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ARTICLE

An efficient five-component synthesis of thio ether containing dihydropyrano[2,3-*c*]pyrazoles : A green domino strategy†

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An efficient route to the synthesis of novel thio ether containing dihydropyrano[2,3-*c*]pyrazoles have been accomplished *via* a solvent-free, catalyst-free *via* one-pot, five component domino strategy. This synthetic approach offers several advantages such as easy work-up, no need of purification techniques, short reaction time with good atom economy and high yields of products (81-86%).

Introduction

Multi component reactions (MCRs) are powerful tools to synthesis of libraries of complex molecules especially in modern organic synthesis and drug discovery in medicinal chemistry.[1] The main advantages of MCRs compared with traditional multistep procedures are high efficiency, mild reaction conditions, experimental simplicity, low cost, avoidance of large quantities of waste, ready availability of reagents/starting materials and the ability to generate a significant variety of products.[2] Dihydropyrano[2,3-*c*]pyrazole derivatives in organic synthesis as essential intermediates[3] and have vital role in medicinal chemistry as it has broad spectrum of biological activities such as antimicrobial,[4] antiinflammatory,[5] anticancer,[6,7] and analgesic.[8] Some of its derivatives acted against vasodilator and hypotensive,[9] hypoglycemic,[5a] insecticidal.[5a,10] Biologically active dihydropyrano[2,3-*c*]-pyrazoles are represented in fig 1. Compound A is having molluscicidal[11,12] activitity. Compound B is a potential inhibitor of human Chk1 kinase.[13] Compound C & D exhibit fungicidal activity[14] and antibacterial activity[13a,15] respectively. In 2002, Shestopalov et al., [16] reported the two or three component synthesis of some sulfur containing dihydropyrano[2,3-*c*]pyrazoles. Since sulfur containing scaffold[17] is expected to have an excellent biological activity, thio ether containing dihydropyrano[2,3-*c*]pyrazoles (TEDHPPs) is also expected to have a better activity than the simple dihydropyrano[2,3-*c*]pyrazoles. Solvent and catalyst free methods are more desirable for making such biologically important scaffolds as they offer a greener synthetic protocol. In continuation of our efforts in the useful synthetic methodology for the synthesis of heterocycles,[18] here in, we present an efficient five component synthesis of thio ether containing dihydropyrano[2,3-*c*]pyrazoles under solvent free condition.

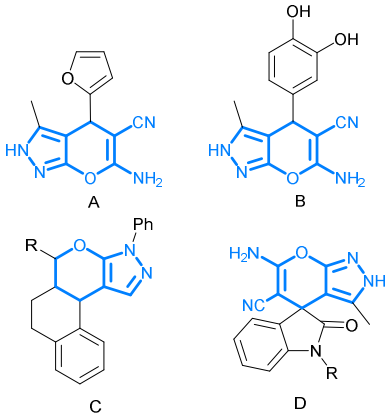
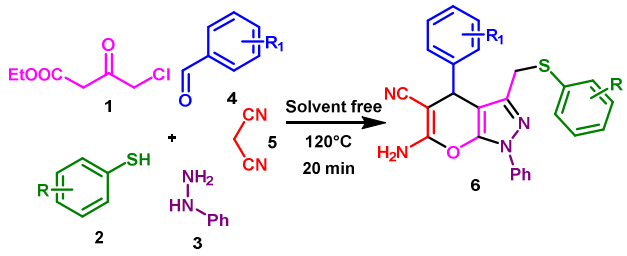


Figure 1. Biologically active dihydropyrano[2,3-c]-pyrazoles



Scheme 1. Synthesis of functionalized pyrano[2,3-c]pyrazoles via a five-component reaction

To the best of our knowledge through careful literature survey, this is the first report for the synthesis of thio ether containing dihydropyrano[2,3-*c*]pyrazoles using a five component domino strategy. The advantages of this reaction is

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† *Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data and copies of* ^{1}H, ^{13}C NMR & Mass spectra of all the synthesized compounds.

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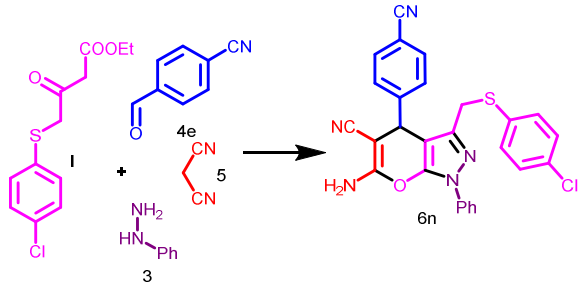
solvent and catalyst free methodology in a short reaction time with no column purification in excellent yields.

Results and discussion



Scheme 2. Synthesis of functionalized pyrano[2,3-*c*]pyrazoles via a four-component reaction

In our initial study, we started with a four component reaction of ethyl 4-((4-chlorophenyl)thio)-3-oxobutanoate **I**, phenyl hydrazine **3**, 4-cyanobenzaldehyde **4e** and malononitrile **5** taken as a model reaction for the synthesis of 6-amino-3-methyl-4-phenyl1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile **6n**. When the reaction was carried out in ethanol at reflux temperature, **6n** was obtained in 86% yield (Table 1, Entry 1) in 180 minutes. The ^{1}H NMR spectrum of **6n** in which the methylene protons appears as two doublets clearly shows the presence of chiral centre in the pyrano-pyrazole system. The presence of methylene group was confirmed with DEPT-135 and the remaining pyrano-pyrazole part was confirmed with the ^{1}H and ^{13}C NMR of the plenty of reported pyrano-pyrazole[19] systems. From the ESI-MS *m/z* analysis the mass for the compound **6n** was found to be 494. Encouraged by this initial success, in our own concern, we have attempted a five component reaction of ethyl 4-chloro-3-oxobutanoate **1**, benzenethiol **2a**, phenyl hydrazine **3**, 4-cyanobenzaldehyde **4e**, and malononitrile **5** in the presence of a base TEA. After the completion of the reaction we have isolated two impurities namely, diethyl 2,5-dioxocyclohexane-1,4-dicarboxylate[20] **A_1** and hydrazone[21] **B** impurity at this stage which suppressed the product formation, furnishing low yield (Table 1, Entry 2). The impurity **A_1** & **B** (Fig. 2) were confirmed by ^{1}H, ^{13}C, DEPT-135 and HRMS spectroscopic techniques (see ESI†). Impurity **A_1** is obtained due to the self-condensation of ethyl 4-chloro-3-oxobutanoate **1** in the presence of base. Impurity **B** is formed due to the condensation of aldehyde **4e** and phenyl hydrazine **3**. It was found that in the absence of TEA, the formation of **A_1** was drastically decreased. In order to decrease the formation of the hydrazone **B** impurity, the reaction was carried out through sequential addition of **1** and **2** at reflux temperature followed by **3** then reflux, subsequent addition of **4** and **3** without base. The product was obtained in good yield (60 %) (Table 1, Entry 3). An effort of gaining the yield by varying the solvents ranging from polar ones to non-polar, such as MeOH, IPA, ACN, water, toluene, xylene, $CHCl_3$, THF and DCE under refluxing conditions was unsuccessful (Table 1, Entry 4-12). On the other hand, the reaction performance was drastically enhanced under solvent-free conditions at 80°C. (Table 1, entry 13).

