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Novel 3,4-diarylpyrazolines as potent cannabinoid CB_1 receptor antagonists with lower lipophilicity

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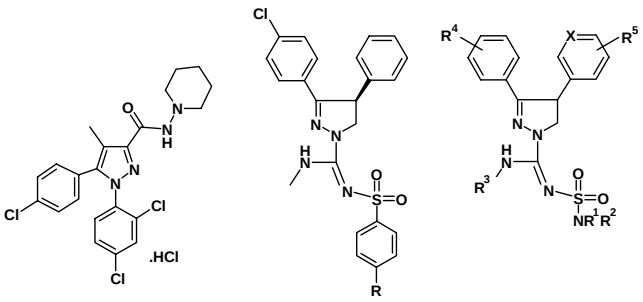
Abstract—Novel 3,4-diarylpyrazolines **1** as potent CB_1 receptor antagonists with lipophilicity lower than that of SLV319 are described. The key change is the replacement of the arylsulfonyl group in the original series by a dialkylaminosulfonyl moiety. The absolute configuration (4*S*) of eutomer **24** was established by X-ray diffraction analysis and **24** showed a close molecular fit with rimonabant in a CB_1 receptor-based model. Compound **17** exhibited the highest CB_1 receptor affinity (K_i = 24 nM) in this series, as well as very potent CB_1 antagonistic activity (pA_2 = 8.8) and a high CB_1/CB_2 subtype selectivity (~147-fold).

Cannabinoids have been used as medicinal agents for centuries.[1,2] However, only within the past 10 years has research in the cannabinoid area revealed vital information about CB receptors and their (endogenous) agonists. The discovery and subsequent cloning[3,4] of two subtypes of cannabinoid receptors (CB_1 and CB_2) have enabled the development of CB receptor screening assays. Recent data suggest that there may be a third cannabinoid receptor[5,6] (CB_3). Wide distribution of the CB_1 receptors in the brain and their apparent role in mediation of neurotransmission[7,8] make the CB_1 receptor an interesting molecular target for CNS-directed drug discovery in the areas of both psychiatric and neurological disorders.[9,10] Several reviews provide a comprehensive overview[11,12] of the current status in the fast-moving cannabinoid research area including CB_1 receptor antagonists.[13–19]

The invention of SR141716A (rimonabant) by Sanofi-Synthelabo[20] as a CB_1/CB_2 subtype selective and orally active CB_1 receptor antagonist has stimulated the search for novel pyrazoles[21–23] and bioisosteres thereof[24–26] as cannabinoid CB_1 receptor antagonists. Rimonabant is in Phase III clinical development for the treatment of obesity and the facilitation of smoking cessation.

Recently, we disclosed[27] the CB_1 receptor antagonists SLV319 and SLV326. Both compounds exhibit high CB_1/CB_2 subtype selectivities and are orally active in CB_1 receptor-mediated pharmacological in vivo models.



In general, the known cannabinoid CB_1 receptor ligands are lipophilic compounds,[28,29] which limit their water solubility and may require sophisticated formulation methodology. In this paper, the design and synthesis of less lipophilic[30,31] structural analogues of SLV319 and SLV326 are described. It was envisaged that replacement of the arylsulfonyl group in the original series by a dialkylaminosulfonyl moiety would result in compounds of general formula **1** with lower lipophilicity and retained cannabinoid CB_1 antagonistic activity.

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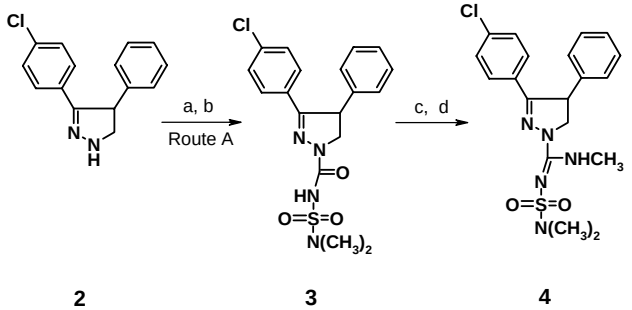
The novel CB_1 antagonists of general formula **1** were prepared via synthesis routes A–D.

