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OVERVIEW OF BIOLOGICAL SIGNIFICANCE OF CHROMONES AND FLAVONES

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Abstract
Chromones is a class of organic compounds having chromone as backbone. The chromone moiety is present in flavonoids. Because of the numerous health benefits that flavonoids derived from plants have been linked to in numerous epidemiological studies, there has been a surge in interest in this field of study. Given the direct correlation between flavonoids and human health by means of nutrition, the structure-function link needs to be evaluated. On the basis of substitution on chromone ring, flavonoids are further classified as 2-Aryl benzopyrans (flavones), 3-Aryl benzopyrans (isoflavones), and 4-Aryl benzopyrans (neoflavonoids). The bioavailability, metabolism, and biological activity of flavonoids depend upon the configuration, total number of hydroxyl groups, and substitution of functional groups about their nuclear structure. Fruits and vegetables are the main dietary sources of flavonoids for humans, along with tea and wine. Most recent researches have focused on the health aspects of flavonoids for humans. Out of all the flavonoid's class, flavones are shown to have wide range of biological activities viz; antioxidative activity, neuroactive agents, hepatoprotective, anti-inflammatory, antimicrobial and anticancer activities, while some flavones exhibit potential antiviral activities. This review highlights the structural features of flavones and their biological activities.

Keywords: Chromone, flavone, polyphenolic, flavonoids.

1 Introduction:

Chromones is a class of organic compounds having chromone as backbone. The chromone moiety is present in flavonoids such as flavones, flavanols and Isoflavones. Flavonoids are a class of heterocyclic substances that include oxygen and are present in a variety of plants. They are low-molecular weight polyphenolic secondary metabolites with important therapeutic values [i]. The word flavonoid is taken from the Latin word 'flavus' which means yellow [ii]. Plant cells that use photosynthetic processes contain flavonoids, which give flowers and fruits their yellow colour. These are present in human and animal

diets in the form of phytonutrients, as they can't be biosynthesized in human or animal bodies [iii]. Khellin was the first furochromone-based heterocyclic drug administered in curative medicine extracted from the seeds of the plant Anni visnaga and used in clinical therapy. At the time of its discovery, around 1950, khellin was used to cure the diseases like angina pectoris and respiratory syndrome [iv]. Due to their diverse pharmacological activities, chromones or chromone derivatives have been investigated for their potential in treating various medical conditions. Hence the study of chromone compounds of pharmacological importance is not only an observation of medicinal chemistry in its broad aspect but also has a very wide scope. The term "chromone" is derived from the Greek word "chroma," which means "colour." It signifies that compounds containing a chromone moiety exhibit a broad range of colours. The core structure of chromones comprises a benzene ring fused to a pyranone ring that is 4H-Benzopyran-4-One (Figure 1.1) [v]. Due to structural diversity chromones can be classified to various types based on substituents and their position. Flavones are aryl substituted benzopyrans (chromones) with 15 carbons in skeleton. Considering the position of the aryl group on chromone, they are classified into three types: 2-Aryl benzopyrans (flavones), 3-Aryl benzopyrans (isoflavones), and 4-Aryl benzopyrans (neoflavonoids) (Figure 1.2) [vi].

