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Design, chemical synthesis, and biological evaluation of novel triazolyl analogues of taranabant (MK-0364), a cannabinoid-1 receptor inverse agonist

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ABSTRACT

Being obese has various health problems that are related to type 2 diabetes mellitus, cardiovascular disease, hypertension, hyperlipidemia, and fibrinolytic abnormalities. Merck's taranabant (MK-0364), a CB1R inverse agonist, is currently in Phase 3 clinical trials, and is being actively pursued by Merck toward obesity market. Merck intends to file for FDA approval of taranabant in 2008. In order to increase solubility and potency of taranabant, or even possibly improve safety, novel triazole analogues of taranabant have been designed and synthesized. We introduced a pivotal asymmetric center via the Evans chiral auxiliary methodology and set up 1,2,4-triazole via substitution of α-bromoketone. Subsequently, diastereoselective reduction was accomplished to install adjacent essential asymmetric center. This method allowed us to prepare readily sub-gram scale of the target compounds in a convenient way. The synthesized analogues were subjected to biological evaluation involving cannabinoid CB1 receptor binding affinity. While the parent taranabant bears highly potent binding affinity to cannabinoid CB1 receptor, neither of the analog structures improved CB1 receptor binding affinities.

1. Introduction

Obesity is a multi-factorial, chronic disorder that has reached epidemic proportions in most industrial countries and is now threatening to become a global epidemic.[1] The number of deaths per year attributable to obesity is about 30,000 in the UK and nearly 400,000 in the USA, where obesity is set to overtake smoking as the main preventable cause of illness and premature death.[2–4] The total direct and indirect costs of obesity were estimated to be approximately €32,800 million per year in the EU and $99.2 billion per year in the USA.[4,5] Obesity poses a major health risk for serious diet-related chronic disease, including type 2 diabetes, cardiovascular disease, hypertension and stroke, and some of cancers.[2] For these reasons, the World Health Organization declared obesity a global epidemic[6,7] and obesity is now considered as disease that needs pharmacological treatments.[8–10]

At the present time, only two drugs are approved by US FDA for the long-term treatment of obesity: the dual serotonin–norepinephrine reuptake inhibitor sibutramine and the pancreatic lipase inhibitor orlistat. While these agents show clinical efficacy, both of them have some tolerability or safety concerns.[11] There is an enormous opportunity to make a significant, positive impact on the health and lives of obese people through the discovery and development of additional pharmacotherapy options. At last it was discovered that modulation of endocannabinoid system by specifically blocking the cannabinoid receptor 1 (CB1) in both the brain and periphery can provide a novel target for the treatment of obesity.[10]

Recently, among arsenal to fight obesity, rimonabant (SR141716), a selective cannabinoid-1 receptor (CB1R) inverse agonist discovered by Sanofi Aventis, is currently on the market in the European Union and in several other countries. On the other hand, Merck's taranabant (MK-0364), another CB1R inverse agonist, is currently in Phase 3 clinical trials and Merck intends to file for FDA approval of taranabant in 2008. Additional CB1 antagonist in the late-stage pipeline includes CP-945,598 (otenabant) developed by Pfizer (Fig. 1).

With our efforts to discover and develop a new medicine for the treatment of obesity,[12] we have recently reported a convenient total synthesis of taranabant (MK-0364), a novel cannabinoid-1 receptor inverse agonist as an anti-obesity agent.[13] Recently, a pharmacophore model for the binding of a low energy conformation of taranabant in the CB1 receptor has been reported.[14] Similar to rimonabant, taranabant interacted with a group of aromatic residues (Phe200, Trp279, Trp356, and Tyr275) of CB1R through the two phenyl rings and with Phe170 and Leu387 through the CF_3-py

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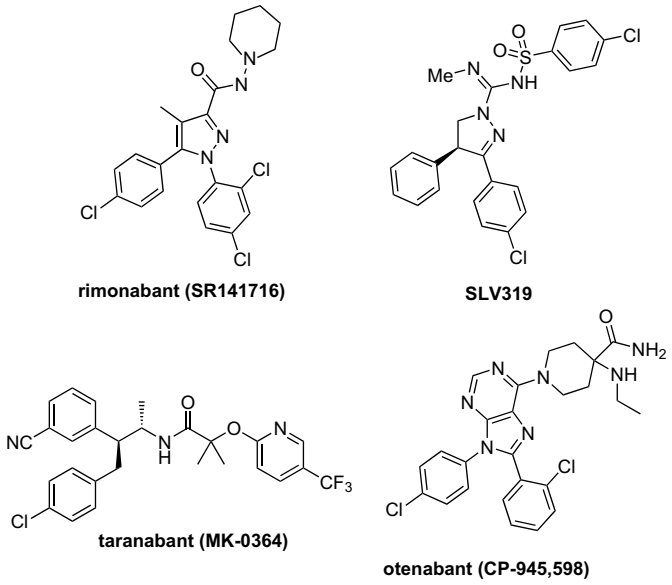


Figure 1. Structures of CB1R antagonists or inverse agonists/rimonabant (SR141716), SLV319, taranabant (MK-0364), and otenabant (CP-945,598).

ring. The strong hydrogen bond formed between the NH of taranabant and the hydroxyl of ser383 was reported to be essential to the superior CB1R binding affinity of taranabant. We envisioned that placement of additional polar functional group or heterocycle onto methyl group adjacent to the amide of taranabant might potentially form hydrogen bond with the hydroxyl of tyr275 residue. Among many heterocycles, we were particularly interested in a triazole or tetrazole as a potential hydrogen acceptor, since these small heterocycles might be able to increase solubility[23] and potency of taranabant, or even possibly improve safety.[24] Herein we wish to describe an asymmetric synthesis and biological evaluation of novel triazole analogues of taranabant (MK-0364) featuring Evans chiral auxiliary methodology to install a pivotal benzylic stereogenic center (Fig. 2).

