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Tris-hydroxymethylaminomethane (THAM): An efficient organocatalyst in diversity-oriented and environmentally benign synthesis of spirochromenes

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ABSTRACT

Tris-hydroxymethylaminomethane has been demonstrated to be an efficient organo-catalyst in diversity-oriented synthesis of medicinally prevalent spirochromenes by one-pot, three-component reactions between isatins, malononitrile, and enolizable C−H acids like dimedone, 4-hydroxycoumarin, 4-hydroxy-N-methylquinolin-2-one, or in situ generated 2-methylpyrazolon-2-one. Biodegradability and extremely low cost of the catalyst are the noteworthy features of this chromatography-free protocol.

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1. Introduction

It is well known that multicomponent reactions constitute a precise synthetic tool for an easy access to multifunctionalized and structurally related drug-like molecules [1,2]. On the other hand, green chemistry principles are playing very dominating role in today's organic synthesis [3]. Consequently, the use of multicomponent reactions in library synthesis of biologically important molecules obeying the demands of green chemistry has become the focal point of current day research [4]. Three main variations involved in green multicomponent synthesis of target molecules are the reaction medium, the energy source, and the catalyst. Compared to reaction medium and energy sources, catalyst can play a very important role in green organic synthesis. Most of the early developments in the field of catalysis were focused on the choice of heterogeneous catalysts; however, in the past few years use of organocatalysts with their well-documented advantages such as ready availability, low cost, low toxicity, and lack of sensitivity toward moisture as well as oxygen is considered as one of the possible solutions to green organic synthesis [5]. A few of the nontoxic organocatalysts practiced in today's organic synthesis are Baker's yeast [6], β-cyclodextrin [7], proline [8], chitosan [9], meglumine [10], thiourea dioxide [11], and so forth. At the same time, search for a new organocatalyst is a constant endeavor.

Indole is the most ubiquitous heterocyclic moiety present in a large number of bioactive natural products [12]. It is known that sharing of indole-3-carbon atom in the formation of spiroindolines and the presence of carbonyl group at C-2 in spiroindolines generate spiro-2-oxindoles (spirooxindoles), which occupy a special place in organic and medicinal chemistry. Several compounds containing spirooxindole as the structural unit of natural and synthetic origin are known to exhibit antimicrobial, antioxidant,

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antitubercular, anticancer, anti-HIV and anti-inflammatory activities (Fig. 1) [13]. Sharing of C-3 in spirooxindoles with pyran ring generates pyran annulated spirooxindoles (spiropyrans or spirochromenes), which are also known to exhibit useful properties like anticoagulant, spasmolytic, diuretic, anticancer, and antianaphylactic activities [14]. The biological potential of spirochromenes has always been the driving force for the chemists to develop efficient protocols for their synthesis.

Classical synthesis of spirochromenes involve one-pot, three-component condensation between isatin, malononitrile, and enolizable C—H acids like dimedone, barbituric acid, naphthols, 4-hydroxycoumarin, and so forth, and the literature is enumerated with several protocols for their synthesis. A focused literature survey toward enviroeconomic protocols developed for the synthesis of spirochromenes revealed that a few catalyst-free protocols have been reported earlier [15]. Notably all the catalyst-free protocols developed for the synthesis of spirochromenes require thermal or electrochemical activation. These reports indirectly project the necessity of a catalyst, an alternate energy source, or the reaction medium for the synthesis of spirochromenes at ambient temperature. During our search on protocols operable at ambient temperature it was noticed that a range of catalysts and reaction media have been reported for their synthesis [16–18]. Each of the reported method has its own merits, whereas a few of the reported protocols suffer from the drawbacks as regards the use of expensive or difficult to prepare catalyst or the reaction medium, and to the best of our knowledge there are only a few protocols wherein the problems of economics and environmental protection have been addressed successfully [18a–c]. With our continued interest in the development of organocatalyzed protocols for the synthesis of chromene-based heterocycles [19], we set out to develop an enviroeconomic and diversity-oriented protocol for the synthesis of spirochromenes.

