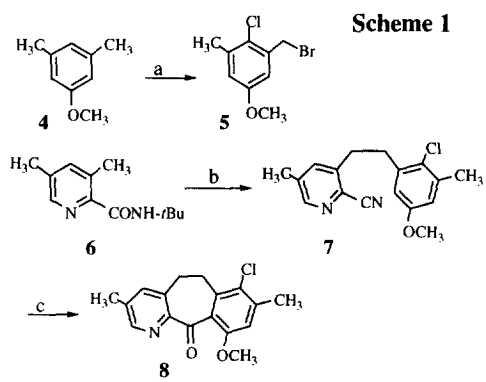
of **1** showed that improvements in the potency and pharmacokinetics of the benzocycloheptapyridine FPT inhibitors were achievable by the introduction of a 3-bromo, a 7- bromo or a 10-bromo substituents, and a C_{11}-piperazine or piperidine pendant ring acylated by a 4-pyridylacetyl N-oxide or a 4-N-carboxamidopiperidinylacetyl group.[6–9] As part of a study to explore novel inhibitor analogs of **1**, we found that an 8-methyl and a 10-methoxy groups are effective equivalents of the 8,10-dihalo substituents resulting in the potent FPT inhibitor **2**.[10] Previous SAR studies of 3-substituted benzocycloheptapyridines established that only nonpolar, hydrophobic substituents with low steric bulk, such as a methyl group, elicited a potency enhancement of FPT inhibition activity similar to that observed for a 3-bromo substituent.[7a] We report here the synthesis and FPT activity of several 3-alkyl substituted compounds **3**. The objective of this study was to explore the FPT activity of C_3 alkyl analogs of **2**.

Chemistry

Compounds **3** were synthesised by applying the general methodology for the synthesis of the bencycloheptapiperidines.[11] For the synthesis of the 3-methyl tricyclic ketone **8** (Scheme 1), picoline **6**[11b,12] was alkylated with the 2-chloro benzyl bromide **5**, obtained from a two step halogenation of **4**, followed by treatment of the *t*-butylamide with phosphorous oxychloride to afford the desired cyclization precursor **7**. The chlorine substituent in **7** was used as a blocking group for the directed triflic acid catalyzed electrophilic cyclization step to

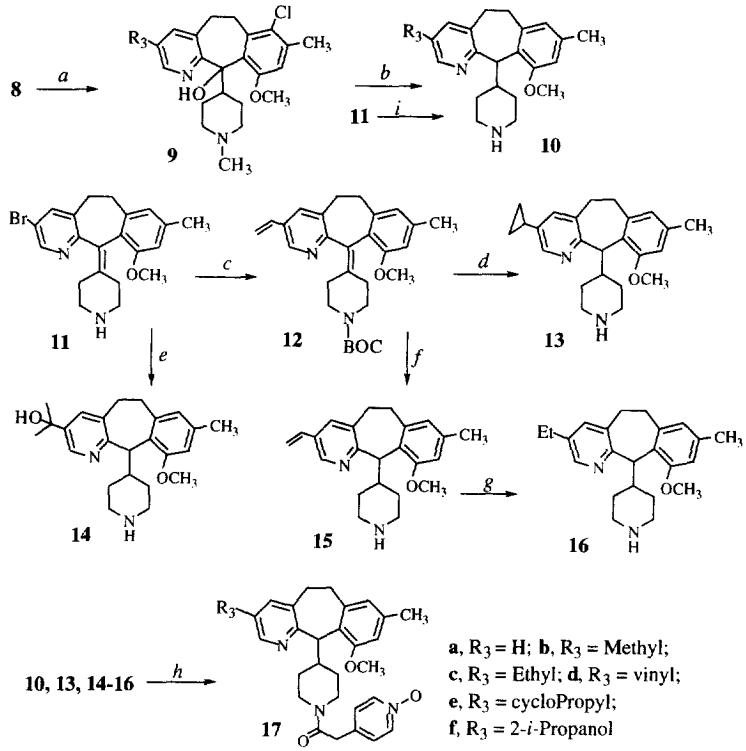
Scheme 1



Reagents: (a) i. N-Cl-succinimide/CH_3CN/70 °C ii. NBS /Benzoyl peroxide/CCl_4. (b) i. LDA/THF, -78 °C/**5** ii. $POCl_3$/$PhCH_3$/80 °C. (c) i. CF_3SO_3H/rt ii. 2 N HCl/110 °C.

