Synthesis, Biological Properties, and Molecular Modeling Investigations of Novel 3,4-Diarylpyrazolines as Potent and Selective CB_1 Cannabinoid Receptor Antagonists

Jos H. M. Lange,* Hein K. A. C. Coolen, Herman H. van Stuivenberg, Jessica A. R. Dijksman, Arnoud H. J. Herremans, Eric Ronken, Hiskias G. Keizer, Koos Tipker, Andrew C. McCreary, Willem Veerman, Henri C. Wals, Bob Stork, Peter C. Verveer, Arnold P. den Hartog, Natasja M. J. de Jong, Tiny J. P. Adolfs, Jan Hoogendoorn, and Chris G. Kruse

Solvay Pharmaceuticals, Research Laboratories, C. J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands

Received September 4, 2003

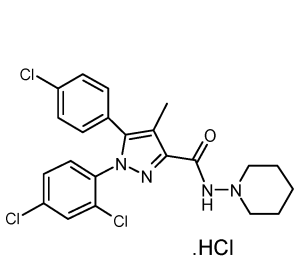
A series of novel 3,4-diarylpyrazolines was synthesized and evaluated in cannabinoid (hCB_1 and hCB_2) receptor assays. The 3,4-diarylpyrazolines elicited potent in vitro CB_1 antagonistic activities and in general exhibited high CB_1 vs CB_2 receptor subtype selectivities. Some key representatives showed potent pharmacological in vivo activities after oral dosing in both a CB agonist-induced blood pressure model and a CB agonist-induced hypothermia model. Chiral separation of racemic **67**, followed by crystallization and an X-ray diffraction study, elucidated the absolute configuration of the eutomer **80** (SLV319) at its C_4 position as 4*S*. Bioanalytical studies revealed a high CNS−plasma ratio for the development candidate **80**. Molecular modeling studies showed a relatively close three-dimensional structural overlap between **80** and the known CB_1 receptor antagonist rimonabant (SR141716A). Further analysis of the X-ray diffraction data of **80** revealed the presence of an intramolecular hydrogen bond that was confirmed by computational methods. Computational models and X-ray diffraction data indicated a different intramolecular hydrogen bonding pattern in the in vivo inactive compound **6**. In addition, X-ray diffraction studies of **6** revealed a tighter intermolecular packing than **80**, which also may contribute to its poorer absorption in vivo. Replacement of the amidine $-NH_2$ moiety with a $-NHCH_3$ group proved to be the key change for gaining oral biovailability in this series of compounds leading to the identification of **80**.

Introduction

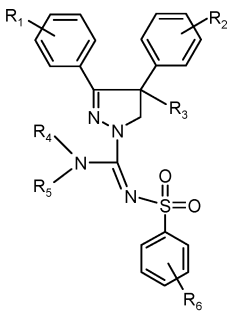
Cannabinoids are present in the Indian hemp *Cannabis sativa L.* and have been used as medicinal agents for centuries.[1−4] However, only within the past 10 years the research in the cannabinoid area has revealed pivotal information on the endocannabinoid system, its receptor subtypes[5,6] (CB_1 and CB_2), and their (endogenous) agonists.[7] Recent data suggest there may be a third cannabinoid receptor[8] ("CB_3"). The CB_1 cannabinoid receptor is expressed at high levels in several brain areas including hippocampus, cortex, cerebellum, and basal ganglia as well as in some peripheral tissues including urinary bladder, testis, and ileum. The CB_2 cannabinoid receptor is principally found in the immune system. CB_1 receptor antagonists may have potential in the treatment of a number of diseases such as neuroinflammatory disorders,[9] cognitive disorders,[10] septic shock,[10] obesity,[10,11] psychosis,[10,12] addiction,[13] and gastrointestinal disorders.[14]

Several types of CB_1 receptor antagonists are known and have recently been reviewed,[9] including the potent and selective[15] rimonabant, which is currently undergoing clinical phase III development for obesity treatment.

In this paper, the discovery of a novel class of diarylpyrazolines of general formula **1** as potent and CB_1-subtype selective receptor antagonists is described.



Rimonabant (SR141716A)



1

Chemistry

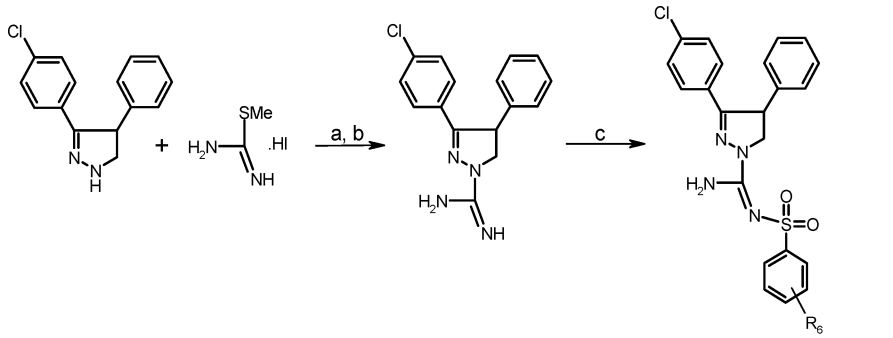
A set of proprietary compounds based on structural resemblance with rimonabant was screened and resulted in the initial discovery of the lead compound **5** as a CB_1 receptor antagonist. A synthesis program based on **5** was devised and carried out.

Reaction of 3-(4-chlorophenyl)-4-phenylpyrazoline[16] **2** with **3** gave the amidine **4**. This amidine was reacted with various arylsulfonyl halides to furnish the target molecules **5**−**9** in good yields (Scheme 1).

* To whom correspondence should be addressed: Dr. J. H. M. Lange, Solvay Pharmaceuticals, Chemical Design & Synthesis Unit, C. J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands. Telephone: +31 (0)294 479731. Fax +31 (0)294 477138. E-mail: jos.lange@solvay.com.

10.1021/jm031019q CCC: $27.50
Published on Web 12/30/2003

Scheme 1[a]

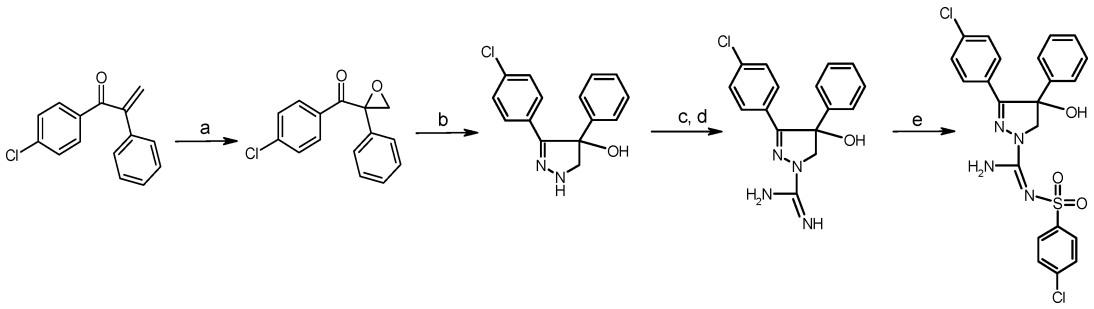


2 **3** **4**

5 R_6 = 4-CH_3
6 R_6 = 4-Cl
7 R_6 = 4-OCH_3
8 R_6 = 2,4,6-$(CH_3)_3$
9 R_6 = 4-F

[a] Reagents and conditions: (a) pyridine, 110 °C; (b) 2 N NaOH; (c) R_6ArSO_2Cl, CH_3CN, DMAP, Et_3N, room temp.

Scheme 2[a]



10 **11** **12** **13** **14**

[a] Reagents and conditions: (a) *m*-CPBA, reflux; (b) $N_2H_4 \cdot H_2O$, EtOH, 35 °C; (c) $H_2NC(SMe)=NH$. 0.5 H_2SO_4, pyridine, 110 °C; (d) 2 N NaOH; (e) *p*-Cl−$PhSO_2Cl$, Et_3N, CH_3CN, room temp.

The synthesis of the target molecule having an additional hydroxy group at the 4-position of the pyrazoline ring started with an epoxidation reaction (using *m*-chloroperbenzoic acid) of 4′-chloro-2-phenylacrylophenone[16] **10** to give the oxirane derivative **11**. Subsequent cyclization of **11** with hydrazine hydrate gave the 4-hydroxypyrazoline congener **12**. The reaction of **12** with methyl imidothiocarbamate delivered the amidated product **13**. The target molecule **14** was obtained from the reaction of **13** with *p*-chlorophenylsulfonyl chloride (Scheme 2).

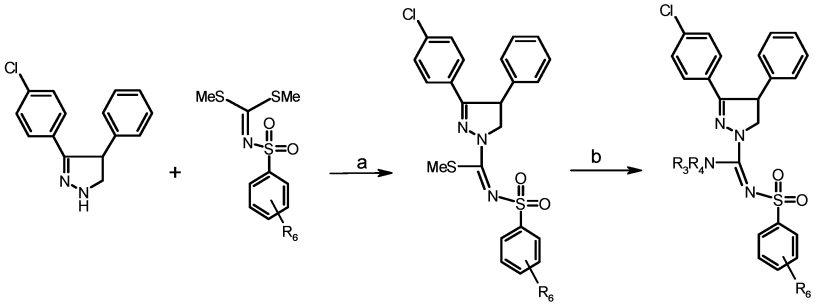
For the synthesis of the target molecules having one or two additional methyl groups on their carboxamidine moiety, a more convergent approach was devised, wherein the NR_3R_4 moiety is introduced in the last step. The arylsulfonyldithioimidocarbonic acid methyl esters **15**−**19** were prepared[17] from the corresponding arylsulfonamides, methyl iodide and CS_2 and subsequently coupled to the 3,4-diarylpyrazoline **2** to furnish the compounds **20**−**24**. Nucleophilic attack by either methylamine or dimethylamine gave the target molecules **25**−**29** in reasonable to good yields (Scheme 3).

To expand the scope of phenyl group substituents on the 3- and 4-position of the 4,5-dihydropyrazole ring, the synthesis of **34** and **35** was undertaken. Compounds **32** and **33** were obtained from **30** and **31**, respectively, using a Mannich reaction/ elimination sequence and further cyclocondensed[16] into **34** and **35** (Scheme 4).

The described synthetic route to compounds **25**−**29** is straightforward but is adversely affected by liberation of the smelly methyl sulfide in the final step. Therefore, an additional synthetic route was developed to avoid this environmental issue. The synthetic strategy is based on the coupling of diarylpyrazolines of general formula **A** with sulfonylated carbamic acid methyl esters of general formula **B**, which were obtained from the corresponding arylsulfonamide and methyl chloroformate, to furnish the products **C**. Chlorination of **C** using phosphorus pentachloride in chlorobenzene yielded the intermediate imidoyl chlorides **D**. The target molecules **E** were obtained from the reaction of **D** with methylamine (Scheme 5). It is interesting to note that the high reactivity of the intermediate imidoyl chlorides **D** enables their quick conversion with a broad range of amines, which makes this route particularly amenable to combinatorial chemistry purposes.

As the 3,4-diarylpyrazoline moiety contains a chiral center at its 4-position, the prepared target compounds of general formula **1** are racemates. To further investigate the stereochemical requirements for binding to the CB_1 receptor in this chiral pyrazoline series in more detail, the key compounds **29** and **67** were separated into their enantiomers by applying chiral preparative HPLC to furnish two optically pure sets of compounds **78**/**79** and **80**/**81**, respectively (Scheme 6).

Scheme 3[a]



2

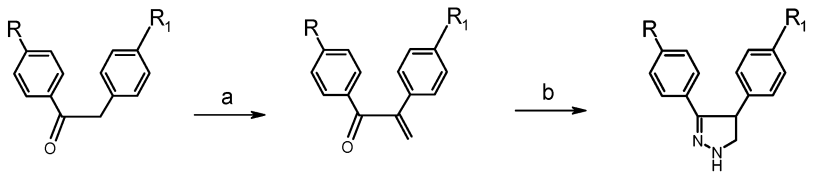
15 R_6 = 4-Cl
16 R_6 = 2-Cl
17 R_6 = 3-Cl
18 R_6 = 4-F
19 R_6 = 4-CF_3

20 R_6 = 4-Cl
21 R_6 = 2-Cl
22 R_6 = 3-Cl
23 R_6 = 4-F
24 R_6 = 4-CF_3

25 R_3 = Me, R_4 = Me, R_6 = 4-Cl
26 R_3 = Me, R_4 = Me, R_6 = 4-F
27 R_3 = H, R_4 = Me, R_6 = 2-Cl
28 R_3 = H, R_4 = Me, R_6 = 3-Cl
29 R_3 = H, R_4 = Me, R_6 = 4-CF_3

[a] Reagents and conditions: (a) Et_3N, CH_3CN, reflux; (b) R_3R_4NH, MeOH, CH_2Cl_2, room temp.

Scheme 4[a]



30 R = Cl, R_1 = F
31 R = F, R_1 = H

32 R = Cl, R_1 = F
33 R = F, R_1 = H

34
35

[a] Reagents and conditions: (a) 37% aq. CH_2O, piperidine, reflux; (b) $N_2H_4 \cdot H_2O$, EtOH, reflux.

An intriguing modification in our target molecules was the replacement of their sulfonyl group by a carbonyl group (Scheme 7). 4-Chlorobenzoylisothiocyanate **82** was prepared[18] from 4-chlorobenzoyl chloride and ammonium isothiocyanate. Nucleophilic addition of pyrazoline **2** to **82** yielded the adduct **83**. The target molecule **84** was obtained from the reaction of **83** with methylamine in the presence of $HgCl_2$ in moderate yield.

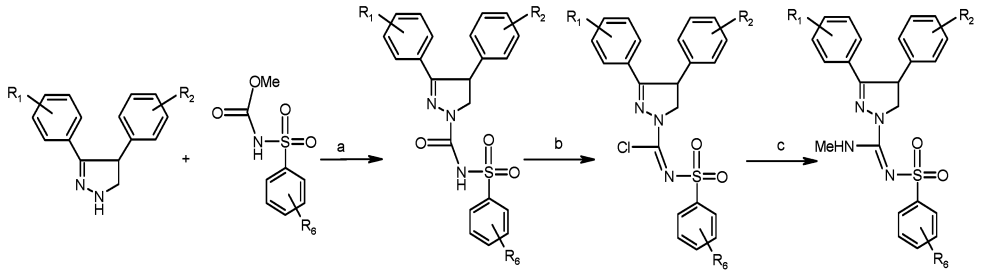
Results and Discussion

The target compounds **5**−**9**, **14**, **24**−**29**, **45**, **67**−**81**, and **84** were evaluated in vitro at the human CB_1 and CB_2 receptor, stably expressed into Chinese hamster ovary (CHO) cells,[19,20] utilizing radioligand binding studies. CB_1 receptor antagonism[21] was measured using an arachidonic acid release-based functional assay, using the same recombinant cell line. The results are reported in Table 1. The CB_1 receptor binding data in the amidine -NH_2 series (compounds **5**−**9**, **14**, and **25**−**27**) revealed that replacement of the 4-Me group in **5** by Cl (**6**) or F (**9**) gave a substantial gain in affinity, whereas OMe substitution (**7**) did not elicit a clear effect on affinity. 2,4,6-Trimethyl substituted **8** also showed considerably higher affinity than the 4-methyl substituted **5**. Incorporation of a 4-OH group in the dihydropyrazole moiety (**14**) reduced affinity as compared to **6**. Relocation of the 4-Cl atom in **6** to the 3-position (**28**) had little effect on affinity, whereas Cl relocation to the 2-position (**27**) reduced CB_1 receptor affinity. Substitution of the 4-methyl group in **5** by the strongly electron withdrawing -CF_3 group (**29**) had little effect on affinity.

Both compounds **25** and **26** from the amidine $N(CH_3)_2$ series had reduced CB_1 affinity as compared to their -NH_2 counterparts **6** and **9**.

