(+)-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-oxo-ethyl]-1-piperidinecarboxamide (SCH-66336): A Very Potent Farnesyl Protein Transferase Inhibitor as a Novel Antitumor Agent

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We have previously shown that appropriate modification of the benzocycloheptapyridine tricyclic ring system can provide potent farnesyl protein transferase (FPT) inhibitors with good cellular activity. Our laboratories have also established that incorporation of either pyridinylacetyl *N*-oxide or 4-*N*-carboxamidopiperidinylacetyl moieties results in pharmacokinetically stable inhibitors that are orally efficacious in nude mice. We now demonstrate that further elaboration of the tricyclic ring system by introducing a bromine atom at the 7- or the 10-position of the 3-bromo-8-chlorotricyclic ring system provides compounds that have superior potency and selectivity in FPT inhibition. These compounds have good serum levels and half-lives when given orally to rodents and primates. In vitro and in vivo evaluation of a panel of these inhibitors has led to identification of **15** (SCH 66336**)** as a highly potent (IC_{50} = 1.9 nM) antitumor agent that is currently undergoing human clinical trials.

Ras, a low molecular weight guanine nucleotide (GTP) binding protein, forms part of a cell growth signaling pathway that extends from the cell membrane to the nucleus.[1] In recent years, the various steps involved in this signaling pathway upstream and downstream of Ras have been elucidated.[2] The constitutive activation of Ras in tumors appears to contribute to their malignant growth properties and ras oncogenes have been implicated in nearly 30% of all human tumors, including approximately 50% of colon and 90% of pancreatic carcinomas.[3] In order for ras p21 to accomplish its role in transmitting the signal for cell growth, it must be bound to the cell membrane. This occurs through a series of posttranslational modifications which include farnesylation of the ras protein using farnesyl pyrophosphate donor and catalysis by the enzyme farnesyl protein transferase (FPT).[4] Inhibition of FPT, therefore, represents an attractive target that could yield novel, noncytotoxic antitumor agents and has recently been a subject of intense studies.[5]

We recently demonstrated that the benzocycloheptapyridine tricyclic class of compounds are potent FPT inhibitors[6] possessing oral and cellular antitumor activity.[7−10] Our original lead compound, 1-(4-pyridylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (SCH 44342), inhibited FPT by 50% at 0.25 μM and ras processing in COS cells at 1 μM. However, as previously described, SCH 44342 and its closely related analogues were extensively metabolized, forming pyridinylacetyl *N*-oxide as the major metabolite.[8,9] With this knowledge at hand, we sought to improve the potency of SCH 44342 and other members of the series and at the same time identify an appropriate moiety that would render subsequent compounds more metabolically stable. Replacement of the pyridinylacetyl moiety with a pyridinylacetyl *N*-oxide functionality afforded inhibitors with greatly improved pharmacokinetics.[8−10] An extensive structure−activity relationship (SAR) study indicated that introduction of a bromine atom at the 3-position of the tricyclic nucleus not only gave compounds with greater FPT potency but also improved the pharmacokinetic (PK) profile.[8] We therefore synthesized 3-bromo 4-pyridylacetyl *N*-oxide **1,** a compound that was found to be a potent, orally active FPT inhibitor with a very good PK profile.[8] Further studies aimed at finding alternative replacements for the pyridinylacetyl *N*-oxide portion of the molecule led to the discovery of the 4-*N*-carboxamidopiperidinylacetyl group,[9] which afforded inhibitors such as **2** with excellent PK profiles.

Herein, we report further developments in the substitution of the benzocycloheptapyridine nucleus whereby halogen atoms have been incorporated at either positions 7 or 10 of the tricyclic ring system. Our studies have led to the discovery of **15** (SCH 66336**)**, a 3,10-dibromo-8-chlorotricyclic-4-*N*-carboxamidopiperidinylacetyl derivative, as a highly potent (IC_{50} = 1.9 nM), orally active antitumor agent which is currently undergoing human clinical trials.

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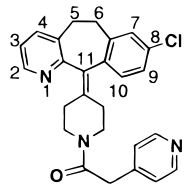
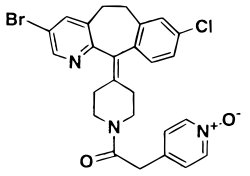
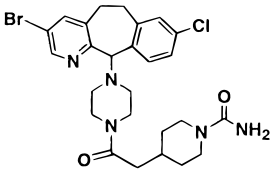


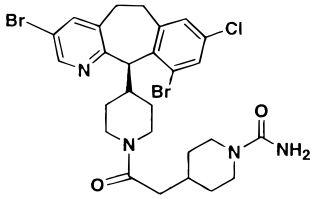
SCH 44342
FPT IC_{50}= 250 nM
COS IC_{50}= 1000 nM
AUC = 0.37 μg.h/mL(mice)



1
FPT IC_{50}= 90 nM
COS IC_{50}= 525 nM
AUC = 12.9 μg.h/mL(mice)



2
FPT IC_{50}= 49 nM
COS IC_{50}= 590 nM
AUC = 70.8 μg.h/mL(mice)



15, SCH 66336

Chemistry

Compounds prepared for this study are shown in Tables 1 and 2, and their synthetic routes are illustrated in Schemes 1−7. Chemistry for the preparation of 3-bromo carbamate **3** utilizing the versatile chemistry that effects regioselective nitration of the benzocycloheptapyridine system at the 3-position of the pyridine has been previously described.[11] Preparation of compounds described in this paper has been greatly facilitated by our finding that electrophilic nitration of the benzocycloheptapyridine ring system using classic nitration conditions occurs mainly at the 9-position of the tricyclic ring system.[11] Thus, nitration of **3** using $NaNO_3-H_2SO_4$ afforded both the 7-nitrocarbamate **4** and 9-nitrocarbamate **5** in 10% and 86% yield, respectively. Reduction of **5** with iron filings and calcium chloride in refluxing 85% aqueous ethanol gave amine **6** in 85% yield. Introduction of a bromine atom at the 10-position of the tricyclic ring system, ortho-directed by the 9-amino group, was effected by treatment of **6** with Br_2−AcOH to provide 3,10-dibromo amino carbamate **7** in 70% yield. Deamination of **7** was carried out by diazotization of amine **7** with $NaNO_2$−HCl, followed by reduction of the resulting diazonium salt with hypophosphorous acid to give trihalo carbamate **8** in 80% yield. Hydrolysis of **8** in refluxing, concentrated HCl afforded the amine **9** in 93% yield. Reduction of the C-11 double bond was carried out using DIBAL-H in refluxing toluene to afford racemic **10**. Separation of the two enantiomers of **10** was achieved using either HPLC on a ChiralPak AD column or by chemical resolution using *N*-acetyl-L-phenylalanine as the resolving agent, to afford the desired **(+)10** and **(−)10** enantiomers. An X-ray diffraction experiment was performed on a single crystal of the *N*-acetyl-L-phenylalanine salt of **(+)10** which established the C-11 absolute configuration of **(+)10** as having *R* stereochemistry (see Figure 1 for ORTEP representation of *N*-acetyl-L-phenylalanine salt of **(+)10**).

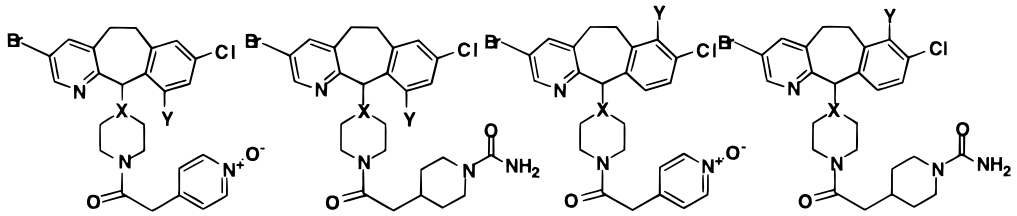
For the preparation of targets of structure type A (where X = CH, Table 1), the appropriate resolved isomer was reacted with pyridinylacetic acid *N*-oxide in a carbodiimide-mediated coupling. Thus, reaction of amine **(+)10** and **(−)10** provided targets **11** and **12** in 89 and 82% yields, respectively. Preparation of carbamoyl analogues of structure type B, (where X = CH, Table 1) was achieved by coupling amine **(+)10** with the N-BOC protected piperidinylacetic acid[9] affording the amide **13** in 81% yield. Hydrolysis of the Boc group with TFA afforded the amine **14** in quantitative yield. Treatment of **14** with TMS−NCO followed by $NaHCO_3$ workup gave the desired target **15** in 82% yield. Compound **16** was prepared in a similar manner starting with amine **(−)10**.

Synthesis of the 3,10-dibromopiperazine targets is outlined in Scheme 2. Thus, oxidative cleavage of carbamate **3** using $NaIO_4$ with a catalytic amount of hydrated $RuCl_3$ provided the azaketone **17** in 64% yield. Nitration of azaketone **17** using $KNO_3-H_2SO_4$ afforded the 7-nitroketone **18** in 11% yield and the 9-nitro azaketone **19** in 61% yield. Reduction of **19,** as described above, gave 9-amino azaketone **20** in 80% yield. Introduction of bromine at position 10 of the tricyclic ring system was effected by treatment of **20** with Br_2−AcOH to afford the trihalogenated azaketone **21** in 60% yield. On the other hand, treatment of **20** with *N*-chlorosuccinimide afforded the 3-bromo 8,10-dichloro amino azaketone **22** in quantitative yield. Fluorination at the 10-position was effected by treatment of **20** with a F^+ source, Accufluor,[12] to give **23** in 27% yield. Aminoazaketones **21**, **22**, and **23** were deaminated as described above to afford the trihalo azaketones **24**, **25**, and **26** in 74, 80, and 59% yields, respectively. Reduction of the carbonyl moieties in **24**, **25**, and **26** with $NaBH_4$ yielded the corresponding alcohols **27**, **28**, and **29** which were subsequently converted to their respective chlorides using thionyl chloride (or to the mesylate in the case of **28** using methane sulfonyl chloride). Further treatment of these intermediates with piperazine in THF gave the tricyclic piperazine intermediates **30**, **31**, and **32**. These amines were resolved by HPLC on ChiralPak AD columns to afford the (+)- and (−)-isomers of **30**, **31**, and **32**. Reaction of these amines with pyridinylacetic acid *N*-oxide as previously described gave the target pyridinylacetamides **33**−**38**. The carbamoyl analogues **39** and **40** (compounds of structure type B where X = N, Table 1) were prepared as described above for the piperidine analogues.

Preparation of the 3,7-dibromo piperidine analogues was achieved as outlined in Scheme 3. Thus, 9-nitrocarbamate **5** was treated with 1,3-dibromo-5,5-dimethylhydantoin to afford the 3,7-dibromo carbamate **41** in 86% yield. Reduction of nitrocarbamate **41** with iron filings−$CaCl_2$ afforded amine **42** in 60% yield. Subsequent deamination of **42** provided 3,7-dibromo 8-chloro carbamate **43** in 70% yield. Hydrolysis of carbamate **43** in refluxing HCl afforded the amine **44**, which was subjected to DIBAL-H reduction to give the C-11 single-bond amine **45**. Resolution of the two enantiomers of **45** was carried out on a ChiralPak AD column on HPLC to afford the two enantiomers **(−)45** and **(+)45**. An X-ray diffraction experiment was performed on a single crystal of the BOC-D-Alanyl amide of **(−)45**, establishing the absolute configuration at C-11 of **(−)45** as *S* (see Figure 1 for ORTEP representation of the BOC-D-alanyl amide **(−)50** and Scheme 4 for its preparation).

