Microwave-Assisted Direct Amidation of Ethyl 1-Phenyl-5-hydroxy-1*H*-pyrazole-4-carboxylate

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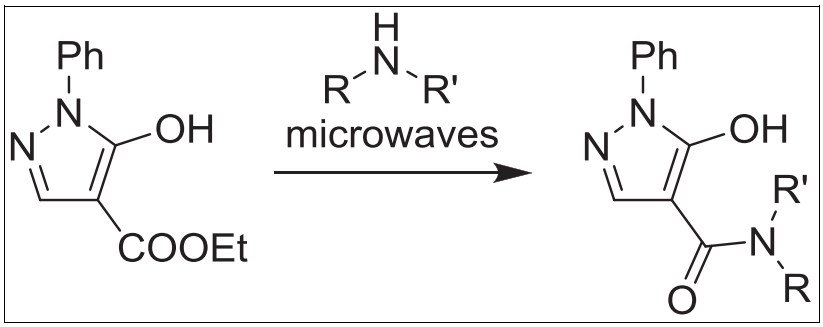


Microwave-assisted treatment of ethyl 5-hydroxy-1-phenyl-1*H*-pyrazole-4-carboxylate with excess primary aliphatic amines in 1-propanol at 140°C and with excess pyrrolidine or piperidine in 2-methoxyethanol at 180°C produced the corresponding carboxamides in good yields.

INTRODUCTION

Pyrazoles [1] are important heterocyclic systems because numerous pyrazole derivatives found widespread applications in medicinal chemistry, catalysis, and material science [2]. Among pyrazoles, hydroxypyrazoles or pyrazolones and their saturated analogs are probably the most important and useful group of pyrazole derivatives. Typical examples of important pyrazolone derivatives include antipyrine (**A**), phenidone (**B**), photographic couples **C**, and azo dyes **D** (Fig. 1) [3].

Despite the fact that this chemistry started more than a century ago, the interest in pyrazolones is still continuing. Moreover, the number of publications on pyrazolone increased again in the last decade, mostly because of the preparation of novel biologically active derivatives [4] and dyes [5] and also because of their recent applications in asymmetric organocatalysis [6].

Because amide linkages are present in many biologically active molecules and natural products, formation of amide bond belongs among the most frequently used transformations in organic, bioorganic, and biochemistry. There are numerous synthetic methods for the preparation of amides, and most of them are based on amidation of the most reactive carboxylic acid derivatives, such as acid chlorides, anhydrides, active esters, and imidazolides. In practice, amidation is usually carried out as a two-step one-pot process starting with *in situ* activation of carboxylic acid, followed by treatment of the reactive intermediate with amine [7]. Because carboxylic acids are often available by hydrolysis of more readily available alkyl esters, direct amidation of alkyl esters represents a valuable shortcut to amides. However, this transformation is usually a slow process requiring prolonged heating with excess amine to achieve satisfactory conversion within a reasonable time [7,8]. Nowadays, several methods for direct amidation of esters are known, most of them utilizing acid or base catalysis combined with microwave acceleration of the process [9].

Recently, a part of our research has been focused on the synthesis of functionalized 3-pyrazolidinones [10] and 3-pyrazolones [11]. Within the context of our work on heterocyclic analogs of amino acids and peptides, we also reported a three-step synthesis of 1-substituted alkyl 5-hydroxy-1*H*-pyrazole-4-carboxylates from diethyl malonate (**1**) [12]. In continuation, we were interested in the preparation of the corresponding carboxamides, because their calculated physicochemical properties showed promising drug-likeness, meaning that they could be easily available and interesting building blocks for pharmaceutical applications. However, an attempted base-catalyzed hydrolysis of ethyl 5-hydroxy-1*H*-pyrazole-4-carboxylate (**3**) failed, and, consequently, we were prompted to find out another way to access the desired carboxamides. As the result of this study, we report the synthesis of 5-hydroxy-1*H*-pyrazole-4-carboxamides **7a–q** via a microwave-assisted direct amidation of the corresponding ethyl 5-hydroxy-1*H*-pyrazole-4-carboxylate (**3**).

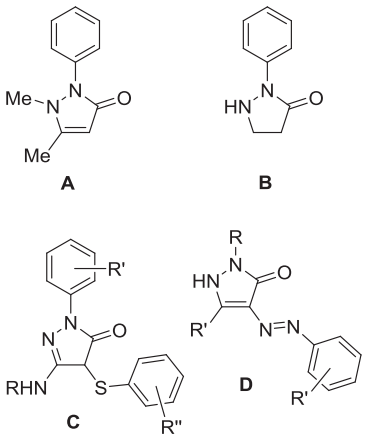


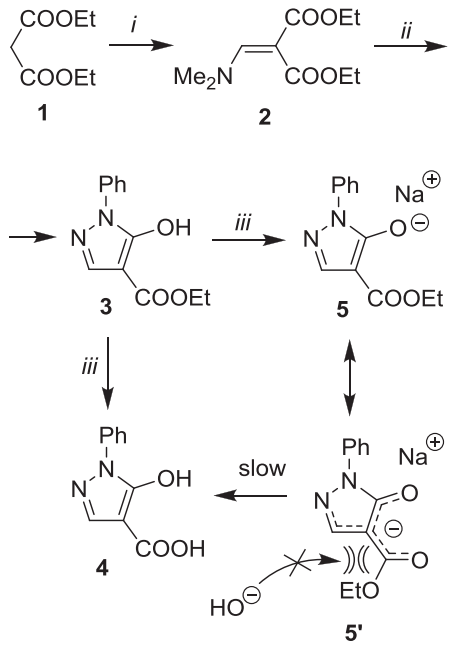
Figure 1. Examples of important pyrazolones.

