Design and Synthesis of Peptidomimetic Protein Farnesyltransferase Inhibitors as Anti-*Trypanosoma brucei* Agents

Junko Ohkanda,[†] Frederick S. Buckner,*[,‡] Jeffrey W. Lockman,[†] Kohei Yokoyama,[§] Dora Carrico,[†] Richard Eastman,[‡] Kate de Luca-Fradley,[∥] Wendy Davies,[∥] Simon L. Croft,[∥] Wesley C. Van Voorhis,[‡] Michael H. Gelb,*[,§] Saïd M. Sebti,[⊥] and Andrew D. Hamilton*[,†]

Department of Chemistry, Yale University, PO Box 208107, New Haven, Connecticut 06520, Department of Medicine, University of Washington, Campus Box 357185, Seattle, Washington 98195, Departments of Chemistry and Biochemistry, Campus Box 351700, University of Washington, Seattle, Washington 98195, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, U.K., and Drug Discovery Program, H. Lee Moffitt Cancer Center & Research Institute, Departments of Oncology and Biochemistry & Molecular Biology, University of South Florida, Tampa, Florida

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On the basis of the structure of the CVIM tetrapeptide substrate of mammalian protein farnesyltransferase, a series of imidazole-containing peptidomimetics was designed and synthesized, and their inhibition activity against *Trypanosoma brucei* protein farnesyltransferase (*Tb*PFT) was evaluated. Peptidomimetics where the 5-position of the imidazole ring was linked to the hydrophobic scaffold showed over 70% inhibition activity at 50 nM in the enzyme assay, whereas the corresponding C-4 regioisomers were less potent. The ester prodrug **23** was found to be a potent inhibitor against cultured *Trypanosoma brucei brucei* and *Trypanosoma brucei rhodesiense* cells with ED_{50} values of 0.025 and 0.0026 μM, respectively. Furthermore, introducing a second imidazole group into **23** led to **31**, which showed the highest inhibition activity against the parasite with an ED_{50} of 0.0015 μM. The potency of the *Tb*PFT inhibitors and the cytotoxicity of the corresponding esters to *T. brucei* cells were shown to be highly correlated. These studies validate *Tb*PFT as a target for the development of novel therapeutics against African sleeping sickness.

Introduction

New drugs are desperately needed for diseases caused by trypanosomatid parasites, such as African sleeping sickness, Chagas disease, and leishmaniasis. The World Health Organization estimates that 300 000 cases of African sleeping sickness occur annually in 36 countries in sub-Saharan Africa, that 16−18 million people in Latin America are chronically suffering from Chagas disease, and that 12 million people worldwide are infected with *Leishmania spp.*[1] The currently used drugs for these diseases are generally highly toxic and often ineffective, and drug resistance has developed in some cases. New and vulnerable protein targets within the cellular processes of the parasite are needed in the search for novel therapeutics.

Protein prenylation represents a potential target as it plays a crucial role in cellular signal transduction, proliferation, and apoptosis. The process of prenylation involves the attachment of farnesyl (C_{15}) or geranylgeranyl groups (C_{20}) onto the C-terminal cysteine residues of small GTP binding proteins, such as the Ras family, in eukaryotic cells. Protein farnesyltransferase (PFT) is a heterodimeric zinc metalloenzyme, and binds to the tetrapeptide sequence of the C-terminus of substrate proteins, CaaX, where C is cysteine, a is usually but not necessarily an aliphatic amino acid, and X is typically methionine, serine, alanine, glutamine, or cysteine. This enzyme catalyzes the transfer of farnesyl from farnesylpyrophosphate (FPP) to the free thiol group of the cysteine residue in the CaaX tetrapeptide sequence of the substrate protein.

Because oncogenically mutated Ras has been found in 30% of human cancers, the disruption of Ras farnesylation has become a new clinical target for anticancer drug design.[2,3] As part of this effort we have been pursuing the design and synthesis of peptidomimetic inhibitors based on the CaaX tetrapeptide as novel antitumor agents.[4−6] We have reported several series of peptidomimetics where the aliphatic dipeptide in CaaX was replaced by structurally restricted 4-amino-2-phenylbenzoic acid scaffolds. These molecules inhibit PFT with sub-nanomolar IC_{50} values and suppress tumor growth in xenograft nude mice models.[7]

We and others have shown that protein farnesylation occurs in trypanosomatids and in the malaria parasite and that inhibitors of PFT are toxic to these parasites.[8−14] A key advantage of developing PFT inhibitors as antiparasitic agents is that these compounds have been extensively developed as anti-cancer agents.[2,15,16] Thus, we envision a "piggy-back" medicinal chemistry approach by which lead PFT inhibitors that have advanced through the drug development process can be used as

* Corresponding authors. A.D.H.: tel, 1-203-432-5570; fax, 1-203-432-3221; e-mail, andrew.hamilton@yale.edu. M.H.G.: tel, 1-206-543-7142; fax, 1-206-685-8665; e-mail, gelb@chem.washington.edu. F.S.B.: tel, 1-206-543-0821; fax, 1-206-685-8681; e-mail, fbuckner@u.washington.edu.
[†] Yale University.
[‡] Department of Medicine, University of Washington.
[§] Departments of Chemistry and Biochemistry, University of Washington.
[∥] London School of Hygiene and Tropical Medicine.
[⊥] University of South Florida.

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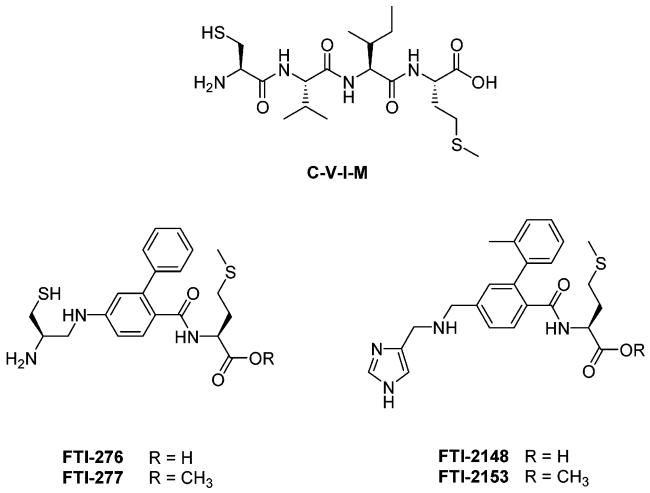


Figure 1. CVIM and peptidomimetic PFT inhibitors.

starting points for the development of antiparasitic agents.

Our design of peptidomimetic PFT inhibitors is based on the extended conformation of the CVIM tetrapeptide (Figure 1), which is seen in the crystal structure of the ternary complex of mammalian PFT with CaaX tetrapeptide and FPP analogues.[17,18] Among our first-generation peptidomimetics, cysteine-containing FTI-276 showed remarkable inhibition activity against mammalian PFT in vitro (IC_{50} = 0.5 nM),[19] although the metabolically unstable free thiol group hampered further development. In the second-generation inhibitors, the cysteine was replaced by an imidazole group to afford FTI-2148, which is a potent inhibitor of mammalian PFT in vitro (IC_{50} = 0.86 nM), and FTI-2153 (in which the C-terminal carboxyl group is converted to its methyl ester to improve transfer across the plasma membrane of cells), which is highly potent at blocking Ras farnesylation in mammalian cells, with an ED_{50} value of 0.02 μM.[7]

In this study, we have prepared an expanded series of imidazole-containing CaaX mimetics and have tested them in vitro as inhibitors of PFT from *Trypanosoma brucei* (the causative agent of African sleeping sickness). We have also tested the compounds for their ability to exert a cytotoxic effect on the bloodstream life cycle form of cultured parasites, which is the clinically most relevant form. We observed an excellent correlation between the potency of inhibition of *T. brucei* PFT (*Tb*PFT) and killing of *T. brucei* bloodstream parasites. These results provide strong pharmacological data to support *Tb*PFT as a valid anti-trypanosomal drug target.

Chemistry

Crystal structures of the ternary complex of rat PFT bound to the tetrapeptide CVIM and an FPP analogue showed that the tetrapeptide binds in an extended conformation with the Cys thiol coordinating to zinc in the active site.[17] The hydrophobic side chains from aliphatic dipeptide Val-Ile in the CVIM bind to a large hydrophobic pocket that involves several aromatic amino acid residues, including Tyr361β, Trp102β, and Trp106β. Furthermore, there are two distinct hydrogen bonds formed, respectively, between the carboxylate of the Met in CVIM and Gln167α and the amido carbonyl group of the Ile in CVIM and Arg202β.

*Tb*PFT has been cloned and expressed in the baculovirus insect cell system and shown to have a size that is 40% larger than that of rat PFT.[12,20,24] A modeling study showed that the amino acid sequence identity between the core regions of *Tb*PFT and rat PFT is 21% for the α-subunit and 36% for the β-subunit and that all the amino acid residues in direct contact with the Caa region of the CaaX substrate in the active site are identical except for the modest change of Tyr-166 in the α-subunit of rat PFT being replaced by Phe in *Tb*PFT.[20] Groups contacting the C-terminal X group show more significant differences between the two enzymes.

Thus, we decided to take a similar strategy for the design of *Tb*PFT inhibitors to that which was successful for inhibitors of mammalian PFT using the same hydrophobic scaffold as well as Cys and Met replacements. In our earlier work on mammalian PFT inhibitors, we successfully replaced the hydrophobic dipeptide moiety in CVIM by a simple 4-amino-2-phenylbenzoic acid, as seen in FTI-276 (Figure 1). On the basis of a similar hydrophobic scaffold, an analogue approach was investigated by introducing various functional groups on the imidazole nitrogen. In the previous study, we also showed that the corresponding methyl ester FTI-277 significantly improved the inhibition activity in whole cells, presumably due to increased membrane permeability. For the prodrug study in this paper, a series of esters were introduced onto the carboxylic acid of the Met residues of the peptidomimetics.

Compounds **3**−**12** were synthesized by a similar procedure to that reported previously (Scheme 1).[5] Briefly, Suzuki aryl coupling of 2-bromo-4-nitrotoluene with phenylboronic acid followed by oxidation of the methyl group afforded the biphenyl scaffold **1**, which was coupled with L-methionine methyl ester. Reduction of the nitro group gave aniline **2**. Compound **2** was reacted with the formylimidazole derivative **37**, **38**, or **40** (which were synthesized by the procedure depicted in Scheme 3) under reductive amination conditions, followed by the hydrolysis of the methyl esters, to give **3**−**12**.

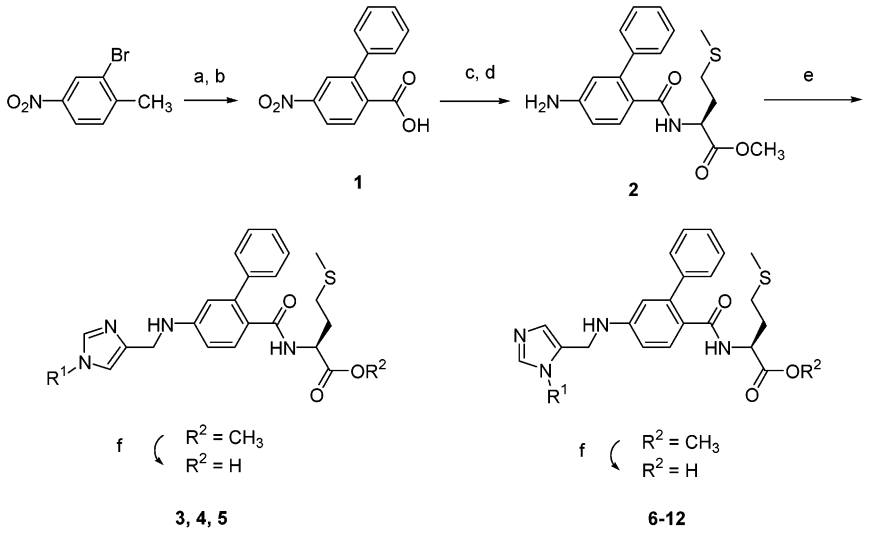
For compounds **15**−**21**, esterification with *tert*-butyl alcohol followed by hydrogenation of the nitro group afforded **13** (Scheme 2). After reductive amination of **13** with **40a** and subsequent deprotection, compound **14** was coupled with a series of amines by an EDCI−HOBt reaction to yield the corresponding amide-substituted derivatives **15**−**21**.

Compounds **22**−**34** were based on a scaffold that possesses one more methylene spacer between the imidazole group and biphenyl scaffold and were prepared by a modification of the procedure used to make **3**−**12**.[21]

Results and Discussion

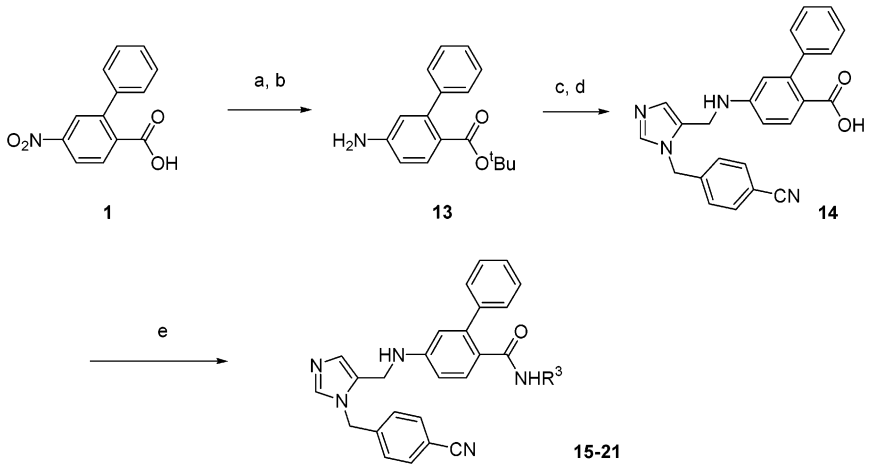
The compounds described in this report were patterned after FTI-276 (and its methyl ester FTI-277), which we previously showed to have potent activity against the *Tb*PFT and against cultured forms of *T. brucei* (Table 1).[12] The newly prepared compounds contain substitutions of the cysteine portion of FTI-276, primarily involving an imidazole or substituted imida-

Scheme 1[a]



[a] Reagents: (a) $PhB(OH)_2$, $Pd(OAc)_2$, K_2CO_3, 89%; (b) $KMnO_4$, 100%; (c) HCl·H-Met-OMe, EDCI, HOBt, NEt_3, 89%; (d) $SnCl_2$, AcOEt, 90%; (e) **37**, **38**, or **40**, $NaBCNH_3$, 69%; (f) LiOH, THF, 54−92%.

