Pharmacological Potentiality of Coumarins as Anti-Viral Agent

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ABSTRACT *In recent times several fatal diseases that emerged as epidemic in various parts of the world are mainly caused by viruses like human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV), influenza, smallpox, viral haemorrhagic fevers (Ebola), dengue, and chikungunya etc. These viral diseases have been the reason for human death which may affect a country's social and economical status. Several organic compounds isolated from nature have proved their effectiveness as antiviral agents. The most important one in this area is organic compounds containing coumarin scaffold. Besides isolation from natural sources, several newly developed coumarin conjugates, synthesized in laboratories, have shown their potentiality in inhibiting several viral activities. This review article provides a comprehensive update of antiviral activities of both naturally occurring and chemically synthesized coumarins.*

Keywords: *Coumarin, Anti-Viral, Anti-HIV, Anti-HCV.*

1. Introduction

Heterocycles are indisputably the most significant structural motifs of a broad range of pharmaceuticals, agrochemicals, commodity chemicals and functional materials. Numerous organic compounds containing heterocyclic scaffold, whether isolated from nature or chemically synthesized have created a strong impact on the advancement of civilization. Of these gatherings, the most important and versatile is the coumarin and its derivatives due to their ample gamut of synthetic and pharmaceutical properties.[1]

Coumarin (2H-chromen-2-one or 2H-1-benzopyran-2-one) is a bicyclic heterocyclic compound and contains a unique structure where benzene ring is fused with □-pyrone ring. This rigid fused ring system in coumarin makes it a versatile scaffold with wide spectrum of pharmacological activities[1,2] of which antiviral activity of coumarin compounds is of prime interest in the arena of medicinal chemistry research. In recent years, there has also been a revolution in the synthetic and medicinal chemistry, mainly in the development of coumarin lead compounds as antiviral agent, either by functionalisation the coumarin scaffold or by tethering it with another pharmacopore.[2] Now, this active trend in designing of new compounds are primarily based upon the structure-activity relationship of naturally occurring coumarins and therefore an emphasis should be given on the study of coumarin compounds obtained from natural sources so that screening may result in the development of effective coumarin lead compounds of therapeutic potentiality.

Virus is a small infectious microorganism which replicates only inside the cell of other organisms. In the present world infections caused by numerous viruses have become a major threat to human health. Among the different diseases the most importants are influenza, hepatitis and AIDS (acquired immune deficiency syndrome) caused by influenza virus, hepatitis virus (*e.g*. hepatitis C virus, HCV) and human immunodeficiency virus (HIV). The treatments of viral diseases involve the inhibition of replication of viruses. However there is always a need of proper antiviral agents for direct destruction of virus without damaging the host cell and this has motivated researchers to search for new antiviral agents. Several compounds isolated from nature have been examined as antiviral agents [4] and among them coumarin derivatives have exhibited their therapeutic potentiality in inhibiting several viral infections. Eextensive researches are going on to search for new coumarin compounds whether from natural sources or chemically synthesized with better drug action and low toxicity. Several review articles have covered antiviral activities of different coumarin compounds with an emphasis on antiviral activities of synthetic coumarins.[2] In this review article antiviral activities of several naturally occuring coumarins along with chemically synthesized modified coumarins have been systematically summarised with the expectation that this review will be a helpful guide for future development of coumarin compounds with broad applicability in the development of anti-viral agents.

2. Anti-viral Activities of Natural Coumarins:

Several naturally occuring coumarins have shown potentiality to act as antiviral agents. Different types of naturally occuring coumarins with their natural sources showing antiviral activity are listed in Table **1**.

Table 1: Examples of Naturally occuring coumarins with Anti-HIV Activities

Entry	Anti-Viral Activity	Compound Name (No.)	Natural Occurance
A	Anti-HIV	Glycylcoumarin (**1**)	*Xi-bei licorice, Glycyrrhiza uralensis*
		Licopyranocoumarin (**2**)	*Xi-bei licorice*
		Suksdorfin (**3**)	*Lomatium suksdorfii*
		Oxypeucedanin (**4**),	*Angelica apaensis, Ferula sumbul*
		Oxypeucedanin hydrate (**5**)	*Angelica apaensis, Ferula sumbul*
		Isoimperatorin (**6**)	*Angelica apaensis*
		Byakangelicol (**7**)	*Angelica apaensis*
		Byakangelicin (**8**)	*Angelica apaensis*
		Mesuol (**9**)	*Marila pluricostata*
		Isomesuol (**10**)	*Marila pluricostata*
		Heraclenol (**11**),	*Ferula sumbul*
		Pranferol (**12**)	*Ferula sumbul*
		Xanthotoxin (**13**)	*Ferula sumbul*
		Psoralen (**14**)	*Prangos tschimganica*
		Saxalin (**15**)	*Prangos tschimganica*
		Bergapten (**16**)	*Prangos tschimganica*
		Calanolide (+)-Calanolide A (**17**)	*Calophyllum inophyllum Linn*
		(+)-Calanolide B (**18**)	
		(+)-Dehydrocalanolide A (**21**)	
		Soullatrilide (**22**)	
		Inophyllums Inophyllums B (**19**)	Calophyllum inophyllum Linn
		Inophyllums P (**20**)	
B	Anti-HCV	Wedelolactone (**23**),	*Wedelia calendulacea,*
		Glycyrin (**24**)	*Glycyrrhiza uralensis*
		Glycyrol (**25**)	*Glycyrrhiza uralensis*
		Chalepin (**26**)	*Ruta angustifolia Pres.*
C	Anti-DENV and Anti-CHIKV	Coumarin A (**27**) and B (**28**)	*Mammea americana*
D	Anti-human influenza	Eleutheroside B1 (**29**)	*Sarcandra glabra*

