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Efficient atom-economic one-pot multicomponent synthesis of benzylpyrazolyl coumarins and novel pyrano[2,3-c]pyrazoles catalysed by 2-aminoethanesulfonic acid (taurine) as a bio-organic catalyst

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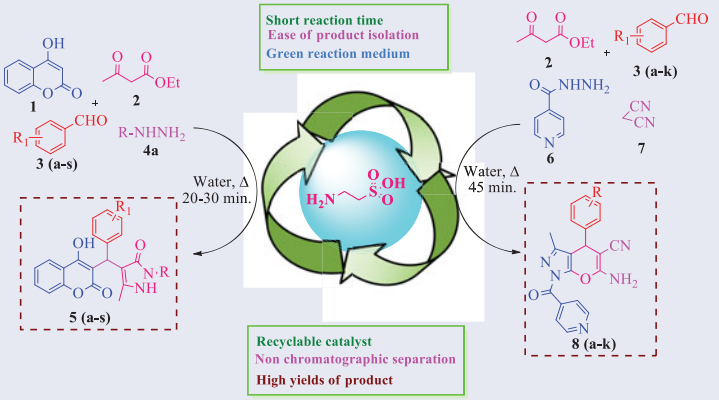
ABSTRACT

The present work describes eco-friendly multicomponent protocol for the synthesis in excellent yields of structurally diverse benzylpyrazolyl coumarin **5 (a–s)** involving the reaction of 4-hydroxycoumarin, ethyl acetoacetate, hydrazine hydrate/phenyl hydrazine hydrate and aldehydes, also novel pyrano[2,3-c]pyrazole derivatives **8 (a–k)** integrated by isonicotinic acid hydrazide from reaction of aldehyde, ethyl acetoacetate, malononitrile with isoniazid, employing water as a reaction medium and 2-aminoethanesulfonic acid (taurine) as the catalyst. This new methodology endowed the advantages such as short reaction time, recovery of catalysts after catalytic reaction and reusing them without losing their activity and alleviate of operation.

GRAPHICAL ABSTRACT



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2-Aminoethanesulfonic acid; benzylpyrazolyl coumarin; green reaction; multicomponent reaction; pyrano[2,3-c]pyrazoles

Introduction

The challenging task in chemistry is to develop practical methods, reaction media, conditions, and the use of materials based on the principles of green chemistry. The concept of "Green Chemistry" has emerged as one of the guiding principles of

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environmentally benign synthesis.[1–3] The use of bio-organic catalyst in organic synthesis has become a subject of intense investigation, in particular, green catalyst which offer advantages in clean and sustainable chemistry as they can be nontoxic, readily accessible, biodegradable and retrievable which successfully used for the synthesis of greener reaction. Thus, there are still some challenges imbedded in this class of cyclizations, such as performing the reaction under green catalysis, and green reaction media.

Organocatalysts have emerged as biomimetic catalysts, displaying advantages of being both greener as well as biocompatible.[4–11] 2-Aminoethanesulfonic acid (Taurine) is a β-amino acid, It is a kind of sulfur-containing amino acid which does not participate in the biosynthesis of protein,[12] but it is considered as a conditionally semi essential amino acid for mammals,[13] as it plays an important role in brain development,[14] also recognized to have the effect on the antitumor activity,[15,16] antioxidant activity,[17] antihypertensive activity[18] and membrane fluidity.[19] At present, the greater demand of taurine from food additives market[20–22] calls for its chemical synthesis. In addition to this, they improve water solubility and are capable to form H-bonds while their strong inductive effect can be utilized to tune pKa values of adjacent or remote amino groups.[23] On the other hand the structural and electronic properties might mimic transition states to tetrahedral intermediates.[24]

In recent times, 2-aminoethanesulfonic acid (taurine) was used for the preparation of bio-active barbituric and thiobarbituric acid derivatives,[25] Knoevenagel reaction between aldehydes and malononitrile,[26] and silica gel supported taurine in the oxidation of sulfides to their corresponding disulfides.[27] Moreover, to the best of our knowledge, there are no other reports of the catalytic activity of this β-amino acid for organic transformations. Currently, conventional step-by-step synthetic methods cannot meet the demands of high-throughput screening to identify potential therapeutic agents in drug research and development. To meet these demands, cascade reactions/domino reaction and multicomponent reaction have been developed, MCRs are atom economical because of accelerating chemical reactions, converting three or more components incorporated into the final product *via* a simple one-pot route.[28] They fulfill the requirements of green chemistry and for producing vast libraries of desired medicinal scaffolds in a benign way.[29]

