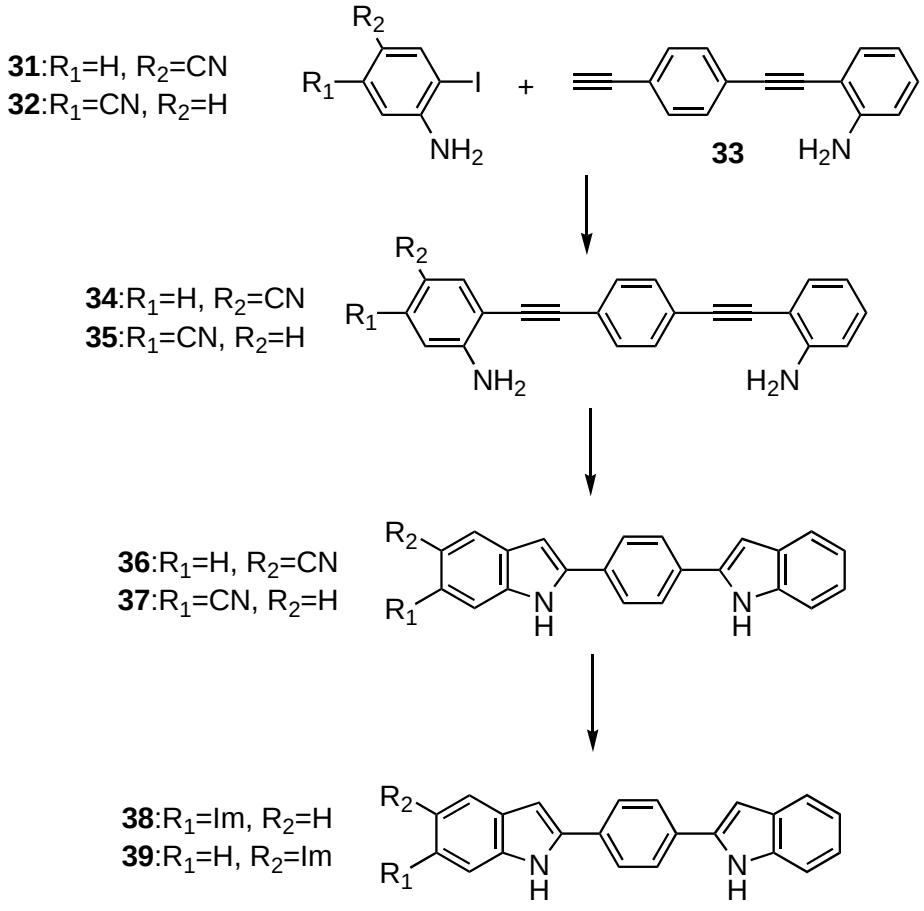
We first synthesized two compound classes: benzimidazoles **11a**-**b** and indoles **26a-b, 27a-b, 28a-b, 29a-b, 30a-b** (Scheme 1 and Table 1). The common intermediates **6** and **9** were prepared by the reaction of **1** or **4** with **5** in the presence of K_2CO_3.[14] For substituted substrates **2** (R_1=Cl, X=CH) and **3** (R_1=OMe, X=CH), Cs_2CO_3 and microwave heating were applied. Condensation of **6** with diaminobenzonitrile



Scheme 1. Synthesis of NSC 240898 analogues (see Table 1).

provided benzimidazole **10**,[15] which was further elaborated to amidine **11a**[16] and imidazoline **11b**.[17] Alternatively, compounds **6-9** were converted to alkynes **12-15**, which underwent Sonogashira coupling[18a] to provide **16-20**. Indole formation catalyzed by Au(I)[18b] proceeded smoothly to provide nitriles **21-25**, which were further derivatized to amidines and imidazolines **26-30**, analogous to the preparations of **11a-b**.

The effect of the diaryl ether segment in the lead structure was explored in more detail with the preparation of bisindole derivatives **38** and **39** (Scheme 2). These compounds were prepared in a Sonogashira coupling from iodoanilines **31** and **32** with alkyne **33**,[19,20] followed by tandem cyclization to the indole and nitrile aminolysis.

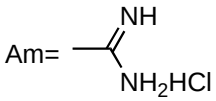


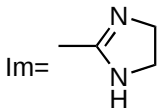
Scheme 2. Synthesis of NSC 240898 analogues (see Table 1).

A summary of the effects of structural modifications on BoNT/A LC inhibitory potency is provided in Table 1. While none of the new analogues were as potent as NSC 240898, relative degrees of inhibition ranging from one third (i.e., of NSC 240898 activity) to nearly equal potency were observed. Comparison of the biological data in Table 1 with the corresponding structures provides a better understanding of the electrostatic and steric requirements for this scaffold in its BoNT/A LC binding site and forms the foundations for future inhibitor refinements.

Table 1. List of synthetic analogues and activity against BoNT A LC (see Schemes 1 and 2).

Compound	*X*	*R'*	R_1	R_2	R_3	*% BoNT/A LC Inhibition (20 μM)****
11a	CH	Am*	—	—	—	24.7 (± 1.5)
11b	CH	Im	—	—	—	34.8 (± 1.4)
26a	CH	Am	H	Am	H	58.8 (± 3.3)
26b	CH	Im**	H	Im**	H	51.4 (± 4.6)
27a	CH	Am	H	H	CF_3	25.2 (± 3.4)
27b	CH	Im	H	H	CF_3	43.3 (± 7.2)
28a	CH	Am	Cl	H	Am	64.4 (± 2.1)
28b	CH	Im	Cl	H	Im	64.8 (± 4.4)
29a	CH	Am	OMe	H	Am	58.0 (± 6.7)
29b	CH	Im	OMe	H	Im	69.8 (± 1.8)
30a	N	Am*	H	H	Am*	52.7 (± 5.5)
30b	N	Im	H	H	Im	46.1 (± 1.2)
38	—	—	Im	H	—	27.4 (± 8.5)
39	—	—	H	Im	—	26.6 (± 5.8)
240898****	CH	Am	H	H	Am	73.5 (± 7.5)





* Formic acid salt

** Acetic acid salt

***All bis-nitrile compounds (**10, 21-25**, **36**, **37**) were inactive.

****NSC 240898 structure with respect to the structures for **26a-b** - **30a-b** shown in Scheme 1.

Changing the substituents at sites **B** and **C** from basic bis-amidines to basic bis-imidazolines had no significant impact on activity (within **a-b** sets of analogues; for example, **28a** vs. **28b** and **29a** vs. **29b**). However, not unexpectedly, replacing the basic amidines with neutral nitrile functions or acidic tetrazoles was not tolerated; in contrast, replacing the amidine group on the indole ring with trifluoromethyl (**27a-b**) resulted in moderately active inhibitors. While our data suggests that a strongly basic amidine or

imidazoline substituent is preferred at the R_3 position (Figure 3), for hydrogen-bonding or ionic interactions with the binding site,[12a,21] it also suggests that there is a degree of binding site plasticity. These results are consistent with recent X-ray co-crystal structures,[22] demonstrating that the BoNT/A LC 370 loop, which is adjacent to the R_3 amidine in the predicted binding mode for NSC 240898,[13] can undergo a conformational flip to present either the polar side chain of Asp370 or the hydrophobic side chain of Phe369 (Figure 4). This reorientation accommodates either basic or hydrophobic inhibitor substituents at the same binding site location, but not an acidic residue as demonstrated by the inactivity of a bis-tetrazole analogue of NSC 240898 (*vide infra*). A binding site plasticity hypothesis is further supported by the fact that switching the amidine from the C-6 position of the indole to the C-5 position (**26a**) results in only a moderate decrease in inhibitory potency.

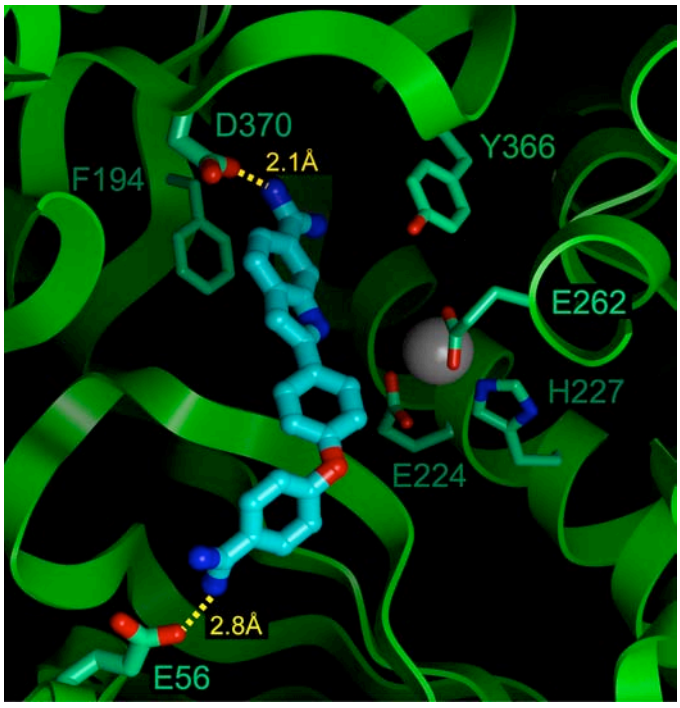


Figure 4. Proposed binding mode for NSC 240898 (shown with cyan carbons). Oxygen atoms are red and nitrogen atoms are blue. The BoNT/A LC backbone is displayed in green ribbons, and the catalytic zinc is gray (space filled). Side chain residues are rendered in stick with green carbons. Hydrogen bonds between NSC 240898 and residues Glu 56 and Asp 370 are displayed as dashed yellow lines.

For analogues **11a-b,** replacing the C-3 carbon of the indole ring with a nitrogen (site **A** in Figure 3), to give the benzimidazole derivative, results in a marked reduction in potency. This is indicative of the presence of a complementary hydrophobic BoNT/A LC contact for the C-3 atom. Similarly, but to a lesser degree, **30a-b** reveal that incorporating a nitrogen in the C-3 position of the central phenyl ring is

not optimal for binding. Again, this is most likely due to unfavorable contacts with a corresponding hydrophobic binding surface. In contrast, substitution on the same position in the central phenyl ring (marked as **D** in Figure 3) with a chloro (**28a-b**) or a methoxy (**29a-b**) group results in a level of BoNT/A LC inhibition that is nearly equipotent to that of NSC 240898. This is an important finding, since it demonstrates that there is available steric volume surrounding this hydrophobic inhibitor binding site, and that this space may be accessed without incurring a dramatic loss in potency.

Analogues **38** and **39** were generated to explore replacing the diaryl ether - amidine portion of NSC 240898 with an indole substituent. Both analogues demonstrated markedly decreased inhibitory potency, most likely due to the loss of the R' amidine, and its complementary H-bonding or ionic contact. Moreover, less favorable steric complementarity between the second indole and the binding site may also contribute to the observed reduction in potency for these compounds.

Finally, a 2D (molecular topology) search of the NCI Open Repository identified an analogue possessing an amine (versus an oxygen) at the biaryl hinge (marked F in Figure 3) of the scaffold. Subsequent biological testing of this derivative, designated NSC 377363, revealed that it was equipotent to the parent (70% inhibition at 20 μM concentration, Figure 2), and thus demonstrated that either a H-bond donor or H-bond acceptor is feasible at this position. In order to shed further light on the biological significance of the diarylether linkage, two thioether analogues, **40a** and **40b** (Figure 5), were prepared.

Nucleophilic aromatic substitution of *p*-fluorobenzaldehyde **1** with thiol **41**[23] provided thioether **42** (Scheme 3). Conversion to the alkyne **43** was followed by a Sonogashira coupling to yield alkyne **44**. In the presence of 5 mol% $AuClPPh_3$ and $AgClO_4$, a dichloromethane solution of **44** led to the desired indole **45**. Conversion of the nitrile to the imidazoline and amidine provided **40a** and **40b**, respectively.

