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Design and synthesis of coumarinyl 1,4-benzodioxanes as potential anti-oxidant

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ABSTRACT

A series of novel coumarinyl 1,4-benzodioxanes were successfully synthesized from electronically diverse 2-[(o-iodophenoxy)methyl]oxiranes and different positional isomers of hydroxycoumarin via one-pot tandem nucleophilic displacement and copper-mediated intramolecular C–O coupling reaction using CuI and 1,10-phenanthroline as the efficient catalytic system. All the compounds were characterized by ^{1}H, ^{13}C NMR, IR, HRMS spectra and a selected set of newly synthesized compounds offered noticeable in vitro free hydroxyl radical scavenging activity in a systematic dose dependent manner which signifies their excellent biological potential.

The compounds containing coumarin moiety have the reputation of possessing immense utility in medicinal and bioorganic chemistry due to their biological and pharmacological activities. Representative examples include Geiparvin (**A**), a coumarin derivative that possesses an efficient anti-tumour activity.[1] Vipirinin (**B**), a coumarin based HIV-1 Vpr inhibitor.[2] 7-Methoxy-8-(4-methyl-3-furyl) coumarin (**C**) is recently isolated from the plant '*Galipea panamensis*' which shows excellent antileishmanial activity.[3] Angelmarin (**D**) is a novel coumarin-based natural product that was isolated from extracts of the medicinal plant '*Angelica pubescens*' and found to exhibit toxicity specifically against the pancreatic cancer cell line PANC-1[4] (Fig. 1).

Again compounds with 2,3-dihydrobenzo-1,4-dioxane moiety have received considerable interest as they are abundant in numerous pharmacologically active molecules which are reported to display potent neuroleptic activity[5], adrenergic neuron blockage, and antihypertensive activity.[6] Historically, the first α_1 antagonist identified was WB-4101 (**E**), a 2-aminomethyl-1,4-benzodioxane derivative which was later found to be slightly selective for α_{1A} and to a minor degree for α_{1D}-ARs with respect to α_{1B}-AR and 5-HT_{1A} serotoninergic receptor.[7] 8-Aza-bicyclo[3.2.1]octane derivatives of 2,3-dihydro-1,4-benzodioxane (**F**) show selective serotonin re-uptake inhibitor activity and 5-HT_{1A} antagonist activity.[8] In addition 5-benzyl and 5-benzylidene-thiazolidine-2,4-diones carrying 2,3-dihydrobenzo-1,4-dioxane pharmacophore (**G**) exhibit excellent glycogen phosphorylase inhibitor activity[9] (Fig. 2).

The formation of carbon heteroatom bonds has been well-known for a long time. Despite the developments in the catalytic carbon-heteroatom coupling reaction, further modification of the copper catalysed methodology is still in progress. Much emphasis in this improvement has been given for the exploitation of newer bases and ligands to achieve the C–O linkage.[10–13] In recent times numerous modifications of such coupling reactions have been explored to afford C–O bond containing linear and cyclic moieties.[14a–i] Ligand-free synthesis of aryl ethers by modified C–O coupling is being investigated by our group very recently.[15a,b] Since the literature advocates the significant therapeutic activity of coumarin as well as 1,4-benzodioxane based compounds, synergism of both the heterocyclic moieties in a single nucleus may integrate the properties of both and result into formation of some worthwhile molecules from the biological point of view.

In continuation of our interest in the synthesis and application of coumarin containing heterocycles[16a,b] it was an exciting challenge and enduring interest for us to prepare coumarin linked 1,4-benzodioxanes and to assess their biological potential. For this, 2-[(2-iodophenoxy)methyl]oxirane (**2a**) (readily prepared from 2-iodophenol through coupling with epichlorohydrin) and 4-hydroxycoumarin (**1b**) were chosen as the model substrate to optimize the conditions of the target cyclization leading to the access of coumarin linked 1,4-benzodioxanes (**3e**) (Scheme 1). Inspired by the excellent scope of organic ligand facilitated Cu-catalysed carbon-heteroatom coupling reactions, a series of commercially available copper salts and nitrogen ligands (Fig. 3) were applied to optimize the desired protocol (Table 1).

The results revealed (Table 1) that among the several copper(I) and copper(II) salts Cu_2O, CuCl, CuBr, and CuI showed the catalytic

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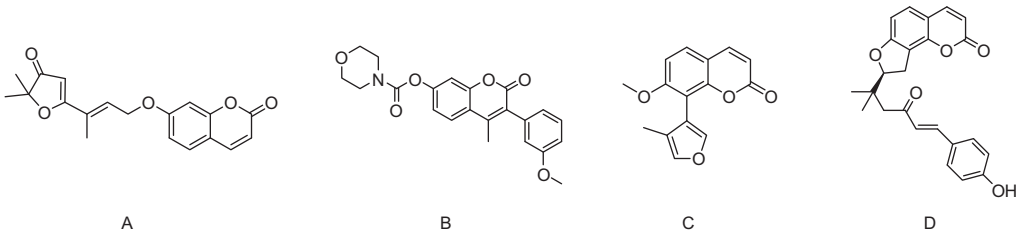


Figure 1. Structures of some biologically active coumarin core containing heterocyclic scaffolds.

