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ORIGINAL ARTICLE

DESIGN, SYNTHESIS, CHARACTERIZATION AND IN VITRO ANTIOXIDANT SCREENING OF NOVEL CHROMONE CHALCONES

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***ABSTRACT*:**

A novel method for the synthesis of Chromone chalcones (4a-f) have been introduced via Claisen-Schmidt synthesis by using recyclable PEG-400 as an alternative reaction medium. Different substituted Chromone chalcones have been carried out by using 3-formyl chromone aldehyde. It highlighten the chemical reactivity of 3-formyl chromones towards the synthesis of Chromone chalcones. Bicyclic chromone moiety has been used as a privileged structure in the development of pharmacologically active compounds as scaffolds used as drug in medicinal chemistry. The structures of the compounds were characterized by IR, ^{1}H NMR and screened for their in vitro antioxidant (DPPH and SOD) activity. DPPH free radical scavenging activity was given by the compounds (4a-f) at with (0.5 mmol/L in methanol). The compounds having substituent hydroxyl, mehtoxy, ethoxy, chloro and nitro as well as chromone moeity in the chalcone structure (4a-f) shows enhancement in antioxidant activity. Particularly in compounds like 4d, 4e, and 4f, shows strongest percentage of inhibition mainly at (C=1mM) . Almost all the compounds indicates moderate to good antioxidant activity compared to that of standard ascorbic acid percentage antioxidant activity (1mM) by DPPH and SOD as 45.28 and 73.17 respectively. The resultant absorbance was recorded at 517 nm after 30 min incubation at 37^{0}C. It was also found to be a potent scavenger of SOD and this property may be responsible for the good anti-inflammatory activity of corresponding chromone chalcones. Almost all the synthesized novel chromone chalcones shows potent antioxidant activity.

KEYWORDS: *Chromones, 3- formyl Chromones, Chromone Chalcones, Vilsmeier - Haack reaction, Claisen-Schmidt synthesis , Antioxidant Activity.*

INTRODUCTION :

Chromones and their derivatives are referred as oxygen-containing heterocyclic compounds. Generally chromone derivatives known for naturally occurring pharmacologically active compounds.[1-3] Chromones may be determined from those Greek expression chroma, significance “color”, which demonstrates that huge numbers chromone subsidiaries show a broad variation of colors. Oxygen holding heterocycles are richly found in environment.[4]

