Bioorganic & Medicinal Chemistry Letters 20 (2010) 4757–4761

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and cannabinoid-1 receptor binding affinity of conformationally constrained analogs of taranabant

Ihor E. Kopka [a], Linus S. Lin [a], James P. Jewell [a,†], Thomas J. Lanza [a], Tung M. Fong [b], Chun-Pyn Shen [b], Zhege J. Lao [b], Sookhee Ha [c], Laurie G. Castonguay [c], Lex Van der Ploeg [b], Mark T. Goulet [a,†], William K. Hagmann [a,*]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ 07065, USA
[b] Department of Metabolic Disorders, Merck Research Laboratories, Rahway, NJ 07065, USA
[c] Department of Molecular Modeling, Merck Research Laboratories, Rahway, NJ 07065, USA

ARTICLE INFO

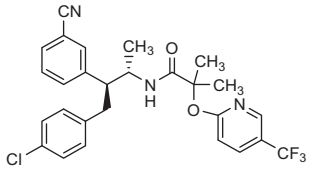
Article history:
Received 22 April 2010
Revised 22 June 2010
Accepted 25 June 2010
Available online 1 July 2010

Keywords:
Cannabinoid
CB1R
Obesity
Conformationally constrained

ABSTRACT

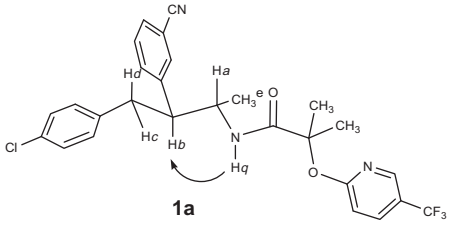
The design, synthesis, and binding activity of ring constrained analogs of the acyclic cannabinoid-1 receptor (CB1R) inverse agonist taranabant **1** are described. The initial inspiration for these taranabant derivatives was its conformation **1a**, determined by ^{1}H NMR, X-ray, and molecular modeling. The constrained analogs were all much less potent than their acyclic parent structure. The results obtained are discussed in the context of a predicted binding of **1** to a homology model of CB1R.

There have been significant efforts toward identifying potent selective antagonists/inverse agonists of the cannabinoid-1 receptor (CB1R) as a treatment for obesity.[1–4] Several compounds progressed to clinical studies and were found to be efficacious in promoting sustained weight loss. One of these, rimonabant, had been approved for marketing in the EU as a treatment for obesity. Unfortunately, the long term safety profile of these agents was found not to be consistent with treating an overweight but otherwise healthy population and development of centrally acting CB1R antagonists/inverse agonists was halted. In our efforts to identify potent, selective CB1R modulators, we discovered taranabant **1** which was fully effective in preclinical and clinical evaluations of weight loss.[5–7] The acyclic nature of structure **1** is different from that of other CB1R antagonists/inverse agonists which generally contain two phenyl rings appended to a heteroaryl ring with additional substitution and/or appended fused rings. A detailed study of the conformation of **1** revealed that it had a rigid structure **1a** (Fig. 1) which overlapped quite well with rimonabant, especially in the region of the diphenylethyl substitution.[8] In an effort to explore this conformation, we describe herein the preparation of a series of simple methyl substitutions along the propyl backbone as well as cyclic structures that overlapped well with **1a**.



1, taranabant

hCB1R IC_{50} 0.74 nM



1a

Figure 1. Structure of taranabant and its conformation as determined from X-ray, ^{1}H NMR, and molecular modeling studies.

The 3-bromophenyl derivative **2** (Fig. 2) was chosen as the acyclic reference compound. The methylated derivatives of **2** were prepared by analogous methods previously described and are outlined below.[9] Binding affinities were determined by inhibition of

* Corresponding author. Tel.: +1 732 594 7249; fax: +1 732 594 5966.
E-mail address: william.hagmann@merck.com (W.K. Hagmann).
† Present address: Merck Research Laboratories, Boston, MA 02115, USA.

