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AN EFFICIENT AND MULTI-COMPONENT SYNTHESIS OF FUNCTIONALIZED PYRAZOLE DERIVATIVES

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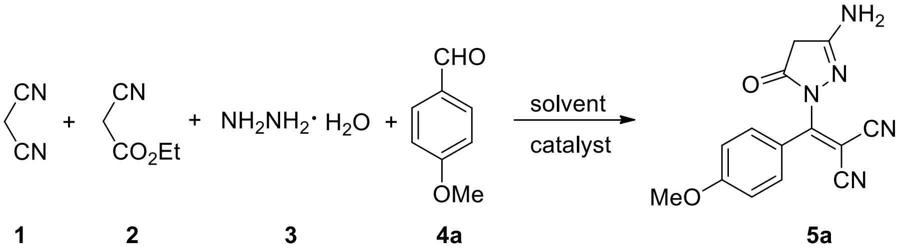
Abstract – A facile and efficient one-pot procedure for the synthesis of functionalized pyrazole derivatives via a four-component reaction of malononitrile, ethyl cyanoacetate, hydrazine hydrate and aldehydes under mild conditions in excellent yield is described. This synthesis was confirmed to follow the group-assisted-purification (GAP) chemistry process, which can avoid traditional recrystallization and chromatography purifications.

Nitrogen containing heterocycles are ubiquitous systems in natural products and are considered as privileged structures in drug discovery.[1] Among them, the pyrazole nucleus plays an essential role in biologically active compounds and also in medicinal chemistry.[2] Compounds bearing the pyrazole moiety exhibit anti-bacterial,[3] anticancer,[4] antiviral,[5] antioxidant,[6] anti-fungal,[7] and antiandrogenic[8] activities. Multi-component reactions (MCRs) are promising and powerful tools in organic, combinatorial, and medicinal chemistry, because of their atom economy, high complexity and diversity of products, multiple bond formation efficiency, and environmental friendliness.[9] These features make MCRs suitable for the easy construction of complex heterocyclic scaffolds from readily available starting.[10] In recent years, some MCRs have been used for the constructions of pyrazole skeletons.[11]

The development of environmentally friendly synthetic methods is a challenge in modern organic synthesis. The need to reduce the amount of toxic wastes and byproducts arising from chemical processes has resulted in an increasing emphasis on the use of less-toxic and environmentally compatible materials in the design of new synthetic methods. Traditional purification methods such as recrystallization and column chromatography have problems in terms of consumption of organic solvents and energy, waste generation, and pollution. The concept of group-assisted purification (GAP) techniques, which avoid traditional recrystallization and chromatographic purification methods and reduce waste generation from silica and solvents, particularly toxic solvents, was first developed by Li's group in the design of asymmetric synthesis of new imine reagents.[12] Up to now, the GAP technology has been used in many asymmetric synthetic reactions[13] and some MCRs.[14] As part of our current studies on the development of GAP techniques for the synthesis of heterocycles by using MCRs,[15] we now describe an efficient and clean synthesis of functionalized pyrazole derivatives using GAP techniques.

Initially, for optimization of the reaction conditions, a representative reaction of malononitrile (**1**), ethyl cyanoacetate (**2**), hydrazine hydrate (**3**), and 4-methoxybenzaldehyde (**4a**), which presumably affords the functionalized pyrazole derivative (**5a**), was performed under various conditions. The effect of solvents catalysts and reaction temperatures were evaluated for this reaction, and the results are summarized in Table 1. It was found that when the reaction was carried out in ethanol at refluxing temperature for 50 min without any catalyst the yield of the desired product was 91% (Table 1, entry 1). Various solvents were evaluated to determine the impact of the solvent on the yield. Of all the solvents tested, i.e., ethanol,

Table 1. Optimization of the reaction conditions for the synthesis of compound **5a**



