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INNOVATIONS IN 4-HYDROXYCOUMARIN DERIVATIVES: A COMPREHENSIVE REVIEW

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ABSTRACT
4-hydroxycoumarin, or 4-hydroxycoumarin-1-benzopyran-2-one, is an organic compound that belongs to the benzopyrone family and has a hydroxyl group at the 4-position on its coumarin backbone. Its derivatives exhibit biological activities that include anti-microbial, anti-bacterial, anti-HIV, anti-TB, and anti-oxidant. For future study and development, we have gathered information about the antimicrobial activity of 4-hydroxycoumarin derivatives in this review.

KEYWORDS: 4-hydroxycoumarin, Anti-microbial, Anti-bacterial, Anti-HIV, Anti-TB, and Anti-oxidant.

INTRODUCTION

Coumarins, also known as benzo-2-pyrone derivatives, are a major family of natural product molecules that play an essential role in synthetic organic chemistry. They have been extensively utilised as starting materials or intermediates in the pharmaceutical, perfumery, and agrochemical industries. Coumarins have multiple applications, including fluorescent brighteners, laser dyes, and food and cosmetic additives.[1-2] Synthetic approaches have produced coumarin analogues with diverse pharmacological properties, including anti-HIV, antibacterial, anti-inflammatory, anticancer, anti-TB, anticonvulsant, anticoagulant, antithrombotic properties, and MAO inhibitory effects.[3-4] Coumarin is classified as a member of the benzopyrone family, which consists of a benzene ring joined to an α-pyrone ring. Coumarin and coumarin-related compounds have been proven for many years to have significant therapeutic potential. Through substituent manipulation of the coumarin scaffold at positions 3, 4, 5, 6, 7, and 8, increased diversity is introduced, which crucially alters the electronic structure and the associated biological properties.[5]

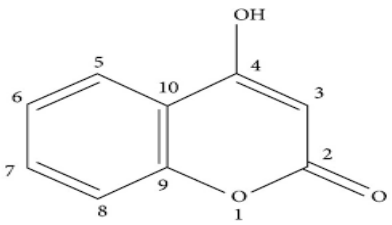


Figure 1: General structure of 4-Hydroxycoumarin.[5]

Review of biological activities

Zeba N. Siddiqui *et.al* (2011), had synthesized many derivatives of 4-hydroxycoumarin. The reaction of 3-bromo-4-hydroxycoumarin with various heteroaldehydes yields good yields. All the synthesised compounds were tested for *in-vitro* antimicrobial activity by using different species of *Streptococcus pyogenes*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, and *Escherichia coli* bacterial strains and fungal cultures of *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton mentagrophytes*, and *Penicillium marneffei* by disc diffusion assay.[6]

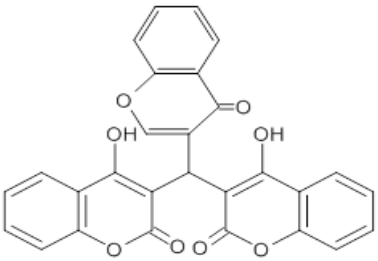


Figure 2: 1-(4-Oxo-4H-1-benzopyran-3-yl)-1, 1-bis (4-hydroxy-1- benzopyran-2-one-3-yl)methane.

Jae-Chul Jung *et.al*. (2009), noticed that the modification of 4-hydroxycoumarin showed encouraging results in many pharmacological actions, including anti-cancer, anti-arthritis, analgesic, anti-pyretic, anti-bacterial, anti-viral, anti-inflammatory, and anticoagulant.[7]

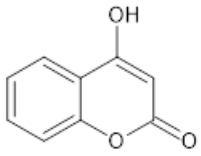


Figure 3: 4-Hydroxycoumarin.

