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ORIGINAL ARTICLE

Unraveling the access to the regioselective synthesis of highly functionalized pyranopyrazoles using an ionic liquid catalyst

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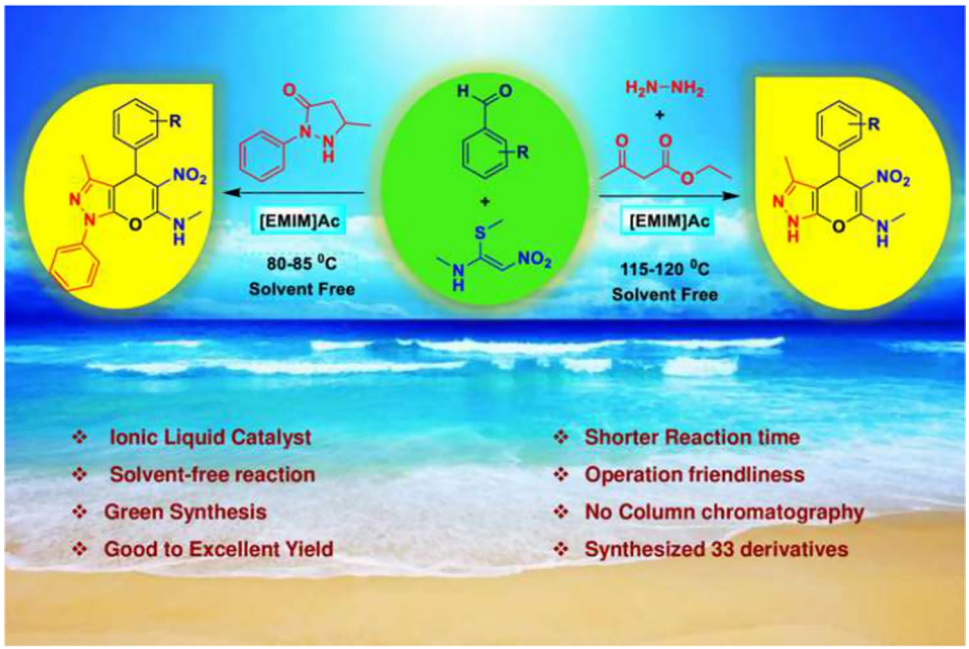
Abstract

An efficient and green strategy for the regioselective synthesis of highly functionalized pyranopyrazole via one-pot condensation of 3-methyl-1-phenyl-5-pyrazolone or EAA and hydrazine hydrate, substituted aromatic aldehydes with NMSM [(*E*)-N-Methyl-1-(methylthio)-2-nitro-ethenamine] in the existence of IL [(EMIM)Ac] as catalyst with solvent-free condition (SFC) is described. This domino protocol produces biologically substantial heterocycles through Knoevenagel condensation proceeded by Michael addition and *O*-cyclization with an eradication of methanethiol group, which create the one stereocenter and creation of "C–C, C–N, C–O, C=C, C=N, bonds." The final product is produced by exceptionally easy filtering after the reaction mass was triturated with ethanol. The strategy's noteworthy features include the use of biodegradable IL catalyst, excellent to exceptional yield with rapid reaction times, applicability to a wide range of substrate, clear reaction profile, and straightforward workup process.

Graphical abstract



Keywords Domino Protocol · (*E*)-N-Methyl-1-(methylthio)-2-nitro-ethenamine (NMSM) · Pyranopyrazole · [(EMIM)Ac] · Solvent-free reactions

Extended author information available on the last page of the article

Introduction

New routes for synthesizing simple and highly functionalized bioactive compounds by adopting a green strategy are highly sought in the current era of research and technology [1, 2]. MCR is one of the most effective strategies used in green synthesis [3]. In MCR, at least three reactants are brought together in a single reactor to generate a complex molecular cascade. Each reactant's structural features are incorporated into the produced molecules. MCRs have many strengths, including good selectivity, atom economy, and simplicity. MCRs are at the heart of combinatorial chemistry and diversity-oriented synthesis (DOS) also it has played a crucial part in developing today's synthetic approach to drug discovery [4–8].

Solvent-free reactions emerged as a valuable technique in synthetic organic chemistry for producing a large variety of bioactive heterocycles in more environmentally friendly routes [9]. Solvent-free processes also have advantages, including rapidity of response, shorter reaction times, reduction in energy use, easier isolation, and high purity with a good yield of products [10, 11]. Ionic liquids (ILs) as a catalyst is an eco-friendly technique in chemical synthesis [12]. Researchers have focused a lot of emphasis on ILs as a solvent and catalyst that is gentle on the environment [13]. ILs have a wide spectrum of solubilities, low viscosity, good thermal stability, and are non-flammable. Ionic liquids (ILs) have the capability to revolutionize synthetic processes by substituting traditional reagents [14].

Pyranopyrazoles are valuable, naturally occurring, fused heterocyclic scaffolds featuring powerful pharmacological and biological effects as well as industrial significance [15]. Anticancer [16], potential Chk1 inhibitor [17, 18], antifungal, antibacterial [19], anti-inflammatory [20], analgesic [21], antiplatelet [22], herbicidal [23], molluscicidal, vasodilator, prostaglandin inhibitory, and anticonvulsant [24] action are only a few of the biological and pharmacological properties of pyranopyrazole (Fig. 1). Furthermore, it works amazingly well in industrial procedures like inhibitors of steel corrosion and antioxidants for lubricating oil [25].

In recent times, many approaches have been reported to synthesize pyranopyrazole concerning the reaction of 1,3 dicarbonyl molecules, hydrazines, malononitrile, and carbonyl compound utilizing a diverse catalysts [26–30]. However, Dr R. R. Kumar and his co-workers are the first to report the synthesis of highly functionalized pyranopyrazole by using NMSM reagent [31]. NMSM is an impactful and valuable synthetic counterpart for a number of synthons because its ethene molecule possesses four operating sites along with three functional groups (Fig. 2).

The nitro group in the NMSM is a potent electron-withdrawing group. In contrast, it works so well as a Michael donor due to the electron-donating methylamino group. The SNV (Substitution Nucleophilic Vinyl) mechanism makes use of the thiomethyl as an excellent leaving group that many other nucleophiles may replace. The ethylene moiety is a nucleophilic and electrophilic extremely polarized push–pull alkene. These characteristics demonstrate that NMSM has the potential to develop innovative strategies for synthesizing bioactive nucleuses.

