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A synthetic approach for (*S*)-(3-benzyl-3-methyl-2,3-dihydro-benzofuran-6-yl)-piperidin-1-yl-methanone, a selective CB2 receptor agonist

Zhushou Luo, Mohamed Naguib *

Anesthesiology Institute, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44106, USA

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ABSTRACT

(*S*)-(3-Benzyl-3-methyl-2,3-dihydro-benzofuran-6-yl)-piperidin-1-yl-methanone, a selective CB2 receptor agonist, was obtained from 3-hydroxy-4-iodo benzoic acid in nine steps with 97.4% ee and 3.4% total yield, which involved palladium catalyzed tandem intramolecular Heck/Suzuki cross coupling reaction, chemical resolution with (+)-norephedrine and Wolf–Kishner reaction as the key steps. (*S*)-(3-Benzyl-3-methyl-2,3-dihydro-benzofuran-6-yl)-piperidin-1-yl-methanone will be evaluated in vivo studies and this approach will be applied in the optimization process of CB2 receptor agonist.

The endogenous cannabinoid system is a complex system consisting of two cannabinoid (CB) receptors (CB1—expressed primarily in the brain and CB2—expressed primarily in the peripheral immune system[1] and in the central nervous system (CNS)[2]), seven endogenous endocannabinoid ligands (arachidonic acid derivatives) including anandamide (*N*-arachidonoylethanolamine) and 2-arachidonoylglycerol (2-AG),[3] and several proteins responsible for the regulation of endocannabinoid metabolic pathways, such as monoacylglycerol lipase and fatty acid amide hydrolase.[4] CB1 and CB2 are seven transmembrane, G protein-coupled receptors, and they share 44% overall identity. Both receptors mediate the inhibition of adenylyl cyclases and stimulation of mitogen-activated protein kinases (MAPK). However, CB1 receptor agonists failed to show efficacy in patients with neuropathic pain compared with placebo, and their use has resulted in a high incidence of psychotropic adverse effects.[5] In contrast, CB2 receptor agonists are neuroprotective and are emerging as treatments for neuropathic pain. Moreover, they lack the psychotropic adverse effects that normally occur with CB1 agonists.[6,7] Increasing interest has been spurred in pharmaceutical companies and academia, and several classes of selective CB2 agonists for the treatment of inflammatory and neuropathic pain conditions have been reported.[6,8]

We initiated a research program aimed at identifying novel selective CB2 agonists for the treatment of neuropathic pain, and we identified (*S*)-(3-Benzyl-3-methyl-2,3-dihydro-benzofuran-6-yl)-piperidin-1-yl-methanone **1** (Fig. 1) as a lead compound.[6b] The absolute stereochemistry of compound **1** has also been determined by X-ray crystal structure. In vitro *h*CB2 GTPγ[^{35}S] functional assay, compound **1** binds selectively to the CB2 receptor (EC_{50}: 108 nM on *h*CB2; >10 μM on *h*CB1), which is better than its corresponding racemate (EC_{50}: 128 nm on *h*CB2; >10 μM on *h*CB1) and *R* enantiomer (EC_{50}: 960 nm on *h*CB2, >10 μM on *h*CB1). Racemate also showed (i) dose-dependent reversal of neuropathic pain in spinal nerve ligation and paclitaxel-induced neuropathy rat models when administered intraperitoneally with ED_{50} value of 7.5 and 24 mg/kg, respectively, and (ii) prevention of paclitaxel-induced neuropathy.[6a] However, compound **1** was only obtained previously in very limited quantity using chiral HPLC separation of the corresponding racemate.[6b] Thus, a scalable and effective approach is needed for the synthesis and optimization of compound **1**.

Compound **1** has a quaternary carbon stereocenter at the benzylic position in the ring system of 2,3-dihydro-1-benzofuran, and presents an interesting synthetic challenge.[9] The key reaction for racemic synthesis of compound **1** and its analogs is shown in Scheme 1. The synthesis utilized palladium catalyzed tandem

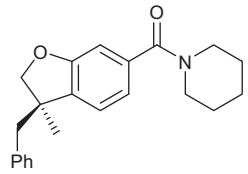

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Figure 1. Structure of (*S*)-(3-benzyl-3-methyl-2,3-dihydro-benzofuran-6-yl)-piperidin-1-yl-methanone.

