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Review Article

# AN INSIGHT TO THERAPEUTIC POTENTIAL OF COUMARINS AS ANTIVIRAL AGENTS

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**ABSTRACT**

Coumarin compounds also known as benzopyran-2-one.Coumarins are made up of a bicycle system, which contains an alpha-pyrone ring and a cooled benzene. Many center patterns appear on the central bicycle system, it alters a variety of biological effects and a number of medicinal and therapeutic properties have been attributed to natural product coumarin. Antivirals are the type of drugs used to treat viral infections as well as bacterial infections. Most antiviral drugs are used for specific virus infections in a broad spectrum of antivirals effective against a wide range of virus. Coumarins has increased significantly recently as it is found in the prevention of HIV (human immunodeficiency virus). It affects the integration and reverse transcriptase and plays a crucial role in the cycle of HIV replication. Gone were the days of focusing on the study of antiviral activity of assay for coumarin derivatives. Natural products have been used to treat viral infections for 1000 years and play a greater role in drug discovery and development. Plant semisynthetic calanolide compounds and semisynthetic in invitro activity against human HIV 1and cytomegalovirus and have been shown to be a naturally occurring non-nucleoside transmerase inhibitor. The reverse transcriptase is an established target for chemotherapeutic agents used for the treatment of HIV infections. These coumarins represent a distinct class of non-nucleoside reverse transcriptase inhibitors. The herbal medicines are commonly used as an alternative medicine by individuals living with HIV. In this review we aim to review the antiviral potential of coumarin as HIV defenders.

**Keywords**: Bioavailability, Pharmacokinetic, Interpretation, Metabolites.

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## INTRODUCTION

Coumarins are the chemical compounds. It occurs in many natural products with pharmacological activity. E.g. wedel lactone, Ellagic acid, Geiparvaine (its naturally occurring compound) [1]. Natural compounds Coumarin are known as benzopyran-2-one.Coumarins is used in food chemicals, perfumes, agrochemicals, cosmetics etc [2].

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Coumarins and its derivatives synthesized by various method like Pechmann, Perkin, Knoevenagel &Wittig reaction [1]. Synthetic coumarins are obtained by structural modification. Substitution can conceptually occur at six available sites of the basic molecule. Coumarins contain wide varieties in structure and activity [4].

Coumarins are obtained by natural compounds (1-benzopyran-2-one). Coumarins done in an identification test for different natural source. The coumarins done in structural modifications in several factors. Identification of Coumarins has done a different test in natural compounds. Coumarins are studied by biological properties and pharmacological properties, biochemical properties, etc. Several biological parameters

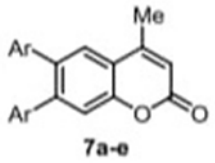
should be evaluated for increase our understanding of mechanism [5].

Coumarins and its derivatives contain different types of substitutions in the basic structure of coumarin and it can effect in the biological activity. Coumarins contain a remarkable array of biochemical and pharmacological actions. Some of which suggest that certain members of this group of compounds may significantly affect the function of various mammalian cellular system [5]. Synthesis of coumarin and its derivatives have received an enhancing attention to synthetic organic chemists and biologist. Coumarin compounds also called as benzopyran-2-one.Coumarins are consists of a bicyclic system, contain fused alpha – pyrone and benzene ring. Many substitution patterns occur on the central bicyclic system, it alters the variety of biological effects and various pharmacological and potential therapeutic properties have been attributed to natural product coumarin.

Antivirals are the class of drugs used the treatment of viral infections other than bacterial infection. Most antiviral drugs are used for specific viral infection in broad spectrum antiviral is effective against a wide range of virus .Most of the antiviral drugs are considered relatively harmless to the host and there for can be used to treat viral infections. It should be distinguished from viricide. This is not a medication but deactivates or destroys virus particles either inside or outside the body [3]. Natural antivirals are obtained by some plants such as eucalyptus and Australian tea tree [2].

