Bioisosteric Replacements of the Pyrazole Moiety of Rimonabant: Synthesis, Biological Properties, and Molecular Modeling Investigations of Thiazoles, Triazoles, and Imidazoles as Potent and Selective CB_1 Cannabinoid Receptor Antagonists

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Received June 4, 2004

Series of thiazoles, triazoles, and imidazoles were designed as bioisosteres, based on the 1,5-diarylpyrazole motif that is present in the potent CB_1 receptor antagonist rimonabant (SR141716A, **1**). A number of target compounds was synthesized and evaluated in cannabinoid (hCB_1 and hCB_2) receptor assays. The thiazoles, triazoles, and imidazoles elicited in vitro CB_1 antagonistic activities and in general exhibited considerable CB_1 vs CB_2 receptor subtype selectivities, thereby demonstrating to be cannabinoid bioisosteres of the original diarylpyrazole class. Some key representatives in the imidazole series showed potent pharmacological in vivo activities after oral administration in both a CB agonist-induced hypotension model and a CB agonist-induced hypothermia model. Molecular modeling studies showed a close three-dimensional structural overlap between the key compound **62** and rimonabant. A structure−activity relationship (SAR) study revealed a close correlation between the biological results in the imidazole and pyrazole series.

Introduction

Cannabinoids are present in the Indian hemp *Cannabis sativa L.* and have been used as medicinal agents for centuries.[1] However, only within the past 14 years, the research in the cannabinoid area has revealed pivotal information on the endocannabinoid system, its receptor subtypes[2,3] (CB_1 and CB_2), and their (endogenous) agonists.[4] Recent data suggest there may be a third cannabinoid receptor[5] ("CB_3"). The CB_1 cannabinoid receptor is expressed[6] at high levels in several brain areas including areas that control movement (cerebellum and basal ganglia), cognition (cerebral cortex), emesis (nucleus of the solitary tract), memory and attention (hippocampus), and pain. In addition, the CB_1 receptor is expressed in some peripheral tissues including urinary bladder, testis, and ileum. The CB_2 cannabinoid receptor is predominantly found in the immune system (spleen, tonsils, immune cells). CB_1 receptor antagonists may have potential in the treatment of a number of diseases[7] such as neuroinflammatory disorders,[8] cognitive disorders,[9] septic shock,[9] obesity,[9,10] psychosis,[9,11] addiction,[12] and gastrointestinal disorders.[13] Several types of CB_1 receptor antagonists are known and have recently been reviewed,[8,14] such as the potent, orally active, and CB_1/CB_2 receptor selective dihydropyrazole SLV319[15] and the pyrazole family, including rimonabant (**1**),[16,17] and its analogues (**2**-**3**),[18] CP-272871 (**4**),[19] SR 144385 (**5**),[20] and the lower lipophilic NIDA-41020 **(6)**.[21]

Bioisosteric replacement[22] forms a rational medicinal chemistry approach for the discovery of new leads or series, based on existing key ligands. The three-dimensional structures of thiazoles, triazoles, and imidazoles maintain a high similarity to that of the pyrazole. As a consequence they can be regarded as isosteres thereof and have been applied in order to discover pyrazole bioisosteres. Studies on antiinflammatory agents[23] have revealed that replacement of pyrazole with the triazole and imidazole skeletons resulted in loss of antiinflammatory activity. Investigations on herbicidals showed[24] that replacement of pyrazole by the imidazole skeleton resulted in decreased herbicidal activity. Both findings demonstrate that isosteric replacement of pyrazole by such five-membered heterocyclics does not necessarily produce bioisosteres, i.e. compounds with retained biological activity. As the success of a bioisosteric replacement is dependent from the involved molecular target[25] it was decided, despite the above-mentioned discouraging results, to embark on an isosterism approach in the cannabinoid research area. Our approach was based on the 1,5-diarylpyrazole ring being present in a number of potent and selective CB_1 receptor antagonists **1**−**6** as outlined in Figure 1. In this paper our results, featuring three classes of heterocycles (thiazoles, triazoles, and imidazoles) as potent and CB_1-subtype selective receptor antagonists are described.

Chemistry

The 4,5-diarylthiazoles were synthesized[26] as shown in Scheme 1. The 1,2-diaryl ketone **7** was prepared in a Grignard reaction from 4-chlorobenzyl chloride and 2,4-dichlorobenzonitrile and subsequently reacted with

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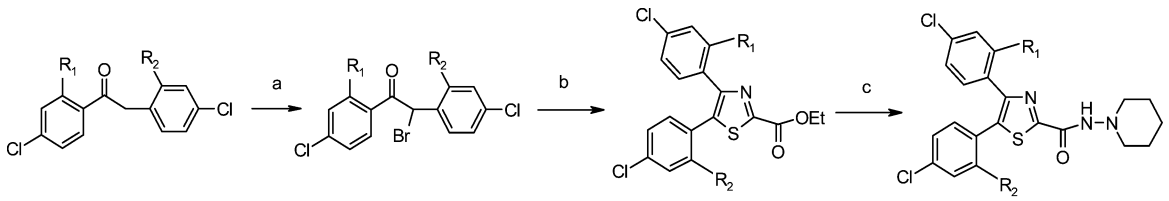
10.1021/jm040843r CCC: $30.25
Published on Web 09/29/2004

Scheme 1[a]



7 R_1 = Cl, R_2 = H
8 R_1 = H, R_2 = Cl

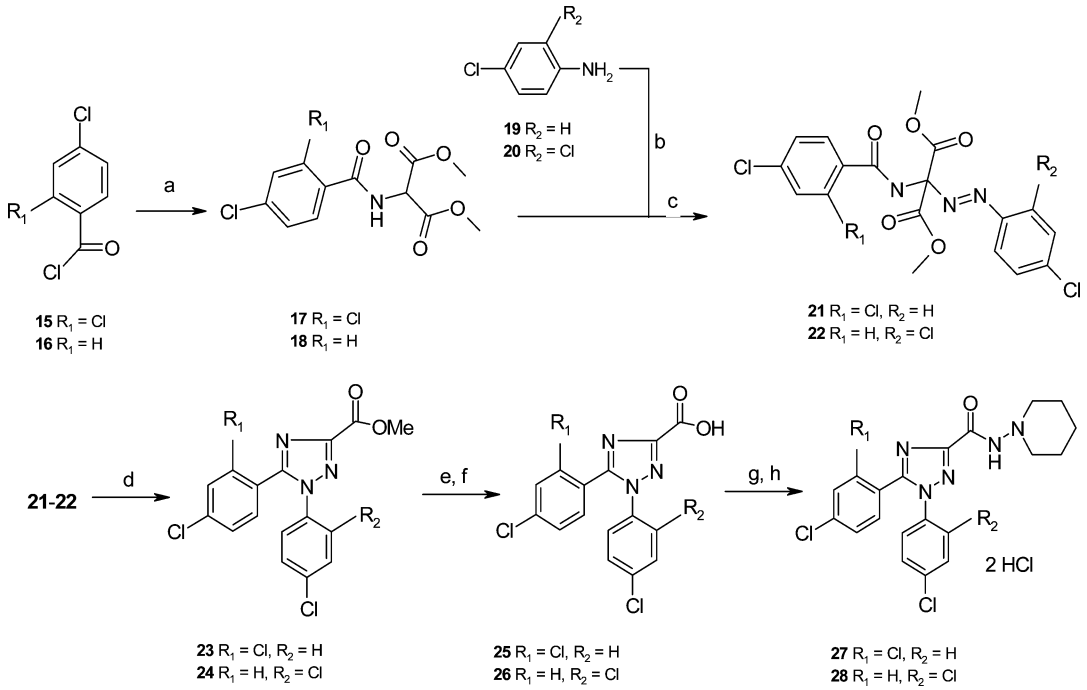
9 R_1 = Cl, R_2 = H
10 R_1 = H, R_2 = Cl

11 R_1 = Cl, R_2 = H
12 R_1 = H, R_2 = Cl

13 R_1 = Cl, R_2 = H
14 R_1 = H, R_2 = Cl

[a] Reagents and conditions: (a) Br_2, benzene, rt, 2 h; (b) $H_2NC(=S)CO_2Et$, EtOH, reflux, 4 h; (c) 1-aminopiperidine, 50 °C, 16 h.

Scheme 2[a]



15 R_1 = Cl
16 R_1 = H

17 R_1 = Cl
18 R_1 = H

19 R_2 = H
20 R_2 = Cl

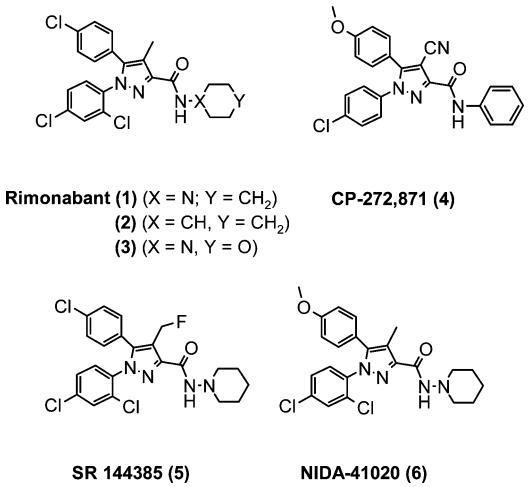
21 R_1 = Cl, R_2 = H
22 R_1 = H, R_2 = Cl

23 R_1 = Cl, R_2 = H
24 R_1 = H, R_2 = Cl

25 R_1 = Cl, R_2 = H
26 R_1 = H, R_2 = Cl

27 R_1 = Cl, R_2 = H
28 R_1 = H, R_2 = Cl

[a] Reagents and conditions: (a) 2-aminodimethyl malonate·HCl, Et_3N, CH_2Cl_2, rt, 16 h; (b) $NaNO_2$, H_2O, HOAc, HCl, −5 °C (c) NaOAc, MeOH, rt, 2 h (d) NaOMe, MeOH, rt, 16 h, followed by HOAc/H_2O; (e) KOH aq, MeOH, reflux, 2 h; (f) HCl, aq, rt; (g) 1-aminopiperidine, DIPEA, HBTU, CH_3CN, rt, 16 h; (h) HCl, EtOAc.



Rimonabant (1) (X = N; Y = CH_2)
(2) (X = CH, Y = CH_2)
(3) (X = N, Y = O)

CP-272,871 (4)

SR 144385 (5)

NIDA-41020 (6)

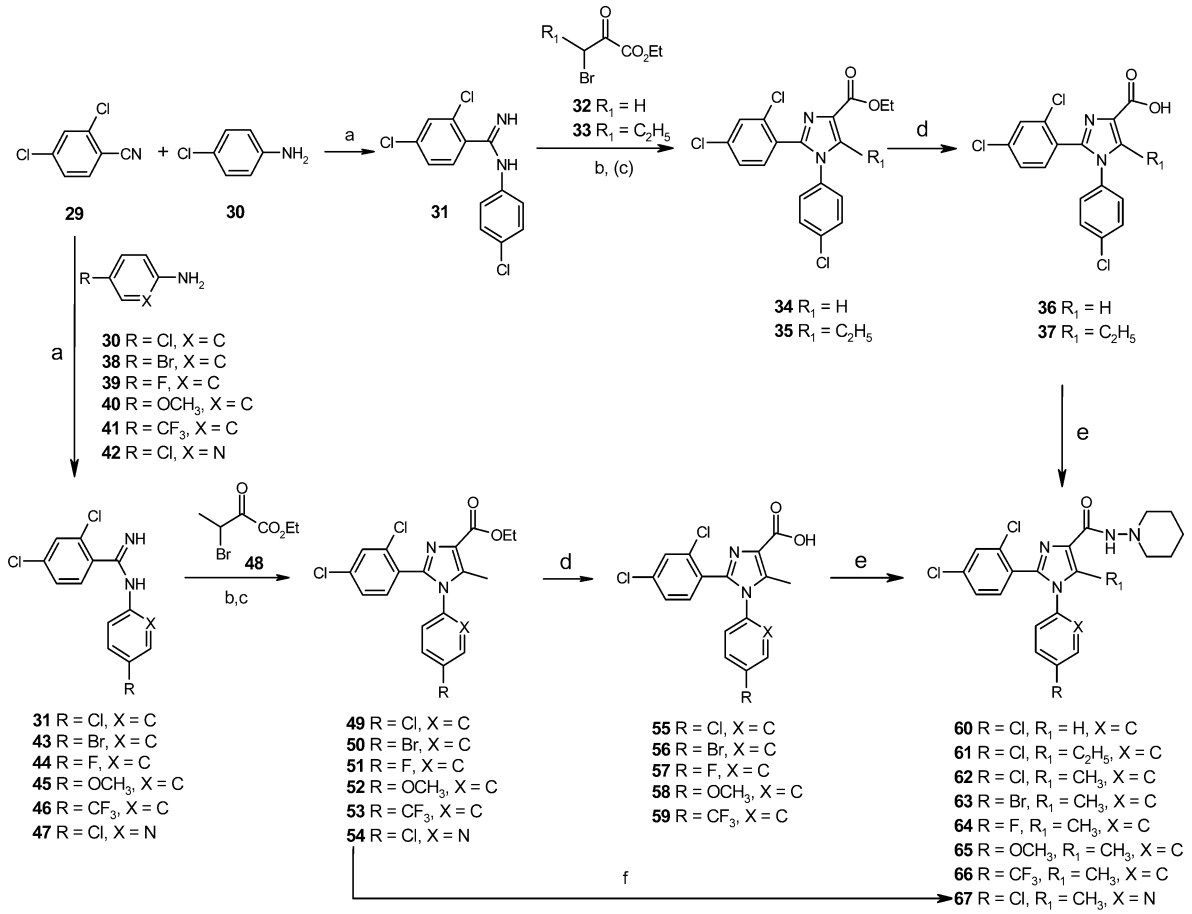
Figure 1. Examples of pyrazole-based CB_1 receptor antagonists **1**−**6**.

bromine in a high yield to give the bromoketone **9**. Ketone **8** was synthesized via a Friedel−Crafts acylation from 2,4-dichlorophenylacetic acid and chlorobenzene and subsequently brominated to **10**. Condensation of **9** with (ethoxycarbonyl)thioamide provided (2-ethoxycarbonyl)-4,5-diaryl thiazole **11** in 63% yield. Similarly, the thiazole **12** was prepared from **10**. The target compounds **13** and **14** were obtained by amidation of **11** and **12**, in 29% and 67% yield, respectively.

A Japp−Klingemann reaction constituted the key step in the synthesis of 1,5-diaryl-1*H*-1,2,4-triazoles[24] as depicted in Scheme 2. The aroyl chloride **15** was amidated with 2-aminodimethylmalonate hydrochloride to give **17** in 47% yield. Similarly, the amide **18** was prepared from **16**. Diazotation of the aniline **19** followed by reaction with **17** afforded the azo intermediate **21** in high yield, which was reacted with sodium methanolate to produce the triazole methyl ester **23**. Saponification of **23** to the corresponding carboxylic acid **25** and subsequent amination with 1-aminopiperidine and HBTU gave the target compound **27**. Similarly, the amide **18** was reacted with **20** and directly converted, without isolation of the azo-intermediate **22**, into ester **24**, hydrolyzed into **26**, and eventually aminated to give the target compound **28**.

