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Expedient route to functionalized and water soluble 5-6-5 imidazole-phenyl-thiazole based α-helix mimetics

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ABSTRACT

A range of small molecule scaffolds have been shown to act as structural and functional mimics of α-helices by mimicking the *i*, *i*+4, and *i*+7 positions, often found at the interface of PPIs. These molecules, though potent, possess complicating features—either low water solubility, or maintenance of conformation by hydrogen-bonding networks. We have addressed these limitations by developing a scaffold with increased water solubility. Herein we present a rapid synthetic pathway to a library of 56 compounds based on a 5-6-5 scaffold, containing an imidazole-phenyl-thiazole core; the route is flexible and allows rapid installation of different substituents via high-yielding Ullman and Suzuki couplings and Hantsch thiazole syntheses.

1. Introduction

Protein–protein interactions (PPIs) play critical roles in many biological processes and have been implicated in numerous diseases, including HIV, diabetes, and neurodegeneration, making them important targets for disruption.[1,2] Recognition between proteins is often facilitated by secondary structure elements, such as α-helices, which interact via one helical face, where interacting residues predominantly occupy the *i*, *i*+3 or *i*+4, and *i*+7 positions.[3–12] Accordingly, these surfaces are critical targets for small molecule mimicry. In an ongoing effort to disrupt α-helix mediated PPIs, we have reported several small molecules that act as structural and functional mimetics of α-helices.[3–8] However, our previous focus has yielded α-helix mimetics with inherently complicating features, either low solubility (terphenyl[13] and terpyridine[14] scaffolds) or hydrogen-bonding networks to maintain their correct orientation (terephthalamide,[15] enaminone,[16] benzoylurea,[17] and trispyridylamide[18] scaffolds). The demand for water soluble α-helix mimetics has been addressed in recent work by Rebek and König by making one side of the scaffold hydrophilic or via a 1,4-dipiperazinobenzene scaffold.[19–21] As a mechanism to overcome the limitations of previous designs, we have developed an α-helix mimetic based on a 5-6-5 imidazole-phenyl-thiazole scaffold that replaces the terminal six-membered aromatic end units with more water soluble five-membered heterocyclic groups.[22] This core scaffold possesses increased water solubility relative to the terphenyl, the more water soluble terpyridine and even the terephthalamide. In addition, we focused on designing a synthetic approach that would allow rapid construction of a diverse array of compounds. To that end, we relied on high-yielding coupling reactions, nucleophilic aromatic substitution (S_NAr) and the Hantsch thiazole synthesis to install the *i*, *i*+4, and *i*+7 sidechain mimics and contribute to an efficient and flexible five-step route to α-helix mimetics. The water soluble core and modular synthetic route suggest that the 5-6-5 imidazole-phenyl-thiazole scaffold will be applicable to various protein targets by simply changing the appended substituents.

Herein, we investigate substitution patterns designed to mimic the PPI between Cdc42 and Dbs, a guanine nucleotide triphosphatase (GTPase) and its corresponding GEF (Guanine nucleotide exchange factor) that have been linked to diabetes and cardiovascular and neurodegenerative diseases.[23] The crystal structure of the complex of these two proteins has been solved and shows that contact is mediated by the Q770, K774, and L777 residues of Dbs, which correspond to the *i*, *i*+4, and *i*+7 of a key Dbs α-helix.[24] Because this PPI is mediated by an α-helix with two polar residues, our strategy incorporates mimics of polar sidechains, highlighting an area of α-helix mimicry that has not been generally explored.[1,22]

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2. Discussion

2.1. Design

Our initial goal for this investigation was to explore scaffolds for α-helix mimicry with increased water solubility in the expectation that this would lead to improved biological properties. Our aim was to develop a novel class of α-helix mimetics that overcame the low water solubility (cf. oligophenylenes) but did not rely on hydrogen-bonding networks to maintain proper orientation (cf. terephthalamides or pyridylcarboxamides). The 5-6-5 imidazole-phenyl-thiazole scaffold offered a possible solution to this goal as it maintains the three substituents (R^1, R^2, R^3) in a similar orientation to those on a terphenyl and has a calculated log *P* (o/w) value of 2.3, substantially lower than the terphenyl, terpyridine, and terephthalamide scaffolds (log *P* (o/w) values of 7.3, 3.4, and 4.4, respectively-calculated for trimethyl or tetramethyl (terephthalamide) substituted core scaffold, Fig. 1).[22]

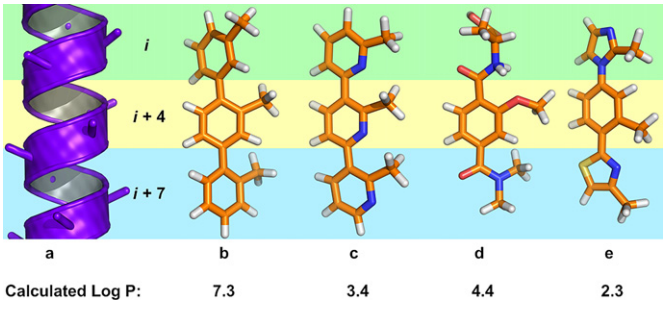


Fig. 1. Energy minimized (a) poly-alanine α-helix displaying *i*, *i*+4, and *i*+7 positions, (b) trimethyl substituted terphenyl, (c) trimethyl substituted terpyridine, (d) tetramethyl substituted terephthalamide, and (d) trimethyl substituted 5-6-5 imidazole-phenyl-thiazole based α-helix mimetics along with their respective calculated log *P* (o/w) values.

A modular synthetic approach was developed capable of functionalizing the 5-6-5 imidazole-phenyl-thiazole scaffolds with a series of amino acid-like sidechains to mimic the *i*, *i*+4, and *i*+7 positions. Our design involved incorporating, onto the *N*-aryl imidazole ring, either flexible or rigid acid groups (R^1 position, Fig. 2b and c), in place of the Q770 residue in the protein.[22] The diacid (Fig. 2c, R^1) serves as a rigidified version of the monoacid (Fig. 2b, R^1) with the second carboxylic acid potentially allowing for increased hydrogen-bonding. Installation of the monoacid and diacid proceeded via Ullman coupling of the corresponding imidazole or benzimidazole with an aryl bromide or S_NAr with an aryl fluoride, depending on the substitution pattern at the *i*+4 position.

