Pergamon

Bioorganic & Medicinal Chemistry 7 (1999) 1845–1855

BIOORGANIC & MEDICINAL CHEMISTRY

Analogues of 1-(3,10-Dibromo-8-chloro-6,11-dihydro-5*H*-benzo-[5,6]-cyclohepta[1,2-*b*]pyridin-11-yl)piperidine as Inhibitors of Farnesyl Protein Transferase

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Received 8 February 1999; accepted 3 March 1999

Abstract—The synthesis of several 4-pyridylacetyl *N*-oxide derivatives of 4-(3-bromo-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]-pyridin-11-yl)piperazine/piperidine **3** is described. This study was aimed at identifying fomesyl protein transferase (FPT) inhibitors in these two series of tricycles containing different phenyl ring substituents. The in vitro activity profile of the initial group of compounds **7a**–**7g** led to the synthesis of the 8-methyl-10-methoxy and 8-methyl-10-bromo analogues **7i**, **13i**, and **13j**. The 11*R*(−) enantiomers of these compounds were found to exhibit potent in vitro FPT inhibition activity.

Introduction

The pathway by which Ras proteins play a role in the signal transduction process in cell proliferation is well established.[1–3] Ras proteins are expressed in the cytosol and require post-translational farnesylation of the cysteine residue in the carboxy terminus CaaX tetrapeptide. Farnesylation, catalyzed by the enzyme farnesyl protein transferase (FPT), enables the Ras protein to participate in signalling pathways by localizing to the plasma membrane.[4,5] In normal cell growth, the intrinsic GTPase activity of Ras allows its cycling between the active GTP-bound Ras and the inactive GDP-bound forms. Oncogenic Ras proteins, which are present in a large percentage of human cancers, are deficient in GTPase activity and hence are constitutively activated to promote uncontrolled cell division.[6,7] Inhibition of FPT catalyzed farnesylation would potentially render oncogenic Ras non-functional and hence this concept has been the subject of intense interest as a therapeutic approach for the development of antitumor agents to treat *ras* associated tumors.[8] Several structural types of potent FPT inhibitors have been reported in the literature during the past few years and this subject has been reviewed.[9]

Our laboratories have recently reported the discovery of the tricycle **1** (Sch 44342) as a novel nonpeptidic, non-thiol-containing selective FPT inhibitor.[10] Subsequently, an extensive structure–activity effort in this series has culminated in the development of the trihalo benzocycloheptapyridine derivative **2** (Sch 66336), as a highly potent (FPT $IC_{50} = 1.9$ nM), orally active antitumor agent that is currently undergoing clinical trials in humans.[11] The prior studies leading to the development of **2** indicated that improvements in the potency and pharmacokinetics (PK) of **1** were achievable by the introduction of a 3-bromo substituent,[12,13] a C_{11}-piperazine or a C_{11}-piperidine,[14] and a 4-pyridylacetyl *N*-oxide or a 4-*N*-carboxamidopiperidinylacetyl group.[15] Additional improvements were achieved by the introduction of a 10- or 7-bromo substituent (Fig. 1).[11]

We report here on a related series of novel benzocycloheptapyridine derivatives **13i** and **13j** that were found to be potent FPT inhibitors comparable to **2**. These C_{11}-piperidine compounds were identified through a structure activity relationship (SAR) study of a series of analogues **3** that contained a 3-bromo group and a C_{11}-piperazine with a 4-pyridylacetyl *N*-oxide acyl group as the fixed functionalities that are essential for activity; the variable functionalities in **3** were the phenyl ring substituents R which were limited to methyl, methoxy, and bromo groups. Our strategy to develop a SAR

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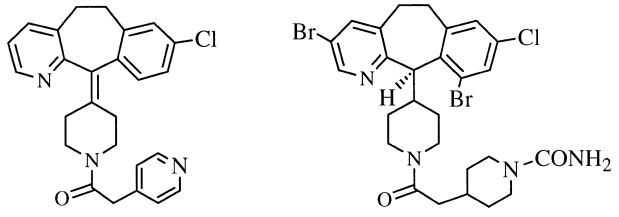
0968-0896/99/$ - see front matter
PII: S0968-0896(99)00103-0

study of C_{11}-piperazines **3** and then synthesize the C_{11}-piperidine analogues of the active compounds **3**, was based on the following considerations: (a) the C_{11}-piperazines **3** are synthetically more accessible than the corresponding C_{11}-piperidines; and (b) our prior findings showed that the FPT activity of C_{11}-piperazines in the benzocycloheptapyridine series correlates well with that of the corresponding C_{11}-piperidine analogues (Fig. 2).

Chemistry

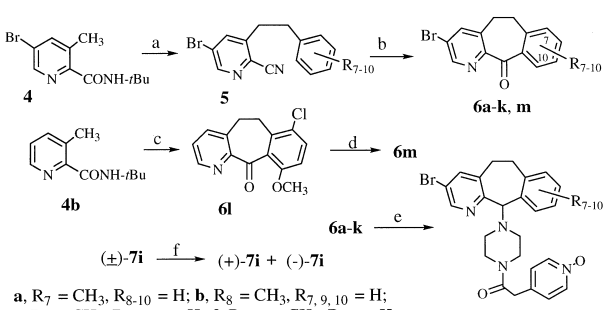
The tricyclic piperazines **7** were synthesised by applying previously described methodology as shown in Scheme 1.[16–21] Thus alkylation of **4** with the appropriate substituted benzyl halide using lithium diisopropylamide (LDA) followed by dehydration of the intermediate *tert*-butylamides with phosphorous oxychloride afforded the nitriles **5**. The tricyclic ketones **6a**–**g** and subsequently,[22] **6h**–**k** were obtained by the electrophilic cyclization of nitriles **5**; cyclization of electron rich substrates such as **5f**–**g** proceeded under mild reaction conditions using $AlCl_3$-dichloroethane, while the cyclization of other substrates required triflic acid,[17] $TiCl_4$-CH_2Cl_2 or $AlCl_3$-fusion[23] conditions. Cyclization of the monosubtituted substrates **5b** and **5f** afforded predominantly the 8-substituted tricyclic ketones **6b** and **6f** while the disubstituted substrates **5h** and **5j** afforded both the regioisomers[24] **6h**, **i** and **6j**, **k**. The 10-methoxy tricyclic ketone **6m** was prepared by applying the same sequence starting with picoline **4b** and 2-Cl-5-OMe-benzylbromide to obtain the 7-chloro tricyclic ketone **6l**. Introduction of the 3-bromo substituent in compound **6l** using the recently described tetrabutylammonium nitrate methodology,[13] followed by hydrogenolysis of the 7-chloro protecting group afforded the tricylic ketone



1 (Sch 44342)
FPT IC_{50} 250 nM

2 (Sch 66336)
FPT IC_{50} 1.9 nM

Figure 1.



a, $R_7 = CH_3$, $R_{8\text{-}10} = H$; **b**, $R_8 = CH_3$, $R_{7,9,10} = H$;
c, $R_9 = CH_3$, $R_{7,8,10} = H$; **d**, $R_{7,10} = CH_3$, $R_{8,9} = H$;
e, $R_{8,10} = CH_3$, $R_{7,9} = H$; **f**, $R_8 = OCH_3$, $R_{7,9,10} = H$;
g, $R_{8,10} = OCH_3$, $R_{7,9} = H$; **h**, $R_8 = OCH_3$, $R_{10} = CH_3$, $R_{7,9} = H$;
i, $R_8 = CH_3$, $R_{10} = OCH_3$, $R_{7,9} = H$; **j**, $R_8 = CH_3$, $R_{10} = Br$, $R_{7,9} = H$;
k, $R_8 = Br$, $R_{10} = CH_3$, $R_{7,9} = H$; **l**, $R_7 = Cl$, $R_{8,9} = H$, $R_{10} = OCH_3$;
m, $R_{7\text{-}9} = H$, $R_{10} = OCH_3$;

Scheme 1. Reagents: (a) i. LDA/THF/−78°C/R-$PhCH_2Br$; ii. $POCl_3$/$PhCH_3$/80°C. (b) i. CF_3SO_3H/rt, or $AlCl_3/CH_2Cl_2$, or $AlCl_2$/150°C; ii. 4N HCL/110°C. (c) i. LDA/THF/−78°C/2-Cl-5-MeO-$PhCH_2Br$; ii. $POCl_3/PhCH_3$/80°C; iii. CF_3SO_3H/rt; iv. 4N HCl/110°C. (d) i. $Bu_4N^+NO_3^-/(CF_3CO)_2O/CH_2Cl_2$/rt; ii. HCO_2NH_4/MeOH/10%Pd-C/reflux; iii. $CuBr_2$/*tert*BuONO/CH_3CN/0°C. (e) i. $NaBH_4$/EtOH; ii. $SOCl_2/CH_2Cl_2$; iii. Piperazine/CH_2Cl_2; iv. EDCI/HOBT/NMM/4-pyridylacetic acid *N*-oxide/DMF. (f) HPLC/ChiralPak AD column.

