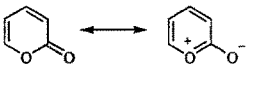
SUMMARY

Introduction

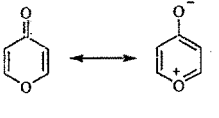
A cyclic organic compound containing all carbon atoms in ring formation is referred as a *carbocyclic* compound. If at least one atom other than carbon forms a part of the ring system then it is designated as a *heterocyclic* compound.

Their study is of great interest both from the theoretical as well as practical standpoint.

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

Furocoumarins and furoflavones have attracted much attention in recent years because of their wide range of pharmacological behaviour. 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.

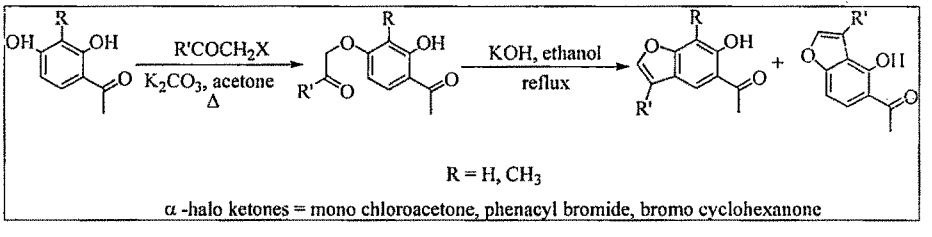
Objective of the work:

- To synthesize new heterocyclic compounds.

- To study the chemistry and orientation with different substituents in the synthesis of heterocyclic compounds.
- To screen the heterocyclic compounds for possible pharmacological action.

The structures of all the compounds have been established on the basis of their elemental analyses and spectral (IR, LCMS and NMR) data for all the chapters. The long range coupling in some of the molecules have been confirmed by ^1H – COSY spectra.

Chapter 2: Regioselective Cyclodehydration of Aryloxyketones to Benzofuran.*



Benzofurans are versatile building blocks serving variety of applications such as pharmaceuticals and fine chemicals. *Ortho*-hydroxy acetyl benzo[*b*]furans are important starting materials in the synthesis of flavonoids, chromones and coumarins. Several methods have been known for the synthesis of benzofurans. The synthetic pathway followed by MacLeod *et al.* has been employed to prepare the title compounds.

Ortho-hydroxy acetyl benzo[*b*]furan derivatives have been synthesized in a regioselective cyclodehydration of α-aryloxyketones obtained from β-resacetophenone and α-halo ketones.

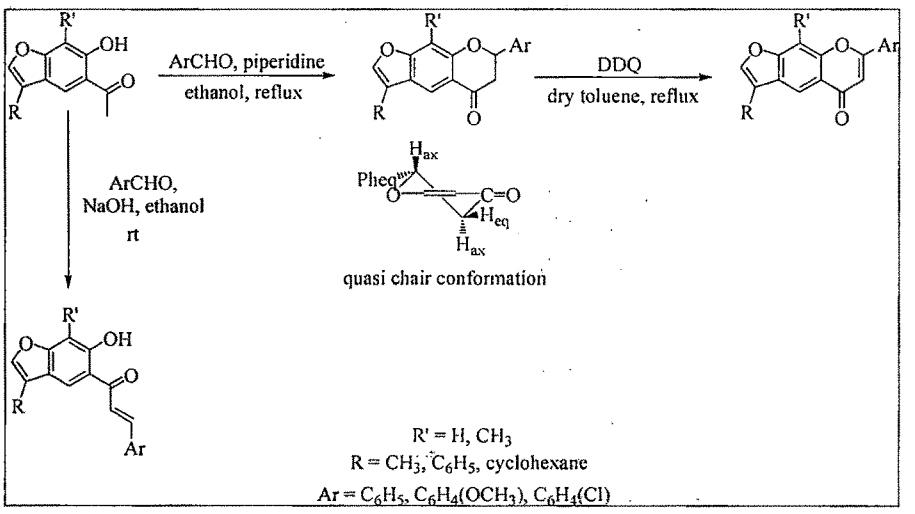
* Jagdish M. Patel and Shubhangi S. Soman, *J. Heterocycl. Chem.* **2007**, 44(1), 945-949.

