Design, Synthesis and Biological Activity of Rigid Cannabinoid CB_1 Receptor Antagonists

Axel Reinhard Stoit, Jos Hubertus Maria Lange,* Arnold Peter den Hartog, Eric Ronken, Koos Tipker, Herman Heinrich van Stuivenberg, Jessica Adriana Rigtje Dijksman, Henri Cornelis Wals, and Chris Gerrit Kruse

Solvay Pharmaceuticals, Research Laboratories; P.O. Box 900, 1380 DA Weesp, The Netherlands.
Received January 24, 2002; accepted April 19, 2002

The design, synthesis and biological activities of potent pyrazole-based tricyclic CB_1 receptor antagonists (2) are described. The key synthetic step involves the ring closure of the lithiated α,γ-keto ester adduct (4). The optimal nitroderivative (28) in this series exhibits a high CB_1 receptor affinity ($pK_i=7.2$) as well as very potent antagonistic activity ($pA_2=8.8$) *in vitro*. The regioselectivity of the pyrazole ring closure is shown to depend strongly on the aromatic substitution pattern of the applied arylhydrazine.

Key words benzocycloheptapyrazole; CB_1 receptor antagonist; molecular modeling; regiochemistry

Cannabinoids are present in the Indian hemp *Cannabis sativa* and have been used as medicinal agents for centuries.[1,2] However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on CB receptors and their (endogenous) agonists. The discovery and the subsequent cloning[3,4] of two subtypes of cannabinoid receptor (CB_1 and CB_2) stimulated the search for novel cannabinoid antagonists and triggered the development of cannabinoid drugs for the treatment of diseases.[5,6]

Several types of CB_1 receptor antagonists are known (Fig. 1). Sanofi disclosed[7—9] their selective CB_1 receptor antagonist SR141716A (rimonabant) which is currently undergoing clinical development for psychotic disorders and obesity treatment. Iodopravadoline AM-630 was introduced in 1995. AM-630 is a moderately active CB_1 receptor antagonist, but sometimes behaves as a weak partial agonist.[10] Researchers from Eli Lilly described[11] the selective CB_1 receptor antagonist LY-320135. 3-Alkyl-5,5′-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated[12] to be cannabinoid antagonists. CP-272871 is a pyrazole derivative, like SR141716A, but less potent and less CB_1 receptor subtype-selective[13] than SR141716A. Recently, Aventis Pharma claimed[14] diarylmethyleneazetidine analogs (**1**) as CB_1 receptor antagonists. Interestingly, many CB_1 receptor antagonists have been reported[15] to behave as inverse agonists *in vitro*. Several reviews describe the current status in the cannabinoid research area.[16—19]

In this paper our approach to tricyclic selective CB_1 receptor antagonists of general formula (**2**) is described.[20] We envisioned that an additional ring constraint from the 4-methyl position in SR141716A to the *ortho*-position of its 5-aryl substituent would provide a novel class of considerably more rigid benzocycloheptapyrazoles (**2**), thereby having good prospects as potent CB_1 antagonists. Moreover, threedimensional comparison of SR141716A with the more rigid counterpart (**2**) and analysis of their pharmacological results is expected to provide a more detailed insight in the required bioactive conformation of such CB_1 receptor antagonists, which is expected to facilitate their rational structure optimisation.

Chemistry

The four step synthesis route to the CB_1 antagonists (**2**) is exemplified by the preparation of **8** (Chart 1). Commercially available 1-benzosuberone (**3**) was deprotonated with lithium bis(trimethylsilyl)amide and subsequently reacted with diethyl oxalate to afford the lithiated keto ester adduct (**4**) as a solid in 99% yield. Subsequent reaction with the arylhydrazine (**5**) in acetic acid gave the benzocycloheptapyrazole ester (**6**) in 51% yield. Mild basic hydrolysis of the carboethoxy group in **6** to the corresponding carboxylic acid proceeded quantitatively. 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC)-activated coupling to *N*-aminoperhydroazepine (**7**) in dichloromethane furnished **8** in 68% yield.

In this specific case the pyrazole ring formation proceeds regioselectively to afford **6** as the sole product. However, as we extended the scope to the reaction of Li-enolate (**4**) with differently substituted arylhydrazines, it was found that the regioselectivity in the pyrazole ring formation is very dependent on the aromatic substitution pattern of the applied arylhydrazine. This phenomenon[21] is exemplified in Chart 2 for

