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Synthesis of Isomeric 3-Piperidinyl and 3-Pyrrolidinyl Benzo[5,6]cyclohepta[1,2-*b*]pyridines: Sulfonamido Derivatives as Inhibitors of Ras Prenylation

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Abstract—Blocking farnesylation of oncogenic Ras proteins is a mechanism based therapeutic approach that is of current interest for the development of antitumor agents to treat *ras* associated tumors. As part of a SAR study on the lead farnesyl protein transferase (FPT) inhibitor **I**, we report here the synthesis of novel geometric isomers **II** and **III** and the FPT inhibition activity of their *N*-acyl and *N*-sulfonamido derivatives **15-65**. The *N*-acyl derivatives are markedly less active than the lead inhibitor **I** thereby demonstrating that the spatial location of the *N*-acyl group in **I** is critical for binding of the compound to FPT. In contrast to **I**, the *N*-sulfonamido-**II** series is a novel lead of non-sulfhydryl, nonpeptidic compounds that are dual FPT/GGPT inhibitors. In light of recent reports on the alternative prenylation of N- and K-Ras, dual FPT/GGPT inhibitors may be required to control cell proliferation in tumors containing activated Ras.

Introduction

ras Oncogenes are present in a majority of human colon and pancreatic carcinomas.[1] The pathway by which Ras proteins regulate cell proliferation is now known; in this pathway, Ras proteins occupy a central role in a signal transduction cascade which is initiated by the binding of extra-cellular growth factors to their tyrosine kinase receptors, and ends in the nucleus with phosphorylation of key transcription factors that regulate gene expression.[2] The upstream signals in this cascade induce a guanine nucleotide exchange that converts the inactive GDP-bound Ras to its active GTP-bound state.[3] Downstream signalling, and hence cell proliferation, proceeds until it is terminated by intrinsic GTPase activity of Ras which returns the active GTP-bound Ras to the inactive GDP-bound state.[2,4] Oncogenic Ras is deficient in GTPase activity and this results in uncontrolled cell proliferation.[1] Ras proteins are expressed in the cytosol and require a post-translational farnesylation on the cysteine residue of the carboxyl terminus CAAX tetrapeptide in order to acquire transforming ability; this prenylation step is catalyzed by the enzyme farnesyl protein transferase (FPT), and the farnesylated-Ras becomes functional by attachment to the inner plasma membrane.[5] A majority of other cellular proteins are prenylated with a geranylgeranyl residue on the cysteine of their carboxyl-terminus sequence; these prenylations are catalyzed by Geranylgeranyl protein transferase (GGPT), an enzyme which is closely related to FPT.[5,6] Selective inhibition of farnesylation of Ras by FPT has been an attractive therapeutic target for the development of antitumor agents to control tumorigenic cell proliferation in *ras* associated tumors.[7,8] However, it is now known that N- and K-Ras can also undergo alternative prenylation.[9–11] Most of the potent FPT inhibitors reported in the literature to date are peptidomimetics or peptides based on the CAAX sequence and contain a free thiol group.[12] FPT inhibitors that are nonthiol peptides have also been reported.[13] However, the peptidic nature or the presence of a free thiol group

Key words: FPT Inhibitors; inhibitors of Ras prenylation; dual FPT/GGPT inhibitors; sulfonamido tricycles as FPT inhibitors; farnesyl protein transferase inhibitors.
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in these FPT inhibitors may have disadvantages in the development of such compounds as therapeutic agents. Recently, our laboratories have reported on the discovery of Sch 44342 (**I**) as a novel, nonpeptidic, non-thiol-containing selective FPT inhibitor.[14] As part of a structure–activity study based on this lead series,[15] it was of interest to determine the effect of shifting the nitrogen atom in the pendant 4-piperidine ring of **I**, to the adjoining position thereby rendering the molecule non-symmetrical and placing the *N*-substituents in two different spatial locations relative to the top benzocycloheptapyridine tricycle; we report here the synthesis of such geometric isomers **IIa–b** and **IIIa–b**, which contain a 3-piperidino or 3-pyrrolidino ring.[16] The FPT inhibition activities of various *N*-acyl and *N*-sulfonamido derivatives of these novel tricycles are reported.

Chemistry

The synthesis of the novel heterocycles **II** and **III** are shown in Scheme 1. Addition of the anion derived from *N*-methyl-2-piperidinone or *N*-benzyl-2-pyrrolidinone to the known tricyclic ketone **1** (R = H or Br)[17,18] followed by acid catalyzed dehydration of the resulting diastereoisomeric mixture of alcohols **2a–c** affords the olefinic *Z*-amides **3a–c** and the *E*-amides **4a–c**. Dehydration of the individual diastereoisomers of **2a–c** gave the same ratio of **3a–c**/**4a–c**.[19a]

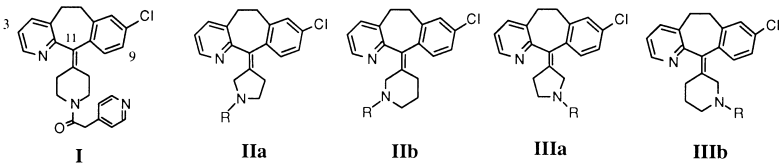
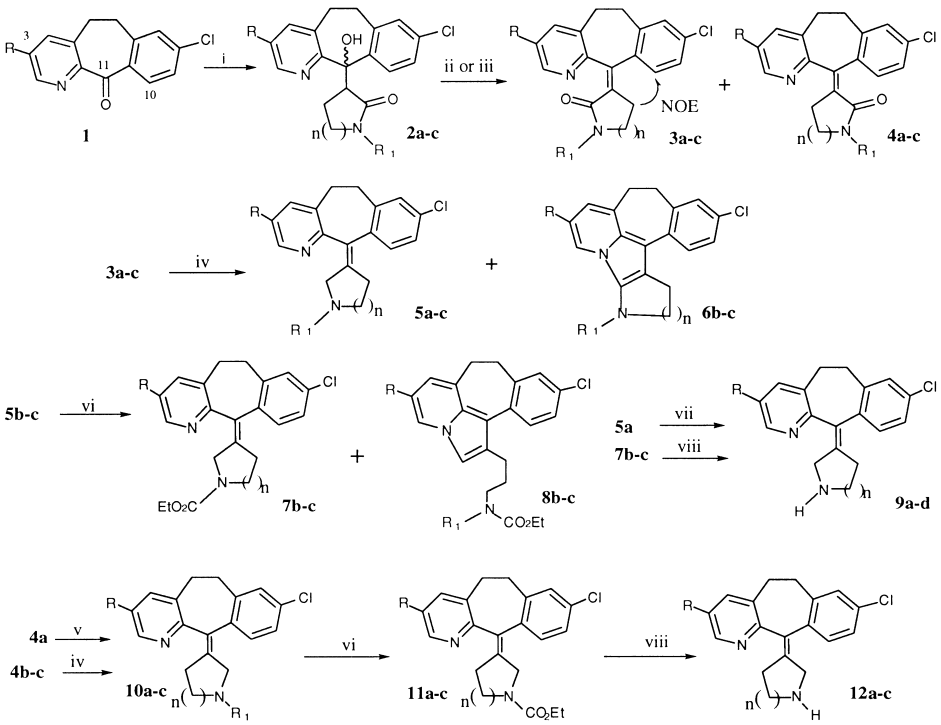


Figure 1.



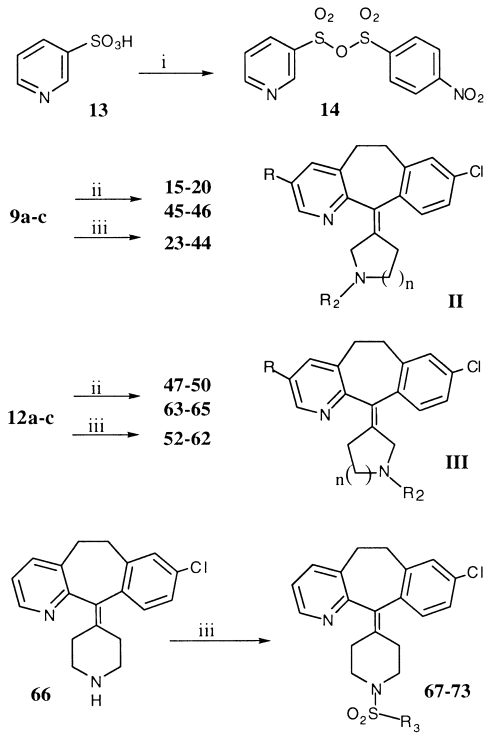
a: n = 1, R = H, R_1 = Bn ; **b:** n = 2, R = H, R_1 = Me ; **c:** n = 2, R = Br, R_1 = Me ;
d: n = 1, R = H, Cl = H.

Scheme 1. Reagents: (i) *N*-Methyl-3-piperidinone or *N*-benzyl-pyrrolidinone, LDA, THF; (ii) concd sulfuric acid; (iii) propionic acid/*p*-TsOH; (iv) LAH in THF; (v) LAH in ether; (vi) $ClCO_2Et$, toluene, triethylamine, 80 °C; (vii) 10% pd/C, 1,4-cyclohexadiene, acetic acid-methanol; (viii) concd HCl, 80 °C.

Reduction of the lactam **3a** with LAH in THF afforded only the desired amine **5a**. LAH reduction of the lactams **3b–c** on the other hand, afforded the desired amines **5b–c** and also the novel rearrangement products **6b–c**.[19b] LAH reduction of lactams **4b–c** in THF afforded the *E*-piperidines **10b–c**. Under these same conditions, **4a** was converted into the isomeric amines **10a** and **5a** in a 1:1 ratio; however, **10a** was formed selectively when the LAH reduction was carried out in ether.

