Flavanone: An overview

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Abstract: The synthesis of flavanones, chalcones, and dihydrochalcones is discussed in this study. Citrus fruits and apples are the primary dietary sources of flavanones and dihydrochalcones, respectively. Isolation, identification, characterization, and functions of flavonoids, as well as their applications on health benefits, are the current trends in research and development activities on flavonoids. The current study seeks to highlight current developments in flavonoid research and development, flavonoid working mechanisms, flavonoid functions and applications, flavonoid prediction as prospective medications in the prevention of chronic diseases, and future research prospects.

Keywords: Flavanone, chalcone, flavonoids, natural flavanone, synthetic flavanone.

Introduction: Flavanone

Flavonoids are widely dispersed in the plant kingdom when they are employed to develop and defend plants. Flavonoids are structurally distinguished by two benzene rings and a heterocyclic pyrone ring, and they are classified into seven subfamilies based on the oxidation and saturation status of the heterocyclic ring. [1]

Flavanones are diverse aromatic colourless ketones generated from flavone that are commonly found in plants as glycosides. [2]

The drug industry is highly interested in heterocycles because of their vast spectrum of biological activity. They are utilised as antibacterial [3], antifungal [4], antiviral [5], antihypertensive, anti-inflammatory, anticancer[6], antimycobecterial [8, antiarrhythmic[9], analgesic[10], muscle relaxant[11] or antituberculosis[12], and anticholesterolemic activity [13] in modern medicine. Flavonoids are plant secondary metabolites that have a lot of potential for treating a variety of diseases. A lot of studies have indicated their ability to prevent cancer from developing by interacting with aberrant cells through various
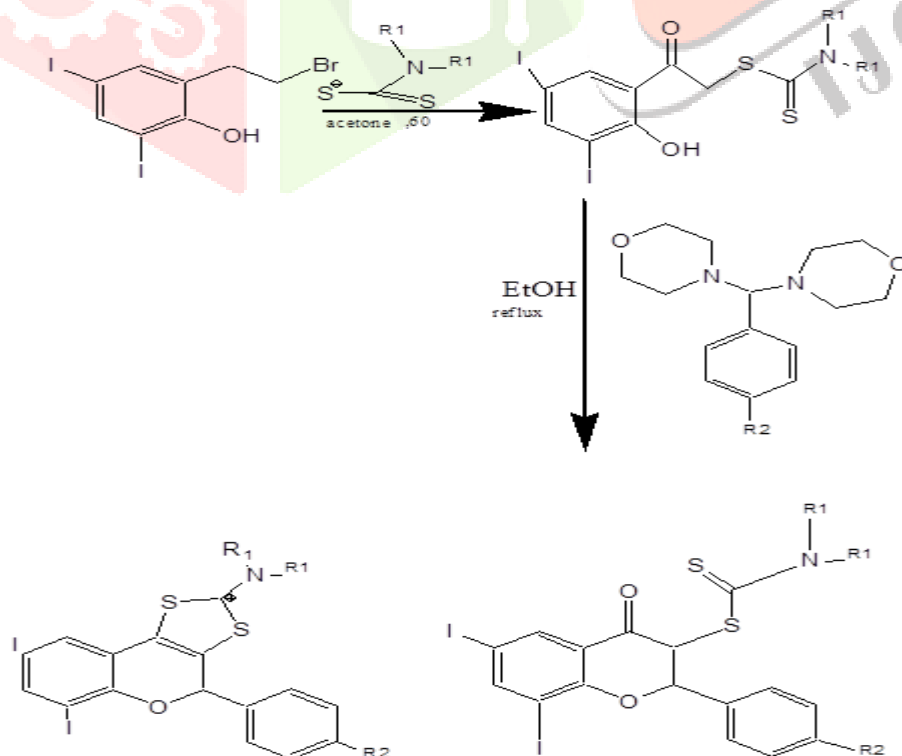
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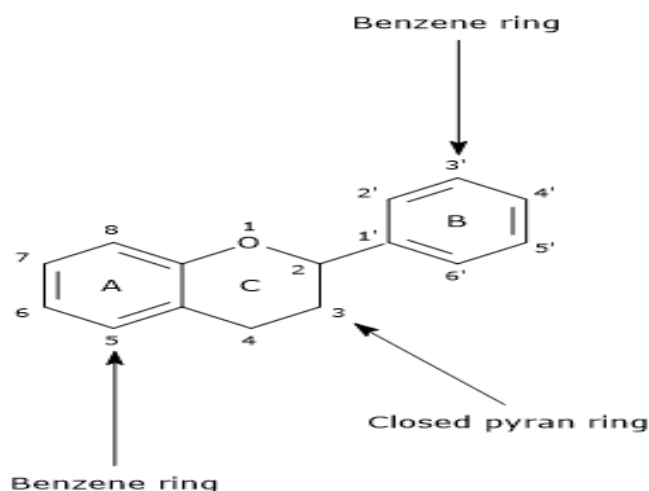
Reduce cell adhesion or induce apoptosis, for example. Green tea, a popular beverage around the world, has a variety of flavonoids that slow down age-related brain degradation, and research on nematode species suggest they can also slow down the ageing process. Flavonoids have also been proven to offer therapeutic potential in the treatment of cardiac disease.

Synthesis of flavanone nucleus:

1. **Synthesis of flavanones novel tricyclic containing iodine** :

Novel iodine-sulphur flavanones were synthesized by reacting a series of phenacyl carbodithioates with different aminals. The latter undergo a cyclocondensation reaction in acidic conditions, resulting in the creation of their corresponding 1,3-dithiolium salts. [14]

2. **Three-step rapid and efficient synthesis of flavanones from cinnamic acid:** A three-step fast and efficient synthesis of flavanones from cinnamic acid has been devised. SOCl2 was used to convert cinnamic acid to cinnamoyl chlorides first. The acid chlorides were subsequently treated with substituted phenols in BF3. OEt2 to produce the matching chalcone in 42 (75%) of the cases. At room temperature, base-catalyzed cyclization of the chalcones yielded matching flavones in 85-95 percent of cases. The position and character of the substituents on the aromatic rings were found to affect the conversion of cinnamic acid derivativs to matching chalcones. [15]

3. **Arylation of chromanones with Arylboronic acids via Palladium (II) – catalyst one-pot synthesis of flavanones via Palladium (II)**: Catalyst one-pot synthesis of flavanones via Palladium (II) – catalyst one-pot synthesis of flavanones via Palladium (II) – catalyst one Flavanones were made by arylation of chromanones, a class of simple ketones with unactivated, with arylboronic acid in a single pot using tandem palladium (II) catalysis. This process opens up a new pathway to flavanones. (16)

4. **Heterogenous synthesis of flavanone:** the heterogenous synthesis of flavanone from benzaldehyde and 2 -hydroxyacetophenoe was examined through a series of MgO samples modified with different anions. CO_2 temperature programed desorption (TDP) was used to characterize the basic properties of these samples. The results indicate that basic sites with different strengths exist on the MgO surface.   [17]

5. Efficient and facile synthesis of flavanones catalysed by N- methylimidazole :

The utilisation of N-methylimidazole as a catalyst for the cyclization of 2- hydroxychalcones to their flavanone counterparts in DMSO was studied. The breadth of this technique was investigated, and a variety of flavanones were produced in high yields. [18]
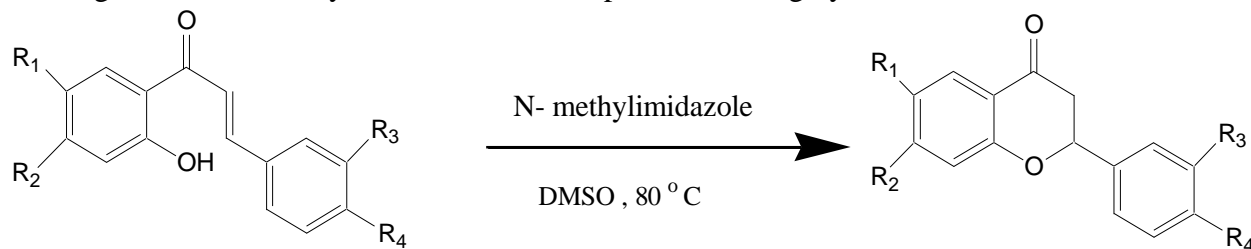

6. **Synthesis of arylidene flavanones in a one pot method:** A heated (25° C) aqueous alcoholic solution of potassium hydroxide (15%) was added to a mixture of 2-hydroxy,4-methoxy acetophenone and aromatic aldehyde, and the solution was agitated to obtain a homogeneous solution. In a sealed container, the solution can be left for four days. Methanol was injected drop by drop to eliminate turbidity that had accumulated throughout the cooling process. The material was separated and rinsed in cold aqueous alcohol (50 percent methanol). Then, using aqueous alcohol, it crystallised. [19]

7. **Flavanone synthesis from 2-methoxybenzoic acids:** 2-methoxyacetophenones were easily produced by treating 2-methoxybenzoic acids with an equivalent of methyllithium in THF for 0.5-2 h at 78° C, yielding 88-93 percent yields. [20]
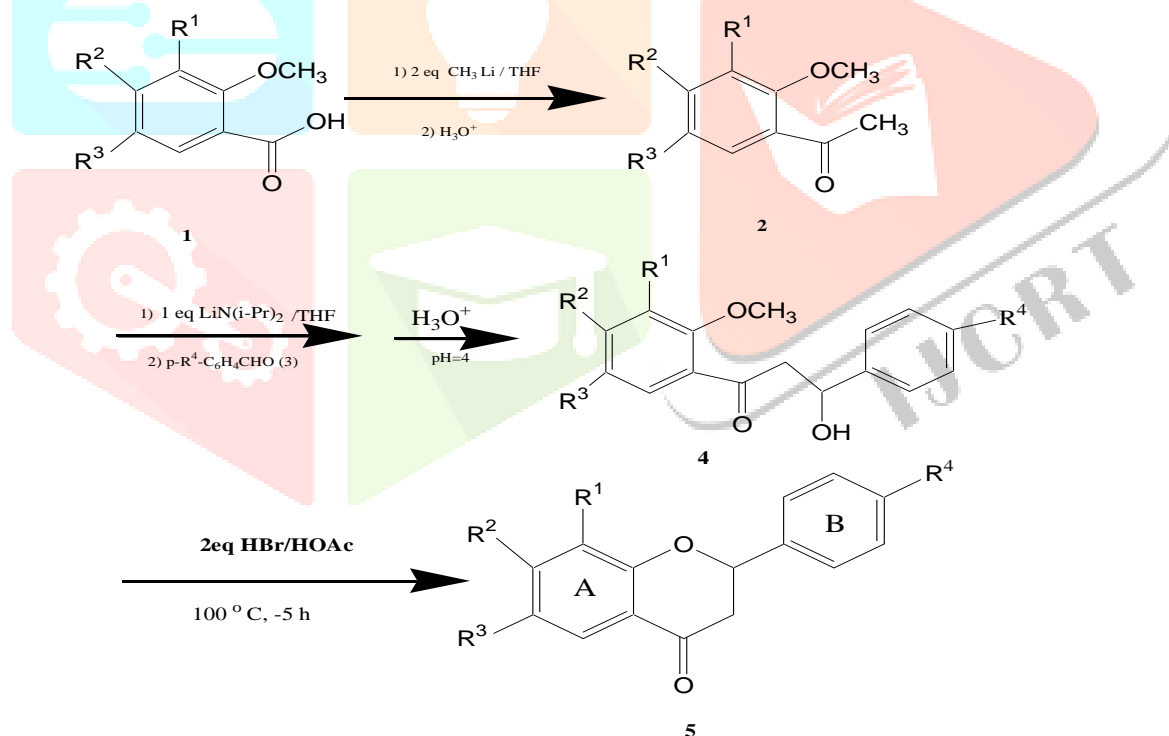
8. **Facile one- pot synthesis of flavanones using tetramethylguanidinum -based ionic liquids as catalysts:** Tetramethylguanidine-based ionic liquids (TMGILs) were prepared, characterized and used as catalysts in pot synthesis of flavanones. The results indicated that TMGILs composed of