Oxygen-containing heterocyclic frameworks exist in many natural products and synthetic pharmaceutics, so the construction of this class of scaffolds has attracted great attention from the organic community,[30] in this perspective, benzylcoumarins skeletal structure exits in a wide range of biologically active drugs and natural products. These biologically active compounds include the warfarin, phenprocumene, and coumatetralyl (Figure 1), showed antibacterial, anti-HIV, antiviral, and anticoagulant activities.[31] Similarly, pyrazolones are another important heterocyclic compounds (Figure 2) with a broad spectrum of biological activities. To list a few phenazone, propyphenazone, and ampyrone (Figure 2) are well known antipyretic and antianalgesic drugs. Also, pyrazolones are generally known for anti-fungal, antimycobacterial, antibacterial, anti-inflammatory, antitumor, antidepressant, and anti-tubercular activities.[32] It is anticipated that the integration of the 3-benzyl coumarin and pyrazolone moieties leading to benzylpyrazolyl coumarin scaffolds could be fascinating and beneficial from the biological point of view. Till date there are few reports available on the synthesis of this benzyl pyrazolylcoumarins.[33–40]

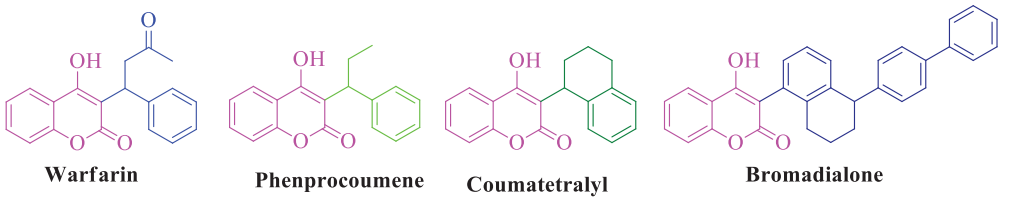


Figure 1. Some biologically active 3-substituted coumarin.

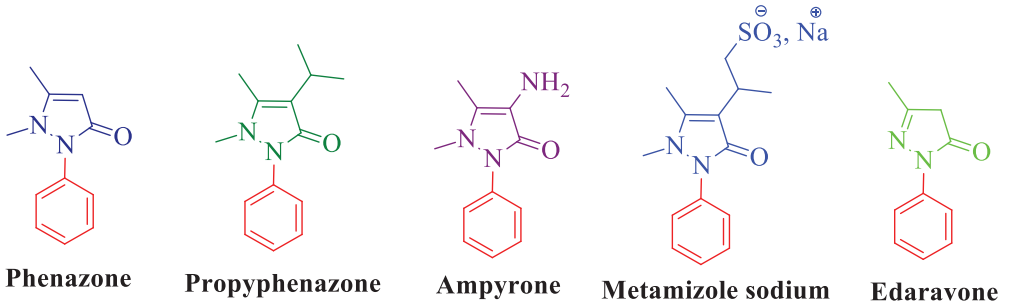


Figure 2. Bioactive pyrazolone moieties.