2.1 Anti-HIV Activities:

Natural coumarins substituted with hydroxyl group, methoxyl group, phenyl, prenyl group or fused with furan and pyran ring in a linear or angular pattern have exhibited this activity (Figure **1** and **2**). In 1988, Okuda *et al*. reported that two coumarins, glycylcoumarin (**1**) and licopyranocoumarin (**2**) isolated from *Xi-bei licorice*, inhibited cytopathic activity of HIV in the OKM-1 cell line without noticiable cytotoxicity.[5]

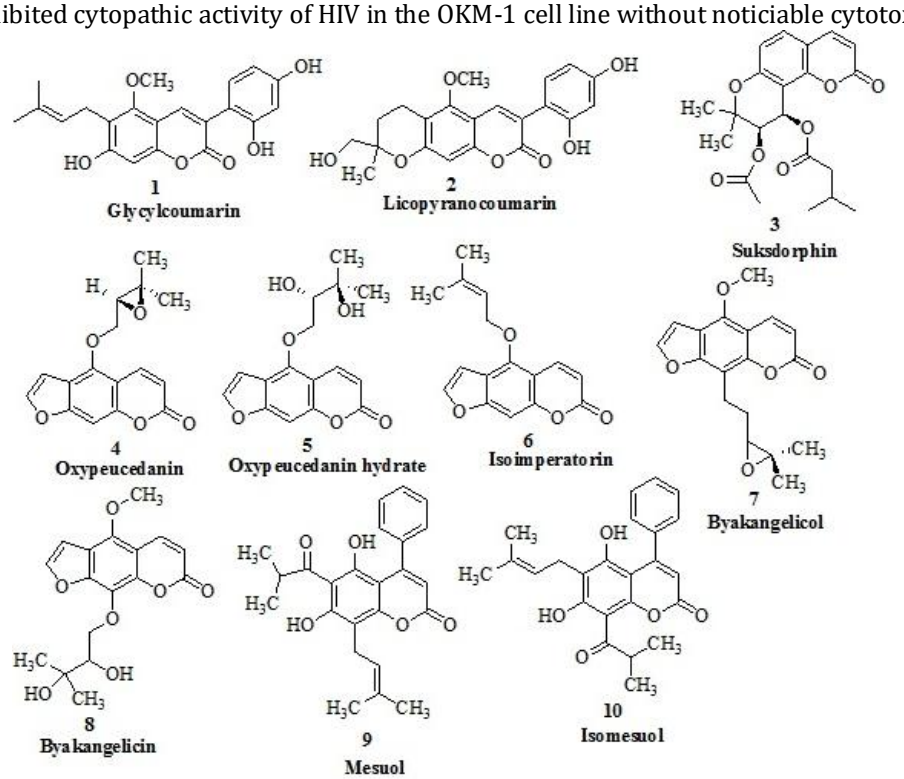


Figure 1: Naturally occuring coumarins with anti-HIV activity

A dihydroseselin type angular pyranocoumarin, suksdorfin (**3**), one member of Khellactone coumarins, isolated from *Lomatium suksdorfii* through a bioactivity-directed fractionation is a novel new class of anti-HIV agent, structurally different from commercially available anti-HIV drugs.[6] This compound exhibited the potentiality to act as anti HIV agent by suppressing viral replication in eleven separate acute HIV-1 infections of H9 lymphocyte cells (average EC_{50} value of 2.6-2.1 □M) along with the suppression of acute HIV-1 infections in fresh peripheral blood mononuclear cells, monocyte/macrophages, and U937 cells, a promonocytic cell line. Gu *et al.* reported that oxypeucedanin (**4**)**,** oxypeucedanin hydrate **(5),** isoimperatorin (**6**)**,** byakangelicol (**7**) and byakangelicin (**8**) extracted from *Angelica apaensis*, exhibited anti-HIV activity. Among these, substantial inhibitory effect against HIV-1virus was demonstrated by oxypeucedanin (**4**).[7] However the quantitative structure activity relationship (QSAR) studies revealed that the epoxy group at the C-5 position of oxypeucedanin **(4)** might be responsible for the maximum inhibitory.

