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Tris-hydroxymethylaminomethane (THAM): a novel organocatalyst for a environmentally benign synthesis of medicinally important tetrahydrobenzo[*b*]pyrans and pyran-annulated heterocycles†

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A simple, efficient and environmentally benign protocol has been developed for the one-pot, multicomponent synthesis of medicinally important tetrahydrobenzo[*b*]pyrans and pyran-annulated heterocycles using a commercially available, inexpensive, non-toxic, and biodegradable tris-hydroxymethylaminomethane (THAM) as a novel organocatalyst. Ambient reaction conditions, wide scope, avoidance of conventional isolation as well as purification techniques and the reusability of the catalyst for five consecutive runs have improved the practical utility of this multicomponent reaction protocol manifold.

Introduction

The first multicomponent reaction was reported by Strecker in 1853 for the synthesis of α-amino acids.[1] Since then, for more than a century or so, the field of multicomponent synthesis appeared dormant, but more recently the last two decades have witnessed spectacular developments in this field.[2,3] These developments were mainly aimed either at the design of new multicomponent reactions or towards making improvements in existing methodologies for known multicomponent reactions. With today's growing concern over environmental protection and with the knowledge that the multicomponent reactions can provide an easy access to the library synthesis of structurally related drug like molecules, interest in the development of environmentally benign and diversity oriented multicomponent synthesis has become the focal point of much present day research.[4,5] In this context, the selection of an alternate reaction medium, energy source and the catalyst is known to play a very significant role. Although the choice of reaction medium, as well as the energy source has some limitations, there are no boundaries on the selection of the catalyst. Thus, a wide variety of homogeneous as well as heterogeneous catalysts have been successfully used in many multicomponent reactions. However, the search for a novel catalyst in the environmentally benign synthesis of compounds with biological and pharmaceutical importance is a constant endeavour.

A literature survey within the framework of organic compounds with pharmaceutical importance revealed that 2-amino-4*H*-chromenes with amino and nitrile functions at the 2 and 3 positions, respectively (A, Fig. 1) are known to possess diverse pharmaceutical properties, such as cytotoxic, myorelaxant, antioxidant, anti-bacterial, anti-proliferative, anti-microbial, anti-HIV, anti-rheumatic, anti-cancer activities, *etc.* (Fig. 1).[6a–h] Many compounds containing 2-amino-3-cyano-4*H*-chromene as the structural unit also find application as cognitive enhancers in the treatment of neurodegenerative diseases like Alzheimer's as well as for Parkinson's disease.[7] Apart from their medicinal importance, compounds belonging to this class are customarily used in the field of cosmetics[8] and agrochemicals,[9] as well as with dyes.[10] Owing to there being such a wide range of applications, the development of an efficient protocol for the synthesis of compounds containing 2-amino-3-cyano-4*H*-chromene as the structural motif is highly desirable.

It is well known that the synthesis of 2-amino-3-cyano-4*H*-chromenes involves a one-pot, three-component condensation between aldehyde, malononitrile and an enolizable C–H acid, such as dimedone, barbituric acid, naphthol (α and β), 4-hydroxy coumarin, resorcinol, 2-hydroxy-1,4-naphthoquinone, Kojic acid, *etc.*, and, furthermore, it is known to proceed *via* a Knoevenagel-carba-Michael–Thorpe–Ziegler type cascade pathway.[3d] As Knoevenagel–Michael cascade reactions can be effectively carried out using basic catalysts, a variety of bases, such as Et_3N,

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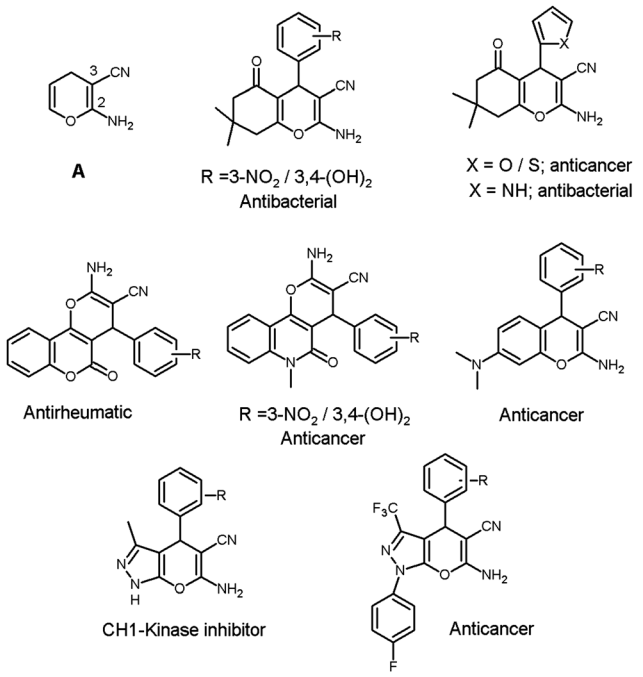


Fig. 1 Selected, medicinally important 2-amino-3-cyano-4*H*-chromenes.

piperidine, K_2CO_3, K_3PO_4, $(NH_3)_2HPO_4$, Mg–Al hydrotalcite, DBU, KF–Al_2O_3, chitosan, basic ionic liquids, hexamethylenetetramine, electro generated bases,[11a–l] *etc.*, have been reported for their synthesis. In addition, their synthesis has also been reported using heteropolyacids[12] or Bronsted acids,[13] as well as by using surfactants as the catalysts.[14a–d] At this stage, it is worth noting that most of these catalysts have been demonstrated to be useful in the synthesis of a particular type of 2-amino-4*H*-chromene. On the other hand, in recent years, substances like 4-dimethylaminopyridine (DMAP), urea, imidazole, potassium phthalimide-*N*-oxyl, meglumine, and ethylenediammonium-diformate, as well as clinoptilolite, have been reported as efficient catalysts in the synthesis of structurally diverse 2-amino-4*H*-chromenes.[15a–g] Although most of these catalysts are efficient, we believe there certainly exists scope for the introduction of a novel catalyst for the synthesis of medicinally significant 2-amino-4*H*-chromenes.

Our contribution towards the introduction of a novel catalyst is concerned with the structure, as well as the reactivity, of a recently reported organocatalyst, namely meglumine (Fig. 2A).[15e] As regards the choice of meglumine, the presence of a secondary amino and four hydroxyl groups have been described as playing a significant role in the library synthesis of 2-amino-4*H*-chromenes.[15e] Thinking along this line, we envisaged that

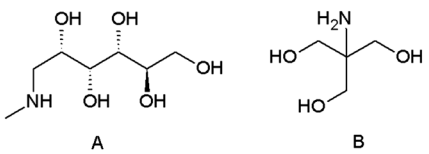
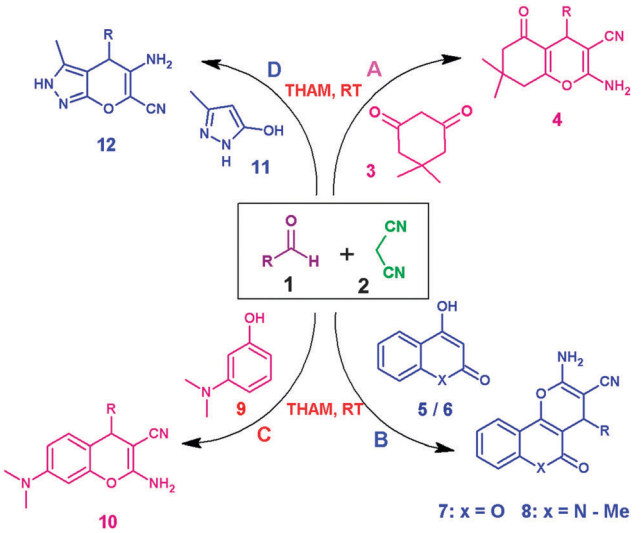


Fig. 2 (A) Meglumine, (B) tris-hydroxymethylaminomethane.