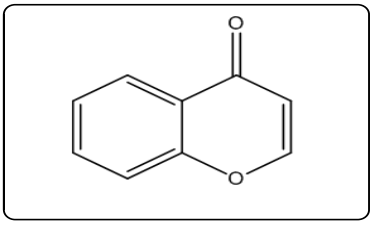


Figure 1.1: Chromone ring

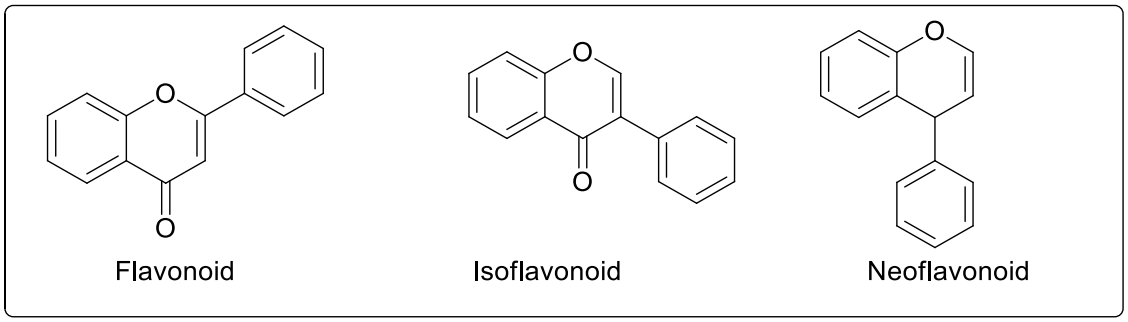


Figure 1.2: Classification of flavones

This chapter is a review which deals with the chemistry of flavones and chromones in terms of general biological activities of these compounds mainly emphasizing on antimicrobial activities.

2. Biological Significance:

Researchers are often focused on tailoring the chromone structure to maximize its pharmacological efficacy. Structure-activity relationship (SAR) studies play a pivotal role in understanding how specific structural alteration comprehensively affects the compound's bioactivity. This knowledge facilitates the design and synthesis of novel chromone derivatives which have less adverse effects and are more effective. Chromones exhibit a broad range of biological activities, making them subject of immense interest and importance in medicinal chemistry. Some evident effects on biological activities are discussed in the following sections:

2.1. Antibiotic Activity:

Gomes. et al., reported the synthesis of 2- styryl chromones (2-SC) and 3-substituted flavones using the Baker–Venkataraman method and tested them as scavengers of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and additionally examined for their ability to chelate metals and decrease activity (Figure 1.3). The findings showed that 2-SC scavenging of ROS and RNS is reduced when hydroxyl groups are methylated. The reduction in the scavenging activities was also due to the methylation at B-ring. Conversely, the addition of a substituent either hydroxyl or methoxyl at position 8 ranged in its effect on the scavenging activities, depending on the reactive species [vii].

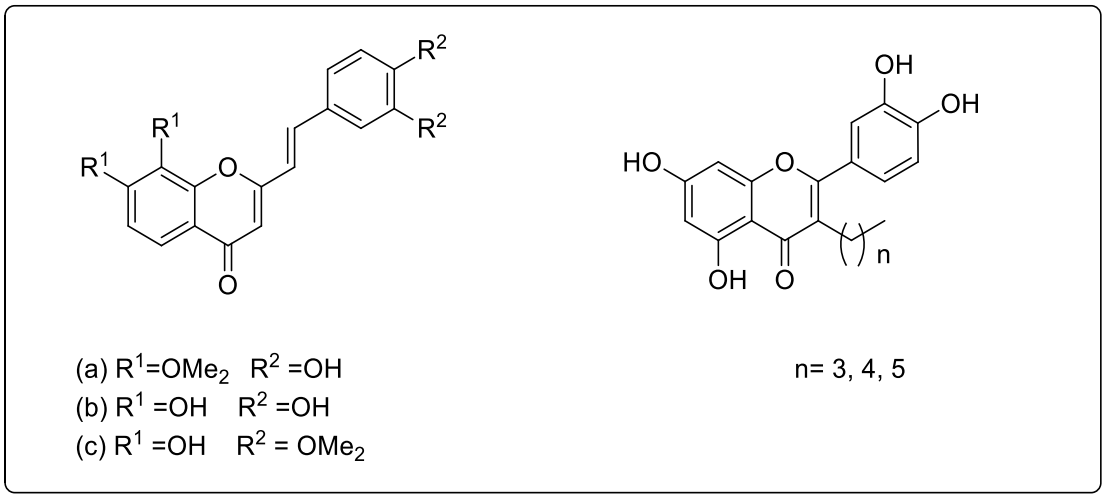
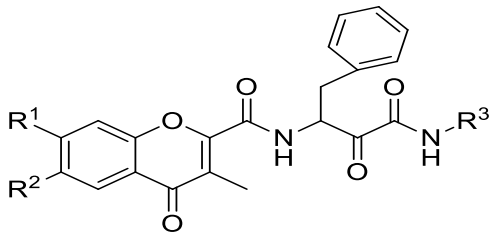


Figure 1.3

Lee. et al., reported new synthetic derivatives of chromone carboxamide to provide alternative m-calpain inhibitors (Figure 1.4). Among the synthesized derivatives, substances h and l have a 4-methoxyphenethyl group attached to the keto-amide position, most significantly lowered m-calpain (IC50 ¼ 0.09e0.10 mM) to levels comparable to that of the parent compound and compound i showed both potent m-calpain inhibitory activity (IC50 ¼ 0.28 mM) and DPPH (1,1,-diphenyl-2-picryl-hydrazil) scavenging and lipid peroxidation inhibitory effects, whereas MDL 28,170 and parent showed no antioxidant activity at concentrations under 100 m M. These results suggested that compounds h, i, and l can be used for further in vitro studies [viii].



