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Review Paper

Aurones and furoaurones: Biological activities and synthesis

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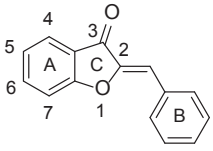
ABSTRACT

Aurones, (*Z*)-2-benzylidenebenzofuran-3(2*H*)-ones, have proved to be promising bioactive compounds with a broad spectrum of activities including anticancer, antioxidant, antiparasitic and antibacterial activities. Aurones exhibited strong antiproliferative properties against cancer cells by acting on variable targets through different modes of action. Furoaurones, (*Z*)-2-benzylidenefurano[3,2-f] benzofuran-3(2*H*)-ones, is a class of semi synthetic compounds derived from naturally furanochromones extracted from of *Ammi visnaga* (L.) fruits. So, this literature review includes different biological activities of aurones and furoaurones and different methods for their synthesis.

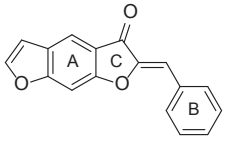
Aurones, (*Z*)-2-benzylidenebenzofuran-3(2*H*)-ones, is a class of plant flavonoids that provides the bright yellow color to some important ornamental flowers. The name "aurone" comes from the Latin word *aurum* (gold) because of its golden yellow color of the pigments in many plants [1]. Aurones have been described as phytoalexins that are used by the plants in their defense mechanism against various infections [2].



General structure of aurones

Aurones are found in a number of flowers of family *Scrophulariaceae* and *Compositae*. The yellow *Snapdragon* flower is probably one of the best sources for aurones in the vacuoles of the epidermal cells of the flowers. However, aurones are also found in the bark, wood, leaves and seedling of different plants [3]. These natural aurones and their synthetic analogues have proved to be promising bioactive compounds with broad spectrum of activities including anticancer [4–12], antioxidant [13–15], antiparasitic [16–19] and antibacterial activities [20,21]. Moreover, some aurones were found to be promising non-nucleoside allosteric inhibitors of hepatitis C virus RNA-dependent RNA polymerase [22,23]. Some aurones showed potent xanthine oxidase inhibitory activity that can help in the treatment of hyperuricemia and gout [24]. Others were used for the treatment of Alzheimer's disease as AChE inhibitors [25].

Furoaurones, (*Z*)-2-benzylidenefurano[3,2-f] benzofuran-3(2*H*)-ones are semi-synthetic compounds derived from khellin and visnagine – naturally furanochromones extracted from of *Ammi visnaga* (L.) fruits [26,27].



General structure of furoaurones

1. Biological activities of aurones

1.1. Antitumor activity

Some aurones have inhibition activity of ATP-dependent enzymes and proteins by mimicking the adenine of ATP, which is essential for the function of enzymes and receptors. In particular, the benzofuranone structure of aurones is assumed to mimic the adenine of ATP that may be a key for the efficiency of aurones [28].

Lawrence et al. [4] synthesized several aurones and tested their cell growth inhibitory properties on the human chronic myelogenous leukemia cell line. The study revealed that, compounds **1–3** showed good activities with IC_{50} = 0.15, 0.11 and 0.15 μM, respectively. The best antitumor activity was obtained by incorporating 3-hydroxyl and 4-methoxy groups of benzylidene moiety, together with 7-methoxy group of benzofuran ring as shown in compound **4** (IC_{50} = 0.05 μM) that showed a significant G2/M cell cycle arrest.

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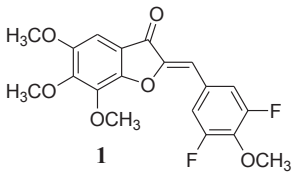

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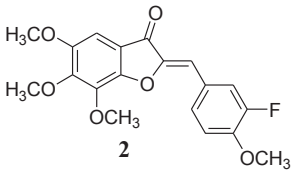

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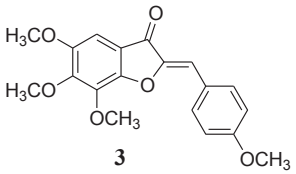

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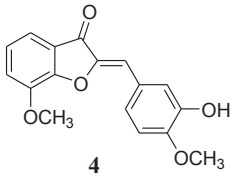
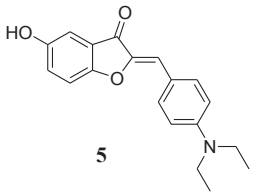


4

Moreover, a series of 5-hydroxyaurone derivatives was synthesized and its inhibitory activity against the proliferation of human umbilical vein endothelial cells (HUVEC) and some cancer cell lines were studied. Some of these compounds functioned as potent inhibitors against the proliferation of endothelial cells. The most active compound **5** (IC_{50} against HUVEC, MCF-7 and A549 = 0.25, 1.81 and 1.25 μM, respectively) and its acetyl analogue **6** (IC_{50} against HUVEC, MCF-7 and A549 = 0.23, 2.95 and 1.29 μM, respectively) effectively inhibited *in vitro* endothelial cell motility and tube formation, which are basic properties for endothelial cells angiogenesis [5].



