Asian Journal of Chemistry; Vol. 35, No. 4 (2023), 771-793

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.23442

REVIEW

Synthetic Routes and Biological Activities of Chromone Scaffolds: An Overview

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Received: 26 November 2022; *Accepted*: 10 February 2023; *Published online*: 30 March 2023; AJC-21174

The central backbones of natural assets and therapeutic medications are chromone and flavone. Utilizing such preferred chalcone analogs in drug research has shown a successful blueprint, yielding new hits/leads and fast optimization procedures. Chromone can create novel molecules with pharmacological promise, particularly in neurological, inflammatory, infectious diseases, cancer and diabetes. The current perspective focuses mainly on flavones and flavonoids of biological significance, such as chromon-4-one analogs, both synthetic and natural sources. Furthermore, because drug repurposing is now a popular drug discovery strategy, current chromone-based medication repurposing research is discussed. As well the methods utilized to synthesize chromones and their derivatives are described in detail in this review. Since it's uses in so many pharmacologically active substances, the stiff bicyclic chalcone fraction has been described as a preferred scaffold in drug development, with few instances as therapeutic agents. Due to their photochemical characteristics, chromone analogs are also utilized as scaffolds for creating bioactive molecules and their application in drug development, such as the production of fluorescent probes.

Keywords: Biological activity, Anti-inflammatory, Anticancer, Antiallergic, Synthesis, Chromone, Chalcones, Applications.

INTRODUCTION

Heterocycles are crucial in the development of new physiologically and pharmacologically active medicinal molecules. Many medications contain mostly vitamins, many natural products, biomolecules and physiologically active chemicals. In synthetic pharmaceuticals and agrochemicals, they are typically found as significant structural units. Solvatochromic, photochromic and biochemi-luminescence characteristics are also present in some of these substances. Chromones are a type of heterocycle that can be found in abundance in plants. Plants create a variety of secondary metabolites, which make up these chemicals. They have colouration in the majority of cases. The flavonoid family includes chromones. They are heterocyclic compounds that contain oxygen and have a benzo-annelated γ-pyrone ring. From algae to conifers, these chemicals and their derivatives have been discovered. They play various roles in plants, including growth maintenance, dormancy inhibition and oxygen uptake stimulation. The most naturally occurring chromone derivatives are eucryphin (rhamnoside of chromone) and 6,7-dimethoxy-2,3-dihydrochromone, both obtained from the bark of *Eucryphia cordifolia* and *Sarcolobus globosus*, respectively. Flavones and isoflavonoids are made up of chromone rings, which are the central structural unit. They are classified as simple chromones and fused chromones, respectively, because of the chromone family's great diversity [1-6]. Chalcones, flavones, flavanones, flavanols and anthocyanidins are among various flavonoids based on their molecular structures (Fig. 1). These natural chemicals are found in ferns, conifers and flowering plants [7-9] and numerous prolific plant secondary metabolites. Many flavonoids have been seen as powerful pigments in flowers, fruits and leaves, offering a spectrum of blue, yellow and red colours [10-13]. Besides having numerous pharmacological advantages, *e.g.*, anticancer, antiallergic, anti-inflammatory, antiviral, *etc.* flavonoids are effective metal chelators, antioxidants and radical scavengers [14-17]. Flavonoids are widely dispersed in the human diet [8,10]. They are thought to be harmless, attracting a lot of interest in developing new therapeutic agents for various disorders.

Chalcones: Chalcones, also known as 1,3-diphenylpropenones (Fig. 2), are among the most common flavonoids found in fruits, soy, tea and vegetables [8,18]. Since ancient times,

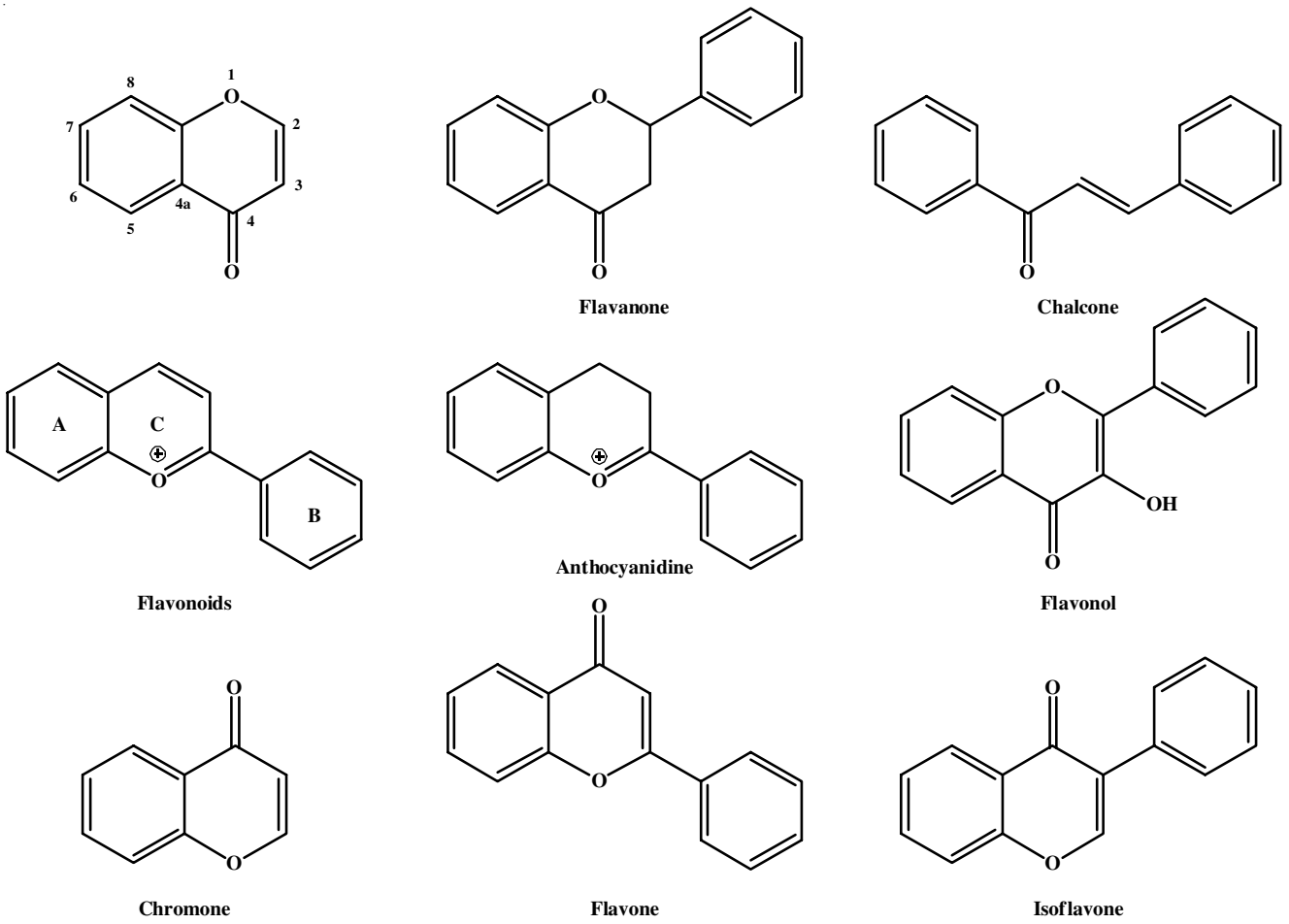


Fig. 1. Basic structures of chromone and chromone derivatives

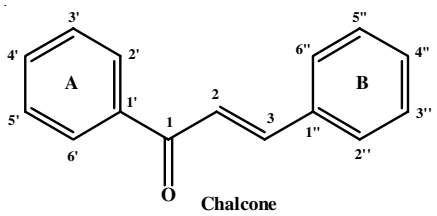


Fig. 2. Numbering and general structure of chalcones moiety

chalcones have been used for medicinal purposes [19] and are connected to the thousands-year-old use of herbs, plants and shrubs to treat various medical ailments. Recent researches have found that chalcones have a broad range of pharmacological activities such as antiproliferative, anticancer, antioxidant and anti-inflammatory [19-22].

The synthesis of flavanones and flavones requires the use of chalcones as a precursor. They are often made from acetophenones and benzaldehydes, employing a polar solvent base (Fig. 3) [23-25]. More unusual synthesis procedures, such as the palladium-arbitrate Suzuki coupling of phenylboronic acids and cinnamoyl chloride or the carbonylative Heck coupling of styrenes and aryl halide or alkyl halides in the presence of CO gas, have also been described [26,27].

Chromone 4-ones and chromones as bioactive chemical scaffolds: The chromone ring system, *i.e.* chromen-4-one, is a crucial component in diverse flavonoids, including flavonols, isoflavones, flavan-3-ols, flavones and flavanones [28]. Chromone is an essential family of oxygen-containing alkaloids having a benzoannelated pyrone ring, such as chromen-4-one or benzopyran-4-one [29]. The word chromone comes from the Greek word "chroma," which means "colour," suggesting that numerous chromone analogs are available in various pigments. From algae to conifers, chromone and similar chemicals are found across the plant world.

Compounds with a chromone moiety are synthetically flexible compounds with a reactive carbonyl group important for their nucleophile reactivity, allowing for creating a diverse range of heterocycles. The substitution pattern determines the biological effects of chromone scaffolds. Chromones are involved in various processes, including dormancy inhibition, growth control, indole ethanoic acid oxidation, cytokinin-like activity and oxygen uptake stimulation in plant tissue [30]. As a result, chromones and chromone-4-ones are regarded as favoured structures, defined as "a single molecular framework able to provide ligands for diverse receptors".

Chromones' natural occurrence and medicinal action: Antiviral, antimicrobial, anti-inflammatory, anticonvulsant, antioxidant and anticancer activities are among the pharmacological effects of natural and synthetic chromone derivatives. In medicinal chemistry, the chromone nucleus is a fundamental

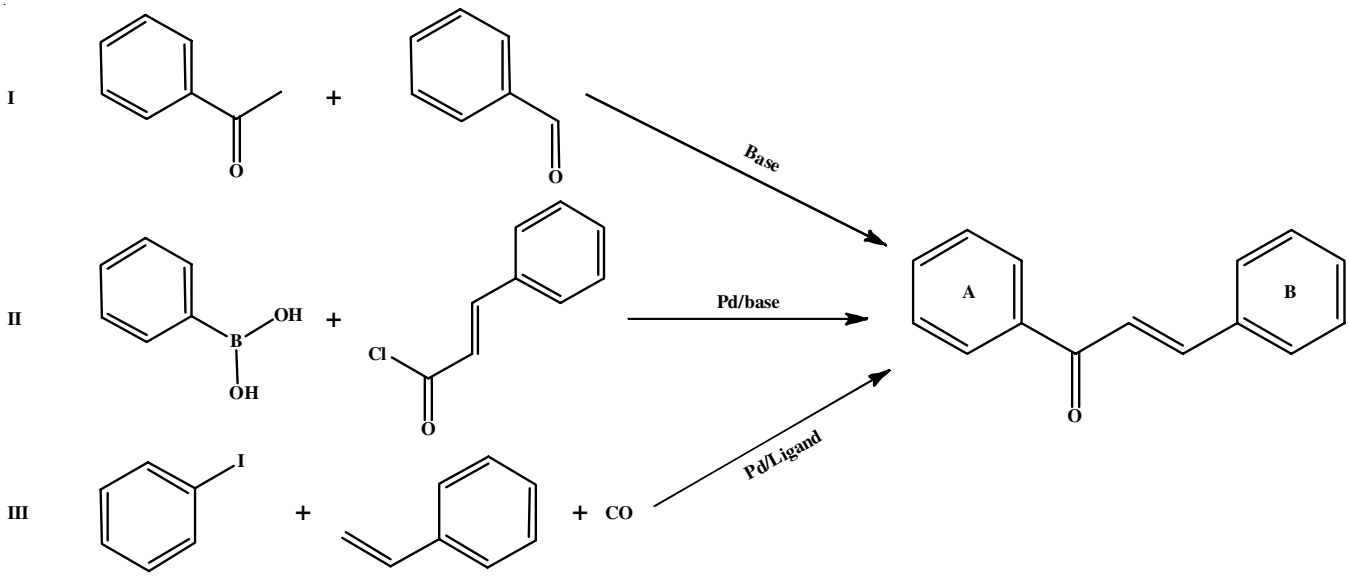


Fig. 3. Various pathways to synthesize chalcones analogs

structural unit. The chromone units have been widely used to synthesize numerous medicines with varying pharmacological actions due to their significance [31-37]. Cromolyn, nedocromil, diosmin, apigenin, flavoxate and khellin are common chromone medicated compounds (Fig. 4) available in the market. Cromolyn is a sodium salt which is the disodium salt of cromoglycic acid, a *bis*-chromone acid derivative used to treat mastocytosis. Nedocromil is a pyranoquinoline acid derivative chemically called nedocromilo, used as an inhaled anti-inflammatory medication to prevent asthma.

