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Flavanone: A Versatile Heterocyclic Nucleus

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Abstract: The chemistry of heterocyclic compounds has been an interesting field of study for a long time. The present review article highlights different synthetic approaches to synthesize flavanone nucleus, natural and synthetic flavanones as well as recently synthesized flavanone possessing important biological activities. It was found that among the important pharmacophores responsible for various activities, flavanone also plays an important role in various medicines.
Keywords: Chalcone, Flavanone, Heterocyclic compounds, Natural Flavanone, Synthetic flavanone, Biological activity.

Introduction

Flavonoids are extensive group of compounds occurring in plants. They are prominent plant secondary metabolites that have been found in dietary components including fruits, vegetables, olive oil, tea, and red wine. It has been observed that even a high take of plant based dietary flavonoids is safe and not associated with any adverse health effect. The basic flavanoid structure is a flavone nucleus, In nature, they are available as flavone, flavonol, flavanone, isoflavone, chalcone and their derivatives[1].

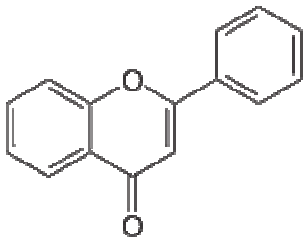
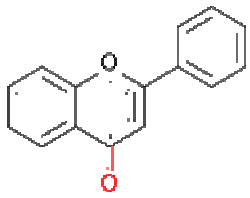
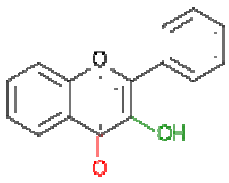
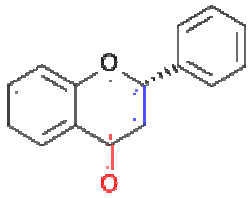
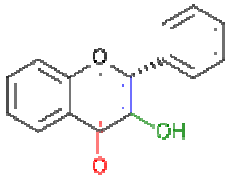


Figure 1: Molecular structure of the flavone backbone (2-Phenyl-1,4-benzopyrone)

Over 5000 naturally occurring flavonoids have been characterized from various plants. They have been classified according to their chemical structure, and are usually subdivided into the following subgroups[2] (Table: 1). Natural and synthetic flavanoids and flavanones have attracted considerable attention because of their interesting biological activity including antimycobacterial[3], antimicrobial[4,5], anti-lung cancer[6], antibacterial[7], antiproliferative[8], anti-tuberculosis[9], antifungal[10], antiarrhythmic[11], antiviral[12], antihypertensive, antioxidant and anti-inflammatory[13].

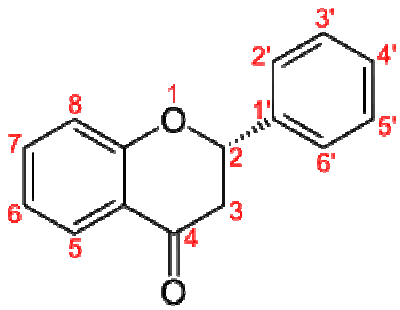
Table 1: Classification of Flavones[14]

Group	Skeleton			Examples
	Description	Functional groups		Structural formula	
		3-Hydroxyl	2,3-Dihydro		
Flavone	**2-phenylchromen-4-one**	✗	✗		Luteolin, Apigenin, Tangeritin
Flavonol or **3-hydroxyflavone**	**3-hydroxy-2-phenylchromen-4-one**	✓	✗		Quercetin, Kaempferol, Myricetin, Fisetin, Isorhamnetin, Pachypodol, Rhamnazin
Flavanone	**2,3-dihydro-2-phenylchromen-4-one**	✗	✓		Hesperetin, Naringenin, Eriodictyol, Homoeriodictyol
Flavanonol or **3-Hydroxyflavanone** or **2,3-dihydroflavonol**	**3-hydroxy-2,3-dihydro-2-phenylchromen-4-one**	✓	✓		Taxifolin (Dihydroquercetin), Dihydrokaempferol

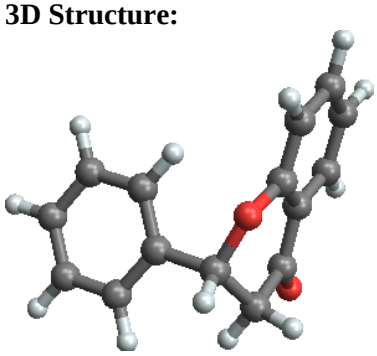
Properties of 2,3-Dihydro-2-Phenylchromen-4-one Nucleus[15]

The flavanones are a type of flavonoids. They are generally glycosylated by a disaccharide at position seven to give flavanone glycosides. Being naturally occurring compounds, flavanones have high availability and good pharmacological profile. It shows many biological activities in the body.

Molecular structure:



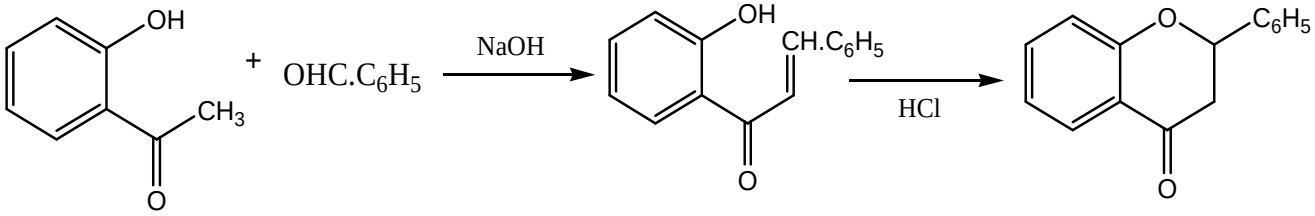
3D Structure:



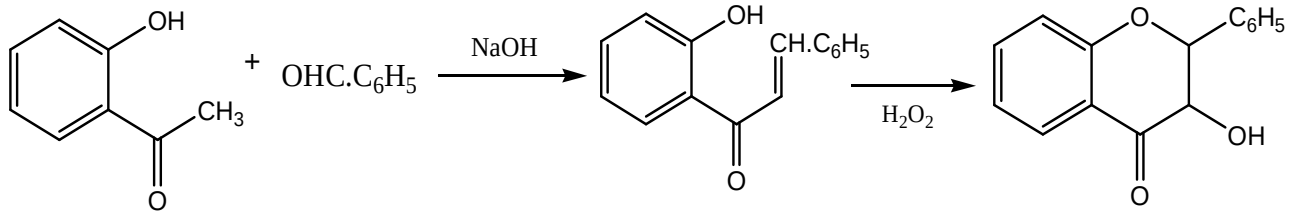
Chemical Name: Flavanone
Chemical formula: $C_{15}H_{12}O_2$
Molecular weight: 224.255
IUPAC Name: 2-Phenyl-2,3-dihydro-4*H*-chromen-4-one
Phase: Solid (White crystals)
Melting point: 77 ºC
Boiling Point: 356 ºC
Solubility: In methanol

