An Efficient One-Pot Synthesis of *N*-(1,3-Diphenyl-1*H*-Pyrazol-5-yl)amides

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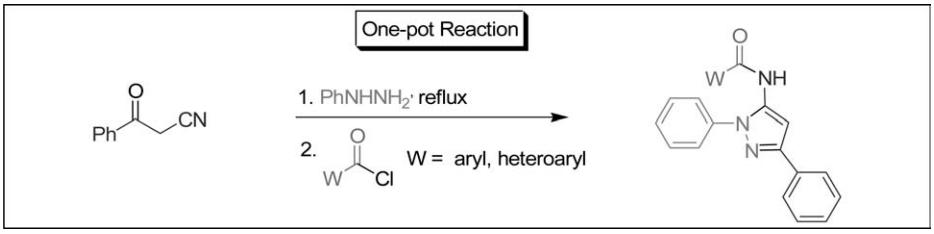
Received September 24, 2008
DOI 10.1002/jhet.343
Published online 4 June 2010 in Wiley InterScience (www.interscience.wiley.com).



A ''one-pot'' method for the synthesis of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amides was developed by cyclization of benzoylacetonitrile (**1**) and phenylhydrazine in neat condition followed by acylation. The corresponding *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amides were provided in good to excellent yields (70–90%). The significant advantages of the new synthetic method are excellent yields and simple work-up procedure without isolation and purification of intermediary 5-amino-1,3-diphenyl pyrazol (**2**).

J. Heterocyclic Chem., **47**, 831 (2010).

INTRODUCTION

Pyrazole compounds have aroused great interest in recent years because of their wide spectrum of biological activities, including anti-inflammatory, antipyretic, gastric secretion stimulatory, antidepressant, antibacterial, anticonvulsant, antifilarial agents, and as analytical reagents [1–4].

A recently reported pyrazole, 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (**16**, CDPPB), was developed as the first centrally active positive allosteric modulator of rat and human metabotropic glutamate receptor $mGluR_5$ subtype [5–7]. The receptors play an important role in controlling neuronal excitability and synaptic transmission in the central nervous system of the mammalian brain [8,9]. *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide derivatives are also considered as potential targets for therapeutic intervention in a variety of neurological and psychiatric illnesses [10]. The detailed structure–activity relationship studies of CDPPB analogs were reported by de Paulis *et al*. in 2006 [11]. Herein, we provided an efficient and convenient one-pot method to synthesize *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amides for the large-scale preparation.

RESULTS AND DISCUSSION

The traditional method for the synthesis of analog **2** [12,13] was the reaction of benzoylacetonitrile (**1**) with phenylhydrazine under different conditions to provide the key intermediate 5-amino-1,3-diphenyl pyrazole (**2**). The conditions include: (1) heated in EtOH [14], (2) microwave radiation [15], and (3) heated in acetic acid (Scheme 1) [15]. Compound **2** was then subjected to acylation to provide model compound **5** [*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide]. These methods all involve two steps, and it is necessary to purify aminopyrazole **2**. To develop a better synthetic methodology for expanding the structural variation of compound **5**, we developed an efficient and convenient ''one-pot'' method for their syntheses. Benzoylacetonitrile (**1**) was allowed to react with neat phenylhydrazine. The resultant **2**, needless to be purified, was subjected to acylation to generate model compound **5** in good to excellent yields (Scheme 1).

We first tried to prepare 5-amino-1,3-diphenyl pyrazole (**2**) by traditional methods to study their feasibility for one-pot reaction of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide derivatives. The first method was refluxing benzoylacetonitrile (**1**) with the same equivalent of

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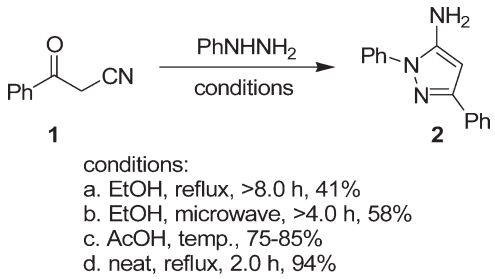
Scheme 1



phenylhydrazine in EtOH for >8.0 h (see Scheme 1, path a) [14]. Compound **2** was generated in only 41% yield *via* tandem condensation and thermal cyclization. Another method was the use of microwave irradiation of 1 with hydrazine in EtOH solution for >4.0 h to provide compound **2** in 58% yield (see Scheme 1, path b) [15]. The two literature-reported methods did not provide compound **2** in satisfactory yield, as a result, not suitable for direct acylation for a one-pot preparation. Use of acetic acid as the solvent could provide **2** in 75–85% yield (see Scheme 1, path c). However, the residual acetic acid should be distilled before acylation. Those methods were troublesome for removing EtOH or acetic acid, especially in large-scale preparation.

We then carried out the reaction in neat condition. Benzoylacetonitrile (**1**) was allowed to react with phenylhydrazine in neat condition at reflux for 2.0 h (see Scheme 1, path d). The desired 5-amino-pyrazole **2** was successfully generated in 94% yield. Compound **2** was fully characterized by spectroscopic method, and the results were consistent with the reported data of previous literature [14,15]. This method is able to promote the cyclization yield and provide the one-pot approach for *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide derivatives.

For searching a better acylation agent to generate **3**, compound **2** was treated with various acylation agents, including acetyl chloride, acetic anhydride, and ethyl acetate (EtOAc) at room temperature or at reflux for 3.0–4.0 h in THF (see Table 1). The corresponding acylated products were obtained in 85%, 83%, and trace yields, respectively. When compound **2** was reacted with ethyl benzoate or ethyl phenylacetate, the reaction gave the corresponding compounds **4** and **5** in 89% and 93% yields (see Table 1).

