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1,2,3-Triazole derivatives as new cannabinoid CB1 receptor antagonists

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ABSTRACT

This letter reports the new entry of novel 1,2,3-triazole derivatives as CB1 receptor antagonists. The design, synthesis and biological evaluation of *N*1 and *N*2 substituted 1,2,3-trizoles are described. The *N*2 substituted, symmetrical 1,2,3-triazoles are more potent ligands than the unsymmetrical analogues. The in vitro activity of these triazoles is further improved by inserting a methylene group between the central core and the carbonyl side chain. The most potent antagonists prepared in this series (IC_{50} < 20 nM) are the triazoles containing benzyl amides. These triazoles also show excellent selectivity between CB1 and CB2 receptors (IC_{50} > 10 μM for CB2; CB2/CB1 > 1000).

Obesity caused by an imbalance between food intake and energy expenditure,[1] is a significant risk factor for cardiovascular disease and diabetes, and associated with significantly reduced life longevity.[2] The World Health Organization (WHO) declared that obesity has become a global epidemic, posing a serious threat to public health.[3] The short-term diet or exercise is not effective as most obese patients readily regain their lost weight thereafter. Therefore, the medical treatment of obesity is an attractive approach.[4] In this respect, cannabinoid-1 receptor (CB1R) and its endogenous ligands (agonists), the endocannabinoids,[5] have been found to be involved in the control of weight via a dual mechanism of food intake modification and the regulation of energy homeostasis.[6] Indeed, the biological effects of the CB1 receptors, which are mainly located within the central nervous system, can be mediated through exposure to agonists or antagonists (inverse agonists).[7] Blocking the effects of the endogenous cannabinoids has become a therapeutic avenue to treat obesity.[8] The other known cannabinoid receptor (CB2R), is predominantly found in the immune system and related to immune regulation.[7] Therefore, good CB1/CB2 selectivity is a desired feature for the development of new anti-obesity drug.[9]

The most clinically advanced CB1 receptor antagonist, Rimonabant (SR141716A) launched by Sanofi-Aventis, binds to the human CB1 receptor with 5.6 ± 0.5 nM (K_i) affinity (Fig. 1).[10a,10b] Later, many small molecule CB1 antagonists with diverse chemical structures have been prepared and reviewed.[11] For example, Ibipinabant (SLV319),[12] Otenabant (CP-945,598) and Taranabant (MK-0364)[13] have been reported to be in various phases of clinical trials.[7,9,14]

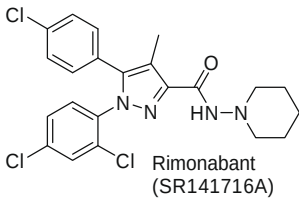

Figure 1.

In addition to the pyrazole core[10] of SR141716A, derivatives of other five membered heterocycles, such as pyrrole,[15] thiophene,[16] thiazole,[17] imidazole,[18,19] oxazole,[18a] and 1,2,4-triazole[19,20] are also known as the CB1 receptor antagonists. However, the derivatives of 1,2,3-triazole have not been explored in this context. Herein, we report our study on the design, synthesis and biological evaluation of 1,2,3-triazoles as new CB1 receptor antagonists. Later, we also notice that these triazoles possess excellent selectivity toward to CB1 and CB2 receptors.

We started our study with the synthesis of 4,5-diaryl-*N*1-substituted-1,2,3-triazoles **1** by the Ru-catalyzed cyclization reaction[21] of diaryl acetylenes[22] and azides (Scheme 1). However, this Ru-catalyzed reaction for the *ortho*-substituted diarylacetylenes is very sluggish.[23]

We found that these 1-substituted triazoles are poor CB1 antagonists (Table 1, vide infra). Therefore, 2-substituted 4,5-diaryl-1,2,3-triazoles were assembled by two strategies (Schemes 2 and 3). The 1,3-dipolar cycloaddition reaction of diarylacetylenes with sodium azide provided the 4,5-diaryl-1,2,3-triazoles, **2–4**. The fol-

