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# Trihalobenzocycloheptapyridine Analogues of Sch 66336 as Potent Inhibitors of Farnesyl Protein Transferase

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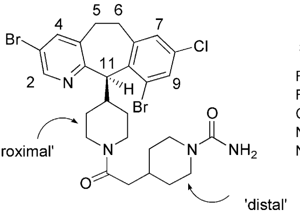
**Abstract**—**SCH 66336** is a trihalo tricyclic compound that is currently undergoing Phase II clinical trials for the treatment of solid tumors. Modifications of **SCH 66336** by incorporating such groups as amides, acids, esters, ureas and lactams off the first or the distal piperidine (from the tricycle) provided potent FPT inhibitors some of which exhibited good cellular activity. A number of these compounds incorporate properties that might improve pharmacokinetic stability of these inhibitors by virtue of their increased solubility or by their change in log P.

It has become evident that inhibition of Farnesyl Protein Transferase (FPT), an enzyme that plays a critical role in cell proliferation, could lead to development of potent anti-tumor agents.[1] A number of FPT inhibitors, have already been advanced to clinical trials in human.[2] Some of these compounds are peptidomimetics whose structure has been derived from the ras-CAAX motif with the appropriate modifications to provide pharmacokinetically more stable targets.[3] Our group has currently advanced **SCH 66336**, a non-peptidic benzocycloheptapyridine analogue for further clinical studies.[4] As summarized below, **SCH 66336** inhibits FPT with $IC_{50} = 1.9\,nM$, is 76% bioavailable in mice and as previously reported, is effective in stopping and regressing a variety of tumors in rodents.[4]

Based on information obtained from **SCH 66336**, we have further explored modifications off the proximal and the distal piperidine moiety (from the tricycle) in an effort to develop compounds with better solubility, bioavailability and pharmacokinetic profile than **SCH 66336**. Herein we describe our work towards synthesis of amides, carboxylic acids, esters, ureas, and lactams as potent FPT inhibitors.



**SCH 66336**

R (+)
FPT $IC_{50}$ = 1.9 nM
COS $IC_{50}$ = 10 nM
NIH-Hras SA $IC_{50}$ = 72 nM
NIH-Kras SA $IC_{50}$ = 500 nM

## Chemistry

A representative synthetic protocol of target molecules bearing a carboxylic acids, esters and amides off the first piperidine (from the tricycle) starts from the previously described amine **1**[4] and was carried out as outlined in Scheme 1. Thus, coupling of amine **1**[4] with carboxylic acid half esters in an EDCI mediated fashion provided esters of type **2a**. Hydrolysis of **2a** with NaOH or LiOH in either MeOH or EtOH provided the carboxylic acids of type **2b**. Primary amides of type **2c** were prepared from coupling of carboxylic acids **2b** with $NH_4Cl$ in an EDCI mediated reactions. Other analogues were prepared in the same way using appropriately spaced $HOOC(CH_2)_nCOOMe$ half ester to give compounds of type A listed in Table 1. Synthesis of carboxylic acids, esters, amides off the distal piperidine, were prepared from previously described amine **3**[4] in a similar manner to analogues in Scheme 1 to give compounds of type B listed in Table 2.

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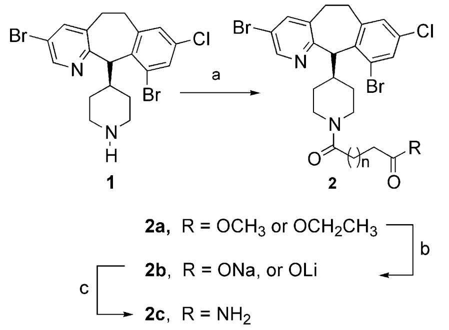
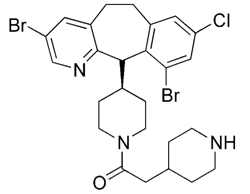


**Scheme 1.** Reagents and conditions: (a) $HOOC(CH_2)_nCOOCH_3$, NMM, HOBT, EDCl; (b) EtOH,NaOH (c) $NH_4Cl$, NMM, HOBT, EDCl.



