A Catalyst-free Green Protocol for the Synthesis of Pyranopyrazoles Using Room Temperature Ionic Liquid Choline Chloride-urea

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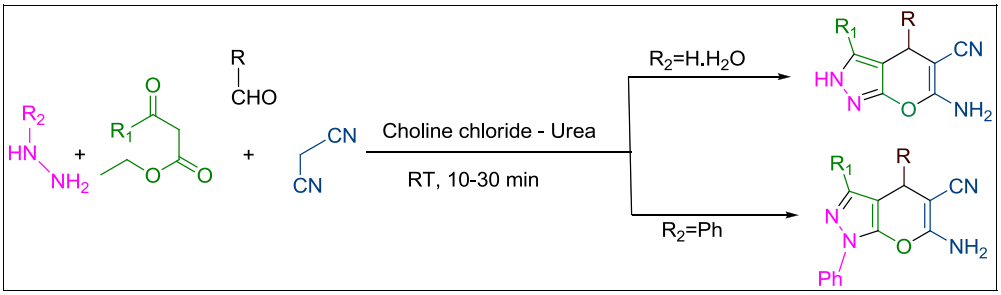

An efficient and rapid four component reaction of aldehydes, malanonitrile, β-ketoesters and hydrazine hydrate (or phenyl hydrazine) in environmentally benign room temperature ionic liquid choline chloride-urea has been developed for the synthesis of substituted 4*H*-pyrano[2,3-c]pyrazoles.

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INTRODUCTION

Substituted 4*H*-pyrano[2,3-c]pyrazoles represent an important class of heterocycles that have shown analgesic [1a], anticancer [1b], anti-inflammatory [1c], molluscidal [1d], and serine/threonine protein kinase inhibitor activity [1e]. They have also shown affinity toward A_1 and A_{2a} adenosine receptors [2]. Because of these diverse biological activities of pyranopyrazoles, many protocols have been developed for their synthesis. The first reported method involves the reaction of tetracyanoethylene with 3-methyl-1*H*-pyrazoline-5-one in presence of triethylamine [3]. Thereafter, numerous methods have been developed for their synthesis in ethanol [4], water [5], microwave irradiation [6], ultrasonic irradiation [7], and solvent-free conditions [8]. In addition, organocatalyzed enantioselective synthesis of pyranopyrazoles has also been reported [9]. Literature survey also reveals their synthesis in room temperature ionic liquid (RTIL) [Bmim]BF_4 using L-proline as catalyst [10]. Although the reported methods are effective, they have limited applicability by the use of toxic and costly catalysts. Therefore, a catalyst free green protocol that overcomes the drawbacks of several earlier procedures still attracts a lot of attention.

Furthermore, utilization of ILs in chemical synthesis has attracted much attention because of their advantages over conventional organic solvents such as negligible vapor pressure, wide liquid range with melting point around room temperature, high solubility for many organic, inorganic, and even polymeric materials [11]. Recently, ILs based on choline chloride and urea (Scheme 1) has been used in the synthesis of microporous crystalline zeolites [12] carbon dioxide fixation [13] and other processes [14]. To the best of our knowledge, applicability of this green IL media in organic synthesis has not been explored.

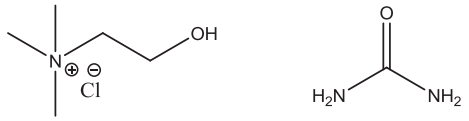
As a part of our research aimed at the development of new synthetic methodologies for biologically important heterocyclic compounds [15], we have recently reported the application of this IL in the synthesis of substituted 4*H*-chromenes [15b].

RESULTS AND DISCUSSION

The required IL was prepared by heating the mixture of commercially available choline chloride and urea (Scheme 1) with a molar ratio of 2:1 at 50°C until a clear homogeneous liquid was formed [15b], then the temperature of the IL was bought to room temperature.