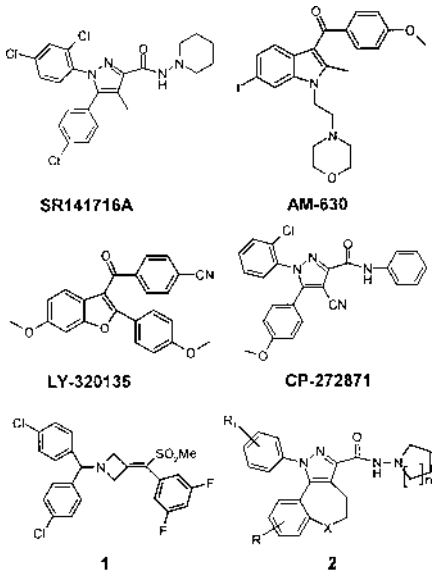
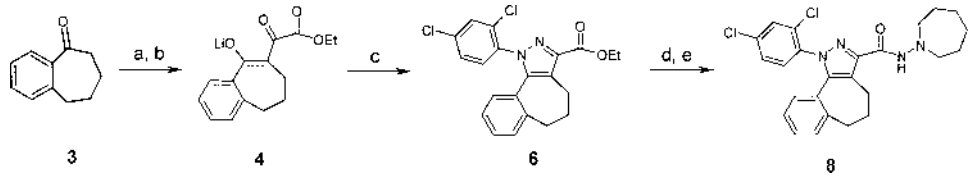


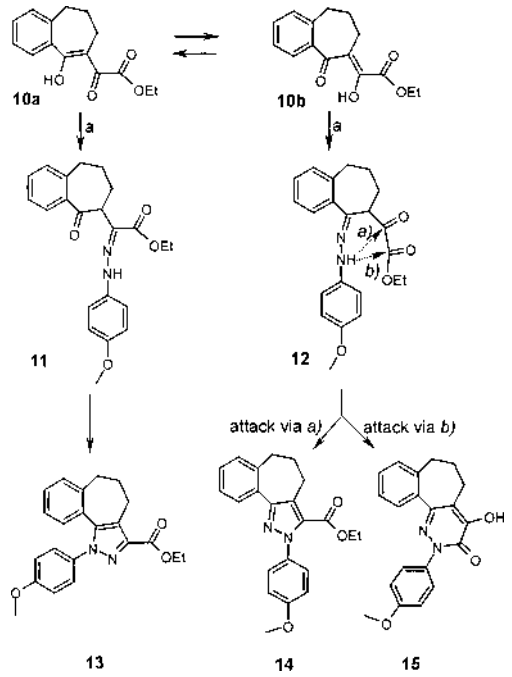
Fig. 1. Chemical Structures of CB_1 Receptor Antagonists

* To whom correspondence should be addressed. e-mail: jos.lange@solvay.com



a) LiHMDS, *n*-hexane; b) diethyl oxalate; c) 2,4-dichlorophenylhydrazine hydrochloride **5**, HOAc; d) LiOH, THF, H_2O; e) 1-aminohexahydro-1*H*-azepine **7**, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC).

Chart 1



a) 4-methoxyphenylhydrazine hydrochloride **9**, HOAc.

Chart 2

the reaction of the Li-enolate (**4**) with 4-methoxyphenylhydrazine (**9**). This reaction yielded a mixture of three products (**13**), (**14**) and (**15**) in 15, 17 and 46% yield, respectively.

The formation of **13**, **14** and **15** can be rationalised by invoking the three pathways depicted in Chart 2. Reaction of the enol tautomer (**10a**) with 4-methoxyphenylhydrazine (**9**) leads to the hydrazone intermediate (**11**) which cyclises to **13**. However, the reaction of the alternative enol tautomer (**10b**) with **9** gives the hydrazone (**12**). The resulting intermediate (**12**) may cyclise *via* route a) to the pyrazole (**14**), or cyclise *via* route b) to the hydroxypyridazinone analogue (**15**). The corresponding reaction with 3-fluorophenylhydrazine gives the same regiochemical outcome. This observation suggests that the regiochemistry of this cyclisation reaction is not simply governed by the electronic properties of the aryl substituent(s) in the applied arylhydrazine. Further derivatisation of the benzocycloheptapyrazoles was accomplished according to Chart 3.

Nitration of the acid[20] (**16**) gave a mixture of the 8- and 9-nitroisomer (**17**) in a yield of 98%. Reaction of this mixture of regioisomers with 1-aminopiperidine in the presence of HBTU, followed by HPLC separation of the resulting regioisomers, furnished hydrazide (**18**) in 52% yield. Nitro group reduction afforded **19** in 91% yield. The hydrazide[20] (**20**) was formed in 20% yield from **19** *via* a Sandmeyer reaction. This low yield is due to partial overreduction of **20** to **21**.

In this series a number of compounds was prepared for pharmacological evaluation (Table 1).

Biological Evaluation and Discussion

The CB_1 receptor affinities of thirteen compounds (**8**, **18**, **20**—**30**) were assessed in receptor binding studies (displacement of the specific binding of the CB receptor ligand [^{3}H]CP-55,940 to the human CB_1 receptor cloned in Chinese hamster ovary (CHO) cells). CB_1 receptor antagonistic activities were determined in a functional cell assay (blockade of the CB agonist CP-55,940 induced c-AMP formation in CHO cells, wherein the human CB_1 receptor has been cloned). CB_1 receptor binding results are expressed as pK_i values. The CB_1 antagonistic potencies of the compounds are expressed as pA_2 values.

