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Investigations on Antioxidant Behaviour of Some Chromone Based Derivatives of Methylhydrazino Carboxilate

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***Abstract*:**
Schiff bases derived from chromone derivatives provides a very efficient route for the synthesis of products in high yield with good purity which can act as precursorsfor the measurement of antioxidant activities where the important flavone derivative exhibits antioxidant activities role of structure-activity in control of antioxidant activities and prevention of damagedue to free radicals generated can be studied.
***Keywords**: Chromone, Antioxidant, Schiff base, DPPH.*

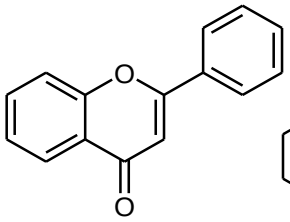
Introduction: Antioxidants are the class of compounds which help to inhibit the oxidative damage of the living cell by inhibiting the formation and growth of free radical species in the body which is the major cause for the oxidative stress. The oxidative stress is a state which possessreactive oxygen or nitrogen species (ROS/RNS, e.g., superoxide anion, hydrogen peroxide, hydroxyl radical etc.) which may lead to oxidation in living system by acting on enzymes, proteins, DNA and lipids. Antioxidants are majorly employed to reduce the damage those substances which have significant capacity toneutralize free radicals. [1]

Various types antioxidantsare classified on the basis of their interaction with solubility medium which can be eitherhydrophilic (soluble in water) or in Hydrophobic (soluble in lipids).Watersoluble antioxidants reacts with the oxidantswhich are present in the cell cytosol and the blood plasma, whereas those which are lipid-soluble antioxidants plays at vital role in the protection of membranes of cell from the process lipid peroxidation.[2]Some of the important antioxidant which are part of dietary component are vitamin C, lipoic acid which are water soluble antioxidants. The lipids soluble antioxidants are like carotene (vitamin A), also vitamin E. Out of these antioxidants uric acid has the highest concentration in human body, with the continuous utilization of oxidative rich food and other nutrient materials, human body needsto constantly refills our antioxidant resources.[3]

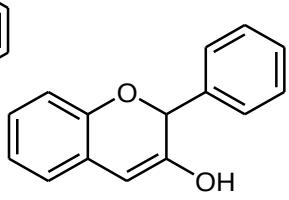
The polyphenols are widely distributed in many organic compounds due to their wide distribution and antioxidant propertiesthese have several health effects on human body, nutritionist have worked and researched more on polyphenols because of their antioxidant properties and behaving antioxidants to fight against the diseases which are curse for human life like cancer. The main and important classes of polyphenols arephenolic acids, flavonoids,stilbenes, phenolic alcohols and lignin's.[4]

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Flavonoids consist of common carbon skeleton of diphenyl propane which contains two benzene rings which are combined by a fixed three-carbon chain.[5]The three-carbon chain forms a closed pyrin ring attached with the benzene rings. Flavonoids are distributed and categorized into six subclasses. This distribution depends on the oxidation state of the pyrin ring which containsflavones, anthocyanins and flavanones.



Flavones



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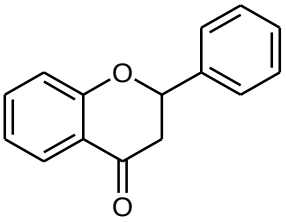
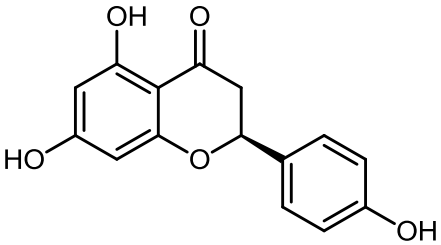
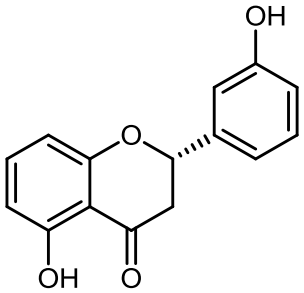


Flavanones

Flavanones and isoflavones are found in high concentrations in fruit like lemon (which is a source of citrus)From recent research the naringenin and eriodictyol found in grapefruit, orange and lemonsact as an important source for the flavone based antioxidants.[6]

