WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Flavone an Important Scaffold for Medicinal Chemistry Research: A Review

**** A Nagaraj[1], G Nageswara Rao[1], K Niranjan[2]***

[1]Department of Chemistry and Research Centre,Telangana University, Nizamabad, Telangana-503322. India
[2]Department of Chemistry, Telangana University,Bhiknoor South Campus, Nizamabad, Telangana-503102. India
E-mail: guthachowdary13@gmail.com

ABSTRACT:

A significant class of flavonoids, flavones exhibit a broad range of biological activities, including neuroprotective, anti-inflammatory, anti-cancer, anti-ulcer, anti-viral, antiprotozoal, anti-HIV, antibacterial, and anti-proliferative properties. Flavone flavopiridol, the first cyclin-dependent kinase inhibitor, is licensed as an orphan medication in Europe for the treatment of chronic lymphocytic leukemia that has relapsed. Thus, these structural motifs may be active under a variety of therapeutic circumstances. Thus, a crucial component of medicinal chemistry is flavone biological activity. This article discusses the biological activities that have been reported in the literature, their applicability in relation to the biological activity that both synthetic and natural flavone derivatives exert, as well as their likely mode of action. It is anticipated that medicinal chemists will find this review useful for their research.

Keywords: Flavone, flavonoids, Biological activity, Medicinal chemistry

INTRODUCTION OF FLAVONE:

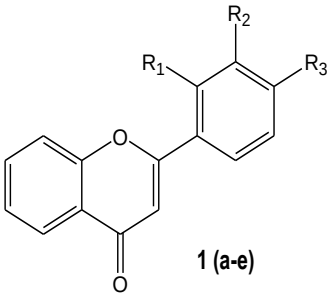
Natural and synthetic heterocyclic compounds play an important role in both drug discovery and chemical biology. Heterocyclic compounds are mainly from the class of alkaloids, chromones, flavones, isoflavones; etc.

Natural heterocycles are plant secondary metabolites that protect the plant from attack by pathogens, fungi, bacteria and insects[1].Several synthetic analogues of these heterocyclic compounds show different biological activity[2]. More than 50% of the drugs used in modern medicine are derived from either synthetic or natural heterocyclic systems.

Among natural heterocyclic compounds, flavone is an important heterocyclic ring and exhibits numerous pathological conditions with antioxidant[3], antiproliferative[4], antitumor[5], and antimicrobial[6] activity. Flavone derivatives have been widely used for multiple targeting in complex diseases such as cancer[7], inflammation[8], cardiovascular disease[9], diabetes[10] and various neurodegenerative disorders[11]. Due to the wide range of biological activities of flavones, their structure-activity relationships have attracted interest among medicinal chemists. The excellent development of flavone derivatives in various diseases in a very short time proves their importance for medicinal chemistry research. This chapter deals with the structural requirements of flavone derivatives for different pharmacological activities, this information may provide an opportunity to design selective, optimized and polyfunctional flavone derivatives for the treatment of multifactorial diseases. Therefore the biological activity of flavone are briefly dicussed in the following few pages.

1.ANTIOXIDANT ACTIVITY:

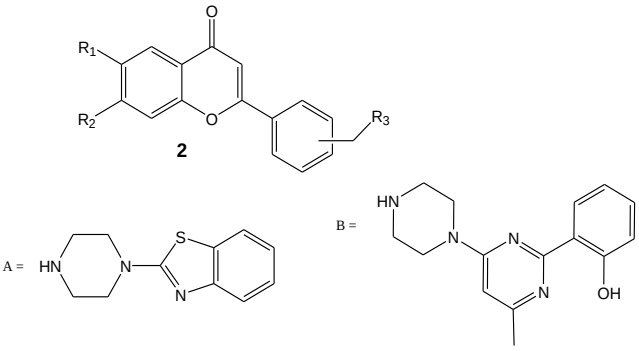
Shoaib *et al*.[12] reported that free radicals are produced by an important chemical process known as oxidation, which in turn initiates chain reactions that damage cells and cause oxidative stress. Flavones have a special position in the field of natural and synthetic organic chemistry research due to their biological abilities as antioxidants. A simple flavone (1a) and substituted flavone derivatives 1(b-e) were synthesized. The antioxidant profile of these compounds was determined using the DPPH and H_2O_2 free radical scavenging assay. Findings have shown that halogenated flavones exhibit greater enzyme inhibition and antioxidant activity than simple flavones and are potential candidates for the treatment of a wide range of diseases.



1 (a-e)

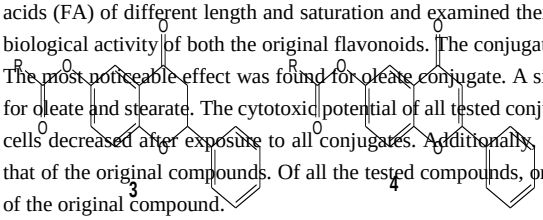
a) $R_1 = R_2 = R_3 = H$
b) $R_1 = R_2 = H$, $R_3 = 4\text{-}(Me)_2N$
c) $R_1 = R_3 = Cl$, $R_2 = H$
d) $R_1 = R_2 = Cl$, $R_3 = H$
e) $R_1 = H$, $R_2 = R_3 = Cl$

The *in vitro* antioxidant potency of novel 2-(2-hydroxyphenyl)pyrimidine/ benzothiazole substituted flavones 2(a-f)[13] was evaluated. All tested compounds acted as free radical scavengers at concentrations of 1.25 and 0.5 mM for hydroxyl (15-45%) and 2,2-diphenyl-1-picrylhydrazyl (17-48%) at 1.25 and 0.5 mM concentrations respectively.The compounds' total antioxidant status activity levels varied from 234.1 to 464.1 micrometre trolox equivalents per gramme, while their total antioxidant capacity ranged from 24.9 to 52.7 micrometre trolox equivalents per gramme. In comparison to compounds with the 2-(2-hydroxyphenyl)pyrimidine group, compounds with the benzothiazole group on the piperazine ring 2(a-c) were more potent antioxidants 2(d-f).



