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Mini-review

Chromones as a privileged scaffold in drug discovery: A review



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ABSTRACT

The chromone and its derivatives are the most important heterocyclic compounds, which is a common and integral feature of a variety of natural products and medicinal agents. These heterocycles show a variety of pharmacological properties, and change of their structure offers a high degree of diversity that has proven useful for the search of new therapeutic agents. A large volume of research has been carried out on chromone and their derivatives, which has proved the pharmacological importance of this heterocyclic nucleus. The present review focuses on the pharmacological profile of chromone derivatives in the current literature with an update of recent research findings on this nucleus and the perspectives that they hold for future research.

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1. Introduction

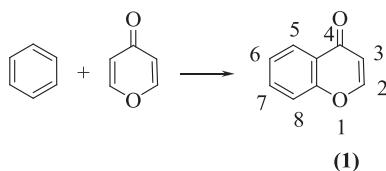
Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds [1]. Chromone (**1**) (4H-chromen-4-one, 4H-1-benzopyran-4-one) is an important class of oxygen-containing heterocyclic compounds with a benzoannelated γ -pyrone ring and they are part of the flavonoid family (Fig. 1). The chromone and related compounds are widespread in the plant kingdom from algae to conifers. Chromones have found to be active in a number of plant cycles, including growth regulation, indole acetic acid oxidation and dormancy inhibition as well as exhibiting cytokinin-type behavior and stimulating oxygen uptake in plant tissue [2].

Chromone derivatives are abundant in nature and exhibit a wide range of pharmacological activity like anti-bacterial, anti-fungal [3,4], anti-cancer [5], anti-oxidant [6], anti-HIV [7], anti-ulcers [8], immunostimulators [9], biocidal [10], wound healing [11], anti-inflammatory [12], and immune-stimulatory [13]. Many chromone derivatives are also photoactive and can be used easily in various photoinduced reactions affording diverse heterocyclic compounds [14]. Chromone derivatives are also active at benzodiazepine receptors [15] and on lipoxygenase and cyclooxygenase [16]. In addition to this, they have been shown to be possessing antimutagenic properties [17] as well as the ability to inhibit electron transport

through inhibition at NADH:ubiquinone oxidoreductase and phorbol ester-induced ornithinedecarboxylase [18,19]. Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis transmembrane conductance regulator [19b]. These compounds also possess low mammalian toxicity and are present in large amounts in the diet of humans due to their origin in plants [16]. To list a few chromone derivatives, which are actively used in pharmacological field are given below (Fig. 2). Although there are a large number of chromone derivatives known for their pharmacological properties there are only a few examples that have been or that are used as therapeutic agents today. Cromolyn or cromoglicate (Cromoglicic acid) is used as a mast cell stabilizer in allergic rhinitis, asthma and allergic conjunctivitis. Nedocromil (Alocril) is used to prevent wheezing, shortness of breath, and other breathing problems caused by asthma. Apigenin (4',5,7-trihydroxyflavone) is used as a potent inhibitor of Cytochrome P450 2C9 (CYP2C9). Diosmin used in the treatment of venous disease, i.e., chronic venous insufficiency (CVI) and hemorrhoidal disease (HD), in acute or chronic haemorrhoids. Flavoxate (2-(1-piperidyl)ethyl 3-methyl-4-oxo-2-phenylchromene-8-carboxylate) is an anticholinergic with antimuscarinic effects [20]. Furthermore, around the 1950s, khellin was used as a smooth muscle relaxant in the treatment of angina pectoris and asthma. Therefore, the vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure [21a]. The main objectives of chromones syntheses are not only for the development of more diverse and complex bioactive compounds for biological activity and structure–activity relationship (SAR) studies but also for

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**Fig. 1.** Chemical structure of chromone.

other applications in medicinal chemistry, such as preparation of fluorescence probes, due to photochemical properties of chromones [21b]. Some reviews on involvement of chromone nucleus in anti-cancer activity [22a] and synthesis part are available in literature [22b]. Some compilations of reports on all activities associated with chromone nucleus are also reported. Sharma et al., have reviewed on the natural occurrence and biological activity of chromones [22c]. Khadem and Marles have reviewed on occurrence and bioactivity of chromone [22d]. Cazarolli et al., have published review on therapeutic potential of chromone nucleus for some activities [22e] but no comprehensive report on varied activities of chromone based compounds is available in literature till date (upto 2013). Hence, the present review gives a comprehensive insight into the current applications of chromone nucleus in varied therapeutic fields. In addition to various therapeutic uses chromone have been found as important intermediates in many organic reactions.

2. Chemistry

The synthesis of chromone derivatives is a research field of great interest and long history [23]. A number of methods have been developed for the synthesis of chromone derivatives: for example, the Allan-Robinson strategy, from chalcones and *via* an intramolecular Wittig strategy [24,25]. One of the most common

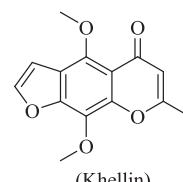
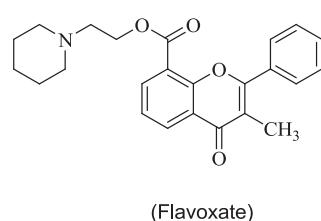
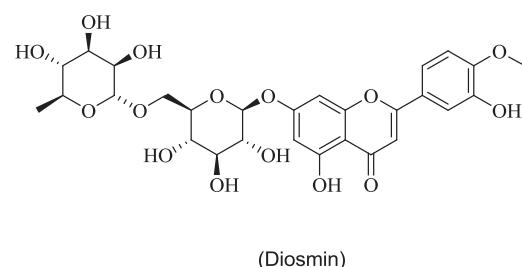
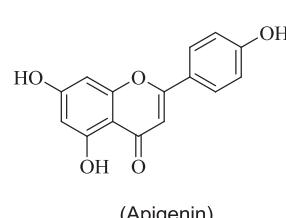
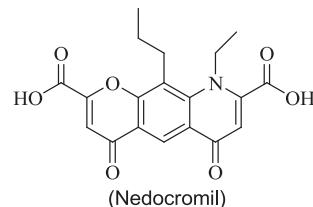
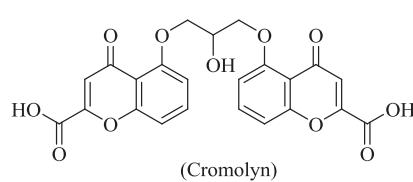
methods involves acylation of an *o*-hydroxyacetophenone with an aromatic acid chloride yielding an aryl ester. The ester is then rearranged by a base (Baker–Venkataraman rearrangement) to a 1,3-diaryl 1,3-diketone, later compound gives a 2-arylchromone on cyclocondensation [26]. This is usually a catalyzed reaction and it has been carried out in different media. Some reaction conditions employed were the use of excess of sulfuric acid in glacial acetic acid [27], cationic exchange resins in isopropanol [28], glacial acetic acid-anhydrous sodium acetate or aqueous potassium carbonate [29] (Fig. 3). Greener procedures have been recently described, using CuCl₂ in ethanol [30], ionic liquid under microwave irradiation, heteropolyacids [31], and *ortho*-fluorobenzoyl chloride in condensation with a 1,3-keto – ester the fluoride is displaced in an intramolecular sense by enolate oxygen, and the chromone obtained directly. *ortho*-Hydroxyaryl alkynyl ketones are intermediates in palladium catalyzed coupling of *ortho*-hydroxyaryl iodides with terminal alkynes in the presence of carbon monoxide, ring closing to chromones *in situ* [32] (Fig. 4).

3. Pharmacological activities of the chromone analogs

Chromone and its analogs are important pharmacophores and privileged structures in medicinal chemistry and have featured in a number of clinically used drugs.

The most relevant and recent studies have revealed that chromones derivatives have a broad spectrum of pharmacological activities which can be classified into the following categories:

1. Anti-cancer agents
2. Anti-HIV agents
3. Anti-oxidant agents
4. Anti-tubercular agents
5. Anti-inflammatory and Analgesic agents

**Fig. 2.** Examples of chromone-based compounds that have been or that are used as pharmaceutical agents.

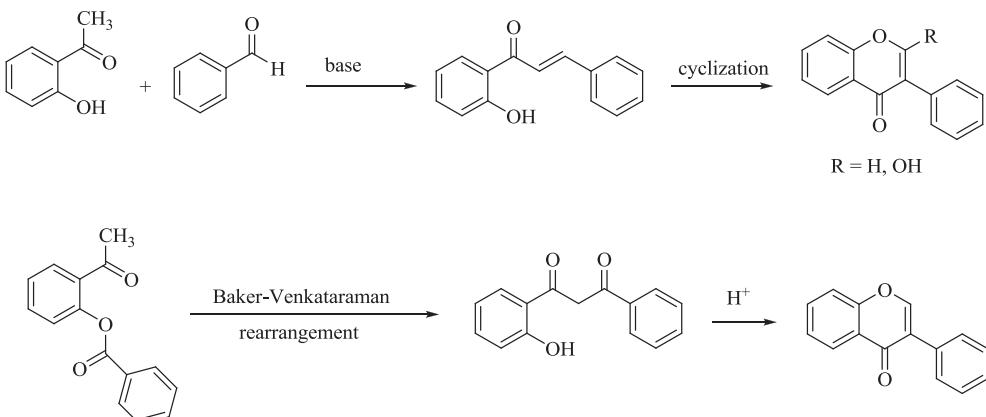


Fig. 3. Common synthetic routes to obtain the chromone structure. I) Synthesis via a chalcone intermediate followed by cyclization (using some catalyst) II) Synthesis via the Baker–Venkataraman rearrangement followed by acid-catalyzed cyclization.

6. Anti-microbial agents
7. Anti-malarial agents
8. Anti-diabetic agents
9. Anti-convulsant agents
10. Anti-platelet agents
11. Gastroprotective agents
12. Antihistaminic agents
13. Antihypertensive agents
14. Calpain inhibitor
15. Insecticidal activity
16. Enzyme and Receptor Agonists/Antagonists
17. Patent literature

3.1. Anti-cancer agents

The number of deaths due to cancer alone is more than those caused by AIDS, malaria, and tuberculosis combined, it is turning into one of the most overwhelming health problems worldwide. In the last 30 years the number of patients with tumors get doubled, by 2020 it will double once more, and by 2030 it will be triple and if new treatments are not found, by 2030, there will be 27 million people with cancer and 17 million deaths annually [33,34]. The available anticancer drugs have suffering some limitations; therefore development of new drugs is essential for the society. The chromone and its analogs have exhibit wide range of anticancer activity and are discussed as follows.

A series of 2,3-diarylcromanones have synthesized under microwave irradiation and screened for their cytotoxicity was by the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay using HL60 cells and PBMC (Peripheral blood mononuclear cells) and antioxidant activity by using lipid peroxidation

assay. Compound, diarylcromanone **2a** exhibited highest cytotoxicity with 73.16 µM and for anti-oxidant activity, the chromanone **2b** possesses highest activity with EC₅₀ value of 129.86 µM. The diarylcromanone derivative **2b** showed the highest radical modulation activity compared to other tested compounds due to the presence of nitro group in the meta position [35]. 2-Styrylcromone analogs synthesized by Shaw et al., and screened for their antiproliferative by using MTT assay, against a panel of five human carcinoma cell lines, including PC-3 (prostate carcinoma cell), A549 (non-small cell lung adenocarcinoma cell), BT483 (mammary gland adenocarcinoma cell), HeLa (cervical epithelioid carcinoma cell) and SKHep (hepatocellular carcinoma cell). Among the tested agents, only **3** exhibited a moderate activity with an IC₅₀ value of 28.9 µM against PC-3 cells which indicates the selectivity of PC-3 cells in response to 2-styrylcromones. Compound **4** demonstrated the most antiproliferative effect with an IC₅₀ value of 4.9 µM against HeLa cells [36].

A series of compounds **5(a–e)** having structural features of styrylcromones and lavendustin A synthesized and evaluated for their cytotoxicities on four tumor cell lines including human lung carcinoma (A-549), human colon cancer cells (HCT-15), human epidermoid carcinoma (KB), and malignant melanoma (SK-MEL-2) using SRB assay. Compounds **5b** and **5c**, which have electron releasing methoxy groups on arylethenylchromone ring showed decreased cytotoxicity when compared to that of **5a**. On the other hand, compounds **5d**, and **5e** which have electron withdrawing bromide or heteroaromatic ring, exhibited potent cytotoxicity with IC₅₀ values in the range of 7.17–11.98 µg/mL on HCT-15 cell. Among tested, compound **5e** showed the most potent cytotoxic activity on HCT-15 cell line with IC₅₀ values of 7.17 µg/mL indicating that lavendustin A derivatives containing 2-arylethenylchromone ring have a potential in anti-tumor application [37].

3-Hydroxycromones prepared and evaluated for anti-proliferative activity against various human cancer cell lines, such as EJ (bladder carcinoma), HCT116, W620 (colon carcinoma), and MDAMB468 (breast carcinoma). Among the synthesized compounds, **6a** and **6b** provided highly potent compounds against the proliferation of various human cancer cell lines because of substitution of the hydroxyl group with –Cl or –Br [38]. Chromone-based lavendustin analog synthesized by Lee and co-workers, and evaluated for their anti-cancer activity against six human cancer cell lines like epidermoid carcinoma (A-431), lung carcinoma (A-549), colon (HCT-15), oral epidermoid carcinoma (KB), malignant melanoma (SK-MEL-2) and ovary malignant (SK-OV3). Most synthesized compounds showed improved cytotoxicities against all cancer cell

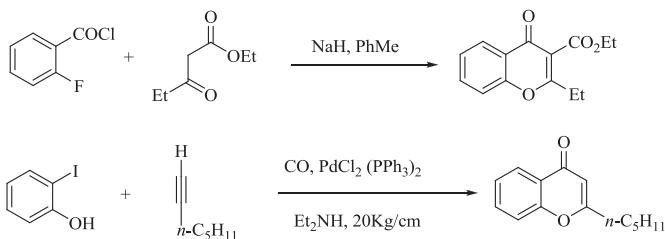


Fig. 4. Common synthetic routes to obtain the chromone structure. I) Synthesis via an intramolecular sense enolate oxygen II) Synthesis via palladium catalyst.

Table 1
Some of the chromone derivatives as anti-cancer agents.

lines with varied potencies when compared to those of the standard compound homothamnione. Compound **7a** and **7b** showed the most potent inhibitory activities with IC_{50} values in the range of 6.01–9.92 $\mu\text{g}/\text{mL}$ on A-549 and HCT-15 cells [39]. A series of chromone derivatives bearing diverse dithiocarbamate moieties synthesized by multi-component reaction and their *in vitro* anti-tumor activities were evaluated by MTT method against HCCLM-7, Hela, MDA-MB-435S, SW-480, Hep-2 and MCF-7. The compounds (3-chloro-4-oxo-4H-chromen-2-yl)methyl piperidine-1-carbodithioate **8** and (6-chloro-4-oxo-4H-chromen-3-yl)methyl piperidine-1-carbodithioate **9**, showed the most promising anti-tumor activity against SW-480 cells and MDA-MB-435 cells [40].

Various 3'R,4'R-disubstituted-2',2'-dimethyldihydropyran[2,3-f]chromone (DSP) derivatives synthesized (**10–15**) and evaluated against a multidrug resistant (MDR) cell line (KB-Vin) with and without vincristine (VCR). All DSP analogs exhibited low intrinsic cytotoxicity. However, in combination treatment, most DSPs reversed resistance to VCR and lowered the GI_{50} value of VCR by 12-

349-fold. At a concentration of 1 $\mu\text{g}/\text{mL}$, three compounds, **10a**, **10b**, and **12**, fully reversed resistance to VCR in KB-Vin cancer cells, a 2-fold increase compared to verapamil, a first-generation chemosensitizer. From SAR study, the compounds having the *p*-substitution on the aromatic ring in the side chain showed good activity compared to the *o*-and *m*-substitution. Small substitutions that can increase electron density or provide hydrogen-bonding capacity at the putative interaction domain on P-gp benefit the activity [41].