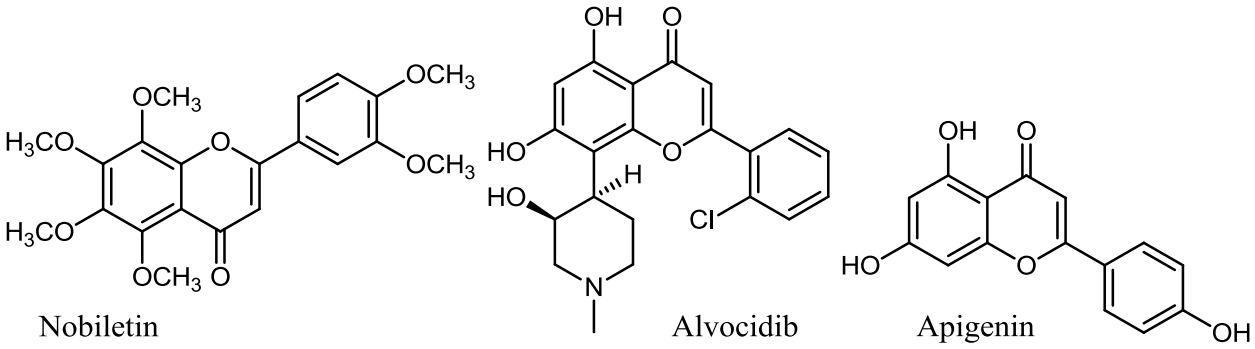




Chromones are the important members of flavone family which are found in nature and are present in normal human diet and showwide varieties of biological activities. They showanti-inflammatory and anticancerousproperties.The major species causing oxidative stress in body isreactive oxygen species (ROS) or of reactive nitrogen species (RNS) generated inside living cells by means of several exogenous and endogenous agents.[7] These species are known for permanent damages to biomolecules and may cause Alzheimer,arteriosclerosis, cancer and even premature aging.Therefore free radical scavengers are considered to act as protective or therapeutic agents against such diseases.[8]

Many of the flavones which have been used for the synthesis of different type of drugs like Nobiletin (Anti-inflammation), Alvocidib (Anti-cancer), Apigenin (Anti-microbial) etc.[9, 10]

ISSN:0971-1260
Vol-22-Issue-37-December -2019

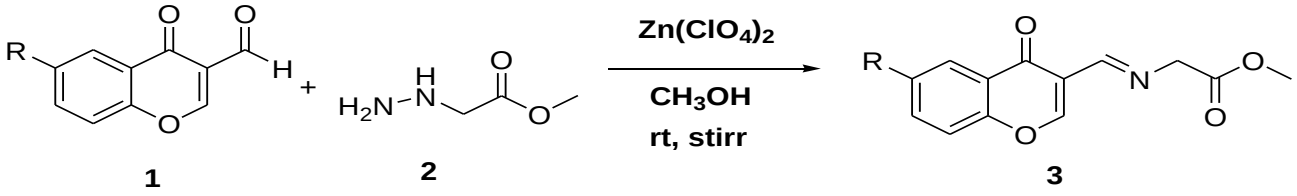


Nobiletin Alvocidib Apigenin

Flavonoids are present in almost all the plant's species. Flavonoids are mainly obtained from seeds, flowers, bark, and peel. They play very vital role in plant growth, reproduction, resistance against predators and pathogens.[11]The flavonoids are made up of large number of healing agents which contain many properties which help to fight against vascular diseases. The vascular disorders are protected by them by reducing the permeability and tenderness of capillaries.[12, 13, 14]The pharmacological effect of flavonoids is due to their inhibition property of certain enzymes and many other pharmacological actions of flavonoids have better explained by their action as antioxidants.[15]

Schiff bases are known as common enzymatic intermediates in which an amine is the terminal group.Compounds with azomethine group are commonly known as Schiff bases (-CH=N-).In general, the formation of these bases is done by the condensation of ketone or aldehydes with primary amine. The Schiff bases formed by aliphatic aldehydes are easily able to get polymerize and are unstable in nature. Schiff bases have a binding site in which metal ions can bind even through the non-bonding electron of nitrogen.

For the synthesis of chromone schiff bases reaction were carried out with variously substituted 6-methyl/ 6-flouro/ 6-bromo/ 6-chloro/ 3formylchromone by reacting with methyl 2-hydrazinylacetatein dry methanol in the presence of zinc per chlorate at room temperature. Progress of the reaction was monitored using TLC. After the completion of reaction solvent was removed under reduced pressure to give a desired product which was recrystallized to afford the pure product in quantitative yields.Percentage yield for these reactions are summarized in Table-1.



