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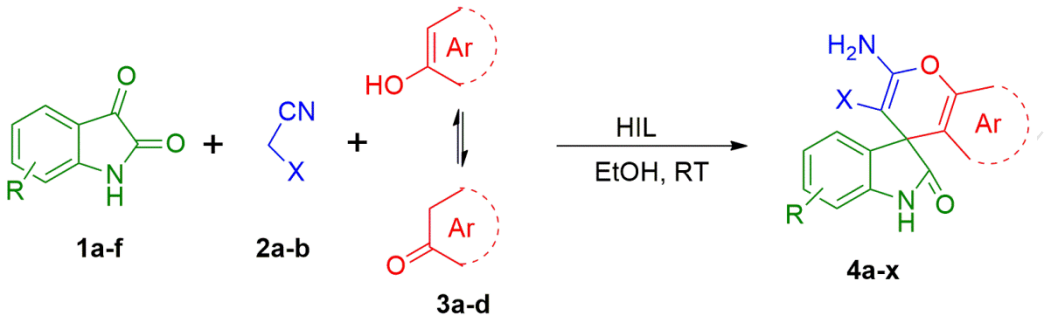
Graphical Abstract



1) Short reaction time
2) Greener process
3) New methodology
4) Shortcutting the product purification process

An efficient approach for the synthesis of spirooxindole derivatives catalyzed by novel sulfated choline based heteropolyanion at room temperature

Shailesh P. Satasia, Piyush N. Kalaria, Jemin R. Avalani, Dipak K. Raval*

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar- 388 120, Gujarat, India

*Corresponding author. Tel.: +91-02692-226856 - Ext. - 208; Fax: +91-02692 236475.
E-mail: shailesh_satasia@yahoo.com

ABSTRACT: A new zwitterionic salt, sulfated choline based heteropolyanion, which was reported earlier by our group, has been found to be very effective for the synthesis of spirooxindole derivatives at room temperature. The heteropolyanion based on sulfated ionic liquid (HIL) showed promising features for the reaction such as shorter reaction time, high product yields (about 90-95%), simple work up, easy removal and reusability of the catalyst for several times without significant loss in its efficiency. This has made the protocol sustainable and economic.

Keywords: Spirooxindoles; Heterogeneous catalyst; Green procedure; Multi-component reactions

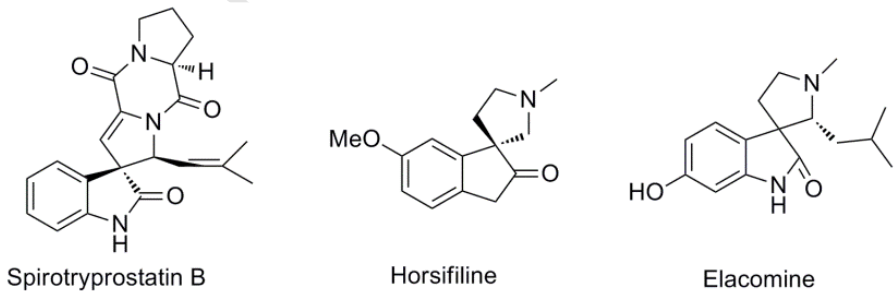
1. Introduction

Green chemistry has attracted much interest in the 21st century. The use of non-hazardous and renewable materials in catalytic protocols for organic synthesis is one of the most important goals of green chemistry.[1] One of the fundamental aspects of green chemistry is linked to the energy conservation involving atom economy and minimum number of steps in synthesis.

Choline based catalysts have exhibited significant activity in organic syntheses.[2] In the present study sulfated choline based heteropolyanion $[Ch\text{-}OSO_3H]_3W_{12}PO_{40}$ (HIL) has been attempted as a novel catalyst for the synthesis of spirooxindole derivatives.

Fast, automated and high throughput generation of organic compounds useful for modern drug discovery process can be synthesized by employing multi-component reactions (MCRs) as the powerful tool.[3] The possibility of performing MCRs with a heterogeneous catalyst could enhance their efficiency from an economic as well as an ecological point of view.[4]

The compounds with spirooxindole ring system are attracting considerable interest as antimicrobial and antitumor agents, and as inhibitors of the human NKI receptor, as well as being found in a number of alkaloids like spirotryprostatin, (+)-elacomine, and horsifiline (Scheme 1).[5] The conformational restriction associated to the structural rigidity significantly affects their biological activity.[6]



Scheme 1. Some examples for alkaloid containing a heterocyclic spirooxindole scaffold.

It has been reported that biological activity could be enhanced to a greater extent by sharing indole 3-carbon atom in the formation of spiroindoline derivatives.[7] The literature is enumerated with several approaches[8] prescribed for structurally diverse heterocyclic

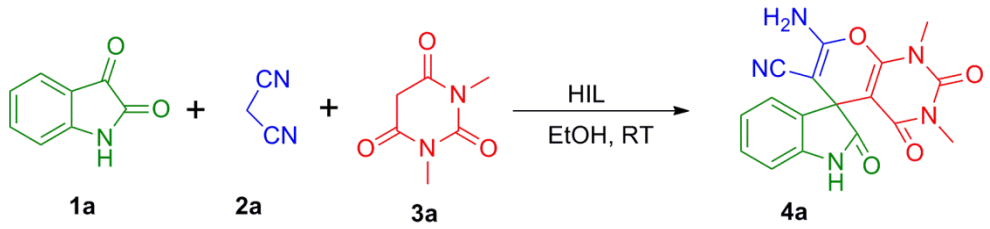
spirooxindoles during the past few years. Most of them suffer from different drawbacks. Owing to their pharmaceutical importance, there is still need to explore a simple and novel method to generate structurally varied spirooxindoles with a variety of substituents.

Based on the above considerations and our interest in the design and development of novel and environmental benign synthetic methodologies[9], attempts were directed to synthesize spirooxindoles by using HIL as the novel catalyst. Herein, we report a simple and efficient method for a library of various spirooxindoles rapidly constructed in ethanol using HIL as the catalyst in the multi-component reaction at room temperature. To the best of our knowledge this is very first report on the synthesis of spirooxindole derivatives catalyzed by sulfated choline based heteropolyacid salt.

2. Results and discussion

The sulfated choline based heteropolyanion salt $[Ch\text{-}OSO_3H]_3W_{12}PO_{40}$ (HIL) was synthesized and characterized as per the earlier report.[9a] To achieve our goal, we embarked the study with the model substrates isatin **1a**, malononitrile **2a** and 1, 3-dimethyl barbituric acid **3a** to understand the importance of prepared catalyst for the desired reaction (Table 1). Numbers of catalysts were tried for the synthesis of spirooxindole derivatives. The model reaction (Scheme 2) was attempted without any catalyst (Table 1, entry 1), which afforded the target compound in poor yield. Amberlyst-15, *L*-proline, H_2SO_4, PEG-600 and iodine also promoted the reaction with low yields (Table 1, entries 8-12). The results indicated that HIL was found to be the most effective catalyst leading to higher yield of spirooxindole derivatives. The efficiency of the reaction was affected by the amount and type of catalyst. It becomes evident that the catalyst played a vital role in the success of the reaction in terms of reaction time and yields of spirooxindole derivatives. It was found that **0.38 mol%** of HIL was the optimum amount of catalyst required to complete the reaction with maximum yield (Table 1, entry 5).

