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Substituted pyrimidines as cannabinoid CB1 receptor ligands

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ABSTRACT

Cannabinoid CB1 receptors have been the avenue of extensive studies since the first clinical results of rimonabant (SR141716) for the treatment of obesity and obesity-related metabolic disorders were reported in 2001. To further evaluate the properties of CB receptors, we have designed and efficiently prepared a series of substituted pyrimidines based on chemical structure of Merck's taranabant, a cannabinoid CB1 receptor inverse agonist. Noticeably, *N*4-((2*S*,3*S*)-3-(3-bromophenyl)-4-(4-chlorophenyl)butan-2-yl)-*N*6-butylpyrimidine-4,6-diamine (**13b**) demonstrated good binding affinity and decent selectivity for CB1 receptor (IC_{50} = 16.3 nM, CB2/CB1 = 181.6).

New development of obesity drugs reveals that it is possible to control appetite and diminish weight by blocking cannabinoid receptors in the brain, liver or muscle, via cannabinoid (CB1) receptor antagonists or CB1 receptor inverse agonists.[1,2] Cannabinoid CB1 receptor antagonist is designed to hinder the effects of endogenous cannabinoids. This type of drug is particularly intriguing since it not only causes weight loss but also reverses the metabolic effects of obesity such as insulin resistance and hyperlipidemia.[3] Cannabinoid CB2 receptor, the other cannabinoid receptor is closely related to immune regulation and neurodegeneration.[4] Therefore, the CB2/CB1 selectivity should be taken into consideration for new drug development of anti-obesity agent.

The first specialized cannabinoid CB1 receptor antagonist, rimonabant was discovered in a high-throughput screening program at Sanofi-Synthélabo in 1994.[5] Several CB1 receptor antagonists including SR141716 (rimonabant), SLV319 (ibipinabant),[6a] CP-945,598 (otenabant)[6b,c] and MK-0364 (taranabant)[7] had been in various phase of clinical trials.[8,9] Unfortunately, some of cannabinoid-1 receptor ligands were recently discontinued from all ongoing clinical developments.[12]

With our efforts to discover and develop a new medicine for the treatment of obesity,[10] we have recently reported a convenient total synthesis of taranabant,[11a] and subsequent evaluation of triazolyl analogues of taranabant.[11b] Recently, a pharmacophore model for the binding of a low energy conformation of taranabant in the CB1 receptor has been reported.[7c] 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-pyr 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.[7c,11b] We envisioned that the key carbonyl group of taranabant might be superseded by the corresponding imine-type moiety or 'imine'-containing heterocycle. Among many heterocycles involving 'imine-type' functionality, we were particularly intrigued by pyrimidine although to the best of our knowledge, pyrimidine has been unknown as a bioisostere for amide.[22] We speculated that replacement of the amide moiety into pyrimidine ring could provide a favorable balance of biological activity and pharmacokinetics to allow for further evaluation.

Herein, we report the design, chemical synthesis, and biological evaluation of substituted pyrimidine analogues as our additional research efforts toward discovery of a novel antiobesity agent (see Fig. 1).[7c]

We started our synthesis with a classical Evans asymmetric reaction route previously developed by our laboratory as shown in Scheme 1.[11a] Our objective was to develop a user-friendly, practical, and efficient chemical synthesis for medicinal chemists to utilize and to provide a reasonable amount of key intermediates. We were able to modify and refine some of the previous procedure to provide the requisite substituted amine **6** in 'tens of grams' amount. Thus, 3-bromophenyl acetic acid **1** was coupled with (*S*)-4-benzyloxazolidin-2-one via pivaloyl mixed anhydride in

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E-mail address: jinhwalee@greencross.com (J. Lee).

