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Probing the cannabinoid CB_1/CB_2 receptor subtype selectivity limits of 1,2-diarylimidazole-4-carboxamides by fine-tuning their 5-substitution pattern

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ABSTRACT

The cannabinoid CB_1/CB_2 receptor subtype selectivity in the 1,2-diarylimidazole-4-carboxamide series was boosted by fine-tuning its 5-substitution pattern. The presence of the 5-methylsulfonyl group in **11** led to a greater than ~840-fold CB_1/CB_2 subtype selectivity. The compounds **10**, **18** and **19** were found more active than rimonabant (**1**) in a CB_1-mediated rodent hypotension model after oral administration. Our findings suggest a limited brain exposure of the P-glycoprotein substrates **11**, **12** and **21**.

Cannabinoids constitute an area of intensive research since the endocannabinoid system plays an important role in many physiological processes.[1] Cannabinoid CB_1 receptor antagonists showed clinical efficacy in the treatment of obesity and improved cardiovascular and metabolic risk factors.[2] They have in addition good prospects in other therapeutic areas,[3] including cognitive disorders.[4] Although the risk of psychiatric side-effects has terminated[5] many development programs of CB_1 receptor blockers such as **1**,[6] **2**,[7] **3**[8] and **4**[9,10] (Fig. 1) for obesity treatment, suggestions have been made to focus on possible therapeutic applications in peripheral pathologies[11] and adapted clinical trials.[12] Very recently, more polar derivatives of **1** were reported[13] which showed significantly decreased CNS/plasma ratios in combination with pronounced weight reduction in obese mice. The majority of the reported[14,15] CB_1 receptor antagonists/inverse agonists can be described in terms of a general pharmacophore model.[16–20]

1,2-Diarylimidazole-4-carboxylates resulted from scaffold hopping, based on the 1,5-diarylpyrazole **1**. Such imidazoles[21–23] showed comparable CB_1 antagonistic/inverse agonistic properties as compared to their pyrazole counterparts. However, it was observed that they were in general less CB_1/CB_2 receptor subtype selective. For example, **5** and **6** exhibited ~20–30-fold CB_1/CB_2 selectivity values, whereas in the same CB_1 and CB_2 receptor assays, **1** showed >60-fold CB_1/CB_2 selectivity (Table 1). This somewhat lower CB_1/CB_2 selectivity in the 1,2-diarylimidazole class can be attributed to their higher CB_2 receptor affinities. Recently, we used this observation in the design of a novel imidazole class as selective CB_2 receptor antagonists.[24]

In considering options to designing agents that would potentially have an improved CB_1/CB_2 selectivity profile relative to the imidazoles **5** and **6**, it was chosen to focus on their 5-substitution since the 5-cyano-substituted **7** showed a slightly improved (~53-fold) CB_1/CB_2 selectivity ratio as compared to **5** and **6**.

Previously, we published an efficient regioselective lithiation[25] reaction,[21] enabling the efficient exploration of other substitutions at the 5-position of the 1,2-diarylimidazole-4-carboxamide class. First, a set of larger substituents (methylsulfanyl, ethylsulfanyl, iodo) was chosen to investigate the potential steric impact of substitution. Second, a set of more polar substituents (methylsulfinyl, methylsulfonyl and hydroxymethyl) which all contain at least one strongly electronegative oxygen atom were selected in order to study in more detail the impact of electronegative substituents, including effects due to potential hydrogen bonding. This led to the synthesis of the target compounds **8–17**. In addition, a smaller set of 4-substituted 1,5-diarylpyrazoles **18–22** was designed in order to compare the structure–activity relationship (SAR) of the most selective 5-substituted-imidazoles with the corresponding 4-substituted 1,5-diarylpyrazole pharmacophore.

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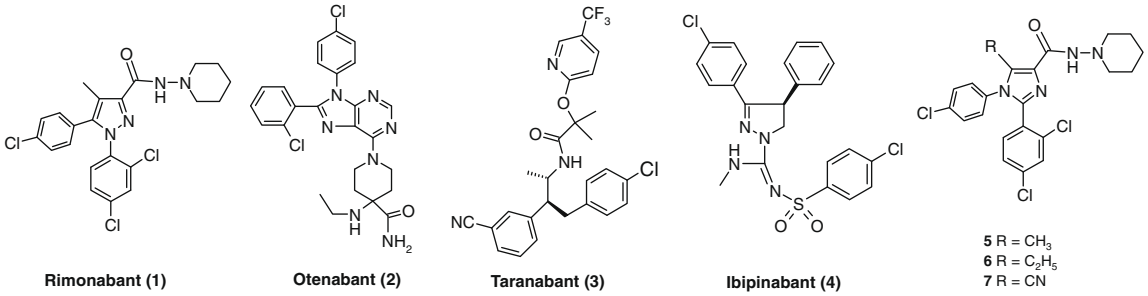


Figure 1. Representative CB_1 antagonists **1**–**4** progressed to clinical development and the preclinical imidazoles **5**–**7**.