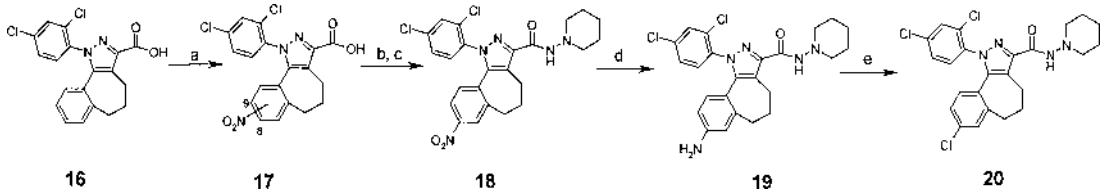
The pharmacological results of the compounds (**8**, **18**, **20**—**30**) are summarized in Table 2.

Our investigations started with compound (**21**). This compound is found less active than SR141716A in both assays. Compound (**8**), wherein the piperidinyl ring of **21** is replaced by the hexahydroazepinyl ring, behaves as a somewhat more potent CB_1 receptor antagonist *in vitro* as compared to **21**. However, this compound is still considerably less potent than SR141716A. These findings prompted to design **20**, which has exactly the aromatic chloro substitution pattern of SR141716A. Compound (**20**) exhibits a decreased CB_1 receptor binding affinity as compared to the binding of SR141716A. However, its CB_1 antagonistic potency is comparable. Compound (**25**) wherein the piperidinyl ring of **20** is replaced by the hexahydroazepinyl ring shows the same activity profile. Nitro substitution at the 8-position gives rise to **18** and **28**, respectively. Both **18** and **28** are very potent CB_1 receptor antagonists, showing nanomolar activities in our CB_1 functional assay.

Structural comparison by molecular modeling analysis of the closest structural analogue (**20**) with SR141716A gives some interesting results (Fig. 2). Both **20** and SR141716A were minimised using the MOPAC/PM3 module of the SYBYL package, version 6.3 (Tripos Associates, Inc., St. Louis, U.S.A.) on a Silicon Graphics Indigo2, Impact 10000.

As can be seen the difference in spatial conformation between both molecules is relatively small. This modeling result would predict comparable cannabinoid activities of the compounds. This is in line with the results from our functional CB_1 antagonist assay. However, SR141716A is considerably more potent than its tricyclic congeners in the CB_1 receptor binding assay.

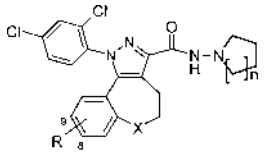
SR141716A has been reported[9] orally active *in vivo*. It is



a) HNO_3, HOAc; b) 1-aminopiperidine, HBTU; c) chromatographic separation of regioisomers; d) Fe/HCl, EtOH, H_2O; e) $NaNO_2$, CuCl, H_2O.

Chart 3

Table 1. Structural Formula of Prepared CB_1 Receptor Antagonists



Compds.	R	X	*n*
8	H	CH_2	3
18	8-NO_2	CH_2	2
20	8-Cl	CH_2	2
21	H	CH_2	2
22	H	CH_2	4
23	H	O	2
24	H	O	3
25	8-Cl	CH_2	3
26	9-Cl	CH_2	2
27	9-Cl	CH_2	3
28	8-NO_2	CH_2	3
29	9-NO_2	CH_2	2
30	9-NO_2	CH_2	3

Table 2. Pharmacological Results

Compds.	$CB_{1\ rb}$ *a,b)*	$CB_{1\ funct}$ *a,b)*
SR141716A	7.6	8.6
8	7.0	7.5
18	6.8	8.9
20	6.9	8.5
21	6.4	7.2
22	6.7	7.2
23	6.3	7.0
24	6.4	7.0
25	6.9	8.8
26	6.6	7.3
27	6.5	7.4
28	7.2	8.8
29	6.3	7.8
30	7.1	7.3

a) $CB_{1\ rb}$: CB_1 receptor binding (pK_i): $CB_{1\ funct}$: CB_1 functional cell assay (pA_2). *b*) All pK_i and pA_2 values are mean values from at least three independent experiments.

interesting to note that compound (**20**) showed neither *in vivo* activity after oral nor i.p. dosing These results prompted to investigate the bioavailability in our series CB_1 antagonists of general formula (**2**) in more detail. After administration of compound (**8**), blood plasma levels in rat were found negligible (<50 ng/ml) at 1 h after *p.o.* (30 mg/kg) and i.p. administration (30 mg/kg), respectively. The low bioavailability of **8** might be ascribed[22] to either its low rate of water dissolution in combination with a poor water solubility or its high lipophilicity (LogP *ca.* 5.9). This bioavailability issue has to be investigated in more detail.

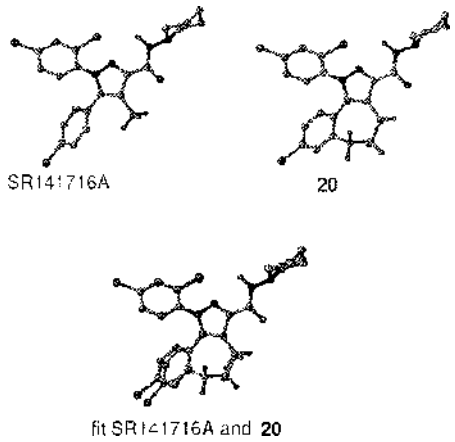


Fig. 2. Molecular Modeling Results of SR141716A and **20**

In conclusion, benzocycloheptapyrazoles (**2**) constitute a class of very potent CB_1 receptor antagonists *in vitro*. The bioavailability issue in this series of rigid cannabinoid receptor antagonists deserves further attention.

