Substituent Effects of *N*-(1,3-Diphenyl-1*H*-pyrazol-5-yl)benzamides on Positive Allosteric Modulation of the Metabotropic Glutamate-5 Receptor in Rat Cortical Astrocytes

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CDPPB [3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide] was recently described as the first centrally active, positive allosteric modulator of rat and human metabotropic glutamate receptor (mGluR) $mGluR_5$ subtype. We explored the structural requirements for potentiation of glutamate-induced calcium release in naturally expressed $mGluR_5$ in cultured rat astrocytes and increasing affinity for the allosteric antagonist binding site by evaluating 50 analogues of CDPPB. In the fluorometric calcium assay, CDPPB exhibited an EC_{50} value of 77 ± 15 nM in potentiating $mGluR_5$-mediated responses in cortical astrocytes and a K_i value of 3760 ± 430 nM in displacing [^{3}H]methoxyPEPy binding in membranes of cultured HEK-293 cells expressing rat $mGluR_5$. The structure−activity relationships showed that electronegative aromatic substituents in the para-position of the benzamide moiety of CDPPB increase potency. Both binding and functional activities were further increased with a halogen atom in the ortho-position of the 1-phenyl ring. These effects of substitution do not match those of either aromatic ring of MPEP [2-methyl-6-(phenylethynyl)-pyridine] for the antagonist allosteric binding site. Combination of the optimal substituents and aromatic positions resulted in 4-nitro-*N*-(1-(2-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl)benzamide (VU-1545) showing K_i = 156 ± 29 nM and EC_{50} = 9.6 ± 1.9 nM in the binding and functional assays, respectively.

Introduction

Metabotropic glutamate receptors (mGluRs) play an important role in controlling neuronal excitability and synaptic transmission in the central nervous system (CNS) of the mammalian brain.[1] As a result, mGluRs are potential targets for therapeutic intervention in a variety of neurological and psychiatric illnesses.[1,2] In particular, agonists at the $mGluR_5$ subtype could be useful as antipsychotic agents because of their ability to facilitate NMDA receptor function without causing NMDA-mediated excitoxicity.[3,4] Direct acting orthosteric $mGluR_5$ agonists, such as 3,5-DHPG [3,5-dihydroxyglycine], have poor subtype selectivity and may cause unwanted side effects.[5] In contrast, indirect agonists that act via allosteric potentiation of receptor function are predicted to be less problematic.[4] In recombinant systems, these agents do not activate $mGluR_5$ when added alone but shift the concentration−response for glutamate to the left. Furthermore, electrophysiological studies have shown that such agents cause an increase in the effect of threshold agonist concentrations in neurons in the hippocampus and subthalamic nucleus without inducing an effect by themselves.[6] Discovery of selective positive allosteric modulators of $mGluR_5$ raises the exiting possibility that such compounds will provide a novel approach for developing therapeutic agents that activate this glutamate receptor subtype. We have now reported discovery of three distinct series of allosteric potentiators of $mGluR_5$.[6−10] A fourth structural series with similar properties, represented by ADX-47273 [(*S*)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)-[1,2,4]oxadiazol-5-yl)piperidine, **1**], was recently presented.[11,12] None of these compounds has intrinsic activity at the orthosteric glutamate binding site but each potentiates the response of $mGluR_5$ to activation by glutamate.

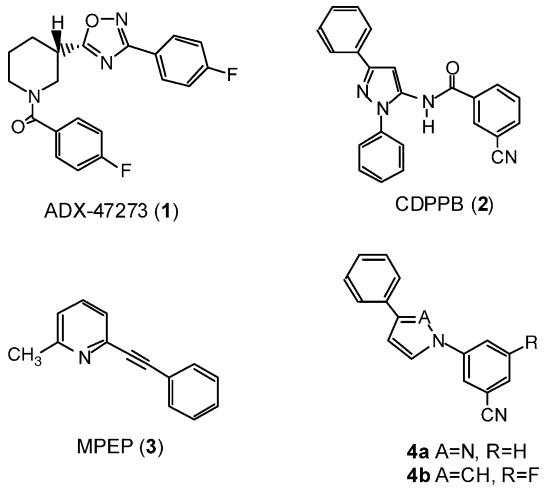

Figure 1. Structures of the positive allosteric modulators ADX-47273 (**1**) and CDPPB (**2**) and the negative modulators MPEP(**3**), pyrazole **4a**, and pyrrole **4b** of $mGluR_5$.

To date, one of the promising positive allosteric modulators of $mGluR_5$ is CDPPB [3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide, **2**]. This compound is centrally active and induces an 8-fold maximal potentiation of glutamate-induced calcium release in cultured CHO cells expressing human $mGluR_5$ with an EC_{50} value of 27 nM.[9] Further, CDPPB reverses amphetamine-induced locomotor activity and impairment of acoustic prepulse inhibition in the rat,[10] two behavioral models in which currently used antipsychotic agents are effective.[2−4] However, the pharmacological and physicochemical properties of CDPPB are probably not optimal, considering that CDPPB was selected from a limited number of structural analogues.[9,13] In addition,

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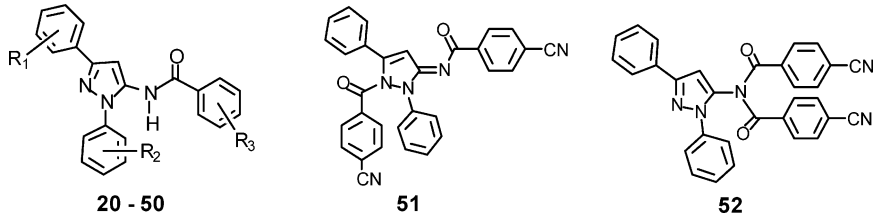


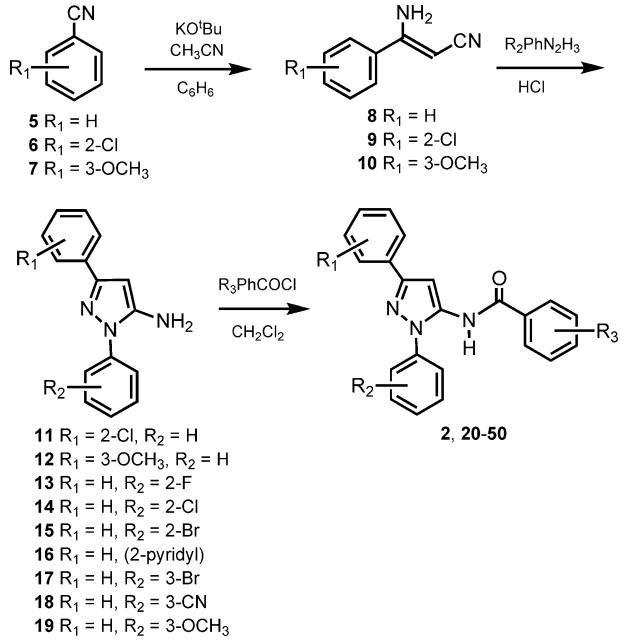
Figure 2. Structures of compounds **20**−**50** (Table 1) and byproduct A (**51**) and B (**52**) (Table 2).

CDPPB lacks ideal selectivity because it is a weak antagonist at the mGluR$_8$ receptor.[10] CDPPB exhibits weak affinity for the antagonist MPEP [2-methyl-6-(phenylethynyl)pyridine, **3**] allosteric binding site of mGluR$_5$, as evidenced by inhibiting the binding of [^{3}H]methoxyPEPy[14] [3-methoxy-5-(pyridin-2-ylethynyl)pyridine] with a K_i of 2.7 μM.[10] To take advantage of the structure−activity relationships of the MPEP series, we wanted to establish whether the aromatic rings of CDPPB could mimic the aryl groups of MPEP and its congeners. It has already been shown that five-membered heterocyclic rings can substitute for the triple bond of MPEP.[15] For example, the 1,3-diarylpyrazole **4a** (Figure 1) binds to the MPEP binding site with an affinity of 530 nM.[16] Replacing the pyrazole with a pyrrole ring and adding a *m*-fluorine atom to become compound **4b** increased affinity 100-fold.[17] Other allosteric mGluR$_5$ antagonists have demonstrated that allosteric action can be altered from negative to positive modulation with aromatic substitution.[7] If the relevant binding site of CDPPB is identical to that of MPEP, it would be possible to control the type of modulation by simply applying the appropriate structural modifications. For example, shifting the 6-methyl group of MPEP to the adjacent 5-position (5-MPEP)[18] completely abolishes the negative allosteric modulation and creates a neutral ligand, while retaining binding affinity for the MPEP site.[19] Here, we present the results of structural modifications of CDPPB in the search for a more potent candidate for future development into a pharmacological tool or therapeutic agent. Part of this study was presented at the Fifth International Symposium on the Metabotropic Glutamate Receptor (Taormina, Italy, Sept 18−23, 2005).[20]

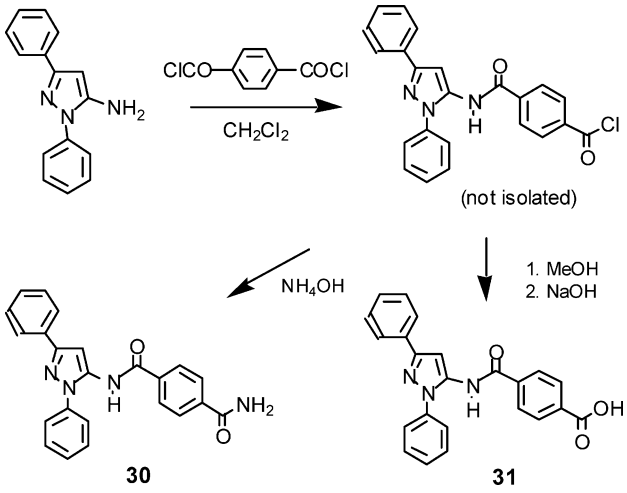
Chemistry

We first investigated the effect of aromatic substituents in the benzamide moiety of CDPPB (Figure 2). In the previous series, Lindsley et al.[9] demonstrated a detrimental effect of having a substituent in the ortho-position of the benzamide phenyl ring and little variation in activity with substituents in the meta- or para-position. Alkyl groups and particularly halogen atoms, such as fluoro or chloro atoms, in either the aromatic 3- or 4-positions of the benzamide seemed to cause a 10-fold increase in activity.[9] We expanded the scope of substituents in these positions to include groups with both strong electronegative and electropositive properties. Reacting 5-amino-1,3-phenyl-1*H*-pyrazole with the appropriately substituted benzoic acids via their acid chlorides gave the desired benzamides **20**−**29** (Scheme 1). Acid chlorides that were unavailable were prepared from the corresponding carboxylic acids using thionyl chloride. The corresponding 4-carboxamide and 4-carboxylic acid derivatives **30** and **31** were prepared by using terephthaloyl dichloride in excess, followed by quenching of the monosubstituted 4-chlorocarboxybenzamide with ammonium hydroxide or methanol, respectively (Scheme 2). Basic hydrolysis of the resulting methyl ester gave compound **31**. The facile preparation of the pyrazole scaffold[21] allowed us to explore the substitution effect on all three phenyl groups of CDPPB. Aryl-substituted 5-amino-1,3-diphenyl-1*H*-pyrazoles (**37**−**50**), having a halogen

Scheme 1



Scheme 2



atom, methoxy, or cyano group in one of the phenyl groups of CDPPB, were prepared by reacting substituted phenylhydrazines[22] with substituted 1-aminocinnamonitriles according to the method of Grandberg[21] (Scheme 1). The latter were obtained by reacting the appropriate arylnitriles in base-catalyzed condensation with acetonitrile.[23] Synthesis of 5-amino-1-(2-pyridyl)-3-phenyl-1*H*-pyrazole (**16**) has been reported starting from benzoylacetonitrile[24] in ethanol or hydrochloric acid[25] or from 3-phenylpropynylnitrile.[26] We obtained compound **16** in good yield using the method of Grandberg.[21]

In the case of benzamides with a cyano or nitro substituent, the amide condensation resulted in a mixture of three products, one of which was the desired compound. Isolation and

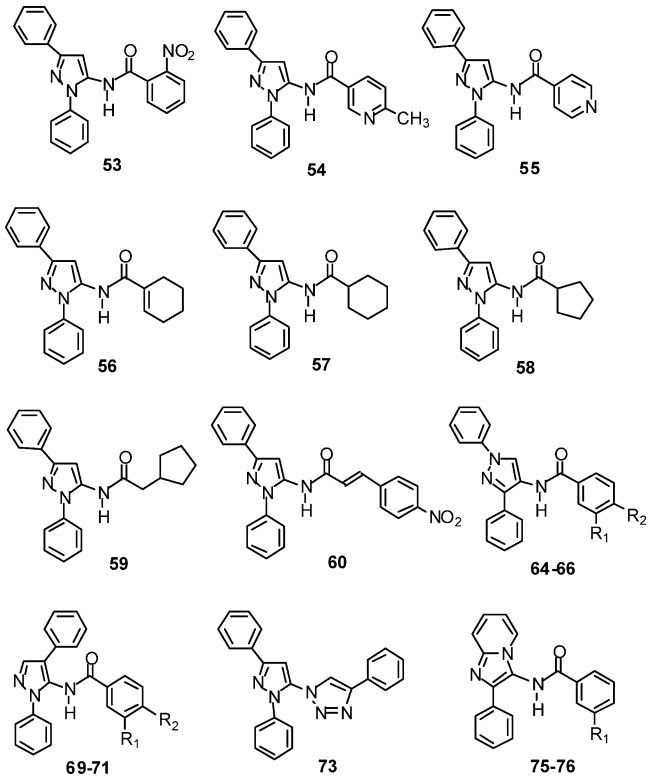
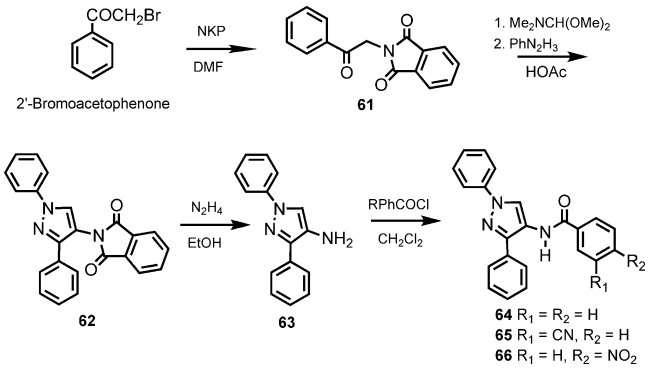


Figure 3. Structures of compounds **53**−**60**, **64**−**66**, **69**−**71**, **73**, and **74**−**76** (Table 2).

