Summary
Chapter 1: Introduction

Cyclic organic compounds 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. Pyrones are heterocyclic compounds containing oxygen as hetero atom other than carbon; its derivatives may contain sulphur, phosphorous, nitrogen etc.

Pyran-2-one or coumarin and pyran-4-one or chromone and its derivatives are widely distributed in nature and show various pharmacological activities. Various heterocycles have been synthesized from coumarin derivatives. Many Scientists are keen to work in this field due to better selectivity and pharmacological activity of these compounds in medicinal chemistry.

Coumarin derivatives are used for fragrances in cosmetics, pharmaceuticals and foods. Coumarin derivatives show various activities like antibacterial, anti fungal, antiviral, insecticidal, CNS activity, analgesic, anti inflammatory, anti HIV-1 integrase inhibitory activity, antioxidant and anticoagulant. They also show anticancer activity against lungs cancer, gastric cancer, pancreatic cancer, skin cancer, intraocular melanoma, uterine cancer, breast cancer, cancer of the endocrine system, and also inhibit the growth of ovarian and nasopharyngeal tumor cells.

Various derivatives synthesized from coumarin show wide range of pharmacological activities like anticonvulsant activity, anti histaminic activity, antiepileptic, hypotensive, hypertension, non steroidal human progesterone receptor agonists, regulation of human cervical carcinoma cell proliferation, dermatological disorders like psoriasis, vitiligo, mycosis and atopic eczema and anti spasmodic, antiallergic agent particularly for bronchial asthma, uricosuric, anti diuretic hyperuricemia and edema.
The study of coumarin, its various derivatives and various heterocycles is of great interest for synthesis and biological activity.

Objectives of the Work:

- Synthesis of coumarin derivatives
- Synthesis of various heterocycles from various coumarin derivatives
- Biological evaluation of various compounds and find out possible QSAR.

The structures of all the synthesized compounds have been established using various analytical methods like IR, $^1$H NMR, $^{13}$C NMR, Mass, Elemental analyses, HPLC and Single Crystal X-Ray Diffraction.

Chapter 2: Synthesis and biological evaluation of isoxazole derivatives

Derivatives of benzoxazole are known to possess wide spectrum of biological activities such as anti-microbial and anti-herbicidal activities. 1, 2-benzoxazole derivatives and various analogues show various activities like antidepressants, anti-inflammatory, antimalarial, antipsychotics, antiviral, general anesthetics, anticonvulsant, dopamine blocking properties and cytoprotective agents.

1-Naphthol on reaction with acetic acid in presence of zinc chloride gave 1-(1-hydroxynaphthalen-2-yl)ethanone which on Hoesch reaction with diethyl carbonate in presence of pulverized sodium gave 4-hydroxy-2H-benzo[h]chromen-2-one. This on Posner reaction with hydroxylamine hydrochloride in presence of sodium bicarbonate afforded 2-(naphtho[2,1-d]isoxazole-3-yl)acetic acid which was then converted into different amides (Scheme 1) by reaction with different amines using dicyclohexylcarbodiimide (DCC) and N, N-dimethyl amino pyridine (DMAP) as catalyst.
Scheme 1:

**Biological Evaluation:** All Synthesized compounds were screened against Melanoma Cancer Cell lines at Hershey Medical Centre, USA and also screened for anticonvulsant activity at Dharmsinh Desai University, Nadidad.

**Chapter 3: Synthesis and biological evaluation of amide derivatives of difuran-2-carboxylic acid**

Various esters, amide, ether and thioether derivatives of furan show antifungal, antimicrobial, cysteine protease inhibitor, ischemic cell death, orexin receptor antagonist, anti angiogenesis, anti osteoarthritis activity and also show CNS depressant effect.

7-hydroxy-4-methyl-coumarin was condensed with chloroacetone in presence of anhydrous K$_2$CO$_3$ in dry acetone gave 4-methyl-7-(2-oxopropoxy)-coumarin which was brominated using N-bromosuccinimide to give 3-bromo-4-methyl-7-(2-oxopropoxy)-coumarin. This bromo derivative was further refluxed with 10% alkaline ethanol gave cyclized 3, 5-dimethylbenzo[1,2-b:5,4-b']difuran-2-carboxylic acid 5 as major product, which was converted into corresponding amides (Scheme 2).
Scheme 2:

Biological Evaluation: All Synthesized compounds were screened against 2 gm +ve bacteria, 2 gm –ve bacteria and one fungi at Micro Care Lab, Surat and also screened for Orexin receptor binding study at University of Helsinki, Finland.

Chapter 4a: Synthesis of amide and ester derivatives of Naphthopyrone 2-carboxylic acid

Chromone derivatives are useful as antiallergic agent particularly for bronchial asthma they inhibit the release of mediators like histamine, several kinins etc. of immediate hypersensitivity reactions. Chromone derivatives have been reported as MAO-B inhibitors, melanin concentrating hormone receptor 1 antagonists and adenosine receptor ligand. Photodimerization and microwave assisted synthesis of Chromone-2-carboxylic acid derivatives have been reported. In this part we have synthesized various amide and ester derivatives of naphthopyrone-2-carboxylic acid.