Experimental

^{1}H- and ^{13}C-NMR spectra were recorded on a Varian UN400 instrument (400 MHz), using DMSO-d_6 or $CDCl_3$ with $(CH_3)_4Si$ as an internal standard, as solvents. Chemical shifts are given in ppm (δ scale). Thin-layer chromatography was performed on Merck precoated 60 F_{254} plates, and spots were visualised with UV light. Column chromatography was performed using silica gel 60 (0.040—0.063 mm, Merck). Melting points were recorded on a Büchi B-545 melting point apparatus and are uncorrected. Mass spectra were recorded with a Micromass GCT or Kratos Concept 1S instrument (compounds (**8**) and (**15**)).

1-(2,4-Dichlorophenyl)-*N*-(hexahydro-1*H*-azepin-1-yl)-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (8) To a cooled solution (0 °C) of **16**[20] (0.70 g, 1.88 mmol) in dichloromethane (15 ml) was successively added 1-aminohexahydro-1*H*-azepine (0.24 ml, 2.07 mmol) and EDC (0.4 g, 2.09 mmol). The resulting solution was allowed to attain room temperature and stirred for 48 h. After addition of brine, followed by extraction with $CHCl_3$, the organics were washed with brine and dried over Na_2SO_4. The product was purified by column chromatography (Et_2O/petroleum ether=1/2 (v/v)) to give **8** (0.60 g, 68%), mp 115—118 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.62—1.68 (m, 4H), 1.72—1.82 (m, 4H), 2.22—2.30 (m, 2H), 2.69 (t, *J*=7 Hz, 2H), 2.80—3.12 (m, 2H), 3.15—3.19 (m, 4H), 6.65 (br d, *J*=8 Hz, 1H), 7.03 (td, *J*=8, 2 Hz, 1H), 7.21 (td, *J*=8, 2 Hz, 1H), 7.30 (br d, *J*=8 Hz, 1H), 7.39 (dd, *J*=8, 2 Hz, 1H), 7.44 (d, *J*=2 Hz, 1H), 7.47 (d, *J*=8 Hz, 1H), 8.13 (br s, 1H). ^{13}C-NMR (DMSO-d_6) δ: 20.0, 26.7, 26.9, 31.8, 32.1, 57.7, 121.3, 126.5, 127.1, 128.89, 128.92, 129.1, 130.1, 130.2, 132.15, 132.23, 135.2, 136.4, 141.6, 142.9, 144.0, 159.9. Electron impact (EI)-MS *m/z*: 468 (M^+) (9), 355 (25), 98 (100). High resolution (HR)-EI-MS *m/z*: 468.1527 (Calcd for $C_{25}H_{26}Cl_2N_4O$: 468.1484).

Synthesis of 13, 14 and 15 Lithium hexamethyldisilazide (83 ml, 1 M solution in *n*-hexane (THF)) was dissolved in dry Et_2O (250 ml) at −78 °C under a nitrogen atmosphere. A solution of 1-benzosuberone (13.3 g,

83.1 mmol) in dry ether (50 ml) was slowly added. The resulting solution is stirred for 30 min at −73 °C and 15 min at 0 °C and cooled to −78 °C. A solution of dimethyl oxalate (11.0 g, 93 mmol) in Et_2O/THF was quickly added. The resulting mixture was allowed to attain room temperature and stirred overnight. The formed precipitate (**4**) (20.9 g, 99%) was collected by filtration and thoroughly washed with Et_2O. Part of the precipitate (1.3 g, 4.89 mmol) was dissolved in acetic acid (20 ml), followed by addition of 4-methoxyphenylhydrazine hydrochloride (0.80 g, 4.58 mmol). The resulting mixture was heated at 100 °C for 15 min, concentrated *in vacuo*, followed by ethylacetate addition. The organics were washed with saturated $NaHCO_3$ solution and dried over Na_2SO_4. Separation by column chromatography (Et_2O/petroleum ether=1/3 (v/v)) gave pure **13** (0.25 g, 15%) and **14** (0.28 g, 17%), respectively, followed by elution with (MeOH/ethylacetate=1/4 (v/v)) to give **15** (0.7 g, 46%).

Ethyl 1-(4-Methoxyphenyl)-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxylate (**13**): mp 95—97 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.35 (t, J=7 Hz, 3H), 2.13—2.22 (m, 2H), 2.68 (t, J=7 Hz, 2H), 2.75 (t, J=7 Hz, 2H), 3.80 (s, 3H), 4.34 (q, J=7 Hz, 2H), 6.71 (d, J=8 Hz, 1H), 6.97 (d, J=8 Hz, 2H), 7.08 (t, J=8 Hz, 1H), 7.22—7.28 (m, 3H), 7.38 (d, J=8 Hz, 1H). EI-MS m/z: 362 (M^+) (70), 316 (45), 289 (88), 288 (100). HR-EI-MS m/z: 362.1637 (Calcd for $C_{22}H_{22}N_2O_3$: 362.1630).