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.06.127

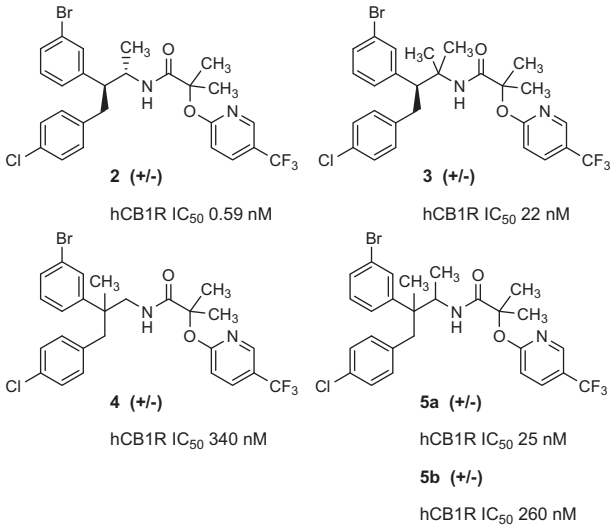


Figure 2. The effect of backbone methyl substitution of **2** on CB1R binding potency.

binding of [^{3}H]-CP55,490 to recombinant human CB1 or CB2 expressed on Chinese hamster ovary (CHO) cells.[10] The reported IC_{50} values are the result of two determinations ($n = 2$). The addition of a methyl group replacing *Ha* of **1a** afforded the geminal dimethyl analog **3** which lost binding potency compared to **2**. This should not be too surprising as a methyl group in the *Ha* position of **1a** is expected to eclipse the adjacent phenyl ring and move it into a different and less favorable conformation. The transposition of the methyl group in **4** to the *Hb* position takes away the contribution of the $CH_3{}^e$ group in stabilizing the conformation of **1a**, resulting in a larger loss of potency. The return of the stabilizing influence of $CH_3{}^e$ is evident in diastereomer **5a** which improves binding potency relative to **4**. The other diastereomer **5b** is much less active. However, none of these methyl substitutions in **3–5** afford compounds with the potency of **2**, demonstrating how important, and perhaps how sensitive, the conformation in **1a** is to the potency of these acyclic CB1R inverse agonists.

The preparation of tetramethyl derivative **3** is outlined in Scheme 1. This synthetic route is particularly long and circuitous as the tetramethyl amine **12** was not the intended target but was rather an unexpected product in the preparation of a benzylic fluorine analog derived from compound **10**. 3-Bromobenzaldehyde was homologated with cyanotrimethylsilane in the presence of zinc chloride followed by esterification to afford α-hydroxy phenylacetate **6**. Treatment of **6** with DAST displaced the hydroxyl group to yield α-fluoro-phenylacetate **7**. Alkylation with 4-chlorobenzylbromide followed by reduction/oxidation gave aldehyde **9**. Reaction with chiral *N-tert*-butylsulfinyl amine afforded chiral sulfinyl imine **10**.[11] Treatment with methylmagnesium bromide resulted in the introduction of two methyl groups, possibly through an aziridine intermediate, to yield **12** without the benzylic fluorine. Cleavage of the N–S bond with HCl gave the dimethyl amine **12** which was coupled to the fibric acid[9] to give the tetramethyl derivative **3**.

The synthesis of the transposed methyl derivative **4** is outlined in Scheme 2. 3-Bromo-phenylacetate was alkylated with 4-chlorobenzylchloride and then with methyliodide to afford **14**. The ester in **14** was reduced with lithium aluminum hydride, followed by sulfonylation with mesylchloride (MsCl) and displacement with sodium azide to yield **16**. The azide **16** was reduced with hydrogen in the presence of platinum oxide and Boc anhydride; the latter was necessary for purification of the desired product. The *N-t*-Boc group was subsequently removed with 4 M HCl in dioxane to afford amine hydrochloride **17**. The fibric acid that was typically used was converted to its acylchloride and reacted with **17** in the presence of *N*-methylmorpholine (NMM) to afford **4**.