Table 1
Pharmacological in vitro results of compounds **1** and **5–21**

Compound	$K_i(CB_1)$[a] (nM)	$pA_2(CB_1)$[b]	$K_i(CB_2)$[c] (nM)	CB_1/CB_2 ratio[d]
1	25 ± 15 (11.5)[6]	8.6 ± 0.1	1580 ± 150 (1640)[6]	63 (143)
5	30 ± 16[21]	8.6 ± 0.1[21]	608 ± 161[21]	20
6	14 ± 12[21]	9.0 ± 0.1[21]	430 ± 141[21]	31
7	30 ± 6[21]	8.6 ± 0.1[21]	1590 ± 467[21]	53
8	10 ± 5	8.8 ± 0.1	1811 ± 550	181
9	51 ± 7	8.6 ± 0.1	>1000	>19
10	12.2 ± 1.6	9.0 ± 0.3	1072 ± 278	88
11	11.9 ± 4.9	8.5 ± 0.2	>10,000	>840
12	49 ± 14	8.2 ± 0.3	>1000	>20
13	12.9 ± 3.2	7.9 ± 0.3	>1000	>77
14	20 ± 7	8.1 ± 0.3	>1000	>50
15	8.9 ± 4.3	8.5 ± 0.2	>1000	>112
16	12.0 ± 5.1	8.9 ± 0.2	325 ± 73	27
17	34 ± 14	8.4 ± 0.2	7504 ± 2496	221
18	3.0 ± 0.8	8.8 ± 0.1	634 ± 204	211
19	13.0 ± 3.6	9.0 ± 0.2	804 ± 222	62
20	27 ± 6	8.6 ± 0.6	371 ± 27	14
21	20 ± 9	8.4 ± 0.1	398[e]	20

[a] Displacement of specific CP-55,940 binding in CHO cells stably transfected with human CB_1 receptor, expressed as K_i ± SEM (nM). The values represent the mean result based on at least three independent experiments.
[b] [^{3}H]-Arachidonic acid release in CHO cells expressed as pA_2 ± SEM values. The values represent the mean result based on at least three independent experiments.
[c] Displacement of specific CP-55,940 binding in CHO cells stably transfected with human CB_2 receptor, expressed as K_i ± SEM (nM). The values represent the mean result based on three independent experiments, unless otherwise noted.
[d] CB_1/CB_2 selectivity values are provided as single values instead of their ranges based on the underlying CB_1 and CB_2 affinity SEM values.
[e] Result of duplicate measurement (individual values 398 and 398 nM).

Due to the presence of the metabolically vulnerable 4-methylsulfanyl substituent, compound **19** might be regarded as a metabolically less stable analog of **1**. This is of particular relevance since it was reported that **1** had a very long terminal half-life in non-obese subjects (6–9 days) and 16 days in obese subjects.[26] Moreover, the metabolic degradation of **1** is characterized by oxidation at its piperidine moiety[27]—to produce metabolites such as SR142923—and amidohydrolysis. The latter process theoretically could lead to the formation of the corresponding carboxylic acid metabolite SR141715 and the mutagenic 1-aminopiperidine,[28] although there is no evidence that **1**—or one of its metabolites—is carcinogenic.

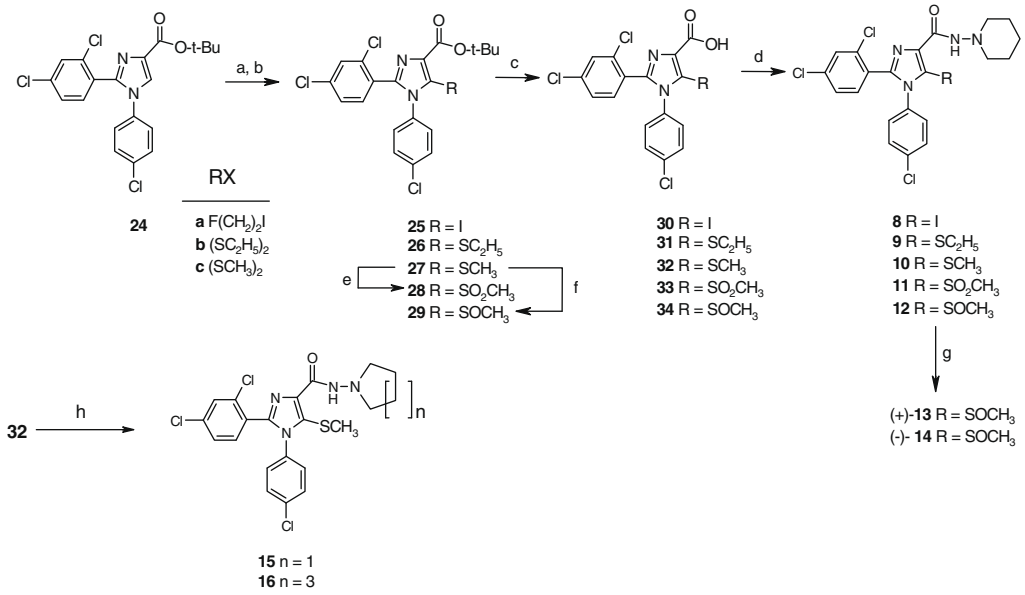
Therefore, a metabolically less stable and structurally related derivative of **1** with a retained cannabinoid CB_1 activity and selectivity profile would be of interest.