N-Dealkylation of the *E*-isomers **10a–c** with ethyl chloroformate afforded the carbamates **11a–c**, which were hydrolyzed under acidic conditions to the desired *E*-amines **12a–c**.[19b] Under the same conditions, *N*-dealkylation of the *Z*-isomers **5b–c** afforded the expected carbamates **7b–c** and the novel indolizidene re-arrangement products **8b–c**; *N*-dealkylation of **5a** using the same reaction conditions favors exclusively the formation of the rearrangement product. The final *Z*-amines **9a–c** were obtained by acid hydrolysis of the carbamates **7b–c** and by careful hydrogenolysis of **5a**; catalytic hydrogenation of **5a** under less controlled conditions afforded **9–d**, the product of hydrogenolyses of both the *N*-benzyl and the 8-chloro groups.

The *Z*- and *E*-amines **9a–d** and **12a–c** were acylated with various carboxylic acids using standard carbodiimide reaction conditions to obtain the *N*-acyl derivatives **15–22**, and **47–50** in the piperidine series, and **45–46** and **63–65** in the pyrrolidine series. Similarly, the *N*-sulfonamido derivatives **23–40**, and **52–60** in the piperidine series and **41–44** and **61–62** in the pyrrolidine series were prepared by conventional sulfonation employing the appropriate sulfonyl chloride and Et_3N in methylene chloride.[19c,20] Miscellaneous derivatives **21**, **22**, and **51** were obtained from the amines **9b** and **12b**. For comparison purposes, a few sulfonamides **67–73** in the lead series **I** were prepared from **66**.



Scheme 2. Reagents: (i) *p*-Nitrobenzenesulfonyl chloride, pyridine, 0 °C; (ii) ArCOOH, EDCI, HOBT, DMF, 0 °C; (iii) Method A: $ArSO_2Cl$, pyridine, 0 °C; Method B (Ref. 16c): **14**, pyridine, 0 °C.

Biology

Compounds **15–73** were tested in an FPT assay; details of this assay have been described previously.[14] The assay measures the inhibition of FPT catalyzed transfer of [^{3}H]farnesyl group from [^{3}H]farnesyl-pyrophosphate to H-Ras-CVLS. Results of these assays are given in Tables 1–3.

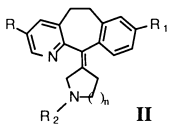
Acyl derivatives of the *Z*- and *E*-isomers in both the 3-piperidino (**15–22** and **47–50**) and 3-pyrrolidino series (**45–46** and **63–65**) are generally less active as FPT inhibitors relative to acyl derivatives in the 4-piperidino series such as **I**.[14,15] The 3-pyridylacetyl derivatives **16** and **47**, and the 4-thiopyridylacetyl derivatives **45** and **63**, are weakly active (IC_{50} 4–7 μM). Thus far, no clear SAR is evident from the acyl derivatives.

Sulfonamido derivatives of the *Z*- and *E*-isomers in both the 3-piperidino (**23–40** and **52–60**) and 3-pyrrolidino series (**41–44** and **61–62**) are generally more active than sulfonamido derivatives of the 4-piperidino series (compounds **67–73**) and follow an opposite SAR. For example the methyl sulfonamide of **II** (compound **23**) is inactive while the same derivative of **I** (compound **67**) is active in the FPT assay; the aromatic sulfonamides of **II** (compounds **24**, **36**, and **37**) are more active than the corresponding derivatives of **I** (compounds **68**, **72**, and **73**).

Sulfonamides **52**, **57**, **59**, **60** of the *E*-isomers are 10 times less active than the corresponding *Z*-compounds **24**, **3**, **36**, and **38**. The discussion that follows below concerns the sulfonamides of the *Z*-isomer in the 3-piperidine and 3-pyrrolidine series **II**.

The activity of the phenylsulfonamide **24** was lost by introducing *para*-substituents on the phenyl ring (e.g. **25–30**). The loss in activity is not attributable to the electronic nature of the substituent since both electron withdrawing and donating groups give rise to less

Table 1. Structure–activity of *Z*-piperidine and pyrrolidine derivatives



II

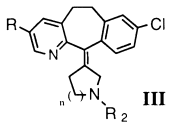
No.	*n*	R	R_1	R_2	Formula[a]	mp (°C)[b]	FPT Activity	
							IC_{50} (μM)	%Inhib. (μM)[c]
15	2	H	Cl	3-Pyridyl-CO-	$C_{25}H_{22}ON_3Cl$			> 14
16	2	H	Cl	3-Pyridyl-CH_2CO-	$C_{26}H_{24}ON_3Cl$		7.8	
17	2	H	Cl	4-Pyridyl-CH_2CO-	$C_{26}H_{24}ON_3Cl$			9 (14)
18	2	H	Cl	Phenyl-CO-	$C_{26}H_{23}ON_2Cl$	215–216		NA
19	2	H	Cl	Phenyl-CH_2CO-	$C_{27}H_{25}ON_2Cl$			> 14
20	2	H	Cl	Phenyl-CH_2CH_2CO-	$C_{28}H_{27}ON_2Cl$			NA
21	2	H	Cl	Phenyl-NH-CO-	$C_{26}H_{24}ON_3Cl$	184–185		10 (46)
22	2	H	Cl	Phenyl-S-CO-	$C_{26}H_{23}ON_2ClS$	187–188		6 (13)
23	2	H	Cl	CH_3SO_2-	$C_{20}H_{21}O_2N_2ClS$	189–190		15 (15)
24	2	H	Cl	Phenyl-SO_2-	$C_{25}H_{23}O_2N_2ClS$		0.71	
25	2	H	Cl	*p*-Acetamido-Phenyl-SO_2-	$C_{27}H_{26}O_3N_3ClS$	162–163		NA
26	2	H	Cl	*p*-Methoxy-Phenyl-SO_2-	$C_{26}H_{25}O_3N_2ClS$	160–161		33 (42)
27	2	H	Cl	*p*-Nitro-Phenyl-SO_2-	$C_{25}H_{22}O_4N_3ClS$	178–179		33 (42)
28	2	H	Cl	*p*-Fluoro-Phenyl-SO_2-	$C_{25}H_{22}O_2N_2FS$	173–174	1.34	
29	2	H	Cl	4-Methyl-Phenyl-SO_2-	$C_{26}H_{25}O_2N_2ClS$			35 (13)
30	2	H	Cl	2,4,6-Tri-Me-Phenyl-SO_2-	$C_{28}H_{29}O_2N_2ClS$	227–229		12 (12)
31	2	H	Cl	Phenyl-CH_2SO_2-	$C_{26}H_{25}O_2N_2ClS$	198–199		13 (13)
32	2	H	Cl	2-Thienyl-SO_2-	$C_{23}H_{21}O_2N_2ClS_2$		0.44	
33	2	H	Cl	5-Chloro-2-Thienyl-SO_2-	$C_{23}H_{20}O_2N_2ClS_2$	154–155	0.19	
34	2	H	Cl	5-Carboxy-2-Thienyl-SO_2-	$C_{24}H_{21}O_4N_2ClS$	228–229		47 (40)
35	2	H	Cl	5-CO2CH3-2-Thienyl-SO_2-	$C_{25}H_{23}O_4N_2ClS$	134–136	4.4	
36	2	H	Cl	3-Pyridyl-SO_2-	$C_{24}H_{22}O_2N_3ClS$	158–159	0.97	
37	2	Br	Cl	2-Thienyl-SO_2-	$C_{23}H_{20}O_2N_2BrClS_2$	183–184	0.84	
38	2	Br	Cl	5-Chloro-2-Thienyl-SO_2-	$C_{23}H_{19}O_2N_2BrCl2S_2$	165–167	0.47	
39	2	Br	Cl	Phenyl-SO_2-	$C_{25}H_{22}O_2N_2BrClS$	184–185	0.58	
40	2	Br	Cl	5-Cl-1,3-diMe-4-Pyrazole-SO_2-	$C_{24}H_{23}O_2N_4BrCl_2S$	251–252		NA
41	1	H	Cl	Phenyl-SO_2-	$C_{24}H_{21}O_2N_2ClS$[d]		0.59	
42	1	H	H	Phenyl-SO_2-	$C_{24}H_{22}O_2N_2S$[d]		2.8	
43	1	H	Cl	2-Thienyl-SO_2-	$C_{22}H_{19}O_2N_2ClS_2$[d]		0.52	
44	1	H	H	2-Thienyl-SO_2-	$C_{22}H_{20}N_2S_2$[d]		3.3	
45	1	H	Cl	4-Pyridyl-S-CH_2-CO-	$C_{25}H_{22}ON_3ClS$[d]		4.2	
46	1	H	Cl	4-Pyridyl-CH_2CO-	$C_{25}H_{22}ON_3Cl$			37 (14)

[a]Except where noted, elemental analysis within 0.4% of theoretical values was obtained.
[b]Melting points are uncorrected; no entries indicates that the compound is amorphous.
[c]See Refs 14 and 21 for assay details; NA indicates that no inhibition activity was observed.
[d]High-resolution mass spectra data was obtained.

potent compounds. Heteroaromatic sulfonamides, such as the 2-thienyl analogues **32–35** and the 3-pyridyl derivative **36** are potent FPT inhibitors, with the 5-chloro-2-thienyl analogue **33** displaying an $IC_{50} = 0.19\,\mu M$. Incorporation of a 3-bromo substituent as in **37–39** does not have a significant effect on the FPT activity; in contrast to this, an 8-chloro substituent enhances the FPT inhibition activity sixfold as in **41**, **43** versus **42**, **44**.