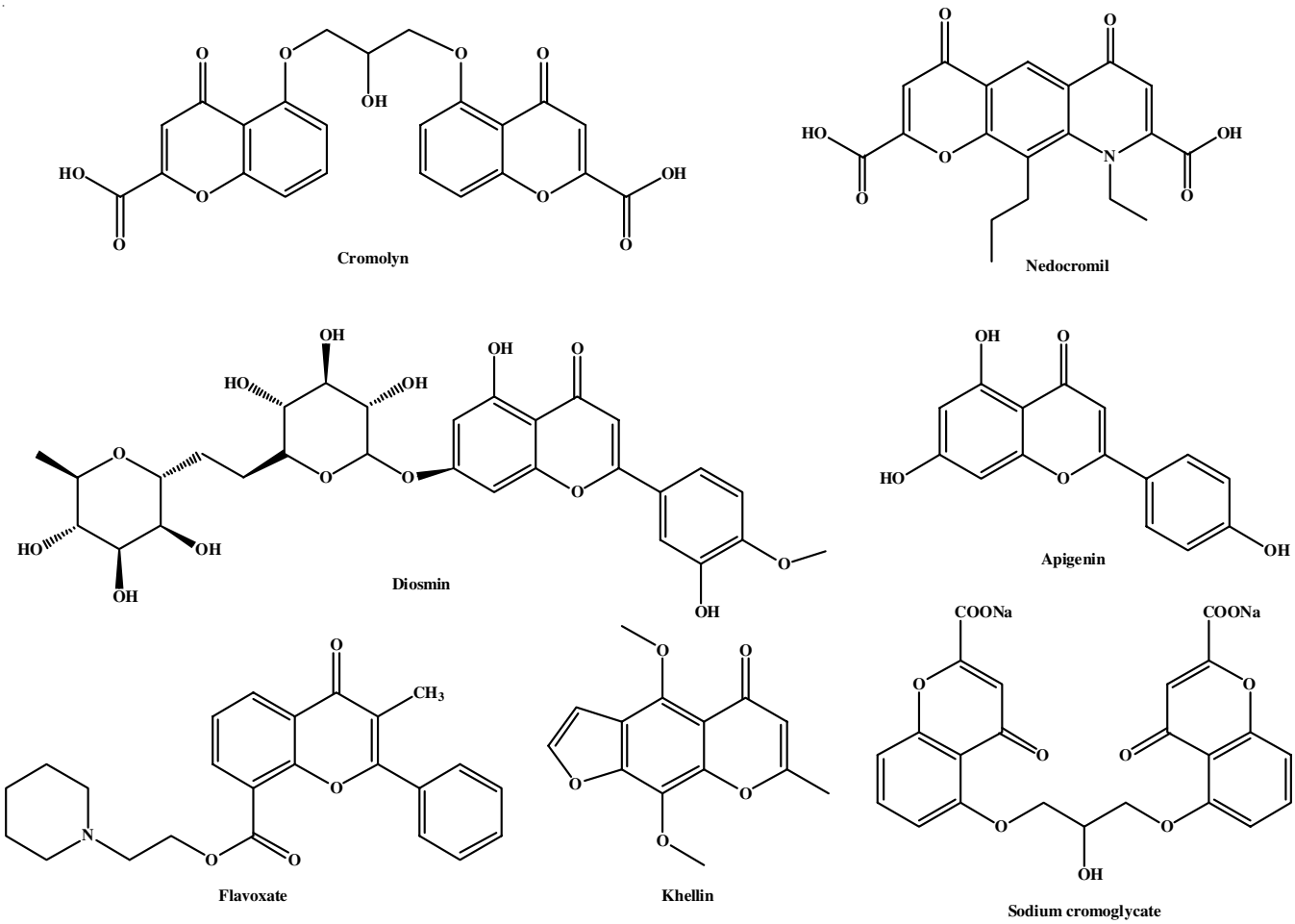


Fig. 4. Compounds with chromone moiety being used as pharmaceutical agents.

Diosmin is a sugar substituted chromone derivative extracted mostly from citrus fruits but may also be synthesized. Diosmin is most often used for hemorrhoids and leg sores caused by poor blood flow and is used to treat various blood vessel problems, including hemorrhoids, varicose veins, venous stasis and eye or gum bleeding. Apigenin (4′,5,7-trihydroxyflavone), also known as chamomile or versulin, is a plant extracted chromone derivative utilized in cancer treatment. Flavoxate, called antimuscarinics, is a muscle relaxant used to treat the bladder and urinary system. Khellin was a furan annulated chromone derivative called furanochrome that has the primary effect of being a vasodilator. Chromen-5-one is a herbal folk medicine used to cure various ailments, including kidney stones, psoriasis, vitiligo, bronchial asthma, coronary artery disease and renal colic [38-42].

Anticancer drugs: Currently, cancer is the leading cause of death. Different types of cancers have been identified which are responsible for the death of patients. All types of cancer involve the uncontrolled proliferation of cells. This results in excess growth and formation of tumors which have the capacity to metastasize. Different cancer therapies include chemotherapy, immunotherapy, radiotherapy and monoclonal antibody based treatment; various drugs used for cancer target different cellular molecules. Chromone scaffold-based drug targets (Fig. 5) have been developed and successfully utilized in cancer therapy [43]. Some of the distinct areas in which chromone based cancer therapy has been applied are summarized below. Phosphatidylinositol 3 kinase inhibitors (PI_3K) are key proteins involved in cell signaling pathways. The inhibition of this protein results in cell death. LY-294002 is a reversible chromone-based PI_3K inhibitor used in prostate cancer treatment [44]. Cyclin dependent kinases (CDK) are involved in DNA proliferation and cell division. Targeting CDK thus would help in the killing of cancer cells. Flavopiridol is a chromone based derivative used as a CDK-based drug to target cancer cells [45].

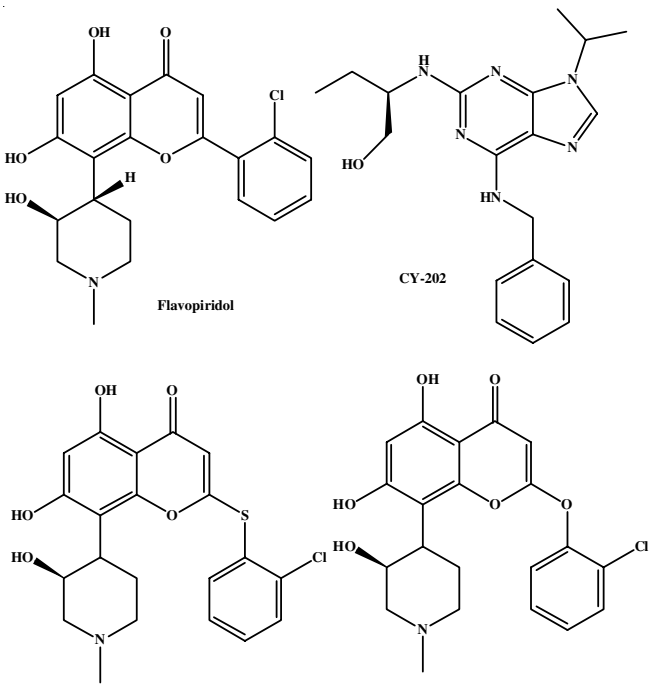
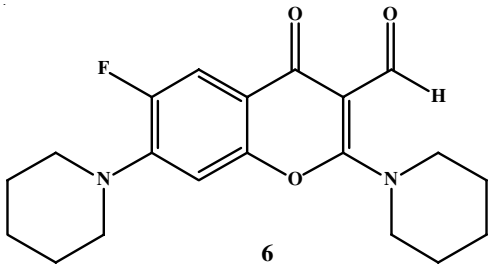


Fig. 5. Chromone derivatives used as CDK inhibitors in cancer-based therapy

Similarly, chromone based scaffold drugs have been developed for targeting DNA-dependent protein kinase inhibitors [46], topoisomerase inhibitors [47] and drug transport inhibitors [48], respectively. Liu *et al.* [49] reported a chromone analogs with a heterocyclic thioether group and tested their anticancer efficacy. The IC_{50} of compound 3-(benzothiazole-2-ylsulfanyl)-chromen-4-one over the MDA-MB-435S cell line was determined and output to be 17.2 M out of these. They led to the realization that adding cyclic tertiary amine or heterocyclic thioether to chromone anticancer action would be beneficial.

Yuan *et al.* [50] produced three methylated quercetin and a series of 3-substituted,3,4-dimethyl substituted quercetin, tetramethylated quercetin moiety and investigated their anticancer potential. Huang *et al.* [51] created a novel class of quercetin derivatives with great success. As inhibitors of Src tyrosine kinase, the new drugs have a better selectivity. IC_{50} cell line values range from 3.2 to 9.9 mM better selectivity than the EGFR tyrosine kinase. Selectivity requires both hydrogen bonding and hydrophobic interactions, according to molecular docking. Liu *et al.* [52] produced ester derivatives of chromone, including chromone family isoflavonequinone and tested their cytotoxicity in LPS-activated murine macrophage cell culture systems using the MTT assay method.

Liu *et al.* [53] investigated ten novel 3-(2-(3-methyl-5-substituted-phenyl-4,5-dihydropyrazol-1-yl)-2-oxo-ethoxy)-2-substituted-phenyl-4*H*-chromen-4-one variants for pharmacological activities such as anticancer activity. Compounds showed high potential activity against the human gastric cancer cell line (SGC-7901) apoptosis in bioassay experiments. Ishar *et al.* [54] investigated new 6-fluoro/chlorochromone compounds as anticancer topoisomerase inhibitors that function in DNA replication (**6**).



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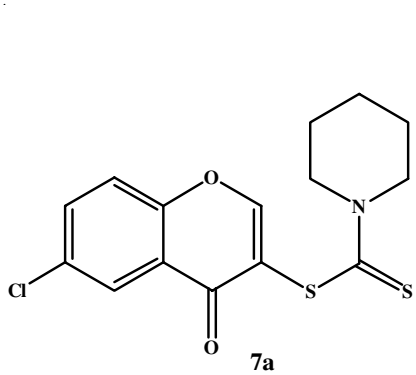
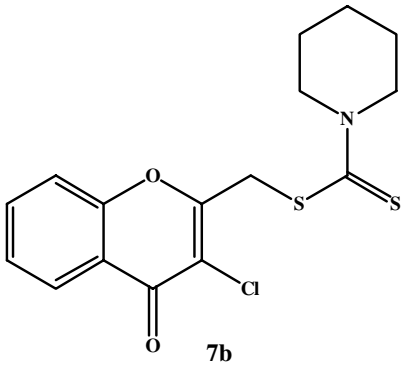
The anticancer activity of a flavonoid moiety containing synthetic compounds and (6-chloro-4-oxo-4*H*-chromen-3-yl)-methyl piperidine-1-carbodithioate (**7a**) and (3-chloro-4-oxo-4*H*-chromen-2-yl)methyl piperidine-1-carbodithioate (**7b**) against the MDA-MB-435 and SW-480 cell line was the best results [55]. When compared to the conventional medication doxorubicin, compound **8** showed cytotoxic activity against a human neuroblastoma cell line (SH-SY5Y) [56].

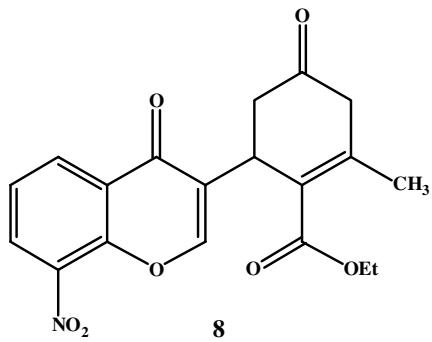
Investigation of chromones as a valuable scaffold for cancer drug development has mainly focused on finding new kinase inhibitors. Other targets, such as carbonic anhydrase [57], NF-B [58], sirtuins [59], topoisomerase [60] and A3 adenosine receptors, have been investigated [61,62]. Other research lines have focused on the creation of chromone based apoptosis modulators, Keap1-Nrf-2 [63-65] and hedgehog signaling pathways [66-68]. Finally, it's essential to emphasize recent research into



7a



7b



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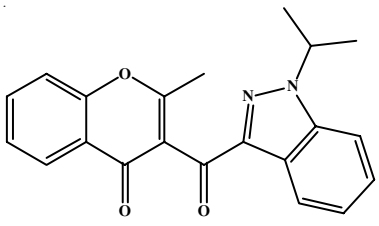
the development of cytotoxic metal-chromone and ferrocenyl-chromone complexes, as well as the screening of a range of chromone based compounds against a variety of cancer cell lines [69-72]. Even though these investigations are still in their early stages, several of them were backed up by strong DNA binding and apoptotic results.

Antibacterial and antifungal drugs: A variety of naturally occurring and synthetic chromones have been shown to exhibit potent antifungal and antibacterial activity. Chromone derivatives containing indolyl, chloroquinolyl and phenyl glycine derivatives are potent antimicrobial agents [73,74].

Bingi *et al*. [75] studied the biological activity of a variety of 3-hydroxy-6-(hydroxymethyl)-2-(2-phenyl-4*H*-chromen-4-yl)-4*H*-pyran-4-ones synthesized inside a one-pot catalyst-free process of 2-hydroxy chalcone with 5-hydroxy-2-(hydroxymethyl)pyran-4-one in methylbenzene under reflux temperature. The compounds were shown to have intense antibacterial action against a variety of bacteria types. Hatzade *et al*. [76] tried to synthesize 7-O-D-glucopyranosyloxy-3-(3-oxo-3-aryl-prop-1-enyl)-4*H*-chromene-4-one in a simple way. The antifungal and antibacterial properties of these compounds were investigated. 7-hydroxy-3-(1-phenyl-3-aryl-1*H*-pyrazol-5-yl) and related O-D-glucopyranosides were computationally assessed and investigated experimentally by Sheikh *et al*. [77]. For their antibacterial and antioxidant activity, 4*H*-chromen-4-ones and related O-D-glucopyranosides analogs. Palakuri & Reddy [78] developed tridentate 3-formyl chromone Schiff bases of Zn(II) and Ni(II), such as 3-((3-hydroxypyridin-2-ylimino)methyl), for Zn(II) and Ni(II). 3-((2-Hydroxyphenylimino)methyl)-4*H*-chromen-4-one, 3-((2-mercaptophenylimino)methyl)chromen-4-one and 3-((3-mercaptophenylimino)methyl)chromen-4-one are all derivatives of 4*H*-chromen-4-one. Compared to the ligands, 4*H*-chromen-4-one significantly affected the bacteria and fungal strains were examined. Some chromone derivatives (**9**) were produced and described as antibacterial agents by Kale & Karale [79].

Disk-diffusion assays were used to screen for antibacterial and antifungal activity of chromene crosslinked dithiazoles and 4-oxo-4*H*-chromene-3-carbothioic-*N*-phenylamides. Compared to fluconazole, dithiazole hybrids (**10a**) containing electron withdrawing (-Cl, -F) groups at C-7 and C-6 positions have potent antifungal activity. The highest growth inhibition for Gram-positive bacteria, *e.g. S. aureus*, was found to be 92.72% (**10b**) [80]. Under microwave irradiation, Musthafa *et al*. [81] synthesized chromone based hybrid of pyrazoles, pyrazolines, dibromo derivatives and dihydropyridines, which were tested for *in vitro* antibacterial activity over an assortment of two Gram-positive bacteria, *B. subtilis*, *S. aureus*, as well as two Gram-negative bacteria, *Salmonella typhimurium*, *E. coli* and *in vitro* antifungal and antimicrobial activity of different substances suggest that they are strong antimicrobial agents (**11a** and **11b**). Nawrot-Modranka *et al*. [82] also synthesized chromone derivatives (**12**) and investigated their antibacterial activity *in vitro*.