The preparation of the benzylic methyl derivatives of **2** are outlined in Scheme 3. 3-Bromophenyl acetone[9] was successively alkylated, first with methyliodide followed by 4-chloro-benzylchloride to yield **19**. Reduction with sodium borohydride gave the alcohol **20**. Treatment with mesylchloride in the presence of triethylamine (TEA) followed by reaction with sodium azide gave a mixture of diastereomeric azides which were separated by column chromatography on silica gel eluted with ethyl acetate/hexanes. These diastereomers were separately reduced as noted above to afford amine **22** and reacted with the acid chloride of the pyridyl fibric acid to afford the isomers **5a** (major, faster eluting) and **5b** (minor, slower eluting).

In order to confirm the speculations about the effect on conformations by the methyl additions or transpositions in compounds **3–5**, minimum energy conformations were determined for **2** and **3–5** and molecular overlays were determined (Fig. 3).[12] All compounds have good overlap in the region of the trifluoropyridyl ether, but the addition/transposition of the backbone methyls on the propyl group causes the phenyl rings to rotate away from that

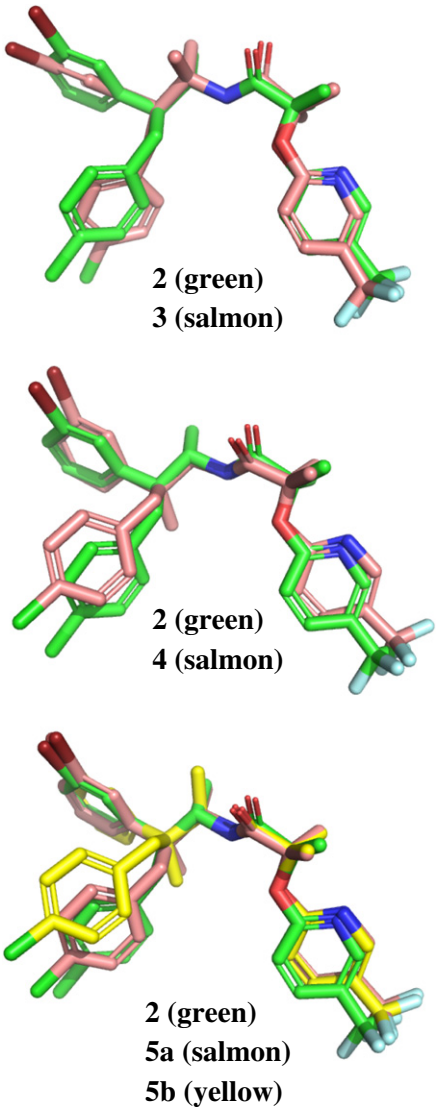
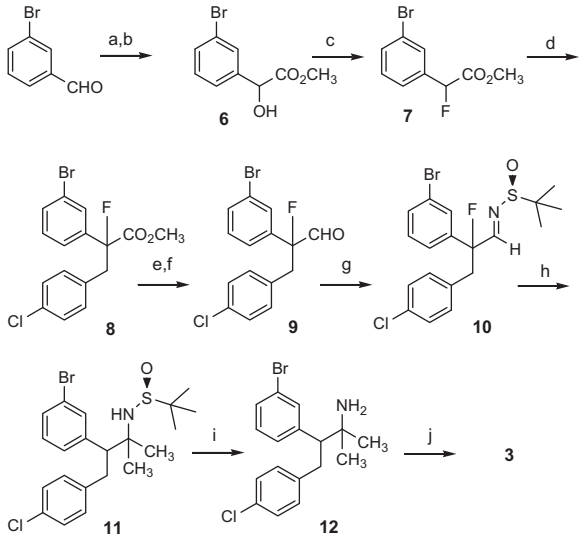
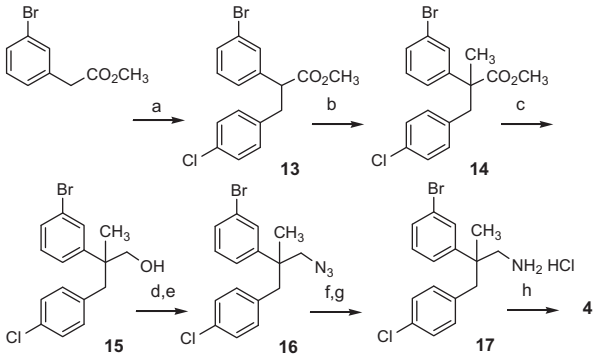