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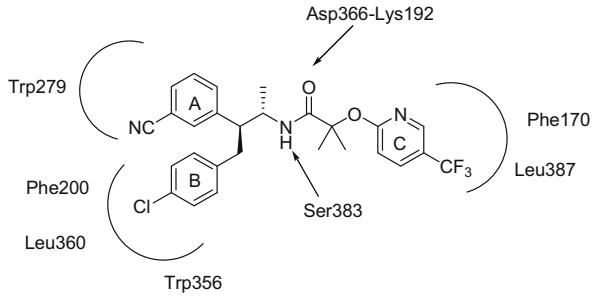
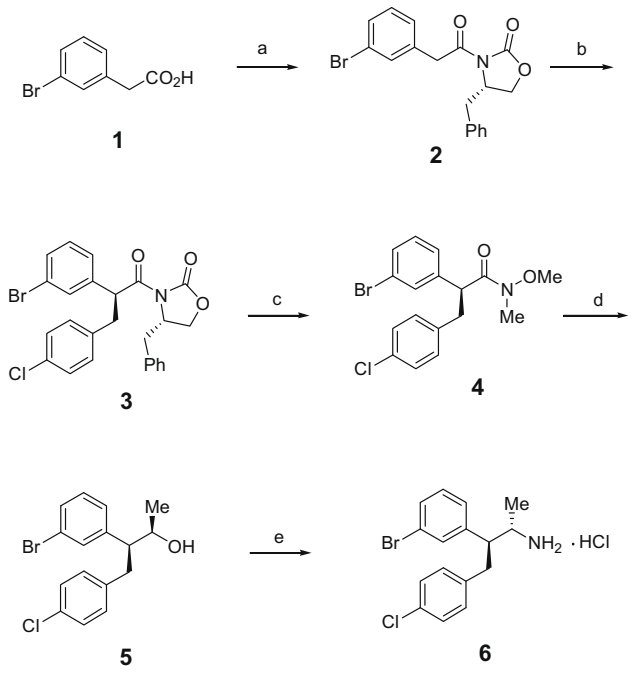


Figure 1. Taranabant (MK-0364) and its potential receptor–ligand interaction.



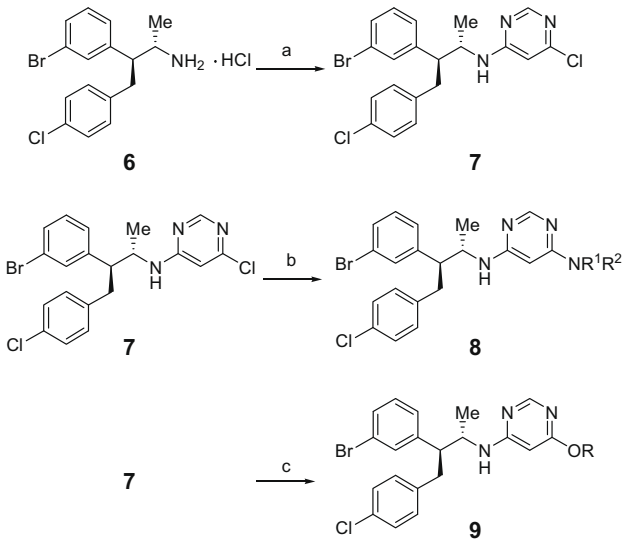
Scheme 1. Reagents and conditions: (a) (i) pivaloyl chloride, Et_3N, THF, 0 °C; (ii) *n*-BuLi, (*S*)-4-benzyloxazolidin-2-one, THF, −78 °C, 72% (two steps); (b) 1-(bromomethyl)-4-chlorobenzene, NaHMDS, THF, −78 °C, 79%; (c) (i) LiOOH, THF, H_2O, 0 °C; (ii) $(COCl)_2$, CH_2Cl_2; (iii) (MeO)NHMe, Et_3N, CH_2Cl_2, 79% (three steps); (d) (i) MeMgBr, THF; (ii) LiBH(*sec*-Bu)$_3$, THF, −78 °C, 96% (two steps); (e) (i) MsCl, Et_3N, toluene; (ii) NaN_3, DMF, 120 °C; (iii) PPh_3, toluene–H_2O; (iv) HCl–isopropanol, 66% (four steps).

