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Assaying Antioxidant Activity of Xanthone Derivatives

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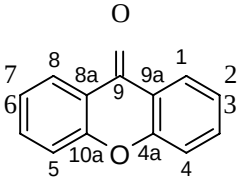
Abstract: *Xanthones are tricyclic dibenzopyrans with various physicochemical and pharmacological properties. As the xanthones obtained from extraction of natural products are relatively limited in the type and substituent's position, synthesis of xanthones derivatives become increasingly important. The present study deals with synthesis of different hydroxyl xanthones (1,6 dihydroxy xanthone, 1,3,8 trihydroxy xanthone, 1-hydroxy-6-(3-methyl-but-2-enyloxy)-xanthen-9- one, 1,8-dihydroxy-3-(3-methyl-but-2-enyloxy)xanthen-9-one and 1-hydroxy xanthione by condensation of substituted benzoic acid and polyhydric phenols like phloroglucinol in the presence of Eaton's reagent as a condensing agent. Substituted xanthone possess a wide range of biological activities such as hepatoprotective, anticancer, antifungal, antimicrobial and antioxidant activities. These compounds were screened for their antioxidant activity by two different methods namely, DPPH (Diphenyl picryl hydrazine) and Ferric chloride assay. All the xanthone derivative have shown good scavenging in DPPH assay as well as reduction of iron (III) in FeCl3 assay. The compound 1,3,8 trihydroxy xanthone was found to be the most active antioxidant agent. The main objective behind the synthesis and selecting these compounds was to study their biological activities as these class of xanthone derivatives are found to be important in various field of Pharmaceutical and chemical drug industries.*
Keywords: *Xanthones, Antioxidant, DPPH.*

I. Introduction

Xanthones are a class of heterocyclic compounds with simple three-membered ring that are mainly found as secondary metabolites in higher plants and microorganisms1. They are a class of yellow coloration heterocyclic organic compounds containing oxygen, with a molecular formula of C13H8O2. They have been classified into five groups: (a) simple oxygenated xanthones, (b) xanthone glycosides, (c) prenylated xanthones, (d) xanthonolignoids and (e) miscellaneous xanthones2. Chemically, xanthones have dibenzo-γ-pyrone as the basic skeleton. The general skeleton of xanthone comprises of a planar three membered ring structure as a backbone which consists of two benzene rings fused together through a carbonyl group and an oxygen atom. Both of these benzene rings are identical to each other, hence it imparts symmetry system in the structure. Due to the multiple double bonds on xanthone structure, there is limitation to free rotation and hence an increase in the rigidity of structure. This rigid framework imparts a tough stability which is capable to resist extreme high temperature while remains its integrity. The xanthone basic skeleton is numbered with carbons 1-4 being assigned as acetate-derived ring and carbon 5-8 assigned as shikimate-derived ring . The other carbon atoms are then being assigned as 4a, 10a, 8a, 9 and 9a for structure elucidation purposes.



Dibenzo-γ-pyrone

These xanthonic compounds show interesting biological activities and pharmacological importance associated with their tricyclic scaffold, depending on the nature and the position of different substituents4. The great interest on xanthones is mainly due to their abundance in nature and also their significant biological properties such as anti-microbial activities5, antithrombotic6, anti-inflammatory7, cytotoxic and anti-tumor properties3,8. In general, the two major sources of xanthone derivatives are synthesis and isolation from natural resources such as higher plants, lower fungi, and lichens9.

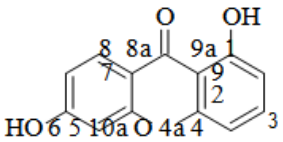
As the xanthones obtained from extraction of natural products are difficult to extract and substituent's position are different, synthesis of new xanthones have increased tremendously. Through synthetic methods, possibilities of new xanthones with different nature and position of substituent on the xanthone building block can be obtained. There are two synthetic ways used to synthesize new xanthones and its derivatives, which are biosynthesis and chemical synthesis. Biosynthesis involves enzymatic reactions in living organisms to produce various xanthone's derivatives from precursor units, while chemical synthesis involves catalytic reactions carried out in laboratory. In chemical synthesis, reaction of benzoic acid derivative with polyhydroxybenzene happens with cyclization to enable both the benzene rings to fuse together forming a tricyclic structure of xanthones.

