Chapter 2

Theoretical
2. Theoretical

The work on the synthesis of new heterocyclic compounds of pharmacological interest has made extensive use of 4-hydroxycoumarin derivatives. The presence of OH group at 4-position gives nucleophilic character at position 3 to 4-hydroxycoumarin. Another possibility is opening of the lactone ring followed by loss of carbon dioxide. During the last thirty years synthesis and the study of the biological activities of coumarin derivatives has been the aim of many researchers. Also the structure activity relationship of coumarins has revealed that the presence of substituents such as methyl, formyl, acetyl, and amino groups at position 3 is an essential feature for their pharmacological action. Based on the findings, we describe the work done by different researcher for the synthesis of compounds featuring different heterocyclic rings fused on to the coumarin moiety. Thus, in the context of further work on 4-hydroxycoumarin a survey of the literature of thirty years was done and some relevant examples are discussed below.

2.1. The reaction of 4-hydroxycoumarins with benzhydroxymoyl chloride.

The condensation reaction of 4-hydroxycoumarin 1a, 8-methyl-4-hydroxycoumarin 1b, and 8-chloro-4-hydroxycoumarin 1c with benzhydroxymoyl chloride in the presence of Et$_3$N gives 3-benzoyl-8-chloro-4-hydroxycoumarin oximes 5a-c. The reaction involves nucleophilic attack of double bond at position 3 of 4-hydroxycoumarin on benzonitrile oxide generated in situ by base treatment of benzhydroxymoyl chloride (Scheme 1).
Scheme 1. Formation of oximes 5a-c by the reaction of 4-hydroxycoumarins 1a-c and benzhydroxymoyl chloride.

2.2. The reaction of 4-hydroxycoumarin with 1,4-Naphthoquinone.

One of the earliest example of 4-hydroxycoumarin 1 with 1,4-naphthoquinone 6 involves Michael addition of 1 to the 1,4-naphthoquinone, oxidation of the resulting quinol 7 by air to give 8 and by more unchanged 1,4-naphthoquinone, a second Michael addition of 1 and another oxidation of the product 9 to give 9a (Scheme 2).
Scheme 2. Formation of quinone 9a by the reaction of 4-hydroxycoumarin 1 and 1,4-naphthoquinone 6, Formation of quinol 9 by the reduction of quinone 9a with sodium dithionite.

The acetylation of 9 forms tetra acetate derivative 10 whereas methylation gives unexpected dimethoxycoumestan derivative 11.
However, when the reaction is extended to 5,5-dimethylcyclohexan-1,3-dione, the reaction occurs in the same manner except that in the final step, cyclization of the disubstituted quinol 12 takes place in preference to oxidation (Scheme 3).

**Scheme 3.** Formation of 3,3,9,9-tetramethyl-3,4,9,10-tetrahydrobenzo [1,2-b:4,5-b'] bis (benzofuran-1,7(2H,8H)-dione 13 by the reaction of 1,4-benzoquinone and dimedone.
The reaction of 1,4-benzoquinone with 4-hydroxycoumarin in aqueous acetic acid is similar to that reported earlier except that the major product is colourless quinol 14. Oxidation of 14 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gives the quinone 15 which was identical with that obtained from the aqueous acetone reaction.

\[ \text{14} \]

\[ \text{15} \]

An extension to such type of reaction of 4-hydroxycoumarin 1a-g is treatment with \( \alpha \)-chlorobenzylphenyl ketone\(^{117} \) 16 in anhydrous potassium carbonate to give 4-(1,2-diphenyl-2-oxoethyloxy) coumarins 17a-g which on stirring with PPA\(^{118} \) (\( \text{P}_2\text{O}_5 \) and \( \text{H}_3\text{PO}_4 \)) undergoes cyclization to furnish the cyclized compound 18a-g (Scheme 4).\(^6 \)
Scheme 4. Formation of coumarins 18a-g by the reaction of 4-hydroxy coumarins 1a-g and α-chlorobenzylphenyl ketone 16.

In a similar type of reaction 3-(2'-cyclopentenyl)-4-hydroxy [1] benzopyran 20 is obtained by refluxing 4-hydroxycoumarin 1 and 3-chlorocyclopentene 19 in acetone potassium carbonate. Compound 20 is finally converted to its acetate derivative 21 by carrying out reaction with Ac$_2$O/NaOAc. The acetate 21 was then converted to chromone derivative 22 by conducting the reaction with pyridine hydrobromide (PyHBr$_3$) in dichloromethane. The same compound 22 is also obtained when compound 20 is treated with PyHBr$_3$ in CH$_2$Cl$_2$. The formation of
chromone 22 is indicated by Infrared (IR) spectroscopy showing absorption band at 1650 cm⁻¹ and a double doublet for proton peri to carbonyl group at δ 8.30 in its nuclear magnetic resonance (NMR) spectrum. However, the isomerisation of chromone 22 into coumarin 23 takes place when the compound 22 is heated with 50% of H₂SO₄ (Scheme 5).⁷

Scheme 5. Formation of chromone 22 and coumarin 23 by the reaction of 4-hydroxycoumarin 1 and 3-chlorocyclopentene 19.
2.3. The reaction of 4-hydroxycoumarin with 1-aryloxy-4-chlorobut-2-yynes.

