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PEG-assisted one-pot three-component synthesis of 1,3-oxazino quinoline and chromeno 1,3-oxazin derivatives under catalyst free condition

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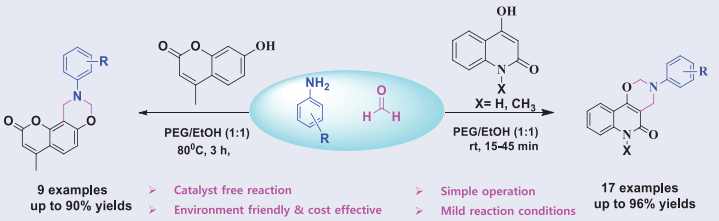
ABSTRACT

A straightforward and greener PEG-assisted protocol has been disclosed for the cascade synthesis of [1,3]Oxazino quinoline, and chromeno[1,3]oxazin derivatives via three component reaction of multifarious aromatic amines with formaldehyde and 4-hydroxyquinoline-2(1H)-one or 4-methylumbelliferone by using very convenient reaction conditions. This methodology represents a sustainable approach for rapid access to a library of diversity oriented highly pure [1,3]oxazino scaffolds with broad substrate scope.

GRAPHICAL ABSTRACT



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KEYWORDS
Chromeno 1,3-oxazin; multicomponent reactions (MCRs); [1,3]oxazino quinoline; polyethylene glycol (PEG-600)

Introduction

In recent years, the development of synthetic chemistry has gained considerable interest in the area of academia, industrial, and pharmaceutical research.[1–2] Synthetic chemists have aimed to replace organic solvent as a reaction media with environmentally acceptable alternatives such as ionic liquid, water, PEG and carried out the reaction under solvent-free condition.[3] Catalyst-free synthetic approaches are also a remarkable tool in scientific society because they have a minimum cost, less problematic in purity, and pollution.[4] Polyethylene glycol (PEG) is a greener alternative in organic synthesis as it has become more favorable over toxic organic solvents due to nontoxicity, biocompatibility, bio-degradability, and miscibility of aqueous or nonaqueous solvent.[5]

Furthermore, the application of PEGs as reaction media for the multicomponent reactions (MCRs) also will be beneficial from the recent innovation in employing bio-

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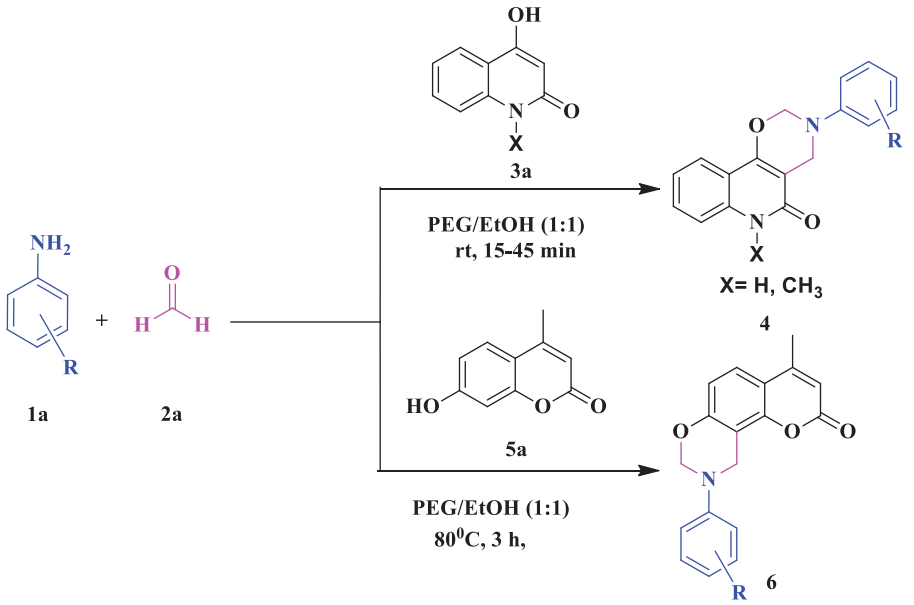


Scheme 1. Synthesis of [1,3]Oxazino quinoline (**4**) and chromeno 1,3-oxazin (**6**) derivatives.

