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ORIGINAL PAPER

A novel synthetic approach towards pyrazole-4-carboxamides using *N*-(3-(dimethylamino)-2-formylacryloyl)formamide

Madhukar N. Jachak · Maruti G. Ghagare · Dilip R. Birari · Ramhari V. Rote · Muddassar A. Kazi · Sanjay M. Jachak · Raghunath B. Toche

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Abstract A novel synthesis of pyrazole-4-carboxamides is reported. The reaction of *N*-(3-(dimethylamino)-2-formylacryloyl)formamide, an intermediate obtained by Vilsmeier–Haack formylation of acetonitrile, with hydrazine hydrate or monosubstituted hydrazines provides such compounds in good yields. This method has advantages over other methods for construction of such ring systems previously described in the literature.

Keywords Hydrolysis · Cyclization · Nucleophilic substitution · N-Alkylation

Introduction

The first primary synthesis of 1-phenyl-3-methyl-5-pyrazolone from ethyl acetoacetate and phenyl hydrazine was carried out by Knorr in 1883 [1]. His interest in quinine led to tests of the antifebrile activity of this and related compounds and resulted in the discovery of antipyrine [2], probably the first antipyretic pyrazole derivative. This stimulated interest in pyrazole chemistry and since then several pyrazole derivatives have been synthesized using different synthetic routes [3–11]. However, methods dealing with the synthesis of pyrazole-4-carboxamides have rarely been explored. The reported procedure for preparation of pyrazole-4-carboxamides consisted in the synthesis of 4-methylpyrazole [12–19] which was oxidized to pyrazole-4-carboxylic acid [20] using $KMnO_4$, followed by reaction with thionyl chloride to give corresponding acid chloride [21, 22]. Subsequently, the acid chloride was quenched with aqueous ammonia solution leading to pyrazole-4-carboxamides. Unfortunately, this method was limited owing to drastic reaction conditions, laborious workup, and a multistep reaction procedure. As a consequence, the introduction of new methods and/or further work on technical improvements to overcome the limitations is still an important experimental challenge.

Pyrazole-4-carboxamides have found widespread applications because of their cannabinoid CB1 receptor [23], herbicidal [24, 25], and anti-platelet [26] activity. Pyrazole-4-carboxamides bearing an aromatic substituent at the N^1 position have immunosuppressant activity [27] equivalent to that of leflunomide and brequinar. As part of a campaign to develop libraries based on this template, we now report that pyrazole-4-carboxamides with a range of different substituents at N^1 can be conveniently prepared from *N*-(3-(dimethylamino)-2-formylacryloyl)formamide **1** and hydrazine hydrate or monosubstituted hydrazines.

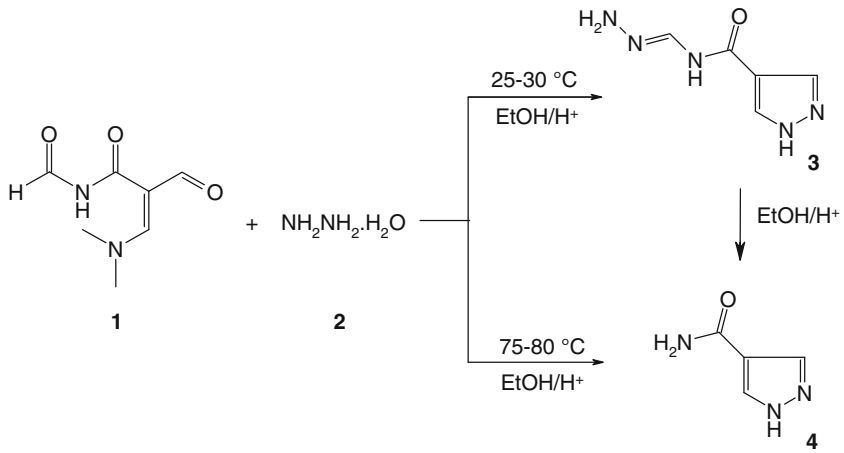
Results and discussion

In connection with our previous work [28], we decided to elaborate the reaction of **1** with hydrazine hydrate and substituted hydrazines as an attractive procedure leading to pyrazole-4-carboxamides. Thus our study began with compound **1**, which was reacted with 1.05 equiv. hydrazine hydrate (**2**) via nucleophilic substitution in ethanol in the presence of a catalytic amount of AcOH at room

M. N. Jachak (✉) · M. G. Ghagare · D. R. Birari · R. V. Rote · M. A. Kazi · R. B. Toche
Department of Chemistry, Organic Chemistry Research Centre, K.T.H.M. College, Gangapur Road, Nashik 422002, Maharashtra, India
e-mail: mn_jachak@hotmail.com

S. M. Jachak
National Institute of Pharmaceutical Education and Research, S.A.S. Nagar, Mohali 160062, Punjab, India

Scheme 1



temperature to give compound **3** in 40% yield (Scheme 1, entry 1). However the same reaction at 75–80 °C led selectively to **4** in 38% isolated yield (Table 1, entry 4). Encouraged by these results, we surveyed a series of reactions using different molar ratios of hydrazine hydrate and temperature (Table 1). We found that either **3** or **4** could be prepared almost exclusively by varying the stoichiometry and reaction conditions. The yields of pyrazoles **3** and **4** were found to be best when 2.5 equiv. hydrazine hydrate relative to **1** were used (Table 1, entries 3 and 6). Use of smaller amounts of hydrazine hydrate was found to be less effective. An interesting observation was that when **1** was added to hydrazine hydrate in boiling ethanol, the *N*-formyl group in **1** was hydrolysed to an amido group in **4**. Noteworthy was that compound **3** heated under reflux separately in ethanol with a catalytic amount of AcOH gave pyrazole-4-carboxamide **4** in quantitative yield.