RESULTS AND DISCUSSION

First, the central intermediate **3** was prepared in two steps from diethyl malonate (**1**) utilizing a one-pot simplified literature procedure for the preparation of closely related compounds [12]. Treatment of **1** with *N*, *N*-dimethylformamide dimethylacetal in refluxing toluene for 1.5 h gave the intermediate enaminone **2**, which was directly reacted further with phenylhydrazine hydrochloride in refluxing 1-propanol to afford **3** in 91% yield (Scheme 1).

To obtain the desired carboxamides, we intended to carry out a base-catalyzed hydrolysis of the ester **3** into 5-hydroxy-1-phenyl-1*H*-pyrazole-4-carboxylic acid (**4**),

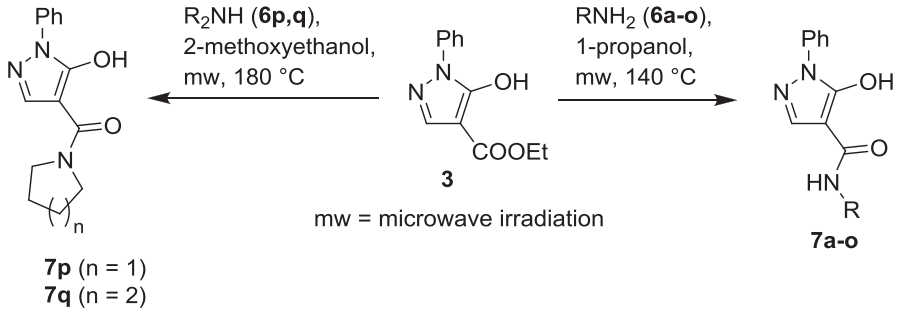
Scheme 1. Reaction conditions: (i) DMFDMA, toluene, reflux; (ii) $PhNHNH_2 \cdot HCl$, 1-propanol, reflux; (iii) 2*M* aq NaOH, MeOH, 50°C.



followed by conventional amidation of **4** using bis (pentafluorophenyl) carbonate as the activating reagent [11c,13]. Although hydrolysis of **3** into **4** by treatment with sodium hydroxide in refluxing ethanol has already been reported by Claisen and Haase more than a century ago [14], this reaction did not work well in our hands. For example, treatment of **3** with aqueous sodium hydroxide in methanol at 50°C for 12 h, followed by cooling to room temperature, and acidification of the reaction mixture furnished mostly the unreacted starting material **3**. Although surprising at first glance, such resistance of the ester **3** toward basic hydrolytic conditions is explainable by deprotonation of the phenolic OH group leading to the phenolate-type anion **5** with widely delocalized negative charge as represented by the resonance structure **5′**, where electronic repulsion prevents the approach of the nucleophile to the carbonyl group (Scheme 1).

The aforementioned experiment showed that the hydrolysis of the ester group was difficult and that trying another amidation method would be more productive thing to do in order to obtain the desired carboxamides. Inspired by numerous examples of successful applications of microwaves in condensation reactions [9,15], we decided to try out a direct, microwave-assisted amidation of the pyrazole ester **3**. The first preliminary experiment was performed by reacting **3** with 5 equiv of 1-butylamine (**6b**) in 1-propanol at 150°C for 30 min under microwave irradiation ($P = 300$ W). Under these reaction conditions, a complete conversion of the starting material **3** into the corresponding carboxamide **7b** took place according to TLC. In spite of this beginner's luck, the screening for optimal reaction conditions was performed by reacting **3** with 2–5 equiv of 1-butylamine (**6b**) in 1-propanol at 120–150°C for 10–30 min. First, it has been established that microwave-assisted heating ($P = 300$ W) of **3** with 5 equiv of 1-butylamine (**6b**) in 1-propanol at 140°C for 20 min could be considered as safe to achieve a complete conversion into the carboxamide **7b**. Either shortening of the reaction time to 10 min, or lowering excess amine **6** to 3 equiv, or lowering the temperature to 120°C resulted in an incomplete conversion according to TLC. The same was observed when the reaction of **3** with 1-butylamine (**6b**) was performed by conventional heating. The use of basic amidation promoters, such as K_2CO_3, Cs_2CO_3, and DBU, did not improve the result. Amidation of **3** with neat 1-butylamine (**6b**) at 140°C resulted in an uncontrolled explosive opening of the reaction vessel caused by the exceeded pressure limit (20 bar). This accident clearly indicated that this method is not suitable for neat amidation with volatile aliphatic amines. To avoid such accidents, final screening was performed in water, 1,4-dioxane, and DMF (i.e., in solvents with bp $\geq$ 90°C). Reaction of **3** with 1-butylamine (**6b**) in water showed no conversion, whereas in 1,4-dioxane, the conversion

Scheme 2



was incomplete. When **3** was reacted with 1-butylamine (**6b**) in DMF at 140°C, *N*-butylformamide was obtained as the product, while the starting material did not react. Thus, DMF acted also as a formylating reagent and not only as a solvent. Finally, a series of amidations of the ester **3** with aliphatic primary amines **6a–o** under the optimized conditions (1-propanol, 5 equiv of **6**, $P = 300$ W, $T = 140$°C, $t = 20$ min) were performed. All these reactions proceeded smoothly to give the corresponding carboxamides **7a–o** in 30–91% yields. On the other hand, amidation of **3** with pyrrolidine (**6p**) as the representative secondary amine was not successful under the aforementioned reaction conditions. This was not really surprising, because acylations of the secondary amines are usually substantially slower because of pronounced steric hindrance by the two alkyl groups. Nevertheless, the treatment of **3** with **6p** in 2-methoxyethanol at 180°C did produce the corresponding amide **7p** in 50% yield. Similarly, the amidation of **3** with piperidine (**6q**) was also successful under these conditions. Unfortunately, attempts to carry out the amidation of **3** with some other secondary amines, such as morpholine, diethylamine, and dibenzylamine, failed (Scheme 2, Table 1).

