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Pharmacological perspectives and molecular mechanisms of coumarin derivatives against virus disease

Zhoupeng Li [a,1], Dehui Kong [b,1], Yongsheng Liu [a], Mingkai Li [a,c,*]

[a] Department of Pharmacology & Key Laboratory of Gastrointestinal Pharmacology of Chinese Materia Medical of the State Administration of Traditional Chinese Medicine, School of Pharmacy, The Fourth Military Medical University, Xi'an, Shanxi 710032, PR China
[b] School of Nursing, Army Medical University (Third Military Medical University), Chongqing 400038, PR China
[c] Precision Pharmacy & Drug Development Center, The Fourth Military Medical University, Xi'an, Shanxi 710032, PR China

Abstract Infections caused by viruses are one of the foremost causes of morbidity and mortality in the world. Although a number of antiviral drugs are currently used for treatment of various kinds of viral infection diseases, there is still no available therapeutic agent for most of the viruses in clinical practice. Coumarin is a chemical compound which is found naturally in a variety of plants, it can also be synthetically produced possessing diverse biological effects. More recently, reports have highlighted the potential role of coumarin derivatives as antiviral agents. This review outlines the advances in coumarin-based compounds against various viruses including human immunodeficiency virus, hepatitis virus, herpes simplex virus, Chikungunya virus and Enterovirus 71, as well as the structure activity relationship and the possible mechanism of action of the most potent coumarin derivatives.

* Corresponding author. Department of Pharmacology & Key Laboratory of Gastrointestinal Pharmacology of Chinese Materia Medical of the State Administration of Traditional Chinese Medicine, School of Pharmacy, The Fourth Military Medical University, Xi'an, Shanxi Province 710032, PR China.
  E-mail address: mingkai@fmmu.edu.cn (M. Li).
  Peer review under responsibility of Chongqing Medical University.
[1] Contribute equally to this work.

Introduction

Viruses containing RNA or DNA has long been considered a serious threat to human being, causing various disease that affect global health and the economy.[1] A wide range of viral diseases such as AIDS, measles, influenza, infectious hepatitis, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are highly contagious with high mortality rates. Currently, outbreak of pandemic Coronavirus disease (COVID-19) has caused several hundred thousand deaths, posing unprecedented threat to the public health.[2] (Table 1—3, Fig. 1—6 and 9).

Since the first nucleoside analog antiviral drug idoxuridine was approved by FDA in 1963, more than 90 antiviral drugs have been approved for the treatment of human infectious diseases induced by viruses, and most of them are targeting the key enzyme such as DNA polymerase, revertase and neuraminidase.[3] However, because of the mutation of viral genes during antiviral drug exposure, the success of therapy is being threatened by the increasing prevalence of drug resistant strains clinically.[4] Therefore, developing new antiviral drugs has become the spotlight in medicinal chemistry field nowadays.

Natural products have been proved to be a particularly crucial source of compounds with antiviral activities, which can be processed into semisynthetic and synthetic drugs, applying to antiviral chemotherapy.[5] Coumarin is a chemical compound found in a variety of different plants, which is composed of fused benzene and α-pyrone rings. Currently, at least 1300 different coumarins have been identified, and they are presenting a wide variety of biological activities such as antioxidant, analgesic, anti-inflammatory, and anti-mutagenic properties. In recent years, coumarins and their derivatives isolated from various plants or synthesized also exhibit bioactivities against many viruses.[6] Meanwhile, coumarins are used as precursors to screen out many derivatives that remarkably restrain viruses, which can further get chemically modified thereon.[7—9] Besides, the coumarin-containing conjugated compounds, combination of coumarin nucleus through different linkers with other antiviral compounds, are also the field to overcome the drug resistance.[10] This review focuses on the status of coumarin derivatives purposing approaches for therapeutic potential against the various viral diseases, and provided the recent advances in the possible structure-activity relationship and molecular mechanisms of coumarin derivatives as antiviral agents.

Therapeutic potential and molecular target of coumarins as antiviral agents

Coumarin derivatives against RNA virus

Anti-human immunodeficiency virus
Human immunodeficiency virus (HIV) is a retrovirus that attacks the immune system by destroying CD4$^+$ T cells.[11] At present, antiretroviral treatment (ART) is playing a pivotal role in the reduction of HIV-related morbidity and mortality, which applies non-nucleoside reverse transcriptase inhibitor (NNRTI), nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), protease inhibitor (PI), as well as integrase inhibitors (INIs).[12—14]

Natural coumarin compounds with anti-HIV activity have been studied for decades.[15] In 1992, researchers discovered (+)-calanolide A (Fig. 1, compound 1), which was extracted from tropical plants of Calophyllurn langierum, had the potent inhibitory activity against HIV-1 virus. This was the first coumarin reported to inhibit HIV-1 reverse transcriptase (HIV-1 RT) with high safety and inhibitory activity against a variety of drug-resistant strains.[16—18] Furthermore, the dipyranocoumarins (−)-calanolide B (compound 2) and (+)-calanolide C (compound 3), the leaf hexane extracts of C. brasiliense, attributed to the properties of anti-HIV-1 RT with slight toxicity in mice.[16] Then a new derivative of Calanolide A, which was termed 10-chloromethyl-11-desmethyl-12-oxy-calanolide-A (F18) (compound 4), showed the inhibitory effect to the HIV-1 nonnucleoside reverse transcriptase against both wild-type and Y181C mutation HIV-1 with higher synergy interaction (SI).[19] Recently, researchers identified that two metabolites of compound 4 (compound 5, 6) had the more potent activity against HIV-1, and the 12-carbonyl group contributes to the bioactivity significantly.[20]

The sulphonic coumarin Suksdorfin (Fig. 2, SKD, compound 7), was isolated from Lomatium suksdorfii and Angelica morii in 1994, which had strong anti-HIV activity with EC$_{50}$ 1.3 μmol/L.[21] As a leading compound, the chemical structure of SKD was modified to a series of analogues, and one of the derivatives named DCK (compound 8) exhibited extremely potent inhibitory activity to HIV-1 replication. Furthermore, the structure analysis showed that the angular pyrano-coumarin skeleton and di-O-(−)-camphanoyl moieties of R-configuration at the 3′- and 4′-positions were crucial for anti-HIV activity.[22—29] The underlying mechanism of these compounds was through uniquely inhibiting HIV-1 RT.[30] In contrast to the currently used nucleoside anti-HIV counterparts such as zidovudine and zalcitabine, DCK and most of its analogues had the potent anti-HIV activities with extremely high selective index (SI) value, which indicated that these coumarins had the more selective activity against the HIV-infected cells.[31—35] Besides, the prenylated coumarins isolated from the fruits of Manilkara zapota also displayed anti-HIV activities with EC$_{50}$ values in range of 0.12—8.69 μM, and compound 9 showed the most efficient activity against HIV RT with an EC$_{50}$ value at 0.12 μM.[36]