Table 1. Optimization of reaction conditions[a]



Scheme 2. Model reaction

Entry	Catalyst	Amount (mol%)	Time (min)[b]	Yield (%)[c]
1	-	-	90	12
2	HIL	0.05	65	45
3	HIL	0.16	60	65
4	HIL	0.27	45	78
5	**HIL**	**0.38**	**40**	**87**
6	HIL	0.43	30	89
7	HIL	0.48	30	90
8	Amberlyst-15	0.38	65	52
9	L-Proline	0.38	70	49
10	H_2SO_4	0.38	85	25
11	PEG-600	0.38	55	41
12	Iodine	0.38	62	33

[a]Isatin (1 mmol), malononitrile (1mmol) and 1, 3-dimethyl barbituric acid (1mmol). [b]All reactions were run in ethanol at RT till completion as indicated by TLC. [c] Isolated yield.

To investigate the effects of solvent, the condensation reaction of the model substrates was carried out in various solvents at room temperature using 0.38 mol% HIL as the catalyst (Table 2).

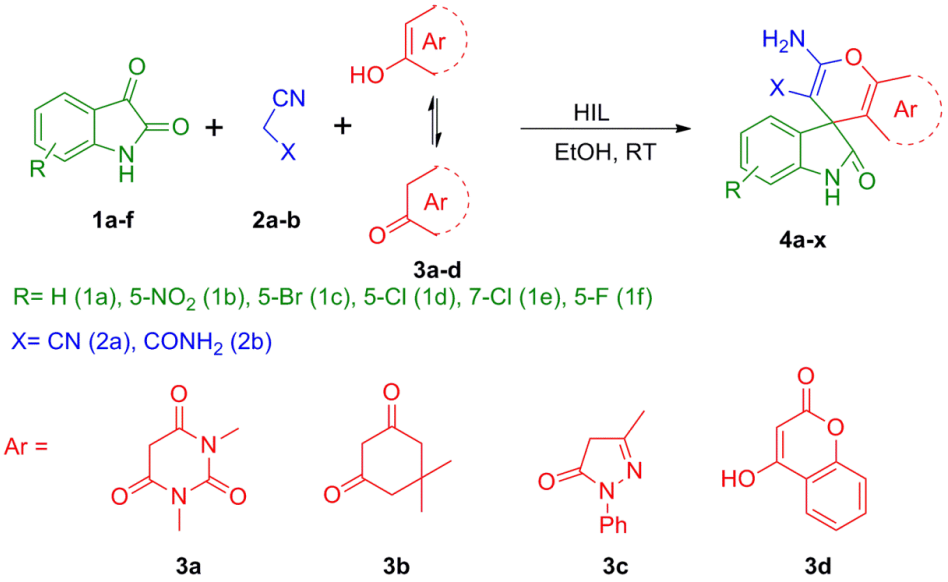
Table 2. Solvent effect on reaction[a]

Entry	Solvent	Time (min)[b]	Yield (%)[c]
1	-	45	65
2	Water	50	78
3	**Ethanol**	**35**	**91**
4	DMF	65	45
5	THF	55	72
6	DCM	40	68

[a]Isatin (1 mmol), malononitrile (1mmol) and 1, 3-dimethyl barbituric acid (1mmol). [b]All reactions were run in ethanol at RT till completion as indicated by TLC. [c] Isolated yield.

Using the optimized reaction conditions, we explored versatility of the present methodology towards various substrates for the synthesis of spirooxindole derivatives. Variously substituted isatins **1a-f** and malononitrile **2a** or ethyl cyanoacetamide **2b** were attempted in the presence of enolizable ketones **3a-d** (Scheme 3). The structural effects of these three building blocks were investigated. The results are summarized in Table 3. Various isatins **1a-f** bearing electron-donating and electron-withdrawing substituent underwent the reaction smoothly with malononitrile **2a** or ethyl cyanoacetamide **2b** and dicarbonyl compounds **3a-d** to afford the desired spirooxindole (**4a-x**) in high yields (Table 3).

Table 3. Synthesized spirooxindoles derivatives (**4a-x**) in the presence of HIL [a]



Scheme 3. Synthesis of spirooxindole derivatives

Entry	Products	Time (min.)[b]	Yield (%)[c]	Entry	Products	Time (min.)[b]	Yield (%)[c]
1	4a	45	91	13	4m	75	86
2	4b	40	85	14	4n	40	93
3	4c	40	89	15	4o	45	85
4	4d	35	90	16	4p	45	92
5	4e	40	87	17	4q	40	93
6	4f	70	85	18	4r	45	87
7	4g	75	82	19	4s	40	88
8	4h	45	91	20	4t	45	87
9	4i	40	93	21	4u	40	86
10	4j	40	92	22	4v	40	84
11	4k	45	89	23	4w	40	89
12	4l	45	91	24	4x	35	83

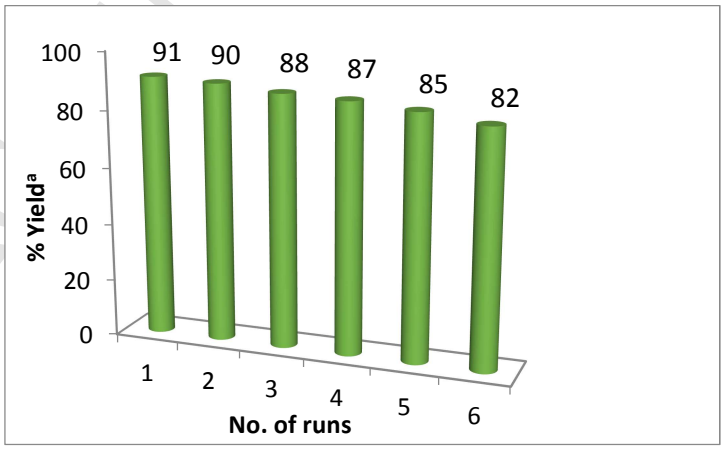
[a]Isatins (1 mmol), active cyanomethanes (1mmol) and enolisable ketones (1mmol). [b]All reactions were run in ethanol at RT till completion as indicated by TLC. [c] Isolated yield.

However, the yield was observed to be relatively low when cyanoacetamide **2b** was used (**4f, 4g, 4m**), which may be due to the low reactivity of the amide group. Additionally, the scope of substrates **3** such as 1,3-dimethyl barbituric acid **3a**, 5,5-dimethylcyclohexane-1,3-dione **3b**, 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one **3c**, and 4-hydroxy coumarin **3d** was also explored. The yield of targeted products was comparatively low using 4-hydroxy coumarin **3d** with isatins **1a-d** and malononitrile **2a** (**4u-4x**), which may be due to the sterically hindered coumarin moiety.

To determine the leaching of the catalyst, the reaction was carried out in the presence of HIL for 20 min, and then the catalyst was separated by simple filtration. The filtrate was then allowed to react, but no significant conversion was observed after 1 h. This test also ruled out the simple contribution of homogeneous conversion of an acid catalyst. It was observed that there was no significant improvement in the yield over the control reaction, indicating no homogeneous catalyst was involved.

Catalyst reusability

To examine the catalytic activity of the recycled catalyst, five successive cycles of the model reaction were run under the optimal reaction conditions using recycled HIL from the previous run (Figure 1).



[a] Loss of catalyst (≤5%) during handling.

Figure 1. Recyclability of HIL for the synthesis of product **4a.**

Figure 1 shows the catalytic recycling property, revealing only a marginal decrease in yield. It was observed that the catalyst displayed very good reusability for at least five times.

3. Experimental

3.1 Materials and method

All the reactions were performed with commercially available reagents. The synthesized compounds were characterized by ^{1}H NMR spectra recorded in DMSO-d_6 on Bruker Avance 400 MHz spectrometer (Bruker Scientific Corporation Ltd., Switzerland). IR spectra were recorded on Bruker 10 alpha E- FTIR spectrophotometer in the range 4000-400 cm-1. IR frequencies of only characteristic peaks are expressed in cm^{-1}. Elemental analyses were performed at SICART, Vallabh Vidyanagar-INDIA on PerkinElmer 2400 series- II elemental analyzer (PerkineElmer, USA). Elements are found within ±0.4% of the theoretical compositions for all samples.

