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New 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole derivatives as selective CB2 receptor agonists

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Abstract—The preparation and evaluation of a novel class of CB2 agonists based on a 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole moiety are reported. They showed binding affinities up to 4.2 nM toward CB2 with sub-nanomolar EC_{50} values. They also showed moderate to good (>350-fold) selectivity over the CB1 receptor.

The endocannabinoid system has been known to mediate several important biological processes including metabolic regulation,[1,2] pain,[3–5] cellular proliferation,[6] cancer,[7] obesity,[8] and different other CNS functions.[9] These effects are mainly regulated via two primary receptors, namely CB1 and CB2. The pharmacology of these two cannabinoid receptors has been extensively reviewed[10–14] over the past few years, putting a much larger emphasis on the more studied CB1 receptor, resulting in huge commercial interests in CB1 receptor ligands. CB1 antagonists are now being evaluated for the treatment of obesity, metabolic syndrome, drug abuse, and smoking cessation,[2] while CB1 agonists are currently in clinical trials for the treatment of acute and chronic pain.[3–5] However, because the CB1 receptor is mainly expressed in the central nervous system, several psychoactive side effects[15–17] such as cognitive disfunction, motor incoordination, or sedation have often been associated with CB1 ligands.

On the other hand, the exact physiological roles of the CB2 receptor still remain to be fully defined even though several reported experimental and clinical data show promising applications in different disease areas. Previous studies have demonstrated that CB2 selective agonists are analgesics in different neuropathic and inflammatory pain models,[18–20] which would confer them some potential therapeutic utility in chronic inflammatory diseases such as atherosclerosis. Beneficial effects of CB2 receptor activation in models of neurodegenerative disorders, such as Huntington and Alzheimer's diseases, were also reported, leading to a possible neuroprotective role for CB2 ligands.[21–23] Other preclinical studies have highlighted the potential of CB2 ligands in the treatment of cancer by eliciting apoptosis of brain and immune system tumor cells.[24,25] Another potential role of the CB2 receptors could include bone regeneration, as selective CB2 agonists were shown to decrease bone loss in animal studies.[26,27] The particular attractive feature about CB2-selective ligands resides in the distribution of this receptor. CB2 is mainly expressed in immune tissues located in the periphery, with only low levels found in neurons of the central nervous system, minimizing therefore the side effects observed with the CB1-selective ligands.

Several classes of CB2 ligands originating from natural and synthetic sources have been reported in the literature.[28–34] Making use of the ever increasing amount of information reported in the literature, along with several hit compounds obtained from a previous screening campaign, a cannabinoid program was instigated at our company a few years ago. This program enabled us to develop several classes of CB1/CB2 ligands, like CB2 selective inverse agonists based on a benzimidazole scaffold.[35] More recently a different scaffold, based upon a 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole moiety, showed good selectivity over CB1 and demonstrated a much dif-

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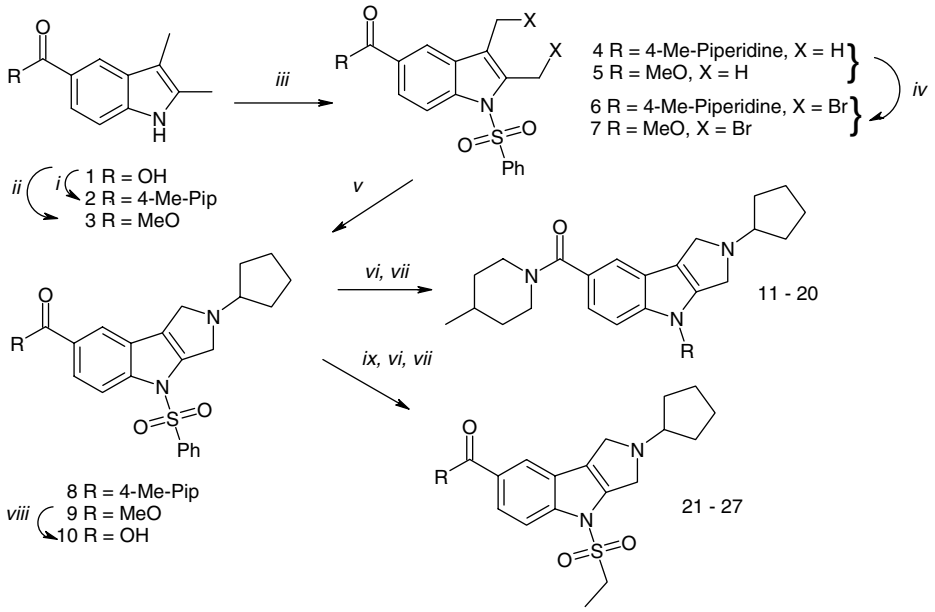
ferent SAR than the one observed with the benzimidazole ligands. We report herein the synthesis and pharmacological evaluation of this novel class of selective CB2 agonists.

