Bioorganic & Medicinal Chemistry Letters 26 (2016) 4403–4407

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

# Development of indole sulfonamides as cannabinoid receptor negative allosteric modulators

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ARTICLE INFO

*Article history:*
Received 14 July 2016
Revised 5 August 2016
Accepted 6 August 2016
Available online 6 August 2016

*Keywords:*
Cannabinoid
Negative allosteric modulator
CB1 NAM
Indole sulfonamide

ABSTRACT

Existing CB1 negative allosteric modulators (NAMs) fall into a limited range of structural classes. In spite of the theoretical potential of CB1 NAMs, published in vivo studies have generally not been able to demonstrate the expected therapeutically-relevant CB1-mediated effects. Thus, a greater range of molecular tools are required to allow definitive elucidation of the effects of CB1 allosteric modulation. In this study, we show a novel series of indole sulfonamides. Compounds **5e** and **6c** (**ABD1075**) had potencies of 4 and 3 nM respectively, and showed good oral exposure and CNS penetration, making them highly versatile tools for investigating the therapeutic potential of allosteric modulation of the cannabinoid system.


Drugs which block cannabinoid receptor activation were expected to find a huge market for the treatment of obesity, addiction and metabolic syndromes (e.g. type-2 diabetes). However, rejection by the FDA and eventual withdrawal in Europe of the first such drug to reach the market (rimonabant) effectively terminated this line of approach, in spite of the apparent therapeutic utility.[1] There are a number of different approaches now being taken to harness the potential of the cannabinoid system, whilst avoiding the side-effects of previous approaches that entailed global antagonism.[2] Such approaches include the use of neutral antagonists, negative allosteric modulators and peripheral restriction.[1,2]

CB1 receptors and endocannabinoids are present in peripheral tissues involved in metabolic dysfunction associated with obesity, including adipose tissue, liver, skeletal muscle and pancreas, and there is evidence for the upregulation of the endocannabinoid system in these tissues in experimental and human obesity.[3] Activation of CB1 receptors in peripheral tissues promotes lipogenesis, lipid storage, insulin secretion, glucagon secretion and adiponectin modulation.[4–6] Furthermore, a peripherally-restricted CB1 receptor antagonist does not affect behavioural responses in mice with genetic or diet-induced obesity, but it does cause weight-independent improvements in glucose homeostasis, fatty liver, and plasma lipid profile.[7] These findings confirm a prominent role for peripheral CB1 receptors on the modulation of metabolism and the potential for therapeutic benefit in the absence of CNS-mediated side-effects.[1]

Allosteric modulators are playing an increasingly prominent role in therapeutics, having the advantage of more subtle modulation of receptor activity than intervention at the orthosteric site, the normal binding site for the endogenous ligand. Furthermore, the allosteric sites of many receptors offer greater opportunities for selectivity, whereas the orthosteric sites of many receptors and subtypes can be too similar to allow a drug to distinguish between them, as they often must bind the same endogenous ligand.[8] In 2005, the first evidence was published indicating that the cannabinoid CB1 receptor contains an allosteric binding site and compounds such as Org27569 were identified that unexpectedly were allosteric enhancers of agonist binding affinity, but functionally were allosteric inhibitors of agonist signalling efficacy.[9] Related analogues of Org27569[10–14] and the diphenylurea PSNCBAM-1[15] were subsequently found to display similar pharmacological profiles. Org27569 and analogues have been widely studied and photo-activated derivatives of Org27569 have been highly effective for mapping of the CB1 allosteric binding site.[16,17] However, in vivo studies using Org27569 gave unexpected results: Org27569 did not modulate agonist-induced catalepsy or nociception,[18,19] though it did antagonize reinstatement of extinguished cocaine and methamphetamine seeking behaviours,[20] and showed conflicting effects on agonist-induced hypothermia.[18,19] Thus, both

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http://dx.doi.org/10.1016/j.bmcl.2016.08.018
0960-894X/

Gamage et al. and Ding et al. have been led to conclude that Org27569 does not function as a CB1 NAM in vivo and is acting by non-CB1 mediated mechanisms.[18,19]

In view of these unexpected results, it is clear that a wider range of potent tool compounds is required in order to provide more definitive evaluation of the effects of CB1 allosteric modulation and therapeutic potential. Our studies focused on bioisosteric replacement of the amide bond in Org27569 (Fig. 1) with a sulfonamide, with the expectation of increasing metabolic stability and perhaps giving access to a greater range of structural motifs, and consequently better control of physiochemical properties than is afforded by the limited range of existing compounds: for example, the preparation of highly-polar peripherally-restricted structures.