Temitope et al synthesized a series of N-benzylated coumarin-azidothymidine (AZT) conjugates (Fig. 3, compound 10) and non-benzylated analogues (compound 11), and the AZT compounds had the dual-action as the HIV-1 protease (HIV-1 PR) and RT inhibitors. Molecular docking indicated that the benzyl group of these compounds could occupy the hydrophobic pocket.[10] In addition, a series of amide coumarin derivatives were synthesized and characterized by various linkers, among which compound 12 and compound 13 manifested potency against both PR and RT.[37] It suggested that some coumarin derivatives had the potential to become dual HIV-1 PR/RT inhibitors, and this possible mechanism promotes the coumarins to be new candidates for the treatment of drug-resistant HIV.

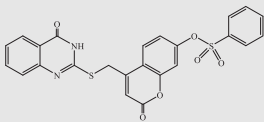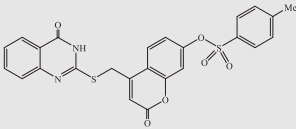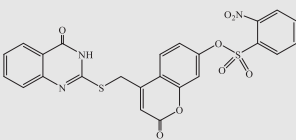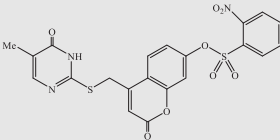**Table 1**   The coumarin derivatives with anti-CHIKV activity.
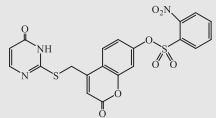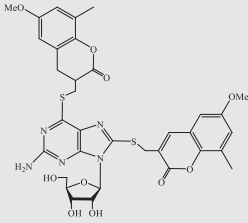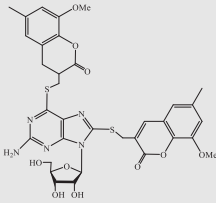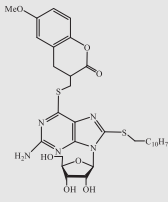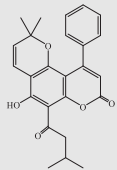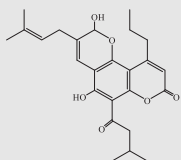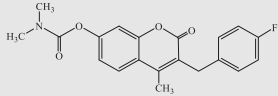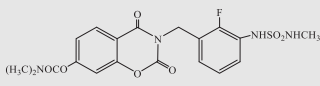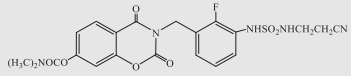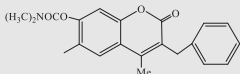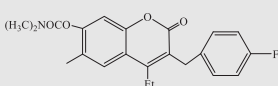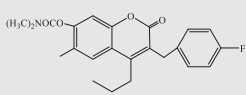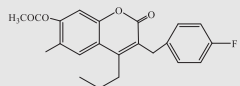
Compound	Chemical structure	CC_{50}[a] (μM)	EC_{50}[b] (μM)	SI
29		178	19.1	9.3
30		117	10.2	11.5
31		144	17.2	8.8
32		107	19.0	5.6
33		75.2	13.0	5.8
34		> 212	9.9	> 21.7
35		96.5	10.3	9.37
36		> 227	13.9	> 16.3

Table 1 (*continued*)
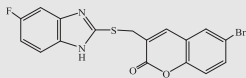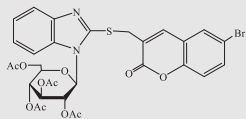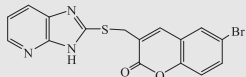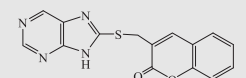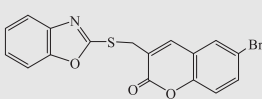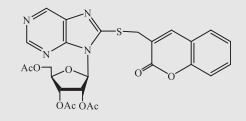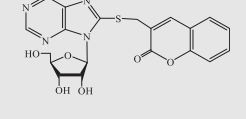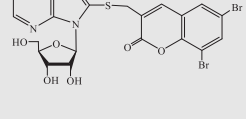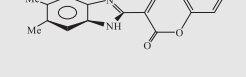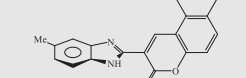
Compound	Chemical structure	CC_{50}^{a} (μM)	EC_{50}^{b} (μM)	SI
37		3150.0	10.7	295.2
38		549.8	0.5	1021.0

[a] CC_{50}: the half cytotoxic concentration.
[b] EC_{50}: the median effective concentration.

Table 2 The coumarin derivatives with anti-EV71 activity.

Compound	Chemical structure	CC_{50} (μM)	EC_{50} (μM)	SI
39		/	0.3	/
40		>100	1.02	>98
41		>100	3.92	>25
42		152	2.5	60.8
43		72.92	10	7.29
44		756.06	3.98	190
45		41.46	18.5	2.24

Table 3 The coumarin derivatives with anti-HCV activity.

Compound	Chemical structure	CC$_{50}$ (μM)	EC$_{50}$ (μM)	SI
59		27	3.4	8
60		43	4.1	10
61		128	6.8	19
62		109	2.0	54
63		131	12	11
64		39	6.6	5.9
65		50	5.5	9.1
66		36	5.9	6.1
67		23	3.0	7.9
68		77	5.5	14

Table 3 (*continued*)

Compound	Chemical structure	CC$_{50}$ (μM)	EC$_{50}$ (μM)	SI
69		127	20	6.4
70		83	7.2	12
71		75	5.1	15
72		173	8.4	21