2. Results and discussion

Tris-hydroxymethylaminomethane (THAM) (Scheme 1) is a biodegradable, noncorrosive, physiologically inert, and thermally stable compound available commercially at extremely low cost [20a]. It contains an amino and three primary alcoholic groups and when dissolved in water or water—ethanol medium, it generates basic reaction medium [20b]. In the recent past, we have reported its use as an efficient organocatalyst in the diversity-oriented synthesis of 2-amino-4H-chromenes by multicomponent condensation between aldehydes and two different C—H acids [19b]. In continuation of the same, we report herein the use of THAM in the diversity-oriented synthesis of spirochromenes by three-component reaction between isatins, malononitrile, and dimedone, 4-hydroxycoumarin, 4-hydroxy-N-methylquinolone, and in situ generated 2-methylpyrazolon-2-one (Scheme 1).

We began our studies with optimization of the reaction conditions for the synthesis of spiro[indoletetrahydrochromene], **4a**, as a model spirochromene (Scheme 1). Accordingly, to an equimolar and well-stirred solution of isatin, **1a**, malononitrile, **2**, and dimedone, **3a**, (1 mmol each) in ethanol (95%, 4 mL) was added THAM (30 mol %) as the catalyst. Stirring was continued at room temperature and progress of the reaction was monitored by thin layer chromatography (TLC). Upon completion of the reaction (4 h), water (5 mL) was added and the resultant solid product was isolated by simple filtration. On the basis of physical and spectral studies, resultant product was identified to be the desired spirochromene, **4a**. In pursuance to make this protocol greener, the model reaction was
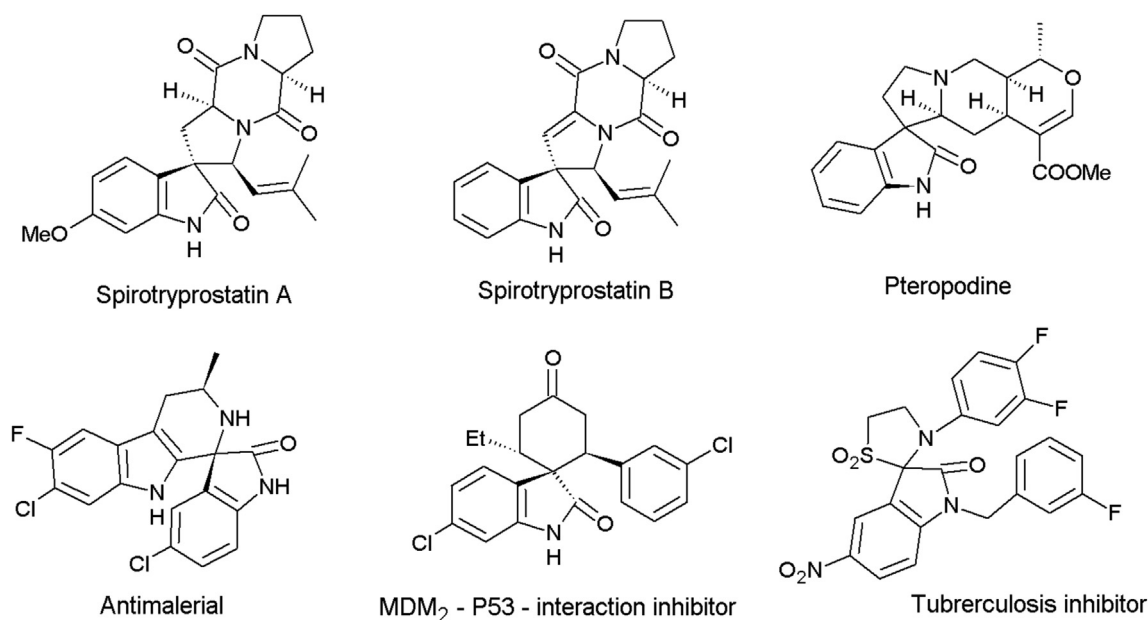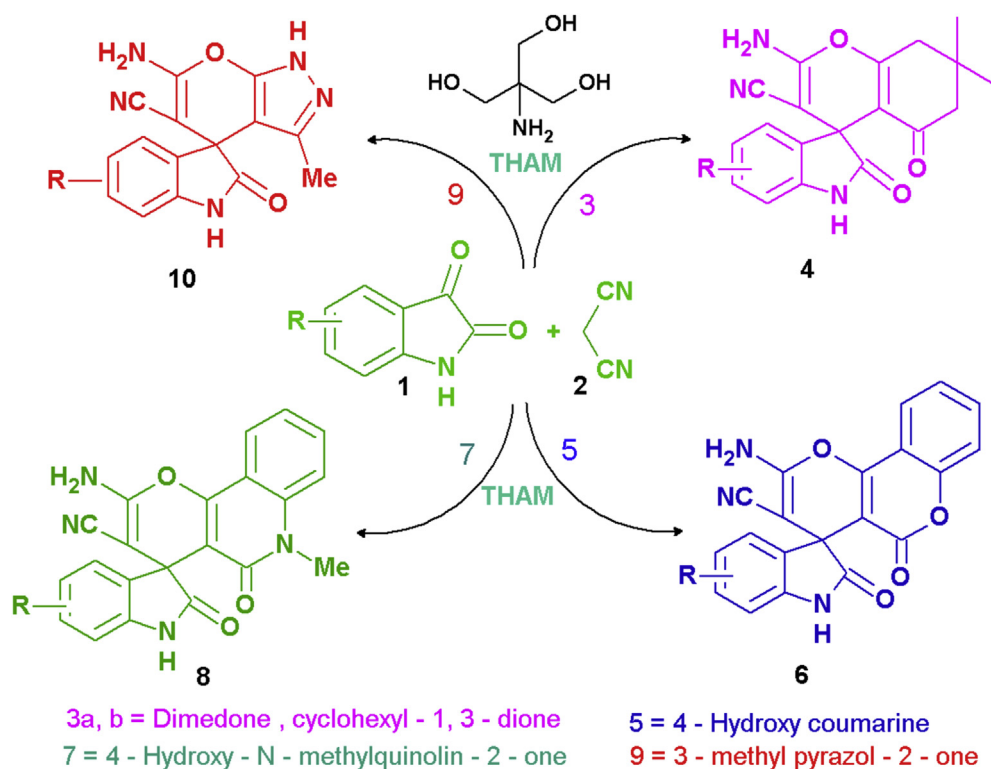

