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ARTICLE

# CsF promoted rapid synthesis of spirooxindole-pyran annulated heterocycles at room temperature in ethanol

Yogesh B. Wagh[1] | Swapnil A. Padvi[2] | Pramod P. Mahulikar[1] | Dipak S. Dalal[1]

[1]School of Chemical Sciences, Kavayitri Bahinabai Chaudhari North Maharashtra University, Jalgaon, India

[2]Department of Chemistry, JET's Z. B. Patil College, Dhule, India

**Correspondence**
Dipak S. Dalal, School of Chemical Sciences, Kavayitri Bahinabai Chaudhari North Maharashtra University, Jalgaon, Maharashtra 425001, India.
Email: dsdalal2007@gmail.com

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**Abstract**

A newer, versatile, and straightforward synthetic strategy for the construction of functionalized spirooxindole-pyran annulated heterocycles is described. The procedure is based on CsF-promoted rapid tandem Knoevenagel-Michael-Cyclocondensation reaction of isatin, malononitrile, and 4-hydroxycoumarin/barbituric acids/pyrazolone at room temperature in ethanol. This methodology has various advantages like easy operational, excellent yields within short reaction time (3-25 min), and simple isolation of products. The CsF has a dual role as a base and carbonyl activator.

## 1 | INTRODUCTION

Efficient synthesis of structurally diverse small molecules affords a validated source of chemical investigations for biomedical research and to address the demand of bioactive small molecules for chemical biology.[1,2] Knoevenagel-Michael-Cyclocondensation reaction between a carbonyl group and a methylene-activated group is known as an excellent tool in organic chemistry to form new C–C bonds.[3] The spirocyclic compounds are important for their unique three-dimensional skeletal units that are extensively distributed in several natural products and biologically active compounds.[4]

The spirooxindole system is used as the core structure of many useful alkaloids and pharmacological agents.[5] These compounds are acknowledged for display of various biological activities like anti-HIV,[6] antitumor,[7] antitubercular,[8] antimalarial,[9] and central nervous system (CNS) activities and effects.[10] Therefore, different catalysts have been used to synthesize these spirooxindole scaffolds such as alum,[11] L-proline,[12] Caspian Isinglass,[13] borax,[14] and gold (III) chloride.[15] Although such protocols reported by others find certain merits of their own. But they suffer from several demerits like prolonged reaction times, poor yields, and expensive reagents. Consequently, there is scope for further work toward the development of the clean, efficient, and high yielding route in short reaction time.

The use of fluoride ion ($F^-$) as a base or catalyst in organic syntheses has gained significant popularity for display a high tolerance for functional groups.[16] We have linked several other investigators in reporting on CsF-catalyzed conversions of various carbonyl compounds with a variety of functional groups like benzamides,[17] disulfides,[18] ethers,[19] amines,[20] and fluoromethanimine.[21] CsF as well famous for the desilylative elimination,[22] palladium, coupling,[23] Julia-Kocienski olefination,[24] Aza-Michael, [25] and Claisen rearrangement.[26] Based on these reports, we anticipated that the CsF shows unique activation of typical carbonyl compounds, but its use as carbonyl activator and base catalyst specifically in multicomponent reactions is still missing.

In the past few years, we investigated the multicomponent reactions by employing easily generated nitrogen based as the main substrates and have successfully developed a few highly efficient protocols for the synthesis of some biologically important nitrogen-containing heterocyclic compounds.[27] Thus, as a part of our research

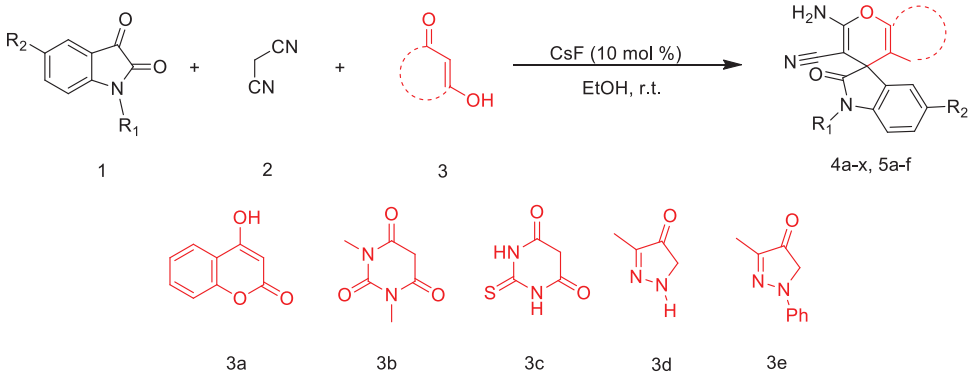
  

program to develop efficient and greener methodologies, herein, a rapid and practical method for the functionalized spirooxindole-pyran annulated heterocycles by the reaction of isatins, malononitrile with C−H activated compounds 4-hydroxycoumarin/1,3-dimethylbarbituric acid/thiobarbituric acids/pyrazolones in the presence of CsF at room temperature in ethanol is described (Scheme 1).

