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Important Advances on Antiviral Profile of Chromone Derivatives

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ABSTRACT

Chromones are chemically 4*H*-1-benzopyran-4-ones which constitute an important class of oxygen atom containing heterocyclic compounds. Chromones and their derivatives show considerable pharmaceutical interest since they exhibit a broad range of biological activities which include antiviral, antimicrobial, antiallergic and antitumor activities etc. In addition, many flavonoids also possess several therapeutically interesting biological activities. Flavonoids have been shown to have antibacterial, antiviral, anti-inflammatory, anti-inflammatory, antiallergic, antimutagenic, antineoplastic, anti-thrombotic and vasodilatory activities etc. The flavones (2-phenylchromones), isoflavones (3-phenylchromones) and the flavanol (quercetin) are the most commonly found phytochemicals. The aim of this review is to summarise the putative biological actions of chromones and their derivatives and to obtain a further understanding of the reported antiviral activity of these substances based on recent most literature survey.

Keywords: Chromone, flavonoids, heterocyclics, antiviral activity.

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INTRODUCTION

Various types of antiviral drugs are being developed and used for the treatment and prevention of viral infections. Use of Antiviral drugs has increased during past decade to treat viral diseases. This has resulted in development of inefficacy of the drug towards the target virus. Moreover almost all antiviral drugs have potential side effects. Therefore, before designing antiviral drugs it is important to know more about viruses as per the information given below:

Viral infection

A virus is a sub-microscopic, non cellular infectious agent that is unable to grow or reproduce outside a host cell. Viruses are obligate intracellular parasites which are the major cause of death and disease [1].

Structure of virus

A virion **(Figure 1)** is an intact infectious viral particle which consists of genome. Every virus contains nucleic acids (genes) either *single or double stranded,* RNA or DNA, but never both. The virus has a coat of protein called capsid around the nucleic acid which protects the genome and gives shape to the virus. Capsid is composed of protein subunits called capsomeres. Viruses are of two types: enveloped viruses and non enveloped viruses. Enveloped viruses have an outer envelope of fat, protein and carbohydrates which are derived from cell membrane of host cell. Example of enveloped virus is the *Influenza virus*. The nonenveloped viruses do not contain envelop. Examples of non-enveloped viruses include norovirus, rotavirus and human papillomavirus (HPV) [1].

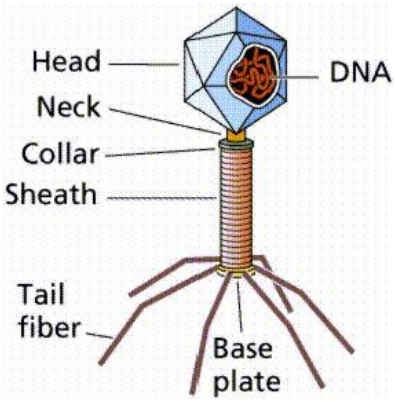

Figure 1- Structure of a Virus

Mechanism of viral infection

The viral infection **(Figure 2)** involves the following steps:

Step 1: The virus attaches itself to its host cell.
Step 2: The virus or its genetic information penetrates the cell.
Step 3: The nucleic acid is uncoated which frees the DNA or RNA from its capsomeres or lipid envelope and permits the host cell to express the genetic functions of the virus.
Step 4: At this stage in the life cycle of many viruses, only a portion of the viral genetic information is expressed, resulting in the synthesis of only the subset of viral-encoded proteins collectively called the early viral gene functions (proteins). These proteins may function in one of several ways. In some cases, they contribute directly to the replication of the viral chromosome. In some cases, these viral proteins turn off many of the host-cell activities, maximizing the cell's available resources for virus production.
Step 5: The viral nucleic acid is then synthesized to produce hundreds or thousands of copies of viral chromosome.
Step 6: At this time, a second subset of the viral genetic information, commonly termed the late proteins, is expressed. These are the structural proteins including the capsomeres of the virus.
Step 7: The capsomeres are assembled to form a new shell around the nucleic acid of the virus.
Step 8: The mature virus having duplicated its new copies, is released from the infected cell to attack a new cell and repeat this process [2].

Going from step 1 to 8, a viral replication cycle displays temporal organization: specific events occur in sequence, each dependent upon the successful completion of the previous step. Both processes require quantitative and qualitative changes over time. Early viral proteins made from the simple genome of the infecting virus, are expressed at low levels while the late proteins are made from the newly replicated viral chromosomes produced in step 5. Quantitative changes are thus initiated and regulated chronologically. So, there are 6 basic steps to viral infections [3].

- Recognition
- Attachment
- Entry
- Integration into the hosts DNA
- Replication
- Release

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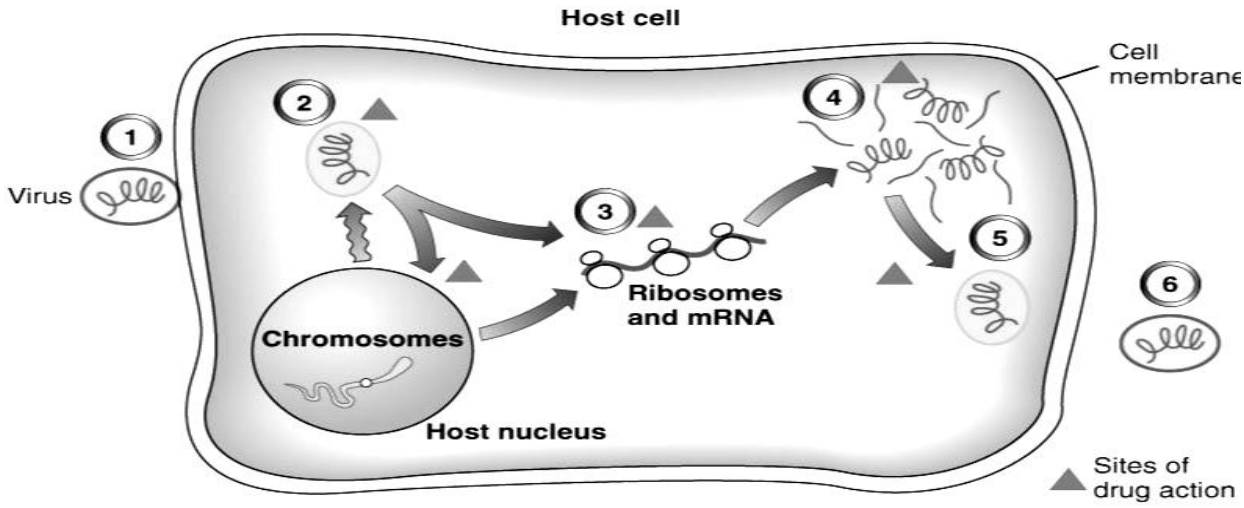