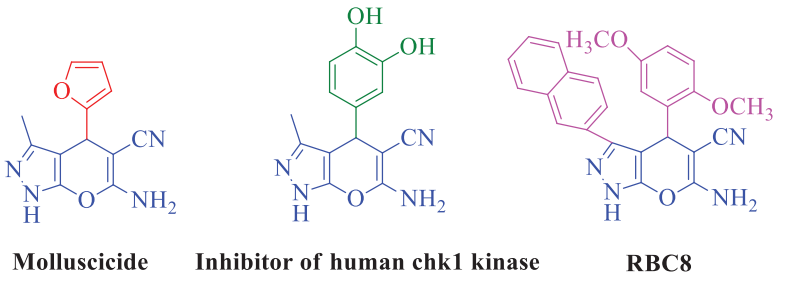
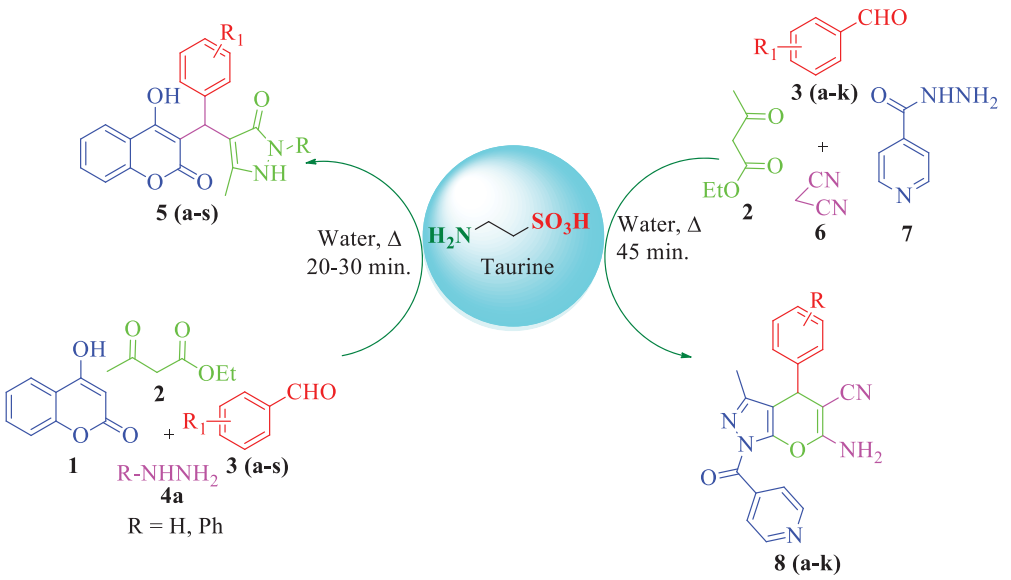


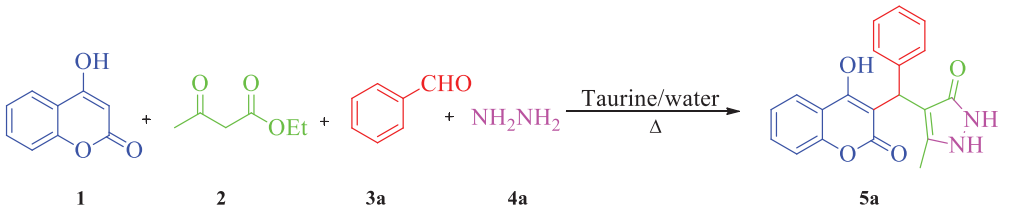
Figure 3. Bioactive pyrano[2,3-c]pyrazoles moieties.

In recent times, various substituted pyrazole and 4H-pyran-annulated heterocyclic scaffolds have been reported to demonstrate diverse biological activities (Figure 3) including anticancer,[41] antimicrobial,[42] antimalarial,[43] anti-HIV,[44] and anti-inflammatory activities.[45] Particularly, 2-amino-3-cyano-4H-pyran containing heterocycles showed encouraging anticancer and antibacterial activities.[46] Hence, it would be an attractive idea to incorporate isoniazid (INH) with pyran and pyrazolo moieties, because it might lead to a new dimension of structural diversity to the molecules. The fictionalization of the INH is possible via its reactive hydrazide group which can easily react with carbonyl compounds to form hydrazones or undergo cyclization reactions. Such a molecular modification can possibly results in enhancement of the activity and sometimes may also help in reducing the toxicity of the molecule. It is surprising that there is no compound possessing such a molecular skeleton reported in the literature to date.

Taking this into account, Herein, we report the synthesis of structurally diverse benzylpyrazolyl coumarins **5 (a–s)** and novel pyrano[2,3-c]pyrazole derivatives **8 (a–k)** integrated by isonicotinohydrazide by the use of tauine organocatalyst, that shows enhanced



Scheme 1. General scheme for the synthesis of benzylpyrazolyl coumarin **5 (a–s)** and novel 6-amino-1-isonicotinoyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile derivatives **8 (a–k)**.



