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FULL-LENGTH PAPER

Catalyst-free, one-pot, three-component synthesis of 5-amino-1,3-aryl-1*H*-pyrazole-4-carbonitriles in green media

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Abstract An efficient, one-pot, three-component synthesis of various biologically important heterocyclic compounds is described via a tandem Knoevengel-cyclo condensation reaction of aromatic aldehydes, malono derivatives, and phenyl hydrazine derivatives in water and ethanol at room temperature.

Keywords Multi-component reactions · MCRs · Catalyst-free · Pyrazole · 5-Amino pyrazole · Green chemistry

Introduction

Nitrogen-linked heterocyclic compounds have received considerable attention in recent times due to their wide applications. The cyclization reaction of suitable linear compounds is one of the most common and popular methods for preparing these heterocyclic compounds [1–7]. Between these aza containing heterocyclic compounds, pyrazoles have a long history of application in agrochemical and pharmaceutical industries [8,9]. These compounds are known to display anti-tumor [10,11], anti-bacterial [12–14], anti-microbial [15–19], anti-fungal [20], anti-inflammatory [21,22], analgesic [23,24], anti-depressant [25], anti-convulsant [26], anti-pyretic activities [27]. anti-parasitic [28,29], anti-malarial [30], anti-tumor [31], and anti-viral activities [32,33]. It is well-known that the study of pyrazole derivatives is significant in pesticide chemistry, because of their herbicidal [34,35], and insecticidal activities [36]. Moreover, applications of pyrazole containing compounds as ligands in coordination chemistry are well-documented in the literature [37,38]. A previous investigation revealed that 5-amino-4-cyanopyrazole derivatives have anti-bacterial activity [39,40]. The pyrazole motif makes the core structure of blockbuster drugs such as Celebrex(R) [41] and Viagra(R) [42] that act as PDE-5 inhibitors, Zoniporide [43] as sodium hydrogen ion exchanger inhibitors, 1-aryl-5-aminopyrazole as NPY5 antagonist [44], and PNU-32945 as HIV-reverse transcriptase inhibitors [45] (Fig. 1).

Many synthetic methods are available for the synthesis of pyrazole derivatives [46–50]. The most popular methods for the preparation of 1,3,4,5-tetrasubstituted pyrazoles are the reactions between 1,3-difunctional compounds with hydrazine derivatives (Scheme 1a) [51], 1,3-dipolar cycloadditions of diazo compounds onto triple bonds (Scheme 1b) [52,53] and the oxidative N–N bond formation of enamines and nitriles (Scheme 1c) [54]. Another used approach is the functionalization of preformed trisubstituted pyrazoles by either nucleophilic substitution or transition metal catalyzed C-N bond formation (Scheme 1d) [55–60]. A survey of the literature shows that the majority of the strategies involve either multistep sequences, or expensive catalysts, inert atmosphere, anhydrous conditions, lengthy reaction times, and laborious workup.

It is well-known that nitriles are widely used as intermediates for a large number of heterocyclic compounds [61,62]. In continuation of our research interest in the synthesis of biologically important heterocyclic compounds, we have synthesized a series of new pyrazole derivatives via a tandem Knoevengel cyclo-condensation reaction of aromatic aldehydes, malono derivatives, and phenyl hydrazinium chloride derivatives, in water and ethanol at room temperature (Scheme 2).

Electronic supplementary material The online version of this article (doi:10.1007/s11030-013-9445-y) contains supplementary material, which is available to authorized users.

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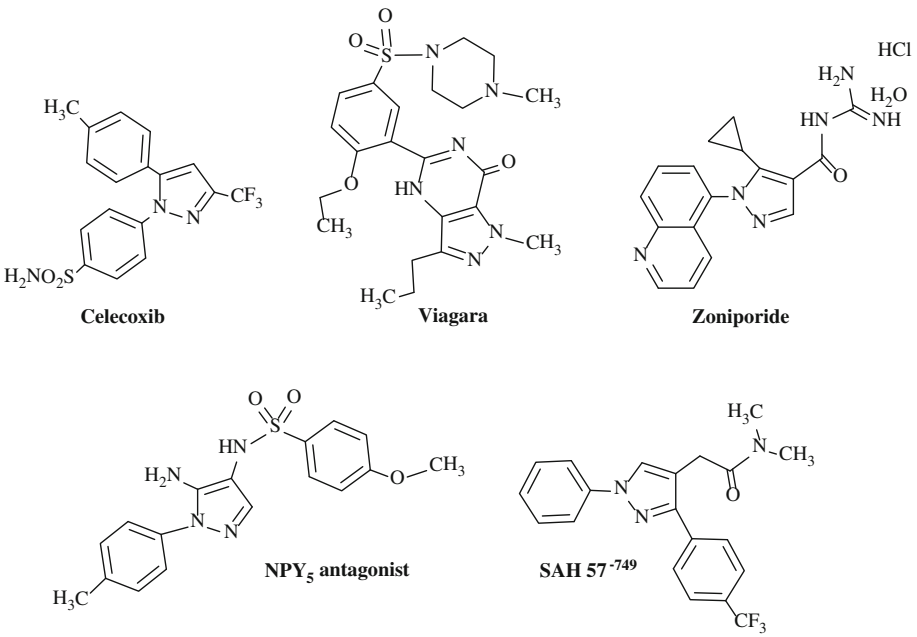
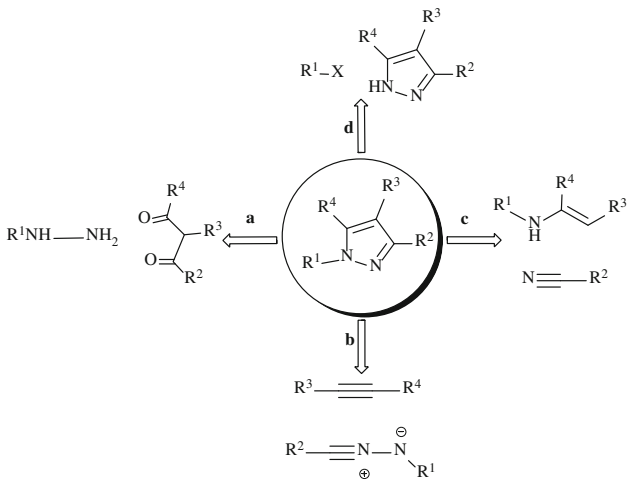
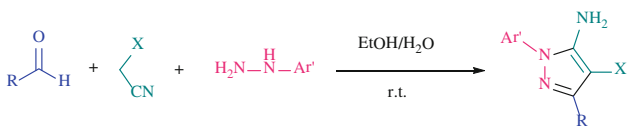
Fig. 1 Biological active compounds based on pyrazole derivatives





