

## Therapeutic Potential of Chromones

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### Abstract

Chromones are found to be natural or natural origin. Several studies have been performed on the types of reagents utilized for the cyclization of chalcones to chromene-4-ones. Chromones are recognized as pharmacophores having a number of biological activities such as anticancer, antiviral, antifungal, antimicrobial, antioxidant, antidepressant and antiobesity etc. There are various synthetic methods reported. Therapeutic potential and brief discussion on synthesis of chromones are reviewed.

**Keywords:** Chromones; Anticancer; Antibacterial; Anti-HIV; Chalcones

### Introduction

Chromone moiety forms the important component of pharmacophores of a number of biologically active molecules having synthetic or natural origin and many of them have useful medicinal applications. Chromones are the heterocyclic compounds with benzopyron network with substituted keto group on pyron ring. Chromone is an isomer of coumarin. Chromone derivatives have a number of biological activities such as anticancer, antihypertensive, antiviral, antifungal, antimicrobial, antioxidant, antidepressant, anti-obesity. These derivatives also possess enzymatic inhibition properties towards different systems such as oxidoreductase, kinase, lipoxygenase and cyclooxygenase.

### Chemistry

The most conventional and common method for the cyclization is through an oxidative ring closure with bromine and a base or by refluxing with SeO<sub>2</sub> in dioxane [1]. In the reaction of chalcone with bromine, besides bromine addition to the olefinic bond, nuclear bromination at position 5 also occurs resulting in the bromoflavone [2] Chalcone dibromide is converted into chromone by the action of pyridine [3]. Ray and Dutta converted chalcone dibromide into the corresponding chromone by heating above the melting point [4]. Rao et al. studied the cyclization of chalcones with DDQ and found that even a slight variation in reaction conditions led to the formation of a mixture of chromone and chroman-4-one [5].

Yao et al. synthesized nitro chromones through regioselective nitration of chalcones followed by cyclization catalyzed by I<sub>2</sub>-DMSO [6]. Huang et al. improved the total synthesis of baicalein, wogonin, and oroxylin from chalcones using I<sub>2</sub>-DMSO as the cyclizing agent [7] and Lokhande et al. also cyclized 2-allyloxychalcones to chromones using I<sub>2</sub>-DMSO [8]. Alam studied the conversion of methylenedioxy chalcones utilizing diphenyl sulphide, I<sub>2</sub>-DMSO or DDQ and found that cyclization with I<sub>2</sub>-DMSO improve the yields, while diphenyl sulphide gave the lowest yields [9].

Kumar and Perumal demonstrated the use of ferric chloride in the oxidative cyclization of o-hydroxychalcones to chromones [10]. Kumazawa et al. prepared a naturally occurring 6-C-glucosylated derivative and the 8-C-glucosylated compound via the cyclization of chalcones [11,12].

Ganguly et al. prepared 3-acylchromones through a modified Baker-Venkataraman rearrangement using DBU and pyridine via a triketo intermediate [13] these 3-acylflavones were then converted into chromones by refluxing with aqueous K<sub>2</sub>CO<sub>3</sub>. Similarly, Pinto et al. used K<sub>2</sub>CO<sub>3</sub>-pyridine under microwave assisted conditions to prepare β-diketone intermediates, which were cyclized to give 3-acylchromones [14].

A synthesis of flavones from ortho-methoxy acetophenones via a two-step process, which utilizes only 1 equiv of LDA to form the lithium enolate has also been reported. The enolate is reacted with benzoyl cyanide to give β-diketone, which on treatment with HI yields the chromones [15]. Creuzet et al. conventionally prepared 3-Hydroxychromones from a methoxy- or benzyloxy-o-hydroxyacetophenone via Baker-Venkataraman rearrangement forming the β-diketones, which undergo cyclization [16,17].

Hageman et al. synthesized 3-Hydroxychromones from chalcones. In this method, o-hydroxychalcone was subjected to base catalyzed epoxidation of the conjugated double bond [Algar-Flynn-Oyamada (AFO)] oxidation followed by ring closure and aromatization to yield hydroxyl chromones [18].

Auwers et al. reported the synthesis of 3-hydroxychromones from aurone via a series of reactions commonly known as the Auwers synthesis [19]. Bromination of the alkene yields a dibromo adduct, which rearranges to hydroxychromone by treatment with KOH via various intermediates. The 4-O-alkyl-derivatives of 5, 7-dihydroxy-chromones were prepared by cyclization of the corresponding chalcones with sodium acetate followed by oxidation of the crude intermediates (chroman-4-ones) with a catalytic amount of iodine in pyridine [20].