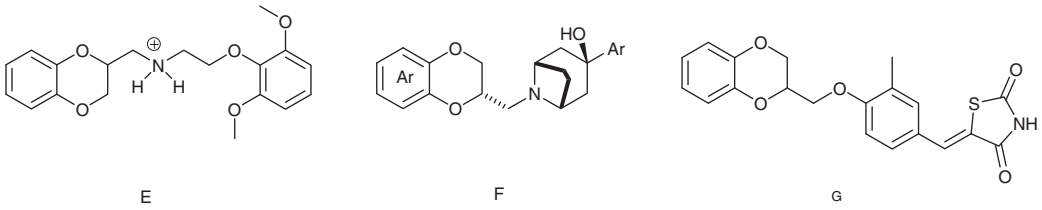
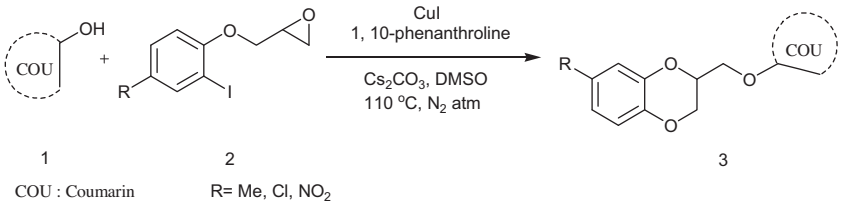


Figure 2. Structures of some biologically active compounds with 1,4-dioxane moiety.



Scheme 1. Synthesis of coumarinyl 1,4-benzodioxanes.

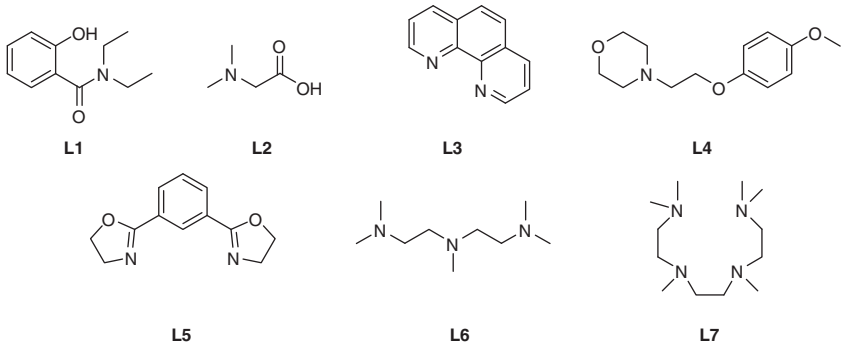


Figure 3. Ligands used in the optimization of the reaction protocol.

activity whereas different copper (II) salts such as CuO, $Cu(OAc)_2$, $Cu(OTf)_2$, and $Cu(acac)_2$ remained completely ineffective. Again yields of the desired product were improved by using different kinds of multidentate chelating ligands among which 1,10-phenanthroline appeared to be the most advantageous. The effect of the ratio of the copper salt and the ligand was also studied. The screening suggested that the catalyst system containing 15 mol % of CuI and 30 mol % of ligand (L3) was the optimal and best choice (Table 1, entry 3). Effect of the catalyst loading has an influence on the yield. When the catalyst loading was reduced to 10 mol %, the reaction gave a yield of 59%. Thus we found copper(I) iodide along with 1,10-phenanthroline to be the most efficient catalyst ligand combination for this coupling reaction giving 80% yield. Finding the right catalyst combination we next concentrated to evaluate the base additives on reaction in a variety of solvents (Table 2). The choice of the base for the activation of the O–H bond in hydroxycoumarin is very crucial because of the sensitivity of the lactone ring in coumarin moiety towards alkaline condition. In the absence of base, no reaction took place even after the prolonged reaction time. Organic bases like DBU and pyridine, owing to their passive character, were unable to drive the reaction to the product side (Table 2, entries 3, 4). Among the inorganic bases applied, Cs_2CO_3 has proved to be exceptionally efficient in comparison to K_2CO_3 and K_3PO_4 (Table 2, entries 1, 2) because of its higher solubility in polar organic solvents (DMSO and DMF). Moreover, it also imparted right basicity to the reaction medium for the reaction to follow the obvious course to the desired product side. Additionally no product was detected following the opening of the lactone ring as it did not interact with the lactone ring of coumarin moiety. Once again best yield of the desired product was obtained