4-phenyl coumarin derivative Mesuol (Fig. 4, **compound 14**) was isolated from the leaf of *Marila pluricostata* in 2005, which could restrain HIV-1 replication through targeting the pathway of nuclear factor-κB (NF-κB).[38] Antiviral RV assay showed that sulfanylphenyl coumarin (**compound 15**) was one of the most valid HIV-1 replication dual-target inhibitors, it also could target the NF-κB pathway and block HIV-1 replication.[39] As a tricyclic coumarin, GUT-
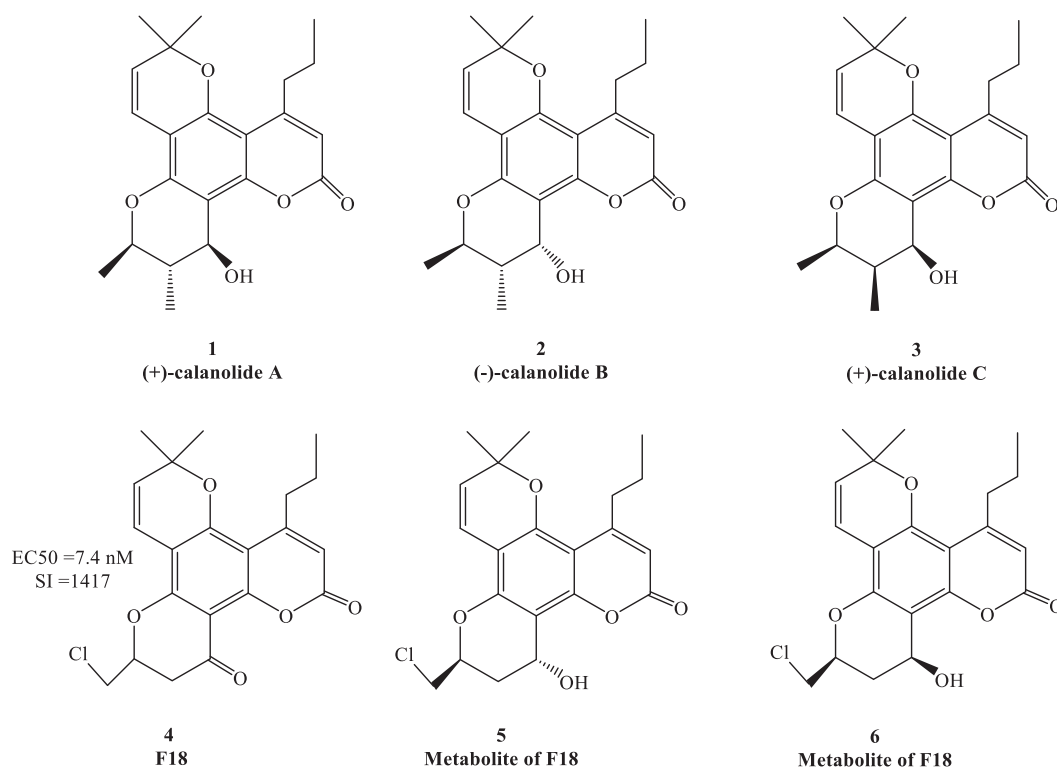
Figure 1 Chemical structure of calanolides and its derivative.
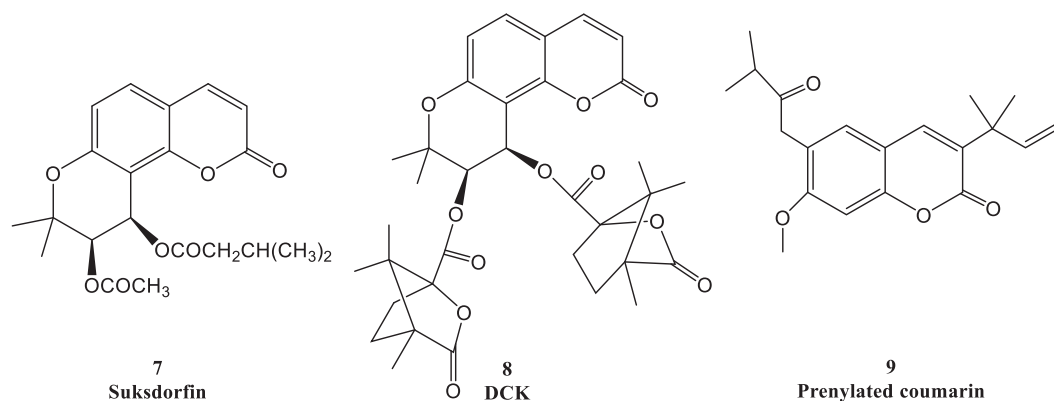
Figure 2 Chemical structures of pyrano and prenylated coumarin derivatives.

70(compound 16), which was extracted from the stem bark of *Chlophyllum brasiliense*, was able to suppress HIV-1 replication by inhibiting NF-κB.[40] Interestingly, it was also confirmed that GUT-70 could block HIV-1 to enter the mammalian cells by stabilizing cell membrane fluidity, and down-regulate the expression of the HIV-1 receptor CD4.[41] These evidences suggested that NF-κB was one of the possible targets of coumarin against HIV infection.

A series of 4-hydroxycoumarin dimmers analogues such as compound 17 and compound 18 (Fig. 5) also exhibited inhibitory activities to the HIV-1 integrase, thereby blocking viral replicative cycle. All of these chemical molecules consist of hydrophobic moiety on the linker, and aryl-substituted structure was attached by the benzoyloxy or sulfonyloxy group, which might contribute to the inhibitory activity.[42] However, it seemed unlikely for these compounds to form covalent bond to the binding site of HIV-1 integrase. Consequently, a novel series of bis-and tetra-coumarin derivatives were synthesized, and the latter (compound 19) with the longest extended

linker showed the increased inhibitory activity to HIV-1 integrase, the spatial distance between each coumarin moiety and linker being crucial to the activity.[43] Furthermore, furocoumarin (compound 20) was also confirmed as potentialHIV-1 integrase inhibitor.[44] In recent years, lens epithelium-derived growth factor/p75 (LEDGF/p75) was confirmed as a cellular binding partner of HIV-1 integrase and a crucial cofactor for HIV-1 replication.[45] The coumarin termed CR (compound 21) could block the interaction of HIV-1 integrase and LEDGF/p75. On the basis of the chemical structure of CR, addition of 8-methyl group (compound 22) was also proved as an HIV-1 integrase-LEDGF/p75 interaction inhibitor after computational study and biological screening.[9] Meanwhile, one of the 4-hydroxypyranobenzopyrancoumarin derivatives (compound 23) was also able to inhibit the activity of both theHIV-1 integrase and RT-associated Ribonuclease H (RNase H).[46]