Fig. 1. Representative structures of biologically active spirooxindoles.

Scheme 1. Diversity-oriented synthesis of spirochromenes using THAM as the catalyst.

repeated using water and water–ethanol (1:1, v/v) as the reaction media. However, the desired product, **4a**, was obtained in slightly lower yields (76% and 82%, respectively). Further optimization of the reaction conditions with respect to catalyst loading revealed that with the use of less than 30 mol % of the catalyst the reaction does not go to completion. In short, use of THAM (30 mol %) as the catalyst and ethanol (95%) as the reaction medium was observed to be the best suited reaction conditions for the optimum yield of the desired product, **4a**. To check the scope of the reaction conditions, another reaction was performed by replacing the dimedone component from the model reaction with 5-methylcyclohexane-1,3-dione, **3b**. In this case too the expected spirochromene, **4g**, resulted in excellent yield. To examine the generality of the reaction conditions, various substituted isatins were then allowed to undergo reaction with malononitrile and dimedone **3a** as well as **3b**. In all the cases, corresponding spirochromenes, **4b**–**i**, were obtained in excellent yield following simple workup procedure. Most gratifyingly, they were noticed to be pure for all analytical purposes.

From the plausible mechanism (Scheme 2), it is apparent that the enolic form of cyclic-1,3-dione is actually involved in the generation of a pyran ring in spirochromenes. On the basis of this hypothesis we surmised that 4-hydroxycoumarin, **5**, and 4-hydroxy-N-methylquinolin-2-one, **7** (Scheme 1), being enolic forms of coumarin-2,4-dione and N-methylquinolin-2,4-dione, respectively, the replacement of dimedone component used in the synthesis of **4a** by **5** and **7** would furnish spiro

[indole-pyrano[3,2-c]chromene], **6a**, and spiro[indole-pyrano[3,2-c]quinolone], **8a**, respectively. The salient objective to undertake this extension was associated with the anti-rheumatic and anticancer activity associated with the compounds containing pyrano[3,2-c]chromene and pyrano[3,2-c]quinolone as the structural units [21].

Using reaction conditions established for the synthesis of **4a**, two model reactions were performed using isatin, malononitrile, and **5**, or **7**, as the substrates (Scheme 1). Most gratifyingly, both the reactions proceeded smoothly (TLC) and the desired spirochromene, **6a**, and spiroquinoline, **8a**, were obtained in decent yields. Under the same reaction conditions, various substituted isatins were also reacted with malononitrile and 4-hydroxycoumarin as well as 4-hydroxy-N-methylquinolin-2-one when corresponding spirooxindole derivatives, **6b**–**f** and **8b**–**g**, were obtained in good to excellent yields (Table 1).

