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A Comprehensive Evaluation of Coumarin Derivatives and Associated Biological Activities

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ABSTRACT

Coumarin and its derivatives have become a highly active class of compounds that demonstrate an assortment of biological actions, besides to their usage as insecticides and fragrances. Numerous techniques have been devised for the synthesis of coumarins. The synthesis of coumarins traditionally involves several established methods, such as the Pechmann condensation,Knoevenagelcondensation,Perkinreaction,andWittigcondensationprocesses. Scholars have conductedimprovements and changes to enhance theeffectiveness and address the constraints of the traditional approach. The present research explores the characterization of coumarin derivatives through the utilization of Fourier Transform Infrared (FTIR) and 11H Nuclear Magnetic Resonance (NMR) spectroscopic techniques. This review study centers on a comprehensive examination of synthesis and characterization techniques employed for the analysis of coumarin derivatives. Additionally, it explores the possible applications of these derivatives across numerous fields. (1-4)

Diverse spectrum of biological activities, including anticancer, antioxidant, and anti- inflammatory properties, have been attributed to coumarin-3-carboxamide derivatives, as reported in previous studies. The observed class additionally exhibits cholinesterase inhibitory properties.

KeyWords: Coumarin-3-carboxamide,Antifungal,Anticancer

I. INTRODUCTION

The search for and discovery of coumarin may be traced back to the year 1820, when Vogel initiallyisolatedcoumarinfromthetonkabean(Dipteryxodorata).Fromachemicalstandpoint, it can be stated that coumarin, also known as 2H-1-benzopyran-2-one, is under the subgroup of lactones. In this study, the compounds referred to as coumarin and chromone, as shown in are benzo-α-pyrone 1 and benzo-γ-pyrone 2, respectively. These compounds exhibit a distinction in the presence of a carbonyl group at position 1 of the pyrone ring. Referred to as 1,2-benzopyrone or o-hydroxycinnamic acid-8-lactone, coumarin containing derivatives are extensively utilized inthefieldsofpharmacyand medicine.Thecharacteristicsandbiological activities of substances are significant factors in the advancement of novel therapeutic medications. Due to this rationale, a multitude of methodologies and strategies have been devised for the synthesis of substituted coumarin. Nevertheless, the synthesis of coumarin derivatives may be achieved using many techniques and utilizing diverse source materials. However,itisimportant tonotethattheyieldsobtainedfromthesesyntheticapproachesoften differ significantly from those obtained from extraction from plants. This discrepancy might beattributedtothetime-dependentandcostlynatureoftheprocessstepsinvolvedinobtaining thefinal product from plants .According to the source provided various traditionaltechniques can be employed for the synthesis of coumarins, including the Perkin reaction, Vilsmeier- Haack and Suzuki cross-coupling processes, Pechmann condensation, Wittig reaction, Knoevenagel condensation, Reformats Ky reaction, and Claisen rearrangement .In general, coumarins can be classified based on

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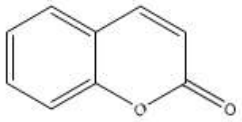
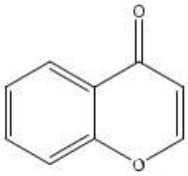
their chemical composition. One classification involves simple coumarins that are substituted differently on the benzene ring to form furan-condensed coumarins. Another classification includes coumarins with substituents in the pyrone ring or pyranocoumarins, which are characterized by a six membered ring attached to the coumarin moiety moreover, these entities are regarded as physiologically active heterocyclic. (5-8)