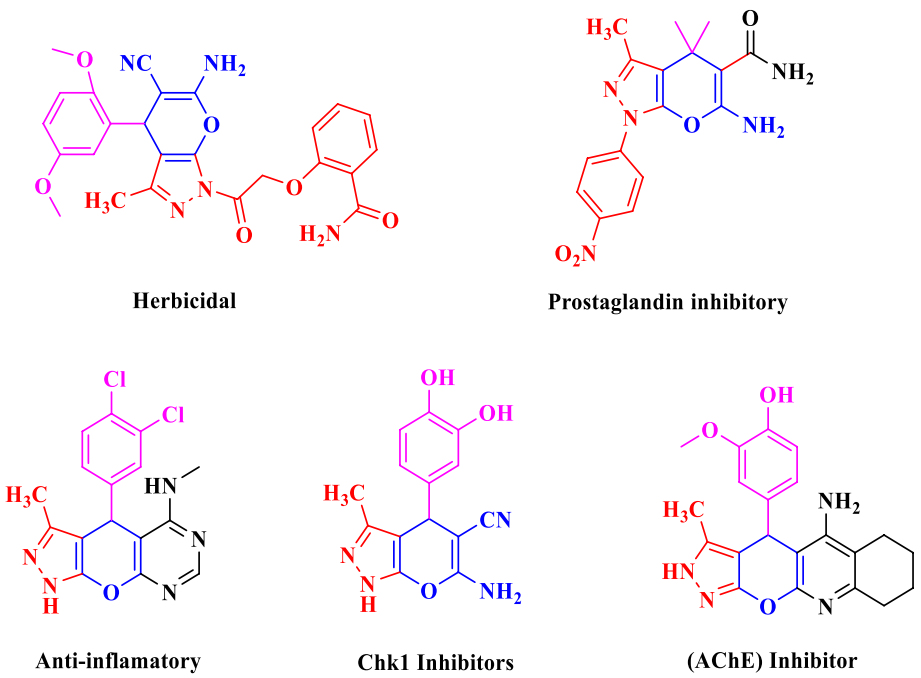


Fig. 1 Bio-active pyranopyrazoles compounds

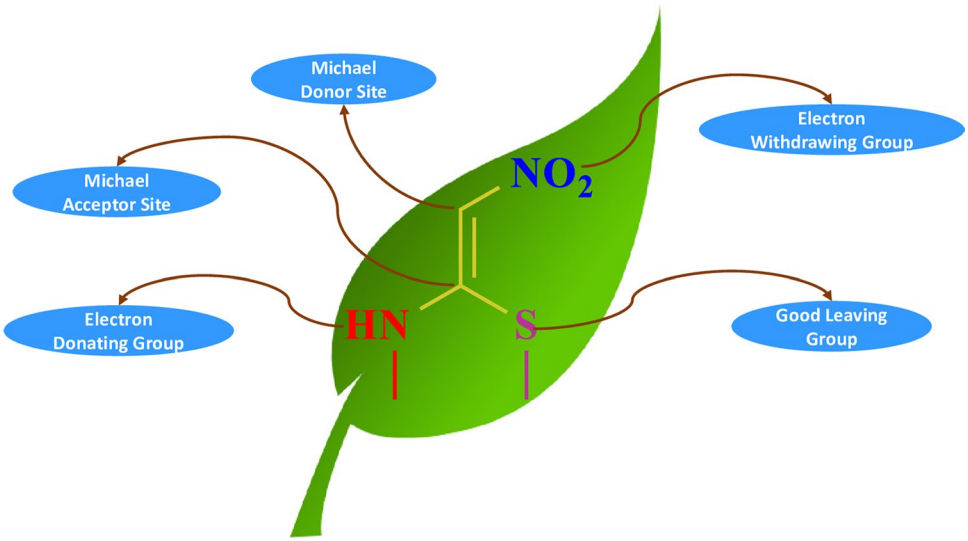


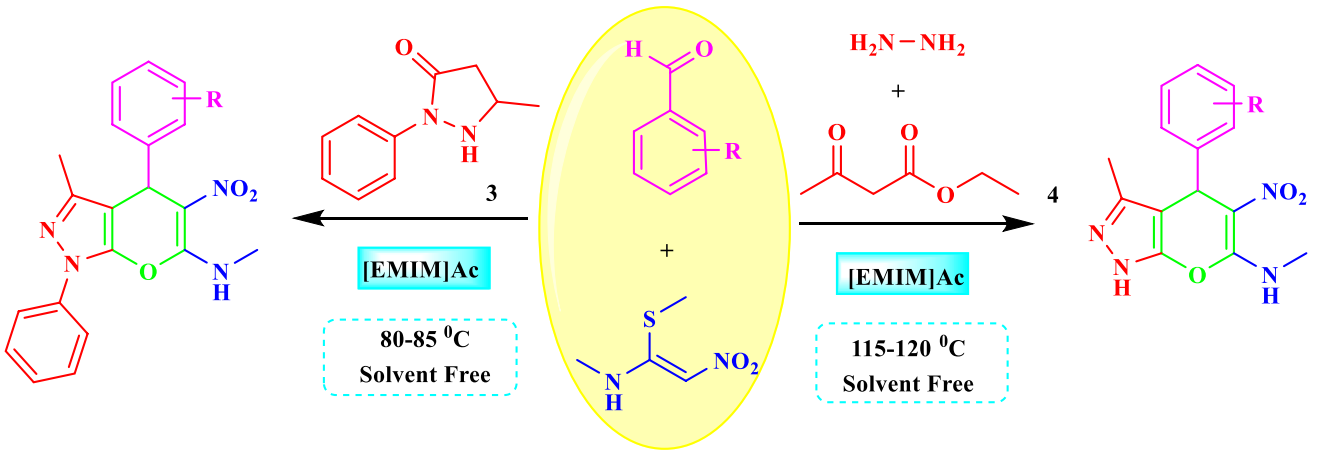
Fig. 2 (E)-N-Methyl-1-(methylthio)-2-nitro-ethenamine (NMSM)

There are only four strategies documented for the synthesis of highly functionalized pyranopyrazole, as per a comprehensive review of the literature by cyclo-condensation of various hydrazines, different esters, carbonyl compounds, and NMSM. R. R. Kumar with his co-workers prepared novel pyranopyrazoles using DIPEA catalyst [31], T. P. Paramasivan and K. Jayabal used piperidine catalyst under SFC [32], V. B. Helavi used Lewis's acid catalyst indium chloride ($InCl_3$) [33], Md. M. Khan and his coworker's carried out catalyst-free synthesis in high-to-exceptional yield [34]. In many cases, the results of these described approaches have been outstanding. However, some synthetic strategies have drawbacks such as low yield, harsh reaction conditions, high quantity of catalyst, and long reaction times.

IL [(EMIM)Ac] has recently been utilized as a catalyst for a variety of organic conversions [35–38]. In furtherance of our study on the development of green pathways for the creation of bioactive heterocycles [39–42] in this instance, we have disclosed a one-pot preparation of extremely functionalized pyranopyrazole by equimolar condensation of hydrazine hydrate, EAA, aromatic aldehydes, and NMSM using 20 mol% of [(EMIM)Ac] at 115–120 °C under solvent-free condition and condensation of 3-methyl-1-phenyl-5-pyrazolone, aromatic aldehydes, and NMSM using 20 mol% of [(EMIM)Ac] at 80–85 °C with SFC in high-to-exceptional yield (Scheme 1).

Result and discussion

A representative reaction utilizing an equimolar quantity of NMSM, 2,4 dichlorobenzaldehyde, and 3-methyl-1-phenyl-5-pyrazolone was carried in lacking catalyst at the room temperature, and at reflux condition in ethanol, no desired product was observed after 12 and 10 h (Table 1, entries 1 & 2). Similarly, a representative reaction was conducted in



Scheme 1 Synthesis of Pyranopyrazole by using [(EMIM)Ac]

Table 1 Influence of various catalysts and reaction conditions on the synthesis of pyranopyrazole from NMSM, 3-methyl-1-phenyl-5-pyrazolone, and aldehyde

Sr. No	Catalyst	Solvent	Condition	Time (Min/h)	Yield[a] (%)
1	–	Ethanol	RT	12 h	–[b]
2	–	Ethanol	Reflux	10 h	–[b]
3	–	Methanol	RT	12 h	–[b]
4	–	Methanol	Reflux	11 h	–[b]
5	–	Neat	RT	6 h	–[b]
6	–	Neat	80 °C	2 h	–[b]
7	Amb.IR-120 (50 mg)	Ethanol	Reflux	9 h	42
8	Amb.IR-120 (50 mg)	Methanol	Reflux	9 h	40
9	Amb.IR-120 (50 mg)	Neat	80–85 °C	2 h	52
10	Glycine (20 mol%)	Ethanol	Reflux	7 h	26
11	Glycine (20 mol%)	Methanol	Reflux	6 h	30
12	p-TSA (20 mol%)	Ethanol	Reflux	10 h	45
13	p-TSA (20 mol%)	Methanol	Reflux	10 h	46
14	p-TSA (20 mol%)	Neat	80–85 °C	2 h	59
15	$SnCl_2$ (20 mol%)	Ethanol	Reflux	6 h	40
16	$SnCl_2$ (20 mol%)	Methanol	Reflux	6 h	33
17	$SnCl_2$ (20 mol%)	Neat	80–85 °C	2 h	54
18	*t*-BuOK (20 mol%)	THF	Reflux	6 h	–[b]
19	[(EMIM)Ac] (20 mol%)	Ethanol	RT	5 min	–[b]
20	[(EMIM)Ac] (20 mol%)	Methanol	RT	10 min	–[b]
21	[(EMIM)Ac] (20 mol%)	Acetonitrile	RT	20 min	–[b]
22	[(EMIM)Ac] (20 mol%)	Neat	RT	2 h	–[b]
23	[(EMIM)Ac] (20 mol%)	Neat	75–80 °C	45 min	74
24	**[(EMIM)Ac] (20 mol%)**	**Neat**	**80–85** °C	**45 min**	**93**
25	[(EMIM)Ac] (20 mol%)	Neat	85–90 °C	45 min	90
26	[(EMIM)Ac] (20 mol%)	Neat	90–95 °C	45 min	88
27	[(EMIM)Ac] (20 mol%)	Neat	95–100 °C	45 min	87
28	[(EMIM)Ac] (20 mol%)	Neat	100–105 °C	45 min	81
29	[(EMIM)Ac] (20 mol%)	Neat	105–110 °C	45 min	81

[a]Isolated yield

[b]Reaction failed to produce product

methanol at ambient and reflux condition for 12 and 11 h. In the absence of a catalyst, it failed to start the reaction and bring about the expected outcome. (Table 1, entries 3, 4). Subsequently, when the reaction was continued in a neat condition at an ambient temperature and 80 °C, the reaction mixture was unchanged (Table 1, entries 5 & 6). These preceding experiment results promoted us to test the use of a catalyst to complete this reaction.[1][b]Reaction failed to produce product

In our subsequent investigation, we decided to conduct a model reaction using an acidic catalyst Amberlite IR— 120 (50 mg). At first, the model reaction was done in ethanol under conditions of reflux, and after 9 h it resulted in 42% of the intended product. (Table 1, entry 7). The obtained product is validated by spectral data. After that, an identical reaction was performed in methanol at reflux conditions which delivers the desired output in 40% of yield in 9 h (Table 1, entry 8). Later, we decided to perform a reaction in SFC as progression of the reaction in the solvent-free condition has fascinated significant attention due to their various green chemistry applications. The solvent-free reaction was performed at 80 °C, and it delivers the desired output in 52% yield in 2 h. (Table 1, entry 9). These results demonstrate that Amberlite IR-120 may initiate the reaction, but it fails to produce the intended product in a reasonable yield.

