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A REVIEW ON SYNTHETIC STRATEGIES AND BIOLOGICAL ACTIVITIES OF COUMARIN LINKED IMIDAZOLE DERIVATIVES

[1]Anitha S*, [2]Apoorva S

[1]Assistant professor (C), department of pharmacy, [2]Student, M. Pharm Chemistry.
Department of Pharmacy,
University College of Technology, Osmania University, Hyderabad-500 007, Telangana, India.
[1]Corresponding author. Tel.: +91-40-27098901; Fax: +91-40-27098472.
E-mail: anithasadula@gmail.com

ABSTRACT: Increasing demand for the novel drugs to combat multiple ailments and resistance to several existing drugs lead to discovery or development of new entities. In the same contest coumarins the natural occurring heterocyclic compound showing variety of biological activities including antifungal activity, antioxidants, enzyme inhibitors, growth regulators, antithrombotic, anticoagulant, antimicrobial, hepatoprotective etc. This coumarin is studied with conjugation of other heterocyclic compound called imidazole, a five membered ring system containing two nitrogen's, at one and three position. It is chosen for conjugation as it has several advantages like is to synthesise, naturally occurring, compound fewer side effects, chemically active with variety of biological actions including gastrointestinal disorders, hypersensitivity, antibacterial, anticancer, antitubercular, antifungal, analgesic. Anti-HIV, antiarrhythmics, convulsions, migraine, etc. so this review is an overview of how the conjugated system will help in combating various problems of resistance and elicit pharmacological actions. Here is complete review on chemistry and pharmacological actions of coumarin and imidazole molecules and their conjugated system which shows several biological activities. This review also contains several synthetic strategies produced in several research papers listed with the scheme.