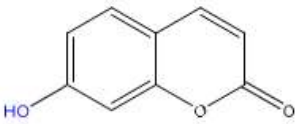
Structure



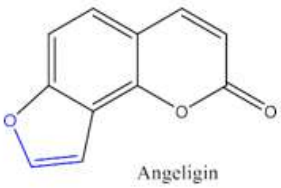
Chromnone



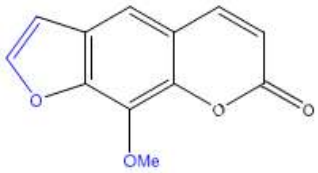
Coumarin



Umbelliferone



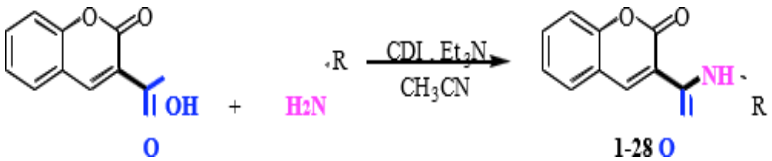
Angeligin



Neuroprotectiveimpactof4-methylcoumarinswasdiscovered,asdocumentedbyadditionally demonstrated the possible anti-breast cancer and ant osteoporotic properties of coumarin and couromene derivatives. also discovered that coumarin and its derivatives has an inhibitory effectonacetylcholinesterase.
Insummary,coumarinsthataresubstitutedatpositions 3and5 have enhanced antioxidant, anticancer, and antiproliferative properties· (9)

Coumarin-3-carboxamidederivativesynthesis

The present study focuses on the utilization of Knoevenagel condensation as a method for synthesizingN-substitutedcoumarin-3-carboxamides.Thiscondensationreactioninvolvesthe reaction of active methylene containing compounds, specifically N-substituted cyanoacetamides and salicylaldehyde, under basic conditions. By employing this synthetic approach, a diverse range of N-substituted coumarin-3-carboxamides can be efficiently prepared. (10-11)



synthesisofcoumarin-3-caeboxamidederivatives

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Physicalpropertiesofcoumarin

Molecularformula	C6H9O2
Molarmass	146.14g/mol
Density	935kg/m3
Meltingpoint	71C
Boiling point	301.7C
Solubility	Solubleinwaterethanolandchloroform

Chemicalpropertiesofcoumarin

ElectrophilicSubstitution

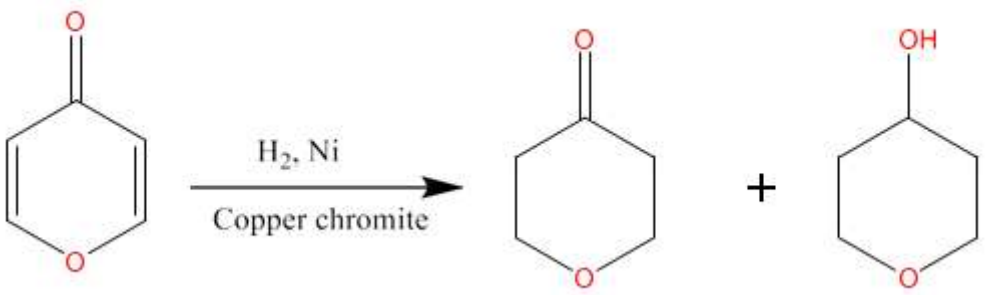
The electrophilic substitution reactivity of pyrones is indicative of their aromatic nature. Both alpha and gamma pyrones can undergo replacement at either the 3-position or the 5-position, namely at the ortho or para positions relative to the carbonyl group. The presence of alkyl substituents on the ring enhances the ease of electrophilic substitution· (12)

Halogenation

α-pyroneundergoesbrominationatthe3-positionbyanaddition-eliminationreaction,rather than being a product of direct electrophilic substitution.

Reactionwithreducingagents

The catalytic hydrogenation reaction, utilizing hydrogen gas (H2) and nickel (Ni) as catalyst, proceeds at the carbon-carbon (C-C) double bonds, resulting in the conversion of unsaturated lactone to its saturated form. The process of hydrogenation provides additional evidence for the presence of double bonds in both α- and γ-pyrones. (13-14)



