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**REGULAR ARTICLE**

# Zinc chloride catalyzed multicomponent synthesis of pyrazolopyridocoumarin scaffolds

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**Abstract.** An efficient synthesis of a series of pyrazolopyridocoumarins is reported by condensation of 4-hydroxycoumarin, benzaldehydes and 1-alkyl-5-amino-pyrazoles in the presence of 10 mol% zinc chloride in ethanol under reflux conditions through one-pot reaction. The significant attraction of this protocol is being a simple procedure, mild reaction condition, and excellent yield. The molecular structure of the compound (**4e**) is established by single crystal X-ray structure determination.

**Keywords.** Coumarins; pyridine; pyrazole; zinc chloride; multicomponent reactions; one-pot synthesis.

## 1. Introduction

Multicomponent reactions (MCRs) efficiently combine three or more reactants simultaneously in one pot that do not need the isolation, purification and characterization of intermediate products. The MCRs have additional benefits of being selective, time-saving, convergent, atom economy and playing an important role in modern synthetic methodology.[1–13]

Fused polyheterocycles are an important class of organic molecules[14–18] because of their widespread applications (Figure 1) as pharmaceuticals (**A, B, C & D**),[19–21] photosensitizer (**E**)[20,21] and fluorescent dye (**F**).[22] Coumarin nucleus fused with pyridine rings have received increasing attention due to their photophysical properties[23] and potential biological activities such as antimicrobial,[24] antiosteoporotic,[25] anti-inflammatory[21] and analgesic.[26]

The synthesis of fused tetracyclic pyrazolopyridocoumarins has evoked much attention as a result of which a variety of synthetic methodologies are reported. Among them, the reaction of 4-hydroxycoumarin, aromatic aldehydes and 5-amino-3-methyl-1-phenylpyrazole is of particular interest.[27] A few protocols have been developed for the preparation of pyrazolopyridocoumarin derivatives with the use of various catalysts such as *n*-tetrabutylammonium tribromide,[28] $Zn(OTf)_2$,[29] glacial acetic acid,[30] piperidine in acetic acid,[31] and iodine.[19,32] However, these methodologies suffer from one or more shortcomings such as long reaction time, low yields and use of excess amounts of expensive and toxic catalysts. Therefore, the development of an efficient and low-cost method for the synthesis of fused tetracyclic pyrazolopyridocoumarins is still in great demand.

Based on the literature survey and in continuation with our ongoing research work on the preparation of biologically active heterocycles,[33–52] we desire to report a novel method for synthesis of pyrazolopyridocoumarins from simple and readily available starting materials, which went through the simultaneous construction of pyrazole and pyridine rings.

## 2. Experimental

### 2.1 *General*

The melting points were determined by an open capillary method using electric melting point apparatus and were not