Since prenylation by GGPT is common to many cellular proteins, selectivity in FPT versus GGPT inhibition has been an important criterion for the development of an FPT inhibitor as an antitumor agent. A selected number of the above FPT inhibitors were therefore evaluated in a GGPT assay, which measures the ability of a compound to inhibit GGPT catalyzed transfer of the [^{3}H]-geranyl-geranyl group from [^{3}H]-geranyl-geranyl pyrophosphate to H-Ras-CVLL. A few compounds from

Table 2. Structure–activity of *E*-piperidine and pyrrolidine derivatives

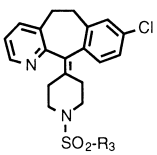


III

No.	*n*	R	R_2	Formula[a]	mp (°C)[b]	FPT Activity[c]	
						IC_{50} (μM)	%Inhib. (μM)
47	2	H	3-Pyridyl-CH_2CO-	$C_{26}H_{24}ON_3Cl$	157–158	5.1	
48	2	H	4-Pyridyl-CH_2CO-	$C_{26}H_{24}ON_3Cl$			42 (14)
49	2	H	3-Pyrdyl-CH = CHCO-	$C_{27}H_{24}ON_3Cl$	165–166		8 (45)
50	2	H	Phenyl-CH_2CH_2CO-	$C_{28}H_{27}ON_2Cl$			27 (45)
51	2	H	*p*-NO_2-Phenyl-S-	$C_{25}H_{22}O_2N_3ClS$	173–174		12 (43)
52	2	H	Phenyl-SO_2-	$C_{25}H_{23}O_2N_2ClS$	235–236	3.3	
53	2	H	*p*-Acetamido-Phenyl-SO_2-	$C_{27}H_{26}O_3N_3ClS$	147–149	33.5	
54	2	H	p-Methoxy-Phenyl-SO_2-	$C_{26}H_{25}O_3N_2ClS$	168–169		32 (42)
55	2	H	*p*-Nitro-Phenyl-SO_2-	$C_{25}H_{22}O_4N_3ClS$	232–233		29 (40)
56	2	H	*p*-Fluoro-Phenyl-SO_2-	$C_{25}H_{22}O_2N_2ClFS$	154–155		45 (43)
57	2	H	2-Thienyl-SO_2-	$C_{23}H_{21}O_2N_2ClS$	254–255	4.8	
58	2	H	5-PhCONHCH2-2-Thienyl-SO_2-	$C_{31}H_{28}O_3N_3ClS_2$			17 (34)
59	2	H	3-Pyridyl-SO_2-	$C_{24}H_{22}O_2N_3ClS$	214–215	8.8	
60	2	Br	5-Chloro-2-Thienyl-SO_2-	$C_{23}H_{19}O_2N_2BrCl_2S_2$	171–172	8.0	
61	1	H	Phenyl-SO_2-	$C_{24}H_{21}N_2O_2ClS$[d]	181 (dec)	4.0	
62	1	H	2-Thienyl-SO_2-	$C_{22}H_{19}N_2O_2ClS_2$[d]	173 (dec)	5.1	
63	1	H	4-Pyridyl-S-CH_2-CO-	$C_{25}H_{22}N_3OClS$[d]		6.9	
64	1	H	4-Pyridyl-CH_2CO-	$C_{25}H_{22}N_3OCl$[d]			11 (14)
65	1	H	2-Furanyl-CO-	$C_{23}H_{19}N_2O_2Cl$[d]	190-192		33 (50)

[a-d]Refer to footnotes under Table 1.

Table 3. Structure–activity of piperidino sulfonamides



No.	R_3	Formula[a]	mp (°C)[b]	FTP Activity[c]	
				IC_{50} (μM)	%Inhib. (μM)
67	CH_3–			1.9[d]	
68	Phenyl-	$C_{25}H_{23}O_2N_2ClS$	174–175		NA
69	*p*-CH_3-Phenyl-	$C_{26}H_{25}O_2N_2ClS$			NA
70	*p*-AcNH-Phenyl-	$C_{27}H_{26}O_3N_3ClS$	157–158		NA
71	*p*-NO_2-Phenyl-	$C_{25}H_{22}O_4N_3ClS$	230–231		> 12[d]
72	2-Thienyl-			13[d]	
73	3-Pyridyl-	$C_{24}H_{22}O_2N_3ClS$	103–105	6.6	

[a-c]Refer to footnotes under Table 1.
[d]Data from Ref. 15c.

this group were also evaluated in a COS assay which measures transient expression and processing (farnesylation) of H-Ras-CVLS in COS monkey kidney cells. Details of these assays have been reported previously,[14] and the results are shown in Table 4. The data in Table 4 indicate that none of the compounds tested shows high selectivity for FPT versus GGPT inhibition; the GGPT inhibitory concentration for these compounds is

Table 4. Prenylation selectivity

No.	FPT[c]		GGPT		COS[c]
	IC_{50} (μM)	% Inhib. (μM)	IC_{50} (μM)	% Inhib. (μM)	IC_{50} (μM)
21		10 (46)	0.8		
24	0.71		2.6		2.5
25		1 (39)	2.6		
28	1.34		4.9		
32	0.44		4.4		
33	0.19			68 (4)	> 5
37	0.84			18 (37)	
39	0.58			29 (38)	
41	0.59		7.1		> 5
42	2.8			47 (50)	
43	0.52			56 (4.5)	
44	3.3			39 (49)	
16	7.8			17 (12)	

[c]Refer to footnotes under Table 1.

only 4–100 times less than their FPT IC_{50}. A 3-bromo substituent decreases the GGPT inhibitory activity thereby increasing the FPT/GGPT selectivity as in **37**, **39** versus **32**, **24**. The prenylation inhibition selectivity can be offset to favor GGPT inhibition by changing the nitrogen substituent as in the acyl derivative **21** and the sulfonamide analogue **25**, which are selective GGPT inhibitors. Of the three compounds tested in the COS assay, **24** has a reasonable ratio for cell-based/in vitro enzyme FPT inhibitory activity.

Conclusions

Several conclusions are evident from the above study. Foremost, it demonstrates that the spatial location of the *N*-acyl group in the lead compound **I** is critical for binding of the compound to FPT; alteration in the location of this *N*-acyl functionality as in *N*-acyl derivatives of **II** and **III** leads to a marked loss in FPT inhibition activity. The *N*-sulfonamido derivatives of the *Z*-isomer **II**, on the other hand, are potent FPT inhibitors relative to the corresponding sulfonamido derivatives of *E*-isomer **III** and the lead tricycle **I**. These *N*-sulfonamido compounds of type **II** do not follow the SAR of the corresponding derivatives of the lead tricycle **I**. More detailed studies of the FPT active *N*-sulfonamido analogues showed that the compounds are also inhibitors of GGPT; the degree of this dual inhibition ranges from 4- to 100-fold in favor of FPT inhibition; a 3-bromo substituent increases the FPT/GGPT selectivity. These findings suggest that the binding mode of **II** to the FPT protein is different from that of **I**, and this change in the spatial location of the *N*-functionality leads to nonselective binding resulting in dual FPT/GGPT inhibitors.

Selective inhibition of farnesylation of Ras by FPT has been an important criterion for the development of antitumor agents to control tumorigenic cell proliferation in tumors containing activated Ras.[7,8] However, it has been recently reported that N-Ras, K-Ras4B and K-Ras4A are in vitro substrates for both FPT and GGPT;[9,10] a more recent report demonstrated that in the presence of the potent FPT inhibitor 3-bromo-**I**, Ras proteins in the human colon carcinoma cell line DLD-1 are alternatively prenylated by GGPT.[11] In light of these reports on the alternative prenylation of N- and K-Ras, dual FPT/GGPT inhibitors may be required to block Ras prenylation and to control cell proliferation in tumors containing activated Ras. In summary, the present N-sulfonamido series **II** is a novel lead of non-sulfhydryl, nonpeptidic compounds that are dual FPT/GGPT inhibitors; further chemical modifications of the series are needed to attain potency and the proper balance of FPT/GGPT inhibition. The SAR developed from this study is being used to design improved FPT inhibitors of the lead compound **I**.

Experimental

Reactions were performed under conventional techniques: employing oven dried glassware, nitrogen atmosphere, and commercial or freshly dried/distilled solvents. Extracts of crude reaction products were dried over anhydrous magnesium sulfate (MgSO4) or sodium sulfate (Na2SO4), evaporated under reduced pressure and purified by flash chromatography using Selecto Scientific 32-63 mesh silica gel. Melting points are uncorrected. ^{1}H NMR spectra were determined on a Varian VXR 200 or Gemini 300 MHz spectrometer using $CDCl_3$, CD_3OD, or DMSO-d_6 solutions and TMS as internal standard. ^{13}C NMR spectra were obtained at 75 MHz with the chemical shifts reported in ppm relative to the central line of CDCl3 (77.00 ppm). Mass spectra were determined either on Extrel 401, Jeol or VG Zab-SE mass spectrometer. Unless otherwise noted elemental analyses were within 0.4% of theoretical value.

3-Bromo-8-chloro-6,11-dihydro-11-hydroxy-11-(1-methyl-2-oxo-piperidin-3-yl)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (2c). n-Butyllithium (2.5 M in hexanes, 18 mL, 45.0 mmol) was added dropwise to a solution of diisopropylamine (7.0 mL, 49.4 mmol) in THF (100 mL) at −78 °C, stirred for 30 min and *N*-methyl-2-piperidone (7.0 mL, 64 mmol) was added dropwise. The resultant solution was stirred for 30 min and then allowed to warm to −5 °C over a 60 min period. The reaction mixture was

cooled to −78 °C and a solution of 3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**1**, R = Br)[18] (12 g, 37.2 mmol) in THF (200 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, then warmed to −10 °C over a 1 h period. Water (25 mL) was added, the mixture concentrated to ca. 100 mL, then extracted with methylene chloride (500 mL). The product crystallized on addition of acetone:ether (50 mL, 1:1). The solid was filtered, washed with ether (10 mL) and dried yielding 11.89 g of **2c**. The mother liquor was concentrated and upon chromatography using ethyl acetate:hexanes (1:3) yielded an additional 1.0 g of **2c** (79.56% total yield, mixture of diastereoisomers): MS(CI) *m/z* 435 (MH^+); Anal. ($C_{19}H_{18}BrClN_2O_2$) C, H, N.

