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Potent imidazole and triazole CB_1 receptor antagonists related to SR141716

Brian Dyck,* Val S. Goodfellow, Teresa Phillips, Jonathan Grey, Mustapha Haddach, Martin Rowbottom, Gregory S. Naeve, Brock Brown and John Saunders

Departments of Medicinal Chemistry, Pharmacology and Molecular Biology, Neurocrine Biosciences Inc., 10555 Science Center Drive, San Diego, CA 92121, USA

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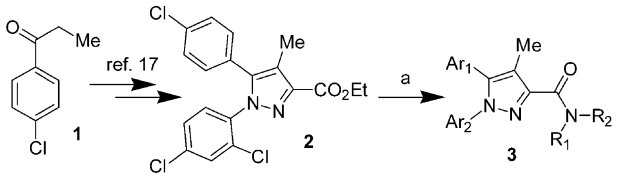
Abstract—Diarylimidazolecarboxamides and diaryltriazolecarboxamides related to SR141716 were synthesized and tested for binding to the human CB_1 receptor. Suitably substituted imidazoles are comparably potent to the clinical candidate, whereas the analogous triazoles are less so due to the absence of an additional substituent on the azole ring.

The pharmacological effects of Δ^9-tetrahydrocannabinol (Δ^9-THC), its metabolites, and other components of related structure, collectively called cannabinoids, have been well documented both in a clinical setting and from the use of marijuana as a recreational drug. The psychotropic component of these effects is the reason for the continued illicit use of cannabis. In spite of the potential for abuse, cannabinoids have a number of potential therapeutic uses including antinociception, suppression of chemotherapy-induced nausea, and appetite stimulation in cachexic patients.[1–8]

Cannabinoids have been shown to impart their physiological effects largely through binding and activation of two cannabinoid receptors, which are G-protein coupled receptors (GPCRs).[6] In particular, the psychoactive effects are thought to arise via stimulation of the centrally distributed CB_1 receptor. Δ^9-THC possesses higher binding affinity for this receptor and a much longer duration of action than the putative endogenous agonist arachidonylethanolamide (anandamide).[9–11] Because the pharmacological effects of the cannabinoids, including appetite stimulation, are mediated via an agonist/receptor pair, the possible use of CB_1 receptor antagonists in the treatment of obesity has been investigated,[12] and at least one of these compounds (SR141716) has advanced into clinical trials.[13]

Diarylpyrazoles are well known ligands for the central cannabinoid receptor and the above mentioned clinical candidate is from this structural class. The affinity of these compounds for this receptor was originally reported by researchers from Sanofi[14] and numerous reports on SAR around this series have been published.[15–21] In connection with our studies on general binding elements of class A GPCRs, we had occasion to study the importance of the pyrazole core on binding to the CB_1 receptor. In particular, since the endogenous ligand is a fatty acid amide, we sought to determine whether the pyrazole core of SR141716 is merely a spacer connecting lipophilic aryl groups to the carboxamide head, or if it contains important binding features itself. For this reason, we investigated the replacement of the pyrazole core of SR141716 with other heterocycles. Several recent patent applications disclosing imidazole-based ligands for CB_1 have prompted us to report our own studies on structure–activity relationships for compounds related to SR141716.[22]

Diarylpyrazoles related to SR141716 were prepared as outlined in Scheme 1. Propiophenone **1** was elaborated



Scheme 1. Reagents: (a) (i) aq NaOH, dioxane, 70 °C (100%); (ii) oxalyl chloride, DCM, cat. DMF; (iii) R_1R_2NH, ACN (24–92%).

* Corresponding author. Tel.: +1-858-658-7778; fax: +1-858-658-7601; e-mail: bdyck@neurocrine.com

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into ethyl diarylpyrazolecarboxylate **2** as previously described.[14,17] This compound was saponified and converted to the acyl chloride with oxalyl chloride, and this intermediate was then treated with various amines in a 96-well plate format to afford amides **3**.

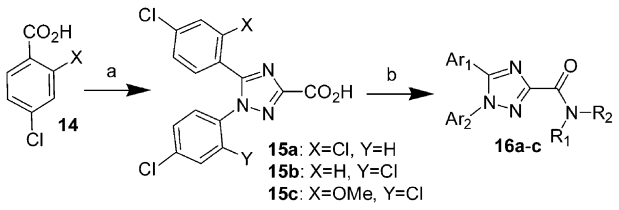
The binding affinities of several key pyrazoles for the CB_1 receptor are shown in Table 1.[23] In our assay, SR141716 (**4**) exhibited a K_i of 12 nM, which is in good agreement with literature values.[15,17] We found the slightly larger bicyclic hydrazide group present in **5** afforded a more potent compound. Replacement of the hydrazide moiety with a simple amide showed a reduction in activity (**7**, **9**, and **10**), which was further compounded by disubstitution on the amide nitrogen atom (**8**). Polar substituents are not well tolerated (**11**–**13**), as all of these substitutions led to significant loss of potency. This is consistent with prior observations.[17,19,21]

A structurally related series of triazoles was prepared as outlined in Scheme 2. Coupling of benzoic acids **14** with dimethyl aminomalonate under standard conditions gave the corresponding amides. These intermediates have been previously used in the preparation of triazolecarboxylates.[24] In an analogous fashion, reaction of these compounds with aryldiazonium salts and treatment of the adducts with sodium methoxide gave moderate yields of the triazolecarboxylate esters. These compounds were then converted to the corresponding amides using the same procedure as their pyrazole counterparts.