Flavones bearing a ferrocenylvinyl substituent in position six of the chromone skeletons were prepared by Kowalski et al., and are screened for their antiproliferative and cytotoxic activities against four human cancer cell lines derived from hematological and solid human cancers: T lymphoblast-like polymorph CCRF-CEM cells, human estrogen receptor-responsive (MCF-7) and estrogen receptor negative (MDA-MB-231) breast cancer cells, liver cancer cells (Hep G2) and T lymphoblast-like polymorph cells (CCRF-CEM). Among them (*E*)-6-ferrocenylvinyl-chromen-4-one **16** showed good activity against T lymphoblast-like polymorph cancerous

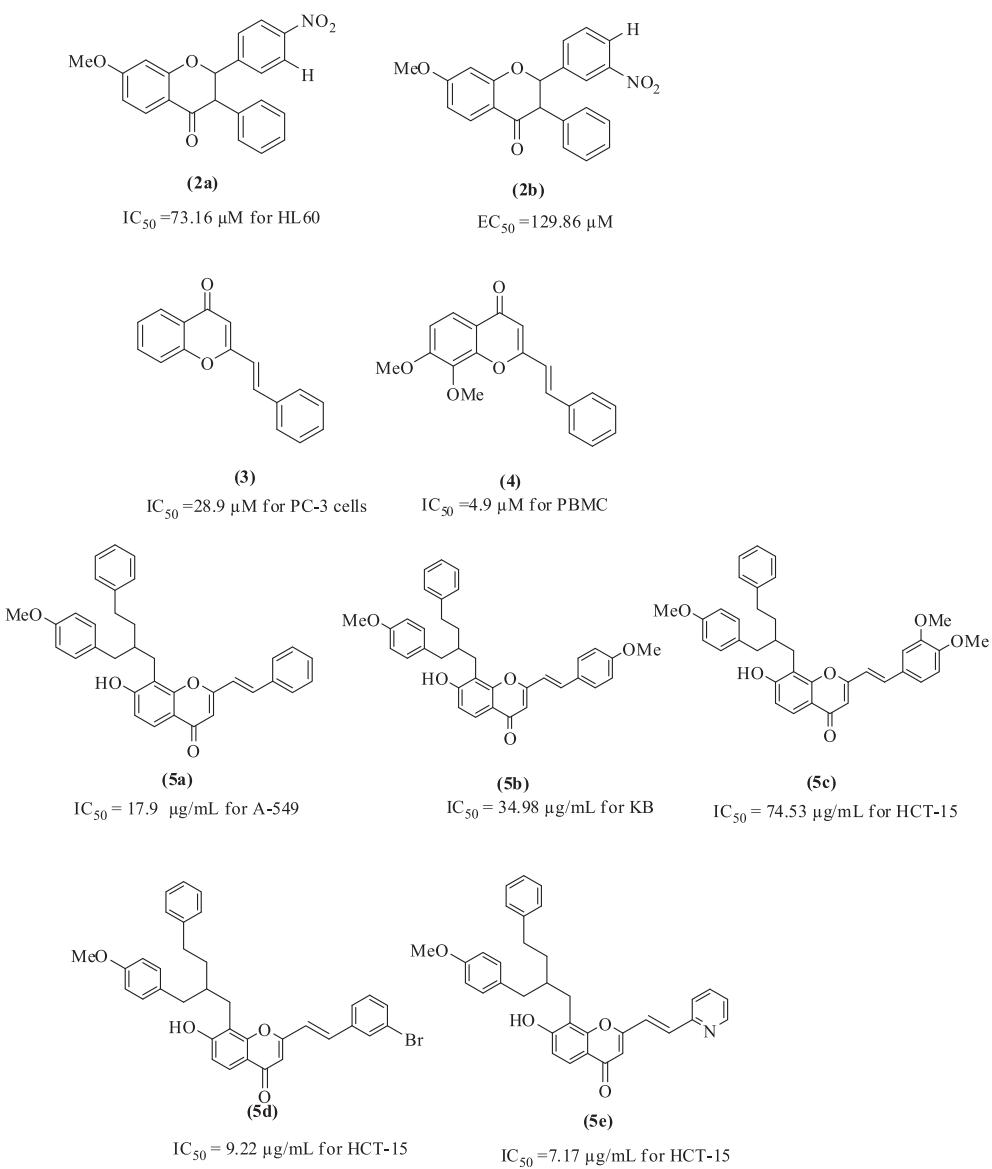
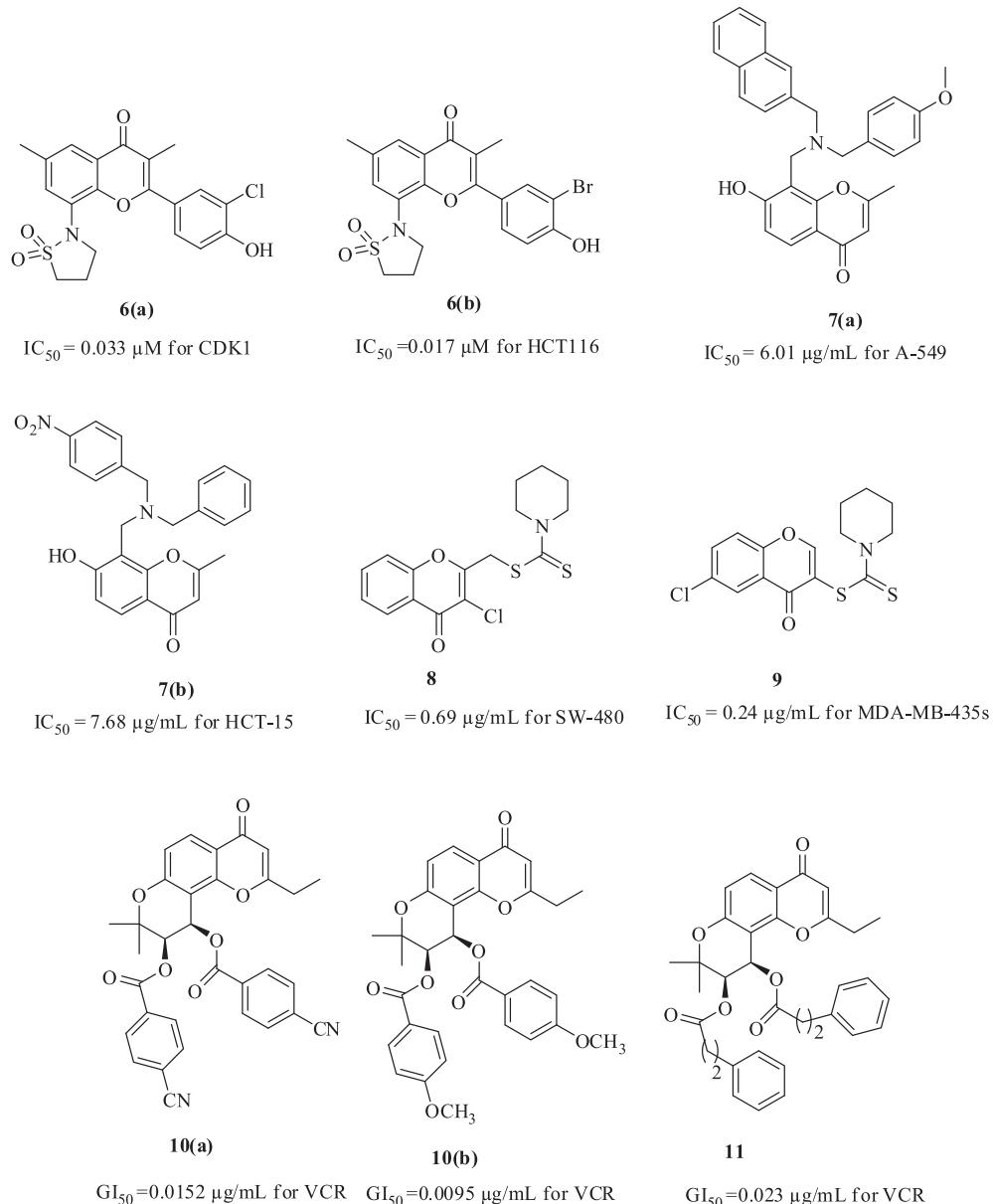


Fig. 5. Chromone as potential anti-cancer agents.

**Fig. 5.** (continued).

CCRF-CEM cell line (the lowest IC_{50} concentrations of $37.5 \pm 0.9 \mu M$) [42]. Raju et al., have synthesized a series of 4H-chromen-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives and screened for their *in vitro* anti-mycobacterial activity against Mycobacterium tuberculosis H37Rv (MTB) and cytotoxicity against three human cancer cell lines including A549, SK-N-SH and HeLa. Compound (**17a**) is most effective anti-mycobacterial activity compared to the standard drugs Ethambutol and Ciprofloxacin. Compound (**17b**) is exhibited cytotoxicity against human neuroblastoma cell line compared to the standard drug Doxorubicin [43].

Geiparvarin analogs (chromone linked with 1,2,3-triazole residues via $-OCH_2-$ bridge) synthesized and evaluated for their *in vitro* cytotoxic activities against one human normal cell line and six human cancer cell lines via MTT method, including L02 (normal human liver cell line), A-549 (human lung adenocarcinoma cell line), HeLa (human cervical carcinoma cell line) and QGY-7701 (human hepatoma cell line), SW480 (human colon carcinoma cell line), SGC7901 (human gastric adenocarcinoma cell line) SGC7901

(human gastric carcinoma cell line), MDA-MB-231 (human breast carcinoma cell line). Compounds **18a**, **18b** and **18c** exhibited broad-spectrum activity against four cancer cell lines. Moreover, compound **18d** displayed highest potency compared with the parent compound geiparvarin [44]. A series of N_1 -(flavon-7-yl)amidrazones incorporating *N*-piperazines and related congeners synthesized and tested *in vitro* for their antitumor activity against breast cancer (MCF-7 and T47D) and Leukemic (K562) cell lines. A number of the synthesized compounds exerted significant antiproliferative activity with therefore mentioned cancer cell lines, particularly compounds **19a**, **19b**, and **19c**, against T47D and MCF-7 cell line [45]. Some of the other chromone derivatives as anticancer agents are listed in Table 1 (Fig. 5).

3.2. Anti-HIV agents

Since first reported in the 1980s, acquired immunodeficiency syndrome (AIDS) has spread rapidly through the human

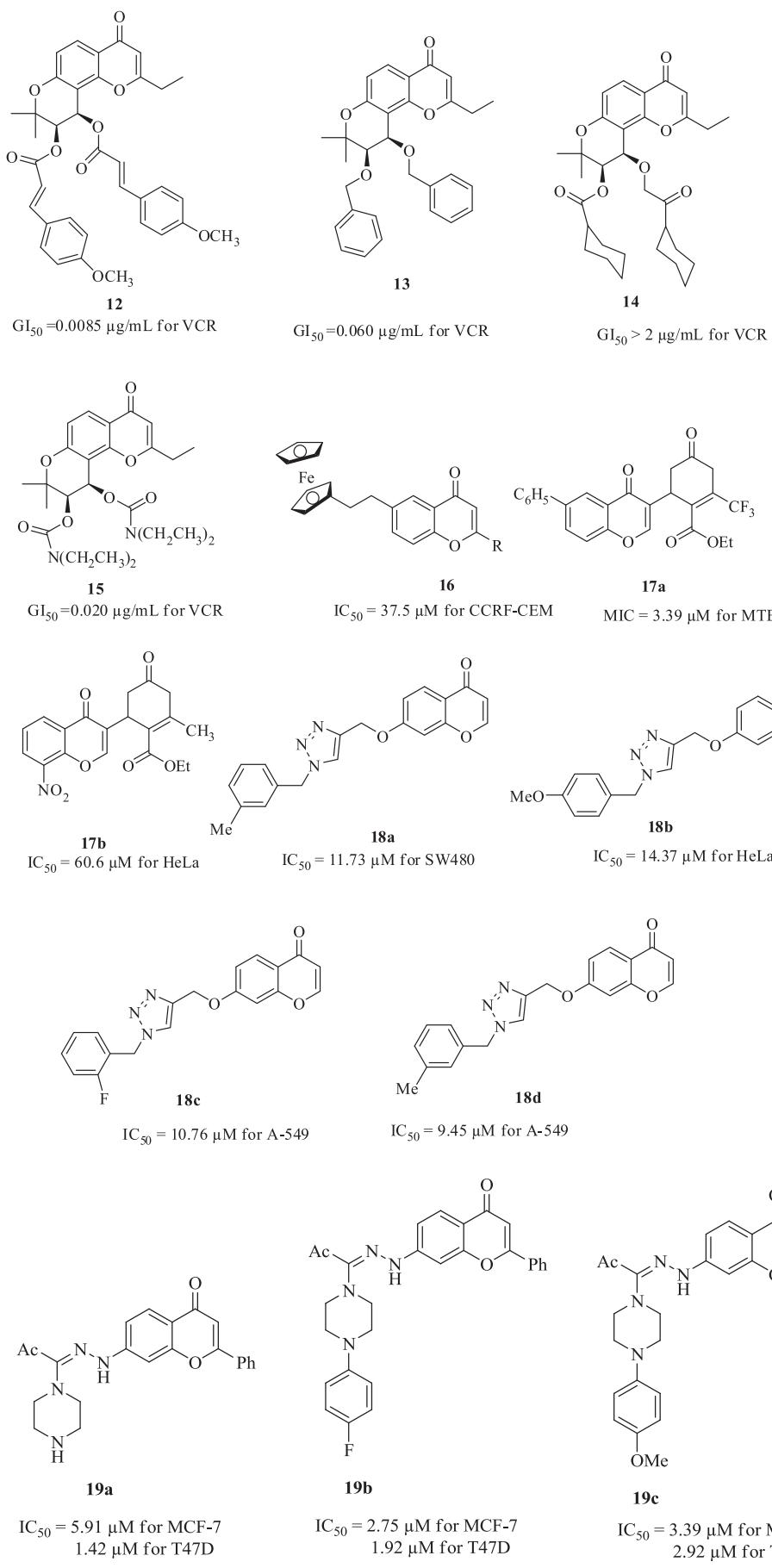


Fig. 5. (continued).

population and become one of the most devastating diseases facing mankind. This disease is caused by infection with the human immunodeficiency virus (HIV) and results in life-threatening opportunistic infections and malignancies [58]. Consequently, the development of new anti-HIV agents continues to focus on novel structures or new action mechanisms. Chromone and its derivatives exhibit a large number of anti-HIV agents and are discussed as follows.

3'R,4'R-di-O-(–)-camphanoyl-2',2'-dimethyldihydropyrano[2,3-f]chromone (DCP) derivatives synthesized, and screened for anti-HIV activity against a non-drug-resistant NL4-3 strain and multiple reverse transcriptase (RT) inhibitor-resistant (RTMDR-1) strain, using 2-EDCP and 2-MDCP as controls. New DCP analogs **32a**, **32b**, **32c**, and **32d** exhibited potent anti-HIV activity against HIV_{NL4-3} with EC₅₀ and therapeutic index (TI) values ranging from 0.036 μM to 0.14 μM and from 110 to 420, respectively. Compounds **32a** and **32b** also exhibited good activity against RTMDR-1 (EC₅₀ 0.049 and 0.054 μM; TI 310 and 200, respectively) [59]. A series of flavonoid derivatives synthesized and evaluated for inhibition of HIV multiplication against HIV-1 (IIIB strain) and HIV-2 (ROD) was based on the inhibition of virus-induced cytopathic effect in MT-4 cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method and antiproliferative activity on *Plasmodium falciparum* parasites. Methoxyflavone **33a** was active in both *P. falciparum* and HIV-1 whereas compounds **33b**, **33c**, and **33d** were specific inhibitors of the HIV-2 multiplication. Para substitution on the B ring is needed to promote antiplasmoidal activity and increase HIV-2 potency [60].

Diphenolic chromone derivatives synthesized by Li et al., and their inhibitory activity on nitric oxide (NO) production and

cytotoxicity were evaluated using LPS-activated murine macrophages RAW 264.7 assay and MTT method, respectively. Among synthesized compounds, fatty acids esters (**34a** and **34b**) and aromatic acids esters **35(a–c)**, showed quite potent inhibitory activity and no cytotoxicity at effective concentrations. The most active compounds **34(a,b)** inhibited NO production by suppressing the expression of iNOS in a dose dependent manner [61]. A new series chromone or chromanone ring as conformationally constrained scaffolds of 1,3-diketo acids synthesized, and tested their ability to inhibit HIV-1 IN-mediated strand transfer. All compounds moderately inhibited HIV-1 IN strand transfer, indicating that conformational restriction of the keto group into chromone or chromanone rings allowed retention of activity. Compounds **36** and **37**, which have hydrophobic benzyl groups, showed greater inhibition [62].

Liu et al., have synthesized series of 3'R,4'R-di-O-(S)-camphanoyl-2',2'-dimethyldihydropyrano[2,3-f]chromone (DCP), and evaluated for inhibition of HIV-1NL4-3 replication in TZM-bl cells. 2-Ethyl-20-monomethyl-10-oxa- and -10-thia-DCP (**38a**, **38b**), as well as 2-ethyl-10-thia-DCP (**38c**) exhibited potent anti-HIV activity with EC₅₀ values of 30, 38 and 54 nM and therapeutic indexes of 152.6, 48.0 and 100.0, respectively [63]. Novel chromone derivatives with a benzopyran-4-one scaffold have been prepared by the one-pot cyclization reaction and *in vitro* inhibitory activity of these new compounds towards HIV-1 protease has been evaluated. 7,8-dihydroxy-2-(3'-trifluoromethylphenyl)-3-(3'-trifluoromethylbenzoyl)chromone (**39**) showed IC₅₀ = 0.34 μM which is more potent than the structurally related HIV-1 PR inhibitors in 4-hydroxycoumarins series [64]. The some of the other chromone derivatives as anti-HIV agents are listed in Table 2 (Fig. 6).

Table 2
Some of the chromone derivatives as anti-HIV agents.

S. No	Structures	Ref.	S. No	Structures	Ref.
1		[65]	3		[67]
	40 EC ₅₀ = 0.06 μM			42 IC ₅₀ = 35.43 μM	
2		[66]	4		[68]
	41 IC ₅₀ = 0.4 μM			43 EC ₅₀ = 1.6 μM	

3.3. Antioxidant agents

Antioxidant compounds in food play an important role as health-protecting factors. Scientific evidence suggests that antioxidants can reduce the risk for chronic diseases including cancer and heart disease. The main characteristic of an antioxidant is its ability to trap free radicals. Highly reactive free radicals and oxygen species are present in biological systems from a wide variety of sources. These free radicals may oxidize nucleic acids, proteins, lipids or DNA and can initiate degenerative disease. Antioxidant compounds like phenolic acids, polyphenols and avonoids scavenge free radicals such as peroxides, hydroperoxides or lipid peroxyls and thus inhibit the oxidative mechanisms that lead to degenerative diseases. Chromone analogs have shows an antioxidants activity and are discussed as follows.

2-Styrylchromones (2-SC) and 3-substituted flavones, synthesized by Fernandes and co-workers and tested for their metal chelating capacity and reducing activity. The methylation of hydroxyl groups decreases the scavenging of ROS and RNS by 2-SC. The decrease in the scavenging activities was, generally, more evident when the methylation occurred in B-ring. The most effective were the 2-SC **44(a–c)** and flavone **46**. The order of potencies found was **44b** > **46** > **44a** > **44c** > **45a** > **45b** > **45c** [69]. Two

naturally occurring homoisoflavonoids **47** and **48** synthesized and evaluated for their anti-oxidant and anti-fungal activities (*Aspergillus niger* and *Penicillium chrysogenum*) determined by superoxide (NBT) and agar cup method respectively. The antioxidant activity studies revealed that the 3-benzylchromones with phenolic hydroxyl group (**47a** & **47b**) exhibited good activity than the compounds with methoxyl groups (**47c** & **47d**). The presence of double bond between C2–C3 has major influence on the activity of compounds. The compounds with 7-oxygenation (i.e., methoxy or hydroxyl group at 7th position) and methoxy or chloro substituents at C-4' were enhanced antifungal activity [70].

