Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 4845–4850
Bioorganic & Medicinal Chemistry Letters

Synthesis of novel bicyclo[4.1.0]heptane and bicyclo[3.1.0]hexane derivatives as melanin-concentrating hormone receptor R1 antagonists

Jing Su,[a,*] Haiqun Tang,[a] Brian A. McKittrick,[a] Huizhong Gu,[b] Tao Guo,[b] Gang Qian,[b] Duane A. Burnett,[a] John W. Clader,[a] William J. Greenlee,[a] Brian E. Hawes,[c] Kim O'Neill,[c] Brian Spar,[c] Blair Weig,[c] Timothy Kowalski[c] and Steve Sorota[d]

[a]*Department of Chemical Research, Schering-Plough Research Institute K15 2545, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[b]*Pharmacopeia, Inc., PO Box 5350, Princeton, NJ 08543-5350, USA*
[c]*Department of Cardiovascular/Metabolic Diseases, Schering-Plough Research Institute K15 3600, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*
[d]*Department of Neurobiology, Schering-Plough Research Institute K15 2600, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA*

Received 8 May 2007; revised 11 June 2007; accepted 13 June 2007
Available online 17 June 2007

Abstract—To address the hERG liability of MCHR1 antagonists such as **1** and **2**, new analogs such as **4** and **5** that incorporated a polar heteroaryl group were designed and synthesized. Biological evaluation confirmed that these new analogs retained MCH R1 activity with greatly attenuated hERG liabilities as indicated in the Rb efflux assay.

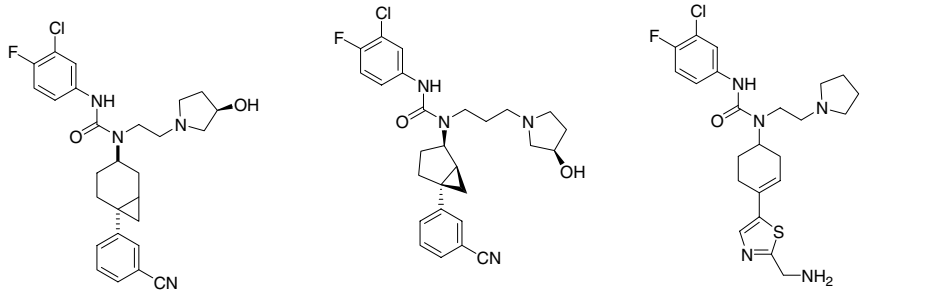
Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid neuropeptide responsible for color changes in fish skin.[1] MCH is present in the brains of all vertebrate species examined so far and it appears to be involved in feeding behavior based on the following observations: direct i.c.v. administration of MCH in rats increases food intake in a dose-dependent manner[2]; MCH mRNA is up-regulated in ob/ob mice and in fasted mice[3a]; MCH overexpressing mice are hyperphagic, mildly obese, hyperglycemic, and insulin resistant[3b]; MCH knockout mice are leaner than wild-type mice.[4] It is generally believed that MCH receptor R1 mediates the orexigenic effects of MCH[5,6] and an extensive number of reports on MCH receptor R1 antagonists for the potential treatment of obesity have appeared in recent years.[7,8]

Recently Schering-Plough reported the discovery of bicyclo[4.1.0]heptane **1**[9] and bicyclo[3.1.0]hexane **2**[8d] as potent MCH R1 receptor antagonists (Fig. 1). Concerns about their strong inhibition of hERG K^+ channel led us to modify these lead structures and the results from our investigation suggested that an increase in the molecular polarity of the lead structures could result in much reduced hERG activity.[10] For example, compound **3** had MCH R1 K_i 13 nM while its hERG activity was significantly reduced compared with **1** in the Rb efflux assay.[11] The encouraging results prompted us to replace the 3-CN or 4-CN phenyl moiety in **1** and **2** with a polar heteroaryl group. We describe herein our synthetic efforts to such targets as **4** and **5** and other analogs as well as their biological activities.