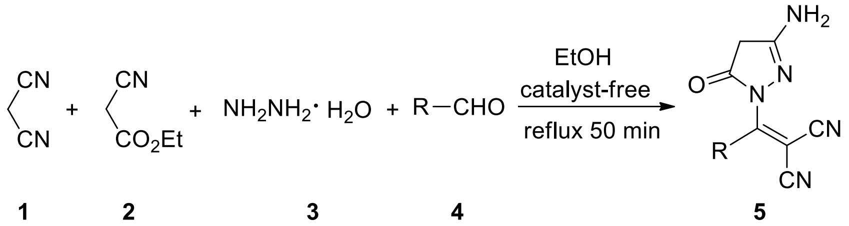
Entry	Solvent	Catalyst (10 mol%)	Temperature (°C)	Time	Yield[a] (%)
1	EtOH	no	reflux	50 min	91
2	MeOH	no	reflux	1 h	87
3	dioxane	no	reflux	4 h	67
4	MeCN	no	reflux	5 h	77
5	THF	no	reflux	5 h	80
6	H_2O	no	reflux	4 h	80
7	EtOH	NaOH	reflux	90 min	76
8	EtOH	KOH	reflux	90 min	76
9	EtOH	Na_2CO_3	reflux	2 h	63
10	EtOH	piperidine	reflux	40 min	87
11	EtOH	EtONa	reflux	5 h	72
12	EtOH	no	25	50 min	trace
13	EtOH	no	40	50 min	trace
14	EtOH	no	60	50 min	67

[a] Yield was isolated yield.

methanol, dioxane, acetonitrile, tetrahydrofuran (THF), and water, ethanol gave the best result (Table 1, entries 1-6). To improve the yield, several catalysts were evaluated, i.e., sodium hydroxide, potassium hydroxide, sodium carbonate, piperidine, and sodium ethoxide. The results showed that the use of catalysts was results no significant improvement of the yield (Table 1, entries 7-11). The reaction was then conducted at different temperatures, such as: 25, 40, 60, and refluxing temperature, to determine the optimum temperature for this transformation. All these experiments were conducted in ethanol under catalyst-free conditions (Table 1, entries 12-14 and 1). So the best temperature for this transformation was at refluxing temperature. Based on all these experiments, the optimum reaction conditions were identified as using ethanol as solvent at refluxing temperature for 50 min under catalyst-free conditions.

The optimized reaction conditions were then tested for library construction with sixteen aldehydes **4a-p**. The corresponding functionalized pyrazole derivatives **5a-p** were obtained in good yields at refluxing temperature in ethanol without any catalyst. The results are summarized in Table 2. It was found that aromatic aldehydes bearing either electron-withdrawing or electron-donating groups, or aliphathic aldehydes (such as cyclopropanecarbaldehyde and 2-phenylacetaldehyde) were tolerated under the

