Identification of Pharmacokinetically Stable 3,10-Dibromo-8-chlorobenzocycloheptapyridine Farnesyl Protein Transferase Inhibitors with Potent Enzyme and Cellular Activities

Arthur G. Taveras,* Jeff Deskus, Jianping Chao, Cynthia J. Vaccaro, F. George Njoroge, Bancha Vibulbhan, Pat Pinto, Stacy Remiszewski, Jocelyn del Rosario, Ronald J. Doll, Carmen Alvarez, Tarik Lalwani, Alan K. Mallams, Randall R. Rossman, Adriano Afonso, Viyyoor M. Girijavallabhan, Ashit K. Ganguly, Birendra Pramanik, Larry Heimark, W. Robert Bishop, Lynn Wang, Paul Kirschmeier, Linda James, Donna Carr, Robert Patton, Mathew S. Bryant, Amin A. Nomeir, and Ming Liu

Anti-infectives and Tumor Biology Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033

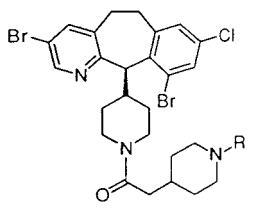
Received February 3, 1999

Farnesyl protein transferase (FPT) is a promising target for the development of cancer chemotherapeutics because it is responsible for the farnesylation of oncogenic p21 Ras proteins which are found in nearly 30% of all human cancers and necessary for cellular development and growth. The recent discovery and progression to phase II clinical trials of trihalobenzocycloheptapyridine Sch-66336 as a potent inhibitor of FPT with oral, in vivo efficacy in mice have spawned extensive structure−activity relationship studies (SAR) of this class of compounds. Of the many trihalobenzocycloheptapyridine analogues prepared, we have identified several which inhibit FPT and cellular proliferation at single-digit nanomolar concentrations *and* which have good pharmacokinetic properties in mice.

Introduction

The discovery of the Ras-mediated signal transduction pathway has led to an explosion of efforts aimed at understanding the mechanisms by which Ras communicates with intracellular components.[1] In recent years, these efforts have focused on the prenyl-transfer event of Ras protein, a process which is required for the inactive, cytosolic Ras to bind to cellular membranes and constitutively signal cellular growth.[2] In vitro and in vivo studies have shown that the inhibition of farnesyl protein transferase (FPT),[3] an enzyme which catalyzes the transfer of the farnesyl group from farnesyl pyrophosphate (FPP) to the CaaX motif of Ras,[3,4] reduces cellular proliferation in Ras-transformed rodent fibroblasts and in Ras transgenic tumors in mice.[5] Subsequently, a diverse array of FPT inhibitors including stable FPP mimics and competitive inhibitors of the CaaX motif (i.e., peptidomimetics, imidazole derivatives, and benzocycloheptapyridines) were identified and found to have antitumor properties in vitro and in vivo.[6]

Our initial discovery of Sch-44342 as a potent, nonpeptidic, nonsulfhydryl, selective inhibitor of FPT[7] prompted an investigation which culminated in the development of Sch-66336 (**5**), a trihalobenzocycloheptapyridine currently undergoing phase II clinical trials in humans.[8,9] Some of the structure−activity relationships (SAR) that have been observed for this class, and which were used to identify a suitable antitumor agent for further evaluation in humans, have been recently reported.[8] Subsequent studies have centered on expanding the scope of the SAR and identifying additional molecules within this class of FPT inhibitors which not only had good in vitro potencies and good pharmacokinetic properties but may also have different physical properties (i.e., crystallinity and solubility). We have discovered that modification of the substituent R attached to the terminal piperidine in **1** affected the biological properties of trihalobenzocycloheptapyridines. Herein, we report the details of our biological and pharmacokinetic studies of urea-, sulfonamide-, carboxamide-, and alkyl-substituted analogues of **1** (Table 1).



Sch-66336 (5), R = $CONH_2$
1, R = H

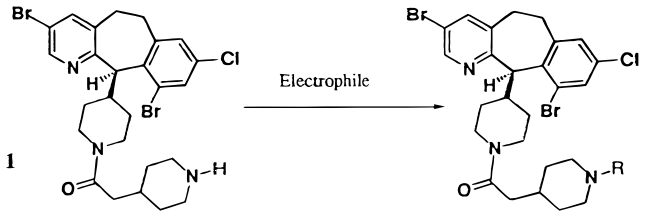
Chemistry

Most of the compounds listed in Table 1 were prepared in good yield as illustrated in Scheme 1 whereby piperidine **1**[8] was condensed with sulfonyl halides, isocyanates, or activated carboxylic acids. Whereas the condensation of **1** with dimethylsulfamoyl chloride afforded dimethylsulfonylurea **14** in excellent yield, the conversion of **1** to sulfonylurea **13** upon treatment with sulfamoyl chloride[10a] and triethylamine (TEA) at 0 °C was inefficient. Presumably a TEA-mediated or **1**-mediated dehydrohalogenation of sulfamoyl chloride generating, concomitantly, *N*-sulfonylamine ($HN{=}SO_2$) was competitive with sulfonylation of the piperidine amine in **1**.[10b] We have found, however, that sulfonylurea **13** could be prepared in good yield by stirring piperidine **1** in an aqueous mixture of sulfamide at reflux.

Aqueous acid hydrolysis of the ethyl ester function in **9**, prepared from ethyl isocyanatoacetate and **1**, gave

10.1021/jm990059k CCC: $18.00
Published on Web 06/23/1999

Scheme 1



acetic acid **7** (44%) which was converted further to carboxamide **8** using 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (DEC) and ammonium chloride.

Carbodiimide-mediated coupling of **1** with 3,5-pyridinedicarboxylic acid afforded **21** in 56% isolated yield. A subsequent DEC-mediated coupling of acid **21** with ammonium chloride in the presence of NMM afforded the desired nicotinamide **22**.

Amino acid analogues of **5** were prepared from *N*-BOC-glycine, *N*-BOC-D-alanine, and *N*-BOC-L-alanine and **1** using DEC and 1-hydroxybenzotriazole (HOBt) (Scheme 2). Trifluoroacetic acid (TFA)-mediated deprotection of the resulting carbamates **2a**−**c** afforded the desired 2-aminoacetamide analogues **15**−**17**, respectively.

Acylation of **1** with chloroacetyl chloride afforded 2-chloroacetamide **3** which was transformed further to the corresponding 2-pyrrolo- and 2-triazoloacetamide analogues **18** and **19**, respectively (Scheme 3). The complexity of the ^{1}H NMR spectrum of **19**, isolated as a single spot via preparative plate chromatography, may be indicative of regioisomeric triazole formation following sodium triazolide displacement of chloride **3** at 100 °C in DMF. However, a variable temperature ^{1}H NMR experiment caused partial coalescence of several resonances at 90 °C suggesting that the spectral complexity of **19** may be a result of rotameric isomerism.

Scheme 4 illustrates the synthesis of oxalamide and acetamide analogues of **5**. Acylation of **1** using ethyl oxalyl chloride in TEA and dichloromethane afforded ethyl oxalamide **4**, which could be further converted to oxalamide **25** by aminolysis under aqueous conditions (42%). Alternatively, oxalyl chloride treatment of **1** afforded an intermediate chloro oxalamide (not isolated) which similarly underwent aminolysis to afford **25**. Dimethyl oxalamide **26** could be prepared from **1** via a carbodiimide-mediated coupling using dimethyloxamic acid. Acetamides **27**−**29** were prepared by alkylation of the piperidine amine nitrogen atom in **1** with several haloacetamides as listed in Scheme 4.

Biological Methods

The FPT activity of the compounds listed in Table 1 was determined by measuring the transfer of [^{3}H]-farnesyl from [^{3}H]farnesyl pyrophosphate to TCA-precipitable His^6-H-Ras-CVLS. Experimental details of the FPT assay used in our study have been previously recorded by Bishop et al.[7a] The effect of compounds on Ras processing in Cos-1 monkey kidney cells transiently expressing either H-Ras-Val^{12}-CVLS or H-Ras-Val^{12} was performed according to the protocol disclosed previously.[7a] Anchorage-independent soft agar growth assays were performed on selected FPT inhibitors as has been previously described for **5**.[8] Pharmacokinetic evaluation of selected compounds listed in Table 2 was made according to the procedures already reported.[8,11]

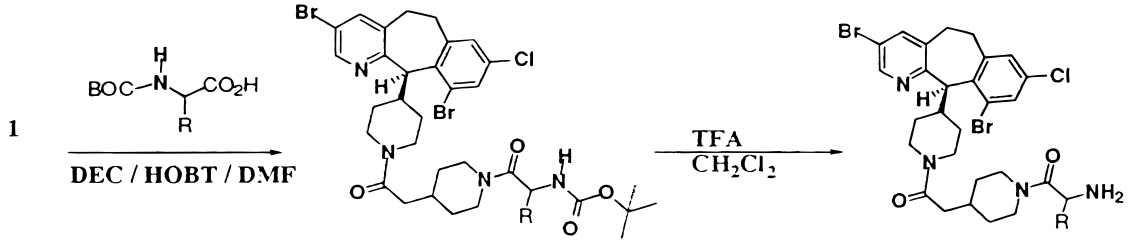
Results and Discussion

The biochemical and pharmacokinetic SAR leading to the discovery of **5** has recently been reported.[8] We have identified additional molecules within this class of compounds which have good binding affinities for FPT, inhibit FPT-mediated cellular growth of Cos cells with single-digit nanomolar potencies, inhibit tumor colony formation on soft agar media, and demonstrate good pharmacokinetic stability in nude mice. These structures differ in the substituent attached to the piperidinylacetamide nitrogen atom in **1** and include sulfonyl, amido, oxalyl, and 2-acetamide analogues of **5**. A list of the compounds prepared and evaluated is provided in Table 1 and described in detail herein.

Ureas. Some of the urea derivatives of **5** (**7** and **8**) listed in Table 1 were found to inhibit FPT-mediated farnesylation of Ras at picomolar concentrations. However, carboxylic acid **7** was found to be 15-fold less potent in the Cos cell assay compared to its acetamide analogue, **8**, possibly as a result of poor cellular penetration commonly exhibited by carboxylic acids. Good cellular potencies could be reinstated by conversion to the ethyl ester **9**. Of the modified ureas prepared, only **6** significantly inhibited tumor colony formation on soft agar.

