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Synthesis and SAR of 1,4,5,6-tetrahydropyridazines as potent cannabinoid CB_1 receptor antagonists

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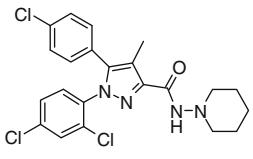
ABSTRACT

The synthesis and structure–activity relationship studies of 1,4,5,6-tetrahydropyridazines are described. The target compounds **3–5** represent a novel class of potent and selective CB_1 receptor antagonists.

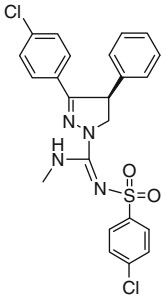
Significant progress has been made in the molecular characterization of endogenous cannabinoids[1] and their receptors[2–4] during the last 20 years. Cannabinoid CB_1 receptor antagonists showed clinical efficacy in the treatment of obesity and improved cardiovascular and metabolic risk factors such as triglyceride levels and HDL cholesterol.[5,6] However, the risk of psychiatric disorders has terminated[7] many development programs for CB_1 receptor blockers for obesity and has suspended market access of rimonabant **1**. It is interesting to note that CB_1 receptor antagonists have also been related[8,9] to the potential treatment of several CNS diseases, including smoking and alcohol addiction and cognitive disorders as well as in the potential treatment of peripherally-mediated disorders such as liver fibrosis, cancer, arthritis and chronic bronchitis.

Scaffold hopping and bioisosteric approaches—in combination with results from pharmacological screening programs—have led to the discovery of selective CB_1 receptor antagonists from different chemical structure classes. However, the majority of the reported CB_1 receptor antagonists and inverse agonists can be described in terms of a general pharmacophore model.[10–12]

Based on this CB_1 pharmocophore knowledge, scaffold hopping approaches seem rather straightforward and have been successfully applied in many cases.[13–15] However, it should be borne in mind that such chemical structure modifications will often lead to fully inactive compounds. This is due to the typical complexity of structure–activity relationships. For example, a number of bioisosteric replacements of the non-aromatic dihydropyrazole moiety[16] based on **2** by several other five-membered heterocycles such as the 4,5-dihydroimidazole, imidazole or oxazole scaffold, were recently published.[17] Surprisingly, the resulting compounds were devoid of CB_1 antagonistic activity in vitro as well as in vivo in a rodent feeding model. On the contrary, replacement of the central aromatic pyrazole ring in **1** by imidazoles[13,18,19] or oxazole[20] led to retained CB_1 antagonistic activities.



Rimonabant (**1**)



Ibipinabant (**2**)

These remarkable results prompted us to design an alternative scaffold hopping modification based on **2** to produce analogues which do have retained CB_1 antagonistic properties. We envisioned that enlargement of the 4,5-dihydropyrazole ring in **2** to a non-aro-

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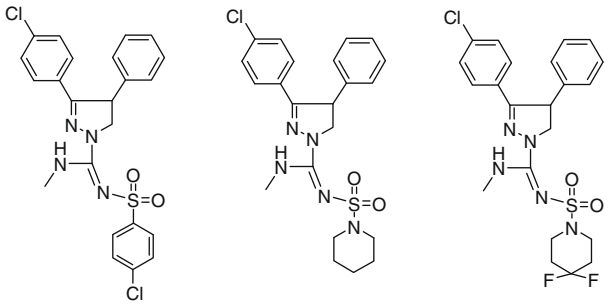
matic six-membered heterocyclic scaffold would lead to pharmacologically active 1,4,5,6-tetrahydropyridazine analogues based on results from in silico CB_1 receptor docking studies. The chiral center in the resulting 1,4,5,6-tetrahydropyridazines is expected to be important—as it is for ibipinabant[16]—but this chirality aspect was not included in this preliminary study. It is interesting to note that the 1,4,5,6-tetrahydropyridazine constitutes a privileged structure[21] since this heterocyclic moiety occurs in many pharmacologically active compounds acting at different molecular targets, such as ACAT inhibitors,[22] progesterone receptor ligands,[23] allosteric $GABA_A$ receptor modulators[24] and neuraminidase inhibitors.[25]

These considerations guided us to the design of three dedicated target compounds **3**–**5**. The 1,4,5,6-tetrahydropyridazines **3**–**5** have been synthesized as depicted in Scheme 1. Commercially available benzyl 4-chlorophenyl ketone **6** was reacted[22] with methyl bromoacetate **7** to yield ester adduct **8** in an excellent 95% yield. Hydrolysis of **8** led to the corresponding carboxylic acid **9** in 88% yield. Treatment of **9** with hydrazine hydrate gave the 4,5-dihydropyridazin-3-one[22] **10** in a yield of 81% The key 1,4,5,6-tetrahydropyridazine intermediate **11** was quantitatively obtained from **10** by reduction with $LiAlH_4$ in THF. Subsequent coupling of **11** with the building blocks **12**–**14** afforded **15**–**17**, respectively, in yields ranging from 73% to 75%. The intermediates **15**–**17** were chlorinated with phosphorus oxychloride in the presence of DMAP and reacted with methylamine to furnish the target compounds **3**–**5** in yields ranging from 81% to 82%.