The CB_1 receptor binding data in the amidine -NHCH$_3$ series **67**−**70** wherein the substituents R_1 and R_2 were varied clearly elicit the CB_1 affinity optimum in the R_1 = Cl and R_2 = H substitution pattern, whereas the other variations, including **68** wherein R_2 represents 4-F, were markedly less tolerated. Comparison of **67** with **27**−**29** and **71**−**77** further clarified the role of the substituent R_6. Replacement of 4-Cl in **67** by H (**71**), F (**72**), or methyl (**73**) and CF_3 (**29**) all resulted in reduced affinity. Replacement of 4-Cl in **67** by 2-Cl (**27**), 3-CF_3 (**74**), and 2,4,6-trimethyl (**75**) gave a small reduction of affinity. The 3-Cl (**28**), 4-OMe (**76**), and the bulky 2-naphthyl substituted analogue **77** elicited a high CB_1 receptor affinity. Compound **84** in which the sulfonyl group is replaced by a carbonyl group showed ~3-fold less affinity than **67**. The negligible affinity of intermediate **45** wherein the amidine group is substituted by an amide moiety underlines the importance of the amidine moiety in the CB_1 pharmacophore. It is interesting to note that the intermediate **24** wherein the amidine NH_2 group is replaced by the SMe group showed also considerable CB_1 receptor affinity. Apparently, limited structural variations are allowed in the carboxamidine part of the pharmacophore. As **29** and **67** are racemates their enantiomerically pure constituents were also tested. In both cases the levorotatory enantiomers **78** and **80,** respectively, had significantly higher CB_1 affinities than their dextrorotatory counterparts **79** and **81**. The highest CB_1 receptor affinity (7.8 nM) was found in the eutomer **80**. This value is in the same order of magnitude as that reported[15] for rimonabant (11.5 nM). The distomer **81** showed ~ 100-

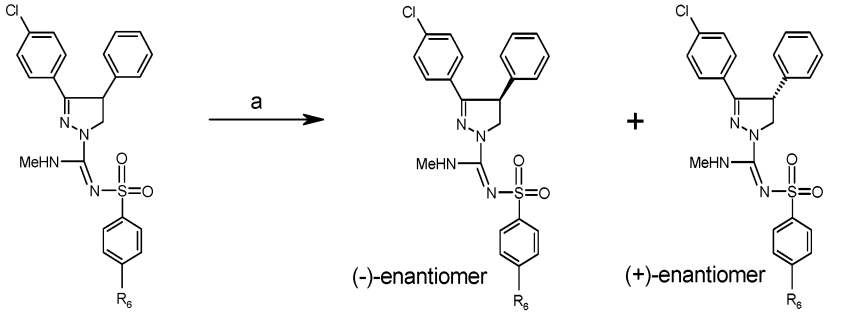
Scheme 5[a]



R_1	R_2	R_6	Formula **A** Compound	Formula **B** Compound	Formula **C** Compound	Formula **D** Compound	Formula **E** Compound
4-Cl	H	4-Cl	**2**[16]	**37**	**45**	**56**	**67**
4-Cl	4-F	4-Cl	**34**		**46**	**57**	**68**
4-F	H	4-Cl	**35**		**47**	**58**	**69**
4-Cl	4-Cl	4-Cl	**36**[16]		**48**	**59**	**70**
4-Cl	H	H		**38**	**49**	**60**	**71**
4-Cl	H	p-F		**39**	**50**	**61**	**72**
4-Cl	H	p-Me		**40**	**51**	**62**	**73**
4-Cl	H	m-CF_3		**41**	**52**	**63**	**74**
4-Cl	H	2,4,6-Me_3		**42**	**53**	**64**	**75**
4-Cl	H	p-OMe		**43**	**54**	**65**	**76**
4-Cl	H	3,4-benzo		**44**	**55**	**66**	**77**

[a] Reagents and conditions: (a) toluene, reflux; (b) PCl_5, chlorobenzene, reflux; (c) $MeNH_2$, CH_2Cl_2, room temp.

Scheme 6[a]



29 R_6 = CF_3
67 R_6 = Cl

78 R_6 = CF_3
80 R_6 = Cl

79 R_6 = CF_3
81 R_6 = Cl

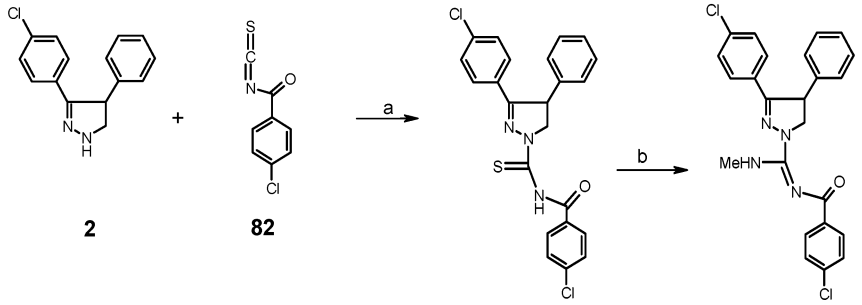
[a] Reagents and conditions: (a) chiral preparative HPLC.

fold less affinity than the eutomer **80**, indicating that these chiral ligands bind stereoselectively to the CB_1 receptor.

The results from the arachidonic acid release-based functional assay (Table 1) clearly reveal the CB_1 receptor antagonistic properties of our target compounds **5**−**9**, **24**−**29**, **67**−**81**, and **84**. In general, the compounds having the highest CB_1 receptor affinities also show strong antagonistic activity. Eight compounds (**6**, **8**, **24**, **29**, **74**−**75**, **78**, and **80**) exhibited subnanomolar CB_1 antagonistic potencies in the arachidonic acid release-based functional assay. Interestingly, the 4-trifluoromethylphenyl substituted **29** revealed strong CB_1 antagonistic properties (pA_2 = 9.3), despite its moderate receptor affinity. In line with the CB_1 receptor affinity results the eutomers **78** and **80** both showed considerably more potent CB_1 antagonistic properties than their distomers **79** and **81**.

It was encouraging to note that a considerable $CB_{1/2}$ receptor selectivity was already observed in the original lead **5**. The results from Table 1 reveal that CB_1/CB_2 receptor subtype selectivity is apparent throughout the

Scheme 7[a]



[a] Reagents: (a) CH_3CN, 0 °C; (b) CH_3NH_2, $HgCl_2$, CH_3CN, room temp.

Table 1. In Vitro Results of the Pyrazoline Derivatives **5**−**9**, **14**, **24**−**29**, **45**, **67**−**81**, **84** and Rimonabant

compound	$K_i(CB_1)$,[a] nM	$pA_2(CB_1)$[b]	$K_i(CB_2)$,[c] nM	compound	$K_i(CB_1)$,[a] nM	$pA_2(CB_1)$[b]	$K_i(CB_2)$,[c] nM
rimonabant	25 ± 15 (11.5)[15]	8.6 ± 0.1	1580 ± 150 (1640)[15]	**68**	584 ± 220		
5	197 ± 152	8.4 ± 0.2	> 1,000	**69**	214 ± 55	7.6 ± 0.1	
6	16.1 ± 6.6	9.5 ± 0.3	> 1,000	**70**	255 ± 105		
7	196 ± 107	8.3 ± 0.2	> 1,000	**71**	170 ± 44	7.5 ± 0.2	
8	24.2 ± 13.0	9.4 ± 0.3	> 1,000	**72**	338 ± 170	8.5 ± 0.3	> 1,000
9	52.6 ± 10.5	9.0 ± 0.3	> 1,000	**73**	119 ± 40	8.6 ± 0.3	
14	713 ± 268			**74**	36.5 ± 21.7	9.1 ± 0.2	> 1,000
24	16.6 ± 11.6	9.7 ± 0.5	> 1,000	**75**	54.2 ± 17.7	9.4 ± 0.5	
25	280 ± 178	8.5 ± 0.3	> 1,000	**76**	22.9 ± 11.0	8.0 ± 0.3	
26	> 1,000	< 7.5	> 1,000	**77**	21.8 ± 3.4	8.5 ± 0.2	
27	75.4 ± 12.3	8.3 ± 0.1	> 1,000	**78**	35.9 ± 10.8	9.0 ± 0.3	3,515 ± 1085
28	13.9 ± 7.9	8.6 ± 0.2	> 1,000	**79**	293 ± 120	7.5 ± 0.1	> 1,000
29	221 ± 130	9.3 ± 0.2	> 1,000	**80**	7.8 ± 1.4	9.9 ± 0.6	7,943 ± 126
45	> 1000			**81**	894 ± 324	< 7.4	> 1,000
67	25.2 ± 7.4	8.7 ± 0.3	> 1,000	**84**	70.6 ± 12.7	8.7 ± 0.2	

[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.

presented dihydropyrazole series. The highest CB_1/CB_2 receptor selectivity (∼1000) was found in the development candidate **80**, which is ∼7-fold higher than the reported[15] CB_1/CB_2 receptor selectivity (143) for rimonabant.

The in vivo activity of some key dihydropyrazoles was investigated in two mechanistic pharmacological models, viz. a CB_1 agonist (CP-55,940) induced hypotension[22] rat model and a CB_1 agonist (WIN-55,212) induced hypothermia[23] mouse model. Their activities were compared with those of rimonabant. The results indicated that both the initial lead **5** and its congener **6** are devoid of in vivo cannabinoid antagonistic activity after oral administration in both models. Therefore, further optimization efforts were directed to improve the bioavailability after oral administration. It was discovered that the test compound **25** from the series wherein the polar $-NH_2$ group of the carboxamidine group is substituted by an $-N(CH_3)_2$ group, showed improved in vivo activity in the hypothermia model after oral administration. This result prompted a further subtle structural carboxamidine modification from the $-N(CH_3)_2$ to the $-NHCH_3$ moiety (compounds **27**−**29** and **67**−**77**). This variation proved to be particularly worthwhile and provided a number of potent in vivo compounds. It was most gratifying to see that the compounds **29** and **67**, which contain a 4-CF_3 substituent and 4-Cl substituent, respectively, at their arylsulfonyl moiety, exhibited strong activities after oral administration in both the CB-agonist induced hypotension and hypothermia model

Table 2. in Vivo Results of Compounds **5**−**6**, **25**, **29**, **67**, **78**−**81**, and Rimonabant

compound	ED_{50}, hypotension, rat[a]	LED, hypothermia, mouse[b]
rimonabant	3.2	3
5	> 30	> 30
6	> 30	> 30
25	> 30	10
29	8.9	3
67	15	3
78	2.0	1
79	> 30	> 30
80	5.5	3
81	> 30	> 30

[a] Antagonism of CB agonist (CP55,940) induced hypotension, rat expressed asED_{50} (mg/kg, po administration). [b] Antagonism of CB agonist (WIN-55,212) induced hypothermia, mouse expressed as least effective dose (LED) (mg/kg, po administration).

(Table 2). In line with the reported in vitro results (vide supra), the levorotatory enantiomers **78** and **80** were active in vivo, whereas no activity was found for the distomers **79** and **81**. Apparently, the CB_1 receptor strongly discriminates between both mirror images indicating that the orientation of the 4-phenyl substituent is strongly involved in CB_1 receptor−ligand interaction. To obtain a better understanding of the structural moieties being critically involved in the CB_1 receptor−ligand interaction in our pyrazoline series additional studies were undertaken. The absolute configuration of the eutomer **80** was assessed by means of an X-ray

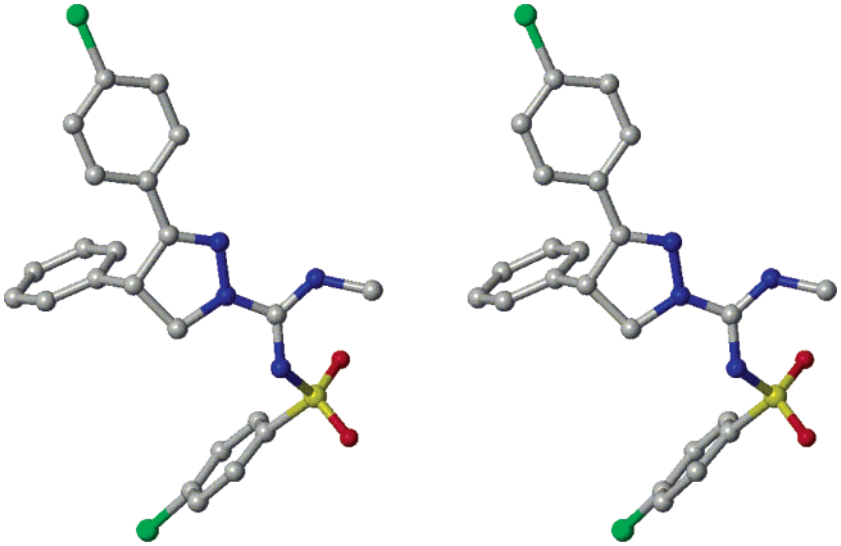


Figure 1. Stereoview of the X-ray diffraction result of **80**.

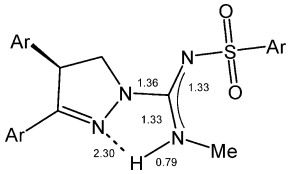


Figure 2. Intramolecular hydrogen bonding in **80**. The intramolecular H-bond is indicated as a dashed line.

diffraction study. The absolute configuration of **80** was found to be 4*S* from the X-ray diffraction data analysis (Figure 1).

The X-ray diffraction result of **80** revealed the presence of an intramolecular hydrogen bond between the hydrogen atom at its amidine moiety and the N atom at the 2-position of the dihydropyrazole ring (Figure 2). The presence of this particular intramolecular hydrogen bond was also found in the modeled lowest energy conformation of **80**. It is remarkable to notice that this H-bond is preferred above the alternative binding to one of the SO_2 oxygen atoms. Furthermore, the delocalization of the double bond electrons of the amidine moiety in **80** is clearly demonstrated by the identical interatomic distances (Figure 2).

Conformational analysis by molecular modeling studies has revealed four low energy conformations of rimonabant,[24] determined by the amide bond (cis [C] or trans [T] configuration) and the conformation of its N-piperidinyl moiety (gauche [g] or skew [s]). Comparable studies on the more flexible **80** gave several easily accessible conformations, mutually differing in the positioning of the sulfonyl carboxamidine chain with respect to the pyrazoline ring. Interestingly, the different MOPAC-minimization methods gave remarkable differences with respect to the angle in the -C=N−SO_2 moiety of the side-chain. The PM3 method appeared to give the best approximation of the angle in comparison with the X-ray structure (AM1: 149.7°; PM3: 138.6°; X-ray: 123.3°). Ten representative conformations of **80** are depicted in Figure 3 and their corresponding energies are summarized in Table 3, all lying within 4 kcal/mol as compared to the minimum energy conformation. This calculated result demonstrates the flexibility of the molecule. Conformation **H** most closely resembles the X-ray structure.

Recently, a model for the binding of rimonabant in the CB_1 receptor has been described in the literature,[25] based on the X-ray structure[26] of bovine rhodopsin (Rho). The original template was modified to the putative inactive R-state with a pronounced proline kink at Pro358 in transmembrane helix 6 (TMH6) as the most remarkable feature.[27,28] It enables a stabilizing salt bridge between Lys214 and Asp338 at the intracellular end of TMHs 3 and 6. It has been postulated,[25] supported by biological data, that rimonabant in its T_g conformation has an interaction with this Lys214, which is only possible when the latter is bridged to Asp338. This implies that rimonabant has a higher affinity for the R-state. Binding of rimonabant is further described by aromatic stacking interactions between the two aromatic rings of rimonabant and an aromatic residue-rich region in TMH 3-4-5-6.

The receptor model was reconstructed.[25] Giving the best fit with rimonabant, the T_g, conformation **80D** was used as starting conformation for manual docking into the receptor, followed by simulated annealing and minimization. In Figure 4 the resulting receptor-based alignment of rimonabant and **80** is given.

One of the SO_2 oxygen atoms in **80** forms a hydrogen bond with the Asp366−Lys192 salt bridge. Compared to rimonabant, binding of **80** is further enhanced by an additional hydrogen bond via its other SO_2 oxygen atom with Ser383. This is also in line with the 3-fold less CB_1 receptor affinity of **84**, wherein the SO_2 moiety is replaced with a carbonyl group that cannot accommodate this additional hydrogen bond, as compared with **67**. The end group of the chain fits well in a pocket formed by various lipophilic residues. In the case of **80**, a stacking interaction between the *p*-chlorophenyl ring and Phe170 is possible. The two aromatic rings attached to the pyrazoline core are enclosed by an arrangement of stacked aromatic residues. The *p*-chlorophenyl ring is bound in a pocket formed by Trp279/Phe200/Trp356 while the other ring fits in a cavity created by Tyr275/Trp255/Phe278. The stereoselectivity in the binding (Table 2) can be rationalized by the latter interaction. In the enantiomer **78**, the aromatic ring points in the wrong direction, away from the lipophilic pocket thereby loosing the favorable stacking interactions.

