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Comprehensive Review on Synthesis and Evauation of Coumarins as Antimicrobials

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Abstract: ***Coumarins contain an outsized of phenolic compound obtained from plants and are manufactured from fused benzene and alpha pyrone ring. The prototypical compound is understood as 1,2 benzopyrone Coumarin has mild antibacterial activity, but long chain hydrocarbon substituted compound like ammoresinol and ostruthin show wide spectrum activity against Gram +ve bacteria like Bacillus megaterium, Micrococcusluteus, Micrococcus lysodeikticus, and Staphylococcus aureus. Another coumarin compound anthogenol from green fruits of Aegle marmelos shows activity against Enterococcus. The target behind this review is to synthesise a brand new caumarin derivative which shows greater efficacy and potency with microbial growth.***

Keywords: Micrococcusluteus, Micrococcus lysodeikticus, and Staphylococcus

1. Introduction

Coumarinor 2*H*-chromen-2-one is an benzene nucleus containing compound with formula $C_9H_6O_2$.Its molecule are often described as hydrocarbon or arenes, with two adjacent hydrogen atoms replaced by a lactone-like chain –(CH)=(CH)–(C=O)–O–, forming a second six-membered heterocyclic that shares two carbons with the benzene nucleus together with Nitrogen,Sulphur and Oxygen Containing. It can be placed in the 2 ketone derivative of benzopyran chemical class, and as a lactone.[1] Coumarin posess bitter including other properties as achromatic crystalline solid with a sweet odor resembling the scent of vanilla [2] It's found in many plants and may be used for the defense against predators. By inhibiting synthesis of antihaemorrhagic factor, it can be often used as anticoagulant. to inhibit formation of blood clots, deep vein thrombosis, and pulmonary embolism a related compound is employed because the prescription warfarin –.The prepration of Coumarin are often done by named reactions like the Perkin reaction between salicylaldehyde and acetic anhydride being a preferred example[3]. The Pechmann condensation may be a method to arrange coumarin and its derivatives; as does the Kostanecki acylation which may even be accustomed produce various chromones[4].

1.1. Natural Occurrence

Coumarin are often obtained from many plants, like in high concentration within the tonka bean (*Dipteryx odorata*). It's also found in vanilla grass (*Anthoxanthum odoratum*), sweet woodruff (*Galium odoratum*), manna grass (*Hierochloe odorata*) and sweet-clover (genus *Melilotus*), which are named because of the sweet essence of the compound[5].

Other plants having mild coumarin content are cassia cinnamon (*Cinnamomum cassia*; which require to not be confused with true cinnamon, *Cinnamomum verum*, or cinnamon Ceylon cinnamon *Cinnamomum zeylanicum* which contain little coumarin),[10] deer tongue (*Dichanthelium clandestinum*), mullein (genus *Verbascum*), and in many cherry blossom tree varieties (of the genus *Prunus*).[11] Coumarin is additionally found in extracts of *Justicia pectoralis*.[12][13] Related compounds are found in some but not all specimens of rosid dicot genus *Glycyrrhiza*, from which the foundation and flavour licorice derives[6].

Coumarin can even be derived naturally from many edible plants like strawberries, black currants, apricots, and cherries [7].

1.2. Uses

Coumarin has appetite-inhibiting properties, which prevents animals from eating plants which contain caumarins although the compound incorporates a pleasant sweet smell, but has bitter taste, and animals tend to avoid consumption of such plants.[8].

1.3. Metabolism

The process of catabolism and anabolism in coumarin in plants is finished by hydroxylation, glycolysis, and cyclization of cinnamic acid In humans, the enzyme encoded by the gene *UGT1A8* has glucuronidase activity which undergo metabolism by glucoronidation with many substrates including coumarins[9].

