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Pyrazoles with a "click" 4-[*N*-(4-fluorobutyl)-1,2,3-triazole] substituent in position 3 are nanomolar CB_1 receptor ligands

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ABSTRACT

Replacement of the 3-carbonylaminopiperidine substitutent with a "click" 4-[*N*-(4-fluorobutyl)-(1,2,3-triazolyl)] group in Rimonabant-type pyrazoles produced a novel class of nanomolar CB_1 receptor ligands. Molecule **1d** is the most promising lead with a K_i = 23 nM for CB_1, which is very close to that displayed by Rimonabant (SR141716), and fairly good CB_1/CB_2 selectivity (K_i CB_2/K_i CB_1 = 35.5), thus representing a promising candidate for [^{18}F]radiolabeling and PET Imaging studies of the CB_1 receptor.

1. Introduction

Cannabinoid receptors are members of the large family of G-protein coupled receptors (GPCRs) [1]. Two types of cannabinoid receptor have been discovered so far, CB_1 and CB_2 [2], and both of them have been extensively studied. CB_1 receptors are localised predominantly in the brain [2] whereas CB_2 receptors are more abundant in peripheral nervous system (PNS) cells [3], although some studies have shown the presence of CB_1 in the PNS [4] and of CB_2 in the central nervous system, albeit in low density [5]. CB_1 receptors have been associated with a number of disorders, including depression [6], anxiety [7], stress [8], schizophrenia [9], chronic pain [10] and obesity [11]. For this reason, several cannabinoid ligands were developed as drug candidates. Among these ligands, a prominent position is occupied by SR141716 (Rimonabant) [12], which is a pyrazole-core inverse agonist discovered by Sanofi-Synthelabo (now Sanofi-Aventis) in 1994, marketed in Europe as an anti-obesity drug but subsequently withdrawn from the market owing to its side-effects, which included severe depression and suicidal thoughts. Since the relationship between (a) the CB_1 receptors' functional modification, density and distribution, and (b) the onset of a pathological state is still not well understood, the development of radio-ligands suitable for *in vivo* PET functional imaging of CB_1 receptors remains an important area of research in medicine and drug development. To date, a few radiotracers [13] based on the structure of SR141716 (Rimonabant) [12] have been synthesised and tested *in vivo* but most of them afforded unsatisfactory brain imaging results due to their poor ability to cross the blood-brain barrier (BBB). A handful of radiolabelled CB_1 PET ligands [14] have also been submitted to clinical trials in humans [15]. In this paper we describe the synthesis of a conceptually new class of high-affinity CB_1 ligands **1**, bearing a "click" *N*-(4-fluorobutyl)-1,2,3-triazolyl function in position 3 of a pyrazolyl ring, as candidate PET tracers. Furthermore, we synthesised the 4-iodo-1,2,3-triazolyl analogue **10** which might be developed into a theranostic or a multi-modal imaging tool by radioiodination.

2. Results and discussion

2.1. Ligands design

Extensive theoretical and experimental structure-activity relationship studies have been performed on Rimonabant analogues for

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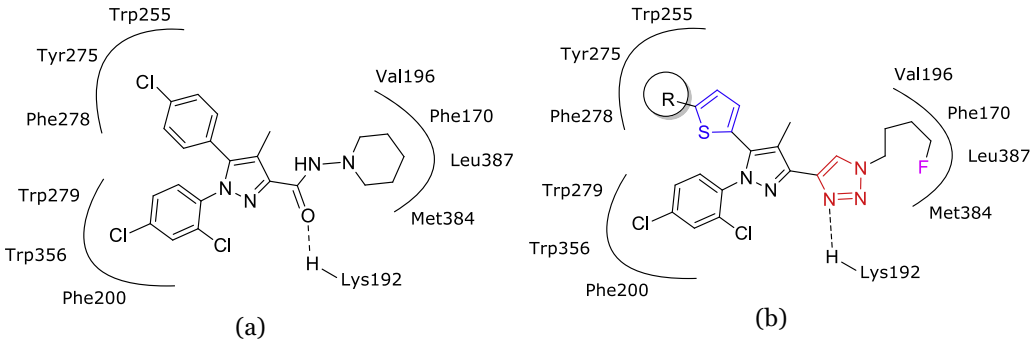


Fig. 1. (a) Rimonabant's pharmacophore. (b) Proposed binding mode of compounds **1** to CB_1.

identifying a general pharmacophore. Hydrophobic interactions between ligands and CB_1 receptor were deemed to be essential. In fact, the two aromatic rings in positions 1 and 5 of the pyrazole ring interact favourably with the residues Trp279/Phe200/Trp356 and Tyr275/Trp255/Phe278 respectively, and likewise the aminopiperidine cyclohexyl with the cavity constituted by Val196/Phe170/Leu387 and Met384 [16] (Fig. 1a). Moreover, the hydrogen bond between the ligand's amidic oxygen and the receptor residue Lys192 plays a crucial role in the binding, favouring the inverse agonism of Rimonabant.

