Chromanone-A Prerogative Therapeutic Scaffold: An Overview

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Received: 28 September 2020 / Accepted: 9 June 2021 / Published online: 30 June 2021
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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, antivascular, antidiabetic, antioxidant, antimicrobial, antifungal, antivirus, antileishmanial, insecticidal, spasmolytic, analgesic, anti-inflammatory, anticoagulant, estrogenic inhibitor, anti-acetylcholinesterase (AchE) inhibitor, antihuman immunodeficiency virus (HIV), anticonvulsant, antidepressants, anticonvulsion and antitubercular activity. Due to these activities, several analogues of chromane are also available in market like tocopherols (vitamin E), taxifolin (antidiabetic), tetrizole (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...
the degree of mitochondrial impairment and metabolic dys-
functions such as cellular energy supply, cell death signal-
ing, irregulation of metabolic pathways, formation of reac-
tive 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 fla-
vonoids, flavonols, flavanones (2-phenyl chroman-4-one 
derivatives) and homoisoflavanones exhibit good anticancer 
potential along with other pharmacological activities such
| Sr. No. | Compound Description | Structure | Evaluation | Inference |
|---------|----------------------|-----------|------------|-----------|
| 1       | (E)-3-benzylidene-7-methoxychroman-4-one derivatives (3-chloro-4,5-dimethoxybenzylidene derivative) | ![Structure](image) | 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 | ![Structure](image) | Evaluated for antiproliferative activity in HUVEC (human umbilical vein endothelial cells) | Exhibited highest potency against proliferation of endothelial cells with IC₅₀ = 19 µM [17] |
| 3       | 6,7-Methylenedioxy-4-chromanone | ![Structure](image) | Evaluated against three breast cancer cell lines (MCF-7, T47D and MDA-MB-231) | Exhibited highest anticancer activity against tested cell lines (IC₅₀ ≤ 9.3 µg/ml) [18] |
| 4       | 3-Benzylidene-chroman-4-one derivatives | ![Structure](image) | Evaluated against K562, MDA-MB-231 and SK-N-M Cell lines | Exhibited potent anticancer activity with IC₅₀ ≤ 3.86 µg/ml [19] |
| 5       | Hydroxy flavanones | ![Structure](image) | Evaluated against colorectal carcinoma cells such as A549, LLC, AGS, SK-Hepl and HAZ2T cancer cells | Exhibited potent cytotoxic activity [20] |
| 6       | Synthetic flavanones (4′,7-dimethoxyflavanone) | ![Structure](image) | Evaluated for antiproliferative activity against MCF-7 (human breast cancer) cells | Exhibited potent cytotoxic activity [21] |
Table 2 (continued)

| Sr. No. | Compound | Structure | Evaluation | Inference |
|---------|----------|-----------|------------|-----------|
| 7       | Halogenated flavanones 3',7-dichloroflavone | ![Structure](image1) | Evaluated against MCF-7, LNCaP, PC3, HepG2, 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] |
| 8       | 3',6-Dichloroflavone | ![Structure](image2) | | |
| 9       | 7, 8-Methylenedioxyflavanones | ![Structure](image3) | Examine cytotoxic potential and apoptosis in human leukemia cells | Exhibit better cytotoxic potency than reference [23] |
| 10      | 2'-Chloro- or 2'-nitro-substituted chroman-4-one compounds | ![Structure](image4) | Tested for cytotoxic activity against Bel-7402, HL-60, BGC-823 and KB (human cancer cell lines) | Showed significant cytotoxic activity [24] |
| 11      | 7-Methoxyisoflavanone | ![Structure](image5) | Evaluated against HL60 (acute myeloblastic leukemia cells) and PBMC (peripheral blood mononuclear cells) using MTT assay | Displayed highest anticancer activity against HL60 cells [25] |
| 12      | Diarylchromanone | ![Structure](image6) | | |
| 13      | 3-Arylideneflavanone and chromanone (E, Z isomers) and 3-arylflavones | ![Structure](image7) | 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), $1.6 \pm 0.3$ (NALM-6), $6.3 \pm 0.5$ (WM-115), $5.77 \pm 0.17$ (HUVEC) [26] |
| Sr. No. | Compound                                      | Structure | Evaluation                                                                 | Inference                                                                                                                                 |