Table 1

Experimental data on carboxamides **7a–q**.

Compound	R	Yield (%)
6a, **7a**	1-Propyl	87
6b, **7b**	1-Butyl	85
6c, **7c**	1-Pentyl	86
6d, **7d**	1-Hexyl	52
6e, **7e**	Benzyl	70
6f, **7f**	4-Methoxybenzyl	91
6g, **7g**	2-Phenylethyl	63
6h, **7h**	3-Phenylprop-1-yl	64
6i, **7i**	Cyclopropyl	30
6j, **7j**	Cyclobutyl	72
6k, **7k**	Cyclopentyl	69
6l, **7l**	Cyclohexyl	75
6m, **7m**	2-Methoxyethyl	77
6n, **7n**	2-Hydroxyethyl	61
6o, **7o**	3-Hydroxypropyl	58
6p, **7p**	$-(CH_2)_4-$	50
6q, **7q**	$-(CH_2)_5-$	46

The structures of all novel compounds **7a–q** were determined by spectroscopic methods (^{1}H nmr, ^{13}C nmr, ir, ms, and hrms) and by elemental analyses for C, H, and N. Spectral data for compounds **7a–q** were in agreement with the data for the related pyrazole derivatives [1,11,12].

CONCLUSION

In conclusion, a simple microwave-assisted direct amidation of ethyl 1-phenyl-5-hydroxy-1*H*-pyrazole-4-carboxylate (**3**) was developed. This is, to the best of our knowledge, the shortest and the easiest way to prepare 5-hydroxypyrazole-4-carboxamides **7**, because the ester **3** is somewhat reluctant to base-catalyzed hydrolysis to the carboxylic acid **4**. So far, the scope of this method is limited to primary aliphatic amines and most reactive cyclic secondary amines, such as pyrrolidine and piperidine, and to the ester **3** as the model substrate. Most probably, this method could also be applied for the preparation of related (het)arenecarboxamides, especially when esters are more easily available than the corresponding carboxylic acids.

EXPERIMENTAL

General methods. Melting points were determined on a Kofler micro hot stage (Leica Microsystems GmbH, Wetzlar, Germany). The nmr spectra were obtained on a Bruker Avance III UltraShield 500 plus at 500 MHz for ^{1}H and at 126 MHz for ^{13}C nuclei, using deuteriochloroform and DMSO-d_6, with TMS as the internal standard, as solvents (Bruker Corporation, Billerica, MA). Mass spectra were recorded on an Agilent 6224 accurate mass TOF LC/MS (Agilent Technologies Inc., Santa Clara, CA) and the ir spectra on a PerkinElmer Spectrum BX FTIR spectrophotometer (Perkin-Elmer Inc., Waltham, MA). Microanalyses were performed on a PerkinElmer CHN Analyzer 2400 II (Perkin-Elmer Inc., Waltham, MA). Microwave irradiations were performed on a CEM Discover laboratory microwave oven (CEM Corporation, Matthews, NC). Flash column chromatography was performed on a silica gel (Fluka, silica gel 60, particle size 0.035–0.070 mm) (Fluka, Buchs, Switzerland).

Amines **6a–q** are commercially available (Sigma-Aldrich) (Sigma-Aldrich, St. Louis, MO). Ethyl 5-hydroxy-1-phenyl-1*H*-pyrazole-4-carboxylate (**3**) was prepared following the literature procedure [5].

General procedure for the microwave-assisted amidation of ethyl 5-hydroxy-1-phenyl-1*H*-pyrazole-4-carboxylate (3). A mixture of ester **3** (0.232 g, 1 mmol), 1-propanol (2 mL), and amine **6** (5 mmol) was stirred in a sealed vessel under microwave irradiation ($P = 300$ W) at 140°C (P ~ 10 bar) for 20 min. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with 1*M* aqueous sodium hydrogen sulfate (2 × 20 mL). The combined organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated *in vacuo* to give **7**.

The following compounds were prepared in this manner.

5-Hydroxy-1-phenyl-N-propyl-1H-pyrazole-4-carboxamide (7a). This compound was prepared from **3** (0.232 g, 1 mmol) and 1-propylamine (**6a**) (0.296 g, 5 mmol). Yield: 0.213 g (87%) of a white solid; mp 125–130°C; ir (potassium bromide): 3272, 1693, 1636, 1595, 1576, 1533, 1499, 1459, 1425, 1323, 1281, 1197, 1084, 962 cm^{-1}. ^1H nmr (DMSO-d_6): 0.99 (3H, t, $J = 7.1$ Hz, CH_2CH_3), 1.64 (2H, br sextet, $J = 7.1$ Hz, CH_2CH_3), 3.23 (2H, br t, $J = 7.1$ Hz, CH_2NH), 7.33 (1H, br t, $J = 7.4$ Hz, *p*-Ph), 7.51 (2H, br t, $J = 7.6$ Hz, *m*-Ph), 7.82 (2H, br d, $J = 7.8$ Hz, *o*-Ph), 8.13 (1H, s, 3-H), 8.43 (1H, br s, NH), 10.94 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 11.4, 22.6, 39.6, 104.5, 126.4, 129.2, 129.5, 129.5, 137.5, 160.3, 161.9. ms: *m/z* 246 (MH^+); hrms Calcd for $C_{13}H_{16}N_3O_2$: *m/z* 246.1243 (MH^+); found: *m/z* 246.1250 (MH^+). *Anal*. Calcd for $C_{13}H_{15}N_3O_2$ (245.28): C, 63.66; H, 6.16; N, 17.13. Found: C, 63.57; H, 6.36; N, 17.01.