Sulfonamides and Sulfonylureas. Sulfonylurea **13** inhibited Ras-mediated transformation of Cos cells slightly less effectively compared to **5**, while dimethylsulfonylurea **14** was just as effective as **5** on a cellular level albeit with a decrease in FPT potency. Steric effects near the sulfonyl moiety are detrimental to the binding affinity of these compounds as is evidenced by the drastic differences observed for methylsulfonamide **10** (IC_{50} = 2.0 nM) and phenylsulfonamide **11** (IC_{50} =

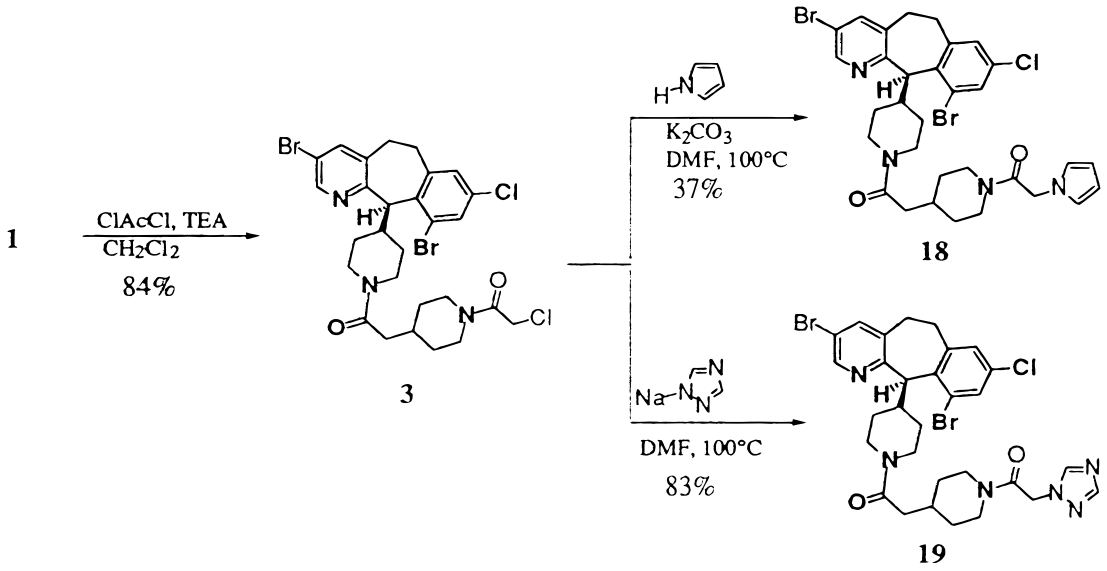
Scheme 2



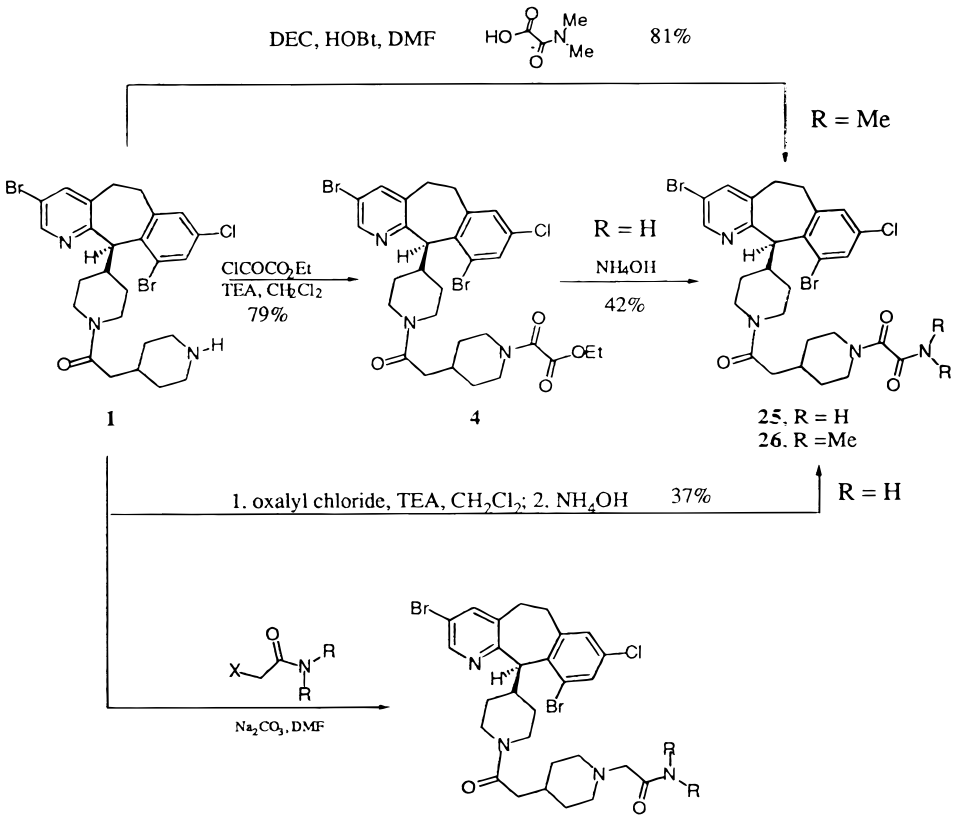
2a, R = H, 85%
2b, R = (R)-Me, 81%
2c, R = (S)-Me, 74%

15, R = H, 68%
16, R = (R)-Me, 64%
17, R = (S)-Me, 68%

Scheme 3



Scheme 4

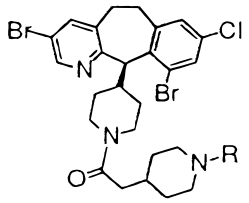


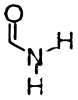
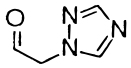
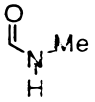
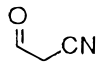
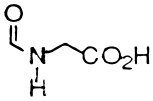
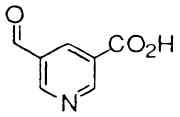
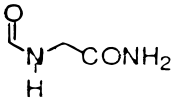
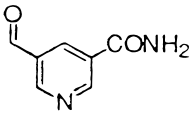
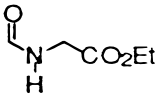
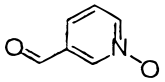
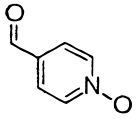
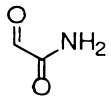
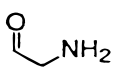
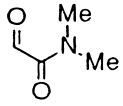
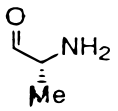
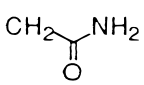
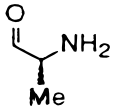
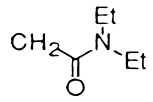
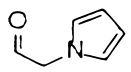
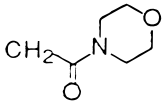
76 nM). Extension of the phenyl substituent by one methylene unit reinstates the FPT potency; however, the cellular potency of benzylsulfonamide **12** is significantly affected.

Amides. Modification of the piperidinylamine **1** with amino acids afforded compounds with reasonably good FPT binding affinities but generally with decreased cellular potencies.[12] An exception was demonstrated by glycyl analogue **15**. Interestingly, α-methyl substitution of the glycyl moiety had profoundly different effects in cell assays. Whereas D-alanyl **16** exhibited Cos cell activities similar to that of **15**, inhibition of tumor colony formation in soft agar media was diminished. The other stereoisomer, L-alanyl **17**, was significantly less effective against Cos cell growth demonstrating an IC_{50} of 140 nM.

α-Imidazole- and α-pyrrole-substituted acetamides demonstrated good biological profiles. Of the many substituted analogues prepared, pyrrole **18** and triazole **19** were found to be the optimal derivatives with the

Table 1. Biological Data of Trihalobenzocycloheptapyridine Analogues



		IC_{50} (nM)					IC_{50} (nM)		
Entry	R	Hras FPT[a]	Cos[b]	Agar[b]	Entry	R	Hras FPT[a]	Cos[b]	Agar[b]
5[c]		1.9 ± 0.1	10	75	19		1.8 ± 0.2	< 10	110
6		1.9 ± 0.1	8.5	100	20		2.6 ± 0.1	< 10	120
7		0.8 ± 0.2	360	>500	21		0.8 ± 0.1	>1000	>500
8		0.9 ± 0.1	25	330	22		2.2 ± 0.1	21	500
9		2.0 ± 0.2	22	310					
10	$S(O)_2Me$	2.0 ± 0.1	30	50	23		2.1 ± 0.1	7	165
11	$S(O)_2Ph$	76.1 ± 6.3			24		2.5 ± 0.0	10	130
12	$S(O)_2CH_2Ph$	17.1 ± 0.2	350						
13	$S(O)_2NH_2$	3.1 ± 0.2	35	200	25		2.7 ± 0.1	< 10	85
14	$S(O)_2N(CH_3)_2$	7.8 ± 0.3	9	100					
15		5.3 ± 0.4	30	75	26		2.1 ± 0.1	10	120
16		7.9 ± 2.2	39	200	27		2.1 ± 0.1	6	70
17		5.2 ± 0.7	140		28		4.3 ± 0.4	40	300
18		4.3 ± 0.2	9	460	29		5.3 ± 0.5	25	100

[a] Data shown are the mean of two experiments. A standard FTI (related to the compounds described) was run with each set of compounds. The range of IC_{50} values for this compound was 0.8−2.2 nM over 33 separate determinations on different days. The mean IC_{50} for this compound was 1.5 ± 0.4 nM (mean + standard deviation). The coefficient of variation for the assay (comparing no inhibitor control values) was typically on the order of 6.8%. [b] Single-point determinations. [c] See ref 8a.

Table 2. Pharmacokinetic Data of Trihalobenzocycloheptapyridine Analogues of **5**

		AUC μg.hr/mL		Cmax μM			
Entry	Vehicle[c]	po	iv	po	iv	$t_{1/2}$ (hr)	Bioavailability (%)
5	HPβCD	24.1	31.8	8.84	20	1.4	75.8
	MC	41.45		16.6			
10	HPβCD	0.95	9.52	1.3	30	0.53	10
13	HPβCD	5.6	26.1	3.6	30	1.5	22
14	HPβCD	0.1	5.95	0.49	30	1.3	1.7
15	HPβCD	5.84	125	2.92	80	1.4	4.7
19	HPβCD	1.97[a]	10.13[a]	2.15	22.58	0.28	19.5
20	MC	0.35	4.09	0.33	23.45	0.76	8.6
23	HPβCD	70.06	61.95	16.2	52.32	1.42	113
	MC	3.60	61.95	0.75	52.32		5.81
	MC	5.75[b]		2.27[b]			9.28[b]
24	HPβCD	15.72	13.68	9.81	19.79	1.2	115
	MC	2.0	13.68	1.07	19.79		14.6
25	HPβCD	44.97	27.08[a]	7.10	26.22	1.1	166
26	HPβCD	2.26[a]	7.53	3.2	26.29	1.04	30
27	HPβCD	12.2	20.3	1.94	30	4	60.2

[a] Run time = 7 h. [b] Micronized sample. [c] HPβCD, 20% aqueous hydroxypropyl-β-cyclodextrin; MC, 0.4% aqueous methyl cellulose. Compounds were administered to nude mice at a dose of 25 mpk, and serum was collected over a 24-h period (or 7 h where indicated).

desired enzyme and cellular potencies. The soft agar assay potency of **19** was found to be better, and hence, this compound was evaluated further in a pharmacokinetic screen. Substitution of the α-carbon with a cyano group also afforded a potent FPT inhibitor (**20**) with good cellular potencies.