|--------|-----------------------------------------------|-----------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 12     | 3-Benzylchroman-4-ones                        | ![Structure](image1.png) | 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-l, 1-dioxide       | ![Structure](image2.png) | 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        | ![Structure](image3.png) | 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 | ![Structure](image4.png) | 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                                      | ![Structure](image5.png) | 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                                        | ![Structure](image6.png) |                                                                                      |                                                                                                                                              |
| Sr. No. | Compound | Structure | Evaluation | Inference |
|---------|----------|-----------|------------|-----------|
| 17      | 6-Methoxy-3-phenyl chroman-4-one | ![Structure](image) | 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 | ![Structure](image) | | |
|         | 1,2,4-Oxadiazole containing benzopyran analog | ![Structure](image) | | |
|         | 6,8-Dimethyl-2-[2-(pyridin-3-yl) ethyl]-benzopyran-4-one | ![Structure](image) | | |
|         | 6-Flurobenzopyran-4-one | ![Structure](image) | | |
| 18      | 2-[(Furan-2-yl) methoxy]-benzopyran-4-one | ![Structure](image) | 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] |
|         | Chromone-2-carboxamide (series I) and chromane-2,4-dione (series II) derivatives | ![Structure](image) | 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] |
| Sr. No. | Compound Description | Structure | Evaluation | Inference |
|---------|----------------------|-----------|------------|-----------|
| 20      | 3-[3/4-(2-aryl-2-oxoethoxy) arylidene] chroman/thiochroman-4-one derivatives | ![Structure](image1) | 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 | ![Structure](image2) | 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]oxadithiin-2',3''-chroman-2'4''-tetrahydrothiopyran]-4'-one | ![Structure](image3) | | |
| 22      | 2-hydroxy-4-chromanone derivatives | ![Structure](image4) | Examined for cytotoxic activity against cancer cells | Potent anticancer agent [36] |
| 23      | Novel noduliprevenone | ![Structure](image5) | Produced from the fungus Nodulisporium species, is an endophyte of a Mediterranean alga | Showed significant cytotoxic activity against tested cell lines [37] |
|         | Tested for cytotoxic activity against 36 cancer cells | | | |
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 flavanoids 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 homoisoflavonones such as silymarin, pinobanksin, silybin, licoritin, 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 homoisoflavonones, 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-Homisoflavonones 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-kB (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 hydroxybenzylidine, 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, glipotrol, tolbutamide, acarbose, pioglitazone, glitins, liraglutide 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 homoisoflavonones containing chromanone pharmacophore such as naringenin, hesperitin, dihydroquercetin,
| Sr. No. | Compound                                      | Structure | Evaluation                                                                 | Inference                                                                 |
|--------|-----------------------------------------------|-----------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 1      | 3-Benzylidene-7-alkoxychroman-4-one derivatives | ![Structure](image1) | Assessed for 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging, ferric reducing antioxidant power (FRAP) and thiobarbituric acid reactive substances | Showed following inhibition values 24.30 ± 0.51 to 35 ± 0.47 (DPPH), 10.96 ± 0.34 to 14.33 ± 0.52 (FRAP) and Fe2+µM = 44.62 ± 0.48 to 71.64 ± 0.47 (TBARS) [45] |
| 2      | 6-Hydroxy-7-methoxy-4-chromanone derivatives   | ![Structure](image2) | (a) Assayed for lipid peroxidation inhibition initiated by Fe2+ 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 | ![Structure](image3) | Examined antioxidant activity | Reduced oxidative stress, LDL level, Mn-SOD levels and SOD2 gene expression of hyperlipidemic rats by endogenous antioxidant enzymes reduction [47] |
| 4      | 3-(4'-Hydroxybenzyl)-5,7-dihydroxy-6-methyl-8-methoxychroman-4-one | ![Structure](image4) | Assayed for DPPH radical inhibition | Showed antioxidant property with DPPH inhibition = 5.90 ± 0.150 to 0.64 ± 0.334 [48] |
| 5      | Benzyl-1,2,3-triazolyl hesperetin derivatives   | ![Structure](image5) | 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] |
| Sr. No. | Compound Structure | Evaluation | Inference |