2a: Position-3: R_1=H; R_2=H; R_3= A
2b: Position-3: R_1=OCH_3; R_2=H; R_3= A
2c: Position-4: R_1=H; R_2=OCH_3; R_3= A
2d: Position-3: R_1=H; R_2=H; R_3= B
2e: Position-3: R_1=OCH_3; R_2=H; R_3=B
2f: Position-4: R_1=H; R_2=OCH_3; R_3=B

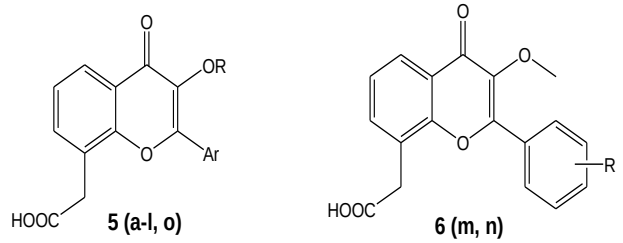
Flavonoids and polyunsaturated fatty acids due to low cytotoxicity in vitro studies are suggested as potential substances in the prevention of diseases associated with oxidative stress. Grazyna *et al*.[14] examined novel 6-hydroxy-flavanone 3(a-e) and 7-hydroxy-flavone conjugates 4(a-e) with selected fatty acids (FA) of different length and saturation and examined their cytotoxic and antioxidant potential and found that the conjugation with FA affects the biological activity of both the original flavonoids. The conjugation of 6-hydroxy-flavanone increased its cytotoxicity towards prostate cancer PC3 cells. The most noticeable effect was found for oleate conjugate. A similar trend was observed for 7-hydroxy-flavone conjugates with the most evident effect for oleate and stearate. The cytotoxic potential of all tested conjugates was not specific towards PC3 because the viability of human keratinocytes HaCaT cells decreased after exposure to all conjugates. Additionally, the esterification of the two flavonoids decreased their antioxidant activity compared to that of the original compounds. Of all the tested compounds, only 6-sorbic flavanone showed a slight increase in antioxidant potential compared to that of the original compound.



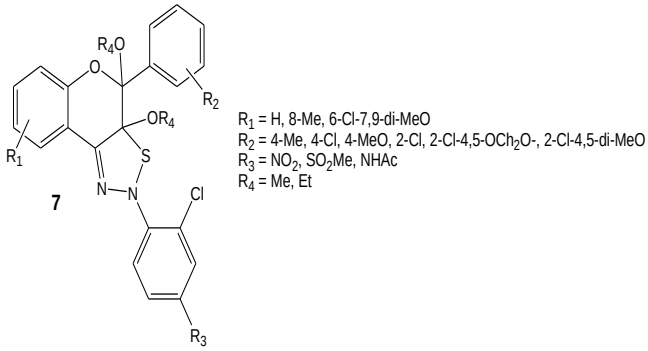
3/4: R = a) C_5H_7, sorbic; b) $C_{17}H_{35}$, stearic; c) $C_{17}H_{33}$, oleic; d) $C_{17}H_{31}$, linoleic; e) $C_{17}H_{29}$, linolenic

2. ANTICANCER ACTIVITY:

Silvia *et al*.[15] reported the analogues of flavone-8-acetic acid, bearing an alkoxy group 5 in position 3 and different substituents on the benzene ring in position 2 of the flavone nucleus 6. The compounds were tested for direct cytotoxicity against four human tumor cell lines and for indirect antitumor effects by measuring their ability to enhance lytic properties of murine macrophages and human monocytes. Though direct toxicity was very low, the compounds were able to induce significant indirect toxicity. Notably, most of them showed important activity on human monocytes and could be regarded as the first flavone derivatives endowed with such activity. Particularly interesting seem to be compounds 6m and 6n, which showed IC_{50} values up to 7 times higher than DMXAA.



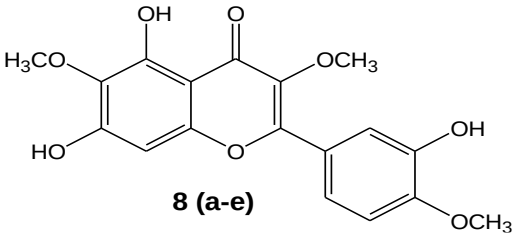
Huazhou *et al*.[16] synthesized a series of 2,4-diarylchromane[4,3-*d*]-Δ1,9b-1,2,3-thiadiazolines 7 from 2-arylchroman-4-one-arylhydrazones and evaluated for their antiproliferative activity *in vitro* against six human tumor cell lines and the highly potent derivative 7a exhibited *in vivo* inhibitory effect on tumor growth. Mechanism research indicated that it is due to 7a that induces DNA fragmentation.



R_1 = H, 8-Me, 6-Cl-7,9-di-MeO
R_2 = 4-Me, 4-Cl, 4-MeO, 2-Cl, 2-Cl-4,5-OCh_2O-, 2-Cl-4,5-di-MeO
R_3 = NO_2, SO_2Me, NHAc
R_4 = Me, Et

Nikta *et al*.[17] reported the synthesis of 2-aryl-trimethoxyquinoline analogues 8(a-e) from methoxylated flavones as the lead and evaluated their cytotoxic activity against four human cancer cell lines including MCF-7, MCF-7/MX, A-2780, and A-2780/RCIS. Compounds 8e showed considerable cytotoxicity

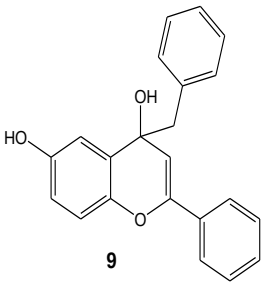
with IC_{50} ranging 7.98-60 μM. The flow cytometry analysis of the four human cancer cell lines treated with synthesized compounds which showed that 8e induced cell cycle arest at G2/M phase and apoptosis as well. The effect of quinolines on tubulin polymerization was suggested that compound 8e showed antiproliferative activity.



8 (a-e)

3. ANTIINFLAMMATORY ACTIVITY:

Flavonoids are natural phenolic compounds found in dietary sources such as plants, fruits, and vegetables. They have a wide range of biological activities including cytostatic and anti-inflammatory effects. Murad *et al*.[18] synthesized flavone derivatives 9 and 10. These compounds were for their anticancer activity against cervical (HeLa), colon cancer cells (CaCo-2), antioxidant and anti-inflamma- tory activities using DPPH and COX inhibition tests and found that the compound 9 potently inhibited the proliferation of CaCo-2 cells with IC_{50}=2.42 μg/mL and compound 10 exhibited considerable antioxidant activity with IC_{50}= 3.53±0.1 μg/mL. The compound 10 also inhibited COX-2 with an IC_{50}=6.02±0.33 μg/mL. The selectivity of compound 10 towards COX-2 enzyme is 6-fold more when compared to the selectivity towards r COX-1 enzymes.



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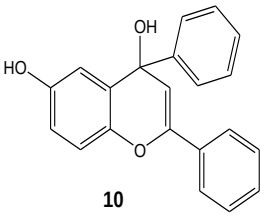
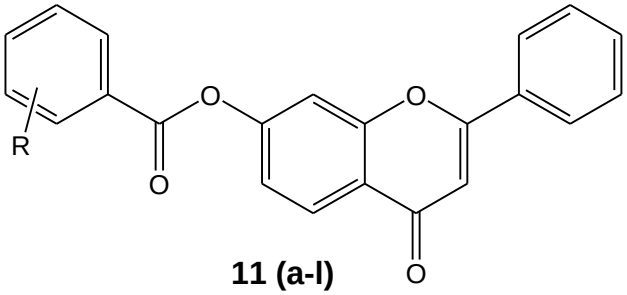