* Corresponding author. Tel.: +1 216 444 6328; fax: +1 216 636 2043.
E-mail address: naguibm@ccf.org (M. Naguib).

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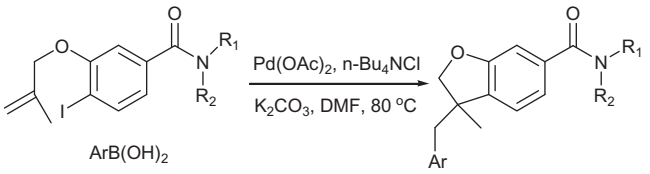
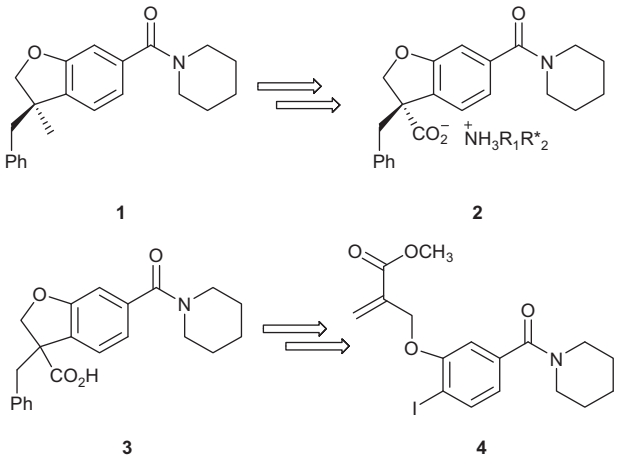


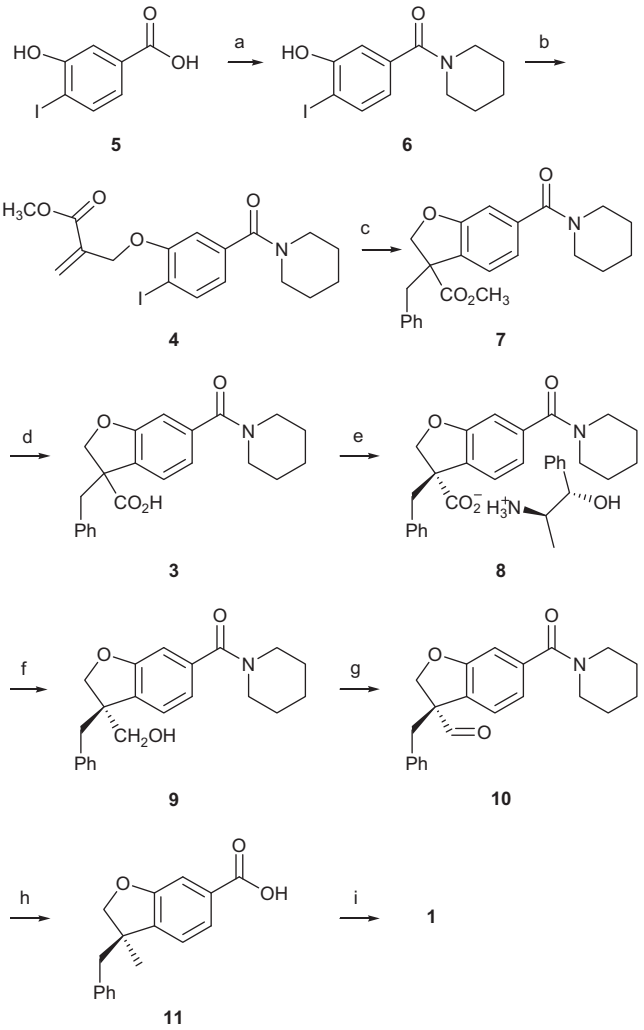
Scheme 1. Synthesis of racemic **1** and its analogs.