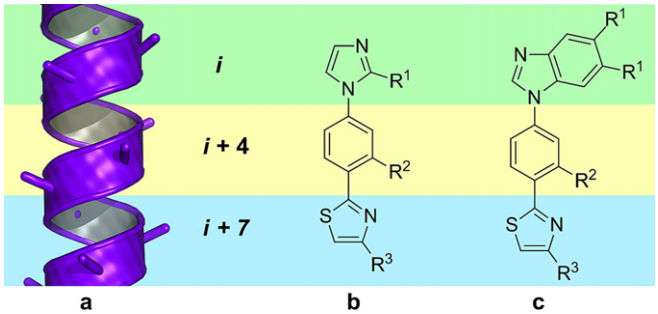


Fig. 2. Schematic representations of (a) an energy minimized poly-alanine α-helix displaying *i*, *i*+4, and *i*+7 positions (b) the flexible acid based 5-6-5 imidazole-phenyl-thiazole core scaffold and (c) the rigid diacid based 5-6-5 imidazole-phenyl-thiazole based core scaffold α-helix mimetics.

The 3-position of the central phenyl ring (*i*+4 position, Fig. 2b and c, R^2), could be readily functionalized with various amines through Suzuki coupling, between an aryl bromide and the necessary boronic acid, or through S_NAr displacement of an aryl fluoride with a suitably substituted alkyl alcohol.

The final thiazole ring could be installed through Hantsch conditions involving conversion of a nitrile at the 4-position of the phenyl ring to a thioamide followed by treatment with an α-haloketone or α-haloketoester, to give the substituent at the 4-position of the thiazole (Fig. 2b and c, R^3).

Merging high-yielding coupling reactions, S_NAr and the Hantsch thiazole synthesis with highly functionalized, commercially available starting materials allows installation of different substituents and rapid accessibility to water soluble α-helix mimetics in five steps.

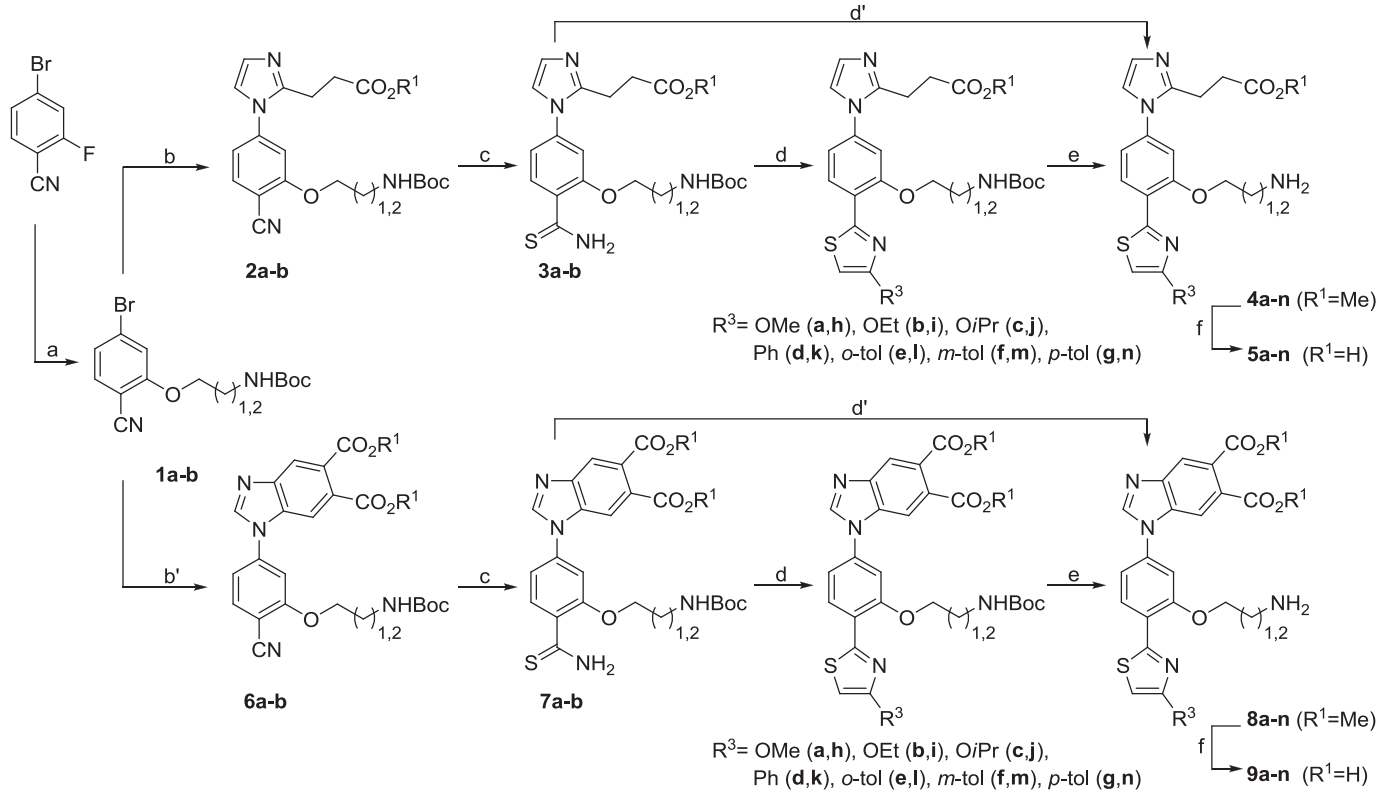
2.2. Synthesis

Two distinct synthetic routes were followed; the benzonitrile starting material chosen and the synthetic route undertaken depend on the *i*+4 position mimic installed. For mimetics with flexible amines at the *i*+4 position, 4-bromo-2-fluorobenzonitrile was subjected to nucleophilic aromatic substitution with *tert*-butyl 3-hydroxypropylcarbamate or *tert*-butyl 2-hydroxyethylcarbamate (KHMDS in THF) to produce **1a**,**b**, in quantitative yield (Scheme 1).

