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Review Article

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Synthesis and biological activities of aurones: A Review

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ABSTRACT

This review highlights the recently synthesized aurone derivatives by different synthetic methods which include green methods and microwave assisted synthesis. One of the advantages of using synthetic strategies as compared to natural product isolation is they can be obtained in high yields. The important biological activities of these synthesized derivatives such as antioxidant, antibacterial, antiplasmodial, antiviral, antimalarial, antiflammatory are also been discussed.

***Key words**: Antibacterial, Antiplasmodial, Antiviral, Antimalarial, Antiflammatory*

INTRODUCTION

Aurones (2-benzelidene benzofuran-3(2H)-ones) are natural compound and are structural isomers of flavones. Aurones are biogenetically related to chalcone and plays important role in yellow coloration of some flower petals[1].Recent investigation have shown that these compound have good biological activities and are better than flavones and chalcones[2]. One of the important objectives of organic and medicinal chemistry is to design, synthesize and produce molecules that have potential as human therapeutic agents. Flavonoids comprise almost of more than 400 higher plant secondary metabolites[3]. Flavonoids other than chalcones, aurones, isoflavones possess the same basic skeleton, a flavanone nucleus containing two hexacarbonic aromatic rings formed by fifteen atoms of carbon(A and B) interconnected with an heterocycle C composed of three carbon atoms and one oxygen atom. This nucleus can undergo many changes such as hydroxylation, alkylation or glycosylation. Depending on these changes the flavonoids are classified into 9 groups viz. chalcones, aurones, flavanones, dihydroflavanols, anthocyans, flavonols and flavanols. Compounds belonging to the same group differ amongst them by the degree and the position of hydroxylation, the presence of substitute on the nucleus and the state of their polymerization. One of the important functions of flavonoids is to render coloration to the plants other than that flavonoids can act as enzyme and microbial inhibitors, chelating agents, protection against UV, and free radicals etc. In addition, flavonoids are biologically relevant as analgesic, anti-inflammatory, antiallergic, and protectors against cardiovascular diseases. These properties are assigned mainly due to their antioxidant activity based on their structure[4].Many flavonoids are identified as water soluble flower pigments. On the basis of their color, flavonoids pigments have been classified into two groups: the red-blue anthocyanin's and yellow anthoxanthins.

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Aurones are a class of flavonoids called anthochlor pigments and occurs rarely in nature. It is present in fruits and flowers where they act as phytoalexins against infections and gives contribution to yellow pigmentation of plant parts[3]. Aurones contribute to bright yellow coloration of flowers of some well known ornamental plants such as Snapdragon and Cosmos. Aurones (2-benzylidenebenzofuran-3(2H)-ones) exist as two isomers with (E) and (Z) configuration. Most of the aurones are in (Z)-configuration, which is a more stable configuration according to Austine Model 1 computation, but there are few aurones with (E) configuration[5]. In aurones the benzofuran is linked with benzylidene and chalcone like group closed into a 5-membered ring.

The general structure of aurone is described in Figure 1:

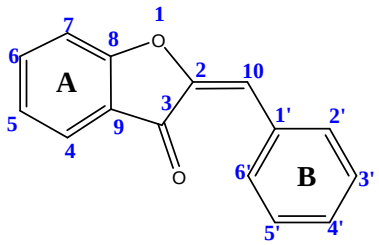

Fig. 1: General structure of aurone

In plant aurones are synthesized from chalcones by oxidation, cyclization and reaarangement involving the enzyme aureusidin synthase[6]. Aureusidin, Sulfuretin and Maritimetin are examples of naturally occurring aurone[7].

The synthetic and natural derivatives of aurones form an interesting and significant group of molecules as they possess a wide range of biological activities such as antioxidant, antibacterial, antiplasmodial, antiviral, antimalarial, antiflammatory etc. Aurones have also been reported to possess insect antifeedant, antiparasitic, antileishmanial, antifungal, inhibitory activities[7]. Aurones can be used as potential cancer chemotherapy agents and as inhibitors of an enzyme involved in the metabolism of thyroid hormones. They have also been reported to be antiproliferative agents, tyrosinase inhibitors, and have been developed as potential amyloid imaging agent which is useful for detecting β-amyloid plaques in Alzheimer's disease[3].

Synthesis:

There are many known methods for the synthesis of aurones and can be classified based on the use of different reactants as follows:

Green synthetic routes:

Microwave reactions:

Microwave-assisted synthesis of aurone in which 3-bromochromone treated with solution of 1-benzylpiperazine and potassium t-butoxide with DMF have been reported by Wei Huang[8].

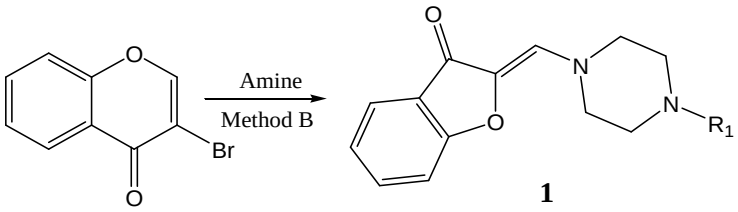

Fig. 2: Microwave-assisted synthesis of aurone; Method : Potassium t-butoxide, DMF, 70^0 C, MW 120 W.

Synthesis of new series of aurone by aldol condensation of N-(Un)substituted quinolone-3-carbaldehyde and unsubstituted benzofuran-3-(2H)-ones by microwave irradiation method was introduced by Hardik Jardosh[9].

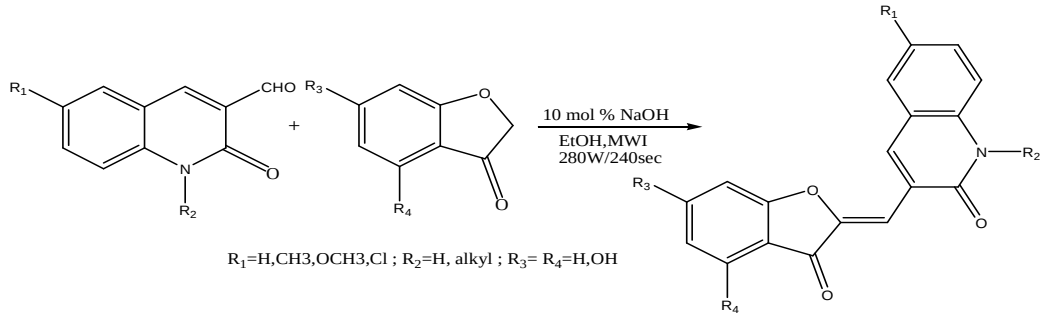

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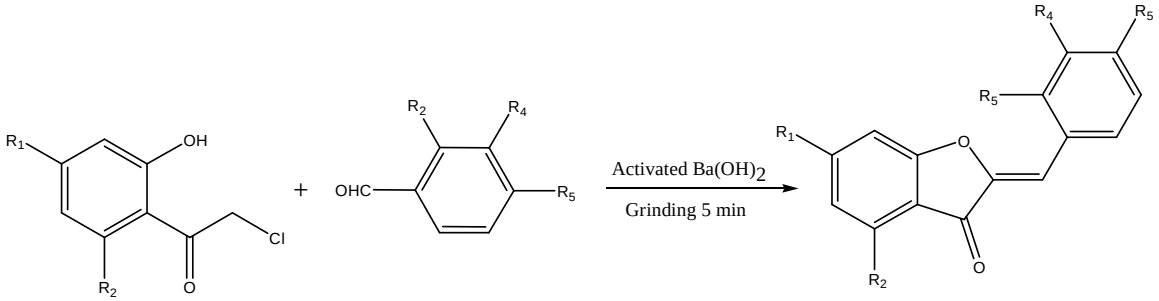
Fig. 3: Synthesis of aurone using microwave irradiation method

An effective and eco-friendly way of synthesis of aurones were accomplished directly from substituted 2-hydroxyphenacyl chloride in a single pot grinding with aryl aldehydes by using activated solid barium hydroxide as base and support[2].