2. Results and discussion

2.1. Synthetic plan

Our synthetic strategy for *N*-((2*R*,3*S*)-4-(4-chlorophenyl)-3-(3-cyanophenyl)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl)-2-methyl-2-(5-(trifluoromethyl)pyridin-2-yloxy)propanamide (**1**) is outlined in Scheme 1. We reasoned that the target compound **1** can be obtained by typical amide bond forming reaction of acid **2** and amine **3**. The amine **3** would then be produced from the corresponding alcohol **4** through mesylation and the subsequent displacement by azide. In turn, we envisioned that the alcohol **4** would be generated by diastereoselective reduction of ketone **5** and subsequent introduction of cyano group via Pd-catalyzed cyanation. The requisite **5** would be best installed by displacement of α-bromoketone **6** with 1,2,4-triazole. In order to provide the requisite bromide **6**, an appropriate carboxylic acid **7** would be required as shown in Scheme 1.

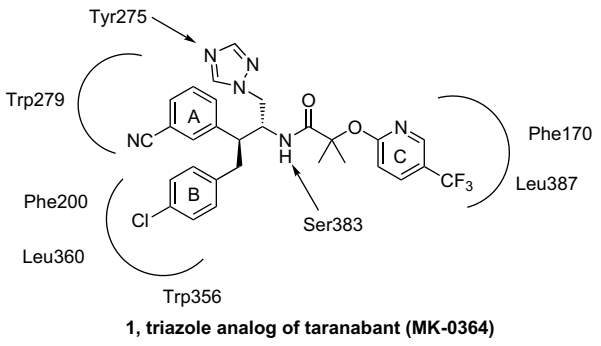


Figure 2. Triazole analog of taranabant (MK-0364) and its potential receptor–ligand interaction.

2.2. Total synthesis of triazolyl analogue of taranabant 1

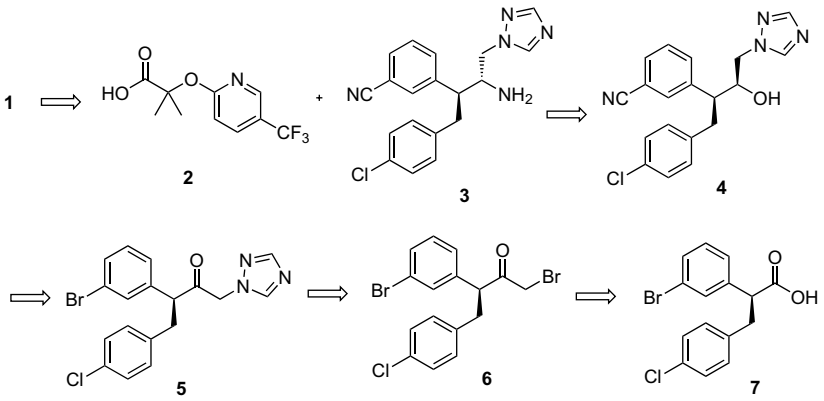
At the outset, the synthesis of carboxylic acid **7** was achieved as described in Scheme 2. We have previously reported the preparation of acid **7** using Evans asymmetric chemistry protocol as shown in method A, Scheme 2.[13] During the course of our anti-obesity program, non-trivial quantity of carboxylic acid **7** was required as an intermediate. While several approaches were considered, one attractive method was revealed by literature search (method B, Scheme 2). This approach was appealing since the chiral auxiliary appears to be relatively cheap, and many starting materials as well as products are reported to be in crystalline forms. According to the reports, the enolates of pseudoephedrine amides undergo highly diastereoselective reactions with various alkyl halides.[15]

Thus, 3-bromophenyl acetic acid **8** was coupled with (+)-pseudoephedrine under conditions of HOBt, EDCI, and NMM in DMF to produce the corresponding tertiary amide **12** as a white solid in 90% yield. Next, alkylation of pseudoephedrine amide **12** was accomplished by dianion formation with LiHMDS in THF in the presence of 6 equiv of lithium chloride, followed by the addition of 1-(bromomethyl)-4-chlorobenzene at −10 °C. As reported, the use of lithium chloride accelerates alkylation reaction and is critical for the complete conversion to **13**. Next, the chiral auxiliary of **13** was cleaved by standard conditions to produce the corresponding acid **7** in 70% yield.

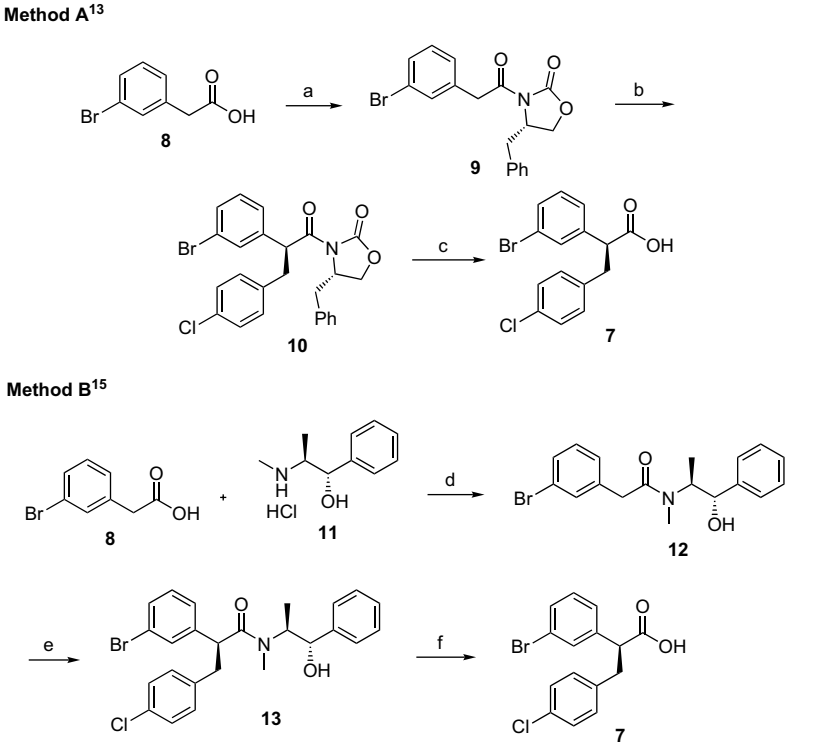
With the requisite carboxylic acid **7** in hand, focus shifted to the efficient preparation of the chiral alcohol **15** (Scheme 3). The first approach toward **15** involves epoxide ring opening reaction using 1,2,4-triazole in the presence of a suitable base.[16] Despite rather extensive experimentation, we were unable to effect the requisite coupling reaction in a satisfactory manner. We then examined the feasibility of reacting 1-[(trimethylsilyl)methyl]-1,2,4-triazole (**17**) with aldehyde **16** in the presence of tetrabutylammonium fluoride (TBAF) to give triazolyl alcohol **15**.[17] The fluoride was anticipated to attack the silyl group to generate triazolylmethyl anion that would then react with aldehyde **16** to lead to alcohol **15**. Under these conditions, starting material **16** was invariably recovered from all our experiments. This is probably due to a tendency to form enolate anion by proton transfer to triazolylmethyl anion.[17]

