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A catalyst- and solvent-free protocol for the sustainable synthesis of fused 4H-pyran derivatives†

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An efficient and cost-effective method was developed for the synthesis of two kinds of fused 4H-pyran derivatives, namely, dihydropyrano[2,3-*c*]pyrazole **4** and pyrano[3,2-*c*]chromenone **6**. The reactions of 3-methyl-1-phenyl-5-pyrazolone/4-hydroxycoumarin with aromatic aldehydes and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM), involving the Knoevenagel, Michael-addition, *O*-cyclization and elimination reactions under thermal heating, afforded the desired products. The synthesized compounds were characterized by standard spectroscopic techniques. Further, the structures of pyrazole-fused 4H-pyran **4a** and coumarin-fused 4H-pyran **6b** were confirmed by single-crystal XRD analysis. The short reaction time, good-to-excellent yields, elimination of the use of expensive, metallic and toxic catalysts or hazardous organic solvents and high atom-economy are some noteworthy features of this protocol.

Introduction

Recent advances in science and technology are focusing on the development of approaches that prevent pollution and minimize the usage of non-renewable resources. Recently, green techniques and processes, which obey green chemistry principles have gained significant ecological and economic interest.¹ Green chemistry not only deals with processes that reduce the generation of hazardous chemicals but also introduces modern synthetic approaches, wherein synthetic chemists construct compounds more ecologically and proficiently.²

In this context, catalyst- and solvent-free multi-component syntheses have appeared as the most powerful strategy in contemporary situations, as they fulfill maximum principles of green chemistry.³ Multicomponent domino reactions (MDRs) are convergent organic reactions, in which three or more reactant molecules with multiple bond-forming tendencies and high atom-economy combine in one pot without the isolation of undesirable intermediates.⁴ Therefore, MDR strategies have been explored to access functionalized organic compounds under green-chemistry conditions and are preferred over step-wise synthetic strategies.⁵

Fused heterocycles represent a dynamic class of organic compounds with notable medicinal and agrochemical

properties.⁶ Among the fused heterocycles, pyrazole- and coumarin-fused oxygen-containing heterocyclic systems, particularly 4H-pyran derivatives, are omnipresent in several natural and unnatural bioactive molecules with promising properties both in pharmacological and materials sciences.⁷ Pyrazole-fused 4H-pyran derivatives have shown several biological activities such as antimalarial,⁸ antibacterial,⁹ antimicrobial,¹⁰ anti-inflammatory,¹¹ anti-tubercular,¹² hypoglycemic and vasodilator activities.¹³ On the other hand, coumarin-fused 4H-pyrans also exhibit several activities like antioxidant,¹⁴ antifungal¹⁵ and anticancer.¹⁶ Fig. 1 provides a glimpse of fused 4H-pyran-based biologically and medicinally active compounds. For example, compounds **I** and **II** have antibacterial characteristics,¹⁷ whereas, compounds **III** and **IV** possess antifungal activity.¹⁸

Recently, (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) was explored as a fascinating building block for the construction of diverse heterocyclic compounds.¹⁹ The starting material NMSM has a polarizable ethylene skeleton, bearing electrophilic and nucleophilic centers at the two ends, as well as electron-withdrawing ($-\text{NO}_2$), electron-donating (CH_3NH^-) and good leaving groups (methylsulfanyl), where each of them plays an important role in the formation of products.

A literature scan revealed that the synthesis of pyrazole-fused 4H-pyran was performed previously using InCl_3 (ref. 20) and piperidine,²¹ whereas coumarin-fused 4H-pyran scaffolds were prepared using catalysts such as STA,²² 6,6'-thiobis(methylene)- β -cyclodextrin dimer²³ and piperidine.²⁴ Regardless of the adequacy of these reported methods, each exhibits one or more shortcomings, such as the required usage of catalysts^{20–24} or solvents^{20,24} and prolonged reaction time.^{20,24} Therefore, there still remains a scope of improvement of the synthetic strategy to

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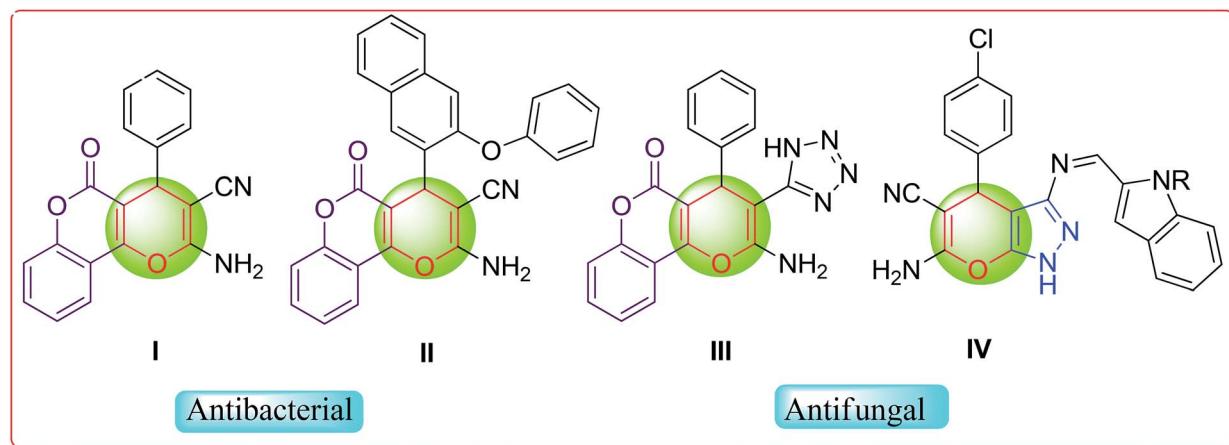


Fig. 1 Some representative examples of biologically active fused 4H-pyrans.

access such important fused 4H-pyrans. In continuation of our effort to develop green and sustainable methodologies for the synthesis of heterocycles by using NMSM and other building blocks,^{25,26} we herein intended to utilize the distinctive reactivity of NMSM and aromatic aldehydes with 3-methyl-1-phenyl-5-pyrazolone/4-hydroxycoumarin for the synthesis of fused 4H-pyran, as depicted in Scheme 1.