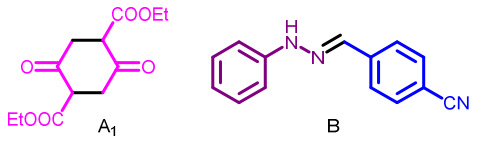
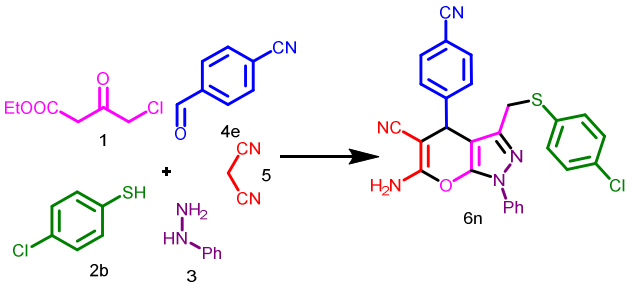


Figure 2. Isolated impurities **A_1** and **B** from the reaction mixture

When the temperature was raised to 120°C (Table 1, Entry 14), the results are in agreement with the expectation. Increasing the reaction time and temperature did not have any impact on the product yield (Table 1, Entry 15 & Entry 16).

Table 1 Optimization of the five component reaction conditions[a]



Entry	Base	Solvent	Temperature (°C)	Time (min)			Yield[b] of **6n**
				I[g]	**II**[h]	**6n**	
1[c]	TEA	EtOH	reflux	--	120	180	86
2[d]	TEA	EtOH	reflux	--	--	240	30[f]
3[e]	--	EtOH	reflux	120	300	20	60
4[e]	--	MeOH	reflux	90	240	20	62
5[e]	--	IPA	reflux	140	420	20	56
6[e]	--	ACN	reflux	140	360	15	57
7[e]	--	H_2O	reflux	90	300	20	60
8[e]	--	Toluene	reflux	240	240	10	40
9[e]	--	Xylene	reflux	240	200	10	45
10[e]	--	$CHCl_3$	reflux	240	360	10	40
11[e]	--	THF	reflux	180	300	10	43
12[e]	--	DCE	reflux	260	320	10	48
13[e]	--	--	80	60	10	10	70
14[e]	**--**	**--**	**120**	**10**	**5**	**5**	**83**
15[e]	--	--	120	30	30	30	84
16[e]	--	--	150	5	5	5	83

[a]Reaction conditions: conventional heating under solvent free condition at 120 °C with 1 (1.0 equiv.), **2b** (1.1 equiv.), **3** (1.1 equiv.), **4e** (1.1 equiv.), **5** (1.1 equiv.) for 20 min; [b] Isolated yield; [c] four component reaction of **I**, **3**, followed by **4e** and **5**; [d] five component one pot reaction; [e]**1** and **2b** was heated and maintained appropriate temperature followed by addition of **3** and maintained same fixed temperature consequent addition of **4e**, **5** and maintained same temperature; [f]purified by column; [g]ethyl 4-((4-chlorophenyl)thio)-3-oxobutanoate (**I**); [h]5-(((4-chlorophenyl)thio)methyl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**II**);

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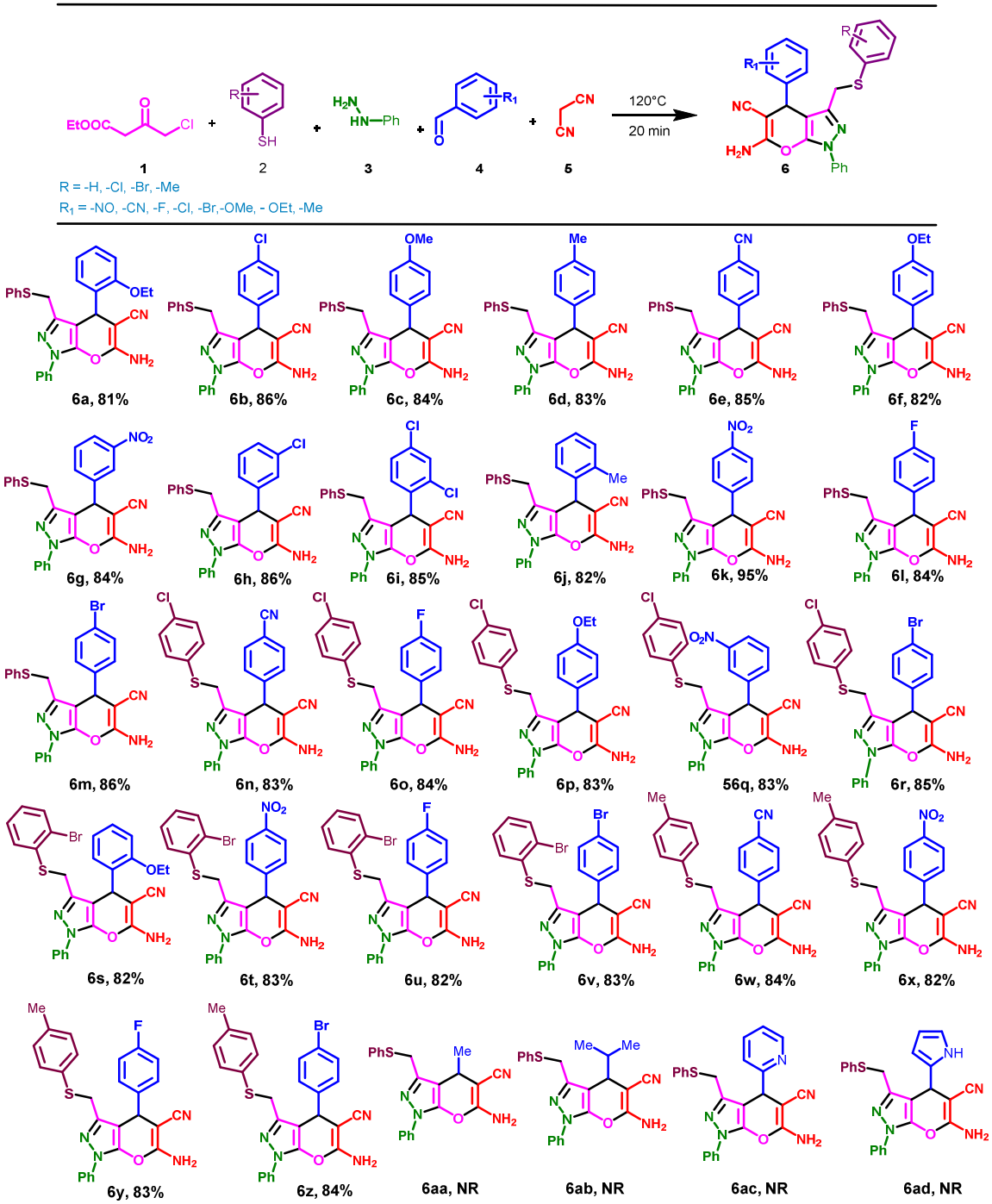
Table 2 Synthesis of dihydropyrano[2,3-*c*]pyrazoles **6a-ad**



NR – No Reaction

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Thus the optimized condition for this reaction was found to be heating the reactants at 120°C under without solvent. (Table 1, Entry 14).