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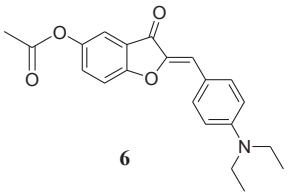
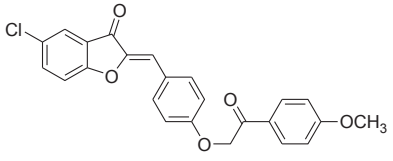


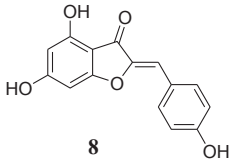
6

In 2015, Demirayak et al. [6] synthesized some 2-[4-(2-aryl-2-oxoethoxy) arylidene]benzofuran-3-one derivatives and their antitumor activities were evaluated by the National Cancer Institute (NCI) USA against 60 human tumor cell lines. The prepared compounds showed enhanced activities against ovarian cancer, breast cancer, colon cancer and leukemia. Results revealed that, 5-chloroaurone extended with 4-methoxyphenyl-2-oxoethoxy group through ring B, compound **7** was claimed to be the most effective one, exhibiting the highest antitumor activity on leukemia cancer type with the growth percentage of 49.47%.



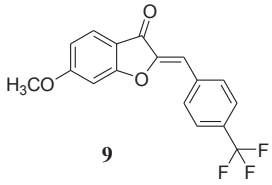
7

Tyrosinase is involved in different biological processes such as melanogenesis and skin hyperpigmentation and it is up-regulated in skin cancer. To investigate naturally occurring aurones as human tyrosinase inhibitors, several aurone derivatives bearing hydroxyl groups on ring A and/or different substituents on ring B were synthesized and evaluated as inhibitors of human melanocyte-tyrosinase. It was found that, unsubstituted aurones were weak inhibitors. However, derivatives with two or three hydroxyl groups were able to induce significant tyrosinase inhibition. The most potent aurone was found to be the naturally occurring (*Z*)-4,6-dihydroxy-2-(4-hydroxybenzylidene)benzofuran-3(2*H*)-one; **8** which induced 75% inhibition at low concentration [7].



8

In 2015, Zheng et al. [8] prepared different aurone derivatives. Their anticancer activity was evaluated against leucocythemia and colorectal carcinoma. SAR analysis revealed that trifluoromethyl group is essential for cytotoxic activity. Compounds **9** and **10** have methoxy or ethoxy moieties at position 6 exhibited a great inhibitory activity with IC_{50} = 2.59 and 1.65 μM, respectively against leucocythemia. They showed better inhibitory activities toward leucocythemia than 5-fluorouracil (IC_{50} = 12.92 μM); the standard drug used in this assay.



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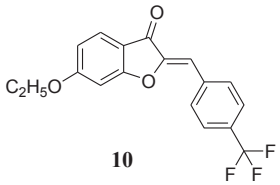
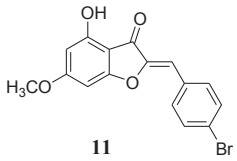


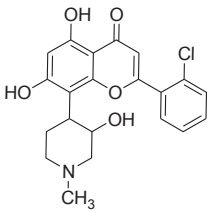
10

In another study, the antitumor activity was evaluated by testing the ability of the derivative to bind to P-glycoprotein (Pgp). Results revealed that substitution gradually enhanced the binding affinity, with a strong dependence on the nature of the halogen, correlating to its hydrophobic character and/or to its size. The most active compound was the bromo derivative **11**, which possessed a high binding affinity (*KD* is the dissociation constant, was 0.15 ± 0.07 μM) [9].