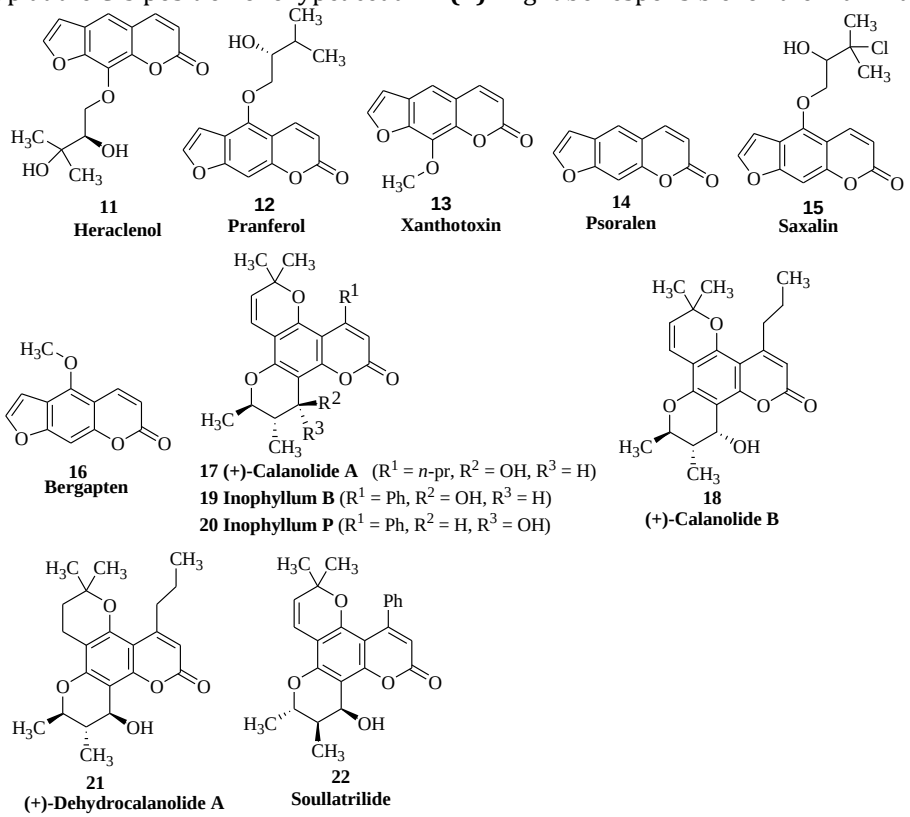


Figure 2: Anti-HIV active naturally occuring coumarins

Coumarin scaffold containing a phenyl moiety at the C-4 position have been observed to exhibit anti-HIV activity. For Example, Marquez *et al*. demonstrated that mesuol (**9**) and isomesuol (**10**), two 4-phenyl coumarins isolated from *Marila pluricostata*, were found to suppress HIV-1 replication in Jurkat T cells without affecting the reverse transcription and integration steps of the viral cell cycle.[8] Again, they also reported that these two compounds targeted the nuclear factor-KB (NF-KB) by inhibiting its phosphorylation and transcriptional activity. Further, Takaishi and co-worker reported that among the several coumarins isolated from dried roots of *Ferula sumbul*, oxypeucedanin (**4**), oxypeucedanin hydrate (**5**), heraclenol (**11**), pranferol (**12**) and xanthotoxin (**13**) were reported to have anti-HIV activity with therapeutic index (TI) value greater than 5.[9] The inhibition of HIV-1 replication were also exhibited by structurally similar coumarins, psoralen (**14**), saxalin (**15**), and bergapten (**16**).[10]

Different tetracyclic coumarins isolated from nature also exhibits HIV inhibitory activity. Boyd and co-worker was the first to discover the presence of eight chiral tetracyclic pyranocoumarins isolated by anti-HIV bioassay-guided fractionation of an extract of *Calophyllum lanigerum*.[11] They also reported that among the eight pyranocoumarins, (+)-Calanolide A (**17**) and (+)-Calanolide B (**18**) were completely protective against HIV-1 replication and cytopathicity (EC_{50} values of 0.1 □M and 0.4 □M, respectively), but were inactive against HIV-2. Later the inophyllum B and P (**19** and **20**) isolated from *Calophyllum inophyllum Linn*, a known source of nutrition for *A. fulica* inhibited HIV reverse transcriptase with IC_{50} values of 38 and 130 □M, respectively, and both were active against HIV-1 in cell culture (IC_{50} 1.4 and 1.6 □M).[12] Again natural

coumarins, (+)-dihydrocalanolide A (**21**) also posses anti HIV activity similar to (+)-Calanolide A.[13] Another interesting feature of (+)-Calanolide A and (+)-dihydrocalanolide A is that these two compounds shows their effectiveness at neutral pH. Another 4-phenyl coumarin, Soullatrilide (**22**), isolated from *Calophyllum ionophyllum* has also exhibited potent anti-HIV activity.[4a]

2.2 Anti-HCV Activities:

Hepatitis C virus (HCV) infection is highly prevalent among global populations. Medicinal plants are promising sources for antiviral agents against HCV virus.[4c] Among the different natural products, coumarin compounds isolated from nature also show their efficacy in inhibiting HCV-infection (Figure **3**). Pandey *et al.* reported that wedelolactone (**23**), a naturally occurring coumestan, exhibited anti-HCV activity by inhibiting NS5BRdRp activity *in vitro* with IC_{50} of 7.7 μM.[14] They also reported that wedelolactone also inhibited HCV replication in cell culture system as 30% and 80% of HCV replications were inhibited at 10 μM and 50 μM concentrations, respectively, as judged by the HCV RNA level.

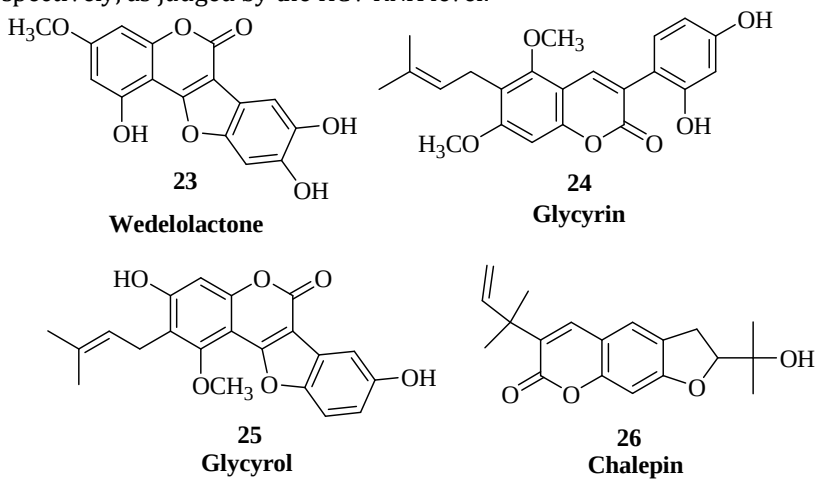


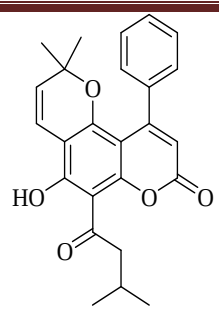
Figure 3: Naturally occuring coumarin with Anti-HCV activity