Cano *et al*. [83] used a multicomponent process to create new 3-tetraazolylmethyl-4*H*-chromen-4-one analogs and tested



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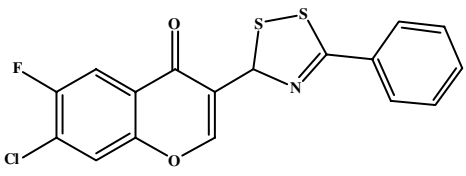
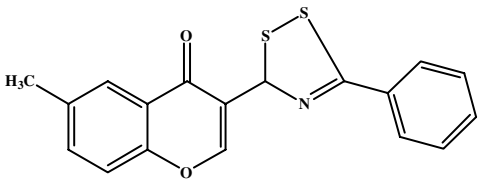


10a



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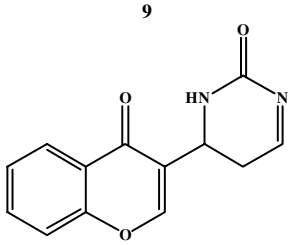
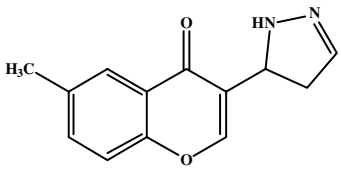
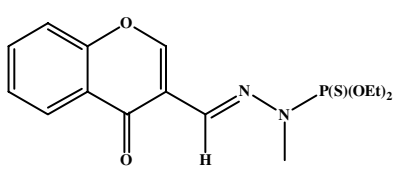


11a



11b



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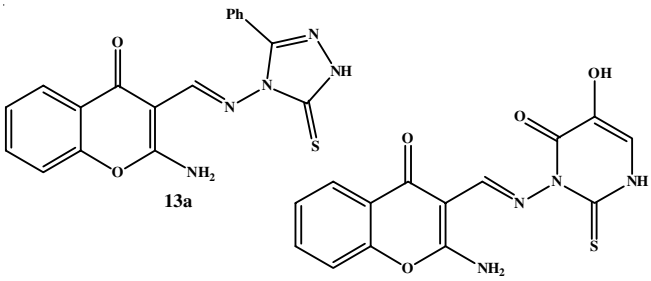
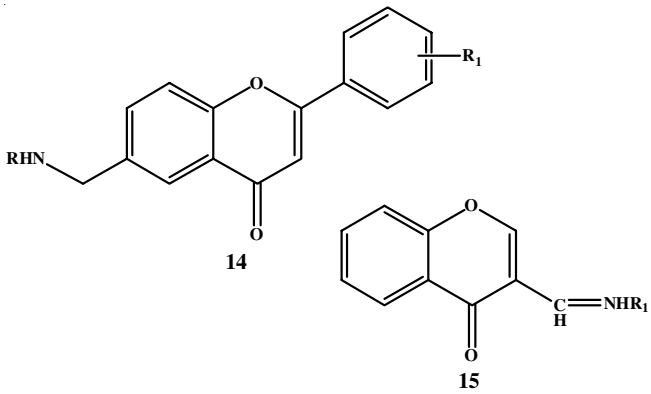
them biologically against *Entamoeba histolytica*, *Trichomonas vaginalis* and *Giardia lamblia*. Through an azomethine linkage, Ibrahim & El-Mahdy [84] synthesized novel nitrogen heterocyclic systems by connecting the chromone analogs with 1,2,4-triazine or 1,2,4-triazole in one molecular structure. They tested their antibacterial properties *in vitro* against *S. pyogenes* and *S. aureus* as Gram-positive bacteria and *Pseudomonas phaseolicola*, *Pseudomonas fluorescens*, act as a Gram-negative bacteria and *A. fumigatus* and *F. oxysporum* as fungi using the technique called disc-agar diffusion. Compounds have a high level of efficacy against the fungi (**13a** and **13b**).



Antiviral drugs: Human rhinoviruses are the agent of cold and respiratory tract infections. 2-Styryl chromones and their derivatives have been used as effective antiviral compounds [85]. In addition, 5-hydroxy chromones are effective against HCV. Several chromones (Fig. 6) are effective against HIV as well [86]. Benzyloxy substituted chromones have been used as monoamine oxidize inhibitors [87]. Alzheimer's disease has been treated using oxychromone inhibitors. In addition, they have been used successfully as antiobesity drugs and as receptor antagonists, respectively [88].

Anti-inflammatory activity: Hasan *et al.* [89] synthesized 6-aminomethyl-2-aryl-1-benzopyran-4-one analogs (**14**) and tested them for analgesic, anti-inflammatory, lipid peroxidation and ulcerogenic activities. Two of the substances examined had a higher level of anti-inflammatory action than the others. Khan *et al.* [90] effectively synthesized 3-formyl-chromone analogs (**15**) and also investigated for their anti-inflammatory properties. The chromones allegedly inhibited multiple processes, including mast cell stabilizers, intercellular adhesion, molecule inhibitors, cyclooxygenase inhibitors and molecule inhibitors, to have an anti-inflammatory effect [91-93], interleukin-5 inhibitors, leukotriene receptor antagonists [94-97], lipoxygenase inhibitors activity [98,99] and nitric oxide (NO) production inhibitors [100-107].



It should be mentioned that used these anti-inflammatory characteristics of chromones for therapeutic reasons, including rheumatoid arthritis, cancer, neuropathies, asthma and neuro-

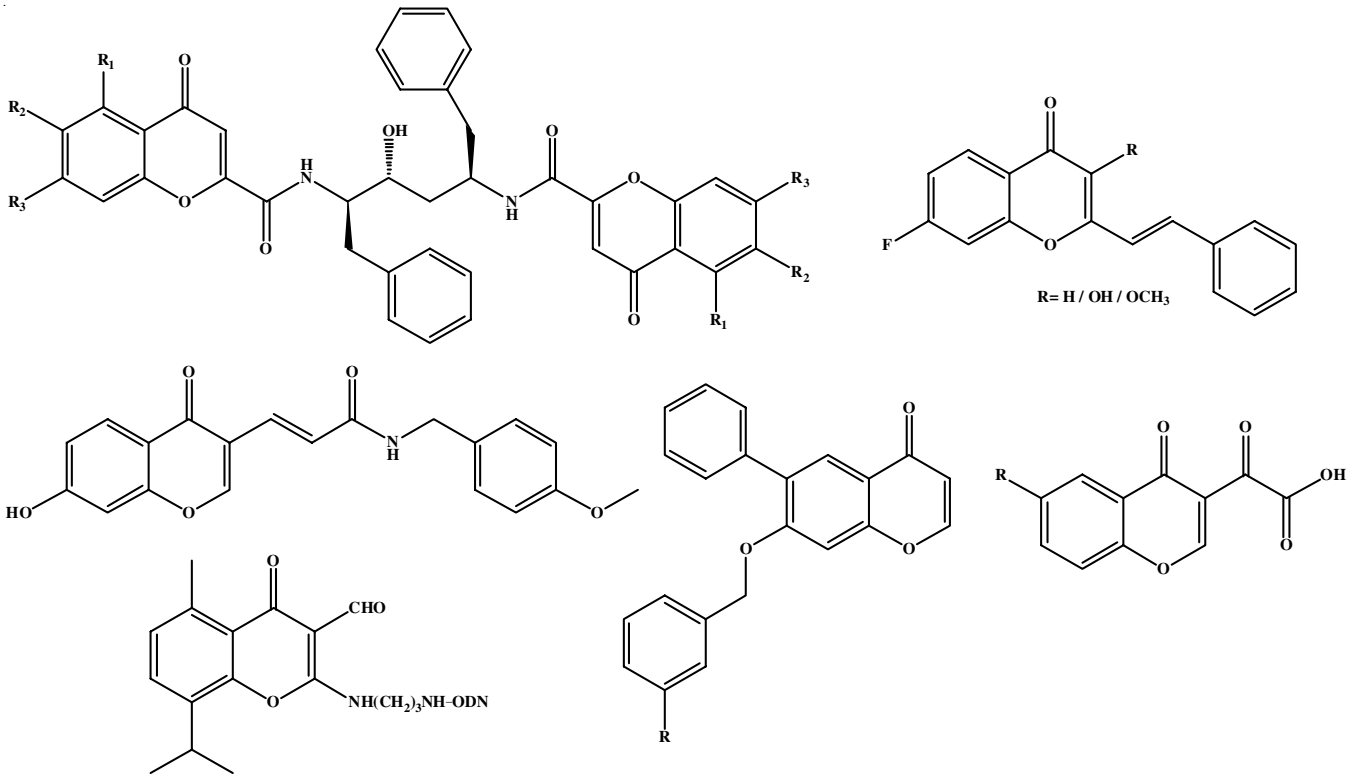
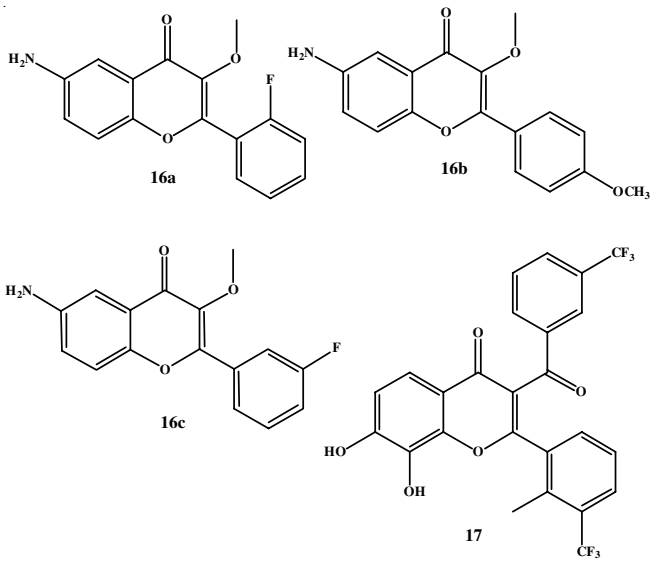


Fig. 6. Structure of various antiviral chromones used in therapy

degenerative disorders [105-110]. 2-(2-Phenylethyl)chromone dimers obtained from Chinese agarwood, *Aquilaria sinensis*, was shown to suppress NO production with IC_{50} values ranging from 0.6 to 37.1 μM. Furthermore, 5-O methylcneorum chromone K was isolated from *Dictyoloma vandellianum* root bark and shown to have anti-inflammatory properties *via* activating the glucocorticoid receptor RU486 [111]. Singh *et al.* [112] reported the COX inhibitor activity for compounds synthesized by combining chrysin, indole and pyrazole moieties.

Anti-HIV activity: Casano *et al.* [113] designed and synthesized various methoxy flavones and investigated their antiproliferative and anti-HIV activities in *Plasmodium falciparum parasites*. Compounds **16a** and **16c** were selective inhibitors of HIV-2 growth, but methoxy flavone (**16b**) was active in both HIV-1 and *P. falciparum*. The *para*-substitution on compound **16b** containing B ring was required to boost antiplasmodial action and improve HIV-2 potency. Ungwitayatorn *et al.* [114] synthesized a series of benzopyran-4-one scaffolds using a one-pot cyclization process and 7,8-dihydroxy-2-(30-trifluoromethylphenyl)-3-(300-trifluoromethylbenzoyl)chromone analogs (**17**) inhibited HIV-1 protease *in vitro* as well that shows antioxidant activity.



Antioxidant activity: Yasar *et al.* [115] synthesized substituted azaflavone analogs for antibacterial and antioxidant activities. The antioxidant properties of the synthesized com-

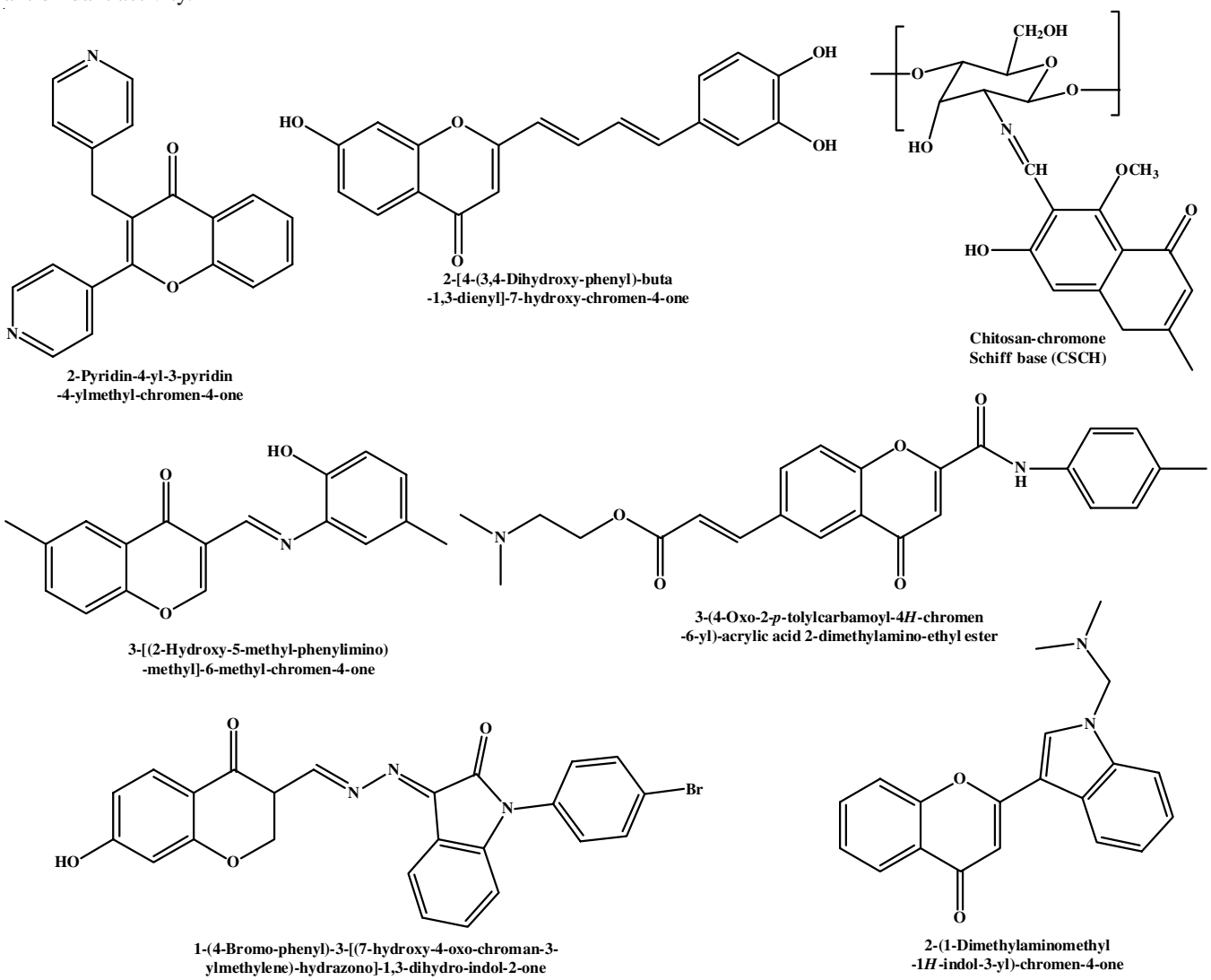


Fig. 7. Chemical structure of different chromones exhibiting antioxidant activity

pounds were also assessed utilizing the ferric reducing antioxidant power (FRAP) assay and their capacity to scavenge the stable radical DPPH assay. Some compounds that shows antioxidant activity were given below structurally (Fig. 7).

