Potent and Selective Non-Cysteine-Containing Inhibitors of Protein Farnesyltransferase

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Received May 13, 1998

Potent and selective non-thiol-containing inhibitors of protein farnesyltransferase are described. FTI-276 (**1**) was transformed into pyridyl ether analogue **19**. The potency of pyridyl ether **19** was improved by modification of the biphenyl core to that of an *o*-tolyl substituted biphenyl core to give **29**. In addition to 0.4 nM in vitro potency, **29** displayed 350 nM potency in whole cells as the parent carboxylic acid. The *o*-tolyl biphenyl core dramatically and unexpectedly enhanced the potency of other compounds as exemplified by **46**, **47**, **48**, and **49**.

Introduction

Oncogenic Ras proteins are found in 20−30% of all human tumors including those of the lung (30%), colon (50%), and pancreas (90%).[1,2] These aberrant proteins are constitutively activated and promote cell division even in the absence of signals from diverse growth factors.[3] To function, Ras protein must undergo a series of posttranslational modifications, of which farnesylation of a cysteine residue near the C-terminus by the enzyme farnesyltransferase (FTase) is critical for activity.[4−8] Inhibition of this enzyme will render Ras inactive and block the uncontrolled mitogenic signaling pathway.

Several structurally distinct classes of farnesyltransferase inhibitors have recently been described.[9−23] The first reported inhibitors were designed to mimic the Ras C-terminal tetrapeptide (CVFM) which is the minimum substrate-derived inhibitor. FTI-276 (**1**, Figure 1) is one of the most potent members of this class.[24,25] This compound incorporates a lipophilic 2-phenyl-4-aminobenzoic acid as an isosteric replacement for the internal Val-Phe dipeptide. The in vitro IC_{50} of **1** is 0.5 nM against farnesyl transferase, and the methyl ester **2** (FTI-277) potently blocks farnesylation of Ras in whole cells (Ras processing, $EC_{50} = 0.1-0.2\ \mu M$).[26] FTI-276 has also demonstrated significant in vivo activity against human tumor xenografts in nude mice.[24]

Despite the impressive activity of **1** and **2**, a number of problems remained. The terminal cysteine residue was highly susceptible to oxidative dimerization, necessitating the use of dithiothreitol (DTT) for in vivo evaluation. In addition, **1** ($EC_{50} \sim 1\ \mu M$) lacks the whole cell potency of **2** ($EC_{50} = 0.1-0.2\ \mu M$), presumably due to the lower membrane permeability of the acid. Therefore, we sought to develop a compound that (1) lacks the reactive sulfhydryl group and (2) is as active in whole cells as the parent carboxylic acid.

Chemistry

We decided that a focused combinatorial library derived from biphenylamine **5** would allow for quick and easy access to a diverse series of compounds. The core FMOC-protected amino acid **5** was prepared from commercially available 2-bromo-4-nitrotoluene **3**. Palladium-catalyzed aryl coupling using Suzuki conditions[27] followed by $KMnO_4$ oxidation, formation of the *tert*-butyl ester, and reduction of the nitro group gave **4** in 56% yield. Protection of the amine with FMOC chloroformate and acid hydrolysis of the *tert*-butyl ester gave the FMOC biphenyl acid **5** in 68% yield. Attachment of this protected amine to a Wang resin[28] containing the requisite methionine residue and deprotection of the FMOC group gave the desired substrate **6** suitable for our library (Scheme 1).

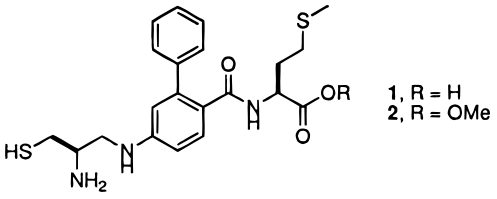
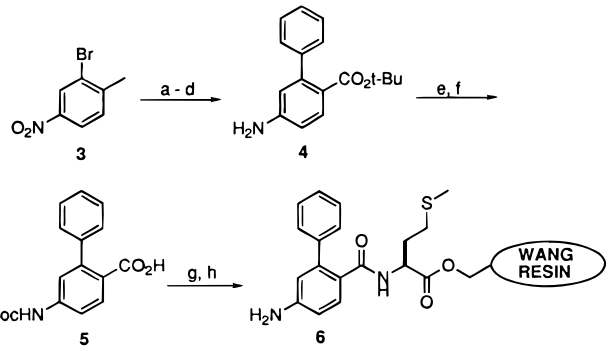


Figure 1.

Scheme 1[a]

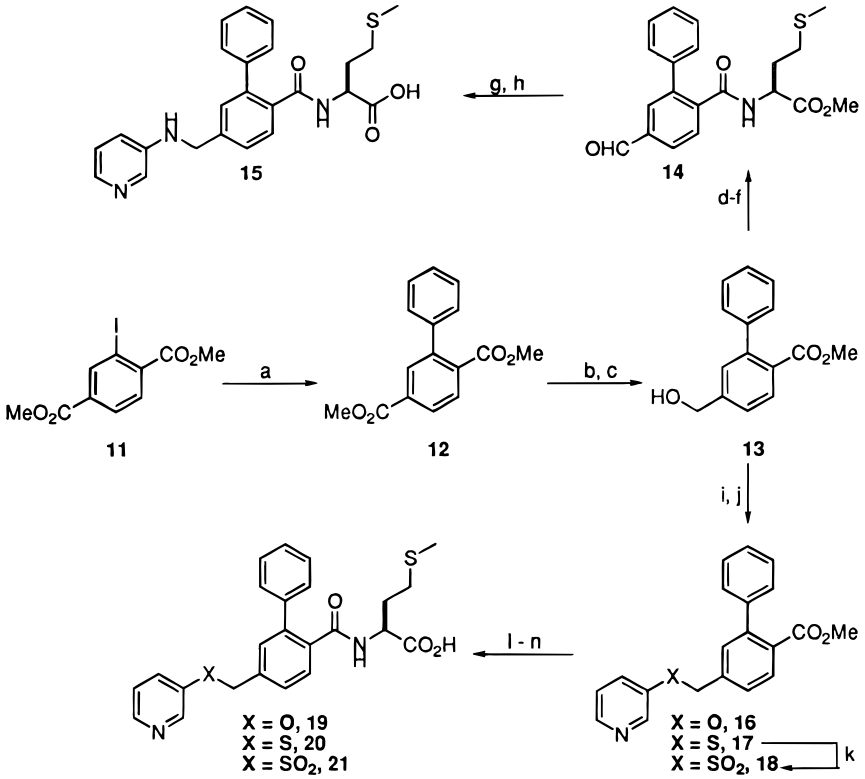


[a] (a) $Pd(PPh_3)_4$, Na_2CO_3, $PhB(OH)_2$, toluene, reflux, 91%; (b) $KMnO_4$, 2:1 H_2O/pyridine, reflux, 87%; (c) H_2SO_4, isobutylene, dioxane, 70%; (d) 10% Pd/C, NH_4CO_2, MeOH, 99%; (e) *i*-Pr_2NEt, FMOC chloroformate, CH_2Cl_2, 92%; (f) TFA, CH_2Cl_2, 96%; (g) L-Met-Wang resin, diisopropylcarbodiimide, HOOBt, NMP; (h) 33% piperidine/DMF.

The initial lead **7** resulted from this library and was modified with more classical medicinal chemistry. The

10.1021/jm980298s CCC: $15.00
Published on Web 09/19/1998

Scheme 2[a]



[a] (a) Ph-B(OH)$_2$, aqueous Na_2CO_3, toluene, reflux, 97%; (b) aqueous KOH, MeOH/THF, rt, 70%; (c) BH_3·THF, rt, 98%; (d) KOH, aqueous MeOH, reflux, 99%; (e) L-methionine, methyl ester hydrochloride, EDAC, HOBT, Et_3N, DMF, rt, 79%; (f) $C_2O_2Cl_2$/DMSO, Et_3N, CH_2Cl_2, −78 °C, 84%; (g) 3-aminopyridine, $NaCNBH_3$, MeOH/AcOH, 73%; (h) LiOH, aqueous THF, 90%; (i) PBr_3/LiBr, DMF, 96%; (j) K-O-(3-Pyr), DME, cat. 18-C-6, 34%; (k) H_2O_2, TFAA, CH_2Cl_2, 94%; (l) NaOH, aqueous MeOH, reflux, 80−100%; (m) L-methionine methyl ester hydrochloride, EDAC, HOBT, Et_3N, DMF, rt, 70−80%; (n) LiOH, aqueous THF.

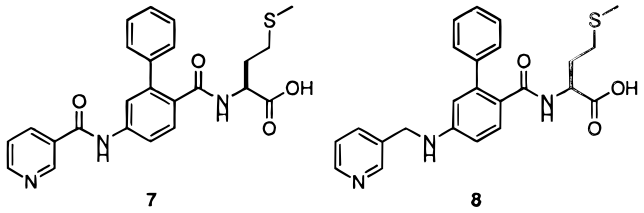


Figure 2.

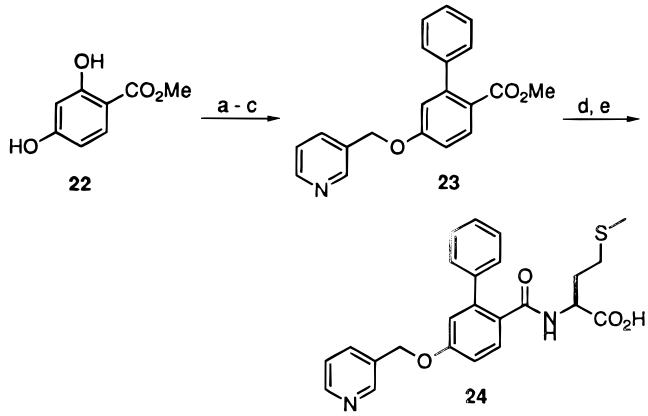
first change involved the removal of the nicotinamide carbonyl to give **8**. This was accomplished by using 3-pyridinecarboxaldehyde in a reductive amination procedure (Figure 2).

The picolinate **9** and isonicotinate **10** were prepared by standard coupling procedures. We also transposed the carbon and nitrogen atoms of compound **8**. We investigated sulfur and oxygen linkers as well. The preparation of these transposed compounds came from the common precursor **13**. From this alcohol we could prepare the benzyl halide or the aldehyde (using Swern's conditions[29]), allowing for the assembly of a variety of target compounds (Scheme 2).

From aldehyde **14**, we prepared a variety of amines exemplified by compound **15**. The intermediate benzyl halide derived from alcohol **13** was used to prepare ether and thioether analogues exemplified by compounds **19** and **20**, respectively (Scheme 2). Retro-inversion of oxygen analogue **19** to give oxygen analogue **24** was carried out as shown in Scheme 3.

In addition to optimizing a cysteine replacement, we investigated substitution of the biphenyl core. Efficient

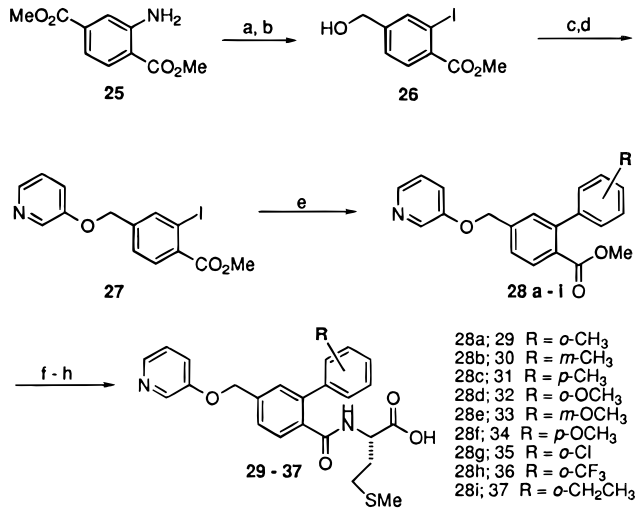
Scheme 3[a]



[a] (a) 3-Chloromethylpyridine·HCl, KOH/aqueous DMF, 24%; (b) Tf_2O, pyridine, −10 °C to rt, 81%; (c) Ph-B(OH)$_2$, aqueous Na_2CO_3, toluene, reflux, 83%; (d) NaOH, aqueous MeOH, reflux, 90%; (e) L-methionine methyl ester hydrochloride, EDAC, HOBT, Et_3N, DMF, rt, 78%; (f) LiOH, aqueous THF.

access to ortho, meta, and para substituted systems was possible from intermediate **27**. Use of iododimethylterephthalate **11** for this purpose was precluded by complete lack of selectivity in differentiation of the carbonyl groups by reduction or hydrolysis. Therefore, we decided to use commercially available dimethylaminoterephthalate **25**. We were able to realize a selective reduction of the distal ester using DIBAL-H. This selectivity is likely due to the vinylogous carbamate character of the proximal ester. The resulting amino alcohol was iodinated under the usual Sandmeyer

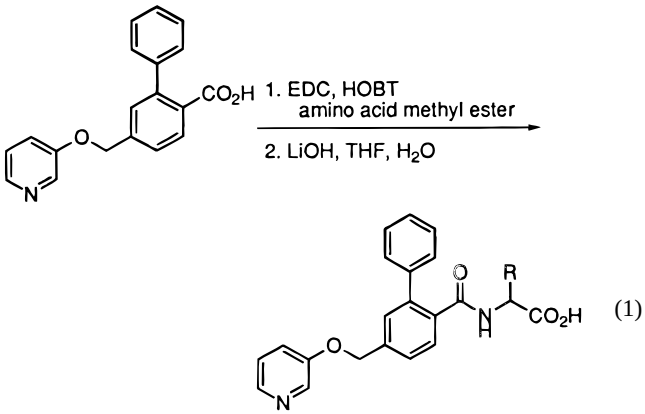
Scheme 4[a]