The target *N*-substituted 1,2-diarylimidazolecarboxamides **60**−**80**, **82**, **91**−**93**, **97**, and **103** were synthesized according to the reaction pathways reported in Schemes 3−8. Reaction of 2,4-dichlorobenzonitrile **29** with 4-chlo-

Scheme 3[a]



[a] Reagents and conditions: (a) $NaN(Si(CH_3)_3)_2$, THF, rt, 16 h; (b) $NaHCO_3$, 2-propanol, reflux, 20 h; (c) TFA, reflux, 16 h; (d) LiOH, aq, THF, 50 °C, 16 h; (e) 1-aminopiperidine, HBTU, DIPEA, CH_3CN, rt, 16 h; 1-aminopiperidine, $(CH_3)_3Al$, CH_2Cl_2, 45 °C, 16 h.

roaniline **30** using sodium bis(trimethylsilyl) amide as a strong nonnucleophilic base[27] afforded the arylbenzamidine **31** in 84% yield (Scheme 3). Subsequent reaction[27] of **31** with ethyl 3-bromo-2-oxopropanoate **32** gave the intermediate ethyl-1,2-diaryl-1*H*-imidazole-4-carboxylate **34** in 65% yield. Saponification of **34** with aqueous LiOH gave the carboxylic acid **36**. Similarly, **31** was reacted with 3-bromo-2-oxovalerate[28] **33**. Subsequent addition of trifluoroacetic acid was required to drive the aromatization to the imidazole ring to completion. The formed ester **35** was saponified to the corresponding acid **37**. Analogously, reaction[27] of 2,4-dichlorobenzonitrile **29** with the anilines **38**−**42** gave the benzamidines **43**−**47**. Conversion of **43**−**47** with 3-bromo-2-oxobutanoate[28] **48** gave rise to the formation of the esters **50**−**54**. The esters **49**−**53** were hydrolyzed to the corresponding carboxylic acids **55**−**59**. The target compounds **60** and **61** were obtained from the precursors **36** and **37** by acid-amine coupling with 1-aminopiperidine by carboxylate activation with HBTU in the presence of DIPEA in acetonitrile. Analogously, **55**−**59** were converted to **62**−**66**. Compound **67** was directly obtained from **54** by a Weinreb amidation[29] in 57% yield.

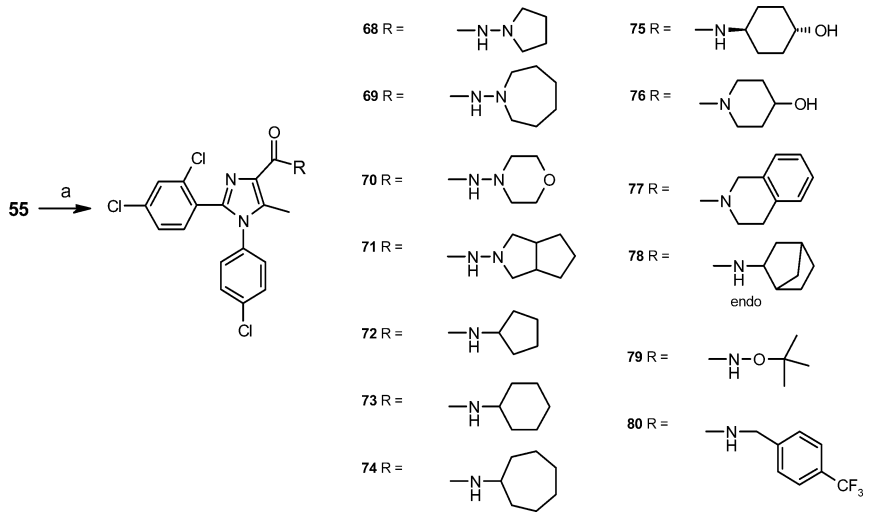
Besides introduction of the 1-aminopiperidinyl group, 13 other amines were coupled to the carboxylic acid **55** in order to produce the target compounds **68**−**80** as reported in Scheme 4.

It was found that directed ortho metalation[30] methodology can be applied in the functionalization at the 5-position of the 1,2-diarylimidazole core when a directing tertiary amide group at its 4-position is present. Illustrative was the synthesis of compound **82**, which was obtained as shown in Scheme 5. The carboxylic acid **36** was coupled with diethylamine to give **81** in 85% yield. The tertiary amide **81** was then ortho-lithiated at its imidazole 5-position by using *s*-BuLi and subsequently reacted with methyl iodide in THF to afford **82** in 41% yield.

To enable access to structural analogues with additional substituents on the 5-position of the imidazole nucleus, the synthetic route based on directed ortho metalation[30] chemistry was adapted to the application of the easily removable *tert*-butyl ester moiety as reported in Scheme 6. The key acid **36** was converted into the corresponding *tert*-butyl ester **83** by using di-*tert*-butyl dicarbonate and 4-(dimethylamino)pyridine in *t*-BuOH in 66% yield. Reaction of **83** with lithium diisopropylamide in THF, followed by quenching with a number of electrophiles R_1X as shown in Scheme 6, gave the products **84**−**87**. Acidic hydrolysis of the *tert*-butyl ester moiety in **84**−**86** with trifluoroacetic acid in CH_2Cl_2 provided the carboxylic acids **88**−**90** in high yields. These acids were aminated with 1-aminopiperidine in the presence of the activator HBTU to yield the target compounds **91**−**93**.

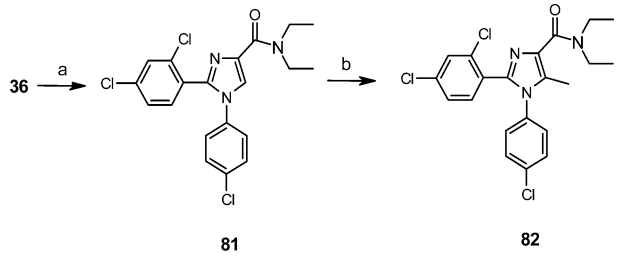
Further benzylic functionalization of the 5-methyl substituent in the key intermediate **49** gave access to the target compound **97** as depicted in Scheme 7. Treatment of **49** with *N*-bromosuccinimide in the presence of dibenzoyl peroxide gave the bromomethyl con-

Scheme 4[a]



[a] Reagents and conditions: (a) RH, HBTU, DIPEA, CH_3CN, rt, 16 h.

Scheme 5[a]



[a] Reagents and conditions: (a) $(C_2H_5)_2NH$, HBTU, DIPEA, CH_3CN, rt, 16 h; (b) s-BuLi, CH_3I, THF, −70 °C ro rt, 1 h.

gener **94** in 53% yield. Substitution of the bromo substituent by fluoro was realized[20] by applying KF in the presence of the crown ether Kryptofix in acetonitrile to give **95** in 39% yield. The target compound **97** was obtained by saponification of **95** into **96**, followed by coupling with 1-aminopiperidine.

Alternative chloro-substitutions on both phenyl rings of the 1,2-diarylimidazoles led to the target compound **103** as depicted in Scheme 8. 4-Chlorobenzonitrile **98** and 2,4-dichloroaniline **99** were converted into the amidine **100**. Subsequent cyclocondensation with **48** gave the imidazole ethyl ester **101**, which was saponified into **102**. The target compound **103** was obtained from **102** by amidation with 1-aminopiperidine.

Results and Discussion

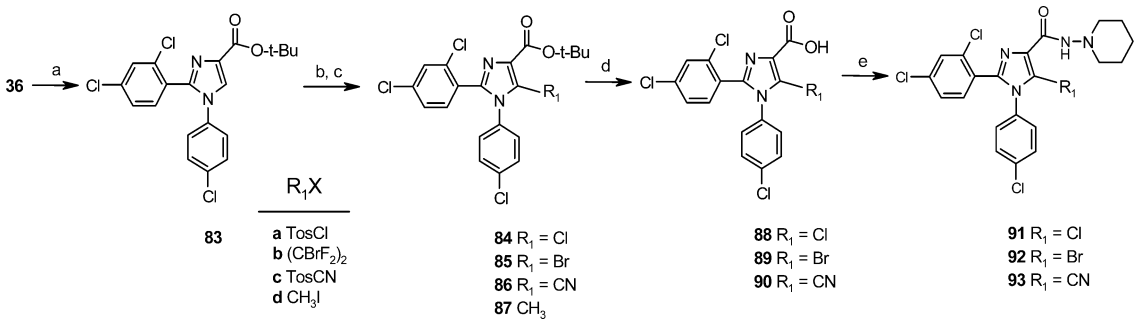
The target compounds **13**, **14**, **27**, **28**, **60**−**80**, **82**, **87**, **91**−**93**, **97**, and **103** were evaluated in vitro at the human CB_1 and CB_2 receptor, stably expressed into Chinese Hamster Ovary (CHO) cells,[15,31−32] utilizing radioligand binding studies. CB_1 receptor antagonism[33] was measured using an arachidonic acid release-based functional assay,[15] using the same recombinant cell line. The results are reported in Table 1.

The CB_1 receptor binding data revealed that the thiazole derivative **13** has at least 4-fold higher CB_1 affinity than its regioisomer **14** which has a different chloro-atom substitution pattern on both of its aromatic rings. In the imidazole series the same phenomenon was observed even more clearly when comparing the CB_1 receptor affinities of **62** and its regioisomer **103,** as the affinity of **62** was ∼13-fold higher. This difference in affinity was not present in the corresponding triazole pair **27** and **28** which elicited comparable affinities. Apparently, the exact nature of the heterocyclic ring to which both aromatic rings are attached is a CB_1 receptor affinity determining factor for these regioisomeric compounds. It is interesting to note that the binding affinity of the thiazole **13** was found 8-fold lower as compared to its imidazole counterpart **62**.

Comparison of compounds **60**−**62** having a differently substituted imidazole 5-position revealed that replacement of the H atom in **60** by a methyl (**62**) substituent slightly decreased affinity whereas ethyl (**61**) substitution increased CB_1 binding affinity. Introduction of a halogen atom at this position such as in **91** and **92** led to high affinity receptor binders. Also, the presence of other groups such as cyano (**93**) and fluoromethyl (**97**) yielded compounds having high CB_1 receptor affinities. In the original pyrazole series **5** was reported[20] to have lower CB_1 receptor affinity as compared with **1**. In our imidazole series **97** was found also less active than **62**. Replacement of the 1-aryl group in **62** by a 2-pyridyl moiety (**67**) led to some decrease in affinitity. The replacement of the 4-chloro substituent (R in Scheme 3) in **62** by other halogen atoms such as Br (**63**) and F (**64**) led to somewhat decreased affinities. CF_3 substitution (**66**) had no impact on affinity but substitution by a 4-methoxy group (**65**) had a detrimental effect. In the original 1,5-diarylpyrazole series the 4-methoxyphenyl substituted **6** was shown[21] to have lower CB_1 receptor affinity than **1**. In our imidazole series **65** showed also lower affinity than its counterpart **62**.

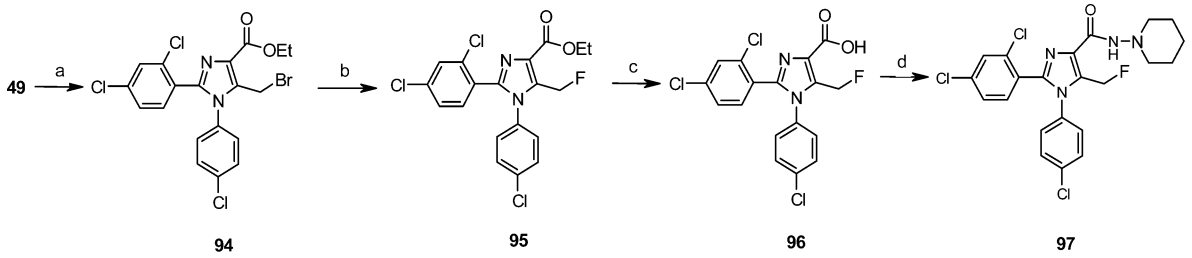
Replacement of the carboxamide *N*-piperidinyl group in **62** led to the analogues **68**−**80** and **82**. Substitution of the piperidinyl group in **62** by pyrrolidinyl (**68**) gave comparable affinity whereas the corresponding seven-membered azepanyl group containing **69** and the 4-morpholinyl derivative (**70**) both elicited clearly decreased affinities. This decreased CB_1 receptor affinity in **70** is in line with the reported[16,18] SAR in the 1,5-diarylpyrazole series, such as for compound **3**. The presence of more bulky bicyclic moieties such as in **71**, **77**, and **78** was well tolerated. Apparently, the CB_1 receptor is capable of accommodating such sterically demanding

Scheme 6[a]



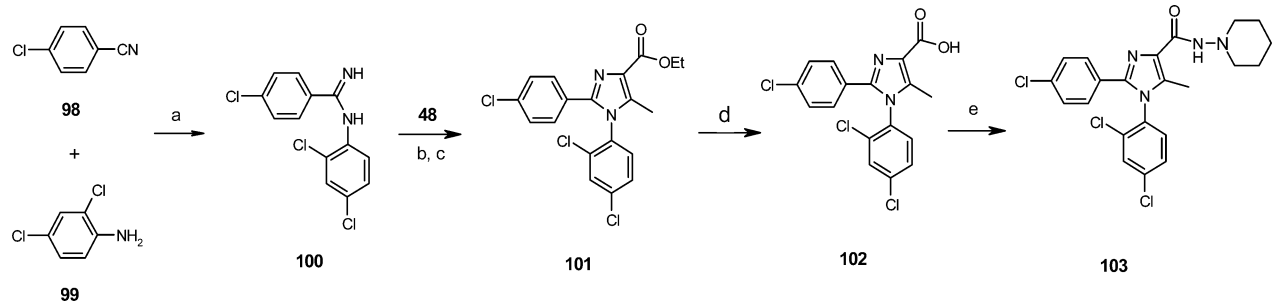
[a] Reagents and conditions: (a) Boc_2O, DMAP, t-BuOH, rt, 16 h; (b) LDA, THF, −70 °C; (c) R_1X; (d) TFA, CH_2Cl_2, rt, 16 h; (e) 1-aminopiperidine, HBTU, DIPEA, CH_3CN, rt, 16 h.

Scheme 7[a]



[a] Reagents and conditions: (a) NBS, CCl_4, dibenzoyl peroxide, reflux, 38 h; (b) KF, Kryptofix, CH_3CN reflux, 1 h; (c) NaOH aq, MeOH, rt, 10 min; (d) 1-aminopiperidine, HBTU, DIPEA, CH_3CN, rt, 16 h.

Scheme 8[a]



[a] Reagents and conditions: (a) $NaN(Si(CH_3)_3)_2$, THF, rt, 16 h; (b) $NaHCO_3$, EtOH, reflux, 20 h; (c) TFA, reflux, 16 h; (d) LiOH aq, THF, 50 °C, 16 h; (e) 1-aminopiperidine, HBTU, DIPEA, CH_3CN, rt, 16 h.