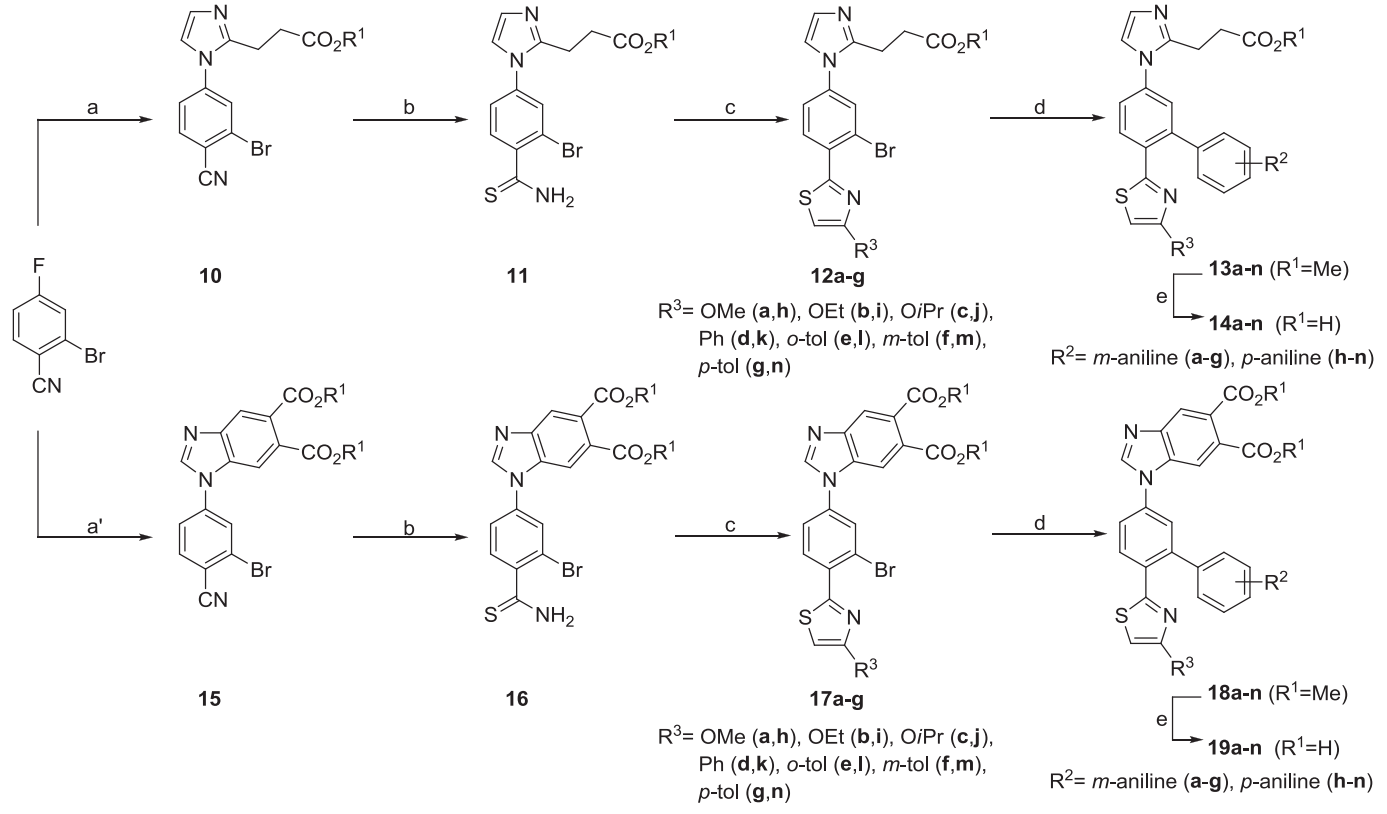
Attempts were made to couple **1a** with methyl 3-(1*H*-imidazol-2-yl)propanoate or dimethyl 1*H*-benzo[*d*]imidazole-5,6-dicarboxylate via Buchwald–Hartwig amination, but no product was observed. Ullmann conditions successfully coupled **1a**,**b** with methyl 3-(1*H*-imidazol-2-yl) propanoate or dimethyl 1*H*-benzo[*d*]imidazole-5,6-dicarboxylate to furnish **2a**,**b** and **6a**,**b** in high yield. Subsequent treatment with phosphorous pentasulfide failed to convert the nitrile in **2a**,**b** and **6a**,**b** to the expected product but aqueous (20%) ammonium sulfide did furnish thioamides **3a**,**b** and **7a**,**b** in excellent yield.[25] Hantsch thiazole conditions[16] with various chloroacetates and bromoacetophenones, and heating for 2 h, converted the thioamides to thiazoles. Subsequent treatment with TFA in DCM removed the Boc protection. Interestingly, increasing the reaction time, for Hantsch thiazole formation, from 2 to 12 h resulted in both thiazole formation and Boc deprotection, presumably by the HCl or HBr by-product, furnishing compounds **4a**–**n** and **8a**–**n**. Acknowledging this success, future efforts bypassed the two-step route, in favor of the one-step alternative, which showed a negligible loss in total yield over the two steps; subsequent hydrolysis produced **5a**–**n** and **9a**–**n**.

For mimetics with a rigid amine (aniline) at the *i*+4 position, S_NAr between 2-bromo-4-fluorobenzonitrile and either methyl 3-(1*H*-imidazol-2-yl) propanoate or dimethyl 1*H*-benzo[*d*]imidazole-5,6-dicarboxylate yielded **10** or **15**, respectively (Scheme 2). Treatment with aqueous (20%) ammonium sulfide and then Hantsch thiazole conditions with various chloroacetates and bromoacetophenones converted thioamides **11** and **16** to thiazoles **12a**–**g** and **17a**–**g**.[26] Suzuki coupling with 3-aminophenylboronic acid or 4-(4,4,5,5)-tetramethyl-1,3,2 dioxaborolan-2-yl aniline in the presence of $PdCl_2$(dppf), followed by hydrolysis furnished **14a**–**n** and **19a**–**n**.[27] Incorporating the Hantsch thiazole synthesis and Suzuki couplings facilitated late stage installation of diversity and rapid accessibility to this 56 compound library.