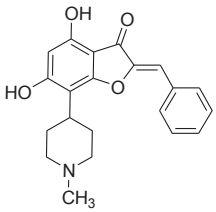


11

Compounds having the ability to inhibit cyclin-dependent kinases (CDKs) enzymes are of a potential value as antiproliferative agents. Based on the structure of flavopiridol, (**12**), a well-established inhibitor of cyclin-dependent kinases, several analogues possessing *N*-(4-methylpiperidinyl) at position 7 have been synthesized and evaluated for their antitumor activity. The prepared aurone **13** was found to be as much active as flavopiridol on CDK1 but at lower extent on CDK2 (binding energy -20.6 kcal/mol) [9].



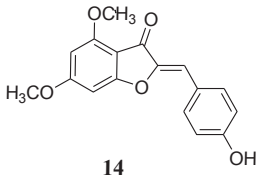
Flavopiridol (**12**)



13

Induction of the enzyme NADPH: quinone oxidoreductase 1 (NQO1) provides the cell with different mechanisms of protection against environmental insults. Briefly, NQO1 detoxifies highly reactive quinones to quinols and maintains endogenous lipid soluble antioxidants in their reduced and active forms [10]. Based on this information, compounds **14** and **15** were prepared and were found to be good inducers of NQO1. An interesting observation was the important role for the exocyclic double bond, where the reduction of the double bond led to a complete

loss of the activity as observed in compound **16**. Also, the presence of hydroxyl group at position 5 of the benzofuran ring led to a less potent inducer **15** (compound **15** did not induce NQO1 activity by 2-fold at the highest concentration tested 25 μM) [10].



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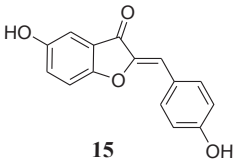

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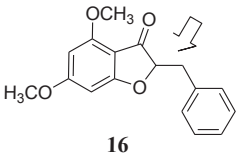
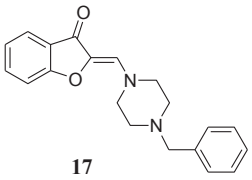


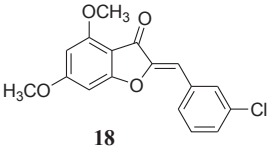
16

Furthermore, several aurone analogues attached to cyclic tertiary amine moiety were designed and synthesized under microwave irradiation. The synthesized compounds were assayed for their antitumor activity against four human solid tumor cell lines including: breast carcinoma, hepatoma, laryngocarcinoma and colon carcinoma. It was shown that *N*-benzylpiperazine derivative; (**17**) was identified as the most promising candidate. Replacement of the benzyl moiety with phenyl or alkyl groups produced less potent derivatives. Further cell cycle studies revealed that the same compound arrested the cell cycle in G0/G1 phase and displayed apoptosis-inducing effect in laryngocarcinoma [11].



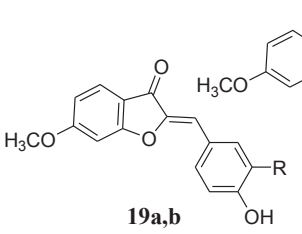
17

Moreover, the antitumor activity was evaluated by the ability to target ATP binding cassette sub family G member 2 (ABCG2), a protein transporter responsible for the breast cancer multidrug resistance mechanism. The results have shown that compound **18** was able to inhibit the ABCG2 efflux transporter in a dose-dependent manner and with a low cytotoxic effect against healthy cell lines [12].



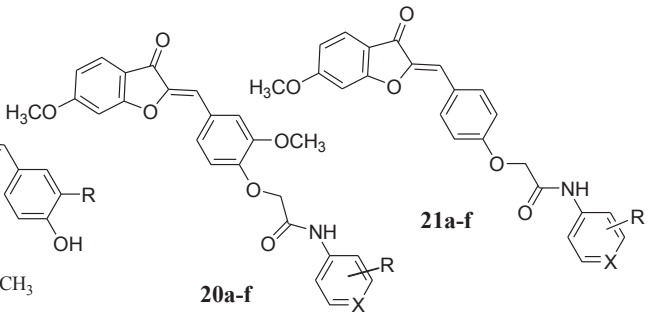
18

In our laboratory, a hybrid pharmacophoric approach between aurone scaffold and the oxymethyl-*N*-arylacetamides in order to extend the aurones core **19a** [6] and **19b** [13] aiming to empower their biological activity. So, compounds **20a–f** and **21a–f** were designed and synthesized to evaluate their antitumor activity. The synthesized compounds were submitted to NCI, Bethesda, USA and screened for their cytotoxicity at 10 μM against 60 cell lines that include nine tumor subpanels, namely leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer cell lines. The aurones **19a**, **20c–f** and **21a–e** revealed mild activity against all cell lines. The results revealed the relatively higher GI% for series **20a–f** than series **21a–f** to explore the effect of the extra methoxy group [14].