## 2 | RESULTS AND DISCUSSION

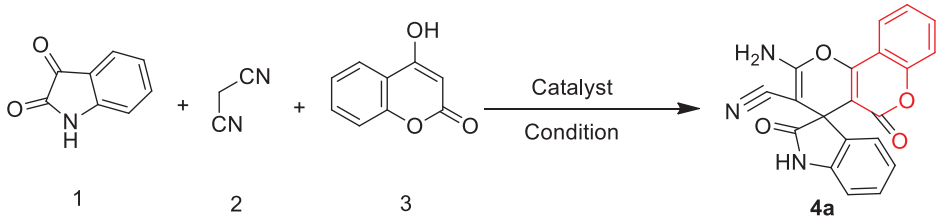
In order to optimize the reaction condition and the performance of CsF as a promoter for 2′-amino-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile **4a**, the reaction between simple isatin, malononitrile, and 4-hydroxy coumarin were selected as a model reaction. We have performed the model reaction in different solvents and observed that ethanol is the best solvent. Similarly, model reactions were performed by using various amounts of catalyst CsF (Table 1).

The best result was obtained for 10 mol% of CsF, affording 96% of **4a** within 5 min (Table 1, entry 4). A further increase in the amount of CsF up to 15 and 20 mol% has no significant effect on the yield and reaction time (Table 1, entries 5 and 6). The role of CsF as the promoter has been confirmed when a similar reaction was carried out in the absence of catalyst, giving only 20% yield with a longer reaction time 3 h (Table 1, entry 2). The reaction between 4-hydroxycoumarin and 2-(2-oxoindolin-3-ylidene) malononitrile requires catalyst, since without catalyst the reaction does not lead to the complete formation of the desired product (Table 1, entries 1 and 2). In order to check




**SCHEME 1** Synthesis of spirooxindole-pyran annulated heterocycles using CsF

**TABLE 1** Optimization of reaction conditions in the synthesis of **4a**

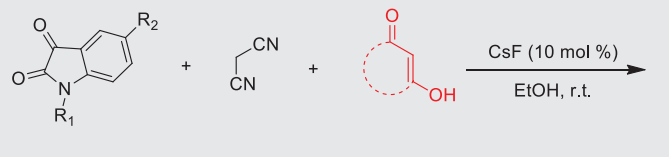



| Entry | Catalyst | Solvent/condition | Time (h/min) | Yields (%)[a] |
|---|---|---|---|---|
| 1 | No catalyst | No solvent, rt | 3 h | Trace |
| 2 | No catalyst | EtOH, rt | 3 h | 20 |
| 3 | CsF (5 mol%) | EtOH, rt | 10 | 89 |
| 4 | **CsF (10 mol%)** | **EtOH, rt** | **5** | **96** |
| **5** | CsF (15 mol%) | EtOH, rt | 5 | 92 |
| 6 | CsF (20 mol%) | EtOH, rt | 5 | 90 |
| 7 | NaF (10 mol%) | EtOH, rt | 30 | 51 |
| 9 | KF (10 mol%) | EtOH, rt | 30 | 49 |
| 10 | $Cs_2CO_3$ (10 mol%) | EtOH, rt | 30 | 46 |

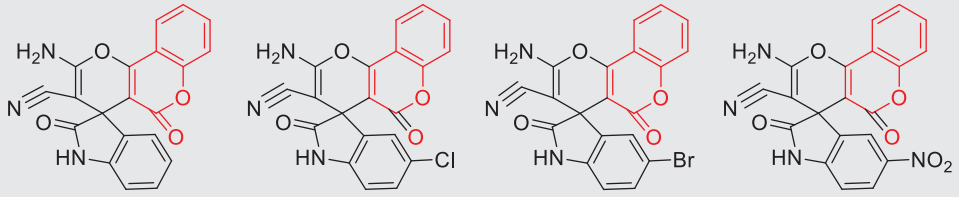
[a]Isolated yield, bold values show the best reaction conditions in terms of reaction time and yield.

the effective participation of CsF in the model reaction, we carried out the reaction with various metal salts including NaF, KF, and $Cs_2CO_3$ (Table 1, entries 7-10). In all cases, the reaction proceeded to completion and the results were insignificant. This clearly indicates that the catalytic role of CsF on the effective synthesis of **4a** to excellent yield and speed up the reaction. Encouraged by the above results, we expanded the scope of the present method to a one-pot synthesis of various spirooxindoles by reacting isatins, C−H-activated compounds and malononitrile. To our surprise, various isatins get reacted with C−H-activated acids like 4-hydroxycoumarin **3a**, 1,3-dimethylbarbituric acid **3b**, thiobarbituric acids **3c**, 1-phenyl-3-methyl-5-pyrazolone **3d**, 3-methyl-2-pyrazolin-5-one **3e** smoothly under the present conditions affording good to the excellent yield of the products in a very short time (Table 2).

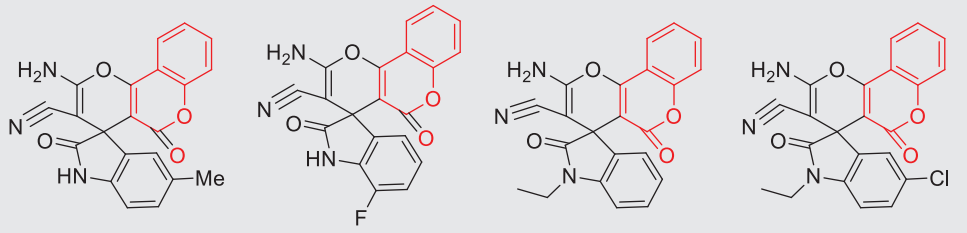
**TABLE 2** Synthesis of spirooxindole-pyran derivatives [**4a-aa**][a]