Scheme 1 Approaches to polysubstituted pyrazoles



Scheme 2 Synthesis of poly-substituted amino pyrazoles

Results and discussion

To find the optimized reaction conditions, we initiated a catalyst screening exercise employing benzaldehyde (1 mmol), malononitrile (1 mmol), and phenylhydrazine (1 mmol) in the presence of various base catalysts such as Et_3N, DABCO, DBU, NaOH, and K_2CO_3 at room temperature. Screening of the reaction conditions established that the nature of the catalyst had no significant effect on the yield of pyrazole. Interestingly, in the absence of any base catalyst, this three-component coupling cyclization reaction proceeded smoothly to afford the desired 5-amino-4-cyano 1, 3 diphenyl pyrazole in excellent yield after 30 min at room temperature in the mixture of water and ethanol (1:1 v/v) as solvent. Therefore, the phenylhydrazine itself is acting as both a Brønsted base catalyst in this reaction and as a nucleophile. This is why the bases had no effect on the reaction yield. Hence, we monitored the effect of the amount of phenylhydrazine on the yield of reaction. With a higher amount of phenylhydrazine no increase in the yield of 5-amino-4-cyano 1, 3 diphenyl pyrazole is observed. However, diminishing the amount of phenylhydrazine resulted in incomplete conversion.

With these optimized conditions in hand, this three-component reaction can be readily diversified through a combination of a range of aryl aldehydes, malono derivatives, and phenyl hydrazine derivatives. Among the malono derivatives, malononitrile afforded excellent yields of products (Table 1, entries 1–17). Remarkably, low nucleophilic malono derivatives also gave products (Table 1, entries 21–24) in excellent yields. Similarly, dialdehydes were also successfully employed to give bis poly-substituted pyrazoles in excellent yields (Table 1, entries 18–20).

To explore the generality of the reaction, aldehydes with electron-withdrawing substituents on aromatic ring were also employed (Table 1, entries 5, 6, 7, 8, 23). It is worth mentioning that sterically bulky aldehydes were readily converted into the desired products (Table 1, entries 3, 7). To further expand the scope of the reaction, the use of heteroaryl aldehydes was investigated (Table 1, entries 11, 12).

Some aliphatic aldehydes were also screened to carry out the three-component coupling by this method and the results