Table 1. In Vitro Results of Compounds **13**, **14**, **27**, **28**, **60**−**80**, **82**, **87**, **91**−**93**, **97**, and **103**

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
1	25- ± 15 (11.5)[16]	8.6 ± 0.1	1580 ± 150 (1640)[16]				
13	227 ± 86	8.1 ± 0.1	5841 ± 2201	**72**	33 ± 11	8.9 ± 0.2	357 ± 103
14	>1000	7.2 ± 0.1	4668 ± 344	**73**	35 ± 9	9.1 ± 0.1	160 ± 79
27	356 ± 75	8.3 ± 0.2	3562 ± 749	**74**	35 ± 15	9.1 ± 0.2	349 ± 154
28	382 ± 129	7.6 ± 0.2	5444 ± 433	**75**	399 ± 161	7.3 ± 0.2	3469 ± 1445
60	23 ± 14	8.2 ± 0.3	542 ± 177	**76**	172 ± 79	<7.5	3959 ± 1364
61	14 ± 12	9.0 ± 0.1	430 ± 141	**77**	34 ± 16	8.4 ± 0.2	696 ± 308
62	30 ± 16	8.6 ± 0.1	608 ± 161	**78**	19 ± 7	9.1 ± 0.2	54 ± 14
63	60 ± 24	8.5 ± 0.2	489 ± 130	**79**	333 ± 120	8.2 ± 0.2	242 ± 46
64	52 ± 22	7.7 ± 0.2	765 ± 145	**80**	171 ± 56	8.9 ± 0.1	1984 ± 684
65	106 ± 43	8.7 ± 0.2	326 ± 159	**82**	828 ± 380	7.4 ± 0.2	2520 ± 740
66	29 ± 10	8.6 ± 0.2	634 ± 249	**87**	94 ± 54	8.6 ± 0.0	815 ± 281
67	55 ± 20	8.4 ± 0.2	758 ± 283	**91**	27 ± 7	8.5 ± 0.2	823 ± 588
68	27 ± 12	8.2 ± 0.1	774 ± 285	**92**	23 ± 13	8.4 ± 0.3	746 ± 430
69	64 ± 8	8.7 ± 0.1	505 ± 250	**93**	30 ± 6	8.6 ± 0.1	1590 ± 467
70	197 ± 108	7.5 ± 0.2	3297 ± 1511	**97**	36 ± 22	8.9 ± 0.3	906 ± 342
71	40 ± 26	9.8 ± 0.2	1412 ± 518	**103**	403 ± 93	7.7 ± 0.1	208 ± 88

[a] Displacement of specific CP-55,940 binding in CHO cells stably transfected with human CB_1 receptor, expressed as Ki ± 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 Ki ± SEM (nM). The values represent the mean result based on at least three independent experiments.

groups. Five- to seven-membered cycloalkyl groups (**72**−**74**) were also good receptor binders. The presence of an additional hydroxy group such as in **75** and **76** was detrimental. Also the replacement by a *tert*-

butoxy (**79**) or a 4-trifluoromethylbenzyl group (**80**) did not lead to high affinity binders. The *N*-diethyl-substituted **82** was found to be a poor CB_1 receptor binder. Interestingly, the intermediate *tert*-butyl ester **87** showed CB_1 receptor affinity as well. Apparently, the amide nitrogen atom in this imidazole series is not a required structural element for CB_1 receptor binding. This finding is in line with the reported[15] hydrogen bonding of the amide oxygen atom in rimonabant and the SO_2 oxygen atom in SLV319 with the Asp366-Lys192 salt bridge in the CB_1 receptor model.

The results from the arachidonic acid release-based functional assay (Table 1) clearly reveal the CB_1 receptor antagonistic properties of our target compounds **13**, **14**, **27**, **28**, **60**−**80**, **82**, **87**, **91**−**93**, **97**, and **103**. In general, the compounds having the highest CB_1 receptor affinities also show strong antagonistic activity. The increased CB_1 antagonistic activities of the 5-substituted 1,2-diarylimidazoles **61**, **62**, **91**−**93**, and **97** as compared with the parent imidazole **60** are in line with our pyrazole-based bioisostere concept as it has been reported[21] in the 1,5-diarylpyrazole series that the additional lipophilicity of substituents on the 3-position of the pyrazole core gives rise to more active compounds. Others rationalized this phenomenon[34] by invoking a directing effect of the additional substituent on the carboxamide nitrogen atom. Four compounds (**71**, **73**, **74**, and **78**) exhibited subnanomolar CB_1 antagonistic potencies in the arachidonic acid release-based functional assay. The functional activity of **62**, wherein the heteroaromatic substitution pattern exactly matches that of **1**, nicely equals its activity.

The results from Table 1 demonstrate that CB_1/CB_2 receptor subtype selectivity is apparent throughout the presented series of compounds, except for **14** and the *tert*-butoxy-amide **79**. The CB_1/CB_2 receptor selectivity of **62** (~20-fold) as compared with its counterpart **1** was found approximately three times lower.

The in vivo activity of the compounds **13**, **27**, **60**−**62**, and **103**, which are structurally most closely related to rimonabant, was investigated in two mechanistic pharmacological models, viz. a CB_1 agonist (CP-55,940)-induced hypotension[35] rat model[15] and a CB_1 agonist (WIN-55,212)-induced hypothermia[36] mouse model.[15] Their activities were compared with those of rimonabant (**1**). The results show that the thiazole **13** and the triazole **27** were found hardly active or inactive after oral administration. It should be notified that both compounds were also found only moderately active in the CB_1 in vitro models (Table 1). Compound **60** which has a hydrogen atom on the 5-position of its imidazole ring was found active in the hypotension test but inactive in the hypothermia assay. Compound **61** has an ethyl group on the imidazole 5-position and was found active in both assays. The 5-methylated imidazole **62** was found very potent in both assays, indicating that a methyl group constitutes the optimal substituent in this series. Its potent in vivo activity is in line with that of **1** thereby again corroborating the bioisosteric concept. The regioisomeric imidazole **103** having a reversed chloro-substitution pattern on both aromatic rings as compared to **62** was found inactive in both the hypotension and hypothermia test which results are in line with its weaker in vitro potency.

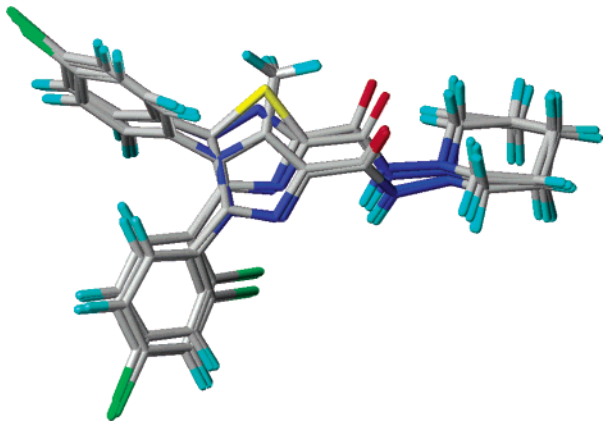


Figure 2. Receptor-based alignment of compounds **1**, **13**, **27**, and **62**.

The reported[37] model for the binding of rimonabant (**1**) in the CB_1 receptor was reconstructed.[15] On the basis of this model, the target compounds **13**, **27**, and **62** were manually docked into the receptor, followed by Simulated Annealing and Minimization. In Figure 2 the resulting receptor-based alignment of **1**, **13**, **27**, and **62** is given. The receptor-based alignment of **1** and the imidazole **62** led to a perfect three-dimensional structural overlap. The central heterocyclic rings of the thiazole **13** and triazole **27**, which both lack the methyl substitutent on their heterocyclic core, have slightly different orientations as compared with **1** and **62**, but their aryl rings and carboxamide moieties nicely overlap.

It was already mentioned above in the in vitro SAR discussion that the aromatic substitution pattern on both aromatic rings in the imidazoles (**62** vs **103**) and thiazoles (**13** vs **14**) had a strong impact on their CB_1 receptor activities, whereas the corresponding regioisomeric triazoles **27** and **28** elicited comparable CB_1 receptor affinities. This phenomenon was further examined with molecular modeling experiments. For these considerations only two parts of the molecules have to be taken into account: the diaryl-substituted azole core and the *N*-piperidinyl-carboxamide chain. These two moieties can have a cis- or trans-orientation with respect to each other due to the conjugation between the chain and the azole core.

Rimonabant (**1**) was reported to bind presumably in the cavity in its most stable $trans_{dichlorophenyl}$ (T_{DC}) conformation,[38] i.e. the dichlorophenyl ring trans-oriented with respect to the carbonyl moiety of the carboxamide chain. The carboxamide oxygen atom of **1** has a hydrogen bond interaction with the salt bridge between Lys192 and Asp366. This salt bridge is supposed[37] to be determinative for the inactive state of the receptor. The aromatic rings form a sophisticated framework of aromatic stacking interactions with several aromatic residues in the binding pocket of the receptor, as was described in the literature[37,39] and confirmed by our model.[15] The 4-chlorophenyl ring has stacking interactions with Trp255, Tyr275, and Phe278. Trp279 is stacked between the two aromatic rings of the ligand. The 2,4-dichlorophenyl ring is further surrounded by Trp356 and Phe200. An additional favorable interaction is caused by the accommodation of the *o*-chloro atom on the 2,4-dichlorophenyl ring in a small lipophilic

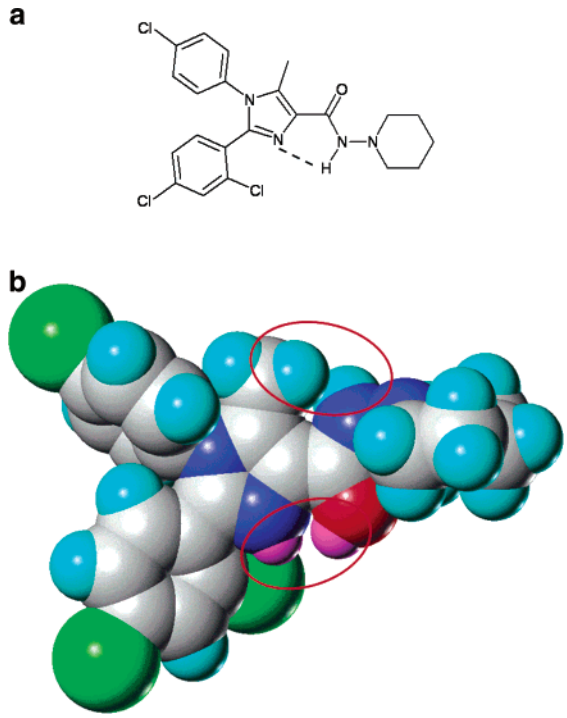


Figure 3. (a) Stabilizing intramolecular H-bonding in the T_{DC} conformation of **62**. (b) Steric (upper red circle) and electrostatic (lower red circle) repulsive interactions in **62** in its C_{DC} conformation.

Table 2. In Vivo Results of Compounds **1**, **13**, **27**, **60**−**62**, and **103**

compound	ED_{50}, hypotension, rat[a]	LED, hypothermia, mouse[b]
Rimonabant (**1**)	3.2	3
13	>30	n.d.[c]
27	23.6	>30
60	11.7	>30
61	15.8	30
62	2.4	10
103	>30	n.d.[c]

[a] Antagonism of CB agonist (CP55,940)iinduced hypotension, rat expressed as ED_{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). [c] Not determined.

pocket in the receptor. This has been reported[16] earlier in the diarylpyrazole series wherein the additional *o*-chloro substituent was shown to cause a 5-fold increase in CB_1 receptor affinity.

The relative positions of the 4-chlorophenyl, the 2,4-dichlorophenyl ring and the carboxamide carbonyl group are clearly defined by the interactions in the cavity as described above. In the $cis_{dichlorophenyl}$ (C_{DC}) conformation,[38] i.e. the 2,4-dichlorophenyl ring cis with respect to the carbonyl group, the *o*-chloro atom of the 2,4-dichlorophenyl ring of **1** would cause a steric clash with either Phe278 or with Val364.

The C_{DC} conformation has a higher calculated energy than the T_{DC} conformation due to steric overlap of the H-atom of the chain amide and the methyl group on the pyrazole core and electrostatic repulsion between the lone pairs of the pyrazole-N_2 atom and the oxygen atom of the carboxamide moiety. We believe that the T_{DC} conformation is further stabilized by a weak hydrogen bond interaction between the NH part of the carboxamide with the nitrogen atom in the pyrazole core. Such a type of intramolecular hydrogen bond was also observed[15] in the X-ray structure of the selective CB_1 receptor antagonist SLV319.

A similar situation is applicable to the comparison of both imidazole compounds **62** and **103**. In **62**, the most stable T_{DC} conformation meets the requirements for optimal binding (Figure 3a). The C_{DC} conformation is less favorable (Figure 3b). In the case of the regioisomer **103** the ligand must adopt its less favorable C_{DC} conformation for binding, explaining the difference in activity (see Tables 1 and 2).

In the thiazole series there is still some degree of steric overlap as a result of the larger van der Waals radius of its sulfur atom (Figure 2). The only interaction that favors the T_{DC} conformation is the hydrogen bond between the carboxamide NH part and the nitrogen atom of the thiazole core. Therefore, the difference is less pronounced as compared with the 5-methylimidazole series. Indeed, compound **13** was found more active than **14**.

In the triazole series there are no unfavorable interactions and a hydrogen bond is possible in both the T_{DC} and C_{DC} conformation. Consequently, **27** and **28** can be considered semisymmetrical for the binding pocket, reflected in the comparable activity profile of the two compounds.

The ester **87** lacks the stabilizing hydrogen bond in its T_{DC} conformation which is thought to stabilize amides such as **62** (Figure 2a). However, its reasonable activity can be explained by the lower degree of steric repulsion in its C_{DC} conformation.

A number of calculated properties and additional in vitro data were collected for target compounds **1**, **13**, **27**, and **62** in order to more closely study resemblances and differences between these heterocyclic cannabinoid 1,5-diarylpyrazole bioisosteres. Table 3 lists the calculated polar surface areas (cPSA), the molecular volumes, P-glycoprotein pump affinities,[15] in vitro membrane passage rates,[15] and experimental lipophilicity values[15] for these four target compounds, respectively.

The molecular polar surface area (PSA) has been shown to correlate well with drug transport properties, such as intestinal absorption or blood−brain barrier penetration.[40] The calculated PSA values for all four compounds are clearly lower than 120 Å^2, which is generally regarded as the oral bioavailability threshold

Table 3. Selected in Vitro Results and Calculated Properties of Compounds **1**, **13**, **27**, and **62**

compound	cPSA[a]	molecular volume[b]	P-glycoprotein affinity[c]	membrane passage[d]	log P_{HPLC}[e]
1	42	347	1.1 ± 0.1	17.2 ± 1.4	5.5
13	77	338	1.7 ± 0.5	8.3 ± 1.1	6.5
27	66	327	1.5 ± 0.2	28.3 ± 3.4	4.7
62	42	347	1.2 ± 0.2	24.2 ± 1.9	5.2

[a] Calculated polar surface area of the presumed binding conformation (Å^2). [b] Calculated molecular volume (Å^3). [c] P-Glycoprotein transport ratio, expressed as the ratio of the bottom to top transport and the top to bottom transport. [d] Membrane passage expressed as the mean percentage of compound transported. [e] Experimental lipophilicity determination by RP-HPLC.

value. Interestingly, the calculated PSA value for the pyrazole **1** exactly equals that of the corresponding imidazole **62**. The four calculated molecular volumes are in the same order of magnitude. Again the calculated molecular volume value for the pyrazole **1** exactly matches with that of the corresponding imidazole **62**. The P-glycoprotein pump is known to actively extrude certain compounds from the CNS, thereby significantly limiting their CNS levels.[41] All four compounds **1**, **13**, **27**, and **62** were found devoid of P-Glycoprotein pump affinity. In contrast both their in vitro membrane passage rates as well as log *P* values vary considerably. According to expectation, the higher lipophilic compounds were found to elicit lower membrane passage rates.