1 **2** **3**

a.R=H
b.R=CH_3
c.R=F
d.R=Cl
e.R=Br

Table.1Melting point, Color and percentage yield of various chromone derivatives

ISSN:0971-1260
Vol-22-Issue-37-December -2019

S.NO	Entry	COLOR	MELTING POINT	YEILD %
1.	3a	Off White	180-182^{0}C	92%
2.	3b	Light Yellow	166-168^{0}C	88%
3.	3c	Brown	143-145^{0}C	81%
4.	3d	Rust Brown	164-166^{0}C	95%
5.	3e	Light Brown	160-162^{0}C	81%

In order to understand the antioxidant behaviour of these compounds, studies were carried out by investigating the quenching action of each of the compound upon the DPPH which is considered as an efficient source of free radicals. To carry out these studies solutions of each of the derivative synthesized were prepared with different concentrations by making a suitable dilutions in DMSO and compound was mixed with standard solution of DPPH which was allowed to stand and a change in the absorption behaviour was studies which was an indicator of the free radical quenching in the solution and results have been calculated using equation as,

DPPH scavenged (%) = ($A_{con} - A_{test}$) / A_{con} X 100

A_{con} – is the absorbance of the control reaction.

A_{test} – is the absorbance of the DPPH in the presence of the sample.

Preparation (E)-methyl 2-((4-oxo-4H-chromen-3-yl)methyleneamino)acetate

3-formylchromone (0.5gm, 1.97x 10^{-3} moles) was added with methyl 2-hydrazinylacetate (0.28gm, 3.1x 10^{-3} moles) in methanol (20ml) in RBF along with zincperchlorate (4-5gm) as catalyst. The reaction mixture is stirred on magnetic stirrer for 2-3 hrs. After the completion of reaction (TLC), solvent was evaporated. The product was dried and crude was recrystallized to obtainoff white powder (0.78gm, 92%), m.p. 180-182^{0}C, IR data (KBr, cm^{-1}) C-H 2950, C=O (keto) 1635, C=N 2380, C-O 1113, C=O (carboxylic) 1724.24.

Preparation (E)-methyl 2-((6-chloro-4-oxo-4H-chromen-3-yl)methyleneamino)acetate

6 chloro-3-formylchromone (0.5gm, 2.39 x 10^{-3} moles) was added with methyl 2-hydrazinylacetate (0.263gm, 2x 10^{-3} moles) in methanol (20ml) in RBF along with zincperchlorate (4-5gm) as catalyst. The reaction mixture is stirred on magnetic stirrer for 2-3 hrs. Progress of the reaction was monitored using TLC (chloroform: ethyl acetate). After the completion of reaction, solvent was evaporated and crude was recrystallized to obtain rust brown powder (0.64gm, 95%), m.p. 164-166^{0}C, IR data (KBr, cm^{-1}) C-Cl 823, C=O(keto) 1640, C=N 2275, C-O 1113.9, C=O(carboxylic) 1720.

Preparation (E)-methyl 2-((6-methyl-4-oxo-4H-chromen-3-yl)methyleneamino)acetate

6 methyl-3-formylchromone (0.5gm, 2.65 x 10^{-3} moles) was added with methyl 2-hydrazinylacetate (0.23gm, 2.92x 10^{-3} moles) in methanol (20ml) in RBF along with zincperchlorate (4-5gm) as catalyst. The reaction mixture is stirred on magnetic stirrer for 2-3 hrs. After the completion of

ISSN:0971-1260
Vol-22-Issue-37-December -2019

reaction (TLC), solvent was evaporated. The product was dried and crude was recrystallized to obtain light yellow powder (0.61gm, 88%), m.p. 166-168^{0}C, IR data (KBr, cm^{-1})C-CH_3 2969, C=O(keto) 1682, C=N 2360, C-O 1323, C=O(carboxylic) 1715.

Preparation (E)-methyl 2-((6-fluoro-4-oxo-4H-chromen-3-yl)methyleneamino)acetate

6 fluoro-3-formylchromone (0.5gm, 2.60 x 10^{-3} moles) was added with methyl 2-hydrazinylacetate (0.281gm, 3.1x 10^{-3} moles) in methanol (20ml) in RBF along with zincperchlorate (4-5gm) as catalyst. The reaction mixture is stirred on magnetic stirrer for 2-3 hrs. Progress of the reaction was monitored using TLC (chloroform: ethyl acetate). After the completion of reaction, solvent was evaporated. The product and crude was recrystallized to obtain a brown powder (0.56gm, 81%), m.p. 140-142^{0}C, IR data (KBr, cm^{-1}) C-F 1322, C=O (keto) 1646, C=N 2363, C-O 1261, C=O (carboxylic) 1691.

