



Chromanone-A Prerogative Therapeutic Scaffold: An Overview

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Abstract

Chromanone or Chroman-4-one is the most important and interesting heterobicyclic compound and acts as a building block in medicinal chemistry for isolation, designing and synthesis of novel lead compounds. Structurally, absence of a double bond in chromanone between C-2 and C-3 shows a minor difference from chromone but exhibits significant variations in biological activities. In the present review, various studies published on synthesis, pharmacological evaluation on chroman-4-one analogues are addressed to signify the importance of chromanone as a versatile scaffold exhibiting a wide range of pharmacological activities. But, due to poor yield in the case of chemical synthesis and expensive isolation procedure from natural compounds, more studies are required to provide the most effective and cost-effective methods to synthesize novel chromanone analogs to give leads to chemistry community. Considering the versatility of chromanone, this review is designed to impart comprehensive, critical and authoritative information about chromanone template in drug designing and development.

Keywords Chroman-4-one · Chromone · Pharmacological activity · Synthesis · Analogues

1 Introduction

Chroman-4-one is one of the most important heterobicyclic moieties existing in natural compounds as polyphenols and as synthetic compounds like Taxifolin, also known as chromanone or benzo-dihydropyran or benzopyran. Structurally, chroman-4-one is a fusion of benzene nucleus (ring A) with

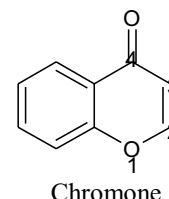
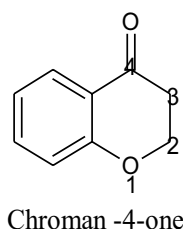
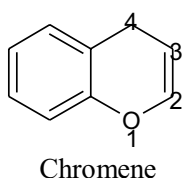
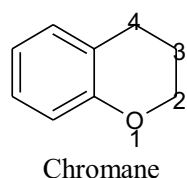
dihydropyran (ring B) which relates to chromane, chromene, chromone and chromenone, but the absence of C2-C3 double bond of chroman-4-one skeleton makes a minor difference (Table 1) from chromone and associated with diverse biological activities [1].

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Natural and synthetic chromanone analogs show various biological activities such as anticancer, tumor necrosis factor- α (TNF- α) inhibitors, antivasular, antidiabetic, antioxidant, antimicrobial, antifungal, antiviral, antileishmanial, insecticidal, spasmolytic, analgesic, anti-inflammatory, anticoagulant, estrogenic inhibitor, anti-acetylcholinesterase (AChE) inhibitor, antihuman immunodeficiency virus (HIV), anticonvulsant, antidepressants, anticoronary and antitubercular activity. Due to these activities, several analogs of chromane are also available in market like tocopherols (vitamin E), taxifolin (antidiabetic), tetrazole (antidiabetic), troglitazone (antidiabetic), ormeloxifene (anticancer) and nebivolol (beta-blocker) [2]. Moreover, several isolated flavanones, flavonols, homoisoflavonoids like naringenin, naringin, myricetin, dihydroquercetin and kaempferol are also under clinical studies [3]. Therefore, among the diverse array of chromane, chroman-4-one/4-chromanone are of considerable interest to researchers due to potency of this clinically useful pharmacophore in the treatment of cancer and several

other diseases [4]. Presently, a number of research groups are working in designing and development of more potent and significant chromanone analogues. So, in the present review, recent literature available up to 2020 about chroman-4-one derivative and their pharmacological activities is accrued. Present review article will offer a platform to the researchers in designing and development of novel potent chroman-4-one analogs.

2 Biological Activities of Chromanone

2.1 Anticancer Activity

Discovery and development of novel anticancer agents with potent cytotoxic activity is one of the top priorities in pharmaceutical research. Several limitations like variable efficacy, poor toxicity profile and adverse effects are associated with the usage of currently available chemotherapeutic agents [5]. Generally, cancer can be measured by assessing

Table 1 Properties of chromanone and chromone

Name	Chroman-4-one	Chromone
IUPAC name	4-Chromanone	4-Chromone
Other names (Synonym)	Chromanone, 4-chromanone, chroman-4-one dihydrobenzo pyran, benzopyran, 2,3-dihydro-4H-1-benzopyran-4-one	Chromone, 4-Chromone, 4H-Chromen-4-one, 4H-1-Benzopyran-4-one
Structure		
Formula	$C_9H_8O_2$	$C_9H_6O_2$
Formula weight	148.15 g/mol	146.14 g/mol
Molecular weight	148.15 g/mol	146.14 g/mol
Density	1.196 ± 0.06 g/cm ³	1.248 ± 0.06 g/cm ³
Xlog P3	1.4 ± 0.24	1.4 ± 0.24
Melting point	36.5 °C	59.0 °C
Composition	72.96%	73.97%
C	5.44%	4.14%
H	21.60%	21.90%
O		



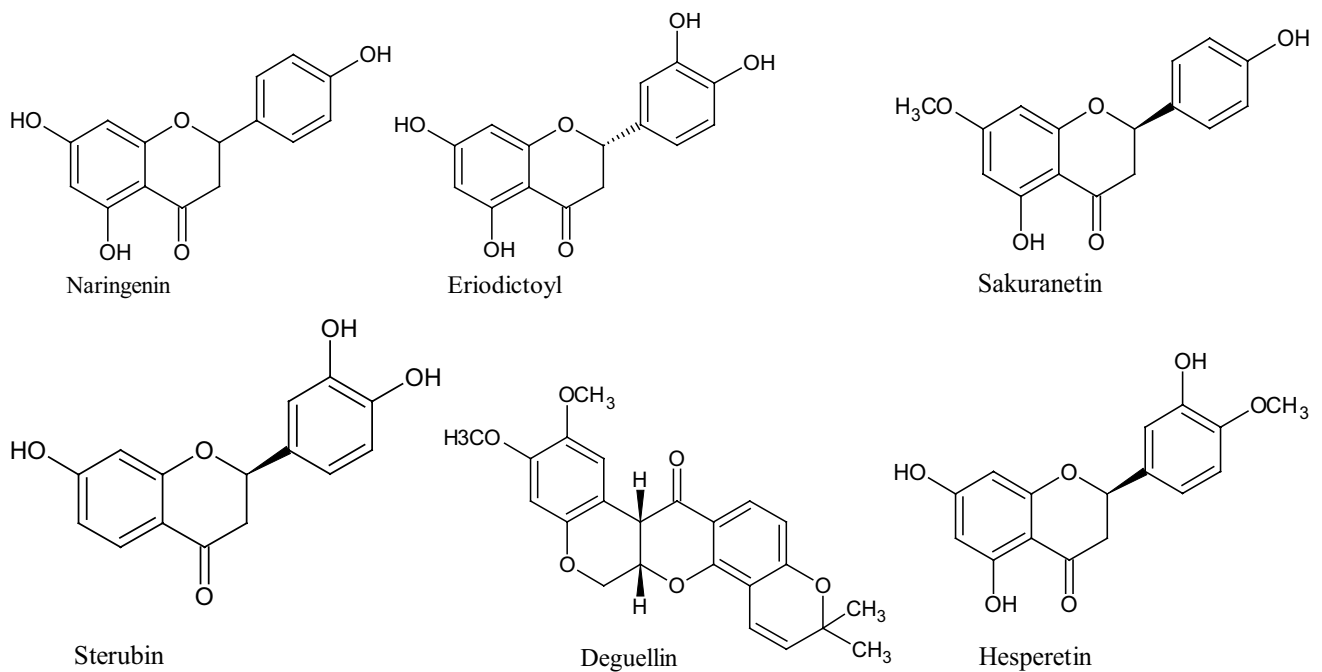


Fig. 1 Natural flavanones containing chroman-4-one as parent moiety

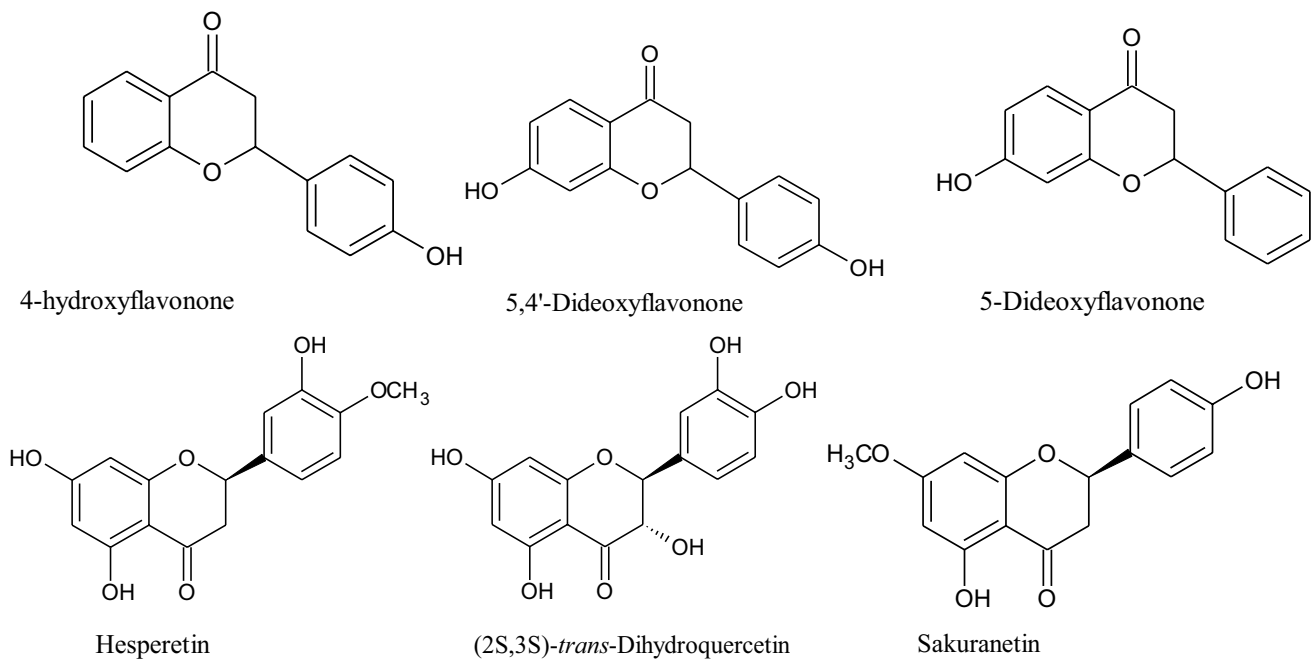


Fig. 2 Chroman-4-one derived structure (under development phase)

the degree of mitochondrial impairment and metabolic dysfunctions such as cellular energy supply, cell death signaling, ireregulation of metabolic pathways, formation of reactive oxygen species (ROS), compromised enzyme actions, aerobic glycolysis augmented in tumor cells, alterations

in lipid metabolism and unbalanced pH [6]. Therefore, to cure such metabolic dysfunctions, naturally occurring flavonoids, flavonols, flavanones (2-phenyl chroman-4-one derivatives) and homoisoflavanones exhibit good anticancer potential along with other pharmacological activities such

Table 2 Chroman-4-one analogs exhibiting anticancer activity

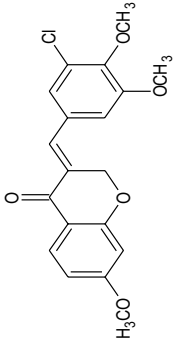
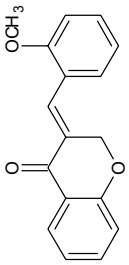
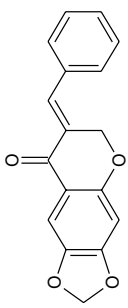
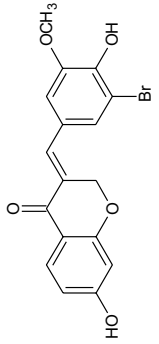
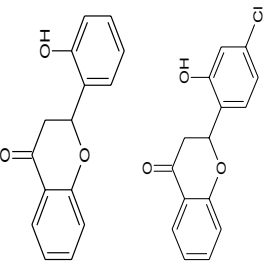
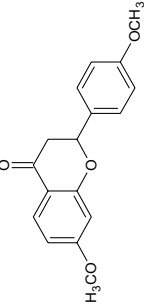
Sr. No.	Compound	Structure	Evaluation	Inference
1	(E)-3-benzylidene-7-methoxychroman-4-one derivatives (3-chloro-4,5-dimethoxybenzylidene derivative)		Evaluated against MDA-MB-231 (breast cancer), KB (nasopharyngeal epidermoid carcinoma) and SK-N-MC (human neuroblastoma) cell lines using MTT assay	Significant inhibition against MDA-MB-231 = 7.56 ± 2.23 , KB = 25.04 ± 10.60 and SK-N-MC = 9.64 ± 2.7 Marked as best anticancer agent among the series [16]
2	(E)-3-(2'-methoxybenzylidene)-4-chromanone		Evaluated for antiproliferative activity in HUVEC (human umbilical vein endothelial cells)	Exhibited highest potency against proliferation of endothelial cells with $IC_{50} = 19 \mu\text{M}$ [17]
3	6,7-Methylenedioxy-4-chromanone		Evaluated against three breast cancer cell lines (MCF-7, T47D and MDA-MB-231)	Exhibited highest anticancer activity against tested cell lines ($IC_{50} \leq 9.3 \mu\text{g/ml}$) [18]
4	3-Benzylidene-chroman-4-one derivatives		Evaluated against K562, MDA-MB-231 and SK-N-M Cell lines	Exhibited potent anticancer activity with $IC_{50} \leq 3.86 \mu\text{g/ml}$ [19]
5	Hydroxy flavanones		Evaluated against colorectal carcinoma cells such as A549, LLC, AGS, SK-Hep1 and HA22T cancer cells	Exhibited potent cytotoxic activity [20]
6	Synthetic flavanones (4',7-dimethoxyflavanone)		Evaluated for antiproliferative activity against MCF-7 (human breast cancer) cells Apoptotic cell population = 34.89%	Exhibited potent cytotoxic activity [21]



Table 2 (continued)

Sr. No.	Compound	Structure	Evaluation	Inference
7	Halogenated flavanones 3',7-dichloroflavanone		Evaluated against MCF-7, LNCaP, PC3, Hep-G2, KB, SK-N-MC cells	Very potent compound ($IC_{50} = 2.9 \mu M$) against MDA-MB-231 cell line than etoposide (reference drug) [22]
	3',6-Dichloroflavanone			
8	7, 8-Methylenedioxyflavanones		Examine cytotoxic potential and apoptosis in human leukemia cells	Exhibit better cytotoxic potency than reference [23]
9	2'-Chloro- or 2'-nitro-substituted chroman-4-one compounds		Tested for cytotoxic activity against Bel-7402, HL-60, BGC-823 and KB (human cancer cell lines)	Showed significant cytotoxic activity [24]
10	7-Methoxyisoflavanone		Evaluated against HL60 (acute myeloblastic leukemia cells) and PBMC (peripheral blood mononuclear cells) using MTT assay	Displayed highest anticancer activity against HL60 cells [25]
	Diarylchromanone			
11	3-Arylidene flavanone and chromanone (E, Z isomers) and 3-arylflavones		Screened against HL-60, NALM-6, WM115 and normal cells HUVEC cancer cell lines	Z-isomer (chromanone) was found to be more cytotoxic, while E-isomer was entirely inactive $IC_{50} = 0.9 \pm 0.2$ (HL60), 1.6 ± 0.3 (NALM-6), 6.3 ± 0.5 (WM-115), 5.77 ± 0.17 (HUVEC) [26]



Table 2 (continued)

Sr. No.	Compound	Structure	Evaluation	Inference
12	3-Benzylchroman-4-ones	<p>(a)</p> <p>(b)</p>	Examined against two cancerous cell lines BT549 (human breast carcinoma), HeLa (human cervical carcinoma) and one noncancerous cell line Vero (normal kidney epithelial cells) by MTT assay	3-Benzylchroman-4-one derivatives (a) was found to be the most active against BT549 (IC ₅₀ = 20.1 mM), HeLa cell lines (IC ₅₀ = 42.8 mM), whereas 3-benzylchroman-4-one derivatives (b) showed significant activity against HeLa cells (IC ₅₀ = 20.45 mM) only [27]
13	3-Methenylthiochroman-4-one-1, 1-dioxide		Tested against Ehrlich ascites carcinoma tumor growth	80% inhibition of Ehrlich ascites carcinoma tumor growth in mice was observed [28]
14	Novel tricyclic heterocyclic chromanone compounds		Examined against lung, breast and CNS cell lines	Showed significant inhibition against all cell lines tested and marked as active anticancer agent [29]
15	Spiro [chroman-2, 4'-piperidin]-4-one derivatives		Examined cytotoxic activity against three human cancer cell lines; MCF-7 (human breast carcinoma), A2780 (human ovarian cancer) and HT-29 (human colorectal adenocarcinoma) using MTT assay	Spiro [chroman-2, 4'-piperidin]-4-one derivatives with a sulfonyl spacer shows the most potent activity with IC ₅₀ = 5.62 ± 1.33 μM (MCF-7) 0.31 ± 0.11 μM (A2780), and 0.47 ± 0.17 μM (HT-29), respectively [30]
16	Silibinin		Tested against T47D (breast cancer cell lines) by MTT assay	Combination of Silibinin and chrysin may have therapeutic value (combination indices < 1) used in treatment of breast cancer [31]
	Chrysin			



Table 2 (continued)