To explore the scope and generality of this domino MCR, we extended the same to construct a library of thio ether containing pyrano[2,3-*c*]pyrazole derivatives **6a-z** under the optimized reaction conditions and it was successful with various aromatic aldehydes and thiophenol (Table 2). A variety of aryl aldehydes (e.g. $-NO_2$, –CN, –F, –Cl, –Br, –OMe, –OEt, –Me) and thiophenols (e.g. –H, –Cl, –Br, –Me) containing different substituents both electron withdrawing and electron donating afforded **6** in good to excellent yields. The electronic effects of the substituent were not observed much in the yields of the products. Furthermore, all the compounds were characterized by ^{1}H & ^{13}C NMR and ESI-MS spectral analysis. One of the synthesized compound **6q** structure was confirmed further using 1D, 2D and ESI-Mass spectral techniques (see ESI†). However, no desired products **6aa-ad** was obtained from the aliphatic aldehydes such as acetaldehyde and isobutyraldehyde and heterocyclic aldehydes such as pyridine-2-carbaldehyde and pyrrole-2-carbaldehyde.

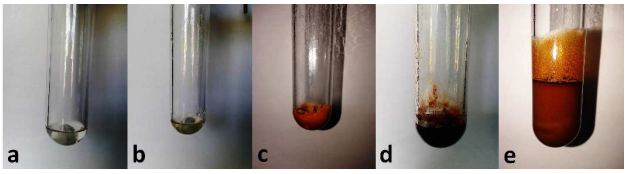
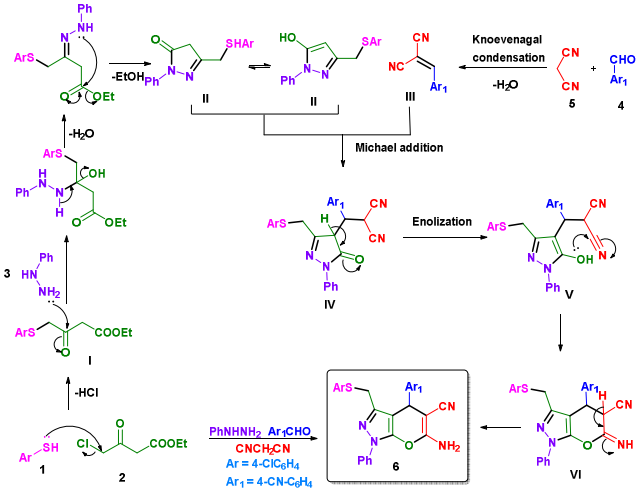


Figure 3. Reaction was done at 1 g scale level; (a) ethyl 4-chloro-3-oxobutanoate (**1**) and 4-chlorobenzenethiol (**2b**) at room temperature; (b) after 10 minutes heat at 120 °C; (c) after phenylhydrazine (**3**) addition maintained 5 minutes at 120 °C; (d) after 4-cyanobenzaldehyde (**4e**) , malononitrile (**5**) was added and heated to 120 °C for 5 minutes; (e) after ethanol addition

The plausible mechanism for the formation of 6-amino-4-(4-aryl)-1-phenyl-3-((phenylthio) methyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile **6** is described (Scheme 3).



Scheme 3. Plausible reaction mechanism for the functionalized pyrano[2,3-*c*]pyrazoles **6**

The formation of the pyrano[2,3-*c*]pyrazole derivative, namely, 6-amino-1,4-diphenyl-3-((phenylthio)methyl)-1,4 dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, proceeds *via* the simultaneous formation of three intermediates, 3-oxo-4-(arylthio)butanoate **I** *via* S_N2 reaction, pyrazolone **II** *via* cyclo condensation and arylidenemalononitrile **III** by Knoevenagel condensation reaction. Intermediate **I** formation the liberated hydrochloride, followed by cyclo condensation with phenylhydrazine to produced intermediate **II**. After which the intermediate **II** undergoes Michael addition with **III** followed by enolization afforded intermediate **V**. Intermediate **V** then undergoes intramolecular electrophilic O-cyclization *via* Thorpe-Ziegler reaction to form **VI**. Finally, after the tautomeric proton shift and affording the desired product thio ether containing pyrano[2,3-*c*]pyrazole derivative **6** is formed.

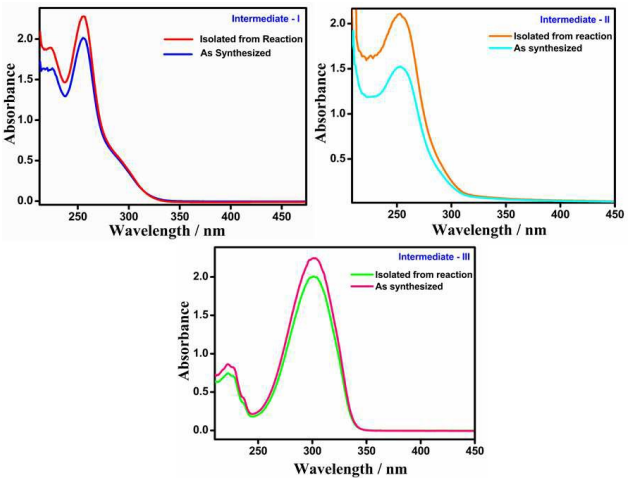


Figure 4. UV-vis spectra of intermediates (**I**, **II** and **III**) were compared with isolated from reaction and synthesized under optimized condition

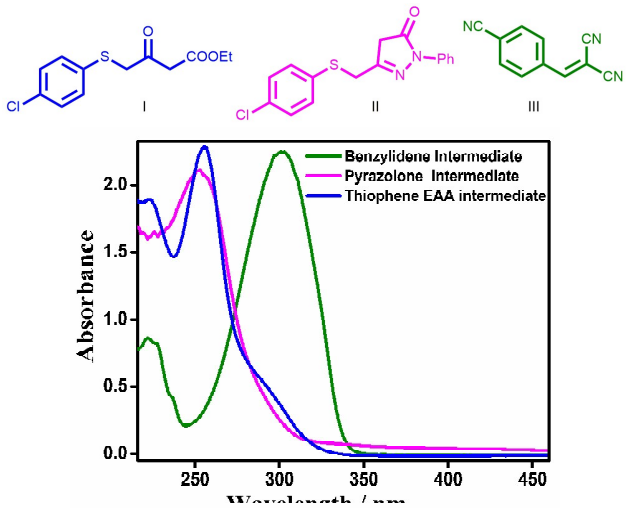


Figure 5. UV-vis spectra of intermediates **I**, **II** and **III**.

To establish the proposed mechanism, we have performed the synthesis of pyrano[2,3-*c*]pyrazole step by step under

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optimized reaction condition. We have synthesized three intermediates **I, II** and **III** separately from the respective starting materials under optimized condition. Also all three intermediates were isolated and purified by column chromatography.

Finally, intermediates **I**, **II** and **III** were mixed under optimized condition affording pyrano[2,3-*c*]pyrazole derivative. The intermediates were confirmed by melting point determination and UV-vis spectroscopic studies. The melting point values are in agreement with synthesized compounds. The formation of these intermediates were further confirmed by ^{1}H, ^{13}C, DEPT-135 and HRMS spectroscopic techniques (see ESI†).

The UV- Vis spectroscopy of all thee (**I, II** and **III**) synthesized intermediate and isolated from reaction mixture were in perfect alignment with (Fig. 4) respective intermediate. The UV-vis spectra of the three different intermediates are shown in Fig. 5. The observed λ_{max} value ethyl 4-((4-chlorophenyl)thio)-3-oxobutanoate (**I**) of 256 nm, pyrazolone (**II**) of 253 and 2-(4-cyanobenzylidene)malononitrile (**III**) of 253 was observed.