10

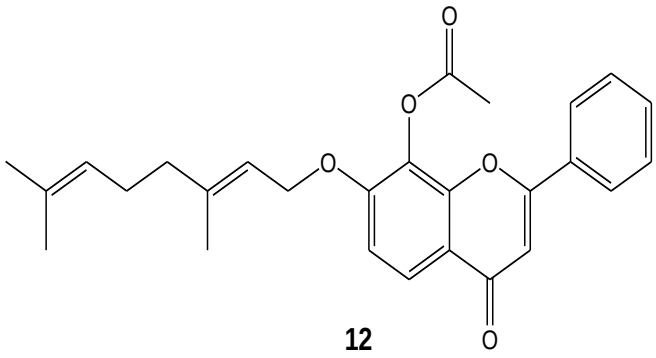
Flavonoids are naturally occurring phytoconstituents that are found in a wide variety of plant materials, including fruits, vegetables, cereals, bark, roots, stems, flowers, tea, and wine. With notable biological relevance such as anti-inflammatory, antioxidant, anticancer, and antimicrobial properties, flavonoids have been recognised as secondary metabolites of plants. As a result, flavonoids are regarded as a crucial ingredient in a number of nutraceutical, pharmacological, therapeutic, and cosmetic applications with a variety of health advantages. With the finding that flavonoids are anti-inflammatory through a number of mechanisms, but the most significant mechanism is the suppression of the enzyme that produces eicosanoids, research on flavonoids received a boost.

The anti-inflammatory effect of a new flavone 11(a-l) synthesised by Sabale *et al*.[19] was evaluated utilising a carrageenan-induced rat paw edoema technique. To establish a link between biological activity and molecular attributes, novel flavone derivatives were used. among the synthesised compounds 11b, 11g, 11i, 11j, and 11l had excellent anti-inflammatory action, whilst 11c, 11e, 11f, 11h, and 11k displayed moderate anti-inflammatory activity equivalent to that of the reference medication indomethacin. Thus, it can be concluded that the flavone moiety may have good anti-inflammatory properties.



11 (a-l)

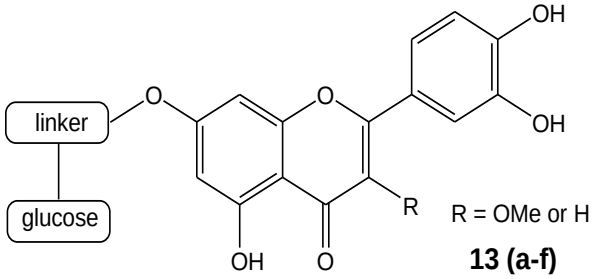
Nine novel 7-geranyloxyflavone compounds with various 8th position substitutions were partially synthesised. The Croton oil ear test, a mouse model of acute inflammation, was used to assess their topical anti inflammatory efficacy. The nonsteroidal anti-inflammatory medication auraptene (7-geranyloxycoumarin), its 8-methoxy (collinin, 1), and its 8-acetoxy chromone 12 (1 lmol/cm^2) caused a 50% reduction in oedema, comparable to 0.25 lmol/cm^2 of the reference medicine indomethacin[20].



12

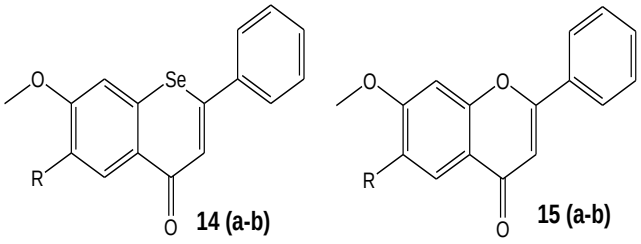
4. NEUROPROTECTIVE ACTIVITY:

Reactive oxygen species can damage cells or tissues by attacking biological molecules because of their high reactivity. Kim *et al*.[21] reported that, a glycosidic bond or ether linkage was used to bind the glucose moiety to the C-7 positions of the quercetin 3-O-methyl ether and luteolin. In primary cultured rat cortical cells, the compounds containing glucose demonstrated strong DPPH and superoxide anion radical scavenging and lipid peroxidation inhibition activities, as well as nearly equivalent protective actions to the parent aglycons against the H_2O_2-induced oxidative neuronal damage. The most potent substances examined were 13b and 13c (IC_{50} values: 7.33 and 5.34 M, respectively), which had effects that were very similar to those of the parent substances quercetin and luteolin (IC_{50}: 3.50 and 3.75 M, respectively).



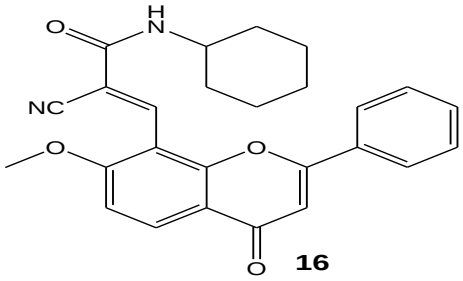
13 (a-f)

A molecule's physicochemical characteristics and antioxidant activity may be enhanced by replacing an oxygen atom with selenium. To test their potential for neuroprotection, Choi *et al*.[22] synthesised selenoflavanones 14(a-b) and flavanones 15(a-b). The selenoflavanones displayed enhanced physicochemical characteristics that may have allowed them to cross the blood-brain barrier (BBB). They did not cause significant cytotoxicity and had in vitro antioxidant properties against hydrogen peroxide. The selenoflavanone treatments also markedly decreased the infarction volumes in a mouse model of transitory ischemia.



14 (a-b) **15 (a-b)**

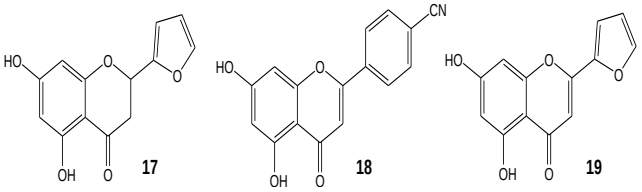
A congeneric set of seventeen flavone-8-acrylamide derivatives 16(a-q) were created in the hunt for new, effective anti-medications for Alzheimer's. These compounds were tested for their ability to inhibit cholinesterase, act as antioxidants, protect neurons, and modulate Aβ aggregation.The target substances demonstrated efficient and focused inhibition of AChE over BuChE. The target compounds also exhibited strong neuroprotective abilities, modest anti-oxidant activity, and dosage-dependently accelerated Aβ aggregation. Jeelan Basha *et al*.[23] provided a thorough analysis of the interactions between AChE and the amino acids 16a, 16d, 16e, 16h, and 16i. Fluorescence emission studies revealed that there was only one binding site, and the binding constants of 2.04 104, 2.22 104, 1.18 104, 9.8 103, and 3.2 104 M1 and the free energy change of 5.83, 5.91, 5.51, and 6.12 k.cal/M at 25 °C, which were well in agreement with the computational calculations, indicated that flavones and AChE had a strong binding affinity. The CD tests also demonstrated that AChE's secondary structure partially unfolded following binding with 16a, 16d, 16e, 16h, and 16i.