O. Nagaraja *et.al*. (2020), was made by reacting diazonium salt solution with 4-hydroxycoumarin in an aqueous KOH solution and stirring for another hour. The acquired coloured precipitates. In this process, N-(4, H 6-dimethyl pyrimidine-2-yl)-4-[(E)-(4-hydroxy-2-oxo-2Hchromen 3yl) diazenyl] benzenesulfonamide is produced in good yield. The azo dyes were tested for anti-microbial, anti-tubercular, DNA cleavage, and in silico molecular docking, revealing efficient binding to the RpsA receptor.[8]

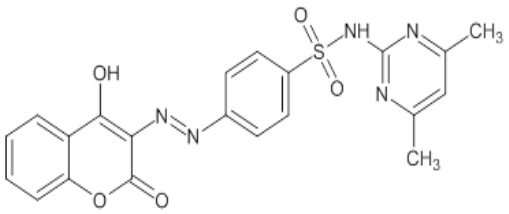


Figure 4: N-(4, 6-dimethylpyrimidine-2-yl)-4-[(E)-(4-hydroxy-2-oxo-2Hchromen3yl) diazenyl] benzenesulfonamide.

Slobodan sukdolak *et.al*. (2004), had reported eight 3-(thiazol-4-yl). -4-hydroxychromen-2-one derivatives were produced in good yield through the reaction of 3-(2-bromoacetyl). -4-hydroxychromen-2-one with thioureas, thioacetamide, thiobenzamide, and ammonium dithiocarbamate. These coumarin derivatives may have bioactive properties.[9]

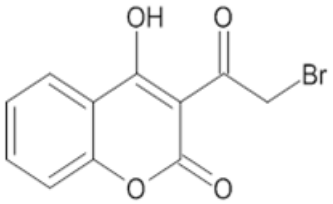
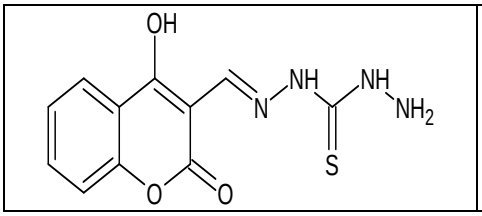


Figure 5: 3-(2-bromoacetyl) -4-hydroxychromen-2-one.

A.I. Mosa *et.al.* (2011), had obtained a new series of stable transition metal complexes of the formula M(L)X·S, where M = Cu(II), Ni(II), Co(III), Cr(III), and Fe(III), and L is the deprotonated ligand of 4-hydroxycoumarin-3-thiocarbohydrazone, X = Cl−, NO3−, or CH3COO−, and S = H2O and/or EtOH. The HL ligand was prepared by the reaction of 3-formyl-4-hydroxycoumarine with thiocarbohydrazide in a molar ratio of 1:1. The HL ligand and its metal complexes were characterized by elemental analysis, 1H NMR, IR, and electronic spectra, molar conductance, magnetic measurements, and thermal gravimetric analysis (TGA).[10]



Compounds	Ar
a	C_6H_4-4-OCH_3
b	C_6H_2-3,4,5-$(OCH_3)_3$
c	3-pyridyl

Figure 6: Structure of the thiocarbohydrazone, HL, ligand.

Omaima M *et.al*. (2010), reported that potential anticoagulant drugs include a class of 4-hydroxycoumarins that have pyridine, pyrimidine, and pyrazole nuclei connected at C-3. These azaheterocycles were chosen due to their past superior antithrombotic effectiveness both *in vivo* and *in vitro*.[11]

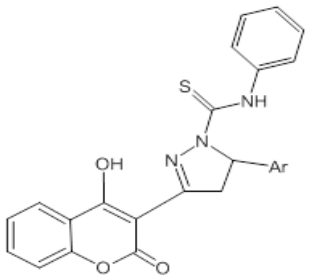


Figure 7: Series of 5-Aryl-4,5-dihydro-3-(4-hydroxy-2-oxo2H-chromen-3-yl)-N-phenyl-pyrazol-1-carbothioamide derivatives(a,b,c).

Arduengo *et.al, (*2015), provided a modification of the standard procedure that produces N-substituted imidazoles in good yields by substituting an amine for one equivalent of ammonia.[12]

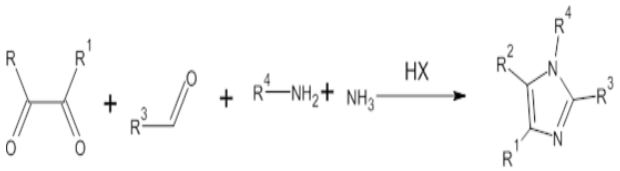


Figure 8: The general formula of Mercaptoimidazole.