Table 2. The synthesis of functionalized pyrazole derivatives **5**

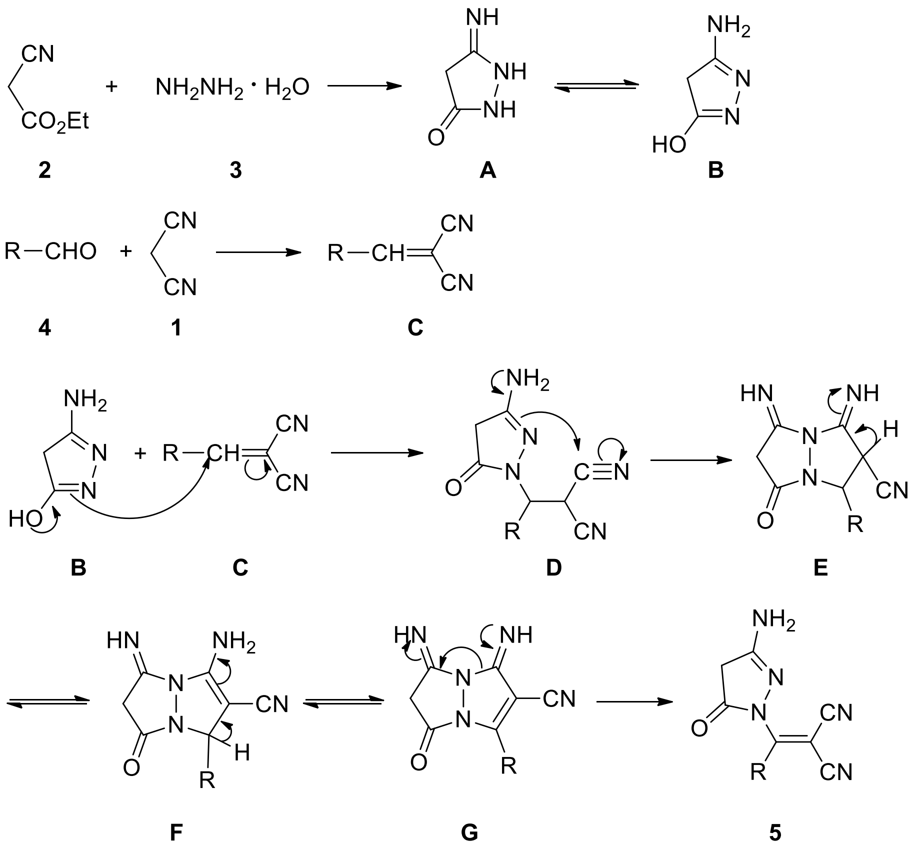


Entry	Compound	R	Isolated Yield (%)
1	**5a**	4-$MeOC_6H_4$	91
2	**5b**	3,4-$(MeO)_2C_6H_3$	85
3	**5c**	4-$(Me)_2NC_6H_4$	85
4	**5d**	4-MeC_6H_4	90
5	**5e**	3,5-$(Me)_2C_6H_3$	90
6	**5f**	4-FC_6H_4	88
7	**5g**	3-ClC_6H_4	88
8	**5h**	3,4-$Cl_2C_6H_3$	85
9	**5i**	2-BrC_6H_4	85
10	**5j**	3-BrC_6H_4	88
11	**5k**	4-BrC_6H_4	88
12	**5l**	2-$NO_2C_6H_4$	85
13	**5m**	3-$NO_2C_6H_4$	85
14	**5n**	4-$NO_2C_6H_4$	85
15	**5o**	*c*-C_3H_5	89
16	**5p**	$C_6H_5CH_2$	89

reaction conditions, leading to the final products in satisfactory yields (85-91%). Moreover, all the pure products can be simply obtained by washing the solid crude products with little cold ethanol. It is indicated that this synthesis was confirmed to follow the GAP (group-assisted-purification) chemistry process, which can avoid the traditional recrystallization and chromatography purifications.

The structures of the products synthesized in the current study were identified using IR, ^{1}H NMR, and ^{13}C NMR spectroscopies, and HRMS analysis.

Based on the references,[16] the proposed mechanism for the synthesis of compound **5** is shown in Scheme 1. The intermediate **A** was formed by the condensation of ethyl cyanoacetate (**2**) with hydrazine hydrate (**3**). The intermediate **A** was then transformed to intermediate **B** by the tautomerization. The intermediate **C** was formed by the Knoevenagel condensation of aldehydes (**4**) with malononitrile (**1**). Then, the Michael addition of the intermediate **B** and **C** was taken placed, and the intermediate **D** was formed. Intermediate **G** was then formed by the cyclization of intermediate **D** and tautomerization of intermediates **E** and **F**. In the last step, pyrazole **5** is formed by a ring-opening reaction of intermediate **G**.



Scheme 1. The proposed mechanism for one-pot domino reaction

In summary, we have developed a clean and efficient protocol for the construction of functionalized pyrazole derivatives via a novel four-component reaction using malononitrile, ethyl cyanoacetate, hydrazine hydrate and aldehydes as starting materials. This protocol has the advantages of mild reaction conditions, short reaction times, convenient operation, high yields, cheap and green solvent and environmental friendliness.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR and ^{13}C NMR were determined on Varian Invoa-400 MHz or Invoa-300 MHz spectrometer in DMSO-d_6 solutions. J values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS analyses were carried out using TOF-MS or GCT-TOF instrument.

Starting Materials. All chemicals used in this study were commercially available.