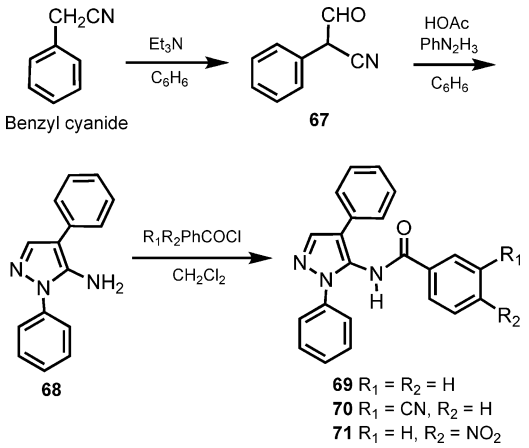
characterization of the individual byproducts showed that they contained two benzoyl moieties in asymmetrical (A) and symmetrical (B) positions, respectively, as examplified by the 4-cyano compounds **51** and **52** (Figure 2). The presence of dimeric byproducts A and B in the reaction mixture was detected by proton NMR as the chemical shift of the pyrazole 4-CH singlet appearing at 6.6−6.7 ppm compared to 7.1−7.2 ppm for the monosubstituted compounds. The formation of byproduct A is the result of a second benzoyl group reacting with the nitrogen atom in the pyrazole 2-position, followed by rearrangement of the pyrazole double bonds. This side reaction has been observed in the acylation of 5-amino-1-phenyl-3-methyl-1*H*-pyrazole.[27] Formation of byproduct B is the result of a second benzoyl group replacing the amide hydrogen atom. A similar diacylation reaction in substituted pyrazoles has been seen in the acylation with 2-nitrobenzoyl chloride.[28] Use of less than 1 equiv of acid chloride resulted in difficulties removing unreacted diphenylpyrazole from the product. The formation of byproduct B could be avoided by using the corresponding benzoic acids, instead of acid chlorides and 1,1′-cyclohexylcarbodiimide as water scavenger, but byproduct A was still formed, and overall yields were not improved.

Compounds **53**−**60** (Figure 3) were prepared from 5-amino-1,3-diphenyl-1*H*-pyrazole by the same methods. Permutation of the pyrazole nitrogen atoms was explored using 4-amino-1,3-diphenyl-1*H*-pyrazole (**63**) and 5-amino-1,4-diphenyl-1*H*-pyrazole (**68**) as starting materials. These pyrazoles were obtained by reacting phenylhydrazine with 2′-phthalimidoacetophenone[29] (Scheme 3) or 1-formyl-1-phenylacetonitrile[30] (Scheme 4), respectively. The latter reaction has erroneously been reported to result in 3-amino-1,4-diphenyl-1*H*-pyrazole with melting point 137−138 °C.[30] In our hands, the resulting compound was identified as **68** with melting point 139−140 °C,[31,32] and the structure was confirmed by crystal crystallographic data (see Supporting Information). Condensation of these aminopyrazoles with substituted benzoyl chlorides as

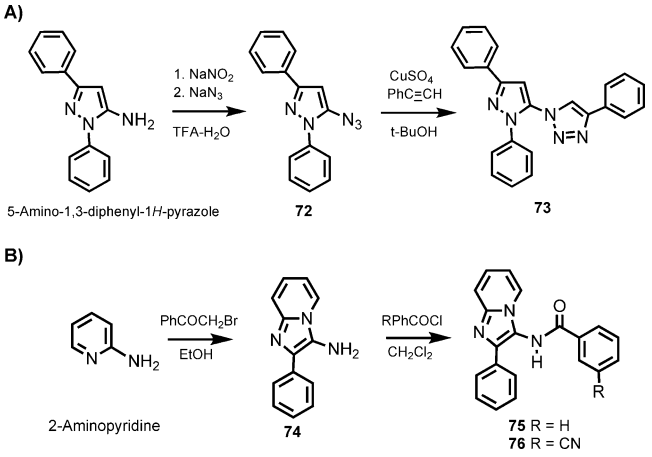
Scheme 3



Scheme 4



Scheme 5



described for CDPPB gave the corresponding substituted *N*-pyrazolylbenzamides **64**−**66** and **69**−**71** in good yields. The triazolylpyrazole **73** was prepared by reacting phenylacetylene with the corresponding 5-azidopyrazole **72** (Scheme 5A). An annelated phenylpyrazole was explored using 3-amino-2-phenylimidazo[1,2-*a*]pyridine (**74**) (Scheme 5B), easily obtained from 2-aminopyridine and 2′-bromoacetophenone using the Tschitschibabin reaction as described for the corresponding 2-(4-methylsulfonylphenyl) derivative,[33] followed by nitrosation.[34] Condensation with the appropriate benzoyl chloride gave compounds **75**[35] and **76**, respectively.

Pharmacology

The results of displacement of the potent MPEP analogue [^{3}H]methoxyPEPy[13] binding to membranes of cultured HEK-

Table 1. Displacement of [^{3}H]MethoxyPEPy Binding in HEK Cells, Expressing Rat mGluR$_5$ Receptors, and Potentiation of Glutamate-Induced Calcium Flux in Cultured Rat Astrocytes

compound	R_1	R_2	R_3	K_i (nM)[a]	EC_{50} (nM)[b]	potent.[c]	log *P*[d]
CDPPB (**2**)	H	H	3-CN	3760 ± 430 (3)[e]	77 ± 15 (7)	4.0	5.2
20	H	H	H	4180 ± 200 (3)	203 ± 35 (4)	4.4	4.0
21	H	H	3-OCH_3	1290 ± 130 (3)	102 ± 21 (4)	3.8	3.9
22	H	H	3-CF3	1650 ± 310 (5)	228 ± 39 (7)	4.0	5.0
23	H	H	3-NO_2	2220 ± 310 (4)	39 ± 18 (5)	5.1	4.8
24	H	H	4-CH_3	780 ± 230 (3)	64 ± 18 (7)	5.0	4.1
25	H	H	4-OCH_3	420 ± 160 (3)	54 ± 9 (6)	4.2	3.9
26	H	H	4-OCF_3	265 ± 63 (3)	18 ± 6 (6)	4.6	5.3
27	H	H	4-CF_3	990 ± 130 (3)	38 ± 11 (6)	3.7	6.5
28	H	H	4-CN	1560 ± 210 (4)	75 ± 13 (7)	5.2	5.3
29	H	H	4-NO_2	250 ± 85 (3)	10.7 ± 4.7 (6)	5.0	4.6
30	H	H	4-$CONH_2$	>10000	inactive		5.0
31	H	H	4-COOH	>10000	inactive		5.0
32	H	H	3,5-NO_2	NT[e]	65 ± 27 (3)	3.3	4.3
33	H	H	3,4-OCH_3	>10000	3530 ± 1310 (3)	3.7	3.8
34	H	H	3,5-OCH_3	>10000	2040 ± 350 (3)	5.9	3.9
35	H	H	3,4-CH_3	430 ± 80 (4)	20 ± 4 (7)	4.0	4.1
36	H	H	3,4-Cl	160 ± 40 (4)	13 ± 5 (6)	5.2	4.7
37	2-Cl	H	H	>10000	2290 ± 620 (2)	5.2	6.2
38	3-OCH_3	H	H	3200 ± 490 (3)	600 ± 100 (3)	5.9	4.0
39	H	2-F	H	2700 ± 430 (3)	104 ± 12 (3)	3.4	5.0
40	H	2-Cl	H	500 ± 210 (3)	62 ± 8 (3)	3.9	4.4
41	H	2-Br	H	2600 ± 700 (3)	200 ± 67 (3)	4.3	4.7
42	H	(2-py)[f]	H	>10000	inactive		4.8
43	H	3-Br	H	>10000	400 ± 150 (3)	4.2	4.9
44	H	3-CN	H	>10000	117 ± 12 (4)	5.4	3.8
45	H	3-OCH_3	H	2100 ± 520 (3)	570 ± 34 (4)	6.7	6.0
46	H	2-F	4-NO_2	160 ± 30 (3)	9.6 ± 1.9 (3)	4.8	4.9
47	H	2-Cl	4-NO_2	110 ± 20 (3)	40 ± 12 (3)	3.3	5.2
48	H	2-Br	4-NO_2	120 ± 30 (5)	61 ± 8 (3)	4.4	5.2
49	H	2-Br	3-NO_2	230 ± 80 (3)	68 ± 24 (3)	3.9	5.3
50	H	2-Br	3-CN	230 ± 70 (4)	50 ± 10 (3)	3.5	5.6
ADX-47273 (**1**)				NT[g]	170 ± 60 (2)	3.8	3.1

[a] Inhibition constant for displacing [^{3}H]methoxyPEPy binding and standard error of the mean (SEM) from *n* number of experiments. [b] Effective concentration and SEM to reach 50% of the maximum potentiation from 200 nM glutamate. [c] Maximum increase in glutamate-induced calcium release. [d] Calculated lipophilicity using SciLogP v1.5 (Scivision, Burlington, MA). [e] Not tested. [f] *N*-(1-(2-Pyridinyl)-3-phenyl-1*H*-pyrazol-1-yl)benzamide. [g] Reported IC_{50} value 3700 ± 400 nM for displacing [^{3}H]MPEP binding in rat cortical membranes.[11]

Table 2. Displacement of [^{3}H]MethoxyPEPy Binding in HEK Cells, Expressing Rat mGluR$_5$ Receptors, and Potentiation of Glutamate-Induced Calcium Flux in Cultured Rat Astrocytes

compd	RCONH-pyrazole[a]	K_i (nM)[b]	EC_{50} (nM)[c]	potent.[d]	log *P*[e]
51	4-CN-phenyl dimer A	5230 ± 2000 (3)[f]	43 ± 6 (4)	3.6	7.4
52	4-CN-phenyl dimer B	3050 ± 1480 (2)	340 ± 70 (3)	3.3	6.8
53	2-NO_2-phenyl	>10000	>10000		5.9
54	3-pyridyl-4-CH_3	3480 ± 3 (2)	280 ± 100 (3)	4.4	5.0
55	4-pyridyl	>10000	2500 ± 250 (3)	4.0	4.8
56	cyclohex-1-enyl	4470 ± 910 (4)	3300 ± 2200 (3)	3.8	4.8
57	cyclohexyl	10140 (1)	>10000		4.2
58	cyclopentyl	11600 ± 3400 (4)	3410 ± 1240 (3)	3.7	4.3
59	cyclopentylmethyl	>10000	350 (1)	1.8	4.3
60	4-NO_2-cinnamoyl	1810 ± 470 (3)	560 ± 46 (3)	3.5	4.0
64	phenyl[g]	>10000	>10000		4.0
65	3-CN-phenyl[g]	>10000	>10000		3.6
66	4-NO_2-phenyl[g]	>10000	>10000		2.9
69	phenyl[h]	1170 ± 440 (4)	antagonist		3.8
70	3-CN-phenyl[h]	1200 ± 900 (3)	antagonist		3.6
71	4-NO_2-phenyl[h]	>10000	>10000		4.3
73		5880 ± 4400 (3)	2600 ± 290 (3)	2.7	7.9
75	phenyl[i]	3920 ± 350 (2)	antagonist		3.0
76	3-CN-phenyl[i]	1990 ± 200 (4)	antagonist		4.3

[a] *N*-(1,3-Diphenyl-1*H*-pyrazol-5-yl)benzamide unless otherwise noted. [b] Inhibition constant for displacing [^{3}H]methoxyPEPy binding and standard error of the mean (SEM) from *n* number of experiments. [c] Effective concentration and SEM to reach 50% of the maximum potentiation from 200 nM glutamate. [d] Maximum increase in glutamate-induced calcium release. [e] Calculated lipophilicity using SciLogP v1.5 (Scivision, Burlington, MA). [f] Number of independent experiments. [g] *N*-(1,3-Diphenyl-1*H*-pyrazol-4-yl)benzamide. [h] *N*-(1,4-Diphenyl-1*H*-pyrazol-5-yl)benzamide. [i] *N*-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)benzamide.

293 cells expressing rat mGluR$_5$ by the CDPPB analogues are shown in Tables 1 and 2. In this assay, CDPPB (**2**) had a K_i of 3.8 ± 0.4 μM in concordance with the previously reported value of 2.6 ± 0.5 μM in CHO cells expressing the human mGluR$_5$.[10] Monosubstituents in either the 3- or 4-position of the benzamide moiety, regardless of their electronic nature, increased binding activity, except for $CONH_2$ and COOH groups in the 4-position (Table 1). Comparison with the unsubstituted analogue (**20**) shows that the increase in binding activity by a 3-CN group was only 11%, while having the cyano group in the para-position (**28**) increased binding activity by 270%. A 4-NO_2 substitution (**29**) resulted in the highest activity. Additional increases were

seen with a halogen atom in the ortho-position of the 1-phenyl ring. The 2′-chloro-4-nitro analogue **47** had $K_i = 113 \pm 24$ nM. In contrast, the 1-(2-pyridyl) analogue **42** was completely devoid of activity. Attempts to correlate the binding data with various QSAR models resulted in the nitro compounds being clustered as outliers. Compound **54** with a 3-pyridinyl group replacing the benzamide ring combined with a 4-methyl group showed activity similar to having a phenyl ring with no substituents (**20**). The same result was reported for the corresponding 2-pyridinyl analogue.[9] However, the 4-pyridinyl analogue **55** displayed no binding activity (Table 2). Thus, all tested compounds with an ortho-substituent in the benzamide moiety and all pyridinylcarboxamides proved to have weak or no activity. With the exception for halogen atoms in the ortho-position of the 1-phenyl ring, all substitutions in the pyrazole phenyl rings proved detrimental. This is in sharp contrast to the effects of aromatic substitution in the MPEP series of negative allosteric modulators, where meta-substituents increase binding activity to the MPEP site.[14−18] For instance, in the MPEP series the binding activity increases with the introduction of a pyridyl ring in either aryl group,[15,16] while decreasing drastically with substitution in the para-position.[18] In the CDPPB series, introducing a *m*-cyano group (**2** vs **20**, Table 1) only marginally increased binding affinity, while a para-substituent (**28**) resulted in a substantial increase. Therefore, none of the aromatic rings of CDPPB seem to mimic the aromatic rings of MPEP, clearly showing that the structural requirement of the binding site of CDPPB is different from that of MPEP or methoxyPEPy.