We then tried to combine the two-step process into a one-pot reaction. Compound **1** was refluxed with the same equivalent amount of phenylhydrazine in neat condition for 2 h. After the reaction was completed, the resultant compound **2** was dissolved in CH_2Cl_2 and stirred in ice-bath. The acylation agents, including acetyl chloride, benzoyl chloride, and phenylacetyl chloride, were diluted with anhydrous CH_2Cl_2, and THF was slowly added to the reaction mixture at 0–10°C. The reaction was stirred for 3–4 h from 0–10°C to the room temperature under N_2, and the corresponding acylation products *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide **3–5** were successfully provided in 78–90% yields in the one-pot reaction (see Table 1).

We then tried to apply this new method to synthesize *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide derivatives by use of different monosubstituted benzoyl halides containing Cl, F, CH_3, CF_3, OMe, CN, and NO_2 functionalities as the acylation agents (Scheme 2 and Table 2). The corresponding *N*-(1,3-diphenyl-1-*H*-pyrazol-5-yl)benzamide **6–19**, which were reported as a novel class of positive allosteric modulation of $mGluR_5$ [5,11], could be obtained in 70–90% yields (Table 2). Use of 2,4-difluorobenzoyl chloride also provided the corresponding product **15** in 88% yields. Compounds **6–19** were fully characterized by spectroscopic methods, and the data were consistent with reported [5,11]. For example, the pyrazole ring in compound **16** presented a peak at δ 6.79 ppm for NH—C=C—^{1}H and a peak at δ 95.7 ppm for NH—^{13}C=C in NMR. Its IR spectrum showed absorption at 2232 cm^{-1} for —CN stretching and 3308 cm^{-1} for —N—H stretching [14]. Being the first centrally active positive allosteric modulator of $mGluR_5$, compound **16** was synthesized by this one-pot method in 73% yield.

The method can also be applied to the synthesis of quinoline-8-sulfonyl and heteroarylaminopyrazoles. Use of quinoline-8-sulfonyl chloride, 2-benzofurancarbonyl chloride, 2-furoyl chloride, isoxazole-5-carbonyl chloride, 2-thiophenecarbonyl chloride, and trimellitic anhydride chloride could successfully provide the corresponding *N*-(1,3-diphenyl-1*H*-pyrazol-5yl)amide **20–25** in 70–90% yields (see Scheme 3 and Table 3).

In conclusion, we have successfully developed a newly one-pot method by treating benzoylacetonitrile (**1**) and phenylhydrazine with various acylation agents,

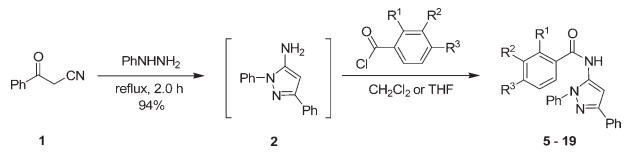
Table 1

The results of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide derivatives **3–5** *via* step-by-step and one-pot synthesis.

Acylation agents	*N*-(1,3-Diphenyl-1 *H*-pyrazol-5-yl)amides	Yields (%)
Acetyl chloride	**3**	85[a], 78[b]
Acetic anhydride	**3**	83[a]
Ethyl acetate	**3**	Trace[a]
Ethyl benzoate	**4**	89[a]
Ethyl phenylacetate	**5**	93[a]
Phenylacetylchloride	**4**	90[b]
Benzoyl chloride	**5**	78[b]

[a] The step-by-step synthesis.
[b] The one-pot synthesis reaction.

Scheme 2



including acetyl chloride, aryl chloride, heteroaryl chloride, quinoline-8-sulfonyl chloride, and trimellic anhydride chloride to give *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amides **3–25** in 70–90% yields. The new strategy has been demonstrated to substantially promote the productive yields in the generation of substituted *N*-(1,3-diphenyl-1-*H*-pyrazol-5-yl)benzamides **6–19** compounds.

EXPERIMENTAL

General procedure. All chemicals were reagent grade and used as purchased. All reactions were carried out under nitrogen atmosphere and monitored by TLC analysis. Flash column chromatography was carried out on silica gel (230–400 mesh). Commercially available reagents were used without further purification unless otherwise noted. Dichloromethane, ethyl acetate, hexanes, and methanol were purchased from ECHO Chemical (USA). Dry tetrahydrofuran (reagent grade) and 3-fluorobenzoyl chloride were purchased from Aldrich (USA). The following compounds were purchased from Acoros Chemical (Japan): acetyl chloride, benzoyl chloride, 3-cyanobenzoic acid, 2,4-difluorobenzoyl chloride, 4-fluorobenzoyl chloride, 3-methylbenzoyl chloride, and 4-methylbenzoyl chloride. Benzoylacetonitrile, 2-chlorobenzoyl chloride, 3-chlorobenzoyl chloride, 4-cyanobenzoyl chloride, 3-methoxylbenzoyl chloride, phenylhydrazine, and quinoline-8-sulfonyl chloride were purchased from TCI Chemical (Japan). Isoxazole-5-carbonyl chloride 2-nitrobenzoyl chloride, 4-(trifluoromethyl)benzoyl chloride, and trimellitic anhydride chloride were purchased from Alfa Chemical. 2-Furoyl chloride was purchased from Merck Chemical (Germany). Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz) spectrometer by use of $CDCl_3$ and d_6-DMSO as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 MHz) spectrometer by the use of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

Table 2

The results of the one-pot synthesis of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide derivative.