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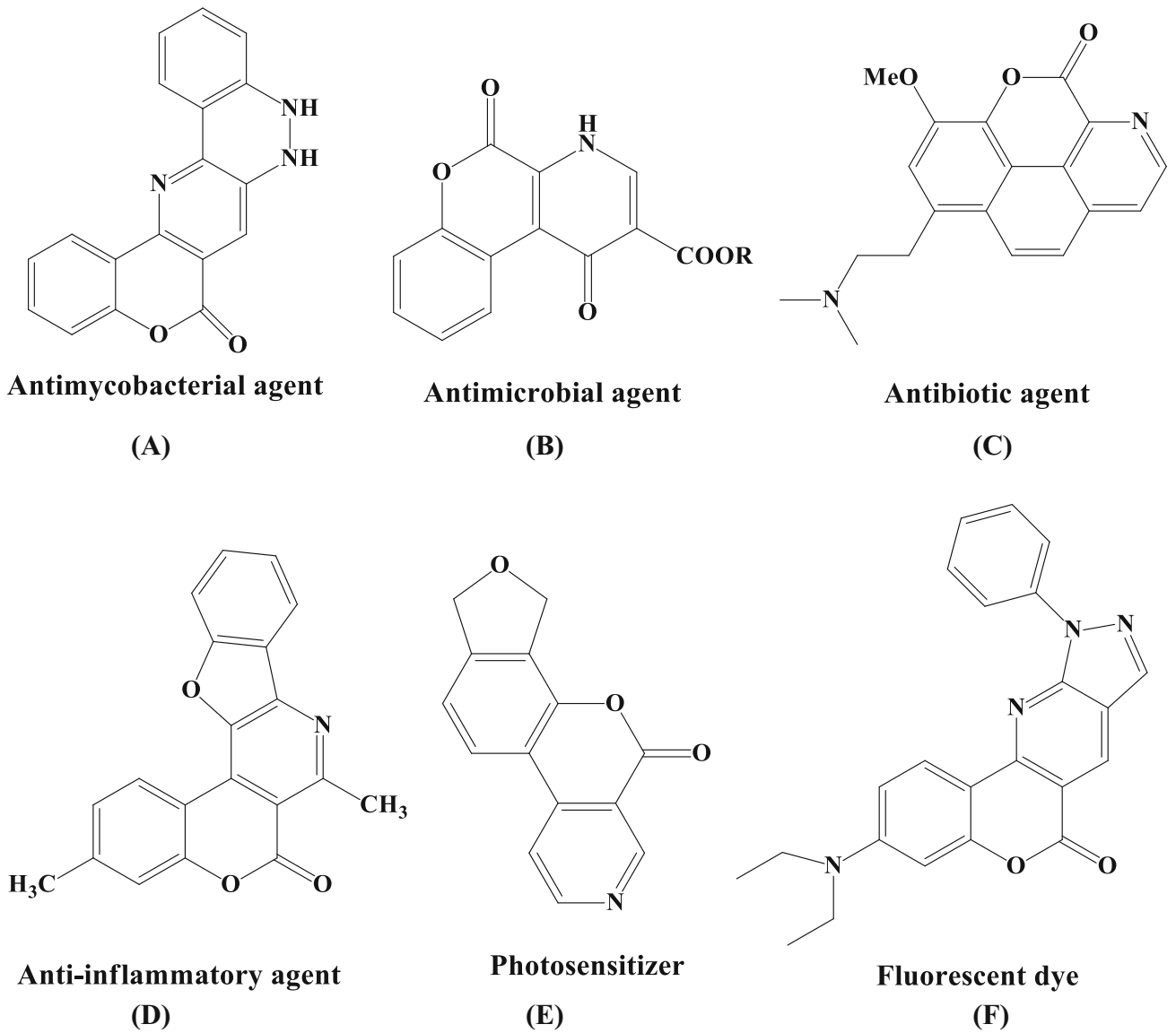



**Figure 1.** Pyridocoumarins in pharmaceuticals, photosensitizer and dye.

corrected. The IR spectra (KBr disc) were measured with a Shimadzu-8400S FT-IR spectrophotometer. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra in $CDCl_3$/DMSO-$d_6$were recorded using a Bruker spectrometer at IISc, Bangalore. Chemical shifts were given in parts per million (ppm) relative to tetramethylsilane. The mass spectrum (ESI-MS) was obtained at IISc, Bangalore. The purity of the compounds was checked by TLC. The elemental analyses were carried out using Elemental Vario Micro Cube CHN Rapid Analyzer. All the compounds gave satisfactory elemental analyses.

## 2.2 *General procedure for the zinc chloride catalysed the multicomponent synthesis of pyrazolopyridocoumarins*

To a stirring solution of 4-hydroxycoumarin **(1)** (0.5 g, 0.003 mol), benzaldehydes **2**(**a**–**h**) (0.003 mol) and 1-alkyl-5-amino-pyrazoles **3**(**a**–**b**) (0.003 mol) in ethanol (15 mL) was added zinc chloride (10 mol%). The reaction flask was refluxed in an oil bath for 6–7 h. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure. The residue left out was dissolved with ethyl acetate and added aqueous $Na_2S_2O_3$ solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (15 mL x 3). The combined organic phase was washed with water and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel [eluent: hexane and ethyl acetate (7:3)] provided the pure title compounds.