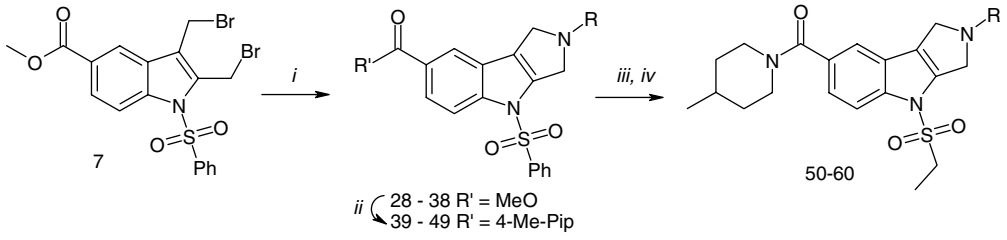
The synthesis of the 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole core, outlined in Scheme 1, was adapted from a previously reported procedure[36] in order to make necessary modifications around it. Compound **8**, an initial hit obtained from our screening campaign, was used as the model compound in this series. However, the highly lipophilic nature of compound **8** made it difficult to be used for biological tests. Therefore, modifications were initially performed on the bottom part of the molecule while keeping the left- and right-hand sides constant. The synthesis started from the commercially available 2,3-dimethyl-1*H*-indole-5-carboxylic acid (**1**) that underwent an amide coupling procedure, using the coupling reagent *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazole-1-yl)uranium hexafluorophosphate (HATU), followed by *N*-sulfonylation to afford compound (**4**). This intermediate was brominated under radical conditions to give the corresponding bis-bromide product (**6**). The 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole core was obtained from the cyclization of compound (**6**) with cyclopentylamine under basic conditions. Deprotection of the indole under basic conditions followed by either *N*-alkylation, acylation, or sulfonylation afforded the final compounds (**11**–**20**).

Modifications on the left-hand side were done following a similar synthetic route (Scheme 1), with the exception that the starting acid (**1**) was initially esterified (compound **3**). After the core cyclization, the ester was saponified under basic conditions to give the acid (**10**), which underwent amide bond formation with different amines. The *N*-phenylsulfonamide was then replaced by an ethylsulfonamide group, which proved to enhance the binding affinity and solubility properties, to give products **21**–**27**.

Finally, modifications on the right-hand side of the molecule (Scheme 2) made use of the previously prepared bis-bromide intermediate (**7**), which was cyclized with different amines under basic conditions (**28**–**38**). Saponification of the ester, followed by amide coupling with 4-methylpiperidine, afforded compounds **39**–**49**. Once again, the *N*-phenylsulfonamide was replaced with an



Scheme 1. Reagents and conditions: (i) 4-methylpiperidine, HATU, DIPEA, DMF, rt; (ii) $TMSCHN_2$, MeOH, 0 °C → rt; (iii) benzenesulfonyl chloride, NaH, DMF, 0 °C → rt; (iv) NBS, benzoyl peroxide, CCl_4, reflux; (v) cyclopentylamine, K_2CO_3, THF, reflux; (vi) 1.5 M KOH, 5:5:2 EtOH/MeOH/H_2O, 65 °C; (vii) RSO_2Cl/R–X/RC(O)Cl, NaH, DMF, 0 °C → rt; (viii) 1 M LiOH, dioxane, 65 °C; (ix) RNH_2, HATU, DIPEA, DMF, rt.



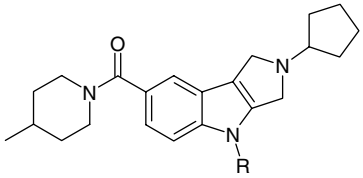
Scheme 2. Reagents and conditions: (i) RNH_2, K_2CO_3, THF, reflux; (ii) a—1 M LiOH, dioxane, reflux; b—4-methylpiperidine, HATU, DIPEA, DMF, rt; (iii) 1.5 M KOH, 5:5:2 EtOH/MeOH/H_2O, 65 °C; (iv) ethanesulfonyl chloride, NaH, DMF, 0 °C → rt.

ethylsulfonamide group to give products **50**–**60**. All final compounds were purified by reversed-phase chromatography with a water/acetonitrile gradient containing 0.05% TFA v/v.