Typical experimental procedure for the synthesis of functionalized pyrazoles 5. A mixture of malononitrile **1** (1 mmol), ethyl cyanoacetate **2** (1 mmol), hydrazine hydrate **3** (1 mmol), aldehydes **4** (1 mmol) and EtOH (2 mL) was stirred at 80 ºC for 50 min. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature. The precipitate was collected and washed with a little cold EtOH to give the pure products **5**.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(4-methoxyphenyl)methylene)malononitrile 5a: yellow solid; mp >300 °C; IR (KBr) 3458, 3396, 3265, 2944, 2843, 2219, 1782, 1672, 1512, 1465, 1414, 1297, 1261, 1179, 1028, 840, 839, 770 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 2H, NH_2), 7.44 (d, J = 8.8 Hz, 2H, ArH), 7.08 (d, J = 8.8 Hz, 2H, ArH), 5.59 (s, 2H, CH_2), 3.83 (s, 3H, CH_3O); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.9, 159.5, 159.4, 156.8, 130.0, 126.6, 116.8, 115.9, 114.1, 86.4, 74.4, 55.5; HRMS Calculated for $C_{14}H_{10}N_5O_2$: $[M-H]^+$ 280.0834, found: 280.0851.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(3,4-dimethoxyphenyl)methylene)malononitrile 5b: yellow solid; mp >300 °C; IR (KBr) 3404, 3290, 2969, 2941, 2844, 2217, 1680, 1646, 1521, 1466, 1424, 1331, 1270, 1152, 1017, 961, 866, 818, 761 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 2H, NH_2), 7.12-7.06 (m, 3H, ArH), 5.66 (s, 2H, CH_2), 3.84 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.5, 159.4, 156.8, 150.4, 148.3, 126.6, 121.3, 116.9, 116.0, 112.1, 111.5, 86.4, 74.4, 55.8, 55.7; HRMS Calculated for $C_{15}H_{12}N_5O_3$: $[M-H]^+$ 310.0940, found: 310.0945.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(4-(dimethylamino)phenyl)methylene)malononitrile 5c: yellow solid; mp >300 °C; IR (KBr) 3378, 3170, 2914, 2824, 2212, 1898, 1686, 1413, 1374, 1292, 1166, 1060, 1006, 955, 863, 818, 766, 743 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 2H, NH_2), 7.36 (d, *J* = 8.4 Hz, 2H, ArH), 6.80 (d, *J* = 8.4 Hz, 2H, ArH), 5.60 (s, 2H, CH_2), 2.99 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 159.7, 156.9, 151.6, 129.7, 120.7, 117.3, 116.4, 111.8, 111.3, 85.6, 73.8; HRMS Calculated for $C_{15}H_{13}N_6O$: $[M-H]^+$ 293.1151, found: 293.1143.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(*p*-tolyl)methylene)malononitrile 5d: yellow solid; mp >300 °C; IR (KBr) 3455, 3402, 3247, 2927, 2174, 1919, 1671, 1524, 1463, 1297, 1184, 1003, 948, 819, 771, 759 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.42 (s, 2H, NH_2), 7.36 (s, 4H, ArH), 5.65 (s, 2H, CH_2), 2.39 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 159.8, 159.5, 156.8, 140.2, 131.8, 129.3, 128.2, 116.7, 115.8, 86.5, 74.5, 21.1; HRMS Calculated for $C_{14}H_{10}N_5O$: $[M-H]^+$ 264.0885, found: 264.0872.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(3,5-dimethylphenyl)methylene)malononitrile 5e: yellow solid; mp >300 °C; IR (KBr) 3433, 3247, 2927, 2873, 2221, 1934, 1671, 1530, 1450, 1287, 1189, 948, 844, 799, 771 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.41 (s, 2H, NH_2), 7.31-7.19 (m, 3H, ArH), 5.64 (s, 2H, CH_2), 2.29 (s, 6H, 2×CH_3); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 160.1, 159.8, 157.1, 139.3, 137.0, 132.5, 130.1, 129.2, 125.9, 116.9, 116.1, 86.8, 74.7, 19.8, 19.8; HRMS Calculated for $C_{15}H_{12}N_5O$: $[M-H]^+$ 278.1042, found: 278.1053.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(4-fluorophenyl)methylene)malononitrile 5f: yellow solid; mp >300 °C; IR (KBr) 3395, 3291, 3198, 3084, 2219, 1683, 1515, 1468, 1286, 1229, 1160, 1103, 994, 948, 846, 802, 769 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.48 (s, 2H, NH_2), 7.57 (m, 2H, ArH), 7.39 (t, *J* = 8.4 Hz, 2H, ArH), 5.67 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 163.2 (d, *J* = 247 Hz), 159.4, 158.8, 156.8, 131.1, 130.8, 116.6, 116.0 (d, *J* = 23 Hz), 86.8, 74.7; HRMS Calculated for $C_{13}H_7FN_5O$: $[M-H]^+$ 268.0635, found: 268.0624.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(3-chlorophenyl)methylene)malononitrile 5g: yellow solid; mp >300 °C; IR (KBr) 3450, 3301, 3200, 3060, 2215, 1678, 1595, 1503, 1465, 1298, 1205, 1172, 1017, 971, 811, 760, 733 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.53 (s, 2H, NH_2), 7.63-7.56 (m, 3H, ArH), 7.47-7.45 (m, 1H, ArH), 5.69 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 159.3, 158.1, 156.8, 136.7, 133.4, 130.8, 130.3, 128.0, 127.0, 116.4, 115.5, 86.7, 74.6; HRMS Calculated for $C_{13}H_7ClN_5O$: $[M-H]^+$ 284.0339, found: 284.0334.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(3,4-dichlorophenyl)methylene)malononitrile 5h: yellow solid; mp >300 °C; IR (KBr) 3418, 3297, 3189, 3068, 2225, 1680, 1525, 1470, 1376, 1299, 1243, 1129, 1030, 1014, 971, 877, 843, 754, 684 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.56 (s, 2H, NH_2), 7.84-7.82 (m, 2H, ArH), 7.51 (d, *J* = 8.0 Hz, 1H, ArH), 5.70 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 159.2, 157.1, 156.7, 135.2, 133.3, 131.6, 131.2, 130.3, 128.7, 116.3, 115.4, 86.6, 74.5;