19a,b

19a R = OCH_3
19b R = H



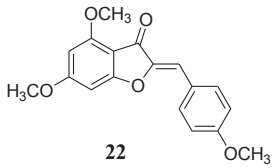
20a-f

21a-f

20a, 21a X = CH, R = H
20b, 21b X = CH, R =2-OCH_3
20c, 21c X = CH, R = 4-OCH_3
20d, 21d X = CH, R = 4-SO_2NH_2
20e, 21e X = CH, R = 4-$SO_2NHC(NH)NH_2$
20f, 21f X = N, R = H

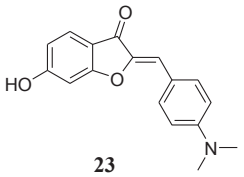
1.2. Antioxidant activity

Inhibitors of lipoxygenases (LOX) have attracted an attention initially as potential agents for the treatment of inflammatory and allergic diseases. The majority of LOX inhibitors are antioxidants or free radical scavengers, since lipoxygenation occurs *via* a carbon centered radical and these compounds can inhibit the formation of the radical or trap it once formed [15]. In 2009, Detsi et al. [15] prepared different aurone derivatives and tested their antioxidant and lipoxygenase inhibitory activities. The prepared compounds have shown lipid peroxidation inhibition activity and free radical scavenger ability. Compound with methoxy group at position 4 on ring B; **22** was found to have the most promising antioxidant-LOX inhibitory profile, while its chloro analogue produced a less potent derivative.



22

Later on, the antioxidant activity of different aurone derivatives was studied by evaluating their iron chelating activity. Compounds **23** and **24** showed an enhanced iron binding capacity in the iron chelating assay. It was revealed that, the presence of electron donating moieties on ring B enhanced the activity. Moreover, the scavenging ability of all of the synthesized compounds was found to be better than ascorbic acid, the reference compound in hydrogen peroxide scavenging assay [16].



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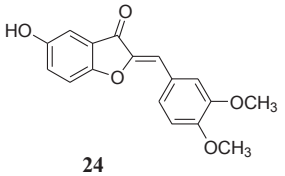
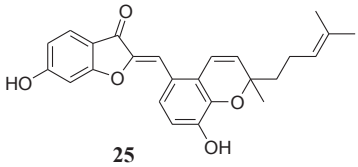


24

Another research group isolated and elucidated a naturally occurring aurone from *Artocarpus altilis*. The structure was elucidated as (*Z*)-6-hydroxy-2-[8-hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-2*H*-1-benzopyran-5-ylmethylene]-3(2*H*)-benzofuranone (**25**). Screening the antioxidant activity of the isolated compound revealed a moderate nitric oxide radical scavenging activity [17].

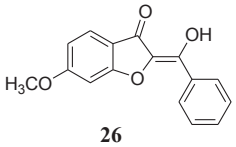


25

1.3. Antiparasitic activity

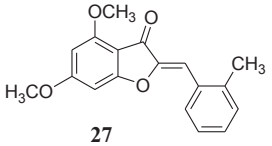
1.3.1. Antileishmania activity

Kayser and Kiderlen [18] studied the antileishmanial activity of different aurone derivatives. The ability of these aurones to inhibit the parasite growth apparently depended on the oxygenation pattern of the substituents. The limited number of oxygenated substituents indicated more lipophilic nature thus enhancing the activity as demonstrated by compound **26**. Addition of hydroxyl groups at positions 3, 4 or 5 on ring B reduced the antiprotozoal activity that may be explained by the shift to a more hydrophilic character.



26

In 2012, different aurone derivatives bearing a variety of substituents on rings A and B were synthesized and evaluated for their antiparasitic activity against the intracellular form of *Leishmania infantum*. The electronic nature of the substituents as well as their position played an important role in the antiparasitic activity. Results revealed that aurones bearing methoxy groups on ring A and electron donating groups on ring B exhibited a good antiparasitic activity. Compounds **27** and **28** bearing methyl group or methoxy group at position 2 on ring B exhibited potent antileishmanial activity (IC_{50}: 1.3 and 1.6 μM respectively) comparable to the activity of the reference drug amphotericin B (IC_{50}: 1.2 μM) [19].