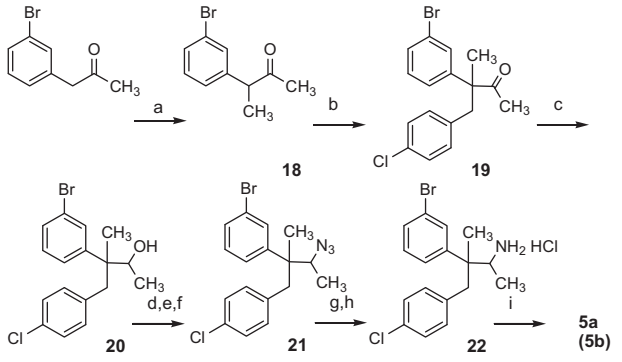
Figure 3. Overlay of minimum energy conformation of compound **2** with compounds **3**, **4**, **5a**, and **5b**.



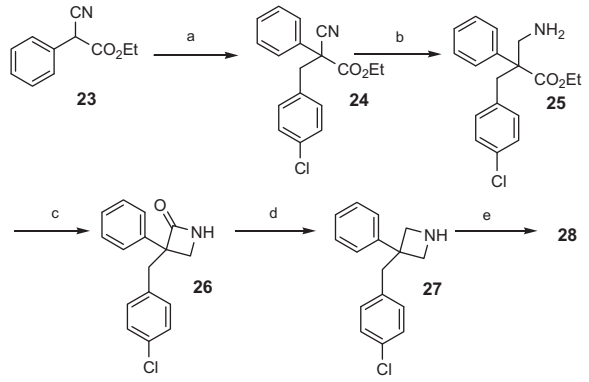
Scheme 1. Preparation of tetramethyl derivative **3**. Reagents and conditions: (a) TMS-CN, $ZnCl_2$, CH_2Cl_2, 0 °C; (b) HCl (g), MeOH, rt; (c) DAST, CH_2Cl_2, 0 °C; (d) KHMDS, $BrCH_2Ph$-4-Cl, THF, −78 °C; (e) LAH, Et_2O, −78 °C; (f) PCC, CH_2Cl_2, 0 °C; (g) (*R*)-*t*-Bu-S(O)NH_2, $Ti(OEt)_4$, THF, rt; (h) CH_3MgBr, CH_2Cl_2, −78 °C; (i) HCl (g), MeOH, dioxane, EtOAc, rt; (j) PyBOP, NMM, CH_2Cl_2, R-CO_2H, 20 h.



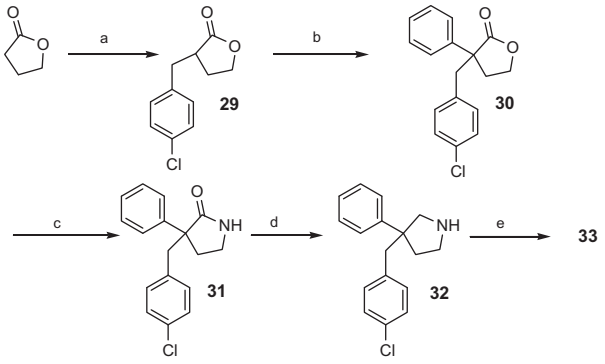
Scheme 2. Preparation of benzylic methyl derivative **4**. Reagents and conditions: (a) KHMDS, $ClCH_2Ph$-4-Cl, THF, −78 °C; (b) KHMDS, CH_3I, THF, −78 °C; (c) LAH, Et_2O, −50 °C; (d) MsCl, TEA, EtOAc, −10 °C to >0 °C; (e) NaN_3, DMF 120 °C to >150 °C, 21 h; (f) $(Boc)_2O$, Pt_2O, H_2, EtOAc; (g) 4 M HCl, dioxane; (h) NMM, CH_2Cl_2, R-COCl, rt.