3.2. General procedure for the synthesis of spirooxindole derivatives.

A mixture of isatins **1a-f** (1 mmol), active cyanomethanes **2a-b** (1 mmol) and enolizable ketones **3a-d** (1 mmol) in ethanol (3 ml) was stirred at room temperature in the presence of HIL (Scheme 2). The reaction progress was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was treated with ethanol to recover the insoluble catalyst by filtration. The filtrate was then concentrated under vacuum and the desired product was obtained. The structures of the products were confirmed by ^{1}H NMR, IR spectroscopy and supported by elemental analysis. The filtered catalyst was dried under vacuum for 2 h and was reused with a fresh charge of solvent and reactants for subsequent runs under the same reaction conditions to observe its catalytic efficiency.

Spectral data:

3.2.1 7'-amino-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-*d*]pyrimidine]-6'-carbonitrile (4a).

Yield: 91%; Found: C, 58.25; H, 3.79; N, 20.14. $C_{17}H_{13}N_5O_4$ requires: C, 58.12; H, 3.73; N, 19.93.;; IR (KBr, ν_{max}, cm^{-1}): 3315 (–NH str.), 1637 (C–O str.), 1267 (C–N str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.03 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 6.79-7.17 (m, 4H, Ar-H), 7.55 (s, 2H, NH_2),10.48 (s, 1H, NH).

3.2.2 7'-amino-1',3'-dimethyl-5-nitro-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-*d*]pyrimidine]-6'-carbonitrile (4b).

Yield: 85%; Found: C, 51.35; H, 3.21; N, 21.11. $C_{17}H_{12}N_6O_6$ requires: C, 51.52; H, 3.05; N, 21.21; IR (KBr, ν_{max}, cm^{-1}): 3323 (–NH str.), 2939 (Ar C–H), 1638(C=O str.), 1261 (C–N str.); 1H NMR (400 MHz, DMSO- d_6): δ 3.04 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 6.83 (s, 1H, CH), 7.28 (d, *J*=2 Hz, 2H, Ar-H), 7.63 (s, 2H, NH_2), 10.62 (s, 1H, NH).

3.2.3 7'-amino-5-bromo-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro [indoline-3,5'-pyrano[2,3-*d*]pyrimidine]-6'-carbonitrile (4c).

Yield: 89%; Found: C, 47.19; H, 2.88; N, 16.18. $C_{17}H_{12}BrN_5O_4$ requires: C, 47.46; H, 2.81; N, 16.28; IR (KBr, ν_{max}, cm^{-1}): 3320 (–NH str.), 2933 (Ar C–H), 1640 (C=O str.), 1265 (C–N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 3.04 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.79 (s, 1H, CH), 7.35 (d, *J*=8 Hz, 2H, Ar-H), 7.55 (s, 2H, NH_2), 10.64 (s, 1H, NH).

3.2.4 7'-amino-5-chloro-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-*d*]pyrimidine]-6'-carbonitrile (4d).

Yield: 90%; Found: C, 52.82; H, 3.23; N, 17.95. $C_{17}H_{12}BrN_5O_4$ requires: C, 52.93; H, 3.14; N, 18.15; IR (KBr, ν_{max}, cm^{-1}): 3356 (–NH str.), 2921 (Ar C–H), 1651 (C=O str.), 1264 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 3.10 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.72 (s, 1H, CH), 7.35 (d, *J*=8 Hz, 2H, Ar-H), 7.49 (s, 2H, NH_2), 10.65 (s, 1H, NH).

3.2.5 7'-amino-7-chloro-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-*d*]pyrimidine]-6'-carbonitrile (4e).

Yield: 87%; Found: C, 52.83; H, 3.44; N, 18.01. $C_{17}H_{12}BrN_5O_4$ requires: C, 52.93; H, 3.14; N, 18; IR (KBr, ν_{max}, cm^{-1}): 3324 (–NH str.), 2943 (Ar C–H), 1639(C=O str.), 1269 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 3.02 (s, 3H, CH3), 3.42 (s, 3H, CH3), 7.39 (m, 3H, Ar-H), 7.52 (s, 2H, NH2), 10.63 (s, 1H, NH).

3.2.6 6'-cyano-1',3'-dimethyl-5-nitro-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-*d*]pyrimidine]-7'-carboxamide (4f).

Yield: 85%; Found: C, 51.05; H, 2.91; N, 19.68. $C_{17}H_{12}BrN_5O_4$ requires: C, 50.95; H, 2.85; N, 19.81; IR (KBr, ν_{max}, cm^{-1}): 3327 (–NH str.), 2948 (Ar C–H), 1634 (C=O str.), 1259 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 3.09 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 6.89 (s, 1H, CH), 7. 39 (d, *J*=8 Hz, 2H, Ar-H), 7.63 (s, 2H, NH_2), 10.61 (s, 1H, NH).

3.2.7 5-bromo-6'-cyano-1',3'-dimethyl-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-*d*]pyrimidine]-7'-carboxamide (4g).

Yield: 82%; Found: C, 47.28; H, 2.66; N, 15.39. $C_{17}H_{12}BrN_5O_4$ requires: C, 47.18; H, 2.64; N, 15.28; IR (KBr, ν_{max}, cm^{-1}): 3314 (–NH str.), 2952 (Ar C–H), 1633 (C=O str.), 1242 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 3.04 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 6.71 (s, 1H, CH), 7. 42 (d, *J*=8 Hz, 2H, Ar-H), 7.65 (s, 2H, NH_2), 10.67 (s, 1H, NH).

3.2.8 2-amino-8,8-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4h).

Yield: 91%; Found: C, 68.16; H, 5.26; N, 12.69. $C_{17}H_{12}BrN_5O_4$ requires: C, 68.05; H, 5.11; N, 12.53; IR (KBr, ν_{max}, cm^{-1}): 3324 (–NH str.), 2949 (Ar C–H), 1653 (C=O str.), 1269 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.15 (s, 6H, CH_3), 2.15-2.29 (m, 4H, CH_2), 7.56 (s, 2H, NH_2), 7.81 (s, 1H, Ar-H), 8.19 (dd, *J*=2.4 Hz, *J*= 8.4, 2H, Ar-H), 11.06 (s, 1H, NH).

3.2.9 2-amino-8,8-dimethyl-5'-nitro-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4i).

Yield: 93%; Found: C, 60.15; H, 4.08; N, 14.68. $C_{19}H_{16}N_4O_5$ requires: C, 60.00; H, 4.24; N, 14.73IR (KBr, v_{max}, cm^{-1}): 3336 (–NH str.), 2942(Ar C–H), 1661 (C=O str.), 1258 (C–N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.03 (s, 6H, CH_3), 2.12-2.22 (m, 4H, -CH_2), 7.97 (s, 1H, Ar-H), 8.16 (dd, *J*=2.4 Hz, *J*= 8.4, 2H, Ar-H), 7.45 (s, 2H, NH_2), 11.18 (s, 1H, NH).

3.2.10 2-amino-5'-bromo-8,8-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4j).

Yield: 92%; Found: C, 55.16; H, 3.69; N, 10.26. $C_{17}H_{12}BrN_5O_4$ requires: C, 55.09; H, 3.89; N, 10.14; IR (KBr, v_{max}, cm^{-1}): 3331 (–NH str.), 2935 (Ar C–H), 1646 (C=O str.), 1268 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.11 (s, 6H, CH_3), 2.11-2.24 (m, 4H, CH_2), 7.84 (s, 1H, Ar-H), 8.09 (dd, *J*=2.4 Hz, *J*= 8.4, 2H, Ar-H), 7.39 (s, 2H, NH_2), 10.94 (s, 1H, NH).