Route A constitutes the coupling of 3,4-diarylpyrazoline[32] **2** with chlorosulfonylisocyanate, followed by nucleophilic attack of dimethylamine to produce the intermediate **3** in 58% yield (Scheme 1). Chlorination of **3** and subsequent reaction with methylamine gave compound **4**. Although this route seemed to be straightforward and the chlorination/amination sequence worked quite well in the synthesis of SLV319,[27] the conversion of **3** into **4** gave a disappointingly low yield of 18%.

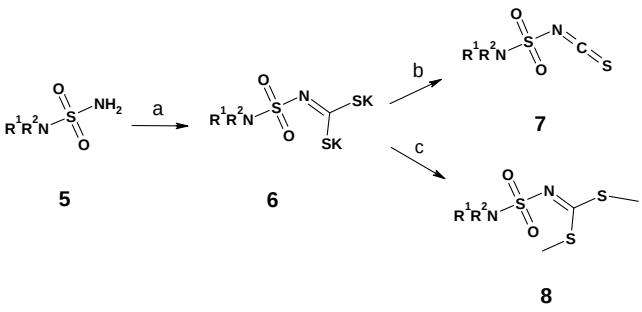
An alternative approach started from aminosulfonamides[33] **5**, which were converted into the corresponding dithioimidocarbamates **6** in yields ranging from 71 to 95% and subsequently reacted with diphosgene (Scheme 2). The isothiocyanates **7** were formed in 55–86% yield and reacted with pyrazoline **2** to furnish the intermediates **9** in 22–90% yield. The target compounds **11–17** were obtained from **9** by amination in the presence of $HgCl_2$ in 38–89% yield (Scheme 3, route B).

In route C, the intermediate **9** was S-alkylated[34] with methyl iodide to afford **10** in 78–95% yield. Subsequent nucleophilic attack by an amine R^3NH_2 gave the target compounds **19–22** in 81–95% yield (Scheme 3). Analogously, compound **18** was easily prepared from 3-(4-chlorophenyl)-4-(3-pyridyl)-4,5-dihydro-(1*H*)-pyrazole. Target compound **23** was synthesized via a slightly modified route (Scheme 3, Route D). The pyrazoline **2** was reacted with **8** (which was obtained from **6** by double *S*-methylation (Scheme 2)) to give intermediate **10** in 78% yield, which was reacted with methylamine to give **23** in 95% yield.

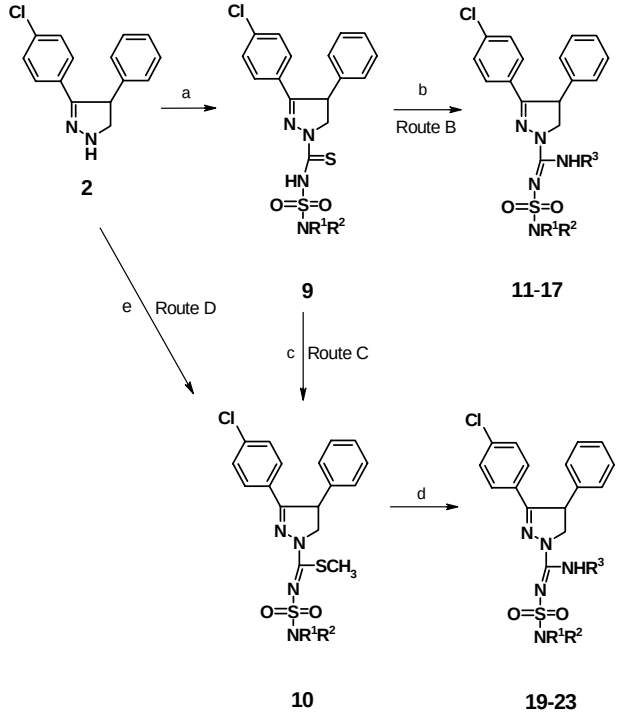
Since the 3,4-diarylpyrazoline moiety contains a chiral centre at its 4-position, the prepared target compounds **4** and **11–23** are racemates. It was reported[27] that the interaction of the structurally related SLV319 with the CB_1 receptor is highly stereoselective. Furthermore, it is interesting to note that both compound **21** and rimonabant contain a piperidin-1-yl moiety, which is anticipated to bind in the same region of the CB_1 receptor. To investigate further the stereochemical requirements for binding to the CB_1 receptor in this pyrazoline series, the racemic **21** was resolved by applying chiral preparative HPLC (stationary phase: Chiralpak AD (20 μm); mobile phase: CH_3OH/0.1% diethylamine) to furnish the optically pure enantiomers (−)-**24**[35] and (+)-**25.**