Figure 2: Virus replication. 1. Attachment to host cell 2. Uncoating of virus & entry of viral nucleic acid into host cell nucleus 3. Control of DNA, RNA &/or protein production 4. Production of viral subunits 5. Assembly of virions 6. Release of virions

Antiviral agents

Like antibiotics for bacteria, antiviral drugs are a class of antimicrobials used specifically for treating viral infections. They are relatively harmless to host because they inhibit the development of pathogens instead of destroying them. Most of the antiviral agents need to be activated by viral and cellular enzymes before exerting antiviral effect **(Table 1)**. Hence, activity of enzymes and concentration of substrates will influence the efficacy of these drugs. In majority of acute infections, viral replication is already at its peak when symptoms appear. Specific events in virus replication identified as targets for antiviral agents are viral adsorption, penetration, uncoating and viral nucleic acid synthesis as well as viral protein synthesis. To be effective, antiviral therapy has to be started in the incubation period, i.e has to be prophylactic. The uses and adverse reactions of common antiviral drugs are given in **Table 2** [4-6].

Table 1: Classification of Antiviral Drugs

Virus	Antiviral Drug	Target
Herpes viruses	Vidarabine	Virus polymerase
Herpes simplex	Acyclovir	Virus polymerase
Cytomegalovirus	Gancyclovir	Virus polymerase
Retroviruses (HIV)	Zidovudine, Didanosine, Zalcitabine, Lamivudine	Reverse transcriptase
Retroviruses (HIV)	Saquinavir, Ritonavir, Indinavir, Nelfinavir	HIV protease
HCV, HSV	Ribavirin	RNA mutagen
Influenza A	Amantadine, Rimantadine	Haemagglutinin protein
Influenza B	Relenza and Tamiflu	Neuraminidase Inhibitor
Picorna viruses	Pleconaril	Blocks attachment
Hepatitis B & C	Interferons	Cell defence proteins

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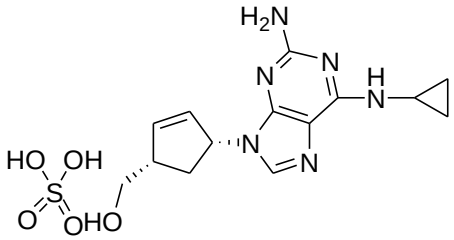
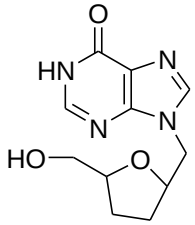
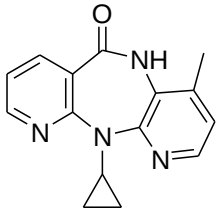
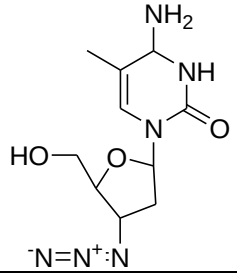
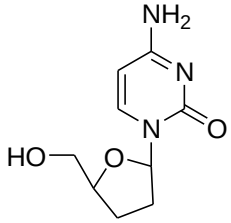
Table 2: Clinically Used Antiviral Drugs

S. No.	Brand Name	Chemical Structure	Use
1.	Ziagen®		AIDS
2.	Videx®		AIDS
3.	Viramune®		AIDS
4.	Retrovir®		AIDS
5.	Hivid®		AIDS

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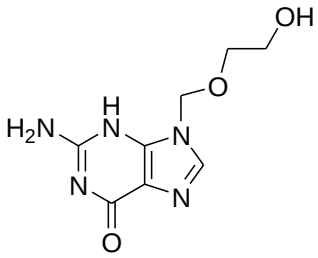
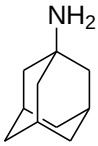
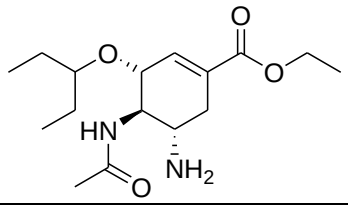
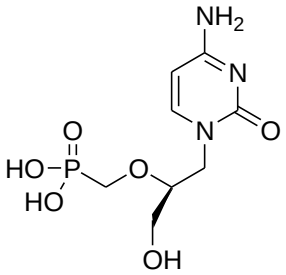
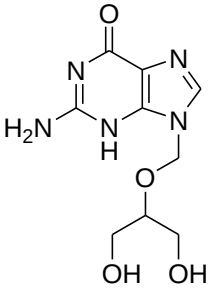
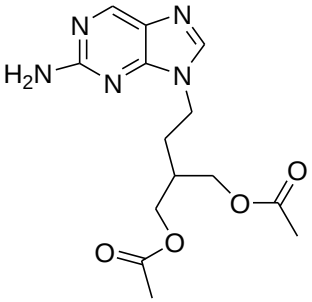
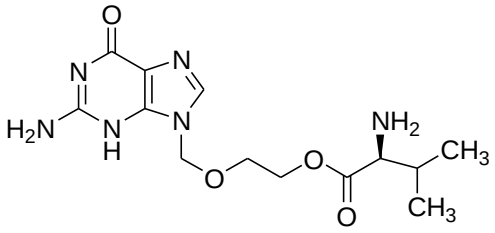
6.	Zovirax®		Chicken pox
7.	Symmetrel®		Influenza A
8.	Tamiflu®		Influenza B
9.	Vistide®		Retinitis
10.	Cytovene®		CMV retinitis
11.	Famvir®		Herpes zoster