Natural and synthetic coumarins (2H-1-benzopyran-2-ones) and their derivatives are endowed with excellent chemical reactivity and different bioactivity [3]. The natural coumarins are play in an important role in plant biochemistry and physiology. Coumarins act as an antioxidant, enzyme inhibitors, and precursor of toxic substances, anticancer, antiviral, antifungal, anti-proliferative, anti-psoriasis, anti-inflammatory, as well as antiviral activity. Coumarins have recently increased significantly because it is found in inhibit HIV (human immunodeficiency virus). It affecting integrates and reverse transcriptase and play a critical role in the replicative cycle of HIV. Now days focused the study of antiviral activity of evaluation for coumarin derivatives [4]. Natural products are used to treat viral diseases for 1000 of years and play in an increasingly critical role in drug discovery and development[8]. Varieties of coumarin based on the natural and synthetic derivatives display a wide range of biological activities like anticancer, antioxidant, anti-inflammatory, antimicrobial efficacies and as well as antiviral activity [3]. To give a compound with higher anti-spring viraemia of carp virus activity a new benzimidazole coumarin derivative [2]. Coumarins and coumarin derivatives especially bicoumarins are widely spread in a nature [7]. These biological properties are known and it contains anticoagulant, spasmolytic, antitumor, antioxidant, and anti HIV effect [4]. Structurally novel coumarin derivatives are reported to demonstrate anti-HIV activity in vitro and in vivo. Plant derived and semisynthetic calanolide compound are exist in invitro activity against HIV 1and human cytomegalovirus and proven to be a naturally occurring non-nucleoside reverse transcriptase inhibitor. The reverse transcriptase is well established target for chemotherapeutic agents used to treat HIV infections. These coumarins represent a unique class of non-nucleoside reverse transcriptase inhibitors. The herbal medicines are frequently used as an alternative therapy by individuals living with HIV[7].

Aws M. et al. Discovered that 4-methyl-6,7-dihydroxycoumarin was selected as the key intermediate for the synthesis of new coumarin analogs. Thus, treatment of the scaffold with trifluoromethane (2.4 equivalents) in the presence of Et 3 N (4.0 equivalents) at -78 ° C gave the bis (triflate) 5 in 75% yield. The reaction of 5 with arylboronic acids (2.2 equiv.) Via the Suzuki-Miyaura reaction gave 4-methyl-6,7-diarylcouarin 7a-e in 70-88% yield. Both electron-poor and electron-rich arylboronic acids have been used successfully. The best yields were obtained using Pd (PPh 3) 4 (6 mol%) as a catalyst and K 3 PO 4 (3.0 equivalents) as a base in dioxane at 120 ° C for 6 hours based on their 1H and 13C -NMR and mass spectra obtained. In the 1H NMR spectra, H-3 of the coumarin ring appeared as a doublet in the regions δ 6.37 - 6.22 ppm (JCH3, H3 ~ 1.2 Hz), while methyl groups on C-4 in region δ 2, 41 - 2.38 ppm also appeared as reverberant duplicates. H-5 and H-8 protons appeared as broad singlets in the regions δ 7.53-7.41 and δ 7.59-7.27 ppm, respectively. The other protons of the aromatic, methoxy and other methyl groups were completely analyzed (see Experimental). The 13C NMR spectra of 7a-e contained similar resonance signals from the coumarin carbon ring C-2 - C-8a. The higher field signals between δC 160.9 and 158.2 ppm were assigned to the carbonyl group of the benzopyran ring (C-2), while the resonances in the ranges from δC 115.1 and 112.4 ppm were assigned to C-3. The ranges δC 154.4-151.4 and 152.5-150.5 ppm were assigned to C-4 and C-8a, respectively. The resonances at δC 141.7-137.1 and δC 118.5-110.9 ppm were assigned to the coumarin carbons C-7 and C-8, respectively. The C-4a carbon atom appeared between δC 120.1 and 117.6 ppm, except for 5, which resonated at δC 112.7 ppm. The resonances in the ranges δC 126.4-125.1 ppm were assigned to C-5, C-6 and carbons of the aromatic ring, while the methyl groups at C-4 occurred in the range δC 20.3-17.6 ppm. The carbon atom of the CF3 group of 5 appeared as a doublet at δC 117.9 ppm