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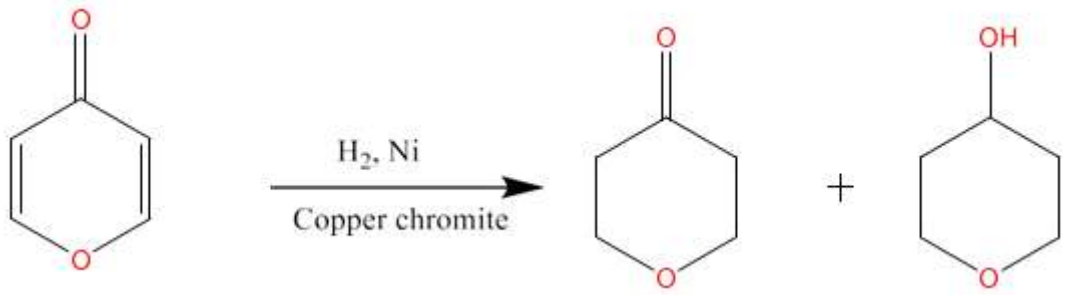
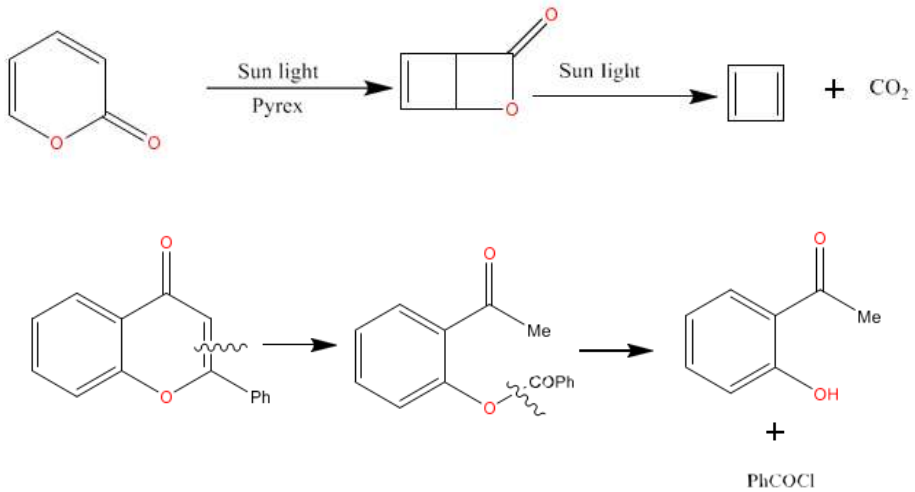
Nucleophilicreaction

Instarkcontrasttotheprocessofelectrophilics ubstitution,pyronesexhibitahighsusceptibility to assault by nucleophilic reagents. The addition of weak nucleophiles occurs mostly at the 2- position, whereas strong nucleophiles tend to add at the 6-position.



Photochemicalreaction

Extensive research has been conducted on the photochemical properties of pyrones, revealing their ability to yield intriguing compounds. During the process of photolysis, α-pyrone undergoes decarboxylation, resulting in the formation of cyclobutadiene.



Pharmacological activity

In practical application, the process of cyclisation occurs in two distinct stages. The process begins with a base-catalyzed rearrangement, resulting in the formation of o-hydroxydinbenzoylmethane. This intermediate compound may be further separated and subjectedtocyclizationinthepresenceofanacidcatalyst,leadingtotheformationofflavone.

Insightsintothebindingaffinitybetweenthepromisingderivativesandtheirtargetedenzymes wereobtainedusingmoleculardockingexperiments,thereforesubstantiatingtheirpotentialas lead compounds for subsequent development of anticancer drugs. The ADME investigations shown favorable pharmacokinetic characteristics, rendering them viable contenders for drug administration.

1. Testingforanticanceractivityinvitro

To determine the impact of the target compounds on various cancer cells, we carefully chose the most positive compounds and assessed their individual cytotoxicity against four distinct typesofhumancancercells.Theseincludedhumanhepatocellularcarcinoma(HepG2),human colorectalcancer(HCT116andSW620),andhumanbreastcancercellstheMCF-7cancercell line was

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evaluated using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT) test. The human breast and cervical cancer cell lines exhibited the highest antiproliferative effects. Significantly, the chemical exhibited specific inhibition of colorectal tumor cell growth while sparing normal cells. The combination of furoxan coumarin hybrids hassignificantanticancer properties,thereforejustifyingtheneedformoreresearchtoexplore their potential as therapeutic options for human cancer. (15)