based chemicals as green solvents.[6] The combination of MCRs and PEGs as a solvent has enhanced a new research direction, which enables simultaneous growth of both MCRs and green solvent toward ideal organic synthesis.[7–10] However, multicomponent reactions (MCRs) are extremely ideal and eco-friendly reaction method and the targeted compounds can be achieved in significantly fewer steps. Due to the advantages of providing sufficient structural diversity, atom economy,[11] molecule complexity,[12] and simple operation the MCRs have been widely used in drug discovery, biology, and natural product synthesis.[13]

Quinoline alkaloids are usually isolated from plant Rutaceae,[14–19] it has been reported that the quinoline alkaloids exhibit an active wide range of biological properties.[20] This active wide range of biological properties has stimulated interest in the synthesis of quinolinone moieties.[21–25] The importance of 1,3-oxazine molecule has been increased because a compound containing the 1,3-oxazine ring system has exhibited a wide spectrum of pharmacological activities, such as anti-bacterial,[26,27] anti-tumor,[28] anti-malarial,[29] and anti-oxidant activities.[30–33] Very lately, Zhou et al. have reported 1,3-oxazine molecule under the catalytic ($ZrOCl_2 \cdot 8H_2O$) condition,[34,35] which is for the environmental perspective using of catalyst is unfriendly. Being a part of our continued interests not to make the environment hostile, in this synthesis of heterocyclic compounds and green chemistry[36–40] we have explored for the PEG-assisted approach and catalyst-free synthesis of [1,3]oxazine[5,6-*c*]quinoline-5-one, and 4-methyl-9-phenylchromeno[8,7-*e*][1,3] oxazine-2(8*H*)-one derivatives under the mild reaction condition (Scheme 1).

Result and discussion

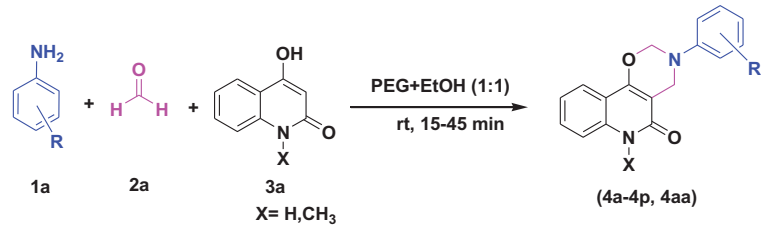
For the introductory investigation, the reaction of 4-hydroxyquinoline-2-(1*H*)-one (**3a**), aniline (**1a**), and formaldehyde (**2a**) in ethanol has been chosen as a simple model

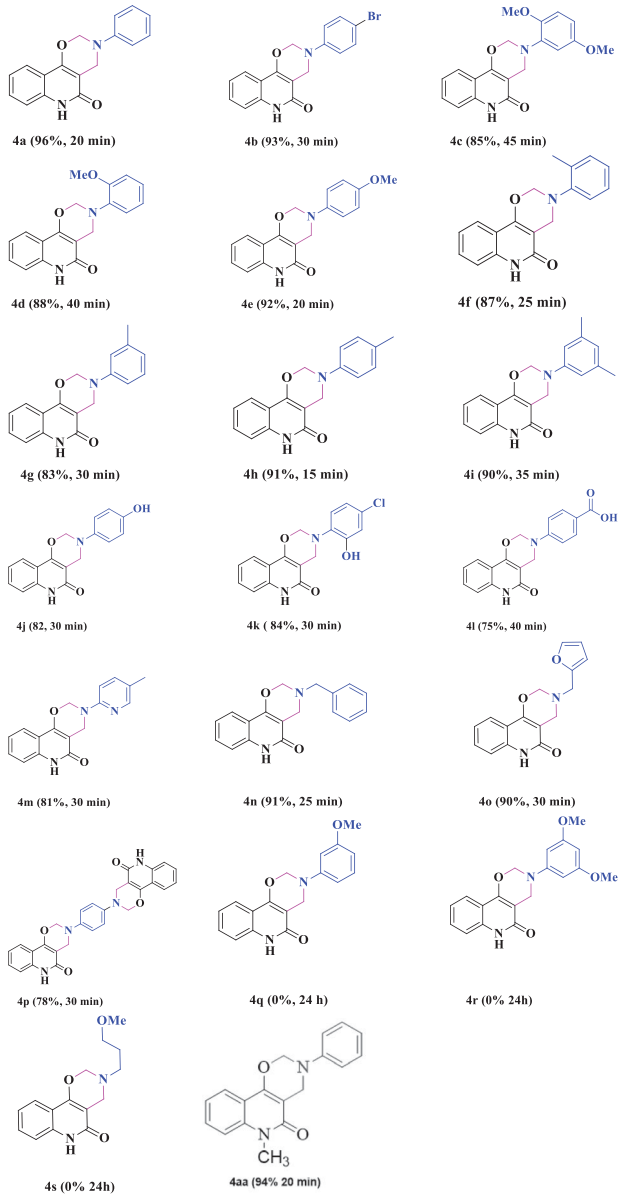
strategy (Scheme 2). The reaction mixture was stirred at room temperature (RT) for 60 min, which afforded 74% of the desired product as a white solid (Table 1, entry 10). The structure of **4a** is assigned with the help of ^{1}H NMR and ^{13}C NMR data. Further, the same reaction has been studied with different solvents like methanol, acetonitrile, dimethylformamide, toluene and tetrahydrofuran at RT, resulting in the desired product in moderate (40–72%) yield (Table 1, Entries 11–17). Screened different catalysts for this reaction, such as $Cu(OTf)_2$ (20%), $InCl_3$ (20%), L-proline (20%), Piperidine (20%), $FeCl_3$ (20%), *p*-TsOH (20%), $Sc(OTf)_3$ (20%), $GaCl_3$ (20%) and $InBr_3$ (20%) (Table 1, Entries 1–9). All screened catalysts were found to be effective for this conversion. However, when the reaction is carried out with PEG-600, the viscosity of the reaction mixture is increased highly at RT and the reaction gets stuck, hence the reactants do not interact effectively. The expected product is obtained a yield of 60% in 60 min (Table 1, Entry 17). However, the reaction rate increased when the solvent was switched from PEG-600 to PEG-600: EtOH. Therefore, the volumetric ratio of PEG and EtOH was screened and the best results were obtained by carrying out the reaction in PEG-600: EtOH with a ratio of 1:1(v/v) (Table 1, Entry 20).