Nagaraja Obaiah *et.al*.(2020), synthesized some novel coumarin derivatives by Knoevenagel condensation reaction using three component systems in the presence of L-proline as a catalyst, showing anti-microbial and ant-oxidant properties.[13]

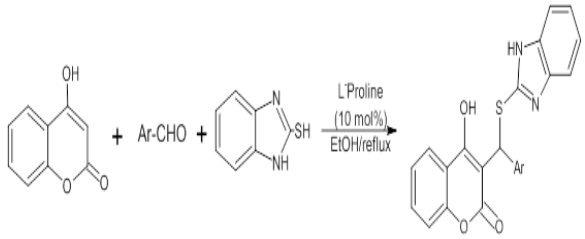


Figure 9: Synthesis of 3-[(1H-benzimidazol-2-ylsulfanyl) (phenyl) methyl]-4-hydroxy-2H-chromen-2-one derivatives.

Mazaahir Kidwai *et.al*., (2007), obtained molecular iodine and used an efficient catalyst for an improved and rapid one-pot synthesis of 3,3′-arylmethylenebis-(4-hydroxycoumarin) and 2,2′-arylmethylenebis(3-hydroxyl-5,5-dimethyl-2-cyclohexen-1-one) in excellent yields using water as a reaction medium. This aqua-mediated Michael addition of various aromatic and heteroaromatic aldehydes with 4-hydroxycoumarin or dimedone using a catalytic amount of molecular iodine is devoid of the use of expensive, corrosive reagents, and toxic solvents and provides operational simplicity.[14]

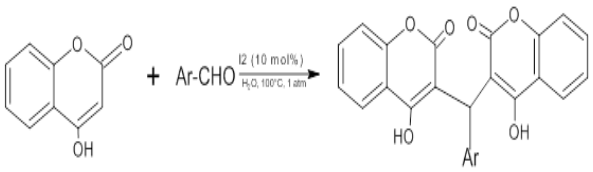
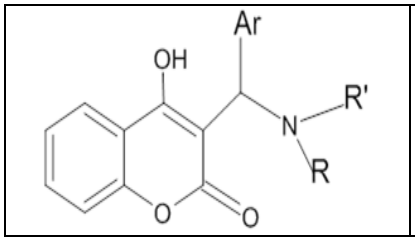


Figure 10: Iodine catalyzed aqua-mediated synthesis of Michael adduct.

Abolfazl Olyaeiet *et.al*.(2023), reported the synthesis of coumarins such as 3-aminoalkyl-4-hydroxycoumarin, 3-aminobenzyl-4-hydroxycoumarin, and 3-amidoalkyl-4-hydroxycoumarin derivatives owing to their tremendous application in various research fields such as biological science and medicinal chemistry. We reviewed the history of a method for synthesizing 4-hydroxycoumarin derivatives with substitution at the C-3 position while using both homogeneous and heterogeneous catalysis under various conditions and their biological activities.[15]



Compound	R	R’
a	H	alkyl
b	Me	Me
c	$(CH_2)_5$	$(CH_2)_5$

Figure 11: Synthesis of 3-substituted-aminomethyl-4-hydroxycoumarin.

Karl Paul Link *et.al.* (1953), had discovered that 3-acetyl-4-hydroxycoumarin is produced when 4-hydroxycoumarin reacts with acetyl chloride. In the presence of pyridine and piperidine, acetyl chloride irreversibly interacts with 4-hydroxycoumarin to produce 4-acetoxycoumain. The acetylpyridinium cation and the anion of 4-hydroxycoumarin are produced when pyridine reversibly cleaves this molecule through a nucleophilic attack on the carbonyl of the ester group. After enolization, this later moiety combines with an additional resonance form of the 4-hydroxycoumarin anion to produce 3-acetyl-4-hydroxycoumarin.[16]

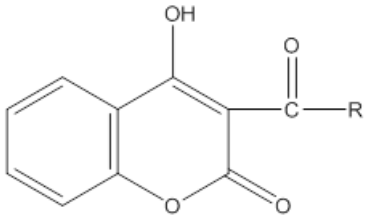


Figure 13: 3-acyl-4-hydroxycoumarine.