The results of evaluating the analogues of CDPPB for their ability to potentiate glutamate-induced calcium release are shown in Tables 1 and 2. The activity of CDPPB at the rat $mGluR_5$ was 77 nM, compared to 27 nM seen at the human $mGluR_5$.[10] This is in concordance with the reported differences between rat and human $mGluR_5$.[9,10] Having no substituent in either meta- or para-position of the benzamide moiety (**20**) produced slightly less activity than that of CDPPB, as demonstrated by Lindsley et al.[9] With the exception of having a *m*-trifluoromethyl group (**22**), electron-donating substituents tended to increase activity. Highest activity was obtained with a nitro group, particularly in the para-position (**29**), while a nitro group in the ortho-position of the benzamide moiety (**53**) completely abolished activity. In fact, having a nitro group in either meta- (**23**) or para-position (**29**) proved to be the most beneficial substitution. The electronically similar 4-carboxylic acid and 4-carboxamide analogues **30** and **31** were inactive. Interestingly, a single electropositive substituent, such as a methoxy group, in either meta- (**21**) or para-position (**26**) bestowed increased activity relative to that of CDPPB. However, two methoxy groups in either 3,4- (**33**) or 3,5-positions (**34**) reduced functional activity 20- and 15-fold, respectively, relative to having no substituent (**20**). In contrast, having two methyl groups (**35**) or chloro atoms (**36**) in the 3,4-positions of the benzamide resulted in 10- and 18-fold increases, respectively. Lindsley et al. found the same result with two fluoro atoms in these positions.[9] Replacing the aromatic benzamide ring with an aliphatic ring decreased activity. The cyclohex-1-enyl-, cyclohexyl-, and cyclopentyl carboxamides **56**−**58** were 10 times less active on the average than the benzoyl analogue **20**. The exception was cyclopentylmethylcarboxamide **59**, which retained functional activity. Extending the position of the 4-nitrophenyl group by two carbon atoms (**60**) reduced activity 10-fold. Varying the positions of the pyrazole nitrogen atoms produced inactive analogues (**64**−**66**, **69**−**71**). In fact, the 1,4-diphenyl-1*H*-pyrazol-5-yl analogues **69** and **70** showed antagonist properties at the highest concentration, rather than potentiation. Confining the amide moiety in a triazole ring (**73**) resulted in decreased activity and produced only 3-fold potentiation (Table 2). No potentiation but weak antagonism was seen with the annelated benzopyrazoles **75** and **76**. This suggests that the 1,3-disubstituted pyrazole ring system plays an important role in interacting with the positive allosteric site. Highest functional potency was seen with the 2′-fluoro-4-nitro analogue **46** with an EC_{50} of 9.6 ± 1.9 nM. Thus, compound **46** had 8 times the functional potency of CDPPB (Table 1). Like CDPPB, the novel allosteric potentiator ADX-47273 (**1**) has shown pharmacokinetic properties that makes it suitable for in vivo studies.[12] In a direct comparison with compound **1**, compound **46** was 10 times more potent in potentiating glutamate-induced calcium release in rat astrocytes (Table 1). The calculated lipophilicity of compound **46** is log $P = 4.9$ versus log $P = 5.2$ for CDPPB (Table 1). Considering that CDPPB is reported to be 10 times more active at the human $mGluR_5$ than at the rat receptor,[10] further studies of **46** are warranted.

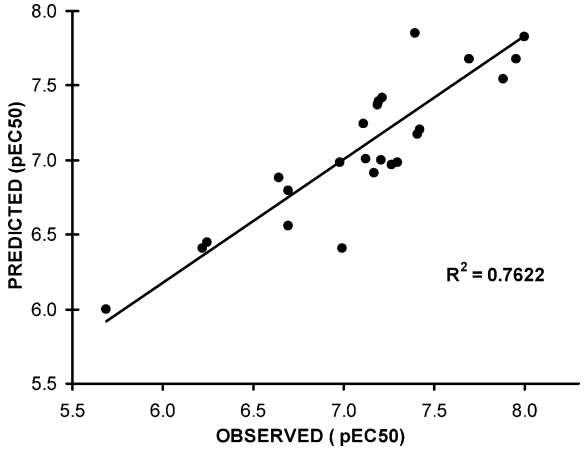


Figure 4. Comparison of predicted versus observed functional activities for the active compounds of Table 1, using HQSAR (Tripos, St. Louis, MO). Correlation coefficient $r = 0.87$ ($n = 29$).

Attempts to find the optimal combination of aromatic substituents, using Hansch 2D QSAR analysis with standard parameters, proved less successful in explaining the high potencies of the nitro analogues **23**, **29**, **46**−**49**, as well as the poor activities of the dimethoxy analogues **33** and **34**. However, HQSAR modeling of the functional activities of the CDPPB analogues presented in Table 1 was able to accurately predict their activities. Comparison of the observed and predicted activities is shown in Figure 4. HQSAR utilizes structural fragments (molecular fingerprints) of varying lengths as descriptors together with partial least-squares (PLS) analysis and cross-validation. In the best model ($r^2 = 0.774$, $q^2 = 0.047$, SE = 0.314), the corresponding 3,4-dinitro compound was predicted to be the most active compound with a calculated EC_{50} value of 3 nM. However, such a compound is not synthetically feasible, but the positional 3,5-dinitro isomer **32** was prepared and found to retain half the functional activity of the 4-nitro compound (**29**), as predicted (Figure 4).

All compounds in this study were considerably less active than MPEP ($K_i = 3.4$ nM)[18] at the [^{3}H]methoxyPEPy binding site and showed higher functional than binding activity. For the CDPPB analogues in Table 1 an average ratio of 16 was obtained between the EC_{50} for potentation of glutamate-induced calcium release and the K_i binding affinity to the antagonist allosteric MPEP site. Although the more potent compounds in

the functional assay, e.g. **26**, **35**, **36**, **46**, and **47**, were also more active at the MPEP binding site, there were several exceptions. For instance, compounds **43**, **44**, and **59** displayed glutamate potentiation with virtually no affinity for the MPEP binding site, while the opposite was seen for compound **57**. The 1,4-diphenylpyrazol-5-ylbenzamides **69** and **70** and the phenylimidazopyridines **75** and **76** displaced [^{3}H]methoxyPEPy binding in the low micromolar range, while showing antagonstic acitivities in the functional assay. Although, it is possible that CDPPB exerts its positive modulation of $mGluR_5$ by binding to the MPEP site, other factors may contribute to its functional activity. The existence of a distinct site, at which positive allosteric modulators of $mGluR_5$ can act, is supported by the observation that CPPHA [*N*-(4-chloro-2-((1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl)phenyl)-2-hydroxybenzamide],[8] a structurally unrelated positive allosteric modulator of $mGluR_5$, has no affinity for the MPEP site. However, recent studies have demonstrated that a neutral ligand at the MPEP site, the corresponding 5-methyl isomer 5-MPEP,[18] can inhibit CDPPB-induced calcium release in cultured astrocytes of the rat.[19] Therefore, the binding site responsible for positive modulation of $mGluR_5$ by CDPPB and its congeners is likely situated in close proximity to the antagonist MPEP binding site. Definitive determination of the role of binding to the MPEP site in mediating allosteric potentiator activity of specific compounds in this series must await further studies.

In conclusion, we found that only the 5-benzamido-1,3-diphenylpyrazole scaffold produced positive allosteric modulators. Replacing the *m*-cyano group of CDPPB (**2**) with a *p*-nitro group (**29**) resulted in a 20-fold increase in binding activity and an 8-fold increase in functional activity. Introducing a halogen atom in the ortho-position of the phenyl ring in the 1-pyrazole position further increased the activity. In particular, the 1-(2-fluorophenyl)-4-nitrobenzamide **46** (VU-1545) displayed pharmacological properties in the low nanomolar range using the rat $mGluR_5$, which warrants further studies, preferably with human mGlu receptors. Compound **46** is only half as lipophilic as CDPPB, which should increase its brain availability. The apparent correlation between binding affinities and functional activities[20] raises the possibility that activity at the MPEP site may be important for positive allosteric modulation. However, there was a 16-fold discrepancy in the average potencies at these two measures and several obvious outliers. Thus, it is possible that the apparent correlation between these two measures is a consequence of coincidental SAR requirements of the aromatic substituents for binding to the MPEP site and that binding to this site is not responsible for functional activity. Whether occupation of the MPEP site is a prerequisite for glutamate potentiation remains to be determined.

Experimental Section

Reagents and starting materials were obtained from Sigma-Aldrich (Milwaukee, WI) unless otherwise noted. ADX-47273 [(*S*)-1-(4-fluorophenyl)-3-(3-(4-fluorophenyl)[1,2,4]oxadiazol-5-yl)-piperidine, **1**] was prepared from (*S*)-1-BOC-nipecotic acid and 4-fluorobenzonitrile as described.[11] MPEP (2-methyl-6-(phenylethynyl)pyridine hydrochloride, **3**) and L-glutamic acid were obtained from Tocris (Ellisville, MO). CDPPB (**2**), *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (**20**), 4-methyl-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (**24**), and 4-trifluoromethyl-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (**27**) were prepared from the corresponding substituted benzoyl chlorides and 5-amino-1,3-diphenyl-1*H*-pyrazole (Alfa-Aesar, Ward Hill, MA) as described.[9,13] [^{3}H]-MethoxyPEPy [3-[^{3}H]methoxy-5-(pyridin-2-ylethynyl)pyridine] was custom radiolabeled (American Radiolabeled Chemicals, St Louis, MO) by *O*-alkylation of the corresponding phenol with [^{3}H]CH_3I as described.[36] Proton and carbon NMR spectra were obtained in $CDCl_3$ on a Bruker instrument operating at 300 and 75 MHz, respectively, with tetramethylsilane as internal standard. Mass spectra were obtained on a triple-quadrupole instrument (Finnigan TSQ-7000, Thermo Electron Corp, San Jose, CA) equipped with an electrospray ionization source and operating in either positive or negative ion mode. High-resolution mass spectra (HRMS) were obtained using electron ionization on a 8 kV 70-VSE instrument at the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinios at Urbana−Champaign. X-ray crystallographic structure of compound **69** was obtained from graphite Mo Kα radiation on a Nonius Kappa CCD diffractometer at Yale University Chemical Instrumentation Center. Melting points were recorded on an OptiMelt automated instrument (Stanford Research Systems, Sunnyvale, CA) operating at a rate of 2 °C/min. Elemental analyses were performed by Atlantic Microlab (Norcross, GA) and were within 0.4% of theory unless otherwise noted.

1-Amino-1-phenylacrylonitrile (8). Benzonitrile (**5**) (10 g, 97 mmol) was dissolved in benzene (250 mL). Acetonitrile (8.0 g, 195 mmol) was added, followed by portions of potassium *tert*-butoxide (25 g, 417 mmol). The mixture was stirred for 24 h at 20 °C. Diethyl ether (200 mL) was added, followed by 2% $NaHCO_3$ (100 mL). Separation of the organic layer, washing with 5 N NaCl (100 mL), drying (Na_2SO_4), and evaporation of the solvent gave 10.5 g (75%), after recrystallization from *i*-Pr_2O (100 mL). Mp: 85−87 °C. Lit.[37] mp: 86 °C. ^{1}H NMR ($CDCl_3$): 7.46 (m, 5H), 7.40 (m, 5H), 5.05 (b, 2H), 4.21 (s, 1H). ^{13}C NMR ($CDCl_3$): 161.3, 135.1, 130.7, 128.7 (2 × CH), 125.7 (2 × CH), 119.3, 63.3.

1-Amino-1-(2-chlorophenyl)acrylonitrile (9) was prepared from acetonitrile and 2-chlorobenzonitrile (**6**) (2.75 g, 20 mmol) as described for compound **8**. Recrystallization from *i*-Pr_2O (10 mL) gave 1.95 g (55%). Mp: 104−106 °C. Lit.[38] mp: 106−107 °C. ^{1}H NMR ($CDCl_3$): 7.43 (m, 1H), 7.39 (dt, 2H), 7.34 (m, 1H), 4.98 (b, 2H), 4.06 (s, 1H). ^{13}C NMR ($CDCl_3$): 159.4, 134.6, 131.4, 130.8 (CH), 130.1 (CH), 129.6 (CH), 126.9 (CH), 118.3, 66.5 (CH).

1-Amino-1-(3-methoxyphenyl)acrylonitrile (10) was prepared from acetonitrile and 3-methoxybenzonitrile (**7**) (5.3 g, 40 mmol) as described for compound **8**. Recrystallization from *i*-Pr_2O (20 mL) gave 4.8 g (69%). Mp: 64−66 °C. Lit.[39] mp: 61−63 °C. ^{1}H NMR ($CDCl_3$): 7.34 (dd, 1H), 7.08 (d, 1H), 7.01 (s, 1H), 6.99 (m, 1H), 4.98 (b, 2H), 4.24 (s, 1H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$): 161.2, 159.6, 136.5, 129.8, 119.2, 118.0, 116.0, 111.4, 63.4, 55.1.

5-Amino-1-phenyl-3-(2-chlorophenyl)-1*H*-pyrazole (11). 2-Amino-2-(2-chlorophenyl)acrylonitrile (**9**) (1.8 g, 10 mmol) was suspended in 2.5 N HCl (10 mL, 25 mmol) and heated to 50 °C. Phenylhydrazine (1.2 g. 11 mmol) was added, followed by 12 N HCl (5 mL, 60 mmol), and the mixture was heated to 110 °C for 20 min. After cooling by adding pieces of ice, 14 N NH_4OH was added dropwise until the solution became basic (7 mL, 100 mmol). Extraction with EtOAc (2 × 150 mL), washing of the combined organic layer with water (100 mL), drying (Na_2SO_4), and evaporation of the solvent gave crude **11**. Recrystallization from *i*-Pr_2O (10 mL) gave 1.02 g (39%). Mp: 139−141 °C. Lit.[38] mp: 137 °C. ^{1}H NMR ($CDCl_3$): 7.88 (dd, 1H), 7.64 (d, 2H), 7.49 (t, 2H), 7.43 (dd, 1H), 7.36 (t, 1H), 7.24 (dq, 2H), 6.20 (s, 1H), 3.85 (b, 2H). ^{13}C NMR ($CDCl_3$): 149.0, 144.6, 138.2, 132.2, 131.9, 130.3, 129.9, 129.2 (2 × CH), 128.5, 127.2, 126.5, 123.8 (2 × CH), 92.0.