β-resacetophenone on condensation with different α-halo ketones *e.g.* α-bromo cyclohexanone, phenacyl bromide and mono chloroacetone, gave the corresponding aryloxyketones. These aryloxyketones when subjected to cyclization in 0.1 *N* ethanolic potassium hydroxide gave linear and angular benzofurans. The mechanism as established by MacLeod *et al.* is an intramolecular aldol condensation in which the phenoxide ion formed promotes attack at the exocyclic carbonyl function through the resonance stabilized carbanion generated at the position *para* to the phenoxide ion. The irreversibility of the process is established by abstraction of the proton from the newly formed ring junction. On acidification water is spontaneously eliminated from the labile β-hydroxy dihydrofuran ring system to give the unsaturated benzofuran. Although the carbanion generated *para* to the phenoxide ion is resonance stabilized, the formation of carbanion generated *ortho* to the phenoxide ion cannot be ruled out and which forms the basis of formation of two isomers. The low yield of angular isomer compared to the linear isomer, which is approximately in the ratio of 1:3, is in accordance with the theory postulated above. The overall yield of the cyclization reaction is lowered by the hydrolysis of ether linkage of aryloxyketones back to β-resacetophenone.

These *o*-hydroxy acetyl benzo[*b*]furans have been used as starting material for the synthesis of various heterocyclic compounds in subsequent chapters.

Chapter 3: Section A: Synthesis of Furoflavones.

Furoflavones are known to exhibit variety of pharmacological properties. Moreover, the α, β-enone function is a favorable unit for dipolar cycloaddition.



Several new furoflavanones have been synthesized from the *in-situ* generated chalcones by the reaction of *ortho*-hydroxy acetyl benzofuran and aryl aldehyde in presence of piperidine. 1% ethanolic sodium hydroxide gave chalcones as the exclusive product. Flavindogenides (3-arylidene flavanones) have been isolated as the co-product along with chalcones and flavanones in cases where excess of aryl aldehyde was used. The stereochemistry of 3-arylidene flavanones has been established by the preparation of both *Z* and *E* diastereomers. Furoflavanones were finally dehydrogenated to furoflavones using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).

Ortho-hydroxy acetyl benzofurans, were condensed with different aryl aldehydes in 1% ethanolic sodium hydroxide to give the corresponding chalcones. Though such a low concentration of alkali was used there was no evidence of formation of flavanones, which was contradictory to the reports in literature, which indicated that low concentration of alkali favoured ring closure whereas high concentration of alkali favoured ring fission.

However, when *ortho*-hydroxy acetyl benzofurans were condensed with different aryl aldehydes in presence of catalytic amount of piperidine, it gave a mixture of

chalcones and flavanones, flavanone being the major product. The flavanone ring proton (C2-H) appeared as a doublet of doublets at δ 5.51-5.47 ppm. The double doublet for one proton centered at δ 3.08-3.15 ppm, *J* 16.8 Hz (geminal coupling – diastereotopic protons) and *J* 12.9 Hz (vicinal diaxial coupling), was assigned to (C3-H) axial proton, and a doublet of doublet again for one proton at δ 2.89-2.94 ppm, *J* 2.6 Hz (vicinal coupling) and *J* 16.8 Hz (geminal coupling – diastereotopic protons) was assigned to (C3-H) equatorial proton forming an ABX system. The coupling constant of (C2-H) proton [viz. 12.9 Hz (vicinal diaxial coupling) and 2.6 Hz (vicinal axial-equatorial coupling)] indicated it to be axial in the quasi chair conformation of the flavanone ring, with phenyl ring equatorial.

