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Synthesis and SAR of novel imidazoles as potent and selective cannabinoid CB_2 receptor antagonists with high binding efficiencies

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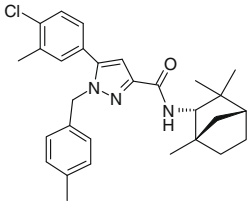
ABSTRACT

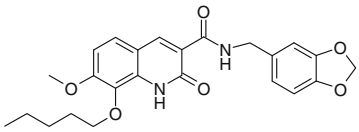
The synthesis and structure–activity relationship studies of imidazoles are described. The target compounds **6**–**20** represent a novel chemotype of potent and CB_2/CB_1 selective cannabinoid CB_2 receptor antagonists/inverse agonists with very high binding efficiencies in combination with favourable log *P* and calculated polar surface area values. Compound **12** exhibited the highest CB_2 receptor affinity (K_i = 1.03 nM) in this series, as well as the highest CB_2/CB_1 subtype selectivity (>9708-fold).

The cannabinoid CB_2 receptor was cloned[1] in 1993 and is almost exclusively expressed in cells of the immune system, spleen, pancreas, tonsils and thymus.[2] Under certain circumstances the CB_2 receptor is also expressed[3,4] in astrocytes, microglia and the brainstem.[5] CB_2 receptor ligands have potential in the therapeutic treatment of several diseases[6] such as inflammation, multiple sclerosis, neuropathic pain,[7] immune regulation,[8] osteoporosis and certain types of cancer. Recently, CB_2 receptor inverse agonists were also shown to block[9] leucocyte recruitment in vivo.

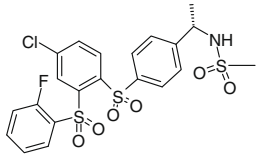
The amino acid sequence of the CB_2 receptor has an overall identity[1] of 44% with the CB_1 receptor. Their homology in the GPCR transmembrane domain amounts to 68%, thereby providing good prospects for the design of CB subtype selective ligands. Intense research efforts have indeed led to the discovery of subtype selective human cannabinoid CB_1 receptor antagonists/inverse agonists,[10] selective CB_2 receptor agonists such as JWH133,[11] HU-308,[12] L759656,[13] AM-1241,[14] A-796260 and A-836339[15] as well as selective CB_2 receptor antagonists/inverse agonists from different chemical series such as the pyrazolecarboxamide[16,17] SR144528 (**1**), the 2-oxoquinoline[18] JTE-907 (**2**) and the triarylbissulfone[19] SCH-356036 (**3**).



SR144528 (**1**)



JTE-907 (**2**)



SCH-356036 (**3**)

Several reviews described[20–25] the medicinal chemistry of CB_2 receptor ligands. Although many efforts have concentrated on the modelling of the CB_2 receptor and their ligands[20] as well as on receptor mutations,[26] it can be concluded that the design of novel CB_2 selective antagonists or agonists by CB_2 receptor modelling or virtual screening is still a challenging task.[27–30] It is interesting

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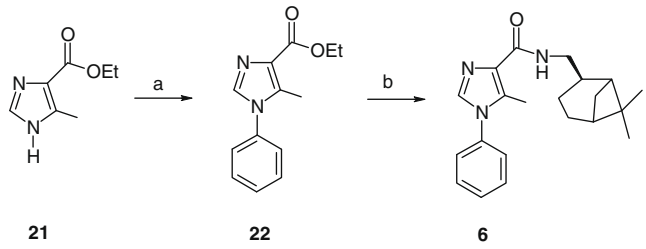
to note that both the selective CB_1 receptor antagonist rimonabant[31] and the selective CB_2 receptor antagonist **1** contain a 5-arylpyrazole-3-carboxamide scaffold. This intriguing observation prompted us to start CB_2 receptor antagonist design efforts based on our[32] CB_1 antagonistic 1,2-diarylimidazoles **4** which can be considered as bioisosters of rimonabant (Scheme 1). The preference for the imidazoles as a starting point for the design of CB_2 selective antagonists was fuelled by the generally observed[31,32] slightly higher CB_2 receptor affinities in the 1,2-diarylimidazole series as compared to the corresponding 1,5-diarylpyrazoles.