[a] (a) DIBAL-H, THF/hexanes, −78 °C, 68%; (b) $NaNO_2$, KI, acetone, −15 °C, 83%; (c) $SOCl_2$, LiCl, DMF, rt, 100%; (d) 3-hydroxypyridine potassium alkoxide, 18-crown-6, toluene, 48%; (e) aryl boronic acids, $Pd(PPh_3)_2Cl_2$, Cs_2CO_3, DMF, 80 °C, 61−96 %; (f) saturated aqueous LiOH, MeOH, reflux, 100%; (g) HOOBT/EDC/DMF, L-methionine methyl ester HCl, 91%; (h) LiOH−THF−H_2O, 86%.

conditions to afford **26** in 56% yield over two steps. Formation of the benzyl chloride followed by displacement with the potassium alkoxide of 3-hydroxypyridine gave the advanced intermediate **27** in 48% yield over two steps. Aryl iodide **27** was utilized to access modifications of the biphenyl core. *o*-, *m*-, and *p*-Tolyl boronic acids and *o*-, *m*-, and *p*-methoxyphenyl boronic acids were coupled to aryl iodide **27** using modified Suzuki coupling conditions[27] (Scheme 4). Biphenyl intermediates **28a**−**f** were obtained in yields of 61−96%. Aryl esters **28a**−**f** were hydrolyzed using LiOH in refluxing aqueous methanol to the corresponding acids which were coupled to L-methionine methyl ester in 65−80% yield over two steps. The methionine esters were hydrolyzed with LiOH in THF−H_2O to give the corresponding acids **29**−**34**. The *o*-Cl **35**, *o*-CF_3 **36** , and *o*-Et **37** substituted biphenyls were prepared analogously.

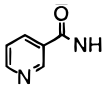
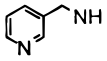
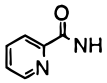
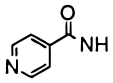
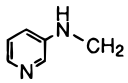
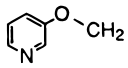
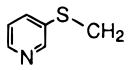
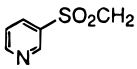
To study amino acids other than methionine as C-terminal substituents, we prepared amides derived from most of the natural amino acids. These were prepared by standard techniques (eq 1). Methionine



(1)

sulfone and homoserine lactone analogues of the aminopyridine were also prepared.

Table 1. Results of Pyridine Modification of Lead Structure **7**

compd	R	IC_{50} (nM)	EC_{50} (μM)
7		70	50[a]
8		20	40[a]
9		> 1000	nd
10		> 1000	nd
15		6.8	10[a]
19		4.3	5[b]
20		10	10[b]
21		550	nd
24		6.6	nd

[a] Methionine methyl ester. [b] Methionine acid. Unless statistical limits are given, the compounds were assayed once. The reliability of the in vitro assay is ±50%. The reliability of the cell-based assay is ±50−100%. Compounds that differ in potency by more than 3-fold should be considered statistically different.

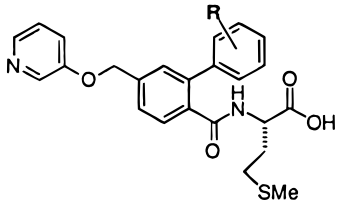
Results and Discussion

Directed combinatorial synthesis generated compound **7** as a 64 nM lead. However, this compound (as its methyl ester) was only modestly active in our cell-based assay (EC_{50} = 50 μM). More traditional medicinal chemistry was employed to modify this lead structure to improve both in vitro and cellular activity (Table 1).

A 3-substituted pyridine, as originally discovered through combinatorial chemistry, proved optimal (compare **7**, **9**, and **10**). Reduction of the amide carbonyl of **7** enhanced the potency 4-fold (**8**). Retro-inversion of the nitrogen provided an additional 2-fold increase in activity (**15**). Compounds incorporating ether (**19**) and thioether (**20**) linking groups were similarly active although the corresponding sulfone (**21**) showed a loss in potency. The reversed oxygen analogue **19** was the most potent, possessing an IC_{50} of 4 nM. However, oxygen analogue **19** was still 10-fold less active than FTI-276. In addition, it displayed similar characteristics as FTI-276, requiring an ester for efficient whole cell activity (EC_{50} methyl ester = 3 μM).

Clearly, regiochemistry and, to a certain extent, the electronic nature of the pyridine affect potency. Although the exact function or binding mode of the pyridine is unknown, one possibility is that it coordinates with the zinc atom known to be present in the

Table 2. SAR of Biphenyl Core Substitution



compd	R	IC_{50} (nM)	EC_{50} (μM)
19	H	4.3 ± 0.5[a]	5[a]
29	*o*-CH_3	0.4 ± 0.2[b]	0.35[a]
30	*m*-CH_3	5.4	nd
31	*p*-CH_3	360	nd
32	*o*-OCH_3	3.3	10
33	*m*-OCH_3	12	nd
34	*p*-OCH_3	230	nd
35	*o*-Cl	0.61	0.4
36	*o*-CF_3	0.50	0.3
37	*o*-CH_2CH_3	0.35	<0.1

* $n = 3$, ** $n = 5$ Unless statistical limits are given, the compounds were assayed once. The reliability of the in-vitro assay is ± 50%. The reliability of the cell-based assay is ± 50−100%. Compounds that differ in potency by more than 3-fold should be considered statistically different.

active site. Another explanation is that the pyridine may serve as a hydrogen bond acceptor.

To improve the activity of oxygen analogue **19**, a structure−activity study of substituents on the biphenyl core was conducted. The underlying premise was that the additional van der Waal interaction of a lipophilic group appended to the unsubstituted phenyl ring might enhance potency, though the optimal position and nature of the substituent was unknown to us. As shown in Table 2, *o*-methyl derivative **29** was 10-fold more potent than parent structure **19**. Compounds **35**, **36**, and **37**, bearing *o*-chloro, trifluoromethyl, and ethyl substituents, respectively, were similarly 7- to 11-fold more potent than **19**. There was a sharp decline in activity as the methyl substituent was moved first to the meta and then to the para position. While the same trend was observed for the *o*-, *m*-, and *p*-methoxy substituted compounds, *o*-methoxy inhibitor **32** was equipotent with unsubstituted compound **19**.

The EC_{50} of **29** for the inhibition of Ras processing in the whole cell assay was 0.35 μM. Thus, we were able to obtain a potent parent carboxylic acid that is as active in whole cells as FTI-277.

The results of the biphenyl core modifications raised some questions regarding the nature of the enhanced potency. The Hansch π constants, in increasing order of lipophilicity, for methoxy, methyl, chloro, trifluoromethyl, and ethyl span 1 order of magnitude. The potency of these molecules span 1 order of magnitude as well. The *o*-methoxy is the least active of the ortho substitutions and provides no potency increase over the parent compound. There is considerable difference between the electronic and lipophilic character of a chloro, trifluoromethyl, and an ethyl substituent. Yet, these molecules are equipotent. While there is some agreement between the degree of lipophilicity and observed in vitro potency (i.e., a beneficial van der Waal interaction may help to enhance potency), there is clearly some other factor responsible for the observed activity. The proton NMR spectrum of **29** reveals two *o*-tolyl methyl signals

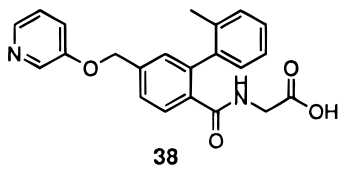


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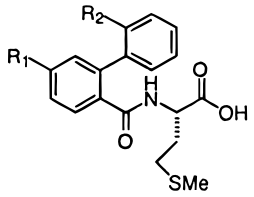
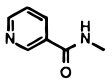
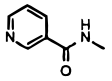
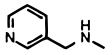
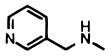
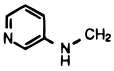
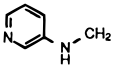
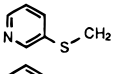
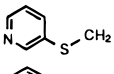
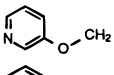
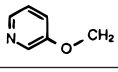
Figure 3.

Table 3. Comparison of Unsubstituted and *o*-Tolyl Biphenyl Derived FTase Inhibitors

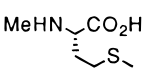
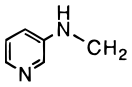
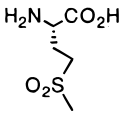
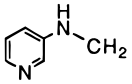
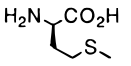
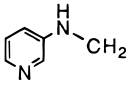
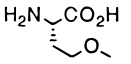
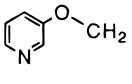
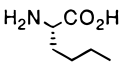
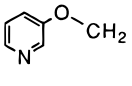
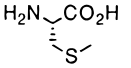
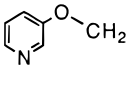
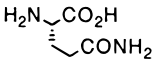
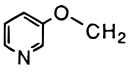


compd	R1	R2	IC_{50} (nM)	fold increase
7		H	70	--
46		Me	1.6	**44**
8		H	20	--
47		Me	1.5	**13**
15		H	6.8	--
48		Me	0.42	**17**
20		H	10	--
49		Me	0.69	**14**
19		H	4.0	--
29		Me	0.4	**10**

and suggests **29** to be a mixture of rotational diastereomers. The proton NMR spectrum of **37** also reveals two methyl triplet signals. Variable temperature NMR experiments of **29** showed that the two *o*-tolyl methyl signals coalesced as the temperature was increased to 70 °C. Variable temperature NMR experiments of **37** displayed nearly identical results. This implies a rotational barrier of 17.4 kcal about the biphenyl carbon−carbon bond, which is, in essence, slow rotation on the NMR time scale at room temperature. This may be indicative of a conformational effect whereby the ortho substituent sterically imparts an orthogonal relationship between the two phenyl rings of the biphenyl core. Apparently, the binding pocket is complementary to the shape of an orthogonal biphenyl system. As further evidence that **29** is a rotational diastereomer, glycine analogue **38** (Figure 3) was prepared.

The NMR spectrum of **38** reveals one signal for the *o*-methyl group. In addition, the NMR spectrum of the *o*-methoxy substituted system **32** reveals one signal for the methyl ether. Apparently, the intervening oxygen allows for free rotation. Thus ortho substitution with

Table 4. Effects of Substituting Methionine with Different Amino Acids

compd	amino acid	R	IC_{50} (nM)	ED_{50} (μM)
39			160	100
40			17	100
41			140	nd
42			1000	nd
43			>1000	nd
44			>1000	nd
45			48	nd

sterically demanding groups (methyl, ethyl, trifluoromethyl, chloro) unexpectedly enhanced potency 7 to 12-fold over **19**, giving compounds that are equipotent with FTI-276.

The *o*-tolyl methyl group has enhanced the in vitro potency of every system studied. The minimum increase was 10-fold (**19** and **29**), which occurred with the most potent initial lead (Table 3). However, different series of compounds exhibit much greater than a 10-fold increase in potency when the *o*-tolyl is incorporated. As a result of enhanced FTI activity, the EC_{50} data were also dramatically improved (**19** $EC_{50} = 5.0\ \mu$M, **29** $EC_{50} = 0.35\ \mu$M).

Replacement of the C-terminal amino acid was less successful. Only a few amino acids displayed good activity (Table 4). Inversion of the methionine stereochemistry (**41**) resulted in a ~50-fold less potent compound. The *N*-methyl-L-methionine[31] (**39**) derivative was equally less potent. Only methionine sulfone (**40**) and glutamine (**45**) were viable substitutions. However, the activity of these analogues was still lower than that of the parent methionine. Some other noteworthy compounds were *O*-methylhomoserine[31] (**42**), norleucine (**43**), and *S*-methylcysteine (**44**). Though very similar in structure to the methionine analogues, these compounds were significantly less active.

The active farnesyltransferase inhibitors described herein (Table 5) possess little or no inhibitory activity against GGTase I. All of these compounds possess an $IC_{50} > 10\ \mu$M against GGTase I, giving rise to ~10 000-fold selectivity. This is a significant accomplishment, given that FTI-276 is only 50-fold selective. The ortho substituted biphenyl compounds were also inactive as inhibitors of GGTase I ($IC_{50} > 10\ \mu$M), showing that the increase in potency observed for FTase is not observed in GGTase I.

Conclusion

In summary, we were successful in transforming FTI-276 **1** into the potent and selective non-cysteine-containing carboxylic acid **29** that is active in whole cells. The *o*-tolylpyridyl ether **29** has 0.4 nM in vitro potency against farnesyltransferase and has a measured EC_{50} of 350 nM for inhibition of Ras processing in whole cells. The *o*-tolyl biphenyl core has a dramatic effect on the potency of every non-cysteine-containing farnesyltransferase inhibitor that we have synthesized. We conducted an exact comparison between many pairs of compounds that contained either *o*-hydrogen or *o*-methyl as the only structural difference. This effect was illustrated by compounds **46**, **47**, **48**, and **49** in Table 3. It seems clear that the *o*-tolyl methyl group sterically imparts an orthogonal relationship to the biphenyl core, and this conformational change makes it more complimentary to the shape of the protein binding site. This discovery has laid the groundwork for the development of even more potent inhibitors of protein farnesyltransferase. Reports of these studies will be published in due course.

