Second-Generation Peptidomimetic Inhibitors of Protein Farnesyltransferase Demonstrating Improved Cellular Potency and Significant in Vivo Efficacy

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The synthesis and evaluation of analogues of previously reported farnesyltransferase inhibitors, pyridyl benzyl ether **3** and pyridylbenzylamine **4**, are described. Substitution of **3** at the 5-position of the core aryl ring resulted in inhibitors of equal or less potency against the enzyme and decreased efficacy in a cellular assay against Ras processing by the enzyme. Substitution of **4** at the benzyl nitrogen yielded **26**, which showed improved efficacy and potency and yet presented a poor pharmacokinetic profile. Further modification afforded **30**, which demonstrated a dramatically improved pharmacokinetic profile. Compounds **26** and **29** demonstrated significant in vivo efficacy in nude mice inoculated with MiaPaCa-2, a human pancreatic tumor-derived cell line.

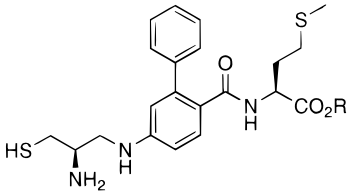
Introduction

Ras proteins are key elements in signal transduction from cell-surface receptor tyrosine kinases through the cytoplasm to the cell nucleus.[1] Mutations in *ras* genes lead to constitutively activated Ras proteins resulting in uncontrolled cell growth.[2,3] Mutated Ras proteins are found in a number (30−50%) of human tumors including ∼30% of lung cancers, 50% of colon cancers, and 90% of pancreatic cancers.[4] Therefore, inhibition of oncogenic Ras function should be a viable therapy for these types of tumors.[5−7]

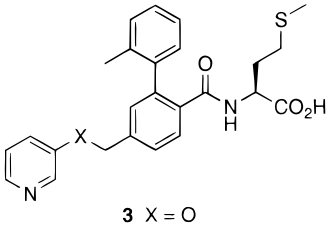
Newly synthesized Ras proteins undergo a series of posttranslational modifications to provide the active species.[8−12] The first modification occurs by the transfer of a farnesyl group from farnesylpyrophosphate to the cysteine near the C-terminus (CAAX box). Farnesylation is followed by proteolytic cleavage of the AAX group and subsequent O-methylation of the new C-terminus. This truncated peptide migrates to the cell surface and anchors to the membrane using the attached farnesyl chain. **The only step required for activation of Ras is the farnesylation of the cysteine thiol.** This reaction is catalyzed by the enzyme protein farnesyltransferase (FTase). Inhibition of this enzyme has been shown to reduce Ras function both in vitro and in vivo.[13−24] Therefore, the inhibition of FTase represents an intriguing target for cancer chemotherapy.[25,26]

We recently reported[27] a series of compounds related to FTI-276, **1**, a potent inhibitor of FTase (Chart 1).[28,29]

Chart 1. Structures of FTase Inhibitors **1**−**4**



1 R = H
2 R = Me



3 X = O
4 X = NH

We successfully replaced the metabolically labile cysteine with a 3-pyridyl substituent and also determined that ortho-substitution of the biphenyl moiety with sterically demanding groups provided an unexpected yet critical boost in potency. Compound **3**, with a 3-oxypyridyl linkage and an *o*-tolylbiphenyl spacer, possesses an IC_{50} value of 0.4 nM. The ability of **3** to prevent farnesylation of Ras in whole cells (Ras processing, ED_{50} = 0.35 μM) equaled that of FTI-277, **2**, an ester prodrug of **1**. Although equipotent to FTI-276, compound **3** was not active against human tumor xenografts (MiaPaCa) in nude mice. We ascribed the inactivity of **3** to several factors. Pharmacokinetic studies in the rat demonstrated a very short plasma half-life, and the overall oral bioavailability (6%) was very poor. In addition, **3**

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may not possess activity sufficient to inhibit the growth of such an aggressive human tumor cell line. Therefore, we set out to improve upon **3** by augmenting its potency and pharmacokinetic profile. Our efforts concentrated on altering the heterocyclic ring electron density and increasing the lipophilicity of **3** and its aminopyridyl analogue **4**. These alterations included substitution on the biphenyl core of **3**, appending groups to the amino linkage of **4**, or replacement of the pyridine ring altogether. The results of our work are presented here.

Chemistry

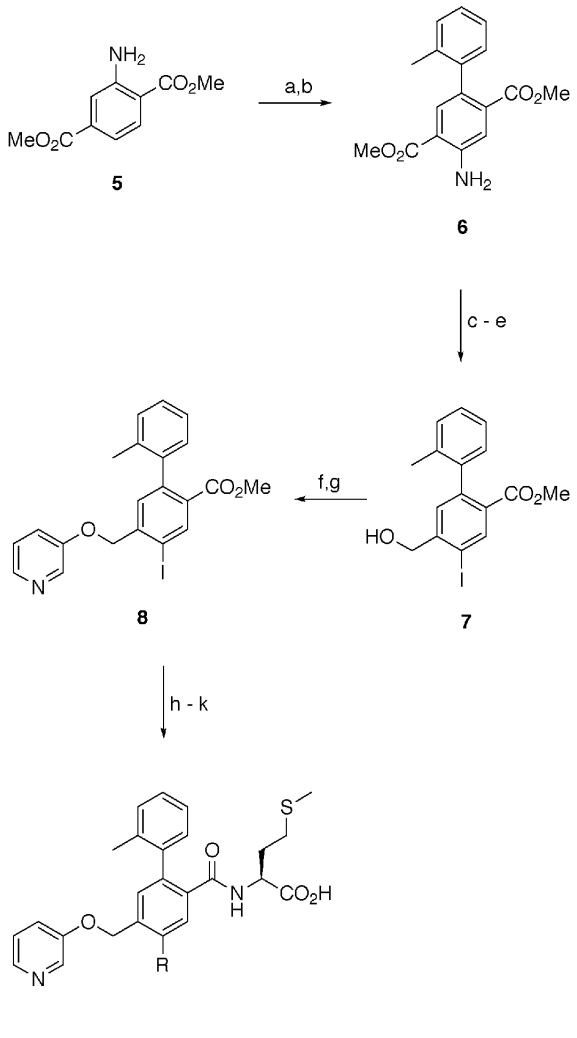
Analogues of **3** substituted at the 5-position of the biphenyl ring were prepared by Suzuki coupling of iodide **7** with boronic acids or alkylboranes according to published procedures (Scheme 1).[30] The boronic acids used were commercially available. The boranes were either purchased (triethylborane, tributylborane, and benzyl-9-BBN), prepared by hydroboration (tripentylborane), or prepared by reaction of the appropriate lithium or Grignard reagents with 9-methoxy-9-BBN (isobutyl, phenethyl, cyclohexylmethyl).[31] The coupled benzoate esters were converted to the final compounds as previously described.[27]

Analogues of amine **4** were prepared in the following manner. The appropriate amino heterocycle was reacted with an aldehyde to form the Schiff base. Reduction with $NaBH_4$ or $Na(OAc)_3BH$ provided the secondary amine, which was deprotonated with *n*-BuLi or sodium bis(trimethylsilylamide) and coupled to a halomethylbiphenyl ester[27] as shown in Scheme 2. 5-Flouro-3-aminopyridine was prepared from the 5-fluoronicotinic acid[32] as shown in Scheme 4, while the pyrimidine analogue was made according to the route outlined in Scheme 5. The amides **23** and **24** were prepared by acylation of 3-aminopyridine with benzoyl or phenylacetyl chloride. The benzenesulfonamide arose from sulfonylation of 3-aminopyridine with benzenesulfonyl chloride. Each of these compounds was deprotonated and reacted with the bromomethylbiphenyl ester using the same procedure as the secondary amines. Thiazole amines were prepared analogously to the amino heterocycles and reacted with the bromide using diisopropylethylamine as an HCl scavenger. Conversion to the final compounds was straightforward.[27]

Results and Discussion

The results of modification of **3** at the 5-position are summarized in Table 1. Examination of the data for **3**, **9**, **10**, and **11** reveals that aryl substitution at the 5-position was severely detrimental to potency against the enzyme with respect to the parent compound, whereas the activity dropped 2−3 orders of magnitude. We were less discouraged by the results of alkyl substitution. Compounds **12**−**15** demonstrate that small alkyl substituents are far better tolerated and that slightly longer, unbranched groups are somewhat favored, suggesting the presence of a narrow hydrophobic pocket. The benzyl and phenethyl analogues of **3** are equipotent to the parent compound. The diminished activity of the similarly lipophilic, yet more sterically demanding, cyclohexylmethyl analogue **18** adds credence to our postulation of a more narrow lipophilic pocket. Each of the 5-substituted analogues of **3** was notably less active in the whole-cell Ras processing assay (ED_{50}'s ≥ 1 μM).