phenolate anion was beneficial for one pot synthesis of flavanones. [21]
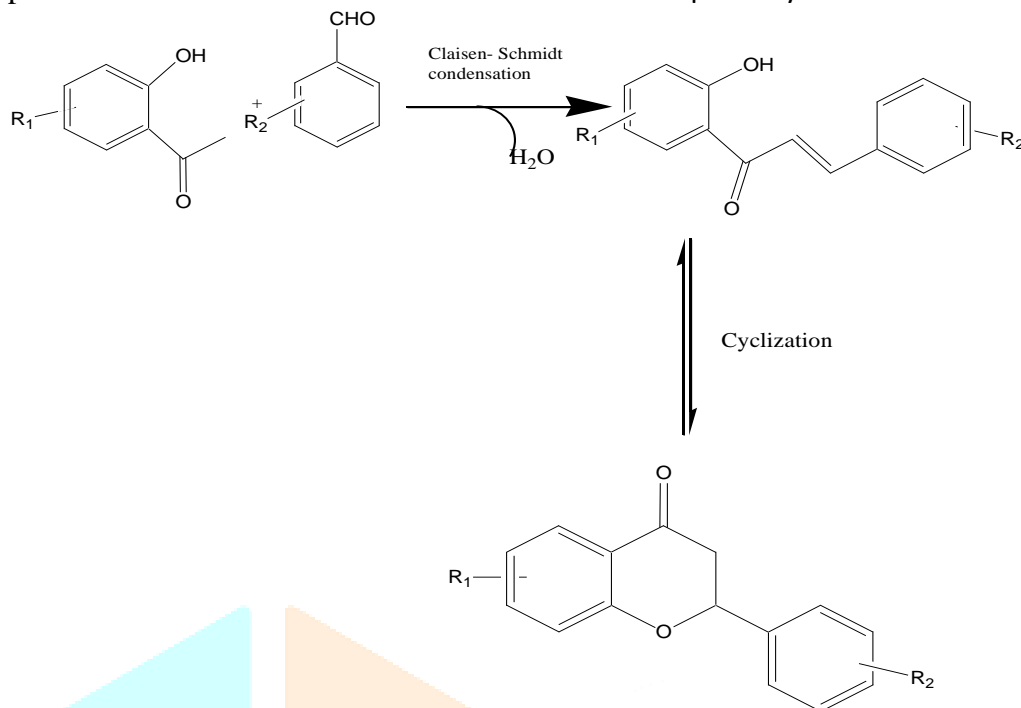
9. Synthesis of chalcone and flavanone derivatives using ZnO nanoparticles as catalyst for antibacterial activity: Using ZnO nanoparticles as catalyst and water as solvent, a green approach for the synthesis of chalcone and flavanone derivatives was devised. [22]


10.
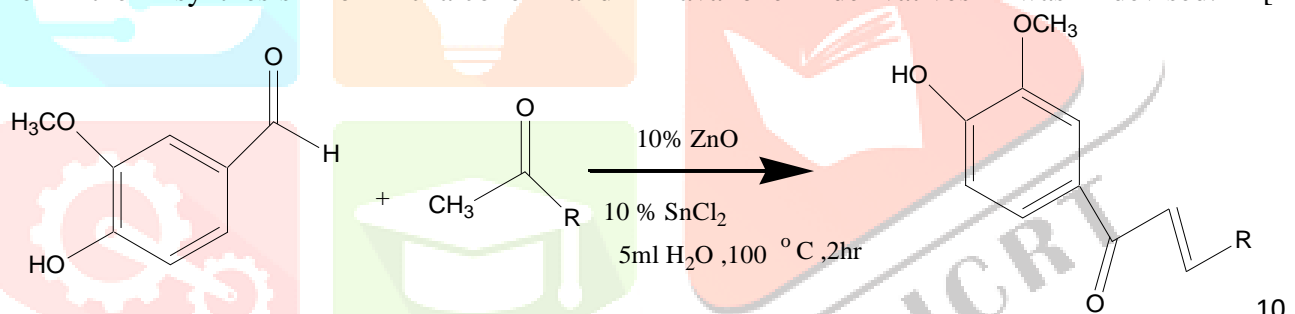
Improved method for the synthesis of flavanones: Flavanones are commonly made by isomerizing 2-hydroxychalcone in acidic alkaline conditions. This process has been improved. By using hot ethanol, diluted alkali, sulfuric, hydrochloric, or phosphoric acid, 2-hydroxychalcone isomerization into the appropriate flavanones can be achieved. [23]
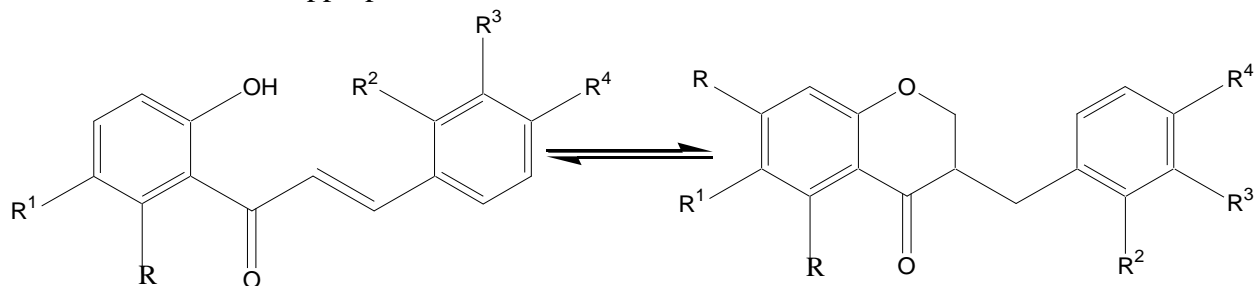
11. Flavanone synthesis using anhydrous potassium carbonate as an effective basic catalyst: Flavanones are made by starting with either 2-hydroxychalcone or 2-hydroxyacetophenones. Refluxing in a solvent with additional catalyst or microwave irradiation on the catalyst were the preferred recation conditions in both situations.[24]
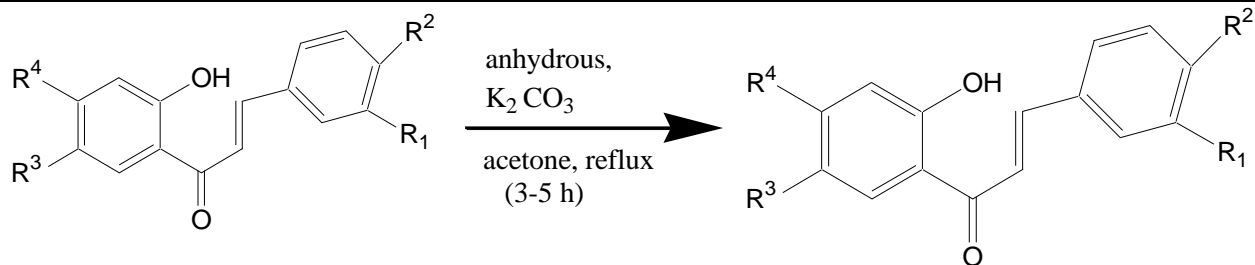
12. Microwave- Assisted synthesis of 1,3-Diaza- flavanone: The cyclization of 2-amino(E)-3"-azachalcone yields the 1,3-diazaflavanone and 1,3-diazaflavone. A simple solid-phase microwave-assisted approach that is environmentally friendly. [25]
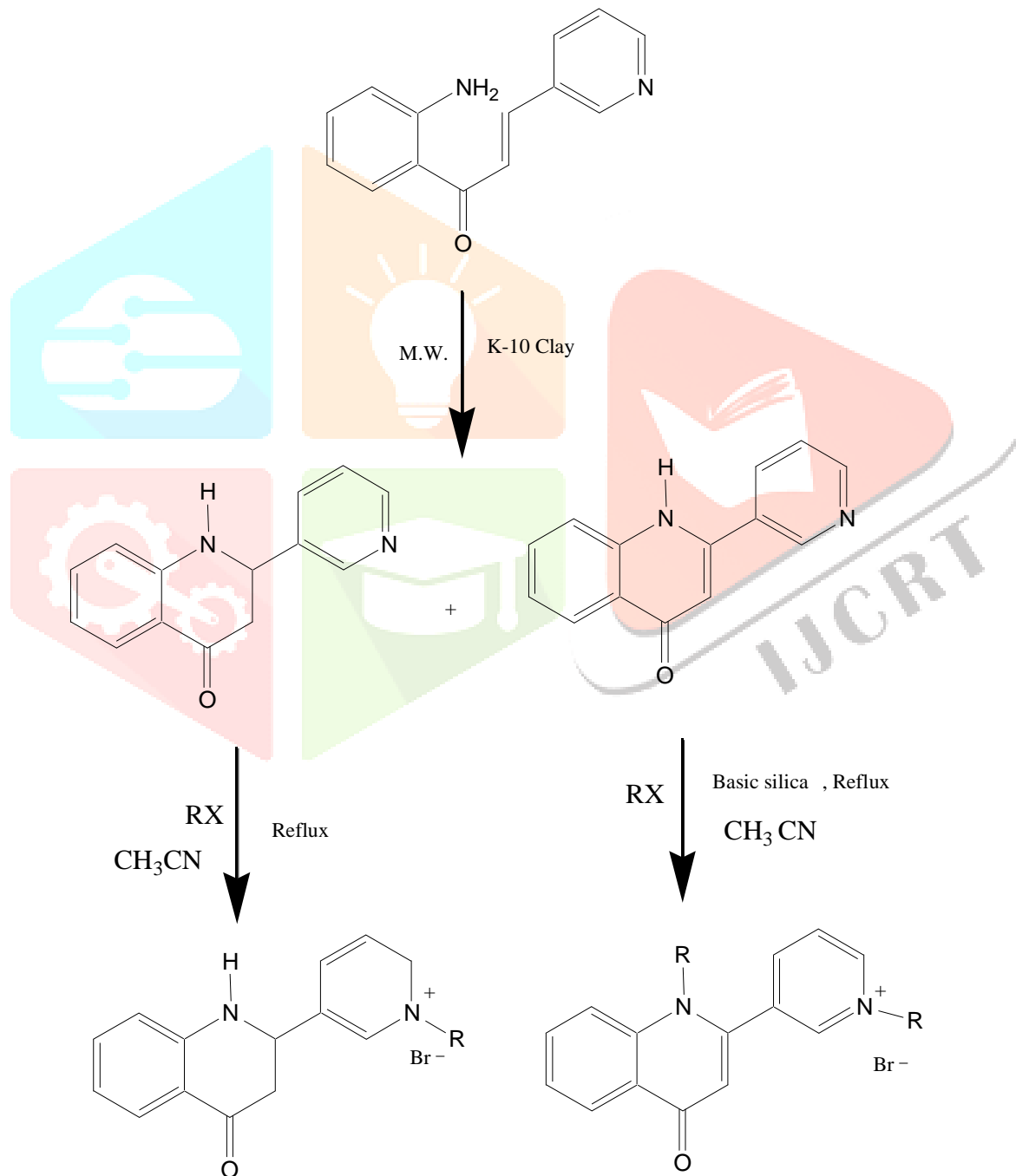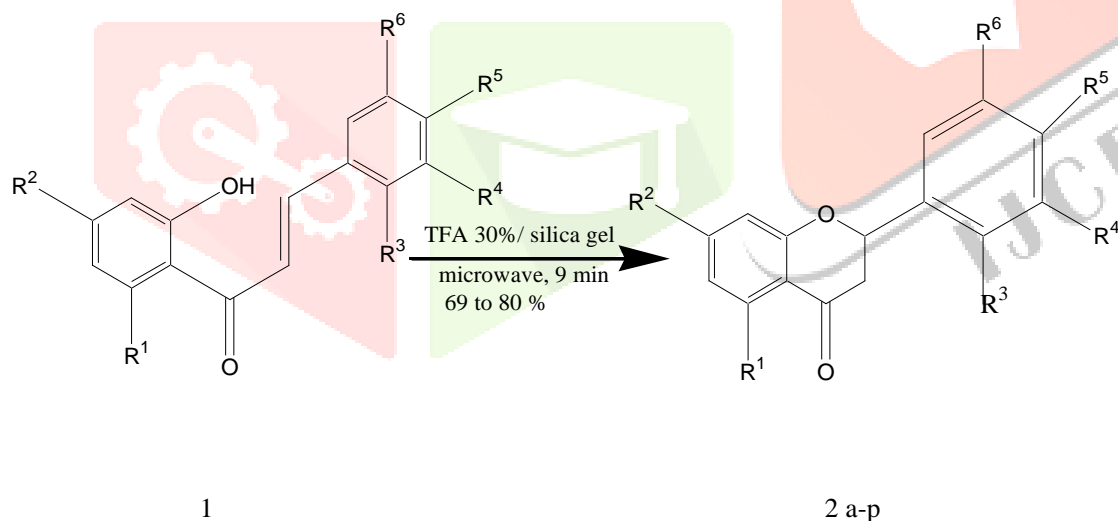
13. Synthesis of stilbine- fused 2- hydroxychalcones and flavanones The green catalytic conversion of 2-hydroxy and 2-amino chalcone to flavanone and tetrahydroquinolones. the synthesis of flavanones and tetrahydroquinolones is intramolecular cyclization of 2-hydroxy and 2-amino chalcones. It can be synthsised almost in the presence of pipperidine and KOH, it can be transformed to flavanone and tetrahydroquinolones in just 2 minutes at room temperature.[26].