When excess of aryl aldehyde was used in the preparation of flavanones, it led to the formation of 3-arylidene flavanones as a co-product, which has been isolated by column chromatography and characterized for some of the reactions. Reaction of two moles of aryl aldehyde with *o*-hydroxy acetyl benzofuran in presence of piperidine gave 3-arylidene flavanones. Stereochemistry of 3-arylidene flavanones has been unambiguously determined by the synthesis of both the *Z* and *E* isomers. Two singlets at δ 6.6 ppm for C2-H proton of the flavanone ring and δ 8.1 ppm for vinylic proton both corresponding to one proton each showed the formation of 3-arylidene flavanones in *E* configuration, vinylic proton being deshielded resulting from the diamagnetic anisotropy of the carbonyl group. The *E* configuration of 3-arylidene flavanones was further confirmed by converting it into the *Z* isomer photochemically using mercury arc 150W lamp and toluene as a solvent. Finally, all the flavanones were dehydrogenated to flavones using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in dry toluene.

Chalcones synthesized are showing better anti-inflammatory activity compared to the standard drug ibuprofen and can be explored further. One of the furoflavone showed growth inhibition upto 74 % against Breast MCF–7 cancer cell line and 40 % against Prostate DU-145 cell line, which continues our interest in flavonoid chemistry.

Section B: Conformation of Furoflavanones.

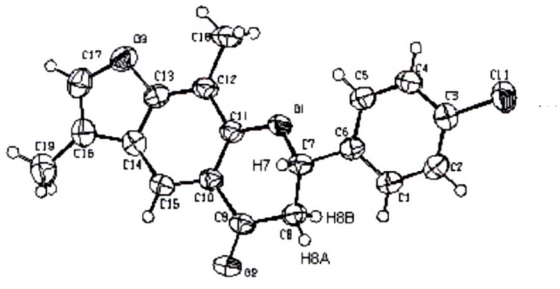


Figure: ORTEP diagram of 7-(4-chloro-phenyl)-3,9-dimethyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one (50% probability factor for thermal ellipsoid with atom numbering scheme).

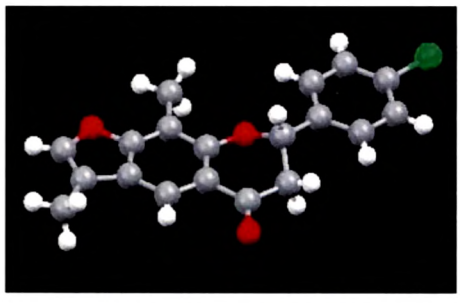


Fig: Crystal structure of furoflavanone.

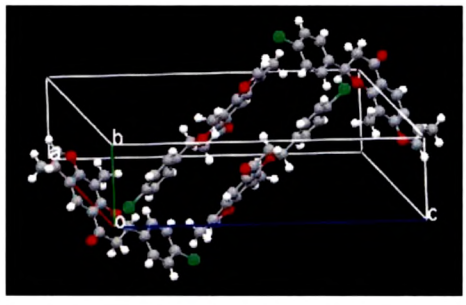


Fig: Packing structure in furoflavanone.

The quasi chair conformation of the flavanone ring has been established on the basis of X-ray crystallography. Single crystal X-ray diffraction data showed the flavanone ring to exist in quasi chair conformation with phenyl ring equatorial and parallel to the plane of the molecule. X-ray quality single crystals were grown in a slow evaporation condition at room temperature. Crystals were obtained from a mixture of ethanol and toluene.

