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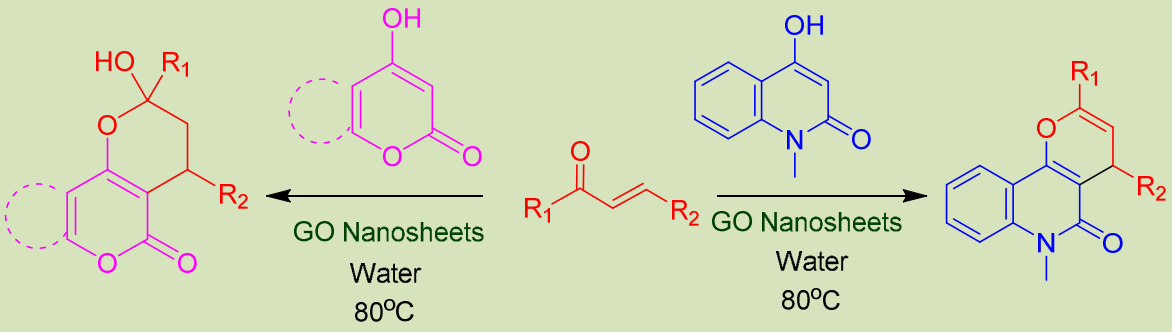
# Graphene Oxide Nanosheets: A Highly Efficient and Reusable Organocatalyst Significantly Improvises The Tandem Michael-Cyclization Reactions of 4-Hydroxycoumarins, 4-Hydroxypyrone and 4-Hydroxy-1-methylquinolinone With Chalcones Derivatives Leading to 4*H*-pyran Scaffold in Aqueous Media

## Graphical Abstract:



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# ARTICLE TYPE

# Graphene Oxide Nanosheets: A Highly Efficient and Reusable Carbocatalyst Catalyzes the Michael-Cyclization Reactions of 4-Hydroxycoumarins, 4-Hydroxypyrone and 4-Hydroxy-1-methylquinolinone With Chalcone Derivatives in Aqueous Media

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Graphene Oxide nanosheets were found to be a highly efficient, reusable and cost-effective carbocatalyst for the facile synthesis of highly diversified 4*H*-pyrans via one-pot, two-component condensation reaction between freshly prepared chalcones and 4-hydroxycoumarin in aqueous media offering excellent yields. The new, green and metal free synthetic method also enables the condensation reaction for the formation of a library of pyranoquinolines and pyranopyrans

## Introduction

Development of innovative synthetic methodologies involving the use of chemicals that reduce the hazards to humans and the environment have engorged key interest in recent decades.[1] In this regard, utilization of catalysts that combine the toxicological assistances of a metal-free synthesis with the facile recovery and recycling of a heterogeneous system is of tremendous importance and the avoidance of hazardous organic solvents follows the fundamental strategy to achieve the usefulness.[2] Use of water reduces the use of harmful organic solvents and is regarded as an essential research topic in green chemistry.[3] In addition, water has unique physical and chemical properties, and by utilizing these it would be possible to tune the reactivity or selectivity that cannot be attained in organic solvents.[4]

2*H*-pyran heterocyclic core is embedded as a fundamental substructure in several subclasses of natural products such as pyranocoumarins,[5] pyranonaphthoquinones,[6] pyranochalcones,[7] pyranoquinolinones,[8] and chromenes.[9] Pyranocoumarins which have wide occurrence in natural products as well as synthetic molecules and exhibit a broad spectrum of biological activities such as antifungal, insecticidal, anticancer, anti-HIV, antiinflammatory, and antibacterial activities.[10] In particular the 2-hydroxy-3,4-dihydro-pyrano[3,2-*c*]chromen-5-one motif is the core of important natural products and a versatile template for the preparation of a variety of biologically active molecules. The antiprotozoan ethuliacoumarins[11] as well as the uterotonic pterophyllins[12,13] (Figure 1) show a wide range of activities may be expected from this family of compounds. Furthermore, quinolinone quinone methides constitute such a class of versatile synthones for the synthesis of naturally occurring biologically active pyranoquinolinones, dimeric quinolinone alkaloids and other polycyclic heterocycles. Modification of this class of compound has been of great interest to researchers as their unique structures led to several applications in different areas. In particular, simulenoline, huajiaosimuline, and zanthodioline are potent inhibitors of platelet aggregation,[14] while N-methylflindersine, isolated from Orixa japonica, acts as an insecticide for livestock.[15] Recently it was reported that pyranoquinolinones zanthosimuline and huajiaosimuline isolated from *Zanthoxylum simulans* exhibit cytotoxic activity against human cancer cells.[7]