Hotta *et al*. demonstrated that the anti-HCV activity of three coumarins, glycycoumarin (**1**), glycyrin (**24**) and glycyrol (**25**) isolated from *Glycyrrhiza uralensis* with IC_{50} being 8.8, 7.2 and 4.6 g/mL.[15] The real-time quantitative RT-PCR and immunoblotting analyses revealed that these three coumarins inhibited HCV RNA replication, resulting in decreased HCV protein synthesis. Again production of HCV infectious particles was also inhibited by glycycoumarin, glycyrin and glycyrol at 1 and 2 days of post-infection. Further the same author demonstrated that chalepin (**26**), a natural coumarin isolated from *Ruta angustifolia Pres*, showed strong anti-HCV activities with 50% inhibitory concentration (IC_{50}) of 1.7 ± 0.5 μg/ml,[16] stronger than that of ribavirin (IC_{50} = 2.8 ± 0.4 μg/ml), a widely used anti- HCV agent. Mode-of-action analyses revealed that chalepin inhibited HCV at the post-entry step and decreased the levels of HCV RNA replication and viral protein synthesis.

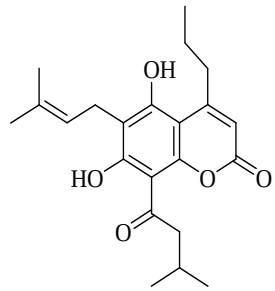
2.3 Miscellaneous Anti-Viral Activities:

Besides anti-HIV and anti-HCV acivities, natural coumarins have been exhibited their antiviral activity against Dengu, Chikungunya and Influenza A viruses (Figure **4**). For Example, Martínez-Gutierrez *et al.* reported that two coumarins, coumarin A (**27**) and coumarin B (**28**) isolated from the seed of *Mammea americana* (*M. americana*) displayed their potentiality to inhibit the transmission of Dengue virus (DENV) and Chikungunya virus (CHIKV).[17] These two compounds showed low toxicity at concentrations ≤ 200 μg/mL. Since coumarin A and B inhibited infections caused by both viruses during the implementation of the two experimental strategies employed here (post-treatment with inhibition percentages greater than 50%, $p < 0.01$; and pre-treatment with percentages of inhibition greater than 40%, $p < 0.01$) these two compounds were considered to be potential antiviral agents for treating Dengue and Chikungunya fever.

In a recent study, Yang, Li and Wang *et al.* reported that eleutheroside B1 (**29**) isolated from *Sarcandra glabra* exhibited wide spectrum of anti-human influenza virus activity with the IC_{50} value of 64–125 mg/ml *in vitro*, but it showed no effects against avian influenza virus.[18] The expression level of cytokines and chemokines were influenced by eleutheroside B1 and the IL-6, CXCL-8, CCL-2 expressions were all inhibited by the eleuthe roside B1 at concentration 200 mg/ml. All the results suggested that eleutheroside B1 could act as potential agent for the prevention and treatment of influenza A virus.



27
Coumarin A



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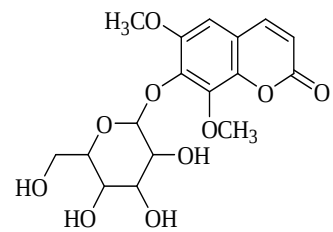
Coumarin B



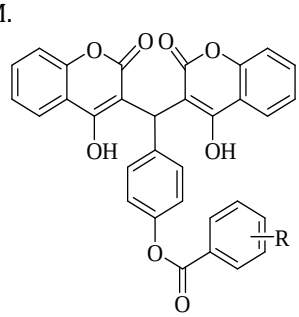
29
Eleutheroside B1

Figure 4: Naturally occuring coumarins showing anti dengu, anti-CHIKV and anti- human influenza virus activity

3. Antiviral Activity of Synthetic coumarins:

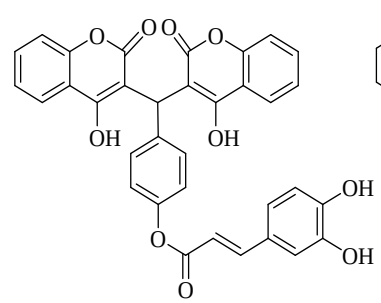
3.1: Anti-HIV activity:

The potentiality of tetrameric coumarin derivatives as inhibitor of HIV-1IN has been well established.[19,20] Hsu *et al.* designed and synthesized a number of tetrameric coumarins (**30, 31** and **32**) bearing free and modified hydroxyl substituent at the benzoyl ring.[21] Although all the compounds were active against HIV-1 IN, compound **30e** and **31** were found to be most potent with an IC_{50} of 1.5 and 2.6 μM. Additionally, compound **32**, with a potent antioxidative lipoyl moiety also exhibited the potency, with IC_{50} of 2.3 ?M.