Our synthesis of bicyclo[4.1.0]heptane **4** is shown in Scheme 1. Contrary to the established synthetic route to **1**,[9] the cyclopropane ring in **4** was built before the introduction of the thiazole ring.[12] Thus, the cyclopropanation of allylic alcohol **6**[13] was achieved in 90% yield under Simmons–Smith condition. To build the thiazole

Keywords: Melanin-concentrating hormone receptor R1 antagonist; Bicyclo[4.1.0]heptane; Bicyclo[3.1.0]hexane; hERG; Cyclopropanation.
* Corresponding author. Tel.: +1 908 740 7489; fax: +1 908 740 7164; e-mail: jing.su@spcorp.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.06.048

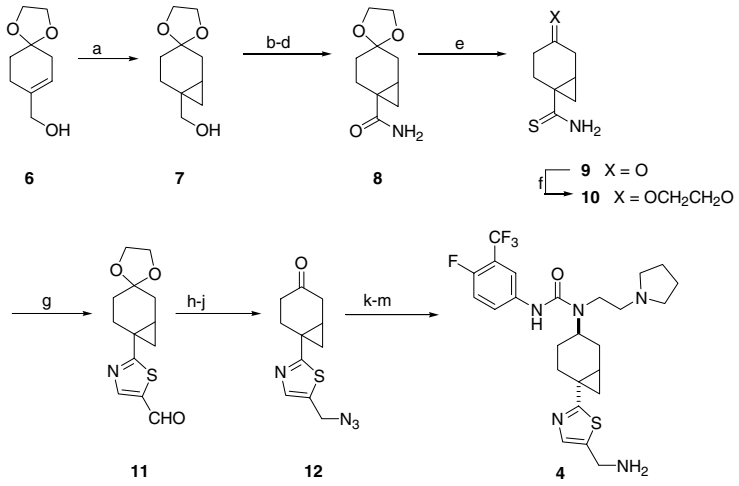


1
MCH R1 Ki 9 nM
Rb efflux: 80% inh. at 5 μg/mL

2
MCH R1 Ki 22 nM
Rb efflux: 86% inh. at 5 μg/mL

3
MCH R1 Ki 13 nM
Rb efflux: 10% inh. at 5 μg/mL

Figure 1. Initial MCH R1 antagonists with various hERG profiles.