Various substituted 3-chlorochromones (**49**) synthesized and tested for their antimicrobial, antiviral and antioxidant activities by agar well diffusion, DPPH method and CPE inhibition assay respectively. Amphotericin B and Vancomycin were used as standards for comparison of antifungal, antibacterial, Trolox as a reference standard for antioxidant activity. Some of the synthesized compounds showed the moderate antimicrobial, antiviral and antioxidant activities [71]. 4'-Azaflavone (**50**, **51**) and 4'-azaflavonium bromides (**52**, **53**) synthesized and screened for their antioxidant activities and antimicrobial by the scavenge the stable radical DPPH (1,1-diphenyl-2-picrylhydrazyl), using the ferric reducing antioxidant power (FRAP) assay and broth micro dilution

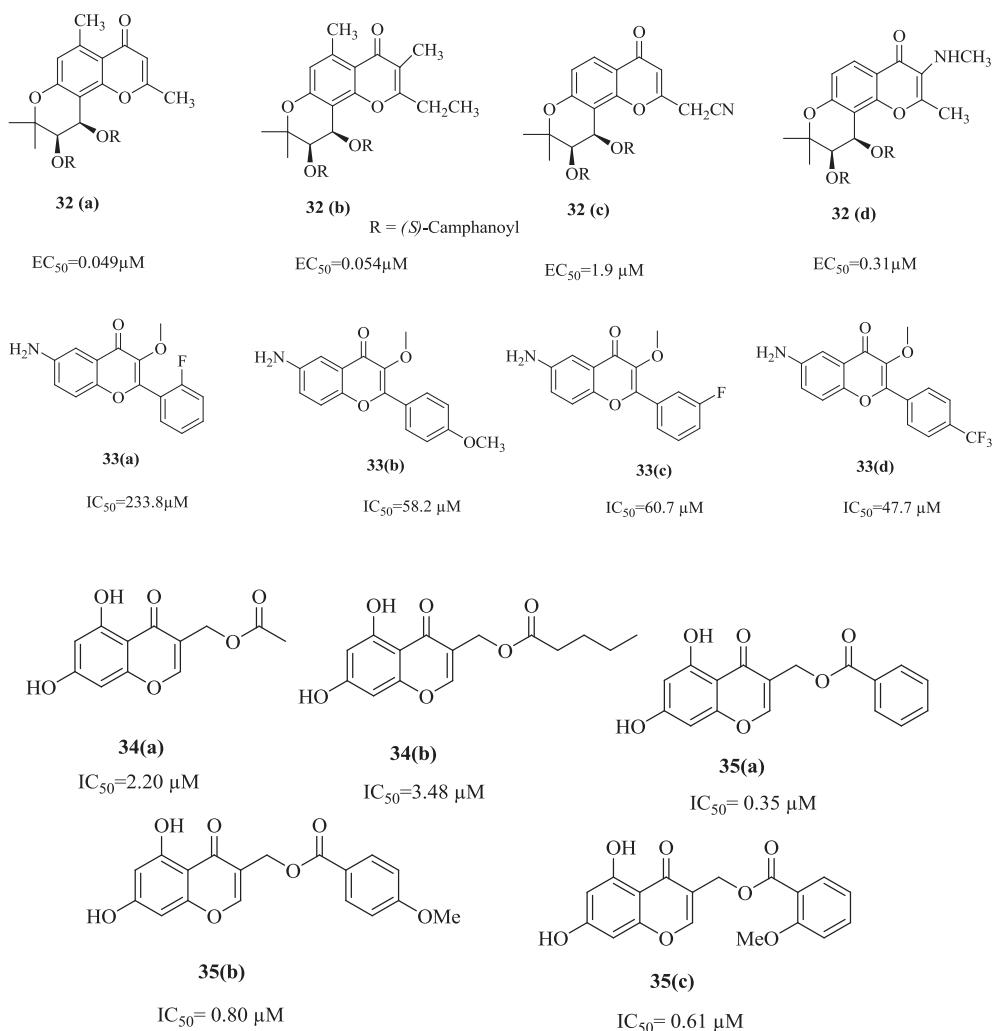
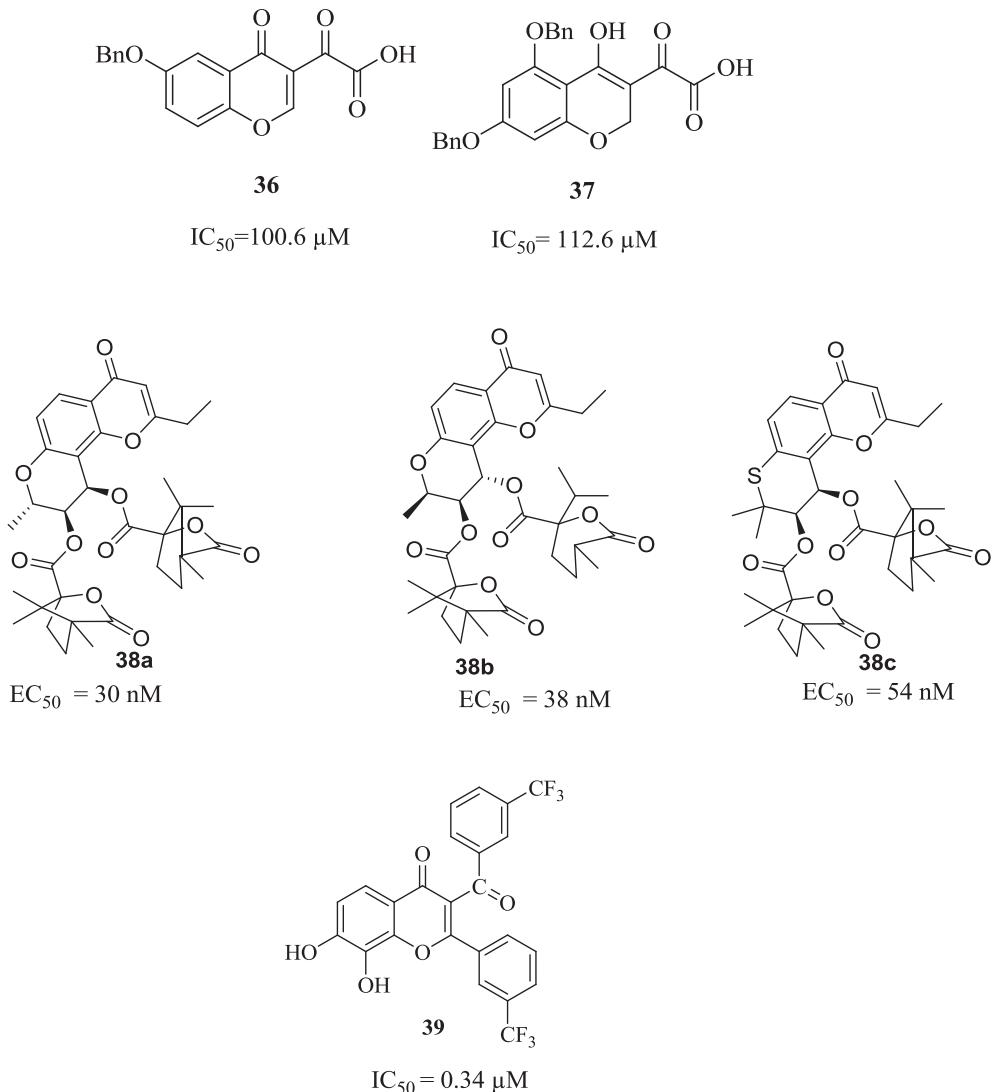


Fig. 6. Chromone as anti-HIV agents.

**Fig. 6. (continued).**

method respectively. The *N*-alkyl-substituted 4'-azaflavonium bromides **52** and **53** showed high antimicrobial activity against the Gram-positive bacteria and the fungus tested, with MIC values close to those of reference antimicrobials ampicilline and fluconazole. The alkylated compounds **52** and **53** also showed a good antioxidant character in the two antioxidant methods, DPPH (1,1-diphenyl-2-picrylhydrazyl) radical-scavenging and ferric reducing/antioxidant power (FRAP) tests [72]. 2,3-di- substituted chromones synthesized and evaluated for antioxidant activity by DPPH method using L-ascorbic acid (antioxidant agent) as a positive control. The compounds, **54a** and **54b** show 91.7% and 89.2% antioxidant activity respectively at 200 µg/mL concentration [73].

A series of halo substituted 2-styrylchromones were prepared and tested for antioxidant activity by using DPPH method, and all compounds show antioxidant activity in the range of 60–71%. The compounds **55a** and **55b** showed significant antioxidant activity 71.40 and 71.11% respectively, while remaining compounds show normal antioxidant behavior. The introduction of functional groups such as iodo/chloro/OH/OCH₃/CH₃ significantly increased antioxidant activity in comparison to unsubstituted styrylchromone [74].

The marine lipid-derived natural product all-(Z)-5,7-dihydroxy-2-(4Z,7Z,10Z,13Z,16Z-nonadecapentaenyl) (**56a**) and four analogs **56(b–e)** have been synthesized and evaluated in the cellular lipid peroxidation antioxidant activity (CLPAA) assay using Hep G2 cells. Compounds (**56a**) and (**56e**) can protect cellular membranes against lipid peroxidation, and compound (**56a**) was almost as potent in the CLPAA-assay [75]. Phosrithong et al., have evaluated some chromone derivatives for their antioxidant activity using DPPH free radical scavenging assay, ferrous ions (Fe²⁺) chelating activity test, total antioxidant activity test (Ferric thiocyanate and Thiobarbituric acid methods), and total reductive capability (potassium ferricyanide reduction). Compounds with, 7,8-dihydroxy derivatives, that is, chromones **57a** ($IC_{50} = 5.93 \mu\text{M}$), **57b** ($IC_{50} = 13.62 \mu\text{M}$), and **57c** ($IC_{50} = 4.95 \mu\text{M}$) exhibited much stronger activity than BHT, vitamin E, and trolox. 7,8-Dihydroxy-2-(3'-trifluoromethylphenyl)-3-(3''-trifluoromethylbenzoyl) chromone **57c** showed outstanding radical scavenging activity, which was more potent than the known antioxidant flavonoids [76]. A series of tacrine-4-oxo-4*H*-chromene hybrids synthesized and evaluated for the inhibition of human AChE, BuChE, and BACE-1, as well as radical scavenger activity. Hybrid **58a** (derived from 6-

chlorotacrine and 5-hydroxy-7-methoxy-4-oxo-4H-chromene) was the best h-AChE inhibitor of this family ($IC_{50} = 35 \mu M$), whereas compound **58b** (derived from tacrine and 6-methoxy-4-oxo-4H-chromene) was the most active toward h-BuChE ($IC_{50} = 38 \mu M$). Hybrid **58c**, derived from 6-chlorotacrine and 6,7-dihydroxy-4-oxo-4 H-chromene, was 1056-fold more potent toward h-AChE than toward h-BuChE. The radical capture capacity was found to be related to the presence of phenolic groups in the flavonoid fragment, compound **58d** (tacrine-6-hydroxy-4-oxo-4H-chromene) being 1.3-fold more potent than trolox, a vitamin E analog [77] (Fig. 7).

3.4. Anti-tubercular agents

Mycobacterium tuberculosis infections are responsible for one in four avoidable adult deaths in developing countries. While there are a number of effective drugs available for treating tuberculosis (TB), current strategies are greatly complicated by the several months of chemotherapy required to eliminate persistent bacteria. Chromone and its derivatives showed a good antimycobacterial activity, and are discussed as follows.

2,10-Dihydro-4[H]-chromeno[3,2-c]pyridin-3-yl derivatives synthesized by Sriram et al., and evaluated for their *in-vitro* anti-mycobacterial activity against MTB and MDR-TB by agar dilution method. Preliminary *in-vitro* and *in-vivo* activity against *M. tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB). Among them *N*-(4aS)-2-(3-methyl-2-pyridinyl)-10-oxo-2,10-dihydro-4aH-chromeno[3,2-c]pyridin-3-yl methyl-4-ethylbenzenecarboxamide **59** and *N*-(2-(3,5-dibromopyridin-2-yl)-10-oxo-4a,10-dihydro-2H-chromeno[3,2-c]pyridin-3-yl)methyl-7-methyl-2-naphthamide **60** were found to be the most active compound *in-vitro* with MIC's of 0.22 and 0.07 $\mu g/mL$ and 1.23 for MTB 0.61 $\mu M/mL$ for MDRTB against respectively. In the *in-vivo* animal model, compound **59** decreased the bacterial load in lung and spleen tissues with 1.11 and 2.94-log₁₀ protections respectively and was considered to be promising in reducing bacterial count in lung and spleen tissues [78].

3-Formylchromones containing aminobenzothiazoles, thienobenzothiazoles and hydrazide derivatives synthesized and screened for their antimicrobial activity using standard plate diffusion method against Gram positive strains (*Staphylococcus aureus*, *Bacillus subtilis*), Gram negative strains (*Escherichia coli*, *Pseudomonas*

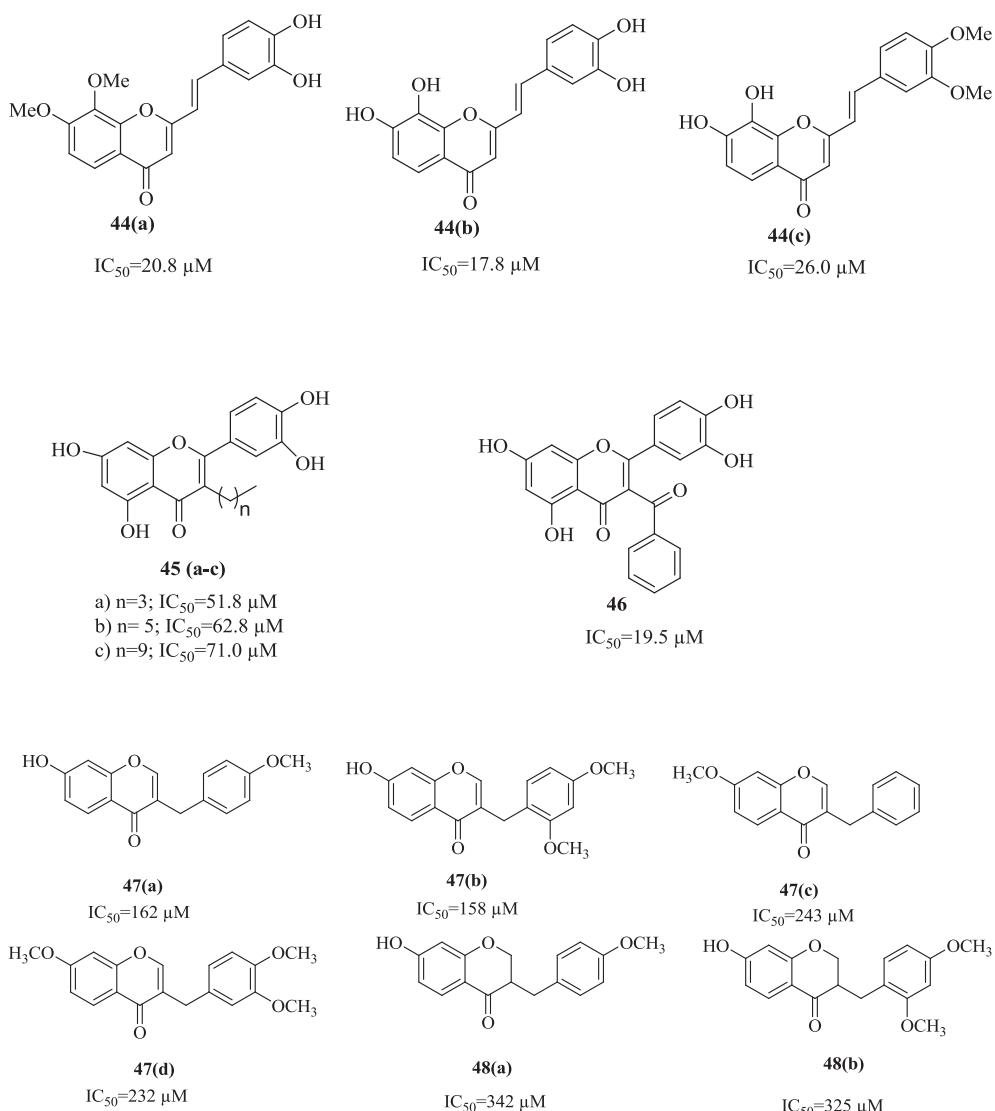
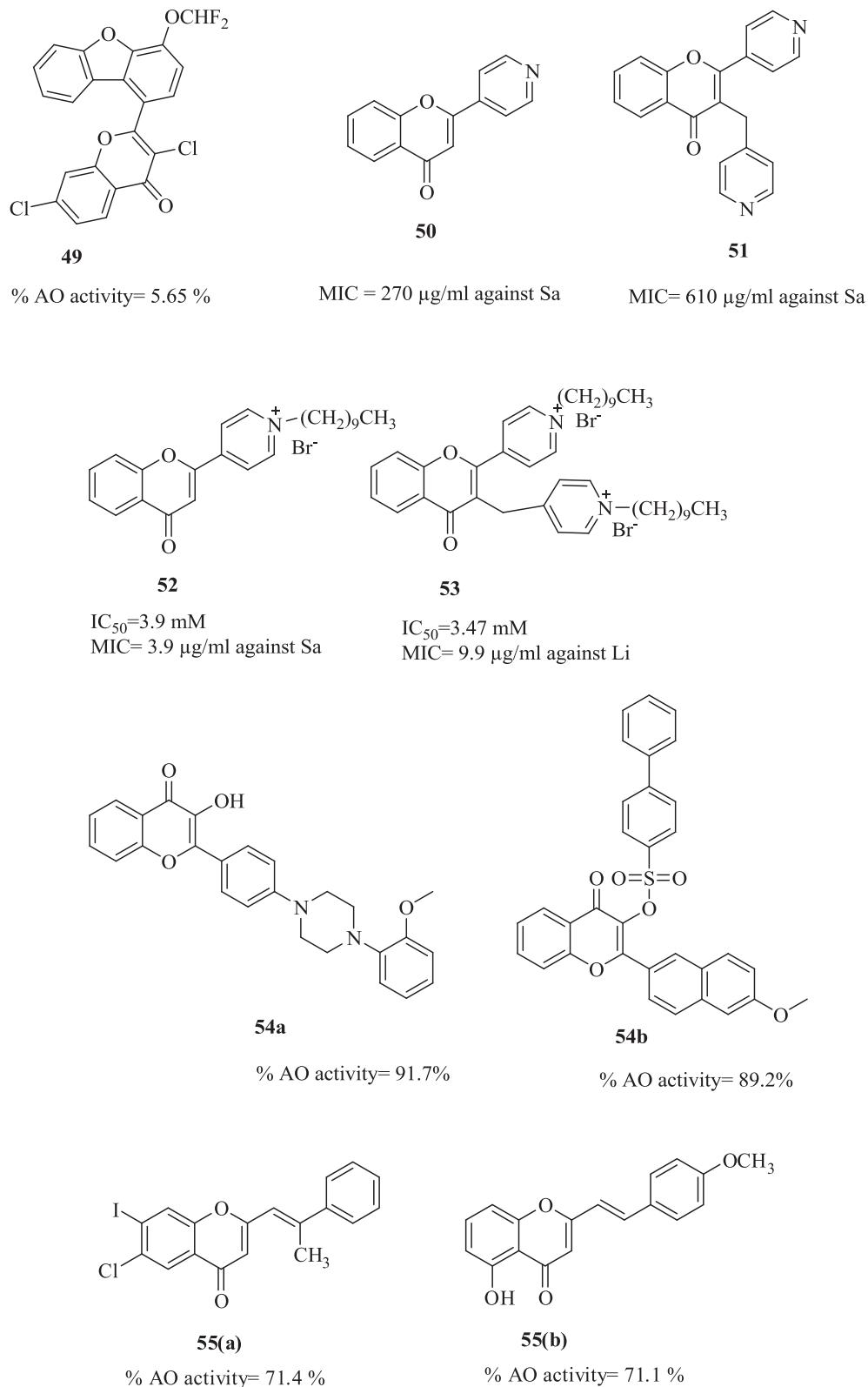