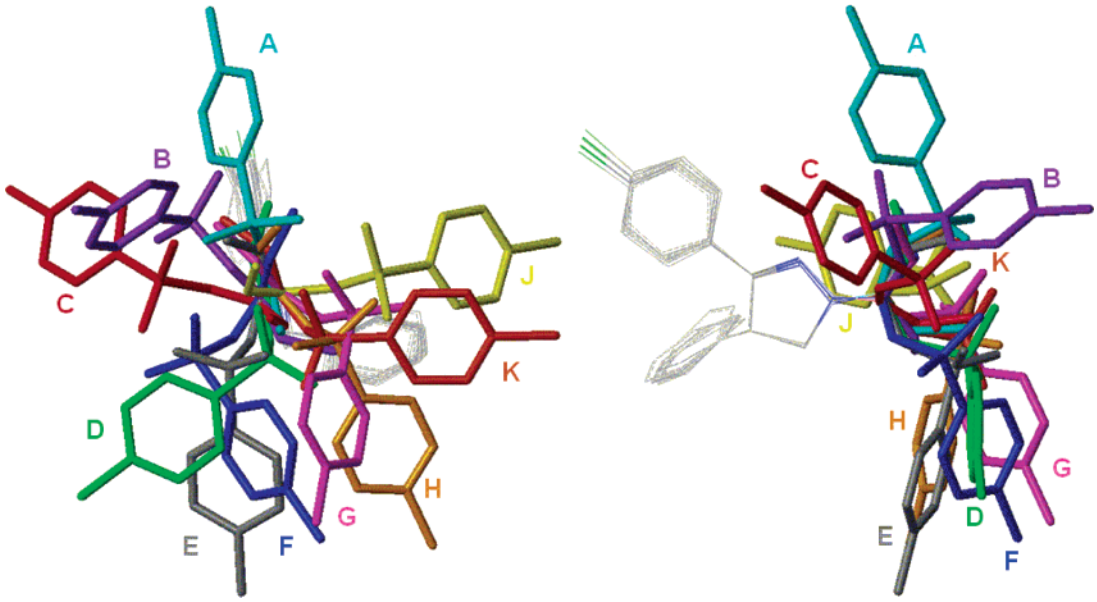


Figure 3. Orthographic drawing (left: front view, right: side view) of 10 representative low energy conformations of **80**, aligned with respect to the pyrazoline core. (The core is grayed out for clarity).

Table 3. Heats of Formation of the Conformations Depicted in Figure 3

conformation	heat of formation (kcal)	conformation	heat of formation (kcal)
A	52.53	**F**	51.91
B	53.30	**G**	51.27
C	54.70	**H**	51.39
D	51.98	**K**	52.67
E	51.50	**L**	51.16

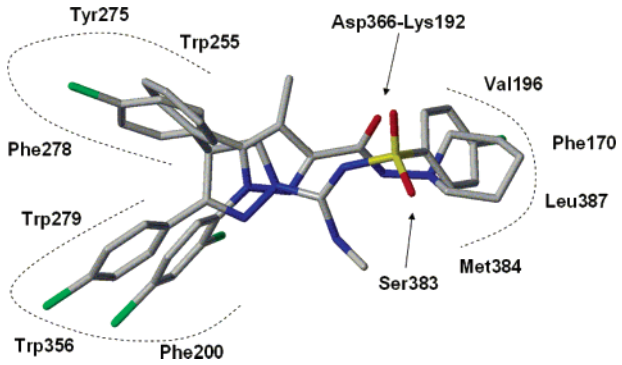


Figure 4. Receptor-based alignments of **80** and rimonabant.

As can be seen in Table 1, the dimethyl derivative **25** is considerably less active than **80**. The binding cavity of the receptor can easily accommodate this additional methyl group. Moreover, conformational studies on **25** showed that the required conformation for binding is only slightly higher (0.83 kcal/mol) than the lowest energy conformation. A possible explanation for the observed reduced CB_1 receptor affinity (Table 1) can be found in the presence of the intramolecular hydrogen bond in **80** (see Figure 2). This interaction conceivably directs the carboxamidine chain toward the binding pocket. In the dimethyl derivative **25**, this directing effect by hydrogen bonding is impossible, which might cause loss of entropy during binding, thereby resulting in a lower binding affinity.[29] In the desmethyl derivative **6**, the above-mentioned preorganizing intramolecular hydrogen bond is also possible. This is in nice agreement with the comparable CB_1 receptor affinities of **6** and **67**

Table 4. ADME Parameters of **6**, **25**, and **80**

compound	ACD log P[a]	P-glycoprotein affinity[b]	membrane passage[c]	cPSA[d]
6	4.3[e]	1.7 ± 0.5	7.0 ± 0.7	122.5
25	4.8	1.4 ± 0.1	15.2 ± 0.6	62.7
80	4.8	1.4 ± 0.1	14.8 ± 2.2	89.3

[a] Calculated log P: ACD log P, version 7; Advanced Chemistry Development, 90 Adelaide St. W. Suite 702, Toronto, ON, Canada M5H 3V9. [b] P-glycoprotein transport ratio, expressed as the mean percentage of compound transported. [c] Membrane passage, expressed as the mean percentage of compound transported. [d] Calculated polar surface area of the presumed binding conformation. [e] Mean value of calculated results from two tautomers.

(Table 1). However, compound **6** showed no in vivo CB_1 receptor mediated activity after oral administration (Table 2). The intriguing phenomenon that the structurally so closely related compounds **6** and **80** showed markedly different potencies in vivo was investigated in more detail. To this purpose, the most important ADME parameters were determined, which are summarized in Table 4.

The common Lipinski parameters[30] (log P, mol weight, number of H-bond donors and acceptors) are in the same order of magnitude as the only difference between the structures **6**, **25**, and **67** (**80**) is the presence of one or two additional methyl groups. In addition, the log P value of compound **80** was determined by RP-HPLC and was found in the same order of magnitude (log P (**80**) = 5.1) as compared to its calculated log P value of 4.8 (Table 4).

It has been described that the P-glycoprotein pump is present in the gut wall and is involved in intestinal absorption. In addition, the P-glycoprotein pump lowers the CNS levels of certain compounds by actively extruding them from the brain.[31] Therefore, the affinities of **6**, **25**, and **80** for this efflux pump were examined. All compounds were shown to be devoid of significant P-glycoprotein pump substrate affinity (Table 4).

The molecular polar surface area (PSA) has been shown to correlate well with drug transport properties, such as intestinal absorption or blood-brain barrier

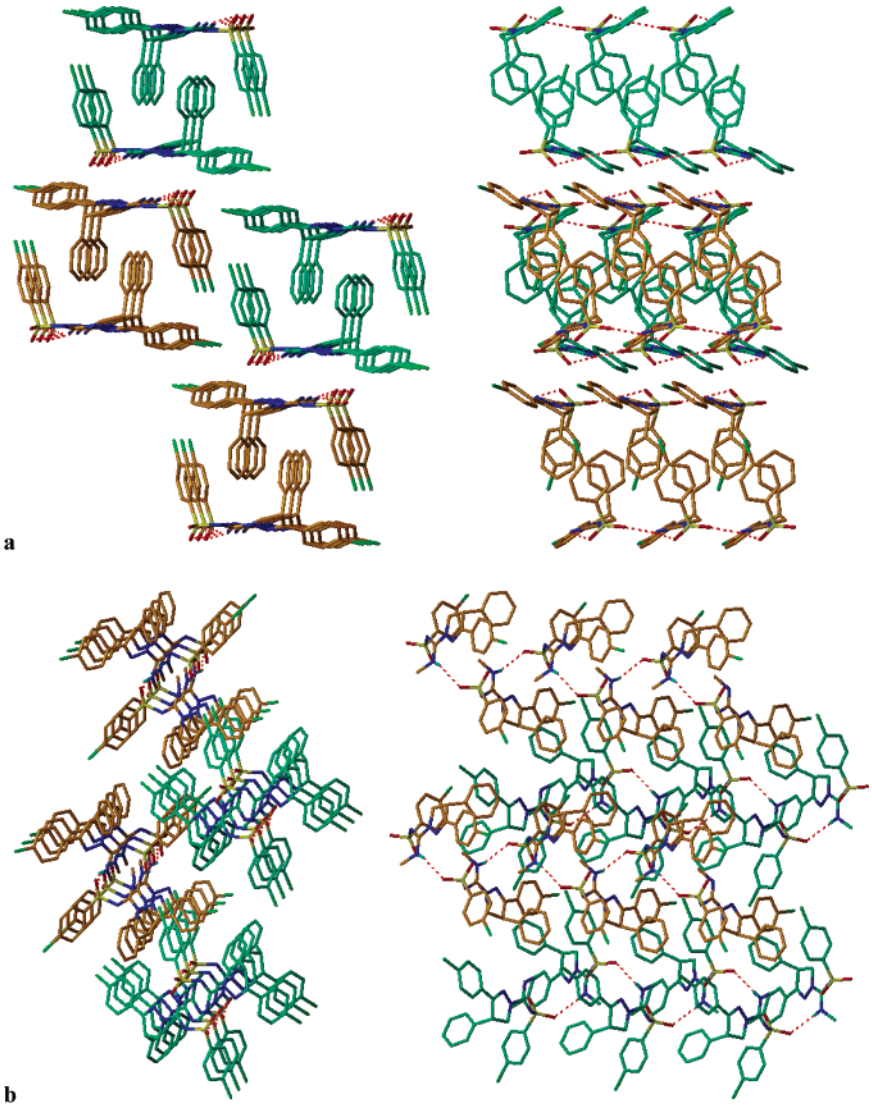


Figure 5. Orthogonal representations of the crystal packing of (a) **6** along the *xy*-diagonal of the unit cell, columns with *S*-configuration colored orange and those with *R*-configuration blue/green and (b) of **80** along the *x*-axis of the unit cell.

penetration.[32,33] PSA thus represents, at least in part, the energy involved in the membrane transport of a compound.[34] Compounds having a PSA value > 120 Å^2 have generally been shown to have a low oral bioavailability. It was anticipated that attachment of apolar methyl groups to the polar amidine moiety of **6** would result in compounds with a lower PSA, showing higher bioavailability after oral dosing. The substantially higher calculated PSA value for **6** as compared to the PSA values for **25** and **80** supports this hypothesis (Table 4). Furthermore, the high PSA value of **6** is in line with its observed lower membrane passage rate and diminished in vivo potency after oral administration as compared to its *N*-methylated congeners **25** and **80**.

Before any absorption can take place, a drug needs to be in solution and therefore dissolution and solubility are important properties to consider. It was found that both compound **6** and **80** are very poorly soluble in water (<1 mg/L at pH = 7). However, the solubility of **6** in the polar organic solvents acetonitrile and ethanol at reflux conditions is moderate, whereas **80** readily dissolved under these conditions. It is known that physical properties of solids such as crystal packing and crystal lattice energy have an impact on the rate of dissolution in solvents, including water. Water solubility and dissolution rate constitute critical determinants for the degree of uptake in the GI tract after oral administration.[35]

An X-ray diffraction study of compound **6** was carried out to assess potential differences in crystal packing between crystalline **6** and **80**.

Remarkably, both enantiomers are present in the unit cell of the X-ray structure of **6**. In the crystal packing of **6** (see Figure 5a), the dihydropyrazole core almost lies in a plane with the sulfonyl carboxamidine substituents and the core *p*-chlorophenyl ring. These units are aligned in a straight sheet kept together by a progression of intramolecular hydrogen bonds between the SO_2 oxygen atoms and the -NH_2 groups. The two remaining phenyl rings are positioned nearly perpendicular with respect to the sheet. Two of these sheets are attached to each other via a network of $\pi-\pi$ stacking interactions forming a columnar packing of two opposite sheets. Interestingly, in the packing the columns exist alternately of molecules having the *R*- and *S*-configuration,

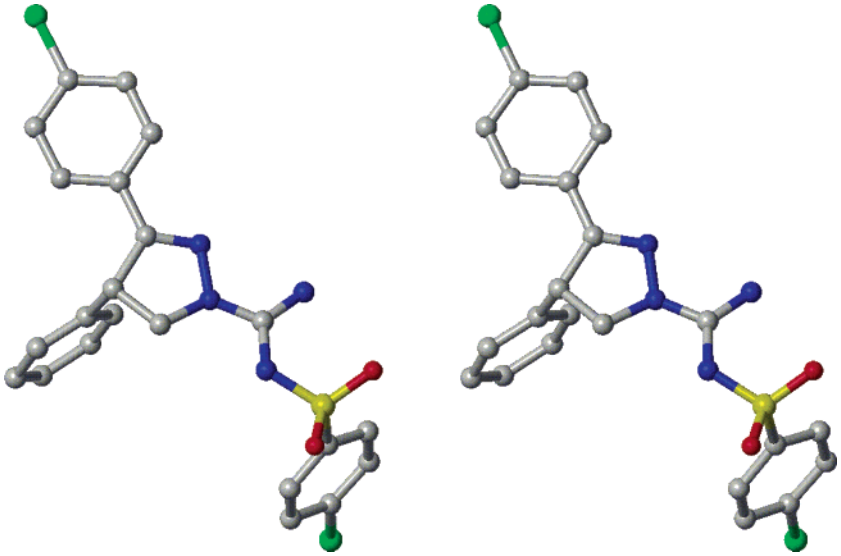


Figure 6. Stereoview of the *S*-enantiomer of the X-ray structure of **6**.

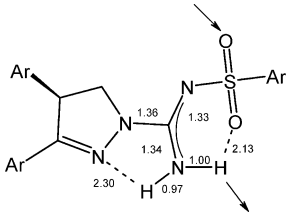


Figure 7. Intramolecular and intermolecular hydrogen bonding in the *S*-enantiomer of **6**. The intermolecular H-bonds are indicated as a dashed arrow.

respectively. These columns are mutually transformable via centers of inversion between them.

The crystal packing of **80** also reveals a columnar orientation along the *x*-axis of the unit cell (Figure 5b). However, as can be clearly seen, this packing is not as tight as with **6**. This is also expressed by the higher melting point of **6** compared to **80** (235 and 170 °C, respectively). A predictive model for solubility has been reported[36,37] based on the log P and the melting point of the compound, wherein in general higher melting points correlate with lower water solubilities. The lower water solubility and dissolution rate of **6** might result in an insufficient dissolution rate in the GI tract to enable in vivo activity.

In Figure 6 the *S*-enantiomer out of the X-ray structure of **6** is shown. Basically, the difference in the packing between **6** and **80** can be explained by the bridging ability of the NH_2 group of **6** forming intramolecular hydrogen bonds with both the dihydropyrazole core and the sulfonyl group. In this constellation, the side-chain is directed in a planar orientation with respect to the core, thereby enabling a strong intermolecular H-bond of one of the SO_2 oxygen atoms with a hydrogen atom of the NH_2 group of another molecule **6** (see Figure 7).

To estimate the CNS availability of our development candidate **80** a bioanalytical study was undertaken to assess its CNS/plasma ratio. The CNS/plasma ratio of **80** was found 1.7, which is in nice agreement with its potent CB_1 receptor mediated activity in the CB agonist-induced hypothermia assay and its negligible P-glycoprotein pump substrate affinity.

Conclusion

The lead optimization of the CB_1 cannabinoid receptor antagonist **5** has led to the development candidates **78** (SLV326) and **80**. Both **78** and **80** are novel subtype selective CB_1 receptor antagonists exhibiting potent pharmacological activity in vitro as well as in vivo after oral administration. It has been demonstrated that the interactions of the enantiomers **78**−**81** with the CB_1 receptor are highly stereoselective. Mono- and dimethylation of the polar carboxamidine moiety in **6** resulted in the compounds **80** and **25** having substantially lower calculated PSA values. These methylations are pivotal in governing the oral bioavailability in the pyrazoline series, conceivably by subtly affecting the degree of dissolution rate in the gastrointestinal tract, as the result of a different intramolecular hydrogen bonding pattern and crystal packing.

Experimental Section

Chemistry. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX600 instrument (600 MHz), Varian UN400 instrument (400 MHz), or a Varian VXR200 instrument (200 MHz) using DMSO-d_6 or $CDCl_3$ as solvents with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ scale) downfield from tetramethylsilane. Coupling constants (J) are expressed in hertz. Thin-layer chromatography was performed on Merck precoated 60 F_{254} plates, and spots were visualized with UV light. Flash chromatography was performed using silica gel 60 (0.040−0.063 mm, Merck). Column chromatography was performed using silica gel 60 (0.063−0.200 mm, Merck). Chiral preparative HPLC was conducted by using a LC80 column (250 × 80 mm). Melting points were recorded on a Büchi B-545 melting point apparatus and are uncorrected. Mass spectra were recorded on a Micromass QTOF-2 instrument with MassLynx application software for acquisition and reconstruction of the data. Exact mass measurement was done of the quasimolecular ion $[M+H]^+$. Optical rotations ($[\alpha]_D$) were measured on an Optical Activity polarimeter. Specific rotations are given as deg/dm, the concentration values are reported as g/100 mL of the specified solvent and were recorded at 23 °C. Elemental analyses were performed on a Vario EL elemental analyzer by Solvay Pharmaceuticals, Hanover, Germany, and were within ±0.4% of theoretical values, unless otherwise stated. Yields refer to isolated pure products and were not maximized.