It was noted that the 1-arylmethyl moiety of **1** adds significant molecular weight and lipophilicity[33] to the molecule. Since, we were particularly interested in novel CB_2 receptor antagonist chemotypes with high ligand efficiencies[34] and favourable log *P* values, attention was given to the chemotype **5** wherein the large arylmethyl group of **1** is replaced by a considerably smaller substituent[35] R^1 at the corresponding imidazole 2-position. Removal of the original 2-aryl moiety in **4** was furthermore anticipated to have a detrimental effect on the CB_1 activity of the compounds, based on our extensive CB_1 SAR knowledge, thereby increasing CB_2/CB_1 subtype selectivity[36,37] In addition, the carboxamide *N*-piperidinyl substituent in **4** was replaced by a lipophilic substituent comparable to the trimethylbicyclo[2.2.1]heptane group in **1**.

In concreto, these design considerations led to a series of fifteen novel imidazole derivatives **6**–**20**. The synthesis of compound **6** is depicted in Scheme 2. The commercially available ester **21** was reacted with benzeneboronic acid in the presence of a catalytic amount of CuI to afford **22** in a modest yield. Weinreb amidation[38] of **22** with (−)-*cis*-myrtanylamine gave the imidazole **6** in 65% yield.

The synthesis of the imidazoles **7**–**13** is depicted in Scheme 3. The commercially available oxo-esters **23**–**25** were reacted with $NaNO_2$ to furnish the oximes **26**–**28**. Subsequent catalytic reductive acetylation with acetic anhydride afforded the crude compounds **29**–**31** which were cycloaromatized with aniline in butyronitrile in the presence of trifluoroacetic acid to the imidazoles **32**–**34**. This sequence of reactions constitutes a powerful route to the synthesis of 1-aryl-2,5-dialkylimidazole-4-carboxylates. It is interesting to note that our optimized reaction conditions led to considerable higher yields as well as less by-product formation as compared with the original procedure[39] which consisted of heating in xylene. Ester hydrolysis of **32**–**34** delivered the corresponding acids **35**–**37** in quantitative yield. The target compounds **7**–**13** were obtained from **35**–**37** via amidation reactions in the presence of a coupling reagent (either HBTU or CIP) in yields ranging from 60–72%.

The target compounds **14** and **15** were prepared[40] according to Scheme 4. The nitroacrylates **38** and **39** were cycloaromatized under reductive conditions with triethylorthopropionate to the 2-ethylimidazoles **40** and **41**, respectively. Ester **40** was hydrolyzed under basic conditions to the carboxylic acid **42**, which was then amidated with 1-adamantamine·HCl to provide target compound **14**. Compound **41** was converted in a straightforward Weinreb amidation[38] to **15**.



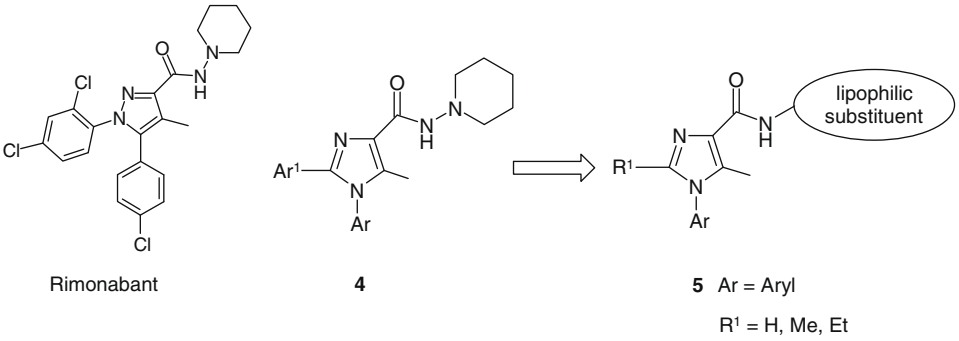
Scheme 2. Reagents and conditions: (a) $C_6H_5B(OH)_2$, CuI, EtOH/H_2O, reflux, 60 h (26%); (b) (−)-*cis*-myrtanylamine, $Al(CH_3)_3$, CH_2Cl_2, 35 °C, 16 h (65%).