6m. Compounds **6a**–**k** were converted in four steps to the final piperazines **7a**–**k**. The 8-methyl-10-methoxy compound **7i** was resolved by high-performance liquid chromatography (HPLC) on a ChiralPak AD column to obtain the C_{11}-enantiomers. An improved procedure for preparing the known[16] bromopicoline **4** was developed (Scheme 2); the tetrabutylammonium nitrate methodology[13] for nitration of pyridines, followed by reduction/bromination was applied to introduce the 5-bromo substituent by starting with **4a** to obtain **4**.

Based on the biological activity of the 8-Me-10-OMe and 8-Me-10-Br piperazines **7i** and **7j**, the C_{11}-piperidine analogues **11**–**13** were prepared starting from the tricyclic ketone **6j**, or from the alkylated picoline **5i**, by the application of previously described methodology as shown in Scheme 3.[11,16–21] Thus, addition of *N*-Me-4-piperidinyl Grignard to the ketone **6j** or to the nitrile **5i** followed by acid catalyzed dehydration or cyclization afforded, after *N*-demethylation, the intermediate piperidines **9i**, **9j**, and **10j**. Finally, reduction of the C_{11}-enes **9** with diisobutylaluminum hydride (DIBAL H)[11] afforded the saturated intermediates **14**. EDCI mediated acylation of the piperidines **9**, **10** and **14** provided the desired compounds **11**, **12**, and **13**. The racemates **10**

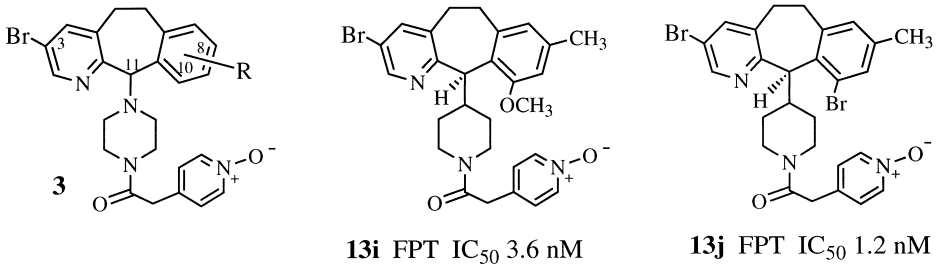
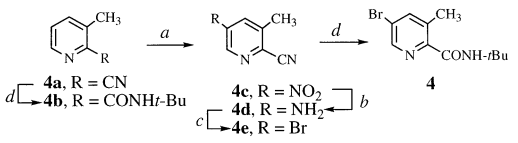
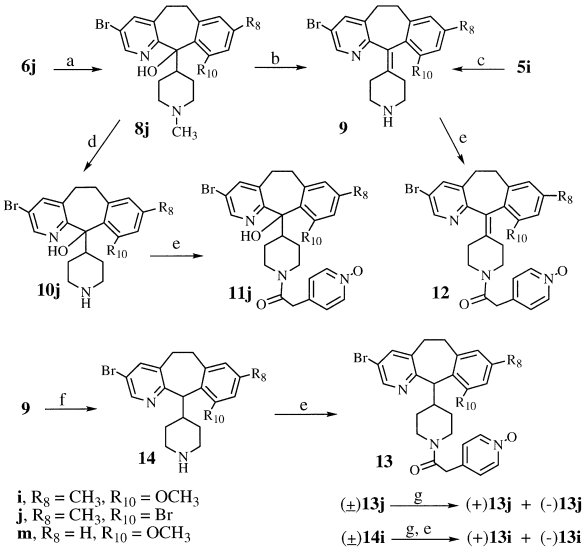


Figure 2.



Scheme 2. Reagents: (a) $Bu_4N^+NO_3^-/(CF_3CO)_2O/CH_2Cl_2$/rt. (b) Fe/$CaCl_2$/EtOH/60°C. (c) $NaNO_2$/HBr/Cu powder/0°C. (d) H_2SO_4/*t*-BuOH.



Scheme 3. Reagents: (a) *N*-Me-4-piperidinyl-MgCl/THF. (b) i. PPA/160°C; ii. $ClCo_2Et/PhCh_3$ 85°C; iii. 4N HCl/130°C. (c) i. *N*-Me-4-piperiddinyl-MgCl/THF; ii. CF_3SO_3H/4°C; iii. $ClCO_2Et/PhCH_3$ 85°C; iv. 4N HCl/130°C. (d) i. $ClCO_2Et/PhCh_3$ 70°C; ii. 4N HCl/110°C. (e) EDCI/HOBT/NMM/4-pyridylacetic acid *N*-oxide/DMF. (f) DIBAL H/$PhCH_3$/rt. (g) HPLC/ChiralPak AD column.

and **14** were resolved by HPLC on a ChiralPak AD column followed by EDCI mediated acylation to afford the C_{11}-enantiomers of compounds **11** and **13**. The 11(*R*) stereochemistry was assigned to the enantiomer of compounds **7i**, **13i**, and **13j** that had an enhanced FPT activity as established previously[11] in the 10-bromo series for **2**. The stereochemistry of the enantiomers of the C_{11}-hydroxy compound **11j** was not assigned.

Biology

In vitro FPT assay results

Compounds **7**–**13** were tested in the in vitro FPT enzyme assay which measures the inhibition of transfer of ^{3}H-farnesyl group from ^{3}H-farnesylpyrophosphate to H-Ras-CVLS. Selected compounds that were active in the FPT enzymatic assay were also evaluated in a cellular H-Ras processing assay (COS cell assay), in an anchorage-independent soft agar growth assay using H-Ras-transformed rodent fibroblasts. Selected FPT-active compounds were tested in the GGPT assay for prenylation selectivity. Details of these assays have been described previously.[10–15] The activities of the compounds in these assays are summarized in Table 1. Test data for two reference halogenated compounds[11,14] **3A** and **3B** are included in the Table.

FPT potency contribution of methyl and methoxy substituents

The initial group of compounds **7a**–**7g** were prepared in order to compare the effect of methyl/methoxy substituents at C_{7-10} on the FPT activity relative to the corresponding halogenated analogues **3A** and **3B**. Introduction of a methyl group at C_7, C_9, or $C_{7,10}$ as in compounds **7a**, **7c**, and **7d** was found to have no significant effect on the potency. The same absence of potency enhancement was observed for a C_8 methoxy substituent as in compound **7f**. An 8-methyl substituent on the other hand, showed a two- to fourfold enhancement in activity relative to a 7- or 9-methyl substituent (compound **7b** versus **7a** and **7c**) and a fivefold enhancement relative to an 8-methoxy group (compound **7b** versus **7f**). A 10-methoxyl group had a marked potency enhancement as seen in compound **7g** versus **7f**. Comparison of the above data with the data for the reference compounds **3A** and **3B** showed that the FPT potency enhancements by an 8-methyl or a 10-methoxy substituent are equivalent to those of a 8-chloro or a 10-bromo substituents, respectively. The above SAR information suggested that disubstituted compounds containing an 8-methyl group and a 10-methoxyl or a 10-bromo substituent would have enhanced potency and hence the analogues **7h**–**7k** were synthesised.

8-Methyl-10-methoxy/bromo compounds

As expected from the SAR of compounds **7a**–**g**, the 10-methoxy and 10-bromo compounds **7i** and **7j** were found to have enhanced activity in the enzymatic assay as well as in the cell based assays, and were more active than the respective regioisomers **7h** and **7k**. The (11*R*)-**7i** enantiomer was found to be a potent FPT inhibitor with an $IC_{50} = 4$ nM. In view of the potencies of compounds **7i** and **7j**, the C_{11}-piperidine analogues were then prepared. The 11*R*-**13j** enantiomer in the 8-methyl-10-bromo series was found to be as active as **2** having an FPT $IC_{50} = 1.2$ nM; the 11*R*-**13i** enantiomer in the 8-methy-10-methoxy series was slightly less potent having an FPT $IC_{50} = 3.6$ nM.

The presence of a C_{11}-hydroxyl group in **11j** did not have an appreciable effect on the potency relative to the C_{11}-H compound **13j**; however, in contrast with the marked difference in potency of the enantiomers of **13j**, there was only a twofold difference in the potency of the enantiomers of **11j**. The C_{11}-ene compounds **12i** and **12j** were slightly less active than the corresponding saturated compounds **13i** and **13j** as racemates. Finally, the 10-methoxy analogue 11*R*-**13m** containing a mono substituted phenyl ring, was found to have considerable potency (FPT $IC_{50} = 9.8$ nM).