16

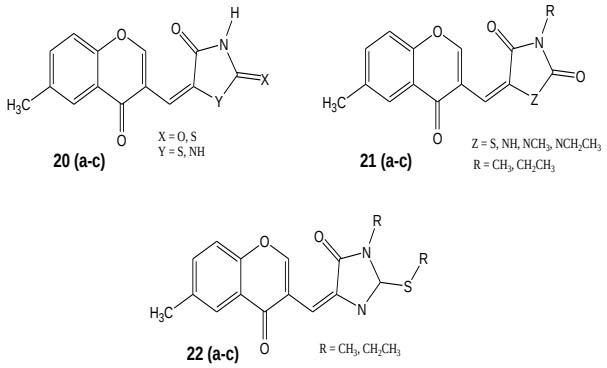
5. ANTI-DIABETES:

Chang *et al*.[24] synthesized two series of flavonoids, 5,7-dihydroxyflavanones and 5,7-dihydroxyflavones, in a study to assess the structural components crucial for the antidiabetic activity of flavonoids. Most flavonoids displayed impressive *in vitro* activity when tested for possible anti-diabetic action, and compounds 17, 18, and 19 were much more effective than the positive control, metformin. The structural change at the ring B moiety of the flavonoid skeleton had the biggest impact on the biological activity. According to the findings, 5,7-dihydroxyflavonoids are potential candidates for the creation of fresh anti-diabetic lead compounds.



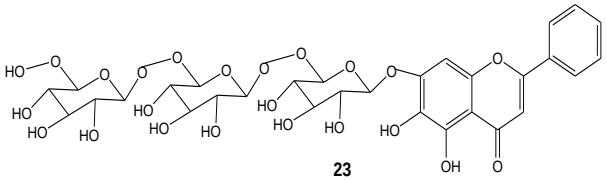
17 **18** **19**

To enhance the pharmacological profile of insulinotropic actions, many compounds have been synthesized. *In vitro* insulin release activity of the 6-methyl-chromonyl-2,4-thiazolidinediones (20a-c, 21a-c, 22a-c) was reported by Meltem *et al*.[25] In the presence of 5.6 mmol/L glucose, compounds 20b, 20c, 21a-c, 22a, and 22c (at lower concentrations; 0.001 mg/mL) were able to stimulate insulin release. The most powerful molecule in this class is 21a, which has a methyl group at the N3 position of the TZD ring.

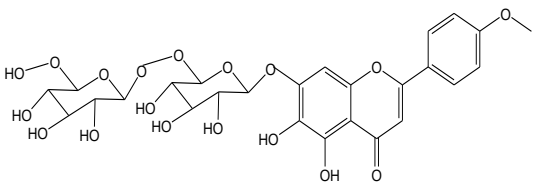


20 (a-c) **21 (a-c)** **22 (a-c)**

Oroxins C and D, which were isolated from the seeds of Oroxylum indicum, were synthesised for the first time succinctly using a convergent method, according to Li *et al*.[26] The inhibitory actions of the synthesized natural products 23 and 24 against -glucosidase, -amylase, and lipase were assessed. The IC_{50} values for compound 23 were 210 and 190 M for -amylase and lipase, respectively, whereas it had no inhibitory effect for -glucosidase. With IC_{50} values of 180 and 80 M for -glucosidase and lipase, respectively, compound 24 demonstrated potent inhibition against both enzymes.



23



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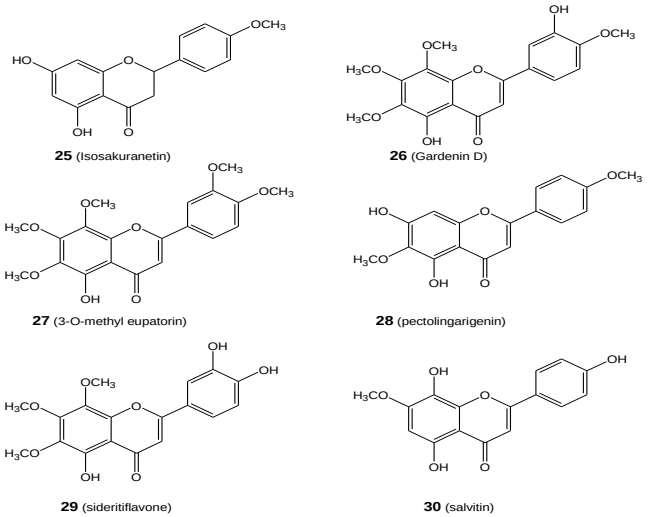
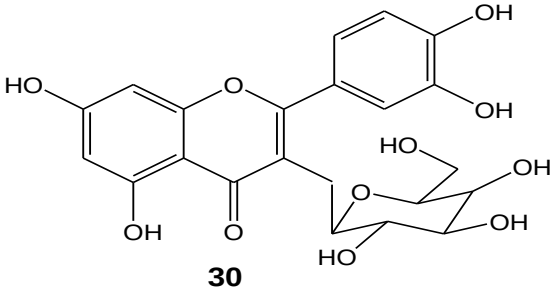
6. ANTI-ULCER ACTIVITY:

Zahran *et al*.[27] reported that the objective of the current study was to identify the bioactive metabolites from the aerial portions of Ocimum forskolei that are responsible for the antiulcer activity of the total ethanol extract (TEE) and various fractions (petroleum ether, dichloromethane, ethyl acetate and aqueous). Following a bioassay-guided fractionation, six flavonoids 25-30 were extracted from the dichloromethane fraction, which was the most active; with an ulcer index value of 2.67, 2.18 and % inhibition of ulcer of 97.7%. In an effort to understand the extracted flavonoids' substantial antiulcer potential, molecular docking analysis was applied. The results showed that salvitin and sideritiflavone were the primary active compounds acting against the M3 and H-2 receptors, respectively. Furthermore, two persistent H-bonds between salvitin and the two amino acids in the active site-Asn507 and Asp147 were shown by a molecular dynamics simulation to form in 42 and 65% of the frames, respectively.

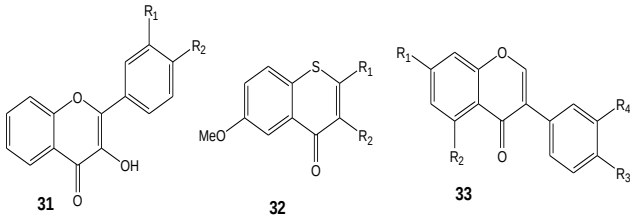


In China, a medicinal plant called Abelmoschus manihot (L.) Medic flower is used to heal many illnesses. Zhang *et al*.[28] conducted the current study to formally validate the gastroprotective action and elucidate the potential mechanism of the total flavones from the flowers of Abelmoschus manihot (L.) Medic (TFA). Mice were subjected to oral ethanol treatment, which caused gastric ulcers. The stomach ulcer index and histological analyses were used to gauge the gastroprotective activity of TFA 30. Homogenate was used to harvest the gastric tissue. Malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD) activity, and protein content were all assessed. Additionally, Western blotting was used to examine the expression of Bax, Bcl-2, TNF-, and NF-B(p65). TFA's impact was contrasted with that of the 100 mg/kg dose of the omeprazole, a common antiulcer medication. The gastroprotective action of TFA might be explained by an increase in SOD and GSH activity, a decrease in MDA levels, as well as a reduction in Bax, TNF-, and NF-B(p65) expression levels and an increase in the Bcl-2 expression level.



