Synthesis M. Mahdavi et al. Paper

Iodine-Mediated Synthesis of Novel Pyrazole Derivatives

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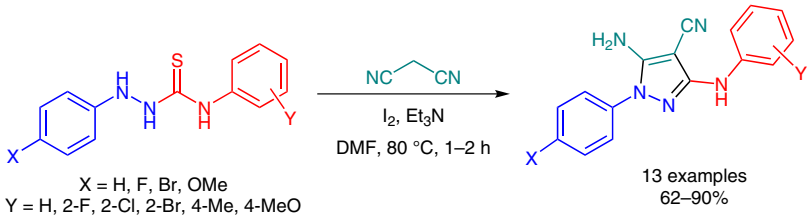

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Abstract The reaction between *N*,2-diarylhydrazinecarbothioamide (generated from arylhydrazines and aryl isothiocyanates) and malononitrile in the presence of iodine/triethylamine in *N*,*N*-dimethylformamide at 80 °C afforded novel pyrazoles, 5-amino-1-aryl-3-(arylamino)-1*H*-pyrazole-4-carbonitriles, in good yields. In this strategy, iodine served as a versatile desulfurizing agent, efficiently promoting the cyclization reaction.

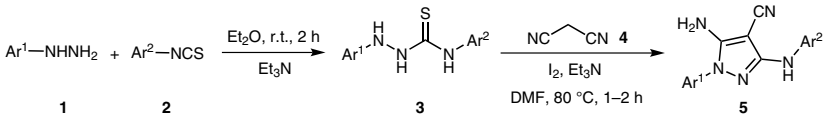
Key words pyrazoles, molecular iodine, heterocycles, isothiocyanates, malononitrile

Molecular iodine has been well documented as an effective Lewis acid catalyst for the promotion of organic transformations[1] as well as polymer synthesis.[2] It is inexpensive, user-friendly, resistant to air and moisture, readily available, and nontoxic. Hence, it is a preferred replacement for toxic and expensive acid catalysts. The application of iodine has been reported in various organic strategies, such as the synthesis of a wide spectrum of heterocycles,[3] the iodination of organic compounds,[4] protection-deprotection of functional groups,[5] Michael additions,[6] Prins-related reactions,[7] and oxidation reactions.[8] Recently, iodine has attracted much attention as an expedient reagent for the synthesis of heterocyclic as well as acyclic compounds starting from isothiocyanates, thioamides, or dithiocarbamates through a desulfurization process.[9] Shibahara et al. reported the synthesis of 2-azaindolizines via iodine-promoted cyclization of *N*-(2-pyridylmethyl)thioamides.[9a] A study by Patel et al. reported the regioselective synthesis of tetrazoles from isothiocyanates; the efficiency of iodine was investigated and compared with another desulfurizing agent (e.g., $HgCl_2$).[9b] Also, iodine has been reported as a useful reagent for the preparation of cyanamides from dithiocarbamate salts.[9c]

Pyrazole derivatives are a key structural motif in a variety of biologically active molecules. Some derivatives have been considered at a clinical level and they are commercially available pharmaceuticals; apixaban, antipyrine, celecoxib, fipronil, novalgine, phenylbutazone, pyrazofurin ramifenazone, and rimonabant are examples in this area.[10] Apart from these pharmaceutical agents, various medicinal properties of pyrazoles, such as analgesic and anti-inflammatory,[11] antibacterial,[12] anticonvulsant,[13] antimalarial,[14] antifungal,[15] antimycobacterial,[16] antioxidant,[17] antitumoral,[18] insecticidal,[19] leishmanicidal,[20] antiglaucoma,[21] and hypoglycemic[22] activity, have been frequently described in the literature. It is clear that new methods for the construction of pyrazole derivatives are still required.