Conclusion

Three classes of heterocycles (thiazoles, triazoles, and imidazoles) that elicited *in vitro* CB_1 antagonistic activities and in general exhibited high CB_1 vs CB_2 receptor subtype selectivities have been discovered as cannabinoid bioisosteres of the original diarylpyrazole class. Some key representatives in the imidazole series elicited potent pharmacological in vivo activities after oral administration. Molecular modeling studies revealed a close three-dimensional structural overlap between the key compound **62** and the known CB_1 receptor antagonist rimonabant (**1**). A Structure Activity Relationship (SAR) study showed a close correlation between the biological results in the imidazole and pyrazole series.

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 Hz. 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). 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 $[M + H]^+$. Elemental analyses were performed on a Vario EL elemental analyzer by Solvay Pharmaceuticals, Hanover, Germany. Yields refer to isolated pure products and were not maximized.

2-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)ethanone (7). To a magnetically stirred mixture of Mg (12.2 g, 0.50 mol) in anhydrous Et_2O (20 mL) were slowly added 4-chlorobenzyl chloride (80.5 g, 0.50 mol) and a tiny I_2 crystal. The resulting mixture was refluxed for 90 min and cooled to room temperature. A solution of 2,4-dichlorobenzonitrile (68.8 g, 0.40 mol) in toluene (400 mL) was slowly added, and the resulting mixture was heated to remove the Et_2O by distillation. An additional portion of toluene (200 mL) was added, and the resulting mixture was heated at 135 °C for 2 h. After cooling to room-temperature, HCl (400 mL of a 2 N solution) was added and the resulting mixture was stirred overnight. The organic layer was collected, washed with water, dried over $MgSO_4$, filtered, and concentrated. The resulting crude residue was dissolved in boiling hexane (500 mL) and filtered over Hyflo. After cooling to room temperature, the formed syrup was separated, purified by flash chromatography (silica gel, petroleum ether 40−60/Et_2O = 3/1 (v/v)), and recrystallized from cyclohexane to give **7**[42] (95.6 g, 80% yield), mp 65−66 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.21 (s, 2H), 7.15 (d, J = 8 Hz, 2H), 7.25−7.40 (m, 4H), 7.45 (d, J = 2 Hz, 1H).

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)ethanone (8). A magnetically stirred mixture of 2,4-dichlorophenylacetic acid (50 g, 24.4 mmol) and $SOCl_2$ (71 mL, 97.6 mmol) was heated at 80 °C for 2 h. After cooling to room temperature and thorough concentration in vacuo, the resulting crude oil was dissolved in chlorobenzene (75 mL) and added to a magnetically stirred suspension of $AlCl_3$ (52 g, 39.0 mmol) in chlorobenzene (175 mL). The resulting mixture was heated at 100 °C for 2 h and subsequently poured onto ice (2 kg). Extraction with CH_2Cl_2 (3 × 500 mL), washing the combined organics with brine, drying over $MgSO_4$, filtration, concentration in vacuo, and subsequent crystallization from cyclohexane gave **8**[43] (66.1 g, 90% yield), mp 127−128.5 °C;^{1}H NMR (200 MHz, $CDCl_3$) δ 4.36 (s, 2H), 7.13−7.27 (m, 2H), 7.40−7.51 (m, 3H), 7.96 (br d, J = 8 Hz, 2H).

2-Bromo-2-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-ethanone (9). Bromine (5.80 g, 0.036 mol) was added dropwise to a magnetically stirred solution of **7** (10.88 g, 0.036 mol) in benzene (100 mL), and the resulting brown solution was allowed to stand at room temperature for 2 h. After concentration in vacuo, the residue was dissolved in CH_2Cl_2 and washed with aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated to give **3** (13.54 g, 99% yield) as a yellow oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (s, 1H), 7.30 (dd, J = 8 and 2 Hz, 1H), 7.34 (br d, $J \sim$ 8 Hz, 2H), 7.38 (d, J = 8 Hz, 1H), 7.42−7. (m, 3H).

2-Bromo-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-ethanone (10). 10 was obtained from **8** (5.00 g, 0.0166 mol) and Br_2 (2.67 g, 0.016 mol) according to the procedure described for **9** in 99% yield as a yellow oil.^{1}H NMR (200 MHz, $CDCl_3$) δ 6.78 (s, 1H), 7.30 (dd, J = 8 and 2 Hz, 1H), 7.42−7.52 (m, 3H), 7.59 (d, J = 8 Hz, 1H), 7.93 (br d, $J \sim$ 8 Hz, 2H).

Ethyl 5-(4-chlorophenyl)-4-(2,4-dichlorophenyl)thiazolecarboxylate (11). A magnetically stirred mixture of **9** (6.24 g, 0.0165 mol) and (ethoxycarbonyl)thioamide (3.29 g, 0.0247 mol) in EtOH (35 mL) was refluxed for 4 h. The formed precipitate was collected and washed with EtOH to give **11** (4.49 g, 63% yield) as a pink solid, mp 117−118 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (t, J = 7 Hz, 3H), 4.51 (q, J = 7 Hz, 2H), 7.15 (br d, $J \sim$ 8 Hz, 2H), 7.25−7.33 (m, 3H), 7.37 (d, J = 8 Hz, 1H), 7.42 (d, J = 2 Hz, 1H).

Ethyl 4-(4-chlorophenyl)-5-(2,4-dichlorophenyl)thiazolecarboxylate (12). 12 was obtained from **10** (13.54 g, 0.036 mol) and (ethoxycarbonyl)thioamide (7.20 g, 0.054 mol) according to the procedure described for **11** in 30% yield, mp 156−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, J = 7 Hz, 3H), 4.52 (q, J = 7 Hz, 2H), 7.22−7.27 (m, 3H), 7.29 (dd, J = 8 and 2 Hz, 1H), 7.41 (d, J = 8 Hz, 2H), 7.53 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.50, 63.03, 127.99, 128.65, 128.90, 129.92, 130.58, 132.25, 133.44, 134.21, 134.81, 135.39, 136.59, 153.54, 157.61, 160.03.

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)thiazolecarboxamide (13). A mixture of **11** (1.00 g, 2.4 mmol) and excess 1-aminopiperidine (10 mL, 92 mmol) was magnetically stirred at 50 °C for 16 h. CH_2Cl_2 and water were added. The organic layer was separated and successively washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue with flash chromatography (EtOAc, petroleum ether 40−60 = 1/3 (v/v)) gave **13** (330 mg, 29% yield) as an amorphous solid; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34−1.40 (m, 2H), 1.60−1.66 (m, 4H), 2.82−2.86 (m, 4H), 7.24 (d, J = 8 Hz, 2H), 7.38 (d, J = 8 Hz, 2H), 7.49 (dd, J = 8 and 2 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.62 (d, J = 2 Hz, 1H), 9.60 (s, 1H); HRMS ($C_{21}H_{19}Cl_3N_3OS$) $[M + H]^+$: found *m/z* 466.0319, calcd 466.0314; Anal. ($C_{21}H_{18}Cl_3N_3OS$) C, H, N.

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)thiazolecarboxamide (14). 14 was obtained from **12** (1.00 g, 2.43 mmol) and 1-aminopiperidine (10 mL, 93 mmol) according to the procedure described for **13** in 67% yield, mp

190−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44−1.52 (m, 2H), 1.75−1.83 (m, 4H), 2.90−2.96 (m, 4H), 7.23−7.30 (m, 4H), 7.37 (d, J = 8 Hz, 2H), 7.51 (d, J = 2 Hz, 1H), 8.04 (s, 1H); HRMS ($C_{21}H_{19}Cl_3N_3OS$) $[M + H]^+$: found *m/z* 466.0319, calcd 466.0314; Anal. ($C_{21}H_{18}Cl_3N_3OS$) C, H, N.

Dimethyl [(2,4-Dichlorobenzoyl)amino]malonate (17). To a cooled (<0 °C) and magnetically stirred solution of dimethyl 2-aminomalonate·HCl (36.7 g, 0.020 mol) in CH_2Cl_2 (200 mL) were successively added Et_3N (61.2 mL, 0.44 mol) and 2,4-dichlorobenzoyl chloride (**15**) (28 mL, 0.20 mol). The resulting mixture was allowed to stand at room temperature for 16 h. Water was added which dissolved the formed precipitate. The water layer was separated and washed with CH_2Cl_2. The combined CH_2Cl_2 layers were successively washed with water, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated to ∼100 mL. Diisopropyl ether (200 mL) was added, and the formed crystals were collected and dried to give **17** (30.0 g, 47% yield), mp 114−117 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.76 (s, 6H), 5.34 (d, J = 7 Hz, 1H), 7.47 (s, 2H), 7.61 (s, 1H), 9.50 (d, J = 7 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 53.20, 56.41, 127.42, 129.56, 130.88, 131.91, 134.26, 135.53, 165.89, 166.70.

Dimethyl [(4-Chlorobenzoyl)amino]malonate (18). 18 was obtained from dimethyl 2-aminomalonate·HCl (25.0 g, 0.136 mol) and 4-chlorobenzoyl chloride (**16**) (23.8 g, 0.136 mol) according to the procedure described for **17** in 74% yield, mp 146−148 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (s, 6H), 5.37 (d, J = 7 Hz, 1H), 7.16 (br d, J ∼ 7 Hz, 1H), 7.45 (br d, J ∼ 8 Hz, 2H), 7.81 (br d, J ∼ 8 Hz, 2H).

Dimethyl [(2,4-Dichlorobenzoyl)amino][(4-chlorophenyl)diazenyl]malonate (21). To a magnetically stirred and cooled (0−5 °C) solution of 4-chloroaniline (**19**) (9.18 g, 0.072 mol) in HOAc (45 mL) and concentrated HCl (15 mL) was slowly added a solution of $NaNO_2$ (5.4 g, 0.078 mol) in H_2O (30 mL), and the resulting mixture was allowed to stand for 30 min. The resulting cold solution was slowly added to a cooled (0−5 °C) and stirred mixture of **17** (19.20 g, 0.060 mol), NaOAc (17.7 g, 0.216 mol), and MeOH (240 mL), and the resulting mixture was allowed to stand at room temperature for 2 h. The formed precipitate was collected by filtration, washed with MeOH/H_2O = 1/1 (v/v) and dried in vacuo at 50 °C to give **21** (27.10 g, 98,5%) as a yellow solid, mp 165.5−167.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.97 (s, 6H), 7.36 (dd, J = 8 and 2 Hz, 1H), 7.44 (br d, J ∼ 8 Hz, 2H), 7.49 (d, J = 2 Hz, 1H), 7.72−7.82 (m, 3H); 8.05 (br s, 1H).

Methyl 1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxylate (23). 21 (0.46 g, 1.00 mmol) was dissolved in methanol (20 mL), and a catalytic amount of NaOMe in MeOH (5 mL) was added. The resulting solution was stirred for 16 h at room temperature. HOAc (2 mL) and H_2O (20 mL) were added. The formed precipitate was collected by filtration to give **23** (0.32 g, 84% yield), mp 108−111 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.07 (s, 3H),), 7.25 (br d, J ∼ 8 Hz, 2H), 7.32−7.46 (m, 4H), 7.51 (d, J = 8 Hz, 1H).

Methyl 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxylate (24). 24 was obtained from **18** (28.55 g, 0.100 mol) and **20** (19.44 g, 0.12 mol) according to the procedure described for **23**, in 30% yield as an amorphous solid,^{1}H NMR (200 MHz, $CDCl_3$) δ 4.05 (s, 3H), 7.25−7.60 (m, 7H). The intermediate dimethyl [(4-chlorobenzoyl)amino][(2,4-dichlorophenyl)diazenyl] malonate (**22**) was not isolated but immediately converted to **24**.

1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic Acid (25). To a stirred suspension of **23** (30.8 g, 0.081 mol) in methanol (200 mL) was added KOH (45% aqueous solution, 10 mL, 0.081 mol) and the resulting mixture was refluxed for 2 h. The mixture was concentrated in vacuo, and water (200 mL) and concentrated HCl were successively added. The formed precipitate was collected by filtration, washed with water, and dried in vacuo to give **25** (25.0 g, 84% yield), mp 102−104 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.10 (br s, 1H), 7.36 (br d, J ∼ 8 Hz, 2H), 7.49 (br d, J ∼ 8 Hz, 2H), 7.58 (dd, J = 8 and 2 Hz, 1H), 7.67 (d, J = 2 Hz, 1H), 7.74 (d, J = 8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 125.92, 126.46, 128.26, 129.75 (2C), 133.94, 133.99, 134.16, 135.94, 136.98, 151.70, 156.87, 161.38.

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxylic Acid (26). 26 was obtained from **24** (11.3 g, 0.0295 mol) and KOH (7.5 mL, 45% aqueous solution, 0.0603 mol) according to the procedure described for **25** in 92% yield, mp 141−144 °C (dec); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.47 (s, 4H), 7.67 (br d, J ∼ 8 Hz, 1H), 7.80−7.90 (m, 3H).

1-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-1,2,4-triazole-3-carboxamide Dihydrochloride (27). To a magnetically stirred solution of **25** (1.48 g, 4.00 mmol) were successively added *N,N*-diisopropylethylamine (Hunig's base, DIPEA) (1.5 mL, 8.4 mmol), *O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU) (1.66 g, 4.40 mmol), and 1-aminopiperidine (0.5 mL, 4.40 mmol), and the resulting mixture was stirred at room temperature for 16 h. $NaHCO_3$ (5% aqueous solution) was added, and the mixture was extracted (3×) with CH_2Cl_2. The combined organics were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue (3.7 g) was purified by flash chromatography (EtOAc/petroleum ether (40−60) = 1/1 (v/v)) to give the free base of **27** (1.2 g, 67% yield) which was dissolved into EtOAc and treated with HCl (5 mL, 1 N solution). The formed precipitate was collected by filtration and successively washed with EtOAc and diisopropyl ether to give **27** as a white powder (0.625 g, 32% yield), mp 234−237 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.48−1.54 (m, 2H), 1.80−1.87 (m, 4H), 3.26−3.33 (m, 4H), 7.41 (d, J = 8 Hz, 2H), 7.52 (d, J = 8 Hz, 2H), 7.60 (dd, J = 8 and 2 Hz, 1H), 7.69 (d, J = 2 Hz, 1H), 7.80 (d, J = 8 Hz, 1H), 11.40 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 21.99, 24.00, 56.33, 125.77, 126.13, 128.36, 129.82, 129.86, 133.89, 134.03, 134.65, 135.51 137.35, 152.13, 155.09, 156.38; HRMS ($C_{20}H_{19}Cl_3N_5O$) $[M + H]^+$: found *m/z* 450.0663, calcd 450.0655. Anal. Calcd for $C_{20}H_{18}Cl_3N_5O$.2.4 HCl; C, N: H: calcd., 3.82; found, 3.38. **27** (free base): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42−1.50 (m, 2H), 1.75−1.82 (m, 4H), 2.87−2.93 (m, 4H), 7.25 (br d, J ∼ 8 Hz, 2H), 7.34 (br d, J ∼ 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.45 (d, J = 2 Hz, 1H), 7.47 (d, J = 8 Hz, 1H), 7.87 (br s, 1H).