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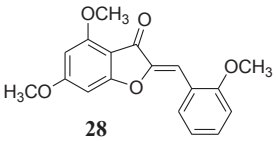
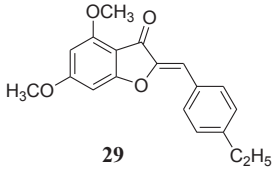


28

1.3.2. Antimalarial activity

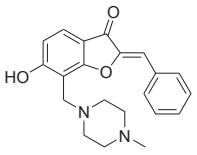
Malaria remains a critical global health problem, with terrible social and economic consequences in countries where this disease is endemic. The problem is exacerbated by the emergence and spread of parasites that are resistant to well-established antimalarial drugs [20].

Souard et al. [21] analyzed several aurones for their potential antimalarial activity. All of the synthesized compounds were found to be non-cytotoxic in human cell lines. SAR analysis revealed that, incorporation of methoxy groups at positions 4 and 6 on ring A increased the antimalarial activity as shown in compound **29**.



29

Moreover, several aurone derivatives with additional structural diversity were synthesized and screened against a chloroquine-resistant *P. falciparum* strain. It was demonstrated that aurones provide a useful scaffold to generate novel bioactive compounds with a good antiplasmodial activity. The results showed that, compounds containing a basic moiety, compounds **30** and **31,** were able to be accumulated in the acidic digestive vacuole of the malaria parasite exerting its activity [20].



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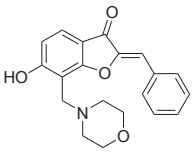
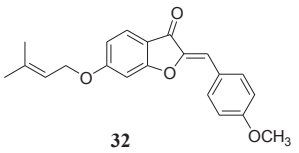


31

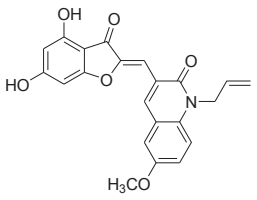
1.4. Antibacterial activity

Several prenyloxy aurones were designed, synthesized and screened for their antibacterial activity against *staphylococcus aureus* and *Escherichia coli*. The results demonstrated that, compound **32** with 4-methoxy group on ring B produced an enhanced activity against Gram positive bacteria *S. aureus*, while its chloro analogue exhibited a weak activity [22].



32

In 2017, Jardosh and Patel synthesized the quinolone based aurone derivative **33** evaluated for its antibacterial activity against Gram positive bacteria *Staphylococcus aureus*. The aurone derivative **33** (MIC = 12.5 μg/mL) was found to exhibit an elegant activity compared to ampicillin, chloramphenicol and ciprofloxacin (MIC = 250, 50 and 50 μg/mL, respectively) [23].

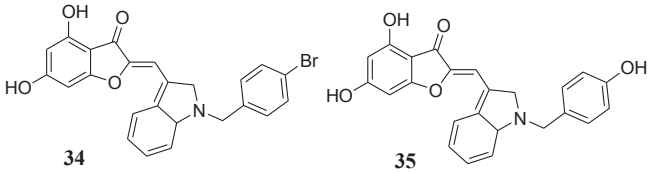


33

1.5. Anti-HCV activity

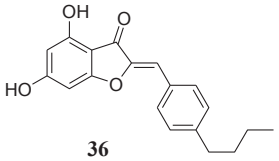
Chronic hepatitis C can progress to cirrhosis, end-stage liver disease, hepatocellular carcinoma and death. Hepatitis C virus (HCV) RNA-dependent RNA polymerase (RdRp) is a particularly attractive target because it is the key enzyme that catalyzes the viral replication [24]. In 2014, ring B of aurones was targeted with the aim to improve structural features associated with higher inhibition of the target polymerase. *In vitro* evaluation of the RdRp inhibitory activity of the synthesized compounds pointed out that the replacement of ring B with *N*-substituted indole moiety produced the highest inhibitory effect. Moreover,

the introduction of aryl moiety to the indole ring improved the inhibitory activity as shown by compounds **34** and **35** [24].



34 **35**

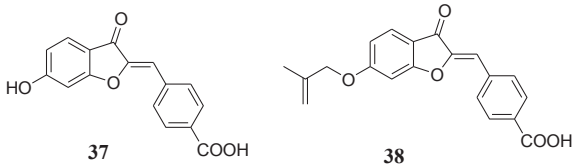
Additionally, Haudecoeur et al. [25] studied the RdRp inhibitory activity of several aurone derivatives. It was found that, the presence of hydroxyl group at position 4 on ring A was important for the inhibitory activity. Addition of hydrophobic substituents at ring B, especially at position 4, enhanced the interactions with the active site. The introduction of methyl and ethyl groups at ring B resulted in a better inhibitory activity. Compounds bearing *n*-butyl or a cyclohexyl groups provided the best inhibitory activity, indicating that both lipophilic and bulky substituents at position 4 of ring B were associated with remarkable activities as illustrated by compound **36**.