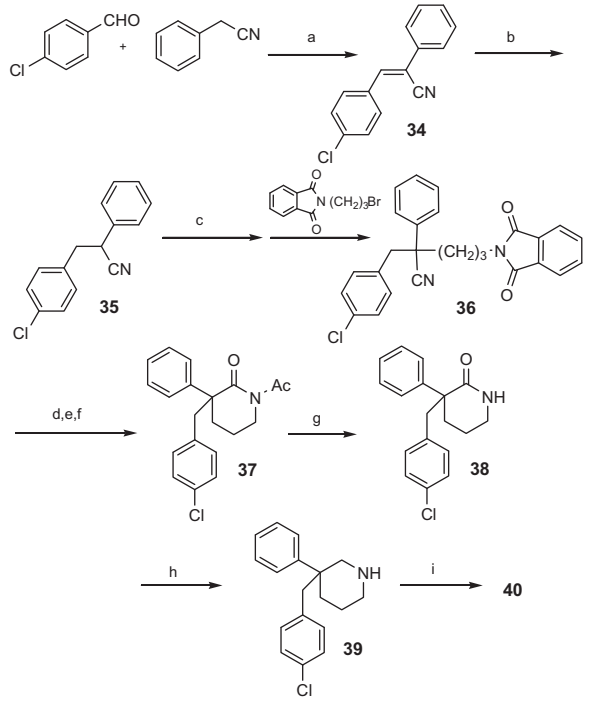
Scheme 3. Preparation of dimethyl derivatives **5a** and **5b**. Reagents and conditions: (a) Cs_2CO_3, CH_3I, AcCN, rt; (b) CsOH, CH_2Cl_2, rt; (c) $NaBH_4$, MeOH, rt, 10 min; (d) MsCl, TEA, EtOAc, 0 °C, 10 min; (e) NaN_3, DMF, 120 °C, 10 h; (f) diastereomers separated onsilica gel chromatography; (g) $(Boc)_2O$, Pt_2O, H_2, EtOAc, rt; (h) 4 M HCl, dioxane, rt; (i) NMM, CH_2Cl_2, R-COCl, rt.



Scheme 4. Synthesis of azetidine derivative **28**. Reagents and conditions: (a) $BrCH_2Ph$-4-Cl, LiHMDS, THF, DMI, −78 °C; (b) W2 RaNi, NH_3, EtOH, 20 psi H_2, (c) *t*-BuMg, Et_2O, 24 °C; (d) DIBAL, reflux, 2 h; (e) PyBOP, DIPEA, CH_2Cl_2, R-CO_2H, 20 h.



Scheme 5. Synthesis of pyrrolidine derivative **33**. Reagents and conditions: (a) $BrCH_2Ph$-4-Cl, LiHMDS, THF, DMI, −78 °C; (b) 5% $Ni(COD)_2$, 8.5% BINAP, 2.15 equiv NaHMDS, 15% $ZnBr_2$, tol, 20 h, 75 °C; (c) $Al(CH_3)_3$, NH_3, DCE, 6 h, 75 °C; (d) DIBAL, tol, reflux, 2 h; (e) PyBOP, DIPEA, CH_2Cl_2, RCO_2H, 20 h.



Scheme 6. Preparation of piperidine derivative **40**. Reagents and conditions: (a) piperidine, EtOH, reflux; (b) $NaBH_4$, 3:1 pyr:MeOH, reflux; (c) LiHMDS, THF, DMI, −78 °C; (d) concd HBr, heat; (e) adjust pH to 6.5; (f) Ac_2O, heat; (g) NaOH, EtOH; (h) DIBAL, tol, reflux 2 h; (i) PyBOP, DIPEA, CH_2Cl_2, RCO_2H, 20 h.

seen with the parent molecule **2**. Compounds **3** and **5a** appear to have better overlays with the conformation of **2** than do compounds **4** and **5b**. These results are consistent with the order of binding potencies of **3**–**5** relative to **2** (Fig. 2).