A crystal structure of a fully functionalized 5-6-5 α-helix mimetic, compound **19i** (Fig. 3), confirmed the extended shape of the molecule and the staggered projections of the substituents in a nonplanar orientation (5-6-5 dihedral angles 42.3° and 39.0°). In addition to projecting functionality in a similar orientation to that of an α-helix, a subset of these compounds, upon conversion from thioamides **7a**,**b** to thiazoles **8a**–**c** and **h**–**j**, were found to be fluorescent under long wave (365 nm) UV light exposure (Fig. S4).[28,29]



Scheme 1. Conditions: (a) *tert*-butyl 3-hydroxypropylcarbamate or *tert*-butyl 2-hydroxyethylcarbamate, KHMDS, THF (99%); (b) methyl 3-(1*H*-imidazol-2-yl)propanoate, L-proline, CuI, K_2CO_3, DMSO, 130 °C (80–84%); (b′) dimethyl 1*H*-benzo[*d*]imidazole-5,6-dicarboxylate, L-proline, CuI, K_2CO_3, DMSO, 130 °C (76–81%); (c) $(NH_4)_2S$ (*aq*) (20%), EtOH, 90 °C (83–92%); (d) R^3COCH_2X (X=Cl or Br), R^3OH or EtOH, 80 °C, 2 h (75–88%); (d′) R^3COCH_2X (X=Cl or Br), R^3OH or EtOH, 80 °C, 12 h (69–84%); (e) TFA, CH_2Cl_2 (99%); (f) $LiOH·H_2O$, THF, H_2O, MeOH (99%).



Scheme 2. Conditions: (a) methyl 3-(1*H*-imidazol-2-yl)propanoate, DIPEA, DMSO, 90 °C (81%); (a′) dimethyl 1*H*-benzo[d]imidazole-5,6-dicarboxylate, DIPEA, DMSO, 90 °C (93%); (b) $(NH_4)_2S$ (*aq*) (20%), EtOH, 90 °C (86–91%); (c) R^3COCH_2X (X=Cl or Br), R^3OH or EtOH, 80 °C, 12 h (81–87%); (d) 3-aminophenylboronic acid or 4-(4,4,5,5)-tetramethyl-1,3,2 dioxaborolan-2-yl aniline, CsF, $PdCl_2$(dppf), DMF, 90 °C (84–93%); (e) $LiOH·H_2O$, THF, H_2O, MeOH (99%).

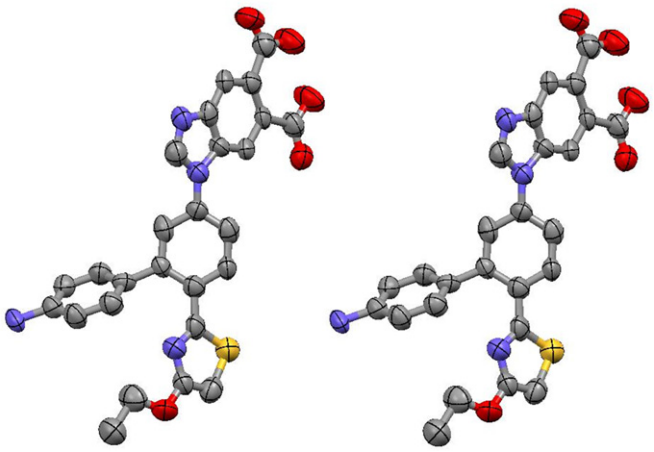


Fig. 3. Stereoview of the X-ray crystal structure of a fully functionalized 5-6-5 imidazole-phenyl-thiazole α-helix mimetic[30] (compound **19i**).

3. Conclusions

In summary, the 5-6-5 imidazole-phenyl-thiazole scaffold avoids the inherent disadvantages of previous mimetics, such as poor water solubility or relying on hydrogen-bonding networks to maintain their proper orientation. Crystal structures of model[12] and fully functionalized 5-6-5 imidazole-phenyl-thiazole α-helix mimetics[30] confirm that substituents are staggered in a nonplanar orientation. Analysis of the 5-6-5 dihedral angles suggests that the *i*, *i*+4, and *i*+7 sidechain mimics are projected in a similar orientation to the corresponding residues on a natural α-helix.

Incorporation of high-yielding Ullman and Suzuki coupling reactions, along with S_NAr and the Hantsch thiazole synthesis form the foundation of five step synthetic routes to fully functionalized, water soluble 5-6-5 imidazole-phenyl-thiazole α-helix mimetics, with total overall yields of 42–67%, from commercially available starting materials. The innate heterocyclic core, installed with Ullman coupling or S_NAr and Hantsch thiazole synthesis, increases water solubility, which may translate to improved bioavailability, protein binding, and pharmacokinetic properties. The ability of these compounds to disrupt PPIs, including studies against GTPase-GEF target proteins, are currently under investigation.

4. Experimental section

4.1. General

All chemicals were obtained from Sigma/Aldrich, Fluka, Lancaster, Atlantic SciTech, TCI America, and Astatech Inc. unless otherwise noted. Solvents CH_2Cl_2, THF, CH_3CN, and DMF were dried using an Innovative Technology SPS-400 dry solvent system. Anhydrous MeOH, EtOH, ^{i}PrOH, and DMSO were purchased from Sigma–Aldrich and used directly from their Sure-Seal bottles. All reactions were performed under an atmosphere of dry nitrogen in oven-dried glassware and were monitored for completeness by thin-layer chromatography (TLC) using silica gel (visualized by UV light or developed by treatment with $KMnO_4$ stain or Hanessian's stain). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 400 MHz and Bruker AM 500 MHz spectrometers in either $CDCl_3$, MeOH-d_4 or DMSO-d_6. Chemical shifts (δ) are reported in parts per million after calibration to residual isotopic solvent. Coupling constants (J) are reported in Hertz. Mass spectrometry (MS) was performed using electrospray ionization on either a Varian MAT-CH-5 (HRMS) or a Waters Micromass ZQ (LRMS) instrument. Analysis and purification by rpHPLC were performed using either Phenomenex Luna 5 μm C18 (2) 250 mm×21 mm column run at 15 mL/min (preparative) or a Microsorb-MV 300 Å C18 250 mm×4.6 mm column run at 1 mL/min (analytical), using gradient mixtures of (A) water with 0.1% TFA and (B) 10:1 acetonitrile/water with 0.1% TFA. Appropriate product fractions were pooled and lyophilized to dryness, affording the inhibitors as fluffy white powders as their TFA salts. Inhibitor purity was confirmed by analytical rpHPLC using linear gradients from 100% A to 100% B, with changing solvent composition of either (I) 4.5% or (II) 1.5% per min after an initial 2 min of 100% A.