Afterward, we decided to switch to the glycine catalyst. We performed the model reaction with it, in ethanol and methanol under reflux environment, which affords the desired product in 26% and 30% after 6 and 7 h, respectively (Table 1, entries 10 & 11). With these unsatisfactory results, we moved on to the next acidic catalyst, p-Toluene sulfonic acid (p-TSA). We conducted the model reaction at reflux condition for 10 h with ethanol, producing the required

[1] [a]Isolated yield

product in a lower yield of 45% (Table 1, entry 12). An identical procedure was carried out in methanol, offering the required product in 46% in 10 h (Table 1, entry 13). To get a good yield, A comparable process was conducted in a solvent-free environment at 80–85 °C for 2 h, offering a noticeable 59% of yield (Table 1, entry 14).

In the quest of improved outcomes, we turned to the Lewis acid catalyst $SnCl_2$ and performed the model reaction using $SnCl_2$ as catalyst. The Standard reaction was done in ethanol and methanol at reflux conditions for 6 h, offering the final products in optimal yield of 40% and 33%, respectively (Table 1, entries 15 & 16). A similar reaction was conducted in neat condition at 80–85 °C for 2 h, offering the necessary product in substantial outcome of 52% (Table 1, entry 17). Referring to the inadequate findings obtained with the acidic catalyst as it initiate the reaction but failed to give cyclized product because acid catalyst is able to do Knoevenagel condensation of 3-methyl-1-phenyl-5-pyrazolone with NMSM and 1,4 Michael addition reaction of another NMSM molecule with formed adduct but acidic catalyst are not able to activate to OH group easily which result in low yield of the desired product or no formation of desired product, we decided to employ a basic catalyst potassium tertiary-butoxide to execute a model reaction in THF as the solvent, which failed to begin the reaction and produce the required product (Table 1, entry 18). Since most basic catalysts have been described in the literature, we chose to execute a model reaction employing a basic ionic liquid catalyst [EMIM(Ac)].

Herein, we investigated the chemistry of ionic liquid [(EMIM)Ac] for the synthesis of pyranopyrazole. A standard reaction was carried out in ethanol with an IL catalyst [EMIM(Ac)] that produced bispyrazolone instead of the expected product in 5 min (Table 1, entry 19). Similar results were obtained when the process was repeated in methanol and acetonitrile (Table 1, entries 20 & 21). The reaction with the catalyst [EMIM(Ac)] does not start at room temperature without solvent. (Table 1, entry 22). Then, we executed the reaction neatly at 75–80 °C and obtained a decent yield of the target product in 45 min. (Table 1, entry 23). We were ecstatic to discover that the reaction went rapidly and delivered excellent results as 93% yield of final molecule in 45 min at 80–85 °C. (Table 1, entry 24). We repeated a similar reaction at a higher temperature. Still, the final product's yield did not rise, and the time required to complete the reaction was unaffected (Table 1, entries 25 to 28).

We evaluated the amount of catalyst necessary to execute a reaction by running multiple experiments by adjusting the proportion of catalyst [(EMIM)Ac] on a model reaction at 80–85 °C, utilizing these pleasant findings produced by employing catalyst [EMIM(Ac)]. Initially, a model reaction was performed at 80–85 °C using 10 mol% of catalyst, producing the desired product in 55% yield within 70 min. Increasing the concentration of the catalyst to 15 mol% desired product is obtained in 73% of yield within 60 min. After that, increasing the catalyst quantity to 20 mol% offers the product in 93% of yield. Furthermore, raising the catalyst concentration to 25 mol% and 30 mol% did not affect the rate or yield of the reaction. It is clear from the preceding observations that using 20 mol% catalysts [(EMIM)Ac] produces excellent results (Fig. 3).

Additionally, to examine the universality and application of the procedure as mentioned earlier, we performed the reaction by employing substituted aromatic aldehydes under identical optimal circumstances. This resulted in excellent yields of the required pyranopyrazole being produced. Aldehydes containing groups that donate and pull electrons produced products without difficulty (Table 2). In the case of substituted hydroxy aldehydes rate of reaction was slowed down, and aldehydes bearing hydroxy groups like 1d, 1h, 1i,

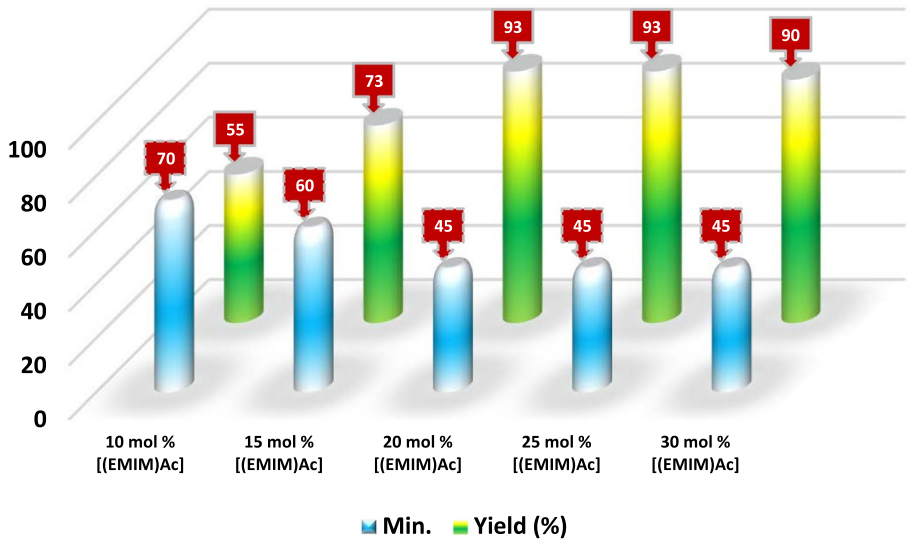
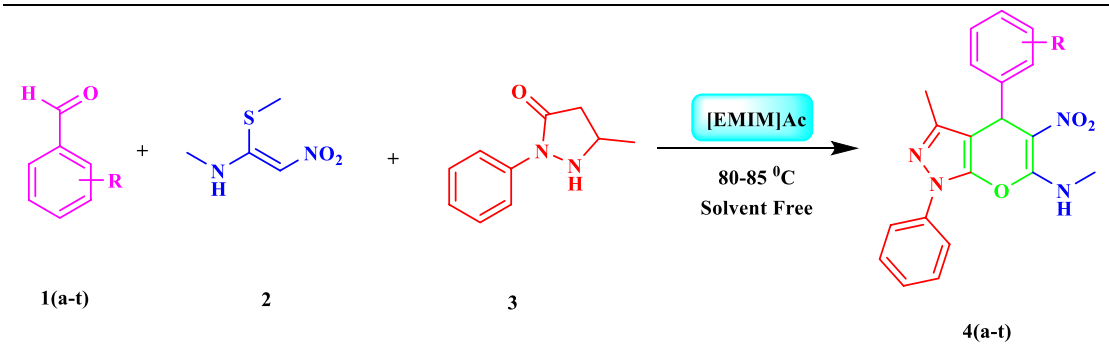
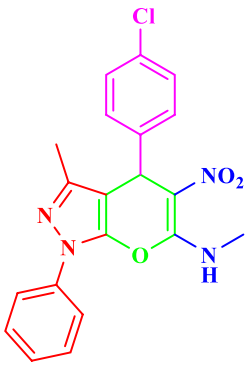


Fig. 3 Influence of catalyst proportion on the synthesis of pyranopyrazole

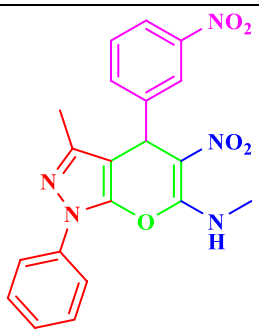
Table 2 Synthesis of pyranopyrazole derivatives using IL [EMIM(Ac)]



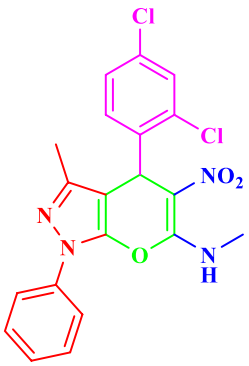
1(a-t) 2 3 4(a-t)