obtain **8**, which was then reacted (Scheme 2) with N-Me-4-piperidinyl magnesium chloride to form the adduct **9b**. Ethylchloroformate mediated N-demethylation of **9b** followed by hydrogenolysis of the 7-chloro group, dehydration with PPA, acid hydrolysis of the N-ethylcarbamate and finally, reduction of the 11-ene with DIBAL afforded **10b**. DIBAL reduction of the 11-ene in **11**,[10] afforded **10a** as a side-product. Protection of the NH in **11** as the N-Boc derivative followed by vinylation using Stille methodology[13] afforded the 3-vinyl derivative **12** in high yield (94%). Cyclopropanation of the vinyl group of **12** with diazomethane-palladium acetate,[14] TFA deprotection of the N-Boc, followed by reduction of the 11-ene with DIBAL afforded the 3-cyclopropyl derivative

Scheme 2



Reagents: (a) N-Me-4-piperidinyl-MgCl. (b) i. $ClCO_2Et/PhCH_3$/70 °C ii. H_2/10%Pd-C/MeOH iii. PPA/70 °C iii. 4 N HCl/110 °C iv. DIBALH/$PhCH_3$/rt. (c) i. $(BOC)_2O/CH_2Cl_2$ ii. $Bu_3SnCH{=}CH_2/Pd(dba)_3/P(2\text{-furyl})_3/LiCl/PhCH_3$/100 °C/24 h. (d) i. CH_2N_2-Et_2O/$Pd(OAc)_2/CH_2Cl_2$ ii. 20% TFA/CH_2Cl_2 iii. DIBALH/$PhCH_3$/rt. (e) i. $(BOC)_2O$/THF ii. BuLi-hexane/THF iii. Me_2CO. (f) i. 20% TFA/CH_2Cl_2 ii. DIBALH/$PhCH_3$/rt. (g) 10%Pd-C/HCO_2NH_4/MeOH/reflux. (h) EDCI/HOBT/NMM /4-pyridyl acetic acid N-oxide/DMF. (i) DIBALH/$PhCH_3$/rt.

13. TFA deprotection of the N-Boc of **12** followed by DIBAL reduction of the 11-ene afforded the 3-vinyl derivative **15**;catalytic hydrogenation of **15** afforded the 3-ethyl derivative **16**. Metalation of the 3-bromo of Boc-**11** with BuLi, reaction with acetone followed by DIBAL reduction afforded the 3-isopropanol derivative **14**. The NH precursors **10**, **13–16** were acylated with 4-pyridyl acetic acid N-oxide in the presence of EDCI to afford the final compounds **17a–f**.[15]

Biology

Compounds **17a–f** were tested in the in vitro FPT assay which measures the inhibition of FPT-catalyzed transfer of ^{3}H-farnesyl group from ^{3}H-farnesylpyrophosphate to H-Ras-CVLS. Details of this test have been described previously.[6] The FPT activity of the compounds in this enzymatic test is summarized in Table 1. Data in the Table show that the 3-unsubstituted compound **17a** is approximately 40x less active than the 3-bromo

reference compound **2**. Introduction of a 3-methyl group as in **17b** improves the inhibitory activity fivefold. The 3-ethyl, and 3-vinyl compounds **17c** and **17d** are comparable in activity to the 3-methyl analog. Replacement of the 3-methyl group by cyclopropyl as in **17e** leads to a loss of activity equivalent to that of the 3-H compound **17a**. The 3-isopropanol derivative is only weakly active as a FPT inhibitor.

Table 1

Entry No.	Substituents R	FPT[a] IC_{50} (μM)
17a	H	0.14
17b	3-Methyl	0.034
17c	3-Ethyl	0.074
17d	3-Vinyl	0.059
17e	3-cycloPropyl	0.200
17f	3-C(OH)Me_2	26% (0.19)
2	Bromo	0.0036

[a]For assay details see references 6–8

Conclusions

Previous SAR studies of 3-substituted 8-chloro-benzocycloheptapyridines have shown that the potency enhancement of FPT inhibition activity by a 3-methyl substituent is equivalent to that of a 3-bromo group and the compounds are 6x more active than the 3-H analog.[7a] In the present series of 8-methyl-10-methoxy-benzocycloheptapyridines, a 3-methyl substituent showed a similar improvement in activity but was found to be much less effective than a 3-bromo group. Furthermore, the 3-bromo group in this series elicits a much higher potency enhancement than in the reported[7a] 8-chloro-benzocycloheptapyridines. Increasing the steric bulk of the 3-substituent leads to a loss in activity. None of the alkyl groups investigated here were found to be useful as replacements for the 3- bromo group.