***Index terms*: Coumarin, imidazole, coumarin linked imidazoles, synthesis, biological activity**

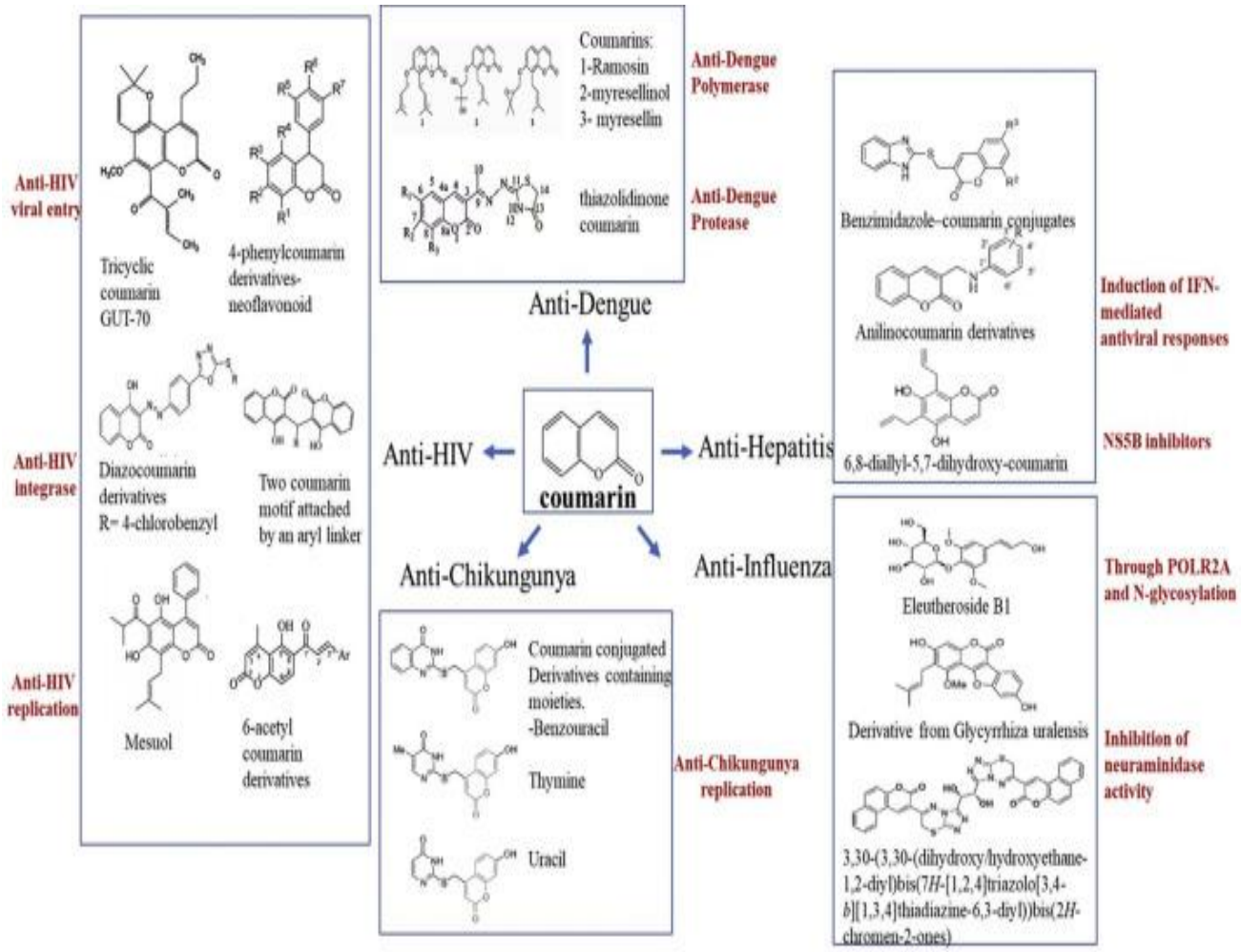
1. Introduction

1.1. Coumarins

Coumarins are a class of naturally occurring benzopyrone derivatives. They are the secondary metabolites, highly distributed in plants, aromatic in nature having bicyclic structure with lactone carbonyl groups. Physiological activity of coumarins depends upon different substitutions in different places. Various biological activities of coumarin include cancer prevention, cytotoxic activity, anti-inflammatory, antibacterial, antimicrobial, antitubercular etc. [1]. Coumarins as lead phytochemicals are also an important class of phenolic compounds which account for specific flavour in food. These phenolic compounds have potent action against gram negative bacteria, fungal agents, antioxidants, enzyme inhibitors, growth regulators, antithrombotic, anticoagulant, antimicrobial, hepatoprotective etc. [2]. Physicochemical properties of these compounds are colourless, yellow solids or liquids(oils). Exist as both aglycones and glycosides. Solubility of coumarins is that they are insoluble in water and soluble in organic solvents like

acetone, ethyl acetate, chloroform and petroleum ether. Chemically there is a benzene ring, alpha pyrone with a double bond and a carbonyl group in sesquiterpene fragment. Synthetic routes developed for the synthesis of coumarins via named reaction includes witting, reformatsky, Knoevenagel condensation etc. [3]. Drugs including coumarin in their structure are listed below in the figure-1:

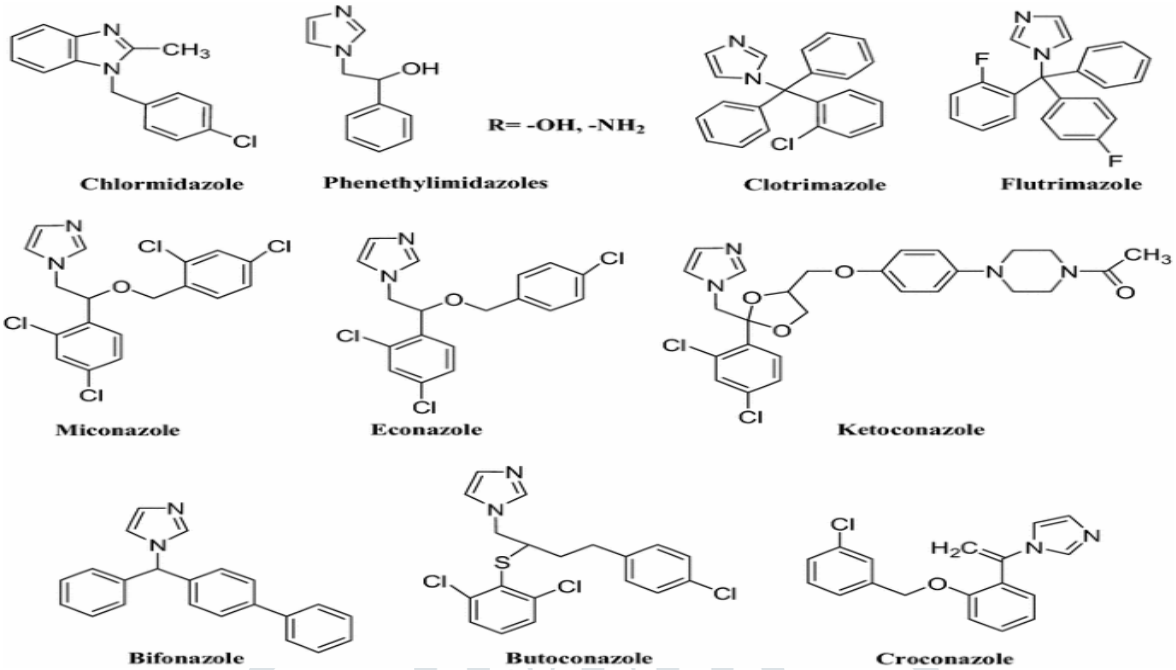
Figure-1: marketed drugs having coumarin as key nucleus with various biological activities[2]



