Structurally Simple, Potent, *Plasmodium* Selective Farnesyltransferase Inhibitors That Arrest the Growth of Malaria Parasites

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Third world nations require immediate access to inexpensive therapeutics to counter the high mortality inflicted by malaria. Here, we report a new class of antimalarial protein farnesyltransferase (PFT) inhibitors, designed with specific emphasis on simple molecular architecture, to facilitate easy access to therapies based on this recently validated antimalarial target. This novel series of compounds represents the first *Plasmodium falciparum* selective PFT inhibitors reported (up to 145-fold selectivity), with lead inhibitors displaying excellent in vitro activity (IC_{50} < 1 nM) and toxicity to cultured parasites at low concentrations (ED_{50} < 100 nM). Initial studies of absorption, metabolism, and oral bioavailability are reported.

Introduction

Malaria is an ancient, infectious disease that continues to inflict suffering and death on a large scale. Current estimates indicate that there are 300−500 million acute cases of malaria each year, resulting in 1−3 million deaths.[1] In the highest risk group, African children under the age of 5, malaria claims a young life every 40 s. Unfortunately, mortality from malaria appears to be increasing and is almost certainly associated with the increasing resistance of malaria parasites to available drugs.[2−4]

Malaria is caused by protozoal parasites of the genus *Plasmodium*, of which four species are known to cause malaria in humans: *falciparum*, *vivax*, *malariae*, and *ovale*. The parasites are transmitted through the bite of infected mosquitoes of the genus *Anopheles*, and following an initial asymptomatic localization and incubation in the liver, the parasites enter circulating erythrocytes and consume hemoglobin and other proteins within the cell. The protozoa replicate inside the blood cells, ultimately inducing cytolysis and release of toxic metabolic byproducts into the blood stream. The clinical symptoms of malaria result exclusively from the erythrocytic stage and include flulike symptoms, jaundice and anemia. Mortality is almost exclusively attributable to infection by *P. falciparum*, which produces specific proteins that embed into the cell membrane of the infected erythrocyte. These cells bind to prevenous capillaries, resulting in obstruction of blood vessels in many areas of the body. Of significant concern is the increasing discovery of *P. falciparum* resistance to existing drugs (chloroquine, mefloquine, sulfadoxime/pyrimethamine),[4,5] with strains now reported that are resistant to all known antimalarial therapies, potentially foreshadowing devastating consequences if new treatments are not identified.

The clear need for new effective antimalarials is complicated by the resource limitations of the countries most affected, with the overwhelming majority of mortality (∼90%) confined to the world's most impoverished nations.[1,6] In this setting, the development of new antimalarial treatments must give critical consideration to the economics of drug development and delivery. In an effort to reduce development costs and accelerate access to new antimalarials, recent attention has been directed toward identifying antimalarial activity from agents developed for the treatment of other diseases.[7−11]

On recognizing the essential role of prenylation for cellular function in lower eukaryotes,[7,12] several groups have investigated the antimalarial potential of inhibitors of protein farnesyltransferase (PFT[a]),[8,13−16] a recognized key target for the interception of aberrant Ras activity common to many (∼30%) human cancers.[17] Nallan et al. have recently surveyed a number of mammalian-cell-optimized PFT inhibitors that are in clinical and preclinical development, including those from Bristol-Myers Squibb (BMS) (e.g., **1**[16] and **2**[8]) and from the Hamilton/Sebti group (e.g., **3a** and **3b**),[13] for their abilities to inhibit *Plasmodium falciparum* PFT (PfPFT[a]) enzyme activity (as determined by IC_{50} values) and to arrest the in vitro growth of the intraerythrocytic forms of *P. falciparum* (as determined by ED_{50} values, Figure 1).[8] The peptidomimetics from Hamilton et al. proved to be potent inhibitors, with **3b** presumably a prodrug of **3a**, facilitating cell entry of the inhibitor and becoming active upon cleavage of the benzyl ester by cellular esterases. More potent still were heterocylic derivatives from BMS, with the tetrahydroquinoline (THQ) scaffold (e.g., **2**) being superior to the benzodiazepine scaffold (e.g., **1**). Recently, Schlitzer et al. have reported potent inhibitors of PfPFT based on a benzophenone scaffold, e.g., **4** (Figure 1).[15]

Treatment of *P. falciparum* infected cells with anticancer PFT inhibitors induces a decrease in farnesylated proteins and

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[a] Abbreviations: PFT, protein farnesyltransferase; *P. falciparum*, *Plasmodium falciparum*; PfPFT, *P. falciparum* protein farnesyltransferase; FPP, farnesyl pyrophosphate; ED_{50}, effective dose that inhibits 50% of *P. falciparum* proliferation; IC_{50}, inhibitor concentration that inhibits 50% of PFT enzyme activity.

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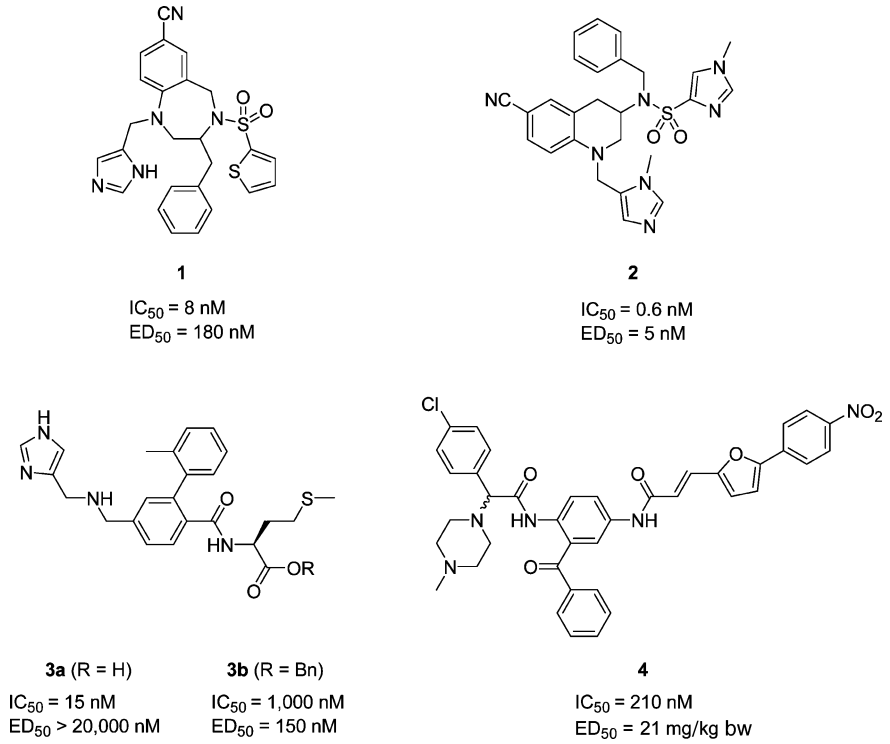


Figure 1. Protein farnesyltransferase (PFT) inhibitors and their activities against *P. falciparum* PFT (IC_{50} values represent the doses that inhibit 50% of the PfPFT enzyme activity) and *P. falciparum* growth (ED_{50} values represent the doses that inhibit 50% of *P. falciparum* growth).

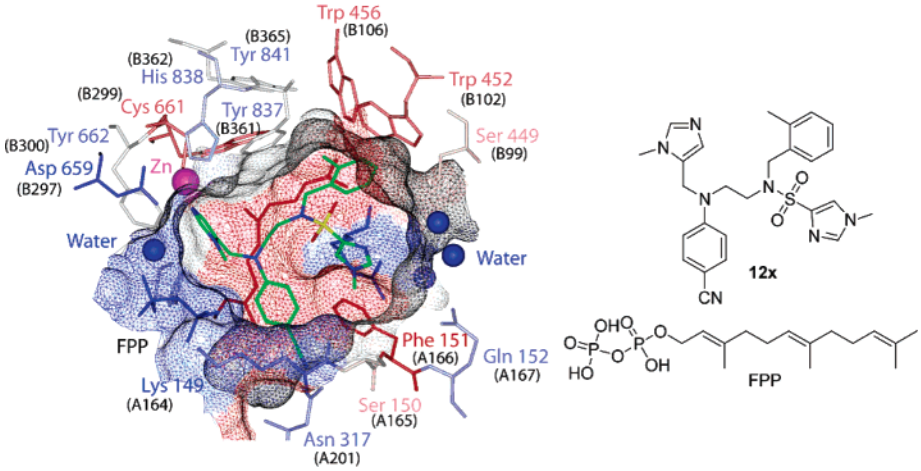


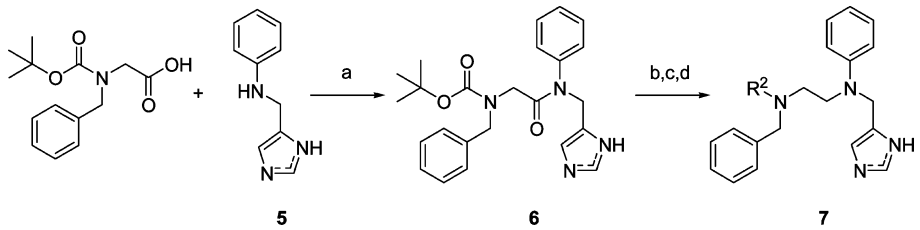
Figure 2. Active site conformation of **12x** (colored by atom type), as determined by flexible ligand docking (GOLD),[19] in the homology model of the active site of *Plasmodium* PFT (red hydrophobic to blue hydrophilic). Values in parentheses refer to the corresponding residues of rat FTase (PDB: 1JCR). FPP is shown in red.

associated lysis of the parasites.[11] Animal studies recently demonstrated that closely related derivatives of anticancer PFT inhibitors cure malaria-infected mice. However, the delivery costs (synthesis and administration) of drugs developed by wealthy nations for the treatment of diseases such as cancer may be prohibitively expensive for third-world nations, even in the absence of the associated costs for research and development. In this manuscript, we elaborate on our previous communication[14] with an extensive SAR study of our series of PFT inhibitors that have been developed specifically as novel antimalarial agents, emphasizing simple molecular architecture and straightforward chemical synthesis as prerequisites for access to low cost treatment for the third world.

Results and Discussion

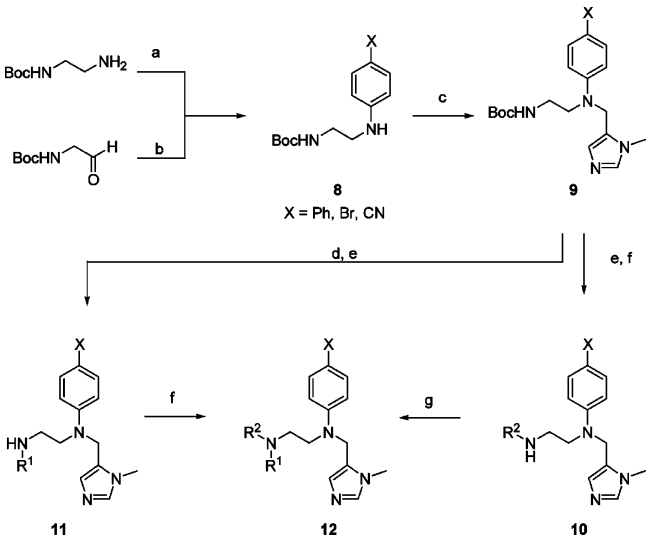
Design. PFT is one of three closely related heterodimeric zinc metalloenzymes (protein farnesyl- and geranylgeranyltransferases I and II) that catalyze the transfer of prenyl groups from farnesyl or geranylgeranyl pyrophosphate to the free thiol of a cysteine residue within a tetrapeptide recognition sequence (CaaX, a = aliphatic amino acid, X often is M, S, A, or Q for PFT) located at the carboxyl terminus of the substrate protein.[18] The X-ray crystal structure of rat PFT complexed with the selenotetrapeptide Ac-Cys-Val-Ile-Met(Se)-OH and a farnesylpyrophosphate (FPP) analogue (1JCR) shows a heterodimeric zinc metalloenzyme composed of a 48 kDa α-subunit and a 46 kDa β-subunit, with the tetrapeptide in an extended conformation and coordinated to the catalytic zinc ion through the cysteine thiol, in proximity to the FPP phosphonate. The sequences of the two subunits of PfPFT were obtained from the PlasmoDB database (gene loci: PFL2050w, α, and chr11.glm_528, β),[18,19] and aligned with the reported structure of rat PFT using the program T-COFFEE.[20] While PfPFT is found to be considerably

Scheme 1[a]



[a] Reagents and conditions: (a) HBTU, DIPEA, DMF; (b) TFA; (c) LAH, THF; (d) alkylsulfonyl chloride (R^2), TEA, DMF.

Scheme 2[a]



[a] Reagents and conditions: (a) 4-fluorobenzonitrile, TEA, DMSO, 120 °C; (b) (1) 4-X-aniline (X = Br, Ph) acetic acid, 3 Å molecular sieves, MeOH, (2) $NaCNBH_3$; (c) LDA, NaH, 5-chloromethyl-1-methyl-1*H*-imidazole·HCl (**16**), THF, −78 °C; (d) NaH, alkyl bromide (R^1), DMF, 0 °C; (e) TFA; (f) sulfonyl chloride (R^2), TEA, DMF; (g) alkyl bromide (R^1), Cs_2CO_3, DMF.

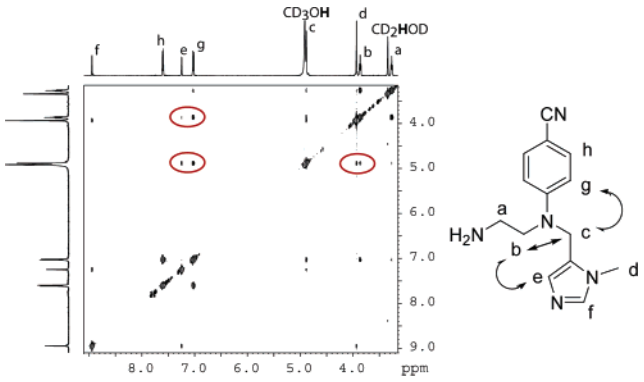
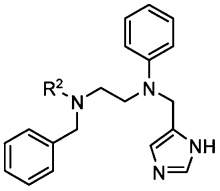
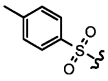
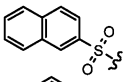
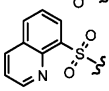
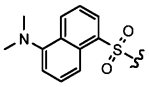


Figure 3. 2D NOESY of deprotected **9** (X = CN) in methanol-d_4 identifies the close spatial arrangement of protons about the imidazole and aniline, confirming chemoselective alkylation of the aniline nitrogen. Strong cross-peaks are observed (highlighted in red) between the methylene protons at c and the protons at g and b, while only a weak cross-peak is observed between protons at c and the methylene at a.

different from rat PFT, being significantly larger in both the α- (472 vs 379 residues) and β-subunits (621 vs 437), the differences are mainly due to insertions in the PfPFT protein sequence, and overall there is minimal difference in the residues that form the active site. A homology model of the active site of *P. falciparum* was generated by our collaborators at the University of Washington by using the sequence alignment of

Table 1. SAR of R^2 Sulfonamide Substitutions

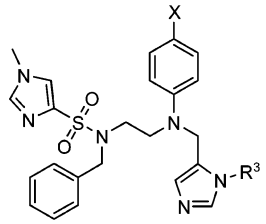


Compound Number	R^2	Inhibition of *Pf*PFT (%) at 50 nM
7a		7
7b		5
7c		32
7d		3
7e		0
7f		0
7g		0

PfPFT on the template crystal structure of rat PFT complexed with the nonsubstrate tetrapeptide inhibitor CVFM and farnesylpyrophosphate (FPP).[20] The homology model (Figure 2) indicates a large, open, and predominantly hydrophobic cavity for the active site (~20 × 20 × 20 Å^3), with the phospholipid binding partner (FPP) extending across the cavity base. The Zn ion coordinates to three residues (Cys 661, Asp 659, and His 838), with a water molecule hydrogen-bonded between the terminal phosphate of FPP and Asp 659 defining the limit of the Zn binding domain. The remainder of the active site cavity includes two well-defined hydrophobic pockets (Lys 149, Asn 317, Ser 150, Phe 151; Trp 456, Trp 452, Tyr 837) and a larger hydrophilic domain formed by Arg 564 and three water molecules participating in a hydrogen-bonded network between Ser 449 and Gln 152.

