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Pentacycle derivatives as cannabinoid CB1 receptor ligands

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ABSTRACT

Cannabinoid CB-1 receptors have been the focus 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 pentacycle derivatives. Five of the new compounds which displayed high in vitro rCB1 binding affinities were assayed for binding to hCB2 receptor. Noticeably, 2-(5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-(5-methyl-1,3,4-thiadiazol-2-yl)-1*H*-pyrazol-3-yl)-5-(1-(trifluoromethyl)cyclopropyl)-1,3,4-oxadiazole (**16l**) demonstrated good binding affinity and decent selectivity for rCB1 receptor (IC_{50} = 1.72 nM, hCB2/rCB1 = 142).

The prevalence of obesity is rapidly increasing globally. Obesity has reached epidemic proportions especially in developed countries. Although obesity is associated with the pathogenesis of major diseases including diabetes or cardiovascular diseases, no satisfactorily safe and effective obesity drugs are available at the moment. Thus, there is a tremendous opportunity to make a significant impact on the lives of the obese through the discovery and development of additional pharmacotherapeutic options. Recently, we reviewed new trends in medicinal chemistry approaches used to develop drugs for treating obesity.[1] Recent development of obesity drugs reveals that it is possible to control appetite and reduce weight by blocking cannabinoid receptors in the brain, liver or muscle, via cannabinoid (CB1) receptor antagonists or CB1 receptor inverse agonists.[2,3] Cannabinoid CB1 receptor antagonist is designed to block the effects of endogenous cannabinoids. This type of drug is particularly interesting since it not only causes weight loss but also reverses the metabolic effects of obesity such as insulin resistance and hyperlipidemia.[4] Another cannabinoid receptor, CB2 is related to immune regulation and neurodegeneration.[5] Therefore, the CB2/CB1 selectivity should be taken into consideration for new drug development of antiobesity agent.

The first specific cannabinoid CB1 receptor antagonist, rimonabant was discovered in a high throughput screening program at Sanofi-Synthélabo in 1994.[6] Several CB1 receptor antagonists including SR141716 (rimonabant), SLV319 (ibipinabant),[7a] CP-945,598 (otenabant)[7b] and MK-0364 (taranabant)[8] had been reported to be in various phase of clinical trials.[9,10,15d,24] However, rimonabant was withdrawn from the market in 2008 due to risks of severe psychiatric problems, including depression, anxiety, and suicidality. Subsequently, taranabant and otenabant were discontinued from developments at phase III, respectively. However, despite consecutive failures of leading CB1 receptor antagonists, works continue to identify novel peripherally restricted CB1 antagonists that are non-brain penetrant and do not induce serious psychiatric disorders.

A pharmacophore model for the binding of a low energy conformation of rimonabant in the CB1 receptor has been well-documented.[10,11] The key receptor–ligand interaction is reported to be a hydrogen bond between the carbonyl group of rimonabant and the Lys192-Asp366 residue of the CB1 receptor, thereby exerting a stabilizing effect on the Lys192-Asp366 salt bridge as shown in Figure 1.[2,25]

To date, various analogs of rimonabant by replacing the key carbonyl group have been designed for the purpose of enhancing

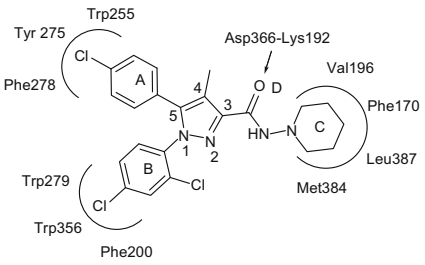

Figure 1. Rimonabant and its receptor–ligand interaction.