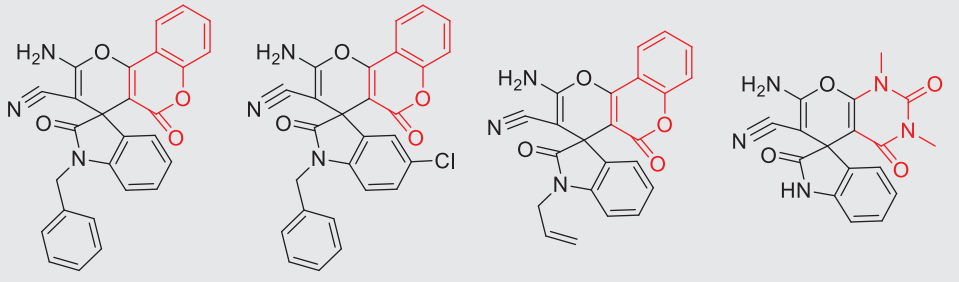

1 2 3 4a-x



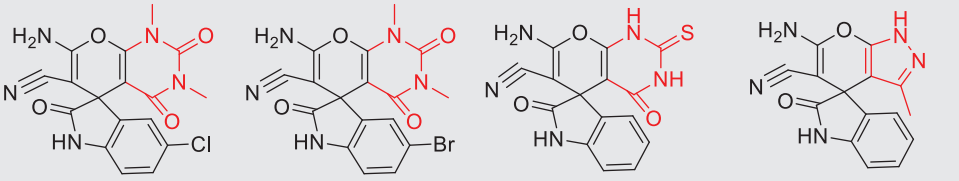
**4a**, 5 min (96%) **4b**, 5 min (92%) **4c**, 5 min (93%) **4d**, 5 min (94%)



**4e**, 10 min (91%) **4f**, 5 min (95%) **4g**, 15 min (92%) **4h**, 15 min (95%)



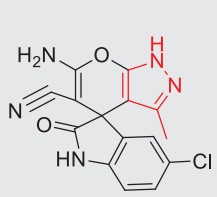
**4i**, 25 min (96%) **4j**, 15 min (95%) **4k**, 15 min (93%) **4l** 10 min (92%)



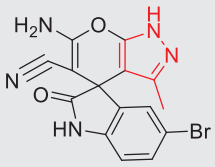
**4m**, 10 min (94%) **4n**, 10 min (93%) **4o**, 10 min (94%) **4p**, 5 min (98%)

(Continues)

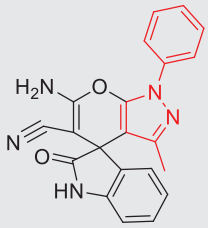
**TABLE 2** (Continued)



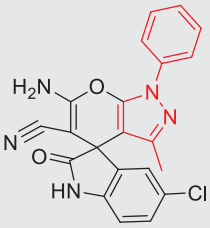
**4q**, 5 min (93%)



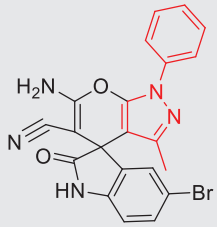
**4r**, 10 min (98%)



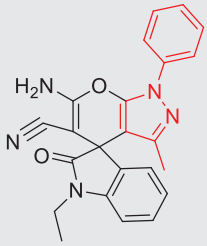
**4s**, 5 min (99%)



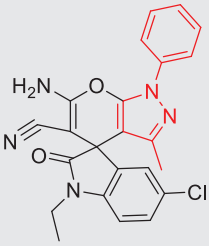
**4t**, 5 min (98%)



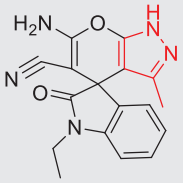
**4u**, 10 min (95%)



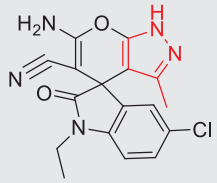
**4v**, 3 min (98%)



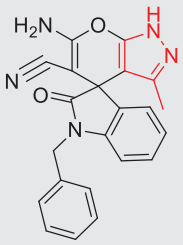
**4w**, 4 min (99%)



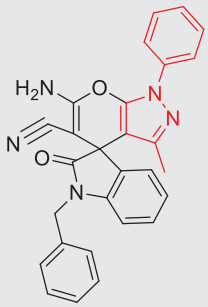
**4x**, 5 min (98%)



**4y**, 5 min (95%)



**4z**, 3 min (98%)



**4aa**, 7 min (99%)

[a]Experimental conditions: Isatin (2.0 mmol), malononitrile (2.2 mmol), carbonyl compounds possessing a reactive C−H-activated compounds like 4-hydroxycoumarin/barbituric acids/pyrazolones (2.0 mmol), CsF (10 mol%), and 8 mL of ethanol at room temperature.

Under the optimum conditions, various substituted isatins as well as N-alkylated isatins were reacted successfully with 4-hydroxycoumarin (Table 2, **4a–4k**), barbituric acids (Table 2, **4r–4o**), and pyrazolones (Table 2, 4**p–4aa**). All reactions furnished the corresponded products in high yields in short reaction time (3-25 min). The reaction of simple isatins with 4-hydroxycoumarin completed within 5 min (Table 2, **4a–4d**) as compared to alkylated isatins need more reaction times (15-25 min) for the completion (Table 2, **4g–4k**). The 5-Nitro (Table 2, **4d**), 5-Methyl (Table 2, **4e**), 7-Fluoro (Table 2, **4f**) substitution on isatin ring also tolerate given reaction conditions to give excellent yield. While all barbituric acids are reacted with isatin within 10 min and yield up to 92%-94% (Table 2, **4r–4o**). In the case of pyrazolones, all reactions take place very smoothly and completed within 3-10 min (Table 2, 4p-4aa). In comparison to all given products, **4z** completed with the lowest time (3 min) and **4f** needed the highest reaction time (25 min) and products **4s**, **4w**, and **4aa** were obtained in high yield up to 99%. The structures of the synthesized compounds were elucidated through IR, $^{1}$H NMR, $^{13}$C NMR, and HRMS analysis. The structure of product **4h** was also confirmed by taking single crystal XRD (Figure 1).