There are various methods for the synthesis of pyrazoles[23] using different synthetic strategies such as the cyclocondensation of arylhydrazines with various monothio-1,3-diketones,[24] four-component coupling of a terminal alkyne, hydrazine/hydroxylamine, carbon monoxide, and an aryl iodide in the presence of a palladium catalyst,[25] reaction of diarylhydrazones and vicinal diols,[26] reaction of vinyl azide, aldehyde, and tosylhydrazine in the presence of base,[27] and acid-catalyzed propargylation of N,N-diprotected hydrazines followed by base-mediated 5-*endo*-*dig* cyclization.[28]

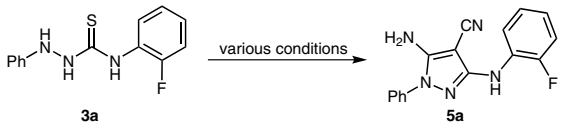
Herein, in continuation of our research program on the synthesis of novel heterocycles,[29] we describe an efficient procedure to access novel pyrazoles, 5-amino-1-aryl-3-(arylamino)-1*H*-pyrazole-4-carbonitrile derivatives **5**,



Scheme 1 Synthesis of 5-amino-1-aryl-3-(arylamino)-1*H*-pyrazole-4-carbonitriles **5**

through iodine-promoted reaction of *N*,2-diarylhydrazinecarbothioamides **3** (prepared from arylhydrazines **1** and aryl isothiocyanates **2**)[30] and malononitrile **4** in *N*,*N*-dimethylformamide at 80 °C (Scheme 1).

Table 1 Optimization of the Reaction Conditions[a]



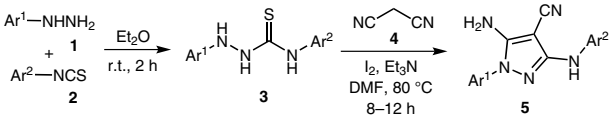
Entry	Solvent	Reagent	Temp (°C)	Yield[b] (%)
1	DMF	I_2	r.t.	–
2	DMF	I_2	80	85
3	DMF	I_2	100	85
4	EtOH	I_2	reflux	60
5	MeCN	I_2	reflux	80
6	CH_2Cl_2	I_2	reflux	45
7	toluene	I_2	reflux	30
8	DMF	CuI	80	20
9	DMF	CuBr	80	35
10	DMF	$HgCl_2$	80	70
11	DMF	DCC	80	trace

[a] Reaction conditions: **3a** (1 mmol), malononitrile (**4**, 1 mmol), reagent (1 equiv), Et_3N (1 equiv), solvent (8 mL), 2 h.
[b] Isolated yield.

Initially, *N*,2-diarylhydrazinecarbothioamide derivatives **3** were easily prepared by the reaction of various arylhydrazines **1** and aryl isothiocyanates **2** in dry diethyl ether in the presence of triethylamine at room temperature (Scheme 1). First, the reaction of *N*-(2-fluorophenyl)-2-phenylhydrazinecarbothioamide (**3a**) with malononitrile (**4**) was examined under varying conditions and solvents with a view to obtain the corresponding product, 5-amino-3-[(2-fluorophenyl)amino]-1-phenyl-1*H*-pyrazole-4-carbonitrile (**5a**) in good yield (Table 1). Focusing on the efficiency of iodine in organic transformations,[1] the reaction of compound **3a** (1 mmol) and malononitrile (1 mmol) was investigated in the presence of iodine and triethylamine under various conditions (Table 1). The presence of base was crucial, and one equivalent of triethylamine was sufficient to obtain the best result. Our studies revealed that the reaction of compound **3a** (1 mmol) and malononitrile (**4**, 1 mmol) was very clean in the presence of iodine (1 mmol) and triethylamine (1 mmol) in *N*,*N*-dimethylformamide yielding only the expected product, compound **5a** (entries 2 and 3); the best results were obtained at 80 °C furnishing product **5a** in 85% yield. Conducting the model reaction in the presence of different desulfurizing reagents, such as copper(I) iodide, copper(I) bromide, mercury(II) chloride, and dicyclohexylcarbodiimide (entries 8–11) resulted in an inefficient reaction that gave several byproducts in addition to **5a**.