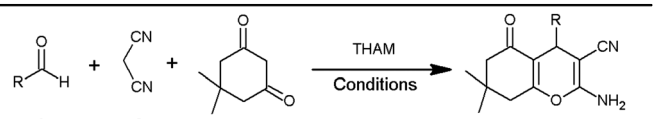
Scheme 1 Diversity oriented synthesis of 2-amino-4*H*-chromenes using THAM as the catalyst.

tris-hydroxymethylaminomethane (THAM) (Fig. 2B), which contains an amino and three alcoholic groups, is structurally related to meglumine and, like meglumine, it is physiologically inert, biodegradable, non-corrosive, and is available commercially at extremely low cost.[16] Customarily, it is used as an excipient in pharmaceutical preparations[17a] or in the analysis of pharmaceuticals,[17b] and when dissolved in water it generates a basic reaction medium.[17a] All these features associated with THAM and our continued interest in the development of green synthetic methodologies[18] prompted us to examine the potential of THAM as a basic catalyst. As an outcome of this philosophy, herein, we describe the use of tris-hydroxymethylaminomethane (THAM) as a novel organocatalyst in a diversity-oriented synthesis of a few medicinally important 2-amino-4*H*-chromenes at ambient temperature (Scheme 1).

Results and discussion

To begin with, the one-pot synthesis of tetrahydrobenzo[*b*]-pyran, **4a**, was performed, whereby, to an equimolar and well-stirred solution of anisaldehyde, malononitrile and dimedone (1 mmol, each) in ethanol was added THAM (10 mol%). Stirring was continued at room temperature and the progress of the reaction was monitored by TLC. The product resulted after two hours and was identified to be a mixture of Knoevenagel condensation products, namely benzylidene malononitrile and the desired 2-amino-3-cyano-4*H*-chromene, **4a**, in nearly a 1 : 1 proportion. An increase in the stirring time did not show any appreciable change in the proportion of the resultant products. Taking clues from these results, we next optimized the reaction conditions to obtain, **4a**, exclusively. In this context, the effects of catalyst loading on the course of the reaction were initially examined. With an increase in the amount of catalyst loading, a gradual increase in the yield of the desired product, **4a**, was noticed. However, it was not obtained as an exclusive

Table 1 Optimization of the reaction conditions for the synthesis of **4a**, using THAM as the catalyst[a]



1 2 3 4

Sr. no.	Catalyst (mol%)	Reaction medium (v/v)	Time (h)	Yield[b] (%)
1	—	EtOH	4	—
2	10	—	2	80[c]
3	10	EtOH	2	50[c]
4	10	EtOH	4	60
5	20	EtOH	2	60
6	30	EtOH	2	70
7	30	H_2O	4	85[d]
8	30	EtOH : H_2O (9 : 1)	2	85
9	30	EtOH : H_2O (8 : 2)	2	87
10	30	EtOH : H_2O (7 : 3)	1.5	90
11	**30**	**EtOH : H_2O (1 : 1)**	**1.5**	**91**
12	20	EtOH : H_2O (1 : 1)	2	80
13	10	EtOH : H_2O (1 : 1)	2	70

[a] Reaction conditions: anisaldehyde, malononitrile and dimedone (1 mmol, each), catalyst, solvent. [b] Isolated yield. [c] Benzylidene malononitrile. [d] Sticky solid.

product (Table 1). During the studies on the effect of the reaction medium, it was truly gratifying to notice an appreciable increase in the yield of the desired product, **4a** with the choice of water as the reaction medium. However, the product was obtained as a sticky solid. Hence, subsequent optimization of the reaction conditions was confined towards the selection of the optimum ethanol–water proportion, and during these studies we affirmed that, with the use of a water–ethanol medium (7 : 3, v/v), the desired product, **4a**, resulted as a free-flowing solid in an excellent yield (Table 1). In pursuance of making this protocol greener and economical, it was found that, water–ethanol (1 : 1, v/v) as the medium gave the desired product, **4a**, in almost same yield.

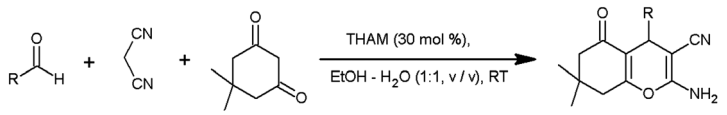
Encouraged by this initial success, we next planned to examine the generality of the reaction conditions. Accordingly, aromatic aldehydes tethered with electron-withdrawing, as well as electron-donating, groups and a few heteroaromatic aldehydes were allowed to react with malononitrile and dimedone under the established reaction conditions. In all the cases, the corresponding tetrahydrobenzo[*b*]pyran derivatives, **4b–k**, were obtained in excellent yields, as well as in high purity (TLC, NMR) (Table 2); although, aliphatic aldehydes failed to furnish the respective pyran derivatives in an acceptable yield. Most of the synthesized compounds being known compounds were characterized by comparison of their melting points with those reported earlier, as well as by spectral methods (IR, ^{1}H-NMR).

A plausible mechanism for the formation of tetrahydrobenzo-[*b*]pyrans is depicted in Scheme 2.

After our initial success, based upon the plausible mechanism (Scheme 2), we envisaged that 4-hydroxycoumarin, **5**, and 4-hydroxyquinolin-2-one, **6**, (Scheme 1) being structurally analogous to the enolized form of dimedone (A, Scheme 2), replacement of the dimedone component employed in the synthesis of, **4**, by either, **5** or **6**, could be expected to furnish 2-amino-3-cyano-pyrano[3,2-*c*]chromen-5(4*H*)ones, **7**, or 2-amino-3-cyano-pyrano[3,2-*c*]quinolin-2-ones, **8**, respectively (Scheme 1, B).

A literature survey revealed that, pyrano[3,2-*c*]chromenes, **7**, are known to possess anti-rheumatic activities, and a useful number of protocols have been reported for their synthesis.[19a–e] On the other hand, despite early reports on the potential of pyrano[3,2-*c*]quinolones, **8**, as anticancer agents, reports on their synthesis are scanty.[20] In light of these observations, we examined

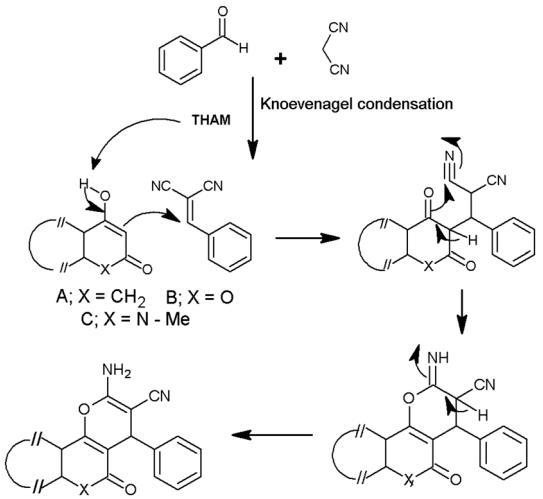
Table 2 THAM catalyzed synthesis of tetrahydrobenzo[*b*]pyrans, **4**[a]



1 2 3 4

Entry	Aldehyde (1)	Product	Time (h)	Yield[b] (%)	Melting point (°C) Obs.	Lit.[ref.]
1	4-Methoxybenzaldehyde	**4a**	1.5	91	196–198	201—203[15h]
2	4-Isopropylbenzaldehyde	**4b**	1.5	86	204–206	198–200[11d]
3	3-Nitrobenzaldehyde	**4c**	2.0	91	214–216	212–214[15h]
4	4-Cyanobenzaldehyde	**4d**	1.5	91	224–226	227–230[11d]
5	4-Methylbenzaldehyde	**4e**	1.5	87	217–219	220–222[15h]
6	3,4-Dimethoxybenzaldehyde	**4f**	2.0	83	172–174	170–173[27b]
7	4-Hydroxybenzaldehyde	**4g**	1.5	85	222–224	224–226[15h]
8	4-Bromobenzaldehyde	**4h**	1.5	87	205–208	205–207[15b]
9	3,4,5-Trimethoxybenzaldehyde	**4i**	1.5	84	208–210	208–210[15b]
10	4-Allyloxybenzaldehyde	**4j**	2.0	87	218–220	223–225[27a]
11	Thiophene-2-carbaldehyde	**4k**	1.5	88	208–210	209–211[15h]
12	Indole-3-carbaldehyde	**4l**	2.0	81	180–182	185–186[14d]
13	Cyclohexanecarbaldehyde	**4m**	2.0	83	208–210	209–211[11e]
14	Piperonal	**4n**	1.5	89	226–228	224–226[14d]
15	*n*-Butyraldehyde	**4o**	4.0	50	170–172	174–176[15b]

[a] Reaction conditions: aldehyde, malononitrile and dimedone (1 mmol, each), THAM (30 mol%), water–ethanol (1 : 1, v/v), RT. [b] Yields refer to pure isolated products. All the known compounds gave satisfactory spectral data (^{1}H-NMR).