Ethyl 2-(4-Methoxyphenyl)-2,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxylate (**14**): mp 89 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (t, J=7 Hz, 3H), 2.02—2.10 (m, 2H), 2.79—2.85 (m, 2H), 3.01 (t, J=7 Hz, 2H), 3.84 (s, 3H), 4.17 (q, J=7 Hz, 2H), 7.01 (d, J=8 Hz, 2H), 7.21—7.26 (m, 3H), 7.37 (d, J=8 Hz, 2H), 7.93—7.98 (m, 1H). EI-MS m/z: 362 (M^+) (100), 333 (35), 289 (24). HR-EI-MS m/z: 362.1653 (Calcd for $C_{22}H_{22}N_2O_3$: 362.1630).

4-Hydroxy-2-(4-methoxyphenyl)-2,5,6,7-tetrahydro-3*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazin-3-one (**15**): mp >245 °C. ^{1}H-NMR (DMSO-d_6, 120 °C) δ: 1.94—2.02 (m, 2H), 2.43 (t, J=7 Hz, 2H), 2.60 (t, J=7 Hz, 2H), 3.80 (s, 3H), 6.92 (d, J=8 Hz, 2H), 7.16—7.30 (m, 3H), 7.51 (dd, J=8, 2 Hz, 1H), 7.57 (d, J=8 Hz, 2H), 4-OH proton is not visible. ^{13}C-NMR (DMSO-d_6) δ: 20.9, 29.2, 31.1, 55.2, 113.2, 126.1, 126.5, 127.6, 128.3, 128.4, 135.5, 137.8, 138.9, 151.6, 158.0, 161.5, 162.8. EI-MS m/z: 334 (M^+) (100). HR-EI-MS m/z: 334.1356 (Calcd for $C_{20}H_{18}N_2O_3$: 334.1317).

Synthesis of 18 and 29 Pure nitric acid (40 ml) is slowly added to cooled (0 °C) acetic acid (40 ml). Acid (**16**)[20] (13.77 g, 36.9 mmol) is added and the resulting mixture is stirred at room temperate overnight and poured onto ice. The formed precipitate is collected by filtration, washed with water and dried to give crude **17** (15.12 g, 98%) which consists of the 8-nitro and 9 nitro-regiosomer in a molar ratio of 4 : 3. To a suspension of crude **17** (6.27 g, 0.015 mol) in dry acetonitrile (120 ml) is successively added diisopropyl ether (5.75 ml, 0.033 mol), HBTU (6.82 g, 0.018 mol) and 1-aminopiperidine (1.94 ml, 0.018 mol) and the resulting mixture is stirred at room temperature overnight. The mixture is concentrated *in vacuo* and the residue is dissolved in ethylacetate, washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Chromatographic purification (Et_2O) gave **18** (3.90 g, 52%) and **29** (2.21 g, 29%), respectively.

1-(2,4-Dichlorophenyl)-8-nitro-*N*-(piperidin-1-yl)-1,4,5,6-tetrahydrobenzo-[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (**18**): mp 179—182 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.48 (m, 2H), 1.70—1.82 (m, 4H), 2.26—2.36 (m, 2H), 2.76—2.92 (m, 6H), 3.20—3.60 (m, 2H), 6.80 (d, J=8 Hz, 1H), 7.42—7.55 (m, 3H), 7.67 (br s, 1H), 7.90 (dd, J=8, 2 Hz, 1H), 8.20 (d, J=2 Hz, 1H). ^{13}C-NMR (DMSO-d_6) δ: 20.4, 23.7, 26.1, 31.7, 32.2, 55.9, 122.1, 123.2, 125.2, 128.6, 129.5, 130.5, 132.2, 132.5, 135.9, 136.07, 136.12, 141.3, 144.0, 144.6, 147.5, 159.7. EI-MS m/z: 499 (M^+) (12), 400 (100), 371 (65), 84 (36). HR-EI-MS m/z: 499.1159 (Calcd for $C_{24}H_{23}Cl_2N_5O_3$: 499.1178).

1-(2,4-Dichlorophenyl)-9-nitro-*N*-(piperidin-1-yl)-1,4,5,6-tetrahydrobenzo-[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (**29**): mp 201—203 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.48 (m, 2H), 1.73—1.80 (m, 4H), 2.22—2.38 (m, 2H), 2.81 (t, J=7 Hz, 2H), 2.85—2.91 (m, 4H), 3.20—3.60 (m, 2H), 7.43 (d, J=2 Hz, 1H), 7.45—7.51 (m, 2H), 7.54 (d, J=2 Hz, 1H), 7.59 (d, J=8 Hz, 1H), 7.67 (br s, 1H), 8.07 (dd, J=8, 2 Hz, 1H). EI-MS m/z: 499 (M^+) (11), 400 (70), 371 (59), 99 (62), 84 (100). HR-EI-MS m/z: 499.1168 (Calcd for $C_{24}H_{23}Cl_2N_5O_3$: 499.1178).