5-Amino-1-phenyl-3-(3-methoxyphenyl)-1*H*-pyrazole (12) was prepared from compound **10** (1.74 g, 10 mmol) and phenylhydrazine (1.19 g, 11 mmol) as described for compound **11**. Recrystallization from *i*-Pr_2O (15 mL) gave 1.35 g (51%). Mp: 110−112 °C. ^{1}H NMR ($CDCl_3$): 7.64 (d, 2H), 7.49 (t, 2H), 7.38 (m, 3H), 7.30 (t, 1H), 6.86 (d, 2H), 5.94 (s, 1H), 3.86 (b, 1H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$): 159.5, 151.1, 145.5, 138.3, 134.6, 129.2 (2 × CH), 127.2, 123.9 (2 × CH), 118.0, 113.6, 110.3, 88.0, 55.0. Anal. ($C_{16}H_{14}N_3O$) C, H, N.

5-Amino-1-(2-fluorophenyl)-3-phenyl-1*H*-pyrazole (13) was prepared from 1-amino-1-phenylacrylonitrile (**8**) (1.44 g, 10 mmol) and 2-fluorophenylhydrazine HCl (1.63 g, 10 mmol) as described for compound **11**. Recrystallization from *i*-Pr_2O (15 mL) gave 0.79 g (31%) as an oil. ^{1}H NMR ($CDCl_3$): 7.80 (d, 2H), 7.61 (dt, 1H),

7.38 (m 3H), 7.30 (m, 3H), 5.98 (s, 1H),3.81 (b, 2H). ^{13}C NMR ($CDCl_3$): 157.8, 154.5, 146.7, 133.0, 129.8, 128.9, 128.2 (2 × CH), 127.7, 125.4 (2 × CH), 124.9, 116.4 (d), 88.1.

5-Amino-1-(2-chlorophenyl)-3-phenyl-1H-pyrazole (14) was prepared from 1-amino-1-phenylacrylonitrile (**8**) (1.44 g, 10 mmol) and 2-chlorophenylhydrazine (1.79 g, 10 mmol) as described for compound **11**. Recrystallization from *i*-Pr_2O (10 mL) gave 1.35 g (52%). Mp: 107−109 °C. ^{1}H NMR ($CDCl_3$): 7.80 (d, 2H), 7.54 (m, 2H), 7.39 (m, 4H), 7.28 (t, 1H), 5.96 (s, 1H), 3.69 (b, 2H). ^{13}C NMR ($CDCl_3$): 162.1, 151.9, 146.7, 135.6, 133.1, 131.9, 130.3, 130.1, 128.2 (2 × CH), 127.8, 127.6, 125.4 (2 × CH), 87.3. Anal. ($C_{15}H_{12}ClN_3$) C, H, N.

5-Amino-1-(2-bromophenyl)-3-phenyl-1*H*-pyrazole (15) was prepared from 1-amino-1-phenylacrylonitrile (**8**) (1.44 g, 10 mmol) and 2-bromophenylhydrazine HCl (2.24 g, 10 mmol) as described for compound **11**. Column chromatoraphy on silica gel in CH_2Cl_2 gave fractions with $R_f = 0.16$ in CH_2Cl_2. Recrystallization from *i*-Pr_2O (20 mL) gave 0.62 g (20%). Mp: 111−114 °C. ^{1}H NMR ($CDCl_3$): 7.81 (d, 2H), 7.74 (d, 1H), 7.55 (dd, 1H), 7.48 (dt, 1H), 7.37 (m, 3H), 7.31 (t, 1H), 5.99 (s, 1H), 3.67 (b, 2H). ^{13}C NMR ($CDCl_3$): 1.51.7, 146.4, 137.2, 133.4, 133.1, 130.6, 130.3, 128.4, 128.2 (2 × CH), 127.6, 125.4 (2 × CH), 122.1, 87.3. Anal. ($C_{15}H_{12}BrN_3$) C, H, N.

5-Amino-1-(2-pyridyl)-3-phenyl-1*H*-pyrazole (16) was prepared from 1-amino-1-phenylacrylonitrile (**8**) (1.44 g, 10 mmol) and 2-pyridylhydrazine•2HCl (1.82 g, 10 mmol) as described for compound **11**. Recrystallization from EtOH (20 mL) gave 0.45 g (19%). Mp: 144−147 °C. Lit.[24] mp: 159−160 °C. ^{1}H NMR ($CDCl_3$):[25] 8.34 (s, 1H), 8.11 (d, 1H), 7.85 (m, 3H), 7.40 (m, 3H), 7.09 (s, 1H), 6.00 (b, 2H), 5.86 (s, 1H). ^{13}C NMR ($CDCl_3$): 162.0, 160.3, 149.3, 146.2, 138.3, 132.9, 128.2 (2 × CH), 127.9, 125.5 (2 × CH), 119.3, 113.5, 86.9.

5-Amino-1-(3-bromophenyl)-3-phenyl-1*H*-pyrazole (17) was prepared from 1-amino-1-phenylacrylonitrile and 3-bromophenylhydrazine as described for compound **11**. Extraction with EtOAc (2 × 100 mL) gave 1.76 g (56%) of an oil. ^{1}H NMR ($CDCl_3$): 7.87 (t, 1H), 7.81 (d, 2H), 7.61 (dt, 1H), 7.48 (dq, 1H), 7.39 (t, 2H), 7.34 (m, 2H), 5.96 (s, 1H), 3.86 (b, 2H). ^{13}C NMR ($CDCl_3$): 151.7, 145.6, 139.7, 132.9, 130.4, 129.9, 128.2 (2 × CH), 127.8, 126.6, 125.4 (2 × CH), 122.7, 121.8, 88.5.

5-Amino-1-(3-cyanophenyl)-3-phenyl-1*H*-pyrazole (18) was prepared from 1-amino-1-phenylacrylonitrile (**8**) (1.0 g, 6.9 mmol) and 3-cyanophenylhydrazine[40] (1.0 g, 7.5 mmol) as described for compound **11**. Recrystallization from *i*-Pr_2O (10 mL) of the residue from combined chromatography fractions gave 0.32 g (18%). Mp: 131−132 °C. ^{1}H NMR ($CDCl_3$): 8.07 (q, 1H), 7.99 (dq, 1H), 7.80 (d, 2H), 7.59 (m, 2H), 7.41 (d, 1H), 7.38 (d, 1H), 7.33 (t, 1H), 6.01 (s, 1H), 3.86 (b, 2H). ^{13}C NMR ($CDCl_3$): 151.9, 145.4, 139.3, 132.4, 129.9, 129.7, 128.1 (2 × CH), 127.8, 126.9, 126.0, 125.2 (2 × CH), 117.6, 113.1, 89.4. Anal. ($C_{16}H_{12}N_4$) C, H, N.

5-Amino-1-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazole (19) was prepared from 1-amino-1-phenylacrylonitrile (**8**) (1.44 g, 10 mmol) and 3-methoxyphenylhydrazine[41] (1.38 g, 10 mmol) as described for compound **11**. Recrystallization from *i*-Pr_2O (12 mL) gave 0.36 g (36%) as an oil. ^{1}H NMR ($CDCl_3$): 7.81 (dt, 2H), 7.38 (dd, 3H), 7.32 (dt, 1H), 7.19 (m, 2H), 6.90 (ddd, 1H), 5.95 (s, 1H), 4.09 (s, 3H), 3.85 (b, 2H).

3-Methoxy-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (21). 3-Methoxybenzoyl chloride (1.0 g, 5.9 mmol) in CH_2Cl_2 (5 mL) was slowly added to a stirred mixture of *N*,*N*-diisopropylethylamine (1.0 g, 7.9 mmol) and 5-amino-1,3-diphenyl-1*H*-pyrazole (Alfa-Aesar) (1.0 g, 4.2 mmol) in CH_2Cl_2 (20 mL) at 4 °C (ice−water). After 3 h at 20 °C, the solvents were evaporated, water (100 mL) was added, and the residue was extracted with ethyl acetate (2 × 100 mL). Washing of the combined organic layer with 1 N HCl, then 1 N NaOH, and then water (25 mL each), drying (Na_2SO_4), and evaporation of the solvent gave a crystallizing residue. Recrystallization from EtOH (20 mL) gave 1.39 g (91%). Mp: 177−179 °C. ^{1}H NMR ($CDCl_3$): 8.08 (b, 1H), 7.92 (d, 2H), 7.60 (m, 4H), 7.49 (t, 1H), 7.3−7.4 (m, 6H), 7.21 (s, 1H), 7.09 (dd, 1H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$): 163.0, 162.0, 159.8, 151.7, 137.6, 136.3, 134.3, 129.7 (2 × CH), 128.3 (2 × CH), 127.9, 125.3 (2 × CH), 124.5 (2 × CH), 118.4, 118.2, 112.3, 95.4, 55.2. Anal. ($C_{23}H_{19}N_3O_2$) C, H, N.

3-Trifluoromethyl-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (22) was prepared from 3-trifluorobenzoyl chloride (1.0 g, 4.8 mmol) as described for compound **21**. Recrystallization from *i*-Pr_2O (40 mL) gave 0.59 g (34%). Mp: 155−156 °C. ^{1}H NMR ($CDCl_3$): 8.09 (b, NH), 8.04 (s, 1H), 7.90 (m, 3H), 7.81 (m, 1H), 7.60 (m, 4H), 7.50 (m, 2H), 7.41 (dt, 2H), 7.37 (m, 1H), 7.19 (s, 1H). ^{13}C NMR ($CDCl_3$): 162.0. 151.8, 137.5, 135.8, 133.7, 131.1, 130.5, 129.8 (2 × CH), 129.4, 128.9, 128.6, 128.3 (2 × CH), 128.0, 125.5 (2 × CH), 124.4 (2 × CH), 124.0, 96.1. Anal. ($C_{23}H_{16}F_3N_3O$•$0.5H_2O$) H, N; C: calcd, 66.34; found, 67.01.

3-Nitro-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (23) was prepared from 3-nitrobenzoyl chloride (0.5 g, 2.7 mmol) as described for compound **21**. The reaction mixture showed three compounds according to TLC in CH_2Cl_2. The product was purified on 100 g of silica gel (Merck 70−230 mesh, 60 A) in CH_2Cl_2. Elution with CH_2Cl_2 gave byproducts A and B (not isolated). Fractions showing the third spot ($R_f = 0.15$) were collected, and the solvent was removed. Recrystallization from EtOH (10 mL) gave 0.38 g (24%). Mp: 192−194 °C. ^{1}H NMR ($CDCl_3$): 8.56 (s, 1H), 8.39 (d, 1H, $J = 8.5$ Hz), 8.18 (b, NH), 8.07 (d, 1H, $J = 8.5$ Hz), 7.88 (d, 2H), 7.67 (t, 1H), 7.58 (m, 4H), 7.47 (q, 1H), 7.39 (m, 4H), 7.14 (s, 1H). MS: 385 (M + H) 100. ^{13}C NMR ($CDCl_3$): 151.8, 148.0, 137.4, 135.5, 134.5, 132.8, 132.4, 130.0, 129.9 (2 × CH), 128.6, 128.4 (2 × CH), 128.0, 126.6, 125.5 (2 × CH), 124.4 (2 × CH), 121.8, 96.4. Anal. ($C_{22}H_{16}N_4O_3$) C, H, N.

4-Methoxy-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (25) was prepared from 4-methoxybenzoyl chloride (0.5 g, 2.9 mmol) as described for compound **21**. Recrystallization from EtOH (20 mL) gave 0.94 g (61%). Mp: 155−156 °C. ^{1}H NMR ($CDCl_3$): 8.07 (s, 1H), 7.89 (d, 2H), 7.56 (m, 4H), 7.45 (m, 3H), 7.34 (m, 1H), 7.15 (s, 1H), 6.92 (d, 2H), 3.82 (s, OCH_3). ^{13}C NMR ($CDCl_3$): 163.1, 162.7, 151.6, 137.7, 136.6, 133.7, 132.7, 129.7 (2 × CH), 128.8 (2 × CH), 128.3 (2 × CH), 127.8, 125.5 (2 × CH), 125.0, 124.5 (2 × CH), 113.9 (2 × CH), 95.8, 60.1. Anal. ($C_{23}H_{19}N_3O_2$) C, H, N.

4-Trifluoromethoxy-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (26) was prepared from 4-trifluoromethoxybenzoyl chloride (1.0 g, 4.8 mmol) as described for compound **21**. Recrystallization from *i*-Pr_2O (30 mL) gave 0.40 g (22%). Mp: 180−181 °C. ^{1}H NMR ($CDCl_3$): 8.09 (b, NH), 7.90 (d, 2H), 7.80 (d, 2H), 7.59 (m 4H), 7.48 (m, 1H), 7.43 (t, 2H), 7.35 (d, 1H), 7.30 (d, 2H), 7.19 (s, 1H). ^{13}C NMR ($CDCl_3$): (2 × CH only) 129.8, 128.8, 128.5, 125.5, 124.5, 120.6. Anal. ($C_{23}H_{16}F_3N_3O_2$) C, H, N.

4-Cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (28) was prepared from 4-cyanobenzoyl chloride (0.8 g, 4.8 mmol) as described for compound **21**. TLC of the reaction mixture in CH_2Cl_2 showed three spots with R_f of 0.28 (byproduct A, **51**), 0.21, (byproduct B, **52**), and 0.12, respectively. Collection of fractions with $R_f = 0.12$ in CH_2Cl_2 and evaporation of the solvent gave 0.47 g of solid. Recrystallization from *i*-Pr_2O (30 mL) gave 0.31 g (24%). Mp: 207−208 °C. ^{1}H NMR ($CDCl_3$): 8.05 (b, NH), 7.91 (dd, 2H), 7.84 (d, 2H), 7.76 (d, 2H), 7.59 (d, 4H), 7.51 (q, 1H), 7.43 (t, 2H), 7.35 (m, 1H), 7.21 (s, 1H). ^{13}C NMR ($CDCl_3$): 151.6, 137.2, 136.4, 135.4, 132.3 (2 × CH), 132.2, 129.7 (2 × CH), 128.4, 128.2 (2 × CH), 127.8, 127.2 (2 × CH), 125.3 (2 × CH), 124.3 (2 × CH), 117.1, 115.6, 95.7. Anal. ($C_{23}H_{16}N_4O$) H, N; C: calcd, 75.81; found, 75.07.