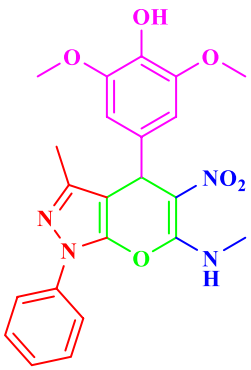
4a, 50 min, 92%



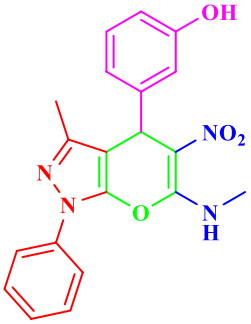
4b, 45 min, 92%



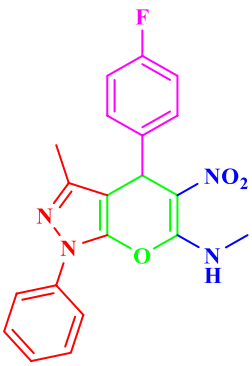
4c, 45 min, 93%



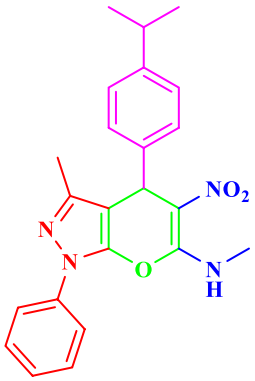
4d, 75 min, -



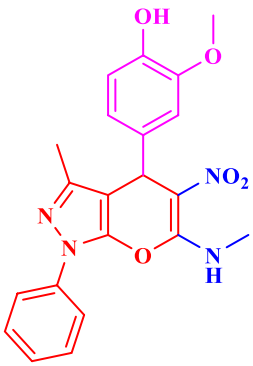
4e, 70 min, 87%



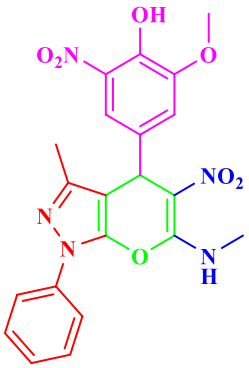
4f, 47 min, 92%



4g, 65 min, 88%

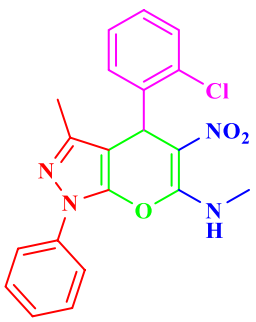


4h, 75 min, -

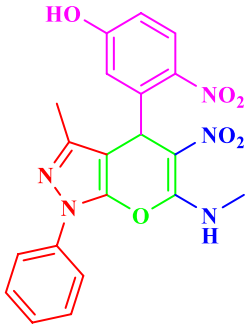


4i, 75 min, -

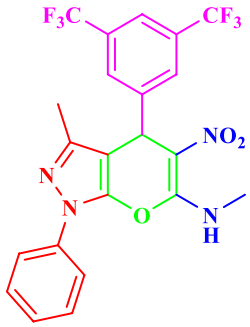
Table 2 (continued)



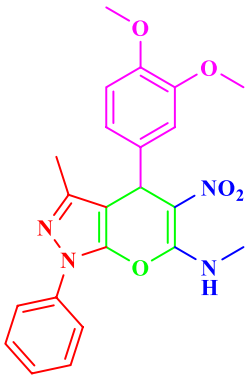
4j, 45 min, 85%



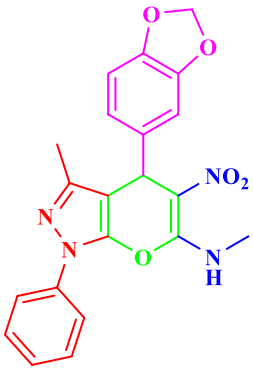
4k, 75 min, -



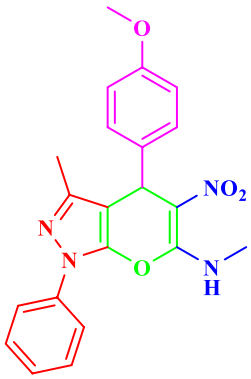
4l, 55 min, 93 %



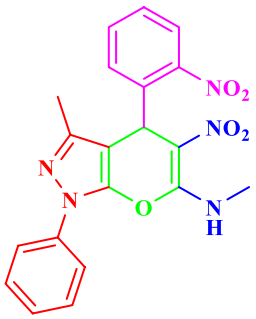
4m, 70 min, 83%



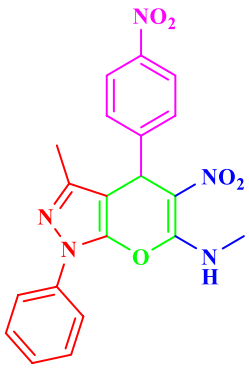
4n, 75 min, -



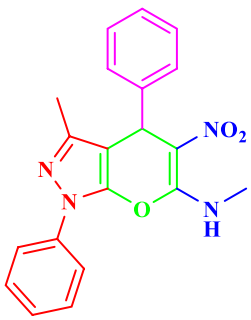
4o, 65 min, 79%



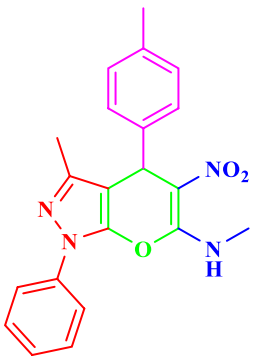
4p, 50 min, 84%



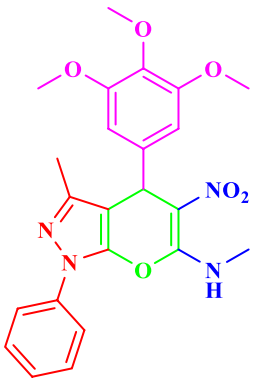
4q, 45 min, 90%



4r, 55 min, 90%



4s, 50 min, 77%



4t, 60 min, 84%

Reaction condition—Condensation of **3** (1 mmol), **1(a-t)** (1 mmol) and NMSM **2** (1 mmol) with 20 mol% of IL [(EMIM)Ac]

& 1k failed to produce the final product even after 75 min. as reaction stuck at intermediate level which is validated by spectral data (See SI).

Similarly, to identify the optimum reaction condition for the preparation of pyranopyrazole using hydrazine hydrate and ethyl acetoacetate instead of 3-methyl-1-phenyl-5-pyrazolone, a model reaction of hydrazine hydrate, ethyl acetoacetate, p-chlorobenzaldehyde, and NMSM is investigated using 20 mol% of IL catalyst [(EMIM)Ac]. Initially, a model reaction is performed in ethanol at reflux, which offers 61% of the desired product in 7 h. Solvents like methanol and acetonitrile give 54% and 51% of yield in 8 and 9 h, respectively (Table 3, Entries 1 to 3).

Later, we attempted the reaction in neat condition at ambient temperature, which failed to commence the reaction after 3 h of stirring (Table 3, Entry 4). Then the reaction was conducted at 80–85 °C, offering a considerable product with 64% yield in 65 min (Table 3, Entry 5). To get a decent result, the influence of temperature on the reaction was assessed. Initially, we raised the temperature of reaction to 85–90 °C, which generated a 69% yield in 50 min. (Table 3, Entry 6). This outcome has given us hope; therefore, we continued the reaction at high temperatures such as 90–95 °C, 95–100 °C, 100–105 °C, and 105–110 °C, offering the desired product in 73% in 45 min., 78% in 45 min., 81% in 40 min., and 86% in 30 min., respectively. (Table 3, Entries 7 to 10). As good results are observed by raising the reaction temperature again, we performed reactions at a higher temperature, which are 110–115 °C, 115–120 °C, 120–125 °C, and 125–130 °C, which resulted in 89% yield in 30 min., 94% in 20 min., 84% in 20 min., and 70% yield in 20 min. (Table 3, Entries 11 to 14). It is clear from the above observations that boosting the temperature of the reaction increased the reaction rate and the extent of the final products and that 115–120 °C is the optimal temperature for executing this reaction. However, raising the temperature further did not change the speed of reaction, and the extent of required product abruptly decreased (Fig. 4).

With these pleasing results achieved by catalyst [EMIM(Ac), we figured out how much catalyst was needed for a reaction by doing several tests with different concentrations of catalyst [(EMIM)Ac] on a model reaction at 115–120 °C. Apparently, a model reaction was conducted around 115–120 °C with 10 mol% catalysts, offering the required product in 57% in 80 min. Boosting catalyst proportion to 15 mol% desired products in 78% yield is attained within 50 min. After that, raising the catalyst amount to 20 mol%, 94% yield of the desired product in 20 min is obtained. Furthermore, enhancing catalyst intensity to 25 mol% and 30 mol% did not influence the reaction rate or yield. We may conclude that utilizing 20 mol% [(EMIM)Ac] delivers good results based on the above observation (Fig. 5).

To evaluate the generality and application of the proposed strategy, we repeated the reaction using substituted aromatic aldehydes under identical optimum circumstances. As a result, high yields of the required pyranopyrazole have been obtained. Aldehydes have both electron-withdrawing and electron-donating groups, easily generated compounds (Table 4).

We compared [(EMIM)Ac] ionic liquid's catalytic activity to previously described methods to synthesize highly functionalized pyranopyrazoles. The reactant is easily converted into the desired product by the ionic liquid [(EMIM)Ac], with a yield of up to 96%. (Table 5).