7. ANTIVIRAL ACTIVITY:

Zhang *et al*.[29] examined the antiviral activity of a new class of thioflavone and flavonoid derivatives against enterovirus 71 (EV71), coxsackievirus B3 (CVB3), and coxsackievirus B6 (CVB6). The antiviral activity of compounds 31d and 33b against EV71 were strong, with IC_{50} values of 8.27 and 5.48 M, respectively. The newly synthesised compound 32f, with IC_{50} values of 0.62 and 0.87 M, demonstrated the highest level of inhibitory action against CVB3 and CVB6, respectively. The CVB3 and CVB6 were both strongly inhibited by compounds 31b, 32a, 33c, and 33e at low concentrations (IC_{50}=1.42-7.15 M), but the CVB6 was weakly inhibited by compounds 31d, 32c, 32e, and 32g (IC_{50}=2.91-3.77 M) and the CVB3 was weakly inhibited by compounds 31d, 32c, 32e, and 32g. Contrary to CVB6 (IC50>8.29 M), compound 31d has more inhibitory efficacy against CVB3 (IC50=6.44 M). Derivatives of thioflavones 32a, 32c, 32d, 32e, 32f, and 32g, represent a new class of lead compounds for the development of novel antiviral agents.



31

a: R_1 = H, R_2 = H
b: R_1 = OCH_3, R_2 = H
c: R_1 = H, R_2 = Cl
d: R_1 = H, R_2 = CH_3

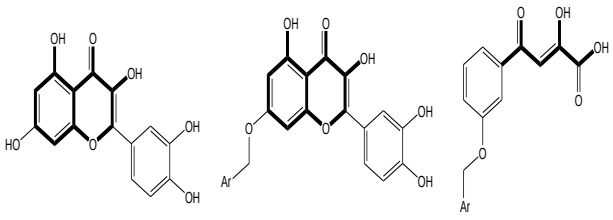
32

a: R_1 = phenyl, R_2 = H
b: R_1 = n-propyl, R_2 = H
c: R_1 = 4-fluorophenyl, R_2 = H
d: R_1 = 4-methoxyphenyl, R_2 = H
e: R_1 = methyl, R_2 = H
f: R_1 = chloromethyl, R_2 = H
g: R_1 = methyl, R_2 = phenyl
h: R_1 = 4-nitrophenyl, R_2 = H
i: R_1 = methyl, R_2 = Cl

33

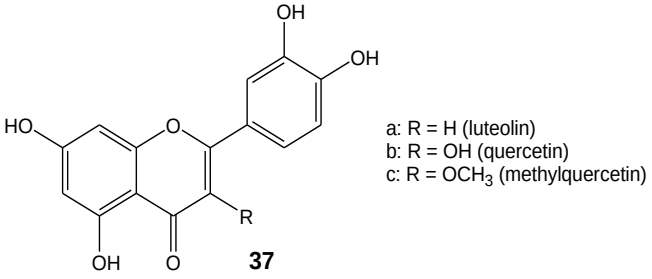
a: R_1 = OH, R_2 = H, R_3 = OH, R_4 = H
b: R_1 = OH, R_2 = H, R_3 = OH, R_4 = OH
c: R_1 = isopropoxy, R_2 = H, R_3 = H, R_4 = H
d: R_1 = OH, R_2 = OH, R_3 = OH, R_4 = H
e: R_1 = OH, R_2 = H, R_3 = OH, R_4 = methoxy
f: R_1 = methoxy, R_2 = OH, R_3 = OH, R_4 = H
g: R_1 = beta-D-glucopyranosyloxy, R_2 = H, R_3 = OH, R_4 = H
h: R_1 = OH, R_2 = OH, R_3 = beta-D-glucopyranosyloxy, R_4 = H

The antiviral activity of aryl diketoacid (ADK), which is widely known, can be increased by adding an aromatic arylmethyl substituent. Quercetin (34) is a naturally occurring flavonoid with a 3,5-dihydroxychromone pharmacophore that interacts bioisosterically with the 1,3-diketoacid (36) moiety of the ADK. Therefore, it was in our best interest to investigate the arylmethylated quercetin derivatives' ability to inhibit the growth of viruses. Park *et al.*[30] synthesised a series of 7-O-arylmethylquercetin derivatives (35) with different aromatic substituents and assessed their antiviral effectiveness against the hepatitis C virus and the SARS-associated coronavirus (SARS-CoV, SCV) (HCV). The biological activity of the 7-O-arylmethylquercetin derivatives (35) was fine-tuned by a single change in the aromatic substituent, resulting in two distinct classes of derivatives that were preferentially active against SCV and HCV.



34 (quercetin) **35** (7-O-arylmethylquercetin) **36** (aryl diketoaceid)

Three flavones, quercetin 37a, luteolin 37b, and 3-methylquercetin 37c, which differ only at ring position 3, were compared for their anti-poliovirus properties by Raf *et al*[31]. Among these, 3-methylquercetin 37c was the most effective. Only when quercetin was shielded by ascorbate from oxidative degradation did it demonstrate antiviral action. Lutein's antiviral activity was on par with quercetin's ascorbate-stabilized counterpart.

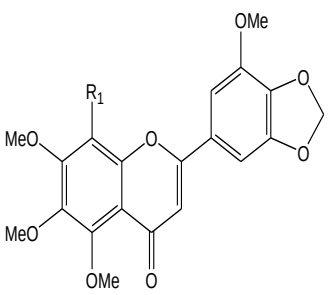


37

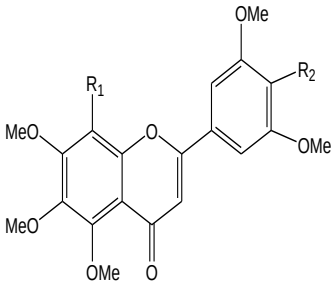
a: R = H (luteolin)
b: R = OH (quercetin)
c: R = OCH_3 (methylquercetin)

8. ANTIPROTOZOAL ACTIVITY:

Ageratum conyzoides L. (Asteraceae), a plant that is frequently used in folk medicine for a variety of ailments including sleeping sickness, has been found to have a notable activity (IC_{50}=0.78 g/mL) against bloodstream forms of Trypanosoma brucei rhodesiense, the etiologic agent of East African Human Trypanosomiasis (East African Sleeping Sickness). Additionally, this extract with compounds 38 and 39 demonstrated discernible activity against Plasmodium falciparum (Malaria tropica, IC_{50}=8.0 g/mL) and Leishmania donovani (Kala-Azar, IC_{50}=3.4 g/mL)[32].