We envisaged accessing these four pockets from a simple aliphatic tether. Application of a flexible scaffold offers several

Table 2. SAR of X and R^3 Substitutions



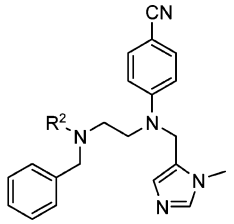
Compound			Inhibition of *Pf*PFT (%) at		ED_{50} (nM)[a]	
Number	X	R^3	50 nM	5 nM	3D7	K1
7c	H	H	32			
12a	Br	H	80			
12b	Br	Me	95	70	675	3200
12c[b]	Ph	Me	85	49	2500	2600
12d	CN	Me	98	86	349	367

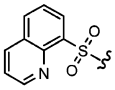
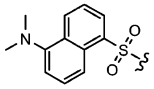
[a] Inhibitor concentration required to decrease hypoxanthine incorporation into parasites by 50%. [b] 2-Methylbenzyl in place of benzyl (see Table 3, R^1).

advantages to the design of a new series of PFT inhibitors. A simple acyclic scaffold may be obtained through a short series of straightforward chemical transformations and may be refractory to resistance arising from mutation of PfPFT.[20] One of the simplest of scaffolds conceivable, ethylenediamine, affords an inexpensive, 4-fold substitutable flexible tether of suitable size to project the appended diversity into the active site pockets. Imidazole provides a convenient zinc binding group, which has been consistently demonstrated to confer activity in other series of inhibitors.[13] To maintain a suitably lipophilic compound, extension from the amines has been restricted to formation of anilines, sulfonamides, and amides. Flexible ligand docking studies (GOLD)[19] of a series of compounds incorporating this basic design demonstrate complementarity to the active site of the homology model (Figure 2).

Synthesis. PFT inhibitors were prepared as outlined in Scheme 1, through a simple series of reductive amination, amide coupling, reduction, and alkylation. This route is not effective for the preparation of compounds bearing strong para electron-withdrawing groups on the aniline. In these systems, the amide coupling becomes increasingly difficult, and in the case of 4-cyanoaniline, the selective reduction of the amide also proves to be problematic. Performing the reductive amination with aniline derivatives (X = Ph and Br) and Boc-glycinal, followed by alkylation of the resulting aniline with chloromethyl-*N*-methylimidazole (**16**) proved to be suitable for the formation of the 4-bromo and 4-phenyl derivatives; however, reductive amination with 4-cyanoaniline proceeded in poor yield (Scheme 2). For the nitrile system, excellent yields of aniline **8c** can be obtained via nucleophillic substitution of *p*-fluorobenzonitrile with monoprotected ethylenediamine. Chemoselective alkylation of aniline **8c**, via double deprotonation with LDA and subsequent alkylation at the anilide anion, proceeds smoothly in THF with no evidence of alkylation of the carbamate (Figure 3). Finally, alkylation of the carbamate, deprotection, and coupling to sulfonyl or acid chlorides furnish the desired series of inhibitors.

Table 3. SAR of R^2 Substitutions with X = CN

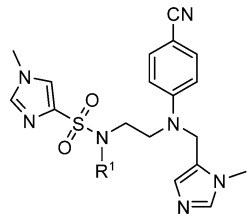


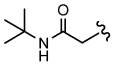
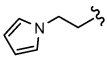
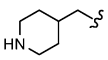
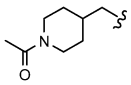
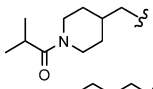
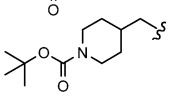
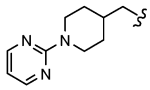
Compound		Inhibition of *Pf*PFT (%)		ED_{50} (nM)	
Number	R^2	at 50 nM	at 5 nM	3D7	K1
12e		69	18	2500	2250
12f		74	17	550	1125
12d		98	86	349	375
12g		95	64	570	2300
12h		35	14	2100	2400
12i		29	6	300	388
12j		56	0	2500	>5000
12k		61	0	2000	>5000

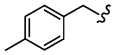
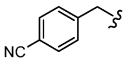
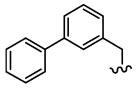
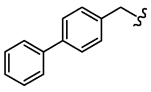
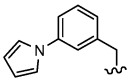
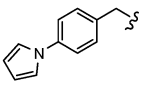
Structure−Activity Relationships. An initial series of inhibitors maintained the zinc binding imidazole and hydrophobic components (R^1 = benzyl, X = H) constant while exploring a small focused diversity set (R^2, seven substitutions) of sulfonamide substitutions predicted by docking studies (GOLD)[19] to reasonably access the hydrophilic pocket. The inhibition of PfPFT for these preliminary inhibitors was determined at a single concentration (50 nM), using a scintillation proximity assay with partially purified PfPFT[12] (Table 1). Four of the seven compounds inhibited PfPFT at 50 nM, with one compound (1-methyl-1*H*-imidazole-4-sulfonamide, **7c**) demonstrating very promising inhibition (32% at 50 nM). Elaboration of **7c**, through incorporation of para-substituted anilines (Br, CN, Ph, Scheme 2), induced at least a 2-fold improvement in activity (compare **12a** and **7c**, Table 2). Inspection of the docked conformations of **12a** and **12c** indicates that the para position of the aniline can reasonably access a hydrophilic domain formed by Ser 150, Asn 317, and Lys 149 at the limit of the mostly hydrophobic pocket occupied by the aniline (Figure 1).

Modification of the zinc binding imidazole has previously led to a significant impact on inhibitor potency in related

Table 4. SAR of R^1 Substitutions with X = CN



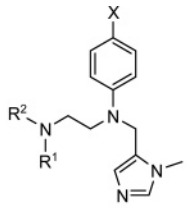
Compound Number	R^1	Inhibition of *Pf*PFT (%) at 50 nM	at 5 nM	ED_{50} (nM) 3D7	K1
12l		42	1	>5000	>5000
12m		77	6	>5000	>5000
12n		80	25	>5000	>5000
12o		6	4	2800	>5000
12p		56	11	>5000	>5000
12q		93	63	220	850
12r		84	28	575	400
12s		5	5	>5000	>5000
12t		44	8	5000	3500
12u		92	57	230	180
12v		96	81	88	54
12w		96	74	130	85
12d		98	86	349	375

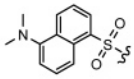
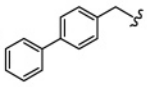
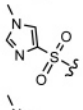
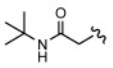
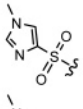
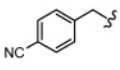
Compound Number	R^1	Inhibition of *Pf*PFT (%) at 50 nM	at 5 nM	ED_{50} (nM) 3D7	K1
12x		99	95	93	150
12y		94	61	300	1000
12z		54	45	2700	>5000
12aa		93	64	750	1000
12ab		74	18	2800	4250
12ac		62	22	3700	5000
12ad		89	45	350	1800
12ae		48	24	1600	4100
12af		93	56	2400	3250
12ag		19	10	700	2500
12ah		74	37	2500	4000
12ai		85	39	257	410

systems[13] and appears to be particularly important for effective activity in whole cells. The homology model for PfPFT indicates that small alkyl groups appended to the imidazole (3-methyl-3*H*-imidazol-) might reasonably be accommodated, and the corresponding methylimidazole inhibitors demonstrated significantly improved activity (compare **12b** to **12a**, Table 2). Inhibitor **12b**, and related methylimidazole inhibitor **12d**, additionally demonstrated inhibition of the growth of parasites in whole cells (3D7: $ED_{50} < 1\ \mu M$), as monitored through incorporation of tritium-labeled hypoxanthine (see Experimental Section for details).

Having identified a potent inhibitor with good whole-cell activity (**12d**), we revisited the series of sulfonamides, now incorporating both methylimidazole and *p*-cyanoaniline (Table 3). Inclusion of 1-methyl-1*H*-imidazole-4-sulfonamide as the R^2 substituent again conferred the best in vitro activity against PfPFT (**12d**, 86% inhibition at 5 nM), with similar potency observed for 2-pyridylsulfonamide (**12g**, 64% inhibition at 5 nM). Phenyl (**12e**), thiophene (**12f**), or quinoline (**12h**) sulfonamides were less active. Replacement of the sulfonamide by small alkylamides (methyl (**12j**) and isopropyl (**12k**)), indicated by docking studies to be able to access a hydrophobic cleft

Table 5. Comparison of Inhibitor Activity against *Plasmodium falciparum* and Rat PFT



Number	X	Compound R^1	R^2	IC_{50} (nM)[a] *Pf*PFT	rat PFT	selectivity[b]
12d	CN			0.5	25	47
12b	Br			2.0	290	145
17	Br			1.9	83	44
12aa	CN			2.1	43	20
12x	CN			0.6	15.5	27
12c	Ph			8.0	>1000	>125
12e	CN			8.9	13	1.5
12i	CN			55	180	3.3
12q	CN			4.5	7.5	1.7
12ag	CN			240	880	3.7
12o	CN			>1000	>1000	
12ae	CN			95	350	3.7

[a] Inhibitor concentration required to decrease farnesyltransferase activity by 50%. [b] Ratio of rat to *Plasmodium falciparum* PFT activity.

inaccessible to the larger sulfonamides, resulted in significantly reduced activity (56% and 61% inhibition at 50 nM, respectively). Good inhibition of the growth of parasites in whole cells (3D7, K1) was observed with methyl-1*H*-imidazole-4-sulfonamide (**12d**, ED_{50} = 349 and 375 nM, respectively) and dansylsulfonamide (**12i**, ED_{50} = 300 and 388 nM, respectively) despite the lower PfPFT activity observed for **12i**.

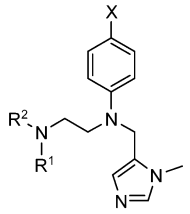
A broader series of substitutions was investigated for the R^1 hydrophobic pocket (~20 compounds) while maintaining the remaining three groups as previously optimized (Table 4). Replacement of the benzyl substituent with small alkyl groups that retained sp^2-hybridized centers (propenyl (**12l**), methylpropenyl (**12m**), bromopropenyl (**12n**), and *tert*-butylacetamidyl (**12o**)) provided inhibitors with reduced activity against PfPFT and no inhibition against the growth of parasites in cells (>5000 nM). Introduction of cyclohexylmethyl (**12q**) as a close comparison for benzyl provided activity similar to that of the parent inhibitor **12d** and offers slight improvement in whole-cell activity (3D7, ED_{50} = 220 nM; K1, ED_{50} = 850 nM). Incorporation of oxygen into the cyclohexyl ring to afford the tetrahydropyran **12r** is tolerated, while the similar piperidine **12s** is inactive. Activity of the piperidine derivatives is recovered with amides **12t**−**v**, with larger amides conferring improved activity. The large *tert*-butoxy carbamate derivative **12v** provides similar in vitro inhibition as the parent benzyl derivative **12d** but is significantly more toxic to erythrocytic parasite growth (3D7, ED_{50} = 88 nM; K1, ED_{50} = 54 nM). The isoelectronic inhibitor **12w** is similarly active against both PfPFT and parasite growth in whole cells.

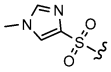
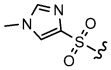
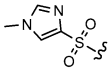
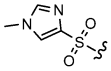
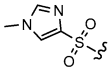
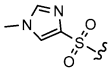
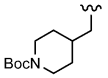
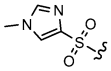
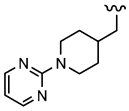
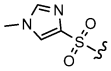
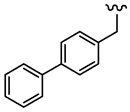
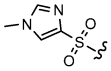
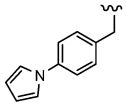
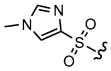
Incorporation of nitrogen in aryl substitutents (pyridine) is tolerated for the ortho position, but not for the meta or para position, and in all cases diminishes toxicity to parasites. A similar trend is observed for methyl and cyano substitution, with 2-methylbenzyl derivative **12x** providing excellent inhibition against both PfPFT and parasite growth in cells. Condensation of both 2-pyridyl (**12aa**) and 2-cyano derivatives with 1-methyl-1*H*-imidazole-4-sulfonyl chloride was problematic, and the latter was not prepared. Large R^1 benzyl substituents (phenyl or pyrrole) can be accommodated at the meta or para position with a modest reduction of PfPFT inhibition. In both cases whole-cell activity was better for the para-substituted compounds (**12ag**, **12ai**), with *p*-pyrrole **12ai** displaying whole-cell activity comparable to that of the unsubstituted benzyl system (**12d**). The 4-phenylbenzyl derivative **12ag** is approximately 4-fold less active than the closely related pyrimidine **12w**, despite their similar structures, while the related 4-pyrrole inhibitor **12ai** displays intermediate activity.

Overall, minor structural modification of any of the four ethylenediamine substituents has significant impact on PfPFT activity, and generally good correlation between PfPFT inhibition and toxicity to cultured parasites is observed, supporting PfPFT as the relevant target for the antimalarial activity. The generally straightforward synthesis of these structurally simple inhibitors facilitates rapid incorporation of diversity at any position and should greatly ease elucidation of inhibitors with "druglike" pharmacokinetics.

Selectivity. Previously reported PFT inhibitors have shown no selectivity for inhibition of parasitic over mammalian farnesyltransferase or are highly selective inhibitors of the mammalian enzyme.[7,8,12] While inhibition of farnesyltransferase has been demonstrated to have limited toxicity to mammalian cells at concentrations required to elicit a therapeutic response,[8] selective inhibition of parasitic farnesyltransferase may yet be an essential goal in the development of safe and effective antimalarial PFT inhibitors. To examine the selectivity of this new series of PFT inhibitors, 12 compounds were chosen on the basis of structural diversity and in vitro PfPFT activity and their 50% inhibition concentrations (IC_{50}) against both PfPFT and rat PFT were determined (Table 5). Eleven of the 12 compounds demonstrated selectivity for inhibition of PfPFT over rat PFT, representing to our knowledge the first reported series of *Plasmodium*-selective farnesyltransferase inhibitors. Six inhibitors displayed better than 10-fold selectivity for *Plasmodium* (**12b**−**d**, **12x**, **12aa**, **17**), with inhibitors **12b** and **12c** displaying over 100-fold selectivity. Examination of low-

Table 6. In Vitro, In Vivo, and Pharmacokinetic Properties of Selected PfPFT Inhibitors



Compound				IC_{50}(nM)[a]	ED_{50} (nM)[b]		Caco-2	Microsome	Oral Availability in Mice[c]		
Number	X	R^1	R^2	*Pf*PFT	3D7	K1	($cm \cdot s^{-1} \times 10^{-6}$)	$t_{1/2}$(min)	AUC ($\mu M \cdot min$)	C_{max} (μM)	$t_{1/2}$ (min)
12d	CN			0.54	349	375	1.1	mouse: 9 rat: 18	112.0	0.74	95.9
12b	Br			2.0	675	3200		muose: 2.9			
12c	Ph			8	2600	2500	0.4	mouse: 9.4 rat: 9.5			
12x	CN			0.6	93	150	0.4	mouse: 8 rat: 20	103[d]	1.05[d]	32.6[d]
12q	CN			4.5	220	850	1.5	mouse: <5 rat: 4			
12aa	CN			2.1	750	1000	1.8				
12v	CN			1.2	88	54	0.9	mouse: 14 rat: 60	414	2.97	70
12w	CN			1.5	130	85		mouse: 17 rat: 40			
12ag	CN			240	700	2500		mouse: 3.0			
12ai	CN			11	257	410		mouse: 3.6			
12g	CN			2.8	570	2300	2.8	mouse: 21 rat: 10.9	20.9	0.31	15.6

[a] Inhibitor concentration required to reduce PfPFT activity by 50%. [b] Inhibitor concentration required to reduce hypoxanthine incorporation into parasites by 50%. [c] Average results for three mice given 50 mg/kg po dose. [d] Average results for three rats given 50 mg/kg po dose.

energy docked conformations (GOLD)[19] of **12b** and **12c** in our homology model shows a consistent position of the para aniline substituent in the pocket formed by Asn 317 and Phe 151, corresponding to two (His 201 and Tyr 166, respectively) of only three residues in the active site that differ between PfPFT and rat PFT (PDB: 1JCR). Further work is being undertaken to better elucidate the binding modes of this series of inhibitors, but these preliminary observations provide tantalizing evidence for the potential development of highly selective PfPFT inhibitors through exploitation of the modest active site structural differences of farnesyltransferase isoforms.