3-(4-Chlorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazole (2). **2** was prepared according to the literature procedure.[16]

3-(4-Chlorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (4). A magnetically stirred mixture of **2** (5.13 g, 20.0 mmol), **3** (5.00 g, 23.0 mmol), and pyridine (10 mL) was heated at 110 °C for 1 h. After one night standing at room temperature, Et_2O was added and the precipitate was collected by filtration and washed three times with Et_2O portions to afford a solid (9.0 g): mp 230 °C. The obtained solid was dissolved in MeOH (20 mL) and a 2 N NaOH solution (12 mL) and water (200 mL) were successively added. The formed precipitate was collected by filtration, washed two times with Et_2O and with diisopropyl ether, and dried in vacuo to yield **4** (5.1 g, 88% yield), mp 187−189 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (dd, J = 11 and 4.5 Hz, 1H), 4.19 (t, J = 11 Hz, 1H), 4.89 (dd, J = 11 and 4.5 Hz, 1H), 5.65 (br s, 3H), 7.20−7.25 (m, 3H), 7.28−7.35 (m, 2H), 7.37 (dt, J = 8 and 2 Hz, 2H), 7.65 (dt, J = 8 and 2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.0, 56.6, 127.5 (2C), 128.3, 128.9, 129.4, 130.6, 133.6, 141.5, 151.1, 155.8.

3-(4-Chlorophenyl)-*N*-[(4-fluorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (9). To a magnetically stirred mixture of **4** (0.50 g, 1.68 mmol) and 4-fluorophenylsulfonyl chloride (0.34 g, 1.75 mmol) in CH_3CN (10 mL) were added *N*,*N*-dimethyl-4-aminopyridine (0.020 g, 0.175 mmol) and Et_3N (1 mL). The resulting solution was stirred at room temperature for 30 min. After addition of a 2 N NaOH solution and extraction with EtOAc (400 mL), the EtOAc layer was concentrated in vacuo. The resulting crude residue was further purified by flash chromatography (petroleum ether (40−60)/Et_2O = 1/1 (v/v), followed by EtOAc) and recrystallized from CH_3CN to afford **9** (0.55 g, 72% yield), mp 214−215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (dd, J = 12 and 4 Hz, 1H), 4.35 (t, J = 12 Hz, 1H), 5.03 (dd, J = 12 and 4 Hz, 1H), 7.16−7.36 (m, 9H), 7.43 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.89−7.94 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.0. 56.0, 116.2 (d, J_{CF} = 22 Hz), 127.6, 127.9, 128.98 (d, J_{CF} = 10 Hz), 129.05, 129.2, 129.5, 129.6, 135.3, 140.4, 140.6 (d, J_{CF} = 3 Hz), 153.2, 157.9, 164.0 (d, J_{CF} = 249 Hz); HRMS ($C_{22}H_{19}ClFN_4O_2S$) [M+H]$^+$: found *m*/*z* 457.0924, calcd 457.0901. Anal. ($C_{22}H_{18}ClFN_4O_2S$) C, H, N.

3-(4-Chlorophenyl)-*N*-[(4-methylphenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (5). 5 was prepared from **4** and *p*-tolylsulfonyl chloride in 93% yield by the same procedure as described for **9**, mp 206−208 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.35 (s, 3H), 3.78 (dd, J = 12 and 4 Hz, 1H), 4.33 (t, J = 12 Hz, 1H), 5.12 (dd, J = 12 and 4 Hz, 1H), 7.15−7.33 (m, 7H), 7.42 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.82−7.92 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.3, 50.0, 56.0, 126.1, 127.6, 127.9, 129.0, 129.3, 129.4, 129.6 (2C), 135.2, 140.5, 141.3, 142.0, 153.1, 157.7; HRMS ($C_{23}H_{22}ClN_4O_2S$) [M+H]$^+$: found *m*/*z* 453.1163, calcd 453.1152. Anal. ($C_{23}H_{21}ClN_4O_2S$) C, H, N.

3-(4-Chlorophenyl)-*N*-[(4-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (6). 6 was prepared from **4** and *p*-chlorophenylsulfonyl chloride in 75% yield by the same procedure as described for **9**, mp 212−213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.79 (dd, J = 11 and 4 Hz, 1H), 4.36 (t, J = 11 Hz, 1H), 5.54 (dd, J = 11 and 4 Hz, 1H), 7.17 (d, J = 8 Hz, 2H), 7.21−7.27 (m, 1H), 7.28−7.34 (m, 2H), 7.43 (d, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.86 (d, J = 8 Hz, 2H), 7.90 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.0, 56.0, 127.6, 127.9, 128.1, 129.1, 129.2, 129.3, 129.5, 129.6, 135.3, 136.7, 140.4, 143.0, 153.2, 158.0; HRMS ($C_{22}H_{19}Cl_2N_4O_2S$) [M+H]$^+$: found *m*/*z* 473.0612, calcd 473.0606. Anal. ($C_{22}H_{18}Cl_2N_4O_2S$) C, H, N.

3-(4-Chlorophenyl)-*N*-[(4-methoxyphenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (7). 7 was prepared from **4** and *p*-methoxyphenylsulfonyl chloride in 79% yield by the same procedure as described for **9**, mp 191−192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.77 (dd, J = 12 and 4 Hz, 1H), 3.81 (s, 3H), 4.33 (t, J = 12 Hz, 1H), 5.02 (dd, J = 12 and 4 Hz, 1H), 7.03 (dt, J = 8 and 2 Hz, 2H), 7.14−7.32 (m, 5H), 7.42 (dt, J = 8 and 2 Hz, 2H), 7.72−7.80 (m, 4H), 7.82 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.0, 55.9, 56.0, 114.3, 127.6, 127.9, 128.1, 129.0, 129.3, 129.4, 129.6, 135.2, 136.1, 140.5, 153.1, 157.6, 161.9; HRMS ($C_{23}H_{22}ClN_4O_3S$) [M+H]$^+$: found *m*/*z* 469.1122, calcd 469.1101. Anal. ($C_{23}H_{21}ClN_4O_3S$) C, H, N.

3-(4-Chlorophenyl)-4-phenyl-*N*-[(2,4,6-trimethylphenyl)-sulfonyl]-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (8). 8 was prepared from **4** and 2,4,6-trimethylphenylsulfonyl chloride in 82% yield by the same procedure as described for **9**, mp 228−229 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3H), 2.59 (s, 6H), 3.74 (dd, J = 11 and 4 Hz, 1H), 4.31 (t, J = 11 Hz, 1H), 5.01 (dd, J = 11 and 4 Hz, 1H), 6.94 (s, 2H), 7.16−7.34 (m, 5H), 7.42 (dt, J = 8 and 2 Hz, 2H), 7.50−7.70 (m, 2H), 7.74 (dt, J = 8 and 2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7, 22.7, 50.0, 56.0, 127.5, 127.9, 129.1, 129.3, 129.4, 129.6, 131.5, 135.2, 137.5, 138.6, 140.5, 140.6, 152.8, 157.4; HRMS ($C_{25}H_{26}ClN_4O_2S$) [M+H]$^+$: found *m*/*z* 481.1467, calcd 481.1465. Anal. ($C_{25}H_{25}ClN_4O_2S$) C, H, N.

(4-Chlorophenyl)(2-phenyloxiran-2-yl)methanone (11). To a magnetically stirred solution of **10**[16] (31.8 g, 0.131 mol) in CH_2Cl_2 (300 mL) was added MCPBA (40 g; 70% solution, 0.162 mol) and the resulting mixture was refluxed for 16 h to give a suspension. After cooling of the sample to room temperature, the mixture was washed with an aqueous $NaHCO_3$ solution (3×) and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give **11** (37.6 g, quantitative yield) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.36 (d, J = 5 Hz, 1H), 3.39 (d, J = 5 Hz, 1H), 7.34−7.40 (m, 5H), 7.57 (d, J = 8 Hz, 2H), 7.94 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 54.2, 63.4, 126.7, 129.5, 129.6, 129.8, 131.8, 133.4, 135.7, 139.7, 194.2.

3-(4-Chlorophenyl)-4-hydroxy-4-phenyl-4,5-dihydro-1*H*-pyrazole (12). 11 (112 g, 0.43 mol) was dissolved in EtOH (650 mL) at 35 °C. To the resulting stirred solution was added $N_2H_4 \cdot H_2O$ (42 mL) and the formed **12** slowly precipitated. After standing for 16 h the crystalline material was collected by filtration and successively washed with EtOH, water, and EtOH and subsequently dried to give pure **12** (92 g, 78% yield). mp 195−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.53 (dd, J = 10 and 2 Hz, 1H), 3.73 (dd, J = 10 and 4 Hz, 1H), 6.41 (s, 1H), 7.19−7.42 (m, 8H), 7.62 (dt, J = 8 and 2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 65.7, 84.8, 124.8, 127.2, 127.9, 128.4, 128.6, 131.1, 132.2, 144.8, 151.3.

3-(4-Chlorophenyl)-4-hydroxy-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (13). 13 was prepared from **12** and methyl imidothiocarbamate hemisulfate in 29% yield by the same procedure as described for **4**, mp 203−205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.90−3.80 (m, 3H), 3.93 (d, J = 12 Hz, 1H), 4.12 (d, J = 12 Hz, 1H), 7.22−7.40 (m, 8H), 7.70 (dt, J = 8 and 2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 64.8, 84.6, 124.7, 127.7, 128.6, 128.7, 128.9, 129.6, 133.4, 143.9, 151.5, 155.2 (broad).

3-(4-Chlorophenyl)-*N*-[(4-chlorophenyl)sulfonyl]-4-hydroxy-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (14). 14 was prepared from **13** and *p*-chlorophenylsulfonyl chloride in 68% yield by the same procedure as described for **9**, mp 222−223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.96 (d, J = 12 Hz, 1H), 4.17 (d, J = 12 Hz, 1H), 7.12 (s, 1H), 7.25−7.40 (m, 7H), 7.60 (dt, J = 8 and 2 Hz, 2H) 7.78 (dt, J = 8 and 2 Hz, 2H) 7.88 (dt, J = 8 and 2 Hz, 2H), 8.10 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 63.9, 84.3, 124.9, 128.0, 128.1, 128.3, 128.8, 129.0, 129.3, 129.7, 135.0, 136.8, 142.7, 142.8, 152.9, 157.3; HRMS ($C_{22}H_{19}Cl_2N_4O_3S$) [M+H]$^+$: found *m*/*z* 489.0569, calcd 489.0555. Anal. ($C_{22}H_{18}Cl_2N_4O_3S$) C, H, N.

[(4-Chlorophenyl)sulfonyl]dithioimidocarbonic Acid Dimethyl Ester (15). 15 was prepared from 4-chlorophenylsulfonamide, MeI, and CS_2 according to the literature procedure.[17] ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.35 (s, 6H), 7.69 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 16.6, 129.0, 129.7, 138.4, 139.6, 187.4.

[(2-Chlorophenyl)sulfonyl]dithioimidocarbonic Acid Dimethyl Ester (16). To a magnetically stirred solution of 2-chlorophenylsulfonamide (11.54 g, 0.0603 mol) in DMF (60 mL) was added CS_2 (4.0 mL, 0.0663 mol). KOH (11.2 mL of a 45% aqueous solution) was slowly added while keeping the temperature <15 °C. The resulting red solution was stirred

for 1 h and MeI was slowly added (7.4 mL, 0.119 mol) to give a yellow solution which was stirred for 2 h. Water (300 mL) was added and the resulting precipitate was collected by filtration, washed with petroleum ether (40−60), and recrystallized from EtOH (125 mL) to give **16** (12.24 g, 69% yield), mp 128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 6H), 7.39−7.45 (m, 1H), 7.48−7.55 (m, 2H), 8.20 (dd, J = 8 and 2 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 16.6, 127.9, 130.2, 131.6, 132.3, 135.0, 138.3, 187.3.

[(3-Chlorophenyl)sulfonyl]dithioimidocarbonic Acid Dimethyl Ester (17). 17 was prepared from *m*-chlorophenylsulfonamide, CS_2, and MeI in 63% yield by the same procedure as described for **16**, mp 80 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.55 (s, 6H), 7.40−7.60 (m, 2H), 7.85−7.92 (m, 1H), 7.97−8.00 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 16.6, 125.8, 126.5, 131.7, 133.5, 134.1, 142.6, 188.0.

[(4-Fluorophenyl)sulfonyl]dithioimidocarbonic Acid Dimethyl Ester (18). 18 was prepared from *p*-fluorophenylsulfonamide, CS_2, and MeI in 89% yield by the same procedure as described for **16**, mp 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 6H), 7.14−7.20 (m, 2H), 7.97−8.03 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 16.5, 116.7 (d, J_{CF} = 23 Hz), 130.2 (d, J_{CF} = 10 Hz), 137.2 (d, J_{CF} = 3 Hz), 164.8 (d, J_{CF} = 251 Hz), 186.9.

[(4-(Trifluoromethyl)phenyl)sulfonyl]dithioimidocarbonic Acid Dimethyl Ester (19). 19 was prepared from *p*-(trifluoromethyl)phenylsulfonamide, CS_2, and MeI in 93% yield by the same procedure as described for **16**, mp 116−117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.60 (s, 6H), 8.00 (d, J = 8 Hz, 2H), 8.15 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.6, 123.8 (d, J_{CF} = 273 Hz), 126.8 (d, J_{CF} = 4 Hz), 128.0, 133.0 (d J_{CF} = 33 Hz), 144.7, 188.4.

3-(4-chlorophenyl)-*N*-[(4-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidothioic Acid Methyl Ester (20). A magnetically stirred mixture of **2** (12.0 g, 46.8 mmol), diester **15** (9.20 g, 31.1 mmol), and Et_3N (15 mL) in CH_3CN (200 mL) was refluxed for 20 h under dry N_2. An additional portion of **2** (12.0 g, 46.8 mmol) was added and the resulting mixture was refluxed for another 16 h. After concentration in vacuo, CH_2Cl_2 was added and the resulting solution was washed twice with water and dried over Na_2SO_4. After filtration and concentration, the residue was further purified by flash chromatography (Et_2O/ petroleum ether (40−60) = 1/1 (v/v)) to give **20** (12.5 g, 80% yield based on **15**), mp 139 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H), 4.48−4.56 (m, 1H), 4.81 (dd, J = 12 and 4 Hz, 1H), 4.94 (br t, J = 12 Hz, 1H), 7.16 (d, J = 8 Hz, 2H), 7.24−7.36 (m, 5H), 7.44 (dt, J = 8 and 2 Hz, 2H), 7.60 (d, J = 8 Hz, 2H), 7.90 (dt, J = 8 and 2 Hz, 2H).

3-(4-Chlorophenyl)-*N*-[(2-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidothioic Acid Methyl Ester (21). 21 was prepared from **2** and **16** in 76% yield by the same procedure as described for **20**, mp 153−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.48−4.56 (m, 1H), 4.81 (dd, J = 11 and 4 Hz, 1H), 5.02 (br t, J = 11 Hz, 1H), 7.16 (br d, J = 8 Hz, 2H), 7.25−7.36 (m, 5H), 7.38 (dd, J = 8 and 2 Hz, 1H), 7.44 (td, J = 8 and 2 Hz, 1H), 7.50 (dd, J = 8 and 2 Hz, 1H), 7.61 (br d, J = 8 Hz, 2H), 8.16 (dd, J = 8 and 2 Hz, 1H).

3-(4-Chlorophenyl)-*N*-[(3-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidothioic Acid Methyl Ester (22). 22 was prepared from **2** and **17** in 75% yield by the same procedure as described for **20**, mp 162−163.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 4.52 (br d, J = 11 Hz, 1H), 4.82 (dd, J = 11 and 4 Hz, 1H), 4.96 (br t, J = 11 Hz, 1H), 7.15 (br d, J = 8 Hz, 2H), 7.25−7.36 (m, 5H), 7.41 (t, J = 8 Hz, 1H), 7.46−7.50 (m 1H), 7.61 (dt, J = 8 and 2 Hz, 2H), 7.85 (dt, J = 8 and 2 Hz, 1H) 7.97 (t, J = 2 Hz, 1H).

3-(4-Chlorophenyl)-*N*-[(4-fluorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidothioic Acid Methyl Ester (23). 23 was prepared from **2** and **18** in 75% yield by the same procedure as described for **20**, mp 176−178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.38 (s, 3H), 4.24−4.30 (m, 1H), 4.76 (t, J = 11 Hz, 1H), 5.22 (dd, J = 11 and 4 Hz, 1H), 7.20−7.28 (m, 3H), 7.31−7.39 (m, 4H), 7.47 (d, J = 8 Hz, 2H), 7.70 (d, J = 8 Hz, 2H), 7.92−7.97 (m, 2H).