intramolecular Heck/Suzuki coupling reactions.[6b,10] Although asymmetric intramolecular Heck reaction has been widely used in organic synthesis including the formation of quaternary chiral carbon center,[11] our attempt of enantioselective synthesis was unsuccessful when we used different reaction conditions, chiral ligands, palladium sources, and appropriate additives. We then utilized chemical resolution approach using chiral resolving agent.[12] As shown in Scheme 2, we expect to obtain chiral separable solid salt **2** by the combination of appropriate chiral amine and racemic acid **3**, followed by further transformation to deliver compound **1**. Racemic acid **3** could be synthesized from tandem intramolecular Heck/Suzuki coupling reactions of compound **4** and phenylboronic acid.[6b,10] Herein, we report our synthetic pathway of compound **1** based on this strategy.

Coupling of 3-hydroxy-4-iodo benzoic acid **5**[13] with piperidine gave amide **6**, which reacted with methyl 2-bromoacrylate to afford **4** (Scheme 3). Compound **4** was subjected to Heck/Suzuki coupling conditions leading to compound **7** in 53% yield. Basic hydrolysis of **7** gave the racemic acid **3**. Among the screened chiral amine for chemical resolution, (+)-norephedrine gave desired results. Acid **3** and (+)-norephedrine were dissolved in ethanol under 75 °C, followed by slow addition of ethyl acetate to form a little cloudy solution. Then the solution was filtered, the filtrate cooled to room temperature, and stood at 4 °C overnight to give white precipitate, which was filtered to give salt **8** in good yields (24–33%) and high ee value (98.0%, see supplementary data). The absolute stereochemistry was not determined at this stage. Salt **8** was then directly transformed into mixed anhydride followed by $NaBH_4$ reduction to afford alcohol **9** in 70% yield. Initially, **9** was converted into its corresponding bromide followed by the treatment with tributyltin hydride and AIBN in refluxing benzene to afford only complex mixture. Finally Wolf–Kishner reaction[14] was chosen to make this transformation. Swern oxidation of primary alcohol **9** gave aldehyde **10**, which reacted with hydrazine in diethylene glycol at 100 °C for 1 h followed by the addition of potassium hydroxide and heating at 195 °C for additional 4 h to afford acid **11**. Acid **11** coupled with piperidine to give the final product **1**. Compound **1** was confirmed as the desired *S* configuration product with 97.4% ee by the comparison of all spectroscopic data with authentic sample, which was previously purified by chiral HPLC and assigned as *S* configuration by X-ray crystallography.[6b]



Scheme 2. Synthetic strategy for compound **1**.



Scheme 3. Reagents and conditions: (a) piperidine, *i*Pr_2NEt, HATU, DMF, 23 °C, 16 h, 56%; (b) methyl 2-bromomethyl-acrylate, K_2CO_3, methyl ethyl ketone, reflux, 3 h, 86%; (c) phenylboronic acid, $Pd(OAc)_2$, *n*-Bu_4NCl, K_2CO_3, DMF, 80 °C, 16 h, 53%; (d) NaOH, dioxane/H_2O = 4/1, 23 °C, 48 h, 91%; (e) (+)-norephedrine, 24–33%; (f) methyl chloroformate, THF, 0–23 °C; then $NaBH_4$, ethanol, −78–0 °C, 70%; (g) $(COCl)_2$, DMSO, then Et_3N, CH_2Cl_2, −78–23 °C, 93%; (h) NH_2NH_2, diethylene glycol, 100 °C, 1 h, then KOH, 195 °C, 4 h, 73%; (i) piperidine, *i*Pr_2NEt, HATU, DMF, 23 °C, 16 h, 92%.

In conclusion, we have developed an effective approach to synthesize (*S*)-(3-benzyl-3-methyl-2,3-dihydro-benzofuran-6-yl)-piperidin-1-yl-methanone **1**, a selective CB2 receptor agonist with 3.4% total yield and high ee (97.4%). This approach involved tandem intramolecular Heck/Suzuki coupling reaction of intermediate **4**, chemical resolution of intermediate acid **3** and Wolf–Kishner reaction for the transformation of intermediate **9** into **1**. Currently compound **1** is evaluated in vivo studies and this approach is used in our lab for the optimization of compound **1**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.076.

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