Scheme 1. Reagents and conditions: (a) $ClSO_2N{=}C{=}O$, CH_2Cl_2, 0 °C, 2 h; (b) $(CH_3)_2NH$, 0 °C, 2 h; (c) PCl_5, chlorobenzene, reflux, 1 h; (d) CH_3NH_2, CH_2Cl_2, rt, 2 h.



Scheme 2. Reagents and conditions: (a) CS_2, KOH, DMF, rt, 4 h; (b) diphosgene, CH_2Cl_2, rt, 20 h; (c) CH_3I, DMF, 0 °C, 2 h.



Scheme 3. Reagents and conditions: (a) **7**, CH_2Cl_2, rt, 2 h; (b) R^3NH_2, $HgCl_2$, CH_3CN, rt, 4 h; (c) CH_3I, Et_3N, acetone, rt, 16 h; (d) R^3NH_2, MeOH, rt, 2 h; (e) **8**, pyridine 100 °C, 40 h.

An X-ray diffraction analysis of **24** (which was crystallized from absolute ethanol) revealed[36] the 4*S* configuration at its C_4 pyrazoline ring atom. A stereoview of the X-ray diffraction result is shown in Figure 1.

The prepared set comprising of 16 target compounds for pharmacological evaluation is given in Table 1.

The CB_1 receptor affinities of the key compounds **4** and **11–25** were assessed in CB_1 and CB_2 receptor binding studies[27] (displacement of the specific binding of [^{3}H]CP-55,940 in CHO human CB_1 or CB_2 receptor transfected cells). CB_1 receptor antagonistic activities were determined in a functional cell assay[27] (blockade of CP-55,940 induced arachidonic acid release in CHO human CB_1 receptor transfected cells). CB_1 and CB_2

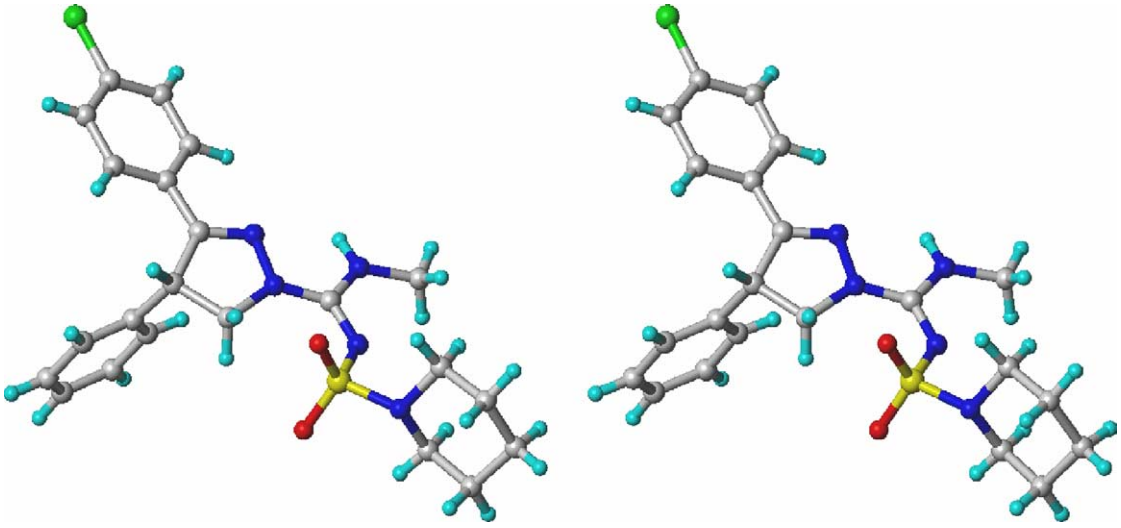
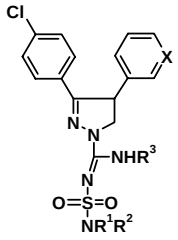


Figure 1. Stereoview of the X-ray diffraction result of **24**.