As a preliminary test, we investigated the reaction of benzaldehyde (**1a**), malanonitrile (**2**), ethyl acetoacetate (**3a**), and hydrazine hydrate (**4a**) in the aforementioned prepared RTIL. Surprisingly, the reaction was completed within 10 min furnishing the product in 95% yield. The isolated product was found to be 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (**5a**) on the basis of spectral and analytical data. In another attempt, when the same reaction was carried out in the absence of IL, the intermediates remain unreacted even after prolonged stirring at room temperature. This proves the essential role of IL as a catalyst as well as solvent.

Scheme 1



Inspired by this success, we next studied the four component reaction of various aldehydes, malanonitrile, ethyl acetoacetate, and hydrazine hydrate in choline chloride-urea RTIL (Scheme 2). Thus, the protocol was compatible with various aryl aldehydes bearing electron donating and electron-withdrawing substituents, and also with heteroaryl aldehydes affording the product 6-amino-3-methyl-4-aryl/heteroaryl-2,4-dihydropyrano[2,3-c]pyraz-ole-5-carbonitrile (**5a–i**) in 80–92% yields (entries 1–9, Table 1).

The scope of this protocol was extended to the reaction of other β-ketoesters such as ethyl isobutyroylacetoacetate (**3b**) and ethyl benzoylacetoacetate (**3c**) with aldehydes (**1c**, **1e**, **1j**, **1h**, and **1a**), **2** and **4a** (Scheme 2). All reactions underwent clearly furnishing pyranopyrazoles (**5j–n)** in moderate to good yields (entries 10–14. Table 1). The present protocol was also found to be effective for phenyl hydrazine. Thus, phenyl hydrazine reacted smoothly with aldehydes (**1a**, **1c**, and **1h**), **2** and **3** affording pyranopyrazoles **(5o–q)** in moderate yields (entries 15–17, Table 1).

It should be noted that the reactions were clean, all products were obtained after filtration and washing with water followed by crystallization from ethanol. All the synthesized compounds were characterized by IR, ^{1}H NMR, LCMS and elemental analysis. ^{1}H NMR spectra of pyranopyrazoles (**5a–q)** show characteristic peak at 4.10–5.0 ppm. The

Scheme 2

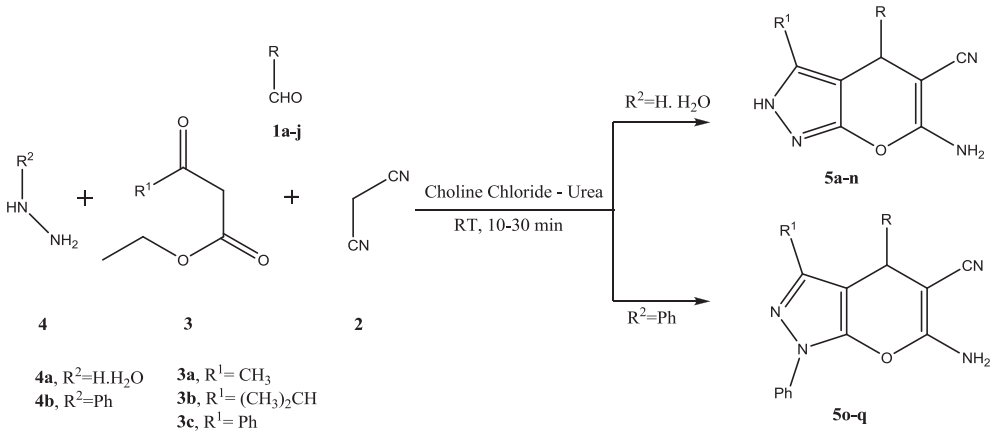


Table 1

Ionic liquid mediated one-pot synthesis of pyranopyrazoles.