Coupling of **(−)45** and **(+)45** to pyridylacetic acid

Table 1. FPT, COS, and Soft Agar Activities of Trihalobenzocycloheptapyridine Tricyclic Compounds



Structure A **Structure B** **Structure C** **Structure D**

compd	struct. type	C-11 config	Y	FPT IC_{50} (nM) H-ras	COS IC_{50} (nM)	soft agar IC_{50} (nM) NIH H-Ras
11	A, X = CH	*R*(+)	Br	1.3	10	50
12	A, X = CH	*S*(−)	Br	>88	850	ND
15[a]	B, X = CH	*R*(+)	Br	1.9	10	72
16	B, X = CH	*S*(−)	Br	>94	2000	ND
33	A, X = N	*R*(+)	Br	1.8	10	<50
34	A, X = N	*S*(−)	Br	>95	2250	ND
35	A, X = N	*R*(+)	Cl	<3.8	45	200
36	A, X = N	*S*(−)	Cl	>110	ND	ND
37	A, X = N	*R*(+)	F	16.7	92	ND
38	A, X = N	*S*(−)	F	33.1	>110	ND
39	B, X = N	*R*(+)	Br	2.5	<20	286
40	B, X = N	*S*(−)	Br	>94	950	ND
46	C, X = CH	*S*(−)	Br	2.6	480	ND
47	C, X = CH	*R*(+)	Br	62	>1000	ND
48	D, X = CH	*S*(−)	Br	5.0	325	500
49	D, X = CH	*R*(+)	Br	78	>1000	ND
54	C, X = N	*S*(−)	Br	2.3	98	750
55	C, X = N	*R*(+)	Br	>99	3000	ND
60	C, X = N	*S*(−)	Cl	6.0	500	ND
62	C, X = N	(±)	F	86	ND	ND
56	D, X = N	*S*(−)	Br	3.1	40	250
57	D, X = N	*R*(+)	Br	>280	ND	ND

[a] SCH 66336.

Table 2. Pharmacokinetic Parameters for Potent FPT Inhibitors

	PK in mice		PK in cynomolgus monkeys		% efficacy po in mice DLD-1	
compd	AUC[a] (μg·h/mL) po	Cmax (μg) po	AUC[b] (μg·h/mL) po	Cmax (μM) po	10 mpk	50 mpk
11	3.0	3.8	3.7	1.2	19	68
15[c]	24.1	8.84	14.7	1.9	40	76
33	36.4	24.6	5.4	1.4	45	64
35			0.04	0.03	ND	ND
39			10.2	1	38	83
46			10.4	2	48	59
48			15.9	2	7	61
54	49.1	13	26.4	3.5	42	57
56			16.7	2	35	61

[a] AUC (0−24 h). [b] AUC (0−48 h). po = oral, iv = intravenous, AUC = area under the concentration time curve. [c] SCH 66336. $t_{1/2}$(iv): mice = 1.4 h, monkey = 3 h. bioav. = 76% in mice; 50% in monkey.

N-oxide gave the 3,7-dibromo 8-chloro targets of type C (Table 1), **46** and **47,** in 88 and 94% yield, respectively. Using similar chemistry to that described above for the piperidine analogues, amines **(−)45** and **(+)45** were converted to their corresponding carbamoyl targets, **48** and **49**.

Synthesis of the 3,7-dibromo 8-chloro tricyclic piperazine analogues of type D (Table 1) was carried out as described in Scheme 5. Thus, tricyclic carbamate **43** underwent oxidative cleavage using $NaIO_4$ with a catalytic amount of RuO_2 to give the azaketone **51** in 76% yield.[13] Reduction of the ketone **51** with sodium borohydride afforded the alcohol **52** in 86% yield. Conversion of **52** to the corresponding chloride with thionyl chloride followed by subsequent reaction with piperazine afforded piperazine adduct **53** in 87% yield. The enantiomers of **53** were separated on a ChiralPak AD column on HPLC to give the enantiomers **(−)53** and **(+)53**. Amines **(−)53** and **(+)53** were coupled with pyridinylacetic acid *N*-oxide to yield acetamides **54** and **55,** respectively. Carbamoyl compounds **56** and **57** were prepared from amines **(−)53** and **(+)53**, respectively, using the previously described protocol.

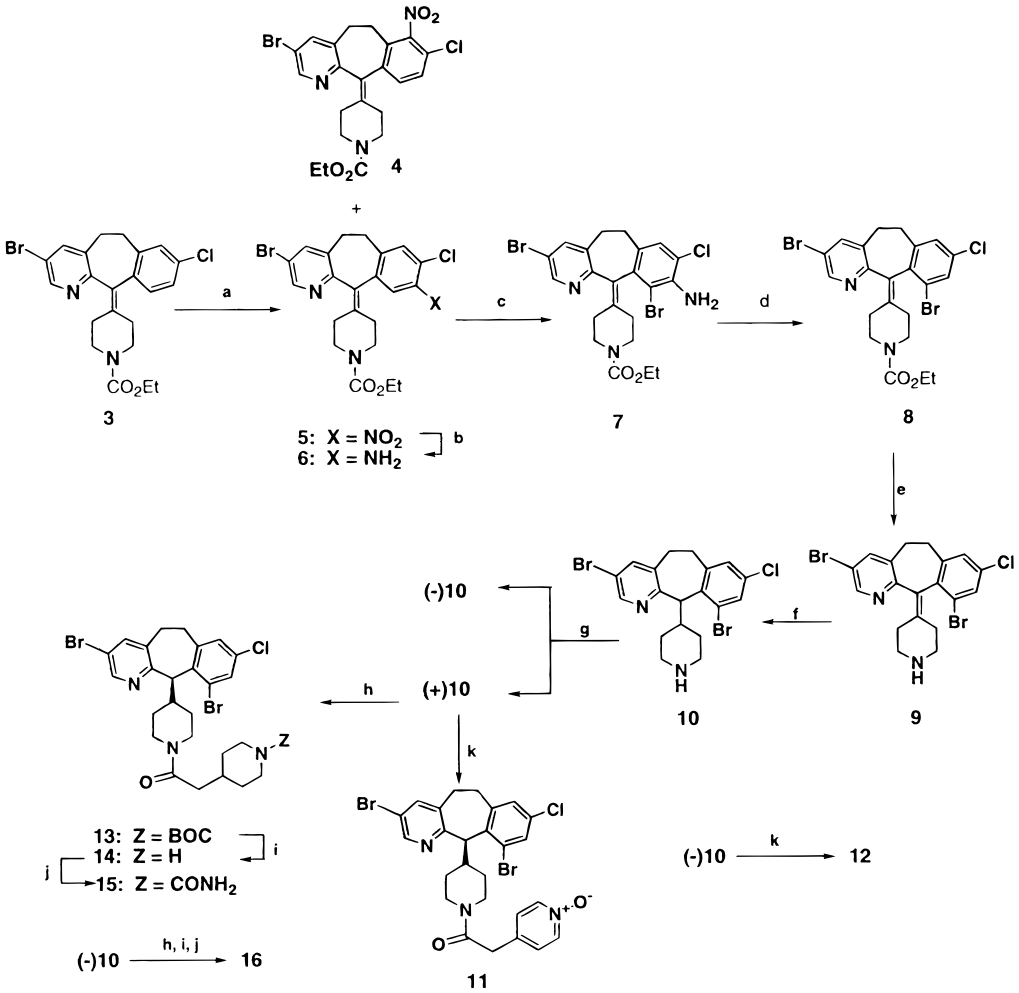
Introduction of chlorine atom at the 7-position of tricyclic nucleus was carried out as outlined in Scheme 6. Thus, reduction of 7-nitroazaketone **18** with iron filings and calcium chloride in refluxing 85% aqueous EtOH gave amino azaketone **58**. Diazotization of amine **58** followed by treatment with CuCl afforded trihalogenated azaketone **59** in 90% yield. Using a procedure similar to that described for preparation of compound **54**, azaketone **59** was converted to the corresponding pyridinyl acetamide *N*-oxide **60**.

Fluorination of the 7 position was effected as outlined in Scheme 7. Thus, treatment of azaketone **17** with Accufluor gave 7-fluoro azaketone **61** in 65% yield. As described for compound **54** above, azaketone **61** was converted to a racemic mixture of pyridinyl acetamide *N*-oxide **62**.

Results and Discussion

Compounds prepared in this study were tested both for their ability to inhibit the transfer of [^{3}H]farnesyl from farnesyl pyrophosphate to H-Ras-CVLS, a process that is mediated by FPT, and for their inhibitory activity

Scheme 1[a]



[a] (a) H_2SO_4−$NaNO_3$, 10% of **4** and 86% **5**; (b) iron filings−$CaCl_2$, 85%; (c) Br_2−AcOH, 70%; (d) HCl−$NaNO_2$, H_3PO_2, 80%; (e) conc. HCl, Δ, 93%; (f) DIBAL-H, 90%; (g) chiral AD separation; (h) N−BOC piperidinyl acetic acid−DEC-HOBT−NMM, 80−90%; (i) TFA; (j) TMS−NCO; (k) 4-pyridinylacetic acid *N*-oxide−DEC-HOBT−NMM.

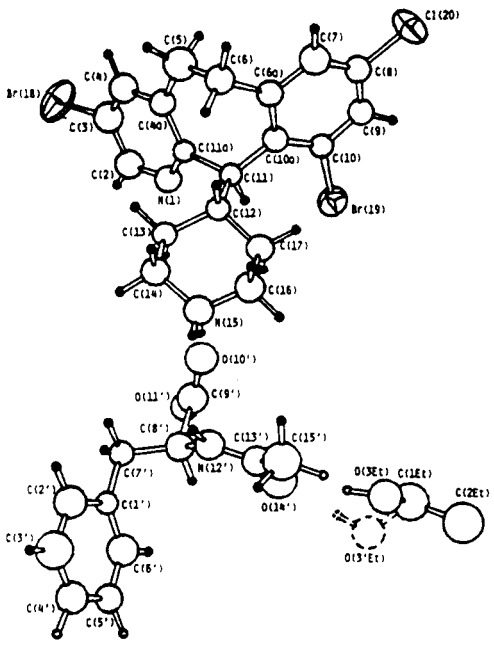
toward the closely related enzyme GGPT-1 that catalyzes the transfer of [^{3}H]geranylgeranyl moiety from geranylgeranyl pyrophosphate to H-Ras-CVLL using conditions previously described.[14] These compounds were also evaluated in a cellular ras-processing assay (COS cell assay) and a colony-forming assay (soft agar assay) as previously described.[14] Biological and pharmacokinetic data for these compounds are summarized in Tables 1−3 and in Figure 2.

As anticipated from previous studies in our laboratories,[8,9] incorporation of either the pyridinylacetyl *N*-oxide or the piperidinylcarbamoyl moiety off the 4-position of the tricyclic piperidyl or piperizinyl nitrogen gave compounds with similar FPT potency and cellular inhibitory activities as can be seen from a number of active targets prepared and represented as structures A−D in Table 1.