Donia Bensalah *et al.* (2020) reported that arylaldehydes, thiourea, ammonium acetate, and 3-acetyl-4-hydroxycoumarin were condensed at reflux in DMC to produce novel thiazolyl coumarin derivatives. It will be undergoing multicomponent reactions, and the chemical structures of the newly synthesized compounds were elucidated using analytical methods (IR, 1H NMR, and 13C NMR). Further, all the compounds were screened for their antioxidant activities.[17]

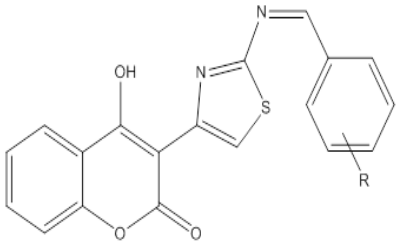


Figure 14: Synthesis of thiazolyl coumarin derivatives.

Shanmugavel Chinnathambi *et al.* (2018), had obtained the biologically active medication N-(diphenylmethyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide, a coumarin derivative, and human serum albumin (HSA) was examined through the use of computational methods and a variety of optical spectroscopic techniques. At three different temperatures (293 K, 298 K, and 303 K), the binding constant (K) and thermodynamical parameters of enthalpy change (ΔH°), entropy change (ΔS°), and Gibbs free energy change (ΔG°) were computed. Additional time-resolved

emission spectroscopy (TRES) investigations between the free HSA and the HSA-coumarin complex were conducted, and the findings validated the drug's presence in the protein molecule without causing cytotoxicity.[18]

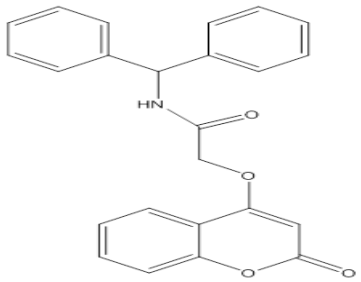


Figure 15: *N*-benzhydryl-2-((2-oxochroman-4-yl) oxy)acetamide.

Giancarlo Cravotto *et al.* (2006), many new 3-acyl derivatives were prepared by reacting 4-hydroxycoumarin with long-chain acyl chlorides. Their structures and activities against Propionibacterium acnes ATCC 11827, Staphylococcus aureus ATCC 6538, and Staphylococcus epidermidis ATCC 12228 were investigated. Enolic tautomers of a tricarbonyl methane group with a lipophilic side chain (under-10-enoyl, undec-10-ynoyl, palmitoyl, or octadec-9-enoyl) were linked to antibacterial activity. Similar action was demonstrated by a recently synthesized 2-acyl derivative of 2H-indene-1,3-dione that had the same tricarbonylmethane motif.[19]

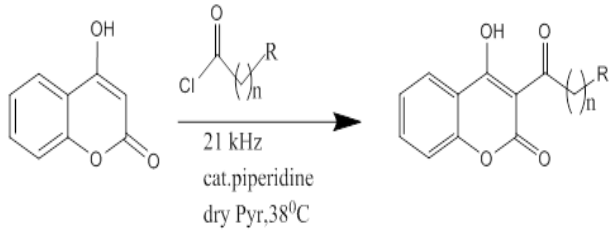
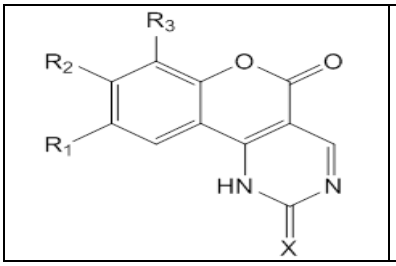


Figure 16: General procedure for the preparation of 3-acyl-4- hydroxy coumarins.

