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Discovery of Novel Nonpeptide Tricyclic Inhibitors of Ras Farnesyl Protein Transferase

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Abstract—A comprehensive structure–activity relationship (SAR) study of novel tricyclic amides has been undertaken. The discovery of compounds that are potent FPT inhibitors in the nanomolar range has been achieved. These compounds are nonpeptidic and do not contain sulfhydryl groups. They selectively inhibit farnesyl protein transferase (FPT) and not geranylgeranyl protein transferase-1 (GGPT-1). They also inhibit H-Ras processing in Cos monkey kidney cells. Copyright © 1997 Elsevier Science Ltd

Introduction

Ras oncogenes and their protein products have been the subject of intense study in recent years.[1a–c] This interest has arisen from the fact that mutated ras oncogenes are present in 20% of all human tumors, including 50% of colon carcinomas and more than 95% of pancreatic carcinomas.[2a,b] Ras is a relatively small guanine nucleotide binding protein (MW=21 KDa) that plays a vital role in signal transduction from the cell surface to the nucleus. Ras proteins exist in two states: a GTP-bound active state and a GDP-bound inactive state. Normal Ras possesses GTPase activity, which leads to the hydrolysis of bound GTP to GDP, resulting in termination of the mitogenic signal. However, mutant forms of Ras have impaired GTPase activity; therefore, mutant Ras proteins remain locked in the active GTP-bound form, leading to unregulated cell proliferation.[3a–d]

Membrane association is important for the oncogenic transformation caused by activated Ras proteins. This is achieved by post-translational modification of the Ras protein by farnesylation of the cysteine residue found in the carboxyl terminal tetrapeptide CaaX motif (where a=aliphatic amino acids, X=Met or Ser). This step is catalyzed by farnesyl protein transferase (FPT), an α,β-heterodimer, zinc metalloenzyme. FPT utilizes farnesyl pyrophosphate as a farnesyl donor.[4a–c]

A closely related prenyltransferase, geranylgeranyl transferase-1 (GGPT-1), catalyzes the geranylgeranylation of proteins ending in CaaX, where X=Leu or Ile.[5,6a,b] Since the number of geranylgeranylated proteins in the cell exceeds[7,8] those of farnesylated proteins, it is desirable to develop a selective FPT inhibitor as a potential anti-Ras agent.

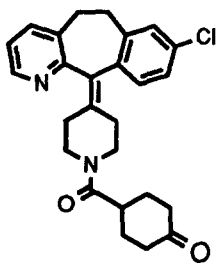
The realization that inhibitors of Ras farnesylation may have therapeutic potential as anti-cancer agents has prompted a great number of researchers to direct their efforts in this area[9,10] and, consequently, a number of very potent FPT inhibitors have been developed. However, most of these compounds are either peptidic in nature or contain a sulfhydryl group.

Recently, we reported the discovery of **SCH 44342** (entry **6f**) as a novel nonsulfhydryl, nonpeptidic FPT inhibitor that demonstrates great selectivity against GGPT-1.[11] **SCH 44342** was also shown to kinetically compete with the ras protein, but not with farnesyl pyrophosphate in binding to FPT.[11] We now present the data that led to the discovery of a more potent compound in this series.

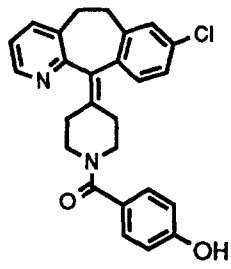
Evaluation of a number of Schering file compounds revealed that the 4-cyclohexanone carboxamide, **SCH 47307**, 4-phenoxy carboxamide, **SCH 44984**, and the sulfonamide, **SCH 37103**, were active FPT inhibitors in the micromolar range (Fig. 1). Based on the results, we evaluated and assayed additional compounds in the tricyclic series and initiated an effort to design and synthesize novel analogues in order to further understand the structure–activity relationship. These efforts resulted in the discovery of **SCH 56580**, a nonpeptide nonsulfhydryl tricyclic analogue that inhibited FPT in the low nanomolar range. In this paper we will report the evaluation of analogues of **SCH 44984**. Work on sulfonamide derivatives of **SCH 37103** will be reported separately.

Chemistry

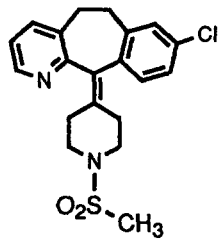
Compounds shown in Tables 1–7 of this paper were synthesized as outlined in Scheme 1; thus, amine **1**, a



SCH 47307
FPT IC_{50} = 1.7 μM



SCH 44984
FPT IC_{50} = 2.3 μM



SCH 37103
FPT IC_{50} = 1.9 μM

Figure 1.

hydrolysis product of Loratadine,[12] was coupled to a variety of aliphatic and aromatic carboxylic acids using standard carbodiimide procedures to give the target compounds. In some cases, the target compounds were formed from the reaction of acid chlorides with amine **1** in the presence of a base.

Compounds **5f–h** were prepared as outlined in Scheme 2; thus reacting the hydroxymethyl compound **5e** with acetyl chloride gave **5f**. Treatment of **5e** with methanesulfonyl chloride in the presence of a base gave compound **5g**. Displacement of the tricyclic mesylate **5g** with sodium thioacetate afforded compound **5h** in 51% yield.

Benzoyl sulfinyl analogue **1j** was prepared by oxidation of **1i** with 1 equiv of *m*-chloroperbenzoic acid (MCPBA) at 0 °C. The corresponding sulfone **1k** was similarly prepared by treatment of **1i** with 2.2 equiv of MCPBA at room temperature.

Tricyclic amides **1a,b,h,q**, **4a–c**, **6b–h** had been prepared previously.[13a–d]

Results and Discussion

Compounds prepared in this study were tested for their ability to inhibit the transfer of tritiated farnesyl group from farnesyl pyrophospate to Ras-CVLS a process that is mediated by FPT using conditions previously described.[11]

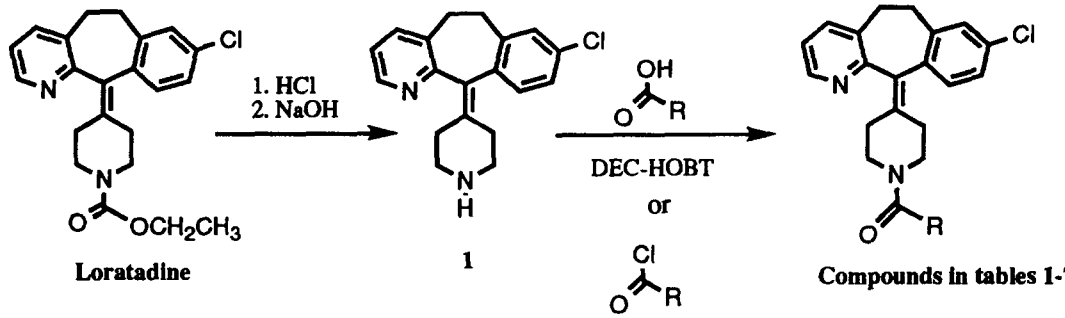
(a) Tricyclic aryl amide derivatives of SCH 44984

As shown in Table 1, various substitutions on the aromatic ring were explored. The unsubstituted phenyl amide, compound **1a**, had an FPT IC_{50} of 5.3 μM. Introduction of various functional groups at the *para*-position (entries **1b–m**) gave compounds that had FPT activity in the 2–9 μM range; both electron-withdrawing as well as electron-donating groups gave similar activities.

Reduction in FPT activity was observed with the 3,4,5-trimethoxy substituted compound **1q**, which was an order of magnitude less active than the lead compound, **SCH 44984**. It is possible that introduction of the three methoxy groups on the phenyl ring could have rendered compound **1q** too bulky to fit well in the enzyme pocket, thus resulting in decreased FPT activity.

(b) Effect of chain length

The effect of a spacer between the amide carbonyl group and the phenyl ring was next studied. As shown in Table 2, introducing a single methylene spacer gave rise to compound **2a** with significantly increased potency over compound **1a** (0.8 versus 5.3 μM). Introduction of two methylene spacers gave rise to compound **2b**, which was twice as active as compound **1a**, but less active than the single methylene spacer, compound **2a**. Further increasing the length of the spacer by three methylene groups provided compound **2c** with FPT activity of 4.3 μM, which was twofold less potent than the two methylene spacer analogue but



Scheme 1.

was still more active than compound **1a**. From this study it was established that the optimum chain length in the tricyclic aryl amide series was one methylene spacer. This SAR was subsequently found to be true with other amide substitutions that we investigated.