72% yield. Next, alkylation of **2** using NaHMDS with 1-(bromomethyl)-4-chlorobenzene provided the alkylated product **3** in 79% yields. Subsequently, the chiral auxiliary of acyloxazolidinone **3** was cleaved by standard conditions to produce the corresponding acid, which was treated with oxalyl chloride provided the corresponding acyl chloride. The Weinreb amide **4** was then obtained by treatment with *N,O*-dimethylhydroxylamine in the presence of triethylamine (79%, three steps). Treatment of the Weinreb amide **4** with MeMgBr, followed by hydride reduction with L-Selectride[7a,11]generated the desired alcohol **5** (>99% de, 96% yield, two steps). Then the next three steps to prepare substituted amine **6** proceeded in a straightforward fashion. Thus, treatment of the alcohol **5** with mesyl chloride provided the corresponding mesylate, which was directly reacted with sodium azide at high temperature (ca. 120 °C) to smoothly produce the corresponding azide (96%, two steps). Transformation of the azide thus obtained to free amine was conducted using the Staudinger reaction conditions (PPh_3 in mildly heated toluene/water).[7,11,13] Finally, key intermediate **6** was obtained by acidification of the free amine with HCl in isopropanol, followed by filtration of the resulting salt form in 75% yield as shown in Scheme 1.

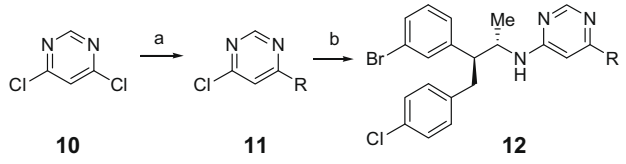
The synthesis of target compounds is illustrated in Scheme 2.[18,19] Reaction of substituted amine **6** with 4,6-dichloropyrimidine in the presence of DIPEA (*N,N*-diisopropylethylamine) under microwave irradiation (160 °C, 30 min) provided chloropyrimidine **7** as a white solid in 91% yield. The key chloropyrimidine **7** thus obtained was useful for preparing a variety of nitrogen, oxygen, and carbon-linked congeners. In the present case, primary and secondary amines react with chloropyrimidine **7** under microwave irradiation (180 °C, 1 h) to give the desired diaminopyrimidines **8** uneventfully. Alternatively, treating chloropyrimidine **7** with in situ generated sodium alkoxide under mildly heated conditions provided the desired alkoxypyrimidines **9** as shown in Scheme 2.

Meanwhile, as shown in Scheme 3, the iron-catalyzed cross-coupling reaction[14] of alkylmagnesium halides and dichloropyrimidine produced chloropyrimidine **11**, which was reacted with substituted amine **6** under microwave irradiation to provide the carbon-linked target compounds **12**.

The target analogues were evaluated in vitro at a rat CB1 binding assay,[15,17]and the results are shown in Table 1.[20] Unsubstituted *N*-propylamine **13a** had modest in vitro activity for rat CB1 receptor (IC_{50} = 48.1 nM). As the size of the carbon chain of amine substituent on pyrimidine increases, increase in the binding affinity for rat CB1 receptor is observed up to C-4 chain. Thus, *n*-butyl **13b** improved rat binding affinity for CB1 receptor in threefold, showing IC_{50} = 16.3 nM, while the binding affinities for CB1 were decreased when the alkyl chain became more prolongated (For example, *N*-pentylamine **13d**, IC_{50} = 195 nM; *N*-hexylamine **13g**, IC_{50} = 342 nM). Branched aliphatic chains displayed moderate binding affinity, showing IC_{50} = 93.6–155 nM for **13c**, **13e**, **13f**, and **13h**.

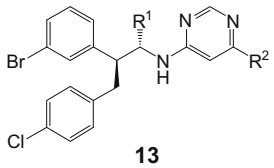


Scheme 2. Reagents and conditions: (a) 4,6-dichloropyrimidine, DIPEA, microwave, 160 °C, 30 min., 91%; (b) R^1R^2NH, microwave, ~50%; (c) NaOR, ROH, 50 °C, ~50%.



Scheme 3. Reagents and conditions: (a) RMgCl, Fe(acac)$_3$, THF–NMP, 0 °C to rt, 20%; (b) **6**, THF, microwave, 180 °C, 20%.