At this stage, we were intrigued by the attractive possibility of converting acid **7** into triazolyl ketone **5** via α-bromoketone **6** in order to adopt diastereoselective reduction using bulky reducing agent such as L-Selectride.[13,18] Thus, acid **7** was converted into an activated acyl chloride. The activated group was displaced with diazomethane or commercially available trimethylsilyldiazomethane ($TMSCHN_2$). Subsequently, α-diazoketone **18** was transformed into an α-bromoketone **6** by exposure to aqueous hydrobromic acid uneventfully.[19] Displacement reaction of bromide **6** with a commercially available 1,2,4-triazole, sodium derivative in DMF at ambient temperature proceeded smoothly to yield the requisite intermediate **5**. Systematic optimization of the reaction sequence allowed us to avoid any tedious purification steps of the corresponding intermediates, thereby providing **5** in 48% yield for four steps from acid **7** (Scheme 4).

The stage was set for the key diastereoselective reduction to install adjacent essential asymmetric center for taranabant



Scheme 1. Retrosynthetic analysis of target compound, a taranabant (MK-0364) analog.



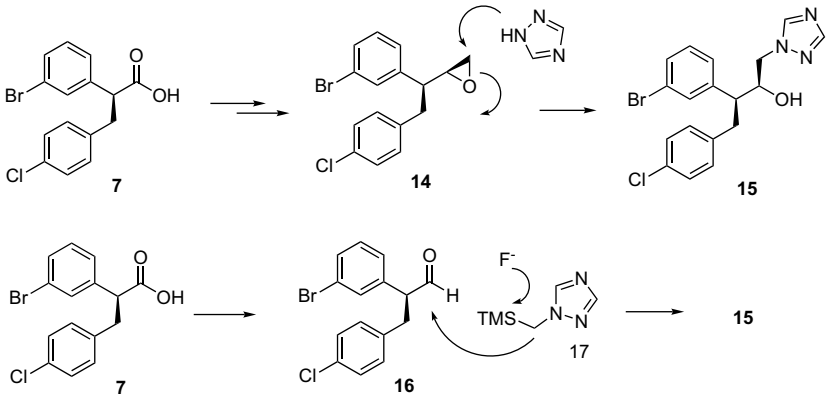
Scheme 2. Preparation of acid **4**. (a) (i) Pivaloyl chloride, Et_3N, THF; (ii) *n*-BuLi, (*S*)-4-benzyloxazolidin-2-one, THF. (b) 1-(Bromomethyl)-4-chlorobenzene, NaHMDS, THF, −78 °C. (c) LiOOH, THF, H_2O. (d) HOBt, EDCI, NMM, DMF. (e) 1-(Bromomethyl)-4-chlorobenzene, LiCl, LHMDS, THF, −78 °C. (f) H_2SO_4, dioxane.

backbone. We previously demonstrated the effectiveness of this process in the synthesis of taranabant.[13] We were delighted to discover that treatment of **5** with L-Selectride provided the desired diastereomer in 99% yield (de >99:<1). Selectivity was measured on Gilson™ reverse-phase preparative HPLC. The Gilson™ HPLC chart of diastereoselective reduction of ketone **5** is shown in Fig. 3. The specific optical rotation of triazolyl alcohol **15** thus obtained was +1.12.

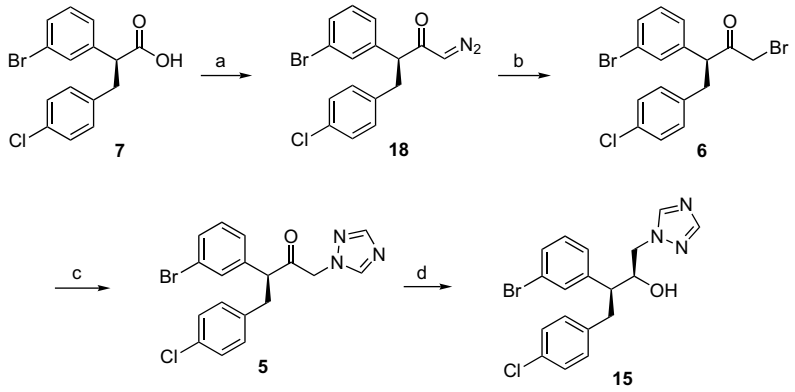
As described in Scheme 5, the cyano group was next introduced to bromo alcohol **15** via a Pd-catalyzed cyanation. Initial experiments to induce the cyanation of bromide **15** to nitrile **4** under the conditions of using $Zn(CN)_2$ and in situ generated Pd [$P(o\text{-tol})_3]_4$ as a catalyst in DMF were unsuccessful. After rather extensive experimentation, we found out that the reaction conditions of using $Zn(CN)_2$ and $Pd(PPh_3)_4$ under microwave irradiation provided the desired nitrile **4** in approximately 50% yield.

Next, the cyano alcohol **4** was converted to cyano azide **20** through mesylation followed by displacement with azide. Transformation of the azide **20** to amine **3** was conducted successfully utilizing the Staudinger conditions (PPh_3 in mildly heated toluene/water).[20] Purification was performed efficiently by Gilson™ reverse-phase prep HPLC using CH_3CN/water system containing 0.1% TFA. Subsequently, the desired amine as a TFA salt form was treated with saturated aqueous $NaHCO_3$ solution to give rise to the free amine form of structure **3**. The specific optical rotation of **3** was estimated to be +0.41.