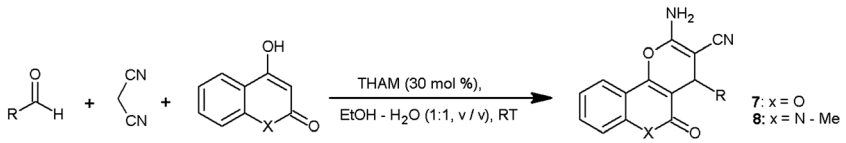


Scheme 2 Plausible mechanism for the formation of 2-amino-4*H*-chromenes.

the scope of THAM as a catalyst in the synthesis of **7**, as well as in the synthesis of **8**. Accordingly, two model reactions were performed using anisaldehyde, malononitrile and 4-hydroxycoumarin, **5**, and anisaldehyde, malononitrile and 4-hydroxy-*N*-methyl-quinolin-2-one, **6**, as substrates and employing the reaction conditions established for the synthesis of, **4**. Both the reactions proceeded smoothly (TLC), and upon completion of the reactions, it was truly gratifying to notice the formation of the desired products **7a** and **8a** in excellent yields. During the examination of the scope of the protocol, it was experienced that, functionally diverse aromatic, as well as heteroaromatic aldehydes, also furnished the corresponding pyrano[3,2-*c*]chromenes, **7b–k**, as well as pyrano[3,2-*c*]quinolones, **8b–k**, (Table 3) in excellent yields and purity. On the other hand, poorly reactive aliphatic aldehydes failed to furnish the desired products, **7**/**8**, in an acceptable yield.

Like the 1,3-diketones, phenols, naphthols as well as resorcinol are known to serve as enolizable C–H acids. The literature survey on the use of these compounds as C–H acids revealed that, although there are many reports on the use of naphthols in the multicomponent synthesis of tetrahydrobenzo[*b*]pyrans,[15,21] reports on the choice of 3-dimethylaminophenol, **9**, as the C–H acid are scarce.[22] Our interest in the selection of 3-dimethylaminophenol

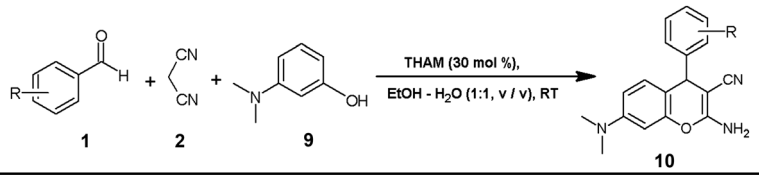
Table 3 THAM-catalyzed synthesis of pyrano[3,2-*c*]chromenes, **7** and pyrano[3,2-*c*]quinolones, **8**[a]



Entry	Aldehyde (1)	Product	Time (h)	Yield[b] (%)	Melting point (°C) Obs.	Lit.[ref.]
1	4-Methoxybenzaldehyde	**7a**	2.5	91	230–232	232–234[19c]
2	4-Methoxybenzaldehyde	**8a**	2.5	88	260–263	267–268[20e]
5	4-Isopropylbenzaldehyde	**7b**	2.5	82	248–250	252–254[19b]
6	4-Isopropylbenzaldehyde	**8b**	3.0	88	226–228	—
8	3-Nitrobenzaldehyde	**7c**	2.5	90	256–258	254–256[19a]
9	3-Nitrobenzaldehyde	**8c**	2.5	85	276–278	274–276[20b]
10	4-Cyanobenzaldehyde	**7d**	2.0	90	284–286	289–290[19a]
11	4-Cyanobenzaldehyde	**8d**	2.0	86	282–284	—
12	3,4,5-Trimethoxybenzaldehyde	**7e**	3.0	81	228–230	230–232[19c]
13	3,4,5-Trimethoxybenzaldehyde	**8e**	3.0	84	268–270	267–269[20b]
14	4-Hydroxybenzaldehyde	**7f**	3.0	79	260–262	265–266[19a]
15	4-Hydroxybenzaldehyde	**8f**	2.5	84	278–280	NR[20c]
16	4-Allyloxybenzaldehyde	**8g**	3.5	80	226–228	—
17	4-Bromobenzaldehyde	**7h**	2.0	85	248–250	254–256[19a]
18	4-Bromobenzaldehyde	**8h**	2.0	89	284–286	285–286[20e]
19	Piperonal	**7i**	2.0	85	178–180	180–181[19d]
20	Piperonal	**8i**	2.5	84	276–278	—
21	Furan-2-carbaldehyde	**7j**	2.5	78	252–254	252–253[19d]
22	Furan-2-carbaldehyde	**8j**	3.0	82	294–296	296–297[20e]
23	Thiophene-2-carbaldehyde	**7k**	2.5	80	232–234	228–230[19c]
24	Thiophene-2-carbaldehyde	**8k**	2.5	86	278–280	NR[20c]
25	Cyclohexanecarbaldehyde	**7l**	4.0	75	268–270	267–269[19a]
26	Cyclohexanecarbaldehyde	**8l**	4.0	83	272–274	—
27	Pyridine-3-carbaldehyde	**7m**	2.5	80	252–254	255–257[19c]
28	Pyridine-3-carbaldehyde	**8m**	2.5	87	276–278	279–280[20e]
29	3,4-Dimethoxybenzaldehyde	**8n**	2.5	84	264–266	—
30	2,5-Dimethylbenzaldehyde	**7n**	3.0	81	235–238	—
31	2,6-Dimethylbenzaldehyde	**7o**	3.5	83	250–252	—
32	4-Allyloxybenzaldehyde	**7p**	3.5	80	225–228	—

[a] Reaction conditions: aldehyde, malononitrile and 4-hydroxycoumarin/4-hydroxyquinoline-2-one (1 mmol, each), THAM (30 mol%), RT. [b] Yields refer to pure isolated products. All the reported as well as new compounds gave satisfactory spectral analysis (^{1}H-NMR); NR: not reported.