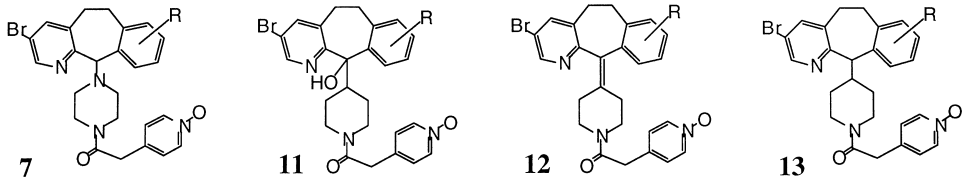
Compounds **7i**, **13i**, and **13j** show good selectivity for FPT versus GGPT and were found to be essentially inactive as GGPT inhibitors showing 3–5% inhibition at 2 μg/mL.

Pharmacokinetic studies

The pharmacokinetic parameters in nude mice were determined for five of the active FPT inhibitors **7f**, **7g**, **7i**, **13i**, and **13j** identified in this study. Details of the methodology used in the pharmacokinetic studies have been described previously.[11,14] The results are given in Table 2.

The 8, 10-dimethoxy compound **7g** had low serum levels po, a low AUC, and was found to be heavily metabolised. The 8,10-dimethyl analogue **7f** on the other hand had a better pharmacokinetic (PK) profile, with higher AUC and serum levels, was orally bioavailable and was not significantly metabolized. The 8-methyl-10-methoxy piperazine analogue **7i**, however, had a reduced serum half-life, and reduced oral bioavailability relative to **7f**,

Table 1.



7 **11** **12** **13**

Entry no.	Type	Substituents *R*	FPT[a] IC_{50} (μM)	COS[a] IC_{50} (μM)	Soft agar[a] IC_{50} (μM) NIHH
7a	7	7-Methyl	0.11		
7b	7	8-Methyl	0.064		
7c	7	9-Methyl	0.28		
7d	7	7,10-Dimethyl	0.13		
7e	7	8,10-Dimethyl	0.043		
7e	7	8-Methoxy	0.29		
7g	7	8,10-Dimethoxy	0.067		
7h	7	8-Methoxy-10-methyl	0.058		
7i (11*RS*)	7	8-Methyl-10-methoxy	0.016	0.014	
7i (−)(11*R*)	7	8-Methyl-10-methoxy	0.0042		0.230
7i (+)(11*S*)	7	8-Methyl-10-methoxy	0.069		
7j	7	8-Methyl-10-bromo	0.0048	0.018	
7k	7	8-Bromo-10-methyl	0.0099	0.063	
11j (±)	11	8-Methyl-10-bromo	0.0050	0.065	0.40
11j (+)	11	8-Methyl-10-bromo	0.010		
11j (−)	11	8-Methyl-10-bromo	0.0054		
12j	12	8-Methyl-10-bromo	0.0054	0.068	> 0.50
12i	12	8-methyl-10-methoxy	0.030		
13j (11*RS*)	13	8-Methyl-10-bromo	0.004	0.012	0.110
13j (+)(11*R*)	13	8-Methyl-10-bromo	0.0012		0.080
13j (−)(11*S*)	13	8-Methyl-10-bromo	43% (0.016)	0.012	0.080
13i (11*RS*)	13	8-Methyl-10-methoxy	0.0032	0.082	
13i (+)(11*R*)	13	8-Methyl-10-methoxy	0.0036	0.011	0.125
13i (−)(11*S*)	13	8-Methyl-10-methoxy	0.220		0.230
13m (+)(11*R*)		10-Methoxy	0.0098	0.019	0.129
3A (11*RS*)	A	8-Chloro	0.045		
3B (11*RS*)	A	8-Chloro-10-bromo	0.002		
3B (11*R*)	A	8-Chloro-10-bromo	0.0018		

[a] For assay see refs 9–14.

Table 2. Pharmacokinetic analysis[a]

	AUC (μgh/mL)		C_{max} (μM)			
Entry	po	iv	po	iv	$t_{1/2}$ (h) serum iv	% oral bioavail.
7g	0.63 (24 h)	5.08 (24 h)	0.96	33		12
7g	17.1 (24 h)	17.62 (24 h)	8.7	22.32	1.6	97
7i	2.37 (24 h)	6.43 (24 h)	5.33	27	0.29	37
13i	0.40 (7 h)	2.7 (7 h)	1.0	17.5	0.20	15
13j	4.5 (6 h)	—	—	—	—	—
2 (Sch 66336)[11]	24.1	—	13	—	—	—

[a] Blood samples were collected at nine time points after a single oral or iv dose of 25 mpk of the compounds administered as solutions of the hydrochloride salts in 20% HPβCD. Three mice were used for each point and quantitation was achieved by LC/MS(CI).

but the overall PK was improved compared to **7g**. Compound **13i** was expected to have an improved PK profile relative to the C_{11}-piperazine analogue **7i**, however, it had a reduced AUC and lower oral bioavailability. The 8-methyl–10-bromo compound **13j** showed a slightly improved AUC po in this series. The data in Table 2 shows that all of these compounds display a poor PK profile as compared to Sch 66336 (**2**).

Conclusions

As part of a study to explore various substituents on the phenyl ring of Sch 66336 (**2**), a small group of compounds **7a**–**7g** was prepared. The SAR developed from this group of compounds identified the 8-methyl and a 10-methoxy substituents as effective equivalents for the halogens at these positions. The novel benzocycloheptapyridines **7i**, **13i**, and **13j** were then synthesised and the 11*R*-enantiomers of these compounds were found to have an in vitro FPT inhibition activity profile comparable to that of **2** in the enzymatic and cellular assays. The compounds are potent and selective inhibitors of FPT with an $IC_{50} = 4.2$, 3.6, 1.2 nM for 11*R*-**7i**, **13i**, **13j**. The pharmacokinetic profile of these compounds, however, was found to be inferior when compared to **2**.

Experimental

Reactions were performed under conventional techniques: employing oven dried glassware, nitrogen atmosphere, and commercial or freshly dried/distilled solvents, and were monitored by thin layer chromatography (TLC) on silica gel plates (Analtech). Extracts of crude reaction products were dried over anhydrous magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4), 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 Gemini 300 MHz spectrometer using $CDCl_3$, CD_3OD or DMSO-d_6 solutions and TMS as internal standard. 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.

5-Bromo-2-cyano-3-picoline (4). Step a: Trifluoroacetic anhydride (85 mL) is added dropwise at 4°C to a solution of **4a** (64 g) and tetrabutylammonium nitrate (184 g) in *t*-butylmethyl ether (650 mL). The mixture is stirred at room temperature for 60 h after which it is neutralized with 20% NaOH, extracted with CH_2Cl_2 and chromatographed on silica gel to afford **4c** that is crystallized from Et_2O (42 g, 57%): mp 74–76°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (s, 3H), 8.49 (d, 1H, $J = 2$ Hz), 9.33 (d, 1H, $J = 2.04$ Hz); MS(CI) *m*/*z* 164 (MH^+). Anal ($C_8H_6N_2O_2$) C, H, N. Step b: A solution of **4c** (2 g) and $CaCl_2$ (0.7 g) in 90% EtOH (60 mL) is stirred with Fe filings (6.2 g) at room temperature for 18 h, filtered and the filtrate is evaporated followed by chromatography on silica gel to afford **4d** (1.4 g, 85%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 4.10 (bs, 2H), 6.79 (s, 1H), 7.93 (s, 1H); MS(CI) *m*/*z* 134 (MH^+). Step c: $NaNO_2$ (10.8 g) is added slowly to a solution of **4d** (17.6 g) in 48% HBr (60 mL) and H_2O (17 mL) at 0°C stirred for 1 h, followed by the addition of Cu powder (1.6 g). After the effervescence subsides, the mixture is heated to reflux for 30 min, cooled, diluted with ice, basified with 50% NaOH, extracted with EtOAc and the product is purified by chromatography to afford **4e** (20.2 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 7.85 (s, 1H), 8.59 (s, 1H); MS(CI) *m*/*z* 197 (MH^+). Step d: A solution of **4e** (0.5 g) in *t*-BuOH (10 mL) is heated to 70°C followed by the dropwise addition of H_2SO_4 (0.4 mL), and after 1 h the mixture is basified with NH_4OH, extracted with EtOAc and the product is purified by chromatography on silica gel (10% acetone–hexane) to afford **4** as an oil (0.58 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.71 (s, 3H), 7.79 (bs, 1H), 7.72 (s, 1H), 8.59 (s, 1H); HRMS (FAB) calcd for $C_{11}H_{16}N_2OBr$ 271.0446, found 271.0447.