Entry	R	1	R^1	Time (min)	Product[a]	% Yield[b]
1	C_6H_5	**1a**	CH_3	10	**5a**[5c]	95
2	3,4-$(MeO)_2C_6H_3$	**1b**	CH_3	18	**5b**[5g]	88
3	4-O_2N-C_6H_4	**1c**	CH_3	10	**5c**[5c]	92
4	4-Me_2N-C_6H_4	**1d**	CH_3	12	**5d**[9]	90
5	3,4,5-$(MeO)_3C_6H_2$	**1e**	CH_3	20	**5e**[9]	85
6	4-$MeOC_6H_4$	**1f**	CH_3	14	**5f**[5c]	86
7	2-Furanyl	**1g**	CH_3	13	**5g**[9]	83
8	3-Pyridinyl	**1h**	CH_3	12	**5h**	80
9	N-methylindol-3-yl	**1i**	CH_3	10	**5i**	84
10	4-O_2N-C_6H_4	**1c**	$(CH_3)_2CH$	10	**5j**	87
11	3,4,5-$(MeO)_3C_6H_2$	**1e**	$(CH_3)_2CH$	20	**5k**	82
12	4-EtO-C_6H_4	**1j**	$(CH_3)_2CH$	15	**5l**	85
13	3-Pyridinyl	**1h**	$(CH_3)_2CH$	13	**5m**	81
14	C_6H_5	**1a**	C_6H_5	25	**5n**	75
15[c]	C_6H_5	**1a**	CH_3	30	**5o**	66
16[c]	4-O_2N-C_6H_4	**1c**	$(CH_3)_2CH$	25	**5p**	70
17[c]	3-Pyridinyl	**1h**	$(CH_3)_2CH$	30	**5q**	62

[a]Literature reference to the compound.
[b]Isolated yields. [c]Phenyl hydrazine (**4b**) was used in the reaction.

possible mechanism for the formation of N-1 unsubstituted pyranopyrazoles (**5a–n**) and N-substituted pyranopyrazoles (**5a–p**) is depicted in Scheme 3. It might involve Knoevenagel condensation between **1** and **2** catalyzed by IL and formation of pyrazolone by reaction between **3** and **4**. IL mediated Michael addition of **7** to **6** followed by cyclization and tautomerization. We have proposed 2,4-dihydrotautomeric form for pyranopyrazoles unsubstituted at N-1 position based on recently reported X-ray crystallographic data [4,8a] and 1,4-dihydrotautomeric form for N-1 substituted pyranopyrazoles.

CONCLUSION

In summary, we have developed an efficient, rapid, first catalyst free green protocol for the synthesis of pyranopyrazoles by four component cyclocondensation reaction in RTIL choline chloride-urea. Mild reaction conditions, short reaction time, ease of work up, high yields and general applicability of various aldehydes, β-ketoesters and hydrazine derivatives such as hydrazine hydrate and phenyl hydrazine, and simple procedure are the noteworthy features of this new protocol. In addition, the work presented here is significant in terms of eco-friendliness, economic viability, and free from catalyst, thus overcoming the drawbacks such as use of costly and toxic catalysts in some of the earlier reported methods. Further application of this methodology toward enantioselective synthesis of pyranopyrazoles is underway in our laboratory.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AMX400 spectrometer in deuterated DMSO solvent with tetramethylsilane as an internal standard. IR spectra were obtained using a Shimadzu FTIR 8300 spectrometer. Mass spectra and purity were determined on a LC-MSD-Trap-XCT. Melting points were determined on a Tropical Labequip apparatus. All analytical thin layer chromatography was performed with E. Merck silica gel $60F_{254}$ aluminum sheets and was visualized with UV light. Chemicals materials were either prepared in our laboratory or purchased from Sigma-Aldrich and Merck Companies (Bangalore, India).

Preparation of ionic liquid [15b]. A mixture of anhydrous choline chloride (5g, 35.8 mmol) and anhydrous urea (4.29g, 71.6 mmol) under nitrogen atmosphere was heated to 50°C for 5–10 min with stirring. After the formation of clear viscous liquid (IL), the reaction mixture was bought to room temperature and this RTIL was used for the reaction.