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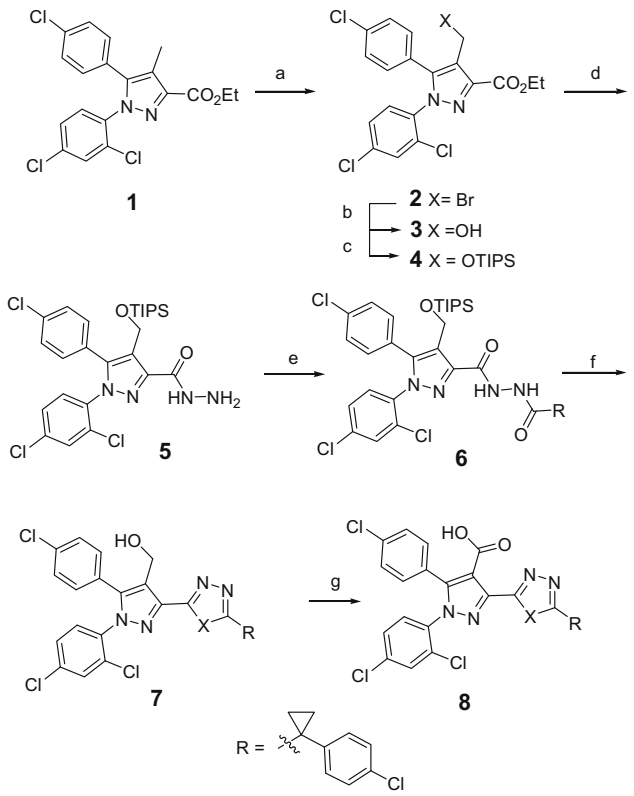
binding affinity and selectivity for the CB1 receptor. We note that such approaches were already demonstrated successfully with imidazole,[12] tetrazole.[13] Subsequently, we also discovered that the oxadiazole scaffold[14a,b] has also been employed for this purpose, even though there are clear differences evident between our previous works[15] and these prior examples.

With our efforts to discover and develop a new medicine for the treatment of obesity, we have reported the diarylpyrazolyl oxadiazole derivatives as potent, selective, orally bioavailable cannabinoid-1 receptor antagonists for the treatment of obesity.[15a] Therein, we demonstrated that incorporation of a 1,2,4-triazole ring onto the C-4 region of pyrazole scaffold via a methylene linker improved in vitro binding affinity, in turn leading to excellent in vivo efficacy on animal model.[16] We also reported that the polar amide groups in the C-4 region of pyrazole scaffold can be accommodated based on the observation that this region is capable of embracing substituents of varying functionality, size, and polarity.[15b] Along this line, we envisioned that a bioisostere of polar amide groups in the C-4 region of pyrazole can provide a novel series of pentacycle derivatives which act as cannabinoid CB1 receptor antagonists for the treatment of obesity.

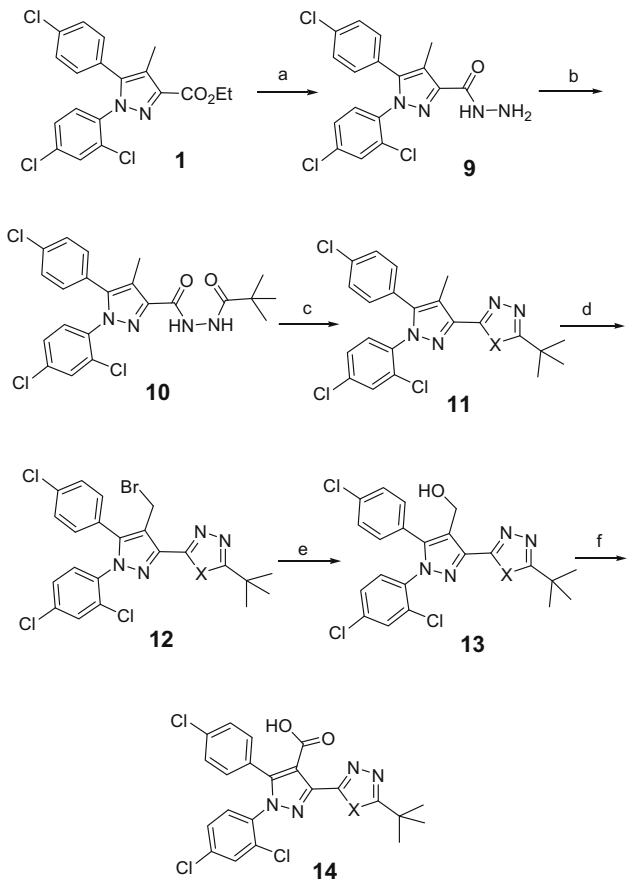
Herein, we wish to describe the chemical synthesis, biological evaluation of a novel series of pentacycle analogues as our additional research efforts toward discovery of a promising antiobesity agent.