Synthesis of Flavanone Nucleus

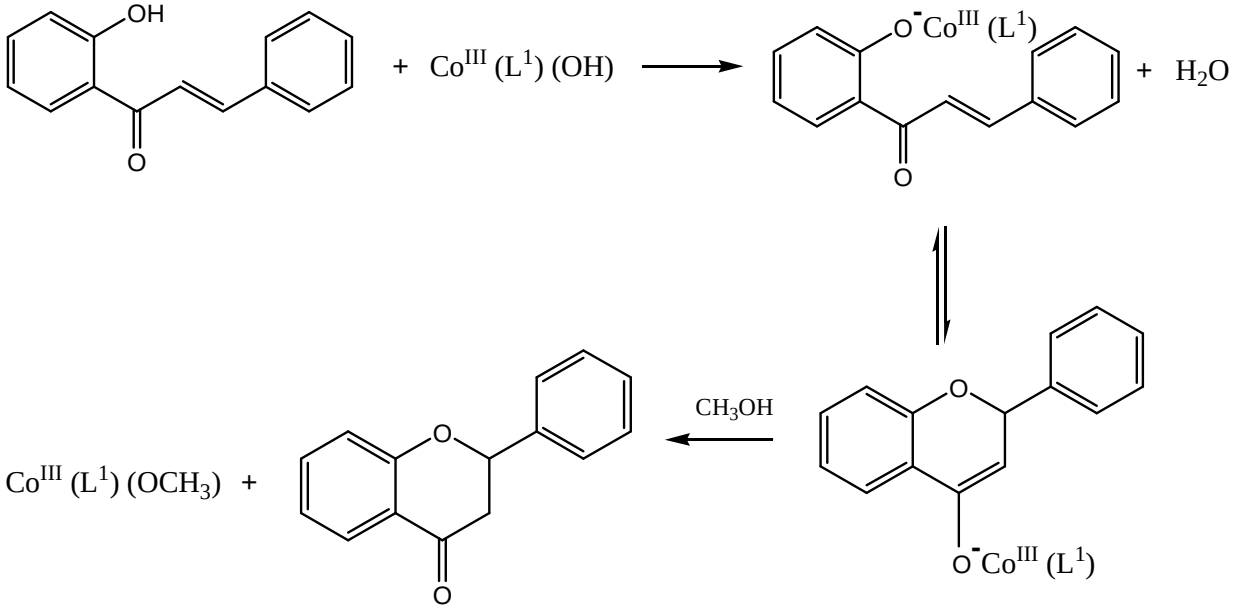
1. Chalcone method: The appropriate 2-hydroxyacetophenone is considered with benzaldehyde or hydroxybenzaldehyde to give chalcone. The chalcone can be converted into flavanone[16].



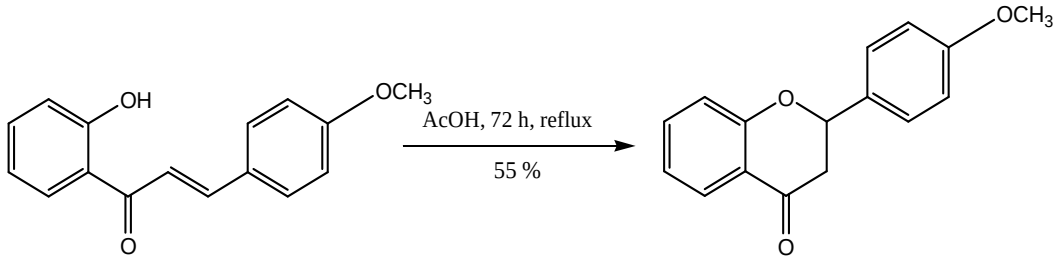
2. Algar-Flynn-Oyamada method: 2-Hydroxychalcone, prepared by the interaction of 2-hydroxyacetophenone and benzaldehyde in presence of alkali, is treated with alkaline hydrogen peroxide to form 3-hydroxy flavanone by oxidative cyclization[17].



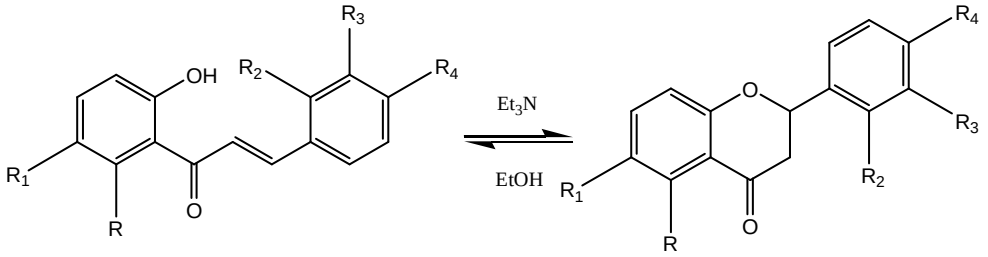
3. Conversion of 2-hydroxychalcones to flavanones catalysed by cobalt Schiff base complex: Co (salpr) catalyzes the conversion of 2-hydroxychalcones to flavanones in methanol under oxygen. Base catalysis by Co (salpr) (OH) produced *in situ* is responsible for the reaction, which is found to proceed reversibly[18].



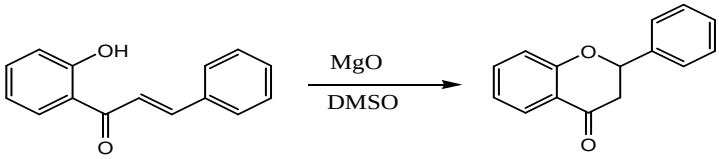
4. Cyclization of 2-hydroxy-4-methoxychalcone to 4-methoxyflavanone: The cyclization of 2-hydroxy-4-methoxychalcone to 4-methoxyflavanone was done by refluxing the corresponding chalcone in acetic acid for 72 hours, although in moderate yield (55%)[19].



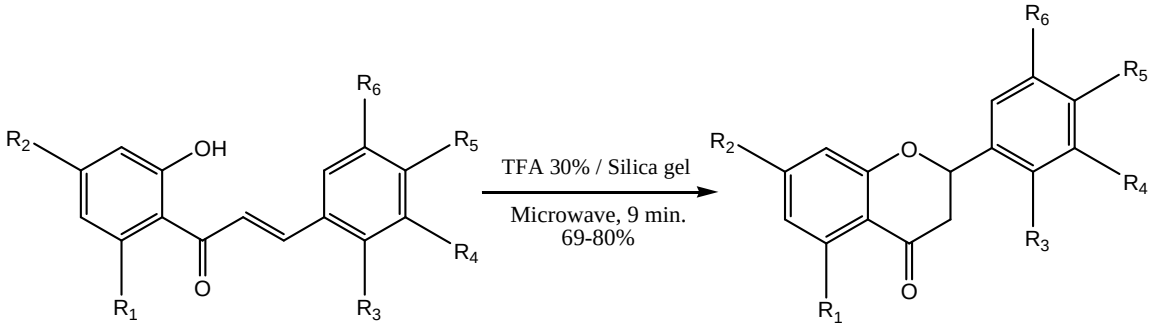
5. Isomerisation of 2-hydroxychalcones to flavanones: An isomerisation of 2-hydroxychalcones into the corresponding flavanones in ethanol in the presence of triethylamine[20].