N-Butyl-5-hydroxy-1-phenyl-1H-pyrazole-4-carboxamide (7b). This compound was prepared from **3** (0.232 g, 1 mmol) and 1-butylamine (**6b**) (0.366 g, 5 mmol). Yield: 0.221 g (85%) of a white solid; mp 100–104°C; ir (potassium bromide): 3301, 1688, 1635, 1595, 1577, 1497, 1458, 1425, 1313, 1292, 1199, 1085, 1060, 964 cm^{-1}. ^1H nmr (deuteriochloroform): 0.93 (3H, t, $J = 7.1$ Hz, $CH_2CH_2CH_3$), 1.39 (2H, br sextet, $J = 7.1$ Hz, $CH_2CH_2CH_3$), 1.55 (2H, br sextet, $J = 7.1$ Hz, $CH_2CH_2CH_3$), 3.38 (2H, br q, $J = 7.1$ Hz, CH_2NH), 6.27 (1H, br s, NH), 7.25–7.51 (3H, m, 3H of Ph), 7.63 (1H, s, 3-H), 7.70–7.80 (2H, m, 2H of Ph), 8.92 (1H, br s, OH). ^{13}C nmr (deuteriochloroform): 13.8, 20.2, 31.8, 39.0, 104.7, 119.0, 121.1, 127.0, 129.3, 129.6, 129.7, 135.7, 161.0, 163.6. ms: *m/z* 260 (MH^+); hrms Calcd for $C_{14}H_{18}N_3O_2$: *m/z* = 260.1399 (MH^+); found: *m/z* 260.1402 (MH^+). *Anal.* Calcd for $C_{14}H_{17}N_3O_2$ (259.30): C, 64.85; H, 6.61; N, 16.20. Found: C, 64.62; H, 6.75; N, 15.84.

5-Hydroxy-N-pentyl-1-phenyl-1H-pyrazole-4-carboxamide (7c). This compound was prepared from **3** (0.232 g, 1 mmol) and 1-pentylamine (**6c**) (0.436 g, 5 mmol). Yield: 0.235 g (86%) of a white solid; mp 108–113°C; ir (potassium bromide): 3128, 1700, 1636, 1594, 1576, 1498, 1458, 1425, 1295, 1201, 1084, 955 cm^{-1}. ^1H nmr (deuteriochloroform): 0.83 (3H, t, $J = 7.1$ Hz, $CH_2CH_2CH_3$), 1.23–1.30 (4H, m, $CH_2CH_2CH_2CH_3$), 1.47–1.55 (2H, m, CH_2CH_2NH), 3.27–3.34 (2H, m, CH_2NH), 6.18 (1H, br s, NH), 7.33 (1H, m, *p*-Ph), 7.43 (2H, m, *m*-Ph), 7.64 (1H, s, 3-H), 7.68–7.74 (2H, m, *o*-Ph), 8.65 (1H, br s, OH). ^{13}C nmr (deuteriochloroform): 14.1, 22.5, 29.2, 29.5, 39.3, 119.1, 121.1, 127.0, 129.3, 135.6, 138.6, 156.8, 162.9. ms: *m/z* = 274 (MH^+); hrms Calcd for $C_{15}H_{20}N_3O_2$: *m/z* 274.1556 (MH^+); found: *m/z* 274.1564 (MH^+). *Anal*. Calcd for $C_{15}H_{19}N_3O_2$ (273.33): C, 65.91; H, 7.01; N, 15.37. Found: C, 65.62; H, 7.06; N, 14.97.

N-Hexyl-5-hydroxy-1-phenyl-1H-pyrazole-4-carboxamide (7d). This compound was prepared from **3** (0.232 g, 1 mmol) and 1-hexylamine (**6d**) (0.505 g, 5 mmol). Yield: 0.150 g (52%) of a light brown solid; mp 93–95°C; ir (KBr): 3402, 2580, 1633, 1556, 1538, 1503, 1352, 1240, 1124 cm^{-1}. ^1H nmr (DMSO-d_6): 0.87 (3H, t, $J = 6.8$ Hz, $CH_3(CH_2)_5$), 1.24–1.34 (6H, m, $3 \times CH_2$), 1.49 (2H, quintet, $J = 6.8$ Hz, CH_3CH_2), 3.26 (2H, t, $J = 7.0$ Hz, CH_2NH), 7.32 (1H, t, $J = 7.4$ Hz, *p*-Ph), 7.50 (2H, t, $J = 8.0$ Hz, *m*-Ph), 7.74 (2H, d, $J = 7.7$ Hz, *o*-Ph), 8.12 (1H, s, 3-H), 8.41 (1H, br s, NH), 10.90 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 13.9, 22.1, 26.1, 29.3, 31.0, 38.1, 97.9, 120.7, 126.3, 129.1, 137.0, 137.5, 157.9, 163.6. ms: *m/z* 288 (MH^+); hrms Calcd for $C_{16}H_{22}N_3O_2$: *m/z* 288.1707 (MH^+); found: *m/z* 288.1708 (MH^+). *Anal*. Calcd for $C_{16}H_{21}N_3O_2 \cdot {}^4/_{10}H_2O$ (294.56): C, 65.32; H, 7.46; N, 14.29. Found: C, 65.38; H, 7.43; N, 14.01.