Finally, coupling of amine **3** with acid **2** under conditions of NMM, EDC, and HOBt in DMF, followed by isolation by Gilson™ preparative HPLC produced triazolyl analog of taranabant **1** in 75% yield. The specific optical rotation of **1** was measured to be +0.21.[17] The relative and absolute stereochemistries of the desired target compound **1** were further secured through single-crystal X-ray



Scheme 3.



Scheme 4. Preparation of triazolyl alcohol **15**. (a) (i) Oxalyl chloride, cat. DMF, DCM, 0 °C; (ii) $TMSCHN_2$, DCM, 0 °C. (b) HBr, ether, 0 °C. (c) 1,2,4-Triazole, sodium derivative, DMF, rt. (d) $LiBH(sec\text{-}Bu)_3$, THF, −78 °C.

analysis as illustrated in Figure 4. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC694621.

2.3. Another triazolyl analog of taranabant (MK-0364) 23

At the outset, we chose to evaluate the phenyl substituents on triazolyl analogue of taranabant **1**.

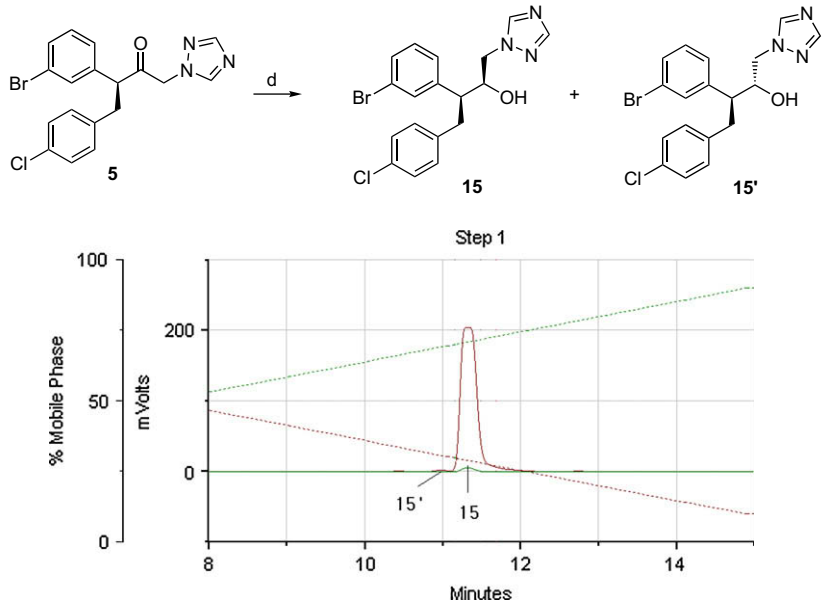
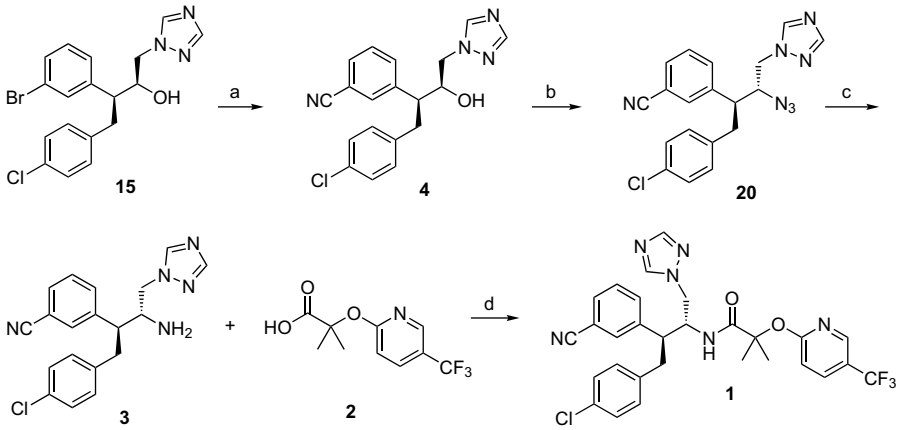


Figure 3. Gilson™ reverse-phase preparative HPLC chart for diastereoselective reduction of **5**.



Scheme 5. Construction of taranabant analog **1** from triazolyl alcohol **4**. (a) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF. (b) (i) MsCl, TEA, ethyl acetate, 0 °C; (ii) NaN_3, DMF, 120 °C, 2 h. (c) PPh_3, toluene/H_2O. (d) EDCI, NMM, HOBt, DMF, rt.

Thus, construction of an analog **23** began with bromo alcohol **15**. The bromo alcohol **15** was converted to bromo azide **21** through mesylation followed by displacement with azide in a similar way previously described toward taranabant. The Staudinger reaction, followed by purification by Gilson™ reverse-phase preparative HPLC using CH_3CN/water containing 0.1% TFA was adopted successfully for transformation of the azide **21** to amine **22** after treatment with aqueous $NaHCO_3$ solution. Finally, coupling of amine **22** with acid **2** under conditions of NMM, EDCI, and HOBt in DMF, followed by isolation by Gilson™ preparative HPLC readily produced analog **23** (Scheme 6).

2.4. Biological evaluation

Triazolyl analog of taranabant (MK-0364) **1** and the structurally similar analog **23** were screened via in vitro rat cannabinoid CB-1 binding assay. The synthesized analogues were subjected to biological evaluation involving cannabinoid CB1 receptor binding affinity. While the parent taranabant bears highly potent binding affinity to cannabinoid CB1 receptor, neither of the analog structures results in better CB1 receptor binding affinities (CB1R IC_{50}=123 nM for **1** vs CB1R IC_{50}=791 nM for **23** via in-house assay).[21,22] Based on this in vitro binding affinity data, it is apparent that the nitrogen atom in the triazolyl moiety is not contributing positively to the affinity of triazolyl analogs of taranabant. It appears that 1,2,4-trizole group at the particular position is not likely to act as an expected hydrogen bond acceptor, but appears to provide only unfavorable steric bulkiness for the domain.