2.7 mol % organic base additive

r.t. , 1 h ,H$_2$O

1a

2a
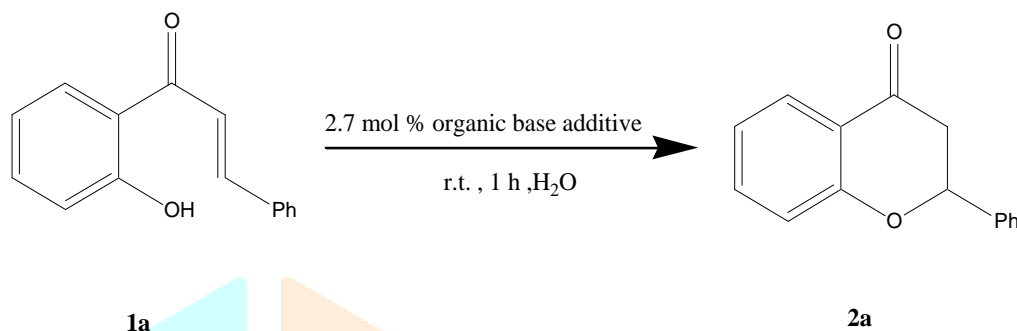
14. Flavanone Synthesis via Microwave Accelerated Solvent-Free Synthesis:

Irradiation of chalcones with 30 percent TFA over silica gel was used to evaluate the synthesis of flavanone in very good yields utilising an unmodified domestic microwave oven, multiple mineral supports, and catalysts .[27].

TFA 30%/ silica gel
microwave, 9 min
69 to 80 %

1

2 a-p

15 . Synthesis of stilbine- fused 2- hydroxychalcones and flavanones: Alkoc et al. (2010) employed retro-synthetic analysis to show that the synthesis of stilbene-fused flavanones or stilbene-fused chalcones required three steps: Addition reactions Claisen- Schmidt, Heck, and Michael [28].
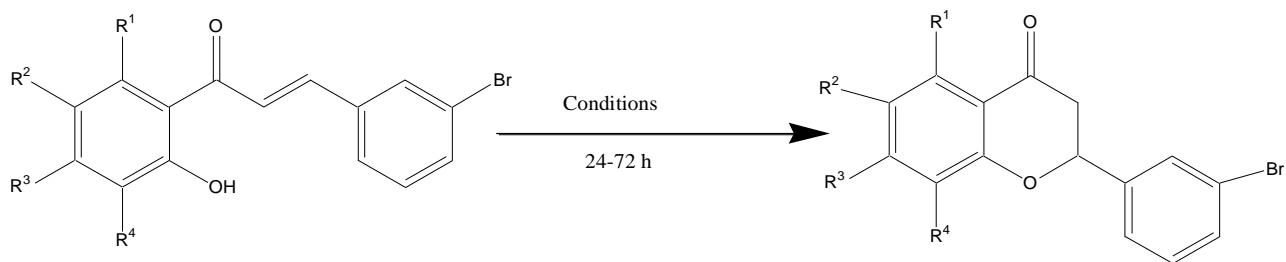
## 16. Synthesis and biological evaluations of chalcones and flavanones with hydroxyl and/or methoxy groups.

Aldol condensation between substituted acetophenones and substituted benzaldehyde utilising NaH and LiHMDS to produce flavanones with hydroxyl and possibly methoxyl groups [29].
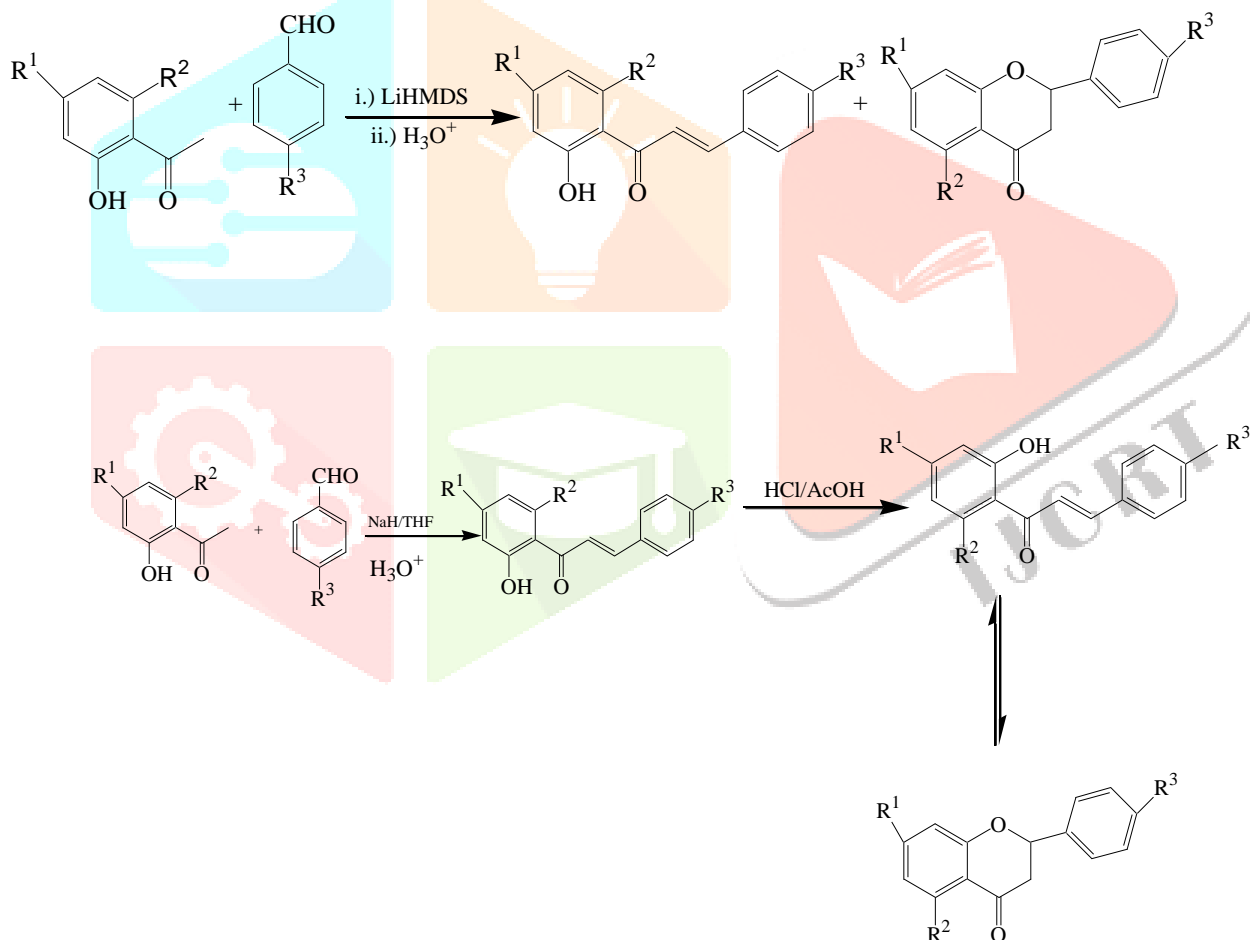