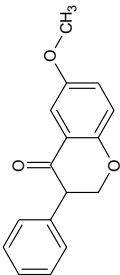
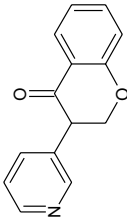
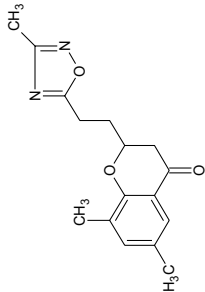
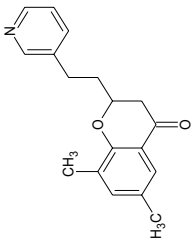
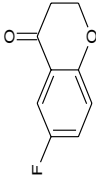
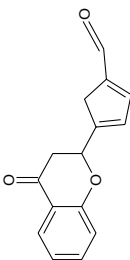
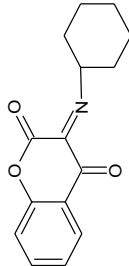
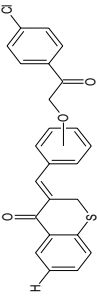
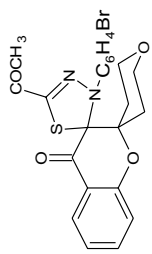
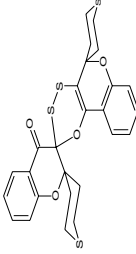
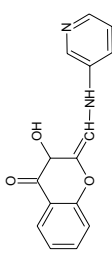
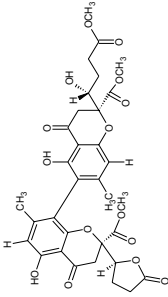
Sr. No.	Compound	Structure	Evaluation	Inference
17	6-Methoxy-3-phenyl chroman-4-one		Tested antiproliferative activity against MCF-7 (breast cancer) and A549 (lung carcinoma) cell lines	Selective Sirtuin 2 (SIRT2) inhibitors exhibited antiproliferative activity for breast cancer and lung carcinoma [7]
	3-(Pyridin-3-yl) chroman-4-one			
	1,2,4-Oxadiazole containing benzopyran analog			
	6,8-Dimethyl-2-[2-(pyridin-3-yl) ethyl]-benzopyran-4-one			
	6-Fluorobenzopyran-4-one			
18	2-[(Furan-2-yl) methoxy]-benzopyran-4-one		Screened against MCF7 mammary adenocarcinoma, HT29 (human colon adenocarcinoma) and A498 (human kidney adenocarcinoma) cell lines using sulforhodamine B dye	Found to possess very potent activity against all the tested cell lines, 7.3 ± 0.3 (MCF7), 4.9 ± 0.5 (HT29), 5.7 ± 0.9 (A498) [32]
19	Chromone-2-carboxamide (series I) and chromane-2,4-dione (series II) derivatives		Cytotoxic activity on HL-60, MOL T -4, and MCF-7 cancer cell lines	Showed highest cytotoxic activity against 64.6 ± 7.1 (HL-60), 68.4 ± 3.9 (MCF7), 33.2 ± 2.1 (MOLT-4) [33]



Table 2 (continued)

Sr. No.	Compound	Structure	Evaluation	Inference
20	3-[3/4-(2-aryl-2-oxoethoxy) arylidene] chroman/thiochroman-4-one derivatives		Screened against leukemia (L, 4 or 6 cell lines), non-small cell lung cancer (NSCLC, 9 cell lines), melanoma (M, 8 or 9 cell lines), colon cancer (CC, 7 cell lines), central nervous system cancer (CNSC, 6 cell lines), ovarian cancer (OC, 6 or 7 cell lines), prostate cancer (PC, 2 cell lines), renal cancer (RC, 8 cell lines), breast cancer (BC, 6 or 8 cell lines)	3-[3-(2-(4-Chlorophenyl)-2-oxoethoxy) benzylidene] thiochroman-4-one was found to be most potent and possessed very significant activity against all the tested cancer cell lines [34]
21	5''-Aceto-3''-(4-bromophenyl)-3''H,4''H-dispiro[chroman-2',4'-tetrahydropyran-3',2''-[1,3,4-thiadiazol]-4'-one		Tested against MCF-7 (human breast adenocarcinoma) cell lines	Exhibited significant anticancer potential [35]
	Trispiro[tetrahydrothiopyran-4,5'-2H-chromano-[3,4-e] [1, 3, 4] oxadithim-2',3''-chroman-2''/4'''-tetrahydrothiopyran]-4''-one			
22	2-hydroxy-4-chromanone derivatives		Examined for cytotoxic activity against cancer cells	Potent anticancer agent [36]
23	Novel noduliprevenone		Produced from the fungus <i>Nodulisporium</i> species, is an endophyte of a Mediterranean alga Tested for cytotoxic activity against 36 cancer cells	Showed significant cytotoxic activity against tested cell lines [37]



as anti-inflammatory, antioxidative, antidiabetic, antibacterial, antimicrobial, antifungal, antimutagenic, antiparasitic and anti-HIV [7, 8]. In this regard, the following naturally occurring flavanones such as naringenin [9], naringin [9], sakuranetin [10], eriodictyol [11], calyxin G, deguelin [12] and sterubin [13] have been reported (Figs. 1, 2) to possess potent cytotoxic profile. Moreover, these naturally occurring flavanones can also regulate cellular metabolism, scavenge free radical and suppress proliferation of cancer cells [12, 13]. However, the precise molecular mechanisms of these flavonoids accountable for cytotoxic potential have not been completely elucidated till now. Moreover, poor yield is also a major hurdle to explore the potential of these compounds. So, synthesis of compounds containing chromanone with efficient cytotoxic action might be a privileged approach in searching new targets for cancer treatment [14]. A number of compounds are found to have significant anticancer activity. For instance, several compounds containing chroman-4-one and its natural and synthetic analogs possessing significant anticancer potential against cancer cell lines are enlisted in Table 2 [15].

2.2 Antioxidant

Excessive production of ROS, suppression of antioxidants as a result of normal biochemical processes due to the effect of several environmental and endogenous factors result in imbalance of oxidative-antioxidant. The excessive ROS higher than physiological concentrations cause oxidative stress [38, 39]. Oxidative stress affects all cellular functioning which may be responsible for generation of severe diseases like diabetes complications, neurological disease, atherosclerosis, skin lesions, inflammation, rheumatoid arthritis, aging, cardiovascular diseases and cancer [39, 40]. Generally, antioxidants react or debilitate excessive level of ROS [41].

There are a number of isolated flavanones and homoisoflavanones such as silymarin, pinobanksin, silybin, liquiritin, isointricatinol reported for their antioxidant activity in 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method. Along with isolated components, synthetic benzylidene chromanone derivatives also showed DPPH radical scavenging and ferric reducing antioxidant power (FRAP) [42, 43]. According to structure activity relationship (SAR) of chromanone analogs, C-2 and C-3 substitution with methoxyphenyl, amine derivatives, aromatic groups, benzylidene and cyclohexyl carbamoyl yields more potent antioxidant compounds which can produce equivalent antioxidant activity like vitamin E and Trolox [44] enlisted in Table 3. Therefore, more synthetic work is required to produce new chroman-4-one scaffolds as effective antioxidant compounds which can be used to manage the pathogenesis of diseases in which oxidative stress plays a significant role.

2.3 Anti-inflammatory Activity

Localized protective reaction to infection or injury well known as inflammatory reaction plays a significant role in the pathological mechanism of various inflammation-related diseases like cancer, Alzheimer, diabetes, atherosclerosis and cardiovascular disorders. Knowledge of etiology and mechanism of inflammation progression can prevent further development of diseases [59].

For treatment of inflammation, diverse range of isolated homoisoflavanones, dihydroflavonols such as dihydromyricetin, hesperitin, stilbin and silybin containing chromanone pharmacophore are reported with vivid bioactivity and play an exclusive role in discovery and development of new anti-inflammatory drugs [60]. Among the isolated compounds from natural sources, chroman-4-one containing stilbin and silybin are used clinically as anti-inflammatory drugs. Moreover, these isolated compounds further pave the way for synthesis of new anti-inflammatory drugs via inhibition of cyclooxygenase 2 (COX-2). 4-Homoisoflavanones enlisted in Table 4 developed as chroman-4-one analogs were found to have significant inhibition for COX 2 receptor binding in range of 0 ± 5.4 to 0 ± 21.3 (% activity) [54, 61]. Likewise, a new chromanone, violacein A produced from *Streptomyces violaceoruber* emerged as potential therapeutic for treatment of inflammation-related disease by suppressing NF- κ B (nuclear factor kappa light chain enhancer of activated B cells) signaling pathways. Moreover, it can be used for the treatment of other diseases like cancer [62]. Generally, SAR studies revealed that C-2 substitution with hydroxybenzylidene, arylidene, hydroxyphenyl, pyridine-3-yl and fluoro-phenyl displayed the best anti-inflammatory activity with significant inhibition. So, exploring the substitutions at C-3, 6, 7 and 8th of chromanone nucleus yields more efficient anti-inflammatory compounds which can compete isolated phytochemicals as well as existing anti-inflammatory drugs [60, 62].

2.4 Antidiabetic Activity

Diabetes mellitus represented as hyperglycemia is increasing globally at very significant pace and has become a complex chronic metabolic disease associated with diabetic complications like diabetic neuropathy and nephropathy [69]. A number of potent antidiabetic drugs like metformin, glitazones, sulfonylureas, insulin, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter-2 inhibitors are available in the market, but long-term use of the antidiabetic drugs may cause serious side effects, and moreover, these drugs are less effective in management of associated diabetic complications [70]. In this regard, a number of isolated compounds as natural flavonols, flavanones and homoisoflavanones containing chromanone pharmacophore such as naringenin, hesperitin, dihydroquercetin,



Table 3 Chroman-4-one analogs exhibiting antioxidant potential

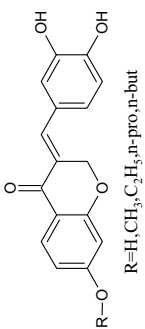
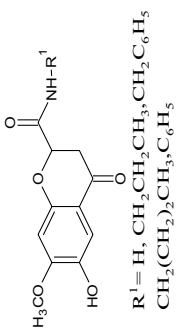
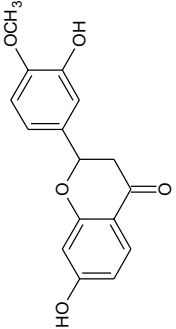
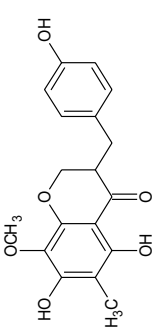
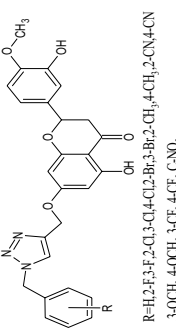
Sr. No.	Compound	Structure	Evaluation	Inference
1	3-Benzylidene-7-alkoxychroman-4-one derivatives	 <p>R=H, CH₃, C₂H₅, n-pro, n-but</p>	Assessed for 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, ferric reducing antioxidant power (FRAP) and thiobarbituric acid reactive substances	Shown following inhibition values 24.30 ± 0.51 to 35 ± 0.47 (DPPH), 10.96 ± 0.34 to 14.33 ± 0.52 (FRAP) and Fe ²⁺ + μM = 44.62 ± 0.48 to 71.64 ± 0.47 (TBARS) [45]
2	6-Hydroxy-7-methoxy-4-chromanone derivatives	 <p>R¹ = H, CH₂CH₂CH₃, CH₂C₆H₅, CH₂(CH₂)₂CH₃, C₆H₅</p>	(a) Assayed for lipid peroxidation inhibition initiated by Fe ²⁺ and ascorbic acid in rat brain homogenates (b) DPPH scavenging activity	Exhibited more potent antioxidant activity than vitamin E and Trolox with following values (a) lipid peroxidation inhibition = 176.8 to 300 (b) DPPH = 66.4 to 213.9 [46]
3	7-Hydroxy-2-(4-Hydroxy-3-Methoxyphenyl)-Chroman-4-one		Examined antioxidant activity	Reduced oxidative stress, LDL level, Mn-SOD levels and SOD ₂ gene expression of hyperlipidemic rats by endogenous antioxidant enzymes reduction [47]
4	3-(4'-Hydroxybenzyl)-5,7-dihydroxy-6-methyl-8-methoxychroman-4-one		Assayed for DPPH radical inhibition	Shown antioxidant property with DPPH inhibition = 5.90 ± 0.150 to 0.64 ± 0.334 [48]
5	Benzyl-1,2,3-triazolyl hesperetin derivatives	 <p>R=H, 2-F, 3-F, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 2-CH₃, 4-CH₃, 2-CN, 4-CN, 3-OCH₃, 4-OCH₃, 3-CF₃, 4-CF₃, C-NO₂</p>	Examined antioxidant activity using DPPH and ABTS assays	Significant antioxidant values obtained as follows 30.75 ± 1.965 to 83.57 ± 0.456 (DPPH) 8.545 ± 0.545 to 39.356 ± 0.644 (ABTS), respectively [49]



Table 3 (continued)

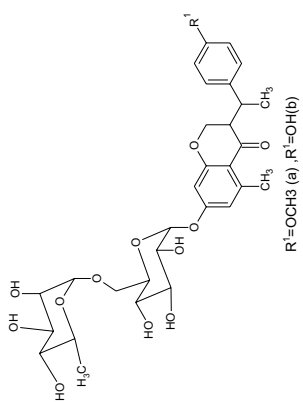
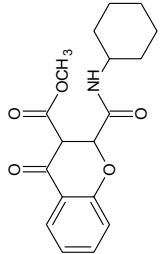
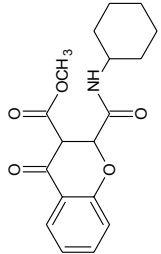
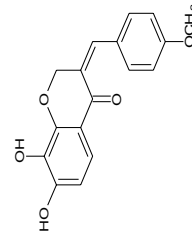
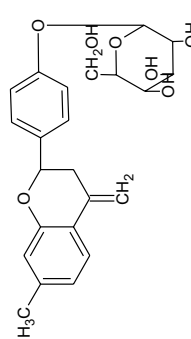
Sr. No.	Compound	Structure	Evaluation	Inference
6	Homoisoflavanone 7-O-[[α -rhamnopyranosyl-(1 \rightarrow 6)- β -glucopyranoside]-5-hydroxy-3-(4-methoxybenzyl)]-chroman-4-one		Assayed for antioxidant property against DPPH radical and β -carotene/linoleic acid system	Both compounds (a) and (b) showed respective antioxidant activity with following significant values (a) 273.1 ± 6.2 (DPPH) and (b) 212.4 ± 3.8 (DPPH) [50]
7	7-O-[[α -rhamnopyranosyl-(1 \rightarrow 6)- β -glucopyranosyl]-5-hydroxy-3-(4'-hydroxybenzyl)]-chroman-4-one		Evaluate lipid peroxidation process	Inhibited lipid peroxidation, and has been reported more potent antioxidants than vitamin E and Trolox [51]
8	Methyl 2-(cyclohexyl carbamoyl)-4-oxochroman-3-carboxylate		Examined DPPH inhibition	Showed DPPH inhibition with significant values [51]
9	Isointricatolol (7,8-dihydroxy-3-(4'-methoxybenzyl) chroman-4-one)		Assayed free radical scavenging effect against DPPH and ABTS radicals	Showed 85.50 mM (DPPH) and 44.13 mM (ABTS) values signify good antioxidant potential. [52]
10	Liquiritin (7-hydroxy-2-[4-[3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] oxyphenyl]-chroman-4-one		Examined for inhibition of enzymes superoxide anion (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) in mice	Showed neuroprotective effect against focal cerebral ischemia/reperfusion (I/R) by inhibition of SOD (75.11 ± 5.80 U/mg), CAT (7.62 ± 0.48 U/mg) and GSH-Px (887.24 ± 79.23 U/mg) [53]



Table 3 (continued)

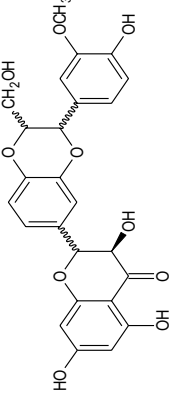
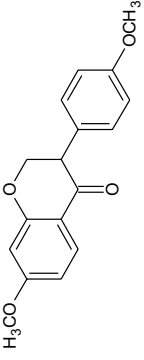
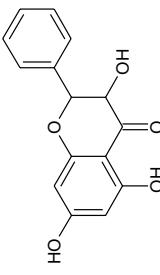
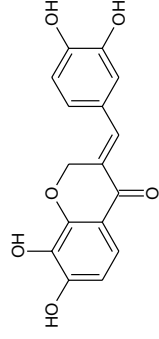
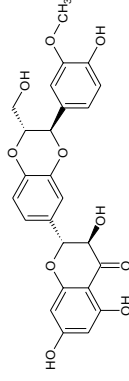
Sr. No.	Compound	Structure	Evaluation	Inference
11	Silybin		Evaluated for inhibition of Cyclic voltammetry (CV), DPPH scavenging and microsomal lipid Peroxidation (LPx)	Exhibited antioxidant potential with significant inhibition of CV (524 Epa mV), DPPH (1745 ± 65) and LPx (33.6 ± 1.2). [54]
12	7-Methoxy-3-(4-methoxyphenyl)-chroman-4-one		Examined for antioxidative capacity	Exhibited protective effects against cardiovascular defects, cancer and other diseases due to its high antioxidant capacity [55]
13	Pinobanksin		Antioxidant capacities were analyzed by HAT, SET-PT and SPLET mechanisms	Showed significant antioxidant effect Among all the compounds, mainly 7-OH group contributes to the antioxidant activities [56]
14	7,8-Dihydroxy-3-[(3,4-dihydroxyphenyl)methylene]chroman-4-one		Antioxidant activity by NBT superoxide scavenging and DPPH free radical scavenging inhibition	NBT = 8.5 μM DPPH = 4.5 μM [57]
15	Silymarin		Antioxidant activity reported against DPPH	Approximately 33% Inhibition of DPPH [58]



