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# SYNTHESIS OF A BIOLOGICALLY PERTINENT MOLECULE, AURONES –AN EXTENSIVE REVIEW

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**ABSTRACT**
Aurones and its derivatives constitute a class of heterocyclic compounds which add a new dimension in drug development containing benzofuranone molecule. Aurones have been isolated from various natural sources and have been reported for their potent Anticancer, antidiabetic, anti-inflammatory activities Chemists were inspired by the unique properties of Aurones to develop various derivatives of aurone and assess their potential biological pertinence. In this review we have compiled and discussed several methods by which aurones and its derivatives can be chemically synthesized, in an effort to pave the way for a medicinal chemist for a comprehensive and target oriented information for development in this promising area of research.

**KEYWORDS:** Aurones, benzofuranone, Anticancer, antidiabetic.

## INTRODUCTION

Flavonoids representing a large class of natural products in the plant kingdom, exhibits numerous biological activities. Aurones, structurally isomeric compounds of flavanoids are also widely distributed in nature. Aurones play an important role in the pigmentation of some flowers and fruits and contribute especially to the bright yellow color of flowers. They also exhibit enormous of biological activities such as anticancer, antidiabetic, anti-inflammatory, antifungal agents, as insect anti-feedant agents, as inhibitors of tyrosinase, and as antioxidants. Aurones chemically, (Z)-2- benzylidene-benzofuran-3(2H)-ones, are one of the less common and lesser-known representatives of a flavonoid subclass. Which probably may be the reason why they have received little attention in comparison to the structurally similar and widely investigated flavones and isoflavones.

The following sections in this review provides the information of about the methods which can be employed to synthesize Aurones derivatives.

### Chemical and biosynthesis of Aurones

Shimokoriyama *et al.* expect an enzymatic interconversion of chalcones to aurones based on the structural and distribution similarity between the both glycosides led. Later the biosynthesis of a polyhydroxyaurone, aureusidin, from a chalcone, in Antirrhinum majus (snapdragon) was elucidated by the involvement of the enzyme, aureusidin synthase. 3',4'-dihydroxy and 3',4',5'-trihydroxyaurone were the only compounds which were associated with the biosynthetic pathway. The mechanisms of the biosynthesis of aurones from chalcones inspired the chemists, to adapt the biosynthesis pathways to the chemical synthesis in laboratory.

In this review we have discussed the novel methods and mechanisms for the synthesis of aurones which are followed till date.

### 1. Synthesis of Aurones by oxidative cyclization of Chalcones

Aurones can be synthesised by oxidative cyclization of Chalcones using various conditions using mercury acetate, copper (II) bromide, tetrabutylammonium tribromide or Hydrogen peroxide with solvents such as Pyridine, DMSO, KOH respectively.as given in the scheme 1.[1-4,9,13,15,16,18,19]

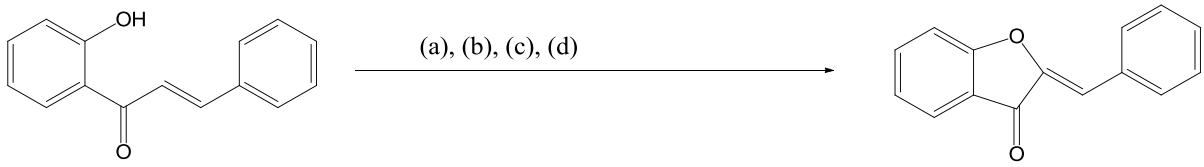
Method 1: As part of this procedure, to a molar amount of mercury (II) acetate in cold pyridine with 2'-hydroxychalcone is refluxed for 3-4 hours. Then the reaction is cooled, treated with diluted HCl, which is then diluted with ice-cold water. Recrystallization leads to the pure Z-isomer of aurone.