8-Chloro-6,11-dihydro-11-hydroxy-11-(1-methyl-2-oxo-piperidin-3-yl)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (2b). Reaction of *N*-methyl-2-piperidone with 8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**1**, R = H)[17] using the procedure for **2c** afforded **2b** (76% yield, 10:1 mixture of diastereoisomers). The diastereoisomers were isolated by chromatography. Diastereomer A (minor product), higher R_f on TLC (40% EtOAc-Hexanes): mp 164–166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, 1H), 7.95 (d, 1H), 7.47 (d, 1H), 7.35 (s, 1H), 7.16 (m, 2H), 7.01 (s, 1H), 3.75 (m, 2H), 3.40 (m, 2H), 3.15 (m, 5H), 2.91 (s, 3H), 1.85 (m, 1H), 1.30 (m, 1H); MS(CI), *m/z* 357 (MH^+). Anal ($C_{20}H_{21}ClN_2O_2$) C, H, N. Diastereomer B (major product) Lower R_f on TLC: mp 164–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, 1H), 7.95 (d, 1H), 7.67 (s, 1H), 7.42 (d, 1H), 7.15 (m, 2H), 7.08 (s, 1 H), 3.60-3.80 (m, 2H), 3.45 (m, 2H), 3.15 (m, 1H), 3.05 (m, 2H), 2.86 (s, 3H), 1.90 (m, 2H), 1.60(m, 1H), 1.50 (m, 1H); MS(CI) *m/z* 357 (MH^+); Anal ($C_{20}H_{21}ClN_2O_2$) C, H, N.

8-Chloro-6,11-dihydro-11-hydroxy-11-(1-benzyl-2-oxo-pyrrolidin-3-yl)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (2a). Reaction of *N*-methyl-2-pyrrolidinone with 8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (**1**, R = H)[17] using the procedure for **2c** afforded **2a**. The less polar diastereoisomer A was insoluble in warm EtOAc and was isolated as a white crystalline solid (42%): mp 164–166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.4 (d, 1H, *J* = 4.8 Hz), 8.1 (d, 1H, *J* = 8.6 Hz), 7.6 (d, 1H, *J* = 6.7 Hz), 7.19–7.45 (m, 9H), 4.5 (apparent q, 2H, *J* = 14.7 Hz), 3.75–3.90 (m, 2H), 3.5–3.6 (m, 1H), 3.35–3.45 (m, 1H), 3.1–3.2 (m, 3H), 1.7–1.9 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.83, 157.96, 144.33, 141.02, 140.03, 137.21, 136.95, 133.13, 132.13, 130.25, 129.78, 128.76, 128.38, 127.53, 126.22, 123.76, 49.79, 46.89, 45.17, 32.56, 31.31, 20.70. MS (CI) *m/z* 385 (MH^+); Anal. ($C_{25}H_{23}N_2O_2Cl$), C, H, N. The more polar diastereoisomer B was isolated by chromatography from the EtOAc soluble fraction (solvent: 2–5% THF/CH_2Cl_2) as an amorphous solid (45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.5 (d, 1H, *J* = 4.2 Hz), 8.1 (d, *J* = 8.5 Hz), 7.8 (s, 1H), 7.6 (d, *J* = 7.8 Hz), 7.2–7.5 (m, 8H), 4.5 (apparent q, 2H, *J* = 14.7 Hz), 3.9–4.0 (m, 1H), 3.6–3.9 (m, 2H), 3.4–3.5 (m, 1H), 3.1–3.3 (m, 3H), 2.15–2.30 (m, 1H), 1.8–1.95 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.95, 157.51, 144.00, 143.95, 141.76, 139.61, 137.67, 136.83, 133.31, 132.29, 130.72, 128.82, 128.78, 128.37, 127.59, 126.50, 123.52, 50.05, 46.91, 45.48, 32.31, 31.33, 21.02. MS (CI) *m/z* 385 (MH^+); Anal ($C_{25}H_{23}N_2O_2Cl$), C, H, N.

3-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-methyl-2-piperidinone (3c and 4c). A solution of **2c** (11.4 g, 26.1 mmol) in concentrated sulfuric acid (100 mL) was stirred at 80 °C for 4 h, then cooled to 20 °C. The reaction mixture was poured into ice (300 g) and basified with 50% NaOH. The precipitated solid was filtered, washed with water (200 mL), dried and chromatographed eluting with ethyl acetate:methanol, 98:2 to yield the *Z*-isomer (**3c**) as a white solid (4.48 g, 41%): ^{1}H NMR δ 8.38 (s, 1H), 7.58 (s, 1H), 7.17 (s, 3H), 3.3–3.6 (m, 4H), 2.92 (s, 3H), 2.7–2.9 (m, 3H), 2.30–2.45 (m, 1H), 1.95–2.15 (m, 2H); MS(CI) *m/z* 417 (MH^+); Anal. ($C_{20}H_{18}BrClN_{2O}$) C, H, N. The *E*-isomer (**4c**) was eluted as a white solid (4.68 g, 43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.61(s, 1H), 7.14 (s, 1H), 7.10 (s, 2H), 3.25–3.60 (m, 4H), 2.94 (s, 3H), 2.70–2.90 (m, 3H), 1.80–2.20 (m, 3H); MS(CI) *m/z* 417 (MH^+); Anal. ($C_{20}H_{18}BrClN_2O$) C, H, N.

Dehydration of **2b** and **2a** by the above procedure followed by chromatography afforded the following compounds **3b**, **4b** and **3a**, **4a**

(*Z*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-methyl-2-piperidinone (3b). White solid (40%): mp 179–181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, 1H), 7.55 (d 1H), δ 8.35 (d, 1H), 7.55 (d, 1H), 7.2 (m, 2H), 7.0–7.1 (m, 2H), 3.3–3.6 (m, 4H), 2.92 (s, 3H), 2.7–2.9 (m, 3H), 2.0–2.2 (m, 2H), 1.90 (m, 1H); MS(CI) *m/z* 339 (MH^+).

(*E*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-methyl-2-piperidinone (4b). White solid (40%): mp 133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, 1H), 7.44 (d, 1H), 7.18 (d, 1H), 7.0–7.15 (m, 3H), 3.3–3.6 (m, 4H), 2.92 (s, 3H), 2.7–2.9 (m, 3H), 2.0–2.2 (m, 2H), 1.90 (m, 1H); MS(CI) *m/z* 339 (MH^+).

(*Z*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-benzyl-2-pyrrolidinone (3a). (83% for **3a/4a** combined): mp 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.5 (δ, 1H, *J* = 5.1 Hz), 7.2–7.6 (m, 10H), 4.63 (AB quartet, 2H, *J* = 14.4 Hz), 3.25–3.60 (m,

5H), 2.85–3.10 (m, 2H), 2.45–2.60 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.81, 156.22, 146.55, 143.01, 138.21, 138.14, 136.27, 138.83, 133.48, 133.22, 131.46, 131.42, 128.52, 128.17, 128.09, 127.45, 125.32, 122.77, 46.95, 42.96, 31.42, 31.39, 24.60; MS(CI), *m*/*z* 401 (MH^+); Anal. ($C_{25}H_{23}N_2OCl$), C, H, N.

(*E*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-ylidene)-1-benzyl-2-pyrrolidinone (4a). Mp 90–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.5 (δ, 1H, *J* = 5.1 Hz), 7.6 (d, 1H, *J* = 7.2 Hz), 7.2–7.5 (m, 9H), 4.5 (AB quartet, 2H, *J* = 14.7 Hz), 3.25–3.58 (m, 4H), 3.1–3.21(m, 1H), 2.85–3.10 (m, 2H), 2.59–2.65 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.49, 157.02, 146.81, 143.72, 139.22, 136.77, 136.52, 136.45, 133.83, 132.23, 131.52, 130.27, 129.06, 128.84, 128.66, 127.78, 126.52, 123.16, 47.37, 43.33, 32.32, 30.78, 24.62; MS(CI), *m*/*z* 401 (MH^+); Anal, ($C_{25}H_{23}N_2OCl$), C, H, N.

(*Z*)-3-Bromo-8-chloro-6,11-dihydro-11-(1-methyl-3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (5c) and 7-bromo-12-chloro-1,2,3,4,9,10-hexahydro-4-methyl-benzo[4,5]cyclohepta[1,2,3-hi]pyrido[3,2-*b*]indolizine (6c). LAH (110 mg, 2.78 mmol) was added to **3c** (1.0 g, 2.39 mmol) in THF (10 mL) at −5 °C and the resultant solution was stirred at this temperature for 2 h. The reaction was quenched by addition of ethyl acetate (2 mL) followed by a solution of 10% potassium sodium tartrate tetrahydrate (20 mL) and 10% sodium hydroxide (5 mL). The mixture was extracted with methylene chloride (150 mL) and chromatographed on silica gel eluting with hexanes:ethylacetate 5:1 yielding the title compound (**6c**) as a solid, which was recrystallized from methanol:ether as yellow needles (240 mg, 25%): mp 155–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.55 (d, 1H), 7.30 (s, 1H), 7.25 (d, 1H), 6.58 (s, 1H), 3.20–3.40 (m, 4H), 2.70–2.90 (m, 4H), 2.67 (s, 3H), 1.80–1.95 (m, 2H); MS(CI) *m*/*z* 402 (MH^+); Anal. ($C_{20}H_{18}BrClN_2$) C, H, N. The title product (**5c**) was eluted with ethyl acetate:methanol (97:3) containing 1% NH_4OH, yielding the product as a tan solid (480 mg, 50%): mp 160–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.56 (s, 1H), 7.10–7.17 (m, 3H), 3.35–3.50 (m, 3H), 2.60–2.95 (m, 2H), 2.78 (s, 3H), 2.0–2.3 (m, 5H), 1.75 (m, 2H); MS(CI) *m*/*z* 403 (MH^+) Anal. ($C_{20}H_{20}BrClN_2$) C, H, N.