Nicotinamides. Nicotinic acid analogues of **5**, exemplified by **21** (IC_{50} = 0.8 nM), were some of the most potent FPT inhibitors prepared in this study. As with other carboxylic acids, the Cos cell growth inhibition was poor (IC_{50} > 1 μM) but could be restored by conversion to nicotinamide **22**. Neither of these compounds, though, were found to inhibit growth of NIH-3T3 cells in the soft agar assay. The removal of the 3-carboxyl function and oxidation of the pyridyl nitrogen atom of **22** gave compounds with good enzyme and Cos cellular activities and with good H-Ras soft agar potencies. *N*-Oxides **23** and **24** were equipotent, inhibiting FPT with IC_{50} concentrations of approximately 2 nM. Their potencies in the Cos cell assay and their tumor colony growth inhibitory properties warranted their further study in vivo.

Oxalamides and Acetamides. Oxalamides **25** and **26** were found to be potent FPT inhibitors and to possess good cellular growth inhibitory properties. The similarity in enzyme and cellular data between the NH_2 and $N(Me)_2$ oxalamides was surprising considering the differences in lipophilicity of each moiety. Other substituted oxalamides prepared in our laboratories (not shown) had good FPT binding affinities but did not inhibit tumor colony growth on soft agar at low concentrations. Reduction of one carbonyl moiety in **25** to a methylene unit afforded acetamides represented by **27** whose in vitro biological profile was nearly identical to that of **5**. Disubstitution of the nitrogen atom of the acetamide (i.e., diethylacetamide **28** or morpholino **29**) resulted in a slight reduction in enzyme potency as well as a decrease in potency in the soft agar assay. Other compounds prepared within this series demonstrated similar activity profiles.

Pharmacokinetic Studies. Of the many compounds prepared in this study, several potent FPT inhibitors that had the desired cellular potencies in both the Cos cell and the soft agar assays were evaluated further for pharmacokinetic stability. The results of this study (Table 2) show significant differences between bioavailability and oral AUC among the 12 compounds studied despite the fact that these structures differ only by the substituent on the piperidinylacetamide nitrogen. The poorest oral bioavailability in mice was seen with all sulfonyl-containing compounds studied (**10**, **13**, **14**), although sulfonylurea **13** had a significantly greater AUC than its dimethyl derivative **14** which may be related to their solubility differences (not determined). A similar effect was noted for dimethyl oxalamide **26** and its dihydrido analogue, **25**. The greater oral bioavailability of **25** (166%) is unusual, yet not unprecedented.[14] Although the exact mechanism for this phenomenon is not known, it is possible that saturation and subsequent inhibition of liver cytochrome P450s by

orally administered **25** could diminish metabolic degradation of this compound relative to the more-dilute concentrations of **25** that the liver would be exposed to following iv administration. Urea **5** is known to be a P450 inhibitor (CYP3A4 $IC_{50} = 300$ nM),[8a] and **25**, being similar in structure, might be expected to share a similar inhibitory activity (not measured). The overall profile of **25** is good, although a small percentage of the product resulting from oxalamide hydrolysis (**1**) was detected in the serum. The major metabolite identified in mice treated with **25** was its pyridyl *N*-oxide analogue.

Acetamide **27** was 60% bioavailable in nude mice with an oral AUC of 12.2 μM·h over a 24-h period. This compound, having a nearly equivalent in vitro profile compared to **5**, had a lower oral C_{max} while maintaining a 3-fold better serum half-life contributing to a pharmacokinetic profile that was slightly inferior to that of **5**. Transposition of the carbonyl function of **27** closer to the piperidinylamine nitrogen atom afforded glycinamide **15** which had a higher iv C_{max} (80 μM), but poor bioavailability. Substitution of the amino function, as in **19**, with triazole improved the bioavailability slightly. However, the half-life of this compound was 5 times less than that of its glycine precursor.

Nicotinamide *N*-oxide **23** was found to be the most promising compound, having an overall in vitro profile nearly equivalent to that of **5** and having better pharmacokinetic properties in mice. Piperidyl *N*-oxides **23** and **24** were depleted from the sera of nude mice at the same rate as **5**, while the bioavailability of the *p*-*N*-oxide **24** was found to be 115%. *m*-*N*-Oxide **23**, with an oral bioavailability of 113%, had an oral AUC of 70 μM·h over 24 h in nude mice using HPβCD as vehicle. When the vehicle was replaced with methyl cellulose, however, the oral bioavailability and AUC values for both *N*-oxides were significantly decreased. The overall pharmacokinetic profile improved when a micronized sample of **23** was suspended in methyl cellulose suggesting that the poorer profile of this compound using this vehicle over HPβCD is related to solubility. Pharmacokinetic evaluation of **23** in mice using other vehicles has not been studied. The greater than 100% bioavailability observed for **23** and **24** may be due to variability between individual animals during the pharmacokinetic study as each time point is a determination based on sera collected from different animals.

Conclusion

We have discovered urea-, sulfonamide-, carboxamide-, and alkyl-substituted derivatives of **1** (Table 1) which have good cellular and enzyme potencies against FPT-mediated farnesylation of Ras. Although many of the differentially substituted analogues listed in Table 1 share similar FPT inhibitory potencies, these modifications greatly influence tumor colony formation as demonstrated by the range of soft agar activities observed for these compounds. These substituents also modulate the pharmacokinetic properties of the molecules. Whereas all of the sulfonylurea, sulfonamide and *N*-acylacetamide analogues of **5** listed in Table 2 showed poor pharmacokinetics in mice, nicotinamides **23** and **24**, oxalamide **25**, and alkylamide **27** were better absorbed and maintained good serum levels in mice when treated orally. In vivo evaluation of these and other compounds for tumor growth inhibitory properties will determine whether these compounds will be progressed further as therapeutic agents.

Experimental Section

General Methods. All reagents were used without further purification. Melting points were determined using an Electrothermal digital melting point apparatus and are uncorrected. Elemental analyses were performed on either a Leeman CE 440 or a FISONS EA 1108 elemental analyzer. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian VXR-200 (200 MHz) or a Varian Gemini-300 (300 MHz) NMR spectrometer using Me_4Si as an internal standard. For ^{13}C NMR, a Nalorac Quad nuclei probe was used. FT-IR spectra were recorded using a BOMEN Michelson 120 spectrometer. Mass spectra were recorded using either EXTREL 401 (chemical ionization), JEOL or MAT-90 (FAB), or VG ZAB-SE (SIMS) mass spectrometers. Microanalyses were performed by the Physical-Analytical Chemistry Department at Schering-Plough Research Institute.

(+)-1,1-Dimethylethyl 2-[4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinyl]-2-oxoethylcarbamate (2a). A mixture of **1** (149 mg, 0.25 mmol), *N*-BOC-glycine (87.3 mg, 0.50 mmol), HOBt (67.4 mg, 0.50 mmol), DEC (95.6 mg, 0.50 mmol), and dry DMF (5 mL) was stirred at 25 °C for 12 h. The mixture was concentrated in vacuo, diluted with CH_2Cl_2, washed with 1 M HCl, washed with 1 M NaOH (aq), and dried over anhydrous $MgSO_4$ to afford the product as a white solid: 159 mg, 85%; mp = 116−123 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81−1.95 (m, 7H), 1.42 (overlapping s, 9H), 1.99−2.50 (m, 6H), 2.63 (m, 1H), 2.74−3.12 (m, 4H), 3.25 (m, 1H), 3.51−4.06 (m, 3H), 3.92 (overlapping s, 2H), 4.57 (m, 2H), 4.90 (d, 1H, J = 10 Hz), 5.54 (m, 1H), 7.16 (s, 1H), 7.50 (s, 1H), 7.53 (s, 1H), 8.45 (s, 1H); MS (FAB) *m*/*z* 751 (MH^+, 16%), 753 ($MH^+ + 2$, 33%), 755 ($MH^+ + 4$, 24%), 651 ($MH^+ -$ BOC, 50%), 653 ($MH^+ + 2 -$ BOC, 90%), 655 ($MH^+ + 4 -$ BOC, 66%); HRFABMS calcd for $C_{33}H_{42}N_4O_4Br^{81}BrCl$ M_r 753.1241 (MH^+), found 753.1212.

(+)-1,1-Dimethylethyl 2-[4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinyl]-1(*R*)-methyl-2-oxoethylcarbamate (2b). Prepared as for **2a** using *N*-BOC-D-alanine: white solid; 104 mg, 81%; mp = 135.1−142.3 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92−1.64 (m, 6H), 1.24 (overlapping d, 3H, J = 7 Hz), 1.39 (overlapping s, 9H), 1.78 (m, 2H), 1.96−2.47 (m, 5H), 2.57 (m, 1H), 2.69−3.12 (m, 4H), 3.20 (m, 1H), 3.57 (m, 1H), 3.76 (m, 2H), 4.53 (m, 3H), 4.85 (d, 1H, J = 10 Hz), 5.53 (d, 1H, J = 7 Hz), 7.09 (s, 1H), 7.44 (d, 1H, J = 2 Hz), 7.50 (s, 1H), 8.39 (d, 1H, J = 2 Hz); $[\alpha]^{22.8}_D$ = +32.38° (10.0 mg/2 mL, CH_2Cl_2); MS (FAB) *m*/*z* 765 (MH^+, 16%), 767 ($MH^+ + 2$, 31%), 769 ($MH^+ + 4$, 22%); 665 ($MH^+ -$ BOC, 19%), 667 ($MH^+ + 2 -$ BOC, 37%), 669 ($MH^+ + 4 -$ BOC, 26%); HRFABMS calcd for $C_{34}H_{44}N_4O_4Br^{81}BrCl$ M_r 767.1397 (MH^+), found 767.1372.

(+)-1,1-Dimethylethyl 2-[4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinyl]-1(*S*)-methyl-2-oxoethylcarbamate (2c). Prepared as for **2a** using *N*-BOC-L-alanine: off-white solid; 95.3 mg, 74%; mp = 135.0−142.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.8−1.58 (m, 6H), 1.24 (overlapping d, 3H, J = 7 Hz), 1.38 (overlapping s, 9H), 1.77 (m, 2H), 1.94−2.45 (m, 5H), 2.58 (m, 1H), 2.69−3.12 (m, 4H), 3.20 (m, 1H), 3.56 (m, 1H), 3.78 (m, 1H), 4.55 (m, 3H), 4.85 (d, 1H, J = 10 Hz), 5.52 (d, 1H, J = 7 Hz), 7.09 (s, 1H), 7.45 (s, 1H), 7.49 (s, 1H), 8.40 (s, 1H); $[\alpha]^{22.5}_D$ = +44.41° (10.0 mg/2 mL, CH_2Cl_2); MS (FAB) *m*/*z* 765 (MH^+, 14%), 767 ($MH^+ + 2$, 28%), 769 ($MH^+ + 4$, 19%); 665 ($MH^+ -$ BOC, 19%), 667 ($MH^+ + 2 -$ BOC, 37%), 669 ($MH^+ + 4 -$ BOC, 25%); HRFABMS calcd for $C_{34}H_{44}N_4O_4Br^{81}BrCl$ M_r 767.1397 (MH^+), found 767.1379.