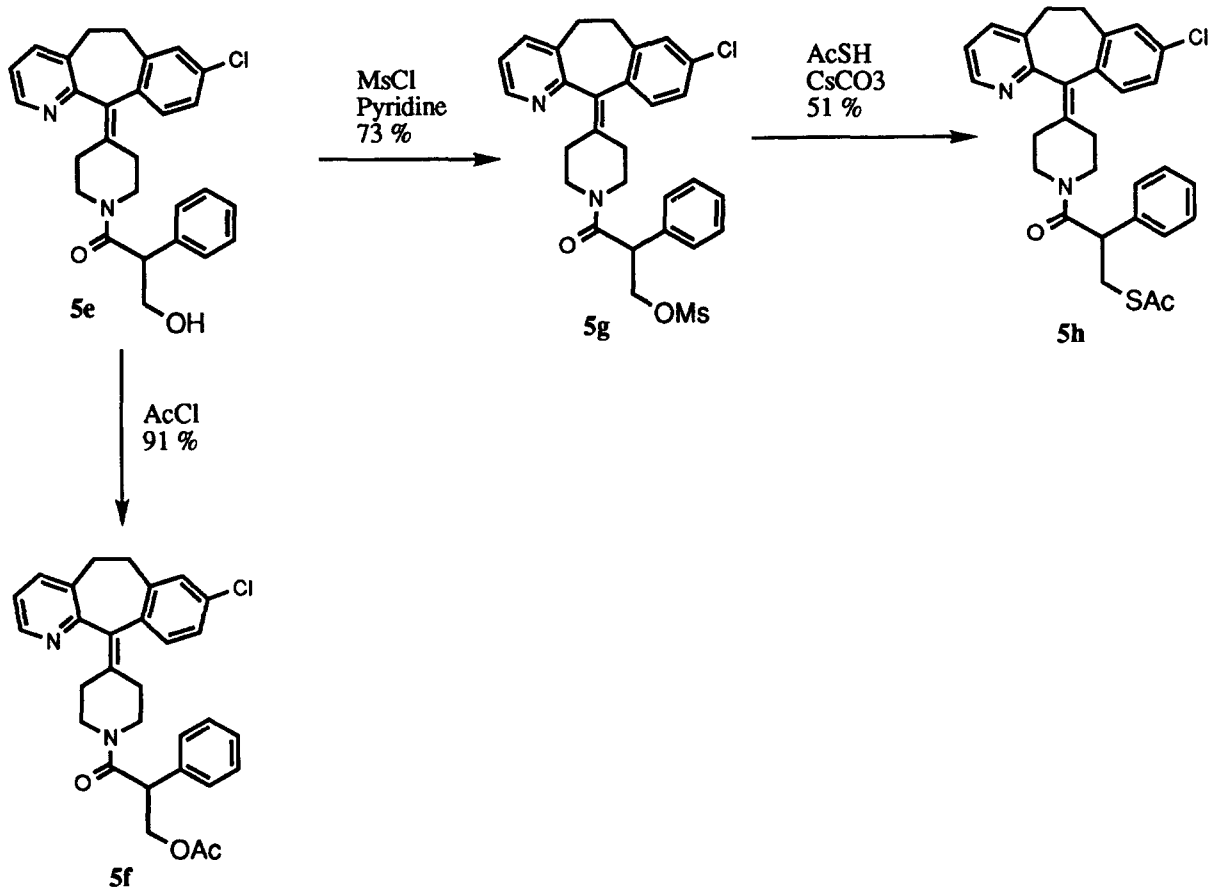
(c) Tricyclic phenylacetamide derivatives

The discovery that one methylene spacer was the optimum chain length for our tricyclic FPT inhibitors prompted us to make a number of tricyclic phenyl acetamides; these results are summarized in Table 3. As indicated earlier, the unsubstituted compound **2a** had an FPT activity of 0.8 μM. Introduction of a hydrophobic group such as a methyl at the *para*-position, compound **3b**, slightly reduced FPT activity to 1.2 μM. Similarly, incorporation of groups such as a methoxy, compound **3c** or a dimethylamino group, compound **3d**, also resulted in reduction of FPT activity. Halogens at the *para*-position had mixed effects; while the fluoro compound **3e** resulted in the loss of activity compared with the unsubstituted analogue **2a**, the 4-bromo, compound **3f**, was more active (IC_{50} 0.6 μM). Compounds with a hydroxyl group either at the 4-position (entry **3a**) or at the 3-position (entry **3g**) or at both of these positions (entry **3j**) were substantially less active than **2a**. The 3-nitro compound **3i** was slightly less active than **2a**. Having a methyl group at the 3-position, compound **3h**, decreased the FPT activity compared with its 4-methyl substituted counterpart compound **3b**.

(d) Alkyl amide analogues

The realization that a phenyl ring with one methylene spacer α to the amide carbonyl group gave enhanced FPT activity (entry **2a**) prompted us to investigate the effect of various straight chains as well as cyclic aliphatic moieties at this position. Results of this study are summarized in Table 4. The simple acetamide compound, entry **4a**, was a poor FPT inhibitor (26.9 μM). However, a compound with an extra carbon, the ethyl tricyclic amide **4b**, was substantially more active than **4a** (8.4 μM). Further lengthening the alkyl chain by two methylene groups did not have significant effect, as shown by compound **4c** (9.7 μM); an effect similar to that was observed in the aryl amide case (see part b).

Cyclopentyl group with a methylene spacer gave compound **4d** with an FPT activity of 2.1 μM; this was four times better than its straight chain counterpart, compound **4b** (2.1 versus 8.4 μM). The corresponding cyclohexyl analogue, compound **4e**, was slightly less active than the cyclopentyl analogue, compound **4d**. With increased bulk as in compound **4f** complete loss of FPT activity was observed.



Scheme 2.

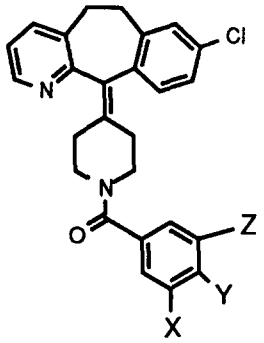
(e) α-Substituted analogues

To understand the nature of groups that could be accommodated in the spacer, we investigated a number of substituents at the α-position of our tricyclic amides. It was also thought that appropriate groups in the α-position could block potential metabolism. The FPT activity for compounds prepared in this study are summarized in Table 5.

Monosubstitution of the α-position with an ethyl group, compound **5a**, resulted in reduction of FPT activity compared with the unsubstituted compound **2a**. Substitution with a bulky isobutyl group, entry **5b**, resulted in an order of magnitude less activity than compound **2a.** Substitution with a cyclopentyl group, compound **5c**, also reduced FPT activity by 50%. This may indicate that the enzyme pocket is not large enough to accommodate bulky carbocyclic moieties. Interestingly, a phenyl group was easily accommodated as evident from the very good activity of compound **5d**.

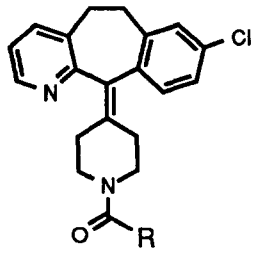
The effect of polar hetero atom substitution was also studied. For example, introduction of a hydroxymethyl

Table 1. Tricyclic benzamide FPT inhibitors



Entry no.	X	Y	Z	EPT (IC_{50}) μM
1a	H	H	H	5.3
1b	H	OH	H	2.3
1c	H	NH_2	H	4.4
1d	H	COOH	H	5.3
1e	H	$HNSO_2CH_3$	H	3.9
1f	H	$HNSO_2CF_3$	H	8.5
1g	H	SO_2NHCH_3	H	3.9
1h	H	$N(CH_3)_2$	H	4.8
1i	H	SCH_3	H	6.9
1j	H	$SOCH_3$	H	4.0
1k	H	SO_2CH_3	H	3.9
1l	H	SO_2NH_2	H	3.4
1m	H	NO_2	H	4.3
1n	H	OH	OH	2.3
1o	NO_2	OH	NO_2	8.3
1p	OCH_3	OH	OCH_3	6.2
1q	OCH_3	OCH_3	OCH_3	26.9

Table 2. Variation of chain length of FPT inhibitors



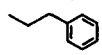
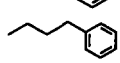
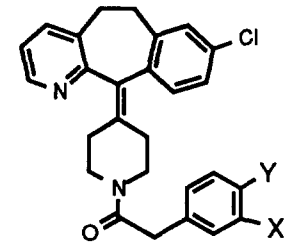
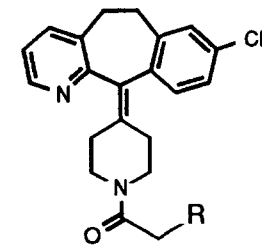
Entry no.	R	FPT (IC_{50}) μM
1a		5.3
2a		0.8
2b		2.7
2c		4.3

Table 3. Tricyclic phenylacetamide FPT inhibitors



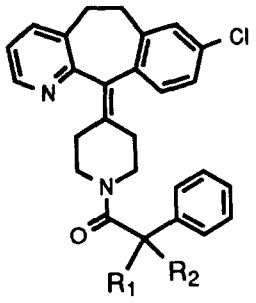
Entry no.	X	Y	FPT (IC_{50}) μM
2a	H	H	0.8
3a	H	OH	3.0
3b	H	CH_3	1.2
3c	H	OCH_3	1.4
3d	H	$N(CH_3)_2$	2.7
3e	H	F	1.5
3f	H	Br	0.6
3g	OH	H	3.7
3h	CH_3	H	2.9
3i	NO_2	H	1.2
3j	OH	OH	2.7

Table 4. Tricyclic alkyl amide FPT ihibitors



Entry no.	R	FPT (IC_{50}) μM
4a	H	26.9
4b	Methyl	8.4
4c	Ethyl	9.7
4d	Cyclopentyl	2.1
4e	Cyclohexyl	3.3
4f	Adamantyl	Inactive

Table 5. α-Substituted tricyclic phenylacetamide FPT inhibitors



Entry no.	R_1	R_2	FPT (IC_{50}) μM
2a	H	H	0.8
5a	Ethyl	H	1.3
5b	*iso*-Butyl	H	5.6
5c	Cyclopentyl	H	1.9
5d	Phenyl	H	0.6
5e	CH_2OH	H	6.1
5f	CH_2OAc	H	0.9
5g	CH_2OMs	H	0.6
5h	CH_2SAc	H	0.3
5i	Me	Me	1.4
5j	OCH_3	CF_3	0.7 (*S*-isomer)
5k	OCH_3	CF_3	2.6 (*R*-isomer)

group gave compound **5e** which had an FPT activity of 6.1 μM (an order of magnitude less active than the unsubstituted compound). However, the acetate, compound **5f**, was a very good inhibitor of FPT (0.9 μM). Similarly, the mesylate **5g**, and the thioacetate **5h**, were found to be the most potent FPT inhibitors in this series with FPT inhibitory values of 0.6 and 0.3 μM, respectively.