General procedure for the synthesis of pyranopyrazoles (5). The mixture of aldehyde (3.0 mmol) and malanonitrile (3.0 mmol) was taken in the earlier prepared IL and stirred for 5 min under nitrogen atmosphere, and then β-ketoester (3.0 mmol) and hydrazine hydrate (or phenyl hydrazene) (3.0 mmol) were added, and the reaction mixture was stirred at room temperature for 5–25 min under nitrogen atmosphere. After the reaction, water was added and solid formed was filtered. The resulting solid was crystallized from ethanol to obtain pure compounds.

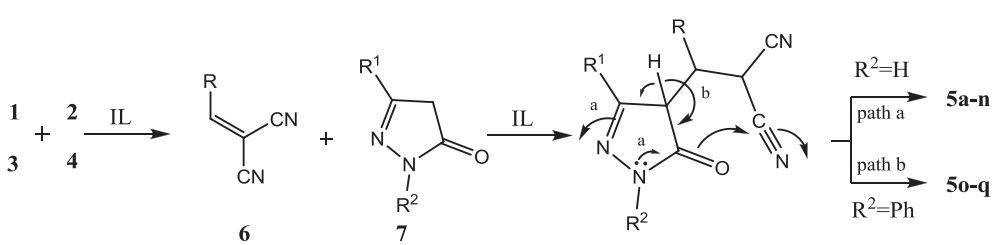
6-Amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5a). White solid. mp 244–246°C. IR (KBr, cm^{-1}) υ: 3350, 3317, 3168, 2182, 1645, 1601, 1495, 1408, 1160, 1149, 1073, 1033, 779, 745, 655, 563. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.76 (s, 3H); 4.57 (s, 1H); 6.64 (s, 2H); 7.14 (d, 2H, J = 7.2 Hz); 7.20 (t, 1H, J = 7.2 Hz); 7.30 (t, 2H, J = 7.6 Hz); 12.05 (s, 1H). ESI-MS: m/z 253.2 $[M+1]^+$. *Anal*. calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.60; H, 4.75; N, 22.15.

6-Amino-4-(3,4-dimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5b). White solid. mp 266–268°C. IR (KBr, cm^{-1}) υ: 3345, 3315, 3160, 2180, 1640, 1600, 1499, 1405, 1166, 1145, 1071, 1030, 775, 741, 654, 560. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.80 (s, 3H); 3.68 (s, 3H); 3.71 (s, 3H); 4.52 (s, 1H); 6.66 (dd, 1H, J = 8.2 Hz, J = 1.8 Hz) 6.73 (d, 1H, J = 2.0 Hz); 6.77 (s, 2H); 6.87 (d, 1H, J = 8.4 Hz); 12.06 (s, 1H). ESI-MS: m/z 313.2 $[M+1]^+$. *Anal*. calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.43; H, 5.26; N, 17.99.

6-Amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5c). White solid. mp 250–252°C. IR (KBr, cm^{-1}) υ: 3335, 3320, 3155, 2195, 1645, 1610, 1505, 1400, 1155, 1140, 1066, 1024, 770, 732, 665, 559. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.78 (s, 3H, CH_3); 4.80 (s, 1H, CH); 7.04 (s, 2H, NH_2); 7.44 (d, 2H, Ar–H, J = 8.4 Hz); 8.18 (d, 2H, Ar–H, J = 8.4 Hz); 12.16 (s, 1H, NH). ESI-MS: m/z 298.2 $[M+1]^+$. *Anal*. calcd for $C_{14}H_{11}N_5O_3$: C, 56.56; H, 3.73; N, 23.56. Found: C, 56.60; H, 3.79; N, 23.59.