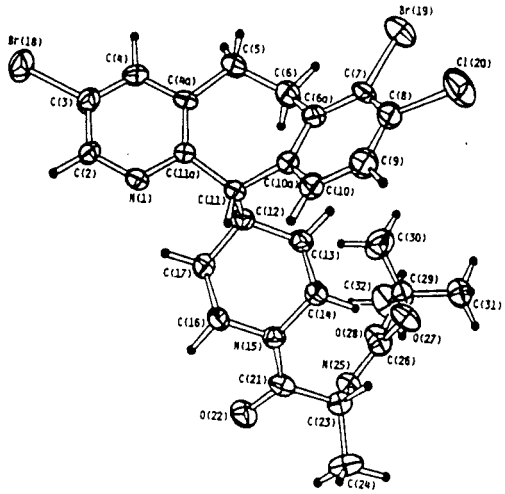
(A) Effects of Halogens at Positions 7 and 10. Introduction of halogens at the 7- or 10-positions of the tricyclic ring system resulted in compounds with greatly enhanced FPT inhibitory activity. Thus, whereas the 3,8-dihalo compounds we previously reported exhibited FPT activity with IC_{50}s of 20 nM and above,[6−10] the active isomer in the 3,7,8- and 3,8,10-trihalogenated tricyclic analogues described in this study showed activity in the low nanomolar range as exemplified by compounds **11, 15, 33, 35, 39, 46, 48, 54**, and **56** (Table 1).

The effect of substituting various halogens at the 10-position of the benzocycloheptapyridine tricyclic ring system on FPT activity was investigated on the piperazine compounds of structure type A. As shown in Table 1, the order of activity was as follows: Br ≥ Cl > F. Thus the bromo compound **33** (IC_{50} = 1.8 nM) was as active as the chloro analogue **35** (IC_{50} = ∼3.8 nM) which, on the other hand, was about 10-fold more active than the fluoro compound **37** (IC_{50} = 16.7 nM). A similar trend was also observed with substitution of various halogens at the 7-position in the piperazine analogues of structure type C (where X = N, Table 1). Thus, the 7-bromo substituted compound **54** (IC_{50} = 2.3 nM) was about three times more potent than the corresponding 7-chloro analogue **60** (IC_{50} = 6.0 nM) which was in turn over 10-fold more active than the racemic 7-fluoro derivative **62** (IC_{50} = 86 nM). These results indicated that a larger hydrophobic halogen was beneficial at the 7- or 10-position for enhanced FPT activity.

(B) Importance of Stereochemistry at C-11. The stereochemistry at C-11 of the trihalobenzocycloheptapyridine tricyclic ring system had a profound effect



(+) **10**. N-Acetyl-(L)-PHE salt

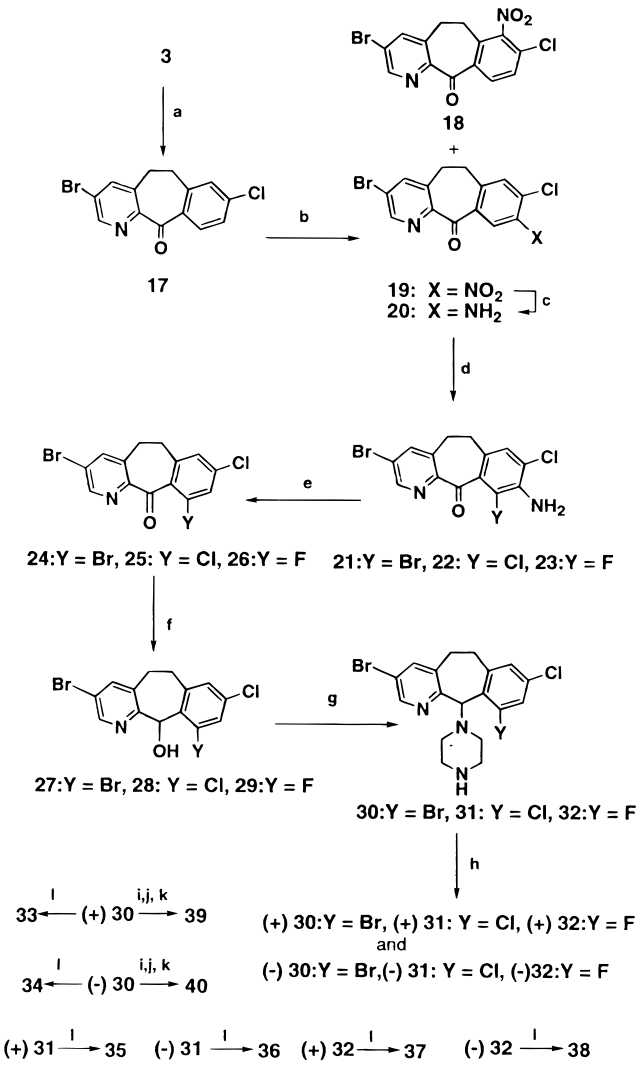


Compound **50**

Figure 1. ORTEP diagram (40% probability ellipsoids) showing the crystallographic atom numbering scheme and solid-state conformation of **(+)10**·*N*-acetyl-(L)-phenylalanine salt in crystals of the ethanol solvate. Small filled circles represent hydrogen atoms; for the ethanol, only those of the disordered O−H are shown.

on FPT activity. In general, it was found that the *R*(+)-isomer containing a halogen at the 10-position had better FPT inhibitory activity than the corresponding *S*(−)-isomer. Thus, in the pyridinylacetamides of type A (X = CH, Table 1), compound **11** *R*(+) had an IC_{50} of 1.3 nM against FPT-mediated H-ras farnesylation, whereas the *S*(−)-isomer counterpart, compound **12,** was not active even at 88 nM. This observation was also true for the piperazine derivatives of type A (where X = N, Table 1) where compound **33**, the *R*(+)-isomer, was more active (IC_{50} = 1.8 nM) than compound **34**, the *S*(−)-isomer(IC_{50} > 95 nM). Similar results were obtained in the carbamoyl derivatives of type B (Table 1) where the *R*(+)-isomers **15** and **39** were more active than their corresponding S(−)-isomers, **16** and **40**. The

Scheme 2[a]

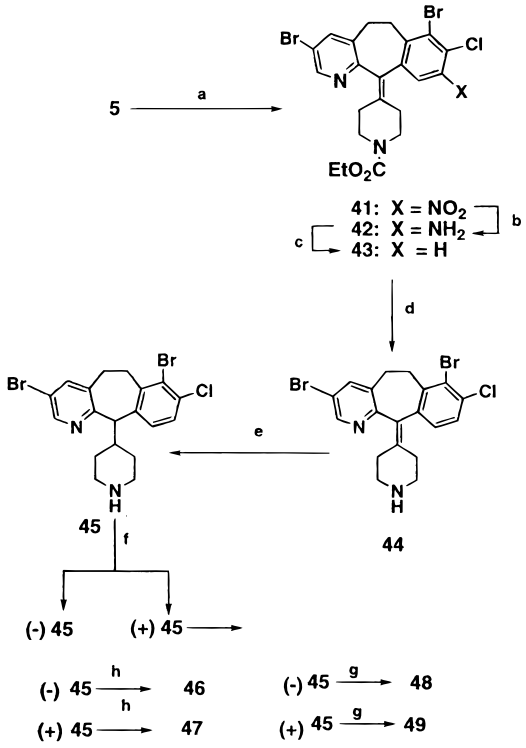


[a] (a) $RuCl_3$−$NaIO_4$, 64%; (b) H_2SO_4−KNO_3, 11% of **18** and 61% of **19**; (c) iron filings−$CaCl_2$, 80%; (d) for Y = Br use Br_2−AcOH, for Y = Cl use NCS, for Y = F use Accufluor; (e) HCl−$NaNO_2$, H_3PO_2; (f) $NaBH_4$; (g) $SOCl_2$ or MsCl, piperazine; (h) chiral AD separation; (i) N-BOC piperidinyl acetic acid−DEC-HOBT−NMM; (j) TFA; (k) TMS−NCO; (l) 4-pyridinylacetic acid *N*-oxide−DEC-HOBT−NMM.

effect was less pronounced with analogues where the 10-position was substituted with a fluorine; thus, whereas the *R*(+)-isomer, compound **37**, had FPT activity with an IC_{50} = 16.7 nM, its corresponding *S*(−)-isomer, compound **38**, was only two times less active (IC_{50}= 33.1 nM). These results are similar to that reported for the 10-H analogues,[10] reflecting the similarility in size between fluorine and hydrogen.

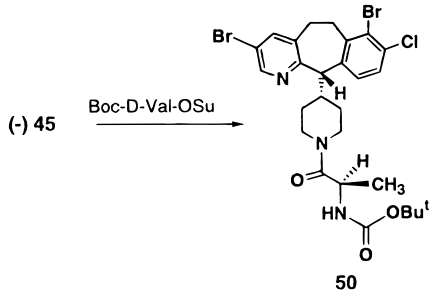
Surprising results were obtained in the 3,7,8-trihalogenated tricyclic analogues of structure types C and D (Table 1). Unlike the 10-halo series where the *R*(+)-isomers were the most active FPT inhibitors (structure types A and B), in the 7-halogenated series the *S*(−)-isomers were found to be more active. Thus, 3,7-dibromopyridinyl acetamide *N*-oxide **46** (FPT IC_{50} = 2.6 nM) was 20 times more active than the corresponding *R*(+)-isomer, **47** (IC_{50} = 62 nM). This was also found to be true in the corresponding carbamoyl analogues of structure type D (Table 1) whereby compound **48,** the *S*(−)-isomer (IC_{50} = 5.0 nM), was more active than the

Scheme 3[a]



[a] (a) 1,3-Dibromo-5,5-dimethyl hydantoin, 86%; (b) iron filings−$CaCl_2$, 60%; (c) HCl−$NaNO_2$, H_3PO_2, 70%; (d) conc. HCl, Δ, 92%; (e) DIBAL-H; (f) chiral AD separation; (g) steps h−j Scheme 1; (h) step k Scheme 1.

Scheme 4

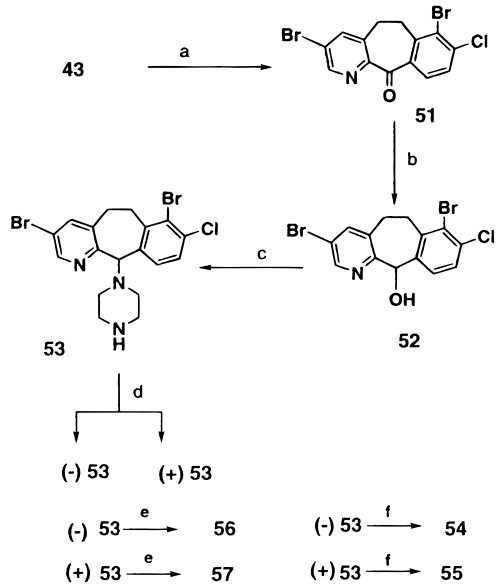


corresponding **49** *R*(+)-isomer (IC_{50} >78 nM). Similar results were also obtained in the amide series where **54** was more active than **55** and where **56** was significantly more active than **57**.

(C) Inhibition of FPT versus GGPT-1. As observed with previously prepared tricyclic compounds in this series,[6−10] the active trihalogenated compounds evaluated in this series also showed very good selectivity for FPT versus the closely related enzyme, GGPT-1. Thus, compounds **11, 15, 33**, and **39** were found to be inactive in inhibition of GGPT-1-mediated prenyl transfer at concentrations as high as 50 μM.

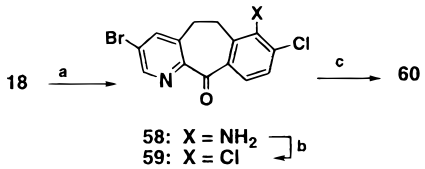
(D) COS Cell Studies. Evaluation of the effectiveness of trihalogenated tricyclic compounds described in this series at inhibiting the farnesylation of H-ras proteins in COS-7 monkey cells transiently expressing H-ras[Val^{12}]-CVLS in the whole cell assay was carried out. The 3,8,10-trihalogenated compounds of structure types A and B (Table 1), compounds **11, 15, 33,** and **35,** inhibited 50% of COS cell farnesylation at ∼10 nM. However, their corresponding 3,7,8-trihalogenated ana-

Scheme 5[a]



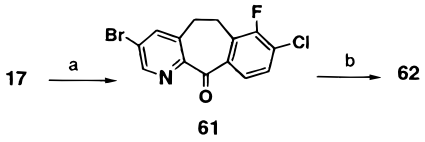
[a] (a) RuO_2−$NaIO_4$, 76%; (b) $NaBH_4$; (c) $SOCl_2$, piperazine; (d) chiral AD separation; (e) steps h−j Scheme 1; (f) step k Scheme 1.