7-O-alkyl derivatives of chromones have been prepared by various workers. Babu et al. prepared 7-O-alkylated derivatives of chrysin, (5, 7-dihydroxychromones) having antibacterial activity using alkyl halides and K<sub>2</sub>CO<sub>3</sub> [21]. Shin et al. also attempted to synthesize regioselective 7-O-alkyl derivatives of chrysin using K<sub>2</sub>CO<sub>3</sub> or KHCO<sub>3</sub>, but obtained a mixture of mono- and di-O-alkylated products [22]. They successfully tried to form 7-O-esters using DCC and DMAP. It was concluded that esterification occurred primarily at C7 because of the shielding of the 5-hydroxy by the 4-keto group.

Jain et al. also attempted nuclear iso-prenylation of chrysin by refluxing it with prenyl bromide, but the results were not satisfactory due to poor yields [23] Comte et al. prepared C-prenylated chromones in low yields by microwave irradiation on a solution of chrysin and tetramethyl ammonium hydroxide in methanol containing tetraethylammonium iodide [24].

Marta Perro Neves et al. successfully synthesized dihydropyranochromones by one-pot synthesis, using Montmorillonite K10 clay as catalyst under microwave irradiation [25]. Ramesh Kamboj et al. synthesized 3-alkoxy-6-chloro-2-(3-methylthiophen-2-yl)-4H-chromen-4-ones in methanol [26] with pyrex filtered UV-light led to the formation of tetracyclic compounds.

A series of bromo-substituted 3-aryl flavanones and flavones have been synthesized [27]. The identities of the new compounds synthesized have been developed on the basis of usual chemical transformation and IR, NMR spectral studies. The diisochromenochromen-4-one has been prepared from the photocyclization reaction of bischromen-4-one. The later compounds are obtained from the O-alkylation of the suitable 3-hydroxy-2-aryl-4H-chromen-4-one with bischloromethyl-diphenyl in dry acetone, anhydrous  $K_2CO_3$ , and PTC ( $Bu_4N^+I^-$ ) under refluxing conditions [28].

Liu Xin-Hua et al. synthesized ten novel 3-(2-(3-methyl-5-substituted-phenyl-4,5-dihydropyrazol-1-yl)-2-oxo-ethoxy)-2-substituted-phenyl-4H-chromen-4-one derivatives [29]. Eeda Venkateswararao et al, a series of (E)-5-alkoxy-3-(3-phenyl-3-oxoprop-1-enyl)-4H-chromen-4-ones and (E)-5-alkoxy-3-(3-hydroxy-3-phenylprop-1-enyl)-4H-chromen-4-ones were synthesized [30]. Qiao Ren et al. synthesized 6, 7-Dimethyl-3-[(methyl-2-(methyl-(1-3-trifluoromethyl-phenyl)-1H-indol-3-yl-methyl)-amino)-ethyl]-chromen-4-one drug that prevent TNF- $\alpha$  binding to its receptor [31].

## Biological activities of chromene-4-ones

### Antibacterial and antifungal activities

Bingi et al. synthesized a number of 3-hydroxy-6-(hydroxymethyl)-2-(2-phenyl-4H-chromen-4-yl)-4H-pyran-4-ones in a one pot catalyst free reaction of 2-hydroxy chalcone with kojic acid in toluene at reflux temperature and studied their biological activities. The compounds showed potent antimicrobial activity against various strains of bacteria [32].

Hatzade et al. attempted a convenient route to synthesis 7-O- $\beta$ -D-glucopyranosyloxy-3-(3-oxo-3-arylprop-1-enyl)-4H-chromene-4-ones. These compounds were evaluated for antibacterial and antifungal activities [33].

Javed Sheikh et al. reported computational evaluation and experimental verification of 7-hydroxy-3-(1-phenyl-3-aryl-1H-pyrazol-5-yl)-4H-chromen-4-ones and their O- $\beta$ -D-glucopyranosides for their antimicrobial and antioxidant activity [34]. Palakuri Kavitha et al. synthesized tridentate 3-formyl chromone Schiff bases of Ni(II) and Zn(II) such as 3-((2-hydroxyphenylimino)methyl)-4H-chromen-4-one, 3-((3-hydroxypyridin-2-ylimino)methyl)-4H-chromen-4-one and 3-((2-mercaptophenylimino)methyl)-4H-chromen-4-one which exhibited pronounced activity against tested bacteria and fungi strains compared to the ligands [35].