12.	Valtrex®		HSV type Zoster

To overcome the limitations of current antiviral drugs, more effective compounds are being developed that allow greater inhibition of viruses, greater selectivity for virus-specific functions and fewer side effects, and may avoid emergence of resistant mutants. Specificity for infected cells may occur when virus-specified enzymes (e.g., thymidine kinase-induced by herpes simplex virus or varicella-zoster virus) activate drugs (e.g., acyclovir) [7].

The increased use of antiviral drugs has resulted in the emergence of antiviral drug resistant strains e.g., acyclovir, ganciclovir and foscarnet. Resistance to acyclovir or ganciclovir have occurred because of deficient intacellular phosphorylation of these agents which is required for drug activation. Resistance to foscarnet is due to viral DNA polymerase mutants that permits viral replication despite the presence of the drug [8].

Heterocyclic compounds **(Figure 3)** play very important role in the medicinal chemistry. This is not because of their abundance, but because of their chemical and biological significance of 12.5 million chemical compounds currently registered; about one half contain heterocyclic system.

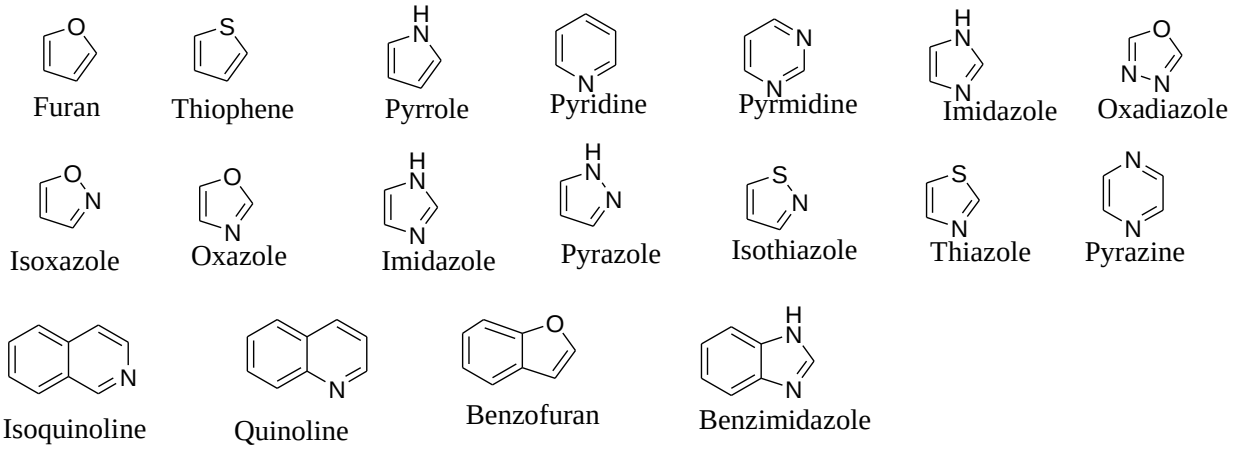


Figure 3: Chemical structures of some heterocyclic compounds

Chromones (1-benzopyran-4-ones) and their structural derivatives are ubiquitously found in the plant kingdom. These phytochemicals have motivated a great interest because of their usefulness as biologically active agents. The chromone moiety is an essential pharmacophore of a large number of bioactive molecules [9-12]. Several reported biological properties of this type of compounds include cytotoxic (anticancer) [13-15], neuroprotective [16, 17], HIV-inhibitory [18, 19], antimicrobial [20], antifungal [21], and antioxidant activity [22].

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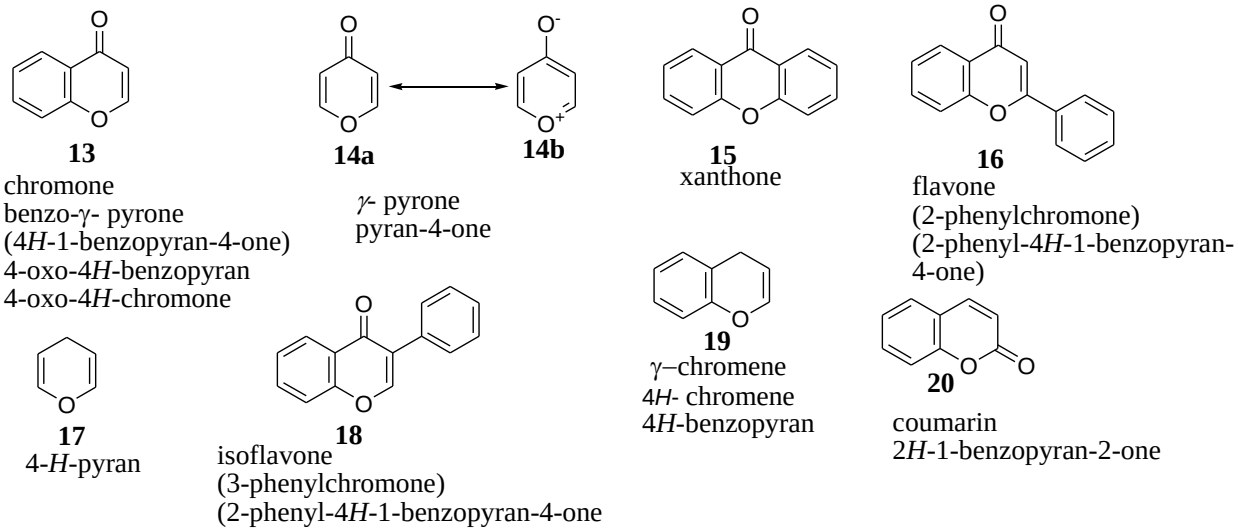
Chromone **13** is the parent structure for the benzo-fused oxygen-containing heterocyclic compounds which contain a γ-pyrone ring **14** [23, 24]. Bloch and Kostanecki [25] used the name "chromone" for several naturally occurring coloured compounds which contain the benzopyran-4-one moiety. Xanthone **15**, a chromone derivative, is doubly benzo- fused, while other common derivatives include flavones **16** (2-phenylchromones), and isoflavones **18** (3-phenylchromones) [26]. The pyran analogues **17** and **19** have no carbonyl group, while coumarin **20** is isomeric with chromone, differing only in the location of the carbonyl group [26, 27].