Antimalarial activity: Isaka *et al*. [116] isolated a novel chromone derivative (**18**) from the wood-decay fungus Rhizina species and investigated for the antimalarial efficacy against *P. falciparum* K_1. With an IC_{50} having conc. 5.1 mg/mL, this derivative showed the better antimalarial efficacy.

Anticonvulsant activity: In the scPTZ test, chromones (**19a** and **19b**) provided 100% protection at 300 mg/kg. All of the substances studied were inert in the MES test, not protect against seizures even at doses of 300 mg/kg body weight, which showed anticonvulsant efficacy [117].

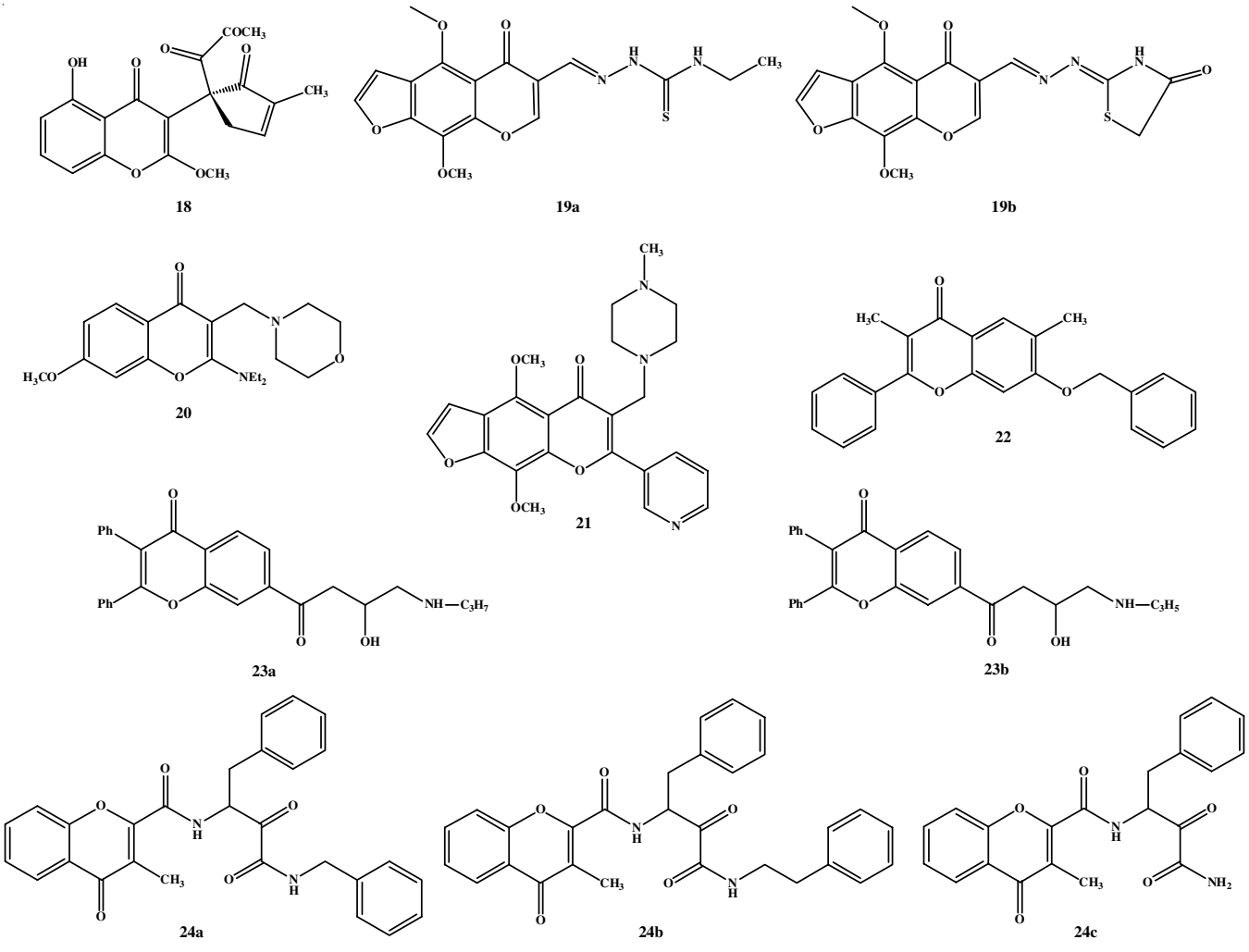
Antiplatelet activity: The activity was highest when 2-amino substituent of the studied chromones (**20**) was diethylamino group [118]. The activity increased when electron releasing substituents like -OH, $-CH_3$ or $-OCH_3$ were present at position 7 but reduced when an electron-withdrawing substituent like 3-NO_2, 6-NO_2 or 6-Cl was present at position 3, 6 or 7.

Gastroprotective activity: The 9- and 6-alkylaminomethyl furochromones (**21**) derived from the naturally occurring chromones khellin and visnagin were tested for gastroprotective effectiveness using the rat ethanol-induced injury model. The furochromones containing a methoxy group at 4, 9 or methoxyphenyl group at 7-position and an alkylaminomethyl group at position-6 showed excellent gastroprotective action an ethanol injury model [119].

H_1 Antihistaminic activity: The antihistaminic activity of 2-phenyl-4*H*-chromen-4-one moiety (**22**) and evaluated using the H_1 antihistaminic activity as a computational technique. The compounds show the most robust antihistaminic properties [120].

Antihypertensive activity: Wu *et al*. [121] synthesized 3-phenylflavonoxy propanolamines (**23a**-**b**) and tested their antihypertensive efficacy in spontaneously hypertensive rats as well as indications of α-adrenoceptor antagonism *in vivo* and *in vitro*.

***m*-Calpain inhibition activity:** Lee *et al*. [122] synthesized chromone carboxamide compounds and used casein-coomassie blue microplate assay to investigate for *m*-calpain inhibition. Compound **24c**, the most potent calpain inhibitor in this series (IC_{50} 14 0.24 mM), inhibited 14.4% and 22.4% of chromone derivatives *m*-calpain, exhibiting excellent selectivity. Regardless of amide, including the dioxane ring in the chromone ring reduced the inhibitory action of parent compound; nevertheless, amide substituents were also essential in the activity. The compounds **24a** and **24c** with benzyl and phenethyl amide



exhibited promising inhibition of *m*-calpain. Still, the potencies were decreased by ten-fold when these substituents were replaced with 2-(morpholin-4-yl) ethyl or isopropyl amide.

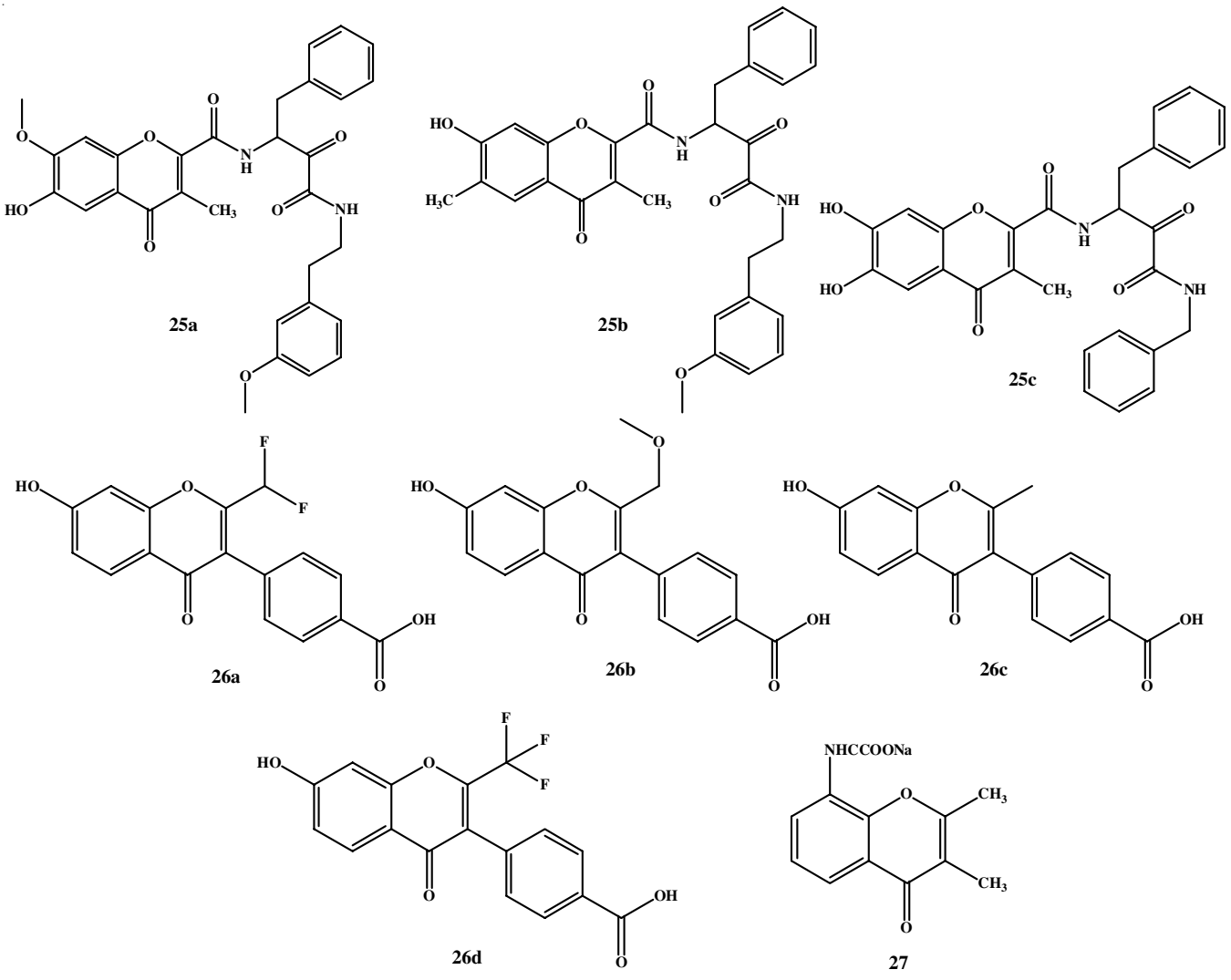
Human erythrocyte-isolated calpain I was used to synthesize and evaluate new chromone carboxamide derivatives. The 4-methoxyphenyl group compounds at the keto-amide position, *i.e.* compounds **25a** and **25b** had the most potent inhibitory activities of *m*-calpain. In comparison, compound **25c** had both potent inhibitory and antioxidant activity of *m*-calpain [123].

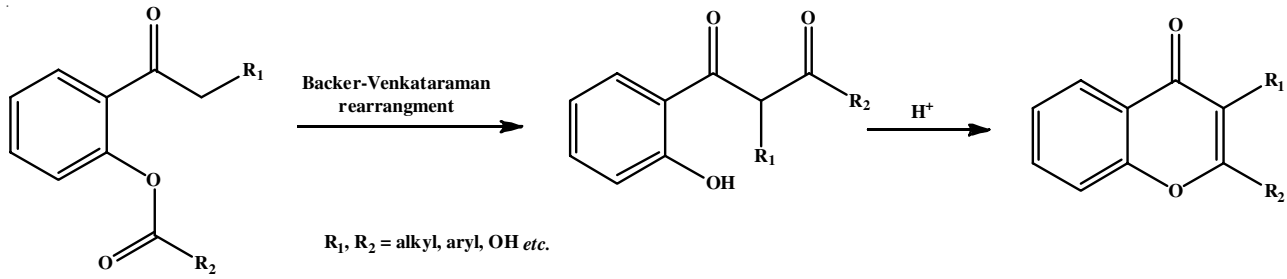
Glutathione reductase activity: As S-nitrosoglutathione reductase (GSNOR) inhibitors, Sun *et al.* [124] reported a series of chromone compounds (**26a-d**). The GSNOR inhibitors in any pharmaceutically suitable dose form, including but not limited to injectables, can be utilized. When compared to GSNOR inhibitors, certain compounds (**26a**-**c**) had IC_{50} values of less than 0.5 mM and compounds **26d** had IC_{50} values of less than 0.1 mM.

Antiallergic activity: Abram *et al.* [125] synthesized 2,3,7-substituted chromone salts (**27**) and tested them for antiallergic action. When given at a dosage of 30 mg/kg, all substances tested showed antiallergic activity in the mouth.

Antimicrobial activity: Infectious illnesses have lately grown as a result of improved human pathogen resistance, creating major medical problems. To address this critical threat, comprehensive actions are required and novel antimicrobial drugs can assist. Cano *et al.* [126] and He *et al.* [127] developed medicines against resistant infections based on the chromone structure. Hiruy *et al.* [128] extracted an antimicrobial compounds from the leaf latex of *Aloe monticola* Reynolds, including aloesin and 7-O-methyl-60-O-coumaroylaloesin. The inhibiting action of chromone derivative from the fungus *Chaetomium brasiliense* against human lung ($Lu0_4$), human neuroma ($N0_4$) and human breast cancer was repored by Li *et al.* [129]. Huang *et al.* [130] found that (20S)-2-(20-hydroxypropyl)-5-methyl-7, 8-dihydroxy-chromone from the mangrove derived fungus penicillium aculeatum has antibacterial activity.