Similar to pyrano[3,2-c]chromene and pyrano[3,2-c]quinolone, dihydropyrano[2,3-c]pyrazole represents an interesting template in medicinal chemistry and several compounds containing dihydropyrano[2,3-c]pyrazole as the structural motif are known to possess antimicrobial [22a], anti-inflammatory [22b], and molluscicidal activity [22c]. Our earlier success in the synthesis of spiro[indole-pyrano[3,2-c]chromenes], **6**, and spiro[indole-pyrano[3,2-c]quinolones], **8**, prompted us to extend our studies toward the synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazol]-2-ones, **10**. A literature pursuance revealed that there are few early reports on the synthesis of title compounds, **10**, involving the reaction between isatin, malononitrile,
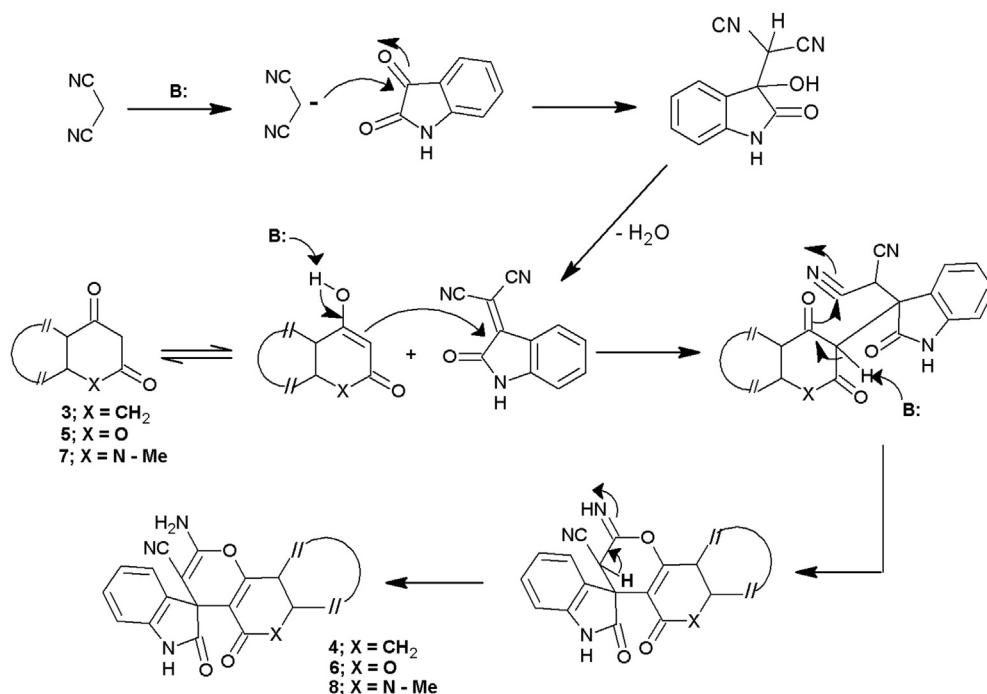
Scheme 2. Plausible mechanism for the formation of spirochromenes.

and 2-methylpyrazolon-2-one [23]. In all these methods, necessary 2-methylpyrazolon-2-one was generated in situ at ambient temperature by the reaction between a β-keto ester and hydrazine hydrate under catalyst-free condition. Taking recourse to these reports, a pseudo four-component reaction was carried out between isatin, malononitrile, ethyl acetoacetate, and hydrazine hydrate (1 mmol, each), using the reaction conditions established for the synthesis of spirochromenes, **4** (Scheme 1). The reaction proceeded smoothly and upon its completion, desired spiro[indoline-3,4′-pyrano-[2,3-c]pyrazol]-2-one, **10a**, was obtained in decent yield. Subsequent reactions of substituted isatins with malononitrile and in situ generated 2-methylpyrazolon-2-one, **9**, also furnished expected spiro [indoline-3,4′-pyrano[2,3-c]pyrazol]-2-ones, **10b**–**e**, in decent yields (Table 1). Noteworthy feature of the protocol developed for the synthesis of spirochromenes **4**, **6**, **8**, and **10** is that all the products were isolated by a simple procedure and none of them required chromatographic purification.