Conclusions

In conclusion, we have developed a simple and efficient five component domino synthesis of thio ether containing dihydropyrano[2,3-*c*]pyrazoles **6** under solvent free, catalyst free condition using commercially available starting materials in a short reaction time. The significant features of this methodology are short reaction time, an excellent yield with good atom economy (80.56%), no column purification, low-cost, operational simplicity, vast structural diversity and minimal environmental waste. The biological studies for the library of compounds synthesized are underway.

Experimental Section

General remarks

The melting points were measured in open capillary tubes and are uncorrected. The reaction was monitored by TLC on Merck GF 254 with detection by UV light for visualization using a mixture of petroleum ether (60-80 ˚C) and ethyl acetate (7:3) as the eluent. Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR) spectra were recorded on a Bruker (Advance) 300 MHz spectrometer in DMSO-d_6 using TMS as an internal standard. Chemical shifts are reported in parts per million (δ), coupling constants (J values) are reported in Hertz (Hz) and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), (multiplet). ^{13}C NMR spectra were routinely run with broadband decoupling. Absorption spectra studies of all samples were recorded on Agilent Technologies 8453 spectrophotometer by taking the solution in a 1 cm path length quartz cell in the wavelength range of 200-1100 nm. Elemental analyses were carried out with Perkin-Elmer 2400 series II analyzer. Electrospray ionization mass spectrometry (ESI-MS) was recorded in LCQ Fleet, Thermo Fisher Instruments Limited, US and High resolution mass spectra were recorded on a Water Q-TOF micro mass spectrometer using ESI mode.

General procedure for the synthesis of 6-amino-1,4-diphenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6)

A mixture of commercially available ethyl 4-chloro-3-oxobutanoate **1** (1.0 equiv.), substituted benzenethiol **2** (1.1 equiv.), was heated to 120°C for 10 minutes under solvent free condition. TLC was checked followed by addition of phenylhydrazine **3** (1.1 equiv.) at 120°C and maintained same temperature for 5 minutes. After monitored by TLC, subsequent addition of aldehyde **4** (1.1 equiv.) and malononitrile **5** (1.1 equiv.) were done under solvent free condition. The completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature followed by addition of ethanol (5 mL). The product appeared as a solid, by trituration with ethanol, was filtered and washed with another 2 mL of EtOH to remove the other impurities. Finally, the product **6** was dried under reduced pressure and was pure enough for the spectral investigations.

6-amino-4-(2-ethoxyphenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6a). Isolated as white solid; R_f = 0.41 (3:7 EtOAc/pet-ether); mp 180–182 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.72 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 15.6 Hz, 2H), 7.34 – 7.12 (m, 10H), 6.94 – 6.84 (m, 2H), 4.87 (s, 1H), 3.91 – 3.84 (m, 3H), 3.47 (d, *J* = 13.8 Hz, 1H), 1.14 (t, *J* = 13.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.4, 157.0, 145.1, 145.0, 137.9, 136.2, 130.9, 129.8, 129.3, 129.3, 129.1, 126.9, 126.6, 120.8, 120.6, 112.9, 99.2, 63.8, 57.9, 33.0, 30.1, 14.9; ESI Calcd *m/z* 480, Found 479 $[(M-1)]^{+}$; Anal. Calcd for: $C_{28}H_{24}N_4O_2S$: C, 69.98; H, 5.03; N, 11.66; O, 6.66%; Found C, 69.95; H, 5.06; N, 11.69%; * One of the $-SCH_2$ proton was merged with $-CH_2$ as –OEt peak.

6-amino-4-(4-chlorophenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6b). Isolated as white solid; R_f = 0.42 (3:7 EtOAc/pet-ether); mp 200–202 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.73 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 15.9 Hz, 2H), 7.38 – 7.34 (m, 3H), 7.29 – 7.16 (m, 9H), 4.68 (s, 1H), 3.91 (d, *J* = 13.8 Hz, 1H), 3.42 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.2, 145.7, 145.0, 143.1, 138.1, 136.3, 132.7, 130.6, 130.2, 129.8, 129.4, 127.5, 127.1, 121.2, 120.6, 99.0, 58.6, 37.2, 30.7; Anal. Calcd for: $C_{26}H_{19}ClN_4OS$: C, 66.31; H, 4.07; N, 11.90%; Found C, 66.34; H, 4.04; N, 11.93%.

6-amino-4-(4-methoxyphenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6c). Isolated as white solid; R_f = 0.37 (3:7 EtOAc/pet-ether); mp 196–198 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.73 (d, *J* = 8.1 Hz, 2H), 7.49 (t, *J* = 15.3 Hz, 2H), 7.36 – 7.13 (m, 12H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.60 (s, 1H), 3.90 (d, *J* = 14.1 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.0, 159.2, 145.8, 144.9, 138.1, 136.3, 136.0, 130.2, 129.8, 127.5, 127.1, 121.2, 120.7, 114.8, 99.7, 59.4, 55.9, 37.0, 30.7; ESI Calcd *m/z* 466, found 465 $[(M-1)]^{+}$; Anal. Calcd for: $C_{27}H_{22}N_4O_2S$: C, 69.51; H, 4.75; N, 12.01%; Found C, 69.54; H, 4.73; N, 12.04%; * One of the $-SCH_2$ proton was merged with water peak.

6-amino-1-phenyl-3-((phenylthio)methyl)-4-(p-tolyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6d). Isolated as white solid; R_f = 0.46 (3:7 EtOAc/pet-ether); mp 178–180 ^{o}C;

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^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.73 (d, *J* = 8.1 Hz, 2H), 7.49 (t, *J* = 15.0 Hz, 2H), 7.36 – 7.21 (m, 10H), 7.11 (s, 2H), 4.60 (s, 1H), 3.90 (d, *J* = 13.8 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.0, 145.7, 144.9, 141.0, 138.1, 137.2, 136.3, 130.2, 130.0, 129.8, 128.6, 127.4, 127.1, 121.2, 120.7, 99.6, 59.2, 37.4, 30.7, 21.6; ESI Calcd *m/z* 450, found 451 $[(M+1)]^+$; Anal. Calcd for: $C_{27}H_{22}N_4OS$: C, 71.98; H, 4.92; N, 12.44%; Found: C, 71.95; H, 4.95; N, 12.47%; * One of the –SCH_2 proton was merged with water peak.

6-amino-4-(4-cyanophenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6e). Isolated as white solid; R_f = 0.30 (3:7 EtOAc/pet-ether); mp 194–196 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.79 – 7.72 (m, 4H), 7.52 – 7.45 (m, 4H), 7.40 – 7.18 (m, 8H), 4.80 (s, 1H), 3.91 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.4, 149.6, 145.6, 145.2, 138.0, 136.2, 133.5, 130.2, 129.9, 129.8, 127.6, 127.1, 121.3, 120.5, 119.6, 110.9, 98.5, 58.0, 37.8, 30.7; ESI Calcd *m/z* 461, found 460 $[(M-1)]^+$; Anal. Calcd for: $C_{27}H_{19}N_5OS$: C, 70.26; H, 4.15; N, 15.17%; Found C, 70.28; H, 4.19; N, 15.20%; * One of the –SCH_2 proton was merged with water peak.