(+)-1-[[1-(Chloroacetyl)-4-piperidinyl]acetyl]-4-(3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta-

[1,2-*b*]pyridin-11-yl)piperidine (3). A solution of **1** (3 g, 5 mmol), anhydrous CH_2Cl_2 (50 mL), triethylamine (1.4 mL, 10 mmol), and chloroacetyl chloride (0.4 mL, 5 mmol) was stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2, washed with 1 M HCl, washed with 1 M NaOH (aq), and dried over anhydrous $MgSO_4$ to afford a light-yellow solid: 2.84 g, 84%; mp = 124.0−134.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.04−1.68 (m, 6H), 1.86 (m, 2H), 2.03−2.54 (m, 5H), 2.57−3.41 (m, 6H), 3.63 (m, 1H), 3.84 (m, 2H), 4.09 (m, 2H), 4.60 (m, 2H), 4.93 (d, 1H, J = 10 Hz), 7.17 (s, 1H), 7.52 (br s, 1H), 7.58 (s, 1H), 8.48 (s, 1H); $[\alpha]^{21.3}_D$ = +54.0° (6.15 mg/2 mL, CH_2Cl_2); MS (FAB) *m*/*z* 670 (MH^+, 42%), 672 ($MH^+ + 2$, 100%), 674 ($MH^+ + 4$, 91%).

(+)-Ethyl 4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-α-oxo-1-piperidineacetate (4). At 0 °C, a solution of **1** (1.5 g, 2.5 mmol), anhydrous CH_2Cl_2 (40 mL), triethylamine (0.6 mL, 4.3 mmol), and ethyl oxalyl chloride (0.4 mL, 3.6 mmol) was prepared and then allowed to stir at room temperature for 3 h. The mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (aq), washed with brine, and dried over anhydrous Na_2SO_4 to afford a residue which was purified by flash column chromatography (silica gel) using 30−80% EtOAc−hexane: 1.2 g, 69%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06−1.69 (m, 9H), 1.85 (m, 2H), 2.03−2.52 (m, 4H), 2.61−3.36 (m, 7H), 3.60 (m, 2H), 3.79 (m, 1H), 4.32 (m, 2H), 4.55 (m, 2H), 4.90 (d, 1H, J = 10 Hz), 7.15 (s, 1H), 7.50 (d, 1H, J = 2 Hz), 7.55 (s, 1H), 8.45 (d, 1H, J = 2 Hz); MS (FAB) *m*/*z* 694 (MH^+, 51%), 696 ($MH^+ + 2$, 100%), 698 ($MH^+ + 4$, 70%). Anal. ($C_{30}H_{34}N_3O_4Br_2Cl\cdot 0.5TEA\cdot 1.3H_2O$) C, H, N.

(+)-4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-*N*-methyl-1-piperidinecarboxamide (6). To a solution of **(+)−1** (75 mg, 0.13 mmol) in anhydrous dichloromethane (1.5 mL) was added methyl isocyanate (0.01 mL, 0.17 mmol). After stirring at 25 °C for 12 h the solution was poured into dichloromethane and washed with aqueous sodium bicarbonate (saturated solution) and brine. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give a white solid: mp = 92.5−95.8; ^{1}H NMR (mixture of rotamers, 400 MHz, $CDCl_3$) δ 1.12−1.58 (m, 5H), 1.78 (m, 2H), 2.03 (m, 1H), 2.23 (m, 2H), 2.39 (m, 2H), 2.81 (overlapping s, 3H), 2.73−2.92 (m, 5H), 3.02 (m, 1H), 3.31 (m, 1H), 3.62 (m, 1H), 3.88 (m, 4H), 4.62 (m, 1H), 5.0 (m, 1H), 7.16 (s, 1H), 7.52 (s, 1H), 7.62, 7.68 (two s, 1H), 8.49, 8.50 (two s, 1H); MS (FAB) *m*/*z* 651 (MH^+, 49%), 653 ($MH^+ + 2$, 100%), 655 ($MH^+ + 4$, 74%).

(+)-[[[4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinyl]carbonyl]amino]acetic Acid (7). A solution of ethyl carboxylate **9** (0.56 g, 0.75 mmol) dissolved in 6 M HCl (aq, 4 mL) was stirred at room temperature for 72 h. Water was added to adjust the molarity of the solution to 1 M, and the resultant mixture was stirred with dichloromethane and concentrated in vacuo. The residue was diluted with 50% MeOH−HOAc and purified by reverse-phase chromatography (C-18 reverse-phase silica equilibrated with 10% MeOH (0.1% HOAc)−H_2O) using 50% MeOH (0.1% HOAc)−H_2O (1 L) and 90% MeOH (0.1% HOAc)−H_2O (1 L) to give the product as a white solid: 232 mg, 44%; mp = 123.4−125.8 °C; ^{1}H NMR (mixture of rotamers, 400 MHz, $CDCl_3$) δ 1.13−1.58 (m, 5H), 1.77 (m, 2H), 2.05 (m, 1H), 2.25 (m, 2H), 2.40 (m, 2H), 2.86 (m, 4H), 3.0 (m, 1H), 3.28 (m, 1H), 3.62 (m, 1H), 3.73−4.13 (m, 6H), 4.61 (m, 1H), 4.89 (dd, 1H, J = 10 Hz, J = 10 Hz), 5.35 (m, 1H), 7.15 (s, 1H), 7.50 (s, 1H), 7.56, 7.59 (two s, 1H), 8.47, 8.53 (two s, 1H); MS (FAB) *m*/*z* 695 (MH^+, 47%), 697 ($MH^+ + 2$, 100%), 699 ($MH^+ + 4$, 72%). Anal. ($C_{29}H_{33}N_4O_4Br_2Cl\cdot H_2O\cdot 0.5CH_2Cl_2$) C, H, N.

(+)-*N*-(2-Amino-2-oxoethyl)-4-[2-[4-(3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide (8). A mixture of **7** (60 mg, 0.09 mmol), ammonium chloride (28 mg, 0.52 mmol), HOBt (17 mg, 0.13 mmol), DEC (25 mg, 0.13 mmol), *N*-methylmorpholine (0.015 mL, 0.13 mmol), and dry DMF (1 mL) was stirred at 25 °C for 12 h. The mixture was diluted with water (10 mL), and after 1 h, the resulting precipitate was filtered and dried in vacuo. The product was isolated as a white solid: mp =144.8−149.8 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03−1.90 (m, 7H), 2.05 (m, 1H), 2.22 (m, 2H), 2.40 (m, 2H), 2.72−3.12 (m, 5H), 3.27 (m, 1H), 3.51−4.08 (m, 7H), 4.60 (m, 1H), 4.90 (d, 1H, J = 10 Hz), 5.24 (m, 1H), 5.42 (m, 1H), 6.36 (m, 1H), 7.15 (br s, 1H), 7.50 (br d, 1H, J = 2 Hz), 7.56 (br s, 1H), 8.45 (br d, 1H, J = 2 Hz); MS (FAB) *m*/*z* 694 (MH^+, 47%), 696 ($MH^+ + 2$, 100%), 698 ($MH^+ + 4$, 70%); HRFABMS calcd for $C_{29}H_{35}N_5O_3Br^{81}BrCl$ M_r 696.0775 (MH^+), found 696.0777. Anal. ($C_{29}H_{34}N_5O_3Br_2Cl\cdot 1.0H_2O$) C, H, N.

(+)-Ethyl [[[4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinyl]carbonyl]amino]-acetate (9). To a solution of **(+)−1** (90 mg, 0.15 mmol) in anhydrous dichloromethane (1.5 mL) was added ethyl isocyanatoacetate (0.04 mL, 0.36 mmol). After stirring at 25 °C for 3 h, the solution was poured into dichloromethane and washed with aqueous sodium bicarbonate (saturated solution) and brine. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give a residue which was purified by flash column chromatography (silica gel) using methanol−dichloromethane (2%, 1 L; 4%, 1 L): white solid; 45 mg, 40% yield: mp = 126.4−128.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.82 (m, 8H), 1.29 (overlapping t, 3H, J = 7 Hz), 2.03 (m, 1H), 2.23 (m, 2H), 2.40 (m, 2H), 2.86 (m, 4H), 3.0 (m, 1H), 3.28 (m, 1H), 3.63 (m, 1H), 3.83 (m, 1H), 3.92−4.03 (m, 4H), 4.22 (q, 2H, J = 7 Hz), 4.61 (m, 1H), 4.93 (m, 2H), 7.15 (br s, 1H), 7.51 (s, 1H), 7.57 (m, 1H), 8.47 (s, 1H); MS (FAB) *m*/*z* 723 (MH^+, 43%), 725 ($MH^+ + 2$, 100%), 727 ($MH^+ + 4$, 77%). Anal. ($C_{31}H_{37}N_4O_4Br_2Cl\cdot H_2O$) C, H, N.

(+)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-[[1-(methylsulfonyl)-4-piperidinyl]acetyl]piperidine (10). A solution of **1** (0.11 g, 0.185 mmol), anhydrous CH_2Cl_2 (10 mL), triethylamine (0.04 mL, 0.28 mmol), and methanesulfonyl chloride (0.02 mL, 0.22 mmol) was stirred at room temperature for 12 h. The mixture was diluted with CH_2Cl_2, washed with 1 M HCl, washed with 1 M NaOH (aq), and dried over anhydrous $MgSO_4$ to afford the product as a white solid: 0.1 g, 80%; mp = 133−136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10−1.60 (m, 5H), 1.60−2.08 (m, 3H), 2.12−2.50 (m, 4H), 2.51−3.10 (m, 6H), 2.72 (overlapping s, 3H), 3.22 (m, 1H), 3.58 (m, 1H), 3.74 (m, 3H), 4.55 (m, 1H), 4.86 (d, 1H, J = 10 Hz), 7.09 (br s, 1H), 7.46 (d, 1H, J = 2 Hz), 7.50 (br s, 1H), 8.40 (d, 1H, J = 2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (mixture of rotamers) 29.71, 30.74, 31.05, 31.32, 31.38, 31.52, 31.63, 31.71, 31.85, 31.94, 33.88, 38.59, 41.33, 41.43, 41.52, 41.69, 45.22, 45.34, 45.77, 57.60, 57.69, 118.48, 128.70, 128.77, 130.63, 130.70, 140.92, 141.06, 142.11, 142.23, 146.91, 147.02, 154.33, 168.87; $[\alpha]^{25}_D$ = +23.8° (2.35 mg/2 mL, DMSO); MS (FAB) *m*/*z* 672 (MH^+, 53%), 674 ($MH^+ + 2$, 100%), 676 ($MH^+ + 4$, 72%); HRFABMS calcd for $C_{27}H_{33}N_3O_3SBr_2Cl$ M_r 672.0298 (MH^+), found 672.0283. Anal. ($C_{27}H_{32}N_3O_3SBr_2Cl$) C, H, N.