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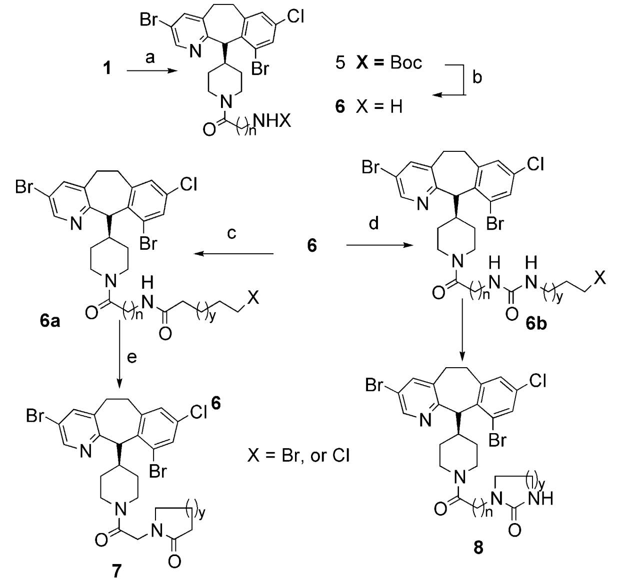
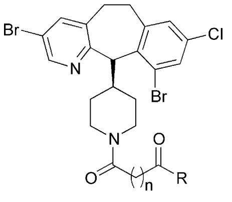


**Scheme 2.** Reactions and conditions: (a) $HOOC\text{-}CH_2\text{-}NH\text{-}Boc$, DMF, HOBT, EDCl; (b) $CH_2Cl_2$, TFA, 0 °C, 24 h; (c) $ClCO(CH_2)_{3-4}Br$, $CH_2Cl_2$; (d) $OCN(CH_2)_{3-4}Cl$, $CH_2Cl_2$; (e) THF, NaH (95%).

Preparation of five- and six-membered lactams were prepared as outlined in Scheme 2, thus amine **1**[4] was coupled to BOC protected amino acids to provide derivative of type **5**. Removal of the BOC group gave amine **6** that was reacted with either bromobutanoyl or pentanoyl bromide to give an intermediates of type **6a** that were subsequently cyclized to lactams of type **7** by treatment with NaH.[5] In the case of five- and six-membered ring cyclic ureas, amine **6** was reacted with either chloropropyl or butylisocyanate to give the intermediate bromo ureas of type **6b**. As in the lactam case, treatment of **6b** with NaH provided the desired cyclic ureas of type **8** (Scheme 2).[6] Biological data on compounds of type C prepared in this series is summarized in Table 3. Using similar chemistry as used for preparation of compounds of type C above, but substituting amine **1** with amine **3**, compounds of type D listed in Table 4 were prepared.

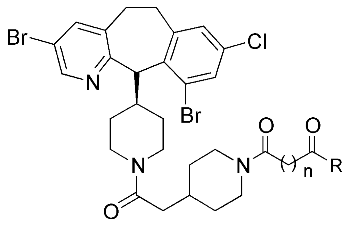
**Table 1.** FPT, COS and soft agar activities of tricyclic esters, acids and amides from piperidine of type A[a]



| Compd. | *n* | R | FPT $IC_{50}$ (nM) | COS $IC_{50}$ (nM) | Soft agar $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| **2b** | 1 | ONa | 120 | NA | NA |
| **2c** | 1 | $NH_2$ | 68 | NA | NA |
| **2d** | 2 | $OCH_3$ | 9.2 | 1000 | > 500 |
| **2e** | 2 | ONa | 270 | NA | > 500 |
| **2f** | 2 | $NH_2$ | 14 | NA | NA |
| **2g** | 3 | ONa | 44 | NA | NA |
| **2h** | 3 | $NH_2$ | 11 | NA | NA |
| **2i** | 4 | $OCH_3$ | 150 | NA | NA |
| **2j** | 4 | ONa | 17 | NA | NA |
| **2k** | 4 | $NH_2$ | 7.7 | 140 | > 500 |
| **2l** | 5 | $OCH_3$ | 11 | NA | NA |
| **2m** | 5 | ONa | 9.1 | 300 | > 500 |
| **2n** | 5 | $NH_2$ | 3.3 | 15 | 380 |

[a] Following the procedure outlined in Scheme 1, using $HOOC\text{–}(CH_2)_n\text{–}COOCH_3$, where $n = 1\text{–}5$ compounds **2b–n** were prepared.