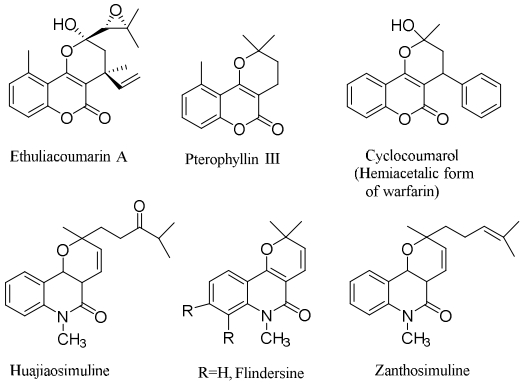


**Figure 1**: Biologically active 2*H*-pyran derivatives

The diversity of the structures encountered, as well as their biological and pharmaceutical relevance, have motivated research aimed at the development of new economical, efficient, and selective synthetic strategies to access these compounds. A variety of methods have been developed to achieve the synthesis

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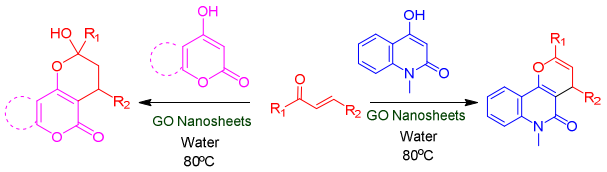
of this 4*H*-pyran nucleus. Most of the methods[16] reported previously have focused on the modification and the optimization of the process parameters of the asymmetric Michael addition of 1,3-cyclic dicarbonyl compounds to α,β-unsaturated carbonyl systems to minimize reaction time and maximize reaction conversion to achieve the desired 4*H*-pyrans in high purity. These methodologies suffer from long reaction times, harsh reaction conditions, the use of high thermal energy, involvement of metal triflate as catalyst along with excess reagents or toxic solvents which give poor yields of products, or have tedious workup procedures.[16] Moreover; the striking disadvantage of almost all reported methods is that the catalysts are consumed in the reaction. This scenario strongly suggests a new approach that meets the requirements of sustainable chemistry and is still worth demanding. Recently, graphene oxide nano sheets have attracted enormous interest in the development of composite materials and catalysts, due to their remarkable physical, chemical and electrical characteristics, including a very high specific surface area. In organic synthesis polycarbon acids and polyacids on carbon nanostructures are considered more vigorous in aqueous media than other solid acids such as ion exchange resins, heteropolyacids and layer transition metal oxides; which facilitates us to report the use of graphene oxide nano sheets, a readily available, inexpensive and efficient carbocatalyst[17], for the synthesis of various 4*H*-pyran compounds in excellent and efficient yields in aqueous media (Scheme 1). The present work materializes as a part of our ongoing research program involving water as the solvent and nanoparticles as the significant catalyst in the synthesis of various biologically active molecules.[18]




**Scheme 1**: Synthesis of 4*H*-pyran scaffolds from reaction between chalcones and 4-hydroxycoumarins/ 4-hydroxypyrone or 4-hydroxy-1-methylquinolinone

## Result and discussion

Graphene oxide nano sheets were prepared by the oxidation of graphite powder via minor modification of known methods [19] under severe oxidizing conditions. The presence of various chemical functionalities on graphene oxide nanosheets and their dispersion in water were examined by XRD and FTIR. Figure 2 shows the XRD patterns obtained for graphene oxide powder. Graphene oxide nano sheet shows a little broad peak (002) centered at 11.61, corresponding to an interlayer spacing of 0.74 nm. The oxidation of graphite powder leads to the introduction of various functional groups. These functional groups are bonded on edges and basal planes of graphitic layers, as well as the presence of trapped water molecules between these layers, expanding the interlayer spacing in graphene oxide nano sheets.