N-Benzyl-5-hydroxy-1-phenyl-1H-pyrazole-4-carboxamide (7e). This compound was prepared from **3** (0.232 g, 1 mmol) and benzylamine (**6e**) (0.536 g, 5 mmol). Yield: 0.205 g (70%) of a white solid; mp 122–128°C; ir (potassium bromide): 3275, 1644, 1558, 1532, 1499, 1455, 1351, 1241, 1185, 901 cm^{-1}. ^1H nmr (deuteriochloroform): 4.41 (2H, br d, $J = 4.5$ Hz, CH_2Ph), 7.16–7.38 (8H, m, 8H of Ph), 7.50–7.60 (2H, m, 2H of Ph), 7.68 (1H, s, 3-H), 8.19 (1H, br s, NH), 10.30 (1H, br s, OH). ^{13}C nmr (deuteriochloroform): 42.8, 99.2, 121.1, 127.2, 127.7, 127.7, 128.7, 129.2, 135.8, 136.1, 137.9, 159.1, 164.4. ms: *m/z* 294 (MH^+); hrms Calcd for $C_{17}H_{16}N_3O_2$: *m/z* 294.1243 (MH^+); found: *m/z* 294.1248 (MH^+). *Anal*. Calcd for $C_{17}H_{15}N_3O_2$ (293.32): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.38; H, 5.20; N, 14.17.

5-Hydroxy-N-(4-methoxybenzyl)-1-phenyl-1H-pyrazole-4-carboxamide (7f). This compound was prepared from **3** (0.232 g, 1 mmol) and 4-methoxybenzylamine (**6f**) (0.686 g, 5 mmol). Yield: 0.294 g (91%) of a white solid; mp 147–156°C; ir (potassium bromide): 3266, 1651, 1351, 1242, 1032, 756 cm^{-1}. ^1H nmr (DMSO-d_6): 3.73 (3H, s, OMe), 4.41 (2H, d, CH_2Ph), 6.90 (2H, br d, $J = 8.6$ Hz, 2H of C_6H_4), 7.25 (2H, br d, $J = 8.6$ Hz, 2H of C_6H_4), 7.32 (1H, br t, $J = 7.5$ Hz, *p*-Ph), 7.50 (2H, br t, $J = 7.6$ Hz, *m*-Ph), 7.72 (2H, br t, $J = 7.7$ Hz, *o*-Ph), 8.16 (1H, br s, 3-H), 8.78 (1H, br s, NH), 10.93 (1H, br s, OH). ^{13}C nmr (deuteriochloroform): 41.2, 55.1, 104.4, 113.8, 117.8, 117.9, 120.8, 126.5, 128.7, 129.2, 129.5, 137.6, 158.3, 163.4. ms: *m/z* 324 (MH^+); hrms Calcd for $C_{18}H_{18}N_3O_3$: *m/z* 324.1248 (MH^+); found: *m/z* 324.1330 (MH^+). *Anal*. Calcd for $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.64; H, 5.32; N, 12.95.

5-Hydroxy-1-phenyl-N-(2-phenylethyl)-1H-pyrazole-4-carboxamide (7g). This compound was prepared from **3** (0.232 g, 1 mmol) and 2-phenylethylamine (**6g**) (0.606 g, 5 mmol). Yield: 0.193 g (63%) of a white solid; mp 127–132°C; ir (potassium bromide): 3319, 1638, 1595, 1579, 1528, 1495, 1359, 1313, 1197, 957 cm^{-1}. ^1H nmr (deuteriochloroform): 2.80 (2H, t, $J = 7.1$ Hz, CH_2Ph), 3.52 (2H, br q, $J = 7.1$ Hz, CH_2NH), 7.11–7.34 (9H, m, Ph and 4H of Ph), 7.55–7.63 (2H, m, 1H of Ph, NH), 7.69 (1H, s, 3-H), 10.42 (1H, br s, OH). ^{13}C nmr (deuteriochloroform): 35.8, 40.4, 99.1, 118.9, 121.4, 126.6, 127.2, 128.6, 128.7, 129.2, 135.9, 138.6, 158.9, 164.7. ms: *m/z* 308 (MH^+); hrms Calcd for $C_{18}H_{18}N_3O_2$: *m/z* 308.1394 (MH^+); found: *m/z* 308.1391 (MH^+). *Anal.* Calcd for $C_{18}H_{17}N_3O_2$ (307.35): C, 65.91; H, 7.01; N, 15.37. Found: C, 70.11; H, 5.58; N, 13.63.