Table 1. Structural formula of prepared CB_1 receptor antagonists **4** and **11**–**25** and pharmacological in vitro results



Compound	X	R^1	R^2	R^3	$CB_{1\ rb}$[a,b]	$CB_{2\ rb}$[a,b]	$CB_{1\ funct}$[a,b]
Rimonabant					25.0 ± 15 (11.5)[15]	1580 ± 150 (1640)[15]	8.6 ± 0.1
SLV319					7.8 ± 1.4	7493 ± 126	9.9 ± 0.6
4	C	CH_3	CH_3	CH_3	223 ± 103	3835 ± 1015	8.3 ± 0.3
11	C	C_2H_5	C_2H_5	CH_3	30 ± 14	3270 ± 1208	8.6 ± 0.2
12	C	CH_3	*i*-C_3H_7	CH_3	32 ± 12	1126 ± 237	8.3 ± 0.3
13	C	CH_3	C_2H_5	CH_3	117 ± 81	1871 ± 1061	8.2 ± 0.3
14	C	$(CH_2)_4$		CH_3	231 ± 66	1601 ± 577	7.6 ± 0.2
15	C	$(CH_2)_6$		CH_3	155 ± 69	1032 ± 401	8.9 ± 0.2
16	C	$(CH_2)_7$		CH_3	125 ± 54	2584 ± 787	8.4 ± 0.1
17	C	$(CH_2)_2S(CH_2)_2$		CH_3	24 ± 14	3526 ± 1015	8.8 ± 0.2
18	N	C_2H_5	C_2H_5	CH_3	141 ± 48	9077 ± 923	7.5 ± 0.3
19	C	C_2H_5	C_2H_5	*i*-C_3H_7	60 ± 20	2755 ± 1148	8.7 ± 0.1
20	C	C_2H_5	C_2H_5	C_2H_5	209 ± 113	2864 ± 1080	8.5 ± 0.3
21	C	$(CH_2)_5$		CH_3	152 ± 68	1321 ± 264	8.7 ± 0.3
22	C	$(CH_2)_2O(CH_2)_2$		CH_3	75 ± 36	5372 ± 1392	8.0 ± 0.2
23	C	$(CH_2)_2S(O_2)(CH_2)_2$		CH_3	832 ± 168	n.d.[c]	8.1 ± 0.2
(*S*)-(−)-**24**	C	$(CH_2)_5$		CH_3	58 ± 19	3495 ± 968	8.7 ± 0.2
(*R*)-(+)-**25**	C	$(CH_2)_5$		CH_3	763 ± 148	n.d.[c]	7.5 ± 0.1

[a] $CB_{1\ rb}$, Displacement of specific CP-55,940 binding in CHO cells stably transfected with human CB_1 receptor, expressed as K_i ± SEM (nM); $CB_{2\ rb}$, displacement of specific CP-55,940 binding in CHO cells stably transfected with human CB_2 receptor, expressed as K_i ± SEM (nM); $CB_{1\ funct}$, CB_1 functional cell assay; [^{3}H]arachidonic acid release in CHO cells, expressed as pA_2 ± SEM values.

[b] All K_i and pA_2 values are mean values from at least three independent experiments.

[c] n.d., not determined.

receptor binding results are expressed as K_i values. The CB_1 antagonistic potencies of the compounds are expressed as pA_2 values.

The pharmacological results of the target compounds **4** and **11**–**25** and the reference compounds rimonabant and SLV319 are given in Table 1.

The CB_1 receptor binding data of the target compounds **4** and **11**–**13** revealed that their affinities depend on the NR^1R^2 substitution pattern. *N*,*N*-Diethyl and *N*-methyl-*N*-isopropyl substitution gave rise to strongly binding compounds. The target compounds **14**–**17** and **21**–**23** wherein the substituents R^1 and R^2 together with the attached nitrogen atom form a heterocyclic ring all elicited

CB_1 receptor affinity. The thiomorpholine analogue **17** displayed the highest affinity, whereas its SO_2 congener **23** was found to be considerably less active. The *S*-enantiomer **24** elicited a 13-fold higher affinity than its mirror image **25** for the CB_1 receptor, which is in line with earlier reported results in the original[27] pyrazoline series wherein SLV319 (which has the *S* configuration) showed an approximately 100-fold higher CB_1 receptor affinity than the corresponding *R* enantiomer.