2. The present study aims to provide an overview of the current research advancements pertaining to coumarins and their derivatives in the context of diabetes management. Currently, the hypoglycemic medications utilized in clinical practice encompass incretin and insulin sensitizers.Furthermore, thereexist many drugs employed forthe purposeof reducing blood glucose levels. These include AMP-activated protein kinase (AMPK15), alpha-glucosidaseinhibitors16,amylases,andinsulinanalogues17.Nevertheless,withinthevast array ofpharmaceutical products available, it isimportant to acknowledge that somenegative effects may arise while attempting to reduce blood glucose levels.Hence, it is imperative to expeditetheexplorationofnovelpharmaceuticalsinordertoaddressandrectifythelimitations inherentinexistingmedications.Inrecentyears,there hasbeenanincreasingfocusonthe investigation of natural goods.

Coumarincompoundsarenotableinthefieldoftherapeuticresearchanddevelopmentbecause totheiradvantageouscharacteristicsofexhibitingmanytargetsandcausinglesshazardousside effects.

3.This study involves the synthesis, biochemical characterization, and molecular modelling of organophosphate-coumarin hybrids. The objective is to assess their potential as effective and selective inhibitors of butyrylcholinesterase.

4.Alkalinephosphatases(APs)areaclassofectonucleotidesenzymesthatplayacrucialrole in the catalytic dephosphorylation of nucleoside phosphates. However, alkaline phosphatases (APs)areenzymesthatexhibitpromiscuityandpossesstheabilitytohydrolyzeadiverserange ofsubstrates.Phosphomonoesters,inconjunctionwith otherphosphate-containingcompounds suchasinorganicpyrophosphate(PPi),polyphosphates,glucosephosphate, andphosphatides, arereferredtoasAPs.widelyrecognizedforitsabilityto facilitatecertaintransphosphorylation processes, and the shown functionality is optimized in alkaline pH conditions. Adenosine monophosphate(AMP)servesasasignificantsubstrate forAP,anditsdephosphorylationleads to the liberation of adenosine, which plays a crucial role in cellular signaling the chemical in question is further associated with purinergic cell gesturing adenosine has a crucial role in the regulation of several immunological and cardiovascular processes. (16)

5. The utilization of coumarin-benzimidazole hybrids as a very effective antibacterial agent. Therecommendations setbytheClinicalandLaboratoryStandards Institute(previouslyknown astheNationalCommitteeforClinicalLaboratoryStandards),wasemployedThecurrentwork involved the screening of 11 newly synthesized coumarin benzimidazole conjugates for their antibacterial activity against recognized Gram-positive and Gram-negative pathogenic bacterial strains. The microdilution method, following for the in vitro assessment of the compounds. The minimum inhibitory concentration (MIC) values were established using ampicillin, kanamycin, tetracycline, and ciprofloxacin as reference antibiotics. The antibacterial activity of several coumarin-benzimidazole conjugates wasvalidatedbyinvitro testing, demonstrating substantial efficacy.

6. Cytotoxicity and molecular docking research were conducted on a range of different amide linked bis-indoles and indole derivatives that featured a coumarin-based moiety. Thiosemicarbazoneswеresynthesizedandafterwards subjectedtoscreeningagainstfouroften encountered human cancer cell lines, namely MCF7 (breast adenocarcinoma cells), HepG2(liver cancer cells), HeLa (cervical cancer cells), SK-Mel2 (melanoma cancer cells), and LU- 1 (lung cancer cells). The compound referred to as the standard 3-(4,5-dimethylthiadiazol-2- yl)-2,5-diphenyltetraz the bromide (MTT) test was utilized to assess the cytotoxicity of the thiosemicarbazones. The experiments involved the use of medicines such as doxorubicin (DOX), Lapatinib, and Erlotinib. The IC50 values of thecompounds against the relevant cancer cell lines were determined. (17)