Scheme 6[a]



[a] (a) Step b Scheme 1; (b) HONO, CuCl, 90%; (c) steps f−h then l Scheme 2.

Scheme 7[a]



[a] (a) Accufluor, 65%; (b) steps f−g, then l Scheme 2.

Table 3. 15 (SCH 66336) Inhibition of Tumor Cell Growth (Soft Agar Assay)

cell line	tissue	ras mutation	IC_{50} (μM)
H-ras NIH		H-ras	0.07
K-ras NIH		K-ras	0.50
HCT-116	colon	K-ras	0.07
Mia Paca	pancreatic	K-ras	0.25
MCF-7	breast	none	0.05
NCI-H146	lung	none	0.05

logues of structure type C and D, compounds **46, 48, 54,** and **56,** had appreciably higher COS inhibitory IC_{50}s (40−480 nM), suggesting that the latter class of compounds were not getting into the cells as well as the 10-halogenated series of type A and B.

(E) Colony-Forming Assay (Soft Agar) Studies. The most potent compounds identified in the COS cell assay (IC_{50} < 50 nM) were evaluated for their ability to inhibit anchorage-independent growth of NIH-H, and NIH-K tumor cell lines in soft agar. As in the COS cell studies, the 10-halo compounds of structure type A and B (Table 1) were found to be more potent in inhibiting the colony formation of tumor cells than the 7-halo compounds of structure type C and D (Table 1). It was

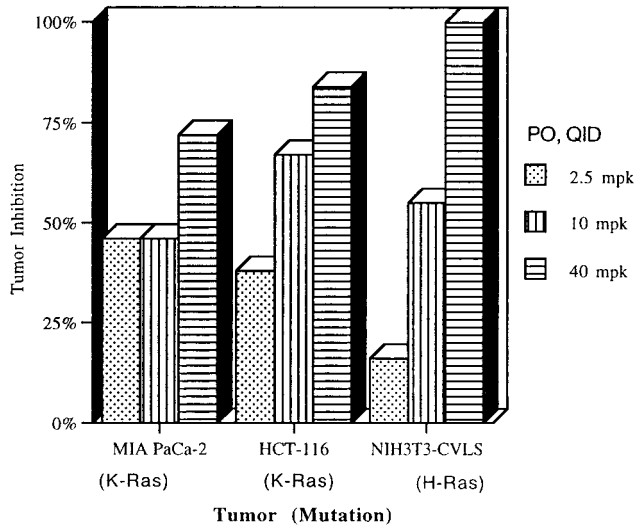


Figure 2. Antitumor activity of **15** (SCH 66336) in MIA PaCa-2, HCT-116, and NIH3T3-CVLS tumor models.

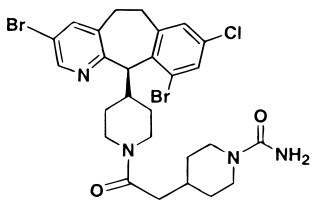
also observed that the activity in soft agar was considerably lower than that observed in the COS cell assay.

Further studies were carried out to asses the extent to which compound **15** would inhibit a panel of human tumor cell lines grown on soft agar. As shown in Table 3, compound **15** was found to inhibit not only cell lines containing ras mutations [i.e., H-ras NIH, K-ras NIH, A549 (lung), HCT-116 (colon), Mia Paca (pancreatic)], but also cell lines that did not have any ras mutations such as MCF-7 (breast), and NCI−H146 (lung).

(F) Pharmacokinetic Studies. The pharmacokinetic properties of the more potent trihalogenated FPT inhibitors reported here (Table 1, structure types A−D) were evaluated in nude mice as well as in cynomolgus monkeys,[15] and the results are listed in Table 2. In general, the 3,7,8-trihalogenated analogues of types C and D, (compounds **48, 54,** and **56)** showed better oral pharmacokinetic profiles in cynomolgus monkeys than the corresponding 3,8,10-trihalogenated analogues. For example, compound **54,** a 7-bromo analogue, demonstrated the best AUC (26.4 μg·h/mL) and Cmax = 3.5 μM. The other 7-bromo derivatives, **48** and **56**, showed AUC's of 15.9 and 16.7 μg·h/mL, respectively, and both had Cmax of 2 μM. In the 10-bromo series, compounds of structure type A and B consistently exhibited lower AUC and Cmax values than their corresponding analogues in the 7-halo series of structure type C and D. In this series, compound **15** was found to have the best PK profile in monkeys with an AUC of 14.7 μg·h/mL and a Cmax of 1.9 μM. The remaining 10-bromo derivatives **11** and **33** showed lower AUCs of 3.7 and 5.4 μg·h/mL, and Cmax values of 1.2 and 1.4 μM, respectively.

(G) In Vivo Antitumor Efficacy Studies in Mice. Efficacy studies for compounds that showed good FPT and COS inhibitory activities were carried out in nude mice carrying DLD-1 tumor cell lines (a human carcinoma cell line) containing mutated K-ras. Results are outlined in Table 2. In general, all of the potent trihalo derivatives prepared in this study were found to be orally effective antitumor agents. Compound **15** showed an efficacy of 76% at 50 mpk with a good dose response. The bioavailability of **15** in mice was 76% and in monkeys was 50%.

Compound **15** was also found to inhibit tumor growth in nude mice treated with cells that contained either K-ras mutations (MIA PACA-2, human pancreatic cancer, and HCT-116, human colon cancer) or H-ras mutations (transformed mouse fibroblast, NIH3T3-CVLS), in a dose-dependent manner (Figure 2).



15, SCH 66336
R(+)
FPT IC_{50}= 1.9 nM
COS IC_{50}= 10 nM
NIH-Hras SA IC_{50}= 72 nM
NIH-Kras SA IC_{50}= 500 nM
Mouse PK 25 mpk
AUC = 24.1 μg.h/mL
po Cmax = 8.84 μM
iv t1/2 = 1.4 h
Bio. Avail. = 76%

Conclusion

SAR studies of the halogenated benzocycloheptapyridine tricyclic ring compounds have revealed that substitution at the 7- or 10-position of this ring system provides compounds with low nanomolar activity against FPT. Further evaluation of these analogues in the COS and soft agar assays showed that compounds containing halogens in the 3-, 8-, and 10-positions were more potent than those that contained halogens at the 3, 7, and 8 positions (Table 1). Consequently, when selecting a compound for clinical evaluation, we primarily considered compounds in the 3,8,10-trihalo class. The data in Table 2 shows that of the compounds in the 3, 8, 10-trihalo class, **15** exhibited good oral pharmacokinetics in monkeys and showed good oral efficacy as an antitumor agent in mice. After considering all of the available data, compound **15** was selected and is currently undergoing clinical trials.

Experimental Section

Melting points were determined with an electrothermal digital melting point apparatus and are uncorrected. Elemental analyses were performed by the Physical-Analytical Chemistry Department, Schering-Plough Research Institute, on either a Leeman CE 440 or a FISONS EA 1108 elemental analyzer. FT-IR spectra were recorded using a BOMEN Michelson 120 spectrometer. Mass spectra were recorded using either EXTREL 401 (chemical ionization), JEOL MAT-90 (FAB), VG ZAB-SE (SIMS), or Finnigan MAT-CH-5 (EI) spectrometer. In general, structures of the compounds were determined by coupling constants, coupling information from the COSY spectra and 1D NOE experiments. The ^{1}H and ^{13}C NMR spectra were obtained on either a Varian VXR-200 (200 MHz, ^{1}H), Varian Gemini-300 (300 MHz, ^{1}H; 75.5 MHz, ^{13}C), or XL-400 (400 MHz, ^{1}H; 100 MHz, ^{13}C) and are reported as ppm downfield from Me_4Si with number of protons, multiplicities, and coupling constants in Hertz (Hz) indicated parenthetically. For ^{13}C NMR, a Nalorac Quad nuclei probe was used. Rotations were recorded on a Perkin-Elmer 243B polarimeter.

4-[3-Bromo-8-chloro-5,6-dihydro-7-nitro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (4) and 4-[3-Bromo-8-chloro-5,6-dihydro-9-nitro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidine-carboxylic Acid Ethyl Ester (5). Tricyclic compound **3**,[8] (25.8 g, 55.9 mmol), was stirred in 250 mL of concentrated H_2SO_4 at room temperature until all the solid had dissolved. The resulting solution was cooled between −10 and − 5 °C (ice−MeOH bath). $NaNO_3$ (4.8 g, 56.4 mmol) was then added portion-wise, keeping the temperature below −5 °C. The reaction mixture was stirred at that temperature for 2 h. It was poured onto ice (600 g) and basified with concentrated NH_4OH. The mixture was

extracted with CH_2Cl_2 (500 mL). Combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and concentrated. Purification on silica gel eluting with 10% EtOAC−hexanes gave 2.8 g (10%) of compound **4** (more polar) as a pale-yellow solid: mp 206−207 °C; MS (CI) *m*/*z* 506 (MH^+).

The less polar 9-nitro compound **5** (24.0 g) was obtained in 86% yield: MS (CI) *m*/*z* 506 (MH^+).

4-[3-Bromo-8-chloro-5,6-dihydro-9-amino-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (6). Nitrocarbamate **5** (6.69 g, 13.1 mmol) was dissolved in 100 mL of 85% EtOH−H_2O. To this solution were added iron filings 6.56 g (117.9 mmol) and $CaCl_2$ 0.66 g (5.9 mmol), and the reaction mixture was refluxed for 16 h. The reaction mixture was filtered through Celite and extensively washed with hot EtOH. The filtrate was then treated with decolorizing charcoal and filtered, and the organic solvents removed to give 7.72 g of amine **6**: MS (FAB) *m*/*z* (rel intens) 478 (100, MH^+).

4-[3,10-Dibromo-8-chloro-5,6-dihydro-9-amino-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (7). Amino carbamate **6** (76.5 g, 160 mmol) was dissolved in AcOH (650 mL) at room temperature. To this solution was added bromine (12.3 mL, 38.4 g, 240 mmol). The resulting mixture was allowed to stir at room temperature for 16 h. Most of the acetic acid and bromine was removed by rotary evaporation. The reaction mixture was then neutralized with 50% aqueous NaOH and extracted with EtOAc. Combined EtOAc fractions were dried over $MgSO_4$, filtered, and concentrated. Purification on silica gel eluting with 10−25% EtOAc−hexanes afforded 61.5 g (70%) of compound **7** as a light-yellow solid: MS (FAB) *m*/*z* (rel intens) 556 (100, MH^+).

4-[3,10-Dibromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (8). To 300 mL of concentrated HCl at −10 °C was added $NaNO_2$ (19 g, 275 mmol), and the mixture was stirred for 10 min. Amino carbamate **7** (51.5 g, 93 mmol) was added. The reaction was warmed from −10 °C to 0 °C over a period of 2 h. The reaction mixture was again cooled to −10 °C, and 750 mL of 50% H_3PO_2 was added and allowed to come to room temperature overnight. The reaction mixture was poured onto ice and basified with 50% aqueous NaOH. The mixture was then extracted with EtOAc, and combined EtOAc extracts were dried over $MgSO_4$, filtered, and concentrated. Purification on silica gel eluting with 15−25% EtOAc−hexanes gave 44.1 g (80%) of compound **8** as an off-white solid: mp 99−100 °C; MS (FAB) *m*/*z* (rel intens) 541 (100, MH^+).