The synthesis of the imidazoles **16**–**18** is depicted in Scheme 5. The ester intermediate **43** was prepared from the corresponding nitroacrylate analogously[40] to the method described in Scheme 4. Ester hydrolysis of **43**, followed by amidation with 1-adamantamine·HCl led to the carboxamide **44**. Subsequent regioselective lithiation of **44** with the strong non-nucleophilic base LDA, followed by treatment with an electrophile led to the target compounds **16**–**18** in reasonable yields. It is interesting to note that this strategy provides a nice alternative for the synthesis of 4-alkylated imidazoles such as **8** and **12**. Compounds **8** and **12** were obtained from **44** via the reaction with CH_3I and C_2H_5I in 70% and 41% yields, respectively.

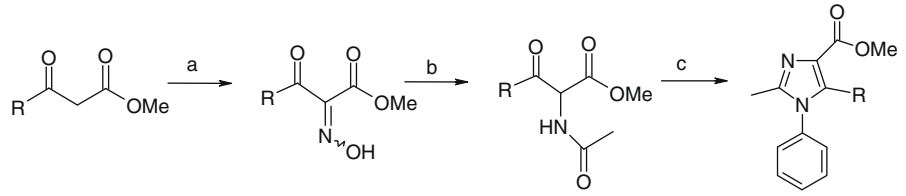
The 2,5-dichloroimidazole derivative **19** was prepared as shown in Scheme 6. The dicarboxylic acid **45** was mono-decarboxylated in acetic anhydride and subsequently esterified with sulfuric acid in ethanol to **46**. N-Arylation with benzeneboronic acid in the presence of CuCl gave a regioisomeric mixture from which **47** was separated by flash chromatography. Basic hydrolysis of the ester group and subsequent amidation with adamantamine·HCl afforded **48**. Prolonged chlorination[41] of **48** with *N*-chlorosuccinimide eventually led to the incorporation of two chloro atoms at the imidazole nucleus and thereby produced the target compound **19**.

The cyclohexylimidazole analogue **20** was prepared according to Scheme 7. The nitroacrylate[40] **49** was reacted with cyclohexylamine to produce the corresponding cyclohexylamino derivative **50** in low yield. Subsequent cycloaromatization under reductive conditions with triethylorthoacetate gave the imidazole ester **51** which was efficiently converted via a Weinreb amidation[38] with 1-adamantamine·HCl to **20**.

The pharmacological data of the reference compounds **1**–**3** and target compounds **6**–**20** are depicted in Table 1. The observed order of CB_2 receptor affinities and CB_1/CB_2 receptor subtype selectivities of the reference compounds **1**–**3** matches the reported data.[16,18,19]



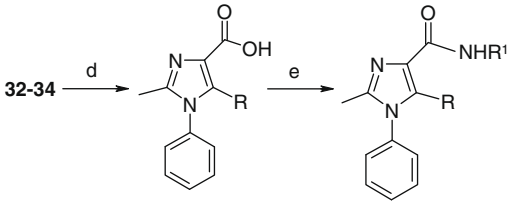
Scheme 1. Design concept of novel imidazoles **5** as selective cannabinoid CB_2 receptor antagonists from CB_1 receptor antagonists **4**.