Method 2: Few milligram of Copper (II) Bromide in Dimethyl sulfoxide and 2-hydroxychalcones is reflexed

for about 60 to 90 min, and cooled with water. Filtration and recrystallization in EtOH yields the desired aurones.

Method 3:

Method 4: 2'-hydroxychalcone oxidizes in the presence of alkaline hydrogen peroxide forms epoxides as intermediate, which on α attach yields Aurones. This reaction is known as Algar, Flynn and Oyamada (AFO) reaction.[17]




Scheme 1 Reagents: (a) $Hg(OAc)_2$ ,Pyridine , (b) $CuBr_2$, DMSO , (c) TBATB, KOH , (d) $H_2O_2$/OH , Methanol

**2. Synthesis of Aurones by Aldolisation of 3-benzofuranone with benzaldehye.**

Aurones can be synthesised by Aldolisation or chronotization of 3-Benzofuranone with benzaldehyde on refluxing with solvents such as potassium hydroxide and methanol, hydrochloric acid and acetic Acid, Sodium hydroxide and sodium methoxide, Chloroform and aluminium trioxide.

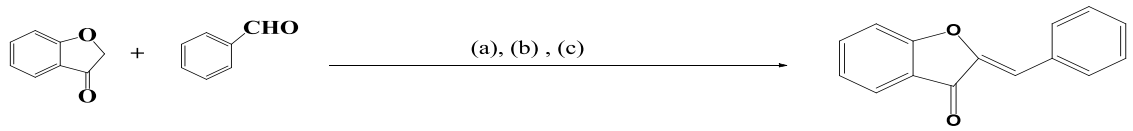
Method 5: To a solution of 3-benzofuranone and benzaldehyde in ethanol, potassium hydroxide is added at room temperature. The reaction mixture is stirred for 2 hrs and cooled in refrigerator overnight. The resulting solid is filtered off, washed with cold water and recrystallized from ethanol to get aurones (Scheme-2).[10]

Method 6: Condensation of benzofurones with α, α, α -trifluoro-p-tolualdehyde in the presence of excess NaOH in H2O/EtOH yields aurones (Scheme-2).[11]

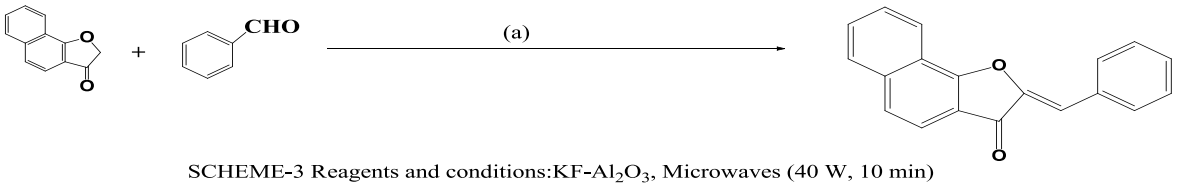
Method 7: Aluminium oxide is added to a solution of benzofuranone and benzaldehyde in $CH_2Cl_2$. The mixture is thoroughly stirred for 6 hours under exclusion of light. The suspension obtained is filtered off, the residue washed with $CH_2Cl_2$, and the washes are combined with the filtrate. The solvent is evaporated and the residue is recrystallized from $CH_2Cl_2$/MeOH (Scheme-2).[14]

Method 8: 3(2)-naphthofuranone with basic catalyst potassium fluoride with alumina on moderate microwave focused irradiation of microwaves (10 min, 40 W) leads to formation of aurones (Scheme-3).[12]

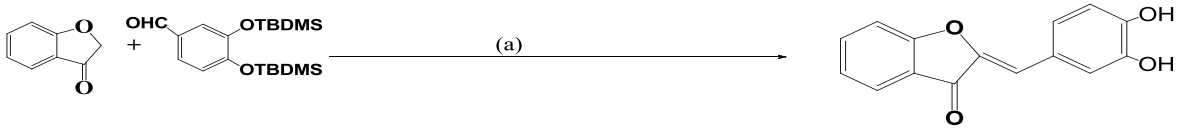
Method 9: tert-butyldimethylsilyl protected benzaldehyde is condensed with benzofuranone in the presence of neutral alumina, further treatment with tetra-butylammonium fluoride affords the deprotected aurone (Scheme-4).[18, 19]