LAH reduction of **3a** and **3b** by the above procedure afforded **5a**, **5b**, and **6b**.

(*Z*)-8-Chloro-6,11-dihydro-11-(1-methyl-3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (5b). White solid (50%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, 1H), 7.40 (d, 1H), 7.0–7.2 (m, 4H), 3.50 (m, 3H), 2.79 (s, 3H), 2.7–2.9 (m, 2H), 2.42 (m, 1H), 2.21 (m, 4H), 1.6–1.8 (m, 2H); MS (CI) *m*/*z* 325 (MH^+).

12-Chloro-1,2,3,4,9,10-hexahydro-4-methyl-benzo[4,5]-cyclohepta[1,2,3-*hi*]pyrido[3,2-*b*]indolizine (6b). Yellow crystals (25%): mp 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.70 (d, 1H), 7.49 (d, 1H), 7.26 (s, 1H), 7.23 (d, 1H), 6.51 (m 1H), 6.46 (m, 1H), 3.17 (m, 4H), 2.70 (m, 4H), 2.66 (s, 3H), 1.80-1.95 (m, 2H); MS(CI) *m*/*z* 322 (MH^+); X-ray; HRMS calcd (MH^+) for $C_{20}H_{20}N_2Cl$ 322.1237, measured 322.1233.

(*Z*)-8-Chloro-6,11-dihydro-11-(1-benzyl-3-pyrrolidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (5a). (54%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.4 (d, 1H, *J* = ∼5 Hz), 7.0–7.4 (m, 10H), 3.55–3.75 (m, 3H), 3.18–3.42 (m, 3H), 2.68–2.94 (m, 4H), 2.5–2.58 (m, 1H), 2.2–2.3 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 156.52, 146.68, 144.34, 140.58, 139.22, 139.11, 138.11, 132.99, 132.91, 131.63, 130.48, 129.04, 128.46, 127.14, 126.55, 122.20, 60.99, 59.39, 53.88, 32.53, 31.68, 31.54. MS(CI) *m*/*z* 386 (MH^+). HRMS calcd. for $C_{25}H_{24}N_2Cl$: 387.1628; Found, 387.1609. Anal. ($C_{25}H_{23}N_2Cl \times 0.25$ mol H_2O) C, H, N.

(*Z*)-Ethyl-3-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidine-carboxylate (7c) and ethyl-[3-(5-bromo-10-chloro-7,8-dihydro-benzo[4,5]cyclohepta[1,2,3-*hi*]indolizin-1-yl)propyl]-methylcarbamate (8c). Ethylchloroformate (1.0 mL, 10.4 mmol) and triethylamine (1.0 mL, 13.6 mmol) were added to a solution of **5c** in toluene (20 mL) at 0 °C, then stirred at 70 °C for 3 h. The solvent was evaporated under reduced pressure, and the residual oil extracted with CH_2Cl_2 (50 mL), washed with H_2O (20 mL) and chromatographed on silica gel. Elution with hexanes:ethylacetate (5:1) yielded an oil which crystallized on standing from ether to afford **8c** as yellow crystals (600 mg, 46.1%): mp 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.43 (d, 1H), 7.15–7.25 (m, 3H), 6.53 (s, 1H) 4.12 (q, 2H), 3.32 (m, 2H), 2.90 (m, 6H), 2.85 s, 3H), 1.80–2.0 (m, 2H), 1.24 (t, 3H); MS(CI) *m*/*z* 475 (MH^+); Anal. ($C_{23}H_{24}BrClN_2O_2$) C, H, N. The second title compound **7c** eluted from the column yielding a solid, which crystallized from ether:methylene chloride as white crystals (510 mg, 40.8%): mp 182–183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.62 (s, 1H), 7.11–7.17, (m, 3H), 4.55 (d, 1H), 4.02 (q, 2H), 4.0 (m, 1H), 3.75 (m, 1H), 3.3 (m, 2H), 3.1 (m, 1H), 2.82 (m, 2H), 2.55 (m, 1H), 2.32 (m, 1H), 1.75 (t, 3H), 1.0 (m, 2H); MS(CI) *m*/*z* 461(MH^+); Anal. ($C_{22}H_{22}BrClN_2O_2$) C, H, N. Ethylchloroformate dealkylation of **5b** using the above procedure afforded **7b** and **8b**.

(*Z*)-Ethyl-3-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (7b). White solid (45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, 1H), 7.43 (d, 1H) , 7.13 (m, 4H), 4.55 (d, 1H), 4.02 (q, 2H), 4.0 (m, 1H), 3,75 (m, 1H), 3.30 (m, 2H), 3,1

(m, 1H), 2.82 (m, 2H), 2.55 (m, 1H), 2.32 (m, 1H), 1.75 (t, 3H), 1.0 , (m, 2H); MS(CI), *m*/*z* 383 (MH^+).

Ethyl-[3-10-chloro-7,8-dihydro-benzo[4,5]cyclohepta[1,2,3-*hi*]indolizin-1-yl) propyl]methylcarbamate (8b). White solid (44%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (d, 1H), 7.57 (s, 1H), 7.50 (d, 1H), 7.29 d, 1H), 7,25 (d, 1H), 6.48 (m, 2H), 4.0 (q, 2H), 3.32 (m, 2H), 2.90 (m, 6H), 2.79 (s, 3H), 1.85 (m, 2H), 1.15 (t, 3H); MS(CI) *m*/*z* 397 (MH^+). HRMS calcd (MH^+) for $C_{23}H_{26}N_2O_2Cl$ 397.1683, measured 397.1681.

(*Z*)-3-Bromo-8-chloro-6,11-dihydro-11-(3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (9c). A solution of **7c** (400 mg, 0.866 mmol) in conc HCl (5 mL) was stirred at 100 °C overnight, then cooled to 0 °C, poured into ice (10 g) and basified with 30% NaOH. The mixture was extracted with CH_2Cl_2 (100 mL), and the organic layer was dried, filtered, and evaporated yielding **9c** as a white foam (320 mg, 94.8%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.40 (d, 1H), 7.14–7.34 (m, 3H), 3.46 (m, 4H), 2.86 (m, 4H), 2.38, (m, 2H), 1.75 (m, 1H), 1.62 (m, 1H); MS(CI) *m*/*z* 389 (MH^+); Anal. ($C_{19}H_{18}BrClN_2$) C, H, N.

Hydrolysis of **7b** by this procedure afforded **9b**.

(*Z*)-8-Chloro-6,11-dihydro-11-(3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (9b). White solid (90%): mp 170–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, 1H), 7.41 (d, 1H), 7.05–7.30 (m, 4H), 3.45 (m, 4H), 2.88 (m, 4H), 2.40 (m, 2H), 1.75 (m, 1H), 1.62 (m, 1H); MS (CI) *m*/*z* 311(MH^+); Anal. ($C_{19}H_{19}ClN_2$) C, H, N.

(*Z*)-8-Chloro-6,11-dihydro-11-(3-pyrrolylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (9a). To a two-necked flask equipped with a reflux condenser and a three-way valve (allowing for evacuation under vacuum and puringing with nitrogen) was added **5a** (1.29 mmol, 500 mg), MeOH (20 mL), acetic acid (5 mL), cyclohexadiene (5 mL), and 10% Pd/C (210 mg). After three cycles of evacuation-nitrogen purging was performed, an empty balloon was placed on top of the condenser so as to expand as hydrogen was evolved. The mixture was heated carefully to 70 °C at which time hydrogen evolution began. If starting material was still present by TLC after 1 h, a full hydrogen balloon was placed over the reaction mixture. The reduction was continued at ~40 °C for an additional 1 h (or until complete by TLC). The contents were then filtered through celite, and the effluent was concentrated under reduced pressure. Toluene was added and the material was evaporated once again to remove the HOAc. Chromatography on SiO_2 using (5% MeOH:CH_2Cl_2 increasing gradually to 10% MeOH:CH_2Cl_2:1% NH_4OH) gave **9a** (221 mg, 58%) as a tan solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.3 (d, 1H, J = 4.7 Hz), 7.3 (d, 1H, J = 6.7 Hz), 7.2 (d, 1H, J = 7.8 Hz), 7.10–7.19 (m, 2H), 7.06 (d, 1H, J = 4.8 Hz), 7.03 (d, 1H, J = 7.8 Hz), 4.09 (d, 1H, J = 16.4 Hz), 3.2–3.4 (m, 3H, containing a d, J = 16.2 Hz), 3.12–3.18 (m, 1H), 2.6–2.9 9m, 5H), 2.12–2.22 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.68, 146.49, 139.56, 138.93, 138.75, 137.17, 135.51, 134.01, 128.71, 128.42, 126.74, 126.55, 122.74, 48.68, 44.80, 32.95, 31.64, 30.09; MS(CI), 296 (MH^+); Anal. ($C_{18}H_{18}NCl \times 0.25$ mol H_2O) C, H, N.