Table 4 THAM-catalyzed synthesis of 2-amino-7-(dimethylamino)-4-aryl-4*H*-chromene-3-carbonitriles, **10**[a]



Entry	Aldehyde (1)	Product	Time (h)	Yield[b] (%)	Melting point (°C) Obs.	Lit.[(ref.)]
1	4-Methoxybenzaldehyde	**10a**	2.0	85	176–178	174–176[22a]
2	Benzaldehyde	**10b**	2.0	87	204–207	206–207[22a]
3	4-Chlorobenzaldehyde	**10c**	2.5	85	202–205	198–200[22b]
4	3-Nitrobenzaldehyde	**10d**	2.0	87	198–201	NR[23d]
5	3,4-Dimethoxybenzaldehyde	**10e**	2.30	82	165–168	160–161[22c]
6	4-Bromobenzaldehyde	**10f**	2.15	84	204–207	202–204[22b]
7	3,4,5-Trimethoxybenzaldehyde	**10g**	3.0	80	178–181	177–181[22c]
8	Cyclohexanecarbaldehyde	**10h**	3.5	83	148–149	148–152[22a]
9	Piperonal	**10i**	2.5	86	237–240	NR[23d]
10	Pyridine-3-carbaldehyde	**10j**	3.0	84	240–242	244–246[22a]
11	4-Methylbenzaldehyde	**10k**	2.5	85	240–242	—
12	4-Isopropylbenzaldehyde	**10l**	3.0	83	226–228	—
13	Thiophene-2-carbaldehyde	**10m**	3.0	84	217–220	—
14	4-Allyloxybenzaldehyde	**10n**	2.5	82	183–185	—
15	4-Hydroxybenzaldehyde	**10o**	2.5	83	234–237	—

[a] Reaction conditions: aldehyde, malononitrile and 3-dimethylaminophenol (1 mmol, each), THAM (30 mol%), RT. [b] Yields refer to pure isolated products. All the known compounds gave satisfactory spectral analysis; NR: not reported.

in the synthesis of 2-amino-7-(dimethylamino)-4-aryl-4*H*-chromene-3-carbonitriles, **10**, stems from the anti-cancer, as well as apoptosis inducer, activities associated with the targeted compounds, **10**, and a few of their structural analogues.[23] Thus, employing the reaction conditions established for the synthesis of **8**, a model reaction was performed between anisaldehyde, malononitrile and 3-dimethylaminophenol. As in earlier cases, the formation of a free-flowing solid was noticed in about two hours. However, the reaction did not go to completion. Modification of the reaction conditions, such as increasing the reaction time as well as the catalyst loading, were not found to be useful in driving the reaction to completion (as verified by TLC). Hence, the resultant solid was filtered and, taking recourse to the solubility behaviour of starting materials as well as the desired product, a non-conventional, chromatography, as well as a crystallization-free route, was developed to obtain pure, **10a**. The filtered solid after drying in air was washed successively with a hexane–chloroform mixture (1 : 1, v/v) and then dried again. The purified product was found to be suitable for practical as well as analytical purposes. Subsequently, the protocol was extended towards various substituted aldehydes to obtain the corresponding 2-amino-7-(dimethylamino)-4-aryl-4*H*-chromene-3-carbonitriles, **10b–o** (Table 4). Among the synthesized compounds, **10d**, **10e** and **10i** have already been reported as apoptosis-inducer agents.

After establishing a general route for the synthesis of tetrahydrobenzo[*b*]pyrans, **4**, as well as pyran-annulated heterocycles, **7**, **8** and **10**, we turned our attention towards the synthesis of another important class of pyran-annulated heterocycles, namely pyrano[3,2-*c*]pyrazoles, **12** (Scheme 1, D). This is because; the compounds belonging to this class hold a position of prominence due to their human chk1 inhibitor activity. The classical synthesis of pyrano[3,2-*c*]pyrazoles, **12**, involves a three-component condensation between aldehyde, malononitrile and 5-methyl-2,4-dihydropyrazol-3-one – as another enolizable C–H acid.[24] In light of the advantages associated with the reduction in the number of steps, in recent years, their synthesis has been reported by a one-pot, four-component condensation between aldehyde, malononitrile, alkyl acetoacetate and hydrazine hydrate in the presence of catalysts like meglumine,[25a] piperidine,[25b] amberlyst-A-21,[25c] per-6-amino-β-cyclodextrin,[25d] Fe_3O_4 nanoparticles,[25e] CTACl,[25f] *etc.*[25g–n] Quite recently a catalyst-free synthesis of title compounds at elevated temperature has also been reported.[27] This particular report indirectly projects the scope for the development of a protocol that can operate at ambient temperature using a catalyst that is less expensive than the cost of energy required for their synthesis under a catalyst-free condition. Thus, we examined the catalytic potential of THAM in the one-pot synthesis of **12**.

Initially, employing the reaction conditions established for the synthesis of **10**, a three-component condensation was attempted using anisaldehyde, malononitrile and 5-methyl-2,4-dihydro-pyrazol-3-one, **11**, as the substrates (Scheme 1, D). As expected, the desired pyrano[3,2-*c*]pyrazole, **12a**, was obtained in good yield (76%). At this stage, it is worth noting that the resultant pyrano[3,2-*c*]pyrazole may exist in two tautomeric forms, namely 2,4-dihydropyrano[3,2-*c*]pyrazole, **12**, and 1,4-dihydropyrano[3,2-*c*]pyrazole, **13** (Fig. 3). However, Gogoi *et al.*[25j] and Vasuki *et al.*[25b] through X-ray crystallographic studies and Al-Matar *et al.*[25n] through NOE studies showed that, the resultant product stays as 2,4-dihydropyrano[3,2-*c*]pyrazole. The observed physical as well as spectral data of **12a** was in complete agreement with that reported earlier for the 2,4-dihydropyrano[3,2-*c*] pyrazole

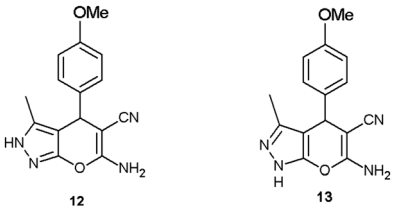


Fig. 3 Tautomers of pyrano[3,2-*c*]pyrazole, **12**.

tautomer.[25k,l] Encouraged by this initial success, a four-component reaction was then performed between anisaldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate employing the same reaction conditions. Interestingly, an appreciable increase in the yield of the desired product, **12a** was noticed (76% → 91%). Next, we examined the scope of the protocol. Thus, the four-component condensation route was extended towards other aromatic aldehydes bearing electron-withdrawing as well as electron-donating groups, as well as towards a few heteroaromatic aldehydes. In all the cases, the corresponding pyrano[3,2-*c*]-pyrazole, **12b–k**, was obtained in an excellent yield (Table 5).

After establishing a general protocol for the synthesis of various medicinally important pyrans, as well as for pyran-annulated heterocycles, we checked the economic as well as environmental compatibility of the developed protocol. In this context, scalability of the protocol and reusability of the catalyst were examined. So as to check the scalability of the protocol, under the established reaction conditions, the synthesis of pyrano[3,2-*c*]chromene, **7a**, as well as pyrano[3,2-*c*]quinolone, **8a**, were carried out on a 10 mmol scale. In both cases, the desired products, **7a** and **8a**, were obtained in an excellent yield (89% and 86%, respectively).

Finally, we turned our attention towards the reusability of the catalyst. In this context, we surmised that, with the catalyst used being completely soluble in the reaction medium, it's isolation for possible reuse would be tedious, as well as expensive. Hence, we checked reusability of the reaction medium. Accordingly, the synthesis of **8a** was performed on a 10 mmol scale. The resultant product was isolated by filtration, and the filtrate obtained was reused for the synthesis of **8a**. Only a slight decrease in the yield of the desired product, **8a**, was noticed (88% → 85%). Hence, this process was repeated three more times. In three consecutive runs, a progressive decrease in the yield was noticed (Fig. 4). In short, the protocol developed is scalable and the catalyst can be reused for at least three consecutive runs.

Finally, a comparison was made between the protocols reported earlier and the protocol developed by us for the synthesis of **8a**, **10a** and **12a**, as model compounds. The results summarized in Table 6 reveal that the protocol developed by us would be the protocol of choice for the synthesis of **8a** and **10a**. On the other hand, based upon the parameters of cost, as well

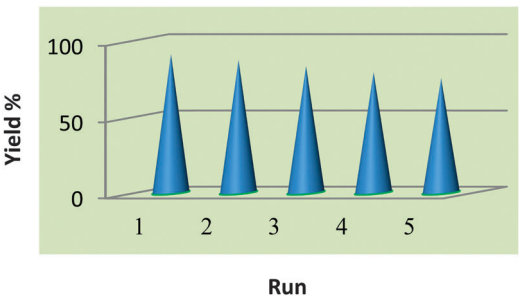
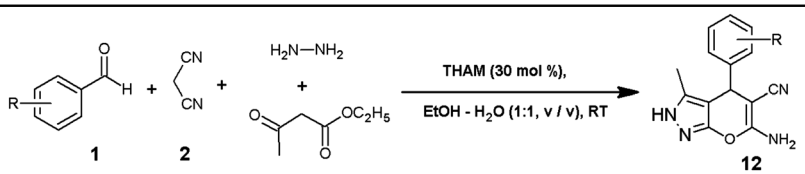


Fig. 4 Reusability of the catalyst.