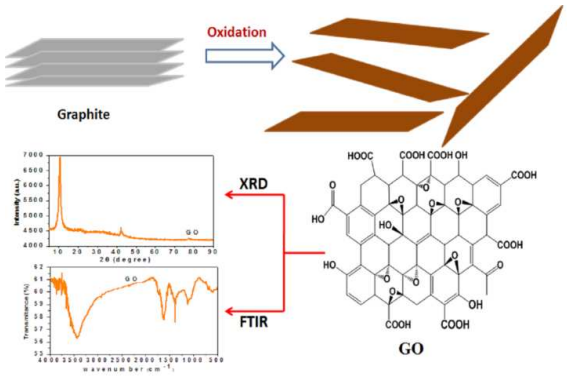



**Figure 2**: Preparation of graphene oxide nanosheets

Further, the nature of the chemical functionalities was characterized by FTIR. An intense and broad peak appeared at 3424cm$^{-1}$, attributed to the stretching mode of a O–H bond, reveals the abundance of hydroxyl groups in graphene oxide. The strong band at 1722 cm$^{-1}$ (νC=O) represents carboxylic acid and carbonyl groups. Furthermore, the bands at 1224 cm$^{-1}$ and 1053 cm$^{-1}$ are attributed to the presence of C–OH and C–O(epoxy) groups, respectively, in graphene oxide nano sheets. Furthermore, the presence of very fine morphological features on the HRTEM and FESEM images of the graphene oxide nanosheets exposes that graphene oxide is composed of a few number of layers, resulting in a high surface area for an efficient catalytic reaction(Figure 3).

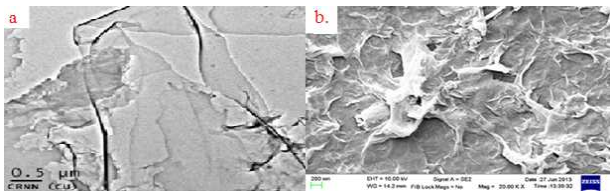



**Figure 3 :(a)**TEM and (b)FESEM images of GO nano sheets

In order to confirm graphene oxide nanosheets to be the key for interpreting the reactions possible in aqueous media, we have studied a screening test employing a series of catalysts and solvents as well as under solvent free conditions with the optimism to maximize the product yield in short reaction time (Table 1). Initially, 3-(4-nitrophenyl)-1-phenylpropenone (1.0 mmol) and 4-hydroxycoumarin (1.0 mmol) were refluxed in the presence of $H_2O$ and ethanol as the solvent without any catalyst source but the reaction even after 24 h failed to afford any product (Table 1, entries 1 and 2). Then the reaction was carried out in water in the presence of *p*-toluenesulphonic acid (PTSA) under reflux condition and the product was isolated in 33% yield (Table 1, entry 3). The reactions were also restrained by using trifluoroacetic acid (TFA), trifluoro methanesulphonic acid (TfOH) acid as the catalyst (Table 1, entries 4 & 5). Lewis acid catalysts, such as $Cu(OAc)_2$, $FeCl_3$ were tested but did not promote the reaction forward(Table 1, entries 6 and 7) while use of ionic liquid, [Bmim][$BF_4$] as a catalyst in aqueous media provided trace amount of the desired product(Table 1, entries 8).

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Interestingly, we observed that GO nano sheets were most effective for the selective formation of desired product due to its high surface area. Again GO nanosheets showed outstanding activity in the formation of desired product than commercially available GO (Table 1, entry 17) in terms of reaction time and yield. Eventually we got satisfaction because the reaction proceeded well affording the desired product in 90% yield within 3 h (Table 1, entry 10).