The synthesis of the target compounds **8–16** is depicted in Scheme 1. The *tert*-butyl ester[21] **24** was lithiated with LDA in anhydrous THF, followed by the reaction with a number of electrophiles RX as shown in Scheme 1 to give **25–27**. The methylsulfonyl analogue **28** was obtained from **27** using more than 2 mol equiv of *m*-CPBA in 74% yield. The methylsulfoxide **29** was obtained analogously from **27** using 1 mol equiv of *m*-CPBA. Acidic hydrolysis of the *t*-butyl ester moiety in **25–29** with TFA in the presence of a small amount of triethylsilane in CH_2Cl_2 provided the carboxylic acids **30–34** in high yields. These acids were amidated with 1-aminopiperidine in the presence of a coupling reagent (HBTU) to yield the target compounds **8–12**, respectively. The chiral sulfoxide **12** in this series was separated into its enantiomers (+)-**13** and (−)-**14** by using chiral preparative HPLC. The acid **32** was amidated with 1-aminopyrrolidine and 1-amino-azepane in the presence HBTU to yield the target compounds **15** and **16**, respectively.

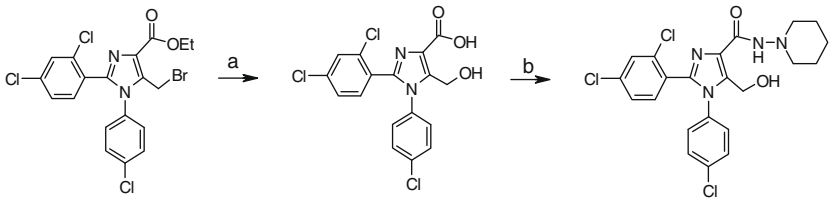
The synthesis of the target compound **17** is shown in Scheme 2. The 5-bromomethyl substituted **35**[21] was converted under basic conditions into **36**, followed by coupling with 1-aminopiperidine in the presence of HBTU and Hünig's base.

The synthesis of the 3-substituted 1,5-diarylpyrazoles **18–21** is depicted in Scheme 3. Initial attempts to couple the methylsulfanyl group to the pyrazole nucleus analogously to the regioselective lithiation method described hereinabove for the imidazoles (Scheme 1) proved to be troublesome. Eventually, we succeeded to perform a 4-bromo-lithium exchange of the carboxylic acid[29] **37** by applying excess *n*-butyllithium and convert it subsequently into **38** by treatment with dimethyldisulfide. Compound **19** was obtained by amidating **38** with 1-aminopiperidine in the presence of HOAt/EDCI.

In the meantime our attention had shifted to an alternative route wherein the methylsulfanylgroup is already present in the reagents from which the pyrazole ring is formed[6] via a cycloaromatization reaction. This versatile synthetic approach to the pyrazole-based



Scheme 1. Reagents and conditions: (a) LDA, anhydrous THF, −20 °C, 1 h; (b) RX, −40 °C→rt, 16 h (61–90%); (c) TFA, cat. Et_3SiH, CH_2Cl_2, rt, 16 h (78%-quantitative); (d) 1-aminopiperidine, HBTU, DIPEA, CH_3CN, rt, 16 h (54–84%); (e) 2.2 mol equiv *m*-CPBA, CH_2Cl_2, rt, 16 h (89%); (f) 1 mol equiv *m*-CPBA, CH_2Cl_2, rt, 16 h (84%); (g) chiral preparative HPLC separation, stationary phase: Chiralpak® AD 20 μm, mobile phase: 25% ethanol/heptane (25/75 (v/v); (h) 1-aminopyrrolidine or 1-amino-azepane, HBTU, DIPEA, CH_3CN, rt, 16 h (35/73%).



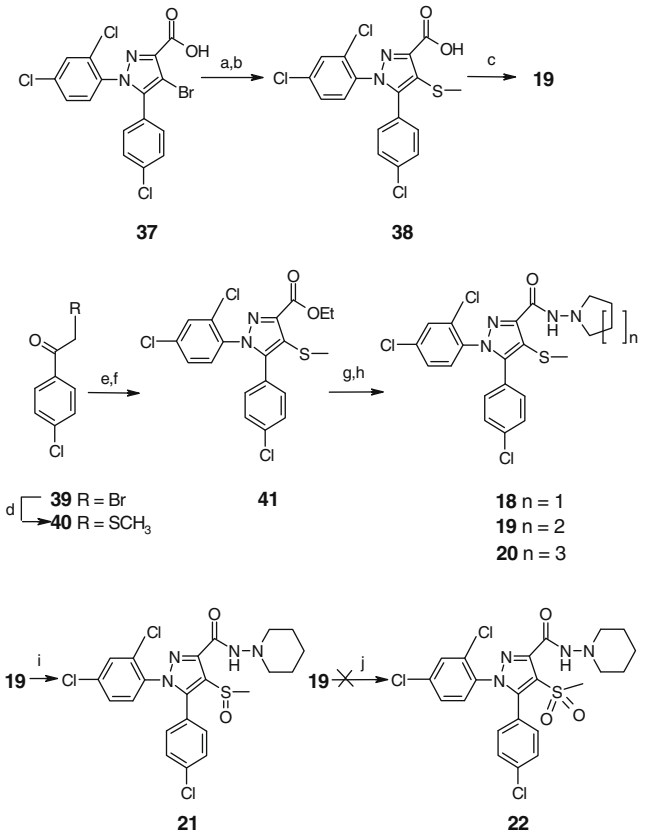
Scheme 2. Reagents and conditions: (a) 2 N NaOH, THF, reflux, 16 h (63%); (b) 1-aminopiperidine, HBTU, DIPEA, CH_3CN, rt, 16 h (37%).