Kale et al. synthesized and characterized some of the chromone derivatives as antimicrobial agents (FIG. 1) [36].

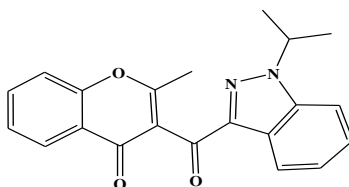


FIG. 1. Chromone derivatives.

Chromone conjugated dithiazoles and 4-oxo-4H-chromene-3-carbothioic-N-phenylamides were synthesized and screened for antibacterial and antifungal by disk-diffusion assay. The dithiazole derivative (FIG. 2a) 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 observed for in FIG. 2b [37].

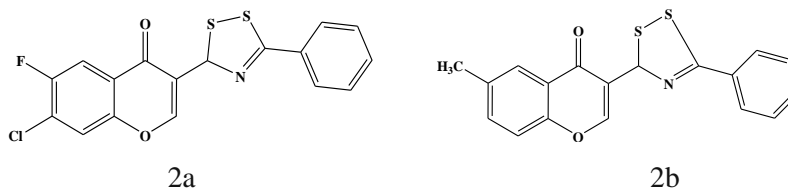


FIG. 2. 4-oxo-4H-chromene-3-carbothioic-N-phenylamides.

Musthafa et al. developed chromone fused pyrazolines, pyrazoles, dibromo derivatives and dihydropyrimidines, under microwave irradiation, and evaluated for *in vitro* antibacterial 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*. The antimicrobial activity of compounds indicates that various compounds are potent antimicrobial agents (FIG. 3a and 3b) [38].

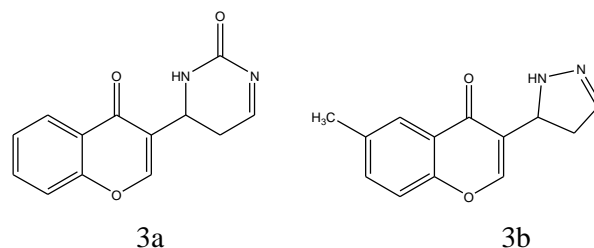


FIG. 3. The antimicrobial activity of compounds indicate that various compounds are potent antimicrobial agents.

Nawrot-Modranka et al. synthesized chromone derivatives and studied their *in vitro* antibacterial activity (FIG. 4) [39].

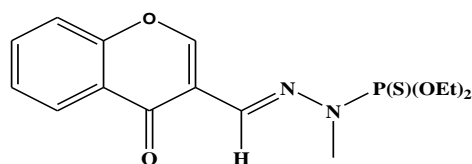


FIG. 4. 3-tetrazolylmethyl-4H-chromen-4-ones.

Pedro et al. synthesized novel 3-tetrazolylmethyl-4H-chromen-4-ones via multicomponent reaction and studied their biological evaluation against *Entamoeba histolytica*, *Giardia lamblia* and *Trichomona vaginalis* [40].

Ibrahima coworkers synthesized new nitrogen heterocyclic systems combining chromone moiety with 1,2,4-triazole or 1,2,4-triazine in one molecular frame through an azomethine linkage 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 phaseolicola* as Gram-negative bacteria, and the fungi *F. oxysporum* and *A. fumigatus* [41]. Compounds showed high activity toward the tested fungi. (FIG. 5a and 5b).

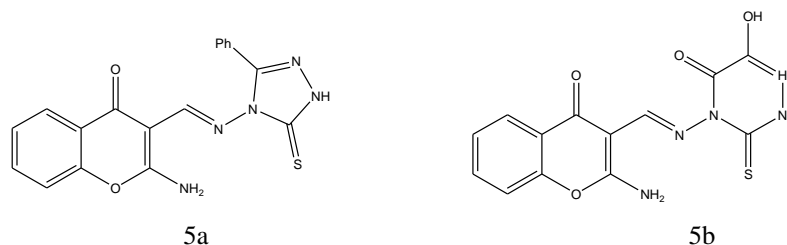


FIG. 5. Nitrogen heterocyclic systems combining chromone moiety with 1,2,4-triazole or 1,2,4 triazine.