Table 4 Chroman-4-one analogs exhibiting anti-inflammatory activity

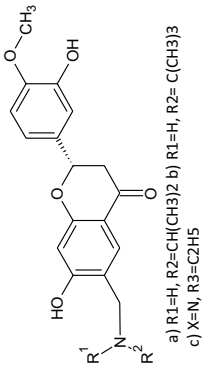
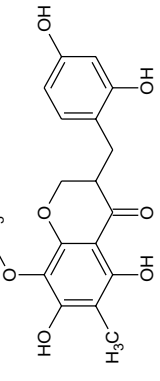
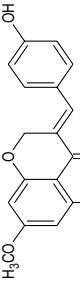
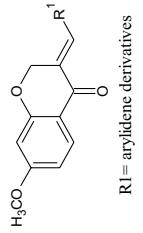
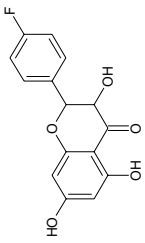
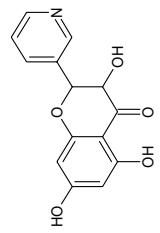
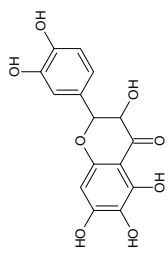
Sr. No.	Name of compound	Structure	Evaluation	Inference
1	Hesperetin derivatives	 <p>a) R1=H, R2=CH(CH3)2 b) R1=H, R2= C(CH3)3 c) X=N, R3=C2H5</p>	Anti-inflammatory activity was tested against IL-6, TNF- α cells	Exhibited significant anti-inflammatory activity by decreasing IL-6, TNF- α with minus log P values -0.26 (a), 0.76 (b) and -0.75(c), respectively [63]
2	4'-O-Demethylpogonone E		Inhibited pro-inflammatory cytokine IL β , IL-6 and phosphorylation of ERK1/2 and JNK in MAPK signaling pathways to decrease NO and cytokines production	IC ₅₀ value for pro-inflammatory cytokine: IL β = 32.5 \pm 3.5 μ g/mL, IL-6 = 13.4 \pm 2.3 μ g/mL which showed potent anti-inflammatory activity [59]
3	Novel (E)-5,7-dimethoxy-3-(4'-hydroxybenzylidene) chroman-4-one		Tested in croton oil-induced edema in animal study	Showed significant anti-inflammatory potential [64]
4	3-Arylidene-7-methoxychroman-4-one	 <p>R1 = arylidene derivatives</p>	Evaluated in Carrageenan induced paw edema in rats	Exhibited significant anti-inflammatory activity [65]
5	3,5,7-Trihydroxy-2-(4'-fluorophenyl) chroman-4-one		Tested for anti-inflammatory activity in IL-1 β , IL-6, and TNF- α cells	Decreased IL-1 β , IL-6, and TNF- α cells inflammation These 3 derivatives showed most significant anti-inflammatory activity and cytotoxicity [65]
	3,5,7-Trihydroxy-2-(pyridin-3-yl) chroman-4-one			
	3,5,6,7-Tetrahydroxy-2-(3',4'-dihydroxyphenyl) chroman-4-one			



Table 4 (continued)

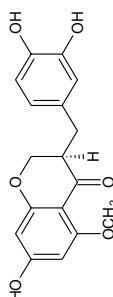
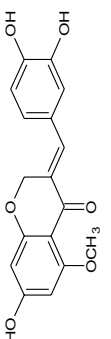
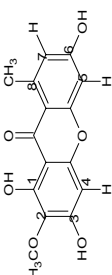
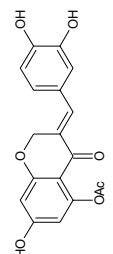
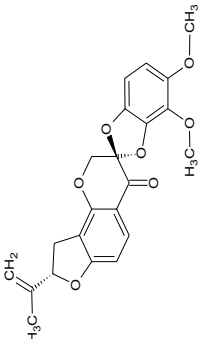
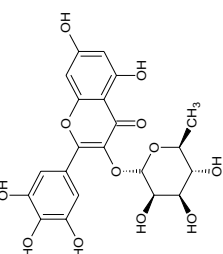
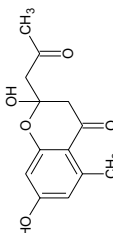
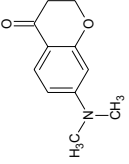
Sr. No.	Name of compound	Structure	Evaluation	Inference
6	(R)-3-(3,4-Dihydroxybenzyl)-7-hydroxy-5-methoxychroman-4-one		Evaluated for COX-2 receptor binding	Shown significant anti-inflammatory activity against COX-2 with % activity = 0 ± 5.4 [61]
	(E)-3-(3,4-dihydroxybenzylidene)-7-hydroxy-5-methoxychroman-4-one			% activity = 0 ± 8.3 [61]
	1,3,6-Trihydroxy-2-methoxy-8-methylxanthin-9-one			% activity = 0 ± 21.3
	Ovatifolionone acetate			
7	Pruisanone A		Inhibited inducible nitric oxide synthase (iNOS) protein expression	% activity = 0 ± 7.8 Shown anti-inflammatory potential with inhibition value 1.96 mM [66]
8	Myricitrin		Significantly inhibited 5-lipoxygenase (5-LO)	Potent anti-inflammatory activity with $IC_{50} = 7.8 \pm 0.2 \mu M$ [67]
9	Violacin A (<i>Streptomyces violaceonther</i>)		Suppressed NF-kB signaling pathways	A potential therapeutic candidate for the treatment of inflammation-related disorders [62]



Table 4 (continued)

Sr. No.	Name of compound	Structure	Evaluation	Inference
10	7-Dimethylamino-4-chromanone		Tested for anti-inflammatory potential	Showed anti-inflammatory activity [68]

eriodictyol, sakuranetin, aromadendrin, butin, pinocembrin, nymphaeol A, sophoraflavanone G and sterubin (Fig. 3) are already reported for their excellent potency in the treatment of diabetic mellitus and diabetes associated complications [2]. These chromanone containing flavanones treat diabetes through inhibition of receptors like glucagon-like peptide 1 (GLP-1), dipeptidyl peptidase-IV (DPP4), peroxisome proliferator receptor gamma (PPAR- γ), Alpha glucosidase (α -glucosidase), phosphatidylinositol 3-kinase (PI3K) in both *in vivo* and *in vitro* experimentation [71]. Moreover, several synthetic chromanone analogs are also reported (enlisted in Table 5) for antidiabetic potential via α -glucosidase inhibition and DPPH radical scavenging activity. Zhu et al. 2019 isolated various chromanone analogs from the seeds of *Psoralea corylifolia* and evaluated for diglyceride acyltransferase (DGAT), protein-tyrosine phosphatase 1B (PTP1B) and α -glucosidase activity. Out of these isolated compounds, (2S)-7-methoxy-6-(2-hydroxy-3-methyl but-3-en-1-yl)-2-(4-hydroxyphenyl)chroman-4-one, (2S)-4'-hydroxyl-7-hydroxy methylene-6-(2'',3''-epoxy-3''-methyl butyl) flavanone and bavachinone B exhibited good antidiabetic effect by inhibition of DGAT, PTP1B and α -glucosidase. Takao K. et al. introduced benzylidene-4-chromanone derivatives as the lead compound for the development of novel α -glucosidase inhibitors as well as significant antioxidative agent due to its potential in significantly inhibiting the level of DPPH. By the virtue of SAR studies, substitution at C-2, 3, 6 and 7th position of parent chromanone provide effective antidiabetic drugs which might help in the synthesis of more efficient novel compounds for the cure of diabetes and its complications [72, 73]. But, the research and published data about the synthetic chromanone containing medicinal compounds as antidiabetic are very less as compared to isolated flavanones, flavonols and homoisoflavanones. Therefore, a very effective synthetic approach is required for the synthesis and evaluation of more chromanone analogs as antidiabetics [72, 74].

2.5 Antibacterial and Antifungal Agents

Increased prevalence of pathogenic microbial infections necessitates the need for new antibacterial agents with distinct mechanism of action and broad spectrum of activity over a wide range of bacterial and fungal strains. Considering this viewpoint, several naturally occurring flavonoids and heterobicyclic compounds containing chromanone pharmacophore were found to have diverse activities ranging from antibacterial to antiviral activity. But these compounds were found to have two major limitations like poor yield and resistance against the general bacterial and fungal strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Aspergillus niger*, *Fusarium oxysporum*, *Penicillium italicum*, *Pythium*



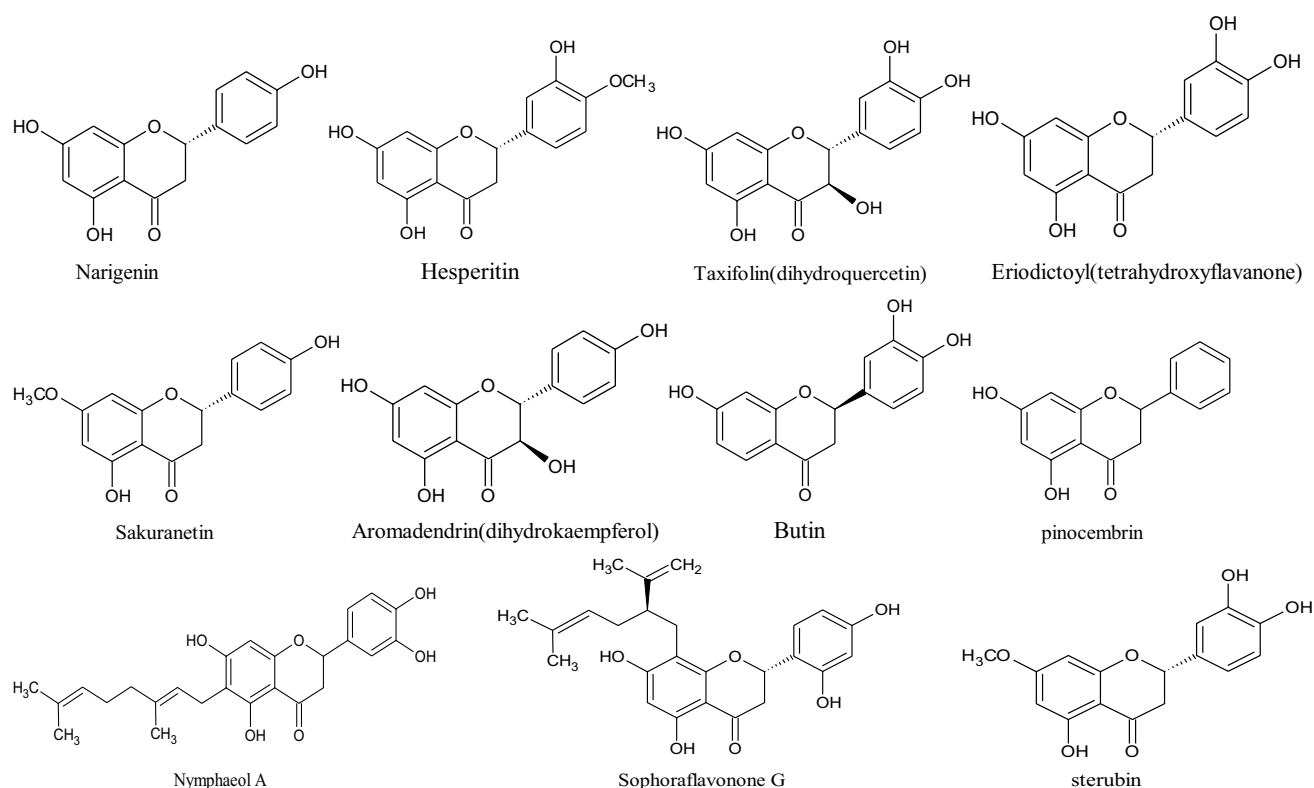


Fig. 3 Natural chromanones exhibiting antidiabetic activity

ultimum, *Sclerotinia sclerotium*, *Phytophthora capsici*, *E. Faecalis*, *C. albicans*, *C. Krusei*, *C. Glabrata* and *A. fumigates* [81]. Therefore, there is a need for new synthetic antibacterial and antifungal compounds containing chromanone moiety.

It was found that substitution at C-2 with pyrazol-4-yl derivatives, methoxyphenyl, alkyl, vinyl, hydroxyl methyl and chlorophenyl group displayed broad spectrum antibacterial activity against tested bacterial strains, whereas azolyl and benzylidene derivatization yields good antifungal agents as shown in Table 6 [82]. Moreover, C-2, 3, 4, 6 and 7 substitutions also predicted efficient antibacterial and antifungal compounds with broad spectrum activity as well as low or no resistance. Likewise, most important series of benzylidene derivatives C-3-substituted 3-(benzo[1,3]dioxol-5-ylmethylene)-7-hydroxychroman-4-one, a 3-benzylidene-4-chromanone exhibited significant antibacterial activity against gram positive and gram negative bacteria, while 3-azolyl-4-chromanone phenyl hydrazones exhibited antifungal potential against *C. albicans*, *S. cerevisiae*, *A. niger* and *M. gypseum pathogens* [83]. Hence, more exhaustive approach for the chromanone scaffold may lead medical chemist to synthesize more potent antibacterial and antifungal compounds with maximum efficacy and minimum resistance.

2.6 Anti TB Agents

Among the available treatments for tuberculosis, first-line and second-line antituberculosis (TB) drugs, DOTS (directly observed treatment short-course) is one of the most competent multidrug effective strategy developed by WHO against *Mycobacterium tuberculosis*. However, the success rate for cure of TB patients struggles to achieve 85% [99]. Therefore, more research is required for the development of novel potent antimycobacterial agents with promising efficacy and less side effects. From the series of heterobicyclic compounds, isolated as well as synthetic chroman-4-one analogs were reported to inhibit *M. tuberculosis* [100, 101]. Chromanone analogs having significant potential for the treatment of TB with greater efficacy and less side effects are enlisted in Table 7. This will provide us a new framework in designing and development of chromanone derivatives and their potent multidrug combinations like spiro chromanones as novel antiTB agents [102].

2.7 Antiviral Agents

A number of viral diseases in human ranging from mild upper respiratory infection to fatal cardiac and neurological illnesses are caused by numerous picornaviruses particularly rhinoviruses (HRVs) and enteroviruses (EVs). A diverse

Table 5 Chroman-4-one analogs exhibiting antidiabetic activity

Sr. No.	Name of compound	Structure	Evaluation	Inference
1	[(E)-8-(3,7-dimethylocta-2,6-dienyl)-5,7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one]		Evaluated for α -glucosidase inhibition	Exhibited antidiabetic activity with α -glucosidase inhibition [75]
2	(2S)-7-methoxy-6-(2-hydroxy-3-methyl but-3-en-1-yl)-2-(4-hydroxyphenyl) chroman-4-one		Isolated from seeds of <i>Psoralea corylifolia</i> Examined for DGAT, PTP1B and α -glucosidase inhibition	Showed antidiabetic activity inhibiting DGAT, PTP1B and α -glucosidase with significant values [73]
(a)				
(b)	(2S)-4'-hydroxy-7-hydroxy methyl-ene-6-(2',3'-epoxy-3"-methyl butyl) flavanone			
(c)	Bavachinone B			
3	7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one		Tested for antidiabetic activity	Increased insulin and decreased blood glucose level, HOMA-IR value and PEPCK gene expression in diabetic rats [76]



Table 5 (continued)

Sr. No.	Name of compound	Structure	Evaluation	Inference
4	2-Methoxy-4-chromanones ligated Cu (II)		Evaluated for α -glucosidase assay	Shown highest α -glucosidase inhibition with $IC_{50} = 0.060 \pm 0.3$ mM and displayed antidiabetic potential [77]
5	3-Benzylidene-4-chromanone derivatives		Assayed for DPPH radical scavenging and α -glucosidase inhibition	Shown significant antioxidant potential [72]
6	5,7-Dimethoxy-3-(2'-hydroxybenzyl)-4-chromanone		Evaluated for antidiabetic activity	Improved postprandial hyperglycemia in streptozotocin-induced diabetic mice by inhibiting carbohydrate digesting enzymes [78]
7	6-Methyl-4-chromanone		<i>in vitro</i> evaluation for antidiabetic effect	Shown good antidiabetic effect using the glucose uptake by isolated rat hemi diaphragm (<i>in vitro</i> model) [79]
8	2H-Chromenylphenylloxazolones derivatives		Evaluated for free radical scavenging and α -glucosidase inhibitory activity	Exhibited antidiabetic activity with antioxidant effect [80]