Scheme 2[a]



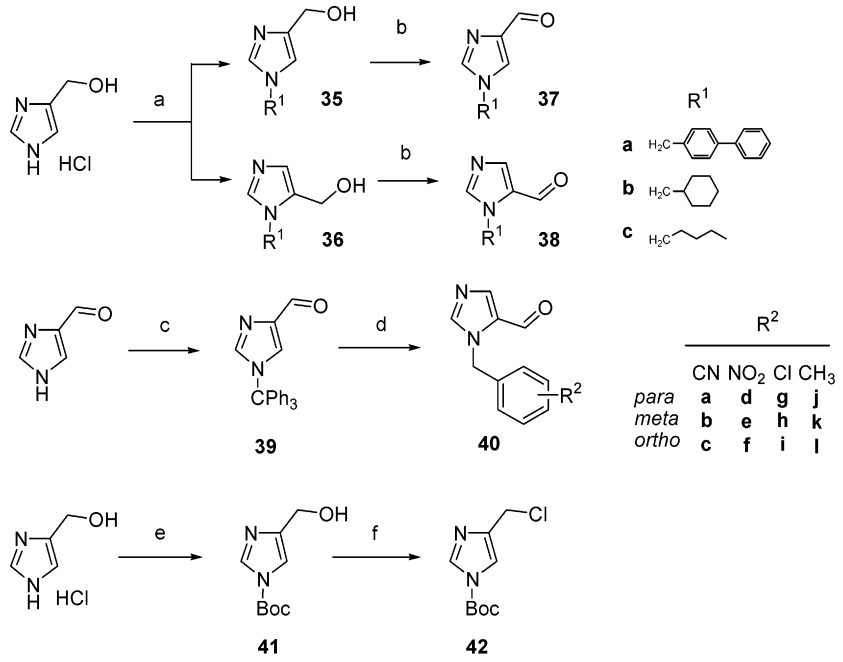
[a] Reagents: (a) $SOCl_2$, Bu^{t}OK, 72%; (b) H_2/10% Pd−C, THF, 100%; (c) 1-(4-cyano)benzyl-5-formylimidazole, $TiCl_4$, $NaBCNH_3$, 73%; (d) 50% TFA in CH_2Cl_2, 100%; (e) R^3NH_2, EDCI, HOBt, NEt_3, 77−86%.

zole group that is intended to coordinate to the zinc in the active site of PFT. Compounds containing a substituted imidazole retain high inhibitory potency against *Tb*PFT, similarly to the PFT inhibitors that block growth of *Plasmodium falciparum* in red blood cells.[13] The linkage position of the imidazole was shown to be important, as demonstrated by the derivatives shown in Table 2. Compounds containing the link from the central aromatic unit to the 5-position of the imidazole (**6**−**8**; Series 2) inhibit *Tb*PFT at 50 nM in the 70−80% range, whereas the analogous compounds containing the link to the 4-position of the imidazole (**3**−**5**; Series 1) were significantly less potent *Tb*PFT inhibitors. It is likely that the imidazole linked at the 5-position is better able to coordinate with the zinc ion in the PFT enzyme than is the corresponding imidazole in compounds of series 1. To further probe the scope of the 1,5-imidazole substitution pattern, we prepared a series of inhibitors **6**, **9**−**12**, in which different benzyl groups were attached to the N-1 position.

The position and nature of the different substitutions of the imidazole-linked phenyl ring significantly affected the PFT inhibitor potency (Table 3). Substitutions in the para-position gave the most potent PFT inhibition, as seen in **6a**−**12a**, followed by those with meta-substitutions (**9c**−**12c**), and compounds with ortho-substitutions such as **9e**−**12e** had the lowest potency (Table 3). The nature of the substituent does not appear to be important, because of the narrow range of IC_{50} values observed within each of the three groups. As expected, the methyl ester form of the compounds (**6b**−**12b**, **9d**−**12d**) had dramatically greater cellular activity against *T. brucei* bloodstream parasites than the free acid counterparts.

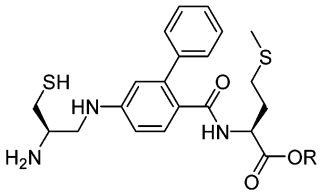
Using the 1-(4-cyanobenzyl)imidazole as a constant zinc-binding domain, we prepared a series of compounds, based around the 2-phenyl-4-aminobenzoic acid scaffold in which the C-terminal methionine group was replaced by various amide substitutions (Table 4). These compounds were nearly all inactive as *Tb*PFT inhibitors (<20% inhibition at 50 nM), and had ED_{50} values >10 μM, showing the importance of the methionine structure in the CaaX mimetics (Table 4). Similarly, a series of analogous compounds containing leucine in place of the methionine did not cause significant inhibition of the *Tb*PFT or parasite growth up to 10 μM (data not shown),

Scheme 3[a]



[a] Reagents: (a) alkyl bromide, Na_2CO_3, DMF at 80 °C; (b) MnO_2, dioxane; (c) Ph_3CCl, Et_3N, DMF, 99%; (d) *o*-, *m*-, or *p*-substituted benzyl bromide, CH_3CN, 60 °C, overnight; (e) Boc_2O, Et_3N, DMF, 70%; (f) $SOCl_2$, 20 min at 0 °C, 83%.

Table 1. Inhibition of *Tb*PFT by Peptidomimetics FTI-276 and FTI-277

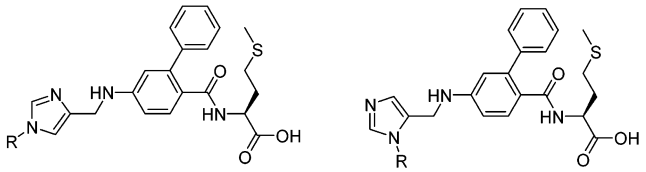


FTI-276 R = H
FTI-277 R = CH_3

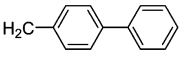
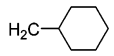
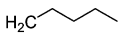
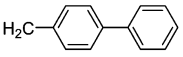
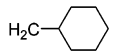
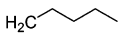
compd	IC_{50}, nM *Tb*PFT	ED_{50}, μM *T. brucei brucei*	ED_{50}, μM *T. brucei rhodesiense*	Murine 3T3 fibroblasts
FTI-276	1.7[a]	>25[a]	9.2	>25
FTI-277	40[a]	0.7[a]	ND	>25

[a] Reference 12.

Table 2. Inhibition of *Tb*PFT by Series 1 and Series 2 Compounds



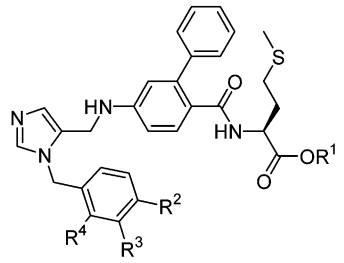
Series 1 Series 2

Series	Compound	R	*Tb*PFT % inhibition at 50 nM (IC_{50} nM)
1	**3**		4.5
	4		12
	5		11.5
2	**6a**		85.6 (8)
	7		69.8
	8		80.6

except for GGTI-297.[12] Since a free carboxylate in the X position of these compounds impairs cell penetration, development of the inhibitors without an acid or hydrolyzable ester should improve the pharmacological properties while the enzyme inhibitory activity is retained.

Increasing the length of the linker between the imidazole and hydrophobic scaffold (Table 5) led to a particularly effective series of *Tb*PFT inhibitors in vitro and in growing parasites. The parent compound **22**, containing a 4-aminomethyl substituent on the phenylbenzoate scaffold, inhibited *Tb*PFT by 96% when tested at 50 nM and had an IC_{50} of 1.8 nM. The methyl ester containing prodrug **23** was considerably more potent than **22** against cultured *T. brucei* cells, as would be predicted from similar observations with the methyl ester congener of FTI-276 (FTI-277) in *T. brucei* cultures.[12] The more hydrophobic methyl ester derivatives are expected to more readily penetrate cells than the free acids. Since the methyl ester derivatives are generally weakly active against the enzyme, we surmise that compounds are converted inside the cell to the free acid form, which then acts on the *Tb*PFT. To further explore the potential for enhanced cellular cytotoxicity, compounds with different ester groups on the methionine were synthesized (Table 5, **24**−**29**). Bulkier hydrophobic groups seemed to lower ED_{50} values, with the isopropyl ester **26** giving the highest potency (ED_{50} = 0.005 μM)

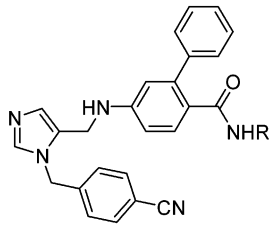
Table 3. Range of *Tb*PFT and Parasite Growth Inhibition for Different Substituted Benzyl Derivatives of Peptidomimetic Inhibitor[a]

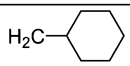
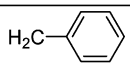
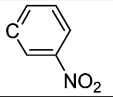
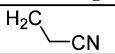
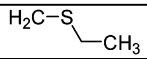
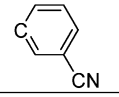


				*						ED$_{50}$ μM	
				6	**9**	**10**	**11**	**12**	*Tb*PFT % inhibn	*T. brucei*	*T. brucei*
R_1	R_2	R_3	R_4	Ph	CN	NO_2	Cl	CH_3	at 50 nM	*brucei*	*rhodesiense*
H	*			**a**	**a**	**a**	**a**	**a**	82−87	>10	14 to >60
CH_3	*			**b**	**b**	**b**	**b**	**b**	0−14	0.5−5	0.14−0.8
H		*			**c**		**c**	**c**	65−74	>10	>60
CH_3		*			**d**	**d**	**d**	**d**	0−17	1−5	0.38−0.92
H			*		**e**		**e**	**e**	29−41	>10	>60
CH_3			*		**f**		**f**	**f**	0	1−10	ND

[a] ED$_{50}$ against murine 3T3 fibroblasts >10 μM for all compounds in the table.

Table 4. *Tb*PFT and Parasite Growth Inhibition by Compounds **15**−**21**[a]



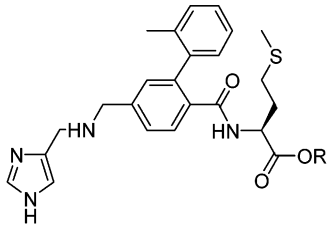
Compound	R	*Tb*PFT % inhibition at 50 nM	*T. brucei brucei* ED$_{50}$ μM	*T. brucei rhodesiense* ED$_{50}$ μM
15		8.4	>10	5.3
16		18.6	1-10	3.2
17		1.2	10	8.2
18		9.1	>10	3.0
19		0	>10	45
20		17.1	>10	3.0
21		2.2	>10	ND

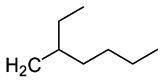
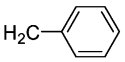
[a] ED$_{50}$ against murine 3T3 fibroblasts >10 μM for all compounds in the table.

against *T. brucei* parasite growth (Table 5). This may be due to the increased stability of the ester in the medium and/or enhanced cell permeability. However, an optimum for this effect seems to be reached since esters bulkier than isopropyl (**27**−**29**) show reduced potency.

Further modifications to the basic design of inhibitor **22** are shown in Table 6. Attachment of a second imidazolylmethyl group onto the aminomethyl-N gave bis-imidazole **30**, which was found to be a potent inhibitor of the *Tb*PFT enzyme (IC$_{50}$ = 5.9 nM), and its methyl ester version, **31**, showed the highest potency against *Trypanosoma brucei rhodesiense* with an ED$_{50}$ of 0.0015 μM (Table 6). The second imidazole group appears to increase binding affinity to the enzyme, presumably due to favorable contacts within the active site. Compound **33** in Table 6 contains simply a methyl group in the 5-position of the imidazole ring. However, this seems to interfere with access of the imidazole to the active site zinc, since the potency is much reduced compared to **22**. Similarly, compound **32** contains an amide in place of the secondary amine in the spacer between the imidazole and biphenyl scaffold, and a methyl group at the N-1 position of the imidazole ring. Although **32** maintains a similar distance between the methionine COOH and the N-3 nitrogen in the imida-

Table 5. *Tb*PFT and *T. brucei* Cell Growth Inhibition by Compounds **22**−**29**



Compound	R	*Tb*PFT % inhibition at 50 nM (IC_{50} nM)	*T. brucei brucei* ED_{50} μM	*T. brucei rhodesiense* ED_{50} μM	Murine 3T3 fibroblasts ED_{50} μM
22	H	96.1 (1.8)	1	0.2	>25
23	CH_3	41	0.025	0.0026	25
24	C_2H_5	10.4	0.01	0.005	10
25		4.9	0.01	0.009	1-10
26		6.2	0.005	0.003	10
27		15.2	0.02	0.02	1-10
28		4.5	0.03	0.018	1-10
29		41.7	0.02	ND	1-10

zole, this compound showed reduced potency compared to **22**, presumably due to the restricted bond rotation of the amide bond or steric hindrance of the N-1 nitrogen from the zinc by the methyl group. Compound **32** and the other compounds with a methyl substitution at the ortho-position on the branching aromatic ring (**22**, **30**) were among the best inhibitors of *Tb*PFT, suggesting an advantage from the increased hydrophobic surface area and conformational constraint of this substitution. Finally, compound **34**, combining the 4-cyanobenzyl substituent of **9a** and the increased spacer length of **22**, showed only modest efficacy in inhibiting parasite growth.

There is a very close correlation in the cellular activity of the compounds against *T. brucei brucei* and against *T. brucei rhodesiense* and the latter, which is the clinically relevant organism, tended to be more sensitive to the PFT inhibitors.