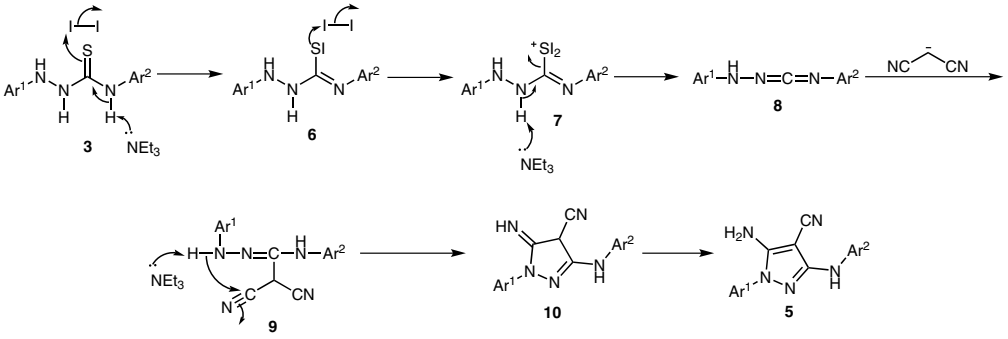
With these results in hand, in order to obtain insight into the role of electronic effects on the reaction, it was performed using various *N*,2-diarylhydrazinecarbothioamide derivatives **3a**–**m** possessing various substituents, including electron-withdrawing and electron-donating groups (Table 2). All of them reacted with malononitrile (**4**) in one to two hours to give 5-amino-1-aryl-3-(arylamino)-1*H*-pyrazole-4-carbonitriles **5a**–**m**. It should be noted that compounds **3a**–**m** possessing electron-donating groups (methoxy and methyl) requires a longer reaction time and lower yields of the corresponding product were obtained compared with the other derivatives.

Table 2 Synthesis of 5-Amino-1-aryl-3-(arylamino)-1*H*-pyrazole-4-carbonitriles **5**



Entry	Ar^1	Ar^2	Product	Yield[a] (%)
1	Ph	2-FC_6H_4	**5a**	85
2	Ph	2-ClC_6H_4	**5b**	75
3	Ph	2-BrC_6H_4	**5c**	80
4	Ph	4-MeC_6H_4	**5d**	70
5	Ph	4-$MeOC_6H_4$	**5e**	70
6	4-FC_6H_4	Ph	**5f**	85
7	4-FC_6H_4	4-$MeOC_6H_4$	**5g**	68
8	4-FC_6H_4	4-MeC_6H_4	**5h**	70
9	4-FC_6H_4	2-FC_6H_4	**5i**	90
10	4-BrC_6H_4	2-FC_6H_4	**5j**	83
11	4-BrC_6H_4	2-ClC_6H_4	**5k**	80
12	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**5l**	65
13	4-$MeOC_6H_4$	4-FC_6H_4	**5m**	62

[a] Isolated yields.



Scheme 2 Plausible mechanism for the formation of product **5**

A plausible mechanism for the formation of 5-amino-1-aryl-3-(arylamino)-1*H*-pyrazole-4-carbonitriles **5a**–**m** is given in Scheme 2. The reaction is initiated by deprotonation of **3** by triethylamine, this is followed by iodination at sulfur to give intermediate **6** and a second iodination at sulfur gives intermediate **7**, which liberates sulfur affording carbodiimide derivative, *N*-[(2-arylhydrazono)methylene]aniline **8**. Intermediate **8** is attacked by malononitrile anion to give **9**, and finally, intramolecular cyclization of **9** gives intermediate **10** that tautomerizes to furnish product **5**.

In continuation of our investigation of the synthesis of pyrazoles, we conducted the reaction of compound **3a** and ethyl cyanoacetate under the optimized conditions; however **5a** was not obtained and clearly malononitrile showed higher activity.

In summary, novel 5-amino-1-aryl-3-(arylamino)-1*H*-pyrazole-4-carbonitriles were synthesized by reaction of *N*,2-diarylhydrazinecarbothioamide (generated from arylhydrazines and aryl isothiocyanates) and malononitrile in the presence of iodine and triethylamine in *N*,*N*-dimethylformamide at 80 °C in a short reaction time (1–2 h). Molecular iodine played important role as a desulfurizing reagent giving the corresponding products in good yields. Considering the bioactivity of pyrazoles, we hope that this protocol will be useful for organic, as well as medicinal, chemists for the construction of pyrazole-based agents possessing valuable medicinal properties.

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker FT-500, 400, and 300 using TMS as an internal standard. The IR spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (in KBr). Mass spectra were documented on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. The elemental analysis was performed with an Elementar Analysensystem GmbH VarioEL CHNS mode.