Further examination of the conformation of **1a** suggested that the proton at *Hb* is near to *Hq* on the amide nitrogen. No NOE was reported between these two protons in the ^{1}H NMR studies, but the overall conformation of **1a** places them in a spatial relationship analogous to 1,3 hydrogens in a cyclohexane chair conformation. Closing a ring between these two positions (the arrow between *Hb* and *Hq* in **1a**, Fig. 1) would not be expected to change the overall conformation of the acyclic backbone. However, docking studies with taranabant into the CB1R homology model suggested an important hydrogen bond between the NH of the amide and Ser383 of CB1R. Alkylation of that nitrogen through cyclization would eliminate that interaction and may introduce unfavorable steric interactions. Simple modeling studies did not distinguish which ring size would be optimum so 4- to 6-membered rings were prepared as shown in Schemes 1–3.

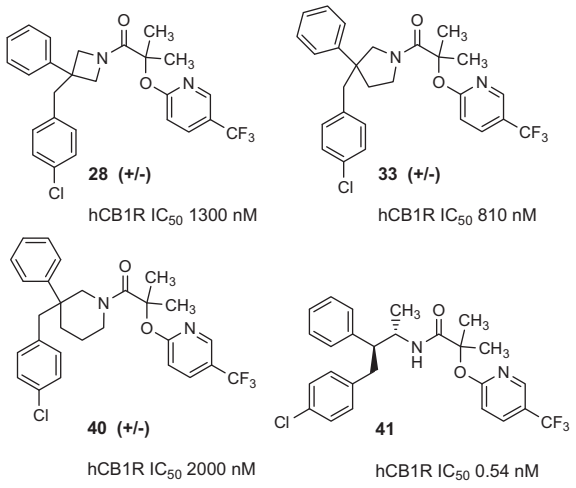


Figure 4. Comparison of acyclic and cyclic taranabant analogs.

The four-membered ring azetidine derivative was prepared as outlined in Scheme 4. Ethyl α-cyanophenylacetate **23** was treated with lithium hexamethyldisilazide (LiHMDS) in the presence of 1,3-dimethyl-2-imidazolidone (DMI) in THF and was alkylated with 4-chlorobenzylbromide to yield cyano ester **24**. Hydrogenation of **24** with Raney nickel catalyst in the presence of ammonia reduced the cyano group to the aminoester **25**. Treatment with *t*-butylmagnesium chloride as a base in ether effected ring closure to azetidinone **26**. DIBAL reduction afforded the azetidine **27** which was coupled to the fibric acid to afford amide **28**.

The pyrrolidine analog was prepared as outlined in Scheme 5. γ-Butyrolactone was treated with LiHMDS, DMI in THF and alkylated with with 4-chlorobenzylbromide to afford lactone **29**. The phenyl ring was introduced employing the nickel–BINAP catalyzed method described by Spielvogel and Buchwald to yield **30**.[13] The lactone was converted to the lactam **31** by treatment with trimethylaluminum/ammonia followed DIBAL reduction to yield pyrrolidine **32**. Coupling with the fibric acid gave the five-membered ring analog **33**.

The synthesis of the piperidine analog began with condensation of 4-chlorobenzaldehyde and phenylacetonitrile to yield *trans*-stilbene derivative **34** (Scheme 6). Reduction with sodium cyanoborohydride afforded diphenylethylene derivative **35** which was treated with lithium hexamethyldisilylamide followed by alkylation with phthalylamidopropylbromide to yield **36**. Treatment of **36** with concentrated hydrogen bromide with heating removed the protecting group which was followed by cooling and pH adjustment to 6.4 which affected ring closure. To facilitate purification, the crude lactam was treated with acetic anhydride to acylate