We showed that **22** and its methyl ester prodrug **23** are among the most potent inhibitors of *Tb*PFT and *T. brucei* cell growth, respectively (Table 5). Compound **23** also caused inhibition of in vivo protein prenylation in bloodstream-form *T. brucei* (Figure 2) as examined by metabolic labeling of cellular proteins with [^{3}H]mevalonolactone in the presence of simvastatin (to block endogenous mevalonic acid production). This compound significantly blocked incorporation of [^{3}H]prenyl groups into a subset of cellular proteins in a dose-dependent manner, most notably in proteins of approximate molecular masses of 100, 75, 50, and 20 kDa. Radiolabeling of the prominent bands in the 28−35 kDa range was not significantly affected by the inhibitor. These bands presumably represent geranylgeranylated substrates of protein geranylgeranyltransferase-II (such as Rab proteins), which would not be expected to be inhibited by CaaX mimetics.

The potency of inhibition of *Tb*PFT in vitro and *T. brucei* cellular cytotoxicity were shown to be highly correlated (Figure 3). These data, along with the biochemical data in Figure 2, provide compelling evidence that PFT inhibition is the cause of cytoxicity in these cells. In addition, PFT inhibitors exhibit very little toxicity to mammals, including humans,[22] suggesting

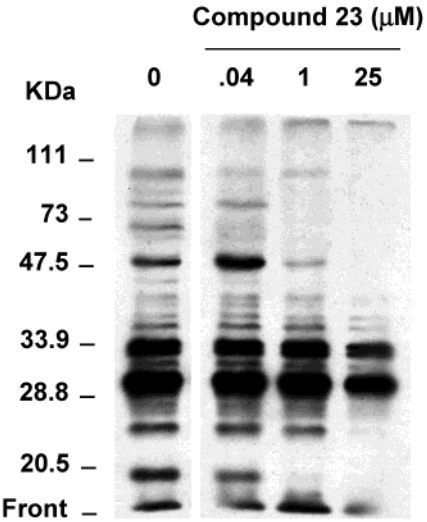
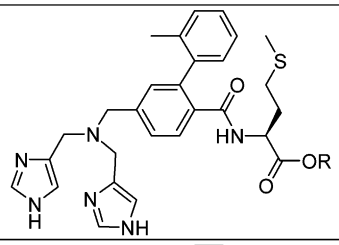
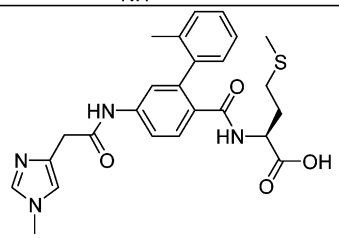
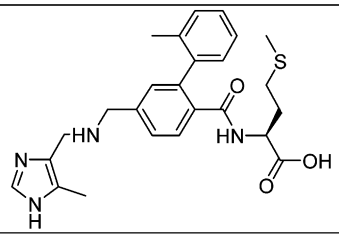
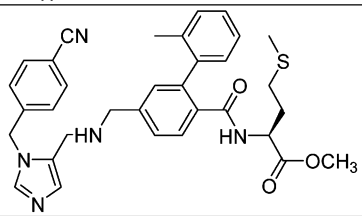


Figure 2. Inhibition of in vivo prenylation in *T. brucei* bloodstream form by **23**. *T. brucei* bloodstream forms (1×10^7 cells) were incubated for 24 h with 100 μCi (0.83 μM) [^{3}H]mevalonolactone and 2 μM simvastatin in the presence of 0, 0.04, 1, or 25 μM **23**. Radiolabeled proteins were analyzed by SDS−PAGE using a 12.5% gel followed by fluorography. The gel was exposed to X-ray film at −80 °C for 7 days.

Table 6. Inhibition of *Tb*PFT and Parasite Growth by Compounds **30**−**34**

Compound	Structure	*Tb*PFT % inhibition at 50 nM (IC_{50} nM)	*T. brucei brucei* ED_{50} μM	*T. brucei rhodesiense* ED_{50} μM	Murine 3T3 fibroblasts ED_{50} μM
30 (R=H)		99 (5.9)	1-10	0.9	>10
31 ($R=CH_3$)		66.2	0.1	0.0015	>10
32		83.2% (6.6)	>25	>60	>25
33		68.5	>10	ND	>10
34		7	0.5	0.1	>10

that *Tb*PFT is a promising target for the development of chemotherapies against *T. brucei* infections.

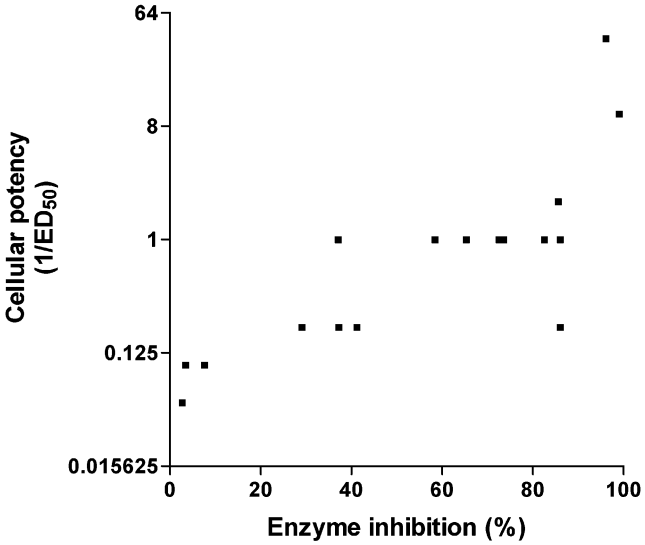


Figure 3. Correlation of inhibition activity against *T. brucei brucei* PFT enzyme and against *T. brucei brucei* bloodstream parasites. The enzyme activity is represented as the percent enzyme inhibition using 50 nM of compound (free acid form). The cellular activity of the corresponding methyl ester compound is represented as the reciprocal of the ED_{50} in μM.

In summary, a series of imidazole-containing CaaX peptidomimetics were synthesized, and their *Tb*PFT inhibition potency was evaluated in an enzyme assay and in whole cells. Compounds based on a 4-aminomethylbenzoic acid scaffold were found to be highly potent inhibitors against *T. brucei* in bloodstream parasites, especially bis-imidazole **31**, which inhibits parasite growth with an ED_{50} value of 0.0015 μM. Since PFT inhibitors are well-tolerated in humans over several months,[22] these compounds are expected to be promising new drug candidates for the treatment of African sleeping sickness. Animal studies using *T. brucei* infected mice models and PFT inhibitors are currently underway in our group.

Experimental Section

Melting points were determined with an Electrothermal capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-500 and 400 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane. All coupling constants are reported in hertz. Elemental analyses were performed by Atlantic Microlab, Inc., GA. Flash column chromatography was performed on silica gel (40−63 μm) under a pressure of about 4 psi. Solvents were obtained from commercial suppliers and purified as follows: tetrahydrofuran and ether were distilled from sodium benzophenone ketyl; dichloromethane was distilled over calcium hydride. Synthesized final compounds were checked for purity by analytical HPLC, which was performed

using a Rainin HP controller and a Rainin UV−C detector with a Rainin 250 mm × 4.6 mm, 5 μm Microsorb C-18 column, eluted with a gradient of 10%−90% CH_3CN in 0.1% TFA in H_2O in 30 min. High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were performed on a Varian MAT-CH-5 (HRMS) or VG 707 (LRMS) mass spectrometer. Compounds **1** and **2**,[5] **39** and **40**,[6] and **41** and **42**[23] were prepared by the previously reported procedures.

4-[*N*-(1-(4-Phenyl)benzyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine Methyl Ester. A solution of **39a** (131 mg, 0.5 mmol) and **2** (197 mg, 0.5 mmol) in MeOH (5 mL) was stirred for 15 min at room temperature (rt). To the solution was added $NaBCNH_3$ (31 mg, 0.5 mmol), and the mixture was stirred overnight at rt. After evaporation of solvents, the product was extracted with CH_2Cl_2 (100 mL) and sat. $NaHCO_3$ (30 mL). The crude material was purified by flash column chromatography (100:10:2 $CHCl_3$/acetone/EtOH) to give the product as a colorless oil (207 mg, 69%). ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 1H, C*H*HCH$_2$), 1.88 (m, 1H, C*H*HCH$_2$), 2.01 (s, 3H, SCH_3), 2.10 (t, J = 7.7 Hz, 2H, CH_2S), 3.64 (s, 3H, CO_2CH_3), 4.31 (s, 2H, CH_2NH), 4.63 (m, 2H, NH and αCH), 5.11 (s, 2H, CH_2N), 5.70 (d, J = 7.7 Hz, 1H, NHCO), 6.50 (d, J = 2.2 Hz, 1H, aryl H), 6.67 (dd, J = 7.7 and 2.2 Hz, 1H, aryl H), 6.85 (s, 1H, imid-5H), 7.23 (d, J = 8.1 Hz, 2H, aryl H), 7.37−7.47 (m, 8H, aryl H and imi-2H), 7.54−7.59 (m, 4H, aryl H), 7.69 (d, J = 7.7 Hz, 1H, aryl H). HRMS (ES): *m*/*z* calcd for $C_{36}H_{36}N_4O_3SNa^+$ 627.2406, found 627.2403.

4-[*N*-(1-(4-Phenyl)benzyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine (3). To a solution of 4-[*N*-((4-phenylbenzyl-1*H*-imidazol-4-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (207 mg, 0.34 mmol) in THF (6 mL) was added 0.1 N LiOH (6.8 mL), and the mixture was stirred at 0 °C for 1 h and 45 min. The mixture was adjusted to pH ∼4 with 5% HCl and concentrated. The product was extracted with $CHCl_3$ (100 mL), and the organic layer was washed with brine and dried (anhydrous Na_2SO_4). Evaporation of the solvent gave the product as a colorless amorphous solid (185 mg, 92%). ^{1}H NMR (CD_3OD): δ 1.73−1.88 (m, 1H, C*H*HCH$_2$), 1.93−1.95 (m, 1H, C*H*HCH$_2$), 2.00 (s, 3H, SCH_3), 2.02−2.10 (m, 1H, C*H*HS), 2.15−2.22 (m, 1H, C*H*HS), 4.38 (s, 2H, CH_2N), 4.43 (q, J = 4.5 Hz, 1H, αCH), 5.31 (s, 2H, CH_2N), 6.56 (d, J = 2 Hz, 1H, aryl H), 6.67 (dd, J = 8 and 2 Hz, 1H, aryl H), 7.27−7.46 (m, 13 H), 7.59−7.65 (m, 4H, aryl H). HRMS (FAB): *m*/*z* calcd for $C_{35}H_{34}N_4O_3SH^+$ 591.2430, found 591.2437.

4-[*N*-(1-Cyclohexyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine Methyl Ester. This compound was prepared from aldehyde **39b** (134 mg, 0.7 mmol) and **2** (276 mg, 0.7 mmol) by a similar procedure to that described for 4-[*N*-(1-(4-phenyl)benzyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine methyl ester. The crude material was purified by flash column chromatography (100:20:4 $CHCl_3$/acetone/EtOH) to give the product as a colorless oil (283 mg, 76%). ^{1}H NMR ($CDCl_3$): δ 7.66 (d, J = 8.5 Hz, 1H, aryl H), 7.35−7.41 (m, 6H, aryl H and imid-2H), 6.76 (s, 1H, imid-5H), 6.65 (dd, J = 2.2 and 8.6 Hz, 1H, aryl H), 6.49 (d, J = 2.2 Hz, 1H, aryl H), 5.74 (d, J = 7.7 Hz, 1H, amido NH), 4.66 (br s, 1H, NH), 4.60 (q, J = 5.4 Hz, 1H, αCH), 4.26 (d, J = 4.8 Hz, 2H, NHCH_2), 3.68 (d, J = 6.9 Hz, 2H, NCH_2), 3.62 (s, 3H, CO_2CH_3), 2.09 (t, J = 4.8 Hz, 2H, SCH_2), 1.99 (s, 3H, SCH_3), 1.88−1.84 (m, 1H, CH), 1.72−1.58 (m, 7H, cyclohexyl and CH), 1.24−1.22 (m, 3H, cyclohexyl), 0.93−0.89 (m, 2H, cyclohexyl). HRMS (ES): *m*/*z* calcd for $C_{30}H_{38}N_4O_3SNa^+$ 557.2562, found 557.2565.

4-[*N*-(1-Cyclohexyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine (4). This compound was prepared from 4-[*N*-(1-cyclohexyl-1H-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine methyl ester (164 mg, 0.31 mmol) by a similar fashion as that described for **3** to yield a colorless amorphous solid (128 mg, 80%). ^{1}H NMR (CD_3OD): δ 7.82 (s, 1H, imid-2H), 7.42 (d, J = 8.5 Hz, 1H, aryl H), 7.30−7.37 (m, 5H, aryl H), 7.07 (s, 1H, imid-2H), 6.67 (dd, J = 2.0 and 8.5 Hz, 1H, aryl H), 6.57 (d, J = 2.0 Hz, 1H, aryl H), 4.41 (br s, 1H, αCH), 4.32 (s, 2H, CH_2NH), 3.84 (d, J = 7.5 Hz, 2H, NCH_2), 2.17 (m, 1H, SC*H*H), 2.06 (m, 1H, SC*H*H), 2.01 (s, 3H, SCH_3), 1.93 (m, 1H, CH), 1.67−1.77 (m, 3H, cyclohexyl), 0.91−0.98 (m, 2H, cyclohexyl). HRMS (FAB): *m*/*z* calcd for $C_{29}H_{36}N_4O_3SH^+$ 521.2586, found 521.2586.

4-[*N*-(1-Pentyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine Methyl Ester. This compound was prepared from aldehyde **39c** (127 mg, 0.76 mmol) and **2** (302 mg, 0.76 mmol) by a similar procedure to that described for 4-[*N*-(1-(4-phenyl)benzyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine methyl ester, as described above. The crude material was purified by flash column chromatography (100:20:4 $CHCl_3$/acetone/EtOH) to give the product as a colorless oil (332 mg, 86%). ^{1}H NMR ($CDCl_3$): δ 7.69 (d, J = 8.5 Hz, 1H, aryl H), 7.28−7.44 (m, 6H, aryl H and imid-2H), 6.82 (s, 1H, imid-5H), 6.67 (dd, J = 2.0 and 8.5 Hz, 1H, aryl H), 6.51 (d, J = 2.0 Hz, 1H, aryl H), 5.77 (d, J = 8.0 Hz, 1H, amido NH), 4.69 (br s, 1H, NH), 4.63 (m, 1H, αCH), 4.29 (d, J = 5.5 Hz, 2H, CH_2), 3.88 (t, J = 7 Hz, 2H, CH_2), 3.65 (s, 3H, CO_2Me), 2.11 (t, J = 7.0 Hz, 2H, CH_2), 2.02 (s, 3H, SCH_3), 1.89 (m, 1H, SCH_2CH), 1.77 (m, 2H, CH_2), 1.65−1.69 (m, 1H, CH), 1.26−1.37 (m, 4H, $(CH_2)_2$), 0.90 (t, J = 7.5 Hz, 3H, CH_3). HRMS (ES): *m*/*z* calcd for $C_{28}H_{36}N_4O_3SNa^+$ 531.2406, found 531.2404.