1.4. Coumrin derivatives as anti-microbial

Coumarins in todays scenario is widely been used due to the several biological activities it possess like antibacterial, antifungal, antiviral, anti-tubercular, anti-malarial, anticoagulant, anti-inflammatory, anticancer, antioxidant properties and more[10]. Several steps for the separation and purification of present coumarins from different plants further more as artificial synthesis of coumarin compounds with novel structures and properties, has been paying attention for the research and development of coumarins as potential drugs[11]. Till now some coumarins, for instance, Warfarin, Acenocoumarol, Armillarisin A, Hymecromone and Carbochromen are approved as pharmacologically active compounds for various uses in clinic. subsequently, an increasing number of coumarin derivatives have shown great potency within the prevention of assorted forms of diseases[12]. Coumarin compounds, containing 2 ketone derivative of benzopyran chemical class,skeleton structurally kind of like clinical anti-infective quinolone drugs with benzopyridone backbone, as a brand new sort of antibiotics

have received specific interest together with the event of multi-drug resistant microbial infections[13]. There are a variety of reports that natural and artificial Coumarin derivatives posses antimicrobial activity.1-14 Novobiocin and Chlorobiocin are established antimicrobials containing a Coumarin (i.e.2H-1-benzopyran-2-ones) skeleton[14].

2. Literature Review

YuanShi et.al (2011)synthesis a series of recent coumarin-based 1,2,4-triazole derivatives and identified its antimicrobial activities in vitro against four different Gram-positive bacteria (*Staphylococcus aureus*, MRSA, *grass Bacillus* and *Micrococcus luteus*) and four different Gram-negative bacteria (*Escherichia coli*, *Proteus vulgaris*, *typhoid bacillus* and *Shigella dysenteriae*) similarly as on three fungi (*Candida albicans*, *brewers's yeast* and *Aspergillus fumigatus*) by two-fold serial dilution method. The bioactive assay showed that some synthesized coumarin triazoles displayed comparitable or even more potent antibacterial and antifungal efficacy as compared with previously synthesised referrence drugs Enoxacin, Chloromycin and Fluconazole. Coumarin bis-triazole compounds exhibited greater efficacy and potency showing antibacterial and antifungal efficiency than their corresponding mono-triazole derivatives

A Arshad, et.al (2011) Two novel series of hydrazinyl thiazolyl coumarin derivatives are been prepared and fully identified by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectral data. The structures of some compounds were further confirmed by X-ray crystallography. All of those derivatives, were analysed *in vitro* for antimicrobial activity against various species including *Mycobacterium tuberculosis* and *Candida albicans*. The compounds exhibited strong antimicrobial activity against all of the tested microbial strains.

SureshKuarm et.al(2011) procured a series of 3-[benzimidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one and 3-[benzothiadiazole- imidazo(1,2-*c*)quinazolin-5-yl]-2*H*-chromene-2-one derivatives that contains a distinct group of substituents at the 6- and/or 8-positions of the coumarin group utilizing cellulose oil of vitriol as a good catalyst under both conventional heating and microwave irradiation therapies. These analogs were examined for their antimicrobial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus pyogenes* (Gram-positive bacteria), *Escherichia Coli*, *Klebsiella pneumonia*, *Salmonella typhimurium* (Gram-negative bacteria), and *Aspergillus niger*, *Candida albicans*, and *Aspergillus flavus* (Fungi). Two analogs, (a 6,8-dichloro analog, $MIC_{[SA]}$ = 2.5 µg/mL; $MIC_{[ST]}$ = 2.5 µg/mL) and (a 6,8-dibromo analog, $MIC_{[ST]}$ = 2.5 µg/mL) were identified as potent antibacterial agents, and two analogs, (a 6-bromo analog, $MIC_{[AF]}$ = 10 µg/mL) and (a 6,8-dibromo analog, $MIC_{[AF]}$ = 15 µg/mL; $MIC_{[CA]}$ = 15 µg/mL), were catagorised as potent antifungal agents supported the MIC data, analogs were considered because the most potent antimicrobial agents in the series.