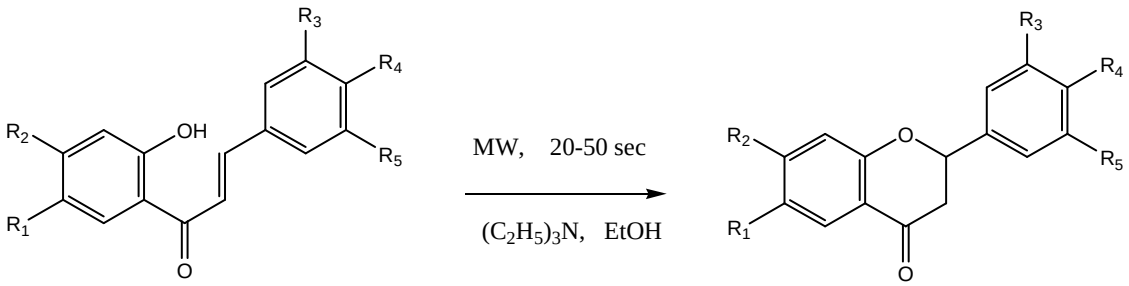
6. Heterogeneous synthesis of Flavanone over MgO catalyst: The effect of several solvents on the heterogeneous synthesis of flavanone from benzaldehyde and 2-hydroxyacetophenenone over a solid MgO catalyst was examined. Among the different high-boiling-point solvents examined for the synthesis of flavanone from benzaldehyde and 2-hydroxyacetophenone over a MgO catalyst, the use of dimethyl sulfoxide (DMSO) was found to significantly promote the yield of flavanone[21].



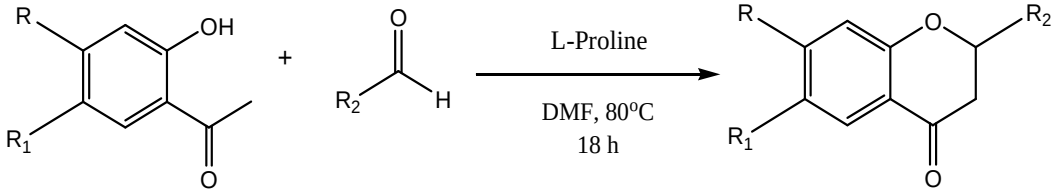
7. Microwave accelerated solvent-free synthesis of flavanones: A study of the microwave-accelerated synthesis of flavanones using an unmodified household microwave oven was undertaken. The use of trifluoroacetic acid (TFA) in refluxing chloroform almost doubled the conversion achieved previously in refluxing acetic acid[22].



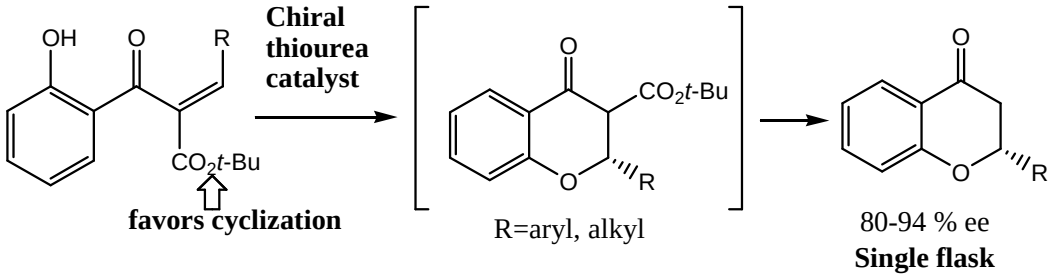
The cyclization of 2'-hydroxychalcones in the presence of triethylamine, a mild base, using Microwave irradiation resulted in a "green-chemistry" procedure with improved yields for the preparation of flavanones[23].



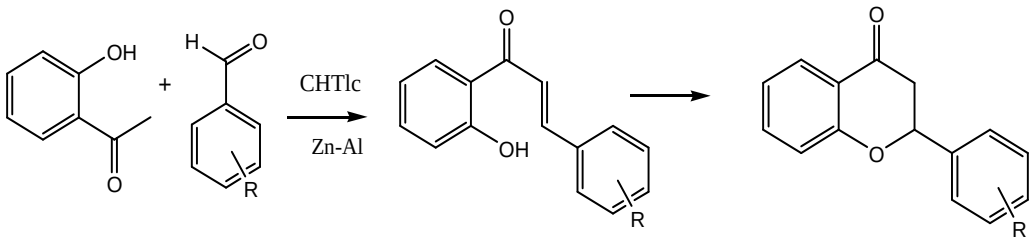
8. Synthesis of flavanones catalysed by L-proline: L-proline is utilized as an efficient organocatalyst for the synthesis of substituted flavanones and chalcones in good yields[24].



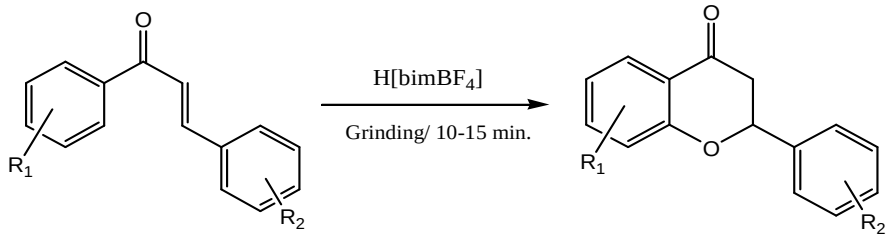
9. Catalytic enantioselective synthesis of flavanones: The enantioselective synthesis of flavanones and chromanones is described. Bifunctional thiourea catalysts promote an asymmetric oxo-conjugate addition to a β-ketoester alkylidene in high yields with excellent enantioselectivity (80−94% ee) for aryl and alkyl substrates. Decarboxylation of the β-ketoester proceeds smoothly in a one-pot procedure to afford the enantioenriched flavanones and chromanones[25].



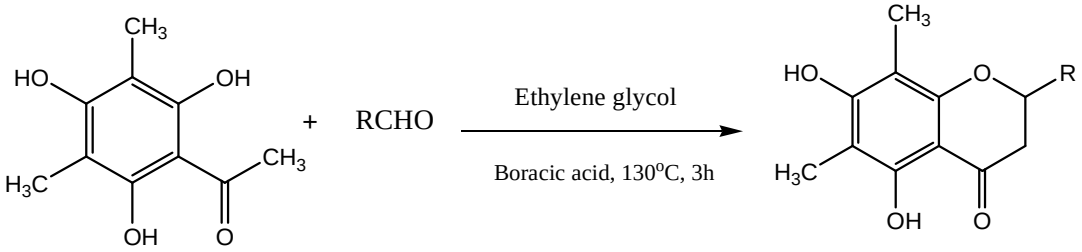
10. Catalytic synthesis of flavanone using Zn-Al hydrotalcite adhere ionic liquid: The Claisen-Schmidt condensation of 2-hydroxy acetophenone and benzaldehyde to chalcone and flavanone show that calcined Zn-Al hydrotalcite is active for synthesis. The activity of this catalyst can be further increased by about 1.5 times by coating ionic liquid triethoxysilane-3-methyl imidazolium chloride on calcined hydrotalcite[26].



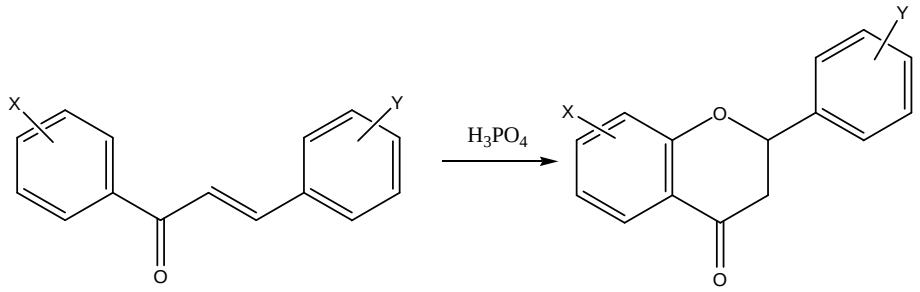
11. Synthesis of flavanone using environmental friendly catalyst H[bimBF4]: A high yielding and fast method for smooth conversion of substituted *α,β*-unsaturated carbonyl compounds chalcones to corresponding substituted 2-phenylchroman-4-one i.e. flavanone by grinding at room temperature using ionic liquid H[bimBF4] which is recyclable[27].