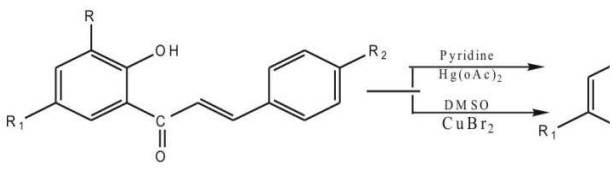
3-14

Fig. 4: An ecofriendly synthesis of aurone

Product	R^1	R^2	R^3	R^4	R^5
3	OH	H	H	H	H
4	OH	H	H	H	OCH_3
5	OH	H	H	OCH_3	OCH_3
6	OCH_3	H	H	H	H
7	OCH_3	H	H	H	OCH_3
8	OCH_3	H	H	OCH_3	OCH_3
9	OH	OH	H	H	H
10	OH	OH	H	H	OCH_3
11	OH	OH	H	OCH_3	OCH_3
12	OCH_3	OCH_3	H	H	H
13	OCH_3	OCH_3	H	H	OCH_3
14	OCH_3	OCH_3	H	OCH_3	OCH_3

From chalcones:

Series of aurone by oxidation of 2'-hydroxy chalcone with molar amount of mercury(II) acetate in pyridine or catalytic amount of CuBr in DMSO were synthesized by Agrawal *et.al.*[10].



15-23

Fig. 5: Synthesis of aurone using Hg(OAc) in pyridine or catalytic amount of CuBr in DMSO

	15	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
R	H	H	H	H	H	H	Br	Br	Br
R_1	H	H	H	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3
R_2	OCH_3	H	Cl	OCH_3	H	Cl	OCH_3	H	Cl

Agrawal et.al also synthesized series of aurones **24-31** from 2'-hydroxy-5'-acetamido chalcone and mercury (II) acetate in pyridine[11].

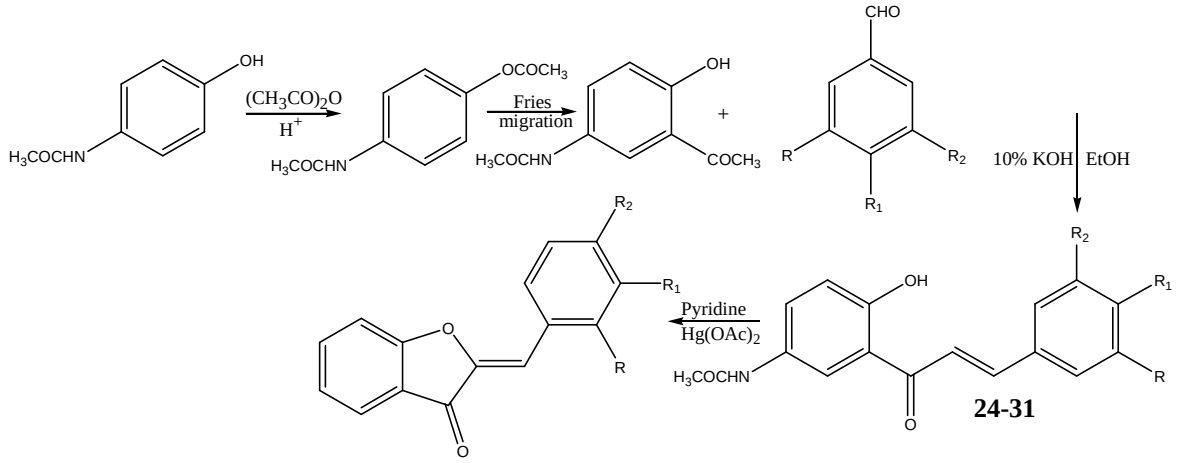
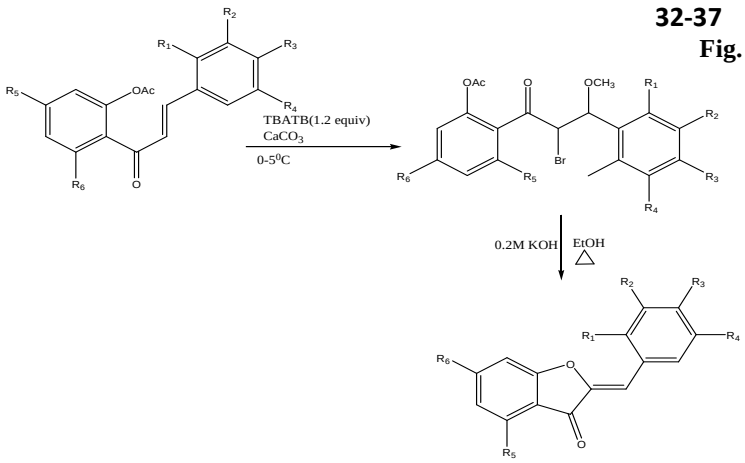


Fig. 6: Synthesis of aurone using 2'-hydroxy-5'-acetamide

	R_1	**R_2**	**R_3**	**R_4**
24	H	H	H	H
25	H	OCH3	H	H
26	H	Cl	H	H
27	OCH3	OCH3	OCH3	H
28	H	H	H	Ph
29	H	OCH3	H	Ph
30	H	Cl	H	Ph
31	OCH3	OCH3	OCH3	Ph

Two steps synthesis of aurones from 2'-acetoxy chalcones were reported Khan *et.al.* In the first step there is bromination using n-tetrabutyl ammonium tribromide (TBATB) in presence of $CaCO_3$ in dichloro methane: methanol (5:2) at 0-5°C, while in the second step cyclization of the brominated product is obtained on treating with 0.2 M ethanolic KOH solution at 0-5°C[12].

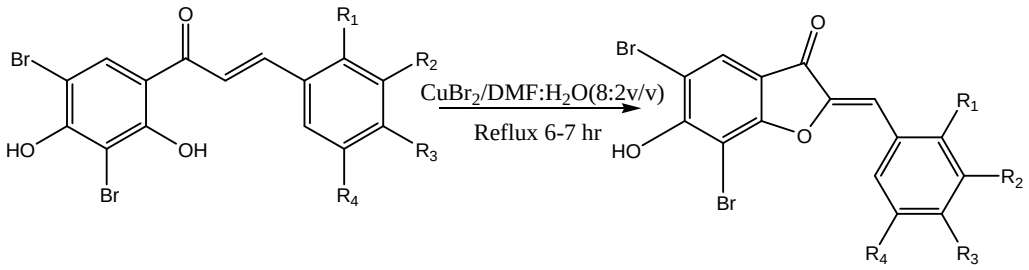


32-37

Fig. 7: Synthesis of aurones from 2'-acetoxy chalcones

	32	**33**	**34**	**35**	**36**	**37**
R_1	H	H	OCH_3	H	H	H
R_2	H	H	OCH_3	OCH_3	OCH_3	H
R_3	OCH_3	OBu	H	OCH_3	OCH_3	OCH_3
R_4	H	H	H	OCH_3	H	H
R_5	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	H
R_6	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	H

Oxidative cyclization using 3',5'- dibromo-2',4'-dihydroxy chalcones and copper bromide in presence of DMF-water mixture (8:2, v/v) were introduced by Ameta *et.al.*[13].

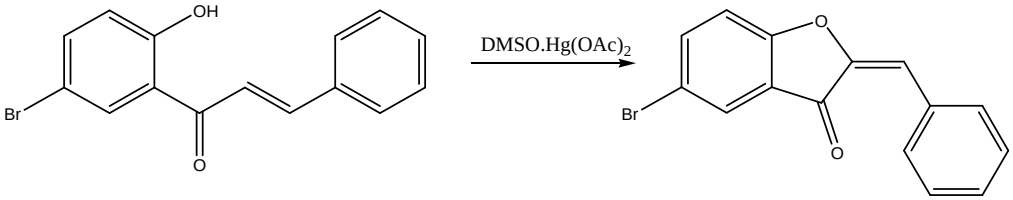


38-51

Fig. 8: Synthesis of aurones from 3',5'- dibromo-2',4'-dihydroxy chalcones

	38	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**
R_1	H	Cl	H	Cl	H	H	H	H	OH	CH_3	H	H	H	H
R_2	H	H	H	H	OH	OCH_3	OCH_3	OCH_3	H	H	H	H	H	NO_2
R_3	H	H	Cl	Cl	OCH_3	OCH_3	OCH_3	OH	H	H	Br	F	OCH_3	H
R_4	H	H	H	H	H	H	OCH_3	Br	Br	H	H	H	H	H

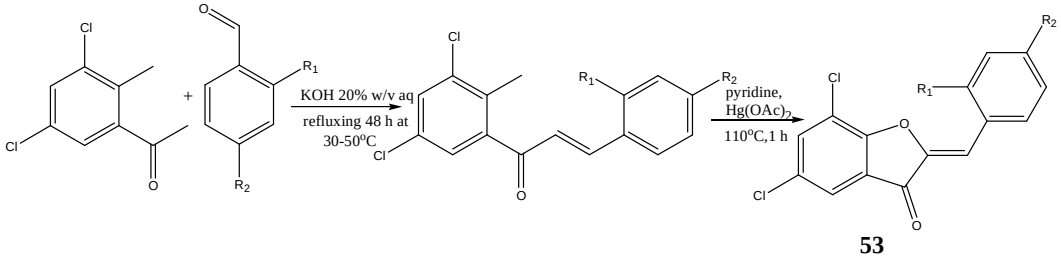
Bromo substituted aurones were formed by cyclization of bromochalcone, mercuric chloride and DMSO[14].