6-Amino-4-(4-(dimethylamino)phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5d). Yellow solid. mp 250–252°C. IR (KBr, cm^{-1}) υ: 3328, 3324, 3150, 2198, 1665, 1620, 1506, 1420, 1145, 1130, 1061, 1029, 755, 731, 655, 549. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.77 (s, 3H, CH_3); 2.84 (s, 6H, $N(CH_3)_2$); 4.42 (s, 1H, CH); 6.63 (d, 2H, Ar–H, J = 8.0 Hz); 6.69 (s, 2H, NH_2); 6.94 (d, 2H, Ar–H, J = 8.0 Hz); 11.98 (s, 1H, NH). ESI-MS: m/z 295.2 $[M+1]^+$. *Anal*. calcd for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.15; H, 5.90; N, 23.79.

Scheme 3



6-Amino-3-methyl-4-(3,4,5-trimethoxyphenyl)-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5e). White solid. mp 226-228°C. IR (KBr, cm^{-1}) υ: 3336, 3322, 3150, 2186, 1631, 1600, 1508, 1415, 1145, 1137, 1056, 1029, 773, 739, 666, 555. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.85 (s, 3H, CH_3); 3.62 (s, 3H, OCH_3); 3.69 (s, 6H, $(OCH_3)_2$); 4.46 (s, 1H, CH); 6.45 (s, 2H, Ar–H,); 6.81 (s, 2H, NH_2); 12.05 (s, 1H, NH). ESI-MS: *m/z* 343.2 $[M+1]^+$. *Anal*. calcd for $C_{17}H_{18}N4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.70; H, 5.40; N, 16.41.

6-Amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5f). White solid. mp 212–214°C. IR (KBr, cm^{-1}) υ: 3338, 3331, 3161, 2196, 1642, 1602, 1512, 1419, 1135, 1142, 1057, 1034, 775, 729, 669, 551. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.76 (s, 3H, CH_3); 3.67 (s, 3H, OCH_3); 4.51 (s, 1H, CH); 6.77 (s, 2H, NH_2); 6.85 (d, 2H, Ar–H, $J=8.8$ Hz); 7.05(d, 2H, Ar–H, $J=8.8$ Hz); 12.03(s, 1H, NH). ESI-MS: *m/z* 283.2 $[M+1]^+$. *Anal*. calcd for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.88; H, 5.11; N, 19.89.

6-Amino-4-(furan-2-yl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile (5g). White solid. mp 233–234°C. IR (KBr, cm^{-1}) υ: 3345, 3339, 3166, 2186, 1645, 1611, 1518, 1418, 1125, 1144, 1067, 1054, 778, 722. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.96 (s, 3H, CH_3); 4.75 (s, 1H, CH); 6.15 (d, 1H, Ar–H, $J=3.2$ Hz);6.34 (t, 1H, Ar–H, $J=3.2$ Hz); 6.89 (s, 2H, NH_2); 7.50 (d, 1H, Ar–H, $J=0.8$ Hz)12.05 (s, 1H, NH). ESI-MS: *m/z* 243.2 $[M+1]^+$. *Anal*. calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.55; H, 4.22; N, 23.19.

6-Amino-3-methyl-4-(pyridin-3-yl)-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile (5h). White solid. mp 150–152°C. IR (KBr, cm^{-1}) υ: 3340, 3336, 3165, 2186, 1645, 1605, 1552, 1429, 1149, 1138, 1067, 1024, 765, 709. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.77 (s, 3H, CH_3); 4.67 (s, 1H, CH); 6.93 (s, 2H, NH_2); 7.32 (q, 1H, Ar–H, $J=5.2$ Hz); 7.50 (d, 1H, Ar–H, $J=8.0$ Hz); 8.42 (s, 2H, Ar–H); 12.24 (s, 1H, NH). ESI-MS: *m/z* 254.2 $[M+1]^+$. *Anal*. calcd for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.65. Found: C, 61.69; H, 4.33; N, 27.55.