When used PEG-600 and EtOH as an eco-friendly reaction medium, the reaction gave an excellent result (96% yield) within 20 min at the ambient temperature. It has been found that the reaction proceeded very well with increased yields, which clearly indicates that the PEG-600 is the most effective reaction medium and promoter for this transformation. From the results depicted in Table 1, we have selected the PEG-600 and ethanol as a suitable reaction medium due to highest yield, in shorter reaction time, and environmentally favorable.

Using these optimized reaction conditions, the generality of this reaction is being verified using different aromatic amines with various substitutes are reacted successfully by bearing electron-donating (such as methyl, methoxy) as well as electron-withdrawing (such as halide) substituents. The reaction proceeded more quickly with aniline containing electron-donating groups (–Me, –OMe) to give the products in excellent yields (**4d–4i**) within 15–45 min. The steric and electronic properties of the substituted amine had very little impact on the efficiency of this reaction. However, when 1,4-phenylenediamine with formaldehyde, and 4-hydroxyquinolin-2(1*H*)-one were used, gave the desired product 3,3′-(1,4-phenylene)bis(3,4-dihydro-2H-[1,3]oxazino[5,6-c]quinolin-5(6H)-one) **4p** was obtained in 78% yield. Similarly, the reaction of 4-hydroxy-1-methylquinolin-2(1*H*)-one with formaldehyde and aniline were used, gave the desired product 3,4-dihydro-6-methyl-3-phenyl-2*H*-[1,3]Oxazino[5,6-*c*] quinolin-5(6*H*)-one **4aa** was obtained in 94% yield. Unfortunately, aromatic amine with methoxy at 3 position or 3,5 dimethoxy substituted aromatic amine could not react with formaldehyde and 4-hydroxyquinolin-2(1*H*)-one to give the desired product (**4q**, **4r**). On the other hand, short-chain aliphatic amine such as 3-methoxypropan-1-amine did not react under the optimized reaction condition (**4s**).