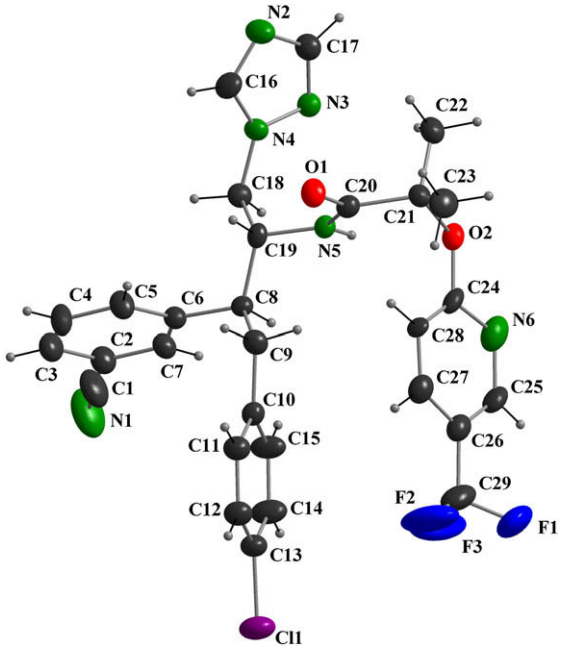


Figure 4. X-ray structure of compound **1**.

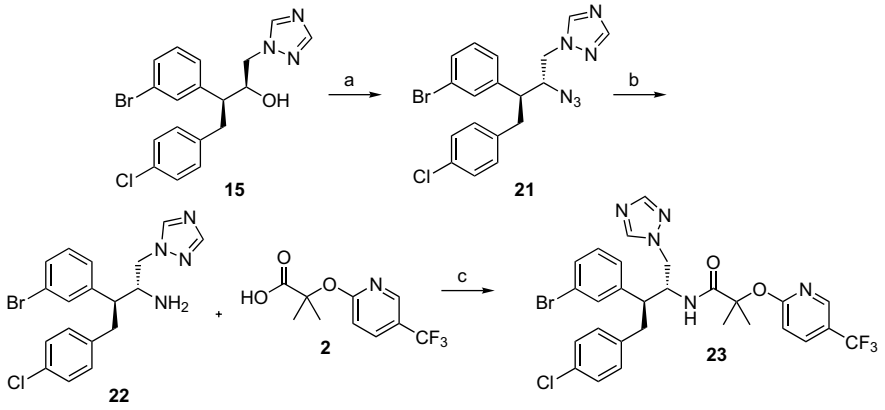
3. Summary

We have achieved a convenient total synthesis of triazolyl analogue of taranabant (MK-0364) **1** by employing Evans asymmetry reaction or Myers' pseudoephedrine technology. We introduced a triazolyl group via substitution of α-bromoketone **6** with 1,2,4-triazole and accomplished subsequent diastereoselective reduction to install adjacent essential asymmetric center for taranabant analog **1**. Using this synthetic route we efficiently prepared a structurally similar analog **23** as well. The synthesized analogues were subjected to biological evaluation involving cannabinoid CB1 receptor binding affinity. While the parent taranabant (MK-0364) bears highly potent binding affinity to cannabinoid CB1 receptor, it was discovered that either **1** or **23** did not improve rat CB1 receptor binding affinities.

4. Experimental

4.1. General

All references to ether are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in degrees centigrade. All reactions are conducted under an inert atmosphere at room temperature unless otherwise noted, and all solvents are of the highest available purity unless otherwise indicated. Microwave reaction was conducted with a Biotage microwave reactor. ^1H NMR spectra were recorded on either a Jeol ECX-400 or a Bruker DPX-300 spectrometer. Chemical shifts were expressed in parts per million (ppm, d units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), and br (broad). Mass spectra were obtained with either Micromass, Quattro LC Triple Quadruple Tandem Mass Spectometer, ESI, or Agilent, 1100LC/MSD, ESI. Fast atom bombardment (FAB) method of Jeol JMS AX505WA spectrometer was adopted for



Scheme 6. Preparation of an analogue **23**. (a) (i) MsCl, Et_3N; (ii) NaN_3, DMF, 120 °C; (b) (i) PPh_3, toluene/H_2O; (ii) 0.1% TFA on Gilson prep HPLC; (iii) aq $NaHCO_3$; (c) NMM, EDCI, HOBt, DMF.

HRMS. Optical rotation data were obtained on a JASCO P-1030 automatic polarimeter. Melting point was measured on a BUCHI Melting Point B-540. For preparative HPLC, ca. 100 mg of a product was injected in 1 mL of DMSO onto a SunFire™ Prep C18 OBD 5 mm 19_100 mm Column with a 10 min gradient from 10% CH_3CN to 90% CH_3CN in H_2O. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh). Most of the reactions were monitored by thin layer chromatography on 0.25 mm E. Merck silica gel plates (60 F_{254}), visualized with UV light using a 5% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution.

4.1.1. 2-(3-Bromophenyl)-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylacetamide ***12***

To a solution of 3-bromopropionic acid **8** (2.06 g, 9.58 mmol) in *N*,*N*-dimethylformamide (20 mL) were added (*S*,*S*)-(+)-pseudoephedrine **11** (2.3 g, 11.5 mmol), EDCI (2.75 g, 14.4 mmol), HOBt·H_2O (1.56 g, 11.5 mmol), and NMM (6.3 mL, 58.0 mmol). The mixture was stirred at room temperature overnight. The product was diluted with ethyl acetate (20 mL) and washed with aqueous 1 N HCl (10 mL), sodium bicarbonate (15 mL), and brine. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. The residue was purified on Gilson™ HPLC system to yield acetamide **12** (3.13 g, 8.64 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 7H), 7.17–7.14 (m, 2H), 4.55–4.51 (m, 2H), 4.18 (br, 1H), 3.79–3.70 (m, 1H), 3.61 (s, 2H), 3.00 (m, 1H), 2.80 (m, 3H), 1.07–1.06 (d, 3H, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 142.3, 137.2, 132.3, 132.2, 130.3, 130.0, 129.0, 128.5, 127.8, 126.7, 122.8, 76.4, 58.3, 41.3, 27.5, 14.6; LC–MS: *m*/*e* 362 (M^++H); HRMS (FAB) calcd for $C_{18}H_{21}O_2NBr$ (M^++1) 362.0677, found 362.0756.