23 R = Me **26** R = Me **29** R = Me **32** R = Me

24 R = Et **27** R = Et **30** R = Et **33** R = Et

25 R = *n*-Bu **28** R = *n*-Bu **31** R = *n*-Bu **34** R = *n*-Bu



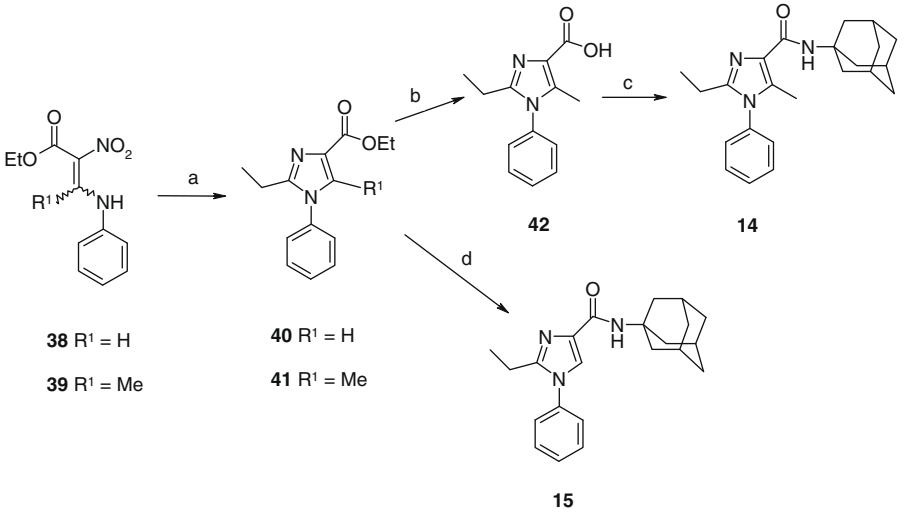
35 R = Me **7-13**

36 R = Et

37 R = *n*-Bu

Compound	R	R^1
7	Me	*cis*-myrtanyl
8	Me	adamantan-1-yl
9	Me	adamantan-2-yl
10	Me	noradamantan-1-yl
11	Me	*o*-(trifluoromethyl)benzyl
12	Et	adamantan-1-yl
13	*n*-Bu	adamantan-1-yl

Scheme 3. Reagents and conditions: (a) $NaNO_2$, H_2O, 4 °C, 2 h; (b) H_2, Pd/C, 1 atm, Ac_2O, AcOH, rt, 20 h (50–65%); (c) $C_6H_5NH_2$, TFA, butyronitrile, reflux, 45 min (40–51%); (d) LiOH, H_2O/THF, 70 °C, 16 h, followed by acidification with 1 N HCl, rt (93–100%); (e) R_1NH_2, HBTU or 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate (CIP), DIPEA, CH_3CN, rt, 16–40 h (60–72%).