Another interesting reaction of 4-hydroxycoumarin is formation of ether 4-(4-aryloxybut-2-ynyloxy) [1] benzopyran-2-ones 25(a-f). The reaction takes place between 1-aryloxy-4-chlorobut-2-yynes 24 and 4-hydroxycoumarin 1 in refluxing acetone in the presence of anhydrous potassium carbonate (Scheme 6).[^1]

\[
\begin{align*}
\text{OH} & \\
\text{O} & \\
\text{O} & \\
\text{MeCO-K}_2\text{CO}_3 & \\
25\text{a-f} & \\
\end{align*}
\]

\[
\begin{align*}
a, \text{Ar} = 2\text{-methylphenyl} & & d, \text{Ar} = 2,4\text{-dimethylphenyl} \\
b, \text{Ar} = 4\text{-methylphenyl} & & e, \text{Ar} = 3,5\text{-dimethylphenyl} \\
c, \text{Ar} = 3\text{-methylphenyl} & & f, \text{Ar} = 4\text{-tert-butylphenyl} \\
\end{align*}
\]

**Scheme 6.** Formation of ether 25a-f by the reaction of 4-hydroxycoumarin 1 and 1-aryloxy-4-chlorobut-2-ynes 24.

When ether 25a is heated in chlorobenzene, two products are obtained. One of the product has been identified as 4-(2-cresoxymethyl) pyrano [3, 2-c] [1] benzopyran-5-(2H)-one 26a and the other product as 27. Ether 25b when refluxed in chlorobenzene also furnishes two products. One of the product is identified as 4-(4-cresoxymethyl) pyrano [3,2-c] [1] benzopyran-5(2H)-one 26b, and the other product as 28 (Scheme 7).
Scheme 7. Formation of pyranopyran 26a-b by the reaction of ether 25a-b and chlorobenzene.

The formation of 27 from 25 may be explained by an initial [3,3] sigmatropic rearrangement to give allene moiety 29 followed by isomerisation to butadiene 30 by a [1,3] $H^+$ shift and acid catalysed cyclisation (enol may also act as an acid) of 30 to 27. The product 26 is also formed from intermediate 29 via enolisation followed by [1,5] $H^+$ shift and electrocyclic ring closure. Further the compound 27 is formed rapidly in preference to product 26a. The product ratio, however, is not changed even when the reaction is carried out in purified chlorobenzene or in the presence of toluene 4-sulfonic acid (Scheme 8).
Scheme 8. Formation of coumarin 27 and 26(a-f) from ether 25.

2.4. The reaction of 3-formyl-4-hydroxycoumarin with amines.

3-Formyl-4-hydroxycoumarin 31a-d is an interesting starting material for the synthesis of a variety of heterocycles. One such example is treatment of 31 with ethanolic solution of hydrazine hydrate, phenylhydrazine and hydroxylamine hydrochloride in acetic acid to give corresponding 1H, 4H-4-oxo-benzopyran [4,3-c] pyrazoles 32a-d, 4H-4-oxo-1-phenylbenzopyran [4,3-c] pyrazoles 32a-h and 4H-4-oxo benzopyran [3,4-c] isoxazoles 33a-d (Scheme 9).9
Another example in this category is the reaction of 3-formyl-4-hydroxycoumarin 31a-d with malonic acid in the presence of zinc chloride to give 2H, 5H-2,5-dioxo-3-pyrano [3,2-c] benzopyranoic acids 34a-d which on treatment with methanol in the presence of thionylchloride furnishes methyl 2H, 5H-2,5-dioxopyrano [3,2-c] benzopyran-3-oates 35a-d. The compounds 35a-d was further converted into its acid hydrazides 36a-d, upon treatment with hydrazine (Scheme 10).
Scheme 10. Formation of hydrazides 36a-d by the reaction of 3-formyl-4-hydroxy coumarin 31a-d with malonic acid, thionylchloride and hydrazine.

K. Rad-Moghadam and M. Moheseni have reported the reaction of 3-formyl-4-hydroxycoumarin 31 with an in situ generated 1:1 adduct of triphenylphosphine and dialkyl acetylenedicarboxylate to form the dialkyl-2H, 5H-pyrano [3,2-c] [1]benzopyran-5-one-2,3-dicarboxylates (pyranocoumarins), 38a-c. The reaction may be rationalized on the basis of well-known Chemistry of trivalent phosphorus nucleophiles. Addition of triphenylphosphine to acetylenic ester results in a zwitterionic 1:1 adducts which upon abstraction of a proton from 31 and concomitant addition of thus formed 3-formylcoumarin-
4-hydroxylate anion produces the key intermediate phosphorane 37. The reaction ultimately entails with an intramolecular Wittig reaction of the postulated phosphorane 37 (Scheme 11).

Scheme 11. Formation of coumarins 38a-c by the reaction of 3-formyl-4-hydroxy coumarin 31 with triphenylphosphine and dialkyl acetylenedicarboxylate.