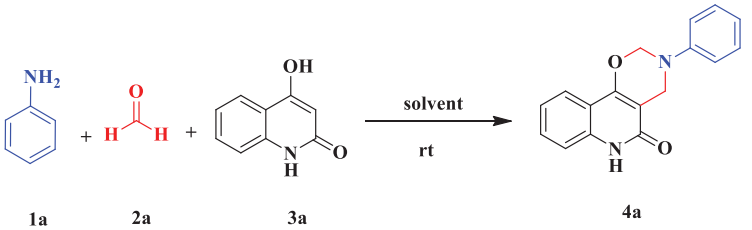
The reaction of 4-methylumbelliferone (**5a**, 1 mmol), formaldehyde (**2a**, 3 mmol, 37% aqueous solution), aniline (**1a**, 1.2 mmol) was carried out in PEG-600: EtOH (1:1, v/v) at 80 °C for 3 h. A study of the effect of temperature on the reaction time as well as on the yield of the product reveals that the reaction is strongly influenced by the temperature. These results are presented in Table 2.





Scheme 2. Synthesis of [1,3]Oxazino quinoline derivatives (**4a–4p**, **4aa**)[a,b].
[a]Reaction conditions: 4-hydroxyquinoline (1 mmol, **3a**), formaldehyde (3 mmol, 37% aqueous solution, **2a**), aromatic amine (1.2 mmol, **1a**), and solvent 4 mL at room temperatures. [b]Isolated yield.

Table 1. Optimization of reaction conditions[a].

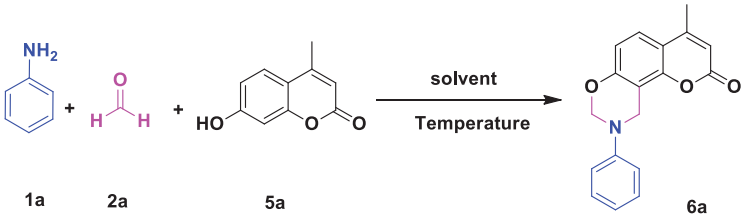


1a 2a 3a 4a

Entry	Promoter (mol. %)	Solvent	Time (min)	Yield (%)[b]
1	$Cu(OTf)_2$ (20)	EtOH	60	82
2	$InCl_3$ (20)	EtOH	60	77
3	L-proline (20)	EtOH	60	80
4	Piperidine (20)	EtOH	60	79
5	$FeCl_3$ (20)	EtOH	60	82
6	*p*-TsOH (20)	EtOH	60	85
7	$Sc(OTf)_3$ (20)	EtOH	60	75
8	$GaCl_3$ (20)	EtOH	60	78
9	$InBr_3$ (20)	EtOH	60	77
10	Catalyst-free	EtOH	60	74
11	Catalyst-free	MeOH	360	45
12	Catalyst-free	CH_3CN	360	40
13	Catalyst-free	DMF	60	72
14	Catalyst-free	DMSO	360	38
15	Catalyst-free	Toluene	360	42
16	Catalyst-free	THF	60	72
17	Catalyst-free	PEG	60	60
18	Catalyst-free	PEG: EtOH(1:5)	30	81
19	Catalyst-free	PEG: EtOH(1:3)	30	89
20	Catalyst-free	PEG: EtOH(1:1)	30	96

[a]Reaction conditions: 4-hydroxyquinolin-2(1*H*)-one (1 mmol, 3a), formaldehyde (3 mmol, 37% aqueous solution, 2a), aniline (1.2 mmol, 1a), and solvent 4 mL at room temperature. [b]Yield.

Table 2. Effect of temperature[a,b].



1a 2a 5a 6a

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	EtOH	RT	12	0
2	EtOH	80	12	52
3	EtOH:PEG	RT	12	0
4	EtOH:PEG	40	12	0
5	EtOH:PEG	60	12	58
6	EtOH:PEG	80	12	93
7	EtOH:PEG	80	6	94
8	EtOH:PEG	80	4	91
9	EtOH:PEG	80	3	90
10	EtOH:PEG	80	1	63

[a]Reaction conditions: 4-methylumbelliferone (1 mmol, **5a**), formaldehyde (3 mmol, 37% aqueous solution, **2a**), aniline (1.2 mmol, **1a**), and solvent 4 mL stirred at different temperatures. [b]Isolated yield.

When the reaction is being carried out under room temperature, the desired product could not be observed, as the starting materials were unreactive (Table 2, Entry 1). The results of screening temperature (Table 2) reveals that 80 °C would be the optimal temperature, at which the reaction proceeds rapidly and produces the best yield 90% (Table 2, Entry 9) in 3 h. Further verified reaction time does not cause any significant change in the product yield. The structure of **6a** is assigned with the help of ^{1}H NMR and ^{13}C NMR data. We have also employed various substituted aromatic amine with electron-donating substituents such as –Me, –OMe, and halogen (Br) which were well tolerated and provided the corresponding products in good to excellent yields. However, p-nitro aniline did not afford the desired product under the optimized reaction conditions (Scheme 3, **6i**).