Table 5. Physical Data and Synthetic Methods for FTase Inhibiting Compounds

compd[a]	formula[b]
7	$C_{24}H_{23}N_3SO_4HCl\cdot 2.15H_2O$
9	$C_{24}H_{23}N_3SO_4\cdot 0.95H_2O$
10	$C_{24}H_{23}N_3SO_4\cdot 1.00H_2O$
15	$C_{24}H_{25}N_3SO_3\cdot 1.25TFA$
19	$C_{24}H_{24}N_2SO_4\cdot 1.14H_2O$
20	$C_{24}H_{24}N_2S_2O_3$
21	$C_{24}H_{24}N_2SO_4\cdot 0.45H_2O$
24	$C_{24}H_{24}N_2SO_4\cdot 1.14H_2O$
29	$C_{25}H_{26}N_2SO_4\cdot 0.60EtOAc$
30	$C_{25}H_{26}N_2SO_4\cdot 0.10CH_2Cl_2$
31	$C_{25}H_{26}N_2SO_4\cdot 0.15CH_2Cl_2$
32	$C_{25}H_{26}N_2SO_5\cdot 0.25H_2O$
33	$C_{25}H_{26}N_2SO_5\cdot 0.55H_2O$
34	$C_{25}H_{26}N_2SO_5$
35	$C_{24}H_{23}N_2SClO_4$
36	$C_{25}H_{23}N_2SO_4F_3\cdot 0.65H_2O$
37	$C_{26}H_{28}N_2SO_4\cdot 0.22H_2O$
38	$C_{22}H_{20}N_2O_4\cdot 1.50H_2O$
39	$C_{25}H_{27}N_3SO_3\cdot 0.65HCl$
40	$C_{24}H_{25}N_3SO_5\cdot 1.30H_2O$
41	$C_{24}H_{25}N_3SO_3\cdot 0.90H_2O$
42	$C_{24}H_{24}N_2O_5\cdot 0.50H_2O$
43	$C_{25}H_{26}N_2O_4\cdot 0.50H_2O$
44	$C_{23}H_{22}N_2SO_4\cdot 0.20H_2O$
45	$C_{24}H_{23}N_3O_5\cdot 2.40HCl$
46	$C_{25}H_{25}N_3SO_4HCl\cdot 0.50H_2O$
47	$C_{25}H_{27}N_3SO_3$
48	$C_{25}H_{27}N_3SO_3\cdot 0.30HCl$
49	$C_{25}H_{26}N_2S_2O_3$

[a] See Tables 1−4 for structures. [b] Compounds were purified using flash chromatography with methanol/methylene chloride or methanol/ethyl acetate and were lyophilized from water/acetonitrile. Salt formation was necessary in some cases in order to obtain well-behaved solids.

Experimental Section

General. Proton magnetic resonance spectra were obtained on a Nicolet QE-300 (300 MHz), a General Electric GN-300 (300 MHz), or a Varian Unity 500 (500 MHz) instrument. Chemical shifts are reported as δ values (ppm) downfield relative to Me_4Si as an internal standard. Mass spectra were obtained with a Hewlett-Packard HP5965 spectrometer; CI/NH_3 indicates chemical ionization mode in the presence of ammonia. Combustion analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Melting points were determined on a Buchi melting point apparatus with a silicone oil bath and are uncorrected. Chromatographies were carried out in flash mode using silica gel 60 (230−400 mesh) from E. Merck. Compounds synthesized by combinatorial chemistry

techniques that displayed biological activity were resynthesized by the project team in order to obtain pure compounds for biological assay.

4-Amino-2-phenylbenzoic Acid, *tert*-Butyl Ester (4). Commercially available 2-bromo-4-nitrotoluene **3** (14.0 g, 64.9 mmol) was dissolved in 300 mL of toluene and degassed with nitrogen for 10 min. $Pd(PPh_3)_4$ (3.0 g, 2.6 mmol, 4.0 mol %) was added. After an additional 10 min, Na_2CO_3 (2.0 M aqueous solution, 150 mL) was added followed by a solution of phenyl boronic acid (8.7 g, 71.4 mmol) in 60 mL of ethanol, and the reaction was heated to reflux for 12 h. TLC analysis indicated the reaction was complete (20% CH_2Cl_2/hexanes), the reaction was poured into a separatory funnel, and the aqueous layer was extracted with 2 × 100 mL portions of ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered, evaporated, and purified by flash chromatography (50% ethyl acetate/hexanes) to give 12.67 g (91%) of 4-nitro-2-phenyltoluene. R_f = 0.3 (20% CH_2Cl_2/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25−8.15 (m, 2H), 7.52−7.38 (m, 4H), 7.35−7.28 (m, 2H), 2.37 (s, 3H). CIMS: MH^+ 214 $C_{13}H_{11}NO_2$.

To a solution of 4-nitro-2-phenyltoluene (12.4 g, 58.2 mmol) in 145 mL of 2:1 H_2O/pyridine was added $KMnO_4$ (46.0 g, 291 mmol, 5 eq.) portionwise over 60 min, and the reaction was heated to reflux for 48 h and then cooled and filtered through Celite. The filtrate was acidified to pH = 2 with concentrated aqueous HCl and extracted with 3 × 100 mL portions of ethyl acetate. The organic layers were combined, dried over Na_2SO_4, filtered, and evaporated to 12.25 g (87%) of 4-nitro-2-phenylbenzoic acid. R_f = 0.2 (10% MeOH/$CHCl_3$ w/ 0.25% HOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 8.26 (dd, 1H), 8.20 (d, 1H), 7.95 (d, 1H), 7.48−7.38 (m, 5H). CIMS: MH^+ 244 $C_{13}H_9NO_4$.

To a solution of 4-nitro-2-phenylbenzoic acid (6.0 g, 34.7 mmol) in 100 mL of dioxane were added 2.4 mL of concentrated sulfuric acid and 100 mL of isobutylene, and the reaction was stirred in a closed pressure apparatus at 1 atm and at room temperature for 6 days. The reaction was carefully vented, and the dioxane was evaporated. The resulting oil was taken up in 100 mL of ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, evaporated, and purified by flash chromatography (25% ethyl acetate/hexanes) to give 5.16 g (70%) of 4-nitro-2-phenyl-*tert*-butylbenzoate. R_f = 0.7 (50% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25−8.20 (m, 2H), 7.9 (dd, 1H), 7.45−7.40 (m, 3H), 7.36−7.32 (m, 2H), 1.26 (s, 9H). CIMS: MH^+ 300 $C_{17}H_{17}NO_4$.

To a mixture of 4-nitro-2-phenyl-*tert*-butylbenzoate (4.84 g, 16.2 mmol) and 10% Pd/C (750 mg) in 60 mL of methanol was added ammonium formate (5.11 g, 81.0 mmol, 5 equiv), and the reaction was heated to reflux for 1 h. The reaction was cooled, filtered through Celite, and evaporated to give 4.31 g (99%) of 4-amino-2-phenylbenzoic acid, *tert*-butyl ester **4**. R_f = 0.5 (50% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, CD_3OD): δ 7.55 (d, 1H), 7.35−7.25 (m, 3H), 7.18 (d, 1H), 6.62 (dd, 1H), 6.48 (d, 1H), 1.16 (s, 9H). CIMS: MH^+ 270 $C_{17}H_{19}NO_2$.

4-(9-Fluorenylmethyloxycarbonylamino)-2-phenylbenzoic Acid (5). To a solution of **4** (4.31 g, 16.0 mmol) in 50 mL of CH_2Cl_2 were added diisopropylethylamine (4.52 g, 35.2 mmol) and FMOC chloroformate (9.1 g, 35.2 mmol), and the reaction stirred for 18 h. The reaction was extracted with 50 mL of 1 N HCl, dried over Na_2SO_4, filtered, evaporated, and purified by flash chromatography (25% ethyl acetate/hexanes) to give 7.19 g (92%) of 4-(9-fluorenylmethyloxycarbonylamino)-2-phenyl-*tert*-butylbenzoate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82−7.75 (m, 3H), 7.6 (d, 2H), 7.45−7.25 (m, 12H), 6.8 (bs, 1H), 4.55 (d, 2H), 4.26 (t, 1H), 1.22 (s, 9H). CIMS: MH^+ 492 $C_{32}H_{29}NO_4$.

To a solution of 4-(9-fluorenylmethyloxycarbonylamino)-2-phenyl-*tert*-butylbenzoate (7.19 g, 14.6 mmol) in 100 mL of CH_2Cl_2 was added 50 mL of TFA. The reaction was complete in 1 h and was evaporated and purified by flash chromatography over silica gel (gradient of 50% ethyl acetate/hexanes followed by 5% methanol/ethyl acetate) to give 6.1 g (96%) of **5** as a white solid. R_f = 0.2 (50% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, 1H), 7.78 (d, 2H), 7.60 (d, 2H), 7.45−7.25 (m, 11H), 4.58 (d, 2H), 4.27 (t, 1H). CIMS: MNH_4^+ 453 $C_{28}H_{21}NO_4$.

General Procedure: Deprotection of FMOC-L-Met-Wang Resin. FMOC-L-Met-Wang resin (8.80 g; 0.47 mmol/g substitution MidWest Biotech Indianapolis, IN; 0.0041 mol) was placed in a manual solid-phase synthesis vessel (100 mL volume). The resin was suspended in *N*-methyl pyrrolidone (NMP, 50 mL) and was rotated for 5 min on a 120° rotary shaker. The solvent was then drained, and the resin was treated with additional NMP (50 mL; 2×; 5 min). The swollen resin was then resuspended in a 75 mL solution of 33% piperidine/dimethylformamide (DMF) and was rotated for 1 h. The resin was drained and then washed as follows: acetone (75 mL, 1×, 5 min); DMF (75 mL, 3×, 5 min); 2-propanol (75 mL, 5×, 5 min); DMF (75 mL, 3 × 5 min); diethyl ether (75 mL, 3 × 5 min); NMP (75 mL, 3×, 5 min).

Coupling of 4-(9-Fluorenylmethyloxycarbonylamino)-2-phenyl Benzoic Acid (5) to l-Met-Wang Resin: General Procedure. The deprotected L-Met-Wang resin was resuspended in NMP (30 mL). To the suspension were then added 4-FMOC-amino-2-phenyl-benzoic acid **5** (2.25 g; 0.0052 mol; 1.25 equiv), diisopropylcarbodiimide (0.65 g; 0.0052 mol; 1.25 equiv), and 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOOBt) (0.84 g; 0.0052 mol; 1.25 equiv). The suspension was rotated for 20 h. The solution was drained, and the resin was washed as follows: acetone (75 mL, 1×; 2 min); DMF (75 mL, 3×, 5 min); 2-propanol (75 mL, 5×, 5 min); DMF (75 mL, 3×, 5 min); methanol (75 mL, 2×, 5 min); diethyl ether (75 mL, 2×, 5 min). A portion (5 mg) of the resin was removed and subjected to quantitative "FMOC-chromophore" analysis[32a−b] in order to determine the amount of coupled FMOC-4-amino-2-phenylbenzoic acid present. Typically the substitution of the biaryl amino acid ranged from 0.39 to 0.42 mmol/g of L-Met-Wang resin.

Deprotection of FMOC-4-amino-2-phenyl-benzamide-L-Met-Wang Resin (6). The coupled resin from the previous step was swollen in DMF (75 mL), rotated for 5 min, and drained. The drained resin was then washed with DMF (75 mL; 2×; 5 min). The resin was then suspended in 75 mL of a 33% piperidine/DMF solution and was rotated for 1 h. The solution was drained, and the resin was washed as follows: acetone (75 mL, 1×, 5 min); DMF (75 mL, 3×, 5 min); 2-propanol (75 mL, 5×, 5 min); DMF (75 mL, 3×, 5 min); diethyl ether (75 mL, 2×, 5 min). The drained resin was then dried in vacuo overnight at ambient temperature. The resin was stored desiccated at ambient temperature until used.

Coupling of Nicotinic Acid to 4-Amino-2-phenyl-benzamide-L-Met-Wang Resin and Subsequent Cleavage. 4-Amino-2-phenyl-benzamide-L-Met-Wang resin (80 mg) (substitution 0.40 mmol/g, 0.000032 mol) was placed in a 5 mL manual solid-phase synthesis reaction vessel. The resin was suspended in NMP (1.0 mL), rotated for 3 min, and drained. The resin was then treated with NMP (1.0 mL, 2×, 3 min). To the now swollen resin were then added 0.200 mL of a 1.92 M solution of diisopropylethylamine (DIEA)/NMP (15 equiv), 1.00 mL of a 0.180 mM NMP solution of nicotinic acid (5 equiv), and finally 0.200 mL of a a 0.90 M bromo-tris-pyrrolidino phosphonium hexafluorophosphate[33] (PyBroP, 5 equiv)/NMP solution. The reaction slurry was mixed for 6 h, and the solution was drained. The resin was then washed as follows: NMP (1.0 mL, 3×, 3 min); 2-propanol (1.0 mL, 5×, 3 min); NMP (1.0 mL, 3×, 5 min); methanol (1.0 mL, 2×, 3 min); and finally diethyl ether (1.0 mL, 2×, 3 min). The resin was then dried in vacuo for several hours. The dried resin was then suspended in a 1.50 mL solution of 95:5 trifluoroacetic acid/water and was rotated for 1.5 h at ambient temperature. The filtrate was removed from the spent polystyrene-resin and the resulting cleavage solution was evaporated in vacuo. The residue (typically 5−10 mg) was analyzed by reversed-phase (C_{18}) analytical HPLC and by electrospray MS. The desired [4-(3-pyridylcarbonylamino)-2-phenylbenzoyl]methionine acid **7** was found to have an HPLC purity of 75%.