30

(a) R = 2-OH (e) R = 3,4-diOH
(b) R = 3-OH (f) R = 2,5-diOH
(c) R = 4-OH (g) R = 3,5-diOH
(d) R = 2,4-diOH



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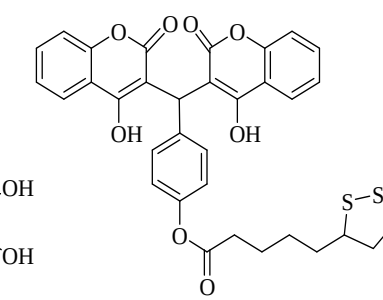
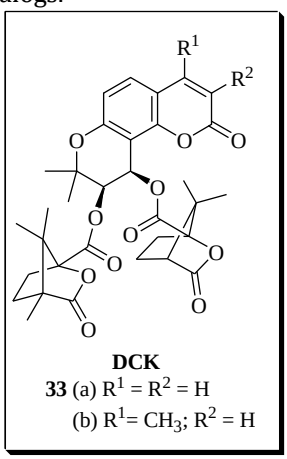


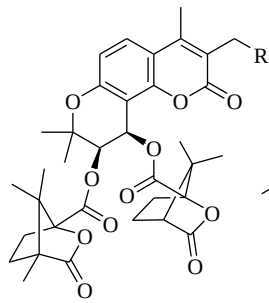
32

Again anti-HIV activity of 3′,4′-di-O-(S)-camphanoyl-(+)-cis-khellactone (DCK, **33a** and **b**) with a remarkable EC_{50} value of 2.56×10^{-4} μM and a therapeutic index (TI) of 1.37×10^{5} against HIV-1IIIB replication in H9 lymphocytes has been well established.[22,23] Extensive researches[24] on the synthesis of modified DCK with anti-HIV activity and SAR studies have revealed that 3′R,4′R-configurations and planarity of the coumarin ring system are important structural features for anti-HIV activity. Alkyl/alkoxyl substituents at the 3-, 4-, and 5-positions on the coumarin are essential for the enhancement of anti-HIV activity and decreased toxicity of DCK. It is also observed that a methyl group on the coumarin and two bulky (S)-camphanoyl groups at the 3′- and 4′-positions are more preferable than other substituents. In a report Lee *et al* demonstrated simple protocol for the synthesis of a library of modified DCK **34**.[25] Further, 3-hydroxymethyl-4-methyl-DCK (**34b**), a modified DCK, exhibited significant anti-HIV activity in H9 lymphocytes and primary peripheral blood mononuclear cells with EC_{50} values of 0.004 and 0.024 μM, respectively. Although compound **34b** was less potent than 3-bromomethyl-4-methyl-DCK (**34a**) which showed EC_{50} and TI values of 0.00011 μM and 189,600, respectively, the water solubility of **33b** like DCK made it suitable candidate for further clinical studies. Further, the design, synthesis and screening of anti-HIV-1 activity *in vitro* of novel seco-DCK analogs **35** were carried out by Chen and Lee *et al*.[26] Among them, moderate activity was exhibited by three compounds **35b** and **35c** whereas compound **35a** showed the best activity with an EC_{50} value of 0.058 μM and a therapeutic index (TI) of 1000. In addition to this compound

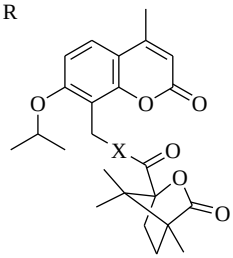
35a displayed antiviral activity against a multi-RT inhibitor-resistant strain (RTMDR) which was insensitive to most DCK analogs.



DCK
33 (a) $R^1 = R^2 = H$
(b) $R^1 = CH_3$; $R^2 = H$

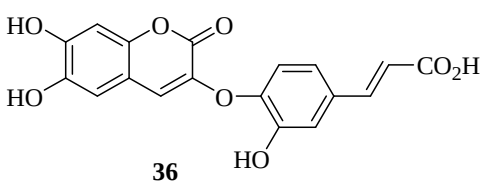


34
(a) R = Br
(b) R = OH

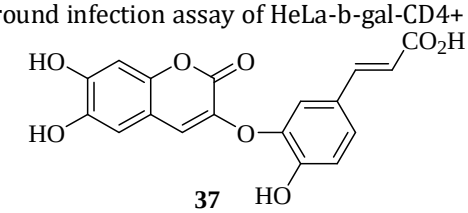


35
(a) X = O
(b) X = S
(c) X = NC_6H_4-*p*OMe

Bailly *et al.* explored an efficient route for the synthesis of two caffeoyl-coumarin conjugates **36** and **37** in six steps starting from ferulic acid, isoferulic acid and sesamol.[27] Both compounds exhibited potent inhibitory activities at micromolar concentrations against HIV-1 integrase in 3/-end processing reaction but were less effective against HIV-1 replication in a single-round infection assay of HeLa-b-gal-CD4+ cells.