2.2a *10-Ethyl-7-phenyl-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclo-penta[b]phenanthren-6-one (**4a**)*: Yield: 86%; Colorless solid; M.p. 301–303 °C; IR (KBr, cm$^{-1}$): 1725 (C=O), 3082, 3173 (NH); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.45 (t, 3H, $CH_3$ of $C_2H_5$ group, $J_{1,2}$ = 7.6 Hz), 3.54 (s, 1H, methine proton), 4.19 (q, 2H, $CH_2$ of $C_2H_5$ group,

$J_{1,2}$ = 7.6 Hz), 6.88–8.74 (m, 10H, Ar-H), 10.67 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 14.0, 45.9, 48.1, 101.1, 104.5, 108.0, 114.5 (2C), 120.9, 121.8, 127.5, 127.7 (2C), 128.3 (2C), 137.0, 137.2, 147.9, 152.0, 157.4, 159.9; Anal. $C_{21}H_{17}N_3O_2$. Cald for: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.36; H, 4.93; N, 12.19.

2.2b *7-(4-Bromo-phenyl)-10-ethyl-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclo-penta[b]phenanthren-6-one (**4b**)*: Yield: 89%; Brown solid; M.p. 311–313 °C; IR (KBr, cm$^{-1}$): 1721 (C=O), 3068, 3192 (NH); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.44 (t, 3H, $CH_3$ of $C_2H_5$ group, $J_{1,2}$ = 7.6 Hz), 3.47 (s, 1H, methine proton), 4.44 (q, 2H, $CH_2$ of $C_2H_5$ group, $J_{1,2}$ = 7.6 Hz), 7.15–8.92 (m, 9H, Ar-H), 10.50 (s, 1H, NH);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 14.0, 45.3, 49.8, 102.8, 103.7, 113.0, 115.9, 119.9, 124.0, 125.5 (2C), 132.9 (3C), 133.1, 142.1, 148.2, 149.2, 151.3, 152.0, 160.15; Anal. $C_{21}H_{16}BrN_3O_2$. Cald for: C, 59.73; H, 3.61; N, 9.95. Found: C, 59.69; H, 3.60; N, 9.88.

2.2c *10-Ethyl-7-(2-hydroxy-phenyl)-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclo-penta[b]phenanthren-6-one (**4c**)*: Yield: 87%; Colorless solid; M.p. 309–311 °C; IR (KBr, cm$^{-1}$): 1722 (C=O), 3076 (OH), 3209, 3447 (NH); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.53 (t, 3H, $CH_3$ of $C_2H_5$ group, $J_{1,2}$ = 7.6 Hz), 3.61 (s, 1H, methine proton), 4.45 (q, 2H, $CH_2$ of $C_2H_5$ group, $J_{1,2}$ = 7.6 Hz), 7.09–8.33 (m, 9H, Ar-H), 9.85 (s, 1H, OH), 10.70 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 14.1, 45.9, 48.0, 102.4, 107.6, 108.3, 112.9 (2C), 114.7, 122.2, 123.9, 127.8, 129.7, 133.9, 139.1, 141.7, 148.3, 150.9, 152.0, 152.9, 160.4. Anal. $C_{21}H_{17}N_3O_3$. Cald For: C, 70.18; H, 4.77; N, 11.69. Found: C, 70.06; H, 4.65; N, 11.62.

2.2d *10-Ethyl-7-(4-methoxy-phenyl)-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclo-penta[b]phenanthren-6-one (**4d**)*: Yield: 92%; Colorless solid; M.p. 274–276 °C; IR (KBr, cm$^{-1}$): 1722 (C=O), 3076, 3254 (NH); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.44 (t, 3H, $CH_3$ of $C_2H_5$ group, $J_{1,2}$ = 7.6 Hz), 3.41 (s, 1H, methine proton), 3.61 (s, 3H, $OCH_3$), 4.45 (q, 2H, $CH_2$ of $C_2H_5$ group, $J_{1,2}$ = 7.6 Hz), 7.16–8.45 (m, 9H, Ar-H), 10.32 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 13.7, 44.6, 48.8, 58.8, 102.1, 106.0 (3C), 114.7, 114.9, 125.6 (2C), 128.1, 129.3, 129.4, 130.5, 133.5, 133.6, 142.6, 149.4, 150.7, 160.4; Anal. $C_{22}H_{19}N_3O_3$. Cald for: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.69; H, 5.04; N, 11.16.