Results and discussion

For the present study, a model reaction was initially conducted between NMSM **1** (1.0 mmol), benzaldehyde **2** (1.0 mmol) and 3-methyl-1-phenyl-5-pyrazolone **3** (1.0 mmol) in the presence of 10 mol% of ZnO nano-catalyst under refluxing ethanol (4 mL) (Table 1, entry 1). The progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of the reaction, the product **4a** was isolated in 60% yield by simple filtration. The structure of the compound **4a** was confirmed by its melting point, IR, ¹H and ¹³C NMR spectroscopies, and the data matched well with the reported data.^{20–24} Encouraged by these results, we proceeded to optimize the reaction conditions. For this process, the model reaction was executed in the presence of different acid and base catalysts (10 mol%) in EtOH (4 mL) as well as without catalyst in EtOH with reflux (Table 1, entries 2–6). Unfortunately, we did not observe any improvement in the results. Therefore, the original reaction was performed without any catalyst or solvent at 80 °C (Table 1, entry 7).

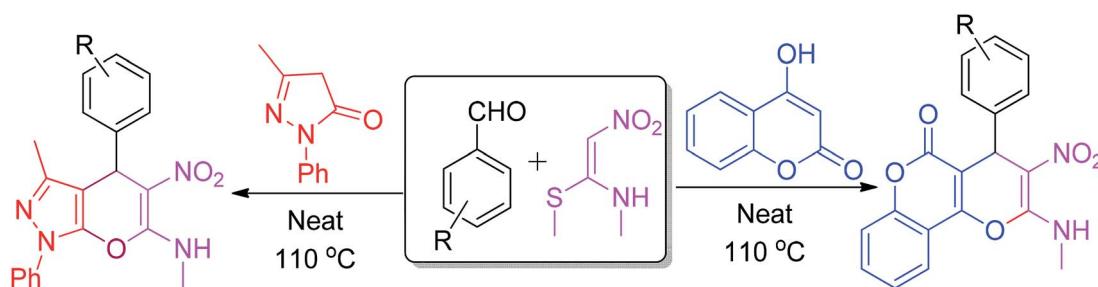
Amusingly, the reaction afforded better results in terms of reaction time and yield.

In addition, the above reaction was executed at different temperatures ranging from 90 to 130 °C under catalyst- and solvent-free conditions (Table 1, entries 8–12) to assess the effect of temperature. We observed that maximum yields were obtained at 110 °C within a short time period, and no further increase in the yield occurred with an increase in the temperature. Thus, the solvent-free and catalyst-free reaction at 110 °C emerged as the optimized condition for the present protocol for the synthesis of compound **4a**.

Similar optimal conditions were found for the synthesis of compound **6a** by performing a series of reactions between 4-hydroxycoumarine, benzaldehyde and NMSM, which are also summarized in Table 1.

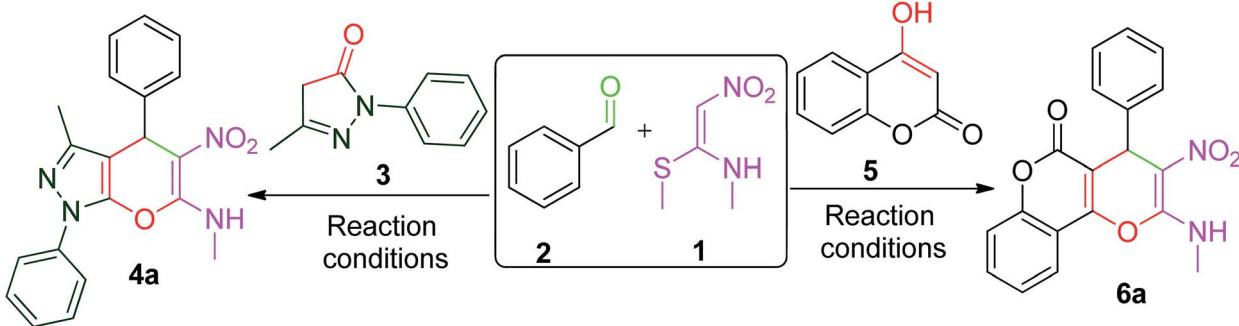
After determining the optimized conditions, we focused on establishing the substrate scope. A reaction was performed between compound **3**, 4-chlorobenzaldehyde and NMSM under the optimized reaction conditions, which gave the desired product **4b** with 85% yield (Table 2).

Next, using the optimized reaction conditions, reactions were performed with other aromatic aldehydes having substituents such as 4-Br, 4-F, 4-Me, 4-Et, 4-NO₂, 4-OMe, 3-Cl, 2-Cl, 3-Br, 3-NO₂, 3,4-(OMe)₂, and 3,4,5-(OMe)₃ with 3-methyl-1-phenyl-5-pyrazolone and NMSM. The reactions afforded corresponding products **4c–4n** with good-to-excellent yields. Similarly, this reaction was also performed with a hetero-aromatic aldehyde,



Scheme 1 Synthesis of pyrazole- and coumarin-fused 4H-pyrans under neat conditions.



Table 1 Optimization of reaction conditions for the synthesis of compounds **4a** and **6a**^a


Entry	Catalyst (mol%)	Solvent	Temp.	4a		6a	
				Time	Yield ^b (%)	Time	Yield ^b (%)
1	Nano ZnO (10 mol%)	EtOH	Reflux	7 h	60	5 h	65
2	DMAP (10 mol%)	EtOH	Reflux	10 h	49	9 h	51
3	Et ₃ N (10 mol%)	EtOH	Reflux	11 h	43	12 h	40
4	I ₂ (10 mol%)	EtOH	Reflux	6 h	55	4 h	61
5	AcOH (10 mol%)	EtOH	Reflux	5 h	50	3 h	53
6	No catalyst	EtOH	Reflux	4 h	34	2 h	55
7	No catalyst	Neat	80 °C	2 h	63	1 h	66
8	No catalyst	Neat	90 °C	1 h	70	55 min	73
9	No catalyst	Neat	100 °C	50 min	78	40 min	82
10 ^c	No catalyst	Neat	110 °C	45 min	87	30 min	91
11	No catalyst	Neat	120 °C	45 min	87	30 min	91
12	No catalyst	Neat	130 °C	40 min	84	30 min	89

^a Reaction conditions: 3-methyl-1-phenyl-5-pyrazolone/4-hydroxy coumarin (1 mmol), benzaldehyde (1 mmol) and NMSM (1 mmol). ^b Isolated yields. ^c Optimized reaction conditions.

i.e. pyridine-3-carbaldehyde, which afforded the expected product **4a** in 83% yield.