target compounds **18–22** is depicted in Scheme 3. The bromoacetophenone congener **39** was converted to the corresponding methylsulfanyl analogue **40**. Reaction of **40** with diethyloxalate under basic conditions and subsequent treatment with 2,4-dichlorophenylhydrazine·HCl led to the formation of the pyrazole ester **41** in a modest yield. This ester was hydrolyzed with LiOH under basic conditions to the corresponding lithium carboxylate which was converted in situ—in the presence of the coupling reagent TBTU—with a set of amines to the target compounds **18–20**, respectively. The sulfoxide **21** was obtained from **19** using 1 mol equiv of *m*-CPBA. However, treatment of **19** with excess *m*-CPBA did not furnish the corresponding sulfone **22**. Although **22** is anticipated to be accessible via oxidation of the ester **41** with excess *m*-CPBA -analogously to the sequence **27**→**28**→**33**→**11** in the imidazole series (Scheme 1)—no further attempts were undertaken to synthesize **22**.

The pharmacological results of the compounds **1** and **5–21** are given in Table 1. They were evaluated in vitro at the human CB_1 and CB_2 receptor, stably expressed into Chinese Hamster Ovary (CHO) cells,[9] utilizing radioligand binding studies (displacement of the specific binding of [^{3}H]-CP-55,940). CB_1 receptor antagonism[9] was measured using a CP-55,940 induced arachidonic acid release functional assay, using the same recombinant cell line.

The known[21] imidazoles **5–7** showed ~20–50-fold CB_1/CB_2 receptor subtype selectivity values which were somewhat lower as compared to the pyrazole **1**. Introduction of larger 5-substituents without strongly electronegative atoms (iodo (**8**), ethylsulfanyl (**9**) and methylsulfanyl (**10**)) at the imidazole core in all three cases led to >1000 nM CB_2 receptor affinity values. For both **8** and **10** high CB_1 receptor affinities were observed (Table 1), thereby resulting into increased CB_1/CB_2 receptor subtype selectivity values, whereas in **9** the larger ethylsulfanyl substituent led to a decrease in CB_1 receptor affinity (51 nM).

Since the observed steric impact on CB_1/CB_2 receptor subtype selectivity apparently is relatively low, more polar substituents (methylsulfonyl (**11**), methylsulfinyl (**12**) and hydroxymethyl (**17**)) were incorporated. Surprisingly, compound **11** turned out to be very CB_1/CB_2 receptor selective (>~840-fold). A shift to the sulfinyl moiety (**12**) led to a decrease in CB_1 receptor affinity. The enantiopure dextrorotatory **13** showed a somewhat higher CB_1 receptor affinity than its levorotatory counterpart **14**, thereby indicating that these chiral ligands bind with a relatively low degree of stereoselectivity at the CB_1 receptor. The presence of the polar hydroxymethyl group in **17** also led to a high degree of CB_1/CB_2 receptor selectivity (~221-fold). These findings revealed that the presence of one or two electronegative oxygen atoms in the imidazole 5-substituent can lead to lower CB_2 receptor affinities, thereby enhancing the resulting CB_1/CB_2 receptor selectivity, provided that the CB_1 receptor affinity is retained, such as in **11**. Apparently, the CB_2 receptor cannot easily accommodate such a polar substituent at this specific position of the imidazole moiety. The effect of ring size on the SAR in this series was also studied (**10** vs **15** and **16**). The pyrrolidinyl analogue **15** was found somewhat more



Scheme 3. Reagents and conditions: (a) excess *n*-BuLi, anhydrous THF, −78 °C, 15 min; (b) $(CH_3S)_2$, THF, −78 °C, 16 h; (c) 1-aminopiperidine, HOAt, EDCI, CH_2Cl_2, rt, 16 h (10%); (d) $NaSCH_3$, MeOH, rt, 2 h (32%); (e) diethyloxalate, NaOEt, EtOH, rt, 20 h; (f) 2,4-dichlorophenylhydrazine·HCl, AcOH, 60 °C, 3 h (27%); (g) LiOH, H_2O, THF, 35 °C, 20 h; (h) amine, TBTU, Et_3N, DMF, 50 °C, 18 h (50–58%); (i) 1.4 mol equiv *m*-CPBA, CH_2Cl_2, rt, 20 h (21%); (j) excess *m*-CPBA, CH_2Cl_2, rt, 100 h.

CB_1/CB_2 selective than **10** and much more selective than **16**. Apparently, an increase in ring size leads to a decreased CB_1/CB_2 selectivity in this series.