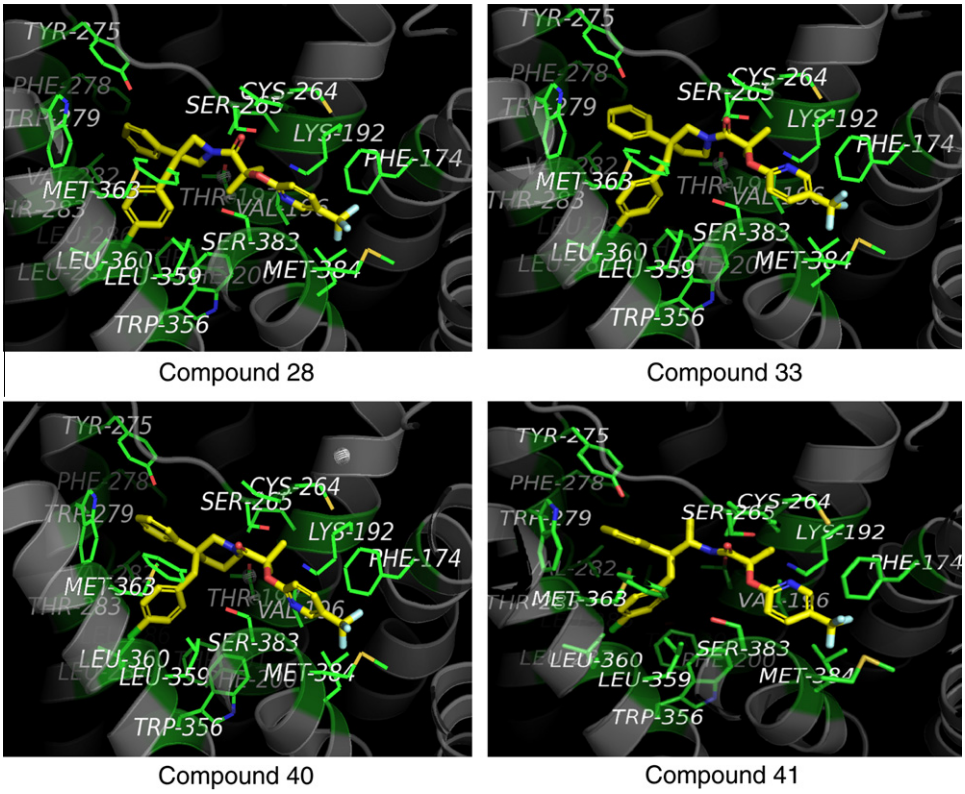


Figure 5. Docking of minimum energy conformations of compounds **28**, **33**, **40**, and **41** into the CB1R homology model.

the NH group to form **37**. Treatment with sodium hydroxide to remove the acetyl group (**38**) followed by DIBAL reduction gave piperidine **39**. Again, coupling with the fibric acid gave the desired product **40**.

The binding potencies of the 4- to 6-membered ring derivatives **28**, **33**, and **40** are shown in Figure 4. The acyclic analog **41** is shown for comparison. Obviously, all of these conformationally constrained analogs lost considerable potency for binding to CB1R relative to the acyclic derivative **41** despite very good molecular overlays. Part of this loss of potency may be for the same reason that the methylated derivatives **4** and **5** lost binding activity; that is, the methyl group at the benzylic position (replacing *Hb*) causes an unfavorable interaction with the chlorobenzyl group which causes a change in its position. The methylene groups of **28**, **33**, and **40** may do the same thing.

Earlier efforts had shown that N-methylation of the acyclic structure caused ~5-fold loss of potency (data not shown), although the reason for that loss is less obvious since replacement of *Hq* would appear to be benign in conformation **1a**. Greater insights as to the reasons for these losses in CB1R activity of the methylated and ring constrained analogs may come less from analyzing the apparent conformation of **1a** but more so from examining the possible binding modes of compounds **28**, **33**, and **40** in a CB1R homology model (Fig. 5).[5,14,15] Docking of compounds was performed with ICM software. An important interaction that pertains to the compounds described herein would seem to be a hydrogen bond formed between the NH of the amide and Ser383. Mutation of this amino acid residue led to a large loss of binding activity for taranabant but not for rimonabant. N-methylation or the ring structures shown in Figure 4 would eliminate this important interaction. In addition, the carbons of the appended, constrained rings of all three compounds appear to point back towards Thr197, making unwanted interactions. It appears that docking of these constrained ring structures into the CB1R homology model was more predictive of their relative binding potencies than was the analysis of conformations of the acyclic parent structure.

In summary, we have described the design, synthesis, and binding activity of ring constrained analogs of the acyclic CB1R inverse agonist, taranabant **1**. The initial inspiration for these taranabant derivatives was careful examination of its conformation **1a**, determined by ^{1}H NMR, X-ray, and molecular modeling. However, our observations were the constrained analog were all much less potent than their acyclic parent structures. With respect to designing novel, constrained derivatives of potent molecules, the present study illustrates, once again, the need to consider potential bound conformations and interactions and not just solution and/or solid state structures.