Further, to investigate the generality and applicability of the above protocol, we executed the reaction by replacing reactant **3** with 4-hydroxycoumarin and **5** using aromatic aldehydes tethered to substituents like 4-Cl, 4-Br, 4-F, 4-Me, 4-OMe, 4-NO₂, 4-Et, 3,4-diOMe, 3,4,5-triOMe, 3-NO₂, 3-Cl, 2-NO₂ and NMSM under similar optimized conditions, which afforded the desired coumarin-fused 4H-pyran **6b-m** in good yields, as shown in Table 3. Aldehydes possessing both electron-withdrawing groups as well as electron-donating groups afforded products smoothly. The reaction of 4-hydroxycoumarin was also performed with thiophene-2-carbaldehyde and NMSM, which furnished the product **6n** in good yield.

All the synthesized compounds were characterized by spectroscopic techniques including IR, ¹H and ¹³C NMR spectroscopies and elemental analysis; the resulting data for several of the reported compounds are well-matched with the literature.²⁰⁻²⁴ Further, the structure and stereochemistry of the compounds **4a** (CCDC 1901104) and **6b** (CCDC 1901105) were unambiguously confirmed by single-crystal X-ray diffraction analysis, and the ORTEP diagrams are shown in Fig. 2 and 3, respectively.

Single crystals of the compounds **4a** and **6b** were mounted on a glass fiber and utilized for XRD data collection. Light

yellow and white-colored crystals of compounds **4a** and **6b**, respectively, were grown by the slow evaporation of CH₃CN solvent for X-ray analysis. The data were obtained from a Super Nova, single source at offset/far and HyPix3000 diffractometer using graphite-monochromated Mo(K α) radiation ($\lambda = 0.71073$ Å) at 293 K.

The crystallized compound of **4a** has a monoclinic crystal system, with the space group *P2₁/c* and the unit cell dimensions $a = 10.7875(3)$ Å, $b = 20.8262(4)$ Å, $c = 8.0335(2)$ Å. On the other hand, the crystallized compound of **6b** also has a monoclinic crystal system with the space group *P2₁/c* and unit cell dimensions $a = 8.5412(2)$ Å, $b = 13.1791(3)$ Å, $c = 14.8906(3)$ Å.

Finally, the formation of the products can be rationalized *via* a domino reaction involving Knoevenagel condensation, Michael-addition, *O*-cyclization and elimination mechanisms, as illustrated in Scheme 2.

The first step is a simple Knoevenagel condensation of an aromatic aldehyde with a 1,3-dinucleophilic oxygen-containing compound (4-hydroxycoumarin or 3-methyl-1-phenyl-5-pyrazolone) to generate an intermediate **I**. The intermediate **I** undergoes a Michael-addition reaction with NMSM to form species **II**. Then, species **II** affords the desired product **4/6** by an intra-molecular *O*-cyclization followed by the elimination of -MeSH *via* species **III**.

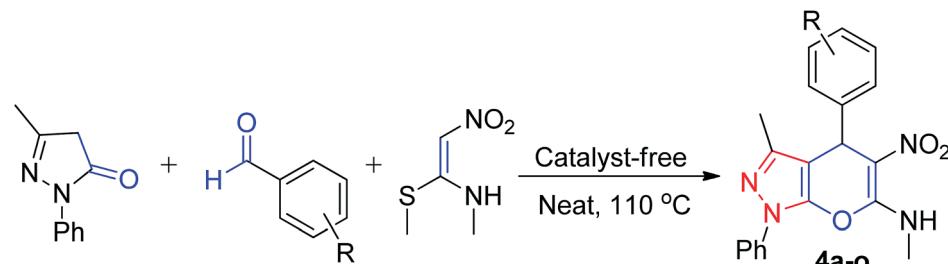


Table 2 Substrate scope for the synthesis of 4a–4o^a

Entry	Ar	Time (min)	Yield ^b (%)	Product	mp (°C)	Reported	Ref.
						mp (°C)	
1	C ₆ H ₅	45	87	4a	206–208	208–209	21
2	4-Cl-C ₆ H ₅	40	85	4b	206–208	210–211	20
3	4-Br-C ₆ H ₅	45	86	4c	208–209	228–229	20
4	4-F-C ₆ H ₅	40	86	4d	202–204	223–224	20
5	4-Me-C ₆ H ₅	50	81	4e	216–218	219–220	21
6	4-Et-C ₆ H ₅	50	79	4f	210–212	—	—
7	4-NO ₂ -C ₆ H ₅	40	89	4g	217–218	217–218	21
8	4-OMe-C ₆ H ₅	45	87	4h	210–212	220–221	20
9	3-Cl-C ₆ H ₅	50	85	4i	254–256	256–258	20
10	2-Cl-C ₆ H ₅	55	83	4j	244–245	244–245	21
11	3-Br-C ₆ H ₅	55	83	4k	238–240	238–239	20
12	3-NO ₂ -C ₆ H ₅	45	86	4l	227–228	228–229	20
13	3,4-OMe-C ₆ H ₅	40	90	4m	216–217	—	—
14	3,4,5-OMe-C ₆ H ₅	45	91	4n	218–220	218–219	20
15	Pyrid-3-yl	50	83	4o	220–221	—	—

^a Reaction conditions: 3-methyl-1-phenyl-5-pyrazolone (1 mmol), aryl aldehydes (1 mmol), NMSM (1 mmol) under neat conditions at 110 °C.

^b Isolated yields.



Conclusion

In summary, we have successfully developed a practical and green method for the synthesis of highly functionalized pyrazole- and coumarin-fused 4*H*-pyrans by the reaction of NMSM or aryl aldehydes with 3-methyl-1-phenyl-5-pyrazolone or 4-hydroxycoumarin, respectively, under thermal heating and neat conditions. The presented protocol is characterized by important features such as a short reaction time, good-to-excellent yields, elimination of the use of toxic catalysts or solvents, easy isolation of compounds without traditional column purification and applicability to a broad range of substrates.

Experimental

General

4-Hydroxycoumarin, 3-methyl-1-phenyl-5-pyrazolone, NMSM and all the aldehydes were procured from Sigma-Aldrich. All the solvents were obtained from Merck and Otto Chemie. All the reactions were completed in a REMI 2MLH thermo-mechanical stirrer. TLC analysis was carried out using silica gel GF-254 from SRL (Alfa Aesar). Melting points were obtained on a Stuart digital melting point apparatus (SMP10) and are uncorrected. IR spectra were performed with potassium bromide (KBr) pellets on a PerkinElmer 10.4.00 IR spectrophotometer. ¹H and ¹³C NMR spectral analyses were performed on Bruker (Avance-II 400 MHz),

Varian-AS400 NMR, and Bruker Bio Spin GmbH spectrometers using tetramethylsilane (TMS) as the internal standard and DMSO-*d*₆ or CDCl₃ as the solvent. Crystal data were collected with a Super Nova, single source at offset/far and HyPix3000 diffractometer (CCD) using graphite monochromated MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) at 296 K. HRMS spectra were recorded on a high-resolution mass spectrometer XEVO G2-XS QTOF.