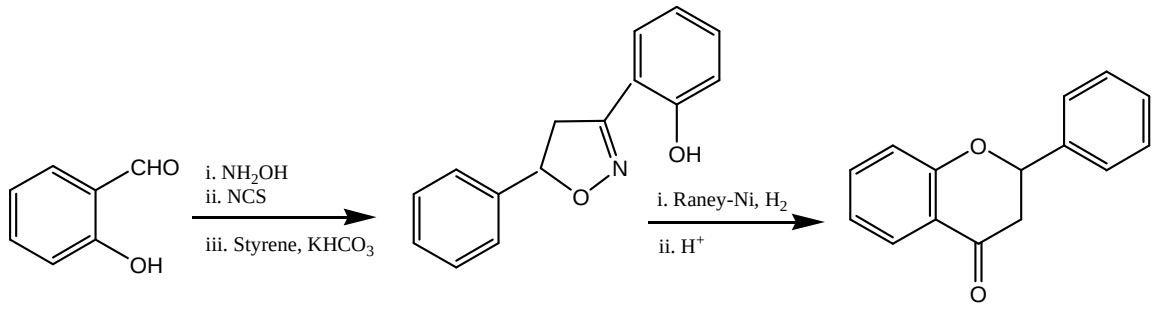
12. Synthesis of flavanone with boracic acid and ethylene glycol: A series of new flavanone derivatives of farrerol was synthesized by convenient method. In a typical synthetic procedure, substituted 2-hydroxyacetophenone was reacted with substituted benzaldehydes, and boracic acid in ethylene glycol at 130ºC to yield the product[28].



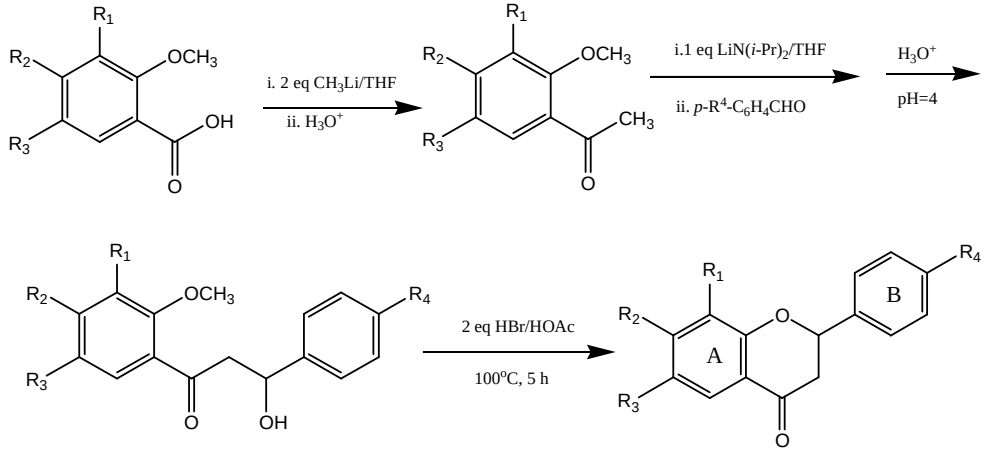
13. Synthesis of flavanone with phosphoric acid: Flavanones were prepared by refluxing the corresponding chalcones with phosphoric acid in alcohols for 2-3 days[29].



14. Synthesis of flavanone via the isoxazoline route: The parent flavanone was prepared by selective chlorination of salicyaldehyde oxime to salicylhydroxamoyl chloride, which was cycloadded to styrene. Reductive cleavage of the isoxazoline ring to the *β*-hydroxy ketone and acid catalyzed cyclization gave parent flavanone[30].

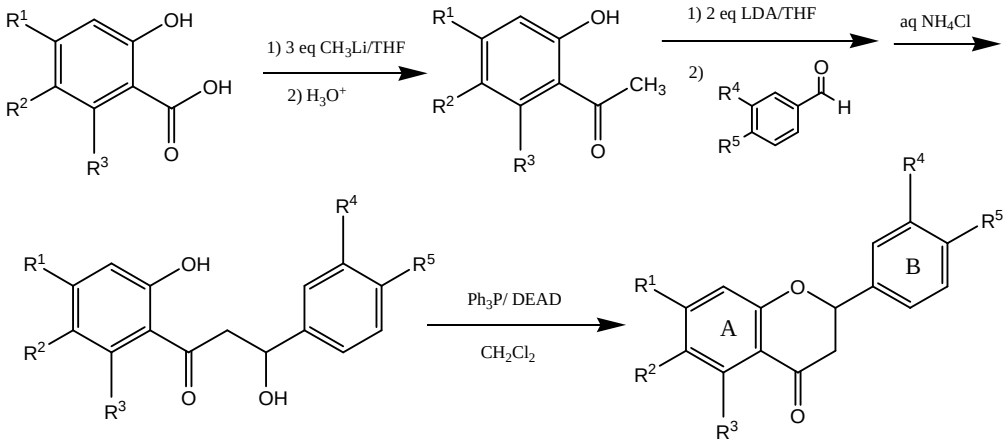


15. Synthesis of flavanones from 2-methoxybenzoic acids: Flavanones can be synthesized *via* 1-(2'-methoxy-phenyl)-1-oxo-propan-3-phenyl-3-ols from 2'-methoxy-acetophenones which were synthesized by treatment of 2-methoxy benzoic acids with 2 equiv of methyl lithium in THF for 0.5-2 h at -78ºC in 88-93% yields as a new synthetic route[31].



16. Synthesis of flavanones from 2-hydroxybenzoic acids:

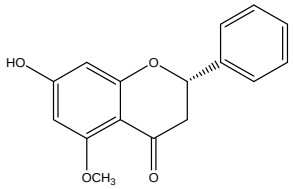
2'-Hydroxyacetophenones were readily prepared by the treatment of 2-hydroxybenzoic acids with 3-equivalent of CH_3Li in THF in 74-93% yields. 1-(2'-Hydroxyphenyl)-1-oxo-propan-3-phenyl-3-ols were prepared by the treatment of the lithium dianions of 2'-hydroxyacetophenones with benzaldehydes, which on cyclodehydration by $Ph_3P/CCl_4/Et_3N$ in CH_3CN or DMF/$(COCl)_2$/ Et_3N (Vilsmeier reagent) in CH_2Cl_2 gives flavanones[32].



Some examples of Natural Flavanones with their Biological activities

1. Alpinetin[33]:

Alpinetin is a phytochemical isolated from a variety of plants including those of the genus Alpinia.

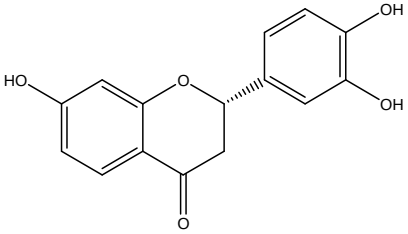


(2S)-7-Hydroxy-5-methoxy-2-phenyl-2,3-dihydro-4*H*-chromen-4-one

Biological Activity[34-36]: Hepatoprotective, antipruritic, anti-inflammatory, neuroprotector, anti-HIV activity and anti-inflammatory.