After the successful synthesis of spiro-4*H*-pyran derivatives **4a–4aa**, the scope of this methodology was further extended toward bis-spiro-4*H* isatin derivatives. The biological activities were usually enhanced when different substitutions are present on the two heterocyclic moieties in the bis-compound.[28] However, the extreme steric conjugation in bis-heterocycles makes the construction of all-carbon quaternary centers a formidable challenge for

synthetic organic chemists.[29] In the literature, an interesting report available on a biologically active bis-heterocycles possessing two spirocyclic rings, each constructed by using heterocyclic moiety.[30] Therefore, we synthesized bis-spirooxindoles from the reaction between bis-isatins, malononitrile and C−H activated compounds were also achieved by this protocol (Table 3). As expected, all the reaction showed good functional compatibility. The given bis-spirooxindole systems are skillfully and proficiently synthesized from simple, readily available starting materials.

All bis-spirooxindole-pyran were formed within short reaction time (10 min) and in excellent yield (92%-96%). The FT-IR spectrum of bis-spirooxindole-pyran structure shows NH band in between 3410 and 3315 $cm^{-1}$. All the products were isolated pure just by pouring in ice water mixture followed by recrystallization from ethanol; no

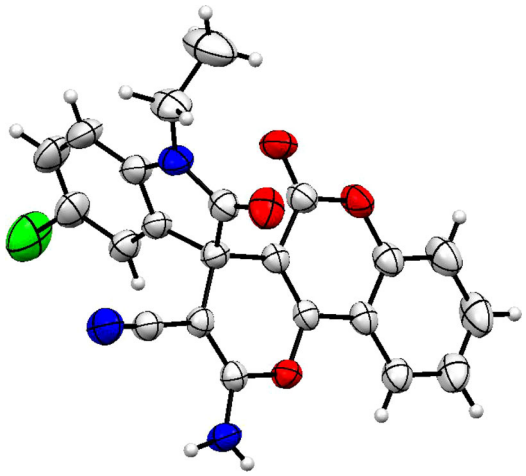
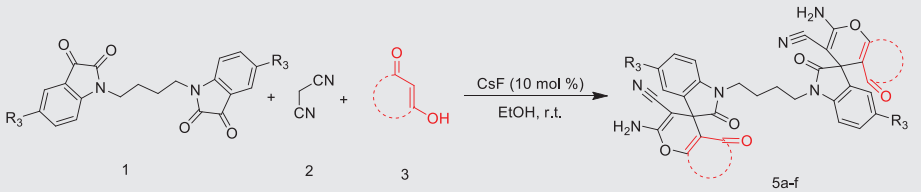
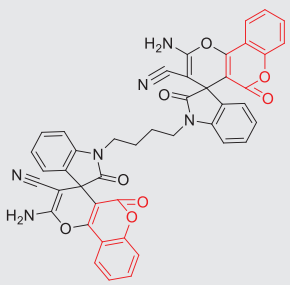


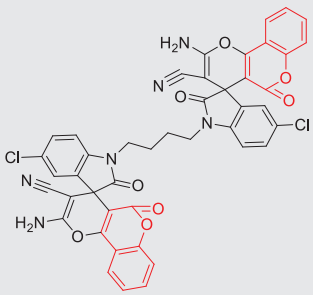
**FIGURE 1** ORTEP diagram for compound **4h** (CCDC 1551670)

**TABLE 3** Synthesis of bis-spirooxindole derivatives [**5a-f**][a]

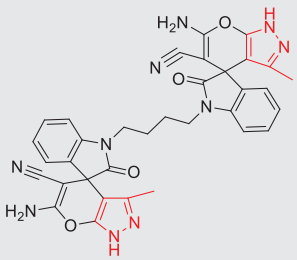


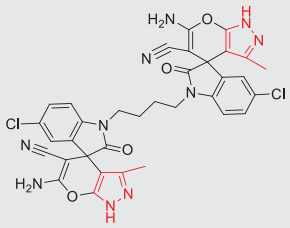
**5a**, 10 min (92%)



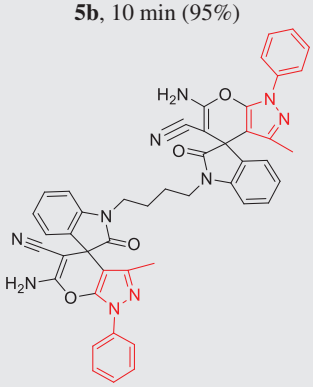
**5b**, 10 min (95%)



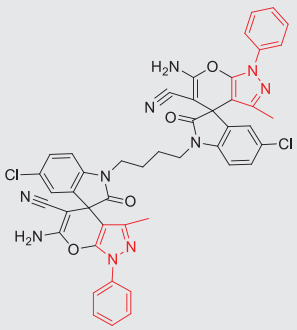
**5c**, 10 min (94%)