6-Amino-3-methyl-4-(1-methyl-1H-indol-3-yl)-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5i). White solid. mp 170–172°C. IR (KBr, cm^{-1}) υ: 3345, 3321, 3166, 2185, 1652, 1610, 1519, 1420, 1142, 1054, 1044, 771. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.75 (s, 3H, CH_3); 3.72 (s, 3H, NCH_3); 4.81 (s, 1H, CH); 6.69 (s, 2H, NH_2); 6.88 (t, 1H, Ar–H, $J=7.2$ Hz); 7.07 (t, 1H, Ar–H, $J=8.0$ Hz); 7.13 (d, 1H, Ar–H, $J=8.0$ Hz); 7.22 (s, 1H, Ar–H); 11.96 (s, 1H, NH). ESI-MS: *m/z* 306.2 $[M+1]^+$. *Anal*. calcd for $C_{17}H_{15}N_5O$: C, 66.87; H, 4.95; N, 22.94. Found: C, 66.81; H, 4.89; N, 22.85.

6-Amino-3-isopropyl-4-(4-nitrophenyl)-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5j). White solid. mp 164–166°C. IR (KBr, cm^{-1}) υ: 3348, 3342, 3152, 2186, 1648, 1612, 1502, 1421, 1145, 1125, 1065, 1024, 729, 664. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 0.76 (d, 3H, CH_3, $J=6.8$ Hz); 0.98 (d,3H, CH_3, $J=6.8$ Hz);2.53 (m, 1H, CH); 4.83 (s, 1H, CH); 6.97 (s, 2H, NH_2); 7.43 (d, 2H, Ar–H, $J=8.4$ Hz); 8.18 (d, 2H, Ar–H, $J=8.4$ Hz); 12.20 (s, 1H, NH). ESI-MS: *m/z* 326.2 $[M+1]^+$. *Anal*. calcd for $C_{16}H_{15}N_5O_3$: C, 59.07; H, 4.65; N, 21.53. Found: C, 59.15; H, 4.75; N, 21.60.

6-Amino-3-isopropyl-4-(3,4,5-trimethoxyphenyl)-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5k). White solid. mp 140–142°C. IR (KBr, cm^{-1}) υ: 3338, 3342, 3168, 2201, 1652, 1600, 1514, 1420, 1144, 1065, 1024, 775. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 0.81 (d, 3H, CH_3, $J=6.4$ Hz); 0.99 (d, 3H, CH_3, $J=7.2$ Hz); 2.40 (m, 1H, CH); 3.61 (s, 3H, OCH_3); 3.68 (s, 6H, $(OCH_3)_2$); 4.57 (s, 1H, CH); 6.42 (s, 2H, Ar–H,); 6.77 (s, 2H, NH_2); 12.12 (s, 1H, NH). ESI-MS: *m/z* 371.2 $[M+1]^+$. *Anal*. calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.66; H, 5.95; N, 15.10.

6-Amino-4-(4-ethoxyphenyl)-3-isopropyl-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5l). White solid. mp 138–140°C. IR (KBr, cm^{-1}) υ: 3342, 3333, 3166, 2198, 1647, 1611, 1522, 1411, 1132, 1149, 1060, 1039, 785, 679, 551. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 0.75 (d, 3H, CH_3, $J=6.8$ Hz); 0.94 (d, 3H, CH_3, $J=7.2$ Hz); 2.48 (m, 1H, CH); 4.51 (s, 1H, CH); 6.72 (s, 2H, NH_2); 6.83 (d, 2H, Ar–H, $J=7.6$ Hz); 7.01 (d, 2H, Ar–H, $J=7.6$ Hz); 12.10 (s, 1H, NH). ESI-MS: *m/z* 325.2 $[M+1]^+$. *Anal*. calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.55; H, 6.27; N, 17.21.