**Table 2.** FPT,COS and soft agar activities of tricyclic esters, acids and amides from piperidine of type B[a]



| Compd. | *n* | R | FPT $IC_{50}$ (nM) | COS $IC_{50}$ (nM) | Soft agar $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| **4a** | 1 | OEt | < 3 | 125 | NA |
| **4b** | 1 | OLi | 0.9 | 250 | > 500 |
| **4c** | 1 | $NH_2$ | 3.3 | < 10 | 95 |
| **4d** | 2 | $OCH_3$ | 5.1 | 39 | 250 |
| **4e** | 2 | ONa | 1.2 | 75 | > 500 |
| **4f** | 2 | $NH_2$ | 2.5 | 25 | 220 |
| **4g** | 3 | Oet | 4.8 | 10 | 410 |
| **4h** | 3 | Ona | 1.1 | 18 | 350 |
| **4i** | 3 | $NH_2$ | 3.9 | 35 | 395 |
| **4j** | 4 | $OCH_3$ | 5.3 | 10 | 320 |
| **4k** | 4 | Ona | 3.6 | 30 | 480 |
| **4l** | 4 | $NH_2$ | 3.5 | 30 | 230 |
| **4m** | 5 | $OCH_3$ | 6.9 | 10 | 220 |
| **4n** | 5 | Ona | 1.4 | 25 | 250 |
| **4o** | 5 | $NH_2$ | 3.3 | 19 | 240 |

[a] Followed the procedure outlined in Scheme 2, using $HOOC\text{–}(CH_2)_n\text{–}COOCH_3$, where $n = 1\text{–}5$ compounds **4a–o** were prepared.

## Biological Results and Discussions

Compounds thus prepared were tested for their ability to inhibit the transfer of [$^3$H]-farnesyl from farnesyl diphosphate to His$^6$-H-Ras-CVLS, a process that is mediated by farnesyl protein transferase (FPT) using conditions previously described.[7] These compounds were also evaluated in a cellular ras processing assay (Cos-7 monkey kidney cells transiently expressing Ha-Ras-[Val12]CVLS )[7] and a colony forming assay (soft agar assay)[8] as previously described. Biological data for these compounds are reported in Tables 1–4.

## Tricyclic Esters, Acids and Amides

As shown in Tables 1 and 2, a variety of esters, acids, amides were prepared both from the proximal piperidine (Structure type A) as well as from the distal piperidine (Structure type B). In general, compounds of type B demonstrated better FPT and cellular activity than the corresponding compounds of structure type A. It is also notable that in structures of type B the COS and soft agar inhibitory activities of amides and esters are better than those of the corresponding carboxylic acids, especially, with compounds where $n=1$ or 2. Compound **4c**, a one-carbon methylene spacer exhibited the best FPT and cellular inhibitory activity in this series with FPT $IC_{50}=3.3$ nM, COS $IC_{50}$ <10 nM and Soft agar $IC_{50}$ 95 nM. In general, the length of the spacer in this series of compounds did not have any profound effect on either FPT or cellular activity.

The structure of **SCH66336** bound to FPTase[9] (Fig. 1) demonstrated that compounds with further substitutions on the distal piperidine should be well tolerated. The distal piperidine is directed in a shallow channel away from the core of FPTase into bulk solvent. Thus compounds of varying length are accommodated with little change in the FPTase affinity. The larger compounds (**2i**–**2n** and **4j**–**4o**) just extend into bulk solvent. Thus, the distal piperidine can be modified to test its effect on solubility, bioavailability and pharmacokinetics almost independent of FPTase affinity.

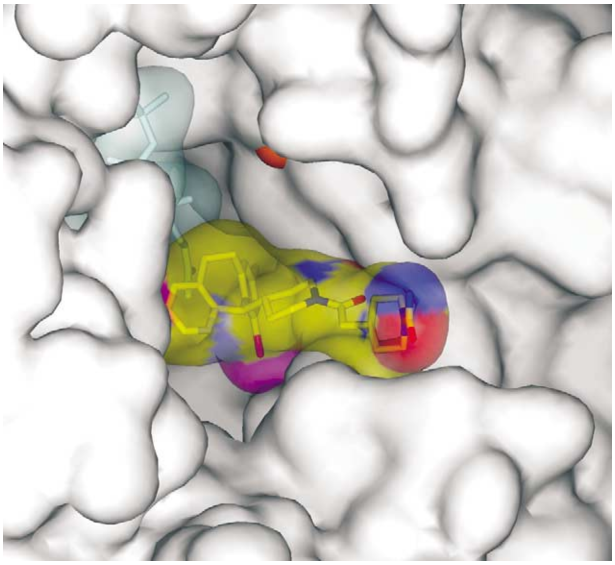
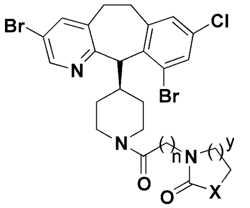