|---------|--------------------|------------|-----------|
| 6       | Homoisoavone(7-O-[α-rhamnopyranosyl-(1→6)-β-glucopyranosyl]-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] |
| (a)    | ![Structure](image) |            |           |
| (b)    | 7-O-[α-rhamnopyranosyl-(1→6)-β-glucopyranosyl]-5-hydroxy-3-(4'-hydroxybenzyl)-chroman-4-one |            |           |
| 7       | Methyl 2-(cyclohexyl carbamoyl)-4-oxochroman-3-carboxylate | Evaluate lipid peroxidation process | Inhibited lipid peroxidation, and has been reported more potent antioxidants than vitamin E and Trolox [51] |
| 8       | Chroman-4-one derivative | Examined DPPH inhibition | Showed DPPH inhibition with significant values [51] |
| 9       | Isointricatinol (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] |
| Sr. No. | Compound                                              | Structure | Evaluation                                      | Inference                                                                                                                                 |
|--------|--------------------------------------------------------|-----------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 11     | Silybin                                                | ![Silybin Structure](image) | 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           | ![7-Methoxy-3-(4-methoxyphenyl)-chroman-4-one Structure](image) | Examined for antioxidative capacity | Exhibited protective effects against cardiovascular defects, cancer and other diseases due to its high antioxidant capacity [55] |
| 13     | Pinobanksin                                            | ![Pinobanksin Structure](image) | 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 | ![7,8-Dihydroxy-3-[(3,4-dihydroxyphenyl) methylene] chroman-4-one Structure](image) | Antioxidant activity by NBT superoxide scavenging and DPPH free radical scavenging inhibition | NBT = 8.5 µM DPPH = 4.5 µM [57] |
| 15     | Silymarin                                              | ![Silymarin Structure](image) | Antioxidant activity reported against DPPH | Approximately 33% Inhibition of DPPH [58] |
| Sr. No. | Name of compound | Structure | Evaluation | Inference |
|--------|------------------|-----------|------------|-----------|
| 1      | Hesperetin derivatives | ![Hesperetin derivatives](image) | 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-Demethylophiopogonane E | ![4′-O-Demethylophiopogonane E](image) | Inhibited pro-inflammatory cytokine ILβ, 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: ILβ = 32.5 ± 3.5 μg/mL, IL-6 = 13.4 ± 2.3 μg/mL, which showed potent anti-inflammatory activity [59] |
| 3      | Novel (E)-5,7-dimethoxy-3-(4′-hydroxybenzyldene) chroman-4-one | ![Novel (E)-5,7-dimethoxy-3-(4′-hydroxybenzyldene) chroman-4-one](image) | Tested in croton oil-induced edema in animal study | Showed significant anti-inflammatory potential [64] |
| 4      | 3-Arylidene-7-methoxychroman-4-one | ![3-Arylidene-7-methoxychroman-4-one](image) | 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 | ![3,5,7-Trihydroxy-2-(4′-fluorophenyl) chroman-4-one](image) | Tested for anti-inflammatory activity in IL-1β, IL-6, and TNF-α cells | Decreased IL-1β, 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 | ![3,5,7-Trihydroxy-2-(pyridin-3-yl) chroman-4-one](image) | | |
|        | 3,5,6,7-Tetrahydroxy-2-(3′,4’-dihydroxyphenyl) chroman-4-one | ![3,5,6,7-Tetrahydroxy-2-(3′,4’-dihydroxyphenyl) chroman-4-one](image) | | |
| Sr. No. | Name of compound | Structure | Evaluation | Inference |
|---------|------------------|-----------|------------|-----------|
| 6       | (R)-3-(3,4-Dihydroxybenzyl)-7-hydroxy-5-methoxychroman-4-one | ![Structure](image1) | Evaluated for COX-2 receptor binding | Showed significant anti-inflammatory activity against COX-2 with % activity = 0 ± 5.4 [61] |
|         | (E)-3-(3,4-dihydroxybenzylidene)-7-hydroxy-5-methoxychroman-4-one | ![Structure](image2) | % activity = 0 ± 8.3 [61] |
| 7       | Pruinosanone A | ![Structure](image3) | Inhibited inducible nitric oxide synthase (iNOS) protein expression | Showed anti-inflammatory potential with inhibition value 1.96 mM [66] |
| 8       | Myricitrin | ![Structure](image4) | Significantly inhibited 5-lipoxygenase (5-LO) | Potent anti-inflammatory activity with IC₅₀ = 7.8 ± 0.2 µM [67] |
| 9       | Violacin A (*Streptomyces violaceoruber*) | ![Structure](image5) | Suppressed NF-κB signaling pathways | A potential therapeutic candidate for the treatment of inflammation-related disorders [62] |
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 homoisoflavonones. 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*...