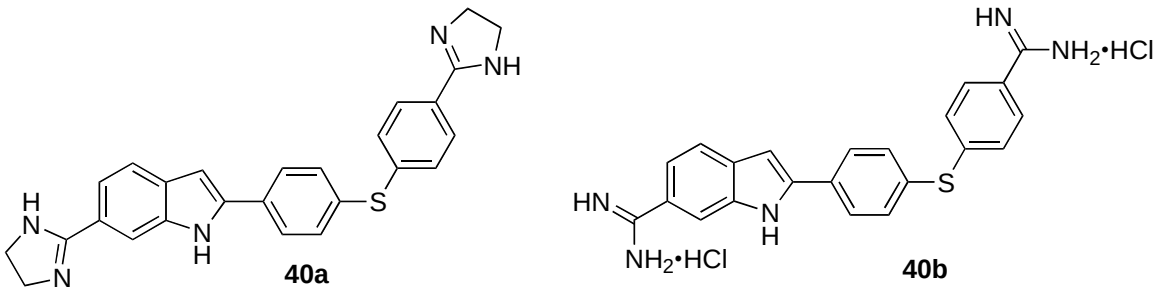
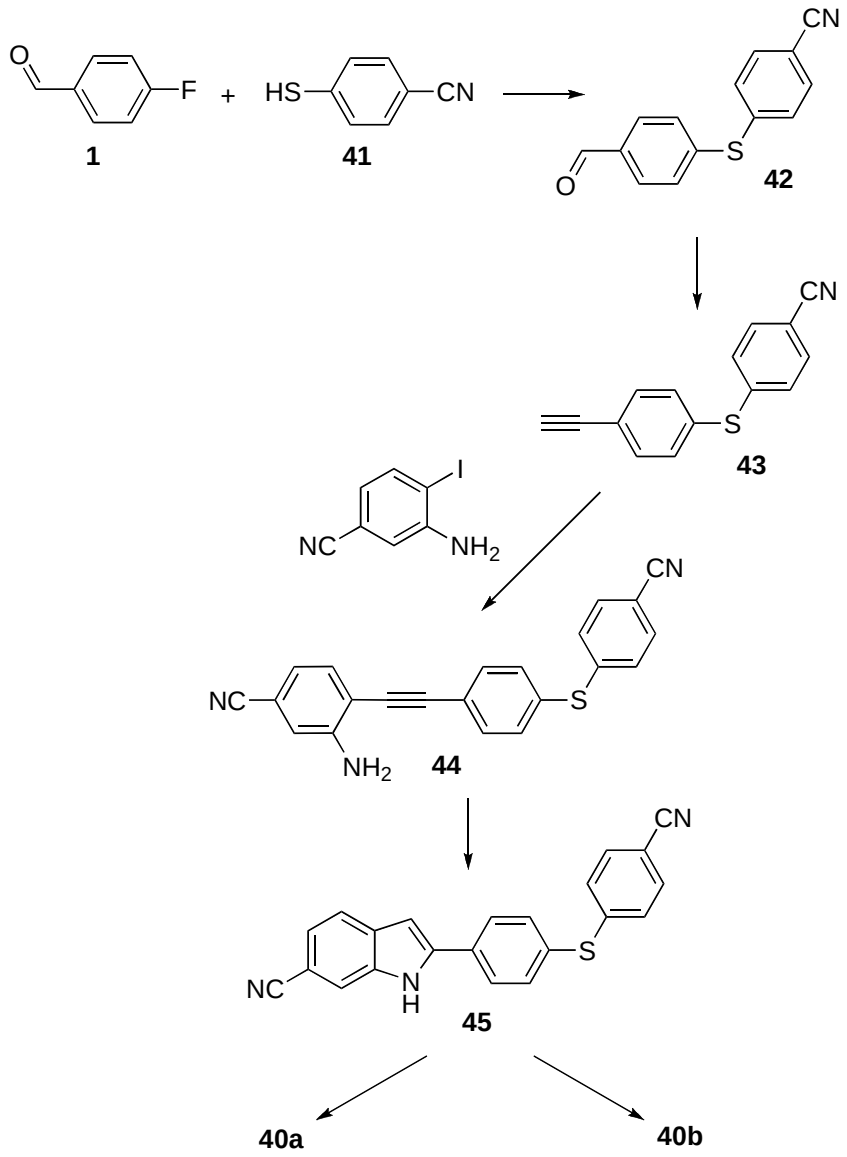


Figure 5. Thioether analogues of NSC 240898.

Biological evaluation of **40a** and **40b** at 20 μM concentrations revealed 80.3 (± 6.7)% and 67.3 (± 3.6)% inhibition of the BoNT/A LC, respectively. While the bis-amidine **40b** is equipotent to the parent, i.e., NSC 240898, the bis-imidazoline **40a** is more active. This surprising finding may indicate that the



Scheme 3. Synthesis of thioether analogues of NSC 240898.

derivative with the imidazoline substituents is binding in a subtly different manner that favors desolvation. Since, for the oxygen analogue of **40a**, the activity is always slightly less (compared to NSC 240898) for the derivative possessing imidazolines, it is hypothesized that the sharper bond angle provided by the sulfur atom of **40a** (versus the oxygen atom at that position) allows for better placement of the larger imidazoline head pieces in the enzyme binding site, such that hydrophobic contacts are improved.

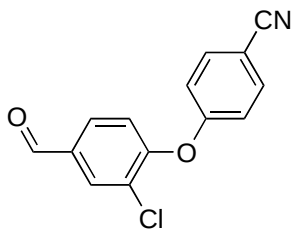
Overall, the SAR provided by these studies will be important for the optimization of the NSC 240898 scaffold during all stages of the development of this potential therapeutic lead. For example, locations where additional steric bulk is tolerated (i.e., substituent size does not significantly decrease potency) delineates inhibitor positions where functional groups can be added to improve target specificity without greatly impacting inhibitory efficacy.

CONCLUSIONS

Based on the NSC 240898 scaffold, a variety of analogues were synthesized by the concise use of transition metal catalyzed cross-couplings and heterocycle annulations. Examination of these derivatives for BoNT/A LC inhibition provides a rich SAR. The bis-amidine substituents of NSC 240898 may be replaced with bis-imidazolines without incurring a significant decrease in potency. In fact, potency for the bulkier bis-imidazolines is improved when the linker atom is a softer sulfur atom, which possesses a bond angle closer to 90°. Furthermore, our findings support an earlier hypothesis that one of the amidine moieties of NSC 240898 interacts with Asp370 located in the 370 loop of the enzyme's substrate cleft. Finally, locations where polar atoms are not tolerated were identified, while a site for increased hydrophobic bulk was located. Identifying such locations in the BoNT/A LC binding site is imperative for prefacing the further optimization of the NSC 240898 lead structure during all phases of development.

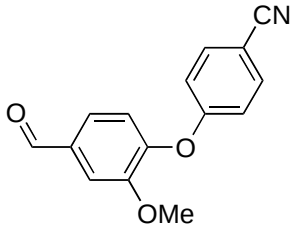
EXPERIMENTAL

General: All moisture-sensitive reactions were performed under an atmosphere of N_2. Glassware was flame dried prior to use. THF and Et_2O were dried by distillation over Na/benzophenone. DCM was dried by distillation over CaH_2. Unless otherwise stated, solvents and reagents were used as received. Analytical thin layer chromatography was performed on pre-coated silica gel 60 F-254 plates and visualization was accomplished with a 254 nm UV light or by staining with an anisaldehyde solution (7.5mL of *p*-anisaldehyde, 25 mL of concentrated H_2SO_4 and 7.5 mL of glacial acetic acid in 675 mL of 95% EtOH) or $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of K_2CO_3 and 2.5 mL of 5% aqueous NaOH in 150 mL of H_2O). Flash chromatography on SiO_2 was used to separate and purify the crude reaction mixtures. Microwave reactions were performed on a Biotage Initiator microwave reactor. NMR spectra were recorded at 300 MHz/75 MHz (^{1}H NMR/^{13}C NMR) at 21 °C. Chemical shifts (δ) are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublet, dt=doublet of triplet, m=multiplet, br=broad, app=apparent). LC/MS analyses were obtained from a Hewlett Packard Series 1100 MSD. Infrared spectra were measured on a Nicolet AVATAR 360 FTIR E.S.P. spectrometer.

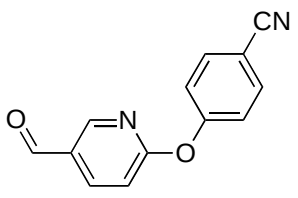


4-(2-Chloro-4-formylphenoxy)benzonitrile (7). A solution of 4-fluoro-3-chlorobenzaldehyde (0.239 g, 1.51 mmol) and 4-cyanophenol (0.182 g, 1.53 mmol) in DMF (4.5 mL) was treated with cesium

carbonate (1.95 g, 6.00 mmol) and irradiated with microwave (180 °C, 40 min). The reaction mixture was poured into water and extracted with EtOAc (3x). The combined organic layers were washed with water (3x) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes: EtOAc = 5:1) afforded 0.256 g (66%) of **7** as a white solid: mp 85.1-87.3 °C; IR (KBr) 3102, 3061, 2839, 2733, 2222, 1907, 1698, 1585, 1484 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.95 (s, 1 H), 8.02 (d, 1 H, *J* = 1.9 Hz), 7.81 (dd, 1 H, *J* = 8.3, 1.9 Hz), 7.68 (d, 2 H, *J* = 8.6 Hz), 7.18 (d, 1 H, *J* = 8.1 Hz), 7.06 (d, 2 H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 189.4, 159.2, 155.5, 134.4, 133.8, 132.0, 129.9, 127.1, 121.2, 118.6, 118.2, 107.5; MS (EI) *m/z* (rel intensity) 63 (44), 75 (61), 102 (28), 164 (27), 193 (22), 194 (24), 220 (14), 257 (100), HRMS (EI) *m/z* calcd for $C_{14}H_8NO_2Cl$ 257.0244, found 257.0236.

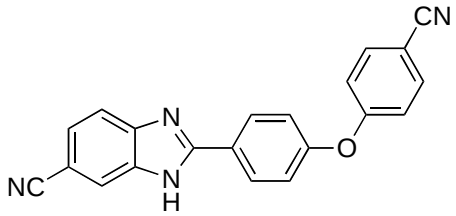


4-(4-Formyl-2-methoxyphenoxy)benzonitrile (8). A solution of 4-fluoro-3-methoxybenzaldehyde (0.493 g, 3.20 mmol) and 4-cyanophenol (0.389 g, 3.25 mmol) in DMF (9.5 mL) was treated with cesium carbonate (4.158 g, 12.8 mmol) and irradiated with microwave (180 °C, 40 min). The reaction mixture was poured into water and extracted with EtOAc (3x). The combined organic layers were washed with water (3x) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes: EtOAc = 5:1) afforded 0.554 g (69%) of **8** as a white solid: mp 116.7-125.7 °C; IR (KBr) 3096, 2943, 2834, 2741, 2226, 1686, 1586, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.96 (s, 1 H), 7.61 (d, 2 H, *J* = 9.4 Hz), 7.55 (d, 1 H, *J* = 1.5 Hz), 7.51 (dd, 1 H, *J* = 8.0, 1.7 Hz), 7.18 (d, 1 H, *J* = 8.0 Hz), 6.99 (d, 2 H, *J* = 9.4 Hz), 3.87 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 190.8, 160.5, 152.0, 148.3, 134.4, 134.1, 125.2, 121.7, 118.6, 117.5, 111.5, 106.4, 56.0; MS (EI) *m/z* (rel intensity) 63 (40), 75 (26), 79 (40), 102 (40), 116 (17), 119 (26), 127 (14), 253 (100); HRMS *m/z* calcd for $C_{15}H_{11}NO_3$ 253.0739, found 253.0729.

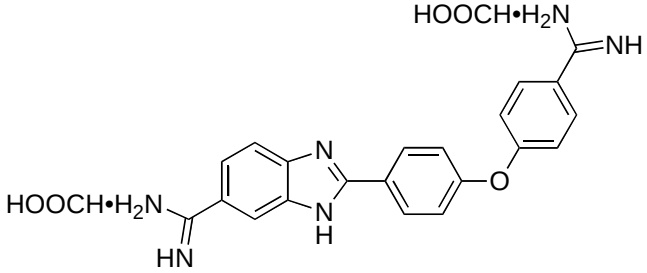


4-(5-Formylpyridin-2-yloxy)benzonitrile (9). A solution of 6-bromo-3-pyridinecarboxaldehyde (1.07 g, 5.75 mmol) and 4-cyanophenol (0.690 g, 5.75 mmol) in DMF (34.5 mL) was treated with potassium carbonate (3.16 g, 22.9 mmol) and heated to 150 °C for 3 h. The reaction mixture was poured into water

and extracted with EtOAc (3x). The combined organic layers were washed with water (3x) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes: EtOAc = 4:1 to 2:1) afforded 0.990 g (77%) of **9** as a yellow solid: mp 132.0-134.1 °C (DCM); IR (KBr) 3424, 3099, 2925, 2867, 2230, 1697, 1609, 1593, 1571, 1505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.99 (s, 1 H), 8.60 (d, 1 H, *J* = 2.0 Hz), 8.24 (dd, 1 H, *J* = 8.5, 2.3 Hz), 7.72 (d, 2 H, *J* = 8.8 Hz), 7.29 (d, 2 H, *J* = 8.8 Hz), 7.13 (d, 1 H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 189.2, 165.9, 156.5, 152.2, 139.4, 134.0, 128.5, 122.6, 118.5, 112.9, 109.2; MS (EI) *m/z* (rel intensity) 142 (35), 168 (50), 195 (45), 224 (100); HRMS *m/z* calcd for $C_{13}H_8N_2O_2$ 224.0586, found 224.0579.