**5d**, 10 min (94%)



**5e**, 10 min (96%)



**5f**, 10 min (96%)

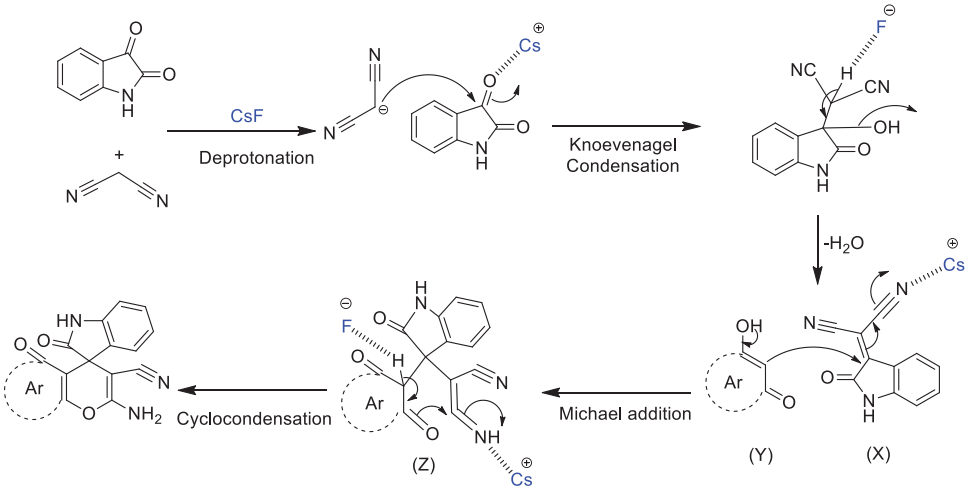
[a]Experimental conditions: Isatin (1.0 mmol), malononitrile (2.2 mmol), 4-hydroxycoumarin/pyrazolone (2.0 mmol), 10 mol% CsF, and 8 mL of ethanol at room temperature.

tedious chromatographic purification was needed. The synthesized products were again characterized based on analytical data and detailed spectral studies. All the known compounds had physical and spectroscopic data identical to the literature values. Herein, we propose a mechanism in Scheme 2, for the formation of functionalized spirooxindole-pyran annulated heterocycles under the reaction conditions where CsF acts as a carbonyl activator as well as base.[31] It is proposed that the intermediate (X) is formed in situ by the Knoevenagel condensation of isatin with malononitrile which is attacked by the enolate (Y) of C−H activated compound through Michael addition giving the adduct (Z). The adduct (Z) undergoes cyclization to afford the desired product.

Finally, to manifest the efficiency and capability of the present protocol in the synthesis of different spirooxindole-pyran derivatives, it has been compared with some of the previously reported and published procedures. Results are summarized in Table 4. Comparison clearly illustrates that the present method is indeed superior to several of the others in terms of high product yield, short reaction time, no additional energy required (ie, heating and ultrasonication), and easy isolation of final products by simple work-up. The above results clearly indicate the present catalytic procedure is extendable to a wide variety of substrates to construct a diversity-oriented library of 4H-pyrans.

## 3 | CONCLUSION

In conclusion, we have developed an efficient, rapid, one-pot, CsF promoted multicomponent method for the synthesis of functionalized spirooxindole-pyran and bis-spirooxindole-pyran derivatives. Using this protocol, 33 compounds were synthesized by reacting isatins and bis-isatins, malononitrile with 4-hydroxycoumarin, 1,3-dimethylbarbituric acid, thiobarbituric acids, 1-phenyl-3-methyl-5-pyrazolone, and 3-methyl-2-pyrazolin-5-one. All reactions were completed within 25 min with excellent yields (92%-99%). The final products were isolated by simple filtration which makes it a valuable alternative to the previously reported methods for constructing libraries of spirooxindole-pyran annulated heterocycles. The




**SCHEME 2** Plausible mechanism for the synthesis of spirooxindole-pyran derivatives

**TABLE 4** Comparison between CsF-catalyzed protocols with earlier reported protocols for the synthesis of **4a**

| Entry | Catalyst (mol%/mg) | Solvent | Temp. (°C)/ power | Time (min) | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| 1 | Alum (0.35 mol%) | $H_2O$ | 80 | 30 | 80 | [11] |
| 2 | L-proline (10 mol%) | $H_2O$ | 80 | 15 | 94 | [12] |
| 3 | Caspian Isinglass (5 mg) | $H_2O$ | 60 | 20 | 90 | [13] |
| 4 | DABCO (6 mol%) | EtOH | Reflux | 24 | 98 | [32] |
| 5 | TEBA (20 mol%) | $H_2O$ | 60 | 180 | 88 | [33] |
| 6 | TBAB (10 mol%) | $H_2O$ | 100 | 60 | 88 | [34] |
| 7 | **CsF (10 mol%)** | **EtOH** | **r.t.** | **5** | **96** | **This work** |

Note: Some reported results for the synthesis of compound **4a**.

interesting activities of the CsF described here will be helpful for further combinatorial synthesis and new protocol designing.