Table 6 Chroman-4-one analogs exhibiting antibacterial and antifungal values

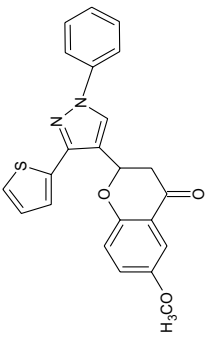
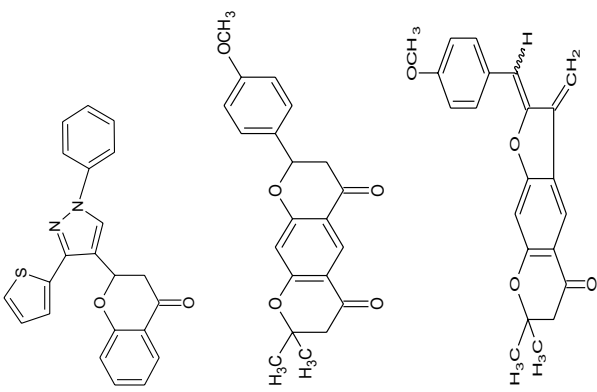
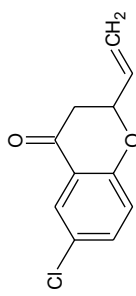
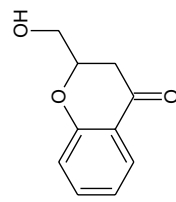
Sr. No.	Name of compound	Structure	Evaluation	Inference
1	2-(1-Phenyl-3-(2-thienyl)-1H-pyrazol-4-yl)chroman-4-one derivatives		<p>Showned antibacterial activity evaluated against <i>Staphylococcus aureus</i>, <i>Bacillus subtilis</i>, <i>Pseudomonas aeruginosa</i> and <i>Escherichia coli</i> using ampicillin (reference drug) -zone of inhibition (mm) measured using cup plate agar diffusion method</p> <p>Exhibited antifungal activity against <i>Aspergillus niger</i>, <i>Fusarium oxysporum</i> and <i>Penicillium italicum</i> using griseofulvin (standard drug)</p>	<p><i>S. aureus</i> = 32 mm <i>B. subtilis</i> = 15 mm <i>P. aeruginosa</i> = 11 mm <i>Escherichia coli</i> = 33 mm [84]</p> <p><i>A. niger</i> = 14 mm <i>F. oxysporum</i> = 30 mm <i>P. italicum</i> = 20 mm [84]</p>
2	2,2-Dimethylchroman-4-one derivatives		<p>Nutrient agar media and Potato Dextrose Agar (PDA) medium used for the measurement of antibacterial and antifungal potential as in zone of inhibition (mm)</p> <p>Exhibited antibacterial and antifungal activities</p>	<p><i>B. subtilis</i> = 31.5 mm, <i>S. aureus</i> = 20.5 mm <i>K. pneumoniae</i> = 34.8 mm <i>E. coli</i> = 33.8 mm <i>A. niger</i> = 10.2 mm <i>F. oxysporum</i> = 17.5 mm [85]</p> <p><i>B. subtilis</i> = 33 mm, <i>S. aureus</i> = 20 mm <i>K. pneumoniae</i> = 33.5 mm <i>E. coli</i> = 30.5 mm <i>A. niger</i> = 15 mm <i>F. oxysporum</i> = 14.5 mm [85]</p>
3	6-Chloro-2-vinyl chroman-4-one		<p>Showned antimicrobial activity against <i>Bacillus Subtilis</i>, <i>Escherichia coli</i> and <i>Staphylococcus aureus</i>-Vinyl group at carbon C-2 is necessary for the biological activity and Chloro group increases the activity</p>	<p><i>B. Subtilis</i> = 4.171g/mL <i>E. coli</i> = 4.171g/mL <i>S. aureus</i> = 7.301g/mL [86]</p>
4	2-Hydroxymethyl-chroman-4-one		<p>Exhibited antifungal activity against <i>P. ultimum</i>, <i>S. sclerotiorum</i> and <i>P. capsici</i> It was also used as intermediate for the synthesis of more effective benzopyranones</p>	<p>ED₅₀ ppm values for <i>P. ultimum</i> = 54.99 ppm <i>S. sclerotiorum</i> = 52.03 ppm <i>P. capsici</i> = 35.77 ppm [87]</p>

Table 6 (continued)

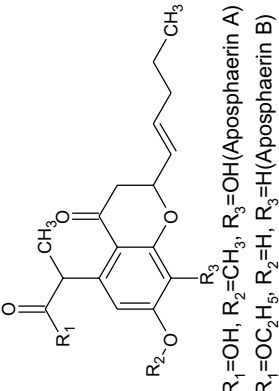
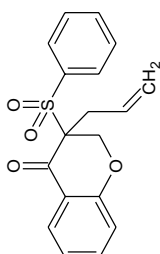
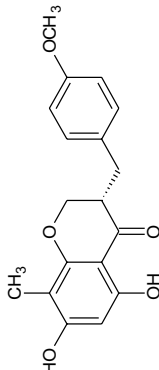
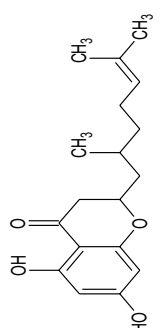
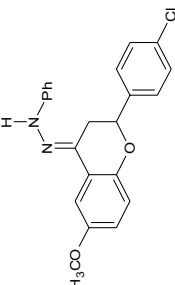
Sr. No.	Name of compound	Structure	Evaluation	Inference
5	Aposphaerin A and B	 <p> $R_1=OH$, $R_2=CH_3$, $R_3=OH$(Aposphaerin A) $R_1=OC_2H_5$, $R_2=H$, $R_3=H$(Aposphaerin B) </p>	These are natural potent antibiotics evaluated for MRSA (methicillin resistant <i>S. aureus</i>) assay	Exhibited significant activity against methicillin resistant <i>S. aureus</i> (MRSA) [88]
6	3-Phenyl/sulfonyl-3-(2-propenyl) chroman-4-one		Evaluated for antimicrobial activity	Exhibited potent antimicrobial activity [89]
7	5,7-Dihydroxy-3-(4-methoxybenzyl)-8-methyl chroman-4-one		Isolated from the rhizomes of <i>Polygonatum verticillatum</i> -Antimicrobial activity assay using nutrient agar plate medium	Displayed significant antimicrobial activity via inhibition of <i>B. subtilis</i> , <i>S. aureus</i> and <i>E. coli</i> [90]
8	2-(2,6-Dimethylhept-5-en-1-yl)-5,7-dihydroxychroman-4-one		Antibacterial evaluation against <i>E. Faecalis</i> , <i>S. aureus</i> MSSA, <i>S. aureus</i> MRSA and <i>E. coli</i> ($\mu\text{g/ml}$)	$E. Faecalis = 6.25(\mu\text{g/ml})$ <i>S. aureus</i> MSSA = 3.13 ($\mu\text{g/ml}$), <i>S. aureus</i> MRSA = 3.13 ($\mu\text{g/ml}$) <i>E. coli</i> = 1.5 $\mu\text{g/ml}$ [91]
9	1-(2-(4-Chlorophenyl)-6-methoxychroman-4-ylidene)-2-phenylhydrazine		Exhibited potent antimicrobial activity against <i>S. aureus</i> , <i>E. coli</i> , <i>C. Albicans</i> and <i>Aspergillus niger</i> using agar diffusion technique	$S. aureus = 15.5 \pm 0.7$ mm <i>E. coli</i> = 21.5 ± 0.7 mm <i>C. albicans</i> = 20.0 ± 0.0 mm <i>A. niger</i> = 20.0 ± 0.0 mm [92]



Table 6 (continued)

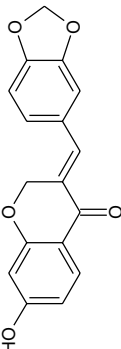
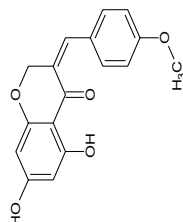
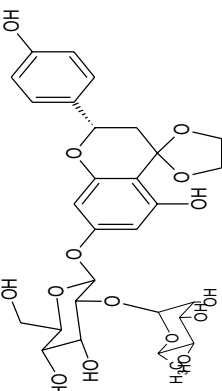
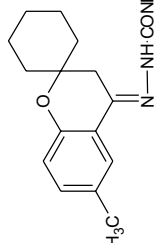
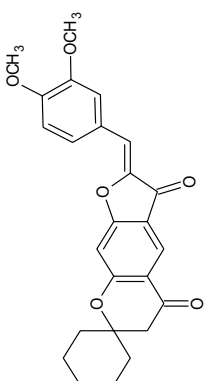
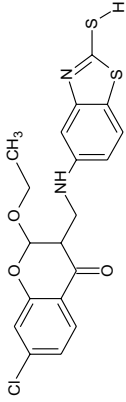
Sr. No.	Name of compound	Structure	Evaluation	Inference
10	3-(Benzo-[1, 3] dioxol-5-ylmethylene)-7-hydroxychroman-4-one, a 3-benzylidene-4-chromanone		Evaluated against gram-negative bacteria	Significant antibacterial activity against <i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>C. violaceum</i> , <i>Pseudomonas aeruginosa</i> [92]
	3-benzylidene-4-chromanones derivatives		Tested antibacterial activity against <i>S. aureus</i>	<i>S. aureus</i> = 0.52 mM
11	(2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>R</i> ,6 <i>S</i>)-2-(((2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>R</i>)-4,5-dihydroxy-2-(((<i>S</i>)-5-hydroxy-2-(4-hydroxyphenyl) spiro [chroman-4,2'-[1,3] dioxolan]-7-yl) oxy)-6-(hydroxymethyl) tetrahydro-2 <i>H</i> -pyran-3-yl) oxy)-6-methyl-tetrahydro-2 <i>H</i> -pyran-3,4,5-triol		Exhibited antibacterial activity for gram-positive and gram-negative bacteria using broth micro-dilution method	<i>S. aureus</i> = 0.125 mg/mL <i>E. coli</i> = No inhibition <i>P. aeruginosa</i> = 0.25 mg/mL <i>S. aureus</i> (MRSA Positive) = 0.125 mg/mL
12	(Spiro[chroman-2,1'-cyclohexan]-4-one) semi carbazone derivative		Also showed antioxidant potential Antifungal activity evaluated against <i>C. albicans</i> , <i>C. Krusei</i> GO3, <i>C. Glabrata</i> HO5 and <i>A. fumigates</i> strains	IC ₅₀ = 18.7 µg/mL [82] Observed a clear zone of inhibition against <i>C. Krusei</i> GO3 strain [93]
13	Novel spiro chromanone–aurone hybrids (Z)-2'-(3,4-Dimethoxybenzylidene) spiro [cyclo-hexane-1,7'-furo[3,2-g]chromene]-3',5'(2'H,6'H)-dione		Exhibited high antibacterial activity for a number of gram +ve and –ve bacteria's using streptomycin and amphotericin B (as standard drugs)	<i>B. subtilis</i> = 21.0 <i>S. aureus</i> = 19.5 <i>P. aeruginosa</i> = 22.5 <i>E. coli</i> = 21.0 <i>A. flavus</i> = 4.5 <i>F. oxysporum</i> = 6.5 [94]
14	2-MBT(2-mercaptobenzothiazole) with chroman-4-one moiety derivatives		Evaluated for antimicrobial potential against <i>S. aureus</i> , <i>B. subtilis</i> , <i>M. tuberculosis</i> , <i>C. albicans</i> and <i>S. cerevisiae</i> strains	Showed potent antimicrobial activity with significant inhibition [95]



Table 6 (continued)

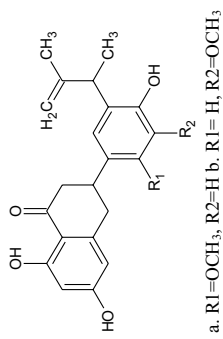
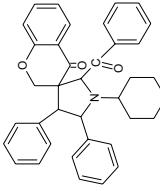
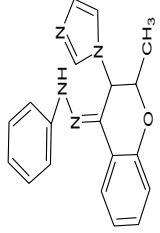
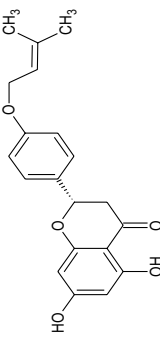
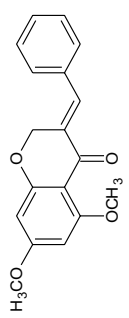
Sr. No.	Name of compound	Structure	Evaluation	Inference
15	Novel flavanone derivatives	 <p>a. R1=OCH₃, R2=H b. R1=H, R2=OCH₃</p>	Antibacterial activity against <i>S. aureus</i> strains including MRSA	MIC value = 16 µg/mL More potent than standard drug oxacillin [96]
16	Spiro[2-benzoyl-cyclohexyl]-4,5-diphenylpyrrolidine-3,3'-chroman-4-one		Evaluated for antifungal and antibacterial activities	Showed significant inhibition against tested pathogen strains [97]
17	3-Azoly-4-chromanone phenylhydrazones		Tested against <i>C. albicans</i> , <i>S. cerevisiae</i> , <i>A. niger</i> and <i>M. gypseum</i> pathogens	MICs values (µg/mL) are: <i>C. albicans</i> = 8 µg/mL, <i>S. cerevisiae</i> = 16 µg/mL, <i>A. niger</i> = 16 µg/mL, <i>M. gypseum</i> = 16 µg/mL. Exhibited Antifungal potential [83]
18	5,7-Dihydroxy-2-[4-(3-methyl-but-2-enyloxy) ~ phenyl] chroman-4-one (selinone)		Antifungal activity against <i>C. albicans</i>	Showed significant inhibition [98]
19	(E)-5,7-dimethoxy-3-benzylidene-4-chromanone		Antifungal activity against <i>C. albicans</i>	Showed significant antifungal activity (MIC ₅₀ ± 25 mM) [81]



Table 7 Chroman-4-one analogs exhibiting antitubercular activity

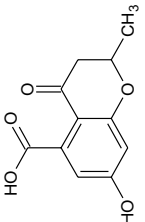
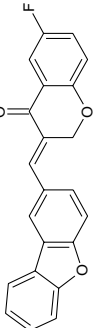
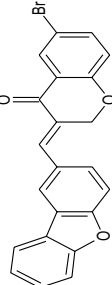
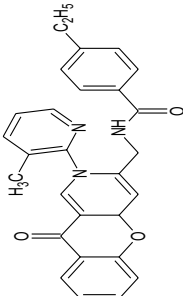
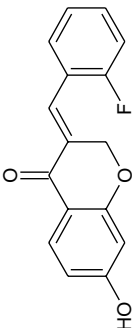
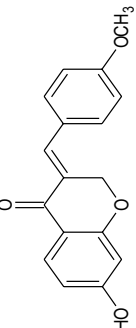
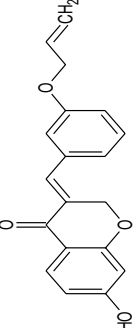
Sr. No.	Name of compound	Structure	Evaluation	Inference
1	7-Hydroxy-2-methyl-4-oxo-3,4-dihydro-2H-benzopyran-5-carboxylic acid		Evaluated for <i>M. tuberculosis</i>	Potential inhibitors of <i>M. tuberculosis</i> (MbtI) with IC ₅₀ = 55.8 μM [103]
2	(E)-3-(dibenzo [b, d] furan-2-ylmethylene)-6-fluorochroman-4-one		Examined for <i>M. tuberculosis</i> H37Rv Inhibition	Inhibited <i>M. tuberculosis</i> H37Rv with MIC 12.5 μg/mL and considered as most potent antitubercular agents [104]
	(E)-3-(dibenzo [b, d] furan-2-ylmethylene)-6-bromochroman-4-one			
3	Chromane-4-one analogs		Tested anti TB activity against <i>M. tuberculosis</i> and MDR-TB <i>in vitro</i>	<i>in vitro</i> study revealed anti TB activity against <i>M. tuberculosis</i> and MDR-TB with MICs of 0.22 and 0.07 μg/mL, respectively, and decreased the bacterial load in lung and spleen tissues with log ₁₀ = 1.11 and 2.94 [105]
4	7-Hydroxy-(E)-3-[(2-fluorophenyl) methyl-ene] chroman-4-one		Screened against <i>Mycobacterium smegmatis</i> <i>mic</i> ² -155 for anti TB potential	Exhibited significant inhibition as efflux pump inhibitors against <i>Mycobacterium smegmatis</i> <i>mic</i> ² -155 [106]
	7-Hydroxy-(E)-3-[(4-methoxyphenyl) methyl-ene] chroman-4-one			
	7-Hydroxy-(E)-3-[(3-allyloxyphenyl) methyl-ene] chroman-4-one			



Table 7 (continued)

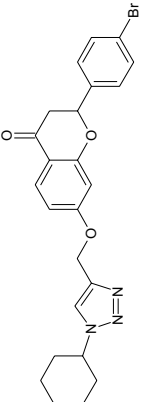
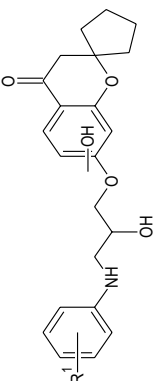
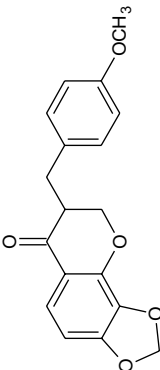
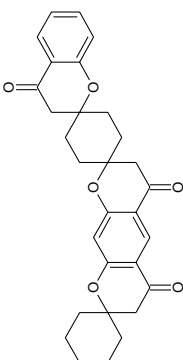
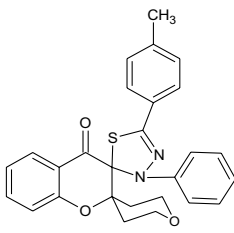
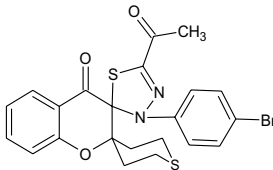
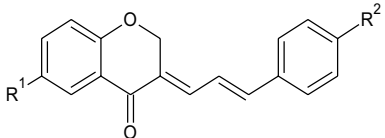
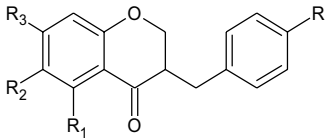
Sr. No.	Name of compound	Structure	Evaluation	Inference
5	Triazolyl methoxy flavanones		Examined for mycobacterial FAS-II and PknG inhibition	Inhibited mycobacterial FAS-II (IC ₅₀ = 20.3 μM) and PknG. The % growth inhibition was 75.1 at 100 μM. [107]
6	Amino alcohol-linked spiro chromones		Tested for <i>M. tuberculosis</i> H37Rv (ATCC27294) cells growth	Inhibited <i>M. tuberculosis</i> H37Rv (ATCC27294) with MIC value of 3.13 μg/mL [108]
7	3-(4'-Methoxybenzyl)-7,8-methylenedioxy-chroman-4-one		Evaluated for <i>M. phlei</i> , <i>M. aurum</i> , <i>M. fortuitum</i> and <i>M. smegmatis</i> inhibition	Displayed antimycobacterial activity against <i>M. phlei</i> (16 μg/mL), <i>M. aurum</i> (32 μg/mL), <i>M. fortuitum</i> (128 μg/mL) and <i>M. smegmatis</i> (256 μg/mL) [109]
8	Bis-spiro chromanones		Examined against strain H37Rv (ATCC 27,294) for antimycobacterial potential	Exhibited antimycobacterial activity against H37Rv (ATCC 27,294) strain with MIC = 3.125 μg/mL [110]