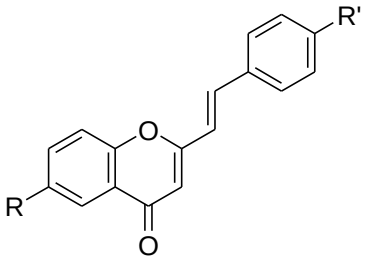
ANTIVIRAL ACTIVITY

The chromone moiety constitutes an important component of the pharmacophore of a number of biologically active molecules [28]. Since the chemistry of chromones has been comprehensively studied [26], which focuses mainly on the more recent literature (since 1980) on synthetic and naturally occurring chromone derivatives exhibiting antiviral activity. The collective term chromones will also be used in reference to chromone derivatives. Antiviral activity of chromone derivatives as per the recent most literature survey has been compiled as given below:

Anti-rhinovirus Activity

2-Styrylchromones (2-SC) are chromone derivatives characterized by the presence of a styryl group to the 2-position of the chromone structure. The 2-Styrylchromone structure bears important biological activities such as antiallergic, antitumor, affinity and selectivity for A3 adenosine receptors, antiviral, antioxidant and anti-inflammatory [29]. Styrylchromones **21a-21h** were synthesised by Desideri et al (2003) as a new class of antirhinovirus flavonoids with antiviral activity which was evaluated in HeLa cell cultures infected with rhinoviruses 1B and 14,

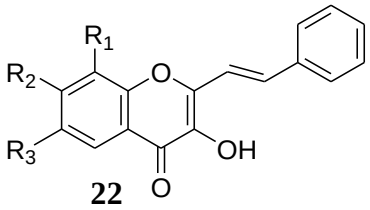
selected as representative serotypes for viral groups B and A of human rhinoviruses (HRVs), respectively. The most active compounds against both serotypes proved to be 4-nitro-2-styrylchromone **21e**, which had IC_{50} of 3.9 and 1.3 µM for HRVs 1B and 14, respectively. The reduction of the hydrophobic nitro group to the hydrophilic amino group resulted in 4-amino-2-styrylchromone **21h** which had lower potency (IC_{50}=15.1 and 13.5 µM) [30].



21

21 a R = R' = H
21 b R = H, R' = CI
21 c R = H, R' = CH_3
21 d R = H, R' = OCH_3
21 e R = H, R' = NO_2
21 f R = R' = CI
21 g R = H, R'= OH
21 h R = H, R' = NH_2

Good anti-rhinovirus agents, namely 3-hydroxy-2-styryl chromones **22a-22e** were synthesised by Desideri et al (2003). These compounds have been obtained in high yields from the corresponding ω 2' -hydroxy- cinnamylidene acetophenones on treatment with hydrogen peroxide-diethylamine in dimethyl sulphoxide (DMSO)-dioxan medium [30].

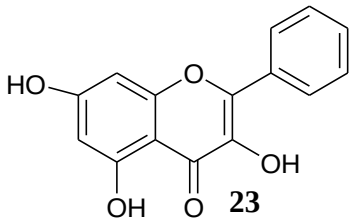


22

22a, R_1= H, R_2= H, R_3= H
22b, R_1= H, R_2= OCH_3, R_3= H
22c, R_1= H, R_2= H, R_3= CH_3
22d, R_1= H, R_2= H, R_3= OCH_3
22e, R_1= OCH_3, R_2=OCH_3, R_3= H

Anti-Herpes simplex virus activity

Meyer et al (1997) reported a naturally occurring flavones, Galangin **23** or 3,5,7-trihydroxyflavone is derived from the perennial herb *Helichrysum aureonitens*, which is particularly a useful compound, since it has shown activity against a wide range of viruses, in particular HSV-1 and Coxsackie B virus type 1 [31].



23

A prenylated flavonoid, moralbanone **24**, along with five known antiviral compounds kuwanon S **25**, cyclomorusin **26**, eudraflavone B hydroperoxide **27**, oxydihydromorusin **28** and leachianone G **29** were isolated from the root bark of *Morus alba* L by Jiang et al (2003).