5-Amino-1-aryl-3-(arylamino)-1*H*-pyrazole-4-carbonitriles 5; General Procedure

A solution of arylhydrazine derivative **1** (1 mmol), isocyanate derivative **2** (1 mmol), and Et_3N (1 mmol) in dry Et_2O (8 mL) was stirred at r.t. for 2 h. After completion of reaction, the precipitated product was filtered off and dried at 50–60 °C to give pure *N*,2-diarylhydrazinecarbothioamide derivative **3**. Then, a mixture of compound **3** (1 mmol), malononitrile **4** (1 mmol), I_2 (1 mmol), and Et_3N (1 mmol) in DMF (8 mL) was stirred at 80 °C for 1–2 h. When the reaction was complete (TLC monitoring), the mixture was filtered off through Celite and the filtrate was extract using sat. $Na_2S_2O_3$ solution and EtOAc. The organic phase was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the crude mixture was purified using column chromatography (silica gel, petroleum ether–EtOAc, 5:1) to give pure pyrazoles **5**. All products were recrystallized (petroleum ether–EtOAc).

5-Amino-3-[(2-fluorophenyl)amino]-1-phenyl-1*H*-pyrazole-4-carbonitrile (5a)

White crystals; yield: 0.25 g (85%); mp 185–186 °C.

IR (KBr): 3452, 3309, 3211, 2216, 1629, 1553 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.09 (s, 1 H, NH), 7.77 (t, *J* = 7.5 Hz, 1 H, H3′), 7.51–7.36 (m, 5 H, H2–H6), 7.19–7.12 (m, 1 H, H6′), 7.06 (t, *J* = 7.5 Hz, 1 H, H5′), 6.89–6.87 (m, 1 H, H4′), 6.70 (s, 2 H, NH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.3 (d, *J* = 241.3 Hz), 151.1, 150.9, 137.7, 130 (d, *J* = 10.6 Hz), 129.4, 127.1, 124.4 (d, *J* = 2.5 Hz), 123.7, 121.1 (d, *J* = 7.3 Hz), 119.7, 115.1 (d, *J* = 18.5 Hz), 114.4, 66.0.

Anal. Calcd for $C_{16}H_{12}FN_5$: C, 65.52; H, 4.12; N, 23.88. Found: C, 65.38; H, 4.31; N, 23.67.

5-Amino-3-[(2-chlorophenyl)amino]-1-phenyl-1*H*-pyrazole-4-carbonitrile (5b)

White crystals; yield: 0.23 g (75%); mp 204–205 °C.

IR (KBr): 3455, 3409, 3312, 2210, 1638, 1608 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (dd, *J* = 8.0, 1.3 Hz, 1 H, H6′), 7.61–7.42 (m, 5 H, H2–H6), 7.36 (dd, *J* = 8.0, 1.3 Hz, 1 H, H3′), 7.14 (t, *J* = 8.0, 1.3 Hz, 1 H, H5′), 6.88 (td, *J* = 8.0, 1.3 Hz, 1 H, H4′), 6.79 (s, 1 H, NH), 4.68 (s, 2 H, NH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.6, 148.9, 137.2, 136.9, 129.9, 129.0, 128.2, 127.7, 123.8, 121.4, 120.5, 117.6, 113.5, 67.2.

Anal. Calcd for $C_{16}H_{12}ClN_5$: C, 62.04; H, 3.90; N, 22.61. Found: C, 61.91; H, 4.15; N, 22.48.

5-Amino-3-[(2-bromophenyl)amino]-1-phenyl-1*H*-pyrazole-4-carbonitrile (5c)

White crystals; yield: 0.28 g (80%); mp 194–196 °C.

IR (KBr): 3450, 3415, 3300, 2220, 1630, 1615 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (dd, *J* = 8.0, 1.2 Hz, 1 H, H3′), 7.56–7.53 (m, 5 H, H2–H6), 7.44 (dd, *J* = 8.0, 1.2 Hz, 1 H, H6′), 7.29 (td, *J* = 8.0, 1.2 Hz, 1 H, H5′), 6.81–6.85 (m, 2 H, NH, H4′), 4.71 (s, 2 H, NH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7, 148.9, 138.0, 137.2, 132.3, 129.9, 128.5, 128.2, 123.8, 121.9, 117.7, 114.1, 111.2, 67.1.