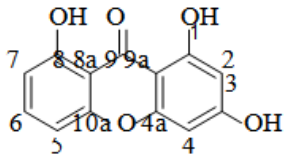
The synthesis of xanthone and substituted xanthones have been carried out by different methods. These compounds are generally synthesized by condensation of appropriately substituted benzoic acid and using phenols or condensation of substituted salicylic acids with benzene derivatives followed by cyclization of the intermediate compounds in sulfuric acid10 or PPA. However, these methods have some disadvantages such as low yields, long reaction times, the use of large amount of concentrated sulfuric acid, and lack of regiochemical control in the ring closure step. Moreover, some of these methods require two steps and are limited to specific benzoic acids or benzene derivatives having electron withdrawing groups and are not applicable to a large number of starting materials.

The present work deals with the synthesis of xanthone derivatives with hydroxyl and prenyl substitution using standard methods. They are,(1)1,6 dihydroxy xanthone12,(2) 1,3,8 trihydroxy xanthone13,(3) 1-hydroxy-6-(3-methyl-but-2-enyloxy)-xanthen-9-one12 (4) 1,8-dihydroxy-3-(3-methyl-but-2-enyloxy)-xanthen-9-one11 and (5) 1-hydroxy xanthione14. Substituted xanthone possess a wide range of biological activities, it was found that these hydroxyxanthones and their derivatives are found to be good antioxidant, antimicrobial and hepatoprotective active15. These compounds were screened for their antioxidant activity by two different methods namely, (1) DPPH (Diphenyl picryl hydrazine), (2) Ferric chloride assay. They were also found to have antimicrobial and hepatoprotective activity .

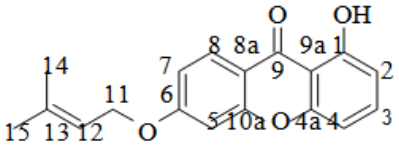
Xanthones are also known to possess antioxidant property. So with the view to extend our approach to screen the biological activities of the synthesized compounds, some representative examples (A-E) were screened for their antioxidant potentials. The synthesized compounds along with their structures are given below.(Structures from A to E).

Scheme I :Structures of (A-E

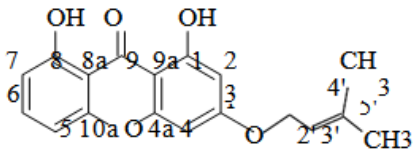




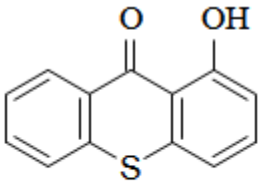
(A) 1, 6-dihydroxyxanthone (B)1,3,8-trihydroxyxanthone



(C) 1-hydroxy-6-(3-methyl-but-2-enyloxy)-xanthen-9-one



(D) 1, 8-dihydroxy-3-(3-methyl-but-2-enyloxy)- xanthen-9-one



1-hydroxyxanthione

II. Experimental Section

All the chemicals and reagents used were of analytical or reagent grade and were not additionally purified. The standard method were used for the preparation of hydroxyl xanthones is the reaction between substituted benzoic acid, Salicylic acid and various types of phenols. In the present work the synthesis of 1,6-Dihydroxyxanthone and 1,3,8-trihydroxyxanthone were carried out from 2,6-dihydroxybenzoic acid and Eaton's reagent. 1-hydroxy-6-(3-methyl-but-2-enyloxy)-xanthen-9-one and 1,8-dihydroxy-3-(3-methyl-but-2-enyloxy)- xanthen-9-one were synthesized using 1,6-Dihydroxyxanthone and 1,3,8-trihydroxyxanthone and The synthesized compound have been characterized and confirmed by IR, NMR and TLC analysis. These compounds were screened for their antioxidant activity by two different methods namely, (1) DPPH (Diphenyl picryl hydrazine), (2) Ferric chloride assay.The free radical scavenging capacity of different xanthone compounds synthesized earlier was tested by its ability to bleach or scavenge the stable DPPH· radical16

DPPH free radical scavenging activity

The free radical scavenging effects were carried out with the test compounds (A-E) by the DPPH assay. DPPH radical scavenging ability is widely used as an index to evaluate the antioxidant potential of medicinal plants. The free radical scavenging of compounds was determined by the method of Blois.M.S17. In its radical form, DPPH absorbs at 517 nm, but upon reduction by an antioxidant or a radical species its absorption decreases. Briefly, 0.1 mM solution of DPPH in methanol was prepared and 4 ml of this solution was added to the test tube containing 1 ml of sample solutions in DMSO at different concentrations (100,200,300,400,500