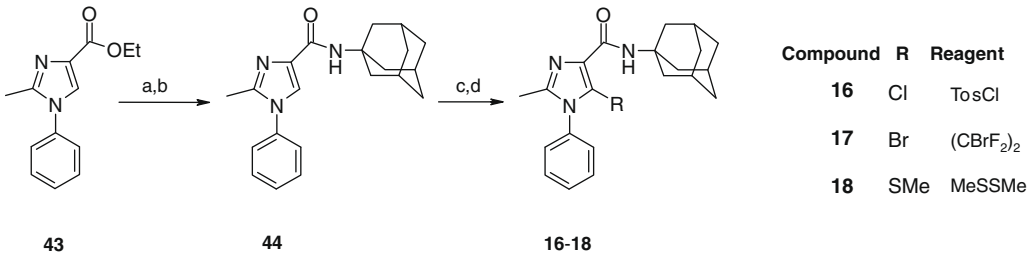
38 R^1 = H **40** R^1 = H **42** **14**

39 R^1 = Me **41** R^1 = Me

15

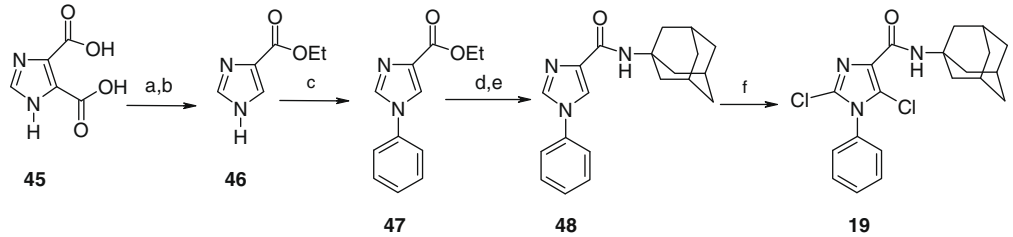
Scheme 4. Reagents and conditions: (a) $EtC(OEt)_3$, H_2, Pd/C, 2.5 atm, 70 °C, 16 h (9–32%); (b) LiOH, H_2O/THF, 70 °C, 16 h, followed by acidification with 1 N HCl, rt (100%); (c) 1-adamantamine·HCl, CIP, DIPEA, CH_2Cl_2, rt, 16 h (52%); (d) 1-adamantamine·HCl, $Al(CH_3)_3$, CH_2Cl_2, 35 °C, 16 h (63%).

In particular, the CB_2 receptor affinity and CB_1/CB_2 receptor subtype selectivity data of Schering's **3** are impressive. The CB_2 receptor binding data of our imidazoles **6**–**20** revealed that five of our target compounds (**8**, **12**, **14**, **17** and **18**) elicited more than 1000-fold CB_1/CB_2 receptor subtype selectivity values. Although compound **12** showed a slightly lower CB_2 receptor affinity as compared with **3**, its observed CB_1/CB_2 receptor subtype selectivity was higher. Compounds **8**, **12** and **14** combined a high CB_2 receptor affinity with a compact, low molecular weight chemical structure. Compound **6** which lacks the 2-methyl group of **7** exhibited a ninefold lower CB_2 receptor affinity. An analogous effect was observed when comparing the CB_2 receptor affinities of compounds **15** and **14**. It can be concluded that the combination of a 1-aryl substituent with a small alkyl substituent on both positions 2 and 5 of the imidazole nucleus leads to very potent and selective CB_2 receptor ligands. The bulky 1-adamantyl group gives the best results in our series of compounds since compound **8** showed a higher CB_2 receptor affinity as compared with **7**, **9**, **10** and **11**, respectively. Replacement of the methyl group in **8** by a halogen substituent or a methylsulfanyl group (**16**, **17**, **18** and **19**) led to lower CB_2 receptor affinities. The replacement of the 5-methyl group in **8** by the larger *n*-butyl group (**13**) also resulted in a lower CB_2 recep-

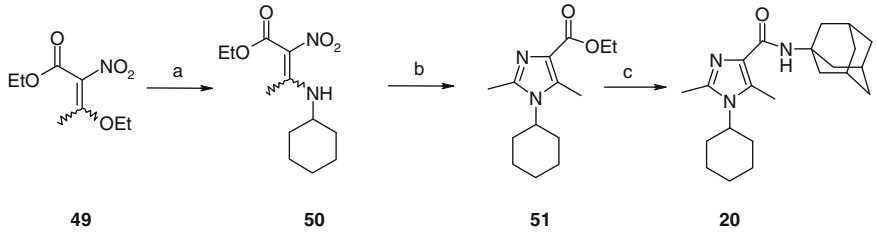


Compound	R	Reagent
16	Cl	TosCl
17	Br	$(CBrF_2)_2$
18	SMe	MeSSMe

Scheme 5. Reagents and conditions: (a) LiOH, H_2O/THF, 70 °C, 16 h, followed by acidification with 1 N HCl, rt (100%); (b) 1-adamantamine·HCl, HBTU, DIPEA, CH_3CN, rt, 16 h (70%); (c) excess LDA, THF, −70 °C, N_2, 1 h; (d) reagent, THF, −70 °C to rt, N_2, 12 h (28–50%).