2.2e *10-Ethyl-7-(2,3-dimethoxy-phenyl)-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclopenta[b]phenanthren-6-one (**4e**)*: Yield: 96%; Colorless solid; M.p. 297–299 °C; IR (KBr, cm$^{-1}$): 1720 (C=O), 3294, 3409 (NH); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.48 (t, 3H, $CH_3$ of $C_2H_5$ group, $J_{1,2}$ = 8.0 Hz), 3.40 (s, 3H, $OCH_3$), 3.44 (s, 1H, methine proton), 3.61 (s, 3H, $OCH_3$), 4.62 (q, 2H, $CH_2$ of $C_2H_5$ group, $J_{1,2}$ = 8.0 Hz), 6.81–8.73 (m, 8H, Ar-H), 10.23 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 14.5, 24.8, 40.1, 55.6, 60.0, 109.6, 113.3, 116.6, 119.2, 120.3, 123.8, 124.5, 125.1, 130.6, 132.7, 134.0, 144.8, 147.9, 149.7, 150.6, 151.9, 152.0, 158.7; ESI-MS: [M+H] 404.1. Anal. $C_{23}H_{21}N_3O_4$. Cald For: C, 68.47; H, 5.25; N, 10.42. Found: C, 68.38; H, 5.16; N, 10.35.

2.2f *10-Ethyl-7-(3,4,5-trimethoxy-phenyl)-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclopenta[b]phenanthren-6-one (**4f**)*: Yield: 93%; Colorless solid; M.p. 297–299 °C; IR (KBr, cm$^{-1}$): 1718 (C=O), 3275, 3337 (NH); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.55 (t, 3H, $CH_3$ of $C_2H_5$ group, $J_{1,2}$ = 7.6 Hz), 2.34 (s, 1H, methine proton), 2.42 (s, 3H, $OCH_3$), 3.48 (s, 3H, $OCH_3$), 3.60 (s, 3H, $OCH_3$), 4.19 (q, 2H, $CH_2$ of $C_2H_5$ group, $J_{1,2}$ = 7.6 Hz), 6.97–8.44 (m, 7H, Ar-H), 10.52 (s, 1H, NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 13.9, 44.1, 49.3, 55.7, 59.0 (2C), 102.1, 108.0, 111.4, 113.7 (2C), 121.3, 123.6, 126.8, 129.8, 131.1, 134.2, 142.9 (2C), 143.1, 149.1, 151.8, 155.9, 160.1; Anal. $C_{24}H_{23}N_3O_5$. Cald for: C, 66.50; H, 5.35; N, 9.69. Found: C, 66.44; H, 5.31; N, 9.62.

