Chapter 1: INTRODUCTION

Today, our world increasingly is conceived of as being molecular. An ever widening range of phenomena are described logically in terms of molecular properties and molecular interactions. The majority of known molecules are heterocyclic and heterocycles dominate the fields of biochemistry, medicinal chemistry, dyestuffs, photographic science and are of increasing importance in many others, including polymers, adhesives, and molecular engineering.

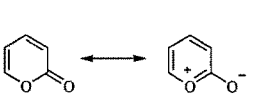
A cyclic organic compound containing all carbon atoms in ring formation is referred as a *carbocyclic* compound. If at least one atom other than carbon forms a part of the ring system then it is designated as a ***heterocyclic*** compound.

Heterocyclic chemistry is an integral part of organic chemistry and constitutes a considerable part of chemistry. Heterocyclic chemistry deals with heterocyclic compounds which are widely distributed in nature and are essential to life. Genetic material DNA is also composed of heterocyclic bases – pyrimidines and purines. A large number of heterocyclic compounds, both synthetic and natural, are pharmacologically active and are in clinical use. Several heterocyclic compounds have applications in agriculture as insecticides, fungicides, herbicides, pesticides etc. They also find applications as sensitizers, developers, antioxidants, copolymers etc. They are used as vehicles in the synthesis of other organic compounds. Chlorophyll - photosynthesizing and hemoglobin - oxygen transporting pigments are also heterocyclic compounds.

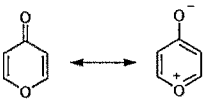
The occurrence of heterocyclic compounds in nature is widespread, and the use of natural and synthetic heterocyclic compounds in many commercially important spheres, is enormous.

Of the large family of heterocycles, α - and γ – pyrones are of utmost importance. Pyrones are six – membered heterocyclic compounds containing one oxygen atom in the ring and five sp^2 hybridized carbons. Two isomeric pyrones namely α -

pyrone and γ – pyrone are possible. They are also known by other names such as 2*H* – pyrone and 4*H* – pyrone respectively.



2*H* – pyrone

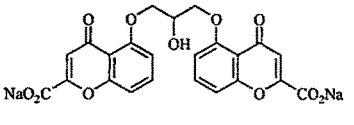


4*H* – pyrone

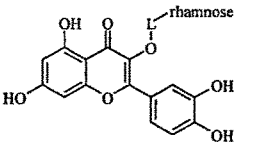
Benzannulated pyrone derivatives of α – pyrones are Coumarins, Isocoumarins, while that of γ – pyrones are Chromones and Xanthones. Both types of pyrones display characteristics which partake some reactions of alkenes and some those of arenes. The α – pyrones behave more in the former manner and they can be used as conjugated enol – lactones, the extent to which they are additionally stabilized by resonance is not clear. On the contrary the reactions of γ – pyrones are observed to be of the pyrylium betaine structure.

Therefore, γ – pyrones have a greater degree of aromaticity than α – pyrones. This has been supported by spectroscopic data. The pyrones are insignificantly basic and their basicities are comparable to those of urea and nitroanilines.

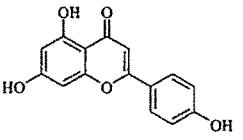
γ – pyrones substituted at second position by aryl group are covered under different class called Flavones. Quercetrin, Apigenin, Intal are some of the well known examples of naturally occurring flavones.



Intal – for bronchial asthama

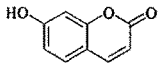


Quercetrin

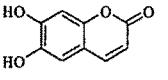


Apigenin

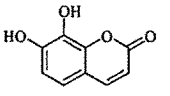
Some of the important naturally occurring coumarins are Umbelliferone, Aesculetin, Daphnetin, Scopoletin, Fraxetin and Ayapin.



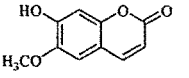
Umbelliferone



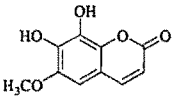
Aesculetin



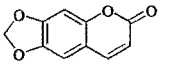
Daphnein



Scopoletin

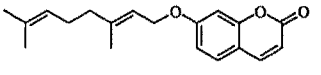


Fraxetin

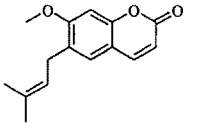


Ayapin

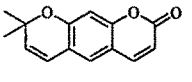
Coumarins substituted with isoprenoid residues are also known.



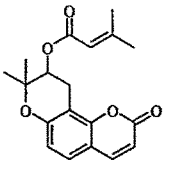
Auraptene



Suberosin



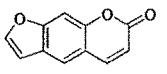
Xanthyletin



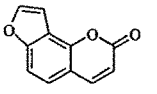
Samidin

Furan ring fused with benzopyrones forms a different class of compounds called Furocoumarins and Furoflavones. These classes of compounds have attracted much attraction because of their wide range of pharmacological behaviour.

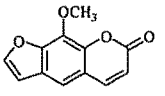
Some of the naturally occurring furocoumarins are Psoralen, Angelicin, Xanthotoxin and Pachyrrhizin.