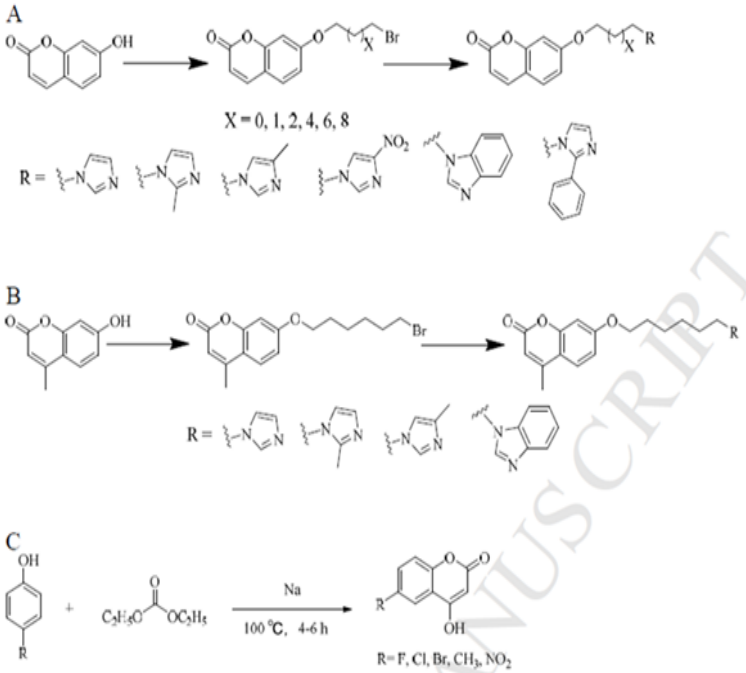



7a-e

| 6,7 | Ar | 7 (%)[a] |
|---|---|---|
| a | 3,5-$(Me)_2C_6H_3$ | 75 |
| b | 4-$MeOC_6H_4$ | 83 |
| c | 4-$ClC_6H_4$ | 83 |
| d | $C_6H_5$ | 70 |
| e | 4-$EtOC_6H_4$ | 88 |

He reported on a new synthesis of arylated coumarins through site-selective Suzuki Miyaura cross-coupling. The synthesized compounds were evaluated for their in vitro anti-HIV inhibitory activity. The derivative shows considerable activity and can be seen as a lead structure for further investigations. However, the selectivity and activity have so far not been sufficient to carry out mode of action studies, which will be carried out in future studies together with additional screening experiments [1].

Lei Liu et al. Examined 44 derivatives synthesized by substitution reaction, Williamson etherification reaction, and Fries rearrangement using three coumarins as the starting material. The details are described in the additional materials and methods available online. Based on these reactions, the yield of each intermediate or final product ranged from 60% to 75%. All intermediates and products were identified by EI-MS, 1 H-NMR and 13 C-NMR. Stock solutions were prepared at a concentration of 50 mg / ml in dimethyl sulfoxide (DMSO) and stored at -20 ° C during the experiment. Due to the structural changes that affect the solubility of these derivatives, the medium containing each compound was sonicated for approximately 10 minutes to ensure that the compounds were completely dissolved and mixed.