After establishing a general protocol for the diversity-oriented synthesis of spirochromenes from environmental point of view, it was quite logical to check the possibility of reuse of the catalyst. However, the catalyst, THAM, being soluble in water, it was surmised that making this nontoxic and biodegradable catalyst reusable would certainly be more expensive than the cost of the catalyst itself. Thus, no attempts were made to check reusability of the catalyst. Finally, a comparison was made between the present protocol and many other protocols reported earlier for the synthesis of **4a** as a model compound. From the results summarized in Table 2, it is evident that the developed

protocol is superior to most of the earlier reported protocols in terms of operational simplicity, yield, cost, easy availability, and environmental compatibility of the catalyst used.
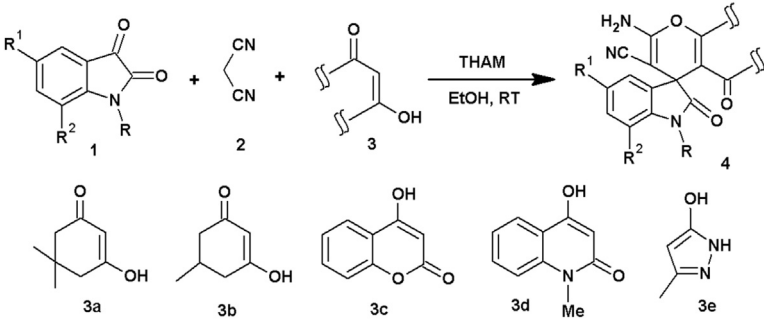
3. Conclusion

We have demonstrated for the first time the use of a commercially available and biodegradable THAM as an efficient organocatalyst in diversity-oriented synthesis of spirochromenes. The protocol mainly exhibits remarkable versatility on various substrates to afford the desired products in good to excellent yields. Ambient reaction conditions, simple workup procedure, and avoidance of conventional purification methods have improved the practical utility of the protocol manifold.

4. Experimental section

4.1. General procedure for the synthesis of spirooxindoles, 4, 6, 8 and 10

To a well-stirred solution of isatin and malononitrile (1 mmol each) in ethanol (95%, 4 mL) was added dimedone, 4-hydroxycoumarin, 4-hydroxy-N-methylquinolin-2-one, or 2-methyl-pyrazol-2-one [generated in situ from ethyl acetoacetate and hydrazine hydrate, 1 mmol each]. To this solution was added THAM (30 mol %) and stirring was continued at ambient temperature. Upon completion of the reaction (TLC), water (5 mL) was added and stirring was continued for 10 min more. Resultant solid product was filtered, washed repeatedly with water, and dried. The

Table 1
THAM catalyzed diversity-oriented synthesis of spirochromenes.[a]

Entry	Isatin (1)			CeH acid (3)	Product	Time (h)	Yield (%)	Reference
	R	R^1	R^2					
1	H	H	H	3a	**4a**	4	94	[18c]
2	H	Me	H	3a	**4b**	4	84	[17b]
3	Me	H	H	3a	**4c**	3.5	86	[18c]
4	H	F	H	3a	**4d**	4	82	[18c]
5	H	NO$_2$	H	3a	**4e**	3	92	[17g]
6	H	Br	Br	3a	**4f**	3.5	89	–
7	H	H	H	3b	**4g**	3	92	–
8	H	Cl	H	3b	**4h**	3.5	83	–
9	H	NO$_2$	H	3b	**4i**	3	95	–
10	H	H	H	3c	**6a**	4	87	[18c]
11	H	Cl	H	3c	**6b**	4	90	[18c]
12	H	Me	H	3c	**6c**	4	85	[16f]
13	H	F	H	3c	**6d**	5	80	[17a]
14	H	NO$_2$	H	3c	**6e**	3	94	[18c]
15	H	H	Cl	3c	**6f**	4	91	–
16	H	Br	Br	3c	**6g**	3	93	–
17	H	Br	H	3c	**6h**	4	89	[18c]
18	H	H	H	3d	**8a**	4	86	[16d]
19	H	Cl	H	3d	**8b**	4	90	–
20	H	Me	H	3d	**8c**	4.5	87	–
21	H	F	H	3d	**8d**	4	84	–
22	H	NO$_2$	H	3d	**8e**	3	92	–
23	H	H	Cl	3d	**8f**	4	90	–
24	H	Br	Br	3d	**8g**	3.5	87	–
25	H	H	H	3e	**10a**	4	84	[18c]
26	Me	H	H	3e	**10b**	4	87	[17g]
27	H	Cl	H	3e	**10c**	5	83	[17g]
28	H	Br	H	3e	**10d**	3	92	[16f]
29	H	NO$_2$	H	3e	**10e**	4	86	[17g]