Table 3 Influence of various experimental parameters and catalysts on the synthesis of pyranopyrazole with EAA, hydrazine, NMSM, and aldehyde

Sr. No	Catalyst	Solvents	Condition	Min/h	Yield[a] %
1	[(EMIM)Ac] (20 mol%)	Ethanol	Reflux	7 h	61
2	[(EMIM)Ac] (20 mol%)	Methanol	Reflux	8 h	54
3	[(EMIM)Ac] (20 mol%)	Acetonitrile	Reflux	9 h	51
4	[(EMIM)Ac] (20 mol%)	Neat	RT	3 h	–[b]
5	[(EMIM)Ac] (20 mol%)	Neat	80–85 °C	65 min	64
6	[(EMIM)Ac] (20 mol%)	Neat	85–90 °C	50 min	69
7	[(EMIM)Ac] (20 mol%)	Neat	90–95 °C	45 min	73
8	[(EMIM)Ac] (20 mol%)	Neat	95–100 °C	45 min	78
9	[(EMIM)Ac] (20 mol%)	Neat	100–105 °C	40 min	81
10	[(EMIM)Ac] (20 mol%)	Neat	105–110 °C	30	86
11	[(EMIM)Ac] (20 mol%)	Neat	110–115 °C	30	89
12	**[(EMIM)Ac] (20 mol%)**	**Neat**	**115–120 °C**	**20 min**	**94**
13	[(EMIM)Ac] (20 mol%)	Neat	120–125 °C	20 min	84
14	[(EMIM)Ac] (20 mol%)	Neat	125–130 °C	20 min	70

[a]Isolated yield

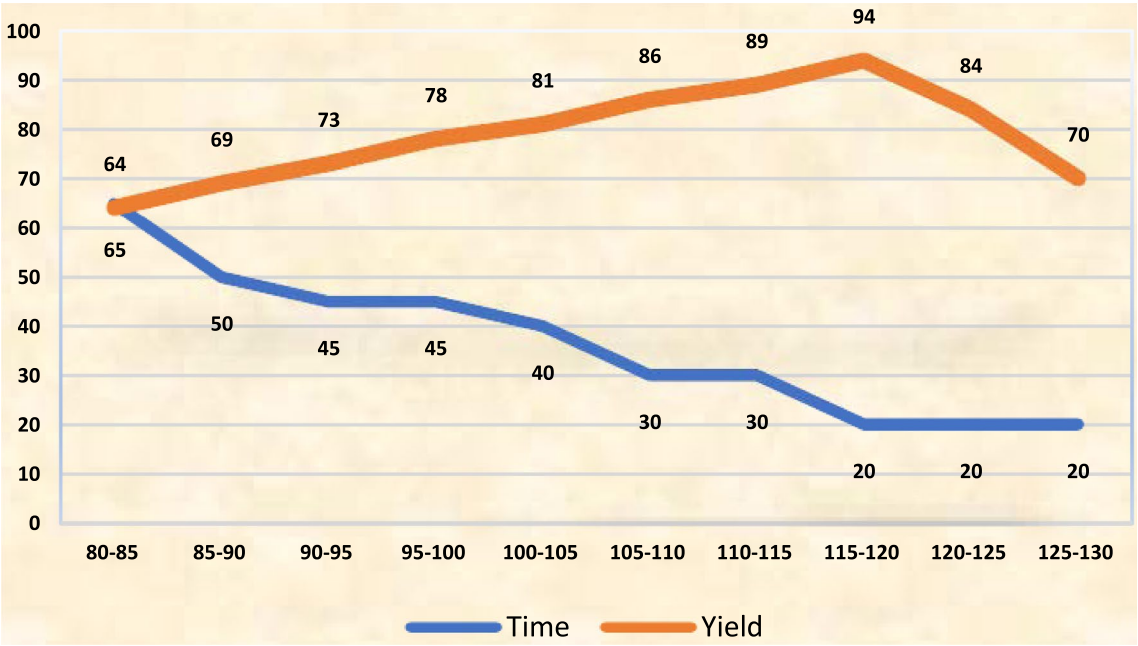


Fig. 4 Effect of temperature on yield and rate of reaction

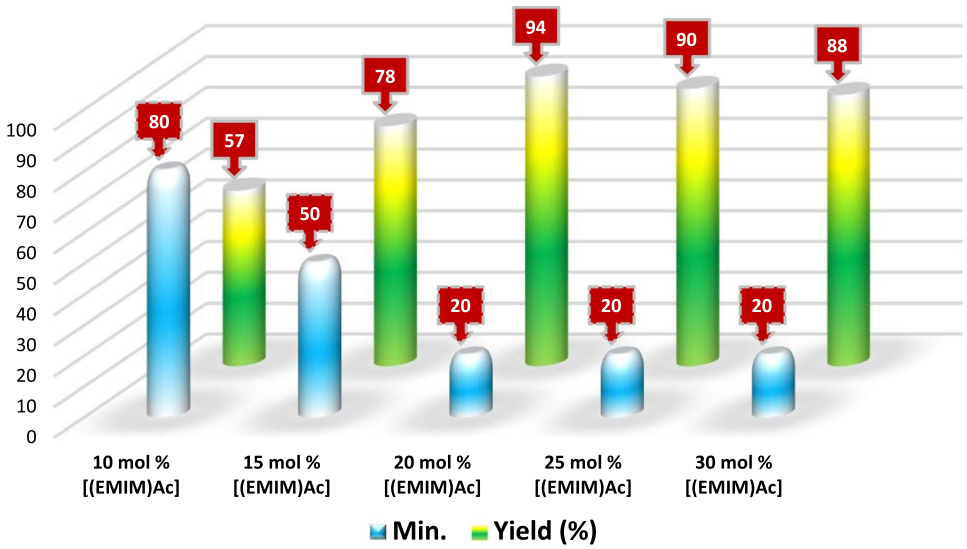


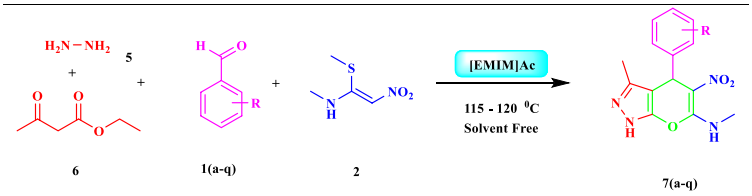
Fig. 5 Influence of catalyst proportion on the preparation of pyranopyrazole using EAA and hydrazine

Taking into consideration of entire outcomes, Fig. 6 illustrates the proposed mechanism for synthesizing pyranopyrazole utilizing [(EMIM)Ac] as a catalyst. The likely process includes polarization of the aromatic aldehyde and activation of the 1,3-dinuleophilic molecule by the IL to entail a Knoevenagel condensation reaction in between and provide an adduct. This newly produced adduct functions as a Michael acceptor and conducts a 1,4 Michael addition reaction with NMSM to produce an intermediate, which is then subjected to *O*-cyclization and methanethiol elimination to produce pyranopyrazole. (Fig. 6).

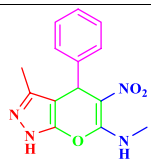
Conclusion

As a result, we designed a regioselective, green, and efficient strategy for producing extremely functionalized pyranopyrazole from readily accessible starting ingredients. The reaction was carried out in one-pot routes in the presence of a

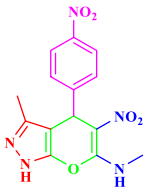
Table 4 Synthesis of pyranopyrazole derivatives using [(EMIM)Ac]



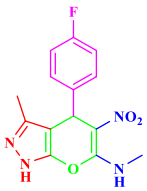
6 1(a-q) 2 7(a-q)



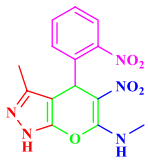
7a, 20 min, 91 %



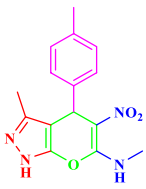
7b, 15 min, 90%



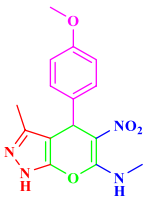
7c, 15 min, 90%



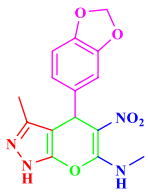
7d, 25 min, 84%



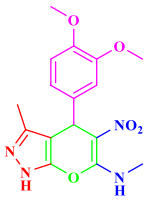
7e, 25 min, 89%



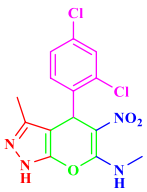
7f, 20 min 77%



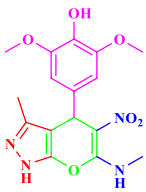
7g, 40 min, 74%



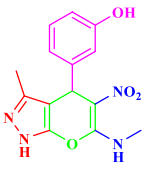
7h, 25 min, 91%



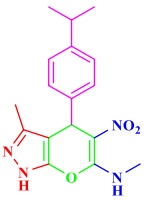
7i, 15 min, 93%



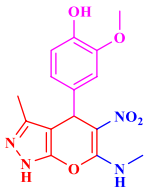
7j, 25 min, 82%



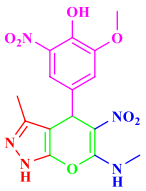
7k, 25 min, 89%



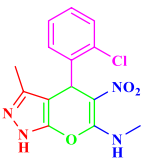
7l, 25 min, 85%



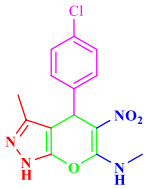
7m, 35 min, 88%



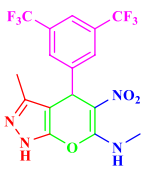
7n, 20 min, 90%



7o, 15 min, 74%



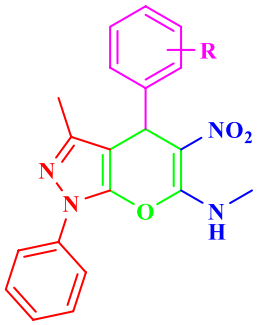
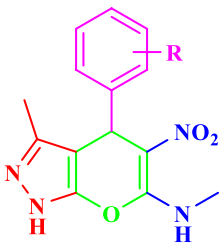
7p, 15 min, 93%



7q, 15 min, 96%

Reaction condition - Condensation of **5** (1 mmol), **6** (1 mmol), 1(a-p) (1 mmol) and NMSM (1 mmol) with 20 mol% [(EMIM)Ac].