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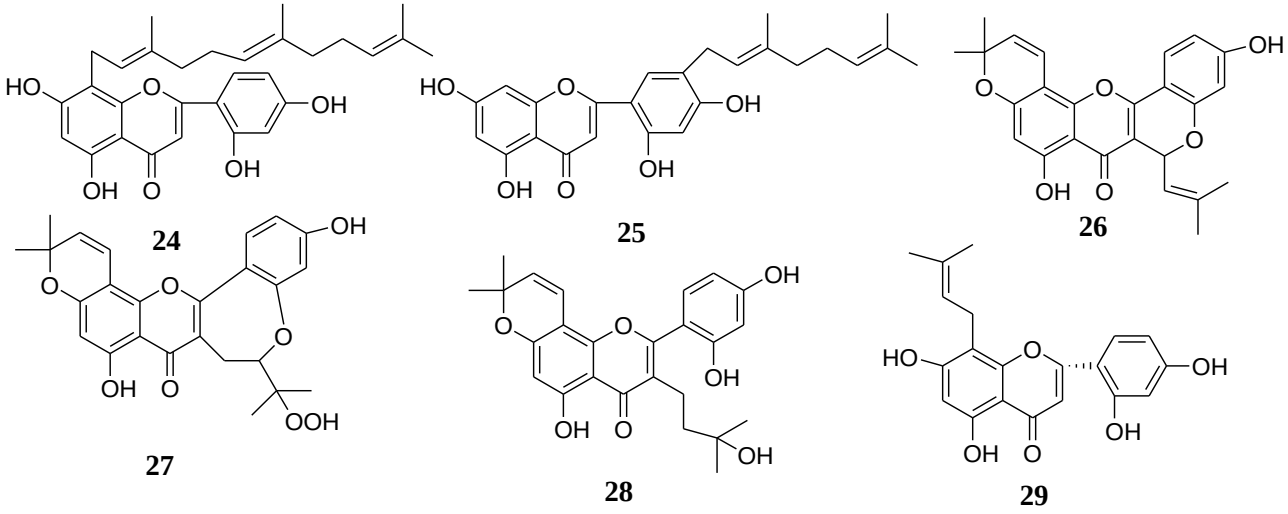
Leachianone G showed potent antiviral activity (IC_{50}=1.6 µg/ml) against herpes simplex type 1 virus (HSV-1) [32].



Anti-HIV activity

Houghton et al (1994) separated chromone alkaloid schumannificine **28** from the non-polar fraction of a methanolic extract of the rootbark of *Schumanniophyton magnificum* and found that this compound was active against human immunodeficiency virus (HIV) and herpes simplex virus (HSV). Other related chromone alkaloids and their derivatives **28-45** displayed the greatest activity against HIV and HSV. The presence of a piperidine ring and unsubstituted hydroxyl groups on the molecules seems to favour the anti-HIV activity. The anti-HIV activity is considered to be due to irreversible binding to gp120 rather than inhibition of reverse transcriptase or protease [33].

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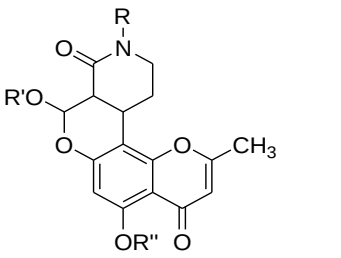
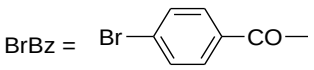
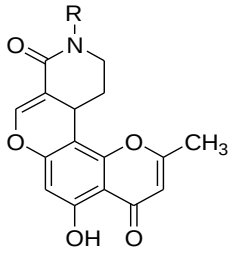
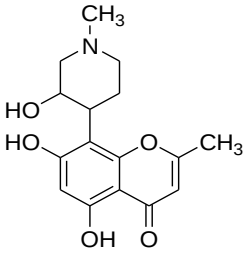


	R	R'	R"
30	H	H	H
31	CH_3	H	H
32	H	BrBz	H
33	H	BrBz	BrBz
34	CH_3CO	CH_3CO	BrBz
35	CH_3CO	CH_3CO	CH_3CO
36	H	$CH_3(CH_2)_2CO$	H
37	H	CH_3	CH_3
38	H	CH_3	H
39	$(CH_3)_2$	H	H





40 R= H
41 R= CH_3



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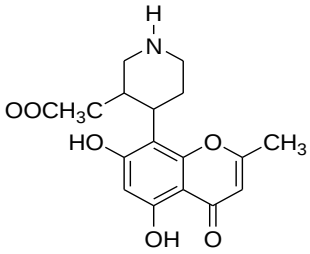

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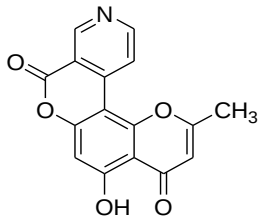

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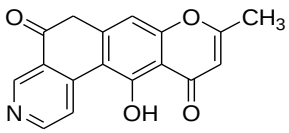

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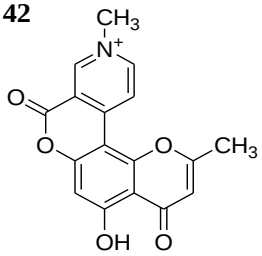

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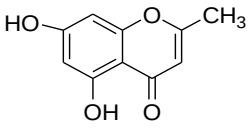

47

Structures of compounds: schumannificine **30**; N- methyl schumannificine **31**; Anhydro schumannificine **40**; N-methylanhydroschumannificine **41**; Rohitukine **42**; N-demethylrohitukine acetate **43**; Schumanniophytine **44**; Isoschumanniophytine **45**; N-methylschumanniophytine **46**; noreugenin **47**; 7'-(4-bromobenzoyl) schumannificine **32**; 7',5-di(4-bromobenzoyl) schumannificine **33**; N,7'-diacetylschumannificine **34**; N, 7'5-triacetylschumannificine **35**; 7'-butylschumannificine **36**; 7'5-dimethoxyschumannificine **37**; 7'-methoxyschumannificine **38**; N,N- dimethyl schumannificine **39**