Divyesh C.Mungraet.al (2011) synthesised a replacemnet class of β-aryloxyquinolines and their pyrano[3,2-*c*] chromene derivatives inserting a validated molecular target *via* a nucleophilic displacement and a one-pot multicomponent reaction respectively. *In vitro* antimicrobial activity of the synthesized compounds were examined against a representative group of pathogenic strains specifically *grass Bacilluss*, *Clostridium tetani*, *Streptococcus pneumoniae*, *Escherichia coli*, *typhoid bacillus*, *Vibrio cholera*, *Aspergillus fumigatus* and *Candida albicans*. Compounds exhibited strong antibacterial activity while one compound exhibited more efficient antifungal activity than that of first line standard drugs. *In vitro* antituberculosis activity was evaluated against *Mycobacterium tuberculosis* H37Rv and is emerged because the promising antimicrobial member with greater antitubercular activity. Majority of the compounds appears to be better antimicrobials but poor antituberculars.

Mohamed S. et.al(2000) Naphtho[2,1-*b*]pyranone reacted with arylmethylenemalononitriles to yield 4-amino-5-oxo-2-aryl-5*H*-dibenzo[*c*,*f*]chromene-3-carbonitriles with ethyl 3,4-dichlorobenzylidene cyanoacetate to furnish dibenzo[*c*,*f*] chromene and with elemental sulfur in dioxane containing piperidine to administer thieno[3,4-*d*] naphtho[2,1-*b*] pyranone. Similarly, naphtho[1,2-*b*]pyranone was reacted with arylmethylenemalononitriles and elemental sulfur to furnish dibenzo[*c*,*h*] chromenes and thieno[3,4-*d*] naphtho[1,2-*b*] pyranone, respectively. Compound underwent cycloaddition reaction with *N*-arylmaleimides to yield benzo [7, 8] chromeno[3,4-*f*]isoindoles. A number of these compounds were examined in vitro for their antimicrobial activities.

Pradeepkumar M.Ronad et.al(2010)A series of 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-one derivatives are prepared by reaction of 7-amino-4-methyl-benzopyran-2-one (1) with an appropriate substituted aldehydes to get various Schiff bases which on treatment with thioglycolic acid afforded the title compounds. Purity of the compounds has been confirmed by TLC. Structure of those compounds were established on the bases IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data. Schiff bases and title compounds were evaluated for antibacterial and antifungal activities against various bacterial and fungal strains. The results showed that compounds 3d, 3f, 4d, 4f and 4i (100 µg/ml) exhibited good antibacterial and antifungal activity as that of normal antibiotics ciprofloxacin and grisofluvin.

HakanGökeret.al (2005) Series of flavones and methyl-4H-1-benzopyran-4-ones carrying mono or diamidinobenzimidazoles at different positions were prepared and examined for antibacterial and antifungal activities against *E. coli*, *S. aureus*, MRSA (methicillin-resistant *S. aureus*), MRSE (methicillin-resistant *S. epidermidis*), *S. faecalis* and *C. albicans*, *C. krusei*. The results showed that while all diamidines doesnot seems to be active, the compounds having monoamidinobenzimidazoles at the C-6 position of the 2-phenyl-4H-1-benzopyran-4-one have greater antibacterial activities, particularly, against Gram-positive bacteria. Compounds posess the most effective inhibitory activity with MIC values of 1.56 µg/mL against *S. aureus*, MRSA, MRSE and 3.12 µg/mL against *C. albicans*, respectively.

FrancoChimentiet.al (2010) N-substituted-3-carboxamido-coumarin derivatives were expermintally synthesised and examined for selective antibacterial activity against 20 isolates of *Helicobacter pylori* clinical strains, including five metronidazole resistant ones. A number of them exhibit the beneficially effective activity against *H. pylori* metronidazole resistant strains with MIC values less than the drug reference (metronidazole). Although, anti-inflammatory activity exhibit the inhibition of the IL-8 production was examined.

Tuncbilek M et.al (2006) prepared 3 (3nitrophenacyl) thiazolidine2, 4dione and 3(substitutedphenacyl) 5[3′(4*H*4oxo1benzopyran2yl) benzylidene] 2, 4thiazolidinediones are shown in this paper. These compounds were synthesised from 3′flavone carboxaldehyde and 3substituted phenacyl2,4thiazolidinediones using Knoevenagel reaction. The structures of all compounds were identified by IR, ^{1}HNMR, mass spectral data, and elemental analyses. The molecules were examined for *invitro* antimicrobial activity against *Staphylococcus aureus, Candida albicans, Candida krusei, Candida glabrata,* and *Candida parapsilosis.* Compounds and showed better repressive activity in comparison to fluconazole against *Candida krusei* and *Candida glabrata*.