4.2. General procedure for preparation of 5a

4.2.1. Methyl 3-(1H-imidazol-2-yl) propanoate. To a round bottom flask charged with 143 mL of methanol was added 1 g (g) (1 equiv, 7.15 mmol) of 3-(1*H*-imidazol-2-yl)propanoic acid (Astatech Inc.). This solution was cooled to 0 °C, then 5.2 mL (10 equiv, 71.5 mmol) of thionyl chloride was added and the reaction stirred for 5 h. Upon completion, the reaction was reduced, diluted with dichloromethane, and washed three times with 0.1 M K_2CO_3. The organic portions were dried with sodium sulfate, filtered, and reduced to afford the HCl salt of methyl 3-(1*H*-imidazol-2-yl) propanoate as a white powder in quantitative yield (1.35 g, 99%). δ_H (500 MHz, DMSO-d_6) 2.98 (s, 2H, CH_2CH_2Im), 3.16 (s, 2H, CH_2CH_2Im), 3.59 (s, 3H, CH_3), 7.52 (s, 2H, Im), 14.58 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 20.44, 29.98, 51.45, 118.20, 145.76, 171.31; HRMS (ES+) calcd for [$C_7H_{10}N_2O_2$+H] 155.08205, found 155.08202.

*4.2.2. tert-Butyl 3-(5-bromo-2-cyanophenoxy)propylcarbamate (**1a**).* To a 0 °C stirring solution of 100 mL tetrahydrofuran, 3 g (1 equiv, 15 mol) 4-bromo-2-fluorobenzonitrile, 2.63 g (1 equiv, 15 mol) *tert*-butyl 3-hydroxypropylcarbamate was added 30 mL (1 equiv, 15 mol) of 0.5 M potassium hexamethyldisilane solution in toluene. The reaction mixture was allowed to warm to room temperature over the course of 6 h. Upon completion the reaction was reduced, then diluted with dichloromethane and washed repeatedly with 0.1 M HCl. The organic portions were collected, dried with sodium sulfate, filtered, and reduced to produce *tert*-butyl 3-(5-bromo-2-cyanophenoxy) propylcarbamate as an off white powder in quantitative yield (5.31 g, 99%).δ_H (500 MHz, DMSO-d_6) 1.37 (s, 9H, $C(CH_3)_3$), 1.84–1.86 (m, 2H, $CH_2CH_2CH_2$), 3.09–3.11 (m, 2H, NCH_2), 4.17 (t, J=6.75 Hz, 2H, CH_2O), 6.90 (br s, 1H, NH), 7.30 (d, J=8.25 Hz, 1H, Ar), 7.49 (s, 1H, Ar), 7.68 (d, J=8.25 Hz, 1H, Ar); δ_C (125 MHz, DMSO-d_6) 27.77, 28.35, 36.03, 54.43, 66.67, 77.07, 99.58, 116.04, 123.65, 128.05, 134.39, 155.14, 160.26; HRMS (ES+) calcd for [$C_{15}H_{19}BrN_2O_3$+H] 355.06573, found 355.06533.

*4.2.3. Methyl 3-(1-(3-(3-(tert-butoxycarbonyl amino)propoxy)-4-cyanophenyl)-1H-imidazol-2-yl) propanoate (**2a**).* To a pressure flask charged with 24 mL anhydrous dimethyl sulfoxide was added 3.04 g (8.56 mmol, 1.1 equiv) *tert*-butyl 3-(5-bromo-2-cyanophenoxy) propylcarbamate, 1.48 g (7.80 mmol, 1.0 equiv) HCl salt of methyl 3-(1*H*-imidazol-2-yl)propanoate, 2.02 g (15.6 mmol, 2 equiv) potassium carbonate, 900 mg (7.8 mmol, 1 equiv) L-proline, and 296 mg (1.56 mmol, 0.2 equiv) copper iodide. The pressure flask was stirred at 130 °C for 48 h, upon completion the reaction mixture was diluted with ethyl acetate and washed three times with 0.1 M HCl solution. The organic portions were collected, dried with sodium sulfate, and the reduced to afford the crude reaction mixture as a brown oil. The crude reaction mixture was dry loaded and purified by silica gel flash column chromatography (eluent: CH_2Cl_2:MeOH:NH_4OH, 92:7:1) to afford methyl 3-(1-(3-(3-(*tert*-butoxycarbony-

lamino)propoxy)-4-cyanophenyl)-1*H*-imidazol-2-yl)propanoate as a brown oil (2.5 g, 80%). δ_H (400 MHz, DMSO-d_6) 1.36 (s, 9H, C(CH_3)$_3$), 1.88 (q, *J*=6.38 Hz, 2H, $CH_2CH_2CH_2$), 2.77 (t, *J*=7.0 Hz, 2H, CH_2CH_2Im), 2.92 (t, *J*=7.0 Hz, 2H, CH_2CH_2Im), 3.12 (q, *J*=6.35 Hz, 2H, NCH_2), 3.55 (s, 3H, CH_3), 4.21 (t, *J*=6.5 Hz, 2H, CH_2O), 6.91 (br t, *J*=5.5, 1H, NH), 6.98 (d, *J*=1.0 Hz, 1H, Im), 7.21–7.19 (m, 1H, Ar), 7.12 (d, *J*=1.0 Hz, 1H, Ar), 7.34 (br s, 1H, Ar), 7.92 (d, *J*=8 Hz, 1H, Im), δ_C (125 MHz, DMSO-d_6) 21.91, 28.07, 28.66, 30.80, 36.47, 51.19, 66.99, 77.39, 99.90, 110.26, 115.58, 117.61, 120.83, 127.55, 134.55, 142.41, 145.90, 155.48, 160.85, 172.38; HRMS (ES+) calcd for [$C_{22}H_{28}N_4O_5$+H] 429.21380, found 429.21377.