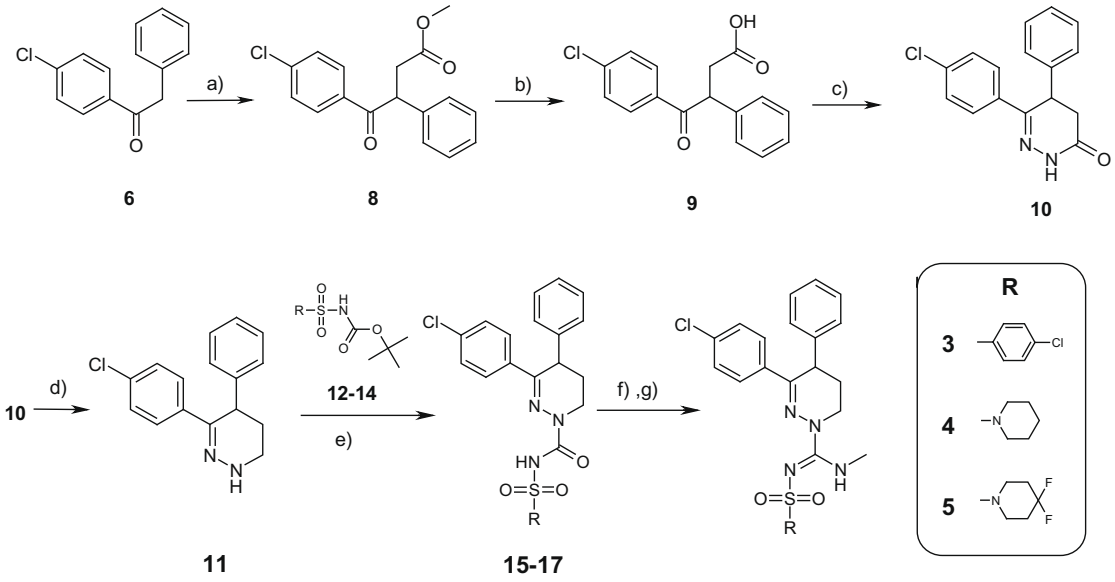
In order to verify the success of our design efforts, the CB_1 antagonistic activities of **3**–**5** were compared with the corresponding dihydropyrazole analogs **18**,[16] **19**[26] and its 4,4-difluoropiperine analogue **20**. The synthesis of the novel compound **20** is depicted in Scheme 2.

4,4-Difluoropiperidine.HCl **21** was reacted with sulfamide in butylacetate in the presence of Hünig's base to produce the sulfamide derivative **22** in 84% yield. Subsequent treatment of **22** with di-*tert*-butyl dicarbonate in the presence of DMAP gave the carbamate ester **14** in 91% yield. Coupling of the dihydropyrazole building block[27] **23** with **14** afforded **24** in 76% yield,[28] which was successively chlorinated with $POCl_3$ in the presence of DMAP and reacted with methylamine to give the difluorinated target compound **20** in a yield of 91%.

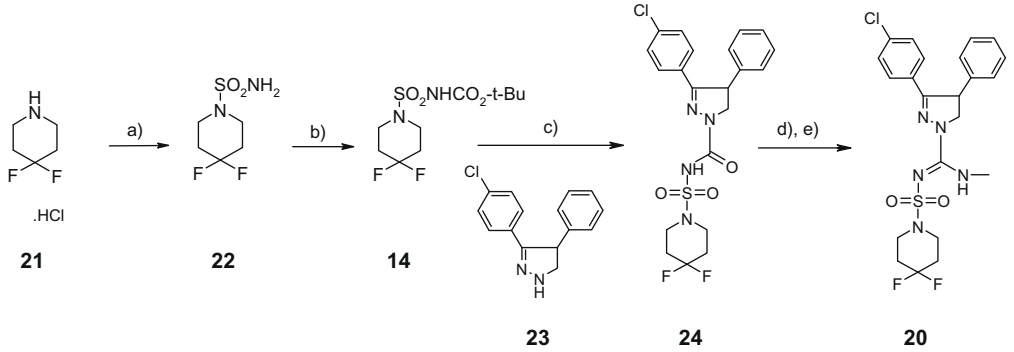
The pharmacological results of the target compounds **3–5** and the corresponding dihydropyrazole analogues **18–20** are given in Table 1. They were evaluated in vitro at the human CB_1 and CB_2 receptor, stably expressed into Chinese Hamster Ovary (CHO) cells,[16] utilizing radioligand binding studies (displacement of the specific binding of [^{3}H]-CP-55,940). CB_1 receptor antagonism[16] was measured using a CP-55,940 induced arachidonic acid release functional assay, using the same recombinant cell line.