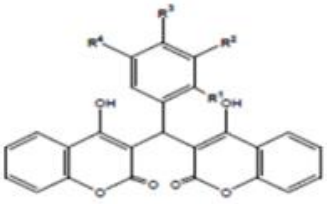

A number of coumarin derivatives were synthesized and tested for their antiviral activity against SVCV (spring virus of the carp virus) in EPC cells. Two coumarin-imidazole hybrid derivatives B4 and C2 were selected from 14 coumarins screened and considered effective anti-SVCV drugs. The results suggest that coumarin B4 and C2 inhibit SVCV by activating the Nrf-2 pathway. It is important that the compound structure can be optimized to improve drug efficacy and reduce toxicity based on a structure-activity relationship analysis in future studies [2].

Yu-Feng Shen et al. Introduced a new benzimidazole coumarin derivative, 7- (4-benzimidazole butoxy) coumarin (BBC), to give a compound with higher anti-SVCV activity this study. As expected, quantitative real-time PCR (RT qPCR) found that BBC in EPC cells showed higher anti-SVCV activity than our previously described imidazole coumarins. Secondary assays, including cytopathic effects (CPE) reduction assays, microtubule structure and nuclear damage test, were used to confirm BBC's anti-SVCV activity in EPC cells. In addition, the anti-SVCV activity of BBC in zebrafish was assessed by RTqPCR, titer assay and survival rate assay.

To find out how BBC protects zebrafish from SVCV infections, the effects of BBC on interferon (IFN) response and antioxidant enzyme activity were also examined. A new coumarin derivative, BBC, was designed, synthesized and its anti-SVCV activity was evaluated. This study demonstrated that BBC plays a positive role in anti-SVCV activity in EPC cells and zebrafish. In addition, BBC treatment can activate the IFN response, maintain the redox balance, and then reduce zebrafish morale. Overall, BBC is considered a new compound with high antiviral activity against SVCV and is expected to be a therapeutic agent against SVCV infections in aquaculture [3].

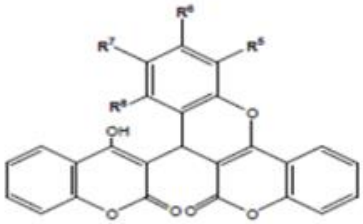
Davorka Zavrsnik et al. Discovered the benzylidene bis (4-hydroxycoumarin) derivatives 1–15 and the condensed benzopyrancumarin derivatives 16–20 following a reaction sequence shown in Scheme 1. In the first synthesis step, the aldol condensation of 4-hydroxycoumarin (4-HC) with an appropriately substituted aldehyde linker and subsequent dehydration of the aldol product (AL) resulted in a chromon (CR). The subsequent in situ reaction of the chromone with excess 4-hydroxycoumarin already present in the reaction mixture gave dimeric coumarin derivatives 1-15 with an aryl substituent in the central methylene linker. In contrast, the chromone derivatives, which contained an ortho-substituted phenyl moiety (R 1 = Cl, F, OH, OCH 3), gave the condensed benzopyranocoumarin with spontaneous cyclization [4].

a)

