Bioorganic & Medicinal Chemistry Letters 26 (2016) 5346–5349

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Tetrahydroindazole derivatives as potent and peripherally selective cannabinoid-1 (CB1) receptor inverse agonists

Jay M. Matthews, James J. McNally, Peter J. Connolly, Mingde Xia, Bin Zhu *, Shawn Black, Cailin Chen, Cuifen Hou, Yin Liang, Yuting Tang, Mark J. Macielag

Janssen Research & Development, L.L.C., Welsh & McKean Roads, Spring House, PA 19477, USA†

ARTICLE INFO

Article history:
Received 3 August 2016
Revised 7 September 2016
Accepted 8 September 2016
Available online 10 September 2016

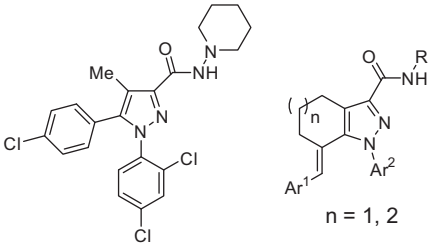
Keywords:
Cannabinoid receptor
CB1 receptor
Inverse agonist
Peripheral selectivity
Peripherally restricted

ABSTRACT

A series of potent and receptor-selective cannabinoid-1 (CB1) receptor inverse agonists has been discovered. Peripheral selectivity of the compounds was assessed by a mouse tissue distribution study, in which the concentrations of a test compound in both plasma and brain were measured. A number of peripherally selective compounds have been identified through this process. Compound **2p** was further evaluated in a 3-week efficacy study in the diet-induced obesity (DIO) mouse model. Beneficial effects on plasma glucose were observed from the compound-treated mice.

The cannabinoid receptors are part of the endocannabinoid system, which regulates many important biological processes. Two such receptors have been identified to date as cannabinoid-1 (CB1) receptor[1] and cannabinoid-2 (CB2) receptor.[2] The CB2 receptor is mainly located in the immune system and regulates inflammatory responses.[3] The CB1 receptor is expressed abundantly in the central nervous system (CNS) and in peripheral tissues such as liver, skeletal muscle, adipose tissue, and pancreas.[4] Antagonism of the CB1 receptor leads to decreasing food intake and increasing insulin sensitivity, and has emerged as an attractive approach to treat obesity and related metabolic diseases such as type 2 diabetes. Unfortunately, undesirable psychiatric side effects led to the withdrawal of the only marketed brain penetrating CB1 receptor inverse agonist/antagonist, rimonabant **1**, as well as the termination of the development of other clinical-stage agents in this class. However, in recent years, an increasing amount of evidence suggested that some of the metabolic benefits seen in treatment with CB1 receptor inverse agonists/antagonists may result from actions in the peripheral tissues. Therefore peripherally restricted CB1 receptor inverse agonists/antagonists that do not cross blood–brain barrier (BBB) may be useful therapeutics for metabolic disease without causing CNS-mediated adverse effects.[5–9]

Herein, we report the discovery of a series of potent and peripherally selective CB1 receptor inverse agonists **2** that originated from our earlier brain-penetrant CB1 receptor inverse agonist program (Fig. 1).[10] The synthesis of compound **2** is illustrated in Scheme 1. Cyclohexanone ($n = 1$) or cycloheptanone ($n = 2$) **3** was reacted with aryl aldehyde **4** in aqueous sodium hydroxide solution at elevated temperature to give the condensation product **5**. Treatment of compound **5** with lithium bis(trimethylsilyl)amide at -78 °C followed by diethyl oxalate led to compound **6**. Condensation of **6** with aryl hydrazine **7** was achieved in the presence of trifluoroacetic acid (TFA) in dioxane at elevated temperature to give pyrazole **8**. Hydrolysis of the ethyl ester of compound **8** under basic conditions yielded carboxylic acid **9**, which was then coupled



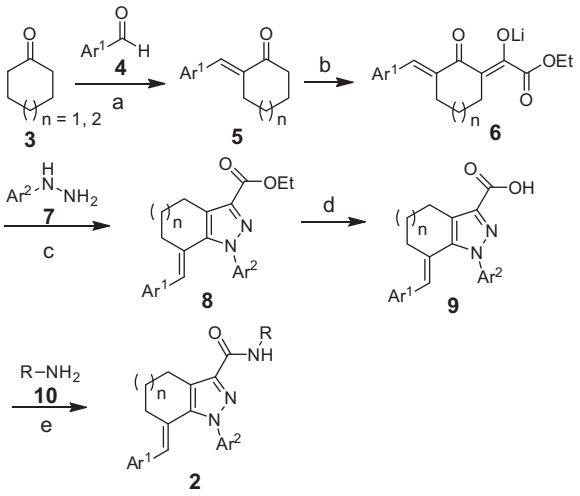
1 (rimonabant) **2**

Figure 1.