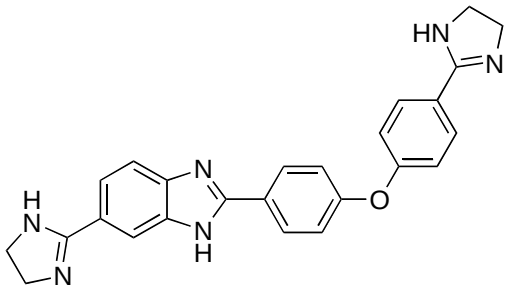


2-(4-(4-Cyanophenoxy)phenyl)-3*H*-benzo[*d*]imidazole-5-carbonitrile (10). A suspension of **6**[14] (0.224 g, 1.00 mmol) in 40% aqueous $NaHSO_3$ (2.0 mL) was stirred at rt for 2 h followed by the treatment with a suspension of 3,4-diaminobenzonitrile (0.173 g, 1.30 mmol) in EtOH (5.0 mL). The mixture was refluxed for 14 h. The reaction mixture was then poured into water and filtered. The precipitate was redissolved in EtOAc, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes:THF = 3:1) afforded 0.305 g (91%) of **10** as a yellow solid: mp 226.0 °C (decomp.) (THF); IR (KBr) 3426, 3269, 3068, 2230, 1623, 1596, 1500, 1483 cm^{-1}; ^1H NMR (DMSO-d_6) δ 13.45 (s, 1 H), 8.30-8.23 (m, 2 H), 8.12 (app br s, 1 H), 7.88 (d, 2 H, *J* = 8.7 Hz), 7.73 (app d, 1 H, *J* = 8.1 Hz), 7.58 (dd, 1 H, *J* = 8.3, 1.2 Hz), 7.35-7.29 (m, 2H), 7.22 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR (DMSO-d_6) δ 160.1, 156.8, 153.7, 134.8, 129.1, 125.7, 120.2, 120.0, 119.0, 118.6, 106.0, 104.0, 159.2, 155.5, 134.4, 133.8, 132.0, 129.9, 127.1, 121.2, 118.6, 118.2, 107.5; MS (EI) *m/z* (rel intensity) 206 (12), 336 (100), HRMS (EI) *m/z* calcd for $C_{21}H_{12}N_4O$ 336.1011, found 336.1001.

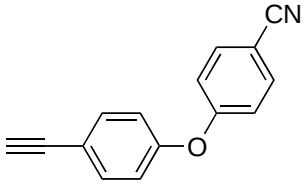


2-(4-(4-Carbamimidoylphenoxy)phenyl)-3*H*-benzo[*d*]imidazole-5-carboximidamide diformate (11a). A solution of **10** (30.4 mg, 0.0903 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 10 mL) at 0 °C was bubbled with

HCl gas for 30 min and then stirred at rt for 24 h. The solvent was evaporated and EtOH (6.0 mL) was added. The solution was bubbled with NH_3 gas at rt for 10 min. After 24 h stirring at rt, the mixture was bubbled with NH_3 gas again and stirred for another 24 h. The solvent was evaporated and the residue was co-evaporated with EtOH (x2). The residue was redissolved in EtOH (2 mL) and filtered. The filtrate was poured into Et_2O (10 mL) and treated with formic acid (final concentration of HCOOH ~ 50% v/v) and stirred 30 min at rt. The precipitate was collected by filtration to yield 11.0 mg (28%) of **11a** as a yellow solid: mp 232.6 °C (decomp.) (DMSO); IR (KBr) 3368, 3136, 1674, 1627, 1599, 1481, 1451, 1401 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.47 (s, 2 H), 9.30 (s, 1 H), 9.26 (s, 1 H), 8.45 (d, 2 H, J = 8.3 Hz), 7.97 (d, 1 H, J = 8.4 Hz), 7.83-7.70 (m, 1 H), 7.57 (app s, 2 H), 7.40 (app s, 2 H); 7.34-7.24 (m, 2 H), 7.23 (app s, 2 H); ^{13}C NMR (DMSO-d_6) δ 166.1, 164.8, 163.0, 160.7, 167.5, 164.4, 143.2, 130.8, 129.9, 129.6, 122.9, 122.4, 121.6, 119.9, 119.2, 118.6, 118.4; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_6O$ 371.1620, found 371.1594.

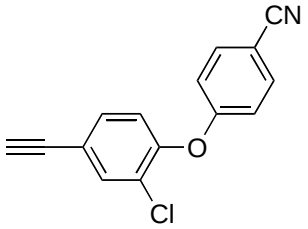


6-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-(4-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy)phenyl)-1*H*-benzo[*d*]imidazole (11b). A mixture of sulfur (1.42 mg, 0.0433 mmol) and **10** (30.0 mg, 0.0892 mmol) was treated with ethylene diamine (0.5 mL), then irradiated with microwave at 110 °C for 30 min. The mixture was suspended in water and filtered, and the solid was rinsed with water (3x). The solid was then dried under vacuum, affording **11b** (30.7 mg, 81%) as a yellow solid: mp 252.9 °C (decomp.) (DMSO); IR (KBr) 3340, 1603, 1507, 1486, 1451 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.26-8.07 (m, 2 H), 8.06-7.98 (m, 1 H), 7.91-7.81 (m, 2 H), 7.79-7.65 (m, 1 H), 7.64-7.49 (m, 1 H), 7.22-7.00 (m, 4 H), 3.64 (s, 4 H), 3.60 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 164.4, 163.0, 157.8, 157.6, 152.5, 142.9, 139.2, 129.2, 129.0, 128.6, 126.3, 125.6, 124.0, 121.6, 120.3, 119.0, 118.5, 49.6, 49.3; HRMS (ESI) m/z calcd for $C_{25}H_{23}N_6O$ 423.1933, found 423.1928.

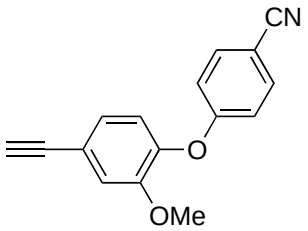


4-(4-Ethynylphenoxy)benzonitrile (12). A solution of lithium diisopropylamide (2.0 M in heptane, diethylbenzene and THF, 1.40 mL, 2.80 mmol) in THF (18.6 mL) at -78 °C was treated with $TMSCHN_2$

(2.0 M in ether, 1.40 mL, 2.80 mmol). The mixture was stirred at -78 °C for 30 min and a solution of **6**[14] (0.519 g, 2.32 mmol) in THF 4.7 mL was added. The mixture was stirred at -78 ºC for 1 h and heated to reflux for 3 h. The reaction mixture was quenched with cold water and extracted with Et_2O (3x). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 10:1) afforded 0.279 g (55%) of **12** as a white solid: mp 87.2-87.9 ºC (acetone); IR (KBr) 3097, 3063, 2224, 1608, 1592, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (d, 2 H, *J* = 9.0 Hz), 7.54 (d, 2 H, *J* = 8.8 Hz), 7.07-6.99 (m, 4 H), 3.10 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 160.8, 155.4, 134.3, 134.2, 120.0, 118.8, 118.7, 118.5, 106.6, 82.7; MS (EI) *m/z* (rel intensity) 190 (25), 219 (100); HRMS (EI) *m/z* calcd for $C_{15}H_9NO$ 219.0684, found 219.0678.

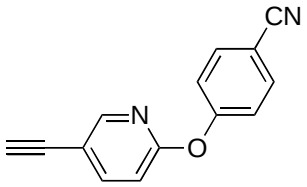


4-(4-Ethynyl-2-chlorophenoxy)benzonitrile (13). To a solution of lithium diisopropylamide (2.0 M in heptane, diethylbenzene and THF, 0.493 mL, 0.986 mmol) in THF (6.6 mL) was added $TMSCHN_2$ (2.0 M in ether, 0.493 mL, 0.986 mmol). This mixture was stirred for 30 min at -78 °C, then a solution of **7** (0.211 g, 0.817 mmol) in dry THF (1.65 mL) was added. This mixture was stirred for 1 h at -78 °C and heated to reflux for 3.5 h. The reaction mixture was quenched with water and extracted with Et_2O (3x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes:EtOAc = 10:1) afforded **13** (0.103 g, 50%) as a white solid: ^1H NMR ($CDCl_3$) δ 7.65-7.61 (m, 3 H), 7.43 (dd, 1 H, *J* = 8.4, 1.9 Hz), 7.05 (d, 1 H, *J* = 8.4 Hz), 6.98 (d, 2 H, *J* = 7.0 Hz), 3.15 (s, 1 H); LCMS (*m/z*) 254.1

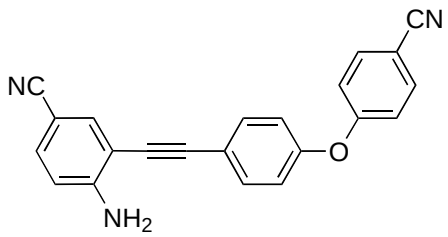


4-(4-Ethynyl-2-methoxyphenoxy)benzonitrile (14). A solution of lithium diisopropylamide (2.0 M in heptane, diethylbenzene and THF, 0.374 mL, 0.748 mmol) in dry THF (4.97 mL) was treated with $TMSCHN_2$ (0.374 mL, 0.748 mmol). This mixture was stirred for 30 min at -78 °C, then a solution of **8** (0.139 g, 0.621 mmol) in dry THF (1.56 mL) was added. This mixture was stirred for 1 h at -78 °C and heated to reflux for 3.5 h. The reaction mixture was quenched with water and extracted with Et_2O (3x).

The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes:EtOAc = 10:1) afforded **14** (0.104 g, 76%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.59 (d, 2 H, *J* = 9.5 Hz), 7.17-7.14 (m, 2 H), 7.02 (d, 1 H, *J* = 8.6 Hz), 6.95 (d, 2 H, *J* = 9.5 Hz), 3.80 (s, 3 H), 3.11 (s, 1 H); LCMS (*m/z*) 250.2.

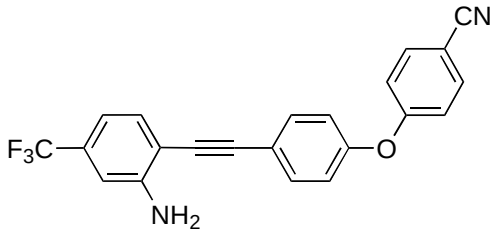


4-(5-Ethynylpyridin-2-yloxy)benzonitrile (15). A solution of lithium diisopropylamide (2.0 M in heptane, diethylbenzene and THF, 2.65 mL, 5.30 mmol) in THF (35.3 mL) at -78 °C was treated with $TMSCHN_2$ (2.0 M in ether, 2.65 mL, 5.30 mmol). The mixture was stirred at -78 °C for 30 min and a solution of **9** (0.990 g, 4.41 mmol) in THF 9.00 mL was added. The mixture was stirred at -78 ºC for 1h and heated to reflux for 3 h. The reaction mixture was quenched with cold water and extracted with Et_2O (3x). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 7:1) afforded 0.475 g (49%) of **15** as a white solid: mp 121.9-123.9 ºC (THF); IR (KBr) 3426, 3250, 3098, 061, 2231, 2224, 1606, 1589, 1562, 1503, 1476 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.30 (d, 1 H, *J* = 1.9 Hz), 7.84 (dd, 1H, *J* = 8.3, 2.3 Hz), 7.71 (d, 2 H, *J* = 8.8 Hz), 7.25 (d, 2 H, *J* = 8.9 Hz), 6.98 (dd, 1 H, *J* = 8.5, 0.5 Hz), 3.20 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 161.6, 157.2, 150.9, 143.0, 13.8, 121.8, 118.5, 115.1, 111.9, 108.2, 80.4, 79.7; MS (EI) *m/z* (rel intensity) 102 (40), 192 (50), 220 (100); HRMS (EI) *m/z* calcd for $C_{14}H_8N_2O$ 220.0637, found 220.0630.

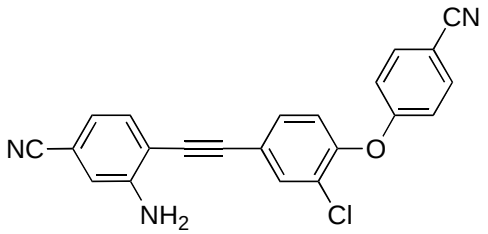


4-Amino-3-((4-(4-cyanophenoxy)phenyl)ethynyl)benzonitrile (16). A solution of **12** (16.1 mg, 0.0734 mmol) and 4-amino-3-iodobenzonitrile (28.7 mg, 0.117 mmol) in MeCN (0.5 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (2.58 mg, 0.00367 mmol) and CuI (1.54 mg, 0.00807 mmol). The mixture was degassed again and treated with Et_3N (51.1 µL, 0.367 mmol). The reaction mixture was heated to reflux for 4 h, diluted with Et_2O and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:EtOAc = 3:1 to 2:1 to 1:1) yielded 21.7 mg (89%) of **16** as a white solid: mp 168.5-171.2 ºC (acetone); IR (KBr) 3457, 3360, 3216, 2224, 2211, 1628, 1594, 1554, 1495

cm^{-1}; ^{1}H NMR (acetone-d_6) δ 7.79 (d, 2 H, J = 9.0 Hz), 7.69 (d, 2 H, J = 8.9 Hz), 7.63 (d, 1 H, J = 2.0 Hz), 7.41 (dd, 1 H, J = 8.6, 2.0 Hz), 7.19-7.13 (m, 4 H), 6.90 (d, 1 H, J = 8.6 Hz), 6.07 (br s, 2 H); ^{13}C NMR (acetone-d_6) δ 161.6, 156.3, 153.5, 136.9, 135.2, 134.4, 133.9, 120.9, 120.1, 119.9, 119.5, 119.0, 114.9, 107.7, 107.4, 99.2, 95.3; MS (EI) m/z (rel intensity) 199 (75), 216 (100), 239 (35), 278 (30), 322 (25), 335 (95); HRMS (EI) m/z calcd for $C_{22}H_{13}N_3O$ 335.1059, found 335.1043.