### Anti-cancer activity

Liu T et al. synthesized chromone analogues bearing heterocyclic thioether moiety and were assayed for their antitumor activity. Out of these, IC<sub>50</sub> of 3-(benzothiazole-2-ylsulfanyl)-chromen-4-one against MDA-MB-435S was found out to be 17.2  $\mu$ M. They concluded that the presence of heterocyclic thioether or cyclic tertiary amine will benefit the antitumor activities of chromones [42].

Three methylated quercetins and a series of O-3-substituted, tetra-O-methylated quercetin derivatives have been synthesized by Jian Yuan et al. and studied their anticancer activity [43]. He Huang et al. successfully prepared a new type of quercetin derivatives, the novel compounds show higher selectivity as inhibitors against Src tyrosine kinase. (IC<sub>50</sub> values ranging from 3.2 mM to 9.9 mM) than against EGFR tyrosine kinase. Molecular docking revealed that both hydrophobic and hydrogen bonding interactions are important to the selectivity [44]. Guo-Biao Liu et al. synthesized (5, 7-dihydroxy-4-oxo-4H-chromen-3-yl) methyl esters and evaluated LPS-activated murine macrophages cell culture systems and cytotoxicity of these compounds was checked using MTT assay [45]. Liu Xin-Hua et al. synthesized ten novel 3-(2-(3-methyl-5-substituted-phenyl-4,5-dihydropyrazol-1-yl)-2-oxo-ethoxy)-2-substituted-phenyl-4H-chromen-4-one derivatives and screened for their anticancer activity (FIG. 6). The bioassay tests show that compounds exhibited potentially high activity against human gastric cancer cell SGC-7901 [46]. Ishar et al. Synthesized and evaluated novel 6-chloro-/fluorochromone derivatives as potential topoisomerase inhibitor anticancer agents [47].

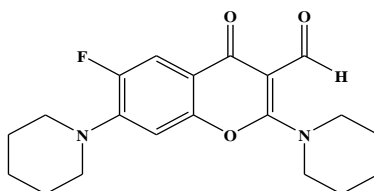


FIG. 6. 6-chloro/fluorochromone derivatives.

The compounds (3-chloro-4-oxo-4H-chromen-2-yl)methyl piperidine-1-carbodithioate (FIG. 7a) and (6-chloro-4-oxo-4H-chromen-3-yl)methyl piperidine-1-carbodithioate (FIG. 7b), showed the most promising antitumor activity against SW-480 cells and MDA-MB-435 cells [48]. Compound exhibited cytotoxicity against human neuroblastoma cell line compared to the standard drug Doxorubicin (FIG. 8) [49].

### Anti-inflammatory activity

Hasan and researcher synthesized 6-Aminomethyl-2-aryl-1-benzopyran-4-one derivatives and tested for anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation actions. Among the tested compounds, two compounds showed higher degree

of anti-inflammatory activity [50]. Khan et al. effectively synthesized and characterized 3-formylchromone and its derivatives. Anti-inflammatory activities were studied of these compounds [51].

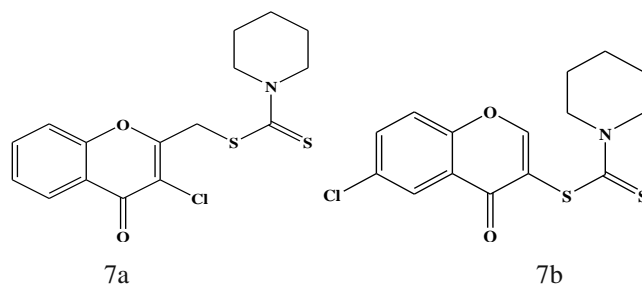


FIG. 7. (3-chloro-4-oxo-4H-chromen-2-yl)methyl piperidine-1-carbodithioate and (6-chloro-4-oxo-4H-chromen-3-yl)methyl piperidine-1-carbodithioate.

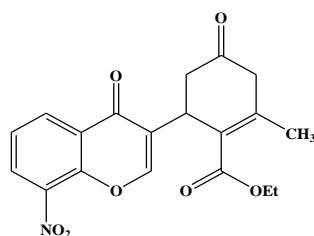


FIG. 8. Doxorubicin.