8-Chloro-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (20) Iron powder (3.5 g) was suspended in a mixture of water (40 ml) and ethanol (15 ml). HCl (2.2 ml, 1 N) was added and the resulting mixture was stirred at 50 °C. After addition of **18** (2.91 g, 5.82 mmol) the mixture was heated for 3 h at 65 °C. After cooling to room temperature ethylacetate and water were added and the iron-containing precipitate was removed by filtration over hyflo. The ethylacetate layer was separated, washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude **19** (2.83 g). Column chromatography (CH_2Cl_2/acetone=4/1 (v/v)) gave the intermediate **19** (2.50 g, 91%) as a syrup. Addition of **19** (2.50 g, 5.32 mmol) to cooled concentrated HCl (40 ml) was followed by addition at 0 °C of a solution of $NaNO_2$ (0.37 g, 5.37 mmol) in water (2 ml). This solution was stirred at 0 °C for 30 min and quickly added to a cooled solution of CuCl (0.27 g, 2.75 mmol) in concentrated HCl (5 ml). The resulting mixture was heated at 55 °C for 1 h, cooled to room temperature, followed by addition of ice and ethylacetate. A mixture of ice and concentrated NaOH was added. The ethylacetate layer was separated and the water layer extracted with ethylacetate. The combined ethylacetate layers were filtered over hyflo, washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in diethyl ether and impurities removed by filtration and the filtrate was concentrated *in vacuo*. Column chromatograpy (CH_2Cl_2/acetone=9/1 (v/v)) gave **20** (0.51 g, 20%) and **21** (0.29 g, 12%), respectively. Compound (**20**): mp 204—205 °C, lit.[20] mp 202 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.48 (m, 2H), 1.71—1.80 (m, 4H), 2.20—2.30 (m, 2H), 2.66 (t, J=7 Hz, 2H), 2.82—2.91 (m, 4H), 3.00—3.40 (m, 2H), 6.57 (d, J=8 Hz, 1H), 7.00 (dd, J=8, 2 Hz, 1H), 7.30 (d, J=2 Hz, 1H), 7.41 (dd, J=8, 2 Hz, 1H), 7.44 (d, J=2 Hz, 1H), 7.47 (d, J=8 Hz, 1H), 7.68 (br s, 1H). EI-MS m/z: 488 (M^+) (15), 389 (57), 362 (82), 360 (76), 84 (100). HR-EI-MS m/z: 488.0901 (Calcd for $C_{24}H_{23}Cl_3N_4O$: 488.0937).

1-(2,4-Dichlorophenyl)-*N*-(piperidin-1-yl)-1,4,5,6-tetrahydrobenzo-[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (21) Procedure as for the preparation of compound (**8**) gave **21**, mp 167—169 °C, lit.[20] mp 170 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.39—1.47 (m, 2H), 1.71—1.79 (m, 4H), 2.21—2.30 (m, 2H), 2.68 (t, J=7 Hz, 2H), 2.80—3.30 (m, 6H), 6.64 (br d, J=8 Hz, 1H), 7.01 (td, J=8, 2 Hz, 1H), 7.20 (td, J=8, 2 Hz, 1H), 7.29 (br d, J=8 Hz, 1H), 7.39 (dd, J=8, 2 Hz, 1H), 7.43 (d, J=2 Hz, 1H), 7.46 (d, J=8 Hz, 1H), 7.68 (br s, 1H). EI-MS m/z: 454 (M^+) (10), 355 (55), 326 (90), 84 (100). HR-EI-MS m/z: 454.1288 (Calcd for $C_{24}H_{24}Cl_2N_4O$: 454.1327).

***N*-(Azocan-1-yl)-1-(2,4-dichlorophenyl)-1,4,5,6-tetrahydrobenzo[6,7]-cyclohepta[1,2-*c*]pyrazole-3-carboxamide (22)** Procedure as for the preparation of compound (**8**) gave **22**, mp 118 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.64—1.76 (m, 10H), 2.22—2.31 (m, 2H), 2.68 (t, J=7 Hz, 2H), 2.76—3.06 (m, 2H), 3.10—3.16 (m, 4H), 6.65 (br d, J=8 Hz, 1H), 7.02 (td, J=8, 2 Hz, 1H), 7.21 (td, J=8, 2 Hz, 1H), 7.30 (br d, J=8 Hz, 1H), 7.38 (dd, J=8, 2 Hz, 1H), 7.43 (d, J=2 Hz, 1H), 7.46 (d, J=8 Hz, 1H), 8.18 (br s, 1H). EI-MS m/z: 482 (7), 355 (75), 112 (100). (M^+) HR-EI-MS m/z: 482.1616 (Calcd for $C_{26}H_{28}Cl_2N_4O$: 482.1640).