4-[*N*-(1-Pentyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine (5). This compound was prepared from 4-[*N*-(1-pentyl-1H-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine methyl ester (320 mg, 0.63 mmol) in a similar fashion to that described for **3** to yield a colorless amorphous solid (235 mg, 75%). ^{1}H NMR (CD_3OD): δ 7.97 (s, 1H, imid-2H), 7.40 (d, J = 8.5 Hz, 1H, aryl H), 7.28−7.34 (m, 5H, aryl H), 7.15 (s, 1H, imid-5H), 6.64 (dd, J = 2.5 and 8.5 Hz, aryl H), 6.56 (d, J = 2.5 Hz, 1H, aryl H), 4.38 (dd, J = 4.5 and 8.5 Hz, 1H, αCH), 4.31 (s, 2H, CH_2), 3.99 (t, J = 7.5 Hz, 2H, CH_2), 2.17 (m, 1H, SC*H*H), 2.08 (m, 1H, SC*H*H), 1.99 (s, 3H, SCH_3), 1.93 (m, 1H, C*H*H), 1.73−1.79 (m, 3H, CH_2 and C*H*H), 1.21−1.35 (m, 4H, $(CH_2)_2$), 0.88 (t, J = 7.0 Hz, 3H, CH_3). HRMS (FAB): *m*/*z* calcd for $C_{27}H_{34}N_4O_3SH^+$ 495.2430, found 495.2430.

4-[*N*-(1-(4-Phenyl)benzyl-1*H*-imidazol-5-yl)methylamino]-2-phenylbenzoylmethionine Methyl Ester (6b). The reductive amination of **40a** (60 mg, 0.23 mmol) and **2** (91 mg, 0.23 mmol) was carried out by a method similar to that described for 4-[*N*-(1-(4-phenyl)benzyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine methyl ester. The crude product was purified by SiO_2 column chromatography (100:20:4 $CHCl_3$/acetone/EtOH) to afford the product as a colorless amorphous solid (127 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 7.65 (d, J = 8.5 Hz, 1H, aryl H), 7.61 (s, imid-2H), 7.49−7.52 (m, 4H, aryl H), 7.42 (t, J = 8.1 Hz, 2H, aryl H), 7.31−7.36 (m, 6H, aryl H), 7.10 (d, J = 8.1 Hz, 2H, aryl H), 7.07 (s, 1H, imid-4H), 6.51 (dd, J = 7.7 and 2.2 Hz, 1H, aryl H), 6.31 (d, J = 2.2 Hz, 1H, aryl H), 5.74 (d, J = 7.7 Hz, 1H, NHCO), 5.19 (s, 2H, CH_2N), 4.60 (q, J = 5.4 Hz, 1H, αCH), 4.17 (d, J = 4.8 Hz, 2H, CH_2NH), 4.01 (m, 1H, NH), 3.63 (s, 3H, CO_2CH_3), 2.08 (t, J = 7.7 Hz, 2H, CH_2S), 2.00 (s, 3H, SCH_3), 1.85−1.89 (m, 1H, C*H*HCH$_2$), 1.63−1.67 (m, 1H, C*H*HCH$_2$). HRMS (FAB): *m*/*z* calcd for $C_{36}H_{36}N_4O_3SH^+$ 605.2586, found 605.2585.

4-[*N*-(1-(1-(4-Phenyl)benzyl-1*H*-imidazol-5-yl)methylamino]-2-phenylbenzoylmethionine (6a). This compound was synthesized in a manner similar to that described for **3**, by the hydrolysis of 4-[*N*-((4-phenylbenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenyl-benzoylmethionine methyl ester (127 mg, 0.21 mmol) with 0.1 N LiOH (4.2 mL) in THF (4 mL) to give the product as a colorless amorphous solid (87 mg, 70%). ^{1}H NMR (CD_3OD): δ 8.33 (s, 1H, imid-2H), 7.51−7.55 (m, 4H), 7.31−7.42 (m, 4H, aryl H), 7.27 (s, 5H, aryl H), 7.22 (d, J = 8 Hz, 2H, aryl H), 7.19 (s, 1H, imi-5H), 6.56 (dd, J = 8 and 2 Hz, 1H, aryl H), 6.37 (d, J = 1.8 Hz, 1H, aryl H), 5.42 (s, 2H, CH_2N), 4.38−4.41 (m, 1H, αCH), 4.28 (s, 2H, CH_2N), 2.12−2.18 (m, 1H, C*H*HS), 201−2.07 (m, 1H, C*H*HS), 1.98 (s, 3H, SCH_3), 1.90−1.94 (m, 1H, C*H*HCH$_2$), 1.70−1.74 (m, 1H, C*H*HCH$_2$). HRMS (FAB): *m*/*z* calcd for $C_{35}H_{34}N_4O_3SH^+$ 591.2430, found 591.2443.

4-[*N*-(1-Cyclohexylmethyl-1*H*-imidazol-5-yl)methylamino]-2-phenylbenzoylmethionine Methyl Ester. This compound was prepared by a similar procedure to that described

for compound 4-[*N*-(1-pentyl-1H-imidazol-5-yl)methylamino]-2-phenylbenzoylmethionine methyl ester to yield a colorless amorphous solid. ^{1}H NMR ($CDCl_3$): δ 7.70 (d, J = 8.5 Hz, 1H, aryl H), 7.39−7.44 (m, 6H, aryl H, imid-2H), 6.99 (s, 1H, imid-4H), 6.67 (dd, J = 2.2, 8.5 Hz, 1H, aryl H), 6.52 (d, J = 2.2 Hz, 1H, aryl H), 5.75 (d, J = 7.4 Hz, amido NH), 4.61 (m, 1H, αCH), 4.29 (d, J = 4.5 Hz, 1H, $NHCH_2$), 4.15 (t, J = 4.5 Hz, 1H, NH), 3.73 (d, J = 7.4 Hz, 2H, NCH_2), 3.64 (s, 3H, CO_2CH_3), 2.16 (t, J = 4.5 Hz, 2H, SCH_2), 2.00 (s, 3H, SCH_3), 1.90−1.86 (m, 1H, CH_2), 1.70−1.55 (m, 7H, cyclohexyl and C*H*H), 1.18−1.12 (m, 3H, cyclohexyl), 0.91−0.87 (m, 2H, cyclohexyl). HRMS (ES): *m*/*z* calcd for $C_{30}H_{38}N_4O_3SNa^+$ 557.2562, found 557.2560.

4-[*N*-(1-Cyclohexylmethyl-1H-imidazol-5-yl)methylamino]-2-phenylbenzoylmethionine (7). This compound was prepared in a manner similar to that described for compound **3** to yield a colorless amorphous solid. ^{1}H NMR (CD_3OD): δ 7.92 (s, 1H, imid-2H), 7.44 (d, J = 8.0 Hz, 1H, aryl H), 7.37−7.32 (m, 5H, aryl H), 7.06 (s, 1H, imid-4H), 6.70 (dd, J = 2.0 and 8.0 Hz, 1H, aryl H), 6.60 (d, J = 2.0 Hz, 1H, aryl H), 4.41 (s, 3H, $NHCH_2$, αCH), 3.91 (d, J = 7.0 Hz, 2H, NCH_2), 2.16 (m, 1H, SC*H*H), 2.06 (m, 1H, SC*H*H), 2.01 (s, 3H, SCH_3), 1.93 (m, 1H, C*H*H), 1.79−1.67 (m, 5H, cyclohexyl and C*H*H), 1.60−1.58 (m, 2H, cyclohexyl), 1.20 (m, 3H, cyclohexyl), 1.01−0.99 (m, 2H, cyclohexyl). HRMS (FAB): *m*/*z* calcd for $C_{29}H_{36}N_4O_3SH^+$ 521.2589, found 521.2591.

4-[*N*-(1-Pentyl-1*H*-imidazol-5-yl)methylamino]-2-phenylbenzoylmethionine Methyl Ester. This compound was prepared from **2** (174 mg, 0.44 mmol) and **40c** (73 mg, 0.44 mmol) by a method similar to that described for 4-[*N*-(1-(4-phenyl)benzyl-1*H*-imidazol-4-yl)methylamino]-2-phenylbenzoylmethionine methyl ester. The crude product was purified by SiO_2 column chromatography (100:20:4 $CHCl_3$/acetone/EtOH) to give the product as colorless oil (179 mg, 80%). ^{1}H NMR ($CDCl_3$): δ 7.68 (d, J = 8.5 Hz, 1H, aryl H), 7.37−7.44 (m, 6H, aryl H and imid-2H), 7.68 (d, J = 8.5 Hz, 1H, aryl H), 6.97 (s, 1H, imid-4H), 6.66 (dd, J = 2.0 and 8.5 Hz, 1H, aryl H), 6.51 (d, J = 2.0 Hz, 1H, aryl H), 5.78 (d, J = 7.5 Hz, 1H, CONH), 4.61 (m, 1H, αCH), 4.28 (s, 3H, NH and $NHCH_2$), 3.89 (t, J = 7.5 Hz, 2H, NCH_2), 3.63 (s, 3H, CO_2CH_3), 2.08 (t, J = 7.5 Hz, 3H, SCH_2), 1.99 (s, 3H, SCH_3), 1.72−1.78 (m, 2H, CH_2CH_2N), 1.88−1.89 (m, 1H, C*H*CH_2S), 1.63−1.69 (m, 1H, C*H*CH_2S), 1.20−1.33 (m, 4H, $(CH_2)_2$), 0.86 (t, J = 3.0 Hz, 3H, CH_3). HRMS (ES): *m*/*z* calcd for $C_{28}H_{36}N_4O_3SNa^+$ 531.2399, found 531.2404

4-[*N*-(1-Pentyl-1*H*-imidazol-5-yl)methylamino]-2-phenylbenzoylmethionine (8). This compound was derived from hydrolysis of 4-[*N*-(1-pentyl-1*H*-imidazol-5-yl)methylamino]-2-phenylbenzoylmethionine methyl ester (179 mg, 0.63 mmol) in a manner similar to that described for **2** to give the product as an amorphous solid (142 mg, 82%). ^{1}H NMR (CD_3OD): δ 8.13 (s, 1H, imid-2H), 7.45 (d, J = 8.5 Hz, 1H, aryl H), 7.39−7.23 (m, 5H, aryl H), 7.14 (s, 1H, imid-4H), 6.72 (dd, J = 2.0 and 8.5 Hz, 1H, aryl H), 6.64 (d, J = 2.0 Hz, 1H, aryl H), 4.44 (s, 2H, $NHCH_2$), 4.40 (dd, J = 4.5 and 8.5 Hz, 1H, αCH), 4.12 (t, J = 7.5 Hz, 2H, NCH_2), 2.20 (m, 1H, SCH), 2.07 (m, 1H, SCH), 2.02 (s, 3H, SCH_3), 1.95 (m, 1H, SCH_2CH), 1.83 (m, 2H, NCH_2CH_2), 1.78 (m, 1H, SCH_2CH), 1.36−1.30 (m, 4H, $(CH_2)_2$), 0.90 (t, J = 6.5 Hz, 3H, CH_3). HRMS (FAB): *m*/*z* calcd for $C_{27}H_{35}N_4O_3SH^+$ 495.2429, found 495.2430.

4-[*N*-((1-*p*-Cyanobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (9a). This compound was prepared from **7b** (58 mg, 0.1 mmol) by hydrolysis by a method similar to that described for **2** to give the product as a colorless amorphous solid (29 mg, 54%). ^{1}H NMR ($CDCl_3$): δ 7.58 (d, J = 8.5 Hz, 2H, aryl H), 7.56 (d, J = 8.5 Hz, aryl H), 7.39−7.44 (m, 3H, aryl H), 7.34−7.32 (m, 2H, aryl H), 7.13 (d, J = 8.5 Hz, 2H, aryl H), 7.08 (br s, 1H, imid-5H), 6.55 (dd, J = 2.5 and 8.5 Hz, 1H, aryl H), 6.33 (d, J = 2.5 Hz, 1H, aryl H), 5.30 (s, 2H, NCH_2), 4.15 (s, 2H, CH_2NH), 2.14 (m, 1H, C*H*HS), 2.03 (m, 1H, C*H*HS), 2.03 (s, 2H, SCH_3), 1.88−1.90 (m, 1H, C*H*HCH_2), 1.62−1.67 (m, 1H, C*H*HCH_2). HRMS (FAB): *m*/*z* calcd for $C_{30}H_{30}N_5O_3SH^+$ 540.2069, found 540.2068.

4-[*N*-((1-*p*-Cyanobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine Methyl Ester (9b). To a solution of **14** (122 mg, 0.24 mmol), H-Met-OCH_3·HCl (48 mg, 0.24 mmol), triethylamine (24 mg, 0.24 mmol), and HOBt (65 mg, 0.48 mmol) in CH_2Cl_2 (2 mL) was added EDCI (46 mg, 0.24 mmol) at 0 °C and the mixture was stirred at rt overnight. Additional CH_2Cl_2 (50 mL) and sat. $NaHCO_3$ were added to the mixture, and the organic layer was washed with brine and dried ($MgSO_4$). Purification of the crude compound by SiO_2 chromatography with 100:40:8 $CHCl_3$/acetone/EtOH gave the product (100 mg, 75%). ^{1}H NMR ($CDCl_3$): δ 7.62 (d, J = 14 Hz, 1H, aryl H), 7.54−7.57 (m, 3H, aryl H and imid-2H), 7.39−7.45 (m, 3H, aryl H), 7.32−7.35 (m, 2H, aryl H), 7.07−7.10 (m, 3H, aryl H and imid-5H), 6.51 (dd, J = 3.5 and 14 Hz, 1H, aryl H), 6.33 (d, J = 3.5 Hz, 1H, aryl H), 5.79 (d, J = 13 Hz, 1H, NHCO), 5.24 (s, 2H, CH_2N), 4.62 (m, 1H, αCH), 4.22 (br s, 1H, NH), 4.14 (s, 2H, CH_2NH), 3.64 (s, 3H, CO_2CH_3), 2.09 (t, J = 13.5 Hz, 2H, CH_2S), 2.00 (s, 3H, SCH_3), 1.63−1.70 (m, 1H, C*H*HCH_2), 1.85−1.92 (m, 1H, C*H*HCH_2). HRMS (FAB): *m*/*z* calcd for $C_{31}H_{31}N_5O_3SH^+$ 554.2226, found 554.2222.