Analogues of 3'R,4'R-di-O-(S)-camphanoyl-(+)-cis-khellactone (DCK), **48** and a series of mono- and disubstituted chromone derivatives of 3'R,4'R-di-O-(-)-camphanoyl-2',2'-dimethyldihydropyrano[2,3-f]chromone (DCP), **50** were designed and synthesized by Xie et al (2004) . All compounds **48-58** showed anti-HIV-1 activity against a non-drug-resistant strain in H9 lymphocytes and a multiple reverse transcriptase (RT) inhibitor-resistant strain in the MT4 cell line with EC(50) values ranging from 0.00032 to 0.0057 microM and remarkable therapeutic indexes (TI) ranging from 5.6 x 10(3) to 1.16 x 10(5). Several DCP analogues **51-57** exhibited extremely high anti-HIV activity but 2-Ethyl DCP **54** exhibited the best anti-HIV activity with an EC (50) value of 0.06 microM and TI of 718 against the multi-RT inhibitor-resistant HIV-1 strain. Further studies on mechanism of action suggest that these compounds inhibit the production of double-stranded viral DNA from the single-stranded DNA intermediate [34, 35].

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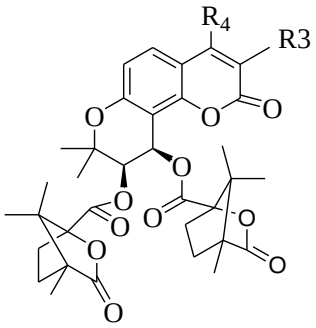
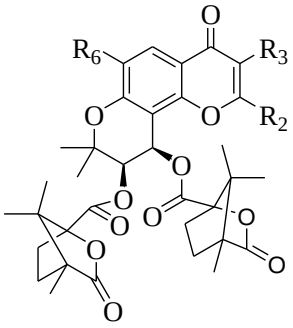
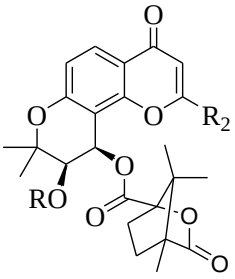
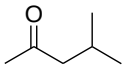


48 R_3= R_4= H, DCK
49 R_3 = H, R_4 = CH_3
50 R_3 = CH_2OH, R_4 = CH_3

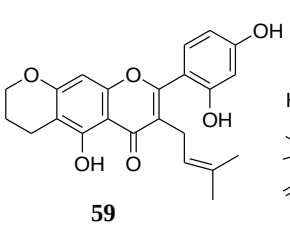


51 R_2 = R_3 = R_6 = H, DCP
52 R_2 = R_6 = H, R_3 = CH_3
53 R_2 = CH_3, R_3 = R_6 = H
54 R_2 = CH_2CH_3, R_3 = R_6 = H
55 R_2 = $CH_2CH_2CH_3$, R_3 = R_6 = H
56 R_2 = $CH(CH_3)_2$,R_3 = R_6 = H
57 R_2 = R_3 = CH_3, R_6 = H



58 R_2 = CH_3, R = 

The organic extract of the bark from the plant *M. tinctoria* (collected in Peru, in February 1988) exhibited moderate anti-human immunodeficiency virus activity. From this extract, the new compounds macluraxanthone B **60**, macluraxanthone C **61**, dihydrocudraflavone B **59**, cudraxanthone **62**, gartanin **63** and 8- desoxygartanin **64** were identified [36].



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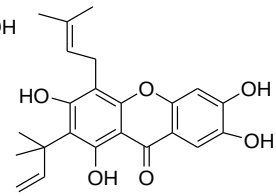

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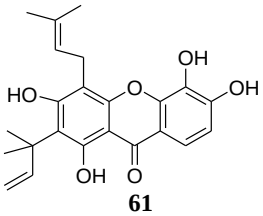

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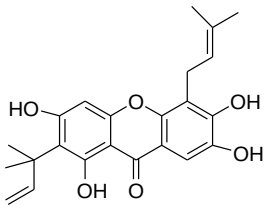

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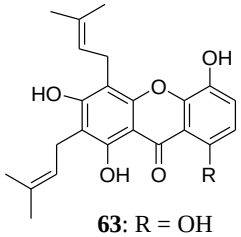

63: R = OH
64: R = H

The natural product (+)-Calanolide A **65** was previously found as an inhibitor of HIV-1 reverse transcriptase. Some other coumarin analogues, such as (+)- inophyllum B **66** [37] and (+)-cordatolide A **67** [38], Pseudocalanolide C **68**, Pseudocordatolide **69** have also been isolated from plants of the genus *Calophyllum* by Dharmaratne et al (1985) and the compounds are identified to be specific HIV-1 reverse transcriptase inhibitors.

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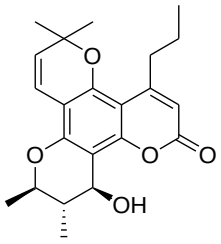
Chemical Structures of the Biologically Active Natural Dipyranocoumarins



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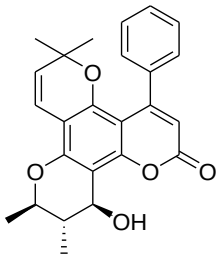

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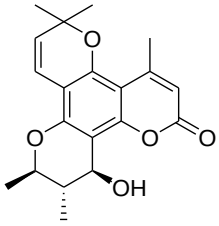

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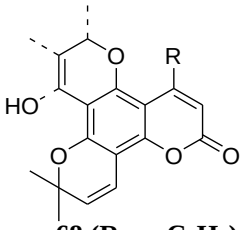
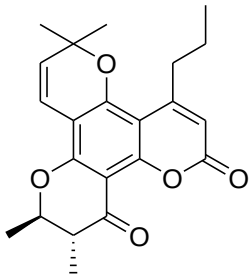