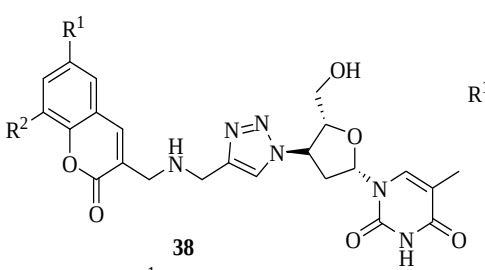


36

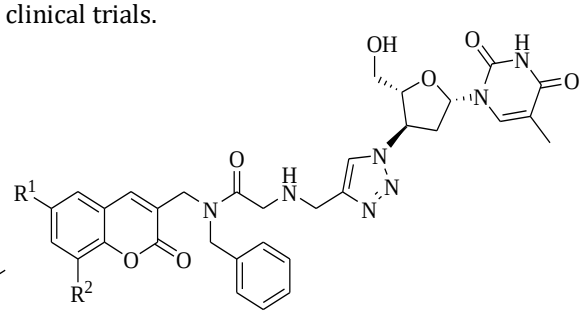


37

Kaye *et al.* described the synthesis of structurally complex coumarin-AZT conjugates **38** by four-step sequences using readily available reactants.[28] The saturation transfer difference (STD) NMR screening experiment and *in silico* modelling studies with these compounds demonstrated their potential as dual-action HIV-1 PR/RT inhibitors. In another report, the same author synthesized and evaluated the potentiality as dual action HIV-1 Reverse Transcriptase (RT) inhibitor and HIV-1 protease (PR) inhibitor of a series of *N*-benzylated coumarin-AZT (**39**) conjugates.[29] All the compounds except the chloro compound showed HIV-1 PR inhibition efficacy (52-60% at 50 μM) and IC_{50} values in a range of 22-35 μM along with up to 99% inhibition of HIV-1 RT at 50 μM which clearly indicated the potentiality of *N*-benzylated coumarin-AZT (**39**) conjugates as anti-HIV agent in further clinical trials.



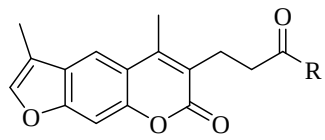
38
R^1 = H, Br, Cl
R^2 = H, OMe, OEt



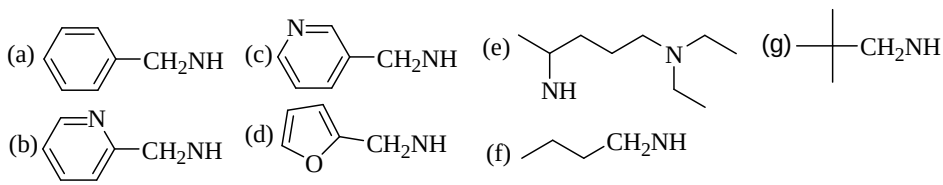
39
R^1 = H, Br, Cl
R^2 = H, OMe, OEt

In 2014, Kaye *et al.* further designed and synthesized a series of novel *N*-substituted 3-{3,5-dimethylfuro[3,2-*g*]coumarin-6-yl}propanamides (**40a-f**) *via* a five-step pathway starting with resorcinol and diethyl 2-acetylglutarate to study their potentiality as HIV-1integrase (IN) inhibitors.[30] Compounds **40a-f** were examined with reference to raltegravir, a known HIV-1 IN inhibitor and among the synthesized compounds, furanocoumarin derivative containing (pyridine-2-yl)methyl was identified as a potential

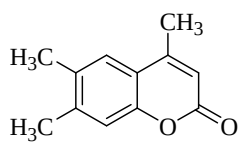
inhibitor at 10 μM based on the virtual interactions with the enzyme active site predicted by the docking studies.



40a-f



Langer *et al.* reported the synthesis of arylated coumarins by site-selective Suzuki–Miyaura cross-coupling reactions.[31] The evaluation for their *in vitro* anti-HIV inhibitory activity in human (MT-4) cells based on an MTT assay revealed that compounds **41** and **42** displayed their efficiency in inhibiting HIV-1 replication in a cell culture with IC_{50} of 4.57 μg mL^{-1} and 13.20 μg mL^{-1} with CC_{50} of 14.40 μg mL^{-1} and 61.34 μg mL^{-1}, respectively, resulting in a selectivity index of 3 and 5. However other compounds, **43**, **44** and **45** exhibited some activity against HIV-1 (IIIB strain) with IC_{50} > 2.13, >2.06 and >2.08 μg mL^{-1}, respectively with no selectivity.



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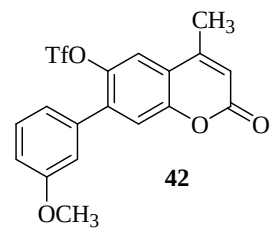

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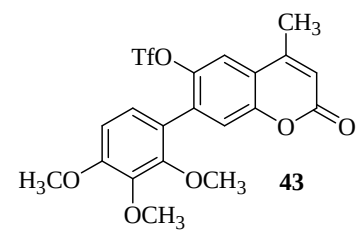

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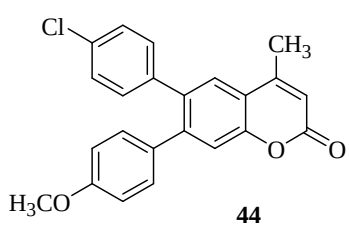