Table 5 THAM-catalyzed four-component synthesis of pyrano[3,2-*c*]pyrazoles, **12**[a]



Entry	Aldehyde	Product	Time (h)	Yield (%)	Melting point (°C) Obs.	Lit.[ref.]
1	4-Methoxybenzaldehyde	**12a**	2.0	91	208–210	211–213[25k]
2	4-Bromobenzaldehyde	**12b**	2.0	89	181–183	179–180[25k]
3	4-Isopropylbenzaldehyde	**12c**	2.5	84	181–184	180–181[25d]
4	3-Nitrobenzaldehyde	**12e**	2.0	90	213–215	214–216[25k]
5	4-Cyanobenzaldehyde	**12f**	2.0	90	196–198	196–198[25l]
6	4-Methylbenzaldehyde	**12g**	2.0	87	201–203	204–206[25k]
7	3,4-Dimethoxybenzaldehyde	**12h**	2.5	81	192–194	192–194[25k]
8	Cyclohexanecarbaldehyde	**12i**	3.0	83	170–172	172–173[25d]
9	Thiophene-2-carbaldehyde	**12j**	2.5	85	226–228	221–223[25m]
10	Piperonal	**12k**	2.0	89	204–207	202–205[25c]
11	Pterphthaldehyde[b]	**12l**	3.0	79	300–302	295–298[26]
12	4-Allyloxybenzaldehyde	**12m**	3.0	84	181–184	—
13	3,5-Dimethylbenzaldehyde	**12n**	2.5	81	211–214	—
14	5-Methylfurfural	**12o**	2.5	82	192–194	—
15	3-Methylthiophene-2-carbaldehyde	**12p**	2.5	83	210–213	—

[a] Reaction conditions: aldehyde, malononitrile, ethyl acetoacetate and hydrazine hydrate (1 mmol, each), THAM (30 mol%), water–ethanol (4 mL, 1 : 1, v/v), RT. [b] Aldehyde (1 mmol), malononitrile, ethyl acetoacetate and hydrazine hydrate (2 mmol, each), THAM (30 mol%), water–ethanol (4 mL, 1 : 1, v/v).

Table 6 Comparison between the THAM-catalyzed protocol with earlier reported protocols for the synthesis of **8a**, **10a** and **12a**

Entry	Catalyst (mol%/mg)	Product	Solvent	Temp. (°C)	Time (min)	Yield (%)[ref.]
1	Triethylamine (50/50)	**8a**	EtOH	Reflux	50	78[20b]
2	Electricity	**8a**	EtOH	70	3	86[20e]
3	Clinoptilolite (/10 mg)	**8a**	H_2O	Reflux	15	88[15g]
4	**THAM (30/35 mg)**	**8a**	**EtOH–H_2O**	**RT**	**2.5**[c]	**88**[b]
5	Piperidine (30/27)	**10a**	EtOH	RT	120	80[23a]
6	Triethylamine (30/30)	**10a**	EtOH	Reflux	30	70[22c]
7	**THAM (30/35)**	**10a**	**EtOH–H_2O**	**RT**	**2**[c]	**85**[b]
8	PACD[a] (0.008 mmol)	**12a**	EtOH	RT	1	99[25d]
9	Meglumine (10/20)	**12a**	EtOH–H_2O	RT	15	91[25a]
10	Piperidine (5/5)	**12a**	H_2O	RT	10	85[25b]
11	Urea (10/6)	**12a**	EtOH–H_2O	RT	8[c]	86[15b]
12	Amberlyst A-21 (15/30)	**12a**	H_2O	RT	35	94[25c]
13	HDBAC (30/120)	**12a**	PTC	RT	60	79[25i]
14	Iodine (5/7)	**12a**	H_2O	RT	7	88[25h]
15	Fe_3O_4 NPs (6/15)	**12a**	H_2O	RT	2	95[25e]
16	**THAM (30/30)**	**12a**	**EtOH–H_2O**	**RT**	**2**[c]	**91**[b]

Reaction conditions: aldehyde, malononitrile and C–H acid (1 mmol, each), THAM (30 mol%,), EtOH–H_2O (1 : 1, 4 mL), RT.[a] Per-6-amino-β-cyclodextrin. [b] Present work. [c] Time in hours.

as the non-toxic nature of the catalyst, the developed protocol could serve as a useful alternative towards the synthesis of **12a**.

Conclusion

In conclusion, we demonstrated for the first time the use of a commercially available, non-toxic, inexpensive, bio-degradable and easy to handle tris-hydroxymethylaminomethane as a novel organocatalyst in the library synthesis of medicinally important tetrahydrobenzo[*b*]pyrans, as well as pyran-annulated heterocycles. Ambient reaction conditions, high to excellent yields, reusability of the catalyst for five consecutive runs, easy isolation of the products and the avoidance of conventional work-up, as well as facile purification procedures, are the key features of this multicomponent protocol. Keeping in view the advantages offered by the catalyst, the present protocol would be useful in the large-scale synthesis of pyran-annulated heterocycles, and this novel catalyst may find application in Knoevenagel-initiated domino reactions for the synthesis of heterocyclic frameworks.

Experimental

General

All aldehydes, 3-dimethylaminophenol and 4-hydroxy coumarin (Aldrich), malononitrile, dimedone, hydrazine hydrate, and ethyl acetoacetate (SD fine chemicals) were used as received. *N*-Methyl quinoline-2-one was received as a gift sample from M/S Bravil Chemicals, Kolhapur, India. All the melting points were recorded using Kumar melting point apparatus. The IR spectra were recorded using a Perkin Elmer Spectrum 1 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance-II spectrometer. High resolution mass spectra (HRMS) were recorded using a Thermo Scientific Q – Exactive, Accela 1250 pump, instrument.

General experimental procedure

To a well-stirred solution of an aldehyde (1 mmol), malononitrile (1 mmol) and an appropriate C–H acid **3**, **5**, **6**, **9** or **11** (1 mmol) in ethanol : water (1 : 1, 4 mL) was added tris-hydroxymethylaminomethane (30 mol%), and stirring was continued at ambient temperature. Upon completion of the reaction (as verified by TLC), water (5 mL) was added and stirring was continued until a free-flowing solid resulted in the reaction mixture. The resultant solid was filtered, washed with water and then dried. The dried solid was successively washed using a mixture of hexane : chloroform (70 : 30, v/v), and then dried. All the resulted products were pure (verified by TLC, NMR).

The NMR spectra provided in the ESI† are of the as-isolated products.

Spectral data of the new compounds

2-Amino-4,5-dihydro-4-(2,5-dimethylphenyl)-5-oxopyrano[3,2-*c*]-chromene-3-carbonitrile, 7n. Solid; M.P.: 235–238 °C; IR (KBr): 3121, 2233, 1733, 1675, 1476, 1399, 1255, 1090 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d$_6$): δ 2.15 (s, 3H), 2.43 (s, 3H), 4.72 (s, 1H), 6.82 (s, 1H), 6.91 (d, 1H, J = 7.4 Hz), 7.03 (d, 1H, J = 7.4 Hz), 7.35 (s, 2H), 7.47 (d, 1H, J = 7.7 Hz), 7.52 (d, 1H, J = 7.8 Hz), 7.72 (t, 1H, J = 7.7 Hz), 7.92 (d, 1H, J = 7.7 Hz); ^{13}C-NMR: (75 MHz, DMSO-d$_6$): δ 19.14, 21.08, 32.90, 58.47, 105.05, 113.44, 117.07, 119.74, 122.91, 125.16, 128.03, 128.05, 130.49, 132.67, 133.32, 135.98, 142.42, 152.54, 153.93, 158.15, 160.08; HRMS: mass calculated for [$C_{21}H_{16}N_2O_3$]: 367.1059 [M + Na]$^+$; obs. mass 367.1053 [M + Na]$^+$.