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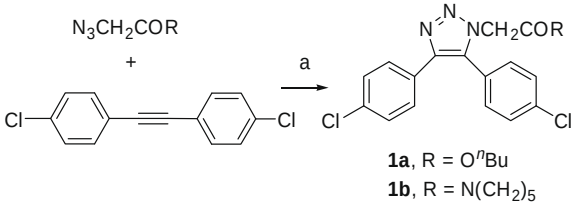
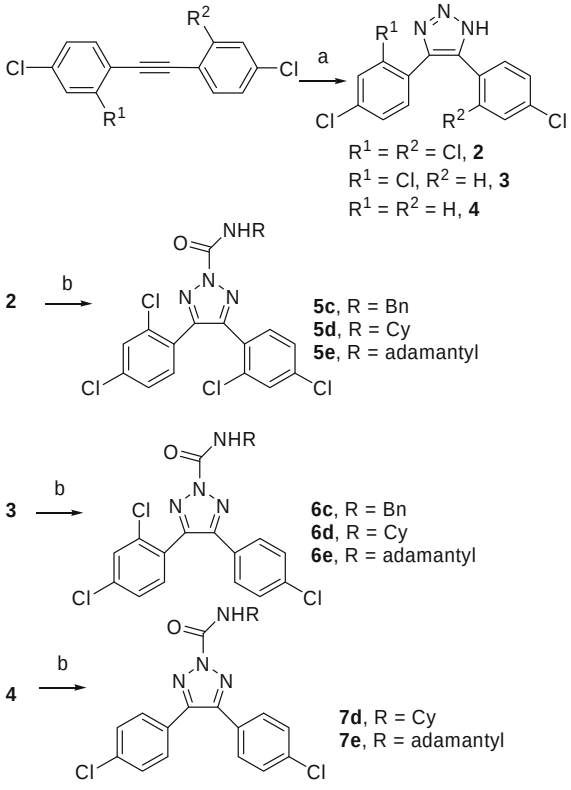


Scheme 1. Reagents and conditions: (a) $RuCpCl(PPh_3)_3$, benzene, reflux, 75–80%.

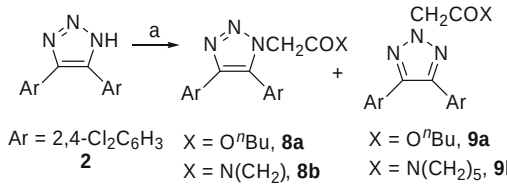
Table 1
Ligand binding assays of 1,2,3-triazoles[25]

Entry	Compound	IC_{50} (hCB1, nM)[a]	EC_{50} (hCB1, nM)[b]	IC_{50} (hCB2)[a] (μM)
1	**1a**	(64.1)[c]	—	—
2	**1b**	(33.0)[c]	—	—
3	**5c**	(23.8)[c]	—	—
4	**5d**	(29.2)[c]	—	—
5	**5e**	4496.8 ± 871.1 (78.9)[c]	—	—
6	**6c**	(18.6)[c]	—	—
7	**6d**	(30.5)[c]	—	—
8	**6e**	(34.5)[c]	—	—
9	**7d**	(19.9)[c]	—	—
10	**7e**	(19.7)[c]	—	—
11	**8a**	(46.1)[c]	—	—
12	**8b**	(55.7)[c]	—	—
13	**11**	(14.3)[c]	—	—
14	**9a**	1173.2 ± 263.4	—	—
15	**9b**	168.9 ± 32.2	122.0 ± 32.1	5.9 ± 0.8
16	**9c**	66.9 ± 8.9	87.0 ± 17.0	>10
17	**13c**	203.5 ± 78.1	216.3 ± 60.7	>10
18	**9d**	144.4 ± 110.0	203.6 ± 112.3	>10
19	**9f**	19.3 ± 3.5	23.5 ± 11.2	>10
20	**13f**	262.2 ± 183.7	256.1 ± 98.7	>10
21	**9g**	11.6 ± 3.4	50.7 ± 11.8	>10
22	**13g**	449.2 ± 67.9	235.2 ± 28.8	>10
23	**9h**	25.7 ± 2.9	35.1 ± 22.2	>10
24	**9i**	81.9 ± 44.2	56.2 ± 8.1	>10
25	**9j**	48.9 ± 12.0	12.2 ± 5.4	>10
26	**9k**	64.8 ± 10.5	17.8 ± 6.7	>10
27	**9l**	22.6 ± 8.8	22.0 ± 6.1	>10
28	**9m**	251.1 ± 88.1	136.2 ± 17.6	>10
29	SR141716A	15.0 ± 1.8	18.2 ± 9.5	1.9 ± 0.1