General procedure for preparing nitriles 5. To a solution of diisopropylamine (16.3 mmol) in THF (20 mL) at −78°C, 2.5 M BuLi in hexanes (16.3 mmol) is added dropwise. After stirring the mixture for 10 min, a solution of 3-bromo picoline **4** (7.4 mmol) in THF (10 mL) is added. The resulting purple reaction mixture is stirred for 10 min before adding a solution of the substituted benzyl halide (11.1 mmol) in THF (10 mL). The reaction mixture is stirred at −78°C for 15 min, 1 h at 0°C and then at room temperature for 1 h. The pale-burgundy color reaction is diluted with ice/water and extracted with dichloromethane. The crude product is flash chromatographed on silica gel (200 mL). Elution with 10% ethylacetate–hexane affords the benzylated picoline intermediate (5.4 mmol) which is dissolved in toluene (20 mL) followed by the dropwise addition of $POCl_3$ (65.7 mmol). The mixture is heated in an oil bath (115°C). After 1 h a droplet of DMF is added, the solution is heated for an additional 4 h and is then cooled to room temperature before evaporation under reduced pressure. The residual oil is dissolved in ethylacetate (50 mL) and ice/water (20 mL) and stirred while adding 10% sodium hydroxide to pH 8. The basic solution is extracted with ethylacetate, and the crude product is dissolved in ethylacetate and filtered through a silica gel plug. The colorless filtrate is concentrated under reduced pressure and diluted slowly with hexane to afford the nitriles **5a** (crystalline solid, 68%): mp 126–127°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.95 (m, 2H), 3.05 (m, 2H), 7.05–7.20 (m, 4H), 7.70 (d, 1H, $J = 2.04$ Hz), 8.62, (d, 1H, $J = 2.04$ Hz); MS(CI) *m*/*z* 301, 303 (MH^+). Anal. ($C_{15}H_{13}BrN_2$) C, H, N. **5b** (white solid, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.94 (m, 2H), 3.10 (m, 2H), 6.96 (d, 1H), 6.97 (s, 1H), 7.05 (d, 1H), 7.20 (m, 1H), 7.70 (s, 1H), 8.60 (s, 1H); MS(CI) *m*/*z* 301 (MH^+). **5c** (crystalline solid 78%): mp 55–69°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.93 (m, 2H), 3.11 (m, 2H), 7.07 (q, 4H), 7.70 (d, 1H, $J = 2.04$ Hz), 8.60 (d, 1H, $J = 2.1$ Hz); MS(CI) *m*/*z* 301, 303 (MH^+). **5d** (crystalline solid, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 6H), 2.92 (m, 2H), 3.05 (m,

2H), 6.87 (s, 1H), 6.96 (d, 1H, $J=7.95$ Hz), 8.61, (d, 1H, $J=2.1$ Hz). **5e** (crystalline solid): m.p. 153–159°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 6H), 2.88 (t, 2H), 3.10 (t, 2H), 6.77 (s, 2H), 6.88 (s, 1H), 7.70 (d, 1H, $J=2.1$ Hz), 8.60, (d, 1H, $J=2.04$ Hz); MS(CI) m/z 315, 317 (MH^+). Anal. ($C_{16}H_{15}BrN_2$) C, H, N. **5f**: (crystalline solid, 71%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 (t, 2H), 3.13.(q, 2H), 3.79 (s, 3H), 6.72 (m, 3H), 7.22 (q, 1H), 7.71 (d, 1H, $J=2.0$ Hz), 8.60 (s, 1H); MS(CI) m/z 317, 319 (MH^+). **5g** (crystalline solid, 85%): mp 106–107°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 (t, 2H), 3.15 (t, 2H), 3.80 (s, 6H), 6.31 (d, 2H, $J=2.1$ Hz), 6.35 (d, 1H, $J=2.1$ Hz), 7.72 (d, 1H, $J=2.1$ Hz), 8.61 (d, 1H, $J=2.1$ Hz); MS(FAB) m/z 347, 349 (MH^+). Anal. ($C_{16}H_{15}BrN_2O_2$) C, H, N. 5h (crystalline solid, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.90 (m, 2H), 3.12 (m, 2H), 3.78 (s, 3H), 6.51 (s, 1H), 6.57 (s, 1H), 6.61 (s, 1H), 7.71 (d, 1H, $J=2.0$ Hz), 8.60 (d, 1H, $J=2.0$ Hz); MS(CI) m/z 329 (MH^+). **5j** (white solid, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.90 (m, 2H), 3.07 (m, 2H), 6.90 (s, 1H), 7.10 (s, 1H), 7.20 (s, 1H), 7.72 (d, 1H, $J=2.3$ Hz), 8.62 (d, 1H, $J=2.2$ Hz); MS(CI) m/z 379 (MH^+).

General methods to prepare ketones 6

Method A. Aluminum chloride (8 mmol) is added in small lots during 10 min to a well stirred solution of nitrile **5** (8 mmol) in dichloroethane (100 mL). The pale-yellow solution is stirred at room temperature for 1 h and is then worked up by the addition of ice/water and 10% sodium hydroxide to pH 10. The mixture is extracted several times with dichloromethane, and the crude product obtained on evaporation of the combined extracts is flash chromatographed on silica gel (100 mL). Elution with 10% methanol–2% ammonium hydroxide–ethylacetate affords the intermediate imine which is dissolved in 2 N hydrochloric acid (100 mL). The solution is heated in an oil bath (120°C) for 1.5 h, cooled, basified with 10% sodium hydroxide and extracted with dichloromethane (4×50 mL). The crude product is obtained by concentration of the combined extract filtered through a silica gel plug; evaporation of the filtrate affords the ketones **6f** (amorphous solid, 28%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (m, 2H), 3.21 (m, 2H), 3.07 (s, 3H), 6.70 (d, 1H, $J=2.3$ Hz), 6.88 (q, 1H, $J=$ 3.2, 8.9 Hz), 7.78 (d, 1H, $J=1.8$ Hz), 8.19 (d, 1H, $J=$ 8.9 Hz), 8.71 (s, 1H); MS(CI) m/z 318 (MH^+). **6g** (amorphous solid, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (m, 2H), 3.20 (m, 2H), 3.79 (s, 3H), 3.85 (s, 3H), 6.33 (d, 1H, $J=1.8$ Hz), 6.38 (d, 1H, $J=1.8$ Hz), 7.73 (d, 1H, $J=1.8$ Hz), 8.71 (d, 1H, $J=1.8$ Hz); MS(CI) m/z 348 (MH^+). Anal. ($C_{16}H_{14}BrNO_3$) C, H, N.

Method B. A solution of the nitrile **5** (2.64 mmol) in triflic acid (10 mL) is stirred at 60°C for 3 h, the solution is then cooled to 20°C, carefully diluted with ice (20 g) and MeOH (10 mL) followed by refluxing for 24 h. The solution is then cooled, poured into ice (100 g) and basified with 50% NaOH at 0°C. The precipitated white solid is filtered, washed with water, dried and purified by chromatography eluting with 20% EtOAc–hexanes to afford the tricyclic ketones **6j** (white solid, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.11 (m, 2H), 3.18 (m, 2H), 6.98 (s, 1H), 7.36 (s, 1H), 7.74 (s, 1H), 8.74 (s, 1H); MS (CI) m/z 380 (MH^+). **6k** (white solid, 40%): ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.09 (m, 2H), 3.21 (m, 2H), 7.24 (s, 1H), 7.31 (s, 1H), 7.75 (s, 1H), 8.71 (s, 1H); MS(CI) m/z 380 (MH^+). **6l** ^{1}H NMR ($CDCl_3$): (8.79 (d, $J=5.6$ Hz, 1H), 7.58 (d, $J=7.5$ Hz, 1H), 7.43–7.33 (m, 2H), 7.79 (d, $J=7.5$, 1H), 3.80 (s, 3H), 3.35–3.28 (m, 2H), 3.24–3.16 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 195.1, 123.1, 131.7, 155.5, 148.6, 139.6, 136.7, 136.6, 132.5, 126.2, 123.9, 111.8, 56.57, 32.33, 28.29; MS(FAB) m/z 274 (MH^+).