36

1.6. Xanthine oxidase inhibitory activity

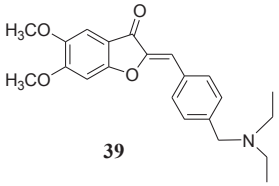
Xanthine oxidase (XO) is a potential target for treatment of hyperuricemia and gout. In 2017, Muzychka et al. [28] synthesized number of A and B ring carboxylated aurone derivatives and evaluated their ability to inhibit xanthine oxidase *in vitro*. According to the results obtained, the aurones with carboxylic acid group at position 4 on ring B were found to be more potent inhibitors of the enzyme with IC_{50} values in micromolar range. The most active derivatives were compounds **37** and **38** showing IC_{50} of 68 and 46 nM respectively, compared with the reference drug, febuxostat (IC_{50} = 10 nM).



37 **38**

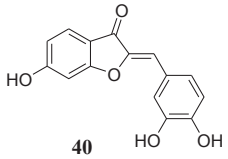
1.7. Anti-Alzheimer's activity

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and one of the most common causes of mental deterioration in the elderly. Acetylcholine esterase (AChE) inhibitors are still the major and most developed class of drugs approved for AD therapy. Thus, several aurone derivatives were designed, synthesized and evaluated for AChE inhibitory activity. Most of the tested compounds demonstrated a high inhibitory activity and selectivity against AChE. The exocyclic double bond was found to enhance the inhibitory activity. Compound **39** with 4-diethylaminomethyl group of ring B was more effective than that substituted at position 3 [29,30].



39

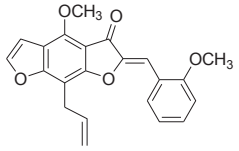
CDK5 belongs to serine/threonine cyclin-dependent kinase (CDK) family. The deregulation of CDK5 is believed to be involved in several neurodegenerative diseases. The activity of (*Z*)-2-(3,4-dihydroxy benzylidene)-6-hydroxybenzofuran-3(2*H*)-one (**40**) was studied by Shrestha et al. [31]. It was found that, this compound had a potential to inhibit CDK5, which could be useful in the treatment of Alzheimer's disease, showing a moderate *in vitro* inhibition capacity.



40

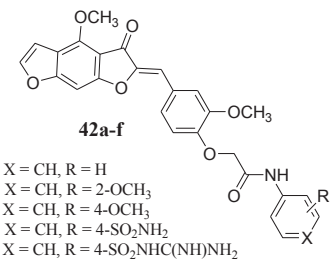
2. Biological activities of furoaurones

In 2014, Ragab et al. [32] designed and synthesized various furoaurones derivatives. The prepared compounds were evaluated for their antiproliferative activity against a panel of 60 cancer cell lines including: lung, ovarian, prostate, renal and CNS cancer. Compound **41** exhibited a great activity toward most of the tested cell lines, especially CNS caner.



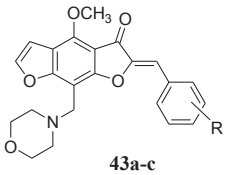
41

Recently, some furoaurones **42a–f** and **43a–c** were synthesized as antiproliferative agents and screened for their cytotoxic activity against 60 cell lines with fewer side effects. In addition, the effect of the biologically active compounds on the cell cycle and the proposed mechanism for apoptosis induction and inhibition were evaluated CDK2 [14].



42a-f

42a X = CH, R = H
42b X = CH, R = 2-OCH_3
42c X = CH, R = 4-OCH_3
42d X = CH, R = 4-SO_2NH_2
42e X = CH, R = 4-$SO_2NHC(NH)NH_2$
42f X = N, R = H