2-Amino-4,5-dihydro-4-(2,6-dimethylphenyl)-5-oxopyrano[3,2-*c*]-chromene-3-carbonitrile, 7o. Solid; M.P.: 250–252 °C; IR (KBr): 3099, 1731, 1600, 1454, 1312, 1278, 887 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d$_6$): δ 2.05 (s, 3H), 2.53 (s, 3H), 5.10 (s, 1H), 6.92 (d, 1H, J = 6.10 Hz), 7.00–7.07 (m, 2H), 7.38 (s, 2H), 7.46 (d, 1H, J = 8.2 Hz), 7.50 (d, 1H, J = 7.7 Hz), 7.71 (t, 1H, J = 7.5 Hz), 7.88 (d, 1H, J = 7.9 Hz); ^{13}C-NMR: (75 MHz, DMSO-d$_6$): δ 18.75, 21.43,

31.89, 55.59, 56.50, 103.40, 112.95, 117.05, 119.35, 122.75, 125.19, 127.32, 128.88, 130.90, 133.41, 136.65, 137.73, 137.84, 152.60, 153.96, 158.44, 159.83; HRMS: mass calculated for $[C_{21}H_{16}N_2O_3]$: 367.1059 $[M + Na]^+$; obs. mass: 367.1053 $[M + Na]^+$.

4-(4-(Allyloxy)phenyl)-2-amino-4,5-dihydro-5-oxopyrano[3,2-*c*]-chromene-3-carbonitrile, 7p. Solid; M.P.: 225–228 °C; IR (KBr): 3111, 1739, 1653, 1453, 1401, 1252, 1043 cm^{-1}; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 4.39 (s, 1H), 4.52 (d, 2H, J = 5.1 Hz), 5.23 (dd, 1H, J = 1.2 & 9.3 Hz), 5.37 (dd, 1H, J = 1.5 & 17.28 Hz), 5.96–6.08 (m, 1H), 6.88 (d, 2H, J = 8.6 Hz), 7.16 (d, 2H, J = 8.5 Hz), 7.38 (s, 2H), 7.46 (d, 1H, J = 8.2 Hz), 7.50 (d, 1H, J = 7.6 Hz), 7.71 (t, 1H, J = 7.2 Hz), 7.89 (d, 1H, J = 6.8 Hz); ^{13}C-NMR: (75 MHz, DMSO-d_6): δ 36.62, 58.63, 68.63, 104.72, 113.47, 115.04, 117.02, 117.85, 119.77, 122.92, 125.13, 129.21, 133.34, 134.22, 136.00, 152.55, 153.58, 157.74, 158.39, 160.01; HRMS: mass calculated for $[C_{22}H_{16}N_2O_4]$: 395.1008 $[M + Na]^+$; obs. mass 395.1002 $[M + Na]^+$.

2-Amino-6-methyl-5-oxo-4-[4-(propan-2-yl)phenyl]-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile, 8b. Off-white solid; M.P.: 226–228 °C; IR (KBr): 3390, 3315, 2947, 2201, 1640, 1605, 860, 765 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.14 (s, 3H), 1.17 (s, 3H), 2.84 (m, 1H), 3.55 (s, 3H), 4.50 (s, 1H), 6.90 (s, 2H), 7.06 (d, 2H, J = 8 Hz), 7.12 (d, 2H, J = 8 Hz), 7.28 (t, 1H, J = 7.5 Hz), 7.41 (d, 1H, 8.6 Hz), 7.59 (t, 1H, J = 8 Hz), 8.1 (d, 1H, J = 7.8 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 24.18, 29.59, 33.60, 37.23, 58.87, 109.82, 113.47, 114.57, 120.15, 122.23, 122.90, 126.45, 127.69, 131.51, 138.99, 141.83, 147.04, 150.67, 159.38, 160.46 ppm; HRMS: mass calculated for $[C_{23}H_{21}N_3O_2]$: 394.1531 $[M + H]^+$; obs. mass: 394.1526 $[M + H]^+$.

2-Amino-4-(4-cyanophenyl)-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile, 8d. Pale yellow solid; M.P.: 282–284 °C; IR (KBr): 3385, 3300, 3058, 2926, 2215, 1672, 1610, 854, 765 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.54 (s, 3H), 4.62 (s, 1H), 7.15 (s, 2H), 7.30 (t, 1H, J = 7.6 Hz), 7.59–7.65 (m, 3H), 8.03 (d, 1H, J = 7.6 Hz), 7.39 (s, 1H), 7.42 (s, 1H), 7.45 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 29.61, 37.90, 57.31, 66.84, 108.31, 110.36, 113.21, 114.77, 118.83, 119.67, 122.41, 123.00, 128.97, 131.92, 132.36, 139.18, 149.86, 151.03, 159.40, 160.28 ppm; HRMS: mass calculated for $[C_{21}H_{14}N_4O_2]$: 355.1195 $[M + H]^+$; obs. mass: 355.1195 $[M + H]^+$.

2-Amino-5,6-dihydro-4-(4-hydroxyphenyl)-6-methyl-5-oxo-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile, 8f. Off-white solid; M.P.: 278–280 °C; IR (KBr): 3440, 3387, 3292, 3070, 2922, 2209, 1672, 1610, 854, 765 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.54 (s, 3H), 4.41 (s, 1H), 6.65 (d, 2H, J = 6.9 Hz), 7.00 (d, 2H, J = 7.1 Hz), 7.22 (s, 2H), 7.39 (t, 1H, J = 7.8 Hz), 7.56 (d, 1H, J = 7.6 Hz), 7.70 (t, 1H, J = 7.1 Hz), 8.01 (d, 1H, J = 7.1 Hz), 9.29 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 29.75, 36.94, 58.78, 110.03, 113.22, 115.41, 115.50, 120.39, 122.61, 128.97, 131.98, 135.16, 139.00, 150.26, 156.65, 159.28, 160.30 ppm; HRMS: mass calculated for $[C_{20}H_{15}N_3O_3]$: 346.1192 $[M + H]^+$ and 368.1011 $[M + Na]^+$; obs. mass: 346.1179 $[M + H]^+$ and 368.1006 $[M + Na]^+$.

2-Amino-6-methyl-5-oxo-4-[4-(prop-2-en-1-yloxy)phenyl]-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile, 8g. White solid; M.P.: 226–228 °C; IR (KBr): 3379, 3313, 2939, 2189, 1665, 1599, 1384, 1257, 1125, 832, 751 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.54 (s, 3H), 4.47 (s, 1H), 4.51 (d, 2H, J = 5.2 Hz), 5.22 (dd, 1H, J = 10.4 & 1.4 Hz), 5.37 (dd, 1H, J = 17.3 & 1.6 Hz), 5.95–6.00 (m, 1H), 6.85 (d, 2H, J = 8.7 Hz), 7.12 (d, 2H, J = 8.6 Hz), 7.39 (t, 1H, J = 7.7 Hz), 7.56 (d, 1H, J = 8.6 Hz), 7.70 (t, 1H, J = 8 Hz), 8.02 (d, 1H, J = 8.1 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 29.76, 36.97, 58.55, 68.63, 109.77, 113.18, 114.93, 115.44, 117.80, 120.32, 122.65, 129.01, 132.06, 134.27, 137.00, 139.04, 150.37, 157.50, 159.30, 160.28, 160.89 ppm; HRMS: mass calculated for $[C_{23}H_{19}N_3O_3]$: 386.1499 $[M + H]^+$; obs. mass: 386.1505 $[M + H]^+$.