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-1,2,4-triazole-3-carboxamide Dihydrochloride (28). 28 was obtained from **26** (1.48 g, 4.00 mmol) and DIPEA (1.5 mL, 8.4 mmol), HBTU (1.66 g, 4.40 mmol), and 1-aminopiperidine (0.5 mL, 4.40 mmol) according to the procedure described for **27** in 77% yield, mp 238−240 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.47−1.52 (m, 2H), 1.78−1.84 (m, 4H), 3.22−3.28 (m, 4H), 7.51 (s, 4H), 7.70 (dd, J = 8 and 2 Hz, 1H), 7.88 (d, J = 2 Hz, 1H), 7.91 (d, J = 8 Hz, 1H), 11.20 (br s, 1H); HRMS ($C_{20}H_{19}Cl_3N_5O$) $[M + H]^+$: found *m/z* 450.0677, calcd 450.0655. Anal.($C_{20}H_{18}Cl_3N_5O$.1.6 HCl) C, H, N. **28** (free base): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44−1.50 (m, 2H), 1.74−1.82 (m, 4H), 2.88−2.94 (m, 4H), 7.34 (br d, J ∼ 8 Hz, 2H), 7.42−7.46 (m, 3H), 7.48 (d, J = 8 Hz, 1H), 7.54 (d, J = 2 Hz, 1H), 7.90 (s, 1H).

***N*-(4-Chlorophenyl)-2,4-dichlorobenzenecarboxamidine (31).** To sodium hexamethyldisilazide ($NaN(Si(CH_3)_3)_2$) (500 mL, 1 M solution in THF) was added dropwise a solution of **30** (63.8 g, 0.500 mol) in anhydrous THF (70 mL) while magnetically stirring under N_2. After the mixture was stirred for 20 min, a solution of **29** (86 g, 0.500 mol) in anhydrous THF (150 mL) was slowly added. The resulting mixture was stirred overnight, poured into ice−water (2 L) and extracted with dichloromethane, dried over Na_2SO_4, and concentrated in vacuo. Crystallization from cyclohexane gave **31** (126.3 g, 84% yield), mp 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (br s, (2H), 6.95 (br d, J ∼ 8 Hz, 2H), 7.20−7.70 (m, 5H).

3-Bromo-2-oxovalerate (33). 33 was prepared according to the literature procedure[24] from 2-oxovalerate (112.4 g, 0.781 mol) and bromine (39.8 mL, 0.781 mol) in quantitative yield as a pale yellow oil, ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.92 (t, J = 7 Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 1.50−1.60 (m, 1H), 1.71−1.80 (m, 1H), 4.28 (q, J = 7 Hz, 2H), 4.35−4.40 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 9.72, 14.15, 25.80, 61.90, 74.71, 163.13, 197.84.

Ethyl 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylate (34). A mixture of **31** (21.53 g, 0.0719 mol), **32** (35.1 g, 0.144 mol), and $NaHCO_3$ (12.1 g, 0.144 mol) in 2-propanol (720 mL) was stirred at reflux temperature for 20 h. After cooling to room temperature, the mixture was concentrated in vacuo and the residue suspended in CH_2Cl_2 and successively washed with H_2O (3 × 50 mL) and brine (3 × 50 mL). The combined aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo and further purified by column chromatography (heptane/EtOAc = 90/10 (v/v)) and crystallization from EtOH to yield **34** (18.44 g, 65% yield), mp 150−152 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.35 (t, J = 7 Hz, 3H), 4.32 (q, J = 7 Hz, 2H), 7.27 (br d, J = 8 Hz, 2H), 7.43 (br d, J = 8 Hz, 2H), 7.49 (dd, J = 8 and 2 Hz, 1H), 7.55 (d, J = 2 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 8.27 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.63, 60.27, 126.81, 127.87, 128.14, 128.30, 129.37, 129.67, 133.22, 133.69, 134.44, 134.51, 135.40, 136.09, 143.99, 162.19.

Ethyl 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-ethyl-1*H*-imidazole-4-carboxylate (35). 35 was obtained from **31** (15.0 g, 0.50 mol), **33** (22.3 g, 0.100 mol), and $NaHCO_3$ (8.4 g, 0.100 mol) according to the procedure described for **34** in 65% yield, with the modification that after the 20 h reflux period, TFA (7.66 mL, 0.100 mol) was added, followed by another 16 h reflux period, mp 238−240 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.01 (t, J = 7 Hz, 3H), 1.34 (t, J = 7 Hz, 3H), 2.80 (q, J = 7 Hz, 2H), 4.31 (q, J = 7 Hz, 2H), 7.35 (br d, J = 8 Hz, 2H), 7.39 (dd, J = 8 and 2 Hz, 1H), 7.48 (br d, J = 8 Hz, 2H), 7.52 (d, J = 2 Hz, 1H), 7.55 (d, J = 8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 13.80, 14.64, 17.91, 59.96, 127.42, 128.21, 128.79, 129.08, 129.77, 129.82, 133.63, 134.50, 134.71, 134.89, 135.75, 142.93, 143.17, 163.04.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylic Acid (36). To a magnetically stirred solution of **34** (18.44 g, 0.0466 mol) in THF (240 mL) was added LiOH (2.24 g, 0.0932 mol) and H_2O (240 mL). The resulting mixture was stirred at 50 °C for 16 h to give a clear solution. After cooling to room temperature, HCl (1 N solution, 95 mL) and H_2O (240 mL) were added to give a precipitate which was collected by filtration, washed with water, and dried in vacuo to give **36** (16.83 g, 98% yield), mp 138−142 °C (decomposition); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.08 (br d, J = 8 Hz, 2H), 7.31−7.37 (m, 4H), 7.45 (d, J = 8 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 126.87, 127.85, 127.91, 128.47, 129.36, 129.66, 133.56, 133.99, 134.44, 134.49, 135.54, 135.99, 143.77, 163.67.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-ethyl-1*H*-imidazole-4-carboxylic Acid (37). 37 was obtained from **35** (10.0 g, 0.0236 mol) and LiOH (1.13 g, 0.047 mol) according to the procedure described for **36** in 87% yield, mp 205 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.00 (t, J = 7 Hz, 3H), 2.81 (q, J = 7 Hz, 2H), 7.34 (br d, J = 8 Hz, 2H), 7.38 (dd, J = 8 and 2 Hz, 1H), 7.47 (br d, J = 8 Hz, 2H), 7.51 (d, J = 2 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 12.25 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 13.88, 17.81, 127.38, 128.84, 128.91, 129.07, 129.72, 129.81, 133.78, 134.47, 134.62, 134.89, 135.66, 142.51, 142.86, 164.63.

***N*-(4-Bromophenyl)-2,4-dichlorobenzenecarboxamidine (43). 43** was obtained from **29** (55.8 g, 0.324 mol), **38** (55.8 g, 0.324 mol), and $NaN(Si(CH_3)_3)_2$ (325 mL, 1 M solution in THF) according to the procedure described for **31** in 68% yield, mp 117−119 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.95 (br s, 2H), 6.90 (br d, J = 8 Hz, 2H), 7.05−7.75 (m, 5H).

2,4-Dichloro *N*-(4-fluorophenyl)benzenecarboxamidine (44). 44 was obtained from **29** (43.0 g, 0.250 mol), **39** (27.8 g, 0.250 mol), and $NaN(Si(CH_3)_3)_2$ (250 mL, 1 M solution in THF) according to the procedure described for **31** in 89% yield, mp 118−120 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.95 (br s, 2H), 6.92−7.18 (m, 4H), 7.32 (dd, J = 8 and 2 Hz, 1H), 7.46 (d, J = 2 Hz, 1H), 7.65 (d, J = 8 Hz, 1H).

2,4-Dichloro *N*-(4-methoxyphenyl)benzenecarboxamidine (45). 45 was obtained from **29** (43.0 g, 0.250 mol), **40** (30.7 g, 0.250 mol), and $NaN(Si(CH_3)_3)_2$ (250 mL, 1 M solution in THF) according to the procedure described for **31** in 88% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.94 (br s, 2H), 6.95 (s, 4H), 7.34 (dd, J = 8 and 2 Hz, 1H), 7.46 (d, J = 2 Hz, 1H), 7.67 (d, J = 8 Hz, 1H).

2,4-Dichloro *N*-(4-(trifluoromethyl)phenyl)benzenecarboxamidine (46). 46 was obtained from **29** (34.4 g, 0.200 mol), **41** (26.8 g, 0.167 mol), and $NaN(Si(CH_3)_3)_2$ (250 mL, 1 M solution in THF) according to a slightly modified procedure as compared to the synthesis of **31** (the $NaN(Si(CH_3)_3)_2$ solution was slowly added to a cooled (- 15 °C) mixture of **29** and **41)** in 39% yield, mp 108−109 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.95 (br s, 2H), 7.10 (d, J = 8 Hz, 2H), 7.35 (dd, J = 8 and 2 Hz, 1H), 7.48 (d, J = 2 Hz, 1H), 7.60−7.72 (m, 3H).

***N*-(5-Chloropyridin-2-yl)-2,4-dichlorobenzenecarboxamidine (47). 47** was obtained from **29** (86.0 g, 0.50 mol), **42** (64.3 g, 050 mol), and $NaN(Si(CH_3)_3)_2$ (500 mL, 1 M solution in THF) according to the procedure described for **31** in 87% yield, mp 167−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (br s, 1H), 7.18 (d, J = 8 Hz, 1H), 7.34 (dd, J = 8 and 2 Hz, 1H), 7.46 (d, J = 2 Hz, 1H), 7.61 (dd, J = 8 and 2 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 8.29 (d, J = 2 Hz, 1H), 10.45 (br s, 1H).

3-Bromo-2-oxobutanoate (48). 48 was prepared according to the literature procedure[24] from 2-oxobutanoate (102 g, 0.785 mol) and bromine (48.0 mL, 0.94 mol) in 94% yield as a pale yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (t, J = 7 Hz, 3H), 1.82 (d, J = 7 Hz, 3H), 4.38 (t, J = 7 Hz, 2H), 5.18 (q, J = 7 Hz, 1H).

Ethyl 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate (49). A mixture of **31** (29.95 g, 0.10 mol), **48** (27.2 g, 0.13 mol), and $NaHCO_3$ (10.9 g, 0.13 mol) in EtOH (250 mL) was stirred at 80 °C for 5 h. After cooling to room-temperature, TFA (7.5 mL, 0.1 mol) was added and the mixture was stirred at 80 °C for 16 h and concentrated in vacuo and the residue suspended in CH_2Cl_2 and twice washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo. Further purification by column chromatography (Et_2O/petroleum ether (40−60) = 90/10 (v/v)) and crystallization from cyclohexane gave **49** (28.9 g, 70% yield) as a white powder, mp 136−144 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.33 (t, J = 7 Hz, 3H), 2.38 (s, 3H), 4.30 (q, J = 7 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 7.41 (dd, J = 8 and 2 Hz, 1H), 7.47 (d, J = 8 Hz, 2H), 7.52 (d, J = 2 Hz, 1H), 7.54 (d, J = 8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.12, 14.70, 59.95, 127.51, 128.76, 128.79, 129.12, 129.63, 129.73, 133.70, 134.49, 134.53, 134.74, 135.75, 137.43, 143.13, 163.25.

Ethyl 1-(4-Bromophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate (50). 50 was obtained from **43** (3.44 g, 10.0 mmol), $NaHCO_3$ (0.92 g, 11.0 mmol), **48** (2.30 g, 10 mmol), and TFA (0.75 mL, 10 mmol) according to the procedure described for **49** in 54% yield, mp 163−164.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7 Hz, 3H), 2.45 (s, 3H), 4.43 (q, J = 7 Hz, 2H), 6.98 (d, J = 8 Hz, 2H), 7.22 (dd, J = 8 and 2 Hz, 1H), 7.28 (d, J = 2 Hz, 1H), 7.34 (d, J = 8 Hz, 1H), 7.51 (d, J = 8 Hz, 2H);

Ethyl 1-(4-Fluorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate (51). 51 was obtained from **44** (15.0 g, 0.0530 mol), $NaHCO_3$ (8.9 g, 0.106 mol), and **48** (24.5 g, 0.117 mol) according to the procedure described for **49** in 55% yield, mp 120−130 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34 (t, J = 7 Hz, 3H), 2.47 (s, 3H), 4.31 (q, J = 7 Hz, 2H), 7.21−7.25 (m, 2H), 7.33−7.37 (m, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.51 (d, J = 2 Hz, 1H), 7.54 (d, J = 8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.11, 14.69, 59.92, 116.61 (d, J_{CF} = 23 Hz), 127.42, 128.63, 128.89, 129.07, 130.08 (d, J_{CF} = 8 Hz), 131.13, 134.49, 134.80, 135.68, 137.54, 143.28, 162.26 (d, J_{CF} = 248 Hz), 163.28.

Ethyl 2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-5-methyl-1*H*-imidazole-4-carboxylate (52). 52 was obtained from **45** (15.0 g, 0.0508 mol), $NaHCO_3$ (8.9 g, 0.106 mol), and **48** (23.5 g, 0.112 mol) according to the procedure described for **49** in 42% yield, mp 130−140 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.33 (t, J = 7 Hz, 3H), 2.35 (s, 3H), 3.76 (s, 3H), 4.30 (q, J = 7 Hz, 2H), 6.93 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 7.38 (dd, J = 8 and 2 Hz, 1H), 7.49−7.53 (m, 2H);

^{13}C NMR (150 MHz, DMSO-d_6) δ 11.13, 14.71, 55.60, 59.85, 114.67, 127.33, 127.39, 128.42, 128.98, 129.04, 129.23, 134.41, 134.90, 135.50, 137.69, 143.42, 159.73, 163.35.

Ethyl 2-(2,4-Dichlorophenyl)-1-(4-(trifluoromethyl)-phenyl)-5-methyl-1*H*-imidazole-4-carboxylate (53). 53 was obtained from **46** (15.0 g, 0.0450 mol), $NaHCO_3$ (7.6 g, 0.0905 mol), and **48** (20.8 g, 0.0995 mol) according to the procedure described for **49** in 52% yield, mp 160−162 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34 (t, J = 7 Hz, 3H), 2.40 (s, 3H), 4.31 (q, J = 7 Hz, 2H), 7.42 (dd, J = 8 and 2 Hz, 1H), 7.51−7.56 (m, 3H), 7.59 (d, J = 8 Hz, 1H) 7.80 (d, J = 8 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.16, 14.68, 60.02, 123.84 (q, J_{CF} = 273 Hz), 126.80 (q, J_{CF} = 3 Hz), 127.59, 128.60, 128.87, 129.00, 129.16, 130.08 (q, J_{CF} = 33 Hz), 134.56, 134.67, 135.87, 137.35, 138.37, 143.01, 163.21.

Ethyl 1-(5-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate (54). 54 was obtained from **47** (30.05 g, 0.100 mol), $NaHCO_3$ (9.24 g, 0.11 mol), and **48** (23.0 g, 0.11 mol) according to the procedure described for **49** in 31% yield, mp 123−126 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34 (t, J = 7 Hz, 3H), 2.50 (s, 3H), 4.32 (q, J = 7 Hz, 2H), 7.40 (d, J = 8 Hz, 1H), 7.43 (dd, J = 8 and 2 Hz, 1H), 7.50 (d, J = 2 Hz, 1H), 7.53 (d, J = 8 Hz, 1H), 8.04 (dd, J = 8 and 2 Hz, 1H), 8.56 (d, J = 2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.20, 14.66, 60.08, 123.40, 127.65, 128.68, 129.05, 129.19, 132.00, 134.29, 134.43, 135.73, 137.18, 139.14, 142.86, 146.74, 148.31, 163.13.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylic Acid (55). 55 was obtained from **49** (16.4 g, 0.040 mol) and LiOH (2.5 g, 0.104 mol) according to the procedure described for **36** in quantitative yield, mp 243−245 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.33 (s, 3H), 7.27 (d, J = 8 Hz, 2H), 7.36 (dd, J = 8 and 2 Hz, 1H), 7.42 (d, J = 8 Hz, 2H), 7.47 (d, J = 2 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 12.20 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 7.80, 124.16, 125.60, 125.80, 126.10, 126.31, 126.37, 130.52, 131.07, 131.20, 131.41, 132.33, 133.67, 139.51, 161.48.