4-[3,10-Dibromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidine (9). To 8 mL of concentrated HCl was added 3,10-dibromo carbamate **8** (0.7 g, 1.4 mmol). The reaction mixture was refluxed for 16 h. It was then cooled, poured into ice, and basified to pH = 10 with aqueous 50% NaOH. The aqueous phase was extracted with CH_2Cl_2. Concentration of the organic phase afforded 0.59 g of the hydrolyzed amine **9:** mp 123.9−124.2 °C; MS (FAB) *m*/*z* (rel intens) 688 (100, MH^+).

(8-Chloro-3,10-dibromo-6,11-dihydro-5-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidine (10). To a solution of amine **9** (8.10 g, 17.3 mmol) dissolved in anhydrous toluene (300 mL) was added 17.3 mL (1 equiv) of diisobutylaluminum hydride (1 M solution in toluene). The solution was brought to reflux under a nitrogen atmosphere and an additional 21 mL (1.2 eq) of 1 M diisobutylaluminum hydride in toluene was added dropwise over 40 min. The solution was cooled in an ice−water bath, and then mixed with 1 M hydrochloric acid (700 mL). The organic phase was discarded, and the aqueous phase was washed with dichloromethane, which was also discarded. The aqueous phase was basified with 50% aqueous NaOH, extracted with dichloromethane and dried over anhydrous $MgSO_4$. Filtration and concentration in vacuo afforded an off-white foam (7.30 g, 90% crude yield) which was purified by HPLC using a Chiralpak AD column and 20% 2-propanol−80% hexane−0.2% diethylamine as eluent. The enantiomeric amines were obtained as solids. **(+)-10**: 3.32 g, 41% isolated yield; mp 148.8 °C; MS(CI) *m*/*z* (rel intens) 469 (MH^+, 44%), 471 (96, $MH^+ + 2$), 473 (62, $MH^+ + 4$); $[\alpha]_D^{25}$ +65.6° (*c* = 0.65, MeOH); **(−)10**: 3.44 g, 42% isolated yield; mp 112 °C; MS (CI) *m*/*z* (rel intens) 469 (MH^+); $[\alpha]_D^{25}$ −65.2° (*c* = 0.18, MeOH).

Resolution of (±)10 via Chiral Salt Formation. Racemic **(±)10** (500 mg, 1.07 mmol) was dissolved in denatured ethanol (Fischer, 15 mL, 0.11 M) by warming to 40 °C for 5 min. Then, *N*-acetyl-L-phenylalanine (240 mg, 1.10 mmol) was added, and the solution was allowed to cool and stand at 23 °C for 48 h. The crystals were collected by filtration and rinsed with Et_2O to give 247 mg of the diastereomeric salt (35% yield based on one enantiomer, 70% overall yield). The free base was obtained by treating the salt with 5% sodium hydroxide followed by extraction into EtOAc. The enantiomeric purity was analyzed by chiral HPLC (Chiralpak AD column, eluting with 10% isopropyl alcohol−hexane-containing 0.2% diethylamine) indicating >97% ee of the (+)-enantiomer was obtained.

Single-crystal X-ray analysis of the diastereomeric salt revealed the absolute configuration at C-11 to be *R*, which corresponds to the enantiomerically pure amine **(*R*)-(+)-10**.

(+)-4-(8-Chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-(4-pyridinylacetyl)-piperidine *N*1-Oxide (11). A mixture of **(+)10** (3.32 g, 7.05 mmol), pyridylacetic acid *N*-oxide (2.38 g, 15.5 mmol), HOBT (1.92 g, 14.2 mmol), DEC (2.70 g, 14.1 mmol), *N*-methylmorpholine (1.56 mL, 14.2 mmol), and dry DMF (50 mL) was stirred at 25 °C for 24 h. The mixture was concentrated in vacuo, diluted with CH_2Cl_2, and washed with 1 N NaOH (aqueous) and saturated NaH_2PO_4 (aqueous). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to provide a residue which was purified by flash column chromatography (silica gel, 2% MeOH/CH_2Cl_2 + NH_4OH) to give the product as a solid (3.82 g, 89% yield). Dissolution of the solid in dichloromethane saturated with hydrogen chloride and concentration in vacuo provided the product **11** as an HCl salt: mp 166.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$, of free base) δ 1.20−1.68 (m, 4H), 2.42 (m, 2H), 2.75−3.10 (m, 3H), 3.26 (m, 1H), 3.59 (m, 1H), 3.64 (s, 2H), 3.80 (m, 1H), 4.57 (m, 1H), 4.90 (d, *J* = 10 Hz, 1H,), 7.14 (overlapping d, *J* = 2 Hz, 1H), 7.15 (d, *J* = 7 Hz, 2H), 7.50 (d, *J* = 2 Hz, 1H), 7.55 (br s, 1H), 8.14 (d, *J* = 7 Hz, 2H), 8.44 (d, *J* = 2 Hz, 1H); $[\alpha]_D^{22}$ +70.8° (*c* = 0.50, MeOH); MS (FAB) *m*/*z* (rel intens) 604 (MH^+, 45.71%), 606 ($MH^+ + 2$, 100%), 608 ($MH^+ + 4$, 71.43%). Anal. ($C_{26}H_{24}N_3O_2Br_2Cl\cdot 2HCl\cdot H_2O$) C, H, N.

(−)-4-(8-Chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl)-1-(4-pyridinylacetyl)piperidine *N*1-Oxide (12). Compound **12** was prepared according to the procedure described for **11**: yield 3.6 g, 82%; mp 129 °C; ^{1}H NMR (200 MHz, $CDCl_3$) spectrum identical to that of **11**; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (mixture of rotamers) 29.5, 30.5, 30.6, 31.4, 31.6, 31.7, 31.8, 38.2, 38.3, 38.4, 41.3, 41.5, 41.8, 41.9, 45.6, 45.8, 57.5, 57.6, 118.5, 126.3, 126.4, 126.5, 126.7, 126.8, 128.7, 128.8, 130.7, 130.8, 132.8, 132.9, 133.9, 134.7, 134.9, 136.4, 138.5, 141.0, 141.1, 142.1, 142.2, 147.0, 147.1, 154.0, 154.2, 166.4; $[\alpha]_D^{25}$ −72.3° (*c* = 0.17, MeOH); MS (FAB) (rel intens) *m*/*z* 604 (MH^+, 43%), 606 ($MH^+ + 2$, 100%), 608 ($MH^+ + 4$, 73%). Anal. ($C_{26}H_{24}N_3O_2Br_2Cl\cdot H_2O$) C, H, N.

(+)-1,1-Dimethylethyl[[[4-(8-chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-piperidinyl]-carbonyl]-methyl]-1-piperidinecarboxylate (13). A mixture of **(+)10** (1.33 g, 2.83 mmol), piperidinylacetic acid N-BOC[9] (1.37 g, 5.67 mmol), HOBT (0.77 g, 5.67 mmol), DEC (1.09 g, 5.67 mmol), and dry DMF (30 mL) was stirred at 25 °C for 24 h. The mixture was concentrated in vacuo, diluted with CH_2Cl_2, and washed with 1 N NaOH (aqueous) and saturated NaH_2PO_4 (aqueous). The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to provide an off-white solid (2.78 g), which was used without further purification. An analytical sample was prepared by flash column chromatography (silica gel eluting with ethyl acetate−hexane 30−50%) to give the product **13** as a white

foam: mp 116.2 °C; $[\alpha]_D^{25}$ +35.8° (2.4 mg/2 mL, MeOH); MS (FAB) (rel intens) *m/z* 694 (27, MH^+), 717 (41, $MH^+ + Na^+$), 719 (83, $MH^+ + 2 + Na^+$), 721 (60, $MH^+ + 4 + Na^+$).

(+)-4-(8-Chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-[(4-piperidinyl)-acetyl]piperidine (14). A solution of **(+)13** (2.78 g, crude residue from previous step), anhydrous dichloromethane (40 mL), and trifluoroacetic acid (30 mL) was stirred at 0 °C for 1 h and then at 25 °C for 24 h. The solution was cooled in ice−water and treated slowly with 50% aqueous sodium hydroxide until basic. The mixture was poured into dichloromethane and washed with water. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give **14** as an off-white solid: 1.72 g, 100% yield from **(+)10**; mp 104.1 °C; $[\alpha]_D^{25}$ +53.4° (11.42 mg/2 mL, MeOH); MS (FAB) *m/z* 594 (50, MH^+), 596 (100, $MH^+ + 2$), 598 (69, $MH^+ + 4$); HRMS (FAB) calcd for $C_{26}H_{30}N_3OBr_2Cl$, 596.0502; found, 596.0494.

(+)-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-piperidin-yl]-2-oxo-ethyl]-1-piperidinecarboxamide (15, SCH-66336). To a solution of **(+)14** (1.58 g, 2.65 mmol) in anhydrous dichloromethane (25 mL) was added trimethylsilylisocyanate (6 mL, 44.3 mmol). After being stirred at 25 °C for 48 h the solution was poured into dichloromethane and washed with saturated aqueous sodium bicarbonate and brine. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give an off-white solid. Further purification by flash column chromatography (silica gel) using 3% methanol−dichloromethane with ammonium hydroxide afforded the target carbamoyl derivative **15** as a white solid: 1.40 g, 82% yield. Recrystallization from acetone provided an analytical sample: mp 214.5−215.9 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.1−1.6 (m, 5H), 1.79 (m, 2H), 2.03 (m, 1H), 2.19−2.63 (m, 4H), 2.74−3.13 (m, 6H), 3.27 (m, 1H), 3.62 (m, 1H), 3.88 (m, 3H), 4.41 (s, 2H), 4.61 (br d, J = 12 Hz, 1H), 4.91 (d, J = 10 Hz, 1H,), 7.15 (s, 1H), 7.50 (d, J = 2 Hz, 1H), 7.55 (s, 1H), 8.45 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of rotamers) 30.2, 31.2, 31.3, 31.8, 32.0, 32.1, 32.2, 33.0, 39.4, 41.8, 42.0, 42.2, 44.4, 44.5, 45.8, 45.9, 58.1, 118.9, 127.2, 127.3, 129.1, 129.2, 131.1, 131.2, 133.2, 135.1, 135.3, 137.1, 137.2, 141.3, 141.5, 142.6, 142.7, 147.4, 147.5, 154.7, 154.8, 157.9, 169.6; $[\alpha]_D^{25}$ +49.1° (c = 0.21, MeOH); MS (FAB) *m/z* 637 (47, MH^+), 639 (100, $MH^+ + 2$), 641 (70, $MH + 4$). Anal. ($C_{27}H_{31}N_4O_2Br_2Cl \cdot H_2O$) C, H, N.

(−)-4-[2-[4-(8-Chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11(*S*)-yl)-1-piperidinyl]-2-oxo-ethyl]-1-piperidinecarboxamide (16). Using a procedure similar to that described for the preparation of compound **15** above, the enantiomer **16** was prepared: yield 1.1 g, (79%); mp = 152 °C; ^{1}H NMR and ^{13}C spectra identical to that of **15**; $[\alpha]_D^{25}$ −62.5° (c = 0.06, MeOH); MS (FAB) *m/z* 637 (MH^+, 48), 639 ($MH^+ + 2$, 91), 641 ($MH^+ + 4$, 64); HRMS (FAB) calcd, 637.0581; found, 637.0568. Anal. ($C_{27}H_{31}N_4O_2Br_2Cl \cdot 2.3H_2O$) C, H, N.