(a) R^1 =OCH_3	R^2 =OCH_3	R^3 = H
(b) R^1= OCH_3	R^2 =OCH_3	R^3 =Benzyl
(c) R^1 =OCH_3	R^2 =OCH_3	R^3 =4-Methoxyphenethyl
(d) R^1 =OCH_3	R^2 =H	R^3 =H
(e) R^1 =OCH_3	R^2 = H	R^3 =Benzyl
(f) R^1 =OCH_3	R^2 = H	R^3 =4-Methoxyphenethyl
(g) R^1 =OCH_3	R^2 = OH	R^3 = Benzyl
(h) R^1 =OCH_3	R^2 = OH	R^3 =4-Methoxyphenethyl
(i) R^1 =OH	R^2 = OH	R^3 =Benzyl
(j) R^1 =OH	R^2 = OH	R^3 =4-Methoxyphenethyl
(k) R^1 =OH	R^2 = H	R^3 =Benzyl
(l) R^1=OH	R^2 H	R^3 =4-Methoxyphenethyl

Figure 1.4

2.2. Anticancer Activity:

Wang. et al., reported the synthesis of a new ligand, 6-hydroxy chromone-3-carbaldehyde thiosemicarbazone and its Ni (II) complex and evaluated them for in vitro biological tests using THP-1, cancer cell lines of Raji and Hela (Figure 1.5). The Ni (II) complex exhibited notable cytotoxic activity against these three cancer cell lines in comparison to the ligand. Then, using viscosity measurement techniques, ethidium bromide displacement assays, and spectrometric titration, the interactions between the ligand L and Ni (II) complex, and calf thymus DNA were examined. According to the outcomes of experiments, the ligand L allowed the Ni (II) complex to bind to DNA by a mechanism of interaction with the intrinsic binding constants (1.10 ± 0.65) _ 106 M_1 and (1.48 ± 0.57) _ 105 M_1, respectively with DNA [ix].

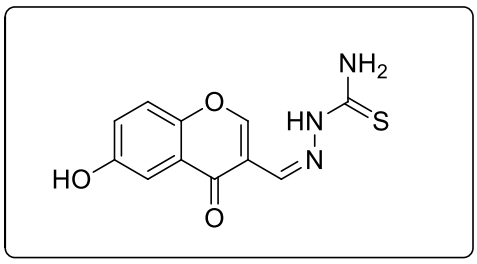


Figure 1.5

Kawase. et al., investigated the urease inhibitory, anti-HIV, anti-Helicobacter pylori, and tumour cell cytotoxic properties of several 3-formylchromone derivatives (Figure 1.6). Cytotoxicity specific to tumour cells was found in some 3-formylchromone compounds when their relative cytotoxicity was compared to three normal human cells and four human tumor cell lines. There was no obvious correlation between the chemical structures of the substances and their cytotoxicity. 6,8-Dichloro-3-formylchromone demonstrated strong urease inhibition against jack bean urease130 and equivalent anti-H-pylori efficacy to metronidazole [x].