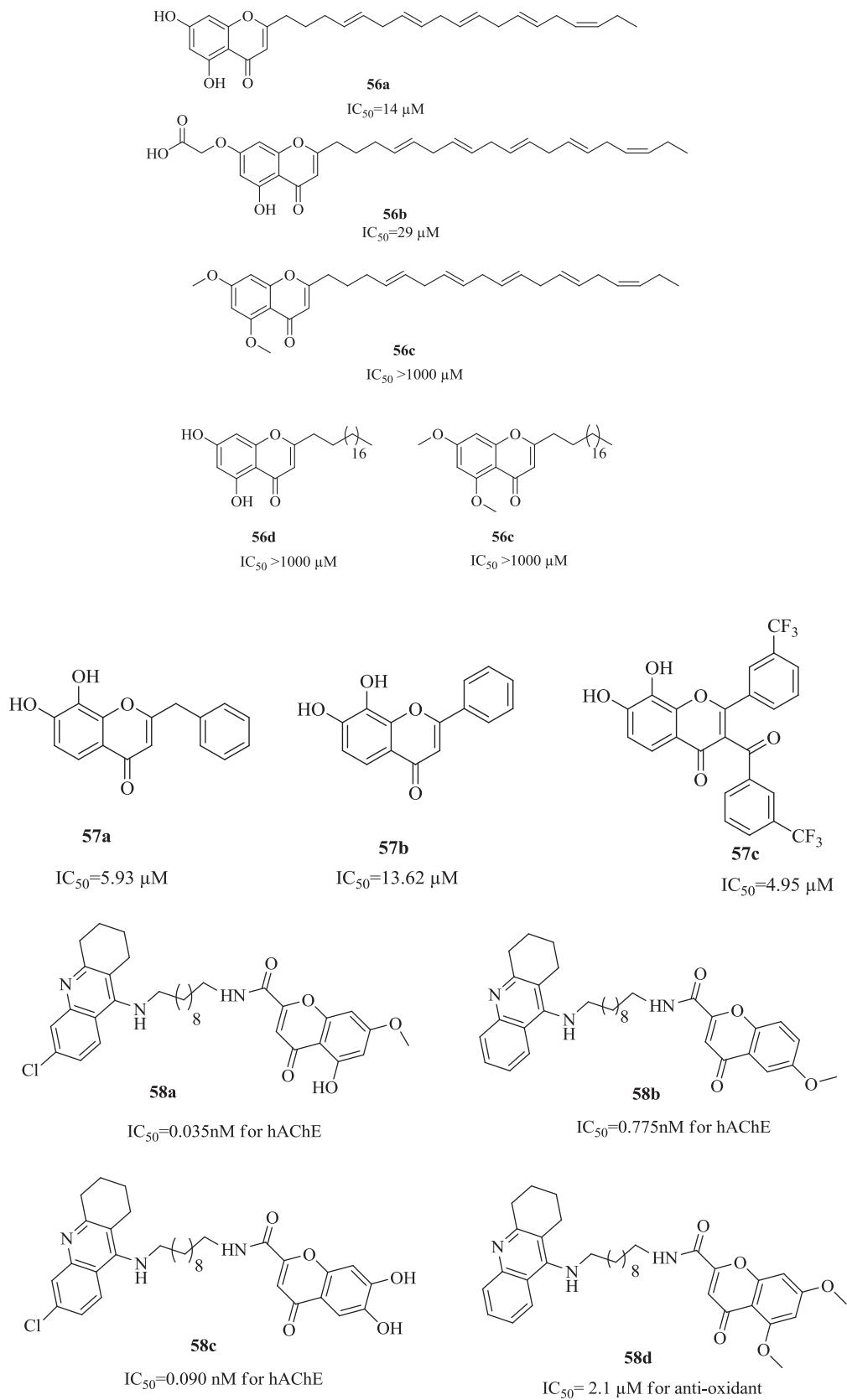
Fig. 7. Potential anti-oxidant agents.

**Fig. 7.** (continued).

aeruginosa); yeasts: *Candida albicans*, *Saccharomyces cerevisiae*; moulds: *Microsporum gypseum*, *Aspergillus niger*, *Scopulariopsis brevicaulis*; and antitubercular against *M. tuberculosis* (H37Rv), *Mycobacterium kansasii* (PFG 8), *Mycobacterium avium* (My80/72), *Mycobacterium fortuitum* (1021). The 3-formylchromones **61** and **64**

exhibit interesting activity gram positive and gram negative strains and compounds (**61**–**64**) showed significant antimycobacterial activity on the same level as that of INH [79].

A series of amino alcohol fused spirochromone conjugates synthesized and screened for their *in vitro* antimycobacterial

**Fig. 7.** (continued).

activity against mycobacterium tuberculosis H37Rv (ATCC27294). Among the synthesized compounds, seven compounds (**65a**, **65b**, **65c**, **65d**, **65e**, **66a**, **66b**) were found to be active with MIC in the range of 3.13–6.25 µg/mL. The compound **65c**, is found to be more active having MIC 3.13 µg/mL among all the compounds screened. Importantly, compound **65c** represents a novel structural chemo-type for which antitubercular properties. From SAR study, compounds possessing cycloalkyl group at 2nd position of the chromone ring favors better activity than piperidinyl moiety [80]. Haveliwala et al., have synthesized new tricyclic chromone-fused thiopyrimidines derivatives and screened for their anti-tubercular activity against Mycobacterium tuberculosis H37Rv [MTCC-200]. The halogen group containing substituted derivatives, **67a** and **67b**, displayed a relatively higher inhibitory activity (99%). Substitution at chromone with a methyl group reduces the anti-tubercular activity. The presence of a dibromo group on chromone caused a remarkable improvement in the anti-tubercular activity [81] (Fig. 8).

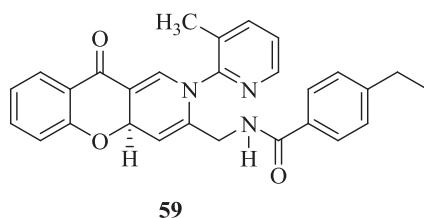
3.5. Anti-inflammatory agents

The development of new non-steroidal anti-inflammatory drugs follows different strategies: selective COX-2 inhibition or the inhibition of inducible nitric oxide synthase (iNOS). iNOS contributes to acute and chronic inflammation by producing nitric oxide as a cytotoxic inflammatory mediator [2]. Synthetic approaches have

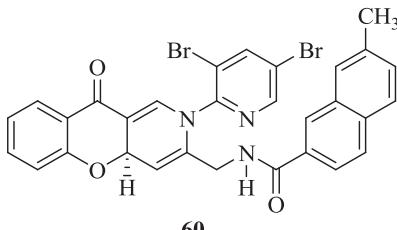
been taken with the aim of improving safety profile and in turn therapeutic window of NSAIDs. Chromone derivatives shows good anti-inflammatory activities and are discussed as follows.

A series of novel acyl-hydrazones bearing chromone synthesized and evaluated for their *in vivo* anti-inflammatory activity, in an acute experimental inflammation. The acute phase bone marrow response, phagocytes activity (PA) and NO evaluated. *In vitro* phagocytosis test, all the newly synthesized compounds reduced significantly PI, **68a** and **68b** being more potent inhibitors than Meloxicam. PA was significantly reduced by the compounds **68a** and **68b**, and more potent than Meloxicam. Two compounds inhibited NO synthesis **68a** and **68b** stronger than Meloxicam, the anti-inflammatory reference drug [82]. 3-Formylchromone and its derivatives synthesized and evaluated for their *in vitro* respiratory burst inhibitory activity, superoxide scavenging activity using xanthineexanthine oxidase system, cyclooxygenase (COX-1, COX-2) and lipoxygenase inhibitory activities and *in vivo* carrageenan-induced rat paw edema study. Some of the derivatives exhibited a significant anti-inflammatory activities in carrageenan-induced rat paw edema model, among compound **69** is the most active compound with an IC₅₀ 40.210 µM and compound **70** was found to be the second most active compound with an IC₅₀ 55.036 µM. Most of the compounds inhibiting superoxide production at IC₅₀ less than 30 µM [83].

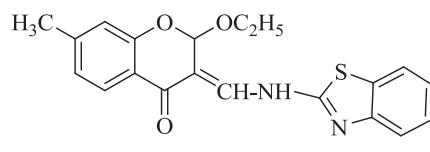
6-Aminomethyl-2-aryl-1-benzopyran-4-one derivatives synthesized by Alam and co-workers, and tested for anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation



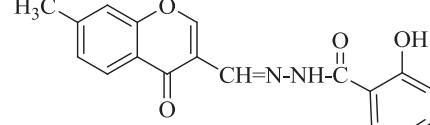
MIC = 0.22 µM for MTB
0.07 µM for MDRTB



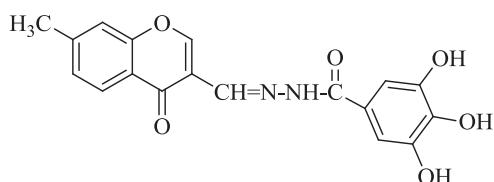
MIC=1.23 µM for MTB
0.61 µM for MDRTB



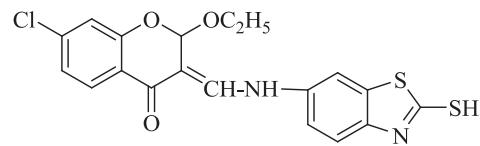
MIC > 100 µM for M. tuberc.



MIC > 100 µM for M. tuberc.

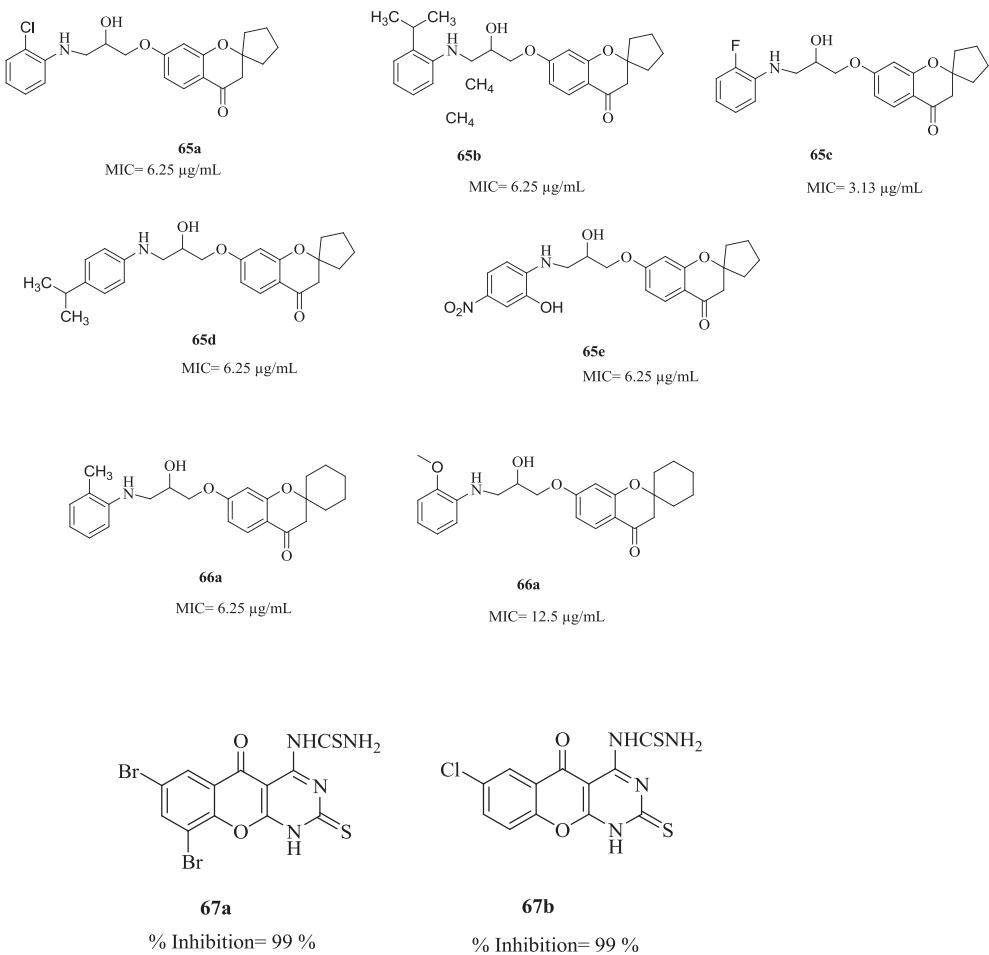


MIC > 100 µM for M. tuberc.



MIC = 2.5 µM for M. tuberc.

Fig. 8. Compounds with anti-tubercular activity.

**Fig. 8.** (continued).

actions. Among the tested compounds, compounds **71a** and **71b** showed higher degree of anti-inflammatory activity (>75% activity of standard drug ibuprofen) [84]. *N,N*-dialkylaminosubstituted chromones synthesized and tested for their ability to affect the O₂[−] production by human neutrophils stimulated with either phorbol myristate acetate (PMA) or formylmethionine-leucine-phenylalanine (f-MLF). The absence of substituents, the chromones express very low inhibitory activity on O₂[−] production. However, the substitution of methyl residue **72a** with propyl residue **72b** promotes a significant increase in inhibition of O₂[−] production by neutrophils stimulated with f-MLF. Chromones having a pyrrolidino residue (**72c**, **72d**) show good inhibitory efficiency on neutrophils stimulated with both PMA and f-MLF. The introduction of a piperidino group (**72e**, **72f**) largely increases the inhibitory effect of f-MLF stimulated neutrophils, without affecting PMA-stimulated neutrophils [85]. A series chromone analog (**73–78**) synthesized and evaluated for their inhibitory activity against interleukin-5 using the IL-5-dependent pro-B Y16 cell line. Among them compounds 5-Cyclohexylmethoxy-3-(4-hydroxybenzyl)-4H-chromen-4-one (**73**, IC₅₀ = 3.0 µM) and 5-Cyclohexylmethoxy-3-(hydroxymethyl)-4H-chromen-4-one (**74**, IC₅₀ = 7.6 µM) showed most potent activity [86].

Hatnapure et al., have synthesized 6-methoxy-2-(piperazin-1-yl)-4H-chromen-4-one and 5,7-dimethoxy-2-(piperazin-1-ylmethyl)-4H-chromen-4-one derivatives and screened for their pro-inflammatory cytokines (TNF-α and IL-6) and antimicrobial activity. Compounds **79(a–f)** found to have promising anti-

inflammatory activity (up to 65–87% TNF-α and 70–93% IL-6 inhibitory activity) at concentration of 10 µM with reference to standard dexamethasone (71% TNF-α and 84% IL-6 inhibitory activities at 1 µM), while some compounds found potent antimicrobial agent showing even 2–2.5-fold more potency than that of standard ciprofloxacin and miconazole at the same MIC value of 10 µg/mL. The presence of highly electron rich group such as -OMe, pyrimidyl, morpholine on piperazine as well as homologation of chromone and piperazine moiety have strong relevance to the anti-inflammatory activity while the amino alkyl, cyano or alkenylalkyl group either on piperazine or chromone found to be effective potent antimicrobial agents [87]. 2-(2-Phenylethyl)chromone derivatives **80(a–e)**, namely, congeners isolated from the resin-deposited wood of *Aquilaria sinensis* (Lour.) Gilg by Tu et al., and screened for their anti-inflammatory activity. All assayed compounds exhibit potent inhibitory activity against NO production in RAW 264.7 cells, with IC₅₀ values of 5.12–2.26 µM; by comparison the positive control ibuprofen, a clinical anti-inflammatory agent, has an IC₅₀ value of 94.12 µM [88] (Fig. 9).

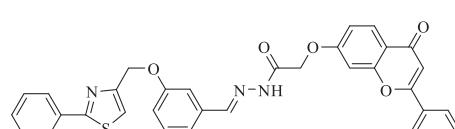
3.6. Antimicrobial agents

Infectious microbial disease remains a pressing problem worldwide, because microbes have resisted prophylaxis or therapy longer than any other form of life. In recent decades, problems of multidrug-resistant microorganisms have reached an alarming level in many countries around the world. Resistance to a number

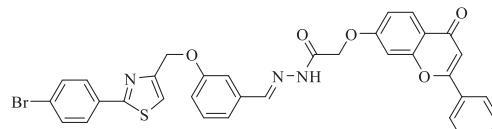
of anti-microbial agents (β -lactam antibiotics, macrolides, quinolones, and vancomycin) among variety of clinically significant species of bacteria is becoming increasingly important global problem. Chromone and its derivatives exhibit large number of anti-microbial activities, and are discussed as follows (Table 3).