1-(2,4-Dichlorophenyl)-6-oxa-*N*-(piperidin-1-yl)-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (23) Procedure as for the preparation of compound (**8**) starting from 1-oxa-5-benzosuberone gave **23** as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.38—1.45 (m, 2H), 1.68—1.78 (m, 4H), 2.80—2.88 (m, 4H), 3.47 (t, J=7 Hz, 2H), 4.38 (t, J=7 Hz, 2H), 6.67 (br d, J=8 Hz, 1H), 6.80 (td, J=8, 2 Hz, 1H), 7.11 (br d, J=8 Hz, 1H), 7.17 (td, J=8, 2 Hz, 1H), 7.31 (d, J=8 Hz, 1H), 7.36 (dd, J=8, 2 Hz, 1H), 7.52 (d, J=2 Hz, 1H), 7.65 (br s, 1H). EI-MS m/z: 456 (M^+) (8), 358 (100), 84 (74). HR-EI-MS m/z: 456.1111 (Calcd for $C_{23}H_{22}Cl_2N_4O_2$: 456.1120).

1-(2,4-Dichlorophenyl)-*N*-(hexahydro-1*H*-azepin-1-yl)-6-oxa-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (24) Procedure as for the preparation of compound (**8**) starting from 1-oxa-5-benzosuberone gave **24** as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.67 (m, 4H), 1.71—1.79 (m, 4H), 3.12—3.17 (m, 4H), 3.49 (t, J=7 Hz, 2H), 4.40 (t, J=7 Hz, 2H), 6.69 (br d, J=8 Hz, 1H), 6.82 (td, J=8, 2 Hz, 1H), 7.12 (br d, J=8 Hz, 1H), 7.19 (td, J=8, 2 Hz, 1H), 7.32 (d, J=8 Hz, 1H), 7.37 (dd, J=8, 2 Hz, 1H), 7.52 (d, J=2 Hz, 1H), 8.10 (br s, 1H). EI-MS m/z: 470 (M^+) (6), 358 (92), 98 (100). HR-EI-MS m/z: 470.1255 (Calcd for $C_{24}H_{24}Cl_2N_4O_2$: 470.1276).

8-Chloro-1-(2,4-dichlorophenyl)-*N*-(hexahydro-1*H*-azepin-1-yl)-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (25) Procedure as for the preparation of compound (**20**) gave **25**, mp 162—164 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.68 (m, 4H), 1.72—1.81 (m, 4H), 2.21—2.31 (m, 2H), 2.66 (t, J=7 Hz, 2H), 3.14—3.50 (m, 6H), 6.57 (d, J=8 Hz, 1H), 7.01 (dd, J=8, 2 Hz, 1H), 7.30 (d, J=2 Hz, 1H), 7.40 (dd, J=8, 2 Hz, 1H), 7.44 (d, J=2 Hz, 1H), 7.47 (d, J=8 Hz, 1H), 7.80—8.60 (m, 1H). EI-MS m/z: 502 (M^+) (8), 389 (78), 98 (100). HR-EI-MS m/z: 502.1086 (Calcd for $C_{25}H_{25}Cl_3N_4O$: 502.1094).

9-Chloro-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (26) Procedure as for the preparation of compound (**20**) gave **26**, mp 232—234 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.48 (m, 2H), 1.72—1.80 (m, 4H), 2.20—2.30 (m, 2H),

2.65 (t, J=7 Hz, 2H), 2.84—3.40 (m, 6H), 6.61 (d, J=2 Hz, 1H), 7.18 (dd, J=8, 2 Hz, 1H), 7.23 (d, J=8 Hz, 1H), 7.43 (dd, J=8, 2 Hz, 1H), 7.46 (d, J=2 Hz, 1H), 7.50 (d, J=8 Hz, 1H), 7.64—7.74 (m, 1H). EI-MS m/z: 488 (M^+) (6), 362 (37), 84 (100). HR-EI-MS m/z: 488.0921 (Calcd for $C_{24}H_{23}Cl_3N_4O$: 488.0937).

9-Chloro-1-(2,4-dichlorophenyl)-*N*-(hexahydro-1*H*-azepin-1-yl)-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (27) Procedure as for the preparation of compound (**20**) gave **27**, mp 150 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.62—1.67 (m, 4H), 1.72—1.80 (m, 4H), 2.20—2.28 (m, 2H), 2.65 (t, J=7 Hz, 2H), 3.14—3.18 (m, 4H), 3.50—3.80 (m, 2H), 6.61 (d, J=2 Hz, 1H), 7.18 (dd, J=8, 2 Hz, 1H), 7.23 (d, J=8 Hz, 1H), 7.43 (dd, J=8, 2 Hz, 1H), 7.46 (d, J=2 Hz, 1H), 7.49 (d, J=8 Hz, 1H), 8.45 (br s, 1H). EI-MS m/z: 502 (M^+) (6), 389 (62), 98 (100). HR-EI-MS m/z: 502.1049 (Calcd for $C_{25}H_{25}Cl_3N_4O$: 502.1094).