2. Butin[37]:

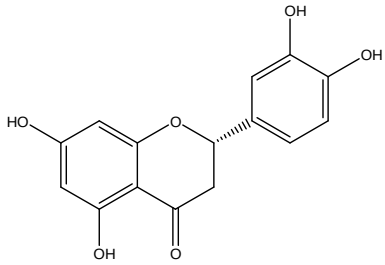
Butin is a flavanone, a type of flavonoid. It can be found in the seeds of *Vernonia anthelmintica*[38] (Asteraceae) and in the wood of *Dalbergia odorifera*[39] (Fabaceae).



(2S)-2-(3,4-Dihydroxyphenyl)-7-hydroxy-2,3-dihydrochromen-4-one
Biological Activity[40,41]: Antioxidant and cytoprotective

3. Eriodictyol[42]:

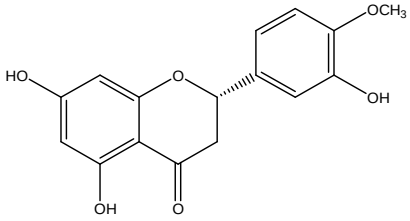
Eriodictyol is a bitter-masking flavanone, a flavonoid extracted from Yerba Santa (*Eriodictyon californicum*), a plant native to North America[43].



(2*S*)-2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-chromanone
Biological Activity[44,45]: Anti-inflammatory and antioxidant

4. Hesperetin[46]:

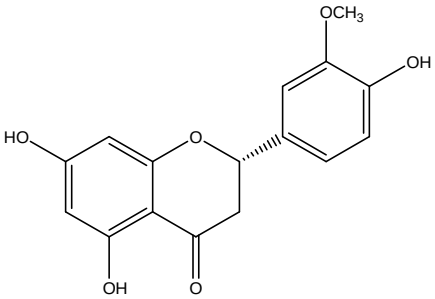
Hesperetin is a bioflavonoid and, to be more specific, a flavanone. Hesperidin (a flavonone glycoside) is water-soluble due to the presence of the sugar part in its structure, so on ingestion it releases its aglycone, i.e, hesperetin.



(*S*)-2,3-Dihydro-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-4*H*-1-benzopyran-4-one
Biological Activity[47-49]: Hypocholesterolemic, anticancer, antioxidant and neuroprotective

5. Homoeriodictyol[50]:

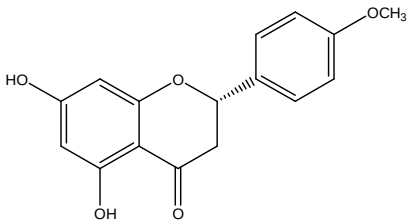
Homoeriodictyol is a bitter-masking flavanone extracted from Herba Santa (*Eriodictyon californicum*) a plant growing in America.



(2*S*)-5,7-Dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-4-chromanone
Biological Activity[51,52]: Anti-osteoporosis and anti-inflammatory

6. Isosakuranetin[53]:

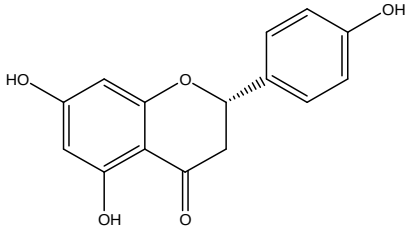
Isosakuranetin is a flavanone, a type of flavonoid. It can be found in the fruit of *Citrus sinensis* (blood orange), in the fruit of *Citrus paradisi* (grapefruit) and in *Monarda didyma* (Scarlet beebalm).



(2*S*)-5,7-Dihydroxy-2-(4-methoxyphenyl)-2,3-dihydrochromen-4-one
Biological Activity[54]: Antioxidative

7. Naringenin[55]:

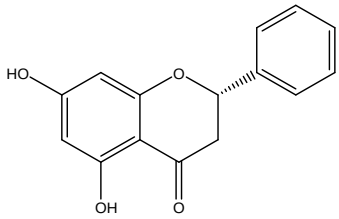
Naringenin is a flavanone, a type of flavonoid that is considered to have a bioactive effect on human health as antioxidant, free radical scavenger, anti-inflammatory, carbohydrate metabolism promoter, and immune system modulator. It is the predominant flavanone in grapefruit.



5,7-Dihydroxy-2-(4-hydroxyphenyl)chroman-4-one
Biological Activity[56.57]: Anti-inflammatory, anti-oxidant and anti-tumor

8. Pinocembrin[58]:

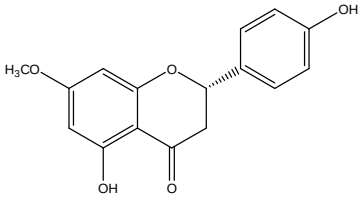
Pinocembrin is a flavanone, a type of flavonoid. It is an antioxidant found in damiana, honey and propolis.



(2*R*,3*R*)-3,5,7-Trihydroxy-2-phenyl-chroman-4-one
Biological Activity[59][5] Antimutagenic

9. Sakuranetin[60]:

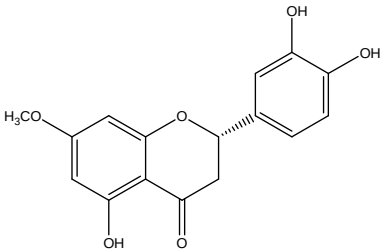
Sakuranetin is a flavanone, a type of flavonoid. It can be found in *Polymnia fruticosa*[61] and rice.



(2*S*)-5-Hydroxy-2-(4-hydroxyphenyl)-7-methoxy-2,3-dihydrochromen-4-one
Biological Activity[62]: Anti-inflammatory

10. Sterubin[63]:

Sterubin is a bitter-masking flavanone extracted from Herba Santa (*Eriodictyon californicum*) a plant growing in America.

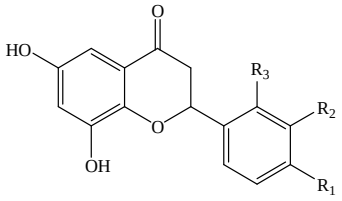


2-(3,4-Dihydroxy-phenyl)-5-hydroxy-7-methoxy-chroman-4-one

Some examples of Synthetic Flavanones with their Biological activities

1. Anti-fungal activity:

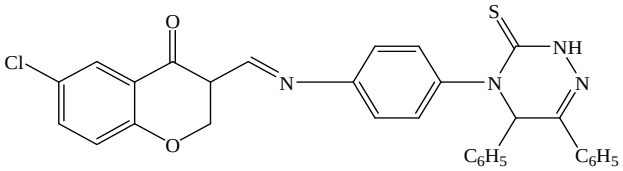
To explore the potency of the flavanone analog library, Fowler et al (2011) tested the ability of non-natural flavanones to inhibit the growth the pathogenic fungi *C. neoformans* and *A. fumigatus*. Of the compounds tested, only the 3-hydroxyflavanone (1b) failed to provide significant antifungal ability on any of the strains tested. The most resistant of the three fungal species was *A. fumigatus* and showed only limited growth inhibition with MIC values all greater than 130 µg/mL. One the other hand, three of the four non-natural flavanones tested demonstrated MIC values of approximately 30 µg/mL for the pathogenic *C. neoformans.* Results of serial dilution on agar growth plates of *C. neoformans* under different exposure times to 4-chloroflavanone (1d) indicates that the effect is not inhibitory but fungicidal[64].