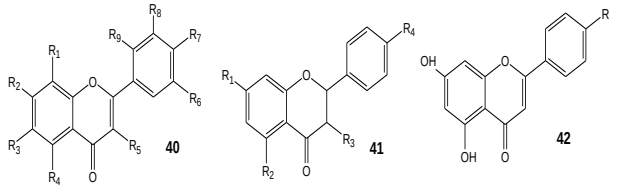
38 a) R_1 = OMe
b) R_1 = H



39 a) R_1 = OMe, R_2 = OMe
b) R_1 = H, R_2 = OMe
c) R_1 = H, R_2 = OH

9. ANTI-HIV ACTIVITY:

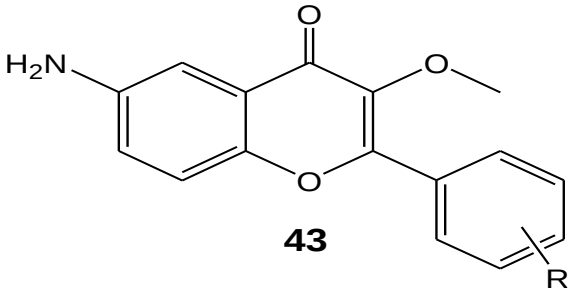
Mantas *et al*.[33] repoted the twenty flavonoids 40(a-n), 41(a-b) and 42(a-c) with anti-HIV activity were the subject of a theoretical analysis of their structural makeup. The AM1 method was used to determine these compounds' structural characteristics. By using the Principal Components Analysis (PCA) method to analyse the collected quantum data, it was discovered that the compounds fall under the structural categories of flavones, flavonols, flavanones, and benzo-pyrones, which are all clearly distinct from one another. In addition, the flavonoids were divided into three groups based on their structural characteristics using the Hierarchical Cluster Analysis (HCA) approach. The outcomes allowed for a very strong relationship to be proposed between the structural properties of their conformers and the conformational equilibrium constants of these substances.



40: a) R_1-R_9=H, b) R_1=R_2=OH, c) R_2=R_4=OH, d) R_1=NO_2, R_2=R_4=OH, e) R_2=R_4=R_7=OH
f) R_2=R_4=OH, R_7=F, g) R_2=R_4=OH, R_3=Cl, h) R_2=R_4=OH, R_8=Cl, i) R_2=R_4=OH, R_7=Cl j) R_2=R_4=OH, R_7=Br,
k) R_2=R_4=R_7=R_8=OH, l) R_3=R_5=R_7=OH, m) R_1-R_8=OH n) R_2=R_4=R_5=R_7=R_8=OH, o) R_2-R_8=OH

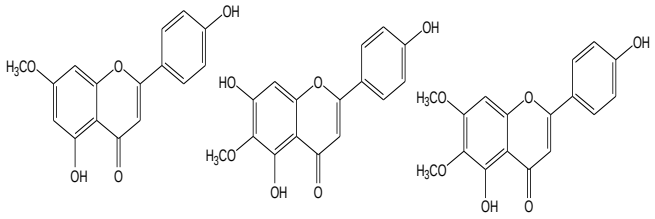
41: a) R_1 = R_2 = R_3 = R_4 = H, b) R_1 = R_2 = R_4 = OH
42: a) R_1 = CH_3, b) R_1 = C_3H_7, c) R_1 = C_6H_{11}

Novel series of flavonoid derivatives and their chalcone intermediates were synthesised for effective anti-HIV and antiplasmodial medicines[34], and they were then tested for their ability to suppress HIV multiplication and to have antiproliferative effects on Plasmodium falciparum parasites. Compared to flavonoids, chalcones showed a more focused antiplasmodial activity. While aminomethoxyflavones shown efficacy against HIV-2, only methylflavone 43 was active against both P. falciparum and HIV-1. The potency of HIV-2 seems to be increased by para substitution on the B ring.



43

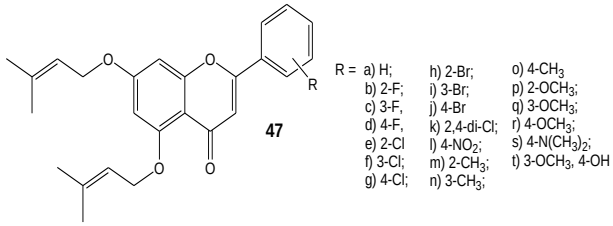
Plant sources are a particularly appropriate place to start when looking for new bioactive natural compounds. Phenolic derivatives are a notable class of natural products, with a number of the molecules demonstrating extraordinary properties. Tamayose *et al*.[35] examined the effect of isolated chemicals on HIV-1 reverse transcriptase and detailed the phenolic makeup of Moquiniastrum floribundum (Asteraceae). Three flavones, Genkwanin 44, Hispidulin 45 and Cirsimaritin 46, as well as eight chlorogenic acid derivatives, including 4,5-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, 3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid methyl ester, The most effective substance was 4,5-di-O-caffeoylquinic acid, which had an IC_{50} of 0.240 mmol L-1 and 65.0 7.9% inhibitory activity on HIV-1 reverse transcriptase.



44 (genkwanin) **45 (hispidulin)** **46 (cirsimaritin)**

10. ANTIBACTERIAL ACTIVITY:

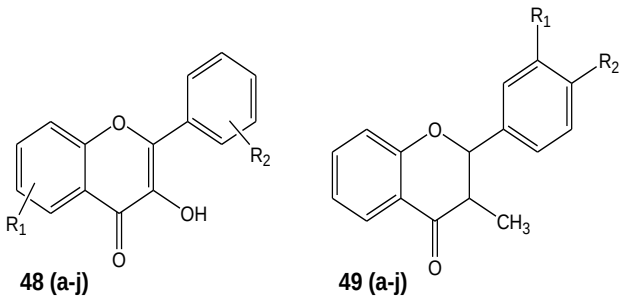
Jin *et al*.[36] synthesized a number of novel 5,7-diisoprenyloxyflavone derivatives 47 and evaluated their antibacterial properties. The majority of these substances had notable antibacterial activity against Gram-positive bacteria, particularly against clinical isolate strains that were multidrug resistant. With minimum inhibitory doses of 4.0–20 M, compounds 47c, 47g, 47i, 47j, 47k, 47l, 47n, 47q and 47t demonstrated substantial levels of antibacterial activity against *Staphylococcus aureus* RN4220. The most effective efficacy against all tested multidrug-resistant clinical isolates was demonstrated by compound 47k. While, none of the substances were effective at dosages of 24-164 Mm against Gram-negative bacteria.