## 4 | EXPERIMENTAL

### 4.1 | General

All solvents and chemicals used in this work were obtained commercially and used as received. Melting points were measured in open capillary tubes and are uncorrected. FT-IR spectra were obtained on Shimadzu IR-Affinity spectrometer (KBr pellets). The NMR were recorded on an NMR spectrometer, model Advance-II (Bruker). The instrument is equipped with a cryomagnet of field strength 9.4 T. Its $^{1}H$ frequency is 400/500 MHz, and $^{13}C$ frequency is 100/125 MHz, using TMS as an internal standard and DMSO-$d_6$ as a solvent. Chemical shifts are given in parts per million ($\delta$) and the coupling constants are given in Hertz. Silica gel-G plates (Merck) were used for thin-layer chromatography (TLC) analysis. CsF was obtained from Sigma Aldrich-Indian company and was used without further purification.

#### 4.1.1 | General procedure for the preparation of spirooxindole-pyran derivatives (4a–4aa)

To a magnetically stirred solution of aromatic aldehydes or isatins (2 mmol), malononitrile (2.2 mmol), C−H-activated acidic compounds (2 mmol), and a catalytic amount of CsF (10 mol%) in ethanol at room temperature. The progress of the reaction was monitored by TLC in mixture of n-hexane and ethyl acetate (7:3) solvent system. During the reaction, solid observed in flask within 3 to 25 min and after complete conversion, the reaction mass was transferred to an ice-water mixture under vigorous stirring. Then the solid was collected by filtration, washed with cold aq. ethanol, and dried. The authenticity of products was established by comparing their melting points with those reported in the literature and by the spectral data of FT-IR, NMR, and mass analysis.

#### 4.1.2 | General procedure for the preparation of bis-spirooxindole derivatives (5a-f)

To a magnetically stirred solution of bis-isatins (1 mmol), malononitrile (2.2 mmol), 4-hydroxycoumarin/1-phenyl-3-methyl-5-pyrazolone/3-methyl-2-pyrazolin-5-one (2 mmol), and a catalytic amount of CsF (10 mol%) in ethanol at room temperature. The progress of the reaction was monitored by TLC in mixture of n-hexane and ethyl acetate (7:3) solvent system. During the reaction, solid observed in flask within 10 min and after complete conversion, the reaction mass was transferred to an ice-water mixture under vigorous stirring. Then the solid was collected by filtration, washed with cold aq. ethanol, and dried. The authenticity of products was established by comparing their melting points with those reported in the literature and by the spectral data of FT-IR, NMR, and mass analysis.

**2′-amino-1-ethyl-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile *(4g)***

White Solid, Yield: 94%; M. P. 292 to 294°C; IR (KBr): $\nu_{max}$ 3302, 3184, 2196, 1710, 1676, 1606, 1473, 1361, 1222, 1093, 966, 761, 561, 499 $cm^{-1}$; $^{1}H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.22 (t, $J$ = 7.0 Hz, 3H), 3.79 (q, $J$ = 7.0 Hz, 2H), 7.01 (t, $J$ = 7.4 Hz, 1H), 7.07 (d, $J$ = 7.8 Hz, 1H), 7.24 (d, $J$ = 7.4 Hz, 1H), 7.31 (t, $J$ = 7.6 Hz, 1H), 7.44 (d, $J$ = 8.3 Hz, 1H), 7.51 (t, $J$ = 7.6 Hz, 1H), 7.68 (s, 2H), 7.74 (t, $J$ = 7.3 Hz, 1H), 7.96 (d, $J$ = 7.2 Hz, 1H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 12.0, 34.5, 47.0, 56.7, 101.2, 108.4, 112.4, 116.5, 116.6, 122.4, 122.7, 123.8, 124.8, 128.9, 132.4, 133.5, 142.5, 152.0, 155.1, 158.1, 158.4, 175.0; HRMS (ESI): *m/z* calcd for $C_{22}H_{15}N_3O_4$ $[M + Na]^+$, 408.0960 found, 408.0933.

**2′-amino-5-chloro-1-ethyl-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile *(4h)***

White Solid, Yield: 95%; M. P. 282 to 284°C; IR (KBr): $\nu_{max}$ 3568, 3441, 3329, 3155, 2204, 1712, 1687, 1606, 1475, 1438, 1357, 1236, 1168, 1089, 968, 819, 759, 601, 565 $cm^{-1}$; $^{1}H$ NMR (500 MHz, DMSO-$d_6$): $\delta$ 1.20 (s, 3H), 3.75 to 3.84 (m, 2H), 7.16 (d, $J$ = 10 Hz 1H), 7.38 (d, $J$ = 10 Hz 1H), 7.48 to 7.56 (m, 3H), 7.76 to 7.79 (m, 3H), 7.96 (d, $J$ = 10 Hz, 1H); $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$ 12.5, 35.2, 47.7, 56.6, 96.5, 109.6, 118.2, 120.6, 123.6, 125.2, 127.0, 129.9, 131.9, 137.7, 142.8, 144.4, 145.5, 161.5, 176.4; HRMS (ESI): *m/z* calcd for $C_{22}H_{14}ClN_3O_4$ $[M + Na]^+$, 442.0571 found, 442.1509.