HRMS Calculated for $C_{13}H_6Cl_2N_5O$: $[M-H]^+$ 317.9949, found: 317.9958.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(2-bromophenyl)methylene)malononitrile 5i: yellow solid; mp >300 °C; IR (KBr) 3416, 3313, 2216, 1686, 1517, 1470, 1430, 1297, 1160, 1116, 1022, 955, 857, 751, 702 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 2H, NH_2), 7.80 (t, *J* = 8.4 Hz, 1H, ArH), 7.57-7.43 (m, 3H, ArH), 5.68 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.5, 159.3, 157.0, 136.3, 133.3, 132.1, 130.0, 128.7, 120.8, 116.0, 115.1, 87.5, 75.4; HRMS Calculated for $C_{13}H_7BrN_5O$: $[M-H]^+$ 327.9834, found: 327.9836.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(3-bromophenyl)methylene)malononitrile 5j: yellow solid; mp >300 °C; IR (KBr) 3447, 3328, 3301, 3201, 3096, 3058, 2216, 1677, 1596, 1505, 1466, 1299, 1204, 1175, 1017, 967, 917, 810, 766, 703 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 2H, NH_2), 7.77-7.73 (m, 2H, ArH), 7.51-7.49 (m, 2H, ArH), 5.69 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.6, 158.3, 157.0, 137.2, 133.5, 131.3, 131.0, 127.6, 122.1, 116.6, 115.7, 86.9, 74.8; HRMS Calculated for $C_{13}H_7BrN_5O$: $[M-H]^+$ 327.9834, found: 327.9838.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(4-bromophenyl)methylene)malononitrile 5k: yellow solid; mp >300 °C; IR (KBr) 3455, 3399, 3270, 2220, 1640, 1597, 1522, 1466, 1294, 1070, 1009, 948, 860, 827, 770, 701 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 2H, NH_2), 7.77 (d, *J* = 8.4 Hz, 2H, ArH), 7.46 (d, *J* = 8.4 Hz, 2H, ArH), 5.67 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-$d_{6,}$) δ 159.3, 158.5, 156.7, 133.9, 131.8, 130.3, 124.0, 116.4, 115.5, 86.5, 74.4; HRMS Calculated for $C_{13}H_7BrN_5O$: $[M-H]^+$ 327.9834, found: 327.9832.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(2-nitrophenyl)methylene)malononitrile 5l: yellow solid; mp >300 °C; IR (KBr) 3446, 3344, 3285, 2858, 2218, 1681, 1512, 1469, 1346, 1234, 903, 846, 793, 768, 726, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 2H, NH_2), 8.34 (d, *J* = 8.0 Hz, 1H, ArH), 7.99 (t, *J* = 7.6 Hz, 1H, ArH), 7.86 (t, *J* = 8.0 Hz, 1H, ArH), 7.69 (d, *J* = 7.6 Hz, 1H, ArH), 5.72 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.1, 157.8, 156.7, 146.4, 135.2, 132.0, 131.0, 129.6, 125.5, 115.8, 114.9, 86.2, 74.2; HRMS Calculated for $C_{13}H_7N_6O_3$: $[M-H]^+$ 295.0580, found: 295.0594.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(3-nitrophenyl)methylene)malononitrile 5m: yellow solid; mp >300 °C; IR (KBr) 3444, 3347, 3299, 2888, 2221, 1670, 1600, 1510, 1450, 1355, 1234, 903, 866, 793, 744, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 2H, NH_2), 8.43-8.41 (m, 2H, ArH), 8.00 (d, *J* = 7.6 Hz, 1H, ArH), 7.88 (t, *J* = 8.0 Hz, 1H, ArH), 5.72 (s, 2H, CH_2); ^{13}C NMR (100 Hz, DMSO-d_6) δ 159.1, 157.3, 156.7, 147.7, 136.2, 135.0, 130.7, 125.1, 123.2, 116.2, 115.3, 86.7, 74.6; HRMS Calculated for $C_{13}H_7N_6O_3$: $[M-H]^+$ 295.0580, found: 295.0598.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(4-nitrophenyl)methylene)malononitrile 5n: yellow solid; mp >300 °C; IR (KBr) 3396, 3291, 3194, 3081, 2848, 2222, 1695, 1516, 1470, 1349, 1290, 1230, 1108, 990, 936, 863, 840, 769, 742 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 2H, NH_2), 8.50-8.30 (m, 2H, ArH), 7.85-7.70 (m, 2H, ArH), 5.71 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.2, 157.7, 156.8, 148.6, 141.0, 130.0, 124.0, 116.2, 115.3, 86.5, 74.4; HRMS Calculated for $C_{13}H_7N_6O_3$: $[M-H]^+$ 295.0580, found: 295.0560.