3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-one (17). Tricyclic carbamate **3** (100 g, 0.21 mol) was dissolved in 3:1 solution of CH_3CN (1.5 L) and water (0.5 L). To this solution were added $NaIO_4$ (231 g, 1.1 mol) and $RuCl_3 \cdot xH_2O$[13] (3.36 g, 16.24 mmol), keeping the temperature below 50 °C using ice bath. The reaction mixture was stirred at room temperature for 1.5 h and filtered to remove any solid material. The mixture was extracted with EtOAc. Combined organic extracts were concentrated to ∼2.5 L and washed with bleach and then with H_2O. The organic phase was extracted with 6 N HCl. The aqueous phase was cooled to ∼0 °C and neutralized with 50% aqueous NaOH to pH = 4. A black solid precipitated out which was crystallized from EtOH to give 38.1 g of the desired ketone **17**.[16] The filtrate was concentrated and chromatographed on silica gel eluting first with 100% hexanes followed by 10% EtOAc−hexanes to give a further 7.0 g of azaketone **17** (64% overall yield): MS (FAB) *m/z* 323 (MH^+).

3-Bromo-8-chloro-5,6-dihydro-9-nitro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-one (18) and 3-Bromo-8-chloro-5,6-dihydro-9-nitro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (19). Nitration of tricyclic azaketone **17** was accomplished using procedures essentially similar to those described for preparation of compounds **4** and **5** above. Recrystallization from acetone afforded nitro azaketones **18** and **19** in 11 and 61% yields, respectively.

Compound 18: MS (FAB) *m/z* 368 (MH^+).

Compound 19: MS (FAB) *m/z* 368 (MH^+).

3-Bromo-8-chloro-9-amino-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-one (20). Reduction of nitroketone **19** was carried out essentially in the same way as that described for preparation of compound **6** above, to give amino azaketone **20** in 93% yield: MS (FAB) *m/z* 338 (MH^+).

9-Amino-3,10-dibromo-8-chloro-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-one (21). Reaction of amino azaketone **20** with Br_2−AcOH in a manner similar to that described for compound **7** provided the 10-bromo amino azaketone **21** in 95% yield: MS (FAB) *m/z* 417 (MH^+).

9-Amino-3-bromo-8,10-dichloro-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-one (22). Amino azaketone **20** (15 g, 44 mmol) was dissolved in CH_3CN (250 mL) and CH_2Cl_2 (200 mL) and the resulting solution warmed to ∼60 °C, after which *N*-chlorosuccinimide (6.5 g, 48.9 mmol) was added. The reaction mixture was refluxed for 4 h, cooled, basified with 1 N NaOH and extracted with CH_2Cl_2. The organic solvents were removed to give 16.56 g of crude **22,** which was used in the next reaction without further purification: MS (FAB) *m/z* 373 (MH^+).

9-Amino-3-bromo-8-chloro-10-fluoro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (23). Amino azaketone **20** (20 g, 59 mmol) was dissolved in CH_3CN (300 mL) and CH_2Cl_2 (400 mL) and the resulting solution warmed to ∼60 °C, after which 1-fluoro-4-hydroxy-1,4-diazoniabicyclo-[2,2,2]octane bis(tetraflurohydrate), Accufluor NFTh, (20.92 g, 65.2 mmol) was added. The reaction mixture was refluxed for 24 h after which another portion of Accufluor (4.2 g, 13 mmol) was added, and refluxing continued for another 6 h. Organic solvents were stripped off and the resulting semisolid was partitioned between 1 N NaOH and CH_2Cl_2. The aqueous phase was further extracted with CH_2Cl_2. Combined CH_2Cl_2 fractions were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography eluting with 5% EtOAc−CH_2Cl_2 afforded 5.77 g (25% yield) of **23**: MS (FAB) *m/z* 356 (MH^+).

3,10-Dibromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-one (24), 3-Bromo-8,10-dichloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (25), and 3-Bromo-8-chloro-10-fluoro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (26). Using a procedure similar to that described for preparation of compound **8** above, trihalo azaketones **24, 25**, and **26** were prepared in 74, 80, and 60% yields, respectively.

Compound 24: MS (FAB) *m/z* 402 (MH^+).

Compound 25: MS (FAB) *m/z* 358 (MH^+).

Compound 26: MS (FAB) *m/z* 341 (MH^+).

(+)- and (−)-Enantiomers of 4-[3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperazine (30), 4-[3-Bromo-8,10-dichloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperazine (31), and 4-[3-Bromo-8-chloro-10-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl]-1-piperazine (32). Using procedures essentially similar to those previously described,[16−17] trihalo azaketones **24**−**26** were reduced with $NaBH_4$ to afford the 11-hydroxy derivatives **27**−**29**. Alcohols **27** and **29** were reacted with thionyl chloride to afford the 11-chloro compounds whereas alcohol **28** was treated with methanesulfonyl chloride to give the corresponding 11-mesyl intermediate. Treatment of either the chloro derivatives from **27** and **29** or the mesylate from **28** with excess piperazine gave amines **30**−**32**.

Separation of the (+)- and (−)-enantiomers of the piperizane compounds **30**−**32** was achieved as described for compound **10**.

Compound 30: MS (FAB) *m/z* 472 (MH^+).

Compound 31: MS (FAB) *m/z* 428 (MH^+).

Compound 32: MS (FAB) *m/z* 412 (MH^+).

(+)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(R)-yl)-4-(4-pyridinylacetyl)piperazine *N*4-Oxide (33). Using a procedure similar to that described for the preparation of compound **11** above, tricyclic acetamide **33** was prepared from intermediate **(+)-30**: mp 167−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40−2.50 (m, 4H), 2.63−2.70 (m, 1H), 2.87−2.95 (m, 1H), 3.39−3.58 (m, 5H), 3.64 (s, 2H), 4.57−4.65 (m, 1H), 5.35 (s, 1H), 7.10−7.15 (m, 3H), 7.47 (s, 1H), 7.58 (s, 1H), 8.15 (d, J = 7.0 Hz, 1H), 8.44 (d, J = 2.0 Hz, 1H);^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.9, 30.2, 31.3, 38.4, 41.1, 45.8, 50.6, 51.1, 75.1, 76.6, 76.5, 77.0, 77.4, 120.4, 126.4, 126.8, 126.9, 127.7, 128.9, 129.6, 130.9, 134.3, 134.8, 136.5, 138.9, 141.8, 143.4, 147.5, 153.2, 167.0; $[\alpha]_D^{25}$ +32.6 (c = 0.49, MeOH); MS (FAB) *m/z* 607 (MH^+); IR (KBr) υ_{max} 3435, 3109, 1641, 1580, 1435, 1230 cm^{-1}. Anal. ($C_{25}H_{23}N_4O_2Br_2Cl\cdot1.8H_2O$) C, H, N.

(−)-4-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl)-4-(4-pyridinylacetyl)piperazine *N*4-Oxide (34). Using a procedure similar to that described for the preparation of compound **11** above, tricyclic acetamide **34** was prepared from intermediate **(−)30**: All data for this enantiomer is identical to that of **33** above, except for the rotation which was found to be $[\alpha]_D^{25}$ −37.2° (c = 0.51, MeOH). Anal. ($C_{25}H_{23}N_4O_2Br_2Cl\cdot1.5H_2O$) C, H, N.

(+)-4-(3-Bromo-8,10-dichloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)-piperazine *N*4-Oxide (35). Using a procedure similar to that described for the preparation of compound **11** above, tricyclic acetamide **35** was prepared from intermediate **(+)31**: mp 145−146 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.32−2.44 (m, 4H), 2.65−2.72 (m, 1H), 2.90 (m, 1H), 3.37−3.51 (m, 5H), 3.65 (s, 2H), 4.55−4.65 (m, 1H), 5.33 (s, 1H), 7.10−7.16 (m, 3H), 7.29 (s, 1H), 7.59 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 7.2 Hz, 1H), 8.44 (d, J = 2.2 Hz, 1H);^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.2, 31.2, 38.5, 42.0, 45.9, 50.6, 51.2, 72.1, 76.6, 77.0, 77.5, 120.4, 126.9, 127.7, 129.0, 133.3, 134.0, 134.2, 135.9, 136.6, 139.0, 141.7, 143.5, 147.5, 153.5, 167.0; $[\alpha]_D^{25}$ +33.6° (c = 0.55, MeOH); MS (FAB) *m/z* 563 (MH^+); IR (KBr) υ_{max} 3435, 3107, 2810, 1643, 1582, 1482, 1232 cm^{-1}. Anal. ($C_{25}H_{23}N_4O_2BrCl_2\cdot2.4\ H_2O$) C, H, N.

(−)-4-(3-Bromo-8,10-dichloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl)-4-(4-pyridinylacetyl)piperazine *N*4-Oxide (36). Using a procedure similar to that described for the preparation of compound **11** above, tricyclic acetamide **36** was prepared from intermediate **(−)31**: All data for this enantiomer is identical to that of **35** above, except for the rotation which was found to be $[\alpha]_D^{25}$ − 43.4° (c = 0.36, MeOH). Anal. ($C_{25}H_{23}N_4O_2BrCl_2\cdot1.7H_2O$) C, H, N.

(+)-4-(3-Bromo-8-chloro-10-fluoro-6,11-dihydro-5*H*--benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-4-(4-pyridinylacetyl)piperazine *N*4-Oxide (37). Using a procedure similar to that described for the preparation of compound **11** above tricyclic acetamide **33** was prepared from intermediate **(+)-32**: ^{1} H NMR (200 MHz, $CDCl_3$) δ 2.33−2.45 (m, 4H), 2.75−2.86 (m, 4H), 2.75−2.86 (m, 2H), 3.39 (t, J = 5 Hz, 2H), 3.60 (m, 2H), 3.64 (s, 1H), 3.79−4.07 (m, 2H), 4.96 (s, 1H), 6.94 (m, 2H), 7.15 (d, J = 7.2 Hz, 1H), 7.62 (d, J = 2.2 Hz, 1H), 8.17 (d, J = 7.2 Hz, 1H), 8.42 (d, J = 2.2 Hz, 1H); $[\alpha]_D^{25}$ +14.7°, (c = 0.31, MeOH); MS (FAB) *m/z* 547 (MH^+). Anal. ($C_{25}H_{23}N_4O_2$-$BrFCl\cdot0.4CH_2Cl_2$) C, H, N.

(−)-4-(3-Bromo-8-chloro-10-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)piperazine *N*4-Oxide (38). Using a procedure similar to that described for the preparation of compound **11** above, tricyclic acetamide **38** was prepared from intermediate **(−)32**: All data for this enantiomer is identical to that of **37** above, except for the rotation which was found to be $[\alpha]_D^{25}$ −12.5° (c = 0.18, MeOH). Anal. ($C_{25}H_{23}N_4O_2BrFCl\cdot0.3CH_2$-$Cl_2$) C, H, N.

(+)-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-piperazinyl]-2-oxo-ethyl]-1-piperidinecarboxamide (39). Using a procedure similar to that described for the preparation of compound **15** above, the tricyclic carbamoyl derivative **39** was prepared from intermediate **(+)30**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.1−1.25 (m, 3H), 1.70−1.80 (m, 2H), 1.90−2.10 (m, 1H), 2.30−2.50 (m, 4H), 2.60−3.00 (m, 4H), 3.35−3.70 (m, 4H), 3.80−3.95 (m, 2H), 4.45 (m, 2H), 4.60−4.75 (m, 1H), 1.35 (s, 1H), 7.15 (s, 1H), 7.45 (d, 1H, J = 2 Hz), 7.55 (s, 1H), 8.45 (d, 1H, J = 2 Hz);^{13}C NMR (300 MHz, $CDCl_3$) δ (mixture of rotamers) 29.9, 31.3, 32.0, 32.9, 39.2, 41.5, 44.3, 44.4, 45.5, 50.8, 51.4, 75.2, 126.4, 129.5, 130.9, 136.5, 141.8, 143.4, 147.4, 157.8, 169.7; IR (film) υ_{max} 3500, 2930, 1645, 1640 cm^{-1}; [α $[\alpha]_D^{25}$ +31.2° (c = 0.41, MeOH); MS (FAB) *m/z* 637 (MH^+). Anal. ($C_{26}H_{30}N_5O_2Br_2Cl\cdot0.5H_2O$) C, H, N.