(*Z*)-6,11-Dihydro-11-(3-pyrrolylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (9d). Compound **5a** (2.3 g, 5.95 mmol) was dissolved in a solution of MeOH (70 mL) and acetic acid (8 mL) along with $Pd(OH)_2$ catalyst (800 mg). The mixture was pressurized to 35 psi with hydrogen gas, and shaken for 3 h. The catalyst was removed by filtration through celite, and the effluent was concentrated under reduced pressure and chromatographed on silica gel eluting with 5% MeOH:CH_2Cl_2 increasing gradually to 10% MeOH:CH_2Cl_2:1% NH_4OH), which afforded 1.49 g (84%) of material as a light tan solid. ^{1}H NMR ($CDCl_3$) δ 8.35 (bs, 1H), 7.0–7.4 (m, 6H), 4.5 (d, 1H, J = 16.3 Hz), 3.7 (d, 1H, J = 16.4 Hz), 3.2–3.5 (m, 4H), 2.7–3.0 (m, 3H), 2.4–2.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.48, 146.45, 139.95, 138.79, 138.63, 138.49, 135.59, 133.82, 128.82, 128.47, 128.10, 126.46, 122.54, 49.58, 45.62, 32.80, 31.72, 31.18; MS(CI) *m*/*z* 263 (MH^+).

(*E*)-3-Bromo-8-chloro-6,11-dihydro-11-(1-methyl-3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (10c). LAH (470 mg, 11.9 mmol) was added to a solution of **4c** (3.4 g, 8.15 mmol) in THF (40 mL, anhydrous) at 0 °C. The solution was stirred at 0 °C for 5 h, then water (5 mL), 10% potassium sodium tartrate tetrahydrate (20 mL), 10% sodium hydroxide (5 mL), and CH_2Cl_2 (150 mL) were added sequentially. The crude product obtained from the organic layer was chromatographed on silica gel eluting with EtOAc:MeOH (98:2) yielding the product as a white solid (1.3 g, 40%): mp 140–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.62 (s, 1H), 7.16 (s, 1H), 7.14 (d, 1H), 7.05 (d, 1H), 3.50 (m, 3H), 3.0 (m, 1H), 2.75–2.80 (m, 3H), 2.26 (m, 2H), 2.23 (s, 3H, NCH3), 2.20 (m, 1H), 1.75 (m, 2H); MS(CI) *m*/*z* 403 (MH^+); Anal. ($C_{20}H_{20}BrClN_2$) C, H, N.

LAH reduction of **4b** by the above procedure afforded **10b**.

(*E*)-8-Chloro-6,11-dihydro-11-(1-methyl-3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (10b). White solid (45%): mp 125–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, 1H), 7.45 (d, 1H), 7.13 (s, 1H), 7.06–7.12 (d, 1H), 7.06 (d, 1H), 3.50 (m, 3H), 3.0 (m, 1H), 2.78–2.80 (m, 3H), 2.25 (m, 2H), 2.23 (s, 3H,

NCH3), 2.20 (m, 1H), 1.75 (m, 2H); MS(CI), *m/z* 325 (MH^+); Anal. ($C_{20}H_{21}N_2Cl$) C, H, N.

(*E*)-8-Chloro-6,11-dihydro-11-(1-benzyl-3-pyrrolylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (10a). To a two-necked flask containing LAH (27.7 mmol, 1.04 g) was added Et2O (75 mL) under a N_2 atmosphere. The solution was cooled to 0 °C, and a THF solution of **4a** (5.49 mmol, 2.20 g) was added via syringe. After the addition was complete a heterogeneous brick red solution resulted. TLC analysis after 2 h indicated all the starting material had been consumed, with no isomerization taking place. The reaction mixture was quenched with EtOAc and MeOH, followed by the addition of 1% NaOH. The aqueous portion was extracted 4×75 mL with EtOAc then with EtOAc:THF (4:1), and the combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a reddish foam. Chromatography on SiO_2 using (15% acetone:EtOAc increasing gradually to 5% MeOH:EtOAc) gave **10a** (1.08 g, 51%) as a tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.4 (d, 1H, $J = \sim 5$ Hz), 7.0–7.4 (m, 10H), 3.5–3.7 (m, 3H), 3.20–3.42 (m, 3H), 2.70–2.92 (m, 4H), 2.48–2.58 (m, 1H), 2.18–2.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.21, 146.37, 146.15, 144.01, 140.25, 138.89, 138.78, 137.79, 132.68, 132.58, 131.31, 130.14 128.72, 128.12, 126.81, 126.21, 121.81, 60.67, 59.06, 53.55, 32.21, 31.36, 31.18; MS (CI) *m/z* 387 (MH^+); Anal. ($C_{25}H_{23}N_2Cl$ (0.25 mol H_2O) C, H, N.

(*E*)-Ethyl-3-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (11c). Ethylchloroformate (0.5 mL, 5.2 mmol) and triethylamine (1.0 mL, 13.6 mmol) were added to a solution of **10c** in toluene (15 mL) at 0 °C then stirred at 70 °C for 3 h. The solvent was evaporated under reduced pressure, and the residual oil extracted with CH_2Cl_2 (50 mL) and washed with H_2O (20 mL). The crude product isolated from the organic extract was chromatographed on silica gel eluting with hexanes:ethylacetate, then crystallized from ether as white crystals (230 mg, 51%): mp 186–187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.60 (s, 1H), 7.11–7.18 (m, 3H), 4.25 (m, 1H), 4.05 (q, 2H), 3.75 (m, 1H), 3.35 (m, 3H), 2.80 (m, 2H), 2.45 (m, 2H), 1.75 (m, 1H), 1.7 (t, 3H), 1.05 (m, 2H); MS(CI) *m/z* 461(MH^+); Anal. ($C_{22}H_{22}BrClN_2O_2$) C, H, N.

Dealkylation of **10a** and **10b** by the above procedure afforded **11a** and **11b**.

(*E*)-Ethyl-3-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (11b). (foam 47%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, 1H), 7.60 (d, 1H), 7.11–7.16 (m, 4H), 4.25 (m, 1H), 4.0 (q, 2H), 3.75 (m, 1H), 3.35 (m, 3H), 2.80 (m, 2H), 2.45 (m, 2H), 1.75 (m, 1H), 1.7 (t, 3H), 1.0 (m, 2H); MS(CI), *m/z* 383 (MH^+).

(*E*)-Ethyl-3-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2*b*]pyridin-11-ylidene)-1-pyrrollidenecarboxylate (11a). (49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.4 (d, 1H, $J = 4.7$ Hz), 7.4 (d, 1H, $J = 6.8$ Hz), 7.1–7.3 (m, 4H), 4.2–4.3 (m, 1H), 4.05–4.15 (q, 2H, $J = 7.2$ Hz), 3.6–3.8 (m, 2H), 3.2–3.4 (m, 3H), 3.0–3.2 (m, 1H), 2.7–3.0 (m, 2H), 2.4–2.5 (m, 1H), 1.2 (t, 3H, $J = 7.2$ Hz). ^{13}C (75 MHz, $CDCl_3$) δ 156.08, 155.24, 146.77, 139.85, 138.09, 133.48, 133.17, 130.00, 128.73, 126.71, 122.55, 61.25, 50.38, 49.84, 45.86, 45.66, 32.20, 31.76, 31.16, 30.51, 15.03. MS(CI), *m/z* 369 (MH^+). Anal ($C_{21}H_{21}N_2O_2Cl$) C, H, N.

(*E*)-3-Bromo-8-chloro-6,11-dihydro-11-(3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin (12c). A solution of **11c** (170 mg, 0.36 mmol) in concn HCl (2 mL) was stirred at 80 °C overnight, then cooled to 0 °C, diluted with H_2O (10 mL), basified with 10% NaOH (10 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic layer was separated, washed with H_2O (20 mL), and the solvent was evaporated yielding a solid, which was recrystallized from CH_2Cl_2:Et_2O as white crystals (140 mg, 97%): mp 166–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.60 (s, 1H), 7.15(s, 1H), 7.11 (d, 1H), 7.05 (d,1H), 3.55 (d, 1H), 3.39 (d, 1H), 3.0 (m, 1H), 2.85 (m, 3H), 2.40 (m, 2H), 2.0 (m, 2H), 1.75 (m, 1H), 1.55 (m, 1H); MS(CI) *m/z* 389 (MH^+); Anal. ($C_{19}H_{18}BrClN_2 \cdot 0.25H_2O$) C, H, N.

This procedure was used to convert **11a** and **11b** to **12a**, **12b**.

(*E*)-8-Chloro-6,11-dihydro-11-(3-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (12b). (90%): mp 139–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, 1H), 7.45 (d, 1H), 7.10 (m, 4H), 3.55 (d, 1H), 3.39 (m, 3H), 3.0 (m, 1H), 2.85 (m, 3H), 2.41 (m, 2H), 1.75 (m, 1H), 1.55 (m, 1H); MS(CI) *m/z* 311 (MH^+); Anal. ($C_{19}H_{19}ClN_2$) C, H, N.

(*E*)-8-Chloro-6,11-dihydro-11-(3-pyrrolylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (12a). (76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.4 (d, 1H, $J = 4.7$ Hz), 7.4 (d, 1H, $J = 7.7$ Hz), 7.02–7.24 (m, 4H), 3.2–3.4 (m, 3H), 3.0–3.2 (m, 3H), 2.7–2.9 (m, 3H). MS (CI) *m/z* 297 (MH^+) HRMS calcd. (MH^+) for ($C_{18}H_{18}N_2Cl$) 297.1159, measured 297.1153.