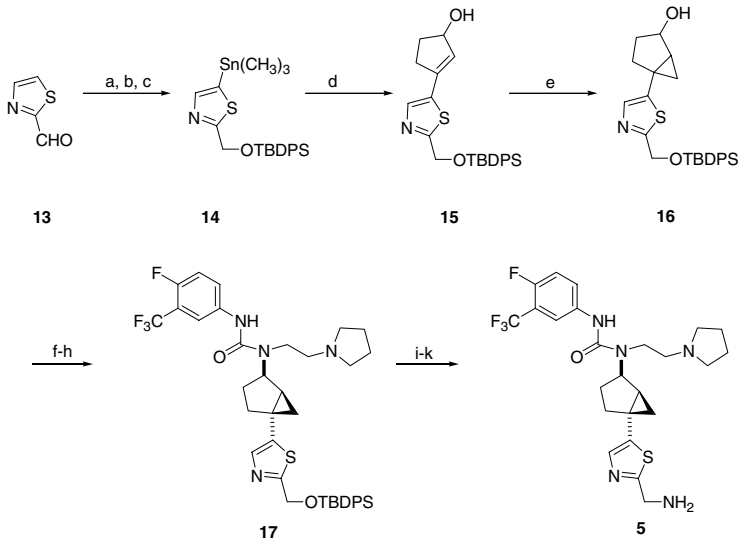


Scheme 1. Synthesis of bicyclo[4.1.0]heptane **4**. Reagents and conditions: (a) $ClCH_2I$ (4 equiv), Et_2Zn (8 equiv), DCE, rt, 72 h, 90%; (b) Dess–Martin, DCM, rt, 3 h, 90%; (c) $NaClO_2$, KH_2PO_4, $CH_3CH{=}C(CH_3)_2$, rt, 15 h; (d) $ClCO_2Et$, Et_3N, DCM, then NH_3 (20 equiv), 43%; (e) Lawesson's reagent (0.5 equiv), THF, rt, 1.5 h, 54% (1:1 **9**:**10**); (f) $(CH_2OH)_2$, TsOH, 73%; (g) $NaHCO_3$ (4 equiv), 2.5 equiv 2-chloromalonaldehyde, THF, 50 °C, 14 h, 94%; (h) $LiAlH_4$, 78%; (i) DPPA (3 equiv), DBU (2 equiv); (j) HCl, H_2O, 89%; (k) 2-pyrrolidin-1-yl-ethylamine (1.04 equiv), $NaBH_4$ (1.04 equiv), MS3Å, DCM, 67% (1:1 mixture of *cis*/*trans* product); (l) 4-fluoro-3-trifluoromethylphenyl isocyanate, 100%; (m) PPh_3, 74%.

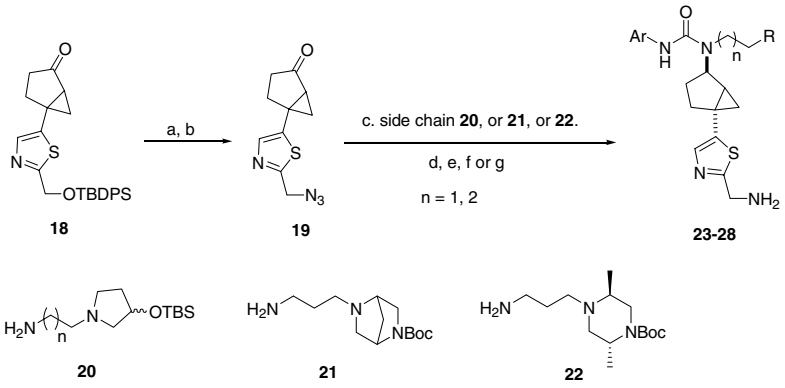
ring, the alcohol **7** was converted to the corresponding amide **8** in 39% yield (three steps).[14] The transformation of **8** to thioamide **10** using Lawesson's reagent afforded a 1:1 mixture of **9** and **10** (54% total yield). Without separation, **9** was converted back to ketal **10** in 73% yield under standard conditions. Applying a literature procedure[15] to the thioamide **10** provided the thiazole **11** in 94% yield. Transformation of **11** to ketone **12** was accomplished in three steps in 69% yield. The reductive amination of **12** with 2-pyrrolidin-1-yl-ethylamine afforded a mixture of *cis* and *trans* products (1:1, 67%). After urea formation, the *cis* and *trans* ureas were separated and the final reduction of the azide afforded the desired product **4** in 25% yield from **12**.

A different synthetic route to bicyclo[3.1.0]hexane **5** was envisioned which would take advantage of the allylic alcohol mediated cyclopropanation (Scheme 2). Compound **14**, prepared from the commercially available aldehyde **13** in three steps, underwent Stille coupling with 3-bromo-cyclopenten-2-ol[8d] to afford **15** in 50–62% yield. Various cyclopropanation reaction conditions were subsequently tried and eventually a modified condition using Sm/CH_2I_2 gave the desired product **16** in 50–55% yield.[16] After Dess–Martin oxidation, reductive amination, and urea formation, the intermediate **17** was obtained in 93% yield and was further converted to the target **5** in 66% yield. Other derivatives of bicyclo[3.1.0]hexanes such as **23**–**28** with different side chains were synthesized via this route (Scheme 3).[17]

The biological data for the above compounds are shown in Table 1.[18] Bicyclo[4.1.0]heptane **4** indeed had much lower hERG activity in the Rb efflux assay (19% inhibition at 5 μg/mL vs 80% for **1**), although it had weak MCH R1 binding (K_i 431 nM). On the other hand, bicyclo[3.1.0]hexane **5** had a better MCH R1 binding (K_i 107 nM) and similar hERG activity (16% inhibition at 5 μg/mL). The addition of a polar group on the side chain kept the binding unchanged (compound **23** K_i 99 nM). When the side chain with pyrrolidine was further extended (compounds **24** and **25**), 2- to 6-fold improvement in MCH R1 binding was observed. Replacing the pyrrolidine ring with 2,5-dimethylpiperazine essentially kept MCHR1 K_i unchanged (compound **26**, K_i 19 nM) while the use of bridged piperazine



