INVESTIGATIONS ON ANTIOXIDANT PROPERTIES OF THIOSEMICARBAZONE BASED SCHIFF BASES OF CHROMONE DERIVATIVES

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ABSTRACT:

Chromone based Schiff bases generated synthetically provides an easy access to the development of new precursors for the measurement of antioxidant activities where the important flavone derivative exhibits activities in lower concentration and indicates a role of structure-activity in control of antioxidant activities and prevention of damage due to free radicals generated.

Keywords: Chromone, Antioxidant, DPPH, Schiff Base, Radical Scavenging.

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INTRODUCTION

Naturally, occurring flavone derivatives are an important source of many significant biological activities, these include a variety of functions which affect the metabolism functions and other vital activities, these flavones are part of regular dietary components which have been taken up to control over various types of ailments occurring in the body.

Fig.-1

Chromone are known to be an integral part of flavone family, and act as basic backbone structure for various derivatives, these chromone possess significant activities such as antioxidants¹, adenosine receptor antagonists², mono-amine-oxidase inhibitor³, protein tyrosine kinase inhibitor⁴, antimalarial⁵, anti-fungal⁶, antiviral⁷, anti-giardial⁸, cytotoxic⁹, phosphoinositide-3-kinase inhibitor¹⁰, anti-erectile-dysfunction¹¹, anti-inflammatory¹², antiplatelet¹³, HIV-inhibitory¹⁴, selective estrogen receptor modulator¹⁵, anti-tumor/anti-proliferative¹⁶, anti-psychotic¹⁷, neuroprotective.¹⁸

With a continuous change of lifestyle and increased level of exposure to various types of pollutants, a continuous threat for the increase in the level of free radicals in the body is observed, which may lead to a number of ailments due to increased radical stress and damage to the cell. Over the years continuous efforts have been made to control the effect of free radicals generated or lower down the damage due to

free radicals. Chromone molecules provide a significant framework of structure which possess important properties for the control of free radical so generated in the body.

Chromone molecules tend to have control over the damage due to free radicals generated in the body by controlling generation of free radicals or quenching the free radical generated in the body or do not allow the free radical to cause oxidative damage. Various types of group which is attached to the parent ring structure of molecules tend to alter the level of activity which these molecules possess. A major factor responsible for the change in the properties is the extent up to which various active sites can get hold of free radicals and inhibit further growth or damage.

Radicals so generated in the living system can be classified as Superoxide ($O^{\cdot-}$), hydroxyl (OH), hydroperoxyl (HO_2), peroxy (ROO), alkoxy (RO) and nitric oxide ($NO^{\cdot}$), peroxy nitrate ($ONOO^{\cdot}$), nitrogen dioxide (NO_2), dinitrogen trioxide (N_2O_3). A continuous chain of free radical can be generated by a combination of one free radical with any molecule to neutralize themselves results in the liberation of another free radical resulting in liberation of large number of free radicals which may lead to aging-related diseases^{19,20}, cancer, arteriosclerosis and coronary heart disease and aging.^{21, 22}

Flavonoid antioxidants obtained from various types of natural resources act as scavengers by rapid donation of a hydrogen atom to radicals, radical scavenging activity of flavonoid is majorly dependent on electron donation and acceptance capacity. DPPH is widely accepted free radical source and it has been used to estimate the free radical scavenging ability of flavonoids²³ and to calculate the extent up to which radical activity can be controlled a respective compound.

Scheme-1: Scavenging of DPPH• (Free Radical) by a Flavonoid (Radical Scavenger).

The electron donation ability of flavonoids can be measured by the study of bleaching action on purple colored 2,2'-diphenyl-1-picrylhydrazyl radical (DPPH) solution. The study includes scavenging action of DPPH by addition of a radical species or antioxidant that leads to the change in color behavior of DPPH solution. The change so observed is proportional to the concentration and potency of the antioxidants. A measurable decrease in the absorbance behavior indicates significant free radical scavenging activity of the compound under test.²⁴

EXPERIMENTAL

An investigation carried was aimed around synthesis flavone derivatives bearing chromone nucleus by the reaction with thiosemicarbazone under catalytic conditions. The method for the synthesis has proven to be an efficient synthesis for the desired compounds in high yield, apart from basic characteristic of flavone nucleus and these molecules have the additional sites available for the interaction which may enhance the availability of π -electron around the chromone nucleus.

A typical reaction was carried over by the addition of respective 3-formylchromone derivative in methanol with thiosemicarbazone under anhydrous conditions using zinc perchlorate as catalyst, which resulted in the liberation of compound in quantitative yields, which were further used for carrying out investigations on radical scavenging activity.

General Procedure For Synthesis

To a stirred solution of respective 3-formylchromone (1.0eq) in dry methanol was added thiosemicarbazide (1.2eq) in the presence of $Zn(ClO_4)_2$ as a catalyst. The solution was continuously stirred at room temperature and progress was monitored using TLC. After the completion of reaction (TLC) the residual solvent was subjected to evaporation under reduced pressure to afford solid product which was triturated with diethyl ether to yield the pure product in quantitative yields.

(E)-1-((4-oxo-3,4-dihydro-2H-chromen-3-yl)methylene)thiosemicarbazide (5a)

Light yellow, 78 %, M. Pt. 176-178⁰ C, IR KBr 1091, 1344, 1521, 1545, 3356 cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ 7.53 (s, 1H, CH); 7.8-9.17 (m, 5H, Ar-H), 10.12 (s, 1H, NH), 11.55 (s, 2H, NH₂).