Pharmacokinetics. On the basis of their in vivo activity and structural diversity, 11 PfPFT inhibitors were evaluated for metabolism and absorption, and in 5 cases oral bioavailability in mice or rats was examined (Table 6). Three of the 11 inhibitors are structurally divergent at the aniline (**12d**, **12b**,

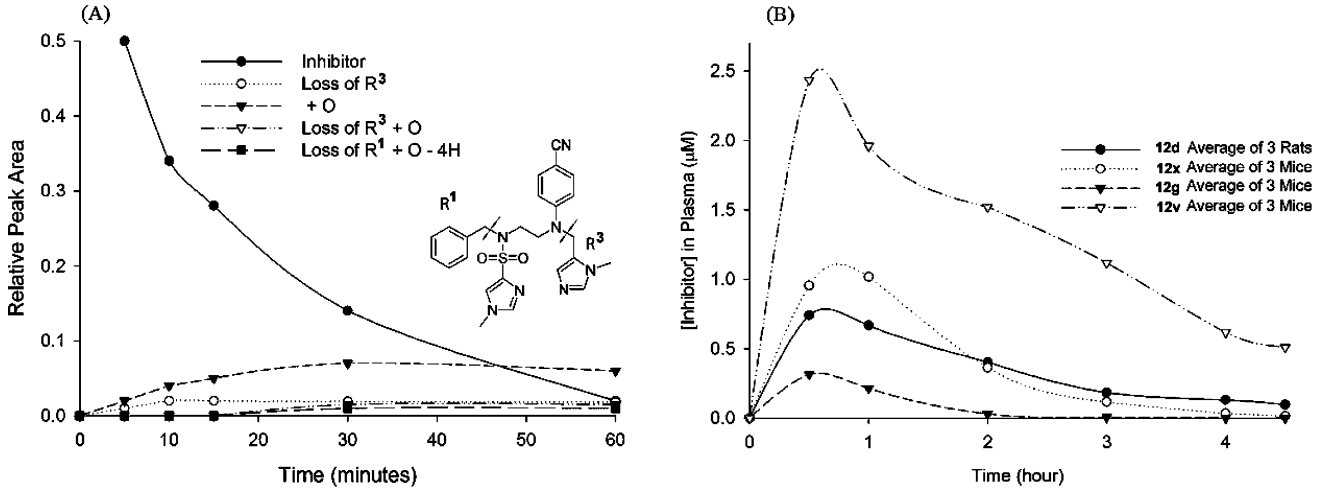


Figure 4. (A) Metabolism of **12d** by rat liver microsomes. (B) Average plasma concentrations of inhibitors **12d**, **12x**, **12g**, and **12v** in three rats or mice after oral gavage (dose: rats 12.5 mg, mice 1 mg).

12c, with X = CN, Br, Ph, respectively). Seven represent modifications of the hydrophobic binding substituent R^1, and one inhibitor differs by the hydrophilic binding sulfonamide R^2 (**12g**). For each of these inhibitors, the concentration required to reduce PfPFT activity by 50% (IC_{50}) has also been determined (Table 6).

Metabolism. Liver microsomes provide a convenient model of in vitro hepatic metabolism, allowing rapid initial assessment of the relative metabolic stability of a series of inhibitors. On treatment of **12d** with rat or mouse liver microsomes, complete metabolism was observed within 1 h (Figure 4A), with inhibitor half-lives of 18 and 9 min, respectively (Table 6). Residual metabolite mass spectrum ionization reflected only a minor proportion of the initial ionization observed (<10%) and corresponded principally to oxidation of the inhibitor (+O), and oxidation with loss of the aniline imidazole ($-R^3 + O$). Despite the presence of the strong para electron-withdrawing group (CN), a metabolism pathway may reasonably involve oxidation of the aniline nitrogen, followed by N-dealkylation.[21] However, the metabolism half-lives of inhibitors **12b** and **12c**, bearing less electronegative para substitution (Br and Ph, respectively), exhibit only relatively minor charges in stability, suggesting that aniline oxidation may not be the primary site of metabolism.

The methylbenzyl inhibitor **12x** displayed a metabolism profile very similar to that of **12d**, despite the additional benzylic position, which may be expected to be readily oxidized. In comparison, **12q**, incorporating cyclohexylmethyl as the hydrophobic substituent in place of the benzyl, is metabolized significantly more rapidly ($t_{1/2}$ < 5 min). The related but larger piperidine derivatives **12v** and **12w** are considerably more stable (rat $t_{1/2}$ = 60 and 40 min, respectively), which does not appear to be directly related to the increased size of this substituent, given the rapid metabolism of the very similar 4-phenyl- and 4-pyrrolebenzyl derivatives **12ag** and **12ai (**mouse $t_{1/2}$ < 4 min). Inhibitors **12v** and **12w** bearing isoelectronic R^1 piperidine substitution represent the most metabolically stable inhibitors observed in this series, and in general, modification of the R^1 position has been found to have the greatest overall impact on the rate of microsome metabolism. Efforts are ongoing to identify the principal metabolic pathway operative for this series of inhibitors.

Absorption. Caco-2 cells cultured on a semipermeable membrane form a highly functionalized epithelial barrier, with remarkable similarity to small intestinal epithelial cells, including high levels of brush border hydrolases and well-developed junctional complexes. The apparent permeability of small molecules across these membranes represents a well established in vitro model of in vivo intestinal wall transport that has demonstrated good correlation with intestinal absorption in humans.[22,23] The apparent permeability coefficients of a selection of ethylenediamine PFT inhibitors were generally low (Table 6, $(0.4-2.8) \times 10^{-6}$ cm/s) but not unacceptably removed from values typically observed for drugs that are fully absorbed in humans ($>1 \times 10^{-6}$ cm/s).[23] Sensitivity to structural modification was observed, with three compounds (**12q**, **12aa**, **12g**) displaying reasonable permeability coefficients ($>1.5 \times 10^{-6}$ cm/s).

Oral Bioavailability. Oral administration is the preferred route of drug delivery but is essential when considering the development of an effective antimalarial for use in the third world. Oral administration of **12d**, an inhibitor with both moderate microsome stability and apparent permeability, in saline (50 mg/kg in 90% saline, 3% ethanol, 7% Tween) to rats with monitoring of inhibitor concentration in plasma over 5 h resulted in a peak inhibitor concentration (C_{max}) of 0.74 μM after 30 min (T_{max}), with an elimination half-life of 96 min ($t_{1/2}$) (Table 6, Figure 4B). Similar inhibitor concentrations in plasma were observed for **12x** after oral dosing in mice (50 mg/kg), with a slightly elevated peak inhibitor concentration (C_{max} = 1.05 μM, T_{max} = 40 min). On the basis of Caco-2 permeability and metabolism profiles similar to those of **12d** and **12x**, **12g** (Caco-2: 2.8×10^{-6} cm/s) was expected to demonstrate improved oral bioavailability. However, oral administration of **12g** to mice identified extremely disappointing concentrations of the inhibitor in plasma, with maximum peak concentrations and clearance rates (C_{max} = 0.31 μM, T_{max} = 30, $t_{1/2}$ = 16 min) significantly lower than those observed for **12d** and **12x** (Table 6). In comparison, **12v**, which demonstrated long half-life stability against liver microsome metabolism (rat $t_{1/2}$ = 60 min), had considerably improved inhibitor availability in blood plasma after oral dosing in mice. An average concentration of **12v** in plasma ~6-fold above the concentration required to reduce parasite growth in erythrocytes by 50% (3D7, ED_{50} = 88 nM; K1, ED_{50} = 54 nM) was maintained for the duration of the experiment (5 h), with an average peak plasma inhibitor concentration 30-fold over the ED_{50} observed within 40 min (Table 6, Figure 4B).

Conclusion

In summary, new, simple acyclic PfPFT inhibitors have been developed and their efficacy against PfPFT and reduction of

parasite load in infected erythrocytes have been evaluated. Compounds based on this readily accessible scaffold are found to be highly active inhibitors of PfPFT, with IC_{50} values as low as 0.5 nM identified from the initial diversity set (~40 compounds). Effective translation of this activity into whole-cell models of parasitemia is observed, with four compounds requiring doses of less than 100 nM to reduce parasite populations (3D7, K1) in erythrocytes by 50%. A preliminary study of the pharmacokinetic profile of this series of inhibitors identifies metabolism and absorption rates, as measured by microsome metabolism and Caco-2 permeability, to be responsive to minor structural modification. Relatively metabolically stable ($t_{1/2} \approx 60$ min) inhibitors have been identified, in addition to compounds with promising Caco-2 permeability. Further, oral gavage of a microsome stable inhibitor to mice identified very encouraging concentrations of inhibitor maintained in blood plasma over 5 h. We are hopeful that elaboration of this series will identity exceptionally potent inhibitors of PfPFT, with suitable pharmacokinetic profiles to allow a drug candidate to progress further. The structural simplicity that underlines the design of these compounds should greatly facilitate third-world nation access to any potential drug emergent from these novel PFT inhibitors.

Experimental Section

***Plasmodium* Strains.** The *P. falciparum* strains used in this study were 3D7 (The Netherlands, sensitive), provided by Dr. Pradipsinh Rathod from the University of Washington, and K1 (Thailand, ChQ-R, Pyr-R), obtained from the MR4 unit of the American Type Culture Collection (ATCC, Manassas, VA).

***P. falciparum* Culture.** Strains of *P. falciparum* were sustained in vitro on the basis of experimental techniques as described by Trager and Jensen.[24] Cultures were maintained in RPMI-1640 (Sigma, St. Louis, MO) with 2 mM L-glutamine, 25 mM HEPES, 33 mM $NaHCO_3$, 20 μg/mL gentamicin sulfate, and 20% (v/v) heat-inactivated human plasma type A+ (RP-20P). Type A+ erythrocytes were obtained from lab donors, washed three times with RPMI, resuspended in 50% RPMI, and stored at 4 °C. Parasites were grown in 10 mL of a 2% hematocrit/RP-20P (v/v) in 50 mL flasks under a 5% CO_2, 5% O_2, and 90% N_2 atmosphere.

***P. falciparum* ED_{50} Determination.** An amount of 1 μL of PfPFT inhibitor dissolved in DMSO was added to each well of a 96-well plate followed by the addition of 200 μL of *P. falciparum* culture at parasitemia and hematocrit of 0.5%. Plates were flushed with 5% CO_2, 5% O_2, and 90% N_2 and then incubated at 37 °C for 48 h. [8-^{3}H]Hypoxanthine (0.3 μCi, 20 Ci/mmol, American Radiolabeled Chemicals) in 30 μL of RP-20P was added to cultures and incubated for an additional 24 h. Cells were harvested onto filter mats by a multiharvester (Skatron, Sunnyvale, CA), and the radioactivity incorporated into the parasites was counted on a β-scintillation counter. The background level detected with uninfected erythrocytes was subtracted from the data. The ^{3}H-incorporation into infected RBCs with 1 μL of DMSO vehicle alone represents 100% malaria growth. ED_{50} values were determined by linear regression analysis of the plots of [^{3}H]hypoxanthine incorporation versus concentration of compound.

PfPFT IC_{50} Determination. Assays for PfPFT activity were performed with a PFT-specific scintillation assay (SPA) kit (Amersham Biosciences, Piscataway, NJ) slightly modified from that previously described.[12] An amount of 1 μM biotinylated lamin B peptide substrate (biotin-YRASNRSCAIM) was used. The concentration of [^{3}H]farnesyl pyrophosphate (FPP) (3.7 MBq) was increased beyond manufacturer's recommendations to 1 μM. IC_{50} values were calculated using linear regression analysis of the plots of [^{3}H]FPP prenylation versus concentration of compounds.

Microsome Metabolism. Liver microsome metabolism assays were performed with female pooled microsomes from BD Biosciences (20 mg/mL). Reaction wells containing phosphate buffer (232 μL, 0.6 M), $MgCl_2$ (12.0 μL, 0.1 M), EDTA (0.8 μL, 0.5 M), 10× NADPH regenerating system (40.0 μL), glucose-6-phosphate deghydrogenase (0.8 μL, 500 U/mL), Milli-Q water (267.8 μL), and liver microsomes (10.0 μL, 20 mg/mL) were heated at 37 °C for 10 min. To each reaction well was added inhibitor (200 μM, 2.0 μL) in DMSO. Control runs included standard compounds such as propanolol and tetrahydroquinoline compounds. Reactions were quenched with acetonitrile (75 μL) and internal standard at designated time points, and the sample was immediately frozen (−20 °C). Metabolites and unreacted inhibitor were quantified by liquid chromatography/mass spectrometry.

Ligand Docking Studies. Ligand energy minimization was peformed with the CVFF force field in InsightII on an SGI O2. Flexible ligand docking studies were subsequently performed with GOLD, version 3.0,[19] on a Linux PC. Default GOLD parameters were utilized with the following exceptions: (i) maximal ligand flexibility was allowed; (ii) the affinity of nitrogen for zinc ion was increased in the GOLD parameters file to better reflect the ability of an imidazole ring to bind to the active site metal ion. Each ligand was used to seed the genetic algorithm 10 times.

Chemistry: General Methods. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 400 MHz and Bruker AM 500 MHz spectrometers. Analysis and purification by reversed-phase HPLC (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 water/0.1% TFA (A) and 10:1 acetonitrile/water (B) with 0.1% TFA. Product fractions were always lyophilized to dryness. 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 minute after an initial 2 min of 100% A. Mass determinations were performed using electrospray ionization on either a Varian MAT-CH-5 (HRMS) or Waters Micromass ZQ (LRMS). Solvents DMF, THF, and CH_2Cl_2 were dried on an Innovative Technology SPS-400 dry solvent system. Methanol, TEA, and DMSO were dried over calcium hydride. Molecular sieves were activated by heating to 300 °C under vacuum overnight.

General Procedure A (Alkylation of Carbamates). Sodium hydride (60% dispersion, 1.5 equiv) was added in one portion to a solution of the carbamate (1.0 equiv) dissolved in DMF (2 mL/mmol) at 0 °C. The resulting suspension was stirred for 5 min before addition of the alkyl halide (1.1 equiv), and stirring was then continued for a further 10 min. The resulting solution was diluted with EtOAc (20 mL/mmol) and washed consecutively with equal portions of 1.0 M aqueous HCl, saturated $NaHCO_3$, and brine. The organic phase was dried over magnesium sulfate, and the solvent was removed under vacuum. The crude reaction product was generally deprotected immediately by dissolving the crude material in TFA (1 mL/mmol) and stirring for 10 min. After removal of the TFA under reduced pressure, the resulting oil was purified by rpHPLC to provide the product amine as the TFA salt.

General Procedure B (Alkylation of Sulfonamides). The required alkyl bromide (1.1 equiv) was added in one portion to a solution of the primary sulfonamide (1.0 equiv) and Cs_2CO_3 (1.5 equiv) in DMF (5 mL/mmol), and the resulting solution was stirred for 2 days at room temperature. Filtration and purification by rpHPLC provided the desired compound as the TFA salt.

General Procedure C (Reaction of Amines with Sulfonyl or Acid Chlorides). The required sulfonyl or acid chloride (1.2 equiv) was added in one portion to a solution of the amine (1.0 equiv) and dry TEA (5.0 equiv) in DMF (2 mL/mmol) at 0 °C. The mixture was stirred for 10 min, diluted with acetonitrile, and purified directly by rpHPLC to provide the desired sulfonamide as the TFA salt.

1-Trityl-1*H*-imidazole-4-carbaldehyde (13). Dry triethylamine (12.6 mL, 90.0 mmol) was added dropwise over 2 h to a slurry of (1,3)-*H*-imidazole-4-carbaldehyde (5.0 g, 52 mmol) and trityl chloride (16.0 g, 57.0 mmol) in acetonitrile (170 mL). After complete addition of the triethylamine, the resulting solution was stirred overnight and then hexane (16.6 mL) and water (170 mL) were added. After the mixture was stirred for an additional 30 min,

the resulting solid was collected and dried overnight under vacuum to provide the title compound as a white solid (16.8 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.29 (m, 10H), 7.04 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.9, 141.9, 141.2, 141.0, 130.0, 129.0, 128.9, 127.2, 76.7.

3-Methyl-3*H*-imidazole-4-carbaldehyde Trifluoromethanesulfonate (14). Methyl triflate (10.0 g, 60.1 mmol) was added dropwise over 5 h to a solution of aldehyde **13** (13.5 g, 40.0 mmol) in CH_2Cl_2 (50 mL), and the resulting solution was stirred overnight at room temperature. The volume of solvent was then reduced under vacuum (~30 mL), and hexane (40 mL) was added. Stirring was continued for a further 30 min, at which time the crude solid of 3-methyl-1-trityl-1*H*-imidazole-4-carbaldehyde trifluoromethanesulfonate was collected and washed with hexane (3 × 25 mL). This solid was immediately dissolved in 2:1 acetone/water (40 mL) and stirred for 4 h at room temperature. The resulting suspension was filtered, the solid washed with water (30 mL), and the supernatant concentrated under vacuum, then lyophilized to afford the title compound as a white solid (9.7 g, 93%). ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.84 (s, 1H), 7.50 (s, 1H), 5.77 (s, 1H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 188.6, 148.4, 140.8, 135.3, 30.2.

(3-Methyl-3*H*-imidazol-4-yl)methanol (15). 3-Methyl-3*H*-imidazole-4-carbaldehyde (**14**) (4.0 g, 15 mmol) was suspended in THF (10 mL), and the resulting solution was cooled to 0 °C. Lithium aluminum hydride (300 mg, 32.0 mmol) was added portionwise over 10 min, and the resulting suspension was stirred for a further 10 min. Excess hydride was quenched by the careful addition of solid $Na_2SO_4 \cdot 10H_2O$ (~1 g) in small portions with vigorous stirring. Additional THF was added as needed to prevent solidification of the resulting slurry. The resulting suspension was stirred for a further hour and then filtered to remove the sulfate salts, and the solvent was removed under reduced pressure to provide the title alcohol (1.3 g, 80%). ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.57 (s, 1H), 6.89 (s, 1H), 4.58 (s, 2H), 372 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 140.1, 132.7, 128.1, 31.9, 31.0.