**Table 1: Screening of catalyst and solvents and reaction conditions:**

| Entry | Catalysts | Solvent | condition | Time(h) | Yield[a,b] (%) |
|---|---|---|---|---|---|
| 1 | - | $H_2O$ | reflux | 24 | -[c] |
| 2 | - | EtOH | reflux | 24 | -[c] |
| 3 | PTSA (10 mol%) | $H_2O$ | reflux | 24 | 33 |
| 4 | TFA (10 mol%) | $H_2O$ | reflux | 24 | 16 |
| 5 | TfOH (10 mol%) | $H_2O$ | reflux | 24 | 28 |
| 6 | $Cu(OAc)_2$(10 mol%) | $H_2O$ | reflux | 24 | -[c] |
| 7 | $FeCl_3$ (10 mol%) | $H_2O$ | reflux | 24 | -[c] |
| 8 | [Bmim][$BF_4$] | $H_2O$ | reflux | 24 | trace |
| 9 | Bulk GO (10 mol%) | $H_2O$ | reflux | 10 | 55 |
| **10** | **GO nano sheet (10 mol%)** | **$H_2O$** | **80** | **3** | **90** |
| 11 | GO nano sheet (5 mol%) | $H_2O$ | reflux | 3 | 67 |
| 12 | GO nano sheet (15 mol%) | $H_2O$ | reflux | 3 | 78 |
| 13 | GO nano sheet (10 mol%) | EtOH | reflux | 3 | 81 |
| 14 | GO nano sheet (10 mol%) | $CH_3CN$ | reflux | 3 | 19 |
| 15 | GO nano sheet (10 mol%) | $CHCl_3$ | reflux | 3 | 26 |
| 16 | GO nano sheet (10 mol%) | Solvent free | 110 $^oC$ | 3 | 11 |
| 17 | Commercial GO nano sheet (10 mol%) | $H_2O$ | 80 | 10 | 71 |

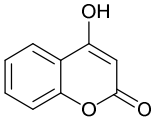
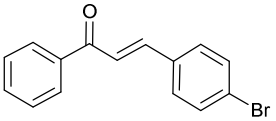
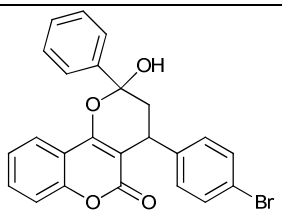
[a]All reactions were carried out with 3-(4-nitrophenyl)-1-phenylpropenone (1.0 mmol) and 4-hydroxycoumarin (1.0 mmol)

[b]Yield of isolated product.

[c] Reaction failed to provide any product.

We then focused our attention by taking graphene oxide nano sheets as the right catalyst for experiment to design and also generalize the favorable condition for the reaction. So, we attempted some screening test with graphene oxide nano sheets. The quantity of the catalyst plays a vital role for the formation of the desired product. The use of 5 mol% GO nano sheets diminished the quantity of yield whereas the yield of the product also decreased when we used 15 mol% GO nano sheets (Table 1, entry 11 and 12).While water was used as a solvent because it showed superiority than other solvents tested which include ethanol (Table 1, entry 13), acetonitrile (Table 1, entry 14) and chloroform (Table 1, entry 15). Under solvent free condition (Table 1, entry 15) at 110$^oC$, GO nano sheets failed to provide satisfactory output and the yield was maximum (90%) in aqueous condition. Hence, this optimized condition was applied for all experiments taking equimolar amounts of substituted chalcone (1) and 4-hydroxy coumarin (2) in the presence of 10 mol % GO nano sheets in aqueous media at 80$^oC$ (Scheme 1). Typically, a mixture of substituted chalcone (1.0 mmol) and 4-hydroxycoumarin/ 4-hydroxy-1-methylquinolinone/ 4-hydroxypyrane (1.0 mmol) and 10 mol % GO nano sheets in 3ml water was refluxed for 2-4 hrs, which afforded a library of 4*H*-pyran derivatives in good to excellent yields (80-90%) (Table 2).

**Table 2:** Substrates Scope for the synthesis of 4*H*-pyran derivatives.

| Sl. no. | substrate | Chalcones | Product | Time (h) | Yield[b](%) |
|---|---|---|---|---|---|
| 1 |  |  |  3a | 3.5 | 88 |