Compound 7-(4-chloro-phenyl)-3,9-dimethyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one crystallizes in a centro symmetric monoclinic space group $P2_1/c$. The asymmetric unit consists of a single flavanone molecule at a normal position. As can be seen from the ORTEP diagram, quasi chair conformation allows a strain less flavanone molecule to have all the atoms, apart from C-7, coplanar. Atom C-

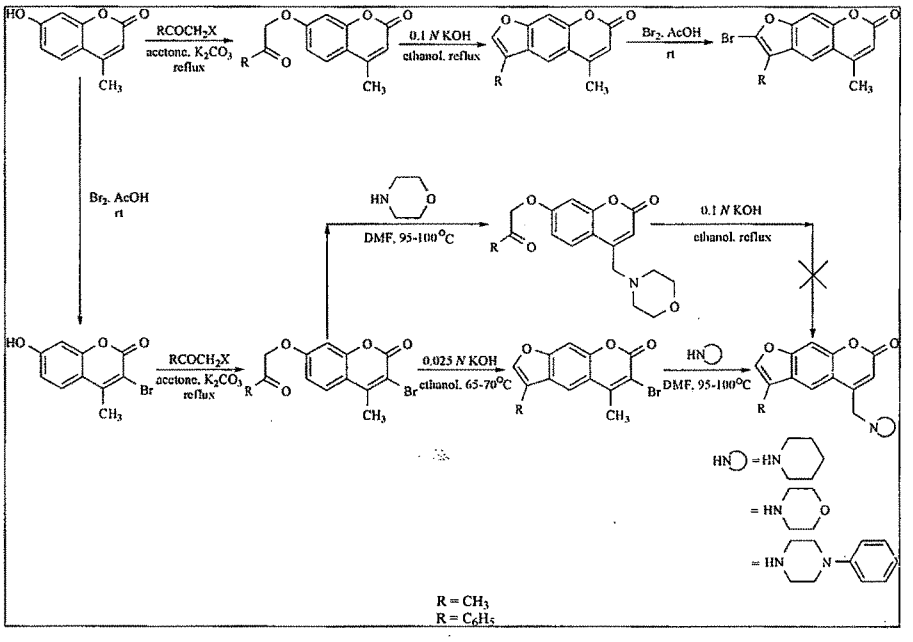
7 deviates from the plane defined by atoms C8/C9/C10/C11/O1 by 0.610 Å. The dihedral angle between O1/C7/C8 and C8/C9/C10/C11/O1 planes is 47.20° whereas the dihedral angle between C1/C2/C3/C4/C5/C6 and C8/C9/C10/C11/O1 planes is 4.56°.

The torsion angles as observed for the molecule are shown below which proves the existence of flavanone ring in the said conformation with phenyl equatorial.

Selected Atoms	Torsion Angle
H7-C7-C8-$H8_A$	-54.31
H7-C7-C8-$H8_B$	-171.97
C6-C7-C8-$H8_A$	66.51
C6-C7-C8-$H8_B$	-51.16
H7-C7-C6-C5	-81.77
H7-C7-C6-C1	95.76

Chapter 4: Studies in Synthesis of New Psoralenamines.

Furocoumarins such as Psoralens are well known photosensitizing drugs used in PUV-A (Psoralen Ultra Violet-A) therapy. Introduction of aminomethyl group in furocoumarins enhances antibacterial activity. Aminopsoralens are used for nucleic acid probe preparations, preparation of conjugates, inhibition of cell proliferation, inactivation of virus for vaccine preparation, and in particular, for the inactivation of pathogens in blood products. The synthetic pathway followed by MacLeod *et al.* and Paradkar *et al.* has been employed to prepare the title compounds.



New amino psoralen derivatives have been synthesized via bromination. Bromination of 3,5-substituted psoralens has been studied. The second position of the furan ring is more susceptible to bromination than the α-position of the chromen-2-one ring in psoralens. Hence the target psoralenamines were synthesized starting with 3-bromo-7-hydroxy-4-methyl-chromen-2-one, which was condensed with different α-halo ketones (phenacyl bromide and mono chloroacetone) and cyclized in ethanolic potassium hydroxide to get the desired 6-bromo psoralens, which were finally converted into psoralenamines.