Scheme 1. Synthesis of FTase Inhibitors Containing an Ether Linkage[a]

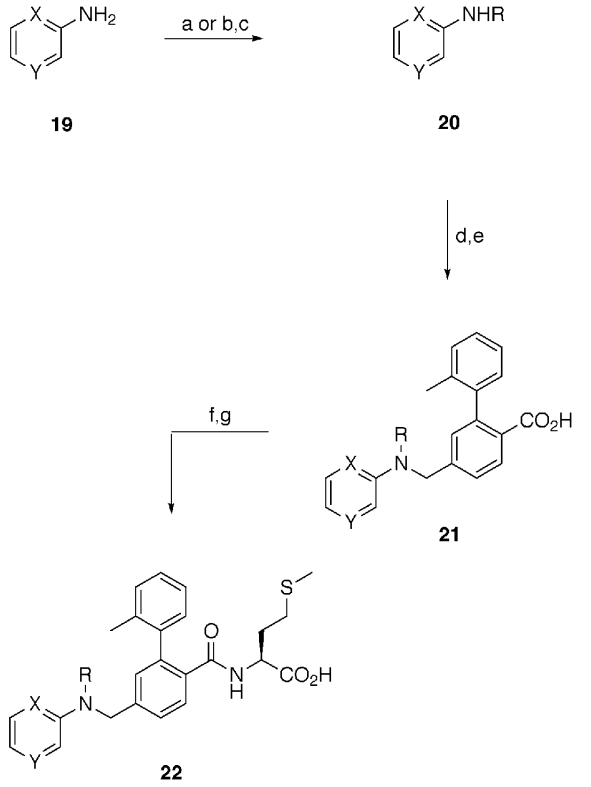


9 R = *p*-tolyl
10 R = 3,5-dichlorophenyl
11 R = 2-thienyl
12 R = butyl
13 R = ethyl
14 R = isobutyl
15 R = n- pentyl
16 R = benzyl
17 R = phenethyl
18 R = cyclyohexylmethyl

[a] Reagents: (a) Br_2, pyridine/CH_2Cl_2; (b) $Pd(OAc)_2$, PPh_3, *o*-tolylboronic acid, aq Na_2CO_3, toluene, reflux; (c) $NaNO_2$, NaI, 3 N HCl, acetone; (d) aq NaOH, THF/MeOH; (e) BH_3·THF; (f) PPh_3/CBr_4, CH_2Cl_2; (g) K-O-3-Pyr, $BnNEt_3Br$, CH_2Cl_2; (h) R-$B(OH)_2$, $Pd(OAc)_2$, PPh_3, aq Na_2CO_3, toluene, reflux; or R_3B/R-9-BBN, $Cl_2PdDPPF$, base, DMF, 65 °C; (i) NaOH, aq EtOH, reflux; (j) Met(OMe)·HCl, NEt_3, EDCI, HOBt, DMF; (k) LiOH, aq THF/MeOH.

The results of modifications of **4**, the amine series, are summarized in Table 2. Acylation or sulfonylation of the nitrogen resulted in significant reduction in potency against the enzyme (compare **23**−**25** with **4**). The benzoyl (53 nM) and phenylacetyl (39 nM) substituted analogues were ∼100 times less active against the enzyme than the NH compound. The sulfonyl derivative **25** was slightly better at 7 nM, a loss of only 15-fold. The reverse effect was observed with N-alkylation. With an IC_{50} value of 100 pM, benzyl derivative **26** demonstrates a 4-fold increase in potency over the parent compound, suggesting that the reduction in potency observed for the acylated analogues was due principally to the electron-withdrawing nature of the substituents.

Scheme 2. Synthesis of FTase Inhibitors Containing an Amino Linkage[a]



23	X=CH	Y=N	R=COPh
24	X=CH	Y=N	R=$COCH_2Ph$
25	X=CH	Y=N	R=SO_2Ph
26	X=CH	Y=N	R=Bn
27	X=CH	Y=N	R=CH_2c-Hex
28	X=N	Y=N	R=Bn
29	X=CH	Y=CH	R=Bn
30	X=CH	Y=CH	R=3,5-DiF-Bn
31	X=CH	Y=N	R=3,5-DiF-Bn

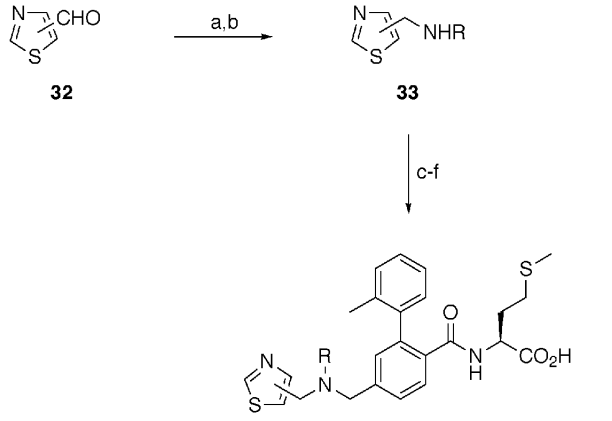
[a] Reagents: (a) R-COCl or R-SO_2Cl, NEt_3, CH_2Cl_2; (b) RCHO, toluene, reflux ($-H_2O$); (c) $NaBH_4$, EtOH; (d) *n*-BuLi or NaHMDS, THF, then methyl 4-bromomethyl-2-(2-methylphenyl)benzoate; (e) NaOH, aq EtOH, reflux; (f) Met(OMe)·HCl, NEt_3, EDCI, HOBt, DMF; (g) LiOH, aq THF/MeOH.

The improvement in cellular potency was even more dramatic, in that the ED_{50} for **26** was measured to be 13 nM, a 20-fold increase. Thus **26** is the first compound we prepared possessing whole-cell activity greater than that of our original lead, FTI-277.

Despite the substantial improvement in the activity demonstrated by **26**, the pharmacokinetic behavior remained poor. The iv half-life was less than 1 h (see column 7, Table 2), and the systemic area under the curve (AUC) was well below 1 μg·h/mL upon intraduodenal (id) dosing, though the portal vein AUC was reasonable at 3 μg·h/mL. The discrepancy in AUC values is indicative of dramatic first-pass effects in the liver. In fact, after dosing compound **26** in rats over 80% of the dose can be recovered from the bile as unchanged drug.

In an attempt to improve upon the pharmacokinetic profile of **26**, we prepared the cyclohexylmethyl analogue **27** and fluoro-substituted pyridine analogue **40**. The rationale was that the cyclohexyl group might add some additional lipophilicity while the 5-fluoro derivative should be less basic than the parent pyridine. Both of these new substrates proved to be essentially equipotent with **26**. However, they each demonstrated a reduced plasma half-life, and both reduced iv and systemic AUCs compared to **26**.

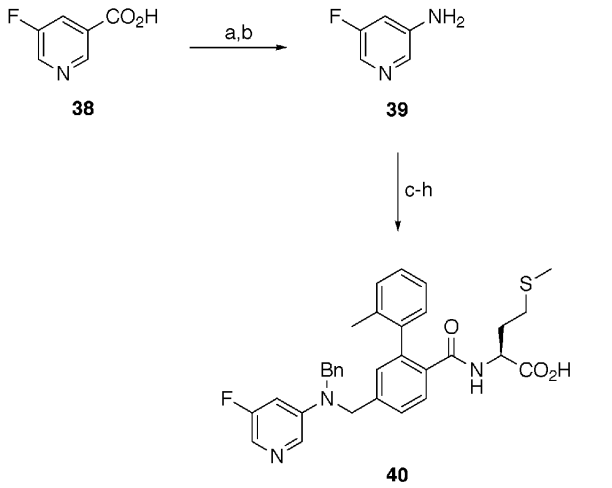
Scheme 3. Synthesis of FTase Inhibitors Containing a Variously Linked Thiazole Moiety[a]



34	2-thiazolyl	R=Bn
35	4-thiazolyl	R=Bn
36	5-thiazolyl	R=Bn
37	5-thiazolyl	R=3,5-DiF-Bn

[a] Reagents: (a) R-NH_2 toluene, reflux ($-H_2O$); (b) $NaBH_4$, EtOH; (c) methyl 4-bromomethyl-2-(2-methylphenyl)benzoate, Et-$NiPr_2$, CH_3CN, rt−60 °C; (d) NaOH, aq EtOH, reflux; (e) Met(OMe)·HCl, NEt_3, EDCI, HOBt, DMF; (f) LiOH, aq THF/MeOH.

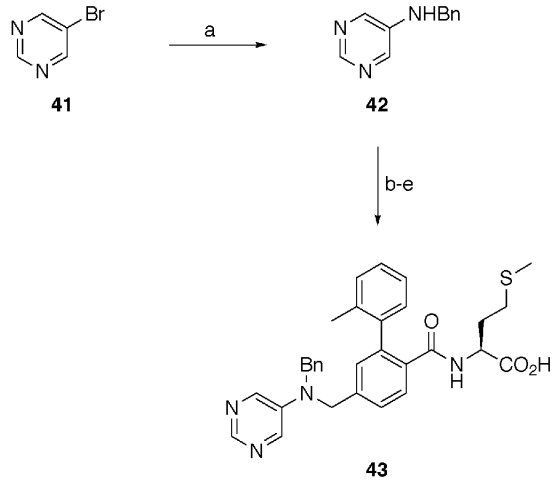
Scheme 4. Synthesis of FTase Inhibitor 3-Fluoropyridine Analogue **40**[a]



[a] Reagents: (a) DPPA, NMM, $ClCH_2CH_2Cl$, rt−80 °C, then BnOH, cat. CuCl, reflux; (b) NH_4HCO_2, Pd/C, MeOH, reflux; (c) RCHO, toluene, reflux ($-H_2O$); (d) $NaBH_4$, EtOH; (e) *n*-BuLi, THF, then methyl 4-bromomethyl-2-(2-methylphenyl)benzoate, -30−0 °C; (f) NaOH, aq EtOH, reflux; (g) Met(OMe)·HCl, NEt_3, EDCI, HOBt, DMF; (h) LiOH, aq THF/MeOH.