**Figure 1.** Structure of SCH66336 (yellow) and FPP (blue) bound to FPTase (white).

## Tricyclic Ureas and Lactams

Evaluation of FPT activity of lactams of structure type C (Table 3, where $X=CH_2$) revealed that the length of the spacer ($n$) in both the five- and six-membered ring

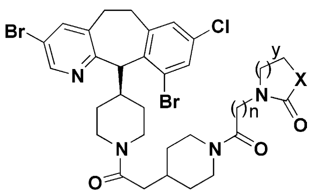
**Table 3.** FPT, COS and soft agar activities of tricyclic cyclic ureas and lactams—type C[a]



| Compd. | $n$ | $y$ | X | FPT $IC_{50}$ (nM) | COS $IC_{50}$ (nM) | Soft agar $IC_{50}$ (nM) |
|---|---|---|---|---|---|---|
| **7a** | 1 | 1 | $CH_2$ | 4 | 500 | >500 |
| **7b** | 2 | 1 | $CH_2$ | 22 | NA | NA |
| **7c** | 3 | 1 | $CH_2$ | 85 | NA | NA |
| **7d** | 1 | 2 | $CH_2$ | 3 | 60 | 300 |
| **7e** | 2 | 2 | $CH_2$ | 19 | NA | NA |
| **7f** | 3 | 2 | $CH_2$ | 80 | NA | NA |
| **8a** | 1 | 1 | NH | 23 | NA | NA |
| **8b** | 2 | 1 | NH | 19 | NA | NA |
| **8c** | 3 | 1 | NH | 16 | NA | 145 |
| **8d** | 1 | 2 | NH | 3 | 16 | NA |
| **8e** | 2 | 2 | NH | 20 | NA | NA |
| **8f** | 3 | 2 | NH | 56 | NA | NA |

[a]Following the procedure outlined in Scheme 2, using HOOC–$(CH_2)_n$–NH–BOC and Cl–CO–$(CH_2)_y$–Br or O=C= N–$(CH_2)_y$–Br, where $n=1$–3 and $y=1$–2 compounds **7a**–**f** and **8a**–**f** were prepared.

**Table 4.** FPT, COS and soft agar activities of tricyclic cyclic ureas and lactams—type D[a]



| Compd. | $n$ | $y$ | X | FPT $IC_{50}$ (nM) | COS $IC_{50}$ (nM) | Soft agar $IC_{50}$ (nM) |
|---|---|---|---|---|---|---|
| **9a** | 1 | 1 | $CH_2$ | 3.2 | 10 | 256 |
| **9b** | 2 | 1 | $CH_2$ | 3.0 | 17 | 350 |
| **9c** | 3 | 1 | $CH_2$ | 4.2 | 14 | 500 |
| **9d** | 1 | 2 | $CH_2$ | 1.4 | 19 | >500 |
| **9e** | 2 | 2 | $CH_2$ | 3.6 | 18 | >500 |
| **9f** | 3 | 2 | $CH_2$ | 5.3 | 41 | >500 |
| **10a** | 1 | 1 | NH | NA | NA | NA |
| **10b** | 2 | 1 | NH | 7.4 | 160 | 500 |
| **10c** | 3 | 1 | NH | NA | NA | NA |
| **10d** | 1 | 2 | NH | 2.5 | 18 | 500 |
| **10e** | 2 | 2 | NH | 2.7 | 68 | 500 |
| **10f** | 3 | 2 | NH | 8.2 | 43 | 500 |