Scheme 2. Standard model reaction.

activity and improved performance in the selected benchmark transformation when compared to typically used other catalysts (Scheme 1).

Result and discussion

During the course of our initial investigation reaction of 4-hydroxycoumarin, ethyl acetoacetate, hydrazine hydrate and benzaldehyde was used as the standard model reaction in a one-pot manner to investigate experimental conditions including catalysts and solvents (Scheme 2). Initially standard model reaction was carried out in the absence of catalyst in water at room temp. to 70 °C for 24 h. It was observed that no remarkable target product was obtained (Table 1, entry 1). In the next step, the model reaction was conducted in the presence of different catalysts, such as PTSA, acetic acid, $Ca(OTf)_2$, β-CD, and taurine (Table 1, entries 2–6), the obtained yields of product was low. When catalytic amounts of taurine was added to the same reaction mixture at 70 °C, the desired product (**5a**) was isolated with moderate yield (66%) after 60 min. After achieving this encouraging result, the reaction conditions were then screened with the aim of optimizing the yield of **5a**. We were delighted to find that taurine (15 mol%) was

Table 1. Effect of different catalyst on **5a**.[a]

Entry	Catalyst	Solvent (10 mL)	Time (min/h)	Temp (°C)	Yield[b] (%)
1.	–	H_2O	24 h	70	–[c]
2.	PTSA	H_2O	24 h	70	30
3.	CH_3-COOH	H_2O	1 h	70	72
4.	$Ca(OTf)_2$	H_2O	3.5 h	70	80
5.	β-CD	H_2O	60 min	70	76
6.	Taurine	H_2O	20 min	70	92

[a]All reactions were carried out using 4-hydroxy coumarin (1 mole), ethyl acetoacetate (1 mole), hydrazine hydrate/phenyl hydrazine hydrate (1 mole), aldehyde (1 mole) and taurine (15 mol%) using water as a solvent.
[b]Isolated yield.
[c]Reaction failed to provide any product.

Table 2. Effect of solvent on the synthesis of **5a**.[a]

Entry	Catalyst (mol %)	Solvent (10 mL)	Temp (°C)	Time (min)	Yield[b] (%)
1.	15	Ethanol	70	180	84
2.	15	Methanol	70	90	79
3.	15	CCl_4	70	210	67
4.	15	CH_3CN	70	180	14
5.	15	Toluene	120	300	61

[a]All reactions were carried out using 4-hydroxy coumarin (1 mole), ethyl acetoacetate (1 mole), hydrazine hydrate/phenyl hydrazine hydrate (1 mole), aldehyde (1 mole) and taurine (1 mole) using water as a solvent.
[b]Isolated yield.

superior for the reaction, and the yield of product **5a** was 92% in water for 20 min (Table 1, entry 6).

Next, we screened protic and aprotic solvents on the reaction. Obviously, protic solvents were better for the reaction, because they stabilize the carbocation intermediate, a polar protic solvent, such as ethanol and methanol, have a permanent dipole which means that the delta negative (partial negative charge) on the molecule will have dipole-dipole interactions with the carbocation, stabilizing it, along with this protic solvent can interact electrostatically with the nucleophile thereby stabilizing it. This reduces the reactivity of the nucleophile which favors a reaction. Encouraged by this result, we carried on with examining the effect of solvents using different aprotic solvents also such as toluene, $CHCl_3$, CCl_4 and CH_3CN using same catalyst equivalents with respect to the substrate on this reaction at heating temperature and results are incorporated in (Table 2, entries 1–5). It was clear that the highest yield of product **5a** was achieved when the reaction was performed in water (Table 1, entry 6). The progress of the reaction at room temperature in water was slow, and became even slower as it proceeded; however, the rate was greatly increased at increasing temperature, so the choice was made to pursue these conditions instead. Furthermore, the influence of the amount of taurine catalyst was examined to increase the efficiency of the reaction (Table 3).