The structure of compound **3** was deduced from its elemental analysis and spectroscopic data. The mass spectrum of **3** contained the molecular ion peak at $m/z = 153$, which was consistent with the molecular weight of **3**. The IR spectrum of **3** contained absorption bands of the amide carbonyl and NH_2 groups at 1,676 cm^{-1} and 3,218 cm^{-1}, respectively, and stretching of the NH group appeared at 3,311 cm^{-1}. The ^1H NMR spectrum of **3** contained three broad singlets readily assigned to an NH_2 group and two NH groups ($\delta = 5.62$, 10.98, and 11.37 ppm, respectively). The pyrazole moiety gave rise to characteristic signals ($\delta = 7.96$ and 8.99 ppm) in the aromatic region of the spectrum. In the ^{13}C NMR spectrum of **3**, the amide carbonyl appeared at 165.8 ppm, the peak at 163.8 ppm corresponded to imine carbon, and the pyrazole ring carbons C^3, C^4, and C^5 appeared at $\delta = 163.3$, 98.7, and 162.1 ppm, respectively.

The IR spectrum of **4** contained absorption bands of the amide carbonyl, NH_2, and NH groups at 1,670 cm^{-1}, 3,164 cm^{-1}, and 3,364 cm^{-1}, respectively. The mass spectrum of **4** contained the molecular ion peak at $m/z = 111$, corresponding to the molecular weight of **4**. In the ^1H NMR spectrum of **4**, the pyrazole-NH resonated at 13.03 ppm, and the C^3H and C^5H appeared at 8.11 and 7.83 ppm. The NH_2 protons appeared separately as two broad singlets at 7.50 and 6.95 ppm because of either restricted rotation or hydrogen bonding between the NH_2 group and the amide carbonyl group. Further ^{13}C NMR spectroscopic analysis showed that the peak at 163.8 ppm could be assigned to the amide carbon. The olefinic carbons resonated at $\delta = 138.8$ and 129.7 ppm. The remaining carbon appeared at 117.8 ppm.

Table 1 Optimization of the reaction conditions[a]

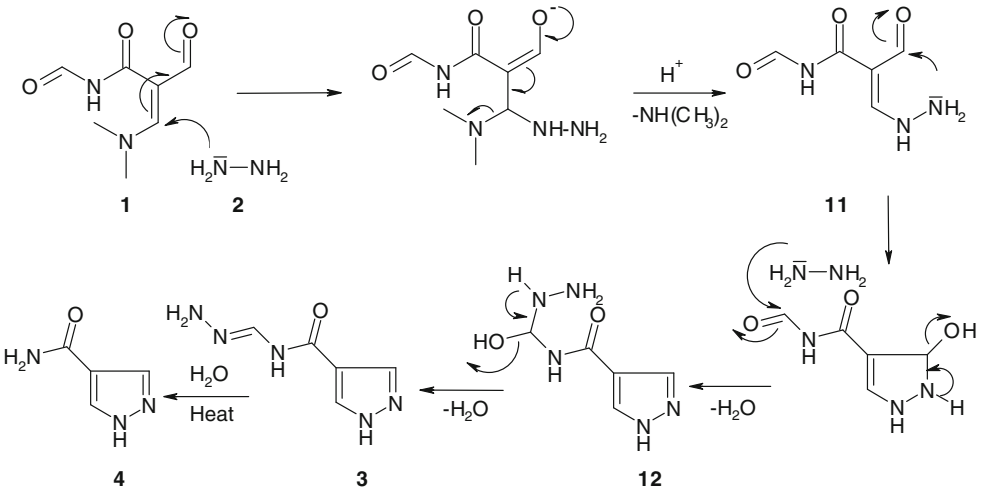
Entry	Equiv. **1**	Equiv. **2**	Temp.	Yield **3** (%)[b]	Yield **4** (%)[b]
1	1	1.05	rt	40	–
2	1	1.50	rt	48	–
3	1	2.50	rt	80	–
4	1	1.05	Reflux	–	38
5	1	1.50	Reflux	–	42
6	1	2.50	Reflux	–	75