Acid chloride			Products	
R^1	R^2	R^3	*N*-(1,3-Diphenyl-1*H*-pyrazol-5-yl) benzamides	Yields (%)
H	H	H	**5**	78
H	F	H	**6**	77
H	H	F	**7**	70
Cl	H	H	**8**	85
H	Cl	H	**9**	71
Me	H	H	**10**	84
H	H	Me	**11**	76
H	H	CF_3	**12**	78
OMe	H	H	**13**	90
H	OMe	H	**14**	72
F	H	F	**15**	88
H	CN	H	**16 (CDPPB)**	73
H	H	CN	**17**	78
NO_2	H	H	**18**	76
H	H	NO_2	**19**	89

Standard procedure for condensation–cyclization to prepare 5-amino-1,3-diphenyl pyrazole (2). [15] Benzoylacetonitrile (**1**, 5.08 g, 35.1 mmol, 1.0 equiv) and phenylhydrazine (3.80 g, 35.1 mmol, 1.0 equiv) were mixed and heated at reflux for 2.0 h. The mixture was purified by column chromatography on silica gel (CH_2Cl_2 as eluant) to give pure 5-amino-1,3-diphenyl pyrazole (**2**, 7.81 g, 33.3 mmol) as yellow solids in 94% yield: mp 129–131°C (lit. [15] mp 129–130°C); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.82 (s, 2 H, NH_2), 5.88 (s, 1 H, Py-H), 7.32–7.49 (m, 6 H, ArH), 7.58 (dd, 2 H, J = 6.6, 1.2 Hz, ArH), 7.80 (dd, 2 H, J = 6.6, 1.2 Hz, ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 88.1, 124.2, 125.6, 127.5, 127.8, 128.5, 129.5, 133.5, 138.7, 145.8, 151.5; IR (KBr) 3427 (brs, NH), 3337 (brs, NH), 3059, 1616, 1598, 1558, 1505, 1456, 1375, 1070, 952, 758, 698 cm^{-1}; MS *m*/*z* (relative intensity) 235 (M^+, 100), 207 (20), 192 (3), 180 (3), 131 (7), 117 (4), 104 (11), 102(10), 92 (7), 77 (17), 65 (3), 51 (8); Anal. Calcd. for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.21; H, 5.79; N, 18.03.

Standard procedure for one-pot synthesis of *N*-(1,3-diphenyl-1*H*-pyrazol-5yl)amide derivatives (3–25). [4,8–10] Benzoylacetonitrile (**1**, 501 mg, 3.45 mmol, 1.0 equiv) and phenylhydrazine (374 mg, 3.46 mmol, 1.0 equiv) were mixed and stirred at reflux for 2.0–3.0 h. After the reaction was completed, the resultant compound **2** was dissolved in CH_2Cl_2 (10 mL) and stirred in ice-bath. Acetyl chloride, benzoxyl chloride, benzyl chloride, or heteroaryl chloride (4.14 mmol, 1.2 equiv)

Scheme 3

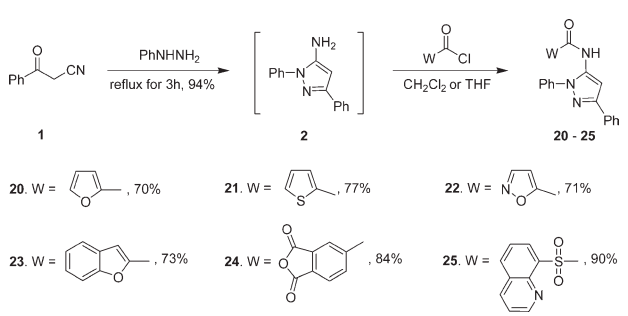


Table 3

The results of the one-pot synthesis of *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)amide derivatives.

Acylation agents	*N*-(1,3-Diphenyl-1*H*-pyrazol-5-yl)amides	Yields (%)
2-Furoyl chloride	**20**	70
2-Thiophenecarbonyl chloride	**21**	77
Isoxazole-5-carbonyl chloride	**22**	71
2-Benzofurancarbonyl chloride	**23**	73
Trimellitic anhydride chloride	**24**	84
Quinoline-8-sulfonyl chloride	**25**	90

in 10 mL of CH_2Cl_2 or THF were slowly added to the reaction mixture at 0°C under N_2, respectively. The reaction was stirred at 0–10°C for 3–4 h. The reaction mixture was washed with water (10 mL) and saturated aqueous $NaHCO_3$ (10 mL × 2). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel or recrystallization to give the corresponding acylation product *N*-(1,3-diphenyl-1*H*-pyrazol-5yl)amide **3**–**25** in 70–90% yields.

N-(1,3-Diphenyl-1H-pyrazol-5-yl)acetamide (3). mp (purified by column chromatography on silica gel) 148–150°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.06 (s, 3 H, Me), 6.95 (s, 1 H, Py-H), 7.32–7.84 (m, 8 H, ArH), 7.81 (dd, 2 H, J = 6.6, 1.7 Hz, ArH), 10.89 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 23.7, 96.4, 124.2, 125.0, 125.7 (2 × CH), 128.1 (2 × CH), 128.6 (2 × CH), 129.8 (2 × CH), 133.0, 136.5, 137.9, 151.8, 167.0; IR (KBr) 3230 (brs, NH), 3061, 1681, 1595, 1560, 1505, 1496, 1468, 1367, 1267, 1072, 954, 763, 692 cm^{-1}; MS *m*/*z* (relative intensity) 277 (M^+, 14), 235 (24), 207 (6), 180 (2), 131 (5), 102 (23), 77 (45), 65 (5), 51 (34), 43 (100); Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.52; H, 5.64; N, 15.49.

2-Phenyl-N-(1,3-diphenyl-1H-pyrazol-5-yl)acetamide (4). mp (purified by column chromatography on silica gel) 132–134°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.69 (s, 2 H, CH_2), 7.05 (s, 1 H, Py-H), 7.09–7.43 (m, 13 H, ArH), 7.83 (d, 2 H, J = 6.6 Hz, ArH), 9.83 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 29.7, 94.9, 123.66 (2 × CH), 124.2, 125.7 (2 × CH), 128.1 (2 × CH), 128.6, 129.5 (4 × CH), 129.6, 129.8 (2 × CH), 132.9, 133.5, 136.5, 137.4, 151.8, 167.3; IR (KBr) 3268 (brs, NH), 3064, 2924, 1700, 1559, 1486, 1458, 1368, 1158, 1073, 954 cm^{-1}; MS *m*/*z* (relative intensity) 353 (M^+, 8), 269 (1), 235 (18), 207 (3), 180 (1), 167 (1), 131 (3), 102 (17), 91 (100), 77 (40), 65 (29), 51 (18); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.01; H, 5.34; N, 11.69.