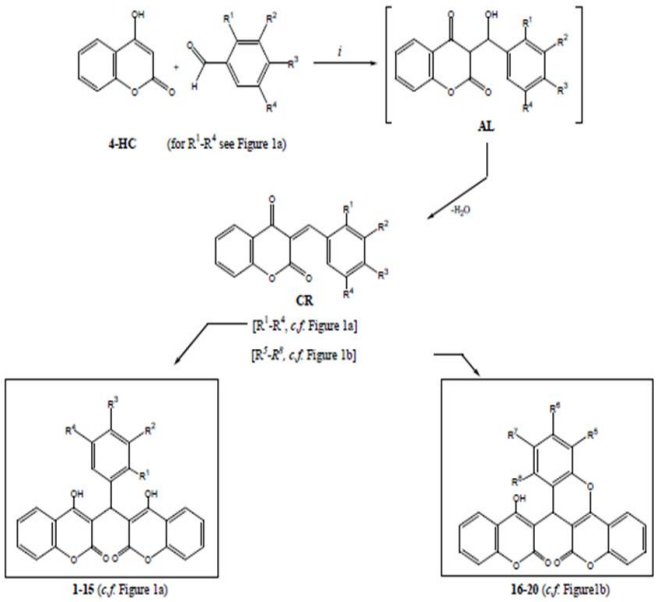


| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $R^1$ | H | H | H | H | $OCH_3$ | H | H | H | $NO_2$ | H | H | H | H | $OCH_3$ | H |
| $R^2$ | H | H | Br | H | H | H | H | H | H | H | H | H | OH | H | $OCH_3$ |
| $R^3$ | H | Br | H | Cl | H | F | $CF_3$ | $NO_2$ | H | $OCH_3$ | $SCH_3$ | $N(CH_3)_2$ | OH | H | OH |
| $R^4$ | H | H | H | H | H | H | H | H | H | H | H | H | H | $OCH_3$ | $NO_2$ |

b)



| | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|
| $R^5$ | H | H | $OCH_3$ | H | H |
| $R^6$ | H | H | H | H | $OCH_3$ |
| $R^7$ | H | Br | H | $NO_2$ | H |
| $R^8$ | H | H | H | H | $OCH_3$ |




Scheme 1. Synthesis of coumarin-dimer derivatives with differently substituted aryl central links (1–15) and fused benzopyranocoumarin derivatives 16–20. Reagents and conditions: (i) EtOH, reflux for 24 h.

A number of the benzylidene bis (4-hydroxycoumarin) derivatives 1-15 and the fused benzopyranocoumarin derivatives 16-20 were synthesized and tested for their antiviral activity on a wide range of DNA and RNA viruses. X-ray crystal structure analysis of 4-trifluoromethylphenyl and 2-nitrophenyl derivatives 7 and 9 revealed intramolecular hydrogen bonds between hydroxyl and carbonyl oxygen atoms of two 4-hydroxycoumarin units, which led to the formation of two eight-membered rings. Accordingly, two 4-hydroxycoumarin units in compounds 7 and 9 are anti-disposed. The 4-bromobenzylidene derivative of bis (4-hydroxycoumarin) (3) exerted some inhibitory activity against HSV-1 (KOS), HSV-2 (G), vaccinia virus and HSV-1 TK-KOS (ACVr) in the range of 9 -12 μM at a minimum cytotoxic concentration (MCC) of more than 20 μM, whereas compounds 4–6, 8 and 20 had a fairly pronounced anti-feline herpes virus activity (EC50 = 5–8.1 μM) , but at only 4 7 MCC times higher than EC50 values [4].

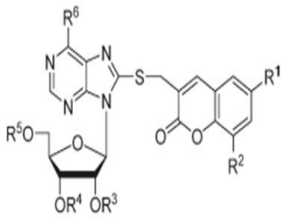
Dr. Rangappa et al. Investigated natural, synthetic and semi-synthetic heterocyclic compounds that play an important role in drug discovery and chemical biology. The heterocycles belong mainly to the classes of alkaloids, flavones, isoflavones, chromanes, chromones, coumarins and chromenes. Synthetic compounds of these classes show different biological activity. It has been found that oxygen-containing heterocyclic compounds play an important role in the development of new classes of structural elements for medical applications. Among the oxygen heterocyclic compounds, coumarin (2H-chromen-2-one or 2H-1-benzopyran-2-one) and its derivatives are important due to their wide range of biological activities. A number of coumarin derivatives have been isolated from various plant sources in recent years and their extracts are used as traditional medicines. These are naturally occurring lactones and are also used as perfume and food flavorings. The first time that parent coumarin was isolated from tonka beans by Vogel in 1820. The coumarin ring can be viewed as the result of the fusion of a pyrone ring with a benzene nucleus. Coumarin numbering begins with the ring oxygen, i.e. H. Oxygen gets position-1, carbonyl-carbon-2 and rotates counterclockwise with the ring [5].