4-Nitro-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (29) was prepared from 4-nitrobenzoyl chloride (0.41 g) as described for compound **21**. TLC of the reaction mixture in CH_2Cl_2 showed three spots with R_f of 0.45 (byproduct A), 0.32 (byproduct B), and 0.18, respectively. Separation on 100 g of silica gel (Merck 70−230 mesh, 60 A) in CH_2Cl_2 gave 0.42 g (26%) with $R_f = 0.18$. Mp: 221−223 °C. ^{1}H NMR ($CDCl_3$): 8.32 (d, 2H, $J = 8.7$ Hz),), 8.09 (b, NH), 7.92 (m, 4H), 7.60 (d, 2H, $J = 4.5$ Hz), 7.51 (q, 1H), 7.43 (t, 1H), 7.37 (t, 1H), 7.23 (s, 1H). ^{13}C NMR ($CDCl_3$): 163.5, 162.0, 150.1, 138.5, 138.3, 136.1, 132.3, 128.8 (2 × CH), 128.6 (2 × CH), 128.1 (2 × CH), 127.5, 126.9, 124.7 (2 × CH), 123.0 (2 ×

CH), 122.9 (2 × CH), 100.4. MS: 385 (M + H) 100. Anal. ($C_{22}H_{16}N_4O_3$·0.5H_2O) C, H, N.

4-Amincarboxyl-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (30). Terephthaloyl dichloride (2.0 g, 10 mmol) in CH_2Cl_2 (15 mL) was slowly added to a stirred mixture of *N*,*N*-diisopropylethylamine (1.0 g, 7.9 mmol) and 5-amino-1,3-diphenyl-1*H*-pyrazole (1.0 g, 4.2 mmol) in CH_2Cl_2 (20 mL) at 4 °C (ice−water) to produce 5-(4-chlorocarbonylbenzamido)-1,3-diphenyl-1*H*-pyrazole. After 1 h, 14 N NH_4OH (10 mL) was added and the mixture stirred for 1 h at 20 °C. Water was added and the product was extracted with EtOAc (2 × 200 mL). Insoluble materials, containing a mixture of product and terephthalic acid according to TLC, were removed by filtration. Drying and evaporation of the solvent gave 0.83 g. Separation on silica gel in CH_2Cl_2−MeOH (10:1) and recrystallization from MeOH gave 0.21 g (23%). Mp: 244−247 °C. ^{1}H NMR (CD_3OD): 7.93 (m, 6H), 7.63 (d, 2H), 7.52 (m, 2H), 7.45 (m, 3H), 7.38 (m, 1H), 6.92 (s, 1H), 5.93 (s, 2H + MeOH). ^{1}H NMR ($CDCl_3$, 100 scans): 8.70 (s, 1H), 7.93 (m, 6H), 7.63 (d, 2H), 7.55 (t, 2H), 7.43 (m, 3H), 7.38 (m, 1H), 7.15 (s, 1H), 6.78 (b, 1H), 5.89 (b, 1H). Anal. ($C_{23}H_{18}N_4O_2$) C, H, N.

4-Carboxyl-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (31). The acid chloride intermediate was prepared as described for compound **30**. After 1 h at 20 °C, the solvents were evaporated, and the residue was dissolved in DMF (10 mL) and treated with MeOH (10 mL) for 30 min at 50 °C. Extraction of the product with EtOAc as described for compound **21**, followed by column chromatography on 100 g of silica gel (Merck 70−230 mesh, 60 A) in CH_2Cl_2, gave pure fractions. Crystallization from *i*-Pr_2O gave 0.93 g (59%) of 4-methoxycarboxyl-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide. Mp: 163−165 °C. ^{1}H NMR ($CDCl_3$): 8.14 (b, 1H), 8.11 (d, 2H), 7.90, d, 2H), 7.79, (d, 2H), 7.58 (m, 4H), 7.49 (m, 1H), 7.42 (t, 2H), 7.36, (m, 1H, 7.19, (s, 1H), 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$): 165.7, 151.8, 137.5, 136.6, 136.0, 133.3, 132.5, 129.9 (2 × CH), 129.8 (2 × CH), 128.5, 128.3 (2 × CH), 128.2, 127.9, 126.9 (2 × CH), 125.5 (2 × CH), 124.5 (2 × CH), 95.9, 52.3. The methyl ester (0.80 g, 2.0 mmol) was dissolved in MeOH (20 mL) and 2 N NaOH (10 mL) was added. The mixture was stirred for 1 h at 60 °C, followed by addition of ice and washing of the aqueous layer with ether (25 mL), and neutralization with 12 N HCl gave 0.54 g (70%). Mp: 233−235 °C. ^{1}H NMR ($CDCl_3$): 9.66 (b, 1H), 8.13 (d, 2H), 8.01 (d, 2H), 7.91 (d, 2H), 7.68 (d, 2H), 7.51 (t, 2H), 7.42 (m, 3H), 7.32 (t, 1H), 7.03 (s, 1H). Anal. ($C_{23}H_{17}N_3O_3$) C, H, N.

3,5-Dinitro-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (32) was prepared from 3,5-dinitrobenzoyl chloride (0.50 g, 2.3 mmol) as described for compound **21** to yield 0.75 g (50%) from EtOH. Mp: 244−246 °C. ^{1}H NMR ($CDCl_3$): 9.21 (s, 1H), 8.93 (s, 2H), 8.18 (b, 1H), 7.92 (d, 2H), 7.62 (m, 4H), 7.45 (m, 1H), 7.40 (m, 3H), 7.21 (s, 1H). Anal. ($C_{22}H_{15}N_5O_5$) C, H, N.

3,4-Dimethoxy-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (33) was prepared from 3,4-dimethoxybenzoic acid (1.0 g, 6.4 mmol) by treatment with thionyl chloride (1.0 mL, 13 mmol) in toluene (20 mL), containing 3 drops of DMF as catalyst, for 2 h at 70 °C. The solvent was evaporated and the resulting 3,4-dimethoxybenzoyl chloride was diluted with CH_2Cl_2 (15 mL) and reacted with 5-amino-1,3-diphenyl-1*H*-pyrazole as described for compound **21**. Recrystallization from *i*-PrO_2 gave 0.82 g (65%). Mp: 184−185 °C. ^{1}H NMR ($CDCl_3$): 8.05 (b, 1H), 7.91 (d, 2H), 7.58 (m, 4H), 7.46 (m, 4H), 7.36 (t, 1H), 7.19 (s, 1H), 7.17 (dd, 1H), 6.86 (d, 1H), 3.93 (s, 3H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$): 162.1, 151.5, 150.9, 148.3, 136.9, 135.8, 131.9, 128.9 (2 × CH), 127.5, 127.5 (2 × CH), 127.1, 124.7 (2 × CH), 123.7 (2 × CH), 118.3, 109.6, 109.3, 94.6, 55.0, 54.9. Anal. ($C_{24}H_{21}N_3O_3$) C, H, N.

3,5-Dimethoxy-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (34) was prepared from 3,5-dimethoxybenzoic acid (0.50 g, 3.2 mmol) as described for compound **33**. Recrystallization from *i*-PrO_2 (5 mL) gave 0.21 g (50%). Mp: 144−146 °C. ^{1}H NMR ($CDCl_3$): 8.03 (b, 1H), 7.90 (d, 2H), 7.58 (m, 4H), 7.42 (m, 4H), 7.19 (s, 1H), 6.85 (s, 2H), 6.61 (d, 1H), 3.80 (s, 6H). ^{13}C NMR ($CDCl_3$): 160.8, 151.2, 137.6, 136.3, 135.0, 132.7, 129.7 (2 × CH), 128.4 (2 × CH), 127.9, 125.5 (2 × CH), 124.5 (2 × CH), 104.7 (2 × CH), 104.0, 95.7, 55.3 (2 × OCH_3). Anal. ($C_{24}H_{21}N_3O_3$) C, H, N.

3,4-Dimethyl-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (35) was prepared from 3,4-dimethylbenzoic acid as described for compound **33**. Recrystallization from EtOH (15 mL) gave 0.39 g (38%). Mp: 163−165 °C. ^{1}H NMR ($CDCl_3$): 8.05 (b, 1H), 7.90 (dt, 2H), 7.61 (m, 2H), 7.54 (m, 3H), 7.47 (m, 1H), 7.40 (m, 3H), 7.33 (t, 1H), 7.20 (s, 1H), 7.19 (d, 1H), 2.30 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$): 163.1, 151.3, 141.2, 137.2, 136.8, 136.1, 132.3, 129.9, 129.3, 129.2 (2 × CH), 127.8 (2 × CH), 127.7, 127.3, 125.0 (2 × CH), 124.0 (2 × CH), 123.5, 95.0, 19.2, 19.1. Anal. ($C_{24}H_{21}N_3O$) C, H, N.

3,4-Dichloro-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (36) was prepared from 3,4-dichlorobenzoic acid as described for compound **33**. Recrystallization from EtOH (20 mL) gave 1.05 g (61%). Mp: 180−181 °C. ^{1}H NMR ($CDCl_3$): 7.95 (b, NH), 7.91 (t, 1H), 7.88 (dd, 2H), 7.58 (d, 4H), 7.52 (m, 2H), 7.47 (m, 1H), 7.41 (d, 2H), 7.35 (m, 1H), 7.17 (s, 1H). Anal. ($C_{22}H_{15}Cl_2N_3O$) C, H, N.

***N*-(1-Phenyl-3-(2-chlorophenyl)-1*H*-pyrazol-3-yl)benzamide (37)** was prepared from benzoyl chloride (0.30 g, 2.1 mmol) and diphenylpyrazole **11** (0.52 g, 2.0 mmol) as described for compound **21**. Recrystallization from *i*-Pr_2O (12 mL) gave 0.31 g (41%). Mp: 165−168 °C. ^{1}H NMR ($CDCl_3$): 8.05 (b, 1H), 7.87 (dd, 1H), 7.75 (d, 2H), 7.62 (m, 3H), 7.55 (d, 2H),7.45 (dd, 4H), 7.37 (s, 1H), 7.30 m, 2H). ^{13}C NMR ($CDCl_3$): 162.0, 137.6, 135.4, 132.2, 130.4, 130.0, 129.7 (2 × CH), 128.9, 128.7 (2 × CH), 128.5, 126.8 (2 × CH), 126.6, 124.5 (2 × CH). Anal. ($C_{22}H_{16}ClN_3O$) C, H, N.

***N*-(1-Phenyl-3-(3-methoxyphenyl)-1*H*-pyrazol-3-yl)benzamide (38)** was prepared from benzoyl chloride (0.28 g, 2 mmol) and diphenylpyrazole **12** (0.52 g, 2 mmol) as described for compound **21**. Recrystallization from *i*-Pr_2O (25 mL) gave 0.38 g (51%). Mp: 140−142 °C. ^{1}H NMR ($CDCl_3$): 8.06 (b, 1H), 7.75 (d, 2H), 7.60 (m, 5H), 7.50 (m, 5H), 7.34 (t, 1H), 7.23 (s, 1H), 6.90 (dd, 1H). ^{13}C NMR ($CDCl_3$): 159.6, 151.7, 137.6, 136.3, 134.1, 132.8, 132.3, 129.8 (2 × CH), 129.3, 128.7 (2 × CH), 128.4, 126.8 (2 × CH), 124.6 (2 × CH), 118.1, 114.3, 110.2, 95.6, 55.1. Anal. ($C_{23}H_{19}N_3O_2$·0.5H_2O) H, N; C: calcd, 73.00; found, 73.51.

***N*-(1-(2-Fluorophenyl)-3-phenyl-1*H*-pyrazol-3-yl)benzamide (39)** was prepared from benzoyl chloride (0.60 g, 4.2 mmol) and diphenylpyrazole **13** (1.0 g, 4.2 mmol) as described for compound **21**. Recrystallization from EtOH (8 mL) gave 0.70 g (50%). Mp: 171−172 °C. ^{1}H NMR ($CDCl_3$): 7.99 (b, 1H), 7.89 (d, 2H), 7.75 (d, 2H), 7.67 (dt, 1H), 7.54 (t, 1H), 7.46 (m, 6H), 7.36 (td, 2H), 7.15 (s, 1H). ^{13}C NMR ($CDCl_3$): 163.9, 157.2, 152.8, 137.5, 133.0, 132.5, 132.2, 130.5 (d), 129.1 (2 × CH), 128.7 (2 × CH), 128.3, 128.0, 126.8 (2 × CH), 125.5 (2 × CH), 125.4, 116.5 (d), 96.4. Anal. ($C_{22}H_{16}FN_3O$) C, H, N.

***N*-(1-(2-Chlorophenyl)-3-phenyl-1*H*-pyrazol-3-yl)benzamide (40)** was prepared from benzoyl chloride (0.30 g, 2.1 mmol) and diphenylpyrazole **14** (0.50 g, 2.0 mmol) as described for compound **21**. Recrystallization from *i*-Pr_2O (15 mL) gave 0.41 g (55%). Mp: 171−173 °C. ^{1}H NMR ($CDCl_3$): 7.90 (d, 2H), 7.79 (b, 1H), 7.71 (d, 2H), 7.63 (dd, 2H), 7.57 (t, 1H), 7.48 (m, 4H), 7.41 (d, 2H), 7.34 (m, 1H), 7.18 (s, 1H). ^{13}C NMR ($CDCl_3$): 152.7, 137.9, 135.3, 133.2, 132.9, 132.5, 131.3, 131.1, 130.6, 130.5, 129.0 (2 × CH), 128.6 (2 × CH), 128.5, 128.2, 127.1 (2 × CH), 125.8 (2 × CH), 95.7. Anal. ($C_{22}H_{16}ClN_3O$) C, H, N.