Table 1 Synthesis of 5-amino-4-cyano 1,3-diaryl-1*H*-pyrazole derivatives

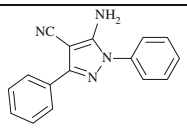
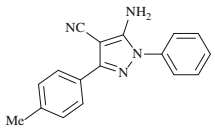
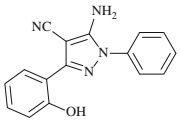
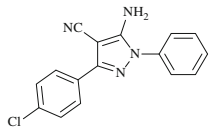
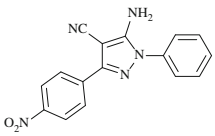
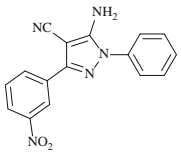
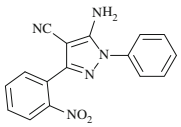
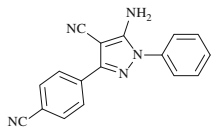
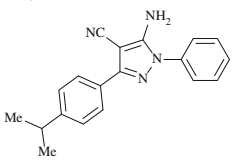
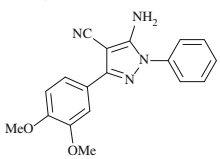
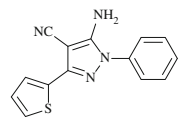
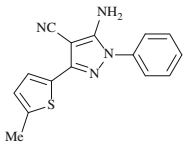
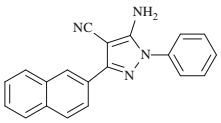
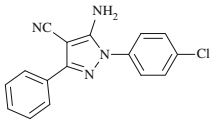
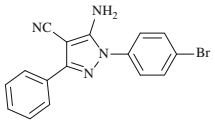
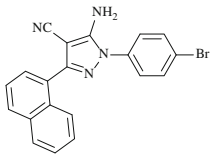
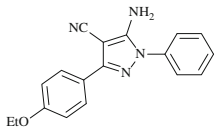
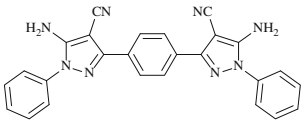
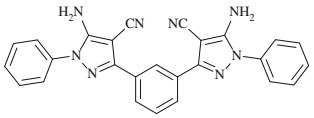
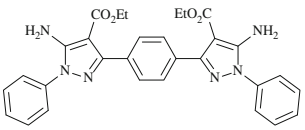
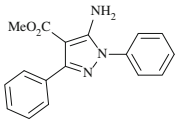
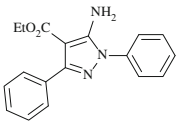
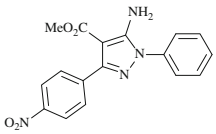
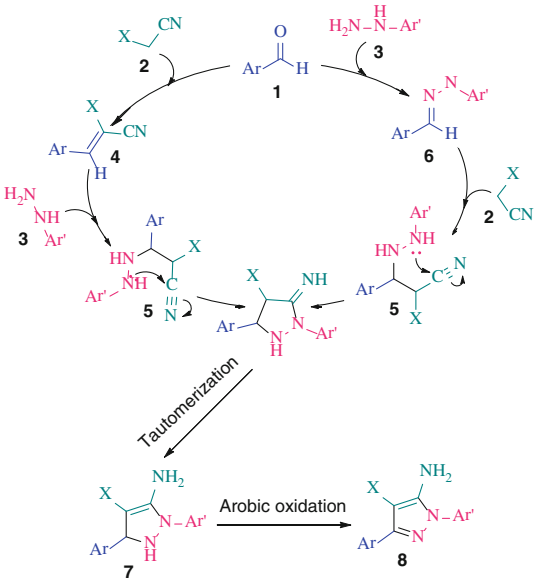
Entry	R	X	Ar '	Product	Time (h)	Yield[a] (%)
1	C_6H_5	CN	C_6H_5		0.50	95
2	4-Me-C_6H_4	CN	C_6H_5		0.65	88
3	2-OH-C_6H_4	CN	C_6H_5		1.30	96
4	4-Cl-C_6H_4	CN	C_6H_5		0.75	92
5	4-NO_2-C_6H_4	CN	C_6H_5		0.35	98
6	3-NO_2-C_6H_4	CN	C_6H_5		0.40	96
7	2-NO_2-C_6H_4	CN	C_6H_5		0.30	95
8	4-CN-C_6H_4	CN	C_6H_5		0.65	90
9	4-isopropyl-C_6H_4	CN	C_6H_5		1.50	78
10	3,4-di- MeO-C_6H_4	CN	C_6H_5		8.00	73
11	2-thienyl	CN	C_6H_5		1.75	88
12	5-Me-2-thienyl	CN	C_6H_5		2.00	90

Table 1 continued

Entry	R	X	Ar'	Product	Time (h)	Yield[a] (%)
13	2-naphthyl	CN	C_6H_5		3.00	93
14	C_6H_5	CN	4-Cl-C_6H_4		1.00	89
15	C_6H_5	CN	4-Br-C_6H_4		0.75	89
16	1-naphthyl	CN	4-Br-C_6H_4		3.00	90
17	4-EtO-C_6H_4	CN	C_6H_5		0.75	86
18	4-OHC-C_6H_4	CN	C_6H_5		0.65	95
19	3-OHC-C_6H_4	CN	C_6H_5		0.80	92
20	4-OHC-C_6H_4	CO_2Et	C_6H_5		2.00	87
21	C_6H_5	CO_2Me	C_6H_5		1.50	93
22	C_6H_5	CO_2Et	C_6H_5		1.50	95
23	4-NO_2-C_6H_4	CO_2Me	C_6H_5		1.00	95
24	$CH_3CH_2CH_2$	CN	C_6H_5	–	15	–
25	$(CH_3)_2CH$	CN	C_6H_5	–	15	–

[a] Isolated yields

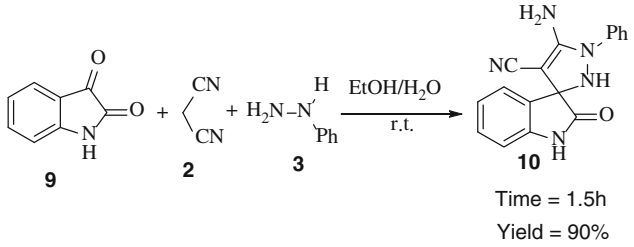
are listed in Table 1. However, no products were obtained when aliphatic aldehydes were involved in this one-pot room temperature catalyst-free reaction (Table 1, entries 24, 25). The trend observed due chiefly to the lower reactivity of alyphatic aldehydes toward nucleophilic addition in comparison with aromatic aldehydes.