Table 1. Binding affinities of pyrazoles **3** for the CB_1 receptor

Compd	R_1	R_2	$K_i \pm$SEM (nM)[a]
4[c]	H	1-Piperidinyl	12±0.7
5	H	3-Azabicyclo[3.3.0]octan-3-yl	5±1
6	H	1-Homopiperidinyl	14±5
7[d]	H	Cyclohexyl	42±13
8	Me	Cyclohexyl	100±32
9	H	$CH(Me)CHMe_2$	41±3
10	H	2-(4-Fluorophenyl)ethyl	91±35
11	H	4-Pyridyl	85±5
12[d]	H	2-Hydroxyethyl	(69)[b]
13	H	2-(Dimethylamino)ethyl	(70)[b]

[a] Values are averaged from at least three experiments.
[b] Inhibition (%) at 20 μM.
[c] SR141716.[14,15]
[d] Previously reported.[21]



Scheme 2. Reagents: (a) (i) dimethyl aminomalonoate, HOBt, EDC, DCM (95–97%); (ii) 4-Cl-2-Y-$C_6H_3NH_2$, $NaNO_2$, aq HCl, AcOH, 0 °C; then NaOMe, MeOH (37–52%); (iii) aq NaOH, dioxane, 70 °C (100%); (b) (i) oxalyl chloride, DCM, cat. DMF; (ii) R_1R_2NH, ACN (9–82%).

In general, the triazoles were less potent ligands for the CB_1 receptor than the corresponding pyrazoles (Table 2). For the bicyclic hydrazide substitution on the triazole core (**17** and **23**), binding constants were 25-fold greater than the related pyrazole **5**. Comparing compounds **17** (K_i 137 nM) and **23** (K_i 164 nM) indicates the relative orientation of the triazole core had little effect on the compound potencies. The binding constants for isomeric compounds within these two series were usually similar and either orientation was capable of providing the more potent example.

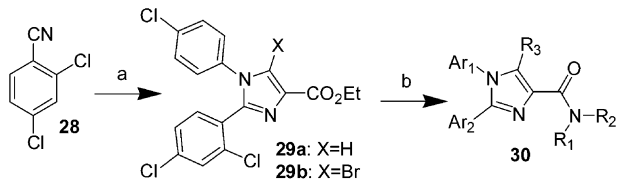
One possible explanation of the reduced affinity of these compounds is the methyl substituent on the pyrazole core of compounds related to SR141716 either fills a small binding pocket or helps to orient the aryl and/or carboxamide groups in a more favorable conformation. Of course, in the triazole series an analogous substitution is impossible due to the reduced valency of nitrogen. However, in an attempt to incorporate a group of comparable size in approximately the same region of the molecule, an additional *ortho* substituent on the monochlorinated phenyl ring was introduced. Unfortunately, this new *ortho* substituent consistently resulted in at least a 2-fold drop in binding potency, as exemplified by the methoxy-substituted compounds **26** and **27**. As with the pyrazole series, lipophilic amide nitrogen atom substituents are best (**18**, **19**, and **20**) and more polar groups are unfavorable (**21**). However, basic nitrogen atoms, and potentially other hydrophilic groups, are well tolerated in this portion of the molecule if an additional liphophile is introduced. This is apparent from **22**, which exhibits a K_i of 29 nM and has a basic nitrogen atom three bonds removed from the amide nitrogen atom. When compared to **21**, which shows only 49% inhibition at 20 μM and yet has the same relative spacing for its basic nitrogen atom, **22** clearly demonstrates additional binding interactions. The potency of substituted phenylpiperazine **25** suggests the presence of an additional binding pocket beyond amide substitutents of compounds like SR141716.