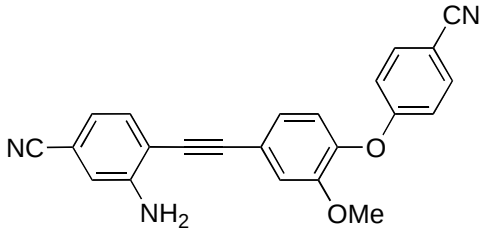


4-(4-((2-Amino-4-(trifluoromethyl)phenyl)ethynyl)-2-chlorophenoxy)benzonitrile (17). A solution of **12** (0.570 g, 2.60 mmol) and 2-iodo-5-trifluoromethylphenylamine[24] (0.672 g, 2.34 mmol) in MeCN (18 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (91.2 mg, 0.130 mmol) and CuI (54.5 mg, 0.286 mmol). The mixture was degassed again and treated with Et_3N (1.81 mL, 13.0 mmol). The reaction mixture was heated to reflux for 1.5 h, diluted with Et_2O and filtered thru a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:THF = 6:1 to 4:1) yielded 0.993 g (100%) of **17** as a yellow solid: mp 121.9-123.8 ºC (THF); IR (KBr) 3482, 3379, 2232, 1621, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2 H, J = 8.9 Hz), 7.58 (d, 2 H, J = 8.8 Hz), 7.45 (d, 1 H, J = 8.1 Hz), 7.10-7.04 (m, 4 H), 7.00-6.93 (m, 2 H), 4.46 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 160.8, 155.4, 148.1, 134.3, 133.6, 132.5, 131.3 (q, J = 31.5 Hz), 120.1, 119.3, 118.8, 118.5, 114.0 (q, J = 3.7 Hz), 110.8, 110.7 (q, J = 3.8 Hz), 106.5, 95.6, 85.0; MS (EI) m/z (rel intensity) 84 (45), 248 (10), 276 (15), 378 (100); HRMS (EI) m/z calcd for $C_{22}H_{13}N_2OF_3$ 378.0980, found 378.0993.

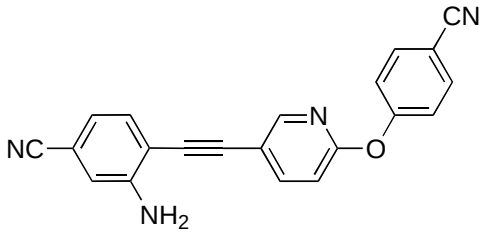


3-Amino-4-((4-(4-cyanophenoxy)-3-chlorophenyl)ethynyl)benzonitrile (18). A solution of **13** (0.170 g, 0.670 mmol) and 3-amino-4-iodobenzonitrile (0.229 g, 0.925 mmol) in MeCN (5.3 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (0.027 g, 0.039 mmol) and CuI (0.011 g, 0.0090 mmol). The mixture was degassed again and treated with Et_3N (0.540 mL, 3.89 mmol), then heated to reflux for 4 h. The reaction mixture was diluted with Et_2O and filtered through a pad of Celite and Florisil (1:1 v/v). The pad was

washed with Et_2O (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes:EtOAc 3:1 to 2:1 to 1:1, all with 1% Et_3N) afforded **18** (0.131 g, 53%) as a yellow solid: mp 169.4-172.9 °C; IR (KBr) 3465, 3394, 3098, 3075, 2223, 1604, 1481, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, 1 H, *J* = 1.9 Hz), 7.65 (d, 2 H, *J* = 8.6 Hz), 7.48 (dd, 1 H, *J* = 8.4, 1.9 Hz), 7.42 (d, 1 H, *J* = 8.3 Hz), 7.11 (d, 1 H, *J* = 8.4 Hz), 7.02-6.99 (m, 4 H), 4.49 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 160.4, 150.0, 148.2, 134.5, 134.2, 133.0, 131.8, 127.1, 122.5, 121.04, 121.01, 118.9, 118.7, 117.7, 117.2, 113.1, 111.6, 106.9, 95.7, 85.9; MS (EI) *m/z* (rel intensity) 267 (10), 369 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{12}N_3OCl$ 369.0669, found 369.0654.

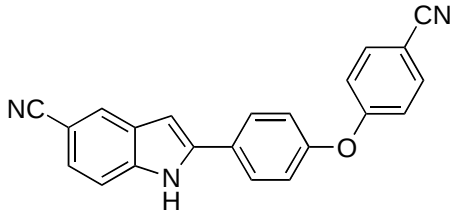


3-Amino-4-((4-(4-cyanophenoxy)-3-methoxyphenyl)ethynyl)benzonitrile (19). A solution of **14** (0.114 g, 0.457 mmol) and 3-amino-4-iodobenzonitrile (0.205 g, 0.840 mmol) in MeCN (3.5 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (0.018 g, 0.026 mmol) and CuI (0.011 g, 0.058 mmol). The mixture was degassed again and treated with Et_3N (0.360 mL, 2.59 mmol), then heated to reflux for 4 h. The reaction mixture was diluted with Et_2O and filtered through a pad of Celite and Florisil (1:1 v/v). The pad was washed with Et_2O (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes:EtOAc 3:1 to 2:1 to 1:1, all with 1% Et_3N) afforded **19** (0.133 g, 79%) as a yellow solid: mp 126.6-132.6 °C; IR (KBr) 3475, 3376, 3090, 2955, 2222, 1620, 1445, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60 (d, 2 H, *J* = 9.6 Hz), 7.44 (d, 1 H, *J* = 8.4 Hz), 7.21-7.18 (m, 2 H), 7.08 (dd, 1 H, *J* = 7.8, 0.9 Hz), 7.02-6.94 (m, 4 H), 4.50 (s, 2 H), 3.83 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 161.4, 151.5, 148.1, 143.6, 134.1, 132.8, 125.2, 122.6, 121.0, 120.6, 119.0, 117.1, 116.9, 116.1, 112.7, 112.1, 105.8, 97.3, 84.7, 56.1; MS (EI) *m/z* (rel intensity) 212 (10), 365 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{15}N_3O_2$ 365.1164, found 365.1178.

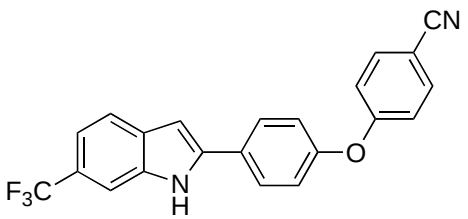


3-Amino-4-((6-(4-cyanophenoxy)pyridin-3-yl)ethynyl)benzonitrile (20). A solution of **15** (0.332 g, 1.51 mmol) and 4-amino-3-iodobenzonitrile (0.334 g, 1.372 mmol) in MeCN (10 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (48.2 mg, 0.0686 mmol) and CuI (28.8 mg, 0.151 mmol). The mixture was degassed again and treated with Et_3N (0.954 mL, 6.86 mmol). The reaction mixture was heated to reflux

for 2 h, diluted with THF and filtered thru a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (Tolene:THF = 3:1, then repurified with DCM:THF = 10:1) yielded 0.4529 g (98%) of **20** as a yellow solid: mp 209.2-212.8 ºC (THF); IR (KBr) 3474, 3372, 3061, 2224, 1623, 1604, 1583, 1550, 1500, 1467 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.42 (dd, 1 H, J = 2.4, 0.6 Hz), 8.11 (dd, 1 H, J = 8.7, 2.4 Hz), 7.86 (d, 2 H, J = 9.0 Hz), 7.46 (d, 1 H, J = 7.8 Hz), 7.40 (d, 2 H, J = 9.0 Hz), 7.19 (dd, 1 H, J = 8.4 , 0.6 Hz), 7.12 (d, 1 H, J = 1.2 Hz), 6.94 (dd, 1 H, J = 8.1, 1.5 Hz); ^{13}C NMR (DMSO-d_6) δ 161.3, 157.2, 150.2, 150.0, 143.1, 134.3, 132.8, 122.0, 118.9, 118.5, 116.4, 115.4, 112.2, 111.8, 109.5, 107.3, 93.2, 87.8; MS (EI) *m/z* (rel intensity) 205 (40), 219 (90), 234 (30), 262 (100), 336 (80); HRMS (EI) *m/z* calcd for $C_{21}H_{12}N_4O$ 336.1011, found 336.1008.

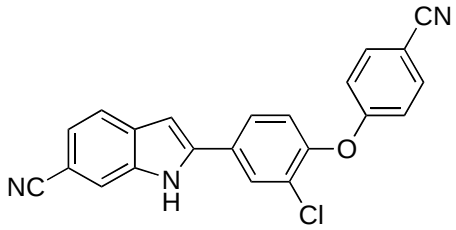


2-(4-(4-Cyanophenoxy)phenyl)-1*H*-indole-5-carbonitrile (21). A solution of **16** (15.0 mg, 0.0446 mmol) in DCM (1.0 mL) was treated with $AuClPPh_3$ (1.0 mg, 0.00223 mmol) followed by $AgClO_4$ (1.0 mg, 0.00491 mmol). The mixture was stirred in the dark at rt for 4 h and filtered thru a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x). The organic phases were combined and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Tolene:Et_2O = 4:1) yielded 13.2 mg (88%) of **21** as a yellow solid: mp 260 ºC (decomp.) (acetone); IR (KBr) 3385, 3123, 2961, 2924, 2220, 1597, 1493 cm^{-1}; ^1H NMR (acetone-d_6) δ 11.28 (br s, 1 H), 8.04-7.96 (m, 2 H), 7.80 (d, 2 H, J = 8.9 Hz), 7.63-7.55 (m, 2 H), 7.42 (dd, 1 H, J = 8.2, 1.6 Hz), 7.26 (d, 2 H, J = 8.8 Hz), 7.20 (d, 2 H, J = 8.9 Hz), 7.06 (dd, 1 H, J = 2.2, 0.7 Hz); ^{13}C NMR (acetone-d_6) δ 161.9, 156.0, 140.6, 139.9, 135.2, 129.8, 126.2, 125.2, 121.5, 120.9, 119.2, 119.0, 113.1, 107.1, 103.6, 100.4; MS (EI) *m/z* (rel intensity) 222 (20), 335 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{13}N_3O$ 335.1059, found 335.1062.

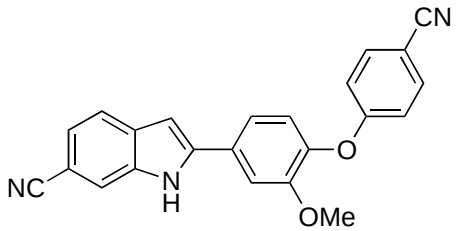


4-(4-(6-(Trifluoromethyl)-1*H*-indol-2-yl)phenoxy)benzonitrile (22). A solution of **17** (0.103 g, 0.271 mmol) in DCM (6.0 mL) was treated with $AuClPPh_3$ (6.08 mg, 0.0134 mmol) followed by $AgClO_4$ (6.080 mg, 0.0298 mmol). The mixture was stirred in the dark at rt for 14 h and filtered thru a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x). The organic phases were combined and

concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:THF = 4:1) yielded 90.2 mg (87%) of **22** as a yellow solid: mp 198.5-201.6 ºC (THF); IR (KBr) 3357, 2228, 1598, 1491, 1460 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.05 (s, 1 H), 7.98 (d, 2 H, J = 9.0 Hz), 7.84 (d, 2 H, J = 9.0 Hz), 7.73-7.67 (m, 2 H), 7.31-7.20 (m, 2 H), 7.15 (d, 2 H, J = 9.0 Hz), 7.00 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 160.8, 154.5, 140.2, 135.9, 134.6, 131.3, 128.4, 127.5, 121.8 (q, J = 30.8 Hz), 120.73, 120.66, 118.7, 118.3, 115.8-115.6 (m), 108.4 (q, J = 4.5 Hz), 105.4, 99.0; MS (EI) m/z (rel intensity) 75 (32), 102 (100), 248 (20), 276 (20), 378 (16); HRMS (EI) m/z calcd for $C_{22}H_{13}F_3N_2O$ 378.0980, found 378.0973.

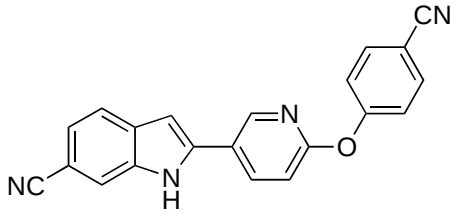


2-(4-(4-Cyanophenoxy)-3-chlorophenyl)-1*H*-indole-6-carbonitrile (23). A solution of **18** (0.0399 g, 0.108 mmol) in DCM (2.4 mL) was treated with $AuClPPh_3$ (0.0024 g, 0.0054 mmol) followed by $AgClO_4$ (0.0024 g, 0.0012 mmol). The mixture was stirred in the dark at rt for 24 h, diluted with THF, and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (4x), and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (toluene:THF = 8:1) afforded **23** (0.032 g, 81%) as a yellow solid: mp 116.3 °C (decomp.); IR (KBr) 3284, 3059, 2958, 2222, 1724, 1598, 1459 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.24 (s, 1 H), 8.22 (s, 1 H), 7.98-7.84 (m, 4 H), 7.70 (app d, 1 H, J = 8.2 Hz), 7.42 (app d, 1 H, J = 8.4 Hz), 7.34 (app d, 1 H, J = 8.2 Hz), 7.17-7.11 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ 160.3, 149.4, 139.6, 136.0, 134.8, 131.7, 130.1, 127.7, 126.3, 124.9, 123.4, 122.4, 121.3, 120.6, 118.6, 117.4, 116.1, 105.7, 103.1, 100.6; MS (EI) m/z (rel intensity) 183 (55), 262 (75), 369 (100); HRMS (EI) m/z calcd for $C_{22}H_{12}N_3OCl$ 369.0669, found 369.0663.