General Procedure for the Solution Synthesis of 7, 9 and 10. [4-(3-Pyridylcarbonylamino)-2-phenylbenzoyl]-

methionine Acid (7). Nicotinic acid (345 mg, 2.8 mmol) was suspended in 10 mL of CH_2Cl_2, and oxalyl chloride (2.8 mL of a 2.0 M solution in methylene chloride) was added by syringe followed by 1 drop of DMF. The reaction stirred at 25 °C for 2 h and was evaporated and azeotroped with toluene. The acid chloride was then dissolved in CH_2Cl_2, and a solution of the 4-amino-2-phenylbenzoylmethionine methyl ester (669 mg, 1.87 mmol) in 5 mL of CH_2Cl_2 was added followed by 4 mL of saturated aqueous $NaHCO_3$. The reaction was stirred at 25 °C for 3 h. The layers were separated, and the organic layer was dried over Na_2SO_4, filtered, and evaporated to give 830 mg (96%) of [4-(3-pyridylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester as an oil. Analysis was performed on the oil. R_f = 0.3 (5% MeOH/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.2 (d, 1H), 8.76 (d, 1H), 8.42 (bs, 1H), 8.2 (dt, 1H), 7.72−7.65 (m, 2H), 7.6 (dd, 1H), 7.45−7.35 (m, 5H), 6.02 (bd, 1H), 4.65 (dq, 1H), 3.68 (s, 3H), 2.20 (t, 2H), 2.01 (s, 3H), 1.98−1.88 (m, 1H), 1.80−1.78 (m, 1H). CIMS: MH^+ 464.

[4-(3-Pyridylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester (830 mg, 1.79 mmol) was dissolved in 8 mL of THF and cooled to 0 °C, and LiOH monohydrate (226 mg, 5.38 mmol) was added followed by 2 mL of H_2O. The reaction was complete in 2 h and was evaporated and acidified to pH = 3 with 1 N HCl, and the resulting precipitate was taken up in EtOAc, washed with water, and dried over Na_2SO_4, and evaporated. The resulting residue was crystallized from hot ethanol to give 281 mg (32%) of the HCl salt of **7** as a white crystalline solid. R_f = 0.2 (10% MeOH/$CHCl_3$ with 0.25% HOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 9.4 (d, 1H), 9.1 (d, 1H), 9.0 (d, 1H), 8.2 (dd, 1H), 7.85−7.80 (m, 2H), 7.58 (dd, 1H), 7.45−7.32 (m, 5H), 4.52−4.45 (m, 1H), 2.20−2.02 (m, 2H), 2.00 (s, 3H1.90−1.80 (m, 2H), 1.15 (t, 1H). CIMS: MH^+ 450. Anal. ($C_{24}H_{23}N_3SO_4HCl\cdot 2.15H_2O$): C, H, N.

[4-(3-Pyridylmethylamino)-2-phenylbenzoyl]methionine Acid (8). 4-Amino-2-phenylbenzoylmethionine methyl ester (1.15 g, 3.21 mmol) and 3-pyridine carboxaldehyde (361 mg, 3.37 mmol) were combined in 15 mL of MeOH, sodium cyanoborohydride (302 mg, 4.81 mmol) was added followed by crushed molecular sieves, the reaction was adjusted to pH = 6 with acetic acid and stirred at 25 °C. After 3 h the reaction was concentrated and transferred directly to a column of silica gel and purified by flash chromatography (5% MeOH/ EtOAc) to give 1.38 g (95%) of the ester as an oil that solidified after standing. R_f = 0.15 (5% MeOH/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.6 (d, 1H), 8.52 (dd, 1H), 7.72−7.65 (m, 2H), 7.45−7.30 (m, 6H), 6.62 (dd, 1H), 6.48 (d, 1H), 5.72 (bd, 1H), 4.64 (dq, 1H), 4.42 (bs, 2H), 3.64 (s, 3H), 2.25−2.05 (m, 3H), 2.00 (s, 3H), 1.95−1.80 (m, 1H), 1.72−1.60 (m, 1H). CIMS: MH^+ 450.

The methyl ester (1.38 g, 3.07 mmol) was dissolved in THF, LiOH monohydrate (387 mg, 9.22 mmol) was added in 2 mL of H_2O at 0 °C, and the reaction stirred at 0 °C for 2 h. The reaction was complete in 2 h and was evaporated and acidified to pH = 3 with 1 N HCl. The resulting precipitate was taken up in EtOAc, washed with water, dried over Na_2SO_4, and evaporated. The resulting residue was crystallized from hot ethanol to give 1.12 g (78%) of the HCl salt of **8** as a white crystalline solid. R_f = 0.2 (10% MeOH/$CHCl_3$ with 0.25% HOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 8.82 (d, 1H), 8.75 (d, 1H), 8.70 (d, 1H), 8.08 (dd, 1H), 7.42−7.30 (m, 6H), 6.72−6.62 (m, 3H), 4.72 (bs, 2H), 4.42 (dd, 1H), 2.22−2.02 (m, 2H), 2.00 (s, 3H), 2.00−1.85 (m, 1H), 1.82−1.70 (m, 1H). CIMS: MH^+ 436. FAB HRMS: MH^+ calcd for $C_{24}H_{26}N_3SO_3$, 436.1695; found, 436.1688.

[4-(2-Pyridylcarbonylamino)-2-phenylbenzoyl]methionine Acid (9). Prepared according to procedure for 7. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.9 (s, 1H), 8.76 (t, 1H), 8.50 (d, 1H), 8.18 (m, 1H), 8.11 (dt, 1H), 8.03−7.96 (m, 2H), 7.72 (m, 1H), 7.46−7.12 (m 6H), 4.30 (m, 1H), 2.35−2.15 (m, 2H), 2.00 (s, 3H), 1.91−1.77 (m, 2H). CIMS: MH^+ 450 $C_{24}H_{23}N_3SO_4$. Anal. ($C_{24}H_{23}N_3O_4S\cdot 0.95H_2O$): C, H, N.

[4-(4-Pyridylcarbonylamino)-2-phenylbenzoyl]methionine Acid (10). Prepared according to procedure for 7. ^{1}H NMR (DMSO-d_6): δ 10.70 (s, 1H), 8.82 (d, 2H), 8.49 (d, 1H), 7.90 (d, 2H), 7.85 (m, 2H), 7.38−7.53 (m, 6H), 4.39 (ddd, 1H), 2.25 (m, 2H), 2.01 (s, 3H), 1.87 (m, 2H). CIMS (DCI, NH_3): 450 (MH^+), 467 ($M + NH_4$)$^+$. CIMS: MH^+ 450 $C_{24}H_{23}N_3SO_4$. Anal. ($C_{24}H_{23}N_3O_4S\cdot 1.00H_2O$): C, H, N.

Dimethyl-2-phenylterephthalate (12). To a stirred solution of 9.60 g (30.00 mmol) of dimethyl iodoterephthalate **11** in 75 mL of toluene at room temperature was added 1.74 g (1.50 mmol) of $Pd(Ph_3)_4$. After the yellow solution was stirred for 10 min, 4.02 g (33.00 mmol) of phenylboronic acid was added in 33 mL of ethanol followed by 70 mL of 2 M aqueous Na_2CO_3. The mixture was vigorously stirred and heated to reflux for 3 h and then allowed to reach room temperature. The mixture was diluted with 200 mL of ethyl ether, and the layers separated. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The dark residue was purified by column chromatography on silica gel (150 g, 2% ethyl acetate/ hexanes) to give 7.86 g (97%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (s, 1H), 8.05 (d, 1H), 7.85 (d, 1H), 7.61 (m, 3H), 7.53 (m, 2H), 3.96 (s, 3H), 3.65 (s, 3H). MS (DCI, NH_3): 288 ($M+NH_4$)$^+$ (100), 271 (MH^+, 17).

Methyl-4-Hydroxymethyl-2-phenyl Benzoate (13). To a solution of 18.4 g (68.1 mmol) of dimethyl-2-phenylterephthalate **12** in 70 mL of 1:1 THF/ methanol was added a solution of 4.56 g (71.5 mmol) of KOH (Fisher 88%) in 30 mL of water dropwise such that the internal temperature remained below 35 °C. The clear solution was stirred overnight, and the organics were removed by evaporation on a rotary evaporator. The aqueous solution was extracted with 2 portions of ethyl acetate and then cooled in an ice bath. To this cold, stirred solution was carefully added 10 mL of concentrated aqueous HCl, and stirring continued for 30 min. The solid formed was collected by vacuum filtration and recrystallized from 100 mL of hot ethanol/water (3:1) to give 10.4 g (60%) of the desired mono acid. The mother liquors were concentrated to dryness, and the residue was chromatographed on 300 g of SiO_2 (97:2:1−96:3:1 $CHCl_3$/MeOH/AcOH) to give an additional 1.7 g (total yield 70%), mp 173−175 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.39 (bs, 1H), 8.02 (dd, 1H), 7.93 (d, 1H), 7.85 (d, 1H), 7.27−7.50 (m, 3H), 7.34 (m, 2H), 3.62 (s, 3H). MS (DCI, NH_3): 274 ($M + NH_4^+$, 100).

To a solution of 10.5 g (41.0 mmol) of the monoacid in 40 mL of dry THF (Aldrich, Gold Label) at 0 °C was added 82 mL of a 1.0 M solution of BH_3−THF in THF dropwise such that the internal temperature remained below 6 °C. The reaction was stirred at 0 °C for 30 min after the addition was complete, and the cooling bath was removed. After it was stirred for 2 h at room temperature, the reaction mixture was cooled to 0 °C in an ice bath and very carefully quenched by the dropwise addition of 100 mL of 3 N aqueous HCl (**caution,** vigorous evolution of H_2). The mixture was stirred for 1 h at room temperature, and the THF was removed on a rotary evaporator. The residue was extracted with 3 × 100 mL of ethyl acetate, and the combined organic phases were back extracted with 2 × 1 N aqueous NaOH, 1× water, and 1× with brine, dried over $MgSO_4$, filtered, and concentrated to give 9.75 g (98%) of **13** that was used directly. An analytical sample was prepared by flash chromatography on silica gel (50% ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, 1H), 7.33−7.44 (m, 4H), 7.31 (m, 2H), 4.79 (d, 2H), 3.63 (s, 3H), 1.78 (t, 1H). MS (DCI, NH_3): 260 ($M + NH_4^+$, 100), 243 (MH^+, 50).

General Benzoate Hydrolysis: 2-Phenyl-4-hydroxymethylbenzoic Acid. To a solution of **13** (9.75 g, 40.2 mmol) in 50 mL of methanol at room temperature was added a solution of 5.13 g (80.4 mmol) of KOH (Fisher, 88%) in 30 mL of water. The mixture was brought to reflux and maintained for 2.5 h. The mixture was cooled to room temperature and the methanol removed on a rotary evaporator. The resulting solution was extracted with 4 × 50 mL of ethyl acetate, and the aqueous phase was then cooled to 0 °C and acidified by the careful addition of 10 mL of concentrated aqueous HCl. The mixture was extracted with 2 portions of ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to give 9.16 g (99%) of the desired compound as a waxy white solid. ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.97 (d, 1H), 7.31−7.46 (m, 6H), 4.81 (s, 2H). MS (DCI, NH_3): 246 ($M + NH_4^+$, 100).

General Amino Acid Coupling Procedure: *N*-[4-Hydroxymethyl-2-phenylbenzoyl]-L-Methionine, Methyl Ester. A solution of 3.42 g (15.00 mmol) 2-phenyl-4-hydroxymethylbenzoic acid in 30 mL of DMF was treated sequentially with 2.20 g (16.30 mmol) of HOBt, 3.12 g (16.3 mmol) of EDAC, and 3.90 g (19.50 mmol) of L-methionine methyl ester hydrochloride. The suspension was stirred for 15 min, 4.00 mL (27.00 mmol) of triethylamine was added, and the mixture stirred for 24 h. The reaction was quenched by pouring into 300 mL of ethyl acetate and extracting with 3 portions of 1 N aqueous HCl, 2 portions of water, 1 portion of saturated aqueous $NaHCO_3$, and 1 portion of brine. The solution was then dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (120 g, 70:30 ethyl acetate/hexanes) to provide 4.40 g (79%) of *N*-[4-hydroxymethyl-2-phenylbenzoyl]-L-methionine methyl ester as an oil that solidified upon standing. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, 1H), 7.34−7.48 (m, 5H), 5.90 (bd, 1H), 4.78 (s, 2H), 4.66 (ddd, 1H), 3.67 (s, 3H), 2.06 (m, 2H), 2.02 (s, 3H), 1.85−1.98 (m, 1H), 1.65−1.79 (m, 1H). ESI MS: 374 $(MH)^+$, 372 (M−H).