(+)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-[[1-(phenylsulfonyl)-4-piperidinyl]acetyl]piperidine (11). A solution of **1** (0.10 g, 0.17 mmol), anhydrous CH_2Cl_2 (10 mL), triethylamine (0.04 mL, 0.26 mmol), and benzenesulfonyl chloride (0.03 mL, 0.21 mmol) was stirred at room temperature for 12 h. The mixture was diluted with CH_2Cl_2, washed with 1 M HCl (aq), washed with 1 M NaOH (aq), and dried over anhydrous $MgSO_4$ to afford the product as a white solid: 0.11 g, 89%; mp = 102−105 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02−1.58 (m, 6H), 1.72 (m, 3H), 1.92−2.43 (m, 6H), 2.65−3.05 (m, 3H), 3.20 (m, 1H), 3.56 (m, 1H), 3.72 (m, 3H), 4.51 (m, 1H), 4.83 (d, 1H, J = 10 Hz), 7.10 (s, 1H), 7.40−8.09 (m, 7H), 8.40 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (mixture of rotamers) 29.71, 30.73, 31.11, 31.20, 31.37, 31.49, 31.61, 31.69, 31.74, 31.86, 38.56, 38.61, 41.29, 41.46, 41.51, 41.65, 45.20, 45.33, 45.95, 57.61, 57.68, 118.46, 126.52, 127.17, 128.53, 128.70, 128.77, 129.25, 130.62,

130.67, 132.26, 134.68, 134.81, 140.91, 141.06, 142.12, 146.89, 146.99, 168.85; $[\alpha]^{25}_D = +18.7°$ (3.85 mg/2 mL, DMSO); MS (FAB) *m/z* 734 (MH^+, 45%), 736 ($MH^+ + 2$, 100%), 738 ($MH^+ + 4$, 72%); HRFABMS calcd for $C_{32}H_{35}N_3O_3SBr_2Cl$ M_r 734.0454 (MH^+), found 734.0448. Anal. ($C_{32}H_{34}N_3O_3Br_2ClS \cdot 0.7CH_2Cl_2$) C, H, N.

(+)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-[[1-[(phenylmethyl)sulfonyl]-4-piperidinyl]acetyl]piperidine (12). A solution of **1** (0.10 g, 0.17 mmol), anhydrous CH_2Cl_2 (10 mL), triethylamine (0.04 mL, 0.26 mmol), and phenylmethanesulfonyl chloride (43 mg, 0.23 mmol) was stirred at room temperature for 12 h. The mixture was diluted with CH_2Cl_2, washed with 1 M HCl (aq), washed with 1 M NaOH (aq), and dried over anhydrous $MgSO_4$ to afford the product as an off-white solid: 87 mg, 69%; mp = 116−132 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95−1.55 (m, 7H), 1.65 (m, 1H), 1.84 (m, 1H), 2.12 (m, 2H), 2.22−2.63 (m, 4H), 2.67−3.08 (m, 3H), 3.22 (m, 1H), 3.56 (m, 3H), 3.75 (m, 1H), 4.16 (s, 2H), 4.54 (m, 1H), 4.85 (d, 1H, J = 10 Hz), 7.11 (s, 1H), 7.35 (s, 5H), 7.45 (s, 1H), 7.50 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (mixture of rotamers) 30.24, 31.26, 31.90, 32.16, 32.23, 32.33, 32.49, 32.58, 39.13, 41.84, 42.02, 42.06, 42.21, 45.75, 45.88, 46.39, 56.85, 58.13, 58.21, 118.99, 127.22, 127.34, 128.77, 128.82, 129.01, 129.06, 129.22, 129.29, 130.74, 131.17, 131.22, 133.26, 135.19, 135.34, 137.11, 137.38, 141.42, 141.55, 142.65, 142.75, 147.45, 147.55, 154.78, 154.89, 169.46; $[\alpha]^{23.7}_D = +42.6°$ (3.38 mg/2 mL, CH_2Cl_2); MS (FAB) *m/z* 748 (MH^+, 47%), 750 ($MH^+ + 2$, 100%), 752 ($MH^+ + 4$, 73%). Anal. ($C_{33}H_{36}N_3O_3Br_2ClS$) C, H, N.

(+)-4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinesulfonamide (13). To a solution of **1** (0.298 g, 0.50 mmol) dissolved in anhydrous CH_2Cl_2 (5 mL), anhydrous acetonitrile (10 mL), and triethylamine (0.22 mL, 1.5 mmol) cooled to 0 °C was added dropwise a solution of sulfamoyl chloride (0.12 g, 1 mmol) dissolved in acetonitrile (2 mL). The resulting mixture was stirred at 0 °C for 1 h and then at 25 °C for 48 h. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, washed with 1 M HCl, washed with 1 M NaOH (aq), and dried over anhydrous $MgSO_4$. The tan residue was purified by preparative plate chromatography (silica gel) using 5% MeOH−CH_2Cl_2 saturated with NH_4OH to afford the product as a white solid: 47 mg, 14%; mp = 151.5−155.6 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12−1.58 (m, 5H), 1.71−2.02 (m, 3H), 2.20 (m, 2H), 2.35 (m, 2H), 2.50−3.05 (m, 6H), 3.22 (m, 1H), 3.45−3.89 (m, 4H), 4.32 (s, 1H), 4.56 (m, 1H), 4.87 (d, 1H, J = 10 Hz), 7.11 (s, 1H), 7.47 (d, 1H, J = 2 Hz), 7.51 (s, 1H), 8.41 (d, 1H, J = 2 Hz); $[\alpha]^{22.5}_D = +47.7°$ (5.37 mg/2 mL, CH_2Cl_2); MS (FAB) *m/z* 673 (MH^+, 47%), 675 ($MH^+ + 2$, 100%), 677 ($MH^+ + 4$, 72%); HRFABMS calcd for $C_{26}H_{32}N_4O_3SBrClBr^{81}$ M_r 675.0230 (MH^+), found 675.0232. Anal. ($C_{26}H_{31}N_4O_3Br_2ClS \cdot H_2O$) C, H, N.

Alternate Procedure for 13. A mixture of **1** (100 mg, 0.17 mmol), sulfamide (0.16 g, 1.7 mmol), and water (20 mL) was stirred at reflux for 5 days. The mixture was concentrated in vacuo, diluted with CH_2Cl_2, and purified by preparative plate chromatography (silica gel) using 5% MeOH−CH_2Cl_2 saturated with NH_4OH to afford the product as a white solid: yield 65% based on recovered **1** (50 mg).

(+)-4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinyl]-2-oxoethyl]-*N*,*N*-dimethyl-1-piperidinesulfonamide (14). A solution of **1** (0.20 g, 0.34 mmol), anhydrous CH_2Cl_2 (10 mL), triethylamine (0.08 mL, 0.50 mmol), and dimethylsulfamoyl chloride (0.04 mL, 0.40 mmol) was stirred at room temperature for 12 h. The mixture was diluted with CH_2Cl_2, washed with 1 M HCl (aq), washed with 1 M NaOH (aq), and dried over anhydrous $MgSO_4$ to afford the product as a white solid: 220 mg, 93%; mp = 107.4−109.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12−1.66 (m, 5H), 1.78 (m, 2H), 1.95 (m, 1H), 2.21 (m, 2H), 2.38 (m, 2H), 2.71−3.10 (m, 6H), 2.80 (overlapping s, 6H), 3.24 (m, 1H), 3.50−3.90 (m, 4H), 4.58 (m, 1H), 4.88 (d, 1H, J = 10 Hz), 7.12 (s, 1H), 7.48 (s, 1H), 7.52 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (mixture of rotamers) 29.72, 30.72, 30.78, 31.38, 31.50, 31.63, 31.72, 32.14, 37.77, 38.75, 41.32, 41.51, 41.55, 41.71, 45.29, 45.41, 46.13, 57.60, 57.67, 118.46, 128.68, 128.75, 130.65, 130.71, 140.86, 141.00, 142.09, 142.22, 146.92, 147.04, 169.03; $[\alpha]^{25}_D = +29.3°$ (4.64 mg/2 mL, DMSO); MS (FAB) *m/z* 701 (MH^+, 46%), 703 ($MH^+ + 2$, 100%), 705 ($MH^+ + 4$, 72%); HRFABMS calcd for $C_{28}H_{36}N_4O_3SBr_2Cl$ M_r 701.0563 (MH^+), found 701.0547. Anal. ($C_{28}H_{35}N_4O_3Br_2ClS \cdot H_2O$) H, N; C: calcd, 46.65; found, 44.83.

(+)-1-[[1-(Aminoacetyl)-4-piperidinyl]acetyl]-4-(3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-yl)piperidine (15). A solution of **2a** (0.145 g, 0.19 mmol) dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic acid (2 mL) was stirred at 25 °C for 12 h. Aqueous NaOH (50%) was slowly added until the reaction mixture was basic followed by brine, and the mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a white solid: 86 mg, 68%; mp = 131−138 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98−1.62 (m, 5H), 1.82 (m, 2H), 1.95−2.51 (m, 9H), 2.64 (m, 1H), 2.74−3.13 (m, 4H), 3.28 (m, 1H), 3.42−3.93 (m, 4H), 4.58 (m, 2H), 4.89 (d, 1H, J = 10 Hz), 7.15 (s, 1H), 7.51 (d, 1H, J = 2 Hz), 7.55 (s, 1H), 8.45 (d, 1H, J = 2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (mixture of rotamers) 29.70, 30.71, 30.76, 31.35, 31.50, 31.61, 31.70, 31.82, 32.08, 32.67, 38.77, 38.88, 41.30, 41.50, 41.60, 41.67, 41.96, 43.88, 45.26, 45.38, 57.59, 57.68, 118.45, 126.79, 128.69, 130.61, 130.68, 132.69, 132.73, 134.65, 134.81, 134.83, 136.53, 136.84, 140.88, 141.01, 142.08, 142.22, 146.88, 147.01, 154.20, 154.35, 168.93; $[\alpha]^{25}_D = +33.8°$ (6.34 mg/2 mL, MeOH); MS (ZAB) *m/z* 651 (MH^+, 52%), 653 ($MH^+ + 2$, 100%), 655 ($MH^+ + 4$, 70%); HRFABMS calcd for $C_{28}H_{34}N_4O_2Br_2Cl$ M_r 651.0737 (MH^+), found 651.0746. Anal. ($C_{28}H_{33}N_4O_2Br_2Cl \cdot 2H_2O$) C, H, N.

(+)-1-(2(*R*)-Amino-1-oxopropyl)-4-[2-[4-(3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]piperidine (16). Prepared as for **15**: off-white solid; 56 mg, 64%; mp = 103 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75−1.59 (m, 6H), 1.20 (overlapping d, 3H, J = 7 Hz), 1.62−2.48 (m, 10H), 2.57 (m, 1H), 2.69−3.11 (m, 4H), 3.13−3.40 (m, 1H), 3.57 (m, 1H), 3.76 (m, 2H), 4.55 (d, 2H, J = 12 Hz), 4.86 (d, 1H, J = 10 Hz), 7.11 (s, 1H), 7.46 (d, 1H, J = 2 Hz), 7.51 (s, 1H), 8.41 (d, 1H, J = 2 Hz); $[\alpha]^{22.7}_D = +44.8°$ (3.48 mg/2 mL, CH_2Cl_2); MS (FAB) *m/z* 665 (MH^+, 45%), 667 ($MH^+ + 2$, 100%), 669 ($MH^+ + 4$, 69%). Anal. ($C_{29}H_{35}N_4O_2Br_2Cl \cdot 0.25CH_2Cl_2$) C, H, N.