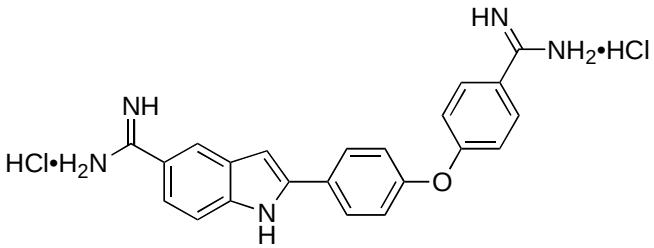


2-(4-(4-Cyanophenoxy)-3-methoxyphenyl)-1*H*-indole-6-carbonitrile (24). A solution of **19** (0.108 g, 0.295 mmol) in DCM (7.2 mL) was treated with $AuClPPh_3$ (0.0072 g, 0.0161 mmol) followed by $AgClO_4$ (0.0072 g, 0.0353 mmol). The mixture was stirred in the dark at rt for 6.5 h, diluted with THF, and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (4x), and the filtrate was concentrated under reduced pressure. The product was suspended in DCM and filtered, and the filter

was washed with DCM (3x). Purification by chromatography on SiO_2 (toluene:THF = 10:1) yielded **24** (0.0569 g, 53%) as a yellow solid: mp 139.4 °C (decomp.); IR (KBr) 3319, 3057, 2961, 2220, 1596, 1498 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.17 (s, 1 H), 7.86 (s, 1 H), 7.79 (d, 2 H, J = 9.0 Hz), 7.75 (d, 1 H, J = 1.8 Hz), 7.72 (d, 1 H, J = 8.1 Hz), 7.59 (dd, 1 H, J = 8.1, 1.5 Hz), 7.34 (dd, 1 H, J = 9.3, 1.5 Hz), 7.31 (d, 1 H, J = 8.1 Hz), 7.16 (d, 1 H, J = 1.5 Hz), 7.02 (d, 2 H, J = 8.7, 2.7 Hz), 3.85 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 161.4, 151.7, 141.8, 141.2, 135.9, 134.5, 131.8, 129.9, 123.1, 122.3, 121.1, 120.7, 118.9, 118.8, 116.5, 115.9, 110.8, 104.5, 102.7, 100.1, 56.0; MS (EI) *m/z* (rel intensity) 192 (5), 365 (100); HRMS (EI) *m/z* calcd for $C_{23}H_{15}N_3O_2$ 365.1164, found 365.1174.

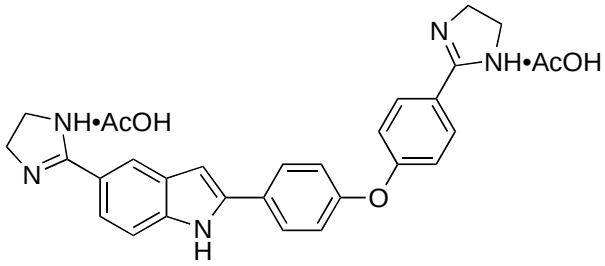


2-(6-(4-Cyanophenoxy)pyridin-3-yl)-1*H*-indole-6-carbonitrile (25). A solution of **20** (185 mg, 0.550 mmol) in MeCN (21.5 mL) in DMF (0.715 mL) was treated with $PdCl_2$ (103 mg, 0.578 mmol). The mixture was stirred at rt for 24 h and filtered thru a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x). The organic phases were combined and concentrated under reduced pressure. Purification by chromatography on SiO_2 (toluene:THF = 10:1) yielded 58.3 mg (32%) of **25** as a yellow solid: mp 256.0 ºC (decomp., THF); IR (KBr) 3140, 3051, 1671, 1599, 1539, 1454, 1406 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.80 (s, 1 H), 9.51 (s, 2 H), 9.37 (s, 2 H), 9.32 (s, 2 H), 9.14 (s, 2 H), 8.88 (d, 1 H, J = 1.8 Hz), 7.98 (s, 1 H), 7.95 (d, 2 H, J = 8.7 Hz), 7.71 (d, 1 H, J = 8.4 Hz), 7.58 (s, 1 H), 7.45 (d, 1 H, J = 9.9 Hz), 7.41 (d, 2 H, J = 8.4 Hz), 7.30 (d, 1 H, J = 8.7 Hz), 7.24 (s, 2 H), 7.11 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 167.0, 165.5, 163.4, 162.2, 158.6, 145.3, 139.0, 138.1, 136.6, 132.9, 130.6, 124.3, 121.7, 120.7, 120.6, 119.3, 112.8, 112.6, 100.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{13}N_4O$ 337.1089, found 337.1058.

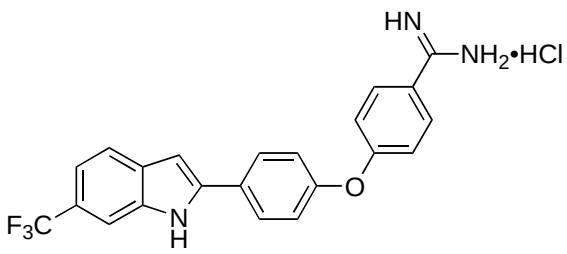


2-(4-(4-Carbamimidoylphenoxy)phenyl)-1*H*-indole-5-carboximidamide dihydrochloride (26a). A solution of **21** (13.2 mg, 0.0394 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 4.4 mL) at 0 ºC was bubbled with HCl gas for 30 min. The mixture was stirred at rt for 20 h and the solvent was removed. The residue was redissolved in EtOH (2.7 mL) and bubbled with NH_3 gas for 20 min at rt. The mixture was stirred for 24 h, re-bubbled with NH_3 gas and stirred for another 24 h. The solvent was evaporated and the residue was

co-evaporated with EtOH (x2). The residue was redissolved in EtOH (1.0 mL) and filtered. The filtrate was poured into Et_2O (5.0 mL) and bubbled with HCl for 1 min. After 30 min stirring, the precipitate was decanted, washed with Et_2O (2x) and dried under vacuum to afford 13.3 mg (76%) of **26a** as a yellow solid: mp 254 ºC (decomp.) (EtOH-Et_2O); IR (KBr) 3144, 1669, 1600, 1517, 1479 cm^{-1}; ^1H NMR (CD_3OD) δ 9.21 (br s, 1 H), 9.06 (br s, 2 H), 8.74 (br s, 1 H), 8.53 (br s, 2 H), 8.12 (d, 1 H, *J* = 1.2 Hz), 7.94 (d, 2 H, *J* = 8.8 Hz), 7.85 (d, 2 H, *J* = 8.9 Hz), 7.61 (d, 1 H, *J* = 8.6 Hz), 7.56 (dd, 1 H, *J* = 8.6, 1.8 Hz), 7.24-7.15 (m, 4 H), 7.01 (s, 1 H); ^{13}C NMR (CD_3OD) δ 169.2, 167.5, 164.0, 156.5, 142.0, 141.4, 131.4, 130.4, 130.1, 128.6, 123.5, 122.3, 121.9, 121.8, 120.0, 119.2, 113.0, HRMS (ESI) *m/z* calcd for $C_{22}H_{20}N_5O$ 370.1668, found 370.1642.

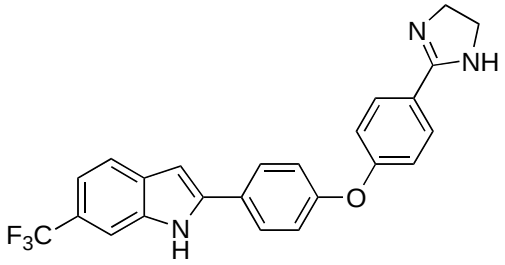


5-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-(4-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy)phenyl)-1*H*-indole diacetate (26b). A solution of **21** (17.2 mg, 0.0513 mmol) and sulfur (0.81 mg, 0.0253 mmol) in ethylenediamine 0.5 mL was irradiated with microwave at 110 °C for 30 min. The product was precipitated out with water (5.0 mL). The precipitation was collected by filtration, washed with water (x3) and dried under vacuum to afford 16.2 mg of crude product. A fraction of this crude product was purified by reverse-phase HPLC (MeOH-1% aq. AcOH) to yield **26b** as a sticky yellow solid: ^1H NMR (DMSO-d_6) δ 11.74 (s, 1 H), 8.01-7.95 (m, 1 H), 7.94-7.88 (m, 2 H), 7.64 (dd, 2 H, *J* = 8.6, 1.4 Hz), 7.38 (d, 1 H, *J* = 8.8 Hz), 7.18-7.11 (m, 2 H), 7.10-7.05 (m. 2 H), 6.94-6.90 (m, 1H), 3.61 (s, 4 H), 3.58 (s, 4 H), 1.81 (s, 6 H); LC-MS (ESI) *m/z* 422.2; MS (EI) *m/z* (rel intensity) 207 (40), 392 (20), 421 (40); HRMS (EI) *m/z* calcd for $C_{26}H_{23}N_5O$ 421.1903, found 421.1922.

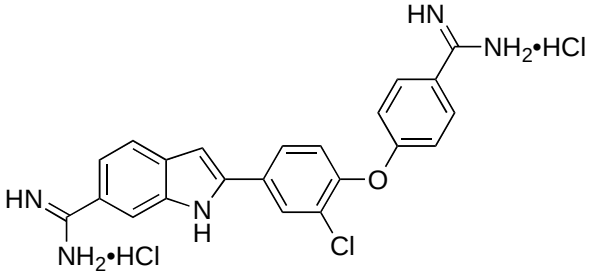


4-(4-(6-(Trifluoromethyl)-1*H*-indol-2-yl)phenoxy)benzimidamide hydrochloride (27a). A solution of **22** (30.0 mg, 0.0793 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 10 mL) at 0 ºC was bubbled with HCl gas for 30 min. The mixture was stirred at rt for 24 h and the solvent was removed. The residue was redissolved in EtOH (6.0 mL) and bubbled with NH_3 gas for 20 min at rt. The mixture was stirred for 24 h, re-bubbled

with NH_3 gas and stirred for another 24 h. The solvent was evaporated and the residue was co-evaporated with EtOH (x2). The residue was redissolved in EtOH (2.0 mL) and filtered thru a pad of SiO_2. The filtrate was poured into Et_2O (10 mL) and bubbled with HCl for 1 min. After 30 min stirring, the precipitate was decanted, washed with Et_2O (2x) and dried under vacuum to afford 23.8 mg (70%) of **27a** as a white solid: mp 206.8 ºC (decomp.; EtOH-Et_2O); IR (KBr) 3126, 1673, 1600, 1513, 1478, 1401 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.38 (s, 1 H), 9.39 (s, 1 H), 9.21 (s, 1 H), 8.18 (d, 1 H, J = 8.8 Hz), 8.05 (app dd, 2 H, J = 8.7, 2.3 Hz), 7.92 (d, 2 H, J = 8.7 Hz), 7.75-7.68 (m, 2 H), 7.51 (app s, 1 H), 7.35-7.15 (m, 4 H), 7.05-7.01 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 164.8, 161.4, 154.8, 140.2, 135.9, 131.2, 130.7, 128.2, 127.6, 122.3, 121.6 (q, J = 30.7 Hz), 120.7, 120.5, 117.8, 117.7, 115.8-115.5 (m), 108.5 (q, J = 3.7 Hz), 98.8, MS (EI) *m/z* (rel intensity) 125 (100), 199 (90), 273 (75), 285 (60), 396 (55); HRMS (EI) *m/z* calcd for $C_{22}H_{16}F_3N_3O$ 395.1245, found 395.1239.