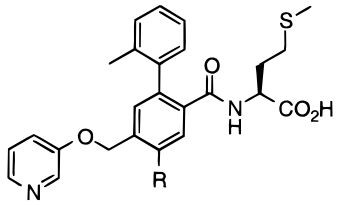
We prepared less basic heterocycles in an attempt to improve pharmacokinetics. The pyrimidine and pyrazine compounds possessed potent in vitro enzyme activity but were of lower potency in the cellular assay (compare compounds **43** and **28** with **26**). The potency of the variously substituted thiazole analogues displayed a clear regiochemical preference (compounds **34**−**36**, Table 2), the 5-substituted derivative proving to be substantially more active (0.5 nM) than either the 2- or 4-substituted isomers (7 and 16 nM, respectively). However, these compounds demonstrated notably reduced activity in the Ras processing assay than the corresponding pyridine analogue (e.g. compound **36**,

Scheme 5. Synthesis of FTase Inhibitor Pyrimidine Analogue **43**[a]



[a] Reagents: (a) 5-aminopyrazine, $BnNH_2$, Cu_2O_3, K_2CO_3, reflux; (b) NaHMDS, THF, then methyl 4-bromomethyl-2-(2-methylphenyl)benzoate, rt, reflux; (c) NaOH, aq EtOH, reflux; (d) Met(OMe)·HCl, NEt_3, EDCI, HOBt, DMF; (e) LiOH, aq THF/MeOH.

Table 1. Results of Substitution at the 5-Position of **3**[a]



compd	R	IC_{50} (nM)	ED_{50} (μM)
3	H	0.4 ± 0.2	0.4
9	4-$(CH_3)C_6H_4$-	370	ND
10	3,5-$Cl_2C_6H_3$-	95	ND
11	2-thiopheneyl	510	ND
12	ethyl	11 ± 1	ND
13	*n*-butyl	3	<10
14	isobutyl	29	>10
15	pentyl	2	1
16	$PhCH_2$-	1	>1
17	$PhCH_2CH_2$-	0.5	1
18	$C_6H_{11}CH_2$-	12	1

[a] 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%. Potencies that differ by more than 3-fold should be considered statistically different.

ED_{50} = 300 nM). Additionally, none of the alternate heterocycles produced an improvement in the pharmacokinetic profile. Interestingly, although the iv AUC for compound **43** (10.4 μg·h/mL) was improved relative to **26**, it was subject to efficient first-pass clearance (systemic AUC ~ 0.02 μg·h/mL).

Carbocyclic replacement of the heterocycle resulted in some interesting findings. Benzene analogue **29** possessed enzyme inhibitory potency comparable to that of the heterocyclic analogues. Though the cellular potency (ED_{50} = 400 nM) was reduced, it was not decreased any more than observed in the non-pyridine heterocycles. Unfortunately, the pharmacokinetics showed no improvement. Compound **29** possessed similar iv half-life and portal vein AUC in rat with respect to **26**, and a similarly low systemic AUC was observed.

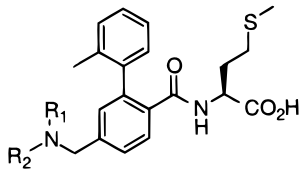
During the process of defining the SAR of **29**, the 3,5-difluorobenzyl analogue **30** was prepared, and this compound provided the best pharmacokinetic profile observed in the entire series, yielding a systemic AUC by oral administration of nearly 11 μg·h/mL. Unfortunately, as we observed previously with other inhibitors, only the in vitro potency was maintained (0.4 nM); the Ras processing efficiency fell off substantially (~1 μM). The remarkable improvement in bioavailability of **30** prompted us to replace the *N*-benzyl substituent with the 3,5-difluorobenzyl moiety in the more potent compounds pyridyl **26** and thiazolyl **36**. Although both compounds maintained comparable in vitro and cellular activity, neither possessed substantially better pharmacokinetics than the parent benzyl derivatives. Other inhibitors (data not shown) bearing this group also failed to demonstrate any improvement in pharmacokinetic behavior. We have no explanation for this isolated observation.

Of the numerous farnesyltransferase inhibitors prepared during the course of our work in this area, several compounds, including some of those reported in this study, were also tested against the related enzyme geranylgeranyltransferase 1 (GGT1ase). In nearly all cases examined the decrease in binding affinity observed was greater than 4 orders of magnitude. For example, compound **3** is 0.4 nM against FTase and 28 μM against GGT1ase.

In Vivo. Based upon the results presented, we investigated the activity of pyridine **26** and aniline **29** in vivo. In selecting these compounds, we compared a potent heterocyclic inhibitor with its carbocyclic counterpart. The compounds were tested against subcutaneous xenografts in nude mice. The first cell line we selected was MiaPaCa-2, which is derived from a human pancreatic tumor containing a *K-ras* mutation at codon 12 (Gly12Cys). In addition, the cell line contains a mutation in the binding domain of p53 at position 248 (Arg248Trp), considered a "hot spot" in human p53 cancers. This cell line quickly (~16 days) produces 1-g tumors and is nonresponsive toward the majority of conventional cytotoxic agents. The ED_{50} of **26** against MiaPaCa-2 is less than 50 nM (91% inhibition of Ras processing at 50 nM). Like data for **29** is not available at this time.

During the experiments approximately 8-week-old nude mice (10/study group) were inoculated subcutaneously in the right flank with 0.5 mL of a 1:20 brei of MiaPaCa cells on study day 0. Therapy was initiated on study day 1 and consisted of continuous once daily dosing of compound **26** at either 25, 50, or 100 mg/kg/day (mpk/day) ip. The protocol involving aniline derivative **29** was identical to that of the pyridine derivative **26**, except that doses of 25 and 12.5 mpk (ip) were used. The vehicle employed was a phosphate-buffered saline (PBS) solution with NaOH added. Vehicle was administered as the untreated control, while cyclophosphamide was used as the positive control. Measurement of tumors began on study day 6. Tumor mass was estimated by measuring length and width of the tumor with digital calipers and applying the following formula: $(L \times W^2)/2$. Mice were euthanized when tumors reached at least 1 g, and death due to drug toxicity was also monitored. Figure 1 shows select examples which illustrate our results. At the 25 mpk/day dose, **26**

Table 2. Results of Modifications to the Aminopyridine Moiety of **4**



compd	R_1	R_2	IC_{50} (nM)	ED_{50} (μM)	$T_{1/2}$ (h)	AUC (μg·h/mL) iv	AUC (μg·h/mL) systemic
4	H	3-pyridyl	0.4	3	ND	ND	ND
23	PhCO-	3-pyridyl	53	>1	ND	ND	ND
24	$PhCH_2CO$-	3-pyridiyl	39	>1	ND	ND	ND
25	$PhSO_2$-	3-pyridyl	7	ND	ND	ND	ND
26	$PhCH_2$-	3-pyridyl	0.10 ± 0.04*	0.013 ± 0.005*	0.83 ± 0.21	3.0 ± 0.7 2.5 ± 0.7	0.5 ± 0.1[a] 0.11 ± 0.03[b]
27	$C_6H_{11}CH_2$-	3-pyridyl	0.1	0.01	<0.4	1.0 ± 0.3	0.1 ± 0.1
40	$PhCH_2$-	5-F-3-pyridyl	0.1	0.03	<0.4	2.4 ± 0.9	0.4 ± 0.3[a]
43	$PhCH_2$-	5-pyrimidyl	0.4	0.09	0.5	10.4 ± 6.0	0.02 ± 0.02[a]
28	$PhCH_2$-	2-pyrazinyl	0.8	0.05	<0.4	1.8 ± 0.3	0.9 ± 0.7[a]
34	$PhCH_2$-	2-thiazolylmethyl	7	>1	ND	ND	ND
35	$PhCH_2$-	4-thiazolylmethyl	16	>1	ND	ND	ND
36	$PhCH_2$-	5-thiazolylmethyl	0.4	0.3	<0.4	3.2 ± 0.3	1.6 ± 0.6[a]
29	$PhCH_2$-	Ph-	1.4 ± 0.5*	0.40 ± 0.06‡	0.8	1.9 ± 0.3	0.6 ± 0.1[a]
30	3,5-F_2-$C_6H_3CH_2$-	Ph-	0.4	1	1.9	14.3 ± 4.4	10.8 ± 5.l[b]
31	3,5-F_2-$C_6H_3CH_2$-	3-pyridyl	1.4	0.05	1.0 ± 0.1	3.56 ± 0.30	0.14 ± 0.02[b]
37	3,5-F_2-$C_6H_3CH_2$-	5-thiazolylmethyl	0.2	0.5	1.13	2.4 ± 0.8	0.3 ± 0.1[b]

[a] Intraduodenal dosing. [b] Oral dosing. *n = 3.
‡ n = 2. 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%. Potencies that differ by more than 3-fold should be considered statistically different.