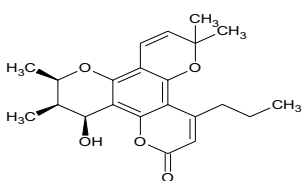
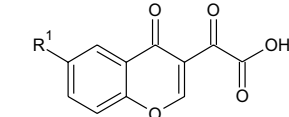
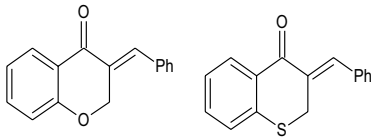
Table 8 Chroman-4-one analogs exhibiting antiviral activity

Sr. No.	Name	Structure	Evaluation	Inference
1	5''-Aceto-3''-phenyl-3''H,4'H-dispiro[chroman-2',4-tetrahydropyran-3',2''-[1,3,4-thiadiazol]-4'-one		Examined for adenovirus type-7 inhibition for antiviral activity	Showed considerable antiviral activity against strained adenovirus type 7 with significant inhibition [35]
	5''-Aceto-3''-(4-bromophenyl)-3''H,4'H-dispiro[chroman-2',4-tetrahydrothiopyran-3',2''-[1,3,4-thiadiazol]-4'-one			
2	Chroman-4-one derivatives		Evaluated against human rhinovirus (HRV) 1B and 14 inhibition	Displayed antiviral potency against tested HRV 1B and 14 strains [114]
3	3-Benzylchroman-4-one's derivatives		Tested for antiviral activity	Showed antiviral activity against Coxsackie virus B1, B3, B4, A9 and echovirus 30 [115] [113]

range of effective antipicornavirus agents are developed and some are in clinical phase study [111]. Literature evidence has established that natural and synthetic flavonoids containing chromane obstruct the replication step of picornavirus

and further prevent the decapsidation of infected viral segments and release of corresponding RNA within cells [112]. Tait S et al. (2006) examined antiviral activity of homoisoflavonoids (3-benzylchroman-4-ones derivatives)

Table 9 Chroman-4-one analogs exhibiting anti-HIV activity

Sr. No.	Name of compound	Structure	Evaluation	Inference
1	Calanolide A		Examined AZT-resistant strains for anti-HIV potency	Showed significant anti-HIV activity against AZT-resistant strains [118] [121]
2	1,3-Diketo acids, new chromone and chromanone derivatives	 R1=H,3-Chromonyl-2-oxo-propionic acid(a) R1=benzyl,6-Benzylchromone-3-yl)-2-oxo-propionic acid (b)	Evaluated for anti-HIV activity	Exhibited anti-HIV activity by inhibition of HIV-1 IN strand transfer (IC ₅₀ , μM = 168.2 and 100.6 for a and b respectively) [122]
3	3-Benzylidene derivatives of chromanone		Tested for anti-HIV effect	Showed significant anti-HIV activity [120]



on enteroviruses replication, and these chromanone analogs showed significant activity against coxsackie virus B1, B3, B4, A9, echovirus 30 and substitution at C-3 of parent chromanone exhibited good efficacy against HRVs growth. Moreover, introduction of thiopyran at C-2 by Hegab, MI et al. (2015) showed considerable antiviral activity against strained adenovirus type 7 with significant inhibition as shown in Table 8. So, following these substitutions, more antiviral chromanone analogs may be designed and synthesized with significant antiviral activity [35, 113].

2.8 Anti-HIV Compounds

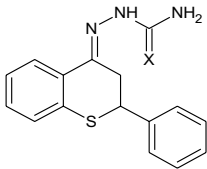
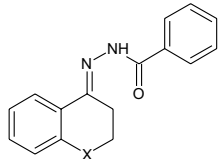
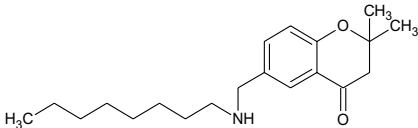
Chromanone derivatives have attained much potential against treatment of Acquired Immune Deficiency Syndrome (AIDS) caused by HIV-1 [116]. In 1994, an isolated calanolide A and inophyllums from *calophyllum* genus reported as a novel anti-HIV chemotype inhibited HIV-1-specific nonnucleoside RT [117]. Furthermore, an enantioselective designing of 2, 3-dimethyl-4-chromanone ring attachment was attempted for the synthesis of potent *calophyllum* coumarins as anti-HIV 1 and it showed significant effect which can compete with currently available protease inhibitors (atazanavir, ritonavir, lopinavir, nelfinavir, saquinavir etc.) approved by Food and Drug Administration (FDA) [118, 119].

Dawood et al. (2005) tested a series of 3-benzylidene derivatives of chromanone and substitution of thio (S) group at the place of oxo(-O) at Ist position displayed impressive anti-HIV activity. Consequently, SAR studies revealed that C-2 and 6 substitution with oxo propionic acid and benzyl group exhibited anti-HIV activity by inhibition of HIV-1 IN strand transfer with good inhibitory values as shown in Table 9. So, more research and development on chromanone analogs can be a prominent approach for synthesis of novel HIV1 inhibitors against the treatment of AIDS [120].

2.9 Antileishmanial Agents

A group of parasites of genus *Leishmania* causes tropical disease known as *Leishmaniasis*, which spreads in living beings by the bite of infected sandflies [123]. These flies have a multifarious life cycle which exhibits an amastigote phase in the host cell as well as a promastigote phase in vector flies. A number of clinical representations, especially cutaneous, visceral and mucosal forms, attain the most serious grade for *Leishmaniasis* [124]. Although diverse treatment for *Leishmaniasis or cutaneous leishmaniasis (CL)* exists, less potency, toxicity and cost issues are some of the significant limitations associated with the present treatment options. So, development of more effective novel compounds against *Leishmaniasis* remains an important

Table 10 Chroman-4-one analogs exhibiting antileishmanial activity

Sr. No.	Name of compound	Structure	Evaluation	Inference
1	Thiochroman-4-one's derivatives	 <p>If X=O, (E)-2-(2-Phenylthiochroman-4-ylidene)hydrazinecarboxamide (IC₅₀=5.4 μM) If X=S, (E)-2-(2-Phenylthiochroman-4-ylidene)hydrazinecarbothioamide (IC₅₀=5.1 μM)</p>	Evaluated for in vitro antileishmanial activity against the intracellular amastigote form of <i>Leishmania panamensis</i>	These compounds showed good antileishmanial activity with significant inhibition [128]
2	Benzoic acid, 2-(2,3-dihydro-4H-1-benzopyran-4-ylidene)hydrazide	 <p>If X=S, Benzoic acid, 2-(2,3-dihydro-4H-1-benzothiopyran-4-ylidene)hydrazide If X=O, Benzoic acid, 2-(2,3-dihydro-4H-1-benzopyran-4-ylidene)hydrazide</p>	<i>In vitro</i> evaluation using macrophage intracellular mastigotes of <i>Leishmania (Viannia) panamensis</i> and <i>L. (V) braziliensis</i> by flow cytometry antileishmanial activity	Showed combined actions of antileishmanial with inflammatory and wound healing properties [129]
3	2,2-Dimethyl-6-(octyl amino) methyl chroman-4-one		Evaluated in romastigotes, axenic amastigotes and <i>Leishmania</i> -infected macrophages	Exhibited antileishmanial potency with IC ₅₀ =24.6 ± 0.4 μM [130]



stratagem. A wide range of natural flavonoids having chromanone pharmacophore and synthetic oxygenated heterocyclic compounds such as hydrazones, thiosemicarbazones and semicarbazones have been reported to exhibit antileishmanial potential. Among these, semicarbazone and thiosemicarbazone derivatives of flavanone and thioflavanone could be considered a potential privileged structure [125]. Using this approach, derivatization of chroman-4-one and thiochroman-4-ones with acyl hydrazones resulted in significant enhancement of antileishmanial potential [126]. As thiochroman-4-one derivatives showed immense similarity with the chroman-4-one compounds so could be considered as potential scaffold with wide range of bioactivity like antiviral, antitumoral, antimalarial, antibacterial and antileishmanial [127]. Therefore, more research in thiochromanone derivatization is required for more novel antileishmanial compounds, and some relevant compounds are reported in Table 10.

2.10 Anti-Acetyl Cholinesterase (AChE) Agents for Alzheimer Treatment

Alzheimer is a complicated neurodegenerative disease that poses severe threat to human health and characterized by memory loss, behavioral abnormalities and cognitive deficits [131]. Alzheimer's Association reported that the number of patients suffering from Alzheimer's disease (AD) is now approximately 47 million and this figure is projected to increase around 100 million by 2050 entire over the world [132]. So, demand of a better treatment for AD around the world is a challenge for the medical science.

Polyphenolic compounds like flavonoids, flavones, isoflavone exhibit broad range of biological properties including inhibition of AChE enzymes and its catalytic steps [133]. In this review, we included a number of chroman-4-one containing flavonoids which exhibit AChE inhibition potential [134]. This study presents that presence of an amino group, piperidinyl of chromanone derivatives and novel dithiocarbamates show potent AChE inhibition in comparison with the standard drugs like Tacrine (Table 11). Therefore, designing and development of new effective chromanone hybrids as AChE inhibitors provide a new framework to the treatment of AD and other neurodegenerative disorders [135].

2.11 Anticonvulsants

Epilepsy is a chronic neurological disease in which patient suffers from seizures, transient attacks that affect at least 70 million people around the world. A number of therapeutic agents are available in the market as antiepileptic drugs such as phenytoin, phenobarbital, benzodiazepines, carbamazepine, ethosuximide and sodium valproate exhibit acceptable management on seizures, but resistance is observed in

30–40% epilepsy patients [140]. Therefore, MDT (multiple-drug therapies) is preferred for the control of seizures. But still no MDT or single drug can prevent the development or treat epilepsy for longer time interval without development of resistance [141]. Considering this viewpoint, more potent compounds which can cure or prevent epilepsy with high efficacy and less side effects are need of the hour.

A series of chroman-4-one derivatives such as azolylchromanones, azolylchromanone oximes and imidazolyl chromanone oxime ethers were tested for their anticonvulsant potential in lithium, pilocarpine induced seizure and pentylenetetrazol (PTZ) kindling model of epilepsy [142]. Among these tested compounds, some analogs (Enlisted in Table 12) showed good anticonvulsant activity with significant seizure latency and seizure duration. SAR studies showed that presence of azolyl ring at 3-position, halogen (Chloro) group at the 7-position and/or an alkyl (especially methyl) group at the 2-position of the chromane ring resulted in an enhancement of anti-seizure efficiency in O-(2,4-dichlorobenzyl) oxime series and no significant difference in efficacy was observed for both (Z)- and (E)-isomers against the seizure durations and seizure latency [143]. Therefore, effective report of promising chroman-4-one analogs (Table 11) in epileptic models can predict potential clinical worth in treatment of adequate epileptic disorder.

2.12 Antidepressants

Depression, a mental disorder, seeks a major concern in medical practice, and it is more common in patient than reported. Its generation is associated with amino acid metabolism in which tryptophan, an essential amino acid metabolizes amines and releases various amine neurotransmitters like serotonin, epinephrine, norepinephrine (NE), melanin and dopamine (DA) controlling the autonomic nervous system (ANS) and central nervous system (CNS) functioning under the catalysis of flavoenzyme monoamine oxidases (MAOs). It exists as in two isomeric forms MAO-A and MAO-B, from which MAO-A selectively metabolizes NE, epinephrine, 5-HT, whereas MAO-B specifically deactivates β -phenethylamine, benzylamine and inactivated by the following inhibitors such as rasagiline and selegiline with many side effects and resistance [146, 147]. So, new MAOs inhibitors are required for developing new antidepressant drugs.

For the development of more effective novel MAO inhibitors, the chromanone scaffolds from natural and synthetic sources displayed a promising effect and exhibited their potency for MAO-B inhibition selectively [148]. In particular, chromanone derivatives substituted with benzyloxy group at C-7 are more potent MAO-B inhibitors and after searching of more chromanone derivatives, DSP-1053, a novel compound examined for serotonin reuptake in vivo with 5-HT_{1A} partial agonistic activity and inhibited serotonin

Table 11 Chroman-4-one analogs exhibiting anti-AChE inhibition

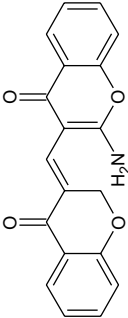
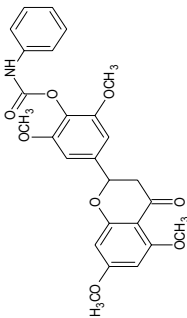
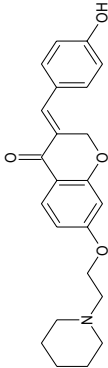
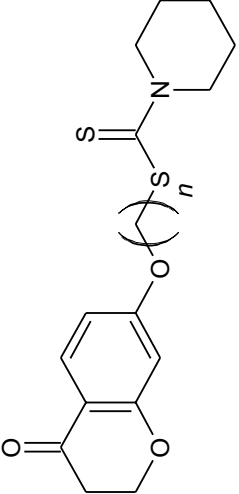
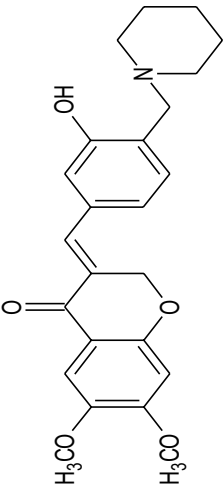
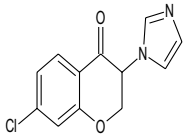
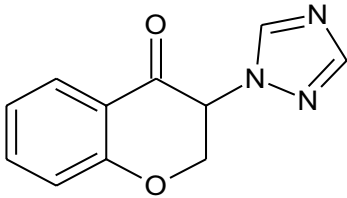
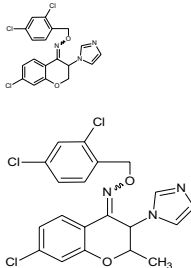
Sr. No.	Name of compound	Structure	Evaluation	Inhibition
1	Chromone-chromanone hybrid		Evaluated for acetylcholine esterase (AChE) inhibition assay	An amino group on the 2-position of chromone ring showed potent AChE inhibition against the reference drug, Tacrine with $IC_{50}=0.27 \mu M$ [135]
2	Flavonoid derivative with carbamate moiety		Evaluated for AChE inhibition and anti-amnesic potential	Exhibited AChE inhibitory activity with $IC_{50}=9.9 \pm 1.6 mM$ [136]
3	Chroman-4-one derivative with the piperidinyloxy side chain and 4-hydroxybenzylidene substitution		Evaluated for AChE activity and docking for finding effective binding pockets	Showed most potent anti-acetylcholinesterase activity ($IC_{50}=1.18 \mu M$) and also showed remarkable interactions with the binding pockets of the ChE enzymes against Butyrylcholinesterase (BChE) and AChE, in the molecular docking study [137]
4	Novel chromanone-dithiocarbamate hybrids (n=5)		Evaluated for AChE-induced Aβ aggregation inhibition	A novel hybrid with n = 5 showed best activity to inhibit AChE ($IC_{50}=0.10 \mu M$) and AChE-induced Aβ aggregation (33.02% at 100 μM) and could effectively inhibit self-induced Aβ aggregation (38.25% at 25 μM) [138]
5	(E)-3-(3-Hydroxy-4-(piperidin-1-ylmethyl)benzylidene)-6,7-dimethoxychroman-4-one		Selective AChE and MAO-B dual inhibitors of homoisoflavonoid Mannich bases were screened against Alzheimer's disease	(E)-3-(3-Hydroxy-4-(piperidin-1-ylmethyl)benzylidene)-6,7-dimethoxychroman-4-one showed excellent AChE and MAO-B inhibitory activities ($IC_{50}=2.49 \pm 0.08 nM$ and $1.74 \pm 0.0581 nM$, respectively), good self- and Cu^{2+} -induced Aβ1-42 aggregation inhibitory potency, antioxidant activity, biometal chelating ability and high BBB permeability. [139]



Table 12 Chroman-4-one analogs exhibiting anticonvulsant activity

Sr. No.	Name of compound	Structure	Evaluation	Inference
1	7-Chloro-3-(1H-imidazol-1-yl) chroman-4-one		Investigated for both anticonvulsant and antiepileptogenic properties using lithium pilocarpine induced seizure and PTZ-induced kindling models	Effective against lithium and pilocarpine induced <i>status epilepticus</i> with seizure latency = 32.12 ± 3.04 and seizure duration = 12.50 ± 1.87 , whereas in PTZ-kindling model of epilepsy, seizure latency and seizure index were observed as 3.75 ± 0.14 and 3.43 ± 0.14 , respectively [144]
2	3-(1H-1,2,4-triazol-1-yl) chroman-4-one		Evaluated for PTZ-kindling model of epilepsy	Produced significant action in delaying seizures as well as effective protection against PTZ-induced seizures (seizure latency = 22.00 ± 4.11 min) and deaths [145]
3	Imidazolyl chromanone oxime		Tested in PTZ-kindling model of epilepsy	Exhibited anticonvulsant activity with Seizure latency (s) = 715 ± 153 Seizure duration (s) = 40.3 ± 4.7 Seizure latency(s) = 776 ± 97 Seizure duration (s) = 342 ± 4.9 [143]

reuptake and considered as fast antidepressant drug in clinical practice (Table 13) [149]. Consequently, after reviewing the clinical data of DSP-1053, a probability comes out that more research in chromanone compounds might add a new class of antidepressant drugs.

