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Synthesis, characterization and antimicrobial activity of some coumarin fused heterocycles

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Widely distributed in nature, coumarins are one of the more common and well-known representatives of a flavonoid class. Nevertheless, they exhibit a strong and broad variety of biological activities. In the present research study, we describe a series of naphthalene and quinoline, furan and thiophene derivatives fused with a coumarin scaffold. The compounds have been interpreted by IR, GCMS, and NMR spectral studies and evaluated *in vitro* for their antimicrobial activities against four different pathogenic bacterial strains such as *E. coli*, *P. aeruginosa*, K. *pneumonia*, *S. aureus* and *S. faecalis* and fungal strains such as *A. flavus*, *A. fumigatus* and *B. albicans*. The coumarins fused with thiophene ring exhibit promising anti-microbial properties.

Keywords: Coumarins, quinoline, furan, thiophene, anti-bacterial

Nitrogen, oxygen and sulfur containing heterocycles play an important role in diverse biological activities. Pyridine, Ffuran and thiophene heterocycles have increasingly been recognized as pharmacophores that offer advantages including superior chemical and pharmacological stability linked with aromatic compounds and more importantly a rich chemistry that enables medicinal chemists to explore molecular diversity in a rapid fashion. Among the well-known heterocycles, those containing coumarin, quinoline, benzofuran and benzothiophene ring systems have been of structural and pharmacological interest. The review on coumarins[1-10], quinolines[11-21], benzofuran[22-25] and benzothiophene[26-30] shows the widespread biological applications of these heterocycles.

A wide range of biological properties inherent in benzofuran, benzothiophene scaffold reaffirm the ample interest in using benzofuran, benzothiophene as building blocks of pharmacological agents[31,32]. Many of the clinically approved drugs are synthetic or naturally occurring substituted benzofuran derivatives, some of which are fused with other heterocyclic moieties[33,34]. However, due to the great biological importance of this scaffold, investigation of various methods for synthesis and structural modification of coumarin based benzofuran derivatives have now become an important goal of several research groups[35-50].

In this context and as part of our continuing research program on the synthesis of nitrogen, oxygen and sulfur containing heterocyclic compounds with potential pharmacological activities, we have designed the synthesis of some new benzofuran, benzothiopehene substituted coumarin moieties.

Results and Discussions

7-Carbonylamino/7-carbethoxyamino-4-(bromomethyl) coumarins **1a-b** were synthesized by the Pechman cyclization of 3-carbonylamino/3-carbethoxyamino-phenols with 4-bromoethylacetoacetate[51]. Fused coumarin-4-heterocles **2a-h** (Scheme I) were obtained when aromatic/heterocyclic salicylates refluxed in alcoholic potassium carbonate underwent an intramolecular aldol reaction due to the presence of active methylene group and *ortho* carbonyl group. The cyclo additions of C,N; C,O heterocyclic rings are formed through aldol condensation as shown in Scheme II. The absence of the methylene protons around δ 4.2 - 5.8 led us to conclude that the initially formed ethers probably underwent a further intramolecular carbanion addition across the aldehyde group located at close spatial proximity (*ortho* position) leading to