3.2.11 2-amino-5'-chloro-8,8-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4k).

Yield: 89%; Found: C, 61.71; H, 4.36; N, 11.36. $C_{17}H_{12}BrN_5O_4$ requires: C, 61.71; H, 4.36; N, 11.36; IR (KBr, v_{max}, cm^{-1}): 3328 (–NH str.), 2935 (Ar C–H), 1651 (C=O str.), 1261 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.07 (s, 6H, CH_3), 2.14-2.29 (m, 4H, -CH_2), 8.04 (s, 1H, Ar-H), 8.19 (dd, *J*=2.4 Hz, *J*= 8.4, 2H, Ar-H), 7.49 (s, 2H, NH_2), 11.09 (s, 1H, NH).

3.2.12 2-amino-7'-chloro-8,8-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4l).

Yield: 91%; Found: C, 61.64; H, 4.43; N, 11.39. $C_{17}H_{12}BrN_5O_4$ requires: C, 61.71; H, 4.36; N, 11.36; IR (KBr, v_{max}, cm^{-1}): 3325 (–NH str.), 2949 (Ar C–H), 1648 (C=O str.), 1268 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.05 (s, 6H, CH_3), 2.04-2.24 (m, 4H, -CH_2), 8.07 (s, 1H, Ar-H), 8.21 (dd, *J*=2.4 Hz, *J*= 8.4, 2H, Ar-H), 7.52 (s, 2H, NH_2), 10.91 (s, 1H, NH).

3.2.13 3-cyano-8,8-dimethyl-5'-nitro-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-2-carboxamide (4m).

Yield: 86%; Found: C, 58.97; H, 4.09; N, 13.75. $C_{17}H_{12}BrN_5O_4$ requires: C, 58.82; H, 3.95; N, 13.72; IR (KBr, ν_{max}, cm^{-1}): 3319 (–NH str.), 2929 (Ar C–H), 1634 (C=O str.), 1277 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 0.98 (s, 6H, CH_3), 2.21-2.32 (m, 4H, -CH_2), 7.91 (s, 1H, Ar-H), 8.25 (dd, *J*=2.4 Hz, *J*= 8.4, 2H, Ar-H), 7.42 (s, 2H, NH_2), 11.09 (s, 1H, NH).

3.2.14 3-cyano-5'-fluoro-8,8-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-2-carboxamide (4n).

Yield: 93%; Found: C, 63.09; H, 4.18; N, 11.13. $C_{17}H_{12}BrN_5O_4$ requires: C, 62.99; H, 4.23; N, 11.02; IR (KBr, ν_{max}, cm^{-1}): 3329 (–NH str.), 2938 (Ar C–H), 1647 (C=O str.), 1266 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 0.97 (s, 6H, CH_3), 2.04-2.19 (m, 4H, -CH_2), 7.94 (s, 1H, Ar-H), 8.21 (dd, *J*=2.4 Hz, *J*= 8.4, 2H, Ar-H), 7.51 (s, 2H, NH_2), 11.06 (s, 1H, NH).

3.2.15 5'-amino-1',3'-dimethyl-2-oxo-1'H-spiro[indoline-3,7'-pyrano[3,2-*c*]pyrazole]-6'-carbonitrile (4o).

Yield: 85%; Found: C, 62.67; H, 4.12; N, 22.85. $C_{17}H_{12}BrN_5O_4$ requires: C, 62.53; H, 4.26; N, 22.79; IR (KBr, ν_{max}, cm^{-1}): 3324 (–NH str.), 2949 (Ar C–H), 1661 (C=O str.), 1268 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.56 (s, 3H, CH_3), 6.84 (s, 1H, Ar-H), 7.36-7.41 (m, 5H, Ar-H), 7.49 (d, 2H, NH_2), 7.61 (d, *J*=7.6 Hz, 2H, Ar-H), 10.64 (s, 1H, NH).

3.2.16 5'-amino-1',3'-dimethyl-5-nitro-2-oxo-1'H-spiro[indoline-3,7'-pyrano[3,2-*c*] pyrazole]-6'-carbonitrile (4p).

Yield: 92%; Found: C, 54.59; H, 3.56; N, 23.72. $C_{17}H_{12}BrN_5O_4$ requires: C, 54.55; H, 3.43; N, 23.85; IR (KBr, ν_{max}, cm^{-1}): 3248 (–NH str.), 2954 (Ar C–H), 1644 (C=O str.), 1270 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.68 (s, 3H, CH_3), 6.94 (s, 1H, Ar-H), 7.31-7.39 (m, 5H, Ar-H), 7.45 (d, 2H, NH_2), 7.51 (d, *J*=7.2 Hz, 2H, Ar-H), 10.61 (s, 1H, NH).

3.2.17 5'-amino-5-bromo-1',3'-dimethyl-2-oxo-1'H-spiro[indoline-3,7'-pyrano[3,2-*c*] pyrazole]-6'-carbonitrile (4q).

Yield: 93%; Found: C, 49.91; H, 3.11; N, 18.24. $C_{16}H_{12}BrN_5O_2$ requires: C, 49.76; H, 3.13; N, 18.13; IR (KBr, ν_{max}, cm^{-1}): 3331 (–NH str.), 2951 (Ar C–H), 1659 (C=O str.), 1261 (C–N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 6.90 (s, 1H, Ar-H), 7.29 (s, 2H, NH_2), 7.49-7.57 (m, 4H, Ar-H), 7.95 (d, *J*=7.4 Hz, 2H, Ar-H), 10.82 (s, 1H, NH).

3.2.18 5'-amino-5-chloro-1',3'-dimethyl-2-oxo-1'H-spiro[indoline-3,7'-pyrano[3,2-*c*] pyrazole]-6'-carbonitrile (4r).

Yield: 87%; Found: C, 56.34; H, 3.67; N, 20.41. $C_{17}H_{12}BrN_5O_4$ requires: C, 56.23; H, 3.54; N, 20.49; IR (KBr, ν_{max}, cm^{-1}): 3327 (–NH str.), 2936 (Ar C–H), 1649 (C=O str.), 1267 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.57 (s, 3H, CH_3), 7.12 (s, 1H, Ar-H), 7.23-7.31 (m, 5H, Ar-H), 7.52 (d, 2H, NH_2), 7.57 (d, *J*=7.2 Hz, 2H, Ar-H), 10.91 (s, 1H, NH).

3.2.19 5'-amino-5-chloro-1',3'-dimethyl-2-oxo-1'H-spiro[indoline-3,7'-pyrano[3,2-*c*] pyrazole]-6'-carbonitrile (4s).

Yield: 88%; Found: C, 56.41; H, 3.39; N, 20.59. $C_{17}H_{12}BrN_5O_4$ requires: C, 56.23; H, 3.54; N, 20.49; IR (KBr, ν_{max}, cm^{-1}): 3330 (–NH str.), 2952 (Ar C–H), 1647 (C=O str.), 1271 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.46 (s, 3H, CH_3), 7.24 (s, 1H, Ar-H), 7.25-7.37 (m, 5H, Ar-H), 7.57 (d, 2H, NH_2), 7.62 (d, *J*=7.2 Hz, 2H, Ar-H), 10.87 (s, 1H, NH).

3.2.20 5'-amino-5-fluoro-1',3'-dimethyl-2-oxo-1'H-spiro[indoline-3,7'-pyrano[3,2-*c*] pyrazole]-6'-carbonitrile (4t).