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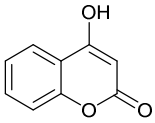
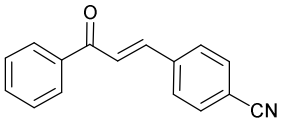
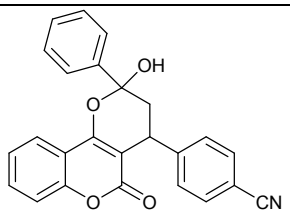
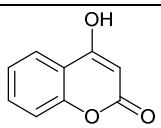
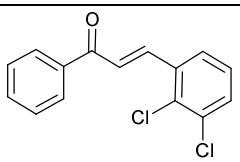
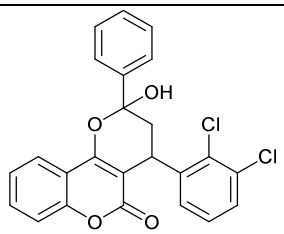
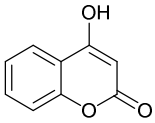
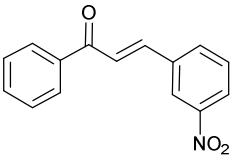
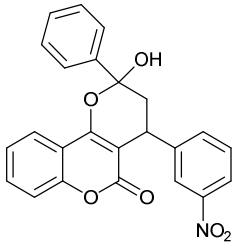
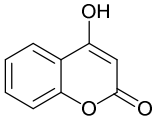
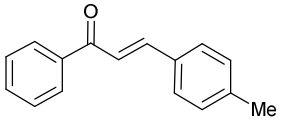
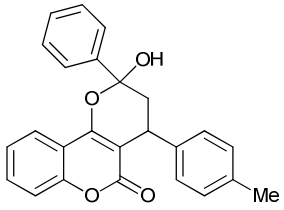
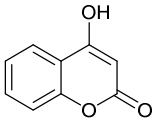
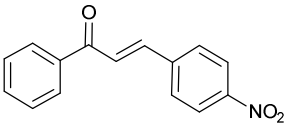
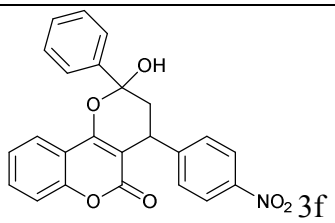
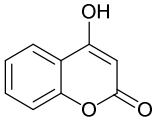
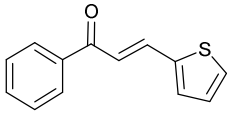
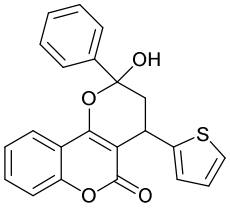
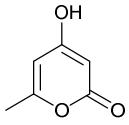
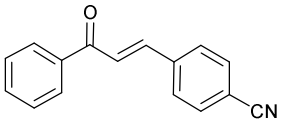
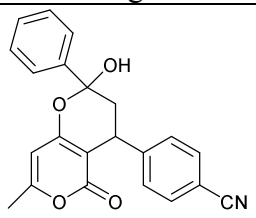
| 2 |  |  |  3b | 3.5 | 92 |
| 3 |  |  |  3c | 3.5 | 90 |
| 4 |  |  |  3d | 3 | 86 |
| 5 |  |  |  3e | 4 | 85 |
| 6 |  |  |  3f | 3 | 92 |
| 7 |  |  |  3g | 4 | 84 |
| 8 |  |  |  3h | 3.5 | 89 |