Scheme 6. Reagents and conditions: (a) Ac_2O, reflux, 5 h (73%); (b) H_2SO_4, EtOH, reflux, 36 h (71%); (c) $C_6H_5B(OH)_2$, CuCl, EtOH/H_2O, reflux, 100 h, (33%); (d) LiOH, H_2O/THF, 60 °C, 16 h, followed by acidification with 1 N HCl, rt (82%); (e) 1-adamantamine·HCl, HBTU, DIPEA, CH_3CN, rt, 16 h (61%); (f) excess NCS, $CHCl_3$, rt, 60 h (32%).



Scheme 7. Reagents and conditions: (a) cyclohexylamine, EtOH, rt, 24 h (14%); (b) $CH_3C(OEt)_3$, H_2, Pd/C, 4 atm, 73 °C, 24 h (58%); (c) 1-adamantamine·HCl, $Al(CH_3)_3$, $ClCH_2CH_2Cl$, 70 °C, 16 h (53%).

tor affinity. The presence of the lipophilic, non-aromatic cyclohexyl group (**20**) instead of the phenyl moiety (**8**) at the 1-position of the imidazole ring gave a sevenfold lower CB_2 receptor affinity.

Compounds **1**–**3** have been reported[16,18,19] to act as inverse agonists[44] at the constitutively active[45] CB_2 receptor. Our target compounds also behave as potent CB_2 receptor inverse agonists since they were able to stimulate cAMP accumulation in a concentration-dependent manner (Table 1). In particular, compounds **8**, **11** and **14** behaved as potent CB_2 receptor inverse agonists. Unexpectedly, a modest pEC_{50} value (7.7 ± 0.5) was initially observed for our key compound **12**. The assay incubation time turned out to be the key factor here since after a prolonged incubation time (4 h) a much higher pEC_{50} value (9.6 ± 0.2) was found. Such an effect of the incubation time on the observed CB_2 inverse agonism was absent for the structural closely related **8** and **15** as well as for the potent reference compound **3** (Table 1). However, **1** was also found more active after a prolonged incubation period.

Furthermore, the reference compounds **1** (pA_2 = 8.2 ± 0.1), **2** (pA_2 = 6.8 ± 0.1), and **3** (pA_2 = 9.0 ± 0.4) were found to antagonize the CB_2 selective agonist JWH133 in a dose-dependent manner in our human CB_2 cAMP accumulation assay (20 min incubation time), based on at least three independent experiments.[43] The observed order of the functional CB_2 receptor antagonistic activities of **1**–**3** is in line with their CB_2 receptor affinities. Our novel imidazoles also functionally behaved as CB_2 receptor antagonists, as exemplified by **14** (pA_2 = 8.3 ± 0.4), and **19** (pA_2 = 8.1 ± 0.1). The key compounds **8** (pA_2 = 8.8 ± 0.4) and **12** (pA_2 = 9.0 ± 0.2) were also found very active as CB_2 receptor antagonists after 4 h of incubation in our cAMP accumulation assay.

The binding efficiency index (BEI) value has been suggested[46] as a better alternative for Hopkins' ligand efficiency[34] metric and accurately reflects the efficiency of a given target-ligand binding interaction. In order to compare their binding efficiencies, the BEI values of the reference compounds **1**–**3** and the target compounds **6**–**20** were calculated (Table 2). From the BEI results of in particular **8**, **12** and **14** it became clear that this new imidazole-scaffolded chemotype incorporates a very efficient binding mode at the CB_2 receptor. The BEI values of **8**, **12** and **14** set a new standard in the CB_2 receptor antagonist/inverse agonist research area since they are significantly higher than those of the known chemotypes that are related to **1**–**3**, respectively. It is interesting to note that **1**–**3**, which were discovered independently by different companies, elicited comparable BEI values (∼16–17) and that the BEI values of **6**–**20** were all higher than those of **1**–**3**. Accordingly, the calculated ligand efficiency (LE) values of **1**–**3** were all lower than 0.40 whereas **7**–**12**, **14**–**18** and **20** showed LE values of 0.40 or higher.