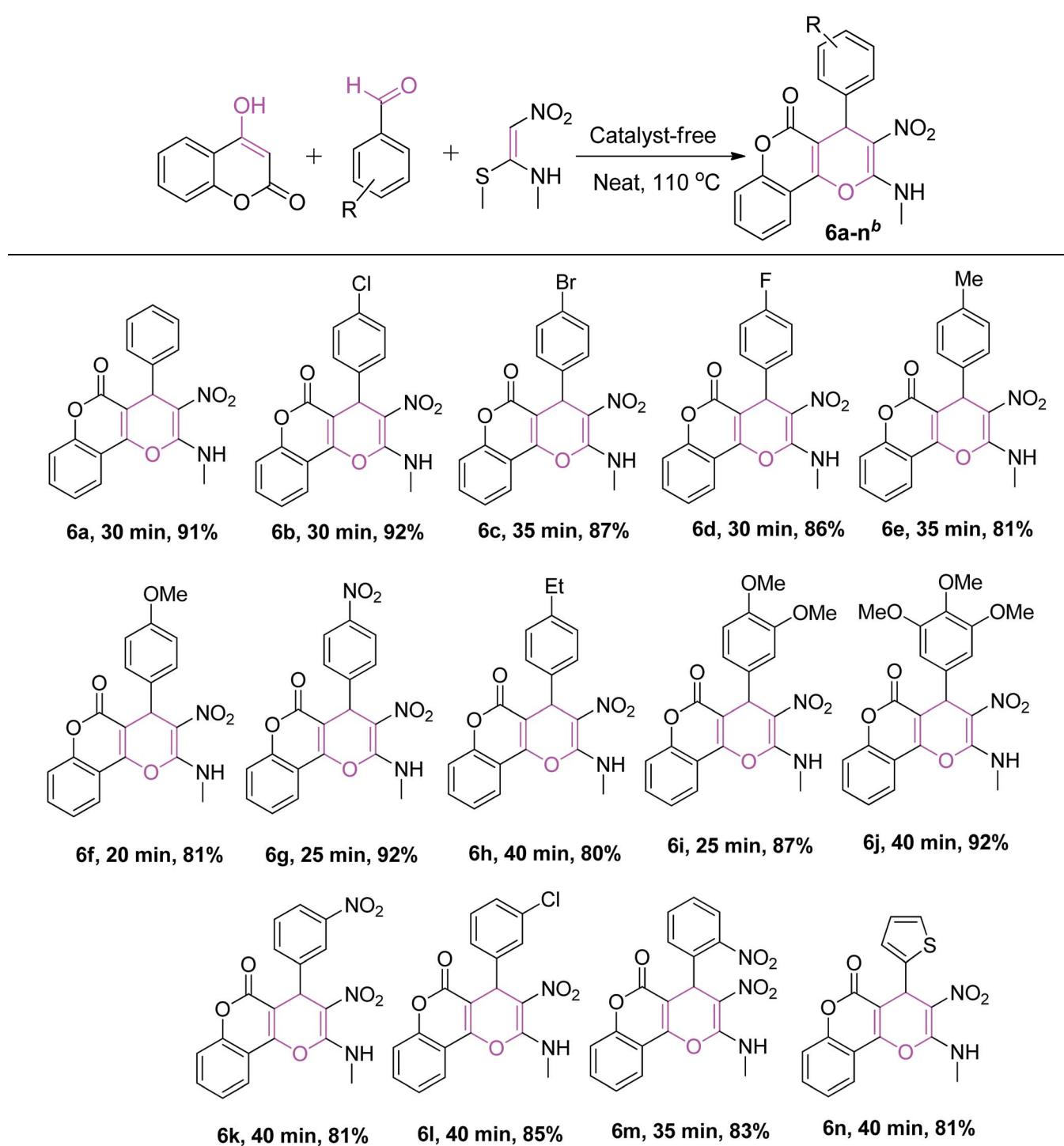
Typical procedure for the preparation of functionalized fused 4*H*-pyrans (4 and 6)

A dried 5 mL round-bottom flask was equipped with a Teflon-coated magnet and charged with a combination of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one/4-hydroxycoumarin (1 mmol), aromatic aldehyde (1 mmol), and NMSM (1 mmol). The mixture of all the reagents was heated at 110 °C with stirring for a specified time under neat conditions. The progress of the reactions was monitored by TLC. After completion of the reaction as indicated by TLC, the resulting precipitate was cooled, and 2 mL of ethanol was added and stirred for 5 min. Next, the precipitate was filtered and washed with 3 mL cold ethanol. Purification of the crude product was done by recrystallization from hot acetonitrile to yield the pure products.

Characterization data of selected compounds

4a: *N*,3-Dimethyl-5-nitro-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazol-6-amine. Isolated as yellow solid; yield: 87%; mp



Table 3 Substrate scope for the synthesis of 6a–6n^a

^a Reaction conditions: 3-methyl-1-phenyl-5-pyrazolone (1 mmol), aromatic aldehydes (1 mmol), NMSM (1 mmol) under neat conditions at 110 °C.

^b Isolated yields.

206–208 °C; IR (KBr, cm^{-1}): 3173, 3067, 3026, 2943, 2920, 1868, 1655, 1519, 1449, 1390, 1265, 1126, 969, 864, 753; ¹H NMR (500 MHz, CDCl_3) δ 2.00 (s, 3H, CH_3), 3.22 (d, $J = 4.0$ Hz, 3H, NCH_3), 5.25 (s, 1H, CH), 7.20 (d, $J = 5.5$ Hz, 1H, ArH), 7.28–7.35 (m, 5H,

ArH), 7.49 (t, $J = 7.0$ Hz, 2H, ArH), 7.69 (d, $J = 7.5$ Hz, 2H, ArH), 10.55 (s, 1H, NH); ¹³C NMR (125 MHz, CDCl_3) δ 12.7, 28.4, 38.4, 101.1, 110.1, 120.7, 126.8, 126.9, 128.0, 128.2, 129.3, 137.4, 141.9, 146.4, 159.2; anal. calcd for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_3$: C, 66.29; H,