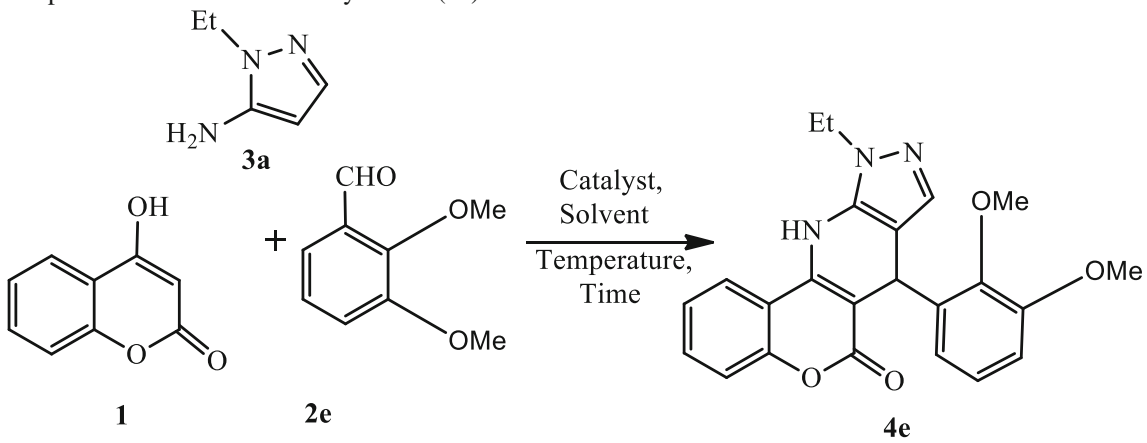
2.2g *7-(4-Chloro-phenyl)-10-methyl-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclopenta[b]phenanthren-6-one (**4g**)*: Yield: 88%; Colorless solid; M.p. 248–250 °C; IR (KBr, cm$^{-1}$): 1721 (C=O), 3184, 3297 (NH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.82 (s, 3H, $CH_3$), 4.27 (s, 1H, methine proton), 6.88–8.10 (m, 9H, Ar-H), 10.33 (s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 36.3, 39.2, 98.9, 106.5, 113.3, 117.5, 121.6, 124.3, 128.5, 128.7, 128.8, 129.1, 131.3, 132.0, 132.6, 143.5, 144.3, 146.9, 152.7, 159.0; Anal. $C_{20}H_{14}ClN_3O_2$. Cald for: C, 66.03; H, 3.88; N, 11.55. Found: C, 65.97; H, 3.81; N, 11.50.

2.2h *10-Methyl-7-(4-nitro-phenyl)-10,11-dihydro-7H-5-oxa-9,10,11-triaza-cyclopenta[b]phenanthren-6-one (**4h**)*: Yield: 81%; Pale yellow solid; M.p. 288–290 °C; IR (KBr, cm$^{-1}$): 1723 (C=O), 3284, 3395 (NH); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.79 (s, 3H, $CH_3$), 4.24 (s, 1H, methine proton), 6.90–8.38 (m, 9H, Ar-H), 10.34 (s, 1H, NH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 36.3, 40.1, 99.0, 107.1, 113.3, 117.5, 121.6, 124.3, 128.3, 128.5, 128.8, 129.1, 131.3, 132.0, 132.6, 144.4, 144.5, 146.0, 152.8, 160.8; Anal. $C_{20}H_{14}N_4O_4$. Cald for: C, 64.17; H, 3.77; N, 14.97. Found: C, 64.12; H, 3.71; N, 14.90.

## 3. Results and Discussion

Our study commenced by optimizing the reaction conditions in order to achieve the title compounds using 4-hydroxycoumarin (**1**), 2,3-dimethoxybenzaldehyde (**2e**) and 1-ethyl-5-amino-pyrazole (**3a**) as a model substrate (Table 1). Initially, when the model reaction was performed without any catalyst in ethanol solvent at room temperature (Table 1, entry 1) and reflux conditions (Table 1, entry 2), no desirable product (**4e**) was obtained even after a prolonged reaction time. This indicated