Yield: 87%; Found: C, 59.19; H, 3.69; N, 21.62. $C_{17}H_{12}BrN_5O_4$ requires: C, 59.08; H, 3.72; N, 21.53; IR (KBr, ν_{max}, cm^{-1}): 3327 (–NH str.), 2941 (Ar C–H), 1629 (C=O str.), 1274 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.67 (s, 3H, CH_3), 6.86 (s, 1H, Ar-H), 7.37-7.42 (m, 5H, Ar-H), 7.51 (d, 2H, NH_2), 7.59 (d, *J*=7.2 Hz, 2H, Ar-H), 10.98 (s, 1H, NH).

3.2.21 2'-amino-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-*c*]chromene]-3'-carbonitrile (4u).

Yield: 86%; Found: C, 67.37; H, 2.95; N, 11.82. $C_{17}H_{12}BrN_5O_4$ requires: C, 67.23; H, 3.10; N, 11.76; IR (KBr, ν_{max}, cm^{-1}): 3319 (–NH str.), 2933 (Ar C–H), 1643 (C=O str.), 1276 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 7.47-7.58 (m, 4H, Ar-H), 8.21 (s, 2H, NH_2), 8.49 (d, J= 7.6 Hz, 2H, Ar-H), 8.68 (s, 1H, Ar-H), 11.11 (s, 1H, NH).

3.2.22 2'-amino-5-nitro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-*c*]chromene]-3'-carbonitrile (4v)

Yield: 84%; Found: C, 59.69; H, 2.68; N, 13.89. $C_{20}H_{10}N_4O_6$ requires: C, 59.71; H, 2.51; N, 13.93;.IR (KBr, ν_{max}, cm^{-1}): 3315 (–NH str.), 2925 (Ar C–H), 1654(C=O str.), 1252 (C–N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 7.44-7.54 (m, 4H, Ar-H), 8.24 (s, 2H, NH_2), 8.42 (d, *J*= 7.6 Hz, 2H, Ar-H), 8.61 (s, 1H, Ar-H), 11.22 (s, 1H, NH).

3.2.23 2'-amino-5-bromo-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-*c*]chromene]-3'-carbonitrile (4w).

Yield: 89%; Found: C, 55.21; H, 2.15; N, 9.81. $C_{17}H_{12}BrN_5O_4$ requires: C, 55.07; H, 2.31; N, 9.63; IR (KBr, ν_{max}, cm^{-1}): 3321 (–NH str.), 2939 (Ar C–H), 1625 (C=O str.), 1275 (C-N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 6.91 (s, 1H, Ar-H), 7.37-7.41 (m, 4H, Ar-H), 7.46 (s, 2H, NH_2), 8.06 (d, *J*= 7.4 Hz, 2H, Ar-H), 10.98 (s, 1H, NH).

3.2.24 2'-amino-5-chloro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile (4x).

Yield: 83%; Found: C, 61.39; H, 2.43; N, 10.85. $C_{20}H_{10}ClN_3O_4$ requires: C, 61.32; H, 2.57; N, 10.73; IR (KBr, ν_{max}, cm^{-1}): 3339 (–NH str.), 2952 (Ar C–H), 1641 (C=O str.), 1276 (C–N str.); ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.62 (s, 3H, CH_3), 6.94 (s, 1H, Ar-H), 7.35-7.38 (m, 5H, Ar-H), 7.47 (d, 2H, NH_2), 7.54 (d, *J*=7.2 Hz, 2H, Ar-H), 10.73 (s, 1H, NH).

4. Conclusion

We have developed a novel methodology for the synthesis of spirooxindole derivatives using sulfated choline based heteropolyanion (HIL) as the catalyst. The present protocol provides very simple, economic and an efficient method for the synthesis of spirooxindole derivatives. The advantages of this method are its facile conditions, tolerance to diversity of the substrates, easy product isolation with excellent purity without the need of column chromatography and recyclability of catalyst without significant loss in its activity. The protocol has been examined in context of combinatorial as well as multicomponent approach.

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An efficient approach for the synthesis of spirooxindole derivatives catalyzed by novel sulfated choline based heteropolyanion at room temperature

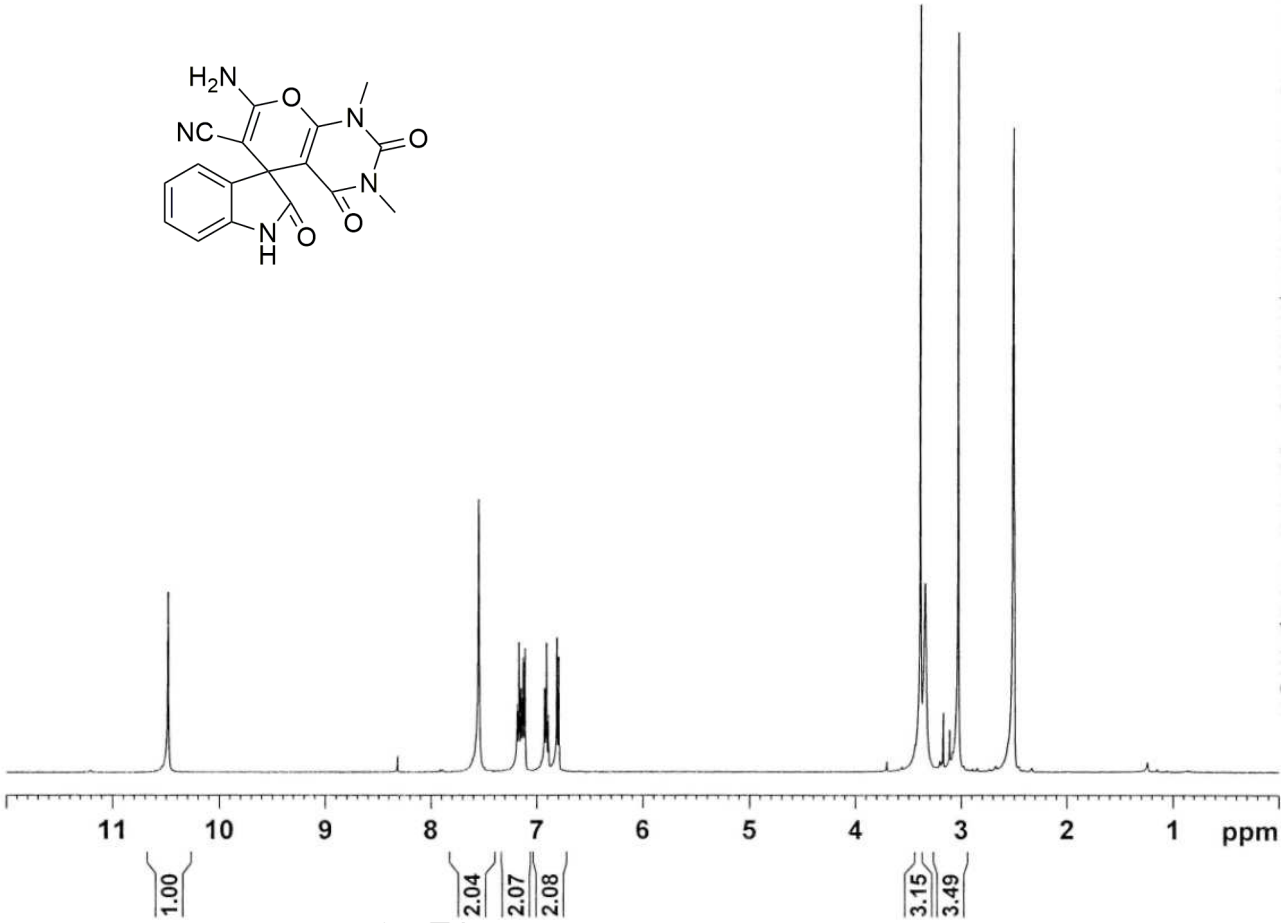
Shailesh P. Satasia, Piyush N. Kalaria, Jemin R. Avalani, Dipak K. Raval*

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar- 388 120, Gujarat, India

*Corresponding author. Tel.: +91-02692-226856 - Ext. - 208; Fax: +91-02692 236475.

