Contents

Abstract:

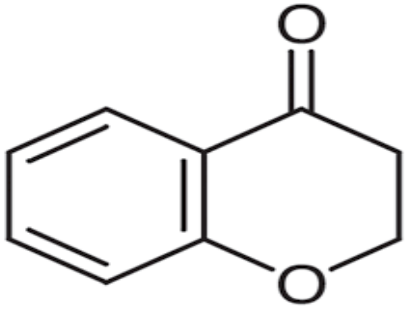
Chromone or Chroman4on is the maximum crucial and thrilling heterobicyclic compound and serves as a element of medicinal chemistry for the isolation, improvement and synthesis of novel lead compounds. Structurally, the shortage of a chromone double bond among C2 and C3 indicates a mild distinction from chromone, however there may be a great distinction in organic activity. Current evaluations function a whole lot of posted research at the synthesis and pharmacological assessment of chromone 4-on analogs, demonstrating the significance of chromone as a flexible scaffold with a extensive variety of pharmacological activities. .. However, because of the low yield of chemical synthesis and the excessive fee of the separation method from herbal compounds, it offers the best and cheaper technique for synthesizing new chromone analogs to offer steering to the chemical community. Needs similarly research. Given the range of chromone, this assessment goals to offer comprehensive, crucial and dependable data on chromone templates in drug layout and improvement.

Section A

Introduction

1.General informaion

4-chromanone belongs to heterocyclic compound which build up of benzene ring fused with 2,3-di hydro pyranone ring is considered as very interesting structure in drug design chemistry
The absence of double bond between C2 and C3 make the chromanone to behave different comparing to chromone **. [1]**



2.Biological activities of 4-chromanone derivativess :

4-Chromanone pharmacophore is an advantaged framework in therapeutic exploration, comprising of two rings in which 2, 3-dihydro-γ-pyranone melded with a sweet-smelling benzene core and derivatization at 2, 3 and 4-places of chromanone skeleton yields more viable groups of flavonoids like 3-benzylidene-chromanones, spirochromanone, hydrazones, oximes, flavanones, homisoflavonones and isoflavanones. This underlying broadening of chromanone involved a significant job in drug field as they owe various organic exercises like anticancer, cell reinforcement, antidiabetic, calming, antiviral, antitubercular, antibacterial, antifungal, antiparasitic, against AchE, anticonvulsant, hostile to HIV and antileishmanial properties. As chromanone platforms show various intense natural exercises, even a few subordinates are novel like DSP-1053 (novel serotonin reuptake inhibitor and quick upper), calanolide A (against HIV), Silibinin and chrysin(anticancer), taxifolin (antidiabetic), tetrazole (antidiabetic), troglitazone (antidiabetic), ormeloxifene (anticancer) and nebivolol (beta-blockers); by and by, the market extent of powerful chromanone analogs is less. Hence, for future forthcoming, more thought is

expected for planning and creating strong engineered chromanone analogs which might offer better restorative benefit. **[2]**

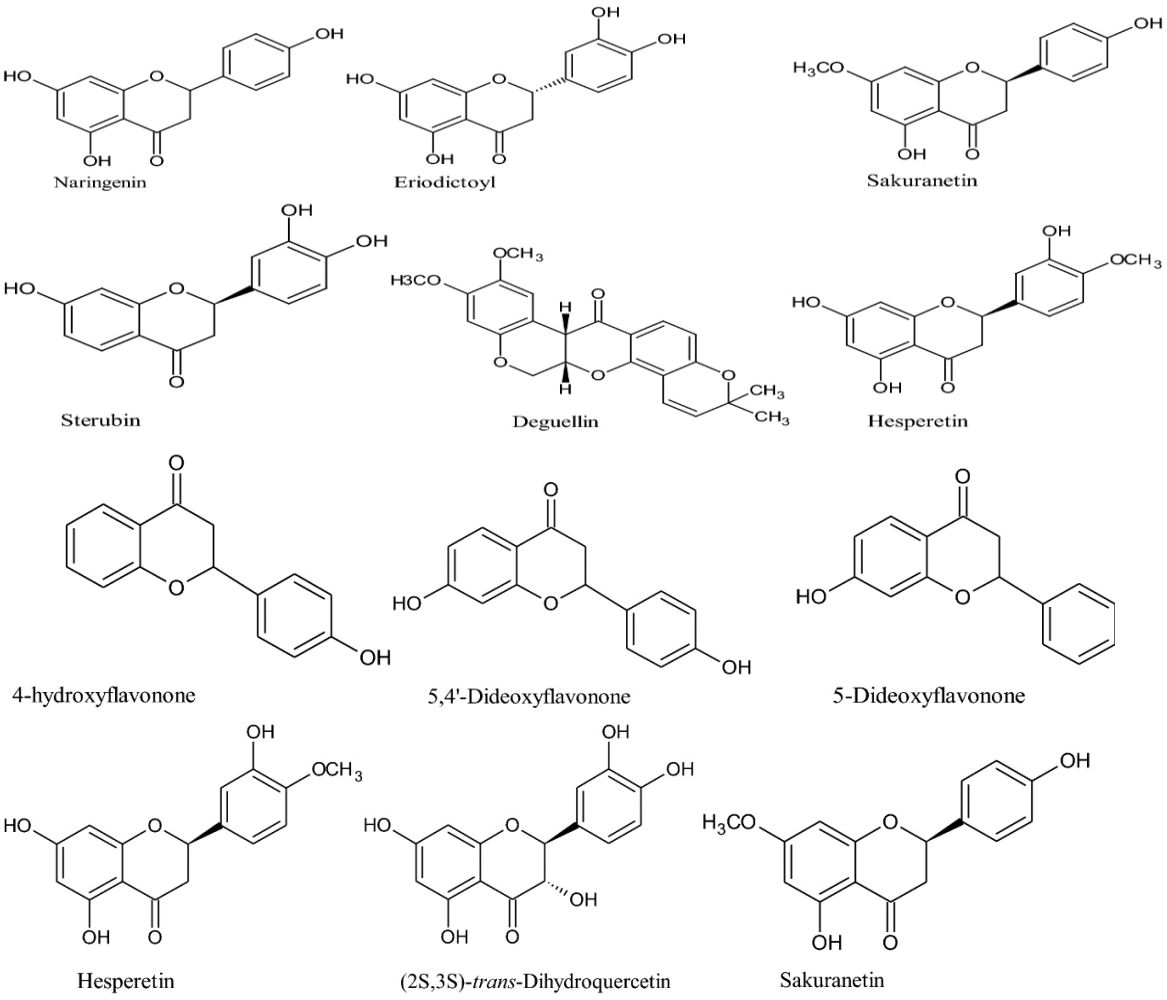
2.1 Anticancer agent

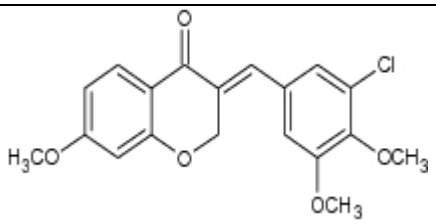
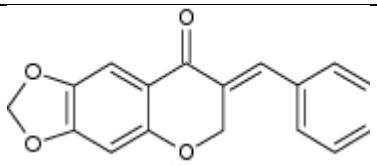
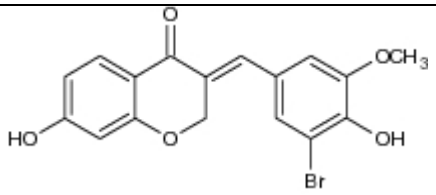
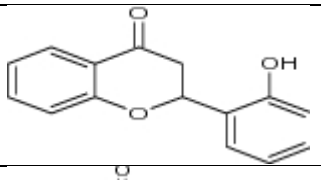
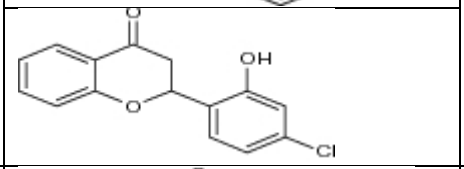
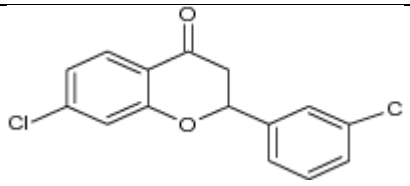
The degree of mitochondrial impairment and metabolic dysfunctions, such as cellular energy supply, cell death signalling, irregulation of metabolic pathways, formation of reactive oxygen species (ROS), compromised enzyme actions, aerobic glycolysis augmented in tumor cells, alterations in lipid metabolism, and unbalanced pH, can all be used to assess the severity of cancer. **[3]**

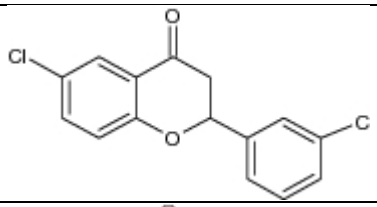
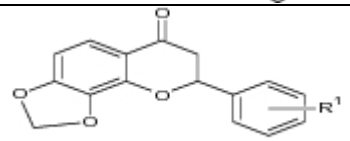
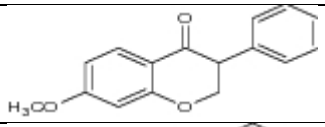
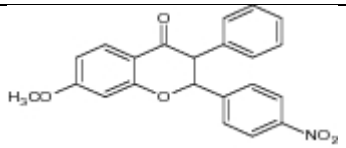
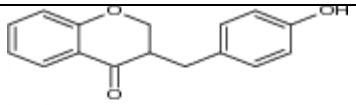
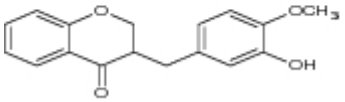
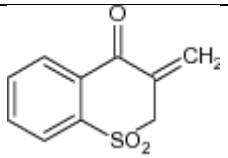
The following natural flavonones using as anti-cancer agents :

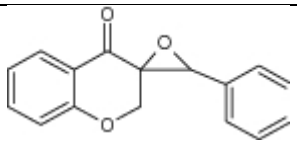
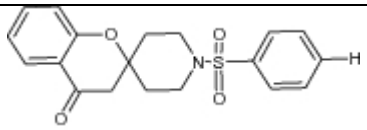
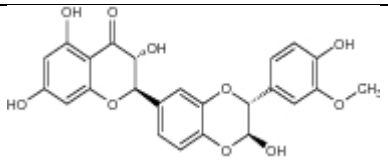
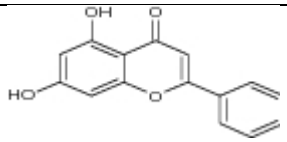
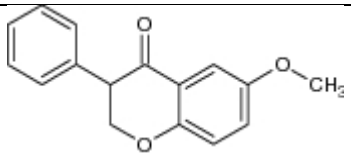
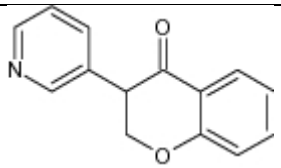
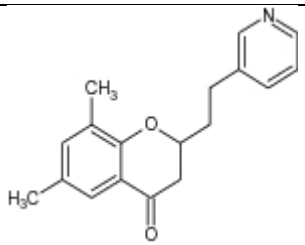
eriodictyol, calyxin G ,naringin , naringenin deguelin , sterubin ,sakuranetin

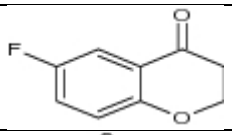
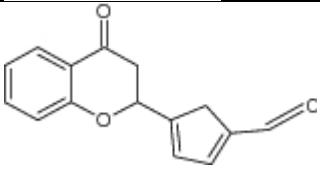
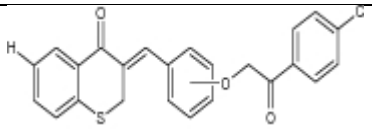
these natural products "flavanones" can organize cellular metabolism, scanning free radical and stop proliferation of cancer cells.