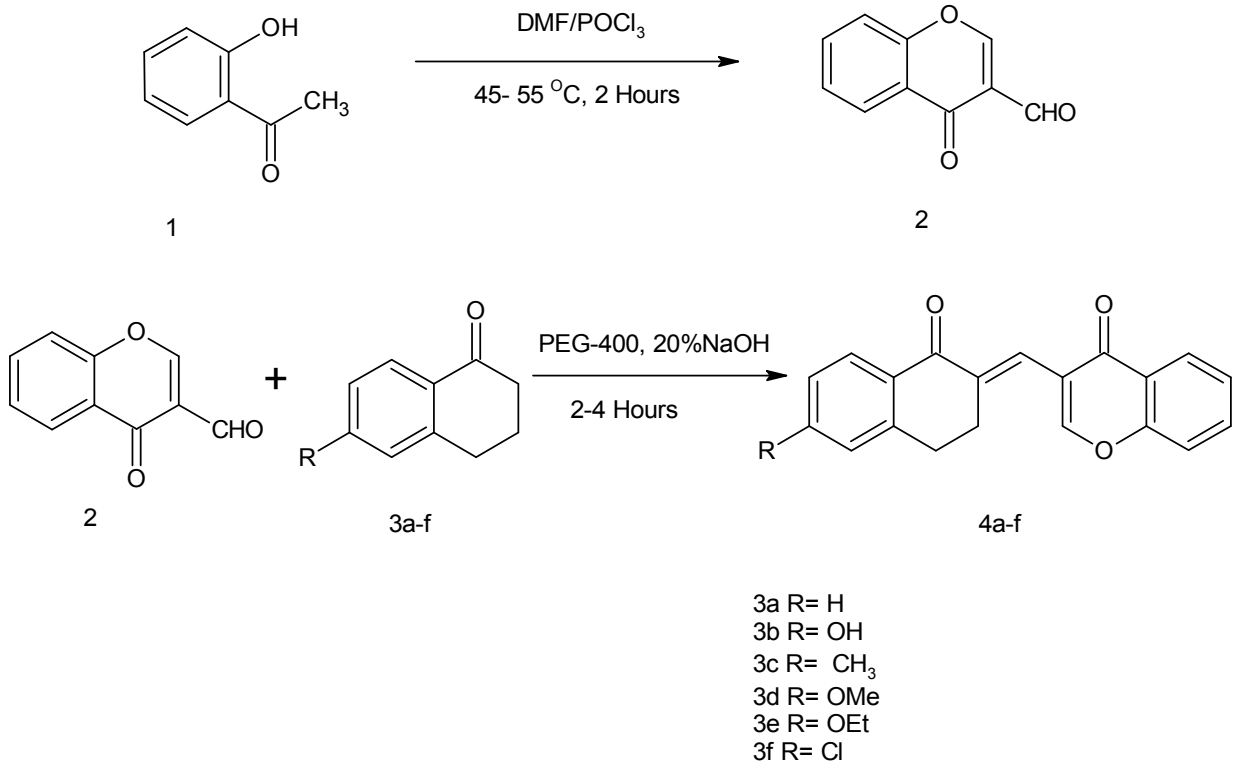
Chromones are synthetically nomenclatured by the name 4H-1-benzopyran-4-ones which constitute a critical class of oxygen containing heterocyclic compounds. It has also some phytoconstituents as chromenes flavones, isoflavones, flavanones, catechins, anthocyanins which are similarly considered as flavonoids and isoflavonoids. Artificially they are sorted as similarl to chromenes, dihydrofurobenzofurans, chromanochromanones, benzofurochromans, xanthones. Bioevaluation of chromone derivatives incorporates cytotoxic, HIV-inhibitory[5], antimicrobial , antibacterial[6], anti-inflammatory[7] antioxidant, antiviral and antifungal. Also chromones have an expansive assorted qualities in curing of ulcers and schizophrenia. Among the 3-functionalized chromones, their 3-formyl derivatives are widely used in heterocyclic synthesis. Chalcones are a good synthon for a variety of synthesis involving heterocyclic compounds.

Generally 3-formyl subsidiaries are utilized widely in heterocyclic synthesis. 3- formyl chromone would be an versatile synthons for the synthesis of a variety of novel heterocyclic systems possessing miscellaneous biological activities in concern with the novel heterocyclic frameworks possessing different living exercises. 3-Formylchromone (4-oxo-4H-1-benzopyran-3-carboxaldehyde) has been frequently used for the synthesis of various heterocyclic derivatives ever since its convenient synthesis was reported.[8] There are several subsidiaries for 3-formyl chromone has been engineered as useful synthetic building blocks in both organic and medicinal chemistry. Derivatives of 3-formyl chromone are 3-formyl chromone has been fabricated for the present study due to the reason that it carries three electron deficient centres viz. α,β-unsaturated keto function, a carbonyl group in the form of formyl group at position 3 and a very sensitive electrophilic centre at C-2.

The aim of the study was to synthesize some different substituted derivative of chromone chalcones using 3- formyl chromone aldehyde and different substituted tetralones as well as to assess them for their antioxidant activity. Amalgamation of Chromone chalcone (4a-f) were carried out in PEG-400 as green solvent.[9] Till today number of various chalcones were prepared in various reaction medium like under acidic medium using HCl[10], BF_3, B_2O_3, p-toluenesulfonic acid, using $SOCl_2$,[11] Water, Na_2CO_3 [12] and ionic liquid.[13] However, many of these methods suffered from harsh reaction condition, toxic reagents, strong acidic or basic conditions, prolonged reaction-times, poor yields and low selectivity. Even though, several modifications have been made to overcome these problems, in persistence to keep with work on chalcones as precursors in the synthesis of various heterocycles. We have intended to focus on green chemistry, using PEG-400 as an alternative reaction medium.[9&14] PEG is an environmentally benign reaction solvent, non-toxic, inexpensive, potentially recyclable and water soluble, clean and product with excellent yield. Reaction occur in shorter reaction time and minimises the use of volatile organic compounds (VOCs). Also it is easier to remove the excess solvents from the reaction mixrure to get pure product.