With the best reaction conditions in hand, we tested the generality of this methodology with different aldehydes and phenyl hydrazine. Results listed in Table 4, demonstrate that most of the amines tested underwent smooth transformation to afford the corresponding products in satisfied yields. The electron-donating and electron-withdrawing groups were successfully converted to the corresponding products in excellent yields (80–94%) within very short time periods (20–30 min); moreover, the electronic effects of the substituent were not observed. The same MCR also proceeds with phenyl hydrazine and also with isoniazid in place of hydrazine hydrate, which indicate that

Table 3. Effect of catalyst (mole %) on **5a**.[a]

Entry	Catalyst (mole %)	Solvent (10 mL)	Temp (°C)	Time (min)	Yield[b] (%)
1.	5	H_2O	70	60	66
2.	10	H_2O	70	56	82
3.	15	H_2O	70	20	92
4.	20	H_2O	70	20	92

[a]All reactions were carried out using 4-hydroxy coumarin (1 mole), ethyl acetoacetate (1 mole), hydrazine hydrate/phenyl hydrazine hydrate (1 mole), aldehyde (1 mole), using water as a solvent.
[b]Isolated yield.

reaction was also smoothly preceded with the hydrazide (Table 4, entry 20). Relatively higher yields of the products were observed in case of phenyl hydrazine. This could be due to the delocalization of the lone pair of one nitrogen atom onto the phenyl ring. Encouraged by the participation of diversely substituted aryl aldehydes, we extended our methodology to check the participation of substituted heterocyclic aldehydes and aliphatic aldehydes, and found all these were equally participating to yield the products in good to excellent yields **(**entries **5j**, **5k**, **5m**, Table 4**)**. No distinct substitution effect was observed for this reaction. The isolated products were extremely pure without the need for any costly purification steps, which can be expensive in terms of time, materials and overall yield.

Inspired by these tempting results obtained for cyclocondensation of benzylpyrazolyl coumarin to be performed to show the ability of taurine in the promotion of these kinds of reactions. we extended the same protocol for synthesis of novel 6-amino-1-isonicotinoyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile derivatives reacting various substituted aldehyde (1 mole) with malononitrile (1 mole), ethyl acetoacetate (1 mole), isoniazid (1 mole) **(Scheme 3)**. Surprisingly, we were delighted to find that the taurine furnished the desired product within short time period with respect to excellent yields of products under similar reaction conditions (Table 5, entries 1–11**)**, suggesting that the taurine is essential to promote the reaction efficiency.

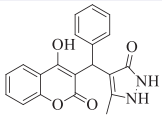
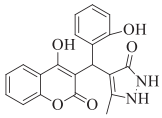
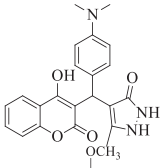
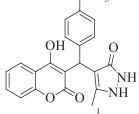
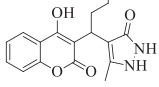
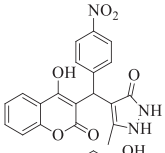
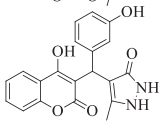
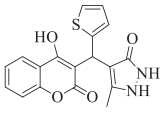
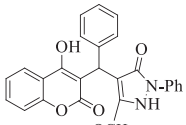
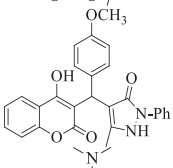
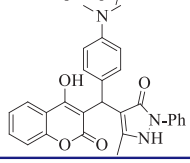
Recycling of the catalyst

The recyclability of taurine-catalyst was studied for synthesis of 4-((4-hydroxy-2-oxo-2H-chromen-3-yl)(phenyl)methyl)-5-methyl-1H-pyrazol-3(2H)-one **(5a)** under the optimized conditions. After completion of the reaction, the catalyst was separated from reaction mixture by simple filtration and filtrate was cooled at 5 °C, the white shiny taurine was reappeared and then filtrates directly, dried and after that applied for repeated reactions for the same transformation under the same reaction conditions (Table 4). To our delight, the catalyst can be reused as a minimum three times with little deactivation an essential aspect of green chemistry (Figure 4).