Anal. Calcd for $C_{16}H_{12}BrN_5$: C, 54.25; H, 3.41; N, 19.77. Found: C, 54.08; H, 3.52; N, 19.58.

5-Amino-1-phenyl-3-(*p*-tolylamino)-1*H*-pyrazole-4-carbonitrile (5d)

White crystals; yield: 0.20 g (70%); mp 168–170 °C.

IR (KBr): 3433, 3335, 3220, 2921, 2202, 1595, 1571, 1543 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.47 (s, 1 H, NH), 7.52–7.47 (m, 4 H, H2, H3, H5, H6), 7.45 (d, *J* = 7.5 Hz, 2 H, H2′, H6′), 7.35 (t, *J* = 7.7 Hz, 1 H, H4), 7.00 (d, *J* = 7.5 Hz, 2 H, H3′, H5′), 6.64 (s, 2 H, NH_2), 2.20 (s, 3 H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 151.2, 151.0, 139.6, 137.9, 129.4, 129.1, 128.9, 128.2, 126.8, 123.4, 116.8, 66.0, 20.3.

Anal. Calcd for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23; N, 24.20. Found: C, 70.41; H, 5.37; N, 24.34.

5-Amino-3-[(4-methoxyphenyl)amino]-1-phenyl-1*H*-pyrazole-4-carbonitrile (5e)

White crystals; yield: 0.21 g (70%); mp 185–186 °C.

IR (KBr): 3441, 3356, 3157, 2923, 2204, 1626, 1600, 1568, 1509 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.38 (s, 1 H, NH), 7.75–7.48 (m, 6 H, H2, H3, H5, H6, H2′, H6′), 7.35 (t, *J* = 7.0 Hz, 1 H, H4), 6.81 (d, *J* = 9.0 Hz, 2 H, H3′, H5′), 6.62 (s, 2 H, NH_2), 3.68 (s, 3 H, OMe).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 154.5, 153.0, 151.5, 138.0, 135.5, 129.3, 126.7, 123.3, 118.2, 114.7, 113.8, 64.3, 55.1.

Anal. Calcd for $C_{17}H_{15}N_5O$: C, 66.87; H, 4.95; N, 22.94. Found: C, 66.71; H, 5.17; N, 23.11.

5-Amino-1-(4-fluorophenyl)-3-(phenylamino)-1*H*-pyrazole-4-carbonitrile (5f)

White crystals; yield: 0.25 g (85%); mp 190–192 °C.

IR (KBr): 3427, 3348, 3315, 2198, 1605, 1550 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.47 (m, 4 H, H2, H6, H2′, H6′), 7.30 (t, *J* = 7.5 Hz, 2 H, H3′, H5′), 7.20 (t, *J* = 8.0 Hz, 2 H, H3, H5), 6.98 (t, *J* = 7.5 Hz, 1 H, H4′), 6.25 (s, 1 H, NH), 4.63 (s, 2 H, NH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.8 (d, *J* = 247.5 Hz), 151.4, 149.0, 140.4, 133.3 (d, *J* = 3.0 Hz), 129.1, 125.9 (d, *J* = 8.6 Hz), 121.3, 117.0, 116.7, 114.0, 66.5.

Anal. Calcd for $C_{16}H_{12}FN_5$: C, 65.52; H, 4.12; N, 23.88. Found: C, 65.68; H, 4.23; N, 23.71.

5-Amino-1-(4-fluorophenyl)-3-[(4-methoxyphenyl)amino]-1*H*-pyrazole-4-carbonitrile (5g)

White crystals; yield: 0.22 g (68%); mp 208–209 °C.

IR (KBr): 3437, 3351, 3224, 2922, 2834, 2204, 1641, 1608 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.38 (s, 1 H, NH), 7.56–7.47 (m, 4 H, H2, H6, H2′, H6′), 7.32 (t, *J* = 8.5 Hz, 2 H, H3, H5), 6.79 (d, *J* = 8.6 Hz, 2 H, H3′, H5′), 6.63 (s, 2 H, NH_2), 3.64 (s, 3 H, OMe).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.5 (d, *J* = 242.5 Hz), 153.0, 151.5, 151.2, 135.4, 134.3 (d, *J* = 2.6 Hz), 126.1 (d, *J* = 8.8 Hz), 118.2, 116.1 (d, *J* = 22.7 Hz), 114.7, 113.8, 64.1, 55.1.