SCHEME-2 Reagents: (a)KOH, Ethanol, (b)a,a,a -trifluoro-p-tolualdehyde , NaOH in $H_2O$/EtOH, (c) $Al_2O_3$, $CH_2Cl_2$



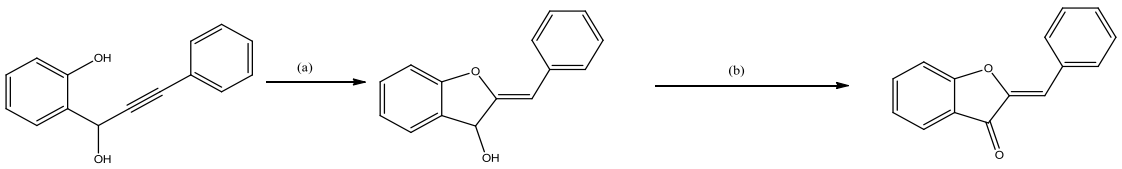

SCHEME-3 Reagents and conditions:KF-$Al_2O_3$, Microwaves (40 W, 10 min)




SCHEME-4 Reagents and conditions:(a) $Al_2O_3$, DCM, rt, overnight, to remove TBDMS TBAF, DCM,rt, 30 min.

**3. Synthesis of Aurones using a gold(I)- catalysed cyclisation of 2-(1-hydroxy-3-arylprop-2-ynyl) phenols**

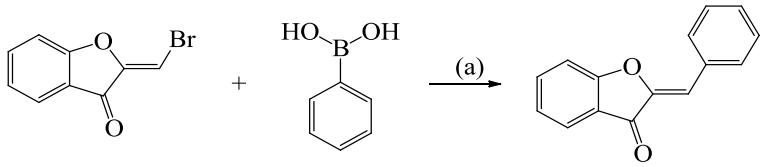
Addition of 2 equivalents of lithium arylacetylides, with or without substituents to 2-(1-hydroxy-3-arylprop-2-ynyl) phenols, at low temperature in THF yields several substituted salicylaldehydes. The propynol obtained in the presence of combination of gold(I)chloride and potassium carbonate undergoes cyclisation to form arylidene alcohol. Oxidation of the corresponding with $MnO_2$ yields respective aurones (Scheme-5).[18]




Scheme-5 Reagents and conditions: (a) Gold (I) catalyst , MeCN, rt , (b) $MnO_2$,$CH_2Cl_2$, rt, 1hr

**4. Synthesis of Aurones by Suzuki coupling**

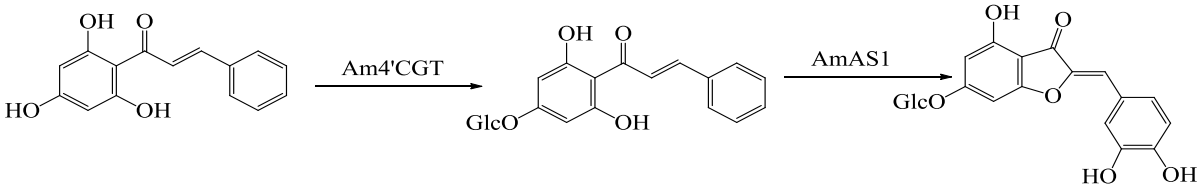
Suzuki coupling with phenyl boronic acid provides aurones. The Suzuki reaction is more commonly conducted with aryl bromides or iodides than with chlorides (Scheme-6).[18]




Scheme-6 Reagents and conditions: (a) $Pd(PPh_3)_4$ (5 mol%) , $K_2CO_3$, DMF Dioxane, rt-90° C

