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A REVIEW ON AURONES AND THEIR DERIVATIVES AS A RELIABLE THERAPEUTIC AGENT

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ABSTRACT

Aurones constitute a subclass of flavonoids which occur rarely distributed in nature. Chemically, aurones are (*Z*)-2-benzylidenebenzofuran-3(2H)-ones, exhibit a strong and broad variety of biological activities. Like antifungal, antifeedant, tyrosinase inhibitors, anticancer agent, antimicrobial, antiparasitic, and antioxidants. They are the less common representatives of a flavonoid subclass and not widely exploited. In this review, an attempt has been made to study various novel biological activities and structure activity relationships of several naturally occurring aurones and their synthetic derivatives as a potent lead compound for establish therapeutically active molecules with high efficiency and less severe side effects.

KEYWORDS: Flavonoids, Aurones, Antifungal, Anticancer, Antioxidant.

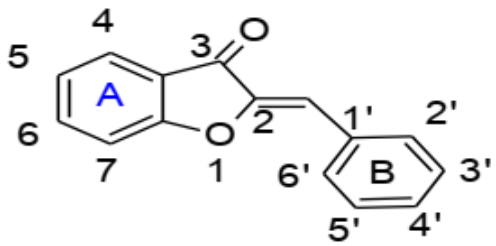
1. INTRODUCTION

Aurones, or (Z)-2-benzylidenebenzofuran-3-(2H)-ones, are naturally occurring flavonoids with great biological potential, also called as anthochlor pigments. Approximately 100 aurones have been reported from natural sources, mainly flowering plants, and a few ferns, mosses and marine brown algae. They are responsible for pigmentation of some flowers and fruits and contribute especially to the bright yellow colour of flowers such as snapdragon, cosmos and dahlia.[1] Aurones function as phytoalexins against infections also exhibit a strong and broad variety of biological activities such as antifungal agents[3], as insect antifeedant agents[4], as inhibitors of tyrosinase[5], and as antioxidants.[6] Aurones are obtained from chalcones by aurone synthase as well as through the biosynthesis of other flavonoid.[2]

Some naturally occurring aurones are aureusidin, sulfuretin and maritimetin, possessing various hydroxylation patterns. A few natural aurones bearing methoxy substituents on either or both rings have been reported. The spectrum of biological activity of this class of compounds has not been extensively studied. However, the existing data on the bioactivity of natural and synthetic aurones is very promising, thus these heterocyclic compounds can be considered as an attractive scaffold for drug design and development.[6,7,8]

2. Chemistry of Aurones

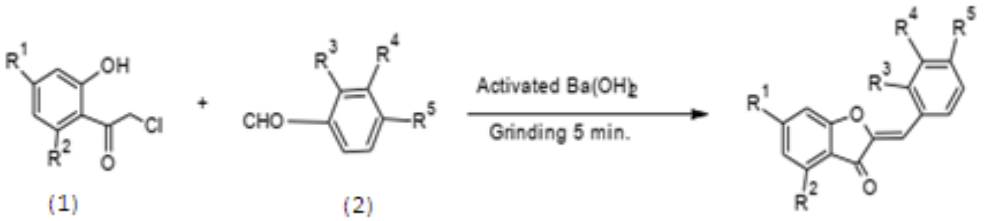
Aurones consist of a heterocyclic nucleus, in which the furan ring on fusion with benzene gives benzofuran. A benzylidene group is attached to the second position of benzofuran nucleus on the second carbon atom, and a carbonyl group is present on third position. A double bond is present between second carbon atom and phenylidene ring system. Most of the naturally occurring aurones possess free hydroxyl group substituents on both ring A and ring B, which is found to be responsible for its activity.[9]



aurone

3. Synthesis of aurones

An efficient and eco-friendly approach for the synthesis of aurones including hydroxyaurones and their methyl ethers has been achieved directly from substituted 2-hydroxyphenacylchloride[1] in a single pot just by grinding with aryl aldehydes[2] using activated barium hydroxide as solid base.[9]