52

Fig. 14: Synthesis of aurone by cyclization of bromochalcone

Series A and B of aurone by oxidative cyclization of 2'-hydroxy chalcone in presence mercury(II) acetate in pyridine were synthesized by Elhadi and co-worker[15].



53

Fig. 9: Synthesis of aurone by oxidative cyclization

Series A			Series B		
	R_1	R_2		R_1	R_2
1a	H	Cl	1b	Cl	H
2a	H	F	2b	Br	H
3a	H	CH_3	3b	OCH_3	H

CRYSTAL STRUCTURE:

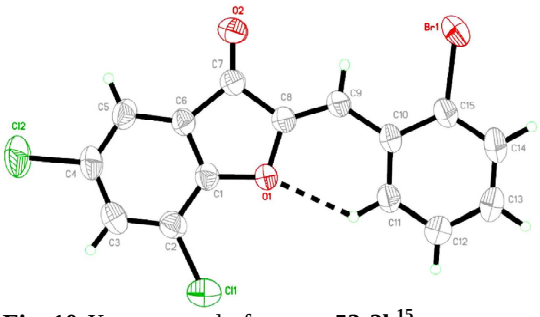


Fig. 10:X-ray crystal of aurone **53-2b**[15]

The compound **53-2b**, $C_{15}H_7O_2C_{l2}Br$, crystallized in a monoclinic space group, P_{21}/c. An intramolecular interaction was observed in the molecular structure of 2b, C11–H11A….O1. Molecules in the crystal structure were found to be linked together by intermolecular interaction of C13–H13A…..O2.

Series of aurone by oxidative cyclization of chalcone using mercury (II) acetate in pyridine were synthesized by Detsi *et.al.*[7].

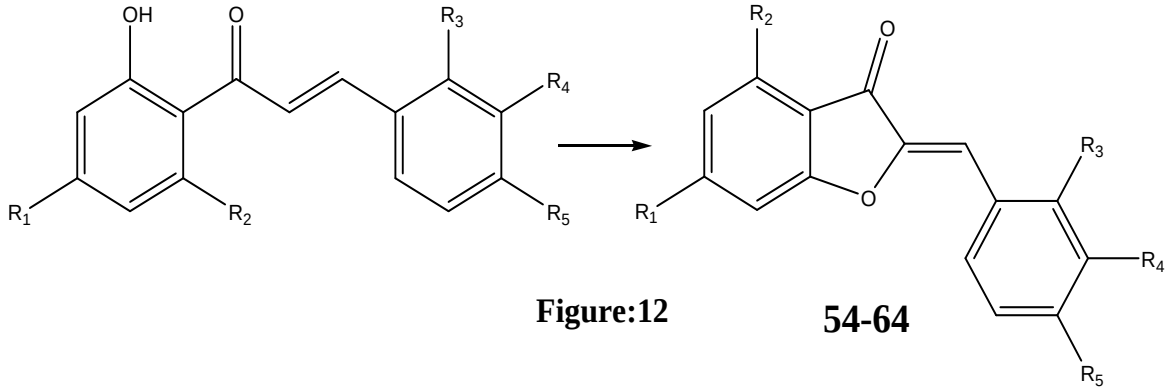


Figure:12 **54-64**

Fig. 11: Synthesis of aurone by oxidative cyclization of chalcone

	R_1	R_2	R_3	R_4	R_5
54	H	H	H	H	OCH_3
55	H	H	H	H	CH_3
56	H	H	H	H	Cl
57	H	H	H	OCH_3	H
58	H	H	OCH_3	H	H
59	H	H	H	OCH_3	OCH_3
60	OCH_3	OCH_3	H	H	OCH_3
61	OCH_3	OCH_3	H	H	Cl
62	OCH_3	OCH_3	H	H	CH_3
63	OCH_3	OCH_3	OCH_3	H	H
64	OMOM	OMOM	H	OMOM	OMOM

Series of aurones **65-76** were synthesized similarly by oxidative cyclization of chalcone using mercury (II) acetate in pyridine by Marina Roussaki *et.al.*[16].

R_1-H,OCH_2CH_3,OCH_3
R_2-H,OCH_2CH_3,OCH_3
R_3- H, ,OCH_3
R_4- H,OCH_2CH_3,OCH_3
R_5-H,OCH_2CH_3,OCH_3,CH_3Cl

A series of trifluoromethylated aurone and 6-hydroxy aurone derivatives by using resorcinol as a starting material were reported by Xing Zheng and co-workers[5].

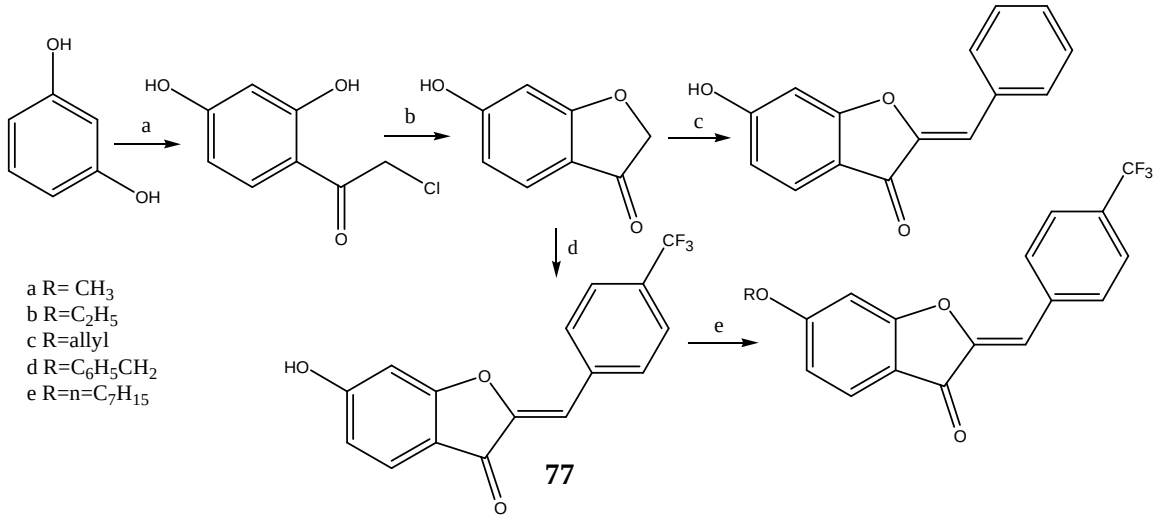


Fig. 12: Synthesis of trifluoromethylated aurone and 6-hydroxy aurone. (a) $ClCH_2CN,HCl_{(g)}$; (b) NaOMe; (c) C_6H_5CHO/NaOH,NaOMe; (d) α,α,α-trifluoro-p-tolualdehyde/NaOH,HCl; (e) RX/K_2CO_3

Different heterocyclic derivatives from 3,4-dimethoxy-2' hydroxy-5'-methyl chalcone were synthesized by Naqvi and co-workers[17].

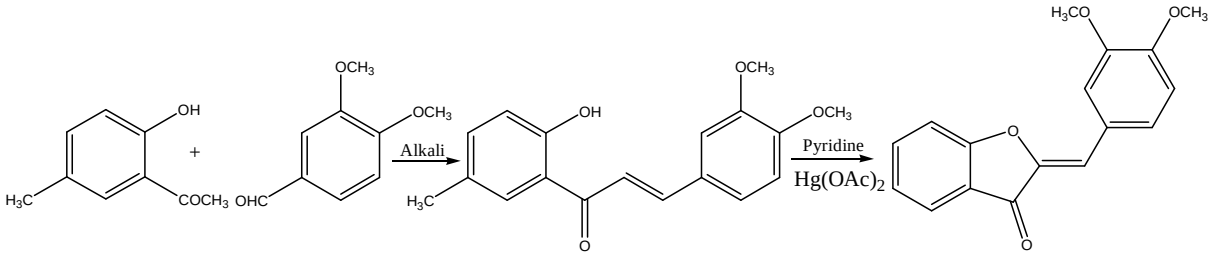


Fig. 13: Synthesis of different heterocyclic derivatives of aurone

From coumaranones:

Aurones were obtained by reacting overnight the coumaranones with substituted benzaldehyde and basic alumina in dichloromethane at room temperature were reported by Morimoto *et.al.*[12].