4.1.2. (S)-2-(3-Bromophenyl)-3-(4-chlorophenyl)-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylpropanamide ***13***

Lithium chloride (541 mg, 12.8 mmol) is transferred to a flask fitted with rubber septum containing a vacuum needle, and was evacuated and immersed in an oil bath at 150 °C. After heating for 15 h at 150 °C, the flask is allowed to cool to 23 °C and was flushed with nitrogen. The reaction flask was charged with tetrahydrofuran (2 mL) and cooled to −15 °C. After 15 min, to the reaction flask was slowly added LHMDS (7.4 mL, 7.44 mmol) and held at that temperature for 1 h, then added 4-chlorobenzyl bromide. After 3 h, the reaction solution was quenched by saturated aqueous ammonium chloride solution. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. Purification by Gilson™ HPLC system (elution with H_2O and acetonitrile) gave 869 mg of **13** (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.99 (s, 1H), 7.57–7.55 (m, 1H), 7.45–7.41 (m, 2H), 7.37–7.35 (m, 1H), 7.15 (d, 2H, J=10.8 Hz), 6.84 (d, 2H, J=8.4 Hz), 4.54–4.53 (m, 1H), 3.81–3.78 (m, 1H), 3.40–3.30 (m, 1H), 2.91–2.82 (m, 1H), 2.59 (s, 3H), 1.02 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 142.3, 141.2, 138.0, 132.4, 131.2, 130.9,130.8, 130.7, 129.1, 128.6, 128.5, 128.4, 127.9, 126.8, 126.7, 126.4, 123.0, 76.3, 58.0, 51.8, 40.5, 27.9, 14.2; LC–MS: *m*/*e* 486 (M^++H); HRMS (FAB) calcd for $C_{25}H_{26}O_2NBrCl$ (M^++1) 486.0757, found 486.0835; mp 53.7 °C.

4.1.3. (S)-2-(3-Bromophenyl)-3-(4-chlorophenyl)propanoic acid ***7***

Acetamide **13** (311 mg, 0.64 mmol) and sulfuric acid (18 N, 1.5 mL) in dioxane (3 mL) were heated at reflux for 2 h and then cooled to 0 °C. The pH of the mixture was adjusted to pH $\geq$10 by slow addition of 50% (w/w) aqueous sodium hydroxide solution, and the resulting mixture was partitioned between water (10 mL) and dichloromethane (20 mL). The aqueous layer was separated and extracted with dichloromethane (20 mL). The aqueous layer was acidified to pH $\leq$2 by the slow addition of 6 N aqueous sulfuric acid solution and extracted with dichloromethane (3×20 mL). The resulting organic layer was dried over sodium sulfate and concentrated to afford acid **7** (70%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (s, 1H), 7.38 (d, 1H), 7.20–7.12 (m, 4H), 7.01 (m, 2H), 3.79–3.72 (m, 1H), 3.36–3.29 (m, 1H), 2.99–2.92 (m, 1H); $[\alpha]^{26.3}$ +74.7 (*c* 3.02, $CHCl_3$).

4.1.4. (S)-3-(3-Bromophenyl)-4-(4-chlorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-one ***5***

To a solution of acid **7** (3.46 g, 10.2 mmol) in dichloromethane (30 mL) at 0 °C were added *N*,*N*-dimethylformamide (one drop) and oxalyl chloride (1.8 mL, 20.4 mmol) dropwise. The reaction mixture was allowed to warm to room temperature for 2 h and concentrated to dryness to give the crude acyl chloride, which was used without further purification. To a solution of diazomethane (2 M solution in diethyl ether, 10.2 mL, 20.4 mmol) in dichloromethane (20 mL) was added acyl chloride in dichloromethane (4 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction solution was concentrated in vacuo. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (m, 1H), 7.41–7.39 (m, 1H), 7.29–7.22 (m, 4H), 7.16–7.14 (m, 2H), 6.08 (br, 1H), 4.04–3.99 (m, 1H), 3.29–3.24 (dd, 1H, J=8.4, 14.0 Hz), 2.94–2.89 (dd, 1H, J=7.4, 14.0 Hz).

The obtained diazoketone **18** (6.07 g, 16.4 mmol) in diethyl ether (70 mL) was treated with 48% aqueous HBr (2.23 mL) and was stirred for 30 min at 0 °C. The reaction mixture was diluted with diethyl ether (30 mL) and then washed with saturated sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.42 (m, 1H), 7.36 (m, 1H), 7.23–7.18 (m, 3H), 7.12–7.10 (m, 1H), 6.99–6.97 (m, 2H), 4.24 (t, 1H,

J=7.6 Hz), 3.79 (d, 1H, *J*=12.4 Hz), 3.70 (d, 1H, *J*=12.8 Hz), 3.39–3.34 (dd, 1H, *J*=7.6, 14.0 Hz), 2.94–2.89 (dd, 1H, *J*=7.2, 14.0 Hz).

To the resulting yellow solution with *N*,*N*-dimethylformamide (125 mL) was added 1,2,4-triazole sodium derivatives (2.23 g, 24.5 mmol) and stirred for 1 h at room temperature. The reaction mixture was quenched with water, extracted with ethyl acetate, and washed with brine. The organic layers were dried over magnesium sulfate, filtrated, and evaporated to dryness to give a residue that was purified by Gilson™ HPLC system (48% in four steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.86 (s, 1H), 7.47–7.45 (m, 1H), 7.30–7.29 (m, 1H), 7.24–7.20 (m, 3H), 7.02–7.00 (m, 1H), 6.96–6.94 (m, 2H), 4.86 (d, 2H, *J*=4.0 Hz), 3.91 (t, 1H, *J*=7.6 Hz), 3.79 (dd, 1H, *J*=7.4, 13.8 Hz), 3.70 (dd, 1H, *J*=7.4, 13.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 152.4, 144.6, 138.5, 136.7, 132.8, 131.7, 131.3, 130.5, 128.9, 127.1, 123.6, 57.8, 57.2, 38.0; LC–MS: *m*/*e* 404 (M^++H); HRMS (FAB) calcd for $C_{18}H_{16}ON_3BrCl$ (M^++1) 404.0087, found 404.0165.