A series of related imidazoles was also synthesized for affinity testing with the CB_1 receptor (Scheme 3). Dichlorobenzonitrile **28** and 4-chloroaniline were heated with aluminum chloride and the resulting amidine was

Table 2. Binding affinities of triazoles **16** for the CB_1 receptor

Compd	Core	R_1	R_2	$K_i \pm$SEM (nM)[a]
17	**16a**	H	3-Azabicyclo[3.3.0]octan-3-yl	137±35
18	**16a**	H	4-Methylcyclohexyl	94±34
19	**16a**	H	1-(4-Chlorophenyl)ethyl	66±17
20	**16a**	H	1-Indanyl	101±34
21	**16a**	H	2-(Dimethylamino)ethyl	(49)[b]
22	**16a**	H	1-Benzylpyrrolidin-3-yl	29±10
23	**16b**	H	3-Azabicyclo[3.3.0]octan-3-yl	164±60
24	**16b**	H	1-Homopiperidinyl	(43)[b]
25	**16b**	$CH_2CH_2N(3\text{-}CF_3C_6H_4)CH_2CH_2$		32±5
26	**16c**	H	3-Azabicyclo[3.3.0]octan-3-yl	270±5
27	**16c**	H	Isopropyl	350±137

[a] Values are averaged from at least three experiments.
[b] Inhibition (%) at 20 μM.



Scheme 3. Reagents: (a) (i) 4-$ClC_6H_4NH_2$, $AlCl_3$, 150 °C; (ii) ethyl bromopyruvate, K_2CO_3, EtOH, reflux (24%); (iii) Br_2, ACN (88%); (b) (i) aq NaOH, dioxane, 70 °C (100%); (ii) oxalyl chloride, DCM, cat. DMF; (iii) R_1R_2NH, ACN; (iv) Bu_3SnR_3 or $SnMe_4$, trifurylphosphine, Pd_2dba_3, NMP, 60 °C (13–60%).

converted to diarylimidazolecarboxylate **29a** by reaction with ethyl bromopyruvate under acidic conditions.[24,25] Imidazole **29a** was then converted to the corresponding imidazolecarboxamides **31**–**35** as described above for the pyrazole- and triazole-based carboxamides. Fortunately, the imidazole core allowed for the introduction of an additional substituent such as the methyl group present in SR141716 (**4**), an opportunity unavailable in the triazole series. For this reason, a portion of **29a** was brominated to give **29b**, which in turn was converted to the analogous amides. With the brominated amides **30** (R_3 = Br) in hand, coupling with organostannanes under Stille-like conditions[26] enabled the introduction of a variety of substituents at this position.

The activities of the imidazole compounds in the CB_1 receptor binding assay are presented in Table 3. The simple examples **31**–**34** were approximately 2-fold more potent than their triazole counterparts, but up to 10-fold less potent than the related pyrazoles. When substituted with groups other than hydrogen, the imidazoles showed potencies comparable to their pyrazole counterparts. With the bicyclic hydrazide substituent, the bromo- (**36**), cyano- (**37**) and methylimidazoles (**38**) possess K_i's ranging from 9 to 14 nM. Other analogues in the methyl-substituted imidazole series such as **40** showed a comparable increase in potency relative to the triazole analogues. Interestingly, an acetylenic substituent at this position drastically dropped the potency (**39**). The inhibition constant of imidazole **38** is twice that of the related pyrazole **5**, and is virtually equipotent to the clinical candidate SR141716 (**4**). Compound **38** exhibited an IC_{50} of 19 ± 2 nM (n = 2) in a GTPγS assay, demonstrating that it is a functional antagonist.

Table 3. Binding affinities of imidazoles **30** for the CB_1 receptor

Compd	R_1	R_2	R_3	K_i ± SEM (nM)[a]
31	H	1-Piperidinyl	H	85 ± 16
32	H	3-Azabicyclo[3.3.0]octan-3-yl	H	66 ± 11
33	H	1-Homopiperidinyl	H	78 ± 14
34	H	Cyclohexyl	H	48 ± 19
35	H	2-(Dimethylamino)ethyl	H	(48)[b]
36	H	3-Azabicyclo[3.3.0]octan-3-yl	Br	11 ± 4
37	H	3-Azabicyclo[3.3.0]octan-3-yl	CN	9 ± 1
38	H	3-Azabicyclo[3.3.0]octan-3-yl	Me	14 ± 4
39	H	3-Azabicyclo[3.3.0]octan-3-yl	CCH	770 ± 206
40	H	1-(4-Chlorophenyl)ethyl	Me	33 ± 9

[a] Values are averaged from at least three experiments.
[b] Inhibition (%) at 20 μM.

Based on these studies, it is clear that high affinity binding of compounds such as SR141716 to the CB_1 receptor relies more heavily on the nature of the side chains, rather than the heterocycle itself. A small substituent such as methyl or cyano on the azole core appears to be important for high affinity binding, possibly by orienting the amide nitrogen substituent. The absence of this small group has a detrimental effect on binding affinity that cannot easily be overcome by substituting the adjacent phenyl group. In the triazole series, it appears possible to incorporate hydrophilic groups into the amide substituent. Although this may be pertinent to the pursuit of less lipophilic analogues which have a variety of applications,[20] the fact that this introduction inevitably requires an additional lipophile to compensate cannot be underestimated. The cannabinoid receptors endogenous ligands are very liphophilic in nature and it appears that from this study a high affinity antagonist will necessarily be very lipophilic as well.

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