1-(2,4-Dichlorophenyl)-*N*-(hexahydro-1*H*-azepin-1-yl)-8-nitro-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (28) Procedure as for the preparation of compound (**18**) gave **28** as an amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.62—1.68 (m, 4H), 1.70—1.82 (m, 4H), 2.26—2.37 (m, 2H), 2.80 (t, J=7 Hz, 2H), 3.14—3.18 (m, 4H), 3.22—3.56 (m, 2H), 6.80 (d, J=8 Hz, 1H), 7.42—7.46 (m, 2H), 7.53 (d, J=8 Hz, 1H), 7.89 (dd, J=8, 2 Hz, 1H), 8.12 (br s, 1H), 8.19 (d, J=2 Hz, 1H). EI-MS m/z: 513 (M^+) (7), 400 (47), 98 (100). HR-EI-MS m/z: 513.1291 (Calcd for $C_{25}H_{25}Cl_2N_5O_3$: 513.1334).

1-(2,4-Dichlorophenyl)-*N*-(hexahydro-1*H*-azepin-1-yl)-9-nitro-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (30) Procedure as for the preparation of compound (**29**) gave **30**, mp 191—193 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.62—1.70 (m, 4H), 1.72—1.80 (m, 4H), 2.25—2.35 (m, 2H), 2.70—2.90 (m, 4H), 3.14—3.20 (m, 4H), 7.42—7.50 (m, 3H), 7.54 (d, J=2 Hz, 1H), 7.59 (d, J=8 Hz, 1H), 8.07 (dd, J=8, 2 Hz, 1H), 8.11 (br s, 1H). EI-MS m/z: 513 (M^+) (19), 400 (89), 371 (32), 98 (100). HR-EI-MS m/z: 513.1318 (Calcd for $C_{25}H_{25}Cl_2N_5O_3$: 513.1334).

Acknowledgements Mrs. Alice Borst and Mr. Karel Stegman are gratefully acknowledged for supply and interpretation of the spectral data.

References and Notes

1) Pertwee R. G., *Forsch. Komplementärmed.*, **6**, 12—15 (1999).
2) "Cannabinoid Receptors," ed. by Pertwee R. G., Academic Press, London, 1995.
3) Matsuda L. A., Lolait S. J., Brownstein B. J., Young A. C., Bonner T. I., *Nature* (London), **356**, 561—564 (1990).
4) Munro S., Thomas K. L., Abu-Shaar M., *Nature* (London), **365**, 61—62 (1993).
5) Consroe P., *Neurobiol. Dis.*, **5**, 534—551 (1998).
6) Williamson E. M., Evans F. J., *Drugs*, **60**, 1303—1314 (2000).
7) Lan R., Liu Q., Fan P., Lin S., Fernando S. R., McCallion D., Pertwee R., Makriyannis A., *J. Med. Chem.*, **42**, 769—776 (1999).
8) Nakamura-Palacios E. M., Moerschbaecher J. M., Barker L. A., *CNS Drug Rev.*, **5**, 43—58 (1999).
9) Kendall D., *Curr. Opin. In CPNS Invest. Drugs*, **2**, 112—122 (2000).
10) Hosohata K., Quock R. M., Hosohata Y., Burkey T. H., Makriyannis A., Consroe P., Roeske W. R., Yamamura H. I., *Life Sci.*, **61**, 115—118 (1997).
11) Felder C. C., Joyce K. E., Briley E. J., Glass M., Mackie K. P., Fahey K. J., Cullinan G. J., Hunden D. C., Johnson D. W., Chaney M. O., Koppel G. A., Brownstein M., *J. Pharmacol. Exp. Ther.*, **284**, 291—297 (1998).
12) Kanyonyo M., Govaerts S. J., Hermans E., Poupaert J. H., Lambert D. M., *Biorg. Med. Chem. Lett.*, **9**, 2233—2236 (1999).
13) Meschler J. P., Kraichely D. M., Wilken G. H., Howlett A. C., *Biochem. Pharmacol.*, **60**, 1315—1323 (2000).
14) Mignani S., Hittinger O., Achard D., Bouchard H., Bouquerel J., Capet M., Grisoni S., Malleron J. L., Patent FR 2,783,246 (2000) [*Chem. Abstr.*, **132**, 236982 (2000)].
15) Landsman R. S., Burkey T. H., Consroe P., Roeske W. R., Yamamura H. I., *Eur. J. Pharmacol.*, **334**, R1—R2 (1997).
16) Pertwee R. G., *Gut*, **48**, 859—867 (2001).
17) Mechoulam R., Fride E., Di Marzo V., *Eur. J. Pharmacol.*, **359**, 1—18 (1998).
18) Pertwee R. G., *Addiction Biol.*, **5**, 37—46 (2000).
19) Goya P., Jagerovic N., *Exp. Opin. Ther. Patents*, **10**, 1529—1538 (2000).
20) During the preparation of this manuscript a group from Sanofi-Synthelabo published a patent application wherein the synthesis of structurally related tricyclic compounds is mentioned. Barth F., Congy C., Martinez S., Rinaldi M., Patent WO 01 32,663 (2001) [*Chem. Abstr.*, **134**, 340504 (2001)].
21) Murray W. V., Wachter M. P., *J. Heterocyclic Chem.*, **26**, 1389—1392 (1989).
22) Chan O. H., Stewart B. H., *Drug Discov. Today*, **1**, 461—473 (1996).