Condensation of 1-naphthol 1 with dimethyl acetylenedicarboxylate (DMAD) in presence of anhydrous K₂CO₃ and dry acetone gave E and Z mixture of dimethyl 2-(naphthalen-1-ylxy)maleate. Since E and Z mixture was not possible to separate into E
and Z isomers, it on mild hydrolysis in aqueous KOH at room temperature gave 2-(Naphthalen-1-yloxy)maleic acid as corresponding mixture of E and Z isomers, which were also not separated. The diacid (E/Z mixture) on cyclization with concentrated sulphuric acid gave 4-Oxo-4H-benzo[h]chromene-2-carboxylic acid. This acid was converted into corresponding amide using two different methods. The chromen-2-acid was converted into various esters using various alcohols and dry HCl gas (Scheme 3).

**Scheme 3:**

![Scheme 3](image_url)

**Chapter 4b: Unusual deacetylation of 1-acetyl 2-naphthol in facile manner**

\(\text{o- Hydroxy ketone is one of most the common starting material used for various reactions. Formation of chalcones or Schiff bases from o-hydroxy ketones is one of the most frequently used reactions in organic synthesis because various heterocyclic rings can be formed further from it. Chalcones, chromenes, imidazoles and other heterocyclic rings show various biological activities. Synthesis of chalcones from various substituted o-hydroxy acetophenone derivatives and formation of flavones from it was reported earlier from our laboratory. We were keen to form first Schiff bases and then heterocyclic ring}}\)
from 1-acetyl 2-naphthol. Instead of that during formation of Schiff base reaction, we have observed novel deacetylation of 1-acetyl 2-naphthol.

Reaction of acetic acid and acetic anhydride with 2-naphthol in presence of zinc chloride gave 1-acetyl 2-naphthol which when refluxed in absolute ethanol with primary aromatic amines and 2-3 drops of acetic acid, we observed formation of two products on TLC, different from starting material. The two products were separated by column chromatography. One product was found to be different anilide derivatives and another product was found to be same in all reactions i.e. 2-naphthol (Scheme 4). Hence we observed deacetylation of 1-acetyl 2-naphthol which we can call it as either retero Friedel Crafts reaction or retero Diels Alder reaction.

Same reaction was repeated with secondary amines. In case of cyclic secondary amines, retero Friedel Crafts reaction occur and then acetyl group is removed as acetic acid from N-acetyl pyrrolidine or N-acetyl morpholine and 2-naphthol was obtained. No reaction was observed with p-nitro aniline, benzotriazole, indole and 3-acetyl naphthopyrone, only starting materials were recovered.

Scheme 4:
**Chapter 5a: Novel Retro Knoevenagel reaction of Substituted Coumarin-3-carboxylate**

Various derivatives of coumarin 3-carboxylate with various substitutions show various activities like anti-helicobacter pylori, human monoamine oxidase inhibition, α-Chymotrypsin inhibitory activity and inhibitory activity of gGAPDH enzyme.

Knoevenagel reaction of various salicylaldehyde derivatives in pyridine and diethyl malonate with catalytic amount of piperidine gave different coumarin-3-carboxylate derivatives, which on reaction with phenyl hydrazine in absolute ethanol gave different phenyl hydrazide derivatives. But to our surprise reaction of various coumarin-3-carboxylate derivatives with hydrazine hydrate gave various hydroxy schiff base derivatives (Scheme 5) which was proved by Single Crystal X-Ray Diffraction.

**Scheme 5:**

![Scheme 5: Knoevenagel reaction of various salicylaldehyde derivatives](image)

**Figure 1:** ORPET diagram of 2, 2'-(1E, 1E)-hydrazine-1, 2-diylidenebis(methan-1-yl-1-ylidene)diphenol and 3-oxo-N'-(propan-2-ylidene)-3H-benzo[f]chromene-2-carbohydrazide
Chapter 5b: Synthesis and anticancer activity of 4-hydroxy Naphtho coumarin derivatives and naphtho coumestans

Coumestan ring system is present in number of natural products. It is found in coumestrol, psoralidin, wedelolactone, norwedelolactone and pterocarsin. Various coumestan derivatives show variety of pharmacological activities such as antihepatotoxic, anti-hypertensive, antitumor, antiphospholipase A₂ and antidote activities against snake venom, treatment for liver diseases and skin disorders, viral infections, antihemostatic activity, estrogenic activity and also binding to central benzodiazepine receptor.

Hoesch reaction of 2-acetyl 1-naphthol with diethyl carbonate in presence of pulverized sodium gave 4-hydroxy-2H-benzo[h]chromen-2-one. This on oxidative cyclization with catachol using sodium acetate and potassium iodate gave corresponding coumestan derivatives 8,9 dihydroxy 6H benzo[h]benzofuro[3,2 c]chromen 6 one. These coumestan derivatives were condensed with dimethyl sulphate and different mono and di halides in presence of base like anhydrous K₂CO₃ and dry acetone gave corresponding condensed or cyclized coumestan (Scheme 6) compounds. 4-hydroxy-2H-benzo[h]chromen-2-one derivative was also condensed with dimethyl sulphate and allyl bromide gave corresponding methoxy and allyloxy derivatives.

Scheme 6:
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**Biological Evaluation:** 2 Intermediate and 7 final synthesized compounds were screened against two melanoma Cancer cell lines UACC-903 and A375M, one breast cancer cell line MCF-7 and fibroblast (FF2441-Precursors of normal cells) at Hershey Medical Centre, USA.