Table 5 Comparison of the current catalytic system to various previously published methods

Entry	Compound	Catalyst	Condition	Yield (%)	Time (min)	References
1		DIPEA	Reflux in ethanol	93	45	[31]
2		Piperidine	Neat at 120 °C	83	90	[32]
3		$InCl_3$	Ethanol:water (4:1), Reflux	92	90	[33]
4		_	Solvent free, 110 °C	87	45	[34]
5		[EMIM(Ac)]	Neat, 80–85 °C	93	45	This work
1		DIPEA	Reflux in ethanol	67	45	[31]
2		Piperidine	Neat at 120 °C	86	90	[32]
3		[EMIM(Ac)]	Neat at 120 °C	94	20	This work

catalytic quantity of IL [EMIM]Ac under proper reaction conditions in all cases. We feel that the strategy outlined here provides an environmentally benign route to these valuable heterocyclic motifs. Furthermore, these processes have a number of benefits, including a rapid reaction time, high atom economy, modestly high yields, operational friendliness, and the lack of column chromatography.

Experimental

TCI was the source of the NMSM. Many aromatic aldehydes were purchased from Sigma-Aldrich, and a few were purchased from sd-fine or Loba chemical firm, respectively; Sigma-Aldrich supplies the ionic liquid [EMIM]Ac that is used as a catalyst in this process. Loba chemicals produced the solvents needed. Using TLC, we were able to monitor the progress of the reaction. Melting points, IR spectra, and HRMS spectra may be recorded using the Digital MP instrument, KBr FT-IR Spectrometer, and Waters Aquity UPLC-SYNAPT G2-HDMS Q-tof mass spectrometer. An NMR spectrum of ^{1}H and ^{13}C was recorded at SAIF P. U. Chandigarh using Bruker's Advanced Neo 500 MHz NMR Spectrometer with TMS as an internal Standard and DMSO-d_6 & $CDCl_3$ as the solvent. Values for chemical shifts are expressed in terms of TMS in the unit of δ (ppm).

General procedure for synthesis of highly functionalized pyranopyrazole

In a clean and dry 10 mL, R.B.F. equipped with a magnetic stirrer charged an equimolar mixture of 3-methyl-1-phenyl-5-pyrazolone/ethyl acetoacetate & hydrazine hydrate, aromatic aldehyde, NMSM, and catalyst ionic liquid [EMIM]Ac (20 mol%). The above mixture was heated at 80–85 °C/115–120 °C under solvent-free conditions for an appropriate time. The progress of the reaction was monitored by TLC; after the accomplishment of the reaction, which was confirmed by TLC, the reaction mass was cooled gradually, and the precipitated solid product was triturated with 2–3 mL ethanol and stirred for 20 min. The resultant reaction mass was filtered and washed with 2–3 mL of cold ethanol. The obtained product was pure enough for spectral investigation.

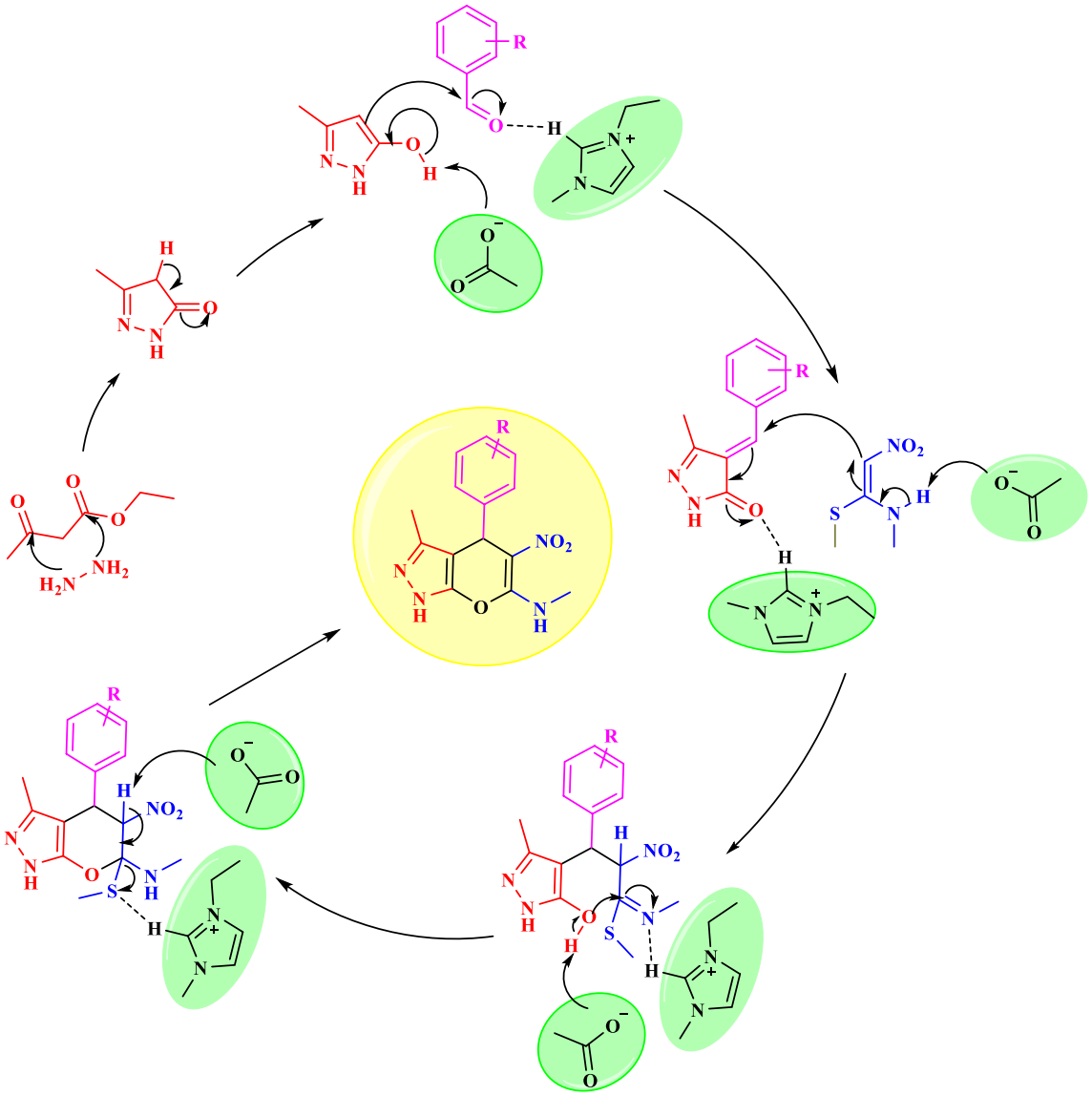


Fig. 6 Plausible mechanism for the synthesis of pyranopyrazole

Spectral data of novel and some of the selected compounds

N,3-dimethyl-5-nitro-4-(3-nitrophenyl)-1-phenyl-1 ,4-dihydropyrano[2,3-c]pyrazol-6-amine (4b)

Yield – 92%, Yellow Solid, M. P.: 226–227 °C, **IR (KBr) cm^{-1}:**758.02, 1051.20, 1128.36, 1346.31, 1388.75, 1521.84, 1653.00, 1869.02, 2866.22, 2945.30, 3446.79. **^{1}H NMR (500 MHz, $CDCl_3$) δ**: 1.97 (s, 3H), 3.28 (d, 3H), 5.36 (s, 1H), 7.34–7.38 (m, 1H), 7.47–7.53 (m, 3H), 7.67–7.69 (td, 2H), 7.74–7.76 (td, 1H), 8.08–8.10 (m, 1H), 10.57 (d, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 28.58, 37.32, 106.58, 107.70, 112.52, 116.49, 122.73, 124.91, 126.95, 127.95, 128.35, 133.05, 141.14, 151.88, 156.68, 159.08. **HRMS**, Calcd. For $C_{20}H_{17}N_5O_5$: 407.10; found 408.1307 $[M+H]^+$.

4-(2,4-dichlorophenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (4c)

Yield – 93%, White Solid, M. P.: 228–230 °C, **IR (KBr) cm^{-1}:** 759.95, 842.89, 1058.92, 1271.09, 1363.67, 1453.18, 1662.64, 2927.94, 3066.82, 3446.79. **^{1}H NMR (500 MHz, $CDCl_3$) δ**: 2.01 (s, 3H), 3.25 (d, 3H), 5.62 (s, 1H), 7.17–7.19 (dd, 1H), 7.24 (d, 1H), 7.33–7.36 (m, 2H), 7.48–7.51 (t, 2H), 7.64–7.66 (dd, 2H), 10.63 (d, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 12.83, 28.54, 36.34, 120, 0.95, 127.07, 127.28, 129.46, 129.84, 130.21, 133.38, 137.17, 137.35,

142.20, 146.34, 159.52. **HRMS**, Calcd. For $C_{20}H_{16}Cl_2N_4O_3$: 430.06; found 431.0680 $[M+H]^+$.