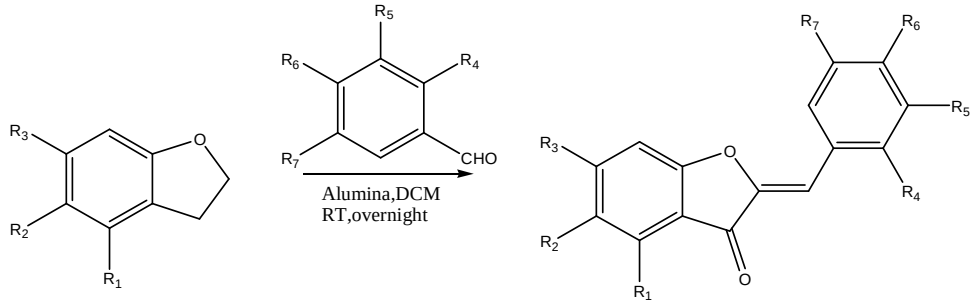
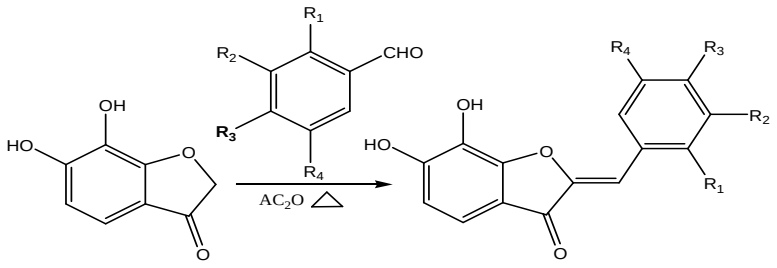


Fig. 14: Synthesis of aurone by using alumina in DCM

	R_1	R_2	R_3	R_4	R_5	R_6	R_7
79	H	H	H	H	H	H	H
80	H	H	H	OCH_3	H	H	H
81	H	H	H	H	OCH_3	H	H
82	H	H	H	H	Cl	H	H

Synthesis of aurone by the acid catalyzed condensation of 6,7-dihydroxy caumaranone with substituted benzaldehyde in acetic anhydride have been reported by Venkateshwarlu *et.al.*[18].



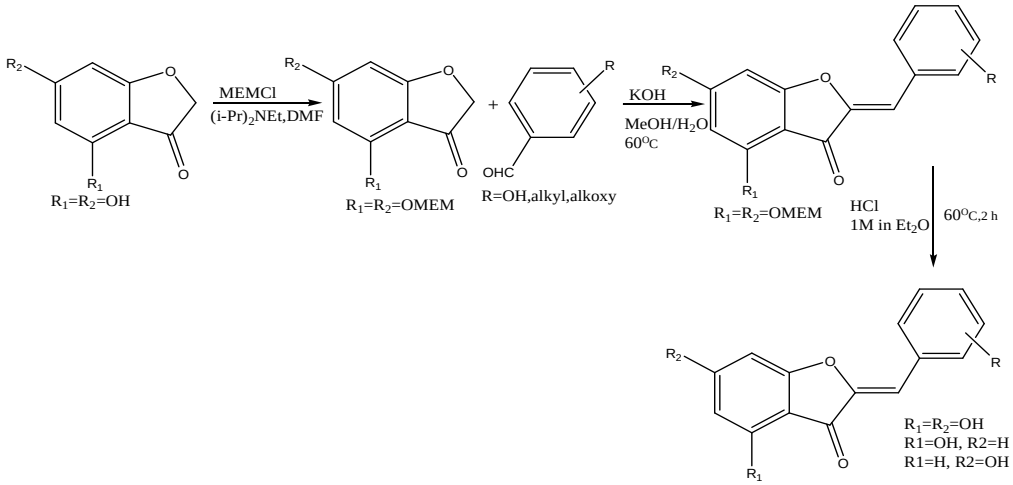
83-88

Fig. 15: Acid catalysed synthesis of aurone

	83	**84**	**85**	**86**	**87**	**88**
R_1	H	H	H	OH	H	H
R_2	OH	OCH_3	H	H	OH	H
R_3	OH	OH	OH	OH	OH	F
R_4	H	H	H	H	OH	H

By Aldol condensation

Series of aurone by aldol condensation of benzofuranone with benzaldehyde derivative were synthesized by Okombi and co-workers[19].



89

Fig. 16: Synthesis of aurone by aldol condensation

Gold catalyzed

Synthesis of aurones in three steps by using substituted salicyaldehyde and phenyl acetylene derivatives through alkynylation, gold-catalyzed cyclization and oxidation were introduced by Harkat & co-worker[20].

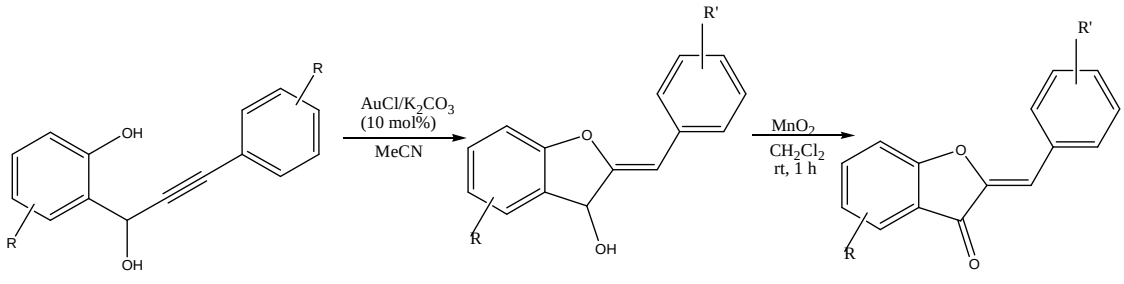


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Fig. 17: Synthesis of aurone by alkynylation, gold-catalyzed cyclization and oxidation method

Synthesis of aurones by gold-catalyzed cyclo-isomerization were reported by Alcaide *et.al.*[21].

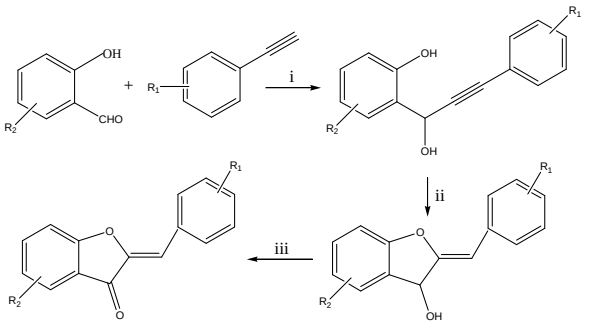

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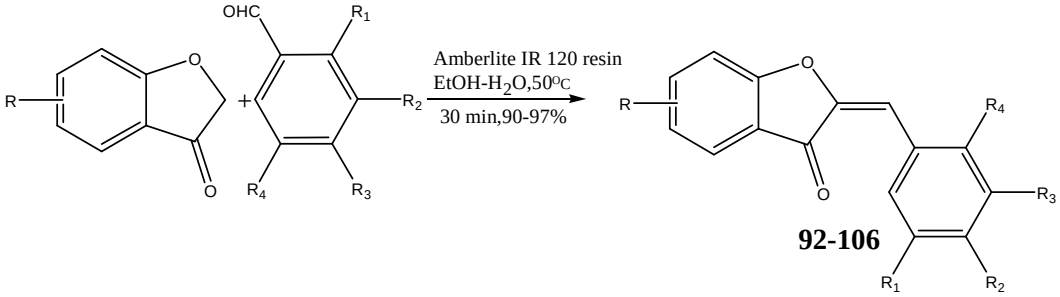
Fig. 18: Gold catalysed synthesis of aurone. Reaction conditions: i) n-BuLi (1 equiv.),THF,-78^{o}C to -40^{o}C,4 h; ii)AuCl (10 mol%),K_2CO_3(10 mol%),MeCN, rt ,30 h; iii)MnO_2(10 equiv.), DCM, rt, 1 h.

Alumina catalyzed

Aurone by condensation benzofuranone with aromatic aldehyde in presence of amberlite IR-120 resin in aqueous ethanol at 50^{o}C were reported by Chen *et.al.* This method resulted in formation of aurone in short period of time with good yield[6].