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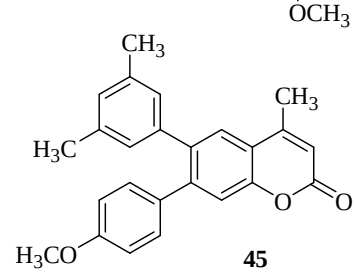
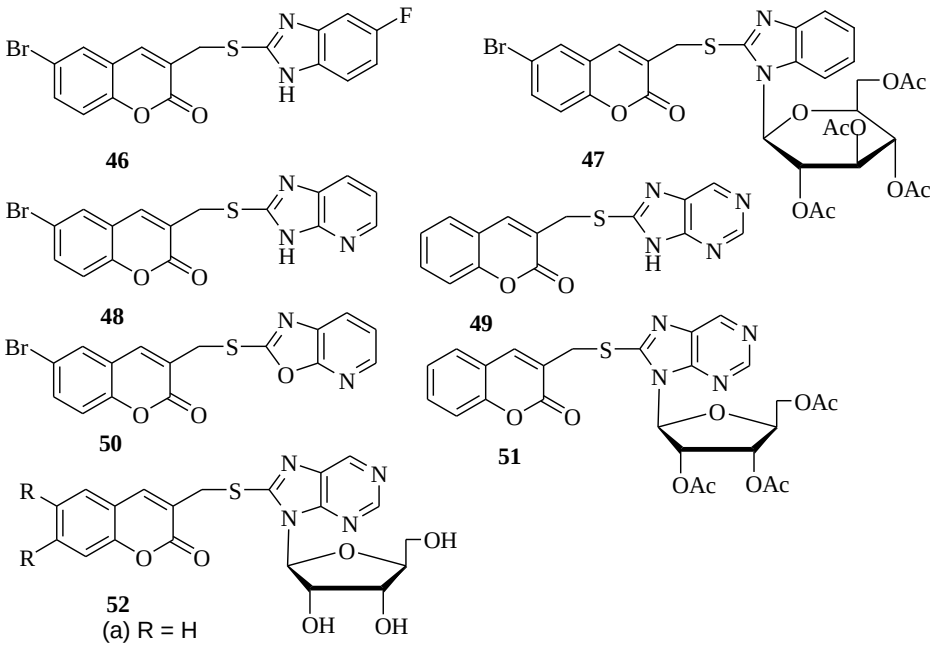


45

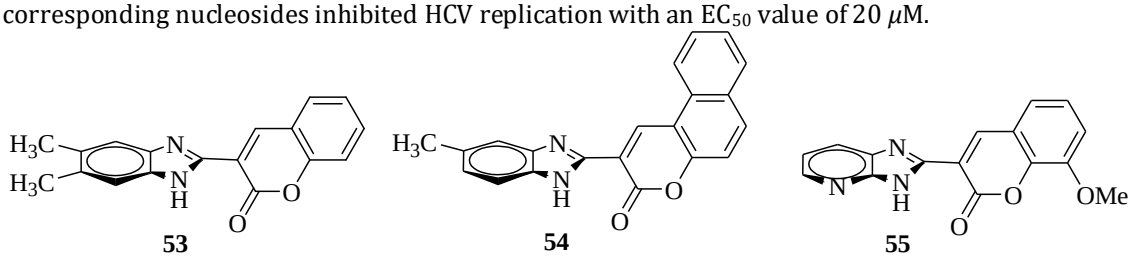
3.2 Anti-HCV Activity:

A series of benzimidazole-coumarin hybrids with thio-methylene linker along with its *N*-glucosidic analogues were successfully synthesized by a one-flask method from benzimidazole or benzimidazol *N*-glucosides and coumarin derivatives.[32] While evaluation the activity against the hepatitis C virus two compounds 2-[(6-bromocoumarin-3-yl)methylenethio]-5-fluorobenzimidazole (**46**) and its derivative 1-[(2,3,4,6-tetra-O-acetyl)glucopyranos-1-yl]-2-[(6 -bromocoumarin-3-yl)methylenethio]benzimidazole (**47**) were found to be most potent with EC_{50} values of 3.4 M and 4.1M, respectively. The compound **47**, at a concentration of 5.0 M, inhibited HCV RNA replication by 90% without exhibiting any effect on cell proliferation. Further the same group synthesized imidazopyridine-, purine-, benzoxazole-, and benzothiazole-coumarin conjugate with thio-methylene linker to evaluate their anti-HCV activity and to establish the structure activity relationship.[33] The 50% inhibitory concentrations for virus replication (EC_{50}), host cell growth (CC_{50}), and the selectivity index (SI) (CC_{50}/EC_{50}) were examined with all the synthesized compounds and imidazopyridine-coumarinconjugate **48**, purine-coumarin conjugate **49** and benzoxazole-coumarin conjugate **50** inhibited HCV replication at EC_{50} values of 6.8, 2.0, and 12 µM, respectively with significant selectivity index values (11-54) of which purine-coumarin conjugate **49** exhibited most potency against HCV virus. In search of new anti-HCV agents Hwu *et al.* again reported the synthesis of a number of coumarin-purine ribofuranoside conjugates with thio-methylene link through the chemical coupling of various 9-(β-D-ribofuranosyl)purine-8-thiones with 3-(chloromethyl)coumarins bearing various substituents.[34] The anti-HCV and cytostatic determination assays were performed and three

conjugates **51**, **52a** and **52b** in the family of 8-(coumarin-3/-yl)methylthio-9-(*β*-D-ribofuranos-1//-yl)purine possessed an appealing ability to inhibit HCV replication with EC_{50} between 5.5 and 6.6 μM and EC_{90} of ~20 μM.

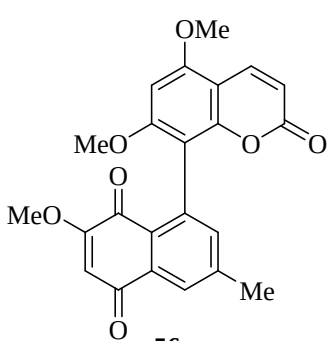


A library of hinged benzimidazole-coumarin hybrids and their *β*-D-ribofuranosides was synthesized and evaluated for their anti-HCV activity.[35] Three of these hybrids **53**, **54** and **55** exhibited appealing EC_{50} values of as low as 3.0, 5.5 and 20 μM, respectively, as well as with remarkable SI values (>14 for hybrid 7).. The corresponding nucleosides inhibited HCV replication with an EC_{50} value of 20 μM.