MATERIALS AND METHODS :

SCHEME -1 : SYNTHESIS OF CHROMONES CHALCONE COMPOUNDS (4a-f) :



3a R= H
3b R= OH
3c R= CH_3
3d R= OMe
3e R= OEt
3f R= Cl

GENERAL INSTRUMENTATION :

Melting points were determined in open capillary tubes and were found uncorrected. IR spectra were recorded on FT-IR spectrometer (Perkin Elmer). 1H NMR spectra were recorded on Varian-NMR-mercury 300 MHz spectrometer in $CDCl_3$ as a solvent. All the reagents and solvents were used of analytical grade and used as supplied unless otherwise stated. TLC was performed on silica gel coated plates for monitoring the reactions.

SYNTHESIS OF 3-FORMYL CHROMEN-4-ONE (2) :

In dry DMF (60 ml) in three neck flask, $POCl_3$ (37.5 ml) was added slowly with vigorous stirring at 50^0C. Heating and stirring was continued for 2 hrs at 45-55^0C. The solution of 2-hydroxyl acetophenone (9.12 gm) in DMF (12.5 ml) was then slowly added with stirring at 50^0C and stirring was continued for 2 hrs. After cooling the mixture was kept overnight at room temperature and diluted slowly by adding ice cold water (250 ml) and was stirred for 6 hour. The red crystalline product separated was filtered and recrystallised from alcohol.[15-17] M.P.- 151-153 ^{0C}.

SYNTHESIS OF CHROMONE CHALCONES (4a-f) :

A mixture of substituted 3-forrmly chromone aldehyde 2 (1 mmol) and substituted tetrlones, 3a-f (1 mmol) was dissolved in 15 ml PEG-400. To this mixture, sodium hydroxide (20%, 1ml) was added and the reaction mixture was stirred at 40-50^{0}C temperature for 2-4 hours. The reaction mixture was then poured into 100 ml ice cold water. The product was separated out, it was filtered and processed out. The obtained products were recrystallised from ethanol to afford pure compounds [9&17] (4a-f).

THE SPECTRAL DATA FOR SYNTHESIZED COMPOUNDS :

4a-3-[(*E*)-(6-methoxy-1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)methyl]-4*H*-chromen-4-one : 1H NMR (CDCl3, 300 MHz):

Tetralones - 7.76 (d,1H) near to C=O, Aromatic C1- H, 7.72 (d,1H) Aromatic C2- H, 7.49 (d, 1H) C3- H, 7.31 (d, 1H) C4- H, 2.59 (t, 2H) C5- H, 2.29 (t, 2H) C6- H,near to C=C, Chromones - 7.22 (s,1H) near to O, C8- H, 6.12 (d,1H), Aromatic C9- H, 7.37 (d,1H), C10- H,7.01 (d,1H), C11- H, 7.64 (d,1H).

4b- 3-[(*E*)-(6-hydroxy-1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)methyl]-4*H*-chromen-4-one :

Tetralones - 7.59 (d,1H) near to C=O, Aromatic C1- H, 6.74 (d, 1H) Aromatic C2- H, 5.0 (s, 1H) C3-OH,6.78 (d, 1H) C4- H, 2.59 (d, 1H) C5- H, 2.29 (t, 2H) C6- H, near to C=C,Chromones – 7.7.48 (s,1H) unsaturated C=C, near to C=O, C7- H, n 7.22 (s,1H) near t0 O, C8- H, 6.92 (d,1H),n Aromatic C9- H, 7.37 (d,1H), nC10- H,7.01 (d,1H), C11- H,7.64 (d,1H).

4c- 3-[(*E*)-(6-methyl-1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)methyl]-4*H*-chromen-4-one :

Tetralones - 7.64 (d,1H) near to C=O, Aromatic C1- H, 7.07 (d, 1H) Aromatic C2- H, 2.35 (s, 3H) C3-OH, methyl protons 7.11 (d, 1H) C4- H, 2.59 (d, 1H) C5- H, 2.29 (t, 2H) C6- H, near to C=C, Chromones – 7.48 (s,1H) unsaturated C=C, near to C=O, C7- H, 7.22 (s,1H) near to O, C8- H, 6.92 (d,1H), Aromatic C9- H, 7.37 (d,1H), C10- H, 7.01 (d,1H), C11- H, 7.64 (d,1H).