92-106

Fig. 19: Synthesis of aurones using amberlite IR-120 resin in aqueous ethanol

	R	R_1	R_2	R_3	R_4
92	H	H	H	H	H
93	H	H	H	NO_2	H
94	H	H	H	H	H
95	H	H	H	H	H
96	H	Me	Me	H	OH
97	H	H	OMe	H	OH
98	H	H	Me	H	H
99	H	H	Cl	H	H
100	H	H	H	OMe	H
101	H	H	H	H	OMe
102	H	H	H	OMe	OMe
103	H	H	F	H	H
104	H	H	CN	H	H
105	4,6-	H	H	H	H
106	4,6-	H	H	H	H

Synthesis of aurone derivative by using dimethoxybenzofuran-3(2H)-one, Al_2O_3 and CH_2Cl_2 were reported by Rong Sheng[22].

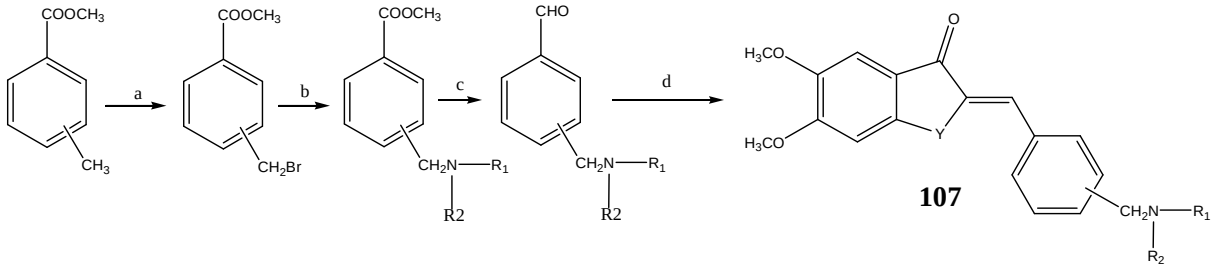


Fig. 20: Synthesis of aurone using dimethoxybenzofuran-3(2H)-one,Al_2O_3 and CH_2Cl_2

(a) NBS, CCl_4, hv, reflux 4 h; (b) secondary amine, CH_2Cl_2, reflux 2 h; (c) $LiAlH_4$-EtNH, pentane, r.t. 2-3 h;(d) Y=O,5,6-dimethoxybenzofuran-3(2H)-one, Al_2O_3,CH_2Cl_2, r.t. 2-4 h

Halogen substituted aurones

Synthesis of substituted and halogen substituted aurones by two different ways were introduced by Gavin H. Denmark and Chavonda J. Mills[23].

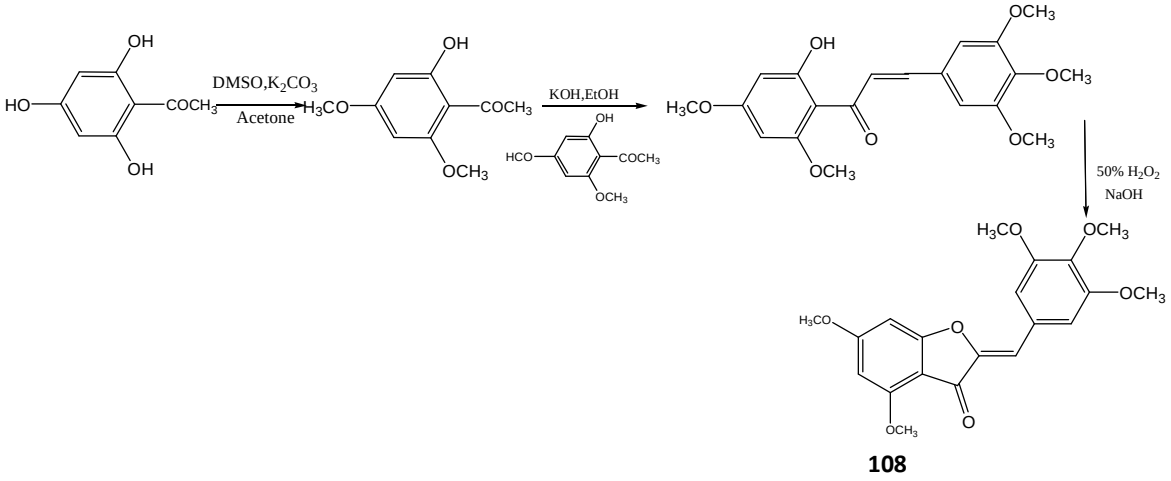


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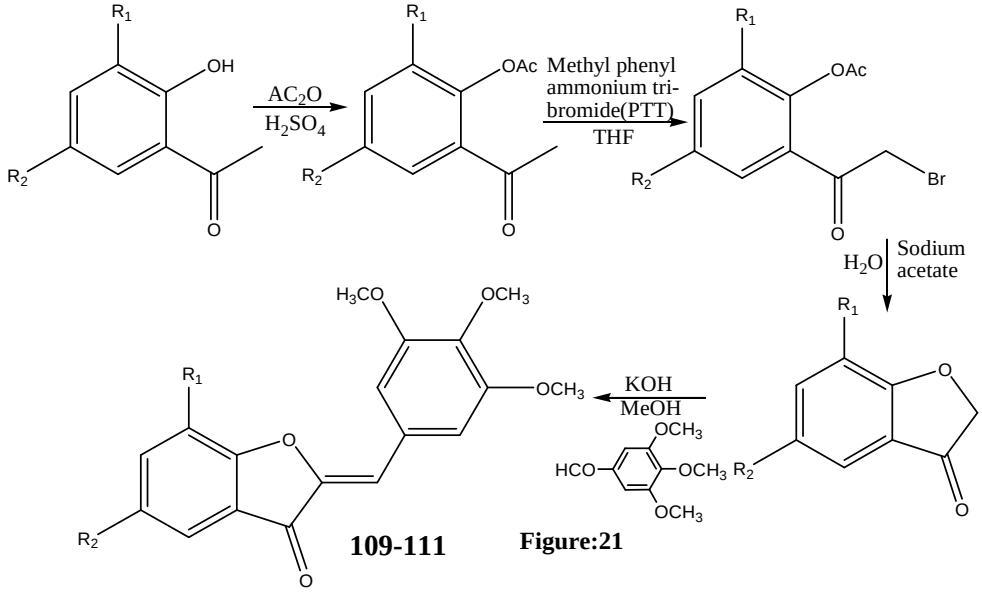
Fig. 21: Synthesis of substituted aurones

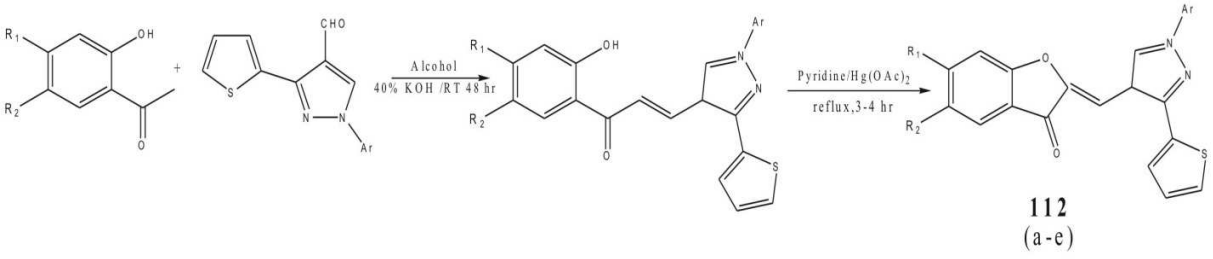


109-111 **Figure:21**

Fig. 22: Synthesis of halogen substituted aurones

109.R_1=H, R_2=Br
110.R_1= R_2=Cl
111.R_1=NO_2, R_2=CH_3

Synthesis of fluorinated aurone which contain thiophene and pyrazol moiety were reported by Karale.*et.al.*[24].