**Table 1.** Optimization studies for the synthesis (**4e**).[a]



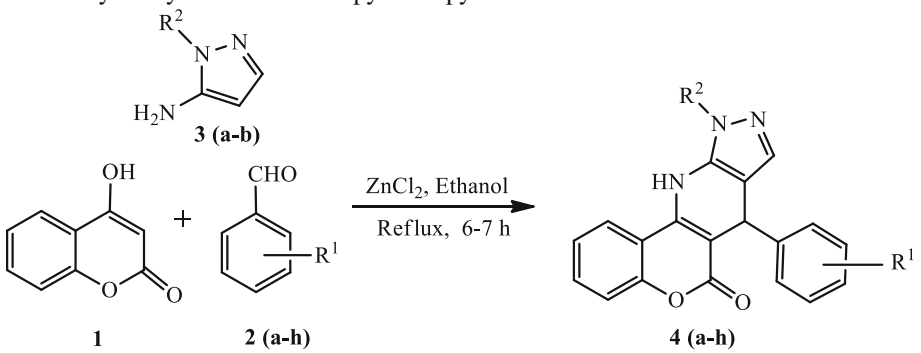

| Entry | Catalyst (10 mol%) | Solvent | Temperature (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | No catalyst | Ethanol | RT | 48 | No Product |
| 2 | No catalyst | Ethanol | Reflux | 48 | No Product |
| 3 | Zeolite | Ethanol | Reflux | 24 | 5 |
| 4 | CuCl | Ethanol | Reflux | 24 | 9 |
| 5 | Iodine | Ethanol | Reflux | 24 | 15 |
| 6 | $ZnCl_2$ | Acetonitrile | Reflux | 9 | 82 |
| 7 | $ZnCl_2$ | DCM | Reflux | 10 | 69 |
| 8 | $ZnCl_2$ | THF | Reflux | 24 | 34 |
| 9 | $ZnCl_2$ | DMF | Reflux | 24 | 23 |
| 10 | $ZnCl_2$ | Toluene | Reflux | 24 | 53 |
| 11 | $ZnCl_2$ | Chloroform | Reflux | 15 | 67 |
| 12 | $ZnCl_2$ | DMSO | Reflux | 24 | 45 |
| 13 | $ZnCl_2$ | Dioxane | Reflux | 12 | 80 |
| 14 | $ZnCl_2$ | Water | Reflux | 24 | Trace |
| 15 | $ZnCl_2$ | Ethanol | RT | 24 | 20 |
| 16 | $ZnCl_2$ | Ethanol | 50 | 12 | 51 |
| 17 | $ZnCl_2$ | Ethanol | 60 | 6 | 82 |
| 18 | $ZnCl_2$ | Ethanol | Reflux | 6 | 96 |
| 19 | $ZnCl_2$ | Ethanol | Reflux | 7 | 96 |

[a]Reaction conditions: **1** (3 mmol, 1 equiv), **2e** (3 mmol, 1 equiv), **3a** (3 mmol, 1 equiv), catalyst (10 mol%), and solvent (15 mL).

that a catalyst must absolutely be necessary for this reaction. We hypothesized that zinc chloride can catalyze the model reaction by forming a better-activated intermediate. A preliminary examination showed that zinc chloride in ethanol efficiently catalyzed the model reaction (Table 1, entry 18). Other catalysts tried has not produced a significant yield (Table 1, entry 3, 4, 5). The role of solvents on the synthesis of pyrazolopyridocoumarin (**4e**) was then studied and the results are depicted (Table 1). When the reaction was carried out in solvents like acetonitrile, DCM, THF, DMF, toluene, chloroform, DMSO, dioxane and water, the desired product (**4e**) was obtained from traces to 82% yield. The best yield of 96% was received in ethanol (Table 1, entry 18). Thus, ethanol was selected as an optimal solvent for the reaction.

The effect of reaction temperature on product yield was evaluated. It was found that increasing temperature led to a high yield of the product (**4e**). It is noteworthy that the ratio of these starting materials has an influence on the yield of the reaction. When the ratio of 4-hydroxycoumarin, 2,3-dimethoxybenzaldehyde and 1-ethyl-5-aminopyrazole was 1.0:1.0:1.0, the total output had reached 96%. Further altering the ratio did not improve the yield. Thus, we chose the above molar ratio of substrates for subsequent studies. When a mixture of 4-hydroxycoumarin, 2,3-dimethoxybenzaldehyde and 1-ethyl-5-amino-pyrazole in ethanol was refluxed in the presence of zinc chloride (10 mol%) for 6 h, the fused heterocyclic product, pyrazolopyridocoumarin (**4e**) was obtained in excellent yield (96%) (Table 1, entry 18). Higher percentage loading of the catalyst

**Table 2.** Zinc chloride catalyzed synthesis of novel pyrazolopyridocoumarins.[b]




| Sl. No. | $R^1$ | $R^2$ | Product | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | H | Ethyl | **4a** | 6 | 86 |
| 2 | 4-Br | Ethyl | **4b** | 6 | 89 |
| 3 | 2-OH | Ethyl | **4c** | 6 | 87 |
| 4 | 4-$OCH_3$ | Ethyl | **4d** | 6 | 92 |
| 5 | 2,3-Dimethoxy | Ethyl | **4e** | 6 | 96 |
| 6 | 3,4,5-Trimethoxy | Ethyl | **4f** | 6 | 93 |
| 7 | 4-Cl | Methyl | **4g** | 6 | 88 |
| 8 | 4-$NO_2$ | Methyl | **4h** | 7 | 81 |