* Corresponding author.

† All authors were employed by Janssen Research & Development, L.L.C. at the time the work reported herein was conducted.

http://dx.doi.org/10.1016/j.bmcl.2016.09.025
0960-894X/



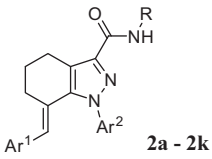
Scheme 1. Reagents and conditions: (a) NaOH, H_2O, 65 °C; (b) (i) LiHMDS, Et_2O, −78 °C; (ii) diethyl oxalate, −78 °C to rt; (c) CF_3CO_2H, 1,4-dioxane; (d) aq NaOH, EtOH; (e) HATU, DIPEA, DMF.

with amine **10** under standard amide formation conditions (HATU, Et_3N) to give final product **2**.

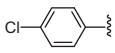
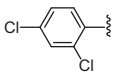
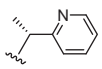
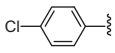
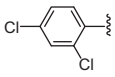
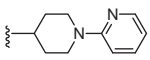
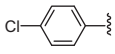
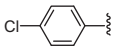
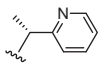
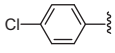
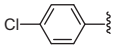
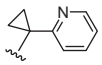
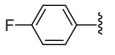
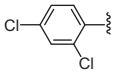
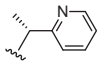
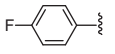
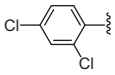
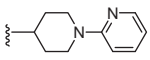
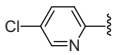
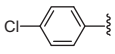
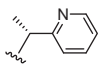
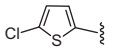
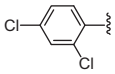
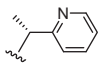
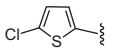
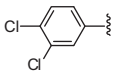
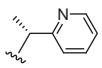
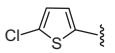
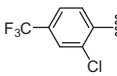
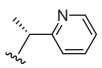
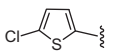
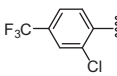
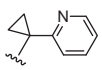
The in vitro CB1 and CB2 receptor inverse agonist activities of compounds **2** were assessed in cell-based functional assays measuring cyclic adenosine monophosphate (cAMP) production.[11] Compounds with acceptable CB1 receptor potency and CB1/CB2 receptor selectivity were then evaluated in a mouse tissue distribution study.[12] In this study, male C57bl/6j mice were dosed orally with a test compound at 20 mg/kg, and the concentrations of the test compound in both plasma and brain were measured at either a 2 h or 4 h time point. The in vitro CB1 and CB2 receptor inverse agonist activity and in vivo tissue distribution data of cyclohexanone-derived compounds **2a**–**k** (6-membered ring series, $n = 1$) are shown in Table 1, and those of cycloheptanone-derived compounds **2l**–**w** (7-membered ring series, $n = 2$) are shown in Table 2. The calculated topological polar surface area (TPSA) and *c*Log*P* data are also included in the tables.

As demonstrated by the data in Table 1, both aryl (**2a**–**f**) and heteroaryl (**2g**–**k**) Ar^1 groups led to good CB1 receptor inverse agonist activity, while substituted aryls are the optimal Ar^2 groups in terms of CB1 potency. Additionally, the R group plays an important role. Compounds with 1-(pyridin-2-yl)piperidin-4-yl as the R

Table 1
In vitro pharmacology and in vivo tissue distribution of compounds **2a**–**k**



2a - 2k

Compd.	Ar^1	Ar^2	R	CB1 EC_{50} (μM)	CB2 EC_{50} (μM)	Plasma Conc. (μM)	Brain Conc. (nmol/g)	B/P ratio	*c*Log*P*	TPSA
2a				0.030	0.854	1.60[a]	0.32[a]	0.20	7.40	59.8
2b				0.034	>10	0.45[a]	0.04[a]	0.09	7.33	63.1
2c				0.127	>10	3.72[b]	0.97[b]	0.26	6.68	59.8
2d				0.007	1.61	1.61[a]	1.28[a]	0.82	6.72	59.8
2e				0.004	>10	1.56[b]	1.39[b]	0.92	6.83	59.8
2f				0.012	>11	1.52[b]	0.035[b]	0.02	7.71	50.2
2g				0.022	>10	2.93[b]	1.91[b]	0.65	5.27	72.7
2h				0.035	3.82	2.96[b]	0.24[b]	0.08	7.32	88.1
2i				0.037	>10	3.18[a]	0.10[a]	0.03	7.20	88.1
2j				0.018	>10	0.46[a]	0.051[a]	0.11	7.56	88.1
2k				0.011	>10	4.63[a]	0.64[a]	0.14	7.59	88.1

[a] Sample was collected at 4 h.
[b] Sample was collected at 2 h. B/P ratio: brain/plasma concentration ratio.