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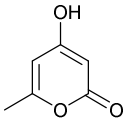
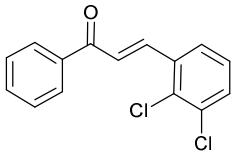
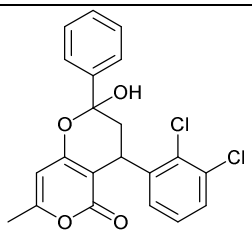
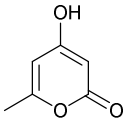
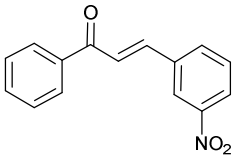
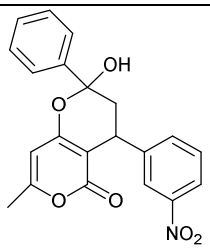
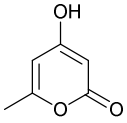
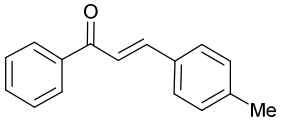
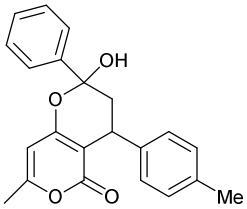
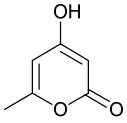
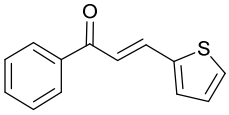
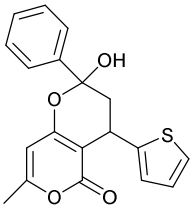
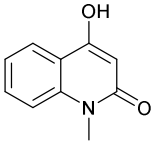
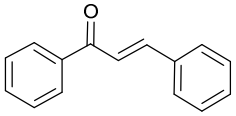
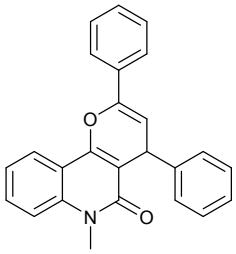
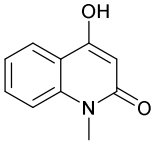
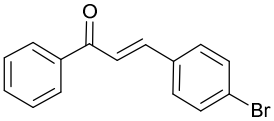
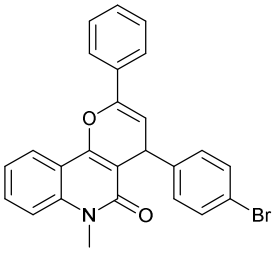
| 9 |  |  |  3i | 3 | 88 |
| 10 |  |  |  3j | 3 | 87 |
| 11 |  |  |  3k | 4 | 85 |
| 12 |  |  |  3l | 3 | 84 |
| 13 |  |  |  3m | 3 | 90 |
| 14 |  |  |  3n | 2.5 | 94 |

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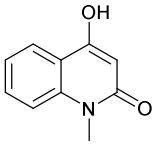
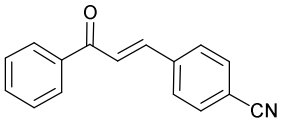
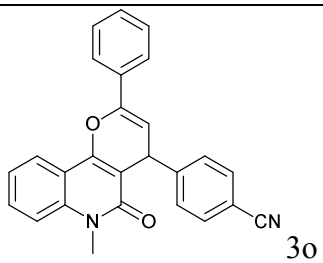
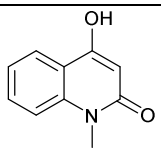
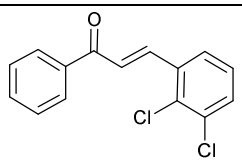
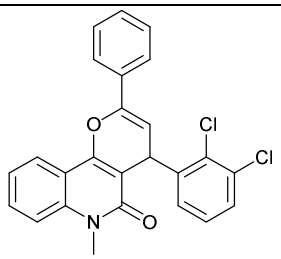
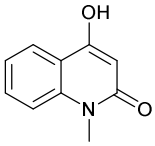
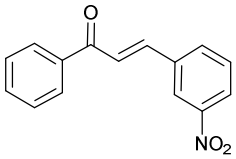
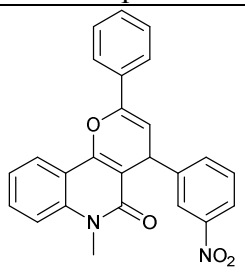
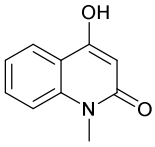
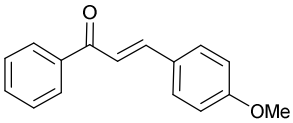
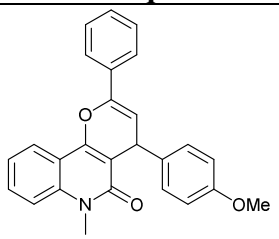
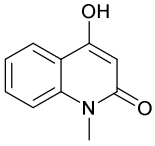
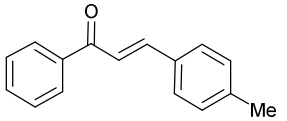
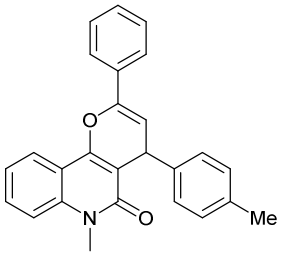
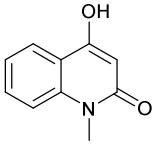
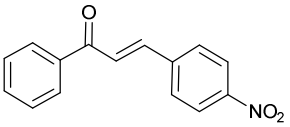
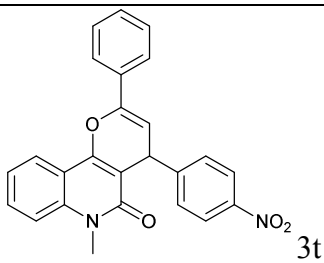
| 15 |  |  |  3o | 2.5 | 95 |
| 16 |  |  |  3p | 2.5 | 93 |
| **17** |  |  |  **3q** | **2** | **91** |
| 18 |  |  |  3r | 3 | 88 |
| 19 |  |  |  3s | 3 | 89 |
| 20 |  |  |  3t | 2 | 95 |