Interestingly, the pyridyl analogue **18** has a substantially lower CB_1 receptor binding affinity than its phenyl-substituted counterpart **11**.

Variation in R^3 (compounds **11**, **19** and **20**) showed that the methyl group is superior to larger alkyl groups.

In general, the compounds in this series elicited considerable CB_1/CB_2 receptor subtype selectivities. Compound **17** showed the highest CB_1 binding affinity and was also found to be the most selective. Its selectivity (~147-fold) is comparable to the reported[20] selectivity of Sanofi's frontrunner rimonabant (~143-fold).

The results from the functional arachidonic acid release-based assay clearly revealed the strong CB_1 antagonistic properties of our target compounds. The azepanyl derivative **15** exhibited the strongest antagonistic potency ($pA_2 = 8.9$) in this series. The antagonistic potency of the eutomer **24** was found to be considerably higher than its mirror image **25**, which is in agreement with the observed CB_1 receptor affinity data.

The in vivo activity of the key dihydropyrazoles **11, 18**, **22** and **24** was investigated in two mechanistic pharmacological models, viz. a CB_1 agonist (CP-55,940) induced hypotension[27] rat model and a CB_1 agonist (WIN-55,212-2) induced hypothermia[27] mouse model, and compared with the known selective CB_1 receptor antagonists SLV319[27] and rimonabant. The log *P* value of the compounds was determined by a validated HPLC method.[27] The P-glycoprotein transport factor[37] of the compounds was also determined in vitro. The results are given in Table 2. They reveal that compounds **11, 22** and **24** elicited in vivo activities after oral administration in both the hypotension rat and hypothermia mouse models that are in line with their in vitro CB_1 activities.

The pyridyl analogue **18** was found to be inactive in the hypotension test, which is in line with its relatively low potency in our in vitro functional assay (Table 1). Moreover, **18** was identified as a P-glycoprotein substrate in vitro, which generally results in reduced CNS penetrability. The other compounds in this series lacked this undesirable property. This is in proper agreement with their in vivo activities in our (CNS-mediated) hypothermia mouse model.

The obtained log *P* values of compounds **11**, **18**, **22** and **24** are all lower than those of rimonabant and SLV319 (Table 2). Compound **18** displayed the lowest log *P* value due to the presence of its 3-pyridyl moiety.

Table 2. Pharmacological in vivo results and log *P* of key compounds

Compound	CB_{BP}[a]	CB_{TEMP}[b]	PGP[c]	log *P*[d]
Rimonabant	3.2	3	1.2	5.5
SLV319	5.5	3	1.4	5.1
11	20	3	1.5	4.8
18	>30	-	3.4	3.2
22	27	3	1.8	3.8
(*S*)-(−)-**24**	8	10	1.4	4.8

[a] Antagonism of CP-55,940 induced hypotension in rat expressed as ED_{50} (mg/kg po administration).
[b] Antagonism of WIN 55,212-2 induced hypothermia in mice expressed as least effective dose (LED, mg/kg po administration).
[c] P-glycoprotein-based membrane transport factor, expressed as the ratio of the bottom to top transport and top to bottom transport.
[d] Log *P* determination using a validated reverse-phase HPLC method.

The reported model for the binding of rimonabant in the CB_1 receptor,[38] based on the 2.8-Å X-ray structure[39] of bovine rhodopsin (Rho), was reconstructed. The original template was modified to the putative inactive R-state. The optimal receptor-based alignment of rimonabant[27] in this model was used as the starting point for aligning the minimized energy conformation of **24** with SLV319. The result is shown in Figure 2. The molecular fit of **24** and SLV319 revealed a high degree of overlap in this protein-based receptor model with comparable modes of interaction with the crucial Asp366-Lys192 salt bridge that has been reported[38] to govern CB_1 inverse agonistic activity. Further comparison with rimonabant (Fig. 3) reveals a closer overlap with the