β-Methyl umbelliferone (7-hydroxy-4-methyl-chromen-2-one) was condensed with different α-haloketones, *e.g.* mono chloroacetone and phenacyl bromide to give the aryloxyketones which when subjected to cyclization in 0.1 *N* ethanolic potassium hydroxide gave the corresponding furocoumarins (psoralens). Psoralen was brominated using bromine in acetic acid to get the desired 6-bromo psoralen, but from the ^{1}H NMR it revealed that the product formed was 2-bromo psoralen. This shows that the second position of the furan ring is more reactive towards halogenation compared to the α-position of the chromen-2-one ring in psoralens.

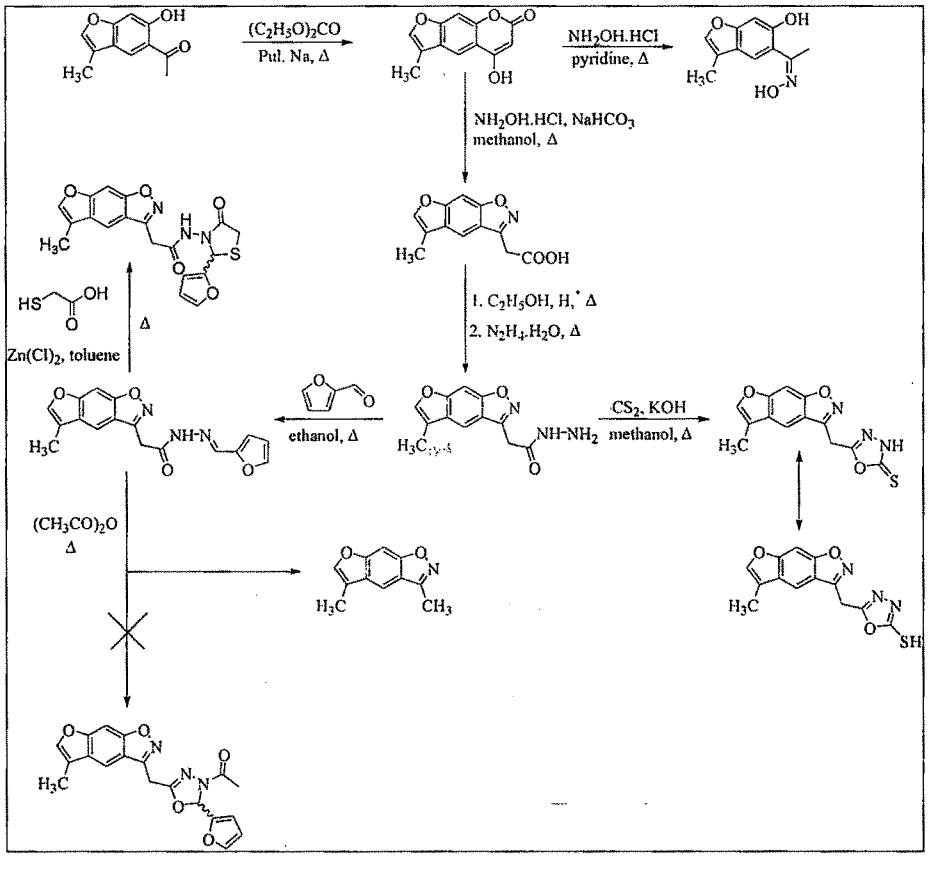
In a slightly modified methodology, β-methyl umbelliferone (7-hydroxy-4-methyl-chromen-2-one) was first brominated using bromine in acetic acid to give 3-bromo-7-hydroxy-4-methyl-chromen-2-one in an addition-elimination reaction, which was then condensed with different α-halo ketones and cyclized to 6-bromo psoralens in a similar fashion. Cyclization of 3-bromo aryloxyketones to 6-bromo psoralens was the bottleneck of the process. Cyclization in 0.1 *N* ethanolic potassium hydroxide at reflux temperature lowered the over all yield of the reaction drastically due to the formation of furocoumarilic acid. Even the idea of first condensing 3-bromo aryloxyketones with amines, followed by cyclization to yield amino psoralens failed, since the cyclization reaction gave mixture of products. Consequently the concentration of ethanolic potassium hydroxide was reduced from 0.1 *N* to 0.025 *N* and the cyclization of 3-bromo aryloxyketones to 6-bromo psoralens was carried out at 65-70 °C, which gave the desired results. Finally, 6-bromo psoralens were condensed with different amines (morpholine, piperidine and N-phenyl piprazine) to give the corresponding amino methyl psoralens.