6-amino-4-(4-ethoxyphenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6f). Isolated as white solid; R_f = 0.44 (3:7 EtOAc/pet-ether); mp 188–190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.72 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 15.3 Hz, 2H), 7.36 – 7.11 (m, 10H), 6.84 (d, *J* = 8.1 Hz, 2H), 4.58 (s, 1H), 3.98 – 3.87 (m, 3H), 1.29 (t, *J* = 13.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.0, 158.5, 145.8, 144.9, 138.1, 136.3, 135.9, 130.3, 129.8, 127.5, 127.1, 121.2, 115.2, 99.7, 39.5, 37.0, 30.7, 15.5; Anal. Calcd for: $C_{28}H_{24}N_4O_2S$: C, 69.98; H, 5.03; N, 11.66%; Found C, 69.95; H, 5.06; N, 11.69%; * One of the ethyl –SCH_2 proton was merged with ethyl –CH_2 and another one –SCH_2 proton was merged with water peak.

6-amino-4-(3-nitrophenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6g). Isolated as white solid; R_f = 0.32 (3:7 EtOAc/pet-ether); mp 192–194 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.12 (d, *J* = 9.6 Hz, 2H), 7.72 (d, *J* = 9.3 Hz, 3H), 7.56 (t, *J* = 15.6 Hz, 1H), 7.50 (t, *J* = 15.3 Hz, 2H), 7.40 – 7.32 (m, 3H), 7.26 – 7.15 (m, 5H), 4.93 (s, 1H), 3.92 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.4, 148.8, 146.4, 145.6, 145.2, 138.0, 136.2, 135.8, 131.1, 130.2, 129.7, 127.6, 127.0, 123.3, 121.3, 120.5, 98.5, 58.1, 37.4, 30.7; Anal. Calcd for: $C_{26}H_{19}N_5O_3S$: C, 64.85; H, 3.98; N, 14.54%; Found C, 64.89; H, 4.01; N, 14.56%; * One of the –SCH_2 proton was merged with water peak.

6-amino-4-(3-chlorophenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6h). Isolated as white solid; R_f = 0.37 (3:7 EtOAc/pet-ether); mp 178–180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.72 (d, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.43 – 7.40 (m, 1H), 7.37 – 7.16 (m, 11H), 5.19 (s, 1H), 3.90 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.6, 149.5, 144.6, 142.1, 140.3, 137.4, 136.0, 134.7, 134.3, 133.9, 133.8, 132.7, 131.6, 131.1, 125.3, 124.4, 102.5, 61.6, 39.1, 34.7; ESI Calcd *m/z* 470, Found 471 $[(M+1)]^+$; Anal. Calcd for: $C_{26}H_{19}ClN_4OS$: C, 66.31; H, 4.07; Cl, 7.53; N, 11.90%; Found C, 66.35; H, 4.10; N, 11.89%; * One of the –SCH2 proton was merged with water peak.

6-amino-4-(2,4-dichlorophenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6i). Isolated as white solid; R_f = 0.40 (3:7 EtOAc/pet-ether); mp 204–206 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.72 (d, *J* = 8.0 Hz, 2H), 7.51 (m, 4H), 7.36 (s, 4H), 7.28 – 7.16 (m, 5H), 5.20 (s, 1H), 3.90 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.7, 149.5, 149.4, 143.9, 142.1, 140.3, 138.3, 137.5, 137.4, 134.3, 133.7, 133.6, 132.9, 131.7, 131.4, 125.3, 124.3, 102.1, 61.2, 38.7, 34.7; Anal. Calcd for: $C_{26}H_{18}Cl_2N_4OS$: C, 61.79; H, 3.59; N, 11.09%; Found C, 61.82; H, 3.62; N, 11.13%; * One of the –SCH_2 proton was merged with water peak.

6-amino-1-phenyl-3-((phenylthio)methyl)-4-(*o*-tolyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6j). Isolated as white solid; R_f = 0.40 (3:7 EtOAc/pet-ether); mp 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.76 (d, *J* = 7.5 Hz, 2H), 7.55 – 7.47 (m, 2H), 7.39 – 7.10 (m, 12H), 5.02 (s, 1H), 3.90 (d, *J* = 13.5 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.3, 144.8, 140.9, 137.4, 135.5, 129.5, 123.0, 128.8, 127.2, 126.9, 126.8, 126.3, 120.5, 120.0, 98.7, 58.0, 33.4, 30.0, 19.1; Anal. Calcd for: $C_{27}H_{22}N_4OS$: C, 71.98; H, 4.92; N, 12.44%; Found C, 71.96; H, 4.95; N, 12.47%; * One of the –SCH_2 proton was merged with water peak.

6-amino-4-(4-nitrophenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6k). Isolated as white solid; R_f = 0.32 (3:7 EtOAc/pet-ether); mp 208–210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.16 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.48 (m, 5H), 7.41 – 7.34 (m, 2H), 7.28 – 7.16 (m, 5H), 4.88 (s, 1H), 3.92 (d, *J* = 13.8 Hz, 1H), 3.50 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.7, 151.0, 146.9, 145.0, 144.5, 137.4, 135.6, 129.5, 129.1, 126.9, 129.1, 124.0, 120.7, 119.7, 97.7, 57.4, 36.9, 30.1; Anal. Calcd for: $C_{26}H_{19}N_5O_3S$: C, 64.85; H, 3.98; N, 14.54%; Found C, 64.88; H, 3.96; N, 14.57%.

6-amino-4-(4-fluorophenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6l). Isolated as white solid; R_f = 0.43 (3:7 EtOAc/pet-ether); mp 180–182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.73 (d, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 15.9 Hz, 2H), 7.37 – 7.24 (m, 10H), 7.21 – 7.10 (m, 3H), 4.69 (s, 1H), 3.91 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.4, 145.0, 144.3, 139.6, 137.4, 135.6, 130.0, 129.9, 129.5, 129.1, 126.8, 126.4, 120.5, 119.9, 115.6, 15.3, 98.6, 58.2, 36.4, 30.0; ESI Calcd *m/z* 454, Found 453 $[(M-1)]^+$; Anal. Calcd for: $C_{26}H_{19}FN_4OS$: C, 68.71; H, 4.21; N, 12.33%; Found C, 68.75; H, 4.24; N, 12.36%;* One of the –SCH_2 proton was merged with water peak.

6-amino-4-(4-bromophenyl)-1-phenyl-3-((phenylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6m). Isolated as white solid; R_f = 0.43 (3:7 EtOAc/pet-ether); mp 196–198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.73 (d, *J* = 8.1 Hz, 2H), 7.49 (t, *J* = 13.5 Hz, 3H), 7.37 – 7.20 (m, 10H), 4.67 (s, 1H), 3.91 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.5, 145.0, 144.3, 142.8, 137.4, 135.6, 131.7, 130.3, 129.5, 129.1, 126.8, 126.4, 120.6, 119.9, 98.3, 57.9, 36.6, 30.1; Anal. Calcd for: $C_{26}H_{19}BrN_4OS$: C, 60.59; H, 3.72; N, 10.87%; Found C, 60.62; H, 3.75; N, 10.85%; * One of the –SCH_2 proton was merged with water peak.