All the products gave satisfactory spectral data.
[a] Reaction conditions: isatin, malononitrile, and enolizable C−H acid (1 mmol each), THAM (30 mol %), ethanol (95%, 4 mL), rt.

dried solid was washed thrice with hexane−chloroform mixture (1:1, v/v) and dried again. Resultant product did not require any further purification.

4.2. Spectral data of new compounds

2-Amino-5′,7′-dibromo-8,8-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile, **4f**: white solid; mp > 280 °C; IR (KBr): 3357, 2197, 1732 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.03 (d, 6H, J = 2.4 Hz), 2.14 (s, 2H), 2.52 (d, 2H, J = 7.2 Hz), 6.78 (d, 1H, J = 8.1 Hz), 6.95 (s, 1H), 7.09 (br s, 2H), 10.47 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 27.89, 28.04, 32.32, 47.57, 50.54, 57.48, 110.86, 110.96, 117.43, 123.49, 126.38, 128.31, 136.57, 141.35, 159.30, 164.68, 178.23, 195.08 ppm.

2-Amino-2′,5-dioxo-7-methyl-5,6,7,8-tetrahydrospiro [chromene-4,3′-indoline]-3-carbonitrile, **4g**: white solid; mp > 280 °C; IR (KBr): 3364, 2192, 1721 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.01 (d, 3H, J = 5.1 Hz), 2.05 (m, 1H), 2.24 (t, 2H, J = 15 Hz), 2.64 (t, 2H, J = 18.3 Hz), 6.78 (d, 1H, J = 7.2 Hz), 6.88 (d, 1H, J = 7.3 Hz), 6.94 (m, 1H), 7.12 (t, 1H, J = 7.5 Hz), 7.19 (br s, 2H), 10.40 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.50, 27.81, 34.68, 34.92, 44.78, 47.31, 58.92, 109.61, 111.86, 112.07, 117.75, 122.02, 123.45, 123.57, 128.51, 134.93, 142.47, 159.14, 165.24, 165.79, 178.6, 195.3 ppm.

2-Amino-2′,5-dioxo-7′-chloro-7-methyl-5,6,7,8-tetrahydro-spiro[chromene-4,3′-indoline]-3-carbonitrile, **4h**: white solid; mp > 280 °C; IR (KBr): 3342, 2202, 1736 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.03 (d, 3H, J = 6 Hz), 2.01−2.08 (m, 1H), 2.24−2.36 (m, 2H), 2.26 (d, 2H, J = Hz), 6.76 (d, 1H, J =

Table 2
Comparison of THAM catalyzed synthesis of **4a** with earlier reported protocols.

Entry	Catalyst	Solvent	Time	Yield (%)	Reference
1	Fe$_3$O$_4$@APTPOSS MNPs	–	45 h	88	[17a]
2	Sulfated choline-based heteropolyanion	Ethanol	45 h	91	[16a]
3	Fe$_2$O$_3$ NPs@SiO$_2$@vitB1-Np[a]	))))), water	10 h	98	[17b]
4	EDDF[b] in PEG 600	SF	12 h	91	[16b]
5	Cesium fluoride	Ethanol	5 h	82	[17c]
6	Nickel oxide nanoparticles	Water	5 h	98	[17e]
7	[Bmim]OH	[Bmim]OH	10 h	96	[16f]
8	Amino-appended β-cyclodextrin	Water	7 h	91	[17h]
9	(DABCO)@mesoporous silica SBA-15	Water	10 h	96	[17f]
10	ZrO$_2$ nanoparticles	SF	1 min	84	[17g]
11	Trisodium citrate trihydrate	Water−EtOH	2 h	92	[18c]
12	Protic guanidinium ionic liquid	SF	5 h	98	[16c]
13	[Bmim]BF$_4$	SF	3 h	94	[16d]
14	(Silica-bonded DBU) Cl	EtOH	2.5 h	97	[17j]
15	FeN$_3$@SiO$_2$ nanoparticles	Water	10 h	95	[17d]
16	CuO nanoparticles	EtOH	8 min	98	[16e]
17	Meglumine	EtOH	18 min	96	[18a]
18	Sodium acetate[c]	EtOH	15 min	95	[18b]
18	THAM	EtOH	4 h	94	This work

[a] Ultrasound.
[b] EDDF: ethylenediammonium diformate.
[c] Grinding.