Scheme 2. Synthesis of bicyclo[3.1.0]hexane **5**. Reagents and conditions: (a) $NaBH_4$, 58%; (b) TBDPSCl, imidazole, 100%; (c) *n*-BuLi, $(CH_3)_3SnCl$, THF, −78 °C, 40 min, 73%; (d) 3-bromo-cyclopenten-2-ol, $Pd(PPh_3)_4$, LiCl, Na_2CO_3, THF, 70 °C, 15 h, 62%; (e) Sm (5 equiv), CH_2I_2 (5 equiv), THF, −25 °C, 1 h, 52%; (f) Dess–Martin, 95%; (g) 2-pyrrolidin-1-yl-ethylamine, MS3Å, DCM, 98%; (h) 4-fluoro-3-trifluoromethylphenyl isocyanate, 100%; (i) TBAF; (j) DPPA, DBU; (k) $LiAlH_4$, 66% in three steps.



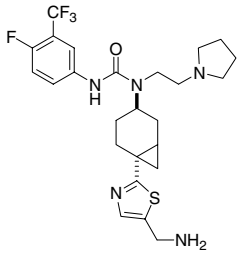
Scheme 3. Synthesis of bicyclo[3.1.0]hexanes **23**–**28**. Reagents: (a) TBAF, 74%; (b) DPPA, DBU, 75%; (c) amine, MS3Å, DCM, $NABH_4$; (d) ArNCO; (e) PPh_3; (f) TBAF; (g) EtOAc/3 N HCl, 10–20% yield.

decreased the binding by 5-fold (compound **28**, K_i 73 nM). An attempt to boost the binding by using 2,6-dichloropyridyl as the urea moiety improved K_i only modestly to 13 nM (compound **27**). Importantly, all these compounds showed much reduced hERG liability in the Rb efflux assay and these results encouraged us to pursue the optically pure compounds to further improve the in vitro binding.

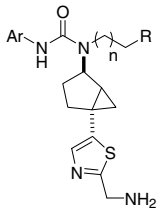
Scheme 4 outlines the synthesis of the optically pure compounds **25**, **32**, and **33**. After screening several different intermediates under several chiral column conditions, it was discovered that the enantiomers of azidoketone **19** could be separated by a chiral AD column.[19] Each enantiomer then underwent reductive amination with three amines **29**–**31**[17] and a total of 6 final targets was synthesized. The data (Table 2) clearly suggested that chirality of the core structure in this series played an important role for the MCH R1 activity. One set of compounds (compounds **25b**, **32b**, **33b**) derived from enantiomer **19a** are 20- to 42-fold more active than the other set of compounds (compounds **25a**, **32a**, **33a**) derived from enantiomer **19b**. In addition, the data indicated that the chirality of the side chain does not affect the MCH R1 binding (compounds **32a** versus **33a**, **32b** vs **33b**). As expected from the profiles of their racemic analogs, all these chiral compounds had much reduced hERG liability.

Four of these chiral compounds were selected for the mouse ex vivo assay to measure the receptor occupancy.[10] Compounds **32a**, **32b**, and **33a** showed modest inhibition of 16%, 20% and 26%, respectively, at 6 h (30 mg/kg, po). To our disappointment, although compound **33b** was 40-fold more active than **33a** in the in vitro assay, **33b** showed only modest improvement in ex vivo binding (39% inhibition). Compared with compound **3**[10] (MCH K_i 13 nM, mouse ex vivo assay: 88% inhibition at 6 h, 30 mg/kg, po), this new type of bicyclo[3.1.0]hexane derivatives showed lower ex vivo efficacy in the mouse model.[20]