1.2. Imidazoles:

Imidazoles are chemically 1,3 azoles naturally present in histidine, purines, histamines, DNA, biotin and many other biomolecules [4]. These molecules gave extensive range of biological activity including from treatment of gastrointestinal disorders, hypersensitivity [5]. Antibacterial, anticancer, antitubercular, antifungal, analgesic. Anti-HIV, antiarrhythmics, convulsions, migraine, etc. chemically it is a 5 membered planar ring soluble in water and other polar solvents. It exists in tautomeric form due to the presence of hydrogen on 2 nitrogen atoms. It is amphoteric i.e. It can function both as acid and base [6]. Marketed drugs which include imidazole as key ring system are drawn in the below figure-2 from different articles of imidazole related molecules.

Figure-2: Marketed drugs which include imidazole as key ring system [7]



Synthesis of imidazole's i.e., disubstituted, trisubstituted can be done by microwave irradiation, grobiker Blackburne bienayme reaction, debus procedure, Radiszewski, Vanleusan etc [8]. Multicomponent approaches were also developed involving use of Di carbonyl compounds aldehydes and ammonia. Green synthesis where solvent free protocols have been developed.

1.3. Coumarin imidazole coupled systems.

Coumarin and imidazoles both as an individual moieties posse a wide variety of biological activities but due to the increasing resistance shown by a large group of microbes and there is a decreasing rate of discovery of new drugs in this area. Hence there is a high demand of new scaffolds which can combat the multi drug resistance which may be leading cause to severe infections and they do not respond to existing drugs. There have been several studies performed in order to develop biologically active scaffolds to combat this resistance and amongst them coumarin has been the lead heterocycle to which several other heterocyclic compounds were linked to increase the therapeutic prospective of the coumarin derivatives [9].

Among several heterocycles coumarin linked with nitrogen containing ring systems show a great importance due to their unique chemical nature. Pyrroles, indoles, triazoles, imidazoles show high potency against various indication amongst all these heterocycles [10].

There is much focus on imidazole linked coumarin as they have been showing promising medicinal importance in various areas of treatment like anti-viral agents, anti -cancer agents, anti-Alzheimer's, anti -microbial, anti- bacterial, anti-fungal, anti- inflammatory etc.

Biological activities of coumarin imidazole derivatives-

(a) Antiviral activity- coumarin imidazoles show polymerase inhibitor effect and majorly used in the treatment of HCV (Hepatitis C Virus) infection. The anti-viral activity of coupled coumarin imidazole compound inhibits viral replication. These high breeds are highly selective and showed greater anti- HCV activities with lower cytotoxicity [11].

(b) Aromatase inhibitor activity- aromatase inhabitation leads to prevention of cancer mainly breast cancer. Earlies aromatase inhabitation showed several side effects due to unwanted inhibition CYP19. Hence imidazolyl coumarins derivatives were developed as potent AR inhibition with good selectivity and therapeutic potential in the breast cancer domain. CYP17 A P450- dependent

enzyme leads to prostate cancer. So, inhibition of this enzyme is also of major importance. So, molecules with selective inhibition of CYP17 and CYP19 and aromatase inhibitory action is focused and this activity Is exhibited by the new coumarin imidazole derivatives. hence act as potent breast and prostate cancer treating agents [12].