**5. Aurone Biosynthesis**

In transgenic flowers, the co-expression of Antirrhinum majus chalcone 4'-O-glucosyltransferase (Am4'CGT) in the cytoplasm and A. majus aureusidin synthase (AmAS1) in the vacuole combines with down-regulation of anthocyanin biosynthesis by RNA interference (RNAi) which results in yellow flowers. These enzymes produces aureusidin 6-O-glucoside via a 2',4',6',4-tetrahydroxychalcone 4'-O-glucoside. The chalcones are 4'-O-glucosylated in the cytoplasm, their 4'-O-glucosides are transported to the vacuole, and enzymatically converted to aurone 6-O-glucosides. Chalcones are found throughout the plant kingdom, the generation of yellow flowers is by production of aureusidin 6- O-glucoside which may be widely applicable to most plant species producing chalcones (Scheme-7).[18]

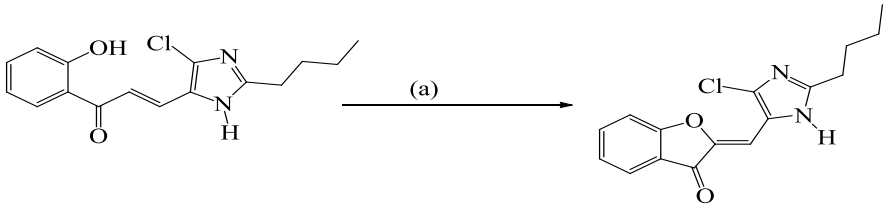



Scheme-7 Biosynthetic pathway for aurone synthesis

**6. Synthesis of Aurones containing imidazole moiety by the oxidation of 2'-hydroxy Chalcones with mercuric (II) acetate in polyethylene glycol (PEG-400)**