Table 1
Binding affinity of substituted acyclic pyrimidines to rCB1 receptor[a]



13

unit: nM
Ref. Rimonabant (5.0 ± 1.0[c])

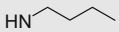
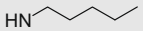
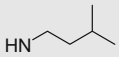
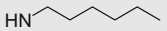
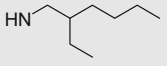
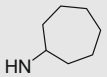
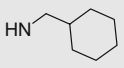
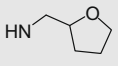
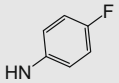
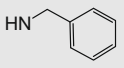
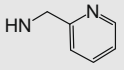
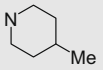
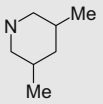
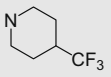
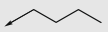
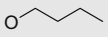
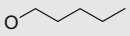
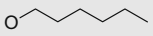
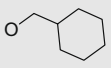
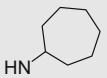
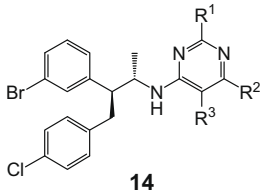
R^1	R^2	Compound	rCB1 IC_{50}[b]
Me		**13a**	48.1
Me		**13b**	16.3
Me		**13c**	155
Me		**13d**	195
Me		**13e**	113
Me		**13f**	93.6
Me		**13g**	342
Me		**13h**	103
Me		**13i**	24.7
Me		**13j**	27.6
Me		**13k**	45.3
Me		**13l**	70.5
Me		**13m**	115
Me		**13n**	67.4
Me		**13o**	97.8
Me		**13p**	195
Me		**13q**	264
Me		**13r**	106

Table 1 (*continued*)

R^1	R^2	Compound	rCB1 IC_{50}[b]
Me		**13s**	69.3
Me		**13t**	116
Me		**13u**	21.0
Me		**13v**	94.4
Me		**13w**	76.5
Me		**13x**	283
Me		**13y**	75.0
Me		**13z**	73.8
Me		**13aa**	39.8
Me		**13ab**	63.1
Me		**13ac**	136
Me		**13ad**	76.6
Me		**13ae**	203
Me		**13af**	135
Me		**13ag**	95.3
Me		**13ah**	136
Et		**13ai**	63.2
Et		**13aj**	569
Et		**13ak**	636
Et		**13al**	285

[a] CB1 receptor was collected from brain tissue of SD rat.
[b] These data were obtained by single determinations.
[c] This data was obtained by multiple determinations.

Table 2
Binding affinity of substituted pyrimidines to rCB1 receptor[a]



14

unit: nM
ref. Rimonabant (5.0 ± 1.0[c])

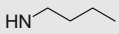
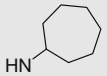
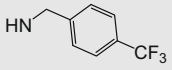
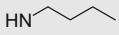
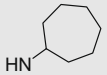
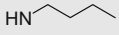
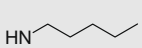
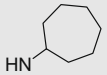
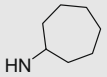
R^1	R^2	R^3	Compound	rCB1 IC_{50}[b]
Me		H	**14a**	82.0
Me		H	**14b**	98.6
Me		H	**14c**	22.1
Me		H	**14d**	66.5
Me		H	**14e**	160
Me		H	**14f**	130
Me		H	**14g**	28.9
SMe		H	**14h**	69.6
SMe		H	**14i**	57.3
SMe		H	**14j**	33.0
SMe		H	**14k**	109
CF3		H	**14l**	43.5
CF3		H	**14m**	59.3
CF3		H	**14n**	22.4
CF3		H	**14o**	38.9
CF3		H	**14p**	196

Table 2 (*continued*)

R^1	R^2	R^3	Compound	rCB1 IC_{50}[b]
H		H	**14q**	319
H		H	**14r**	811
H		H	**14s**	1540
H		H	**14t**	71.1

[a] CB1 receptor was collected from brain tissue of SD rat.
[b] These data were obtained by single determinations.
[c] This data was obtained by multiple determinations.