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References

1. (a) Egan, S. E.; Weinberg, R. A. *Nature* **1993,** *365* , 781; (b) Marshal, M. S. *Trends Biochem. Sci.* **1993,** *18*, 250; (c) Hall, A. *Science* **1994,** *264*, 1413.
2. (a) Casey, P. J.; Solski, P. A.; Der, C. J.; Buss, J. E. *Pro. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 8323. (b) Zhang, F. L.; Casey, P. J. *Annu. Rev. Biochem.* **1996**, *65*, 241.
3. For leading references describing the biology of *ras* see: (a) Barbacid, M. *Annu. Rev. Biochem.* **1987**, *56*, 779; (b) Bos, J. L. *Cancer Res.* **1989**, *49*, 4682.
4. Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971.
5. Ayral-Kaloustian, S.; Skotnicki, J. S. *Annu. Rep. Med. Chem.* **1996**, *31*, 2971.
6. Njoroge, G. F.; Taveras, A.G.; Kelly, J.; Remiszewski, S.; Mallams, A. K.; Wolin, R.; Afonso, A.; Cooper, A. B.; Rane, D. F.; Liu,Y.-T.; Wong, J.; Vibulbhan, B.; Pinto, P.; Deskus, J.; Alvarez, C. S.; del Rosario, J.; Connolly, M.; Wang, J.; Desai, J.; Rossman, R.; Bishop, W. R.; Patton, R.; Wang, L.; Kirshmeier, P.; Bryant, M.; Nomeir, A. A.; Lin, C.-C.; Liu, M.; McPhail, A. T.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *J. Med. Chem.* **1998**, *41*, 4890