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-hydroxycroman-4-one, a 3-benzylidene-4-chromanone exhibited significant antibacterial activity against gram positive and gram negative bacteria, while 3-azolyl-4-chromanone phenyl hydrazone 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
| Sr. No. | Name of compound | Structure | Evaluation | Inference |
|---------|------------------|-----------|------------|-----------|
| 1       | [(E)-8-(3,7-dimethylocta-2,6-dienyl)-5,7-di-hydroxy-2-(4-hydroxyphenyl) chroman-4-one)] | ![Structure](image1.png) | 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—hydroxy-phenyl) chroman-4—one | ![Structure](image2.png) | Isolated from seeds of *Psoralea corylifolia* | Showed antidiabetic activity inhibiting DGAT, PTP1B and α-glucosidase with significant values [73] |
|         | (b) (2S)-4′-hydroxyl—7-hydroxy methyl-ene-6—(2′,3′—epoxy—3′—methyl butyl) flavanone | ![Structure](image3.png) | Examined for DGAT, PTP1B and α-glucosidase inhibition | |
|         | (c) Bavachinone B | ![Structure](image4.png) | | |
| 3       | 7-hydroxy-2—(4-hydroxy-3-methoxyphenyl)—chroman-4—one | ![Structure](image5.png) | 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)               | ![structure](H2O) | Evaluated for α-glucosidase assay               | Showed highest α-glucosidase inhibition with IC50 = 0.060 ± 0.3 mM and displayed antidiabetic potential [77] |
| 5       | 3-Benzylidene-4-chromanone derivatives                | ![structure](OH) | Assayed for DPPH radical scavenging and α-glucosidase inhibition | Showed significant antioxidant potential [72]                                                 |
| 6       | 5,7-Dimethoxy-3-(2′-hydroxybenzyl)-4-chromanone       | ![structure](OH) | Evaluated for antidiabetic activity              | Improved postprandial hyperglycemia in streptozotocin-induced diabetic mice by inhibiting carbohydrate digesting enzymes [78] |
| 7       | 6-Methyl-4-chromanone                                 | ![structure](H3O) | *in vitro* evaluation for antidiabetic effect    | Showed good antidiabetic effect using the glucose uptake by isolated rat hemidiaphragm (*in vitro* model) [79] |
| 8       | 2H-Chromenylphenyloxazolones derivatives             | ![structure](Cl) | 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 | ![Structure](image) | Showed antibacterial activity evaluated against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli* using ampicillin (reference drug) -zone of inhibition (mm) measured using cup plate agar diffusion method | *S. aureus* = 32 mm *B. subtilis* = 15 mm *P. aeruginosa* = 11 mm *E. coli* = 33 mm [84] |
|         |                  | ![Structure](image) | Exhibited antifungal activity against *Aspergillus niger*, *Fusarium oxysporum* and *Penicillium italicum* using griseofulvin (standard drug) | *A. niger* = 14 mm *F. oxysporum* = 30 mm *P. italicum* = 20 mm [84] |
| 2       | 2,2-Dimethylchroman-4-one derivatives | ![Structure](image) | Nutrient agar media and Potato Dextrose Agar (PDA) medium used for the measurement of antibacterial and antifungal potential as in zone of inhibition (mm) Exhibited antibacterial and antifungal activities | *B. subtilis* = 31.5 mm *S. aureus* = 20.5 mm *K. pneumonia* = 34.8 mm *E. coli* = 33.8 mm *A. niger* = 10.2 mm *F. oxysporum* = 17.5 mm [85] |
|         |                  | ![Structure](image) | | *B. subtilis* = 33 mm *S. aureus* = 20 mm *K. pneumonia* = 33.5 mm *E. coli* = 30.5 mm *A. niger* = 15 mm *F. oxysporum* = 14.5 mm [85] |
| 3       | 6-Chloro-2-vinyl chroman-4-one | ![Structure](image) | Showed antimicrobial activity against *Bacillus Subtilis*, *Escherichia coli* and *Staphylococcus aureus*-Vinyl group at carbon C-2 is necessary for the biological activity and Chloro group increases the activity | *B. Subtilis* = 4.17lg/mL *E. coli* = 4.17lg/mL *S. aureus* = 7.30lg/mL [86] |
| 4       | 2-Hydroxymethyl-chroman-4-one | ![Structure](image) | Exhibited antifungal activity against *P. ultimum*, *S. sclerotiorum* and *P. capsici* It was also used as intermediate for the synthesis of more effective benzopyranones | ED50 ppm values for *P. ultimum* = 54.99 ppm *S. sclerotiorum* = 52.03 ppm *P. capsici* = 35.77 ppm [87] |