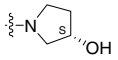
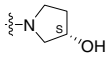
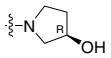
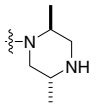
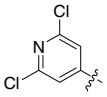
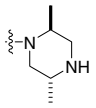
Table 1. MCH R1 binding and hERG data for racemic compounds

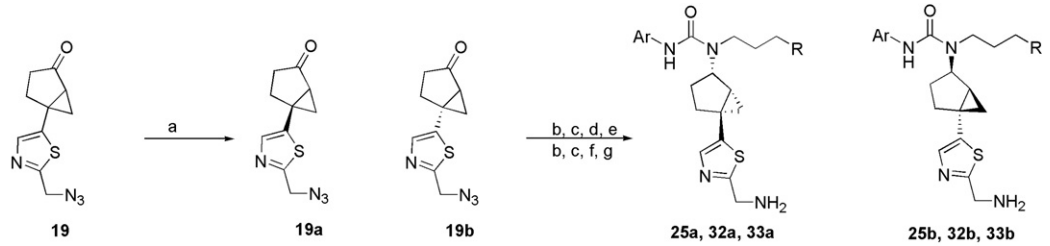


4

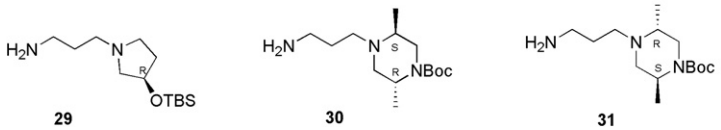


5, 23-28

Compound	Ar	*n*	R	MCH R1 K_i (nM)	Rb % inh. at 5 μg/mL
4	4-F,3-CF_3Ph			431 ± 3	19
5	4-F,3-CF_3Ph	1		107 ± 3	16
23	4-F,3-CF_3Ph	1		99 ± 8	8
24	4-F,3-CF_3Ph	2		45 ± 2	−4
25	4-F,3-CF_3Ph	2		17 ± 1	−4
26	4-F,3-CF_3Ph	2		19 ± 2	−8
27		2		13.1 ± 0.3	3
28	4-F,3-CF_3Ph	2		73 ± 7	14



19 **19a** **19b** **25a, 32a, 33a** **25b, 32b, 33b**

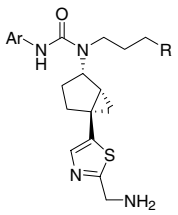


29 **30** **31**

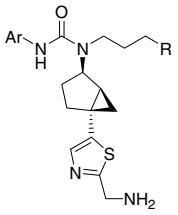
Scheme 4. Synthesis of optically pure bicyclo[3.1.0]hexanes **25**, **32**, and **33**. Reagents: (a) chiral AD column, IPA/hexane; (b) amine, MS3Å, DCM, $NABH_4$; (c) 4-fluoro-3-trifluoromethylphenyl isocyanate; (d) PPh_3; (e) TBAF, 10% yield in four steps; (f) EtOAc/3 M HCl; (g) PPh_3 (resin bound).

In summary, we have developed two different synthetic routes to heteroaryl substituted bicyclo[4.1.0]heptane and bicyclo[3.1.0]hexane analogs, respectively. Optically pure compounds were also obtained and some of these compounds retained strong binding with the MCH R1 receptor. All of these compounds had significantly attenuated hERG liabilities in the Rb efflux assay, thereby solving one of the key hurdles in the development of the MCH R1 antagonists.