***N*-(1-(2-Bromophenyl)-3-phenyl)-1*H*-pyrazol-3-yl)benzamide (41)** was prepared from benzoyl chloride (0.5 g, 3.6 mmol) and diphenylpyrazole **15** (1.0 g, 3.2 mmol) as described for compound **21**. Recrystallization from EtOH (15 mL) gave 0.45 g (34%). Mp: 162−163 °C. ^{1}H NMR ($CDCl_3$): 8.45 (d, 2H), 7.80 (dd, 1H), 7.74 (b, 1H), 7.71 (d, 2H), 7.61 (dd, 1H), 7.4−7.5 (m, 5H), 7.36 (t, 1H), 7.18 (s, 1H). ^{13}C NMR ($CDCl_3$): 163.6, 161.8, 152.3, 137.5, 136.6, 133.6, 133.0, 132.6, 132.2, 131.2, 130.5, 128.8, 128.7 (2 × CH), 128.3 (2 × CH), 127.9, 126.8 (2 × CH), 125.6 (2 × CH), 121.2, 95.3. Anal. ($C_{22}H_{16}BrN_3O$) C, H, N.

***N*-(1-(2-Pyridyl)-3-phenyl-1*H*-pyrazol-3-yl)benzamide (42)** was prepared from benzoyl chloride (0.31 g, 2.1 mmol) and pyridylphenylpyrazole **16** (0.47 g, 2.0 mmol) as described for compound **21**.

Recrystallization from EtOH (15 mL) gave 0.23 g (68%). Mp: 152−154 °C. ^{1}H NMR ($CDCl_3$): 8.45 (dt, 1H), 8.27 (d, 1H), 8.05 (d, 2H), 7.98 (d, 2H), 7.91 (tt, 1H), 7.58 (m, 3H), 7.46 (m, 3H), 7.38 (t, 1H), 7.21 (dd, 1H). ^{13}C NMR ($CDCl_3$): 163.2, 162.0, 154.4, 145.8, 140.9, 139.3, 133.6, 132.4, 132.0, 128.6 (2 × CH), 128.3 (2 × CH), 127.1 (2 × CH), 125.8 (2 × CH), 120.1, 114.0, 94.7. Anal. ($C_{22}H_{16}N_4O$) C, H, N.

***N*-(1-(3-Bromophenyl)-3-phenyl-1*H*-pyrazol-3-yl)benzamide (43)** was prepared from benzoyl chloride (0.31 g, 2.2 mmol) and diphenylpyrazole **17** (0.62 g, 2.0 mmol) as described for compound **21**. Recrystallization from *i*-Pr_2O (10 mL) gave 0.13 g (16%). Mp: 180−181 °C. ^{1}H NMR ($CDCl_3$): 8.05 (b, NH), 7.88 (dt, 2H), 7.83 (t, 1H), 7.77 (d, 2H), 7.55 (m, 2H), 7.50, (m, 3H), 7.46 q, 1H), 7.41 (d, 2H), 7.35 (m, 1H), 7.14 (s, 1H). ^{13}C NMR ($CDCl_3$): 163.8, 162.0, 152.2, 138.9, 136.3, 132.7, 132.4, 131.2, 130.8, 128.8 (2 × CH), 128.4 (2 × CH), 128.1, 127.6, 126.8 (2 × CH), 125.5 (2 × CH), 123.2, 122.4, 96.8. Anal. ($C_{22}H_{16}BrN_3O$) C, H, N.

***N*-(1-(3-Cyanophenyl)-3-phenyl-1*H*-pyrazol-3-yl)benzamide (44)** was prepared from benzoyl chloride (0.31 g, 2.2 mmol) and diphenylpyrazole **18** (0.52 g, 2.0 mmol) as described for compound **21**. Recrystallization from *i*-Pr_2O (10 mL) gave 0.31 g (43%). Mp: 202−204 °C. ^{1}H NMR ($CDCl_3$): 7.97 (t, 1H), 7.87 (m, 4H), 7.78 (d, 2H), 7.68 (dt, 1H), 7.64 (d, 1H), 7.59 (m, 1H), 7.3−7.5 (m, 5H), 7.07 (s, 1H). ^{13}C NMR ($CDCl_3$): 151.4, 137.8, 135.0, 131.5, 131.3, 130.9, 130.0, 129.2, 127.7 (2 × CH), 127.3 (2 × CH), 127.1, 126.6, 126.2, 125.7 (2 × CH), 124.3 (2 × CH), 116.1, 112.6, 97.6. Anal. ($C_{23}H_{16}N_4O$) C, H, N.

***N*-(1-(3-Methoxyphenyl)-3-phenyl-1*H*-pyrazol-3-yl)benzamide (45)** was prepared from benzoyl chloride (0.31 g, 2.2 mmol) and diphenylpyrazole **19** (0.53 g, 2.0 mmol) as described for compound **21**. Recrystallization from EtOH (7 mL) gave 0.17 g (23%). Mp: 161−163 °C. ^{1}H NMR ($CDCl_3$): 8.18 (b, 1H), 7.92 (dt, 2H), 7.76 (d, 2H), 7.57 (m, 1H), 7.45 (m, 5H), 7.34 (m, 1H), 7.24 (s, 1H), 7.15 (m, 2H), 7.01 (dq, 1H). ^{13}C NMR ($CDCl_3$): 163.0, 160.5, 151.5, 138.4, 136.2, 132.7, 132.4, 132.0, 130.2, 128.5 (2 × CH), 128.1 (2 × CH), 127.7, 126.6 (2 × CH), 125.3 (2 × CH), 115.7, 114.5, 110.0, 95.1, 55.1. Anal. ($C_{23}H_{19}N_3O_2$) C, H, N.

4-Nitro-*N*-(1-(2-fluorophenyl)-3-phenyl-1*H*-pyrazol-5-yl)benzamide (46) was prepared from 4-nitrobenzoyl chloride (0.78 g, 4.2 mmol) and diphenylpyrazole **13** (1.0 g, 4.0 mmol) as described for compound **21**. TLC of the reaction mixture in CH_2Cl_2 showed three spots, corresponding to the *N*,2- and *N*,*N*-diacylated byproducts (A and B) and the desired product, respectively. Separation on 100 g of silica gel (Merck 70−230 mesh, 60 A) in CH_2Cl_2 gave fractions with $R_f = 0.12$. Recrystallization from EtOH (15 mL) gave 0.38 g (34%). Mp: 222−224 °C. ^{1}H NMR ($CDCl_3$): 8.32 (d, 2H), 7.98 (b, NH), 7.91 (m, 4H), 7.71 (t, 1H), 7.3−7.5 (m, 6H), 7.16 (s, 1H). ^{13}C NMR ($CDCl_3$): 154.4, 153.5, 153.1, 150.4, 147.5, 139.1, 137.4, 133.7, 133.0, 131.2 (2 × CH), 130.5 (2 × CH), 129.6 (2 × CH), 129.1, 128.9, 128.8, 128.4, 126.3, 126.2, 126.1, 125.7 (2 × CH), 124.5, 117.4 (2 × CH), 117.1 (2 × CH), 98.0, 88.8. Anal. ($C_{22}H_{15}FN_4O_3$) C, H, N.

4-Nitro-*N*-(1-(2-chlorophenyl)-3-phenyl-1*H*-pyrazol-5-yl)benzamide (47) was prepared from 4-nitrobenzoyl chloride (0.35 g, 1.8 mmol) and diphenylpyrazole **14** (0.50 g, 1.8 mmol) as described for compound **21**. Separation on 50 g of silica gel (Merck 70−230 mesh, 60 A) in CH_2Cl_2 gave fractions with $R_f = 0.12$. Recrystallization from EtOH (10 mL) gave 0.19 g (28%). Mp: 176−179 °C. ^{1}H NMR ($CDCl_3$): 8.31 (d, 2H), 7.89 (m, 4H), 7.80 (m, 1H), 7.64 (dd, 2H), 7.51 (dd, 2H), 7.46 (m, 2H), 7.36 (t, 1H), 7.17 (s, 1H). Anal. ($C_{22}H_{15}ClN_4O_3 \cdot 0.5H_2O$) C, H, N.

4-Nitro-*N*-(1-(2-bromophenyl)-3-phenyl-1*H*-pyrazol-5-yl)benzamide (48) was prepared from 4-nitrobenzoyl chloride (0.37 g, 2.0 mmol) and diphenylpyrazole **15** (0.62 g, 2.0 mmol) as described for compound **21**. Separation on 50 g of silica gel (Merck 70−230 mesh, 60 A) in CH_2Cl_2 gave fractions with $R_f = 0.14$. Recrystallization from EtOH (10 mL) gave 0.14 g (18%). Mp: 251−253 °C. ^{1}H NMR ($CDCl_3$): 8.32 (d, 2H), 7.90 (t, 4H), 7.82 (dd, 1H), 7.74 (b, 1H), 7.63 (dd, 1H), 7.55 (dt, 1H), 7.45 (m, 3H), 7.36 (d, 1H), 7.18 (s, 1H). Anal. ($C_{22}H_{15}BrN_4O_3$) C, H, N.

3-Nitro-*N*-(1-(2-bromophenyl)-3-phenyl-1*H*-pyrazol-5-yl)benzamide (49) was prepared from 3-nitrobenzoyl chloride (0.33 g, 1.8 mmol) and diphenylpyrazole **15** (0.50 g, 1.6 mmol) as described for compound **21**. Recrystallization from EtOH (10 mL) gave 0.31 g (42%). Mp: 172−176 °C. ^{1}H NMR ($CDCl_3$): 8.53 (s, 1H), 8.37 (d, 1H), 8.04 (d, 1H), 7.89 (m, 3H), 7.80 (dd, 1H), 7.62 (m, 2H), 7.52 (t, 1H), 7.42 (m, 4H), 7.10 (s, 1H). ^{13}C NMR ($CDCl_3$): 161.4, 152.3, 148.0, 136.7, 136.5, 134.6, 133.6, 132.7, 132.3, 131.3, 131.3, 130.4, 130.0, 128.9, 128.4 (2 × CH), 128.1, 126.6, 125.5 (2 × CH), 121.9, 120.9, 96.3. Anal. ($C_{22}H_{15}BrN_4O_3$) C, H, N.

3-Cyano-*N*-(1-(2-bromophenyl)-3-phenyl-1*H*-pyrazol-5-yl)-benzamide (50) was prepared from 3-cyanobenzoyl chloride (0.20 g, 1.2 mmol) and diphenylpyrazole **15** (0.32 g, 1.0 mmol) as described for compound **21**. Yield 0.29 g (66%). Mp: 180−181 °C. ^{1}H NMR ($CDCl_3$): 7.99 (s, 1H), 7.91 (m, 3H), 7.82 (dt, 2H), 7.75 (b, 1H), 7.61 (m, 2H), 7.54 (dd, 1H), 7.43 (m, 3H), 7.34 (t, 1H), 7.13 (s, 1H). ^{13}C NMR ($CDCl_3$): 162.0, 152.1, 147.3, 136.7, 136.5, 135.2, 133.1, 132.4, 131.4, 130.9, 130.6, 130.5, 129.7, 128.9, 128.4 (2 × CH), 128.1, 125.5 (2 × CH), 117.3, 113.2, 96.1. HRMS: obsd, 442.0431; calcd, 442.0429. Anal. ($C_{23}H_{15}BrN_4O$) C, H, N.

5-(4-Cyanobenzoyl)imino-2-(4-cyanobenzoyl)-1,3-diphenyl-1,2-dihydropyrazole (51) was isolated as byproduct A in the preparation of compound **28** (yield 0.20 g, 19%). TLC on silica with CH_2Cl_2 showed $R_f = 0.27$. Mp: 161−163 °C. ^{1}H NMR ($CDCl_3$): 8.37 (d, 2H), 7.99 (d, 2H), 7.94 (d, 2H), 7.74 (m, 4H), 7.65 (dd, 2H), 7.53 (t, 2H), 7.44 (t, 1H), 7.33 (m, 3H), 6.57 (s, 1H). ^{13}C NMR ($CDCl_3$): 162.0, 160.6, 151.4, 146.7, 141.3, 138.7, 135.2, 132.8 (2 × CH), 132.4 (2 × CH), 130.9, 130.6 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.1, 124.7, 125.2 (2 × CH), 124.7 (2 × CH), 118.2, 117.6, 117.1, 115.3, 96.5. Anal. ($C_{31}H_{19}N_5O_2$) C, H, N

***N*,*N*-Bis(4-cyanobenzoyl)-1,3-diphenyl-5-amino-1*H*-pyrazole (52)** was isolated as byproduct B in the preparation of **28** (yield 0.34 g, 43%). TLC in CH_2Cl_2 showed $R_f = 0.32$. Mp: 179−181 °C. ^{1}H NMR ($CDCl_3$): 7.81 (dd, 2H), 7.63 (d, 4H), 7.61 (d, 4H), 7.41 (m, 6H), 7.79 (m, 2H), 6.76 (s, 1H). Anal. ($C_{31}H_{19}N_5O_2$) C, H, N.

2-Nitro-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (53) was prepared from 2-nitrobenzoyl chloride (0.50 g, 2.3 mmol) as described for compound **21**. Yield 0.14 g (16%) after recrystallization from EtOH. Mp: 226−229 °C. Lit.[28] mp: 230−232 °C. ^{1}H NMR ($CDCl_3$): 8.13 (d, 1H), 7.91 (d, 2H), 7.65 (m, 2H), 7.56 (m, 4H), 7.44 (t, 2H), 7.37 (q, 1H), 7.23 (s, 1H).

***N*-(6-Methyl-3-pyridinoyl)-1,3-diphenyl-5-amino-1*H*-pyrazole (54)** was prepared from 6-methylnicotinic acid (0.50 g, 3.6 mmol) and thionyl chloride as described for compound **33** with 5 equiv of *N*,*N*-diisopropylethylamine. Extraction of the product with EtOAc followed by column chromatography on 50 g of silica gel (Merck 70−230 mesh, 60 A) in CH_2Cl_2 gave pure **54** after crystallization from *i*-Pr_2O (yield 0.17 g, 18%). Mp: 172−175 °C. ^{1}H NMR ($CDCl_3$): 8.77 (d, 1H), 8.13 (b, 1H), 8.02 (dd, 1H), 7.89 (d, 2H), 7.58 (dd, 4H), 7.44 (m, 3H), 7.34 (tt, 1H), 7.25 (d, 1H), 7.18 (s, 1H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$): 162.7, 161.9, 151.7, 146.8, 137.5, 135.9, 135.5, 132.6, 129.8 (2 × CH), 128.5, 128.3 (2 × CH), 127.9, 126.0, 125.5 (2 × CH), 124.5 (2 × CH), 123.3, 95.9, 24.4. Anal. ($C_{22}H_{18}N_4O$) C, H, N.