2-[3-[(Substituted benzylamino-methyl)-phenyl]-4H-benzopyrane-4-one and *N*-substituted benzyl-N-[3-(4-oxo-4H-benzopyrane-2-yl)benzyl]-3-phenyl-acrylamide derivatives prepared by Ertan et al., and screened for their *in vitro* antifungal and antibacterial activities by the agar diffusion method. Compound **81a** showed the good antifungal activity against *C. albicans* compared with miconazole. Compound **81b** and **82** showed good antibacterial activity against *S. aureus* and *E. coli* respectively compared with the control drug ampicillin [89]. 2-Alkenylchroman-4-ones and 2-alkenylthiochroman-4-ones synthesized by using regioselective trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf)-mediated reaction and evaluated their antimicrobial activities against the Gram-positive bacteria *S. aureus* and *B. subtilis*, the Gram negative

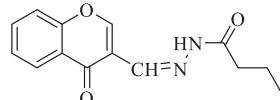
E. coli and the yeast *Candida maltose*. Compounds **83** and **84** showed good activity against *S. aureus* and *E. Col* respectively, and other compounds are inactive against the different strains. The best antimicrobial activities are observed for 2-vinylchroman-4-ones containing an unsubstituted vinyl group and a halogen atom attached to the benzene moiety. The activity decreases for 2-vinylthiochroman-4-ones and for 2-vinylchroman-4-ones containing a substituted vinyl group [90]. 3-Hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl) chromones synthesized, by Algar Flynn Oymanda (AFO) reaction and tested *in vitro* for their antifungal activity against three phytopathogenic fungi, namely *Helminthosporium* species (Hs), *Fusarium oxysporum* (Fo) and *Alternaria alternate* (Aa) by Poisoned Food Technique. Compounds **85(a–e)** exhibited good antifungal activity than commercial antifungal compound Actidione (cycloheximide) against all three phytopathogenic fungi. Chromones with electron releasing groups the antifungal activity increased while as the aryl proton is replaced with electron withdrawing group the antifungal activity decreased [91].

**68a**

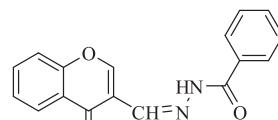
Neutrophilesa (%) = 71.7 %

**68b**

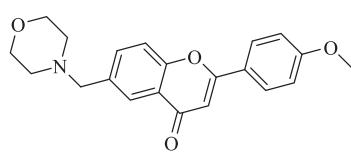
Neutrophilesa (%) = 57.4 %

**69**

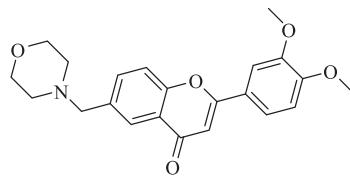
Respiratory burst inhibitory activity $\text{IC}_{50}=40.21 \mu\text{M}$
Superoxide scavenging activity $\text{IC}_{50}=77.27 \mu\text{M}$

**70**

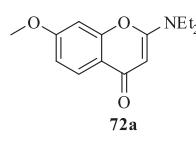
Respiratory burst inhibitory activity $\text{IC}_{50}=55.036 \mu\text{M}$
Superoxide scavenging activity $\text{IC}_{50}=0.439 \mu\text{M}$

**71a**

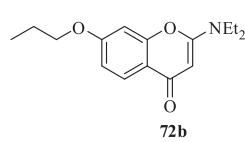
(% inhibition at 2hr = 62.6 %)

**71b**

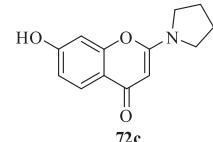
(% inhibition at 2hr = 61.7 %)



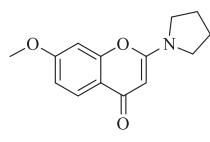
% inhibition of f-MLF = 40 %



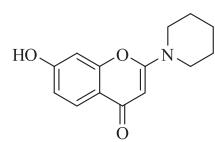
% inhibition of f-MLF = 66 %



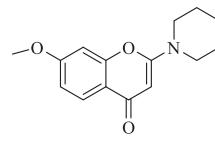
% inhibition of f-MLF = 29 %



% inhibition of f-MLF = 37 %

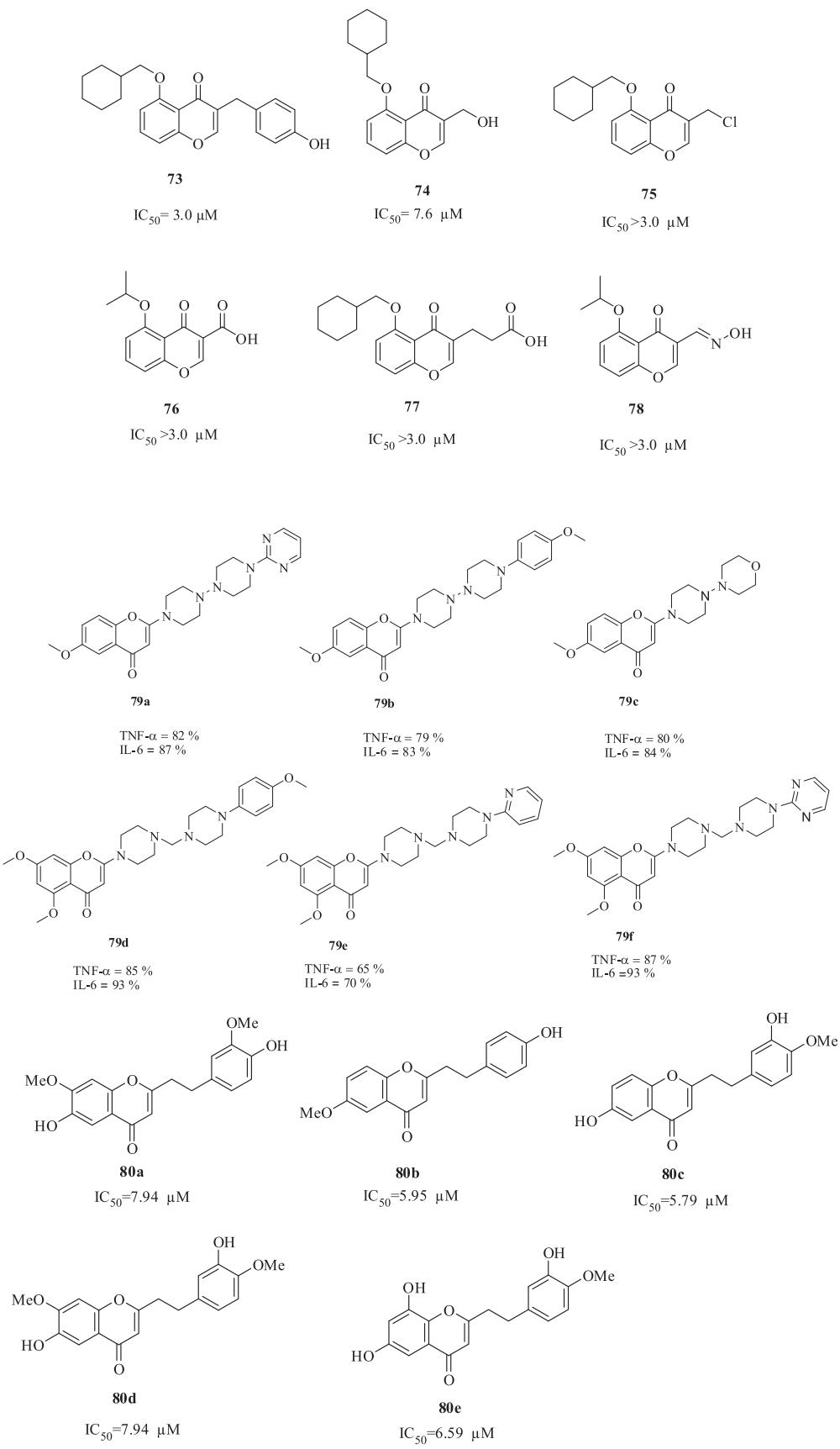


% inhibition of f-MLF = 100 %



% inhibition of f-MLF = 100 %

Fig. 9. Compounds with anti-inflammatory activity.

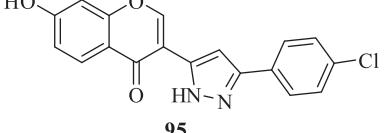
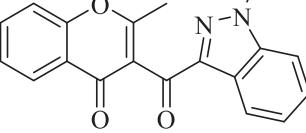
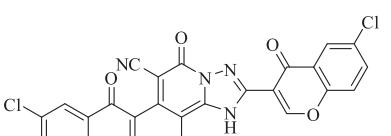
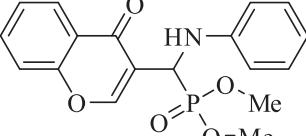
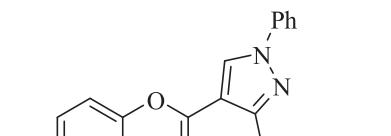
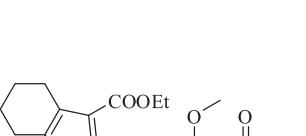
**Fig. 9.** (continued).

Chromone conjugated dithiazoles and 4-oxo-4H-chromene-3-carbothioic-N-phenylamides synthesized and screened for anti-bacterial and antifungal by disk-diffusion assay. The dithiazole derivative **86a** bearing electron withdrawing ($-F$, $-Cl$) groups at C₆ and C₇ positions shows high antifungal activity in comparison to fluconazole. For Gram positive bacteria *S. aureus*, maximum growth inhibition of 92.72% was showed for **86b** followed by 90.90% for compound **87** [92]. Chromone fused pyrazolines, pyrazoles, dibromo derivatives and dihydropyrimidines, (**88–91**) have synthesized under microwave irradiation, and evaluated *in vitro* anti-bacterial activity against an assortment of two Gram-positive bacteria, *S. aureus*, *B. subtilis*, and two Gram-negative bacteria, *E. coli*, *Salmonella typhimurium*, *in vitro* antifungal activity was tested against three fungal strains, *C. albicans*, *A. niger* and *Aspergillus fumigatus* (laboratory isolate). The antimicrobial activity of compounds showed that various compounds are potent antimicrobial agents [93].

New nitrogen heterocyclic systems combining chromone moiety and 1,2,4-triazole or 1,2,4-triazine in one molecular frame through an azomethine linkage synthesized and evaluated *in vitro* for their antimicrobial activities, using the disc-agar diffusion method, against *S. aureus* and *Streptococcus pyogenes* as Gram

positive bacteria, *Pseudomonas fluorescens* and *Pseudomonas phaeolicola* as Gram-negative bacteria, and the fungi *F. oxysporum* and *A. fumigatus*. Compounds **92c**, **92d**, and **92e** showed high activity toward the tested fungi, while compounds **92a** and **92f** showed moderate activity with respect to the references used [94]. Chate et al., have synthesized a series of 2-phenylchromone-pyridine conjugated compounds **93(a–g)** using ultrasound irradiation. The standardized agar well diffusion method [22] was followed to determine the activity of the synthesized compounds against the sensitive organisms *S. aureus* (MRSA E710) and *E. coli* (25922) as a gram positive bacteria, and two species of fungi, *C. albicans* and *Aspergillus fumigates*. The vancomycin was used as reference in the case of antibacterial, while amphotericin B was used in the case of antifungal reference. The compounds **93d**, **93e** and **93f** showed highest antibacterial activity and **93a**, **93b**, **93d**, **93e**, and **93g** possess good antifungal activity comparable with that of standard drugs tested [95]. 3a,9a-Dihydro-1-ethoxycarbonyl-1-cyclopenteno[5,4-b]benzopyran-4-ones have synthesized and evaluated *in vitro* for antifungal activity against *A. niger*, *S. cerevisiae* and *C. albicans*. Compounds **94(a–c)** bearing electron withdrawing group such as –chloro at position 6 and 8, –fluoro at position 7 of chromone ring showed significant inhibitory activity [96] (Fig. 10).

Table 3
Some of the chromone derivatives as antimicrobial agents.

S. No	Structures	Ref.	S. No	Structures	Ref.
1		[97]	4		[100]
	Inhibition zone at 100 µg/ml = 16 mm against <i>E. coli</i>				
2		[98]	5		[101]
	Inhibition zone at 100 µg/ml = 26 mm against <i>S. pyogenes</i>				
3		[99]	6		[102]
	Inhibition zone at 100 µg/ml = 15 mm against <i>F. moniliformae</i>				
	Inhibition zone at 100 µg/ml = 16 mm against <i>E. coli</i>				
	Inhibition zone 1.25 mm against <i>E. coli</i>				

3.7. Anti-malarial/antiplasmodial agents

Malaria caused by *P. falciparum* is a major parasitic infection disease in the world and continues to cause morbidity and mortality on a large scale in tropical countries. According to WHO, it is a threat to over 2 billion people living in areas of high incidence. A major contributor to malarial morbidity and mortality is almost certainly the increasing resistance of malaria parasites to available drugs [103]. Some of the chromone derivatives have exhibit an anti-malarial activity and are discussed as follows.

Flavonoid derivatives containing a piperazinyl chain have synthesized and *in vitro* antiplasmodial activity assayed against the chloroquine-resistant Fcb1 strain of *P. falciparum*, and their toxicity was evaluated against the human diploid embryonic lung cell line MRC5. The compounds **101(a–d)** have shown good anti-malarial activity. The most active compounds, which have a 2,3,4-trimethoxybenzylpiperazinyl chain attached to the flavone at the 7-phenol group, showed *in vitro* activity against chloroquine-sensitive (Thai) and resistant (FcB1,K1) *P. falciparum* strains in the micromolar to submicromolar range [104]. A new chromone derivative **102a**, together with the known oxepino[2,3-*b*]chromones,

microsphaeropsones A 102b and **B 102c**, and **xanthopinone 102d**, isolated from the wood-decay fungus *Rhizina* sp. BCC 12292 by Isaka et al., and evaluated antimalarial activity against *P. falciparum* K1 and cytotoxicity against cancer cell lines (KB, MCF-7, and NCI-H187) and nonmalignant Vero cells. Compound **102a** exhibited antimalarial activity with an IC₅₀ of 5.1 µg/mL and cytotoxic activities against NCI-H187 and Vero cell lines with respective IC₅₀ of 6.4 and 1.6 µg/mL [105] (Fig. 11).

3.8. Anti-diabetic agents

Diabetes mellitus (DM) is a non-communicable disease and the most daunting challenges posed by chronic, complex and a multifarious group of disorders that disturbs the metabolism of carbohydrates, fats and proteins resulting from insulin deficiency or insulin resistance. Insulin resistance is associated with a deficit in protein tyrosine phosphorylation in insulin signal transduction cascade. Diabetic nephropathy, a serious chronic diabetic microvascular complication has become most important cause of end-stage renal disease, followed by neuropathy, cataracts and retinopathy, which practically are not controlled by

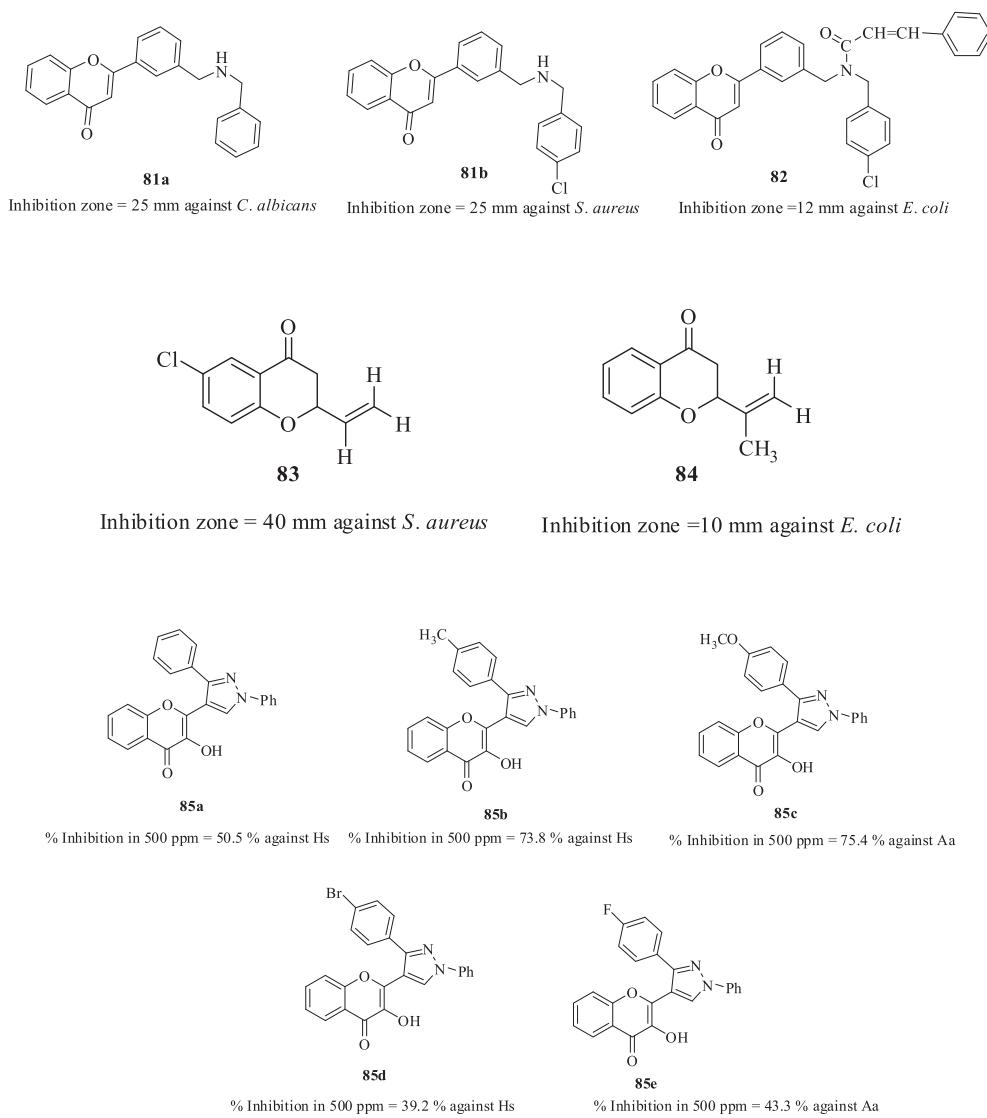


Fig. 10. Structures of compounds with an antimicrobial potential.