Chapter 5: Section A: Heterocycles from 4-Hydroxy Coumarin.

Furobenzisoxazole derivatives are reported to possess hypotensive, uricosuric and diuretic activities and hence are useful as therapeutics for treatment of hyperuricemia, edama and hypertension; which prompted us to synthesize new furobenzisoxazole derivatives.

Flucloxacillin, Oxacillin, Cloxacillin and Dicloxacillin belong to the class of new isoxazole penicillin in current clinical use.

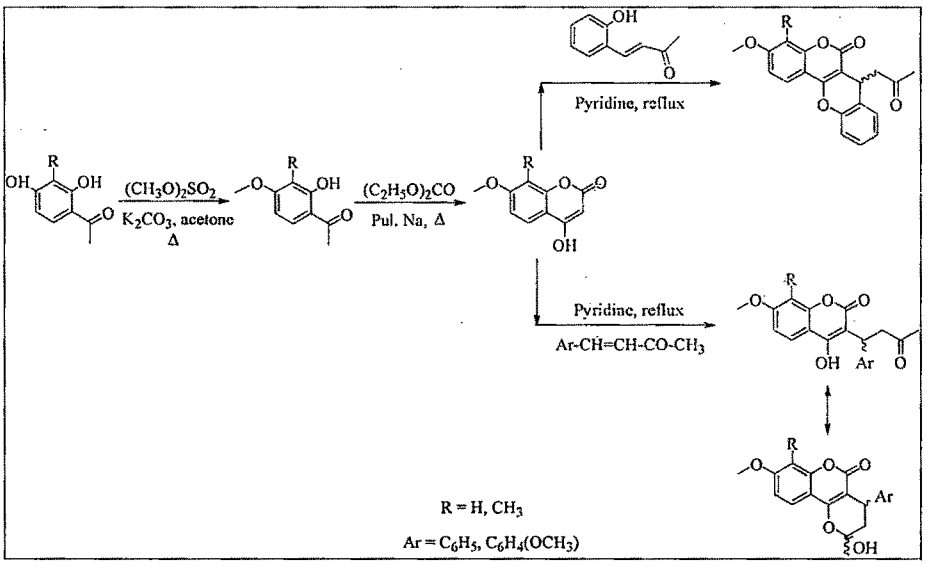
We have synthesized new hydroxy furocoumarin which on Posner reaction, with hydroxylamine gave furobenzisoxazole. New derivatives of furobenzisoxazole have been synthesized and interesting observations have been recorded during the course of study.



5-Hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one has been synthesized from 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone, using diethyl carbonate and pulverized sodium. Posner reaction, of 5-hydroxy-3-methyl-furo[3,2-*g*]chromen-7-one with hydroxyl amine in methanol gave (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid as the major product, whereas; in pyridine, 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone oxime was the major product obtained. The acid was then converted into (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid hydrazide. The hydrazide was condensed with furfuraldehyde to give the schiff base, (5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetic acid furan-2-ylmethylene-hydrazide. Schiff base on reaction with thioglycolic acid in presence of zinc chloride gave *N*-(2-furan-2-yl-4-oxo-thiazolidin-3-yl)-2-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-yl)-acetamide However, reaction of schiff base with acetic anhydride gave 3,5-

dimethyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazole instead of the desired 1-[2-furan-2-yl-5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazol-3-yl]-ethanone which was not expected. In a different approach, the hydrazide on reaction with carbon disulfide gave 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-3*H*-[1,3,4]oxadiazole-2-thione. This oxadiazoline exists in tautomeric equilibrium with 5-(5-methyl-furo[2',3':4,5]benzo[1,2-*d*]isoxazol-3-ylmethyl)-[1,3,4]oxadiazole-2-thiol as concluded from ^{1}H NMR.