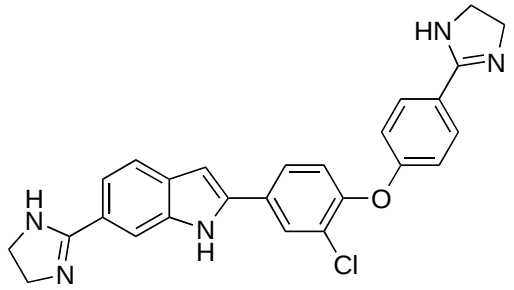


2-(4-(4-(4,5-Dihydro-1*H*-imidazol-2-yl)phenoxy)phenyl)-6-(trifluoromethyl)-1*H*-indole (27b). A mixture of sulfur (0.846 mg, 0.0215 mmol) and **22** (20.0 mg, 0.0529 mmol) was treated with ethylene diamine (0.5 mL), then irradiated with microwave at 130 °C for 30 min. The mixture was suspended in water and filtered, and the solid was rinsed with water (3x). The solid was then dried under vacuum, affording **27b** (14.2 mg, 42%) as a sticky yellow solid: IR (Neat) 3222, 1603, 1563, 1506, 1492, 1461 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.03 (s, 1 H), 7.94 (d, 2 H, J = 9.0 Hz), 7.86 (d, 2 H, J = 9.0 Hz), 7.72, 7.67 (s, 1 H), 7.28 (d, 1 H, J = 9.0 Hz), 7.19(d, 2 H, J = 9.0 Hz), 7.10 (d, 2 H, J = 9.0 Hz), 7.00 (s, 1 H), 3.66 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 163.0, 158.1, 156.1, 140.4, 135.8, 131.3, 129.1, 127.3, 127.2, 126.0, 123.6, 121.6 (q, J = 30.7 Hz), 120.6, 119.6, 118.0, 115.8-115.5 (m), 108.3 (q, J = 4.5 Hz); MS (EI) *m/z* (rel intensity) 177 (20), 196 (22), 378 (15), 392 (45), 421 (100); HRMS (EI) *m/z* calcd for $C_{24}H_{18}N_3OF_3$ 421.1402, found 421.1391.

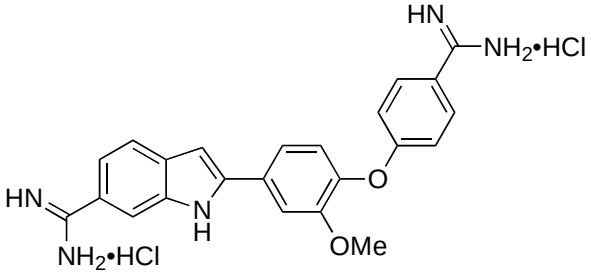


2-(4-(4-Carbamimidoylphenoxy)-3-chlorophenyl)-1*H*-indole-6-carboximidamide dihydrochloride (28a). A suspension of **23** (0.0210 g, 0.0440 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 6.9 mL) at 0 °C was

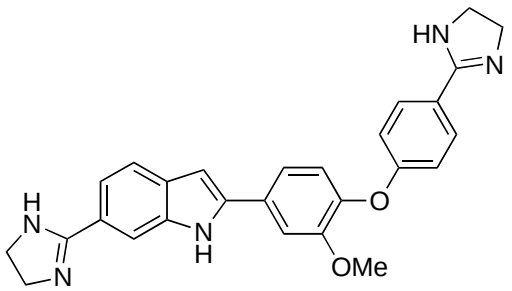
bubbled with HCl gas for 30 min. The mixture was stirred at rt for 20 h and the solvent was evaporated. The residue was redissolved in EtOH (3.4 mL) and bubbled with NH_3 gas for 20 min at rt. The mixture was stirred at rt for 24 h, rebubbled with NH_3 gas, and stirred for another 24 h. The solvent was evaporated and the remaining NH_3 was removed by coevaporating with EtOH (2x). The residue was redissolved in EtOH (2 mL) and filtered. The filtrate was suspended in Et_2O and bubbled with HCl gas for 1 min. After 30 min stirring, the precipitate was filtered out, washed with Et_2O (2x) and dried under vacuum, affording **28a** (0.0120 g, 46%) as a sticky green solid: IR (KBr) 3142, 2221, 1672, 1477, 1255 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.57 (s, 1 H), 9.36 (s, 1 H), 9.32 (s, 1 H), 9.14 (s, 3 H), 9.02 (s, 3 H), 8.42 (s, 1 H), 8.08 (app d, 1 H, J = 8.8 Hz), 7.95 (app s, 1 H), 7.89 (app d, 2 H, J = 8.3 Hz), 7.75 (app d, 1 H, J = 8.3 Hz), 7.44 (m, 2 H), 7.27-7.10 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ 166.5, 164.8, 161.0, 149.5, 139.7, 136.3, 132.4, 130.7, 130.2, 127.8, 126.5, 126.3, 123.4, 122.4, 120.6, 120.5, 118.9, 116.6, 112.2, 100.3; MS (ESI) m/z calcd for $C_{22}H_{18}ClN_5O$ 403.1, found 404.0.



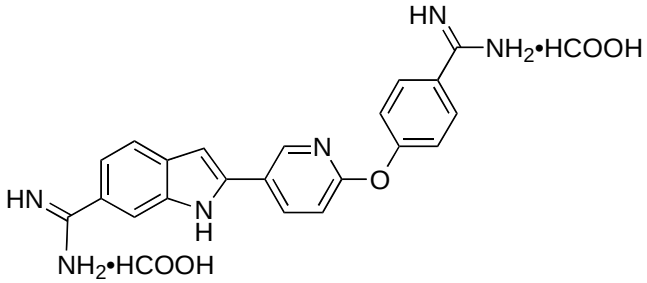
6-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(4-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy)-3-chlorophenyl)-1*H*-indole (28b). A mixture of sulfur (0.00240 g, 0.0470 mmol) and **23** (0.061 g, 0.164 mmol) was treated with ethylenediamine (0.5 mL) and irradiated with microwave at 110 °C for 30 min. The mixture was suspended in water and filtered, and the solid was rinsed with water (3x). The solid was then dried under vacuum, affording **28b** (0.057 g, 77%) as a yellow solid: mp 205.6 °C (decomp.); IR (KBr) 3212, 2937, 2868, 1608, 1487, 1246, 824 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.98 (s, 1H), 8.17 (app s, 1 H), 7.92-7.83 (m, 4 H), 7.54 (app s, 2 H), 7.27 (d, 1 H, J = 8.5 Hz), 7.04-7.01 (m, 3 H), 3.63 (s, 4 H), 3.58 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 164.7, 162.9, 158.1, 150.1, 137.6, 136.7, 130.1, 129.9, 129.1, 127.1, 125.9, 125.7, 125.6, 123.9, 122.3, 119.6, 119.1, 116.6, 110.5, 99.8, 49.6, 49.3; MS (EI) m/z (rel intensity) 383 (25), 412 (30), 426 (25), 455 (100); HRMS (EI) m/z calcd for $C_{26}H_{22}N_5OCl$ 455.1513, found 455.1525.



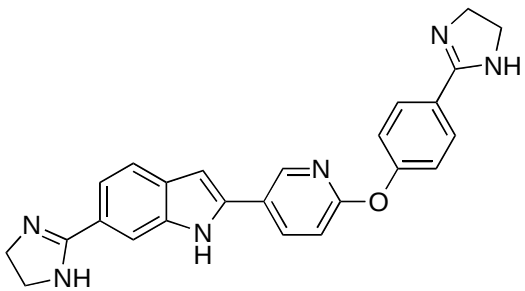
2-(4-(4-Carbamimidoylphenoxy)-3-methoxyphenyl)-1*H*-indole-6-carboximidamide dihydrochloride (29a). A suspension of **24** (0.0220 g, 0.0610 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 7.4 mL) at 0 °C was bubbled with HCl gas for 30 min. The mixture was stirred at rt for 20 h and the solvent was evaporated. The residue was redissolved in EtOH (4.6 mL) and bubbled with NH_3 gas for 20 min at rt. The mixture was stirred at rt for 24 h, bubbled again with NH_3 gas, and stirred for another 24 h. The solvent was evaporated and the remaining NH_3 was removed by coevaporating with EtOH (2x). The residue was redissolved in EtOH (2 mL) and filtered. The filtrate was suspended in Et_2O and bubbled with HCl gas for 1 min. After 30 min stirring, the precipitate was filtered out, washed with Et_2O (2x) and dried under vacuum, affording **29a** (0.0255 g, 89%) as a green solid: mp 221.7 °C (decomp.); IR (KBr) 3158, 1672, 1480, 1402, 1272 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.60 (s, 1 H), 9.31 (app s, 2 H), 9.09 (s, 3 H), 9.03 (s, 3 H), 7.95 (s, 1 H), 7.89 (s, 1 H), 7.84 (app d, 2 H, J = 8.8 Hz), 7.73 (app d, 1 H, J = 8.3 Hz), 7.67 (dd, 1 H, J = 8.2, 1.7 Hz), 7.46-7.43 (m. 2 H), 7.28 (s, 1 H), 7.05 (app d, 2 H, J = 8.7 Hz), 3.87 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 166.7, 164.9, 162.2, 151.7, 141.9, 141.5, 136.1, 132.16, 130.5, 130.0, 123.0, 121.2, 120.2, 120.23, 120.18, 118.9, 118.8, 115.7, 112.1, 111.2, 99.6, 56.0; HRMS (ESI) *m/z* calcd for $C_{23}H_{22}N_5O_2$ 400.1774, found 400.1755.



6-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-(4-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy)-3-methoxyphenyl)-1*H*-indole (29b). A mixture of sulfur (0.00210 g, 0.0411 mmol) and **24** (0.0308 g, 0.0821 mmol) was treated with ethylenediamine (0.5 mL) and irradiated with microwave at 110 °C for 30 min. The mixture was suspended in water and filtered, and the solid was rinsed with water (3x). The solid was then dried under vacuum, affording **29b** (0.0275 g, 72%) as a yellow solid: mp 194.8 °C (decomp.); IR (KBr) 3213, 2940, 2870, 1607, 1500, 1261, 1234 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.75 (s, 1 H), 7.87 (s, 1 H), 7.76 (app d, 2 H, J = 8.7 Hz), 7.68 (app s, 1 H), 7.53-7.51 (m, 3 H), 7.19 (app d, 1 H, J = 8.1 Hz), 7.00 (app s, 1 H), 6.90 (app d, 2 H, J = 8.7 Hz), 3.85 (s, 3 H), 3.62 (s, 4 H), 3.56 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 164.8, 163.1, 159.4, 151.7, 142.5, 139.2, 136.5, 130.2, 129.9, 128.8, 124.8, 124.0, 122.4, 119.4, 119.0, 118.2, 115.4, 110.4, 110.3, 99.2, 55.9, 49.5; MS (EI) *m/z* (rel intensity) 196 (21), 422 (19), 451 (100); HRMS (EI) *m/z* calcd for $C_{27}H_{25}N_5O_2$ 451.2008, found 451.1988.

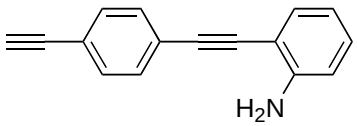


2-(6-(4-Carbamimidoylphenoxy)pyridin-3-yl)-1*H*-indole-6-carboximidamide diformate (30a). A solution of **25** (30.0 mg, 0.0892 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 10 mL) at 0 °C was bubbled with HCl gas for 30 min and then stirred at rt for 24 h. The mixture was bubbled with HCl gas again and stirred for another 24 h at rt. The solvent was evaporated and EtOH (6.0 mL) was added. The solution was bubbled with NH_3 gas at rt for 10 min. After 24 h stirring at rt, the mixture was bubbled with NH_3 gas again and stirred for another 24 h. The solvent was evaporated and the residue was co-evaporated with EtOH (x2). The residue was redissolved in EtOH (1 mL) and filtered. The filtrate was treated with formic acid (final concentration of HCOOH ~ 50% v/v) and stirred 30 min at rt. Ether (10 mL) was added and the precipitate was collected by filtration to yield 30.5 mg (74%) of **30a** as a yellow solid: mp 232.6 °C (DMSO, dec.); IR (KBr) 3368, 3136, 1674, 1627, 1599, 1481, 1451, 1401 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.47 (s, 2 H), 9.30 (s, 1 H), 9.26 (s, 1 H), 8.45 (d, 2 H, J = 8.3 Hz), 7.97 (d, 1 H, J = 8.4 Hz), 7.83-7.70 (m, 1 H), 7.57 (app s, 2 H), 7.40 (app s, 2 H); 7.34-7.24 (m, 2 H), 7.23 (app s, 2 H); ^{13}C NMR (DMSO-d_6) δ 166.1, 164.8, 163.0, 160.7, 167.5, 164.4, 143.2, 130.8, 129.9, 129.6, 122.9, 122.4, 121.6, 119.9, 119.2, 118.6, 118.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_6O$ 371.1621, found 371.1614.

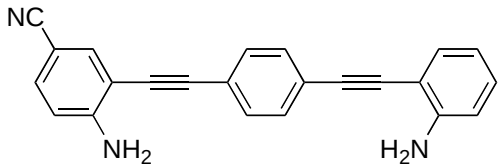


6-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-(6-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenoxy)pyridin-3-yl)-1*H*-indole (30b). A mixture of sulfur (0.723 mg, 0.0226 mmol) and **25** (15.2 mg, 0.0452 mmol) was treated with ethylene diamine (0.5 mL), then irradiated with microwave at 110 °C for 30 min. The mixture was suspended in water and filtered, and the solid was rinsed with water (3x). The solid was then dried under vacuum, affording **30b** (12.4 mg, 65%) as a yellow solid: mp 188.2 °C (ethylene diamine/H_2O, dec.); IR (KBr) 3420, 2928, 2868, 1603, 1570, 1513, 1457 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.86 (s, 1 H), 8.71 (d, 1 H, J = 2.0 Hz), 8.35 (dd, 1 H, J = 8.5, 2.2 Hz), 7.90-7.83 (m, 3 H), 7.54 (app s, 2 H), 7.24-7.17 (m, 3 H), 3.64 (s, 4 H), 3.61 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 164.7, 163.0, 162.0, 155.5, 144.3, 137.0, 136.6, 136.5,

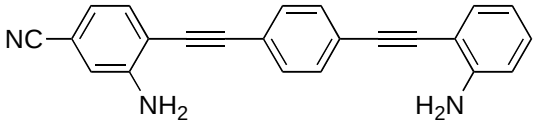
130.2, 128.6, 126.9, 123.9, 123.4, 120.5, 119.5, 119.1, 112.0, 110.5, 99.3; MS (EI) *m/z* (rel intensity) 182 (30), 393 (30), 422 (100); HRMS (EI) *m/z* calcd for $C_{25}H_{22}N_6O$ 422.1855, found 422.1842.