(−)-4-[2-[4-(8-Chloro-3,10-dibromo-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(S)-yl)-1-piperazinyl]-2-oxo-ethyl]-1-piperidinecarboxamide (40). Using a procedure similar to that described for the preparation of compound **15** above, the tricyclic carbamoyl derivative **40** was prepared from intermediate **(−)30.** All data for this enantiomer are identical to that of **37** above, except for the rotation which was found to be $[\alpha]_D^{25}$ −31.3° (c = 0.45, MeOH); Anal. ($C_{26}H_{30}N_5O_2Br_2Cl\cdot0.6H_2O$) C, H, N.

4-(3,7-Dibromo-8-chloro-5,6-dihydro-9-nitro-11*H*-benzo-[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidine)-1-piperidinecarboxylic Acid Ethyl Ester (41). Nitrocarbamate **5** (20 g, 40.5 mmol) was dissolved in concentrated sulfuric acid (200 mL) at 20 °C and then cooled to 0 °C. To this solution was added 1,3-dibromo-5,5-dimethyl hydantoin (7.12 g, 24.89 mmol), and the reaction mixture was stirred for 3 h at 20 °C. Another portion of 1,3-dibromo-5,5-dimethyl hydantoin (1.0 g, 3.5 mmol) was added at 0 °C, and the reaction mixture was stirred at 20 °C for an additional 1 h. The reaction mixture was poured onto ice (400 g) and then basified with concentrated ammonium hydroxide at 0 °C. The precipitated solid was filtered, washed with water (300 mL), and triturated with acetone (200 mL) yielding compound **41** as a white powder (19.8 g, 86%): mp 236−237 °C; MS (CI) *m/z* 586 (MH^+).

4-(9-Amino-3,7-dibromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidine)-1-piperidinecarboxylic Acid Ethyl Ester (42). Compound **42** was prepared as described for preparation of compound **6**. Chromatography on silica gel eluting with 30% EtOAc−CH_2Cl_2 furnished **42** as a white solid (60%): mp 211−212 °C; MS (CI) *m/z* 556 (MH^+).

4-[3,7-Dibromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidine]-1-piperidinecarboxylic Acid Ethyl Ester (43). Deamination of amino carbamate **42** was accomplished as described for compound **8** above. Chromatography on silica gel eluting with 25% EtOAc−hexanes yielded **43** as a white solid (70%): MS (CI) *m/z* 541 (MH^+).

4-(3,7-Dibromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidine)-1-piperidine (44). Hydrolysis of **43** as described for compound **9** above afforded **44** as a white solid (5.4 g, 92%): MS (CI) *m/z* 468.9 (MH^+).

(±)-3,7-Dibromo-8-chloro-6,11-dihydro-11-(4-piperidinyl)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (45). Reduction of the double bond of the tricyclic compound **44** as described for compound **9** afforded **45** as a white solid: MS (FABS) *m/z* 469 (MH^+). Resolution on Chiralpak AD column eluting with 5% 2-propanol−95% hexane−0.2% diethylamine afforded the enantiomeric amines **(+)45**: (retention time = 13.8 min), [α[α]$_D^{25}$ +43.5° (c = 0.40, MeOH) and **(−)45**: (retention time = 16.6 min), $[\alpha]_D^{25}$ −41.8° (c = 0.33, MeOH).

(−)-4-(8-Chloro-3,7-dibromo-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl)-1-(4-pyridinylacetyl)piperidine *N*1-Oxide (46). Using the procedure described for preparation of compound **11** above, tricyclic acetamide **46** was prepared from intermediate **(−)45**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.0−1.4 (m, 2H), 1.4−1.6 (m, 1H), 1.8−2.0 (m, 2H), 2.3−2.6 (m, 2H), 2.8−3.1 (m, 2H), 3.2−3.5 (m, 2H),

3.65 (s, 2H), 3.75−3.95 (m, 2H), 4.55−4.65 (m, 1H), 7.02 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.58 (br s, 1H), 8.15 (d, J = 6.9 Hz, 2H), 7.15 (d, J = 6.7 Hz, 2H), 8.38 (br s, 1H); $[\alpha]_D^{25}$ −30.4 (11.19 mg/2 mL, EtOH, free base); $[\alpha]_D^{25}$ −63.2° (c = 0.50, EtOH, HCl salt); MS (FABS) m/z 606 (MH^+); IR (film) υ_{max} 3393, 2938, 1643, 1634, 1443, 1243, 1175, 1096, 1038, 806, 733. Anal. ($C_{26}H_{24}N_3O_2Br_2Cl \cdot 1.9H_2O$) C, H, N.

(+)-4-(8-Chloro-3,7-dibromo-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-(4-pyridinylacetyl)piperidine *N*1-Oxide (47). Using a procedure similar to that described for the preparation of compound **11** above, tricyclic acetamide **47** was prepared from intermediate **(+)45**: All the data for this enantiomer is identical to that of **46** above, except for the rotation which was found to be $[\alpha]_D^{25}$ +34.1° (c = 0.55, EtOH).

(−)-4-[2-[4-(3,7-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide (48). Using a procedure similar to that described for the preparation of compound **15** above, tricyclic carbamoyl derivative **48** was prepared from intermediate **(−)45:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ (mixture of rotamers) 1.16−1.21 (m, 4H), 1.45 (m, 1H), 1.76 (d, J = 9 Hz, 2H), 2.0 (m, 1H), 2.22 (d, J = 4.8 Hz, 2H), 2.48 m, 2H), 2.85 (m, 4H), 3.48 (m, 3H), 3.90 (d, J = 7.5 Hz, 1H), 3.92 (m, 3H), 4.41 (s, 2H), 4.65 (d, J = 7.5 Hz, 1H), 7.04 (m, 1H), 7.24 (s, 1H), 7.59 (br s, 1H), 8.39 (s, 1H); $[\alpha]_D^{25}$ −33° (c = 0.53, EtOH); HRMS (FAB) calcd for $C_{27}H_{32}N_4O_2Br_2Cl$, 637.0581; found, 637.0568.

(+)-4-[2-[4-(3,7-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 (49). Using a procedure similar to that described for the preparation of compound **15** above, the carbamoyl derivative **49** was prepared from intermediate **(+)45**: All the data for this enantiomer are identical to that of **48** above, except for the rotation which was found to be $[\alpha]_D^{25}$ = +32° (c = 0.57, EtOH); MS (FABS) m/z 637 (MH^+). Anal. ($C_{27}H_{31}N_4O_2Br_2Cl$) C, H, N.

1-Dimethylethyl-[2-[4-3,7-dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl-1-piperidinyl]-1(*R*)-methyl-2-oxoethyl]carbamate (50). To a solution of **(−)45** (0.03 g, 0.06 mmol) in dry DMF (0.6 mL) were added BOC-D-alanine-*O*-succinimide (0.036 g, 0.13 mmol) and diisopropylethylamine (1 drop), and the reaction mixture was stirred at 25 °C overnight. The mixture was then diluted with toluene and concentrated by rotary evaporation. Purification by chromatography on silica gel eluting with 10% acetone−hexanes provided tricyclic amide **50** which was further recrystallized from EtOAc to give 25 mg of white prisms. Single-crystal X-ray analysis of **50** revealed the absolute configuration at C-11 to be *S*: mp 210−212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) (1:1 mixture of rotamers) δ (1:1) 1.25 (m, 3H), 1.46 (d, J = 7.5 Hz, 9H), 2.45 (m, 4H), 2.95 (m, 4H), 3.45 (m, 3H), 3.85 (m, 2H); 4.54, (m, 1H); 4.54 (m, 1H); 5.55 (d, J = 7.5 Hz, 1H); 7.25 (m, 1H), 7.05 (m, 1H), 7.56 (s, 1H); 8.38 (s, 1H); HRMS (FABS) calcd MH^+ ($C_{27}H_{33}N_3O_3Br_2Cl$), 640.0577; found, 640.0565.

3,7-Dibromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridine-11-one (51). Carbamate **43** (16.6 g, 0.03 mmol) was slurried in a mixture of 70 mL of acetonitrile and 212 mL of water. To this was added $NaIO_4$ (32.8 g, 0.15 mole) followed by RuO_2 (0.31 g, 2.30 mmol), and the mixture was stirred for 1.3 h. It was filtered, and the resulting solids were washed with CH_2Cl_2. The filtrate was concentrated in vacuo and the residue dissolved in 200 mL of CH_2Cl_2. Insoluble materials were filtered, and the filtrate was washed with bleach (100 mL) followed by water (100 mL). The organic layer was extracted with 6 N HCl until a pH of 2 remained. The acid extracts were combined, cooled to 0 °C, and then adjusted to pH = 4 by adding 50% aqueous NaOH dropwise with stirring. The crude product was extracted with two 100 mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from 20 mL of ethanol at 0 °C giving 7.95 g (66%) of a white solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.15 (m, 2H), 3.45 (m, 2H), 7.50 (d, 2H), 7.85 (m, 6H), 8.7 (s, 1H).

3,7-Dibromo-8-chloro-5,6-dihydro-11-(1-piperazinyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (53). Using procedures essentially similar to those described earlier,[9,16−17] trihalo azaketone **50** was reduced with $NaBH_4$ to afford the 11-hydroxy derivative **52** which was subsequently reacted with thionyl chloride to afford the 11-chloro compound. This was, in turn, reacted with excess piperazine to give, after flash chromatography on silica gel using a gradient of 5−10% MeOH−CH_2Cl_2 saturated with ammonia, racemic tricyclic piperazine **53** in 85% yield: mp 79.7−81.9 °C; ^{1}H NMR (400 MHz $CDCl_3$) δ 2.15−2.25 (m, 2H), 2.3−2.4 (m, 2H), 2.75−2.9 (m, 5H), 3.15−3.25 (m, 1H), 3.85−3.95 (m, 1H), 4.25−4.35 (m,-1H), 4.35 (s, 1H), 7.15 (d, J = 5.6 Hz, 1H), 7.25 (d, J = 5.6 Hz, 1H), 7.6 (s, 1H), 8.35 (s, 1H). The enantiomers were separated on a Chiralpak AD column (5 cm × 50 cm) using 20% isopropyl alcohol−80% hexane−0.2% diethylamine and a flow rate of 100 mL/min. **(+)53** enantiomer: mp 74.5−77.5 °C; $[\alpha]_D^{25}$ +97.4° (c = 0.42, MeOH); MH^+ = 471.9. **(−)53** enantiomer: mp 82.9−84.5 °C; $[\alpha]_D^{25}$ −97.4° (c = 0.42, EtOH); MS (FABS) m/z 471.8 (MH^+).