(+)-1-(2(*S*)-Amino-1-oxopropyl)-4-[2-[4-(3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]piperidine (17). Prepared as for **15**: off-white solid; 53.2 mg, 68%; mp = 122.7−128 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.7−1.1 (m, 9H), 1.64−2.46 (m, 10H), 2.58 (m, 1H), 2.70−3.11 (m, 4H), 3.21 (m, 1H), 3.58 (m, 1H), 3.78 (m, 2H), 4.56 (m, 2H), 4.84 (d, 1H, J = 10 Hz), 7.11 (s, 1H), 7.46 (s, 1H), 7.50 (s, 1H), 8.40 (s, 1H); $[\alpha]^{23.1}_D = +45.5°$ (4.84 mg/2 mL, CH_2Cl_2); MS (FAB) *m/z* 665 (MH^+, 50%), 667 ($MH^+ + 2$, 100%), 669 ($MH^+ + 4$, 74%); HRFABMS calcd for $C_{29}H_{36}N_4O_2BrClBr^{81}$ M_r 667.0873 (MH^+), found 667.0886. Anal. ($C_{29}H_{35}N_4O_2Br_2Cl \cdot 0.5CH_2Cl_2$) C, H; N: calcd, 7.90; found, 6.90.

(+)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-[[1-[(1*H*-pyrrol-1-yl)acetyl]-4-piperidinyl]acetyl]piperidine (18). To a mixture of pyrrole (0.07 mL, 1.1 mmol) and sodium hydride (0.05 g, 1.1 mmol, 60% dispersion in mineral oil) in anhydrous DMF (8 mL) was added **3** (150 mg, 0.22 mmol), and the resulting mixture was stirred at 80 °C for 12 h. After cooling to 25 °C and diluting with CH_2Cl_2, the mixture was filtered and the filtrate concentrated in vacuo. Purification by preparative plate chromatography (silica gel) afforded an off-white solid: 58.1 mg, 37%; mp = 123.4 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.8−1.9 (m, 8H), 1.97−2.50 (m, 4H), 2.62 (m, 1H), 2.73−3.16 (m, 4H), 3.25 (m, 1H), 3.48−3.89 (m, 4H), 4.56 (m, 2H), 4.69 (s, 2H), 4.90 (d, 1H, J = 10 Hz), 6.16 (br s, 2H), 6.65 (s, 2H), 7.15 (s, 1H), 7.50 (d, 1H, J = 2 Hz), 7.55 (br s, 1H), 8.44 (d, 1H, J = 2 Hz); $[\alpha]^{25}_D = +35.5°$ (1.1 mg/2 mL, MeOH);

MS (FAB) *m/z* 701 (MH^+, 54%), 703 ($MH^+ + 2$, 100%), 705 ($MH^+ + 4$, 78%). Anal. ($C_{32}H_{35}N_4O_2Br_2Cl$) C, H, N.

(+)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-[[1-[(1*H*-1,2,4-triazol-1-yl)acetyl]-4-piperidinyl]acetyl]piperidine (19). A mixture of 1,2,4-triazole (sodium derivative, 81.3 mg, 0.89 mmol) and **3** (200 mg, 0.30 mmol) in anhydrous DMF (10 mL) was stirred at 80 °C for 24 h. After cooling to 25 °C and diluting with CH_2Cl_2, the mixture was filtered and the filtrate concentrated in vacuo. Purification by preparative plate chromatography (silica gel) using 5% MeOH−CH_2Cl_2 saturated with NH_4OH afforded the product as a white solid: 173 mg, 83%; mp = 125.3 °C dec; ^{1}H NMR (mixture of rotamers, 300 MHz, DMSO-d_6) δ 0.91−1.33 (m, 5H), 1.43 (m, 1H), 1.71 (m, 2H), 1.94 (m, 1H), 2.23 (m, 2H), 2.41 (m, 1H), 2.60 (m, 2H), 2.80−3.13 (m, 4H), 3.35 (m, 1H), 3.59 (m, 1H), 3.86 (br d, 2H, J = 10 Hz), 4.25 (br d, 1H, J = 12 Hz), 4.37 (m, 1H), 4.75 (d, 1H, J = 8 Hz), 5.23 (m, 2H), 7.46 (s, 1H), 7.65 (d, 1H, J = 2 Hz), 7.85 (s, 1H), 7.94 (s, 1H), 8.03 (s, 0.4H), 8.41 (s, 1H), 8.46 (d, 1H, J = 2 Hz), 8.83 (s, 0.4H); $[\alpha]^{24.7}_D$ = +41.5° (1.64 mg/2 mL, MeOH); MS (FAB) *m/z* 703 (MH^+, 46%), 705 ($MH^+ + 2$, 100%), 707 ($MH^+ + 4$, 74%); HRFABMS calcd for $C_{30}H_{34}N_6O_2BrClBr^{81}$ M_r 705.0778 (MH^+), found 705.0775. Anal. ($C_{30}H_{33}N_6O_2Br_2Cl\cdot H_2O\cdot NH_3$) C, H, N.

(+)-1-[[1-(Cyanoacetyl)-4-piperidinyl]acetyl]-4-(3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-yl)piperidine (20). Prepared as for **2a** using cyanoacetic acid: white solid; 0.24 g, 43%; mp = 124.8−125.6 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.04−1.60 (m, 6H), 1.80 (d, 1H, J = 12 Hz), 1.91 (d, 1H, J = 12 Hz), 2.05−2.47 (m, 5H), 2.67 (dt, 1H, J = 12 Hz, J = 3 Hz), 2.75−3.06 (m, 3H), 3.10−3.32 (m, 2H), 3.39−3.88 (m, 5H), 4.57 (m, 2H), 4.90 (d, 1H, J = 10 Hz), 7.14 (s, 1H), 7.50 (d, 1H, J = 2 Hz), 7.56 (br s, 1H), 8.45 (d, 1H, J = 2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (mixture of rotamers) 24.94, 30.07, 31.07, 31.13, 31.68, 32.01, 32.07, 32.27, 32.34, 32.42, 32.71, 32.82, 38.88, 38.91, 38.99, 39.02, 41.71, 41.90, 41.97, 42.18, 42.87, 45.62, 45.71, 46.77, 57.68, 57.71, 113.98, 118.93, 127.10, 127.24, 129.10, 129.16, 131.08, 131.15, 131.20, 133.21, 141.67, 141.71, 141.75, 141.87, 142.37, 142.40, 142.43, 142.57, 147.03, 147.06, 147.09, 147.13, 159.57, 169.11, 169.18; MS (FAB) *m/z* 661 (MH^+, 47%), 663 ($MH^+ + 2$, 100%), 665 ($MH^+ + 4$, 81%). Anal. ($C_{29}H_{31}N_4O_2Br_2Cl\cdot 0.3H_2O$) C, H, N.

4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]piperidinyl]carbonyl]-3-pyridinecarboxylic Acid (21). A mixture of **1** (200 mg, 0.34 mmol), 3,5-pyridinedicarboxylic acid (284 mg, 1.7 mmol), HOBt (69 mg, 0.51 mmol), DEC (163 mg, 0.85 mmol), *N*-methylmorpholine (0.06 mL, 0.54 mmol), and dry DMF (3 mL) was stirred at 25 °C for 1.5 h. The mixture was diluted with water, and the solid was filtered and purified by flash column chromatography (silica gel) using 5−10% MeOH− CH_2Cl_2 saturated with NH_4OH to afford a white solid which was dried in vacuo: 143 mg, 56%; mp = 183.7−185.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.0−1.91 (m, 7H), 2.11 (m, 1H), 2.11−2.53 (m, 4H), 2.6−3.11 (m, 6H), 3.30 (m, 1H), 3.62 (m, 1H), 3.80 (m, 1H), 3.98 (m, 1H), 4.53 (m, 1H), 4.63 (m, 1H), 4.88 (d, 1H, J = 10 Hz), 7.13 (s, 1H), 7.46 (s, 1H), 7.57, 7.66 (two s, 1H), 8.17, 8.34 (two s, 1H), 8.45 (s, 1H), 8.51, 8.75 (two br s, 1H), 8.98, 9.13 (two br s, 1H); MS (FAB) *m/z* 743 (MH^+, 46%), 745 ($MH^+ + 2$, 100%), 747 ($MH^+ + 4$, 72%). Anal. ($C_{33}H_{33}N_4O_4Br_2Cl\cdot 1.6H_2O\cdot NH_3$) C, H, N.

(+)-5-[[4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]piperidinyl]carbonyl]-3-pyridinecarboxamide (22). Prepared as in **8** using **21:** off-white solid; 1.49 g, 82%; mp = 81.8−83.9 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03−1.65 (m, 5H), 1.67−2.51 (m, 7H), 2.59 (m, 1H), 2.75−3.36 (m, 6H), 3.52−3.93 (m, 3H), 4.51−4.82 (m, 2H), 4.90 (d, 1H, J = 10 Hz), 5.82 (m, 1H), 6.43 (m, 1H) 7.15 (br s, 1H), 7.52 (s, 1H), 7.57 (br s, 1H), 8.20 (br s, 1H), 8.45 (d, 1H, J = 2 Hz), 8.78 (s, 1H), 9.08 (s, 1H); MS (FAB) *m/z* 742 (MH^+, 43%), 744 ($MH^+ + 2$, 100%), 746 ($MH^+ + 4$, 76%). Anal. ($C_{33}H_{34}N_5O_3Br_2Cl\cdot 2DMF$) C, H, N.

(+)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-[[1-(3-pyridinylcarbonyl)-4-piperidinyl]acetyl]piperidine *N*1-Oxide (23). Prepared as in **21** using nicotinic acid *N*-oxide: white solid; 137 mg, 57%; mp = 157.2 °C dec; ^{1}H NMR (mixture of rotamers, 200 MHz, $CDCl_3$) δ 1.02−1.65 (m, 5H), 1.75−2.54 (m, 8H), 2.72−3.39 (m, 6H), 3.64 (m, 2H), 3.82 (m, 1H), 4.63 (m, 2H), 4.94 (d, 1H, J = 10 Hz), 7.18 (s, 1H), 7.30 (m, 2H), 7.52 (br s, 1H), 7.60 (m, 1H), 8.23 (br s, 2H), 8.48 (br s, 1H); $[\alpha]^{23.2}_D$ = +48° (1.75 mg/2 mL, MeOH); MS (FAB) *m/z* 715 (MH^+, 47%), 717 ($MH^+ + 2$, 100%), 719 ($MH^+ + 4$, 70%). Anal. ($C_{32}H_{33}N_4O_3Br_2Cl\cdot 2H_2O$) C, H, N.