***N*-Isonicotinoyl-1,3-diphenyl-5-amino-1*H*-pyrazole (55)** was prepared from 4-pyridylcarboxyl chloride hydrochloride (0.48 g, 2.7 mmol) as described for compound **21** with 5 equiv of *N*,*N*-diisopropylethylamine. The yield was 0.40 g (28%) from EtOH. Mp: 185−187 °C. ^{1}H NMR ($CDCl_3$): 8.79 (d, 2H), 8.12 (s, NH), 7.91 (d, 2H), 7.59 (m, 6H), 7.52 (dd, 1H), 7.44 (t, 2H), 7.36 (m, 1H), 7.24 (s, 1H). Anal. ($C_{21}H_{16}N_4O$) C, H, N.

***N*-Cyclohex-1-enecarboxyl-1,3-diphenyl-5-amino-1*H*-pyrazole (56).** Cyclohex-1-enecarboxylic acid chloride (0.48 g, 1.2 mmol) was added to 1,3-diphenylpyrazole (0.24 g, 1.0 mmol) as described for compound **21**. Mp: 196−198 °C. ^{1}H NMR ($CDCl_3$): 7.89 (m, 2H), 7.66 (b, 1H), 7.57 (s, 4H), 7.3−7.5 (m, 4H), 7.15 (s, 1H), 6.71 (m, 1H), 2.21 (m, 4H), 1.65 (m, 4H). ^{13}C NMR ($CDCl_3$): 164.1, 151.7, 137.7, 136.6, 132.8, 132.2, 129.7 (2

× CH), 128.3 (2 × CH), 127.8, 125.5 (2 × CH), 124.5 (2 × CH), 95.0, 25.3, 23.8, 21.6, 21.0. Anal. ($C_{22}H_{21}N_3O$) C, H, N.

***N*-Cyclohexanecarboxyl-1,3-diphenyl-5-amino-1*H*-pyrazole (57)** was prepared from cyclohexanecarboxylic acid chloride (0.18 g, 1.2 mmol) as described for compound **21**. Chromatography on silica with hexanes−EtOAc (1:4) gave 0.17 g (49%). Mp: 185−186 °C. ^{1}H NMR ($CDCl_3$): 7.88 (m, 2H), 7.47 (m, 1H), 7.42 (m, 3H), 7.34 (t, 1H), 7.06 (s, 1H), 2.20 (m, 1H), 1.90 (m, 2H), 1.82 (m, 2H), 1.71 (m, 1H), 1.47 (m, 2H), 1.24 (m, 3H). ^{13}C NMR ($CDCl_3$): 173.1, 152.2, 138.3, 137.0, 133.4, 130.3 (2 × CH), 128.9 (2 × CH), 128.4 (2 × CH), 126.1 (2 × CH), 125.8 (2 × CH), 96.3, 45.9, 29.7, 25.9 (2 × CH_2), 25.8 (2 × CH_2). HRMS ($C_{22}H_{23}N_3O$): obsd, 345.1826; calcd, 345.1830. Anal. ($C_{22}H_{23}N_3O$) C, H, N.

***N*-Cyclopentanecarboxyl-1,3-diphenyl-5-amino-1*H*-pyrazole (58)** was prepared from cyclopentanecarboxylic acid (1.1 g, 10 mmol) as described for compound **33** (yield 15%). TLC in CH_2Cl_2 showed $R_f = 0.16$. Mp: 162−164 °C. ^{1}H NMR ($CDCl_3$): 7.87 (d, 2H), 7.54 (m, 4H), 7.47 (m, 1H), 7.40 (t, 2H), 7.33 (d, 1H), 7.30 (b, 1H), 7.07 (s, 1H), 2.63 (q, 1H), 1.80 (m, 6H), 1.60 (m, 2H). ^{13}C NMR ($CDCl_3$): 137.2, 129.6 (2 × CH), 128.3 (2 × CH), 127.8, 125.4 (2 × CH), 124.6 (2 × CH), 95.4, 30.0 (2 × CH_2), 29.7, 25.6 (2 × CH_2). Anal. ($C_{21}H_{21}N_3O$) C, H, N.

***N*-(Cyclopentylmethyl)carboxyl-1,3-diphenyl-5-amino-1*H*-pyrazole (59)** was prepared from cyclopentylacetic acid (0.5 g, 3.9 mmol) as described for compound **33** (yield 0.25 g, 32%). Mp: 168−170 °C. ^{1}H NMR ($CDCl_3$): 7.87 (dt, 2H), 7.53 (s, 4H), 7.44 (m, 3H), 7.34 (m, 2H) 7.05 (s, 1H), 2.32 (d, 2H), 2.20 m, 1H), 1.84 (m, 2H), 1.59 (m, 4H), 1.53 (m, 2H). Anal. ($C_{22}H_{23}N_3O$) C, H, N.

***N*-(4-Nitrocinnamoyl)-1,3-diphenyl-5-amino-1*H*-pyrazole (60)** was prepared from 4-nitrocinnamic acid (0.64 g, 3.3 mmol) and 1,3-diphenyl-1*H*-pyrazole (0.78 g, 3.3 mmol) as described for compound **33** (yield 0.31 g, 23%). Mp: 195−197 °C. ^{1}H NMR ($CDCl_3$): 8.22 (d, 2H), 7.89 (d, 2H), 7.81 (d, J = 15.5 Hz, 1H), 7.64 (m, 3H), 7.57 (d, 4H), 7.49 (m, 1H), 7.42 (t, 2H), 7.37 (m, 1H), 7.19 (s, 1H), 6.54 (d, J = 15.4 Hz, 1H). Anal. ($C_{24}H_{18}N_4O_3$) C, H, N (accounted 88 wt %).

***N*-(2-Phenyl-2-oxoethyl)phthalimide (61).** 2′-Bromoacetophenone (10 g, 50 mmol) was dissolved in anhydrous DMF (40 mL). Potassium phthalimide (10 g, 54 mmol) was added in portions at 20 °C. After stirring for 1 h at 20 °C, $CHCl_3$ (60 mL) was added followed by water (200 mL). Extraction with chloroform (2 × 60 mL), washing of the combined organic layer with 0.5 N NaOH (50 mL) and then water (50 mL), drying (Na_2SO_4), and evaporation gave 10.6 g (80%) of crystalline residue. Mp: 164−166 °C. Lit.[42] mp: 165−167 °C. ^{1}H NMR ($CDCl_3$): 8.00 (d, 2H), 7.90 (dd, 2H), 7.75 (dd, 2H), 7.64 (tt, 1H), 7.52 (t, 2H), 5.14 (s, 2H). ^{13}C NMR ($CDCl_3$): 190.7, 167.6, 134.1, 133.8, 133.7 (2 × CH), 131.9, 128.6 (2 × CH), 127.9 (2 × CH), 123.3 (2 × CH), 43.9.

4-Phthalimido-1,3-diphenyl-1*H*-pyrazole (62). Compound **61** (5.3 g, 20 mmol) was suspended in *N*,*N*-dimethyldimethoxyformamide (3.8 g, 48 mmol) and heated to 110 °C for 16 h. Phenylhydrazine hydrochloride (3.2 g, 22 mmol) was added followed by 90% aqueous EtOH (100 mL). The mixture was stirred at 90 °C for 2 h. After cooling the precipitated product was collected by filtration and washed with EtOH (2 × 10 mL) (yield 6.84 g, 92%). Mp: 232−234 °C. Lit.[29] mp: 233−235 °C. ^{1}H NMR ($CDCl_3$): 7.89 (dd, 2H), 7.81 (s, 1H), 7.75 (dd, 2H), 7.30 (s, 5H), 7.27 (m, 2H), 7.22 (m, 3H). ^{13}C NMR ($CDCl_3$): 167.4, 140.4, 139.4, 138.5, 134.1 (2 × CH), 131.5 129.0 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.4 (2 × CH), 127.8, 127.4, 124.7 (2 × CH), 123.6 (2 × CH), 112.6.

4-Amino-1,3-diphenyl-1*H*-pyrazole (63). Compound **62** (3.7 g, 10 mmol) was suspended in EtOH (50 mL), 50% hydrazine hydrate (1.5 g, 30 mmol) was added, and the mixture was stirred at 60 °C for 1.5 h. After cooling to 20 °C the precipitated phthaloyl hydrazide was removed by filtration, and the mother liquors were reduced to 15 mL by evaporation. Addition of *i*-Pr_2O (15 mL) and cooling gave 1.68 g (71%). Lit.[29] yield: 90% (no data). Mp: 126−128 °C. ^{1}H NMR ($CDCl_3$): 7.47 (s, 1H), 7.38 (d, 1H), 7.33 (m, 2H), 7.24 (m, 7H).

***N*-(1,3-Diphenyl-1*H*-pyrazol-4-yl)benzamide (64)** was prepared from benzoyl chloride (0.32 g, 2.1 mmol) and diphenylpyrazole **63** (0.48 g, 2.0 mmol) as described for compound **21** to give 0.39 g (26%) after recrystallization from EtOH (10 mL). Mp: 169−171 °C. ^{1}H NMR ($CDCl_3$): 8.46 (s, 5-CH), 7.76 (d, 2H), 7.70 (b, NH), 7.50 (t, 1H), 7.42 (m, 6H), 7.29 (m, 6H). ^{13}C NMR ($CDCl_3$): 164.8, 139.4, 134.4, 133.7, 131.6, 129.1 (4xCH), 128.7, 128.6 (2 × CH), 128.4 (2 × CH), 128.3, 127.0, 126.7 (2 × CH), 124.3 (2 × CH), 120.2. MS: 338 (M^-) 100. Anal. ($C_{22}H_{17}N_3O$) C, H, N.

3-Cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-4-yl)benzamide (65) was prepared from 3-cyanobenzoyl chloride (0.39 g, 2 mmol) and diphenylpyrazole **63** (0.48 g, 2 mmol) as described for compound **21**. Recrystallization from EtOH (12 mL) gave 0.17 g (23%). Mp: 217−219 °C. MS: 363 (M^-) 100. ^{1}H NMR ($CDCl_3$): 8.73 (b, NH), 7.90 (s, 1H), 7.86 (d, 1H), 7.71 (d, 1H), 7.60 (s, 1H), 7.43 (t. 1H), 7.34 (m, 5H), 7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): 165.4, 138.8, 138.0, 135.1, 133.7, 131.5, 130.9, 130.3, 129.5, 129.0 (2 × CH), 128.6 (2 × CH), 128.1, 127.0, 126.7 (2 × CH), 123.9 (2 × CH), 119.7, 117.5, 112.6. Anal. ($C_{23}H_{16}N_4O$) C, H, N.

4-Nitro-*N*-(1,3-diphenyl-1*H*-pyrazol-4-yl)benzamide (66) was prepared from 4-nitrobenzoyl chloride (0.39 g, 2.1 mmol) and diphenylpyrazole **63** (0.47 g, 2.0 mmol) as described for compound **21**. Separation on 50 g of silica gel (Merck 70−230 mesh, 60 A) in CH_2Cl_2 gave fractions with $R_f = 0.11$. Recrystallization from EtOH (20 mL) gave 0.13 g (17%). Mp: 174−175 °C. ^{1}H NMR ($CDCl_3$): 8.20 (d, 2H), 8.02 (b, 1H), 7.82 (d, 2H), 7.79 (s, 1H), 7.39 (m, 9H), 7.29 (t, 1H). ^{13}C NMR ($CDCl_3$): 129.0, 128.7, 128.4, 126.8, 124.0, 123.8 (2 × CH only). Anal. ($C_{22}H_{16}N_4O_3$) C, H, N.

1-Formyl-1-phenylacetonitrile (67). Sodium methoxide (5.4 g, 104 mmol) was added to a stirred solution of benzyl cyanide (11.7 g, 100 mmol) in benzene (200 mL) at 20 °C. Ethyl formate (8.2 g, 110 mmol) was slowly added and the mixture was heated to 40 °C for 30 min and then allowed to reach room temperature for 1 h. Water (200 mL) was added and the aqueous layer was collected. Neutralization with 6 N HCl (18 mL), cooling to 0 °C, filtering, and washing of the precipitation with water (20 mL) gave 7.50 g (48%). Mp: 158−160 °C. Lit.[31] mp: 159−160 °C.

5-Amino-1,4-diphenyl-1*H*-pyrazole (68). Acetic acid (2.5 g, 42 mmol) was added to a mixture of compound **67** (2.9 g, 20 mmol) and phenylhydrazine (2.8 g, 26 mmol) in benzene (25 mL) and the mixture was heated to reflux temperature for 5 h. Water was removed azeotropically using a Dean−Stark water trap. After cooling, 5 mL of 6 N HCl (30 mmol) was added, followed by neutralization with 14 N NH_4OH. Extraction with EtOAc (2 × 50 mL), washing of the combined organic layer with water (2 × 50 mL), drying (Na_2SO_4), and evaporation of the solvents gave 2.88 g (61%) after crystallization from *i*-Pr_2O (10 mL). Mp: 139−140 °C. Lit.[32] mp: 136−137 °C. Lit.[33] mp: 140−141 °C. ^{1}H NMR ($CDCl_3$): 7.66 (s, 1H), 7.62 (d, 2H), 7.52 (d, 2H), 7.48 (m, 1H), 7.44 (m, 4H), 7.39 (m, 1H), 7.24 (m, 1H). ^{13}C NMR ($CDCl_3$): 140.4, 138.3, 137.6, 128.7 (2 × CH), 128.2 (2 × CH), 126.7, 125.4 (2 × CH), 124.9, 123.1 (2 × CH), 105.1.