**2′-amino-1-benzyl-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile *(4i)***

White Solid, Yield: 96%; M. P. 280 to 282°C; IR (KBr): $\nu_{max}$ 3568, 3348, 3186, 3074, 2929, 2204, 1681, 1610, 1475, 1359, 1178, 1097, 958, 754, 694, 555 $cm^{-1}$; $^{1}H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.06 (dd, $J$ = 16.1, 11.4 Hz, 2H, $-CH_2$), 6.75 (d, $J$ = 7.7 Hz, 1H), 7.00 (t, $J$ = 7.48 Hz, 1H), 7.17 to 7.22 (m, 2H), 7.26 (d, $J$ = 7.16 Hz, 1H), 7.30 to 7.33 (m, 2H ), 7.40 (d, $J$ = 8.3 Hz, 1H), 7.45 to 7.49 (m, 3H), 7.65 (s, 2H, $NH_2$), 7.71(t, $J$ = 7.4 Hz, 1H), 8.00

(d, $J$ = 7.4 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 43.7, 47.4, 56.8, 101.2, 109.1, 112.5, 116.4, 117.0, 122.8, 122.9, 123.7, 124.7, 127.0, 127.1, 128.3, 128.8, 132.2, 133.4, 135.7, 142.7, 152.1, 155.3, 158.36, 158.7, 175.9; HRMS (ESI): $m/z$ calcd for $C_{27}H_{17}N_3O_4$ $[M + Na]^+$, 470.1117 found, 442.1509.

### 2′-amino-1-benzyl-5-chloro-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile *(4j)*

White Solid, Yield: 95%; M. P. 296 to 298°C; IR (KBr): $\nu_{max}$ 3481, 3450, 3332, 2960, 2196, 1685, 1593, 1346, 1253, 1112, 1039, 829, 621 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.99 (dd, $J$ = 16.2, 5.4 Hz, 2H), 6.77 (d, $J$ = 8.36 Hz, 1H), 7.21 to 7.34 (m, 4H), 7.40 to 7.52 (m, 5H), 7.73 (d, $J$ = 7.32 Hz, 1H), 7.77 (s, 2H), 8.00 (d, $J$ = 7.28 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 43.6, 47.4, 56.0, 100.5, 100.3, 112.5, 116.4, 116.8, 122.8, 124.2, 124.7, 126.9, 127.1, 127.2, 128.3, 128.6, 133.4, 134.0, 135.2, 141.5, 152.1, 155.5, 158.4, 158.7, 175.5; HRMS (ESI): $m/z$ calcd for $C_{27}H_{16}ClN_3O_4$ $[M + Na]^+$, 504.0727 found, 504.1324.

### 1-allyl-2′-amino-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile *(4k)*

White Solid, Yield: 93%; M. P. 296 to 298°C; IR (KBr): $\nu_{max}$ 3454, 3271, 3153, 2198, 1703, 1602, 1479, 1361, 1192, 1062, 948, 688, 497 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.30 to 4.35 (m, 1H), 4.41 to 4.46 (m, 1H), 5.19 (d, $J$ = 10.52 Hz, 1H), 5.44 (d, $J$ = 17.2 Hz, 1H), 5.82 to 5.91 (m, 1H), 6.94 (d, $J$ = 7.8 Hz, 1H), 7.02 (t, $J$ = 7.4 Hz, 1H ), 7.24 to 7.30 (m, 2H), 7.44 (d, $J$ = 8.28 Hz, 1H), 7.51 (t, $J$ = 7.6 Hz, 1H), 7.70 (s, 2H), 7.72 to 7.76 (m, 1H), 7.96 to 7.98 (m, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 42.1, 47.2, 56.6, 101.1, 109.0, 112.4, 116.5, 116.7, 116.8, 122.6, 122.7, 123.7, 124.8, 128.8, 131.3, 132.1, 133.5, 142.7, 152.0, 155.1, 158.2, 158.5, 175.3; HRMS (ESI): $m/z$ calcd for $C_{23}H_{15}N_3O_4$ $[M + Na]^+$, 420.0960 found, 420.1235.

### 6′-amino-5-chloro-1-ethyl-3′-methyl-2-oxo-1′-phenyl-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile *(4w)*

White Solid, Yield: 99%; M. P. 210 to 212°C; IR (KBr): $\nu_{max}$ 3392, 3329, 3196, 2960, 2193, 1681, 1365, 1251, 1211, 1159, 1091, 1035, 559 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 1.23 (t, $J$ = 7.1 Hz, 3H), 1.56 (s, 3H), 3.81 to 3.84 (m, 2H), 7.24 to 7.25 (m, 2H), 7.35 to 7.38 (m, 2H), 7.43 to 7.46 (m, 1H), 7.51 to 7.55 (m, 2H), 7.67 (s, 2H, $-NH_2$), 7.80 to 7.82 (m, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 12.3, 12.9, 35.3, 47.9, 55.9, 95.9, 110.9, 118.1, 120.7, 125.6, 127.1, 127.8, 129.8, 134.2, 137.7, 141.2, 144.2, 145.6, 161.5, 175.6; HRMS (ESI): $m/z$ calcd for $C_{23}H_{18}ClN_5O_2$ $[M + Na]^+$, 431.1149 found, 432.1160.

### 2′-amino-1-(4-(2′-amino-3′-cyano-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromen]-1-yl)butyl)-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile *(5a)*

Brown Solid, Yield: 92%; M. P. >310°C; IR (KBr): $\nu_{max}$ 3410, 3315, 3047, 2872, 2193, 1647, 1610, 1598, 1510, 1487, 1427, 1155, 1070, 871, 796, 559 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 1.79 (s, 2H), 3.72 to 3.82 (m, 2H), 6.99 to 7.02 (m, 1H), 7.12 to 7.14 (m, 1H), 7.26 to 7.30 (m, 2H), 7.50 to 7.51 (m, 1H), 7.54 to 7.57 (m, 1H), 7.73 (s, 2H), 7.76 to 7.81 (m, 1H), 7.96 to 7.98 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 24.22, 24.26, 47.1, 56.7, 101.2, 108.7, 112.3, 116.6, 116.7, 122.6, 123.8, 124.9, 129.0, 132.2, 133.6, 142.9, 151.9, 155.1, 158.1, 158.4, 175.5; HRMS (ESI): $m/z$ calcd for $C_{44}H_{28}N_6O_8$ $[M + Na]^+$, 791.1866 found, 791.3235.