Sr. No.	Compound	Structure	Evaluation	Inference
1	(E)-3-benzylidene-7-methoxychroman-4-one derivatives (3-chloro-4,5-dimethoxybenzylidene derivative)		Using the MTT assay, the cell lines MDA-MB-231 (breast cancer), KB (nasopharyngeal epidermoid carcinoma), and SK-N-MC (human neuroblastoma) were evaluated.	MDA-MB-231 = 7.56 2.23, KB = 25.04 10.60, and SK-N-MC = 9.64 2.7 showed significant inhibition. Among the series, it has been designated as the best anticancer agent. **[4]**
2	6,7-Methylenedioxy-4-chromanone		Compared to three breast cancer cell lines (MCF-7, T47D and MDA-MB-231)	The highest anticancer activity was observed against tested cell lines (IC50 9.3 g/ml). **[5]**
3	3-Benzylidene-chroman-4-one derivatives		Compared to the K562, MDA-MB-231, and SK-N-M cell lines	C50 ≤ 3.86 **µg / ml showed strong anticancer activity [6]**
4	Hydroxy flavanones	 	**Evaluation for** colorectal **cancer** cells such as A549, LLC, AGS, **SKHepl,** HA22T cancer cells	Showed strong cytotoxic activity **[7]**
5	Halogenated flavanones 3′,7-dichloroflavanone		Rating for MCF7, LNCaP, PC3, HepG2, KB, and SKNMC cells	Very potent compound for MDAMB231 cell line as etoposide (reference drug) (IC50 = 2.9 µM) **[8]**

	3′,6-Dichloroflavanone			
6	7, 8-Methylenedioxyflavanones	 R1=2′-Cl or 2′-NO2	Investigate the potential cytotoxicity and apoptosis in human leukemia cells	Shows better cytotoxic efficacy than reference **[9]**
7	7-Methoxyisoflavanone		Evaluation for HL60 (acute myeloid leukemia cells) and PBMC (peripheral blood mononuclear cells) using MTT assay	Showed the highest anti-cancer activity against HL60 cells **[10]**
	Diarylchromanone			
8	3-Benzylchroman-4-ones	 (a)  (b)	Assayed by MTT assay for two cancer cell lines BT549 (human breast cancer), HeLa (human cervical cancer) and non-cancerous cell line Vero (normal renal epithelial cells)	The 3-benzyl chromane 4-one derivative (a) proved to be the most active against BT549 (IC50 = 20.1 mM), HeLa cell line (IC50 = 42.8 mM), but the 3-benzylchroman 4-one derivative (IC50 = 42.8 mM). b) showed significant activity only against HeLa cells (IC50 = 20.45 mM). **[11]**
9	3-Methenylthiochroman-4-one-l, 1-dioxide		Ehrlich Tested for growth of ascites cancer tumor	80% inhibition of Erich ascites cancer tumor growth was observed in mice **[12]**

10	Novel tricyclic heterocyclic chromanone compounds		Tested against lung, CNS cell lines and breast	Tested and showed significant inhibition against all cell lines labeled as active anti-cancer agents **[13]**
11	Spiro [chroman-2, 4′-piperidin]-4-one derivatives		The cytotoxic activity was examined against three human cancer cell lines; MCF7 (human breast carcinoma), A2780 (human ovarian cancer) and HT29 (human rectal adenocarcinoma) using the MTT test	The spiro derivatives [chroman2,4′piperidine] 4one with sulfonyl buffers showed the greatest activity with IC50 = 5.62 ± 1.33µM (MCF7) 0.31 ± 0.11µM (A2780) and 0.47 ± 0.17 µM (HT29), respectively **[14]**
12	Silibinin		Test for T47D (breast cancer cell line) by MTT assay	The combination of silibinin and chrysin may have therapeutic value in the treatment of breast cancer (combination index <1) **[15]**
	Chrysin			
13	6-Methoxy-3-phenyl chroman-4-one		Antiproliferative activity tested against cell lines MCF7 (breast cancer) and A549 (lung cancer).	Selective **sirtuin** 2 (SIRT2) inhibitors **show** antiproliferative activity **in** breast and lung **cancer [16]**
	3-(Pyridin-3-yl) chroman-4-one			
	6,8-Dimethyl-2-[2-(pyridin-3-yl) ethyl]-benzopyran-4-one			

	6-Flurobenzopyran-4-one			
14	2-[(Furan-2-yl) methoxy]-benzopyran-4-one		Screening for MCF7 breast adenocarcinoma), HT29 (human colon adenocarcinoma) and A498 (human kidney adenocarcinoma) cell lines using sulforhodamine B dye	Found to have very strong activity against all cell lines tested, 7.3 ± 0.3 (MCF7), 4.9 ± 0.5 (HT29), 5.7 ± 0.9 (A498) **[17]**
15	3-[3/4-(2-aryl-2-oxoethoxy) arylidene] chroman/thio chroman-4-one derivatives		Leukemia (L, 4 or 6 cell line), non-small cell lung cancer (NSCLC, 9 cell line), melanoma (M, 8 or 9 cell line), colon cancer (CC, 7 cell line), central nervous system screening system Cancer (CNSC, 6 cell line)), ovarian cancer (OC, 6 or 7 cell line), prostate cancer (PC, 2 cell line), kidney cancer (RC, 8 cell line), breast cancer (BC, 6) Or 8 cell lines).).	3 [3 (2 (4 chlorophenyl) 2 oxoethoxy) benzylidene] thiochroman 4one was the most potent and showed very significant activity against all cancer cell lines tested. **[18]**

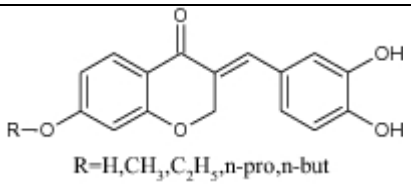
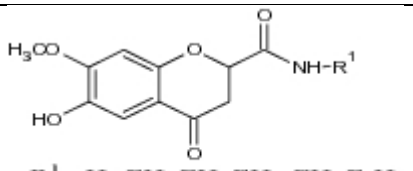
However the exact molecular mechanism of these compounds have not proved till now.

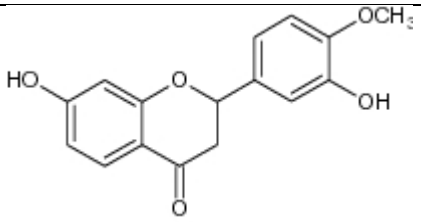
2.2. Antioxidant agents :

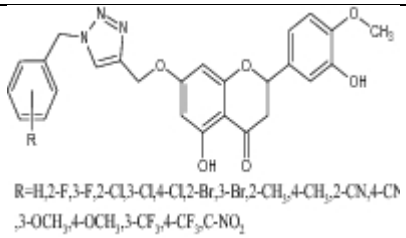
Antioxidant is a molecule which can stop the oxidation of chemical reaction in the human body. The oxidation process will produce free radicals which can link with many diseases and then damage body cells . The function of antioxidant is neutralize the free radicals .

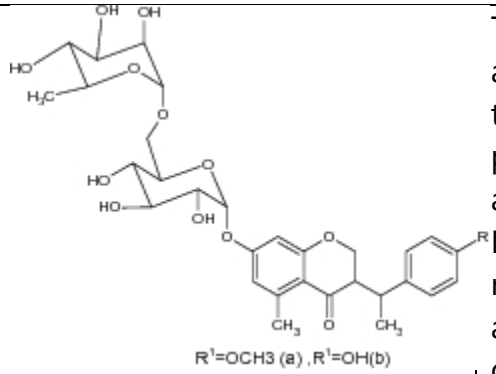
Vitamin E considered as the most common natural antioxidant .

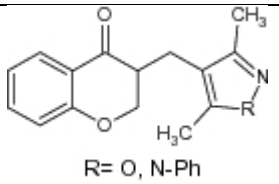
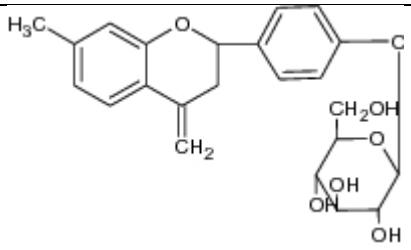
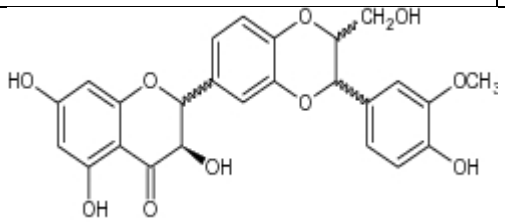
Chromanone derivatives on C2 and C3 is with some functional groups like phenyl , benzylidiene amine , and amide can act as effective antioxidant . **[19]**

Sr. No.	Compound	Structure	Evaluation	Inference
1	3-Benzylidene-7-alkoxychroman-4-one derivatives	 R=H,CH_3,C_2H_5,n-pro,n-but	Evaluated for 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavengers, ferric reducing antioxidant power (FRAP) and thiobarbituric acid reactive substances.	Showed the following inhibition values 24.30 ± 0.51 to 35 ± 0.47 (DPPH), 10.96 ± 0.34 to 14.33 ± 0.52 (FRAP), and Fe2 + µM = 44.62 ± 0.48 to 71.64 ± 0.47 (TBARS) **[20]**
2	6-Hydroxy-7-methoxy-4-chromanone derivatives	 R^1= H, $CH_2CH_2CH_3$,$CH_2C_6H_5$ $CH_2(CH_2)_2CH_3$,C_6H_5	(a) Investigation of Fe2+ and ascorbic acid triggered inhibition of lipid peroxidation in rat homogenates. (b) DPPH scavenging activity.	Showed stronger antioxidant activity than vitamin E and Trolox with the following values (a) Inhibition of lipid peroxidation = 176.8 to 300 (b) DPPH = 66.4 to 213.9. **[21]**