Ilia Manolov et al., Who studied a large number of structurally new coumarin derivatives, were reported to show anti-HIV activity in vitro and in vivo. Herbal and semi-synthetic calanolide compounds have shown activity in vitro against HIV-1 and the human cytomegalovirus and have been shown to be a naturally occurring non-nucleoside reverse transcriptase (RT inhibitor). Tipravirin, a new HIV-1 protease inhibitor, was developed from a non-peptide coumarin template [6].

Mazumder et al. Found antiviral, antiprotease, and anti-integrase activities when testing the effects of several HIV-1 protease inhibitors containing 4-hydroxycoumarin residues. Coumarin and a number of derivatives, including warfarin (W), have been reported to have a cytotoxic effect on tumor cell growth and metastasis spread. Here we present the coordination ability of 4-hydroxy-3- (3-oxo-1-phenylbutyl) -2H-1-benzopyran-2-one (warfarin) (W) and 3,3_-benzylidenebis [4-hydroxycoumarin] at the Complexation reaction with Ce (cer), La (lanthanum) and Nd (neodymium). An increased anti-HIV activity of La (W) (IC 50 = 21.4 μM) compared to (W) (7.1% inhibition at

maximum non-toxic concentration - MNC) was shown. Further studies have shown that the anti-HIV effectiveness of Nd (W), Ce and Nd is limited. Therefore, none of the complexes appear to be suitable for entering clinical trials. Studies clearly showed that HIV-1 RT and protease were not the targets of antiviral activity for all complexes [7].

Jih Ru Hwu et al., Who are investigating some purine ribofuranosides, have anti-HCV activity (hepatitis C virus). Intended to produce the mono- and bisribofuranoside derivatives shown in Scheme 1 for biological testing. Silylation of purine-8-thione (2) with bis (trimethylsilylacetamide (BTSA) followed by the addition of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose at 80 ° C provided the desired mono -N -9 nucleoside 3 and the by-product bis (ribofuranosyl) purine-8-thione 4 (Scheme 1). For the monoglycosylation product v21, we only isolated the N-9 isomer (instead of the N-7 isomer) Preparation of 3 was attributed to the use of the Vorbrüggen method22 using the Lewis acid Me3SiOTf as a catalyst and under suitable conditions that favored the formation of more thermodynamically stable N-9 regioisomers. Somewhat surprisingly, these two compounds (i.e. 3 and 4) no significant anti-HCV activity.



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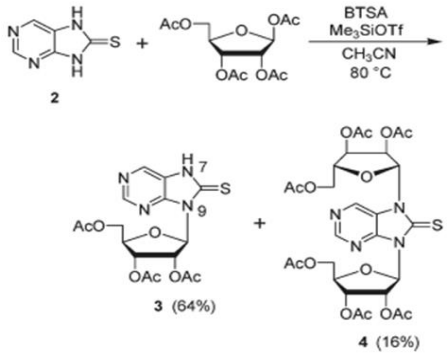
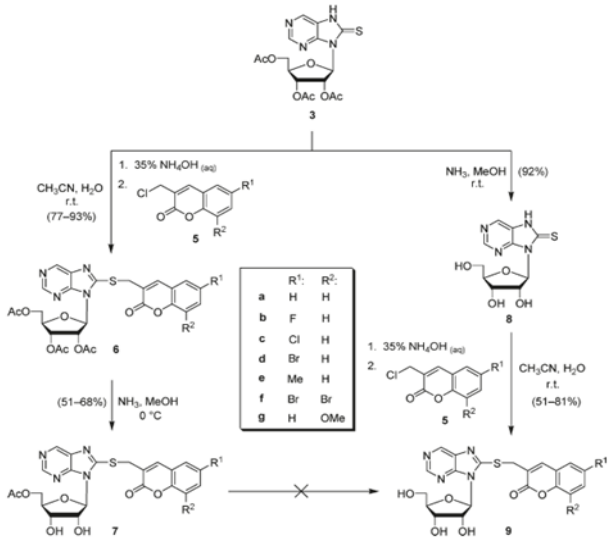
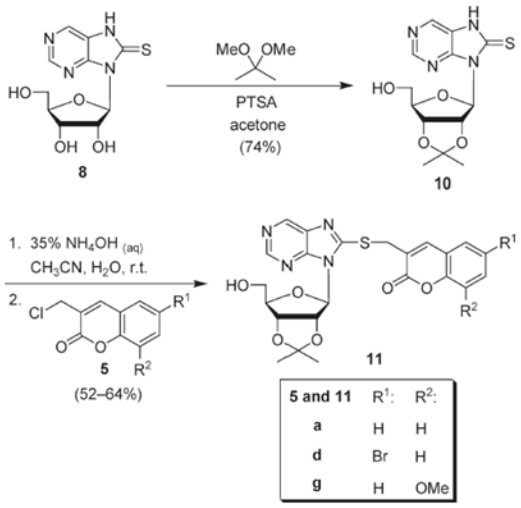
**Scheme 1. Coupling of Purine-8-thione (2) with a Polyacetyl β-D-Ribofuranose To Give Nucleosides 3 and 4**