[a]Followed the procedure outlined in Scheme 2, using HOOC–$(CH_2)_n$–NH–BOC and Cl–CO–$(CH_2)_y$–Br or O=C=N–$(CH_2)_y$–Br, where $n=1$–3 and $y=1$–2 compounds **9a**–**9f** and **10a**–**f** were prepared.

was important. The shorter the spacer the more potent were the compounds. Thus, in the five-membered ring lactams (*y* = 1), the order of FPT activity was **7a** > **7b** > **7c**. Similarly, in the six-membered ring lactams (*y* = 2), the order of FPT activity was **7d** > **7e** > **7f**. In the case of cyclic urea of structure type D (Table 3, compounds **8a–f**), the length of the spacer (*n*) was not critical for enhanced FPT activity. However, the six-membered urea **8d** ($IC_{50}$ 3 nM) with a single methylene spacer was slightly more active than analogous compounds in that series.

In compounds of structure type D (Table 4), the FPT activity for both the five- and the six-membered ureas and lactams were found to be very similar. The length of spacer (*n*) did not impart any advantages in either FPTor cellular activity of these compounds.

## Conclusions

We have examined a number or acids, esters, amides, cyclic ureas and lactams for their FPT and cellular inhibitory activity. In all the cases examined, introduction of the above functionalities off the distal piperidine (from tricycle) provided inhibitors that are in general more potent than those off the first (proximal)piperidine. The FPT and cellular activities of compound **4c**[10] were equivalent to that of **SCH 66336** and is therefore a potential candidate for further pharmacokinetic evaluation.

## Experimental

### Preparation of representative compounds

**Methyl-4-(3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo [5,6]cyclo-hepta [1,2-*b*]pyridin-11(*R*)-yl)-$\gamma$ oxo-1-piperidine butanoate (2d).** To a stirred solution of amine **1** (0.30 g, 0.64 mmol) in anhydrous DMF (10.0 mL) under nitrogen inlet at room temperature, was added 4-methyl morpholine (0.08 g, 0.83 mmol), HOBT (0.112 g, 0.83 mmol), EDCI (0.158 g, 0.83 mmol) and mono-methyl succinate (0.11 g, 0.83 mmol). The resulting solution was stirred at room temperature overnight and then concentrated to dryness, followed by extraction with $CH_2Cl_2$–$H_2O$. The combined organic layer was then washed with saturated $NaHCO_3$, 10% $Na_2H_2PO_4$, dried over $MgSO_4$, filtered and concentrated to dryness to give compound **2d** as a white solid (0.27 g, 72% yield); mp 78.7–79.5 °C; IR (KBr) ν 3434, 2993, 2945, 2850, 1737, 1643, 1580, 1551, 1437, 1367, 1205, 1207, 1160 cm$^{-1}$; $^{1}$H NMR ($CDCl_3$): 1.2–1.55 (4H, m), 2.2–2.4 (2H, m), 2.45–2.65 (4H, m), 2.65–3.0 (4H, m), 3.2–3.3 (1H,tt, *J* = 3.5, 15), 3.67 (3H, s), 3.8 (1H, t, *J* = 7.5), 4.4–4.6 (1H, m), 4.85 (1H, d), 7.05 (1H, s), 7.4 (1H, s), 7.5 (1H, d), 8.4 (1H, s); $^{13}$C NMR ($CDCl_3$) δ 28.4; 29.5; 31.4; 32.3; 32.5; 42.5; 45.7; 52.2; 119.4; 127.7; 129.5; 129.6; 131.6; 131.6; 133.6; 135.9; 137.6; 142.1; 142.3; 147.6; 155.1; 169.7; 174.1; MS (FAB) *m*/*z* 584.9 $(M+H)^+$.

Compounds **2i**, **2l**, **4a**, **4d**, **4j**, and **4m** were prepared in a similar way.

**4-(3,10)-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-*b*] pyridin-11(*R*)-yl)-$\gamma$ oxo-1-piperidine butanoic acid (2e).** To a stirred solution of compound **2d** (0.25 g, 0.43 mmol) in EtOH (10 mL, 200 proof) at room temperature, was added NaOH (0.02 g, 0.51 mmol) and $H_2O$ (0.6 mL). The resulting solution was stirred at room temperature overnight, then concentrated to dryness and dried under vacuum to give **2e** as a light yellow solid (0.23 g, 94% yield); mp 270 °C–decomposed; IR (KBr) ν 3417, 1919, 2852, 1850, 1439, 968 cm$^{-1}$; MS (FAB): *m*/*z* 570.9 $(M+H)^+$

Compounds **2b**, **2g**, **2j**, **2m**, **4b**, **4e**, **4h**, **4k** and **4n** were prepared in a similar way.

