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Original article

Design, synthesis, biological evaluation, and comparative docking study of 1,2,4-triazolones as CB1 receptor selective antagonists

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ABSTRACT

Cannabinoids are potentially useful for the treatment of several diseases. In the present work, we report the syntheses and biological evaluations of 1,2,4-triazolone derivatives designed using a combined approach of scaffold hopping and pharmacophore-oriented method. These compounds exhibited interesting antagonistic activity to the cannabinoid CB1 receptor. The preliminary structure–activity relationships were further discussed. In addition, docking simulations were performed on the good bioactive compound **5c** and the low potent compound **5d**, respectively, on the basis of homology models of the CB1 and CB2 receptors, which were constructed based on human β2-adrenoreceptor and optimized in a membrane environment by MD simulations. Calculation of the binding modes gave us insights into the structural requirements for improving the cannabinoid receptor bioactivity and selectivity.

1. Introduction

Cannabinoid (CB) receptors belong to the rhodopsin-like G protein-coupled receptors (GPCRs) family. Up to now, it has been identified of two subtypes of cannabinoid receptors, namely, CB1 receptor and CB2 receptor [1]. The CB1 receptor is predominantly located within the central nervous system (CNS) and also identified in peripheral nerve terminals and other cell types, while the CB2 receptor is expressed mainly in the peripheral immune tissues and cells. Activation of either CB1 or CB2 receptor mediates inhibition of adenylate cyclase and activation of mitogen-activated protein (MAP) kinase [2,3]. In addition, the CB1 receptor's activation also results in inhibition of N- and P/Q-type calcium channels and stimulation of potassium channels. The endocannabinoid system (ECS) comprises the cannabinoid receptors, endocannabinoids, and the corresponding enzymes involved in synthesis and degradation of endocannabinoids. The pharmacological studies have shown that the ECS regulates many physiological functions and processes including pain, energy balance, emotional regulation, etc [4–7]. For instance, S-777469 [8] (structure A in Fig. 1), as a CB2 receptor agonist, has completed phase II clinical trials for the treatment of atopic dermatitis. Yang et al. [9–11] reported the novel trisubstituted sulfonamides and bisamide derivatives as the CB2 receptor inverse agonists showing potent inhibitory activity on RANKL-induced osteoclast formation, which offered a wonderful beginning to develop a novel agent for the treatment of osteoporosis. The CB1 receptor selective antagonists were effective as therapeutic agents for obesity and related chronic diseases, such as type II diabetes, cardiovascular disease [12,13]. For example, Rimonabant (SR141716A, structure B in Fig. 1) was developed as an anti-obesity drug by reducing food intake in Europe. However, Rimonabant was withdrawn from the market owing to its significant psychiatric side effects. By now, the treatment choices of obesity are limited while the number of obesity people is increasing in every year, so there remains a significantly unsatisfied need for the development of anti-obesity agents. Rimonabant displays comprehensive pharmacological effects for obesity and associated metabolic disorders, indicating the CB1 receptor is an attractive target for drug discovery [14]. In order to avoid the adverse effects in CNS, the new strategy is designing novel ligands of the CB1 receptor with lower blood–brain barrier (BBB) penetration [15].

In recent years, the identification and optimization of novel cannabinoid ligand has been a hot topic in drug discovery [16]. The first reported CB1 receptor selective antagonist, SR141716A ([N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide]), was discovered by Sanofi-Aventis in 1994 [17]. Later, SR144528 ([N-[(1S)-*endo*-1,3,3-trimethylbicycle[2.2.1]-heptan-2-yl]-5-(4-chloro-3-methylphenyl

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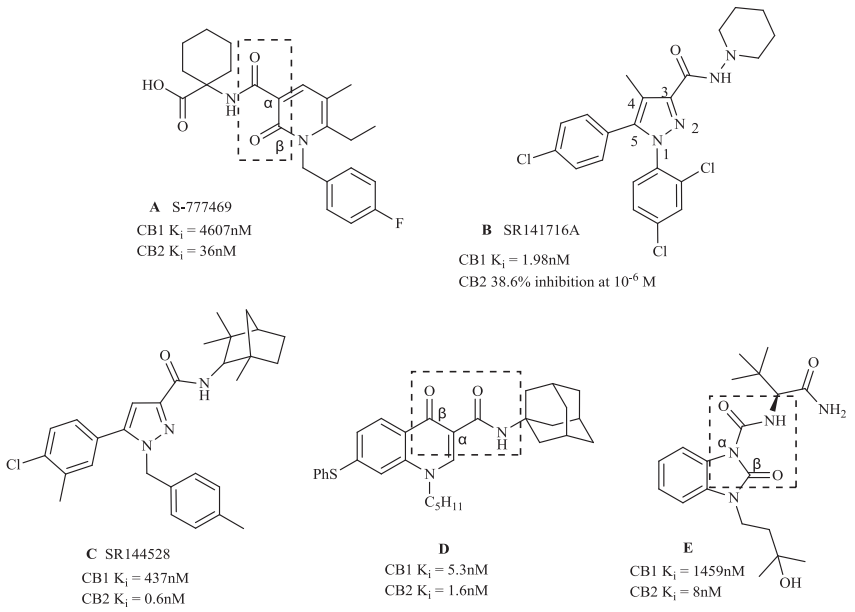

Fig. 1. Chemical structures of some known cannabinoid ligands.