E-mail: shailesh_satasia@yahoo.com

Supporting information



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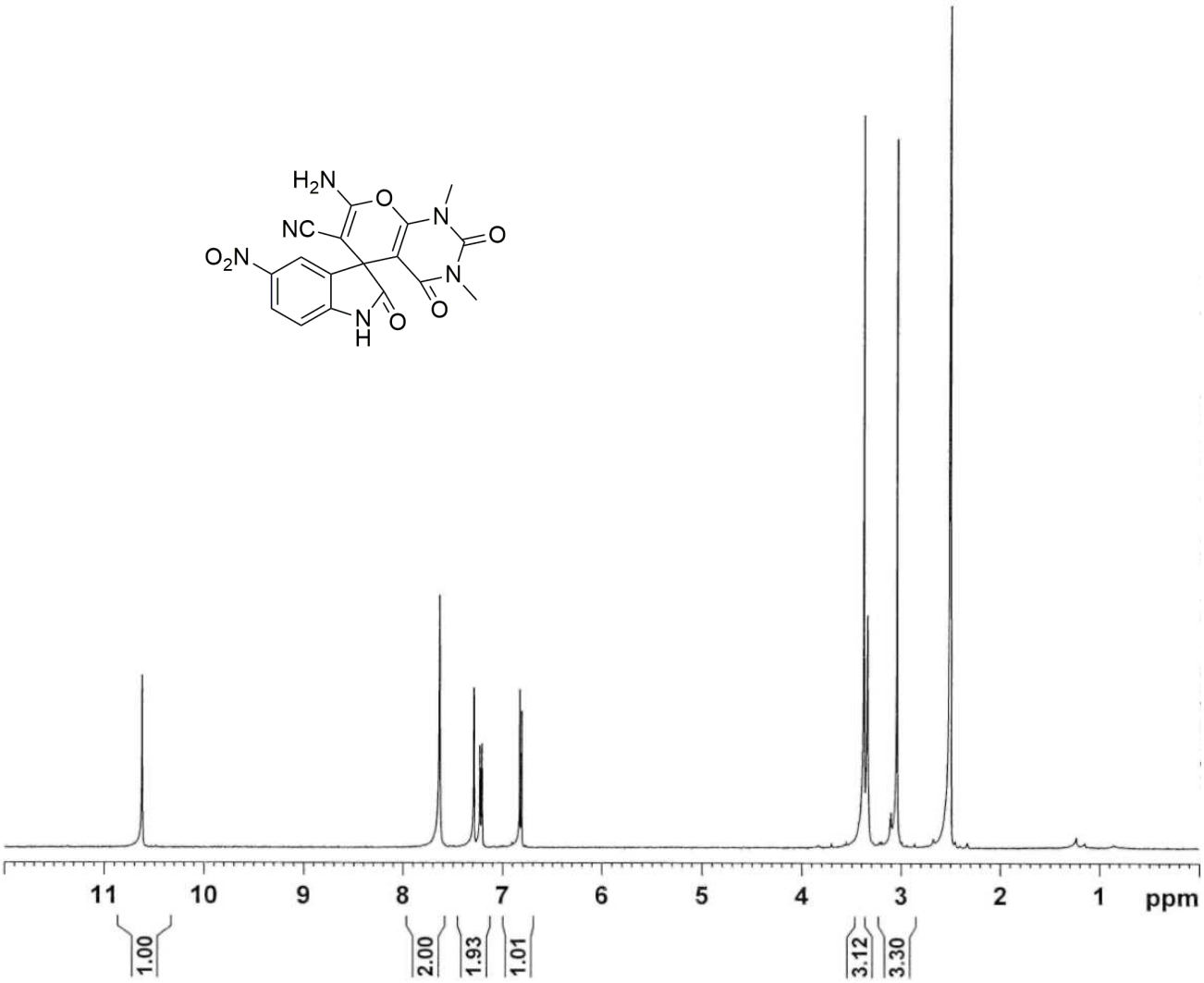

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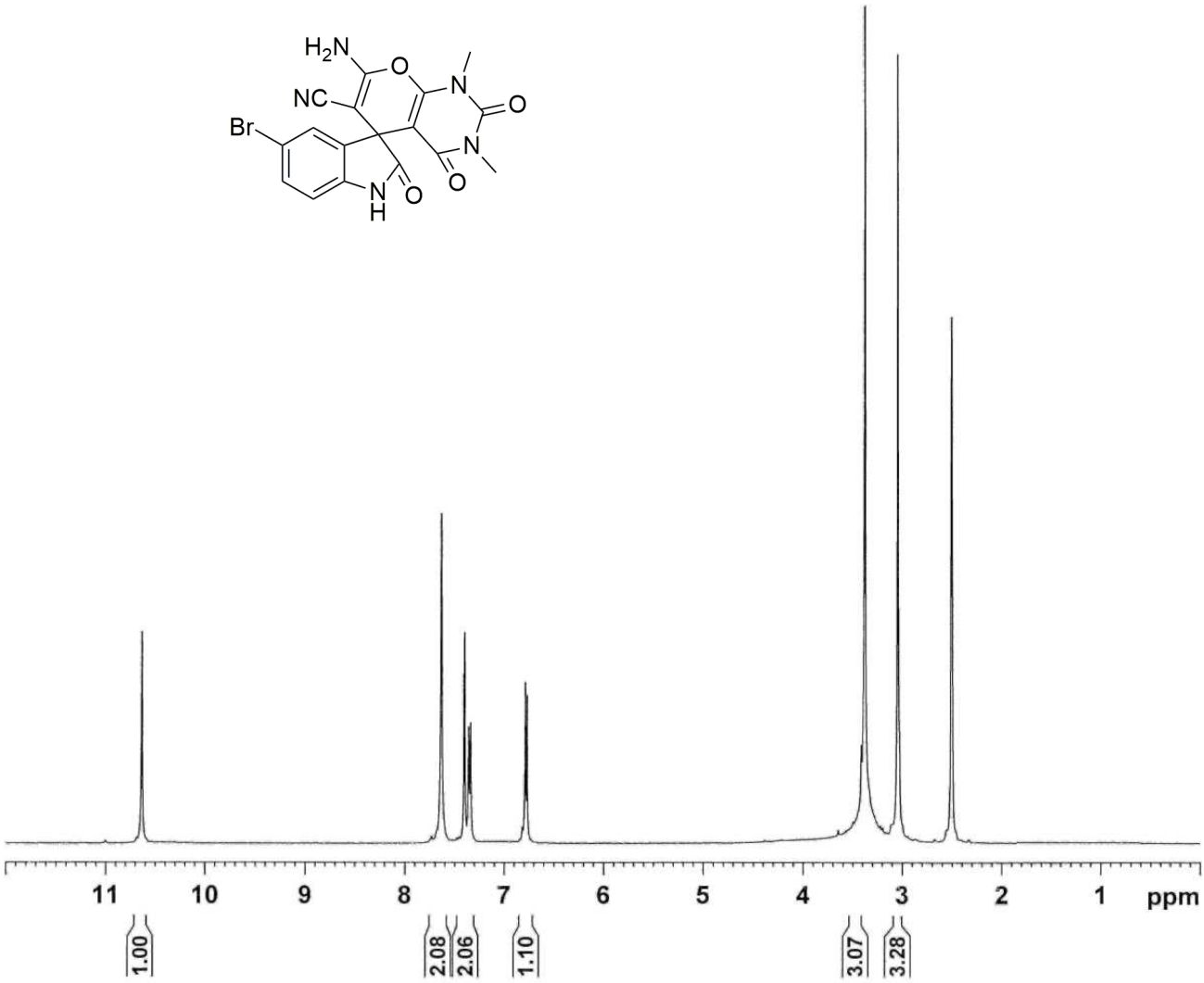