4-[*N*-((1-*m*-Cyanobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (9c) was a white oily solid (68%). ^{1}H NMR (CD_3OD): δ 8.51 (s, 1 H), 7.58−7.62 (m, 2 H), 7.40−7.52 (m, 4 H), 7.25−7.39 (m, 10 H), 6.50 (d, 1 H, J = 8 Hz), 6.38 (s, 1 H), 5.50 (s, 2 H), 4.42 (m, 1 H), 4.31 (s, 2 H), 2.18 (m, 1 H), 2.07 (m, 1 H), 1.99 (s, 3 H), 1.93 (m, 1 H), 1.74 (m, 1 H).^{13}C NMR (CD_3OD): δ 174.480, 173.303, 150.832, 143.568, 142.823, 138.758, 133.569, 133.426, 132.425, 131.618, 131.488, 130.158, 129.897, 129.702, 129.056, 128.979, 125.964, 119.768, 115.507, 114.417, 112.227, 53.842, 44.655, 38.346, 32.448, 31.376, 15.547. HRMS (FAB, M + H): calcd for $C_{30}H_{30}N_5O_3S$ 540.2069, found 540.2069.

4-[*N*-((1-*m*-Cyanobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (9d) was a white oily solid (12%). ^{1}H NMR ($CDCl_3$): δ 7.58 (d, 2 H, J = 9 Hz, Ar), 7.55 (s, 1 H, imid), 7.34−7.44 (m, 5 H, Ar), 7.25−7.29 (m, 3 H, Ar), 7.08 (s, 1 H, imid), 6.52 (dd, 1 H, J = 9 and 2 Hz, Ar), 6.36 (d, 1 H, J = 2 Hz, Ar), 5.98 (d, 1 H, J = 7 Hz, amide NH), 5.24 (s, 2H, CH_2Ar), 4.57 (m, 2 H, α-C and amine NH), 4.15 (d, 2 H, J = 3 Hz, CH_2N), 2.09 (t, 2 H, J = 8 Hz, CH_2S), 2.00 (s, 3 H, SCH_3), 1.83−1.91 (m, 1 H, CH_2), 1.64−1.72 (m, 1 H, CH_2). ^{13}C NMR ($CDCl_3$): δ 172.053, 168.675, 148.653, 147.055, 141.753, 140.797, 137.788, 131.821, 131.101, 130.943, 130.163, 129.904, 129.616, 128.800, 128.676, 128.662, 127.989, 127.926, 127.862, 124.296, 118.125, 113.976, 113.196, 111.678, 53.872, 52.589, 52.333, 51.860, 51.733, 49.403, 48.127, 38.447, 37.689, 31.751, 31.540, 29.549, 29.291, 15.280. HRMS (FAB, M + H): calcd for $C_{31}H_{32}N_5O_3S$ 554.2226, found 554.2227.

4-[*N*-((1-*o*-Cyanobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (9e) was an off-white amorphous solid (59%). ^{1}H NMR (CD_3OD): δ 7.71 (d, 1 H, J = 7 Hz),), 7.54 (t, 1 H, J = 7 Hz), 7.44 (t, 2 H, J = 6 Hz), 7.30−7.38 (m, 8 H), 7.09 (bs, 1 H), 6.53 (d, 1 H, J = 7 Hz), 6.39 (s, 1 Hz), 5.63 (s, 2 H), 4.42 (m, 1 H), 4.30 (s, 2 H), 2.15 (m, 1 H), 2.06 (m, 1 H), 1.99 (s, 3 H), 1.92 (m, 1 H), 1.74 (m, 1 H). ^{13}C NMR (CD_3OD) δ 173.89, 193.85, 150.40, 143.01, 142.37, 139.64, 137.50, 134.80, 134.51, 130.90, 130.29, 129.75, 129.65, 129.38, 129.38, 128.42, 125.43, 117.70, 115.08, 112.33, 111.94, 110.35, 74.06, 53.26, 44.10, 38.08, 31.92, 30.87, 25.71, 21.31. 15.0. HRMS (FAB, M + H): calcd for $C_{30}H_{30}N_5O_3S$ 540.2069, found 540.2068.

4-[*N*-((1-*o*-Cyanobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (9f) was an off-white amorphous solid (23%). ^{1}H NMR ($CDCl_3$): δ 7.68 (dd, 1 H, J = 8 and 1 Hz), 7.64 (d, 1 H, J = 8 Hz), 7.36−7.57 (m, 10 H), 7.14 (s, 1 H), 6.94 (d, 1 H, J = 8 Hz), 6.51 (dd, 1 H, J = 8 and 2 Hz), 6.40 (d, 1 H, J = 2 Hz), 5.71 (d, 1 H, J = 8 Hz), 5.39 (s, 2 H), 4.61 (m, 1 H), 4.26 (d, 2 H, J = 5 Hz), 3.98 (t, 1 H, J = 5 Hz), 2.09 (t, 2 H, J = 8 Hz), 2.01 (s, 3 H), 1.87 (m, 1 H), 1.64 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 172.311, 169.489, 149.137, 141.918, 141.022, 139.505, 139.046, 133.851, 133.461, 131.080, 129.074, 128.974, 128.797, 128.040, 127.866, 123.641, 116.933, 114.178, 111.813, 111.201, 52.481, 52.076, 51.979, 49.688, 49.518, 49.346, 49.176, 49.006, 48.834, 48.664, 47.197, 37.699, 31.509, 29.624, 15.257. HRMS (FAB, M + H): calcd for $C_{31}H_{32}N_5O_3S$ 544.2259, found 554.2227.

4-[*N*-((1-*p*-Nitrobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (10a) was a yellow solid (75%). ^{1}H NMR (CD_3OD): δ 8.11 (d, 2 H, J = 9 Hz), 7.24−7.36 (m, 9 H), 7.15 (s, 1 H), 6.54 (dd, 1 H, J = 9 and 2 Hz), 6.31 (d, 1 H, J = 2 Hz), 5.49 (s, 2 H), 4.40 (m, 1 H), 4.27 (s, 2 H), 3.72 (m, 1 H), 2.15 (m, 1 H), 2.05 (m, 1 H), 2.00 (s, 3 H), 1.95 (m, 1 H), 1.75 (m, 1 H). ^{13}C NMR (CD_3OD): δ 173.40, 167.27, 151.03, 149.36, 147.49, 145.40, 143.49, 142.87, 131.38, 130.04, 129.85, 129.27, 128.93, 125.61, 125.39, 115.39, 112.09, 69.29, 53.83, 44.60, 38.38, 32.42, 31.37, 26.93, 15.50. HRMS (FAB, M + H): calcd for $C_{29}H_{30}N_5O_5S$ 560.1961, found 560.1960.

4-[*N*-((1-*p*-Nitrobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (10b) was a yellow amorphous solid (67%). ^{1}H NMR ($CDCl_3$): δ 8.04 (d, 2 H, ortho to NO_2), 7.54 (s, 1 H, ortho to CONH), 7.52 (s, 1 H, NC*H*N), 7.27−7.38 (m, 5 H, biphenyl aryl), 7.11 (d, 2 H, meta to NO_2), 7.04 (s, 1 H, NC*H*CCH_2), 6.48 (dd, 1 H, para to biphenyl), 6.29 (d, 1 H, ortho to biphenyl), 5.96 (d, 1 H, CON*H*), 5.30 (s, 2 H, NCH_2Ar), 4.78 (t, 1 H, CH_2N*H*Ar), 4.56 (m, 1 H, met α-C*H*), 4.14 (d, 2 H, CH_2NHAr), 3.63 (s, 3 H, COOCH_3), 2.08 (t, 2 H, CH_2SCH$_3$), 1.99 (s, 3 H, SCH_3), 1.82−1.91 (m, 1 H, met CH_2), 1.62−1.71 (m, 1 H, met CH_2). ^{13}C NMR ($CDCl_3$): δ 172.08, 168.74, 148.93, 147.46, 143.67, 141.65, 140.75, 138.94, 130.99, 129.53, 128.66, 128.53, 128.30, 127.93, 127.32, 124.08, 123.52, 113.91, 111.47, 99.66, 55.86, 52.38, 51.82, 48.06, 37.52, 31.35, 29.52, 25.04, 15.54, 15.24. LRMS (M^+): 574.2. HRMS (FAB): calcd for $C_{30}H_{32}N_5O_5S$ 574.2124, found 574.2125.

4-[*N*-((1-*m*-Nitrobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (10d) was a yellow amorphous solid (66%). ^{1} H NMR ($CDCl_3$): δ 8.10 (d, 1 H, J = 9.5 Hz, Ar), 7.87 (s, 1 H, Ar), 7.62 (s, 1 H, imid), 7.55 (d, 1 H, J = 8 Hz, Ar), 7.47 (t, 1 H, J = 8 Hz, Ar), 7.31−7.43 (m, 6 H, Ar), 7.08 (s, 1 H, imid), 6.49 (dd, 1 H, J = 2 and 9.5 Hz, Ar), 6.35 (d, 1 H, J = 2 Hz, Ar), 5.92 (d, 1H, J = 8 Hz, amide NH), 5.31 (s, 2 H, CH_2Ar), 4.58 (m, 1 H, α-C), 4.17 (d, 2 H, J = 5 Hz, CH_2N), 3.67 (s, 3 H, COOCH_3), 2.10 (t, 2 H, J = 7 Hz, CH_2S), 2.01 (s, 3 H, SCH_3), 1.86−1.90 (m, 1H, CH_2), 1.65−1.72 (m, 1 H, CH_2). ^{13}C NMR ($CDCl_3$): δ 172.037, 168.603, 148.692, 148.522, 141.717, 140.794, 138.952, 138.352, 132,550, 131,054, 130.110, 130.028, 129.703, 128.668, 128.629, 128.223, 127.920, 127.837, 124.068, 123.318, 123.162, 122.272, 121.661, 113.929, 111.657, 53.888, 52.340, 51.855, 48.115, 37.654, 31.919, 31.758, 31.576, 29.646, 29.544, 29.349, 29.293, 22.683, 15.281, 14.117. HRMS (FAB, M + H): calcd for $C_{30}H_{32}N_5O_5S$ 574.2124, found 574.2125.

4-[*N*-((1-*p*-Chlorobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (11a) was a white amorphous solid (63%). ^{1}H NMR ($CDCl_3$/CD_3OD): δ 7.27−7.37 (m, 9 H, Ar), 7.17 (s, 1 H, imid), 7.12 (d, 2 H, J = 7 Hz, Ar), 6.53 (dd, 1 H, J = 2 and 9 Hz, Ar), 6.39 (d, 1 H, J = 2 Hz, Ar), 5.35 (s, 2 H, CH_2Ar), 4.38 (m, 1 H, α-C), 4.24 (s, 2 H, CH_2N), 2.14−2.20 (m, 1 H, CH_2S), 2.03−2.08 (m, 1 H, CH_2S), 1.98 (s, 3 H, SCH_3), 1.89−1.97 (m, 1 H, CH_2), 1.72−1.79 (m, 1 H, CH_2). ^{13}C NMR (CD_3OD): δ 174.660, 173.495, 149.320, 141.890, 141.241, 137.685, 134.199, 134.073, 131.013, 129.802, 129.017, 128.830, 128.490, 128.249, 127.302, 124.927, 124.208, 123.577, 113.878, 110.744, 78.059, 73.030, 53.608, 52.619, 43.302, 36.890, 34.169, 31.011, 29.728, 29.685, 13.924. HRMS (FAB, M + H): calcd for $C_{29}H_{30}N_4O_3SCl$ 549.1727, found 549.1725.

4-[*N*-((1-*p*-Chlorobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (11b) was a white amorphous solid (38%). ^{1}H NMR ($CDCl_3$): δ 7.62 (d, 1 H, 8 Hz, ortho to CONH), 7.51 (s, 1 H, NC*H*N), 7.33−7.43 (m, 5 H, biphenyl aryl), 7.08 (d, 2 H, 8 Hz, meta to CH_3), 6.91 (d, 2 H, 8 Hz, ortho to CH_3), 6.48 (dd, 1 H, 8 and 2 Hz, para to biphenyl), 6.30 (d, 1 H, 2 Hz, ortho to biphenyl), 5.84 (d, 1 H, 8 Hz, CON*H*), 5.08 (s, 2 H, NCH_2Ar), 4.59 (ddd, 1 H, met α-CH), 4.23, (t, 1 H, 5 Hz, CH_2N*H*Ar), 4.12 (d, 2 H, 5 Hz, CH_2-NHAr), 3.63 (s, 3 H, COOCH_3), 2.08 (t, 2 H, 7 Hz, CH_2SCH$_3$), 2.00 (s, 3 H, SCH_3), 1.84−1.91 (m, 1 H, met CH), 1.63−1.70 (m, 1 H, met CH). ^{13}C NMR ($CDCl_3$): 172.05, 168.52, 148.93, 141.58, 141.00, 138.01, 132.98, 131.12, 129.71, 129.44, 128.68, 127.81, 126.69, 123.50, 114.10, 111.59, 99.62, 55.82, 53.96, 52.30, 51.79, 48.73, 37.67, 31.77, 29.48, 25.02, 21.02, 15.52, 15.25. HRMS (FAB): calcd for $C_{30}H_{32}N_4O_3S$ 563.1884, found 563.1884.