3	7-Hydroxy-2-(4-Hydroxy -3-Methoxyphenyl)-Chroman-4-one		Examined antioxidant activity	Reduces oxidative stress, LDL levels, MnSOD levels, and SOD2 gene expression in hyperlipidemic rats by reducing endogenous antioxidant enzymes **[22]**

4	Benzyl-1,2,3-triazolyl hesperetin derivatives	 R=H,2-F,3-F,2-Cl,3-Cl,4-Cl,2-Br,3-Br,2-CH_3,4-CH_3,2-CN,4-CN ,3-OCH_3,4-OCH_3,3-CF_3,4-CF_3,C-NO_2	Antioxidant activity examined using DPPH and ABTS assays	Antioxidant activity assayed using significant antioxidant values obtained as follows: 30.75 ± 1.965 to 83.57 ± 0.456 (DPPH) 8.545 ± 0.545 to 39.356 ± 0.644 (ABTS), or DPPH and ABTS assays. **[23]**

5 (a)	Homoisoflavanone 7-O-[α-rhamnopyranosyl-(1 → 6)-β-glucopiranoside]-5-hydroxy3-(4-methoxybenzyl)-chroman-4-one	 R^1=OCH3 (a) , R^1=OH(b)	Tested for antioxidant properties against DPPH radicals and β-carotene / linoleic acid systems	Both compounds (a) and (b) showed corresponding antioxidant activity with the following significant values: (a) 273.1 ± 6.2 (DPPH) and (b) 212.4 ± 3.8 (DPPH). **[24]**
(b)	7-O-[α-rhamnopyranosyl-(1 → 6)-β-glucopiranosyl]-5-hydroxy-3-(4′-hydroxybenzyl)-chroman-4-one			

6	Chroman-4-one derivative		Examined DPPH inhibition	DPPH inhibition demonstrated with significant values **[25]**
7	Liquiritin (7-hydroxy-2-[4-[3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] oxyphenyl]-chroman-4-one		Investigating the inhibition of the enzymes superoxide anion (SOD), catalase (CAT) and glutathione peroxidase (GSHPx) in mice	Inhibition of SOD (75.11 ± 5.80 U / mg), CAT (7.62 ± 0.48 U / mg), and GSHPx (887, 24 ± 79.23 U / mg) against localized cerebral ischemia / reperfusion (I / R) Showed a neuroprotective effect. **[26]**
8	Silybin		Assessing inhibition of cyclic voltammetry (CV), DPPH scavenging, and microsomal lipid peroxidation (LPx)	An antioxidant potential with significant inhibition of CV (524 EPA MV), DPPH (1745 ± 65) and LPX (33.6 ± 1,2) was shown. **[27]**

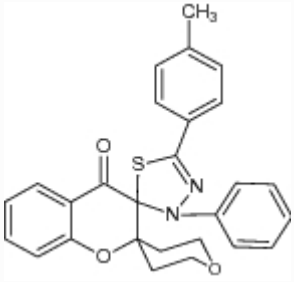
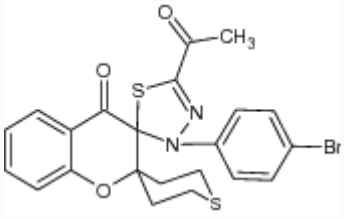
2.3. Antiviral agents :

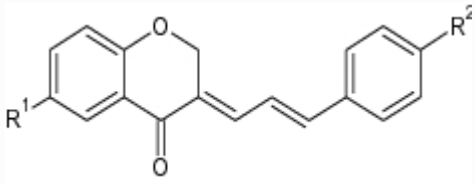
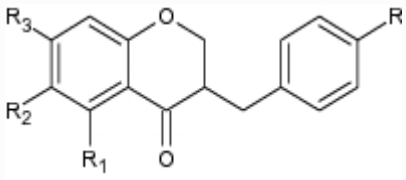
There are many kinds of diseases occur by viruses which may found in respiratory system , cadiac and neurological disease caused by picornaviruses especially rhinoviruses .

Evidence from the literature suggests that chroman-containing natural and synthetic flavonoids impede the replication step of picornaviruses and further prevent uncoating of infected viral fragments and release of corresponding RNAs in cells [112]. Tate S et al. (2006) studied the antiviral activity of high isoflavones (3-benzylchroman-4-one derivatives) against replication of enteroviruses, these chromone analogs against coxsackievirus B1, B3, B4, A9, Echovirus The 30 and C-3 substitutions have significant activity. The parental chromogen showed a good effect on the growth of HRVs. **[28]**

In addition, Hegab, MI et al. introduced thiopyran at C-2. (2015) showed significant antiviral activity against challenged adenovirus type 7 with significant inhibitory effects, as shown in

Table 8. Therefore, after these substitutions, more antiviral chromone analogs with significant antiviral activity can be designed and synthesized

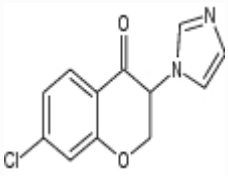
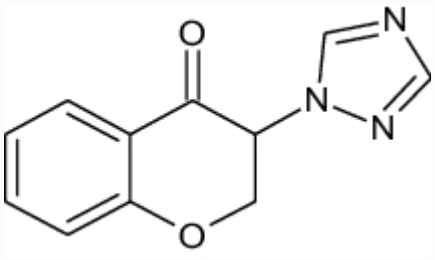
Sr. No.	Name	Structure	Evaluation	Inference
1	5′′-Aceto-3′′-phenyl-3′′H,4′H-dispiro[chroman-2′,4-tetrahydropyran-3′,2′′-[1,3,4-thiadiazol]-4′-one		Tested for inhibition of antiviral activity by adenovirus type 7	Significant antiviral activity against challenged adenovirus type 7 and significant inhibition **[29]**
	5′′-Aceto- 3′′-(4-bromophenyl)- 3′′H, 4′H-dispiro[chroman-2′,4-tetrahydrothiopyran-3′,2′′-[1,3,4-thiadiazol]-4′-one			

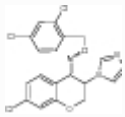
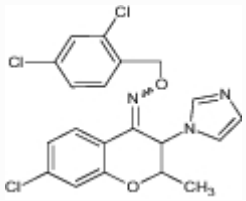
2	Chroman-4-one derivatives		Evaluated for inhibition of human rhinovirus (HRV) 1B and 14	Declared antiviral efficacy against tested HRV1B and 14 strains **[30]**
3	3-Benzylchroman-4-one's derivatives		Test antiviral activity	Showed antiviral activity against Coxsackievirus B1, B3, B4, A9 and Echovirus 30 **[31]**

2.4. Anticonvulsants agents :

Epilepsy is a neurological disorder in which people experience epileptic seizures, which affect at least 70 million people worldwide. There are many antiepileptic common drugs , such as phenytoin, carbamazepine, ethosuximide, and sodium valproate, which are acceptable in the treatment of seizures, but in Drug resistance is observed in 30-40% of epilepsy patients . Therefore, MDT (multidrug therapy) is the first choice for seizure control. However, there is still no MDT or single agent that can prevent or treat epilepsy long-term without developing drug resistance . With this in mind, there is a need for more effective compounds to treat or prevent epilepsy with high potency and fewer side effects. Many 4-chromanone derivatives, such as azolylchromanone and imidazolylchromanone oxime ether, have been investigated for anticonvulsant potential in lithium, pilocarpine, and pentylenetetrazole (PTZ) epilepsy-inflammatory models. Among these tested compounds, some analogs showed good anticonvulsant activity with significant seizure latency and seizure duration. SAR studies have shown that the presence of an azolyl ring at the 3-position of the chroman ring, the presence of a

halogen (chloro) group at the 7-position, and/or the presence of an alkyl group (especially methyl) at the 2-position results in O-(2,4- The anticonvulsant efficacy of the dichlorobenzyl) oxime series was increased, and the potency of the (Z)- and (E)-isomers was not significantly different in terms of seizure duration and seizure latency . **[32]**

Sr. No.	Name of compound	Structure	Evaluation	Inference
1	7-Chloro-3-(1H-imidazol-1-yl) chroman-4-one		The characteristic-s of anticonvulsants and antiepileptic drugs were investigated using lithium pilocarpine-induced seizures and PTZ-induced kindling models.	Effective against seizure latency 32.12 ± 3.04 and seizure duration 12.50 ± 1.87 in status epilepticus induced by lithium and pilocarpine, while 3.75 ± 0.14 and 3.4 in the PTZkindling model of seizure latency and seizure index. 3 ± 0.14 and 3.4 3 ± 2 were observed. **[33]**
2	3-(1H-1,2,4-triazol-1-yl) chroman-4-one		Evaluation of the PTZ kindling model of epilepsy	Not only did it delay seizures, but it also had a great effect on effective protection against them. PTZ-induced seizures (seizure latency = 22.00 ± 4.11 minutes) and death **[34]**

3	Imidazolyl chromanone oxime		Tested on PTZ inflammation model of epilepsy	Seizure latency (s) = 715 ± 153 Seizure duration (s) = 40.3 ± 4.7 Proven anticonvulsant effect
				Seizure latency = 776 ± 97 Seizure duration = 342 ± 4.9 **[32]**

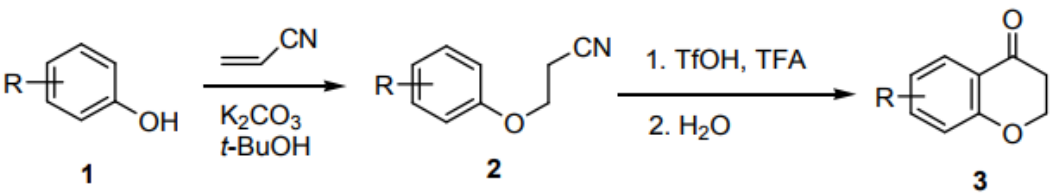
3.Synthesis of 4-chromanone

3.1.Synthesis of chroman-4-one by Michael addition:

Efficient and practical synthesis of **various 4-chromanone** 3 **in 2 steps,** Zhong et al. The synthetic pathway is initiated by the Michael addition of phenol 1 bis Acrylonitrile in tert-butanol and in the

presence of potassium carbonate as a catalyst. Intermolecular Houben-Hoesch reaction of 3-aryloxypropanenitrile 2 using trifluoromethane Sulfonic acid (1.5 eq.) And trifluoroacetic acid (5 eq.) Give 3 inches of the desired 4-chromanone. Excellent return

[35]

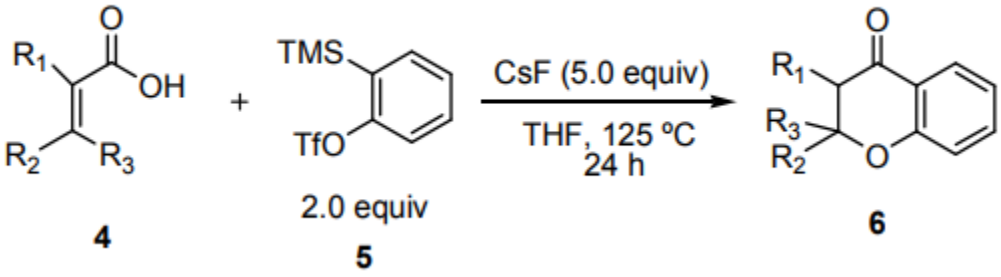


1 2 3

3.2. O-(Trimethylsilyl) Synthesis of chromane ions from phenyltriflate and acrylic acid

Heating of acrylic acid 4 and o (trimethylsilyl) phenyltriflate 5 as shown in FIG.