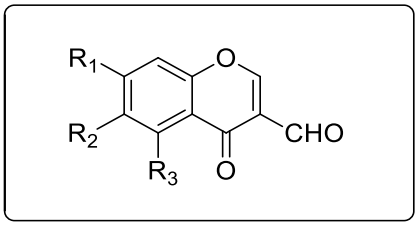


Figure 1.6

2.3. Antidiabetic activity:

Agents elevated blood glucose levels brought on by inefficient insulin synthesis are the cause of diabetes mellitus. All around the world, this issue is highly prevalent [xi]. Current anti-diabetic medications have a number of negative effects [xii]. Ceylan. et al., reported the 2,4-imidazolidindione and 2,4-thiazolidindione chromone derivatives (Figure 1.7). Heterocyclic ring attachment in the third place resulted in more active derivatives than at the second position. Comparing chromone compounds 2,4-imidazolidindione (142.7 17.60%) and 2,4-thiazolidindione (155.4 35.16%) to the conventional medication glibenclamide (138 13.99%), the former demonstrated significant in vitro insulinotropic potential at a dose of 1µg/mL. Similar activity was seen when methyl and ethyl groups were incorporated into the heterocyclic ring compared to unsubstituted derivatives. Eventually, heterocyclic cores of imidazolidindione, 2,4-thiazolidindione, and 2-thioxoimidazolidine-4-one were created in chromone derivatives synthesised by Ceylan. et al.,. The most active drug has a methyl group at heterocyclic nitrogen, while derivatives with modified 2,4-thiazolidinione rings showed improved activity [xiii].

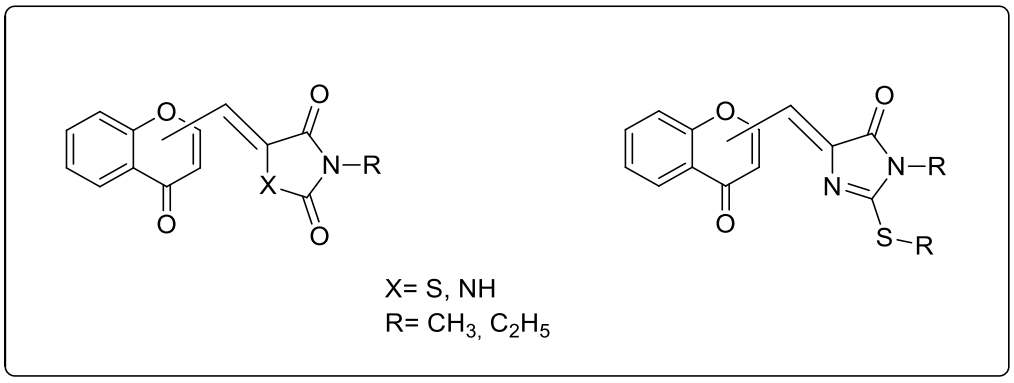


Figure 1.7

2.4. Anti-inflammatory:

There are very few substantial targets that have been identified and linked to the inflammatory process in the last 20 years of the target-based drug development period. The majority of these play a biological function through enzymatic interactions like cyclooxygenases 1 and 2 (COX-1 and COX-2, respectively) and LT receptors. These antagonists work against natural pro- inflammatory agents including histamine, prostaglandins, and leukotrienes (LTs). Several investigations were conducted in this field with the goal of discovering and developing new anti-inflammatory medicines taken from the chromone scaffold. Analogues of 7-methanesulfonylamino-6-phenoxychromone were synthesized and assessed for both immediate and persistent inflammation. (Figure 1.8) [xiv].

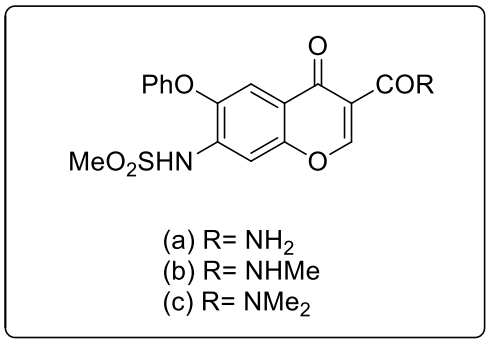


Figure 1.8

Gautam. et al., synthesized and assessed many derivatives of stellatin (5-Hydroxy-6,7-dimethoxy-2-methylchromone) in relation to COX-1 and COX-2, drawing inspiration from stellatin (Figure 1.9), a naturally occurring chromone separated from Dysophylla stellatais characterized as a cyclooxygenase inhibitor. Additionally, they demonstrated a greater degree of anti-inflammatory efficacy than stellatin in the TPA (12-O-tetradecanoylphorbol-13-acetate) -induced mouse ear edema experiment [xv].