The CB_1 receptor binding data of the target compounds **3–5** revealed that their somewhat larger 1,4,5,6-tetrahydropyridazine scaffold as compared to the dihydropyrazole moiety in **18–20** has only a small influence on the observed CB_1 receptor affinities (Table 1). Moreover, the functional CB_1 receptor antagonistic properties of **3–5** are in line with the observed values of **18–20.** The 1,4,5,6-tetrahydropyridazines **3–5** showed approximately five to eight fold $CB_{1/2}$ receptor subtype selectivities. It is interesting to note that in particular compound **18** from the original dihydropyrazole series elicited a much higher (~40-fold) $CB_{1/2}$ receptor subtype selectivity value, whereas compounds **19** and **20** elicit more comparable values as compared to **4** and **5**, respectively. It can therefore be concluded that the 1,4,5,6-tetrahydropyridazine scaffold is a valid bioisosteric replacement of the 4,5-dihydropyrazole moiety in this series of CB_1 receptor antagonists.



Scheme 1. Reagents and conditions: (a) methyl bromoacetate (**7**), NaH, DMSO, rt, 1 h; (b) aqueous 25% NaOH, EtOH/H_2O = 1/1 (v/v), rt, 16 h; (c) $H_2NNH_2{\cdot}H_2O$, EtOH, reflux, 16 h; (d) $LiAlH_4$, THF, reflux, 30 min; (e) toluene, reflux, 2 h; (f) $POCl_3$, DMAP, CH_2Cl_2, reflux, 3 h; (g) CH_3NH_2.HCl, DIPEA, CH_2Cl_2, 6 °C → rt, 16 h.



Scheme 2. Reagents and conditions: (a) sulfamide, DIPEA, butylacetate, reflux, 16 h; (b) di-*tert*-butyl dicarbonate, Et_3N, DMAP, toluene, 50 °C, 2 h; (c) toluene, reflux, 3 h; (d) $POCl_3$, DMAP, CH_2Cl_2, reflux, 3 h; (e) CH_3NH_2·HCl, DIPEA, 6 °C → rt, 16 h.

Table 1
Pharmacological results of compounds **3**–**5** and **18**–**20**

Compound	$K_i(CB_1)$[a], nM	$pA_2(CB_1)$[b]	$K_i(CB_2)$[c], nM
3	43 ± 12	9.0 ± 0.2	318 ± 80
4	74 ± 5	8.7 ± 0.3	571 ± 216
5	47 ± 3	9.0 ± 0.1	247 ± 135
18	25 ± 7	8.7 ± 0.3	>1000
19	152 ± 68	8.7 ± 0.3	1321 ± 264
20	12.2 ± 4.6	9.2 ± 0.3	219 ± 91

[a] Displacement of specific CP-55,940 binding in CHO cells stably transfected with human CB_1 receptor, expressed as K_i ± SEM (nM).
[b] [^{3}H]-Arachidonic acid release in CHO cells expressed as pA_2 ± SEM values.
[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 at least three independent experiments.

Novel 1,4,5,6-tetrahydropyridazines **3–5** were designed as potential CB_1 receptor antagonists. Whereas former bioisosteric replacement efforts of the dihydropyrazole ring in **2** with other five-membered heterocyclic moieties failed, it is demonstrated herein that scaffold hopping to a six-membered 1,4,5,6-tetrahydropyridazine ring constitutes a successful strategy to obtain potent CB_1 receptor antagonists.