Method C. A mixture of nitrile **5** (2.5 mmol) and $AlCl_3$ (8.5 mmol) is homogenized with a glass rod and then heated in an oil bath at 180°C for 1 to 2 min. The mixture is then cooled to room temperature, treated with 4 N HCl and the solution is refluxed for 16 h. Basification with 4 N NaOH, extraction with CH_2Cl_2 followed by purification by chromatography affords the tricyclic ketones **6a** (crystalline solid, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.15 (s, 4H), 7.26 (m, 3H), 7.35 (s, 1H), 7.78 (s, 1H), 8.67 (s, 1H); MS(CI) m/z 302, 304 (MH^+). Anal. ($C_{15}H_{12}NOBr$) C, H, N. **6b**: (pale-yellow solid, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.17 (m, 4H), 7.05 (s, 1H), 7.20 (d, 1H, $J=8$ Hz), 7.79 (s, 1H), 8.03 (d, 1H, $J=8$ Hz), 8.72 (s, 1H); MS(CI) m/z 302 (MH^+). **6c** (crystalline solid, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.14 (m, 2H), 3.21 (m, 2H), 7.13 (d, 1H, $J=7.7$ Hz), 7.28 (d, 1H, $J=7.9$ Hz), 7.79 (s, 1H), 7.78 (s, 1H), 7.86 (s, 1H), 8.72 (d, 1H, $J=2.0$ Hz); MS(CI) m/z 302, 304 (MH^+). Anal. ($C_{15}H_{12}NOBr$) C, H, N. **6d** (crystalline solid, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.35 (s, 3H), 3.14 (m, 2H), 3.21 (m, 4H), 7.01 (d, 1H, $J=7.7$ Hz), 7.14 (d, 1H, $J=7.7$ Hz), 7.72 (d, 1H, $J=1.8$ Hz), 8.67 (d, 1H, $J=2$ Hz); MS(CI) m/z 316, 318 (MH^+). Anal. ($C_{16}H_{14}NOBr$) C, H, N. **6e** (crystalline solid, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 6H), 3.09 (m, 2H), 3.17 (m, 2H), 6.87 (s, 3H), 6.96 (s, 3H), 7.73 (d, 1H, $J=2.1$ Hz), 8.70 (d, 1H, $J=1.9$ Hz); MS(FAB) m/z 316, 318 (MH^+). Anal. ($C_{16}H_{14}NOBr$) C, H, N.

Method D. A suspension of **5i** (0.93 g) in $TiCl_4$ (6 mL) is heated at 100°C for 15 min; the resulting dark solution is then cooled, carefully diluted with ice, basified with NaOH and extracted with CH_2Cl_2. The crude imine intermediate is then hydrolyzed at 140°C in 4 N HCl (50 mL) for 7 h, basified with NaOH followed by extraction with CH_2Cl_2 and chromatography on silica-gel to afford **6h** (crystalline solid, 60%): mp 116–117°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.09 (m, 2H), 3.21 (m, 2H), 3.83 (s, 3H), 6.57 (d, 1H, $J=2.2$ Hz), 6.66 (d, 1H, $J=2.0$ Hz), 7.74 (s, 1H), 8.71 (d, 1H, $J=1.9$ Hz); MS(CI) m/z 332, 334 (MH^+) and **6i** (solid, 12%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.06 (m, 2H), 3.17 (m, 2H), 3.79 (s, 3H), 6.62 (s, 1H), 6.65 (s, 1H), 7.61 (s, 1H), 8.57 (s, 1H); MS(CI) m/z 332, 334 (MH^+).

Ketone 6m. Step i: TFAA (5.42 mL, 1.05 equiv) is added dropwise to **6l** (10.0 g, 36.53 mmol) and $Bu_4N^+NO_3^-$ (12.8 g, 1.1 equiv) in CH_2Cl_2 (100 mL) at 0°C. The

resulting solution is warmed to room temperature over 3 h and stirred overnight. The reaction mixture is then diluted with 1 N NaOH until basic and extracted with CH_2Cl_2 (3×100 mL). The crude product is purified by flash chromatography using a 1% acetone in CH_2Cl_2 solution as eluent to give the 3-nitro-8-chloro ketone as a yellow solid (5.22 g, 45% yield). ^{1}H NMR ($CDCl_3$) δ 9.40 (d, J=3.75 Hz, 1H), 8.39 (d, J=3.75 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 6.84 (d, J=7.5 Hz, 1H), 3.83 (d, J=7.5 Hz, 4H), 3.36 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 193.4, 157.5, 155.1, 148.3, 143.1, 139.0, 135.6, 133.9, 132.8, 130.1, 125.7, 111.7, 56.25, 31.63, 27.64; MS(FAB) m/z 319 (MH^+). Step ii: 10% Pd/C (0.5 g) is added to the 3-nitro-8-chloro ketone from step i (5.00 g, 15.69 mmol) in MeOH (200 mL) followed by HCO_2NH_4 (9.9 g, 10 equiv). The resulting solution is heated at reflux 3 h. The reaction mixture is cooled and additional HCO_2NH_4 (9.9 g, 10 equiv) is added and the solution is heated at reflux overnight. The reaction mixture is cooled, filtered through a plug of Celite and concentrated in vacuo. The residue is diluted with CH_2Cl_2 (250 mL) and H_2O (250 mL), separated and the aqueous layer is extracted with CH_2Cl_2. The crude product is purified by flash chromatography using a 10% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to give the 3-amino ketone as a tan solid (3.44 g, 86% yield). ^{1}H NMR ($CDCl_3$) δ 8.10 (d, J=3.75 Hz, 1H), 7.33–7.26 (m, 2H), 6.85–6.75 (m, 1H), 6.66 (d, J=3.75 Hz, 1H), 4.16 (bs, 2H), 3.78 (s, 3H), 3.10–2.95 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 194.0, 157.0, 144.5, 140.0, 138.9, 136.2, 131.2, 130.1, 121.0, 119.4, 109.9, 55.84, 34.31, 32.34; FABMS m/z 255 (MH^+). Step iii: A solution of the 3-amino ketone from step ii (2.50 g, 9.83 mmol) in CH_3CN (50 mL) is added to a solution of Cu(II)Br (2.64 g, 1.2 equiv) and *tert*-BuONO (1.75 mL, 1.5 equiv) in CH_3CN (40 mL) at 0°C. The resulting solution is warmed slowly to room temperature over 2 h and stirred overnight. The reaction mixture is then diluted with 1 N HCl, neutralized with 20% NH_4OH and extracted with EtOAc (3×75 mL). The crude product is purified by flash chromatography using 50% EtOAc–hexanes solution as eluent to give **6m** as a white solid (2.7 g, 87% yield). ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1H), 7.71 (s, 1H), 7.33 (t, J=7.5 Hz, 2H), 6.83 (d, J=7.5 Hz, 1H), 6. 80 (d, J=7.5 Hz, 1H), 3.79 (s, 3H), 3.22–3.15 (m, 2H), 3.12–3.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 194.8, 156.8, 151.7, 149.2, 141.0, 139.3, 138.1, 132.0, 129.4, 122.9, 119.7, 110.1, 55.91, 33.41, 31.66; MS (EI) m/z 318 (M^+).

General procedure for preparing compounds 7. Step i: Sodium borohydride (2.3 mmol) is added in portions with stirring, to a solution of tricyclic ketone **6** (2.3 mmol) in methanol (20 mL) at 0°C. The reaction is then stirred at room temperature for 1 h, and worked up by acidification with AcOH–water followed by evaporation, basification with 10% NaOH and extraction with ethylacetate (4×50 mL). The combined extract is filtered through a plug of silica gel and the filtrate is evaporated to afford the intermediate alcohol. Steps ii–iii: A solution of the alcohol from step i (1.43 mmol) in toluene (5 mL) is cooled to 15°C and treated with $SOCl_2$ (7.2 mmol) in toluene (5 mL). The heterogeneous mixture is stirred at room temperature for 2 h followed by evaporation under reduced pressure. The oily residue is dissolved in CH_3CN (8 mL). Piperazine (5.7 mmol) is then added, the solution is stored at room temperature for 24 h and then worked-up by evaporating under reduced pressure, diluting with water, and basifying with 10% NaOH (5 mL). The product is extracted with dichloromethane (5×20 mL) and purified by flash chromatography on silica gel (10% methanol–2% ammonium hydroxide–dichloromethane) to afford the C_{11}-piperazine intermediate. Step iv: A solution of the C_{11}-piperazine intermediate (0.48 mmol), 1-hydroxybenzotriazole (0.96 mmol) and 4-pyridyl acetic acid *N*-oxide (0.96 mmol) in DMF (3.0 mL) is cooled in ice and treated with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (0.96 mmol) followed by *N*-methyl morpholine (2.9 mmol). The mixture is allowed to warm to room temperature overnight and is then evaporated under reduced pressure. The residual gum is stirred with 10% sodium carbonate and extracted with dichloromethane. The crude product obtained by evaporation of the extract is flash chromatographed on silica gel (30 mL). Elution with 5% methanol–2% ammonium hydroxide–dichloromethane affords the following compounds.