Preparation (E)-methyl 2-((6-bromo-4-oxo-4H-chromen-3-yl)methyleneamino)acetate

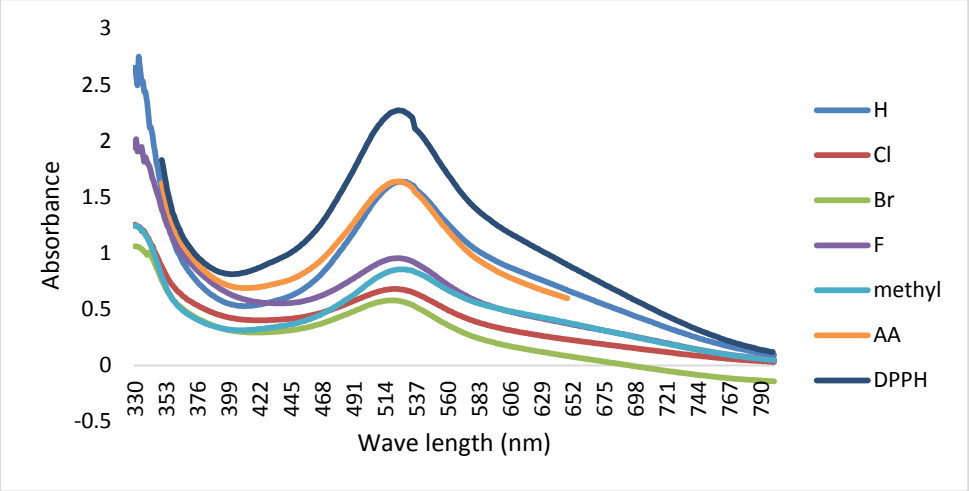
6-bromo-3-formylchromone (0.5gm, 1.97x 10^{-3} moles) was added with methyl 2-hydrazinylacetate (0.195gm, 2x 10^{-3} moles) in methanol (20ml) in RBF along with zincperchlorate (4-5gm) as catalyst. The reaction mixture was stirred on magnetic stirrer for 2-3 hrs. Progress of the reaction was monitored using TLC (chloroform: ethyl acetate). After the completion of reaction, solvent was evaporated. The product was dried and crude was recrystallized to obtain light brown powder (0.41gm, 64%), m.p. 160-162^{0}C , IR data (KBr, cm^{-1}) C=O(keto) 1683, C=N 2234, C-O 1087, C=O(carboxylic) 1640.

RESULT AND DISCUSSION

Antioxidant Studies

For the studies of the antioxidant behavior of chromone derivatives the DPPH assay is used. The chromone derivatives are mixed with the prepared DPPH solution at different concentrations of compounds 100ppm, 50ppm, 20ppm, and 10ppm dissolved in DMSO and acetonitrile respectively. A blank sample of DPPH is subjected to have absorption spectrum in UV-visible spectral range which is marked as control. And various absorption peaks were also recorded. In order to investigate radical quenching effect of chromone derivatives on DPPH sample. Firstly the DPPH sample was mixed with ascorbic acid solution with the concentration of 100ppm, 50ppm, 20ppm, and 10ppm. Also the absorption spectrum was recorded which clearly shows the effect of an antioxidant on DPPH. For studies chromone derivatives are reacted with DPPH at different concentrations for 30 mins incubation period. This reaction shows the change in the absorption behavior of DPPH, this indicates the antioxidant activity of chromone derivatives over DPPH. Differently substituted chromone derivatives at variable concertation were studied to establish the effect of change in concentration to radical scavenging activity.

ISSN:0971-1260
Vol-22-Issue-37-December -2019



Graph-1: Relative absorption behaviour of various chromone derivatives and their comparison with standard Ascorbic Acid solution

A complete study of absorption behaviour indicates a clear role of chrome derivative as an oxidants, where derivative with electron withdrawing group attached show a good radical scavenging activity due to presence more electronegative group which alters the overall scavenging activity. In order to study the role of chromone derivatives a comparative study was made with ascorbic acid which show a comparable radical scavenging activity.

Entry	10ppm	20ppm	50ppm	100ppm
3a	49.25	58.19	73.77	89.93
3b	68.45	73.56	89.46	91.86
3c	63.36	64.35	67.44	70.25
3d	65.17	76.67	88.49	94.93
3e	53.52	60.81	76.98	90.96
Ascorbic Acid	69.4	75.24	83.37	91.29

Table-2: Data for radical scavenging activity of various chromone derivatives with change of concentration

CONCLUSION

This investigation is based upon the synthesis of chromone derivatives by one of the best method which results into high yield. These chromone derivatives are synthesized in pure form and during methodology minimal purification was required. Antioxidant activity of these derivatives is increased

ISSN:0971-1260
Vol-22-Issue-37-December -2019

because of schiff base formation between chromone and methyl 2-hydrazinylacetate. These chromone derivatives have been evaluated for their antioxidant activities keeping a known antioxidant in a positive controli.e. ascorbic acid at different concentrations viz. 10ppm, 20ppm, 50ppm, 100ppm. Due to the presence of electron withdrawing groups attached to the chromone ring(such as fluoro, chloro, bromo) results in the increase ofantioxidant activity of these derivatives.

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