The CB1/CB2 binding results are summarized in Tables 1–3. The mixed CB1/CB2 agonists WIN55212-2 [37] and Δ^9-THC were tested as standards for comparison purposes (Table 1). The results of Table 1 showed that the sulfonamide derivatives (**8**, **15**–**19**) had higher CB2 binding affinities than the corresponding alkyl (**12**–**14**) or amide (**20**) derivatives. Some bulkiness can be tolerated at this site as the isopropylsulfonamide derivative (**17**) showed a CB2 binding affinity of 4.2 nM with a selectivity factor of 36 over CB1. Longer alkyl chains (**19**) or aromatic substituents (**8**, **14**) decreased the binding affinity among the sulfonamides, these bottom chains being probably too bulky to fit properly in the receptor-binding pocket.

The different substitutions made on the left-hand side of the molecule seem to have less influence on the CB2 affinity (Table 2). The removal of the methyl group (**21**) or the introduction of polar atoms/groups at the position 4 of the piperidine ring (compounds **22**–**24**) reduced the CB2 affinity. Open-chain alkyl derivatives (**25**–**27**) also showed decreased CB2 affinity when compared to compound (**16**), which might be due to the entropy cost introduced by the additional rotatable bonds.

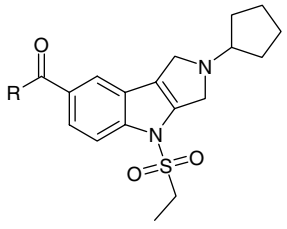
Table 1. CB2 binding results of 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles with bottom part modifications



Compound	R	hCB1 K_i (nM)	hCB2 K_i (nM)	hCB1/hCB2	hCB2 EC_{50}[a] (nM)
WIN55,212-2	—	40.9 ± 1.7	2.9 ± 0.3	14.1	1.5 ± 0.1 (100%)
Δ^9-THC	—	20.1 ± 3.4	140 ± 42	0.14	13.5 ± 3.0 (64%)
8	PhenylSO_2	259 ± 27	17.9 ± 4.5	14.5	15.6 ± 2.4 (−62%)
11	H	>8000	4724 ± 182	—	nd
12	Methyl	1811 ± 59	84.7 ± 15.1	21.4	nd
13	Allyl	695 ± 41	23.3 ± 3.2	29.8	5.0 ± 0.6 (92%)
14	Benzyl	658 ± 11	106 ± 26	6.2	nd
15	MethylSO_2	279 ± 56	7.9 ± 1.6	35.3	0.6 ± 0.04 (105%)
16	EthylSO_2	66.3 ± 14.6	7.0 ± 0.2	9.4	0.8 ± 0.1 (110%)
17	IsopropylSO_2	150 ± 12	4.2 ± 0.5	35.7	0.5 ± 0.1 (105%)
18	CyclopropylSO_2	137 ± 44	9.4 ± 2.5	14.6	1.5 ± 0.1 (101%)
19	*n*-PropylSO_2	195 ± 41	22.3 ± 3.0	8.7	6.7 ± 1.0 (90%)
20	Acetyl	2331 ± 181	88.1 ± 17.3	26.5	nd

nd = not determined.
[a] E_{max} are reported in brackets.

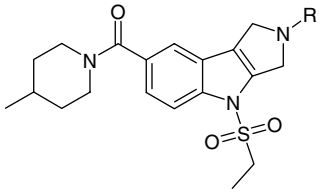
Table 2. CB2 binding results of 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles with left-hand side modifications



Compound	R	hCB1 K_i (nM)	hCB2 K_i (nM)	hCB1/hCB2	hCB2 EC_{50}[a] (nM)
16	4-Me-piperidine	66.3 ± 14.6	7.0 ± 0.2	9.5	0.8 ± 0.1 (110%)
21	Piperidine	818 ± 92	17.5 ± 2.8	46.7	1.7 ± 0.3 (107%)
22	4-F-piperidine	2914 ± 251	44.2 ± 5.1	65.9	nd
23	Morpholine	>8000	308 ± 11	>25	nd
24	4-MeO-piperidine	2131 ± 264	27.6 ± 7.3	77.2	nd
25	Isopropylmethylamine	7222 ± 251	107 ± 44	67.5	nd
26	*n*-Butylmethylamine	779 ± 164	22.3 ± 5.1	34.9	4.0 ± 0.6 (111%)
27	Isoamylmethylamine	1473 ± 184	38.1 ± 9.3	38.7	nd

nd = not determined.
[a] E_{max} are reported in brackets.