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28. The purity of the compounds used in the pharmacological assays was ⩾95%, based on ^{1}H NMR (400 MHz) peak integration measurements. Selected data for compounds **3–5**, **11**, **14**, **15–17**, **20** and **24**. *Compound* **3**: mp 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98–2.18 (m, 2H), 3.12 (dt, J = 13 Hz and 4 Hz, 1H), 3.38 (d, $J \sim 5$ Hz, 3H), 4.10–4.20 (m, 2H), 7.07 (br d, J = 7 Hz, 2H), 7.22–7.41 (m, 8H), 7.53 (br d, J = 8 Hz, 2H), 7.88 (br d, J = 9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 32.2, 38.0, 38.2, 127.2, 127.4, 127.5, 127.9, 128.7, 128.8, 129.2, 134.5, 135.6, 137.2, 140.4, 144.0, 148.0, 154.1 (broad); ESI$^+$-MS exact mass calcd for $C_{24}H_{22}Cl_2N_4O_2SNa$ m/z, 523.0738 ([MNa$^+$]), found: 523.0788. *Compound* **4**: mp 204–205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42–1.50 (m, 2H), 1.62–1.71 (m, 4H), 2.06–2.25 (m, 2H), 3.10 (br t, J = 5 Hz, 4H), 3.18 (dt, J = 13 Hz and 4 Hz, 1H), 3.37 (d, J = 5 Hz, 3H), 4.19 (br d, J = 5 Hz, 1H), 4.41 (br d, J = 13 Hz, 1H), 7.11 (br d, J = 7 Hz, 2H), 7.16–7.36 (m, 6H), 7.52 (br d, J = 9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 25.1, 26.5, 32.0, 37.6, 38.1, 47.9, 127.2, 127.4, 128.0, 128.8, 129.2, 134.8, 135.2, 140.9, 146.0, 154.2 (broad); ESI$^+$-MS exact mass calcd for $C_{23}H_{29}ClN_5O_2S$ m/z, 474.1731 ([MH$^+$]), found: 474.1770. *Synthesis of compound* **5**: To a magnetically stirred solution of **17** (1.27 g, 2.56 mmol) dissolved in CH_2Cl_2 (30 ml) was added DMAP (1.37 g; 11.24 mmol), followed by slow addition of $POCl_3$ (0.30 ml; 3.32 mmol; solution in CH_2Cl_2 (3 ml)). The reaction mixture was heated at reflux temperature for 3 h. After cooling to 6 °C, CH_3NH_2·HCl (0.78 g; 11.50 mmol) was added, followed by dropwise addition of DIPEA (3.06 ml; 17.9 mmol). The reaction mixture was stirred overnight at room temperature. HCl (1 N) was added to acidify the mixture. The layers were separated. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Flash chromatographic purification (silica gel, gradient: $CH_2Cl_2 \rightarrow CH_2Cl_2$/2% MeOH (v/v)) followed by crystallization gave 3-(4-chlorophenyl)-4-phenyl-*N*-methyl-*N*′-[(4,4-difluoropiperidinyl)sulfonyl]-1,4,5,6-tetrahydropyridazine-1-carboxamidine (**5**) (1.12 g; 82% yield). mp 225–226 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03–2.25 (m, 6H), 3.17 (dt, J = 13 Hz and 4 Hz, 1H), 3.31 (br t, J = 5 Hz, 4H), 3.38 (d, J = 5 Hz, 3H), 4.20 (br d, J = 4 Hz, 1H), 4.36 (br d, J = 13 Hz, 1H), 7.09 (br d, J = 7 Hz, 2H), 7.19–7.36 (m, 6H), 7.52 (br d, J = 9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 31.8, 33.4 (t, J_{CF} = 24 Hz), 37.7, 38.1, 44.4 (t, J_{CF} = 6 Hz), 121.4 (t, J_{CF} = 242 Hz), 127.3, 127.5, 127.9, 128.8, 129.2, 134.7, 135.4, 140.6, 146.8, 154.1 (broad); ESI$^+$-MS exact mass calcd for $C_{23}H_{26}ClF_2N_5O_2SNa$ m/z, 532.1362 ([MNa$^+$]), found: 532.1385. *Synthesis of compound* **11**: To $LiAlH_4$ (4.76 g, 125 mmol) was added THF (200 ml) at 0 °C. Compound[22] **10** (11.91 g, 41.8 mmol) was also dissolved in THF (200 ml) and added dropwise to the magnetically stirred $LiAlH_4$/THF solution at 0 °C. Hereafter,