Preferable in vitro binding affinity displayed for the carbocycle (*N*-cyclopentylamine, **13i**, IC_{50} = 24.7 nM) than straight chain (*N*-pentylamine, **13d**, IC_{50} = 195 nM) or branched chain (*N*-isopentylamine, **13e**, IC_{50} = 113 nM or *N*-(pentan-3-yl)amine, **13f**, IC_{50} = 93.6 nM) if the same number of carbons are counted. As the size of carbocycle increases, the binding affinity for CB1 receptor slightly decreases. For example, *N*-cycloheptylamine, **13k** showed the weaker binding affinity for CB1 receptor (IC_{50} = 45.3 nM), whereas *N*-cyclopentylamine, **13i** showed the good binding affinity for CB1 receptor (IC_{50} = 24.7 nM). Methylene-linked carbocycle such as *N*-(cyclohexyl)methylamine, **13l** (IC_{50} = 70.5 nM) deteriorated the binding affinity for CB1 receptor in approximately threefold, compared to *N*-cyclohexylamine, **13j** (IC_{50} = 27.6 nM). Methylene-linked heterocycle such as *N*-(tetrahydrofuranyl)methylamine, **13m**, even further weakened the binding affinity for CB1 receptor (IC_{50} = 115 nM). This tendency for CB1 receptor binding affinity is also observed in *N*-phenylamine series. Thus, methylene-linked arylamine such as *N*-benzylamine, **13p** (IC_{50} = 195 nM) deteriorated the binding affinity for CB1 receptor in approximately threefold, compared to *N*-cyclohexylamine, **13n** (IC_{50} = 67.4 nM). Methylene-linked heteroaryl such as pyridinylmethylamine **13q** once again even got worse in terms of CB1 receptor binding affinity (IC_{50} = 264 nM), indicating the importance of non-polar moiety in order to optimally bind to a hydrophobic area of CB1 receptor. *N,N*-Disubstituted amines such *N*-ethyl-*N*-methyl **13r** or morpholine **13s** appeared to be tolerated for the replacement to a degree. As the size of rings become bigger, the binding affinities for CB1 receptor were fluctuated. Among the rings with different size tested on pyrimidine, the best result was obtained when pyrimidine has simple piperidine **13u**. It showed reasonable binding affinity for rat CB1R (IC_{50} = 21.0 nM). In order to evaluate the binding affinity levels of piperiniylpyrimidine analogues for the CB1 receptor, a structural derivatization of piperidine moiety was undertaken. 4-Methylpiperidinylpyrimidine **13w** decreased binding affinity for CB1 receptor in 3–4-fold, showing IC_{50} = 76.5 nM. Replacement of 4-methyl group with 4-trifluoromethyl group in **13y** did not affect but simply maintain its CB1 binding affinity (IC_{50} = 75.0 nM). Disubstitution on piperidine ring as in **13x** even more deteriorated its binding affinity for CB1 receptor (IC_{50} = 283 nM), suggesting that drug size or shape may be critical to the interaction of the substituted pyrimidine series of compounds with the CB1 receptor binding site.

Simple aliphatic chain or carbocycles (**13z, 13aa, 13ab**) seemed to be tolerated for the replacement to a degree (IC_{50} = 39.8–73.8 nM), but none appeared more potent than the parent piperidine group. A structurally related series of alkoxypyrimidine or

cycloalkyloxypyrimidine derivatives was prepared in an analogous fashion as shown in Scheme 2. The binding affinity data of these oxygen-linked pyrimidines demonstrate that replacement of nitrogen-linked pyrimidine with oxygen-linked pyrimidine tends to decrease binding affinity in 2–5-fold (see Table 1: **13b**, **13j**, **13l** vs **13ad**, **13ag**, **13ah**), with the exception of *n*-hexyloxypyrimidine **13af**. The structure–activity trends change dramatically in the case of extension of methyl to ethyl on R^1 substitution. Thus, ethyl-substituted aminopyrimidines **13ai**, **13aj**, **13ak**, and **13al** provided an approximately 1 order of magnitude decrease in activity. The interesting compound such as **13b** was further evaluated with observation of the hCB2 receptor binding affinity. The IC_{50} value was measured for the recombinant human CB2 receptor expressed in CHO cells and employing [3H]WIN-55,212-2 as a radio-ligand.[16] The binding affinity of **13b** against hCB2 receptor was reasonably good (IC_{50} = 2960 nM), thereby showing decent CB2/CB1 selectivity (CB2/CB1 = 181.60) for the compound.