5-Hydroxy-1-phenyl-N-(3-phenylprop-1-yl)-1H-pyrazole-4-carboxamide (7h). This compound was prepared from **3** (0.232 g, 1 mmol) and 3-phenylpropylamine (**6h**) (0.675 g, 5 mmol). Yield: 0.207 g (64%) of a light brown solid; mp 77–

82°C; ir (potassium bromide): 3440, 2923, 1634, 1610, 1526, 1498, 1458, 1320, 1294, 1180, 1080, 1062, 958 cm^{-1}. ^1H nmr (DMSO-d_6): 1.81 (2H, quintet, $J = 7.4$ Hz, $CH_2CH_2CH_2$), 2.63 (2H, t, $J = 7.7$ Hz, CH_2Ph), 3.27 (2H, t, $J = 7.1$ Hz, CH_2NH), 7.17 (1H, t, $J = 7.2$ Hz, *p*-Ph), 7.74 (2H, d, $J = 6.4$ Hz, *o*-Ph), 7.28 (2H, t, $J = 7.5$ Hz, *m*-Ph), 7.32 (1H, t, $J = 7.2$ Hz, *p*-Ph), 7.50 (2H, t, $J = 7.9$ Hz, *m*-Ph), 7.74 (2H, d, $J = 7.8$ Hz, *o*-Ph), 8.12 (1H, s, 3-H), 8.46 (1H, br s, NH), 10.91 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 31.0, 32.5, 37.7, 97.9, 120.6, 125.7, 126.3, 128.3, 128.3, 129.1, 137.0, 137.5, 141.5, 157.8, 163.6. ms: *m/z* = 320 ($[M - H]^-$); hrms: *m/z* = 320.1408 ($[M - H]^-$); $C_{19}H_{18}N_3O_2$ requires: *m/z* = 320.1405 ($[M - H]^-$). *Anal*. Calcd for $C_{19}H_{19}N_3O_2 \cdot {}^2/_3H_2O$ (333.38): C, 68.45; H, 6.13; N, 12.60. Found: C, 68.48; H, 6.23; N, 12.28.

N-Cyclopropyl-5-hydroxy-1-phenyl-1H-pyrazole-4-carboxamide (7i). This compound was prepared from **3** (0.232 g, 1 mmol) and cyclopropylamine (**6i**) (0.285 g, 5 mmol). The product was purified by flash column chromatography (ethyl acetate). Fractions containing the product were combined and evaporated *in vacuo* to give **6i**. Yield: 0.070 g (30%) of a light brown solid; mp 184–186°C; ir (KBr): 3417, 2964, 1621, 1558, 1504, 1455, 1362, 1085, 936 cm^{-1}. ^1H nmr (DMSO-d_6): 0.53 (2H, br s, CH_2), 0.71 (2H, br d, $J = 5.7$ Hz, CH_2), 2.81 (1H, br s, C*H*NH), 7.29 (1H, t, $J = 7.4$ Hz, *p*-Ph), 7.47 (2H, t, $J = 8.0$ Hz, *m*-Ph), 7.71 (2H, d, $J = 7.8$ Hz, *o*-Ph), 8.09 (1H, s, 3-H), 8.46 (1H, br s, NH), 10.82 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 6.1, 21.4, 118.0, 122.3, 126.9, 129.1, 137.9, 140.3, 155.1, 163.0. ms: *m/z* 244 (MH^+); hrms Calcd for $C_{13}H_{14}N_3O_2$: *m/z* 244.1081 (MH^+): *m/z* 244.1081 (MH^+). *Anal*. Calcd for $C_{13}H_{13}N_3O_2 \cdot {}^1/_5H_2O$ (246.86): C, 57.55; H, 5.98; N, 15.48. Found: C, 57.66; H, 5.31; N, 14.87.

N-Cyclobutyl-5-hydroxy-1-phenyl-1H-pyrazole-4-carboxamide (7j). This compound was prepared from **3** (0.232 g, 1 mmol) and cyclobutylamine (**6j**) (0.355 g, 5 mmol). Yield: 0.190 g (72%) of a white solid; mp 165–169°C; ir (KBr): 2964, 1634, 1595, 1575, 1533, 1498, 1459, 1425, 1312, 1293, 1212, 1128, 1094, 1060, 1028, 964 cm^{-1}. ^1H nmr (DMSO-d_6): 1.63–1.72 (2H, m, CH_2), 1.99 (2H, doublet of quintet, $J = 2.8$, 9.3 Hz, CH_2), 2.20–2.27 (2H, m, CH_2), 4.39 (1H, quintet, $J = 7.3$ Hz, C*H*NH), 7.33 (1H, t, $J = 7.5$ Hz, *p*-Ph), 7.50 (2H, t, $J = 7.9$ Hz, *m*-Ph), 7.74 (2H, d, $J = 7.8$ Hz, *o*-Ph), 8.11 (1H, s, 3-H), 8.58 (1H, br s, NH), 10.91 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 17.8, 30.5, 43.5, 59.4, 117.9, 120.7, 126.5, 129.2, 137.1, 137.5, 157.7, 162.8. ms: *m/z* 256 ($[M - H]^-$); hrms Calcd for $C_{14}H_{16}N_3O_2$: *m/z* 258.1237 (MH^+); found: *m/z* 258.1236 (MH^+). *Anal*. Calcd for $C_{14}H_{15}N_3O_2 \cdot {}^1/_7H_2O$ (259.86): C, 64.71; H, 5.93; N, 16.17. Found: C, 64.82; H, 5.82; N, 15.52.