| Sr. No. | Name of compound | Structure | Evaluation | Inference |
|--------|------------------|-----------|------------|-----------|
| 5      | Aposphaerin A and B | ![Structure](#) | These are natural potent antibiotics evaluated for MRSA (*methicillin resistant S. aureus*) assay | Exhibited significant activity against *methicillin resistant S. aureus* (MRSA) [88] |
|        | ![Structure](#) | R₁=R₂=OH, R₃=CH₃, R₄=OH (Aposphaerin A) R₁=OC₂H₅, R₂=H, R₃=H (Aposphaerin B) |          |          |
| 6      | 3-Phenylsulfonyl-3-(2-propenyl) chroman-4-one | ![Structure](#) | Evaluated for antimicrobial activity | Exhibited potent antimicrobial activity [89] |
| 7      | 5,7-Dihydroxy-3-(4-methoxybenzyl)-8-methyl chroman-4-one | ![Structure](#) | Isolated from the rhizomes of *Polygonatum verticillatum*-Antimicrobial activity assay using nutrient agar plate medium | Displayed significant antimicrobial activity via inhibition of *B. subtilis, S. aureus* and *E. coli* [90] |
| 8      | 2-(2,6-Dimethylhept-5-en-1-yl)-5,7-dihydroxychroman-4-one | ![Structure](#) | Antibacterial evaluation against *E. Faecalis, S. aureus MSSA, S. aureus MRSA* and *E. coli* (µg/ml) | *E. Faecalis* = 6.25(µg/ml) *S. aureus MSSA* = 3.13 (µg/ml), *S. aureus MRSA* = 3.13 (µg/ml) *E. coli* = 1.5 µg/ml [91] |
| 9      | 1-(2-(4-Chlorophenyl)-6-methoxychroman-4-yldene)-2-phenylhydrazine | ![Structure](#) | Exhibited potent antimicrobial activity against *S. aureus, E. coli, C. Albicans* and *Aspergillus niger* using agar diffusion technique | *S. aureus* = 15.5 ± 0.7 mm *E. coli* = 21.5 ± 0.7 mm *C. albicans* = 20.0 ± 0.0 mm *A. niger* = 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 | ![Structure](image1.png) | Evaluated against gram-negative bacteria | Significant antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus sphaericus*, *Klebsiella aerogenes*, *C. violaceum*, *Pseudomonas aeruginosa* [92] |
|         | 3-benzylidene-4-chromanones derivatives                                          | ![Structure](image2.png) | Tested antibacterial activity against *S. aureus* | *S. aureus* = 0.52 mM                                                  |
| 11      | (2S,3R,4R,5R,6S)-2-(((2S,3R,4R,5S,6R)-4,5-dihydroxy-2-((S)-5-hydroxy-2-(4-hydroxyphenyl) spiro [chroman-4,2'-1H,6H-pyran-3-yl) oxy)-6-(hydroxymethyl) tetrahydro-2H-pyran-3-yl) oxy)-6-methyl-tetrahydro-2H-pyran-3,4,5-triol | ![Structure](image3.png) | Exhibited antibacterial activity for gram-positive and gram-negative bacteria using broth micro-dilution method | *S. aureus* = 0.125 mg/mL, *E. coli* = No inhibition, *P. aeruginosa* = 0.25 mg/mL, *S. aureus* (MRSA Positive) = 0.125 mg/mL |
|         | (Spiro[chroman-2,1'-cyclohexan]-4-one) semi carbazole derivative                  | ![Structure](image4.png) | Also showed antioxidant potential               | *IC_{50} = 18.7 μg/mL* [82]                                           |
| 12      | (Spiro[chroman-2,1'-cyclohexan]-4-one) semi carbazole derivative                  | ![Structure](image5.png) | Antifungal activity evaluated against *C. albicans*, *C. Krusei GO3*, *C. Glabrata GO5* and *A. fumigates* strains | Observed a clear zone of inhibition against *C. Krusei GO3* strain [93] |
| 13      | Novel spiro chromanone-auroine hybrids (Z)-2'-(3,4-Dimethoxybenzylidene) spiro{cyclo-hexane-1,7'furo[3,2-g] chromene}-3',5'(2'H,6'H)-dione | ![Structure](image6.png) | Exhibited high antibacterial activity for a number of gram +ve and -ve bacteria's using streptomycin and amphotericin B (as standard drugs) | *B. subtilis* = 21.0, *S. aureus* = 19.5, *P. aeruginosa* = 22.5, *E. coli* = 21.0, *A. flavus* = 4.5, *F. oxyporum* = 6.5 [94] |
| 14      | 2-MBT(2-mercaptobenzothiazole) with chroman-4-one moiety derivatives             | ![Structure](image7.png) | Evaluated for antimicrobial potential against *S. aureus*, *B. subtilis*, *M. tuberculosis*, *C. albicans* and *S. cerevisiae* strains | Showed potent antimicrobial activity with significant inhibition [95] |
### Table 6 (continued)

| Sr. No. | Name of compound | Structure | Evaluation | Inference |
|---------|------------------|-----------|------------|-----------|
| 15      | Novel flavanone derivatives | ![Structure](image) | Antibacterial activity against *S. aureus* strains including MRSA | MIC value = 16 µg/mL, More potent than standard drug oxacillin [96] |