Section B: Studies in the Synthesis and Tautomerism of New Warfarins.



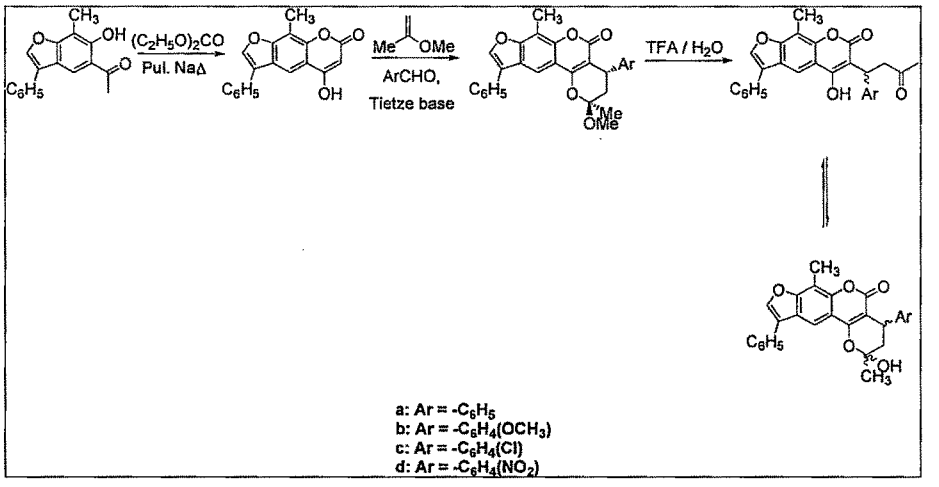
4-Hydroxy coumarin derivatives are known to be useful anticoagulant drugs. Warfarin and its derivatives have also been used as non-peptidic HIV protease inhibitor.

Substituted 4-hydroxy-7-methoxy-benzopyran-2[*H*]-one on Michael condensation with different α, β-unsaturated ketones gave various warfarin derivatives. ^{1}H NMR studies of these compounds in deuteriochloroform showed three interconverting tautomeric structures, two of which are cyclic diastereomeric hemiketals, while the third one is the open-chain intermediate form. Whereas the

^1H NMR in deuteriodimethylsulfoxide showed existence of only two diastereomeric hemiketal forms.

β-resacetophenone was first mono methylated using dimethyl sulfate and then converted into 4-hydroxy coumarin using diethyl carbonate and pulverized sodium. Michael condensation of 4-hydroxy coumarin with benzalacetone and anisalacetone in pyridine gave the corresponding Warfarin. However, on condensation with salicylalacetone the Michael condensation product spontaneously eliminates water to give alkali insoluble dehydrated product as shown in the Scheme.

Section C: Synthesis of New Warfarins via Hetero-Diels-Alder Cycloadditon.



Warfarins today dominate coumarin anticoagulant owing to its excellent potency and good pharmacokinetic profile. The pharmacological potency varies for enantiomers. The anti-coagulant activity of the (*S*)-(-) enantiomer of Warfarin is known to be six times higher than that of the (+)-enantiomer.

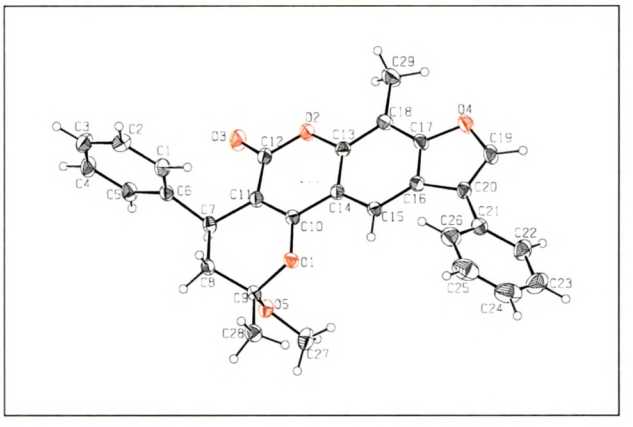


Fig: ORTEP diagram of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa-cyclopenta[*b*]phenanthren-5-one **w**ith atom numbering scheme (40% probability factor for the thermal ellipsoids).