[a] All reactions were carried out on approximately 1.46 mmol scale

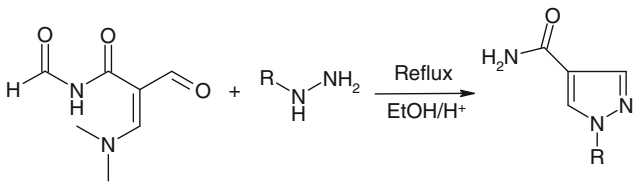
[b] Isolated yields

The reaction mechanism could be explained by initial substitution of the dimethylamino group in **1** to give the enehydrazine intermediate **11**. Simultaneously the second molecule of hydrazine hydrate attacks the electrophilic carbon of the *N*-formyl group leading, after condensation with the aldehyde carbonyl group, to intermediate **12**. Extrusion of one water molecule gives **3**. In order to trap the open-chain intermediate, we carried out reactions of compound **1** and hydrazine hydrate **2** at −5, −10, −15, and −20 °C, but the cyclization process was so fast that in all cases **3** was obtained as the sole product. When the reaction temperature was 75–80 °C, intermediate **3** was mainly hydrolysed by water to give intermediate **4** (Scheme 2).

Scheme 2



With the optimized reaction conditions we attempted the preparation of a new series of pyrazole-4-carboxamides by reaction of **1** with substituted hydrazines **5**. As expected, in the substituted hydrazines the unsubstituted nitrogen was more nucleophilic. The corresponding pyrazole-4-carboxylic acid amide derivatives **6** were obtained in 79–90% yields without any side reaction. In this case the required reaction time was longer, probably because of the insufficient basicity of the substituted hydrazines that underwent the cyclisation. Here also the *N*-formyl group in **1** was hydrolysed to the amido group in **6** (Scheme 3).



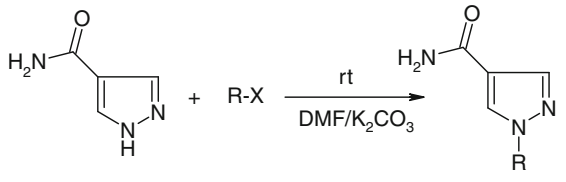
5, 6	R
a	C_6H_5
b	-C(=S)NH_2
c	4-($CH_3NHSO_2CH_2$)C_6H_4
d	2,4-di-$NO_2C_6H_3$
e	4-(NH_2SO_2)C_6H_4
f	4-($CH_3NHSO_2(CH_2)_2$)C_6H_4
g	4-([1,2,4]triazol-1-ylmethyl)phenyl
h	4-[(1-pyrrolidinylsulfonyl)methyl]phenyl

Scheme 3

Once the structure of pyrazole-4-carboxamide **4** was confirmed, we utilized its NH functionality for the alkylation to obtain different analogues of pyrazole-4-carboxamides **8**. Thus, compound **4** was subjected to N-alkylation with 1.1 equiv. **7** using K_2CO_3 in DMF at room temperature to give N-alkylated pyrazole-4-carboxamides **8** in 78–85% yields (Scheme 4).

The scope of this reaction was explored by using a variety of substituted anilides **9** to afford **10** in 85–90% yields (Scheme 5). The ^{1}H NMR spectrum of **10a** contained a broad singlet instead of a triplet at 10.81 ppm for the –NH proton and a singlet instead of doublet at 5.08 ppm corresponding to the –CH_2 group, clearly indicating the N-alkylation at the N^1 position and not on the amide NH_2.

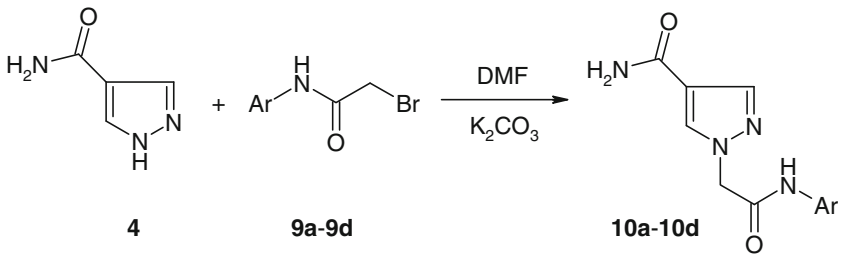
In conclusion, we have discovered a simple and scalable synthesis of pyrazole-4-carboxamides using *N*-(3-(dimethylamino)-2-formylacryloyl)formamide as a convenient precursor. A bidentate nucleophile such as hydrazine



7, 8	R	7, 8	R
a	CH_3	**f**	$CH_3(CH_2)_4$
b	CH_3CH_2	**g**	Cyclopentyl
c	$CH_3CH_2CH_2$	**h**	$CH_3CH_2OCOCH_2$
d	$CH_3CH_2CH_2CH_2$	**i**	$(CH_3CH_2O)_2CHCH_2$
e	$(CH_3)_2CHCH_2$		

Scheme 4

Scheme 5



4 **9a-9d** **10a-10d**

9, **10**	Ar
a	4-Cl-3-(F_3C)C_6H_3
b	4-MeC_6H_4
c	2,4-*di*-ClC_6H_3
d	4-ClC_6H_4

hydrate reacted with *N*-(3-(dimethylamino)-2-formylacryloyl)formamide giving two products **3** and **4**. At room temperature exclusive formation of **3** was observed, whereas compound **4** was obtained as the sole product at reflux. The NH group at position 1 in **4** could be alkylated to give different analogues of pyrazole-4-carboxamides. The method is a facile means of construction of the heteroaromatic ring, which could be widely used for synthesis of biologically active molecules and advanced materials. The simplicity and very good yields make this method one of the most attractive approaches towards pyrazole derivatives.