Furanocoumarin imperatorin (Fig. 6, compound 24) is distributed in citrus fruits and culinary herbs, which can
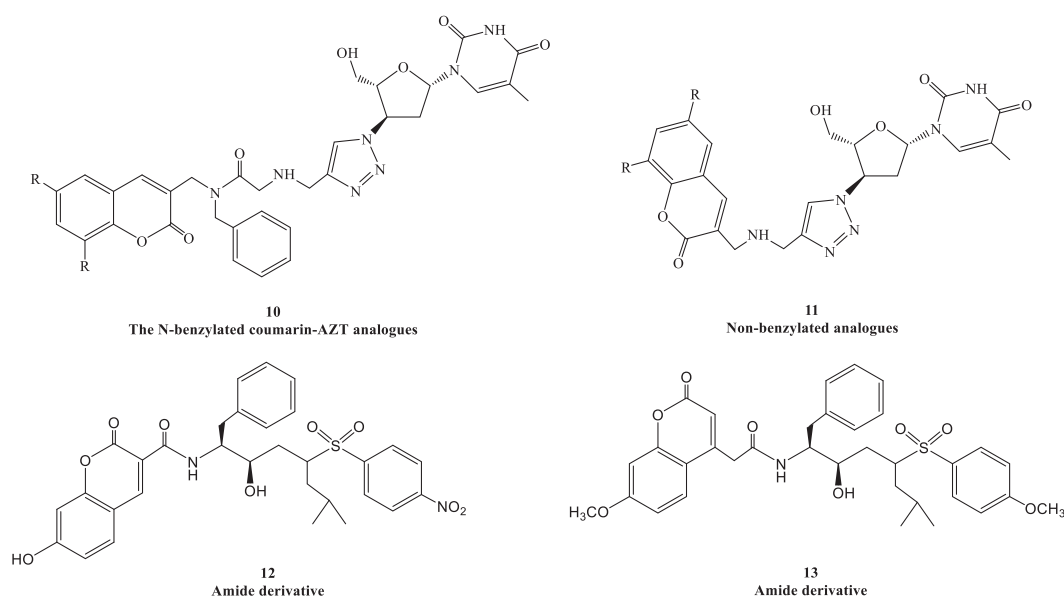
Figure 3 Chemical structures of benzylaminomethyl and amide coumarin derivatives.
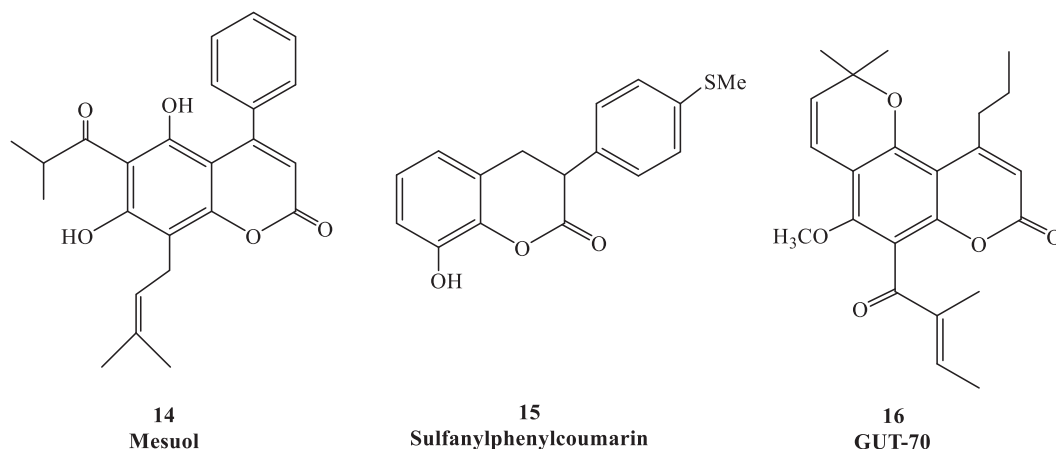
Figure 4 Chemical structures of coumarin derivatives targeting NF-κB pathway.

inhibit gp160 protein enveloped recombinant HIV-1 infection in several T cell lines and in HeLa cells, and arrest the cells at the G (1) phase of the cell cycle through Sp1 transcription factor dependent pathway.[47,48] Similarly, BPRHIV001 **(compound 25)** also had strong inhibitory activity to HIV-1 replication, but it might act on Tat-mediated HIV-1transactivation by suppressing the PI3K/Akt pathway,[49] while Psoralen **(compound 26)** extracted from the dried aerial parts of *Prangos tschimganica* also showed the potent anti-HIV activity by inhibiting HIV-1 replication.[50] Because HIV-1 viral

protein R (Vpr) plays important roles at multiple stages of the HIV-1 viral life cycle, it can promote virus replication and disease progression.[51,52] 3-phenyl coumarin derivative vipirinin **(compound 27)** could arrest the cell cycle by binding to a hydrophobic region of HIV-1Vpr, and 5-methoxy moiety of the phenyl ring is essential to its antiviral activity.[53] 2-(coumarin-4-yloxy)-4,6-(substituted)-s-triazine **(compound 28)** was reported as a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with anti-HIV effect, and modification at position 4 and 6 by introducing amino acid or
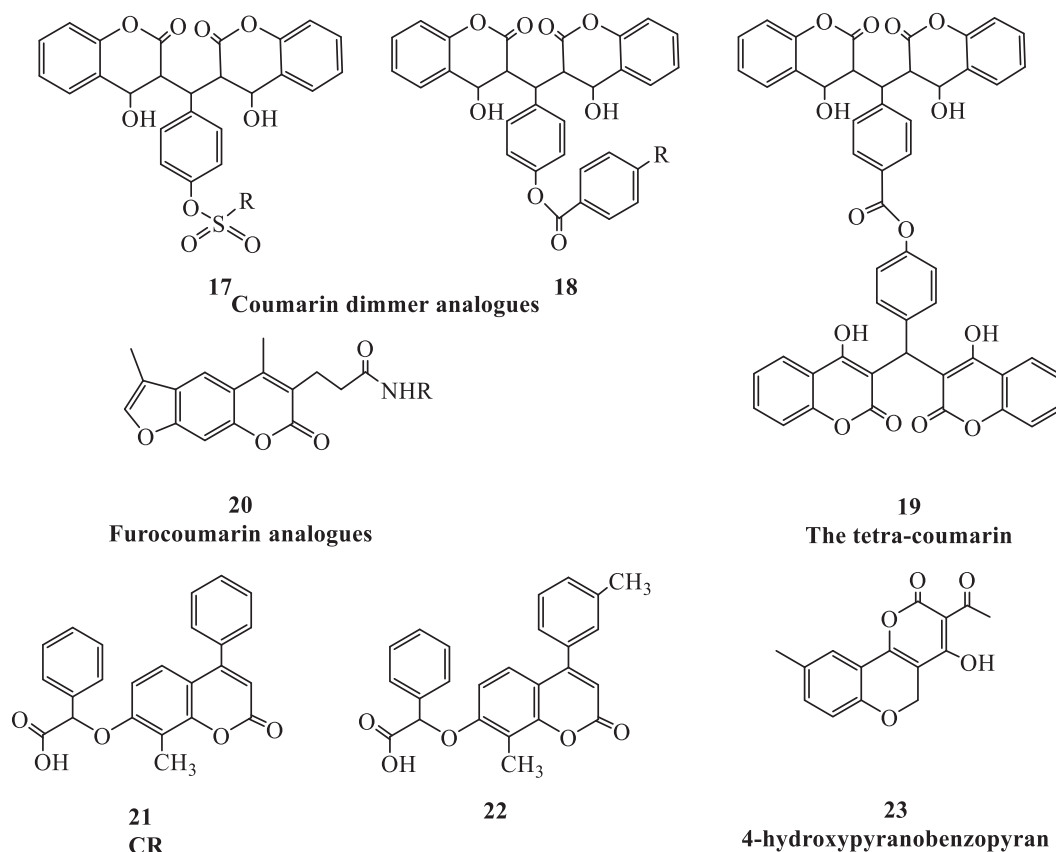
Figure 5 Chemical structures of coumarin derivatives targeting HIV-1 integrase.