(c) Anti-Alzheimer's disease is a neurodegenerative disorder associated with several path ways including deficiency in neuro-transmission, inflammation , peptide metabolism etc. acetylcholine esterase butyryl cholinesterase and monoamine oxidases play important role in the pathogenesis. Heterocyclic compounds with coumarin as pharmacophore significantly show anti Alzheimer's disease activity coumarin derivatives with fused hectocycle's containing azoles show increasing binding efficiency with catalytic sites on AchE enzymes and increase levels of ACH and MAO which aid in treatment of AD [13].

(d) Antimicrobial- attachment of imidazole to coumarin nucleus showed at high activity variety of biological actions including against both gram positive and gram-negative bacterial strains. Sulphonated coumarin imidazole molecules showed much higher results when compare to unsubstituted constituents. Hence, they are active antibacterial agents.

(e) Antifungal activity- coumarin imidazole conjugates showed antifungal activity against scopulariopsis. spp and A. terraus organisms with high MIC values sulphonated conjugates had good activity against both bacterial and fungal strains.

(f) Anti-inflammatory activity- screening of anti-inflammatory of coumarin imidazole scaffolds was done using gelatin zymography technic that detects degrading gelatin generated by proteolytic enzymes. In physiological system there are several gelatinase enzymes which has key role in inflammation and auto immunity. Thus, such techniques were utilized. So, testing conjugate system of coumarin of imidazole with such procedure shows potential and promising activity against matrix metalloproteinase that have important role in the anti-inflammatory activity [9].

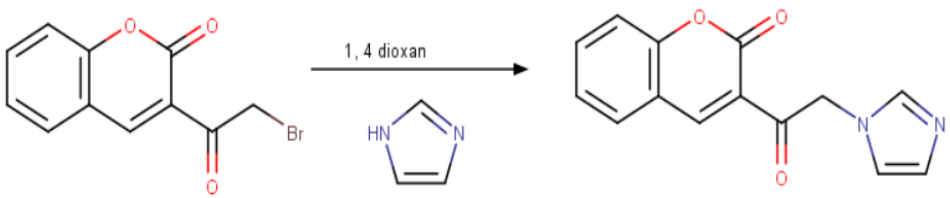
1.4. Synthetic strategies of coumarin linked imidazole systems:

Impressed with wide variety of biological activities of coumarin imidazole scaffolds, many researchers have proposed few synthetic strategies to synthesize coumarin linked imidazole derivatives. Scheme for the synthesis were collected from few research papers and presented as an overall review of various synthetic approaches:

(a) Preparation of 3-(1*H* – imidazol-1-yl-acetyl) coumarin.

An accurate 0.01mole of 3-bromo acetyl coumarin was mixed with 0.01 mole of imidazole, to this dry mixture 30ml of 1,4 dioxane was mixed by continuous stirring using magnetic stirrer for about 2 hours. Thus, obtained precipitate was filtered and washed thoroughly with acetone and recrystallized with ethanol [14].

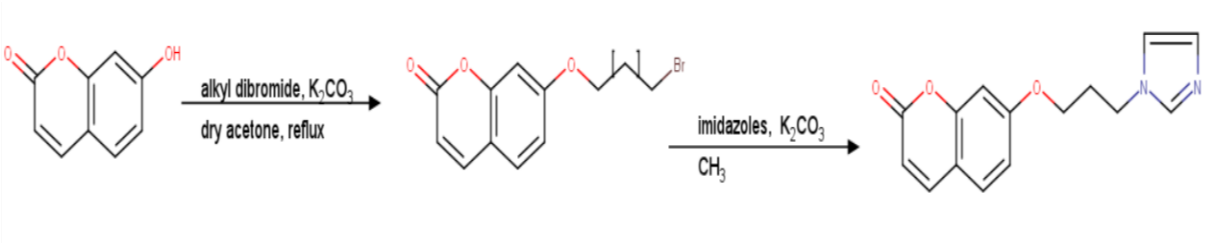
Scheme 1: Preparation of 3-(1*H* – imidazol-1-yl-acetyl) coumarin.[14]



(b) Preparation of coumarin containing substituted imidazole's.