4.1.5. (2S,3S)-3-(3-Bromophenyl)-4-(4-chlorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol ***15***

L-Selectride (1 M solution in THF, 15.4 mL) was added to a solution of ketone **5** (4.14 g, 10.2 mmol) in anhydrous THF (50 mL) under N_2 at −78 °C. The mixture was stirred at −78 °C for 1.5 h and warmed to −40 °C. The aqueous NaOH (3 N, 15.4 mL) and 30% H_2O_2 (7.7 mL) were added slowly and stirred vigorously for 2 h at 0 °C. The reaction mixture was diluted with ethyl acetate and the organic phase was separated. The organic phase was washed with water, saturated $Na_2S_2O_3$, and brine, and dried over $MgSO_4$. After evaporation, the residue was purified using Gilson™ HPLC system to give the desired products **15** (4.10 g, 99%) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.93 (s, 1H), 7.78 (s, 1H), 7.52 (m, 1H), 7.43–7.40 (m, 1H), 7.24–7.18 (m, 4H), 7.07–7.04 (m, 2H), 4.15–4.10 (m, 2H), 3.81–3.77 (m, 1H), 3.71 (d, 1H, *J*=4.0 Hz), 3.25 (dd, 1H, *J*=8.0, 13.5 Hz), 2.97 (dd, 1H, *J*=7.5, 13.5 Hz), 2.88–2.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 143.9, 142.4, 137.9, 132.4, 132.3, 132.2, 130.7, 130.3, 128.8, 128.1, 122.9, 70.4, 55.2, 51.1, 38.7; LC–MS: *m*/*e* 406 (M^++H); HRMS (FAB) calcd for $C_{18}H_{18}ON_3BrCl$ (M^++1) 406.0244, found 406.0322; mp 61.1 °C; $[\alpha]^{27.2}$ +1.12 (*c* 0.73, $CHCl_3$).

4.1.6. 3-((2S,3S)-1-(4-Chlorophenyl)-3-hydroxy-4-(1H-1,2,4-triazol-1-yl)butan-2-yl)benzonitrile ***4***

A dried heavy-walled Pyrex tube was charged with bromide alcohol **15** (243.6 mg, 0.6 mmol), $Zn(CN)_2$ (70.5 mg, 0.6 mmol), and $Pd(PPh_3)_4$ (41.4 mg, 24 μmol) in DMF (3 mL). The reaction mixture was exposed to microwave irradiation (180 °C) for 5 min. The reaction tube was allowed to reach room temperature before the reaction mixture was diluted in acetonitrile and filtered with syringe filter. Purification by Gilson™ HPLC system (elution with H_2O and acetonitrile) gave 65.7 mg of **4** (47%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (s, 1H), 7.79 (s, 1H), 7.70 (s, 1H), 7.58–7.54 (m, 2H), 7.42 (t, 1H, *J*=8.0 Hz), 7.21–7.19 (m, 2H), 7.03 (d, 2H, *J*=8.0 Hz), 4.18–4.16 (m, 1H), 4.12–4.09 (m, 1H), 3.96 (br, 1H), 3.73–3.69 (m, 1H), 3.27 (dd, 1H, *J*=7.0, 12.5 Hz), 3.01–2.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 143.8, 141.6, 137.5, 134.1, 133.0, 132.5, 131.1, 130.6, 129.4, 128.8, 118.9, 112.8, 70.3, 55.2, 50.9, 38.8; LC–MS: *m*/*e* 353 (M^++H); HRMS (FAB) calcd for $C_{19}H_{18}ON_4Cl$ (M^++1) 353.1091, found 353.1169; mp 70.4 °C; $[\alpha]^{26.6}$ +8.63 (*c* 0.60, $CHCl_3$).

4.1.7. 3-((2S,3R)-3-Amino-1-(4-chlorophenyl)-4-(1H-1,2,4-triazol-1-yl)butan-2-yl)benzonitrile ***3***

To a solution of alcohol (1.1 g, 3.1 mmol) in ethyl acetate (15 mL) at 0 °C were added triethylamine (0.52 mL, 3.74 mmol) and methanesulfonyl chloride (0.36 mL, 4.68 mmol). After stirring at 0 °C for 1.5 h, the reaction was quenched by addition of saturated aqueous sodium bicarbonate (2 mL). After stirring at room temperature for 1 h, the organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to afford methanesulfonate, which was used without further purification. To a solution of methanesulfonate in DMF (12 mL) was added sodium azide (1.04 g, 16 mmol). After stirring at 120 °C for 2 h, the reaction mixture was poured into water (10 mL) and the product was extracted with ether (30 mL). The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. The residue was purified using Gilson™ HPLC system to give the desired products **20** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.99 (s, 1H), 7.57–7.55 (m, 1H), 7.45–7.41 (m, 2H), 7.37–7.35 (m, 1H), 7.15 (d, 2H, *J*=10.8 Hz), 6.84 (d, 2H, *J*=8.4 Hz), 4.21 (td, 1H, *J*=3.6, 8.8 Hz), 4.14 (dd, 1H, *J*=3.2, 14.0 Hz), 3.96 (dd, 1H, *J*=8.8, 14.0 Hz), 3.36 (dd, 1H, *J*=3.6, 13.2 Hz), 3.00 (m, 1H), 2.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 144.4, 140.9, 136.3, 132.7, 132.0, 130.4, 130.1, 128.9, 65.7, 52.0, 50.3, 38.2; LC–MS: *m*/*e* 378 (M^++H); HRMS (FAB) calcd for $C_{19}H_{17}N_7Cl$ (M^++1) 378.1156, found 378.1234.