Experimental

Melting points were determined on a Buchi model B-545 melting-point apparatus. The ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). The solvent for NMR spectra was DMSO-d_6 unless otherwise stated. Infrared spectra were taken on a Thermo Electron Nicolet 380 FTIR instrument in potassium bromide pellets unless otherwise stated. Mass spectra were recorded on a Shimadzu GC–MS QP 2010A mass spectrometer with an ionization potential of 70 eV. Elemental analysis was performed on a Hosli CH-Analyzer, and results were within ±0.4% of the theoretical values. All reactions were monitored by thin-layer chromatography, carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.

N-(Hydrazonomethyl)-1H-pyrazole-4-carboxamide (**3**, $C_5H_7N_5O$)

To a solution of 0.5 g **1** (2.93 mmol) and a catalytic amount of acetic acid (0.05 cm^3) in 12.5 cm^3 ethanol at room temperature was added 0.367 g hydrazine hydrate (**2**, 7.24 mmol). The reaction mixture was stirred at room temperature for 0.5 h (TLC monitoring, chloroform–methanol, 9.5:0.5), and the solid obtained was isolated by filtration and washed with ethanol to give **3** as a yellow solid. This solid was purified by column chromatography using 95:5 *v*/*v* dichloromethane–methanol as eluent. M.p.: 175–178 °C; yield 0.35 g (80%); IR (KBr): $\bar{\nu}$ = 3,311, 3,218, 2,994, 1,708, 1,442, 1,403, 1,312, 1,237, 1,128 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.62 (bs, 2H, NH_2), 7.96 (s, 1H, CH), 8.99 (s, 1H, CH), 9.13 (d, J = 12 Hz, 1H, CH), 10.98 (bs, 1H, NH), 11.37 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 98.7, 162.1, 163.3, 163.8, 165.8 ppm; MS (ESI): m/z = 153 [M$^+$].

1H-Pyrazole-4-carboxamide (**4**)

To a solution of 0.5 g **1** (2.93 mmol) and a catalytic amount of acetic acid (0.05 cm^3) in 12.5 cm^3 ethanol was added 0.367 g hydrazine hydrate (**2**, 7.24 mmol). The reaction mixture was stirred at reflux for 1 h (TLC monitoring, chloroform–methanol, 9.5:0.5). It was then cooled to rt, and the solid obtained was isolated by filtration and washed with ethanol. The crude solid was recrystallized from ethanol to afford **4** as a yellow crystalline solid. M.p.: 225–227 °C; yield 0.24 g (75%); IR (KBr): $\bar{\nu}$ = 3,364, 3,164, 1,670, 1,596, 1,560, 1,493, 1,440, 1,336 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.95 (bs, 1H, NH_2), 7.50 (bs, 1H, NH_2), 7.83 (s, 1H, CH), 8.11 (s, 1H, CH), 13.03 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 117.8, 129.7, 138.8, 163.8 ppm; MS (ESI): m/z = 111 [M$^+$].

*General procedure for synthesis of **6a–6h***

To a solution of 0.5 g **1** (2.93 mmol) and a catalytic amount of acetic acid (0.05 cm^3) in 12.5 cm^3 ethanol was added substituted hydrazine **5** (7.24 mmol). The reaction mixture was stirred at reflux for 1.5–2.0 h (TLC monitoring, chloroform–methanol, 9.5:0.5). The reaction mixture was then cooled to rt, filtered, and the residue was recrystallized from ethanol to afford **6** in 79–90% yields.

1-Phenyl-1H-pyrazole-4-carboxamide (**6a**, $C_{10}H_9N_3O$)
Under reflux for 2 h. Colourless solid, m.p.: 235–237 °C (Ref. [29] 217–220 °C, Ref. [30] 160.3 °C (MeOH)); yield 0.42 g (79%); IR (KBr): $\bar{\nu}$ = 3,238, 3,127, 3,067, 2,922, 1,722, 1,685, 1,597, 1,553 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.37–7.87 (m, 5H, ArH), 8.39 (s, 1H, CH-pyrazole), 9.21 (bs, 1H, NH_2), 9.24 (s, 1H, CH-pyrazole), 11.50 (bs, 1H, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 111.9, 121.5, 132.4, 137.2, 139.3, 144.5, 146.5, 166.7 ppm; MS (ESI): m/z = 187 [M^+].