(+)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-[[1-(4-pyridinylcarbonyl)-4-piperidinyl]acetyl]piperidine *N*1-Oxide (24). Prepared as in **21** using isonicotinic acid *N*-oxide: white solid; 144 mg, 60%; mp = 151.3 °C dec; ^{1}H NMR (mixture of rotamers, 200 MHz, $CDCl_3$) δ 1.05−1.66 (m, 5H), 1.89 (m, 2H), 2.09−2.53 (m, 6H), 2.76−3.42 (m, 6H), 3.52−3.94 (m, 3H), 4.61 (m, 2H), 4.97 (d, 1H, J = 10 Hz), 7.18 (s, 1H), 7.36 (d, 2H, J = 7 Hz), 7.53 (d, 1H, J = 2 Hz), 7.62 (m, 1H), 8.25 (d, 2H, J = 7 Hz), 8.49 (s, 1H); $[\alpha]^{23.6}_D$ = +38.7° (4.65 mg/2 mL, CH_2Cl_2); MS (FAB) *m/z* 715 (MH^+, 45%), 717 ($MH^+ + 2$, 100%), 719 ($MH^+ + 4$, 72%); HRFABMS calcd for $C_{32}H_{34}N_4O_3BrClBr^{81}$ M_r 717.0666 (MH^+), found 717.0658. Anal. ($C_{32}H_{33}N_4O_3Br_2Cl\cdot 2H_2O$) C, H, N.

(+)-1-[[1-(2-Amino-1,2-dioxoethyl)-4-piperidinyl]acetyl]-4-(3,10-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-yl)piperidine (25). To a cooled solution of oxalyl chloride (1.0 mL) in CH_2Cl_2 (10 mL) was added pyridine (0.08 mL) followed by a solution of **1** (0.205 g, 0.34 mmol) in CH_2Cl_2 (10 mL). After the mixture stirred at 0 °C for 5 min, concentrated NH_4OH (excess) was added dropwise and the resulting basic mixture (pH paper) was stirred at 25 °C overnight. The mixture was diluted with CH_2Cl_2 and washed with water and then brine. The organic phase was washed with 1 M HCl, 1 M NaOH (aq), and brine and dried over anhydrous $MgSO_4$ to afford a solid. Purification by preparative plate chromatography (silica gel) using 5% MeOH−CH_2Cl_2 saturated with NH_4OH afforded a white solid: 86 mg, 37%; mp = 152.8 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80−1.61 (m, 6H), 1.68−2.5 (m, 7H), 2.57−3.37 (m, 6H), 3.43−3.92 (m, 2H), 4.30−4.82 (m, 3H), 4.89 (d, 1H, J = 10 Hz), 5.70 (br s, 1H, exchangeable w/ D_2O), 6.95 (br s, 1H, exchangeable w/ D_2O), 7.16 (s, 1H), 7.50 (s, 1H), 7.55 (s, 1H), 8.45 (s, 1H); $[\alpha]^{23.4}_D$ = +32.8° (2.99 mg/2 mL, CH_2Cl_2); MS (FAB) *m/z* 665 (MH^+, 42%), 667 ($MH^+ + 2$, 100%), 669 ($MH^+ + 4$, 70%). Anal. ($C_{28}H_{31}N_4O_3Br_2Cl\cdot 0.7CH_2Cl_2$) C, H, N.

Alternate Procedure for 25. A mixture of **4** (150 mg, 0.22 mmol) was stirred with concentrated NH_4OH (aq, 2 mL) at 25 °C for 12 h, then concentrated in vacuo , diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ (aq), and dried over anhydrous Na_2SO_4. The organic phase was filtered and concentrated in vacuo to afford **25** (61.2 mg, 42%).

(+)-4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-*N*,*N*-dimethyl-α-oxo-1-piperidineacetamide (26). Prepared as in **21** using dimethyloxamic acid:[13] white solid; 95.3 mg, 81%; mp = 95.0 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05−1.63 (m, 6H), 1.69 (m, 1H), 1.82 (br d, 2H, J = 12 Hz), 2.22 (m, 2H), 2.38 (m, 2H), 2.61−3.36 (m, 6H), 2.98 (overlapping br s, 6H), 3.60 (m, 2H), 3.81 (m, 1H), 4.45−4.69 (m, 2H), 4.89 (d, 1H, J = 10 Hz), 7.15 (s, 1H), 7.50 (s, 1H), 7.55 (s, 1H), 8.44 (s, 1H); $[\alpha]^{24.5}_D$ = +64.2° (2.15 mg/2 mL, 10% MeOH/CH_2Cl_2); MS (FAB) *m/z* 693 (MH^+, 47%), 695 ($MH^+ + 2$, 100%), 697 ($MH^+ + 4$, 72%); HRFABMS calcd for $C_{29}H_{34}N_4O_4BrClBr^{81}$ M_r 697.0615 (MH^+), found 697.0605. Anal. ($C_{30}H_{35}N_4O_3Br_2Cl\cdot 0.4CH_2Cl_2$) C, H, N.

(+)-4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidineacetamide (27). A mixture of 2-bromoacetamide (27.4 mg, 0.2 mmol), Na_2CO_3 (anhydrous, 40 mg, 0.4 mmol), and **1** (113 mg, 0.19 mmol) in anhydrous DMF (2 mL) was stirred at 25 °C for 12 h. Water was added,

and the resulting precipitate was filtered and washed with water, then dissolved in CH_2Cl_2, and dried over anhydrous $MgSO_4$. The filtrate was concentrated in vacuo to afford the product as an off-white solid: 84 mg, 68%; mp = 131 °C dec; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10−1.62 (m, 6H), 1.78 (m, 3H), 2.05−2.51 (m, 6H), 2.68−3.10 (m, 5H), 2.95 (overlapping s, 2H), 3.23 (m, 1H), 3.61 (m, 1H), 3.82 (m, 1H), 4.57 (br d, 1H, J = 12 Hz), 4.89 (d, 1H, J = 10 Hz), 5.59 (br s, 1H, exchangeable w/ D_2O), 7.06 (br s, 1H, exchangeable w/ D_2O), 7.12 (s, 1H), 7.48 (s, 1H), 7.52 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (mixture of rotamers) 30.18, 31.24, 31.29, 31.84, 32.11, 32.19, 32.27, 32.42, 32.53, 39.59, 41.79, 41.99, 42.18, 45.91, 46.05, 54.19, 58.11, 58.17, 61.64, 118.96, 127.18, 127.30, 129.19, 129.26, 131.11, 131.19, 133.18, 133.24, 135.17, 135.36, 137.02, 137.38, 141.43, 141.59, 142.57, 142.74, 147.36, 147.51, 154.70, 154.92, 169.99, 173.57; MS (FAB) *m/z* 651 (MH^+, 44%), 653 (MH^+ + 2, 100%), 655 (MH^+ + 4, 77%); HRFABMS calcd for $C_{28}H_{34}N_4O_2Br_2Cl$ M_r 651.0737 (MH^+), found 651.0743. Anal. ($C_{28}H_{33}N_4O_2Br_2Cl\cdot0.3CH_2Cl_2$) C, H, N.

(+)-4-[2-[4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-*N*,*N*-diethyl-1-piperidineacetamide (28). Prepared as in **27** using 2-chloro-*N*,*N*-diethylacetamide: white solid; 78.7 mg, 62%; mp = 110−114 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98−1.60 (m, 11H), 1.71 (m, 3H), 1.98−2.52 (m, 7H), 2.7−3.06 (m, 5H), 3.13 (s, 2H), 3.19 (m, 1H), 3.33 (m, 4H), 3.60 (m, 1H), 3.82 (m, 1H), 4.57 (br d, 1H, J = 12 Hz), 4.88 (d, 1H, J = 10 Hz), 7.11 (s, 1H), 7.47 (s, 1H), 7.51 (s, 1H), 8.12 (s, 1H); $[\alpha]^{22.5}_D$ = +48.5° (5.32 mg/2 mL, CH_2Cl_2); MS (FAB) *m/z* 707 (MH^+, 46%), 709 (MH^+ + 2, 100%), 711 (MH^+ + 4, 71%). Anal. ($C_{30}H_{37}N_4O_3Br_2Cl\cdot0.5H_2O$) C, H, N.

(+)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-[2-[1-[2-(4-morpholinyl)-2-oxoethyl]-4-piperidinyl]acetyl]piperidine (29). Prepared as in **27** using morpholinochloroacetamide: white solid; 63.2 mg, 52%; mp = 126.9−131.9 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12−1.62 (m, 5H), 1.76 (m, 3H), 2.02−2.51 (m, 7H), 2.68−3.38 (m, 6H), 3.19 (overlapping s, 2H), 3.63 (br s, 9H), 3.82 (m, 1H), 4.60 (br d, 1H, J = 12 Hz), 4.90 (d, 1H, J = 10 Hz), 7.15 (s, 1H), 7.52 (s, 1H), 7.55 (s, 1H), 8.45 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (mixture of rotamers) 30.21, 31.24, 31.29, 31.90, 32.13, 32.20, 32.31, 32.60, 39.63, 41.77, 41.95, 42.04, 42.22, 45.91, 46.04, 46.20, 53.61, 58.12, 58.20, 61.44, 67.05, 118.95, 127.20, 127.32, 129.17, 129.25, 131.13, 131.20, 133.19, 133.23, 135.14, 135.31, 137.08, 137.41, 141.39, 141.54, 142.57, 142.73, 147.40, 147.53, 154.78, 154.97, 168.1, 170.02; $[\alpha]^{24.2}_D$ = +39.7° (1.16 mg/2 mL, CH_2Cl_2); MS (FAB) *m/z* 721 (MH^+, 50%), 723 (MH^+ + 2, 100%), 725 (MH^+ + 4, 66%). Anal. ($C_{32}H_{39}N_4O_3Br_2Cl\cdot0.5H_2O$) C, H, N.

Acknowledgment. The authors wish to thank their colleagues in the Physical and Analytical Group for providing the spectral and analytical data.

References

(1) (a) Barbacid, M. ras Genes. *Annu. Rev. Biochem.* **1987**, *56*, 779−827. (b) Der, C.; Cox, A. D. Isoprenoid Modification and Plasma Membrane Association: Critical Factors for Ras Oncogenicity. *Cancer Cells* **1991**, *3*, 331−340. (c) Willumsen, B. M.; Norris, K.; Papageorge, A. G.; Hubbert, N. L.; Lowry, D. R. Harvey Murine Sarcoma Virus p21 Ras Protein: Biological and Biochemical Significance of the Cysteine Nearest the Carboxyl Terminus. *EMBO J.* **1984**, *3*, 2581−2585. (d) Lowry, D. R.; Willumsen, B. M. New Clue to the Ras Lipid Glue. *Nature (London)* **1989**, *341*, 384−385. (e) Gibbs, J. B. *Cell* **1991**, *65*, 1−4. (f) Khosravi-Far, R.; Cox, A. D.; Kato, K.; Der, C. J. *Cell Growth Differen.* **1992**, *3*, 461−469.