4-[*N*-((1-*m*-Chlorobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (11c) was a yellow oily solid (95%). ^{1}H NMR (CD_3OD): δ 8.71 (s, 1 H), 7.13−7.40 (m, 16 H), 6.55 (d, 1 H, J = 8 Hz), 6.45 (s, 1 H), 5.47 (s, 2 H), 4.42 (m, 1 H), 4.33 (s, 2 H), 2.18 (m, 1 H), 2.06 (m, 1 H), 2.00 (s, 3 H), 1.93 (m, 1 H), 1.75 (m, 1 H). ^{13}C NMR (CD_3OD): δ 174.252, 173.302, 150.794, 143.644, 142.832, 138.561, 136.542, 132.243, 131.519, 130.295, 130.160, 129.922, 129.875, 129.624, 129.118, 128.969, 127.389, 127.260, 126.099, 115.712, 112.341, 74.603, 53.712, 51.246, 44.510, 38.510, 32.390, 31.390, 15.529. HRMS (FAB, M + H): calcd for $C_{29}H_{30}N_4O_3SCl$ 549.1727, found 549.1725.

4-[*N*-((1-*m*-Chlorobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (11d) was a yellow oily solid (24%). ^{1}H NMR ($CDCl_3$): δ 7.62 (d, 1 H, J = 9 Hz, Ar), 7.54 (s, 1 H, imid), 7.34−7.44 (m, 5 H, Ar), 7.20−7.26 (m, 2 H, Ar), 7.03 (d, 2 H, J = 12 Hz, Ar), 6.89 (d, 1 H, J = 8 Hz, Ar), 6.52 (dd, 1 H, J = 2 and 9 Hz, Ar), 6.37 (d, 1 H, J = 2 Hz, Ar), 5.82 (d, 1 H, J = 8 Hz, amide NH), 5.14 (s, 2 H, CH_2Ar), 4.59 (m, 1 H, α-C), 4.30 (t, 1 H, J = 6 Hz, amine NH), 4.15 (d, 2 H, J = 6 Hz, CH_2N), 2.08 (t, 2 H, J = 8 Hz, CH_2S), 2.00 (s, 3 H, SCH_3), 1.84−1.92 (m, 1 H, CH_2), 1.61−1.69 (m, 1 H, CH_2). ^{13}C NMR ($CDCl_3$): δ 172.044, 168.511, 148.920, 148.837, 141.718, 140.915, 138.910, 138.107, 135.077, 131.192, 130.365, 129.432, 128.692, 128.652, 128.546, 128.448, 128.165, 127.886, 127.523, 126.799, 124.794, 123.826, 114.056, 113.519, 111.728, 53.920, 52.581, 52.319, 51.830, 49.858, 49.601, 48.298, 38.503, 38.416, 37.698, 31.757, 31.592, 29.527, 29.290, 15.277. HRMS (FAB, M + H): calcd for $C_{30}H_{32}N_4O_3SCl$ 563.1884, found 563.1884.

4-[*N*-((1-*o*-Chlorobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (11e) was a white solid (90%). ^{1}H NMR (CD_3OD): δ 7.20−7.44 (m, 11 H), 7.02 (d, 1 H, J = 6 Hz), 6.57 (d, 1 H, J = 7 Hz), 6.44 (s, 1 H), 5.51 (s, 2H), 4.40 (m, 1 H), 4.33 (s, 2 H), 3.34 (s, 1 H), 2.17 (m, 1 H), 2.05 (m, 1 H), 1.99 (s, 3 H), 1.92 (m, 1 H), 1.76 (m, 1 H). ^{13}C NMR (CD_3OD): δ 174.781, 173.192, 151.059, 150.973, 143.659, 143.582, 142.895, 134.832, 133.973, 131.917, 131.584, 131.497, 131.094, 130.183, 129.901, 129.863, 129.365, 128.981, 125.993, 125.749, 115.641, 112.544, 75.122, 74.652, 54.075, 53.606, 53.274, 52.568, 44.833, 44.576, 38.640, 32.619, 32.020, 31.417, 31.358, 15.600. HRMS (FAB, M + H): calcd for $C_{29}H_{30}N_4O_3$-SCl, 549.1723, found 549.1725.

4-[*N*-((1-*o*-Chlorobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (11f) was a yellow oil (25%). ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 1 H, J = 9 Hz, Ar), 7.52 (s, 1 H, imid), 7.34−7.44 (m, 6 H, Ar), 7.24 (t, 1 H, J = 8 Hz, Ar), 7.15 (t, 1 H, J = 8 Hz), 7.07 (s, 1 H, imid), 6.70 (d, 1 H, J = 9 Hz, Ar), 6.52 (dd, 1 H, J = 3 and 9 Hz, Ar), 6.37 (d, 1 H, J = 3 Hz, Ar), 5.75 (d, 1 H, J = 8 Hz, amide NH), 5.24 (s, 2 H, CH_2Ar), 4.60 (m, 1 H, α-C), 4.21 (d, 2 H, J = 5 Hz, CH_2N), 4.14 (t, 1 H, J = 5 Hz, amine NH), 3.64 (s, 3 H, COOCH_3), 2.08 (t, 2 H, J = 8 Hz, CH_2S), 2.00 (s, 3 H, SCH_3), 1.84−1.91 (m, 1 H, CH_2), 1.62−1.69 (m, 1 H, CH_2). ^{13}C NMR ($CDCl_3$): δ 172.059, 168.360, 148.746, 141.695, 140.980, 139.240, 133.766, 132.715, 131.274, 129.914, 129.590, 129.526, 128.738, 128.682, 127.945, 127.921, 127.532, 123.958, 114.109, 111.862, 52.323, 51.847, 46.497, 37.867, 31.714, 29.547, 15.309. HRMS (FAB, M + H): calcd for $C_{30}H_{32}N_4O_3SCl$ 563.1884, found 563.1884.

4-[*N*-((1-*p*-Tolylmethyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (12a) was a white amorphous solid (75%). ^{1}H NMR ($CDCl_3$/CD_3OD): δ 7.28−7.39 (m, 8 H, Ar), 7.09−7.14 (m, 4 H, Ar), 6.54 (dd, 1 H, J = 2 and 9 Hz, Ar), 6.36 (d, 1 H, J = 2 Hz, Ar), 5.38 (s, 2 H, CH_2Ar), 4.39 (m, 1 H, α-C), 4.29 (s, 2 H, CH_2N), 2.27 (s, 3 H, $ArCH_3$), 2.13−2.21 (m, 1 H, CH_2S), 2.03−2.08 (m, 1 H, CH_2S), 1.99 (s, 3 H, SCH_3), 1.91−1.97 (m, 1 H, CH_2), 1.73−1.78 (m, 1 H, CH_2). ^{13}C NMR (CD_3OD): δ 175.08, 172.98, 150.86, 143.60, 142.86, 140.41, 138.61, 133.54, 133.18, 131.54, 131.39, 130.17, 129.98, 129.08, 126.60, 126.09, 126.04, 123.13, 115.76, 112.73, 74.70,

54.47, 54.38, 51.57, 45.08, 38.69, 35.82, 32.87, 31.43, 21.68, 15.67. HRMS (FAB, M + H): calcd for $C_{30}H_{33}N_4O_3S$ 529.2273, found 529.2274.

4-[*N*-((1-*p*-Tolylmethyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (12b) was a clear oil (52%). ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 1 H, 8 Hz, ortho to CONH), 7.52 (s, 1 H, NC*H*N), 7.33−7.44 (m, 5 H, biphenyl aryl), 7.25 (d, 2 H, 9 Hz, ortho to Cl), 7.03 (s, 1 H, NC*H*CCH$_2$), 6.95 (d, 2 H, 9 Hz, meta to Cl), 6.52 (dd, 1 H, 3 and 8 Hz, para to biphenyl), 6.35 (d, 1 H, 3 Hz, ortho to biphenyl), 5.82 (d, 1 H, 7 Hz, CON*H*), 5.12 (s, 2 H, NCH_2Ar), 4.60 (ddd, 1 H, met α-CH), 4.26 (t, 1 H, 5.5 Hz, CH$_2$N*H*), 4.12 (d, 1 H, 5.5 Hz, CH_2-NH), 3.64 (s, 3 H, COOCH_3), 2.08 (t, 2 H, 7 Hz, CH_2SCH$_3$), 2.00 (s, 3 H, CH$_2$SCH_3), 1.83−1.92 (m, 1 H, met CH), 1.61−1.70 (m, 1 H, met CH). ^{13}C NMR ($CDCl_3$): δ 172.09, 168.36, 148.69, 141.73, 140.82, 139.09, 134.51, 134.20, 131.31, 129.90, 129.29, 128.73, 128.68, 127.98, 124.00, 114.11, 111.75, 55.85, 52.38, 51.80, 48.31, 37.78, 31.62, 29.48, 25.05, 15.54, 15.30 (expect 18 aryl C, observed 15). HRMS (FAB): calcd for $C_{31}H_{35}N_4O_3S$ 543.2430, found 543.2428.

4-[*N*-((1-*m*-Tolylmethyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (12c) was a white oily solid (77%). ^{1}H NMR (CD_3OD): δ 8.50 (s, 1 H), 7.25−7.38 (m, 8 H), 7.19 (t, 1 H, J = 7 Hz), 7.11 (d, 1 H, J = 7 Hz), 6.95−7.01 (m, 2 H), 6.50 (dd, 1 H, J = 3 and 8 Hz), 6.42 (d, 1 H, J = 3 Hz), 5.35 (s, 2 H), 4.40 (m, 1 H), 4.26 (s, 2 H), 2.22 (s, 3 H), 2.17 (m, 1 H), 2.06 (m, 1 H), 1.97 (s, 3 H), 1.91 (m, 1 H), 1.75 (m, 1 H). ^{13}C NMR (CD_3OD): δ 175.017, 173.093, 150.916, 143.596, 142.883, 140.787, 138.746, 136.321, 133.365, 131.534, 130.888, 130.654, 130.177, 129.982, 129.916, 129.732, 129.573, 128.990, 126.115, 126.029, 123.321, 115.763, 112.462, 74.736, 54.300, 53.490, 53.283, 51.592, 51.435, 45.012, 38.584, 32.734, 31.452, 31.377, 21.905, 15.635. HRMS (FAB, M + H): calcd for $C_{30}H_{33}N_4O_3S$ 529.2273, found 529.2274.

4-[*N*-((1-*m*-Tolylmethyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (12d) was a yellow amorphous solid (24%). ^{1}H NMR ($CDCl_3$): δ 7.63 (d, 1 H, J = 9 Hz, Ar), 7.56 (s, 1 H, imid), 7.34−7.45 (m, 5 H, biphenyl), 7.19 (t, 1 H, J = 8 Hz, Ar), 7.09 (d, 1 H, J = 8 Hz, Ar), 7.03 (s, 1 H, imid), 6.83 (d, 2 H, J = 6 Hz, Ar), 6.48 (dd, 1 H, J = 9 and 2 Hz, Ar), 6.35 (d, 1 H, J = 2 Hz, Ar), 5.80 (d, 1 H, J = 7 Hz, amide NH), 5.11 (s, 2 H, CH$_2$Ar), 4.61 (m, 1 H, α-C), 4.15 (s, 2 H, CH$_2$N), 3.61 (s, 3 H, COOCH$_3$), 2.08 (t, 2 H, J = 7 Hz, CH$_2$S), 2.00 (s, 3 H, SCH$_3$), 1.83−1.91 (m, 1 H, CH$_2$), 1.62−1.69 (m, 1 H, CH$_2$). ^{13}C NMR ($CDCl_3$): δ 172.051, 168.446, 148.876, 141.671, 140.987, 139.004, 135.931, 131.208, 130.986, 129.414, 129.031, 129.005, 128.851, 128.709, 128.652, 128.301, 127.883, 127.404, 124.593, 123.773, 123.691, 123.521, 114.093, 111.750, 52.614, 52.305, 51.831, 51.691, 51.372, 48.973, 38.538, 38.452, 37.738, 31.646, 29.531, 29.295, 25.510, 21.313, 15.284. HRMS (FAB, M + H): calcd for $C_{31}H_{35}N_4O_3S$ 543.2430, found 543.2428.

4-[*N*-((1-*o*-Tolylmethyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine (12e) was an off-white foam (71%). ^{1}H NMR (CD_3OD): δ 7.20−7.39 (m, 11 H), 7.12 (t, 1 H, J = 8 Hz), 6.87 (d, 1 H, J = 8 Hz), 6.88 (d, 1 H, J = 10 Hz), 6.44 (s, 1 H), 5.45 (s, 2 H), 4.41 (m, 1 H), 4.33 (s, 2 H), 2.24 (s, 2 H), 2.13 (m, 2 H), 2.06 (m, 1 H), 1.99 (s, 3 H), 1.74 (m, 1 H). ^{13}C NMR (CD_3OD): δ 174.779, 173.465, 151.024, 150.944, 143.705, 143.631, 142.870, 138.020, 134.005, 132.486, 131.516, 130.386, 130.181, 129.954, 129.895, 129.858, 129.077, 128.991, 128.285, 126.072, 125.833, 115.640, 112.563, 75.111, 53.605, 53.490, 53.253, 52.557, 44.835, 44.578, 38.677, 32.588, 32.010, 31.422, 31.348, 19.516, 15.585. HRMS (FAB, M + H): calcd for $C_{30}H_{33}N_4O_3S$ 529.2273, found 529.2274.

4-[*N*-((1-*o*-Tolylmethyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoylmethionine methyl ester (12f) was a yellow amorphous solid (33%). ^{1}H NMR ($CDCl_3$): δ 7.66 (d, 1 H, J = 8 Hz), 7.48 (s, 1 H), 7.35−7.43 (m, 5 H), 7.13−7.22 (m, 4 H), 7.10 (s, 1 H), 6.60 (d, 1 H, J = 7 Hz), 6.48 (dd, 1 H, J = 3 and 8 Hz), 6.35 (d, 1 H, J = 3 Hz), 5.70 (d, 1 H, J = 7 Hz), 5.13 (s, 2 H), 4.63 (m, 1 H), 4.18 (d, 2 H, J = 5 Hz), 3.83 (t, 1 H, J = 5 Hz), 3.65 (s, 3 H), 2.09 (t, 2 H, J = 8 Hz), 2.01 (s, 3 H), 1.87 (m, 1 H). ^{13}C NMR ($CDCl_3$): 172.07, 168.38, 148.86, 141.70, 140.95, 139.15, 135.51, 133.93, 131.28, 130.79, 129.47, 128.72, 128.68, 128.32, 128.18, 127.92, 126.74, 126.60, 123.84, 114.10, 111.80, 52.33, 51.84, 46.99, 37.90, 31.68, 29.53, 18.99, 15.30. HRMS (FAB, M + H): calcd for $C_{31}H_{35}N_4O_3S$ 543.2430, found 543.2428.