Disubstitution of the α-position was also investigated. Introduction of a *gem*-dimethyl group at that position gave compound **5i** that was an order of magnitude less active than **2a**. Compounds **5j** and **5k**, derived from Mosher's acid, had interesting activity; for example, the *S* isomer of Mosher's acid, compound **5j**, had FPT activity of 0.7 μM, whereas, compound **5k** derived from the *R* isomer of Mosher's acid had much lower FPT activity (2.6 μM). This difference in the activity of compounds derived from the enantiomeric Mosher's acids may indicate that absolute stereochemistry at the α-position might be important in the way these molecules bind to the enzyme.

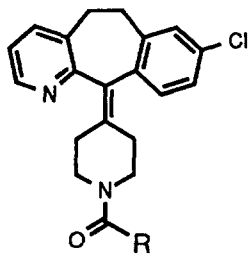
(f) Phenyl versus pyridyl substituents

We further investigated the effect of substituting the phenyl ring with a hetero aromatic moiety such as pyridine. Results of this study are summarized in Table 6. In the case of nonmethylene spacer compounds, i.e. the benzamides and pyridylamides, the 4-pyridine analogue compound **6b** was slightly less active than the phenyl analogue, compound **1a**. However, the 3-pyridyl amide **6c** was less active than the phenyl amide **1a** (6.3 μM) and was also less active than the 4-pyridyl compounds. The 2-pyridyl analogue was substantially less active than the phenyl analogue **1a**. A different pattern was observed in the case of the aryl acetamide tricyclics **2a** and **6f–h**. Phenyl acetamide tricyclic compound **1a** was four times less active than the 4-pyridyl acetamide **6f** which exhibited an FPT activity of 0.25 μM. The 3-pyridyl acetamide **6g** was twice as active as phenyl acetamide **2a**. As expected, the 2-pyridyl compound **6h** was less active than the phenyl compound **2a** and also less active than the 3- and 4-pyridyl counterparts. From this study it was generally observed that the order of activity of the pyridyl compounds either in the nonmethylene case or in the single methylene case was as follows: 4-pyridyl > 3-pyridyl > 2-pyridyl. This observation was very important to us since it allowed us to make the decision that future targets would contain 4-pyridyl acetyl moiety.

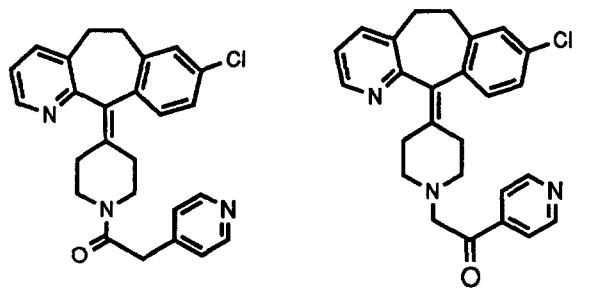
(g) Position of piperidine amide bond

In another study we explored the significance of the position of the amide bond and its relation to FPT activity. Compound **8**, was prepared from the reaction of amine **1** with 4-(2-bromoacetyl)pyridine (Fig. 2). Compound **8** which had a carbonyl moiety transposed one carbon away from the amino group was found to be an order of magnitude less active than compound **6f**. This result indicated that the presence of an amido group on the piperidine ring was important for FPT activity. It is possible that either the amide bond is involved in some form of hydrogen bonding with the enzyme or that a nonbasic nitrogen was required for enhanced FPT potency.

Table 6. Comparison of phenyl versus pyridyl substitution of FPT inhibitors



Entry no.	R	FPT (IC_{50}) μM
1a		5.3
6b		4.7
6c		6.3
6d		8.0
2a		0.8
6f		0.25
6g		0.47
6h		2.0



Compound **6f**
FPT IC_{50} = 0.25 μM

Compound **8**
FPT IC_{50} = 15.8 μM

Figure 2.

(h) Substituents on the tricyclic ring system

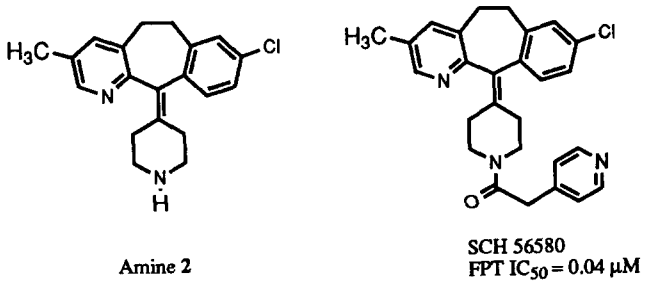
Having explored the SAR of the piperidine substitution of the tricyclic ring, we then turned our attention to modifications of the tricyclic ring system itself. From a detailed study we have identified a compound with a methyl group at position 3 of the tricyclic ring, **SCH 56580**, with an IC_{50} of 40 nM that is inactive toward GGPT (Fig. 3). This is a very significant enhancement in enzyme potency compared with the rest of the compounds described in this paper. **SCH 56580** was prepared from amine **2**[13a,14] using the same coupling method reported in Scheme 1.

(i) Inhibition of FPT versus GGPT

Since GGPT is an enzyme closely related to FPT, and since geranylgeranylation is a more common modification than farnesylation,[7,8] it is critical to have a compound with selectivity towards inhibiting FPT. A panel of tricyclic compounds were selected and evaluated for both FPT and GGPT activities.[11] These results are summarized in Table 7. It is evident that in all cases evaluated our FPT inhibitors were poor inhibitors of GGPT.

(j) Cos cell inhibition

Compounds with good FPT activity were evaluated for their ability to inhibit the processing of ras in intact cells.[11] Results of these studies are also summarized in Table 7. Unlike the peptidomimetics reported in the literature that are very potent FPT inhibitors but have IC_{50}s in cell-based assays that are 200–2000 times higher[11,15–17] (except a compound reported by Byk and coworkers[18]), our tricyclic inhibitors are generally 5–20 times less potent in cell based assays than in enzyme assays. Improved cellular potency of our tricyclic compounds should have an advantage in in vivo activity.



Amine **2**

SCH 56580
FPT IC_{50} = 0.04 μM

Figure 3.

Table 7. FPT, GGPT and Cos data on tricyclic amides

Entry no.	FPT (IC_{50}) μM	GGPT (IC_{50}) μM	Cos (IC_{50}) μM
1b	2.3	>45	ND
2a	0.8	15.4	11.6
2b	2.7	>50	ND
3b	1.2	>45	11.1
3c	1.4	14.3	10.7
3d	2.7	41	ND
3f	0.6	>39	9.7
3g	3.7	>50	ND
3h	2.9	>50	ND
3i	1.2	>50	4.2
5a	1.3	>50	10.7
5d	0.6	>50	5.8
5g	0.6	>37	7.4
5h	0.3	>39	9.7
5j	0.7	>40	>10
5k	2.6	>38	ND
6f	0.25	>114	1.0
6g	0.47	>46	3.7
6h	2.0	>46	10
SCH 56580	0.04	>40	1.0

ND = Not determined.

Conclusions

We have discovered novel tricyclic compounds that inhibit FPT in the nanomolar range and are devoid of peptidic and sulfhydryl groups. The comprehensive SAR generated above has shown that we require a methylene spacer between the amide carbonyl and the aryl ring. It has also been established that the 4-pyridyl acetyl moiety is a superior substituent for enhanced FPT activity. These compounds have been found to be inactive towards inhibition of GGPT-1 at these concentrations. The compounds reported here show good activity in inhibiting farnesylation of p21 in whole cells. We are currently investigating their ability to intercept the oncogenic Ras signaling pathway and their antitumor efficacy.

Experimental

Melting points were determined with an electrothermal digital melting point apparatus and are uncorrected. The ^1H NMR spectra were obtained on Varian instruments EM-390 (90 MHz) and XL 200 (200 MHz) and are reported as ppm downfield from Me_4Si with number of protons, multiplicities, and coupling constants in Hz indicated parenthetically. The IEMS were determined with a Finnigan MAT-CH-5 spectrometer. Microanalyses were performed by the Physical-

Analytical Chemistry Department, Schering-Plough Research Institute.

Chemistry

General method of coupling amine 1 to carboxylic acids

Method A. Amine **1** (1.6 mmol) was dissolved in 10 mL of dry DMF (or CH_2Cl_2) and the solution cooled to ~4 °C. To this solution was added the appropriate carboxylic acid (1.6 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (DEC; 2.5 mmol, 1.5 equiv), *N*-hydroxybenzotriazole hydrate (HOBT; 1.6 mmol, 1 equiv), 4-methyl morpholine (NMM; 1.6 mmol, 1 equiv) and stirred under nitrogen at this temperature for 0.5 h. The reaction mixture was allowed to warm to room temperature and stirred for 14 h. DMF was then stripped off and the resulting mixture was partitioned between EtOAc and H_2O. The organic phase was first washed with 10% NaH_2PO_4 and then satd $NaHCO_3$, dried over $MgSO_4$ and concentrated. Final purification was either by flash chromatography or on normal phase HPLC using silica gel.