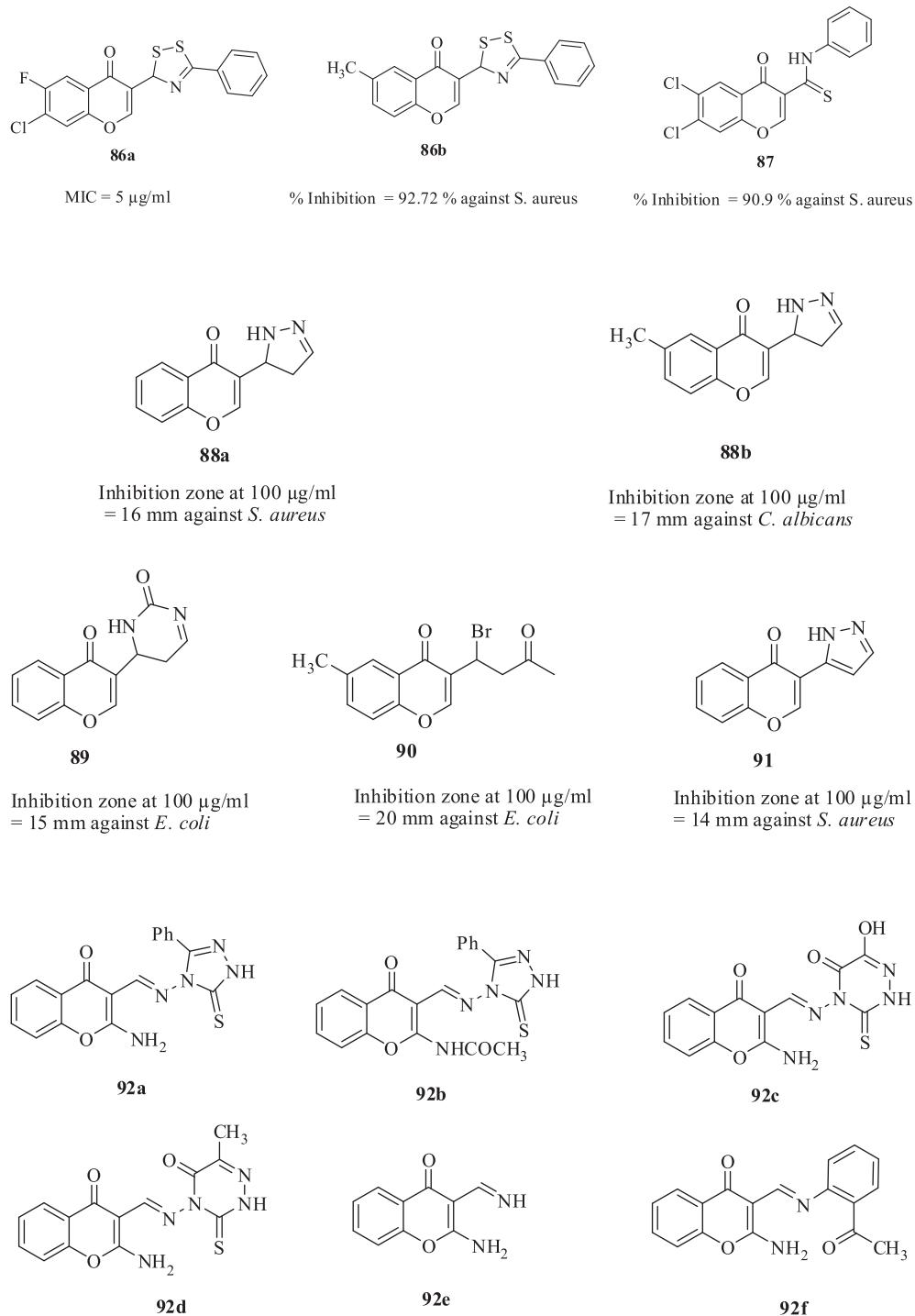


Fig. 10. (continued).

insulin. Sulfonylureas are the most widely used antidiabetic agents [106].

Chromonyl-2,4-thiazolidinediones/imidazolidinediones/2-thioxo-imidazolidine-4-ones was prepared by Knoevenagel reaction and tested for their insulinotropic activities in INS-1 cells. Compounds **103a** and **103b** (at lower concentration, 1 µg/mL) able to increase insulin release in the presence of 5.6 mmol/L glucose but to a lower extent than the reference compound glibenclamide. The introducing a 4-oxo-4*H*-chromen-3-yl methylene group at the fifth position of 2,4-imidazolidinedione and 2-thioxo-imidazolidine-4-

one rings increased the insulinotropic effect [107]. Several species of the genus *Artemisia capillaris* extracted and their inhibitory potential against α -glucosidase and protein tyrosine phosphatase 1B inhibitors (PTP1B) was evaluated in order to evaluate the anti-diabetic potential of the genus. Several *A. capillaris* isolated constituents have been shown to possess the most potent α -glucosidase and PTP1B inhibitory activities. Quercetin (**106a**), isorhamnetin (**106b**), and cirsilineol (**106c**), showed potential α -glucosidase and PTP1B inhibitory activities. In addition, 6-methoxy capillrisin (**106d**) has more potent PTP1B inhibitors than α -glucosidase [108] (Fig. 12).

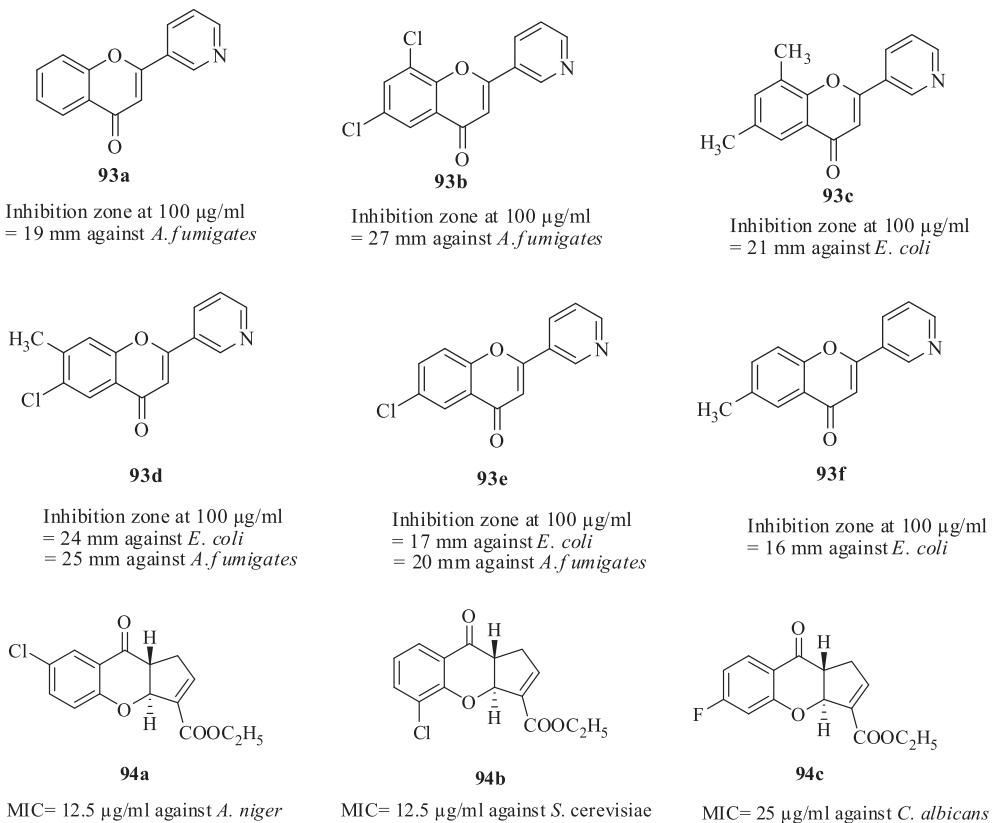


Fig. 10. (continued).

3.9. Anti-convulsant agents

Epilepsy is a neurological disorder characterized by unprovoked seizures affecting at least 50 million people worldwide. There is a continuing demand for new anticonvulsant agents as it has not been possible to control every kind of seizure with the currently available antiepileptic drugs. About one third of patients do not respond well to current multiple drugs therapy. Currently employed drugs such as phenobarbital and mephobarbital are very effective in controlling the seizures but they suffer from major side effects such as sedation and hypnosis [109]. Furochromone, and 2-phenylchromone (flavone) derivatives substituted with thiosemicarbazide or thiazolidin-4-one moieties synthesized by Eissa and co-workers, tested for their anticonvulsant activity in subcutaneous pentylenetetrazole induced seizures (scPTZ) and maximal electric shock induced seizures (MES) tests using valproic acid and phenytoin respectively as reference standards. Five compounds belonging to the different synthesized series **107**, **108**, and **109** showed 100% protection at a dose of 300 mg/kg in scPTZ test. In the MES test; all the tested compounds were inactive showing no protection against the seizures induced even up to a dose of 300 mg/kg body weight [110] (Fig. 13).

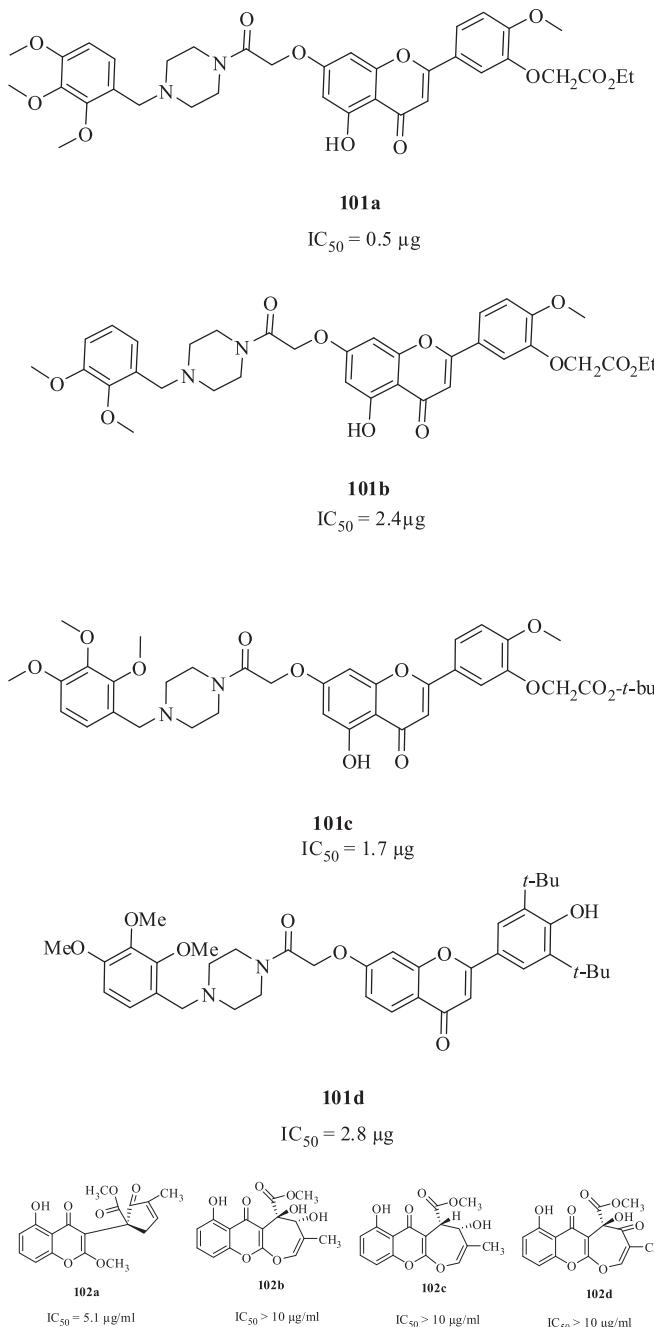
3.10. Anti-platelet agents

As platelets play an important role not only in hemostasis and thrombosis but also in atherogenesis and arterial spasm, efforts have been made to synthesize compounds which are significantly more active than acetylsalicylic acid (ASA) in inhibiting platelet aggregation [111]. Substituted 2-(diethylamino) or 2-(ethylamino) chromones synthesized, and evaluated *in vitro* for their inhibitory activities against human platelet aggregation induced by collagen,

ADP and arachidonic acid. Many compounds showed activity and some were more active than acetylsalicylic acid in the tests with ADP and arachidonic acid especially the compounds **110(a-d)** show a high degree of selectivity towards arachidonic acid. When the 2-amino substituent of tested chromones was a diethylamino group **110d**, the highest activity was found. The presence in position 7 of electron releasing substituents ($-OH$, $-OCH_3$, $-CH_3$) led to an increase of activity, whereas a decrease occurred when an electron withdrawing substituent was present in position (3- NO_2) or (6- NO_2 , 6-Cl) [112]. 7-Aminofurochromones and their dihydro derivatives in which the aminoethoxy side chain synthesized and screened for their ability to inhibit ADP-induced human platelet aggregation using 2-aminochromone as a control. The thiomorpholine derivative, **111** and **112** proved extremely potent in a canine model of platelet dependent thrombus formation. The hemodynamic effects associated with this series of compounds appear to be due to their ability to inhibit platelet cAMP dependent phosphodiesterase leading to elevated levels of cAMP [113]. A series of synthetic 2-morpholinochromones have synthesized and evaluated their anti-platelet activity against isolated PDE3A in a screening assay at 50 µM. Some of the compounds **113a**, and **113b** have shown good anti-platelet activity. The most potent inhibitors in this screen, all 8-methyl-7-substituted compounds, which reaffirmed the original postulate that members of this class of compounds are, in general, inhibitors of PDE3A [114] (Fig. 14).

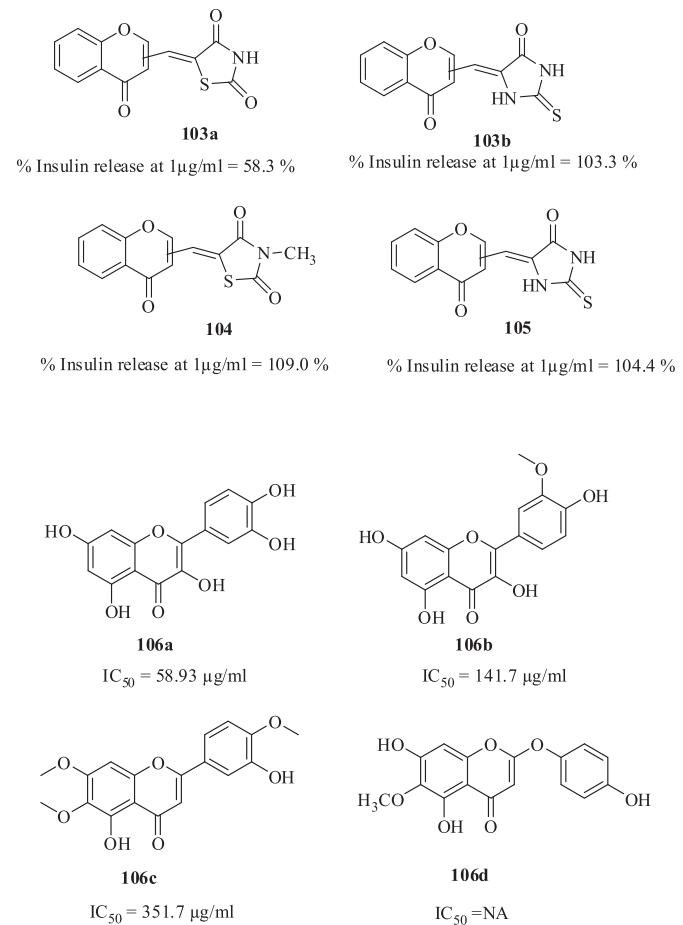
3.11. Gastroprotective agents

Gastric damage can affect as many as 25% of all patients taking non-steroidal anti-inflammatory drugs (NSAID's) on a chronic basis, and it probably represents the most frequent drug side effect in the United States. Standard anti-ulcer medications are largely

**Fig. 11.** Compound with anti-malarial/antiplasmodial activity.

ineffective in preventing this damage. For these reasons, the development of a safe and effective gastroprotective drug, which can be coadministered to patients taking NSAID's, represents an important medical need [115].

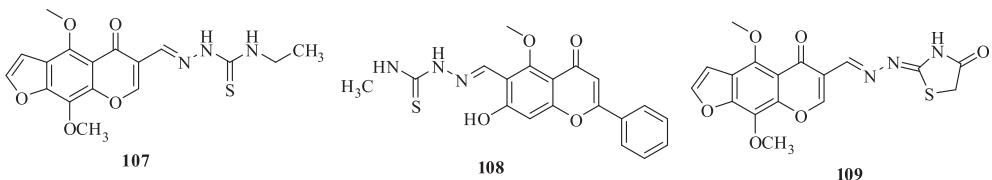
9- and 6-Alkylaminomethyl furoflavones synthesized from the naturally occurring chromones visnagin and khellin and screened for gastroprotective activity in the rat ethanol-induced damage model. The compounds (**114–118**) showed remarkable gastroprotective activity. The presence of methoxy group (either in 4, 9 or 7-position as methoxyphenyl) and through the appropriate substitution in 6-position with alkylaminomethyl group, furoflavones exhibited good gastroprotective activity in the ethanol damage model [116].

**Fig. 12.** Compounds with anti-diabetic activity.

Several analogs flavones have been synthesized by Outt et al., and evaluated for their gastroprotective properties in the rat ethanol-induced damage model. The chromone with heterocycle moiety **119a** or methoxydiketone **119b** showed good gastroprotective activity. A C₂–C₃ double bond and an intact C ring appear necessary for optimum activity. Activity can be retained by replacing the 2-phenyl substituent with other groups but is eliminated when this ring is moved from the 2- to the 3-position [117]. Mono- and disubstituted flavone are synthesized and screened for their gastroprotective activity in the rat ethanol-induced damage model. Substitution with methoxy or hydroxy groups in the 3-, 6-, or 8-positions led to reduction in gastroprotective activity. In the 5-position, substitution with a methoxy group **120a** provided a high level of gastroprotection. All other substitutions in the 5-position led to reduction in activity. In the 7-position, two of the substituents examined (methoxy, **120b** and methyl, **120c**) produced a potent level of gastroprotection. The addition of fluorine to the 4'-position **120d** or addition of a trifluoromethyl to the 3'-position **120e** produced levels of gastroprotective activity comparable to the parent compound. Out of these compounds, 5-methoxy-4'-fluoroflavone **120d**, has also shown gastroprotective activity following oral administration in the rat indomethacin damage model [118] (Fig. 15).