Synthesis of pentacycle derivatives began with the generic carboxylate **1** as shown in Scheme 1.[17] This reaction sequence was developed and reported previously by our laboratory. We were able to modify and refine some of the previous procedure to provide the required carboxylic acid **8** in 'tens of grams' amount. Thus, the carboxylate **1** was converted to the bromide **2** in 55% yield using NBS (*N*-bromosuccinimide) in the presence of a catalytic amount of AIBN [2,2′-azobis(2-methylpropionitrile)],[8] and this intermediate was then treated with silver nitrate in aqueous acetone[18] to afford the corresponding alcohol **3** in 96% yield. Subsequently, alcohol **3** was protected with TIPSCl (triisopropylsilyl chloride) in the presence of a suitable base such as imidazole to provide **4**. Treatment of the ester **4** with hydrazine efficiently gave rise to hydrazide **5** in 97% yield for the two steps which was used to couple with an acid in the presence of appropriate coupling reagents such as EDC {1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide} and HOBt (1-hydroxybenzotriazole) to provide acylhydrazide **6** in 75% yield. Cyclization was then performed smoothly using either Burgess reagent[19a,b] or Lawesson's reagent[19c] under reflux conditions. These reactions can be carried out under microwave irradiation as well. Subsequent removal of triisopropylsilyl group with TBAF (tetrabutylammonium fluoride) was conducted to afford alcohols **7** in high yields. Oxidation of the alcohols **7** to the corresponding aldehydes was achieved through the use of Dess–Martin periodinane (80% yield).[20] Aldehydes were further oxidized to acids **8** in high yields by use of sodium chlorite and monobasic potassium phosphate in aqueous *t*-BuOH as shown in Scheme 1.[15a,b]

Alternatively, acids **14** can be prepared by benzylic bromination-type reaction on pyrazoles **11** as illustrated in Scheme 2.



Scheme 1. Reagents and conditions: (a) NBS, AIBN, CCl_4, reflux, 55% (b) $AgNO_3$, acetone–H_2O, rt, 96%; (c) TIPSCl, imidazole, DMF, rt; (d) NH_2NH_2, EtOH, 90 °C, 97% (two steps); (e) 1-(4-chlorophenyl)cyclopropanecarboxylic acid, EDC, HOBt, NMM, DMF, rt, 75%; (f) (i) Burgess reagent (X = O) or Lawesson's reagent (X = S), THF, reflux, 84% (X = O), 79% (X = S), (ii) TBAF, THF, rt, 96% (X = O), 93% (X = S); (g) (i) Dess–Martin periodinane, CH_2Cl_2, rt, 78% (X = O), 81% (X = S), (ii) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, *t*-BuOH–H_2O, rt, 92% (X = O), 95% (X = S).



Scheme 2. Reagents and conditions: (a) NH_2NH_2, EtOH, 90 °C, 95%; (b) pivalic acid, EDC, HOBt, NMM, DMF, rt, 87%; (c) Burgess reagent (X = O) or Lawesson's reagent (X = S), THF, reflux, 81% (X = O), 83% (X = S); (d) NBS, AIBN, CCl_4, reflux, 87% (X = O), 79% (X = S) (e) (i) NaOAc, THF–H_2O, rt, 91% (X = O), 88% (X = S), (ii) LiOH, THF–H_2O, rt, 92% (X = O), 93% (X = S); (f) (i) Dess–Martin periodinane, CH_2Cl_2, rt, 85% (X = O), 79% (X = S), (ii) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, *t*-BuOH–H_2O, rt, 91% (X = O), 96% (X = S).