



Synthesis and CB1 cannabinoid receptor affinity of 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles

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ARTICLE INFO

Article history:

Received 15 October 2008

Revised 24 November 2008

Accepted 26 November 2008

Available online 6 December 2008

Keywords:

Cannabinoid receptors

Triazoles

Click chemistry

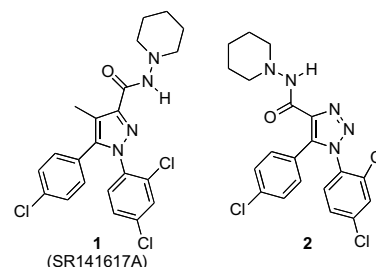
ABSTRACT

A series of 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles were synthesized regioselectively using click chemistry and evaluated at CB1 cannabinoid receptors. The *n*-propyl ester **11** (K_i = 4.6 nM) and phenyl ester **14** (K_i = 11 nM) exhibited the most potent affinity of the series.

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The wide range of pharmacological effects of cannabinoid and endogenous cannabinoid ligands, are mediated by two subtypes of transmembrane G-protein coupled receptors: CB1 and CB2.^{1–4} CB1 receptors are expressed in the central nervous system (CNS) with high density in the cerebellum, hippocampus and striatum.⁵ CB1 receptors are found in some peripheral tissues (urinary bladder, testis, and ileum) as well. CB2 receptors are predominantly located in the immune system (tonsils, spleen, and immune cells) with very low concentration in the CNS.⁶ CB1 agonists have potential therapeutic applications in developing drugs for pain, nausea, glaucoma, stroke, cancer, and neurological disorders such as multiple sclerosis and Parkinson's disease.^{7,8} The potential applications of CB1 antagonists include the therapeutic treatment of obesity and related metabolic disorders as well as medications for drug addiction.^{7–9} The role of CB1 receptors in these disease states and disorders, the nature of the receptors active sites, and the molecular interactions between the receptors and ligands are not fully understood and are under intensive investigation.

Our interest in developing new effective medications for drug abuse has focused our attention on the CB1 receptors because of their selective presence within CNS and their mediation of the effects of psychostimulants on brain circuitry.⁹ Pharmacological studies have shown that CB1 receptor antagonists or inverse agonists have the ability to attenuate the elevation of dopamine levels that occurs with psychostimulant use, suggesting their potential applications in the treatment of drug abuse disorders.^{9–11}



The pyrazole derivative SR141716 (**1**) was the first compound reported to be a potent and selective antagonist for the CB1 receptor.¹² However, further characterization of SR141716 has shown it to possess an inverse agonist pharmacological profile.¹³ This prototypical CB1 receptor antagonist/inverse agonist has been studied as a potential therapeutic for the treatment of obesity, smoking cessation and a variety of other CB1 receptor mediated pathological conditions.¹⁴ However, inverse agonists typically elicit pharmacological responses opposite to agonists and thus are not ideally suited for the treatment of drug addiction due to potential dysphoric side effects associated with these drugs. These include increased nociceptive sensitivity, decreased food intake and body weight, disruption of operant behavior and potential nausea in humans.^{15–19} Such side effects undoubtedly would lead to low compliance and relapse among addicts. Moreover, recent reports that describe increased levels of anxiety and depression in patients, along with a higher incidence of suicide (3 to 1 over placebo) in clinical trials with the

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diet drug Rimonabant (SR141716) strongly disfavor its development as a drug abuse medication.²⁰

Based upon the structure of 1,5-diarylpyrazole core template in SR141716 (**1**), bioisosteric replacement has been an important approach to discover new lead compounds of potent CB1 ligands and a variety of bioisosteric analogs of SR141716 have been synthesized and identified as potent ligands.^{14,21} In reviewing the literature, the absence of 1,2,3-triazole analogs was significant. To explore this deficiency, our aim was to synthesize and characterize a series of 1,2,3-triazole analogs of **1**, and explore further the binding motifs of CB1 receptor ligands.