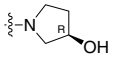
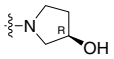
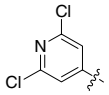
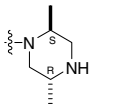
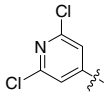
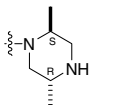
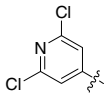
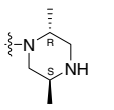
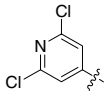
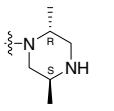
Table 2. MCH R1 binding, hERG, and mouse ex vivo data for optically pure compounds



25a,32a,33a



25b,32b,33b

Compound	Ar	R	MCH R1 K_i (nM)	Rb % inh. at 5 μg/mL	Mouse ex vivo % inh. at 6 h (30 mg/kg, po)
25a	4-F,3-CF_3Ph		167 ± 10	6	
25b	4-F,3-CF_3Ph		6.6 ± 0.2	8	
32a			117 ± 8	−13	20 ± 2
32b			6.1 ± 0.5	−12	16 ± 2
33a			171 ± 61	17	26 ± 3
33b			4.0 ± 0.2	22	39 ± 2

Acknowledgments

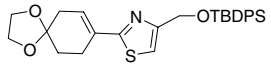
We thank Dr. Andrew Evans for some of the NMR work. Drs. Michael Czarniecki, Michael Graziano, Li Qiang, Mark McBriar, T.K. Sasikumar, Wen-Lian Wu, and Ruo Xu for their support, suggestions, and encouragement.

References and notes

1. Kawauchi, H.; Kawazoe, I.; Tsubokawa, M.; Kishida, M.; Baker, B. L. *Nature* **1983**, *305*, 321.
2. Rossi, M.; Choi, S.; O'Shea, D.; Miyoshi, T.; Ghatei, M. A.; Bloom, S. R. *Endocrinology* **1997**, *138*, 351.
3. (a) Qu, D.; Ludwig, D. S.; Gammeltoft, S.; Piper, M.; Pelleymounter, M.; Cullen, M. J.; Mathes, W. F.; Przypek, J.; Kanarek, R.; Maratos-Flier, E. *Nature* **1996**, *380*, 243; (b) Ludwig, D. S.; Tritos, N. A.; Mastaitis, J. W.; Kulkarni, R.; Kokkotou, E.; Elmquist, J.; Lowell, B.; Flier, J. S.; Maratos-Flier, E. *J. Clin. Invest.* **2001**, *107*, 379.
4. Shimada, M.; Tritos, N.; Lowell, B.; Flier, J.; Maratos-Flier, E. *Nature* **1998**, *396*, 670.
5. (a) Chambers, J.; Amers, R. S.; Bergsma, D.; Muir, A.; Fitzgerald, L. R.; Hervieu, G.; Dytko, G. M.; Foley, J. J.; Martin, J.; Liu, W.-S.; Park, J.; Ellis, C.; Ganguly, S.; Konchar, S.; Cluderay, J.; Leslie, R.; Wilson, S.; Sarau, H. M. *Nature* **1999**, *400*, 261; (b) Saito, Y.; Nothacker, H. P.; Wang, Z.; Lin, H. S.; Leslie, F.; Civelli, O. *Nature* **1999**, *400*, 265; (c) Sailer, A. W.; Sano, H.; Zeng, Z.; McDonald, T.; Pan, J.; Pong, S.-S.; Feighner, S. D.; Tan, C. P.; Fukami, T.; Iwaasa, H.; Hreniuk, D. L.; Morin, N. R.; Sadowski, S. J.; Ito, M.; Bansal, A.; Ky, B.; Figueroa, D. J.; Jiang, Q.; Austin, C. P.; MacNeil, D. J.; Ishihara, A.; Ihara, M.; Kanatani, A.; Van der Ploeg, L. H. T.; Howard, A. D.; Liu, Q. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 7564.
6. Goodfellow, V.; Rowbottom, M.; Dyck, B. P.; Tamiya, J.; Zhang, M.; Grey, T. D. WO 04081005 A1, 2004.
7. For a recent review, see: Handlon, A. L.; Zhou, H. *J. Med. Chem.* **2006**, *49*, 4017.
8. (a) Dyck, B.; Markison, S.; Zhao, L.; Tamiya, J.; Grey, J.; Rowbottom, M. W.; Zhang, M.; Vickers, T.; Sorensen, K.; Norton, C.; Wen, J.; Heise, C. E.; Saunders, J.; Conlon, P.; Madan, A.; Schwarz, D.; Goodfellow, V. S. *J. Med. Chem.* **2006**, *49*, 3753; (b) Kym, P. R.; Souers, A. J.; Campbell, T. J.; Lynch, J. K.; Judd, A. S.; Iyengar, R., et al. *J. Med. Chem.* **2006**, *49*, 2339; (c) Kowalski, T. J.; Spar, B. D.; Weig, B.; Farley, C.; Cook, J.; Ghibaudi, L.; Fried, S.; O'Neil, K.; Del Vecchio, R. A.; McBriar, M. D.; Guzik, H.; Clader, J.; Hawes, B. E.; Hwa, J. *Eur. J. Pharmacol.* **2006**, *535*, 182; (d) McBriar, M. D.; Guzik, H.; Shapiro, S.; Paruchova, J.; Xu, R.; Palani, A.; Clader, J. W.; Cox, K.; Greenlee, W. J.; Hawes, B. E.; Kowalski, T. J. O.; Neil, K.; Spar, B. D.; Weig, B.; Weston, D. J.; Farley, C.; Cook, J. *J. Med. Chem.* **2006**, *49*, 2294; (e) Palani, A.; Shapiro, S.; McBriar, M. D.; Clader, J. W.; Greenlee, W. J.; Spar, B.; Kowalski, T. J.; Farley, C.; Cook, J.; van Heek, M.; Weig, B.; O'Neil, K.; Graziano, M.; Hawes, B. *J. Med. Chem.* **2005**, *48*, 4746; (f) Vasudevan, A.; LaMarche, M. J.; Blackburn, C.; Che, J. L.; Luchaco-Cullis, C. A.; Lai, S., et al. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4174; (g) Kym, P. R.; Iyengar, R.; Souers, A.