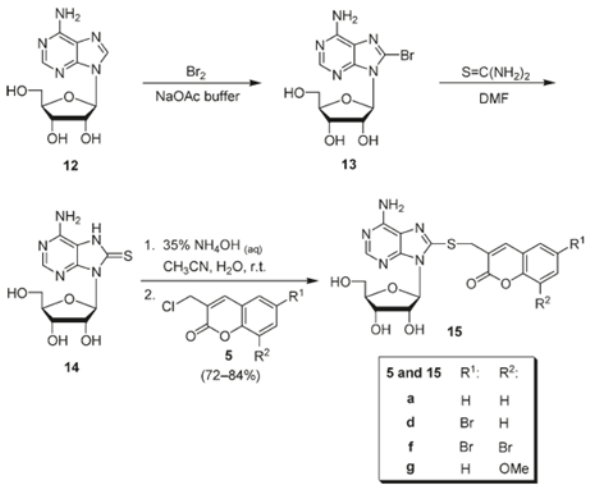

Scheme 2. Synthesis of conjugated coumarin-thiopurine nucleosides with the three hydroxyl groups that are complete, partial, or unprotected.



**Scheme 3. Synthesis of Acetalized Coumarin−Purine Ribofuranosides**




**Scheme 4. Synthesis of Conjugated Compounds of Coumarin−Adenosine Ribofuranosides**




A new compound library has been established through chemical synthesis; it contained 26 conjugates of coumarin-purine ribofuranosides with a -SCH2 linker. In order to establish the structural activity relationship with respect to its anti-HCV activity, the coumarin unit was allowed to have various substituents, including F, Cl, Br, Me and OMe. The purine unit can contain an amino group. The hydroxyl groups in ribofuranosides can be protected with an acyl or acetal group. Seven of the 26 new compounds inhibited HCV replication of the subgenomic replicon in the Huh 5-2 cell line. The most attractive results have been associated with conjugates 6a, 9a and 9f, which individually inhibited HCV replication at EC50 values of 6.6, 5.5 and 5.9 μM. In addition, guidelines were derived from the analysis of their structures and their anti-HCV activity. It is essential that the coumarin unit present in the conjugated compounds shows antiviral activity. This unit, which carries various substituents, can be linked to purine ribofuranosides in the C (8) position via a -SCH2 linker. The presence of a ribofuranose unit resulted in an increase in HCV inhibition, leaving the OH groups unmasked at all 20, 30 and 50 positions, leading to a reduction in their cytotoxicity. These guidelines will be of value to medical scientists to design and synthesize new conjugated compounds in the future [8].