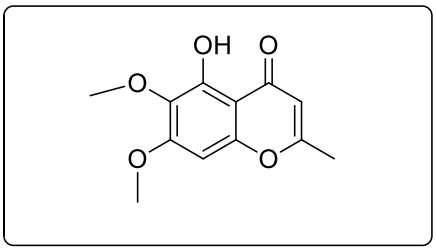


Figure 1.9

2.5. Neuroactive:

Takao. et al., published a variety of 2-azolylchromone derivatives and examined them for respective inhibitory capabilities in an effort to find new potent chromone-based inhibitors of MAO (monoamine oxidase) A and B for the treatment of neurological disorders (Figure 1.10). The results of the study demonstrated that the derivatives exhibited strong inhibitory activities against MAO-A, with the most potent compound having an IC50 (half-maximal inhibitory concentration) value of 0.023–0.32 μM. In contrast, the most potent compound against MAO-B had an IC50 value of 0.019–0.73 μM. This suggests that 6-methoxy substitution was effective in inhibiting MAO-A, and 7-methoxy substitution was feasible in inhibiting MAO-B. The study emphasizes how crucial 2-triazolylchromone is for creating novel MAO inhibitors [xvi].

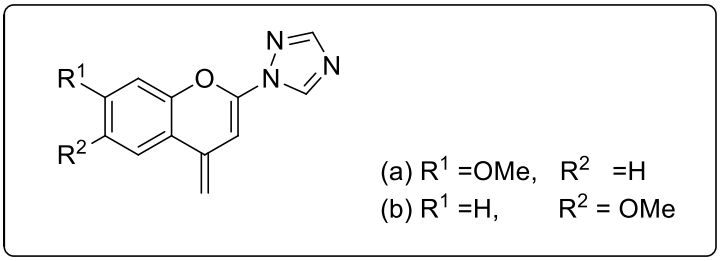


Figure 1.10

Reis. *et al.*, synthesized chromone-based MAO-B inhibitor and biologically evaluated against MAO-B with an IC_{50} value of 0.67 μM as a non-competitive reversible inhibitor (Figure 1.11). The biological activities were enhanced by the direct connection of the carbonyl group to the γ-pyrone ring and the presence of meta and para substituents in the exocyclic ring. Additionally, it had a good toxicological profile and physicochemical characteristics that

indicated BBB (blood-brain barrier) permeability, making it a good option for further research on animals. [xvii]

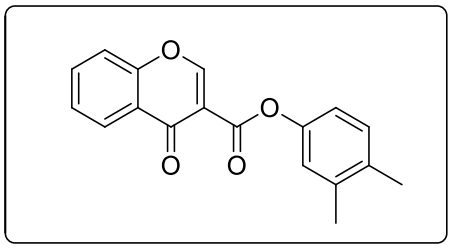
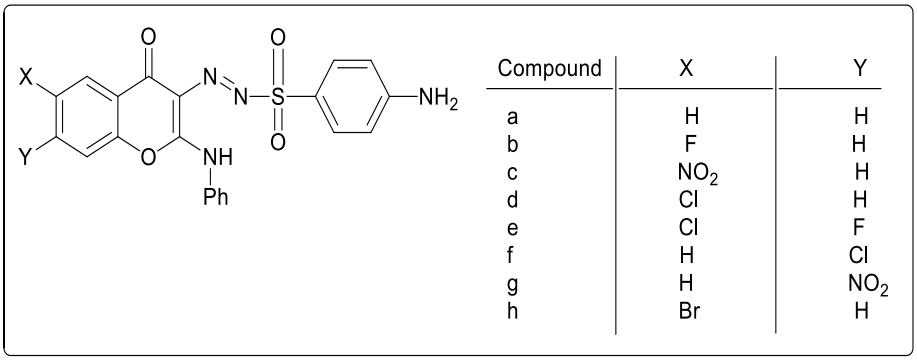