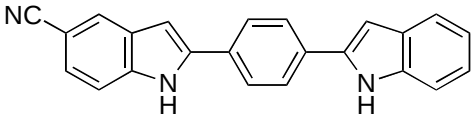
2-((4-Ethynylphenyl)ethynyl)benzenamine (33). To a solution of 2-((4-((trimethylsilyl)ethynyl)phenyl)ethynyl)benzenamine (1.16 g, 4.00 mmol) in MeOH (60 mL) and THF (100 mL) was added K_2CO_3 (2.20 g, 16.0 mmol). The reaction mixture was stirred for 2 h at rt, and filtered through a pad of Celite/Florisil (1:1 v/v). The pad was washed with Et_2O (4x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes:EtOAc, 98:2) afforded **33** (0.50 g, 60%) as a white solid: mp 88-90 °C; IR (KBr) 3487, 3388, 3270, 2206, 1610, 1486, 1452, 1312, 837, 753 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.58 (d, 2 H, *J* = 8.7 Hz), 7.51 (d, 2 H, *J* = 8.7 Hz), 7.29 (dd, 1 H, *J* = 7.8, 1.5 Hz), 7.12 (dt, 1 H, *J* = 8.7, 1.5 Hz), 6.80 (dd, 1 H, *J* = 8.1, 0.6 Hz), 6.61 (dt, 1 H, *J* = 7.5, 1.2 Hz), 5.20 (bs, 2 H), 3.80 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 150.6, 132.9, 132.7, 132.2, 131.0, 125.0, 123.5, 117.4, 115.1, 107.2, 105.6, 96.5, 94.5, 89.7; MS (EI) *m/z* (rel intensity) 189 (26), 217 (100), 250 (56), 341 (25); HRMS (EI) *m/z* calcd for $C_{16}H_{11}N$ 217.0891, found 289.1286.



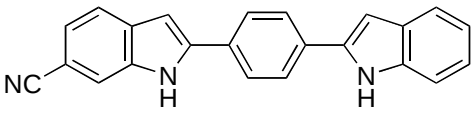
4-Amino-3-((4-((2-aminophenyl)ethynyl)phenyl)ethynyl)benzonitrile (34). To a solution of **33** (15.2 mg, 0.07 mmol) in MeCN (0.50 mL) was added $PdCl_2(PPh_3)_2$ (2.8 mg, 0.0035 mmol) and CuI (1.4 mg, 0.007 mmol), followed by Et_3N (50 μL, 0.35 mmol) and 4-amino-3-iodobenzonitrile (17.1 mg, 0.07 mmol). The reaction mixture was heated at reflux for 2 h and filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x) and the filtrate was concentrated under reduced pressure. Purification of the residue by chromatography on SiO_2 (hexanes:, 9:1 to 8:2 to 7:3) afforded **34** (15.2 mg, 65%) as a pale yellow solid: mp 184-186 °C (decomp.); IR (KBr) 3460.5, 3395.5, 3324.1, 2359.7, 2216.2, 1620.9, 1510.5 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.68 (d, 1 H, *J* = 1.8 Hz, 1 H), 7.62 (d, 4 H, *J* = 1.8 Hz), 7.44 (dd, 1 H, *J* = 8.4, 1.8 Hz), 7.30 (dd, 1 H, *J* = 7.8, 0.9 Hz), 7.13 (dt, 1 H, *J* = 7.2, 1.2 Hz), 6.92 (d, 1 H, *J* = 8.7 Hz), 6.81 (d, 1 H, *J* = 8.1 Hz), 6.62 (dt, 1 H, *J* = 8.1, 0.9 Hz), 6.12 (bs, 1 H), 5.20 (bs, 1 H); ^{13}C NMR (acetone-d_6) δ 153.8, 150.6, 137.2, 134.2, 132.9, 132.5, 132.3, 131.0, 124.8, 123.3, 119.9, 117.5, 115.2, 115.1, 107.8, 107.3, 99.5, 95.9, 94.6, 89.7, 86.8; MS (EI) *m/z* (rel intensity) 81 (73), 88 (100), 91 (94), 117 (46), 333 (18); HRMS (EI) *m/z* calcd for $C_{23}H_{15}N_3$ 333.1266, found 333.1260.



3-Amino-4-((4-((2-aminophenyl)ethynyl)phenyl)ethynyl)benzonitrile (35). To a solution of **33** (100.8 mg, 0.46 mmol) in MeCN (3.5 mL) was added $PdCl_2(PPh_3)_2$ (16.8 mg, 0.023 mmol) and CuI (8.0 mg, 0.042 mmol), followed by Et_3N (320 μL, 2.3 mmol) and 3-amino-4-iodobenzonitrile (112.5 mg, 0.46 mmol). The resulting mixture was heated at reflux for 4 h, filtered through a pad of Celite and Florisil (1:1, v/v). The pad was washed with Et_2O (3x) and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (hexanes:EtOAc, 7:3) afforded **35** (146.1 mg, 95%) as a yellow solid: mp 178-180 °C; IR (KBr) 3412, 3333, 2360, 2340, 2215, 1616, 1552, 1515, 834 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.63 (d, 4 H, J = 1.8 Hz), 7.47 (d, 1 H, J = 7.8 Hz), 7.31 (d, 1 H, J = 6.6 Hz), 7.09-7.14 (m, 1 H), 6.95 (dd, 1 H, J = 7.8, 1.2 Hz), 6.80 (d, 1 H, J = 8.1 Hz), 6.62 (t, 1 H, J = 6.9 Hz), 5.69 (bs, 1 H), 5.20 (bs, 1 H); ^{13}C NMR (acetone-d_6) δ 150.7, 150.6, 133.8, 132.9, 132.5, 132.2, 131.0, 125.0, 123.1, 120.1, 119.5, 117.5, 117.4, 115.1, 113.6, 111.8, 107.2, 97.8, 94.6, 89.8, 87.5; MS (TOF ES) m/z (rel intensity) 191 (13), 272 (14), 334 (32); HRMS (TOF ES) m/z calcd for $C_{23}H_{15}N_3$ $[M+H]^+$ 334.1344, found 334.1333.

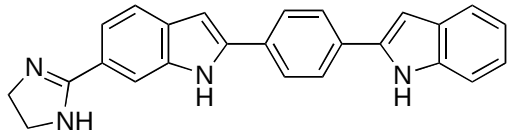


2-(4-(1*H*-Indol-2-yl)phenyl)-1*H*-indole-5-carbonitrile (36). To a solution of **34** (15.0 mg, 0.045 mmol) in DMF (0.5 mL) was added $Pd(PhCN)_2Cl_2$ (3.4 mg, 0.009 mmol). The reaction mixture was heated to 80 °C for 30 min, cooled to rt, quenched with water (1 mL) and extracted with EtOAc (3x). The combined organic layers were washed with water (1x) and brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 (hexanes:THF, 1:1) to give **36** (5.7 mg, 38%) as a yellow solid: mp 198 °C (decomp.); IR (neat) 3432, 2220, 1616, 1434, 789 cm^{-1}; ^1H NMR (acetone-d_6) δ 11.28 (s, 1 H), 10.75 (s, 1 H), 8.05 (s, 1 H), 8.00 (s, 4 H), 7.60 (dd, 2 H, J = 8.4, 4.5 Hz), 7.44 (dd, 2 H, J = 8.4, 1.5 Hz), 7.11 (dt, 2 H, J = 7.2, 1.2 Hz), 6.98-7.08 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 140.0, 138.9, 137.3, 137.0, 131.0, 129.8, 128.6, 128.4, 125.8, 125.4, 124.3, 121.8, 120.7, 120.1, 119.5, 112.4, 111.3, 101.5, 99.4, 99.3; MS (EI) m/z (rel intensity) 68 (38), 183 (53), 262 (67), 333 (100); HRMS (EI) m/z calcd for $C_{23}H_{15}N_3$ 333.1266, found 333.1276.

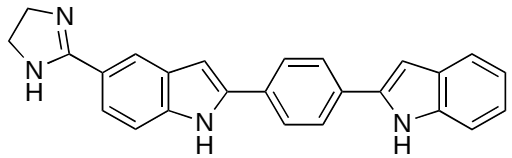


2-(4-(1*H*-Indol-2-yl)phenyl)-1*H*-indole-6-carbonitrile (37). To a solution of **35** (130.0 mg, 0.390 mmol) in DMF (3.9 mL) was added $Pd(PhCN)_2Cl_2$ (31 mg, 0.078 mmol). The reaction mixture was heated to 80

°C for 1 h, cooled to rt, quenched with water (5 mL) and extracted with EtOAc (5x). The combined organic layers were washed with water (1x) and brine, dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified by chromatography on SiO_2 (hexanes:THF, 1:1) to give **37** (70.1 mg, 54%) as a yellow solid: mp 192 °C (decomp.); IR (neat) 3432, 2360, 2340, 2218, 1616, 1485, 1435 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.18 (s, 1 H), 11.60 (s, 1 H), 8.00 (s, 4 H), 7.71 (d, 1 H, J = 8.1 Hz), 7.54 (d, 1 H, J = 7.8 Hz), 7.42 (d, 1 H, J = 8.1 Hz), 7.35 (d, 1 H, J = 8.1 Hz), 7.09-7.14 (m, 2 H), 6.98-7.03 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 141.5, 137.3, 137.0, 136.0, 132.1, 131.9, 129.7, 128.6, 126.0, 125.4, 122.3, 121.9, 121.0, 120.7, 120.1, 119.5, 115.8, 111.3, 102.6, 99.7, 99.4; MS (EI) m/z (rel intensity) 68 (46), 71 (36), 76 (40), 91 (57), 205 (100), 333 (37); HRMS (EI) m/z calcd for $C_{23}H_{15}N_3$ 333.1266, found 333.1256.

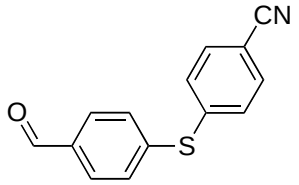


2-(4-(1*H*-Indol-2-yl)phenyl)-6-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-indole (38). A solution of sulfur (1.0 mg, 0.031 mmol) and **37** (25.0 mg, 0.075 mmol) in ethylenediamine (2.0 mL) was heated in a microwave reactor at 130 °C for 28 min, quenched with water and filtered. The solid was rinsed with water (3x) and dried under vacuum to afford **38** (10.2 mg, 41%) as a yellow solid: mp 197.6-198.3 °C (decomp.); IR (KBr) 3421, 2924, 2360, 1601, 1451, 1349, 1302 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.84 (s, 1 H), 11.60 (s, 1 H), 7.99 (app s, 4 H), 7.91 (s, 1 H), 7.50-7.66 (m, 3 H), 7.42 (d, 1 H, J = 7.8 Hz), 7.12 (t, 1 H, J = 7.2 Hz), 6.96-7.07 (m, 3 H), 3.67 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 165.5, 141.5, 137.0, 136.3, 132.3, 132.0, 130.0, 128.6, 126.0, 125.3, 121.8, 120.1, 119.5, 119.1, 111.7, 111.3, 99.5, 99.3, 45.8; MS (TOF MS ES) m/z (rel intensity) 377 (100), 378 (50); HRMS (TOF MS ES) m/z calcd for $C_{25}H_{21}N_4$ - $[M+H]^+$ 377.1766, found 377.1766.