In order to investigate CB1 receptor binding affinity levels of C2- or C5-substituted pyrimidine derivatives, a series of pyrimidine derivatives was prepared in a comparable fashion previously described in Scheme 2. The CB1 binding affinity data of these C2-or C5-substituted pyrimidine derivatives are exhibited in Table 2. 2-Methylpyrimidines (see **14a**–**14g**) or 2-(methylthio)pyrimidines (see **14h**–**14k**) showed moderate binding affinities, while 2-(trifluoromethyl)pyrimidines (see **14l**–**14o**) slightly improved binding affinities for CB1 receptor. The surprisingly poor result for 5-methylpyrimidines (see **14q**–**14s**) suggested that there might be an unfavorable steric interaction of the 5-substituted pyrimidine to hinder good binding to the active site of CB1 receptor.

Up to date, the best results in the substituted pyrimidine series were obtained when cyclohexylamine was introduced on 2-methylpyrimidine **14c** (IC_{50} = 22.1 nM) or 2-(trifluoromethyl)pyrimidine **14n** (IC_{50} = 22.4 nM).

In conclusion, we investigated a series of substituted pyrimidine derivatives for their binding affinity for cannabinoid CB1 receptor. Several compounds in this series exhibited reasonably good CB1 receptor binding affinities, but in comparison with taranabant, the binding affinity of substituted pyrimidines for CB1 receptor was significantly diminished. This reduced affinity might be attributed to the rigidity of pyrimidine linker which may position the C-4 substituent of pyrimidine at somewhat narrow and deep pocket that can accommodate *n*-butyl or chair-like conformation of cyclohexane ring.[21] Additional PK and in vivo efficacy studies in addition to further SAR studies of the substituted pyrimidine derivatives will be the subject of future investigations.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.06.069.

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12. As of November 5, 2008, Sanofi-Aventis, Merck, and Pfizer announced that they have decided to withdraw their ongoing clinical trials about rimonabant (SR141,716), taranabant (MK-0364), and otenabant (CP-945,598), respectively based upon changing regulatory prospects on the risk-benefit profile of the CB1 class and probable new regulatory requirements for approval.
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17. CB1 and CB2 Receptor Binding Assay**.** For the CB1 receptor binding studies, rat cerebellar membranes were prepared aspreviously described by the methods of Kuster et al.[15] MaleSprague-Dawley rats (200–300 g) were sacrificed by decapitation and the cerebella rapidly removed. The tissue was homogenized in 30 volumes of TME buffer (50 mM Tris–HCl, 1 mM EDTA, 3 mM $MgCl_2$, pH 7.4) using a Dounce homogenizer. The crude homogenates were immediately centrifuged (48,000*g*) for 30 min at 4 °C. The resultant pellets were resuspended in 30 volumes of TME buffer, and protein concentration was determined by the method of Bradford and stored at −70 °C until use. For the CB2 receptor binding studies, CHO K-1 cells were transfected with the human CB2 receptor as previously described, and cell membranes were prepared as described above.[16] Competitive binding assays were performed as described. Briefly, approximately 10 μg of rat cerebella membranes (containing CB1 receptor) or cell membranes (containing CB2 receptor) were incubated in 96-well plate with TME buffer containing 0.5% essentially fatty acid free bovine serum albumin (BSA), 3 nM [3H]WIN55,212-2 (for CB2 receptor, NEN; specific activity 50–80 Ci/mmol) or 3 nM ([3H]CP55,940, [3*H*]2-[(1*S*,2*R*,5*S*)-5-hydroxy-2-(3-hydroxypropyl) cyclohexyl]-5-(2-methyloctan-2-yl)phenol, for CB1 receptor, NEN; specific activity 120–190 Ci/mmol) and various concentrations of the synthesized cannabinoid ligands in a final volume of 200 μL. The assays were incubated for 1 h at 30 °C and then immediately filtered over GF/B glass fiber fiber filter (PerkinElmer Life and Analytical Sciences, Boston, MA) that had been soaked in 0.1% PEI for 1 h by a cell harvester (PerkinElmer Life and Analytical Sciences, Boston, MA). Filters were washed five times with ice-cold TBE buffer containing 0.1% essentially fatty acid free BSA, followed by oven-dried for 60 min and then placed in 5 mL of scintillation fluid (Ultima Gold XR; PerkinElmer Life and Analytical Sciences, Boston, MA), and radioactivity was quantitated by liquid scintillation spectrometry. In CB1 and CB2 receptor competitive binding assay, nonspecific binding was assessed using 1 μM rimonabant and 1 μM WIN55,212-2, respectively. Specific binding was defined as the difference between the binding that occurred in the presence and absence of 1 μM concentrations of rimonabant or WIN55,212-2 and was 70–80% of the total