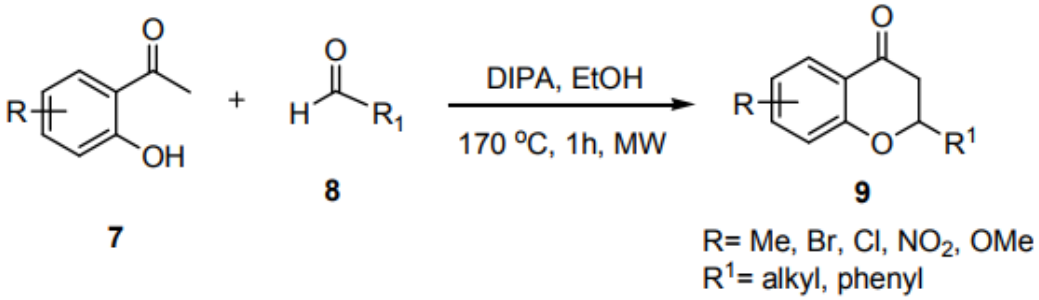
Using THF in the presence of CsF (5.0 eq) gives the desired 4-chromanon 6. **[36]**



3.3. Synthesis of chroman4ones by aldol condensation of 2′hydroxyacetophenones with

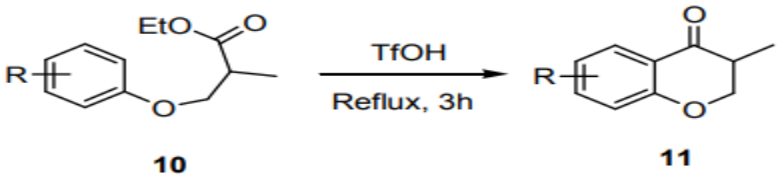
aldehydes :

For example, FridénSaxin and colleagues synthesized 4chromanone 29 substituted using microwave radiation. Aldol condensation of 2′hydroxyacetophenones 7 with aldehydes 8 by heating their ethanol mixture to 160-170°C using microwaves (MW). irradiation in the presence of DIPA as a base resulted in the desired 2alkylchroman4ones 9. the The substitution pattern of acetophenone affects the outcome of the reaction. In general, better yield obtained by the electron-deficient 2'hydroxyacetophenones . **[37]**



3.4. Synthesis of chroman-4-one from ethyl 3-phenoxypropanoate derivative

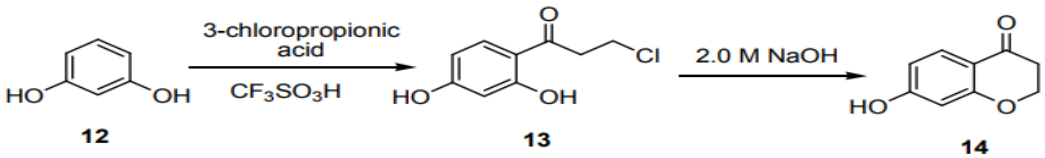
Electrophilic cyclization of ethyl 3-phenoxypropanoate derivative 10 using TfOH (Bronsted Acid) leads to chroman-4-ones11 under reflux . **[38]**



3.5. Synthesis of 7-hydroxychroman 4-one from resorcinol

The synthesis of 7-hydroxychroman 4-one (14) can be started with resorcinol.

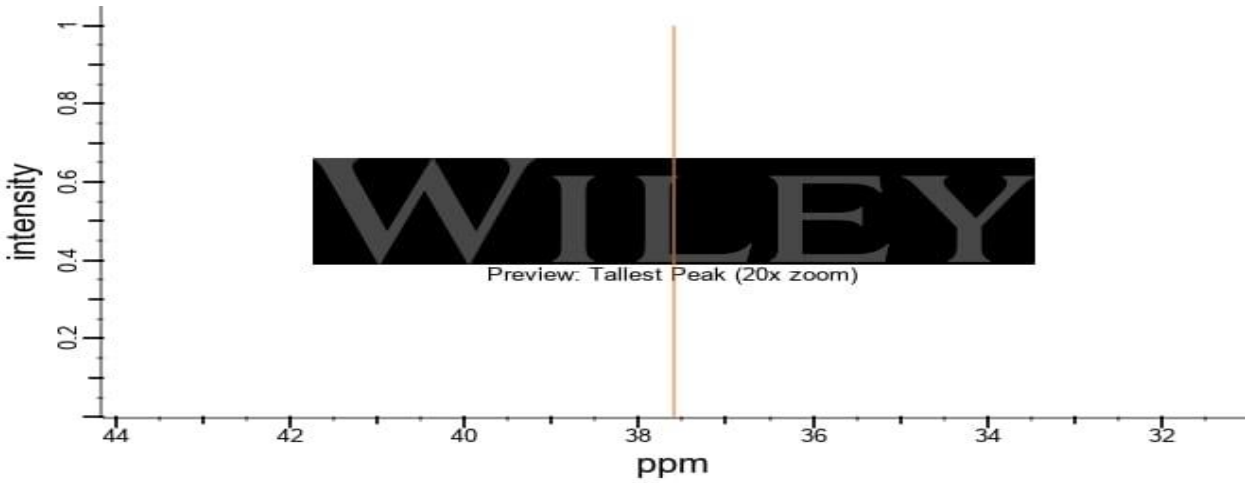
Acylation of resorcinol (12) with 3-chloropropionic acid in the presence of trifluoromethane Sulfonic acid resulted in 2', 4'-dihydroxy 3-chloropropiophenone (13). Compound cyclization 13 was carried out in 2M NaOH solution to give 7-hydroxychroman 4one. **[39]**



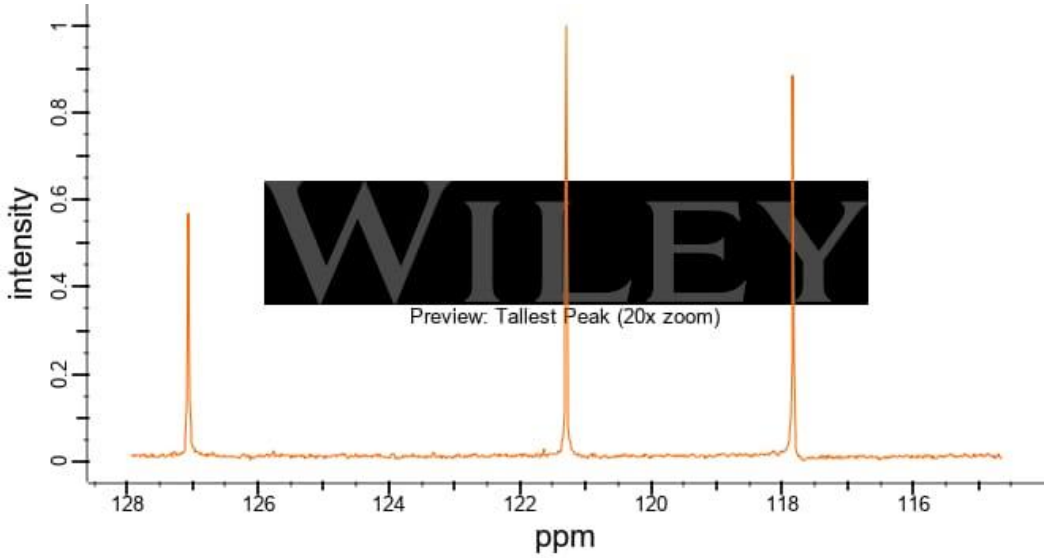
4. 4-Chromanone spectrum : [40]

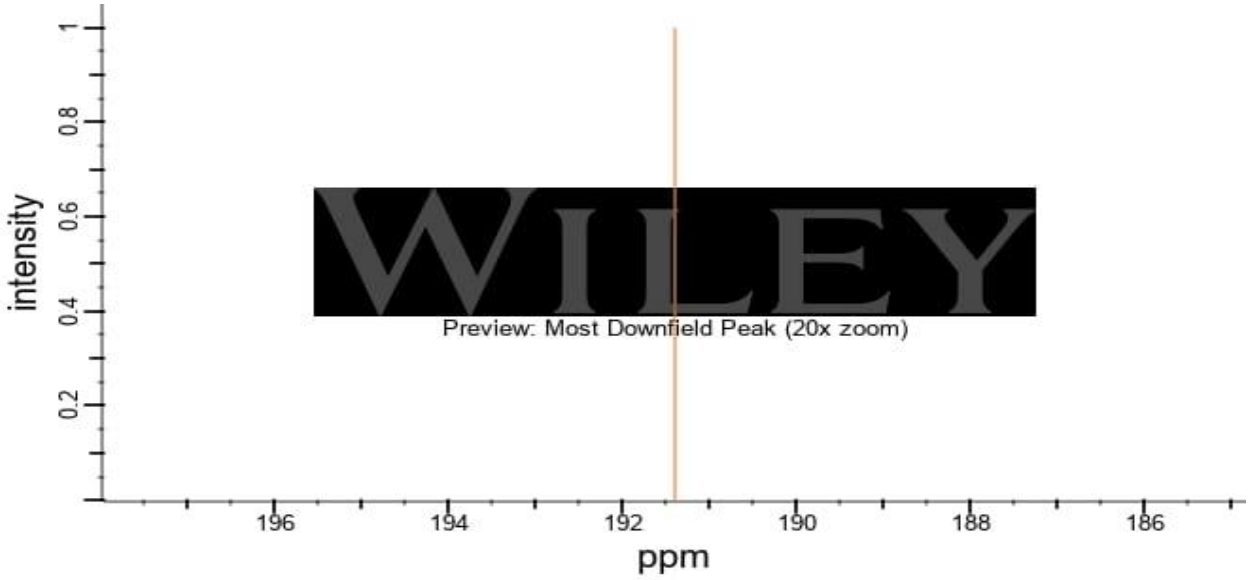
4.1. 13C NMR :