8.1 Hz), 6.95 (d, 1H, J = 4.5 Hz), 7.08 (s, 1H), 7.12 (br s, 2H), 10.46 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.51, 20.66, 27.71, 27.89, 44.87, 47.60, 58.92, 110.89, 111.48, 123.50, 123.62, 126.46, 128.25, 141.17, 159.21, 165.50, 178.31, 195.08 ppm.

2-Amino-2′,5-dioxo-7-methyl-7′-nitro-5,6,7,8-tetrahydro-spiro[chromene-4,3′-indoline]-3-carbonitrile, **4i**: white solid; mp > 280 °C; IR (KBr): 3365, 2199, 1726 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.02 (s, 3H), 2.00 (s, 1H), 2.24−2.56 (m, 4H), 6.71−7.18 (m, 5H), 10.44 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz):δ 20.55, 27.90, 35.15, 58.92, 111.42, 114, 126.31, 131.10, 159.17, 165.80, 178.24, 195.32 ppm.

2′-Amino-7-chloro-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile, **6f**: off-white solid; mp > 280 °C; IR (KBr): 3361, 2197,1737 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.97 (t, 1H, J = 7.8 Hz), 7.26 (q, 2H, J = 9.3 Hz), 7.54 (q, 2H, J = 8.4 Hz), 7.77 (s, 3H), 7.95 (d, 1H, J = 6.9 Hz), 11.15 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.00, 48.95, 56.50, 56.97, 101.40, 112.89, 114.20, 117.19, 117.28, 123.21, 123.40, 123.85, 125.54, 129.48, 134.28, 135.21, 140.43, 152.56, 155.73, 158.87, 158.99, 177.66 ppm.

2′-Amino-5,7-dibromo-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile, **6g**: white solid; mp > 280 °C; IR (KBr): 3361, 2205, 1734 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.54 (q, 2H, J = 8.4 Hz), 7.65 (d, 2H, J = 10.8 Hz), 7.78 (d, 1H, J = 7.5 Hz), 7.83 (s, 2H), 7.94 (d, 1H, J = 7.8 Hz), 11.19 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.00, 49.40, 56.49, 100.86, 103.07, 113.04, 114.77, 117.19, 117.24, 123.27, 125.52, 127.11, 143.09, 134.29, 136.84, 141.74, 152.60, 156.04, 159.05, 159.09, 177.37 ppm.

2-Amino-6-methyl-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile, **8a**: yellowish solid; mp > 280 °C; IR (KBr): 3420, 2199, 1721, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.48 (s, 3H), 6.84−7.00 (m, 2H), 7.02 (d, 1H, J = 7.2 Hz), 7.17 (t, 1H, J = 7.4 Hz), 7.46 (s, 3H), 7.59 (d, 1H, J = 8.7 Hz), 7.76 (t, 1H, J = 4.5 Hz), 8.06 (d, 1H, J = 7.8 Hz), 10.52 (S, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz):

δ 29.69, 48.65, 57.75, 106.97, 109.68, 112.76, 115.50, 117.89, 122.15, 122.87, 123.88, 128.77, 132.72, 134.74, 139.14, 142.97, 151.96, 159.22, 159.36,178.29 ppm.

2-Amino-6-methyl-5′-chloro-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile, **8b**: brown color solid; mp > 280 °C; IR (KBr):3417, 2192, 1717, 1670 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.49 (s, 3H), 6.80−6.84 (m, 1H), 7.00−7.05 (m, 1H), 7.41−7.46 (m, 1H), 7.53−7.60 (m, 3H), 7.37−7.8 (m, 1H), 8.04 (d, 1H, J = 7.8 Hz), 10.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 29.72, 49.17, 57.19, 106.41, 110.21, 110.32, 111.71, 112.82, 115.09, 115.51, 117.81, 122.89, 122.94, 132.77, 136.38, 136.48, 139.20, 152.17, 159.28, 159.46, 178.38 ppm.