24
Imperatorin Chemical Structure

25
BPRHIV001.

26
Psoralen

27
The morpholine derivative vipirinin

28
Triazine derivative
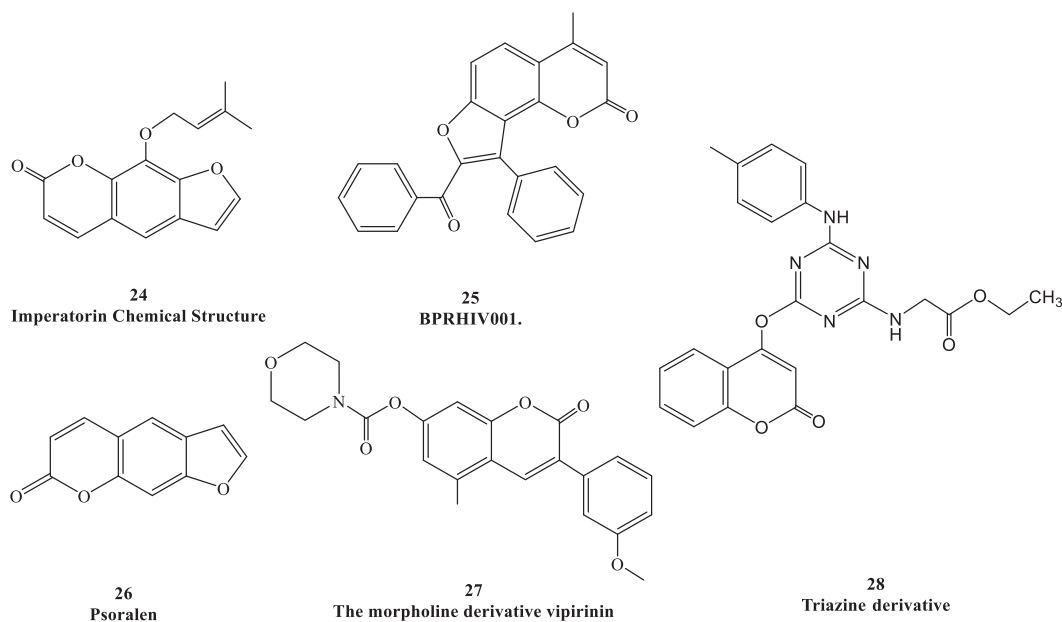
Figure 6   Chemical structures of coumarin derivatives targeting other proteins.
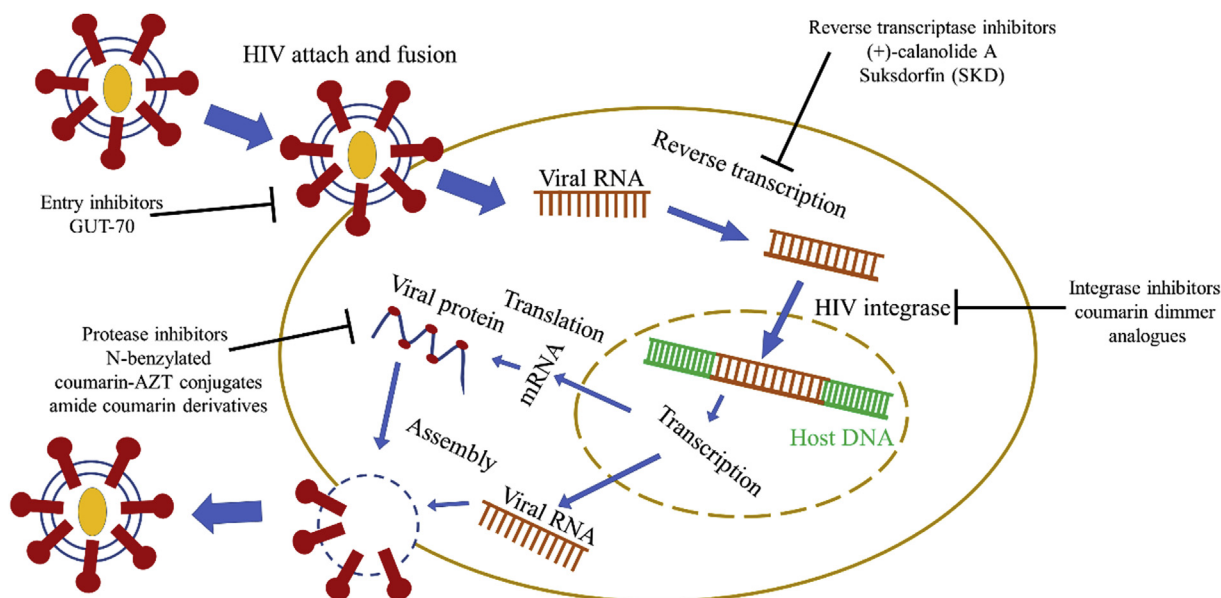
Figure 7   Anti-HIV mechanisms of coumarin derivatives.

various aryl ureas and aryl amines could enhance the anti-HIV activity of this kind of coumarin derivatives.[54]

Hence, the above evidences indicated that different coumarin derivatives could target different stages of HIV. For example, GUT-70 could block the attachment and fusion stage of HIV to the cellular wall or plasma membrane. (+)-calanolide A could inhibit the reverse transcription, while coumarin dimmer analogues could inhibit the HIV integrase, N-benzylated coumarin-AZT conjugates and amide coumarin derivatives could affect the assembly of HIV (Fig. 7 and 8).