4.1.1 . Spectra in TMS solvent



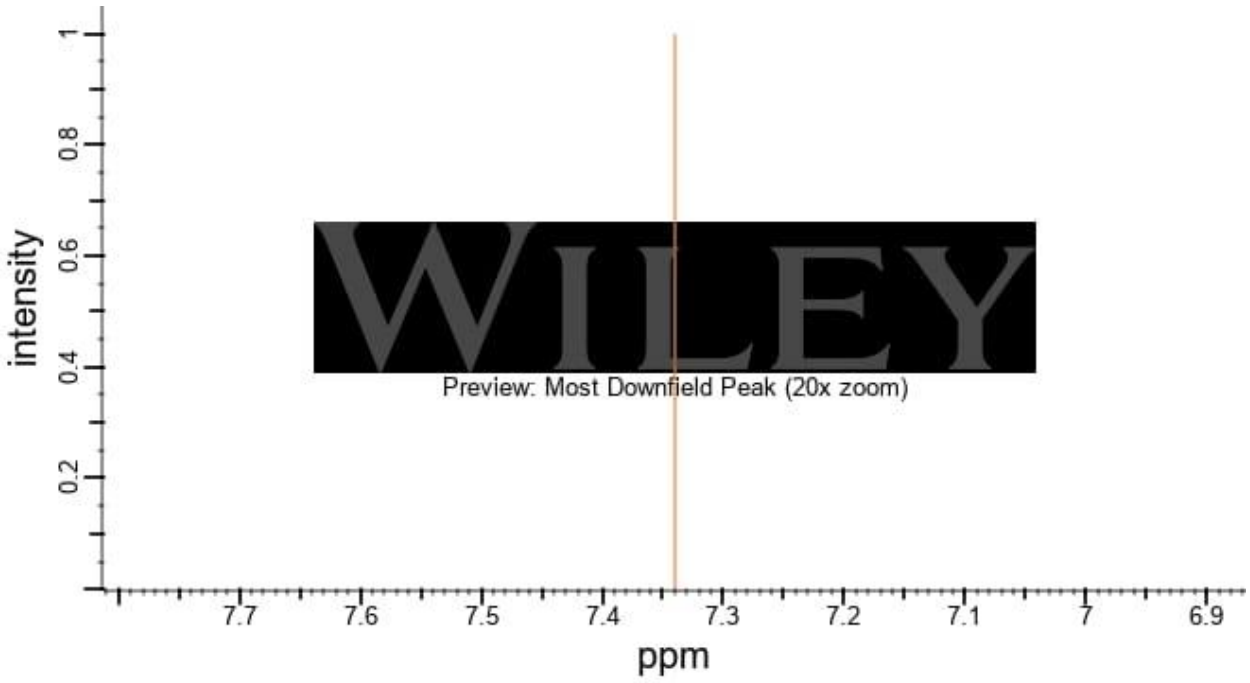
4.1.2. Spectra in CDCl3 solvent :



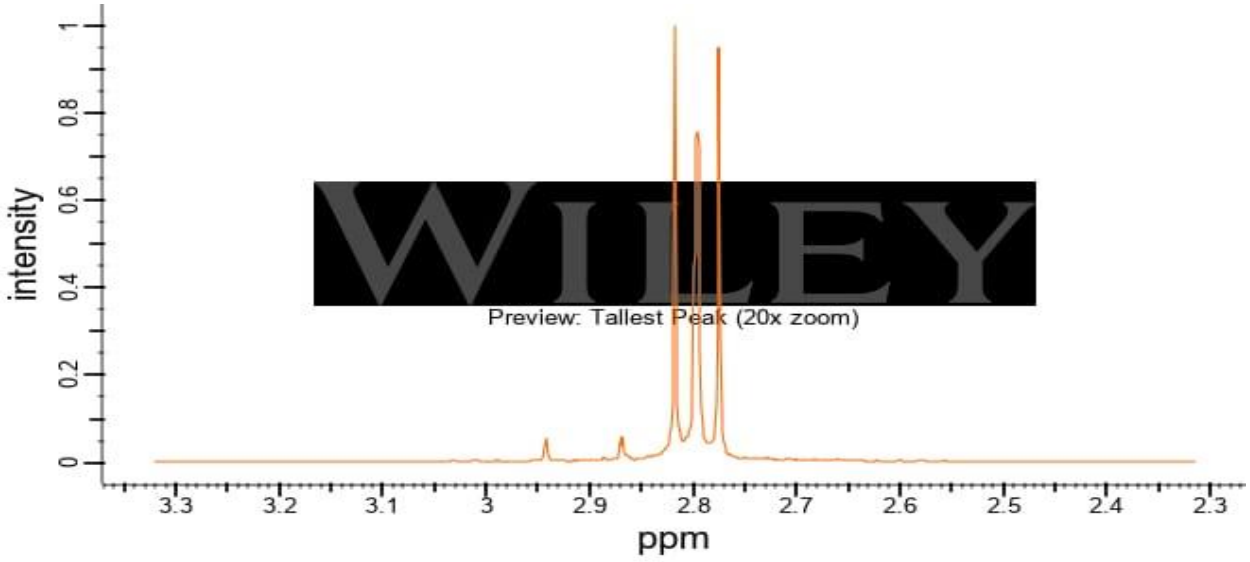


4.2. 1H NMR spectroscopy :

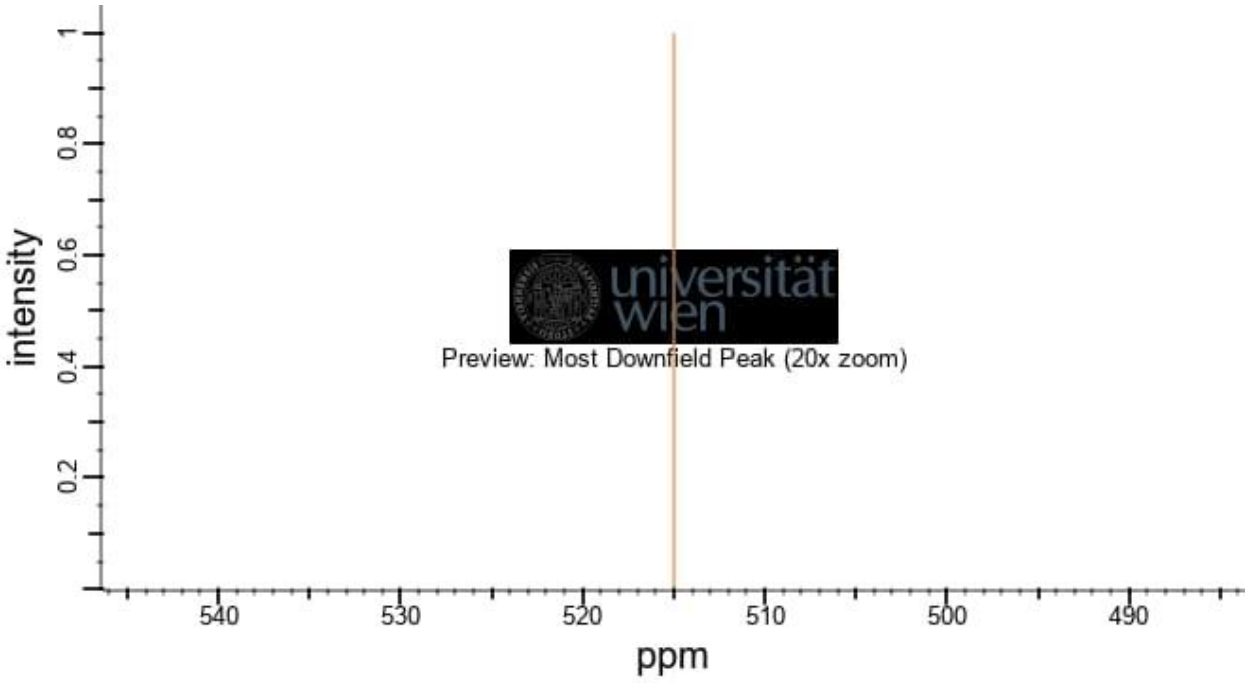
4.2.1. in CCl4 solvent :



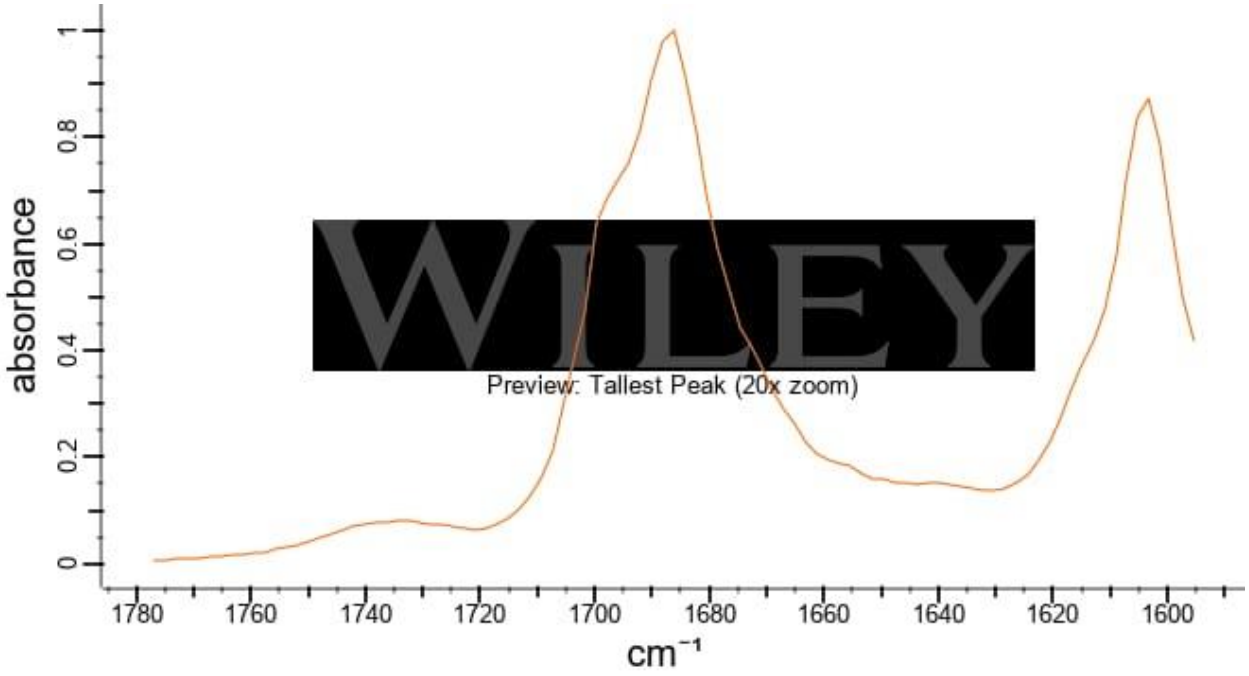
4.2.2. in CDCl3 solvent :