After having successfully developed a one-pot strategy for the construction of 3-phenyl-3,4-dihydro-2*H*-[1,3]oxazino[5,6-*c*]quinolin-5(6*H*)-one, we examined the synthetic utility of this reaction. Consequently, we performed the reaction on a gram-scale (10 mmol, 1.60 g) under the standard reaction conditions and isolated desired product **4a** in 90% yield (Scheme 4).

We have proposed a plausible reaction mechanism (Fig. 1). Initially, aniline (**1a**) reacts with formaldehyde (**2a**) to form Schiff base **A** by Mannich type condensation, 4-hydroxyquinolin-2(1H)-one (**3a**) undergoes nucleophilic addition with **A** to form intermediate **B**. Next, the intermediate **B** reacts with second molecule of formaldehyde (**2a**) to afford the intermediate **C**. Then intermediate **C** undergoes intramolecular cyclization followed by water elimination to afford the desire product [1,3] Oxazino[5,6-*c*] quinoline-5-one (**4a**). The results from all the above studies clearly indicate, that the present non-catalytic protocol is compatible for a wide range of substrates to construct a diversity-oriented library of 1,3-Oxazino quinoline and chromeno 1,3-oxazin derivatives.

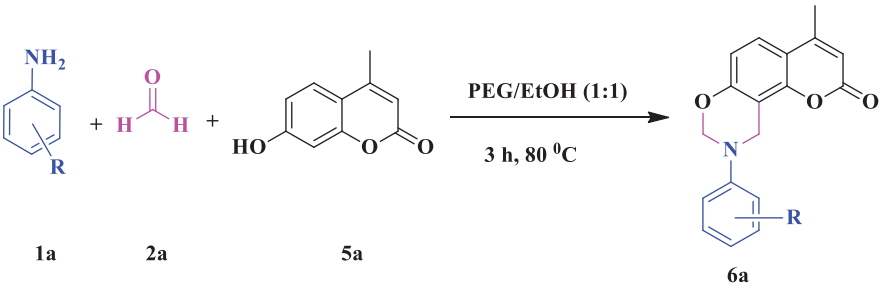
Conclusion

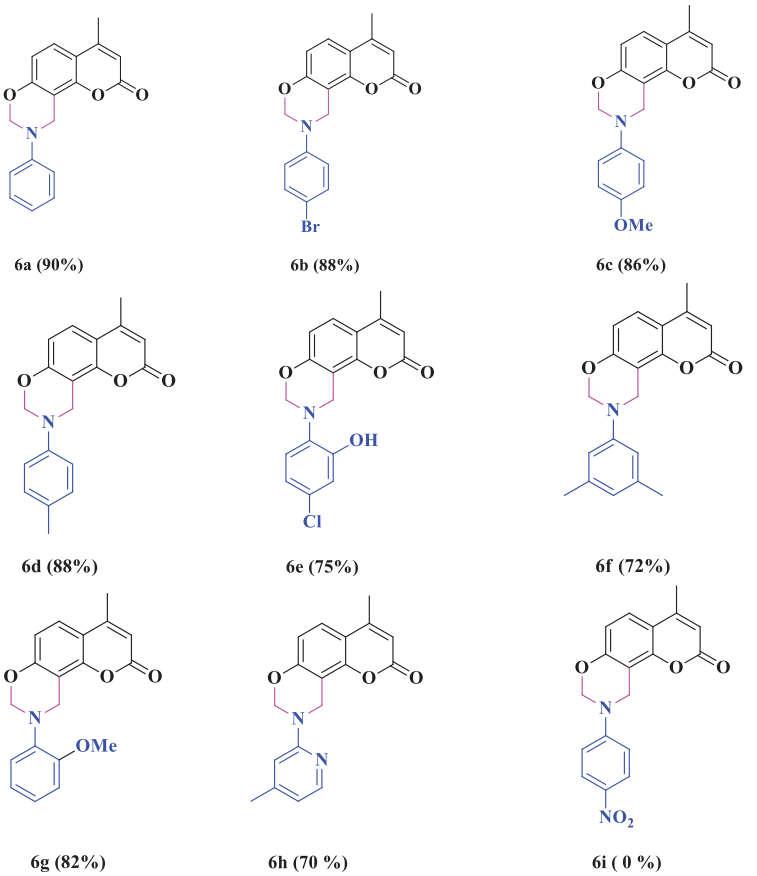
In summary, we have developed a convergent and robust greener protocol for the synthesis of 1,3-Oxazino quinoline and chromeno 1,3-oxazin derivatives by the three-component reaction of various aromatic amines with formaldehyde and 4-hydroxyquinoline-2(1H)-one or 4-methylumbelliferone by using PEG-600: EtOH as an effective reaction medium under catalyst free-conditions. The simple straightforward, rapid, atom-economic, high yielding, as well as inexpensive and eco-friendly nature, are the key benefits of this method, which constitutes an attractive tool addressing the access to 1,3-oxazine molecules for bioactive applications.