### Anti-HIV activity

Casano et al. developed and synthesized a series of methoxy flavones and studied their antiproliferative activity on *Plasmodium falciparum* parasites and anti-HIV activity. Methoxyflavone (FIG. 9a) was active in both *P. Falciparum* and HIV-1 whereas compounds (FIG. 9b) and (FIG. 9c) were specific inhibitors of the HIV-2 multiplication. Author suggested that para substitution on the B ring is needed to promote antiplasmodial activity and increase HIV-2 potency [52].

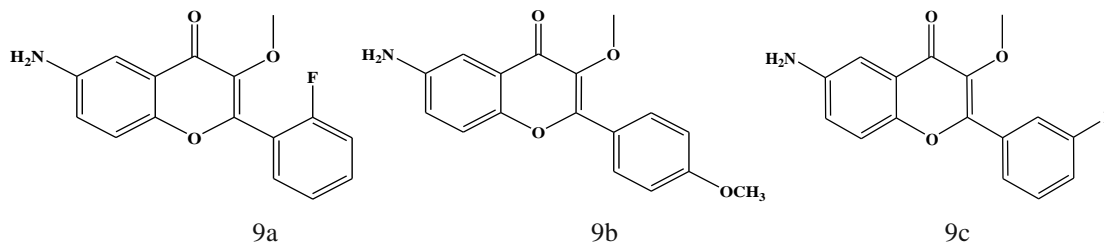


FIG. 9. Methoxyflavone.

Among a series of benzopyran-4-one scaffolds synthesized by Ungwitayatorn et al. via one pot cyclization reaction, 7,8-dihydroxy-2-(30-trifluoromethylphenyl)-3-(300-trifluoromethylbenzoyl) chromone (FIG. 10) showed HIV-1 protease inhibition *in vitro* [53].

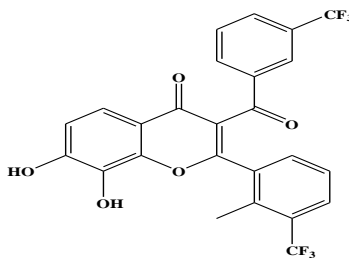


FIG. 10. 7,8-dihydroxy-2-(30-trifluoromethylphenyl)-3-(300-trifluoromethylbenzoyl) chromone.

#### Antioxidant activity

Yasar et al. synthesized azaflavone (FIG. 11) and evaluated their antioxidant activities and antimicrobial activities [54].

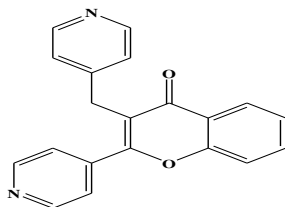


FIG. 11. Azaflavone.

#### Anti-malarial activity

A new chromone derivative (FIG. 12) was isolated from the wood-decay fungus *Rhizina* species by Isaka et al. and evaluated for antimalarial activity against *P. falciparum* K1. This derivative exhibited antimalarial activity with an IC<sub>50</sub> of 5.1 mg/mL.

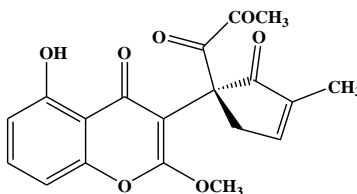


FIG. 12. New chromone derivative isolated from the wood-decay fungus *Rhizina* species.

#### Anti-convulsant activity

Following FIG. 13a and 13b chromone showed 100% protection 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.

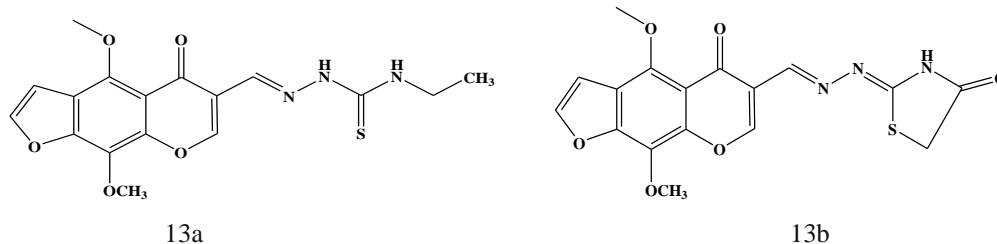


FIG. 13. Chromone derivatives.