Table 3. CB2 binding results of 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indoles with right-hand side modifications



Compound	R[a]	hCB1 K_i (nM)	hCB2 K_i (nM)	hCB1/hCB2	hCB2 EC_{50}[b] (nM)
16	Cyclopentyl	66.3 ± 14.6	7.0 ± 0.2	9.5	0.8 ± 0.1 (110%)
50	3-THF	973 ± 150	27.8 ± 1.3	35	nd
51	4-THP	3021 ± 505	216 ± 40	14	nd
52	2-THP	6183 ± 443	17.6 ± 2.8	351	1.7 ± 0.3 (107%)
53	Allyl	263 ± 71	6.4 ± 0.4	41.1	0.3 ± 0.03 (104%)
54	Isopropyl	418 ± 21	8.9 ± 0.7	47	0.9 ± 0.1 (101%)
55	*n*-Propyl	604 ± 49	11.1 ± 1.1	54.4	0.8 ± 0.2 (104%)
56	*n*-Butyl	341 ± 47	16.8 ± 1.7	20.3	2.7 ± 0.3 (105%)
57	–CH_2-cyclopropyl	176 ± 32	6.3 ± 1.2	27.9	0.5 ± 0.1
58	–CH_2-cyclohexyl	339 ± 73	935 ± 149	0.4	nd
59	–$(CH_2)_2$-cyclohexyl	2742 ± 280	1982 ± 182	1.4	nd
60	Benzyl	1273 ± 132	37.0 ± 8.2	34.4	nd

nd = not determined.

[a] Abbreviations: THF = tetrahydrofuran; THP = tetrahydropyran.

[b] E_{max} are reported in brackets.

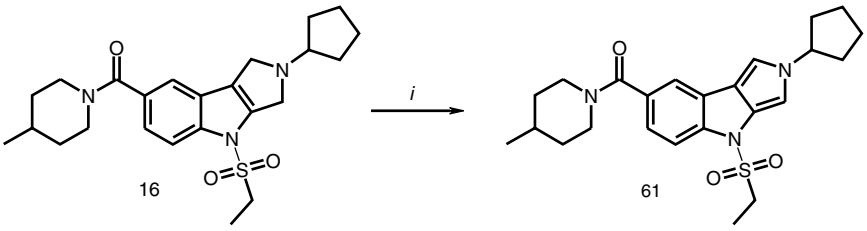
The modifications on the right-hand side of the molecule yielded analogues with decent CB2 binding affinity (Table 3). Polar atoms and their position in the ring of the substituent had a great impact on the CB2 binding (**50**–**52**). For example, compounds (**50**) and (**52**) showed good CB2 affinity while compound (**51**) displayed poor CB2 affinity. In addition, good binding affinities were obtained with small alkyl substituents (**53**–**57**). However, the CB2 binding affinity was shown to decrease with the length and/or bulkiness of the side chain (**58**–**59**), demonstrating a restricted hydrophobic pocket in the receptor. The addition of an aromatic substituent (**60**) also resulted in a relatively lower CB2 binding affinity (K_i = 37 nM).

Most of the compounds demonstrated moderate to good CB1/CB2 selectivity, with compound (**52**) having the best selectivity ratio of >350. Only the compounds with a CB2 K_i < 25 nM were tested in a CB2 GTPγ[^{35}S] assay. They all showed low to sub-nanomolar EC_{50} values with full agonist properties (relative to WIN55,212-2) with the exception of compound (**8**), which proved to be an inverse agonist. This is probably due to the presence of the aromatic sulfonamide bottom chain which constraints the molecule in a different mode of binding.

The discrepancies observed between the binding and functional assay data could be a result in the difference of tissues used and the sensitivity of the assays, even though such discrepancies have previously been reported in the literature for other GPCR assays.[38,39]

To investigate the potential of the corresponding oxidized class of compounds, bearing a 2,4-dihydropyrrolo[3,4-*b*]indole core, as CB2 ligands, compound (**16**) was oxidized using DDQ (Scheme 3) to give the corresponding 2,4-dihydropyrrolo[3,4-*b*]indole analogue (**61**). However, the CB2 binding affinity of this compound proved to be about 23-fold lower than the corresponding 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole analogue (**16**), with a CB2 K_i value of 146 ± 61 nM.

In conclusion, these molecules, based on a 1,2,3,4-tetrahydropyrrolo[3,4-*b*]indole moiety, represent new scaffolds in the development of cannabinoid agonists. These ligands demonstrated good binding affinities and potencies toward the CB2 receptor, showing moderate to good selectivity over the CB1 receptor. The biological evaluation of this new class of ligands is currently underway in our laboratories in order to look at their potential biological application.



Scheme 3. Reagents and condition: (i) DDQ, toluene, rt.

Supplementary data

Selected syntheses and compound characterization along with the description of the biological tests are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.09.019.

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