4d -3-[(*E*)-(6-methoxy-1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)methyl]-4*H*-chromen-4-one :

Tetralones - 7.65 (d,1H) near to C=O, Aromatic C1- H, 7.78 (d, 1H) Aromatic C2- H, 3,73 (s, 3H) C3-OCH3, methoxy protons 6.82 (d, 1H) C4- H, 2.59 (d, 1H) C5- H, 2.29 (t, 2H) C6- H, near to C=C, Chromones – 7.48 (s,1H) unsaturated C=C, near to C=O, C7- H, 7.22 (s,1H) near to O, C8- H, 6.92 (d,1H), Aromatic C9- H, 7.37 (d,1H), C10- H, 7.01 (d,1H), C11- H, 7.64 (d,1H).

4e - 3-[(*E*)-(6-ethoxy-1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)methyl]-4*H*-chromen-4-one :

Tetralones - 7.65 (d,1H) near to C=O, Aromatic C1- H, 6.78 (d, 1H) Aromatic C2- H, 3,98 (s, 2H) C3-OCH2 and 1.33 (t, 3H), ethoxy protons 6.82 (d, 1H) C4- H, 2.59 (d, 1H) C5- H, 2.29 (t, 2H) C6- H, near to C=C, Chromones – 7.48 (s,1H) unsaturated C=C, near to C=O, C7- H, 7.22 (s,1H) near to O, C8- H, 6.92 (d,1H), Aromatic C9- H, 7.37 (d,1H), C10- H, 7.01 (d,1H), C11- H, 7.64 (d,1H).

4f - 3-[(*E*)-(6-chloro-1-oxo-3,4-dihydronaphthalen-2(1*H*)-ylidene)methyl]-4*H*-chromen-4-one :

Tetralones - 7.70 (d,1H) near to C=O, Aromatic C1- H, 7.28 (d, 1H) Aromatic C2- H, 7.32 (d, 1H) C4- H, 2.59 (d, 1H) C5- H, 2.29 (t, 2H) C6- H, near to C=C, Chromones – 7.48 (s,1H) unsaturated C=C, near to C=O, C7- H, 7.22 (s,1H) near to O, C8- H, 6.92 (d,1H), Aromatic C9-H, 7.37 (d,1H), C10- H, 7.01 (d,1H), C11- H, 7.64 (d,1H).

BIOLOGICAL STUDY

ANTIOXIDANT ACTIVITY OF CHROMONES CHALCONES:

The synthesized compounds were evaluated for their *in vitro* antioxidant activity by 1,1-diphenyl-2- picrylhydrazyl (DPPH) radical scavenging method. DPPH is a stable free radical that can accept an electron or hydrogen radical to become a stable diamagnetic molecule. Due to its odd electron, the methanolic solution of DPPH shows a strong absorption band at 517 nm. DPPH radical reacts with various electron donating molecules (reducing agents or antioxidants). This results in the formation of the colourless 1,1-diphenyl-1-picryl hydrazine. Reduction of the DPPH radicals can be estimated quantitatively by measuring the decrease in absorbance at 517 nm. A radical scavenging antioxidant reacts with DPPH stable free radical and converts to DPPH-H. The change in the absorbance produced in this reaction has been used to measure antioxidant properties.

DPPH RADICAL SCAVENGING ACTIVITY :

The molecule 1, 1-diphenyl-2-picrylhydrazyl (a,a-diphenyl-bipicrylhydrazyl; DPPH) is characterized as a stable free radical by virtue of the delocalisation of the spare electron over the molecule as a whole, so that the molecule does not dimerize, as would be the case with most other free radicals. The delocalization of electron also gives rise to the deep violet color, characterized by an absorption band in ethanol solution centered at about 517 nm. When a solution of DPPH is mixed with that of a substrate (AH) that can donate a hydrogen atom, then this gives rise to the reduced form with the loss of this violet color. The ability of Compounds to scavenge.

PROCEDURE :

DPPH radical was assessed using Murthi et.al.[18] with modification. Briefly, 1 ml of synthesized compounds as 1 mM was mixed with 3.0 mL DPPH (0.5 mmol/L in methanol), the resultant absorbance was recorded at 517 nm after 30 min. incubation at 37^0C.