Molecular weight and lipophilicity are key physicochemical properties for drug candidates since it has been reported that the mean molecular weight of orally administered drugs in development decreases on passing through each of the different clinical phases and that the most lipophilic compounds are being discon-

Table 1
Pharmacological data of reference compounds **1–3** and target compounds **6–20**

Compound	K_i (CB_2),[a] nM	K_i (CB_1),[b] nM	CB_2/CB_1 ratio	pEC_{50}(CB_2),[c]
1	21 ± 3	>1000	>46	7.4 ± 0.4 (8.3 ± 0.3)[d]
1	(0.60 ± 0.13)[16]	(437 ± 33)[16]		(7.6 ± 0.1)[16]
1	(1.99 ± 0.94)[18]	(50.3 ± 8.37)[18]		
2	130 ± 630	3924 ± 642	30	<6.5
2	(35.9 ± 7.32)[18]	(2370 ± 297)[18]		
3	0.8 ± 0.3	3538 ± 638	4423	8.1 ± 0.2 (8.3 ± 0.3)[d]
3	(1.0)[19]	(4378)[19]		(8.0)[19]
6	175 ± 77	>10,000	>57	6.8 ± 0.2
7	20 ± 5	3995 ± 1173	200	7.5 ± 0.7
8	2.7 ± 0.9	4887 ± 1796	1810	9.1 ± 0.2 (9.1 ± 0.3)[d]
9	13.8 ± 4.9	3008 ± 679	218	8.2 ± 0.6
10	9.7 ± 5.5	5444 ± 433	561	8.1 ± 0.1
11	3.5 ± 2.2	1422 ± 163	406	9.7 ± 0.8
12	1.03 ± 0.20	>10,000	>9708	7.7 ± 0.5 (9.6 ± 0.2)[d]
13	9.8 ± 5.7	1995	>102	8.3 ± 0.2
14	1.6 ± 0.8	4152 ± 2157	2595	8.8 ± 0.8
15	12.7 ± 3.2	>1000	>79	7.9 ± 0.1 (8.2 ± 0.3)[d]
16	23.8 ± 3.9	>10,000	>420	7.2 ± 0.4
17	8.4 ± 2.1	>10,000	>1190	n.d.[e]
18	10.0 ± 2.9	>10,000	>1000	8.2 ± 0.1
19	50 ± 13	>1000	>20	7.1 ± 0.1
20	20.0 ± 7.9	>10,000	>500	6.9 ± 0.5

[a] Displacement of specific CP-55,940 binding in CHO cells stably transfected with human CB_2 receptor,[42] expressed as K_i ± SEM (nM) The values represent the mean result based on at least three independent experiments.
[b] Displacement of specific CP-55,940 binding in CHO cells stably transfected with human CB_1 receptor,[42] expressed as K_i ± SEM (nM). The values represent the mean result based on at least three independent experiments.
[c] Functional hCB_2 cAMP accumulation assay,[43] expressed as pEC_{50} values (result after 20 min incubation time; see Supplementary data for detailed protocol). The values represent the mean result based on at least three independent experiments.
[d] Result after 4 h incubation time.
[e] n.d.: Not determined.

Table 2
Calculated and experimental physicochemical parameters of compounds **1–3** and **6–20**