2.13 Insecticides

As per the literature, it is reported that for the development and metamorphosis regulation in insect, mainly 20-hydroxyecdysone and juvenile hormones are necessary and play promoting roles in endocrine systems of insects as growth regulators [153]. In 1988, 1-tert-Butyl-1, 2-dibenzoyl hydrazine, first non-steroidal ecdysone agonist, was reported. Further, a variety of ecdysone agonists were identified among them diacyl hydrazine compounds produced significant response for the growth and regulation of the insect structure [154, 155]. In 2007, Zhao et al. have introduced new design of insecticidal agents as chromanone derivatives of diacylhydrazines in which chromafenozide group was attached on a chromanone moiety instead of chromane structure (Table 14). This study provided significant evidence that chromanone derivatives of diacylhydrazines exhibited more potency for insecticidal activity as compared to reference

compound ANS-118 (commercial insecticide containing chroman moiety) [156].

2.14 Diagnostic agents

Ganand et al. synthesized a series of (E)-3-benzylidenechroman-4-one's derivatives (homoisoflavonoids) and evaluated for their diagnostic imaging potential for pathogenesis of AD by targeting β -amyloid ($A\beta$) plaques. *In vitro* studies revealed that (E)-3-(4-methoxybenzylidene)-6-bromo-chroman-4-one and (E)-3-(4-dimethylamino-benzylidene)-6-bromo-chroman-4-one derivatives exhibited high binding affinities to $A\beta$ plaques with 9.98 and 9.10 nM (K_i values), respectively, as compared to [^{125}I] 2-(4'-dimethylaminophenyl)-6-iodoimidazo[1,2- α] pyridine (IMPY) (reference compound) [1, 158], whereas fluorescent staining test (applied on the brain sections of AD patients) and biodistribution data revealed that (E)-3-(4-dimethylamino-benzylidene) derivatives can selectively label $A\beta$ plaques in brain sections and [^{125}I]-radio labeled compound showed adequate brain uptake for brain scanning (Table 15) [1]. Chroman-4-one derivatives may be helpful diagnostic imaging agent for early finding of $A\beta$ plaques in AD brain. Hence, further research and development of novel chromanone derivatives

Table 13 Chroman-4-one analogs displaying antidepressant potential

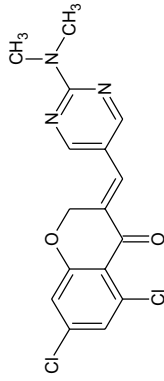
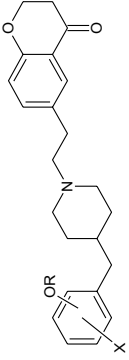
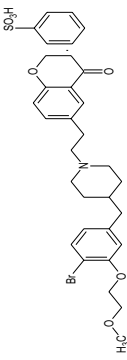
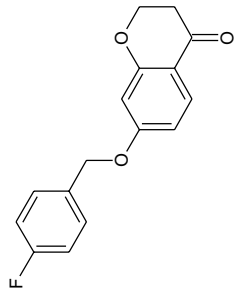
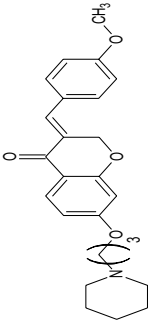
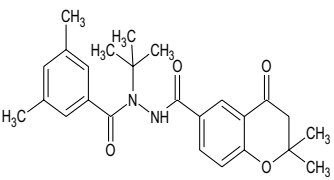
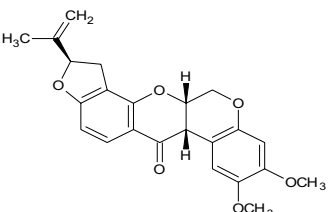
Sr. No.	Name of compound	Structure	Evaluation	Inference
1	(E)-3-Heteroarylidenchroman-4-ones		In vitro investigation to inhibit the enzymatic action of both human monoamine oxidase (hMAO) isoforms such as hMAO-A and B	Showed highest hMAO-B potency ($IC_{50} = 10.58$ nM) and selectivity ($SI > 9452$) with respect to the standard inhibitor selegiline ($IC_{50} = 19.60$ nM, $IC_{50} > 3431$) [150]
2	Chroman-4-one derivatives		Evaluated for the inhibition of serotonin transporter (SERT) and 5-HT1A receptor	Exhibit as novel dual inhibitors of the SERT/5-HT1A receptors [151]
3	DSP-1053 (Novel compound)		Examined for serotonin reuptake Inhibition with 5-HT1A partial agonistic activity in vivo study	Inhibited serotonin transporter with an IC_{50} value of 2.74 ± 0.41 nmol/L and had an intrinsic activity for 5-HT _{1A} receptors of $70.0 \pm 6.3\%$ -A novel serotonin reuptake inhibitor showed fast antidepressant effect [149]
4	7-((4-Fluorobenzyl) oxy) chroman-4-one		Evaluated for hMAO-B inhibitory activity in vitro	Inhibit MAO-B inhibition with $IC_{50} = 8.62$ nM and $SI > 11,627.9$ -fold-Showed low neurotoxicity in SH-SY5Y cells in vitro-Used to treat neurodegenerative disease [152]
5	(E)-3-(4-methoxybenzylidene)-7-(3-(piperidin-1-yl) propoxy) chroman-4-one		Evaluation for dual acetyl cholinesterase (AChE) and monoamine oxidase (MAO-B) inhibition	Inhibition of AChE and hMAO-B enzymes activities, with IC_{50} value of 3.94 and 3.44 nM, respectively [147]



Table 14 Insecticidal evaluation of chroman-4-one analogs

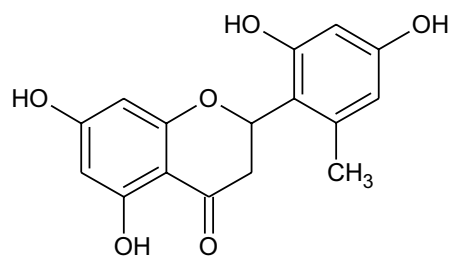
Sr. No.	Name of compound	Structure	Evaluation	Inference
1	Chromanone derivatives of diacylhydrazines		Tested killing property against <i>Mythima separata</i>	Showed insecticidal potency against <i>Mythima separata</i> [156]
2	Rotenone		Evaluated for insecticide activity	Exhibited impressive insecticidal effect [157]

for their diagnostic potential creates a great interest in the field of medicinal chemistry.

3 Miscellaneous

3.1 Antidengue

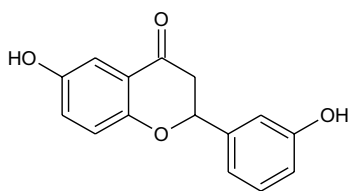
M. M. V. Ramana et al. (2015) reported a docking study of isolated flavanones and designed chroman-4-one compounds against NS2B/NS3 protease (dengue virus protein). As per literature survey, naringenin and pinocembrin are known to have effective potential as antidengue agent with good dock score. Similarly, *in-silco* experimentation revealed the antidengue activity of isolated eriodictyol having Leu 149 and Asn 152 hydrogen bonding and 2-(2, 4-dihydroxy-6-methylphenyl)-5, 7-dihydroxychroman-4-one [designed compound] also showed interactions with Asp 75 and Asn 152 with a comparable glide score -7.31 that characterizes its antidengue activity [159].



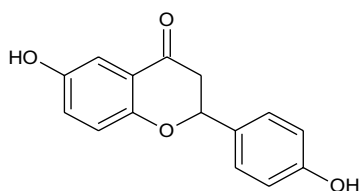
2-(2, 4-dihydroxy-6-methylphenyl)-5, 7-dihydroxychroman-4-one

3.2 Antiparasitic

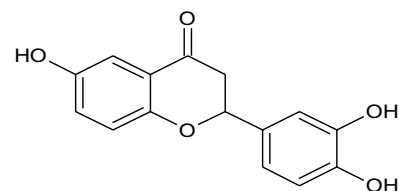
Chroman-4-one analogs 6-hydroxy-2-(3-hydroxyphenyl) chroman-4-one, 6-hydroxy-2-(4-hydroxyphenyl) chroman-4-one and 2-(3,4-dihydroxyphenyl)-6-hydroxychroman-4-one displayed antiparasitic activity by targeting pteridine reductase-1 and showed significant inhibition against *T. brucei* and *L. infantum* at 10 μM and 50 μM . Therefore, more research on chroman-4-one derivatives as antiparasitic may provide a new platform for the development of new antiparasitic agents. [160].



6-hydroxy-2-(3-hydroxyphenyl) chroman-4-one



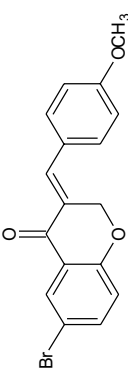
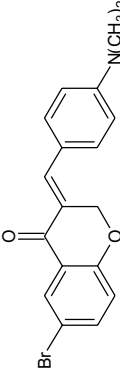
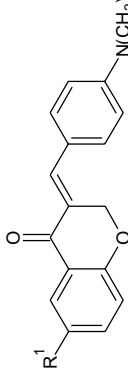
6-hydroxy-2-(4-hydroxyphenyl) chroman-4-one



2-(3,4-dihydroxyphenyl)-6-hydroxychroman-4-one

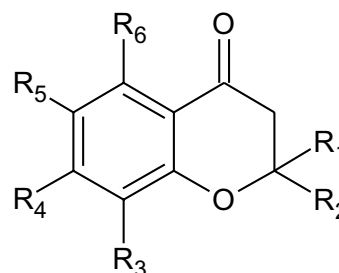


Table 15 Chroman-4-one analogs evaluated as diagnostic agents

Sr. No.	Name of compound	Structure	Evaluation	Inference
1	(E)-3-(4-Methoxybenzylidene)-6-bromo-chroman-4-one		Diagnosis of Alzheimer's disease	Exhibited high binding affinities to A β plaques with 9.98 and 9.10 nM (K _i values), respectively, against [125I] IMPY (reference compound) Helpful diagnostic imaging agent for early finding of A β plaques in Alzheimer's disease brain [158]
	(E)-3-(4-Dimethylamino-benzylidene)-6-bromo-chroman-4-one			
	Iodine labeled 3-benzylidenechroman-4-one's derivative, R1 = ¹²⁵ I			

3.3 Anti-aging

Chroman-4-one derivatives were used as active compound in cosmetic preparations for care, improvement and refreshment of texture of the skin and hairs, for treatment of skin as well as hair-related defects like inflammation, allergies or wound healing process. Furthermore, cosmetic formulations containing vitamin A and its derivatives like retinol esters, retinoic acid have shown their action on the differentiation process of epithelial cells and therefore used against psoriasis, acne, skin spotting, wrinkles and discoloration. Therefore, chroman-4-one scaffolds have significant cosmetic value along with pharmacological activities [160].

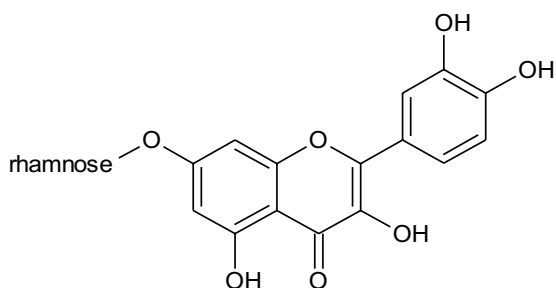


chroman-4-one derivatives

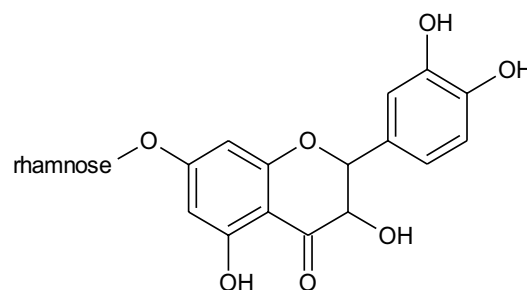
3.4 Anticoronol

Kwon Dur-Han, et al. proposed inhibitory potential of an isolated flavanone, quercetin-7-rhamnoside against viral propagation. Furthermore, experimentation showed effective results against inhibition of coronavirus via specific inhibition of PEDV (porcine epidemic diarrhea virus) proliferation in Vero cells with good inhibitory activity = -7.143 $CC_{50}/IC_{50} = > (100 \text{ g/mL})$ as compared to standard antiviral drug (ribavirin). Accordingly, *in vitro* inhibiting activity of quercetin-7-rhamnoside against PEDV, a number of flavonoids such as quercetin, luteolin, apigenin showed effective inhibition in vero cells. In spite of PEDV inhibition, quercetin-7-rhamnoside also exhibited antiviral potential against porcine transmissible gastroenteritis virus (TGEV) with inhibition value > 1.58 [$CC_{50}/IC_{50} = > (100 \text{ g/mL}/63.3 \text{ } \mu\text{g/ml})$] and porcine respiratory coronavirus (PRCV) with inhibition value > 1.67 [$CC_{50}/IC_{50} = > (100 \text{ g/mL}/59.8 \text{ } \mu\text{g/ml})$]. Therefore, quercetin-7-rhamnoside displayed better antiviral inhibition potential against three types of coronaviruses like TGEV, PEDV and PRCV than reference drug (ribavirin) *in vitro*. In conclusion, more experimentation on chromanone containing flavonoids as anticoronol for the inhibition of other classes of corona virus might be led a new frame for drug discovery and development [161]





Quercetin-7-rhamnoside



dihydroquercetin-7-rhamnoside

4 Conclusion

Chroman-4-one/chromanone pharmacophore is a privileged scaffold in medicinal research, consisting of two rings in which 2, 3-dihydro- γ -pyranone fused with an aromatic benzene nucleus and derivatization at 2, 3 and 4-positions of chromanone skeleton yields more effective families of flavonoids like 3-benzylidene-chromanones, spirochromanone, hydrazones, oximes, flavanones, homisoflavonones and isoflavanones. This structural diversification of chromanone occupied an important role in pharmaceutical field as they owe numerous biological activities like anticancer, antioxidant, antidiabetic, anti-inflammatory, antiviral, antitubercular, antibacterial, antifungal, antiparasitic, anti-AchE, anticonvulsant, anti-HIV and antileishmanial properties. As chromanone scaffolds exhibit numerous potent biological activities, even some derivatives are novel like DSP-1053 (novel serotonin reuptake inhibitor and fast antidepressant), calanolide A (anti-HIV), Silibinin and chrysin (anticancer), taxifolin (antidiabetic), tetrazole (antidiabetic), troglitazone (antidiabetic), ormeloxifene (anticancer) and nebivolol (beta-blockers); nevertheless, the market proportion of potent chromanone analogs is fewer. Therefore, for future prospective, more consideration is required for designing and developing potent synthetic chromanone analogs which may provide better therapeutic value.

References

- Emami, S.; Ghanbarimasir, Z.: Recent advances of chroman-4-one derivatives: synthetic approaches and bioactivities. *Eur. J. Med. Chem.* **93**, 539–563 (2015)
- Panche, A.N.; Diwan, A.D.; Chandra, R.: Flavonoids: an overview. *J. Nutr. Sci.* **5**(47), 1–15 (2016)
- Christophe Carola H., Ralf Roskopf M.: Use of chroman-4-one derivatives.: United States Patent application publication., US 2010/0028278 A1,1, 1–24 (2010).
- Cotelle, N.: Role of flavonoids in oxidative stress. *Curr. Top. Med. Chem.* **1**(2001), 569–590 (2001)
- Jaracz, S.; Chen, J.; Kuznetsova, L.V., et al.: Recent advances in tumor-targeting anticancer drug conjugates. *Biomed. Pharmacother.* **13**, 5043–5054 (2005)
- Schindler, R.; Mentlein, R.: Flavonoids and vitamin E reduce the release of the angiogenic peptide vascular endothelial growth factor from human tumor cells. *J. Nutr.* **136**, 1477–1482 (2006)
- Piyush, K.; Kuldeep, S.; Azizur, R.M., et al.: A review of benzopyran derivatives in pharmacotherapy of breast cancer. *Asian J. Pharm. Clin. Res.* **11**(7), 43–46 (2018)
- Raj, V.; Lee, J.: 2H/4H-Chromenes-A versatile biologically attractive scaffold. *Front. Chem.* **8**, 623 (2020)
- Felgines, C.; Texier, O.; Morand, C., et al.: Bioavailability of the flavanone naringenin and its glycosides in rats. *Am. J. Physiol. Gastrointest. Liver Physiol.* **279**(6), 1148–1154 (2000)
- Kodama, O.: Sakuranetin, a flavanone ultraviolet-irradiated phytoalexin from rice leaves. *Phytochemistry* **31**(11), 3807–3809 (1992)
- Ley, J.P.: Evaluation of bitter masking flavanones from herba santa (*Eriodictyon californicum* (H. & A.) Torr., Hydrophyllaceae). *J. Agric. Food Chem.* **53**, 6061–6066 (2005)
- Kumar, D.; Sharma, P.; Singh, H., et al.: The value of pyrans as anticancer scaffolds in medicinal chemistry. *RSC Adv.* **7**(59), 36977–36999 (2017)
- Gordo, J.; Cabrita, E.; Oliva, A., et al.: *Thymus mastichina*: chemical constituents and their anti-cancer activity. *Nat. Prod. Commun.* **7**(11), 1491–1494 (2012)
- Lopez-Lazaro, M.: Flavonoids as anticancer agents: structure-activity relationship study. *Curr. Med. Chem. - Anti-Cancer Agents.* **2**(6), 691–714 (2002)
- Kopustinskiene, D.M.; Jakstas, V.; Savickas, A., et al.: Flavonoids as anticancer agents. *Nutrients* **12**(2), 1–24 (2020)
- Noushini, S.; Alipour, E.; Emami, S., et al.: Synthesis and cytotoxic properties of novel (E)-3-benzylidene-7-methoxychroman-4-one derivatives. *DARU J. Pharm. Sci.* **21**(1), 1–10 (2013)
- Ivanova, L.; Varinska, L.; Pilatova, M., et al.: Cyclic chalcone analogue KRP6 as a potent modulator of cell proliferation: An *in vitro* study in HUVECs. *Mol. Bio. Rep.* **40**(7), 4571–4580 (2013)
- Alipour, E.; Mousavi, Z.; Safaei, Z., et al.: Synthesis and cytotoxic evaluation of some new[1,3]dioxolo[4,5-g]chromen-8-one derivatives. *DARU J. Pharm. Sci.* **22**, 41 (2014)
- Bahram, L.: Synthesis and *in vitro* cytotoxic activity of novel chalcone-like agents. *Iran J. Basic Med. Sci.* **16**, 1155–1162 (2013)
- Shen, S.; Ko, H.; Tseng, S., et al.: Structurally related antitumor effects of flavanones *in vitro* and *in vivo*: involvement of caspase 3 activation, p21 gene expression, and reactive oxygen species production. *Toxicol. Appl. Pharmacol.* **197**, 84–95 (2004)