Scheme 3 Proposed mechanism for the synthesis of poly-substituted amino pyrazoles

The selectivity in the synthesis of 5-amino-1,3-aryl-1-1*H*-pyrazole-4-carbonitriles can be explained by the strict sequence of the reactions shown in Scheme 3. On the basis of this suggested mechanism, olefin (**4**) readily prepares *in situ* from Knoevenagel condensation of aromatic aldehyde (**1**) with a highly reactive malono derivative (**2**). Phenylhydrazine derivative (**3**), to be able to react easily with olefin (**4**) and to eventually give rise to the formation of intermediate (**5**), which then causes the inner molecular ring to be formed after a tautomeric proton shift to produce 2,3-dihydropyrazole derivative (**7**). Finally, atmospheric oxygen acts as an oxidant to convert 2,3-dihydropyrazole derivative to the corresponding pyrazole (**8**). In this study, we did not see any dependence of reaction time and yield to the order of addition of reactants to the reaction mixture. Therefore, another plausible mechanism can be possible for the formation of imine (**6**) from the reaction of aryl aldehyde (**1**) with phenylhydrazine derivative (**3**). Malono derivative (**2**), to be able to react with imine (**6**) to give rise to the formation of intermediate (**5**) that finally convert to pyrazole (**8**) (Scheme 3).

There are various reports in the literature that pyrazole to be formed through the oxidation of initially formed dihydropyrazole (pyrazoline), using atmospheric oxigen as oxidant (the reaction was run in air) [63] or nickel peroxide or manganese dioxide or DDQ in benzene [64–66] served as the oxidant for this transformation. However, because of the difficulties of the separation of pyrazoline intermediate even under an inert atmosphere, we selected isatin (an active ketone) as a model to clarify that this reaction proceed through the pyrazoline intermediate. The reaction of isatin (**9**) with malononitrile (**2**) and phenylhydrazine (**3**)



Scheme 4 Synthesis of 5′-Amino-2-oxo-1′-phenyl-1′,2′-dihydrospiro [indoline-3,3′-pyrazole]-4-carbonitrile from the reaction of isatin malononitrile and phenylhydrazine

yielded a spirosystem with 2-oxoindole and pyrazoline fragment (**10**). The first stage of the reaction potentially follows a classic mechanism of a nucleophilic attack of the malononitrile in position C3 on isatin throgh the formation of 2-(2-oxoindolin-3-ylidene)malononitrile followed by Michael addition of phenylhydrazine and then intramolecular cyclization with toutomerization to 5′-amino-2-oxo-1′-phenyl-1′, 2-dihydrospiro[indoline-3,3′-pyrazole]-4-carbonitrile (Scheme 4).

Thus, from a practical point of view, the newly developed protocol is a significant proof of the fact that nitrile is one of the most versatile functional groups as it can be readily transformed into various other functional groups. Significantly, the reaction occurred in a catalyst-free fashion with high selectivity and atom economy. To our knowledge, the use of catalyst-free reactions, namely Knoevenagel reaction, Michael-type reaction, ring closure, and subsequent aromatization, in one pot has not been previously reported.

Conclusions

In conclusion, we have disclosed a novel and convenient one-pot synthesis of polysubstituted amino pyrazole analogues *via* multi-component reactions. This catalyst-free reaction proceeded smoothly in good to excellent yields and offered several other advantages including short reaction time, simple experimental workup procedures, and no toxic by-products. The approach to pyrazole systems presented herein avoids the use of catalyst, toxic organic solvent, and anhydrous conditions. This protocol represents a promising green route for the synthesis of this class of compounds.

Experimental

Chemicals and apparatus

All chemicals were purchased from Merck or Fluka Chemical Companies and they were used as received. The ^{1} H NMR (500 MHz, 400 MHz) and ^{13} C NMR (125 MHz, 100 MHz) spectra were recorded on a Bruker Avance DPX-250, FT-

NMR spectrometer (δ in ppm). Tetramethylsailane (TMS) was used as internal standard. The abbreviations used for NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected.

General procedure for the preparation of 5-Amino-1,3-diaryl-1 *H*-pyrazole-4-carbonitriles derivatives

Phenyl hydrazine derivative, (1 mmol) aromatic aldehyde (1 mmol), and malono derivative (1 mmol) were added in a 25 ml round-bottomed flask contained water and ethanol (50 % v/v) (6 mL), and the resulting mixture was stirred at room temperature. After completion of the reaction (as monitored by TLC), crystals of the product were formed, collected by filtration and then recrystallized from hot ethanol to obtain pure products.

Selected spectral data of the products

5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 1)

White powder (0.247 g, 95 %), M.P. = 160 − 161 °C, ν_{max} (KBr) 3485, 3341, 3083, 2359, 1599, 1412, 1253, 1126, 1100, 1075 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.91 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 7.6 Hz, 2H), 7.29–7.35 (m, 3H), 7.41 (t, J = 7.7 Hz, 2H), 7.64 (s, 1H), 7.70 (d, J = 7.2 Hz, 2H), 7.72 (s, 1H). ^{13} C NMR ($CDCl_3$, 125 MHz): δ (ppm) 112.80, 113.26, 120.58, 126.65, 128.9, 129.05, 129.75, 135.74, 137.81, 145.09, 150.41, 156.50. MS (*m/z*): 260 (M+). Anal.Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.52 %. *Found*: C, 73.48; H, 4.86; N, 21.72 %.

5-Amino-1-phenyl-3-p-tolyl-1H-pyrazole-4-carbonitrile (Table 1, entry 2)

Pink powder (0.241g, 88%), M.P. = 117–118 °C, ν_{max} (KBr) 3482, 3319, 3095, 2925, 2359, 1598, 1415, 1257, 1127, 1113, 1096 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.41 (s, 3H), 6.91 (dd, J = 3.5 Hz and J = 7.3 Hz, 1H), 7.15 (d, J = 7.76 Hz, 2H), 7.22 (d, J= 7.9 Hz, 2H), 7.29–7.33 (m, 2H), 7.59 (d, J = 7.9 Hz, 2H), 7.70 (s, 2H). ^{13} C NMR ($CDCl_3$, 125 MHz): δ (ppm) 21.90, 104.65, 113.22, 120.44, 126.62, 129.71, 129.77, 132.95, 138.14, 138.97, 145.20, 148.82, 153.20. Anal.Calcd for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.42 %. *Found*: C, 74.88; H, 5.18; N, 20.12 %.