1-(4-Hydroxybenzoyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (1b). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 5% MeOH (satd with ammonia)–CH_2Cl_2: compound **1b** was obtained in 50% yield as a white glass. ^{1}H NMR ($CDCl_3$): δ 2.20–2.60 (4H, m), 2.70–2.95 (2H, m), 3.20–3.45 (4H, m), 3.55–4.20 (1H, m), 3.30–3.50 (1H, br m), 6.75 (2H, d, J=10.5 Hz), 7.10–7.30 (6H, m), 7.50 (1H, d, J=7.5 Hz), 7.80 (1H, m), 8.40 (1H, m); FABMS: *m/z* 431 (MH^+). Anal. calcd for $C_{26}H_{23}ClN_2O \cdot 0.5H_2O$: C, 70.98; H, 5.50; N, 6.37. Found: C, 71.25; H, 5.42; N, 6.03%.

1-[(4-Aminophenyl)carbonyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (1c). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 4.5% MeOH (satd with ammonia)–CH_2Cl_2. Recrystallization was carried out using a diisopropylether–chloroform solvent system: compound **1c** was obtained in 50% yield as a white glass. ^{1}H NMR ($CDCl_3$): δ 2.00–2.60 (4H, m), 2.75–2.95 (2H, m), 3.20–3.45 (4H, m), 3.75–4.10 (2H, m), 6.60 (2H, d, J=10 Hz), 7.10–7.30 (6H, m), 7.45 (1H, d, J=7.5 Hz), 8.40 (1H, m) ; FABMS: *m/z* 429 (M^+) Anal. calcd for $C_{26}H_{24}ClN_3O \cdot 0.5H_2O \cdot 0.15$ diisopropyl ether: C, 71.17; H, 6.18; N, 8.87. Found: C, 71.11; H, 5.01; N, 7.80%.

1-(4-Carboxybenzoyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (1d). The corresponding ester, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-carbomethoxybenzoyl)piperidine was prepared from amine **1** according to method A. The final product was purified via flash chromatography (1–2% methanol satd with ammonia in methylene chloride) and then triturated with pentane/isopropylether to afford 1.08 g (71%) of the ester as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.22–2.71 (4H, m), 2.73–2.95 (2H, m), 3.11–3.48 (4H, m), 3.49–3.63 (1H, m), 3.94 (3H, s), 4.11–4.28 (1H, m), 7.04–7.24 (4H, m), 7.39–7.52 (3H, m), 8.07 (2H, d, J=9 Hz), 8.32–8.48 (1H, m); FABMS: *m/z* 473 (MH^+). Anal. calcd for $C_{28}H_{25}ClN_2O_3 \cdot 0.1C_6H_{14}O$: C, 71.09; H, 5.51; N, 5.80; Cl, 7.34. Found: C, 70.71; H, 5.63; N, 5.50; Cl, 6.82%.

A mixture of 529 mg (1.12 mmol) of the ester in 10 mL of 1.0 N aq sodium hydroxide and 10 mL of methanol was stirred at room temperature for 5 h. The mixture was carefully acidified with aq hydrochloric acid and extracted three times with methylene chloride. The combined organic portions were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography (3–6% methanol and 1% acetic acid in methylene chloride) to afford a solid which was triturated with pentane/isopropylether to afford compound **1d** as a white solid; mp 191–198 °C. ^{1}H NMR (DMSO-d_6, 80 °C): δ 2.22–2.54 (4H, m), 2.76–3.43 (6H, m), 3.55–3.78 (2H, m), 7.06–7.30 (4H, m), 7.48 (2H, d, J=9 Hz), 7.55 (1H, d, J=8 Hz), 7.96 (2H, d, J=9 Hz), 8.32 (1H, m); CIMS: *m/z* 459 (MH^+). Anal. calcd for $C_{27}H_{23}ClN_2O_3 \cdot 0.33C_6H_{14}O \cdot 0.5H_2O$: C, 69.39; H, 5.76; N, 5.58; Cl, 7.06. Found: C, 69.29; H, 6.04; N, 5.25; Cl, 7.47%.

1-[(4-Methylsulfonamido)benzoyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (1e). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 2–4% MeOH (satd with ammonia)–CH_2Cl_2: compound **1e** was obtained in 51% yield as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.20–2.65 (4H, m), 2.70–2.90 (2H, m), 3.00 (3H, s), 3.25–3.50 (4H, m), 3.65 (1H, m), 4.20 (1H, m), 7.15–7.60 (9H, m), 8.45 (1H, m); FABMS: *m/z* 508 (MH^+). Anal. calcd for $C_{27}H_{26}ClN_3O_3S$: C,63.83; H, 5.16; N, 8.27. Found: C, 63.73; H, 5.24; N, 8.47%.

1-[(4-Trifluoromethylsulfonamido)benzoyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (1f). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 0.1% AcOH–EtOAc: compound **1f** was obtained in 36% yield as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.20–2.65 (4H, m), 2.80–3.00 (2H, m), 3.15–3.50 (4H, m), 3.60 (1H, m), 4.15 (1H, m), 7.15–7.30 (10H, m), 7.55 (1H, d, J= 7.5 Hz), 8.45 (1H, m); FABMS: *m/z* 562 (MH^+). Anal. calcd for $C_{27}H_{23}ClF_3N_3O_3S \cdot 1.5H_2O$: C, 55.06; H, 4.45; N, 7.13. Found: C, 54.70; H, 4.05; N, 6.73%.

1-[(4-Methylaminosulfonyl)benzoyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (1g). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 2% MeOH–EtOAc: compound **1g** was obtained in 46% yield as a white solid; mp 220 °C. ^{1}H NMR ($CDCl_3$): δ 2.20–2.65 (4H, m), 2.75 (3H, d, J=7.5 Hz), 2.80–3.00

(2H, m), 3.15–3.50 (4H, m), 4.20 (1H, m), 4.55 (1H, m), 7.15–7.30 (4H, m), 7.55 (1H, d, J= 7.5 Hz), 7.60 (1H, m), 7.90 (1H, d, J= 7.5 Hz), 8.45 (1H, m); FABMS: m/z 508 (M^+). Anal. calcd for $C_{27}H_{26}ClN_3O_3S$: C, 63.83; H, 5.16; N, 8.27. Found: C, 63.71; H, 5.18; N, 8.53%.

1-(4-Dimethylaminobenzoyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (1h). Prepared according to method A. The final product was purified via flash chromatography (3% methanol satd with ammonia in methylene chloride) to afford 81 mg (11%) of compound **1h** as a white solid: mp 200–204 °C. ^{1}H NMR ($CDCl_3$): δ 2.28–2.62 (4H, m), 2.72–3.00 (2H, m), 2.97 (6H, s), 3.18–3.47 (4H, m), 3.85–4.10 (2H, m), 6.65 (2H, d, J=9 Hz), 7.06–7.20 (4H, m), 7.37 (2H, d, J=9 Hz), 7.44 (1H, d, J=8 Hz), 8.39 (1H, m); FABMS: m/z 458 (MH^+). Anal. calcd for $C_{28}H_{28}ClN_3O$: C, 73.43; H, 6.16; N, 9.18. Found: C, 73.36; H, 6.28; N, 8.92%.

1-[(4-Methylthio)benzoyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (1i). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with EtOAc: compound **1i** was obtained in 97% yield as a white solid; mp 170 °C. ^{1}H NMR ($CDCl_3$): δ 2.20–2.65 (5H, m), 2.45 (3H, s), 2.80–3.00 (2H, m), 3.20–3.50 (4H, m), 3.70 (1H, m), 7.15–7.45 (8H, m), 7.55 (1H, d, J= 7.5 Hz), 8.45 (1H, m); FABMS: m/z 461 (MH^+). Anal. calcd for $C_{27}H_{25}ClN_2OS \cdot 0.5H_2O$: C, 68.99; H, 5.57; N, 5.90. Found: C, 68.61; H, 5.47; N, 6.29%.

1-[(4-Methylsulfinyl)benzoyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (1j). Compound **1i** (1.0 g, 2.20 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C, *m*-chloroperbenzoic acid (80%) (0.52 g, 2.4 mmol) was then added and the reaction mixture stirred for 90 min. It was then washed with satd $NaHCO_3$, brine and then dried over $MgSO_4$ and concentrated. The final product was purified by flash chromatography using silica gel and eluting with 15% MeOH–EtOAc: compound **1j** was obtained in 74% yield as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.20–2.55 (5H, m), 2.75 (3H, s), 2.80–2.90 (2H, m), 3.20–3.60 (4H, m), 4.20 (1H, m), 7.15–7.20 (4H, m), 7.45 (1H, m), 7.55(2H, d, J= 7.5 Hz), 7.65 (2H, d, J= 7.5 Hz), 8.45 (1H, m); FABMS: m/z 477 (M^+). Anal. calcd for $C_{27}H_{25}ClN_2O_2S \cdot 1.0H_2O$: C, 65.50; H, 5.50; N, 5.56. Found: C, 65.84; H, 5.26; N, 5.38%.