21. Choi, E.J.; Lee, J.I.; Kim, G.: Effects of 4', 7-Dimethoxyflavone on cell cycle arrest and apoptosis in human breast cancer MCF-7 Cells. *Arch. Pharm. Res.* **34**(12), 2125–2130 (2011)
22. Safavi, M.; Esmati, N.; Kabudanian, S., et al.: Halogenated flavanones as potential apoptosis-inducing agents: synthesis and biological activity evaluation. *Eur. J. Med. Chem.* **58**, 573–580 (2012)
23. Orlikova, B.: Methylenedioxy flavonoids: assessment of cytotoxic and anti-cancer potential in human leukemia cells. *Eur. J. Med. Chem.* **84**, 173–180 (2014)
24. Shi, L.; Feng, X.E.; Rong, J., et al.: Synthesis and biological activity of flavanone derivatives. *Bioorg. Med. Chem. Lett.* **20**(18), 5466–5468 (2010)
25. Kanagalakshmi, K.; Premanathan, M.; Priyanka, R., et al.: Synthesis, anticancer and antioxidant activities of 7-methoxyisoflavanone. *Eur. J. Med. Chem.* **45**(6), 2447–2452 (2010)
26. Kupcewicz, B.; Balcerowska-Czerniak, G.; Małeczka, M., et al.: Structure-cytotoxic activity relationship of 3-arylidene flavanone and chromanone (E, Z isomers) and 3-arylflavones. *Bioorganic Med. Chem. Lett.* **23**(14), 4102–4106 (2013)
27. Simon, L.; Abdul Salam, A.A.; Kumar, S., et al.: Synthesis, anticancer, structural, and computational docking studies of 3-benzylchroman-4-one derivatives. *Bioorg. Med. Chem. Lett.* **27**(23), 5284–5290 (2017)
28. Holshouser, M.H.; Loeffler, J.L.: Synthesis and antitumor testing of 3-methenylthiochroman-4-one-1,1-dioxide. *J. Pharm. Sci.* **71**(6), 715–717 (1982)
29. Ei-fotooh, A.: Synthesis of novel tricyclic heterocyclic compounds as potential anticancer agents using chromanone and thiochromanone as synthons. *Indian J. Chem. -Section B.* **42**(August), 1985–1993 (2003)
30. Abdelatef, S.A.; El-Saadi, M.T.; Amin, N.H., et al.: Synthesis and anticancer screening of novel spiro[chroman-2,4'-piperidin]-4-one derivatives with apoptosis-inducing activity. *J. Appl. Pharm. Sci.* **8**(1), 009–016 (2018)
31. Maasomi, Z.J.; Soltanahmadi, Y.P.; Dadashpour, M., et al.: Synergistic anticancer effects of silibinin and chrysin in T47D breast cancer cells. *Asian Pacific J. Cancer Prev.* **18**(5), 1283–1287 (2017)
32. Murti, Y.; Mishra, P.: Synthesis and evaluation of flavanones as anticancer agents. *Indian J. Pharm. Sci.* **76**(2), 163–166 (2014)
33. Gaspar, A.; Mohabbati, M.; Cagide, F., et al.: Searching for new cytotoxic agents based on chromen-4-one and chromane-2,4-dione scaffolds. *Res. Pharm. Sci.* **14**(1), 74–83 (2019)
34. Demirayak, S.; Yurttas, L.; Gundogdu-Karaburun, N., et al.: New chroman-4-one/thiochroman-4-one derivatives as potential anticancer agents. *Saudi Pharm. J.* **25**(7), 1063–1072 (2017)
35. Hegab, M.I.; Morsy, E.; Mageed, A.E., et al.: Synthesis and characterization of new 3'',5''-diaryl-3''H,4''H-dispiropyran/thiopyran[4,2'-chroman-3'',2''-[1,3,4-thiadiazol]-4'-one derivatives and related compounds as anticancer and antiviral agents, Phosphorus, Sulfur, and Silicon and the Related Elements. *190*(11):00–00 (2015).
36. Siddiqui, Z.N.; Farooq, F.A.: Practical one pot synthesis of novel 2-hydroxy-4-chromanone derivatives from 3-formylchromone. *J. Chem. Sci.* **124**(5), 1097–1105 (2012)
37. Pontius, A.; Krick, A.; Kehraus, S., et al.: Noduliprevenone: A novel heterodimeric chromanone with cancer chemopreventive potential. *Chem. Eur. J.* **14**, 9860–9863 (2008)
38. Bolwell, G.P.; Wojtaszek, P.: Mechanisms for the generation of reactive oxygen species in plant defence: a broad perspective. *Physiol. Mol. Plant Pathol.* **51**(6), 347–366 (1997)
39. Chen, Q.; Vazquez, E.J.; Moghaddas, S., et al.: Production of reactive oxygen species by mitochondria: central role of complex III. *J. Biol. Chem.* **278**(38), 36027–36031 (2003)
40. Miyake, Y.; Yamamoto, K.; Tsujihara, N., et al.: Protective effects of lemon flavonoids on oxidative stress in diabetic rats. *Lipids* **33**(7), 689–695 (1998)
41. Gholamian-Dehkordi, N.; Luther, T.; Asadi-Samani, M., et al.: An overview on natural antioxidants for oxidative stress reduction in cancers; a systematic review. *Immunopathol. Persa.* **3**(2), 12 (2017)
42. Karak, P.: Biological activities of flavonoids: an overview. *Int. J. Pharm. Sci. Res.* **10**(4), 1567–1574 (2019)
43. Chen, X.; Mukwaya, E.; Wong, M.S., et al.: A systematic review on biological activities of prenylated flavonoids. *Pharm. Biol.* **52**, 655–660 (2014)
44. Huyut, Z.; Beydemir, S.; Gulcin, I.: Antioxidant and antiradical properties of selected flavonoids and phenolic compounds. *Biochem. Res. Int.* **2017**, 7616791 (2017)
45. Foroumadi, A.; Samzadeh-Kermani, A.; Emami, S., et al.: Synthesis and antioxidant properties of substituted 3-benzylidene-7-alkoxychroman-4-ones. *Bioorganic Med. Chem. Lett.* **17**(24), 6764–6769 (2007)
46. Lee, H.; Lee, K.; Jung, J.K., et al.: Synthesis and evaluation of 6-hydroxy-7-methoxy-4-chromanone- and chroman-2-carboxamides as antioxidants. *Bioorganic Med. Chem. Lett.* **15**(11), 2745–2748 (2005)
47. Ayunda, R.D.; Prasetyastuti, H.P.: Effect of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one on level of manganese-superoxide dismutase (Mn-sod) and superoxide dismutase 2 (SOD2) gene expression in hyperlipidemia rats. *Indones. J. Pharm.* **30**(3), 180–186 (2019)
48. Wang, D.; Zeng, L.; Li, D., et al.: Antioxidant activities of different extracts and homoisoflavanones isolated from the *Polygonatum odoratum*. *Nat. Prod. Res.* **27**(12), 1111–1114 (2013)
49. Mistry, B.; Patel, R.V.; Keum, Y.: Access to the substituted benzyl-1, 2, 3-triazolyl hesperetin derivatives expressing antioxidant and anticancer effects. *Arab. J. Chem.* **10**(2), 157–166 (2017)
50. Calvo, M.I.: Homoisoflavanones from *Ledebouria floribunda*. *Fitoterapia* **80**(2), 96–101 (2009)
51. Hu, H.; Chen, X.; Sun, K., et al.: Silver-catalyzed radical cascade cyclization toward 1,5-/1,3-dicarbonyl heterocycles: an atom-/step-economical strategy leading to chromenopyridines and isoxazole-/pyrazole-containing chroman-4-ones. *Org. Lett.* **20**(19), 6157–6160 (2018)
52. Roy, S.K.; Agrahari, U.C.; Gautam, R., et al.: Isointrinsicanol, a new antioxidant homoisoflavanoid from the roots of *Caesalpinia digyna* Rottler. *Nat. Prod. Res.* **26**(8), 690–695 (2012)
53. Sun, Y.X.; Tang, Y.; Wu, A.L., et al.: Neuroprotective effect of liquiritin against focal cerebral ischemia/reperfusion in mice via its antioxidant and antiapoptosis properties. *J. Asian Nat. Prod. Res.* **12**(12), 1051–1060 (2010)
54. Gazak, R.; Svobodova, A.; Psotova, J., et al.: Oxidised derivatives of silybin and their antiradical and antioxidant activity. *Bioorganic Med. Chem.* **12**(21), 5677–5687 (2004)
55. Peng, Z.Y.; Liu, X.Y.; Yang, Y.L., et al.: 7-Methoxy-3-(4-methoxyphenyl) chroman-4-one. *Acta Cryst.* **E68**, 250 (2012)
56. Zheng, Y.Z.; Deng, G.; Chen, D.F., et al.: Theoretical studies on the antioxidant activity of pinobanksin and its ester derivatives: effects of the chain length and solvent. *Food Chem.* **240**, 323–329 (2018)
57. Siddaiah, V.; Maheswara, M.; Venkata Rao, C., et al.: Synthesis, structural revision, and antioxidant activities of antimutagenic homoisoflavanoids from *Hoffmannosseggia intricata*. *Bioorg. Med. Chem. Lett.* **17**(5), 1288–1290 (2007)
58. Hadaruga, D.I.; Hadaruga, N.G.: Antioxidant activity of hepatoprotective silymarin and *silybum marianum* L. extract. *Chem. Bull.* **54**(68), 104–107 (2009)
59. Zhao, J.W.; Chen, D.S.; Deng, C.S., et al.: Evaluation of anti-inflammatory activity of compounds isolated from the rhizome of

- Ophiopogon japonicas*. BMC Complement Altern. Med. **17**(1), 1–12 (2017)
60. Ali, K.A.; Abdelhafez, N.A.A.; Ragab, E.A., et al.: Design and synthesis of novel fused heterocycles using 4-chromanone as synthon. Russ. J. Gen. Chem. **85**(12), 2853–2860 (2015)
 61. Waller, C.P.; Thumser, A.E.; Langat, M.K., et al.: COX-2 inhibitory activity of homoisoflavanones and xanthenes from the bulbs of the southern african *ledebouria socialis* and *ledebouria ovatifolia* (Hyacinthaceae: Hyacinthoideae). Phytochemistry **95**(6), 284–290 (2013)
 62. Ma, J.; Cao, B.; Chen, X., et al.: Violacin A, a new chromanone produced by *Streptomyces violaceoruber* and its anti-inflammatory activity. Bioorganic Med. Chem. Lett. **28**(5), 947–951 (2018)
 63. Wang, Q.Q.; Shi, J.B.; Chen, C., et al.: Hesperetin derivatives: Synthesis and anti-inflammatory activity. Bioorganic Med. Chem. Lett. **26**(5), 1460–1465 (2016)
 64. Shaikh, M.M.; Kruger, H.G.; Bodenstern, J., et al.: Anti-inflammatory activities of selected synthetic homoisoflavanones. Nat. Prod. Res. **26**(16), 1473–1482 (2012)
 65. Hu, C.; Zhou, Z.; Xiang, Y., et al.: Design, synthesis and anti-inflammatory activity of dihydroflavonol derivatives. Med. Chem. Res. **27**(1), 194–205 (2018)
 66. Zheng, C.; Wang, L.; Han, T., et al.: Pruinosanones A-C, anti-inflammatory isoflavone derivatives from *Caragana pruinosa*. Sci Rep. **6**, 2–9 (2016)
 67. Winekenstadde, D.; Angelis, A.; Waltenberger, B., et al.: Phytochemical profile of the aerial parts of sedum sediforme and anti-inflammatory activity of myricitrin. Nat. Prod. Commun. **10**(1), 83–88 (2015)
 68. Wright, George C., Goldenberg, Marvin M.: 7-Dimethylamino-4-chromanone United States Morton-Norwich Products, Inc. (Norwich, NY), 4108872 (1978).
 69. Edwards, J.L.; Vincent, A.M.; Cheng, H.T., et al.: Diabetic neuropathy: Mechanisms to management. Pharmacol. Therap. **2008**, 1–34 (2008)
 70. Unnikrishnan, M.K.; Veerapur, V.; Nayak, Y., et al.: Antidiabetic, antihyperlipidemic and antioxidant effects of the flavonoids. Polyphenols Hum. Health Dis **2013**, 143–161 (2013)
 71. Adams, G.L.; Velazquez, F.; Jayne, C., et al.: Discovery of chromane propionic acid analogues as selective agonists of GPR120 with *in vivo* activity in rodents. ACS Med. Chem. Lett. **8**(1), 96–101 (2017)
 72. Takao, K.; Yamashita, M.; Yashiro, A.; Sugita, Y.: Synthesis and biological evaluation of 3-Benzylidene-4-chromanone derivatives as free radical scavengers and α -Glucosidase inhibitors. Chem. Pharm. Bull. **64**(8), 1203–1207 (2016)
 73. Zhu, G.; Luo, Y.; Xu, X., et al.: Anti-diabetic compounds from the seeds of *Psoralea corylifolia*. Fitoterapia **139**, (2019)
 74. Kocivar, N.; Glavac, I.; Kreft, S.: Flavonoidi. Farm Vestn. **58**(4), 145–148 (2007)
 75. Lotulung, P.D.N.; Fajriah, S.; Sundowo, A., et al.: Anti diabetic flavanone compound from the leaves of *Artocarpus communis*. Indones. J. Chem. **9**(3), 505–508 (2010)
 76. Sadewa, A.H.: Effect of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl) - chroman-4-one (swietenia macrophylla king seed) on retinol binding protein-4 and phosphoenolpyruvate carboxykinase gene expression in type 2 diabetic rats. Rom. J. Diabetes Nutr. Metab. Dis. **23**(3), 255–265 (2016)
 77. Sneha Jose, E.; Philip, J.E.; Shanty, A.A.: Novel class of mononuclear 2-methoxy-4-chromanones ligated Cu (II), Zn (II), Ni (II) complexes: synthesis, characterisation and biological studies. Inorganica Chim. Acta. **478**(1), 155–165 (2018)
 78. Park, J.; Seo, Y.; Han, J.: *in vitro* and alleviates postprandial hyperglycemia in diabetic mice. Eur. J. Pharmacol. **863**(September), (2019)
 79. Ravi, S.; Sadashiva, C.T.; Tamizmani, T.: *In vitro* glucose uptake by isolated rat hemi-diaphragm study of *Aegle marmelos* correa root. Bangladesh J. Pharmacol. **4**(1), 65–68 (2009)
 80. Raju, B.C.; Tiwari, A.K.; Kumar, J.A., et al.: α -Glucosidase inhibitory antihyperglycemic activity of substituted chromenone derivatives. Bioorg. Med. Chem. **18**(1), 358–365 (2010)
 81. Shaikh, M.M.; Kruger, H.G.; Smith, P., et al.: Crystal structure and potent antifungal activity of synthetic homoisoflavanone analogues. J. Pharm. Res. **6**(1), 1–5 (2013)
 82. Tiratsuyan, S.G.; Hovhannisyanyan, A.A.; Karapetyan, A.V., et al.: Synthesis and biological activities of novel pyridazine derivatives. Mor. J. Chemi. **63**(5), 698–704 (2016)
 83. Ayati, A.; Falahati, M.; Irannejad, H., et al.: Synthesis, *in vitro* antifungal evaluation and *in silico* study of 3-azolyl-4-chromanone phenylhydrazones. DARU J. Pharm. Sci. **20**(46), 1–7 (2012)
 84. Dongamanti, A.; Naji, H.H.; Bommidi, V.L., et al.: Microwave-assisted one-pot synthesis and antimicrobial evaluation of 2-(1-phenyl-3-(2-thienyl)-1H-pyrazol-4-yl)chroman-4-one derivatives. Heterocycl. Commun. **22**(5), 259–264 (2016)
 85. Ashok, D.; Kumar, R.S.: Solvent-free microwave-assisted synthesis and biological evaluation of auronones and flavanones based on 2, 2-dimethylchroman-4-one. Chem. Heterocycl. Compd. **52**(7), 453–459 (2016)
 86. Hoettecke, N.; Rotzoll, S.; Albrecht, U.: Synthesis and antimicrobial activity of 2-alkenylchroman-4-ones, 2-alkenylthiochroman-4-ones and 2-alkenylquinol-4-ones. Bioorg. Med. Chem. **16**(24), 10319–10325 (2008)
 87. Kang, J.G.; Shin, S.Y.; Kim, M.J., et al.: Isolation and anti-fungal activities of 2-hydroxymethyl-chroman-4-one produced by *Burkholderia sp.* MSSP. J. Antibiot. **57**(11), 726–731 (2004)
 88. Albrecht, U.; Lalk, M.; Langer, P.: Synthesis and structure-activity relationships of 2-vinylchroman-4-ones as potent antibiotic agents. Bioorg. Med. Chem. **13**(5), 1531–1536 (2005)
 89. Sriram, D.; Srinivasan, S.; Santhosh, K.C.: 3-phenylsulfonyl-3-(2-propenyl)chroman-4-one. Acta Crystallogr. Cryst Struct. Commun. **53**(6), 793–794 (1997)
 90. Sharma, S.; Patial, V.; Singh, D., et al.: Antimicrobial homoisoflavanoids from the Rhizomes of *Polygonatum verticillatum*. Chem. Biodivers. **15**(12), 1800430 (2018)
 91. Feng, L.; Maddox, M.M.; Alam, M.Z., et al.: Synthesis, structure-activity relationship studies, and antibacterial evaluation of 4-chromanones and chalcones, as well as olympicin A and derivatives. J. Med. Chem. **57**(20), 8398–8420 (2014)
 92. Albogami, A.S.; Alkhatlan, H.Z.; Saleh, T.S., et al.: Microwave-assisted synthesis of potent antimicrobial agents of flavanone derivatives. Orient J. Chem. **30**(2), 435–443 (2014)
 93. Pawar, M.J.; Burungale, B.; Karale, B.K.: Synthesis and antimicrobial activity of spiro [chromeno [4, 3- thiadiazolone compounds. ARKIVOC: Online. J. Org. Chem. **2009**, 97–107 (2009)
 94. Ramana Kishore, N.; Ashok, D.; Sarasija, M., et al.: Microwave-assisted synthesis of novel spirochromanone–aurone hybrids and their antimicrobial activity. Russ. J. Gen. Chem. **88**(5), 1015–1019 (2018)
 95. Alsarhni, A.; Eldeen, Z.M.; Alkaissi, E., et al.: Synthesis and structural elucidation of amino acetylenic and thiocarbamates derivatives for 2-mercaptobenzothiazole as antimicrobial agents. Int. J. Pharm. Sci. **9**(2), 192 (2017)
 96. Qing-hui, X.U.; Ji-zhen, L.I.; Jiang-hua, H.E., et al.: Synthesis of novel flavanone derivatives and their anti *Staphylococcus aureus* evaluation. Chem. Res. Chin. Univ. **29**(4), 695–698 (2013)
 97. Thinagar, S.; Velmurugan, D.; Amalraj, R.R.: Crystal structure of spiro [2-benzoyl-cyclohexyl-4, 5-diphenylpyrrolidine-3,3'-chroman-4-one]. Cryst Res. Technol. **35**(8), 979–986 (2000)