17. Synthesis of Flavanone from the isooxazoline:

Flavanone was made by chlorinating salicyaldehyde oxime selectively to produce salicylhydroxamoyl chloride, which was then cycloloaded to styrene. Flavanone was produced by reductive cleavage of the isoxazoline ring to the - hydroxy ketone and acid catalysed cyclization [30].
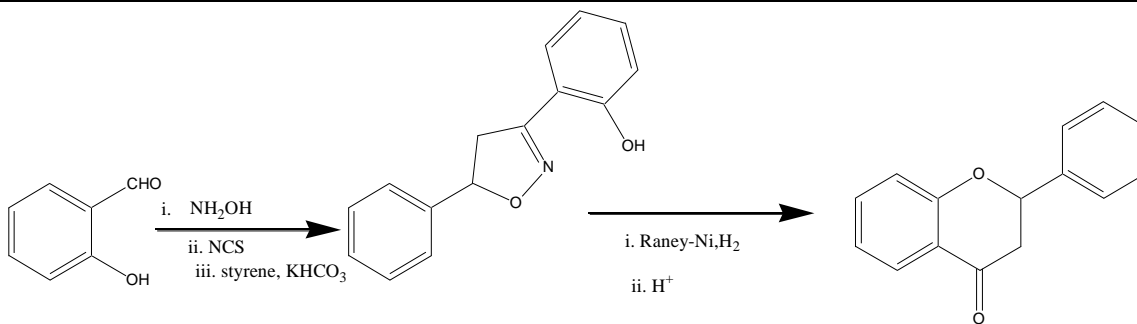
18. Flavanone synthesis with phosphoric acid: Flavanone is synthesised by refluxing matching chalcones with phosphoric acid in alcohols for 2-3 days [31].
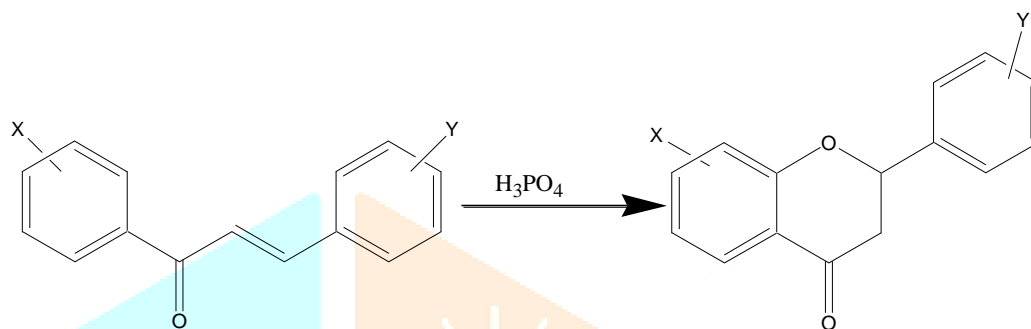
19. Synthesis of Flavanone using catalyst H[bimBF4] : By grinding substituted,- unsaturated carbonyl compounds chalcones to substituted 2-phenylchroman-4-one i.e., flavanone using an environmentally friendly catalyst H[bimBF4], it is a fast method for converting substituted,- unsaturated carbonyl compounds chalcones to substituted 2-phenylchroman-4-one i.e. flavanone [32].
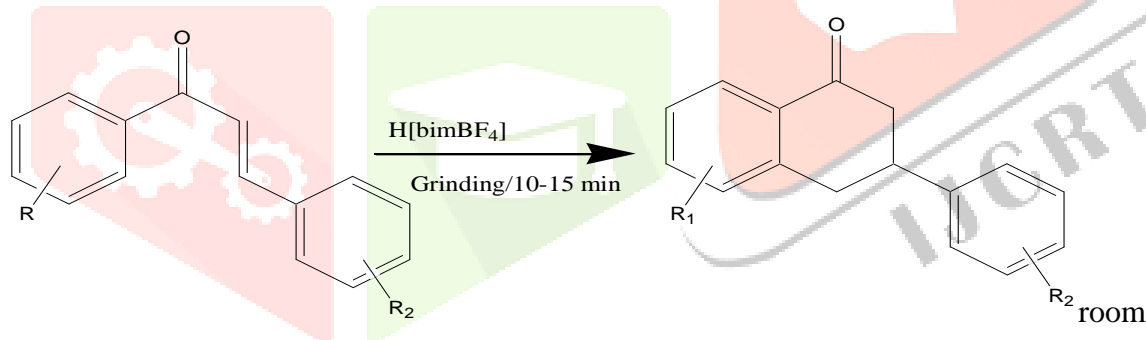

20. Flavanone Synthesis Catalyzed by L-Proline: L-Proline as a catalyst for flavanone and chalcone synthesis produces a satisfactory result. [33].
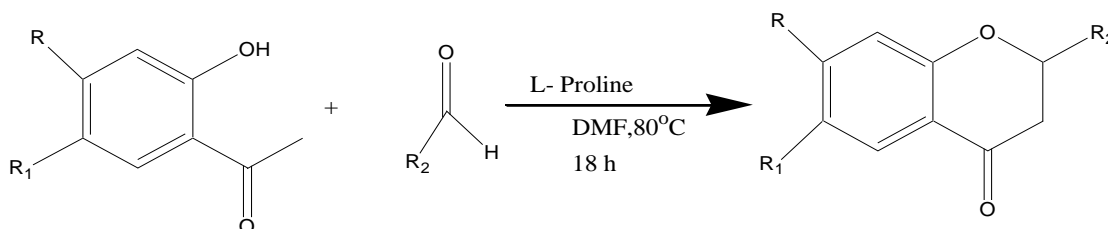
**21. Flavanone synthesis with Zn-Al hydrotalcite adhere ionic liquid:**

The Claisen- Schmidt condensation of 2-hydroxy acetophenone and benzaldehyde to chalcone and flavanone demonstrates the synthetic activity of calcined Zn-Al hydrotalcite. By covering calcined hydrotalcite with ionic liquid triethoxysilane-3-methyl imidazolium chloride, this catalyst can be enhanced by around 1.5 times. [34].
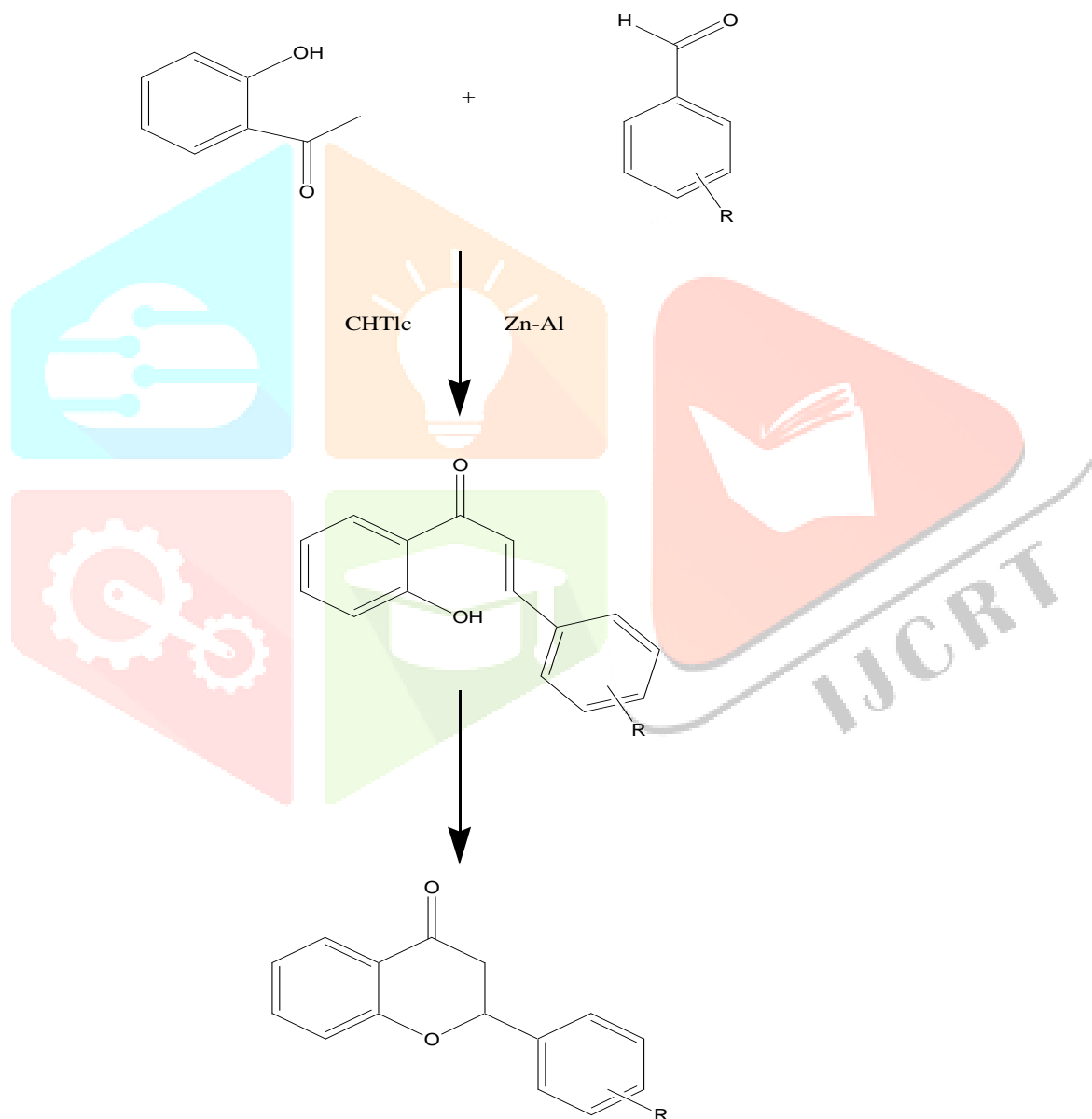
22. flavanone synthesis by boracic acid and ethylene glycol: Substitutes 2- hydroxyacetophenone was reacted with substituted benzaldehyde and boracic acid in ethylene glycol at 130 ^{0}C to give the product in a conventional process. A simple approach was used to create a novel flavanone derivative of farrerol. [35].
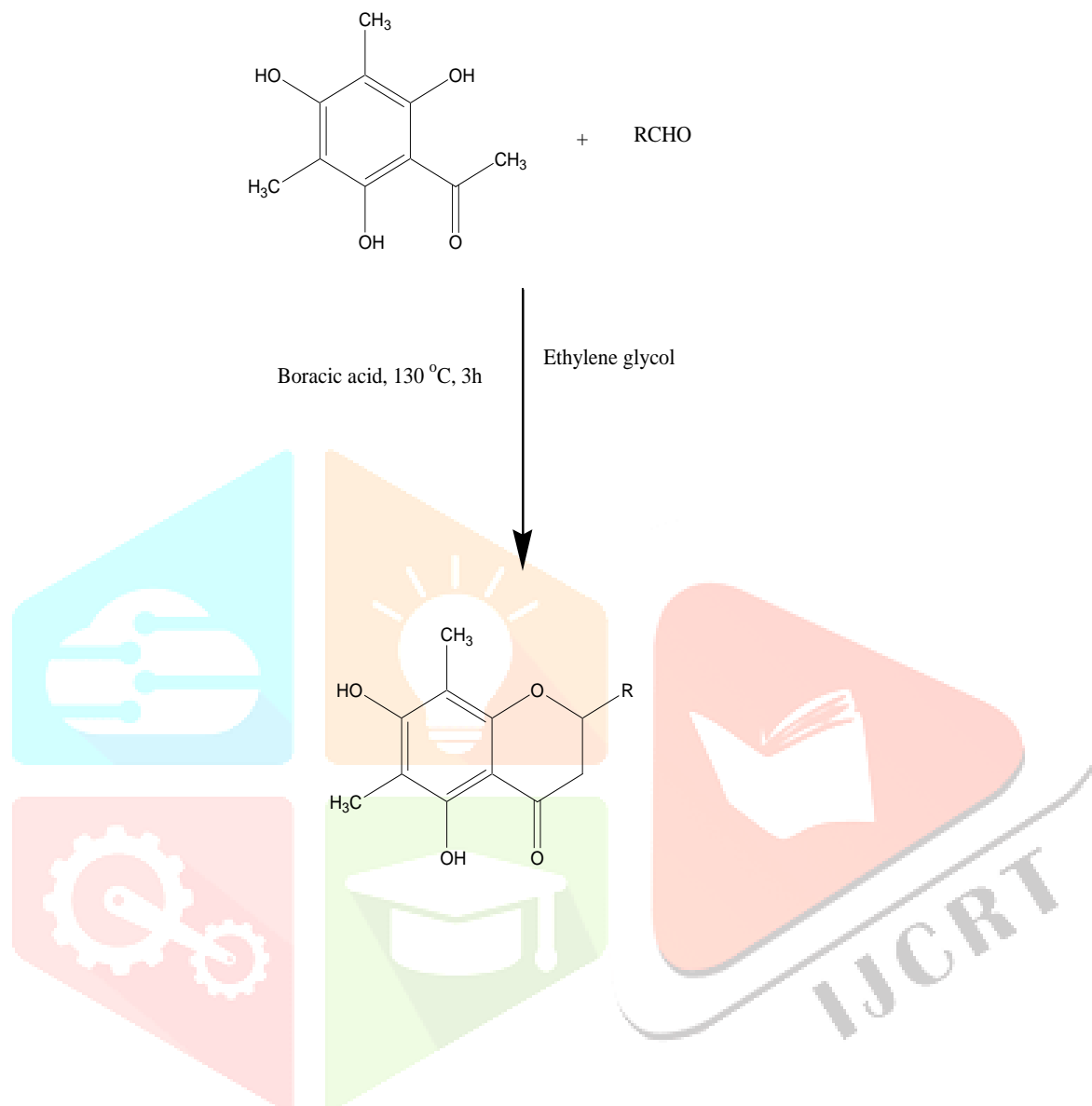
23. Synthesis of flavanone by isomerization of 2- hydroxychalcone: Synthesis of flavanone by isomerization of 2-hydroxychalcones in ethanol in the presence of triethylamine by Aitmambetov et al.[36]
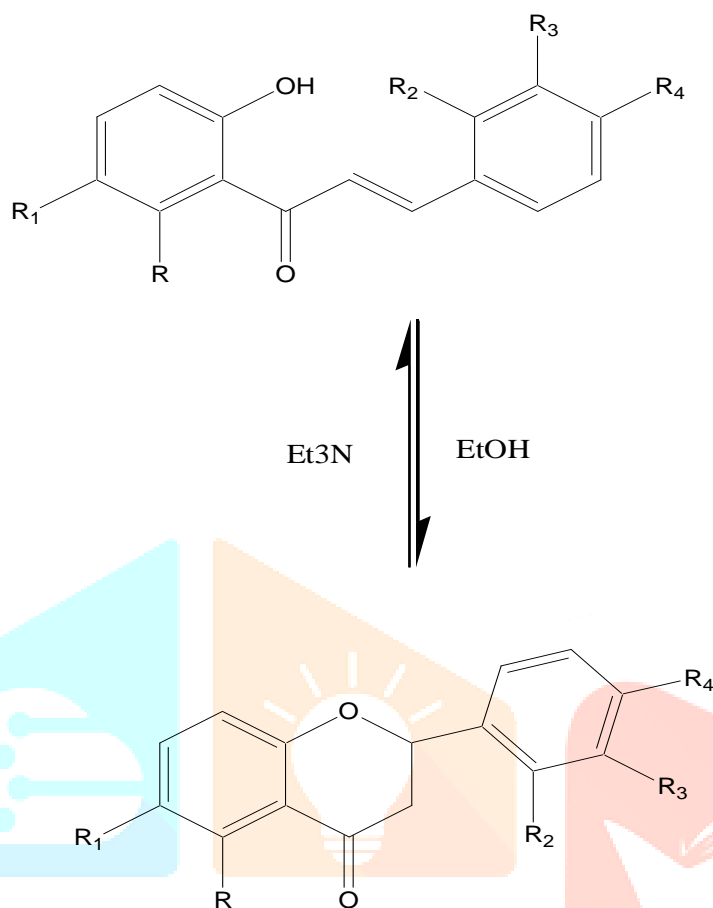
24. Heterogeneous synthesis flavanone: Over a solid MgO catalyst, the heterogeneous synthesis of flavanone from benzaldehyde and 2-hydroxyacetophenone was investigated. For the synthesis of flavanone, various high boiling point solvents were investigated. The addition of DMSO was found to considerably increase flavanone yield [37].
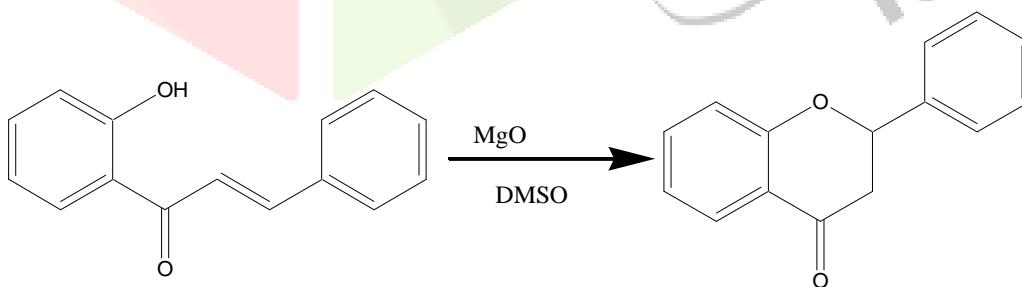