3.3 Miscellaneous anti-viral activity:

Ishikawa *et al*. reported the synthesis of toddacoumaquinone **56**, a coumarin-naphthoquinone dimer through Diels alder reaction between 8-(1-acetoxy-3-methyl-1,3-butadienyl)-5,7-dimethoxycoumarin and 2-methoxy-1,4-benzoquinone.[36] The evaluation of antiviral activities of **56** against different viruses revealed weak activity (EC_{50} = 10 μg/ml) against herpes simplex virus type 1 (HSV 1) and herpes simplex virus type 2 (HSV 2).

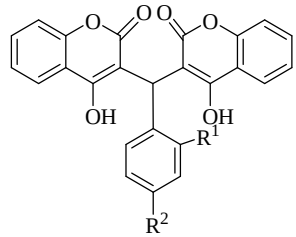


56

Toddacoumaquinone

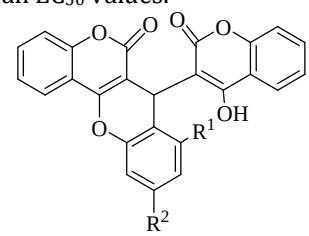
Mintas *et al.* demonstrated that 4-hydroxycoumarin dimers bearing an aryl substituent on the central linker and fused benzopyranocoumarin derivatives, synthesized in laboratory, exhibited inhibitory activity against HSV-1 (KOS), HSV-2 (G), vaccinia virus and HSV-1 TK- KOS (ACVr) at a concentration of 9-12

μM and at a minimum cytotoxic concentration (MCC) greater than 20 μM.[37] Compounds **57a-d** and **58** were active against feline herpes virus (50% effective concentration, EC_{50} = 5-8.1 μM), but with minimum cytotoxic concentration (MCC) at only 4-7-fold higher than EC_{50} values.



57

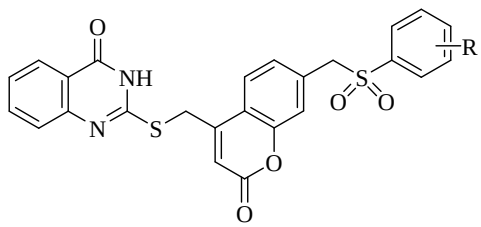
(a) R^1 = H; R^2 = Cl
(b) R^1 = OCH_3; R^2 = H
(c) R^1 = H; R^2 = Cl
(d) R^1 = H; R^2 = NO_2



58

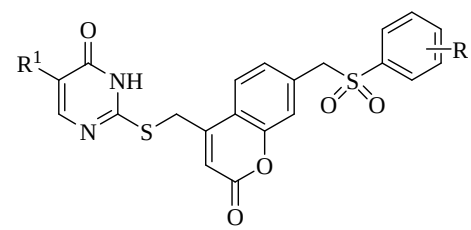
R^1 = R^2 = OCH_3

Coumarin conjugates has also been effective against Chikungunya virus (CHIKV) an arbovirus that was first recognized in an epidemic form in East Africa in 1952–1953. Hwu and Neyts *et al*. reported the synthesis and anti-CHIKV evaluation of a series of uracil–coumarin-arene triple comjugates.[38] The coumarin moiety in the conjugated compounds was the central moiety attached to a pyrimidine unit at the C-4/ position through a SCH_2 linker on one side and an arene group at the C-7/ position through a $–SO_2–$ linker on the other side. The triply conjugated uracil–coumarin–arenes by use of the $–SO_2–$ (not OCH_2) linker was vital to their anti-CHIKV activity and among the synthesized compounds, **59** and **60** were found to inhibit CHIKV replication at EC_{50} values of with a range10.2-19.1 μM.



59

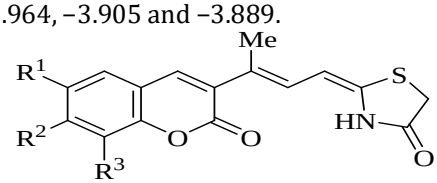
R = H, 4-Me, 2-NO_2



60

(a) R = 2-NO_2; R^1 = H
(b) R = 2-NO_2; R^1 = CH_3

Yusufzai *et al*. reported the synthesis and the anti-dengue potential of the 4-thiazolidinone coumarin hybrids as two-component NS2B/NS3 DENV favivirus serine protease inhibitors by using computational molecular docking approach, with reference to the standards 4-hydroxypanduratin, panduratin and ethyl 3-(4-(hydroxymethyl)-2-methoxy-5-nitrophenoxy) propanoate with DS of −3.379, −3.189 and −3.381, respectively.[39] The results of molecular docking studies revealed that the synthesized compounds exhibited potent anti-dengue activity among which compounds **61a-d** were found to be the best ones with docking scores of −4.014, −3.964, −3.905 and −3.889.



61

(a) R^1 = R^2 = H; R^3 = OCH_3
(b) R^1 = OCH_3; R^2 = R^3 = H
(c) R^1 = R^3 = H; R^2 = OH
(d) R^1 = R^3 = H; R^2 = OCH_3

4. Conclusion:

Among the different heterocyclic compounds coumarin and its derivatives have received a considerable attention due its widespread biological applications especially in the development of antiviral

agents. Several natural coumarins with structural diversity have shown potentiality to act as antiviral agent in different virus diseases like HIV, HCV etc. The structural activity relationship (SAR) studies of these compounds have resulted in a revolution in the development of structurally modified coumarin scaffolds with commendable antiviral activities. This review article provides a complete knowledge of natural and synthetic coumarins as antiviral agents with a hope to be a horizon for researchers for future development molecule with better and effective antiviral activity.

Conflict of interest

The authors confirm that this article content has no conflicts of interest.

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