Compound	Molecular weight	BEI[a]	LE[b]	LLE[c]	A log *P*	Log P_{HPLC}[d]	cPSA[e]
1	476	16	0.31	0.1	7.6	n.d.[f]	47
2	438	16	0.29	3.4	3.5	4.4[g]	95
3	532	17	0.38	4.9	4.2	1.8[g]	140
6	337	20	0.36	3.2	3.6	n.d.[f]	47
7	351	22	0.40	3.8	3.9	n.d.[f]	47
8	349	25	0.45	4.9	3.7	3.2[h]	47
9	349	23	0.41	4.1	3.8	n.d.[f]	47
10	335	24	0.44	4.7	3.3	n.d.[f]	47
11	373	23	0.43	4.4	4.1	n.d.[f]	47
12	363	25	0.45	4.7	4.3	3.5[h]	47
13	391	20	0.38	2.7	5.3	n.d.[f]	47
14	363	25	0.44	4.4	4.4	n.d.[f]	47
15	349	23	0.41	3.7	4.2	n.d.[f]	47
16	370	21	0.40	3.6	4.0	n.d.[f]	47
17	414	20	0.42	4.0	4.1	n.d.[f]	47
18	381	21	0.40	3.8	4.2	n.d.[f]	72
19	390	19	0.38	2.7	4.6	n.d.[f]	47
20	355	22	0.40	3.7	4.0	n.d.[f]	47

[a] Binding efficiency index (BEI); BEI = $pK_i/(MW/1000)$.
[b] Ligand efficiency index (LE); $LE = -(RT\ln K_d)/N \approx 1.36\ pK_i/N$, wherein N represents the number of non-hydrogen atoms.
[c] ligand-lipophilicity efficiency (LLE); $LLE = pK_i - c\log P \approx pK_i - A\log P$.
[d] Experimental log *P* value determined by a validated RP-HPLC method.[42]
[e] Calculated polar surface area (Å^2).
[f] n.d.; not determined.
[g] Determined at pH 7.
[h] Determined at pH 11.

tinued from development.[47] In addition, lipophilicity plays a role in promoting binding to unwanted biological targets.[48] In order to position these important key physicochemical properties of our imidazoles **6–20** against the known CB_2 antagonist reference compounds **1–3**, their A log *P*[49] and molecular polar surface area (PSA) values were calculated (Table 2). It can be concluded from these lipophilicity results that Sanofi's **1** has a very high lipophilicy whereas all the other compounds from Table 2 show favourable A log *P* values. Ligand-Lipophilicity Efficiency[48,50] (LLE) (also referred to as Lipophilic Efficiency (LipE)) has recently been introduced as a parameter that combines both potency and lipophilicity. The LLE value of **1** is very low due to its high lipophilicity. The LLE value of compound **8** equals the value of Schering's **3**. Noteworthy, the A log *P* data for the imidazoles **8** and **12** are somewhat higher than the experimental data obtained from our validated RP-HPLC lipophilicity assay[42] (Table 2.) The calculated

A log *P* result for **3** is also higher than its experimental log P_{HPLC} value.

Calculated PSA values have been shown to closely correlate with drug transport properties, such as intestinal absorption or blood-brain barrier penetration.[51–53] Compounds having a PSA value >120 Å^2 have generally been shown to have restricted oral bioavailability. It is clear that Schering's **3** does not comply with this PSA threshold. The potent bissulfone **3** combines a high polarity with a high molecular weight. The other compounds depicted in Table 2 have low cPSA values, with the exception of JTE-907 which exhibits an intermediate cPSA value of 95 Å^2. Additional in vitro permeability testing revealed that the compounds **8**, **12** and **14** were not substrates of P-glycoprotein-mediated transport.[54]

Imidazole-4-carboxamides **6**–**20** were designed as a new chemotype of CB_2 receptor antagonists. It was demonstrated herein that these novel compounds **6**–**20** are potent and highly CB_2/CB_1 selective CB_2 receptor antagonists/inverse agonists with very high binding efficiency index values, which exceeded the BEI values of the CB_2 reference compounds **1**–**3**. Furthermore, the imidazoles **6**–**20** as a class exhibited both favourable A log *P* and calculated molecular polar surface area values, which are major in silico indicators for their pharmacokinetic properties.

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Supplementary data

Supplementary data (selected analytical and synthesis data for compounds **6**–**8**, **12**, **14** and **16**–**20**. The protocol for the human cannabinoid CB_2 cAMP accumulation assay) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.12.032.

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