Scheme 25: Converting chalcones to flavones is a two-step process (Scheme 1). The first step is chalcone isomerization to flavanone, followed by flavanone dehydrogenation to flavone. Acids, bases, and UV radiation can alter isomerization, whereas various oxidants can be used to convert flavanone to flavones. [38]
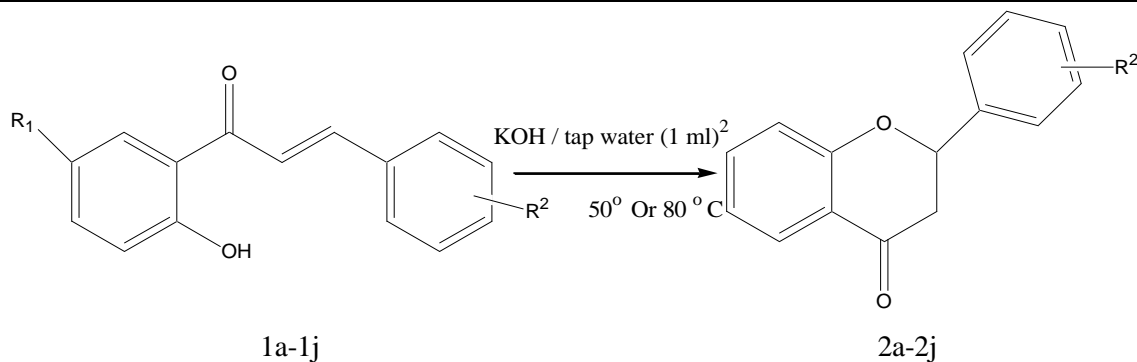
Entry	R^1	R^2	T/h	2(Yield %)[b]
1	H	H	20	2a, 84%
2	H	o-Cl	12	2b, 74%
3	H	m-Cl	12	2c, 82%
4	H	p-Cl	12	2d, 81%
5	H	p-OCH$_3$	24	2e, 65%
6	H	p-Me	24	2f ,48%
7	H	p- Br	12	2g, 73%
8[cd]	-	-	24	2h[e],42%
9[cd]	OCH$_3$	H	24	2i, 28%

Scheme 26: The microwave irradiation synthesis of chalcone derivatives and efficient catalyst systems to promote their isomerization into flavanones. They used both microwave irradiation for chalcone synthesis and efficient catalysts to promote their isomerization into flavanone.[39]
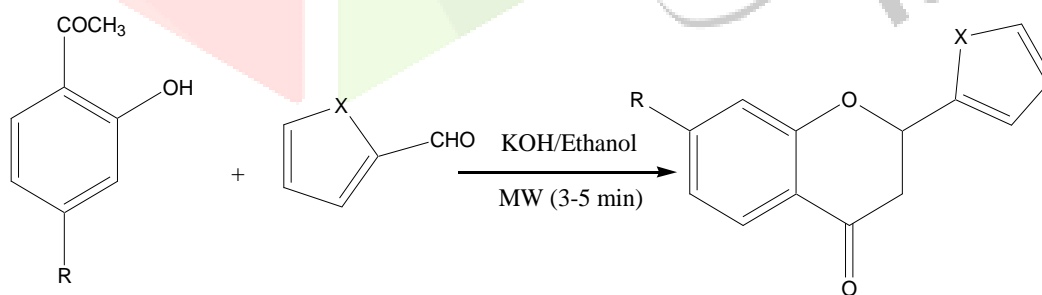
(2-Hydroxy -4- Substituted acetophenone) (Substituted Flavanone)

15a-15f

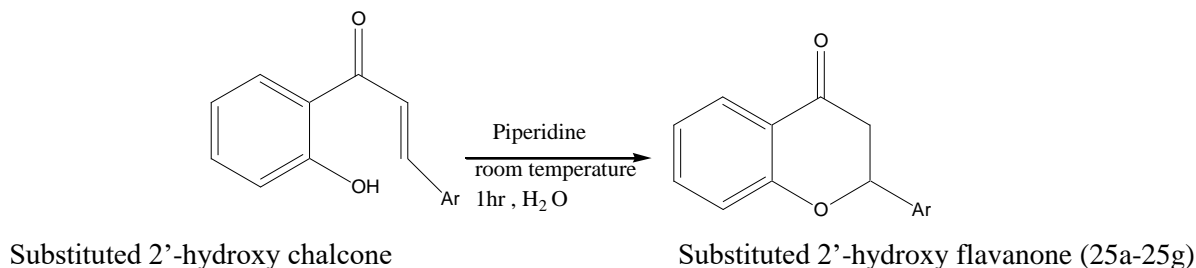| Compound	R	X
15a	H	S
15b	OH	S
15c	OCH$_3$	S
15d	H	O
15e	OH	O
15f	OCH$_3$	O

Scheme 27: Description An environmentally friendly catalytic system for the cyclization of 2-hydroxy chalcones to flavanones in tap water without the use of organic solvent. Various catalysts and temperature settings were examined in order to determine the optimal circumstances for the reaction, and potassium hydroxide (5 percent) was determined as the best base for the reaction, with temperatures ranging from 50 to 80 degrees Celsius. Low yield was observed when the reaction temperature was raised over 80 degrees Celsius, which could be attributable to the generation of oil at higher temperatures. At 50 or 80 degrees Celsius, nine substituted 2-hydroxychalcones were converted to the respective flavanones with moderate to good yields. S 16 [40]