3.12. Antihistaminic agents

Histamine is an intercellular chemical messenger and plays a critical role in several diverse physiological processes. Four human



Protection at a dose of 300 mg/kg in scPTZ test (**107-109**) = 100%

Fig. 13. Compounds with anti-convulsant activity.

G-protein coupled histamine receptor subtypes (H_{1-4}) are currently recognized to mediate various actions of monoamine histamine. Among the four subtypes, the histamine H_1 receptor has been an attractive target for drug discovery for several years and H_1 receptor antagonist have proved to be effective therapeutic agents for respiratory distress, thus contributing to an important class of drugs today [119].

A series of 2-phenyl-4H-chromen-4-one analogs was evaluated for the H1 antihistaminic activity computational method. Compound **121a** and **121b** showed the highest antihistaminic activity [120]. Chromone moiety with (diphenylmethylene)-, (diphenylmethylb, or (diphenylmethoxy)piperidine *via* an alkyloxy spacer, synthesized and tested for their inhibitory effects on both histamine- and LTD₄ -induced contraction in isolated guinea pig

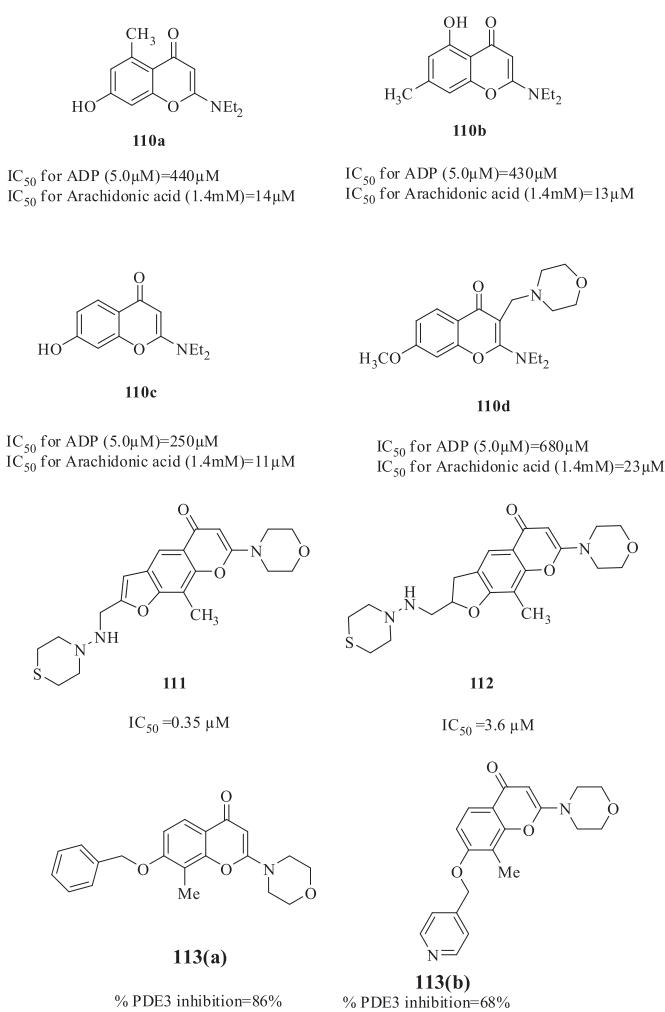


Fig. 14. Structures of compounds with anti-platelet activity.

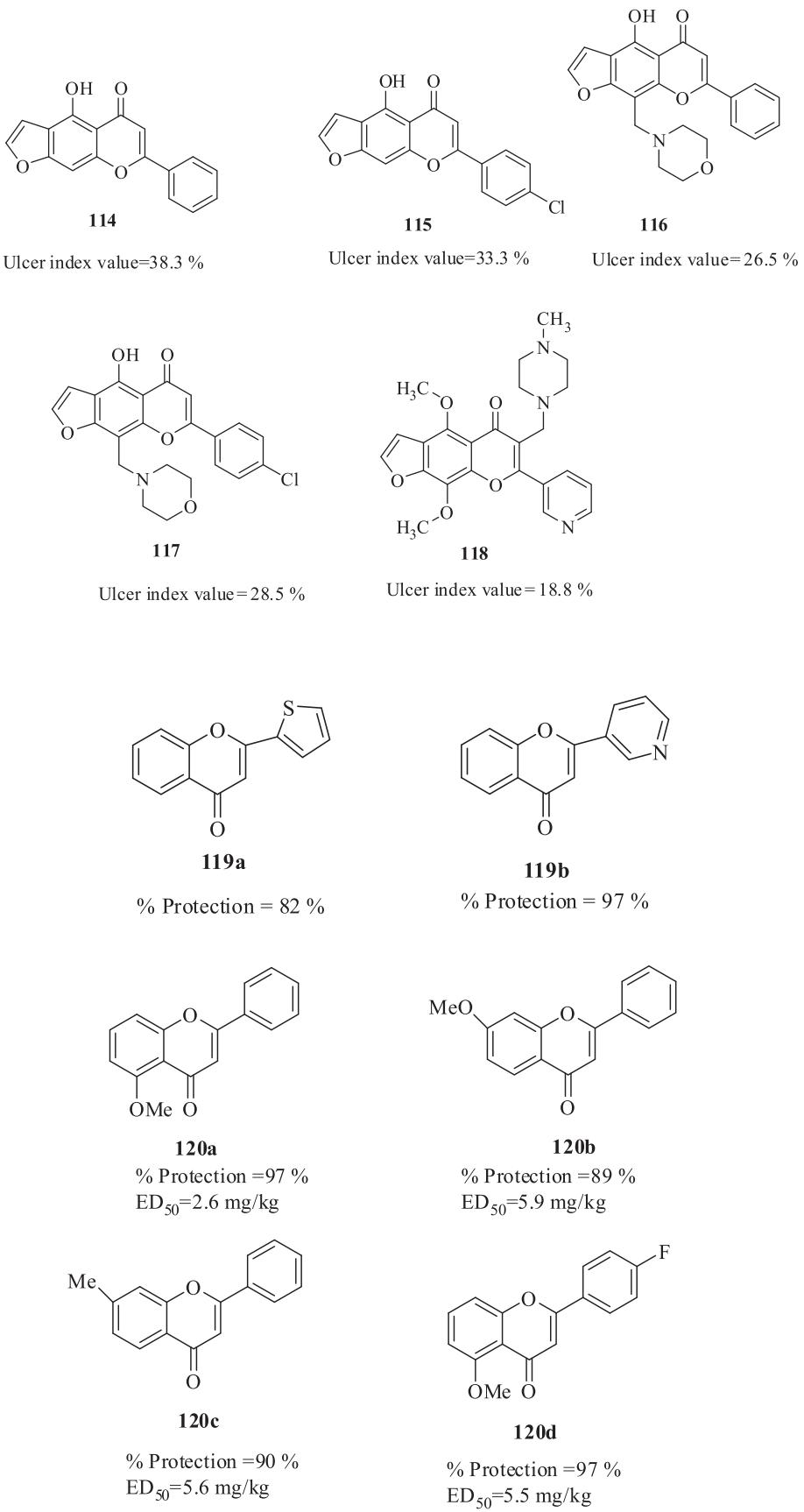
ileum. Some compounds showed more potent antihistaminic activity than the reference drug terfenadine. Chromone derivative **122a** with propyl substituent is potent as compared to the butyl, pentyl, and hexyl congeners. The compounds of this series also showed moderate anti-LTD₄ activity with a few members being equipotent to the reference agent FPL55712. One compound of this series **122b** identified to inhibit both *in vitro* and *in vivo* action of histamine and LTD₄ [121] (Fig. 16).

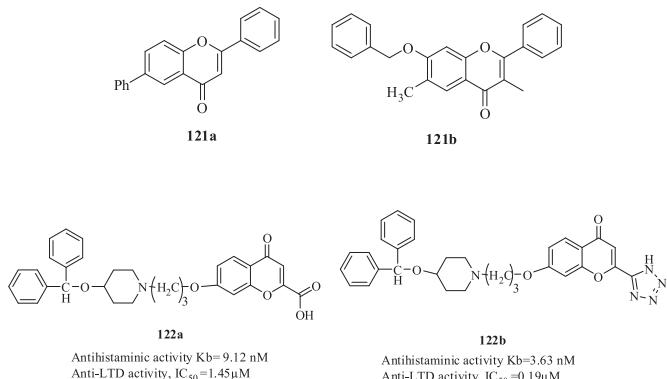
3.13. Antihypertensive agents

New therapeutic approaches in the management of hypertension have been directed toward modification of autonomic nervous activity by various agents such as dopamine receptor agonist inhibitors of dopamine β -hydroxyl sympatholytics associated with catecholamine depletion [122]. (3-Phenylflavonoxy)propanolamines is synthesized by Wu et al., and evaluated for potential antihypertensive activity in spontaneously hypertensive rats, as well as for *in vivo* and *in vitro* evidence of β -adrenoceptor antagonism. Some of the compounds of this series exhibited effective antihypertensive properties but did not antagonize β -adrenergic receptors. The compounds in lowering systolic blood pressure of SHR were the n-propyl-substituted compound **123a** and the cyclopropyl-substituted compound **123b**. Both compounds were active in lowering blood pressure at 8 mg/kg, PO; however, **123a** exhibited a much longer duration of activity than did **123b** [123]. Flavonoxypropanolamines was prepared and evaluated for their antihypertensive activity in male spontaneously hypertensive rats (SHR) of the Wistar-Kyoto strain. Arterial systolic blood pressure was measured by indirect tail cuff method. The greater activity of the straight *N*-alkyl analogs (**124a** and **124b**) and *N*-cycloalkyl analogs relative to their branched *N*-alkyl isomers (**124c** and **124d**) reveals the steric preference for a linear or cycloalkyl radical substituted on the nitrogen atom. A structure–activity relationship of these derivatives indicates that the position of the oxypropanolamine side chain, the hydroxy group of the side chain, steric bulkiness and length of *N* substituents, degree of the *N*-substitution, phenyl group at the 2-position of the chromone nucleus, and substituents of the phenyl group or B ring of the flavones play significant roles in imparting pharmacological effects [124] (Fig. 17).

3.14. Calpain inhibitors

Calpains are calcium-dependent, intracellular proteolytic enzymes and found in many cells. Calpains are referred to as cysteine proteases because they include a cysteine residue in the catalytic process. Excessive calpain activation contributes to serious cellular damage or even cell death and has been found in a number of pathological conditions, for example, cerebral ischemia, myocardial infarction, traumatic brain injury, Alzheimers disease, cataract of eyes, and inflammation to implicate that these diseases are presumably associated with elevated intracellular calcium concentrations [125].

**Fig. 15.** Compounds with gastroprotective agents.

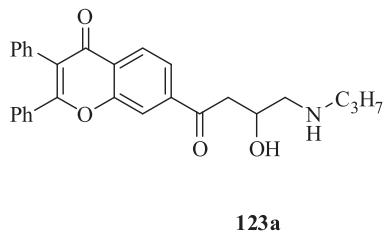
**Fig. 16.** Compound with anti-antihistaminic agents.

Chromone carboxamide derivatives were prepared by Lee et al., and evaluated for μ -calpain inhibition using a casein-Coomassie blue microplate assay. Compound **125c**, the most potent calpain inhibitor of this series ($IC_{50} = 0.24 \mu\text{M}$), exhibited 14.4% and 22.4% inhibition on the activities of cathepsin B and cathepsin L, respectively, at the same concentration, demonstrating high selectivity of

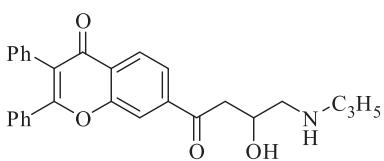
chromone derivatives for μ -calpain. The introduction of dioxane ring in the chromone ring generally resulted in the decreased inhibitory activity of the parent compound irrespective of amide; however, amide substituents were also important in the activity. Compounds **125a** and **125c** possessing benzyl and phenethyl amide showed good inhibition of μ -calpain, while the potencies were decreased about 10-fold when these substituents were replaced by 2-(morpholin-4-yl)ethyl or isopropyl amide [126]. New chromone carboxamide derivatives synthesized and evaluated using human calpain I isolated from erythrocytes, and Suc-Leu-Tyr-AMC as the fluorogenic substrate and also antioxidant activities by DPPH scavenging and lipid peroxidation inhibitory effects. Compounds with 4-methoxyphenethyl group at the keto-amide position, i.e., **126a** and **126b** exhibited the most potent μ -calpain inhibitory activities ($IC_{50} = 0.09\text{--}0.10 \mu\text{M}$), and compound **126c** showed both potent μ -calpain inhibitory activity ($IC_{50} = 0.28 \mu\text{M}$) and antioxidant activities in DPPH scavenging and lipid peroxidation inhibition assay [127] (Fig. 18).

3.15. Insecticidal activity

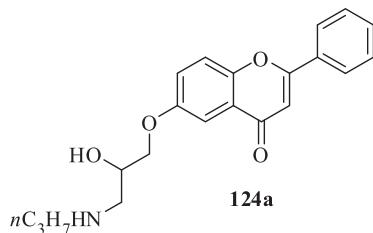
A series of chromanone and chromone analogs of diacylhydrazine derivatives synthesized Yang et al., and evaluated for insecticidal activity against *Aphis medicagini* (*A. medicagini*),

**123a**

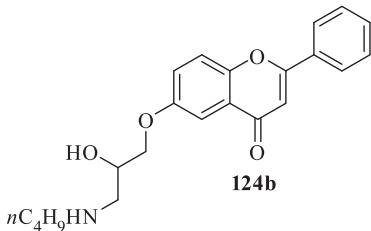
Lowering BP at 8 mg/kg
Antihypertensive activity in SHR= 191 mmHg

**123b**

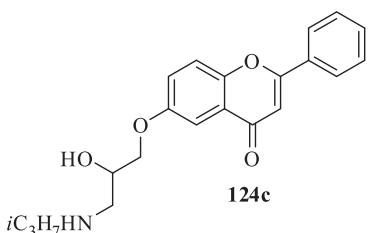
Lowering BP at 8 mg/kg
Antihypertensive activity in SHR= 188 mmHg



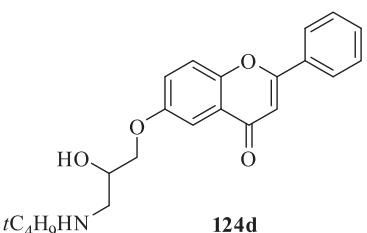
Antihypertensive activity in SHR= 196 mmHg



Antihypertensive activity in SHR= 202 mmHg

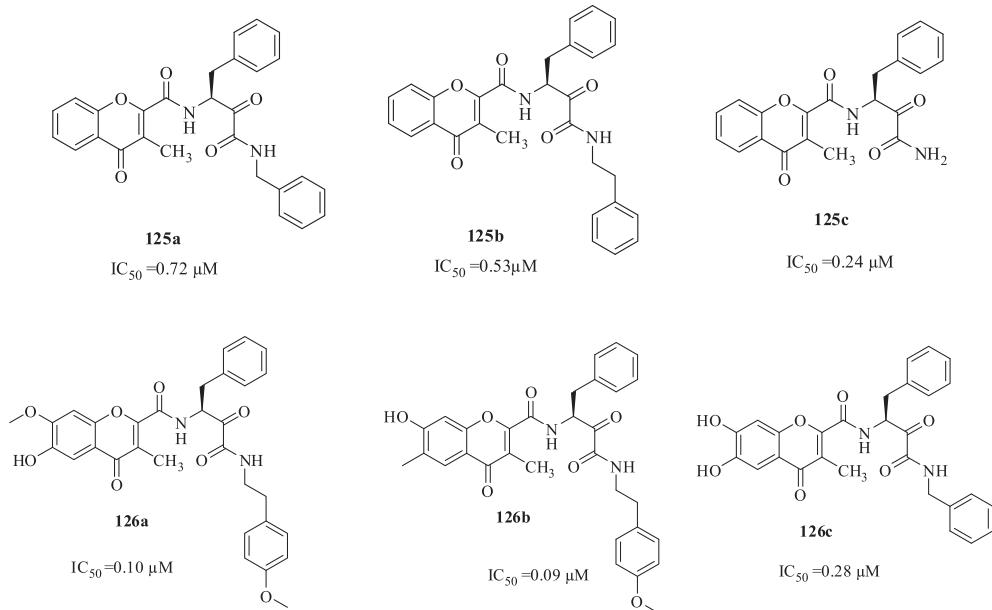


Antihypertensive activity in SHR= 199 mmHg



Antihypertensive activity in SHR= 201 mmHg

Fig. 17. Compound with antihypertensive agents.

**Fig. 18.** Structures of Calpain inhibitors.

Nilaparvata legen (*N. legen*), *Mythima separata* (*M. separata*), and *Tetranychus cinnabarinus* (*T. cinnabarinus*) at the dosage of 500 mg/L. Some of the chromanone analogs exhibited good insecticidal activity against *M. separata*, especially the compounds, **127a**, **127b**, and **127c** are showed 80%, 84.2%, and 100% inhibition respectively [128] (Fig. 19).

3.16. Enzyme and receptor agonists/antagonists

Several chromone derivatives have been reported to act on various enzymes and receptors. Some examples of chromone acting as agonists or antagonists of various receptors and enzymes are listed in Table 4.

3.17. Patent literature

A series of chromone compounds as S-nitrosoglutathione reductase (GSNOR) inhibitors synthesized by Sun et al., These

GSNOR inhibitors can be utilized in any pharmaceutically acceptable dosage form, including but not limited to injectable dosage forms, liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, dry powders, tablets, capsules, controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, etc. The some of the compounds **143(a–c)** have showed IC_{50} less than 0.5 μM and compound **(143d)** showed IC_{50} less than 0.1 μM against the GSNOR inhibitors [144]. 6',2-(2'-Arylchromonyl) propionic acids synthesized and screened for anti-inflammatory and analgesic by the carrageenan induced edema and acetic test methods. Compounds **144(a–e)**, showed good analgesic activity compared with aspirin as a control. Compounds **144(a–d)** showed good anti-inflammatory activity compared with phenylbutazone [145].