N-(1,3-Diphenyl-1H-pyrazol-5-yl)benzamide (5). [11] mp (purified by column chromatography on silica gel) 171–173°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.20 (s, 1 H, Py-H), 7.30–7.64 (m, 9 H, ArH), 7.88 (dd, 2 H, J = 6.6, 1.6 Hz, ArH), 7.87 (dd, 2 H, J = 6.6, 1.6 Hz, ArH), 8.06 (dd, 2 H, J = 6.6, 1.6 Hz, ArH), 9.42 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 95.9, 124.9 (2 × CH), 125.8 (2 × CH), 127.1 (2 × CH), 128.2, 128.5 (2 × CH), 129.0 (2 × CH), 129.3, 130.1 (2 × CH), 130.2, 132.5, 133.0, 133.7, 136.7, 137.9, 171.1; IR (KBr) 3275 (brs, NH), 3062, 1645, 1558, 1365, 1258, 1072, 954, 763, 711, 698 cm^{-1}; MS *m*/*z* (relative intensity) 339 (M^+, 74), 234 (2), 206 (2), 105 (100), 77 (45), 51 (5); Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.56; H, 5.24; N, 12.47.

3-Fluoro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (6). [12] mp (recrystallized from CH_2Cl_2/MeOH) 175–177°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.18 (s, 1 H, Py-H), 7.31–7.41 (m, 8 H, ArH), 7.57 (dd, 4 H, J = 4.2, 1.4 Hz, ArH), 7.88 (dd, 2 H, J = 6.6, 1.4 Hz, ArH), 8.21 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 96.4, 114.5, 114.9, 119.4, 119.8, 122.4 (2 × CH), 124.7 (2 × CH), 125.8, 128.6, 128.7 (2 × CH), 130.1 (2 × CH), 130.6, 130.8, 132.9, 135.3, 135.4, 136.3,137.8, 152.0, 160.4, 162.6, 165.3; IR (KBr) 3269 (brs, NH), 3064, 1684, 1589, 1458, 1365, 1290, 1072, 956, 692 cm^{-1}; MS *m*/*z* (relative intensity) 357 (M^+, 15), 356 (15), 206 (2), 123 (100), 101 (18), 95 (35), 77 (17), 51 (10); Anal. Calcd. for $C_{22}H_{16}FN_3O$: C, 73.94; H, 4.51; N, 11.76. Found: C, 73.66; H, 4.46; N, 11.41.

4-Fluoro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (7). [14] mp (recrystallized from CH_2Cl_2/MeOH) 187–189°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.12 (t, 1 H, J = 8.7 Hz, ArH), 7.18 (s, 1 H, Py-H), 7.32–7.48 (m, 4 H, ArH), 7.55–7.58 (m, 4 H, ArH), 7.70–7.77 (m, 2H, ArH), 7.88 (dd, 4 H, J = 7.9, 1.3 Hz, ArH), 8.12 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 96.0, 116.0, 116.4, 124.8 (2 × CH), 125.8 (2 × CH), 128.2, 128.6 (2 × CH), 128.7, 129.4, 129.6, 130.1 (2 × CH), 132.9, 136.5, 137.9, 146.2, 152.1, 162.6; IR (KBr) 3217 (brs, NH), 3045, 1685, 1529, 1504, 1460, 1367, 1286, 1234, 1072, 918, 760, 694 cm^{-1}; MS *m*/*z* (relative intensity) 357 (M^+, 15), 234 (1), 206 (1), 123 (100), 102 (24), 95 (46), 77 (24), 51 (12); Anal. Calcd. for $C_{22}H_{16}FN_3O$: C, 73.94; H, 4.51; N, 11.76. Found: C, 73.75; H, 4.61; N, 11.43.

2-Chloro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (8). [14] mp (purified by column chromatography on silica gel) 147–149°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.14 (s, 1 H, Py-H), 7.22–7.68 (m, 11 H, ArH), 7.70–7.94 (m, 3 H, ArH), 8.64 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 96.2, 125.5 (2 × CH), 125.8 (2 × CH), 127.5, 128.2, 128.6 (2 × CH), 128.9, 129.5 (2 × CH), 130.5, 131.2, 132.0,132.5,132.9,136.6, 137.6, 151.9, 162.7, 168.9; IR (KBr) 3256 (brs, NH), 3066, 1666, 1566, 1502, 1460, 1369, 1263, 1117, 1051, 765, 696 cm^{-1}; MS *m*/*z* (relative intensity) 373 (M^+, 10), 338 (18), 234 (1), 206 (2), 141 (44), 139 (100), 111 (36), 102 (34), 77 (36), 51 (16); Anal. Calcd. for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 4.31; N, 11.24. Found: C, 70.29; H, 4.51; N, 11.14.

3-Chloro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (9). [14] mp (purified by column chromatography on silica gel) 168–170°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.14 (s, 1 H, Py-H), 7.22–7.61 (m, 10 H, ArH), 7.65–7.94 (m, 3 H, ArH), 8.04 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 96.4, 124.8 (2 × CH), 124.9, 125.8 (2 × CH), 127.7, 128.2, 128.6 (2 × CH), 128.8, 130.1 (2 × CH), 130.3, 132.6, 133.7, 134.9, 136.2, 137.8, 152.1, 162.6, 169.6; IR (KBr) 3248 (brs, NH), 3052, 1675, 1573, 1498, 1455, 1431, 1358, 1292, 1252, 1061, 758, 692 cm^{-1}; MS *m*/*z* (relative intensity) 373 (M^+, 15), 343 (1), 234 (2), 206 (3), 141 (33), 139 (100), 111 (46), 102 (32), 77 (33), 75 (27), 51 (19). Anal. Calcd. for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 4.31; N, 11.24. Found: C, 70.41; H, 4.24; N, 11.48.