Figure 1.11

2.6. Antimicrobial activity:

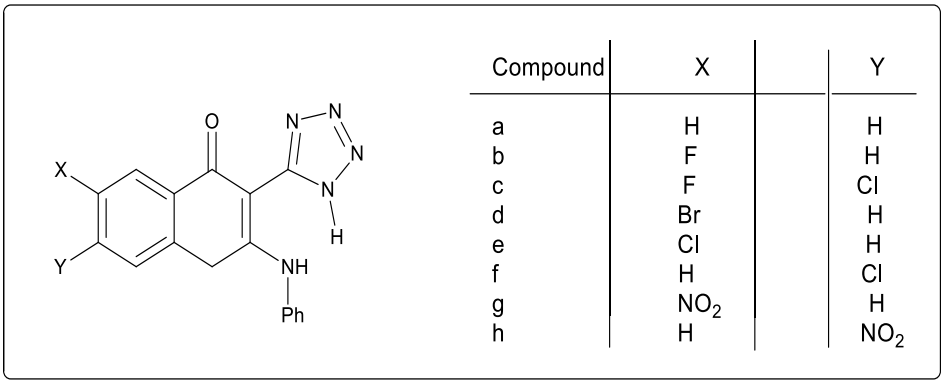
When it comes to drug discovery, chromones are the most significant structural class. Indeed, there are so many compounds containing this moiety that it is nearly difficult to summarize their whole spectrum of biological activity. As a result, only some possible scope of activities shall be discussed**.** Chopra. et al., reported the synthesis of derivatives of 4- amino-N-[(4-oxo-2-(phenylamino)-4h-chromen-3-yl) methylene] benzenesulfonamide and also evaluated for antibacterial and antifungal activity against *Escherichia Coli, Staphylococcus aureus, Bacillus subtilis, Pseudomonas aerogenosa, Aspergillus niger, and Candida albicans* (Figure 1.12). All compounds showed good potency (at 30µg/ml) in comparison to the standard medications fluconazole and ciprofloxacin at the same concentration [xviii].



Compound	X	Y
a	H	H
b	F	H
c	NO_2	H
d	Cl	H
e	Cl	F
f	H	Cl
g	H	NO_2
h	Br	H

Figure 1.12

Chopra. et al., reported the synthesis of chromone-tetrazole hybrids (a–h) and evaluated for antibacterial and antifungal activities by using the Kirby-Bauer disc diffusion method compared with the standard drugs Ciprofloxacin and Fluconazole (Figure 1.13). The results showed that compounds a, b, and e were more potent against gram-positive and gram-negative bacteria, and compounds d, f, g, and h were more effective against gram-positive bacteria. Out of all compounds, c was determined to be most effective against gram-negative bacteria. Antifungal studies showed that compounds b and f were effective against *C. albicans and A. niger.* Compounds a, d, e, and h were more effective against *C. albicans* only. Compounds c and g showed more potent activity against *A. niger* [xix].



Compound	X	Y
a	H	H
b	F	H
c	F	Cl
d	Br	H
e	Cl	H
f	H	Cl
g	NO_2	H
h	H	NO_2

Figure 1.13

Chromone-dihydroquinazolinone derivatives, a, b & c contain bromine atom developed and assessed for antimicrobial activities and the results revealed that compound a & b were most effective against *S. aureus* and *E. coli* with Minimal Inhibition Concentration (MIC) 62.5µg/mL when compared with ciprofloxacin (MIC=25-50µg/mL) (Figure 1.14). Compound c containing halogen atom exhibited moderate antifungal activity against *C. Albicans* (MIC=200µg/mL) when compared with griseafulvin (MIC=500µg/mL) [xx].