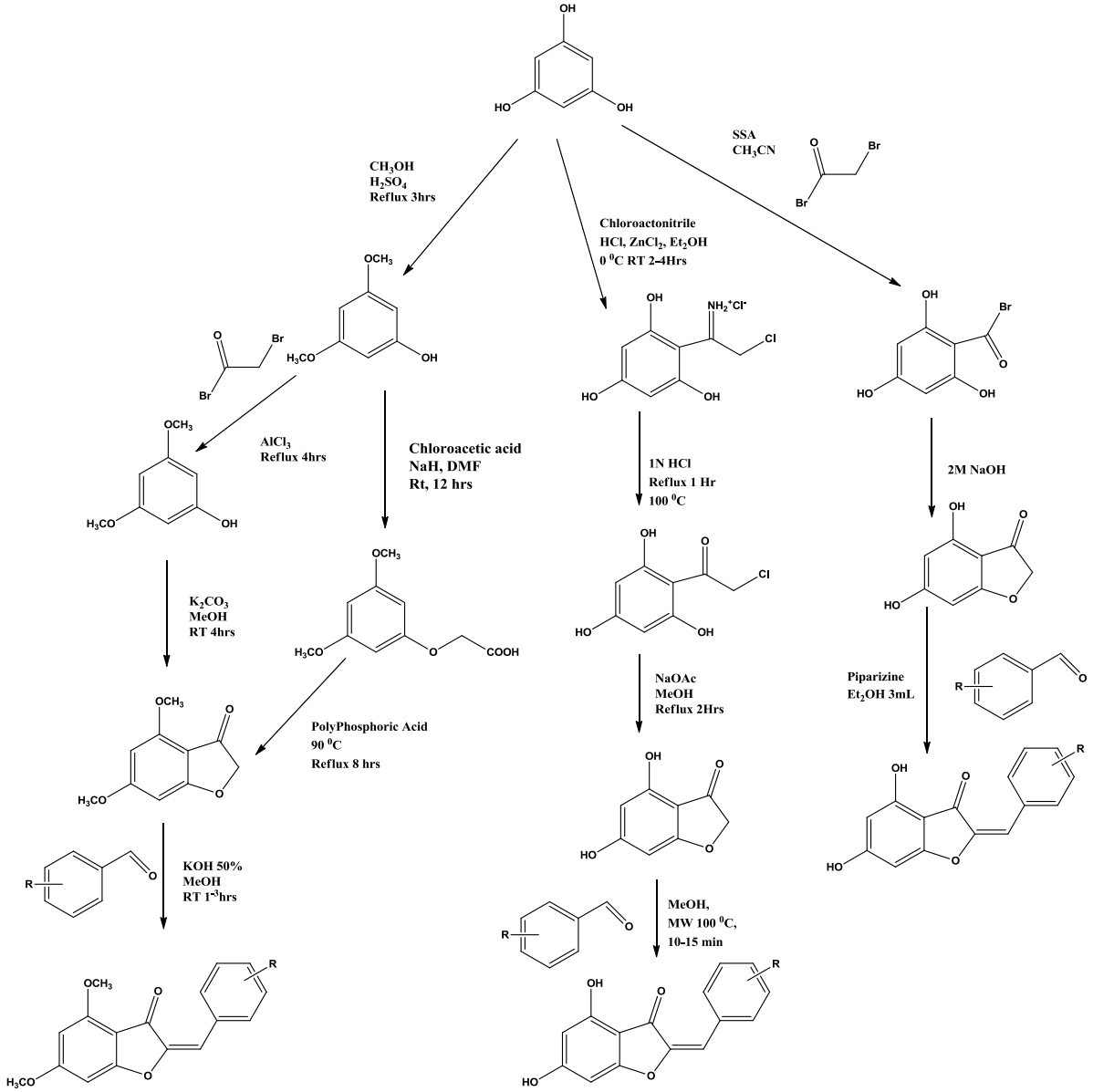
An equimolar mixture of substituted 2-hydroxy acetophenone, 2-butyl-4-chloro-5-formyl-imidazole and KOH is stirred in polyethylene glycol (PEG-400) at 40 °C for 1 hour provides substituted-benzofuran-3-ones, ice cold water is added to the crude mixture. Product separated out is filtered and crystallized from ethanol to give pure yellow crystalline product of substituted 2'-hydroxy chalcones. Filtrate is then evaporated to remove water leaving PEG behind.

An equimolar mixture of substituted 2'-hydroxy chalcones, and mercuric (II) acetate are dissolved in polyethylene glycol (PEG-400) and is refluxed at 120-130 °C for 2 hrs, ice cold water is added to the crude mixture. The solution is acidified with 2-3 drops of dilute HCl. Separate the residue, filter dry and recrystallize from acetic acid to give the pure corresponding Aurones containing imidazole moiety (Scheme-8).[5]




Scheme-8 Reagents and conditions: (a) $Hg(OAC)_2$/PEG-400, reflux 120-130° C

**7. Synthesis if aurones using Pluroglucinol as initial reactant**




**Therapeutic Potential of Aurones**

Aurones being a class of flavonoids have been and are being investigated in different therapeutic areas. The structural similarity existing between aurones, chalcones and flavones has led to the investigation of aurones on the biological activities that have been reported for various flavonoids subclasses. They were investigated for their antioxidant activities and cancer chemoprevention, antihepatitis, antimicrobial and antiviral activities, antifungal, anti-inflammatory activities, antithyroxinase activity, diagnosis tools and treatment of Alzheimer's disease, anti-diabetic and anti-obesity activities.[20-28]

**CONCLUSION**

The therapeutic potential of aurones is wide and promising and henceforth the above reviewed methods of synthesis would serve as a support for the development of a potent anticancer drug design with aurone as the basic ring. Various modifications can be done in the rings and different positions of the above class of flavonoids to improve its activity with decreased dosage and in turn reduce the dose related side-effects.

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