Anal. Calcd for $C_{17}H_{14}FN_5O$: C, 63.15; H, 4.36; N, 21.66. Found: C, 63.28; H, 4.42; N, 21.80.

5-Amino-1-(4-fluorophenyl)-3-(*p*-tolylamino)-1*H*-pyrazole-4-carbonitrile (5h)

White crystals; yield: 0.21 g (70%); mp 216–218 °C.

IR (KBr): 3440, 3338, 3224, 2920, 2820, 2201, 1640, 1602, 1576 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.47 (s, 1 H, NH), 7.55 (dd, *J* = 8.7, 4.5 Hz, 2 H, H2, H6), 7.45 (d, *J* = 8.5 Hz, 2 H, H2′, H6′), 7.34 (t, *J* = 8.7 Hz, 2 H, H3, H5), 6.99 (d, *J* = 8.5 Hz, 2 H, H3′, H5′), 6.65 (s, 2 H, NH_2), 2.20 (s, 3 H, OMe).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.6 (d, *J* = 242.5 Hz), 151.2, 139.5, 134.3, 128.9, 128.8, 128.2, 126.1 (d, *J* = 8.7 Hz), 116.8, 116.1 (d, *J* = 22.5 Hz), 114.6, 64.4, 20.3.

Anal. Calcd for $C_{17}H_{14}FN_5$: C, 66.44; H, 4.59; N, 22.79. Found: C, 66.57; H, 4.68; N, 22.86.

5-Amino-1-(4-fluorophenyl)-3-[(2-fluorophenyl)amino]-1*H*-pyrazole-4-carbonitrile (5i)

White crystals; yield: 0.28 g (90%); mp 205–206 °C.

IR (KBr): 3443, 3363, 3227, 2213, 1650, 1629 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.08 (s, 1 H, NH), 7.76 (t, *J* = 8.0 Hz, 1 H, H3′), 7.55–7.51 (m, 2 H, H2, H6), 7.33 (t, *J* = 8.2 Hz, 2 H, H3, H5), 7.15 (t, *J* = 8.0 Hz, 1 H, H5′), 7.06 (t, *J* = 8.0 Hz, 1 H, H4′), 6.88 (d, *J* = 8.0 Hz, 1 H, H6′), 6.70 (s, 2 H, NH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.7 (d, *J* = 243.1 Hz), 152.3 (d, *J* = 241.2 Hz), 151.3, 150.9, 134.0 (d, *J* = 2.7 Hz), 129.9 (d, *J* = 10.7 Hz), 126.4 (d, *J* = 8.7 Hz), 124.4 (d, *J* = 3.3 Hz), 121.2 (d, *J* = 7.2 Hz), 119.8, 116.2 (d, *J* = 22.8 Hz), 115.1 (d, *J* = 18.7 Hz), 114.4, 65.8.

Anal. Calcd for $C_{16}H_{11}F_2N_5$: C, 61.73; H, 3.56; N, 22.50. Found: C, 61.85; H, 3.67; N, 22.64.

5-Amino-1-(4-bromophenyl)-3-[(2-fluorophenyl)amino]-1*H*-pyrazole-4-carbonitrile (5j)

White crystals; yield: 0.31 g (83%); mp 180–182 °C.

IR (KBr): 3443, 3397, 3202, 2213, 1639, 1580 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.12 (s, 1 H, NH), 7.76 (t, *J* = 8.0 Hz, 1 H, H3′), 7.67 (d, *J* = 7.8 Hz, 2 H, H3, H5), 7.46 (d, *J* = 7.8 Hz, 2 H, H2, H6), 7.15 (t, *J* = 8.0 Hz, 1 H, H5′), 7.06 (t, *J* = 8.0 Hz, 1 H, H4′), 6.89 (d, *J* = 8.0 Hz, 1 H, H6′), 6.78 (s, 2 H, NH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 160.4 (d, *J* = 241.0 Hz), 151.3, 151.1, 137.0, 132.2, 129.8 (d, *J* = 10.9 Hz), 125.6, 124.4, 121.3 (d, *J* = 7.0 Hz), 120.0, 119.7, 115.1 (d, *J* = 19.0 Hz), 114.3, 66.1.