1-(3-Bromo-6,11-dihydro-7-methyl-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)piperazine N1-oxide (7a). Pale-tan foam (89%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (m, 2H), 2.29 (s, 3H), 2.81 (m, 2H), 3.38 (s, 2H), 3.56 (s, 2H), 3.63 (s, 2H), 3.86 (m, 1H), 4.00 (m, 1H), 4.36 (s, 1H), 7.03 (m, 3H), 7.12 (s, 1H), 7.60 (d, 1H, J=2.0 Hz), 8.13 (s, 1H), 8.16 (s, 1H), 8.37 (d, 2H, J=2.0 Hz); HRMS(FAB) calcd for $C_{26}H_{27}N_4O_2Br$ 507.1396, found 507.1380 (MH^+).

1-(3-Bromo-6,11-dihydro-8-methyl-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)piperazine N1-oxide (7b). Pale-tan foam (70%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (m, 2H), 2.28 (s, 3H), 2.38 (m, 2H), 2.77 (m, 2H), 3.40 (bs, 2H), 3.56 (bs, 2H), 3.64 (s, 2H), 3.80 (m, 1H), 4.00 (m, 1H), 4.33 (s, 1H), 6.94 (s, 2H), 7.13 (s, 1H), 7.14 (d, 2H, J=5.5 Hz), 7.58 (s, 1H), 8.14 (d, 1H, J=5.4 Hz), 8.35 (s, 1H); MS(FABS) m/z 507 MH^+).

1-(3-Bromo-6,11-dihydro-9-methyl-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)piperazine N1-oxide (7c). Pale-tan foam (84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (m, 2H), 2.28 (s, 3H), 2.36 (m, 2H), 2.78 (m, 2H), 3.37 (bs, 2H), 3.56 (bs, 2H), 3.64 (s, 2H), 3.82 (m, 1H), 4.01 (m, 1H), 4.29 (s, 1H), 7.04 (s, 2H), 7.13 (s, 1H), 7.15 (s, 1H), 7.27 (s, 1H), 7.58 (d, 1H, J=1.9 Hz), 8.14 (s, 1H), 8.16 (s, 1H), 8.36 (d, 1H, J=2.0 Hz); HRMS(FAB) calcd for $C_{26}H_{28}N_4O_2Br$ 507.1396, found 507.1395 (MH^+). Anal. ($C_{26}H_{27}N_4O_2Br$ (0.8H2O) C, H, N.

1-(3-Bromo-6,11-dihydro-7,10-dimethyl-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)piperazine N1-oxide (7d). Pale-tan foam (76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.39 (s, 3H), 2.45 (m, 5H), 2.85 (q, 2H), 3.40 (s, 2H), 3.49 (s, 2H), 3.64 (s, 2H), 4.53 (m, 1H), 4.92 (s, 1H), 6.91 (d, 2H), 7.05 (d, 1H),

7.14 (s, 1H), 7.16 (s, 1H), 7.55 (s, 1H), 8.15 (s, 1H), 8.16 (s, 1H), 8.37 (s, 1H); HRMS(FAB) calcd for $C_{27}H_{30}N_4O_2Br$ 521.1552, found 521.1531 (MH^+).

1-(3-Bromo-6,11-dihydro-8,10-dimethyl-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)piperazine N1-oxide (7e). Pale-tan foam (49%); mp 117–129°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.38 (s, 3H), 2.46 (m, 4H), 2.62 (m, 1H), 2.90 (m, 1H), 3.43 (m, 4H), 3.65 (s, 3H), 4.50 (m, 1H), 4.85 (s, 1H), 6.84 (s, 2H), 7.14 (s, 1H), 7.16 (s, 1H), 7.54 (d, 1H, $J=1.7$ Hz), 8.14 (s, 1H), 8.16 (s, 1H), 8.35 (d, 1H, $J=1.9$ Hz); HRMS(FAB) calcd for $C_{27}H_{30}N_4O_2Br$ 521.1552, found 521.1536 (MH^+).

1-(3-Bromo-6,11-dihydro-8-methoxy-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)piperazine N1-oxide (7f). Pale-tan foam (84%); mp 104–111°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (m, 2H), 2.37 (m, 2H), 2.77 (m, 2H), 3.38 (s, 2H), 3.55 (m, 2H), 3.64 (s, 2H), 3.79 (s, 3H), 4.03 (m, 1H), 4.30 (s, 1H), 6.68 (m, 2H), 7.14 (m, 2H), 7.59 (d, 1H, $J=2.0$ Hz), 8.14 (s, 1H), 8.36 (d, 1H, $J=2.2$ Hz); HRMS(FAB) calcd for $C_{26}H_{28}N_4O_3Br$ 523.1345, found 523.1333 (MH^+).

1-(3-Bromo-6,11-dihydro-8,10-dimethoxy-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)piperazine N1-oxide (7g). Pale-tan foam; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 6H), 5.17 (s, 1H), 6.29, 6.30 (s, 2H), 7.13 (d, 2H, $J=6.8$ Hz), 7.57 (s, 1H), 8.14 (d, 2H, $J=6.8$ Hz) 8.37 (d, 1H, $J=1.7$ Hz); HRMS(FAB) calcd for $C_{27}H_{29}N_4O_4Br$ 553.1450, found 553.1430 (MH^+).

1-(3-Bromo-6,11-dihydro-8-methoxy-10-methyl-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)-piperazine N1-oxide (7h). Tan solid (67%); mp 85–105°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (m, 2H), 2.39 (s, 3H), 2.43 (m, 2H), 2.60 (m, 1H), 2.90 (m, 1H), 3.33 (m, 4H), 3.64 (s, 2H), 3.76 (s, 3H), 4.51 (m, 1H), 4.80 (s, 1H), 6.56 (m, 2H), 7.13 (s, 1H), 7.15 (s, 1H), 7.54 (s, 1H), 8.13 (s, 1H), 8.16 (s, 1H), 8.35 (d, 1H, $J=2.2$ Hz); HRMS(FAB) calcd for $C_{27}H_{30}N_4O_3Br$ 537.1501, found 537.1502 (MH^+).

1-(3-Bromo-6,11-dihydro-8-methyl-10-methoxy-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl) piperazine N1-oxide (7i). Tan solid (quant); mp 80–105°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.41 (m, 2H), 2.74 (m, 2H), 3.35 (m, 2H), 3.63 (s, 2H), 3.79 (s, 3H), 4.08 (m, 1H), 5.23 (s, 1H), 6.56 (s, 1H), 6.58 (s, 1H), 7.13 (s, 1H), 7.15 (s, 1H), 7.56 (d, 1H, $J=2.1$ Hz), 8.13 (s, 1H), 8.15 (s, 1H), 8.37 (d, 1H, $J=2.2$ Hz); HRMS(FAB) calcd for $C_{27}H_{30}N_4O_3Br$ 537.1501, found 537.1512 (MH^+).

Compound (±)-**7i** is resolved by HPLC using a ChiralPak AD 5 (50 cm column (Daicel Chemical) using 30% hexane–0.2% Et_2NH-*i*-PrOH as the eluting solvent. The first peak eluted affords (−)-**7i** as a pale-tan foam $[\alpha]_D^{20}-18.8°$ (*c* 0.3, EtOH), and the second peak affords (+)-**7i** as a pale-tan foam $[\alpha]_D^{20}+19.6°$ (*c* 0.29, EtOH).

1-(3-Bromo-6,11-dihydro-8-methyl-10-bromo-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)-piperazine N1-oxide (7j). Tan solid (69%); mp 101–115°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.40 (m, 5H), 2.64 (m, 1H), 2.88 (m, 1H), 3.64 (s, 2H), 4.53 (m, 1H), 5.30 (s, 1H), 5.34 (s, 1H), 6.94 (s, 1H), 7.13 (s, 1H), 7.15 (s, 1H), 7.28 (s, 1H), 7.56 (d, 1H, $J=1.9$ Hz), 8.13 (s, 1H), 8.15 (s, 1H), 8.42 (d, 1H, $J=2.1$ Hz); HRMS(FAB) calcd for $C_{26}H_{27}N_4O_2Br$ 587.0480, found 587.0465 (MH^+).

1-(3-Bromo-6,11-dihydro-8-bromo-10-methyl-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-4-(4-pyridinylacetyl)-piperazine N1-oxide (7k). Tan solid (92%); mp 97–100°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 2H), 2.39 (s, 3H), 2.62 (m, 1H), 3.91 (m, 1H), 3.40 (m, 3H), 3.64 (s, 2H), 4.56 (m, 1H), 4.83 (s, 1H), 4.85 (s, 1H), 7.13 (s, 1H), 7.15 (s, 1H), 7.18 (s, 1H), 7.40 (d, 1H, $J=1.9$ Hz), 8.13 (s, 1H), 8.15 (s, 1H), 8.27 (d, 1H, $J=2.1$ Hz); HRMS(FAB) calcd for $C_{26}H_{27}N_4O_2Br$ 587.0480, found 587.0490 (MH^+).