3-(4-Chlorophenyl)-*N*-{[4-(trifluoromethyl)phenyl]sulfonyl}-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboximidothioic Acid Methyl Ester (24). 24 was prepared from **2** and **19** in 89% yield by the same procedure as described for **20**, mp 173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.42 (s, 3H), 4.29 (br d, J = 11, 1H), 4.80 (t, J = 11 Hz, 1H), 5.26 (dd, J = 11 and 4 Hz, 1H), 7.24−7.30 (m, 3H), 7.33−7.38 (m, 2H), 7.48 (d, J = 8 Hz, 2H), 7.73 (d, J = 8 Hz, 2H), 7.94 (d, J = 8 Hz, 2H), 8.13 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 16.4 (broad), 50.9, 60.1 (broad), 123.9 (q, J_{CF} = 273 Hz), 126.5 (q, J_{CF} = 4 Hz), 127.1, 127.7, 128.2, 128.4, 129.4, 129.75, 129.82, 132.0 (q, J_{CF} = 32 Hz), 136.3, 139.7, 149.9 (broad), 161.9 (broad), 163.0 (broad); HRMS ($C_{24}H_{20}ClF_3N_3O_2S_2$) $[M+H]^+$: found m/z 538.0668, calcd 538.0638. Anal. ($C_{24}H_{19}ClF_3N_3O_2S_2$) C, H, N.

***N^1*-Dimethyl-*N^2*-[(4-chlorophenyl)sulfonyl]-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1*H*-pyrazole-1-carboxamidine (25).** To a magnetically stirred mixture of **20** (4.20 g, 8.30 mmol) in MeOH (75 mL) was added cold dimethylamine (10 mL, 40% aqueous solution, 160 mmol) and CH_2Cl_2 (75 mL) and the resulting solution was stirred at room temperature for 6 h. Evaporation in vacuo and subsequent flash chromatographic purification (Et_2O/petroleum ether (40−60) = 1/1 (v/v), followed by Et_2O) gave a crude solid which was further purified by recrystallization from diisopropyl ether to yield **25** (2.63 g, 63% yield), mp 189−190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.15 (s, 6H), 3.71 (dd, J = 11 and 4 Hz, 1H), 4.46 (t, J = 11 Hz, 1H), 4.96 (dd, J = 11 and 4 Hz, 1H), 7.21−7.34 (m, 5H), 7.41 (d, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 2H), 7.62 (d, J = 8 Hz, 2H), 7.79 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.5, 49.4, 58.5, 127.4, 127.85, 127.88, 129.1 (2C), 129.2, 129.4, 129.5, 135.2, 135.8, 140.2, 145.3, 154.4, 157.4; HRMS ($C_{24}H_{23}Cl_2N_4O_2S$) $[M+H]^+$: found m/z 501.0911, calcd 501.0919. Anal. Calcd. for ($C_{24}H_{22}Cl_2N_4O_2S$: C, H, N.

***N^1*-Dimethyl-*N^2*-[(4-fluorophenyl)sulfonyl]-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1*H*-pyrazole-1-carboxamidine (26). 26** was prepared from **23** and dimethylamine in 74% yield by the same procedure as described for **25**, mp 176−177 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.15 (s, 6H), 3.72 (dd, J = 11 and 4 Hz, 1H), 4.47 (t, J = 11 Hz, 1H), 4.97 (dd, J = 11 and 4 Hz, 1H), 7.21−7.35 (m, 7H), 7.42 (d, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 7.82−7.88 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.5, 49.3, 58.5, 116.0 (d, J_{CF} = 22 Hz), 127.83, 127.87, 128.3 (d, J_{CF} = 9 Hz), 129.1, 129.2, 129.4, 129.5, 135.1, 140.2, 142.8 (d, J_{CF} = 3 Hz), 154.3, 157.4, 163.5 (d, J_{CF} = 248 Hz); HRMS ($C_{24}H_{23}ClFN_4O_2S$) $[M+H]^+$: found m/z 485.1222, calcd 485.1214. Anal. ($C_{24}H_{22}ClFN_4O_2S$) C, H, N.

3-(4-Chlorophenyl)-*N*-[(2-chlorophenyl)sulfonyl]-*N*′-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (27). 27 was prepared from **21** and methylamine in 65% yield by the same procedure as described for **25**, mp 191−192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.95 (d, J = 4 Hz, 3H), 4.00 (dd, J = 11 and 4 Hz, 1H), 4.48 (t, J = 11 Hz, 1H), 7.20−7.35 (m, 5H), 7.41−7.56 (m, 5H), 7.77 (dt, J = 8 and 2 Hz, 2H), 8.02 (dd, J = 8 and 2 Hz, 1H), 8.19 (br d, J = 4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.6 (broad), 50.0, 58.0, 127.5, 127.6, 127.9, 128.7, 129.1, 129.2, 129.55, 129.57, 130.8, 131.7, 132.8, 135.4, 140.3, 143.1 (broad), 152.6, 157.9; HRMS ($C_{23}H_{21}Cl_2N_4O_2S$) $[M+H]^+$: found m/z 487.0752, calcd 487.0762. Anal. ($C_{23}H_{20}Cl_2N_4O_2S$) C, H, N.

3-(4-Chlorophenyl)-*N*-[(3-chlorophenyl)sulfonyl]-*N*′-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (28). 28 was prepared from **22** and methylamine in 85% yield by the same procedure as described for **25**, mp 167−168 °C; NMR (400 MHz, $CDCl_3$) δ 3.24 (d, J = 4 Hz, 3H), 4.12 (dd, J = 11 and 4 Hz, 1H), 4.54 (t, J = 11 Hz, 1H), 4.65 (dd, J = 11 and 4 Hz, 1H), 7.12 (br d, J = 8 Hz, 2H), 7.18 (br s, 1H), 7.24−7.34 (m, 5H), 7.37 (d, J = 8 Hz, 1H), 7.40−7.44 (m, 1H), 7.52 (dt, J = 8 and 2 Hz, 2H), 7.80 (br d, J = 8 Hz, 1H), 7.92 (br t, J = 2 Hz, 1H). HRMS ($C_{23}H_{21}Cl_2N_4O_2S$) $[M+H]^+$: found m/z 487.0762, calcd 487.0762. Anal. ($C_{23}H_{20}Cl_2N_4O_2S$) C, H, N.

3-(4-Chlorophenyl)-*N*-{[(4-trifluoromethyl)phenyl]sulfonyl}-*N′*-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (29). 29 was prepared from **24** and methylamine in 76% yield by the same procedure as described for **25**, mp 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90−2.97 (m, 3H), 3.95 (dd, J = 11 and 4 Hz, 1H), 4.48 (t, J = 11 Hz, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.17−7.32 (m, 5H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.74 (dt, J = 8 and 2 Hz, 2H), 7.84 (d, J = 8 Hz, 1H), 8.04 (d, J = 8 Hz, 1H) 8.24−8.30 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6)) δ 30.6 (broad), 50.1, 57.9, 124.0 (q, J_{CF} = 273 Hz), 126.3 (q, J_{CF} = 3 Hz), 126.4, 127.6, 127.9, 129.2, 129.3, 129.55, 129.58, 131.1 (q, J_{CF} = 32 Hz), 135.4, 140.3, 150.2 (broad), 152.5, 158.1; HRMS ($C_{24}H_{21}ClF_3N_4O_2S$) $[M+H]^+$: found m/z 521.1005, calcd 521.1026. Anal. ($C_{24}H_{20}ClF_3N_4O_2S$) C, H, N.

1-(4-Chlorophenyl)-2-(4-fluorophenyl)prop-2-en-1-one (32). To a magnetically stirred solution of 1-(4-chlorophenyl)-2-(4-fluorophenyl)ethanone (**30**) (31.9 g, 0.128 mol) in MeOH (500 mL) was successively added piperidine (1.2 mL, 12.1 mmol), AcOH (1.2 mL, 20.8 mmol), and formaline (40 mL: 37% aqueous solution, 0.532 mol), and the resulting mixture was refluxed for 4 h, followed by concentration in vacuo. Water was added to the residue and the mixture was extracted with CH_2Cl_2. The organic layer was separated, washed with water (3×), dried over Na_2SO_4, filtered, and concentrated to give **32** (33.4 g, quantitative yield), mp 77 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.63 (s, 1H), 6.05 (s, 1H), 6.97−7.10 (m, 2H), 7.35−7.47 (m, 4H), 7.83 (dt, J = 8 and 2 Hz, 2H).

3-(4-Chlorophenyl)-4-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazole (34). A solution of **32** (33.4 g, 0.128 mol), hydrazine hydrate (630 mL) in EtOH (300 mL) was refluxed for 3 h under dry N_2. After cooling of the sample to room temperature the mixture was concentrated in vacuo, water was added, and extraction was performed with CH_2Cl_2. The organic layer was twice washed with water, dried over Na_2SO_4, and concentrated. The residue was crystallized from EtOH to give **34** (20.0 g, 59% yield), mp 115 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.51 (dd, J = 11 and 4.5 Hz, 1H), 3.93 (t, J = 11 Hz, 1H), 4.47 (dd, J = 11 and 4.5 Hz, 1H), 5.65 (br s, 1H), 6.92−7.03 (m, 2H), 7.15−7.27 (m, 4H), 7.83 (dt, J = 8 and 2 Hz, 2H).

1-(4-Fluorophenyl)-2-phenylprop-2-en-1-one (33). 33 was prepared from 1-(4-fluorophenyl)-2-phenylethanone **31** in quantitative yield by the same procedure as described for **32**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.62 (s, 1H), 6.05 (s, 1H), 7.03−7.13 (m, 2H), 7.30−7.45 (m, 5H), 7.90−8.00 (m, 2H).

3-(4-Fluorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazole (35). 35 was prepared from **33** in 84% yield by the same procedure as described for **34**, mp 110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.52 (dd, J = 11 and 4.5 Hz, 1H), 3.97 (t, J = 11 Hz, 1H), 4.49 (dd, J = 11 and 4.5 Hz, 1H), 5.70 (br s, 1H), 6.85−7.00 (m, 2H), 7.20−7.35 (m, 5H), 7.49−7.60 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 50.4, 57.7, 116.0 (d, J_{CF} = 21 Hz), 127.4, 128.1, 128.4 (d, J_{CF} = 8 Hz), 129.4, 129.8 (d, J_{CF} = 3 Hz), 142.2, 151.9, 162.4 (d, J_{CF} = 245 Hz).

3,4-Bis-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (36). 36 was prepared according to the literature procedure.[16]

***N*-[(4-Methylphenyl)sulfonyl]carbamic Acid Methyl Ester (40).** To a magnetically stirred solution of *p*-toluenesulfonamide (6.48 g, 0.040 mol) and Et_3N (10.12 g, 0.100 mol) in anhydrous CH_3CN (40 mL) was slowly added methyl chloroformate (4.43 mL, 0.060 mol), and the resulting solution was stirred at room temperature for 6 h and evaporated in vacuo. The residue was dissolved in EtOAc and aqueous $NaHCO_3$ was added. The water layer was separated and acidified with a mixture of ice and concentrated HCl to give an oily precipitate which slowly crystallized upon standing. The crystals were collected by filtration, washed with water, and dried to give **40** (4.09 g, 45% yield), mp = 107−109 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.71 (s, 3H), 7.35 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H), 7.40−7.65 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 21.4, 53.2, 127.8, 129.9, 136.7, 144.6, 152.0.

***N*-[(4-Chlorophenyl)sulfonyl]carbamic Acid Methyl Ester (37). 37** was prepared from *p*-chlorophenylsulfonamide in 75% yield by the same procedure as described for **40**, mp = 132 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (s, 3H), 7.53 (dt, J = 8 and 2 Hz, 2H), 8.00 (dt, J = 8 and 2 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 53.4, 129.77, 129.79, 138.3, 139.0, 152.0.

***N*-(Phenylsulfonyl)carbamic Acid Methyl Ester (38). 38** was prepared according to the literature procedure.[38]

***N*-[(4-Fluorophenyl)sulfonyl]carbamic Acid Methyl Ester (39). 39** was prepared from *p*-fluorophenylsulfonamide in 53% yield by the same procedure as described for **40**, mp = 102 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.72 (s, 3H), 5.00 (br s, 1H), 7.17−7.30 (m, 2H), 8.04−8.14 (m, 2H).

***N*-{[3-(Trifluoromethyl)phenyl]sulfonyl}carbamic Acid Methyl Ester (41). 41** was prepared from *m*-(trifluoromethyl)-phenylsulfonamide in 69% yield by the same procedure as described for **40**, mp 105−108 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.73 (s, 3H), 7.67−7.77 (m, 1H), 7.93 (br d, J = 8 Hz, 1H), 8.24−8.33 (m, 2H), NH proton invisible.

***N*-[(2,4,6-Trimethylphenyl)sulfonyl]carbamic Acid Methyl Ester (42). 42** was prepared from 2,4,6-trimethylphenylsulfonamide in 44% yield by the same procedure as described for **40**, mp 169 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.70 (s, 6H), 3.70 (s, 3H) 7.01 (s, 2H), NH proton invisible.

***N*-[(4-Methoxyphenyl)sulfonyl]carbamic Acid Methyl Ester (43). 43** was prepared from *p*-methoxyphenylsulfonamide in 53% yield by the same procedure as described for **40**, mp = 108 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.88 (s, 3H), 5.00 (br s, 1H), 7.00 (dt, J = 8 and 2 Hz, 2H), 7.97 (dt, J = 8 and 2 Hz, 2H).

***N*-[(2-Naphthyl)sulfonyl]carbamic Acid Methyl Ester (44). 44** was prepared from 2-naphthylsulfonamide in 62% yield by the same procedure as described for **40**, mp 140−142 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.66 (s, 3H), 7.68−7.72 (m, 1H), 7.73−7.77 (m, 1H), 7.90 (dd, J = 8 and 2 Hz, 1H), 8.07 (d, J = 8 Hz, 1H), 8.17 (d, J = 8 Hz, 1H), 8.24 (d, J = 8 Hz, 1H), 8.62 (br s, 1H), 12.20 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 53.3, 122.5, 128.16, 128.23, 129.4, 129.73, 129.77, 129.8, 131.8, 135.0, 136.4, 152.0.

3-(4-Chlorophenyl)-*N*-[(4-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (45). To a solution of **37** (29.94 g, 0.120 mmol) in toluene (600 mL) was added **2** (33.86 g, 0.132 mmol), and the resulting mixture was refluxed for 4 h. After cooling of the sample to room temperature **45** slowly crystallized. The crystals were collected and washed with MTBE (2×) to yield pure **45** (55.67 g, 98% yield), mp 210−212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.68 (dd, J = 12 and 4 Hz, 1H), 4.28 (t, J = 12 Hz, 1H), 4.98 (dd, J = 12 and 4 Hz, 1H), 7.16−7.34 (m, 5H), 7.43 (dt, J = 8 and 2 Hz, 2H), 7.72 (dt, J = 8 and 2 Hz, 2H), 7.82 (dt, J = 8 and 2 Hz, 2H), 8.02 (dt, J = 8 and 2 Hz, 2H), 11.55 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.8, 54.9, 127.6, 127.9, 129.0, 129.4, 129.54 (2C), 129.56, 130.0, 135.1, 138.7, 139.2, 140.5, 148.9, 156.3; HRMS ($C_{22}H_{18}Cl_2N_3O_3S$) $[M+H]^+$: found m/z 474.0436, calcd 474.0446. Anal. Calcd. for $C_{22}H_{17}Cl_2N_3O_3S$; H, N: C: calcd., 55.70; found, 55.24.

***N*-[(4-Chlorophenyl)sulfonyl]-3-(4-chlorophenyl)-4-(4-fluorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide (46). 46** was prepared from **34** and **37** in 78% yield by the same procedure as described for **45**, mp 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.68 (dd, J = 11 and 4 Hz, 1H), 4.26 (t, J = 11 Hz, 1H), 5.02 (dd, J = 11 and 4 Hz, 1H), 7.10−7.16 (m, 2H), 7.21−7.26 (m, 2H), 7.44 (dt, J = 8 and 2 Hz, 2H), 7.73 (dt, J = 8 and 2 Hz, 2H), 7.81 (dt, J = 8 and 2 Hz, 2H), 8.01 (dt, J = 8 and 2 Hz, 2H), 11.55 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 48.9, 54.8, 116.3 (d, J_{CF} = 21 Hz), 129.0, 129.3, 129.5, 129.6, 129.7 (d, J_{CF} = 8 Hz), 130.0, 135.1, 136.7 (d, J_{CF} = 3 Hz), 138.6, 139.3, 149.0, 156.1, 161.7 (d, J_{CF} = 244 Hz).