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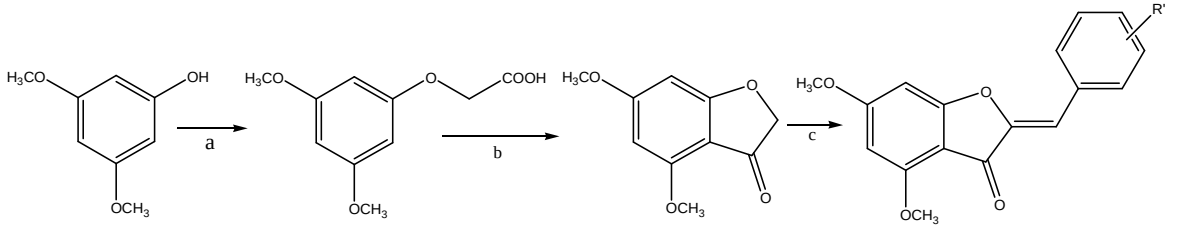
(a-e)

Fig. 23: Synthesis of fluorinated aurone

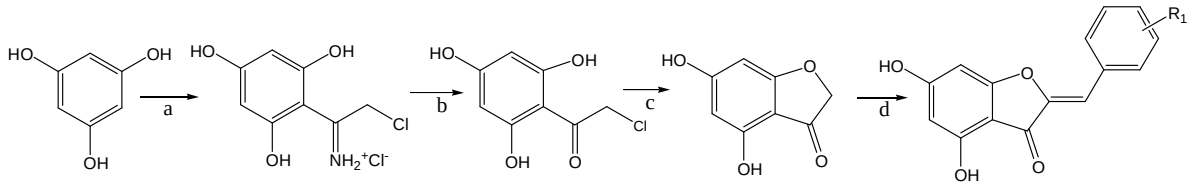
Different methods for synthesis of aurone from series 1 to 5 were reported by Lee *et.al.*[25].



113

Fig. 24: Synthesis of aurone using series-1

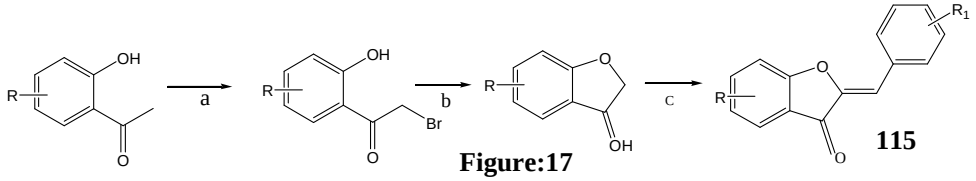
Series 1: (a) Chloro acetic acid ,NaH, DMF,r.t,12 h (b) polyphosphoric acid , 90^{o}C, 8 h. (c) substituted benzaldehyde, KOH 50% water, MeOH , r.t, 1-3 h.



114

Fig. 25: Synthesis of aurone using series-2

Series 2: (a) Chloroacetonitrile, HCl, $ZnCl_2$, Et_2O,0^{o}C,r.t.,24 h. (b) 1 N HCl, 100^{o}C,1 h. (c) NaOAc, MeOH, reflux (d) substituted benzaldehyde, KOH, 50% in water, MeOH, microwave heating 110^{o}C, 10-15 min.



R=5-OH

115

Figure:17

Fig. 26: Synthesis of aurone using series-3

Series 3: (a) $CuBr_2$, $CHCl_3$-ethyl acetate, reflux, 8 h. (b) KOH 50%/H_2O, MeOH, reflux, 2h substituted benzaldehyde, KOH 50%/H_2O,MeOH,60^{o}C,1 h.

Series 4: Compounds of series-4 were synthesized similar to that of series-3 except that 2',4'-dihydroxyacetophenone was used as the starting material.

Series 5: Benzofuran-3(2H)-one directly reacted with 2-hydroxy benzaldehyde and 2-chloro benzaldehyde by heating in a oil bath at 60^{o}C for 1 h.

Four different methods for synthesis of aurones were reported by Romain Haudecoeur[26].

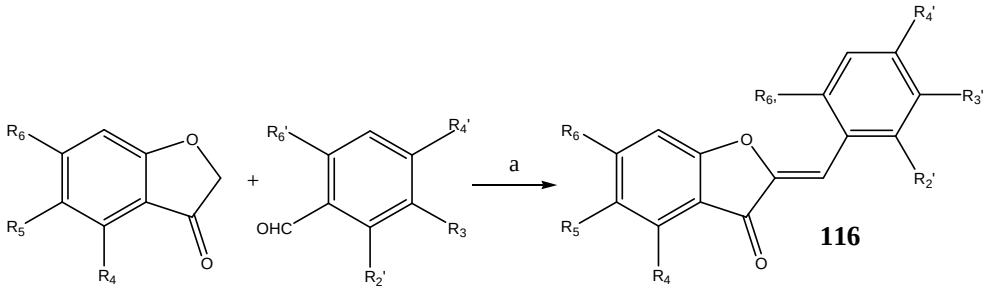


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Fig. 27: Synthesis of aurone using**(a)**For procedure A: KOH/MeOH,60^{O}C,1-18 h.

For procedure B: KOH/EtOH, 80^{o}C,2-5 h.For Procedure C: Al_2O_3, CH_2Cl_2, r.t., 16 h.

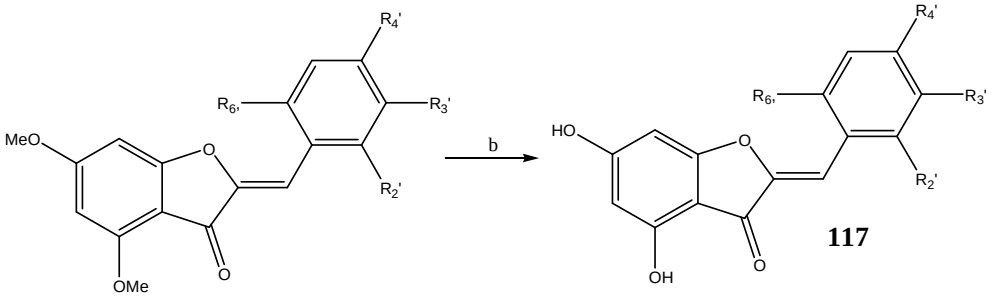


Fig. 28: Synthesis of aurone using **(b)**BBr_3, CH_2Cl_2,0^oC to room temp., 24-72 h.

Synthesis of ferrocenyl aurones and organic aurones was obtained by refluxing appropriate chalcone in pyridine with 2 eq. $Hg(OAc)_2$ reported by Keshri Nath Tiwari and co-worker[27].

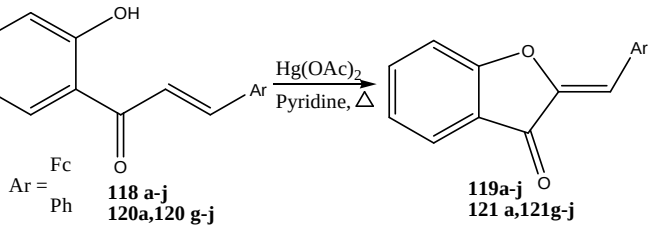


Fig.29: Synthesis of ferrocenyl aurones
a=unsubstituted; b=5-Cl; c=5-Br; d=5,7-diF; e=5,7-diCl; f=5,7-diBr; g=6-OMe; h=5-OMe; i=4-OMe; j=4,6-diOMe

Synthetic route to form aurone starting from xylene reported by Fan Rui and co-worker[28].