Scheme 28 : A class of anticancer chalcones and flavanones distinguished by the presence of a heterocyclic component (R) in their structures. The Claisen-Schmidt condensation method was used in conjunction with the grinding process to complete the synthesis. 80-94 percent of high purity chalcones and flavanones were produced. [41]
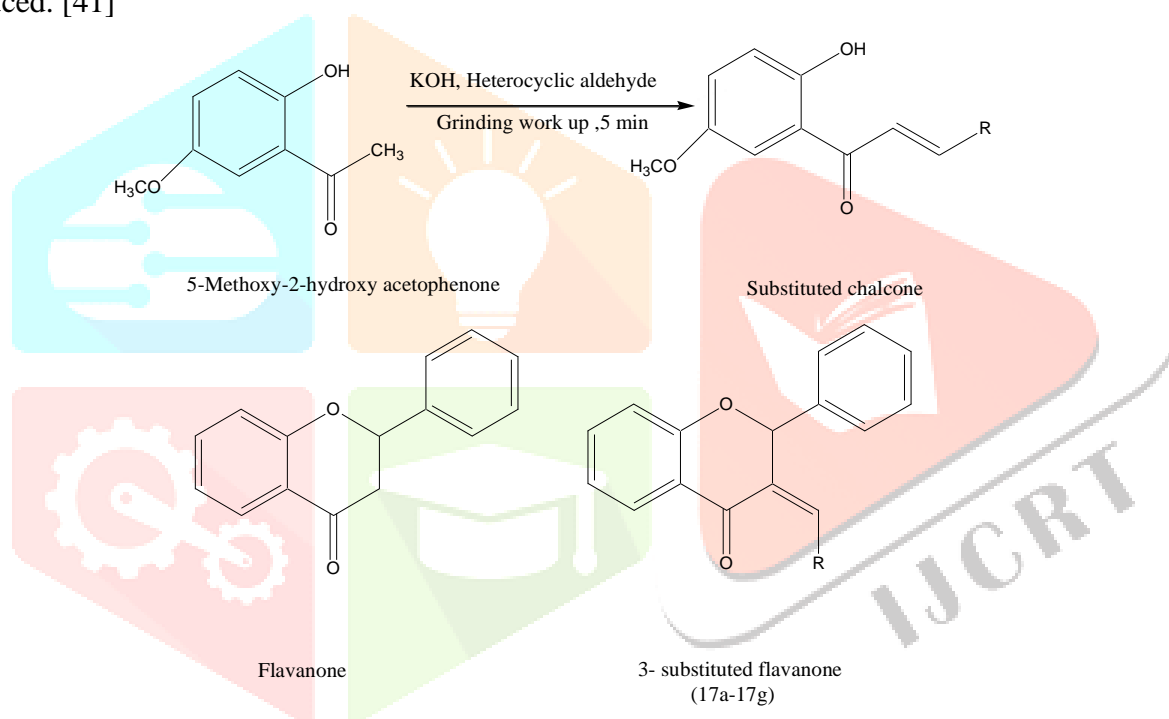

compound	R	Compound	R
17a		17e	
17b		17f	
17c		17g	
17d			

Scheme 29: Description In a water suspension media, a process for converting 2'-hydroxychalcones to flavanones and got appreciable results. They used ground 2'-hydroxy chalcones and made a suspension in water containing piperidine, with stirring at room temperature for 1 h . The reaction mixture was a suspension in the water, hence synthesized flavanones were separated easily by simple filtration followed by recrystallization [42].

Substituted 2'-hydroxy chalcone   Substituted 2'-hydroxy flavanone (25a-25g)

| Compound	Ar
25a	C_6H_5
25b	o-$CH_3OC_6H_4$
25c	m-$CH_3OC_6H_4$
25d	p-$CH_3OC_6H_4$
25e	o-ClC_6H_4
25f	m-ClC_6H_4
25g	p-ClC_6H_4

Scheme 30: Flavanone and chromanone enantioselective synthesis is presented. For aryl and alkyl substrates, bifunctional thiourea catalysts promote an asymmetric oxo-conjugate addition to a -ketoester alkylidene in high yields with outstanding enantioselectivity (80-94 percent ee). The enantioenriched flavanones and chromanones are obtained by decarboxylation of the -ketoester in a one-pot process.
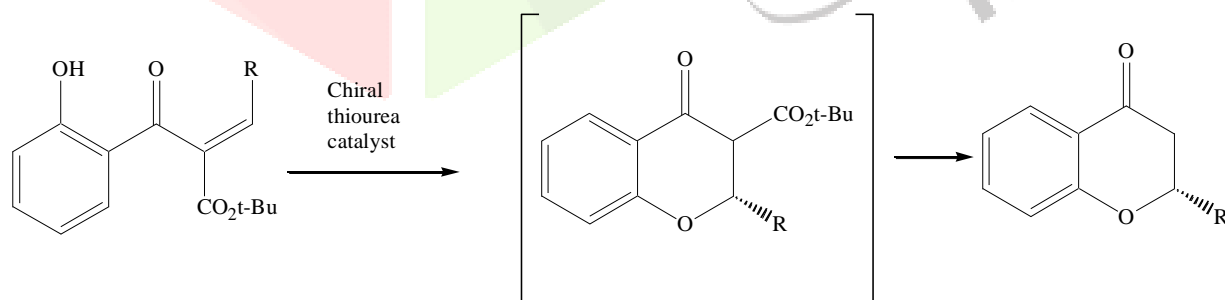

R = aryl, alkyl   (**80-90 %**)

Scheme 31: Cobalt Schiff base complex catalyses the conversion of 2-hydroxychalcones to flavanones: In the presence of oxygen, Co (salpr) catalyses the conversion of 2-hydroxychalcones to flavanones in methanol. The reaction is caused by base catalysis by Co (salpr) (OH) generated in situ, and it is found to be reversible [44].
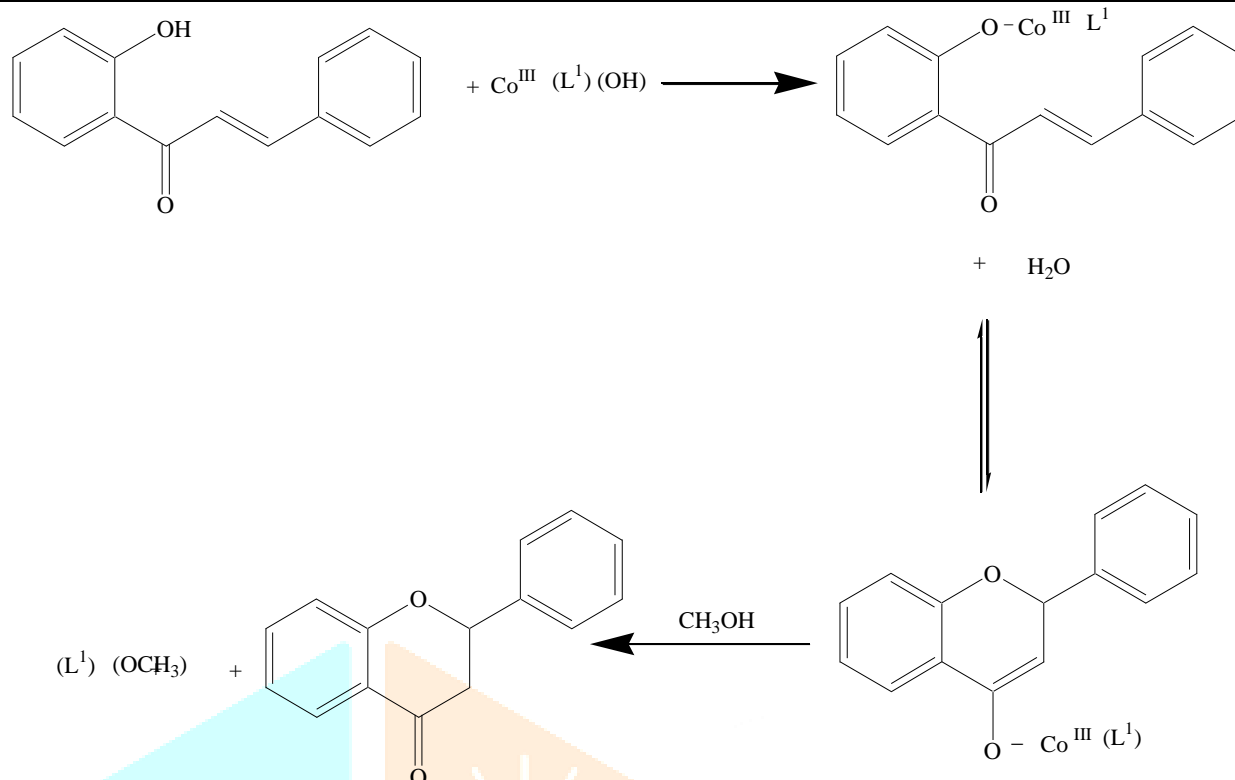
**Scheme 32:** Chalcone is made by combining the appropriate 2-hydroxyacetophenone with benzaldehyde or hydroxybenzaldehyde. It is possible to convert chalcone to flavanone [45].
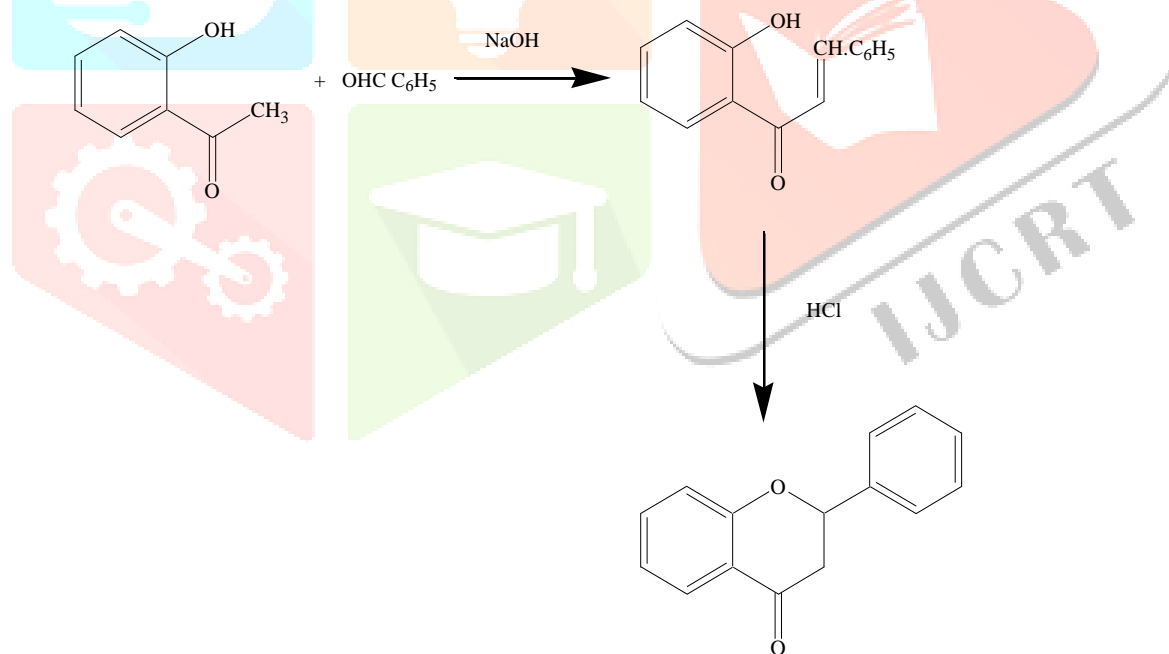

Scheme 33: 2-Hydroxychalcone is formed via oxidative cyclization of 2-hydroxyacetophenone and benzaldehyde in the presence of alkali, followed by treatment with alkaline hydrogen peroxide to create 3-hydroxy flavanone[46].
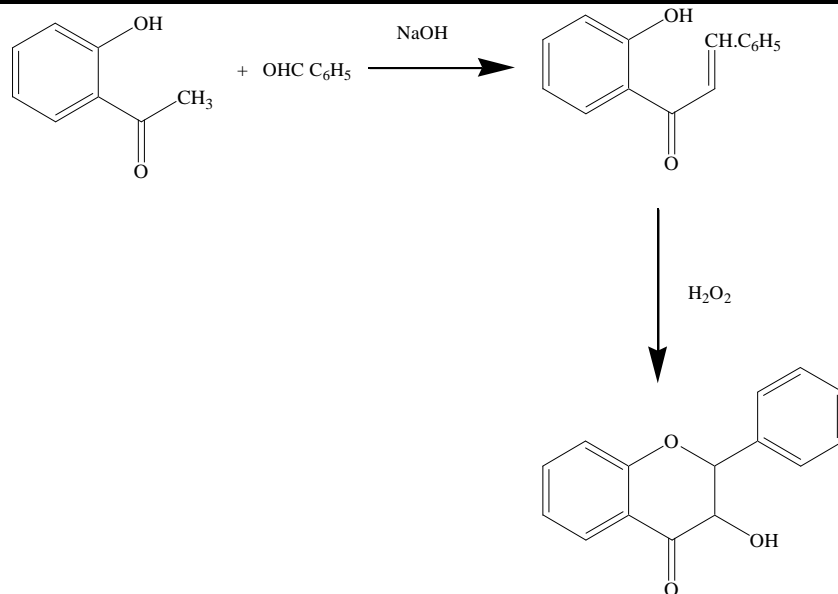
Some biological activity of flavanone:

1. **Antimicrobial activity:** By using the broth dilution method with penicillin G and streptomycin as standards, the twelve synthesised flavanones were tested for antibacterial activity against six bacterial strains, including B. subtilis, S. aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae. Nonyl and dodecyl chalcones having 2,6'-dimethoxy-2' hydroxy substitution patterns, such as compounds 15 and 16, are clearly more active than other produced compounds. [47,48]
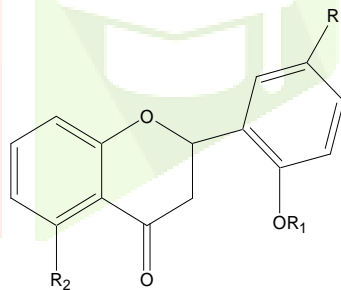
Compound	R_1	R_2	R
15	CH_3	OCH_3	C_9H_{19}
16	CH_3	OCH_3	$C_{12}H_{25}$

2.Antifungal screening : Based on the N-phenethylazole pharmacophore of azole antifungals, a series of new 3-(1,2,4-triazol-1-yl)flavanones were synthesised. The antifungal activity of 4'-fluoroflavanone derivative 4c was found to be the best against Candida and Saccharomyces strains in an antifungal experiment. Compound 4c was 4-16 times more effective against Candida albicans and Saccharomyces cerevisiae than the reference medication fluconazole. 3-(1,2,4-triazol-1-yl) flavanone

prototype is a promising lead for the future development of azole antifungal medicines due to its good drug-like property. [49,50]
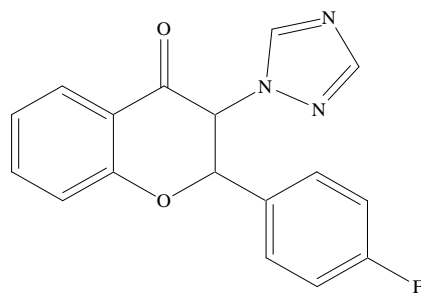
(Compound 4c)

3. Anti-Leishmanial Activity: In vitro antileishmanial assays were used to evaluate produced drugs against L. donovani promastigotes. Conclusion: The majority of the compounds had moderate leishmanicidal activity, but several, such as 4b, 10b, 5b, and 3a, showed potential antileishmanial activity against L. donovani promastigotes. The anti-leishmanial activity of compound 10b, which also had the best docking into the pteridine reductase active site. [51,52,53]
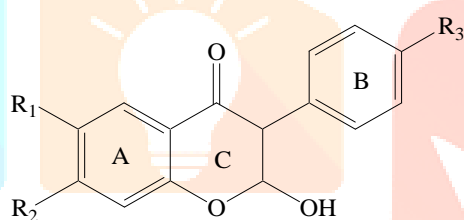
(10 b)
Compound 10 b: R_1, R_2 & R_3= H

4. Apoptosis- inducing Activity:

Apoptosis is a specific type of cell death that differs from necrosis, which is a more common type of cell death. Previous research has shown that inducing apoptosis in tumour cells inhibits cellular inflammatory responses and improves cancer treatment outcomes compared to necrosis. 2-hydroxychalcones were used to make halogenated flavanones, which were then assessed for cytotoxicity against a panel of human cancer cell lines. 3',7- dichloroflavanone (2d) had the best action against MCF-7, LNCaP, PC3, Hep-G2, KB, and SK-NMC cells among the produced compounds. However, the most effective chemical against MDA-MB-231 cell was 3',6-dichloroflavanone (2g) with an IC50 of 2.9 0.9 M. being approximately 12 times more active than etoposide as reference drug. According to the flow-cytometric analysis, compound **2g** can induce apoptosis by 66.19 and 21.37% in PC3 and MDA-MB-231 cells, respectively. [54,55,56]
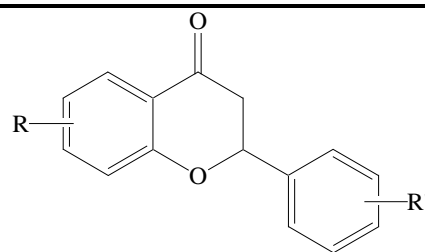
(2g)

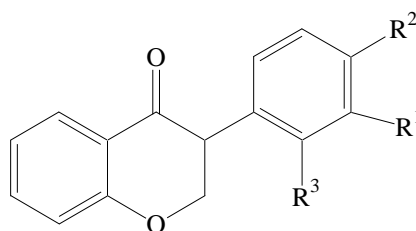| Compound	R	R'
2a	H	H
2b	7-Cl	H
2c	7-Cl	2'-Cl
2d	7-Cl	3'-Cl
2e	7-Cl	4'-Cl
2f	6-Cl	2'-Cl
2g	6-Cl	3'-Cl
2h	6-Cl	4'-Cl
2i	H	2'-Cl
2j	H	3'-Cl
2k	H	4'-Cl

5. Antitumoral Activity:

Cabrera and his colleagues (2006), The cytotoxic effects of 53 flavonoids and related compounds were tested against three different human tumoral cells, TK-10, MCF-7, and HT-29. In general, no cytotoxic selectivity was seen amongst the various cellular lines. Fourteen of the investigated compounds (derivatives 1, 2, 4–8, 11, 13, 15, 18, 24, 33, and 46) were extremely cytotoxic against at least two of the tested cells, indicating a definite structure–activity relationship. Chalcones were thus found to be more cytotoxic than flavanones and flavones (compare activities of chalcones 5 and hydroxychalcone 18 to flavanone 46 and flavone 53). The activities of flavanones may be the consequence of metabolic transformation into the equivalent hydroxychalcones, but they may also be the result of their own flavanone activity in rare cases (compare activities of chalcone 12 and flavanone 43). [57]

Compound	R^1	R^2	R^3
43	-H	-Br	-H
46	-H	-OMe	-H

6. Antihyperglycemic activity:

The compound **2a** showed excellent antihyperglycemic activity in diabetic rats while 2c exhibited good activity in normal hyperglycemic rats. The determined positions of nitro group at ring 'B' of chalcones exhibited antihyperglycemic activity. The comprehensive intra-molecular charge transfer has been perceived from the HOMOs to the LUMOs. The smaller IP and BDE values for the 2a revealed that this drug would show proficient antioxidant behavior which is in good agreement with the experimental data. In future, compound 2a can be further used to explore its beneficial impacts at molecular level.[58]
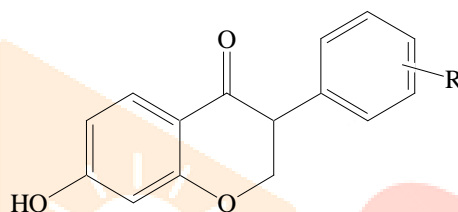
Compound	R
2a	2- Nitro
2b	3-Nitro
2c	4- Nitro
2d	3- Nitro
2e	4-Nitro

7. Anti-inflammatory activity:

A novel series of synthetic 2`- hydroxychalcones (1a-h), 2' -methoxy chalcones (2a-i), flavanones (3a-k) and flavones (4a-f) have been synthesized and evaluated for their anti-inflammatory activity in carrageenan induced rat paw oedema model. Compounds 1a, 1e-g, 2e-g, **3j**, and 4f showed potent anti-inflammatory activity comparable to the reference drug indomethacin with insignificant ulceration. Compound 1f showed mild inhibition against the enzymatic activity of ovine COX-1 and COX-2 (in-vitro). Compound 1f also exhibited inhibitory activity in LPS induced TNF-a production.[59]
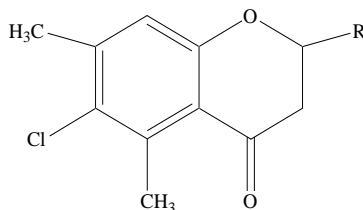
Compound	R
3a	phenyl
3b	4- methoxyphenyl
3c	4-chlorophenyl
3d	2-chlorophenyl
3e	3,4-dimethoxyphenyl
3f	3,4,5-trimethoxyphenyl
3g	3-hydroxyphenyl
3h	2-hydroxyphenyl
3i	3-nitrophenyl
3j	**4-N, N-dimethylaminophenyl**
3k	3-hydroxy-3-methoxyphenyl

8. **Anti-oxidant activity :**. The free radical scavenging activity was measured by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay . A 0.30 μM solution of DPPH in ethanol was prepared. Each sample (5 μL) of different concentrations (62.5–500 μg) was mixed with DPPH solution (95 μL). The mixture was dispersed in 96 well plates and incubated at 37 °C for 30 min. The absorbance at 515 nm was measured by microtiter plate reader and percent radical scavenging activity was determined in comparison with the methanol treated control. Compound **11** is the most potent antioxidant with IC50 49.7 μM which is comparable to standard butylated hydroxyanisole having IC50 value of 44.2 μM. Compounds 12, 4 and 6 also have significant antioxidant activity with IC50 value 56.5, 59.5 and 58.2 μM, respectively. [60,61]
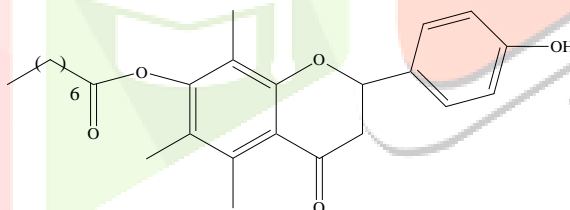
Compound 11

9. **Antibacterial activity:** In anti-bacterial studies, all compounds were found to be active against E.Only compound B showed activity against Pseudomonas. Compound C showed good activity against Staphylococcus aureus. Compound B as well as compound C showed good activity against Bacillus subtilis.[62] completed

10. **Antiherpetic Activities:** Flavonoids inhibit the formation of plaques of HSV-1 and 2 in Vero cells. The degree of inhibition was determined by calculating the concentration of substances required to reduce virus-induced plaque regression analysis as the most effective plaque reduced concentration. As a result, among flavanols, EC and ECG demonstrated strong antiviral activity (EC; 80% inhibition at 5 M, ECG; 85% inhibition at 10 M), and galangin and kaempferol demonstrated potent antiviral activity (galangin; 80% inhibition at 10 M, kaempferol; 90% inhibition at 50 M) against HSV-I. Catechin, EGC, EGCG, naringenin, chrysin, baicalin, fisetin,

myricetin, and quercetin are also present. and genistein had moderate inhibitory effects ranging from 50% to 80%. Flavones such as apigenin, luteolin, and rutin, on the other hand, inhibited HSV-1 by 50% or less, indicating that these flavonoids have little effect on the virus. Furthermore, at 100 M, ECG alone had a strong inhibitory effect on HSV-2. Overall, the flavonoids tested had stronger antiherpetic activity against HSV-1 than against HSV-2. Yield. [63]