□g/ ml). Thirty minutes later after incubation at room temperature, the absorbance was measured at 517 nm. The absorbance of the similar reaction mixtures of methanol or methanol: water (1:1) (without test compounds) with DPPH served as control. (Corrected Absorbance of the DPPH with added blank - 0.405)

FeCl3 assay

The Fe+++ reducing power of the test drugs (A-E) was determined according to the method of Ganesan. et. Al18. Different concentrations (250, 500, 1000 µg/ml) of the samples were prepared in DMSO. 1 ml of these solutions was mixed with 2.5 ml of phosphate buffer (0.2 M, pH- 6.6) and 2.5 ml of potassium ferricyanide (1

%). Reaction mixture was incubated at 500C for 20 min. After incubation, 2.5 ml of trichloroacetic acid (10%) was added and centrifuged (650g) for 10 min. From the upper layer, 2.5 ml solution was mixed with 2.5 ml distilled water and 0.5 ml FeCl3 (0.1% w/v in water). Appropriate blank control was maintained containing the solvent DMSO. Absorbance of all the sample solutions was measured at 700 nm. The absorbance of the similar reaction mixtures without test compounds served as control. Increased absorbance indicated increased reducing power.

III. Results And Discussion

The in vitro tests carried out with the test drugs (A- E) showed significant antioxidant activity. From the percentage DPPH· free radical scavenging values, it was found that the xanthone compound B was the most potent scavenger followed by xanthone compound A,D,C and E at different concentration. However at 100

□g/ml concentration the xanthone compound E was a good scavenger than xanthone compound A but, at 500

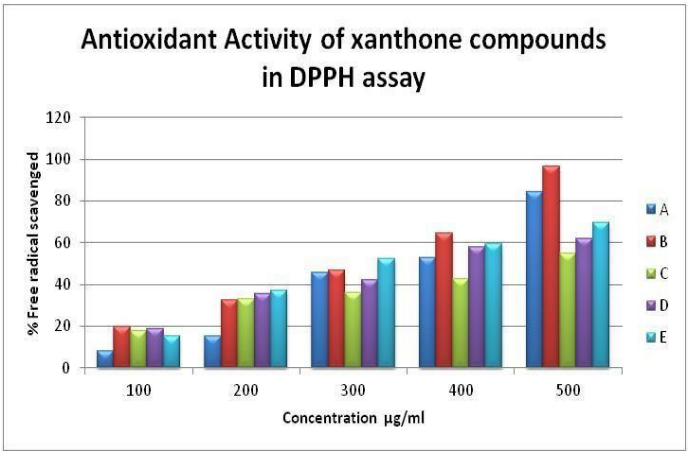
□g/ ml xanthone compound B was more effective as compared to other compounds.

From the percentage scavenging values in FeCl3 assay, it was found that the xanthone compounds C and E were the most effective at reducing the iron (III) at 300 and 200 □g/ml respectively,followed by xanthone compound D at 500 □g/ ml concentration.

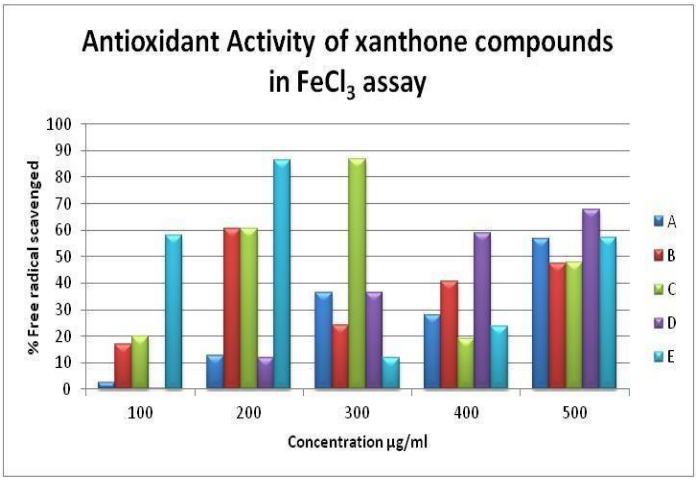
IV. Conclusion

The antioxidant for all the compounds was investigated. All the compounds xanthone derivative (A-E) have shown good scavenging in DPPH assay as well as reduction of iron (III) in FeCl3 assay. The compound B was found to be the most active antioxidant agent. The benefits of antioxidants have been the subject of thousands of studies in recent years due to their possible role in preventing heart disease, cancer and other illnesses.

Antioxidant activity of Xanthone compounds in DPPH assay



Antioxidant activity of Xanthone compounds in FeCl3 assay



Acknowledgments

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