| 16      | Spiro[2-benzoyl-cyclohexyl-4,5-diphenylpyrrolidin-3,3’-chroman-4-one] | ![Structure](image) | Evaluated for antifungal and antibacterial activities | Showed significant inhibition against tested pathogen strains [97] |
| 17      | 3-Azolyl-4-chromanone phenylhydrazones | ![Structure](image) | Tested against *C. albicans*, *S. cerevisiae*, *A. niger* and *M. gypseum* pathogens | MICs values (µg/mL) are: C. *albicans* = 8 µg/mL, S. *cerevisiae* = 16 µg/mL, A. *niger* = 16 µg/mL, M. *gypseum* = 16 µg/mL Exhibited Antifungal potential [83] |
| 18      | 5,7-Dihydroxy-2-[4-(3-methyl-but-2-enyloxy)-phenyl] chroman-4-one{selinone) | ![Structure](image) | Antifungal activity against *C. albicans* | Showed significant inhibition [98] |
| 19      | (E)-5,7-dimethoxy-3-benzylidene-4-chromanone | ![Structure](image) | Antifungal activity against *C. albicans* | Showed significant antifungal activity (MIC<sub>50</sub> ± 25 mM) [81] |
| Sr. No. | Name of compound | Structure | Evaluation | Inference |
|---------|------------------|-----------|------------|-----------|
| 1       | 7-Hydroxy-2-methyl-4-oxo-3,4-dihydro-2H-benzopyran-5-carboxylic acid | ![Structure](image1) | Evaluated for *M. tuberculosis* | Potential inhibitors of *M. tuberculosis* (MbtI) with IC50 = 55.8 µM [103] |
| 2       | (E)-3-(dibenzo [b, d] furan-2-ylmethylene)-6-fluorochroman-4-one | ![Structure](image2) | Examined for *M. tuberculosis* H37Rv Inhibition | Inhibited *M. tuberculosis* H37Rv with MIC 12.5 µg/mL and considered as most potent antitubercular agents [104] |
| 3       | Chromane-4-one analogs | ![Structure](image3) | Tested anti TB activity against *M. tuberculosis* and MDR-TB *in vitro* study revealed anti TB activity against *M. tuberculosis* 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 log10 = 1.11 and 2.94 [105] |
| 4       | 7-Hydroxy-(E)-3-[(2-fluorophenyl)methylene] chroman-4-one | ![Structure](image4) | Screened against *Mycobacterium smegmatis* mc² 155 for anti TB potential | Exhibited significant inhibition as efflux pump inhibitors against *Mycobacterium smegmatis* mc² 155 [106] |
|         | 7-Hydroxy-(E)-3-[(4-methoxyphenyl)methylene] chroman-4-one | ![Structure](image5) | | |
|         | 7-Hydroxy-(E)-3-[(3-allyloxyphenyl)methylene] chroman-4-one | ![Structure](image6) | | |
| Sr. No. | Name of compound                        | Structure                                      | Evaluation                                                                 | Inference                                                                                                                                 |
|--------|----------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 5      | Triazolyl methoxy flavanones           | ![Structure](image1.png)                      | 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    | ![Structure](image2.png)                      | Tested for *M. tuberculosis* H37Rv (ATCC27294) cells growth                | Inhibited *M. tuberculosis* H37Rv (ATCC27294) with MIC value of 3.13 µg/mL [108]                                                       |
| 7      | 3-(4′-Methoxybenzyl)-7,8-methylenedioxy- | ![Structure](image3.png)                      | Evaluated for *M. phlei*, *M. aurum*, *M. fortuitum* and *M. smegmatis* inhibition | Displayed antimycobacterial activity against *M. phlei* (16 µg/mL), *M. aurum* (32 µg/mL), *M. fortuitum* (128 µg/mL) and *M. smegmatis* (256 µg/mL) [109] |
| 8      | Bis-spiro chromanones                   | ![Structure](image4.png)                      | 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]                                      |
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 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'-tetrahydropryan-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] |
| 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 Coxackie virus B1, B3, B4, A9 and echovirus 30 [115] [113] |

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 | Evaluated for anti-HIV activity | Exhibited anti-HIV activity by inhibition of HIV-1 IN strand transfer (IC50, 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 1st 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