Basanagouda M et.al (2010) prepared series of latest and novel coumarin-6-sulfonamides with a free C4-azidomethyl group as antimicrobials in three steps ranging from 7-methyl-4-bromomethylcoumarin 1. The reaction of 1 with chlorosulfonic acid was found to yield the corresponding 6-sulfonylchloride 2, which when reacted with sodium azide led to intermediate 3. The title sulfonamides 5a–y were obtained from the reaction of three with various aromatic amines 4 in refluxing benzene. The chemical structures of the compounds were evaluated by IR, NMR and LC-MS spectral data. All the prepared compounds are examined for their in vitro anti-bacterial and anti-fungal activities. A number of the compounds are found to be move against both bacterial species at a level of 1 mg/mL.

Identification and Characterization
The prepared compounds were charaterised and evaluated by following methods:

Thin Layer Chromatography (TLC)
TLC is a evaluation method which is employed to look at the number of components in an exceedingly mixture,to identity compounds and also the purity of a compound. By analysing the looks of a product or the disappearance of a reactant, it may also be accustomed to distinguise the progress of a reaction. TLC is a sensitive technique can be analyzed microgram (0.000001 g) quantities and it takes little time for an analysis (about 5-10 minutes). It's supported the Rf value since style of compounds have different Rf values. TLC plates of silica gel G prepared by spreading method which are dried in air and so activated by heating in hot air oven at 110°C for half an hour.Proper solvent system are used as solvent systems. The spots will located by exposure to iodine vapours or under UV-light.

$$\mathbf{Rf} = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by solvent}}$$

Melting Point Determination
The temperature of caumarin containing chemical compound would be determined by open capillary tube method. The estimation of temperature is the most beneficial and easy way of differentiating the physical constant of one compound from other compound

Infra-Red Spectroscopy (IR)
A beneficial tool of the organic chemist is Infrared Spectroscopy which is acquired on a special instrument, called IR spectrometer. IR is vital to gather information about the structure of a compound and used as analytical tool to assess the efficacy of a compound. IR spectra are quick and easy to run. Infrared radiation is absorbed by chemical compounds and converted into energy of molecular vibration. In IR spectroscopy, a chemical compound is exposed to infrared radiation when energy matches the energy of a particular molecular vibration, absorption occurs. Thus IR spectra of each and every different bond are formed. The infrared spectra compounds were recorded on IR Affinity-1 SHIMADZU Ltd. (range 4000-500 cm-1) spectrometer.

Nuclear Magnetic Resonance Spectroscopy (NMR)
Nuclear Magnetic Resonance (NMR) spectroscopy is an analytical chemistry technique employed in quality control and research for the determination of efficacy and purity of a sample likewise as its molecular structure. Nuclear magnetic resonance (NMR) is a physical process in which nuclei in an exceedingly magnetic force applied absorb and emit electromagnetic waves. The principle behind NMR is that several nuclei have spin and all these nuclei are electrically charged. If an external magnetic field is applied, an energy transfer is feasible between the lower energy to a higher energy level. The transfer of energy takes place at a particular wavelength that corresponds to radio frequencies and when the spin returns to its base level, energy is liberated at the identical frequency. The signal that matches this transfer is measured in many ways and processed so as to yield an NMR spectrum for the nucleus concerned.

3. Conclusion

Infectious diseases is one every of the greatest global challenges in medicine in our time. An oversized number of new infectious diseases have emerged: major threats to the planet with the diseases like tuberculosis, AIDS and SARS, but also less threatening infections, like those caused by Campylobacter spp, Borrelia spp, *Bartonella henselae*, *Clostridium difficile*, Hanta viruses which have created major changes in clinical practice, microbiological services, public health activities, and biomedical research.