Shirodkar JM *et al*. (2002), 4-Hydroxy-2*H*-2-oxo-3-methylidene-urea [1]benzopyrans, 4-hydroxy-2*H*-2-oxo-3-methylidene-thiourea[1]benzopyrans 4-hydroxy-2*H*-2-oxo-3-methylideneguanidine[1]benzopyrans are obtained from on treatment with urea, thiourea, and guanidine respectively in ethanol-acetic acid. Compounds on heating with P_2O_5 give 1, 2-dihydro-5*H*-2, 5-dioxo[1]benzopyrano [4,3-*d*] pyrimidines, 1, 2-dihydro-5*H*-2-thio-5-oxo[1]benzopyrano [4,3-*d*] pyrimidines, and 1, 2-dihydro-5*H*-2-imino-5-oxo[1] benzopyrano [4,3-*d*] pyrimidines. 1*H*, 4*H*-4-Oxo-benzopyrano pyrazoles, 4*H*-4-oxo-1-phenyl-benzopyrano[4,3-*c*]pyrazoles, 4*H*-4-oxo-benzopyrano[3, 4-*c*]isoxozoles, 3-benzamido-2, 5-dioxopyrano [3,2-*c*]benzopyrans and 3-acetamido-2, 5-dioxo-pyrano[3,2-*c*] benzopyrans are obtained by refluxing with hydrazine hydrate, phenylhydrazine, hydroxylamine hydrochloride, hippuric acid and N-acetyl glycine, respectively in ethanol-acetic acid solution.[20]



Compound	R_1	R_2	R_3	X
a	H	H	H	O
b	CH_3	H	H	O
c	H	CH_3	H	O
d	H	H	CH_3	O

Figure 17: Derivatives of the 2-Dihydro-5*H*-2,5-dioxop[1]benzopyrano[4,3-d]pyrimidines.

Stanchev S *et al* (2011), synthesized six novel 4-hydroxycoumarin derivatives that were rationally synthesized, verified, and characterized by molecular docking using crystal HIV-1 protease. Molecular docking studies predicted antiprotease activity. The most significant functional groups, responsible for the interaction with HIV-1 protease by hydrogen bond formation are pyran oxygen, atom, lactone carbonyl oxygen, and one of the hydroxyl groups. The newly synthesized compounds were biologically tested in MT-4 cells for inhibiting HIV-1 replication, exploring the protection of cells from the cytopathic effect of HIV measured by cell survival in the MTT test. One derivative -7 showed 76-78% inhibition of virus infectivity with IC (50) = 0.01 nM, much less than the maximal nontoxic concentration (1 mM). Antiprotease activity of 7 in two different concentrations was detected to be 25%. Nevertheless, the results of the study (7) encourage using it as a pharmacophore for further synthesis and evaluation of anti-HIV activity.[21]

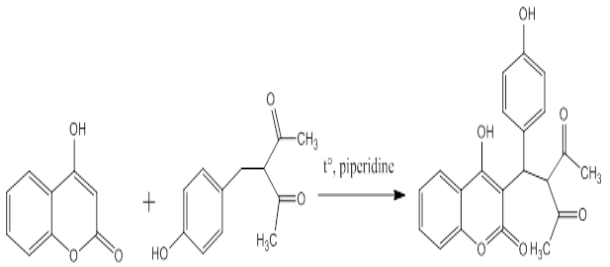


Figure 18: The Michael addition of 4-hydroxycoumarin and 3-(4-hydroxy) phenylmethylene-2,4-pentanedione.

