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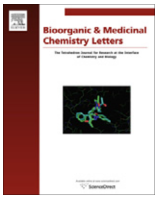

Design, synthesis, and structure–activity relationship study of bicyclic piperazine analogs of indole-3-carboxamides as novel cannabinoid CB1 receptor agonists

Elizabeth M. Moir[a], Kazuya Yoshiizumi[a], Jim Cairns[a], Phillip Cowley[a], Morag Ferguson[a], Fiona Jeremiah[a], Takao Kiyoi[a], Richard Morphy[a], Jason Tierney[a], Grant Wishart[a], Mark York[a], James Baker[b], Jean E. Cottney[b], Andrea K. Houghton[b], Petula McPhail[b], Andrew Osprey[b], Glenn Walker[b], Julia M. Adam[a,*]

[a] *Department of Chemistry, Merck Research Laboratories, MSD Ltd, Newhouse, Lanarkshire ML1 5SH, UK*
[b] *Department of Pharmacology, Merck Research Laboratories, MSD Ltd, Newhouse, Lanarkshire ML1 5SH, UK*

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Bicyclic piperazine derivatives were synthesized as conformationally constrained analogs of *N*-alkyl piperazines and were found to be potent CB1 receptor agonists. The CB1 receptor agonist activity was dependent upon the absolute configuration of the chiral center of the bicyclic ring system. Although the conformational constraint did not protect the compounds from metabolism by N-dealkylation, several bicyclic analogs were found to be more potent than the unconstrained lead compound. Compound **8b** demonstrated potent antinociceptive activity in vivo.

The CB1 cannabinoid receptor is a member of G-protein coupled receptor (GPCR) superfamily, which is characterized by seven-transmembrane receptors.[1] The CB1 receptor is located primarily in the central nervous system but is also expressed on peripheral neurones. Activation of the CB1 receptor has been suggested as a potential strategy for the treatment of pain and several other diseases including glaucoma, traumatic brain injury, and multiple sclerosis,[2] while inhibition of CB1 receptors has been explored as a strategy for the treatment of obesity and addiction.[3] Several lines of evidence have been reported regarding the analgesic effects of CB1 receptor agonists in both experimental animal models and clinical studies. While limited in clinical utility by their small therapeutic window with respect to psychotropic side effects, a couple of CB1 receptor agonists including Δ^9-tetrahydrocannabinol (Δ^9-THC, Fig. 1), one of the major bioactive components of cannabis, are used clinically as antiemetics in cancer chemotherapy or appetite stimulants in AIDS patients.[4] Sativex™, a medicinal cannabis extract containing a mixture of Δ^9-THC and cannabidiol, has been recently launched for treatment of multiple sclerosis (MS)- and cancer-associated neuropathic pain, and for MS-associated spasticity. In addition, several lines of research are being progressed toward identifying novel cannabinoid related medicines that avoid or minimize the adverse effects associated with administration of classical cannabinoid agonists.[5] Moreover, the classical cannabinoid agonists represented by Δ^9-THC are highly lipophilic and the administration methods are still limited.

Previous publications described indole-3-carboxamide derivatives as water soluble CB1 receptor agonists suitable for intravenous administration as potential post-operative analgesics.[6,7] This Letter describes a series of bicyclic piperazine analogs in which the piperazine *N*-alkyl substituent is tethered back onto the piperazine ring (Fig. 2). Metabolite identification studies on initial compounds in the mono-cyclic series indicated piperazine N-dealkylation as a major route of metabolism. It was proposed that tethering the *N*-alkyl group back onto the piperazine ring system would favorably affect the metabolic stability of these compounds and, in addition, potentially improve potency within the series. The impact of stereochemistry and effects of substitution in the bicyclic piperazine system on CB1 receptor agonist potency and microsomal stability were investigated.

Compounds were synthesized as described in Scheme 1. Fourteen optically pure bicyclic piperazines **6a–n** were prepared using parallel synthesis techniques, applying the previously reported method for the synthesis (*S*)-1,4-diazabicyclo[4.3.0]nonane.[8] Reaction of amino acid methyl esters **2** and cyclic carboxylic acids **3** afforded amides **4**. Boc deprotection and cyclization followed by reduction of the amide carbonyl afforded bicyclic piperazines **6a–n**. Introduction of the piperazinylcarbonyl moiety to *N*-cyclohexylmethyl-7-methoxyindole **7** was performed by direct amide

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* Corresponding author. Tel.: +44 1698 736000; fax: +44 1698 736187.
E-mail address: julia.adam@merck.com (J.M. Adam).

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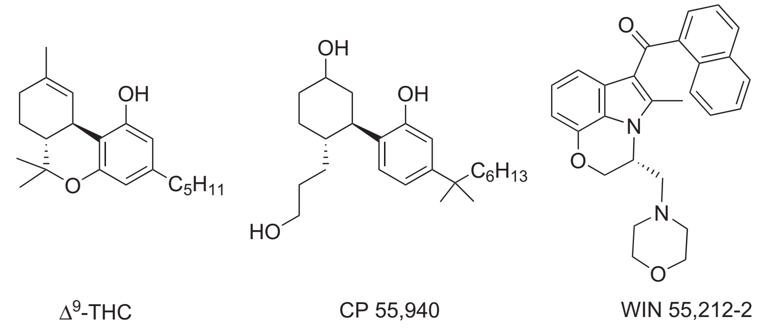


Figure 1. Representative naturally occurring and synthetic cannabinoid receptor agonists.