N-Cyclopentyl-5-hydroxy-1-phenyl-1H-pyrazole-4-carboxamide (7k). This compound was prepared from **3** (0.232 g, 1 mmol) and cyclopentylamine (**6k**) (0.425 g, 5 mmol). Yield: 0.190 g (69%) of a light brown solid; mp 180–183°C; ir (KBr): 3446, 2957, 2868, 1688, 1633, 1595, 1574, 1498, 1459, 1427, 1320, 1293, 1204, 1135, 1088, 1059, 1028, 958 cm^{-1}. ^1H nmr (DMSO-d_6): 1.49 (2H, sextet, $J = 6.5$ Hz, CH_2), 1.52–1.60 (2H, m, CH_2), 1.64–1.72 (2H, m, CH_2), 1.49 (2H, sextet, $J = 6.3$ Hz, CH_2), 4.20 (1H, quintet, $J = 6.8$ Hz, C*H*NH), 7.32 (1H, t, $J = 7.4$ Hz, *p*-Ph), 7.50 (2H, t, $J = 7.9$ Hz, *m*-Ph), 7.73 (2H, d, $J = 8.1$ Hz, *o*-Ph), 8.14 (1H, s, 3-H), 8.34 (1H, br s, NH), 10.93 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 23.5, 32.5, 50.0, 98.0, 120.6, 126.4, 129.2, 136.9, 137.5, 158.0, 163.3. ms: *m/z* 272 (MH^+); hrms Calcd for $C_{15}H_{18}N_3O_2$: *m/z* 272.1394 (MH^+); found: *m/z* 272.1367 (MH^+). *Anal*. Calcd for $C_{15}H_{17}N_3O_2 \cdot {}^1/_5H_2O$ (274.92): C, 65.51; H, 6.38; N, 15.29. Found: C, 65.57; H, 6.40; N, 15.02.

N-Cyclohexyl-5-hydroxy-1-phenyl-1H-pyrazole-4-carboxamide (7l). This compound was prepared from **3** (0.232 g, 1 mmol) and cyclohexylamine (**6l**) (0.496 g, 5 mmol). Yield: 0.214 g (75%) of a white solid; mp 160–168°C; ir (potassium bromide): 3286, 3117, 1700, 1630, 1596, 1575, 1527, 1498, 1458, 1427, 1321, 1290, 1058, 961 cm^{-1}. ^1H nmr (deuteriochloroform): 1.14–1.29 (3H, m, 3H of C_6H_{11}), 1.32–1.44 (2H, m, 2H of C_6H_{11}), 1.61–1.68 (1H, m, 1H of C_6H_{11}), 1.72–1.88 (2H, m, 2H of C_6H_{11}), 1.93–2.02 (2H, m, 2H of C_6H_{11}), 3.86–3.95 (1H, m, CH of C_6H_{11}), 5.82 (1H, br s, NH), 7.30 (1H, br t, $J = 7.3$ Hz, *p*-Ph), 7.45 (2H, br t, $J = 7.8$ Hz, *m*-Ph), 7.68 (1H, br s, 3-H), 7.79 (2H, br d, $J = 7.2$ Hz, *o*-Ph), 8.18 (1H, br s, OH). ^{13}C nmr (deuteriochloroform): 25.0, 25.6, 33.3, 48.3, 121.1, 127.0, 129.3, 129.6, 135.4, 137.6, 158.0, 164.5. ms: *m/z* 286 (MH^+); hrms Calcd for $C_{16}H_{20}N_3O_2$: *m/z* 286.1556 (MH^+); found: *m/z* 286.1565 (MH^+). *Anal*. Calcd for $C_{16}H_{19}N_3O_2$ (285.34): C, 67.35; H, 6.71; N, 14.73. Found: C, 67.11; H, 6.78; N, 14.61.

5-Hydroxy-N-(2-methoxyethyl)-1-phenyl-1H-pyrazole-4-carboxamide (7m). This compound was prepared from **3** (0.232 g, 1 mmol) and 2-methoxyethylamine (**6m**) (0.376 g, 5 mmol). Yield: 0.201 g (77%) of a white solid; mp 110–116°C; ir (potassium bromide): 3301, 3134, 1709, 1616, 1583, 1507, 1461, 1429, 1315, 1264, 1194, 1114, 963 cm^{-1}. ^1H nmr (deuteriochloroform): 3.41 (3H, s, OMe), 3.54 (2H, br t, $J = 4.8$ Hz, CH_2NH), 3.61 (2H, br q, $J = 4.8$ Hz, CH_2OMe), 6.42 (1H, br s, NH), 7.29 (1H, br t, $J = 7.3$ Hz, *p*-Ph), 7.43 (2H, br t, $J = 7.4$ Hz, *m*-Ph), 7.69 (1H, br s, 3-H), 7.75–7.81 (2H, m, *o*-Ph), 9.17 (1H, br s, OH). ^{13}C nmr (deuteriochloroform): 38.9, 59.0, 71.1, 119.0, 121.1, 127.0, 129.2, 129.7, 135.7, 157.6, 165.8. ms: *m/z* 262 (MH^+); hrms Calcd for $C_{13}H_{16}N_3O_3$: *m/z* 262.1192 (MH^+); found: *m/z* 262.1165 (MH^+). *Anal*. Calcd for $C_{13}H_{15}N_3O_3$ (261.28): C, 59.76; H, 5.79; N, 16.08. Found: C, 59.44; H, 5.82; N, 16.00.

5-Hydroxy-N-(2-hydroxyethyl)-1-phenyl-1H-pyrazole-4-carboxamide (7n). This compound was prepared from **3** (0.232 g, 1 mmol) and 2-aminoethanol (**6n**) (0.305 g, 5 mmol). Yield: 0.150 g (61%) of a white solid; mp 135–138°C; ir (KBr): 3449, 3248, 2941, 2876, 1653, 1581, 1520, 1497, 1460, 1440, 1406, 1354, 1290, 1249, 1228, 1185, 1089, 1060, 1047, 933 cm^{-1}. ^1H nmr (DMSO-d_6): 3.33 (2H, t, $J = 5.9$ Hz, CH_2NH), 3.51 (2H, t, $J = 5.9$ Hz, CH_2OH), 4.68 (1H, br s, CH_2O*H*), 7.32 (1H, t, $J = 7.4$ Hz, *p*-Ph), 7.50 (2H, t, $J = 8.0$ Hz, *m*-Ph), 7.73 (2H, d, $J = 7.7$ Hz, *o*-Ph), 8.17 (1H, s, 3-CH), 8.46 (1H, br s, NH), 10.93 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 41.0, 59.9, 117.9, 120.7, 126.4, 129.2, 136.9, 137.7, 158.1, 163.6. ms: *m/z* 248 (MH^+); hrms Calcd for $C_{12}H_{14}N_3O_3$: *m/z* 246.0884 ($[M - H]^-$); found: *m/z* 246.0884 ($[M - H]^-$). *Anal*. Calcd for $C_{12}H_{13}N_3O_3$ (247.25): C, 58.29; H, 5.30; N, 16.99. Found: C, 58.19; H, 5.07; N, 16.82.