Experimental

Materials

Chemical were purchased from Sigma Aldrich and Alfa Aesar chemical companies and used without further purification. NMR spectra were recorded in parts per million (ppm) in DMSO-d_6 and Chloroform-d on a Jeol JNM ECP 400 NMR instrument using TMS as internal standard abbreviation were used to denoted signals multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplate). HRMS were obtained by EI on a double-focusing mass analyzer, ESI (positive ion mode) on TOF mass





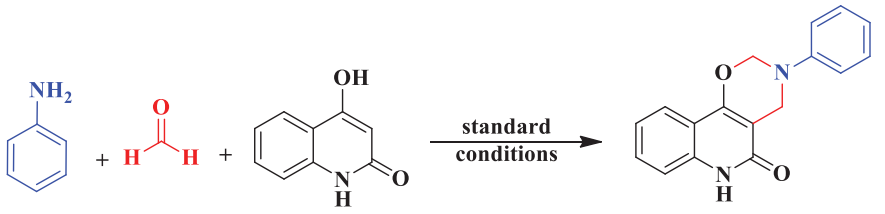
Scheme 3. Synthesis of chromeno 1,3-oxazin derivatives (**6a–6i**)[a,b]
[a]Reaction conditions: 4-methylumbelliferone (1 mmol, **5a**), formaldehyde (3 mmol, 37% aqueous solution, **2a**), aromatic amine (1.2 mmol, **1a**), and solvent 4 mL stirred at 80 °C for 3 h. [b]Isolated yield.

analyzer. All melting points were determined using open capillaries on an Electro thermal-9100(Japan) instrument and are uncorrected.

General procedure

General procedure for synthesis of [1,3]oxazino quinoline derivatives (4a)

A mixture of 4-hydroxyquinoline-2(1H)-one (**3a**, 1 mmol), aniline (**1a**, 1.2 mmol) and formaldehyde (**2a**, 3 mmol 37% aqueous solution) in 4 mL of PEG-600 and EtOH (V/V, 1:1)



Scheme 4. Gram scale reaction.