Our design rationale was to incorporate the 1,2,3-triazole ring system into the vicinal diaryl group which is presumed to interact with a unique region of the CB1 receptors.^{22–24} While it was envisaged that the 1,2,3-triazole moiety in target molecule **2** could replace the pyrazole ring and provide good overlap of the vicinal diaryl system, it was not clear at that time how the juxtaposition of the carboxamide moieties of the triazole analog **2** relative to **1** would affect molecular recognition at cannabinoid receptors. However, the reduced lipophilicity of the 1,2,3-triazole **2** (ClogP 5.33) relative to **1** (ClogP 6.26) and potentially enhanced bioavailability made **2** an attractive target for investigation.^{25,26}

The construction of the 1,2,3-triazole ring system was envisaged to exploit the 1,3-dipolar cycloaddition of an azide and a terminal alkyne. To this end, the click chemistry developed by Sharpless and coworkers²⁷ would allow rapid regioselective ring construction as well as provide suitable intermediates for parallel synthesis of potential analogs. To explore the potential of this approach, a model 1,2,3-triazole ring system was prepared (Scheme 1). The 4-chloroaniline (**3a**) was conveniently converted into the azide **4a** with triflyl azide in 89% yield.²⁸ The subsequent reaction of **4a** with 4-chloroacetylene (**5**) under the Sharpless click chemistry conditions resulted in the formation of the intermediate 1,5-diaryl-1,2,3-triazole-4-magnesium chloride (**6a**). Subsequent quench of the reaction mixture with aqueous NH₄Cl furnished the 1,2,3-triazole **7a** in 85% yield. Alternatively, the 4-methoxycarbonyl-1,5-diaryl-1,2,3-triazole **8a** was obtained in 67% yield by

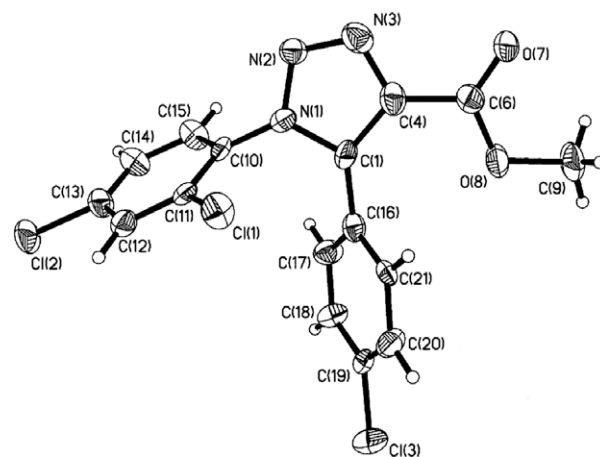
treatment of **6a** with methyl chloroformate. It was noteworthy that only one triazole regioisomer was isolated from these reactions.

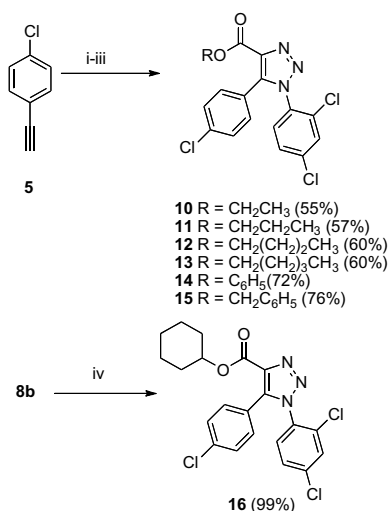
Upon successful generation of the 1,5-diaryl-1,2,3-triazole ring system, our attention focused on the construction of the 1,2,3-triazole analog **2**. The synthesis of **2** required the initial preparation of 2,4-dichlorophenylazide (**4b**). The conditions used to prepare **4a** did not furnish useful quantities of the azide **4b**. Fortunately, the copper catalyzed procedure [CuI, *trans*-1,2-di(aminomethyl)-cyclohexane (*t*-DAMCH)] for the conversion of iodobenzenes into the corresponding azides²⁹ provided **4b** in 54% yield from 2,4-dichloriodobenzene (**3b**).