2-Methyl-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (10). mp (recrystallized from CH_2Cl_2/hexane) 187–189°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3 H, CH_3), 6.82 (s, 1 H, Py-H), 6.91–7.56 (m, 12 H, ArH), 7.86 (dd, 2 H, J = 7.1, 1.0 Hz,

ArH), 10.4 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 19.7, 102.8, 125.2, 125.7, 125.9, 127.3, 128.2, 128.6, 129.1, 129.4, 131.3 (5 × CH), 132.8, 134.3 (2 × C), 137.6, 138.3 (2 × C), 151.8, 172.1; IR (KBr) 3064 (brs, NH), 1718, 1683, 1599, 1549, 1501, 1458, 1383, 1319, 1233, 1140, 1108, 1078, 953, 901, 841 cm^{-1}; MS *m*/*z* (relative intensity) 354 (M^+, 14), 336 (13), 307 (11), 289 (11), 262 (8), 235 (9), 219 (12), 178 (9), 154 (68), 136 (65), 119 (100), 107 (36), 91 (79), 77 (50), 69 (43), 55 (50); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.19; H, 5.47; N, 11.69.

4-Methyl-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (11). [11] mp (recrystallized from CH_2Cl_2/hexane) 181–183°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 2.39 (s, 3 H, CH_3), 7.19 (s, 1 H, Py-H), 7.24–7.65 (m, 12 H, ArH), 7.89 (dd, 2 H, J = 7.3, 1.4 Hz, ArH), 8.12 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 21.5, 95.7, 124.8 (2 × CH), 125.8 (2 × CH), 127.1 (2 × CH), 128.1, 128.6 (2 × CH), 129.6, 129.7 (2 × CH), 130.0 (2 × CH), 130.3, 133.0, 136.8, 137.9, 143.3, 152.0, 163.6; IR (KBr) 3277 (brs, NH), 1654, 1558, 1505, 1459, 1387, 1282, 1074, 1018, 953, 915, 834 cm^{-1}; MS *m*/*z* (relative intensity) 354 (M^+, 6), 233 (2), 205 (2), 177 (1), 167 (1), 130 (3), 119 (100), 102 (19), 91 (56), 77 (19), 65 (8), 51 (5); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.05; H, 5.34; N, 11.71.

3-Trifluoromethyl-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (12). [11] mp (recrystallized from CH_2Cl_2/ hexane) 196–198°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.19 (s, 1 H, Py-H), 7.29–7.49 (m, 4 H, ArH), 7.56–7.58 (m, 4 H, ArH), 7.71 (d, 2 H, J = 8.7 Hz, ArH), 7.82–7.91 (m, 4 H, ArH), 8.21 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 96.4, 124.0, 124.7 (2 × CH), 125.8 (2 × CH), 126.1, 127.6 (2 × CH), 128.3, 128.6 (2 × CH), 128.6, 128.8, 129.4, 130.1 (2 × CH), 130.5, 131.1, 133.8, 136.1, 1 137.8, 152.1, 162.6; IR (KBr) 3205 (brs, NH), 3051, 1658, 1593, 1556, 1537, 1498, 1460, 1367, 1303, 1168. 1066, 854, 758, 688 cm^{-1}; MS *m*/*z* (relative intensity) 407 (M^+, 30), 377 (2), 234 (4), 206 (4), 173 (100), 145 (54), 131 (6), 102 (38), 77 (38), 51 (15); Anal. Calcd. for $C_{23}H_{16}F_3N_3O$: C, 67.81; H, 3.96; N, 10.31. Found: C, 68.12; H, 4.10; N, 10.21.

2-Methoxy-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (13). mp (purified by column chromatography on silica gel) 196–198°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.52 (s, 3 H, Me), 6.91 (d, 1 H, J = 6.9 Hz, ArH), 7.10 (t, 1 H, J = 6.4 Hz, ArH), 7.13 (s, 1 H, Py-H), 7.33–7.89 (m, 8 H, ArH), 7.91 (dd, 2 H, J = 6.7, 1.3 Hz, ArH), 8.43 (dd, 1 H, J = 6.7, 1.3 Hz, ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 55.6, 94.6, 111.4, 120.1, 121.8, 125.8 (2 × CH), 125.9 (2 × CH), 128.0, 129.8 (2 × CH), 132.7 (2 × CH), 133.1, 133.9, 135.1, 136.7, 138.1, 152.1, 157.2, 161.2; IR (KBr) 3306 (brs, NH), 3062, 2924, 1674, 1598, 1570, 1496, 1483, 1371, 1296, 1244, 1163. 1018, 759, 694 cm^{-1}; MS *m*/*z* (relative intensity) 369 (M^+, 2), 206 (1), 135 (100), 120 (3), 102 (15), 92 (25), 77 (49), 63 (7), 51 (11); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 74.78; H, 5.18; N, 11.37. Found: C, 74.98; H, 5.43; N, 11.48.

3-Methoxy-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (14). [11] mp (purified by column chromatography on silica gel) 175–177°C (lit. [11] mp 177–179°C); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.84 (s, 3 H, CH_3), 7.19 (s, 1 H, Py-H), 7.28–7.72 (m, 12 H, ArH), 7.88 (d, 2 H, J = 8.0 Hz, ArH), 8.21 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 55.5, 96.1, 112.6, 118.6, 118.7, 124.4 (2 × CH), 124.8, 125.9 (2 × CH), 128.2, 128.6 (2 × CH), 129.6, 130.0 (2 × CH), 133.0, 134.6, 136.6, 137.9, 152.0, 160.1, 163.7; IR (KBr) 3257 (brs, NH), 3066, 2843, 1667, 1597, 1560, 1502, 1460, 1369, 1284, 1230, 1041, 769, 702 cm^{-1}; MS *m*/*z* (relative intensity) 369 (M^+, 1), 234 (2), 206 (2), 135 (100), 107 (27), 92 (25), 77 (52), 64 (13), 51 (12); Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 74.78; H, 5.18; N, 11.37. Found: C, 74.56; H, 5.42; N, 11.61.