3-(3-methyl-6-(methylamino)-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenol (4e)

Yield – 87%, White Solid, M. P.: 240–241 °C, **IR (KBr) cm^{-1}:**775.38, 800.46, 1053.13, 1267.23, 1392.61, 1487.12, 1517.98, 1651.07, 1870.95, 2619.33, 2945.30, 3018.60, 3186.40, 3288.63. **^{1}H NMR (500 MHz, $CDCl_3$) δ**: 1.96 (s, 3H), 3.17 (d, 3H), 5.14 (s, 1H), 6.52–6.63 (m, 1H), 6.68–6.69 (t, 1H), 6.74–6.75 (dd, 1H), 7.05–7.11 (m, 2H), 7.34–7.37 (t, 1H), 7.52–7.55 (t, 1H),7.73–7.75 (dd, 1H), 9.29 (s, 1H), 10.55–10.58 (q, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 12.51, 28.62, 37.76, 100.72, 108.79, 113.52, 114.54, 118.48, 120.31, 126.55, 128.94, 129.43, 137.07, 141.65, 144.48, 145.31, 157.07, 158.60. **HRMS**, Calcd. For $C_{20}H_{18}N_4O_4$: 378.13; found 379.1411 $[M+H]^+$.

4-(4-fluorophenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (4f)

Yield – 92%, White Solid, M. P.: 223–224 °C, **IR (KBr) cm^{-1}:** 758.02, 835.18, 1049.28, 1217.08, 1392.61, 1508.33, 1654.92, 1907.06, 2945.30, 3066.82, 3446.79. **^{1}H NMR (500 MHz, $CDCl_3$) δ**: 1.98 (s, 3H), 3.23 (d, 3H), 5.23 (s, 1H), 6.94–6.98 (tt, 2H), 7.25–7.26 (t, 1H), 7.26–7.27 (t, 1H), 7.32–7.35 (td, 1H), 7.47—7.51 (td, 2H), 7.66–7.68 (dt, 2H), 10.56 (q, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 12.74, 28.53, 37.69, 100.86, 110.43, 115.04, 115.21, 120.79, 126.96, 128.73, 129.73, 137.43, 137.63, 141.96, 146.38, 159.69, 160.70, 162.73. **HRMS**, Calcd. For $C_{20}H_{17}FN_4O_3$: 380.13; found 381.1359 $[M+H]^+$.

4-(4-isopropylphenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (4 g)

Yield – 88%, White Solid, M. P.: 214–216 °C, **IR (KBr) cm^{-1}:**827.46, 1045.42, 1124.50, 1359.82, 1517.98, 1654.92, 2868.15, 2956.87, 3462.22. **^{1}H NMR (500 MHz, $CDCl_3$) δ**: 1.19 (d, 6H), 2.01 (s, 3H), 2.82–2.86 (d, 3H), 3.23–3.24 (d, 3H), 5.23 (sept, 1H), 7.11 (d, 2H), 7.18–7.20 (d, 2H), 7.31–7.34 (t, 1H), 7.47–7.50 (t, 2H), 7.66–7.68 (dd, 2H), 10.56 (d, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm):12.62, 23.87, 23.93, 23.95, 28.50, 33.69, 37.90, 101.41, 120.78, 126.33, 126.83, 127.00, 127.92, 129.42, 137.53, 139.15, 141.98, 146.50, 147.49, 159.27. **HRMS**, Calcd. For $C_{23}H_{24}N_4O_3$: 404.18; found 409.1920 $[M+H]^+$.

4-(2-chlorophenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (4j)

Yield – 85%, White Solid, M. P.: 248–249 °C, **IR (KBr) cm^{-1}:**831.32, 854.47, 908.47, 1056.99, 1138.00, 1361.74, 1394.53, 1519.91, 1662.64, 2949.16, 3068.75, 3178.69, 3446.79. **^{1}H NMR (500 MHz, $CDCl_3$) δ**: 2.00 (s, 3H), 3.26 (d, 3H), 5.65 (s, 1H), 7.13–7.16 (m, 1H), 7.17–7.21 (m, 1H), 7.32–7.35 (m, 1H), 7.47–7.51 (t, 2H), 7.65–7.67 (dt, 2H), 10. 64 (d, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz),** δ_C (ppm): 12.41, 28.63, 99.21, 108.08, 120.42, 126.66, 127.22, 127.62, 128.28, 129.25, 129.44, 129.90, 132.33, 132.55, 136.98, 142.02, 145.11, 158.77. **HRMS**, Calcd. For $C_{20}H_{17}ClN_4O_3$: 396.10; found 419.0885 $[M+Na]^+$.

4-(3,5-bis(trifluoromethyl)phenyl)-N,3-dimethyl-5-nitro-1-phenyl-1,4-dihydropyrano[2,3-c] pyrazol-6-amine (4 l)

Yield – 93%, White Solid, M. P.: 243–245 °C, **IR (KBr) cm^{-1}:** 837.11, 1008.77, 1056.99, 1340.53, 1373.32, 1525.69, 1676.14, 1734.01, 2945.30, 2978.09, 3261.63, 3462.22. **^{1}H NMR (500 MHz, $CDCl_3$) δ**: 1.96 (s, 3H), 3.28 (d, 3H), 5.39 (s, 1H), 7.35–7.38 (t, 1H), 7.49–7.53 (t, 2H), 7.68–7.70 (d, 2H), 7.75 (s, 3H), 10.56 (d, 1H). **^{13}C NMR ($CDCl_3$, 125 MHz),** δ_C (ppm): 12.39, 28.71, 98.70, 98.70, 107.72, 120.42, 124.37, 126.65, 128.69, 128.85, 129.37, 129.73, 129.99, 136.98, 141.81, 145.27, 146.71, 158.68. **HRMS**, Calcd. For $C_{22}H_{16}F_6N_4O_3$: 498.11; found 499.1211 $[M+H]^+$.

(E)-4-(4-hydroxy-3-methoxy-5-nitrobenzylidene)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (4i-Intermediate)

IR (KBr) cm^{-1}: 883.40, 937.40, 999.13, 1062.78, 1138.00,1280.73, 1541.72, 1653.00, 1683.86, 2841.15, 3099.61, 3446.79 **^{1}H NMR (500 MHz, $CDCl_3$) δ**: 2.34 (s, 3H), 4.08 (s, 3H), 6.32 (s, 1H), 6.99–7.00 (d, 1H), 7.19 (t, 1H), 7.31 (s, 1H), 7.39–7.43 (t, 2H), 7.50–7.52 (dd, 1H), 7.93–7.95 (dd, 2H), 9.20 (s, 1H).

(E)-4-(4-hydroxy-3,5-dimethoxybenzylidene)-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (4d-Intermediate)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 4.02 (s, 6H), 7.17 (q, 1H), 7.28 (s, 1H), 7.39–7.43 (t, 2H), 7.93–7.95 (dd, 1H), 8.01 (s, 2H). **^{13}C NMR ($CDCl_3$, 125 MHz),** δ_C (ppm): 13.39, 56.64, 111.73, 119.52, 124.88, 125.15, 125.23, 128.81, 138.52, 140.30, 146.84, 147.49, 150.85, 162.33.

N,3-dimethyl-5-nitro-4-(2-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (7d)

Yield – 84%, Yellow Solid, M. P.: 248–249 °C, **IR (KBr) cm^{-1}:** 792.74, 1008.77, 1072.42, 1217.08, 1354.03, 1525.69, 1647.21, 3028.24, 3066.82, 3273.20. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.97 (s, 3H), 3.15 (d, 3H), 5.74 (s, 1H), 7.24–7.26 (dd, 1H), 7.39–7.42 (dd, 1H), 7.54–7.57 (ddd, 1H), 7.81–7.83 (dd, 1H), 10.63 (d, 1H), 12.47 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm):9.63, 28.18, 97.29, 109.06, 122.93, 127.49, 130.53, 132.96, 136.49, 137.51, 149.68, 153.62, 159.25. **HRMS**, Calcd. For $C_{14}H_{13}N_5O_5$: 331.0917; found 332.0988 $[M+H]^+$.

4-(1,3-dihydroisobenzofuran-5-yl)-N,3-dimethyl-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (7 g)

Yield – 74%, White Solid, M. P.: 264–266 ^{0}C, **IR (KBr) cm^{-1}:** 810.10, 921.97, 1055.06, 1363.67, 1444.68, 1502.55, 1637.56, 2887.44, 2972.31, 3130.47, 3209.55. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.96 (s, 3H), 3.14 (d, 3H), 5.12 (s, 1H), 5.94 (s, 2H), 6.68–6.70 (dd, 1H), 6.77–6.78 (t, 2H), 10.65 (d, 1H), 12.29 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm):9.63, 28.11, 99.04, 100.65, 101.60, 105.87, 107.63, 107.73, 108.46, 108.87, 120.29, 124.98, 135.97, 137.99, 145.39, 146.87, 153.01, 159.71, 160.56. **HRMS**, Calcd. For $C_{15}H_{14}N_4O_5$: 330.09; found 331.1048 $[M+H]^+$.