(*Z*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-*N*-phenyl-1-piperidinecarboxamide (21). Triethylamine (0.2 mL, 2.72 mmol) was added to a solution of the amine **(9b)** (70 mg, 0.225 mmol) and phenylisocyanate (0.2 mL, 1.53 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction was stirred overnight at

20 °C. The reaction was quenched by addition of H_2O (15 mL), and the organic layer was separated, dried and chromatographed on silica gel eluting with 20% v/v EtOAc:Hexanes as a white foam, which crystallized from Ether (10 mL) as white crystals (75 mg, 78%): mp 184–185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) ° 10.05 (brs, 1H), 8.20 (d, 1H), 7.30 (dd, 2H), 7.0–7.4 (m, 8H), 4.75 (d, 1H), 4.50 (m, 1H), 3.50 (m, 1H), 3.30 (m, 2H), 2.90 (m, 2H), 2.80 (m, 1H), 2.60 (m, 1H), 2.05 (m, 1H), 1.75 (m, 2H); MS(CI) m/z 430 (MH^+); Anal. ($C_{26}H_{24}ClN_3O$) C, H, N.

(*Z*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarbothioc acid *S*-phenyl ester (22). Phenylchlorothiolformate (0.2 g, 1.13 mmol) was. added to a solution of **9b** (25 mg, 0.0806 mmol) and triethylamine (0.2 mL, 2.72 mmol) in pyridine (2 mL) at 0 °C. 4-Dimethylamino pyridine, DMAP (5 mg, 0.0416 mmol) was added and the solution stirred at 20 °C overnight. The solvent was evaporated, and the residue extracted with EtOAc (25 mL), washed with H_2O (20 mL) and and chromatographed on silica gel eluting with 5% v/v MeOH/EtOAc as a solid, which was triturated with hexanes yielding a white solid (30 mg, 83%): mp 187–188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, 1H), 7.48 (d, 1H), 7.37 (m, 2H), 7.16 (s,1H), 7.14 (d, 1H,), 4.52 (d, 1H), 3.95 (d, 1H), 3.45 (m, 3H), 3.10 (m, 1H), 2.85 (m, 2H), 2.55 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H); MS (CI) m/z 447 (MH^+); HRMS calcd (MH^+) for $C_{26}H_{24}ClN_2OS$ 447.1298, measured 447.1297; Anal. ($C_{26}H_{23}ClN_2OS{\cdot}2H_20$) C, H, N.

(*Z*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(4-pyridinyl)acetyl]-piperidine (17). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide, EDCI (50 mg, 0.26 mmol) and 1-hydroxybenztriazole, HOBT (40 mg, 0.296 mmol) were added sequentially to a solution of **9b** (50 mg, 0.161 mmol) and 4-pyridylacetic acid (30 mg, 0.22 mmol) in DMF (5 mL) and *N*-methylmorpholine, NMM (0.5 mL) at 0 °C, then stirred overnight at 20 °C. The solvent was evaporated under reduced pressure, and the residual oil extracted with EtOAc (50 mL), washed with H_2O (25 mL), dried and chromatographed on silica gel eluting with 5% v/v MeOH:EtOAc containing 2% v/v NH_4OH, yielding the product as a white solid (foam, 52 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, 1H), 8.43 (dd, 2H), 7.48 (d, 1H), 7.09–7.20 (m, 4H), 6.83 (dd,), 4.35 (d, 1H), 4.20 (m, 1H), 4.05 (d, 1H), 3.65 (m, 1H), 3.45 (d, 1H), 3.35 (d, 1H), 3.25 (m, 2H), 2.80 (m, 2H), 2.40 (m, 2H), 1.77 (m, 1H), 1.55 (m, 1H); MS(CI) m/z 430 (MH^+); Anal. ($C_{26}H_{24}N_3ClO{\cdot}H_2O$) C, H, N.

(*E*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(4-pyridinyl)acetyl]-piperidine (48). The procedure as described for **17** was used to acylate **12b**, to obtain **48** as a white solid (foam, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, 1H), 8.43 (dd, 2H), 7.48 (d, 1H), 7.09–7.23 (m, 4H), 7.06 (d, 1H), 6.72 (d, 1H), 4.50 (m, 1H), 4.35 (d, 1H), 3.65 (d, 1H), 3.60 (d, 1H), 3.35 (d, 1H), 3.25 (m, 2H), 3.15 (d, 1H), 2.85 (m, 2H), 2.45-2.60 (m, 2H), 1.75 (m, 1H), 1.65 (m, 1H); MS(CI) m/z 430 (MH^+); Anal. ($C_{26}H_{24}N_3ClO{\cdot}1.25$ H_2O) C, H, N.

Compounds **15–20**, **45–50**, **63–65**. The acylation procedure described for **17** was used to prepare these *N*-acyl compounds.

Compound **41**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, 1H, $J = \sim 3$ Hz), 7.81 (apparent d, 2H, $J = 7.4$ Hz), 7.50–7.64 (m, 3H), 7.41 (d, 1H, $J = 6.7$ Hz), 7.08–7.20 (m, 4H), 4.27 (d, 2H, $J = 15.4$ Hz), 3.84 (d, 1H, $J = 15.4$ Hz), 3.10–3.40 (m, 4H), 2.60–2.94 (m, 3H), 2.25–2.38 (m, 1H). HRMS calcd (MH^+) for ($C_{24}H_{21}N_2O_2ClS$) 437.1087, measured 437.1091.

Compound **42**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, 1H, $J = 4.7$ Hz), 7.81 (apparent d, 2H, $J \sim 7$ Hz), 7.50–7.64 (m 3H), 7.41 (d, 1H, $J = 7.6$ Hz), 7.08–7.21 (m, 5H), 4.28 (d, 1H, $J = 15.2$ Hz), 3.86 (dd, 1H, $J = 1.6$, 15.2 Hz), 3.2–3.4 (m, 4H), 2.60–2.95 (m, 3H), 2.25–2.40 (m, 1H). HRMS calcd (MH^+) for ($C_{24}H_{22}N_2O_2S$) 403.1480, measured 403.1480.

Compound **43**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.4 (d, 1H, $J = 4.7$), 7.56–7.64 (m, 2H), 7.42 (d, 1H, $J = 7.3$ Hz), 7.10–7.20 (m, 5H), 4.34 (d, 1H, $J = 15.6$ Hz), 3.85 (d, 1H, $J = 15.5$ Hz), 3.36 (apparent t, 2H, $J = 7.1$ and 7.4 Hz), 3.16–3.26 (m, 2H), 2.80–2.94 (m, 1H), 2.64–2.78 (m, 2H), 2.30–2.42 (m, 1H); HRMS calcd. (MH^+) for ($C_{22}H_{19}N_2O_2ClS_2$) 443.0655, measured 443.0649.

Compound **44**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, 1H, $J = \sim 3$ Hz), 7.56–7.62 (m, 2H), 7.4 (d, 1H, $J = 7.0$ Hz), 7.01–7.21 (m, 6H), 4.36 (d, 1H, $J = 15.4$ Hz), 3.85 (d, 1H, $J = 15.4$ Hz), 3.36 (apparent t, 2H, $J = 6.8$ and 7.7 Hz), 3.15–3.30 (m, 2H), 2.80–2.94 (m, 1H), 2.60–2.80 (m, 2H), 2.30–2.42 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_=$) δ 155.16, 146.40, 139.32, 138.26, 138.14, 137.94, 135.83, 135.08, 133.20, 132.42, 131.85, 128.45, 128.22, 127.81, 127.52, 126.17, 122.34, 52.05, 47.51, 32.38, 31.37, 30.67. HRMS calcd. (MH^+) for ($C_{22}H_{20}N_2OS$) 448.1259, measured 448.1250.

Compound **45**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36–8.44 (m, 3H), 7.43 (dd, 1H, $J = 1.6$, 7.8 Hz), 7.05–7.35 (m, 6H), 4.91 (d, 1H, rotomer A, $J = 15.9$ Hz), 4.67 (d, 1H, rotomer B, $J = 17.9$ Hz), 3.88–4.08 (m, 1H), 3.48–3.82 (m, 5H), 3.2–3.4 (m, 2H), 2.72–3.02 (m, 2H), 2.40–2.62 (m, 1H); HRMS calcd (MH^+) for ($C_{25}H_{22}N_3OClS$) 448.1250, measured 448.1248.

Compound **46**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48–8.58 (m, 2H), 8.39–8.46 (m, 1H), 7.44 (dd, 1H, J = 1.2, 7.5 Hz), 7.08–7.26 (m, 6H), 4.81 (d, 1H, rotomer A, J = 15.9 Hz), 4.66 (d, 1H, rotomer B, J = 17.9 Hz), 4.0 (d, 1H, J = 17.1 Hz), 3.9 (d, 1H, J = 15 Hz), 3.54–3.76 (m, 2H), 3.18–3.44 (m, 3H), 2.7–3.0 (m, 3H), 2.38–2.58 (m, 1H); Anal. ($C_{25}H_{22}N_3OCl$) C, H, N.

Compound **61**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.80 (m, 2H), 7.40–7.66 (m, 4H), 7.04–7.22 (m, 4H), 3.9 (d, 1H, J = 14.6 Hz), 3.7 (d, 1H, J = 14.8 Hz), 3.3–3.4 (m, 2H), 3.04–3.24 (m, 3H), 2.66–2.90 (m, 2H), 2.30–2.41 (m, 1H); HRMS calcd (MH^+) for ($C_{24}H_{21}N_2O_2ClS$) 437.1092, measured 437.1091.

Compound **63**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30–8.42 (m, 3H), 7.30–7.50 (m, 1H), 7.02–7.25 (m, 6H), 4.89 (d, 1H, rotomer A, J = 16 Hz), 4.66 (d, 1H, rotomer B, J = 18 Hz), 3.6-6–4.04 (m, 4H), 3.10–3.36 (m, 3H), 2.70–3.00 (m, 3H), 2.40–2.56 (m, 1H); HRMS calcd (MH^+) for ($C_{25}H_{22}N_3OClS$) 448.1255, measured 448.1250.