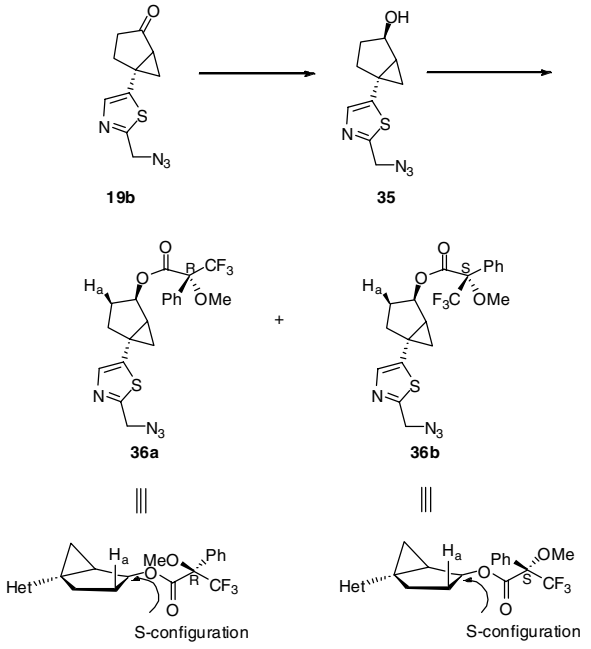
J.; Lynch, J. K.; Judd, A. S.; Gao, J., et al. *J. Med. Chem.* **2005**, *48*, 5888; (h) McBriar, M. D.; Guzik, H.; Xu, R.; Paruchova, J.; Li, S.; Palani, A.; Clader, J. W.; Greenlee, W. J.; Hawes, B.; Kowalski, T. J.; O'Neil, K.; Spar, B.; Weig, B. *J. Med. Chem.* **2005**, *48*, 2274; (i) Su, J.; McKittrick, B. A.; Tang, H.; Czarniecki, M.; Greenlee, W. J.; Hawes, B. E.; O'Neill, K. *Bioorg. Med. Chem.* **2005**, *13*, 1829; (j) Vasudevan, A.; Wodka, D.; Verzal, M. K.; Andrew, J.; Gao, J.; Brodjian, S.; Fry, D.; Dayton, B.; Marsh, K. C.; Hernandez, L. E.; Ogiela, C. A.; Collins, C. A.; Kym, P. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4879; (k) Arienzo, R.; Clark, D. E.; Cramp, S.; Daly, S.; Dyke, H. J.; Lockery, P.; Norman, D.; Roach, A. G.; Stuttle, K.; Tomlinson, M.; Wong, M.; Wren, S. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4099; (l) Carpenter, A. J.; Hertzog, D. L. *Exp. Opin. Ther. Patents* **2002**, *12*, 1639; (m) Borowsky, B.; Durkin, M. M.; Ogozalek, K.; Marzabadi, M. R.; DeLeon, J.; Lagu, B.; Heurich, R.; Lichtblau, H.; Shaposhnik, Z.; Daniewska, I.; Blackburn, T. P.; Branchek, T. A.; Gerald, C.; Vaysse, P. J.; Forray, C. *Nat. Med.* **2002**, *8*, 1039.