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6-amino-3-(((4-chlorophenyl)thio)methyl)-4-(4-cyanophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6n). Isolated as white solid; R_f = 0.31 (3:7 EtOAc/pet-ether); mp 200–202 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.79 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.53 – 7.47 (m, 4H), 7.38 – 7.32 (m, 5H), 7.25 (d, *J* = 8.1 Hz, 2H), 4.85 (s, 1H), 3.92 (d, *J* = 14.1 Hz, 1H), 3.51 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.6, 149.0, 144.5, 137.3, 134.6, 132.8, 131.1, 130.6, 129.5, 129.2, 128.9, 126.9, 120.7, 119.8, 118.9, 110.2, 97.7, 57.3, 37.0, 29.9; ESI Calcd *m/z* 495, Found 494 $[(M-1)]^+$; Anal. Calcd for: $C_{27}H_{18}ClN_5OS$: C, 65.38; H, 3.66; N, 14.12%; Found C, 65.41; H, 3.69; N, 14.15%.

6-amino-3-(((4-chlorophenyl)thio)methyl)-4-(4-fluorophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6o). Isolated as white solid; R_f = 0.40 (3:7 EtOAc/pet-ether); mp 182–184 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.72 (d, *J* = 8.1 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.25 (m, 10H), 7.14 (t, *J* = 8.7 Hz, 2H), 4.73 (s, 1H), 3.92 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.4, 144.7, 144.3, 139.6, 137.4, 134.7, 131.1, 130.6, 130.0, 129.9, 129.5, 128.9, 126.8, 120.6, 119.9, 115.6, 115.4, 98.6, 58.2, 36.3, 30.0; Anal. Calcd for: $C_{26}H_{18}ClFN_4OS$: C, 63.87; H, 3.71; N, 11.46%; Found C, 63.89; H, 3.74; N, 11.44%; * One of the –SCH_2 proton was merged with water peak.

6-amino-3-(((4-chlorophenyl)thio)methyl)-4-(4-ethoxyphenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6p). Isolated as white solid; R_f = 0.43 (3:7 EtOAc/pet-ether); mp 184–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.72 (d, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.34 – 7.20 (m, 9H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.62 (s, 1H), 4.01 – 3.88 (m, 3H), 1.30 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.0, 158.5, 145.5, 144.9, 138.1, 135.8, 135.5, 131.7, 131.3, 130.2, 129.7, 127.5, 121.2, 120.7, 115.2, 99.7, 63.8, 59.4, 37.0, 30.7, 15.5; Anal. Calcd for: $C_{28}H_{23}ClN_4O_2S$: C, 65.30; H, 4.50; N, 10.88%; Found C, 65.32; H, 4.54; N, 10.86%; * One of the ethyl –SCH_2 proton was merged with ethyl-CH_2 and another one –SCH_2 proton was merged with water peak.

6-amino-3-(((4-chlorophenyl)thio)methyl)-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6q). Isolated as white solid; R_f = 0.31 (3:7 EtOAc/pet-ether); mp 186–188 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.14 (s, 1H), 7.78 (t, *J* = 9.0 Hz, 3H), 7.65 (t, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 2H), 7.44 (s, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 5.01 (s, 1H), 3.97 (d, *J* = 13.9 Hz, 1H), 3.61 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 158.7, 147.1, 144.7, 143.6, 143.5, 136.3, 134.0, 133.6, 130.1, 129.6, 129.4, 128.5, 127.8, 125.9, 121.6, 121.5, 119.7, 118.7, 96.8, 56.5, 35.7, 29.0; ESI Calcd *m/z* 515, found 514 $[(M-1)]^+$; Anal. Calcd for: $C_{26}H_{18}ClN_5O_3S$: C, 60.52; H, 3.52; N, 13.57%; Found C, 60.56; H, 3.50; N, 13.61%.

6-amino-4-(4-bromophenyl)-3-(((4-chlorophenyl)thio)methyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6r). Isolated as white solid; R_f = 0.45 (3:7 EtOAc/pet-ether); mp 208–210 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.72 (d, *J* = 6.9 Hz, 2H), 7.50 (d, *J* = 6.3 Hz, 5H), 7.34 – 7.21 (m, 8H), 4.71 (s, 1H), 3.92 (d, *J* = 13.8 Hz, 1H), 3.46 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO- d_6) δ: 160.2, 145.4, 145.1, 143.5, 132.4, 131.8, 131.4, 131.0, 130.2, 129.7, 127.6, 121.3, 120.6, 99.0, 58.6, 37.3, 30.7; ESI Calcd *m/z* 548, found 549 $[(M+1)]^+$; Anal. Calcd for: $C_{26}H_{18}BrClN_4OS$: C, 56.79; H, 3.30; N, 10.19%; Found C, 56.82; H, 3.34; N, 10.21%.

6-amino-3-(((2-bromophenyl)thio)methyl)-4-(2-ethoxyphenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6s). Isolated as white solid; R_f = 0.38 (3:7 EtOAc/pet-ether); mp 184–186 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.75 (d, *J* = 7.2 Hz, 2H), 7.59 – 7.48 (m, 4H), 7.35 – 7.08 (m, 8H), 6.94 – 6.84 (m 2H), 4.94 (s, 1H), 3.96 – 3.86 (m, 3H), 1.15 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.9, 157.3, 145.4, 144.6, 138.2, 133.4, 131.1, 130.2, 130.3, 130.2, 129.5, 129.5, 128.9, 128.6, 127.7, 127.4, 122.6, 121.3, 121.0, 113.2, 99.7, 64.1, 58.0, 29.5, 15.3; Anal. Calcd for: $C_{28}H_{23}BrN_4O_2S$: C, 60.11; H, 4.14; Br, N, 10.01%; Found C, 60.14; H, 4.18; Br, N, 10.03%; * One of the ethyl –SCH_2 proton was merged with ethyl-CH_2 and another one –SCH_2 proton was merged with water peak.

6-amino-3-(((2-bromophenyl)thio)methyl)-4-(4-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6t). Isolated as white solid; R_f = 0.30 (3:7 EtOAc/pet-ether); mp 192–194 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.11 (d, J = 8.4 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 2H), 7.52 – 7.33 (m, 10H), 7.06 (t, *J* = 6.0 Hz, 1H), 4.93 (s, 1H), 3.96 (d, *J* = 13.8 Hz, 1H), 3.70 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.4, 151.7, 147.6, 145.3, 144.9, 138.0, 197.8, 133.4, 130.2, 130.1, 128.9, 127.8, 127.7, 124.7, 122.7, 121.4, 120.3, 98.6, 58.0, 37.6, 29.7; ESI Calcd *m/z* 559, found 558 $[(M-1)]^+$; Anal. Calcd for: $C_{26}H_{18}BrN_5O_3S$: C, 55.72; H, 3.24; N, 12.50%; Found C, 55.75; H, 3.21; N, 12.54%.

6-amino-3-(((2-bromophenyl)thio)methyl)-4-(4-fluorophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6u). Isolated as white solid; R_f = 0.43 (3:7 EtOAc/pet-ether); mp 180–182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.74 (d, *J* = 7.8 Hz, 2H), 7.59 – 7.48 (m, 4H), 7.35 – 7.28 (m, 6H), 7.14 – 7.06 (m, 3H), 4.73 (s, 1H), 3.95 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.1, 145.0, 144.9, 140.2, 138.1, 137.9, 133.5, 130.7, 130.3, 130.0, 129.0, 127.9, 127.6, 122.9, 121.4, 120.7, 116.4, 116.1, 112.9, 99.5, 58.9, 37.1, 29.8; Anal. Calcd for: $C_{26}H_{18}BrFN_4OS$: C, 58.54; H, 3.40; N, 10.50%; Found C, 58.57; H, 3.44; N, 10.52%; * One of the –SCH_2 proton was merged with water peak.