*4.2.4. Methyl 3-(1-(3-(3-(tert-butoxycarbonyl amino)propoxy)-4-carbamothioylphenyl)-1H-imidazol-2-yl) propanoate (**3a**).* To a round bottom flask was added 1.00 g (2.34 mmol, 1 equiv) methyl 3-(1-(3-(3-(*tert*-butoxycarbonyl amino)propoxy)-4-cyanophenyl)-1*H*-imidazol-2-yl) propanoate, 30 mL ethanol and 2.0 mL 20% ammonium sulfide (aq). The reaction stirred at 90 °C for 2 h. The crude mixture was dry loaded and purified by silica gel flash column chromatography (eluent: CH_2Cl_2:MeOH:NH_4OH, 92:7:1) to produce methyl 3-(1-(3-(3-(*tert*-butoxycarbonylamino)propoxy)-4-carbamothioyl phenyl)-1*H*-imidazol-2-yl)propanoate as a bright yellow powder (860 mg, 92%).δ_H (400 MHz, DMSO-d_6) 1.34 (s, 9H, C(CH_3)$_3$), 1.81–1.84 (m, 2H, $CH_2CH_2CH_2$), 2.78 (t, *J*=6.9 Hz, 2H, CH_2CH_2Im), 2.89 (t, *J*=6.9 Hz, 2H, CH_2CH_2Im), 3.10–3.13 (m, 2H, NCH_2), 3.56 (s, 3H, CH_3), 4.06 (t, *J*=6.2 Hz, 2H, CH_2O), 6.91 (br t, *J*=5.8, 1H, NH), 6.95 (d, *J*=1.6, 1H, Im), 7.02–7.03 (m, 1H, Ar), 7.12 (d, *J*=2.0 Hz, 1H, Ar), 7.30 (d, *J*=1.6, 1H, Im), 7.76 (d, *J*=8.0 Hz, 1H, Ar), 9.39 (s, 1H, NH_2), 10.09 (s, 1H, NH_2); δ_C (125 MHz, DMSO-d_6) 21.85, 28.04, 30.82, 35.64, 36.28, 51.20, 65.74, 77.51, 109.70, 116.64, 120.91, 127.17, 130.27, 131.44, 139.03, 145.78, 153.82, 155.64, 172.41, 197.91; HRMS (ES+) calcd for [$C_{22}H_{30}N_4O_5S$+H] 463.20152, found 463.20150.

*4.2.5. Methyl 3-(1-(3-(3-aminopropoxy)-4-(4-methoxythiazol-2-yl) phenyl)-1H-imidazol-2-yl) propanoate (**4a**).* To a pressure flask charged with 1 mL methanol was added 70 mg (0.156 mmol, 1 equiv) methyl 3-(1-(3-(3-(*tert*-butoxycarbonylamino)propoxy)-4-carbamo thioylphenyl)-1*H*-imidazol-2-yl) propanoate and 19 mg (0.172 mmol, 1.1 equiv) methyl 2-chloroacetate. The pressure flask stirred at 90 °C for 14 h. The crude reaction mixture was dry loaded and purified by silica gel flash column chromatography (eluent: CH_2Cl_2:MeOH:NH_4OH, 92:7:1) to yield methyl 3-(1-(3-(3-amino-propoxy)-4-(4-methoxythiazol-2-yl)phenyl)-1*H*-imidazol-2-yl) propanoate as a reddish powder (49 mg, 78%). δ_H (500 MHz, DMSO-d_6) 2.07 (t, *J*=5.0 Hz, 2H, CH_2), 2.56 (s, 3H, CH_3), 2.83 (t, *J*=5.0 Hz, 2H, CH_2), 3.00 (q, *J*=5.0 Hz, 2H, CH_2), 3.28 (m, 2H, CH_2), 3.62 (s, 3H, CH_3), 4.34 (t, *J*=5.0 Hz, 2H, CH_2), 6.38 (s, 1H, Ar), 7.07 (s, 1H, Ar), 7.22 (d, *J*=8.0 Hz, 1H, Ar), 7.34 (s, 1H, Ar), 7.44 (s, 1H, Ar), 8.36 (d, *J*=8.0 Hz, 1H, Ar); δ_C (125 MHz, DMSO-d_6) 21.94, 28.21, 31.01, 36.86, 50.99, 91.53, 109.84, 112.17, 117.64, 121.00, 124.85, 127.99, 130.96, 132.24, 135.62, 145.90, 155.62, 156.26, 162.20, 172.33; HRMS (ES+) calcd for [$C_{19}H_{22}N_4O_4S$+H] 403.1440, found 403.1451.

*4.2.6. 3-(1-(3-(3-Aminopropoxy)-4-(4-methoxy thiazol-2-yl) phenyl)-1H-imidazol-2-yl) propanoic acid (**5a**).* A round bottom flask was charged with 1 mL of 3:1:1 (MeOH:THF:H_2O), 20 mg (0.049 mmol, 1 equiv) methyl 3-(1-(3-(3-aminopropoxy)-4-(4-methoxy thiazol-2-yl) phenyl)-1*H*-imidazol-2-yl) propanoate and 7.0 mg (0.150 mmol, 3 equiv) lithium hydroxide monohydrate. The reaction mixture stirred at room temperature for 20 h. The crude reaction mixture was dry loaded and purified by silica gel flash column chromatography (eluent: CH_2Cl_2:MeOH:NH_4OH, 92:7:1) to afford 3-(1-(3-(2-aminoethoxy)-4-(4-methoxythiazol-2-yl)phenyl)-1*H* -imidazol-2-yl) propanoic acid (19 mg, 99%). The final compound, **5a**, was additionally purified by HPLC to obtain the TFA salt of **5a**, this salt was used to determine the NMR spectrum. δ_H (500 MHz, DMSO-d_6) 1.87 (t, *J*=6.0 Hz, 2H, CH_2), 2.56 (s, 3H, CH_3), 2.71 (t, *J*=5.0 Hz, 2H, CH_2), 3.02 (q, *J*=5.0 Hz, 2H, CH_2), 3.12 (m, 2H, CH_2), 4.19 (t, *J*=5.0 Hz, 2H, CH_2), 6.93 (m, 2H, Ar), 7.31 (d, *J*=5.0 Hz, 1H, Ar), 7.50 (s, 1H, Ar), 7.72 (m, 1H, Ar), 8.02 (d, *J*=8.0 Hz, 1H, Ar); δ_C (125 MHz, DMSO-d_6) 21.26, 27.05, 31.31, 50.18, 99.24, 110.64, 114.65, 125.38, 129.31, 130.99, 140.05, 141.57, 143.90, 146.62, 148.30, 153.76, 158.00, 160.89, 172.10; HRMS (ES+) calcd for [$C_{19}H_{22}N_4O_4S$+H] 403.14400, found 403.14409.