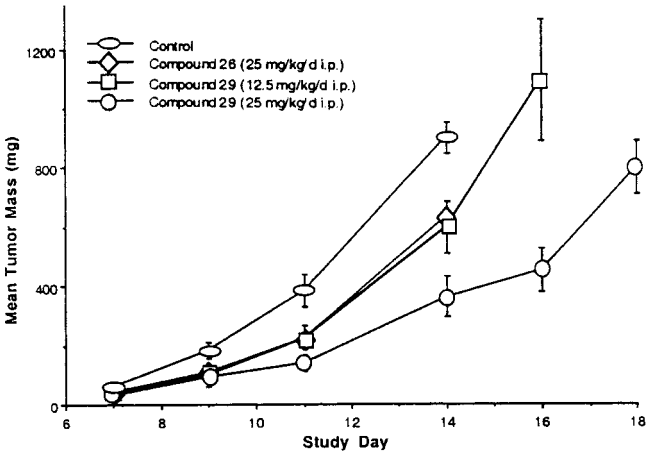


Figure 1. Antitumor efficacy of **26** and **29** vs untreated control against MiaPaCa-2 subcutaneous tumors in nude mice. Mice were inoculated subcutaneously in the right flank on study day 0. Therapy was initiated on study day 1 and consisted of continuous once daily dosing ip of compound **26** or **29** at the indicated doses.

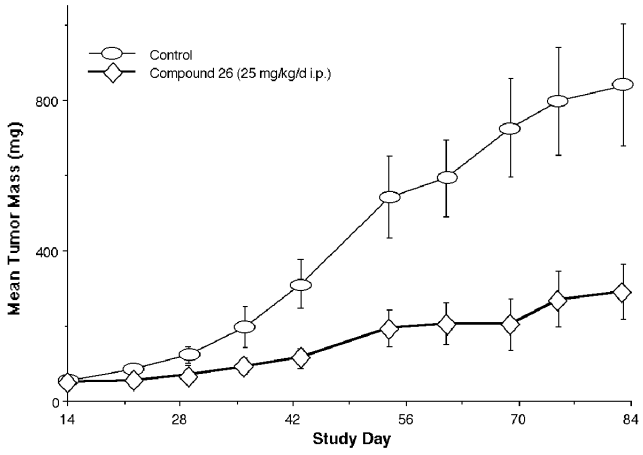


Figure 2. Antitumor efficacy of **26** vs untreated control against A-549 subcutaneous tumors in nude mice. Mice were inoculated subcutaneously in the right and left flanks on study day 0. Therapy was initiated on study day 19 and consisted of continous once daily dosing of compound **26** at 25 mpk/day ip. Injections were stopped from days 45−53 and restarted on day 54.

demonstrates a notable reduction in mean tumor mass for the animals studied. Compound **29** nearly matches this reduction at one-half the dosage (12.5 mpk/day) and shows a marked further improvement at the original higher dose. Thus, initial evidence of a dose−response has been established.

In a similar study we investigated the antitumor efficacy of **26** against the slower developing human lung adenocarcinoma A-549, one of the NCI panel of 60 cell lines. The genetic lesions found in A-549 include a point mutation in *K-ras* at codon 12 (Gly12Ser). The cell line exhibits low levels of P-glycoprotein and bcl-2 expression in comparison to the other cell lines in the panel. A-549 displays wild-type p53, and so presumably the p53-dependant pathway of growth arrest and apoptosis may still function. The ED_{50} of **26** against A-549 is about 1 μM, suggesting the compound to be far less active against this line than the MiaPaCa-2 line.

Here therapy was initiated on study day 19 and consisted of continuous once daily dosing of compound **26** at 25 mpk/day ip. Injections were stopped from days 45−53 and restarted on day 54. The data presented in Figure 2 illustrates that a noteworthy reduction in mean tumor mass was once again observed in animals treated with **26** versus untreated controls.

In the MiaPaCa trial with inhibitors **26** and **29**, all mice inoculated with transformed cells developed tumors. The mean value for days to reach 1 g of tumor mass within the untreated control group was 16. Treat-

ment with cyclophosphamide at 25 mg/kg on days 1, 5, and 9 as a positive control produced a mean delay to 1 g of tumor mass of 3 days. At an equivalent dosage, daily administration of the pyridine analogue **26** produced a mean delay in tumor growth of 2 days, while results from the aniline analogue **29** equaled that of the positive control at 3 days. This result was intriguing because we had observed previously that cellular potency was often predictive of in vivo efficacy, and yet **29** had demonstrated reduced activity in the cellular potency assay with respect to **26**. None of the numerous other compounds in the aniline series demonstrated significant in vivo efficacy against the MiaPaCa cell line (data not shown). The reason for the increased efficacy of **29** is not clear to us at this time. The pharmacokinetic profiles of the two compounds are not markedly different, as both inhibitors possess rather short half-lives and neither provides a systemic AUC above 1 μg·h/mL. One plausible explanation is that the aniline derivative may experience better tissue distribution, but we have no experimental confirmation of this at present. Despite this unexpected finding, these experiments clearly highlight the potential of farnesyltransferase inhibitors as effective antitumor drugs.

Conclusion

We have demonstrated that certain tertiary amine derivatives of CAAX mimetics are extremely potent inhibitors of farnesyltransferase. *N*-Benzyl-3-aminopyridine analogue **26** possesses potent in vitro and cellular activity and demonstrated significant activity in MiaPaCa and A-549 xenografts in nude mice. Aniline derivative **29** is also a potent inhibitor of farnesyltransferase in vitro as well as in vivo. Efforts are currently underway to improve the in vivo profile of these inhibitors, and the results will be presented in due course.

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.

General Procedure for the Hydrolysis of Benzoate Esters to Benzoic Acids. To a solution of the biphenyl benzoate[27] in MeOH at room temperature was added a solution of 4 M NaOH in water (total reaction concentration ~1 M). The mixture was brought to reflux and maintained until TLC analysis indicated complete consumption of starting material. The mixture was cooled to room temperature and the MeOH removed on a rotary evaporator. The resulting solution was extracted with ethyl acetate, and the aqueous phase was then cooled to 0 °C and acidified by the careful addition of concentrated aq HCl. The mixture was extracted with 2 portions of ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to give the desired compound.

General Procedure for the Conversion of Benzoic Acids to Benzoylmethionine Methyl Esters. A solution of benzoic acid in DMF was treated sequentially with HOBt (110 mol %), EDCI (110 mol %), and L-methionine methyl ester hydrochloride (130 mol %). The suspension was stirred for 15 min, then triethylamine (180 mol %) was added, and the mixture was stirred for 24 h. The reaction was quenched by transfer into ethyl acetate and extraction with water, saturated aqueous $NaHCO_3$, and brine. The solution was then dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexanes) to provide the desired compound.

General Procedure for Hydrolysis of Methionine Methyl Esters. The methionine ester was dissolved in 3:1 THF/MeOH and cooled in an ice bath. The solution was treated with aqueous LiOH (200 mol %) 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 or if the solid was not isolable, the aqueous mixture was extracted with ethyl acetate, and the extracts were dried over sodium sulfate, filtered, and concentrated. These procedures generally gave material of suitable purity. If not, the compound was purified by column chromatography on silica gel or reverse-phase preparative HPLC.

Dimethyl 2-Amino-5-(2-methylphenyl)terephthalate (6). To a −12 °C suspension in dichloromethane of 2-aminoterephthalate (10.5 g, 50.0 mmol) and pyridine (8.1 mL, 100.0 mmol) was added a solution of bromine (2.6 mL, 52.5 mmol) in dichloromethane (25 mL) over 0.5 h, and the reaction mixture was warmed slowly to ambient temperature and stirred overnight. Aqueous workup followed by recrystallization from 95% ethanol gave the desired compound (11.13 g, 77%, mp 113−116 °C). ^{1}H NMR ($CDCl_3$): δ 8.09 (s, 1H), 7.05 (s, 1H), 5.80 (bs, 2H), 3.93 (s, 3H), 3.88 (s, 3H). MS (DCI, NH_3): 305 $(M + NH_4)^+$. A solution of palladium acetate (0.26 g, 1.2 mmol) and triphenylphosphine (1.21 g, 4.6 mmol) in 100 mL of toluene was stirred for 10 min at ambient temperature, and then the above product (11.13 g, 38.6 mmol), 2-methylphenylboronic acid (5.77 g, 42.4 mmol), ethanol (18 mL), and aqueous 2 M sodium carbonate (157 mL) were added. The reaction mixture was warmed to reflux and stirred for 18 h. The reaction mixture was cooled to ambient temperature and diluted with ether. The aqueous phase was extracted with ether. The combined organic layers were washed with water, dried, filtered, and concentrated in vacuo to give an orange oil. Chromatography on silica gel (25% ethyl acetate−hexanes) gave compound **6** (9.6 g, 83%) as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.54 (s, 1H), 7.66 (s, 1H), 7.17−7.32 (m, 3H), 7.04 (d, 1H), 3.93 (s, 3H), 3.63 (s, 3H), 2.05 (s, 3H). MS (CI/NH_3): 428 $(M + NH_4)^+$.