***N*-[4-Formyl-2-phenylbenzoyl]-L-Methionine, Methyl Ester (14).** A solution of 1.50 mL (17.70, mmol) of oxalyl chloride in 50 mL of CH_2Cl_2 was cooled to −75 °C, and a solution of 1.70 mL (23.60 mmol) of DMSO in 10 mL of CH_2Cl_2 was added such that the internal temperature did not exceed −60 °C. After the mixture was stirred for 20 min, a solution of 4.40 g (11.80 mmol) of *N*-[4-hydroxymethyl-2-phenylbenzoyl]-L-methionine methyl ester in 25 mL of CH_2Cl_2 was added via cannula such that the internal temperature did not exceed −65 °C. After it was stirred for 2 h, the mixture was quenched by the dropwise addition of 6.60 mL (47.20 mL) of Et_3N, and after 10 min of stirring, the cooling bath was removed. The solution was allowed to warm to ∼10 °C and then was poured into a separatory funnel. The mixture was extracted with 2 portions of water and 2 portions of 3 N aqueous HCl. The combined aqueous phases were back extracted with 25 mL of CH_2Cl_2, and the combined organic phases were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (120 g, 40%−60% ethyl acetate/hexanes) to give 3.68 g (84%) of the **14** as a light yellow oil that solidified on standing. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.11 (s, 1H), 7.93 (dd, 1H), 7.90 (d, 1H), 7.84 (d, 1H), 7.46 (m, 5H), 5.99 (bd, 1H), 4.69 (ddd, 1H), 3.69 (s, 3H), 2.07 (m, 2H), 2.01 (s, 3H), 1.84−2.00 (m, 1H), 1.70−1.83 (m, 1H). MS (DCI, NH_3): 372 (MH^+, 80), 389 ($M + NH_4^+$, 100).

***N*-4-[(3-Pyridylaminomethyl)-2-phenyl]benzoylmethionine, Methyl Ester.** A solution of 2.50 g (6.73 mmol) of the aldehyde **14** in 15 mL of methanol at room temperature was treated with 0.94 g (10.00 mmol) of 3-aminopyridine, and then 5 mL of acetic acid was added. After the mixture was stirred for 1 h, 0.85 g (13.50 mmol) of $NaCNBH_3$ was added. After 2 h of stirring an additional 0.42 g (6.73 mmol) of $NaCNBH_3$ was added, and stirring continued for an additional hour. The mixture was poured into 100 mL of 1 N aqueous NaOH and extracted with 3 portions of ethyl acetate. The combined organic phases were washed twice with saturated $NaHCO_3$, 3 times with water, once with brine, and then dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (150 g, ethyl acetate) to give 2.20 g (73%) of *N*-4-[(3-pyridylaminomethyl)-2-phenyl]-benzoylmethionine methyl ester as a thick oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (bs, 1H), 8.00 (bd, 1H), 7.70 (d, 1H), 7.41 (m, 6H), 7.36 (d, 1H), 7.07 (dd, 1H), 6.86 (ddd, 1H), 5.88 (bd, 1H), 4.68 (ddd, 1H), 4.44 (d, 2H), 4.21 (bt, 1H), 3.65 (s, 3H), 2.07 (m, 2H), 2.01 (s, 3H), 1.84−1.98 (m, 1H), 1.65−1.79 (m, 1H). CIMS (NH_3): 450 (MH^+, 100).

General Procedure for Hydrolysis of Amino Esters. The methionine ester was dissolved in 3:1 THF/methanol and cooled in an ice bath. The solution was treated with 200 mol % of aqueous lithium hydroxide, and the mixture stirred until judged complete by TLC analysis. The solution was concentrated to remove the organic fractions and diluted with water, and the pH of the solution adjusted to ∼4 with aqueous HCl. If a solid precipitate formed, the product was collected by filtration. If an oil formed, the aqueous mixture was extracted with ethyl acetate, and the extracts were dried over sodium sulfate, filtered, and concentrated. If a solid was not isolable by filtration, the material was extracted into ethyl acetate and the organic phase dried over Na_2SO_4, filtered, and concentrated. These procedures generally gave material of suitable purity. If not, the compound was purified by column chromatography on silica gel or reversed-phase preparative HPLC.

***N*-4-[(3-Pyridylaminomethyl)-2-phenyl]benzoylmethionine (15).** The amino ester was hydrolyzed according to the general procedure for hydrolysis of amino esters above and purified by HPLC using acetonitrile/0.1% aqueous trifluoroacetic acid as the mobile phase. The product was obtained by lyophilization. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.48 (d, 1H), 8.17 (m, 1H), 7.97 (m, 1H), 7.56 (m, 2H), 7.29−7.44 (m, 7H), 4.51 (bd, 2H), 4.48 (ddd, 1H), 2.24 (m, 2H), 1.99 (s, 3H), 1.85 (m, 2H). CIMS (NH_3): $C_{24}H_{25}N_3O_3S$ 436, (MH^+), 418, 319, 287, 194, 165. Anal. ($C_{24}H_{25}N_3O_3S$·1.26TFA): C, H, N.

4-Bromomethyl-2-phenylbenzoic, Methyl Ester. A solution of 1.81 g (7.47 mmol) of alcohol **13** and 0.66 g (7.47 mmol) lithium bromide in DMF (10 mL) was chilled in an ice−water bath, and then 0.71 mL (7.47 mmol) phosphorus tribromide was added. After 2 h the reaction was partitioned between water (200 mL) and Et_2O (200 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL), and then the combined Et_2O layers were washed with water (2 × 50 mL), brine, and dried over Na_2SO_4. Filtration and concentration resulted in 2.20 g (96%) of an oil that solidified on standing. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 1H), 7.35−7.47 (m, 4H), 7.27−7.34 (m, 2H), 4.52 (s, 2H), 3.64 (s, 3H). CIMS (NH_3): 322/324 ($M + NH_4^+$).

2-Phenyl-4-(3-pyridyloxymethyl)benzoic Acid, Methyl Ester (16). A solution of 3-hydroxypyridine 9.51 g (0.10 mol) in 50 mL of methanol was treated with 50.0 mL of 2.0 M aqueous KOH, and the solution was concentrated to dryness. The resulting solid was dried in a vacuum oven at over 100 °C to provide 13.25 g (99%) of the potassium salt. A suspension of 1.73 g (13.00 mmol) of this salt and 1.19 g (4.50 mmol) of 18-crown 6 in 20 mL of DME was cooled to −10 °C, and a solution of 3.05 g (10.00 mmol) of 4-bromomethyl-2-phenylbenzoic methyl ester in 10 mL of DME was added dropwise. Stirring continued for 24 h during which time the bath melted. The reaction mixture was poured into water and extracted 3 times with ethyl acetate, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (100 g, 60% ethyl acetate/hexanes) to provide 1.10 g (34%) of **16**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (m, 1H), 8.25 (dd, 1H), 7.87 (d, 1H), 7.42−7.50 (m, 2H), 7.35−7.42 (m, 3H), 7.27−7.41 (m, 3H), 7.19−7.26 (m, 2H), 5.18 (s, 2H), 3.64 (s, 3H). CIMS (NH_3): 320 (MH^+), 337 ($M + NH_4^+$).

2-Phenyl-4-(3-pyridyloxymethyl)benzoic Acid. A solution of 1.40 g (4.38 mmol) of **16** in 10 mL of methanol at room temperature was treated with 1.2 mL of a 4 N aqueous NaOH solution (5.26 mmol), and the mixture was heated to reflux for 20 h. The solution was cooled to ambient temperature and concentrated to remove the methanol. The solution was diluted with water and the pH adjusted to 5 with aqueous HCl. The solid was collected by filtration and dried in the air to give 1.31 g (98%) of 2-phenyl-4-(3-pyridyloxymethyl)benzoic acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.79 (bs, 1H), 8.41 (d, 1H), 8.21 (dd, 1H), 7.76 (d, 1H), 7.29−7.36 (m, 2H), 7.47 (s, 1H), 7.19−7.24 (m, 7H), 5.21 (s, 2H). CIMS (NH_3): 306 (MH^+), 323 ($M + NH_4^+$).

***N*-4-[(3-Pyridyloxymethyl)-2-phenyl]benzoylmethionine, Methyl Ester.** Using the general amino acid coupling procedure 2-phenyl-4-(3-pyridyloxymethyl)benzoic acid (225 mg, 0.74 mmol) provided 247 mg (74%) of the desired compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (m, 1H), 8.24 (dd, 1H), 7.75 (d, 1H), 7.48 (dd, 1H), 7.36−7.46 (m, 6H), 7.19−7.27

(m, 2H), 5.91 (d, 1H), 5.18 (s, 3H), 4.57 (ddd, 1H), 3.66 (s, 3H), 2.08 (m, 2H), 2.02 (s, 3H), 1.87−1.98 (m, 1H), 1.66−1.80 (m, 1H). APCI MS: 451 (MH^+).

***N*-4-[(3-Pyridyloxymethyl)-2-phenyl]benzoylmethionine (19).** Using the general amino ester hydrolysis procedure, the acid was prepared. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.66 (bs, 1H), 8.58 (d, 1H), 8.38 (d, 1H), 8.17 (dd, 1H), 7.30−7.56 (m, 10H), 5.29 (s, 2H), 4.29 (ddd, H), 2.23 (m, 2H), 1.98 (s, 3H), 1.84, (m, 2H). CIMS (NH_3): 437 (MH^+), 454 (M + NH_4^+). Anal. ($C_{24}H_{24}N_2O_4S\cdot1.14H_2O$): C, H, N.

3-Mercaptopyridine, Sodium Salt. A solution of 3-(*N*, *N*-dimethylaminocarbonyl)mecaprtopyridine (1.23 g, 6.70 mmol) in 10 mL of methanol was treated with 3.5 mL of 2 N aqueous NaOH (7.0 mmol), and the mixture was heated to reflux for 2 h. After cooling to room temperature, the mixture was concentrated to dryness to give the sodium salt of 3-mercaptopyridine which was used directly.[30]

2-Phenyl-4-(3-pyridylthiomethyl)benzoic Acid, Methyl Ester (17). A solution of 4-bromomethyl-2-phenylmethyl benzoate (916 mg, 3.00 mmol) in 10 mL of DME was cooled in an ice/acetone bath and treated with sodium 3-mercaptopyridine[30] (450 mg, 3.25 mg), and the mixture was stirred overnight. The brown mixture was poured into water and extracted with 3 portions of ethyl acetate. The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel, 40% ethyl acetate/hexanes gave 611 mg (60%) of **17**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, 1H), 8.45 (dd, 1H), 7.77 (d, 1H), 7.56 (dq, 1H), 7.33−7.42 (m, 3H), 7.16−7.31 (m, 5H), 4.13 (s, 2H), 3.63 (s, 3H). DCIMS (NH_3): 336 (MH^+, 100), 353 (M + NH_4^+, 40).

***N*-4-[(3-Pyridylthiomethyl)-2-phenyl]benzoylmethionine, Methyl Ester.** Using the general benzoate hydrolysis protocol, the title compound was prepared. The resulting aryl acid was coupled to L-methionine methyl ester HCl using the general amino acid coupling procedure. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (m, 1H), 8.45 (dd, 1H), 7.66 (d, 1H), 7.38 (ddd, 1H), 7.30−7.47 (m, 6H), 7.21 (m, 2H), 5.87 (bd, 1H), 4.65 (ddd, 1H), 4.14 (s, 2H), 3.67 (s, 3H), 2.06 (m, 2H), 2.01 (s, 3H), 1.92 (m, 1H), 1.74 (m, 1H). DCIMS (NH_3): 467 (MH^+). Anal. Calcd for $C_{25}H_{26}N_2O_3S_2$: C, 64.35; H, 5.62; N, 6.00. Found: C, 64.21; H, 5.61; N, 6.00.

***N*-4-[(3-Pyridylthiomethyl)-2-phenyl]benzoylmethionine (20).** *N*-4-[(3-Pyridylthiomethyl)-2-phenyl]benzoylmethionine, methyl ester, was converted to **20** by the general amino ester hydrolysis procedure. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (m, 1H), 8.39 (dd, 1H), 7.83 (m, 2H), 7.29−7.47 (m, 8H), 4.39 (s, 2H), 4.24 (m, 1H), 2.25 (m, 2H), 1.98 (s, 3H), 1.85 (m, 2H). DCIMS (NH_3): 453 (MH^+). Anal. ($C_{24}H_{24}N_2O_3S_2$): C, H, N.

2-Phenyl-4-(3-pyridylsulfonylmethyl)benzoic Acid, Methyl Ester (18). Trifluoroacetic anhydride (2.5 mL, 17.9 mmol) was dissolved in 10 mL of CH_2Cl_2, and the solution cooled in an ice bath. Hydrogen peroxide (0.56 mL of a 30% aqueous solution, 5.4 mmol) was slowly added (**caution**: a vigorous exothermic reaction occurs), and the mixture stirred until the internal temperature returned to <5 °C. A solution of pyridylthioether **17** (600 mg, 1.79 mmol) in 5 mL of CH_2Cl_2 was added dropwise, and stirring continued for 1 h at 0 °C and 30 min at room temperature. The mixture was diluted with 50 mL of ethyl ether and extracted with 50 mL of 2 N aqueous NaOH. The aqueous phase was extracted with an additional portion of ether, and the combined organic phases were extracted with 20% aqueous Na_2SO_3, water, brine. The solution was dried over Na_2SO_4, filtered, and concentrated to give 620 mg (94%) of **18** as an off-white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.91 (dd, 1H), 8.85 (dd, 1H), 7.91 (dq, 1H), 7.77 (d, 1H), 7.34−7.46 (m, 4H), 7.22 (dd, 1H), 7.14−7.19 (m, 2H), 7.08 (d, 1H), 4.43 (s, 2H), 3.63 (s, 3H). DCIMS (NH_3): 368 (MH^+, 90), 385 (M + NH_4^+, 100).