2-Amino-4-(1,3-benzodioxol-5-yl)-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile, 8i. Off-white solid; M.P.: 276–278 °C; IR (KBr): 3394, 3340, 3180, 2209, 1648, 1260, 1140, 790 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.56 (s, 3H), 4.47 (s, 1H), 5.96 (s, 2H), 6.69 (s, 1H), 6.75 (s, 1H), 6.80 (s, 1H), 7.27 (s, 2H), 7.40 (s, 1H), 7.59 (s, 1H), 7.71 (s, 1H), 8.03 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 29.78, 37.45, 58.47, 101.36, 108.46, 108.52, 109.52, 113.20, 115.46, 120.20, 121.09, 122.65, 122.69, 132.10, 138.86, 139.11, 146.48, 147.62, 150.48, 159.30, 160.29 ppm; HRMS: mass calculated for $[C_{21}H_{15}N_3O_4]$: 374.1141 $[M + H]^+$ and 396.0960 $[M + Na]^+$; obs. mass: 374.1135 $[M + H]^+$ and 396.0955 $[M + Na]^+$.

2-Amino-5,6-dihydro-6-methyl-5-oxo-4-(thiophen-2-yl)-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile, 8k. Yellow solid; M.P.: 278–280 °C; IR (KBr): 3350, 3144, 2189, 1650, 1610, 1475, 1410, 1060, 847 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.61 (s, 3H), 4.90 (s, 1H), 6.85 (s, 1H), 6.98 (s, 1H), 7.04 (s, 2H), 7.10 (s, 1H), 7.27 (t, 1H, J = 7.4 Hz), 7.41 (d, 1H, J = 7.4 Hz), 7.59 (t, 1H, J = 7.3 Hz), 7.99 (d, 1H, J = 7.6 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 29.60, 32.43, 58.91, 109.63, 113.49, 114.27, 122.20, 123.02, 124.12, 124.79, 126.77, 131.48, 138.96, 148.38, 150.43, 159.76, 160.47 ppm; HRMS: mass calculated for $[C_{18}H_{14}N_3O_2S]$: 336.0807 $[M + H]^+$; obs. mass: 355.0795 $[M + H]^+$.

2-Amino-4-cyclohexyl-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano-[3,2-*c*]quinoline-3-carbonitrile, 8l. Off-white solid; M.P.: 272–274 °C; IR (KBr): 3390, 3327, 2940, 2190, 1640, 1590, 1470, 1280, 880, 789 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.93–1.03 (m, 3H), 1.13–1.25 (m, 1H), 1.35–1.43 (m, 1H), 1.60–1.75 (m, 6H), 3.40 (s, 1H), 3.64 (s, 3H), 7.21 (s, 2H), 7.35 (t, 1H, J = 7.4 Hz), 7.58 (d, 1H, J = 8.6 Hz), 7.69 (t, 1H, J = 7.4 Hz), 7.93 (d, 1H, J = 7.9 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 26.03, 26.45, 26.68, 27.32, 29.92, 31.08, 37.51, 43.64, 52.83, 110.04, 113.22, 115.45, 121.72, 122.33, 122.60, 131.84, 138.90, 151.81, 160.63, 161.86 ppm; HRMS: mass calculated for $[C_{20}H_{21}N_3O_2]$: 336.1712 $[M + H]^+$ and 358.1531 $[M + Na]^+$; obs. mass: 336.1697 $[M + H]^+$ and 358.1526 $[M + Na]^+$.

2-Amino-4-(3,4-dimethoxyphenyl)-6-methyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile, 8n. Off-white solid; M.P.: 264–266 °C; IR (KBr): 3379, 3318, 3186, 3043, 2945, 2187, 1662, 1599, 1464, 1384, 848, 755 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.55 (s, 3H), 3.70 (s, 6H) 4.48 (s, 1H), 6.67 (d, 1H, J = 8 Hz), 6.85 (d, 2H), 7.24 (s, 2H), 7.39 (t, 1H, J = 7.5 Hz), 7.56 (d, 1H, J = 8.6 Hz), 7.71 (t, 1H, J = 8.0 Hz), 8.02 (d, 1H, J = 7.8 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 29.79, 37.30, 56.00, 58.48, 109.69, 112.23, 112.44, 113.20, 115.46, 119.84, 120.32, 122.66, 132.07, 137.37, 139.07, 145.72, 148.20, 148.85, 150.40, 159.34, 160.35 ppm; HRMS: mass calculated for $[C_{22}H_{19}N_3O_4]$: 412.1273 $[M + Na]^+$; obs. mass: 412.1258 $[M + Na]^+$.

2-Amino-7-(dimethylamino)-4-(3-nitrophenyl)-4*H*-chromene-3-carbonitrile, 10d. White solid; M.P.: 198–201 °C; IR (KBr): 3414, 3325, 3170, 2958, 2215, 1640, 1580, 1360, 1220, 1125, 780 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.88 (s, 6H), 4.71 (s, 1H), 6.26–6.37 (m, 3H), 6.36 (d, 1H, J = 8.6 Hz), 6.68 (d, 1H, J = 8 Hz), 7.46 (t, 1H, J = 7.9 Hz), 7.53 (d, 1H, J = 7.8 Hz), 7.93 (s, 1H), 7.99 (d, 1H, J = 8 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 40.32, 57.11, 99.27, 108.93, 109.63, 120.48, 121.82, 122.45, 129.47, 129.66, 134.16, 148.43, 148.47, 149.46, 150.62, 160.59 ppm; HRMS: mass calculated for $[C_{18}H_{16}N_4O_3]$: 337.1301 $[M + H]^+$ and 359.1120 $[M + Na]^+$; obs. mass: 337.1295 $[M + H]^+$ and 359.1115 $[M + Na]^+$.

2-Amino-4-(benzo[*d*][1,3]dioxol-6-yl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile, 10i. Yellowish solid; M.P.: 237–240 °C; IR (KBr): 3375, 3387, 3310, 3092, 2927, 2195, 1662, 1599, 840, 755 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.87 (s, 6H), 4.45 (s, 1H), 5.88 (d, 2H, J = 5.1 Hz), 6.14 (s, 1H), 6.20 (d, 1H, J = 2.1 Hz), 6.37 (m, 2H), 6.53 (s, 1H), 6.64–6.73 (m, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 40.41, 57.74, 99.08, 101.00, 107.98, 108.03, 109.53, 110.70, 120.76, 129.64, 140.65, 146.37, 147.91, 149.37, 150.40, 160.46 ppm; HRMS: mass calculated for $[C_{19}H_{17}N_3O_3]$: 336.1348 $[M + H]^+$ and 358.1168 $[M + Na]^+$; obs. mass: 336.1341 $[M + H]^+$ and 358.1158 $[M + Na]^+$.

2-Amino-7-(dimethylamino)-4-(4-methylphenyl)-4*H*-chromene-3-carbonitrile, 10k. Off-white solid; M.P.: 240–242 °C; IR (KBr): 3390, 3324, 3181, 2959, 2203, 1695, 1604, 1384, 1176, 1053, 839, 762 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H), 2.86 (s, 6H), 4.47 (s, 1H), 5.97 (s, 2H), 6.21 (s, 1H), 6.32 (d, 1H, J = 8 Hz), 6.67 (d, 1H, J = 8.7 Hz), 6.99 (s, 4H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 21.07, 40.40, 58.30, 99.17, 109.49, 110.80, 127.69, 129.19, 129.65, 135.90, 143.32, 149.40, 150.29, 160.28 ppm; HRMS: mass calculated for $[C_{19}H_{19}N_3O]$: 306.1606 $[M + H]^+$ and 328.1426 $[M + Na]^+$; obs. mass: 306.1601 $[M + H]^+$ and 328.1420 $[M + Na]^+$.