2.5. The reaction of 3-formyl-4-hydroxy coumarin with phosphorus hydrazides.

3-Formyl-4-hydroxy coumarin 31 reacts with phosphorus hydrazine derivatives NH₂-NR₂-P(S)(OR₃)₂ to give phosphorus hydrazide of coumarin 40a-c/41a-c. The same product 40a-c/41a-c is also obtained when chromone-3-carboxylic ester 39 is treated with phosphorus hydrazines. The reaction
involved conversion of chromone-3-carboxylic ester to 3-formyl-4-hydroxycoumarin under basic conditions followed by reaction with phosphorus hydrazine to give 40a-c which tautomered to 41a-c (Scheme 12: Route A). However, formyl group of 31 also directly reacts with phosphorus hydrazine to give 40a-c which then tautomerizes to 41a-c (Scheme 12: Route B). Both the tautomers are present in solution form as well as solid form and are inseparable.

Scheme 12: Route A. Synthetic route to the phosphorus hydrazides of coumarin 41a-c and benzopyran-2,4-dione 40a-c.
Scheme 12: Route B. Synthetic route to the phosphorus hydrazides of coumarin 40a-c and benzopyran-2,4-dione 41a-c.

2.6. The reaction of 3-acetyl-4-hydroxycoumarin with hydroxylamine.

3-Acetyl-4-hydroxycoumarin 42 is another interesting starting material for the synthesis of heterocyclic compounds of pharmacological value. Thus, in 1955 Klosa\textsuperscript{15} reported that 43 affords crystalline oximes on treatment with excess of hydroxylamine hydrochloride and potassium acetate in refluxing ethanol. However, Desai and coworkers\textsuperscript{16} suggested that the oxime of Klosa was a...
cyclodehydrated product 44. They also said that the oxime 43 is obtained only at room temperature and did not undergo Beckmann rearrangement upon treatment with SOCl₂ or PCl₃ and instead gives cyclodehydrated product 44 (Scheme 13). Some authors also have reported the formation of isoxazole 44 at room temperature under basic conditions. In order to clarify this discrepancy the reaction of 3-acetyl-4-hydroxycoumarin 42 with hydroxylamine hydrochloride was reinvestigated by Chantegrel et al. and found that the reaction of 42 with hydroxylamine under Klosa’s reaction conditions affords a mixture of 45 and 46. The formation of 45 involves the oxime 43 as intermediate and a nucleophilic attack at the C-2 lactone carbonyl by the hydroxyimino group with ring opening (Scheme 14). The Compound 46 is obtained by interaction of 45 with an excess of hydroxylamine (Scheme 15).

Scheme 13. Formation of isoxazole 44 by the reaction of 3-acetyl-4-hydroxycoumarin 42 and hydroxylamine.
Scheme 14. Formation of isoxazole 45 by the reaction of 3-acetyl-4-hydroxycoumarin 42 and hydroxylamine under the Klosa’s reaction conditions.

Scheme 15. Formation of isoxazole 46 by the reaction of 45 and excess of hydroxylamine.
2.7. The reaction of 3-acetyl-4-hydroxycoumarin with thiourea and arylsulfonamides.

In another reaction, 3-acetyl-4-hydroxycoumarin 42 is used for the synthesis of some antibacterial compounds by carrying out reaction with thiourea and benzenesulfonamides.\(^\text{19}\)

In this context, 3-acetyl-4-hydroxycoumarin 42 is treated with phenyl trimethyl ammonium bromide to afford 3-bromoacetyl-4-hydroxycoumarin 47 which is then treated with thiourea to give 48 in the form of a bromide salt. The final compound sulfonamide 49a-d is obtained by treating 48 with arenesulfonyl chlorides (Scheme 16).

\[
\begin{align*}
\text{OH} & \quad \text{OH} & \quad \text{OH} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\text{HO} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{OH} & \quad \text{NH}_2\text{HBr} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{OH} & \quad \text{NH}_2\text{HBr} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{OH} & \quad \text{NH}_2\text{HBr} \\
\text{O} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

(I) Phenyl trimethyl ammonium tribromide, THF, 25 °C, 15 min.

(II) \((\text{NH}_2)_2\text{CS}\), ethanol, reflux 30 min.

(III) \(\text{Ar SO}_2\text{Cl}\), pyridine, 25 °C, 12 hrs.

**Scheme 16.** Formation of sulfonamide 49a-d from 3-acetyl-4-hydroxycoumarin 42.
2.8. The reaction of 3-acetyl-4-hydroxycoumarin with phenylhydrazine.

Recently authors have shown the conversion of 3-acetyl-4-hydroxycoumarin 42 into its hydrazone derivatives by performing the reaction under microwave irradiation using Zn [L-proline]_2 complex as catalyst in order to obtain the high yield of the product as compared to the one obtained under the conventional heating procedure. The reaction involved nucleophilic addition of hydrazine on acetyl carbon followed by cyclodehydration to form the product 50a-c (Scheme 17).

Scheme 17. Formation of pyrazoles 50a-c by the reaction of 3-acetyl-4-hydroxy coumarin 42 and phenylhydrazines under the microwave irradiation.