2-Phenyl-4-(3-pyridylsulfonylmethyl)benzoic Acid. Using the general aryl acid hydrolysis, **18** was converted to 2-phenyl-4-(3-pyridylsulfonylmethyl)benzoic acid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.91 (dd, 1H), 8.85 (dd, 1H), 8.13 (dq, 1H), 7.67 (m, 2H), 7.28−7.44 (m, 4H), 7.10−7.18 (m, 3H), 4.95 (s, 2H). DCIMS (NH_3): 354 (MH^+, 55), 371 (M + NH_4^+, 100).

***N*-4-[(3-Pyridylsulfonylmethyl)-2-phenyl]benzoylmethionine, Methyl Ester.** 2-Phenyl-4-(3-pyridylsulfonylmethyl)benzoic acid was coupled to L-methionine methyl ester HCl using the general amino acid coupling procedure, mp 152−154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.95 (d, 1H), 8.87 (dd, 1H), 7.94 (ddd, 1H), 7.66 (d, 1H), 7.43 (m, 4H), 7.30 (m, 2H), 7.21 (dd, 1H), 7.10 (d, 1H), 5.91 (bd, 1H), 4.66 (ddd, 1H), 4.42 (s, 2H), 3.68 (s, 3H), 2.08 (t, 2H), 2.02 (s, 3H), 1.93 (m, 1H), 1.75 (m, 1H). MS (DCI, NH_3) 516 (M + NH_4^+), 499 (MH^+). Anal. Calcd for $C_{25}H_{26}N_2O_5S_2$: C, 60.22; H, 5.25; N, 5.62. Found: C, 60.28; H, 4.94; N, 5.56.

***N*-4-[(3-Pyridylsulfonylmethyl)-2-phenyl]benzoylmethionine (21).** Prepared using the general amino ester hydrolysis procedure. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.68 (bs, 1H), 8.92 (m, 2H), 8.59 (bd, 1H), 8.18 (ddd, 1H), 7.68 (m, 1H), 7.32 (m, 7H), 7.18 (d, 1H), 4.94 (s, 1H), 4.29 (ddd, 1H), 2.22 (m, 2H), 1.99 (s, 3H), 1.85 (m, 2H). MS (DCI, NH_3): 502 (M + NH_4^+), 485 $(MH)^+$. Anal. ($C_{24}H_{24}N_2O_5S_2\cdot0.45H_2O$): C, H, N.

4-(3-Pyridylmethyloxy)-2-hydroxybenzoic Acid, Methyl Ester. A solution of methyl 2,4-dihydroxybenzoate **22** (16.82 g, 0.10 mol) and 3-chloromethylpyridine hydrochloride (19.68 g, 0.12 mol) in 150 mL of DMF was treated with KOH (14.66 g, 0.23 mol) in 50 mL of water, and the mixture was heated to 55−60 °C for 18 h. The mixture was treated with an additional 16.40 g (0.10 mol) of 3-chloromethylpyridine hydrochloride and KOH (9.67 g, 0.15 mol) in 20 mL of water, and heating continued for 6 h. The mixture was cooled and poured into 1.5 L of water, and the solid was collected by filtration. Recrystallization from 1:1 ethanol/water (~125 mL) provided 6.15 g (24%) of 4-(3-pyridylmethyloxy)-2-hydroxymethyl benzoate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.98 (s, 1H), 8.69 (bs, 1H), 8.61 (bd, 1H), 7.77 (d, 2H), 7.34 (dd, 1H), 6.53 (s, 1H), 6.50 (dd, 1H), 5.10 (s, 2H), 3.93 (s, 3H). MS (DCI, NH_3): 260 (MH^+).

4-(3-Pyridylmethyloxy)-2-trifluoromethanesulfonyloxybenzoic Acid, Methyl Ester. 4-(3-Pyridylmethyloxy)-2-hydroxymethyl benzoate (560 mg, 2.16 mmol) was dissolved in 3 mL of dry pyridine and cooled in an ice/acetone bath to −10 °C. Triflic anhydride (0.73 mL, 4.32 mmol) was added dropwise such that the temperature remained below 5 °C. The bath was removed after completion of the addition, and the mixture stirred at ambient temperature for 96 h. The mixture was quenched by pouring into 20 mL of water, and the pH was made basic by the addition of 2 N aqueous NaOH. The solution was extracted with 3 portions of ethyl acetate, and the combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (30 g, 1:1 ethyl acetate/hexanes) to give 685 mg (81%) of 4-(3-pyridylmethyloxy)-2-trifluoromethanesulfonyloxybenzoic acid, methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (d, 1H), 8.64 (dd, 1H), 8.09 (d, 1H), 7.77 (dt, 1H), 7.36 (dd, 1H), 7.04 (dd, 1H), 6.88 (d, 1H), 5.15 (s, 2H), 3.94 (s, 3H). MS (DCI, NH_3): 392 (MH^+), 409 (M + NH_4^+).

4-(3-Pyridylmethyloxy)-2-phenylbenzoic Acid, Methyl Ester (23). Using the same palladium-catalyzed coupling procedure used to prepare **12**, 4-(3-pyridylmethyloxy)-2-trifluoromethanesulfonyloxybenzoic acid, methyl ester, was converted to **23** in 83% yield after chromatography on silica gel. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (d, 1H), 8.62 (dd, 1H), 7.90 (d, 1H), 7.78 (dt, 1H), 7.24−7.43 (m, 6H), 6.98 (dd, 1H), 6.94 (d, 1H), 5.14 (s, 2H), 3.62 (s, 3H). MS (DCI, NH_3): 320 (MH^+), 337 (M + NH_4^+).

4-(3-Pyridylmethyloxy)-2-phenylbenzoic Acid. Prepared using the general benzoate hydrolysis. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.40 (bs, 1H), 8.69 (d, 1H), 8.56 (dd, 1H), 7.89 (dt, 1H), 7.78 (d, 1H), 7.28−7.48 (m, 6H), 7.09 (dd, 1H), 6.96 (d, 1H), 5.27 (s, 2H). MS (DCI, NH_3): 306 (MH^+), 323 (M + NH_4^+).

***N*-[4-(3-Pyridylmethyloxy)-2-phenyl]benzoylmethionine (24).** Employed the general amino acid coupling procedure

and the general methionine hydrolysis protocol to give **24**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.69 (bs, 1H), 8.55 (bd, 1H), 8.39 (d, 1H), 7.88 (dt, 1H), 7.40 (m, 6H), 7.07 (dd, 1H), 7.03 (d, 1H), 5.17 (s, 2H), 4.28 (ddd, 1H), 2.25 (m, 2H), 2.00 (s, 3H), 1.84 (m, 2H). MS (CI, NH_3): 454 ($M + NH_4^+$), 437 (MH^+), 419, 320, 288. Anal. ($C_{24}H_{24}N_2O_4S \cdot 0.23H_2O$): C, H, N.

Methyl-4-Hydroxymethyl-2-iodo benzoate (26). To a solution of dimethylaminoterphthalate **25** (3.07 g, 14.7 mmol) in 30 mL of a 2:1 mixture of THF/Et_2O at −78 °C was added neat DIBAL (6.27 g, 44.1 mmol, 3.0 equiv), and the reaction was warmed to 0 °C for 4 h and quenched with 5 mL of MeOH followed by 5 mL of saturated aqueous Na-tartrate. The reaction mixture stirred overnight and was taken up in EtOAc, and the layers were separated. The EtOAc layer was washed with 20 mL of saturated aqueous $NaHCO_3$ and brine and then dried over Na_2SO_4, filtered, evaporated to an oil, and purified by flash chromatography over silica gel (50% EtOAc/hex) to give 1.03 g (39%) of 4-hydroxymethyl-2-amino-methyl benzoate as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, J = 8.09 Hz, 1H), 6.68 (bs, 1H), 6.60 (dd, J = 8.46 Hz, 1.84, 1H), 4.62 (s, 2H), 3.86 (s, 3H). CIMS: $C_9H_{11}NO_3$ MH^+ 182.

To a stirred solution of 4-hydroxymethyl-2-amino-methyl benzoate (152 mg, 0.84 mmol) in 20 mL of acetone and 20 mL of 3 N H_2SO_4 at −15 °C was added $NaNO_2$ (1.34 g, 19.4 mmol) in 10 mL of H_2O dropwise by addition funnel. After the addition was complete, urea (210 mg, 3.52 mmol) was added followed by KI (5.11 g, 30.8 mmol) in 5 mL of H_2O, the ice bath was removed, and the reaction warmed to ambient temperature. The reaction was complete at 2 h and was quenched with 10 mL of saturated aqueous $NaHSO_3$, the acetone was then evaporated, and the aqueous layer was extracted with EtOAc 50 mL × 3. The EtOAc layers were combined and dried over Na_2SO_4, filtered, evaporated to an oil, and purified by flash chromatography (25% EtOAc/hex) to give 4.31 g (84%) of the 4-hydroxymethyl-2-iodo-methyl benzoate **26** as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 2 Hz, 1H), 7.82 (d, J = 8 Hz, 1H) 7.38 (dd, J = 8, 2 Hz, 1H), 4.72 (s, 2H), 3.86 (s, 3H). CIMS: $C_9H_9O_3I$ MH^+ 292.

Methyl-4-(3-Pyridyloxymethyl)-2-iodo benzoate (27). To a solution of **26** (6.01 g, 20.6 mmol) in 30 mL DMF were added $SOCl_2$ and LiCl. The reaction was stirred at 25 °C and was complete in 5 min. The reaction was taken up in EtOAc (100 mL), washed with H_2O (20 mL × 3) and saturated aqueous NaCl (10 mL × 4), dried over Na_2SO_4, filtered, and evaporated to give 4-chloromethyl-2-iodo-methyl benzoate as an oil that was carried on to the displacement reaction. The benzyl chloride (6.39 g, 20.6 mmol) was dissolved in toluene, 18-crown-6 (8.17 g, 30.9 mmol) was added followed by the potassium alkoxide of 3-hydroxypyridine, and the reaction was heated to reflux. The reaction was complete in 2 h, and the mixture was cooled, transferred to a separatory funnel, washed with H_2O (50 mL × 3), dried over Na_2SO_4, filtered, evaporated to an oil, and purified by flash chromatography over silica gel (gradient of 50% EtOAc/ hexanes to 75% EtOAc/ hexanes) to give 3.01 g (40%) of the pyridyl ether **27**. R_f = 0.3 (50% EtOAc/ hex). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (bs, 1H), 8.28 (t, J = 2.94 Hz, 1H), 8.08 (d, J = 1.11 Hz, 1H), 7.84 (d, J = 7.72 Hz, 1H), 7.47 (dd, J = 8.08, 1.83 Hz, 1H), 7.25 (d, J = 2.58 Hz, 1H), 5.18 (s, 2H), 3.94 (s, 3H)1.86 (bs, 1H). CIMS: $C_{14}H_{12}O_3NI$ MH^+ 370.

General Procedure for Preparation of Compounds with Modified Biphenyl Core (Compounds 29−37). 4-(3-Pyridyloxymethyl)-2-(2-trifluoromethylphenyl)benzoic Acid, Methyl Ester (28h). To a solution of the aryl iodide **27** (365 mg, 0.96 mmol) in 4 mL of DMF at 25 °C was added the catalyst $PdCl_2(PPh_3)_2$ (67 mg, 0.096 mmol, 10 mol %) followed by 2-trifluoromethyl boronic acid (366 mg, 1.93 mmol), and Cs_2CO_3 (629 mg, 1.93 mmol) and the reaction was heated to 80 °C for 12 h. The reaction was then cooled and taken up in 50 mL of EtOAc and washed with H_2O (5 × 10 mL), dried over Na_2SO_4, filtered, evaporated to an oil, and purified by radial chromatography using a gradient of 25% EtOAc/hexanes to 75% EtOAc/hexanes to give 261 mg (70%) of 4-(3-pyridyloxymethyl)-2-(2-trifluoromethylphenyl)methyl benzoate as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (bs, 1H), 8.26 (bs, 1H), 8.09 (d, J = 8.14 Hz, 1H) 7.72 (dd, J = 8.48, 0.69 Hz, 1H), 7.60−7.44 (m, 4H), 7.36−7.23 (m, 3H) 5.21 (s, 2H), 3.62 (s, 3H). CIMS: $C_{21}H_{16}O_3NF_3$ MH^+ 388.

4-(3-Pyridyloxymethyl)-2-(2-trifluoromethylphenyl)-benzoic Acid. 4-(3-Pyridyloxymethyl)-2-(2-trifluoromethylphenyl)methyl benzoate (241 mg, 0.62 mmol) was dissolved in 5 mL of MeOH, 1 mL of saturated aqueous LiOH was added, and the reaction was heated to reflux for 1 h. The reaction was then evaporated, and 1 mL of formic acid was added to acidify the crude product to pH = 3. The reaction was evaporated again to remove formic acid, and 5 mL of EtOAc and 1 mL of H_2O were added to completely solubilize the reaction mixture. The aqueous layer was extracted with EtOAc (5 mL × 3), and the EtOAc layers were combined and dried over Na_2SO_4, filtered, and evaporated to give 231 mg (100%) of 4-(3-pyridyloxymethyl)-2-(2-trifluoromethylphenyl)-benzoic acid as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (bs, 1H), 8.26 (bs, 1H), 8.15 (d, J = 8.13 Hz, 1H), 8.11−8.06 (m, 1H), 7.70 (d, J = 7.46 Hz, 1H), 7.55−7.40 (m, 3H), 7.40−7.20 (m, 3H), 5.21 (s, 2H). CIMS: $C_{20}H_{14}O_3NF_3$ MH^+ 374.