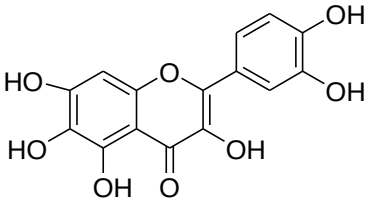
68 (R= n-C_3H_7)
69 (R= CH_3)

The three chromanone derivatives, (+)-, (-)-, and (+/-)-12-oxocalanolide A **70**, were evaluated for in vitro antiviral activities against HIV and simian immunodeficiency virus (SIV) by Ze-Qi et al (1998). The compounds were determined to be inhibitors of HIV-1 reverse transcriptase (RT) and exhibited activity against a variety of viruses selected for resistance to other HIV-1 nonnucleoside RT inhibitors. They are the first reported calanolide analogues capable of inhibiting SIV [39].



70

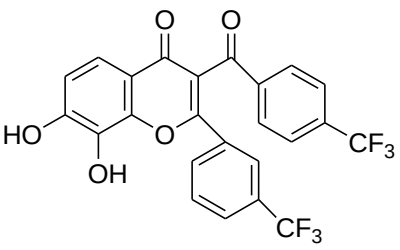
Quercategetin **71**, a flavone isolated by Nicklaus et al (1997) and Fesen et al (1994) from *Sculletaria baicarensis,* is known as the most potent HIV-1 integrase (IN) inhibitor, with the activity being attributed to the numerous hydroxyl groups [40-42].



71

Ungwitayatorn et al (2004) have synthesised chromone derivatives **72-78**. All the compounds have shown excellant anti-HIV-1 protease (PR) activity with inhibition efficiencies of 93.6%, 93.3%, 92.2% and 92.02%, respectively [46]. The chromone xanthone derivatives **75**, **76** were found in *Penicillium glabrum* (Wehmer) Westling extract by Wrigley et al (1994). These compounds exhibited CD4 binding activity in an enzyme-linked immunosorbent assay (ELISA) on

the binding of the monoclonal antibody, anti Leu 3a, to soluble recombinant CD4 [47]. CD4 is a glycoprotein expressed on the surface of mature helper/inducer T-lymphocytes; it has a crucial role in many immune responses and functions as a cellular receptor for HIV. Anti Leu 3a blocks both CD4 dependent T-cell responses and the binding of HIV to the T cells. These compounds thus have potential as immunosuppressive and anti-HIV agents [43].



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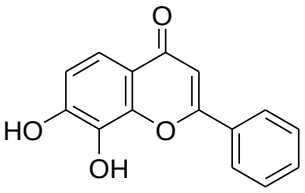

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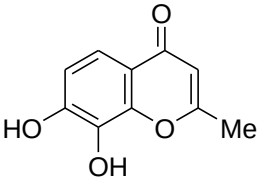

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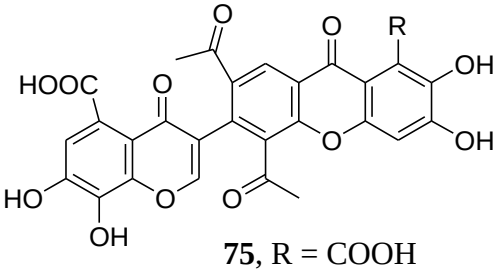
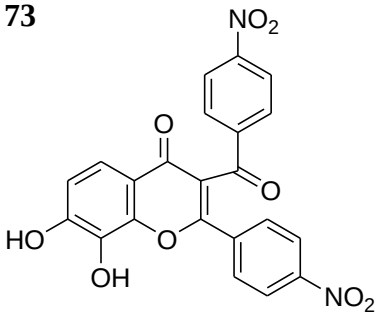


75, R = COOH
76, R= H



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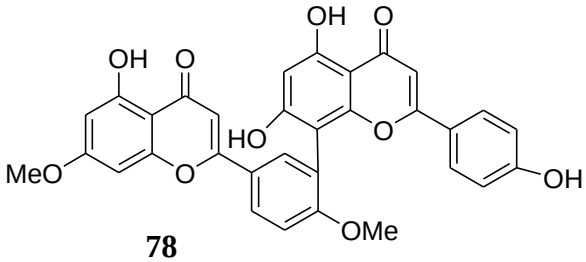

78

Anti- Hepatitis C virus activity

Park et al (2011) reported anti HCV activity of aryl diketoacid (ADK) which is due to the presence of two pharmacophoric elements, α, β-diketo acid moiety and substituted aryl ring [44]. 2-arylmethylaminomethyl-5,6-dihydroxychromone derivatives **79a-d** of which the dihydroxychromone moiety as well as the arylmethylaminomethyl substituent (R-$PhCH_2NHCH_2$–) were in exact match with the pharmacophore model of the ADK. The dihydroxychromone derivatives **79a–79d**, thus prepared, showed selective anti-HCV effect (EC(50)=2.0-14.0 µM, CC(50)>100 µM) with the substituent groups such as Cl, Br, I, and Me specifically at the 3-position of the aromatic ring [45].

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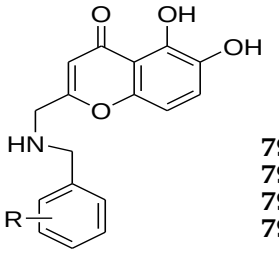
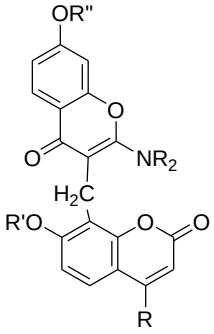


	R
79a,	3-Cl
79b,	3-Br
79c,	3-I
79d,	3-Me

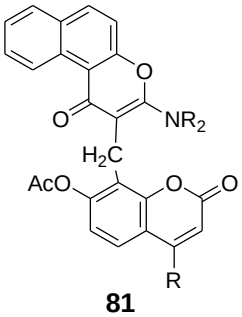
79

Mazzei et al (2008) have synthesised some unsymmetrical methylene derivatives **80**, **81,** namely coumarins bridged to chromones, which were found moderately active against Flaviviridae and in particular, HCV surrogate viruses in antiviral tests [46].