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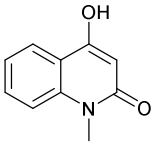
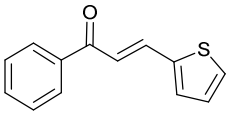
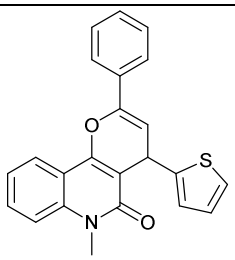
| 21 |  |  |  3u | 3 | 88 |

[b]Yield of isolated product.

A wide range of activated as well as unactivated chalcones with electron-deficient and electron-rich aryl groups were highly compatible under the developed protocol and provided good to excellent yields of the corresponding products. The structures of the desired products were characterized by $^{1}H$ and $^{13}C$ NMR, IR and HRMS spectral data. The X-ray crystal structure of 6-methyl-4-(4-nitrophenyl)-2-phenyl-4,6-dihydro-5*H*-pyrano[3,2-*c*]quinolin-5-one (**3q**) (Figure 4) further confirmed the product identity.

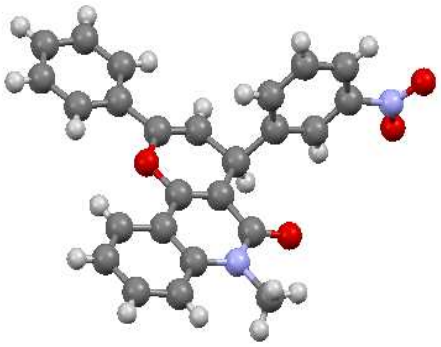
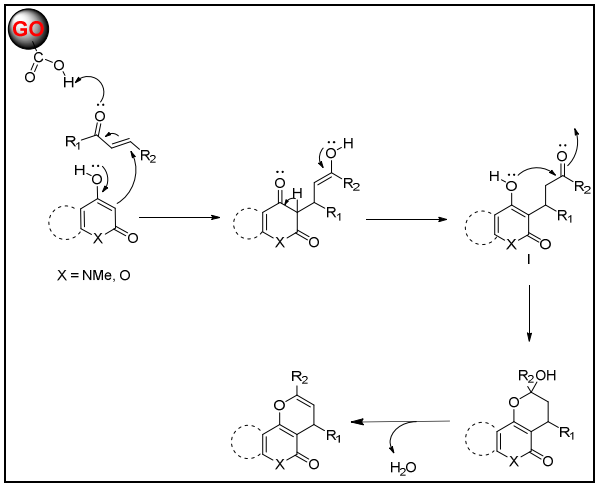


**Figure 4:** Single crystal structure of compound **3q** (CCDC 1025207)

Presumably, this transformation occurs via Michael addition of chalcone and 4-hydroxy-1-methylquinolinone. The intermediate I then undergoes sequential intramolecular cyclization followed by dehydration in order to fabricate the targeted molecule (Scheme 2).




**Scheme 2:** Plausible reaction pathway for 4*H*-pyrans

During the formation of pyranocoumarins and pyranopyrans, the reaction proceeds via the similar Michael addition and intramolecular cyclization pathway but the dehydration step was not observed under the imposed reaction condition after prolonged heating. No side products were isolated on both of the cases which further proved the operational simplicity with excellent yields. It is seen that when methylquinolinone was used as substrate, the dehydration products were obtained owing to the presence of high electron rich nitrogen centre which may abstract the β-hydrogen of the OH-group and facilitated the dehydration product.