Anti-chikungunya virus

Chikungunya virus (CHIKV), a cytoplasmic positive-stranded RNA virus, which is mainly transmitted by mosquito, has caused major epidemic outbreaks in Africa, Asia and Americas.[55] Although compounds targeting key inflammatory pathways, as well as attenuated virus vaccines, have shown some success in animal models, there is still no available anti-virus therapeutic against CHIKV infection, and the treatment mainly focuses on relieving symptoms, such as taking acetaminophen or paracetamol to reduce fever and pain.[56]
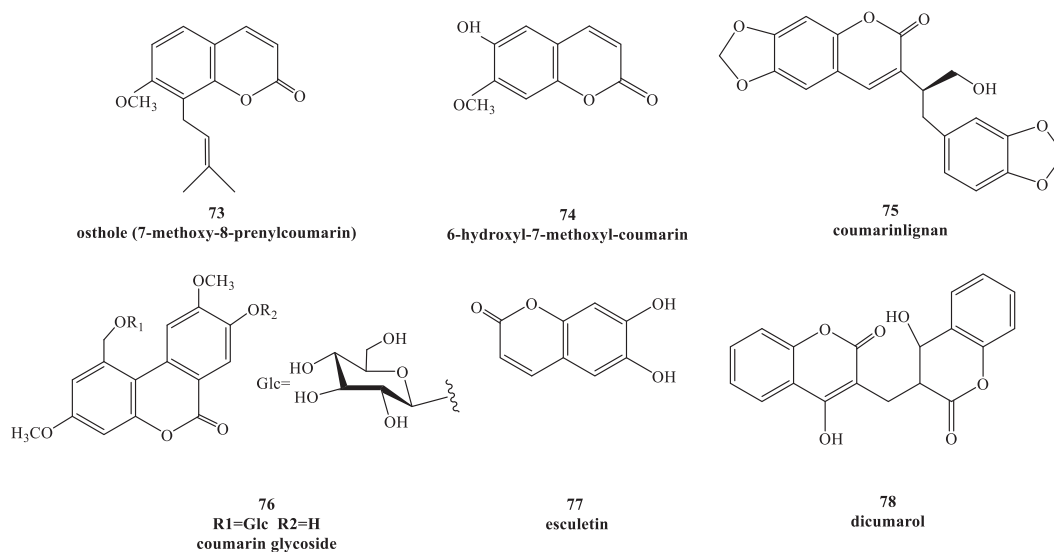
Figure 8 Chemical structures of coumarin derivatives against HBV.

Recently, the progress of coumarin derivatives with anti-CHIKV activity was obtained. Five uracil-coumarin-aromatics compounds (Table 1, **compound 29—33**) showed significant inhibitory activity to CHIKV in Vero cells, and the structure—activity relationship indicated that the coumarin nucleus played an important role in anti-CHIKV activity. Moreover, the structure of benzouracil-SCH2-coumarin-OSO2-arene also presented the efficient anti-CHIKV activity, and the triply conjugated compounds combined by the linking unit in coumarin-arene through —OSO2- joint were of vital importance to anti-CHIKV bioactivity.[57] In 2018, based on the above structures, a series of new coumarin-thioguanosine conjugates were synthesized, three of which **(compound 34—36)** exhibited inhibitory effect against CHIKV replication in Vero cells with an EC_{50} value ranging from 9.9 μM to 13.9 μM, and the coumarin moiety of these compounds was indispensable with regard to their activity, which was further enhanced by the coumarin-guanosine conjugates containing the eOMe group.[58] Meanwhile, some coumarins extracted from natural products also showed the activity against CHIKV. For instance, two coumarins **(compound 36, compound 38)** isolated from the seeds of *M. americana* could remarkably inhibit both entry into the cell and replication of CHIKV in VERO cells.[59]

Anti-enterovirus 71

Enterovirus 71 (EV71) is a non-enveloped, positive-sense, single-stranded RNA virus, it is an important neurotropic enterovirus and one of the major pathogens causing both neurological and mucocutaneous diseases, and the latter most commonly presents as hand, foot and mouth disease (HFMD) or herpangina in infants and young children.[60] In recent years, serious outbreaks of HFMD were reported frequently in the Asia-Pacific region, including China and Korea.[61] Since HFMD caused by EV71 tends to be associated with fatal complications, there is an urgent need to develop the vaccine or therapeutic to treat EV71 infection.[62]

Increasing evidence show that Ras/Raf/MEK/ERK, one of the mitogen-activated protein kinase (MAPK) pathways, is involved in EV71 RNA replication after entering the host cell, which suggests that blocking of this path way might contribute to the impairment of the replication of EV71.[63] In 2005, carbamate-substituted coumarin G8935 (Table 2, **compound 39**) was confirmed as the inhibitor of MEK activation.[64] Then a series of derivatives with coumarin scaffold as ATP-noncompetitive MEK1/2 inhibitor were designed and synthesized, and these compounds could suppress the EV71 replication effectively, such as 3-benzyl-1,3-benzoxazine-2,4-diones**(compound 40, compound 41)** could restrain the unphosphorylation of MEK1, and then inhibit the replication of EV71 without obvious cytotoxicity,[65] while 3-benzyl-coumarins **(compound 42—45)** had potent MEK1 binding affinity as well as significant inhibitory effect of ERK pathway, thereby inhibiting the replication of EV71. Moreover substituent group of N,N-dimethylcarbamoyloxyl or acetoxyl substitution at C7 position contributed to antiviral activity.[66]

Anti-hepatitisC virus

Viral hepatitis is a major threat to human health associated with significant morbidity and mortality. Five major biologically hepatotropic viruses including hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV), except the HBV belongs to the DNA virus, other hepatitis virus belong to RNA virus. The hepatitis virus cause most of the global burden of viral hepatitis,[67] and most deaths from viral hepatitis are due to HBV and HCV.[68,69]