***N*-[(4-Chlorophenyl)sulfonyl]-3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (47). 47** was prepared from **35** and **37** in 60% yield by the same procedure as described for **45**, mp 114 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.68 (dd, J = 12 and 4 Hz, 1H), 4.26 (t, J = 12 Hz, 1H), 4.98 (dd, J = 12 and 4 Hz, 1H), 7.17−7.34 (m, 7H), 7.72 (dt, J = 8 and 2 Hz, 2H), 7.83−7.88 (m, 2H), 8.02 (dt, J

= 8 and 2 Hz, 2H), 11.55 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.9, 54.9, 115.9 (d, J_{CF} = 22 Hz), 127.1 (d, J_{CF} = 3 Hz), 127.6, 127.8, 129.50, 129.53, 129.9, 130.2 (d, J_{CF} = 9 Hz), 138.6, 139.3, 140.6, 149.0, 156.3, 163.4 (d, J_{CF} = 249 Hz).

3,4-Bis-(4-chlorophenyl)-*N*-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-1*H*-pyrazole-1-carboxamide (48). 48 was prepared from **36** and **37** in 71% yield by the same procedure as described for **45**, mp 260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.70 (dd, J = 11 and 4 Hz, 1H), 4.27 (t, J = 11 Hz, 1H), 5.02 (dd, J = 11 and 4 Hz, 1H), 7.22 (dt, J = 8 and 2 Hz, 2H), 7.37 (dt, J = 8 and 2 Hz, 2H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.73 (dt, J = 8 and 2 Hz, 2H), 7.81 (dt, J = 8 and 2 Hz, 2H), 8.02 (dt, J = 8 and 2 Hz, 2H), 11.55 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.0, 54.7, 129.0, 129.3, 129.50, 129.54 (2C), 129.6, 130.0, 132.5, 135.2, 138.7, 139.2, 139.4, 149.0, 155.9.

3-(4-Chlorophenyl)-4-phenyl-*N*-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide (49). 49 was prepared from **2** and **38** in 81% yield by the same procedure as described for **45**, mp 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.67 (dd, J = 11 and 4 Hz, 1H), 4.26 (t, J = 11 Hz, 1H), 4.96 (dd, J = 11 and 4 Hz, 1H), 7.15−7.33 (m, 5H), 7.42 (dt, J = 8 and 2 Hz, 2H), 7.82 (dt, J = 8 and 2 Hz, 2H), 8.02 (dt, J = 8 and 2 Hz, 2H), 11.50 (br s, 1H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 49.7, 54.9, 127.6, 127.85, 127.9, 128.9, 129.3, 129.50, 129.54, 129.56, 133.7, 135.0, 140.4, 140.6, 149.0, 156.1.

3-(4-Chlorophenyl)-*N*-[(4-fluorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (50). 50 was prepared from **2** and **39** in 96% yield by the same procedure as described for **45**, mp 220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.68 (dd, J = 12 and 4 Hz, 1H), 4.28 (t, J = 12 Hz, 1H), 4.98 (dd, J = 12 and 4 Hz, 1H), 7.16−7.52 (m, 9H), 7.82 (d, J = 8 Hz, 2H), 8.06−8.12 (m, 2H), 11.55 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.7, 54.9, 116.3 (d, J_{CF} = 22 Hz), 127.6, 127.8, 128.9, 129.46, 129.54, 129.56, 131.2 (d, J_{CF} = 10 Hz), 135.1, 136.7 (d, J_{CF} = 3 Hz), 140.5, 149.0, 156.2, 165.0 (d, J_{CF} = 252 Hz).

3-(4-Chlorophenyl)-*N*-[(4-methylphenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (51). 51 was prepared from **2** and **40** in 72% yield by the same procedure as described for **45**, mp 219−221 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.40 (s, 3H), 3.67 (dd, J = 12 and 4 Hz, 1H), 4.25 (t, J = 12 Hz, 1H), 4.96 (dd, J = 12 and 4 Hz, 1H), 7.16−7.32 (m, 5H), 7.43 (d, J = 8 Hz, 4H), 7.82 (dt, J = 8 and 2 Hz, 2H), 7.90 (d, J = 8 Hz, 2H), 11.40 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.3, 49.7, 54.9, 127.6, 127.8, 128.0 (2C), 128.9, 129.5 (2C), 129.7, 135.0, 137.6, 140.5, 144.2, 149.0, 156.0.

3-(4-Chlorophenyl)-4-phenyl-*N*-{3-[(trifluoromethyl)-phenyl]sulfonyl}-4,5-dihydro-1*H*-pyrazole-1-carboxamide (52). 52 was prepared from **2** and **41** in 71% yield by the same procedure as described for **45**, mp 187−190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.69 (dd, J = 11 and 4 Hz, 1H), 4.29 (t, J = 11 Hz, 1H), 4.99 (dd, J = 11 and 4 Hz, 1H), 7.16−7.33 (m, 4H), 7.44 (dt, J = 8 and 2 Hz, 2H), 7.80 (dt, J = 8 and 2 Hz, 2H), 7.90−7.94 (m, 1H), 8.10−8.14 (m, 1H), 8.28−8.34 (m, 2H), 11.60 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.8, 54.9, 123.8 (q, J_{CF} = 272 Hz), 124.6 (q, J_{CF} = 4 Hz), 127.6, 127.9, 128.9, 129.4, 129.5, 129.6, 129.9 (q, J_{CF} = 23 Hz), 130.49, 130.52, 131.1, 132.1, 135.1, 140.5, 141.5, 148.9, 156.5.

3-(4-Chlorophenyl)-4-phenyl-*N*-[(2,4,6-trimethylphenyl)-sulfonyl]-4,5-dihydro-1*H*-pyrazole-1-carboxamide (53). 53 was prepared from **2** and **42** in 80% yield by the same procedure as described for **45**, mp 245−250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.26 (s, 3H), 2.66 (s, 6H), 3.66 (dd, J = 11 and 4 Hz, 1H), 4.24 (t, J = 11 Hz, 1H), 4.95 (dd, J = 11 and 4 Hz, 1H), 7.04 (s, 2H), 7.15−7.34 (m, 5H), 7.42 (dt, J = 8 and 2 Hz, 2H), 7.87 (dt, J = 8 and 2 Hz, 2H), 11.55 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.8, 22.5, 49.7, 54.8, 127.6, 127.8, 128.9, 129.53, 129.56, 129.7, 131.9, 134.9, 139.8 (2C), 140.6, 142.8, 149.6, 155.9.

3-(4-Chlorophenyl)-*N*-[(4-methoxyphenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (54). 54 was prepared from **2** and **43** in 71% yield by the same procedure as described for **45**, mp 243−244 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.67 (dd, J = 11 and 4 Hz, 1H), 3.85 (s, 3H), 4.35 (t, J = 11 Hz, 1H), 4.96 (dd, J = 11 and 4 Hz, 1H), 7.12−7.32 (m, 7H), 7.43 (dt, J = 8 and 2 Hz, 2H), 7.82 (dt, J = 8 and 2 Hz, 2H), 7.95 (dt, J = 8 and 2 Hz, 2H), 11.40 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.7, 54.9, 56.1, 114.5, 127.6, 127.8, 128.9, 129.5 (3C), 130.3, 131.9, 135.0, 140.6, 149.1, 155.9, 163.2.

3-(4-Chlorophenyl)-4-phenyl-*N*-[(2-naphthyl)sulfonyl]-4,5-dihydro-1*H*-pyrazole-1-carboxamide (55). 55 was prepared from **2** and **44** in 81% yield by the same procedure as described for **45**, mp 216−220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.66 (dd, J = 11 and 4 Hz, 1H), 4.24 (t, J = 11 Hz, 1H), 4.96 (dd, J = 11 and 4 Hz, 1H), 7.15−7.30 (m, 5H), 7.43 (d, J = 8 Hz, 2H), 7.69−7.78 (m, 2H), 7.82 (d, J = 8 Hz, 2H), 8.01−8.23 (m, 4H), 8.35 (br s, 1H), 11.60 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.7, 54.9, 123.1, 127.6, 127.8, 128.0, 128.2, 128.9, 129.42, 129.45, 129.52 (2C), 129.56 (2C), 129.8, 131.8, 134.9, 135.0, 137.4, 140.5, 149.0, 156.1.

3-(4-Chlorophenyl)-*N′*-[(4-chlorophenyl)sulfonyl]-*N*-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (67). A mixture of **45** (3.67 g, 7.75 mmol) and PCl_5 (1.69 g, 8.14 mmol) in chlorobenzene (40 mL) was refluxed for 1 h. After thorough concentration in vacuo, the formed **56** was suspended in CH_2Cl_2 and reacted with cold methylamine (1.5 mL). After stirring of the sample at room temperature for 1 h, the mixture was concentrated in vacuo. The residue was crystallized from EtOH to give **67** (2.29 g, 61% yield): mp 96−98 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.94 (d, J = 4 Hz, 3H), 3.96 (dd, J = 11 and 4 Hz, 1H), 4.46 (t, J = 11 Hz, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.20−7.35 (m, 5H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.53 (dt, J = 8 and 2 Hz, 2H), 7.77 (dt, J = 8 and 2 Hz, 2H), 7.82 (dt, J = 8 and 2 Hz, 2H), 8.19 (br d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.6 (broad), 50.1, 57.9, 127.5, 127.6, 127.9, 129.1 (2C), 129.2, 129.5, 129.6, 135.4, 135.8, 140.3, 145.4 (broad), 152.5, 157.9; HRMS ($C_{23}H_{21}Cl_2N_4O_2S$) $[M+H]^+$: found m/z 487.0745, calcd 487.0762. Anal. ($C_{23}H_{20}Cl_2N_4O_2S$) C, H, N.

3-(4-Chlorophenyl)-*N′*-[(4-chlorophenyl)sulfonyl]-4-(4-fluorophenyl)-*N*-methyl- 4,5-dihydro-1*H*-pyrazole-1-carboxamidine (68). 68 was prepared from **46** via **57** in 68% yield by the same procedure as described for **67,** mp 93−94 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.92 (br d, J = 4.5 Hz, 3H), 3.90 (dd, J = 11 and 4 Hz, 1H), 4.41 (t, J = 11 Hz, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.10−7.16 (m, 2H), 7.20−7.25 (m, 2H), 7.42 (d, J = 8 Hz, 2H), 7.50 (dt, J = 8 and 2 Hz, 2H), 7.72 (d, J = 8 Hz, 2H), 7.79 (dt, J = 8 and 2 Hz, 2H), 8.16−8.21 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 31.0 (broad), 49.5, 58.1, 116.7 (d, J_{CF} = 21 Hz), 127.8, 129.40, 129.44, 129.8, 130.0 (d, J_{CF} = 8 Hz), 135.8, 136.1, 136.8 (d, J_{CF} = 3 Hz), 145.7 (broad), 152.8, 158.1, 162.1 (d, J_{CF} = 244 Hz); HRMS ($C_{23}H_{20}Cl_2FN_4O_2S$) $[M+H]^+$: found m/z 471.1054, calcd 471.1058.

***N′*-[(4-Chlorophenyl)sulfonyl]-3-(4-fluorophenyl)-*N*-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (69). 69** was prepared from **47** via **58** in 43% yield by the same procedure as described for **67**, mp 146−148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.93 (d, J = 4 Hz, 3H), 3.96 (dd, J = 11 and 4 Hz, 1H), 4.45 (t, J = 11 Hz, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.20−7.36 (m, 7H), 7.53 (dt, J = 8 and 2 Hz, 2H), 7.77−7.84 (m, 4H), 8.17 (br d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.6 (broad), 50.2, 57.9, 116.1 (d, J_{CF} = 22 Hz), 126.9 (d, J_{CF} = 3 Hz), 127.5, 127.6, 127.9, 129.1, 129.6, 130.2 (d, J_{CF} = 9 Hz), 135.8, 140.4, 145.4 (broad), 152.5, 158.1, 163.5 (d, J_{CF} = 249 Hz); HRMS ($C_{23}H_{21}ClFN_4O_2S$) $[M+H]^+$: found m/z 471.1065, calcd 471.1058. Anal. ($C_{23}H_{20}ClFN_4O_2S$) C, H, N.

3,4-Bis-(4-chlorophenyl)-*N′*-[(4-chlorophenyl)sulfonyl]-*N*-methyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (70). 70 was prepared from **48** via **59** in 55% yield by the same procedure as described for **67**, mp 107−108 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.95 (br d, J = 4 Hz, 3H), 3.94 (dd, J = 11 and 4 Hz, 1H), 4.45 (t, J = 11 Hz, 1H), 5.08 (dd, J = 11 and 4 Hz, 1H), 7.24 (dt, J = 8 and 2 Hz, 2H), 7.53 (dt, J = 8 and 2

Hz, 2H), 7.40 (dt, J = 8 and 2 Hz, 2H), 7.46 (dt, J = 8 and 2 Hz, 2H), 7.53 (dt, J = 8 and 2 Hz, 2H), 7.75 (dt, J = 8 and 2 Hz, 2H), 7.82 (dt, J = 8 and 2 Hz, 2H), 8.22 (br d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.6 (broad), 49.3, 57.7, 127.5, 129.0, 129.1, 129.2, 129.5, 129.6 (2C), 132.5, 135.5, 135.9, 139.1, 145.3 (broad), 152.5, 157.5; HRMS ($C_{23}H_{20}Cl_3N_4O_2S$) $[M+H]^+$: found m/z 521.0353, calcd 521.0373.

3-(4-Chlorophenyl)-*N*-methyl-4-phenyl-*N*′-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (71). 71 was prepared from **49** via **60** in 53% yield by the same procedure as described for **67**, mp 130−132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.95 (d, J = 4 Hz, 3H), 3.98 (dd, J = 11 and 4 Hz, 1H), 4.47 (t, J = 11 Hz, 1H), 5.04 (dd, J = 11 and 4 Hz, 1H), 7.20−7.28 (m, 3H), 7.30−7.35 (m, 2H), 7.42−7.50 (m, 5H), 7.77 (dt, J = 8 and 2 Hz, 2H), 7.80−7.84 (m, 2H), 8.13 (br d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.7 (broad), 50.0, 58.0, 125.5, 127.6, 127.9, 129.0, 129.1, 129.3, 129.5, 129.6, 131.2, 135.3, 140.3, 146.4, 152.5, 157.7; ($C_{23}H_{22}ClN_4O_2S$) $[M+H]^+$: found m/z 453.1158, calcd 453.1152. Anal. ($C_{23}H_{21}ClN_4O_2S$) C, H, N.

3-(4-Chlorophenyl)-*N*′-[(4-fluorophenyl)sulfonyl]-*N*-methyl-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (72). 72 was prepared from **50** via **61** in 39% yield by the same procedure as described for **67,** mp 147−149 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.95 (d, J = 4 Hz, 3H), 3.97 (dd, J = 11 and 4 Hz, 1H), 4.46 (t, J = 11 Hz, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.20−7.35 (m, 7H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.76 (dt, J = 8 and 2 Hz, 2H), 7.84−7.90 (m, 2H), 8.16 (br d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.7 (broad), 50.0, 58.0, 116.1 (d, J_{CF} = 22 Hz), 127.6, 127.9, 128.3 (d, J_{CF} = 9 Hz), 129.1, 129.2, 129.5, 129.6, 135.4, 140.3, 142.9 (broad), 152.4, 157.8, 163.4 (d, J_{CF} = 249 Hz); HRMS ($C_{23}H_{21}ClFN_4O_2S$) $[M+H]^+$: found m/z 471.1054, calcd 471.1058. Anal. ($C_{23}H_{20}ClFN_4O_2S$) C, H, N.

3-(4-Chlorophenyl)-*N*-methyl-*N*′-[(4-methylphenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (73). 73 was prepared from **51** via **62** in 50% yield by the same procedure as described for **67**, mp 170−172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.32 (s, 3H), 2.95 (d, J = 4 Hz, 3H), 3.95 (dd, J = 11 and 4 Hz, 1H), 4.45 (t, J = 11 Hz, 1H), 5.03 (dd, J = 11 and 4 Hz, 1H), 7.19−7.27 (m, 5H), 7.30−7.35 (m, 2H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.69 (d, J = 8 Hz, 2H), 7.75 (dt, J = 8 and 2 Hz, 2H), 8.09 (br d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.2, 30.7 (broad), 50.0, 58.0, 125.5, 127.6, 127.9, 129.1, 129.3, 129.4, 129.5, 129.6, 135.3, 140.4, 141.1, 143.6, 152.4, 157.6. HRMS ($C_{24}H_{24}ClN_4O_2S$) $[M+H]^+$: found m/z 467.1337, calcd. 467.1309. Anal. Calcd. for $C_{24}H_{23}ClN_4O_2S$: C, H, N.