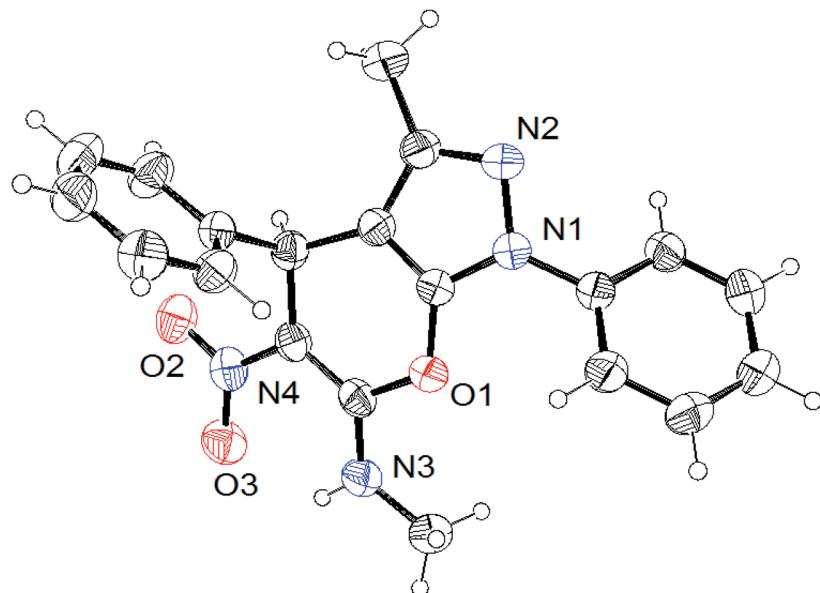


Fig. 2 ORTEP representation of compound 4a (CCDC 1901104).

5.01; N, 15.46%. Found: C, 66.19; H, 5.05; N, 15.39%. EI-HRMS: anal. calcd for $[C_{20}H_{18}N_4O_3 + H^+]$: anal. calcd: 363.1412, found: 363.1452.

4b: 4-(4-Chlorophenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine. Isolated as white solid; yield: 85%; mp 206–208 °C; IR (KBr, cm^{-1}): 3411, 3184, 3073, 2946, 2887, 1656, 1617, 1514, 1430, 1296, 1266, 1158, 1016; ^1H NMR (400 MHz, CDCl_3) δ 1.98 (s, 3H, CH_3), 3.23 (d, $J = 5.16$ Hz, 3H, NCH_3), 5.23 (s, 1H, CH), 6.95 (t, $J = 8.0$ Hz, 2H, ArH), 7.25–7.27 (m, 2H, ArH), 7.34 (t, $J = 8$ Hz, 1H, ArH), 7.49 (t, $J = 7.2$ Hz, 2H, ArH), 7.68 (dd, $J = 8.8$ Hz, 1.0 Hz, 2H, ArH), 10.56 (d, $J =$

4.4 Hz, 1H, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 12.7, 28.5, 37.6, 100.8, 110.3, 115.0, 115.2, 120.7, 126.9, 129.4, 129.8, 137.3, 141.9, 146.3, 154.5, 159.0, 160.5, 163.6; anal. calcd for $C_{20}H_{17}\text{ClN}_4O_3$: C, 60.53; H, 4.32; N, 14.12%. Found: C, 60.50; H, 4.36; N, 14.10%.

4c: 4-(4-Bromophenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine. Isolated as white solid; yield: 86%; mp 208–209 °C; IR (KBr, cm^{-1}): 3433, 3185, 3068, 2923, 2368, 1654, 1518, 1388, 1232, 1125, 1012, 904; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.98 (s, 3H, CH_3), 3.23 (d, $J = 5.0$ Hz, 3H, NCH_3), 5.20 (s, 1H, CH), 7.16–7.20 (m, 2H, ArH), 7.34 (m, 1H, ArH), 7.40 (d, $J = 8.0$ Hz, 2H, ArH), 7.49 (t, $J = 7.9$ Hz, 2H, ArH), 7.67 (dd, $J = 8.6, 1.1$ Hz, 2H, ArH), 10.55 (d, $J = 5.5$ Hz, 1H, NH); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 12.7, 28.5, 37.9, 100.4, 110.0, 120.7, 120.8, 126.9, 129.4, 129.9, 131.3, 137.3, 140.9, 141.8, 146.3, 159.0; anal. calcd for $C_{20}H_{17}\text{BrN}_4O_3$: C, 54.44; H, 3.88; N, 12.70. Found: C, 54.34; H, 3.85; N, 12.73%.

4d: 4-(4-Fluorophenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine. Isolated as white solid; yield: 86%; mp: 202–204 °C; IR (KBr, cm^{-1}): 3435, 2924, 2855, 1656.7, 1513.4, 1466.6, 1364, 1231, 1048, 753, 664, 530; ^1H NMR (400 MHz, CDCl_3) δ 1.98 (s, 3H, CH_3), 3.23 (d, $J = 5.2$ Hz, 3H, NCH_3), 5.22 (s, 1H, CH), 7.24 (s, 4H, ArH), 7.34 (t, $J = 7.52$ Hz, 1H, ArH), 7.49 (t, $J = 7.6$ Hz, 2H, ArH), 7.67 (d, $J = 8.8$ Hz, 2H, ArH), 10.56 (d, $J = 4.8$ Hz, 1H, NH); ^{13}C NMR (100 MHz, CDCl_3) δ 12.8, 28.5, 37.8, 100.5, 110.1, 120.8, 127.0, 128.4, 129.4, 129.5, 132.7, 137.3, 140.4, 141.9, 146.3, 159.0; anal. calcd for $C_{20}H_{17}\text{FN}_4O_3$: C, 63.15; H, 4.50; N, 14.73%. Found: C, 63.10; H, 4.47; N, 14.75%.