The SAR in the related pyrazole series showed the same trend as compared to the imidazoles. The CB_1 and CB_2 receptor affinities and the functional CB_1 antagonistic potencies of **10** and **19** are in the same order of magnitude. Comparison of the sulfoxides **12** and **21** revealed that the pyrazole **21** elicited higher CB_1 and CB_2 receptor affinities. Interestingly, in the pyrazole series the pyrrolidinyl-substituted **18** behaved as a very strong CB_1 receptor binder (3 nM), which in addition gave a high CB_1/CB_2 selectivity value (~211-fold). The effect on the CB_1/CB_2 selectivity by increasing the ring size in the 1,5-diarylpyrazole series from five to seven (**18–20**) was in line with the observed order in the 1,2-diarylimidazole series (**10**, **15** and **16**), respectively.

The compounds **5–21** elicited significant functional CB_1 antagonistic potencies. In particular the compounds **10** and **19** behaved as potent CB_1 receptor antagonists (pA_2 = 9.0).

The in vivo activities of a smaller set of compounds **1**, **10–12**, **18**, **19** and **21** after oral administration were investigated in our CB_1 agonist-induced anaesthetized rat hypotension model.[9]

Some of the novel compounds were very potent in this mechanistic model (Table 2). It is interesting to note that three of our novel compounds (the imidazole **10** and the pyrazoles **18** and **19**) were found more potent in this model than rimonabant (**1**)[9] (ID_{50} = 3.2 mg/kg). The corresponding sulfoxides and sulfones were less active in vivo although these compounds also showed high activities in vitro.

Table 2
In vivo pharmacological data and physicochemical parameters of compounds **1**, **10–12**, **18**, **19** and **21**

Compound	Hypotension rat,[a] ID_{50}	PGP[b]	cPSA[c]	*A* log *P*	Log P_{HPLC}[d]
1	3.2	1.2 ± 0.1	50	6.6	5.4
10	1.9	1.4 ± 0.1	75	6.3	4.8
11	29	6.0 ± 1.3	93	5.3	3.5
12	>30	7.7[e]	86	5.2	3.7
18	1.9	n. d.[f]	75	6.2	4.7
19	1.5	1.5 ± 0.1	75	6.7	5.1
21	>30	8.0 ± 0.8	86	5.6	3.7

[a] Antagonism of CB agonist (CP-55,940) induced hypotension[9] (anaesthetized rat), expressed as ID_{50} (mg/kg, po administration).
[b] P-Glycoprotein-based membrane transport factor, expressed as the ratio of the bottom to top transport and top to bottom transport.[9]
[c] Calculated polar surface area (Å^2).
[d] Experimental log *P* value determined by a validated RP-HPLC method, determined at pH 7.[9]
[e] Result of duplicate measurement (individual values 7.7 and 8.3).
[f] n. d. = not determined.

In order to support whether pharmacokinetic properties are responsible for this difference in the observed in vivo oral potencies, we determined their propensity to undergo P-glycoprotein-mediated transport, calculated their polar surface area (PSA) and lipophilicity (*A* log *P*).

The P-glycoprotein pump is known to lower the CNS levels of certain compounds by actively extruding them from the brain.[30] Therefore, the affinities of **1**, **10–12**, **18**, **19** and **21** for this efflux pump were examined. Compounds **1**, **10** and **19** were shown to be devoid of significant P-glycoprotein pump substrate affinity. However, the compounds **11** and **21**—possessing the additional electronegative oxygen-atom containing substituent—were P-glycoprotein substrates (Table 2). As a consequence, **11**, **12** and **21** are expected to attain limited brain/plasma ratios. It is of interest to note from a SAR viewpoint that relatively small modifications of the 5-methylsulfanyl substituent in **10** which is no P-glycoprotein substrate, led to the P-glycoprotein substrates **11** and **12**, respectively. Analogously, replacement of the methylsulfanyl group in **19** by the more polar methylsulfinyl moiety gave rise to the P-glycoprotein substrate **21**.

PSA values have been shown to closely correlate with drug transport properties, such as intestinal absorption or blood–brain barrier (BBB) penetration. Compounds having a PSA value <65 Å^2 generally readily cross the BBB, whereas compounds above a threshold of 90 Å^2 been shown to have a low probability to cross the BBB.[31–33] It should be noted that **11**, **12** and **21** have relatively high calculated PSA values, which are nearby or higher than this threshold of 90 Å.[2] The highly CB_1/CB_2 selective **11** might be considered as a prototypic pharmacological tool to study peripherally-mediated CB_1 antagonistic effects,[13] because it is a P-glycoprotein substrate, in combination with a relatively high calculated PSA value. It should be born in mind that due to the very high abundance of CB_1 receptors in the brain[34] it would *a priori* be expected that only CB_1 receptor antagonists with a very low CNS exposure will be devoid of centrally mediated side-effects.