Reaction mechanism

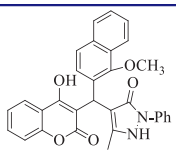
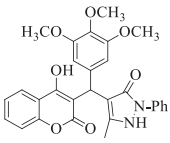
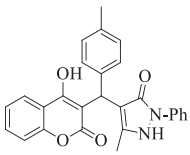
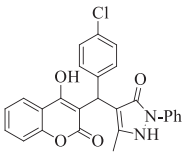
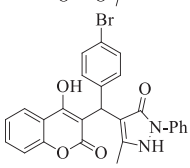
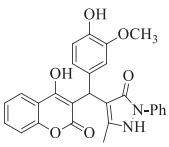
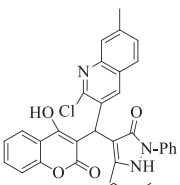
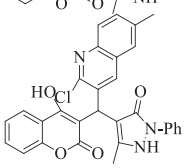
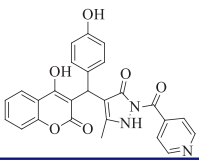
As shown in (Scheme 4), the possible mechanism for the construction of benzylpyrazolyl coumarin, first ethylacetoacetate and phenylhydrazine will react to give the pyrazolone (**I**), which will undergo Knoevenagel condensation with aldehydes to give the adduct Knoevenagel adduct (**II**). In the next step pyrazolone (**I**) and Knoevenagel adduct (**II**) will undergo taurine-catalyzed Michael addition to form **(III)** and the final product (**5a**).

Table 4. Taurine-catalyzed synthesis of benzylpyrazolyl coumarin derivatives[a] **5 (a–t)**.

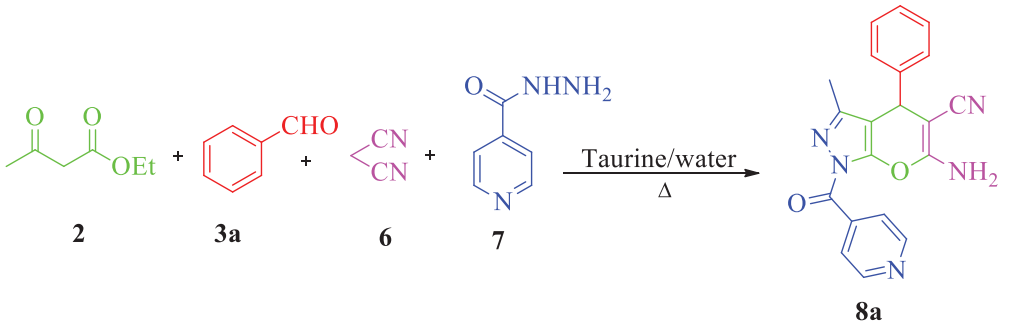
Sr. No.	Entry	Product	Time (min.)	Yield[b] (%)	M. P. (°C) Found	M. P. (°C) Report. [33–40]
1.	**5a**		20	92	230–233	232–234
2.	**5b**		20	83	221–223	–
3.	**5c**		25	88	227–229	–
4.	**5d**		25	82	200–202	201–203
5.	**5e**		25	83	225–227	–
6.	**5f**		25	88	237–239	–
7.	**5g**		20	86	217–219	–
8.	**5h**		25	85	223–225	–
9.	**5i**		20	87	231–234	233–235
10.	**5j**		20	80	204–206	207–209
11.	**5k**		25	86	218–220	–

(*continued*)

Table 4. Continued.

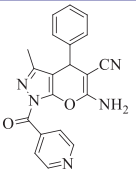
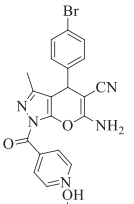
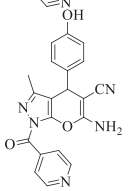
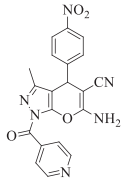
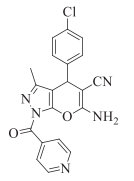
Sr. No.	Entry	Product	Time (min.)	Yield[b] (%)	M. P. (°C) Found	M. P. (°C) Report. [33–40]
12.	**5l**		20	88	215–217	–
13.	**5m**		20	76	207–209	–
14.	**5n**		25	85	219–221	223–225
15.	**5o**		25	81	222–224	225–227
16.	**5p**		20	78	241–243	244–247
17.	**5q**		20	83	233–235	–
18.	**5r**		20	91	220–222	–
19.	**5s**		20	89	216–218	–
20.	**5t**		20	85	187–190	–

[a]All reactions were carried out using 4-hydroxy coumarin (1 mole), ethyl acetoacetate (1 mole), hydrazine hydrate/phenyl hydrazine hydrate (1 mole), aldehyde (1 mole) and using taurine (15 mole%) in water as a solvent (10 mL).
[b]Isolated yield.