4-Amino-2-phenylbenzoic Acid *tert*-Butyl Ester (13). To compound **2** (2 g, 8.2 mmol) was added $SOCl_2$ (20 mL) dropwise at rt, and the mixture was stirred overnight at rt. After removal of the $SOCl_2$ under reduced pressure, the residue was dissolved in CH_2Cl_2 (20 mL), and ^{t}BuOK (1.38 g, 12.3 mmol) was added slowly into the mixture. After stirring for 2 h at rt, the reaction was quenched with sat. $NaHCO_3$ (30 mL) and was extracted with Et_2O (100 mL). The crude material was purified by SiO_2 column chromatography (10:1 hexane/AcOEt) to afford 4-nitro-2-phenylbenzoic acid *tert*-butyl ester as a yellow crystalline solid (1.84 g, 72%). Mp: 81−82 °C. ^{1}H NMR ($CDCl_3$): δ 8.24 (d, J = 8.0 Hz, 1H, aryl H), 8.22 (s, 1H, aryl H), 7.90 (d, J = 8.0 Hz, 1H, aryl H), 7.34−7.46 (m, 5H, aryl H), 1.27 (s, 9H, ^{t}Bu). ^{13}C NMR ($CDCl_3$): δ 166.43, 148.65, 143.29, 139.44, 138.74, 130.52, 128.46, 128.43, 128.17, 125.29, 121.90, 82.80, 27.51.

A solution of 4-nitro-2-phenylbenzoic acid *tert*-butyl ester (100 mg, 0.32 mmol) and 10% Pd−C (14 mg) in THF (5 mL) was stirred under atmospheric hydrogen for 2 days. The catalyst was filtered off, and the solvent was evaporated to give the desired product as a yellow solid (97 mg, 100%). Mp: 86−87 °C. ^{1}H NMR ($CDCl_3$): δ 7.72 (d, J = 8.5 Hz, 1H, aryl H), 7.25−7.35 (m, 5H, aryl H), 6.30 (dd, J = 2.0 and 8.5 Hz, 1H, aryl H), 6.51 (d, J = 2.0 Hz, 1H, aryl H), 3.95 (br s, 2H, NH$_2$), 1.20 (s, 9H, ^{t}Bu). ^{13}C NMR ($CDCl_3$): δ 166.60, 147.96, 143.70, 141.75, 131.37, 127.37, 126.67, 125.66, 120.86, 115.49, 111.84, 79.14, 26.60.

5-{[3-(4-Cyanobenzyl)-3*H*-imidazol-4-ylmethyl]amino}-biphenyl-2-carboxylic Acid (14). To a solution of **13** (1.27 g, 4.73 mmol) and **42** (1.0 g, 4.73 mmol) in CH_2Cl_2 (40 mL) was added $TiCl_4$ (0.26 mL, 2.37 mmol) dropwise at rt, and the mixture was stirred for 30 min. To the solution was added $NaBCNH_3$ (297 mg, 4.73 mmol) in MeOH (6 mL) dropwise, and the mixture was stirred overnight. The solvent was removed by evaporation, and the material was extracted with CH_2Cl_2 (200 mL) and sat. $NaHCO_3$ (50 mL). The crude product was purified by SiO_2 column chromatography (100:40:8 $CHCl_3$/acetone/EtOH) to afford 4-[*N*-((1-*p*-cyanobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenyl-benzoic acid *tert*-butyl ester as a colorless amorphous solid (1.61 g, 73%). ^{1}H NMR ($CDCl_3$): δ 7.74 (d, J = 8.5 Hz, 1H, aryl H), 7.61 (s, 1H, imid-2H), 7.58 (d, J = 7.5 Hz, 2H, aryl H), 7.34−7.40 (m, 3H, aryl H), 7.23−7.25 (m, 2H, aryl H), 7.13 (s, 1H, imid-4H), 7.08 (d, J = 7.5 Hz, 2H, aryl H), 6.50 (d, J = 1.5 and 8.5 Hz, 1H, aryl H), 6.32 (d, J = 1.5 Hz, 1H, aryl H), 5.24 (s, 2H, CH$_2$), 4.14 (d, J = 4.5 Hz, 1H, CH$_2$), 3.90 (t, J − 4.5 Hz, 1H, NH), 1.21 (s, 9H, ^{t}Bu). Anal. Calcd for $C_{29}H_{28}N_4O_2 \cdot 0.5H_2O$: C, 73.55; H, 6.17; N, 11.83. Found: C, 73.93; H, 6.21; N, 11.45.

A solution of 4-[*N*-((1-*p*-cyanobenzyl-1*H*-imidazol-5-yl)methyl)amino]-2-phenylbenzoic acid *tert*-butyl ester (1.18 g, 2.54 mmol) and TFA (5 mL) in CH_2Cl_2 (5 mL) was stirred for 1 h and evaporated to give the desired product as a colorless amorphous solid (2.14 g, 39% TFA w/w, 100%). ^{1}H NMR (CD_3OD) 7.74 (d, J = 8.5 Hz, 1H, aryl H), 7.63 (d, J = 8.0 Hz, 2H, aryl H), 7.59 (s, 1H, imid-2H), 7.29−7.34 (m, 6H, aryl H and imid-4H), 7.18 (d, J = 8.0 Hz, 2H, aryl H), 6.53 (dd, J = 2.5 and 8.5 Hz, 1H, aryl H), 6.23 (d, J = 2.5 Hz, 1H, aryl H), 5.62 (s, 2H, CH$_2$N), 4.38 (s, 2H, CH_2NH). HRMS (FAB): *m*/*z* calcd for $C_{25}H_{20}N_4O_2$ 409.1664, found 409.1666.

5-{[3-(4-Cyanobenzyl)-3*H*-imidazol-4-ylmethyl]amino}-biphenyl-2-carboxylic Acid Isopropylamide (15). To a solution of 5-{[3-(4-cyanobenzyl)-3*H*-imidazol-4-ylmethyl]amino}-biphenyl-2-carboxylic acid (39% TFA w/w, 100 mg, 0.12 mmol), isopropylamine (10 μL, 0.12 mmol), Et_3N (64 μL, 0.46 mmol), and HOBt (32 mg, 0.24 mmol) in CH_2Cl_2 (1 mL) was added EDCI (23 mg, 0.12 mmol) at −10 °C, and the mixture was stirred at rt overnight. To the mixture was added CH_2Cl_2 (50 mL) and sat. $NaHCO_3$ (50 mL), and the organic layer was washed with sat. $NaHCO_3$ (50 mL) and brine and dried

($MgSO_4$). The crude material was purified by SiO_2 column chromatography (10:1 $CHCl_3$/MeOH) to give the desired product as a colorless amorphous solid (50 mg, 93%). HPLC purity: 94%. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, J = 8.5 Hz, 1H, aryl H), 7.54 (d, J = 5.0 Hz, 2H, aryl H), 7.52 (s, 1H, imid-2H), 7.38−7.43 (m, 2H, aryl H), 7.28−7.32 (m, 3H, aryl H), 7.07−7.08 (m, 3H, aryl H and imid-4H), 6.52 (dd, J = 2.5 and 8.5 Hz, 1H, aryl H), 6.32 (d, J = 2.5 Hz, 1H, aryl H), 5.24 (s, 2H, NCH_2), 4.88 (d, J = 7.5 Hz, 1H, amido NH), 4.22 (t, J = 4.5 Hz, NH, 1H), 4.12 (d, J = 4.5 Hz, 2H, CH_2NH), 3.92 (m, 1H, CH), 0.80 (d, J = 6.0 Hz, 6H, 2 × CH_3). HRMS (FAB): m/z calcd for $C_{28}H_{27}N_5OH^+$ 450.2294, found 450.2295.

5-{[3-(4-Cyanobenzyl)-3*H*-imidazol-4-ylmethyl]amino}-biphenyl-2-carboxylic Acid Cyclohexylmethylamide (16). This compound was prepared from cyclohexylmethylamine (14 mg, 0.12 mmol) by a similar procedure to that described for **15**. The crude material was purified by column chromatography (100:40:8 $CHCl_3$/acetone/EtOH) to give the product as a colorless amorphous solid (48 mg, 80%). ^{1}H NMR ($CDCl_3$): δ 7.64 (d, J = 8.5 Hz, 1H, aryl H), 7.58 (s, 1H, imid-2H), 7.55 (d, J = 8.0 Hz, 2H, aryl H), 7.41−7.44 (m, 3H, aryl H), 7.28−7.40 (m, 2H, aryl H), 7.09 (s, 1H, imid-4H), 7.09 (d, J = 8.0 Hz, 2H, aryl H), 6.53 (dd, J = 2.6 and 8.5 Hz, 1H, aryl H), 6.31 (d, J = 2.6 Hz, 1H, aryl H), 5.25 (s, 2H, NCH_2), 5.19 (t, J = 4.0 Hz, 1H, NHCO), 4.13 (d, J = 4.0 Hz, 2H, CH_2), 4.05 (t, J = 4.0 Hz, 1H, NH), 2.94 (t, J = 6.3 Hz, 2H, NHCH_2), 1.57−1.59 (m, 3H, cyclohexyl), 0.88−1.27 (m, 6H, cyclohexyl), 0.61−0.63 (m, 2H, cyclohexyl). HRMS (FAB): m/z calcd for $C_{32}H_{33}N_5OH^+$ 504.2763, found 504.2762.

5-{[3-(4-Cyanobenzyl)-3*H*-imidazol-4-ylmethyl]amino}-biphenyl-2-carboxylic Acid Benzylamide (17). This compound was prepared from benzylamine (13 mg, 0.12 mmol) by a similar procedure to that described for **15**. The crude material was purified by column chromatography (100:40:8 $CHCl_3$/acetone/EtOH) to give the product as colorless amorphous solid (46 mg, 77%). ^{1}H NMR ($CDCl_3$): δ 7.67 (d, J = 8.5 Hz, 1H, aryl H), 7.57 (s, 1H, imid-2H), 7.55 (d, J = 8.5 Hz, 2H, aryl H), 7.34−7.35 (m, 3H, aryl H), 7.28−7.30 (m, 2H, aryl H), 7.19−7.20 (m, 3H, aryl H), 7.10 (s, 1H, imid-4H), 7.08 (d, J = 8.5 Hz, 2H, aryl H), 6.87−6.89 (m, 2H, aryl H), 6.53 (dd, J = 2.2 and 8.5 Hz, 1H, aryl H), 6.31 (d, J = 2.2 Hz, 1H, aryl H), 5.45 (t, J = 5.5 Hz, 1H, CONH), 5.23 (s, 2H, NCH_2), 4.28 (d, J = 5.5 Hz, 1H, CH_2), 4.13 (d, J = 5.2 Hz, 2H, CH_2NH), 3.90 (t, J = 5.2 Hz, 1H, NH). HRMS (FAB): m/z calcd for $C_{32}H_{27}NOH^+$ 498.2294, found 498.2296.

5-{[3-(4-Cyanobenzyl)-3*H*-imidazol-4-ylmethyl]amino}-biphenyl-2-carboxylic Acid (3-Nitrophenyl)amide (18). This compound was prepared from 3-nitroaniline (17 mg, 0.12 mmol) by a similar procedure to that described for **15**. The crude material was purified by column chromatography (100:40:8 $CHCl_3$/acetone/EtOH) to give the product as a pale yellow amorphous solid (42 mg, 67%). ^{1}H NMR ($CDCl_3$): δ 8.19 (d, J = 8.8 Hz, 1H, aryl H), 8.00 (d, J = 8.6 Hz, 1H, aryl H), 7.64 (s, 1H, imid-2H), 7.59 (d, J = 8.1 Hz, aryl H), 7.48 (t, J = 7.7 Hz, 1H, aryl H), 7.32−7.41 (m, 8H, aryl H, NHCO), 7.17 (s, 1H, imid-4H), 7.10 (d, J = 8.1 Hz, 2H, aryl H), 6.60 (dd, J = 2.6 and 8.6 Hz, 1H, aryl H), 6.42 (d, J = 2.6 Hz, 1H, aryl H), 5.25 (s, 2H, CH_2N), 4.33 (t, J = 5.2 Hz, 1H, NH), 4.23 (d, J = 5.2 Hz, 2H, CH_2).

5-{[3-(4-Cyanobenzyl)-3*H*-imidazol-4-ylmethyl]amino}-biphenyl-2-carboxylic Acid (2-Cyanoethyl)amide (19). This compound was prepared from 3-aminopropionitrile fumarate (15 mg, 0.12 mmol) by a similar procedure to that described for **15**. The crude material was purified by column chromatography (100:40:8 $CHCl_3$/acetone/EtOH) to give the product as a colorless amorphous solid (42 mg, 76%). HPLC purity: 95%. ^{1}H NMR ($CDCl_3$): δ 7.53−7.60 (m, 4H, aryl H and imid-2H), 7.42−7.44 (m, 3H, aryl H), 7.29−7.32 (m, 2H, aryl H), 7.07−7.10 (m, 3H, aryl H and imid-4H), 6.50 (dd, J = 3.5 and 12.0 Hz, 1H, aryl H), 6.33 (d, J = 3.5 Hz, 1H, aryl H), 5.70 (t, J = 11 Hz, 1H, CONH), 5.24 (s, 2H, NCH_2), 4.13 (s, 3H, CH_2NH), 3.34 (q, J = 11 Hz, 2H, CH_2), 2.37 (t, J = 11 Hz, 2H, CH_2). HRMS (FAB): m/z calcd for $C_{28}H_{24}N_6OH^+$ 461.2090, found 461.2093.