4-(3-Pyridyloxymethyl)-2-(2-trifluoromethylphenyl)-benzoylmethionine, Methyl Ester. 4-(3-Pyridyloxymethyl)-2-(2-trifluoromethylphenyl)benzoic acid (231 mg, 0.62 mmol) was dissolved in 4 mL of DMF, and HOOBT (152 mg, 0.93 mmol) was added followed by methionine methyl ester HCl (185 mg, 0.93 mmol), EDC (179 mg, 0.93 mmol), and TEA (0.18 mL, 1.24 mmol). The reaction stirred for 12 h at 25 °C and was taken up in EtOAc and washed 3 × 10 mL with H_2O and 3 × 10 mL with saturated aqueous NaCl. The EtOAc layer was dried over Na_2SO_4, filtered, evaporated to an oil, and purified by radial chromatography (25% EtOAc/hexanes to 50% EtOAc/hexanes to 5% MeOH/EtOAc) to give 291 mg (91%) of 4-(3-pyridyloxymethyl)-2-(2-trifluoromethylphenyl)benzoyl-methionine methyl ester as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (bs, 1H), 8.25 (bs, 1H), 8.02 (m, 3 H)7.84−7.73 (m, 2H), 7.57−7.53 (m, 3H), 7.36−7.34 (m, 1H), 7.24−7.22 (m, 1H), 6.16 (m, 1H), 5.18 (s, 2H), 4.63−4.58 (m, 1H), 3.78 (s, 3H), 2.56−2.53 (m, 1H), 2.30−2.16 (m, 1H), 1.98−1.88 (m, 4H contains methionine SMe), 1.80−1.70 (m, 1H). CIMS: $C_{24}H_{25}O_4N_2SF_3$ MH^+ 519.

4-(3-Pyridyloxymethyl)-2-(2-trifluoromethylphenyl)-benzoylmethionine (36). 4-(3-Pyridyloxymethyl)-2-(2-trifluoromethylphenyl)benzoyl] methionine methyl ester (291 mg, 0.56 mmol) was dissolved in 4 mL of THF, 1 mL of saturated aqueous LiOH and 1 mL of water were added, and the reaction stirred at room temperature. After 1 h, the reaction was thoroughly evaporated, and formic acid was added until pH = 3 was obtained at which time the reaction was evaporated to dryness and 10 mL of EtOAc was added followed by a minimum quantity of H_2O (∼1 mL) to completely solubilize the free acid and the water soluble salts, respectively. The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL × 3). The EtOAc layers were combined, dried over Na_2SO_4, filtered, evaporated, and then lyophilized to give 242 mg (86%) of the final acid **36** as an amorphous white solid. R_f = 0.1 (10% MeOH/$CHCl_3$ with 1.0% HOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 8.30 (bs, 1H), 8.14 (m, 1H), 7.76−7.33 (m, 9H), 5.28 (s, 2H), 4.87−4.40 (m, 1H), 2.40−2.06 (m, 2H), 2.04−1.94 (m, 4H contains methionine SMe), 1.92−1.80 (m, 1H). CIMS: MH^+ 505. Anal. ($C_{25}H_{23}O_4N_2SF_3 \cdot 0.65H_2O$): C, H, N. HRMS FAB Calcd m/z MH^+ for $C_{25}H_{23}O_4N_2SF_3$: 505.1409. Found: 505.1408.

4-(3-Pyridyloxymethyl)-2-(2-methylphenyl)benzoylmethionine (29). Compound **29** was prepared according to the general procedure for the preparation of compounds with modified biphenyl core as compd **36**. R_f = 0.1 (10% MeOH/$CHCl_3$ with 1.0% HOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 8.30 (d, 1H), 8.15 (dd, 1H), 7.68 (bd, 1H), 7.58−7.48 (m, 2H), 7.40−7.30 (m, 2H), 7.26−7.16 (m, 4H), 5.25 (s, 2H), 4.50−4.40 (m, 1H), 2.20−2.02 (m, 5H, contains both signals for o-tolyl methyl group), 2.00 (s, 3H. methionine methyl), 2.00−1.90 (m, 1H),

1.80−1.68 (m, 1H). CIMS: MH^+ 451. Anal. ($C_{25}H_{26}N_2O_4S\cdot 0.60EtOAc$): C, H, N.

4-(3-Pyridyloxymethyl)-2-(3-methylphenyl)benzoylmethionine (30). Compound **30** was prepared according to the general procedure for the preparation of compounds with a modified biphenyl core as in compound **36**. $R_f = 0.1$ (10% MeOH/$CHCl_3$ with 1.0% HOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 8.30 (d, 1H), 8.15 (d, 1H), 7.68−7.48 (m, 6H), 7.40−7.16 (m, 4H), 5.25 (s, 2H), 4.50−4.40 (m, 1H), 2.40 (s, 3H), 2.18−1.75 (m, 7H). CIMS: MH^+ 451. Anal. ($C_{25}H_{26}N_2O_4S\cdot 0.10CH_2Cl_2$): C, H, N.

4-(3-Pyridyloxymethyl)-2-(4-methylphenyl)benzoylmethionine (31). Compound **31** was prepared according to the general procedure for the preparation of compounds with a modified biphenyl core as in compound **36**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.30 (d, 1H), 8.15 (d, 1H), 7.58−7.44 (m, 4H), 7.40−7.28 (m, 3H), 7.24−7.10 (m, 3H), 5.25 (s, 2H), 4.42 (dd, 1H), 2.10−1.90 (m, 6H), 1.84−1.70 (m, 1H). CIMS: MH^+ 451. Anal. ($C_{25}H_{26}N_2O_4S\cdot 0.15CH_2Cl_2$): C, H, N.

4-(3-Pyridyloxymethyl)-2-(2-methoxyphenyl)benzoylmethionine (32). Prepared according to the general procedure for the preparation of compounds with a modified biphenyl core as in compound **36**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.30 (d, 1H), 8.15 (d, 1H), 7.68 (bd, 1H), 7.54−7.50 (m, 2H), 7.38−7.32 (m, 3H), 7.22 (dd, 1H), 7.04−6.98 (m, 2H), 5.25 (s, 2H), 4.42 (dd, 1H), 3.74 (s, 3H), 2.16−2.08 (m, 2H), 2.00 (s, 3H), 1.98−1.86 (m, 1H), 1.78−1.64 (m, 1H). CIMS: MH^+ 467. Anal. ($C_{25}H_{26}N_2O_5S\cdot 0.25H_2O$): C, H, N.

4-(3-Pyridyloxymethyl)-2-(3-methoxyphenyl)benzoylmethionine (33). Compound **33** was prepared according to the general procedure for the preparation of compounds with a modified biphenyl core as in compound **36**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.34 (s, 1H), 8.15 (d, 1H), 7.60−7.54 (m, 4H), 7.38−7.24 (m, 3H), 7.02−6.90 (m, 3H), 5.25 (s, 2H), 4.44 (dd, 1H), 3.82 (s, 3H), 2.18−1.90 (m, 6H), 1.92−1.82 (m, 1H). CIMS: MH^+ 467. Anal. ($C_{25}H_{26}N_2O_5S\cdot 0.55H_2O$): C, H, N.

4-(3-Pyridyloxymethyl)-2-(4-methoxyphenyl)benzoylmethionine (34). Compound **34** was prepared according to the general procedure for the preparation of compounds with a modified biphenyl core as in compound **36**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.34 (s, 1H), 8.15 (bs, 1H), 7.72−7.42 (m, 6H), 7.40−7.35 (m, 2H), 6.96−6.90 (m, 2H)5.25 (s, 2H), 4.44 (dd, 1H), 3.84 (s, 3H), 2.20−1.90 (m, 6H), 1.88−1.76 (m, 1H). CIMS: MH^+ 467. Anal. ($C_{25}H_{26}N_2O_5S$): C, H, N.

4-(3-Pyridyloxymethyl)-2-(2-chlorophenyl)benzoylmethionine (35). Compound **35** was prepared according to the general procedure for the preparation of compounds with a modified biphenyl core as in compound **36**. $R_f = 0.1$ (10% MeOH/$CHCl_3$ with 1.0% HOAc). ^{1}H NMR (500 MHz, CD_3OD): δ 8.31 (bs, 1H), 8.14 (d, $J = 4.4$ Hz, 1H), 7.70−7.34 (m, 9H), 5.29 (s, 2H), 4.48−4.45 (m, 1H), 2.30−2.22 (m 1 H), 2.20−2.15 (m, 1H), 2.05−1.95 (m, 4H,contains SMe), 1.86−1.76 (m, 1H). CIMS: MH^+ 471. Anal. ($C_{24}H_{23}O_4N_2SCl$): C, H, N. HRMS FAB Calcd *m/z* MH^+ for $C_{24}H_{23}O_4N_2SCl$: 471.1145. Found: 471.1165.

4-(3-Pyridyloxymethyl)-2-(2-ethylphenyl)benzoylmethionine (37). Compound **37** was prepared according to the general procedure for the preparation of compounds with a modified biphenyl core as in compound **36**. $R_f = 0.1$ (10% MeOH/$CHCl_3$ with 1.0% HOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 8.30 (bs, 1H), 8.14 (d, $J = 4.4$ Hz, 1H), 7.71−7.17 (m, 9H), 5.29 (s, 2H), 4.87−4.43 (m, 1H), 2.54−2.37 (m 2 H), 2.24−1.84 (m, 7H, contains SMe), 1.90−1.82 (m, 1H), 1.04 and 0.97 (rotameric triplets, $J = 7.3$ Hz, 3H). CIMS: MH^+ 465. Anal. ($C_{26}H_{28}O_4N_2S\cdot 022H_2O$): C, H, N. HRMS FAB Calcd *m/z* MH^+ for $C_{26}H_{28}O_4N_2S$: 465.1848. Found: 465.1865.

4-(3-Pyridyloxymethyl)-2-(2-methylphenyl)benzoylglycine (38). Compound **38** was prepared according to the general procedure for the preparation of compounds with a modified biphenyl core as in compound **36** except that glycine methyl ester HCl was substituted for L-methionine methyl ester HCl in the coupling. $R_f = 0.15$ (10% MeOH/$CHCl_3$ with 1.0% HOAc). ^{1}H NMR (500 MHz, d_6DMSO): δ 8.37−8.33 (m, 2H), 8.17 (dd, $J = 4.7$, 1.4 Hz, 1H), 7.59 (d, $J = 8.14$ Hz, 1H), 7.53 (dd, $J = 8.14$, 1.7 Hz, 1H), 7.46 (ddd, $J = 4.41$, 3.05, 1.35 Hz, 1H), 7.34 (dd, $J = 8.48$, 5.08 Hz, 1H), 7.28 (d, $J = 1.0$ Hz, 1H), 7.21−7.06 (m, 4H), 5.27 (s, 2H), 3.68 (d, 5.8 Hz, 2H)2.04 (s, 3H). CIMS: MH^+ 377. Anal. ($C_{22}H_{20}O_4N_2\cdot 1.50H_2O$): C, H, N.

***N*-Methyl-*N*-4-(3-pyridylaminomethyl)-2-phenylbenzoylmethionine (39).** This amino acid modification was accomplished using the 3-aminopyridyl analogue of **23** followed by the general benzoate hydrolysis procedure, the general amino acid coupling procedure, and the general amino ester hydrolysis procedure. ^{1}H NMR (300 MHz, CD_3OD): δ 7.94 (d, 1H), 7.78 (d, 1H), 7.40 (m, 7H), 7.20 (m, 1H), 7.11 (m, 1H), 5.20, 4.52 (both m, total 1H), 4.47 (s, 2H), 2.85−1.66 (m, 10H). MS (DCI/NH_3): 450 (MH^+). Anal. ($C_{25}H_{27}N_3O_3S\cdot 0.65HCl$): C, H, N.

***N*-4-(3-Pyridylaminomethyl)-2-phenyl)benzoylmethionine Sulfone (40).** This amino acid modification was accomplished using the 3-aminopyridyl analogue of **23** followed by the general benzoate hydrolysis procedure, the general amino acid coupling procedure, and the general amino ester hydrolysis procedure. ^{1}H NMR (300 MHz, D_2O): δ 7.95 (m, 1H), 7.92 (m, 1H), 7.40−7.64 (m, 10H), 4.58 (s, 2H), 4.22 (ddd, 1H), 3.01 (s, 3H), 2.71 (m, 1H), 2.48 (m, 1H), 2.17 (m, 1H), 1.93 (m, 1H). FAB MS: 468 (MH^+); FAB(−) 466 (MH^-). Anal. ($C_{24}H_{25}N_3O_5S\cdot 1.30H_2O$): C, H, N.

***N*-4-(3-Pyridylaminomethyl)-2-phenyl)benzoyl-D-methionine (41).** This amino acid modification was accomplished using the 3-aminopyridyl analogue of **23** followed by the general benzoate hydrolysis procedure, the general amino acid coupling procedure, and the general amino ester hydrolysis procedure. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.75−1.91 (m, 2H), 1.98 (s, 3H), 2.16−2.27 (m, 2H), 4.27 (m, 1H), 4.39 (d, $J = 6.4$ Hz, 2H), 6.62 (t, $J = 6.4$ Hz, 1H), 6.90 (ddd, $J = 1.4$, 2.7, 8.5 Hz, 1H), 7.03 (dd, $J = 4.6$, 8.3 Hz, 1H), 7.30−7.41 (m, 8H), 7.40 (d, $J = 4.1$ Hz, 1H), 7.97 (d, $J = 2.7$ Hz, 1H), 8.50 (d, $J = 7.8$ Hz, 1H), 12.65 (br s, 1H). MS (DCI): *m/e* 436 (MH^+). Anal. ($C_{24}H_{25}N_3O_3S\cdot 0.90H_2O$): C, H, N.