2-((3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)(cyclopropyl)methylene)malononitrile 5o: yellow solid; mp >300 °C; IR (KBr) 3411, 3249, 2994, 2927, 2873, 2218, 1943, 1678, 1299, 1187, 965, 777 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H, NH_2), 5.54 (s, 2H, CH_2), 2.06-1.99 (m, 1H, CH), 1.13-1.08 (m, 2H, CH_2), 1.03 (t, J = 5.6 Hz, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.7, 159.6, 156, 116.1, 115.3, 87.0, 75.2, 15.0, 8.1; HRMS Calculated for $C_{10}H_8N_5O$: $[M-H]^+$ 214.0729, found: 214.0729.

2-(1-(3-Amino-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)-2-phenylethylidene)malononitrile 5p: yellow solid; mp >300 °C; IR (KBr) 3323, 3221, 2987, 2854, 2219, 1717, 1610, 1546, 1499, 1267, 1156, 1000, 933, 754 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 2H, NH_2), 7.35-7.30 (m, 5H, ArH), 5.54 (s, 2H, CH_2), 3.98 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 159.4, 156.9, 136.3, 128.9, 128.4, 127.2, 116.6, 115.6, 87.1, 74.6; HRMS Calculated for $C_{14}H_{10}N_5O$: $[M-H]^+$ 264.0885, found: 264.0900.

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