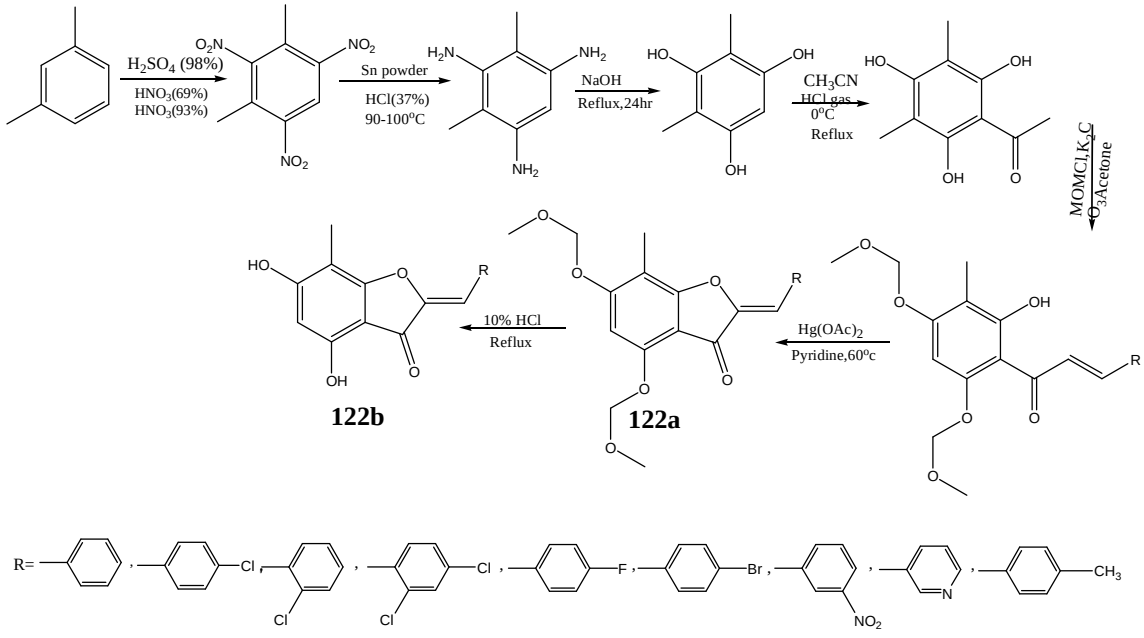
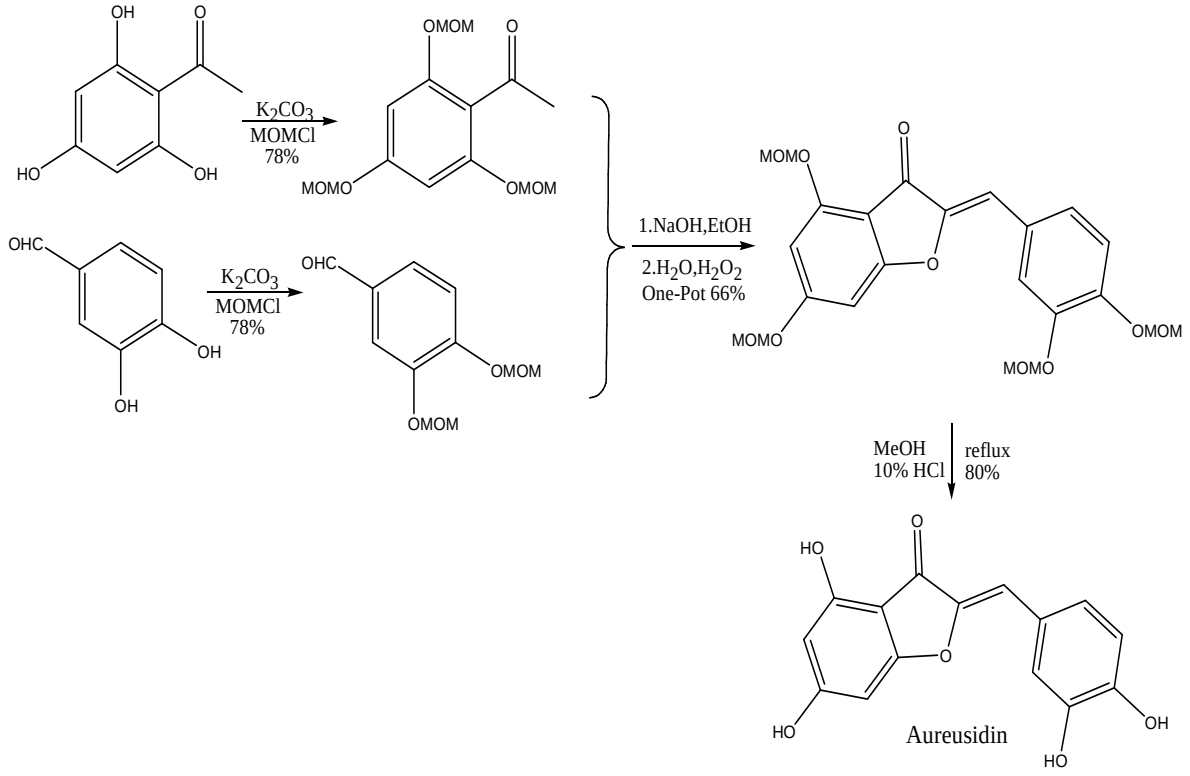


Fig. 30: Synthesis of aurone using xylene

Synthesis of aurones on the basis of Algar-Flynn-Oyamada reaction were reported by Xiaolong Zhao and co-worker. By using this method series of aurones (123a-123g) were synthesized using acetophenone and benzaldehyde as starting material. To confirm the usefulness of this method they prepared aureusidin, an inhibitor of iodothyroninede iodinase, in 41% overall yield[29]



123

Fig. 31: Synthesis of aureusisdin

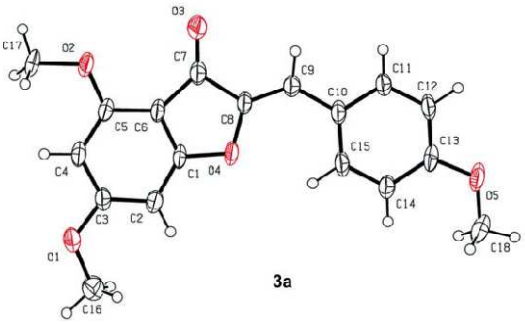


Fig. 32-X-ray crystal of aurone **3a**[29]

BIOLOGICAL ACTIVITY:

Anti-oxidant Activity:

Anti-oxidant activity of synthesized fluorinated aurone **112 (a-e)** were determined by DPPH method by using Trolox as reference standard. From compound a to e % the ant-oxidant activity decreases[24].

Table 1- Antioxidant activity results (primary screening data of DPPH assay with test conc. 1.25µg/mL)

Compound	% AO activity	Compound	% AO activity	Compound	% AO activity
2a	2.71	**3a**	45.14	**4a**	2.45
2b	0.85	**3b**	18.23	**4b**	1.37
2c	1.30	**3c**	12.53	**4c**	1.04
2d	37.69	**3d**	17.93	**4d**	0.19
2e	0.07			**4e**	0.00

Synthesized aurones in series **83-88** were evaluated for anti-oxidant activity by NBT and DPPH method. Compounds **a** and **e** showed good anti-oxidative activity by both the method[18].

Table 2- Antioxidant activities of aurones 1a-1f

Compound activity	NBT superoxide scavenging activity (IC_{50} µM)	DPPH radical scavenging (IC_{50} µM)
1a	6.5	8.3
1b	9.0	8.7
1c	10	10.4
1d	12.3	10.1
1e	4.3	7.9
1f	20.2	11.0
BHT	301.8	13.4
Vitamin C	670.5	23.3
Vitamin E	530.2	>1000
Resveratrol	482.5	35.5

Aurone derivatives **(2)** weretested for their anti-oxidant activity. Compounds with R_3=R_4=OH were found to be potent antioxidants[9].

Table 3- Antioxidant activity result of compound 3a-x

Compound	? OD (593nm)	FRAP value	Compound	? OD (593nm)	FRAP value
3a	1.162	233.47	3n	0.964	190.07
3b	0.912	183.24	3o	1.098	220.61
3c	1.304	262.01	3p	0.996	200.12
3d	0.992	199.32	3q	1.505	302.39
3e	1.932	388.19	3r	1.610	323.49
3f	2.272	456.51	3s	1.896	380.96
3g	2.221	456.51	3t	1.428	286.92
3h	1.806	362.87	3u	2.138	495.69
3i	2.464	470.37	3v	2.283	458.72
3j	2.291	460.32	3w	2.440	490.26
3k	2.024	495.08	3x	2.312	464.54
3l	2.249	451.88	A.A	2.476	
3m	0.779	156.52			

A.A= ascorbic acid
Concentration of compounds used = 200 µg/mL
Concentration of standard (A.A) = 176 µg/mL
A.A mm/ 100 g sample

Antioxidant activity of series of aurone derivatives **(54-65)** were tested by five different assay. Radical scavenging activity were evaluated against DPPH stable free radiacal, Superoxide anion radical $O_2^{\cdot-}$ and hydroxyl radical ($OH^{\cdot}$). By using peroxyoxalatechemiluminescence method ability of compounds to scavenge hydrogen peroxide were evaluated and finally ability of compounds to inhibit 2,2'-azobis(2-amidino propane) dihydrochloride APPH induced lipid peroxidation were tested.Result of all antioxidant activities showed that substituent present on ring A and B plays important role in such type of activity[7].

Antimicrobial activity:

Antifungal activity of synthesized compound **112 (a-e)** were tested against *C. albicans* and *A. fumigates* and antibacterial activity tested against *S. aureus* and *E. coli.* None of compounds was antifungal and antibacterial activity[24].