2-Amino-7-(dimethylamino)-4-[4-(propan-2-yl)phenyl]-4*H*-chromene-3-carbonitrile, 10l. Off-white solid; M.P.: 226–228 °C; IR (KBr): 3429, 3310, 3181, 2957, 2197, 1633, 1525, 1394, 1233, 1114, 1032, 866, 786 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.85 (s, 6H), 3.63 (s, 3H), 3.76 (s, 3H), 4.96 (s, 1H), 6.19 (brs, 3H), 6.33 (d, 1H, J = 8.4 Hz), 6.48 (s, 1H), 6.63 (d, 1H, J = 8.2 Hz), 6.78–6.83 (m, 2H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 24.33, 24.35, 33.48, 40.44, 56.98, 99.00, 109. 88, 111.21, 121.37, 126.88, 127.65, 129.90, 144.56, 146.96, 149.44, 150.64, 160.86 ppm; HRMS: mass calculated for $[C_{21}H_{23}N_3O]$: 334.1919 $[M + H]^+$ and 356.1739 $[M + Na]^+$; obs. mass: 334.1914 $[M + H]^+$ and 356.1728 $[M + Na]^+$.

2-Amino-7-(dimethylamino)-4-(thiophen-3-yl)-4*H*-chromene-3-carbonitrile, 10m. Creamy solid; M.P.: 217–220 °C; IR (KBr): 3414, 3292, 3170, 2915, 2190, 1640, 1515, 1380, 1210, 1100, 1045, 840, 760 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.88 (s, 6H), 4.88 (s, 1H), 6.20 (s, 1H), 6.42 (d, 1H, J = 8.2 Hz), 6.63 (s, 2H), 6.86–6.91 (s, 3H), 7.19 (d, 1H, J = 5.6 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 35.85, 40.37, 99.05, 109.48, 110.43, 124.03, 124.79, 126.73, 129.61, 149.18, 150.65, 151.91, 160.79 ppm; HRMS: mass calculated for $[C_{16}H_{15}N_3OS]$: 298.1014 $[M + H]^+$ and 320.0834 $[M + Na]^+$; obs. mass: 298.1009 $[M + H]^+$ and 320.0750 $[M + Na]^+$.

2-Amino-7-(dimethylamino)-4-[4-(prop-2-en-1-yloxy)phenyl]-4*H*-chromene-3-carbonitrile, 10n. Yellowish solid; M.P.: 183–185 °C; IR (KBr): 3427, 3321, 3190, 2930, 2195, 1634, 1540, 1398, 1238, 1116, 1011, 818, 786 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.84 (s, 6H), 4.44 (s, 1H), 4.46 (s, 1H), 4.47 (s, 1H), 5.20 (dd, J = 1H, 10.1 & 1.3 Hz), 5.33 (dd, 1H, J = 16.6 & 1.5 Hz), 5.90–6.10 (m, 1H), 6.19 (d, 1H, J = 2.3 Hz), 6.33–6.36 (m, 3H), 6.71 (d, 1H, J = 8.5 Hz), 6.76 (d, 2H, J = 8.6 Hz), 7.02 (d, 2H, J = 8.6 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 39.60, 40.43, 57.27, 68.66, 98.99, 109.87, 111.31, 115.10, 117.77, 121.28, 128.83, 129.90, 134.31, 139.35, 149.41, 150.64, 157.35, 160.72 ppm; HRMS: mass calculated for $[C_{21}H_{21}N_3O_2]$: 348.1712 $[M + H]^+$; obs. mass: 348.1707 $[M + H]^+$.

2-Amino-7-(dimethylamino)-4-(4-hydroxyphenyl)-4*H*-chromene-3-carbonitrile, 10o. White solid; M.P.: 234–237 °C; IR (KBr): 3440, 3385, 3315, 3165, 2210, 1685, 1595, 1340, 1160, 1085, 845, 780 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.85 (s, 6H), 4.47 (s, 1H), 6.21 (s, 1H), 6.45 (d, 1H, J = 8.7 Hz), 6.66–6.77 (m, 5H), 6.95 (d, 2H, J = 8.1 Hz), 9.24 (brs, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 40.44, 57.41, 98.96, 109.83, 111.58, 115.63, 12.35, 128.80, 129.91, 137.49, 149.37, 150.55, 156.44, 160.64 ppm; HRMS: mass calculated for $[C_{18}H_{17}N_3O_2]$: 308.1399 $[M + H]^+$ and 330.1218 $[M + Na]^+$; obs. mass: 306.1237 $[M + H]^+$ and 328.1056 $[M + Na]^+$.

5-Amino-7-[4-(prop-2-en-1-yloxy)phenyl]-2,7-dihydropyrano-[3,2-*c*]pyrazole-6-carbonitrile, 12m. Off-white solid; M.P.: 181–184 °C; IR (KBr): 3471, 3258, 2186, 1640, 1404, 1050, 741 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.78 (s, 3H), 4.53 (brs, 3H), 5.25 (d, 1H, J = 10.6 Hz), 5.40 (d, 1H, J = 17.2 Hz), 5.97–6.08 (m, 1H), 6.81 (brs, 2H), 6.88 (d, 1H, J = 8.2 Hz), 7.06 (d, 1H, J = 8.3 Hz), 12.06 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 10.20, 35.92, 58.07, 68.63, 98.34, 114.96, 117.81, 121.27, 128.93, 134.29, 135.99, 137.12, 155.23, 157.40, 161.17 ppm; HRMS: mass calculated for $[C_{17}H_{16}N_4O_2]$: 309.1352 $[M + H]^+$ and 331.1171 $[M + Na]^+$; obs. mass: 309.1346 $[M + H]^+$ and 331.1165 $[M + Na]^+$.

5-Amino-7-(3,5-dimethylphenyl)-2,7-dihydropyrano[3,2-*c*]-pyrazole-6-carbonitrile, 12n. Off-white solid; M.P.: 211–214 °C; IR (KBr): 3300, 3119, 2189, 1640, 1494, 1408, 1048, 760 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.79 (s, 3H), 2.23 (s, 6H), 4.49 (s, 1H), 6.75 (s, 2H), 6.80 (s, 2H), 6.85 (s, 1H), 12.05(s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 10.24, 21.41, 36.65, 57.90, 98.19, 121.25, 125.63, 128.71, 136.02, 137.75, 144.86, 155.23, 161.30 ppm; HRMS: mass calculated for $[C_{16}H_{16}N_4O]$: 281.1402 $[M + H]^+$ and 303.1222 $[M + Na]^+$; obs. mass: 281.1397 $[M + H]^+$ and 303.1216 $[M + Na]^+$.

5-Amino-7-(5-methylfuran-3-yl)-2,7-dihydropyrano[3,2-*c*]pyrazole-6-carbonitrile, 12o. Off-white solid; M.P.: 191–194 °C; IR (KBr): 3247, 3140, 2197, 1647, 1497, 1409, 1038, 786 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.00 (s, 3H), 2.19 (s, 3H), 4.69 (s, 1H), 5.95 (s, 1H), 6.03 (d, 2H, J = 2.8 Hz), 6.92 (s, 2H), 12.13 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 10.09, 13.81, 30.39, 54.64, 95.73, 106.76, 106.76, 121.07, 136.30, 151.19, 154.34, 155.26, 161.91 ppm; HRMS: mass calculated for $[C_{13}H_{12}N_4O_2]$: 257.1039 $[M + H]^+$ and 279.0858 $[M + Na]^+$; obs. mass: 257.1025 $[M + H]^+$ and 279.0852 $[M + Na]^+$.

5-Amino-7-(4-methylthiophen-3-yl)-2,7-dihydropyrano[3,2-*c*]-pyrazole-6-carbonitrile, 12p. Off-white solid; M.P.: 210–213 °C; IR (KBr): 3440, 3180, 2186, 1660, 1601, 1494, 1405, 1060, 840 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.83 (s, 3H), 2.22 (s, 3H), 5.01 (s, 1H), 6.77 (d, 1H, J = 5.1 Hz), 6.83 (brs, 2H), 7.26 (d, 2H, J = 5.2 Hz), 12.14 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 10.07, 13.98, 29.67, 58.09, 98.21, 121.06, 123.83, 130.18, 133.18, 136.38, 142.87, 154.92, 160.88 ppm; HRMS: mass calculated for [$C_{13}H_{12}N_4OS$]: 273.0810 $[M + H]^+$ and 295.0630 $[M + Na]^+$; obs. mass: 273.0805 $[M + H]^+$ and 295.0624 $[M + Na]^+$.

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