7. (a) Njoroge, G. F.; Vibulbhan, B.; Rane, D. F.; Bishop, W. R.; Petrin, J.; Patton, R.; Bryant, M. S.; Chen, K.-J.; Nomeir, A. A.; Lin, C.-C.; Liu, M.; King, I.; Chen, J.; Lee, S.; Yaremko, B.; Dell, J.; Lipari, P.; Malkowski, M.; Li, Z.; Catino, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *J. Med. Chem.* **1997**, *40*, 4290. (b) Njoroge, G. F.; Vibulbhan, B.; Pinto, P.; Chan, T.-M.; Osterman, R.; Remiszewski, S.; del Rosario, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *J. Org. Chem.* **1998**, *63*, 445.
8. Mallams, A. K.; Rossman, R.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K.; Petrin, J.; Wang, L.; Patton, R.; Bishop, W. R.; Carr, D. M.; Kirshmeier, P.; Catino, J.; Bryant, M. S.; Chen, K.-J.; Korfmacher, W. A.; Nardo, C.; Wang, S.; Nomeir, A. A.; Lin, C.-C.; Li, Z.; Chen, J.; Lee, S.; Dell, J.; Lipari, P.; Malkowski, M.; Yaremko, B.; King, I.; Liu, M. *J. Med. Chem.* **1998**, *41*, 877.
9. Njoroge, G. F.; Vibulbhan, B.; Pinto, P.; Bishop, W. R.; Bryant, M. S.; Nomeir, A. A.; Lin, C.-C.; Liu, M.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *J. Med. Chem.* **1998**, *41*, 1561.
10. Afonso, A.; Weinstein, J.; Kelly, J.; Wolin, R.; Rosenblum, S. B.; Connolly, M.; Guzi, T.; James, L.; Carr, D.; Patton, R.; Bishop, W. R.; Kirshmeier, P.; Liu, M.; Heimark, L.; Chen, K. J.; Nomeir, A. A. *Bioorg. Med. Chem.* **1999**, *7*, *in press*.
11. (a) Schumacher, D. P.; Murphy, B. L.; Clark, J. E.; Tahbaz, P.; Mann, T. A. *J. Org. Chem.* **1989**, *54*, 2242. (b) Wong, J. K.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Anthes, J. C.; Billah, M. M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1073. (c) Piwinski, J. J.; Wong, J. K.; Chan, T. K.; Green, M. J.; Ganguly, A. K. *J. Org. Chem.* **1990**, *55*, 3341. (d) Piwinski, J. J.; Wong, J. K.; Green, M. J. U.S. Patent 5, 422, 351 June 6, 1995; *Chem. Abstr.* **1992**, *116*, 235654. (e) Villani, F.J.; Daniels, P.J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C. *J. Heterocycl. Chem.* **1971**, *8*, 73. (f) Villani, F.J.; Daniels, P.J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C.; Wefer, E. A. *J. Med. Chem.* **1972**, *15*, 750.
12. Blank, B.; DiTullio, N. W.; Krog, A. J.; Saunders, H. L. *J. Med. Chem.* **1979**, *22*, 840.
13. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnan, B. J. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
14. Hildebrand, J. P.; Marsden, S. P. *Synlett* **1996**, 893.
15. Physical data for compounds: **7:** cryst. solid (66%): MS(CI) *m/z* 301 (MH^+).**8**: cryst solid (76%): mp 188–190 °C; MS(CI) *m/z* 302, 304 (MH^+). **9b**: white powder (76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H),2.34 (s, 3H), 2.79 (s,3H), 3.89 (s, 3H), 6.83 (s, 1H), 7.67 (s, 1H), 8.22 (s, 1H); HRMS (FAB) calcd for $C_{23}H_{30}N_2O_2Cl$ 401.1996, found 401.2001. **10b**: off-white powder (27%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.28 (s, 3H), 3. 76 (s, 3H), 4.83 (d, 1H, J = 10.4 Hz), 6.65 (s, 1H), 6.57, (s, 1H), 7.17 (s, 1H), 8.17 (s, 1H); MS(CI) *m/z* 337 (MH^+). **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s,9 H), 2.15 (m, 1H), 2.25 (m, 1H), 2.31 (s, 3H), 2.37 (m, 1H), 2.57 (m, 1H), 2.70 (m, 1H), 2.90 (m,1 H), 3.0-3.2 (m, 2H), 3.2-3.5 (m, 2H), 3.75 (s, 3H), 5.28 (d, 1H, J = 10.9 Hz), 5.73 (d, 1H, J = 17.5 Hz), 6.57 (s, 1H), 6.62 (m, 1H), 6.66 (s, 1H), 7.38 (s, 1H), 8.41 (s,1H); MS(CI) *m/z* 445 (MH^+). **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (d, 2H, J = 4 Hz), 0.93 (d, 2H, J = 8.4 Hz), 2.28 (s, 3H), 3.76 (s, 3H), 4.82 (d, 1H, J = 10.5 Hz), 6.55, (s, 1H), 6.56 (s, 1H), 6.96 (s, 1H), 8.14 (d, 1H, J = 2 Hz); HRMS (FAB) calcd for $C_{24}H_{31}N_2O$