2,4-Difluoro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (15). mp (recrystallized from CH_2Cl_2/hexane) 162–164°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 6.74–6.89 (m, 1 H, ArH), 7.92–7.10 (m, 1 H, ArH), 7.26 (s, 1 H, Py-H), 7.31–7.51 (m, 4 H, ArH), 7.55–7.59 (m, 4 H, ArH), 7.88 (dd, 2 H, J = 6.7, 1.4 Hz, ArH), 8.14–8.39 (m, 1 H, ArH), 8.74 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 95.5, 104.0, 104.5, 105.0, 112.9, 113.3, 116.7, 116.9, 117.0, 125.1 (2 × CH), 125.8 (2 × CH), 128.2, 128.6 (2 × CH), 128.8, 130.0 (2 × CH), 132.9, 134.2, 134.4, 136.7, 152.0, 158.2, 164.3; IR (KBr) 3423 (brs, NH), 3061, 1693, 1614, 1570, 1494, 1289, 1111, 970, 766, 694 cm^{-1}; MS *m*/*z* (relative intensity) 376 (M^+, 100), 358 (3), 336 (3), 304 (3), 282 (5), 262 (3), 234 (6), 219 (4), 207 (5), 154 (5), 141 (98), 113 (7), 92 (4), 77 (12), 57 (4). Anal. Calcd. for $C_{22}H_{15}F_2N_3O$: C, 70.39; H, 4.03; N, 11.19. Found: C, 70.64; H, 4.23; N. 11.46.

3-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (16, CDPPB). [11,14,15] mp (purified by column chromatography on silica gel) 207–208°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 6.90 (s, 1 H, Py-H), 7.26–7.45 (m, 11 H, ArH), 7.79–7.92 (m, 3 H, ArH), 8.86 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 100.5, 112.7, 117.1, 124.3 (2 × CH), 125.3 (2 × CH), 128.3 (2 × CH + CH), 128.7, 129.0, 129.5 (2 × CH), 129.6, 131.2, 131.8, 134.4, 135.3, 135.7, 138.6, 151.7, 164.3; IR (KBr) 3309 (brs, NH), 3068, 2922, 2852, 2232 (s, C≡N), 1689, 1654, 1560, 1498, 1458, 1363, 1292, 1190, 1072, 916 cm^{-1}; MS *m*/*z* (relative intensity) 364 (M^+, 59), 234 (11), 207 (6), 147 (8), 130 (100), 102 (49), 91 (2), 77 (15), 64 (1), 51 (8); Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 75.49; H, 4.65; N, 15.18.

4-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (17). [11] mp (purified by column chromatography on silica gel) 207–209°C (lit. [11] mp 207–208°C); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.02 (s, 1 H, Py-H), 7.35–7.49 (m, 6 H, ArH), 7.66–7.72 (m, 3 H, ArH), 7.90–7.95 (m, 3 H, ArH), 8.12–8.20 (m, 2 H, ArH), 8.27 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 99.7, 112.7, 117.7, 124.0 (2 × CH), 125.3 (2 × CH), 127.7, 127.9, 128.6 (2 × CH), 129.9 (2 × CH), 129.9, 131.3, 132.1, 133.4, 134.9, 135.3, 136.8, 139.2, 150.7, 163.8; IR (KBr) 3250 (brs, NH), 3087, 2308 (s, C[tbond]N), 1686, 1578, 1501, 1296, 769, 699 cm^{-1}; MS *m*/*z* (relative intensity) 364 (M^+, 100), 335 (6), 262 (3), 234 (12), 206 (7), 130 (98), 102 (44), 77 (16), 51 (5); Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 76.12; H, 4.42; N, 15.14.

2-Nitro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (18). [11] mp (recrystallized from CH_2Cl_2/hexane) 229–231°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 7.00 (s, 1 H, Py-H), 7.36–7.89 (m, 12 H, ArH), 8.08–8.26 (m, 3 H, ArH + NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 100.1, 124.4 (2 × CH), 124.8, 125.7 (2 × CH), 128.6, 129.2 (2 × CH), 129.7, 130.2 (2 × CH), 132.0, 133.1, 134.6, 135.6, 137.0, 138.9, 144.4, 147.0, 150.8, 167.8; IR (KBr) 3261 (brs, NH), 3061, 1718, 1533, 1502, 1354, 1249, 757, 690 cm^{-1}; MS *m*/*z* (relative intensity) 385 (M^+, 66), 370 (27), 339 (22), 323 (10), 307 (45), 289 (39), 285 (18), 262

(15), 234 (32), 206 (22), 178 (31), 165 (48), 154 (100); Anal. Calcd. for $C_{22}H_{16}N_4O_3$: C, 68.74; H, 4.20; N, 14.58. Found: C, 68.81; H, 4.15; N, 14.81.

4-Nitro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (19). [11] mp (recrystallized from CH_2Cl_2/hexane) 221–223°C (lit. [11] mp 221–223°C); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 6.95 (s, 1 H, Py-H), 7.21–7.89 (m, 9 H, ArH + NH), 8.18 (d, 2 H, J = 6.5 Hz, ArH), 8.34 (d, 2 H, J = 6.5 Hz, ArH), 8.39–8.54 (m, 1 H, ArH) 9.64 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 100.1, 122.9 (2 × CH), 123.0 (2 × CH), 124.7 (2 × CH), 126.9, 127.5, 128.1 (2 × CH), 128.6 (2 × CH), 128.8 (2 × CH), 132.3, 136.1, 138.3, 138.5, 150.5, 162.0, 164.2; IR (KBr) 3250 (brs, NH), 3087, 1686, 1578, 1501, 1296, 769, 699 cm^{-1}; MS m/z (relative intensity) 364 (M^+, 100), 335 (6), 262 (3), 234 (12), 206 (7), 130 (98), 102 (44), 77 (16), 51 (5); Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found: C, 76.12; H, 4.42; N, 15.14.