7.The present study investigates the

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antiproliferative activity of hybrid thiosemicarbazone compounds that contain coumarin and D-galactose moieties, together with their EGFR inhibitory action.
The sugar moiety is commonly employed as a polar constituent in the development and production of biologically active compounds, generally speaking. More specifically, it finds significantapplicationinthiosemicarbazones.Thiosemicarbazonesthatpossessasugarmoiety have been shown to have a range of biological characteristics, including antibacterial, antifungal,anticancer,andantioxidantactivities,amongothers.Thisstudypresentsacollection ofthiosemicarbazonesthatincludeasugarmoiety andhavenotableanticancerproperties.The thiosemicarbazone which has a D-glucose moiety, exhibits noteworthy antiproliferative properties against breast cancer. (18)

8. The present study focuses on the biological evaluation of derivatives of pyrazolo coumarin. In this study, a strong compound with anticholinesterase, anti-5-lipoxygenase, ant tyrosinase, and anticancer properties was synthesized. The compound, known as 1,2,3-triazole linked pyrazole coumarin, was derived from pyrazole fused coumarin. A variety of novel 1,2,3- triazole linked pyrazolo coumarins were synthesized by the process of propargylation at the nitrogen atoms of both pyrazole rings using 3propargylbromide. This reaction was catalyzed by copper(I) and involved alkyne-azide cycloaddition. The beginning, intermediate, and goal compounds demonstrated anticholinesterase, anti-tyrosinase, anti 5-lipoxygenase, and cytotoxic properties. In consideration of an academic standpoint, the user in the conducted investigation, it was determined that the incorporation of a triazole moiety into the initial pyrazolocoumarincompoundthroughthemethylenegroupasaconnectingunitexhibitedmore potency compared to other modifications.
The presence and accessibility of many pharmaceutical products for marketing purposes, including celecoxib, which exhibits therapeutic benefits and functions as an inhibitor. The compounds mentioned include COX-2 inhibitors, such as rimonabant, which acts as a cannabinoid receptor and is employed in the treatment of obesity. Additionally, fomepizole is known for its ability to inhibit alcohol dehydrogenase, while sildenafil is recognized for its inhibitoryeffectsonphosphodiesterase.Onthecontrary,naturalandnon-naturalcoumarinsare agroupofphenoliccompoundsthatarecomprised.Thestructureunderconsiderationconsists of fused benzene and a-pyrone rings. known for their many biological activities. their compoundshavebeenextensivelystudiedfortheirpotentialuseinsunscreenandanticoagulant therapies. Umbelliferon, Warfarin, and Dicoumarol are examples of natural coumarin derivatives that have demonstrated effectiveness in their respective areas renowned for their extensive and exceptional biological features. (19)

9. AReviewofCoumarinDerivativesinPharmacotherapyofBreast Cancer.
The process of cleaving sulfated steroid hormone precursors, such as estrone sulphate, into active hormones by STS, serves as the initial stage in the localized synthesis of estrogen and androgens.Consequently,thesuppressionofthisenzyme,knownasSTS,isexpectedtoresult in a reduction in biosynthesis. Theuse of active hormones has emerged as a novel therapeutic approach in the management of hormone dependent disorder including Breast, endometrial, andprostatecancers,as wellasacneand androgenicalopecia,havebeenidentifiedasmedical conditions of concern the enzyme STS facilitates the process of hydrolyzing sulphate monoesterlinkagesinseveralphysiologicalcontexts.Theinclusionofasulfamateestermoiety into the substrates the incorporation of an aryl ring was seen as a crucial step in the advancement of highly effective STS inhibitors has been documented in previous studies. In addition, efforts were made to discover non-steroidal inhibitors of STS. The research has contributed to the advancement of several bicyclic and tricyclic coumarin sulfamates, which have demonstrated activity in both in vitro and in vivo setting several possible inhibitors of STShavebeenidentified.Thecurrentstageofdevelopmentforthisparticularsubject isinthe preclinical phase, with a limited sample size of 667.COUMATE is scheduled to commence clinical studies for the treatment of hormone-dependent breast cancer in post-menopausal women.(25-26)

10. Antioxidant
Anantioxidantcanbedefinedasasubstancethatretards,hinders,oreradicatesoxidativeharm to a specific molecule this view encompasses both tiny chemicals, such as vitamin C, and big molecules,suchassacrificialproteinslikealbumin.Antioxidantseffectivelymitigateoxidative stress by the