1-[(4-Methylsulfonyl)benzoyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (1k). Compound **1i** (1.0 g, 2.20 mmol) was dissolved in CH_2Cl_2 (25 mL) and *m*-chloroperbenzoic acid (80%; 1.03 g, 4.8 mmol) was then added and the reaction mixture stirred at room temperature for 2 h. It was then washed with satd $NaHCO_3$, brine and then dried and concentrated. The final product was purified by flash chromatography using silica gel and eluting with 5% MeOH–EtOAc: compound **1k** was obtained in 39% yield as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.20–2.55 (4H, m), 2.80–2.90 (2H, m), 3.00 (3H, s), 3.20–3.60 (5H, m), 4.20 (1H, m), 7.05–7.20 (4H, m), 7.45 (1H, m), 7.55 (2H, d, J=7.5 Hz), 7.95 (2H, d, J= 7.5 Hz), 8.45 (1H, m); FABMS: m/z 493 (M^+). Anal. calcd for $C_{27}H_{25}ClN_2O_3S \cdot 1.0H_2O$: C, 63.45; H, 5.33; N, 5.48. Found: C, 62.95; H, 5.05; N, 5.22%.

1-[(4-Aminosulfonyl)benzoyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (1l). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 3% MeOH–EtOAc: compound **1l** was obtained as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.20–2.65 (4H, m), 2.70–2.90 (2H, m), 3.20–3.55 (5H, m), 4.25 (1H, m), 7.15–7.20 (4H, m), 7.45 (3H, d, J= 7.5 Hz), 7.90 (2H, d, J= 7.5 Hz), 8.45 (1H, m); FABMS: m/z 495 (MH^+). Anal. calcd for $C_{26}H_{24}ClN_3O_3S$: C, 63.20; H, 4.90; N, 8.51. Found: C, 62.81; H, 4.89; N, 8.40%.

1-(4-Nitrobenzoyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (1m). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 3% MeOH–CH_2Cl_2: compound **1m** was obtained in 72% yield as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.10–2.55 (4H, m), 2.80–2.90 (2H, m), 3.10–3.50 (5H, m), 3.95–4.05 (1H, m), 7.05–7.40 (4H, m), 7.60 (1H, m), 7.70 (2H, d, J=7.5 Hz), 8.30 (2H, d, J=7.5 Hz) 8.35 (1H, m); FABMS: m/z 460 (MH^+). Anal. calcd for $C_{26}H_{22}ClN_3O_3$: C, 67.90; H, 4.82; N, 9.14. Found: C, 67.88; H, 4.64; N, 8.97%.

1-[(3,4-Dihydroxyphenyl)carbonyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (1n). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 3–5% MeOH–CH_2Cl_2: compound **1n** was obtained in 33% yield as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.10–2.60 (4H, m), 2.70–2.95 (2H, m), 3.15–3.45 (4H, m), 3.60–3.80 (1H, m), 3.90–4.20 (1H, br m), 6.75–6.85 (3H, m), 6.80 (1H, s), 7.10–7.30 (4H, m), 7.60 (1H, d, J=7.5 Hz), 8.35 (1H, m); FABMS: m/z 446 (M^+). Anal. calcd for $C_{26}H_{23}ClN_2O_3 \cdot 0.25CH_2Cl_2 \cdot 0.3H_2O$: C, 65.94; H, 5.19; N, 6.27. Found: C, 66.55; H, 5.16; N, 5.76%.

1-[(3,5-Dinitro-4-hydroxyphenyl)carbonyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (1o). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 7% MeOH–EtOAC: compound **1o** was obtained in 34% yield as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.20–2.45 (4H, m), 2.75–2.90 (2H, m), 3.25–3.40 (4H, m), 3.70–3.85 (2H, m), 7.10 (1H, d, J=7.5 Hz), 7.15–7.25 (2H, m), 7.30 (1H, d, J=1.5 Hz), 7.60 (1H, dd, J=7.5, 1.5 Hz), 7.80 (2H, s), 8.35 (1H, m); FABMS: m/z 521

(MH^+). Anal. calcd for $C_{26}H_{23}ClN_2O_3 \cdot 0.5EtOAc \cdot 0.2H_2O$: C, 59.94; H, 3.78; N, 9.42. Found: C, 56.58; H, 3.78; N, 9.42%.

1-[(3,5-Dimethoxy-4-hydroxyphenyl)carbonyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (1p). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 2% MeOH–CH_2Cl_2: compound **1p** was obtained in 81% yield as a white solid. ^1H NMR ($CDCl_3$): δ 2.30–2.65 (4H, m), 2.75–2.95 (2H, m), 3.20–3.50 (4H, m), 3.70–4.20 (2H, m), 3.90 (6H, s), 6.70 (2H, s), 7.10–7.20 (4H, m), 7.50 (1H, m), 8.40 (1H, m); FABMS: *m/z* 490 (M^+). Anal. calcd for $C_{26}H_{23}ClN_2O_3 \cdot 0.5CH_2Cl_2 \cdot 0.2H_2O$: C, 65.99; H, 5.55; N, 5.44. Found: C, 66.21; H, 5.17; N, 5.11%.

1-(Phenylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (2a). Phenyl acetyl chloride (0.25 g 1.6 mmol) was dissolved in 5 mL of THF. Amine **1** (0.5 g, 1.6 mmol) dissolved in 6 mL of pyridine was then added to the reaction mixture and stirred at room temperature under N_2 for 48 h. The volatiles were then removed by rotary evaporation and the resulting oily product was partitioned between EtOAc and 10% NaH_2PO_4. The aqueous phase was washed with EtOAc. Combined EtOAc fractions were washed with satd $NaHCO_3$, dried over Na_2SO_4 and concentrated to give rise to a yellow oil which was purified on normal phase HPLC (silica gel column) eluting with 8% MeOH (satd with ammonia)–CH_2Cl_2 to give pure **2a** (0.25 g, 36% yield); mp 112–114 °C. ^1H NMR ($CDCl_3$): δ 2.10 (2H, m), 2.30–2.50 (3H, m), 2.70–2.90 (2H, m), 3.10–3.25 (2H, m), 3.25–3.40 (2H, m), 3.60–3.70 (1H, m), 3.75 (2H, s), 7.00–7.45 (10H, m), 8.45 (1H, m); FABMS: *m/z* 429 (MH+). Anal. calcd for $C_{27}H_{25}ClN_2O \cdot 0.2H_2O$: C, 74.92; H, 5.87; N, 6.40. Found: C, 74.92; H, 5.82; N, 6.55%.

1-(1-Oxo-3-phenylpropyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (2b). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 10% MeOH (satd with ammonia)–CH_2Cl_2: compound **2b** was obtained in 91% yield; mp 66.8–67.8 °C. ^1H NMR (DMSO): δ 2.10–2.40 (4H, m), 2.60 (2H, m), 2.80 (2H, d J= 7.32 Hz), 2.85 (2H, m), 3.10–3.40 (4H, m), 3.65 (1H, m), 3.85 (1H, m), 7.10–7.40 (9H, m), 7.60 (1H, dd, J=8, 1.4 Hz), 8.35 (1H, m); FABMS: *m/z* 443 (MH^+). Anal. calcd for $C_{28}H_{27}ClN_2O \cdot 0.4H_2O$: C, 74.70; H, 6.05; N, 6.22. Found: C, 74.76; H, 5.97; N, 6.20%.

1-(4-Phenylbutylcarbonyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (2c). Prepared in a similar manner to compound **2a** above using 4-phenyl butyl acid chloride as the starting material. The final product was purified by flash chromatography using silica gel and eluting with 5% MeOH-CH_2Cl_2: compound **2c** was obtained as a white solid. ^1H NMR ($CDCl_3$): δ 2.00 (2H, q, J= 8 Hz), 2.30 (5H, m), 2.40–2.60 (1H, m), 2.65 (2H, d, J=8.0 Hz), 2.70–2.95 (2H, m), 3.15–3.45 (4H, m), 3.55–3.70 (1H, m), 4.00–4.20 (1H, m), 7.10–7.35 (9H, m), 7.45 (1H, dd, J=8, 1.4 Hz), 8.45 (1H, m); FABMS: *m/z* 457 (MH^+). Anal. calcd for $C_{29}H_{29}ClN_2O \cdot 0.3H_2O$: C, 75.29; H, 6.24; N, 5.91. Found: C, 75.22; H, 6.31; N, 6.05%.

1-(4-Hydroxyphenylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (3a). Prepared according to method A. Compound **3a** was obtained in 79% yield; mp 219–220 °C. ^1H NMR (DMSO): δ 1.90–2.40 (4H, m), 2.80 (2H, m), 3.10–3.40 (4H, m), 3.55 (2H, s), 3.60–3.90 (2H, m), 6.70 (2H, d, J= 8 Hz), 7.05 (2H, d, J=8 Hz), 7.10 (1H, d, J=8 Hz), 7.20 (1H, m), 7.25 (1H, m), 7.40 (1H, s), 7.55 (1H, d, J=8 Hz), 8.35 (1H, m), 9.25 (1H, s); FABMS: *m/z* 445 (MH^+). Anal. calcd for $C_{27}H_{25}ClN_2O_2 \cdot 1.05H_2O$: C, 69.91; H, 5.84; N, 6.04. Found: C, 69.91; H, 5.75; N, 6.13%.