We set about synthesising a range of sulfonamide analogues of Org27569, using the methodology shown in Scheme 1.[21]

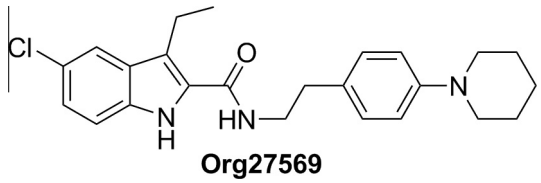
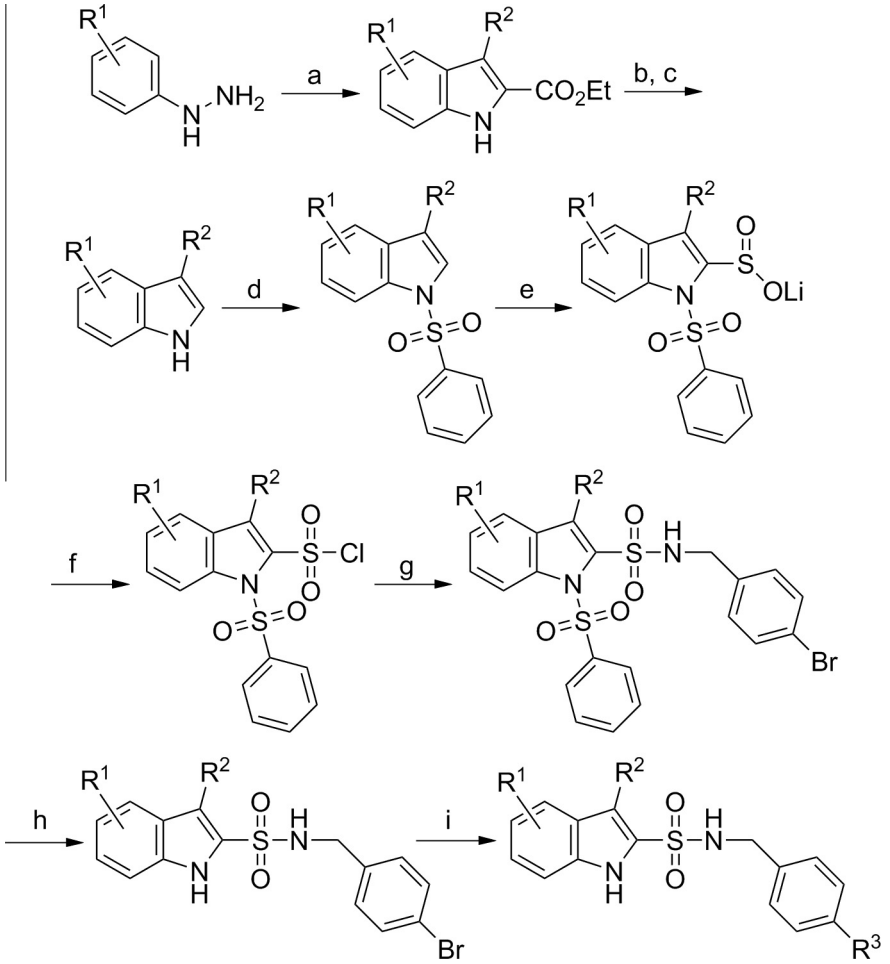



**Figure 1.** Structure of Org27569.

Substituted indoles were commercially-available or prepared as described previously.[22] The indole products were *N*-protected, deprotonated at the 2-position with *n*-butyllithium in THF, and reacted with sulfur dioxide to give the corresponding lithium sulfinates. Reaction with *N*-chlorosuccinimide in DCM gave the corresponding sulfonyl chlorides, which were subsequently coupled with the amine of choice and *N*-deprotected (to generate compounds **1a**–**1w**, **2a**, **2b**, **2t** and **2u**) or with the required 4-bromobenzylamine, *N*-deprotected, and further Suzuki coupling performed (to give compounds **2c**–**2u** and **2v**–**2z**).

Initial studies, on compounds closely related to Org27569, suggested that the sulfonamide analogues were around 100-fold less potent than their amide counterparts and had very low metabolic stability, and thus were of limited developmental value (Tables 1 and 3). However, a breakthough in potency was seen when 4-phenylbenzylamine was used as the side chain, giving compounds **2a** and **2b**, with $IC_{50}$ values of 8 and 2 nM respectively in the PathHunter hCB1 β-Arrestin assay,[12] comparable to that of Org27569 (Fig. 2, Tables 1–3).

Additional substituents could be introduced on the outer phenyl ring by reacting the sulfonyl chloride with 4-bromobenzylamine to give an intermediate that could be coupled with the required benzeneboronic acid by standard Suzuki coupling methods. This was used to give further potent compounds: 4′-fluoro, 4′-methoxy, 4′-dimethylamino and 4′-methyl groups, all with




**Scheme 1.** Synthesis of indole-2-sulfonamides **2a**–**2z**. Reagents and conditions (a) 2-oxovaleric acid PTSA, EtOH (reflux, 20 h); (b) 5% NaOH, EtOH (40 °C, overnight); (c) Cu, quinoline (microwaved for 25 min at 250 °C); (d) NaH, $BzSO_2Cl$, DMF (rt, 18 h); (e) 1.6 M *n*-BuLi, THF, $SO_2$, (−78 °C to rt, 2 h); (f) NCS, DCM (0 °C to rt, 2 h); (g) 4-bromobenzylamine, pyridine, DCM (0 °C to rt, 18 h); (h) 10% NaOH, EtOH, (reflux, 2 h); (i) substituted benzeneboronic acid, $(PPh_3)_4Pd$, ethanol, toluene, 2 M $Na_2CO_3$, (reflux, 3 h).