***N*-4-(3-Pyridyloxymethyl)-2-phenylbenzoyl-*O*-methylhomoserine (42).** This amino acid modification was accomplished beginning with **23** followed by the general benzoate hydrolysis procedure, the general amino acid coupling procedure, and the general amino ester hydrolysis procedure. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.57 (d, 1H), 8.43 (d, 1H), 8.22 (d, 1H), 7.60 (m, 1H), 7.53 (m, 2H), 7.40 (m, 7H), 5.33 (s, 2H), 4.26 (m, 1H), 3.08 (s, 3H), 3.07 (m, 2H), 1.90 (m, 1H), 1.75 (m, 1H). MS (APCI): 421 (MH^+). Anal. ($C_{24}H_{24}N_2O_5\cdot 0.50H_2O$): C, H, N.

***N*-4-(3-Pyridyloxymethyl)-2-phenylbenzoylnorleucine (43).** This amino acid modification was accomplished beginning with **23** followed by the general benzoate hydrolysis procedure, the general amino acid coupling procedure, and the general amino ester hydrolysis procedure. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.60 (d, 1H), 8.53 (d, 1H), 8.37 (d, 1H), 7.90 (dd, 1H), 7.70 (dd, 1H), 7.52 (d, 1H), 7.51 (s, 1H), 7.42 (m, 3H), 7.38 (m, 3H), 5.38 (s, 2H), 4.16 (m, 1H), 1.60 (m, 2H), 1.20 (m, 2H), 1.10 (m, 2H), 0.82 (t, 3H). MS (DCI/NH_3): 419 (MH^+). Anal. ($C_{25}H_{26}N_2O_4\cdot 0.50H_2O$): C, H, N.

***N*-4-(3-Pyridyloxymethyl)-2-phenylbenzoyl-*S*-methylcysteine (44).** This amino acid modification was accomplished beginning with **23** followed by the general benzoate hydrolysis procedure, the general amino acid coupling procedure, and the general amino ester hydrolysis procedure. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.77 (d, 1H), 8.59 (d, 1H), 8.35 (d, 1H), 7.85 (dd, 1H), 7.63 (dd, 1H), 7.50 (m, 5H), 7.35 (m, 3H), 5.38 (s, 2H), 4.42 (m, 1H), 2.89 (dd, 1H), 2.72 (dd, 1H), 2.04 (s, 3H). MS (DCI/NH_3): 423 (MH^+). Anal. ($C_{23}H_{22}N_2O_4S\cdot 0.20H_2O$): C, H, N.

***N*-4-(3-Pyridyloxymethyl)-2-phenylbenzoylglutamine (45).** This amino acid modification was accomplished beginning with **23** followed by the general benzoate hydrolysis procedure, the general amino acid coupling procedure, and the general amino ester hydrolysis procedure. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.79 (m, 1H), 1.95 (m, 1H), 2.09 (m, 2H), 4.18 (m, 1H), 5.42 (s, 2H), 6.80 (bs, 1H), 7.25 (m, 2H),

7.35 (m, 3H), 7.45 (m, 2H), 7.55 (m, 3H), 7.86 (dd, $J = 5.2$, 8.5 Hz, 1H), 8.10 (d, $J = 7.7$ Hz, 1H), 8.46 (d, $J = 4.4$ Hz, 1H), 8.69 (d, $J = 8.1$ Hz, 1H), 8.71 (bs, 1H). MS (DCI): *m/e* 434 (MH^+). Anal. ($C_{24}H_{23}N_3O_5 \cdot 2.40HCl$): C, H, N.

4-(3-Pyridylcarbonylamino)-2-(2-methylphenyl)-methionine (46). To a stirred solution of 4-amino-2-(2-methylphenylbenzoyl)methionine methyl ester (85 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) were added nicotinic acid chloride hydrochloride (81 mg, 0.46 mmol) and saturated $NaHCO_3$ (2 mL). The reaction was stirred at room temperature for 2 h. TLC (CH_2Cl_2/ MeOH 20:1) showed the formation of new products. The reaction was diluted with CH_2Cl_2 (10 mL), the layers separated, and the organic layer was washed with saturated $NaHCO_3$ (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (CH_2Cl_2/MeOH 50:1) and crystallization from EtOAc gave 87 mg (80%) of a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.10 (dd, 1 H, $J = 2.4$, 1.0 Hz), 8.80 (dd, 1 H, $J = 4.7$, 1.7 Hz), 8.21 (ddd, 1 H, $J = 7.8$, 2.4, 1.7 Hz), 8.09−8.00 (m, 2 H), 7.71−7.66 (m, 1 H), 7.64−7.61 (m, 1 H), 7.46 (ddd, 1 H, $J = 7.8$, 4.7, 1.0 Hz), 7.35−7.20 (m, 4 H), 5.92 (bd, $J = 7.5$ Hz), 4.67−4.57 (m, 1 H), 3.66 (s, 3 H), 2.23−2.01 (4s and m, 8 H), 2.13−2.00 (m, 1 H), 1.65−1.52 (m, 1 H). MS: *m/z* 478 (MH^+, 100). To a stirred solution of the methionine methyl ester (140 mg, 0.29 mmol) in THF (6 mL) was added a solution of $LiOH \cdot H_2O$ (37 mg, 88 mmol) in H_2O (1 mL), and the resulting solution stirred for 2 h at ambient temperature. TLC analysis (20:1 CH_2Cl_2/MeOH) showed the formation of new products. The reaction was concentrated in vacuo, 1 N HCl was added to the residue, and the resulting precipitate was filtered and washed with H_2O. Lyophilization gave 87 mg (59%) of a white powder. ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C): δ 9.12 (d, $J = 2.4$ Hz, 1 H), 8.74 (dd, $J = 4.9$, 1.9 Hz, 1 H), 8.31 (dt, $J = 7.9$, 1.8 Hz, 1 H), 7.84 (dd, $J = 7.9$, 1.8 Hz, 1 H), 7.63 (s, 1 H), 7.61 (d, $J = 2.4$ Hz, 1 H), 7.54 (dd, $J = 7.9$, 4.9 Hz, 1 H), 7.45 (d, $J = 7.9$ Hz, 1 H), 7.23−7.21 (m, 2 H), 7.19−7.15 (m, 2H), 4.30−4.26 (m, 1 H), 2.28−2.22 (m, 1 H), 2.20−2.14 (m, 1 H), 2.11 (s, 3 H), 1.98 (s, 3 H), 1.88−1.81 (m, 1 H), 1.75−1.68 (m, 1 H). MS: *m/z* 464 (MH^+, 100), 446. Anal. ($C_{25}H_{25}N_3O_4S \cdot HCl \cdot 0.5H_2O$): C, H, N.

4-(3-Pyridylmethylamino)-2-(2-methylphenyl)benzoyl-methionine (47). 4-Amino-2-(2-methylphenylbenzoyl)methionine methyl ester (180 mg, 0.48 mmol) and 3-pyridine carboxaldehyde (55 mg, 0.51 mmol) were combined in 4 mL of MeOH, and sodium cyanoborohydride (48 mg, 0.77 mmol) was added followed by 100 mg of crushed molecular sieves. The reaction was adjusted to pH = 6 with acetic acid and stirred at 25 °C. After 3 h the reaction was concentrated and transferred directly to a column of silica gel and purified by flash chromatography (5% MeOH/ EtOAc) to give 182 mg (82%) of 4-(3-pyridylmethylamino)-2-(2-methylphenyl)benzoylmethionine methyl ester as an oil that solidified after standing. $R_f = 0.19$ (5% MeOH/EtOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 8.54 (d, $J = 2.4$ Hz, 1H), 8.40 (dd, $J = 5.1$, 1.3 Hz, 1H), 7.84 (bd, $J = 8.4$ Hz, 1H), 7.65−7.55 (m, 1H), 7.40 (dd, $J = 7.8$, 4.7 Hz, 1H), 7.30−7.10 (m, 4H), 6.66 (dd, $J = 8.8$, 2.3 Hz, 1H), 6.37 (d, $J = 2.3$ Hz, 1H), 4.45 (s, 2H), 3.64 (s, 3H), 2.10−1.98 (m, 8H), 1.90−1.78 (m, 1H), 1.65−1.55 (m, 1H). CIMS: MH^+ 464. HRMS FAB Calcd *m/z* MH^+ for $C_{26}H_{29}O_3N_3S$: 464.2008. Found: 464.2023.

The methionine methyl ester (102 mg, 0.22 mmol) was converted to the methionine acid using the general amino ester hydrolysis protocol and then lyophilized as the HCl salt from MeCN/H_2O to give 68 mg (68%) of **47** as a light tan solid. $R_f = 0.18$ (10% MeOH/$CHCl_3$ with 0.25% HOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 8.81 (bs, 1H), 8.76 (bd, $J = 11.8$ Hz, 1H), 8.64−8.61 (m, 1H), 8.07 (dd, $J = 8.5$, 6.1 Hz, 1H), 7.65−7.58 (m, 1H), 7.28−7.18 (m, 4H), 6.70 (dd, $J = 8.5$, 2.4 Hz, 1H), 6.40 (d, $J = 2.3$ Hz, 1H), 4.68 (s, 2H), 4.44−4.38 (m, 1H), 2.14−1.99 (m, 8H), 1.90−1.80 (m, 1H), 1.65−1.55 (m, 1H). CIMS: MH^+ 450. Anal. ($C_{25}H_{28}O_3N_3SCl \cdot 1.10H_2O$ and 0.80 HCl): C, H, N. HRMS FAB Calcd *m/z* MH^+ for $C_{25}H_{27}O_3N_3S$: 450.1851. Found: 450.1864.

***N*-4-(3-Pyridylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (48).** Compound **48** was synthesized in identical fashion to **15** except with the *o*-tolyl biphenyl core present in **29**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.08 (d, 1H), 7.97 (d, 1H), 7.72 (d, 1H), 7.46 (d, 1H), 7.43 (dd, 1H), 7.17 (m, 3H), 7.10 (m, 2H), 7.03 (dd, 1H), 6.89 (m, 1H), 6.55 (t, 1H), 4.37 (d, 2H), 4.20 (m, 1H), 2.00−2.24 (m, 2H), 1.99 (bs, 3H), 1.93 (s, 3H), 1.63−1.88 (m, 2H). CIMS: 450 (MH^+). Anal. ($C_{25}H_{27}N_3O_3S \cdot 0.30HCl$): C, H, N.

***N*-4-(3-Pyridylthiomethyl)-2-(2-methylphenyl)benzoyl-methionine (49).** Compound **49** was synthesized in identical fashion to **20** except with the *o*-tolyl biphenyl core present in **29**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.55 (bs, 1H), 8.50 (d, 1H), 8.37 (dd, 1H), 8.11 (d, 1H), 7.78 (dt, 1H), 7.43 (s, 2H), 7.30 (dd, 1H), 7.18 (m, 2H), 7.11 (m, 2H), 7.04 (bs, 1H), 4.36 (s, 2H), 4.20 (ddd, 1H), 2.00−2.22 (m, 2H), 1.96 (bs, 3H), 1.94 (s, 3H), 1.63−1.88 (m, 2H). CIMS: 467 (MH^+). Anal. ($C_{25}H_{26}N_2O_3S_2$): C, H, N.

In Vitro Enzyme Assays. In vitro IC_{50} data were determined against FTase and GGTase 1 (purified from bovine brain) using the SPA assay (scintillation proximity assay, Amersham, Arlington Heights). The substrates used were ^{3}H-farnesyl pyrophosphate and a biotin-linked Kras(B) decapeptide (KKSKTKCVIM, for FTase) or the CVLL decapeptide for GGTase 1. The radioactivity captured by the SPA beads were counted by a Packard Topcount, and data were stored and analyzed in an Oracle-based database.

Cellular Assays for Inhibition of Ha-Ras Processing: Subconfluent NIH3T3 Ras transformed cells were used for the Ras processing assay. Briefly, cells were dosed with various compounds, and lysates were prepared. They were boiled for 5 min in the Laemmli sample buffer, and proteins were resolved on a 15% Tris-glycine gel (Bio-Rad, Richmond, CA). Proteins were then transferred to nitrocellulose membranes. The blots were probed with antibody Y13−238 to Ras purified from hybridoma. Ras bands were visualized by the ECL technique (ECL kit, Amersham, Arlington Heights, IL), and signals were quantified by densitometry using the image analysis program Image-Pro Plus (Media Cybernetics, Silver Spring, MD).

Acknowledgment. The authors thank Professors A. D. Hamilton and S. M. Sebti for fruitful discussions during the course of this research. The authors also thank Dr. Paul West, Dr. Tom Pagano, Dr. Xiaolin Zhang, and Ms. Carmina Presto of the structural chemistry department for their assistance in obtaining NMR and mass spectra, Mr. William Arnold for large-scale preparation of several key intermediates, and Dr. Stefan Loren for preparing several boronic acids used in the biphenyl core modification study.

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JM980298S