5-Chloromethyl-1-methyl-1*H*-imidazole (16). DMF (1 drop) was added to a slowly stirred solution of (3-methyl-3*H*-imidazol-4-yl)methanol (**15**) (1.8 g, 16 mmol) dissolved in thionyl chloride (12 mL). After 30 min the solvent was removed under reduced pressure, and the resulting solid was triturated with diethyl ether (20 mL). The resulting semisolid was dried overnight under vacuum and used without further purification. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.98 (s, 1H), 7.63 (s, 1H), 4.85 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 138.3, 132.6, 120.5, 34.5, 33.9.

Benzyl-{[(3*H*-imidazol-4-ylmethyl)phenylcarbamoyl]methyl}-carbamic Acid *tert*-Butyl Ester (6). HBTU (2.2 g, 5.8 mmol) was added in one portion to a solution of (benzyl-*tert*-butoxycarbonylamino)acetic acid[25] (1.6 g, 5.8 mmol) and DIPEA (4.9 mL, 29 mmol) dissolved in DMF (300 mL), and the resulting solution was stirred for 10 min before addition of (3*H*-imidazol-4-ylmethyl)-phenylamine (**5**) (1.0 g, 5.8 mmol). The mixture was stirred at room temperature for 1 h, after which the volume of solvent was reduced (~20 mL) under vacuum and the resulting residue dissolved in EtOAc (500 mL) and washed successively with 1.0 M HCl (2 × 200 mL), saturated $NaHCO_3$ (2 × 200 mL), and brine (200 mL). The organic layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure. Purification by flash column chromatography (1:4 MeOH/EtOAc) provided the title compound (1.88 g, 77%). LRMS calcd for $C_{24}H_{29}N_4O_3^+$ 421.2, found 421.4. NMR data were consistent with the proposed structure but complicated by the presence of configurational isomers of the carbamate and or amide. Full characterization is reported on the deprotected and reduced products below.

***N′*-Benzyl-*N*-(3*H*-imidazol-4-ylmethyl)-*N*-phenylethane-1,2-diamine (7).** Carbamate **6** (500 mg, 1.20 mmol) was dissolved in TFA/water (100:1, 25 mL) and the resulting solution stirred for 20 min. The solvent was removed under reduced pressure and the residue triturated with ether and dried under vacuum. The resulting viscous oil was dissolved in THF (50 mL), and LAH (190 mg, 5.00 mmol) was added in portions. After the mixture was stirred for 1 h at room temperature, $Na_2SO_4 \cdot 10H_2O$ (~1.0 g) was added, and the resulting suspension was stirred overnight. The mixture was filtered and solvent removed under reduced pressure to afford the title compound, which was purified by rpHPLC (230 mg, 63%). LRMS calcd for $C_{19}H_{23}N_4^+$ 307.2, found 307.1. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.61 (s, 1H), 7.33 (m, 5H), 7.19 (s, 1H), 7.15 (m, 2H), 7.01 (t, J = 7.15 Hz, 1H), 6.82 (d, J = 8.61 Hz, 2H), 4.53 (s, 2H), 4.15 (s, 2H), 3.62 (t, J = 6.86 Hz, 2H), 3.15 (t, J = 6.83 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 138.0, 134.7, 131.6, 129.9, 129.5, 129.2, 128.8, 126.7, 118.2, 113.3, 53.7, 50.2, 48.0, 46.9.

***N*-Benzyl-*N*-{2-[(3*H*-imidazol-4-ylmethyl)phenylamino]ethyl}-benzenesulfonamide (7a, X = H, R^1 = Benzyl, R^2 = Phenylsulfonyl, R^3 = H).** Reaction of **7** was carried out according to procedure C. Yield 71%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.71 (s, 1H), 7.79 (d, J = 7.17 Hz, 2H), 7.61 (tt, J = 1.17, 7.10 Hz, 1H), 7.54 (m, 2H), 7.24 (m, 5H), 7.05 (s, 1H), 7.13 (m, 2H), 6.93 (t, J = 7.10 Hz, 1H), 6.79 (d, J = 8.45 Hz, 2H), 4.31 (s, 2H), 4.18 (s, 2H), 3.54 (m, 2H), 3.19 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.4, 138.3, 138.0, 135.0, 131.3, 130.9, 129.7, 129.4, 129.2, 128.8, 126.5, 119.8, 116.8, 113.8, 55.3, 51.8, 48.9, 46.7. HRMS calcd for $C_{25}H_{26}N_4O_2SH^+$ 447.1849, found 447.1840. Retention time for analytical rpHPLC: condition I, 10.42; condition II, 13.10 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid Benzyl-{2-[(3*H*-imidazol-4-ylmethyl)phenylamino]ethyl}amide (7c, X = H, R^1 = Benzyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = H). Reaction of **7** was carried out according to procedure C. Yield 62%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.74 (s, 1H), 7.75 (s, 1H), 7.69 (s, 1H), 7.28 (m, 5H), 7.22 (s, 1H), 7.04 (t, J = 7.40 Hz, 2H), 6.64 (t, J = 7.30 Hz, 1H), 6.45 (d, J = 8.02 Hz, 2H), 4.40 (s, 2H), 4.22 (s, 2H), 3.73 (m, 5H), 3.30 (obscured). ^{13}C NMR (100 MHz, MeOH-d_4): δ 148.6, 141.8, 138.3, 135.7, 133.5, 131.4, 130.7, 130.6, 130.2, 129.6, 127.0, 119.6, 118.4, 114.8, 55.2, 52.3, 46.8, 46.6, 34.7. HRMS calcd for $C_{23}H_{26}N_6O_2SH^+$ 451.1916, found 451.1908. Retention time for analytical rpHPLC: condition I, 10.49; condition II, 12.95 min.

***N*-Benzyl-*N*-{2-[(3*H*-imidazol-4-ylmethyl)phenylamino]ethyl}-*C*-*p*-tolylmethanesulfonamide (7d, X = H, R^1 = Benzyl, R^2 = 4-Methylbenzylsulfonyl, R^3 = H).** Reaction of **7** was carried out according to procedure C. Yield 71%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.61 (s, 1H), 7.39 (m, 5H), 7.32 (s, 1H), 7.23 (d, J = 7.80 Hz, 2H), 7.19 (m, 2H), 7.05 (d, J = 7.78 Hz, 2H), 6.87 (d, J = 8.58 Hz, 2H), 6.83 (t, J = 7.33 Hz, 1H), 4.54 (s, 2H), 4.09 (s, 2H), 3.97 (s, 2H), 3.60 (t, J = 6.96 Hz, 2H), 3.12 (t, J = 6.95 Hz, 2H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 148.4, 138.5, 135.7, 132.7, 132.6, 132.4, 131.8, 131.5, 131.2, 131.1, 130.5, 121.9, 118.6, 117.7, 114.9, 58.6, 55.4, 52.8, 47.7, 45.5, 21.6. HRMS calcd for $C_{27}H_{30}N_4O_2SH^+$ 475.2168, found 475.2154. Retention time for analytical rpHPLC: condition I, 10.65; condition II, 13.39 min.

Naphthalene-2-sulfonic Acid Benzyl-{2-[(3*H*-imidazol-4-ylmethyl)phenylamino]ethyl}amide (7e, X = H, R^1 = Benzyl, R^2 = 2-Naphthylsulfonyl, R^3 = H). Reaction of **7** was carried out according to procedure C. Yield 65%. ^{1}H NMR (500 MHz, MeOH-d_4): δ 8.30 (s, 1H), 7.89 (m, 5H), 7.52 (m, 2H), 7.42 (m, 4H), 7.26 (s, 1H), 7.21 (m, 3H), 6.85 (d, J = 7.04 Hz, 2H), 6.79 (t, J = 7.36 Hz, 1H), 4.57 (s, 2H), 4.39 (s, 2H), 3.71 (t, J = 6.86 Hz, 2H), 3.27 (t, J = 6.79 Hz, 2H). ^{13}C NMR (125 MHz, MeOH-d_4): δ 148.4, 135.9, 135.8, 134.3, 132.7, 131.4, 131.2, 131.1, 130.7, 130.2 (2C), 129.8, 129.2, 128.9, 128.3, 126.9, 124.5, 121.8, 118.5, 117.5, 52.9, 48.1, 46.7, 45.8. HRMS calcd for $C_{29}H_{28}N_4O_2SH^+$ 497.2006, found 497.1998. Retention time for analytical rpHPLC: condition I, 10.71; condition II, 12.93 min.

Quinoline-8-sulfonic Acid Benzyl-{2-[(3*H*-imidazol-4-ylmethyl)-phenylamino]ethyl}amide (7f, X = H, R^1 = Benzyl, R^2 = 8-Quinolinesulfonyl, R^3 = H). Reaction of **7** was carried out according to procedure C. Yield 70%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.79 (dd, J = 1.45, 4.26 Hz, 1H), 8.63 (dd, J = 1.38, 7.48 Hz, 1H), 8.39 (dd, J = 1.75, 8.41 Hz, 1H), 8.32 (dd, J = 1.36, 8.26, 1H), 8.21 (d, J = 1.25 Hz, 1H), 7.77 (t, J = 7.61 Hz, 1H), 7.57 (dd, J = 4.29, 8.40 Hz, 1H), 7.43 (m, 5H), 7.20 (s, 1H), 6.99

(dd, $J = 7.38$, 8.80 Hz, 2H), 6.61 (m, 3H), 4.32 (s, 2H), 4.21(s, 2H), 3.74 (t, $J = 5.53$ Hz, 2H), 3.28 (t, $J = 5.52$ Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 155.5, 150.86, 146.8, 144.3, 143.1, 140.8, 140.5, 137.5, 136.7, 135.3, 133.5, 133.3, 133.0, 132.9, 132.7, 129.3, 126.7, 122.0, 119.9, 117.1, 54.8, 53.0, 52.0, 49.7. HRMS calcd for $C_{28}H_{27}N_5O_2SH^+$ 498.1964, found 498.1956. Retention time for analytical rpHPLC: condition I, 10.62; condition II, 13.43 min.

5-Dimethylaminonaphthalene-1-sulfonic Acid Benzyl-{2-[(3*H*-imidazol-4-ylmethyl)phenylamino]ethyl}amide (7g, X = H, R^1 = Benzyl, R^2 = Dimethylaminonaphthalenesulfonyl, R^3 = H). Reaction of **7** was carried out according to procedure C. Yield 63%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.68 (dd, $J = 0.85$, 8.51 Hz, 1H), 8.43 (dd, $J = 1.20$, 7.49 Hz, 1H), 8.16 (d, $J = 8.69$ Hz, 1H), 7.99 (d, $J = 1.37$, 1H), 7.65 (dd, $J = 7.53$, 8.51 Hz, 1H), 7.54 (dd, $J = 7.70$, 8.62, Hz, 1H), 7.53 (s, 1H), 7.36 (m, 5H), 7.26 (d, $J = 7.67$ Hz, 1H), 6.99 (dd, $J = 7.36$, 8.78 Hz, 2H), 6.63 (t, $J = 7.30$, 1H), 6.59 (d, $J = 7.96$ Hz, 2H), 4.30 (s, 2H), 4.17 (s, 2H), 3.72 (t, $J = 5.24$ Hz, 2H), 3.24 (obscured), 2.83 (s, 6H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 154.3, 148.6, 143.3, 139.0, 135.0, 134.0, 133.1, 132.8, 131.6, 131.4, 131.3, 131.1, 130.9, 130.7, 130.6, 125.0, 120.0, 118.7, 117.6, 117.2, 115.1, 52.6, 51.0, 48.8, 47.4, 46.1. HRMS calcd for $C_{31}H_{33}N_5O_2SH^+$ 540.2428, found 540.2419. Retention time for analytical rpHPLC: condition I, 10.70; condition II, 13.51 min.

[2-(4-Bromophenylamino)ethyl]carbamic Acid *tert*-Butyl Ester (8b, X = Br). A solution of 4-bromoaniline (6.5 g, 37 mmol), (2-oxoethyl)carbamic acid *tert*-butyl ester (2.0 g, 12 mmol), and acetic acid (790 μL, 12.4 mmol) in dry methanol (20 mL) with dry 3 Å molecular sieves (1.0 g) was stirred under nitrogen for 20 min. Sodium cyanoborohydride (0.79 g, 12 mmol) was added in one portion, and the resulting solution was stirred for a further hour under nitrogen, at which time EtOAc (300 mL) was added and the organic phase washed consecutively with 1.0 M aqueous HCl (1 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), and brine (1 × 100 mL). The organic phase was dried over magnesium sulfate, and the solvent was removed under vacuum to provide the title compound as a viscous yellow oil (3.1 g, 79%) after flash column chromatography (1:4 EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, $J = 8.88$ Hz, 2H), 6.38 (d, $J = 8.89$ Hz, 2H), 4.88 (br s, 1H), 3.26 (br s, 2H), 3.09 (br t, $J = 5.94$ Hz, 2H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 147.5, 132.6, 114.6, 109.2, 80.1, 44.5, 40.3, 29.0.

{2-[(4-Bromophenyl)-(3*H*-imidazol-4-ylmethyl)amino]ethyl}-carbamic Acid *tert*-Butyl Ester (9b-H, X = Br, R^3 = H). A solution of aniline **8b** (0.50 g, 1.6 mmol) and 3*H*-imidazole-4-carbaldehyde (0.30 g, 3.2 mmol) in dry methanol (5.0 mL) with dry 3 Å molecular sieves (0.20 g) was stirred under nitrogen for 20 min. Sodium cyanoborohydride (0.20 g, 3.2 mmol) was added in one portion, and the resulting solution was stirred overnight under nitrogen at 50 °C. The resulting solution was diluted with EtOAc (100 mL) and then washed consecutively with 1.0 M aqueous HCl (1 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), and brine (1 × 100 mL). The organic phase was dried over magnesium sulfate, and the solvent was removed under vacuum to provide the title compound as a viscous yellow oil, which was purified by flash column chromatography (10:1 CH_2Cl_2/MeOH) (0.21 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.16 (d, $J = 9.02$ Hz, 2H), 6.71 (s, 1H), 6.60 (d, $J = 9.04$ Hz, 2H), 4.36 (s, 2H), 3.40 (t, $J = 6.31$ Hz, 2H), 3.21 (t, $J = 6.30$ Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 147.7, 135.4, 132.2 (2C), 117.1, 115.0, 109.2, 80.0, 51.8, 48.6, 38.8, 28.7.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Bromophenyl)-(3*H*-imidazol-4-ylmethyl)amino]ethyl}amide (10b, X = Br, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = H). Reaction of **9b**-H was carried out according to procedure C after deprotection of Boc group with TFA. Yield 71%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.76 (s, 1H), 7.63 (s, 1H), 7.54 (s, 1H), 7.30 (s, 1H), 7.24 (d, $J = 8.86$ Hz, 2H), 6.63 (d, $J = 8.91$ Hz, 2H), 4.59 (s, 2H), 3.65 (s, 3H), 3.48 (t, $J = 6.36$ Hz, 2H), 3.08 (t, $J = 6.17$ Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 148.0, 141.6, 141.0, 135.8, 133.4, 133.3, 126.3, 118.5, 117.0, 111.5, 52.9, 44.7, 41.6, 34.7.

1-Methyl-1*H*-imidazole-4-sulfonic Acid Benzyl-{2-[(4-bromophenyl)-(3*H*-imidazol-4-ylmethyl)amino]ethyl}amide (12a, X = Br, R^1 = Benzyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = H). Reaction of **10b** was carried out according to procedure B. Yield 65%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.83 (s, 1H), 7.83 (s, 1H), 7.80 (s, 1H), 7.38 (m, 5H), 7.23 (s, 1H), 7.22 (d, $J = 9.01$ Hz, 2H), 6.46 (d, $J = 9.05$ Hz, 2H), 4.46 (s, 2H), 4.32 (s, 2H), 3.82 (s, 3H), 3.37 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 147.6, 141.5, 139.4, 138.0, 135.6, 133.1, 130.5, 129.9, 129.5, 129.3, 126.7, 118.2, 116.1, 110.8. HRMS calcd for $C_{23}H_{26}BrN_6O_2S^+$ 529.1021, found 529.1036. Retention time for analytical rpHPLC: condition I, 13.36; condition II, 21.53 min.