4-(3,10-Dibromo-8-methyl-11-hydroxy-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11*RS*-yl)-1-methylpiperidine (8j). A 0.8 M solution of 1-methyl-4-piperidyl magnesium chloride in THF (13.2 mL) is added dropwise to a solution of compound **6j** (1.6 g) in THF (30 mL) at ice-bath temperature and after 30 min is then diluted with ice/water followed by extraction with CH_2Cl_2 and purification by chromatography; elution with 10% MeOH–3% NH_4OH–CH_2Cl_2 affords **8j**. ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (m, 4H), 2.21 (s, 3H), 2.29 (s, 3H), 2.31 (m, 2H), 2.75 (m, 1H), 2.7–3.1 (m, 4H), 3.40 (m, 1H), 3.60 (m, 1H), 6.83 (s, 1H), 6.85 (s, 1H), 7.43 (s, 1H), 7.61 (s, 1H), 8.42 (s, 1H); (HRMS) (FABS) calcd for $C_{21}H_{25}N_2O(81)Br(79)Br$ 481.0313, found 481.0320.

4-(3-Bromo-10-methoxy-8-methyl-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (9i). Steps i–ii: A 0.5 M solution of 1-methyl-4-piperidyl magnesium chloride in THF (28 mL) is added dropwise to a solution of compound **5i** (4.8 g) in THF (60 mL) under argon. The dark color reaction is heated at 55°C for 15 min, cooled in an ice bath, quenched with water and the intermediate imine is isolated by extraction with ethylacetate (4×50 mL) and hydrolyzed in 4 N HCl (40 mL) and methanol (20 mL) on the steam bath for 1 h. The resulting ketone is isolated after adding 10% NaOH to pH 8 followed by extraction with ethylacetate. Step iii: The crude product is purified by flash chromatography using 10% ethylacetate–hexane and cyclized by dissolving in triflic acid (55 mL) and storing the solution at 4°C overnight. The reaction mixture is worked up by pouring on ice, basifying with 50% NaOH, followed by extraction with dichloromethane (3×50 mL). The crude product is flash chromatographed on silica gel. Elution with 5% methanol–dichloromethane affords the *N*-*Me*-**9i** (1.37 g, 30%); MS *m*/*z* 413 (MH^+). Step iv: A solution of $ClCO_2Et$ (1.5 mL) in toluene (20 mL) is added dropwise during 10 min with stirring to a solution of the *N*-*Me*-**9i** (1.3 g) and Et_3N (0.9 mL) in toluene (30 mL) and the mixture is

heated in an oil bath at 85°C for 45 min, followed by quenching with ice/water–10% Na_2CO_3. The crude product is isolated by extraction with EtOAc and is purified by flash chromatography to afford the *N*-CO_2Et-**9i**; MS *m*/*z* 473 (MH^+). Step v: A solution of the *N*-CO_2Et-**9i** (0.5 g) in 4 N HCl (20 mL) is heated in an oil bath at 130°C for 14 h, is then cooled, basified with 50% NaOH, extracted with CH_2Cl_2 followed by evaporation of the extract to afford the free amine **9i** as a pale-tan powder (88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (m, 4H), 2.31 (s, 3H), 2.40 (m, 2H), 2.70 (m, 3H), 2.85 (m, 1H), 3.25 (m, 1H), 3.05 (m, 2H), 3.38 (m, 2H), 3.76 (s, 3H), 6.57 (s, 1H), 6.65 (s, 1H), 7.49 (d, 1H, J = 2.0 Hz), 8.44 (d, 1H, J = 2.0 Hz); HRMS (FABS) calcd for $C_{21}H_{24}N_2OBr$ 399.1072, found 399.1088.

4-(3,10-Dibromo-8-methyl-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine (9j). Step i: A solution of **8j** (2.4 g, 5.02 mmol) in PPA (20 g) is stirred at 160°C for 30 min. The reaction is poured onto ice (200 g), basified with 10% NaOH, and extracted with EtOAc (2×200 mL). The organic extracts are combined, dried over $MgSO_4$, filtered and the solvent is evaporated to yield 4-(3,10-dibromo-8-methyl-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-methylpiperidine as a light-tan solid (2.0 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.48 (s, 1H), 7.27 (s, 1H), 6.98 (s, 1H), 3.45 (m, 1H), 3.25 (m, 1H), 2.6–3.0 (m, 4H), 2.40 (s, 3H), 2.20 (s, 3H), 2.20-2.60 (m, 4H), 1.6–1.9 (m, 2H), 1.30 (m, 1H); HRMS (FABS) calcd for $C_{21}H_{23}N_2Br_2$ 463.0207, found 463.0206. Step ii: Ethyl chloroformate (0.70 mL, 7.39 mmol) in toluene (3 mL) is added dropwise to a preheated solution of the olefin from step i (1.7 g, 3.69 mmol) and triethylamine (0.80 mL, 5.75 mmol) in toluene (20 mL) at 80°C. The solution is stirred at 80°C for 1 h, cooled to 0°C, diluted with water (50 mL) and 10% NaOH (20 mL) followed by extraction with EtOAc. The crude product is chromatographed on silica gel eluting with 30% EtOAc–hexanes to yield 4-(3,10-dibromo-8-methyl-5,6-dihydro-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidine ethylcarbamate as a white solid (1.7 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H), 2.0–2.1 (m, 1H), 2.29 (s, 3H), 2.31 (m, 1H), 2.5–3.0 (m, 4H), 3.1–3.5 (m, 4H), 3.80 (m, 2H), 4.1 (q, 2H), 6.99 (s, 1H), 7.28 (s, 1H), 7.50 (s, 1H), 8.50 (s, 1H); MS(EI) *m*/*z* 519. Step iii: A solution of the carbamate from step ii (1.6 g, 3.08 mmol) in concd HCl (10 mL) is stirred at 80°C overnight, then cooled, and poured onto ice (50 g). The mixture is basified with 10% NaOH, then extracted with CH_2Cl_2 (3×100 mL). The organics are combined, dried ($MgSO_4$), filtered and solvent evaporated to yield **9j** as a white solid (1.3 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (m, 1H), 2.28 (s, 3H), 2.31 (m, 1H), 2.45 (m, 2H), 2.75 (m, 3H), 2.90 (m, 2H), 3.15 (m, 2H), 3.25 (m, 2H), 6.98 (s, 1H), 7.27 (s, H), 7.49 (s, 1H), 8.49 (s, 1H); MS(EI) *m*/*z* 447.

(±)4-(3,10-Dibromo-8-methyl-11-hydroxy-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11*RS*-yl)-piperidine (10j). Demethylation of **8j** using the procedure described for **9i** (steps iv–v) affords **10j** as a white solid (190 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (m, 1H), 1.4–1.7 (m, 3H), 2.20 (s, 3H), 2.32 (m, 1H), 2.45 (m, 2H), 2.81 (m, 1H), 3.05 (m, 3H), 3.41 (m, 1H), 3.66 (m, 1H), 6.84 (s, 1H), 6.86 (s, 1H), 7.41 (s, 1H), 7.61 (s, 1H), 8.41 (s, 1H); HRMS (FABS) calcd for ($C_{20}H_{23}Br_2N_2O$) 465.0177, found 465.0170.

(±)4-(3,10-Dibromo-8-methyl-11-hydroxy-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11*RS*-yl)-1-(4-pyridinylacetyl)-piperidine-N1-oxide (11j). Acylation of (±)-**10j** as described for compounds **7** (step v) affords (±)-**11j** as a white solid (60 mg, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.0 (m, 1H), 1.50 (m, 2H), 1.75 (m, 1H), 2.21 (s, 3H), 2.45 (m, 1H), 2.95 (m, 4H), 3.35 (m, 1H), 3.61 (s, 1H), 3.64 (s, 2H), 3.85 (m, 1H), 4.60 (m, 1H), 6.88 (s, 1H), 6.94 (s, 1H), 7.13 (d, 2H, J = 5.3 Hz), 7.42 (s, 1H), 7.64 (s, 1H), 8.13 (d, 2H, J = 6.7 Hz), 8.43 (s, 1H); HRMS (FABS) calcd for $C_{27}H_{28}N_3O_3Br_2$ 602.0477, found 602.0483. (±)-**11j** is resolved into its component enantiomers on Chiralpak AD column eluting with 30% isopropanol–hexanes containing 0.2% diethylamine. The (+)-**11j** enantiomer $[\alpha]_D^{20}$ + 10.4° (*c* 0.12, EtOH), and the the (−)-**11j** enantiomer $[\alpha]_D^{20}$ −7.3° (*c* 0.13, EtOH), are obtained as a off-white powders.