Over the past few decades, the hunt for newer antimicrobials remains a part of investigation within field of medicinal chemistry due to development of resistance by microorganism for different antibiotics. Antimicrobials are the foremost great tool in fighting bacterial infections. Throughout history, there has always been a battle between humans and also the microorganisms that cause infection

and diseases. Coumarin derivatives have a large range of structural deviation and modification , and they can function as a templates for brand new drugs. Coumarin derivatives are an useful and potent antimicrobial agents.

References

[1] Vogel A. Darstellung von Benzoesäure aus der Tonka Bohne und aus den Melilotenoder Steinklee Blumen. Annalen der Physik. 1820;64(2):161-6.
[2] Chen CH, Fox JL, Duarte FJ, Ehrlich JJ. Lasing characteristics of latest coumarin-analog dyes: broadband and narrow-linewidth performance. Applied optics. 1988 Feb 1;27(3):443-5.
[3] Chen, C. H.; Fox, J. L.; Duarte, F. J. (1988). "Lasing characteristics of new-coumarin-analog dyes: broadband and narrow-linewidth performance". *Appl. Opt*. 27 (3): 443–445.
[4] Duarte FJ, Liao LS, Vaeth KM, Miller AM. Widely tunable green laser emission using the coumarin 545 tetramethyl dye because the gain medium. Journal of Optics A: Pure and Applied Optics. 2006 Jan 13;8(2):172.
[5] Fang B, Zhou CH, Rao XC. Synthesis and biological activities of novel amine-derived bis-azoles as potential antibacterial and antifungal agents. European journal of medicinal chemistry. 2010 Sep 1;45(9):4388-98.
[6] Zhang FF, Gan LL, Zhou CH. Synthesis, antibacterial and antifungal activities of some carbazole derivatives. Bioorganic & medicinal chemistry letters. 2010 Mar 15;20(6):1881-4.
[7] Wang XL, Wan K, Zhou CH. Synthesis of novel sulfanilamide-derived 1, 2, 3-triazoles and their evaluation for antibacterial and antifungal activities. European journal of medicinal chemistry. 2010 Oct 1;45(10):4631-9.
[8] Drlica K, Hiasa H, Kerns R, Malik M, Mustaev A, Zhao X. Quinolones: action and resistance updated. Current topics in medicinal chemistry. 2009 Aug 1;9(11):981-98
[9] Rashdan HR, Nasr SM, El-Refai HA, Abdel-Aziz MS. A completely unique approach of potent antioxidant and antimicrobial agents containing coumarin moiety accompanied with cytotoxicity studies on the newly synthesized derivatives. Journal of Applied Pharmaceutical Science. 2017 Jul;7(07):186-96.
[10] Fylaktakidou KC, Hadjipavlou-Litina DJ, Litinas KE, Nicolaides DN. Natural and artificial coumarin derivatives with anti-inflammatory/antioxidant activities. Current pharmaceutical design. 2004 Nov 1;10(30):3813-33.
[11] Shilling WH, Crampton RF, Longland RC. Metabolism of coumarin in man. Nature. 1969 Feb 15;221(5181):664-5.
[12] Sandhu S, Bansal Y, Silakari O, Bansal G. Coumarin hybrids as novel therapeutic agents. Bioorganic & medicinal chemistry. 2014 Aug 1;22(15):3806-14.
[13] Sashidhara KV, Kumar A, Kumar M, Sarkar J, Sinha S. Synthesis and in vitro evaluation of novel coumarin–chalcone hybrids as potential anticancer agents. Bioorganic & medicinal chemistry letters. 2010 Dec 15;20(24):7205-11.
[14] Smyth T, Ramachandran VN, Smyth WF. A study of the antimicrobial activity of selected present and artificial coumarins. International journal of antimicrobial agents. 2009 May 1;33(5):421-6.