| Sr. No. | Name of compound | Structure | Evaluation | Inference |
|---------|-----------------|-----------|------------|-----------|
| 1       | Thiochroman-4-one’s derivatives | ![Structure](Image1) | Evaluated for in vitro antileishmanial activity against the intracellular amastigote form of Leishmania panamensis | These compounds showed good antileishmanial activity with significant inhibition [128] |
| 2       | Benzoic acid, 2-(2,3-dihydro-4H-1-benzopyran-4-ylidene) hydrazide | ![Structure](Image2) | In vitro evaluation using macrophage intracellular mastigotes of Leishmania (Viannia) panamensis and L. (V) braziliensis 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 | ![Structure](Image3) | Evaluated in romastigotes, axenic amastigotes and Leishmania-infected macrophages | Exhibited antileishmanial potency with IC50 = 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 flavonone and thioflavanone could be considered a potential privileged structure [125]. Using this approach, derivatization of chroman-4-one and thiocroman-4-ones with acyl hydrazones resulted in significant enhancement of antileishmanial potential [126]. As thiocroman-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 thiocromanone 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 azolylichromanones, azolylichromanone oximes and imidazolyl chromanone oxime ethers were tested for their anticonvulsant potential in lithium, pilocarpine induced seizure and pentylentetrazol (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-phenylethylamine, 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 benzylxy 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-HT1A 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                                                       | ![Structure](structure1.png)                                             | 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$_{50} = 0.27$ µM [135] |
| 2       | Flavonoid derivative with carbamate moiety                                       | ![Structure](structure2.png)                                             | Evaluated for AchE inhibition and anti-amnestic potential                  | Exhibited AchE inhibitory activity with IC$_{50} = 9.9 \pm 1.6$ mM [136]  |
| 3       | Chroman-4-one derivative with the piperidinyl ethoxy side chain and 4-hydroxybenzylidene substitution | ![Structure](structure3.png)                                             | Evaluated for AchE activity and docking for finding effective binding pockets | Showed most potent anti-acetylcholinesterase activity (IC$_{50} = 1.18$ µM) and also showed remarkable interactions with the binding pockets of the ChE enzymes against Butrylcholinesterase (BuchE) and AchE, in the molecular docking study [137] |
| 4       | Novel chromanone-dithiocarbamate hybrids (n = 5)                                 | ![Structure](structure4.png)                                             | Evaluated for AchE-induced Aβ aggregation inhibition                       | A novel hybrid with n = 5 showed best activity to inhibit AchE (IC$_{50} = 0.10$ µM) 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-dimethoxycroman-4-one | ![Structure](structure5.png)                                             | 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-dimethoxycroman-4-one showed excellent AchE and MAO-B inhibitory activities (IC$_{50} = 2.49 \pm 0.08$ nM and 1.74 ± 0.058 lM, respectively), good self- and Cu$^{2+}$-induced Aβ1-42 aggregation inhibitory potency, antioxidant activity, biometal chelating ability and high BBB permeability. [139] |
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 (Aβ) 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 Aβ plaques with 9.98 and 9.10 nM (Ki values), respectively, as compared to [125I]-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 Aβ plaques in brain sections and [125I]-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 Aβ plaques in AD brain. Hence, further research and development of novel chromanone derivatives