3-(4-Chlorophenyl)-*N*-methyl-*N*′-{[3-(trifluoromethyl)-phenyl]sulfonyl}-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (74). 74 was prepared from **52** via **63** in 44% yield by the same procedure as described for **67**, mp 167−168 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.93 (d, J = 4 Hz, 3H), 3.98 (dd, J = 11 and 4 Hz, 1H), 4.49 (t, J = 11 Hz, 1H), 5.07 (dd, J = 11 and 4 Hz, 1H), 7.20−7.28 (m, 3H), 7.30−7.36 (m, 2H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.72−7.77 (m, 3H), 7.90 (br d, J = 8 Hz, 1H), 8.06 (br s, 1H), 8.14 (br d, J = 8 Hz, 1H), 8.23−8.29 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.5 (broad), 50.1, 57.9, 121.9 (q, J_{CF} = 4 Hz), 123.9 (q, J_{CF} = 272 Hz),127.6, 127.88, 127.95, 129.09, 129.15, 129.54, 129.58, 129.63 (q, J_{CF} = 22 Hz), 129.64, 130.7, 135.4, 140.3, 147.6, 152.5, 158.1; HRMS ($C_{24}H_{21}ClF_3N_4O_2S$) $[M+H]^+$: found m/z 521.1041, calcd. 521.1026. Anal. Calcd. for $C_{24}H_{20}ClF_3N_4O_2S$: C, H, N.

3-(4-Chlorophenyl)-*N*-methyl-*N*′-[(2,4,6-trimethylphenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (75). 75 was prepared from **53** via **64** in 35% yield by the same procedure as described for **67**, mp 171−172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.19 (s, 3H), 2.53 (s, 6H), 2.91 (br d, J = 4 Hz, 3H), 3.85 (dd, J = 11 and 4 Hz, 1H), 4.41 (t, J = 11 Hz, 1H), 5.00 (dd, J = 11 and 4 Hz, 1H), 6.89 (br s, 2H), 7.16−7.34 (m, 5H), 7.43 (dt, J = 8 and 2 Hz, 2H), 7.74 (dt, J = 8 and 2 Hz, 2H), 8.14 (br d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.6, 22.8, 30.6, 49.9, 58.0, 127.5, 127.9, 129.1, 129.3, 129.5, 129.6, 131.3, 132.0, 135.3, 136.7, 139.7, 140.3, 152.3, 157.5; HRMS ($C_{26}H_{28}ClN_4O_2S$) $[M+H]^+$: found m/z 495.1592, calcd 495.1622.

3-(4-Chlorophenyl)-*N*-methyl-4-phenyl-*N*′-[(4-methoxyphenyl)sulfonyl]-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (76). 76 was prepared from **54** via **65** in 39% yield by the same procedure as described for **67**, mp 180−181 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.97 (d, J = 4 Hz, 3H), 3.78 (s, 3H), 3.97 (dd, J = 11 and 4 Hz, 1H), 4.46 (t, J = 11 Hz, 1H), 5.03 (dd, J = 11 and 4 Hz, 1H), 6.98 (dt, J = 8 and 2 Hz, 2H), 7.19−7.27 (m, 3H), 7.30−7.35 (m, 2H), 7.44 (dt, J = 8 and 2 Hz, 2H), 7.73 (dt, J = 8 and 2 Hz, 2H), 7.76 (dt, J = 8 and 2 Hz, 2H), 8.05 (br d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.8 (broad), 49.3, 55.8, 58.0, 114.0, 127.5, 127.6, 127.9, 129.1, 129.3, 129.5, 129.6, 135.3, 138.5 (broad), 140.4, 152.4, 157.5, 161.3; HRMS ($C_{24}H_{24}ClN_4O_3S$) $[M+H]^+$: found m/z 483.1289, calcd 483.1258. Anal. ($C_{24}H_{23}ClN_4O_3S$) C, H, N.

3-(4-Chlorophenyl)-*N*-methyl-4-phenyl-*N*′-[(2-naphthyl)sulfonyl]-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (77). 77 was prepared from **55** via **66** in 29% yield by the same procedure as described for **67**, mp 162−164 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.96 (br d, J = 4 Hz, 3H), 4.02 (dd, J = 11 and 4 Hz, 1H), 4.50 (t, J = 11 Hz, 1H), 5.03 (dd, J = 11 and 4 Hz, 1H), 7.19−7.27 (m, 3H), 7.28−7.33 (m, 2H), 7.43 (dt, J = 8 and 2 Hz, 2H), 7.59−7.66 (m, 2H), 7.75 (dt, J = 8 and 2 Hz, 2H), 7.88 (dd, J = 8 and 2 Hz, 1H), 7.95−8.02 (m, 2H) 8.07−8.10 (m, 1H), 8.14−8.20 (m, 1H), 8.42 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.7 (broad), 50.0, 58.0, 122.7, 125.0, 127.5, 127.6, 127.9, 128.0, 128.2, 129.0, 129.1, 129.2, 129.4, 129.5, 129.6, 132.1, 133.9, 135.4, 140.3, 143.6 (broad), 152.5, 157.7. HRMS ($C_{27}H_{24}ClN_4O_2S$) $[M+H]^+$: found m/z 503.1280, calcd. 503.1309. Anal. Calcd. for $C_{27}H_{23}ClN_4O_2S$: C, H, N.

(4*S*)-(−)-3-(4-Chlorophenyl)-*N*-methyl-*N*′-[(4-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (80) and **(4*R*)-(+)-3-(4-chlorophenyl)-*N*-methyl-*N*′-[(4-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (81).** Chiral preparative HPLC separation of racemic **67** (18 g, 0.037 mol) using a Chiralpak AD, 20 μm chiral stationary phase yielded **80** (7.16 g, 0.0147 mol) and **81** (7.46 g, 0.0153 mol), respectively. The mobile phase consisted of a mixture of *n*-hexane/ethanol (80/20 (v/v)) and 0.1% NH_4OH (25% aqueous solution). **80**: $[\alpha_D^{25}] = -150°$, c = 0.01, MeOH; mp 171−172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.94 (d, J = 4 Hz, 3H), 3.96 (dd, J = 11 and 4 Hz, 1H), 4.46 (t, J = 11 Hz, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.20−7.35 (m, 5H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.53 (dt, J = 8 and 2 Hz, 2H), 7.77 (dt, J = 8 and 2 Hz, 2H), 7.82 (dt, J = 8 and 2 Hz, 2H), 8.19 (br d, J = 4 Hz, 1H); HRMS ($C_{23}H_{21}Cl_2N_4O_2S$) $[M+H]^+$: found m/z 487.0768, calcd 487.0762. Anal. ($C_{23}H_{20}Cl_2N_4O_2S$) C, H, N. **81**: $[\alpha_D^{25}] = +150°$, c = 0.01, MeOH; mp 171−172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.94 (d, J = 4 Hz, 3H), 3.96 (dd, J = 11 and 4 Hz, 1H), 4.46 (t, J = 11 Hz, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.20−7.35 (m, 5H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.53 (dt, J = 8 and 2 Hz, 2H), 7.77 (dt, J = 8 and 2 Hz, 2H), 7.82 (dt, J = 8 and 2 Hz, 2H), 8.19 (br d, J = 4 Hz, 1H); HRMS ($C_{23}H_{21}Cl_2N_4O_2S$) $[M+H]^+$: found m/z 487.0749, calcd 487.0762. Anal. ($C_{23}H_{20}Cl_2N_4O_2S$) C, H, N.

(−)-3-(4-Chlorophenyl)-*N*-methyl-*N*′-{[4-(trifluoromethyl)phenyl]sulfonyl)}-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (78) and **(+)-3-(4-chlorophenyl)-*N*-methyl-*N*′-{[4-(trifluoromethyl)phenyl]sulfonyl}-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamidine (79).** Racemic amidine **29** was analogously separated by chiral preparative HPLC as described for **67** using a mixture of heptane/2-propanol (85/15 (v/v)) as the mobile phase and Chiralcel OD as the stationary phase to give optically pure **78** and **79**, respectively. **78**: $[\alpha_D^{25}] = -131°$, c = 0.01, $CHCl_3$; mp: 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90−2.97 (m, 3H), 3.95 (dd, J = 11 and 4 Hz, 1H), 4.48 (t, J = 11 Hz, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.17−7.32 (m, 5H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.74 (dt, J = 8 and 2 Hz, 2H), 7.84 (d, J = 8 Hz, 1H), 8.04 (d, J = 8 Hz, 1H) 8.24−8.30 (m, 1H); HRMS ($C_{24}H_{21}ClF_3N_4O_2S$) $[M+H]^+$: found m/z 521.1016, calcd 521.1026. Anal. ($C_{24}H_{20}$-

$ClF_3N_4O_2S$) C, H, N. **79**: $[\alpha_D^{25}] = +131°$, $c = 0.01$, $CHCl_3$, mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90−2.97 (m, 3H), 3.95 (dd, J = 11 and 4 Hz, 1H), 4.48 (t, J = 11 Hz, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.17−7.32 (m, 5H), 7.45 (dt, J = 8 and 2 Hz, 2H), 7.74 (dt, J = 8 and 2 Hz, 2H), 7.84 (d, J = 8 Hz, 1H), 8.04 (d, J = 8 Hz, 1H), 8.24−8.30 (m, 1H); HRMS ($C_{24}H_{21}ClF_3N_4O_2S$) $[M+H]^+$: found m/z 521.1033, calcd 521.1026. Anal. ($C_{24}H_{20}ClF_3N_4O_2S$) C, H, N.

4-Chlorobenzoylisothiocyanate (82). 82 was prepared according to the literature procedure[18] from 4-chlorobenzoyl chloride and NH_4NCS and immediately reacted with **2**.

***N*-(4-Chlorobenzoyl)-3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-thiocarboxamide (83). 2** (2.57 g, 0.01 mol) was added to a magnetically stirred and cooled (0 °C) solution of **82** (2.07 g, 0.0105 mol) in anhydrous CH_3CN (40 mL), and the resulting mixture was stirred at room temperature for 1 h. The formed precipitate (NH_4Cl) was removed by filtration and thoroughly washed with CH_3CN. The filtrate was concentrated in vacuo and the formed solid material was collected and further purified by column chromatography (CH_2Cl_2), followed by recrystallization from CH_3CN to give pure **83** (2.07 g, 46% yield), mp 173−175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.17 (dd, J = 11 and 4 Hz, 1H), 4.71 (t, J = 11 Hz, 1H), 5.10 (dd, J = 11 and 4 Hz, 1H), 7.24−7.37 (m, 5H), 7.42 (d, J = 8 Hz, 2H), 7.60−7.66 (m, 4H), 8.05 (d, J = 8 Hz, 2H), 11.30 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 49.5, 60.3, 127.7, 128.0, 128.9, 129.1, 129.3, 129.6 (2C), 130.7, 132.6, 136.0, 137.8, 140.3, 161.0, 164.4, 173.7.

N′-(4-Chlorobenzoyl)-3-(4-chlorophenyl)-*N*-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (84). To a stirred suspension of **83** (1.82 g, 4.0 mmol) in CH_3CN (20 mL) was added excess cold methylamine (3 mL) to give a clear green colored solution. A solution of $HgCl_2$ (1.20 g, 4.40 mmol) in CH_3CN (20 mL) was slowly added, and the resulting dark suspension was stirred for 3 h. The precipitate was removed by filtration over Hyflo super cel (Fluka). The filtrate was successively concentrated in vacuo, dissolved in EtOAc, washed with a 2 N NaOH solution, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was further purified by column chromatography (petroleum ether (40−60)/EtOAc = 1/1 (v/v)) and recrystallized from EtOH to yield **84** (0.57 g, 32% yield), mp 164−165 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.90 (br s, 3H), 3.84 (br s, 1H), 4.40 (br s, 1H), 5.05 (dd, J = 11 and 4 Hz, 1H), 7.20−7.26 (m, 3H), 7.30−7.35 (m, 2H), 7.42 (d, J = 8 Hz, 2H), 7.46 (d, J = 8 Hz, 2H), 7.78 (d, J = 8 Hz, 2H), 8.02 (d, J = 8 Hz, 2H), 8.22 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.5 (broad), 50.2 (broad), 56.9 (broad), 127.6, 127.8, 128.1, 129.1, 129.4, 129.5, 129.8, 130.2 (2C), 135.1, 135.6 (broad), 137.5, 140.7, 157.0, 157.3. HRMS ($C_{24}H_{21}Cl_2N_4O$) $[M+H]^+$: found m/z 451.1109, calcd. 451.1092. Anal. Calcd. for $C_{24}H_{20}Cl_2N_4O$: C, H, N.

Receptor Binding Assays. 1. CB_1 Assay. CB_1 receptor affinities were determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB_1 receptor is stably transfected[19] in conjunction with [^{3}H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [^{3}H]-radioligand, with or without addition of test compound, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting. The IC_{50} values from at least three independent measurements were combined and converted to K_i values using the assumptions of Cheng and Prusoff.[39]

CB_2 Assay. CB_2 receptor affinities were determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB_2 receptor is stably transfected[20] in conjunction with [^{3}H]CP-55,940 as radioligand.[40] After incubation of a freshly prepared cell membrane preparation with the [^{3}H]-radioligand, with or without addition of test compound, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting. The IC_{50} values from at least two independent measurements were combined and converted to K_i values using the assumptions of Cheng and Prusoff.[39]

In Vitro Pharmacology. Measurement of Arachidonic Acid Release. CB_1 receptor antagonism[21] was assessed with the human CB_1 receptor cloned in Chinese hamster ovary (CHO) cells. CHO cells were grown in a Dulbecco's modified Eagle's medium (DMEM) culture medium, supplemented with 10% heat-inactivated fetal calf serum. Medium was aspirated and replaced by DMEM, without fetal calf serum, but containing [^{3}H]-arachidonic acid and incubated overnight in a cell culture stove (5% CO_2/95% air; 37 °C; water-saturated atmosphere). During this period [^{3}H]-arachidonic acid was incorporated in membrane phospholipids. On the test day, medium was aspirated and cells were washed three times using 0.5 mL of DMEM, containing 0.2% bovine serum albumin (BSA). Stimulation of the CB_1 receptor by WIN 55,212-2 led to activation of PLA_2 followed by release[21] of [^{3}H]-arachidonic acid into the medium. This WIN 55,212-2-induced release was concentration dependently antagonized by CB_1 receptor antagonists. The CB_1 antagonistic potencies of the test compounds were expressed as pA_2 values.

In Vivo Pharmacology. 1. CP-55,940 Induced Hypotension in Rat. Male normotensive rats (225−300 g; Harlan, Horst, The Netherlands) were anaesthetized with pentobarbital (80 mg/kg ip). Blood pressure was measured, via a cannula inserted into the left carotid artery, by means of a Spectramed DTX-plus pressure transducer (Spectramed B. V., Bilthoven, The Netherlands). After amplification by a Nihon Kohden Carrier amplifier (Type AP-621G; Nihon Kohden B. V., Amsterdam, The Netherlands), the blood pressure signal was registered on a personal computer (Compaq Deskpro 386s), by means of a Po-Ne-Mah data-acquisition program (Po-Ne-Mah Inc., Storrs, USA). Heart rate was derived from the pulsatile pressure signal. All compounds were administered orally as a microsuspension in 1% methylcellulose 30 min before induction of the anesthesia which was 60 min prior to administration of the CB_1 receptor agonist CP-55,940. The injection volume was 10 mL kg^{-1}. After haemodynamic stabilization the CB_1 receptor agonist CP-55,940 (0.1 mg kg^{-1} i.v.) was administered and the hypotensive effect[22] established. Typical blood pressure after administration of CP-55,940 was approximately 60% as compared to vehicle treated animals.

2. WIN 55,212-2 Induced Hypothermia in Isolated Mouse. Male NMRI mice (Charles River, Sulzfeld, Germany) weighing ca. 12−14 g upon arrival in the laboratory, were housed in groups of five animals per cage (dimensions: 34 × 22 × 15 cm) under nonreversed 12 h light−12 h dark cycle conditions (lights on from 07.00 to 19.00 h). The animals were housed at constant room temperature (21 ± 2 °C) and relative humidity (60 ± 10%) with food and water freely available. Experiments were carried out between 9.00 a.m. and 3 p.m. The day preceding the experiment, the mice were individually housed with free access to food and water. According to a balanced design mice were allocated to times of day and treatments in each experiment. The number of animals per treatment group was eight. The experiments were performed with a dose range of the test compound administered in a volume of 10 mL/kg orally. Simultaneously, WIN 55,212-2 (5 mg/kg, suspended in 1% methyl cellulose with 5% mannitol) was administered in a volume of 10 mL/kg s.c. After 60 min, the temperature was measured by inserting a thermistor probe for a length of 2 cm into the rectum of the mice. Digital recordings of the temperature were determined with an accuracy of 0.1 °C by means of a Keithley 871A digital thermometer (NiCr−NiAl thermocouple). The body temperatures of all groups were compared to the 1 h saline pretreated group (n = 24). Effects on body temperature were analyzed using ANOVA statistics. Hypothermia[23] was determined by the difference in temperature between the control group and the WIN 55,212-2 test group. The lowest effective dose (LED) was defined as the dose of the administered test compound (in the presence of WIN 55,212-2) giving a significant increase of the body temperature as compared with the WIN 55,212-2 treated animals. Typical temperature measurements in vehicle

treated animals were of the range of 37.5−38.5 °C and administration of WIN-55,212-2 reduced the temperature to 33−34 °C.