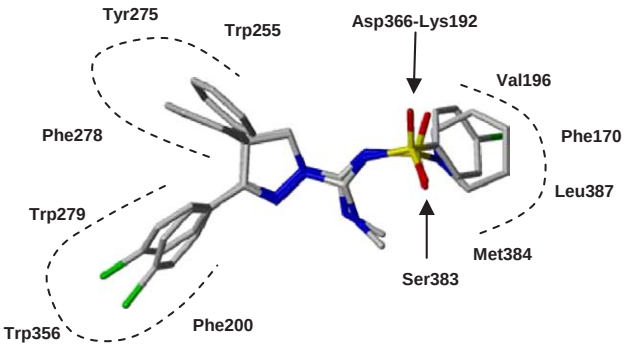


Figure 2. Alignment of SLV319 and **24** in the CB_1 receptor binding site.

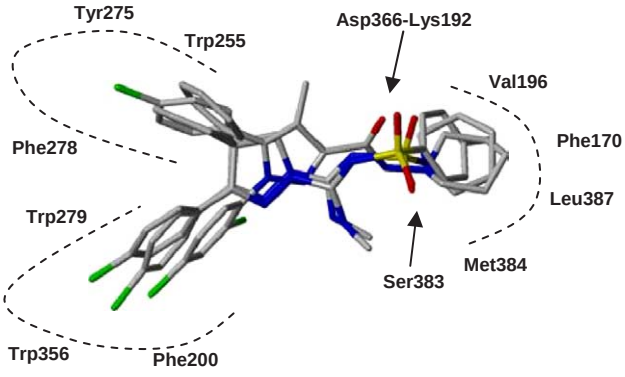


Figure 3. Alignment of rimonabant, SLV319 and **24** in the CB_1 receptor binding site.

exception of the 4-methyl group that is present in rimonabant and is lacking in both SLV319 and **24**. Furthermore, the amidine $NHCH_3$ moiety that is present in both SLV319 and **24** clearly has no counterpart in this molecular fit with rimonabant.

In conclusion, a series of novel 3,4-diarylpyrazolines with lower lipophilicity than the parent compounds SLV319, SLV326 and rimonabant was identified in vitro as potent and $CB_{1/2}$ subtype selective CB_1 receptor antagonists. Representative compounds shared favourable activities in vivo after oral administration.

Acknowledgments

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35. Analytical data for (*S*)-(−)-*N*-methyl-*N*-[(piperidin-1-yl)sulfonyl]-3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-(1*H*)-pyrazole-1-carboxamidine (**24**): $[\alpha_D^{25}] = -139$ (*c* 0.6, CH_3OH); mp 150–151 °C; ^1H NMR (600 MHz; DMSO-d_6) 1.41–1.46 (m, 2H), 1.53–1.60 (m, 4H), 2.94–3.00 (m, 4H), 3.04 (br s, 3H), 4.07 (br d, $J \sim 11$ Hz, 1H), 4.51 (t, $J \sim 11$ Hz, 1H), 5.00 (dd, $J \sim 11$ and 4 Hz, 1H), 7.21–7.26 (m, 3H), 7.30–7.34 (m, 2H), 7.38 (d, $J = 8$ Hz, 2H), 7.74 (d, $J = 8$ Hz, 2H); ESI^+-MS exact mass calcd for $C_{22}H_{27}ClN_5O_2S$ *m/z*, 460.1574 ([MH^+]), found: 460.1586. Anal. Calcd for $C_{22}H_{26}ClN_5O_2S$: C, 57.44; H, 5.70; N, 15.22. Found: C, 57.42; H 5.53; N, 15.23.
36. Selected crystallographic data for **24**: temperature: 150 K, wavelength: 0.71073 Å, X-ray exposure time: 6.6 h, crystal size: $0.10 \times 0.25 \times 0.35$ mm, crystal system: orthorhombic, space group: $P2_12_12_1$, unit cell dimensions: $a = 9.0320$; $b = 10.9733$; $c = 22.475$ Å, calculated density: 1.372 g cm^{-3}, completeness: 99.9%, total number of reflections: 65,533, number of unique reflections: 5109, number of refined parameters: 359. Flack *x*-parameter: 0.02.
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