Methyl 2-(2-Methylphenyl)-4-hydroxymethyl-5-iodobenzoate (7). A mixture of compound **6** (7.00 g, 23.4 mmol) and aqueous 3 M HCl (50 mL) in acetone (500 mL) was cooled to 0 °C and a solution of $NaNO_2$ (1.78 g, 25.7 mmol) in water (20 mL) was added dropwise. The reaction mixture was stirred for 1 h, and then urea (0.53 g, 8.88 mmol) was added followed by a solution of KI (6.79 g, 40.9 mmol) in water (20 mL), during which time the reaction temperature remained below 0 °C. The reaction mixture was stirred for 0.5 h, then the cold bath was removed, and stirring was continued for 2 h. The reaction mixture was diluted with water (400 mL), and $NaHSO_3$ was added until the brown color disappeared. The reaction mixture was filtered, and the solid material collected was recrystallized from 5% aqueous ethanol to give the desired compound (6.46 g, 67%), mp 105−109 °C. ^{1}H NMR ($CDCl_3$) δ: 8.53 (s, 1H), 7.65 (s, lH), 7.37−7.51 (m, 3H), 7.06 (d, 1H), 3.93 (s, 3H), 3.64 (s, 3H), 2.07 (s, 3H). MS (CI/NH_3): 428 $(M + NH_4)^+$. This material was dissolved in 60 mL of THF and cooled in an ice bath. The ice-cold solution was treated sequentially with 15 mL of MeOH and aqueous LiOH (0.69 g in 25 mL of water), and the mixture was stirred for 68 h during which time the bath melted. The solution was concentrated to remove the organics and diluted with 100 mL of water. The aqueous mixture was extracted with 2 portions of ether and set aside. The ethereal extracts were combined and washed with water. The aqueous fractions were combined, and the pH was

adjusted to <2 with 1 M aq $NaHSO_4$. The mixture was extracted with 3 portions of ether, and the combined ethereal extracts were dried over $MgSO_4$, filtered, and concentrated to provide the crude acid (5.71 g, 92%) which was used without further purification. The acid (5.60 g, 14.06 mmol) was dissolved in 30 mL of dry THF and cooled in an ice bath. Borane (28.0 mL of a 1 M in THF, 28.0 mmol) was added dropwise, and the mixture was stirred for 2 h. The ice bath was removed, and after 2 h stirring, the solution was recooled to in an ice bath and quenched by the careful addition of 25 mL of 20% aqueous THF (*caution!!* vigorous evolution of gas), followed by 25 mL of 4 N aqueous H_2SO_4. The mixture was stirred an additional 10 min and diluted with 200 mL of water. This mixture was extracted with 3 portions of ethyl acetate, and the combined extracts were washed with water and saturated aqueous $NaHCO_3$. The solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (20% ethyl acetate/hexanes) to give compound **7**, 3.93 g (73%, 67% overall). ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H), 7.34 (s, 1H), 7.17−7.39 (m, 3H), 7.06 (d, 1H), 4.72 (d, 2H), 3.62 (s, 3H), 2.06 (s, 3H). MS (CI/NH_3): 400 $(M + NH_4)^+$.

Methyl 2-(2-Methylphenyl)-4-(3-pyridyloxymethyl)-5-iodobenzoate (8). Compound **7** (830 mg, 2.17 mmol) in dichloromethane was cooled in an ice/acetone bath, carbon tetrabromide (864 mg, 2.60 mmol) was added, followed by triphenylphosphine (626 mg, 2.39 mmol), and the reaction mixture was warmed to 0 °C over 1 h. The cold bath was then removed, and stirring was continued for 2 h. The reaction mixture was concentrated in vacuo and purified by chromatography on silica gel (5% ethyl acetate−hexanes) to give the bromide (1.1 g) which also contained some triphenylphosphine. This material was used directly. To a solution of benzyltriethylammonium bromide (1.18 g, 4.34 mmol) in 10 mL of CH_2Cl_2 was added 3-hydroxypyridine potassium salt (586 mg, 4.34 mmol), and the mixture was stirred for 15 min. A solution of the above bromide (960 mg, 2.17 mmol) in 4 mL of CH_2Cl_2 was added, and the reaction mixture was stirred overnight. The reaction mixture was washed with water, dried, filtered, and concentrated in vacuo. Chromatography on silica gel (35% ethyl acetate−hexanes) gave compound **8** (480 mg, 49%). ^{1}H NMR ($CDCl_3$): δ 8.45 (s, 1H), 8.39 (bs, 1H), 8.28 (m; 1H), 7.39 (s, 1H), 7.15−7.31 (m, 3H), 7.03 (d, 1H), 5.14 (s, 2H), 3.63 (s, 3H), 2.02 (s, 3H). MS (CI/NH_3): 460 $(MH)^+$.

General Procedures for Conversion of Iodide 8 to Aryl- or Alkylbiphenyl. Procedure A: Arylboronic Acids. 4-(3-Pyridyloxymethyl)-5-(4-methylphenyl)-2-(2-methylphenyl)benzoylmethionine (9). To a solution of tetrakis(triphenylphosphine)palladium(0) (2 mg) in toluene (1 mL) was added a solution of **8** (100 mg, 0.22 mmol) in toluene (3 mL). The mixture was stirred for 10 min; then a solution of 4-methylphenylboronic acid (33 mg, 0.24 mmol) in ethanol (2 mL) and aqueous 2 M sodium carbonate were added. The reaction mixture was stirred overnight at reflux, additional catalyst (20 mg), boronic acid (20 mg), and base (0.5 mL) were added, and reflux was continued for 4 h. The reaction mixture was cooled to ambient temperature, diluted with ether, washed with water and brine, dried over sodium carbonate, filtered, and concentrated in vacuo. Chromatography on silica gel (30% ethyl acetate−hexanes) gave the *p*-tolyl analogue (98 mg). Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR ($CDCl_3$): δ 8.31 (d, 1H), 8.19 (d, 1H), 7.90 (d, 1H), 7.42 (s, 1H), 7.40−7.20 (m, 10 H), 6.07 (d, 1H), 5.08 (m, 2H), 4.62 (m, 1H), 2.40 (s, 3H), 2.25−2.10 (m, 5H), 2.02 (s, 3H), 2.00−1.55 (m, 2H). MS (CI/NH_3): 541 $(M + H)^+$. Anal. ($C_{29}H_{34}N_2O_4S\cdot 0.50H_2O$) C, H, N.

4-(3-Pyridyloxymethyl)-5-(3,5-dichlorophenyl)-2-(2-methylphenyl)benzoylmethionine (10). The side chain was attached using procedure A and commercial 3,5-dichlorophenylboronic acid. Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR ($CDCl_3$): δ 8.37 (d, 1H), 8.21 (d, 1H), 7.85 (d, 1H), 7.44 (s, 1H), 7.40−7.20 (m, 9H), 6.08 (d, 1H), 5.03 (s, 2H), 4.62 (m, 1H), 2.25−2.05 (m, 5H), 2.02 (s, 3H), 1.95 (m, 1H) 1.64 (m, 1H). MS (CI/NH_3): 595 $(M + H)^+$. Anal. ($C_{31}H_{28}Cl_2N_2O_4S\cdot 0.20H_2O$) C, H, N.

4-(3-Pyridyloxymethyl)-5-(2-thienyl)-2-(2-methylphenyl)benzoylmethionine (11). The side chain was attached using procedure A and commercial 2-thienylboronic acid. Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR ($CDCl_3$): δ 8.38 (d, 1H), 8.20 (dd, 1H), 8.03 (s, 1H), 7.43 (s, 1H), 7.39 (dd, 1H), 7.38−7.20 (m, 6H), 7.15 (dd, 1H), 7.08 (m, 1H), 6.07 (d, 1H), 5.10 (m, 2H), 4.61 (m, 1H), 2.20−2.05 (m, 5H), 2.02 (s, 3H), 1.93 (m, 1H) 1.62 (m, 1H). MS (CI/NH_3): 533 (MH^+). Anal. ($C_{29}H_{27}LiN_2O_4S_2\cdot 0.45H_2O$) C, H, N.

Procedure B: Commercial Alkylboranes. *N*-2-(2-Methylphenyl)-4-(3-pyridyloxymethyl)-5-butylbenzoylmethionine (12). Tributylborane (0.10 mL, 0.41 mmol) was added to 2 mL of degassed DMF followed by the sequential addition of 150 mg (0.33 mmol) of iodide **8**, 8 mg (0.01 mmol) of Cl_2PdDPPF, and 212 mg (1.0 mmol) of K_2CO_3. The mixture was placed in an oil bath preheated to 65 °C and stirred at that temperature for 3 h. The mixture was poured into water and extracted with 2 portions of ethyl acetate. The combined aqueous layers were rinsed with water and brine, dried over Na_2SO_4, filtered, and concentrated to give the crude product, which was used directly. Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR (DMSO-d_6): δ 8.35 (d, 1H), 8.18 (dd, 1H), 8.09 (dd, 1H), 7.47 (m, 1H), 7.37 (s, 1H), 7.35 (dd, 1H), 7.26 (s, 1H), 7.19 (m, 2H), 7.11 (m, 2H), 5.26 (s, 2H), 4.2 (m, 1H), 2.73 (dd, 2H), 1.98−2.21 (m, 5H), 1.96 (s, 3H), 1.77−1.90 (m, 4H), 1.40 (sextet, 2H), 0.93 (t, 3H). MS (CI/NH_3): 507 (MH^+). Anal. ($C_{29}H_{34}N_2O_4S\cdot 0.50H_2O$) C, H, N.