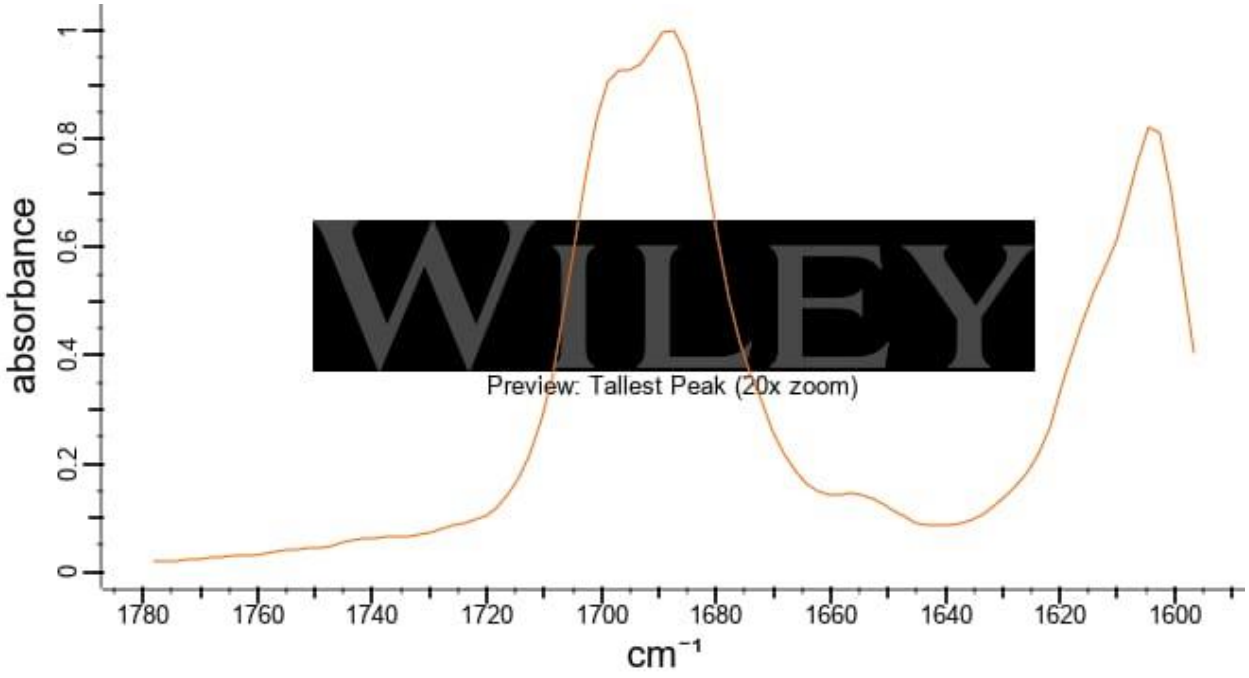
4.3. 170 NMR : (in CHCl3 Solvent)



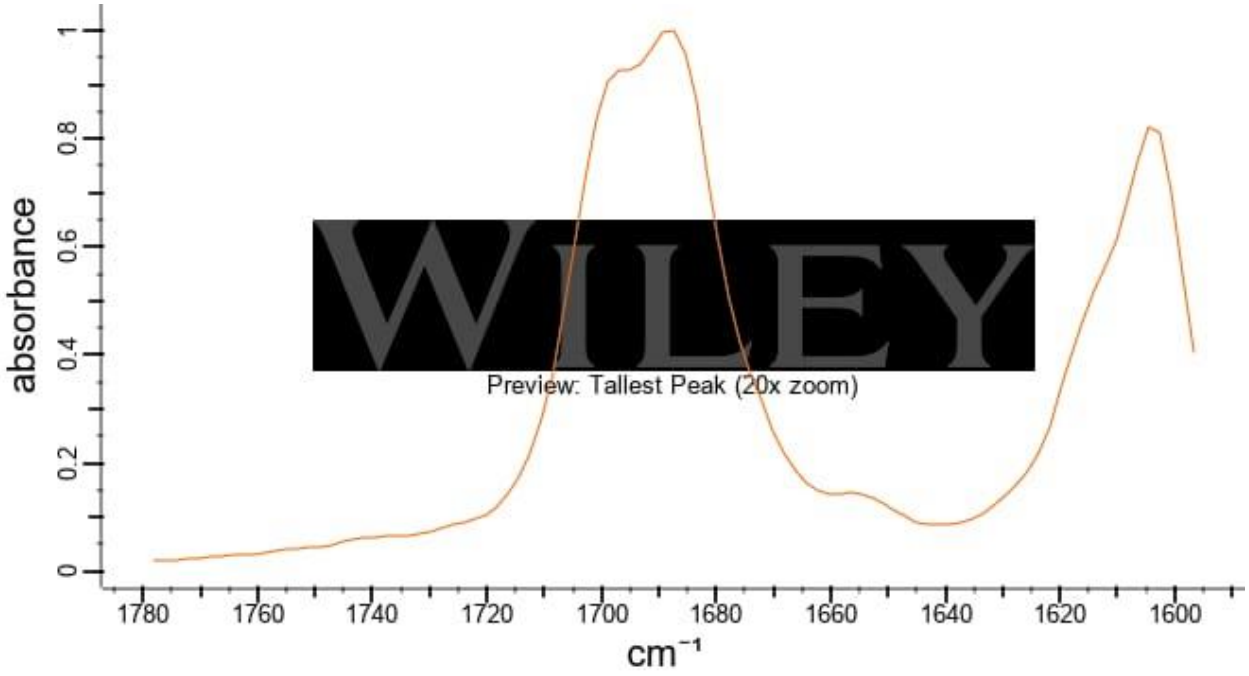
4.4. ATR-IR spectra



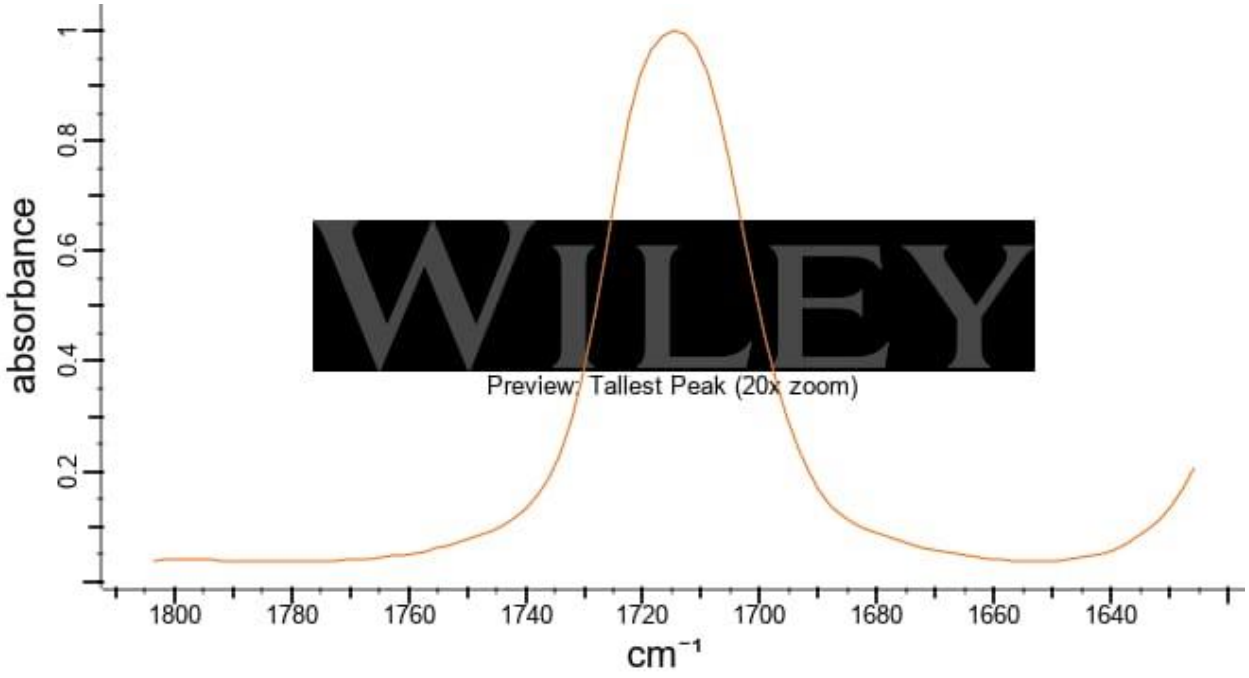
4.5. Transmission IR spectroscopy : (Neat technique)



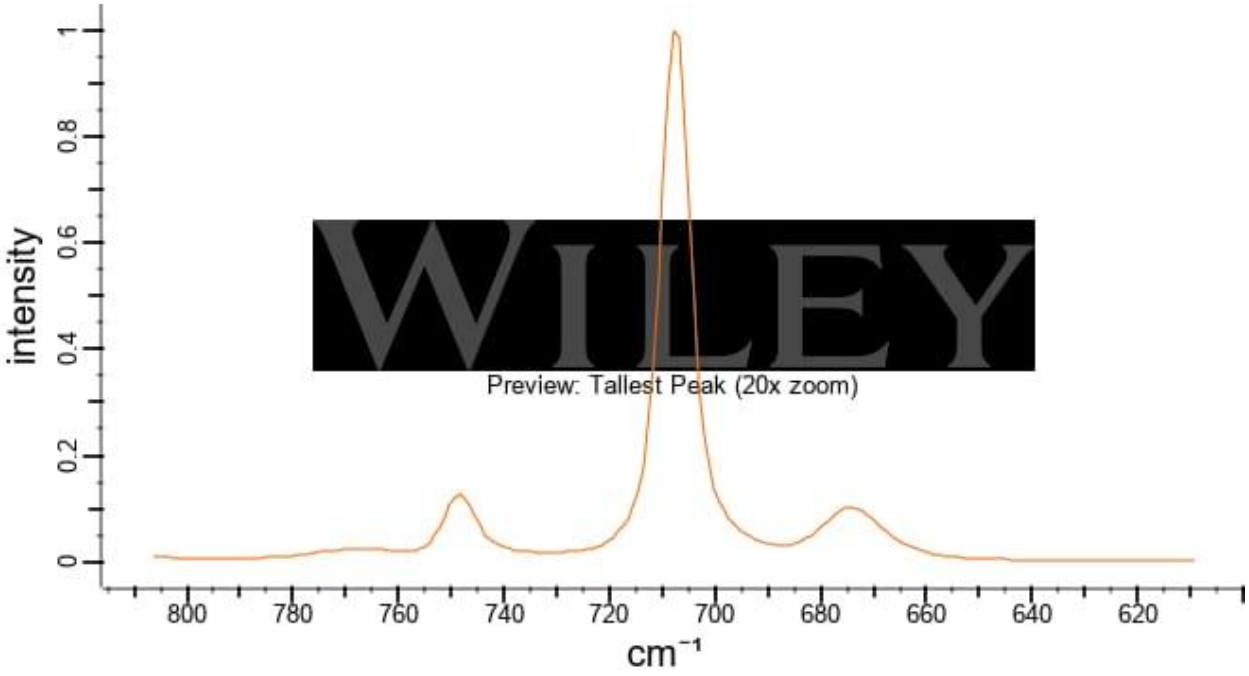
4.6 vapour phase IR:



4.7 Raman spectra :



4.8 Ms spectra :



Section B

Presnet work

1. Overview

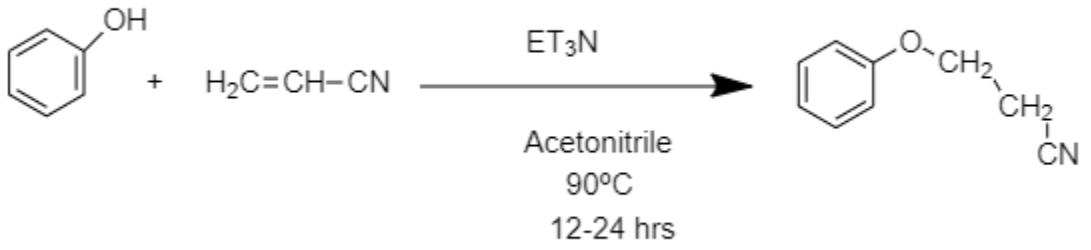
The outline work of benzylidene chromonone 4 may be a critical and surprisingly critical auxiliary substance which has a place to the category of oxygen containing heterocyclic compounds. it's one such natural particle that shows a wide sort of critical natural and pharmaceutical action. Chromonone seem moreover be considered as substituted cyclic ketone. Synthesis of benzylidine chromonone derivatives are observed as radical scavenger, the hostile to oxidant action and alpha glucosidase action These compounds are detailed to be an fundamentally a portion of numerous characteristic items with natural activity. specifically pre benzylidene chromonone share basic homology with broadly happening common item disconnected from Hyacinthaceae and Caesalpinioideae . an extremely close similarity of benzylidene chromanones may well be related with the show compounds like flavanones, flavones, chromones, and coumarins. We in this manner synthesized 3-benzylidene chroman-4-one subsidiaries to be assessed for their bio-logical efficacy. Literature prove uncovers 3-benzylidene chroman-4-ones to have tall organic efficacies counting anti-microbial, anti-can-cer, anti-inflammatory, and anti-oxidant properties .However, assessment of bioactivities in connection to the structure movement relationship that interfaces distinctive sorts of efficacies would be advantageous and fulfilling. The point of the display ponder was to decide the antifungal, anti-oxidant, and anticancer impacts of 3-benzylidene chromanone analogs. They display a wide assortment of well reported natural movement counting antimalarial, antimicrobial, Antihythmatic, and antidiabetic conjointly the foremost vital being against cancer movement which makes it of most extreme significance in pharma fields.

2. synthesis of 4-methoxy 3-benzylidene 4-chromanone :

The synthesis of 4-methoxy 3-benzylidene 4-chromanone is a multistep system that contain different reactions and reagents following reaction mechanisms 4 stages are seen.

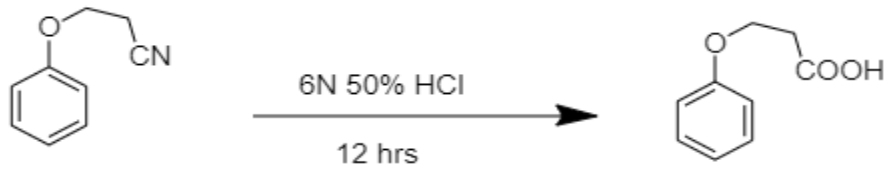
2.1.the preparation of 3-phenoxy propanonitrile

In this stage an oven dried round bottom flask is taken and phenol is poured into it. To this round bottom flask triethyamine, acrylonirtile are added dissolved in acetonitrile solvent and further keeping it under reflux for about 12 hours. Pour the reaction mixture jn ice cold water and separate the compound using ethyl acetate about 3 times. Wash the solution with 10N NaOH solution finally with water. Now separate the organic layer and evaporate the excess solvent with rota vapor



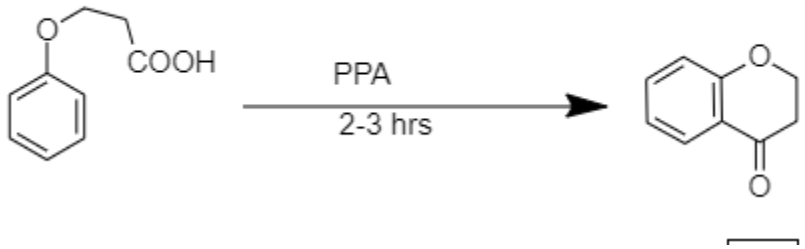
2.2. preparation of 3-phenoxy propionic acid from 3-phenoxy propanonitrile (hydrolysis):

A clean oven dried RB is taken and to that the previously prepared 3-phenoxy propanonitrile is added to which 6N HCl is added and stirred at 120°C for about 12hrs at reflux. After 12 hrs of reflux the reaction mixture id cooled to room temperature and poured into a beaker containing ice. Stir it well and it is observed that a white precipitate is formed. This product that is formed is 3-phenoxy propionic acid. The product thus obtained is subjected to suction and n hexane is added to it, dry and weight it.



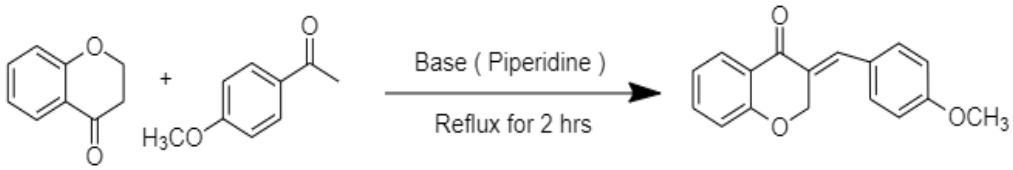
2.3. cyclization of 3 phenoxy propionic acid by using the cyclization agent polyphosphoric acid(PPA) :

To the second stage product which is obtained after suction and fully dried i.e 3-phenoxy propionic acid taken in a clean oven dried RB , nearly 5 times of PPA is added and continuously stirred for about 30mins keeping the RB in hot condition using a water bath. Red color solution is observed which is runny, then it's time to keep the RB in reflux using an oil bath for about 1hr. After reflux the RM is taken into a beaker containing ice. Add cold water and stir well, to that ethyl acetate is added. Stir it well and separate the organic layer by using a separating funnel. Separation is again done with aqueous layer by adding ethyl acetate to it. Finally add some anhydrous sodium sulphate and keep it in rota vapour for the solvent to evaporate.



2.4. condensation :

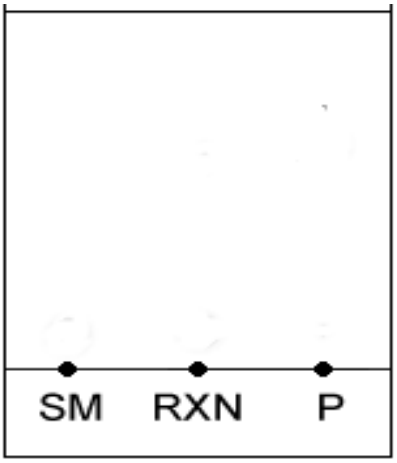
The 4 chromanone in the last stage is now condensed with 4-methoxy benzaldehyde in the presence of the base (piperidine)by keeping under reflux fir about 2 hours. The reaction mixture is tested using TLC.



3.TLC test :

One drop of benzaldehyde should be taken and diluted with ethyl acetate, this spot must also be kept in TLC plate while checking the spot for reaction mixture. The 4-methoxy benzaldehyde spot must be kept at one end of plate so as to avoid the clumsiness. The solvent polarity is modified for clarity in spots in TLC. The reaction mixture has to be dissolved in water in order to avoid unnecessary byproduct or colored compounds. As water is added to the reaction mixture all the unnecessary compounds get dissolved in it and reaches the aqueous phase (at bottom). Our desired product is left over at the top and to this we run the TLC. After running the TLC in full hexane solvent, the reaction mixture shows three spots.

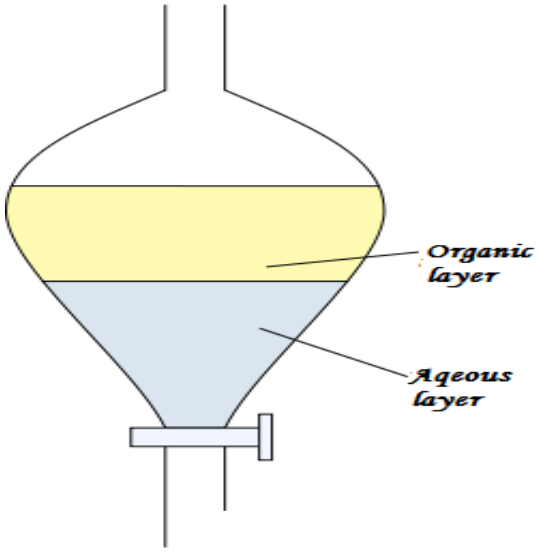
Out if these three spots the ones which imply to us about the contents in the reaction mixture are the upper smudge which indicates the 4-methoxy benzaldehyde, the middle spot that indicates 4-methoxy 3-benzylidine 4-chromanone, the bottom spot indicates 4-chromanone .



4. Workup :

4.1. Separation of components :

Seperation of product is done by adding HCl and then using ethyl acetate thouroughly shaking is done so as to separate the organic and aqueous layers using separating funnel. The organic layer is taken in round bottom flask and connected to the rota vapour in order to remove the excess solvent. As the reaction mixture 3spots corresponding to the two reactants and one product, these are further separated by means of column chromatography.



4.2. Column chromatography :

The compound that is obtained after keeping the obtained product under rota vapour. To it dichloromethane (DCM) is addedas it has a low BP and then silica is addedto the same RB. Now this RB is kept in a hot water bath and is observed keenly so as to mix perfectly and form a powder. This power thus obtained is ready to be entering into column for separation by column chromatography. To proceed to the next step i.e chromatography packing of column is very important. Firstly cotton plug or silicon glass wool is taken then upto it a silica gel bed is prepared, silica gel is taken about three times to that of slurry.

It can be directly added or silica gel dissolved in haxane is added solvent hexane is taken for even spreading of the silica bed. Always one thing is to be kept in mind that selection of the perfect solvent run is very essential, for our compound firstly hexane is to be run so that in case there is any coloured impurity or unwanted byproducts will run down first along with hexane.

The polarity of the chosen solvent can be changed according to the characteristics of the desired product . Above to the silica bed the reaction mixture and silica gel combined powder that was previously formed is added slowly and some slurry must be left behind in the RB so as to run it in TLC for reference. Now pack the column with cotton plg and solvent is added to this column at regular intervals. To run out the TLC, slurry left behind in the RB is dissolved in ethyl acetate and is taken for reference and the other spots from different test tubes are spotted.