{2-[(4-Bromophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]-ethyl}carbamic Acid *tert*-Butyl Ester (9b-Me, X = Br, R^3 = Methyl). Lithium diisopropylamide (2.0 M, 4.9 mL, 9.8 mmol) was added dropwise to a solution of **8b** (1.01 g, 3.23 mmol) in dry THF (40 mL) at −78 °C, and the resulting orange solution was stirred for 1.5 h at −78 °C under nitrogen. In a separate flask sodium hydride (60%, 194 mg, 4.85 mmol) was added to a solution of 5-chloromethyl-1-methyl-1*H*-imidazole·HCl (594 mg, 3.55 mmol) in dry THF (15 mL) at 0 °C. The suspension of sodium chloride and imidazole was added to the dianion of **8b** via cannula under nitrogen, and the resulting solution was stirred for 1 h at −78 °C. The reaction was quenched by addition of brine (1 mL), and THF was evaporated. After dilution with EtOAc (200 mL), the organic layer was washed consecutively with water (3 × 50 mL) and brine (1 × 50 mL). The organic phase was dried over sodium sulfate, and the solvent was removed under vacuum. Purification by flash column chromatography (1:7:292 NH_4OH/MeOH/CH_2Cl_2) provided the title compound as a white solid (600 mg, 98% yield based on recovered starting material). ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.78 (s, 1H), 7.22 (d, $J = 9.01$, Hz, 2H), 7.17 (s, 1H), 6.74 (d, $J = 9.14$ Hz, 2H), 4.58 (s, 2H), 3.79 (s, 3H), 3.40 (t, $J = 6.87$ Hz, 2H), 3.14 (t, $J = 6.70$ Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 148.5, 137.9, 134.0, 133.6, 119.6, 118.5, 111.5, 80.6, 51.9, 46.7, 39.1, 34.6, 29.1.

***N′*-Benzyl-*N*-(4-bromophenyl)-*N*-(3-methyl-3*H*-imidazol-4-ylmethyl)ethane-1,2-diamine (11b, X = Br, R^1 = Benzyl, R^3 = Methyl).** Reaction of **9b**-Me was carried out according to procedure A. Yield 73%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.75 (s, 1H), 7.35 (s, 5H), 7.26 (d, $J = 9.02$ Hz, 2H), 7.12 (s, 1H), 6.75 (d, $J = 9.06$ Hz, 2H), 4.57 (s, 2H), 4.14 (s, 2H), 3.74 (s, 3H), 3.60 (t, $J = 7.11$ Hz, 2H), 3.17 (t, $J = 7.20$ Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 147.5, 138.2, 133.9, 133.3, 132.7, 131.4, 131.2, 130.8, 119.8, 118.5, 113.5, 53.0, 48.5, 46.6, 45.3, 34.6.

1-Methyl-1*H*-imidazole-4-sulfonic Acid Benzyl-{2-[(4-bromophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-amide (12b, X = Br, R^1 = Benzyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11b** was carried out according to procedure C. Yield 65%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.71 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 7.23 (m, 5H), 7.17 (s, 1H), 7.07 (d, $J = 9.10$ Hz, 2H), 6.30 (d, $J = 9.15$ Hz, 2H), 4.33 (s, 2H), 4.16 (s, 2H), 3.69 (s, 3H), 3.21 (obscured, 4H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 147.8, 141.9, 139.6, 138.2, 135.9, 133.4, 133.0, 130.6, 130.2, 129.7, 127.1, 118.5, 116.4, 111.2, 55.3, 52.7, 46.7, 46.6, 34.7. HRMS calcd for $C_{24}H_{27}BrN_6O_2SH^+$ 543.1178, found 543.1186. Retention time for analytical rpHPLC: condition I, 14.26; condition II, 29.12 min.

[2-(Biphenyl-4-ylamino)ethyl]carbamic Acid *tert*-Butyl Ester (8a, X = Ph). **8a** was prepared as described for **8b**. Yield 52%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.54−7.51 (m, 3H), 7.46 (d, $J = 8.83$ Hz, 2H), 7.35 (t, $J = 7.70$ Hz, 2H), 7.21 (t, $J = 7.33$ Hz, 1H), 6.96 (d, $J = 8.83$ Hz, 2H), 6.78 (s, 1H), 4.52 (s, 2H), 3.58 (s, 3H), 3.41 (t, $J = 6.75$ Hz, 2H), 3.17 (t, $J = 6.75$ Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 159.1, 149.6, 142.8, 131.0, 129.8, 128.7, 127.1, 127.0, 114.2, 80.3, 44.8, 41.0, 28.9.

{2-[Biphenyl-4-yl-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]-ethyl}carbamic Acid *tert*-Butyl Ester (9a, X = Ph, R^3 = Methyl). **9a** was prepared as described for **9c**. Yield 36%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.54−7.51 (m, 3H), 7.46 (d, $J = 8.83$ Hz, 2H), 7.35 (t, $J = 7.70$, 2H), 7.21 (t, $J = 7.33$ Hz, 1H), 6.96 (d, J

= 8.83, 2H), 6.78 (s, 1H), 4.52 (s, 2H), 3.58 (s, 3H), 3.41 (t, J = 6.75 Hz, 2H), 3.17 (t, J = 6.75, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 158.7, 149.3, 142.5, 140.1, 131.8, 131.7, 129.9, 128.8, 128.7, 127.3, 127.2, 115.4, 80.3, 50.7, 45.7, 38.9, 32.3, 29.0.

***N*-Biphenyl-4-yl-*N′*-(2-methylbenzyl)-*N*-(3-methyl-3*H*-imidazol-4-ylmethyl)ethane-1,2-diamine (11a, X = Phenyl, R^1 = *o*-Methylbenzyl, R^3 = Methyl).** Reaction of **9a** was carried out according to procedure A. Yield 43%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.87 (s, 1H), 7.57−7.54 (m, 4H), 7.43−7.37 (m, 4H), 7.32−7.25 (m, 4H), 7.05 (d, J = 8.8 Hz, 2H), 4.76 (s, 2H), 4.30 (s, 2H), 3.87 (s, 3H), 3.81 (t, J = 7.3 Hz, 2H), 3.38 (t, J = 7.3 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 147.3, 141.7, 138.8, 137.6, 134.1, 133.2, 132.2, 131.3, 130.8, 129.8, 129.1, 127.8, 127.7 127.3, 119.3, 116.8, 114.4, 49.8, 48.0, 46.2, 45.4, 34.3, 19.2.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[Biphenyl-4-yl-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(2-methylbenzyl)-amide (12c, X = Phenyl, R^1 = *o*-Methylbenzyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11a** was carried out according to procedure C. Yield 44%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.84 (s, 1H), 7.82 (s, 1H), 7.79 (s, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.39−7.20 (m, 9H), 7.16 (s, 1H), 6.52 (d, J = 8.8 Hz, 2H), 4.41 (s, 2H), 4.28 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.29−3.19 (m, 4H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 147.6, 142.0, 141.5, 139.6, 138.6, 137.5, 135.0, 133.5, 132.2, 132.1, 132.0, 129.8, 129.7, 128.8, 127.4, 127.2, 126.8, 119.4, 114.6, 53.9, 51.4, 45.8, 44.9, 34.4, 34.2, 19.4. HRMS (ESI): m/z calcd for $C_{31}H_{34}N_6O_2SH^+$ 555.2542, found 555.2533. Retention time for analytical rpHPLC: condition I, 14.62; condition II, 30.89 min.

[2-(4-Cyanophenylamino)ethyl]carbamic Acid *tert*-Butyl Ester (8c, X = CN). Freshly distilled TEA (8.9 mL, 90 mmol) was added to a solution of (2-aminoethyl)carbamic acid *tert*-butyl ester (5.0 g, 30 mmol) and 4-fluorobenzonitrile (3.6 g, 30 mmol) in dry DMSO (250 mL), and the resulting solution was heated to 120 °C for 2 days. A distillation head and condenser were fitted to the reaction vessel, and the volume of solvent was reduced to ∼20 mL under reduced pressure. The resulting solution was dissolved in EtOAc (300 mL) and washed consecutively with 1.0 M aqueous HCl (1 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), and brine (1 × 100 mL). The organic phase was dried over magnesium sulfate, and the solvent was removed under vacuum to provide the title compound as a yellow solid (7.0 g, 89%) after flash column chromatography (1:1 EtOAc/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 8.64 Hz, 2H), 6.58 (d, J = 8.62 Hz, 2H), 3.41 (br s, 2H), 3.29 (br t, J = 5.67 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 147.7, 134.1, 117.2, 112.5, 110.1, 79.6, 46.6, 40.5, 28.7.

{2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]-ethyl}carbamic Acid *tert*-Butyl Ester (9c, X = CN, R^3 = Methyl). The title compound was prepared as described for **9b** and purified by flash column chromatography (1:7:292 NH_4OH/MeOH/CH_2Cl_2, 85% yield based on recovered starting material). ^{1}H NMR (500 MHz, MeOH-d_4): δ 8.82 (s, 1H), 7.42 (d, J = 8.97 Hz, 2H), 7.15 (s, 1H), 6.88 (d, J = 9.00 Hz, 2H), 4.70 (s, 2H), 3.82 (s, 3H), 3.51 (t, J = 6.69 Hz, 2H), 3.20 (obscured t, J = 6.70 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 156.5, 151.4, 139.4, 134.0, 129.1, 127.2, 120.5, 112.9, 99.4, 80.0, 49.5, 44.9, 38.1, 32.1, 28.7.

4-[(2-Benzylaminoethyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]benzonitrile (11d, X = CN, R^1 = Benzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 65%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.88 (s, 1H), 7.55 (d, J = 8.73 Hz, 2H), 7.45 (s, 5H), 7.19 (s, 1H), 6.95 (d, J = 8.87 Hz, 2H), 4.82 (s, 2H), 4.20 (s, 2H), 3.87 (s, 3H), 3.34 (br s, 2H), 3.24 (br s, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ. 151.7, 138.2, 134.2, 133.4, 132.5, 131.3, 131.1, 130.8, 122.0, 116.2, 114.6, 102.0, 53.2, 47.9, 46.0, 45.2, 34.7.

1-Methyl-1*H*-imidazole-4-sulfonic Acid Benzyl-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-amide (12d, X = CN, R^1 = Benzyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11d** was carried out according to procedure C. Yield 66%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.79 (s, 1H), 7.73 (s, 1H), 7.69(s, 1H), 7.32 (d, J = 9.07 Hz, 2H), 7.25 (m, 5H), 7.06 (s, 1H), 6.48 (d, J = 8.90 Hz, 2H), 4.44 (s, 2H), 4.17 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.35 (m, 2H), 3.27 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.9, 141.9, 139.3, 138.2, 135.1, 133.1, 130.8, 130.2, 129.7, 127.2, 121.2, 119.5, 114.0, 100.6, 55.6, 51.5, 46.8, 45.3, 34.7, 34.6. HRMS calcd for $C_{25}H_{28}N_7O_2S^+$ 490.2025, found 490.2028. Retention time for analytical rpHPLC: condition I, 12.77; condition II, 24.84 min.

***N*-Benzyl-*N*-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}benzenesulfonamide (12e, X = CN, R^1 = Benzyl, R^2 = Phenylsulfonyl, R^3 = Methyl).** Reaction of **11d** was carried out according to procedure C. Yield 67%. ^{1}H NMR (500 MHz, MeOH-d_4): δ 8.78 (s, 1H), 7.81 (s, 1 H), 7.80 (s, 1 H), 7.60 (t, J = 7.40 Hz, 1H), 7.54 (m, 2H), 7.33 (d, J = 9.08 Hz, 2H), 7.22 (m, 5H), 7.03 (s, 1H), 6.50 (d, J = 9.13 Hz, 2H), 4.40 (s, 2H), 4.18 (s, 2H), 3.72 (s, 3H), 3.33 (m, 2H), 3.15 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4): δ 151.8, 140.0, 138.2, 138.0, 135.1, 134.8, 133.1, 131.0, 130.8, 130.3, 129.8, 128.9, 119.5, 114.1, 101.4, 55.7, 51.5, 46.8, 45.4, 34.6. HRMS calcd for $C_{27}H_{27}N_5O_2SH^+$ 486.1958, found 486.1963. Retention time for analytical rpHPLC: condition I, 13.35; condition II, 26.31 min.

Thiophene-2-sulfonic Acid Benzyl-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}amide (12f, X = CN, R^1 = Benzyl, R^2 = 2-Thiophenesulfonyl, R^3 = Methyl). Reaction of **11d** was carried out according to procedure C. Yield 59%. ^{1}H NMR (500 MHz, MeOH-d_4): δ 8.79 (s, 1H), 7.79 (dd, J = 1.17, 5.01 Hz, 1H), 7.61 (dd, J = 1.19, 3.70 Hz, 1H), 7.34(d, J = 8.97 Hz, 2H), 7.25 (m, 5H), 7.16 (dd, J = 3.82, 4.97 Hz, 1H), 7.04 (s, 1H), 6.51 (d, J = 8.98 Hz, 2H), 4.39 (s, 2H), 4.19 (s, 2H), 3.72 (s, 3H), 3.39 (m, 2H), 3.17 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4): δ 151.8, 139.6, 138.2, 137.8, 135.1, 134.4, 134.3, 133.0, 130.8, 130.3, 129.9, 129.5, 121.1, 129.6, 114.1, 100.8, 55.9, 51.5, 47.1, 45.4, 34.6. HRMS calcd for $C_{25}H_{26}N_5O_2S_2^+$ 492.1528, found 492.1515. Retention time for analytical rpHPLC: condition I, 13.91; condition II, 22.82 min.

Pyridine-2-sulfonicAcidBenzyl-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}amide (12g, X = CN, R^1 = Benzyl, R^2 = 2-Pyridylsulfonyl, R^3 = Methyl). Reaction of **11d** was carried out according to procedure C. Yield 57%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 8.66 (d, J = 5.41 Hz, 1H), 8.00 (td, J = 1.37, 7.73 Hz, 1H), 7.89 (d, J = 7.78 Hz, 1H), 7.63 (dd, J = 4.69, 7.57 Hz, 1H), 7.41 (d, J = 8.82 Hz, 2H), 7.22 (m, 5H), 7.13 (s, 1H), 6.55 (d, J = 8.96 Hz, 2H), 4.44 (s, 2H), 4.36 (s, 2H), 3.65 (s, 3H), 3.29 (m, 4H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 157.1, 150.7, 150.3, 139.4, 137.0, 136.8, 133.7, 130.7, 128.9-(2C), 128.2, 127.9, 122.8, 120.3, 118.0, 112.7, 98.1, 53.3, 49.4, 45.6, 44.0, 33.7. HRMS calcd for $C_{26}H_{27}N_6O_2S^+$ 487.1916, found 487.1903. Retention time for analytical rpHPLC: condition I, 13.47; condition II, 21.41 min.

Quinoline-8-sulfonic Acid Benzyl-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}amide (12h, X = CN, R^1 = Benzyl, R^2 = 8-Quinolinesulfonyl, R^3 = Methyl). Reaction of **11d** was carried out according to procedure C. Yield 63%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.92 (dd, J = 1.72, 4.20 Hz, 1H), 8.79 (s, 1H), 8.41 (dd, J = 1.32, 7.39 Hz, 1H), 8.37 (dd, J = 1.67, 8.40 Hz, 1H), 8.15 (dd, J = 1.19, 8.21 Hz, 1H), 7.64 (t, J = 7.67 Hz, 1H), 7.56 (dd, J = 4.23, 8.35 Hz, 1H), 7.35 (d, J = 9.04 Hz, 2H), 7.18 (m, 5H), 7.06 (s, 1H), 6.57 (d, J = 9.07 Hz, 2H), 4.46 (s, 2H), 4.40 (s, 2H), 3.74 (s,3H), 3.64 (m, 2H), 3.53 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 152.9, 152.0, 145.5, 138.8, 138.6, 138.2, 135.8, 135.1, 134.8, 133.1, 131.1, 130.5, 130.1, 129.6, 127.2, 124.0, 121.2, 119.5, 114.1, 100.6, 55.5, 31.6, 47.3, 45.4, 34.6. HRMS calcd for $C_{30}H_{29}N_6O_2S^+$ 537.2073, found 537.2073. Retention time for analytical rpHPLC: condition I, 14.34; condition II, 24.08 min.

5-Dimethylaminonaphthalene-1-sulfonic Acid Benzyl-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-amide (12i, X = CN, R^1 = Benzyl, R^2 = 5-Dimethylaminonaphthalenesulfonyl, R^3 = Methyl). Reaction of **11d** was carried out according to procedure C. Yield 64%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.78 (s, 1H), 8.58 (d, J = 8.54 Hz, 1H), 8.28 (d, J

= 8.66 Hz, 1H), 8.09 (d, *J* = 7.34 Hz, 1H), 7.53 (d, *J* = 7.30 Hz, 1H), 7.49 (d, *J* = 7.16 Hz, 1H), 7.32 (d, *J* = 9.04 Hz, 2H), 7.23 (d, *J* = 7.39 Hz, 1H), 7.18 (m, 5H), 6.99 (s, 1H), 6.48 (d, *J* = 9.09 Hz, 2H), 4.41 (s, 2H), 4.37 (s, 2H), 3.71(s,3H), 3.32 (m, 4H), 2.82 (s, 6H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 153.5, 151.2, 138.2, 138.0, 136.1, 135.1, 133.5, 133.1, 132.2, 131.8, 131.1, 130.6, 130.2, 129.8, 129.7, 124.9, 121.2, 119.4, 117.1, 114.1, 100.9, 54.2, 50.7, 46.2, 45.7, 45.6, 34.6. HRMS calcd for $C_{33}H_{35}N_6O_2S^+$ 579.2542, found 579.2546. Retention time for analytical rpHPLC: condition I, 14.67; condition II, 30.30 min.