### 2′-amino-1-(4-(2′-amino-5-chloro-3′-cyano-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromen]-1-yl)butyl)-5-chloro-2,5′-dioxo-5′H-spiro[indoline-3,4′-pyrano[3,2-c]chromene]-3′-carbonitrile *(5b)*

Brown Solid, Yield: 95%; M. P. 232 to 234°C; IR (KBr): $\nu_{max}$ 3473, 3290, 3221, 3197, 3045, 2889, 2195, 1654, 1597, 1581, 1516, 1490, 1400, 1350, 1327, 1199, 1076, 1049, 987, 758 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.80 (s, 2H), 3.80 (s, 2H), 7.13 to 7.60 (m, 5H), 7.76 (s, 3H), 7.97 to 7.99 (m, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 18.4, 24.0, 47.3, 56.1, 100.6, 110.1, 112.5, 116.5, 116.7, 122.8, 124.2, 124.7, 126.8, 128.7, 133.5, 134.1, 141.8, 152.1, 155.4, 158.3, 158.6, 175.4; HRMS (ESI): $m/z$ calcd for $C_{44}H_{26}Cl_2N_6O_8$ $[M + Na]^+$, 859.1087; found, 859.2521.

### 6′-amino-1-(4-(6′-amino-5-chloro-5′-cyano-3′-methyl-2-oxo-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazol]-1-yl)butyl)-5-chloro-3′-methyl-2-oxo-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile *(5d)*

Brown Solid, Yield: 94%; M. P. 258 to 260°C; IR (KBr): $\nu_{max}$ 3311, 3228, 3180, 3126, 2845, 2196, 1732, 1645, 1593, 1481, 1398, 1346, 1161, 1085 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.48 to 1.51 (m, 3H), 1.72 (s, 2H), 3.8 (s, 2H), 7.16 to 7.21 (m, 3H), 7.33 (s, 2H), 12.34 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 9.1, 24.4, 47.1, 54.4, 94.4, 110.5, 118.5, 124.5, 127.3, 127.39, 128.9, 134.03, 134.05, 134.7, 134.8, 141.0, 141.1, 155.2, 162.6, 176.1; HRMS (ESI): $m/z$ calcd for $C_{34}H_{26}Cl_2N_{10}O_4$ $[M + Na]^+$, 731.1413 found, 731.2646.

**6′-amino-1-(4-(6′-amino-5′-cyano-3′-methyl-2-oxo-1′-phenyl-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazol]-1-yl)butyl)-3′-methyl-2-oxo-1′-phenyl-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile *(5e)***

Pale Yellow Solid, Yield: 96%; M. P. 188 to 190°C; IR (KBr): $\nu_{max}$ 3633, 3441, 3311, 3172, 3066, 2196, 1707, 1649, 1599, 1510, 1381, 1139, 1080, 925, 752, 551 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): $\delta$ 1.47 (s, 3H), 1.82 (s, 2H), 3.87 (s, 2H), 7.12 (s, 1H), 7.25 (s, 2H), 7.36 (s, 2H), 7.53 (s, 2H), 7.67 (s, 2H), 7.83 (s, 2H); $^{13}C$ NMR (125 MHz, DMSO-$d_6$): $\delta$ 12.3, 25.1, 47.9, 56.6, 96.5, 109.6, 118.2, 120.6, 123.6, 125.2, 127.0, 129.9, 131.9, 137.7, 142.8, 144.4, 145.5, 161.5, 176.4; HRMS (ESI): *m/z* calcd for $C_{34}H_{26}Cl_2N_{10}O_4$ $[M + Na]^+$, 815.2819 found, 815.4206.

**6′-amino-1-(4-(6′-amino-5-chloro-5′-cyano-3′-methyl-2-oxo-1′-phenyl-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazol]-1-yl)butyl)-5-chloro-3′-methyl-2-oxo-1′-phenyl-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile *(5f)***

Pale Yellow Solid, Yield: 96; M. P. 238 to 240°C; IR (KBr): $\nu_{max}$ 3641, 3448, 3315, 3174, 2939, 2196, 1712, 1649, 1599, 1504, 1388, 1153, 1072, 815, 750, 559 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.50 to 1.51 (m, 3H), 1.76 (s, 2H), 3.85 (s, 2H), 7.28 (t, $J$ = 7.4 Hz, 1H), 7.35 to 7.45 (m, 3H), 7.53 (t, $J$ = 7.6 Hz, 2H), 7.72 (s, 2H, $-NH_2$), 7.81 (d, $J$ = 7.8 Hz, 2H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 11.8, 24.3, 47.4, 55.2, 95.2, 95.3, 110.7, 117.7, 120.2, 124.9, 126.5, 127.3, 129.2, 129.3, 133.5, 137.1, 141.0, 143.6, 145.0, 161.0, 175.5; HRMS (ESI): *m/z* calcd for $C_{46}H_{34}Cl_2N_{10}O_4$ $[M + Na]^+$, 883.2039 found, 883.3267.

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## ORCID

*Yogesh B. Wagh* https://orcid.org/0000-0002-3364-7519

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