6-Amino-3-isopropyl-4-(pyridin-3-yl)-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile (5m). White solid. mp 170–172°C. IR (KBr, cm^{-1}) υ: 3345, 3322, 3166, 2202, 1647, 1608, 1515, 1425, 1140, 1061, 1044, 778, 739. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 0.74 (d, 3H, CH_3, $J=7.2$ Hz); 0.96 (d, 3H, CH_3, $J=7.2$ Hz); 2.51 (m, 1H, CH); 4.70 (s, 1H, CH); 6.90 (s, 2H, NH_2); 7.32 (q, 1H, Ar–H, $J=4.8$ Hz); 7.49 (d, 1H, Ar–H, $J=8.0$ Hz); 8.43 (d, 1H, Ar–H); 8.43 (s, 1H, Ar–H); 12.16 (s, 1H, NH). ESI-MS: *m/z* 282.2 $[M+1]^+$. *Anal*. calcd for $C_{15}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.90. Found: C, 64.10; H, 5.35; N, 24.95.

6-Amino-3,4-diphenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5n). White solid. mp 162–164°C. IR (KBr, cm^{-1}) υ: 3344, 3311, 3171, 2182, 1645, 1610, 1518, 1420, 1145, 1135, 1061, 1042, 779, 730, 673. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 4.74 (S, 1H, CH); 7.4 (m, 10H, Ar–H); 12.16 (s, 1H, NH). ESI-MS: *m/z* 315.2 $[M+1]^+$. *Anal*. calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82. Found: C, 72.66; H, 4.55; N, 17.88.

6-Amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile (5o). White solid. mp 156–158°C. IR (KBr, cm^{-1}) υ: 3341, 3325, 3165, 2210, 1645, 1611, 1514, 1425, 1145, 1135, 1065, 1040, 783, 734, 551. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.93 (s, 3H, CH_3); 4.74 (s, 1H, CH); 7.25 (m, 5H, Ar–H); 7.35 (m, 5H, Ar–H); 8.56 (s, 2H, NH_2). ESI-MS: *m/z* 329 $[M+1]^+$. *Anal*. calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 73.25; H, 4.95; N, 17.10.

6-Amino-3-isopropyl-4-(4-nitrophenyl)-1-phenyl-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5p). White solid. mp 148–150°C. IR (KBr, cm^{-1}) υ: 3341, 3339, 3165, 2201, 1645, 1609, 1522, 1420, 1147, 1136, 1061, 1041, 771, 725, 671. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.31 (d, 6H, CH_3); 3.44 (m, 1H, CH); 4.74 (s, 1H, CH); 7.5 (m, 10H, Ar–H); 8.56 (s, 2H, NH_2). ESI-MS: *m/z* 402 $[M+1]^+$. *Anal*. calcd for $C_{22}H_{19}N_5O_3$: C, 56.83; H, 4.77; N, 17.45. Found: C, 56.93; H, 4.71; N, 17.49.

6-Amino-3-isopropyl-1-phenyl-4-(pyridin-3-yl)-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (5q). White solid. mp 178–180°C. IR (KBr, cm^{-1}) υ: 3341, 3339, 3165, 2210, 1645, 1600, 1519, 1425, 1145, 1141, 1061, 1037, 781, 731. ^{1}H NMR (DMSO-d_6, δ, 400 ppm): 1.31 (d, 6H, CH_3); 3.43 (m, 1H, CH); 4.74 (s, 1H, CH); 7.25 (t, 1H, $J=7.0$ Hz); 7.50 (m, 6H, Ar–H); 8.4 (m, 2H, Ar–H); 8.56 (s, 2H, NH_2). ESI-MS: *m/z* 358 $[M+1]^+$. *Anal*. calcd for $C_{21}H_{19}N_5O$: C, 70.57; H, 5.36; N, 19.59. Found: C, 70.60; H, 5.45; N, 19.65.

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