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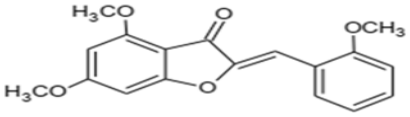
4. Pharmacological Activities of Aurones

4.1. Aurones as antiparasitic agents

4,6-dimethoxy-2-(2'-methoxy benzylidene) benzofuran-3-one [3] is a potent anti-leishmanial aurone derivative which is found to be toxic to *Leishmania infantum;* an organism responsible for leishmaniasis and shows cytotoxicity against human THP1-differentiated macrophages.[10]

4, 6-dimethoxy-2-(4' ethyl benzylidene)-benzofuran [4] is an antimalarial aurone derivative possess ability to kill *Plasmodium* species.[11]



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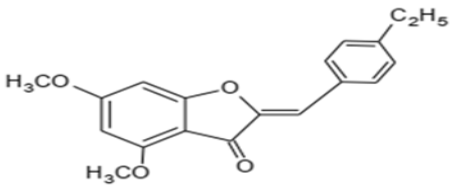

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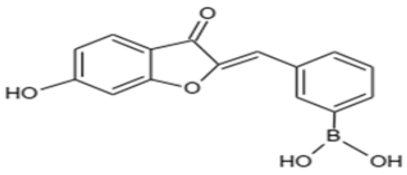
4.2. Aurones as antimicrobial agents

The antitubercular activity of boronic aurone was found to be due to its selective action towards the extracellular antigen 85 responsible for mycolation activity and protection of cell wall of *Mycobacterium tuberculi*. 6-hydroxy-boronic aurone is a potent anti-tubercular compound [5].[12]

Another one 4, 5-dimethoxy-2, 2-(dipyrolidinyl)-benzofuranone [6] was found to be an anti-fungal compound.[11]



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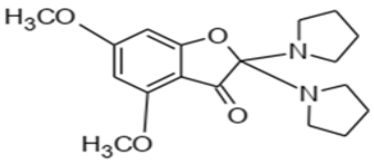

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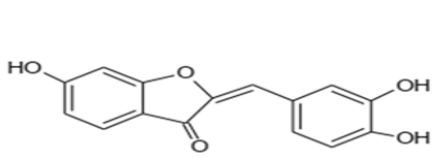
4.3. Aurones as anti-viral agents

Sulfuretin[7], a naturally found aurone shows neuraminidase inhibiting activity thus possess activity against influenza virus.[13] 6-hydroxy-2-(N-butyl indolidene)-benzofuranone [8], and about six other aurone derivatives shown potent inhibitory activity on Hepatitis C virus RNA-dependent RNA polymerase; thus can be used to treat hepatitis.[12]



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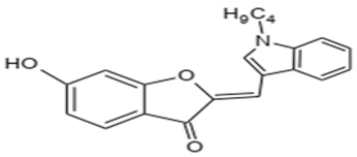

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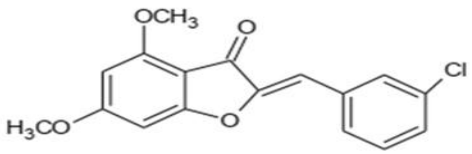
4.4. Aurones as anti-cancer agents

4, 6-dimethoxy-2-(3'-chlorobenzylidene)-benzofuranone [9] have been effective in treatment of breast cancer; since they were able to target ABCG2 (ATP – binding cassette sub – family G member 2), an ABC protein transporter responsible for the breast cancer multidrug resistance mechanism.[14]

A series of 4'–substituted 5–hydroxyaurone derivatives were studied regarding their ability to inhibit cell motility and angiogenesis, two processes implicated in cancer cell invasion and metastasis development, and trimethoxy-3'-hydroxy-4'-methoxy aurone [10] was found to be effective in buccal cancer. Both are not harmful to normal human cells.[11]