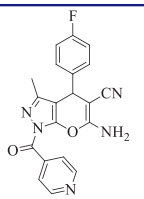
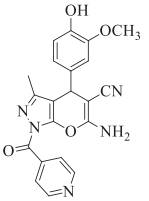
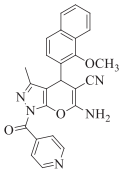
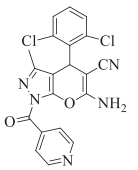
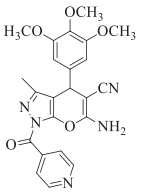
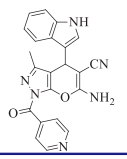
Scheme 3. Synthesis of pyrano[2,3-c]pyrazole-5-carbonitrile.

Table 5. Taurine-catalyzed synthesis of 6-amino-1-isonicotinoyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile derivatives[a] **8 (a–k)**.

Sr. No.	Entry	Product	Time (min.)	Yield[b] (%)	M. P. (°C)
1.	**8a**		35	90	99–101
2.	**8b**		35	89	121–123
3.	**8c**		30	88	161–164
4.	**8d**		30	80	118–120
5.	**8e**		35	89	126–128

(*continued*)

Table 5. Continued.

Sr. No.	Entry	Product	Time (min.)	Yield[b] (%)	M. P. (°C)
6.	**8f**		30	86	120–123
7.	**8g**		35	81	133–135
8.	**8h**		35	84	98–100
9.	**8i**		30	81	154–158
10.	**8j**		35	84	110–112
11.	**8k**		35	89	177–180

[a]All reactions were carried out using ethyl acetoacetate (1 mole), aldehyde (1 mole), malononitrile (1 mole), isoniazid (1 mole), and using taurine (15 mole%) in water as a solent (10 mL).
[b]Isolated yield.

The possible formation mechanism of densely functionalized novel pyrano[2,3-c]pyrazole is suggested in (Scheme 5). During the reaction, the aldehydes are activated, and the Knoevenagel products **(II)** are formed via reaction of anion **(I)** with activated aldehydes and hydrazine of isoniazid attacked the carbonyl group of the activated ethyl acetoacetate. Then, loss of H_2O, and intramolecular nucleophilic attack by another NH

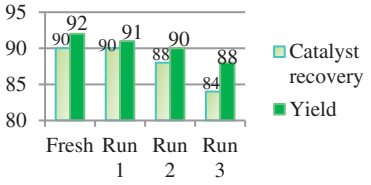
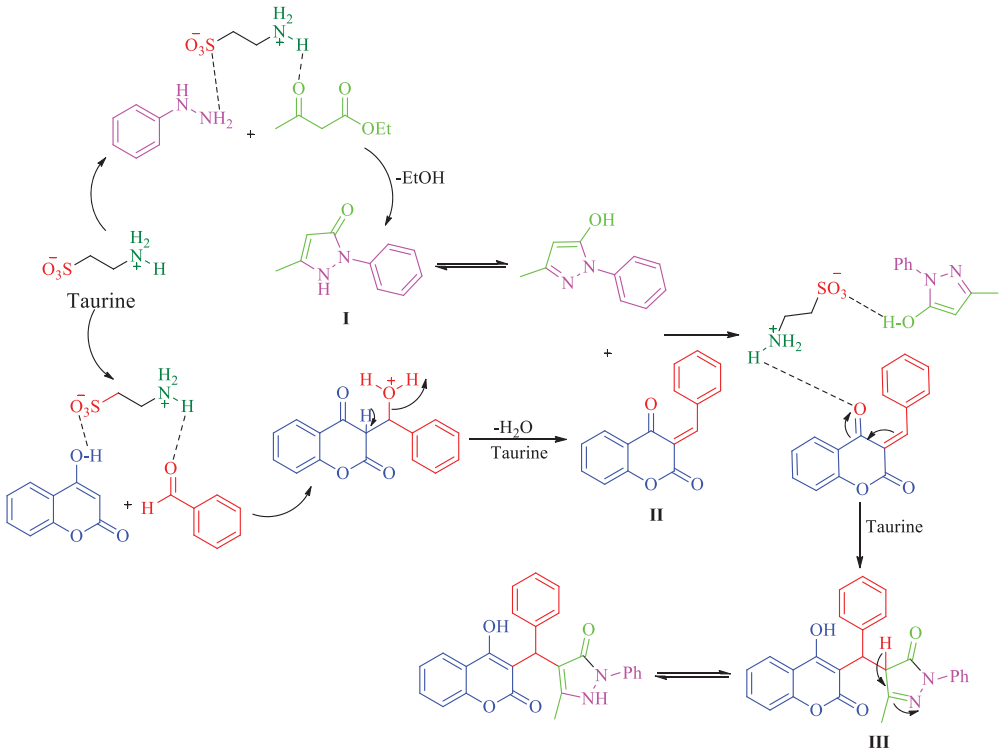