[b] Reaction conditions: **1** (3 mmol, 1 equiv), **2(a–h)** (3 mmol, 1 equiv), **3(a–b)** (3 mmol, 1 equiv) $ZnCl_2$ (10 mol%) and ethanol (15 mL) at reflux condition for 6–7 h. The reaction was conducted on gram scale.

neither increased the yield nor lowered the reaction time.

With the optimal conditions in hand, the scope and limitations of the reaction with respect to the benzaldehyde was evaluated (Table 2). It was found that benzaldehydes containing electron donating 2-hydroxy, 4-methoxy, 2,3-dimethoxy and 3,4,5-trimethoxy groups tolerate the reaction conditions to afford excellent yields (Table 2, entry 3, 4, 5, 6). The introduction of electron withdrawing substitutions on phenyl ring such as 4-Br and 4-Cl resulted in high yield (Table 2, entry 2, 7). The yield obtained was somewhat less for phenyl ring bearing 4-$NO_2$ group (Table 2, entry 8). We also found that 5-amino pyrazole tethered with 1-methyl and 1-ethyl group could also be used to synthesize pyrazolopyridocoumarins successfully with high yields.

The structure of (**4e**) was unambiguously confirmed by single crystal X-ray structure (Figure 2) determination.[53]

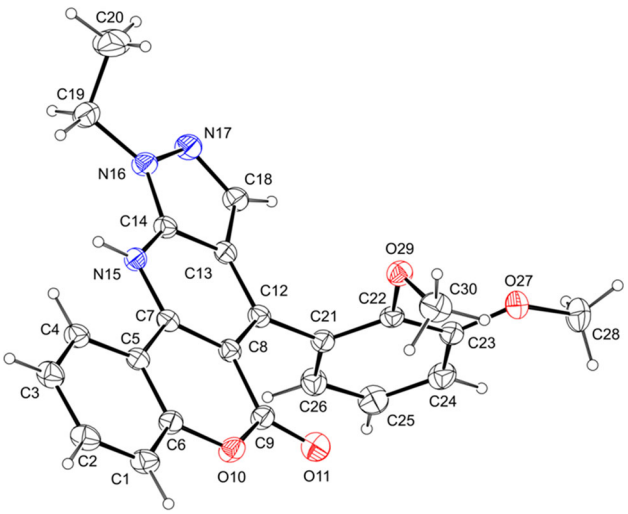
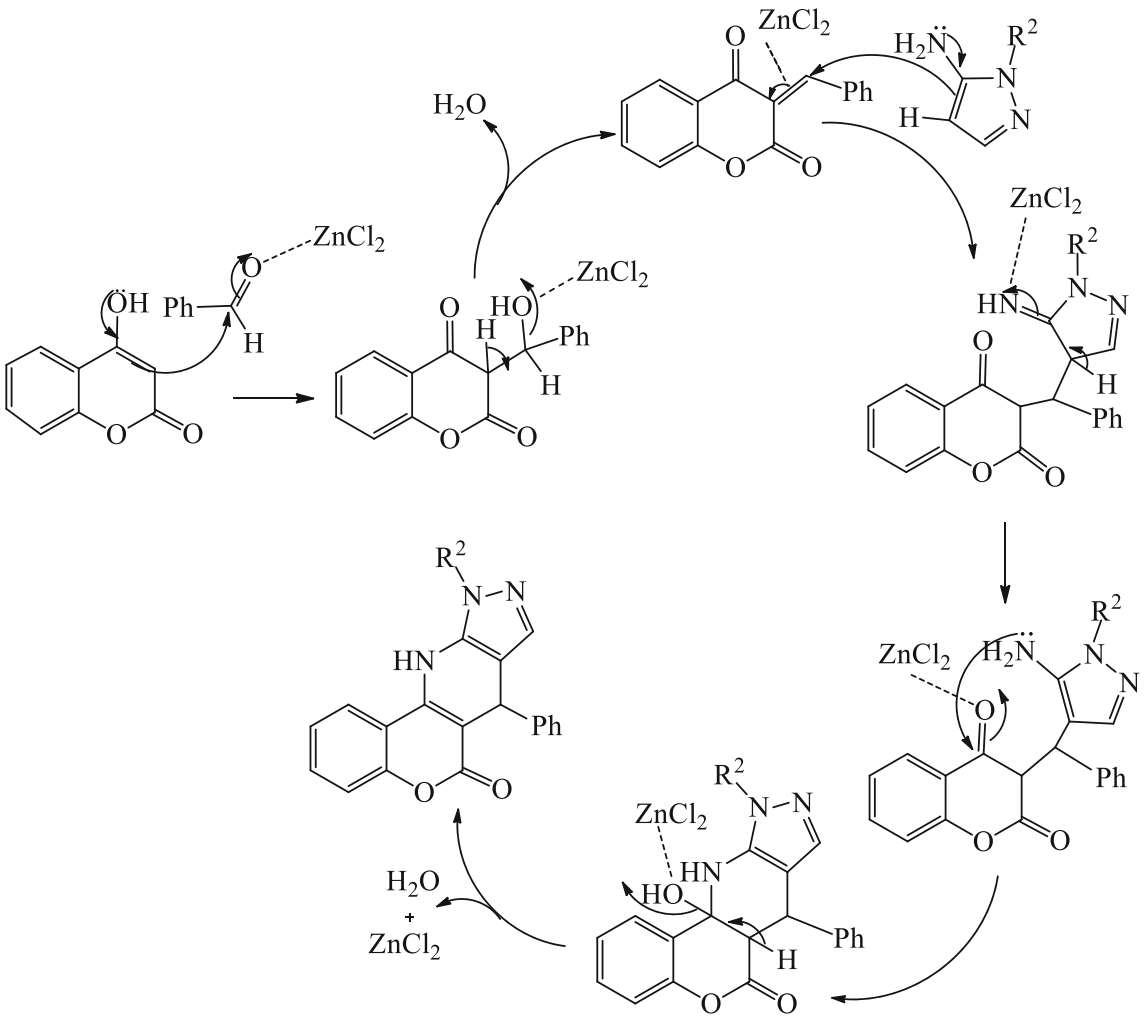



**Figure 2.** ORTEP diagram of the molecule (**4e**) at 50% probability.

A plausible explanation for the formation of pyrazolopyridocoumarins is illustrated (Scheme 1) which is similar to the established mechanism as reported in the literature.