47

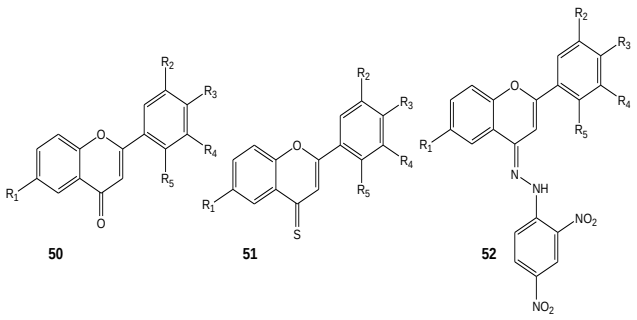
R = a) H; b) 2-F; c) 3-F, d) 4-F, e) 2-Cl f) 3-Cl; g) 4-Cl; h) 2-Br; i) 3-Br; j) 4-Br k) 2,4-di-Cl; l) 4-NO_2; m) 2-CH_3; n) 3-CH_3; o) 4-CH_3 p) 2-OCH_3; q) 3-OCH_3; r) 4-OCH_3; s) 4-$N(CH_3)_2$; t) 3-OCH_3, 4-OH

The majority of antimicrobial medications currently on the market have developed resistance, and some of them have extremely harmful side effects. Therefore, it is necessary to find novel compound(s) that are strong as well as less hazardous and expensive. Kamlesh *et al*.[37] reported the synthetic antibacterial compounds with low toxicity and significant potency, such as 3-substituted flavone/flavanone derivatives 48(a-j) and 49(a-j). For *in vitro* antibacterial and antifungal activities against various strains, the synthesized compounds were tested agiant 3-Gram positive, 3-Gram negative bacterial strains and 2-fungal strains. Among the several derivatives of 3-hydroxyl flavones 48 and 3-methyl flavanones 49 elicited strong antibacterial action. The research showed that while 3-methyl flavanone derivatives were effective against Gram positive bacteria, 3-hydroxy flavone derivatives were most effective against Gram negative bacteria.



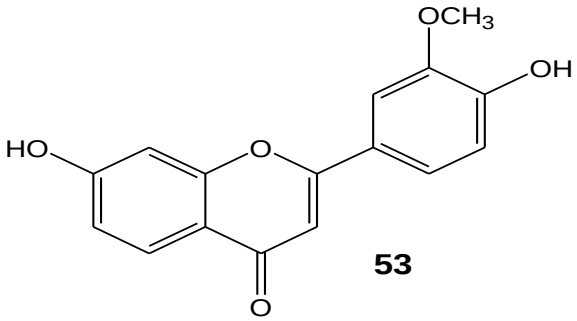
48 (a-j) **49 (a-j)**

According to Ehsan *et al*.[38], the synthesis of flavones 50, 4-thioflavones 51, and 4-iminoflavones 52 was carried out by substituting methyl, methoxy, and nitro groups in the A, B, and AB rings of the corresponding compounds, and evaluation of their antibacterial activity. The majority of the synthesized compounds were discovered to be effective against *Pseudomonas aeruginosa*, *Shigella flexneri*, *Salmonella aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Bacillus subtilis*. It was discovered that 4-thioflavones and 4-iminoflavones had more biological activity than their comparable flavone analogues. The antibacterial activity of the investigated compounds was improved by substituents such F, OMe, and NO_2 at the 4-position in ring-B, and electronegative groups were directly related to the antibacterial activity of the investigated compounds.



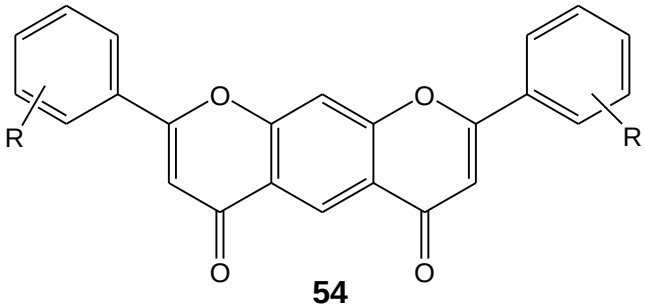
50 **51** **52**

Murthy *et al*.[39] reported the synthesis of 7,4-dihydroxyflavone and 3-methoxy flavones 53 and evaluated for their antibacterial activity and found inhibition zones (MIC- mm's) were calculated which are encouraging.



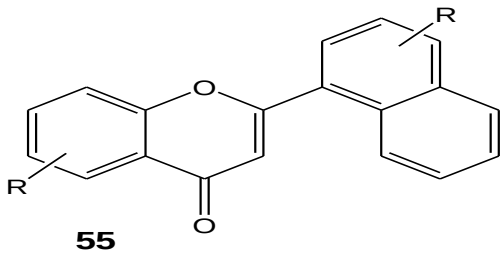
53

Asif and others[40] synthesized a number of flavone derivatives 54 and screened for their antimicrobial activity against a number of different microorganisms. According to the results of the antimicrobial evaluation, some of the synthetic compounds have effective antibacterial.



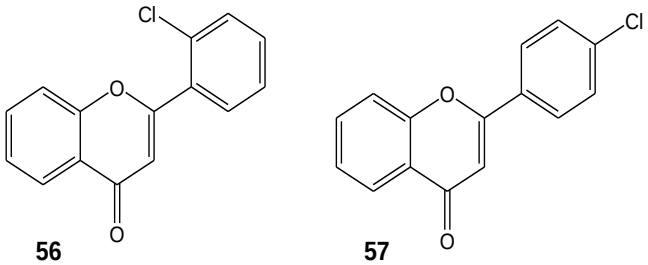
54

The structures of seven novel chalcones and flavones that have a substituted naphthalene nucleus in their structure were validated by spectroscopic data. Escherichia coli and Staphylococcus aureus were used as test organisms for the newly synthesised compounds' antibacterial activity, and it was discovered that these compounds demonstrated significant antimicrobial properties[41].



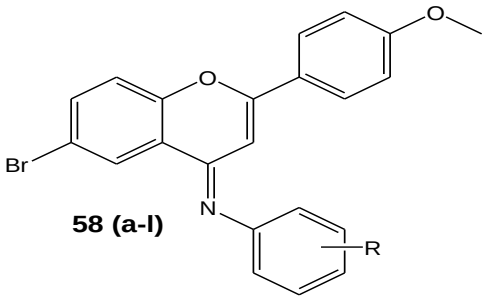
55

Two chloroflavones 56 and 57 have been synthesized and tested for their antibacterial and antifungal activities against six human pathogenic bacteria, including *Bacillus cereus* (G+), *Staphylococcus aureus* (G+), *Escherichia coli* (G-), *Vibrio choloriae* (G-), *Pseudomonas aeruginosa* (G-), and *Salmonella typhi.* The minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of these synthesised compounds in contrast to ampicillin were determined and found that some of these compounds showed higher activities[42].



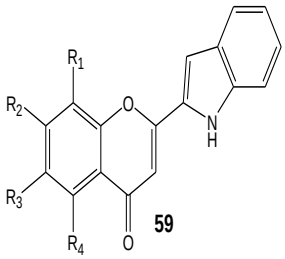
56 **57**

Patil *et al*.[43] reported the synthesis of 6-bromo-4-methoxy-4-(substituted phenyl) imino flavones 58(a-l) by the reaction of 2-hydroxy-5-bromo-4-methoxychalcone- imine on refluxing in DMSO in presence of catalytic amount of iodine and conc. H_2SO_4. The newly synthesized compounds were screened for their antimicrobial and antifungal activities and found that most of these compounds showed considerable antimicrobial activities.