9. Xu, R.; Li, S.; Paruchova, J.; McBriar, M. D.; Guzik, H.; Palani, A.; Clader, J. W.; Cox, K.; Greenlee, W. J.; Hawes, B. E.; Kowalski, T. J.; O'Neil, K.; Spar, B. D.; Weig, B.; Weston, D. J. *Bioorg. Med. Chem.* **2006**, *14*, 3285.
10. Su, J.; McKittrick, B. A.; Tang, H.; Burnett, D. A.; Clader, J. W.; Greenlee, W. J.; McNemar, C.; Graziano, M.; Hawes, B. E.; O'Neil, K.; Spar, B.; Weig, B.; Kowalski, T.; Sorota, S.; Li, C.; Liu, T. *Bioorg. Med. Chem.* http://dx.doi.org/10.1016/j.bmc.2007.05.068.
11. For hERG, see: (a) Roche, O.; Trube, G.; Zuegge, J.; Pflimlin, P.; Alanine, A.; Schneider, G. *ChemBioChem* **2002**, *3*, 455; (b) Vandenberg, J. I.; Walker, W. D.; Campbell, T. J. *Trends Pharm. Sci.* **2001**, *22*, 240; (c) Sorota, S.; Zhang, X.-S.; Margulis, M.; Tucker, K.; Priestly, T. *Assay Drug Dev. Technol.* **2005**, *3*, 47.
12. Direct cyclopropanation of a thiazole substituted cyclohexene **34** using our initial route[9] was tried under many conditions without success.



34

13. Genet, J. P.; Juge, S.; Achi, S.; Mallart, S.; Ruiz Montes, J.; Levif, G. *Tetrahedron* **1988**, *44*, 5263.
14. Engel, P. S.; Bodager, G. A. *J. Org. Chem.* **1988**, *53*, 4748.
15. Tully, W. R.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. *J. Med. Chem.* **1991**, *34*, 2060.
16. Lautens, M.; Ren, Y. *J. Org. Chem.* **1996**, *61*, 2210.
17. The synthesis of side chain amines **17-19**, **29-31** was according to: Janeka, J. W.; Furness, M. S.; Zhang, X.; Coop, A.; Folk, J. E.; Mattson, M. V.; Jacobson, A. E.; Rice, K. C. *J. Org. Chem.* **2003**, *68*, 3976.
18. All compounds were tested with human MCH R1 receptor. Selected compounds were also tested with mouse and rat MCH R1 receptors and very similar K_i values were obtained.
19. Chiral AD column, 45% *i*-PrOH/hexane, **19a** 17.6 min, **19b** 32.9 min. Isomer **19b** was then reduced to the corresponding *trans* alcohol **35** which was converted to Mosher's esters **36a** and **36b.** Based on chemical shift difference of Ha in **36a** and **36b** ($\Delta\delta = \delta_{\mathbf{36a}} - \delta_{\mathbf{36b}} = 0.06$ ppm) as well as that for other protons, the absolute stereochemistry was then determined. See also: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512,



20. We assume the lower ex vivo binding of this new series is related with its PK profiles, although no experimental data are available.