References and notes

1. Lee, H.-K.; Choi, E. B.; Pak, C. S. *Curr. Top. Med. Chem.* **2009**, *9*, 482.
2. Janero, D. R.; Makriyannis, A. *Expert Opin. Emerg. Drugs* **2009**, *14*, 43.
3. Akbas, F.; Gasteyger, C.; Sjodin, A.; Astrup, A.; Larsen, T. M. *Obes. Rev.* **2009**, *10*, 58.
4. Lange, J. H. M.; Kruse, C. G. *Chem. Rec.* **2008**, *8*, 156.
5. Fong, T. M.; Guan, X.-M.; Marsh, D. J.; Shen, C.-P.; Stribling, D. S.; Rosko, K. M.; Lao, J.; Yu, H. G.; Feng, Y.; Xiao, J. C.; Van der Ploeg, L. H. T.; Goulet, M. T.; Hagmann, W. K.; Lin, L. S.; Lanza, T. S. J., Jr.; Jewell, J. P.; Liu, P.; Shah, S. K.; Qi, H.; Tong, X.; Wang, J.; Xu, S. S.; Francis, B.; Strack, A. M.; MacIntyre, D. E.; Shearman, L. P. *J. Pharmacol. Exp. Ther.* **2007**, *321*, 1013.
6. Hagmann, W. K. *Arch. Pharm.* **2008**, *341*, 405.
7. Addy, C.; Wright, H.; Van Laere, K.; Gantz, I.; Erondu, N.; Musser, B. J.; Lu, K.; Yuan, J.; Sanabria-Bohorquez, S. M.; Stoch, A.; Stevens, C.; Fong, T. M.; De Lepeleire, I.; Cilissen, C.; Cote, J.; Rosko, K.; Gendrano, I. N., III; Nguyen, A. M.; Gumbiner, B.; Rothenberg, P.; de Hoon, J.; Bormans, G.; Depre, M.; Eng, W.; Ravussin, E.; Klein, S.; Blundell, J.; Herman, G. A.; Burns, H. D.; Hargreaves, R. J.; Wagner, J.; Gottesdiener, K.; Amatruda, J. M.; Heymsfield, S. B. *Cell Metab.* **2008**, *7*, 68.
8. Lin, L. S.; Ha, S.; Ball, R. G.; Tsou, N. N.; Castonguay, L. A.; Doss, G. A.; Fong, T. M.; Shen, C.-P.; Xiao, J. C.; Goulet, M. T.; Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 2108.
9. Lin, L. S.; Lanza, T. J., Jr.; Jewell, J. P.; Liu, P.; Shah, S. K.; Qi, H.; Tong, X.; Wang, J.; Xu, S. S.; Fong, T. M.; Shen, C.-P.; Lao, J.; Xiao, J. C.; Shearman, L. P.; Stribling, D. S.; Rosko, K.; Strack, A.; Marsh, D. J.; Feng, Y.; Kumar, S.; Samuel, K.; Yin, W.; Van der Ploeg, L. H. T.; Goulet, M. T.; Hagmann, W. K. *J. Med. Chem.* **2006**, *49*, 7584.
10. Felder, C. C.; Joyce, K. E.; Briley, E. M.; Mansouri, J.; Mackie, K.; Blond, O.; Lai, Y.; Ma, A. L.; Mitchell, R. L. *Mol. Pharmacol.* **1995**, *48*, 443.
11. Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883.
12. One hundred conformations of each compound were generated with jg, a conformer generator in-house software tool. The conformers were minimized by Batchmin with MMFF force field calculations. Low energy conformers from compounds **3**–**5** were selected and overlaid with the lower conformer of compound **2**.
13. Spielvogel, D. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 3500.
14. Salo, O. M. H.; Lahtela-Kakkonen, M.; Gynther, J.; Jarvinen, T.; Poso, A. *J. Med. Chem.* **2004**, *47*, 3048.
15. Lange, J. H. M.; Kruse, C. G. *Drug Discov. Today* **2005**, *10*, 693.