5-Amino-3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 3)

Yellow powder (0.252g, 96 %), M.P. = 161–162 °C, ν_{max} (KBr) 3583, 3487, 3341, 3102, 2358, 2197, 1602, 1413, 1222, 1192, 1108, 1050 cm^{-1} .^{1}H NMR (DMSO–d_6, 500 MHz): δ (ppm) 6.76 (t, J = 7.3 Hz, 1H), 6.85–6.90 (m, 2H), 6.96 (d, J = 7.6 Hz, 2H), 7.14–7.18 (m, 1H), 7.24 (dd, J = 7.5 Hz and J = 8.3 Hz, 2H), 7.53 (dd, J = 1.5 Hz and J = 7.7 Hz, 1H), 8.14 (s, 1H), 10.38 (s, 1H), 10.52 (s, 1H).^{13} C NMR (DMSO–d_6, 125 MHz): δ (ppm) 112.60, 116.80, 119.83, 120.25, 121.35, 125.45, 128.17, 130.05, 130.15, 138.13, 145.62, 150.55, 152.30, 156.51. Anal.Calcd for $C_{16}H_{12}N_4$ O: C, 69.55; H, 4.38; N, 20.28 %. *Found*: C, 69.48; H, 4.46; N, 20.35 %.

5-Amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 4)

White powder (0.279g, 92 %), M.P. = 129–130 °C, ν_{max} (KBr) 3448, 3315, 3074, 2358, 1595, 1414, 1293, 1254, 1133, 1083 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.93 (t, J = 7.3 Hz, 1H), 7.15 (d, J = 7.7 Hz, 2H), 7.29–7.34 (m, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.67 (s, 2H).^{13} C NMR ($CDCl_3$, 125 MHz): δ (ppm) 110.24, 113.29, 120.85, 127.71, 129.26, 129.77, 134.26, 134.44, 136.35, 144.78, 150.21, 155.45. Anal.Calcd for $C_{16}H_{11}ClN_4$: C, 65.20; H, 3.76; N, 19.01 %. *Found*: C, 65.37; H, 3.81; N, 18.95 %.

5-Amino-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 5)

Red powder (0.298 g, 98 %), M.P. = 164–165 °C, ν_{max} (KBr) 3467, 3350, 3102, 2359, 1600, 1415, 1457, 1344, 1256, 1123, 1107, 1095 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.98 (s, 1H) 7.18 (d, J = 7.5 Hz, 2H), 7.29–7.34 (m, 2H), 7.73–7.79 (m, 3H), 8.05 (s, 1H), 8.24 (d, J = 7.6 Hz, 2H). MS (*m/z*): 305 (M+). Anal.Calcd for $C_{16}H_{11}N_5O_2$: C, 62.95; H, 3.63; N, 22.94 %. *Found*: C, 63.05; H, 3.58; N, 23.03 %.

5-Amino-3-(3-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 6)

Orange powder (0.292 g, 96 %), M.P. = 129–130 °C, ν_{max} (KBr) 3452, 3324, 3103, 2357, 1594, 1478, 1447, 1344, 1338, 1263, 1147, 1100, 1096 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.97 (t, J=7.2 Hz, 1H), 7.18 (d, J=8.4 Hz, 2H), 7.35 (t, J=7.5 Hz, 2H), 7.56 (t, J=7.9 Hz, 1H), 7.74 (s, 1H), 7.89 (s, 1H), 8.01 (d, J=7.5 Hz, 1H), 8.14 (d, J=8.0 Hz, 1H), 8.48 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 112.44, 113.42, 121.10, 121.38, 122.98, 129.85, 129.94, 131.80, 134.30, 137.72, 144.27,149.16, 156.41. Anal.Calcd for $C_{16}H_{11}N_5O_2$: C, 62.95; H, 3.63; N, 22.94 %. *Found*: C, 62.78; H, 3.77; N, 22.90 %.

5-Amino-3-(2-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 7)

Red powder (0.289 g, 95 %), M.P. = 160–161 °C, ν_{max} (KBr) 3439, 3296, 3024, 2358, 1600, 1497, 1469, 1342, 1333, 1298, 1254, 1163, 1134 cm^{-1}. ^{1}H NMR (DMSO–d_6, 500 MHz): δ (ppm) 6.81 (t, J = 7.3 Hz, 1H), 7.11 (d, J = 7.7 Hz, 2H), 7.25 (t, J = 7.6 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.95 (d, J = 7.5 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 8.26 (s, 1H), 10.88 (s, 1H). Anal.Calcd for $C_{16}H_{11}N_5O_2$: C, 62.95; H, 3.63; N, 22.94 %. *Found*: C, 63.12; H, 3.55; N, 22.85 %.