4f: 4-(4-Ethylphenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine. Isolated as white solid; yield: 79%; mp 210–212 °C; IR (KBr, cm^{-1}): 3435, 3177, 3048, 3021, 2962, 2929, 2875, 1654, 1519, 1474, 1392, 1267, 1195, 1050, 963; ^1H NMR (400 MHz, CDCl_3) δ 1.19 (t, $J = 7.6$ Hz, 3H, CH_3), 2.0 (s,

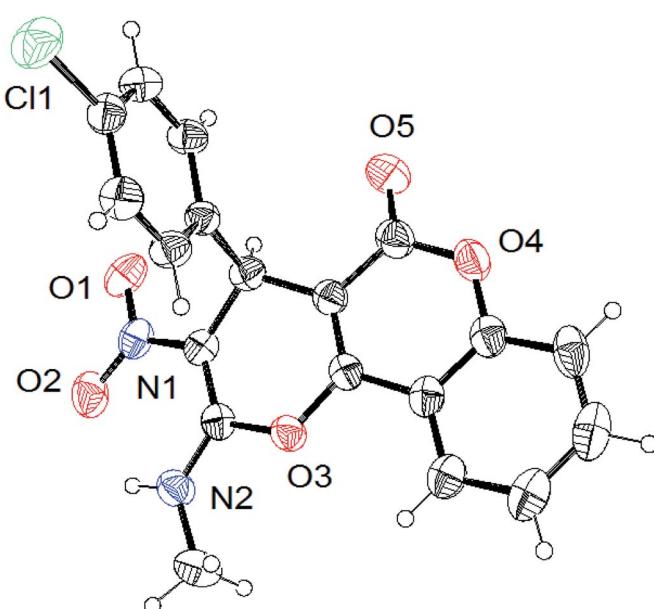
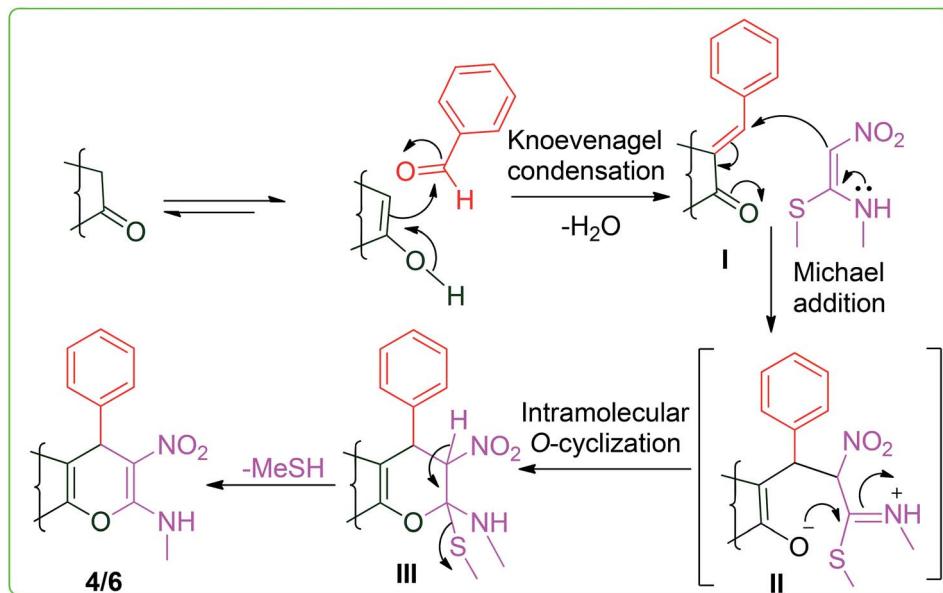


Fig. 3 ORTEP representation of compound 6b (CCDC 1901105).



Scheme 2 Plausible mechanism for the synthesis of the pyrazole- and coumarin-fused 4H-pyran.

3H, CH₃), 2.59 (q, *J* = 7.6 Hz, 2H, CH₂), 3.19 (d, *J* = 5.2 Hz, 3H, NCH₃), 5.22 (s, 1H, CH), 7.10 (d, *J* = 8.0 Hz, 2H, ArH), 7.20 (d, *J* = 8.0 Hz, 2H, ArH), 7.30–7.34 (m, 1H, ArH), 7.46–7.50 (m, 2H, ArH), 7.61–7.68 (m, 2H, ArH), 10.55 (d, *J* = 5.2 Hz, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ 12.8, 15.4, 28.4, 28.4, 37.9, 101.2, 110.6, 120.6, 126.7, 127.7, 127.9, 129.4, 137.4, 139.0, 141.8, 142.8, 146.4, 159.1; anal. calcd for C₂₂H₂₂N₄O₃: C, 67.68; H, 5.68; N, 14.35%. Found: C, 67.60; H, 5.65; N, 14.40%.

4g: N,3-Dimethyl-5-nitro-4-(4-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine. Isolated as white solid; yield: 89%; mp: 217–218 °C; IR (KBr, cm^{−1}): 3439, 2927, 1653, 1458, 1558, 1391, 1350, 1235, 1270, 1127, 1058, 821, 754, 714, 691; ¹H NMR (500 MHz, CDCl₃) δ 1.98 (s, 3H, CH₃), 3.28 (d, *J* = 4.0 Hz, 3H, NCH₃), 5.36 (s, 1H, CH), 7.37 (t, *J* = 7.5 Hz, 1H, ArH), 7.49–7.53 (m, 4H), 7.69 (d, *J* = 7.5 Hz, 2H, ArH), 8.16 (d, *J* = 8.0 Hz, 2H, ArH), 10.57 (d, *J* = 2.0 Hz, 1H, NH); ¹³C NMR (125 MHz, CDCl₃) δ 12.7, 28.6, 38.4, 99.6, 109.4, 120.8, 123.5, 127.1, 129.1, 129.4, 137.2, 141.9, 146.0, 146.9, 149.3, 159.0; anal. calcd for C₂₀H₁₇N₅O₅: C, 58.97; H, 4.21; N, 17.19%. Found: C, 58.90; H, 4.25; N, 17.25%.

4h: 4-(4-Methoxyphenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine. Isolated as white solid; yield: 87%; mp: 210–212 °C; IR (KBr, cm^{−1}): 3430, 3185, 1654, 1611, 1515, 1494, 1448, 1386, 1355, 1260, 1128, 756, ¹H NMR (500 MHz, CDCl₃) δ 2.01 (s, 3H, CH₃), 3.23 (d, *J* = 4.9 Hz, 3H, NCH₃), 3.78 (s, 3H, OCH₃), 5.22 (s, 1H, CH), 6.82 (d, *J* = 8.0 Hz, 2H, ArH), 7.22 (d, *J* = 8.0 Hz, 2H, ArH), 7.34 (t, *J* = 7.3 Hz, 1H, ArH), 7.50 (t, *J* = 7.5 Hz, 2H, ArH), 7.70 (d, *J* = 7.8 Hz, 2H, ArH), 10.56 (s, 1H, NH); ¹³C NMR (125 MHz, CDCl₃) δ 12.7, 28.4, 37.5, 55.2, 101.3, 110.7, 113.6, 114.9, 120.7, 126.7, 129.3, 134.0, 137.5, 141.9, 146.4, 158.5, 159.1; anal. calcd for C₂₁H₂₀N₄O₄: C, 64.28; H, 5.14; N, 14.28%. Found: C, 64.32; H, 5.17; N, 14.30%.