***N*-Benzyl-*N*-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}acetamide (12j, X = CN, R^1 = Benzyl, R^2 = Acetyl, R^3 = Methyl).** Reaction of **11d** was carried out according to procedure C. Yield 74%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.08 (s, 1H), 6.71 (d, *J* = 9.08 Hz, 2H), 6.59 (br t, *J* = 7.15 Hz, 2H), 6.54 (br t, *J* = 7.32 Hz, 1H), 6.47 (br t, *J* = 7.12 Hz, 2H), 6.40 (br s, 1H), 6.10 (d, *J* = 9.11 Hz, 2H), 3.92 (s, 2H), 3.84 (s, 2H), 3.07 (s,3H), 2.77 (m, 2H), 2.52 (s, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 172.5, 130.1, 136.2, 136.0, 132.9, 131.2, 128.3, 127.2, 126.4, 119.0, 117.2, 112.1, 98.5, 52.5, 43.2, 42.9, 32.5, 32.4, 19.9. HRMS calcd for $C_{23}H_{26}N_5O^+$ 388.2137, found 388.2131. Retention time for analytical rpHPLC: condition I, 12.74; condition II, 18.88 min.

***N*-Benzyl-*N*-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}isobutyramide (12k, X = CN, R^1 = Benzyl, R^2 = Isopropylcarbonyl, R^3 = Methyl).** Reaction of **11d** was carried out according to procedure C. Yield 71%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.09 (s, 1H), 6.70 (d, *J* = 9.05 Hz, 2H), 6.61 (br t, *J* = 7.21 Hz, 2H), 6.54 (br t, *J* = 7.36 Hz, 1H), 6.45 (br t, *J* = 7.23 Hz, 2H), 6.39 (br s, 1H), 6.15 (d, *J* = 9.05 Hz, 2H), 3.93 (s, 2H), 3.91 (s, 2H), 3.08 (s, 3H), 2.79 (m, 2H), 2.52 (s, 2H), 2.12 (m, 1H), 0.26 (d, *J* = 6.60 Hz, 6H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 178.4, 149.7, 136.1, 135.5, 132.5, 130.7, 127.7, 226.6, 125.6, 118.5, 111.5, 97.9, 30.9, 46.1, 42.8, 42.7, 32.0, 29.3, 17.6. HRMS calcd for $C_{25}H_{30}N_5O^+$ 416.2450, found 416.2436. Retention time for analytical rpHPLC: condition I, 13.24; condition II, 20.24 min.

4-[(2-Allylaminoethyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]benzonitrile (11l, X = CN, R^1 = Allyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 65%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.92 (s, 1H), 7.56 (d, *J* = 8.95 Hz, 2H), 7.22 (s, 1H), 7.00 (d, *J* = 8.95 Hz, 2H), 5.97 (m, 1H), 5.53 (m, 1H), 5.36 (m, 1H), 4.81 (s, 2H), 3.91 (s, 3H), 3.84 (t, *J* = 7.25 Hz, 2H), 3.72 (d, *J* = 6.80 Hz, 2H), 3.31 (t, *J* = 7.25 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.4, 137.9, 134.9, 129.1, 124.4, 118.8, 114.3, 101.4, 52.8, 51.2, 47.5, 45.7, 44.5, 37.4, 34.2.

4-[[2-(2-Methylallylamino)ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11m, X = CN, R^1 = 2-Methylallyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 60%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.93 (s, 1H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.22 (s, 1H), 7.00 (d, *J* = 9.0 Hz, 2H), 5.20 (s, 1H), 5.1 (s, 1H), 4.86 (s, 2H), 3.92−3.89 (m, 5H), 3.68 (s, 2H), 3.31 (m, 2H), 1.88 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.2, 137.9, 137.8, 134.9, 132.7, 120.6, 118.8, 118.1, 114.2, 101.3, 54.1, 47.3, 45.6, 44.8, 34.2, 20.7.

4-[[2-(2-Bromoallylamino)ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11n, X = CN, R^1 = 2-Bromoallyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 60%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.92 (s, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.22 (s, 1H), 7.00 (d, *J* = 9.0 Hz, 2H), 4.86 (s, 2H), 4.03 (d, *J* = 2.5 Hz, 2H), 3.92−3.89 (m, 5H), 3.42 (t, *J* = 7.2 Hz, 2H), 3.25 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.2, 137.9, 135.0, 132.6, 126.5, 120.6, 118.8, 114.3, 114.2, 101.5, 47.3, 45.6, 44.4, 37.7, 34.2.

***N*-*tert*-Butyl-2-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethylamino}acetamide (11o, X = CN, R^1 = *N*-*tert*-Butylacetamido, R^3 = Methyl).** Reaction of **9c** was carried out according to procedure A. Yield 52%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.98 (s, 1H), 7.56 (d, *J* = 9.01 Hz, 2H), 7.28 (s, 1H), 7.01 (d, *J* = 9.01 Hz, 2H), 4.86 (s, 2H), 4.83 (s, 2H), 3.91 (s, 3H), 3.83 (t, *J* = 7.13 Hz, 2H), 3.23 (t, *J* = 7.13 Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 165.6, 151.3, 140.2, 135.0, 132.7, 122.7, 120.6, 114.3, 101.3, 52.7, 52.2, 45.6, 37.4, 34.5, 29.1, 28.8.

4-{(3-Methyl-3*H*-imidazol-4-ylmethyl)-[2-(2-pyrrol-1-ylethylamino)ethyl]amino}benzonitrile (11p, X = CN, R^1 = Ethylpyrrole, R^3 =Methyl). Reaction of **9c** was carried out according to procedure A. Yield 23%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.81 (s, 1H), 7.46 (d, *J* = 8.97 Hz, 2H), 7.07 (s, 1H), 6.85 (d, *J* = 9.13 Hz, 2H), 6.68 (t, *J* = 2.06 Hz, 2H), 6.02 (t, *J* = 2.03 Hz, 2H), 4.69 (s, 2H), 4.21 (t, *J* = 6.20 Hz, 2H), 3.79 (s, 3H), 3.71 (t, *J* = 7.52 Hz, 2H), 3.38 (t, *J* = 6.22 Hz, 2H), 3.03 (t, *J* = 7.50 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.6, 138.4, 135.4, 133.0, 122.2, 120.9, 119.3, 114.7, 110.8, 101.9, 50.1, 47.9, 46.9, 46.0, 45.7, 34.6.

4-[[2-(Cyclohexylmethylamino)ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11q, X = CN, R^1 = Cylohexylmethyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 59%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.84 (s, 1H), 7.48 (d, *J* = 9.09 Hz, 2H), 7.14 (s, 1H), 6.91 (d, *J* = 9.13 Hz, 2H), 4.76 (s, 2H), 3.82 (s, 3H), 3.78 (t, *J* = 7.45 Hz, 2H), 3.19 (obscured), 2.84 (d, *J* = 6.96 Hz, 2H), 1.68 (m, 6H), 1.22 (m, 3H), 0.94 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.7, 138.4, 135.4, 133.1, 121.0, 119.2, 114.6, 101.8, 55.8, 47.7, 46.0, 37.0, 34.6, 31.8, 27.4, 26.9.

4-((3-Methyl-3*H*-imidazol-4-ylmethyl)-{2-[(tetrahydropyran-4-ylmethyl)amino]ethyl}amino)benzonitrile (11r, X = CN, R^1 = Tetrahydropyran-4-ylmethyl, R^3 = Methyl). Molecular sieves were added to a solution of tetrahydropyran-4-carbaldehyde (25 mg, 0.22 mmol), 4-[(2-aminoethyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile ditrifluoroacetic acid salt (0.11 g, 0.22 mmol), and acetic acid (13 μL, 0.23 mmol) in dry MeOH (2.0 mL), and the reaction mixture was stirred at room temperature for 1 h. $NaCNBH_3$ (20 mg, 0.33 mmol) was then added in one portion, and stirring continued for a further hour. Brine was added, and the reaction was extracted into EtOAc. The organic layer was purified by flash column chromatography (1:5:50 Et_3N/MeOH/CH_2Cl_2) to provide the title compound in 90% yield. ^{1}H NMR (400 MHz, MeOH-d_4): δ 7.63 (s, 1H), 7.50 (d, *J* = 9.05 Hz, 2H), 6.97 (d, *J* = 9.05 Hz, 2H), 6.70 (s, 1H), 4.70 (s, 2H), 3.93 (dd, *J* = 10.66, 3.98 Hz, 2H), 3.70−3.64 (m, 5H), 3.40 (dt, *J* = 11.82, 1.64 Hz, 2H), 2.91 (t, *J* = 7.47 Hz, 2H), 2.63 (d, *J* = 6.89 Hz, 2H), 1.82 (m, 1H), 1.67 (dd, *J* = 13.11, 1.89 Hz, 2H), 1.36 (t, *J* = 7.28 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 152.5, 140.3, 134.8, 129.6, 128.1, 121.3, 114.1, 99.6, 56.3, 53.8, 47.9, 46.9, 45.9, 35.6, 32.3, 32.2.

4-[[2-(2-Methylbenzylamino)ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11x, X = CN, R^1 = *o*-Methylbenzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 62%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.56 (d, *J* = 8.67 Hz, 2H), 7.45 (d, *J* = 7.43 Hz, 2H), 7.34−7.26 (m, 3H), 7.20 (s, 1H), 7.00 (d, *J* = 8.67 Hz, 2H), 4.86 (s, 2H), 4.32 (s, 2H), 3.93−3.89 (m, 5H), 3.43 (t, *J* = 7.53 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.3, 138.8, 138.0, 135.0, 132.7, 132.2, 131.3, 130.9, 130.8, 127.8, 120.6, 118.8, 114.3, 101.4, 50.0, 47.4, 45.6, 45.2, 34.2, 19.2.

4-[[2-(3-Methylbenzylamino)ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11y, X = CN, R^1 = *m*-Methylbenzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 46%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.55 (d, *J* = 8.99 Hz, 2H), 7.35−7.26 (m, 4H), 7.20 (s, 1H), 6.97 (d, *J* = 8.99 Hz, 2H), 4.85 (s, 2H), 4.23 (s, 2H), 3.89−3.86 (m, 5H), 3.35 (t, *J* = 7.40 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.2, 140.4, 138.0, 134.9, 132.7, 132.3, 131.6, 131.4, 130.2, 128.0, 120.6, 118.8, 114.3, 101.4, 52.7, 47.5, 45.6, 44.8, 34.2, 21.3.

4-[[2-(4-Methylbenzylamino)ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11z, X = CN, R^1 = *p*-Methylbenzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 29%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.55 (d, *J* = 8.85 Hz, 2H), 7.38 (d, *J* = 7.84 Hz, 2H), 7.26 (d, *J* = 7.84 Hz, 2H), 7.20 (s, 1H), 6.96 (d, *J* = 8.85 Hz, 2H), 4.84 (s, 2H), 4.22 (s, 2H), 3.89−3.85 (m, 5H), 3.33 (t, *J* = 7.22 Hz,

2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.2, 141.1, 138.0, 134.9, 132.6, 131.0, 130.9, 129.3, 120.6, 118.8, 114.2, 101.4, 52.5, 47.5, 45.6, 44.6, 34.2, 21.2.

4-((3-Methyl-3*H*-imidazol-4-ylmethyl)-{2-[(pyridin-2-ylmethyl)-amino]ethyl}amino)benzonitrile (11aa, X = CN, R^1 = 2-Pyridyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 57%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.95 (s, 1H), 8.64 (d, J = 4.73 Hz, 1H), 7.89 (dt, J = 7.74, 1.68 Hz, 1H), 7.59 (d, J = 8.99 Hz, 2H), 7.45 (d, J = 7.83 Hz, 1H), 7.44 (dd, J = 7.36, 5.07 Hz, 1H), 7.26 (s, 1H), 7.03 (d, J = 9.04 Hz, 2H), 4.90 (s, 2H), 4.48 (s, 2H), 3.98 (t, J = 7.20 Hz, 2H), 3.93 (s, 3H), 3.45 (t, J = 7.18 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 152.7, 151.7, 150.9, 139.4, 138.4, 135.4, 133.1, 125.5, 124.6, 121.0, 119.2, 114.8, 101.9, 52.4, 48.8, 47.9, 46.1, 34.7.

4-((3-Methyl-3*H*-imidazol-4-ylmethyl)-{2-[(pyridin-3-ylmethyl)-amino]ethyl}amino)benzonitrile (11ab, X = CN, R^1 = 3-Pyridyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 64%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.92 (br s, 2H), 8.82 (d, J = 5.36 Hz, 1H), 8.47 (d, J = 6.41 Hz, 1H), 7.90 (dd, J = 7.92, 5.45 Hz, 1H), 7.57 (d, J = 9.00 Hz, 2H), 7.23 (s, 1H), 7.02 (d, J = 9.02 Hz, 2H), 4.89 (s, 2H), 4.48 (s, 2H), 3.95 (t, J = 7.17 Hz, 2H), 3.92 (s, 3H), 3.49 (t, J = 7.12 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.7, 148.3, 147.7, 145.6, 138.3, 135.4, 133.1, 132.0, 127.7, 121.0, 119.1, 114.7, 101.8, 49.7, 47.9, 46.0, 45.9, 34.6.

4-((3-Methyl-3*H*-imidazol-4-ylmethyl)-{2-[(pyridin-4-ylmethyl)-amino]ethyl}amino)benzonitrile (11ac, X = CN, R^1 = 4-Pyridyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 60%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.94 (s, 1H), 8.83 (d, J = 6.14 Hz, 2H), 7.96 (d, J = 6.33 Hz, 2H), 7.58 (d, J = 8.93 Hz, 2H), 7.24 (s, 1H), 7.03 (d, J = 9.00 Hz, 2H), 4.88 (s, 2H), 4.54 (s, 2H), 3.97 (t, J = 7.13 Hz, 2H), 3.92 (s, 3H), 3.50 (t, J = 7.39 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.6, 148.9, 147.4, 138.4, 135.4, 133.1, 128.0, 121.0, 119.2, 114.7, 101.8, 51.4, 47.9, 46.2, 46.0, 34.6.

4-[[2-(3-Cyanobenzylamino)ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11ad, X = CN, R^1 = *m*-Cyanobenzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 49%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.90 (s, 1H), 7.85−7.81 (m, 2H), 7.64 (t, J = 7.80 Hz, 1H), 7.56 (d, J = 8.77 Hz, 2H), 7.21 (s, 1H), 6.99 (d, J = 8.77 Hz, 2H), 4.86 (s, 2H), 4.35 (s, 2H), 3.93−3.90 (m, 5H), 3.41 (t, J = 7.27 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.6, 138.4, 136.3, 135.4, 135.2, 134.8, 134.6, 133.1, 131.8, 121.0, 119.4, 119.2, 114.7, 114.6, 114.3, 101.8, 52.1, 47.9, 46.1, 45.6, 34.6.

4-[[2-(4-Cyanobenzylamino)ethyl]-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11ae, X = CN, R^1 = *p*-Cyanobenzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 35%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.82 (d, J = 8.19 Hz, 2H), 7.70 (d, J = 8.19 Hz, 2H), 7.56 (d, J = 8.88 Hz, 2H), 7.21 (s, 2H), 6.99 (d, J = 8.88 Hz, 2H), 4.86 (s, 2H), 4.37 (s, 2H), 3.92−3.90 (m, 5H), 3.41 (t, J = 7.33 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.2, 138.0, 137.7, 135.0, 134.0, 132.6, 132.0, 120.6, 119.0, 118.8, 114.6, 114.2, 101.4, 52.0, 47.4, 45.6, 45.3, 34.2.

4-[{2-[(Biphenyl-3-ylmethyl)amino]ethyl}-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11af, X = CN, R^1 = 3-Phenylbenzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 58%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.82 (s, 1H), 7.72 (s, 1H), 7.63 (d, J = 7.60 Hz, 1H), 7.56 (d, J = 7.19 Hz, 2H), 7.45 (m, 6H), 7.29 (t, J = 7.24 Hz, 1H), 7.11 (s, 1H), 6.89 (d, J = 9.04 Hz, 2H), 4.76 (s, 2H), 4.23 (s, 2H), 3.82 (t, J = 7.33 Hz, 2H), 3.80 (s, 3H), 3.32 (t, J = 7.23 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.6, 143.9, 141.8, 138.4, 135.4, 133.5, 133.1, 131.3, 130.4, 130.3, 130.1, 129.6, 129.3, 128.4, 121.0, 119.2, 114.7, 101.7, 53.1, 47.9, 46.0, 45.2, 34.6.