80

compound	NR_2	R	R'	R"
80a	$N(CH_3)_2$	H	CH_3CO	CH_3
80b	$N(CH_3)_2$	CH_3	CH_3CO	CH_3
80c	$N(C_2H_5)_2$	H	CH_3CO	CH_3
80d	$N(C_2H_5)_2$	CH_3	H	CH_3
80e	$N(C_2H_5)_2$	CH_3	CH_3CO	CH_3CO
80f	$N(C_2H_5)_2$	CH_3	CH_3CO	$CH_3(CH_2)_7$
80g	pirrolidin-1-yl	H	H	CH_3
80h	pirrolidin-1-yl	CH_3	H	CH_3
80i	piperdin-1-yl	H	CH_3CO	CH_3
80j	$N(CH_2CH_2OCH_3)_2$	H	CH_3CO	CH_3
80k	$N(CH_2CH_2OCH_3)_2$	CH_3	CH_3CO	CH_3



81

compound	NR_2	R
81a	$N(CH_3)_2$	H
81b	$N(C_2H_5)_2$	H
81c	$N(C_2H_5)_2$	CH_3
81d	piperdin-1-yl	H
81e	$N(CH_2CH_2OCH_3)_2$	H
81f	$N(CH_2CH_2OCH_3)_2$	CH_3

Anti-influenza virus activity

An ethanolic extract and the ethyl acetate fraction prepared from *Mosla scabra* (EFMS) prepared by Wu et al (2010) contained various compounds which showed potential inhibition against influenza viruses. On the basis of spectral analysis, the compounds isolated from EFMS were elucidated to be 5-hydroxy-6,7-dimethoxyflavone **82**, 5-hydroxy-7,8-dimethoxyflavone **83**, apigenin **84** and acacetin **85**. Compounds **82**, **83**, **84** and **85** showed significant anti-influenza viruses activities [47].

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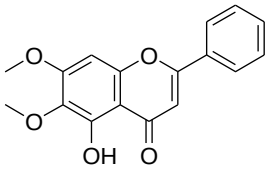
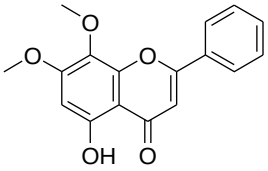


82



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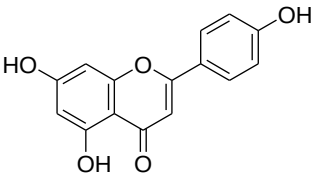

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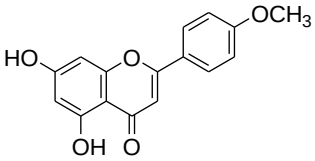
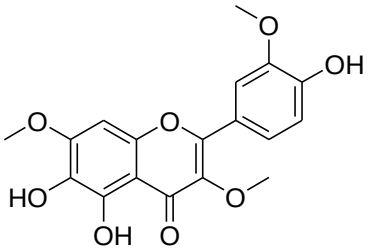


85

Antipicornaviral activity

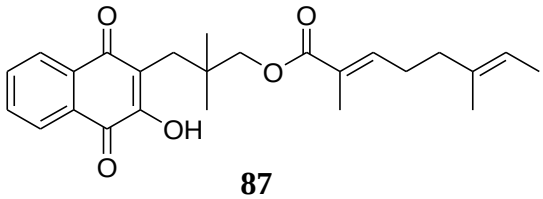
Semple et al (1999) have separated the antipicornaviral flavonoid chrysosplenol C (3,7,3′-trimethoxy-5,6,4′-trihydroxyflavone, **86**) from an ethanolic extract of the green aerial parts of the Australian plant *Pterocaulon sphacelatum* (Labill.) Benth. & Hook. f. ex F. Muell. This plant has been a favoured traditional medicine, used for the treatment of colds by the Australian Aboriginal people. This compound **86** is a 4′-hydroxy-3-methoxyflavone, one of a group of compounds known to be potent and specific inhibitors of picornaviral replication. These compounds inhibit the replication of rhinoviruses, the most frequent causative agent of the common cold. The coumarin 6,7,8-trimethoxycoumarin was also isolated from the ethanolic extract [48].



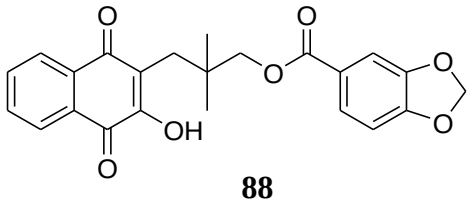
86

Anti- cytomegalovirus activity

The antiviral activity of rhinacanthin-C **87** and rhinacanthin-D **88** against cytomegalovirus in mice (mCMV) and human (hCMV) influenza viruses type–A, herpes simplex viruses type 2 and respiratory syncytial viruses were compared with gancyclovir, amantadine, acyclovir and ribavirin by Sendl *et al* (1996) [49].



87



88

CONCLUSION

Chromone and its derivatives are synthetic and natural heterocyclic compounds which show diversified pharmacological activities especially antiviral activities as per the literature mentioned in this manuscript. The valuable information provided in this review article may be significantly utilised by medicinal chemists to develop potent antiviral compounds having target specific mode of action for safer and effective treatment of fatal viral infections to save valuable lives of patients.

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