(−)-1-(8-Chloro-3,7-dibromo-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridine-11(*S*)-yl)-4-(pyridinylacetyl)piperazine *N*4-Oxide (54). Compound **54** was prepared by essentially the same procedure as described for preparation of compound **11**: mp 148.9−150.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.2−1.5 (m, 4H), 2.75−3.0 (m, 1H), 3.2−3.35 (m, 1H), 3.45 (t, J = 3 Hz, 2H), 3.55−4.9 (m, 5H), 4.2−4.4 (m, J = 3 Hz, 1H), 4.45 (s, 1H), 7.1−7.3 (m, 4H), 7.65 (d, J = 2 Hz, 1H), 8.25 (d, J = 5 Hz, 2H), 8.4 (d, J = 2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.3, 30.6, 38.1, 41.5, 45.5, 50.7, 51.2, 76.0, 76.2, 76.5, 76.6, 76.8, 77.0, 78.9, 120.0, 125.9, 126.4, 127.4, 130.6, 133.6, 135.3, 136.1, 138.5, 138.6, 140.5, 140.8, 146.9, 153.9, 166.6; $[\alpha]_D^{25}$ −56.4° (c = 0.47, MeOH); MS (FAB): m/z (rel intens) 607 (30, MH^+), 386 (100), 308 (20), 222 (35); Anal. ($C_{26}H_{24}N_4O_2Br_2Cl \cdot 0.5CH_2Cl_2$) C, H, N.

(+)-1-(8-Chloro-3,7-dibromo-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-4-(pyridinylacetyl)-piperazine *N*4-Oxide (55). The chemistry used to prepare **54** was performed on the (+)-enantiomer of amine **53** to yield **55** as a white solid: mp 149.0−150.5 °C; ^{1}H NMR (200 MHz $CDCl_3$) δ 2.2−1.5 (m, 4H), 2.75−3.0 (m, 1H), 3.2−3.35 (m, 1H), 3.45 (t, J = 3 Hz, 2H), 3.55−4.9 (m, 5H), 4.2−4.4 (m, J = 3 Hz, 1H), 4.45 (s, 1H), 7.1−7.3 (m, 4H), 7.65 (d, J = 2 Hz, 1H), 8.25 (d, J = 5 Hz, 2H), 8.4 (d, J = 2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.3, 30.6, 38.1, 41.5, 45.5, 50.7, 51.2, 75.99, 76.2, 76.5, 76.6, 76.8, 77.0, 78.9, 112.0, 125.9, 126.4, 127.4, 130.6, 133.6, 135.3, 136.1, 138.5, 138.6, 140.5, 140.8, 146.9, 153.9, 166.6; $[\alpha]_D^{25}$ +67.1° (c = 0.35, MeOH); MS (FAB) m/z (rel intens) 607 (70, MH^+), 509 (20), 386 (100), 307 (40), 289 (40), 232 (70), 220 (70). Anal. ($C_{25}H_{23}N_4O_2Br_2Cl \cdot 0.2H_2O$) C, H, N.

(−)-4-[2-[4-(3,7-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl)-1-piperidinyl]-2-oxoethyl]-1-piperidinecarboxamide (56). The chemistry used to prepare **15** was performed on the (−)-enantiomer of amine **53** to yield **56** as a white solid: mp 150.5−153.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.1−1.2 (m, 2H), 2.75 (m, 2H), 2.0 (m, 1H), 2.2 (d, J = 2 Hz, 2H), 2.2−2.3 (m, 2H), 2.3−2.5 (m, 2H), 2.8−2.95 (m, 2H), 3.3 (m, 1H), 3.4−3.7 (m, 4H), 3.85 (m, 1H), 3.95 (m, 2H), 4.3−4.4 (m, 1H), 4.5 (s, 2H), 7.15 (d, J = 2 Hz, 1H), 7.3 (d, J = 2 Hz, 1H), 7,65 (s, 1H), 8.4 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.3, 30.7, 31.8, 32.5, 38.8, 41.1, 43.95, 45.2, 51.0, 51.4, 76.2, 76.4, 76.6, 76.8, 77.0, 79.1, 119.9, 125.9, 127.3, 130.6, 135.2, 136.1, 136.3, 140.5, 140.8, 146.8, 154.2, 157.5, 169.3; $[\alpha]_D^{25}$ −61.4° (c = 0.41, MeOH); MS (FAB): m/z (rel intens) 640 (80, MH^+), 386 (100), 307 (20), 289 (20), 253 (30), 232 (80), 214 (30). Anal. ($C_{26}H_{30}N_5O_2Br_2Cl \cdot 0.3H_2O$) C, H, N.

(+)-4-[2-[4-(3,7-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 (57). The chemistry used to prepare **56** was performed on the (+)-enantiomer of

amine **53** to yield **57** as a white solid: mp 150−153 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.1−1.2 (m, 2H), 2.75 (m, 2H), 2.0 (m, 1H), 2.2 (d, J = 2 Hz, 2H), 2.2−2.3 (m, 2H), 2.3−2.5 (m, 2H), 2.8−2.95 (m, 2H), 3.3 (m, 1H), 3.4−3.7 (m, 4H), 3.85 (m, 1H), 3.95 (m, 2H), 4.3−4.4 (m, 1H), 4.5 (s, 2H), 7.15 (d, J = 2 Hz, 1H), 7.3 (d, J = 2 Hz, 1H), 7,65 (s, 1H), 8.4 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.3, 30.7, 31.6, 32.5, 38.8, 41.1, 44.0, 45.2, 51.0, 51.4, 76.2, 76.4, 76.6, 76.8, 77.0, 79.1, 119.9, 125.9, 127.3, 130.6, 135.2, 136.1, 136.3, 140.5, 140.8, 146.8, 154.2, 157.5, 169.3; $[\alpha]_D^{25}$ +63.9° (c = 0.51, MeOH); MS (FAB) m/z (rel intens) 640 (80, MH^+), 386 (100), 307 (20), 289 (20), 253 (30), 232 (80), 214 (30). Anal. ($C_{26}H_{30}N_5O_2Br_2Cl\ CH_2Cl_2 \cdot 0.5H_2O$) C, H, N.

7-Amino-3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-one (58). Nitro azaketone **18** was reduced in a manner similar to that described for compound **5** to provide amino azaketone **58**: MS (FAB) m/z 338 (MH^+).

3-Bromo-7,8-dichloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-one (59). To 3 mL of concentrated H_2SO_4 at ∼0 °C was added $NaNO_2$ (0.24 g, 3.4 mmol), and the mixture was stirred for 30 min. Amino azaketone **58** (1.0 g, 3 mmol) dissolved in 12 mL of AcOH was added. The slurry was poured into a cold solution of CuCl (0.56 g, 5.9 mmol) in 10 mL of HCl at ∼0 °C. The reaction mixture was poured onto ice and basified with concentrated NH_4OH to pH = 9. The mixture was then extracted with CH_2Cl_2, and the combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and concentrated to give 0.9 g of **59**: MS (FAB) m/z 355 (MH^+).

(−)-1-(3-Bromo-7,8-dichloro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11(*S*)-yl)-4-(4-pyridinylacetyl)-piperazine *N*4-Oxide (60). Using a procedure similar to that described for the preparation of compound **54** above, tricyclic acetamide **60** was prepared: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20−2.40 (m, 4H), 2.75−2.90 (m, 1H), 3.15−3.25 (m, 1H), 3.40 (m, 2H), 3.50−3.60 (m, 2H), 3.65 (s, 2H), 3.80−3.90 (m, 1H), 4.05−4.15 (m, 1H), 4.40 (s, 1H), 7.05−7.20 (m, 3H), 7.25−7.35 (m, 2H), 7.60 (s, 1H), 8.15 (d, J = 5 Hz, 2H), 8.40 (d, J = 2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.0, 29.4, 38.5, 41.9, 45.8, 51.1, 51.6, 76.6, 79.2, 120.0, 120.4, 126.8, 127.8, 130.4, 133.4, 133.6, 134.5, 136.5, 136.6, 138.9, 139.0, 140.5, 141.1, 147.3, 153.5, 166.9; $[\alpha]_D^{25}$ −47.3° (c = 0.39, MeOH); MS (FAB) m/z 561 (MH^+). Anal. ($C_{25}H_{23}N_4O_2BrCl_2 \cdot 1.5H_2O$) C, H, N.

3-Bromo-7-fluoro-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-one (61). A solution of NFTH (Accufluor) (1.75 g, 5.45 mmol) was added to a solution of **17** (1.5 g, 4.67 mmol) in concentrated sulfuric acid (5 mL) at room temperature, and then the mixture was stirred at 140 °C for 7 h. The resultant black solution was cooled to room temperature, poured onto ice (50 g), basified with 10% NaOH (10 mL), extracted with CH_2Cl_2 (2 × 50 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated. The residue was chromatographed on silica gel eluting with 3% EtOAc−hexanes, yielding compound **61** as a white solid (1.02 g, 65% yield): MS (CI) m/z 340 (MH^+).

(±)-1-(3-Bromo-8-chloro-7-fluoro-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)-piperazine *N*4-Oxide (62). Using a procedure similar to that described for the preparation of compound **54** above, tricyclic acetamide **62** was prepared: ^{1}H NMR ($CDCl_3$) δ 2.75 (m, 1H), 3.00 (m, 1H), 3.39 (br s, 2H), 3.56 (br s, 2H), 3.63 (s, 2H), 3.67 (m, 1H), 4.05 (m, 1H), 4.36 (s, 1H), 6.99 (d, J = 3.8 Hz, 1H), 7.14 (d, J = 6.4 Hz, 2H), 7.18 (m, 1H), 7.63 (s, 1H), 8.14 (d, J = 6.7 Hz, 2H), 8.39 (s, 1H); MS (FABS) m/z 545 (MH^+). Anal. ($C_{25}H_{23}BrClFN_4O_2 \cdot H_2O$) C, H, N.

In Vitro Enzyme Assays. The FPT activity was determined by measuring the transfer of [^{3}H]farnesyl from [^{3}H]-farnesyl pyrophosphate to trichloroacetic acid-precipitable Ha-Ras-CVLS as previously described.[14] GGPT-1 activity was similarly determined using [^{3}H]geranylgeranyl diphosphate and Ha-Ras-CVLL as substrates.[14]

Cellular Assays for Inhibition of H-Ras Processing and Transforming Function. Inhibition of intracellular processing of H-Ras by the inhibitors was measured in transfected Cos cells as described previously.[14]

Cell Lines for in Vivo Studies. The human colon carcinoma DLD-1, HCT-116, A549, and Mia Paca cell lines were obtained from the American Type Culture Collection (Rockville, MD).

In Vivo Efficacy Studies. All animal studies were carried out in the animal facility of Schering-Plough Research Institute in accordance with institutional guidelines as described previously.[8−10]

Pharmacokinetic Studies. Nude mice were also used to study the pharmacokinetic properties of the tricyclic inhibitors. Blood samples were collected at nine time points (2 min, 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 7 h, and 24 h) after a single oral or intravenous (tail vein) dose of 25 mg/kg inhibitor in 20% HPβCD. Two mice were used for each time point, and samples were collected by cardiac puncture after euthanasia with carbon dioxide. After clotting on ice, serum was isolated by centrifugation. Quantitation of inhibitor serum levels was achieved using acetonitrile precipitation, followed by high performance liquid chromatography−atmospheric pressure chemical ionization (APCI) tandem mass spectrometry. A detailed description of the analytical methodology has been described for an earlier analogue in this series.[15]

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Supporting Information Available: ^{1}H NMR data for intermediate compounds, **4**−**10, 13**−**14**, **17**−**26**, **30**−**32**, **41**−**45**, **51**, **58**−**59,** and **61**, crystallographic data and data collection parameters, tables of fractional atomic coordinates and temperature factor parameters, bond lengths, bond angles, and torsion angles for **10**·NAcPhe·EtOH and **50** (20 pages). See any current masthead page for ordering information.

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