Synthesis of chromone derivatives: The earliest method for chromone synthesis included decarboxylation of chromone-2-carboxylic acid [131]. However, the yields were not very high and several newer methods have been developed to synthesize chromones. Chromones have been synthesized in both acidic and basic conditions. Various substituted chromones have been prepared either by Baker Venkatraman rearrangement (**Scheme-I**) [132] or *via* Claisen ester condensation, respectively [133]. The use of acid is generally harsh and the conditions are extreme. Acid has been used as catalyst in successful ring closure reactions





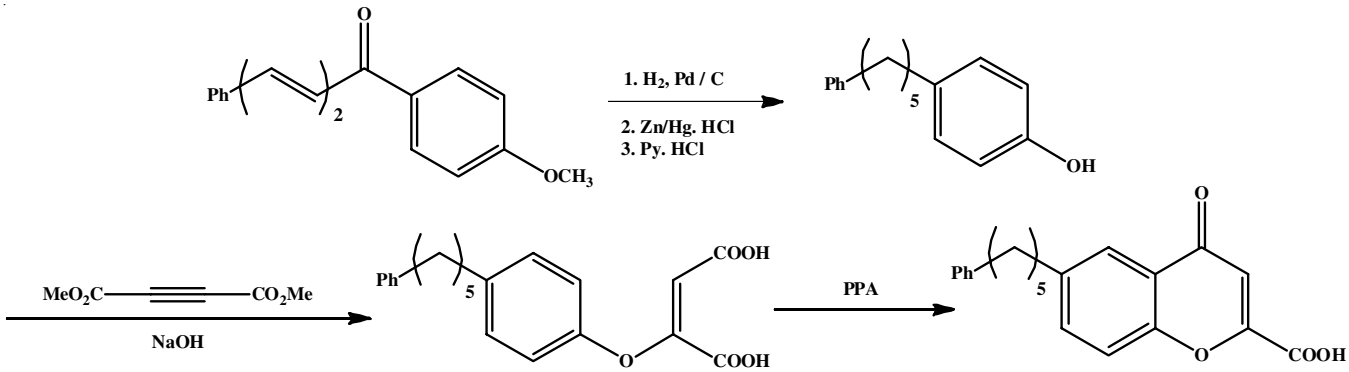
Scheme-I: Baker Venkatraman rearrangement for the synthesis of chromones

associated with chromones. A few of such chromone synthesis methods utilizing various acids have been illustrated below. Polyphosphoric acid has been used in the synthesis of chromones from phenols. The final ring closure of 2-chromone carboxylic acid derivatives was achieved using polyphosphoric acid (**Scheme-II**) [134].

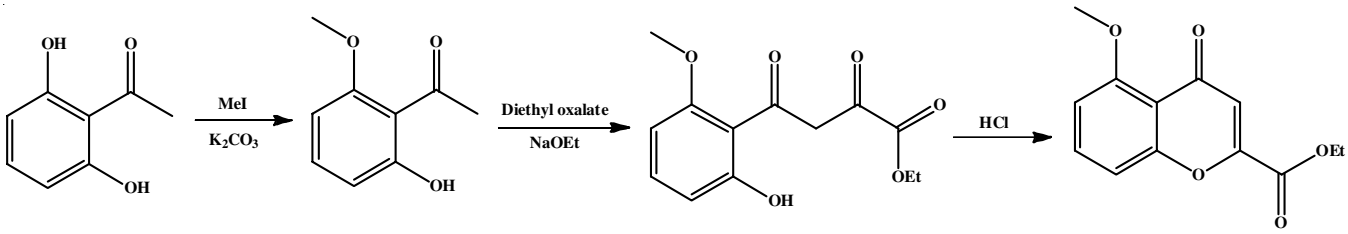
2,6-Dihydroxy acetophenone was used as starting material for the synthesis of various chromones. Finally, the ring closure was achieved using HCl as a catalyst (**Scheme-III**) [135]. $POCl_3$ is the most widely used catalyst for chromone ring closure. Phenolic ringcontaining compounds and carbonyl compounds are refluxed in the presence of $POCl_3$ to generate chromone derivatives (**Scheme-IV**) [136]. Sulfuric acid was used as catalyst to synthesize chromone ring closure in the terminal step of reaction (**Scheme-V**) [137].

Base catalyzed synthesis methods: Different bases have been used for chromone biosynthesis, including pyridine, sodium hydride, sodium methoxide, potassium *t*-butoxide and potassium carbonate. Pyridine was used in ring closure and synthesis of chromone derivatives. In addition, the method was found to be suitable for the synthesis of chromones from acyl phenols (**Scheme-VI**) [138]. The ring closure and synthesis of chromone derivatives of marine products were successfully achieved using K_2CO_3 as catalyst (**Scheme-VII**) [139].

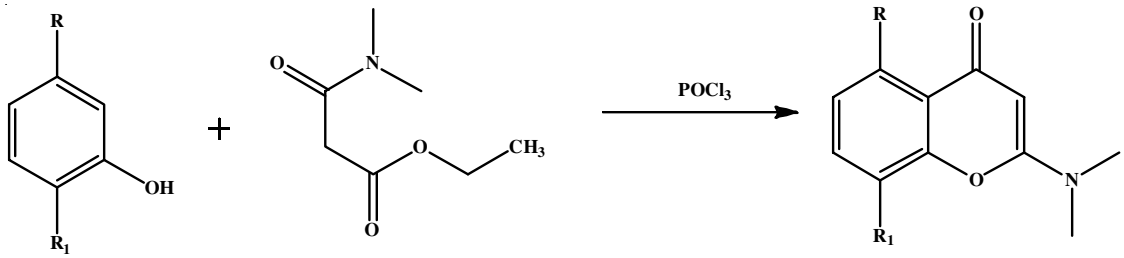
Microwave irradiation methods: Though acid and base-catalyzed are the classical methods, they suffer from the harsh



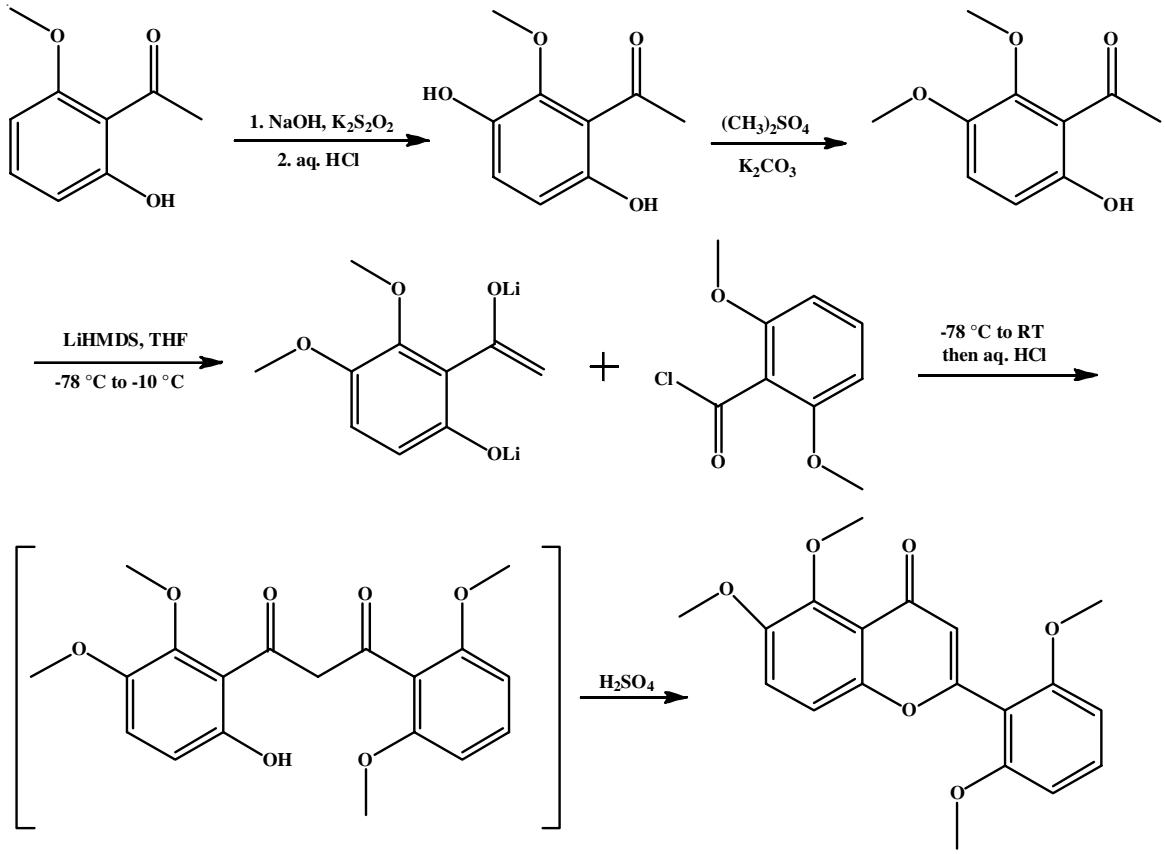
Scheme-II: Synthesis of chromones from phenol using polyphosphoric acid



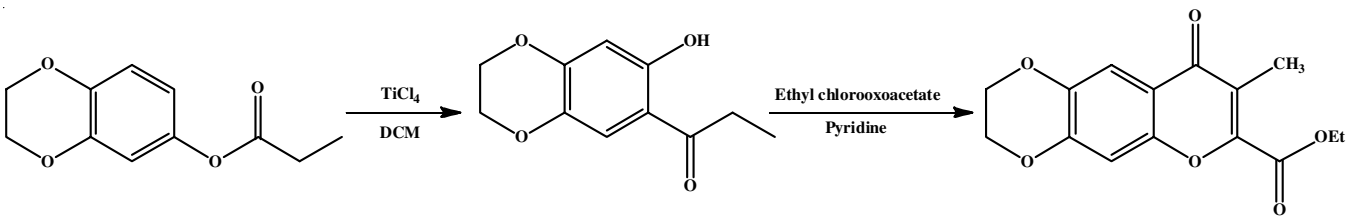
Scheme-III: Hydrochloric acid mediated synthesis of chromones



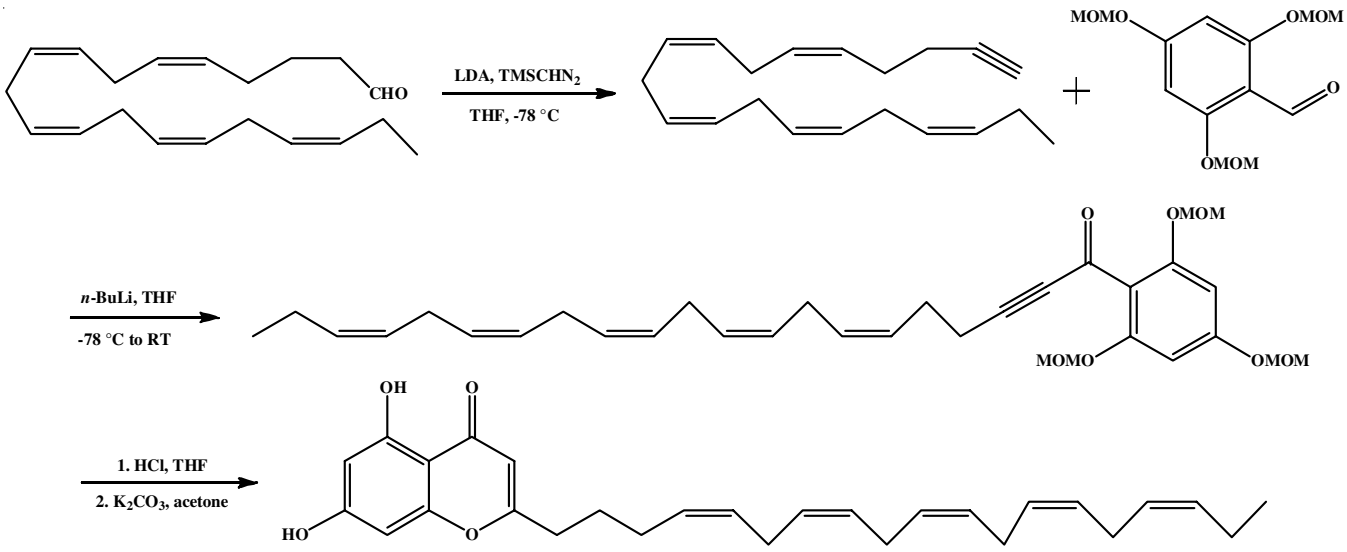
Scheme-IV: $POCl_3$ catalyzed synthesis of chromones from phenol and carbonyl groups



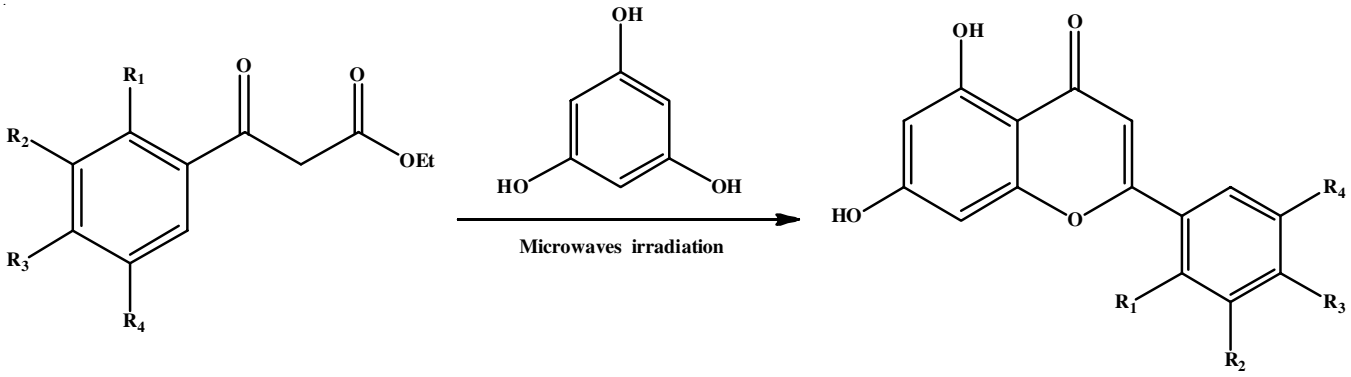
Scheme-V: Ring closer synthesis of substituted chromone using sulfuric acid



Scheme-VI: Synthesis of chromones from acyl phenols



Scheme-VII: Synthesis of chromones using potassium carbonate

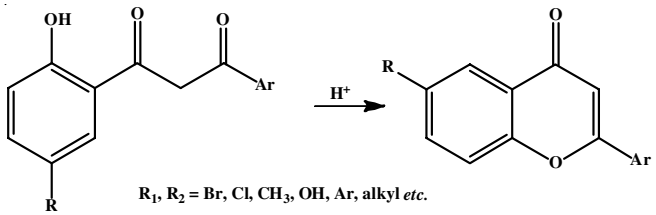


Scheme-VIII: Synthesis of functionalized flavones by microwave irradiation

conditions employed in the whole process. The use of alternative methods that are safe and environmentally friendly has resulted in microwave irradiated methods. The green chemical methods are usually solvent-free and easy to perform with minimal time required to synthesize chromones. Functionalized flavones have been synthesized by the microwave irradiation method (**Scheme-VIII**). Such methods have produced chromones in yield ranging from 60-90%, respectively [140].