1-[(4-Methylphenyl)acetyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (3b). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 5% MeOH (satd with ammonia)–CH_2Cl_2: compound **3b** was obtained in 93% yield; mp 84–85 °C. ^1H NMR (DMSO): δ 1.97–2.40 (4H, m), 2.26 (3H, s), 2.80 (2H, m), 3.10–3.55 (4H, m), 3.60–3.90 (4H, m), 7.04–7.15 (2H, m), 7.10 (4H, s), 7.20 (1H, dd, J=7.5, 5.0 Hz), 7.31 (1H, d, J=7.5 Hz), 7.57 (1H, d, J=7.8 Hz), 8.3 (1H, brt, J=5 Hz); FABMS: *m/z* 443 (MH^+). Anal. calcd for $C_{27}H_{25}ClN_2O_2 \cdot 0.3H_2O$: C, 74.91, H, 6.20; N, 6.24. Found: C, 74.91; H, 6.06; N, 6.27%.

1-(4-Methoxyphenylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (3c). Prepared in a similar manner to compound **2a** above using 4-methoxy phenyl acetyl chloride as the starting material. The final product was purified on normal phase HPLC eluting with 8% MeOH (satd with ammonia)–CH_2Cl_2: compound **3c** was obtained in 40% yield. ^1H NMR ($CDCl_3$): δ 2.10–2.20 (1H, m), 2.25–2.50 (3H, m), 2.70–2.90 (2H, m), 3.10–3.25 (2H, m), 3.25–3.45 (2H, m), 3.65 (2H, s), 3.70 (1H, m), 3.80 (3H, s), 4.00–4.15 (1H, m), 6.85 (2H, d, J=7.5 Hz), 7.00–7.20 (6H, m), 7.45 (1H, d, J=7.5 Hz), 8.35 (1H, m); FABMS: *m/z* 459 (MH^+). Anal. calcd for $C_{28}H_{27}ClN_2O_2 \cdot 0.3H_2O$: C, 72.30; H, 5.94; N, 6.02. Found: C, 72.30; H, 5.85; N, 6.09%.

1-[(4-Dimethylamino)phenylacetyl])-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (3d). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 3% MeOH (satd with ammonia)–CH_2Cl_2: compound **3d** was obtained in 71% yield; mp 182–183 °C. ^1H NMR ($CDCl_3$): δ 2.10–2.20 (1H, m), 2.25–2.50 (3H, m), 2.70–2.90 (2H, m), 2.95 (6H, s), 3.10–3.25 (2H, m), 3.25–3.40 (2H, m), 3.65 (2H, s), 3.65–3.70 (1H, m), 4.05–4.20 (1H, m), 6.70 (2H, d,

J=7.5 Hz), 7.00–7.20 (4H, m), 7.10 (2H, d, J=7.5 Hz), 7.40 (1H, d, J=5 Hz), 8.40 (1H, m); FABMS: *m/z* 472 (MH^+). Anal. calcd for $C_{29}H_{30}ClN_3O \cdot 0.6H_2O$: C, 74.97; H, 6.45; N, 8.69. Found: C, 71.97; H, 6.34; N, 8.66%.

1-(4-Fluorophenylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (3e). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 3% MeOH–EtOAc: compound **3e** was obtained as a white solid; mp 76–78 °C. ^1H NMR ($CDCl_3$): δ 2.10–2.50 (4H, m), 2.80 (2H, m), 3.10–3.40 (4H, m), 3.60–3.80 (3H, m), 4.10 (1H, m), 6.95–7.30 (8H, m), 7.45 (1H, d, J= 8.0 Hz), 8.45 (1H, m); FABMS: *m/z* 446 (M^+). Anal. calcd for $C_{27}H_{24}ClFN_2O \cdot 0.6H_2O$: C, 70.77; H, 5.55; N, 6.13. Found: C, 70.77; H, 5.58; N, 6.08%.

1-(4-Bromophenylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (3f). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 2% MeOH (satd with ammonia)–CH_2Cl_2: compound **3f** was obtained in 83% yield; mp 93–95 °C. ^1H NMR (DMSO): δ 2.03–2.38 (4H, m), 2.81 (2H, m), 3.10–3.40 (4H, m), 3.60–3.90 (2H, m), 3.71 (2H, s), 7.04–7.30 (5H, m), 7.31 (1H, s), 7.50 (2H, d, J=7.5 Hz), 7.59 (1H, d, J=7.5 Hz), 8.35 (1H, m); FABMS: *m/z* 508 (MH^+). Anal. calcd for $C_{27}H_{24}BrClN_2O \cdot 0.3H_2O$: C, 63.18; H, 64.71; N, 5.46. Found: C, 63.14; H, 4.78; N, 5.49%.

1-[(3-Hydroxyphenyl)acetyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (3g). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 8% MeOH (satd with ammonia)–CH_2Cl_2: compound **3g** was obtained in 78% yield; mp 137–138 °C. ^1H NMR (DMSO): δ 1.97–2.37 (4H, m), 2.80 (2H, m), 3.00–3.50 (4H, m), 3.55–3.90 (2H, m), 3.63 (2H, s), 6.57–6.68 (2H, m), 6.66 (1H, s), 7.08 (2H, m), 7.20 (2H, m), 7.31 (1H, d, J=2 Hz), 7.57 (1H, d, J=7.70 Hz), 8.34 (1H, t, J=5.5 Hz), 9.34 (1H, s, exchangeable with D_2O); FABMS: *m/z* 445 (MH^+). Anal. calcd for $C_{27}H_{25}ClN_2O_2 \cdot 1.1H_2O$: C, 69.77; H, 5.90; N, 6.30. Found: C, 69.71; H, 5.54; N, 6.01%.

1-[(3-Methylphenyl)acetyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (3h). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 5% MeOH (satd with ammonia)–CH_2Cl_2: compound **3h** was obtained in 93% yield; mp 70–72 °C. ^1H NMR (DMSO): δ 1.97–2.40 (4H, m), 2.26 (3H, s), 2.80 (2H, m), 3.10–3.55 (4H, m), 3.60–3.90 (4H, m), 6.98–7.12 (4H, m), 7.19 (3H, m), 7.31 (1H, d, J=2 Hz), 7.57 (1H, d, J=7.8 Hz), 8.3 (1H, brt, J=4.4 Hz); FABMS: *m/z* 443 (MH^+). Anal. calcd for $C_{27}H_{25}ClN_2O_2 \cdot 0.3H_2O$: C, 75.00; H, 6.20; N, 6.25. Found: C, 75.00; H, 6.04; N, 6.26%.

1-(3-Nitrophenylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (3i). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 7% MeOH (satd with ammonia)–CH_2Cl_2: compound **3i** was obtained in 85% yield; mp 94–95 °C. ^1H NMR (DMSO): δ 2.10–2.46 (4H, m), 2.83 (2H, m), 3.12–3.43 (4H, m), 3.79 (2H, m), 3.80 (2H, s), 7.11 (1H, d, J=8.1 Hz), 7.22 (2H, m), 7.33 (1H, s), 7.61 (2H, t, J=7.7 Hz), 7.71 (1H, d, J=6.80 Hz), 8.14 (2H, m), 8.36 (1H, d, J=4.4 Hz); FABMS: *m/z* 474 (MH^+). Anal. calcd for $C_{27}H_{24}ClN_3O_3 \cdot 0.4H_2O$: C, 66.97; H, 5.74; N, 8.68. Found: C, 67.12; H, 5.07; N, 8.71%.

1-[4-(3,4-Dihydroxyphenyl)acetyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (3j). Prepared according to method A. Compound **3j** was obtained in 90.3% yield; mp 214 °C (decomp). ^1H NMR ($CDCl_3$): δ 2.00–2.50 (4H, m), 2.60–2.85 (2H, m), 2.90–3.40 (4H, m), 3.55–3.90 (2H, m), 3.90–4.20 (2H, m), 6.50 (1H, d, J=7.5 Hz), 6.70 (2H, m), 6.80 (1H, d J=7.5 Hz), 7.00–7.20 (4H, m), 7.50 (1H, m), 8.30 (1H, m); FABMS: *m/z* 461 (MH^+). Anal. calcd for $C_{27}H_{25}ClN_2O_3 \cdot 1.4H_2O$: C, 66.67; H, 5.72; N, 6.30. Found: C, 66.67; H, 55.51; N, 5.82%.

1-(Cyclopentylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (4d). Prepared according to method A. The final product was purified on silica gel flash chromatography eluting with 1–2% MeOH–CH_2Cl_2: compound **4d** was obtained in 32% yield; mp 213–214 °C. ^1H NMR ($CDCl_3$): δ 1.15 (2H, m), 1.45–1.65 (6H, m), 1.85 (2H, m), 2.2–2.40 (8H, m), 2.80–2.90 (2H, m), 3.15 (1H, m), 3.20 (1H, m), 3. 40 (2H, m), 3.70 (1H, m), 4.10 (1H, m), 7.10–7-20 (4H, m), 7.50 (1H, m), 8.40 (1H, m); FABMS: *m/z* 421 (MH^+). Anal. calcd for $C_{26}H_{28}ClN_2O \cdot 0.3H_2O$: C, 73.22; H, 6.86; N, 6.39. Found: C, 73.22; H, 6.86; N, 6.57%.