N-(2-Furancarbonyl)-1,3-diphenyl-5-amino-1H-pyrazole (20). mp (purified by column chromatography on silica gel) 143–145°C; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 6.54 (dd, 1 H, J = 3.6, 1.7 Hz, Furan-H), 7.18 (s, 1 H, Py-H), 7.25 (d, 1 H, J = 3.6 Hz, Furan-H), 7.32–7.51 (m, 6 H), 7.56–7.60 (m, 3 H), 7.89 (dd, 2 H, J = 8.0, 1.3 Hz, ArH), 8.34 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 95.4, 112.8, 116.4, 124.7 (2 × CH), 125.8 (2 × CH), 128.1, 128.6 (3 × CH), 130.0 (2 × CH), 133.0, 136.0, 137.9, 144.8, 146.8, 152.0, 154.2; IR (KBr) 3400 (brs, NH), 3277, 3138, 3061, 1672, 1587, 1556, 1537, 1500, 1471, 1415, 1365, 1288, 1228, 1157, 1074, 1012, 954, 883, 763, 692 cm^{-1}; MS m/z (relative intensity) 330 (M^+, 100), 315 (9), 262 (11), 236 (14), 221 (16), 207 (12), 154 (28), 121 (42), 119 (58), 95 (95), 79 (57), 69 (100), 55 (99); HRMS Calcd. for $C_{20}H_{15}N_3O_2$: 329.1164, Found 329.1167.

N-(2-Thiophenecarbonyl)-1,3-diphenyl-5-amino-1H-pyrazole (21). [14] ^{1}H-NMR ($CDCl_3$) δ 7.04 (dd, 1 H, J = 4.9, 3.8 Hz, thiophene-H), 7.13 (s, 1 H, Py-H), 7.36–7.66 (m, 10 H, ArH), 7.86–7.90 (m, 2 H, thiophene-H), 7.90 (b, 1 H, NH); ^{13}C-NMR ($CDCl_3$) δ 96.0, 124.7 (2 × CH), 125.8 (2 × CH), 128.1, 128.2, 128.6 (2 × CH + CH), 129.2, 130.1 (2 × CH), 131.8, 132.9, 136.2, 137.4, 137.8, 152.0, 158.1. IR (KBr) 3061 (brs, NH), 2922, 2851, 1654, 1554, 1537, 1504, 1365, 1283, 1214, 1171, 1065, 1038, 888 cm^{-1}; MS m/z (relative intensity) 345 (M^+, 42), 236 (4), 207 (3), 111 (100), 102 (11), 83 (2), 77 (10), 51 (3); HRMS Calcd. for $C_{20}H_{15}N_3OS$: 345.0936, Found 345.0939.

N-Isoxazole-5-carbonyl-1,3-diphenyl-5-amino-1H-pyrazole (22). mp (purified by column chromatography on silica gel) 153–155°C; ^{1}H-NMR ($CDCl_3$) δ 7.04 (d, 1H, J = 1.8 Hz, Isoxazole-H), 7.19 (s, 1 H, Py-H), 7.35–7.58 (m, 8 H, ArH), 7.87 (dd, 2 H, J = 6.6, 1.4 Hz, ArH), 8.35 (d, 1 H, J = 1.8 Hz, Isoxazole-H), 8.51 (b, 1 H, NH); ^{13}C-NMR ($CDCl_3$) δ 96.2, 107.9, 124.7 (2 × CH), 125.8 (2 × CH), 128.3, 128.6 (2 × CH), 128.9, 130.2 (2 × CH), 132.7, 135.0, 137.5, 151.4, 151.7, 152.0, 161.5; IR (KBr) 3399 (brs, NH), 3306, 3151, 3085, 1700, 1559, 1498, 1457, 1418, 1364, 1330, 1270, 1204, 1162, 1073, 1018, 825 cm^{-1}; MS m/z (relative intensity) 331 (M^+, 62), 262 (15), 236 (11), 203 (11), 169 (12), 154 (22), 121 (21), 119 (41), 95 (74), 79 (53), 69 (96), 55 (100); HRMS Calcd. for $C_{19}H_{14}N_4O_2$: 330.1117, Found 330.1187; Anal. Calcd. for $C_{19}H_{14}N_4O_2$: C, 69.68; H, 4.27; N, 16.96. Found: C, 69.58; H, 4.15; N, 16.86.

N-(2-Benzofurancarbonyl)-1,3-diphenyl-5-amino-1H-pyrazole (23). mp (purified by column chromatography on silica gel) 164–166°C; ^{1}H-NMR ($CDCl_3$) δ 7.24–7.72 (m, 14 H, ArH), 7.90 (dd, 2 H, J = 8.1, 1.6 Hz, ArH), 8.62 (b, 1 H, NH); ^{13}C-NMR ($CDCl_3$) δ 95.8, 111.9, 112.5, 123.0, 124.2, 124.7 (2 × CH), 125.8 (2 × CH), 127.3, 127.5, 127.7 (2 × CH + CH), 128.2, 128.6 (2 × CH), 130.1, 132.9, 135.8, 137.8, 147.2, 152.1, 154.8; IR (KBr) 3061 (brs, NH), 2922, 2850, 1554, 1504, 1365, 1282, 1170, 1142 cm^{-1}; MS m/z (relative intensity) 379 (M^+, 47), 351 (16), 246 (4), 233 (2), 206 (3), 180 (1), 145 (100), 131 (4), 102 (15), 89 (33), 77 (14), 63 (5), 51 (4); HRMS Calcd. for $C_{24}H_{17}N_3O_2$: 379.1321, Found 379.1318.