[a] Displacement of specific [^{3}H]-CP55940 binding in HEK 293 cells stably transfected with human CB1 receptor or human CB2 receptor.
[b] Functional activity (EC_{50}) determined by inhibition of Eu-GTP binding to hCB1 transfected HEK 293 membrane.
[c] Percent inhibition at 10 μM.



Scheme 2. Reagents and conditions: (a) NaN_3, DMF, 170 °C, 3–4 h, 75–88%; (b) isocyanate, DMAP, THF, reflux, 1–2 h, 20–90%.



Scheme 3. Reagents and conditions: (a) $BrCH_2CO_2{}^nBu$ or $BrCH_2CON(CH_2)_5$, NaH, Bu_4NI, THF, rt, 1 h. **8a:9a** = 1:4 (63%); **8b:9b** = 1:5 (66%).

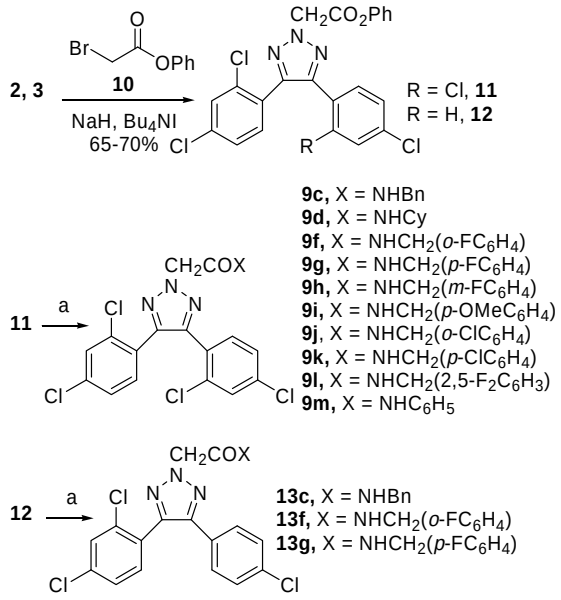
lowing coupling reactions using various isocyanates generated the ureas **5–7** with good yields (Scheme 2). Here, we found that the acylation only occurred at N-2 position according to the analysis of ^{1}H- and ^{13}C-NMR.[24]

Alternatively, alkylation of compound **2** with bromoacetate or bromoacetamide gave the mixture of 1-and 2-substituted triazoles (**8** and **9**, respectively), which are separable by column chromatography (Scheme 3). The two regioisomer of **8** and **9** was unmistakably assigned by the ^{1}H and ^{13}C NMR spectroscopies. Later, we adopted phenyl bromoacetate (**10**) as the alkylation reagent to prepare the 2-(phenoxycarbonyl)methyl triazoles **11** and **12** as the convenient precursors to various amides (**9** and **13**, Scheme 4).