With that in mind, we decided to replace the carbonyl-aminopiperidine residue in position 3 with a 4-(1,2,3-triazolyl) function, since either of the triazolyl sp^2 nitrogen atoms could act as hydrogen bond acceptor with Lys192. The 1,2,3-triazole would carry a *N*-(4-fluorobutyl) group, which should be readily amenable to [^{18}F]radiofluorination and could be accommodated in the lipophilic Val196/Phe170/Leu387/Met384 pocket. Finally, we planned to replace the 4-chlorophenyl group in 5-position with a 5-substituted 2-thiophenyl residue, which was previously shown to be a very advantageous structural modification leading to high-affinity CB_1 ligands, such as NESS125A [17].

2.2. Synthesis of 1,2,3-triazolyl compounds *1*

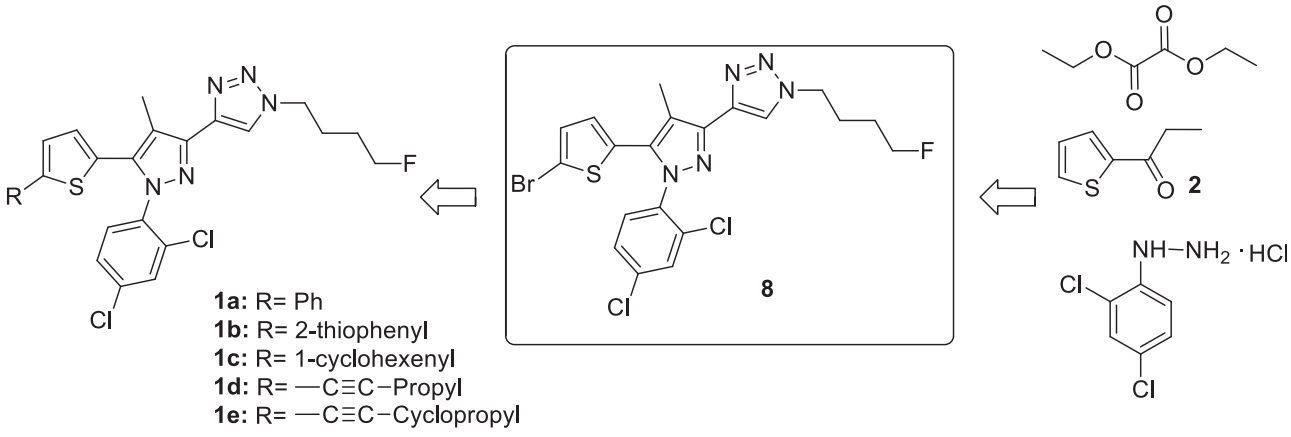
The synthesis of target compounds **1** envisaged the use of a key intermediate **8** (Scheme 1) which was obtained in a few synthetic steps from commercially available reagents such as diethyl oxalate, 1-(thiophen-2-yl) propan-1-one **2**, and 2,4-dichlorophenylhydrazine hydrochloride, and directly converted *via* a palladium-catalysed cross coupling reactions, into the desired target pyrazoles **1a–e**.

The synthesis started from **2** (Scheme 2), which was condensed with diethyl oxalate in the presence of sodium ethylate to give, in 85% yield, the 1,3-diketoester **3** as a tautomeric mixture, predominantly containing the alkenylidene structure. Subsequently, tricarbonyl compound **3** and 2,4-dichlorophenylhydrazine were heated in ethanol [18] to afford the pyrazole **4** in rather modest yield (32%). The latter was regioselectively brominated, [19] employing NBS as bromine source, to afford the corresponding bromothiophene **5** in good yield (83%). The following conversion was accomplished through a DIBAL-H hydride reduction, providing the aldehyde **6** which was homologated under Bestmann-Ohira alkynylation conditions [20] to generate the alkyne **7** in a moderate yield (55%). Finally, the key triazole **8** was achieved by means of a copper-catalyzed azide-alkyne cycloaddition protocol [21] in an acceptable 55% yield.

With the intermediate **8** in hand, compounds **1a–c** were obtained by means of a palladium-catalysed Suzuki–Miyaura cross coupling [22] using the respective commercially available boronic acids, while compounds **1d–e** were synthesised employing a copper-palladium catalysed Sonogashira cross coupling [23] using the appropriate alkyne (Scheme 3).

2.3. Synthesis of 5-iodo-1,2,3-triazolyl compound *10*

The synthesis of 4-iodo-1,2,3-triazolyl derivative **10** (Scheme 4) started from the intermediate **7** that was iodinated in a good yield (74%) using 4-iodomorpholine as iodine source. Next, a



Scheme 1. Retro-synthesis of 1,2,3-triazolyl analogues **1a–e**.