)-1-(4-methylbenzyl)-pyrazole-3-carboxamide], structure **C** in Fig. 1), an analog of SR141716A, was developed to be the first CB2 receptor selective inverse agonist/antagonist [18,19]. With further research of the potent diarylpyrazole derivatives, several structural modifications were achieved on the basis of these parent compounds. Some compounds with different substituents on the pyrazole ring or the carboxamide part were synthesized [20–24], and others were prepared with isosteric replacement of the pyrazole core structure [25–27]. In the meantime, a number of cannabinoid ligands with different chemical scaffolds have emerged. As shown in Fig. 1, bioactive cannabinoid compounds **A**, **D** [28], and **E** [29] share similarly structural characteristics containing a carbonyl group at the β-position of the carboxamide part, inducing a privileged structure for designing original cannabinoid ligands. In addition, the scaffold hopping strategy is a useful approach for drug discovery by modifying the core structure of promising compounds. Combination of scaffold hopping and bioisostere method has been previously applied in identification of novel cannabinoid ligands [30,31].

In the present paper, we describe the design, syntheses, biological evaluations, preliminary structure–activity relationship (SAR) analyses, and docking simulations of a new serious of cannabinoid ligands with 1,2,4-triazolone scaffold. At first, the structural skeleton was designed using a combined method of scaffold hopping and privileged structure-oriented approaches. Structural modifications were then carried out with guideline of a pharmacophore model derived from the previous reported 3D-QSAR model [32]. The cell-based calcium current assays were applied to study the functional activity of synthesized 1,2,4-triazolone derivatives. The bioactive tests indicated that our designed compounds displayed interesting antagonistic activity towards either CB1 or CB2 receptor.

In order to calculate the interaction modes of our synthesized 1,2,4-triazolones binding to the CB1 and CB2 receptors, respectively, 3D homology models of both CB1 and CB2 receptors were constructed based on the crystal structure of β2-adrenergic receptor [33], and the conformations of both CB receptors were then optimized by molecular dynamics (MD) simulations with the proteins embedded in a hydrate bilayer system. Based on the generated homology models of both CB1 and CB2 receptors, flexible docking simulations were performed to gain insight to the receptor-ligand interactions and to explain the possibly selective characteristics of the compounds with different substituents. The docking simulations provided more information on the differences between the two binding sites of CB1 and CB2 receptors, which would afford guidelines for the design of new cannabinoid ligand with improved bioactive and selective profiles.

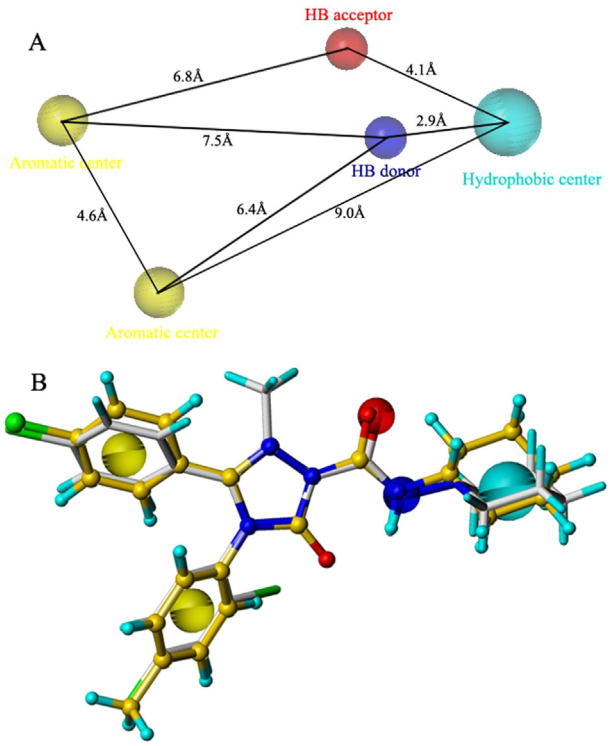

Fig. 2. Pharmacophore model based on the reported favorable conformation of pyrazole compounds for the CB1 receptor (A) and molecular alignment of both SR141716A, which carbon atoms were drawn in white, and typical compound of 1,2,4-triazolone with carbon atoms colored in orange (B). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)