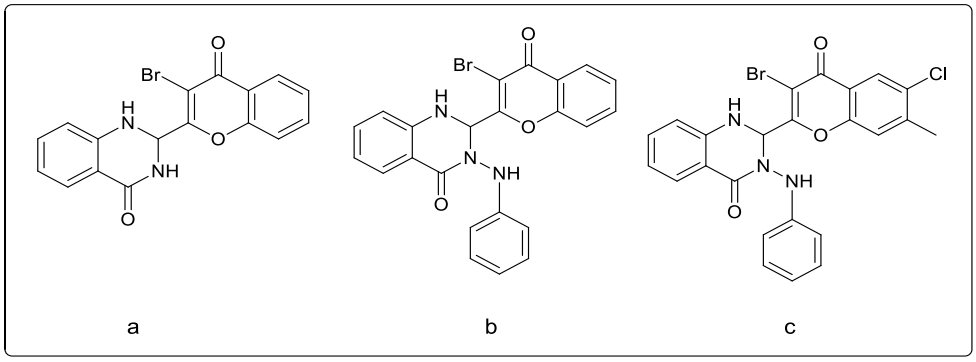


Figure 1.14

Tiwari. et al., reported the green synthesized novel Chromone-Pyrimidine coupled derivatives, 1(a-f) and 2(a-f) and evaluated them against *S. aureus* (NCIM-2901), *E. coli* (1411) and *E. coli* SM1411 for antibacterial activity (Figure 1.15). The compound 1c was found to be the most potent against tested pathogens with MIC_{100}=14µg/mL, 14µg/mL, 32µg/mL respectively. The compound 2c was discovered to be the most effective with the MIC100 (30µg/mL) against *S. aureus*. Compounds 1(a-f) and 2(a-f) were also assessed for their antifungal activity against *C. albicans*, *Candida glabrata*, *Fusarium oxysporum*, *Aspergillus fumigatus*, *A. niger* and *Cryptococcus neoformans* with the MIC_{100}=15µg/mL-33µg/mL. All derivatives were found to be from mediocre to excellent with reference to the standard miconazole drug [xxi].

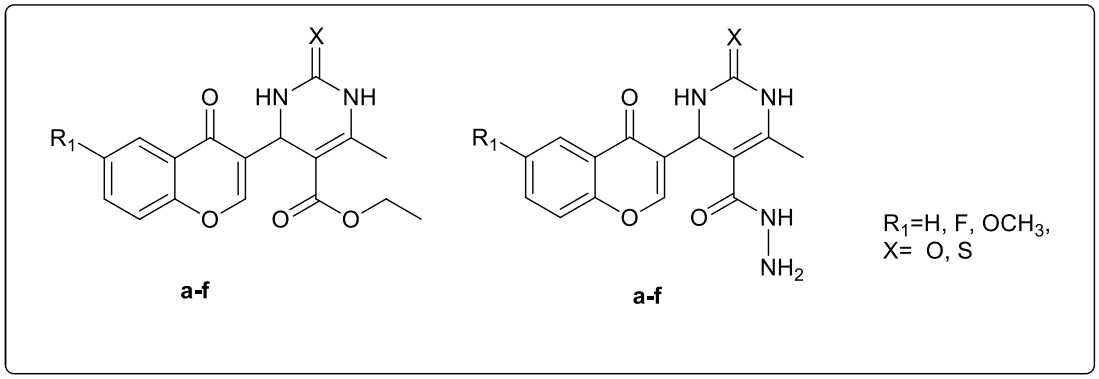


Figure 1.15

Sayed et al., synthesized 8-hydroxy-5-phenyl-furo[2,3-h] benzo (b) pyran-7-one and assessed it for antibacterial effects against gram-positive and gram-negative bacteria *Shigella dysenteriae*, *Salmonella typhi*, *Streptococcus b-haemolyticus* and *Staphylococcus aureus* at the concentration of 100 mg/disc and 200 mg/disc (Figure 1.16) and reported MIC level is 64 mg/ml against both *S dysenteriae* and *S β-haemolyticus* respectively [xxii].

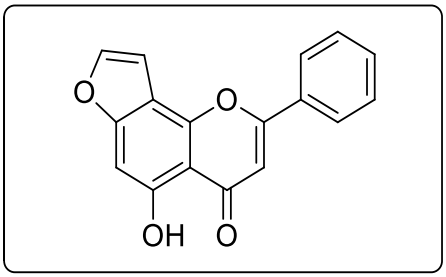


Figure 1.16

3. Conclusion:

It is well recognized that flavonoids, particularly flavones, can prevent and treat disease. Flavones occur naturally in fruits and vegetables. Numerous flavones that are present in nature each have distinct chemical, physiological, and physical characteristics. The flavone structure-activity connection is the summit of important biological activities. Numerous flavones and chromones have well-established antibacterial, hepatoprotective, anti-inflammatory, anticancer, and antiviral properties when used medicinally. The usage of these drugs is more widespread in developing countries. New chemicals' potential for therapeutic application needs to be confirmed by particular biochemical assays. Flavone production is currently viable through genetic modification.

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Conflict of Interests:

The authors declare that they do not have any conflict of interests

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