Figure 4. Recycle and recovery of 2-Aminoethanesulfonic acid (Taurine) and its effect on yield.

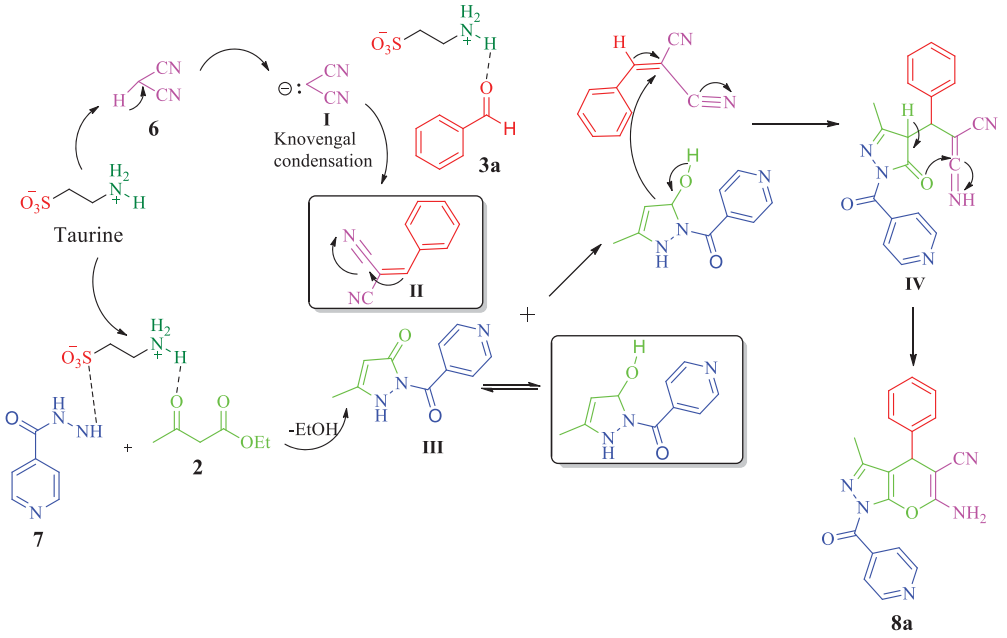


Scheme 4. A possible mechanism for the formation of benzylpyrazolyl coumarin.

group of hydrazine of isonizid to the next carbonyl group of ethyl acetoacetate afforded **(III)** after removing one molecule of EtOH. In the next step, the Michael addition occurred between (**II**) and (**III**) in the presence of taurine, which gave intermediate (**IV**). After intramolecular cyclization and oxidation, final products (**8a**) were formed.

Conclusion

In this work, a novel, convenient, and efficient approach to the synthesis of potentially active benzylpyrazolyl coumarin **5 (a–s)** and novel pyrano[2,3-c]pyrazole **8 (a–k)** has been reported based on the multicomponent reaction in good to excellent yield in a short period of time. Additionally the use of readily available and inexpensive catalyst taurine make this system more atom economical, minimally available starting materials, which makes the overall synthesis, is applicable in the quick access to relevant pharmaceutical molecules with pyrazole and isoniazide core heterocycle



Scheme 5. A possible mechanism for the formation of 6-amino-1-isonicotinoyl-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile.

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