## CONCLUSION

In this project, the anti-viral property of the Coumarin and their derivatives are being discussed briefly by thoroughly reviewing various journals, scientific thesis and articles published till recent. At the end we were able to conclude that the Coumarin nucleus does possess certain level of antiviral activity. A new synthesis of arylated coumarins by cross-coupling reaction Suzuki-Miyaura site selective. The synthesized compounds were evaluated for their anti-HIV inhibitory activity in vitro. Two derivatives show considerable activities and can be considered as main structures for future research. Series of coumarin derivatives synthesized and evaluated were designed to determine the antiviral efficacy against SVCV in EPC cells. Two hybrid coumarin-imidazole derivatives B4 and C2 were selected from 14 selected coumarin B4 and C2 that exerted the inhibitory effect on SVCV through activation of the Nrf-2 pathway. Importantly, the optimization of the structure of the compound can be performed to improve the potency of the drug and decrease the toxicity on analysis of the structure-activity relationship in future studies.

Our study provided evidence that the BBC(7-(4-benzimidazole-butoxy)-coumarin) played a positive role in the anti-SVCV effect in EPC(epithelioma papulosum Cyprinid) cells and zebrafish. In addition, BBC treatment can activate the IFN response, maintain the balance of the redox state and then reduce the morality of the zebrafish. In total, BBC (7- (4-benzimidazol-butoxy) -coumarin) is considered as a new compound with a high antiviral activity against SVCV and is expected to be a therapeutic agent against SVCV infection in aquaculture. A series of the benzylidene-bis series derivatives of (4-hydroxycoumarin) and the fused benzopyranocoumarin derivatives were synthesized and evaluated for their antiviral activities in a broad panel of DNA and RNA viruses. Analysis of the crystalline x-ray structure of 4-trifluoromethylphenyl and 2-nitrophenyl derivatives revealed an intramolecular hydrogen bond between the hydroxyl and carbonyl oxygen atoms of two 4-hydroxycoumarin residues, which resulted in the formation of two rings of eight members. Accordingly, two 4-hydroxycoumarin residues in are anti-eliminated.

The 4-bromobenzylidene derivative of bis (4-hydroxycoumarin) exerted some inhibitory activity against HSV-1 (KOS), HSV-2 (G), vaccinia virus and HSV-1 TK-KOS (ACVr) in the range 9-12 μM at a minimum cytotoxic concentration (CCM) greater than 20 μM, while compounds 4–6, 8 and 20 exhibited a fairly pronounced anti-feline herpes virus activity (EC50 = 5-8.1 μM) but with CCM only 4 -7 times higher than EC50 values.

A new library of compounds was established by chemical synthesis; It contained 26 conjugates of coumarin-purine ribofuranosides with a -SCH2- connector. For the establishment of the structure-activity relationship in its anti-HCV activity, the rest of coumarin was allowed to possess several substituents, including F, Cl, Br, Me and OMe. The purine moiety may contain an amino group. The hydroxyl groups in the ribofuranosides can be protected with an acyl or acetal group. It was found that seven of the 26 new compounds inhibited the replication of the HCV subgenomic replicon in the Huh 5-2 cell line. The most attractive results were associated with conjugates 6a, 9a and 9f, which inhibited HCV replication at EC50 values of 6.6, 5.5 and 5.9 μM, individually. In addition, the guidelines were deduced from the analysis of their structures and anti-HCV activity. It is essential that the rest of coumarin present in the conjugated compounds exhibit antiviral activity. This moiety carrying several substituents can be linked to purine ribofuranosides at position C (8) through a -SCH2 connector. The presence of a ribofuranose residue led to an increase in HCV inhibition, in which the -OH groups remained unmasked in all positions 20, 30 and 50 led to the reduction of their cytotoxicity. These guidelines will be valuable for medicinal scientists to design and synthesize new conjugated compounds in the future.

**AKNOWLEDGEMENT**

Nil

**CONFLICT OF INTEREST**

Nil

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