The results of the displacement ligand binding assay[25] using the 1,2,3-triazoles and SR141716A are summarized in Table 1. Compounds **1** and **8** showed that the 1-substituted triazoles are poor ligands for CB1 receptor (Table 1, entries 1–2, 11–12). However, the triazoles with 2-carbamoyl group (**5c–d, 6c–d** and **7d**, entries 3–4, 6–7 and 9) provide even lower bioactivity. We were puzzled by this result at first: although **6d** and SR141716A are structurally similar, they have very different affinity to CB1 receptor. Later, we noticed the series of the three triazoles **5e, 6e** and **7e**, all with a sterically bulky adamantyl group, but **5e** clearly showed better potency than the other two (Table 1, entries 5, 8 and 10). On the other hand, the series of **5d, 6d** and **7d**, all with the less bulky cyclohexyl group, and the pairs of **5c** and **6c**, both with a benzyl group, show much smaller difference in CB1 binding assay (Table 1, entries 4, 7 and 9; entries 3 and 6). A reasonable conjecture for these observations is that the *ortho*-chlorines and the hindered adamantly group in **5e** force the carbonyl group twisting away from the plane of triazole (Fig. 2).

This result prompted us to modify our design to increase the rotational freedom of the carbonyl group. Thus, triazoles **9** and **13**, with an additional methylene group between the triazole and the carbonyl moiety, were synthesized. This new design greatly increased their efficacy to the CB1 receptor. For example, around three order increase in the ligand binding ability was observed (**5c** versus **9c** and **5d** versus **9d**), and the IC_{50} and EC_{50} values of these triazoles consistently fall into nanomolar range (entries 14–28).

Among the triazoles screened, symmetrical triazoles **9** with 4,5-bis-(2,4-dichlorophenyl) substituents are more potent than the unsymmetrical 4-(2,4-dichlorophenyl)-5-(4-chlorophenyl) ana-



Scheme 4. Reagents and conditions: (a) amine, toluene, reflux, 4–12 h, 65–98%.

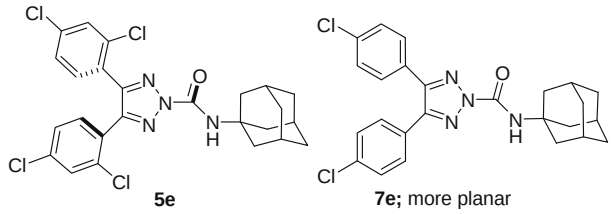


Figure 2. Twist of the carbonyl group away from the plane of triazole due to the steric hindrance of the admantyl group and *ortho*-chlorines.

logues **13**. We also noticed that the benzyl amides and its derivatives (**9c** and **9f–l**) are more effective than the esters (**11** and **9a**) or other amides (**9b, 9d**, and **9m**) prepared. Indeed, halogenated benzyl amides (**9f** and **9g**) show the best potency (IC_{50} < 20 nM). These triazoles were further screened toward CB2 receptor, and the results showed that they have very low affinity to CB2R. Such huge CB1/CB2 selectivity is rather unusual among the reported antagonists.[7,26] However, we do not know the reasons for such discrimination at this moment.

Comparing with other heterocycles as the central unit of CB1 antagonists, the number of substituents for 1,2,3-triazole is limited to three, due to the low valence number of nitrogen (there are four substituents in pyrazole, for example). The few substituents ease the steric repulsions around the central core and lead to strong conjugation between the carbonyl group and the 1,2,3-triazole of ureas **5–7**, thus enhanced the double bond character in the bonding of N-2 and the carbon. The key receptor–ligand interaction is proposed to be the hydrogen bond between the carbonyl group and the Lys192-Asp366 residue of the CB1 receptor.[12c,14a,27] Thus, the rigid conformation in these ureas (**5–7**) holds back the important hydrogen bond for the ligand–receptor interaction. On the other hand, the disruption of conjugation by inserting a methylene group not only changes the distance, but also allows the orientation of the carbonyl group more suitable for the key hydrogen bonding; therefore, better potency.

In summary, we have reported the 1,2,3-triazoles as effective, new CB1 antagonists. These compounds exhibit high level in vitro activity for CB1 receptor as well as good selectivity of CB1 over CB2 receptor. These feature should merit further studies, such as in vivo assays, on 1,2,3-triazoles as CB1 antagonists.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.bmcl.2008.11.029.

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