***N*-2-(2-Methylphenyl)-4-(3-pyridyloxymethyl)-5-ethylbenzoylmethionine (13).** The side chain was attached using procedure B and commercial triethylborane. Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR (DMSO-d_6): δ 8.38 (d, 1H), 8.18 (d, 1H), 7.93 (m, 1H), 7.51 (m, 1H), 7.40 (s, 1H), 7.35 (m, 1H), 7.28 (bs, 1H), 7.20 (m, 2H), 7.13 (m, 2H), 5.27 (s, 2H), 4.12 (m, 1H), 2.78 (q, 2H), 2.20−2.00 (m, 5H), 1.96 (s, 3H), 1.90−1.60 (m, 2H), 1.26 (t, 3H). MS (CI/NH_3): 479 (MH^+). Anal. ($C_{27}H_{30}N_2O_4S\cdot 1.00H_2O$) C, H, N.

***N*-2-(2-Methylphenyl)-4-(3-pyridyloxymethyl)-5-pentylbenzoylmethionine (15).** The side chain was attached using procedure B and tripentylborane (prepared in situ by the hydroboration of 1-pentene with $BH_3\cdot$THF). Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR (DMSO-d_6): δ 8.37 (d, 1H), 8.18 (dd, 1H), 8.09 (dd, 1H), 7.48 (m, 1H), 7.36 (s, 1H), 7.34 (m, 1H), 7.26 (bs, 1H), 7.19 (m, 2H), 7.13 (m, 2H), 5.26 (s, 2H), 4.21 (m, 1H), 2.73 (m, 2H), 2.20−2.00 (m, 5H), 1.96 (s, 3H), 1.90−1.60 (m, 4H), 1.36 (m, 4H), 0.86 (t, 3H). MS (CI/NH_3): 521 (MH^+). Anal. ($C_{30}H_{36}N_2O_4S$) C, H, N.

4-(3-Pyridyloxymethyl)-5-phenylmethyl-2-(2-methylphenyl)benzoylmethionine (16). The side chain was attached using procedure B and commercial 9-methoxy-9-BBN. Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR ($CDCl_3$): δ 8.27 (d, 1H), 8.19 (dd, 1H), 7.88 (s, 1H), 7.40−7.00 (m, 12H), 6.00 (d, 1H), 5.08 (d, 1H), 5.01 (d, 1H), 4.62 (m, 1H), 4.15 (s, 2H), 2.20−2.05 (m, 5H), 2.02 (s, 3H), 1.92 (m, 1H) 1.60 (m, 1H). MS (CI/NH_3): 541 (MH^+). Anal. ($C_{32}H_{32}N_2O_4S\cdot 0.25H_2O$) C, H, N.

Procedure C: Synthetic Alkylboranes. *N*-2-(2-Methylphenyl)-4-(3-pyridyloxymethyl)-5-isobutylbenzoylmethionine (14). To a solution of *t*-butyllithium (0.75 mL of a 1.7 M solution in pentane, 1.28 mmol) in 1 mL of dry ether at −78 °C was added a solution of 74 μL (0.64 mmol) of isobutyl iodide in 1 mL of ether. After stirring for 30 min at −78 °C, 9-methoxy-9-BBN (0.66 mL of a 1.0 M solution in hexanes, 0.66 mmol) was added, and the mixture was warmed to 0 °C for 30 min and then allowed to reach room temperature. The mixture was treated with 218 mg (0.53 mmol) of iodide **8** in 4 mL of degassed DMF followed by 13 mg (0.02 mmol) of Cl_2-

PdDPPF and 338 mg (1.59 mmol) of anhydrous K_3PO_4. The solution was heated to 65 °C at first under a N_2 stream (to remove the volatile organics) and then for 2 h additional. After cooling to room temperature, the mixture was poured into water and extracted with 3 portions of ethyl acetate. The combined organic extracts were washed water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (18 g SiO_2, 30% ethyl acetate/hexanes) to provide the isobutyl derivative. Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR (DMSO-d_6): δ 8.35 (d, 1H), 8.18 (dd, 1H), 8.06 (dd, 1H), 7.49 (dq, 1H), 7.35 (s, 1H), 7.33 (dd, 1H), 7.27 (s, 1H), 7.18 (m, 2H), 7.03 (m, 2H), 5.25 (s, 1H), 4.22 (m, 1H), 2.63 (dd, 2H), 2.12 (heptet, 1H), 2.03 (m, 4H), 1.96 (s, 3H), 1.64−1.90 (m, 3H), 0.96 (d, 6H). MS (CI/NH_3): 507, 489, 221, 204. Anal. ($C_{29}H_{34}N_2O_4S\cdot 0.50H_2O$) C, H, N.

***N*-2-(2-Methylphenyl)-4-(3-pyridyloxymethyl)-5-phenethylbenzoylmethionine (17).** The side chain was attached using procedure C and commercial phenethyl bromide. Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR ($CDCl_3$): δ 8.47 (m, 1H), 8.26 (d, 1H), 8.13 (dd, 1H), 7.65 (dd, 1H), 7.50 (s, 1H), 7.48 (m, 1H), 7.40−7.25 (m, 4H), 7.25−7.00 (m, 6H), 5.30 (s, 2H), 4.22 (m, 1H), 2.99 (m, 4H), 2.25−2.00 (m, 5H), 1.97 (s, 3H), 1.95−1.60 (m, 2H). MS (CI/NH_3): 555 (MH^+). Anal. ($C_{33}H_{34}N_2O_4S\cdot 1.00$TFA) C, H, N.

***N*-2-(2-Methylphenyl)-4-(3-pyridyloxymethyl)-5-cyclohexylmethylbenzoylmethionine (18).** The side chain was attached using procedure C and commercial bromomethylcyclohexane. Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR ($CDCl_3$): δ 12.60 (bs, 1H), 8.40−8.20 (m, 1H), 8.20−8.10 (m, 2H), 7.52 (m, 1H), 7.40−7.25 (m, 4H), 7.20 (m, 2H), 7.14 (m, 2H), 5.23 (s, 2H), 4.21 (m, 1H), 2.62 (m, 1H), 2.20−2.00 (m, 5H), 1.96 (s, 3H), 1.90−1.50 (m, 3H), 1.30−0.90 (m, 5H). MS (CI/NH_3): 547 (MH^+). Anal. ($C_{32}H_{38}N_2O_4S\cdot 0.35CH_3CN$) C, H, N.

***N*-Benzoyl-3-aminopyridine.** A solution of 3-aminopyridine (0.94 g, 10.00 mmol) and *N*-methylmorpholine (1.32 mL, 12.00 mmol) in 10 mL of CH_2Cl_2 was cooled in an ice/acetone bath and treated dropwise with benzoyl chloride (1.20 mL, 11.00 mmol). The mixture was stirred for 6 h during which time the cold bath melted. The solution was diluted with 50 mL of ethyl ether and extracted with water, 2 M aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (3:1 ethyl acetate/hexanes) to give 1.52 g (77%) of *N*-benzoyl-3-aminopyridine. ^{1}H NMR ($CDCl_3$): δ 8.70 (d, 1H), 8.37 (m, 2H), 8.28 (m, 1H), 7.90 (m, 2H), 7.57 (m, 1H), 7.49 (m, 2H), 7.34 (dd, 1H). MS (CI/NH_3): 199 $(MH)^+$.

General Procedure for the Formation of Tertiary Amines and Amides. Procedure D: *N*-[4-(*N*-Benzoyl-*N*-pyrid-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine (23). A solution of methyl 2-(2-methylphenyl)-4-bromomethylbenzoate (175 mg, 0.55 mmol) in 1 mL of dry DMF was cooled in an ice bath and treated with NaH (26 mg of a 60% mineral oil dispersion, 0.66 mmol) followed by a solution of *N*-benzoyl-3-aminopyridine (119 mg, 0.60 mmol) in 1 mL of dry DMF. The mixture was stirred for 3 h and quenched by the addition of water. The suspension was poured into water and extracted with 3 portions of ethyl acetate. 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 (1:1 ethyl acetate/hexanes) to give the alkylated product. Hydrolysis, methionine methyl ester coupling, and methyl ester hydrolysis were carried out as previously described. ^{1}H NMR (DMSO-d_6): δ 12.54 (bs, 1H), 8.24 (dd, 1H), 8.13 (m, 2H), 7.61 (m, 1H), 7.43 (m, 2H), 7.29 (m, 6H), 7.00−7.21 (m, 5H), 5.21 (s, 2H), 4.18 (m, 1H), 1.97−2.22 (m, 2H), 1.94 (s, 6H), 1.63−1.88 (m, 2H). MS (CI/NH_3): 554 (MH^+). Anal. ($C_{32}H_{31}N_3O_4S\cdot 0.50H_2O$) C, H, N.

***N*-[4-(*N*-Phenylacetyl-*N*-pyrid-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine (24).** Prepared using procedure D and phenylacetyl chloride. ^{1}H NMR (DMSO-d_6): δ 8.49 (d, 1H), 8.30 (d, 1H), 8.09 (d, 1H), 7.61 (dt, 1H), 7.42 (m, 2H), 7.24 (dd, 1H), 6.91−7.23 (m, 10H), 4.91 (bs, 2H), 4.19 (m, 1H), 3.50 (bs, 2H), 1.98−2.22 (m, 2H), 1.96 (bs, 6H), 1.62−1.88 (m, 2H). MS (CI/NH_3): 568 (MH^+). Anal. ($C_{33}H_{33}N_3O_4S$) C, H, N.