(1)

Compound No.	R_1	R_2	R_3
1a	H	H	F
1b	H	OH	H
1c	H	F	H
1d	Cl	H	H
1e	F	H	H
1f	F	Br	H
1g	F	Cl	H
1h	F	OCH_3	H

Synthesis and fungicidal activity of some new 4*Z*-chromen-4-ones containing some 1,3-thiazole, 1,3-thiazine, 1,2,4-triazine moieties were done by the Ali T.E.S. (2007). All the new compounds then screened for their fungicidal activity. Among the compounds so formed, 4(4-{[(6-Chloro-4-oxo-4*H*-chromen-3-yl)methylene] amino}phenyl)-2,5-dihydro-5,6-diphenyl-3-thioxo-1,2,4-triazine was found to be the most potent compound (2)[65].

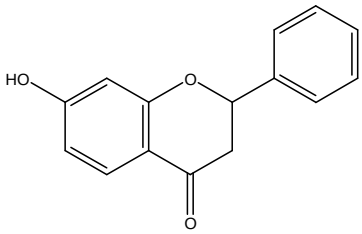


(2)

2. Antibacterial Activity:

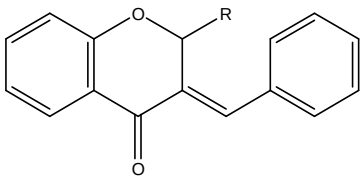
In an effort to improve the bacterial toxicity of flavanones, a small library of non-natural flavanones was created by Fowler et al (2011). Synthesis of the non-natural flavanones was completed in four reaction steps, which form protected chalcone intermediates and then follow with de-protection and ring closure. The library was first screened against the bacterial species *E. coli* and *B. subtilis* in 96-well plate growth assays and CFU counting assays. Similar to the natural flavanones, the non-natural analogs alone failed to have any potent activity to limit growth of *E. coli*. However in the presence of the RND inhibitor PABN, the potency of the non-natural analogs was significantly increased by up to 7-fold for 4-chloroflavanone (1d). It is important to note that 3OH-flavanone (1b) was found to have a low aqueous solubility (approximately 2 mM), making the potential production and use of this molecule challenging[64].

Flavanone was synthesized and tested for antibacterial effects against *Bacillus Subtalis, Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* by Sheikh et al (2010). The screening results indicate that only compound (3) was active against a gram-negative bacteria, *Escherichia coli* with a mean zone of inhibition 12.5 ± 0.3 mm[27].



(3)

A set of three E-3-arylidene flavanones were synthesized by simple base catalysed condensation of appropriate aryl aldehydes and 2'-hydroxy-4-methoxy acetophenone by Joseph et al (2008). In antibacterial studies all compounds exhibit activity against *E. coli*. Only compound 4b showed activity against *Pseudomonas*. Compound 4c showed good activity against *Staphylococcus aureus*. Compound 4b as well as compound 4c showed good activity against *Bacillus subtilis*[66].

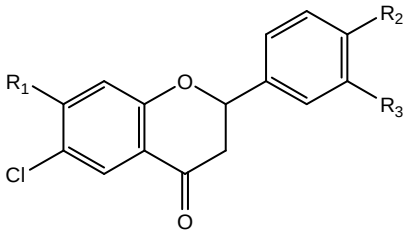


(4)

Compound No.	R
4a	Furfuraldehyde
4b	*p*-Methoxy benzaldehyde
4c	*p*-Chloro benzaldehyde

3. Antimicrobial Activity:

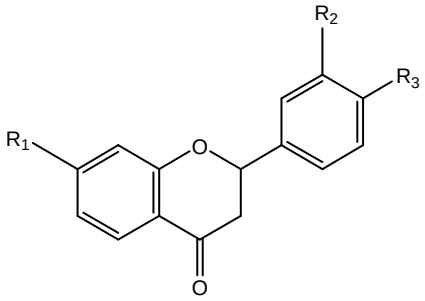
The cyclization of the 2'-hydroxychlcones under microwave irradiations afforded the variously substituted flavanones. All the synthesized flavanones were tested for antimicrobial activity by Kamboj et al (2011). The flavanones 5a and 5b were found to be most effective against two bacteria, *S. aureus* (MTCC 96) and *B. subtilis* (MTCC 121) and flavanones 5a, 5b along with 5c also effective against two fungi, *A. niger* and *A. flavous*[23].



(5)

Compound No.	R_1	R_2	R_3
5a	H	H	OH
5b	H	OH	H
5c	CH_3	CH_3	H

Vatkar et al (2010) were synthesized various analogs of flavanone by oxidative cyclization of chalcones. The synthesized compounds (6a-f) were screened for their in-vitro antibacterial activity against *E. coli* and *P. aeruginosa* and antifungal activity against *A, niger* and *A. flavus* by measuring the zone of inhibition. Compounds 6a, 6b, 6d & 6e possessed good antibacterial activity and Compounds 6a,6b,6c,6d & 6f have been found to be good antifungal activity[67].

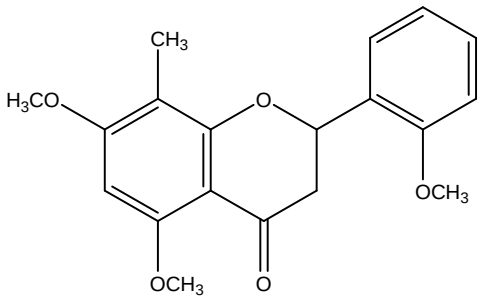


(6)

Compound No.	R_1	R_2	R_3
6a	H	NO_2	H
6b	H	H	F
6c	H	H	CH_3
6d	OH	OH	H
6e	OH	NO_2	H
6f	OH	H	CH_3

4. Anti-tubercular Activity:

A new class of alkylated flavanones were synthesized by Babu et al (2013) and screened for anti-tubercular activity on *Mycobacterium tuberculosis*. Among 17 compounds compound 7 was found most potent[68].



(7)

5. Antioxidant Activity:

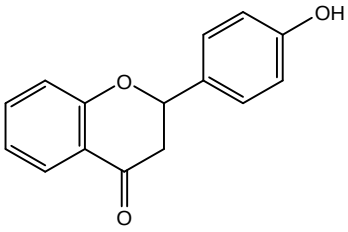
Three E-3-arylidene flavanones have been synthesized by one pot method which reduces the usual tedious multistep involved in the synthesis of medicinal compounds by Joseph et al (2008). Considering anti-oxidant activity, compound 4c showed maximum activity and compound 4b showed least activity[66].

6. Analgesic Activity:

All the synthesized compounds synthesized by Joseph et al (2008) were expected to exhibit analgesic activity, as per the studies two were found to exhibit analgesic action. The results shows less analgesic activity for all tested compounds than the standard drug namely Diclofenac sodium. Among the three compounds compound 4c showed maximum analgesic activity. Compound 4b showed least analgesic activity. Among the three compounds exhibited analgesic activity, the compound 4c showed more activity than others, probably due to the presence of halogen atom[66].

7. Anti-inflammatory Activity:

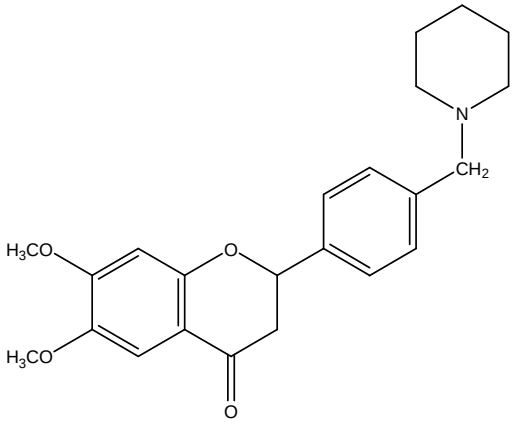
A series of chalcones and related compounds were prepared by Claisen-Schmidt condensation of appropriate acetophenone with appropriate aromatic aldehydes and the anti-inflammatory activities of these synthetic compounds were studied on inhibitory effects on the activation of mast cells and neutrophils by Hsieh et al (1998). Only one flavanone i.e. 4'-hydroxyflavanone (8) exhibited potent inhibitory effects on the release of β–glucuronidase and lysozyme from rat neutrophils stimulated with formyl-Met-Leu-Phe (fMLP)[69].