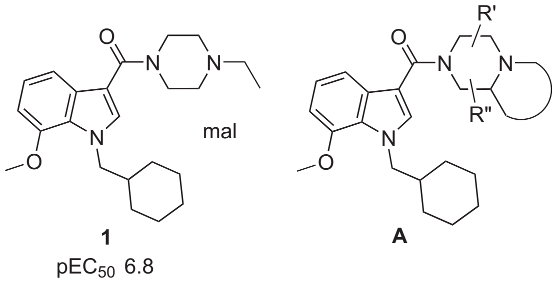


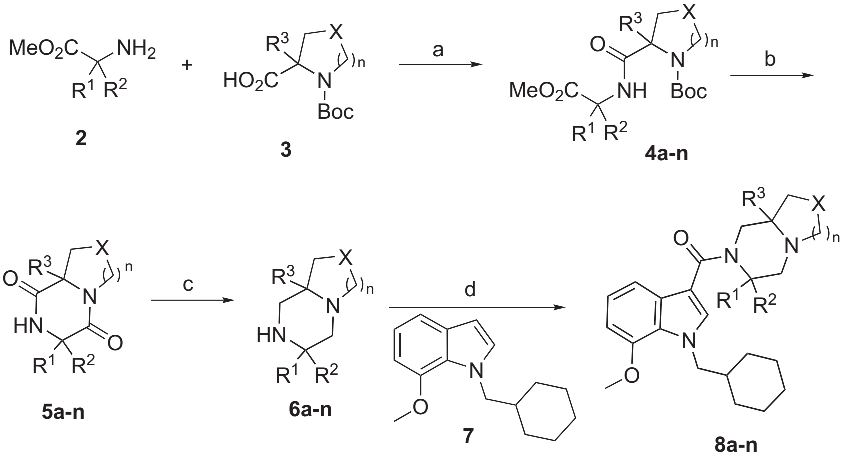
Figure 2. The structure of the original lead compound **1** and newly designed scaffold **A**.

formation[6] using oxalyl chloride in 1,1,2,2-tetrachloroethane at 120 °C for 2 h, followed by addition of bicyclic piperazine **6a–n** and triethylamine, to form the piperazine amides **8a–n**.

The prepared compounds were tested for CB1 receptor agonist activity using CHO cells doubly transfected with human CB1 and a luciferase reporter gene.[9] As shown in Table 1, a number of bicyclic piperazine analogs were more potent at CB1 than the unconstrained *N*-ethyl piperazine **1** (Fig. 2), for example, compound **8b** with $pEC_{50} = 7.9$ versus $pEC_{50} = 6.8$ for compound **1**. In general, for analogs with one chiral center (**) at the bridgehead position, the (*S*)-isomer was more potent than the (*R*)-isomer. This was true for 6,6- and 6,5-bicyclic piperazine ring systems, comparing derivative **8b** with **8a**, and derivative **8d** with **8c**. This general rule also held true for the R^1, R^2 dimethyl analogs, comparing derivative **8j** with **8i**. In cases where there was a single substituent at R^1 and R^2 = H (examples **8e–h**), the combined effect of stereochemistry at the two chiral centers (* and **) was less clear cut. Replacement of methyl with the larger isobutyl substituent at R^1 was not tolerated, illustrated by the reduced potency of compounds **8k** and **8l** in comparison with derivatives **8e** and **8f**, respectively. Addition of a methyl substituent at the bridgehead position, R^3, was detrimental to activity (comparing analog **8m** with **8d**). Incorporation of a further heteroatom into the bicyclic piperazine system was tolerated. Indeed for X = S (example **8n**), there was an improvement in potency from $pEC_{50} = 6.3$ for compound **8g** to $pEC_{50} = 7.5$ for **8n**. Where tested, different salt forms (e.g., HCl salt/free base) had no effect on the in vitro potency (data not shown).

Microsomal stability was determined for all compounds in Table 1 but no improvement in stability over the initial lead, **1**, was observed. Compounds **8a–n** all showed a half-life of <5 min in human and mouse liver microsome preparations.

In order to investigate whether tethering back the *N*-alkyl substituent had perhaps shifted the major site of metabolism to a different region of the molecule, compound **8b** was briefly incubated with human liver microsomes (5 min) and the profiles of the metabolites were analyzed by LC–MS–MS (Scheme 2 and Table 2). To our surprise, the major metabolites were still found to correspond to metabolism in the bicyclic piperazine portion of the molecule, with N-dealkylation remaining a significant metabolic pathway as demonstrated by formation of metabolite **M2**. The enzymes responsible for this metabolism have not been characterized; however,



Scheme 1. Reagents and conditions (reaction yields depicted below were from synthesis of **8b** as a typical example): (a) $(Me)_2N(CH_2)_3N{=}C{=}NEt{\cdot}HCl$, HOBt, NEt_3, DCM, rt, 40 h, 98%; (b) (i) CF_3COOH, rt, 2 h, (ii) NEt_3, MeOH, reflux, 6 h, two steps 52%; (c) $LiAlH_4$, THF, reflux, 3 h, 68%; (d) oxalyl chloride, 1,1,2,2-tetrachloroethane, 120 °C, 2 h, then NEt_3 and **7**, rt, 7 h, 61%.