(2) Barbacid, M. *Eur. J. Clin. Invest.* **1990**, *20*, 225−235.

(3) Casey, P. J.; Solski, P. A.; Der, C. I.; Buss, J. E. p21 Ras is Modified by a Farnesyl Isoprenoid. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 8323−8327.

(4) (a) Reiss, Y.; Goldstein, J. L.; Seabra, M. C.; Casey, P. J.; Brown, M. S. *Cell* **1990**, *62*, 81−88. (b) Hancock, J. F.; Magee, A. I.; Childs, J. E.; Marshall, C. J. *Cell* **1989**, *57*, 1176−77.

(5) (a) James, G. L.; Goldstein, J. L.; Brown, M. S.; Rawson, T. E.; Somers, T. C.; McDowell, R. S.; Crowley, C.; Lucas, B.; Levinson, A.; Masters, J. C. *Science* **1993**, *260*, 1937−1942. (b) Kohl, N. E.; Mosser, S. D.; DeSolms, J.; Giuliani, E. A.; Pompliano, D. L.; Graham, S. L.; Smith, R. L.; Scolnick, E. M.; Oliff, A.; Gibbs, J. B. *Science* **1993**, *260*, 1934−1937. (c) Garcia, A. M.; Rowell, C.; Ackermann, K.; Kowalczyk, J. J.; Lewis, M. D. *J. Biol. Chem.* **1993**, *268*, 18415−18418. (d) Vogt, A.; Qian, Y.; Blaskovich, M. A.; Fossum, R. D.; Hamilton, A. D.; Sebti, S. M. *J. Biol. Chem.* **1995**, *270*, 660−664. (e) Kohl, N. E.; Wilson, F. R.; Mosser, S. D.; Giuliani, E.; DeSolms, S. J.; Conner, M. W.; Anthony, N. J.; Holtz, W. J.; Gomez, R. P.; Lee, T.-J.; Smith, R. L.; Graham, S. L.; Hartman, G. D.; Gibbs, J. B.; Oliff, A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 9141−9145.

(6) (a) Gibbs, J. B. Ras C-Terminal Processing Enzyme-New Drug Targets. *Cell* **1991**, *65*, 1−4. (b) Gibbs, J. B.; Oliff, A.; Kohl, N. Farnesyltransferase Inhibitors: Ras Research Yields a Potential Cancer Therapeutics. *Cell* **1994**, *77*, 175−178. (c) Graham, S. L Inhibitors of Protein Farnesylation: A New Approach to Cancer Chemotherapy. *Exp. Opin. Ther. Patents* **1995**, *5*, 1269−1285. (d) Leonard, D. M. Ras Farnesyltransferase: a New Therapeutic Target. *J. Med. Chem.* **1997**, *40*, 2971−2990. (e) McNamara, D. J.; Dobrusin, E.; Leonard, D. M.; Shuler, K. R.; Katltenbronn, J. S.; QuinnII, J.; Bur, S.; Thomas, C. E.; Doherty, A. M.; Scholten, J. D.; Zimmerman, K. K.; Gibbs, B. S.; Gowan, R. C.; Latash, M. P. *J. Med. Chem.* **1997**, *40*, 3319−3322. (f) Leftheris, K.; Kline, T.; Vite, G. D.; Cho, Y. H.; Bhide, R. S.; Patel, D. V.; Patel, M. M.; Schmidt, R. J.; Weller, H. N.; Andahazy, M. L.; Carboni, J. M.; Gullo-Brown, J. L.; Lee, F. Y. F.; Ricca, C.; Rose, W. C.; Yan, N.; Barbacid, M.; Hunt, J. T.; Meyers, C. A.; Seizinger, B. R.; Zahler, R.; Manne, V. Development of Highly Potent Inhibitors of Ras Farnesyltransferase Possessing Cellular and in Vivo Activity. *J. Med. Chem.* **1996**, *39*, 224−236.

(7) (a) Bishop, W. R.; Bond, R.; Petrin, J.; Wang, L.; Patton, R.; Doll, R.; Njoroge, N.; Windsor, W.; Syto, R.; Schwartz, J.; Carr, D.; James, L.; Kirschmeier, P. *J. Biol. Chem.* **1995**, *270*, 30611−30618. (b) Mallams, A. K.; Njoroge, F. G.; Doll, R. J.; Snow, M. E.; Kaminski, J. J.; Rossman, R.; Vibulbhan, B.; Bishop, W. R.; Kirschmeier, P.; Liu, M.; Bryant, M. S.; Alvarez, C.; Carr, D.; James, L.; King, I.; Li, Z.; Lin, C.-C.; Nardo, C.; Petrin, J.; Remiszewski, S.; Taveras, A.; Wang, S.; Wong, J.; Catino, J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem.* **1997**, *5*, 93−99. (c) Njoroge, F. G.; Doll, R. J.; Vibulbhan, B.; Alvarez, C.; Bishop, W. R.; Petrin, J.; Kirschmeier, P.; Carruthers, N. I.; Wong, J. K.; Albanese, M. M.; Piwinski, J. J.; Catino, J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem.* **1997**, *5*, 101−114. (d) Njoroge, F. G.; Vibulbhan, B.; Rane, D. F.; Bishop, W. R.; Petrin, J.; Patton, R.; Bryant, M. S.; Chen, K.-J.; Nomeir, A. A.; Lin, C.-C.; Liu, M.; King, I.; Chen, J.; Lee, S.; Yaremko, B.; Dell, J.; Lipari, P.; Malkowski, M.; Li, Z.; Catino, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. Structure−Activity Relationship of 3-Substituted *N*-Pyridinylacetyl-4-(8-chloro-5,6-dihydro-11H-benzo[5,6-]cyclohepta[1,2-b]pyridinyl-11-ylidene)piperidine Inhibitors of Farnesyl-Protein Transferase: Design and Synthesis of in Vivo Active Antitumor Compounds. *J. Med. Chem.* **1997**, *40*, 4290−4301.

(8) (a) Njoroge, F. G.; Taveras, A. G.; Kelly, J.; Remiszewski, S. W.; Mallams, A. K.; Wolin, R.; Afonso, A.; Cooper, A. B.; Rane, D.; Liu, Y.-T.; Wong, J.; Vibulbhan, B.; Pinto, P.; Deskus, J.; Alvarez, C.; Del Rosario, J.; Connolly, M.; Wang, J.; Desai, J. A.; Rossman, R. R.; Bishop, W. R.; Patton, R.; Wang, L.; Kirschmeier, P.; Bryant, M. S.; Nomeir, A. A.; Lin, C.-C.; Liu, M.; McPhail, A. T.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. (+)-4-[2-[4-(8-Chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo[5,6]cyclohepta-[1,2-b]pyridin-11(*R*)-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide (Sch-66336): A Very Potent Farnesyl Protein Transferase Inhibitor as a Novel Antitumor Agent. *J. Med. Chem.* **1998**, *41*, 4890. (b) Liu, M.; Bryant, M. S.; Chen, J.; Lee, S.; Yaremko, B.; Lipari, P.; Malkowski, M.; Ferrari, E.; Nielsen, L.; Prioloi, N.; Dell, J.; Sinha, D.; Syed, J.; Korfmacher, W. A.; Nomeir, A. A.; Lin, C.-C.; Wang, L.; Taveras, A. G.; Doll, R. J.; Njoroge, G.; Mallams, A. K.; Remiszewski, S.; Catino, J. J.; Girijavallabhan, V. M.; Kirschmeier, P.; Bishop, W. R. Antitumor Activity of Sch-66336, an Orally Bioavailable Tricyclic Inhibitor of Farnesyl Protein Transferase, in Human Tumor Xenograft Models and Wap-*ras* Transgenic Mice. *Cancer Res.* **1998**, *58*, 4947−4956.

(9) Njoroge, F. G.; Taveras, A. G.; Kelly, S.; Remiszewski, S. W.; Mallams, A. K.; Doll, R. J.; Girijavallabhan, V.; Afonso, A.; Wolin, R.; Alvarez, C.; Cesarz, D.; Connolly, M.; Cooper, A. B.; Del Rosario, J.; Desai, J. A.; Deskus, J.; Dritz, J.; Hollinger, F.; Kiminski, J. J.; Liu, Y.-T.; Pinto, P.; Rane, D.; Rossman, R. R.; Saksena, A. K.; Snow, M. E.; Vibulbhan, B.; Wang, J.; Ganguly, A. K.; Bishop, W. R.; Kirschmeier, P.; Carr, D.; James, L.; Patton, R.; Bryant, M. S.; Nomeir, A. A.; Liu, M.; Wang, S.; Nardo, C.; Kumari, P.; Chen, K.-J.; Watkins, R.; Korfmacher, W. A.; Lin, C.-C. Orally Active, Trihalobenzocycloheptapyridine Farnesyl Protein TransferaseInhibitor Antitumor Agents. Presentation at the 8th American Association for Cancer Research Meeting, New Orleans, LA, March 28−April 1, 1998.

(10) (a) Appel, R.; Berger, G. *Chem. Ber.* **1958**, *91*, 1339−1341. (b) Atkins, G. M., Jr.; Burgess, E. M. *J. Am. Chem. Soc.* **1967**, *89*, 2502−2503.
(11) Bryant, M. S.; Korfmacher, W. A.; Wang, S.; Nardo, C.; Nomeir, A. A.; Lin, C.-C. Pharmacokinetic Screening for Selection of New Drug Discovery Candidates is Greatly Enhanced Through the Use of Liquid Chromatography-Atmospheric Pressure Ionization Tandem Mass Spectrometry. *J. Chromatogr.* **1997**, *777*, 61−66.
(12) For similar modifications made to dihalobenzocycloheptapyridines, see: Mallams, A. K.; Rossman, R. R.; Doll, R. J.; Girijavallabhan, V. M.; Ganguly, A. K.; Petrin, J.; Wang, L.; Patton, R.; Bishop, W. R.; Carr, D. M.; Kirschmeier, P.; Catino, J. J.; Bryant, M. S.; Chen, K.-J.; Korfmacher, W. A.; Nardo, C.; Wang, S.; Nomeir, A. A.; Lin, C.-C.; Li, Z.; Chen, J.; Lee, S.; Dell, J.; Lipari, P.; Malkowski, M.; Yaremko, B.; King, I.; Liu, M. Inhibitors of Farnesyl Protein Transferase. 4-Amido, 4-Carbamoyl, and 4-Carboxamido Derivatives of 1-(8-Chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)piperazine and 1-(3-Bromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)piperazine. *J. Med. Chem.* **1998**, *41*, 877−893.
(13) Coppa, F.; Fontana, F.; Lazzarini, E.; Minisci, F. A facile, convenient and selective homolytic carbamoylation of heteroaromatic bases. *Heterocycles* **1993**, *36*, 2687−2696.
(14) Unpublished observations during pharmacokinetic analysis of experimental compounds at Schering-Plough.

JM990059K