Log *P* is an important Lipinski parameter.[35–37] The values for the selected compounds were calculated (*A* Log *P*)[38] and in parallel determined by applying our RP-HPLC method at neutral pH.[9] Typically, a 1–2 log unit distance was observed between the calculated *A* log *P* and our experimentally determined values throughout the whole compound range. This can be rationalized by invoking an intramolecular hydrogen bond potential[39] between the N–H of the hydrazide and the N_2 atom of the pyrazole ring, c.q. the N_3 atom of the imidazole moiety.[40] In line with expectation, the sulfoxides and sulfones showed significantly lower log *P* values than

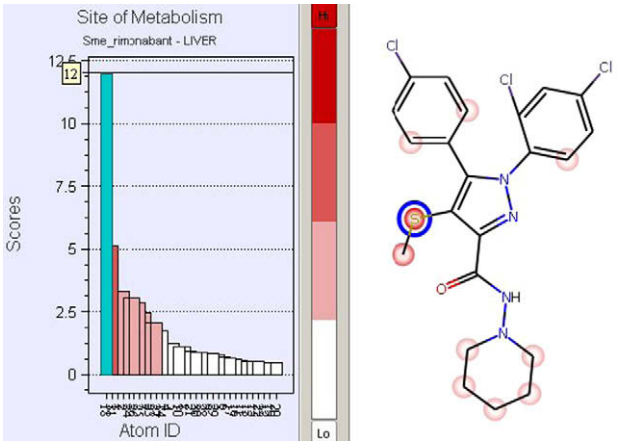


Figure 2. MetaSite™ prediction of the sites of metabolism of **19**.

the corresponding sulfanes but their values remain in a favorable range to enable efficient cell membrane passage.

The involvement of the central nervous system in the complex effects of cannabinoids on blood pressure has been studied previously. Initially, it was found that blood pressure significantly decreased after central injection of Δ^9-tetrahydrocannabinol in anaesthetized animals.[41,42] More recently, it has also been reported that hypotension is caused by activation of peripheral cannabinoid CB_1 receptors.[43] These diverse findings suggest that the observed effects in our CB_1 agonist-induced anaesthetized rat hypotension model[9] can be either centrally or peripherally mediated or by a combination of both. Interestingly, **11**, **12** and **21** all were found poorly orally active in our rodent hypotension assay, whereas **1**, **10** and **19** all elicited potent activity therein. The observed lower activity of **11**, **12** and **21** in our hypotension model may be either attributed to a lower CNS exposure of these compounds or to their lower oral bioavailability. Determination of their CNS and plasma levels after oral administration will be mandatory to resolve this issue.

As postulated above, the presence of the metabolically vulnerable methylsulfanyl moiety in **19** was anticipated be of interest with respect to its cytochrome P450 Phase I metabolism.[44]

Cruciani's Metasite™ is a computational tool[45] to predict the preferred sites of metabolism related to cytochrome-mediated reactions in Phase I metabolism. Metasite™ was applied[46] to predict the primary sites of metabolism of **19**. In accordance with our expectations, **19** was predicted to indeed metabolize primarily via oxidation at its sulfur atom (as represented by the large green bar in Fig. 2), but also to some extend by oxidation at the methyl part of its methylsulfanyl group, its piperidinyl group and the *ortho*-positions of its 4-chlorophenyl group.

In conclusion, the CB_1/CB_2 receptor subtype selectivity in the 1,2-diarylimidazole-4-carboxamide series[47] was boosted by fine-tuning their 5-substitution pattern. The presence of the methylsulfonyl group in **11** led to a greater than ~840-fold CB_1/CB_2 subtype selectivity. The methylsulfanyl substituted pyrazoles **18** and **19** showed potent oral activities in vivo. Our findings suggest a limited brain exposure of the more polar compounds **11**, **12** and **21**, which all were found to act as P-glycoprotein substrates.