4-(3,4-dimethoxyphenyl)-N,3-dimethyl-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (7 h)

Yield – 91%, Pale Solid, M. P.: 260–261 °C, **IR (KBr) cm^{-1}:** 813.96, 1062.78, 1141.86, 1238.30, 1336.67, 1521.84, 1635.64, 2833.43, 3080.32, 3169.04, 3313.71. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.98 (s, 3H), 3.14 (d, 3H), 3.68 (s, 3H), 3.70 (s, 3H), 5.14 (s, 1H), 6.63–6.66 (dd, 1H), 6.80–6.81 (d, 1H), 6.85 (d, 1H), 10.63 (d, 1H), 12.26 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 9.68, 28.10, 55.36, 55.48, 99.20, 108.81, 111.58, 118.68, 118.77, 135.91, 136.61, 147.13, 148.16, 150.02, 159.75 **HRMS**, Calcd. For $C_{16}H_{18}N_4O_5$: 346.13; found 347.1364 $[M+H]^+$.

4-(2,4-dichlorophenyl)-N,3-dimethyl-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (7i)

Yield –93%, Pale Yellow Solid, M. P.: 250–253 °C, **IR (KBr) cm^{-1}:** 702.09, 864.11, 1074.35, 1361.74, 1467.83, 1641.42, 2947.23, 3016.67, 3061.03, 3089.96, 3273.20. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.91 (s, 3H), 3.14 (d, 3H), 5.53 (s, 1H), 7.30–7.34 (m, 2H), 7.50 (d, 1H), 10.69 (q, 1H), 12.37 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 9.60, 28.16, 97.13, 107.76, 127.35, 128.54, 131.44, 131.64, 132.82, 136.18, 139.13, 153.21, 153.85. **HRMS**, Calcd. For $C_{14}H_{12}Cl_2N_4O_3$: 354.03; found 355.0370 $[M+H]^+$.

2,6-dimethoxy-4-(3-methyl-6-(methylamino)-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenol (7j)

Yield – 82%, Yellow Solid, M. P.: 265–266 °C, **IR (KBr) cm^{-1}:** 810.10, 1060.85, 1215.15, 1361.74, 1463.97, 1639.49, 2756.28, 2833.43, 2972.31, 3170.97. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 2.01 (s, 3H), 3.14 (d, 3H), 3.68 (s, 6H), 5.53 (s, 1H), 6.4 (s, 2H), 8.13 (s, 1H), 10.65 (d, 1H), 12.25 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 9.80, 28.13, 55.91, 56.01, 99.21, 104.80, 108.66, 134.12, 134.25, 135.98, 147.62, 153.02, 159.02. **HRMS**, Calcd. For $C_{16}H_{18}N_4O_6$: 362.12; found 363.1309 $[M+H]^+$.

3-(3-methyl-6-(methylamino)-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenol (7 k)

Yield – 89%, White Solid, M. P.: 269–270 °C, **IR (KBr) cm^{-1}:** 781.17, 1008.77, 1066.64, 1213.23, 1249.87, 1363.67, 1458.18, 1608.63, 1641.42, 2885.51, 2947.23, 2916.76, 3253.91. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.97 (s, 3H), 3.14 (d, 3H), 5.09 (s, 1H), 6.52–6.53 (m, 1H), 6.54–6.56 (m, 1H), 6.63–6.65 (d, 1H), 7.01–7.04 (t, 1H), 9.22 (s, 1H), 10.63 (d, 1H), 12.28 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm):9.68, 28.11, 99.07, 108.07, 113.20, 113.78, 117.91, 128.89, 135.92, 145.34, 153.06, 157.07, 159.78. **HRMS**, Calcd. For $C_{14}H_{14}N_4O_4$: 302.10; found 303.1100 $[M+H]^+$.

4-(4-isopropylphenyl)-N,3-dimethyl-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (7 l)

Yield – 85%, White Solid, M. P.: 260–62 °C, **IR (KBr) cm^{-1}:** 702.09, 823.60, 1060.85, 1074.35, 1354.03, 1467.83, 1647.21, 2870.08, 2889.37, 2958.80, 3182.55, 3298.28. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.14 (d, 6H), 1.94 (s, 3H), 2.76–2.85 (sept, 1H), 3.02 (d, 3H), 5.15 (s, 1H), 7.10 (s, 4H), 10.63 (d, 1H), 12.28 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm):9.68, 23.77, 23.80, 28.16, 32.89, 99.27, 108.99, 125.94, 127.03, 135.90, 141.37, 146.11, 153.14, 159.86. **HRMS**, Calcd. For $C_{17}H_{20}N_4O_3$: 328.15; found 329.1664 $[M+H]^+$.

2-methoxy-4-(3-methyl-6-(methylamino)-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenol (7 m)

Yield – 88%, Pale Yellow Solid, M. P.: 274–276 °C, **IR (KBr) cm^{-1}:** 748.38, 817.82, 1064.71, 1269.16, 1338.60, 1392.61, 1514.12, 1635.64, 2937.59, 3026.31, 3250.05, 3419.79. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.99 (s, 3H), 3.14 (d, 3H), 3.72 (s, 3H), 5.10 (s, 1H), 6.51–6.53 (dd, 1H), 6.63–6.65 (d, 1H), 6.82 (d, 1H), 8.74 (s, 1H), 10.65 (d, 1H), 12.26 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 9.70, 28.11, 55.65, 99.46, 108.99, 111.95, 115.17, 119.09, 135.06, 135.90, 144.85, 146.96, 153.07, 159.80. **HRMS**, Calcd. For $C_{15}H_{16}N_4O_5$: 332.1121; found 333.1216 $[M+H]^+$.

2-methoxy-4-(3-methyl-6-(methylamino)-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)-6-nitrophenol (7n)

Yield – 90%, Brown Red Solid, M. P.: 280–81 °C, **IR (KBr) cm^{-1}:** 779.24, 1068.56, 1257.59, 1338.60, 1359.82, 1541.12, 1639.49, 2953.02, 2987.74, 3032.10, 3136.25, 3184.48, 3566.38, 3618.46. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.99 (s, 3H), 3.15 (d, 3H), 3.82 (s, 3H), 5.22 (s, 1H), 7.19 (d, 1H), 7.22 (d, 1H), 9.74 (s, 1H), 10.68 (d, 1H), 12.34 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm):9.76, 28.18, 56.61, 98.17, 108.08, 113.74, 115.77, 134.34, 136.33, 136.62, 141.57, 149.18, 152.97, 159.76. **HRMS**, Calcd. For $C_{15}H_{15}N_5O_7$: 377.10; found 378.1057 $[M+H]^+$.

4-(2-chlorophenyl)-N,3-dimethyl-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (7o)

Yield – 74%, White Solid, M. P.: 255–256 °C, **IR (KBr) cm^{-1}:** 758.02, 1033.85, 1078.21, 1213.23, 1373.32, 1396.46, 1460.11, 1608.63, 1637.56, 2949.16, 3142.04, 3261.63. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.90 (s, 3H), 3.15 (d, 3H), 5.34 (s, 1H), 7.17–7.20 (td, 1H), 7.21–7.24 (td, 1H), 7.27–7.28 (d, 1H), 7.33–7.35 (dd, 1H),10.70 (d, 1H), 12.33 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm):9.60, 28.14, 97.63, 108.07, 127.14, 127.95, 129.25, 130.23, 131.88, 136.05, 140.40, 153.25, 159.52. **HRMS** For $C_{14}H_{12}ClN_4O_3$: 320.05; found 321.0755 $[M+H]^+$.

4-(4-chlorophenyl)-N,3-dimethyl-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (7p)

Yield – 93%, White Solid, **M. P.**: 244–246 °C, **IR (KBr) cm^{-1}:** 817.82, 1006.84, 1209.37, 1363.67, 1604.77, 1643.35, 2819.93, 2981.95, 3022.45, 3238.48. **^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.93 (s, 3H), 3.14 (d, 3H), 5.20 (s, 1H), 7.24–7.27 (dt, 2H), 7.29–7.31 (dt, 2H), 10.66 (d, 1H), 12.33 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 9.58, 28.14, 98.49, 108.51, 137.93, 128.97, 129.12, 129.90, 130.61, 136.15, 142.96, 152.97, 159.69, 160.47. **HRMS**, For $C_{14}H_{12}ClN_4O_3$: 320.07; found 321.0752 $[M+H]^+$.

4-(3,5-bis(trifluoromethyl)phenyl)-N,3-dimethyl-5-nitro-1,4-dihydropyrano[2,3-c]pyrazol-6-amine (7q)

Yield – 96%, White Solid, **M. P.**: 267–269 °C, **IR (KBr) cm^{-1}:** 902.69, 1074.35, 1130.29, 1166.93, 1278.81, 1352.10, 1465.90, 1641.42, 2974.23, 3024.38, 3066.82, 3246.20.**^{1}H NMR (500 MHz, DMSO-d_6) δ**: 1.88 (s, 3H), 3.16 (d, 3H), 5.51 (s, 1H), 7.91 (s, 1H), 8.02 (s, 2H), 10.75 (d, 1H), 12.41 (s, 1H). **^{13}C NMR (DMSO-d_6, 125 MHz),** δ_C (ppm): 9.52, 28.23, 97.28, 107.65, 120.09, 122.17, 124.33, 126.51, 128.19, 129.52, 129.78, 130.03, 136.59, 147.52, 152.86, 159.81. **HRMS**, Calcd. For $C_{16}H_{12}F_6N_4O_3$: 422.0814; found 423.0901 $[M+H]^+$.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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