**4-(3,10)-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-*b*] pyridin-11(*R*)-yl)-$\gamma$ oxo-1-piperidine butanamide (2f).** To a stirred solution of compound **2e** (0.23 g, 0.40 mmol) in anhydrous DMF (10 mL) under nitrogen inlet at room temperature, was added 4-methyl morpholine (0.05 g, 0.52 mmol), HOBT (0.07 g, 0.52 mmol), EDCI (0.10 g, 0.52 mmol) and ammonium chloride (0.028 g, 0.52 mmol). The resulting solution was stirred at room temperature overnight and then concentrated to dryness, followed by extraction with $CH_2Cl_2$–$H_2O$. The combined organic layer was then washed with saturated $NaHCO_3$, 10%$Na_2H_2PO_4$, brine, dried over $MgSO_4$, filtered and concentrated to dryness to give a crude material. The crude product was purified by column chromatography on silica gel, eluting with 5%MeOH–$NH_3$/95%$CH_2Cl_2$ to give **2f** as off white solid (0.051 g, 45% yield); mp 134.1–135.0 °C; IR (KBr): ν 3407, 3198, 2938, 2851, 1673, 1633, 1552, 1439, 1271, 1206 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$): 1.3–1.7 (4H, m); 2.3–2.6 (6H, m), 2.7–3.0 (4H, m), 3.2–3.4 (1H, tt), 3.6 (1H, t), 3.85 (1H, t), 4.5–4.65 (1H, m), 4.8–5.0 (1H, d), 5.4 (1H, s), 6.15 (1H, s), 7.2 (1H, s), 7.5 (2H, d), 8.45 (1H, s), $^{13}$C NMR ($CDCl_3$): δ 28.7, 30.8, 31.8, 32.13, 41.9, 45.3, 57.9, 118.9, 127.2, 129.2, 131.2, 133.2, 141.7, 142.5, 147.3, 154.69, 169.9, 174.9; MS (FAB) *m*/*z* 570.0 $(M+H)^+$.

Compounds **2c**, **2h**, **2k**, **2n**, **4c**, **4f**, **4I**, **4l**, and **4o** were prepared in a similar way.

**4-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-*b*]pyridin-11(*R*)-yl)-1-[2-oxo-1-piperidinyl]acetyl piperidine (7d).** To a stirred solution of amine **1** (1.50 g, 3.20 mmol) in anhydrous DMF (30 mL) under nitrogen inlet at room temperature, was added 4-methyl morpholine (0.42 g, 4.1 mmol), HOBT (0.56 g, 4.1 mmol), EDCI (0.79 g, 4.1 mmol) and BOC-glycine (0.73 g, 4.1 mmol). The resulting solution was stirred at room temperature overnight and then concentrated to dryness, followed by extraction with $CH_2Cl_2$–$H_2O$. The combined organic layer was then washed with saturated $NaHCO_3$, 10% $Na_2H_2PO_4$, dried over $MgSO_4$, filtered and concentrated to dryness to give compound **5** as a white solid (2.2 g, $MH^+ = 628$). Compound **5** was dissolved in 20 mL of $CH_2Cl_2$ and the reaction mixture cooled to 0 °C. TFA (10 mL) was added and reaction mixture stirred for 2 h. It was then basified with NaOH(50% w/w) and the aqueous phase extracted with $CH_2Cl_2$. The organic phase was dried over $MgSO_4$ and concentrated to give 2.04 g of **6** ($MH^+ = 528$. To a stirred solution of compound **6** (0.40 g, 0.76 mmol) in $CH_2Cl_2$ (10 mL) under nitrogen at room temperature was added 5-bromovaleryl chloride (0.15 mL, 1.13 mmol) and $Et_3N$ (0.23 mL, 1.67 mmol). The resulting solution was stirred at room temperature overnight and washed with saturated $NaHCO_3$. The combined organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to give compound **6a** (0.53 g, $MH^+ = 690$) as a yellow solid. To a stirred cooling solution of compound **6a** (0.49 g, 0.76 mmol) in THF (10 mL) under nitrogen at −10 °C was added 95% NaH solution (0.09 g, 3.8 mmol). The resulting solution was stirred at room temperature overnight and concentrated to dryness, followed by extraction with EtOAc–satd $Na_2SO_4$ and $CH_2Cl_2$. The combined organic layer was dried over $Na_2SO_4$, filtered, concentrated to dryness and purified by column chromatography on silica gel, eluting with 4%MeOH-$NH_3$/$CH_2Cl_2$ to give compound **7d** (0.233 g, 50% yield) as a white solid; mp 138.8–139.5 °C; IR (KBr): ν 3443, 3041, 2940, 2863, 1640, 1580, 1493, 1441, 1350, 1272, 1160, 1094; $^1H$ NMR (300 MHz, $CDCl_3$): 1.2–1.5 (8H, m), 1.65 (1H, m), 2.0 (2H, m), 2.15–2.4 (4H, m), 2.7–3.0 (3H, m), 3.2–3.5 (2H, m), 3.5–3.7 (1H, m); 3.8 (1H, s), 4.5 (1H, d), 4.7 (1H, d), 7.05 (1H, s), 7.45 (1H, d), 7.55 (1H, s), 8.4 (1H, m), $^{13}C$ NMR ($CDCl_3$): δ 21.7, 23.5, 30.4, 31.2, 31.4, 32.15, 32.4, 32.5, 42.3, 42.4, 42.6, 45.2, 45.4, 48.7, 49.4, 49.5, 58.1, 119.4, 129.5, 129.6, 131.5, 131.6, 133.6, 147.5; MS (FAB) *m*/*z* 610 $(M+H)^+$.