4-[{2-[(Biphenyl-4-ylmethyl)amino]ethyl}-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]benzonitrile (11ag, X = CN, R^1 = 4-Phenylbenzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 64%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.73 (d, J = 8.26 Hz, 2H), 7.59 (m, 6H), 7.47 (t, J = 7.3 Hz, 2H), 7.40 (t, J = 7.36 Hz, 1H), 7.22 (s, 1H), 6.99 (d, J = 9.06 Hz, 2H), 4.87 (s, 2H), 4.34 (s, 2H), 3.91 (m, 5H), 3.40 (t, J = 7.21 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.6, 144.3, 141.7, 138.4, 135.4, 133.0, 132.0, 131.7, 130.4, 129.4, 129.2, 128.4, 121.0, 119.3, 114.7, 101.9, 52.8, 47.9, 46.0, 45.2, 34.6.

4-{(3-Methyl-3*H*-imidazol-4-ylmethyl)-[2-(3-pyrrol-1-ylbenzyl-amino)ethyl]amino}benzonitrile (11ah, X = CN, R^1 = 3-Pyrrolebenzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 62%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.82 (s, 1H), 7.59 (s, 1H), 7.46 (m, 4H), 7.28 (d, J = 7.43 Hz, 1H), 7.15 (t, J = 2.26 Hz, 2H), 7.12 (s, 1H), 6.89 (d, J = 9.07 Hz, 2H), 6.23 (t, J = 2.23 Hz, 2H), 4.76 (s, 2H), 4.25 (s, 2H), 3.81 (obscured), 3.80 (s, 3H), 3.31 (t, J = 7.56 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.6, 143.1, 138.4, 135.4, 134.5, 133.1, 132.1, 128.1, 122.5, 122.2, 120.9, 120.3, 119.2, 114.7, 112.4, 101.9, 52.8, 47.9, 46.1, 45.3, 34.6.

4-{(3-Methyl-3*H*-imidazol-4-ylmethyl)-[2-(4-pyrrol-1-ylbenzyl-amino)ethyl]amino}benzonitrile (11ai, X = CN, R^1 = 4-Pyrrolebenzyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure A. Yield 58%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.81 (s, 1H), 7.48 (m, 5H), 7.45 (s, 1H), 7.14 (t, J = 2.16 Hz, 2H), 6.88 (d, J = 9.10 Hz, 2H), 6.21 (t, J = 2.17 Hz, 2H), 4.75 (s, 2H), 4.20 (s, 2H), 3.80 (m, 5H), 3.28 (t, J = 7.20 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.6, 138.4, 135.4, 133.1, 129.4, 121.5, 121.0, 120.3, 119.2, 114.7, 112.5, 111.4, 101.8, 52.5, 47.9, 46.0, 45.2, 34.6.

1-Methyl-1*H*-imidazole-4-sulfonic Acid Allyl-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-amide (12l, X = CN, R^1 = Allyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11l** was carried out according to procedure C. Yield 68%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.81 (s, 1H), 7.67 (s, 1H), 7.63(s, 1H), 7.45 (d, J = 9.15 Hz, 2H), 7.21 (s, 1H), 6.86 (d, J = 9.18 Hz, 2H), 5.60 (m, 1H), 5.05 (m, 2H), 4.73 (s, 2H), 3.80 (s, 3H), 3.68 (m, 5H), 3.57 (m, 2H), 3.28 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 152.2, 141.9, 139.7, 138.2, 135.2, 133.2, 133.3, 127.0, 122.4, 121.2, 119.7, 114.4, 100.8, 54.0, 31.4, 46.0, 41.8, 34.7, 34.6. HRMS calcd for $C_{21}H_{26}N_7O_2S^+$ 440.1869, found 440.1855. Retention time for analytical rpHPLC: condition I, 12.31; condition II, 17.86 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(2-methylallyl)-amide (12m, X = CN, R^1 = 2-Methylallyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11m** was carried out according to procedure C. Yield 71%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.78 (s, 1H), 7.74 (s, 1H), 7.53 (d, J = 9.03 Hz, 2H), 7.29 (s, 1H), 6.95 (d, J = 9.03 Hz, 2H), 4.79 (s, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 3.73−3.69 (m, 4H), 3.36 (t, J = 3.95 Hz, 2H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.7, 142.6, 141.4, 139.2, 137.9, 134.8, 132.8, 126.6, 120.8, 119.3, 114.0, 100.4, 57.3, 50.8, 46.0, 45.2, 34.3, 34.3, 34.2, 20.0. HRMS (ESI): m/z calcd for $C_{22}H_{27}N_7O_2SH^+$ 454.2025, found 454.2013. Retention time for analytical rpHPLC: condition I, 14.29; condition II, 18.51 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid (2-Bromoallyl)-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-amide (12n, X = CN, R^1 = 2-Bromoallyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11n** was carried out according to procedure C. Yield 67%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.90 (s, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.55 (d, J = 9.03 Hz, 2H), 7.32 (s, 1H), 7.00 (d, J = 9.03 Hz, 2H), 4.85 (s, 2H), 4.07 (d, J = 2.42 Hz, 2H), 3.91 (s, 3H), 3.82 (t, J = 6.75 Hz, 2H), 3.77 (s, 3H), 3.55 (t, J = 6.75 Hz, 2H), 2.64 (t, J = 2.42 Hz, 1H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.9, 141.3, 138.6, 137.8, 134.8, 133.0, 127.1, 120.8, 119.3, 114.1, 100.4, 78.2, 75.3, 50.5, 46.0, 45.6, 39.3, 34.3, 34.3 HRMS (ESI): m/z calcd for $C_{21}H_{24}BrN_7O_2SH^+$ 518.0974, found 518.0980. Retention time for analytical rpHPLC: condition I, 10.70; condition II, 16.36 min.

***N*-*tert*-Butyl-2-[{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(1-methyl-1*H*-imidazole-4-sulfonyl)-amino]acetamide (12o, X = CN, R^1 = *N*-*tert*-Butylacetamido, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3=Methyl).** Reaction of

11o was carried out according to procedure C. Yield 83%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.94 (s, 1H), 7.77 (s, 1H), 7.66 (s, 1H), 7.52 (d, J = 8.95 Hz, 2H), 7.29 (s, 1H), 6.92 (d, J = 8.95 Hz, 2H), 4.82 (s, 4H), 3.91 (s, 3H), 3.74 (s, 3H), 3.65 (t, J = 6.23 Hz, 2H), 3.21 (t, J = 6.23 Hz, 2H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 165.6, 151.7, 141.1, 140.5, 140.0, 134.8, 133.0, 125.8, 123.1, 120.8, 113.9, 100.3, 52.7, 52.2, 51.5, 46.0, 41.3, 34.5, 34.3, 28.7. HRMS calcd for $C_{24}H_{32}N_8O_3SH^+$ 513.2396, found 513.2392. Retention time for analytical rpHPLC: condition I, 12.14; condition II, 17.82 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(2-pyrrol-1-yl-ethyl)amide (12p, X = CN, R^1 = 2-Pyrrol-1-ylethylsulfonyl, R^2 = 4-methyl-1*H*-imidazole, R^3 = Methyl). Reaction of **11p** was carried out according to procedure C. Yield 71%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.79 (s, 1H), 7.69 (s, 1 H), 7.67 (s, 1 H), 7.42 (d, J = 9.09 Hz, 2H), 7.01 (s, 1H), 6.78 (d, J = 9.11 Hz, 2H), 6.59 (d, J = 1.95, 3.57 Hz, 2H), 5.89 (d, J = 2.12 Hz, 2H), 4.90 (s, 2H), 4.02 (t, J = 5.37 Hz, 2H), 3.78 (s, 3H), 3.69 (s, 3H), 3.45 (t, J = 5.63 Hz, 2H), 3.12 (m, 2H), 3.02 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 150.9, 140.9, 138.3, 137.1, 134.1, 132.2, 126.1, 121.4, 120.1, 118.5, 113.1, 108.6, 99.6, 52.6, 50.3, 50.2, 49.9, 44.6, 33.6, 33.5. HRMS calcd for $C_{24}H_{29}N_8O_2S^+$ 493.2129, found 493.2122. Retention time for analytical rpHPLC: condition I, 11.26; condition II, 14.39 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}cyclohexylmethylamide (12q, X = CN, R^1 = Cylohexylmethyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11q** was carried out according to procedure C. Yield 75%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.82 (s, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.47 (d, J = 9.04 Hz, 2H), 7.21 (s, 1H), 6.91 (d, J = 9.14 Hz, 2H), 4.78 (s, 2H), 3.82 (s, 3H), 3.69 (m, 5H), 3.30 (m, 2H), 2.82 (d, J = 7.32 Hz, 2H), 1.57 (m, 5H), 1.34(m, 1H), 1.05(m, 3H), 0.76 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 152.2, 141.7, 139.5, 138.3, 135.3, 133.4, 127.0, 121.2, 119−61 114.3, 100.8, 58.6, 51.61 48.4, 45.8, 38.4, 34.7, 32.3, 27.9, 27.3. HRMS calcd for $C_{25}H_{34}N_7O_2S^+$ 496.2495, found 496.2497. Retention time for analytical rpHPLC: condition I, 14.92; condition II, 27.55 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}(tetrahydropyran-4-ylmethyl)amide (12r, X = CN, R^1 = Tetrahydropyran-4-ylmethyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11r** was carried out according to procedure C. Yield 67%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.77 (s, 1H), 7.76 (s, 1H), 7.56 (d, J = 8.95 Hz, 2H), 7.27 (s, 1H), 7.01 (d, J = 8.95 Hz, 2H), 4.87 (s, 2H), 3.91 (s, 3H), 3.89−3.80 (m, 4H), 3.78 (s, 3H), 3.41 (t, J = 7.11 Hz, 2H), 3.26 (t, J = 10.99 Hz, 2H), 2.99 (d, J = 7.30 Hz, 2H), 1.73 (m, 1H), 1.58 (d, J = 13.02 Hz, 2H), 1.19 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.7, 141.4, 138.9, 137.9, 134.9, 132.9, 126.8, 120.8, 119.1, 114.0, 100.4, 68.5, 57.5, 51.1, 48.1, 45.4, 35.5, 34.3, 34.2, 31.7. HRMS (ESI): m/z calcd for $C_{24}H_{31}N_7O_3SH^+$ 498.2287. found 498.2287. Retention time for analytical rpHPLC: condition I, 10.97; condition II, 19.75 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}piperidin-4-ylmethylamide (12s, X = CN, R^1 = Piperidin-4-ylmethyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). 4-{[{2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(1-methyl-1*H*-imidazole-4-sulfonyl)amino]methyl}piperidine-1-carboxylic acid *tert*-butyl ester (0.15 g, 0.25 mmol) was dissolved in TFA (2.0 mL) and the solution stirred at room temperature for 15 min. The solvent was removed under reduced pressure, and the crude product was purified by rpHPLC to provide the title compound. Yield 94%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.55 (d, J = 9.02 Hz, 2H), 7.23 (s, 1H), 7.02 (d, J = 9.02 Hz, 2H), 4.87 (s, 2H), 3.91 (s, 3H), 3.82 (t, J = 7.51 Hz, 2H), 3.78 (s, 3H), 3.42−3.34 (m, 4H), 3.08 (d, J = 7.12 Hz, 2H), 2.86 (dt, J = 2.31, 11.46 Hz, 2H), 1.93−1.84 (m, 3H), 1.39 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.7, 141.5, 138.6, 137.8, 134.9, 132.9, 126.9, 120.8, 118.9, 114.0, 100.3, 56.5, 51.2, 51.1, 48.2, 45.3, 44.7, 34.4, 34.3, 27.6. HRMS (ESI): m/z calcd for $C_{24}H_{32}N_8O_2SH^+$ 497.2447, found 497.2444. Retention time for analytical rpHPLC: condition I, 11.33; condition II, 18.l2 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid (1-Acetylpiperidin-4-ylmethyl)-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]ethyl}amide (12t, X = CN, R^1 = 1-Acetylpiperidin-4-ylmethyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). To a solution of 1-methyl-1*H*-imidazole-4-sulfonic acid {2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-piperidin-4-ylmethylamide CF_3CO_2H salt (**12s**) (37 mg, 0.061 mmol) and TEA (51 μL, 0.37 mmol) in DMF (0.30 mL) at 0 °C was added acetic anhydride (7.0 μL, 0.070 mmol). The mixture was stirred at 0 °C for 10 min, then diluted with acetonitrile and purified directly by rpHPLC to provide the title compound. Yield 85%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.77 (S, 1H), 7.75 (s, 1H), 7.56 (d, J = 9.06 Hz, 2H), 7.27 (s, 1H), 7.01 (d, J = 9.06 Hz, 2H), 4.87 (s, 2H), 4.41 (d, J = 13.27 Hz, 1H), 3.91 (s, 3H), 3.88−3.81 (m, 3H), 3.78 (s, 3H), 3.42 (t, J = 7.18 Hz, 2H), 3.02−2.94 (m, 3H), 2.51 (dt, J = 2.26, 12.64 Hz, 1H), 2.07 (s, 3H), 1.79−1.67 (m, 3H), 1.06 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 171.4, 151.8, 141.4, 138.9, 137.9, 134.9, 133.0, 126.8, 120.8, 119.1, 114.0, 100.4, 57.1, 51.2, 45.4, 42.5, 36.5, 34.3, 34.3, 31.3, 30.6, 21.2. HRMS (ESI): m/z calcd for $C_{26}H_{34}N_8O_3SH^+$ 539.2553, found 539.2544. Retention time for analytical rpHPLC: condition I, 12.42; condition II, 21.08 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(1-isobutyryl-piperidin-4-ylmethyl)amide (12u, X = CN, R^1 = 1-Isobutyryl-piperidin-4-ylmethyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Acylation with isobutyric anhydride following the same procedure as described above provided the title compound in 73% yield. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 7.76 (s, 1H), 7.75 (s, 1H), 7.57 (d, J = 8.99 Hz, 2H), 7.29 (s, 1H), 7.01 (d, J = 8.99 Hz, 2H), 4.86 (s, 2H), 4.45 (d, J = 12.09 Hz, 1H), 4.00 (d, J = 13.70 Hz, 1H), 3.91 (s, 3H), 3.83−3.78 (m, 5H), 3.44 (m, 2H), 3.01−2.89 (m, 4H), 2.50 (t, J = 11.62 Hz, 1H), 1.78−1.68 (m, 3H), 1.14−0.95 (m, 8H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 177.7, 151.8, 141.4, 138.8, 137.9, 134.9, 132.9, 126.8, 120.8, 119.1, 114.0, 100.4, 57.1, 51.2, 46.5, 45.4, 42.8, 36.7, 34.3, 31.8, 31.1, 30.7, 19.9, 19.7. HRMS (ESI): m/z calcd for $C_{28}H_{38}N_8O_3SH^+$ 567.2866, found 567.2840. Retention time for analytical rpHPLC: condition I, 12.76; condition II, 22.13 min.