1-(Cyclohexylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (4e). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 2% MeOH (satd with ammonia)–CH_2Cl_2: compound **4e** in 61% yield; mp 89–91 °C. ^1H NMR ($CDCl_3$): δ 0.95–1.40 (5H, m), 1.80 (6H, m), 2.20–2.70 (6H, m), 2.90 (2H, m), 3.10–3.50 (4H, m), 3.80 (1H, m), 4.15 (1H, m), 7.20 (4H, m), 7.55 (1H, d, J=7.5 Hz), 8.50 (1H, d, J=7.5 Hz); FABMS: *m/z* 435 (MH^+). Anal. calcd for $C_{27}H_{31}ClN_2O \cdot 0.2H_2O$: C, 73.71; H, 7.14; N, 6.37. Found: C, 73.71; H, 7.08; N, 6.42%.

1-(Adamantylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (4f). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 2% MeOH (satd with ammonia)–CH_2Cl_2: compound **4f** in 81% yield; mp 124–126 °C. ^1H NMR ($CDCl_3$): δ 1.60–1.80 (12H, m), 2.00 (3H, br m), 2.40–2.70 (4H, m), 2.90 (2H, m), 3.15–3.50 (4H, m),

3.85 (1H, m), 4.20 (1H, m) 7.20–7.30 (3H, m), 7.35 (1H, s), 7.50 (1H, d, $J=7.5$ Hz), 8.50 (1H, br m); FABMS: *m/z* 487 (MH^+). Anal. calcd for $C_{31}H_{35}ClN_2O \cdot 0.3H_2O$: C, 75.60; H, 7.24; N, 5.69. Found: C, 75.60; H, 7.16; N, 5.72%.

1-[(*R*)-(−)-1-Oxo-2-phenylbutyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (5a). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 2% MeOH (satd with ammonia)–CH_2Cl_2: compound **5a** in 100% yield; mp 83–84 °C. ^1H NMR (DMSO): δ 0.79 (3H, m), 1.45–1.75 (2H, m), 1.85–2.38 (4H, m), 2.68–2.88 (2H, m), 3.01 (1H, m), 3.10–3.40 (4H, m), 3.69 (1H, m), 3.79–4.08 (1H, m), 6.80–7.48 (9H, m), 7.56 (1H, m), 8.25 (1H, m); FABMS: *m/z* 458 (MH^+). Anal. calcd for $C_{29}H_{29}ClN_2O \cdot 0.6H_2O$: C, 74.45; H, 6.51; N, 5.99. Found: C, 74.55; H, 6.35; N, 6.23%.

1-(3-Methyl-1-oxo-2-phenylpentyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (5b). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 2% MeOH (satd with ammonia)–CH_2Cl_2: compound **5b** in 90% yield; mp 96–97 °C. ^1H NMR (DMSO): δ 0.55 (1H, d, $J=5$ Hz), 0.66–1.27 (5H, m), 1.38–1.92 (2H, m), 1.93–2.36 (5H, m), 2.79 (2H, m), 3.00–3.48 (4H, m), 3.40–3.95 (3H, m), 6.90–7.43 (9H, m), 7.57 (1H, m), 8.33 (1H, m); FABMS: *m/z* 486 (MH^+). Anal. calcd for $C_{31}H_{33}ClN_2O \cdot 0.3H_2O$: C, 75.91; H, 6.91; N, 5.71. Found: C, 76.07; H, 6.80; N, 5.82%.

1-[(Cyclopentyl)phenyacetyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (5c). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 5% MeOH (satd with ammonia)–CH_2Cl_2: compound **5c** in 83% yield; mp 113–114 °C. ^1H NMR (DMSO): δ 0.94–1.28 (2H, m), 1.30–1.68 (4H, m), 1.80 (3H, m), 1.92–2.33 (3H, m), 2.49 (1H, m), 2.79 (2H, m), 2.95–3.48 (4H, m), 3.64–3.98 (3H, m) 6.87–7.42 (9H, m), 7.56 (1H, m), 8.27–8.38 (1H, m); FABMS: *m/z* 497 (MH^+). Anal. calcd for $C_{32}H_{32}ClN_2O \cdot 0.4H_2O$: C, 76.37; H, 6.57; N, 5.57. Found: C, 76.47; H, 6.60; N, 5.61%.

1-(4-Diphenylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (5d). Prepared according to method A. Final product purified on normal phase HPLC eluting with 3% MeOH (satd with ammonia)–CH_2Cl_2: compound **5d** in 86% yield; mp 114–115 °C. ^1H NMR (DMSO): δ 1.80–2.05 (2H, m), 2.10–2.40 (2H, m), 2.80 (2H, m), 3.50 (4H, m), 3.65–3.95 (2H, m), 5.55 (1H, s), 6.95–7.40 (14H, m), 7.55(1H, d, $J=7.5$ Hz),), 8.30 (1H, dd, $J=7.5$ Hz, $J=1.5$ Hz); FABMS: *m/z* 506 (MH^+). Anal. calcd for $C_{32}H_{30}ClN_2O$: C, 78.32; H, 5.98; N, 5.54. Found: C, 77.22; H, 5.75; N, 5.51%.

1-(3-Hydroxy-1-oxo-2-phenylpropyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (5e). Prepared according to method A. The final product was purified on normal phase HPLC eluting with 7% MeOH (satd with ammonia)–CH_2Cl_2: compound **5e** in 97 % yield; mp 109–110 °C. ^1H NMR (DMSO): δ 1.65 (1H, m), 1.95–2.43 (3H, m), 2.69–2.90 (3H, m), 2.95–3.54 (5H, m), 3.69 (1H, m), 3.86–4.17 (2H, m), 4.70 (1H, m, exchangeable with D_2O), 6.88–7.45 (9H, m), 7.56 (1H, m), 8.26–8.39 (1H, m); FABMS: *m/z* 459 (MH^+). Anal. calcd for $C_{28}H_{27}ClN_2O_2 \cdot 0.8H_2O$: C, 71.04; H, 6.09; N, 5.92. Found: C, 71.05; H, 5.88; N, 5.99%.

1-(3-Acetyl-1-oxo-2-phenylpropyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (5f). Compound **5e** (0.22 g, 0.49 mmol) was dissolved in 1.0 mL of acetyl chloride (3.2 mmol, 6.5 equiv) and the reaction mixture stirred at room temperature for 4 h. All the volatiles were then stripped off and the resulting crude product was purified by flash chromatography using silica gel and eluting with 7% MeOH (satd with ammonia)–CH_2Cl_2 to give compound **5f** as a white solid in 91% yield; mp 107–108 °C. ^1H NMR (DMSO): δ 2.10 (3H, 2s), 2.20–2.40 (3H, m), 2.65–3.70 (6H, m), 3.90 (1H, m), 4.25 (2H, m), 4.35 (2H, m), 4.65 (1H, m) 6.88–7.50 (10H, m), 8.30–8.45 (1H, m); FABMS: *m/z* 501 (MH^+). Anal. calcd for $C_{30}H_{28}ClN_2O_3 \cdot 0.4H_2O$: C, 71.00; H, 5.60; N, 5.50. Found: C, 71.00; H, 5.99; N, 5.35%.

1-[3-[(Methylsulfonyl)oxy]-1-oxo-2-phenylpropyl]-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]-pyridin-11-ylidene)piperidine (5g). Compound **5e** (0.4 g, 0.89 mmol) was dissolved in 10 mL of pyridine and methanesulfonyl chloride (0.15 g, 1.3 mmol) was added. The reaction mixture stirred at room temperature for 12 h. All the volatiles were then stripped off and the resulting crude product was triturated with ether (2×50 mL) and then purified on normal phase HPLC eluting with 2% MeOH (satd with ammonia), to give compound **5g** as a white solid in 73 % yield; mp 110–111 °C. ^1H NMR ($CDCl_3$): δ 1.50–2.0 (2H, s), 2.20–2.4 (2H, m), 2.50–3.70 (9H, m), 4.25 (2H, m), 4.30 (2H, m), 4.80 (1H, m) 6.88–7.50 (10H, m), 8.30–8.45 (1H, m); FABMS: *m/z* 537 (M^+). Anal. calcd for $C_{29}H_{29}ClN_2O_4S \cdot 0.1H_2O$: C, 64.85; H, 5.44; N, 5.22. Found: C, 64.68 H, 5.49; N, 5.19%.

1-(3-Acetylthio-1-oxo-2-phenylpropyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (5h). $CsCO_3$ (0.19 g, 0.6 mmol) was dissolved in 20 mL of MeOH and stirred under nitrogen. To this solution was added thioacetic acid (0.137 g, 1.8 mmol, 0.13 mL) and the reaction mixture stirred for 1 h at room temperature. MeOH was then removed and chased with toluene. Mesylate **5g** dissolved in 5 mL of DMF was added to the cesium thio acetate salt. The reaction was stirred at room temperature under nitrogen for 14 h. It was then heated at 80 °C for another 14 h and then purified on

normal phase HPLC eluting 70% EtOAC–hexanes to give compound **5h** as a white solid in 51% yield; mp 92–93 °C. ^{1}H NMR ($CDCl_3$): δ 1.50–2.0 (2H, s), 2.20–2.4 (2H, m), 2.50–3.70 (9H, m), 4.25 (2H, m), 3.90 (2H, m), 4.4 (1H, m) 6.88–7.50 (10H, m), 8.30–8.45 (1H, m); FABMS: *m/z* 518 (MH^+).