### Anti-platelet activity

Highest activity was found, when the 2-amino substituent of tested chromones (FIG. 14) was a diethylamino group. Activity was increased, when the presence of electron releasing substituents (-OH, -OCH<sub>3</sub>, -CH<sub>3</sub>) was at position 7, whereas a decrease occurred when an electron withdrawing substituent was present in position (3-NO<sub>2</sub>) or (6-NO<sub>2</sub>, 6-Cl).

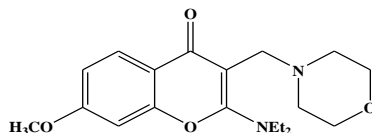


FIG. 14. Diethylamino group.

### Gastroprotective activity

9-and 6-Alkylaminomethyl furochromones (FIG. 15) synthesized from the naturally occurring chromones visnagin and khellin were screened for gastroprotective activity in the rat ethanol-induced damage model. 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, furochromones exhibited good gastroprotective activity in the ethanol damage model.

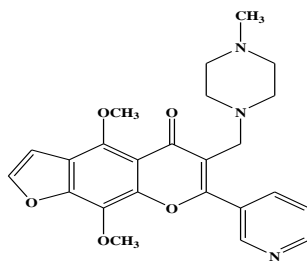


FIG. 15. 9-and 6-Alkylaminomethyl furochromones.

### H1 Anti-histaminic activity

2-phenyl-4H-chromen-4-one (FIG. 16) analogs were evaluated for the H1 antihistaminic activity computational method, the compounds showed highest antihistaminic activity.

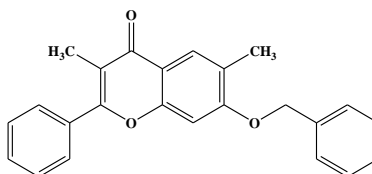


FIG. 16. 2-phenyl-4H-chromen-4-one.



### Antihypertensive activity

Wu et al. synthesized 3-Phenylflavonoxy propanolamines (FIG. 17a and 17b) and evaluated for potential antihypertensive activity in spontaneously hypertensive rats as well as for *in vivo* and *in vitro* evidence of  $\beta$ -adrenoceptor antagonism. Compounds were active in lowering blood pressure at 8 mg/kg.

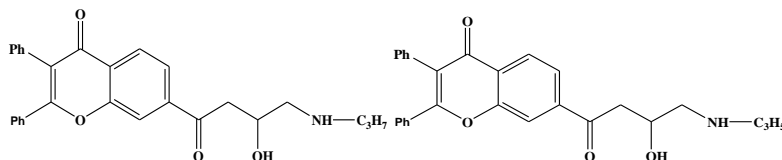


FIG. 17. 3-Phenylflavonoxy propanolamines.

### m-calpain inhibition activity

Lee et al. prepared chromone carboxamide derivatives and evaluated for m-calpain inhibition using a casein-coomassie blue microplate assay. Compound (FIG. 18c), was the most potent calpain inhibitor of this series ( $IC_{50}$  0.24 mM), exhibited 14.4% and 22.4% inhibition, demonstrating high selectivity of chromone derivatives for m-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.

The compounds (FIG. 18) possessing benzyl and phenethyl amide showed good inhibition of m-calpain, while the potencies were decreased about 10-fold when these substituents were replaced by 2-(morpholin-4-yl) ethyl or isopropyl amide.

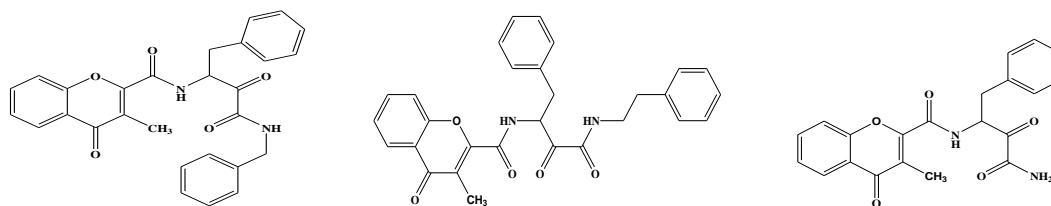


FIG. 18. Benzyl and phenethyl amide combined with m-calpain forms 2-(morpholin-4-yl) ethyl or isopropyl amide.