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46. Metasite™ version 3.0.6 (2009) was used. Validation of the method by the originators has shown that the primary site of metabolism was found in the top three Metasite predictions for more than 85% of the cases.
47. Yields refer to isolated pure products unless otherwise noted and were not maximized. Selected data for target compounds **8**, **10**, **11**, **13**, **14**, **17**, **19** and **21**, synthesis of key intermediate **41** and selected data for the intermediates **25**, **30**, **32** and **36**. *Compound* ***8***: mp 196–201 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34–1.40 (m, 2H), 1.60–1.66 (m, 4H), 2.77–2.82 (m, 4H), 7.32 (d, J = 8 Hz, 2H), 7.41 (dd, J = 8 and 2 Hz, 1H), 7.47 (d, J = 8 Hz, 2H), 7.53 (d, J = 2 Hz, 1H), 7.63 (d, J = 8 Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 23.32, 25.68, 55.90, 82.22, 127.46, 128.69, 129.07, 129.42, 130.59, 134.55, 134.73, 134.82, 135.30, 136.12, 136.47, 146.15, 158.81; HRMS exact mass calcd for $C_{21}H_{19}Cl_3IN_4O$ m/z 574.9669 [MH]$^+$, found 574.9694. Anal. Calcd for $C_{21}H_{18}Cl_3IN_4O{\cdot}1/2H_2O$: C, 43.14; H, 3.28; N, 9.58. Found: C, 43.06; H, 2.94; N, 9.51. *Compound* **10**: mp 170 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.35–1.42 (m, 2H), 1.62–1.67 (m, 4H), 2.35 (s, 3H), 2.80–2.84 (m, 4H), 7.29 (d, J = 8 Hz, 2H), 7.42 (dd, J = 8 and 2 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 7.52 (d, J = 2 Hz, 1H), 7.62 (d, J = 8 Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 19.26, 23.32, 25.63, 55.98, 127.52, 128.61, 129.14, 129.23, 129.86, 130.12, 130.18, 133.86, 134.45, 134.66, 136.01, 137.12, 144.04, 158.98; HRMS exact mass calcd for $C_{22}H_{22}Cl_3N_4OS$ m/z 495.0580 [MH]$^+$, found 495.0592. *Synthesis of compound* **11**: To a cooled (−20 °C) and magnetically stirred solution of **24** (10.59 g, 25.0 mmol), in anhydrous THF (100 ml) was added LDA (15.0 ml, 2 M solution in heptane/THF, 30.0 mmol) and the resulting mixture was stirred for 1 h under N_2. A solution of $(CH_3S)_2$ (2.7 ml, 30.0 mmol) in anhydrous THF (20 ml) was added and the resulting solution was successively stirred at −40 °C for 1 h, allowed to attain rt and stirred for another 16 h. A saturated aqueous NH_4Cl solution (250 ml) was added and the resulting solution was extracted twice with EtOAc. The combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated to give **27** in 90% yield as an oil which slowly solidified; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.66 (s, 9H), 2.28 (s, 3H), 7.05 (br d, $J \sim$ 8 Hz, 2H), 7.25 (dd, J = 8 and 2 Hz, 1H), 7.28 (d, J = 2 Hz, 1H), 7.32–7.41 (m, 3H). To a magnetically stirred solution of **27** (6.00 g, 12.8 mmol) in CH_2Cl_2 (25 ml) was slowly added a solution of *m*-CPBA (6.90 g, 70% grade, 0.282 mol) in CH_2Cl_2 and the resulting mixture was stirred for 16 h. The reaction mixture was twice washed with 2 N NaOH solution and dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (silicagel, Et_2O/petroleum ether = 2/1 (v/v)) to give **28** (4.76 g, 74% yield) as a white solid, mp 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 9H), 3.34 (s, 3H), 7.15 (br d, $J \sim$ 8 Hz, 2H), 7.20–7.26 (m, 2H), 7.32–7.41 (m, 3H). To a magnetically stirred solution of **28** (4.76 g, 9.49 mmol) in CH_2Cl_2 (60 ml) was added excess TFA (9.40 ml, 0.2124 mol) and Et_3SiH (3.8 ml, 0.0238 mol). The solution was reacted at rt for 16 h and concentrated in vacuo. Water was added and the formed precipitate was collected by filtration and subsequently dried to give **33** in quantitative yield, mp ∼130 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (s, 3H), 3.50 (br s, 1H), 7.40 (br d, $J \sim$ 8 Hz, 2H), 7.42 (dd, J = 8 and 2 Hz, 1H), 7.50 (br d, $J \sim$ 8 Hz, 2H), 7.59 (d, J = 2 Hz, 1H), 7.61 (d, J = 8 Hz, 1H). To a magnetically stirred suspension of **33** (2.23 g, 5.01 mmol) in anhydrous CH_3CN (50 ml) was successively added *N*,*N*-diisopropylethylamine (Hünig's base) (1.90 ml, 11.0 mmol), *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) (2.27 g, 5.99 mmol) and 1-aminopiperidine (0.65 ml, 6.03 mmol). After stirring for 16 h at rt, the resulting mixture was concentrated. The residue was dissolved in EtOAc, successively washed with aqueous $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated to give a crude solid. This solid was further purified by flash chromatography (silicagel, EtOAc) and triturated with MTBE to give **11** in 84% yield, mp 181–185 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.35–1.41 (m, 2H), 1.61–1.66 (m, 4H), 2.80–2.84 (m, 4H), 3.52 (s, 3H), 7.38 (d, J = 8 Hz, 2H), 7.42 (dd, J = 8 and 2 Hz, 1H), 7.46 (d, J = 8 Hz, 2H), 7.57 (d, J = 2 Hz, 1H), 7.62 (d, J = 8 Hz, 1H), 9.40 (s, 1H); HRMS