HCV is the cause of hepatitis C and some cancers such as liver cancer and lymphomas in humans.[70] Since 2011, many anti-HCV drugs such as interferons alpha, DNA and RNA polymerase inhibitors, NS3/4A RNA protease inhibitors, NS5 RNA serine protease inhibitors, NS5B RNA polymerase inhibitors have been approved for clinical use, while the effectiveness of anti-HCV drugs depends on the presence of resistance associated variants (RAV), and it was demonstrated that 5—20% RAV occurred at the second day of monotherapy.[71,72] Therefore, the new chemical compounds
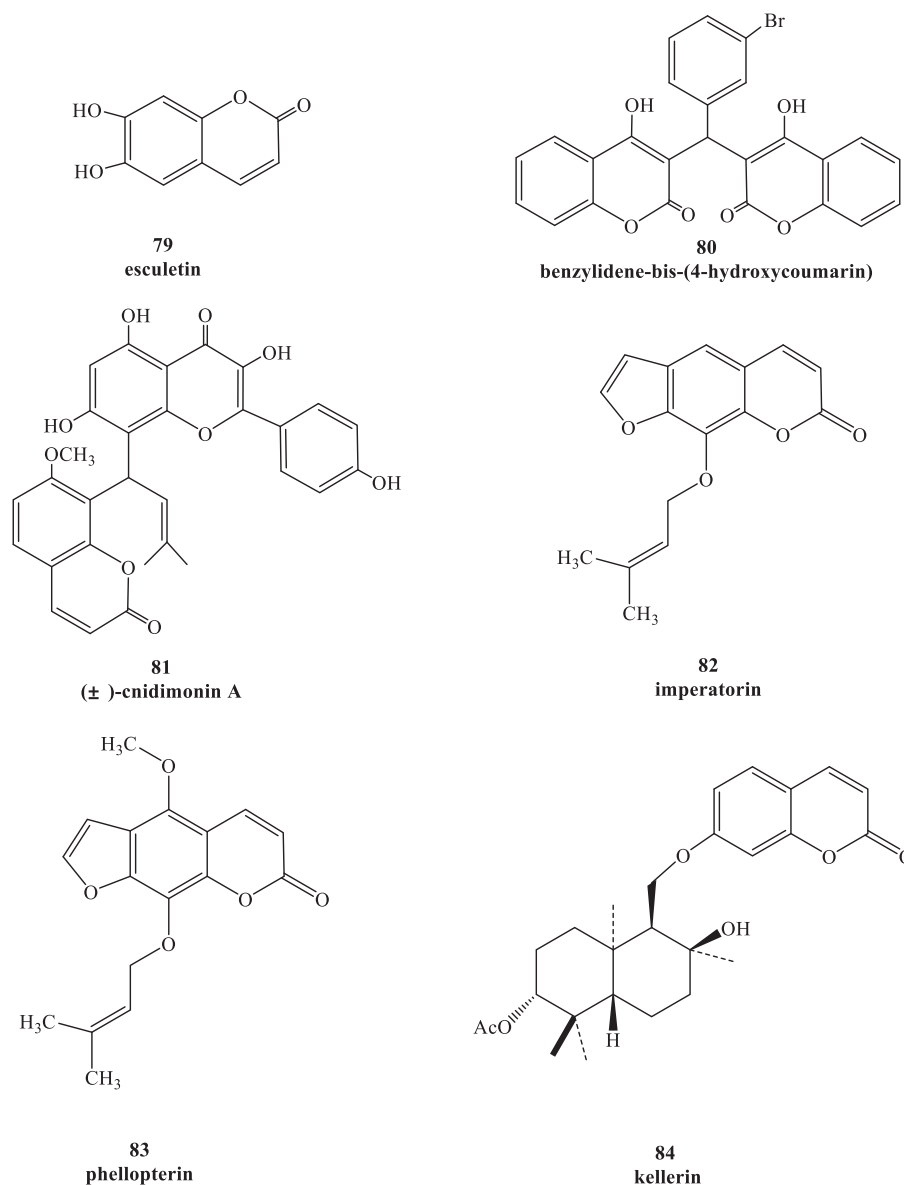
Figure 9 The chemical structures of coumarin derivatives with anti-HSV activity.

inhibiting directly the function of HCV proteins or reduced viral access to human cells, thus inhibiting viral replication, being hopeful for RAV treatment.

In 2008, Neyts et al synthesized and found that two benzimidazole—SCH₂—coumarin (Table 3, **compound 59, compound 60**) conjugates could inhibit HCV subgenomic replicon replication. Structure-activity relationship (SAR) revealed that the bromo or methoxyl group on the coumarin nucleus enhanced the inhibitory activity of these compounds to the HCV.[73] Then they designed and synthesized another series of analogues by incorporating heteroatoms into the benzimidazole moiety, and connected the heterocyclic including imidazopyridine, purine, benzoxazole with coumarin nucleus, forming three conjugated coumarin derivatives(**compound 61—63**), which exhibited excellent antiviral potency.[74] In 2011, a novel class of conjugated compounds with 3-(chloromethyl) coumarins and 9-(β-D-ribofuranosyl) purine-8-

thiones bearing different substituents were synthesized, three of which exhibited inhibitory effects on HCV subgenomic replicon replication (**compound 64—66**), and introducing coumarin moiety in the conjugated compounds was essential to the anti-HCV activity of these compounds.[75] In 2013, the same research team synthesized a series of hinged benzimidazole-coumarin hybrids and β-d-ribofuranosides, and three of them could inhibit HCV replication remarkably (**compound 67—69**), and the attachment of a methyl group to the benzimidazole nucleus attributed to the anti-HCV activity. On this basis, the triple conjugated compound also exhibited anti-HCV activity with a significant SI value.[76] In 2016, they also synthesized a sequence of imidazole—coumarin conjugates compounds with a —SCH2-linking group, some of which showed significant anti-HCV activity (**compound 70—72**). In accordance with the SAR, hybrid compounds bearing a simple imidazole nucleus showed greater anti-HCV

activity. Hence, introducing a substituent into the coumarin nucleus could improve both potency and selectivity of the conjugates.[77] Due to the new chemical structure and novel anti-viral mechanism, coumarins will be the possible candidates against the resistance-associated variant.