1-(Aminothioxomethyl)-1H-pyrazole-4-carboxamide (**6b**, $C_5H_6N_4OS$)
Under reflux for 1.5 h. Yellow solid, m.p.: 190–193 °C; yield 0.39 g (81%); IR (KBr): $\bar{\nu}$ = 3,415, 3,299, 3,017, 1,822, 1,670, 1,594 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.30 (bs, 1H, NHCO), 7.91 (bs, 1H, NHCO), 8.18 (s, 1H, ArH), 9.18 (s, 1H, ArH), 9.64 (bs, 1H, NH_2), 10.14 (bs, 1H, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 121.4, 135.9, 138.6, 162.1, 176.6 ppm; MS (ESI): m/z = 170 [M^+].

1-[4-[(Methylaminosulfonyl)methyl]phenyl]-1H-pyrazole-4-carboxamide (**6c**, $C_{12}H_{14}N_4O_3S$)
Under reflux for 2 h. Yellow solid, m.p.: 262–265 °C (decomp.); yield 0.74 g (87%); IR (KBr): $\bar{\nu}$ = 3,434, 3,199, 2,977, 1,915, 1,686, 1,609 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.58 (d, J = 4.8 Hz, 3H, CH_3), 4.39 (s, 2H, CH_2), 6.97 (q, J = 4.8 Hz, 1H, NH_2), 7.20 (bs, 1H, NH_2), 7.51 (d, J = 8.7 Hz, 2H, ArH), 7.68 (bs, 1H, NH), 7.85 (d, J = 8.7 Hz, 2H, ArH), 8.11 (s, 1H, C_5H), 8.88 (s, 1H, C_3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.9, 55.0, 118.5, 120.6, 129.1, 130.1, 134.8, 138.6, 142.5, 165.9 ppm; MS (ESI): m/z = 294 [M^+].

1-(2,4-Dinitrophenyl)-1H-pyrazole-4-carboxamide (**6d**, $C_{10}H_7N_5O_5$)
Under reflux for 2 h. Yellow solid, m.p.: 258–260 °C; yield 0.69 g (85%); IR (KBr): $\bar{\nu}$ = 3,471, 3,371, 3,107, 1,760, 1,667, 1,596 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.34 (bs, 1H, NH_2), 7.81 (bs, 1H, NH_2), 8.15 (d, J = 8.7 Hz, 1H, ArH), 8.18 (s, 1H, C_5H), 8.64 (dd, J = 2.7, 8.7 Hz, 1H, ArH), 8.87 (d, J = 2.7 Hz, 1H, ArH), 8.88 (s, 1H, C_2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 121.0, 121.7, 126.0, 128.0, 132.6, 135.3, 138.4, 140.7, 143.7, 164.1 ppm; MS (ESI): m/z = 277 [M^+].

1-[4-(Aminosulfonyl)phenyl]-1H-pyrazole-4-carboxamide (**6e**, $C_{10}H_{10}N_4O_3S$)
Under reflux for 2 h. Yellow solid, m.p.: 250–252 °C; yield 0.67 g (86%); IR (KBr): $\bar{\nu}$ = 3,395, 3,196, 1,647, 1,619, 1,599 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.25 (bs, 1H, NH_2), 7.43 (bs, 2H, NH_2), 7.73 (bs, 1H, NH_2), 7.94 (d, J = 9.0 Hz, 2H, ArH), 8.03 (d, J = 9.0 Hz, 2H, ArH), 8.16 (s, 1H, C_5H), 8.99 (s, 1H, C_2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 118.6, 121.1, 127.2, 129.7, 137.1, 138.2, 140.9, 165.6 ppm; MS (ESI): m/z = 266 [M^+].

1-[4-[2-(Methylaminosulfonyl)ethyl]phenyl]-1H-pyrazole-4-carboxamide (**6f**, $C_{13}H_{16}N_4O_3S$)
Under reflux for 2 h. Yellow solid, m.p.: 176–179 °C; yield 0.81 g (90%); IR (KBr): $\bar{\nu}$ = 3,393, 3,309, 3,193, 1,747, 1,647, 1,617 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.54 (t, J = 7.8 Hz, 2H, CH_2), 2.60 (d, J = 5.4 Hz, 3H, CH_3), 3.31 (t, J = 8.7 Hz, 2H, CH_2), 7.00 (q, J = 5.4 Hz, 1H, NH), 7.17 (bs, 1H, NH_2), 7.43 (d, J = 8.1 Hz, 2H, ArH), 7.67 (bs, 1H, NH_2), 7.75 (d, J = 8.1 Hz, 2H, ArH), 8.07 (s, 1H, C_5H), 8.85 (s, 1H, C_2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.6, 34.3, 50.1, 118.6, 120.3, 128.9, 129.5, 135.2, 136.5, 142.3, 165.9 ppm; MS (ESI): m/z = 308 [M^+].