5-{[3-(4-Cyanobenzyl)-3*H*-imidazol-4-ylmethyl]amino}-biphenyl-2-carboxylic Acid (2-Ethylsulfanylethyl)amide (20). This compound was prepared from 2-(ethylthio)ethylamine hydrochloride (17 mg, 0.12 mmol) by a similar procedure to that described for **15**. The crude material was purified by column chromatography (100:40:8 $CHCl_3$/acetone/EtOH) to give the product as a colorless amorphous solid (45 mg, 76%). HPLC purity: 90%. ^{1}H NMR ($CDCl_3$): δ 7.54−7.61 (m, 4H, aryl H and imid-2H), 7.31−7.42 (m, 5H, aryl H), 7.07−7.10 (m, 3H, aryl H and imid-4H), 6.52 (dd, J = 5.5 and 12 Hz, 1H, aryl H), 6.35 (d, J = 5.5 Hz, 1H, aryl H), 5.55 (t, J = 10.5 Hz, 1H, NHCO), 5.24 (s, 2H, NCH_2), 4.13 (s, 3H, CH_2NH), 3.28 (q, J = 10.5 Hz, 2H, NHCH_2), 2.30−2.38 (m, CH_2SCH_2), 1.16 (t, J = 12.0 Hz, 3H, CH_3). HRMS (FAB): m/z calcd for $C_{29}H_{29}N_5OSH^+$ 496.2171, found 496.2173.

5-{[3-(4-Cyanobenzyl)-3*H*-imidazol-4-ylmethyl]amino}-biphenyl-2-carboxylic Acid (3-Cyanophenyl)amide (21). This compound was prepared from 3-aminobenzonitrile (14 mg, 0.12 mmol) by a similar procedure to that described for **15**. The crude material was purified by column chromatography (100:40:8 $CHCl_3$/acetone/EtOH) and gel permeation with Sephadex LH-20 (1:1 $CHCl_3$/MeOH) to give the product as a pale yellow amorphous solid (10 mg, 16%). ^{1}H NMR ($CDCl_3$): δ 8.13 (d, J = 8.5 Hz, 1H, aryl H), 7.95 (d, J = 8.0 Hz, 1H, aryl H), 7.26−7.58 (m, 11H, aryl H and imid-2H), 7.05−7.11 (m, 3H, aryl H and imid-4H), 6.59 (d, J = 2.5 and 8.5 Hz, 1H, aryl H), 6.41 (d, J = 2.5 Hz, 1H, aryl H), 5.21 (s, 2H, CH_2N), 4.82 (br s, 1H, NHCO), 4.21 (d, J = 3.5 Hz, 2H, CH_2NH), 4.15 (d, J = 3.5 Hz, 1H, NH). HRMS (FAB): m/z calcd for $C_{32}H_{24}N_6OH^+$ 509.2090, found 509.2094.

1-(4-Phenylbenzyl)-4- or -5-(hydroxymethyl)imidazole (35a and 36a). A solution of 4-hydroxymethylimidazole hydrochloride (500 mg, 3.72 mmol), 4-phenylbenzyl chloride (829 mg, 4.09 mmol), and Na_2CO_3 (789 mg, 7.44 mmol) in dry DMF (6 mL) was stirred at 80 °C overnight. After removal of DMF by distillation, the residue was dissolved in CH_2Cl_2 (100 mL) and the organic layer was washed with H_2O and brine and dried (Na_2SO_4). The oily crude products were separated by SiO_2 column chromatography with acetone to give the products.

Compound **35a** was a white solid (370 mg, 38%). Mp: 141−145 °C. ^{1}H NMR ($CDCl_3$): δ 7.69−7.72 (m, 5H, aryl H), 7.62 (s, 1H, imid-2H), 7.38−7.55 (m, 4H, aryl H), 7.01 (s, 1H, imid-5H), 5.21 (s, 2H, CH_2N), 4.47 (s, 2H, CH_2O). Anal. Calcd for $C_{17}H_{16}N_2O\cdot0.2H_2O$: C, 76.20; H, 6.17; N, 10.46. Found: C, 75.97; H, 6.06; N, 10.28.

Compound **36a** was a white solid (66 mg, 7%). Mp: 202−204 °C. ^{1}H NMR ($CDCl_3$): δ 7.35−7.56 (m, 5H, aryl H), 7.28 (s, 1H, imid-2H), 7.20−7.22 (m, 2H, aryl H), 7.04 (s, 1H, imid-4H), 5.28 (s, 2H, CH_2N), 4.55 (s, 2H, CH_2O). HRMS (FAB): m/z calcd for $C_{17}H_{16}N_2OH^+$ 265.1341, found 265.1338.

1-Cyclohexylmethyl-4- or -5-(hydroxymethyl)imidazole (35b and 36b). These compounds were prepared from 1-bromomethylcyclohexane (1.5 g, 8.2 mmol) by a method similar to that described for **35a** and **36a**.

Compound **35b** was a white solid (185 mg, 13%). Mp: 84−86 °C. ^{1}H NMR ($CDCl_3$): δ 7.36 (s, 1H, imid-2H), 6.82 (s, 1H, imid-5H), 4.58 (s, 2H, CH_2O), 3.69 (d, J = 6.5 Hz, 2H, NCH_2), 1.61−1.73 (m, 6H, CH_2), 1.12−1.25 (m, 3H, $CHCH_2$), 0.88−0.95 (m, 2H, CH_2). Anal. Calcd for $C_{11}H_{18}N_2O\cdot0.1H_2O$: C, 67.39; H, 9.36; N, 14.29. Found: C, 67.47; H, 9.24; N, 14.01.

Compound **36b** was a white solid (73 mg, 5%). Mp: 111−114 °C. ^{1}H NMR ($CDCl_3$): δ 7.33 (s, 1H, imid-2H), 6.80 (s, 1H, imid-4H), 4.58 (s, 2H, CH_2O), 3.81 (d, J = 7.5 Hz, 2H, NCH_2), 1.60−1.74 (m, 6H, $(CH_2)_3$), 1.16−1.18 (m, 3H, CH_2CH), 0.92−0.95 (m, 2H, CH_2). Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.01; H, 9.34; N, 14.42. Found: C, 67.79; H, 9.39; N, 14.20.

1-Pentyl-4- or -5-(hydroxymethyl)imidazole (35c and 36c). These compounds were prepared in a manner similar to that described for **35a** and **36a** with 4-(hydroxymethyl)-imidazole hydrochloride (1.0 g, 7.4 mmol), 1-bromopentane (1.2 g, 8.2 mmol), and Na_2CO_3 (1.6 g, 14.9 mmol) in DMF (12 mL).

Compound **35c** was a pale yellow oil (180 mg, 23%). ^{1}H NMR ($CDCl_3$): δ 7.36 (s, 1H, imid-2H), 6.81 (s, 1H, imid-5H), 4.52

(s, 2H, CH_2OH), 3.82 (t, J = 7.0 Hz, 2H, NCH_2), 1.71 (q, J = 7.0 Hz, 2H, CH_2), 1.21−1.28 (m, 4H, $(CH_2)_2$), 0.84 (t, J = 7.0 Hz, 3H, CH_3). HRMS (FAB): m/z calcd for $C_9H_{16}N_2OH^+$ 169.1341, found 169.1342.

Compound **36c** was a pale yellow oil (60 mg, 8%): ^{1}H NMR ($CDCl_3$): δ 7.42 (s, 1H, imid-2H), 6.78 (s, 1H, imid-4H), 4.60 (s, 2H, CH_2OH), 3.98 (t, J = 7.0 Hz, 2H, NCH_2), 1.78 (q, J = 7.0 Hz, 2H, CH_2), 1.30−1.35 (m, 4H, $(CH_2)_2$), 0.89 (t, J = 7.0 Hz, 3H, CH_3). HRMS (FAB): m/z calcd for $C_9H_{16}N_2OH^+$ 169.1341, found 169.1340.

1-(4-Phenylbenzyl)-4-imidazolecarboxyaldehyde (37a). A solution of **35a** (132 mg, 0.5 mmol) and manganese dioxide (435 mg, 5 mmol) in dioxane (2.5 mL) was stirred at 80 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and filtered over Celite. The filtrate was concentrated to give the desired product as a white solid (183 mg, 100%). This aldehyde was used for the next reaction without further purification.

1-(4-Phenylbenzyl)-5-imidazolecarboxyaldehyde (38a). This aldehyde was synthesized in a manner similar to that described for **37a** with **36a** (62 mg, 0.23 mmol) to afford the product as a colorless amorphous solid (60 mg, 100%). This aldehyde was used for the next reductive amination immediately without further purification.

1-Cyclohexylmethyl-4-imidazolecarboxyaldehyde (37b). This aldehyde was synthesized in a manner similar to that described for **37a** with **35b** (157 mg, 0.80 mmol) to afford the product as colorless oil, 134 mg (87%). This aldehyde was used for the next reductive amination immediately without further purification.

1-Cyclohexylmethyl-5-imidazolecarboxyaldehyde (38b). This aldehyde was synthesized in a manner similar to that described for **37a** with **36b** (62 mg, 0.80 mmol) to afford the product as colorless oil (62 mg, 100%). This aldehyde was used for the next reductive amination immediately without further purification.

1-Pentyl-4-imidazolecarboxyaldehyde (37c). This aldehyde was synthesized in a manner similar to that described for **37a** with **35c** (215 mg, 1.11 mmol) to afford the product as a yellow oil (127 mg, 87%). This aldehyde was used for the next reductive amination immediately without further purification.

1-Pentyl-5-imidazolecarboxyaldehyde (38c). This aldehyde was prepared by a method similar to that described for **36a** with **36c** (94 mg, 0.48 mmol) to give the product as a colorless oil (73 mg, 91%, R_f = 0.9 with acetone). This aldehyde was used for the next reductive amination immediately without further purification.

1-*tert*-Butoxycarbonyl-4-hydroxymethylimidazole (41).[23] To a solution of 4(5)-hydroxymethylimidazole hydrochloride (4.5 g, 33 mmol) in DMF (10 mL) was added Et_3N (4.6 mL, 33 mmol) in DMF (5 mL) at 0 °C and Boc_2O (7.20 g, 33 mmol) in THF (50 mL) dropwise at 0 °C. The mixture was stirred at rt overnight, and the solvent was evaporated. To the residue was added AcOEt (400 mL) and H_2O (300 mL), and the organic layer was washed with H_2O (300 mL × 2) and brine and dried (Na_2SO_4). Evaporation of the solvent gave the product (4.33 g, 66%). ^{1}H NMR ($CDCl_3$): 8.06 (s, 1H, imid-2H), 7.32 (s, 1H, imid-5H), 5.40 (br s, 1H, OH), 4.58 (s, 2H, CH_2OH), 1.61 (s, 9H, Bu).

1-*tert*-Butoxycarbonyl-4-chloromethylimidazole (42).[23] To a solution of 1-*tert*-butoxycarbonyl-4-hydroxymethylimidazole (4.33 g, 22 mmol) and a drop of DMF in CH_2Cl_2 (100 mL) was added $SOCl_2$ (2.9 mL, 40 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred at 0 °C for 20 min. After evaporation of the solvent, the residue was dissolved in AcOEt (400 mL), and then the organic layer was washed with sat. $NaHCO_3$, H_2O, and brine and dried (Na_2SO_4). The crude product was purified by SiO_2 column chromatography with 4:1 hexane/AcOEt to afford the product as a colorless oil (4.0 g, 83%). ^{1}H NMR ($CDCl_3$): 8.05 (s, 1H, imid-2H), 7.40 (s, 1H, imid-5H), 4.55 (s, 2H, CH_2), 1.62 (s, 9H, Bu).

PFT Inhibition Assays. Recombinant *Tb*PFT was produced in the baculovirus/Sf9 cell expression system and purified as described previously.[24] Assays were carried out with 5 ng of *Tb*PFT, 5 μM RAS-CVIM, 0.75 μM (0.3 μCi) [^{3}H]FPP, and test inhibitor (1 μL DMSO solution) in a total volume of 20 μL containing 30 mM potassium phosphate (pH 7.7), 5 mM DTT, 0.5 mM $MgCl_2$, and 20 μM $ZnCl_2$. After incubation at 30 °C for 15 min, the amount of [^{3}H]farnesylated protein product was determined by the glass fiber filter method as described.[25] For all of the inhibitors, the percent inhibition was measured in the presence of 50 nM compound. In some cases (as noted in the tables), IC_{50} values were determined from assays done in the presence of several inhibitor concentrations.

Parasite Cultures and Drug Screening Assays. *T. brucei brucei* (bloodstream-form strain 427 from K. Stuart, Seattle Biomedical Research Institute, Seattle, WA) was cultured in HMI-9 medium containing 10% fetal bovine serum, penicillin, and streptomycin at 37 °C with 5% CO_2.[26] Drug sensitivity of the *T. brucei* strain was determined in 96-well microtiter plates in triplicate with an initial inoculum of 1×10^4 trypomastigotes per well. Compound stock solutions were prepared in DMSO at 20 mM and added in serial dilutions for a final volume of 200 μL/well. Parasite growth was quantified at 48 h by the addition of Alamar Blue (Alamar Biosciences, Sacramento, CA).[27] Pentamidine isethionate (Aventis, Dagenham, UK) was included in each assay as a positive control.

T. brucei rhodesiense (strain STIB 900) bloodstream-form trypomastigotes were cultured in HMI-18 medium[26] supplemented with nonessential amino acids, glucose, and 15% heat-inactivated fetal calf serum at 37 °C in a 5% CO_2/95% air mixture. Inhibition assays of *T. brucei rhodesiense* were done using the same technique as above, except that the cultures were incubated for 72 h before developing with Alamar Blue (Alamar Biosciences). The ED_{50} and IC_{50} values were calculated using Microsoft Excel and X/fit.

Murine 3T3 fibroblasts were grown in RPMI 1640 plus 10% fetal bovine serum supplemented with penicillin and streptomycin. Cells were incubated at 37 °C in a 5% CO_2/95% in the presence of compounds. After 72 h, cell viability was quantified by incubating with Alamar Blue for 4−6 h.

Mevalonolactone Labeling Experiments. Bloodstream-form *T. brucei brucei* (1×10^7 cells) was cultured with 2 mL of medium containing 100 μCi (0.83 μM) (*RS*)-[5-^{3}H]mevalonolactone (15 Ci/mmol, American Radiolabeled Chemicals) and 2 μM saponified simvastatin in the presence or absence of **23** (added as 1 μL of the DMSO solution). The radiolabeled prenylated proteins were subjected to SDS−PAGE analysis using a 12.5% gel and visualized by fluorography as described.[10]

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