2-Amino-6-methyl-5′-methyl-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile, **8c**: off-white solid; mp > 280 °C; IR (KBr):3420, 2192, 1721,1660 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.19 (s, 3H), 3.46 (s, 3H), 6.93−7.09 (m, 3H), 7.08 (s, 1H), 7.28 (t, 1H, J = 7.5 Hz), 7.45 (t, 1H, J = 7.5 Hz), 7.52 (s, 2H), 7.58 (d, 1H, J = 8.7 Hz), 7.76 (t, 1H, J = 7.2 Hz), 8.08 (d, 1H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 26.94, 29.73, 48.26, 57.33, 106.85, 108.60, 112.74, 115.56, 117.77, 122.90, 123.65, 129.01, 132.08, 133.86, 139.15, 144.45, 151.99, 159.17, 159.47, 176.84 ppm.

2-Amino-6-methyl-5′-fluoro-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile, **8d**: off-white solid; mp > 280 °C; IR (KBr): 3416, 2197, 1721, 1670 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.49 (s, 3H), 6.85 (d, 1H, J = 7.8 Hz), 7.21 (d, 2H, J = 7.8 Hz), 7.44 (t, 1H, J = 7.5 Hz), 7.58 (t, 3H, J = 9.9 Hz), 7.76 (t, 1H, J = 7.5 Hz), 8.06 (d, 1H, J = 7.8 Hz), 10.67 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 29.75, 48.94, 57.02, 106.27, 111.03, 112.86, 115.53, 117.81, 122.91, 122.97, 124.21, 126.16, 128.66, 132.78,136.78, 139.21, 141.93, 152.25, 159.30, 159.49, 178.14 ppm.

2-Amino-6-methyl-5′-nitro-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,3′-indoline]-3-carbonitrile, **8e**:

off-white solid; mp > 280 °C; IR (KBr): 3430, 2192, 1730, 1665, 1520, 1337 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.48 (s, 3H), 7.07 (d, 1H, J = 8.4 Hz), 7.46 (t, 1H, J = 7.5 Hz), 7.59 (d, 1H, J = 8.4 Hz), 7.67 (s, 2H), 7.77 (t, 1H, J = 7.5 Hz), 8.07 (d, 2H, J = 8.7 Hz), 8.17 (d, 1H, J = 8.7 Hz), 11.29 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 29.79, 48.83, 56.19, 105.71, 109.82, 112.91, 115.59, 117.70, 119.94, 123, 123.06, 126.33, 132.90, 135.78, 139.26, 142.98, 149.51, 152.60, 159.39, 159.74, 179 ppm.

2-Amino-6-methyl-7′-chloro-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinoline-4,30-indoline]-3-carbonitrile, **8f**: brown colored solid; mp > 280 °C; IR (KBr):3370, 2200, 1724, 1674 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.49 (s, 3H), 6.90 (t, 1H, J = 7.8 Hz), 7.03 (d, 1H, J = 7.2 Hz), 7.24 (d, 1H, J = 7.8 Hz), 7.45 (t, 1H, J = 7.2 Hz), 7.58 (s, 3H), 7.76 (t, 1H, J=7.5 Hz), 8.06 (d, 1H, J = 3.2 Hz), 10.99 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 29.75, 49.51, 57.11, 106.47, 112.71, 113.97, 115.59, 117.76, 122.66, 122.93, 123, 123.48, 128.90, 132.88, 136.46, 139.18, 140.72, 152.06, 159.26, 159.44, 178.32 ppm.

2-Amino-6-methyl-5′,7′-dibromo-2′,5-dioxo-5,6-dihydro-spiro[pyrano[3,2-c]quinolone-4,3′-indoline]-3-carbonitrile, **8g**: off-white solid; mp > 280 °C; IR (KBr): 3455, 3260, 2200, 1723, 1671 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.50 (s, 3H), 7.42—7.48 (m, 2H), 7.63 (d, 4H, J = 5.7 Hz), 7.77 (t, 1H, J = 7.5 Hz), 8.06 (d, 1H, J = 7.8 Hz), 11.03 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 29.81, 50.02, 56.50, 56.54, 102.85, 105.90, 112.86, 114.38, 115.61, 117.72, 123.03, 126.29, 132.92, 133.50, 138.21, 139.25, 142.05, 152.34, 159.34, 159.57, 178.01 ppm.

Acknowledgments

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.crci.2018.05.005.

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