1-[4-([1,2,4]Triazol-1-ylmethyl)phenyl]-1H-pyrazole-4-carboxamide (**6g**, $C_{13}H_{12}N_6O$)
Under reflux for 2 h. Brown solid, m.p.: 195–197 °C; yield 0.63 g (82%); IR (KBr): $\bar{\nu}$ = 3,383, 3,194, 3,102, 1,782, 1,655, 1,620 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.45 (s, 2H, CH_2), 7.19 (bs, 1H, NH_2), 7.42 (d, J = 8.4 Hz, 2H, ArH), 7.68 (bs, 1H, NH_2), 7.82 (d, J = 8.4 Hz, 2H, ArH), 7.98 (s, 1H, CH-pyrazole), 8.09 (s, 1H, CH-pyrazole), 8.67 (s, 1H, CH-triazole), 8.86 (s, 1H, CH-triazole) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 51.4, 118.8, 120.6, 129.0, 129.1, 134.8, 138.6, 140.5, 142.1, 144.6, 164.9 ppm; MS (ESI): m/z = 268 [M^+].

1-[4-[(1-Pyrrolidinylsulfonyl)methyl]phenyl]-1H-pyrazole-4-carboxamide (**6h**, $C_{15}H_{18}N_4O_3S$)
Under reflux for 2 h. Yellow solid, m.p.: 265–275 °C (decomp.); yield 0.86 g (88%); IR (KBr): $\bar{\nu}$ = 3,386, 3,192, 2,970, 1,725, 1,646, 1,613, 1,562 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.77 (t, J = 6.3 Hz, 4H, 2 CH_2), 3.14 (t, J = 6.3 Hz, 4H, 2 CH_2), 4.48 (s, 2H, CH_2), 7.20 (bs, 1H, NH_2), 7.54 (d, J = 8.7 Hz, 2H, ArH), 7.69 (bs, 1H, NH_2), 7.84 (d, J = 8.7 Hz, 2H, ArH), 8.10 (s, 1H, CH-pyrazole), 8.88 (s, 1H, CH-pyrazole) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 118.4, 120.6, 128.6, 129.1, 131.9, 133.7, 137.6, 166.9 ppm; MS (ESI): m/z = 334 [M^+].

*General procedure for synthesis of **8a–8i***

To a stirred suspension of 0.5 g **4** (4.5 mmol) and 0.622 g K_2CO_3 (4.5 mmol) in 5 cm^3 DMF at room temperature

was added **7** (5.3 mmol) dropwise within 10 min. The reaction mixture was then stirred at room temperature for 4–5 h (TLC monitoring, chloroform–methanol, 9.5:0.5). The reaction mass was quenched in ice-cold water and extracted with ethyl acetate (3×5 cm^3). The combined organic layer was then dried over sodium sulfate and concentrated to a residue which was recrystallized from ethanol to afford compound **8**.

1-Methyl-1H-pyrazole-4-carboxamide (**8a**, $C_5H_7N_3O$)
At rt for 4 h. White solid, m.p.: 168–170 °C; yield 0.45 g (82%); IR (KBr): $\bar{\nu}$ = 3,370, 3,157, 1,676, 1,624, 1,562, 1,415, 1,316, 1,283, 1,133 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (s, 3H, NCH_3), 6.95 (bs, 1H, NH_2), 7.49 (bs, 1H, NH_2), 7.79 (s, 1H, CH), 8.07 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 38.8, 118.4, 132.1, 138.7, 163.5 ppm; MS (ESI): m/z = 125 [M$^+$].

1-Ethyl-1H-pyrazole-4-carboxamide (**8b**, $C_6H_9N_3O$)
At rt for 4 h. Colourless crystals, m.p.: 135–137 °C; yield 0.52 g (85%); IR (KBr): $\bar{\nu}$ = 3,386, 3,200, 2,984, 1,650, 1,608, 1,560, 1,424, 1,358, 1,300 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.38 (t, J = 7.3 Hz, 3H, CH_3), 4.15 (q, J = 7.3 Hz, 2H, CH_2), 6.95 (bs, 1H, NH_2), 7.49 (bs, 1H, NH_2), 7.79 (s, 1H, CH), 8.10 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 15.3, 46.4, 118.1, 130.6, 138.5, 163.5 ppm; MS (ESI): m/z = 139 [M$^+$].

1-Propyl-1H-pyrazole-4-carboxamide (**8c**, $C_7H_{11}N_3O$)
At rt for 4.5 h. Colourless crystals, m.p.: 120–124 °C; yield 0.54 g (80%); IR (KBr): $\bar{\nu}$ = 3,409, 3,225, 2,973, 1,651, 1,607, 1,561, 1,425, 1,316, 1,295, 1,136 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.83 (t, J = 7.3 Hz, 3H, CH_3), 1.82 (m, 2H, CH_2), 4.06 (t, J = 6.9 Hz, 2H, CH_2), 6.96 (bs, 1H, NH_2), 7.51 (bs, 1H, NH_2), 7.80 (s, 1H, CH), 8.09 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 10.8, 23.0, 53.0, 117.9, 131.3, 138.5, 163.5 ppm; MS (ESI): m/z = 153 [M$^+$].