The percentage of scavenging activity was derived using the following formula,

Percentage of inhibition (%) = [(A control – A sample) / A control] x 100
Where, A control - absorbance of DPPH
A sample - absorbance reaction mixture (DPPH with Sample).

SCAVENGING OF SUPEROXIDE RADICAL BY ALKALINE DMSO METHOD (KUNCHANDY E, 1990)

To the reaction mixture containing 1 mL of alkaline DMSO, 0.3 mL of the drug samples

and standard was added in DMSO at various concentrations followed by 0.1 mL of NBT (0.1 mg) to give a final volume of 1.4 mL. The absorbance was measured at 560 nm.

TABLE 1: ANTIOXIDANT ACTIVITY OF DIFFERENT SUBSTITUTED CHALCONE DERIVATIVES

Sr. No.	Entry	% antioxidant activity (1MM) by DPPH	% antioxidant activity (1MM) by SOD
1	4a	38.51	55.65
2	4b	38.90	58.48
3	4c	39.52	61.75
4	**4d**	**43.02**	**72.38**
5	**4e**	**40.57**	**70.14**
6	**4f**	**40.35**	**65.31**
11	**Standard Ascorbic acid**	**45.28**	**73.17**

RESULTS AND DISCUSSION :

CHEMISTRY

In the present investigation, in our laboratory, the Chromone chalcones (4a-f) have been prepared by the Claisen-Schmidt condensation of 3- formyl chromone aldehyde and different substituted tetralones using sodium hydroxide in PEG-400 as a alternative reaction medium as shown in above (Scheme 1). All the compounds were obtained in good to excellent yields. The 3- formyl chromone aldehyde is prepared by the Vilsmeir-Haack reaction using DMF/POCl3 by using O- hydroxy acetophenone. The reaction was simple and efficient and yields the title compounds almost in pure form. However the resultant compounds were purified by recrystallization in ethanol solvent. The structures of the synthesized compounds were confirmed by IR, ^{1}H NMR. The IR spectra of final compounds showed an absorption band at 3300-3600 cm-^{1} indicates the presence of -OH stretching. The compounds containing halogen group viz. monosubstituted chloro, showed an absorption band in the region of 1398 - 1388 cm^{-1}, 785 - 756cm^{-1} and 661 -625 cm^{-1}, respectively. The compounds with methoxy substitution exhibited absorption band in the region of 1033 – 1016 cm^{-1} stretching vibration. The NMR spectra of title compounds showed singlets in the region of δ 6.9 - 7.4 due to the protons of phenolic hydroxy group. In compound the spectra of the compounds showed singlets in the region of δ 3.3 - 3.8 indicative of methyl protons. In the compounds containing methoxy group exhibited characteristic signals in the region of δ 3.8 -3.9 δ, 6.4 -8.2 aromatic protons in all the NMR spectra of final compounds confirm the structures of title compounds.

The synthesis and antioxidant activity of a series of new series of chromone chalcones were reported mild to good antioxidant properties. This is due to the presence of electron donating –OMe and -OEt. From the study, the antioxidant activity of the synthesized compounds can be shown as the following order d > e > f > a> b> c . Their studies revealed that the influence of the nature of the functional linkage (electron donating or electron withdrawing groups) and the position of the substituent on the phenyl ring chalcone play the role in determining the antioxidant activities.

CONCLUSION :

An eco-friendly and easy method has been used to synthesize the title compounds. The method includes mild reaction conditions, use of recyclable solvent and easy work-up procedure for the isolation of products. The reaction lead to the expected products with high yield and in all most all cases the products obtained in pure form. The present research work revealed that the Chromone chalcone compound **4d, 4e** and **4f** showed greater antioxidant activity in DPPH radical scavenging model**. 4a, 4b** and **4c** showed moderate antioxidant activity in DPPH radical scavenging model. Hence, these compounds can be developed as useful therapeutic agents after establishing their safety pharmacology and toxicity profile. In all these observations in this therapeutic area, the results obtained gives support might be provide exciting and motivating potentially promising results, that can finally be applied for enriching our knowledge and experience in the development of new pharmalogical assumptions with this specific pharmacological activity.

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CONFLICT OF INTEREST:

The authors confirm that this article content has no conflict of interest.

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