1-(1-Oxo-2-methyl-2-phenylpropyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (5i). Prepared according to method A. The final product was purified on flash chromatography eluting with 75% EtOAc–hexane to give compound **5i** in 72% yield; mp 80–81 °C. ^{1}H NMR ($CDCl_3$): δ 1.20–1.30 (1H, m), 1.50–1.70 (8H, m), 2.20–2.50 (3H, m), 2.75–3.00 (3H, m), 3.20–3.60 (2H, m), 3.80–3.90 (1H, m), 6.95–7.45 (10H, m), 8.30 (1H, m); FABMS: *m/z* 459 (M^+).

1-[(*S*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (5j). Prepared according to method A. The final product was purified on flash chromatography eluting with 40–50% EtOAc–hexane: compound **5j** was obtained in 38% yield; mp 108–109 °C. ^{1}H NMR ($CDCl_3$): δ 2.20–2.50 (3H, m), 2.60–3.00 (4H, m), 3.15–3.55 (3H, m), 3.60 and 3.75 (3H, s), 3.90–4.10 (1H, m), 4.30–4.55 (1H, m), 6.85–7.60 (10H, m), 8.30–8.45 (1H, brt, m); FABMS: *m/z* 527 (MH^+).

1-[(*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (5k). Prepared according to method A. The final product was purified on flash chromatography eluting with 40–50% EtOAc–hexane: compound **5k** was obtained in 43% yield; mp 113–114 °C. ^{1}H NMR ($CDCl_3$): δ 2.20–2.50 (3H, m), 2.60–3.00 (4H, m), 3.15–3.55 (3H, m), 3.60 and 3.75 (3H, s), 3.90–4.10 (1H, m), 4.30–4.55 (1H, m), 6.80–7.60 (10H, m), 8.25–8.45 (1H, brt, m); FABMS: *m/z* 527 (MH^+).

1-(4-Pyridinylcarbonyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (6b). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 5% MeOH–CH_2Cl_2. Compound **6b** was obtained in 27% yield. ^{1}H NMR ($CDCl_3$): δ 2.10–2.55 (4H, m), 2.70–2.95 (2H, m), 3.10–3.60 (4H, m), 4.10–4.20 (1H, m), 7.10–7.30 (6H, m), 7.45 (1H, m), 8.35 (1H, m), 8.30–8.45 (1H, m), 8.70 (1H, m); FABMS: *m/z* 416 (MH^+). Anal. calcd for $C_{25}H_{22}ClN_3O\cdot0.5H_2O$: C, 70.66; H, 5.46; N, 9.89. Found: C, 70.66; H, 5.54; N, 9.22%.

1-(3-Pyridinylcarbonyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (6c). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 4% MeOH–CH_2Cl_2. Compound **6c** was obtained in 15% yield. ^{1}H NMR ($CDCl_3$): δ 2.20–2.70 (4H, m), 2.75–2.95 (3H, m), 3.20–3.45 (4H, m), 3.55–3.70 (1H, m), 4.10–4.25 (1H, m), 7.05–7.50 (6H, m), 7.75 (1H, d, J=7.5 Hz), 8.30–8.45 (1H, m), 8.65 (2H, m); FABMS: *m/z* 416 (MH^+). Anal. calcd for $C_{25}H_{22}ClN_3O\cdot0.5H_2O$: C, 70.66; H, 5.46; N, 9.89. Found: C, 69.95; H, 5.18; N, 9.77%.

1-(2-Pyridinylcarbonyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (6d). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 6% MeOH–CH_2Cl_2. Compound **6d** was obtained in 23% yield. ^{1}H NMR ($CDCl_3$): δ 2.30–2.70 (4H, m), 2.75–2.95 (2H, m), 3.25–3.45 (4H, m), 3.75–3.80 (1H, m), 4.15–4.30 (1H, m), 7.05–7.20 (4H, m), 7.25–7.35 (1H, m), 7.45 (1H, t, J=7.5 Hz), 7.60 (1H, d, J=7.5 Hz), 7.80 (1H, t, J=7.5 Hz), 8.40 (1H, m), 8.55 (1H, m); FABMS: *m/z* 416 (MH^+). Anal. calcd for $C_{25}H_{22}ClN_3O\cdot0.5H_2O$: C, 70.66; H, 5.46; N, 9.89. Found: C, 69.97; H, 5.32; N, 9.72%.

1-(4-Pyridylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (6f). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 3% MeOH (satd with ammonia)–CH_2Cl_2. Compound **6f** was obtained in 48% yield; mp 152–155 °C. ^{1}H NMR ($CDCl_3$): δ 2.15–2.55 (4H, m), 2.70–2.95 (2H, m), 3.10–3.45 (4H, m), 3.55–3.70 (1H, m), 3.70 (2H, s), 4.00–4.20 (1H, m), 7.00–7.20 (6H, m) 7.45 (1H, d, J= 8 Hz), 8.35 (1H, m), 8.50 (2H, d, J=8 Hz); FABMS: *m/z* 430 (MH^+). Anal. calcd for $C_{26}H_{24}ClN_3O\cdot0.1CH_2Cl_2$: C, 71.52; H, 5.56; N, 9.59. Found: C, 71.58; H, 5.50; N, 9.36%.

1-(3-Pyridylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (6g). Prepared according to method A. The final product was purified by flash chromatography using silica gel and eluting with 3% MeOH (satd with ammonia)–CH_2Cl_2. Compound **6g** was obtained in 65% yield; mp 163–164 °C. ^{1}H NMR ($CDCl_3$): δ 2.15–2.55 (4H, m), 2.70–2.95 (2H, m), 3.10–3.45 (4H, m), 3.60–3.70 (1H, m), 3.70 (2H, s), 4.00–4.20 (1H, m), 7.00–7.30 (5H, m), 7.45 (1H, d, J= 8 Hz), 7.60 (1H, d, J= 8 Hz), 8.35 (1H, m), 8.50 (2H, m); FABMS: *m/z* 430 (MH^+). Anal. calcd for $C_{26}H_{24}ClN_3O$: C, 72.63; H, 5.63; N, 9.77. Found: C, 72.38; H, 5.71; N, 9.47%.

1-(2-Pyridylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (6h). Prepared according to method A. The final product was purified via flash chromatography (3% methanol satd with ammonia in methylene chloride) and recrystallized from ether to afford 897 mg (65%) of compound **6h** as a white solid; mp 122–125 °C. ^{1}H NMR ($CDCl_3$): δ 2.14–2.56 (4H, m), 2.69–2.95 (2H, m), 3.06–3.50 (4H, m), 3.76–4.00 (1H, m), 3.95 (2H, s), 4.00–4.20 (1H, m), 7.02–7.22 (5H, m), 7.30–7.48 (2H, m), 7.57–7.71 (1H, m), 8.35–8.44 (1H, m), 8.45–8.56 (1H, m); FABMS *m/z* 430 (MH^+). Anal. calcd for $C_{26}H_{24}ClN_3O$: C, 72.63; H, 5.63; N, 9.77; Cl, 8.25. Found: C, 72.77; H, 5.75; N, 9.76; Cl, 8.36%.

4-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-[2-[(4-pyridinylacetyl)]]piperidine (8). To a cooled solution of amine **1** (0.8 g, 4 mmol) and triethylamine (0.6 mL, 4 mmol) in CH_2Cl_2 (50 mL) was added 4-(2-bromoacetyl)pyridine (1.03 g, 3.3 mmol). After stirring for 1.5 h, the reaction mixture was diluted with CH_2Cl_2 and washed with a saturated solution of sodium bicarbonate and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography (silica gel) using 2% MeOH–CH_2Cl_2 as eluent to provide compound **8** as a glassy material (0.59 g, 53% yield). ^{1}H NMR ($CDCl_3$): δ 2.32–2.70 (6H, m), 2.87 (4H, m), 3.42 (2H, m), 3.82 (2H, s), 7.10–7.23 (4H, m), 7.48 (1H, dd, J= 7 Hz, J= 1 Hz), 7.82 (2H, br d, J= 7 Hz), 8.43 (1H, dd, J=5, 1 Hz), 8.83 (2H, brd, 2H, J=7 Hz); FABMS: *m/z* 430 (MH^+). Anal. calcd for $C_{24}H_{22}ClN_3O \cdot 0.4H_2O$: C, 71.16; H, 5.70; N, 9.57. Found: C, 71.16; H, 5.70; N, 9.58%.

1-(4-Pyridineacetyl)-4-(8-chloro-3-methyl-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine (SCH 56580). Prepared according to method A except that amine **1** is replaced with amine **2**. The final product was purified on silica gel flash chromatography eluting with 4% MeOH (satd with ammonia)–CH_2Cl_2: **SCH 56580** was obtained in 63% yield; mp 94 °C. ^{1}H NMR ($CDCl_3$): δ 2.20 (3H, s), 2.25–2.55 (3H, m), 2.60–2.90 (2H, m), 3.10–3.45 (4H, m), 3.50–3.75 (1H, m), 3.76 (3H, s), 4.10–4.20 (1H, m), 7.00–7.30 (6H, m), 8.20 (1H, d, J=1.5 Hz), 8.50 (2H, d, J= 1.5 Hz); FABMS: *m/z* 444 (MH^+). Anal. calcd for $C_{27}H_{26}ClN_3O \cdot 0.8H_2O$: C, 70.64; H, 6.03; N, 9.20. Found: C, 70.64; H, 65.86; N, 9.00%.

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