58 (a-l)

By adding a heteroaryl moiety to chromone derivatives in the C-2 position, flavone's biological activity has been improved. As a result, matching chalcone was used to create 2-(1*H*-indol-3-yl)-4*H*-chromen-4-one derivatives 59 and 2-(2-chloroquinolin-3-yl)-4*H*-chromen-4-one derivatives 60 and their antibacterial properties were assessed. The outcomes demonstrated this skeletal framework's notable potency as an antibacterial agent[44].



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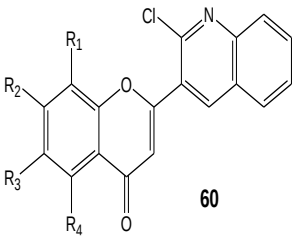
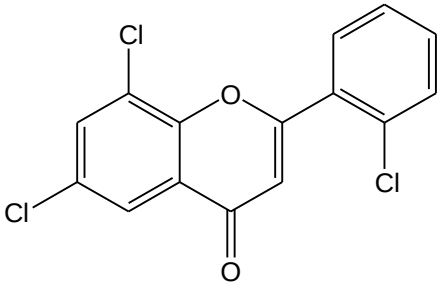


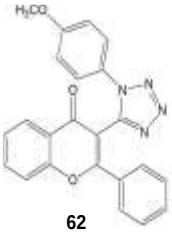
60

Mane *et al*.[45] described the cyclization of hydroxyl chalcones in the presence of iodine in DMSO to produce flavone derivatives 61. *Escherichia coli*, *S. aureus*, has been examined for the ability of the synthesised flavones to inhibit microbial growth. Antimicrobial activity research revealed substances with good to moderate activity.



61

Nagaraj et al.[46] A range of derivatives of flavones have been produced antibacterial properties assessed in vitro. Compounds having 4-methoxyphenyl 62c, 4-fluorophenyl 63d, and 2, 5-fluorophenyl 64h substituents on the tetrazole ring demonstrated the highest activity against the organisms tested, according to the antibacterial screening data.



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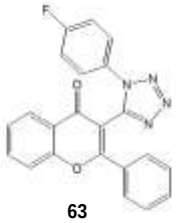

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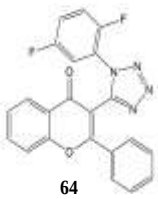
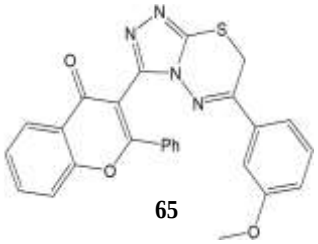


64

Nagaraj et al.[47] A new series of 2-phenyl-3-(6-aryl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-4H-4-chromenone has been synthesized by the reaction of 3(4-amino-5-sulfanyl-4H-1,2,4-triazol-3-yl)-2-phenyl-4H-4-chromenone 7 with a variety of phenacyl bromides in ethanol under reflux.The in vitro antibacterial properties of each newly synthesized drug against S. aureus, B. cereus, and P. aeruginosa were evaluated. Compounds 65d and 66h demonstrated strong activity against Bacillus cereus.



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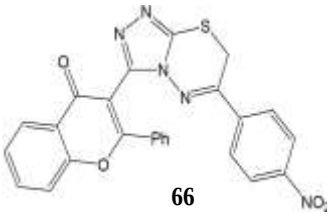
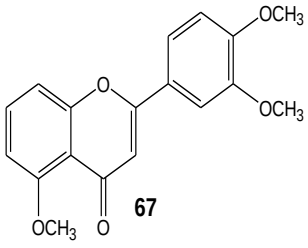


66

11. ANTIPROLIFERATIVE ACTIVITY:

According to Satoru *et al*.[48] report a number of methoxylated 67 and hydroxylated flavones 68 were synthesised, and their cytotoxic and anti-proliferative activity was assessed in leukemic HL60 cells. The significance of the 5,4'- and 3',4'-dihydroxyl moieties in the flavone nucleus was shown by the association between the methoxylation/hydroxylation pattern and antiproliferative action.



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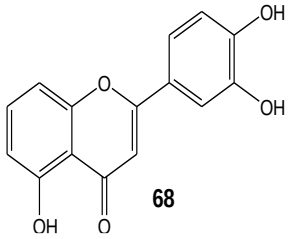
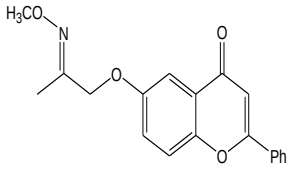


68

Wang *et al*.[49] reported that the synthesis of oxime- and methyloxime-containing flavone and isoflavone derivatives and tested for their antiproliferative activity against cancerous cells. Additionally, the whole panel of 60 human tumour cell lines were examined for selective compounds, and their mean GI_{50} values were determined. According to preliminary tests, isoflavone-7-yl derivatives are the best antiplatelet agents, while flavone-6-yl derivatives are the most cytotoxic. The following are some of them: (E)-6-(2-methoxyiminopropoxy)-2-phenyl-4H-1-benzopyran-4-one 69 and (Z)-2-phenyl-4H-1-benzopyran-4-one 70a. Three of the most effective antiproliferative compounds are 2-phenyl-4H-1-benzopyran-4-one 70c, which had GI_{50} values of 0.8, 0.7, and 0.8 lM against the growth of SKHep1 cells and 0.9, 0.8, and 1.0 lM against the growth of HeLa cells. The only flavone derivative with a GI_{50} value of less than 1 lM against the expansion of SAS is compound 70c, which is also the most cytotoxic with a mean GI_{50} value of 0.08 lM against the entire panel of 60 human tumour cell lines.



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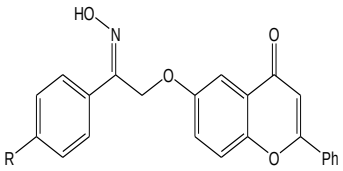
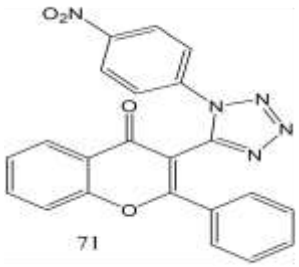


70 (a-c) R: a) H b) F, c) OCH_3

12.ANTI-FUNGAL ACTIVITY

Nagaraj et al.[46] A molecule with 4-nitrophenyl 71g on the tetrazole ring showed the strongest activity against A. niger, whereas a compound with 4-methoxyphenyl 72c group showed good activity against C. albicans, according to the results of the antifungal screening.



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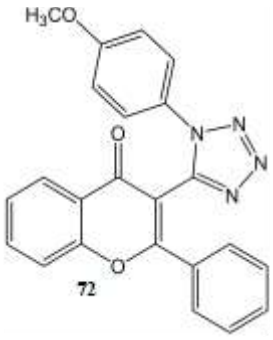

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