Solid-phase support synthesis: Solid-phase support has distinct advantages over reactions in the solution phase. Chromone ring closures have been achieved by solid-phase support. Phosphomolybdic acid or phosphotungstic acid have been used bound to silica for chromone ring closure. The method successfully synthesized flavones and substituted chromones with silica material being completely regenerated post-reaction (**Scheme-IX**) [141]. Oxidation of 2-hydroxy chalcones under solvent-free conditions generates flavones. This was achieved by using silica gel supporting Indium salts and the yields were greater than 80% (**Scheme-X**) [142].

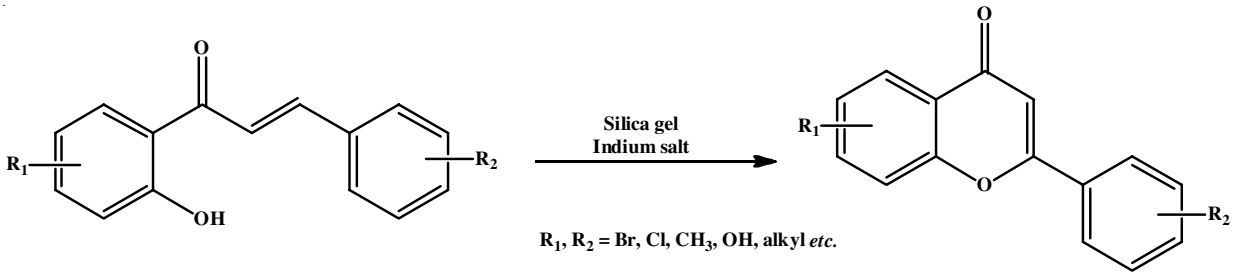
Other than these traditional methods, various other catalysts such as trimethylsilyl chloride, sodium and iodine have also been used to synthesize chromones. Ahmed *et al.* [143] reported the synthesis of 4*H*-chromen-4-one by the treatment of (*E*)-3-



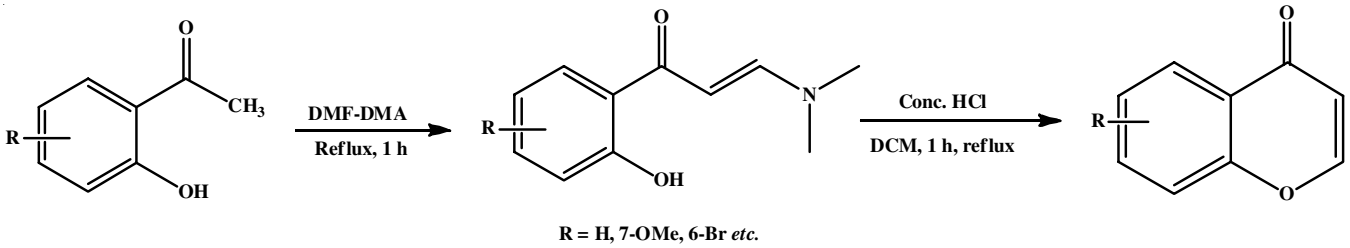
Scheme-IX: Synthesis of chromones using phosphomolybdic and tungstic acids

(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one with conc. HCl acid in dichloromethane medium at reflux condition for 1 h (**Scheme-XI**). Iaroshenko *et al.* [144] reported a novel synthetic method to synthesize various chromone derivatives from corresponding 2-hydroxy acetophenone enamineones by treating TMSCl in DMF under argon gas at 90-110 ºC for 4 h (**Scheme-XII**). Guo *et al.* [145] reported a synthesis of 3-chromone thioaryl derivative by the reaction of (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one and aryl sulphonyl hydrazine reacts with 50 mol% of KIO_3 catalyst in DMF medium at 130 ºC for 24 h (**Scheme-XIII**).

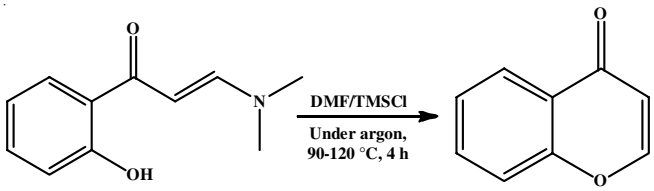
Foehlisch [146] reported in early 1970s the synthesis of 4*H*-chromen-4-one by the cyclization of (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one in the presence of dil.



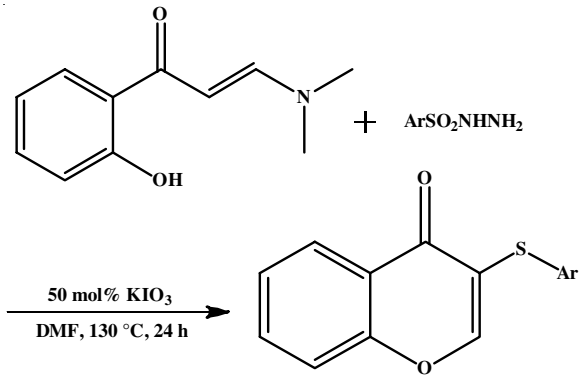
Scheme-X: synthesis of flavones by oxidation reaction



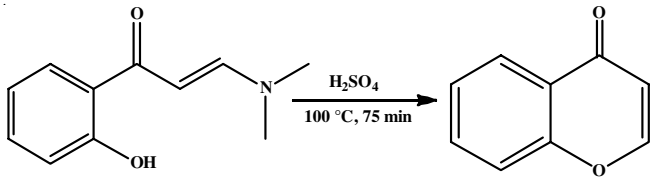
Scheme-XI: Synthesis of flavones using DMF-DMA and conc HCl in DCM



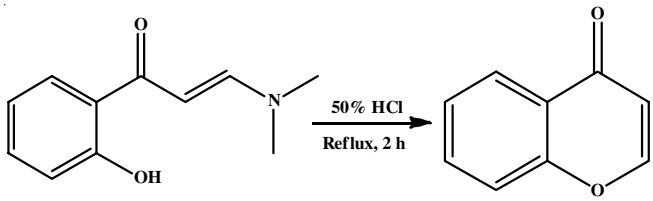
Scheme-XII: Synthesis of chromone using 2-hydroxy acetophenone enamineones as astarting materials under inert condition



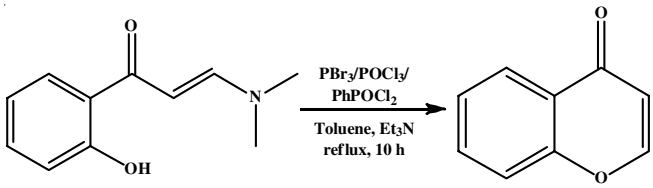
Scheme-XIII: Synthesis of 3-chromone thioaryl derivative using (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one and aryl sulphonyl hydrazine



Scheme-XIV: Preparation of 4*H*-chromen-4-one in acidic medium



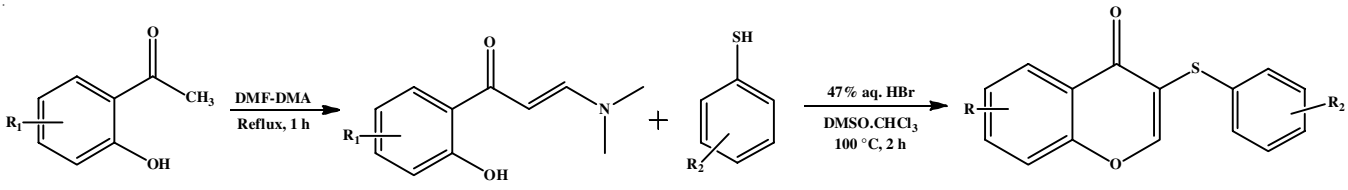
Scheme-XVI: Synthesis using 2-hydroxy acetophenone enaminone with 50% hydrochloric acid



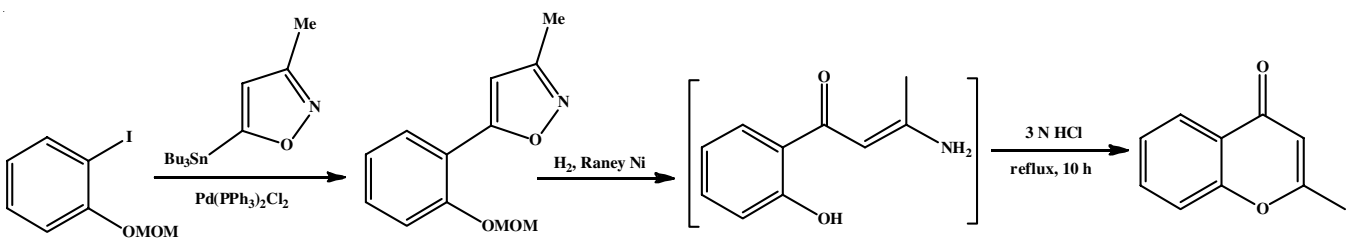
Scheme-XVII: Synthesis of chromone derivatives using the corresponding enaminone with phosphorus halide under toluene

H_2SO_4 at 100 ºC for 75 min (**Scheme-XIV**). Sorabad & Maddani [147] developed a synthesis of thioaryl chromone from 2-hydroxy acetophenone enaminone. The reaction was carried out under aqueous HBr (47 mol%) in DMSO:$CHCl_3$ at 100 ºC for 2 h (**Scheme-XV**). Ibrahim [148] also reported the synthesis of chromone derivatives. The reaction proceeds by treating 2-hydroxy acetophenone enaminone with 50% HCl at reflux condition for 2 h (**Scheme-XVI**). Ali *et al*. [149] reported the synthesis of chromone derivatives from corresponding enaminones using three different phosphorus halide catalysts. The reaction proceeds by treating the corresponding enaminone with phosphorus halide under toluene:triethylamine medium at reflux condition for 10 h (**Scheme-XVII**). The synthesis of chromone derivatives from (*E*)-3-(dimethylamino)-1-(2-(methoxymethoxy)phenyl)prop-2-en-1-one by treatment of 3N HCl at reflux condition for 10 h (**Scheme-XVIII**) is reported by Sakamoto *et al*. [150].

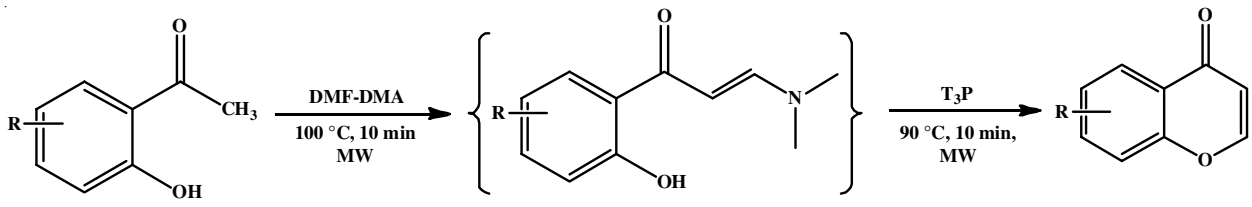
An efficient one-pot microwave-assisted propyl phosphonic anhydride mediated synthesis of chromone derivatives from various 2-hydroxy acetophenones *via* corresponding substituted enaminones at 90 ºC for 10 min (**Scheme-XIX**) is reported by Balakrishna *et al*. [151]. Various chromone derivatives from corresponding 2-hydroxy acetophenone were obtained by reacting 2-hydroxy acetophenones with NaH in ethyl formate at 0 ºC for 2 h (**Scheme-XX**) [152]. Rodríguez-Ramos *et al*. [153] reported the synthesis of 2-substituted chromone derivatives. The chromone products were synthesized from corresponding 2-acetylphenolic esters using DBU in pyridine medium at 80 ºC for 6 h (**Scheme-XXI**). Wang *et al*. [154] reported the synthesis



Scheme-XV: Synthesis of thio aryl chromone from 2-hydroxy acetophenone enaminone

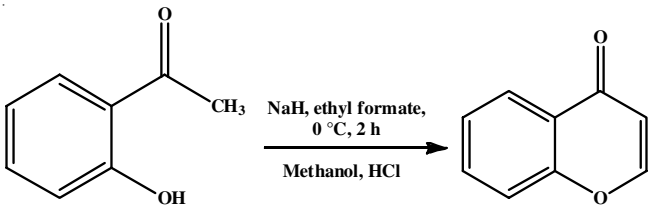


Scheme-XVIII: Synthesis of chromone derivatives using H_2 and Raney Ni as catalyst



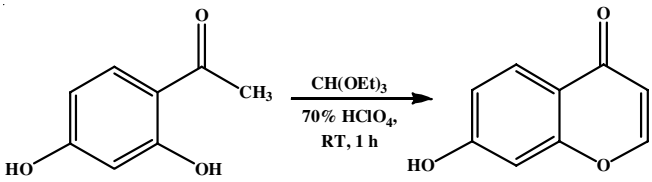
R = H, Me, OMe, Halo, Aryl, Hetero aryl *etc.*

Scheme-XIX: One-pot microwave-assisted propyl phosphonic anhydride mediated synthesis of chromone derivatives



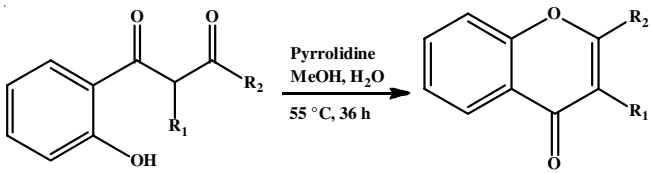
Scheme-XX: Preparation of flavones from 2-hydroxy acetophenones with sodium hydride at 0 °C

of 7-hydroxy-4*H*-chromen-4-one directly from 1-(2,4-dihydroxy phenyl)ethanone by the treatment of ethyl orthoformate under 70% of $HClO_4$ at room temperature for 1 h (**Scheme-XXII**).