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**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 | ![Structure](image1.png) | Investigated for both anticonvulsant and antiepileptogenic properties using lithium pilocarpine induced seizure and PTZ-induced kindling models | Effective against lithium and pilocarpine induced *status epilepticus* 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 | ![Structure](image2.png) | 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 | ![Structure](image3.png) | 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] |
| Sr. No. | Name of compound | Structure | Evaluation | Inference |
|---------|------------------|-----------|------------|----------|
| 1       | (E)-3-Heteroarylidenechroman-4-ones | ![Structure](image1) | In vitro investigation to inhibit the enzymatic action of both human monoamine oxidase (MAO) isoforms such as MAO-A and B | Showed highest hMAO-B potency (IC₅₀ = 10.58 nM) and selectivity (SI > 9452) with respect to the standard inhibitor selegiline (IC₅₀ = 19.60 nM, IC₅₀ > 3431). [150] |
| 2       | Chroman-4-one derivatives | ![Structure](image2) | 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) | ![Structure](image3) | Examined for serotonin reuptake inhibition with 5-HT₁A partial agonistic activity in vitro study | Inhibited serotonin transporter with IC₅₀ = 2.74 ± 0.41 μM and had an intrinsic activity for 5-HT₁A receptors of 70 ± 6.3%. A novel serotonin reuptake inhibitor showed fast antidepressant effect. [149] |
| 4       | 7-(4-Fluorobenzyl) oxy chroman-4-one | ![Structure](image4) | Evaluated for in vitro MAO-B inhibitory activity | Inhibited MAO-B inhibition with IC₅₀ = 8.42 μM and showed low neurotoxicity in SH-SY5Y cells, hence used to treat neurodegenerative disease. [152] |
| 5       | (E)-3-(4-Methoxybenzylidene)-7-(3-(piperidin-1-yl) propoxy) chroman-4-one | ![Structure](image5) | Evaluated for dual acetyl cholinesterase (AchE) and monoamine oxidase (MAO-B) inhibition | Inhibition of AchE and MAO-B enzymes activities, with IC₅₀ value of 3.94 and 3.44 μM, respectively. [147] |
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-silico 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-dihydroxycroman-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].

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-hydroxycroman-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].
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](image)

### Table 15

| Sr. No. | Name of compound | Structure | Evaluation | Inference |
|--------|------------------|-----------|------------|-----------|
| 1      | (E)-3-(4-Methoxybenzylidene)-6-bromo-chroman-4-one | ![Structure](image) | Diagnosis of Alzheimer’s disease | Exhibited high binding affinities to Aβ plaques, with Ki values of 9.98 and 9.10 nM against [125I] IMPY (reference compound) Helpful diagnostic imaging agent for early finding of Aβ plaques in Alzheimer’s disease brain [158] |
| 2      | (E)-3-(4-Dimethylamino-benzylidene)-6-bromo-chroman-4-one | ![Structure](image) | Iodine labeled 3-benzylidenechroman-4-one’s derivative, R1 = 125I | Effective 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 [CC50/IC50 = > (100 g/mL/63.3 µg/ml)] and porcine respiratory coronavirus (PRCV) with inhibition value > 1.67 [CC50/IC50 = > (100 g/mL/59.8 µg/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 antiviral for the inhibition of other classes of corona virus might be led a new frame for drug discovery and development [161] |

**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 CC50/IC50 = > (100 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 [CC50/IC50 = > (100 g/mL/63.3 µg/ml)] and porcine respiratory coronavirus (PRCV) with inhibition value > 1.67 [CC50/IC50 = > (100 g/mL/59.8 µg/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 antiviral for the inhibition of other classes of corona virus might be led a new frame for drug discovery and development [161].
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-benzyldiene-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, anti-diabetic, anti-inflammatory, antiviral, 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 (anti-diabetic), tetrazole (anti-diabetic), troglitazone (anti-diabetic), 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.

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