[18] Zinc chloride can serve as a mild Lewis acid catalyst for the reaction of 4-hydroxycoumarin and benzaldehydes to give the benzylidene-chroman-2,4-diones. The Michael addition of 1-alkyl-5-aminopyrazoles on the benzylidene-chroman-2,4-diones, followed by intramolecular cyclization would eventually afford the final pyrazolopyridocoumarins. Zinc chloride is likely to enhance the rate of this multicomponent reaction.




**Scheme 1.** Plausible mechanism for the formation of pyrazolopyridocoumarins in the presence of zinc chloride catalyst.

## 4. Conclusions

In summary, we have developed a zinc chloride catalyzed multicomponent reaction of 4-hydroxycoumarin, benzaldehydes and 1-alkyl-5-aminopyrazoles for the synthesis of pyrazolopyridocoumarins in ethanol at reflux temperature. Zinc chloride is used as a readily available and cheap catalyst. This procedure is simple and the reaction conditions are mild. These advantages make the methodology an attractive process for the preparation of pyrazolopyridocoumarins.

## Supplementary Information (SI)

Supplementary information of this manuscript is available at www.ias.ac.in/chemsci.

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## Compliance with ethical standards

**Conflicts of interest** There are no conflicts of interest to declare.

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53. CCDC NO. 1423436 - Contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223 762911; email: deposit@ccdc.cam.ac.uk]