4.3. General procedure for preparation of 19b

4.3.1. Dimethyl 1H-benzo[d]imidazole-5,6-dicarboxylate. To a pressure flask was added 2.0 g (9.71 mmol, 1 equiv) of benzimidazole dicarboxylic acid and 97.1 mL methanol. After stirring for 10 min, 7.0 mL (97.1 mmol, 10 equiv) of thionyl chloride was added dropwise. Continuous stirring for 10 min allowed the components to mix thoroughly and then the pressure flask was placed at 80 °C for 12 h. The reaction was reduced and then diluted with dichloromethane and washed three times with 0.1 M K_2CO_3. The organic layer was dried and reduced to furnish dimethyl 1*H*-benzo[*d*]imidazole-5,6-dicarboxylate in 95% yield (2.16 g) with no further purification necessary. δ_H (500 MHz, DMSO-d_6) 3.82 (s, 6H, CH_3), 7.89 (s, 1H, Ar), 8.00 (s, 1H, Ar), 8.50 (s, 1H, Ar), 12.99 (br, 1H, NH); δ_C (125 MHz, DMSO-d_6) 52.32, 112.94, 119.97, 134.31, 145.92, 167.78; HRMS (ES+) calcd for [$C_{11}H_{10}N_2O_4$+H] 235.07188, found 235.07137.

*4.3.2. Dimethyl 1-(3-bromo-4-cyanophenyl)-1H-benzo[d]imidazole-5,6-dicarboxylate (**15**).* A pressure flask was charged with 20 mL DMSO, 3.8 g (16.2 mmol, 1 equiv) dimethyl 1*H*-benzo[*d*]imidazole-5,6-dicarboxylate, and 3.24 g (16.2 mmol, 1 equiv) 2-bromo-4-fluorobenzonitrile. After stirring for 10 min, 14 mL (81.0 mmol, 5 equiv) of DIPEA was added and the reaction was placed at 90 °C for 30 h. The reaction was diluted with minimal ethyl acetate and washed three times with 0.1 M K_2CO_3, then dried and reduced. The crude reaction mixture was dry loaded and purified by silica gel flash column chromatography (eluent: CH_2Cl_2:MeOH:NH_4OH, 92:7:1) to afford dimethyl 1-(3-bromo-4-cyanophenyl)-1*H*-benzo [*d*] imidazole-5,6-dicarboxylate in 93% yield (1.46 g). δ_H (500 MHz, $CDCl_3$ and MeOD) 3.92 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 7.65–7.63 (m, 1H, Ar), 7.87 (s, 1H, Ar), 7.90 (s, 1H, Ar), 7.92 (s, 1H, Ar), 8.25 (s, 1H, Ar), 8.28 (s, 1H, Ar); δ_C (125 MHz, $CDCl_3$) 52.49, 52.59, 111.57, 115.46, 115.83, 121.79, 121.80, 122.76, 127.64, 127.94, 128.61, 133.45, 135.87, 139.25, 144.47, 144.92, 167.68(2); HRMS (ES+) calcd for [$C_{18}H_{12}BrN_3O_4$+H] 414.00894, found 414.00843.

*4.3.3. Dimethyl 1-(3-bromo-4-carbamothioyl phenyl)-1H-benzo[d] imidazole-5,6-dicarboxylate (**16**).* To a pressure flask was added 6.70 g (16.2 mmol, 1 equiv) dimethyl 1-(3-bromo-4-cyanophenyl)-1*H*-benzo[d]imidazole-5,6-dicarboxylate, 40 mL ethanol and 10.0 mL 20% ammonium sulfide (aq). The reaction stirred at 90 °C for 1.5 h. The crude mixture was dry loaded and purified by silica gel flash column chromatography (eluent: CH_2Cl_2:MeOH:NH_4OH, 92:7:1) to produce dimethyl 1-(3-bromo-4-carbamothioylphenyl)-1*H*-benzo [*d*] imidazole-5,6-dicarboxylate as a yellow powder (5.43 g, 91%). δ_H (500 MHz, DMSO-d_6) 3.82 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 7.65 (d, *J*=9.2, 1H, Ar), 7.80 (d, *J*=8.0, 1H, Ar), 7.92 (s, 1H, Ar), 8.01 (s, 1H, Ar), 8.16 (s, 1H, Ar), 8.22 (s, 1H, Ar), 9.81 (s, 1H, NH), 10.33 (s, 1H, NH); δ_C (125 MHz, DMSO-d_6) 53.05, 53.13, 111.98, 119.01, 122.57, 123.38, 123.90, 128.67, 129.37, 131.35, 134.53, 136.71, 143.75, 145.05, 145.16, 168.20(2), 201.23; HRMS (ES+) calcd for [$C_{18}H_{14}BrN_3O_4S$+H] 447.99666, found 447.99633.