1-(4-Bromophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylic Acid (56). 56 was obtained from **50** (1.36 g, 3.0 mmol) and LiOH (0.13 g, 6.0 mmol) according to the procedure described for **36** in 93% yield, mp 236−238 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.00 (d, J = 8 Hz, 2H), 7.24 (dd, J = 8 and 2 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.34 (d, J = 2 Hz, 1H), 7.53 (d, J = 8 Hz, 2H), OH proton invisible;^{13}C NMR (100 MHz, DMSO-d_6) δ 11.42, 123.19, 127.73, 129.22, 129.42, 129.81, 130.15, 132.93, 134.61, 134.75, 135.07, 135.99, 137.21, 143.08, 165.06.

2-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)-5-methyl-1*H*-imidazole-4-carboxylic Acid (57). 57 was obtained from **51** (5.00 g, 0.0127 mol) and LiOH (0.61 g, 0.0254 mol) according to the procedure described for **36** in 74% yield, mp 220−221 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.36 (s, 3H), 7.21−7.25 (m, 2H), 7.33−7.37 (m, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.51 (d, J = 2 Hz, 1H), 7.53 (d, J = 8 Hz, 1H), 12.20 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.12, 116.55 (d, J_{CF} = 23 Hz), 127.42, 129.03, 129.08, 129.27, 130.10 (d, J_{CF} = 8 Hz), 131.28, 134.50, 134.79, 135.58, 137.11, 142.97, 162.20 (d, J_{CF} = 248 Hz), 164.84.

2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-5-methyl-1*H*-imidazole-4-carboxylic Acid (58). 58 was obtained from **52** (5.00 g, 0.0123 mol) and LiOH (0.59 g, 0.0246 mol) according to the procedure described for **36** in 87% yield, mp 189−191 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.32 (s, 3H), 3.74 (s, 3H), 6.91 (d, J = 8 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 7.36 (dd, J = 8 and 2 Hz, 1H), 7.46−7.51 (m, 2H), 12.20 (br s, 1H).

2-(2,4-Dichlorophenyl)-5-methyl-1-(4-(trifluoromethyl)-phenyl)-1*H*-imidazole-4-carboxylic Acid (59). 59 was obtained from **53** (5.00 g, 0.0113 mol) and LiOH (0.54 g, 0.0225 mol) according to the procedure described for **36** in 84% yield, mp 224−226 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.40 (s, 3H), 7.42 (d, J = 8 Hz, 1H), 7.51 (d, J = 2 Hz, 1H), 7.54 (d, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 1H), 7.79 (d, J = 8 Hz, 2H), 12.25 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.17, 123.83 (q, J_{CF} = 273 Hz), 126.78 (q, J_{CF} = 3 Hz), 127.55, 128.73, 128.84, 129.16, 129.65, 130.00 (q, J_{CF} = 32 Hz), 134.54, 134.66, 135.78, 136.92, 138.51, 142.72, 164.76.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (60).[34] To a magnetically stirred suspension of **36** (1.10 g, 3.00 mmol) in anhydrous CH_3CN (50 mL) were successively added *N,N*-diisopropylethylamine (Hunig's base) (1.15 mL, 6.6 mmol), *O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU) (1.36 g, 3.6 mmol), and 1-aminopiperidine (0.39 mL, 3.6 mmol). After stirring for 16 h, the resulting mixture was concentrated in vacuo. The residue was dissolved in EtOAc, successively washed with aqueous $NaHCO_3$ solution, water, and brine, dried over Na_2SO_4, filtered, and concentrated to give a crude solid. This solid was further purified by flash chromatography (EtOAc/petroleum ether = 80/20 (v/v)), followed by crystallization from CH_3CN to give **60** (0.81 g, 62% yield), mp 220−222 °C;^{1}H NMR (600 MHz, DMSO-d_6) δ 1.35−1.42 (m, 2H), 1.61−1.67 (m, 4H), 2.79−2.83 (m, 4H), 7.25 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 2H), 7.49 (dd, J = 8 and 2 Hz, 1H), 7.54 (d, J = 2 Hz, 1H), 7.68 (d, J = 8 Hz, 1H), 8.08 (s, 1H), 8.80 (s, 1H); HRMS ($C_{21}H_{20}Cl_3N_4O$) [M + H]$^+$: found *m/z* 449.0714, calcd 449.0703. Anal. ($C_{21}H_{19}Cl_3N_4O$) C, H, N.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-ethyl-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (61). 61 was obtained from **37** (3.11 g, 7.88 mmol), HBTU (3.58 g, 9.46 mmol), DIPEA (3.0 mL, 17.0 mmol), and 1-aminopiperidine (1.02 mL, 9.46 mmol) according to the procedure described for **60** in 69% yield, mp 133−136 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.97 (t, J = 7 Hz, 3H), 1.34−1.41 (m, 2H), 1.61−1.66 (m, 4H), 2.77−2.82 (m, 4H), 2.84 (q, J = 7 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 7.39 (dd, J = 8 and 2 Hz, 1H), 7.46 (d, J = 8 Hz, 2H), 7.50 (d, J = 2 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 8.75 (s, 1H); HRMS ($C_{23}H_{24}Cl_3N_4O$) [M + H]$^+$: found *m/z* 477.1022, calcd 477.1016. Anal. ($C_{23}H_{23}Cl_3N_4O\cdot H_2O$) C, H, N.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (62). 62 was obtained from **55** (3.81 g, 10.0 mmol), HBTU (4.20 g, 11.1 mmol), DIPEA (3.70 mL, 21.0 mmol), and 1-aminopiperidine (1.20 mL, 11.1 mmol) according to the procedure described for **60** in 59% yield, mp 164−166 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34−1.42 (m, 2H), 1.60−1.67 (m, 4H), 2.39 (s, 3H), 2.77−2.82 (m, 4H), 7.29 (d, J = 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.44 (d, J = 8 Hz, 2H), 7.50 (d, J = 2 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 8.60 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.53, 23.31, 25.65, 56.14, 127.45, 128.86, 129.09, 129.56, 129.63, 130.53, 133.80, 134.02, 134.34, 134.62, 134.76, 135.74, 141.87, 160.49; HRMS ($C_{22}H_{22}Cl_3N_4O$) [M + H]$^+$: found *m/z* 463.0876, calcd 463.0859. Anal. ($C_{22}H_{21}Cl_3N_4O$) C, H, N.

1-(4-Bromophenyl)-2-(2,4-dichlorophenyl)-5-methyl-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (63). 63 was obtained from **56** (1.32 g, 3.10 mmol), HBTU (1.41 g, 3.72 mmol), DIPEA (1.19 mL, 6.82 mmol), and 1-aminopiperidine (0.40 mL, 3.72 mmol) according to the procedure described for **60** in 69% yield, mp > 204 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34−1.42 (m, 2H), 1.60−1.67 (m, 4H), 2.39 (s, 3H), 2.76−2.82 (m, 4H), 7.20−7.24 (m, 2H), 7.39−7.42 (m, 1H), 7.50 (d, J = 2 Hz, 1H), 7.56−7.60 (m, 3H), 8.65 (s, 1H); HRMS ($C_{22}H_{22}BrCl_2N_4O$) [M + H]$^+$: found *m/z* 507.0350, calcd 507.0354; Anal. ($C_{22}H_{21}BrCl_2N_4O\cdot H_2O$) C, H, N.

2-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)-5-methyl-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (64). 64 was obtained from **57** (1.00 g, 2.74 mmol), HBTU (1.25 g, 3.30 mmol), DIPEA (1.05 mL, 6.01 mmol), and 1-aminopiperidine (0.35 mL, 3.26 mmol) according to the procedure described for **60** in 58% yield, mp 223−224 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.35−1.41 (m, 2H), 1.60−1.66 (m, 4H), 2.38 (s, 3H), 2.77−2.82 (m, 4H), 7.18−7.24 (m, 2H), 7.30−7.34 (m, 2H), 7.39 (dd, J = 8 and 2 Hz, 1H) 7.49 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 8.60 (s, 1H); HRMS ($C_{22}H_{22}Cl_2FN_4O$) [M + H]$^+$: found *m/z* 447.1152, calcd 447.1155; Anal. ($C_{22}H_{21}Cl_2FN_4O\cdot 0.5H_2O$) C, H, N.

2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-5-methyl-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (65). 65 was obtained from **58** (1.00 g, 2.65 mmol), HBTU (1.21 g, 3.19

mmol), DIPEA (1.02 mL, 5.83 mmol), and 1-aminopiperidine (0.34 mL, 3.17 mmol) according to the procedure described for **60** in 71% yield, mp 90 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.35−1.41 (m, 2H), 1.61−1.66 (m, 4H), 2.35 (s, 3H), 2.77−2.82 (m, 4H), 3.76 (s, 3H), 6.92 (d, J = 8 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 7.38 (dd, J = 8 and 2 Hz, 1H), 7.49 (d, J = 2 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 8.60 (s, 1H);^{13}C NMR (150 MHz, DMSO-d_6) δ 10.53, 23.32, 25.65, 55.56, 56.18, 114.59, 127.29, 127.51, 128.94, 129.02, 129.30, 130.18, 134.26, 134.51, 134.91, 135.47, 142.11, 159.61, 160.62; HRMS ($C_{23}H_{25}Cl_2N_4O_2$) [M + H]$^+$: found *m/z* 459.1347, calcd 459.1355; Anal. ($C_{23}H_{24}Cl_2N_4O_2$·1.33.Cyclohexane) C, H, N.

2-(2,4-Dichlorophenyl)-5-methyl-*N*-(piperidin-1-yl)-1-(4-(trifluoromethyl)phenyl)-1*H*-imidazole-4-carboxamide (66). 66 was obtained from **59** (1.00 g, 2.41 mmol), HBTU (1.10 g, 2.90 mmol), DIPEA (1.05 mL, 6.00 mmol), and 1-aminopiperidine (0.31 mL, 2.88 mmol) according to the procedure described for **60** in 72% yield, mp 173−174 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.36−1.42 (m, 2H), 1.61−1.66 (m, 4H), 2.41 (s, 3H), 2.78−2.82 (m, 4H), 7.42 (dd, J = 8 and 2 Hz, 1H), 7.48−7.54 (m, 3H), 7.62 (d, J = 8 Hz, 1H), 7.77 (d, J = 8 Hz, 2H), 8.70 (s, 1H); HRMS ($C_{23}H_{22}Cl_2F_3N_4O$) [M + H]$^+$: found *m/z* 497.1126, calcd 497.1123; Anal. ($C_{23}H_{21}Cl_2F_3N_4O$·H_2O) C, H, N.

1-(5-Chloropyridin-2-yl)-2-(2,4-dichlorophenyl)-5-methyl-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (67). To a cooled (0 °C) and magnetically stirred solution of 1-aminopiperidine (4.31 mL, 0.040 mol) in anhydrous CH_2Cl_2 (100 mL) was added $(CH_3)_3Al$ (20 mL, 2 M solution in *n*-heptane, 0.040 mol) under N_2. The resulting solution was allowed to attain room temperature and stirred for 1 h. A solution of **54** (8.21 g, 0.020 mol) in CH_2Cl_2 (100 mL) was added, and the resulting mixture was stirred at 45 °C for 16 h and carefully poured onto H_2O (300 mL). The formed precipitate was removed by filtration. The CH_2Cl_2 layer from the filtrate was collected, dried over Na_2SO_4, filtered, concentrated in vacuo, purified by column chromatography (EtOAc), and crystallized from Et_2O to give **67** (5.26 g, 57% yield), mp 179−182 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.35−1.41 (m, 2H), 1.60−1.66 (m, 4H), 2.50 (s, 3H), 2.78−2.84 (m, 4H), 7.40 (d, J = 8 Hz, 1H), 7.46 (dd, J = 8 and 2 Hz, 1H), 7.52 (d, J = 2 Hz, 1H), 7.59 (d, J = 8 Hz, 1H), 8.04 (dd, J = 8 and 2 Hz, 1H), 8.54 (d, J = 2 Hz, 1H), 8.70 (br s, 1H);^{13}C NMR (150 MHz, DMSO-d_6) δ 10.64, 23.30, 25.64, 56.05, 123.35, 127.67, 128.84, 129.17, 130.79, 131.78, 133.82, 134.26, 134.63, 135.65, 139.09, 141.71, 146.93, 148.25, 160.34; HRMS ($C_{21}H_{21}Cl_3N_5O$) [M + H]$^+$: found *m/z* 464.0809, calcd 464.0812; Anal. ($C_{21}H_{20}Cl_3N_5O$) C, H, N.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-*N*-(pyrrolidin-1-yl)-1*H*-imidazole-4-carboxamide (68). 68 was obtained from **55** (1.52 g, 4.00 mmol), DIPEA (2.92 mL, 16.8 mmol), HBTU (1.67 g, 4.41 mmol), and 1-aminopyrrolidine·HCl (540 mg, 4.40 mmol) according to the procedure described for **60** in 68% yield, mp 205−206 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.76−1.82 (m, 4H), 2.40 (s, 3H), 2.90−2.96 (m, 4H), 7.30 (d, J = 8 Hz, 2H), 7.41 (dd, J = 8 and 2 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 7.51 (d, J = 2 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 8.75 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.55, 22.25, 54.31, 127.46, 128.88, 129.09, 129.58, 129.65, 130.53, 133.81, 133.93, 134.32, 134.63, 134.77, 135.73, 141.88, 161.46; HRMS ($C_{21}H_{20}Cl_3N_4O$) [M + H]$^+$: found *m/z* 499.0698, calcd 499.0703. Anal. ($C_{21}H_{19}Cl_3N_4O$) C, H, N.