(8)

8. AChE Inhibitor Activity:

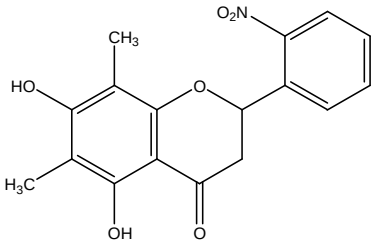
A new series of flavonoid derivatives have been designed, synthesized and evaluated as potent AChE inhibitors by Sheng et al (2009). Most of them showed more potent inhibitory activities to AChE than rivastigmine. The most potent inhibitor flavonone derivative (9) inhibit AChE with a IC_{50} of 0.248 µM and showed high BChE/AChE inhibition ratio (194-fold), superior to donepezil (IC_{50}=12nM, 389-fold). Molecular docking studies were also performed to explore the detailed interaction with AChE[70].



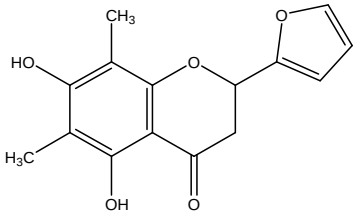
(9)

9. Anti-VSMCs Vegetation Activity:

A series of new flavanone derivatives of farrerol was designed and synthesized by Shi et al (2011) as a potent inhibitor of vascular smooth muscle cells (VSMCs) vegetation according to a convenient method. The biological activities of these compounds against VSMCs *in vitro* were evaluated. The assay results indicate that two compounds, 5,7-dihydroxy-6,8-dimethyl-2-(2-nitrophenyl)chroman-4-one (10a) and 2,3-dibromo-4,5-dihydroxydiphenyl methanone (10b) exhibited high activity against VSMCs *in vitro* with IC_{50} values of 9.9 and 6.7 µmol/L, respectively, and the preliminary structure-activity relationship (SAR) was described[71].



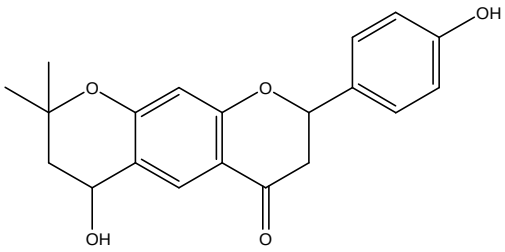
(10a)



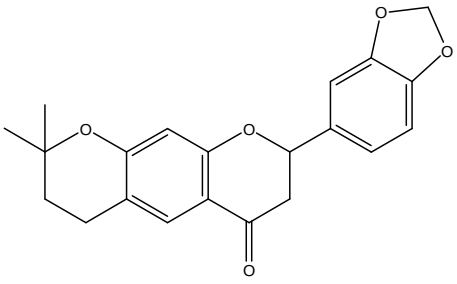
(10b)

10. Vasorelaxant Activity:

A series of 6-prenyl (or its isomers)-flavanones were synthesized and evaluated for their vasorelaxant activities against rat aorta rings pretreated with 1 µM phenylephrine (PE) by Dong et al, 2011. In this study, some synthesized flavonoid derivatives were characterized as agents with remarkable vasorelaxant activities. The preliminary structure-activity relationships studies revealed that the introduction of a cyclic prenyl group resulted in good vasorelaxant activity, as exemplified in dihydropyranoflavones 11a and 11b [72].

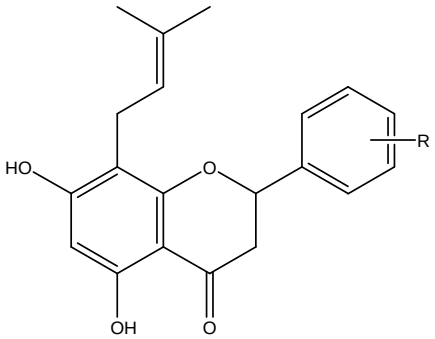


(11a)



(11b)

Support vector machine (SVM) was applied by Dong et al, 2008 to predict vasorelaxation effect of different structural molecules. A good classification model had been established, and the model was used to predict the activity of a series of prenylated flavonoids. According to the estimated result, different chalcones, flavones and flavanones were selected and synthesized. Their vasodilatory activities were determined experimentally in rat aorta rings that were pretreated with phenylephrine (PE). Structure–activity relationship (SAR) analysis revealed that flavanone derivatives showed the most potent activities, while flavone and chalcone derivatives exhibited medium activities [73].

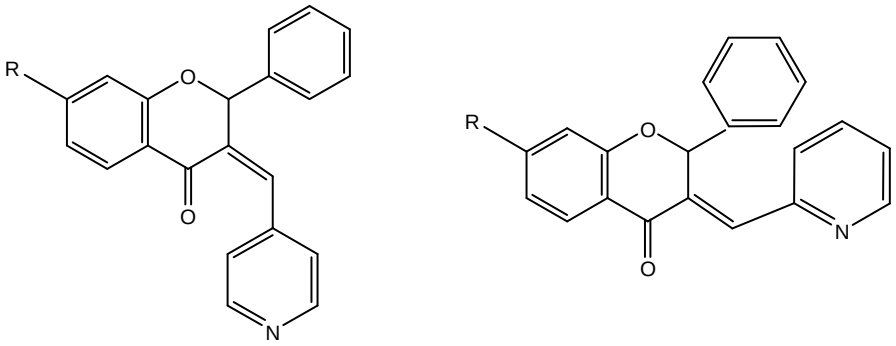


(12)

Compound No.	R
12a	H
12b	3’,4’-OCH_2O-
12c	3’-Br
12d	3’-OCH_3, 4’-OH

11. Aromatase inhibitory Activity:

Two (*E*)-pyridinyl-substituted flavanone derivatives were synthesized and UV irradiation of these compounds afforded a Z-enriched mixture. These products were tested for their ability to inhibit the cytochrome P450 aromatase. It was observed that the introduction of a pyridinylmethylene group at carbon 3 on flavanone nucleus led to significant increase of aromatase inhibitory effect. Morever, configuration had a substantial influence on the aromatase inhibitory activity since (*E*)-isomers were found to be more active that (Z)-isomers[74].