New chromone carboxamide derivatives were synthesized and evaluated using human calpain I isolated from erythrocytes. Compounds with 4-methoxyphenethyl group at the keto-amide position, i.e., (FIG. 19a) and (FIG. 19b) exhibited the most potent m-calpain inhibitory activities ( $IC_{50}$  0.09e0.10 mM), and compound (FIG. 19c) showed both potent m-calpain inhibitory activity ( $IC_{50}$  0.28 mM) and antioxidant activities in DPPH scavenging and lipid peroxidation inhibition assay reported by Kim et al. [54].

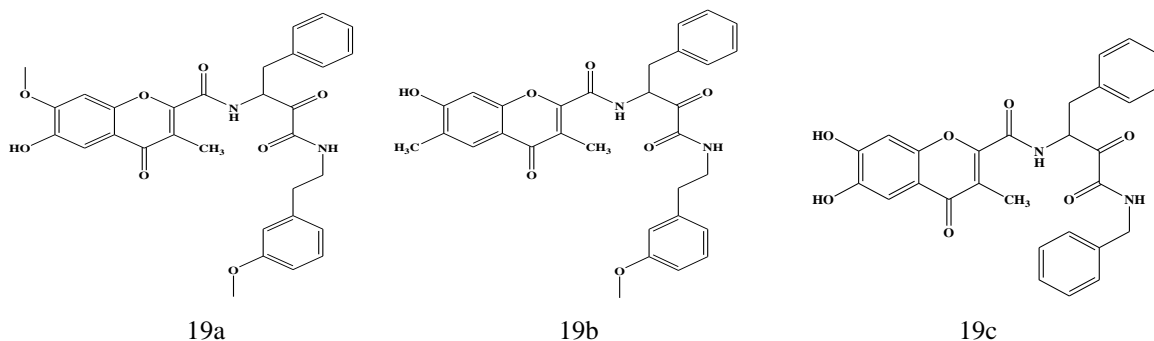


FIG. 19. Keto-amide position exhibited the most potent m-calpain inhibitory activities.

### Glutathione reductase activity

A series of chromone compounds (FIG. 20a-20d) were synthesized as S-nitrosogluthathione reductase (GSNOR) inhibitors by Sun et al. These GSNOR inhibitors can be utilized in any pharmaceutically acceptable dosage form, including but not limited to injectable. Some of the compounds (FIG. 20a to 20c) have showed IC<sub>50</sub> less than 0.5 mM and compound (20d) showed IC<sub>50</sub> less than 0.1 mM against the GSNOR inhibitors [55].

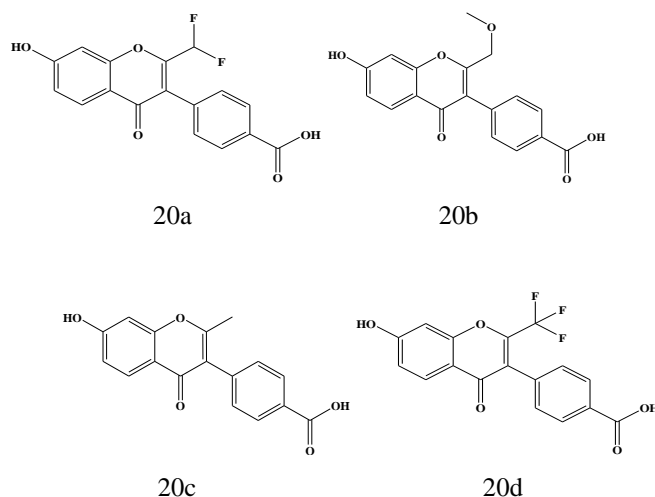


FIG. 20. S-nitrosogluthathione reductase (GSNOR) inhibitors.

### Anti-allergic activity

Abram et al. [56] synthesized 2,3,7-Substituted chromone salts (FIG. 21) and screened for their antiallergic activity. All compounds tested exhibited oral antiallergic activity when administered at a concentration of 30 mg/kg.

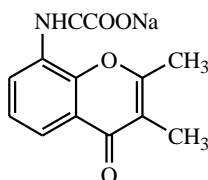


FIG. 21. 2,3,7-Substituted chromone salts.

## Conclusion

Therapeutic potential and synthetic brief of chromones are reviewed. There have been several synthetic methods developed. Noticeably, cyclization of chalcones to chromene-4-ones is one of the most utilized synthetic tools used in the synthesis of chromones. These moieties are recognized as pharmacophores having a number of biological activities such as anticancer, antiviral, antifungal, antimicrobial, antioxidant, antidepressant, anti-HIV and antiobesity etc.

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