Coumarin derivatives against DNA virus

Anti-hepatitisB virus

HBV is a small double-stranded DNA virus with unusual features similar to retroviruses.[78,79] It is estimated that more than 250 million individuals worldwide are infected with chronic HBV infection. Although vaccine can prevent hepatitis B, so far there is no specific therapeutic agents.[80] Several classes of coumarins from natural products or coumarin derivatives have been evaluated for inhibitory effects against HBV. 7-Methoxy-8-prenylcoumarin Osthol (Fig. 8, compound 73) mainly extracted from the root of *Angelica pubescens*, could reduce hepatitis B surface antigen (HBsAg) secretion up to 70% by glycosylation, and exhibited the anti-HBV activity.[81] 6-Hydroxyl-7-methoxyl-coumarin (compound 74), one of the extract compound from the root and bark of streblus asper, showed the anti-HBV activity, and the C-6 hydroxy groups contributed to the potency of this compound.[82] A coumarin compound (compound 75) from the stem of Kadsura heteroclite also exhibited inhibitory activity up to 57% and 48% towards HBsAg and hepatitis B e-antigen (HBeAg) in HpeG 2.2.15 cells, respectively,[83] and a new coumarin glycoside (compound 76) from the seeds of *H. caudigerum* was proved as a promising anti-HBV agent by suppressing the secretion of HBsAg.[84] Recently, a coumarin compound esculetin (compound 77) was isolated from *Microsorium fortunei* (Moore) Ching, and it could obviously inhibit the expression of not only HBsAg and HBeAg, but HBV DNA and the hepatitis B virus X (HBx) *in vitro*. Furthermore, esculetin also could suppress the DHBV replication *in vivo*, alleviating liver injury caused by HBV, as well as reducing the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).[85] HBV covalently closed circular DNA (cccDNA) serves as the transcription template for HBV RNAs, and is responsible for the establishment of viral infection and persistence.[86,87] According to the reported literature, the host molecules that modulated the cccDNA minichromosome were potential targets of anti-HBV therapy.[88] At present, only one research showed that dicumarol (compound 78), one of the coumarin derivatives, could inhibit HBV replication and reduce the HBV-ccDNA level in HBV infected cells.[79]

Anti-herpes simplex virus

Herpes simplex virus (HSV) is a double-stranded DNA virus which was categorized into two distinct herpesvirus species, herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2) due to the differences in antigenicity.[89] WHO estimated that about 3.7 billion people under the age of 50 had HSV-1 infection, and 491 million people aged 15−49 years worldwide were living with the genital herpes infection caused by HSV-2.[90] However, there are only a few

therapies targeting the worldwide prevalent virus with no preventive vaccine.

In 2009, esculetin (Fig. 9, compound 79) was the first reported coumarin compound with anti-HSV-1 activity at a concentration of 0.14 mM, which was evaluated in VERO cells by cytopathic effect (CPE) assay.[91] Then the 4-bromobenzylidene derivative of bis-(4-hydroxycoumarin) (compound 80) exerted potential inhibitory activity against HSV-1and HSV-2 in human embryonic lung (HEL) cell cultures, and 50% inhibitory concentration (EC$_{50}$) values of both were 9 μM, while minimum cytotoxic concentration (MCC) was more than 20 μM.[92] As coumarin−flavonol compound (±)-cnidimonin A (compound 81) was found in the fruits of *Cnidium monnieri*, and the bioassay data showed that this racemic mixture (±)-1 possessed strong activity against HSV-1 with EC$_{50}$ values of 1.23 μM in VERO cells.[93] In additional, these compounds extracted from fruits of *Angelica archangelica* L also had antiviral activity against HSV-1, which was proved using cytopathic effect (CPE) inhibitory assay and virus titer reduction assay in the Vero cell line. Barbara Rajtar and colleagues found that imperatorin (compound 82) and phellopterin (compound 83) had the potent anti-HSV-1 activity. These coumarin derivatives could reduce the virus replication markedly with the concentration ranging from 3.90 μg/mL to 31.25 μg/mL, and the SAR manifested that the isopentenyloxy moiety at C-8 position contributed significantly to the antiviral activity.[94] As a sesquiterpene coumarin separated from the gum-resin of Ferula assa-foetida, kellerin (compound 84) was a promising antiviral agent by suppressing the replication of HSV-1with EC$_{50}$ at 38 μg/mL in Vero cells, and it also could significantly inhibit cytopathic effects (CPE), reducing the viral titer of HSV-1 DNA viral strain KOS.[95]

Conclusion

As a natural product, coumarin has received more and more attention in the field of drug development since its discovery in 1812. In recent years, with the development of drug screening technologies and methods, coumarin and its semi-synthetic derivatives have showed antiviral activity, and many coumarin-based anti-viral agents with high efficiency and low side effects were obtained. This review provides the main insights on current development in the area of antiviral agents of coumarin and its derivatives, and also discusses the structure activity relationship of potent coumarin derivatives.

Although there is no coumarin candidate used in clinical as antiviral drug, some coumarin candidates were developed as the anticoagulants (dicoumarol, warfarin, acenocoumarol), antibiotics (novobiocin, coumermycin) and antidermatosis drugs (methoxsalen). These evidence indicated that coumarin derivatives had the potential druggability.[96−98] Furthermore, numerous attempts have been made for modifying the different position of coumarin nucleus to improve their anti-viral activities, and make the coumarin such as DCK and the analogues as the promising candidates against HIV. Meanwhile, some coumarin derivatives have obvious toxic effects in rodents and the toxicity of coumarins in different animals and organs are significantly different, and toxic reactions occurred mainly

in the coumarin metabolism after high dose oral administration.[99,100] Other possible reasons include the high liposolubility and photosensitization of some coumarins, certainly, and the toxicity and efficiency varies based on the chemical structure.

Since modifications on the nucleus of chemical structure can increase the inhibitory activity of coumarin against viruses including many RNA and DNA viruses, it results in a large number of compounds having diverse mechanism of actions, and the selective targeting proteins of these compounds include not only the specific stages of certain virus, but the common process of viral life cycle, such as viral attachment to the cells or replication in the cells.

In this article we mainly focus on the current developments of coumarin-based antiviral agents and the hybrid compounds bearing coumarin nucleus with antiviral activity. At present, these coumarins are undergoing preclinical research, and in-depth study of the antiviral activity mechanism of such compounds is still to be explored. We believe this review is helpful for medicinal chemists or pharmacologist to rational design and development of potential coumarin-related antiviral drugs with more activity and less toxicity.

Conflict of interests

The authors declare no conflict of interest.

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