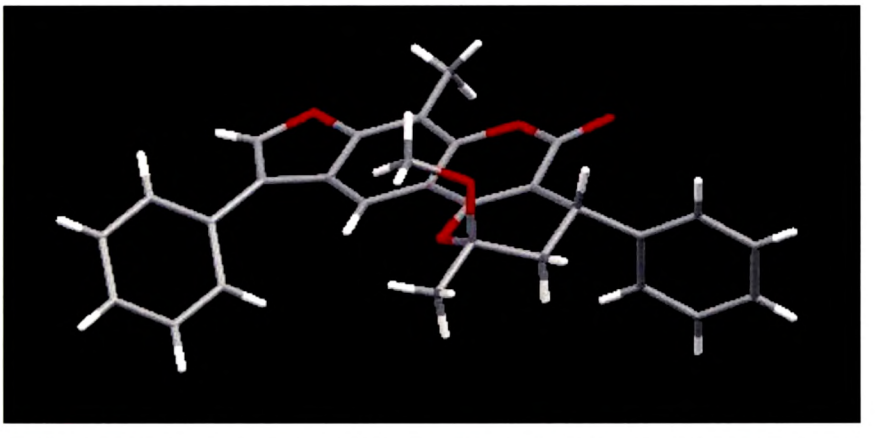
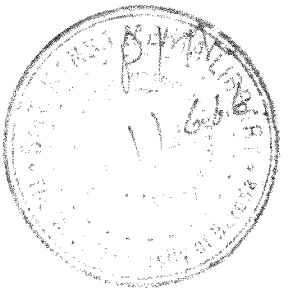


Fig: Single Crystal structure of 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa- cyclopenta[*b*]phenanthren-5-one

Synthesis of new Warfarins has been carried out via hetero-Diels-Alder cycloadditon reaction from 4-hydroxy coumarin using *iso*-propenyl ether.

The synthetic pathway employed by Giancarlo Cravotto *et al.* has been employed to prepare the title compounds. 1-(6-hydroxy-7-methyl-3-phenylbenzofuran-5-yl)-ethanone on condensation with diethyl carbonate and pulverized sodium gave 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one which when subjected to a one-pot tandem Knoevenagel-hetero-Diels-Alder reaction gave the cyclic ketal.

The *in-situ* *Z*-6-arylidene-5,7-chromanedione derived from the Knoevenagel condensation of 5-hydroxy-9-methyl-3-phenyl-furo[3,2-*g*]chromen-7-one with aldehyde, undergoes HDA cycloaddition with 2-methoxypropene. Single crystal X-ray analysis of compound 2-methoxy-2,7-dimethyl-4,10-diphenyl-3,4-dihydro-2*H*-1,6,8-trioxa- cyclopenta[*b*]phenanthren-5-one, shows that the HDA-cycloadduct exists in *exo (trans)* configuration. The pyran ring of the molecule adopts the half chair conformation. Exposure of ketals to trifluroacetic acid-water gave the desired results. Coumachlor and Acenocoumarol type of warfarin derivatives have been prepared using *p*-chloro benzaldehyde and *p*-nitro benzaldehyde respectively.



Studies in the Synthesis of Heterocyclic Compounds

A

SUMMARY

OF THE

THESIS SUBMITTED TO

THE MAHARAJA SAYAJIRAO UNIVERSITY OF BARODA

FOR

THE DEGREE

OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

By

Jagdish M. Patel

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