To the toluene (5 mL) solution of azide **20** from the previous step was added water (1 mL) and the batch was heated to 75 °C. A solution of PPh_3 (1.2 g, 4.68 mmol) in toluene (1 mL) was added to the batch (slowly in order to control nitrogen evolution). The batch was aged for an additional 17 h and then cooled to ambient temperature. Purification by Gilson™ HPLC system (elution with 0.1% TFA of H_2O and acetonitrile) gave amine of the TFA salt form.

The obtained amine of the TFA salt form was neutralized with $NaHCO_3$, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness to yield free amine **3** (482 mg, 1.37 mmol, 44% for three steps). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.39 (s, 1H), 7.93 (s, 1H), 7.67 (s, 1H), 7.61 (d, 1H), 7.65–7.39 (m, 2H), 7.18 (d, 2H), 7.01 (d, 2H), 4.08–4.02 (m, 1H), 3.88–3.82 (m, 1H), 3.38–3.24 (m, 2H), 2.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 144.2, 142.6, 137.3, 133.1, 132.3, 132.0, 131.1, 130.4, 129.7, 128.7, 118.7, 113.0, 55.3, 54.6, 52.4, 37.9; LC–MS: *m*/*e* 352 (M^++H); HRMS (FAB) calcd for $C_{19}H_{19}N_5Cl$ (M^++1) 352.1251, found 352.1329; $[\alpha]^{26.9}$ +0.41 (*c* 0.97, $CHCl_3$).

4.1.8. N-((2R,3S)-4-(4-Chlorophenyl)-3-(3-cyanophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-yl)-2-methyl-2-(5-(trifluoromethyl)pyridin-2-yloxy)propanamide ***1***

To a solution of 2-methyl-2-(5-(trifluoromethyl)pyridin-2-yloxy)-propanoic acid (364 mg, 1.46 mmol) in acetonitrile (5 mL) were added amine (428 mg, 1.22 mmol), cyanuric chloride (135 mg, 0.73 mmol), and then EDC (253 mg, 1.32 mmol). The mixture was stirred at room temperature overnight. The product was extracted with dichloromethane (10 mL). The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness. The residue was purified on Gilson™ HPLC system to yield taranabant-triazole analogue **1** (560 mg, 0.77 mmol, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (m, 1H), 7.87 (s, 1H), 7.83 (dd, 1H, *J*=8.8, 2.4 Hz), 7.54 (s, 1H), 7.51 (d, 1H, *J*=7.6 Hz), 7.42 (d, 1H, *J*=9.2 Hz), 7.33 (t, 1H, *J*=8.0 Hz), 7.24 (s, 1H), 7.05–7.02 (m, 3H), 6.96 (d, 1H, *J*=8.8 Hz), 6.53 (d, 2H, *J*=8.4 Hz), 4.80–4.73 (m, 1H), 3.97 (d, 2H, *J*=3.6 Hz), 3.15 (d, 1H, *J*=10.4 Hz), 2.71–2.61 (m, 2H), 1.76 (d, 6H, *J*=9.6 Hz); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 174.54, 164.13, 152.67, 144.60, 144.46, 144.42, 141.85, 136.82, 136.44, 136.42, 133.03, 132.48, 131.60, 131.52, 130.14, 129.96, 128.69, 121.37, 121.11, 118.36, 113.47, 112.99, 81.96, 52.28, 50.30, 50.08, 39.09, 25.62, 25.22; LC–MS: *m*/*e* 583 (M^++H); HRMS (FAB) calcd for $C_{29}H_{27}O_2N_6F_3Cl$ (M^++1) 583.1758, found 583.1836; mp 184.8 °C; $[\alpha]^{27.2}$ +0.21 (*c* 3.115, $CHCl_3$).

4.2. Pharmacological test: in vitro activity analysis

The compounds of the present invention were analyzed for their binding characteristics for CB_1 and CB_2 and the pharmacological activity thereof in accordance with the method disclosed in Ref. 21. The analysis was performed using [^{3}*H*]CP-55940, which is

a selectively radioactivity-labeled 5-(1,1-dimethyheptyl)-2[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol, purchased from PerkinElmer Life Sciences, Inc. (Boston, Massachusetts, USA), through a rat CB-1 receptor binding protocol as follows.

The tissue obtained from the brain of SD rats was homogenized with a Dounce homogenate system in TME (50 mM Tris, 3 mM $MgCl_2$, and 1 mM EDTA, pH 7.4) at 4 °C, and the homogenate was centrifuged at 48,000 g for 30 min at 4 °C. The pellet was resuspended in 5 mL of TME and the suspension was divided into aliquots and stored at −70 °C until its use in the following assay.

The test compound (2 μL) was diluted in dimethylsulfoxide and was added to a deep well of a polypropylene plate, to which 50 μL of [^3H]CP-55940 diluted in a ligand buffer solution (0.1% bovine serum albumin(BAS)+TME) was added. The tissue concentrations were determined by Bradford protein analysis, and 148 μL of brain tissue of the required concentration was added to the plate. The plate was covered and placed in a 30 °C incubator for 60 min, and then transformed on GF/B filtermat pretreated in polyethylenimine (PEI) using a cell harvester. Each filter was washed five times and dried at 60 °C for 1 h. Then, the degree of radioactivity retained by the filter was measured using Wallac Microbeta™ (PerkinElmer Life Sciences, Inc., Massachusetts, USA) and the activity of the compound for inhibiting CB_1 receptor was determined therefrom.

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Supplementary data

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22. For comparison, taranabant (MK-0364) demonstrated rat CB1 receptor binding affinity IC_{50}=0.86 nM, while rimonabant (SR141716) displaying IC_{50}=4.50 nM via in-house assay.
23. Triazole is small and constitutes three nitrogens in the ring. Thus, by substituting H into a triazole, hydrophilicity of a molecule increases. Concurrent alteration of physicochemical properties including solubility was observed.
24. Currently, Merck's taranabant is in Phase 3 clinical trial for the treatment of obesity in USA. Taranabant is not toxic per se, but people speculate that it might have potential problem to cause depression or anxiety in human beings when it is used in medium to high dose.