Section C

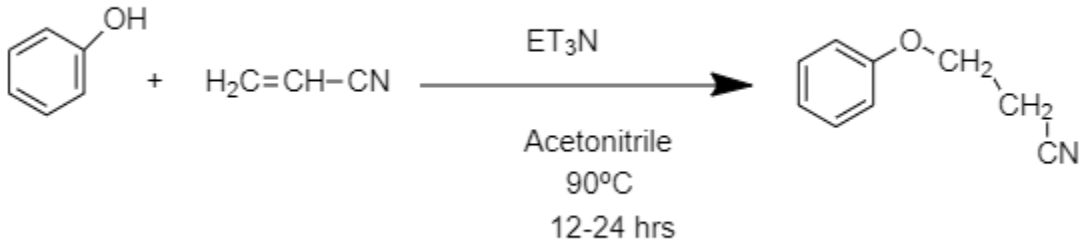
Experimental Section

General procedure for the preparation of 4-methoxy

Benzylidene)-4- Chromanone:-

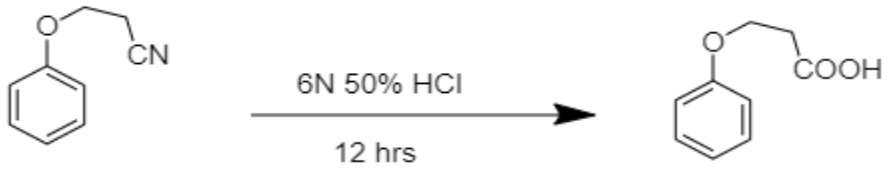
The synthesis of para 4-methoxybenzylidene 4-chromanone is a multistep process that involve different reactions and reagents following reaction mechanisms four stages are seen. First stage is the preparation of 3-phenoxy propanonitrile which is an addition reaction. In this stage an oven dried round bottom flask is taken and **5g** of phenol is poured into it. To this round bottom flask take **5.37g** of triethyamine, **8.46g** of acrylonirtile are added dissolved in acetonitrile solvent and further keeping it under reflux for about 12 hours. Pour the reaction mixture jn ice cold water and separate the compound using ethyl acetate about 3 times. Wash the solution with 10N NaOH solution finally with water. Now separate the organic layer and evaporate the excess solvent with rota vapour. Before the sample is subjected to rota vapour, the weight of product is **86.5g.**

After the sample is subjected to rota vapour the weight becomes **75.93g.**



Procedure for the preparation of 3- phenoxy propanoic acid:-

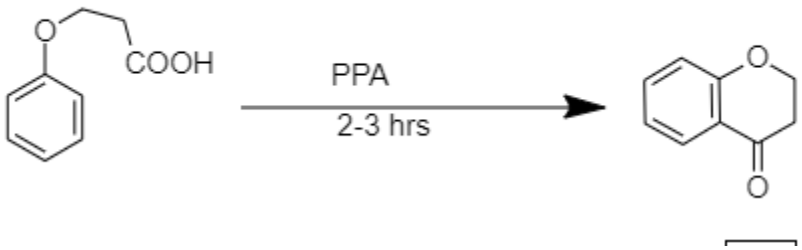
The next stage is the preparation of 3phenoxy propionic acid from 3phenoxy propanonitrile which is the hydrolysis of the -CN group into -COOH functional group. A clean oven dried RB is taken and to that the previously prepared 3 phenoxy propanonitrile is added to which 6N HCl is added and stirred at 120°C for about 12hrs at reflux. After 12 hrs of reflux the reaction mixture id cooled to room temperature and poured into a beaker containing ice. Stir it well and it is observed that a white precipitate is formed. This product that is formed is 3 phenoxy propionic acid. The product thus obtained is subjected to suction and n hexane is added to it, dry and weight it. The weight of 3 phenoxy propanoic acid is **6.89g.**



Procedure for the cyclisation of 3- phenoxy propanoic acid into 4- chromoanone by polyphosphoric acid:-

The next stage is the cyclization of 3 phenoxy propionic acid by using the cyclization agent polyphosphoric acid(PPA). To the second stage product which is obtained after suction and fully dried i.e 3 phenoxy propionic acid about 3 grns of it is taken in a clean oven dried RB , nearly 5 times of PPA I. E about 15g is added and continuously stirred for about 30mins keeping the RB in hot condition using a water bath. Red colour solution is observed which is runny, then it's time to keep the RB in reflux using an oil bath for about 1hr. After reflux the RM is taken into a beaker containing ice. Add cold water and stir well, to that ethyl acetate is added. Stir it well and

separate the organic layer by using a separating funnel. Separation is again done with aqueous layer by adding ethyl acetate to it. Finally add some anhydrous sodium sulphate and keep it in rota vapour for the solvent to evaporate. The fourth stage being the condensation step and is very crucial. In this step the reaction mixture is taken and washed with 1M HCl and then followed by ethyl acetate.



Procedure for the condensation of 4- chromanone and/ with4-methoxybenzaldehyde to give 3 (4-methoxy Benzylidene) – 4- chromanone

The 4-chromanone in the last stage is now condensed with para methoxy benzaldehyde in the presence of the base piperidine by keeping under reflux fir about 2hours. Chromanone is taken 0.8g and then 1g of para methoxy benzaldehyde is added to which further piperidine base is added carefully at about0.5508g . The reaction mixture is tested using TLC .

TLC plate :

One drop of p-methoxy benzaldehyde should be taken and diluted with ethyl acetate, this spot must also be kept in TLC plate while checking the spot for reaction mixture. The 4-methoxy benzaldehyde spot must be kept at one end of plate so as to avoid the clumsiness.

The solvent polarity is modified for clarity in spots in TLC. The reaction mixture has to be dissolved in water in order to avoid unnecessary by product or coloured compounds. As water is added to the reaction mixture all the unnecessary compounds get dissolved in it and reaches the aqueous phase (at bottom). Our desired product is left over at the top and to this we run the TLC.

After running the TLC in full hexane solvent, the reaction mixture shows three spots. Out if these three spots the ones which imply to us about the contents in the reaction mixture are the upper

smudge which indicates the 4-methoxy benzaldehyde, the middle spot that indicates 4-methoxy benzylidine chromanone, the bottom spot indicates 4-chromanone .

Workup:

The workup of this condensed product is done by adding 1M HCl and then using ethyl acetate to thoroughly shaking is done so as to separate the organic and aqueous layers using separating funnel. The organic layer is taken in round bottom flask and connected to the rota vapour in order to remove the excess solvent. As the reaction mixture 3spots corresponding to the two reactants and one product, these are further separated by means of column chromatography.

Preparation of HCl (1M) :

N1V1=N2V2

11.6 x V1= 1 x 25 =2.155ml

N1 = normality of lab HCl

N2=1N

V1=volume of lab HCl in ml

V2= volume of 1N HCl. In ml.

The compound that is obtained after keeping the obtained product under rota vapour. To it dichloromethane (DCM) is added as it has a low BP and then silica is added to the same RB. Now this RB is kept in a hot water bath and is observed keenly so as to mix perfectly and form a powder. This power thus obtained is ready to be entering into column for separation by column

chromatography. To proceed to the next step i.e. chromatography packing of column is very important. Firstly cotton plug or silicon glass wool is taken then unto it a silica gel bed is prepared, silica gel is taken about three times to that of slurry. It can be directly added or silica gel dissolved in hexane is added solvent hexane is taken for even spreading of the silica bed. Always one thing is to be kept in mind that selection of the perfect solvent run is very essential, for our compound firstly hexane is to be run so that in case there is any coloured impurity or unwanted by-products will run down first along with hexane. The polarity of the chosen solvent can be changed according to the characteristics of the desired product . Above to the silica bed the reaction mixture and silica gel combined powder that was previously formed is added slowly and some slurry must be left behind in the RB so as to run it in TLC for reference. Now pack the column with cotton plug and solvent is added to this column at regular intervals. To run out the TLC, slurry left behind in the RB is dissolved in ethyl acetate and is taken for reference and the other spots from different test tubes are spotted. Note: Methanol spray is used sometimes to identify the spot corresponding to the para bromobenzylidene chromanone respectively. Since it can't be observed clearly under UV light. Preparation: Methanol spray = 9:1 ratio of methanol and concentrated sulfuric acid And then keep the organic layer in rota vapour once the identification is done.

Calculations:

Theoretical yield = (Quantity of reference compound x mol.wt of product obtained) / mol. wt of reference compound.

= (0.5 x 266) / 148 = **0.8g**

Yield obtained experimentally = 0.27g

Percentage yield = (experimental yield / theoritical yield) x 100 %

= (0.27/0.8) x100% = **33.8%**

Result: The 4-methoxy benzylidene chromanone obtained is 0.27g

Conclusion:

All the synthesized 3-benzylidene-4-chromanone derivatives shared similar chemical functions and purposeful groups, which include the presence of hydroxyl and methoxy groups, and had been evaluated for his or her potential1,1-diphenyl-2-picrylhydrazyl (DPPH) loose radical scavenging and α-glucosidase inhibitory sports. As proven in Table 1,change of the 3-benzylidene-4-chromanones at the chromanone ring (A-ring) and the phenyl organization (B-ring) of the benzylidene moiety found out a few thrilling SAR.

Introduction of the methoxy, monohydroxyl or dimethylamino organization, or a halogen atom (F or Cl) substituent, at the B-ring did now no longer bring about DPPH radical scavenging hobby,while creation of the 3′,4′-dihydroxyl (catechol) organization led to mighty hobby (compounds 5, thirteen, 18, with EC 50 values thirteen, 14, thirteen μ M , respectively). These findings had been regular with the preceding reviews that confirmed compound thirteen)and18) had a sturdy DPPH radical scavenging hobby. The catechol organization withinside the B-ring of 3-benzylidene4chromanones is understood to be an critical structural function for antioxidant

hobby.) It changed into referred to that the creation of a hydroxyl organization on the 7-function at the A-ring did now no longer boom the DPPH radical scavenging hobby of 3benzylidene-4-chromanones.

The α-glucosidase inhibitory sports of the 3-benzylidene-4-chromanones had been determined (Table 1), and seven of the 18 compounds (compounds 4, 5, 6, 12, thirteen, 14, 18) werefound to have higher inhibitory α-glucosidase inhibitory hobby than a industrial anti-hyperglycemic drug, acarbose (IC 50 =900 μ M). Compound 12 changed into the maximum mighty inhibitor (IC 50 =15 μ M). It changed into referred to that the creation of a hydroxylgroup on the 7-function at the A-ring increased the hobby (compounds 12, 14), even as the creation of a methoxy organization on the A-ring reduced the hobby (compounds 17,19), besides for catecholsubstituted compounds (compounds13, 18). Consequently, catechol substitution at the B-ring might also additionally play an critical position in α-glucosidase inhibitory hobby (compounds 5, thirteen, 18). These effects imply that hydroxylation of the A- and B-earrings is critical for α-glucosidase inhibitory hobby. It has been pronounced that a few flavonoids and polyphenols, as nicely as sugar derivatives, are powerful inhibitors of α-glucosidase hobby,) suggesting that the polyphenols found in 3-benzylidene-4-chromanones are critical for α-glucosidase inhibitory hobby.Interestingly, compound 18 confirmed each mighty DPPH loose radical scavenging and α-glucosidase inhibitory sports. Accumulated evidence

shows that oxidative strain is worried withinside the pathogenesis of diabetes

mellitus and similarly exacerbates diabetic complications. 3-Benzylidene4chromanone

derivatives which include compound 18 might also additionally function lead compounds

for novel α-glucosidase inhibitors.

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