Jia and Farrow have reported 7-hydroxychromes (7-HC) (**145a–b**) that exhibit potent antioxidant activity and 7-HC derivatives are effective in inhibiting free radical and oxidation caused damage through the simultaneous suppression of free radical generation and the suppression of the production of reactive oxygen species (ROS). This also includes methods for preventing and treating ROS mediated diseases and conditions and diseases and conditions associated with other oxidative processes. The method for preventing and treating ROS mediated diseases and conditions with other oxidative processes is comprised of administering to a host in need thereof an effective amount of a composition comprised of a 7-hydroxychrome or a mixture of 7-hydroxychromones and a pharmaceutically acceptable carrier [146,147]. Warren et al., have synthesized substituted cycloalkenochromones (**146**) and the anti-allergic activity was determined by measuring the inhibition of allergic release of spasmogens from mean percentage of cells undergoing degranulation in the tubes treated with phospholipase A (PL-A) only, and “2” represents the mean percentage of cells undergoing degranulation in the PL-A-negative tubes. The cromoglycate compound has also been shown to specifically inhibit the allergic release of

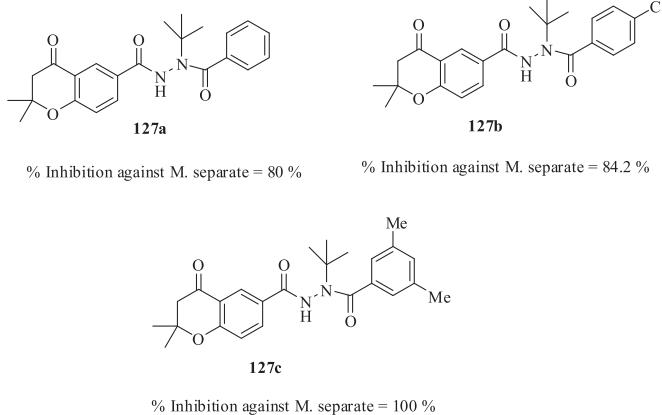
**Fig. 19.** Compound with insecticidal activity.

Table 4

Chromone derivatives that act on enzymes/receptors.

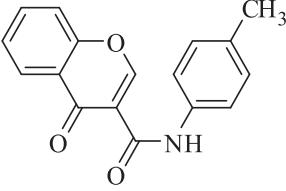
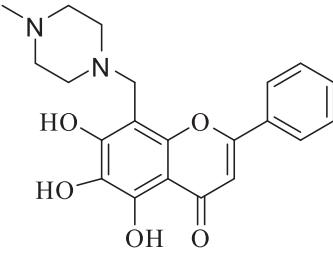
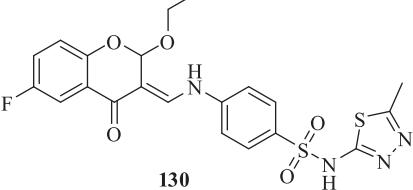
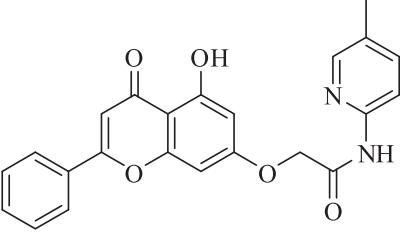
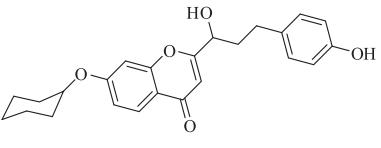
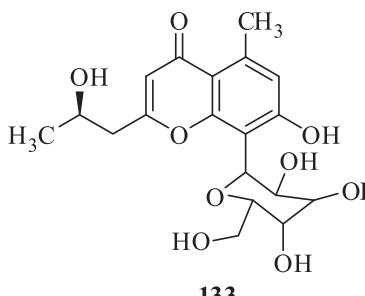
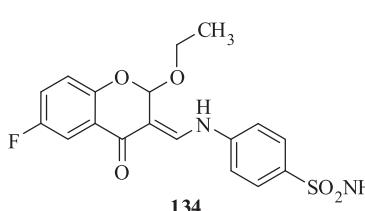
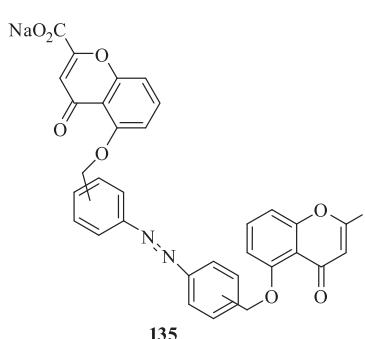
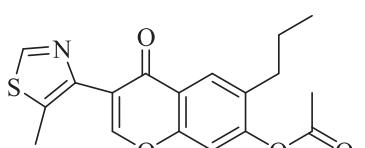
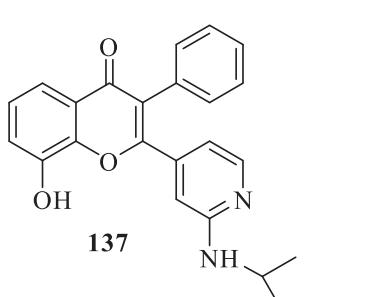
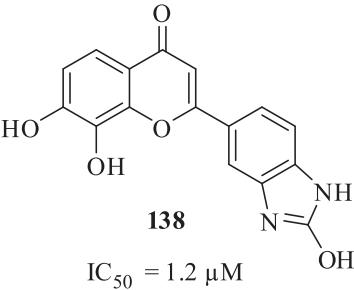
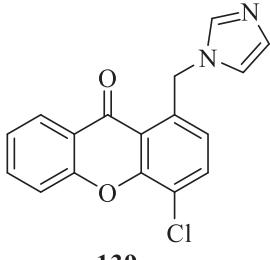
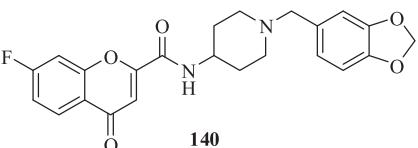
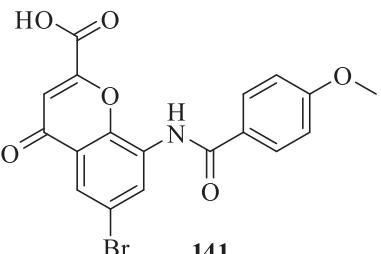
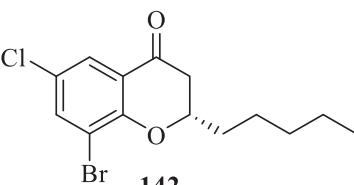
S. No	Structures	Enzyme/receptor	Activity	Ref.
1		Monoamine oxidase (MAO-B) inhibitors	Antagonists (neurodegenerative diseases)	[129]
	128			
	$IC_{50} = 0.068 \mu M$			
2		Cyclin-dependent kinases (CDK1/cyclin B inhibitors)	Antagonists	[130]
	129			
	$IC_{50} = 0.27 \mu M$			
3		Alkaline phosphatases	Antagonists	[131]
	130			
	$IALP (K_1 \mu M) = 0.01$ $TNALP (K_1 \mu M) = 21$			
4		Wid type-Break-point cluster region-Abelson (BCR-ABL) tyrosine kinase	Antagonists	[132]
	131			
	$ABL (IC_{50} \mu M) = 0.26$			
5		Interleukin-5 inhibitors	Antagonists	[133]
	132			
	$IC_{50} = 4.0 \mu M$			

Table 4 (continued)

S. No	Structures	Enzyme/receptor	Activity	Ref.
6	 133	Mushroom tyrosinase inhibitors	Antagonists	[134]
	% Inhibition = 91.33%			
7	 134	Inhibitors of bovine cytosolic carbonic anhydrase	Agonist/antagonist	[135]
	$IC_{50} = 4.31 \mu M$			
8	 135	Photoswitchable Mast Cell Activation Inhibitors	Antagonists	[136]
	$IC_{50} = 100 \mu M$			
9	 136	Adenosine A _{2A} Receptor	Antagonists	[137]
	A2ApK1 = 8.51			
10	 137	p38 MAP kinase inhibitors	Antagonists	[138]
	$IC_{50} = 17 \text{ nm}$			

(continued on next page)

Table 4 (continued)

S. No	Structures	Enzyme/receptor	Activity	Ref.
11		Telomerase Inhibitors	Antitumor activity	[139]
	138 $IC_{50} = 1.2 \mu M$			
12		Steroid 11β-Hydroxylase Inhibition	Antagonist	[140]
	139 CYP19 $IC_{50} = 480 \text{ nm}$ CYP17 $IC_{50} = 260 \text{ nm}$			
13		Melanin Concentrating Hormone Receptor 1	Antagonist	[141]
	140 IC_{50} for Ca flux= 29 nM IC_{50} for hERG= 15.1 nM			
14		Orphan G Protein-Coupled Receptor GPR35	Agonists	[142]
	141 $hGPR35 K_D = 5.27 \mu M$			
15		<i>Sirtuin 2</i> -Selective Inhibitors	Antagonists	[143]
	142 $SIRT2 IC_{50} = 1.2 \mu M$			

spasmogens in immediate hypersensitivity reactions in several animals [148].

The quinolinyl-chromone (**147**) conjugated compounds synthesized by Huang et al., and their pharmacological activity particularly as lipoxygenase inhibitors and/or leukotriene antagonists possessing anti-inflammatory and anti-allergic properties screened. Some of the tested compounds for this invention exhibit valuable properties which are useful in the treatment of inflammatory conditions and allergic responses [149]. Aono and Mizuno have synthesized some chromone derivatives (**148**, **149**) and screened for M5076 tumor cells and some of the compounds showed a strong antitumor activity [150]. 5-Substituted chromones (**150**) and their salts were synthesized, and their antiallergic activity of the compounds determined by a passive cutaneous anaphylaxis reaction (PCA reaction). All compounds tested advantageously exhibited oral antiallergic activity when administered at a concentration of 30 mg/kg [151]. Igarashi et al., have synthesized a series of chromone derivative (**151**) as an aldose reductase inhibitor. The synthesized compounds exhibit superior inhibitory action on aldose reductase and are useful for the treatment of

various complications of diseases in diabetes, such as cataract, retinopathy, keratopathy, nephropathy, and neuropathy [152] (Fig. 20).

4. Conclusions

Chromone and its analogs have proved for of potentially great importance in medicinal chemistry and drug development. They come from a wide variety of natural sources and new chromone derivatives are being discovered or synthesized on a regular basis. Chromone is a simple molecule and many of its derivatives have been known for more than a century. These scaffolds might bind to a multitude of receptors and therefore their synthesis represents a promising way for new lead compounds. This article has outlined the chemistry and pharmacological activities of chromone scaffold. There is much scope in this promising moiety as a number of different molecular targets, future investigations of this scaffold could give some more encouraging results in the field of medicine. It is anticipated that this information would give rise to design of better molecules with enhanced biological properties and higher

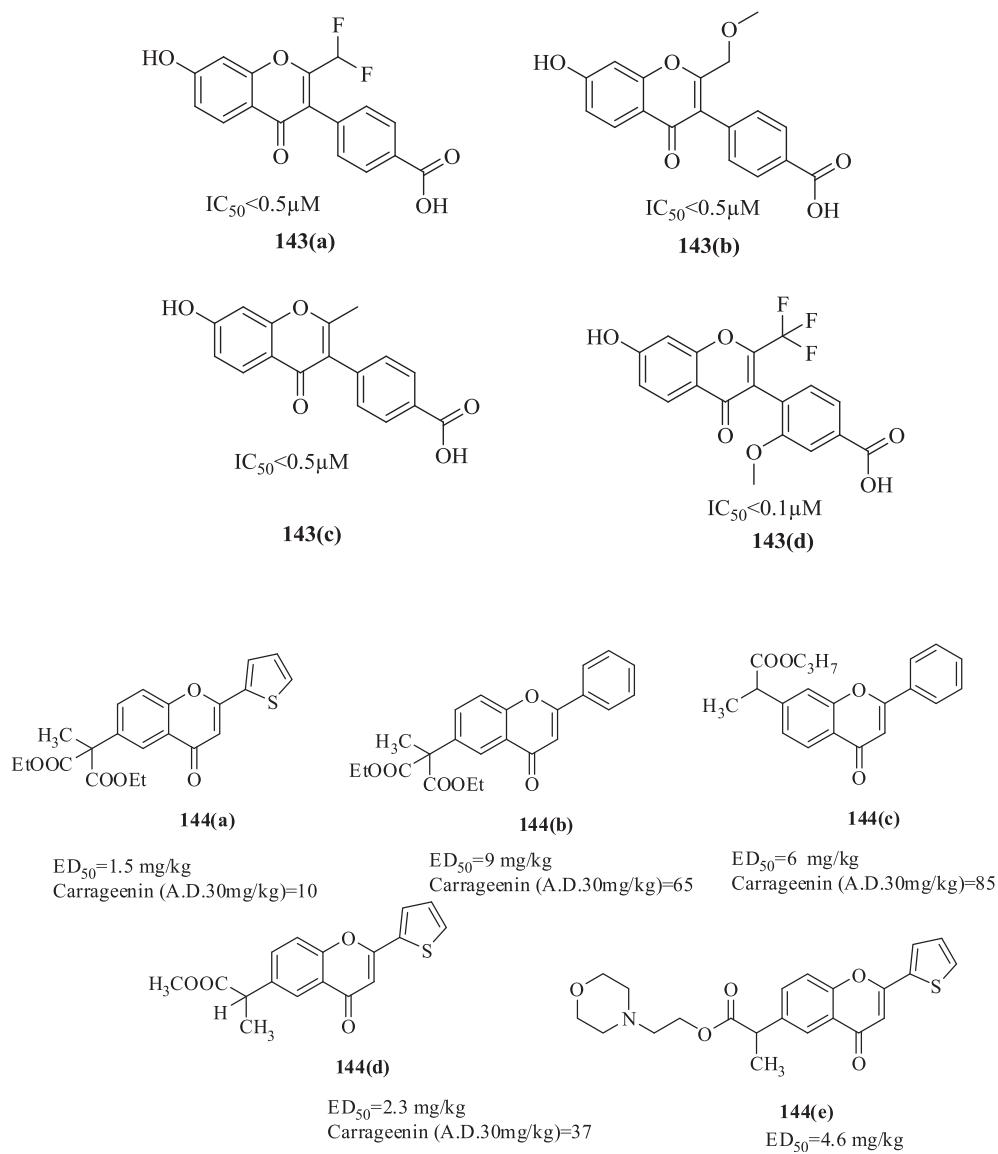


Fig. 20. Compounds with miscellaneous activities.

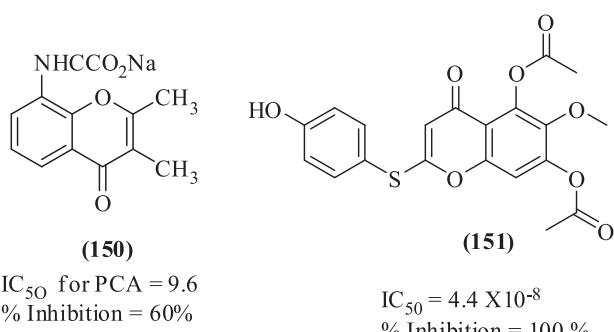
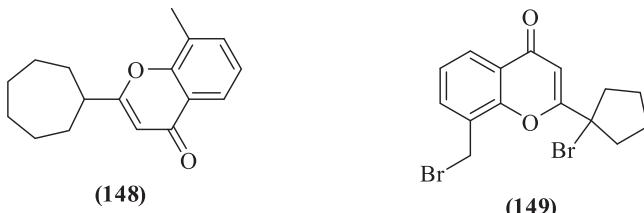
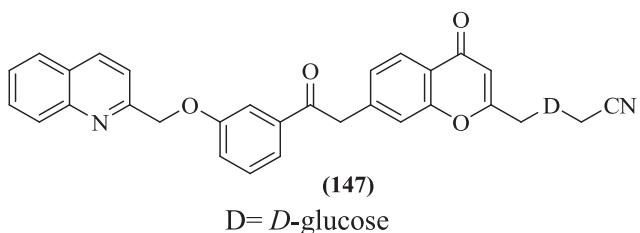
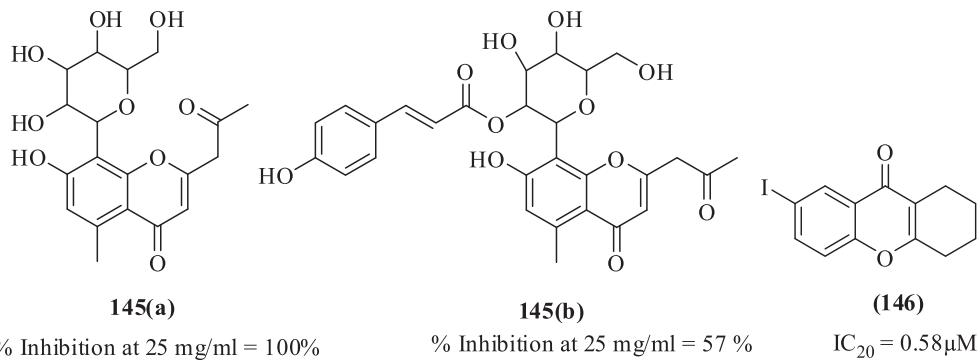


Fig. 20. (continued).

specificity, and together with development of novel synthetic strategies.

Acknowledgments

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Glossary

AIDS: acquired immune deficiency syndrome

COX: cyclooxygenase

DNA: deoxyribonucleic acid

DPH: 2,2-diphenyl-1-picrylhydrazyl

FRAP: ferric reducing antioxidant power

HCT: human colon cancer cells

HIV: Human immunodeficiency virus

Hep G2: human liver-derived cells

LDL: low density lipoproteins

MCF-7: breast human cancer cell line

MDR-TB: multi-drug-resistant tuberculosis

f-MLF: formylmethionine-leucine-phenylalanine

MES: maximal electric shock induced seizures

MIC: minimum inhibitory concentration

MTB: mycobacterium tuberculosis

MTT: 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide

NAD: nicotinamide adenine dinucleotide

NK: natural killer

NSAID: non-steroidal anti-inflammatory drugs

iNOS: nitric oxide synthase

PBMC: peripheral blood mononuclear cells

PC: prostate carcinoma cell

PMA: phorbol myristate acetate

ROS: reactive oxygen species

RT: reverse transcriptase

SAR: structure–activity relationship

2-SC: 2-styrylchromones

scPTZ: subcutaneous pentylene tetrazole induced seizures

TB: tuberculosis

TNF: tumor necrosis factor

WHO: world health organization