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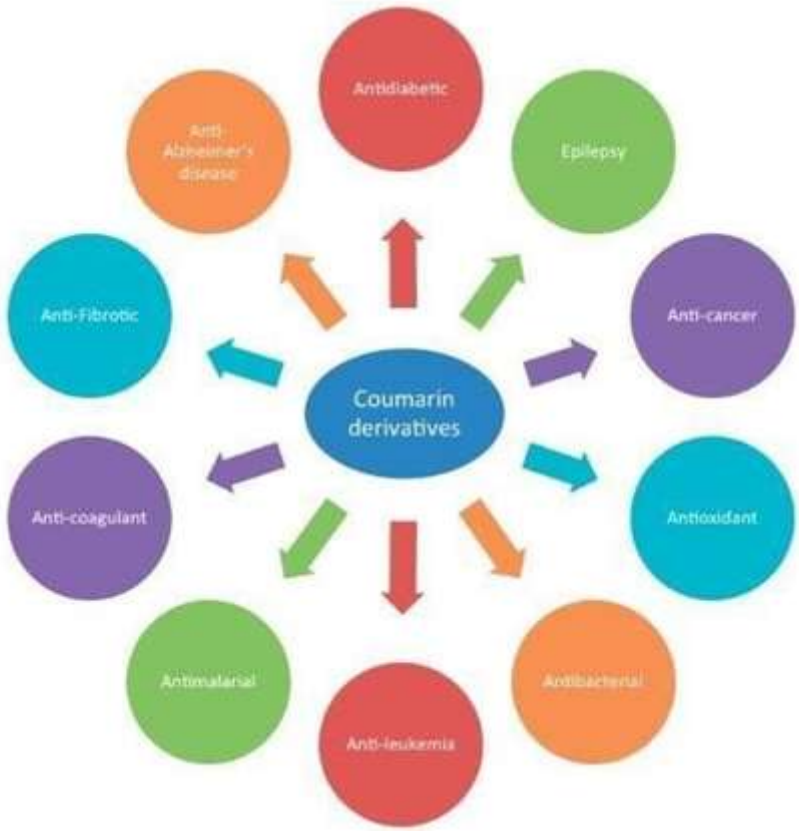
neutralization of reactive oxygen species (ROS), hence counteracting their detrimental effects. Hence, it maybeinferred that theypossess advantageous properties in the treatment ofailments associated with oxidativestress antioxidants can beclassified into many groups depending on their activity, solubility, and size coumarin derivatives have been identified as highly effective antioxidants. The compounds possess antioxidant characteristics that can disrupt the generation and elimination of reactive oxygen species (ROS). Coumarins have been shown to possess the ability to mitigate oxidative damage induced by reactive oxygen species (ROS) and have potential in retarding or averting pathogenic alterations. In a study conducted by Paya et al. (1994) on scavenging capability, it was shown that only 7,8-dihydroxy coumarins exhibited activity. The hydroxycoumarins contain phenolic compounds that exhibit properties of free radical scavenging and powerful metal chelation· (27-30)



II. CONCLUSION

Extensive research endeavors are undertaken to synthesize coumarin derivatives dueto their exceptional biological features and diverse uses across numerous disciplines. Consequently, many methodologies have been applied in order to synthesize novel variants, including the implementation of catalysts to enhance production efficiency and yield. Fourier Transform Infrared Spectroscopy (FTIR) has the potential to be employed for the purpose of characterizing coumarin derivatives. The technique identifies several functional groups by the absorption of infrared radiation emitted by the sample material. The use of H NMR spectroscopy is employed to ascertain details regarding the structure, reaction state, and chemical environment of coumarin derivatives. Additional techniques, such as ultraviolet-visible spectroscopy (UV-Vis) and micro elemental analysis (CHNO), can be employed for the characterization of coumarin derivatives. Coumarin derivatives encompass a range of functional groups that have demonstrated significant potential in terms of their biological activity, toxicological properties, and uses in the fragrance industry. Ongoing research efforts are being conducted by researchers to explore the possible industrial uses of coumarin derivatives,

owing to their diverse biological activities.

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