N-(5-Isobenzofurancarbonyl)-1,3-diphenyl-5-amino-1H-pyrazole (24). ^{1}H-NMR ($CDCl_3$) δ 6.78 (s, 1 H, Py-H), 6.95 (s, 1 H, isobenzofurane-H), 7.27–7.50 (m, 10 H, ArH), 7.72–7.89 (m, 3 H, ArH), 8.06 (d, 1 H, J = 6.4 Hz, isobenzofurane-H), 8.5 (b, 1 H, NH); ^{13}C-NMR ($CDCl_3$) δ 97.6, 104.1, 122.7, 124.4 (2 × CH), 124.8, 125.7 (2 × CH), 128.5, 128.7, 129.4 (2 × CH + CH), 129.8, 130.0, 131.8, 132.4, 133.9, 135.7, 137.9, 139.4, 151.9, 152.1 165.0; IR (KBr) 3062 (brs, NH), 2924, 1735, 1674, 1558, 1497, 1458, 1367, 1087 cm^{-1}; MS m/z (relative intensity) 409 (M^+, 4), 364 (100), 336 (5), 313 (6), 262 (4), 234 (12), 206 (12), 180 (5), 131 (4), 103 (10), 91 (9), 77 (27), 55 (6); Anal. Calcd. for $C_{24}H_{15}N_3O_4$; C, 70.41; H, 3.69; N, 10.26. Found: C, 70.34; H, 3.57; N, 10.22.

N-Quinoline-8-sulfonyl-1,3-diphenyl-5-amino-1H-pyrazole (25). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 6.38 (s, 1 H, Py-H), 7.25–7.68 (m, 12 H, ArH + quinoline-H), 8.01 (dd, 1 H, J = 8.4, 1.4 Hz, quinoline-H), 8.20 (dd, 1 H, J = 8.4, 1.7 Hz, quinoline-H), 8.35 (dd, 1 H, J = 7.3, 1.4 Hz, quinoline-H), 8.47 (dd, 1 H, J = 4.3, 1.7 Hz, quinoline-H), 10.2 (b, 1 H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 96.4, 122.3, 123.7, 125.2 (2 × CH), 125.5 (2 × CH), 125.7, 127.4, 128.1, 128.3, 128.5 (2 × CH), 129.3 (2 × CH), 131.5, 132.6, 134.0, 135.0, 136.4, 137.1, 137.8, 151.0, 151.4; IR (KBr) 3450 (brs, NH), 3061, 1597, 1544, 1502, 1460, 1379, 1173, 1146, 766, 696 cm^{-1}; MS m/z (relative intensity) 427 (M^+, 86), 395 (59), 337 (13), 289 (13), 281 (20), 235 (59), 221 (23), 207 (28), 194 (15), 185 (46), 176 (38), 165 (32), 154 (80), 109 (86), 83 (100), 71 (100), 57 (100); HRMS Calcd. for $C_{24}H_{18}N_4O_2S$: 427.1150, Found 427.1123; Anal. Calcd. for $C_{24}H_{18}N_4O_2S$: C, 67.59; H, 4.25; N, 13.14. Found: C, 67.25; H, 4.56; N, 12.97.

Acknowledgment. The authors are grateful to the China Medical University (CMU95-191) for financial support.

REFERENCES AND NOTES

[1] Cralg, P. N. In Comprehensive Medicinal Chemistry; Drayton, C. J., Ed.; Pergamon Press: New York, 1991; Vol. 8.

[2] Southon, I. W.; Buckinggham, J. In Dictionary of Alkaloids; Saxton, J. E., Ed.; Chapman and Hall: London, 1989.

[3] Negwer, M. In Organic-Chemical Drugs and Their Synonyms (An International Survey), 7th ed.; Akademie Verlag GmbH: Berlin, 1994.

[4] For the biological activities of pyrazole derivatives, see: Singh, P.; Paul, K.; Holzer, W. Bioorg Med Chem 2006, 6, 5061 and references cited therein.

[5] Lindsley, C. W.; Wisonoski, D. D.; Leister, W. H.; O'Brien, J. A.; Lemaire, W.; Williams, D. L., Jr.; Burno, M.; Sur, C.; Kinney, G. G.; Pettibone, D. J.; Tiller, P. R.; Smith, S.; Duggan, M. E.; Hartman, G. D.; Conn, P. J.; Huff, J. R. J Med Chem 2004, 47, 5825.

[6] Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.;

Varney, M. A.; Prasit, P.; Cosford, N. D. P. J Med Chem 2004, 47, 4645.

[7] Poon, S. F.; Eastman, B. W.; Chapman, D. F.; Chung, J.; Cramer, M.; Holtz, G.; Cosford, N. D. P.; Smith, N. D. Bioorg Med Chem Lett 2004, 14, 5477.

[8] Conn, P. J.; Pin, J. P. Annu Rev Pharmacol Toxicol 1997, 37, 205.

[9] Marino, M. J.; Conn, P. J. Curr Opin Pharmacol 2006, 6, 98.

[10] Ritzen, A.; Mathiesen, J. M.; Thomsen, C. Basic Clin Pharmacol Toxicol 2005, 97, 202.

[11] de Paulis, T.; Hemstapat, K.; Chen, Y.; Zhang, Y.; Saleh, S.; Alagille, D.; Baldwin, R. M.; Tamagnan, G. D.; Conn, P. J. J Med Chem 2006, 49, 3332.

[12] Elnagdi, M. H.; Khalifa, M. A. E. J Heterocycl Chem 1981, 18, 877.

[13] For the synthesis of pyrazole derivatives, see: (a) Elguero, J. In Comprehensive Heterocyclic Chemistry; Katrizky, A., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, p 277; (b) Elguero, J. In Comprehensive Heterocyclic Chemistry II; Shinkai, I., Ed.; Elsevier: Oxford, 1996; Vol. 3, p 3; (c) Elguero, J. In Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds; Katrizky, A. R., Rees, C. W., Ed.; Pergamon: New York, NY, 1996; Vol. 5, p 111.

[14] Pinkerton, A. B.; Huang, D.; Cube, R. V.; Hutchinson, J. H.; Struthers, M.; Ayala, J. M.; Vicario, P. P.; Patel, S. R.; Wisniewski, T.; DeMartino, J. A.; Vernier, J.-M. Bioorg Med Chem Lett 2007, 17, 807.

[15] Our spectroscopic data are consistent with the literature: Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. J Org Chem 2004, 69, 5578.