GENERAL INTRODUCTION

The heterocyclic compounds, where one or more carbon atoms have been replaced with heteroatoms like nitrogen, oxygen, sulfur, selenium, etc., have been among the molecules of forefront interest in science. To withstand evolutionary pressure plants and animals resorted to synthesis and effective utilization of heterocyclic compounds in myriad of ways. Unraveling such intricately connected mysteries of Nature is the crux of modern science particularly chemical biology. Many heterocyclic compounds are fundamental to life, examples include Life supporting heterocyclic compounds like phorphyrins (eg. chlorophyll, vitamin B₁₂), nucleic acids (eg. adenine, cytosine), carbohydrates (ribose, glucose), some amino acids (tryptophan, histidine). History of heterocyclic chemistry can be traced to Bregnatelli who isolated allexan from uric acid way back in 1818. Some notable early contributions came from Dobereiner, Runge, Friedlander and Triebs who laid foundation for modern heterocyclic chemistry. Preamble to heterocyclic chemistry as we know today came from Chargaff who formulated rules for genetic coding and linked them with the behavior of heterocyclic compounds. In the journey of heterocyclic chemistry research for two decades our laboratory made some notable contributions for the development of this science particularly in the areas of oxygen, nitrogen and sulfur heterocyles.

Our basic interest is in the synthesis of oxygen heterocyles which are among the important class of molecules in heterocyclic chemistry and chemical biology. Benzopyrans are bicyclic oxygen incorporated heterocyclic compound that results from the fusion of a benzene ring to the pyran ring. According to IUPAC nomenclature it is called chromene. Common benzene fused pyran derivatives like chromene 1, isochromene 2, coumarin 3, chromanone 4, flavone 5 and flavanone 6 are gathered in Figure 1. There are two isomers of benzopyran that vary by the orientation of the fusion of the two rings compared to the oxygen, resulting in 1-benzopyran (chromene) and 2-benzopyran (isochromene) the number denotes where the oxygen atom is located by standard naphthalene-like nomenclature. Commonly, benzopyran is encountered in the reduced state, where it is partially saturated with one hydrogen, introducing a tetrahedral CH₂ group in the pyran ring. There are thus many different structural isomers due to multiple possible positions of the oxygen atom and the tetrahedral carbon.
Figure 1. Structures of benzene fused six membered oxygen heterocyles chromene 1, isochrmene 2, coumarin 3, chromanone 4, flavone 5 and flavanone 6.

Synthesis and characterization of analogs of naturally occurring benzopyrans heterocycles like flavonoids, coumarins and chromenes is of contemporary interest as they exhibit profound biological activities. Hybrid heterocyclic molecules can exhibit properties of both and individual and combined molecular entities. For the present research work we have carried out synthesis and characterization of conjugates / hybrids of oxygen heterocycles like 7-10 that incorporate several new coumarin, chromene and flavanones structural motifs.

Figure 2. Structures of chromene-coumarin conjugate 7, hybrid spiro bis-coumarins 8, hybrid spiroflavanones 9, hybrid coumarin flavone 10.

Following are the objectives of the present research.

1. To study the synthesis of various hybrids and conjugates of coumarins, chromenes and flavones.
2. To study how the physical and biological properties are effected due to their structural diversity.
3. To develop the suitable methodologies for synthesis of targeted heterocyles.
Present thesis entitled “Synthetic Studies on Oxygen Heterocycles: Conjugates / Hybrids of Coumarins, Chromenes, Flavanones and Pyranones” is divided into three chapters. In Chapter 1 we have shown that 4-methylsulfanyl-4H-chromenes are useful starting compounds for the synthesis of a range of 4H-chromene 4-hyrdroxy-2-pyrone, 4H-chromene 4-hyrdroxycoumarin and 4H-chromene and 2-hydroxy-1,4-naphthoquinone conjugates. Furthermore, the 4H-chromene 4-hyrdroxy-2-pyrone conjugates were transformed into acetoacetylcoumarins and 4H-chromene 4-hyrdroxycoumarin conjugates into trans-2,3-disubstituted dihydrofuro[3,2-c]coumarins. As the products prepared in present study possess structural characteristics of privileged medicinal scaffolds, we evaluated some of the derivatives for their biological activities. Selective antibacterial and antifungal screening showed that two of the newly synthesized conjugates 4H-chromenes display impressive biological activity.

In the second chapter we described the synthesis and structural characterization of several novel heterocycles embedded in spirobindane motif and having structural features of chromanone, flavanones, coumarins etc. Where required we have carried out theoretical calculations to support stereochemical assignments and in some cases we have evaluated fluorescence emission characteristics.

In the third Chapter we have described a short and facile two-step synthesis of 3-arylcoumarin-flavone hybrids from 7-hydroxy flavone and α-oxoketene dithioacetals.