***N*-(Azepan-1-yl)-1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxamide (69). 69** was obtained from **55** (1.52 g, 4.00 mmol), DIPEA (1.46 mL, 8.4 mmol), HBTU (1.67 g, 4.41 mmol), and 1-aminoazepan (0.51 mL, 4.40 mmol) according to the procedure described for **60** in 82% yield, mp 147−149 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.57−1.62 (m, 4H), 1.65−1.70 (m, 4H), 2.39 (s, 3H), 3.00−3.04 (m, 4H), 7.29 (d, J = 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 7.51 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.52, 26.49, 26.89, 58.00, 127.46, 128.85, 129.11, 129.57, 129.64, 130.56, 133.82, 133.89, 134.31, 134.60, 134.74, 135.71, 141.84, 160.60; HRMS ($C_{23}H_{24}Cl_3N_4O$) [M + H]$^+$: found *m/z* 477.1015, calcd 477.1016.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-*N*-(morpholin-4-yl)-1*H*-imidazole-4-carboxamide (70). 70 was obtained from **55** (1.52 g, 4.00 mmol), DIPEA (1.46 mL, 8.4 mmol), HBTU (1.67 g, 4.41 mmol), and 4-aminomorpholine (0.43 mL, 4.40 mmol) according to the procedure described for **60** in 98% yield, mp 225 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.40 (s, 3H), 2.86−2.90 (m, 4H), 3.68−3.72 (m, 4H), 7.29 (d, J = 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 7.50 (d, J = 2 Hz, 1H), 7.59 (d, J = 8 Hz, 1H), 9.00 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.54, 55.09, 66.38, 127.44, 128.85, 129.07, 129.54, 129.64, 130.44, 133.76, 134.21, 134.37, 134.61, 134.78, 135.77, 141.93, 160.84; HRMS ($C_{21}H_{20}Cl_3N_4O_2$) [M + H]$^+$: found *m/z* 465.0662, calcd 465.0652.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-(hexahydrocyclopenta[*c*]pyrrol-2-(1*H*)yl)-5-methyl-1*H*-imidazole-4-carboxamide (71).[34] **71** was obtained from **55** (1.52 g, 4.00 mmol), DIPEA (2.92 mL, 16.8 mmol), HBTU (1.67 g, 4.41 mmol), and hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-amine·HCl (0.716 g, 4.40 mmol) according to the procedure described for **60** in 84% yield, mp 143−146 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.42−1.76 (m, 6H), 2.39 (s, 3H), 2.54−2.58 (m, 2H), 2.93−2.95 (m, 2H), 3.08−3.12 (m, 2H), 7.28 (d, J = 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.44 (d, J = 8 Hz, 2H), 7.50 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 8.60 (s, 1H); HRMS ($C_{24}H_{24}Cl_3N_4O$) [M + H]$^+$: found *m/z* 489.1045, calcd 489.1016. Anal. ($C_{24}H_{23}Cl_3N_4O$·1.25H_2O) C, H, N.

1-(4-Chlorophenyl)-*N*-cyclopentyl-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxamide (72). 72 was obtained from **55** (1.526 g, 4.00 mmol), DIPEA (1.53 mL, 8.80 mmol), HBTU (1.82 g, 4.80 mmol), and cyclopentylamine (0.473 mL, 4.80 mmol) according to the procedure described for **60** in 80% yield, mp 172 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.50−1.58 (m, 4H), 1.66−1.73 (m, 2H), 1.88−1.93 (m, 2H), 2.40 (s, 3H), 4.21−4.28 (m, 1H), 7.29 (d, J = 8 Hz, 2H), 7.41 (dd, J = 8 and 2 Hz, 1H), 7.46 (d, J = 8 Hz, 2H), 7.51 (d, J = 2 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.64 (d, J = 7 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.54, 23.81, 32.67, 50.16, 127.48, 128.91, 129.10, 129.58, 129.65, 131.28, 133.35, 133.85, 134.28, 134.61, 134.76, 135.70, 141.79, 162.74; HRMS ($C_{22}H_{21}Cl_3N_3O$) [M + H]$^+$: found *m/z* 448.0784, calcd 448.0750.

1-(4-Chlorophenyl)-*N*-cyclohexyl-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxamide (73). 73 was obtained from **55** (1.526 g, 4.00 mmol), DIPEA (1.53 mL, 8.80 mmol), HBTU (1.82 g, 4.80 mmol), and cyclohexylamine (0.475 g, 4.80 mmol) according to the procedure described for **60** in 94% yield, mp 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11−1.32 (m, 3H), 1.34−1.47 (m, 2H), 1.60−1.67 (m, 1H), 1.72−1.80 (m, 2H), 1.98−2.05 (m, 2H), 2.48 (s, 3H), 3.90−4.00 (m, 1H), 7.03 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 7.24 (dd, J = 8 and 2 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.32−7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.88, 25.35, 25.86, 33.58, 48.02, 127.38, 128.64, 128.89, 129.83, 129.91, 131.90, 133.48, 133.91, 134.04, 135.37, 135.49, 136.66, 142.19, 162.68; HRMS ($C_{23}H_{23}Cl_3N_3O$) [M + H]$^+$: found *m/z* 462.0924, calcd 462.0907. Anal. Calcd for $C_{23}H_{22}Cl_3N_3O$·H_2O; C, N: H: calcd., 5.03; found, 4.56.

1-(4-Chlorophenyl)-*N*-cycloheptyl-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxamide (74). 74 was obtained from **55** (1.526 g, 4.00 mmol), DIPEA (1.53 mL, 8.80 mmol), HBTU (1.82 g, 4.80 mmol), and cycloheptylamine (0.61 mL, 4.80 mmol) according to the procedure described for **60** in 81% yield, mp 155 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.42−1.69 (m, 10H), 1.82−1.89 (m, 2H), 2.39 (s, 3H), 3.94−4.01 (m, 1H), 7.30 (d, J = 8 Hz, 2H), 7.41 (dd, J = 8 and 2 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 7.51 (d, J = 2 Hz, 1H), 7.55−7.60 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.53, 24.24, 27.95, 34.90, 49.61, 127.48, 128.91, 129.10, 129.59, 129.63, 131.29, 133.36, 133.87, 134.26, 134.62, 134.74, 135.68, 141.77, 161.91; HRMS ($C_{24}H_{25}Cl_3N_3O$) [M + H]$^+$: found *m/z* 476.1078, calcd 476.1063. Anal. ($C_{24}H_{24}Cl_3N_3O$·0.25H_2O) C, H, N.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-(*trans*-4-hydroxycyclohexyl)-5-methyl-1*H*-imidazole-4-carboxamide (75). 75 was obtained from **55** (1.52 g, 4.00 mmol), DIPEA (2.92 mL, 16.8 mmol), HBTU (1.67 g, 4.40 mmol), and *trans*-4-hydroxycyclohexylamine·HCl (0.667 g, 4.40 mmol) according to the procedure described for **60** in 86% yield, mp 160 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.22−1.31 (m, 2H), 1.38−1.46 (m, 2H), 1.79−1.89 (m, 4H), 2.39 (s, 3H), 3.38−3.44 (m, 1H), 3.71−3.80 (m, 1H), 4.53 (d, J = 6 Hz, 1H), 7.28 (d, J = 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.44 (d, J = 8 Hz, 2H), 7.50 (d, J = 2 Hz, 1H), 7.54 (d, J = 7 Hz, 1H), 7.57 (d, J = 8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.54, 30.79, 34.53, 47.05, 68.54, 127.45, 128.90, 129.09, 129.55, 129.62, 131.25, 133.44, 133.84, 134.31, 134.58, 134.76, 135.71, 141.79, 162.40; HRMS ($C_{23}H_{23}Cl_3N_3O_2$) [M + H]$^+$: found *m/z* 478.0841, calcd 478.0856. Anal. ($C_{23}H_{22}Cl_3N_3O_2$) C, H, N.

1-[(1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazol-4-yl)carbonyl]piperidin-4-ol (76). 76 was obtained from **55** (1.52 g, 4.00 mmol), DIPEA (1.46 mL, 8.4 mmol), HBTU (1.67 g, 4.40 mmol), and piperidin-4-ol (0.447 g, 4.40 mmol) according to the procedure described for **60** in 72% yield as an amorphous solid, ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.38−1.46 (m, 2H), 1.76−1.84 (m, 2H), 2.23 (s, 3H), 3.12−3.22 (m, 1H), 3.45−3.54 (m, 1H), 3.73−3.79 (m, 1H), 4.04−4.12 (m, 1H), 4.33−4.41 (m, 1H), 4.72 (d, J = 6 Hz, 1H), 7.28 (d, J = 8 Hz, 2H), 7.38 (dd, J = 8 and 2 Hz, 1H), 7.44−7.48 (m, 3H), 7.53 (d, J = 2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.76, 23.10, 66.21, 67.73, 127.47, 128.88, 129.33, 129.50, 129.69, 132.66, 133.72, 134.15, 134.17, 134.30, 134.83, 135.46, 141.03, 163.47; HRMS ($C_{22}H_{21}Cl_3N_3O_2$) [M + H]$^+$: found *m/z* 464.0687, calcd 464.0699. Anal. ($C_{22}H_{20}Cl_3N_3O_2$·H_2O) C, H, N.

1-[(1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazol-4-yl)carbonyl]-1,2,3,4-tetrahydroisoquinoline (77). 77 was obtained from **55** (1.52 g, 4.00 mmol), DIPEA (1.46 mL, 8.4 mmol), HBTU (1.67 g, 4.40 mmol), and 1,2,3,4-tetrahydroisoquinoline (0.55 mL, 4.40 mmol) according to the procedure described for **60** in 84% yield, mp 143−146 °C ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.27 (s, 3H), 2.88−2.98 (m, 2H), 3.85−3.91 (m, 1H), 4.18−4.22 (m, 1H), 4.77−4.81 (m, 1H), 5.21−5.25 (m, 1H), 7.02−7.22 (m, 4H), 7.30 (d, J = 8 Hz, 2H), 7.38 (dd, J = 8 and 2 Hz, 1H), 7.44−7.48 (m, 3H), 7.54−7.57 (m, 1H); HRMS ($C_{26}H_{21}Cl_3N_3O$) [M + H]$^+$: found *m/z* 496.0750, calcd 496.0750. Anal. ($C_{26}H_{20}Cl_3N_3O$) C, H, N.

***N*-(*Endo*-[2.2.1]bicyclohept-2-yl)-1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxamide (78). 78** was obtained from **55** (1.52 g, 4.00 mmol), DIPEA (2.92 mL, 16.8 mmol), HBTU (1.67 g, 4.40 mmol), and *endo*-[2.2.1]bicyclohept-2-ylamine·HCl (0.650 g, 4.40 mmol) according to the procedure described for **60** in 67% yield, mp 194−195 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.02−1.06 (m, 1H), 1.30−1.61 (m, 6H), 1.94−2.01 (m, 1H), 2.18−2.22 (m, 1H), 2.39 (s, 3H), 2.40−2.44 (m, 1H), 4.12−4.18 (m, 1H), 7.28 (d, J = 8 Hz, 2H), 7.40 (dd, J = 8 and 2 Hz, 1H), 7.45 (d, J = 8 Hz, 2H), 7.51 (d, J = 2 Hz, 1H), 7.52−7.59 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.55, 21.59, 29.65, 36.25, 36.65, 38.18, 40.55, 50.33, 127.46, 128.85, 129.14, 129.55, 129.64, 131.17, 133.35, 133.83, 134.32, 134.57, 134.79, 135.73, 141.82, 163.25; HRMS ($C_{24}H_{23}Cl_3N_3O$) [M + H]$^+$: found *m/z* 474.0895, calcd 474.0907. Anal. ($C_{24}H_{22}Cl_3N_3O$·$0.25H_2O$) C, H, N.

***N*-(*Tert*-butoxy)-1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxamide (79). 79** was obtained from **55** (1.50 g, 3.93 mmol), DIPEA (2.75 mL, 15.7 mmol), HBTU (1.79 g, 4.70 mmol), and *O*-*tert*-butylhydroxylamine·HCl (0.59 g, 4.70 mmol) according to the procedure described for **60** in 75% yield, mp 166−169 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.25 (s, 9H), 2.39 (s, 3H), 7.32 (d, J = 8 Hz, 2H), 7.42 (dd, J = 8 and 2 Hz, 1H), 7.46 (d, J = 8 Hz, 2H), 7.51 (d, J = 2 Hz, 1H), 7.59 (d, J = 8 Hz, 1H), 10.40 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 10.56, 26.88, 81.08, 127.48, 128.83, 129.11, 129.60, 129.64, 129.72, 133.78, 134.25, 134.33, 134.66, 134.76, 135.73, 142.08, 162.86; HRMS ($C_{21}H_{21}Cl_3N_3O_2$) [M + H]$^+$: found *m/z* 452.0724, calcd 452.0699. Anal. ($C_{21}H_{20}Cl_3N_3O_2$) C, H, N.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-*N*-[4-(trifluoromethyl)benzyl]-1*H*-imidazole-4-carboxamide (80). 80 was obtained from **55** (6.104 g, 16.0 mmol), DIPEA (6.12 mL, 35.2 mmol), HBTU (7.28 g, 19.2 mmol), and 4-(trifluoromethyl)benzylamine (2.74 mL, 19.2 mmol) according to the procedure described for **60** in 86% yield, mp 232 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.40 (s, 3H), 4.51−4.54 (m, 2H), 7.31 (d, J = 8 Hz, 2H), 7.40−7.43 (m, 1H), 7.46 (d, J = 8 Hz, 2H), 7.52−7.60 (m, 4H), 7.64 (d, J = 8 Hz, 2H), 8.70 (br s, 1H); HRMS ($C_{25}H_{18}Cl_3F_3N_3O$) [M + H]$^+$: found *m/z* 538.0461, calcd 538.0468. Anal. ($C_{25}H_{17}Cl_3F_3N_3O$) C, H, N.

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-*N*,*N*-diethyl-1*H*-imidazole-4-carboxamide (81). 81 was obtained from **36** (7.35 g, 20.0 mmol), DIPEA (7.66 mL, 44.0 mmol), HBTU (9.10 g, 24.0 mmol) and diethylamine (2.50 mL, 24.0 mmol) according to the procedure described for **60** in 85% yield, mp 177−179 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.12−1.25 (m, 6H), 3.40−3.48 (m, 2H), 3.68−3.94 (m, 2H), 7.24 (d, J = 8 Hz, 2H), 7.43 (d, J = 8 Hz, 2H), 7.46 (dd, J = 8 and 2 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.58 (d, J = 2 Hz, 1H), 7.59 (s, 1H).

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-*N*,*N*-diethyl-5-methyl-1*H*-imidazole-4-carboxamide (82). To a cooled (−70 °C) and magnetically stirred solution of **81** (2.52 g, 6.00 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA (0.90 mL, 6.00 mmol) in anhydrous THF (60 mL) was added *s*-BuLi (4.62 mL, 1.3 M solution in cyclohexane/hexane 92/8 (v/v)), 6.00 mmol) under N_2. The resulting mixture was allowed to attain room temperature. A solution of MeI (0.57 mL, 9.00 mmol) in THF (30 mL) was added, and the resulting solution was stirred for 1 h and subsequently quenched in aqueous NH_4Cl. The solution was extracted with Et_2O. The organic layer was washed with water, dried over $MgSO_4$, filtered, concentrated, and further purified by column chromatography (EtOAc). Crystallization from diisopropyl ether (∼ 25 mL) gave **82** (1.09 g, 41% yield), mp 101−104 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.14−1.24 (m, 6H), 2.25 (s, 3H), 3.41−3.48 (m, 2H), 3.72−3.79 (m, 2H), 7.27 (d, J = 8 Hz, 2H), 7.36 (dd, J = 8 and 2 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.46 (d, J = 8 Hz, 2H), 7.53 (d, J = 2 Hz, 1H); HRMS ($C_{21}H_{21}Cl_3N_3O$) [M + H]$^+$: found *m/z* 436.0762, calcd 436.0750. Anal. ($C_{21}H_{20}Cl_3N_3O$) C, H, N.

***tert*-Butyl 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylate (83).** To a magnetically stirred mixture of **36** (20.77 g, 0.0565 mol) and di-*tert*-butyl dicarbonate (Boc_2O) (24.63 g, 0.113 mol) in *t*-BuOH (275 mL) was added 4-(dimethylamino)pyridine (DMAP) (2.07 g, 0.017 mol), and the resulting mixture was stirred for 16 h. After concentration in vacuo, toluene was added and the mixture was again concentrated. The residue was purified by column chromatography (CH_2Cl_2/acetone = 95/5 (v/v)) and recrystallized from diisopropyl ether to give **83** (15.75 g, 66% yield), mp 178−180 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.63 (s, 9H), 7.05 (br d, J ∼ 8 Hz, 2H), 7.25−7.37 (m, 4H), 7.52 (d, J = 8 Hz, 1H), 7.80 (s, 1H).