5-Amino-3-(4-cyanophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 8)

Yellow powder (0.256 g, 90 %), M.P. = 159–160 °C, ν_{max} (KBr) 3438, 3306, 3279, 2359, 2224, 1593, 1478, 1262, 1159, 1107, 1093 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.80 (t, J = 7.2 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 7.24 (t, J = 7.4 Hz, 2H), 7.78–7.81 (m, 4H), 7.87 (s, 1H), 10.73 (s, 1H). Anal.Calcd for $C_{17}H_{11}N_5$: C, 71.57; H, 3.89; N, 24.55 %. *Found*: C, 71.35; H, 3.70; N, 24.50 %.

5-Amino-3-(4-isopropylphenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 9)

Pink powder (0.235 g, 78 %), M.P. = 139–140 °C, ν_{max} (KBr) 3417, 3295, 3102, 2923, 2357, 1600, 1481, 1257, 1125, 1096, 1048 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 1.33 (d, J = 6.9 Hz, 6H), 2.94–3.00 (m, 1H), 6.91 (t, J = 7.2 Hz, 1H), 7.15 (d, J = 7.8 Hz, 2H), 7.27–7.33 (m, 4H), 7.63 (d, J = 7.965 Hz, 2H), 7.70 (s, 1H), 8.35 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 24.32, 34.45, 111.28, 113.17, 120.38, 126.69, 127.14, 129.71, 133.39, 137.99, 145.27, 149.32, 149.93, 156.43. Anal.Calcd for $C_{19}H_{18}N_4$: C, 75.47; H, 6.00; N, 18.53 %. *Found*: C, 75.25; H, 5.78; N, 19.05 %.

5-Amino-3-(3,4-dimethoxyphenyl)-1-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 10)

White powder (0.233 g, 73 %), M.P. = 122–123 °C, ν_{max} (KBr) 3432, 3295, 3007, 2939, 2357, 1600, 1476, 1331, 1264, 1236, 1167, 1130, 1018 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 3.93 (s, 3H), 3.99 (s, 3H), 6.86–6.94 (m, 2H), 7.06 (d, J = 7.1 Hz, 1H), 7.13 (d, J = 8.2 Hz, 2H), 7.30 (t, J = 7.4 Hz, 2H), 7.40 (s, 1H), 7.63 (s, 1H), 9.90 (s, 1H). ^{13} C NMR ($CDCl_3$, 125 MHz): δ (ppm) 56.20, 56.23, 113.62, 114.70, 118.87, 118.96, 119.56, 120.43, 131.71, 131.91, 132.85, 133.19, 138.59, 140.46, 150.73, 156.47. Anal.Calcd for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49 %. *Found*: C, 67.37; H, 5.10; N, 17.52 %.

5-Amino-1-phenyl-3-(thiophen-2-yl)-1H-pyrazole-4-carbonitrile (Table 1, entry 11)

Yellow powder (0.234 g, 88 %), M.P. = 140–141 °C, ν_{max} (KBr) 3412, 3325, 3092, 2357, 1600, 1478, 1298, 1264, 1138, 1069 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.92 (t, J = 7.3 Hz, 1H), 7.05 (dd, J = 3.6 Hz and J = 4.9 Hz, 1H), 7.12 (d, J = 7.4 Hz, 3H), 7.31 (dd, J = 5.0 Hz and J = 14.1 Hz, 3H), 7.56 (s, 1H), 7.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 113.24, 114.21, 120.64, 122.44, 126.33, 126.89, 127.66, 129.76, 132.70, 140.91, 144.86, 155.22. Anal.Calcd for $C_{14}H_{10}N_4S$: C, 63.14; H, 3.78; N, 21.04 %. *Found*: C, 63.33; H, 3.82; N, 20.88 %.

5-Amino-3-(5-methylthiophen-2-yl)-1-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 12)

Yellow powder (0.252 g, 90 %), M.P. = 131–132 °C, ν_{max} (KBr) 3427, 3303, 3102, 2919, 2357, 1600, 1469, 1257, 1230, 1126, 1100, 1070 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.53 (s, 3H), 6.68–6.71 (m, 1H), 6.88–6.92 (m, 2H), 7.10 (d, J = 7.7 Hz, 2H), 7.28–7.32 (m, 2H), 7.46 (s, 1H), 7.76 (s, 1H). ^{13} C NMR ($CDCl_3$, 125 MHz): δ (ppm) 16.08, 113.15, 114.13, 120.42, 125.86, 126.10, 127.16, 129.71, 133.18, 138.66, 141.38, 145.05, 156.73. Anal.Calcd for $C_{15}H_{12}N_4$ S: C, 64.26; H, 4.31; N, 19.98 %. *Found*: C, 64.37; H, 4.25; N, 20.05 %.

5-Amino-3-(naphthalene-6-yl)-1-phenyl -1H-pyrazole-4-carbonitrile (Table 1, entry 13)

Yellow powder (0.264 g, 93 %), M.P. = 229–230 °C, ν_{max} (KBr) 3403, 3341, 3112, 2358, 1600, 1478, 1252, 1122, 1113, 1082 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.87–6.98 (m, 1H), 7.20 (d, J = 7.4 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.50–7.52 (m, 2H), 7.70 (s, 1H), 7.79–7.94 (m, 5H), 8.07 (d, J = 8.5 Hz, 1H).^{13} C NMR ($CDCl_3$, 125 MHz): δ (ppm) 113.27, 114.81, 120.66, 123.43, 126.63, 126.83, 126.95, 127.63, 128.28, 128.44, 128.83, 129.77, 130.58, 132.22, 133.98, 137.87, 143.30, 155.97. Anal.Calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05 %. *Found*: C, 77.18; H, 4.72; N, 18.13 %.