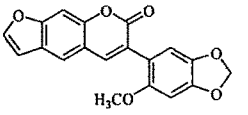
Psoralen



Angelicin

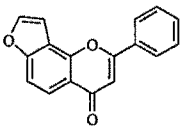


Xanthotoxin

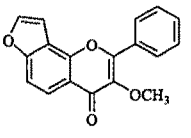


Pachyrrhizin

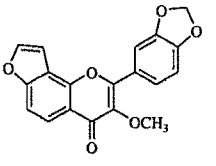
Naturally occurring furoflavones include,



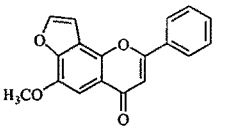
Lanceolatin B



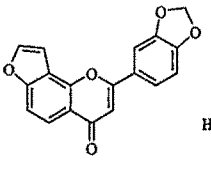
Karanjin



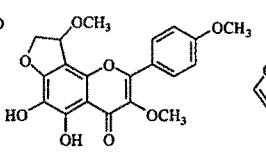
Pongapin



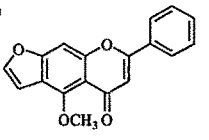
Kanjone



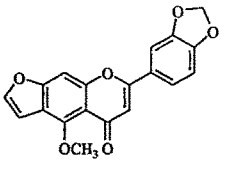
Pongaglabrone



Atanasin



Gamatin

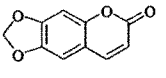


Pinnatin

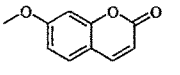
Many natural coumarins affect the living cells of plants and animals in various ways. Bose,[1] has reviewed the biochemical properties of natural coumarins, whereas, Sigmund,[2] observed the effects of both aesculetin and daphnetin on seed

germination and noted that coumarin itself inhibits the germination and subsequent root growth of plants. There is also a good probability that coumarins act as growth regulators in a number of plants.[3]

Sedative and hypnotic properties of coumarin have also been studied.[4] Herniarin and Ayapin have been found to possess remarkable haemostatic properties and are active both *in vitro* and *in vivo*.[5]

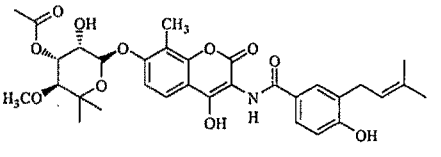


Ayapin



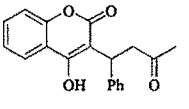
Herniarin

Novobiocin,[6] an antibiotic isolated from streptomyces sp., has been found to be a coumarin derivative.



Novobiocin

Coumarins are also known for anticoagulant and rodenticidal properties. Warfarin developed as rodenticide is a useful anticoagulant drug.



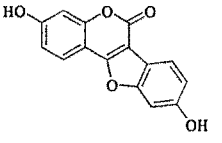
Warfarin

3,4-diamino coumarins and 4-amino coumarins have neutropic activity.[7] Moreover, the derivatives of coumarins are found to have blood cholesterol lowering,[8] and antispermatogenic activity.[9]

Okamoto and coworkers,[10] synthesized coumarins, which were claimed for the treatment of liver diseases, whereas Trkovnik *et. al.*,[11] used coumarin derivatives for the treatment of digestive tract disorders and for reducing concentration or activity of transaminoses.

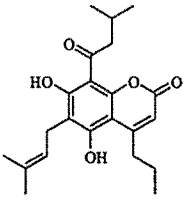
Sardari *et. al.*,[12] synthesized non toxic coumarins and angular furobenzopyrones which showed antifungal activity. These furobenzo-α-pyrones are also widely used in the treatment of skin liaisons such as psoriasis,[13] vitiligo,[14] etc in combination with UV-A light.

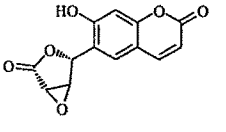
There is another class of naturally occurring coumarin derivatives known as Coumestan or benzofurobenzo-α-pyrones. These compounds possess estrogenic and phytoalexin properties.[15]



Coumestan

Anti-tumor activity of coumarins have also been reported for following compounds.[16, 17]





Comprehensive reviews about the chemistry of naturally occurring furocoumarins are documented. Juices of plants such as parsley, celery, fig and parsnip after contact with the skin and exposure to sunlight causes change on mammalian skin manifested by erythema and increased pigmentation. The discovery of this unique

activity of furocoumarins stimulated the research in this area. These are also widely utilized for the treatment of hyperproliferative skin diseases as chemical probes for chromatin structure and more recently, in the treatment of AIDS.[18]

Several naturally occurring furoflavones such as Lanceolatin B, Karanjin, Pongapin, Kanjone, Pongaglabrone, Atansin, Gamatin, Pinnatin, Pongamoleti are known to exhibit variety of biological activities.[19]

Flavonoids, ubiquitously occurring and widely consumed secondary metabolites of plants such as Quercetin, Acacetin, Apigenin, Kaempferol and Morin inhibit topoisomerase-1 catalyzed DNA relegation.[20] Flavon-8-acetic acid inhibits endothelial cell proliferation *in vitro* and selectively destroys tumor vasculature, leading to tumor cell death by ischemia. Flavonoids exhibiting spasmolytic and vasodilatatory properties have also been studied.[21] M. S. Y. Khan and Sandhya Bawa have reported the synthesis and anti-inflammatory activity of new α - pyranochalcones and α-pyranoflavones.[22]

These furocoumarins and furoflavones can be prepared by starting with suitably substituted α - pyrone or γ - pyrone derivatives and then building up furan ring over it or by building up the pyrone ring on hydroxy benzofurans.

So the first step towards the synthesis of furopyrones was to synthesize hydroxy benzofurans. Chapter 2 deals with the synthesis of hydroxy benzofurans which has been used as starting/building blocks in subsequent chapters.

References

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