***tert*-Butyl 5-chloro-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylate (84).** To a cooled (−70 °C) and magnetically stirred solution of **83** (4.24 g, 10.0 mmol) in anhydrous THF (80 mL) was added lithium diisopropylamide (LDA) (5.0 mL, 2 M solution in heptane/THF, 10.0 mmol), and the resulting mixture was stirred for 1 h under N_2. A solution of *p*-toluenesulfonyl chloride (TosCl) (2.10 g, 11.0 mmol) in THF (20 mL) was added, and the resulting solution was stirred at −70 °C for 1 h, allowed to attain room temperature and stirred for another 16 h. $NaHCO_3$ (5% aqueous solution) was added and extracted with Et_2O. The organic layer was washed with water, dried over Na_2SO_4, filtered, concentrated, and further purified by column chromatography (CH_2Cl_2), Recrystallization from diisopropyl ether gave **84** (5.24 g, 57% yield), mp 200−202 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 9H), 7.08 (br d, J ∼ 8 Hz, 2H), 7.21−7.43 (m, 5H).

***tert*-Butyl 5-Bromo-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylate (85). 85** was obtained from **83** (4.24 g, 10.0 mmol), LDA (5.0 mL, 2 M solution in heptane/THF, 10.0 mmol) and $(CBrF_2)_2$ (1.80 mL, 15.0 mmol) according to the procedure described for **84** in 73% yield, mp 198−200.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 9H), 7.08 (br d, $J \sim 8$ Hz, 2H), 7.25 (dd, $J = 8$ and 2 Hz, 1H), 7.29 (d, $J = 2$ Hz, 1H), 7.32−7.41 (m, 3H).

***tert*-Butyl 1-(4-Chlorophenyl)-5-cyano-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylate (86). 86** was obtained from **83** (4.24 g, 10.0 mmol), LDA (5.0 mL, 2 M solution in heptane/THF, 10.0 mmol), and TosCN (1.88 g, 11.0 mmol) according to the procedure described for **84** in 57% yield, mp 210−212 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.66 (s, 9H), 7.16 (br d, $J \sim 8$ Hz, 2H), 7.28−7.46 (m, 5H).

***tert*-Butyl 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate (87). 87** was obtained from **83** (0.47 g, 1.10 mmol), LDA (0.55 mL, 2 M solution in heptane/THF, 1.10 mmol) and CH_3I (0.18 mL, 3.0 mmol) according to the procedure described for **84** in 54% yield, mp 182−184 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.56 (s, 9H), 2.34 (s, 3H), 7.30 (d, $J = 8$ Hz, 2H), 7.40 (dd, $J = 8$ and 2 Hz, 1H), 7.48 (d, $J = 8$ Hz, 2H), 7.52 (d, $J = 2$ Hz, 1H), 7.54 (d, $J = 8$ Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.31, 28.42, 80.25, 127.47, 128.94, 129.08, 129.65, 129.68, 129.97, 133.80, 134.42, 134.54, 134.74, 135.69, 136.55, 142.90, 162.53. Anal. ($C_{21}H_{19}Cl_3N_2O_2$) C, H, N.

5-Chloro-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylic Acid (88). To a magnetically stirred solution of **84** (5.24 g, 11.4 mmol) in CH_2Cl_2 (60 mL) was added excess TFA (15 mL, 0.197 mol). The solution was reacted at room temperature for 16 h, concentrated in vacuo, and crystallized from diisopropyl ether to give **88** (4.53 g, 99% yield), mp 199−201 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.50 (br s, 1H), 7.12 (br d, $J \sim 8$ Hz, 2H), 7.23−7.45 (m, 5H).

5-Bromo-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylic Acid (89). 89 was obtained from **85** (4.30 g, 7.28 mmol) and TFA (10 mL, 0.132 mol) according to the procedure described for **88** in 83% yield, mp 205−207 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.50 (br s, 1H), 7.12 (br d, $J \sim 8$ Hz, 2H), 7.23−7.45 (m, 5H).

1-(4-Chlorophenyl)-5-cyano-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylic Acid (90). 90 was obtained from **86** (2.57 g, 5.73 mmol) and TFA (10 mL, 0.132 mol) according to the procedure described for **88** in 87% yield, mp 200−202 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.20 (br s, 1H), 7.18 (br d, $J \sim 8$ Hz, 2H), 7.21−7.48 (m, 5H).

5-Chloro-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (91). 91 was obtained from **88** (1.13 g, 2.81 mmol), DIPEA (1.08 mL, 6.18 mmol), HBTU (1.28 g, 3.37 mmol) and 1-aminopiperidine (0.36 mL, 3.37 mmol) according to the procedure described for **60** in 57% yield, mp 164−166 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34−1.41 (m, 2H), 1.60−1.65 (m, 4H), 2.79−2.84 (m, 4H), 7.36 (d, $J = 8$ Hz, 2H), 7.44 (dd, $J = 8$ and 2 Hz, 1H), 7.48 (d, $J = 8$ Hz, 2H), 7.54 (d, $J = 2$ Hz, 1H), 7.67 (d, $J = 8$ Hz, 1H), 8.95 (s, 1H); HRMS ($C_{21}H_{19}Cl_4N_4O$) $[M + H]^+$: found *m/z* 483.0319, calcd 483.0313. Anal. ($C_{21}H_{18}Cl_4N_4O$) C, H, N.

5-Bromo-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (92). 92 was obtained from **89** (1.34 g, 3.00 mmol), DIPEA (1.15 mL, 6.60 mmol), HBTU (1.36 g, 3.59 mmol), and 1-aminopiperidine (0.39 mL, 3.62 mmol) according to the procedure described for **54** in 79% yield, mp 181.5−183 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34−1.40 (m, 2H), 1.60−1.64 (m, 4H), 2.79−2.82 (m, 4H), 7.35 (d, $J = 8$ Hz, 2H), 7.44 (dd, $J = 8$ and 2 Hz, 1H), 7.48 (d, $J = 8$ Hz, 2H), 7.55 (d, $J = 2$ Hz, 1H), 7.66 (d, $J = 8$ Hz, 1H), 8.90 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 23.31, 25.67, 55.84, 109.28, 127.57, 128.27, 129.14, 129.58, 130.23, 132.23, 133.49, 134.66, 134.71, 134.98, 136.27, 144.18, 158.35; HRMS ($C_{21}H_{19}BrCl_3N_4O$) $[M + H]^+$: found *m/z* 526.9828, calcd 526.9808. Anal. ($C_{21}H_{18}BrCl_3N_4O$) C, H, N.

1-(4-Chlorophenyl)-5-cyano-2-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (93). 93 was obtained from **90** (0.97 g, 2.47 mmol), DIPEA (0.95 mL, 5.43 mmol), HBTU (1.12 g, 2.96 mmol), and 1-aminopiperidine (0.33 mL, 2.96 mmol) according to the procedure described for **60** in 60% yield, mp 231−233.5 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.34−1.42 (m, 2H), 1.60−1.66 (m, 4H), 2.80−2.86 (m, 4H), 7.47 (d, $J = 8$ Hz, 2H), 7.50 (dd, $J = 8$ and 2 Hz, 1H), 7.54 (d, $J = 8$ Hz, 2H), 7.60 (d, $J = 2$ Hz, 1H), 7.74 (d, $J = 8$ Hz, 1H), 9.55 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 23.29, 25.66, 55.52, 109.00, 110.51, 126.71, 127.87, 128.90, 129.38, 129.97, 132.59, 134.43, 134.67, 135.52, 136.90, 144.07, 146.64, 156.81; HRMS ($C_{22}H_{19}Cl_3N_5O$) $[M + H]^+$: found *m/z* 474.0682, calcd 474.0655. Anal. ($C_{22}H_{18}Cl_3N_5O.0.5CH_3CN$) C, H, N.

Ethyl 5-Bromomethyl-1-(4-chlorophenyl)-2-(2,4-dichlorophenyl)-1*H*-imidazole-4-carboxylate (94). To a magnetically stirred mixture of **49** (2.05 g, 5.00 mmol) in CCl_4 (25 mL) were added *N*-bromosuccinimide (NBS) (1.34 g, 7.53 mmol) and dibenzoyl peroxide (10.0 mg, assay 75%, 0.0310 mmol), and the resulting mixture was refluxed for 38 h. The formed precipitate was removed by filtration. The filtrate was successively washed with brine and water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/acetone = 98/2 (v/v)) to give **94** (1.29 g, 53% yield) as an amorphous solid, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (t, $J = 7$ Hz, 3H), 4.48 (q, $J = 7$ Hz, 2H), 4.72 (s, 2H), 7.18−7.43 (m, 7H).

Ethyl 1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-fluoromethyl-1*H*-imidazole-4-carboxylate (95). To a magnetically stirred mixture of **94** (5.46 g, 11.18 mmol) in anhydrous CH_3CN (150 mL) was added anhydrous KF (6.4 g, 13.1 mmol) and 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-[8.8.8]hexacosane (Kryptofix) (4.0 g, 10.6 mmol). The resulting mixture was refluxed for 1 h and concentrated in vacuo. EtOAc was added to the residue, and the resulting solution was washed with water, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/acetone = 99/1 (v/v)) and recrystallized from diisopropyl ether to give **95** (1.88 g, 39% yield), mp 124−125 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (t, $J = 7$ Hz, 3H), 4.47 (q, $J = 7$ Hz, 2H), 5.59 (d, $J = 48$ Hz, 2H), 7.15 (br d, $J = 8$ Hz, 2H), 7.20−7.42 (m, 5H).

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-fluoromethyl-1*H*-imidazole-4-carboxylic Acid (96). To a magnetically stirred mixture of **95** (1.88 g, 4.40 mmol) in MeOH (50 mL) was added NaOH (10 mL of a 4 N solution, 40.0 mmol). The resulting mixture was stirred at room temperature for 10 min and poured onto HCl (150 mL of a 1 N solution, 0.150 mol). The formed precipitate was collected by filtration, washed with H_2O, and dried at 60 °C in vacuo to yield **96** (1.74 g, 99% yield), mp 187−190 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.10 (br s, 1H), 5.60 (d, $J = 48$ Hz, 2H), 7.15 (br d, $J \sim 8$ Hz, 2H), 7.20−7.45 (m, 5H).

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-5-fluoromethyl-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (97). 97 was obtained from **96** (0.87 g, 2.18 mmol), DIPEA (0.84 mL, 4.80 mmol), HBTU (0.99 g, 2.62 mmol) and 1-aminopiperidine (0.28 mL, 2.62 mmol) according to the procedure described for **60** in 64% yield, mp 162−163 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.35−1.41 (m, 2H), 1.61−1.66 (m, 4H), 2.80−2.84 (m, 4H), 5.63 (d, $J = 48$ Hz, 2H), 7.36 (d, $J = 8$ Hz, 2H), 7.44 (dd, $J = 8$ and 2 Hz, 1H), 7.48 (d, $J = 8$ Hz, 2H), 7.55 (d, $J = 2$ Hz, 1H), 7.67 (d, $J = 8$ Hz, 1H), 9.10 (s, 1H); HRMS ($C_{22}H_{21}Cl_3FN_4O$) $[M + H]^+$: found *m/z* 481.0760, calcd 481.0765. Anal. ($C_{22}H_{20}Cl_3FN_4O$) C, H, N.

***N*-(2,4-Dichlorophenyl)-4-chlorobenzenecarboxamidine (100). 100** was obtained from $NaN(Si(CH_3)_3)_2$ (100 mL, 1 M solution in THF, 0.10 mol), **98** (13.75 g, 0.10 mol), and **99** (16.2 g, 0.10 mol) according to the procedure described for **31** in 83% yield, mp 130−131 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.78 (br s, 2H), 6.93 (d, $J = 8$ Hz, 1H), 7.22 (dd, $J = 8$ and 2 Hz, 1H), 7.41−7.46 (m, 3H), 7.84 (d, $J = 8$ Hz, 2H).

Ethyl 2-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylate (101). 101 was obtained from **100** (2.99 g, 0.010 mol), $NaHCO_3$ (1.008 g, 0.012 mol), trifluoroacetic acid (0.76 mL, 0.010 mol), and **48** (2.508 g, 0.012

mol) according to the procedure described for **49** in 75% yield as an amorphous solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44 (t, J = 7 Hz, 3H), 2.35 (s, 3H), 4.45 (q, J = 7 Hz, 2H), 7.18 (d, J = 8 Hz, 1H), 7.23 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 7.39 (dd, J = 8 and 2 Hz, 1H), 7.60 (d, J = 2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.01, 14.96, 61.08, 128.27, 129.04, 129.16, 129.95, 130.06, 131.15, 131.29, 133.09, 134.26, 135.65, 137.21, 138.71, 146.13, 164.10.

2-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-5-methyl-1*H*-imidazole-4-carboxylic Acid (102). 102 was obtained from **101** (4.17 g, 0.010 mol) and LiOH (0.48 g, 0.020 mol) according to the procedure described for **55** in 72% yield, mp 141−144 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (s, 3H), 7.34 (s, 4H), 7.61 (dd, J = 8 and 2 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.82 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.96, 128.89, 129.04, 129.68, 129.79, 130.14, 130.90, 132.36, 133.02, 133.42, 134.65, 136.49, 138.17, 145.18, 165.04.

2-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-imidazole-4-carboxamide (103). 103 was obtained from **102** (2.76 g, 0.072 mol), *N*,*N*-diisopropylethylamine (2.77 mL, 0.0159 mol), HBTU (3.275 g, 0.086 mol), and 1-aminopiperidine (0.93 mL, 0.086 mol) according to the procedure described for **60** in 65% yield, mp 209−210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41−1.50 (m, 2H), 1.74−1.82 (m, 4H), 2.37 (s, 3H), 2.86−2.94 (m, 4H), 7.18 (d, J = 8 Hz, 1H), 7.22−7.30 (m, 4H), 7.38 (dd, J = 8 and 2 Hz, 1H), 7.58 (d, J = 2 Hz, 1H), 7.98 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.27, 23.64, 25.71, 57.44, 128.27, 128.89, 128.99, 129.32, 130.94, 131.05, 131.07, 133.02, 134.11, 135.38, 135.73, 136.89, 144.44, 160.90. Anal.$C_{22}H_{21}Cl_3N_4O$ Anal. ($C_{22}H_{21}Cl_3N_4O$) C, H, N.

Molecular Modeling. All modeling studies were carried out on a Silicon Graphics Octane workstation running *Sybyl* V6.9.1.[44] The ligands were manually docked into the previously described receptor model,[15] 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 supply and interpretation of the spectral data. Dr. Anneke Mühlebach is gratefully acknowledged for supply of the elemental analysis data. Mr. Piet Hoogkamer is acknowledged for supply of the RP-HPLC lipophilicity data.

Note Added after ASAP Posting

In the third paragraph of the Chemistry section of the manuscript version posted September 29, 2004, esters **49**−**53** are changed to esters **50**−**54**, and esters **49**−**54** are changed to esters **49**−**53**. The revised version of the manuscript was posted October 4, 2004.

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

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JM040843R