43a-c

43a R = H
43b R = 4-OCH_3
43c R = 3-OCH_3, 4-OH

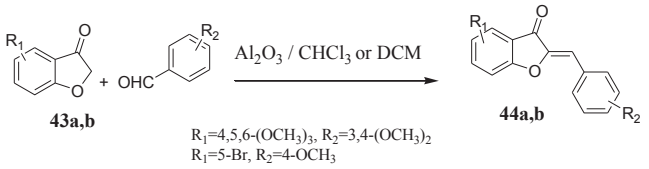
The unsubstituted furoaurone derivative, **42a** was found to be the most active one exhibiting promising growth inhibition against leukemia, K562 (GI% = 70.33) and melanoma, MDA-MB-435 cells (GI % = 79.61) at concentration 10 μM. It induced apoptosis in both cell lines by activation of caspase-3 with 9.6 and 7.9 fold. Compound **42a** has inhibitory effect of CDK2 with IC_{50} 1.11 and 1.14 μM, more potent than the reference drug erlotinib with IC_{50} 3.29 and 7.05 μM in leukemia, K562 and melanoma, MDA-MB-435 cells, respectively. Considering that IC_{50} value of compound **42a** to normal kidney RPTEC/TERT1 cell line is (76.9 ± 1.8 μM) and normal liver THLE2 cell line (61.7 ± 1.1 μM). It did not seem to have any significant *in vitro* effect on normal kidney and liver cells [14].

3. Synthesis of Aurones

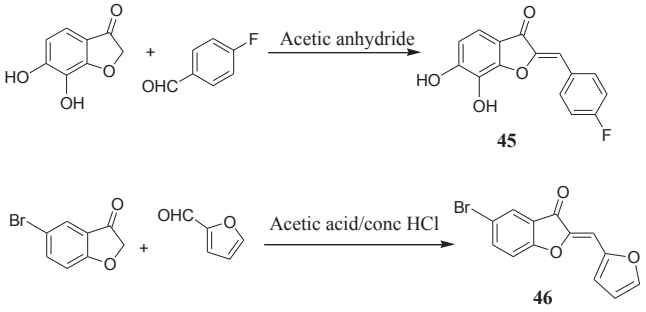
There are mainly two major routes for the synthesis of aurones that are summarized as shown below.

3.1. Condensation of benzofuran with different aldehydes

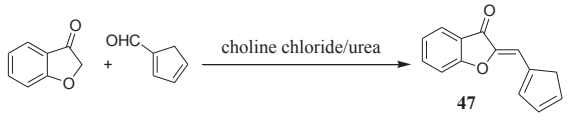
It was found that, condensation reaction could be carried out using basic alumina that proceeded in few minutes with no undesirable by-products [33]. Active alumina was added to a solution of benzofuran derivatives **43a,b** and substituted aromatic aldehydes in dry dichloromethane or chloroform to yield aurone derivatives **44a,b** in good yields (84.7% and 85.7%, respectively) [34,35].



Also, condensation reaction could be carried out in acidic conditions. In 2004, Venkateswarlu et al. [36] prepared aurone derivative **45** by reacting 6,7-dihydroxybenzofuran with 4-fluorobenzaldehyde in acetic anhydride. Later on, Gou et al. [37] performed the reaction in glacial acetic acid with few drops of concentrated hydrochloric acid to produce the aurone; **46**.

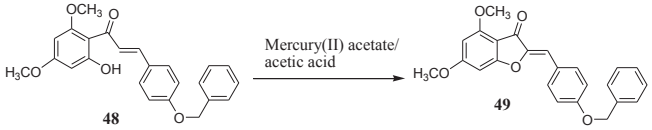


Deep eutectic mixtures are mixtures composed of two or more materials where the melting point is drastically reduced compared to that of the original two components. The choline chloride/urea (CC/U) deep eutectic solvent is a quite interesting mixture being inexpensive, readily available in large quantities and non-toxic. Compound **47** was prepared with a good yield using this simple and fast method [38].

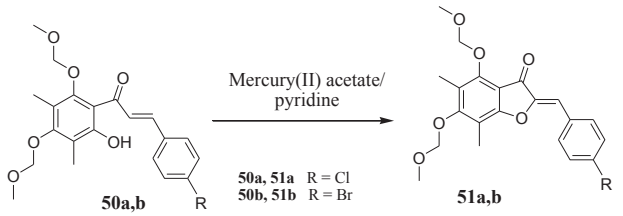


3.2. Oxidative cyclization of 2′-hydroxy chalcones

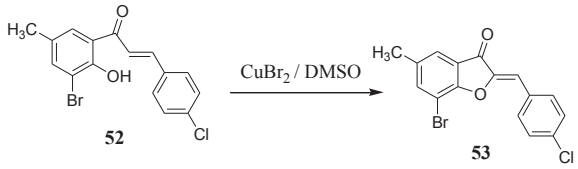
Oxidative cyclization of 2′-hydroxy chalcones into aurones could be obtained using mercury (II) acetate in pyridine or acetic acid [39–41] Oxidative cyclization of 2′-hydroxy chalcone derivative **48** was carried out using mercury (II) acetate/acetic acid to produce the corresponding aurone; **49** with a moderate yield (62%), but with a long reaction time [40].