5-Amino-1-(4-chlorophenyl)-3-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 14)

Pink powder (0.261 g, 89 %), M.P. = 134–135 °C, ν_{max} (KBr) 3421, 3318, 3098, 2356, 1597, 1477, 1257, 1135, 1096, 1074 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.08 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.35–7.36 (m, 1H) 7.41 (t, J = 7.9 Hz, 2H), 7.55 (s, 1H), 7.68 (d, J = 7.7 Hz, 2H), 7.72 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 112.10, 114.32, 125.10, 126.70, 129.08, 129.12,

129.62, 132.32, 135.43, 138.40, 143.70, 155.98. Anal.Calcd for $C_{16}H_{11}ClN_4$: C, 65.20; H, 3.76; N, 19.01 %. *Found*: C, 64.97; H, 3.87; N, 19.11 %.

5-Amino-1-(4-bromophenyl)-3-phenyl-1H-pyrazole-4-carbonitrile (Table 1, entry 15)

White powder (0.299 g, 89 %), M.P. = 130–131 °C, ν_{max} (KBr) 3425, 3317, 3114, 2357, 1597, 1480, 1253, 1137, 1094, 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.03 (d, J = 8.8 Hz, 2H), 7.36 (d, J= 7.3 Hz, 1H), 7.39–7.43 (m, 4H), 7.59 (s, 1H), 7.68 (d, J = 5.1 Hz, 2H), 7.68 (s, 1H).^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 112.29, 114.78, 125.65, 126.73, 129.10, 129.16, 130.12, 132.51, 135.41, 138.50, 144.15, 151.78. Anal.Calcd for $C_{16}H_{11}BrN_4$: C, 56.66; H, 3.27; N, 16.52 %. *Found*: C, 56.97; H, 3.15; N, 16.43 %.

5-Amino-1-(4-bromophenyl)-3-(naphthalen-1-yl)-1H-pyrazole-4-carbonitrile (Table 1, entry 16)

Yellow powder (0.260 g, 90 %), M.P. = 139–140 °C, ν_{max} (KBr) 3470, 3306, 3082, 2358, 1591, 1480, 1250, 1137, 1096, 1068 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.08 (d, J= 8.4 Hz, 2H), 7.43 (d, J= 8.5 Hz, 2H), 7.51–7.59 (m, 2H), 7.63 (t, J = 8.1 Hz, 1H), 7.72 (s, 1H), 7.87 (t, J= 6.2 Hz, 2H), 7.92 (d, J = 8.0 Hz, 1H), 8.32 (s, 1H), 8.76 (d, J= 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 112.37, 114.81, 119.02, 124.21, 124.63, 125.87, 126.42, 127.24, 128.12, 128.86, 129.25, 129.75, 130.79, 132.59, 134.44, 138.04, 144.10, 156.32. Anal.Calcd for $C_{20}H_{13}BrN_4$: C, 61.71; H, 3.37; N, 14.39 %. *Found*: C, 61.55; H, 3.44; N, 14.28 %.

5-Amino-3-(4-ethoxyphenyl)-1H-pyrazole-4-carbonitrile (Table 1, entry 17)

White powder (0.261 g, 86 %), M.p. = 123–124 °C, ν_{max} (KBr) 3416, 3329, 3102, 2921, 2358, 1602, 1481, 1252, 1126, 1118, 1096 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 1.47(t, J = 6.9 Hz, 3H), 4.10 (q, J = 6.9 Hz, 2H), 6.88 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.29–7.32 (m, 2H), 7.57 (s, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.70 (s, 1H). ^{13} C NMR ($CDCl_3$, 125 MHz): δ (ppm) 15.231, 63.98, 112.34, 113.27, 115.108, 120.38, 123.55, 128.16, 129.70, 138.01, 138.32, 138.52, 145.89, 159.99. Anal.Calcd for $C_{18}H_{16}N_4$ O: C, 71.04; H, 5.30; N, 18.41 %. *Found*: C, 71.22; H, 5.16; N, 18.52 %.

3,3′-(1,4-phenylene)bis(5-amino-1-phenyl-1H-pyrazole-4-carbonitrile) (Table 1, entry 18)

Orange powder (0.420 g, 95 %), M.P > 230 °C, ν_{max} (KBr) 3422, 3302, 3108, 2357, 1594, 1469, 1254, 1140, 1102, 1055 cm^{-1}. ^1H NMR (DMSO–d_6, 500 MHz): δ (ppm) 6.76 (t, J = 7.6 Hz, 2H) 7.09 (d, J = 7.7 Hz, 4H), 7.23 (t, J = 7.5 Hz, 4H), 7.65 (d, J = 4.2 Hz, 4H), 7.87 (s, 2H), 10.38 (s, 2H). ^{13}C NMR (DMSO–d_6, 125 MHz): δ (ppm) 112.92, 113.86, 119.69, 124.30, 126.75, 130.00, 136.21, 137.06, 146.07, 156.76. MS (*m/z*): 442 (M+). Anal.Calcd for $C_{26}H_{18}N_8$: C, 70.58; H, 4.10; N, 25.32 %. *Found*: C, 70.82; H, 3.95; N, 25.21 %.