363.2436, found 363.2441. **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54, 1.56 (s, 6H), 2.28 (s, 3H), 3.71 (s, 3H), 4.85 (d, 1H, *J* = 10.5 Hz), 6.55, (s, 1H), 6.58 (s, 1H), 7.48 (d, 1H, *J* = 2 Hz), 8.13 (d, 1H, *J* = 6.8 Hz), 8.43 (d, 1H, *J* = 2 Hz); HRMS (FAB) calcd for $C_{24}H_{33}N_2O_2$ 381.2542, found 381.2544. **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (m, 4H), 2.25 (m, 1H), 2.28 (s, 3H), 2.45 (m, 2H), 2.8-3.1 (m, 4H), 3.37 (m, 1H), 3.57 (m, 1H), 3.77 (s, 3H), 4.86 (d, 1H, *J* = 10.5Hz), 5.28 (d, 1H, *J* = 10.5 Hz), 5.74 (d, 1H, *J* = 17.7 Hz), 6.56 (s, 1H), 6.58 (s, 1H), 6.63 (m, 1H), 7.41 (s, 1H), 8.35 (s, 1H); HRMS (FAB) calcd for $C_{23}H_{28}N_2O$ 349.2280, found 349.2280. **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H,*J* = 7.4 Hz), 1.7 (m, 5H), 2.28 (s, 3H), 2.55 (q, 2H, *J* = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, *J* = 10.2 Hz), 6.52 (s, 1H), 6.55 (s, 1H), 7.16 (s, 1H), 8.09 (s, 1H); MS(ES) *m/z* 351 (MH^+). **17a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.54 (m, 2H), 2.89 (m, 4H), 3.32 (m, 2H), 3.65 (s, 2H), 3.78 (s, 3H), 4.50 (m, 1H), 4.97 (m, 1H), 6.57 (s, 1H), 6.59 (s, 1H), 7.09 (m, 1H), 7.14 (s, 1H), 7.16 (s, 1H), 7.39 (d, 1H, *J* = 7.3 Hz), 8.15 (s, 1H), 8.17 (s, 1H), 8.35 (d, 1H *J* = 3.7 Hz); HRMS (FAB) calcd for $C_{28}H_{32}N_3O_3$ 458.2444, found 458.2436. **17b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.29 (s, 3H), 3.64 (s, 2H), 3.76 (s, 3H), 6.56 (s, 1H), 6.59 (s, 1H), 7.14 (d, 2H, *J* = 6.8 Hz), 7.20 (s, 1H), 8.14 (d, 2H *J* = 6.8 Hz), 8.18 (s, 1H) ; HRMS (FAB) calcd for $C_{29}H_{33}N_3O_3$ 472.2600 found 472.2605. **17c**: ^{1}H NMR (400 MHz,$CDCl_3$) δ 1.20 (t, 3H, *J* = 7.48 Hz), 1.47 (m, 4H), 2.29 (s, 3H), 2.35 (m, 1H), 2.53 (m, 1H), 2.55 (q, 2H), 2.85 (m, 1H), 2.92 (m, 2H), 3.28 (m, 1H), 3.48 (m, 1H), 3.64 (s, 2H), 3.74 (m, 1H), 3.77 (s, 3H) 4.50 (m, 1H), 4.83 (m, 1H), 6.56 (s, 1H), 6.59 (s, 1H), 7.14 (d, 2H, *J* = 6.16 Hz), 7.19 (s, 1H), 8.14 (d, 2H, *J* = 5.24 Hz), 8.18 (s, 1H); HRMS (FAB) calcd for $C_{30}H_{36}N_3O_3$ 486.2757, found 486.2755. **17d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (m, 4H), 2.29 (s, 3H), 2.35 (m, 1H), 2.52 (m, 1H), 2.86 (m, 3H), 3.35 (m, 1H), 3.55 (m, 1H), 3.64 (s, 2H), 3.74 (m, 1H), 3.77 (s, 3H), 4.50 (m, 1H), 4.87 (m, 1H), 5.32 (d, 1H, *J* = 11.2 Hz), 5.76 (d, 1H, *J* = 17.7 Hz), 6.57 (s, 1H), 6.59 (s, 1H), 6.64 (m, 1H), 7.14 (d, 2H, *J* = 6.57 Hz), 7.42 (s, 1H), 8.14 (d, 2H, *J* = 6.72 Hz), 8.35 (s, 1H); HRMS (FAB) calcd for $C_{30}H_{34}N_3O_3$ 484.2600, found 484.2601. **17e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.65 (d, 2H, *J* = 4 Hz), 0.96 (d, 2H, *J* = 8 Hz), 2.28 (s, 3H), 3.64 (s, 2H), 3.75 (s, 3H), 4.80, 4.81 (d, 1H, *J* = 10.2 Hz), 6.55, (s, 1H), 6.58 (s, 1H), 6.96 (s, 1H), 7.14 (d, 2H, *J* = 6.2 Hz), 8.12 (bs, 3H, *J* = 2 Hz); HRMS (FAB) calcd for $C_{31}H_{36}N_3O_3$ 498.2757, found 498.2752. **17f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55, 1.56 (s, 6H), 2.29 (s, 3H), 3.63 (s, 2H), 3.75 (s, 3H), 4.50 (bt, 1H), 4.86, 4.85 (d, 1H, *J* = 10.3 Hz), 6.56, (s, 1H), 6.59 (s, 1H), 7.13 (d, 1H, *J* = 6.8 Hz), 7.50 (s, 1H), 8.13 (d, 1H, *J* = 6.8 Hz), 8.44 (s, 1H); HRMS (FAB) calcd for $C_{31}H_{38}N_3O_4$ 516.2862, found 516.2862.