6-amino-4-(4-bromophenyl)-3-(((2-bromophenyl)thio)methyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6v). Isolated as white solid; R_f = 0.38 (3:7 EtOAc/pet-ether); mp 196—198 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.74 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 3.6 Hz, 2H), 7.53 – 7.46 (m, 4H), 7.37 – 7.31 (m, 4H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.11 – 7.06 (m, 1H), 4.71 (s, 1H), 3.96 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.2, 145.0, 144.8, 143.4, 138.0, 137.8, 135.9, 133.4, 132.4, 130.9, 130.2, 130.0, 128.9, 128.2, 127.9, 127.6, 122.8, 121.3, 120.6, 112.9, 99.1, 58.5, 37.3, 29.7; ESI Calcd *m/z* 592, found 593 $[(M+1)]^+$; Anal. Calcd for: $C_{26}H_{18}Br_2N_4OS$: C, 52.54; H, 3.05; N, 9.43%; Found C, 52.52; H, 3.09; N, 9.47%; * One of the –SCH_2 proton was merged with water peak.

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6-amino-3-(((2-bromophenyl)thio)methyl)-4-(4-cyanophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6w). Isolated as white solid; R_f = 0.30 (3:7 EtOAc/pet-ether); mp 194–196 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.76 – 7.72 (m, 4H), 7.57 – 7.45 (m, 5H), 7.38 – 7.32 (m, 4H), 7.10 – 7.05 (m, 1H), 4.84 (s, 1H), 3.95 (d, *J* = 13.8 Hz, 1H), 3.65 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.4, 149.6, 145.3, 144.9, 138.0, 137.8, 133.5, 130.2, 129.8, 129.1, 129.0, 127.9, 127.7, 122.9, 121.5, 120.3, 119.6, 111.0, 98.7, 58.1, 37.8, 29.8; ESI Calcd *m/z* 539, found 538 $[(M-1)]^+$; Anal. Calcd for: $C_{27}H_{18}BrN_5OS$: C, 60.01; H, 3.36; N, 12.96%; Found C, 60.04; H, 3.38; N, 12.94%.

6-amino-4-(4-nitrophenyl)-1-phenyl-3-((p-tolylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6x). Isolated as white solid; R_f = 0.29 (3:7 EtOAc/pet-ether); mp 210–212 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.16 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.54 – 7.47 (m, 4H), 7.40 – 7.35 (m, 3H), 7.09 (q, *J* = 8.1 Hz, 4H), 4.80 (s, 1H), 3.85 (d, *J* = 13.8 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.4, 151.7, 147.5, 145.8, 145.1, 138.0, 137.0, 132.3, 130.7, 130.4, 130.2, 130.1, 127.6, 124.7, 121.3, 120.4, 98.4, 57.9, 37.5, 31.4, 21.4; ESI Calcd *m/z* 495, found 494 $[(M-1)]^+$; Anal. Calcd for: $C_{27}H_{21}N_5O_3S$: C, 65.44; H, 4.27; N, 14.13%; Found C, 65.48; H, 4.31; N, 14.09%; * One of the $-SCH_2$ proton was merged with water peak.

6-amino-4-(4-fluorophenyl)-1-phenyl-3-((p-tolylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6y). Isolated as white solid; R_f = 0.34 (3:7 EtOAc/pet-ether); mp 186–188 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.71 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.35 – 7.25 (m, 6H), 7.16 – 7.07 (m, 5H), 4.60 (s, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.1, 145.8, 144.9, 140.3, 138.1, 137.0, 132.4, 130.8, 130.4, 130.2, 127.5, 121.2, 120.6, 116.3, 116.0, 99.3, 59.0, 37.0, 31.5, 21.4; Anal. Calcd for: $C_{27}H_{21}FN_4OS$: C, 69.21; H, 4.52; N, 11.96%; Found C, 69.25; H, 4.56; N, 11.98%; * One of the $-SCH_2$ proton was merged with water peak. ESI Calcd m/z 468, found 467 $[(M-1)]^+$

6-amino-4-(4-bromophenyl)-1-phenyl-3-((p-tolylthio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6z). Isolated as white solid; R_f = 0.34 (3:7 EtOAc/pet-ether); mp 206–208 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.71 (d, *J* = 7.5 Hz, 2H), 7.51 – 7.46 (m, 4H), 7.36 – 7.29 (m, 3H), 7.20 – 7.07 (m, 7H), 4.59 (s, 1H), 3.84 (d, *J* = 13.8 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.2, 145.8, 145.0, 143.6, 138.1, 137.0, 132.4, 131.0, 130.9, 130.5, 130.2, 127.5, 121.2, 120.6, 98.9, 58.6, 37.2, 31.5, 21.4; ESI Calcd *m/z* 528, found 527 $[(M-1)]^+$; Anal. Calcd for: $C_{27}H_{21}BrN_4OS$: C, 61.25; H, 4.00; N, 10.58%; Found C, 61.28; H, 4.04; N, 10.61%; * One of the $-SCH_2$ proton was merged with water peak.

diethyl 2,5-dioxocyclohexane-1,4-dicarboxylate (A_1). Isolated as yellowish crystalline solid; R_f = 0.88 (3:7 EtOAc/pet-ether); mp 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.21 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 4H), 3.18 (s, 4H), 1.32 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.3, 168.4, 93.2, 60.7, 28.5, 14.2; ES^+ HRMS m/z calcd for $C_{12}H_{16}O_6$ 257.1025 [M +H], found 257.1026 [M + H].

(E)-4-((2-phenylhydrazono)methyl)benzonitrile (B) Isolated as yellowish solid; R_f = 0.58 (3:7 EtOAc/pet-ether); mp 152–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.67 (d, *J* = 6.3 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 3H), 7.27 (d, *J* = 7.1 Hz, 2H), 7.11 (d, *J* = 6.7 Hz, 2H), 6.91 (t, *J* = 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.2, 140.3, 134.7, 132.8, 129.8, 126.6, 121.4, 119.6, 113.4, 111.1; ES^+ HRMS m/z calcd for $C_{14}H_{11}N_3$ 222.1031 [M +H], found 221.1028 [M + H].

ethyl 4-((4-chlorophenyl)thio)-3-oxobutanoate (I) Isolated as yellowish liquid; R_f = 0.75 (3:7 EtOAc/pet-ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 – 7.26 (m, 4H), 4.21 (q, *J*= 7.1 Hz, 2H), 3.80 (s, 2H), 3.62 (s, 2H), 1.28 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.9, 167.3, 133.8, 132.9, 131.7, 129.8, 62.0, 46.9, 44.4, 14.4.

5-(((4-chlorophenyl)thio)methyl)-2-phenyl-2,4-dihydro-3H-pyrazol-3-one[20] (II) Isolated as brown solid; R_f = 0.81 (3:7 EtOAc/pet-ether); mp 89–91 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.34 – 7.28 (m, 4H), 7.19 (t, *J* = 7.2 Hz, 1H), 3.90 (s, 2H), 3.54 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 155.8, 138.1, 134.0, 132.7, 132.2, 129.9, 129.3, 125.8, 119.4, 40.8, 34.8; ES^+ HRMS m/z calcd for $C_{16}H_{13}ClN_2OS$ 317.0515 [M +H], found 317.0514 [M + H].