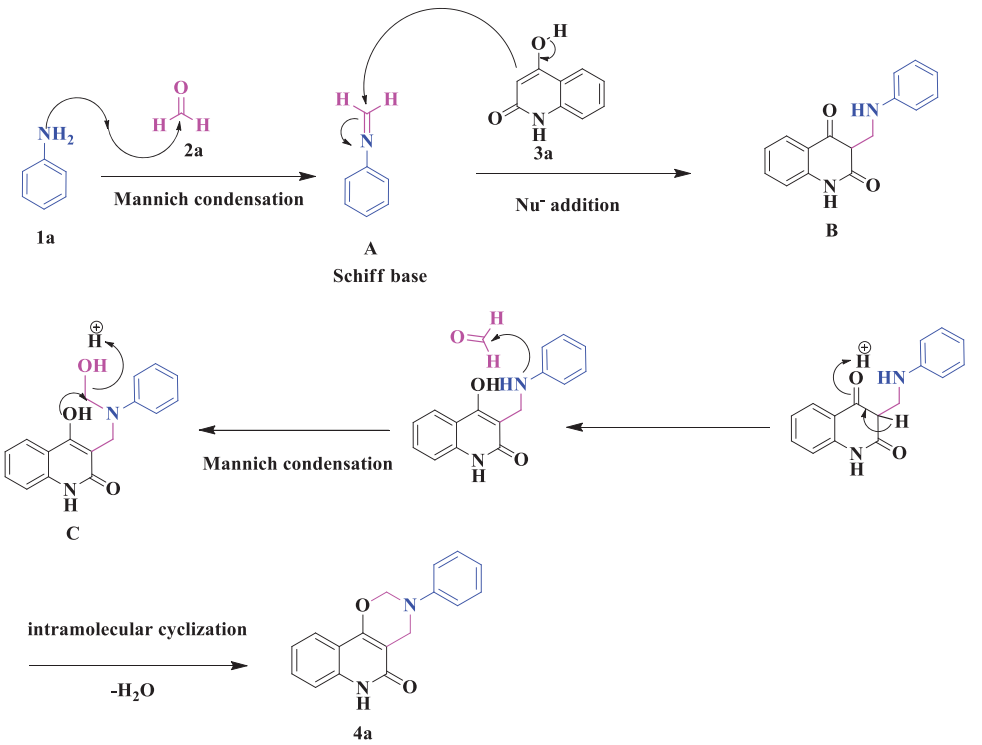


Figure 1. A plausible mechanism for the [1,3]Oxazino [5,6-*c*]quinoline-5-one.

was magnetically stirred at room temperature for 15–45 min. Reaction was monitored by thin-layer chromatography (eluent: 60% ethyl acetate/hexane, $Rf = 0.60$). After completion of the reaction, solid products was filtered under vacuum, air dried, to obtain the analytically pure products. The compounds **4a–4p** and **4aa** were also synthesized by adopting this procedure.

It was obtained as white solid; Yield: 96%; MP:198–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.53 (s, 1H), 7.68 (d, $J = 8.1$ Hz, 1H), 7.48 (t, $J = 8.4$ Hz, 1H), 7.26 (dd, $J = 13.9$, 7.4 Hz, 3H), 7.15 (dd, $J = 8.4$, 1.3 Hz, 3H), 6.90 (t, $J = 7.3$ Hz, 1H), 5.66 (s, 2H), 4.38 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.89, 157.85, 148.24, 137.94, 136.05, 130.98, 129.77, 122.84, 121.06, 118.29, 115.83, 114.30, 106.04, 80.69, 45.73; HRMS (ESI, *m*/*z*): calcd. for $C_{17}H_{14}N_2O_2$ ($M + H^+$) 278.1055, found: 279.1057.

General procedure for gram scale reaction (4a)

A mixture of 4-hydroxyquinoline-2(1H)-one (**3a**, 10 mmol), aniline (**1a**, 12 mmol) and formaldehyde (**2a**, 30 mmol 37% aqueous solution) in 12 mL of PEG-600 and EtOH (V/V, 1:1) was magnetically stirred at room temperature for 30 min. Reaction was monitored by thin-layer chromatography. After completion of the reaction, solid product was filtered under vacuum, air dried, to obtain the analytically pure products.

General procedure for synthesis 4-methyl-9-phenylchromeno [8,7-e][1,3]oxazin-2(8H)-one (6a)

A mixture of 4-Methylumbelliferone (**5a**, 1 mmol), aniline (**1a**, 1.2 mmol) and formaldehyde (**2a**, 3 mmol 37% aqueous solution) in 4 mL of PEG-600 and EtOH (V/V, 1:1) was magnetically stirred at 80 °C for 3 h. Reaction was monitored by thin layer chromatography (eluent: 5% methanol/dichloromethane, $Rf = 0.40$). As the reaction mixture cooled, the raw product precipitate in to white-yellow crystals. Finally, recrystallization from toluene yielded white needle like crystals. The compounds **6a–6h** were also synthesized by adopting this procedure.

It was obtained as white solid; Yield: 90%; MP:148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, $J = 8.8$ Hz, 1H), 7.28 (dd, $J = 9.6$, 6.4 Hz, 2H), 7.15 (d, $J = 7.7$ Hz, 2H), 6.96 (t, $J = 7.3$ Hz, 1H), 6.78 (d, $J = 8.8$ Hz, 1H), 6.13 (s, 1H), 5.44 (s, 2H), 4.83 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.29, 157.82, 153.38, 151.44, 148.18, 129.67, 123.86, 122.30, 118.79, 113.91, 113.55, 111.98, 109.13, 80.11, 46.58, 19.02; HRMS (ESI, m/z): calcd. for $C_{18}H_{15}NO_3$ (M + H+) 293.1052, found: 294.1052.

Experimental details, ^{1}H and ^{13}C NMR spectra have been provided in supporting information.

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