***N*-(1,4-Diphenyl-1*H*-pyrazol-5-yl)benzamide (69)** was prepared by dropwise addition of benzoyl chloride (0.17 g, 1.2 mmol) to diphenylpyrazole **68** (0.23 g, 1.0 mmol) in a mixture of *N*,*N*-diisopropylethylamine (0.64 g, 4 mmol) and THF (10 mL) at 20 °C. After 2 h, water (2 mL) was added and the product extracted with EtOAc (3 × 20 mL). Purification on silica with hexane−EtOAc (1:4), followed by conversion to the hydrochloride, gave 0.20 g (53%). Mp: 143−145 °C. ^{1}H NMR ($CDCl_3$): 7.08 (t, 1H), 7.14 (t, 1H), 7.18 (t, 2H), 7.23 (t, 2H), 7.33 (t, 2H), 7.39 (d, 2H), 7.54−7.47 (m, 3H), 7.86 (s, 1H), 7.98 (d, 2H). ^{13}C NMR ($CDCl_3$): 112.7, 123.4 (2 × CH), 126.6 (2 × CH), 127.3, 127.9, 128.1, 129.3 (2 × CH), 129.4 (2 × CH), 129.7 (2 × CH), 130.9 (2 × CH), 131.3, 135.0, 138.4, 139.2, 141.1, 163.4. HRMS ($C_{22}H_{17}N_3O$): obsd, 339.1372; calcd, 339.1371. Anal. ($C_{22}H_{17}N_3O$·0.5HCl) C, H, N.

3-Cyano-*N*-(1,4-diphenyl-1*H*-pyrazol-5-yl)benzamide (70) was prepared from 3-cyanobenzoyl chloride (0.16 g, 1.0 mmol) and diphenylpyrazole **68** as described for compound **21**. Chromatography on silica with hexane−EtOAc (1:4) yielded 68% of an off-

white solid. Mp: 214−215 °C. ^{1}H NMR ($CDCl_3$): 7.04 (s, 1H), 7.75−7.38 (m, 9H), 7.92 (d, 2H), 8.01 (d, 1H), 8.02 (d, 1H), 8.33 (s, 1H), 10.7 (s, 1H). ^{13}C NMR ($CDCl_3$): 101.7, 112.1, 118.5, 123.7 (2 × CH), 125.5 (2 × CH), 127.9, 128.5, 129.1 (2 × CH), 129.6 (2 × CH), 130.4, 131.7, 132.8, 133.0, 134.5, 136.0, 137.0, 139.1, 150.6, 164.6. HRMS ($C_{23}H_{16}N_4O$): obsd, 364.1326; calcd, 364.1324. Anal. ($C_{23}H_{16}N_4O$) C, H, N.

4-Nitro-*N*-(1,4-diphenyl-1*H*-pyrazol-5-yl)benzamide (71) was prepared from 4-nitrobenzoyl chloride (1.0 g, 5.4 mmol) and diphenylpyrazole **68** (1.0 g, 4.2 mmol) as described for compound **21**. Recrystallization from EtOH (20 mL) gave 0.82 g (51%). Mp: 224−226 °C. ^{1}H NMR ($CDCl_3$): 8.20 (d, 2H), 8.02 (b, 1H), 7.83 (d, 2H), 7.79 (s, 1H), 7.38 (m, 9H), 7.29 (t, 1H). ^{13}C NMR ($CDCl_3$): 129.0 (2 × CH), 128.7 (2 × CH), 128.4 (2 × CH), 126.8 (2 × CH), 124.0 (2 × CH) 123.8 (2 × CH). Anal. ($C_{22}H_{15}N_4O_3$) C, H, N.

5-Azido-1,3-diphenyl-1*H*-pyrazole (72). 1,3-Diphenyl-1*H*-pyrazol-5-ylamine (0.50 g, 2.1 mmol) was dissolved in 5 mL of trifluoroacetic acid and a solution of $NaNO_2$ (0.66 g, 9.5 mmol) in 1 mL of H_2O was added at 0 °C. After stirring for 10 min, a solution of NaN_3 (1.38 g, 21 mmol) in 4 mL of H_2O was added, and the mixture was stirred for 30 min at 20 °C, subjected to extraction with EtOAc (3 × 30 mL), washed with H_2O, dried (Na_2SO_4), evaporated, and purified by silica gel chromatography in hexanes−EtOAc (7:3) to give 0.47 g (86%) of the azido derivative as a solid. ^{1}H NMR ($CDCl_3$): 6.29 (s, 1H), 7.21−7.16 (m, 2H), 7.30−7.24 (m, 4H), 7.54 (d, 2H), 7.70 (d, 2H). ^{13}C NMR ($CDCl_3$): 152.1, 139.1, 138.7, 133.0, 129.4 (2 × CH), 129.1 (2 × CH), 128.8, 127.8, 126.0 (2 × CH), 123.7 (2 × CH), 93.7.

5-(4-Phenyl-1,2,3-triazol-1-yl)-1,3-diphenyl-1*H*-pyrazole (73). The azido derivative **72** (0.32 g, 0.9 mmol) was suspended in 50% aqueous *tert*-butyl alcohol, and phenylacethylene (0.14 mL, 0.9 mmol), sodium ascorbate (0.1 mg, 0.09 mmol), and $CuSO_4$ (3 mg, 9 umol) were added. After stirring for 18 h at 20 °C, the reaction was quenched with H_2O (5 mL), extracted with EtOAc (3 × 10 mL), and dried over Na_2SO_4, and the solvent was evaporated, and the residue was purified by silica gel chromatography with hexanes−EtOAc (7:3). Collection of the fractions showing a single spot on TLC gave 0.28 g (52%) of product. Mp: 120−121 °C. ^{1}H NMR ($CDCl_3$): 6.84 (s, 1H), 7.22−7.14 (m, 6H), 7.30−7.24 (m, 5H), 7.66 (s, 1H), 7.67 (d, 2H), 7.77 (d, 2H). ^{13}C NMR ($CDCl_3$): 152.1, 148.4, 138.0, 135.8, 132.4, 129.8 (2 × CH), 129.4 (2 × CH), 129.3 (2 × CH), 129.2, 129.0 (2 × CH), 126.3 (2 × CH), 126.2 (2 × CH), 124.1 (2 × CH), 122.3, 102.7. Anal. ($C_{23}H_{17}N_5$·0.2H_2O) C, H, N.

3-Amino-2-phenylimidazo[1,2-*a*]pyridine (74). 2-Phenylimidazo[1,2-*a*]pyridine[35] (0.20 g) was dissolved in AcOH glacial (5 mL) and then a saturated solution of $NaNO_2$ was added dropwise until a heavy green precipitate was formed and filtered off. The precipitated nitroso derivative was added to a suspension of Zn (0.40 g) in 5 mL of AcOH−EtOH (1:1), and the resulting mixture was stirred for 2 h at 20 °C. Addition of 3 N NaOH until pH 12, extraction with EtOAc, drying over Na_2SO_4, evaporation, and purification by silica gel chromatography (EtOAc) provided the desired compound as a solid in 95% yield. Mp: 210−212 °C. Lit.[37] mp: 210−212 °C. ^{1}H NMR ($CDCl_3$): 6.63 (td, 1H), 6.97 (td, 1H), 7.08 (t, 1H), 7.19 (t, 2H), 7.45 (d, 1H), 7.61 (d, 2H), 7.89 (d, 1H). ^{13}C NMR ($CDCl_3$): 176.5, 138.9, 131.2, 129.0 (2 × CH), 128.0, 127.1 (2 × CH), 126.4, 124.7, 123.0, 115.0, 113.6.

***N*-(2-Phenylimidazo[1,2-*a*]pyridin-3-yl)benzamide (75)** was prepared from benzoyl chloride (0.16 g, 1.1 mmol) and 3-amino-2-phenylimidazo[1,2-*a*]pyridine (**74**, 0.23 g, 1.0 mmol) as described by Holzwart.[37] Chromatography on silica with hexane−EtOAc (1:4) gave pure product according to TLC. Conversion to the hydrochloride gave 0.17 g (52%). Mp: >240 °C. Lit.[37] mp: 240−242 °C. ^{1}H NMR ($CDCl_3$): 6.65 (t, 1H), 7.06 (t, 1H), 7.19−7.11 (m, 3H), 7.42−7.38 (m, 3H), 7.52 (t, 1H), 7.58 (d, 1H), 7.68 (d, 2H), 7.91 (d, 2H), 8.65 (s, 1H). ^{13}C NMR ($CDCl_3$): 112.7, 115.3, 117.6, 123.5, 124.5, 125.6, 127.5 (2 × CH), 128.1 (2 × CH), 128.3, 128.9 (2 × CH), 129.3 (2 × CH), 131.3, 131.9, 132.9, 133.1, 165.1. Anal. ($C_{20}H_{15}N_3O$·HCl·0.3H_2O) C, H, N. HRMS ($C_{20}H_{15}N_3O$): obsd, 313.1214; calcd, 313.1215.

3-Cyano-*N*-(2-phenylimidazo[1,2-a]pyridin-3-yl)benzamide (76) was prepared from 3-cyanobenzoyl chloride (0.16 g, 1 mmol) and compound **74** (0.22 g, 1 mmol) as described for compound **21**. Chromatography on silica with hexane−EtOAc (1:4). Conversion to the hydrochloride yielded 48% of an off-white solid. Mp: >260 °C. ^{1}H NMR ($CDCl_3$): 6.83 (t, 1H), 7.23 (d, 2H), 7.31−7.28 (m, 2H), 7.62−7.56 (m, 2H), 7.83−7.78 (m, 2H), 8.45 (d, 1H), 8.53 (s, 1H), 10.9 (s, 1H). ^{13}C NMR ($CDCl_3$): 113.2, 113.4, 115.5, 116.2, 117.0, 118.5, 123.9, 125.2, 126.7, 127.6 (2 × CH), 128.7, 129.0 (2 × CH), 130.2, 132.6, 133.2, 134.1, 135.7, 165.5. HRMS ($C_{21}H_{14}N_4O$): obsd, 338.1162; calcd, 338.1167. Anal. ($C_{21}H_{14}N_4O$·HCl·0.7H_2O) C, H; N: calcd, 14.46; found, 13.72.

QSAR Modeling. Prediction of the activities of novel analogues of CDPPB was performed using HQSAR (holographic quantitative structure−activity relationships) modeling (Tripos, St Louis MO). This method uses multiple fragments of varying length of the connection table of each compound to generate overlapping permutations, encoded into the frequency of occurrence, which serve as molecular descriptors in the analysis. This technique allows for rapid modeling independent of geometry optimization or positioning. Molecular fragment descriptors using four to eight atom lengths of the test set were obtained from Sybyl line notation of their 2D representations (ChemDraw 9.0). The HQSAR program cuts each molecular fingerprint into strings that are set at the length of 12 prime numbers ranging from 53 to 401. The numerical representation of the test set was then subjected to partial least-squares analysis of the binding and functional activities, respectively. Except for compound **33**, compounds with K_i or EC_{50} values >10 000 nM were excluded from the analysis.

Competition Binding Assay. Membranes were prepared from stable human embryonic kidney (HEK) cells, expressing rat $mGluR_{5a}$. The cells were homogenized (Polytron) and stored at −80 °C until used. After thawing, membranes were resuspended (Dounce) in ice-cold buffer containing 50 mM Tris HCl and 0.9% saline at pH 7.4. Displacement of [^{3}H]methoxyPEPy binding was performed as described.[10,14] Test compounds were dissolved in 100% DMSO and then serially diluted in assay buffer to 5× stock solution at 0.63% DMSO. The stock solution was added in triplicate to 96-well plates (0.1 mL) to yield final concentrations of 0.13% DMSO, 2 nM [^{3}H]methoxyPEPy, and 0.1 mg of cell protein/mL of buffer. The plates were incubated for 60 min at room temperature with gentle shaking.[43] Bound radioligand was separated from free ligand by rapid filtration using a Brandel 96-well harvester (Brandel, Gaithersburg MD) on GF/B filters (Unifilter-96, PerkinElmer Life Sciences, Boston MA). Scintillation fluid (Microscint, PerkinElmer Life Sciences, Boston, MA) (30 μL) was added to each filter, and membrane-bound radioactivity was determined in a microplate scintillation counter (TopCount NXT, PerkinElmer Life Sciences, Downers Grove, IL). Nonspecific binding was defined by binding in the presence of 5 μM MPEP. Inhibition constants (K_i) were calculated from IC_{50} values using GraphPad Prism v. 4.01 nonlinear curve fit and are presented as the average result of three separate experiments ± standard error of the mean (SEM).

Cell Culture. Secondary cortical astrocytes from 2−4-day-old Sprague Dawley rats were dissected and grown for 1 week under 5% carbon dioxide at 37 °C in Dulbecco's modified Eagle medium (DMEM), containing 10% fetal bovine serum (FBS), 2 mM glutamine, 20 mM *N*-(hydroxyethyl)piperazine-*N*′-(2-ethanesulfonic acid) (HEPES), and antibiotics and antimycotics (Invitrogen, Carlsbad CA) as described.[4] The cells were trypsinized on day 0 and plated onto poly-D-lysine-coated 96-well plates. On day 1, the culture medium was changed to fresh medium, supplemented with G-5 growth factor (1:100) (Invitrogen, Carlsbad, CA), and incubated for 2 days. On day 3, medium was switched to glutamine-free DMEM containing 10% dialyzed FBS. Assay was performed on day 4.

Calcium Mobilization Assay. Measurement of calcium transients in cultured cortical rat astrocytes was performed as described.[19] On the day of assay, indicator dye[45] (Calcium-3 Kit,

Molecular Devices, Sunnyvale CA) was added to the cells, which incubated for 1 h at 37 °C under 5% carbon dioxide. The dye was washed once and replaced with Hank's balanced salt solution (HBSS) (Invitrogen, Carlsbad CA) containing 20 mM HEPES and 2.5 mM probenecid, adjusted to pH 7.4. Test compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and serially diluted in assay buffer to a 5× stock solution containing 0.63% DMSO. The stock solution was added to each well to 0.13% final DMSO concentration. Test compounds were added 5 min before the addition of an EC_{20} concentration of glutamate (200−300 nM). Time-dependent calcium flux was measured in a fluorometric imaging plate reader operating at 384 nm (FlexStation II, Molecular Devices, Sunnyvale, CA). Effective concentrations (EC_{50}) were calculated using GraphPad Prism v. 4.01 nonlinear curve-fit and presented as the average result of three separate experiments ± SEM.

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Supporting Information Available: Results from elemental analyses of new compounds and X-ray crystallography of compound **69**. This material is available free of charge via the Internet at http://pubs.acs.org.

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