binding. IC50 was determined by nonlinear regression analysis using GraphPad PRISM. All data were collected in triplicate in our experiments.

18. *Preparation of chloropyrimidine* **7**: (*2S,3S*)-3-(3-bromophenyl)-4-(4-chlorophenyl)butan-2-amine HCl **(6)** (3.00 g, 8.00 mmol) was added to a microwave reactor tube containing 4,6-dichloropyrimidine (2.38 g, 16.0 mmol) and DIPEA (4.18 mL, 24.0 mmol) in acetonitrile (24 mL). The capped reactor was placed in a microwave reactor and the mixture was irradiated at 160 °C for 30 min. The reaction mixture was evaporated in vacuo, diluted with EtOAc and extracted three times. Collected organic layer was dried over $MgSO_4$ and purified by preparative HPLC to obtain 3.27 g (7.26 mmol, 91%) of **7** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.36 (d, J = 8.00 Hz, 1H), 7.25 (s, 2H), 7.18–7.12 (m, 3H), 6.99–6.94 (m, 3H), 6.18 (br, 1H), 3.11–3.07 (m, 1H), 3.02–2.99 (m, 1H), 2.94–2.88 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H). MH+ 450.
19. *Preparation of the target compound* **13b**: chloropyrimidine **7** (150 mg, 0.33 mmol) was added to a microwave reactor tube containing *n*-butylamine (1 mL). The capped reactor was placed in a microwave reactor and the mixture was irradiated at 180 °C for 1 h. The reaction mixture was evaporated in vacuo and purified by preparative HPLC to obtain 76.4 mg (0.16 mmol, 47%) of **13b** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.25 (s, 3H), 7.12–7.03 (m, 3H), 7.00–6.96 (m, 2H), 4.94 (br, 1H), 3.9 (br, 1H), 3.26–2.89 (m, 5H), 1.66–1.59 (m, 2H), 1.51–1.39 (m, 2H), 1.10 (d, J = 6.8 Hz, 2H), 0.97 (t, J = 7.2 Hz, 3H). MH+ 487.
20. In this Letter, CB1R data were obtained by single determinations. Whenever we use rimonabant as our reference in our in-house assay, the CB1R binding affinity for rimonabant showed a certain number in the close range (IC_{50} = 5.0 ± 1.0 nM) in each different assay (>1500 compounds tested). Therefore, we believe that all SAR discussions in the manuscript are scientifically meaningful.
21. As pointed out by a referee, substituted pyrimidines described in this report do not look like derivatives of acyclic amide taranabant. Rather they might look more like analogues of rimonabant, having pyrimidine heterocycle at the center replacing pyrazole.
22. This Letter describes conformationally constrained analogues of taranabant. Such conformationally constraining approaches have already been described for the CB1 receptor antagonist rimonabant.