4j: 4-(2-Chlorophenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine. Isolated as white solid;

yield: 85%; mp 244–245 °C; IR (KBr, cm^{−1}): 3177, 3064, 2946, 2486, 2275, 1661, 1520, 1361, 1267, 1131, 908; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.91 (s, 3H, CH₃), 3.20 (d, *J* = 4.8 Hz, 3H, NCH₃), 5.60 (s, 1H, CH), 7.17–7.22 (m, 2H, ArH), 7.32 (d, *J* = 7.6 Hz, 2H, ArH), 7.49 (t, *J* = 8.0 Hz, 2H, ArH), 7.68–7.71 (m, 3H, ArH), 10.62 (d, *J* = 5.2 Hz, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 12.4, 28.5, 38.8, 108.1, 120.2, 120.5, 126.4, 126.9, 128.0, 129.1, 132.5, 137.0, 141.8, 145.1, 158.7; anal. calcd for C₂₀H₁₇ClN₄O₃: C, 60.53; H, 4.32; N, 14.12%. Found: C, 60.45; H, 4.37; N, 14.10%.

4l: N,3-Dimethyl-5-nitro-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine. Isolated as white solid; yield: 86%; mp 227–228 °C; IR (KBr, cm^{−1}): 3615, 3178, 3078, 2924, 1870, 1794, 1656, 1527, 1457, 1349, 1266, 1128, 1053, 927; ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.90 (s, 3H, CH₃), 3.19 (d, *J* = 5.2 Hz, 3H, NCH₃), 5.46 (s, 1H, CH), 7.37 (t, *J* = 7.6 Hz, 1H, ArH), 7.53–7.62 (m, 3H, ArH), 7.77 (d, *J* = 7.6 Hz, 2H, ArH), 7.88 (d, *J* = 8.0 Hz, 1H, ArH), 8.09 (dd, *J* = 8.4, 1.2 Hz, 1H, ArH), 8.27 (s, 1H, ArH), 10.67 (d, *J* = 4.8 Hz, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 12.5, 28.7, 37.6, 99.4, 108.1, 120.4, 121.7, 122.4, 126.7, 129.4, 134.8, 137.0, 141.8, 145.3, 147.6, 158.6; anal. calcd for C₂₀H₁₇N₅O₅: C, 58.97; H, 4.21; N, 17.19%. Found: C, 58.90; H, 4.25; N, 17.20%.

4n: N,3-Dimethyl-5-nitro-1-phenyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyrano[2,3-c]pyrazol-6-amine. Isolated as white solid; yield: 89%; mp 218–220 °C; IR (KBr, cm^{−1}): 3436, 2947, 1655, 1620, 1595, 1495, 1355, 1234, 1127, 1054, 923; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.08 (s, 3H, CH₃), 3.28 (d, *J* = 5.2 Hz, 3H, NCH₃), 3.82 (s, 3H, OCH₃), 3.84 (s, 6H, OCH₃), 5.24 (s, 1H, CH), 6.51 (s, 2H, ArH), 7.34–7.38 (m, 1H, ArH), 7.52 (t, *J* = 16.0, 8.0 Hz, 2H, ArH), 7.70 (dd, *J* = 8.6 Hz, 1.0 Hz, 2H, ArH), 10.60 (d, *J* = 5.2 Hz, 1H, NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 13.0, 28.6, 38.7, 56.2, 60.8, 100.8, 105.5, 110.2, 120.7, 126.9, 129.4, 137.1, 137.5, 141.8, 142.4, 146.5, 153.0, 159.1; anal. calcd



for $C_{23}H_{24}N_4O_6$: C, 61.05; H, 5.35; N, 12.38%. Found: C, 61.10; H, 5.37; N, 12.40%.

4o: *N*,3-Dimethyl-5-nitro-1-phenyl-4-(pyridin-3-yl)-1,4-dihydropyrano[2,3-*c*]pyrazol-6-amine. Isolated as white solid; yield: 83%; mp 220–221 °C; IR (KBr, cm^{-1}): 3399, 3184, 3060, 2993, 2920, 1654, 1620, 1595, 1520, 1490, 1388, 1265, 925; 1H NMR (500 MHz, $CDCl_3$) δ 1.98 (s, 3H, CH_3), 3.24 (d, J = 4.0 Hz, 3H, NCH_3), 5.26 (s, 1H, CH), 7.21 (d, J = 5.5 Hz, 1H, ArH), 7.35 (t, J = 7.0 Hz, 1H, ArH), 7.50 (t, J = 7.2 Hz, 2H, ArH), 7.62 (d, J = 6.5 Hz, 1H, ArH), 7.68 (d, J = 7.5 Hz, 2H, ArH), 8.45 (d, J = 3.5 Hz), 8.58 (s, 1H, ArH), 10.55 (s, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7, 28.5, 36.5, 99.9, 109.6, 114.9, 120.8, 123.2, 127.0, 129.4, 135.6, 137.3, 137.4, 142.0, 146.1, 148.3, 149.8, 159.0; anal. calcd for $C_{19}H_{17}N_5O_5$: C, 62.80; H, 4.72; N, 19.27%. Found: C, 62.85; H, 4.75; N, 19.30%.

6a: 2-(Methylamino)-3-nitro-4-phenylpyrano[3,2-*c*]chromen-5(4*H*)-one (6a). Isolated as yellow solid; yield: 91%; mp: 278–280 °C; IR (KBr, cm^{-1}): 3438, 3200, 3061, 2927, 1727, 1672, 1629, 1455, 1358, 1268, 1154, 1013, 949; 1H NMR (500 MHz, $DMSO-d_6$) δ 3.69 (s, 3H, NCH_3), 5.04 (s, 1H, CH), 6.820 (d, J = 7.0 Hz, 2H, ArH), 7.24 (d, J = 7.0 Hz, 2H, ArH), 7.48–7.52 (m, 3H, ArH), 7.73 (t, J = 7.0 Hz, 1H, ArH), 8.01 (d, J = 7.0 Hz, 1H, ArH), 10.36 (s, 1H, NH); ^{13}C NMR (125 MHz, $DMSO-d_6$) δ 29.1, 36.7, 55.5, 107.3, 108.4, 113.1, 113.9, 114.9, 117.0, 123.2, 125.4, 129.9, 133.5, 152.1, 152.4, 157.2, 158.7, 159.6; anal. calcd for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00%. Found: C, 65.85; H, 4.07; N, 8.03%. EI-HRMS: anal. calcd for $[C_{19}H_{14}N_2O_5 + H^+]$: caclcd: 351.0936, found: 351.0979.