[15] Shi Y, Zhou CH. Synthesis and evaluation of a category of latest coumarin triazole derivatives as potential antimicrobial agents. Bioorganic & medicinal chemistry letters. 2011 Feb 1;21(3):956-60.
[16] Arshad A, Osman H, Bagley MC, Lam CK, Mohamad S, Zahariluddin AS. Synthesis and antimicrobial properties of some new thiazolyl coumarin derivatives. European journal of medicinal chemistry. 2011 Sep 1;46(9):3788-94.
[17] Kuarm BS, Reddy YT, Madhav JV, Crooks PA, Rajitha B. 3-[Benzimidazo-and 3-[benzothiadiazoleimidazo-(1, 2-c) quinazolin-5-yl]-2H-chromene-2-ones as potent antimicrobial agents. Bioorganic & medicinal chemistry letters. 2011 Jan 1;21(1):524-7.
[18] Mungra DC, Patel MP, Rajani DP, Patel RG. Synthesis and identification of β-aryloxyquinolines and their pyrano [3, 2-c] chromene derivatives as a replacement class of antimicrobial and antituberculosis agents. European journal of medicinal chemistry. 2011 Sep 1;46(9):4192-200.
[19] El-Gaby MS, Zahran MA, Ismail MM, Ammar YA. A completely unique synthesis of dibenzo [c, f] chromenes, dibenzo [c, h] chromenes and benzo [7, 8] chromeno [3, 4-f] isoindoles as antimicrobial agents. Il Farmaco. 2000 Mar 1;55(3):227-32.
[20] Ronad PM, Noolvi MN, Sapkal S, Dharbhamulla S, Maddi VS. Synthesis and antimicrobial activity of 7-(2-substituted phenylthiazolidinyl)-benzopyran-2-one derivatives. European journal of medicinal chemistry. 2010 Jan 1;45(1):85-9.
[21] Göker H, Boykin DW, Yıldız S. Synthesis and potent antimicrobial activity of some novel 2-phenyl or methyl-4H-1-benzopyran-4-ones carrying amidinobenzimidazoles. Bioorganic & medicinal chemistry. 2005 Mar 1;13(5):1707-14.
[22] Chimenti F, Bizzarri B, Bolasco A, Secci D, Chimenti P, Granese A, Carradori S, Rivanera D, Zicari A, Scaltrito MM, Sisto F. Synthesis, selective anti-Helicobacter pylori activity, and cytotoxicity of novel N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides. Bioorganic & medicinal chemistry letters. 2010 Aug 15;20(16):4922-6.
[23] Tuncbilek, Meral, and Nurten Altanlar. "Synthesis of latest 3(Substituted Phenacyl)5[3′(4H4oxo1benzopyran2yl)benzylidene]2, 4thiazolidinediones and their Antimicrobial Activity." Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry 339, no. 4 (2006): 213-216.
[24] Basanagouda M, Shivashankar K, Kulkarni MV, Rasal VP, Patel H, Mutha SS, Mohite AA. Synthesis and antimicrobial studies on novel sulfonamides containing 4-azidomethyl coumarin. European journal of medicinal chemistry. 2010 Mar 1;45(3):1151-7.
[25] Y. Aoyama, T. Katayama, M. Yamamoto, H. Tanaka, and K. Kon, "A new antitumor antibiotic product, demethylchartreusin. Isolation and biological activities," The Journal of Antibiotics, vol. 45, no. 6, pp. 875–878, 1992.
[26] M. Iranshahi, M. Askari, A. Sahebkar, and D. HadjipavlouLitina, "Evaluation of antioxidant, anti-

inflammatory and lipoxygenase inhibitory activities of the prenylated coumarin umbelliprenin," DARU, vol. 17, no. 2, pp. 99–103, 2009.
[27] W. C. Evans, Trease and Evans Pharmacognosy, Elsevier Ltd., 16th edition, 2009.
[28] J. A. Mead, J. N. Smith, and R. T. Williams, "Studies in detoxication. 72. The metabolism of coumarin and of o-coumaric acid," The Biochemical Journal, vol. 68, no. 1, pp. 67–74, 1958. [5] C. Spino, M. Dodier, and S. Sotheeswaran, "Anti-HIV coumarins from calophyllum seed oil," Bioorganic and Medicinal Chemistry Letters, vol. 8, no. 24, pp. 3475–3478, 1998.