1-Butyl-1H-pyrazole-4-carboxamide (**8d**, $C_8H_{13}N_3O$)
At rt for 4 h. Colourless crystals, m.p.: 115–117 °C; yield 0.61 g (82%); IR (KBr): $\bar{\nu}$ = 3,410, 3,218, 2,958, 1,652, 1,608, 1,562, 1,456, 1,308, 1,138 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.89 (t, J = 7.3 Hz, 3H, CH_3), 1.27 (m, 2H, CH_2), 1.68–1.77 (m, 2H, CH_2), 4.10 (t, J = 6.9 Hz, 2H, CH_2), 6.95 (bs, 1H, NH_2), 7.49 (bs, 1H, NH_2), 7.79 (s, 1H, CH), 8.09 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.4, 19.1, 31.6, 51.0, 118.0, 131.2, 138.5, 163.4 ppm; MS (ESI): m/z = 167 [M$^+$].

1-(2-Methylpropyl)-1H-pyrazole-4-carboxamide
(**8e**, $C_8H_{13}N_3O$)
At rt for 4.5 h. Colourless crystals, m.p.: 155–157 °C; yield 0.60 g (80%); IR (KBr): $\bar{\nu}$ = 3,396, 3,186, 3,109, 2,955, 1,658, 1,615, 1,564, 1,425, 1,295 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.29 (d, J = 6.9 Hz, 6H, CH_3), 2.55 (m, 1H, CH), 4.33 (d, J = 6.9 Hz, 2H, CH_2), 7.38 (bs, 1H, NH_2), 7.92 (bs, 1H, NH_2), 8.22 (s, 1H, CH), 8.49 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 19.7, 29.1, 58.7, 118.1, 131.8, 138.7, 163.6 ppm; MS (ESI): m/z = 167 [M$^+$].

1-Pentyl-1H-pyrazole-4-carboxamide (**8f**, $C_9H_{15}N_3O$)
At rt for 4.5 h. Colourless crystals, m.p.: 133–136 °C; yield 0.66 g (83%); IR (KBr): $\bar{\nu}$ = 3,395, 3,210, 2,956, 1,650, 1,607, 1,558, 1,418, 1,306, 1,135 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.86 (t, J = 7.0 Hz, 3H, CH_3), 1.29 (m, 2H, CH_2), 1.32–1.34 (m, 2H, CH_2), 1.70–1.79 (m, 2H, CH_2), 4.09 (t, J = 6.7 Hz, 2H, CH_2), 6.95 (bs, 1H, NH_2), 7.49 (bs, 1H, NH_2), 7.79 (s, 1H, CH), 8.09 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.0, 21.8, 28.2, 29.5, 51.5, 118.1, 131.3, 138.6, 163.6 ppm; MS (ESI): m/z = 181 [M$^+$].

1-Cyclopentyl-1H-pyrazole-4-carboxamide
(**8g**, $C_9H_{13}N_3O$)
At rt for 5 h. Colourless crystals, m.p.: 123–126 °C; yield 0.68 g (85%); IR (KBr): $\bar{\nu}$ = 3,367, 3,188, 2,956, 1,664, 1,614, 1,557, 1,427, 1,302, 1,144 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.60–1.68 (m, 2H, CH_2), 1.71–1.79 (m, 1H, CH_2), 1.82–1.93 (m, 2H, CH_2), 2.01–2.09 (m, 2H, CH_2), 4.64–4.69 (m, 1H, CH), 6.94 (bs, 1H, NH_2), 7.48 (bs, 1H, NH_2), 7.79 (s, 1H, CH), 8.14 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 23.7, 32.5, 62.2, 117.8, 129.8, 138.5, 163.4 ppm; MS (ESI): m/z = 179 [M$^+$].

4-(Aminocarbonyl)-1H-pyrazole-1-acetic acid ethyl ester
(**8h**, $C_8H_{11}N_3O_3$)
At rt for 4.5 h. Colourless crystals, m.p.: 131–133 °C; yield 0.44 g (78%); IR (KBr): $\bar{\nu}$ = 3,377, 3,199, 2,986, 1,755, 1,654, 1,609, 1,562, 1,428, 1,333, 1,215 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.23 (t, J = 7.0 Hz, 3H, CH_3), 4.18 (q, J = 7.2 Hz, 2H, CH_2), 5.08 (s, 2H, CH_2), 7.03 (bs, 1H, NH_2), 7.59 (bs, 1H, NH_2), 7.85 (s, 1H, CH), 8.11 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.0, 52.6, 61.1, 118.8, 133.0, 139.1, 163.1, 167.7 ppm; MS (ESI): m/z = 197 [M$^+$].

1-(2,2-Diethoxyethyl)-1H-pyrazole-4-carboxamide
(**8i**, $C_{10}H_{17}N_3O_3$)
At rt for 4.5 h. Colourless crystals, m.p.: 135–137 °C; yield 0.79 g (78%); IR (KBr): $\bar{\nu}$ = 3,397, 3,217, 2,979, 1,652, 1,606, 1,558, 1,434, 1,351, 1,290, 1,129 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.97–1.06 (m, 6H, CH_3), 3.38–3.43 (m, 2H, CH_2), 3.55–3.65 (m, 2H, CH_2), 4.17 (d, J = 5.4 Hz, 2H, CH_2), 4.78 (t, J = 5.5 Hz, 1H, CH), 6.98 (bs, 1H, NH_2), 7.54 (bs, 1H, NH_2), 7.81 (s, 1H, CH), 8.07 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6):

δ = 15.1, 54.0, 62.1, 100.2, 118.3, 132.3, 138.8, 163.3 ppm; MS (ESI): m/z = 227 [M^+].