The synthesized aurones **(78)** evaluated for antibacterial activity against bacteria namely *Escherichia coli, Pseudomonas pneumoniae, Staphylocous aures* and *Klebsiella pneumonia* by NCCLS method and tested for antifungal activity against fungi namely *Candida albicans, Cryptococus neoformans, Sporothrix schenckii, Trichopyton mentagrophytes, Aspergillus fumigates* and *Candida parapsilosis*by NCCLS method. All compounds showed MIC either =50µg/ml or >50µg/ml[17].

Aurone derivatives **(2)** were assayed for antibacterial activity against bacteria *Staphylococcus aureus, Bacillus subtills, Clostridium tetani, Pseudomonas aeruginosa, Vibrio cholera* and antifungal activity against fungi *Candida albicans, Aspergillusclavatus.*Most of the compounds showed powerful activities with standard drugs.From result observed that antimicrobial activity of compounds depends on substituents on ring A,B and C[9].

Antileishmanial activity:

all synthesized aurones **(65-76)** tested for antiparasitic activity against intracellular amastigote form of *Leishmania infantum* and their cytotoxicity against human THP1-differentiated macrophages. Compound containing OCH_3 group at A ring and electron donating group at 2' position of B ring showed good antileishmanial activity[16].

Table 4- Antileishmanial activity and cytotoxicity of the synthesized aurones

Compound (SI)	IC50 (μM) L.*infantum* intracellular amastigotes	IC50 (μM) THP1-differentiated macrophages	Selectivity index
4a	nd	16.5 ± 3.1	nd
4b	nd	8.5 ± 0.8	nd
4c	nd	14.5 ± 2.1	nd
4d	nd	17.5 ± 3.1	nd
4e	4.7 ± 0.5	54.2 ± 7.3	11.5
4f	nd	20.5 ± 1.2	nd
4g	5.1 ± 0.3	62.5 ± 1.3	12.4
4h	nd	19.6 ± 2.5	nd
4i	1.3 ± 0.1	75.4 ± 4.7	57.5
4j	1.6 ± 0.2	68.1 ± 2.1	43.4
4k	12.2 ± 1.4	>100	>8.2
4l	2.1 ± 0.9	57.5 ± 3.4	26.9
Amphotericin B	1.2 ± 0.1	23.8 ± 2.3	20.6

The selectivity index represents the ratio of IC_{50} on THP1-differentiated macrophages to the IC_{50} on intracellular parasite.

nd: not determined, for compounds with IC_{50} values below 20 µM on THP1-differentiated macrophages.

Trypanocidal Activity:

Synthesized series of aurones **(38-51)** evaluated for Trypanocidal activity against *Trypanosoma cruzi*. Compound b and k in series were powerful and considered as active. Then both the compound tested for cytotoxicity and results were good comparable with standard drugs[13].

Table 5- Biological evaluation of active samples against *Trypanosoma cruzi*; IC50 and Cytotoxicity

Entry	Concentration used	% Growth Inhibition	[*a]**IC50** (ug/mL)	[b]**Cytotoxicity** (ug/mL)
2b	10 ug/mL	54.37	8.37	25
2k	10 ug/mL	68.03	5.06	37
Nifurtimox	10 ug/mL	68.50	0.47	27
Benznidazole	10 ug/mL	86.77	0.81	>50

Antiviral Activity:

Antiviral activity of auronederivatives **112 (a-e)** tested against Herpes simplex virus-2 by CPE inhibition assay. Amongst all tested compound only some compounds showed good antiviral activity[24].

AchE inhibitory:

Different derivatives of compound **(107)** tested for ChE inhibitory activities in vitro. Most of the evaluated compounds showed high activities against AchE and no activities against BchE vitro[22].

Anticancer Activity:

The trifluoromethylated aurone derivative **(77)** were tested for their in vitro anticancer activity against HL-60 nad HT-29 cell. All derivative showed stronger cytotoxicity toward HL-60 cell and showed better inhibitory activities toward HT-29 cell[5].

Table 6- The anticancer activities of the target compounds 5 and 6a–e in vitro

Compound	HL-60 (IC50 mmol/L)	HT-29(IC50 mmol/L)
4	3.74	9.12
5	1.54	8.90
6a	2.59	5.90
6b	1.65	9.12
6c	3.53	4.12
6d	3.46	4.12
6e	2.67	4.32
5-Fluorouracil	12.92	9.56

The given values are the average values of three experiments

Derivative of aurone (**53)** of series A and B were tested for anticancer activity in vitro against human colorectal tumor (HCT 116), human chronic myelogenous leukemia (K 562) and hormone dependent breast cancer (MCF-7) cell lines. Compound of series B showed higher cytotoxic effect on cancer cell lines compared to compound of series A[15].

Table 7- IC50 (μM) values of the synthesized aurone series (A) and(B) against three cancer cell lines

Compound	IC50 (μM)		
	HCT116	MCF-7	K562
1a	54	266	61
2a	>500	145	30
3a	40	24	20
1b	36	23	23
2b	112	239	42
3b	153	156	103
5-Fluorouracil	15	–	–
Tamoxifen	–	8.7	–
Betulinic acid	–	–	15

Aurone Derivative **(92-106)** wereevaluated for anticancer activity against MDA-MB-231 and MCF-7 cancer cell lines. Compound e and f showed good anti-proliferatie properties against tested cancer cell lines[6].

Table 8- Effects of 3e and 3f on cell cycle progression in MCF-7 cells

Compound	Control				**3e** (5 μM)				**3f** (4 μM)			
	Sub-G_0	G_0/G_1	S	G_2/M	Sub-G_0	G_0/G_1	S	G_2/M	Sub-G_0	G_0/G_1	S	G_2/M
24 hours	0	46.15	29.35	24.45	4.70	44.88	22.99	32.15	0	55.90	25.01	19.09
36 hours	0	46.71	39.19	14.33	4.97	58.74	23.88	17.50	5.58	63.06	18.48	18.55
48 hours	0	41.98	33.63	24.42	18.23	75.88	17.86	6.35	16.45	73.70	20.88	5.40

Antitumor Activity:

Antitumor activity of synthesized aurones **(1)** were tested against four type of human tumor cell lines HCCLM-7, MDA-MB-435S and SW-480. Compound in series with piperazinyl moiety showed strong antitumor activity[8].

Table 9- Antiproliferative activity of the compounds 4a–g and 5a–f

Compound	Cytotoxicity IC50a (lM)			
	HCCLM-7	Hep-2	MDA-MB-435S	SW-480
4a	>50	>50	>50	>50
4b	>50	40.2	>50	>50
4c	>50	47.7	>50	>50
4d	>50	>50	>50	>50
4e	>50	31.3	17.1	45.2
4f	>50	29.6	26.1	36.4
4g	>50	42.6	30.3	>50
5a	>50	>50	47.8	>50
5b	>50	>50	40.3	>50
5c	>50	>50	>50	>50
5d	45.1	27.7	25.1	36.4
5e	9.6	5.7	7.6	6.6
5f	12.1	4.7	4.1	13.1
5-FU	18.6	128.7	14.5	8.1

The IC_{50} values represent the concentration resulting in a 50% decrease in cell growth after 72-h incubation, which were mean values of three repeated experiments.

Anti-VSMC Vegetation Activity:

Synthesized aurones were evaluated against anti-VSMC vegetation activity *in vitro via* MTT assay with tetrandrine as positive reference. Hydroxyl protected compounds **(122a)** with *para* and *meta* substituents at B ring showed good activity. While hydroxyl protected compounds with *para*-halogen group at B ring after deprotection showed decreased activity[28].

Table 10- Anti-VSMC vegetation activities of the synthesizedcompounds at 5 μg/mL dose

Compd.	Inhibition rate(%)	Compd.	Inhibition rate(%)
Tetrandrine	69.40	**6**e	14.25
5a	31.71	**7**e	–0.39
6a	–0.53	**5**f	34.21
7a	15.24	**6**f	43.48
5b	27.69	**7**f	–20.48
6b	41.05	**5**g	–4.73
7b	18.96	**6**g	42.87
5c	36.90	**7**g	18.45
6c	–1.09	**5**h	45.47
7c	23.53	**6**h	–0.20
5d	29.13	**7**h	12.15
6d	–2.91	**5**i	20.74
7d	26.47	**6**i	69.59
5e	2.38	**7**i	47.42

Soybean lipoxygenase (LOX) inhibitory activity:

All synthesized aurones **(54-65)** were tested for soybean lipoxygenase inhibitory activity by the UV-absorbance-based enzyme assay.Among all tested aurones the compounds with two methoxy group showed good LOX inhibitory activity[7].

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