11. **Anti-carcinogenic effect:** synthetic flavanone derivatives using an MTT assay in MCF-7 and MDA-MB-453 cells. When cells were treated with synthetic flavanone derivatives in concentrations ranging from 1 to 200 μM for 48 h, cell growth decreased at concentrations >50 μM. 4'-Chloroflavanone is more potent than flavanone among the synthetic flavanone derivatives. Exposure to 4'-chloroflavanone at 50 μM for 48 h caused cell cycle arrest in both MCF-7 and MDA-MB-453 cells.[64]
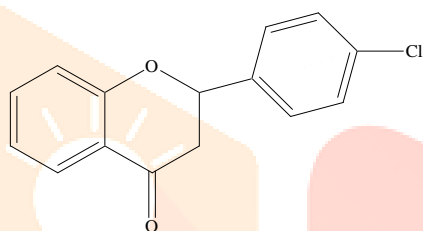
(4'-Chloroflavanone)

12. **Antitubercular activity:** Antituberculosis activity of flavanones was investigated. Compounds 5 and 4a inhibited M. tuberculosis at minimum inhibitory concentrations (MIC) ranging from 25 to 50 g/mL. The remaining 15 compounds also inhibited M. tuberculosis at MICs ranging from 50

g/mL to 100 g/mL. [65,66]
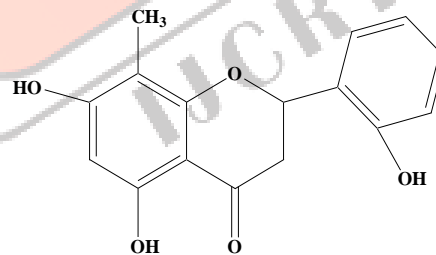
(**Compound 15**)

13. **Analgesic activity:** The synthesised compounds were expected to have analgesic activity, and according to the studies, two of them. The results show that all tested compounds have less analgesic activity than the standard drug, Diclofenac sodium. Compound C demonstrated the greatest analgesic activity of the three compounds tested. [67]
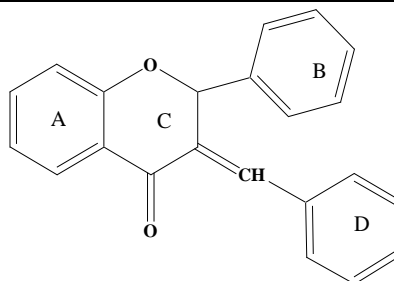
(**Compound c)**

14. **Antiviral activity:** The antiviral activity of the flavanone naringenin has also been reported against some viruses. On the whole, the favorable effects of naringenin lead to a conclusion that naringenin may be considered as a promising treatment strategy against COVID-19. The antiviral activity of the flavanone naringenin against some viruses such as HCV, Chikungunya virus (CHIKV), Dengue virus (DENV), and Zika virus (ZIKV) has been tested. [68,69]

15. **AChE Inhibitor Activity**: All of the compounds inhibited AChE, with carbamate substituted 5,7-dimethoxyflavanone derivatives (5a' –5g') being the most potent, with IC50 values ranging from 21.5 1.8 to 9.9 1.6 nM. The compounds were tested in vitro for AChE inhibitory activity using donepezil as the control drug. The Morris water maze test was used to evaluate the most potent test compound (5f) in vivo for memory restorative actions in scopolamine (0.4 mg/kg)-induced amnesia in mice. [70]
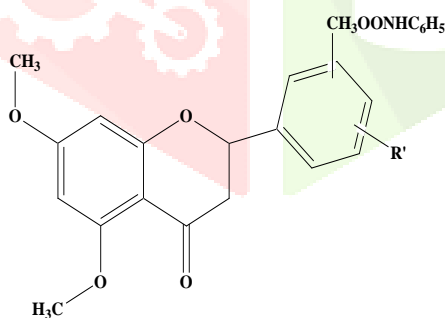
(5a'-5g')

Compound	R	R'	-COONHC$_6$H$_5$
5a'	-	H	Ortho
5b'	-	H	Meta
5c'	-	H	Para
5d'	-	4'-OMe	Meta
5e'	-	3'-OMe	Para
5f '	-	3',5'-di-OMe	Para
5g'	-	3'-OMe&5'-NO$_2$	para

16. **Vasorelaxation activity:** Flavonoid derivatives were designed and synthesized, and their vasorelaxant activities against rat aorta rings pretreated with phenylephrine were tested experimentally (PE). Among them, 6-hydroxy-8-allyl-4' -chloro-flavanone 8q had the greatest vasodilatory activity (EC50 = 4.6 lM, Emax = 95.1%). The comparative molecular field analysis (CoMFA) method was used for the 3D-QSAR analysis, and a statistically reliable model with good predictive power (r 2 = 0.872 and q2cv=0.496) was established.[71,72]
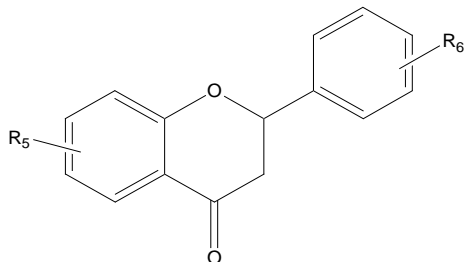
Compound	R$_5$	R$_6$
8a	5,7-DiOH	3'-Br
8b	5,7-DiOH	3' ,4' -OCH$_2$O
8d	6-OH	3' -Br
8e	5,7-DiOH-8-Allyl	3' -Br
8f	5,7-DiOH-8-Allyl	3' -Cl
8g	5,7-DiOH-8-Allyl	4'-Cl
8h	5,7-DiOH-8-Allyl	4' -OMe
8i	5,7-DiOH-8-Allyl	3' -OH
8j	5,7-DiOH-8-Allyl	4' -OH
8k	7-OH-8-Allyl	3' ,4' -OCH$_2$O
8l	7-OH-8-Allyl	4' -OH
8m	7-OH-8-Allyl	3'-OMe
8n	7-OH-8-Allyl	4' -Cl
8o	6-OH-8-Allyl	4'-OH
8p	6-OH-8-Allyl	3' -OH
8q	6-OH-8-Allyl	4' -Cl

17. **Trypanocidal Activity:** T. cruzi activity of twenty eight 3-benzoylflavanones against amastigote and trypomastigote parasite forms was tested in vitro. The majority of the compounds tested showed promising activity against T. cruzi intracellular forms. The IC50 value of flavanone 2z with a nitrofuran moiety was lower than that of the reference drug Benznidazole. The most potent flavanone with a nitrofuran moiety outperformed the reference drug, Benznidazole, in anti-Trypanosoma cruzi activity.

[73,74,]
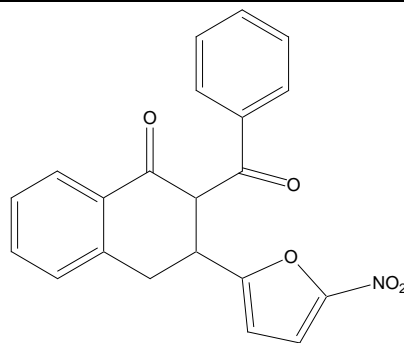
(**2z**)

18. **Atherosclerosis activity**: A series of new flavanone derivatives of farrerol was synthesized by a convenient method. in vitro anti-atherosclerosis activity was tested on vascular smooth muscle cells by the MTT method using tetrandrine as a positive contrast drug. The structures of all compounds synthesized were confirmed by 1 H, 13C NMR and ESI-MS. [75]

19. **Antidepressant-like effects:** The antidepressant-like activity of natural and synthetic flavonoid, chalcone and flavanone compounds that have been published in the last fifteen years (2000-2015). These results suggested that compounds **100** (4´-bromo-7-prenyloxy-2,3-dihydroflavanone) and **101** (2´, 4´-Dichloro-7-prenyloxy-2, 3-dihydroflavanone) displayed potent antidepressant-like property that were mediated via neurochemical systems. [76].

20. **Anticancer activity:** The inhibitory concentration (IC50) values of naringenin derivatives. IC50 values of 3(4-chlorobenzylidene)-5,7-dihydroxy-2(4-hydroxyphenyl) chroman-4-one are 10.35 μM (MCF-7) & 12.03 μM (HT-29), it is most potent compound (**12**) in these derivatives. Novel heterocycle containing flavanone derivatives were synthesized and studied for *in vitro* anticancer activity, and a furan ring containing analogue **YP-4** had highest anticancer potency compared with those of other flavanones. These results suggested that furan ring may be crucial for anticancer activity. On the basis of the above study, these flavanones scaffolds can be selected as skeleton for the development of heterocycle containing flavanones with potential as anticancer agents. [77,].

21. **Estrogenic activity:** Flavanone naringenin is known to possess only weak estrogenic properties, but some of its derivatives such as 8-prenylnaringenin are potent phytoestrogens. The study was to further clarify structure–function relationships of flavanones regarding their estrogenic or antiestrogenic properties via characterizing the new chemically synthesized naringenin derivative 7-(O-prenyl) naringenin-4 -acetate (7-O-PN). A yeast-based reporter gene assay and MVLN cells, a MCF-7-derived cell line that possesses a luciferase reporter gene under the control of a vitellogenin estrogen responsive element, were used to investigate estrogenic actions of 7-O-PN in vitro. Estradiol (E2) has been used as a positive control. Subsequently a 3-day rat uterotrophic assay was performed to test for estrogenic effects. In addition, mRNA expression of estrogen sensitive genes in the uteri of these rats was measured using real time rtPCR.[78].

22. : . **Anti-VSMCs Vegetation Activity:** Shi et al (2011) designed and synthesized a series of new flavanone derivatives of farrerol as a potent inhibitor of vascular smooth muscle cell (VSMCs) vegetation using a simple method. The biological activities of these compounds against VSMCs were tested in vitro. The results of the assay show 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 IC50 values of 9.9 and 6.7 mol/L, respectively, and the preliminary structure-activity relationship (SAR) was described [79].
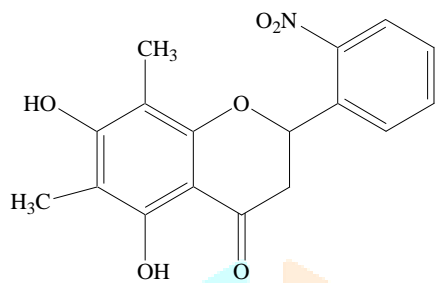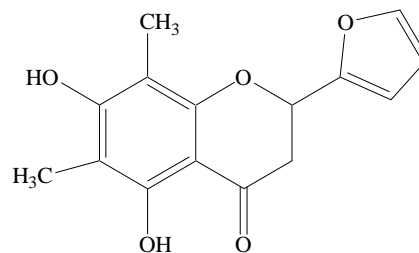
(10a) **(10b)**

23. 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 pyridinyl methylene 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 [80].
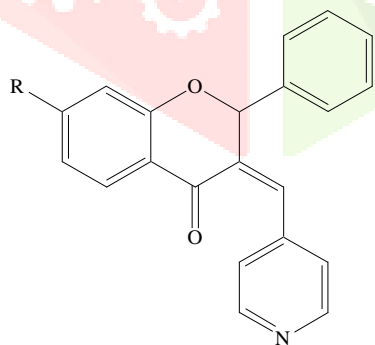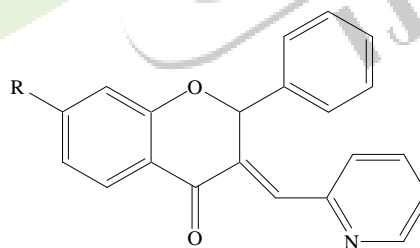
(E) **(Z)**

Compound	R
13a	H
13b	OCH$_3$

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