4-(3-Bromo-8-methyl-10-methoxy-6,11-dihydro-5*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinyl-acetyl)-piperidine N1-oxide (12i). Acylation of **9i** as described for compounds **7** (step v) affords **12i** as a white solid (77%): mp 108–115°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (m, 1H), 2.31 (m, 2H), 2.32 (s, 3H), 2.67 (m, 2H), 2.87 (t, 1H), 3.33 (m, 4H), 3.69 (s, 1H), 3.71 (s, 1H), 3.76 (s, 3H), 6.59 (s, 1H), 6.67 (s, 1H), 7.17 (t, 2H), 7.51 (s, 1H). 8.14 (t, 2H), 8.44 (s, 1H); (HRMS) (FAB) calcd for $C_{28}H_{29}N_3O_3Br$ 534.1392, found 534.1395.

4-(3,10-Dibromo-8-methyl-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)-piperidine N1-oxide (12j). Acylation of **9j** as described for compounds **7** (step v) affords **12j** as a tan powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0 (m, 2H), 2.33 (s, 3H), 2.37 (m, 2H), 2.60–2.90 (m, 3H), 3.3–3.5 (m, 3H), 3.69 (s, 1H), 3.71 (s, 2H), 4.0 (m, 1H), 7.0 (s, 1H), 7.18 (m, 2H, rotamers), 7.28 (s, 1H), 7.51 (s, 1H), 8.14 (d, 2H, J = 7 Hz), 8.50 (m, 1H, rotamers); HRMS (FAB) calcd for $C_{27}H_{26}N_3O_2Br_2$ 584.0371, found 584.0373.

(±)4-(3-Bromo-8-methyl-10-methoxy-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11*RS*-yl)-1-(4-pyridinyl-acetyl)piperidine N1-oxide (13i). Acylation of (±)-**14i** as described for compounds **7** (step v) affords (±)-**13i** as a tan powder (74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 2H), 2.78, 2.30 (s, 3H, rotamers), 2.53 (t, 1H), 2.87 (m, 3H), 3.29 (m, 1H), 3.49 (m, 1H), 3.64 (s, 2H), 3.77, 3.78 (s, 3H, rotamers), 4.50 (t, 1H), 4.82 (q, 1H), 6.58 (s, 2H), 7.14 (d, 2H, J = 7 Hz), 7.53 (s, 1H), 8.15 (d, 2H), 8.39 (d, 1H, J = 2.2 Hz); HRMS (FAB) calcd for $C_{28}H_{31}N_3O_3Br$ 536.1549, found 536.1560.

(−)4-(3-Bromo-8-methyl-10-methoxy-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11*S*-yl)-1-(4-pyridinyl-acetyl)piperidine N1-oxide (13i). Acylation of (−)-**14i** as described for compounds **7** (step v) affords (−)-**13i**: $[\alpha]_D^{20}$ −31.6° (*c* 0.3, EtOH). (+)4-(3-Bromo-8-methyl-10-

methoxy-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]-pyridin-11*R*-yl)-1-(4-pyridinylacetyl)piperidine N1-oxide (+)-**13i**: Acylation of (+)-**14i** as described for compounds **7** (step v) affords (+)-**13i**: $[\alpha]_D^{20}+31.9°$ (*c* 0.28, EtOH).

(±)4-(3,10-Dibromo-8-methyl-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11*RS*-yl)-1-(4-pyridinylacetyl)-piperidine N1-oxide (13j). Standard acylation conditions on **14j** furnishes (±)-**13j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4 (m, 3H), 2.27 (s, 3H), 2.48 (m, 2H), 2.6–3.0 (m, 4H), 3.25 (m, 1H), 3.55 (m, 1H), 3.65 (s, 2H), 3.75 (m, 1H), 4.55 (m, 1H), 4.90 (d, H, $J=10.3$ Hz), 6.94 (s, 1H), 7.15 (d, 2H, $J=4$ Hz), 7.31 (s, 1H), 7.53 (s, 1H), 8.14 (d, 2H, $J=4$ Hz), 8.43 (s, 1H); HRMS (FAB) calcd for $C_{27}H_{28}N_3O_2Br_2$ 586.0528 found, 586.0511.

(±)-**13j** is resolved into its component enantiomers on Chiralpak AD column eluting with 30% isopropanol–hexanes containing 0.2% diethylamine. The (−)-**13j** enantiomer $[\alpha]_D^{20}-47.5°$ (*c* 0.21, EtOH), and the (+)-**13j** enantiomer $[\alpha]_D^{20}+36.2°$ (*c* 0.13, EtOH), are obtained as off-white powders.

(+)4-(3-Bromo-10-methoxy-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11*R*-yl)-1-(4-pyridinylacetyl)-piperidine N1-oxide (13m). Standard acylation conditions on **14m** furnish **13m** as a tan powder: mp 128–131°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10–1.63 (m, 5H), 2.25–2.56 (m, 2H), 2.77–3.03 (m, 4H), 3.23–3.35 (m, 1H), 3.45–3.85 (m, 5H), 4.43–4.58 (m, 1H), 4.85–4.93 (m, 1H), 6.74 (d, 2H, $J=7.5$ Hz), 7.10–7.17 (m, 3H), 7.63 (m, 1H), 8.10–8.18 (m, 2H), 8.40 (m, 1H); MS(ES) *m*/*z* 522 (MH^+); $[\alpha]_D^{20}+51.7°$ (*c* 0.21, EtOH). Anal. ($C_{27}H_{28}N_3O_2Br$ (1.4 H_2O), C, H, N.

(±)4-(3-Bromo-10-methoxy-8-methyl-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11*RS*-yl)-piperidine (14i). A 1 M solution of diisobutylaluminumhydride in toluene (4.8 mL) is added dropwise with stirring to a solution of **9i** (0.45 g) in dry toluene (10 mL) at 15°C. The reaction mixture is stirred at room temperature for 2 h and is then quenched by addition of water (10 mL) and 10% sodium hydroxide. The mixture is extracted with dichloromethane and the crude product is chromatographed on silica gel (30 mL). Elution with 10% methanol–2% ammonium hydroxide–dichloromethane affords compound (±)-**14i** (42% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (m, 3H), 2.20 (m, 3H), 2.29 (s, 3H), 2.45 (t, 2H), 2.83 (m, 2H), 3.02 (t, 2H), 3.22 (m, 1H), 3.52 (m, 1H), 3.78 (s, 3H), 4.82 (d, 1H, $J=10.5$ Hz), 6.57 (s, 2H), 7.51 (d, 1H, $J=2.2$ Hz), 8.39 (d, 1H, $J=2.2$ Hz); HRMS (FAB) calcd for $C_{21}H_{26}N_2O_2Br$ 401.1228 found, 401.1230.

Compound (±)-**14i** (0.58 g) is resolved by HPLC using a ChiralPak AD 5×50 cm column (Daicel Chemical) and 25% *i*-PrOH–hexane–0.2% Et_2NH as the eluting solvent. The first peak affords (+)-**14i** (0.26 g) as a pale-yellow foam $[\alpha]_D^{20}+2.7°$ (*c* 0.26, EtOH), followed by elution of the second peak to afford (−)-**14i** (0.23 g) as a pale-yellow foam $[\alpha]_D^{20}-4.74°$ (*c* 0.4, EtOH).

(±)4-(3,10-Dibromo-8-methyl-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11*RS*-yl)-piperidine (14j). A 1 M DIBAL H solution in toluene (2 mL, 2 mmol) is added to a solution of **9j** (280 mg, 0.627 mmol) in toluene (3 mL) at 0°C, then stirred overnight at room temperature. Water (25 mL) and 10% NaOH are added, and the mixture is extracted with CH_2Cl_2 (3×80 mL). The crude product is chromatographed on silica gel eluting with 10% MeOH–CH_2Cl_2 containing 0.2% NH_4OH yielding **14j** as a white solid (220 mg, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (m, 2H), 1.45 (m, 2H), 2.26 (s, 3H), 2.32 (m, 2H), 2.45 (m, 2H), 2.75 (m, 1H), 3.0 (m, 3H), 3.25 (m, 1H), 3.65 (m, 1H), 4.88 (d, 1H, $J=10.3$ Hz), 6.91 (s, 1H), 7.30 (s, 1H), 7.51 (s, 1H), 8.43 (s, 1H); HRMS (FAB) calcd for $C_{20}H_{23}N_2Br_2$ 451.0207, found 451.0212.

Acknowledgements

The authors thank Dr. M. Puar for NMR structure assignments, the analytical services for physical data, Mr. R. Tiberi and Dr. J. Wong for large scale preparations, and Drs. G. Njoroge and R. Doll for helpful chemistry discussions.

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