98. Agnes Kenez, L.J., et al.: A simple synthesis of selinone, an antifungal component of *monotes engleri*. *Heterocycl. Commun.* **8**(6), 543–548 (2002)
99. Kaufmann, S. H. E., van Helden P.: *Handbook of tuberculosis: Clinics, Diagnostics, Wiley-VCH, therapy and epidemiology*. Weinheim (2008).
100. Saengchantara, S.T.; Wallace, T.W.: Chromanols, chromanones, and chromones. *Nat. Prod. Rep.* **3**, 465–475 (1986)
101. Alvey, L.; Prado, S.; Saint-joanis, B., et al.: Diversity-oriented synthesis of furo [3, 2- f] chromanes with antimycobacterial activity. *Eur. J. Med. Chem.* **44**, 2497–2505 (2009)
102. Wu, M.; Peng, C.; Chen, I., et al.: Antitubercular chromones and flavonoids from *Pisonia aculeata*. *J. Nat. Prod.* **5**(74), 976–982 (2011)
103. Pini, E.; Poli, G.; Tuccinardi, T., et al.: New chromane-based derivatives as inhibitors of *mycobacterium tuberculosis* salicylate synthase: Preliminary biological evaluation and molecular modeling studies. *Molecules* **23**(7), 1–14 (2018)
104. Yempala, T.; Sriram, D.; Yogeewari, P., et al.: Molecular hybridization of bioactives: synthesis and antitubercular evaluation of novel dibenzofuran embodied homoisoflavonoids via Baylis-Hillman reaction. *Bioorganic Med. Chem. Lett.* **22**(24), 7426–7430 (2012)
105. Asif, M.A.: Brief overview on recent advances in the development of anti-tubercular compounds containing different heterocyclic ring systems. *Appl. Microbiol. Open Access.* **02**(04), 1–14 (2016)
106. Roy, S.K.; Kumari, N.; Gupta, S., et al.: 7-Hydroxy-(E)-3-phenylmethylene-chroman-4-one analogues as efflux pump inhibitors against *Mycobacterium smegmatis* mc² 155. *Eur. J. Med. Chem.* **66**, 499–507 (2013)
107. Anand, N.; Singh, P.; Sharma, A., et al.: Synthesis and evaluation of small libraries of triazolylmethoxy chalcones, flavanones and 2-aminopyrimidines as inhibitors of mycobacterial FAS-II and PknG. *Bioorg. Med. Chem.* **20**(17), 5150–5163 (2012)
108. Mujahid, M.; Gonnade, R.G.; Yogeewari, P., et al.: Synthesis and antitubercular activity of amino alcohol fused spirochromone conjugates. *Bioorg. Med. Chem. Lett.* **23**(5), 1416–1419 (2013)
109. Donnell, G.; Bucar, F.; Gibbons, S.: Phytochemistry and antimycobacterial activity of *Chlorophytum inornatum*. *Phytochemistry* **67**, 178–182 (2006)
110. Dongamanti, A.; Aamate, V.K.; Devulapally, M.G., et al.: Bis-spirochromanones as potent inhibitors of *Mycobacterium tuberculosis*: synthesis and biological evaluation. *Mol. Divers.* **21**(4), 999–1010 (2017)
111. Lee H, Kr D, Kim JH.: (12) United States Patent. Vol. 2. 1–5(2011).
112. Gaikwad, M.S.; Mane, A.S.; Hangarge, R.V., et al.: Synthesis of newer selenadiazoles and thiadiazoles from their chroman-4-one precursors. *Indian J. Chem. Sect. B.* **42**(January), 189–191 (2003)
113. Tait, S.; Laura, A.; Desideri, N.; Fiore, L.: Antiviral activity of substituted homoisoflavonoids on enteroviruses. *Antiviral Res.* **72**, 252–255 (2006)
114. Conti, C.; Proietti, L.; Desideri, N.: Design, synthesis and in-vitro evaluation of novel chroman-4-one, chroman, and 2 H-chromene derivatives as human rhinovirus capsid-binding inhibitors. *Bioorg Med Chem.* **19**(24), 7357–7364 (2011)
115. Quaglia, M.G.; Desideri, N.; Bossu, E., et al.: Enantioseparation and anti-rhinovirus activity of 3-Benzylchroman-4-ones. *Chirality* **500**, 495–500 (1999)
116. Kang, Y.; Mei, Y.; Du, Y.; Jin, Z.: Total synthesis of the highly potent anti-HIV natural product daurichromenic acid along with its two chromane derivatives, rhodaurichromenic acids A and B. *Organic Lett.* **5**(23), 4481–4484 (2003)
117. Rama Rao, A.V.; Galtonde, A.S., et al.: A concise selective synthesis of the chromanol moiety of anti-HIV agent calanolide A. *Tetrahedron Lett.* **35**(34), 6347–6350 (1994)
118. Ishikawa, T.; Oku, Y.; Tanaka, T., et al.: An approach to anti-HIV-1 active Calophyllum coumarin synthesis: an enantioselective construction of 2,3-dimethyl-4-chromanone ring by quinine-assisted intramolecular Michael-type addition. *Tetrahedron Lett.* **40**(19), 3777–3780 (1999)
119. Pokorna, J.; Machala, L.; Rezacova, P.; Konvalinka, J.: Current and novel inhibitors of HIV protease. *Viruses* **1**, 1209–1239 (2009)
120. Dawood, K.M.: Regio and stereoselective synthesis of bis-spiropyrazoline-5,3'- chroman(thiochroman)-4-one derivatives via bis-nitrilimines. *Tetrahedron* **61**(22), 5229–5233 (2005)
121. Sekino, E.; Kumamoto, T.; Tanaka, T., et al.: Concise synthesis of anti-HIV-1 Active (+)-Inophyllum B and (+)-Calanolide A by application of (-)-quinine-catalyzed intramolecular oxo-michael addition. *J. Org. Chem.* **69**(8), 2760–2767 (2004)
122. Park, J.H.; Lee, S.U.; Kim, S.H., et al.: Chromone and chromanone derivatives as strand transfer inhibitors of HIV-1 integrase. *Arch. Pharm. Res.* **31**(1), 1–5 (2008)
123. Nagle, A.S.; Khare, S.; Kumar, A.B., et al.: Recent developments in drug discovery for leishmaniasis and human African trypanosomiasis. *Chem. Rev.* **114**, 11305–11347 (2014)
124. Kaye, P.; Scott, P.: Leishmaniasis: complexity at the host-pathogen interface. *Nat. Publ. Gr.* **9**(8), 604–615 (2011)
125. Boer, M.D.; Argaw, D.; Jannin, J., et al.: Leishmaniasis impact and treatment access. *Clin Microbiol. Infect.* **17**(10), 1471–1477 (2011)
126. Cywin, C.L.; Firestone, R.A.; Mcneil, D.W., et al.: The design of potent hydrazones and disulfides as cathepsin S inhibitors. *Bioorg. Med. Chem.* **11**, 733–740 (2003)
127. Das, P.; De, T.; Chakraborti, T.: Leishmania donovani secretory serine protease alters macrophage inflammatory response via COX-2 mediated PGE-2 production. *Indian J. Biochem. Biophys.* **51**(December), 542–551 (2014)
128. Id, E.V.; Echeverri, F.; Upegui, Y.A., et al.: Hydrazone derivatives enhance antileishmanial activity of thiochroman-4-ones. *Molecules* **23**(70), 1–12 (2018)
129. Upegui, Y.; Rios, K.; Quinones, W., et al.: Chroman-4-one hydrazones derivatives: synthesis, characterization, and *in vitro* and *in vivo* antileishmanial effects. *Med. Chem. Res.* **28**(12), 2184–2199 (2019)
130. Castro, H.; Aguiar, P.D.; Cardoso, S., et al.: Synthesis and evaluation of novel chromanone and quinolinone analogues of uniflorol as anti-leishmanial agents. *Heliyon.* **6**(March), 1–11 (2020)
131. Roberson, E.D.; Mucke, L.: 100 years and counting: Prospects for defeating Alzheimer's disease. *Science* **80**(314), 781–784 (2006)
132. Association, A.: Alzheimer's disease facts and figures. *Alzheimer's and Dementia.* **15**(3), 321–387 (2019)
133. Jung, M.; Park, M.: Acetylcholinesterase inhibition by flavonoids from *agrimonia pilosa*. *Molecules* **12**, 2130–2139 (2007)
134. Shen, Y.; Zhang, J.; Sheng, R., et al.: Synthesis and biological evaluation of novel flavonoid derivatives as dual binding acetylcholinesterase inhibitors. *J. Enzyme Inhib. Med. Chem.* **24**(April), 372–380 (2009)
135. Parveen, M.; Malla, A.M.; Yaseen, Z., et al.: Synthesis, characterization, DNA-binding studies and acetylcholinesterase inhibition activity of new 3-formyl chromone derivatives. *J. Photochem. Photobiol. B Biol.* **130**, 179–187 (2014)
136. Anand, P.; Singh, B.: A review on cholinesterase inhibitors for Alzheimer's disease. *Arch. Pharm. Res.* **36**(4), 375–399 (2013)
137. Shamsimeyandi, R.; Pourshojaei, Y.; Eskandari, K., et al.: Design, synthesis, biological evaluation, and molecular dynamics of novel cholinesterase inhibitors as anti-Alzheimer's agents. *Arch. Pharm.* **352**, 7 (2019)

138. Jiang, N.; Ding, J.; Liu, J., et al.: Novel chromanone-dithiocarbamate hybrids as multifunctional AchE inhibitors with β -amyloid anti-aggregation properties for the treatment of Alzheimer's disease. *Bioorg. Chem.* **89**(May), (2019)
139. Li, Y.; Qiang, X.; Luo, L., et al.: Multitarget drug design strategy against Alzheimer's disease: Homoisoflavonoid mannich base derivatives serve as acetylcholinesterase and monoamine oxidase B dual inhibitors with multifunctional properties. *Bioorg. Med. Chem.* **25**(2), 714–726 (2017)
140. Kwan, P.; Brodie, M.J.: Early identification of refractory epilepsy. *N. Engl. J. Med.* **342**(5), 314–319 (2000)
141. Sabers, A.; Gram, L.: Newer anticonvulsants comparative review of drug interactions and adverse effects. *Drugs* **60**(1), 23–33 (2000)
142. Gentry, J.R.; Hill, C.; Malcolm, R.: New Anticonvulsants: a review of applications for the management of substance abuse disorders. *Ann. Clin. Psychiatry.* **14**(4), 233–245 (2002)
143. Emami, S.; Kebriaeezadeh, A.; Ahangar, N., et al.: Imidazolylchromanone oxime ethers as potential anticonvulsant agents: Anticonvulsive evaluation in PTZ-kindling model of epilepsy and SAR study. *Bioorg. Med. Chem. Lett.* **21**(2), 655–659 (2011)
144. Kebriaeezadeh, A.; Emami, S.; Ebrahimi, M.: Anticonvulsant and antiepileptogenic effects of azolylchromanones on lithium pilocarpine induced seizures and pentylenetetrazole-kindling model of epilepsy. *Biomed. Pharmacother.* **62**, 208–211 (2008)
145. Emami, S.; Kebriaeezadeh, A.; Zamani, J.; Shafiee, A.: Azolylchromans as a novel scaffold for anticonvulsant activity. *Bioorganic Med. Chem. Lett.* **16**, 1803–1806 (2006)
146. Tang, S.W.; Helmeeste, D.M.; Leonard, B.E.: Antidepressant compounds: a critical review. *Depression Psychopathol. Pharmacother.* **27**, 1–19 (2010)
147. Wang, Y.; Sun, Y.; Guo, Y., et al.: Dual functional cholinesterase and MAO inhibitors for the treatment of Alzheimer's disease: synthesis, pharmacological analysis and molecular modeling of homoisoflavonoid derivatives Dual functional cholinesterase and MAO inhibitors for the treatment. *J. Enzyme Inhib. Med. Chem.* march **2015**, 1475–6374 (2015)
148. Dupuy, J.M.; Ostacher, M.J.; Huffman, J., et al.: A critical review of pharmacotherapy for major depressive disorder. *Int. J. Neuropsychopharmacol.* **14**, 1417–1431 (2011)
149. Kato, T.; Matsumoto, Y.; Yamamoto, M., et al.: DSP-1053, a novel serotonin reuptake inhibitor with 5-HT 1A partial agonistic activity, displays fast antidepressant effect with minimal undesirable effects in juvenile rats. *Pharmacol. Res. Perspect.* **3**(3), 1–17 (2015)
150. Desideri, N.; Fioravanti, R.; Biava, M., et al.: (E)-3-Heteroarylidenochroman-4-ones as potent and selective monoamine oxidase-B inhibitors Nicoletta. *Eur. J. Med. Chem.* **3**, 1–30 (2016)
151. Seifert, T.; Malo, M.; Kokkola, T., et al.: Chroman-4-one- and chromone-based sirtuin 2 inhibitors with antiproliferative properties in cancer cells. *J. Med. Chem.* **57**, 9870–9888 (2014)
152. Lan, J.S.; Xie, S.S.; Huang, M., et al.: Chromanones: selective and reversible Monoamine Oxidase B inhibitors with nanomolar potency. *Med. chem. comm.* 1–33(2015).
153. Toya, T.; Fukasawa, H.; Masui, A.; Endo, Y.: Potent and selective partial Ecdysone agonist activity of chromafenozide in Sf9 Cells. *Biochem. Biophys. Res. Commun.* **292**, 1087–1091 (2002)
154. Wing, K.D.: 5849, a nonsteroidal Ecdysone agonist: effects on a drosophila cell line. *Science* **241**(4864), 467–469 (1988)
155. Michael, G.: Recent advances in our knowledge of ecdysteroid biosynthesis in insects and crustaceans. *Insect. Biochem. Molec. Biol.* **24**(2), 115–132 (1994)
156. Zhao, P.; Li, J.; Yang, G.: Synthesis and insecticidal activity of chromanone and chromone analogues of diacylhydrazines. *Bioorg. Med. Chem.* **15**, 1888–1895 (2007)
157. Dev, S.; Koul, O.: *Insecticides of natural origin.* Harwood Academic Publishers, The Netherlands (1997)
158. Gan, C.; Zhao, Z.; Nan, D., et al.: Homoisoflavonoids as potential imaging agents for β -amyloid plaques in Alzheimer's disease. *Eur. J. Med. Chem.* **76**, 125–131 (2014)
159. Ramana, M.M.V.; Ranade, P.B.; Betkar, R.R., et al.: Flavanones: Potential dengue targets in silico approach. *J. Chem. Pharm Res.* **7**(9), 469–474 (2015)
160. Pisa, F.D.; Landi, G.; Iacono, L., et al.: Chroman-4-one derivatives targeting pteridine reductase 1 and showing anti-parasitic activity. *Molecules* **22**(426), 1–16 (2017)
161. Kwon, D.H.; Choi, W.J.; Lee, C.H.; Kim, J.H.; Kim, M.B.: Flavonoid compound having an antiviral activity.2. United States Patent, 1–5 (2011).