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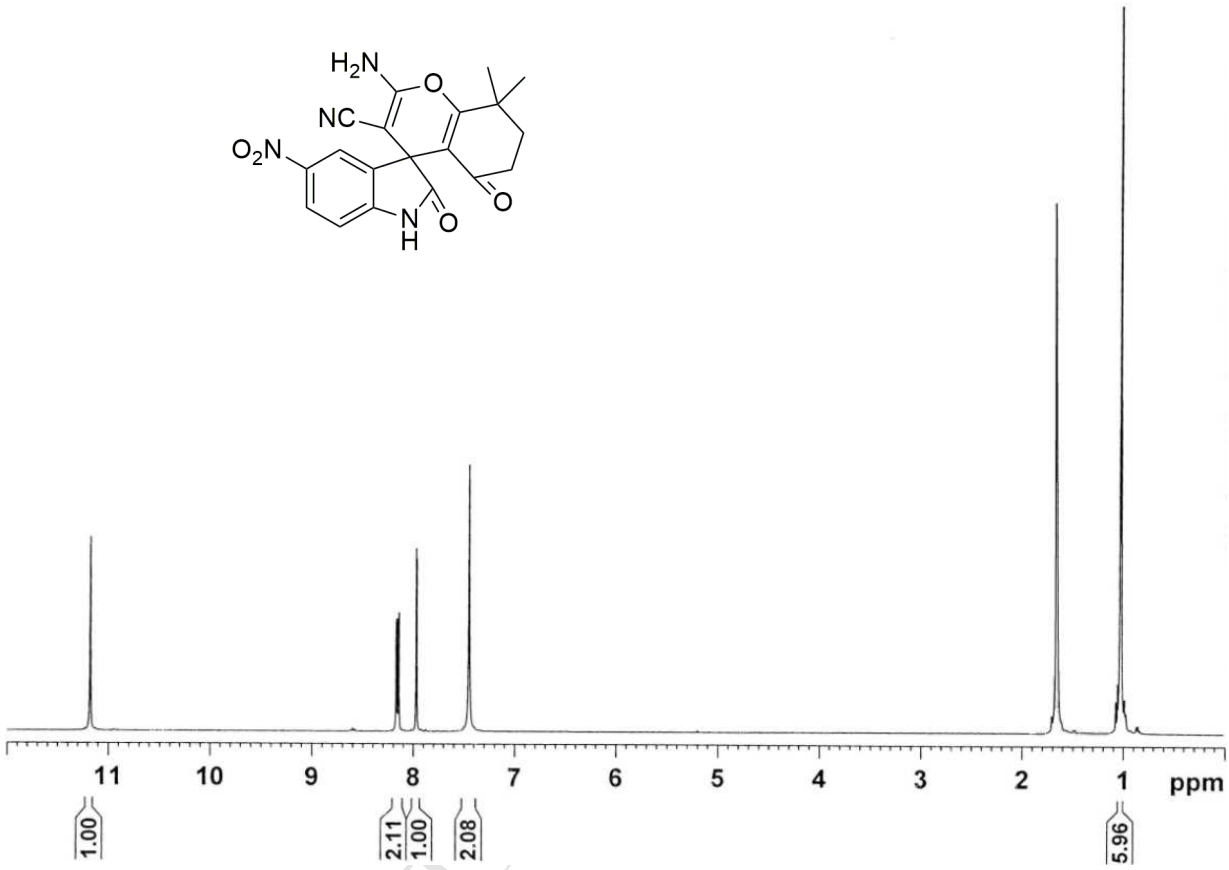

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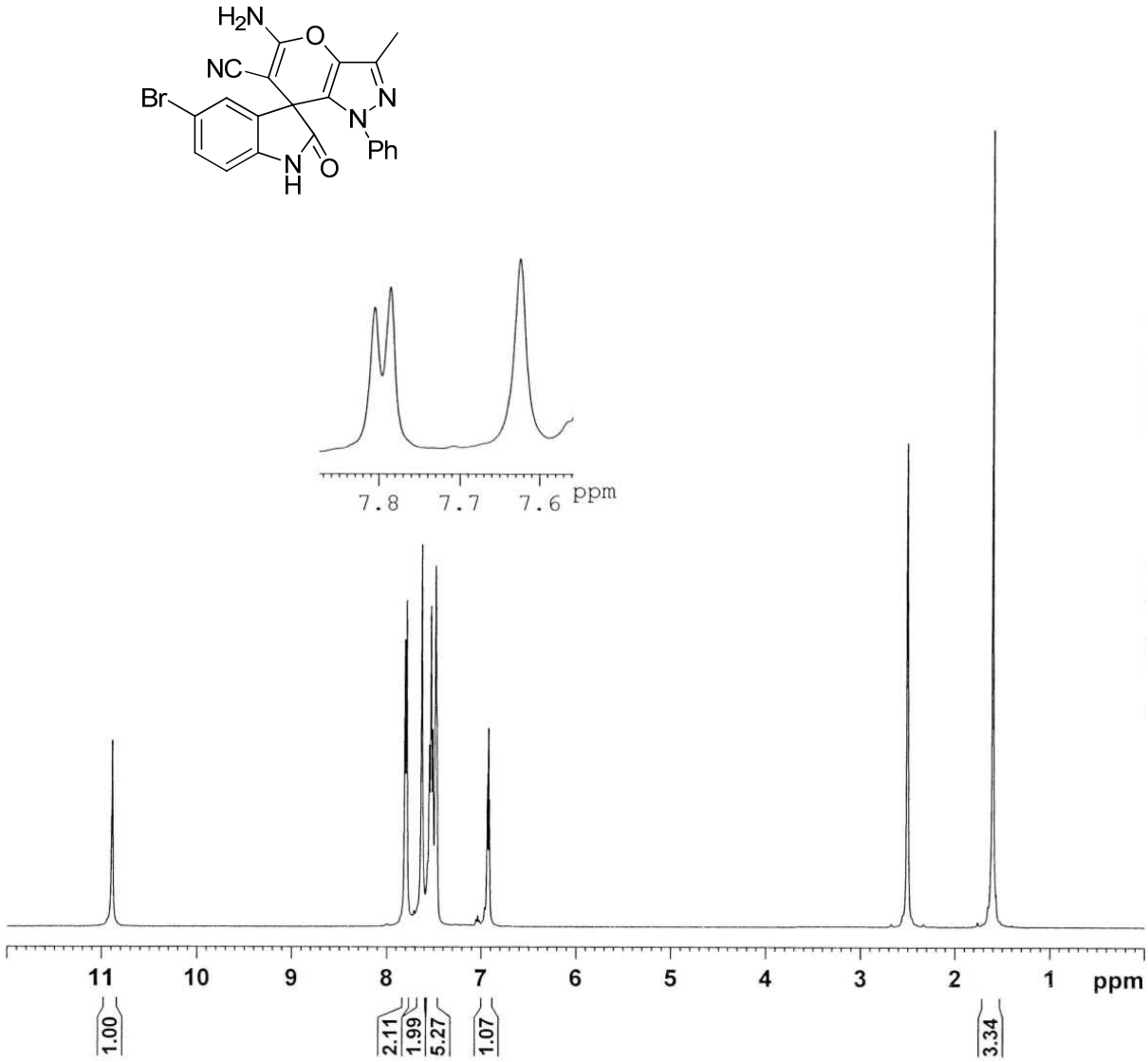