Anal. Calcd for $C_{16}H_{11}BrFN_5$: C, 51.63; H, 2.98; N, 18.82. Found: C, 51.77; H, 3.21; N, 18.67.

5-Amino-1-(4-bromophenyl)-3-[(2-chlorophenyl)amino]-1*H*-pyrazole-4-carbonitrile (5k)

White crystals; yield: 0.31 g (80%); mp 234–235 °C.

IR (KBr): 3463, 3411, 3360, 2205, 1630, 1579 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.80 (d, J = 8.0 Hz, 1 H, H6′), 7.69 (d, J = 8.5 Hz, 2 H, H3, H5), 7.57 (s, 1 H, NH), 7.48 (d, J = 8.5 Hz, 2 H, H2, H6), 7.40 (d, J = 8.0 Hz, 1 H, H3′), 7.24 (t, J = 8.0 Hz, 1 H, H5′), 6.91 (t, J = 8.0 Hz, 1 H, H4′), 6.86 (s, 2 H, NH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 151.1, 150.9, 138.1, 136.9, 132.3, 129.3, 127.8, 125.8, 121.9, 121.4, 119.8, 119.0, 114.1, 66.3.

MS: m/z (%) = 391 $[M + 4]^+$ (3), 389 $[M + 2]^+$ (12), 387 $[M]^+$ (9), 354 (61), 337 (13), 273 (33), 246 (20), 155 (23), 119 (16), 75 (26).

Anal. Calcd for $C_{16}H_{11}BrClN_5$: C, 49.45; H, 2.85; N, 18.02. Found: C, 49.69; H, 2.72; N, 17.88.

5-Amino-1-(4-methoxyphenyl)-3-[(4-methoxyphenyl)amino]-1*H*-pyrazole-4-carbonitrile (5l)

White crystals; yield: 0.22 g (65%); mp 184–186 °C.

IR (KBr): 3416, 3356, 3225, 2205, 1630, 1601, 1570 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.33 (s, 1 H, NH), 7.48 (d, J = 9.0 Hz, 2 H, H2, H6), 7.40 (d, J = 8.5 Hz, 2 H, H2′, H6′), 7.05 (d, J = 8.5 Hz, 2 H, H3′, H5′), 6.79 (d, J = 9.0 Hz, 2 H, H3, H5), 6.47 (s, 2 H, NH_2), 3.80 (s, 3 H, OMe), 3.67 (s, 3 H, OMe).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.1, 152.9, 151.2, 150.9, 135.6, 130.8, 125.6, 118.1, 114.9, 114.5, 113.8, 63.7, 55.4, 55.1.

Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.58; H, 5.20; N, 20.71.

5-Amino-3-[(4-fluorophenyl)amino]-1-(4-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile (5m)

White crystals; yield: 0.20 g (62%); mp 194–195 °C.

IR (KBr): 3417, 3357, 3226, 2206, 1631, 1601, 1570 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.44 (s, 1 H, NH), 7.40 (dd, J = 9.0, 5.0 Hz, 2 H, H2′, H6′), 7.33 (d, J = 8.5 Hz, 2 H, H2, H6), 7.14 (dd, J = 9.0 Hz, 2 H, H3′, H5′), 6.93 (d, J = 8.5 Hz, 2 H, H3, H5), 6.63 (s, 2 H, NH_2), 3.77 (s, 3 H, OMe).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 159.0 (d, J = 240.0 Hz), 157.6, 155.5, 151.1, 139.2, 136.1, 128.7, 126.5 (d, J = 7.5 Hz), 114.5 (d, J = 22.5 Hz), 114.2, 113.5, 55.3, 45.2. 55.3.

Anal. Calcd for $C_{17}H_{14}FN_5O$: C, 63.15; H, 4.36; N, 21.66. Found: C, 63.28; H, 4.22; N, 21.51.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560553.

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