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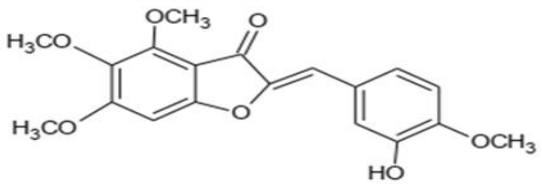

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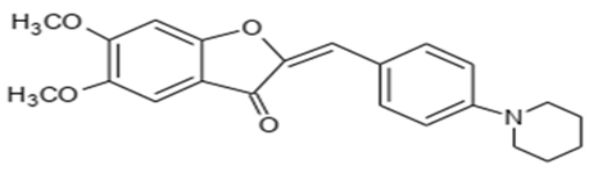
4.5 Aurones as Acetyl choline esterase inhibitor

Some aurone derivatives including, 5, 6-dimethoxy-2-(4'-pyperidyl benzylidene)-benzofuranone [11] were found to be effective as acetylcholine esterase inhibitor, hence have a significant role in development of effective drug for treatment of Alzheimer's disease.[11]



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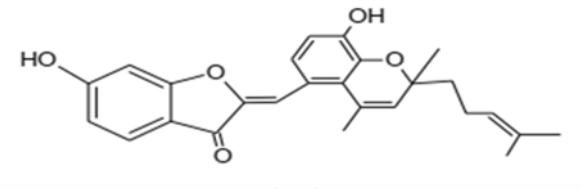
4.6 Aurones as antioxidant

Aurones present in nature are phytoalexins; responsible for the protection of plant from metabolic wastes such as free radicals; involved in tissue damage in plants as well as in

human being; responsible for several pathological conditions ranging from mild inflammation to severe cancers. All aurones and their derivatives possess antioxidant activity and free radicals scavenging activity.[6]

Eg: Compound [12] shows antioxidant activity.



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5. Structure activity relationship

Antileishmanial activity: The most active and one of the less toxic compound 2',4,6-trimethoxy aurone bears a methoxy group exhibit potent antileishmanial activity. Changing electron donating methoxy group on the same position exhibit comparable antileishmanial activity but slightly higher toxicity. When position 2' is occupied by electron withdrawing Cl atom, antiparasitic activity is substantially lower, whereas compound is nontoxic to mammalian cell. When it is unsubstituted, possess significant antileishmanial activity although lower than substituted.[14,15,16]

Antioxidant activity: Some of the aurones are moderate to good DPPH radical (1, 1-diphenyl-2-picryl-hydrazyl radical) scavenger, with exception of aureusidin and aurone subtituted with a methoxy group on C3', which exhibit scavenging activity. Although both have different lipopphilicity. Aurones which doesnot bear methoxy group on ring A are more active. The electron withdrawing or donating group is not important for this type of activity. Among aurones bearing(–OCH3 on C3' and C4') and (–OCH3 on C4 and C6 and –CH3 on C4') respectively, showed highest Superoxide anion scavenging activity.[8,11]

Anti-inflammatory Activity: Aurones obtained from Bidensparviflora wild shows inhibitory effect on histamine release from rat peritonial exudate cells induced by antigen-antibody reaction. Hydroxy functional group at C6 is important to decrease synthesis of PGE2. Methoxy group on ring A are useful to reduce the production of NO. Presence of double bond between C2 and C3, and carbonyl group at C4 are essential for anti-histaminic action. Free

hydroxyl groups are also necessary. Presence of two ortho-hydroxyl group at C3' and C4' produces a greater inhibition of histamine release.[17]

6. CONCLUSION

Aurones are the important type of flavanoid, responsible for the bright yellow colour of flower. Present study highlights the structural activity relationships of several nature derived aurones and their synthetic derivatives for their exhibiting biological activity. The aurones exhibit anticancer activity, antiinflammatory, antiviral, antioxidant and antimicrobial properties. Aurones shows with three methoxy substituent on position 2', 4, 6 is found to possess potent potent antiparasitic activity including anti-leishmanial activity, anti-malarial activity. In almost all studies Aurones are identified as a lead compound. Hence their significance in therapeutics proves the eligibility and reliability of Aurones and their derivatives.

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