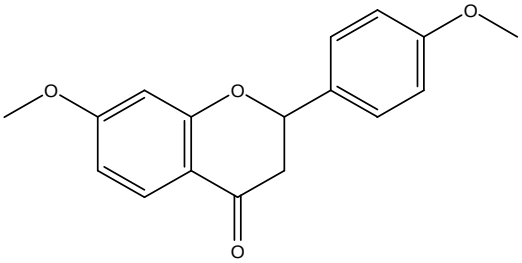
(*E*) (*Z*)

(13)

Compound No.	R
13a	H
13b	OCH_3

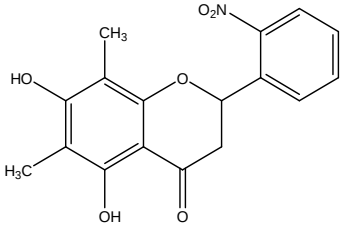
12. Anti-tumor Activity:

Choi et al (2011) were designed this study to investigate the anticancer activity of 4',7-dimethoxyflavanone (14) *in vitro*. When human breast cancer MCF-7 cells were treated with compound 7 at various concentrations (1–200 μM) for 24 h, antiproliferative effects were first observed at 1 μM and the IC_{50} was 115.62 μM. Conversely, compound 14 was not cytotoxic (measured as lactate dehydrogenase release in CHO-K1 cells) under the same conditions. MCF-7 cells exposed to the compound 14 at the IC_{50} concentration showed cell cycle arrest and apoptosis. Compared to the respective control level, exposure to compound 14 resulted in a remarkable increase of small DNA fragments at the sub-G1 phase and an increase in the G2/M phase cell population. Moreover, when compound 14 treatment caused G2/M phase arrest, an increase in CDK1 together with an increase in cyclin B was observed. Based on these results, compound 14 may be a useful anticancer agent[75].



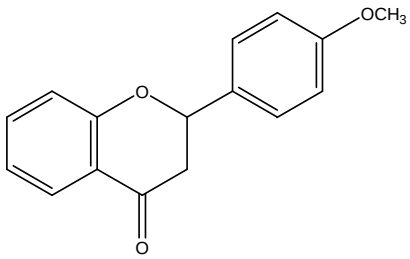
(14)

A series of new flavanone derivatives of farrerol was synthesized by Shi L. et al (2010) and evaluated against human Bel-7402, HL-60, BGC-823 and KB cell line for anti-tumor activity. The data indicate that compound 15 with an ortho nitro group on ring B, had the strongest activity (IC_{50}=9.9μM)[28].



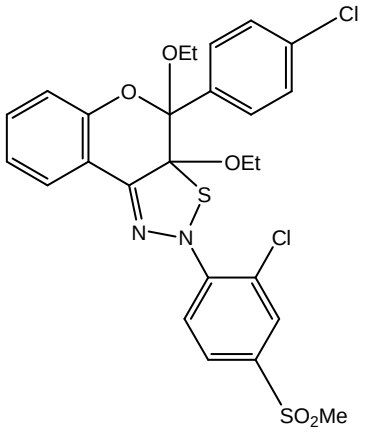
(15)

A series of synthetic chalcones, flavanones and flavones has been synthesized by Cabrera et al (2007) and evaluated for antitumor activity against the human kidney carcinoma cells TK-10, human mammary adenocarcinoma cells MCF-7 and human colon adenocarcinoma cells HT-29. Fourteen out of 53 analyzed compounds resulted very active against at least two of the studied tumoral cells. Flavanone 16 was very cytotoxic in the series and this activity could be the result of metabolic hydroxyl chalcones[76].



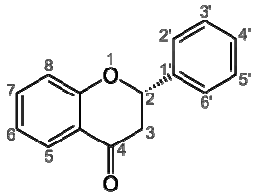
(16)

A series of 2,4-diarylchromane[4,3-*d*]-$\Delta^{1,9b}$-1,2,3-thiadiazolines were synthesized by cyclization of corresponding 2-arylchroman-4-one-arylhydrazones with $SOCl_2$ then treated with alcohol by Ying et al (2007). All the compounds were tested for their antiproliferative activity *in vitro* against six human tumor cell lines including Bel-72, ECA-109, PC-3, MCF-7, HL-60 & A-549 cells; and the highly potent derivative 17 exhibited *in vivo* inhibitory effect on tumour growth[77].



(17)

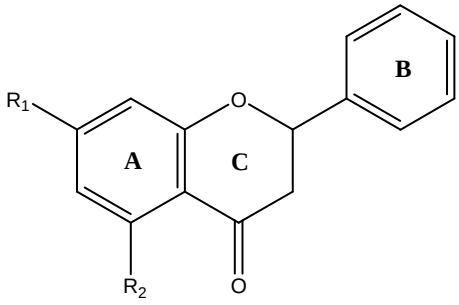
The antitumor effects in colorectal carcinoma cells (HT29, COLO205, and COLO320HSR) of eight flavanones including flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone, 7-OH flavanone, naringenin, nargin, and taxifolin were investigated by Shen et al (2004). Results of the MTT assay indicate that 2'-OH flavanone showed the most potent cytotoxic effect on these three cells, and cell death induced by 2'-OH flavanone was via the occurrence of DNA ladders, apoptotic bodies, and hypodiploid cells, all characteristics of apoptosis. Induction of caspase 3 protein processing and enzyme activity associated with cleavage of poly (ADP-ribose) polymerase (PARP) was identified in 2'-OH flavanone-treated cells, and a peptidyl inhibitor (Ac-DEVD-FMK) of caspase 3 attenuated the cytotoxicity of 2'-OH flavanone in COLO205 and HT-29 cells. Elevation of p21 (but not p53) and a decrease in Mcl-1 protein were found in 2'-OH flavanone-treated COLO205 and HT-29 cells. Elevation of intracellular reactive oxygen species (ROS) was detected in 2'-OH flavanone-treated cells by the 2',7'-dichlorodihydrofluorescein diacetate (DCHF-DA) assay, and ROS scavengers including 4,5-dihydro-1,3-benzene disulfonic acid (tiron), catalase, superoxide dismutase (SOD), and pyrrolidine dithiocarbamate (PDTC) suppressed the 2'-OH flavanone-induced cytotoxic effect. Subcutaneous injection of COLO205 induced tumor formation in nude mice, and 2'-OH flavanone showed a significant inhibitory effect on tumor formation. The appearance of apoptotic cells with H&E staining, and an increase in p21, but not p53, protein by immunohistochemistry were observed in tumor tissues under 2'-OH flavanone treatment. Primary tumor cells (COLO205-X) derived from a tumor specimen elicited by COLO205 were established, and 2'-OH flavanone showed an significant apoptotic effect in COLO205-X cells in accordance with the appearance of DNA ladders, caspase 3 protein processing, PARP protein cleavage, and increasing p21 protein. These results revealed *in vitro*, *ex vivo*, and *in vivo* antitumor activities of 2'-OH flavanone via apoptosis induction, and indicates that 2'-OH flavanone is an active compound worthy of development for cancer chemotherapy[78].



(18)

Compound Name	-OH	-rhamnoglucoside
Flavanone	-	-
2'-OH flavanone	2'	-
4'-OH flavanone	4'	-
6- OH flavanone	6	-
7 -OH flavanone	7	-
Naringin	4', 5	7
Naringenin	4',5,7	-
Taxifolin	3,3',4',5,7	-

Several classes of flavanoids (flavones, flavanones, 2'-hydroxychalcones and flavan-4-ols) having a variety of substituents on A ring were investigated by Pouget et al (2001) for their antiproliferative activity against MCF-7 human breast cancer cells. Structure-activity relationships of these compounds were discussed. Methoxylated flavanones (19a-c) were found to be potent inhibitors of MCF-7 cell growth[79].



(19)

Compound No.	R_1	R_2
19a	OCH_3	H
19b	H	OCH_3
19c	OCH_3	OCH_3

Conclusion

This particular review article, in reference, would extend great deal of help to researchers as one of the goal of medicinal chemistry research and drug discovery is to develop compounds that both show desirable biological activities and are easily accessible. Such compounds should be either isolated from natural resources or they should be easily synthesized in large amounts in the laboratory. The present literature survey of flavanone nucleus have rendered that flavanones are significantly important class of heterocyclic compounds and their applications in ever challenging chemotherapy of various ailments.

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