*General procedure for the synthesis of **10a–10d***

To a stirred suspension of 0.5 g **4** (4.5 mmol) and 0.622 g K_2CO_3 (4.5 mmol) in 5 cm^3 DMF at room temperature was added **9** (4.9 mmol). The reaction mass was stirred at room temperature for 4–5 h (TLC monitoring, chloroform–methanol, 9.5:0.5). The reaction mass was then quenched in ice-cold water, the solid obtained was isolated by filtration under suction, washed with water, and recrystallized from ethanol to afford **10** in good yield.

4-Aminocarbonyl-N-[4-chloro-3-(trifluoromethyl)phenyl]-1H-pyrazole-1-acetamide (**10a**, $C_{13}H_{10}ClF_3N_4O_2$)
At rt for 4.5 h. White solid, m.p.: 222–224 °C; yield 1.43 g (92%); IR (KBr): $\bar{\nu}$ = 3,481, 3,322, 3,281, 3,195, 1,701, 1,654, 1,601, 1,556, 1,483, 1,418, 1,320 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.08 (s, 2H, CH_2), 7.03 (bs, 1H, NH_2), 7.60 (bs, 1H, NH_2), 7.66–7.78 (m, 3H, ArH), 7.84 (s, 1H, ArH), 8.16 (s, 1H, ArH), 10.81 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 54.6, 117.7, 120.7, 123.8, 124.3, 126.5, 126.9, 132.1, 133.4, 134.8, 136.2, 166.3, 168.7 ppm; MS (ESI): m/z = 346 [M^+], 348 [M + 2].

4-Aminocarbonyl-N-(4-methylphenyl)-1H-pyrazole-1-acetamide (**10b**, $C_{13}H_{14}N_4O_2$)
At rt for 4.5 h. Colourless crystals, m.p.: 250–252 °C; yield 0.98 g (85%); IR (KBr): $\bar{\nu}$ = 3,393, 3,273, 3,190, 2,943, 1,684, 1,652, 1,617, 1,540, 1,515, 1,428, 1,314 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.25 (s, 3H, CH_3), 5.01 (s, 2H, CH_2), 7.01 (bs, 1H, NH_2), 7.10 (d, J = 8.4 Hz, 2H, ArH), 7.43 (d, J = 8.1 Hz, 2H, ArH), 7.58 (bs, 1H, NH_2), 7.83 (s, 1H, ArH), 8.15 (s, 1H, ArH), 10.25 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.5, 54.6, 118.5, 119.0, 129.1, 132.5, 133.2, 135.8, 137.0, 166.3, 169.5 ppm; MS (ESI): m/z = 258 [M^+].

4-Aminocarbonyl-N-(2,4-dichlorophenyl)-1H-pyrazole-1-acetamide (**10c**, $C_{12}H_{10}Cl_2N_4O_2$)
At rt for 4.0 h. White solid, m.p.: 220–223 °C; yield 1.21 g (87%); IR (KBr): $\bar{\nu}$ = 3,356, 3,252, 3,190, 2,939, 1,690, 1,666, 1,628, 1,566, 1,528, 1,474, 1,432 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.15 (s, 2H, CH_2), 7.02 (bs, 1H, NH), 7.39 (d, J = 8.7 Hz, 2H, ArH), 7.59 (bs, 2H, NH_2), 7.67 (s, 1H, ArH), 7.76 (d, J = 8.7 Hz, 2H, ArH), 7.85 (s, 1H, ArH), 8.16 (s, 1H, ArH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 54.3, 118.6, 126.4, 126.7, 127.5, 128.9, 129.4, 133.1, 133.3, 135.2, 166.2, 169.6 ppm; MS (ESI): m/z = 313 [M^+], 317 [M + 4].

4-Aminocarbonyl-N-(4-chlorophenyl)-1H-pyrazole-1-acetamide (**10d**, $C_{12}H_{11}ClN_4O_2$)
At rt for 5 h. White solid, m.p.: 252–255 °C; yield 1.0 g (87%); IR (KBr): $\bar{\nu}$ = 3,391, 3,265, 3,187, 1,675, 1,651, 1,618, 1,598, 1,546, 1,492, 1,425, 1,313 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.03 (s, 2H, CH_2), 7.01 (bs, 2H, NH_2), 7.35 (d, J = 6.9 Hz, 2H, ArH), 7.38 (d, J = 6.7 Hz, 2H, ArH), 7.83 (s, 1H, ArH), 8.15 (s, 1H, ArH), 10.48 (bs, 1H, NH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 54.6, 118.5, 120.5, 127.0, 128.6, 133.2, 137.2, 138.2, 168.2, 170.9 ppm; MS (ESI): m/z = 278 [M^+], 280 [M + 2].

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