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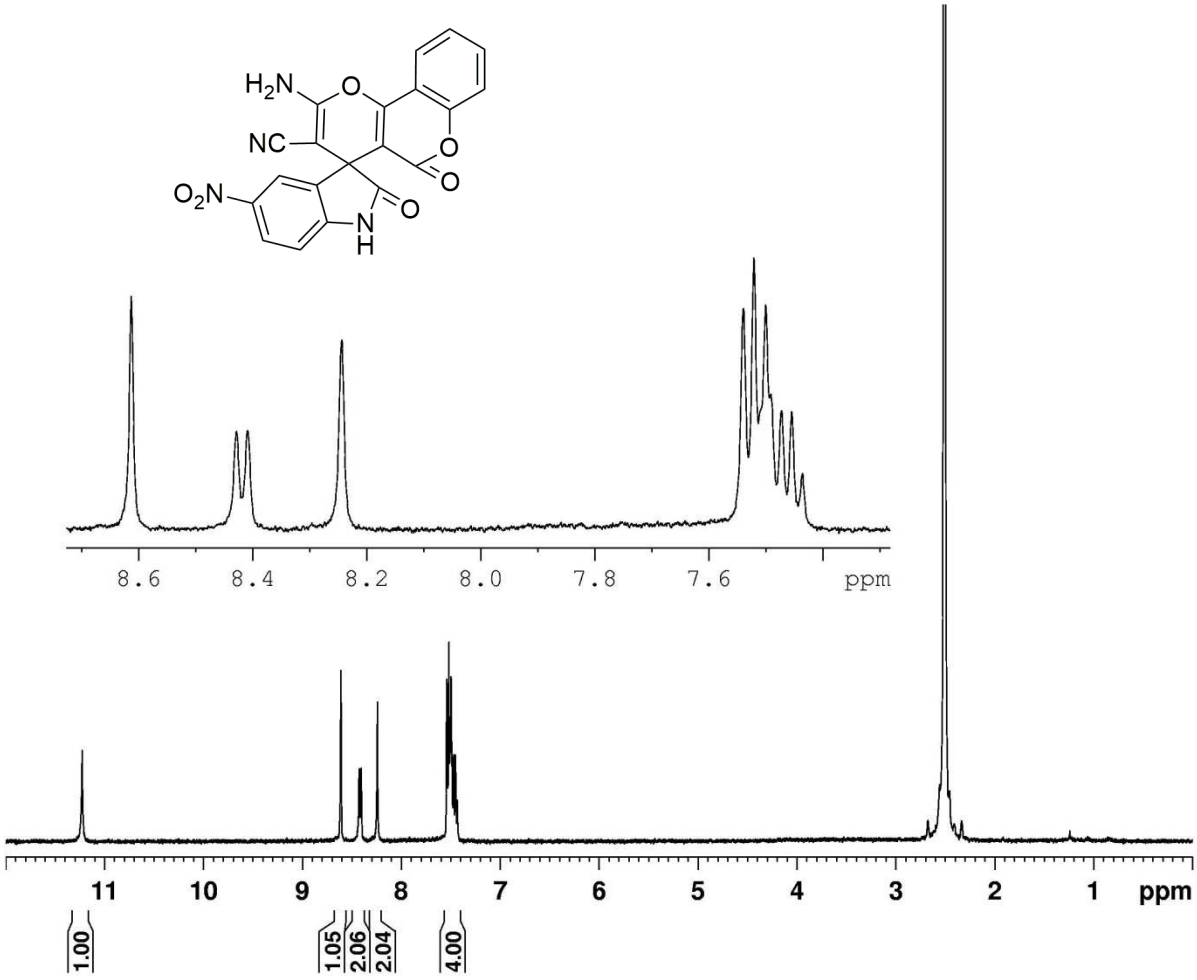

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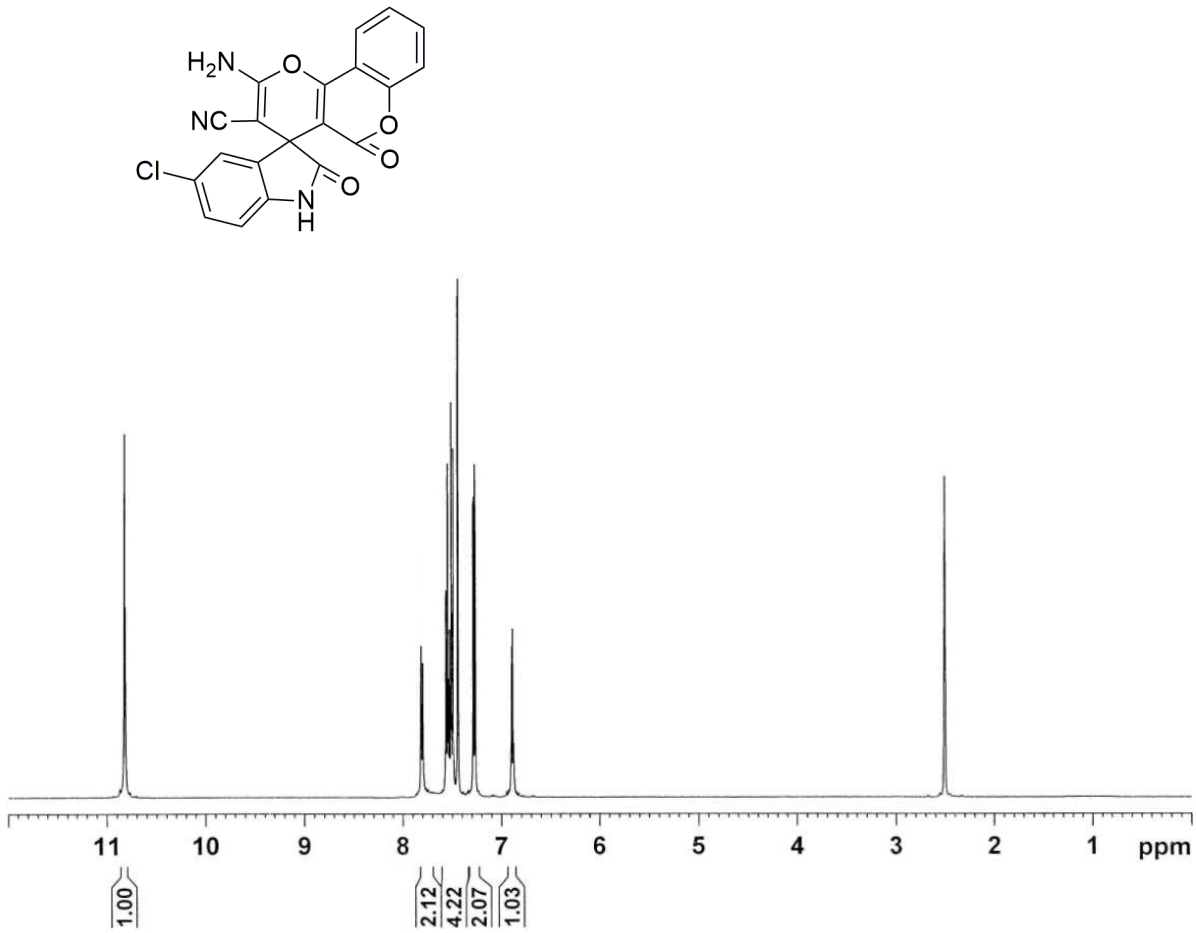

^{1}HNMR of compound 4x