2-(4-cyanobenzylidene)malononitrile[21] (III) Isolated as white solid; R_f = 0.85 (3:7 EtOAc/pet-ether); mp 154–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 7.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ: 158.6, 134.8, 133.4, 133.3, 131.2, 131.1, 117.8, 117.1, 113.3, 112.2, 86.5. * one of the proton was merged with aromatic proton.

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Notes and references

1 (a) B. H. Rotstein, S. Zaretsky, V. Rai and A. K. Yudin, *Chem. Rev.,* 2014, **114**, 8323−8359; (b) R. C. Cioc, E. Ruijter and R. V. A. Orru, *Green Chem.,* 2014, **16**, 2958−2975; (c) A. T. Khan and D. K. Das, *Tetrahedron Lett.,* 2012, **53**, 2345-2351; (d) A. Domling and I. Ugi, *Angew. Chem. Int. Ed.,* 2000, **39**, 3168–3210; (e) G. Balme, E. Bossharth and N. Monteiro, *Eur. J. Org. Chem*., 2003, 4101–4111; (f) W. M. Abdou, R. F. Barghash and M. S. Bekheit, *RSC Adv.,* 2013, **3**, 1528-1540; (g) X. Wang, L . Shen-yan, P. Ying-ming, W. Heng-shan, L. Hong, C. Zhen-feng and Q. Xiao-huan, *Org. Lett.,* 2014, **16**, 580-583.

2 (a) S. Maiti, S. Biswas and U. Jana, *J. Org. Chem.,* 2010, **75**, 1674−1683. (b) I. A. Azath, P. Puthiaraj and K. Pitchumani, *ACS Sustainable Chem. Eng.,* 2013, **1**, 174−179.

3 A. V. Stachulski, N. G. Berry, A. C. L. Low, S. L. Moores, E. Row, D. C. Warhurst, I. S. Adagu and J. F. Rossignol, *J. Med. Chem.,* 2006, **49**, 1450.

4 a) E. H. El-Tamany, F. A. El-Shahed and B. H. Mohamed, *J. Serb. Chem. Soc.,* 1999, **64**, 9-18. (b) N. R. Kamdar, D. D Haveliwala, P. T. Mistry and S. K. Patel, *Eur. J. Med. Chem.,* 2010, **45**, 5056-5063. (c) W. P. Smith, L. S. Sollis, D. P.

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DOI: 10.1039/C6NJ02313D

Howes, C. P. Cherry, D. I. Starkey and N. K. Cobley, *J. Med. Chem.,* 1998, **41**, 787-797; (d) K. Mazaahir, S. Shilpi, R. K. Khalilur and S. T. Sharanjit, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 4295-4298.

5 a) M. R. Nadia, Y. K. Nahed, A. Fahmyb and A. A. El-Sayeda, *Pharma Chem.,* 2010, **2**, 400-417. (b) M. E. A. Zaki, E. M. Morsy and M. Abdul, *Heterocycl. Commun*., 2004, **10**, 97-102.

6 J. L. Wang, D. Liu, Z. J. Zheng, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri and Z. Huang, *Proc. Natl. Acad. Sci*., U.S.A. 2000, **97**, 7124-7129.

7 S. Bhavanarushi, V. Kanakaiah, E. Yakaiah, V. Saddanapu, A. Addlagatta and V. J. Rani, *Med. Chem. Res.,* 2013, **22**, 2446.

8 S. C. Kuo, L. J. Huang and H. Nakamura, *J. Med. Chem.,* 1984, **27**, 539-544.

9 (a) K. Jayabal and T. P. Paramasivan, *Tetrahedron Letters*. 2014, **55**, 2010-2014. (b) V. K. Ahluwalia, A. Dahiya, V. Indian, *Indian J. Chem.,* 1997, **36B**, 88-90.

10 (a) Z. H. Ismail, G. M. Aly, M. S. El-Degwi, H. I. Heiba and M. M Ghorab, *Egypt J. Biotechnol*., 2003, **13**, 73.

11 F. M. Abdelrazek, P. Metz, N. H. Metwally, and S. F. El-Mahrouky, *Arch. Pharm.,* 2006, **339**, 456–460.

12 F. M. Abdelrazek, P. Metz, O. Kataeva, A. Jaeger and S. F. El-Mahrouky, *Arch. Pharm.,* 2007, **340**, 543–548.

13 (a) N. Foloppe, L. M. Fisher, R. Howes, A. Potter, A. G. S. Robertson and A. E. Sungenor, Bioorg. *Med. Chem.,* 2006, **14**, 4792-4802. (b) S. Gogoi and C. G. Zhao, *Tetrahedron Lett*., 2009, **50**, 2252-2255.

14 (a) R. Y. Santhivardhana, M. Santigopal, S. Eringathodi and A. T. Biju, *Org. Lett.,* 2015, **17**, 1417-1420; (b) A. Feurer, J. Luithle, S. Wirtz, G. Koenig, J. Stasch, E. Stahl, R. Schreiber, F. Wunder, and D. Lang, Bayer Healthcare AG, Germany, PCT Int. Appl., WO 2004009589; *Chem. Abstr.,* 2004, **140**, 146157.

15 (a) S. R. Mandha, S. Siliveri, M. Alla, V. R. Bommena, M. R. Bommineni and B. Balasubramanian, *Bioorg. Med. Chem. Lett*., 2012, **22**, 5272-5278.

16 A. M. Shestopalov, A. P. Yakubov, D. V. Tsyganov, Yu. M. Emel'yanova and V. N. Nesterov, *Chemistry of Heterocyclic Compounds*, 2002, **38**, 1180-1189.

17 P. Sgarbossa, S. M. Sbovata, R. Bertani, M. Mozzon, F. Benetollo, C. Marzano, V. Gandin and R. A. Michelin, *Inorg. Chem.,* 2013, **52**, 5729−5741.

18 (a) P. Dhanalakshmi and S. Sivakumar, *RSC Adv.,* 2014, **4**, 29493-29501. P. Dhanalakshmi, S. S. Babu, S. Thimmarayaperumal and S. Sivakumar*, RSC Adv.,* 2015, **5**, 33705-33719.

19 (a) A. Gupta, R. Jamatia and A. K. Pal, *New J. Chem.,* 2015, **39**, 5636-5642; (b) A. Hasaninejada, N. Golzar, M. Beyrati, A. Zare, M. M. Doroodmand, *Journal of Molecular Catalysis A: Chemical*., 2013, **372**, 137–150.

20 C. Lemouchi, C. S. Vogelsberg, L. Zorina, S. Simonov, P. Batail, S. Brown and M. A. Garcia-Garibay, *J. Am. Chem. Soc.,* 2011, **133**, 6371–6379.

21 (a) P. Li, C. Wu, J. Zhao, D. C. Rogness and F. Shi, *J. Org. Chem.* 2012, **77**, 3149−3158. (b) S. Pratapan, P. M. Scaria, K. Bhattacharyya, P. K. Das and M. V. George, *J. Org. Chem.,* 1986, **51**, 1972-1976.

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Table of Contents:

A one-pot, five component domino synthesis of novel thio ether containing dihydropyrano[2,3-*c*]pyrazoles under solvent-free, catalyst-free is demonstrated.