6b: 4-(4-Chlorophenyl)-2-(methylamino)-3-nitropyrano[3,2-*c*]chromen-5(4*H*)-one. Isolated as white solid; yield: 92%; mp: 256–258 °C; IR (KBr, cm^{-1}): 3188, 2978, 2834, 1731, 1242, 1125, 1606, 1426; 1H NMR (400 MHz, $DMSO-d_6$) δ 3.32 (d, J = 4.0 Hz, 3H, NCH_3), 5.15 (s, 1H, CH), 7.45 (d, J = 5.6 Hz, 1H, ArH), 7.50 (t, J = 5.2 Hz, 1H, ArH), 7.65 (d, J = 6.0, 2H, ArH), 7.62–7.77 (m, 1H, ArH), 8.0 (d, J = 5.2 Hz, 1H, NH); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 29.1, 38.1, 105.6, 107.4, 112.8, 117.0, 123.4, 123.5, 125.6, 127.1, 130.5, 133.9, 146.9, 149.1, 152.5, 152.7, 157.0, 159.7. Anal. calcd for $C_{19}H_{13}ClN_2O_5$: C, 59.31; H, 3.41; N, 7.28%. Found: C, 59.35; H, 3.43; N, 7.31%.

6d: 4-(4-Fluorophenyl)-2-(methylamino)-3-nitropyrano[3,2-*c*]chromen-5(4*H*)-one. Isolated as yellow solid; yield: 86%; mp: 262–264 °C; IR (KBr, cm^{-1}): 3421, 3066, 2942, 1722, 1672, 1505, 1384, 1271, 1158, 1069, 908; 1H NMR (400 MHz, $DMSO-d_6$) δ 3.33 (d, J = 5.04 Hz, 3H, NCH_3), 5.07 (s, 1H, CH), 7.08 (t, J = 8.8 Hz, 2H, ArH), 7.38 (dd, J = 5.3 Hz, 2H, ArH), 7.51 (q, J = 7.6 Hz, 2H, ArH), 7.74 (m, 1H, ArH), 8.0 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 10.4 (d, J = 4.72, 1H, NH); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 28.6, 36.8, 106.3, 107.6, 112.5, 114.6, 114.8, 116.5, 122.8, 125.0, 130.4, 130.5, 133.1, 137.3, 151.8, 151.9, 156.6, 159.1, 159.9, 162.3; anal. calcd for $C_{19}H_{13}FN_2O_5$: C, 61.96; H, 3.56; N, 7.61%. Found: C, 61.91; H, 3.51; N, 7.60%.

6h: 4-(4-Ethylphenyl)-2-(methylamino)-3-nitropyrano[3,2-*c*]chromen-5(4*H*)-one. Isolated as yellow solid; yield: 83%; mp: 256–258 °C; IR (KBr, cm^{-1}): 3213, 3022, 2961, 2932, 2871, 1734, 1674, 1630, 1460, 1569, 1360, 1268, 1106, 948, 839; 1H NMR (400 MHz, $DMSO-d_6$) δ 1.12 (t, J = 7.7 Hz, 3H), 2.53 (t, J = 7.6 Hz, 2H),

3.32 (d, J = 5 Hz, 3H, NCH_3), 5.0 (s, 1H, CH), 7.0 (d, J = 8.2 Hz, 2H, ArH), 7.23 (d, J = 8.2 Hz, 2H, ArH), 7.49 (m, 2H, ArH), 7.73 (m, 1H, ArH), 8.0 (dd, J = 7.9, 1.5 Hz, 1H, ArH), 10.39 (d, J = 4.8 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 15.5, 27.7, 28.6, 103.6, 106.7, 107.8, 112.5, 115.5, 116.5, 122.7, 125.0, 127.1, 127.4, 128.3, 133.1, 138.5, 142.5, 151.7, 151.9, 152.3, 156.7, 159.2. Anal. calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40%. Found: C, 66.18; H, 4.77; N, 7.35%.

6j: 2-(Methylamino)-3-nitro-4-(3-nitrophenyl)pyrano[3,2-*c*]chromen-5(4*H*)-one. Isolated as light yellow solid; yield: 81%; mp 258–260 °C; IR (KBr, cm^{-1}): 2927, 1726, 1674, 1631, 1460, 1272, 1163, 1105, 1072; 1H NMR (400 MHz, $DMSO-d_6$) δ 3.32 (d, J = 5.0, 3H, NCH_3), 6.07 (s, 1H, CH), 7.47–7.59 (m, 5H, ArH), 7.74 (m, 1H, ArH), 7.90–7.93, (dd, J = 8.2, 2.3, Hz, 1H, ArH), 8.03 (dd, J = 8.0, 1.6 Hz, 1H, ArH), 10.51 (d, J = 5.2 Hz, 1H, NH); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 28.7, 105.2, 107.0, 116.6, 118.2, 122.1, 123.0, 123.3, 125.0, 129.4, 133.4, 135.4, 143.3, 147.3, 152.2, 156.6, 159.4; anal. calcd for $C_{19}H_{13}N_3O_7$: C, 57.73; H, 3.31; N, 10.63%. Found: C, 57.77; H, 3.28; N, 10.60%.

6l: 4-(3-Chlorophenyl)-2-(methylamino)-3-nitropyrano[3,2-*c*]chromen-5(4*H*)-one. Isolated as yellow solid; yield: 85%; mp: 270–272 °C; IR (KBr, cm^{-1}): 3206, 2926, 2855, 1729, 1610, 1435, 1015; 1H NMR (400 MHz, $DMSO-d_6$), δ 3.33 (d, J = 4.8 Hz, 3H, NCH_3), 5.06 (s, 1H, CH), 7.25–7.34 (m, 3H, ArH), 7.41 (s, 1H), 7.47–7.53 (m, 2H, ArH), 7.72–7.76 (m, 1H), 8.0 (dd, J = 7.6, 1.2 Hz, 1H), 10.44 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ 28.7, 37.4, 105.7, 107.2, 112.5, 116.5, 122.9, 124.9, 127.0, 127.3, 128.4, 129.8, 132.5, 133.2, 143.5, 152.0, 156.5, 159.1; anal. calcd for $C_{19}H_{13}ClN_2O_5$: C, 59.31; H, 3.41; N, 7.28%. Found: C, 59.27; H, 3.39; N, 7.35%.

Conflicts of interest

There are no conflicts to declare.

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