The syntheses of the corresponding substituted 1,5-diaryltriazole derivatives **7b** and **8b** were achieved via the one-pot three-step transformation described above (Scheme 1) in 87% and 61% yield, respectively. As shown in Figure 1, X-ray crystallographic analysis of 4-methoxycarbonyl-1-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-1,2,3-triazole **8b**, served to confirm the regioselectivity of the click chemistry and unequivocally establish the regiochemistry of the triazole ring system.³⁰

The esters **8a** and **8b** were readily converted into the desired SR141716 analogs **9** and **2** by hydrolysis and concomitant amidation with 1-aminopiperidine (Scheme 1).

The binding affinities of the triazole derivatives (Table 1) were determined by the inhibition of [³H]SR141716 binding in homoge-





Scheme 2. Reagents and conditions: (i) EtMgCl, THF, rt, 1 h; (ii) **4b**, 50 °C, 2 h; (iii) ClCO₂R; (iv) cyclohexanol, BuLi, THF, 0 °C, 2 h.

nates of rat cerebellum.³¹ For direct comparison of ligand affinity at CB1 receptors with **1**, [³H]SR141716 was used as the radioligand.

For each compound, each concentration was tested in triplicate and each experiment was replicated three times. The binding data were analyzed using the non-linear regression analysis program of GraphPad Prism®.

The *K_i* values summarized in Table 1 indicated that the SR141716 analog **2** exhibited only modest affinity (*K_i* = 590 nM) for CB1 receptors. In addition, the mono-chloro-substituted 5-aryl derivatives **9**, and the unfunctionalized 1,5-diaryl triazoles **7a** and **7b** exhibited low affinity for cannabinoid receptors. However, it was serendipitous to find that the methyl ester **8b** (*K_i* = 66 nM) was nearly an order of magnitude more potent than **2**. This then provided a new lead compound for investigation.

As illustrated in Scheme 2, a series of 1,2,3-triazole analogs with varying ester groups were prepared using the click chemistry described earlier. The esters **10–15** were prepared efficiently in 55–76% yield by trapping the 1,5-diaryl-1,2,3-triazole-4-magnesium chloride intermediate **6b** (Scheme 1) with the corresponding commercially available chloroformates. The cyclohexyl ester derivative **16** was prepared by a simple transesterification of the methyl ester **8b**.

The esters **10–16** were evaluated for binding affinity at CB1 receptors as described above (Table 1). The *n*-propyl ester **11** (*K_i* = 4.6 nM) was the most potent derivative of the series and was slightly more potent than SR141716A (11.5 nM).²¹ It is worth noting that the potent triazole ester **11**, exhibited similar lipophilicity to that of SR141716A (Clog*P* 6.26).²⁵ The phenyl ester **14** (*K_i* = 11 nM) also exhibited high affinity for CB1 receptors while the affinity of the benzyl ester **15** was somewhat diminished. The larger alkyl ester congeners **12** and **13** exhibited high lipophilicity (Table 1, Clog*P* 6.70, 7.23) and were difficult to handle in the binding assay leading to inconsistent results. However, the binding data generally indicated that **12** and **13** exhibited diminished binding affinity relative to **11** and thus were not pursued. In general, analogs with either decreased or increased lipophilicity relative to **11** exhibited diminished affinity. This seems to suggest that a narrow window of lipophilic character may exist for binding of these triazoles at CB1 receptors.

In summary, we have reported the discovery and regioselective synthesis of a series of 4-alkoxy-carbonyl-1,5-diaryl-1,2,3-triazoles as a novel class of potent cannabinoid receptor ligands. The further in vitro and in vivo evaluation of the potent analogs **11** and **14** is currently under investigation and will be reported elsewhere.

Acknowledgments

We thank Prof. Gregory C. Fu at M.I.T. for the assistance provided to Ms. Hong Shu after Hurricane Katrina. This research was funded by the National Institute on Drug Abuse (DA023916).

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