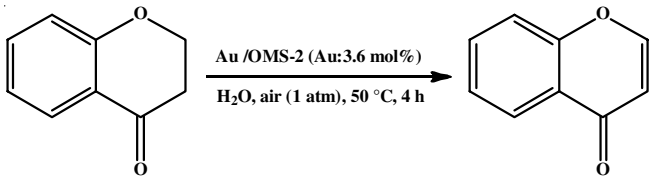


Scheme-XXII: Synthesis of hydroxy-substituted chromone using ethyl orthoformate as a catalyst in an acidic medium

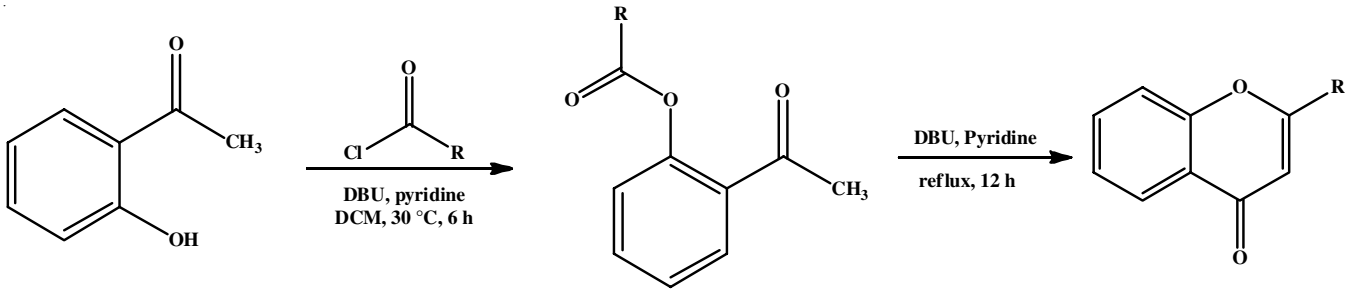
Wen *et al*. [155] synthesized the chromone derivatives by the cyclization of 2-hydroxy phenyl 1,3-diketo compounds by using pyrrolidine as catalyst in a water medium at 55 ºC for 36 h (**Scheme-XXIII**). Yoshii *et al*. [156] also described the synthesis of various chromone derivatives by the oxidation of chromenone using heterogeneous reusable gold nanoparticles supported on manganese oxide (Au/OMS-2) catalyst underwater medium at 50 ºC for 4 h (**Scheme-XXIV**). A one-pot synthesis of 3-fluoro chromone derivative from 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione, which further the treatment with selected fluor in acetonitrile medium at room temperature for 15 h yields cyclized product, followed the desired dehydrogenated product obtained by the treatment with conc. sulfuric acid at room temperature (**Scheme-XXV**) [157].



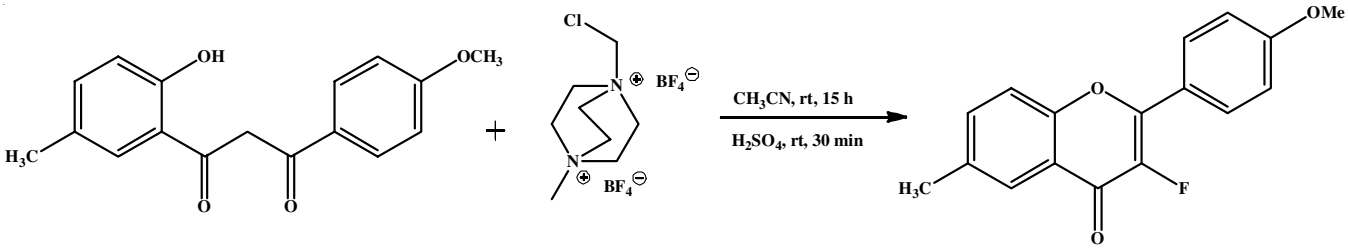
Scheme-XXIII: Synthesis of disubstituted chromone derivatives by cyclization



Scheme-XXIV: Synthesis of various chromone derivatives by the oxidation of chromenone using heterogeneous reusable gold nanoparticles



Scheme-XXI: Synthesis of 2-substituted chromone derivatives from corresponding 2-acetylphenolic esters using DBU in pyridine medium

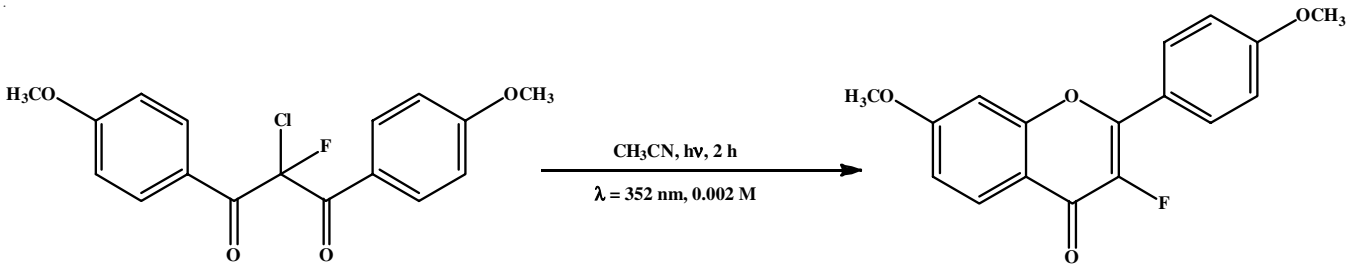


Scheme-XXV: One-pot synthesis of 3-fluoro chromone derivative with select fluor in acetonitrile medium at room temperature

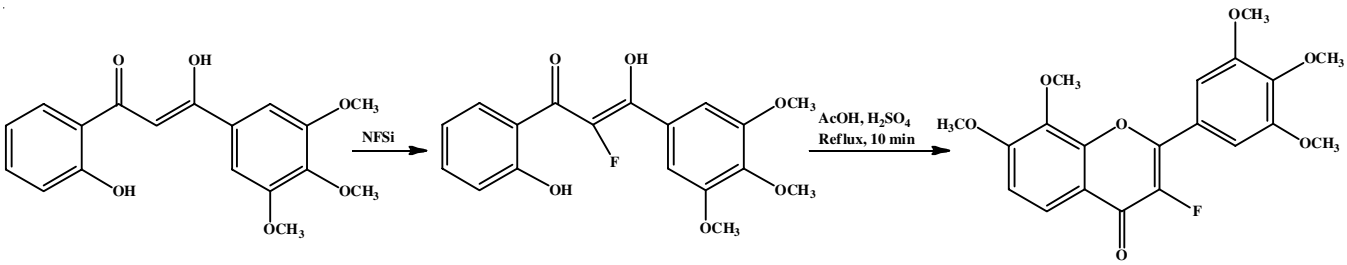
Košmrlj & Šket [158] described a photocycliazation of 2-chloro-2-fluoro-1,3-*bis*(4-methoxyphenyl)propane-1,3-dione to 3-fluoro-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one. The reaction preceded by photochemical irradiation in acetonitrile medium at the wavelength of 352 nm and 0.002 M (**Scheme-XXVI**). Britton *et al.* [159] reported the synthesis of 3-fluoro-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-4-one by the cyclization of 2-fluoro-3-hydroxy-1-(2-hydroxyphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one in the presence of acetic acid and conc. H_2SO_4 at reflux condition for 10 min (**Scheme-XXVII**).

Menichincheri *et al.* [160] reported the synthesis of 2-(3,4-dimethoxyphenyl)-3-fluoro-7,8-dimethoxy-4*H*-chromen-4-one by 1 h treatment of 1-(3,4-dimethoxyphenyl)-2-fluoro-3-(2-hydroxy-3,4-dimethoxyphenyl)propane-1,3-dione with acetic acid and 96% H_2SO_4 at reflux condition (**Scheme-XXVIII**). Bolos *et al.* [161] described the synthesis of substituted-3-fluorochromone derivatives. The cyclization of the corresponding enaminone prepared the product in the presence of 85% 1-fluoro-2,4,6-trimethylpyridinium triflate in dichloromethane and acetonitrile medium at reflux condition for 1 h (**Scheme-XXIX**).

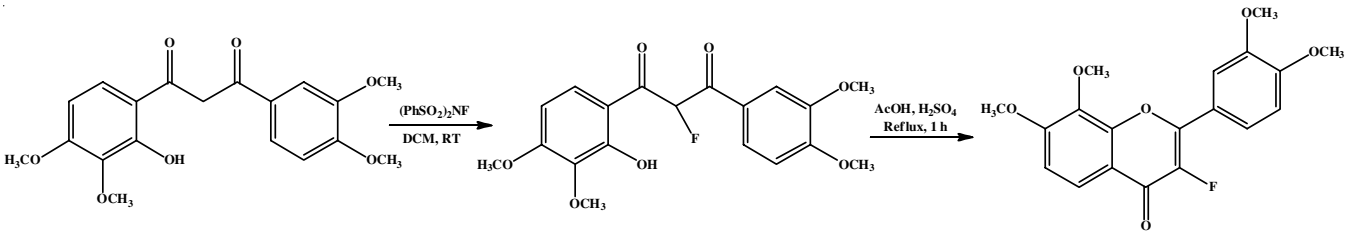
Hydriodic acid as catalyst: The use of hydriodic acid as catalyst in the ring closure of a combination of 2-methyl-8-hydroxy-6,7 benzochromone and 2-methyl-8-methoxy-6,7-benzochromone has been reported (**Scheme-XXX**) [162]. A Pd-catalyzed copper-free carbonylative Sonogashira coupling method was achieved at ambient temperature using water as a solvent under balloon pressure of CO with Et_3N as base [163]. Using the recently reported method, flavones were successfully synthesized (**Scheme-XXXI**).



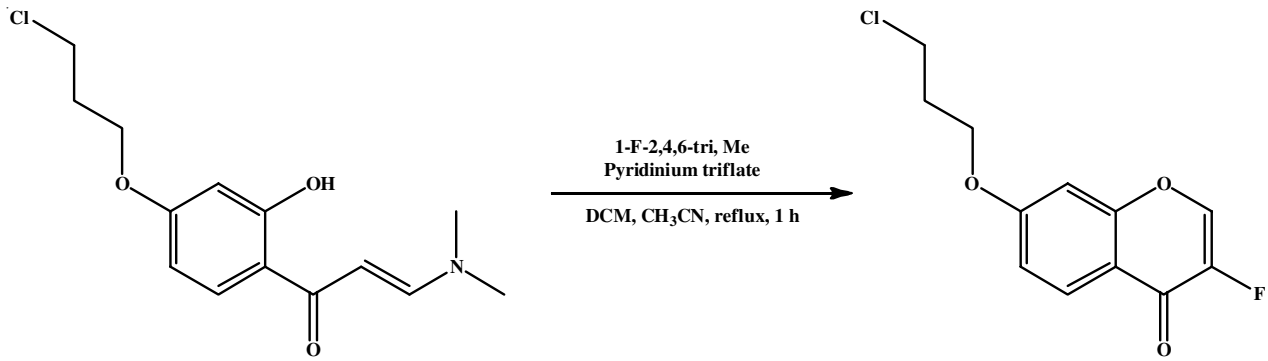
Scheme-XXVI: Synthesis of 3-fluoro chromone derivative by photocycli-zation method



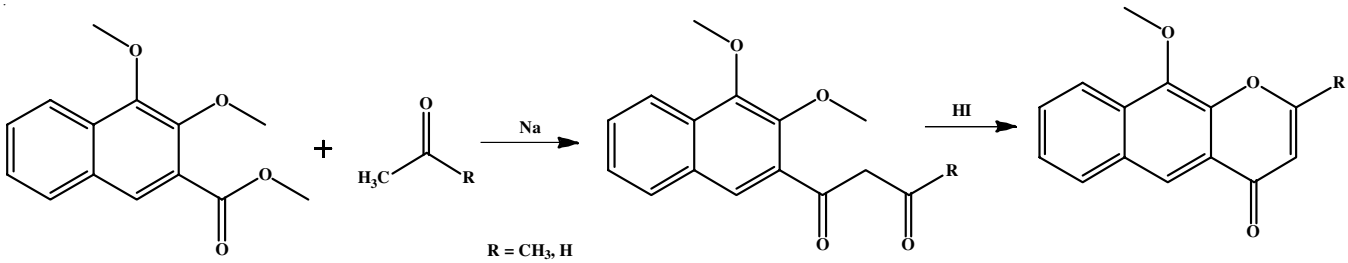
Scheme-XXVII: Synthesis of 3-fluoro-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-4-one by the cyclization



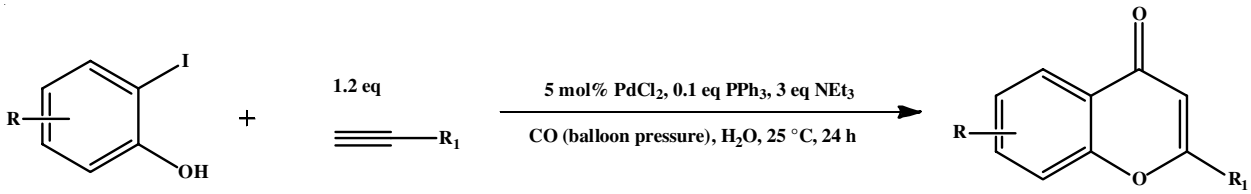
Scheme-XXVIII: Synthesis of substituted chromone using $Ph(SO_2)_2NF$ as Catalyst in DCM and acidic medium at room temperature



Scheme-XXIX: Synthesis of substituted-3-fluorochromone derivatives using cyclization of the corresponding enaminone

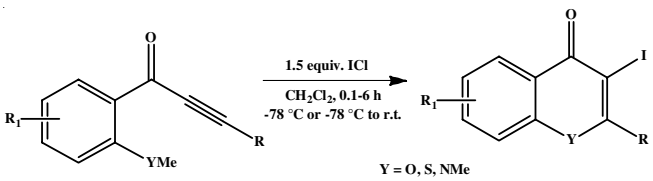


Scheme-XXX: Synthesis of substituted chromone analogs by using Na metal and HI

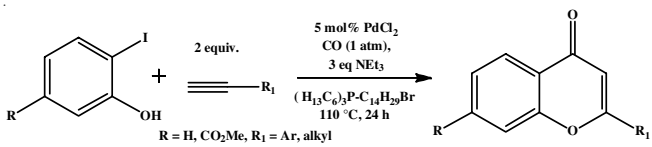


Scheme-XXXI: Synthesis of flavones by a Pd-catalyzed copper-free carbonylative Sonogashira coupling method

A straightforward and efficient route to different 3-iodochromones, iodothiochromenones, iodoquinolinones and analogues in good to outstanding yields was provided by moderate ICl-induced cyclization of heteroatom-substituted alkynones. Following palladium-catalyzed reactions, molecule complexity rapidly increases (**Scheme-XXXII**) [164]. To easily obtain structurally diverse 2,3-disubstituted chromones in high yields, a tandem deprotection-cyclization process of 1,1-diacylcyclopropanes has been reported. Awuah & Capretta [165] reported a successful synthesis of bromophycoic acid E scaffold, a power-ful antibacterial oceanic natural product, exemplified the process's utility (**Scheme-XXXIII**).