4-{[{2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)-amino]ethyl}(1-methyl-1*H*-imidazole-4-sulfonyl)amino]methyl}-piperidine-1-carboxylic Acid *tert*-Butyl Ester (12v, X = CN, R^1 = Methylpiperidine-1-carboxylic Acid *tert*-Butyl Ester, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **10c** was carried out according to procedure B. Yield 47%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.90 (s, 1H), 7.76 (s, 1H), 7.75 (s, 1H), 7.58 (d, J = 9.07 Hz, 2H), 7.29 (s, 1H), 7.01 (d, J = 9.07 Hz, 2H), 4.87 (s, 2H), 3.99 (d, J = 13.22 Hz, 2H), 3.82−3.78 (m, 5H), 3.42 (t, J = 6.99 Hz, 2H), 2.97 (d, J = 6.85 Hz, 2H), 2.61 (br s, 2H), 1.65−1.62 (m, 3H), 1.44 (s, 9H), 1.01 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 156.5, 151.8, 141.4, 138.9, 137.8, 134.9, 133.0, 126.8, 120.8, 119.1, 114.0, 100.4, 81.0, 57.3, 51.2 48.2, 45.4, 36.5, 34.3, 34.2, 30.8, 28.7. HRMS (ESI): m/z calcd for $C_{29}H_{40}N_8O_4SH^+$ 597.2971, found 597.2974. Retention time for analytical rpHPLC: condition I, 13.25; condition II, 24.68 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)−(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}(1-pyrimidin-2-ylpiperidin-4-ylmethyl)amide (12w, X = CN, R^1 = 1-Pyrimidin-2-ylpiperidin-4-ylmethyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). To a solution of 1-methyl-1*H*-imidazole-4-sulfonic acid {2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]-ethyl}piperidin-4-ylmethylamide CF_3CO_2H salt (**12s**) (35 mg, 0.057 mmol) in THF (600 μL) at 0 °C was added LDA (2.0 M, 71 μL, 0.14 mmol), and the resulting solution was stirred for 1 h. 2-Chloropyrimidine (6.5 mg, 0.057 mmol) was then added, and the mixture was stirred overnight. The mixture was diluted with EtOAc and washed with brine. The organic phase was dried over magne-

sium sulfate, and solvent was removed under reduced pressure. The residue was purified by rpHPLC. Yield 46%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 8.36 (d, J = 4.89 Hz, 2H), 7.77 (s, 1H), 7.75 (s, 1H), 7.57 (d, J = 8.90 Hz, 2H), 7.28 (s, 1H), 7.02 (d, J = 8.97 Hz, 2H), 6.66 (t, J = 4.92 Hz, 1H), 4.88 (s, 2H), 4.59 (d, J = 13.33 Hz, 2H), 3.92 (s, 3H), 3.83 (t, J = 7.05 Hz, 2H), 3.78 (s, 3H), 3.44 (t, J = 7.05 Hz, 2H), 3.01 (d, J = 7.16 Hz, 2H), 2.88 (t, J = 11.76 Hz, 2H), 1.85−1.80 (m, 3H), 1.14 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 160.3, 158.7, 151.8, 141.4, 138.9, 137.9, 134.9, 133.0, 126.8, 120.8, 119.1, 114.0, 110.6, 100.4, 57.3, 51.2, 48.3, 45.4, 45.2, 36.6, 34.4, 34.3, 30.5. HRMS (ESI): *m*/*z* calcd for $C_{28}H_{34}N_{10}O_2SH^+$ 575.2665, found 575.2661. Retention time for analytical rpHPLC: condition I, 12.94; condition II, 19.66 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(2-methylbenzyl)amide (12x, X = CN, R^1 = 2-Methylbenzyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11x** was carried out according to procedure C. Yield 83%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.87 (s, 1H), 7.84 (s, 1H), 7.81 (s, 1H), 7.38 (d, J = 8.91 Hz, 2H), 7.30−7.17 (m, 4H), 7.10 (s, 1H), 6.48 (d, J = 8.91 Hz, 2H), 4.40 (s, 2H), 4.25 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.29 (br s, 4H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.5, 141.6, 139.8, 138.2, 137.8, 134.9, 134.7, 132.6, 132.2, 132.1, 129.8, 127.2, 127.0, 120.8, 119.0, 113.5, 100.0, 54.0, 51.0, 45.6, 44.6, 34.4, 34.2, 19.3. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{29}N_7O_2SH^+$ 504.2182, found 504.2177. Retention time for analytical rpHPLC: condition I, 14.68; condition II, 22.48 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(3-methylbenzyl)amide-*m*-toluene (12y, X = CN, R^1 = 3-Methylbenzyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11y** was carried out according to procedure C. Yield 87%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.88 (s, 1H), 7.82 (s, 1H), 7.78 (s, 1H), 7.39 (d, J = 9.07 Hz, 2H), 7.22 (t, J = 7.71 Hz, 1H), 7.14−7.11 (m, 4H), 6.56 (d, J = 9.07 Hz, 2H), 4.52 (s, 2H), 4.21 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.47 (t, J = 6.86 Hz, 2H), 3.35 (t, J = 6.86 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.9, 141.9, 140.2, 139.3, 138.2, 138.0, 135.1, 133.1, 131.4, 130.4, 130.1, 127.9, 127.2, 121.3, 119.5, 114.0, 100.5, 55.7, 51.5, 46.8, 45.4, 34.8, 34.6, 21.9. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{29}N_7O_2SH^+$ 504.2182, found 504.2186. Retention time for analytical rpHPLC: condition I, 14.78; condition II, 20.99 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(4-methylbenzyl)amide (12z, X = CN, R^1 = 4-Methylbenzyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11z** was carried out according to procedure C. Yield 74%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.88 (d, J = 0.82 Hz, 1H), 7.81 (d, J = 1.02 Hz, 1H), 7.78 (d, J = 1.22 Hz, 1H), 7.38 (d, J = 9.04 Hz, 2H), 7.20 (d, J = 8.02 Hz, 2H), 7.15 (d, J = 1.29 Hz, 1H), 7.12 (d, J = 7.87 Hz, 2H), 6.54 (d, J = 9.07 Hz, 2H), 4.56 (s, 2H), 4.19 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.43 (t, J = 7.45 Hz, 2H), 3.34 (t, J = 7.45 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.5, 141.5, 139.3, 138.8, 137.8, 134.6, 132.8, 130.4, 126.8, 120.8, 119.1, 113.5, 100.0, 55.1, 51.0, 46.4, 45.1, 34.3, 34.2, 21.2. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{29}N_7O_2SH^+$ 504.2182, found 504.2184. Retention time for analytical rpHPLC: condition I, 14.92; condition II, 21.40 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}pyridin-2-ylmethylamide (12aa, X = CN, R^1 = 2-Pyridylmethyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11aa** was carried out according to procedure C. Yield 62%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.91 (s, 1H), 8.53 (d, J = 5.17 Hz, 1H), 7.97 (td, J = 1.52, 7.77 Hz, 1H), 7.83 (s, 1 H), 7.81 (s, 1 H), 7.64 (d, J = 7.91 Hz, 1H), 7.48 (d, J = 9.10 Hz, 2H), 7.47 (obscured, 1H), 7.21 (s, 1H), 6.80 (d, J = 9.11 Hz, 2H), 4.73 (s, 2H), 4.55 (s, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.66 (m, 2H), 3.54 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 155.9, 150.6, 147.1, 140.6, 140.1, 137.6, 136.8, 133.8, 131.8, 126.1, 124.9, 124.3, 119.8, 118.0, 112.8, 99.3, 54.1, 49.5, 46.6, 44.2, 33.4, 33.2. HRMS calcd for $C_{24}H_{27}N_8O_2S^+$ 491.1978, found 491.1970. Retention time for analytical rpHPLC: condition I, 11.13; condition II, 14.43 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}pyridin-3-ylmethylamide (12ab, X = CN, R^1 = 3-Pyridylmethyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11ab** was carried out according to procedure C. Yield 63%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.90 (s, 1H), 8.62 (s, 1H), 8.56 (d, J = 6.49 Hz, 1H), 8.15 (d, J = 8.01 Hz, 1H), 7.84 (s, 2H), 7.62 (dd, J = 5.26, 7.87 Hz, 1H), 7.47 (d, J = 9.05 Hz, 2H), 7.17 (s, 1H), 6.74 (d, J = 9.11 Hz, 2H), 4.69 (s, 2H), 4.48 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.66 (m, 2H), 3.50 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.8, 147.4, 146.9, 142.9, 142.2, 138.9, 138.3, 137.3, 135.2, 133.0, 127.7, 127.0, 121.1, 119.4, 114.1, 100.8, 52.6, 51.1, 48.1, 45.6, 34.8, 34.6. HRMS calcd for $C_{24}H_{27}N_8O_2S^+$ 491.1978, found 491.1969. Retention time for analytical rpHPLC: condition I, 11.21; condition II, 14.84 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}pyridin-4-ylmethylamide (12ac, X = CN, R^1 = 4-Pyridylmethyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11ac** was carried out according to procedure C. Yield 71%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.79 (s, 1H), 8.43 (d, J = 6.11 Hz, 1H), 7.73 (d, J = 6.58 Hz, 1H), 7.49 (s, 1H), 7.48 (s, 1H), 7.37 (d, J = 9.04 Hz, 2H), 7.08 (s, 1H), 6.65 (d, J = 9.01 Hz, 2H), 4.59 (s, 2H), 4.38 (s, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 3.57 (t, J = 6.60 Hz, 2H), 3.39 (t, J = 6.65 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.8, 148.5, 142.2, 138.9, 138.3, 135.2, 133.1, 127.7, 126.2, 126.1, 121.1, 119.5, 114.1, 100.9, 54.5, 51.0, 48.3, 45.5, 34.8, 34.6. HRMS calcd for $C_{24}H_{27}N_8O_2S^+$ 491.1978, found 491.2003. Retention time for analytical rpHPLC: condition I, 11.13; condition II, 14.43 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid (3-Cyanobenzyl)-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-amidemcyanobenzyl (12ad, X = CN, R^1 = 3-Cyanobenzyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11ad** was carried out according to procedure C. Yield 67%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.88 (s, 1H), 7.82 (s, 1H), 7.80 (s, 1H), 7.64−7.60 (m, 3H), 7.48 (d, J = 7.93 Hz, 1H), 7.44 (d, J = 8.95 Hz, 2H), 7.16 (s, 1H), 6.67 (d, J = 8.95 Hz, 2H), 4.61 (s, 2H), 4.34 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.57 (t, J = 6.67 Hz, 2H), 3.44 (t, J = 6.67 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.4, 141.7, 139.9, 138.7, 137.8, 134.7, 133.5, 132.8, 132.7, 130.9, 127.1, 120.8, 119.4, 119.0, 113.6, 113.5, 100.4, 54.4, 50.8, 47.3, 45.2, 34.4, 34.3. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{26}N_8O_2SH^+$ 515.1978, found 515.1971. Retention time for analytical rpHPLC: condition I, 13.78; condition II, 18.94 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid (4-Cyanobenzyl)-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-amide (12ae, X = CN, R^1 = 4-Cyanobenzyl, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11ae** was carried out according to procedure C. Yield 60%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.88 (s, 1H), 7.82 (s, 1H), 7.80 (s, 1H), 7.61 (d, J = 8.22 Hz, 2H), 7.48 (d, J = 8.22 Hz, 2H), 7.42 (d, J = 9.01 Hz, 2H), 7.15 (s, 1H), 6.64 (d, J = 9.01 Hz, 2H), 4.63 (s, 2H), 4.35 (s, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.57 (t, J = 6.72 H, 2H), 3.42 (t, J = 6.72 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.3, 143.7, 141.7, 138.5, 137.8, 134.6, 133.5, 130.8, 127.1, 120.8, 119.4, 119.0, 113.6, 112.9, 100.2, 54.9, 50.8, 47.5, 45.2, 34.4, 34.2. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{26}N_8O_2SH^+$ 515.1978, found 515.1970. Retention time for analytical rpHPLC: condition I, 13.84; condition II, 18.91 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid Biphenyl-3-ylmethyl-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]-ethyl}amide (12af, X = CN, R^1 = Biphenyl-3-ylmethyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11af** was carried out according to procedure C. Yield 69%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.71 (s, 1H), 7.72 (s, 2H), 7.50 (m, 4H), 7.38 (m, 2H), 7.31 (m, 2H), 7.23 (d, J = 7.72 Hz, 1H), 7.20 (d, J = 9.04 Hz, 2H), 7.03 (s, 1H), 6.48 (d, J = 9.09 Hz, 2H), 4.40 (s, 2H), 4.26 (s, 2H), 3.70 (s, 3H), 3.63 (s, 3H), 3.39 (m, 2H), 3.34

(m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.8, 143.1, 142.0, 141.9, 139.4, 138.8, 138.1, 135.0, 133.0, 130.9, 130.5, 129.8, 129.3, 129.2, 128.3, 128.1, 127.3, 121.2, 119.4, 113.9, 100.5, 55.7, 51.5, 47.1, 45.4, 34.8, 34.5. HRMS calcd for $C_{31}H_{32}N_7O_2S^+$ 566.2338, found 566.2321. Retention time for analytical rpHPLC: condition I, 14.51; condition II, 24.77 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid Biphenyl-4-ylmethyl-{2-[(4-cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]-ethyl}amide (12ag, X = CN, R^1 = Biphenyl-4-ylmethyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11ag** was carried out according to procedure C. Yield 74%. ^{1}H NMR (500 MHz, MeOH-d_4): δ 8.77 (s, 1H), 7.80 (s, 1 H), 7.77 (s, 1 H), 7.58 (dd, J = 1.28, 8.50 Hz, 2H), 7.56 (d, J = 8.23 Hz, 2H), 7.44 (t, J = 7.47 Hz, 2H), 7.37 (d, J = 8.21 Hz, 2H), 7.36 (tt, J = 1.14, 7.38 Hz, 1H), 7.29 (d, J = 9.05 Hz, 2H), 7.12 (s, 1H), 6.53 (d, J = 9.10 Hz, 2H), 4.54 (s, 2H), 4.26 (s, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.48 (m, 2H), 3.38 (m, 2H). ^{13}C NMR (125 MHz, MeOH-d_4): δ 149.1, 139.9, 139.2, 139.0, 136.5, 135.4, 134.3, 132.3, 130.4, 128.7, 127.8, 126.4, 125.8, 125.5, 124.6, 118.4, 116.7, 111.2, 97.8, 52.8, 48.8, 44.4, 42.8, 32.0, 31.8. HRMS calcd for $C_{31}H_{32}N_7O_2S^+$ 566.2338, found 566.2358. Retention time for analytical rpHPLC: condition I, 15.69; condition II, 30.13 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}-(4-pyrrol-1-yl-benzyl)amide (12ai, X = CN, R^1 = 4-Pyrrol-1-ylbenzyl, R^2 = 4-methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **11ai** was carried out according to procedure C. Yield 54%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.72(s, 1H), 7.74 (m, 4H), 7.49 (s, 1H), 7.32 (m, 4H), 7.13 (s, 1H), 7.06 (s, 1H), 6.52 (m, 3H), 6.24 (t, J = 2.54 Hz, 2H), 4.49 (s, 2H), 4.12 (s, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.40 (m, 2H), 3.32 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.4, 144.4, 138.4, 136.7, 135.3, 133.9, 129.5, 127.5, 121.2, 121.0, 120.2, 119.2, 114.7, 112.4, 111.4, 101.8, 52.5, 51.4, 47.7, 46.2, 34.7, 34.5. HRMS calcd for $C_{29}H_{31}N_8O_2S^+$ 555.2285, found 555.2292. Retention time for analytical rpHPLC: condition I, 13.21; condition II, 20.55 min.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Cyanophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}amide (10c, X = CN, R^2 = 1-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **9c** was carried out according to procedure C after deprotection of Boc group. Yield 82%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.89 (s, 1H), 7.78 (s, 1H), 7.67 (s, 1H), 7.52 (d, J = 9.02 Hz, 2H), 7.24 (s, 1H), 6.91 (d, J = 9.02 Hz, 2H), 4.83 (s, 2H), 3.90 (s, 3H), 3.75 (s, 3H), 3.66 (t, J = 6.31 Hz, 2H), 3.21 (t, J = 6.31 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.8, 141.2, 140.4, 137.7, 130.0, 125.9, 120.9, 119.1, 114.0, 100.2, 51.5, 46.0 41.2 34.4, 34.3.

***N*-(4-Bromophenyl)-*N*-(3-methyl-3*H*-imidazol-4-ylmethyl)-*N*′-pyridin-2-ylmethylethane-1,2-diamine (18, X = Br, R^1 = 2-Pyridylmethyl, R^3 = Methyl).** Reaction of **9b** was carried out according to procedure A. Yield 52%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.78 (s, 1H), 8.46 (d, J = 4.86 Hz, 1H), 7.73 (dt, J = 7.70, 1.63 Hz, 1H), 7.31 (d, J = 7.83 Hz, 1H), 7.28 (dd, J = 5.03, 7.55 Hz, 1H), 7.25 (d, J = 9.07 Hz, 2H), 7.14 (s, 1H), 6.78 (d, J = 9.00 Hz, 2H), 4.59 (s, 2H), 4.30 (s, 2H), 3.74 (s, 3H), 3.66 (t, J = 7.06 Hz, 2H), 3.22 (t, J = 7.10 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 151.3, 149.5, 146.2, 137.9, 136.7, 132.4, 132.0, 124.1, 123.2, 118.3, 117.3, 112.1, 50.9, 47.1, 45.4, 44.2, 33.0.

1-Methyl-1*H*-imidazole-4-sulfonic Acid {2-[(4-Bromophenyl)-(3-methyl-3*H*-imidazol-4-ylmethyl)amino]ethyl}pyridin-2-yl-methylamide (17, X = Br, R^1 = 2-Pyridylmethyl, R^2 = 4-Methyl-1*H*-imidazolesulfonyl, R^3 = Methyl). Reaction of **18** was carried out according to procedure C. Yield 24%. ^{1}H NMR (400 MHz, MeOH-d_4): δ 8.75 (s, 1H), 8.42 (d, J = 5.18 Hz, 1H), 7.88 (td, J = 1.69, 7.76 Hz, 1H), 7.71 (s, 1H), 7.67 (s, 1H), 7.54 (d, J = 7. 93 Hz, 1H), 7.39 (dd, J = 5.23, 7.51 Hz, 1H), 7.15 (d, J = 9.11 Hz, 2H), 7.12 (s, 1H), 6.53 (d, J = 9.14 Hz, 2H), 4.49 (s, 2H), 4.43 (s, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 3.41 (m, 2H), 3.35 (m, 2H). ^{13}C NMR (100 MHz, MeOH-d_4): δ 157.3, 148.2, 147.9, 142.0, 141.7, 139.1, 138.0, 133.7, 133.5, 127.5, 126.3, 125.7, 119.7, 116.9, 111.7, 55.3, 51.3, 48.1, 45.8, 34.8, 34.6. HRMS calcd for $C_{23}H_{27}N_7O_2S^+$ 544.1130, found 544.1145. Retention time for analytical rpHPLC: condition I, 11.21; condition II, 14.74 min.

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Supporting Information Available: HPLC retention times, purity, and HRMS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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