It is important to emphasize on the catalyst recyclability that is a crucial feature of the green chemistry. The reusability of the catalyst was studied through the condensation of 3-(4-nitrophenyl)-1-phenylpropenone (1.0 mmol) and 4-hydroxycoumarin (1.0 mmol). The separated catalyst was collected, followed by washing with acetone several times to remove all the organic substances. It was then dried at room temperature and was recycled five consecutive times with almost unaltered catalytic activity (recovery amount 92% and yield, 86% after 5th run)(Figure 5). Furthermore, to take advantage of the highly efficient green protocol, the reaction was scaled up to 10 mmol scale, excellent results were obtained in the stipulated time as mentioned in Table 2.

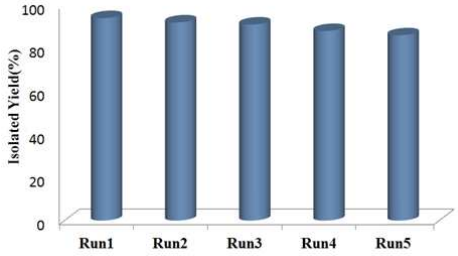



**Figure 5:** Reusability study of GO nano sheets

**Experimental Section:**

**General Procedure for the synthesis of Chalcones:** Acetophenone (5mol%) was added to NaOH (0.05%) in 2 ml EtOH solution in a round bottom flask immersed in an ice bath. Aldehyde (5mol%) was then added dropwise from a dropping funnel with constant stirring. Reaction mixture was stirred vigorously for 2 h, then kept in refrigerator overnight and finally filtered. The product thus appeared, was washed with cold water followed by ice-cold ethanol to get pure chalcones.

**Preparation of GO nano sheets:**

The graphene oxide nanosheets were synthesized from natural graphite powder .Graphite powder (1gm) and $NaNO_3$ (1gm) were

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added into 50 ml 98% concentrated $H_2SO_4$ under vigorous stirring condition in a 250 ml conical flask placed in an ice bath. After a few minutes the whole mass was converted to black slurry. Then $KMnO_4$ (6 gm) was added slowly into the slurry maintaining the reaction temperature 15°C to 20°C. After 3 h, the whole system was taken out from the ice bath and diluted with 100 ml water and then stirred for 3 h at ambient temperature. To control the pH of the reaction medium and also to terminate the reaction, 200 ml hot water followed by 30% $H_2O_2$ were added to the above reaction mixture until excess permanganate and manganese dioxide were reduced to colourless soluble manganese sulfate. The resultant yellow precipitate was washed with distilled water several times and the residue was subjected to centrifuge to get the pure graphene oxide powder. After repeated centrifugation, salts and ions from the oxidation process can be removed from GO suspensions. The GO nano sheets sample was collected and dried at 60°C for 24 h. GO nano particles were characterized using its FESEM and TEM images (Figure 3).

**General Procedure for the synthesis of 4*H*-pyran derivatives:**

A mixture of freshly prepared chalcone (1 mmol) and hydroxyquinolinone/hydroxy-chromene/pyrone derivative (1mmol) were added to a well stirred solution of GO nanosheets (8mg, 10 mol%) in 3ml $H_2O$ at room temperature. The mixture was then stirred at 80 °C for the required period of time (TLC). After completion of each reaction, the crude product mixture was extracted with ethyl acetate (3x10ml). Removal of ethyl acetate under reduced pressure and purification of the crude product by column chromatography (silica gel 100-200 mesh) provided pure products. All compounds were well characterized by $^1H$, $^{13}C$ NMR, FT-IR and HRMS analysis.

**Conclusion**

In conclusion, an extremely efficient method has been developed for the synthesis of pyranoquinolinones pyranocoumarins and pyranopyrans *via* a one-pot two-component condensation reaction in aqueous media using GO nano sheets as an eco-friendly degradable organocatalyst for the first time. This method is bestowed with several green chemistry principles, such as high conversions, simplicity in operation, and use of cost efficient eco friendly reaction medium, simple workup procedure, high yields of products and only water as the byproduct. Application of nano reusable catalyst in synthesis of complex molecules extends the scope and may contribute to progress further in chemical research.

**Acknowledgement**

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