3,3′-(1,3-phenylene)bis(5-amino-1-phenyl-1H-pyrazole-4-carbonitrile) (Table 1, entry 19)

Yellow powder (0.406 g, 92 %), M.P> 230 °C, ν_{max} (KBr) 3482, 3305, 3076, 2357, 1592, 1480, 1252, 1133, 1101, 1072 cm^{-1}. ^1H NMR (DMSO–d_6, 500 MHz): δ (ppm) 6.77 (t, J = 7.2 Hz, 2H), 7.11 (d, J = 7.9 Hz, 4H), 7.24 (t, J = 7.6 Hz, 4H), 7.41 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.86 (s, 1H), 7.92 (s, 2H), 10.38 (s, 2H). ^{13} C NMR (DMSO–d_6, 125 MHz): δ (ppm) 112.94, 113.70, 119.72, 121.80, 123.95, 125.81, 129.84, 130.02, 137.09, 137.13, 146.13, 156.44. MS (*m/z*): 442 (M+). Anal.Calcd for $C_{26}H_{18}N_8$: C, 70.58; H, 4.10; N, 25.32 %. *Found*: C, 70.45; H, 4.17; N, 25.39 %.

Diethyl 3,3′-(1,4-phenylene)bis(5-amino-1-phenyl-1H-pyrazole-4-carboxylate) (Table 1, entry 20)

Yellow powder (0.466 g, 87 %), M.P> 230 °C, ν_{max} (KBr) 3486, 3348, 3108, 2996, 1722, 1598, 1475, 1251, 1130, 1121, 1079 cm^{-1}. ^1H NMR (DMSO–d_6, 400 MHz): δ (ppm) 1.43 (t, J = 7.2 Hz, 6H), 4.42 (q, J = 7.2 Hz, 4H), 6.96 (t, J = 7.2 Hz, 2H), 7.18 (d, J = 7.6 Hz, 4H), 7.34 (t, J = 8.0 Hz, 4H), 7.71 (s, 2H), 7.79 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 8.25 (s, 2H). MS (*m/z*): 536 (M+). Anal.Calcd for $C_{30}H_{28}N_6O_4$: C, 67.15; H, 5.26; N, 15.66 %. *Found*: C, 67.23; H, 5.33; N, 15.54 %.

Methyl 5-amino-1,3-diphenyl-1H-pyrazole-4-carboxylate (Table 1, entry 21)

White powder (0.272 g, 93 %), M.p. = 161–162 °C, ν_{max} (KBr) 3463, 3312, 3104, 2985, 1719, 1600, 1481, 1254, 1134, 1118, 1083 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.68 (s, 3H), 6.93 (t, J = 7.2 Hz, 1H), 7.16 (d, J = 8 Hz, 2H), 7.29–7.37 (m, 3H), 7.42 (t, J= 7.4 Hz, 2H), 7.61 (s, 1H), 7.68 (s, 1H), 7.70 (d, J = 7.6 Hz, 2H). MS (*m/z*): 293 (M+). Anal.Calcd for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85 %. *Found*: C, 70.94; H, 4.54; N, 13.78 %.

Ethyl 5-amino-1,3-diphenyl-1H-pyrazole-4-carboxylate (Table 1, entry 22)

White powder (0.292 g, 95 %), M.p. = 163–164 °C, ν_{max} (KBr) 3459, 3316, 3078, 2988, 1718, 1593, 1479, 1256, 1128, 1114, 1106 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.36

(t, J= 7.6 Hz, 3H), 4.8 (q, J= 7.6 Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H), 7.17 (d, J = 7.6 Hz, 2H), 7.32–7.37 (m, 3H), 7.42 (t, J = 7.4 Hz, 2H), 7.62 (s, 1H), 7.66 (s, 1H), 7.71 (d, J = 7.2 Hz, 2H). MS (*m/z*): 307 (M+). Anal.Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24 %. *Found*: C, 71.38; H, 4.89; N, 13.45 %.

Methyl 5-amino-3-(4-nitrophenyl)-1-phenyl-1H-pyrazole-4-carboxylate (Table 1, entry 23)

Red powder (0.321 g, 95 %), M.p. = 162–163 °C, ν_{max} (KBr) 3452, 3339, 3110, 2989, 1723, 1600, 1482, 1497, 1348, 1254, 1133, 1120, 1081 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 3.80 (s, 3H), 6.98 (t, J = 7.4 Hz, 1H), 7.18 (d, J= 7.6 Hz, 2H), 7.36 (t, J = 4 Hz, 2H), 7.73 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 8.02 (s, 1H), 8.25 (d, J = 8.8 Hz, 2H). MS (*m/z*): 338 (M+). Anal.Calcd for $C_{18}H_{12}N_4O_4$: C, 62.07; H, 3.47; N, 16.09 %. *Found*: C, 62.50; H, 3.63; N, 15.79 %.

5′-Amino-2-oxo-1′-phenyl-1′,2′-dihydrospiro[indoline-3,3′-pyrazole]-4-carbonitrile (10, Scheme 4)

Yellow powder M.p. = 214–216 ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 88.92 9s, 1H), 6.96 (d, J=7.75 Hz, 1H), 7.09–7.127 (m, 1H), 7.15(d, J=7.56, 1H), 7.27 (dd, J=4.0 Hz, J=8.0 Hz, 1H), 7.39–7.42 (m, 4H), 7.68 (d, J=7.5 Hz, 1H), 8.26 (s, 1H), 12.74 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 103.84, 110.70, 114.88, 119.60, 122.54, 123.077, 123.81, 127.52, 128.48, 129.86, 138.55, 141.72, 142.96, 155.22, 164.09.

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