(E)-1-((6-chloro-4-oxo-3,4-dihydro-2H-chromen-3-yl)methylene)thiosemicarbazide (5b)

Yellow solid, 75 %, M. Pt. 174-176⁰ C, IR KBr 1089, 1344, 1460, 1521, 3350, cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ 7.73 (s, 1H, CH); 7.72-9.13 (m, 4H, Ar-H), 10.0 (s, 1H, NH), 11.57 (s, 2H, NH₂).

(E)-1-((6-bromo-4-oxo-3,4-dihydro-2H-chromen-3-yl)methylene)thiosemicarbazide (5c)

Yellow solid, 65 %, M. Pt. 169-172⁰ C, IR KBr 1090, 1340, 1460, 1519, 3350, cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ 7.00 (s, 1H, CH); 7.5-9.1 (m, 4H, Ar-H), 10.1 (s, 1H, NH), 11.55 (s, 2H, NH₂).

Scheme-2

(E)-1-((6-fluoro-4-oxo-3,4-dihydro-2H-chromen-3-yl)methylene)thiosemicarbazide (5d)

Yellowish orange solid, 75 %, M. Pt. 180-182⁰ C, IR KBr 1107, 1342, 1474, 1523, 3421, cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ 7.50 (s, 1H, CH), 7.75-9.2 (m, 4H, Ar-H), 10.1 (s, 1H, NH), 11.56 (s, 2H, NH₂).

(E)-1-((6-methyl-4-oxo-3,4-dihydro-2H-chromen-3-yl)methylene)thiosemicarbazide (5e)

Dark yellow solid, 82 %, M. Pt. 192-195⁰ C, IR KBr 1084, 1343, 1461, 1557, cm⁻¹, ¹H NMR (300 MHz, DMSO-d₆): δ 2.35 (s, 3H, CH₃), 7.00 (s, 1H, CH), 7.57-9.1 (m, 4H, Ar-H), 10.13 (s, 1H, NH), 11.56 (s, 2H, NH₂).

RESULTS AND DISCUSSION

Present investigations involving chromone nucleus were aimed around study off antioxidant behavior where the important chromone ring structure could exhibit significant results. For the study of antioxidant behavior Schiff bases involving chromone nucleus and thiosemicarbazone were synthesized under catalytic conditions using zinc perchlorate in anhydrous methanol. The major advantage of the process involves synthesis of Schiff bases in high yield with considerably high purity level which could be achieved without any further purification with chromatographic techniques. Final desired products so obtained were crystalized directly and characterized spectroscopically which indicates the synthesis of desired product with purity.

The products so synthesized were further used to carry out investigations involving the study of antioxidant behavior. Purified products were dissolved directly in DMSO. After obtaining a clear stock solution various dilutions (20, 50 and 100 ppm) were prepared using stock solutions and to make the dilutions by further addition of DMSO.

In order to study the antioxidant behavior of the compounds, each of the resulting solutions was mixed with DPPH solution and it was allowed to stand for 30 minutes in order to have completed quenching of free radical, the change in absorption behavior of DPPH solution was recorded with and without the addition of chromone derivatives. Upon the addition of chromone derivative solution to the DPPH it was observed that the solution show a significant change in the absorption behavior under UV radiations (UV-

spectrum recorded on Shimadzu UV-1800S double beam spectrophotometer using glass cuvette) and scavenging activity of each of the compound was calculated by:

$$\text{DPPH scavenged (\%)} = (A_{\text{con}} - A_{\text{test}}) / A_{\text{con}} * 100$$

Where,

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

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

A complete change in the absorption behavior was recorded using different concentrations of chromone derivative solution which have shown some of significant and encouraging results, a change in the absorption behavior and effect on radical scavenging activity is given in Fig.-2 and Table-1.

Fig.-2: Relative Absorption Behaviour of Various Chromone Derivatives (5a - E) And Their Comparison With DPPH And Ascorbic Acid Solution.

To further establish the role of chromone derivative towards the antioxidant behavior results so obtained were compared with a standard solution of ascorbic acid which is known to possess antioxidant properties. A comparative analysis of chromone derivation solution and ascorbic acid solution indicates a similar type of change in the absorption pattern of DPPH which suggests that these chromone derivatives participate actively in the radical scavenging activities which could be established by the change in change in the absorption behavior.

Table-1: Data for Radical Scavenging Activity of Various Chromone Derivatives At 10, 20, 50 And 100 Ppm

Entry	% Scavenging			
	10ppm	20ppm	50ppm	100ppm
5a	49.25	58.19	73.77	89.93
5b	68.45	73.56	89.46	91.86
5c	63.36	64.35	67.44	70.25
5d	65.17	76.67	88.49	94.93
5e	53.52	60.81	76.98	90.96
Ascorbic Acid	69.4	75.24	83.37	91.29

Fig.-3: Relative Absorption of the Compounds (5a – e and Ascorbic Acid) at Different Concentrations

A detailed investigation indicated that a significant radical scavenging can be observed with chromone derivatives at a concentration of 50 ppm, however a further increase in the concentration of solution does not result in significant change in the absorption behavior which is an indicator that these derivatives are significantly active in their lower concentrations where a significant radical scavenging activity can be obtained.

CONCLUSION

Present investigations provide access to understand the role of chromone derivatives in the scavenging activities of free radical using Schiff bases derived from chromone nucleus. The presence of various types of substituents effect the scavenging activities indicating the role of electron-donating and electron-withdrawing groups where it is observed that groups with higher electronegativity show good scavenging activity. These products could be easily synthesized by simple synthetic methodologies and could provide lead molecules for further investigations in order to study the role of flavone derivatives at molecular level.

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