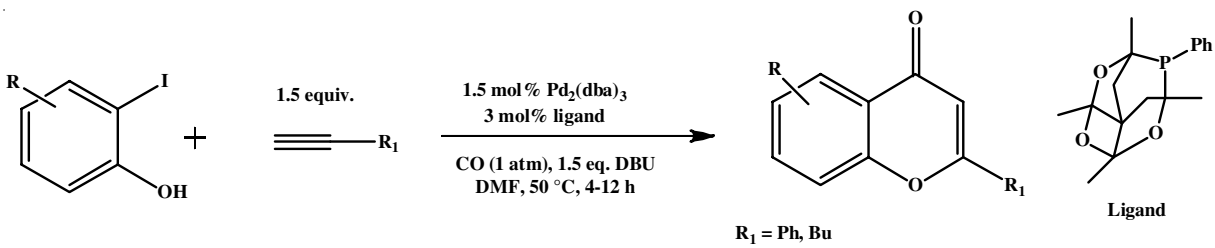


Scheme-XXXII: Synthesis of heteroatom-substituted flavones by ICl-induced cyclization process

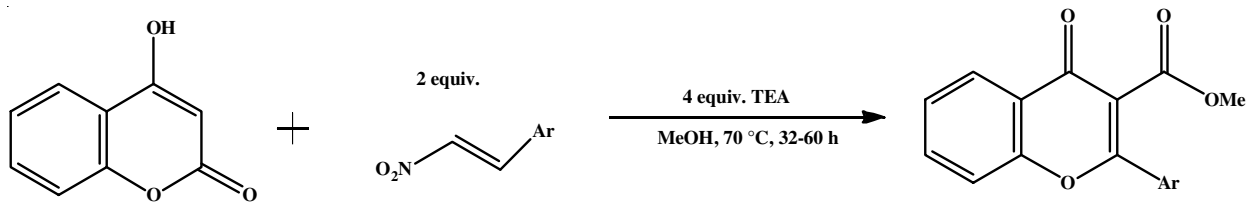


Scheme-XXXIII: Preparation of 2,3-disubstituted chromones by using 5-substituted-2-iodophenol as a starting material

Under atmospheric CO pressure, an efficient and selective palladium-catalyzed ligand-free cyclocarbonylation reaction of *o*-iodophenol with terminal acetylenes gives a wide range of chromones in good yields [166]. The cyclocarbonylation process is more efficient when a phosphonium salt ionic liquid was used as the reaction media (**Scheme-XXXIV**). 4-Oxo-2-aryl-4*H*-chromene-3-carboxylate (flavone-3-carboxylate) derivatives result from an unique alcohol-mediated reaction between 4-hydroxycoumarins and -nitroalkenes. The transition occurs when Michael adduct is formed *in situ*, followed by an alkoxide ion-mediated rearrangement of the intermediate (**Scheme-XXXV**). Different media's impacts on the reaction were also examined [167].



Scheme-XXXIV: A ligand catalyzed synthesis of substituted chromone



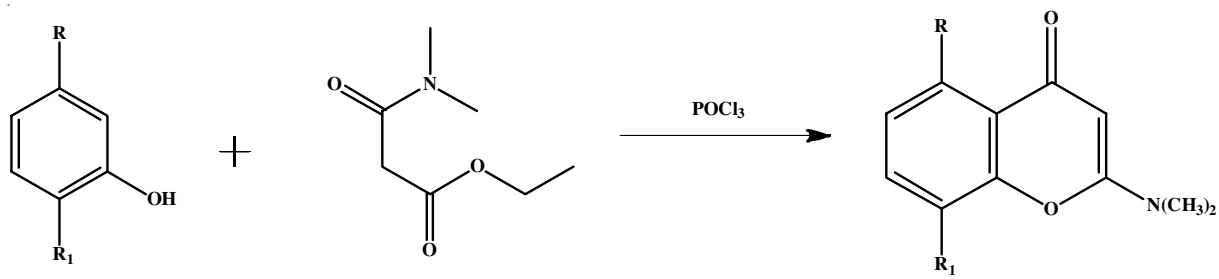
Scheme-XXXV: Synthesis of flavone-3-carboxylate derivatives from a unique alcohol-mediated reaction

The chromone ring closure is the most common use for this catalyst and the chromone ring can be constructed in two ways. One method is to reflux phenolic and carbonyl compounds in phosphorus oxychloride, while another approach is to reflux phenolic compounds with acyl side chains in $POCl_3$. Baker *et al*. [168] used $POCl_3$ as catalyst to synthesize the chromone rings in 2005 (**Scheme-XXXVI**). Under moderate conditions, chromone derivatives were synthesized in excellent yields from 2,3-allenoic acids and benzynes. To synthesize chromone derivatives, the benzyne intermediate undergoes 1,2-addition with the carbonyl group, followed by ring-opening, conjugate addition and protonolysis, due to the substituent-loading capacity 2,3-allenoic acids and benzynes (**Scheme-XXXVII**) [169].

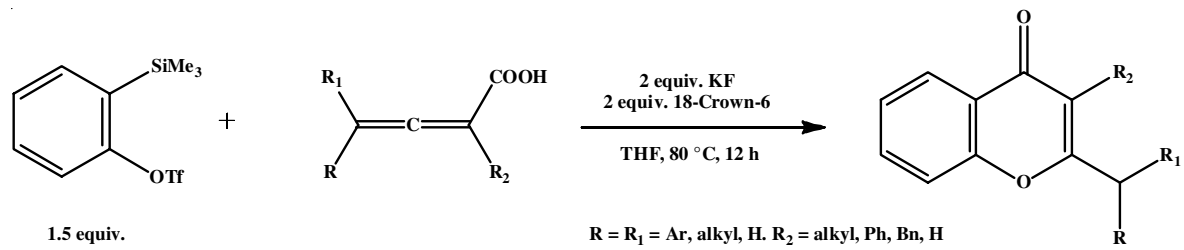
There are few methods to synthesize 3-aryl chromones, which are of vital importance because they possess enhanced biological activities [170-174]. The palladium-catalyzed Suzuki and Stille couplings of 3-iodochromones with aryl boronic acids or aryl stannanes are the commonly used methods for the synthesis of 3-aryl chromones [175-182]. However, the synthesis of nucleophilic coupling partners such as heteroaryl boronic acids and stannanes is challenging. The oxidative [4+2] cycloaddition of salicylaldehydes and internal alkynes using Rh [183], Co [184] and Ru [185] represents an attractive route to synthesize 2,3-diaryl chromones (**Scheme-XXXVIII**) [186-188]. Recently, Wu *et al*. [189] reported the transition metal-catalyzed three-component reactions to asse-mble 2,3-diaryl chromones (**Scheme-XXXVIX**). However, those synthetic methods are not transferable to heteroaryl substituted substrates, probably due to the strong coordinative properties of heteroarenes.

To synthesize 2-substituted chromones, the intramolecular O-arylation through transition metal-catalyzed Ullmann reaction [190] or base promoted nucleophilic aromatic substitution (SNAr) [191-200] has been successfully explored (**Scheme-XL**). Transition metals or strong bases, on the other hand, are frequently required. As a result, developing a new transition metal-free and additive-free synthesis technique to overcome the aforementioned deficiency would provide unique chances to integrate heteroaryl chromones into therapeutic candidates.

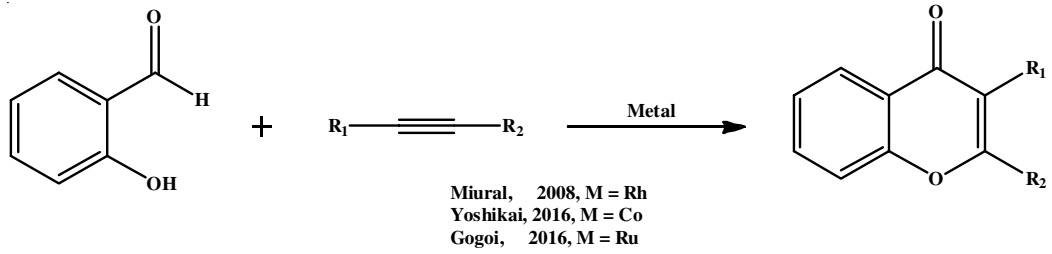
To synthesize 1,2,3-trisubstituted 4-quinolones from *ortho*-holagenphenyl ynones, a base-promoted Michael addition/Smiles rearrangement/N-arylation cascade process is reported [201]. As part of continuation interest in ynones chemistry [202-213], a unique and effective technique for synthesizing 3-heteroaryl chromones by tandem [3+2] cycloaddition/ring-opening/O-arylation reaction from readily available ynones and heteroarene *N*-oxides is also reported (**Scheme-XLI**) [214-223]. Wang *et al*. [224] presented an excellent study in which 3-(2-quinolyl) chromones were produced through an acid-mediated cascade reaction of quinoline *N*-oxides with *ortho*-hydroxyphenyl ynones while this work was being reviewed.



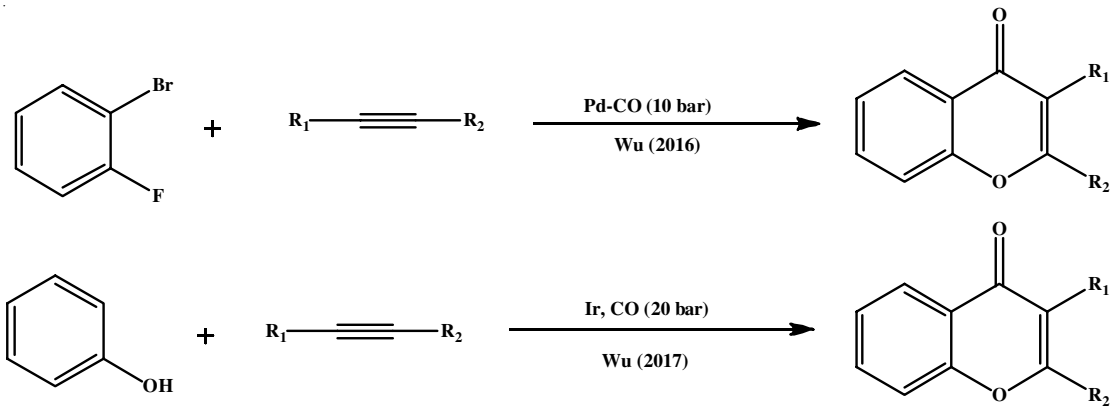
Scheme-XXXVI: Synthesis of chromone analogs using phenolic and carbonyl compounds in phosphorus oxychloride in reflux condition



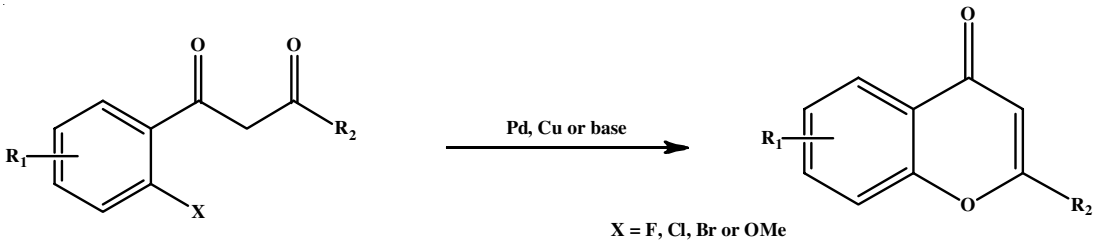
Scheme-XXXVII: Preparation of chromone derivatives by using 18-crown-6 in THF as a solvent



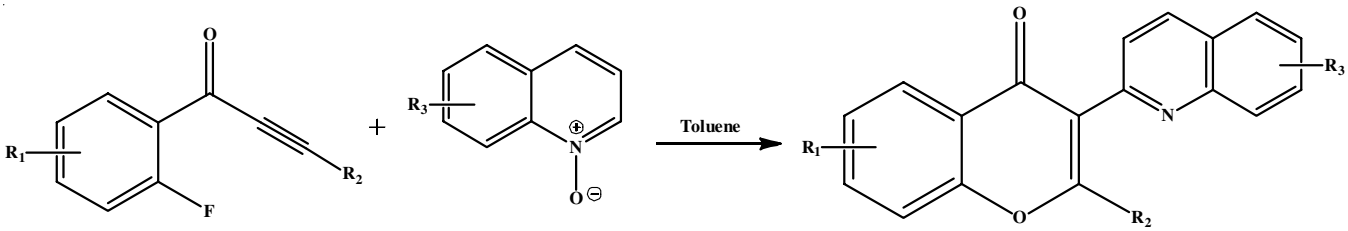
Scheme-XXXVIII: Transition metal-catalyzed annulation to 2,3-diaryl chromone



Scheme-XXXVIX: Transition metal-catalyzed three-component reaction to 2,3-diaryl chromone



Scheme-XL: Intramolecular Ullmann-type O-arylation to 2-substituted chromones



Scheme-XLI: Tandem [3+2] cycloaddition/ring opening/O-arylation form substituted chromone analog

Conclusion

It is apparent from the literature survey that researchers are still keen to isolate and synthesize chromone compounds in order to evaluate their biological properties. The synthetic techniques utilized to synthesize the chromone core were identified a long time ago and usually entailed harsh temperature and pH conditions. Although these technologies are still in use owing to their effectiveness, they urgently need to be replaced by creative, environmentally friendly and long-term solutions. Overall, developing pharmacologically active molecules based on legitimate scaffolds, such as chromone core and developing new and better druglike libraries, are critical for accelerating the identification of novel medicines. Research on chromone-based derivatives is likely to yield favourable results in the domains covered in this review article in future. This review goes through the methods used to make chromones and several of their derivatives in great detail. Due to its use in a wide range of pharmacologically active compounds, stiff bicyclic chromone fragment has been described as a preferred structure in drug development, with few instances as therapeutic agents. Due to their photochemical characteristics, chromones are also used as scaffolds for generating bioactive compounds and their use in medicinal chemistry, such as creating fluorescence probes.

ACKNOWLEDGEMENTS

The author express their gratitude to the Department of Chemistry. Dr.Ambedkar College, Deekshabhoomi, Nagpur and Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, India for the Smruti Sanshodhan fellowship in the form of financial support.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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