P-Glycoprotein Assay. The capability of the human MDR1 P-glycoprotein pump to translocate compounds over a cellular monolayer of PK1 LLC MDR cells was assessed. The transport method essentially described in the literature[31] was used. Compounds were added at the start of the experiment at 1 μg/mL to one side of the cellular layer. The bottom to top transport was measured as well as the top to bottom transport. The P-glycoprotein (Pgp) factor was expressed as the ratio of the bottom to top transport and top to bottom transport. The membrane passage was expressed as the mean percentage of compound transported from bottom to top and from top to bottom at 3 h after adding the compound. Compound detection was performed using a LC/MS method.

X-ray Crystallographic Analysis of 6. Crystallographic analyses and the structure determination of compound **6** were performed by Dr. H. Kooijman and A. L. Spek, Bijvoet Centre for Biomolecular Research, Utrecht University, Utrecht, The Netherlands. Suitable crystals were obtained by recrystallization of **6** from EtOH. A colorless, plate shaped crystal was fixed to the tip of a glass fiber and transferred into the cold nitrogen stream on a rotating anode X-ray diffractometer. The structure was solved by automated direct methods. Non-hydrogen atoms were refined with anisotropic atomic displacement parameters. The hydrogen atoms were refined with fixed isotropic displacement parameters related to the value of the equivalent isotropic displacement parameters of their carrier atoms by a factor 1.2. All calculations were performed on a DEC Alpha station 255 (UNIX). Relevant data collection parameters: temperature: 150 K, wavelength: 0.71073 Å (Mo Ka), X-ray exposure time: 5.5 h, crystal size: 0.05 × 0.12 × 0.15 mm, crystal system: monoclinic, space group: $P2_1/c$: unit cell dimensions: a = 17.1654; b = 5.759; c = 24.882 Å, calculated density: 1.535 g cm^{-3}, completeness: 100%, total number of reflections: 47244, number of unique reflections: 3748, number of refined parameters: 334.

X-ray Crystallographic Analysis of 80. Crystallographic analyses and the structure determination of compound **80** were performed by Dr. H. Kooijman and A. L. Spek, Bijvoet Centre for Biomolecular Research, Utrecht University, Utrecht, The Netherlands. Suitable crystals were obtained by recrystallization of **80** from EtOH. A colorless, block-shaped crystal, cut from a larger crystal, was glued to the tip of a glass fiber and transferred into the cold nitrogen stream on a rotating anode X-ray diffractometer. The structure was solved by automated direct methods. Hydrogen atoms were located on an electron-density map and their coordinates were included as parameters in the refinement. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Relevant data collection parameters: Temperature: 150 K, wavelength: 0.71073 Å (Mo Ka), X-ray exposure time: 3 h, crystal size: 0.25 × 0.25 × 0.35 mm, crystal system: orthorhombic, space group: $P2_12_12_1$: unit cell dimensions: a = 9.018; b = 15.084; c = 16.073 Å, calculated density: 1.481 g cm^{-3}, completeness: 99.9%, total number of reflections: 49341, number of unique reflections: 5006, number of refined parameters: 350. Flack x-parameter: − 0.02.

Experimental Lipophilicity Determination by RP-HPLC. Partition coefficients (n-octanol/water) were measured by a high-performance liquid chromatographic (HPLC) method based on an Organization for Economic Cooperation and Development (OECD) method,[41] using a mobile phase buffered at pH > 11 and an aluminum-based octadecyl modified stationary phase. The retention factor k of a compound was correlated with its partition coefficient using a calibration graph based on 10 reference compounds with well-known log P_{ow} in the range 2.1−5.7.

CNS/Plasma Ratio of Compound 80. Preliminary kinetic data in rats were gathered by administration of 1 mg/kg intravenously and 10 mg/kg orally to Wistar rats. A group of 10 animals received 1 mg/kg intravenously; blood samples were taken at time points 10, 30, 60, 180, and 420 min after dosing, two animals per time point. A group of 12 animals received 10 mg/kg per os, blood and brain samples were taken at 60, 120, 360, and 1440 min in triplicate. Plasma samples were analyzed after liquid−liquid extraction on a reversed phase liquid chromatographic system with ultraviolet detection at 314 nm. Brain samples were analyzed on the same system after homogenization and solid-phase extraction. Levels in the samples were calculated from a concentration versus response curve obtained from spiked blanc matrix samples which were processed and analyzed in the same way as the samples (extracted calibration curve). The CNS/plasma ratio was estimated using the plasma (ng/mL) over brain (ng/g) concentration over the entire oral dosing time range. The average value found was 1.7 (s_{mean} = 0.14, n = 12).

Molecular Modeling. All modeling studies were carried out on a Silicon Graphics Octane workstation running Sybyl V6.9.1.[42] Confort was used to generate a collection of maximally diverse low energy conformations of **80**, followed by MOPAC minimization using the PM3 method. The protein model was created using the 2.8-Å crystal structure of bovine rhodopsin.[26] The residues were mutated according to the amino acid sequences alignment made with ClustalX.[43] The loops were omitted. Standard geometries for the side-chains were given by the Biopolymer module. This rough model was minimized with Kolmann charges in the Kollmann All-atom force field, holding the TMH backbones fixed. Subsequently, the kink in TMH6 at Pro358 was introduced[25] to enable the salt bridge between Lys192 and Asp366 and the model was further minimized. The ligands were manually docked into the receptor, followed by minimization with the Tripos force-field using the charges obtained by earlier calculations, with a range-constraint of 2.5−3.0 Å on the N-atom of Lys192 and the O-atom of the ligand to which it is bound. Finally, the complex was subjected to a simulated annealing procedure of five cycles (starting at 500 K for 500 fs annealing to 200 K via exponential ramping during 1000 fs) with the same constraints as mentioned above.

Acknowledgment. Mr. Karel Stegman and Mr. Jan Jeronimus are gratefully acknowledged for supplying and interpreting the spectral data. Dr. Mia Pras-Raves is acknowledged for supplying the X-ray diffraction data. Dr. Anneke Mühlebach and Mrs. Ingrid Gehrmann are gratefully acknowledged for supplying the elemental analysis data. Mr. Piet Hoogkamer is acknowledged for supplying the RP-HPLC lipophilicity data.

Supporting Information Available: Microanalytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Robson, P. Therapeutic aspects of cannabis and cannabinoids. *Br. J. Psychiatry* **2001**, *178*, 107−115.
(2) Croxford, J. L. Therapeutic potential of cannabinoids in CNS disease. *CNS Drugs* **2003**, *17*, 179−202.
(3) Glass, M. The role of cannabinoids in neurodegenerative diseases. *Progr. Neuro-Psychopharmacol., Biol. Psychiat.* **2001**, *25*, 743−765.
(4) Consroe, P. Brain cannabinoid systems as targets fore the therapy of neurological disorders. *Neurobiol. Dis.* **1998**, *5*, 534−551.
(5) Matsuda, L. A.; Lolait, S. J.; Brownstein, B. J.; Young, A. C.; Bonner. T. I. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* **1990**, *356*, 561−564.
(6) Munro, S.; Thomas, K. L.; Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **1993**, *365*, 61−62.
(7) Wilson, R.; Nicoll, R. A. Endocannabinoid signaling in the brain. *Science* **2002**, *296*, 678−682.
(8) Breivogel, C. S.; Griffin, G.; Di Marzo, V.; Martin, B. R. Evidence for a new G protein-Coupled Cannabinoid receptor in mouse brain. *Mol. Pharmacol.* **2001**, *60*, 155−163.
(9) Adam, J.; Cowley, P. Recent advances in the cannabinoids. *Expert Opin. Ther. Pat.* **2002**, *12*, 1475−1489.
(10) Pertwee, R. G. Neuropharmacology and therapeutic potential of cannabinoids. *Addict, Biol.* **2000**, *5*, 37−46.

(11) Gomez, R.; Navarro, M.; Ferrer, B.; Trigo, J. M.; Bilbao, A.; Del Arco, I.; Cippitelli, A.; Nava, F.; Piomelli, D.; De Fonseca, F. R. A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. *J. Neurosci.* **2002**, *22*, 9612−9617.
(12) Hall, W. Cannabis and psychosis. *Drug Alcohol Rev.* **1998**, *17*, 433−444.
(13) Hungund, B. L.; Basavarajappa, B. S.; Vadasz, C.; Kunos, G.; de Fonseca, F. R.; Colombo, G.; Serra, S.; Parsons, L.; Koob, G. F. Ethanol, endocannabinoids, and the cannabinoidergic signaling system. *Alcohol Clin. Exp. Res.* **2002**, *26*, 565−574.
(14) Pertwee, R. G. Cannabinoids and the gastrointestinal tract. *Gut* **2001**, *48*, 859−867.
(15) Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S. R.; McCallion, D.; Pertwee, R.; Makriyannis, A. Structure−activity relationships of pyrazole derivatives as cannabinoid receptor antagonists. *J. Med. Chem.* **1999**, *42*, 769−776.
(16) Grosscurt, A. C.; Van Hes, R.; Wellinga, K. 1-Phenylcarbamoyl-2-pyrazolines, a new class of insecticides. 3. Synthesis and insecticidal properties of 3,4-diphenyl-1-phenylcarbamoyl-2-pyrazolines. *J. Agric. Food Chem.* **1979**, *27*, 406−409.
(17) Gompper, R.; Hägele, W. *N*-Sulfonyl-iminodithiokohlensäureester und *N*-Sulfonyl-dithiourethane. *Chem. Ber.* **1966**, *99*, 2885−2899.
(18) Cho, N. S.; Shon, H. I. Synthesis of 5-(aroylamino)-2-methyl-2*H*-1,2,4-thiadiazol-3-ones by oxidative cyclisation of 1-aroyl-5-methyl-2-thiobiurets. *J. Heterocycl. Chem.* **1991**, *28*, 1645−1649.
(19) Gerard, C. M.; Mollereau, C.; Vassart, G.; Parmentier, M. Molecular cloning of a human cannabinoid receptor which is also expressed in testis. *Biochem J.* **1991**, *279*, 129−134.
(20) Showalter, V. M.; Compton, D. R.; Martin, B. R.; Abood, M. E. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): Identification of cannabinoid receptor subtype selective ligands. *J. Pharmacol. Exp. Ther.* **1996**, *278*, 989−999.
(21) Bayewitch, M.; Rhee, R. H.; Avidorreis, T.; Breuer, A.; Mechoulam, R.; Vogel, Z. (−)-Delta(9)-Tetrahydrocannabinol antagonizes the peripheral cannabinoid receptor-mediated inhibition of adenylyl cyclase. *J. Biol. Chem.* **1996**, *271*, 9902−9905.
(22) Wagner, J. A.; Jarai, Z.; Batkai, S.; Kunos, G. Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB1 receptors. *Eur. J. Pharmacol.* **2001**, *423*, 203−210.
(23) Rawls, S. M.; Cabassa, J.; Geller, E. B.; Adler, M. W. CB1 receptors in the preoptic anterior hypothalamus regulate WIN 55,212−2 [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)-6*H*-pyrrolo[3,2,1ij]quinolin-6-one]-induced hypothermia. *J. Pharmacol. Exp. Ther.* **2002**, *301*, 963−968.
(24) Shim, J.; Welsh, W. J.; Cartier, E.; Edwards, J. L.; Howlett, A. C. Molecular interaction of the antagonist *N*-piperidin-1-yl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide with the CB_1 cannabinoid receptor. *J. Med. Chem.* **2002**, *45*, 1447−1459.
(25) Hurst, D. P.; Lynch, D. L.; Barnett-Norris, J.; Hyatt, S. M.; Seltzman, H. H.; Zhong, M.; Song, Z.-H.; Nie, J.; Lewis, D.; Reggio, P. H. *N*-(Piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (SR141716A) Interaction with LYS 3.28(192) is crucial for its inverse agonism at the Cannabinoid CB1 receptor. *Mol. Pharmacol.* **2002**, *62*, 1274−1287.
(26) Palczewski, K.; Kumasaka, T.; Hori, T.; Behnke, C. A.; Motoshima, H. B. A.; Fox, B. A.; LeTron, I.; Teller, D. C.; Okada, T.; Stenkamp, R. E. Crystal structure of Rhodopsin: a G-protein-coupled receptor. *Science* **2000**, *289*, 739−745.
(27) Barnet-Norris, J.; Hurst, D. P.; Buehner, K.; Ballesteros, J. A.; Guarnieri, F.; Reggio P. H. Agonist alkyl tail interaction with Cannabinoid CB1 receptor V6.43/I6.46 groove induces a Helix 6 active conformation. *Int. J. Quantum. Chem.* **2002**, *88*, 76−86.
(28) Jensen, A. D.; Guarnieri, F.; Rasmussen, S. G. F.; Asmar, F.; Ballesteros, J. A.; Gether, U. Agonist-induced conformational changes at the cytoplasmic side of transmembrane segment 6 in β_2 adrenergic receptor mapped by site-selective Fluorescent Labeling. *J. Biol. Chem.* **2001**, *276*, 9279−9290.
(29) Klebe, G.; Böhm, H.-J. Energetic and entropic factors determining binding affinity in protein−ligand complexes. *J. Receptor Signal Transduct. Res.* **1997**, *17*, 459−473.
(30) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **1997**, *23*, 3−25.
(31) Schinkel, A. H.; Wagenaar, E.; van Deemter, L.; Mol, C. A. A. M.; Borst, P. Absence of the mdr1a P-glycoprotein in mice affects tissue distribution and pharmacokinetics of dexamethasone, digoxin and cyclosporin A. *J. Clin. Invest.* **1995**, *96*, 1698−1705.
(32) Palm; K.; Stenberg, P.; Luthman, K.; Artursson, P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. *Pharm. Res.* **1997**, *14*, 568−571.
(33) Kelder, J.; Grootenhuis, P. D. J.; Bayada, D. M.; Delbressine, L. P. C.; Ploemen, J.-P. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. *Pharm. Res.* **1999**, *16*, 1514−1519.
(34) Van de Waterbeemd, H.; Jones, B. C. Predicting oral absorption and bioavailability. In *Progress in Medicinal Chemistry*; King, F. D.; Oxford, A. W., Eds.; Elsevier Science B. V.: Amsterdam, 2003; Vol. 41, pp 1−59.
(35) Halbert, G. W. Pharmaceutical Development. In *The Textbook of Pharmaceutical Medicine*, 3rd ed.; Griffin, J. P., O'Grady, J., D'Arcy, P. F., Eds.; The Queen's University of Belfast: Belfast, 1998; pp 33−35.
(36) Yalkowsky, S. H.; Valvani, S. C.; Solubility and partitioning. I. Solubility of nonelectrolytes in water. *J. Pharm. Sci.* **1980**, *69*, 912−922.
(37) Jain, N.; Yalkowsky, S. H.; Estimation of the aqueous solubility I. Application to organic nonelectrolytes. *J. Pharm. Sci.* **2001**, *90*, 234−252.
(38) Franz, J. E.; Osuch, C. The reactions of sulfonamides with oxalyl chloride. *J. Org. Chem.* **1964**, *29*, 2592−2595.
(39) Cheng, Y.; Prusoff, W. H. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50% (IC_{50}) of an enzymatic reaction. *Biochem. Pharmacol.* **1973**, *22*, 3099−3108.
(40) Reggio, P. H.; Basu-Dutt, S.; Barnett-Norris, J.; Castro, M. T.; Hurst, D. P.; Seltzman, H. H.; Roche, M. J.; Gilliam, A. F.; Thomas, B. F.; Stevenson, L. A.; Pertwee, R. G.; Abood, M. E. The bioactive conformation of aminoalkylindoles at the cannabinoid CB1 and CB2 receptors: Insights gained from (E)- and (Z)-naphylidene indenes *J. Med. Chem.* **1998**, *41*, 5177−5187.
(41) OECD Guideline for Testing of Chemicals no. 117, adopted at 30-03-1989.
(42) Tripos Inc., St. Louis, MO 63144.
(43) Thompson, J. D.; Gibson, T. J.; Plewniak, F.; Jeanmougin, F.; Higgins, D. G. The ClustalX windows interface: flexible strategies for multiple sequence alignment aided by quality analysis tools. *Nucleic Acids Res.* **1997**, *24*, 4876−4882.

JM031019Q