***N*-[4-(*N*-Phenylsulfonyl-*N*-pyrid-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine (25).** Prepared using procedure D and *p*-toluenesulfonyl chloride. ^{1}H NMR (DMSO-d_6): δ 8.42 (d, 1H), 8.30 (s, 1H), 8.12 (d, 1H), 7.76 (m, 1H) 7.60−7.73 (m, 4H), 7.53 (m, 1H), 7.38 (m, 3H), 7.19 (m, 2H), 6.90−7.15 (m, 3H), 4.91 (s, 2H), 4.17 (m, 1H), 1.93−2.20 (m, 3H), 1.92 (s, 3H), 1.61−1.90 (m, 6H). MS (CI/NH_3): 590 (MH^+). Anal. ($C_{31}H_{31}N_3O_5S_2\cdot 0.31H_2O$) C, H, N.

General Procedure E: Preparation of *N*-Alkylamino Heterocycles. *N*-Benzyl-3-aminopyridine. A mixture of 94.12 g (1.00 mol) of 3-aminopyridine and 102 mL (1.00 mol) of benzaldehyde in 300 mL of toluene were heated to reflux. A Dean−Stark trap was used to collect the water removed by the azeotrope. When the theoretical amount of water was collected (∼3 h) the mixture was cooled to room temperature and concentrated in vacuo to remove the toluene. The residue was dissolved in 300 mL of ethanol and added dropwise to a solution of 55.70 g (1.50 mol) of $NaBH_4$ in ethanol at 0 °C. The ice bath was removed, and the thick solution was stirred for 2 h at ambient temperature and 6 h at reflux. The mixture was cooled to 50 °C and treated with 1 L of 4 N aqueous NaOH such that the temperature was maintained between 50 and 60 °C, and stirring was continued overnight. The cooled mixture was extracted with 3 portions of ethyl acetate, and the combined organic extracts were washed with 2 portions of water and 2 portions of brine, dried over Na_2SO_4, filtered, and concentrated to a volume of ∼500 mL. This concentrate was heated to obtain a solution, filtered hot, and allowed to slowly cool to room temperature. The solid was collected by filtration, the mother liquor was concentrated to approximately 250 mL, and the same procedure was repeated. The total amount of crystalline material collected was 138.90 g (75%). ^{1}H NMR ($CDCl_3$): δ 8.09 (d, 1H), 7.97 (dd, 1H), 7.28−7.44 (m, 5H), 7.06 (dd, 1H), 6.98 (ddd, 1H), 4.35 (d, 2H), 4.16 (bs, 1H). MS (CI/NH_3): 185 (MH^+).

Methyl 4-(*N*-Benzyl-*N*-3-pyridylaminomethyl)-2-(2-methylphenyl)benzoate. A solution of *n*-BuLi (49.8 mL of a 1.6 M solution in hexanes, 79.7 mmol) in 50 mL of dry THF was cooled to −30 °C and treated dropwise with a solution of 15.0 g (81.7 mmol) of *N*-benzyl-3-aminopyridine in 20 mL of dry THF. The mixture was stirred at this temperature for 30 min, and then methyl 4-bromomethyl-2-(2-methylphenyl) benzoate[27] (13.0 g, 40.9 mmol) in 30 mL of dry THF was added dropwise. The temperature was raised to −10 °C, stirred for 2 h, and quenched with water. The solvent was removed in vacuo and the residue partitioned into ether. The ether layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (50% ethyl acetate/hexanes) to give 13.5 g (78%) of the desired compound. ^{1}H NMR ($CDCl_3$): δ 8.17 (d, 1H), 7.97 (dd, 1H), 7.94 (d, 1H), 7.14−7.38 (m, 10H), 6.90−7.13 (m, 4H), 4.72 (s, 2H), 4.68 (s, 2H), 3.62 (s, 3H), 2.02 (s, 3H). MS (CI/NH_3): 423 (MH^+).

4-(*N*-Benzyl-*N*-3-pyridylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (26). The ester obtained above was converted to the final product as previously described. ^{1}H NMR (DMSO-d_6): δ 8.18 (d, 1H), 8.03 (bs, 1H), 7.82 (bs, 1H), 7.48 (d, 1H), 7.30 (m, 6H), 7.19 (m, 2H), 7.10 (m, 4H), 4.84 (s, 2H), 4.79 (s, 2H), 1.96−2.23 (m, 5H), 1.96 (s, 3H), 1.63−1.89 (m, 2H). MS (CI/NH_3): 540 (MH^+). Anal. ($C_{32}H_{33}N_3O_3S$) C, H, N.

4-(*N*-Cyclohexylmethyl-*N*-3-pyridylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (27). Prepared by the same sequence as compound **26** substituting cyclohexanecarboxaldehyde for benzaldehyde. ^{1}H NMR (DMSO-d_6): δ 8.18 (d, 1H), 7.79 (d, 1H), 7.44 (d, 1H), 7.25 (d, 1H), 7.03−7.19 (m, 6H), 6.97 (s, 1H), 4.71 (s, 2H), 4.19 (ddd, 1H), 2.14 (m, 1H), 1.96−2.10 (m, 4H), 1.95 (s, 3H), 1.57−1.89 (m, 8H), 1.17 (m, 3H), 1.01 (m, 2H). MS (ESI+): 546 (MH^+); (ESI−): 544 (M − H). Anal. ($C_{32}H_{39}N_3O_3S\cdot 0.99H_2O$) C, H, N.

4-(*N*-Benzyl-*N*-3-pyrazinylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (28). Prepared by the same sequence as compound **26** substituting aminopyrazine for 3-aminopyridine. ^{1}H NMR (DMSO-d_6): δ 1.46−2.09 (comp, 10H), 3.59−3.70 (br, 1H), 4.83−4.95 (comp, 4H), 6.90−6.95 (br, 1H), 7.00 (s, 1H), 7.04−7.34 (comp, 10H), 7.49 (d, 1H), 7.80 (d, 1H), 8.04−8.05 (m, 1H), 8.07−8.10 (m, 1H). HRMS (ESI+) calcd for the protonated acid $C_{31}H_{32}N_4O_3S$, 541.2273; obsd, 541.2268. Anal. ($C_{31}H_{31}LiN_4O_3S\cdot1.40H_2O\cdot0.25CH_3CN$) C, H, N.

4-(*N*-Benzyl-*N*-phenylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (29). Prepared by the same sequence as compound **26** substituting aniline for 3-aminopyridine. ^{1}H NMR (MeOH-d_4): δ 1.55−1.69 (m, 1H), 1.73−2.14 (comp, 9H), 4.16−4.28 (br, 1H), 4.65 (s, 2H), 4.70 (s, 2H), 6.59−6.66 (m, 1H), 6.73 (d, 2H), 7.03−7.13 (comp, 3H), 7.15−7.28 (comp, 8H), 7.34 (dd, 1H), 7.62 (d, 1H). MS (CI/NH_3): 539 (MH^+). Anal. ($C_{33}H_{33}LiN_2O_3S\cdot1.0LiOH\cdot0.85H_2O$) C, H, N.

4-(*N*-3,5-Difluorobenzyl-*N*-phenylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (30). Prepared by the same sequence as compound **26** substituting aniline for 3-aminopyridine and 3,5-difluorobenzaldehyde for benzaldehyde. ^{1}H NMR (MeOH-d_4): δ 7.7−7.8 (m, 1H), 7.3−7.4 (d, 1H), 7.0−7.3 (m, 7H), 6.8−6.9 (m, 3H), 6.6−6.8 (m, 4H), 4.88 (s, 2H), 4.85 (s, 2H), 4.1−4.22 (m, 1H), 1.7−2.1 (m, 10H). MS (ESI−): 573 (M − Li). Anal. ($C_{33}H_{31}F_2N_2O_3SLi\cdot1.70H_2O$) C, H, N.

4-(*N*-3,5-Difluorobenzyl-*N*-3-pyridylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (31). Prepared by the same sequence as compound **26** substituting 3,5-difluorobenzaldehyde for benzaldehyde. ^{1}H NMR (DMSO-d_6): δ 1.48−1.76 (comp, 2H), 1.85−2.05 (comp, 8H), 3.62−3.74 (br, 1H), 4.80 (s, 2H), 4.86 (s, 2H), 6.92−7.23 (comp, 11H), 7.33 (dd, 1H), 7.52 (d, 1H), 7.84 (dd, 1H), 8.03 (d, 1H). MS (CI/NH_3): 576 (MH^+). Anal. ($C_{32}H_{30}LiF_2N_3O_3S\cdot2.15H_2O$) C, H, N.

***N*-Benzyl-2-aminomethylthiazole.** Prepared by the same method as *N*-benzyl-3-aminopyridine using benzylamine and 2-thiazolecarboxaldehyde. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, 1H), 7.29−7.40 (m, 3H), 7.13−7.18 (m, 3H), 4.16 (s, 2H), 3.88 (s, 2H), 1.93 (bs, 1H). MS (CI/NH_3): 205 (MH^+).