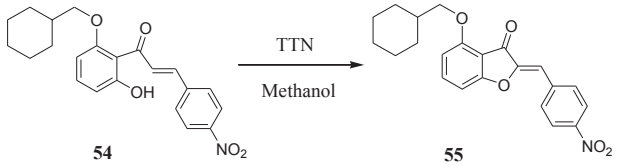
Rui et al. [41] prepared the aurone derivatives **51a,b** from their corresponding chalcones **50a,b** using mercury (II) acetate in pyridine and the reaction mixture was heated to 60 °C for only 2 h (%yield 86.7–90.2).



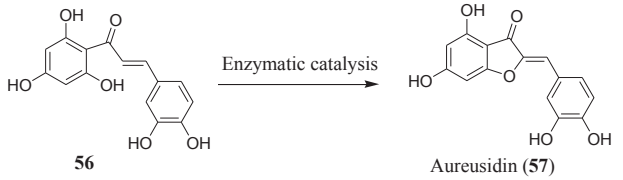
Cupric bromide has a good oxidizing property, so it was utilized in dimethyl sulfoxide by Agrawal and Soni [42] in attempt for the synthesis of aurone derivative **53**. This method produced the target compounds within only one hour.



Oxidative cyclization of 2′-hydroxy chalcones by treatment with the thallium (III) nitrate (TTN) was studied by Thanigaimalai et al. [43]. The pathway of the cyclic oxidation depended on the nature of substituents present at the starting chalcones. Aurone derivative **55** having an electron withdrawing group was only produced with no other by-products.

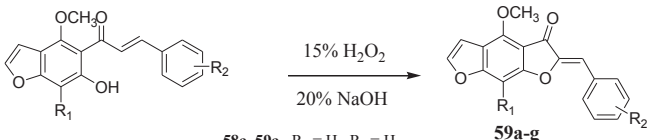


Peroxidases (PODs) are common enzymes that catalyze a variety of oxidative transformations using hydrogen peroxide. Moussouni et al. [44] developed a method for the preparation of a peroxidase-active crude extract from onion solid wastes to be used as a source for POD. The crude enzyme preparation effectively promotes the cyclization of 2′,3,4,4′,6′-pentahydroxy-chalcone (**56**) into aureusidin (**57**).



4. Synthesis of Furoaurones

Furoaurones, 2-benzylidenefurano[3,2-f]benzofuran-3(2*H*)-ones, are chemically related to aurones, in which a furan ring is fused to the benzofuran system. Thus, there is a great similarity between the methods used for preparing aurones and furoaurones. Furoaurones; **59a**, **59b** [45], **59c**, **59d** [46], **59e** [47], **59f** and **59g** [14] were mainly prepared starting from the naturally occurring furochromones, visnagine and khellin, 4-methoxy-7-methyl-5*H*-furo[3,2-g]benzopyran-5-one and 4,9-dimethoxy analogue, respectively [45]. Oxidative cyclization using hydrogen peroxide in alkaline medium is one of the easiest methods used for cyclization of 2′-hydroxy chalcones to the corresponding furoaurones.

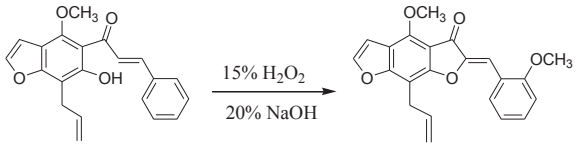


58a-g

59a-g

58a, **59a** $R_1 = H$, $R_2 = H$
58b, **59b** $R_1 = OCH_3$, $R_2 = H$
58c, **59c** $R_1 = H$, $R_2 = 4\text{-}OCH_3$
58d, **59d** $R_1 = H$, $R_2 = 3,4\text{-}(OCH_3)_2$
58e, **59e** $R_1 = H$, $R_2 = Cl$
58f, **59f** $R_1 = H$, $R_2 = 3,4,5\text{-}(OCH_3)_3$
58g, **59g** $R_1 = H$, $R_2 = 4\text{-}OH, 3\text{-}OCH_3$

Furoaurone derivative **41** was prepared by Ragab et al. [32] from their corresponding chalcone by refluxing with 15% hydrogen peroxide and 20% sodium hydroxide solution in ethanol for 24 h.



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