Compound **62**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.4 (bs, 1H), 7.45–7.65 (m, 3H), 7.10–7.30 (m, 5H), 3.99 (d, 1H, J = 15.1 Hz), 3.75 (d, 1H, J = 15 Hz), 3.38–3.46 (m, 2H), 3.15–3.30 (m, 3H), 2.70–2.90 (m, 2H), 2.33–2.44 (m, 1H); HRMS calcd (MH^+) for ($C_{22}H_{219}N_2O_2ClS_2$) 443.0654, measured 443.0655.

Compound **64**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.5 (bs, 2H), 4.4 (d, 1H, J = 4.6 Hz), 7.4 (d, 1H, J = 7.3 Hz), 7.10–7.26 (m, 7H), 7.30–7.44 (m, 1H), 3.70–3.88 (m, 2H), 3.06–3.58 (m, 6H), 2.70–3.00 (m, 2H), 2.44–2.62 (m, 1H); HRMS calcd (MH^+) for ($C_{25}H_{22}N_3OCl$) 416.1550, measured 416.1530.

Compound **65**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.4 (d, 1H, J = 3.0 Hz), 7.12–7.60 (m, 7H), 6.7 (bs, 1H), 4.85–4.52 (m, 1H), 3.80–4.20 (m, 2H), 3.20–3.70 (m, 4H), 2.70–3.00 (m, 2H), 2.45–2.65 (m, 1H); HRMS calcd (MH^+) for ($C_{23}H_{19}N_2O_2Cl$) 391.1218, measured 391.1213.

(*E*)-8-Chloro-6,11-dihydro-11-[1-[(4-nitrophenyl)thio]-3-piperidinylidene]-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (51). 4-Nitrobenzenesulfenyl chloride (130 mg, 0.65 mmol) was added to a solution of **12b** (100 mg, 0.322 mmol) in methylene chloride (3 mL) at 20 °C. Triethylamine (0.3 mL) was added and the solution stirred overnight. Water (20 mL) was added and the reaction was extracted with methylene chloride (25 mL). The organic layer was separated, dried and chromatographed on silica gel eluting with 20% v/v EtOAc:hexanes yielding an oil, which crystallized from methanol as yellow crystals (100 mg, 66%): mp 173–174 °C; MS(CI) m/z 464 (MH^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, 1H), 8.10 (d, 2H), 7.65 (d, 1H), 7.28–7.31 (m, 4H), 7.07 (s, 2H), 3.77 (q, 2H), 3.55 (m, 2H), 3.25 (m, 1H), 3.15 (m, 1H), 2.91 (m, 2H), 2.45 (m, 2H), 1.82 (m, 2H); Anal. ($C_{25}H_{22}ClN_3O_2S$) C, H, N.

(*E*)-3-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(5-chloro-2-thienyl)sulfonyl]-piperidine (60). Method A. 5-Chloro thiophene-2-sulfonyl chloride (0.2 g, 0.921 mmol) was added to a solution of **12c** (80 mg, 0.204 mmol) in pyridine (2 mL) at 0 °C. DMAP (3 mg, 0.0245 mmol) was added, and the solution was stirred at 20 °C overnight. The solvent was evaporated under reduced pressure, and the residue extracted with methylene chloride (40 mL), and the crude product was chromatographed on silica gel eluting with 20% EtOAc:hexanes as a solid which recrystallized from ether (15 mL) as white crystals (70 mg, 59.8%): mp 171–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.60 (s, 1H), 7.20 (s, 1H), 7.16 (m, 2H), 7.08 (d, 1H), 6.91 (d, 1H), 3.79 (d, 1H), 3.63 (d, 1H), 3.2–3.5 (m, 3H), 3.05 (m, 1H), 2.85 (m, 2H), 2.35 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H); MS (CI) m/z (569 (MH^+); Anal. ($C_{23}H_{19}BrCl_2N_2O_2S_2$) C, H, N, S.

(*Z*)-3-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(5-chloro-2-thienyl)sulfonyl]-piperidine (38). Prepared from **9c** by following Method A described for **60**. Obtained **38** as white crystals (65.4%): mp 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.64 (s, 1H), 7.20 (s, 1H), 7.16 (m, 2H), 7.08 (d, 1H), 6.93 (d, 1H), 4.25 (d, 1H), 3.75 (d, 1H), 3.51 (d, 1H), 3.37 (m, 2H), 2.79 (m, 3H), 2.48 (m, 1H), 2.10 (m, 1H), 1.85 (m, 1H), 1.65 (m, 1H); MS(CI) m/z 569 (MH^+); Anal. ($C_{23}H_{19}BrCl_2N_2O_2S_2$) C, H, N. The above Method A was used to prepare sulfonamides **23–35**, **37–44**, **52–58**, and **60–62**.

(*Z*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(3-pyridinesulfonyl)-piperidine (36) and (Z)-3-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(4-nitrophenyl)sulfonyl]-piperidine (27). Method B. 4-Nitrobenzenesulfonyl-chloride (100 mg, 0.406 mmol) was added to a solution of 3-pyridinesulfonic acid(100 mg, 0.626 mmol) in pyridine (3 mL) at 0 °C. DMAP (5 mg) was added and the mixture stirred at 0 °C for 7 h. (*Z*)-8-Chloro-6,11-dihydro-11-(3-[piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine **(9b)** (80 mg) was added and the mixture stirred 1 h at 0 °C, then overnight at 20 °C. Water (25 mL) and CH_2Cl_2 (50 mL) were added and the organic layer separated, washed with water (10 mL), dried, and chromatographed on silica gel eluting with 20% v/v EtOAc:Hexanes to afford the less polar product **27**, which was recrystallized from methanol as white crystals (37 mg, 15%): mp 178–179 °C; MS(CI) m/z 496 (MH^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d,

1H), 8.32 (d, 2H), 7.88 (d, 2H), 7.48 (d, 1H), 7.15–7.19 (m, 3H), 7.02 (d, 1H), 4.31 d, 1H), 3.75 (d, 1H), 3.50 (d, 1H), 3.34 (m, 2H), 2.78 (m, 3H), 2.50 (m, 1H), 2.10 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H); Anal. ($C_{25}H_{22}ClN_3O_4S$) C, H, N. Compound **36** was eluted with 5% v/v MeOH:EtOAc containing 1% NH_4OH yielding a solid that was crystallized from ether as white crystals (180 mg, 68.9%): mp 158–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.80 (d, 1H), 8.48 (d, 1H), 7.95 (d, 1H), 7.5 (m, 2H), 7.19 (m, 3H), 7.04 (d, 1H), 4.38 (d, 1H), 3.80 (d, 1H), 3.45 (m, 3H), 2.85 (m, 3H), 2.50 (m, 1H), 2.05 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H); MS(CI) *m*/*z* 452 (MH^+) Anal. ($C_{24}H_{22}ClN_3O_2S$) C, H, N.

(*E*)-3-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(3-pyridinesulfonyl)-piperidine (59) and (*E*)-3-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[(4-nitrophenyl)sulfonyl]-piperidine (55). Prepared from **12b** by using Method B described for **36**. The less polar sulfonamide **55** was obtained as white crystals from methanol (25%): mp 232–233 °C; ^{1}H NMR δ 8.39 (d, 1H), 8.31 (d, 2H), 7.88 (d, 2H), 7.43 (d, 1H), 7.09–7.15 (m, 3H), 7.06 (d, 1H), 3.84 (d, 1H), 3.58 (d, 1H), 3.55 (m, 1H), 3.25 (m, 2H), 3.10,(m, 1H), 2.80 (m, 2H), 2.35 (m, 2H), 1.85 (m, 1H), 1.65 (m, 1H); MS(CI) *m*/*z* 496 (MH^+); Anal ($C_{25}H_{22}ClN_3O_4S$) C, H, N. The major product **59** was obtained as white crystals (67%): mp 214–215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (s, 1H). 8.80 (d, 1H). 8.48 (d, 1H). 7.95 (d, 1H). 7.45 (m, 2H), 7.15 (m, 3H), 7.08 (d, 1H), 3.85 (d, 1H), 3.55 (d, 1H), 3.50 (m, 1H), 3.65 (m, 2H), 3.05 (m, 1H), 2.75 (m, 2H), 2.33 (m, 2H), 1.85 (m, 1H), 1.75 (m, 1H); MS(CI) *m*/*z* 452 (MH^+); Anal ($C_{24}H_{22}ClN_3O_2S$) C, H, N.

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16. The terms 4-piperidino, 3-piperidino and 3-pyrrolidino are used for convenience to denote the carbon of the pendant piperidine or pyrrolidine ring that forms the olefinic bond at C-11 of the benzocycloheptapyridine tricycle.

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19. (a) The olefinic geometries were established by NMR studies wherein an NOE effect in the *Z*-isomers **3b** was observed between the C-10 proton and the allylic protons on the lactam ring. (b) X-Ray crystallographic data on **6b** and **56** is available from the authors. (c) The mixed sulfonic anhydride **14** obtained by reacting 3-pyridinesulfonic acid with *p*-nitrobenzenesulfonyl chloride (Scheme 2) was used to preparare the 3-pyridylsulfonamides **36** and **59**.

20. The chemical shifts of the allylamino protons in the sulfonamido derivatives of *Z*-compounds **II** are deshielded by 0.2–0.3 ppm relative to the corresponding derivatives of the *E*-compounds **III**.

21. FPT and GGPT assays were performed over a wide range of inhibitor concentrations in half-log increments. Each data point was typically generated by duplicate determinations and the mean value was used to calculate percent inhibition relative to a vehicle (DMSO) control. Duplicates were within $\pm 5\%$ of the mean value.