exact mass calcd for $C_{22}H_{22}Cl_3N_4O_3S$ 527.0478 [MH]$^+$, found m/z 527.0469. *Compound* **13**: mp 243–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.48 (m, 2H), 1.72–1.80 (m, 4H), 2.82–2.90 (m, 4H), 3.10 (s, 3H), 7.18–7.27 (m, 4H), 7.29 (br d, J = 8 Hz, 2H), 7.38 (d, J = 2 Hz, 1H), 7.92 (br s, 1H); ESI$^+$-MS exact mass calcd for $C_{22}H_{22}{}^{35}Cl_3N_4O_2S$ m/z, 511.0529 ([MH$^+$]), found: 511.0513; $[\alpha]_D^{25}$ = +23 *c* 0.94 (g/100 ml, CH_3OH): ee = 99.5%. *Compound* **14**: mp 242–244 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.48 (m, 2H), 1.72–1.80 (m, 4H), 2.82–2.90 (m, 4H), 3.10 (s, 3H), 7.18–7.27 (m, 4H), 7.29 (br d, J = 8 Hz, 2H), 7.38 (d, J = 2 Hz, 1H), 7.92 (br s, 1H); ESI$^+$-MS exact mass calcd for $C_{22}H_{22}{}^{35}Cl_3N_4O_2S$ m/z, 511.0529 ([MH$^+$]), found: 511.0540; $[\alpha]_D^{25}$ = −19, *c* 0.94 (g/100 ml, CH_3OH): ee = 97.2%. *Compound* **17**: mp 212–214 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34–1.41 (m, 2H), 1.61–1.66 (m, 4H), 2.80–2.84 (m, 4H), 4.61–4.64 (m, 2H), 5.43–5.47 (m, 1H), 7.34 (d, J = 8 Hz, 2H), 7.41–7.46 (m, 3H), 7.52 (d, J = 2 Hz, 1H), 7.61 (d, J = 8 Hz, 1H), 9.00 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 23.29, 25.63, 52.57, 55.95, 127.53, 128.61, 129.13, 129.40, 129.58, 131.88, 133.78, 134.29, 134.69, 134.73, 135.88, 137.41, 142.66, 160.46; HRMS exact mass calcd for $C_{22}H_{22}Cl_3N_4O_2$ m/z 479.0808 [M+H]$^+$, found: 479.0832. Anal. Calcd for $C_{22}H_{21}Cl_3N_4O_2{\cdot}1/2H_2O$: C, 54.06; H, 4.54; N, 11.46. Found: C, 54.14; H, 4.25; N, 11.49. *Compound* **19**: mp 110–112 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41–1.49 (m, 2H), 1.72–1.81 (m, 4H), 2.40 (s, 3H), 2.83–2.95 (m, 4H), 7.15 (br d, J = 8 Hz, 2H), 7.28–7.35 (m, 4H), 7.42 (br d, J = 2 Hz, 1H), 7.94 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.03, 23.32, 25.29, 57.02, 113.66, 126.20, 127.99, 128.74, 130.36, 130.48, 131.24, 132.85, 135.59, 135.64, 136.41, 147.08, 147.30, 158.62; ESI$^+$-MS exact mass calcd for $C_{22}H_{22}{}^{35}Cl_3N_4OS$ m/z, 495.0580 ([MH$^+$]), found: 495.058. *Compound* **21**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41–1.49 (m, 2H), 1.72–1.81 (m, 4H), 2.84–2.96 (m, 4H), 3.11 (s, 3H), 7.15 (br d, J = 8 Hz, 2H), 7.27–7.32 (m, 4H), 7.43 (br s, 1H), 8.70 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.28, 25.22, 41.84, 56.97, 122.91, 124.67, 128.03, 128.66, 130.41, 130.63, 131.60, 133.01, 134.54, 136.51, 136.98, 144.62, 144.85, 157.60; ESI$^+$-MS exact mass calcd for $C_{22}H_{22}{}^{35}Cl_3N_4O_2S$ m/z, 511.0529 ([MH$^+$]), found: 511.0550. *Synthesis of* **41**: To a magnetically stirred solution of **39** (16.8 g, 72 mmol) in CH_3OH (200 ml) was added $NaSCH_3$ (5.23 g, 72 mmol) to give an exothermic reaction. The resulting mixture was reacted for 2 h at rt, concentrated and suspended in CH_2Cl_2 (150 ml) and washed with water, dried over $MgSO_4$, filtered and concentrated to give **40** (5.1 g, 32% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13 (s, 3H), 3.72 (s, 2H), 7.44 (br d, J = 8 Hz, 2H), 7.92 (br d, J = 8 Hz, 2H). Sodium metal (2 g, 87 mmol) was slowly dissolved in EtOH (80 ml). The resulting solution was added to a magnetically stirred solution of diethyl oxalate (6 g, 41 mmol) and **40** (8.0 g, 40 mmol). The resulting mixture was reacted for 20 h at rt and subsequently poured into HCl (200 ml, 1 N). The resulting mixture was extracted twice with MTBE (200 ml), dried over $MgSO_4$, filtered and concentrated. The resulting residue was dissolved in AcOH (200 ml), 2,4-dichlorophenylhydrazine·HCl (8.6 g, 40 mmol) was added and the resulting mixture was heated at 60 °C for 3 h. The reaction mixture was allowed to attain rt, concentrated to ∼50 ml and poured into water (200 ml), followed by extraction with MTBE (3 × 150 ml). The combined organic layers were washed with 5% aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (silica gel, heptane/EtOAc = 90/10 (v/v)) gave **41** (4.9 g, 27% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44 (t, J = 7 Hz, 3H), 2.32 (s, 3H), 4.46 (q, J = 7, 2H), 7.10–7.45 (m, 7H). *Compound* **25**: mp 234–237 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 9H), 7.08 (br d, $J \sim$ 8 Hz, 2H), 7.20–7.45 (m, 5H). *Compound* **30**: mp 182–186 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.50 (br s, 1H), 7.12 (br d, $J \sim$ 8 Hz, 2H), 7.22–7.45 (m, 5H). *Compound* **32**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.60 (br s, 1H), 7.08 (br d, $J \sim$ 8 Hz, 2H), 7.26 (dd, J = 8 and 2 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.35 (d, J = 2 Hz, 1H), 7.37 (br d, $J \sim$ 8 Hz, 2H). *Compound* **36**: mp 138 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.05 (br s, 1H), 4.67 (s, 2H), 7.05–7.42 (m, 7H).