Nenad Vukovic *et al.* (2009), A series of imino and amino derivatives of 4-hydroxycoumarin were synthesized and evaluated for antioxidant potential,

through different in vitro models such as (DPPH) free radical-scavenging activity, linoleic acid emulsion model system, reducing power assay and phosphomolybdenum method. Also, the antimicrobial activity of obtained coumarins was evaluated against 13 bacteria and eight fungi. All prepared compounds possessed good antioxidant activity and among them, a p-nitrophenol derivative with IC50 at 25.9 lM possessed radical-scavenging activity which was comparable to BHT. Observed data for antibacterial activity indicated strong activity of all tested amino derivatives, while imines showed better antifungal properties.[22]

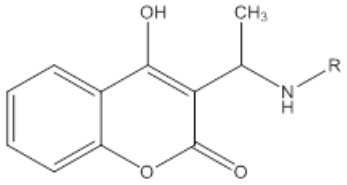


Figure 19: Synthesis of Imino and Amino derivatives of 4-hydroxy coumarins.

T Patonay *et al*. (1984), had synthesized 3-Acylamino-, -arylsulfonylamino-, -(N'-arylureido)-, -arylideneamino- and -arylcarbamoyl-4-hydroxycoumarins have been synthesized and tested for antibacterial and antifungal activity. 3-Arylcarbamoyl-4-hydroxycoumarins have been shown to possess significant activity against Gram-positive bacteria; 3-acylamino-4-hydroxycoumarins have moderate antibacterial and antifungal effects whereas the additional compounds are inactive.[23]

Sergio A. Rodríguez *et al*. (2011), The antioxidant activity of 4-hydroxycoumarin synthetic derivatives and 4-methylumbelliferone was determined by taking 4-hydroxycoumarin as the reference compound. Six 3-aryl-4-hydroxycoumarin derivatives were synthesised from 4-hydroxycoumarin as a precursor to evaluating changes in their antioxidant properties due to their C3-aryl substituent nature. The free radical scavenging capacities of these compounds against two different species, DPPHradical dot and ABTSradical dot+, and their protecting ability towards the β-carotene-linoleic acid co-oxidation enzymatically induced by lipoxygenase were measured. In addition, the relationship between the activities of these molecules against DPPH radicals and the bond dissociation energy of O-H (BDE) calculated using methods of computational chemistry was evaluated.[24]

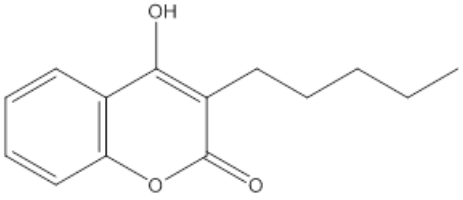


Figure 20: 3-aryl-4-hydroxycoumarin.

Saleem A *et al* (2020), obtained a new series of 4-hydroxycoumarin derivatives that exhibit a wide range of pharmacological uses. This study reports the synthesis of a new series of 4-hydroxycoumarin derivatives synthesised by Knovenegal condensation; FT-IR, NMR, and UV-Vis spectroscopies were used to characterise the compounds. The antibacterial activity of the synthesised compounds was assessed against strains of Salmonella typhimuriusm and Staphylococcus aureus. The compounds showed favourable antibacterial activity with a zone of inhibition of 26.5± 0.84, 26.0± 0.56, and 26.0± 0.26 against *Staphylococcus aureus* (ram-positive), respectively. However, the two compounds were found to be more active, with 19.5 ± 0.59 and 19.5 ± 0.32 zones of inhibition against *Salmonella typhimurium* (gramme-negative). Whereas, in the urease inhibition assay, none of the synthesized derivatives showed significant anti-urease activity, although, in the carbonic anhydrase-II inhibition assay, the compounds showed enzyme inhibition activity with IC_{50} values of 263±0.3 and 456±0.1, respectively.[25]

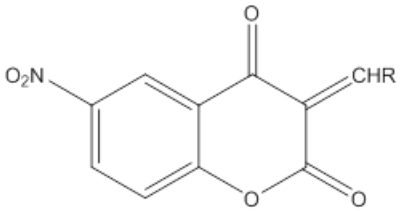


Figure 21: General synthetic route for 4-Hydroxycoumarin derivatives.

CONCLUSION

The biological significance of 4-hydroxycoumarin and its many derivatives exhibit a range of biological activities including anti-microbial, anti-bacterial, anti-HIV, anti-TB, anti-oxidant, and other activities. This data indicates that further research and screening should be done on the 4-hydroxycoumarin moiety.

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