7 hydroxy coumarin was treated with several alkyl bromides and was refluxed in the presence of K_2CO_3 leading to formation of coumarin derivatives in high yields. This was further treated with imidazole in the presence of CH_3CN which led to formation of imidazole coumarins.[15]

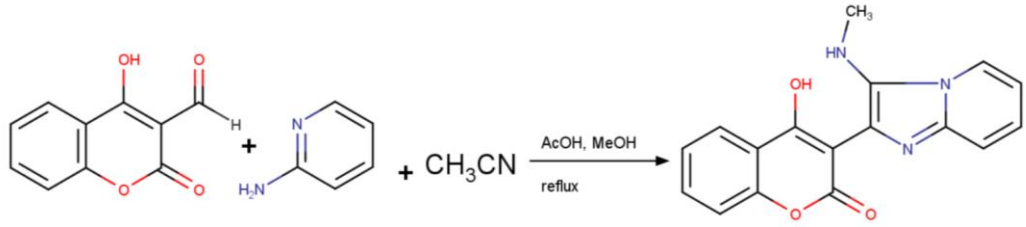
Scheme 2: Preparation of coumarin containing substituted imidazole's.[15]



(c) Synthesis of imidazo [1, 2-a] pyridine-coumarin.

Imidazole coumarin hybrid was synthesized through Blackburn Bienaymen multicomponent reaction where 4-hydroxy-3-formyl coumarin was treated with 2 amino azines and isocyanides in the presence of acetic acid and refluxed.[15]

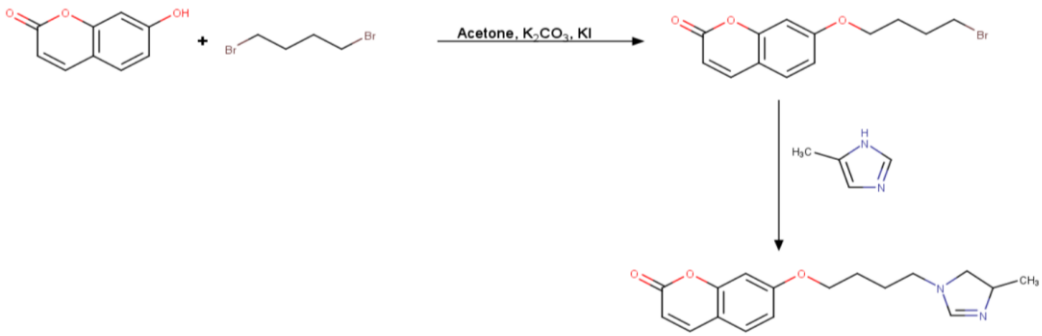
Scheme 3: Synthesis of imidazo [1, 2-a] pyridine-coumarin.[15]



(d) Preparation of 7- (4-(4- methyl-4,5-dihydro-1*H*- imidazole-1-yl)butoxy)- 2*H*- chrome-2-one.

7 hydroxy -2*H*- chrome -2-one was reacted with 1,4- dibromo butane to yield 7-(4- bromo butoxy)-2*H*- chrome-2 -one. On further reaction with 4-methyl-1*H*- imidazole in acetonitrile led to final product. This product showed activity against rhabdovirus infection in fish [14].

Scheme 4: Preparation of 7- (4-(4- methyl-4,5-dihydro-1*H*- imidazole-1-yl)butoxy)- 2*H*- chrome-2-one.[15]



CONCLUSION:

Coumarin and imidazole were found to be active naturally occurring heterocyclic compounds which are pharmacologically active with several activities in treatment of several ailments. These both compounds have several advantages individual so an approach to study the linked molecule was successfully performed. This study revealed that the conjugated system has several advantages over the individual entities as it will help in combating the microbial resistance, several anticancer activities with specific targeting approach towards breast and prostate cancer. Apart from treatment such chronic conditions it is also helpful in treatment of viral infections, inflammations, neurodegenerative disorders etc. A detailed study on synthetic strategies was reviewed and presented with the scheme. Finally, it can be concluded by saying that coumarin linked imidazole moieties are good choice of treatment and there is wide scope for the research in this conjugated system as the synthetic methods are also of great ease and easy to develop.

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CONFLICT OF INTEREST:
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