*4.3.4. Dimethyl 1-(3-bromo-4-(4-ethoxythiazol-2-yl)phenyl)-1H-benzo [d]imidazole-5,6-dicarboxylate (**17b**).* A pressure flask was charged

1.5 mL ethanol and (0.150 mmol, 1.1 equiv) ethyl 2-chloroacetate and 50 mg (0.136 mmol, 1 equiv) dimethyl 1-(3-bromo-4-carbamothioylphenyl)-1*H*-benzo[*d*] imidazole-5,6-dicarboxylate. The reaction stirred at 80 °C for 4 h, the crude mixture was dry loaded and purified by silica gel flash column chromatography (eluent: CH_2Cl_2:MeOH:NH_4OH, 92:7:1) to produce dimethyl 1-(3-bromo-4-(4-ethoxythiazol-2-yl) phenyl)-1*H*-benzo[d]imidazole-5,6-dicarboxylate as a reddish powder (50 mg, 82%). δ_H (500 MHz, $CDCl_3$) 1.39 (t, *J*=7.5 Hz, 3H, CH_3), 3.83 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.15 (q, *J*=6.3 Hz, 2H, CH_2), 6.25 (s, 1H, Ar), 7.48–7.50 (m, 1H, Ar), 7.79 (d, *J*=4.0 Hz, 1H, Ar), 7.81 (s, 1H, Ar), 8.16 (s, 1H, Ar), 8.24 (s, 1H, Ar), 8.36 (d, *J*=4.0 Hz, 1H, Ar); δ_C (125 MHz, $CDCl_3$) 14.71, 31.56, 34.85, 67.21, 111.23, 115.89, 117.84, 121.43, 122.98, 123.90, 125.67, 128.58, 129.21, 131.99, 132.84, 135.67, 137.92, 143.66, 144.12, 152.87, 167.69, 168.11; HRMS (ES+) calcd for [$C_{22}H_{18}BrN_3O_5S$+H] 516.02288, found 516.02281.

*4.3.5. Dimethyl 1-(4′-amino-6-(4-ethoxythiazol-2-yl)biphenyl-3-yl)-1H-benzo[d]imidazole-5,6-dicarboxylate (**18i**).* A pressure flask was charged with 22 mg (0.052 mmol, 1 equiv) dimethyl 1-(3-bromo-4-(4-ethoxythiazol-2-yl)phenyl)-1*H*-benzo[*d*]imidazole-5,6-dicarboxylate, 34.2 mg (0.156 mmol, 3 equiv) 4-(4,4,5,5)-tetramethyl-1,3,2 dioxaborolan-2-yl aniline, 43 mg (0.220 mmol, 5.2 equiv) cesium fluoride, 10 mg (0.0104 mmol, 20 mol %) $PdCl_2(dppf)_2$, and 1.0 mL DMF. The reaction mixture stirred for 12 h at 90 °C and was then diluted with ethyl acetate and washed three times with 0.1 M HCl. The organic layers were combined and then dried and reduced, the crude reaction mixture was dry loaded and purified by silica gel flash column chromatography (eluent: CH_2Cl_2:MeOH:NH_4OH, 92:7:1) to produce dimethyl 1-(4′-amino-6-(4-ethoxythiazol-2-yl) biphenyl-3-yl)-1*H*-benzo[*d*]imidazole-5,6-dicarboxylate in 89% yield (20.3 mg). δ_H (500 MHz, DMSO-d_6) 1.34 (t, *J*=7.5 Hz, 3H, CH_3), 3.82 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 4.10 (q, *J*=6.3 Hz, 2H, CH_2), 5.35 (br, 2H, NH_2), 6.53 (s, 1H, Ar), 6.62 (d, *J*=8.0 Hz, 2H, Ar), 7.02 (d, *J*=8.0 Hz, 1H, Ar), 7.62 (s, 1H, Ar), 7.76 (d, *J*=8.0 Hz, 1H, Ar), 7.95 (s, 1H, Ar), 8.00 (s, 1H, Ar), 8.15 (d, *J*=4 Hz, 2H, Ar), 8.95 (s, 1H, Ar); δ_C (125 MHz, DMSO-d_6) 30.75, 35.89, 52.63, 64.97, 92.84, 112.10, 113.70, 121.07, 122.39, 125.23, 126.38, 127.24, 130.44, 130.59, 131.66, 134.18, 135.43, 143.03, 144.78, 149.21, 161.93, 162.27, 162.33, 163.01, 167.54(2); HRMS (ES+) calcd for [$C_{28}H_{24}N_4O_5S$+H] 529.15457, found 529.15468.

*4.3.6. 1-(4′-Amino-6-(4-ethoxythiazol-2-yl) biphenyl-3-yl)-1H-benzo [d]imidazole-5,6-dicarboxylic acid (**19i**).* To a round bottom flask was added 20 mg (0.046 mmol, 1.0 equiv) dimethyl 1-(4′-amino-6-(4-ethoxythiazol-2-yl)biphenyl-3-yl)-1*H*-benzo [*d*] imidazole-5,6-dicarboxylate, 6.0 mg (0.138 mmol, 3.0 equiv) $LiOH \cdot H_2O$ and 1.0 mL (3:1:1 of MeOH, THF, H_2O). The reaction was left to stir at room temperature for 24 h, upon completion the reaction was dry loaded and purified by silica gel flash column chromatography (eluent: CH_2Cl_2:MeOH:NH_4OH, 25:7:1) to afford 1-(4′-amino-6-(4-ethoxythiazol-2-yl)biphenyl-3-yl)-1*H*-benzo[*d*]imidazole-5,6-dicarboxylic acid in quantitative yield (19 mg, 99%). The final compound, **19i**, was additionally purified by HPLC to obtain the TFA salt of **19i**, this salt was used to determine the NMR spectrum. δ_H (500 MHz, DMSO-d_6) 1.33 (t, *J*=7.5 Hz, 3H, CH_3), 4.09 (q, *J*=6.3 Hz, 2H, CH_2), 6.55 (s, 1H, Ar), 6.84 (d, *J*=8.0 Hz, 2H, Ar), 7.16 (d, *J*=6.0 Hz, 1H, Ar), 7.64 (d, *J*=8.0 Hz, 1H, Ar), 7.81–7.84 (m, 1H, Ar), 7.93 (s, 1H, Ar), 8.05 (s, 1H, Ar), 8.15 (d, *J*=6.0 Hz, 2H, Ar), 8.92(s, 1H, Ar); δ_C (125 MHz, DMSO-d_6) 14.11, 30.10, 35.07, 52.33, 65.23, 100.43, 103.21, 105.66, 112.19, 121.10, 123.95, 124.98, 126.21, 127.14, 129.09, 130.11, 131.54, 133.23, 135.13, 139.00, 161.24, 162.96, 168.01(2); HRMS (ES+) calcd for [$C_{26}H_{20}N_4O_5S$+H] 501.12327, found 501.12320.

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Supplementary data

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30. CCDC 737619 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.