Compounds **7a–c**, **7e**, **7f**, and **9a–f**, were prepared in a similar way.

**4-(3,10-Dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6] cyclohepta[1,2-*b*]pyridin-11-(*R*)-yl)-1-[(hexahydro-2-oxo-1-pirimidinyl)acetyl]piperidine (8d).** To a stirred solution of compound **6** (0.40 g, 0.76 mmol) in $CH_2Cl_2$ (10 mL) under nitrogen at room temperature was added 3-chloropropyl isocyanate (0.16 mL, 1.52 mmol). The resulting solution was stirred at room temperature overnight and washed with saturated $NaHCO_3$. The combined organic layer was dried over $MgSO_4$, filtered and concentrated to dryness to give compound **6b** (0.51 g, $MH^+ = 649$) as a yellow solid. To a stirred cooling solution of compound **6b** (0.49 g, 0.76 mmol) in THF (10 mL) under nitrogen at −10 °C was added 95% NaH solution (0.09 g, 3.8 mmol). The resulting solution was stirred at room temperature overnight and concentrated to dryness, followed by extraction with EtOAc–satd $Na_2SO_4$ and $CH_2Cl_2$. The combined organic layer was dried over $Na_2SO_4$, filtered, concentrated to dryness and purified by column chromatography on silica gel, eluting with 4%MeOH–$NH_3$/$CH_2Cl_2$ to give compound **8d** (0.26 g, 56% yield) as white solid; mp 155.6–156.1 °C; IR (KBr); ν 3440, 3059, 2938, 2885, 1651, 1580, 1551, 1514, 1444, 1305, 1273, 1204, 1169; $^1H$ NMR (300 MHz, $CDCl_3$): 1.35 (3H, m), 1.5 (3H, m), 1.95 (3H, m), 2.2–1.5 (3H, m), 2.7–2.89 (2H, m), 2.9–3.0 (1H, m), 3.15–3.41 (8H, m), 3.5–3.65 (2H, m), 3.75 (2H, d), 4.0 (2H, q), 4.2 (2H, q), 4.5 (1H, m), 4.85 (2H, d), 7.1(1H, s), 7.5 (2H, d), 8.4 (1H, s), MS (FAB): *m*/*z* 611 $(M+H)^+$

Compounds **8a–c**, **8e**, **8f**, and **10a–f**, were prepared in a similar way.

## Uncited References

bib [10] is not cited in text

## References and Notes

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10. Some predicted log P's using Pallas program from CompuDrug are as follows: **SCH 66336** (5.0), compound **4c** (4.5), compound **10d** (4.7).