Methyl 4-(*N*-Benzyl-*N*-2-aminomethylthiazolylmethyl)-2-(2-methylphenyl)benzoate. A solution of 373 mg (1.0 mmol) of methyl 4-bromomethyl-2-(2-methylphenyl)benzoate, 225 mg (1.1 mmol) of *N*-benzyl-2-aminomethylthiazole, and 0.21 mL (1.2 mmol) of *N*,*N*-diisopropylethylamine in 2 mL of CH_3CN was heated to reflux for 4 h. The mixture was poured into water and extracted with 3 portions of ethyl acetate. The combined organic extracts were washed with 2 portions of water, and 1 portion of brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (25% ethyl acetate/hexanes) to give 279 mg of the desired product. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, 1H), 7.69 (d, 1H), 7.55 (dd, 1H), 7.41 (m, 2H), 7.17−7.38 (m, 8H), 7.06 (d, 1H), 3.94 (s, 2H), 3.72 (d, 2H), 3.68 (d, 2H), 3.60 (s, 3H), 2.03 (s, 3H). MS (CI/NH_3): 443 (MH^+).

***N*-[4-(*N*-Benzyl-*N*-thiazol-2-ylmethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine (34).** The ester obtained above was converted to the final product as previously described. ^{1}H NMR (DMSO-d_6): δ 8.09, (d, 1H), 7.72 (d, 1H), 7.66 (d, 1H), 7.50 (m, 2H), 7.38 (m, 4H), 7.23 (m, 4H), 7.14 (m, 2H), 4.20 (ddd, 1H), 3.89 (s, 2H), 3.70 (s, 2H), 3.68 (s, 2H), 2.09 (m, 4H), 1.96 (s, 3H), 1.63−1.90 (m, 2H). MS (CI/NH_3): 560 (MH^+). Anal. ($C_{31}H_{33}N_3O_3S_2\cdot0.32H_2O$) C, H, N.

***N*-[4-(*N*-Benzyl-*N*-thiazol-4-ylmethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine (35).** Prepared by the same sequence as compound **34** substituting 4-thiazolecarboxaldehyde for 2-thiazolecarboxaldehyde. ^{1}H NMR (DMSO-d_6): δ 9.08 (d, 1H), 8.13 (d, 1H), 7.58 (d, 1H), 7.49 (s, 2H) 7.40 (d, 2H) 7.31 (t, 2H), 7.22 (m, 4H) 7.11 (m, 2H), 4.21 (m, 1H), 3.77 (s, 2H), 3.67 (s, 2H), 3.62 (s, 2H), 1.98−2.23 (m, 5H), 1.97 (s, 3H), 1.63−1.90 (m, 2H). MS (ESI−): 558 (M − H). Anal. ($C_{31}H_{33}N_3O_3S_2\cdot0.49H_2O$) C, H, N.

***N*-[4-(*N*-Benzyl-*N*-thiazol-5-ylmethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine (36).** Prepared by the same sequence as compound **34** substituting 5-thiazolecarboxaldehyde for 2-thiazolecarboxaldehyde. ^{1}H NMR (DMSO-d_6): δ 12.4 (bs, 1H), 9.03 (s, 1H), 8.12 (d, 1H), 7.79 (s, 1H), 7.48 (dd, 2H), 7.35 (m, 4H), 7.04−7.28 (m, 6H), 4.21 (ddd, 1H), 3.81 (s, 2H), 3.61 (s, 2H), 3.58 (s, 1H), 1.98−2.21 (m, 5H), 1.96 (s, 3H), 1.61−1.89 (m, 2H). MS (CI/NH_3): 560 (MH^+). Anal. ($C_{31}H_{33}N_3O_3S_2\cdot0.78H_2O$) C, H, N.

4-(*N*-3,5-Difluorobenzyl-*N*-5-thiazolylmethylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (37). Prepared by the same sequence as compound **34** substituting 5-thiazolecarboxaldehyde for 2-thiazolecarboxaldehyde and 3,5-difluorobenzylamine for benzylamine. ^{1}H NMR (MeOH-d_4): δ 8.95 (s, 1H), 7.78 (s, 1H), 7.6−7.7 (m, 1H), 7.4−7.5 (m, 1H), 7.05−7.30 (m, 5H), 6.95−7.05 (m, 2H), 6.85−6.95 (m, 1H), 4.95 (s, 2H), 4.1−4.22 (m, 1H), 3.9 (s, 2H), 4.7 (m, 2H), 4.6 (s, 2H), 2.25 (s, 2H), 1.6−2.1 (m, 8H). MS (ESI−): 594 (M − Li). Anal. ($C_{31}H_{31}F_2N_3O_3S_2\cdot0.41H_2O$) C, H, N.

3-Fluoro-5-aminopyridine (39). A suspension of 423 mg (3.0 mmol) of 5-fluoronicotinic acid (**38**) in 10 mL of $ClCH_2CH_2Cl$ was added 0.36 mL (3.3 mmol) of NMM. After stirring for 10 min, 0.71 mL (3.3 mmol) of DPPA was added dropwise and stirring continued for 30 min. The mixture was then slowly heated to 75 °C, wherein gas bubbles began to evolve. The temperature was maintained at 75 °C for 1 h, then 0.46 mL (4.5 mmol) of benzyl alcohol and ∼10 mg of CuCl were added, and the mixture was heated to reflux for 3 h. After cooling to room temperature, the mixture was concentrated in vacuo and the residue purified by column chromatography (40% ethyl acetate/hexanes) to give 415 mg (56%) of 3-fluoro-5-benzyloxycarbonylaminopyridine. ^{1}H NMR ($CDCl_3$): δ 8.21 (s, 1H), 8.18 (d, IH), 7.98 (dd, 1H), 7.31−7.43 (m, 5H), 7.05 (bs, 1H), 5.22 (s, 2H). MS (CI/NH_3): 247 (MH^+). The benzyloxycarbonyl derivative (408 mg, 1.66 mmol) was dissolved in 10 mL of MeOH, and the solution was degassed by a vacuum/N_2 purge sequence. To the solution were added 50 mg of 10% Pd/C and 522 mg of ammonium formate, and the mixture was heated to reflux for 1.5 h before cooling to room temperature. The mixture was diluted with 40 mL of ethyl acetate and filtered through a 1 in. by 2 in. pad of SiO_2, which was washed well with ethyl acetate. The filtrate was concentrated to give 181 mg (97%) of aminopyridine **39**. ^{1}H NMR ($CDCl_3$): δ 7.93 (t, 1H), 7.89 (d, 1H), 6.71 (dt, 1H). MS (CI/NH_3): 113 (MH^+).

4-(*N*-Benzyl-*N*-5-fluoro-3-pyridylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (40). Prepared by the same sequence as compound **26** substituting 5-fluoro-3-aminopyridine for 3-aminopyridine. ^{1}H NMR (DMSO-d_6): δ 8.12 (d, 1H), 7.91 (t, 1H), 7.75 (d, 1H), 7.47 (d, 1H), 7.21−7.38 (m, 6H), 7.19 (m, 2H), 7.10 (m, 3H), 6.92 (dt, 1H), 4.86 (s, 2H), 4.82 (s, 2H), 4.21 (m, 1H), 1.96−2.22 (m, 5H), 1.95 (s, 3H), 1.74−1.89 (m, 2H). MS (CI/NH_3): 558 (MH^+). Anal. ($C_{32}H_{32}FN_3O_3S\cdot0.46H_2O$) C, H, N.

***N*-Benzyl-5-aminopyrimidine (42).** A heterogeneous mixture of 5-bromopyrimidine (**41**) (1.62 g, 10.0 mmol), benzylamine (6.49 g, 60.0 mmol), potassium carbonate (1.66 g, 12.0 mmol), and CuO (40.0 mg, 0.500 mmol) was heated to reflux for 18 h. Vacuum filtration was followed by concentration of the filtrate. Flash column chromatography eluting with 30:70 hexane/ethyl acetate afforded 1.40 g of the title compound (76% yield). ^{1}H NMR ($CDCl_3$): δ 4.22−4.33 (br, 1H), 4.36 (d, 2H), 7.27−7.41 (comp, 5H), 8.13 (s, 2H), 8.59 (s, 1H). MS (CI/NH_3): 186 (MH^+).

4-(*N*-Benzyl-*N*-pyrimid-5-ylaminomethyl)-2-(2-methylphenyl)benzoylmethionine (43). Compound **42** was converted to the title compound in 24% overall yield by the same protocol as for **28**. ^{1}H NMR (DMSO-d_6): δ 1.48−1.74 (br comp, 2H), 1.86−2.08 (br comp, 8H), 3.62−3.74 (br, 1H), 4.83 (s, 2H), 4.89 (s, 2H), 6.92−7.03 (br, 1H), 7.04−7.38 (comp, 11H), 7.52 (d, 1H), 8.22 (s, 2H), 8.42 (s, 1H). HRMS (FAB+) calcd for $C_{31}H_{32}N_4O_3S$, 541.2273; obsd, 541.2254. Anal. ($C_{31}H_{31}LiN_4O_3S\cdot1.75H_2O$) C, H, N.

In Vitro Enzyme Assays. In vitro IC_{50} data were determined against FTase and GGTase1 (purified from bovine brain) using the SPA assay (scintillation proximity assay; Amersham, Arlington Heights, IL). The substrates used were

[^{3}H]farnesyl pyrophosphate and a biotin-linked k-Ras(B) decapeptide (KKSKTKCVIM for FTase or CVLL decapeptide for GGTase1). 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-Gly 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 ECL technique (ECL kit, Amersham, Arlington Heights, IL), and signals were quantified by densitometry using an image analysis program Image-Pro Plus (Media Cybernetics, Silver Spring, MD).

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