the mixture was successively stirred for 30 min at reflux temperature and cooled in an ice bath. 2 N NaOH was added carefully and the formed mixture was extracted with EtOAc. The organic layer was successively dried over Na_2SO_4, filtered and concentrated in vacuo to furnish **11** (12.04 g; 99.9%). ^{1}H NMR (400 MHz $CDCl_3$) δ 1.95–2.04 (m, 1H), 2.28–2.39 (m,1H), 3.16–3.22 (m, 2H), 4.06 (dd, J = 6 and 3 Hz, 1H), 5.96 (br s, 1H), 7.14 (br d, J = 9 Hz, 2H), 7.17–7.32 (m, 5H), 7.45 (br d, J = 9 Hz, 2H). *Synthesis of compound* **14**: To a magnetically stirred solution of **22** (6.0 g, 30 mmol) was successively added Et_3N (4.4 ml, 31.5 mmol) and DMAP (0.37 g, 3 mmol) and the resulting mixture was heated at 50 °C. Di-*tert*-butyl dicarbonate (7.9 g, 36 mmol) was dropwise added and the resulting mixture was heated at 50 °C for 2 h. The mixture was allowed to attain room temperature and toluene (100 ml) and HCl (50 ml, 1 N) were successively added. The organic layer was successively washed with water (twice), dried over Na_2SO_4, filtered and concentrated in vacuo to afford **14** (8.21 g, 91%). mp 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.03–2.15 (m, 4H), 3.53–3.58 (m, 4H), 6.98 (br s, 1H). *Selected data for compounds* **15**–**17**: *Compound* **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03–2.18 (m, 2H), 3.04 (dt, J = 14 and 5 Hz, 1H), 4.15–4.23 (m, 2H), 7.06 (br d, J = 7 Hz, 2H), 7.22–7.36 (m, 5H), 7.50–7.57 (m, 4H), 8.13 (br d, J = 9 Hz, 2H), 9.25 (br s, 1H). *Compound* **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54–1.62 (m, 2H), 1.67–1.74 (m, 4H), 2.07–2.23 (m, 2H), 3.10 (dt, J = 14 and 5 Hz, 1H), 3.48 (br t, J = 5 Hz, 4H), 4.18–4.31 (m, 2H), 7.10 (d, J = 6 Hz, 2H), 7.24–7.36 (m, 5H), 7.52 (br d, J = 9 Hz, 2H), 8.98 (br s, 1H). *Compound* **17**: To a magnetically stirred solution of **14** (1.04 g; 3.47 mmol) in toluene (20 ml) was added **11** (1.00 g; 3.47 mmol) and the resulting solution was heated at reflux temperature for 2 h. The mixture was allowed to attain room temperature and the volatiles were removed in vacuo. Diisopropyl ether (75 ml) was added to the residue and, after stirring for 15 minutes, compound **17** was filtered off (1.29 g; 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08–2.24 (m, 6H), 3.11 (dt, J = 13 and 4 Hz, 1H), 3.67 (br t, J = 6 Hz, 4H), 4.20–4.30 (m, 2H), 7.10 (br d, J = 7 Hz, 2H), 7.24–7.37 (m, 5H), 7.52 (br d, J = 9 Hz, 2H), 9.01 (br s, 1H). *Selected analytical data for compound* **20**: mp 158.5–159.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.05–2.14 (m, 4H), 3.24 (d, J = 7 Hz, 3 H), 3.26–3.34 (m, 4H), 4.10–4.18 (m, 1H), 4.57 (t, J = 12 Hz, 1H), 4.67 (dd, J = 12 and ~5.5 Hz, 1H), 6.80 (br s, 1H), 7.15 (d, J = 8 Hz, 2H), 7.25–7.29 (m, 3H), 7.30–7.35 (m, 2H), 7.53 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5 (broad), 33.3 (t, J_{CF} = 24 Hz), 44.3 (t, J_{CF} = 6 Hz), 50.9 (broad), 57.3, 121.4 (t, J_{CF} = 242 Hz), 127.3, 128.1, 128.5, 128.6, 129.0, 129.5, 136.3, 139.2, 152.8 (broad), 156.4; ESI$^+$-MS exact mass calcd for $C_{22}H_{25}ClF_2N_5O_2S$ *m/z*, 496.1386 ([MH^+]), found: 496.1429. *Selected analytical data for compound* **24**: mp 215–216 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06–2.19 (m, 4H), 3.62–3.67 (m, 4H), 3.97 (dd, J = 11 and 5.5 Hz, 1H), 4.39 (t, J = 11 Hz, 1H), 4.76 (dd, J = 11 and 5.5 Hz, 1H), 7.15 (br d, J = 8 Hz, 2H), 7.25–7.36 (m, 5H), 7.53 (br d, J = 8 Hz, 2H), 8.51 (br s, 1H).