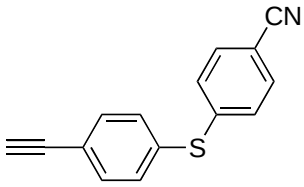


2-(4-(1*H*-Indol-2-yl)phenyl)-5-(4,5-dihydro-1*H*-imidazol-2-yl)-1*H*-indole (39). A solution of sulfur (0.9 mg, 0.025 mmol) and **36** (5.7 mg, 0.017 mmol) in ethylenediamine (2.0 mL) was heated in a microwave reactor at 130 °C for 20 min, quenched with water and filtered. The solid was rinsed with water (3x) and dried under vacuum to afford **39** (3.6 mg, 56%) as a brown-yellow solid. Purification on RP HPLC (MeCN:0.1% TFA in water (3:7) to 0.1% TFA in water) gave pure **39** (2.8 mg) as yellow solid: mp 198-201 °C (decomp.); IR (KBr) 3413, 3221, 1598, 1441, 1341, 1301 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.26 (s, 1 H), 11.61 (s, 1 H), 10.29 (s, 1 H), 8.26 (s, 1 H), 8.01 (m, 4 H), 7.66 (dd, 1 H, J = 8.1 Hz), 7.62

(d, 1 H, *J* = 8.7 Hz), 7.54 (d, 1 H, *J* = 7.5 Hz), 7.41 (d, 1 H, *J* = 8.1 Hz), 7.23 (s, 1 H), 7.11 (t, 1 H, *J* = 7.2 Hz), 6.98-7.10 (m, 2 H), 4.01 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 165.9, 140.3, 140.2, 137.3, 136.9, 131.9, 129.8, 128.6, 128.4, 125.8, 125.4, 121.8, 121.2, 120.1, 119.5, 112.9, 112.0, 111.3, 100.0, 99.3, 44.2; MS (TOF MS ES) *m/z* (rel intensity) 139 (10), 377 (100), 378 (50); HRMS (TOF MS ES) *m/z* calcd for $C_{25}H_{21}N_4$ $[M + H]^+$ 377.1766, found 377.1774.

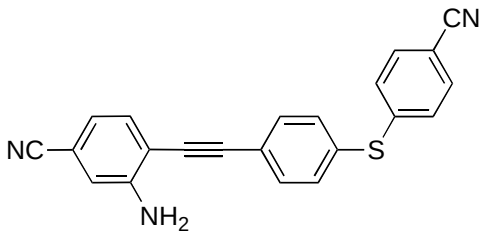


4-(4-Formylphenylthio)benzonitrile (42). A solution of **1** (1.61 mL, 15.0 mmol) and 4-mercaptobenzonitrile[23] (2.03 g, 15.0 mmol) in DMF (90 mL) was treated with potassium carbonate (2.28 g, 16.5 mmol) and heated to 120 °C for 14 h. The reaction mixture was poured into water and extracted with EtOAc (3x). The combined organic layers were washed with 5% aqueous K_2CO_3 (2x), water (3x) and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes: EtOAc = 8:1) afforded 2.93 g (77%) of **42** as a white solid: mp 111.7-112.5 °C (Hexanes-EtOAc); IR (neat) 3427, 3078, 2835, 2744, 2231, 2225, 1701, 1690, 1671, 1586, 1561, 1483 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.0 (s, 1 H), 7.86 (d, 2 H, *J* = 8.4 Hz), 7.61 (d, 2 H, *J* = 8.4 Hz), 7.50 (d, 2 H, *J* = 8.1 Hz), 7.42 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 191.1, 141.7, 141.5, 135.6, 133.0, 131.4, 130.9, 130.7, 118.4, 111.1; MS (EI) *m/z* (rel intensity) 84 (100), 127 (10), 209 (15), 239 (50); HRMS *m/z* calcd for $C_{14}H_9NOS$ 239.0405, found 239.0393.

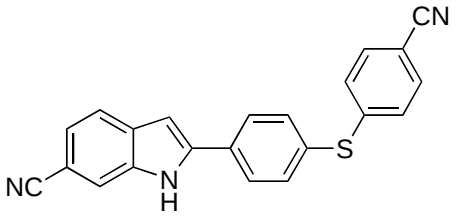


4-(4-Ethynylphenylthio)benzonitrile (43). A solution of lithium diisopropylamide (2.0 M in heptane, diethylbenzene and THF, 0.187 mL, 0.374 mmol) in THF (2.50 mL) at -78 °C was treated with $TMSCHN_2$ (2.0 M in ether, 0.187 mL, 0.374 mmol). The mixture was stirred at -78 °C for 30 min and a solution of **42** (0.0747 g, 0.312 mmol) in THF 0.63 mL was added. The mixture was stirred at -78 ºC for 1h and heated to reflux for 2 h. The reaction mixture was quenched with cold water and extracted with Et_2O (3x). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (Hexanes:Et_2O = 10:1) afforded 0.0397 g (54%) of **43** as a white solid: mp 76.4-78.2 ºC (DCM); IR (neat) 3286, 2226, 1590, 1482 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 4 H, *J* = 8.4 Hz), 7.42 (d, 2 H, *J* = 8.4 Hz), 7.23 (d, 2 H, *J* = 8.7 Hz), 3.19 (s, 1 H); ^{13}C NMR

($CDCl_3$) δ 144.4, 133.6, 133.5, 132.8, 132.7, 128.5, 123.1, 118.7, 109.7, 82.8, 79.4; MS (EI) *m/z* (rel intensity) 190 (10), 235 (100); HRMS (EI) *m/z* calcd for $C_{15}H_9NS$ 235.0456, found 235.0455.

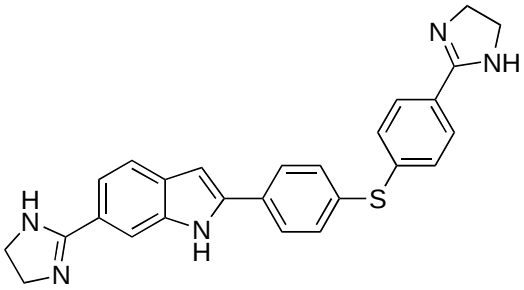


3-Amino-4-((4-(4-cyanophenylthio)phenyl)ethynyl)benzonitrile (44). A solution of **43** (39.7 mg, 0.169 mmol) and 3-amino-4-iodobenzonitrile (41.1 mg, 0.169 mmol) in MeCN (1.23 mL) was degassed and treated with $PdCl_2(PPh_3)_2$ (5.94 mg, 0.00845 mmol) and CuI (3.55 mg, 0.0186 mmol). The mixture was degassed again and treated with Et_3N (118 μL, 0.845 mmol). The reaction mixture was stirred at rt for 48 h, diluted with THF and filtered thru a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x) and the filtrate was concentrated under reduced pressure. Purification by chromatography on SiO_2 (first with Hexanes:THF = 4:1 to 1:1, then repurified with tolene:Et_2O = 20:1) yielded 65.5 mg (73%) of **44** as a yellow solid: mp 198.0-200.2 ºC (THF); IR (neat) 3468, 3369, 2221, 1621, 1586, 1506, 1481 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.76 (d, 2 H, *J* = 8.1 Hz), 7.74 (d, 2 H, *J* = 6.9 Hz), 7.53 (d, 2 H, *J* = 8.4 Hz), 7.39 (d, 1 H, *J* = 7.8 Hz), 7.32 (d, 2 H, *J* = 8.4 Hz), 7.06(s, 1 H), 6.89 (d, 1 H, *J* = 7.8 Hz), 6.09 (br s, 2 H); ^{13}C NMR (DMSO-d_6) δ 150.0, 143.4, 133.2, 133.0, 132.9, 131.8, 128.3, 122.9, 118.9, 118.5, 118.3, 116.4, 111.8, 109.6, 108.7, 96.1, 87.1; MS (EI) *m/z* (rel intensity) 117 (70), 235 (35), 351 (100); HRMS (EI) *m/z* calcd for $C_{22}H_{13}N_3S$ 351.0830, found 351.0840.

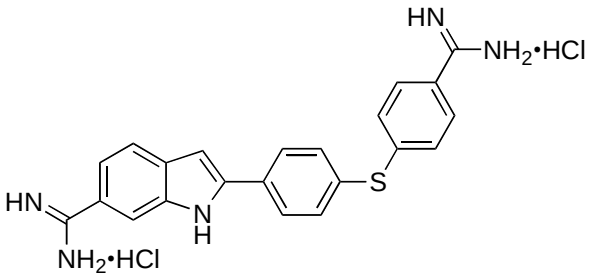


2-(4-(4-Cyanophenylthio)phenyl)-1*H*-indole-6-carbonitrile (45). A solution of **44** (43.3 mg, 0.123 mmol) in DCM (2.75 mL) was treated with $AuClPPh_3$ (3.04 mg, 0.00670 mmol) followed by $AgClO_4$ (3.04 mg, 0.0149 mmol). The mixture was stirred in the dark at rt for 14 h and filtered thru a pad of Celite and Florisil (1:1, v/v). The pad was washed with THF (3x). The organic phases were combined and concentrated under reduced pressure. Purification by chromatography on SiO_2 (toluene:Et_2O = 10:1) yielded 32.0 mg (74%) of **45** as a yellow solid: mp 270 ºC (decomp.) (DMSO); IR (neat) 3315, 3052, 2238, 1619, 1598, 1589, 1498, 1482 cm^{-1}; ^1H NMR (acetone-d_6) δ 12.25 (s, 1 H), 7.85 (s, 1 H), 7.75 (d, 2 H, *J* = 8.4 Hz), 7.71 (d, 1 H, *J* = 8.4 Hz), 7.64 (d, 2 H, *J* = 8.4 Hz), 7.40-7.28 (m, 3 H), 7.15 (d, 1 H, *J* =

0.9 Hz); ^{13}C NMR (acetone-d_6) δ 144.6, 141.0, 136.5, 134.8, 133.4, 132.4, 130.9, 128.2, 127.4, 122.7, 121.7, 120.9, 119.0, 116.5, 108.7, 103.5, 101.0; MS (EI) *m/z* (rel intensity) 91 (100), 172 (40), 351 (30); HRMS (EI) *m/z* calcd for $C_{22}H_{13}N_3S$ 351.0830, found 351.0839.



6-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-(4-(4-(4,5-dihydro-1*H*-imidazol-2-yl)phenylthio) phenyl)-1*H*-indole (40a). A mixture of sulfur (1.46 mg, 0.0456 mmol) and **45** (32.0 mg, 0.0911 mmol) was treated with ethylenediamine (1.0 mL), then irradiated in the microwave at 110 °C for 30+30 min. The mixture was suspended in water and filtered, and the solid was rinsed with water (3x). The solid was then dried under vacuum, affording (22.3 mg, 56%) of **40a** as a yellow solid: mp 154 ºC (decomp.) (ethylenediamine-H_2O); IR (neat) 3407, 2934, 2866, 1606, 1502, 1480 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.86 (s, 1 H), 7.92 (d, 2 H, *J* = 8.4 Hz), 7.88 (s, 1 H), 7.79 (d, 2 H, *J* = 8.4 Hz), 7.53 (s, 2 H), 7.48 (d, 2 H, *J* = 8.4 Hz), 7.33 (d, 2 H, *J* = 8.4 Hz), 6.98 (s, 1 H), 3.62 (s, 4 H), 3.58 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 164.7, 163.0, 138.7, 137.9, 136.7, 132.7, 132.2, 131.5, 130.1, 129.24, 129.15, 128.1, 126.3, 123.9, 119.6, 119.0, 110.5, 99.6, 49.4; HRMS (EI) *m/z* calcd for $C_{26}H_{24}N_5S$ 438.1752, found 438.1737.



2-(4-(4-Carbamimidoylphenylthio)phenyl)-1*H*-indole-6-carboximidamide dihydrochloride (40b). A solution of **45** (45.0 mg, 0.128 mmol) in EtOH:$CHCl_3$ = 1:1 (v/v, 10 mL) at 0 ºC was bubbled with HCl gas for 30 min. The mixture was stirred at rt for 24 h and the solvent was removed. The residue was redissolved in EtOH (6.0 mL) and bubbled with NH_3 gas for 20 min at rt. The mixture was stirred for 24 h, re-bubbled with NH_3 gas and stirred for another 24 h. The solvent was evaporated and the residue was co-evaporated with EtOH (x2). The residue was redissolved in EtOH (2.0 mL) and filtered thru a pad of SiO_2. The filtrate was poured into Et_2O (10 mL) and bubbled with HCl for 1 min. After 30 min stirring, the precipitate was decanted, washed with Et_2O (2x) and dried under vacuum to afford 42.0 mg (72%) of

40b as a brown solid: mp 246 ºC (decomp.) (EtOH-Et_2O); IR (neat) 3367, 3150, 1669, 1622, 1595, 1539, 1473, 1457 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.69 (s, 1 H), 9.49 (s, 2 H), 9.37 (s, 2 H), 9.30 (s, 2 H), 9.15 (s, 2 H), 8.12 (d, 1 H, *J* = 8.4 Hz), 7.99 (s, 1 H), 7.83 (d, 2 H, *J* = 8.4 Hz), 7.73 (d, 1 H, *J* = 8.1 Hz), 7.60 (d, 2 H, *J* = 8.4 Hz), 7.46 (d, 1 H, *J* = 8.4), 7.39 (d, 2 H, *J* = 8.7 Hz), 7.15 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 167.1, 165.4, 144.6, 141.3, 136.8, 134.3, 133.0, 132.4, 131.6, 129.6, 128.3, 127.6, 125.9, 121.0, 120.0, 120.9, 112.7, 100.6, HRMS (ESI) *m/z* calcd for $C_{22}H_{20}N_5S$ 386.1439, found 386.1432.

Assay of BoNT/A light chain proteolytic activity in the presence of different small molecule inhibitors. The HPLC based assay for BoNT/A SNAP-25 cleavage was conducted as described previously without modification.[25] The BoNT/A inhibition activities of different compounds were compared by measuring reaction velocities in the presence of 20 μM inhibitor and then calculating percent inhibition values using uninhibited control reactions. Assays were conducted at 100 μM substrate concentration and reported percent inhibition values are the averages of two independent experiments.

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