5-Hydroxy-N-(3-hydroxypropyl)-1-phenyl-1H-pyrazole-4-carboxamide (7o). This compound was prepared from **3** (0.232 g, 1 mmol) and 3-amino-1-propanol (**6o**) (0.376 g, 5 mmol). Yield: 0.150 g (58%) of a white solid; mp 160–163°C; ir (potassium bromide): 3450, 1637, 1570, 1458, 1352, 1295, 1209, 1080, 1063, 944 cm^{-1}. ^1H nmr (DMSO-d_6): 1.66 (2H, quintet, $J = 6.6$ Hz, $CH_2CH_2CH_2$), 3.32 (2H, t, $J = 7.0$ Hz, CH_2NH), 3.47 (2H, t, $J = 6.3$ Hz, CH_2OH), 4.53 (1H, br s, CH_2O*H*), 7.33 (1H, t, $J = 7.4$ Hz, *p*-Ph), 7.50 (2H, t, $J = 8.0$ Hz, *m*-Ph), 7.74 (2H, d, $J = 7.7$ Hz, *o*-Ph), 8.31 (1H, s, 3-H), 8.42 (1H, br s, NH), 10.95 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 32.5, 35.5, 58.5, 118.0, 120.7, 126.5, 129.2, 137.5, 139.1, 160.4, 162.0. ms: *m/z* 262 (MH^+); hrms Calcd for $C_{13}H_{16}N_3O_3$: *m/z* 262.1186 (MH^+); found:

m/z 262.1185 (MH^+). *Anal*. Calcd for $C_{13}H_{15}N_3O_3$ (261.28): C, 59.76; H, 5.79; N, 16.08. Found: C, 59.90; H, 5.75; N, 15.85.

(5-Hydroxy-1-phenyl-1H-pyrazol-4-yl)(pyrrolidin-1-yl)methanone (7p). This compound was prepared from **3** (0.232 g, 1 mmol) and pyrrolidine (**6p**) (0.355 g, 5 mmol). Yield: 0.130 g (50%) of a light reddish solid; mp 142–144°C; ir (potassium bromide): 3417, 2958, 1636, 1615, 1506, 1616, 1356,1054, 973 cm^{-1}. ^1H nmr (DMSO-d_6): 1.82–2.03 (4H, m, CH_2CH_2), 3.47–3.76 (4H, m, $2\times CH_2N$), 7.32 (1H, t, $J=7.4$ Hz, *p*-Ph), 7.51 (2H, t, $J=8.0$ Hz, *m*-Ph), 7.84 (2H, d, $J=7.5$ Hz, *o*-Ph), 7.96 (1H, s, 3-H), 10.23 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 23.6, 25.4, 46.5, 47.2, 118.1, 120.0, 126.3, 129.2, 137.7, 138.1, 160.1, 164.1. ms: $m/z=258$ (MH^+); hrms Calcd for $C_{14}H_{16}N_3O_2$: $m/z=258.1237$ (MH^+); found: *m/z* 258.1237 (MH^+). *Anal*. Calcd for $C_{14}H_{15}N_3O_2$ (259.29): C, 65.35; H, 5.88; N, 16.33. Found: C, 65.30; H, 5.97; N, 16.07.

(5-Hydroxy-1-phenyl-1H-pyrazol-4-yl)(piperidin-1-yl)methanone (7q). This compound was prepared from **3** (0.232 g, 1 mmol) and piperidine (**6q**) (0.425 g, 5 mmol). Yield: 0.130 g (46%) of a light brownish solid; mp 97–100°C; ir (KBr): 4338 (NH), 2934, 1637 (C═O), 1601, 1560, 1298, 1205, 1116, 1058, 1008, 963 cm^{-1}. ^1H nmr (DMSO-d_6): 1.48–1.59 (6H, m, $CH_2CH_2CH_2$), 3.36–3.67 (4H, m, $2\times CH_2N$), 7.23 (1H, t, $J=6.8$ Hz, *p*-Ph), 7.43 (2H, t, $J=7.8$ Hz, *m*-Ph), 7.72 (2H, d, $J=7.2$ Hz, *o*-Ph), 7.93 (1H, s, 3-H), 10.60 (1H, br s, OH). ^{13}C nmr (DMSO-d_6): 24.0, 25.6, 44.9, 116.8, 120.7, 126.4, 128.8, 138.6, 139.6, 160.3, 171.2. ms: $m/z=270$ ($[M-H]^-$); hrms Calcd for $C_{15}H_{18}N_3O_2$: *m/z* 272.1394 (MH^+); found: 272.1395 (MH^+). *Anal*. Calcd for $C_{15}H_{17}N_3O_2\cdot\frac{1}{8}H_2O$ (273.57): C, 65.86; H, 6.36; N, 15.36. Found: C, 65.98; H, 6.25; N, 15.20.

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