Review

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Review

Flavones and Related Compounds: Synthesis and Biological Activity

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Abstract: This review focuses on the synthesis and biological activity of flavones and their related flavonoidic compounds: flavonols and aurones. Among the biological activities of flavones and aurones, the anticancer, antioxidant and antimicrobial properties are highlighted and detailed in this review. The most applied method for the synthesis of flavones and aurones is based on the oxidative cyclisation of o-hydroxychalcones. Depending on the reaction conditions and the structure of the precursor, in some cases several cyclization products result simultaneously: flavones, flavanones, flavonols and aurones. Based on the literature data and the results obtained in our research group, our aim is to highlight the most promising methods for the synthesis of flavones, as well as the synthetic routes for the other structurally related cyclization products, hydroxyflavones and aurones, considering that in practice it is difficult to predict which is the main or exclusive cyclisation product of o-hydroxychalcones under certain reaction conditions.

Keywords: chalcones; flavones; flavonols; aurones

1. Introduction

Flavonoids are a widely distributed group of natural polyphenolic compounds, found in plants usually in glycosylated form, that have been shown to possess a wide range of biological activities, including antioxidant, anti-inflammatory, antibacterial, antiviral and anti-cancer properties, making them an attractive target for synthesis and further study.

Structurally, flavonoids are functional aromatic compounds constituted by a C6-C3-C6 structure. The bioprecursor of flavonoids is the amino acid L-phenylalanine, which is transformed into phenyl-propenoyl-S-CoA with the involvement of the enzyme phenylalanin-ammonia lyase. Enzymatic condensation of phenyl-propenoyl-S-CoA with three malonyl-S-CoA units, followed by cyclisation, conduct to o-hydroxychalcones, that are structurally 1,3-diaryl-propen-1-ones [1].

The reactive α,β-unsaturated ketone structure and the presence of hydroxy groups in o-hydroxychalcones make possible their cyclisation, resulting different flavonoidic compounds. Similar to biochemical cyclisation pathways, in organic synthesis the cyclization of o-hydroxychalcones represent the most useful way to obtain compounds from the class of aurones, flavanones, flavones, flavonols, flavilium salts. The cyclisation occurs differently, depending on the reaction conditions, the catalysts used, as well as on the nature and the position of the substituents grafted on the aromatic moieties.

The outstanding biological potential of natural flavonoids has attracted interest in the medical field, so that many of their synthetic analogues are currently known as promising candidates in the therapy of cancer, microbial, fungal and viral infections, inflammatory diseases and diabetes.

Among flavonoidic compounds, flavones and flavonols are related by the fact that they possess the same basic skeleton, the 2-phenyl-chromen-4-one system. Flavones represent one the most studied sub-class of flavonoids, due to their wide distribution in plants and their wide structural diversity.

Flavonols, also called hydroxyflavones, differ from flavones by the presence of a hydroxy group at position 3 in the chromen-4-one ring (C ring, Figure 1). Although they have very similar structures,

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natural flavonols are not formed from chalcones *via* flavones as intermediates, but through another biochemical pathway, with the involvement of other enzymes, via flavanones. Flavanones are common bioprecursors for flavones and flavonols.

Aurones, 2-benzylidenebenzofuran-3(2H)-ones, are also belonging to flavonoids class, being structural isomers of flavones (Figure 1). Even if aurones are less known compared to flavones, their study has experienced significant development in recent years, due to their promising therapeutic potential.

Due to their related structure, flavones, flavonols and aurones have common properties, such as the interesting way they exert their antioxidant properties, anticancer properties and other pharmacological properties.

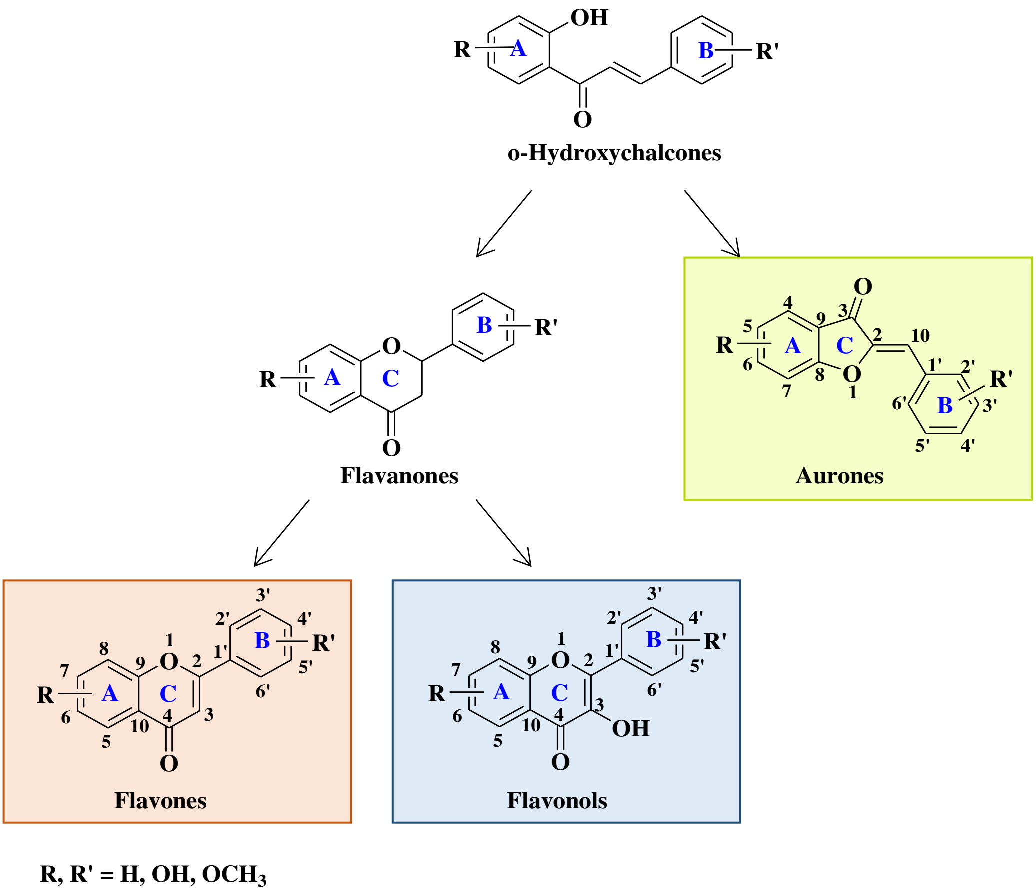

Figure 1. General structures of flavones, flavonols, aurones and their common precursors, the o-hydroxychalcones.

In recent years, various methods have been developed for synthesizing flavones and related compounds such as hydroxyflavones and aurones, including chemical synthesis, biochemical synthesis, enzymatic synthesis and total synthesis. Chemical synthesis is based on different approaches, involving the use of different precursors or reagents, the earliest developed synthesis methodologies for flavones being from late 1890s-1900s (the von Kostanecki methodology and von Auwers synthesis [2]).

This review aims to present the most relevant methods for flavones and aurones synthesis, starting with the earliest and concluding with the recent methods. We consider it important to specify some examples from the literature and from our own research in which aurones and hydroxyflavones were obtained by cyclisation of o-hydroxychalcones, considering that they are structurally related compounds and sometimes it is difficult to predict which is the main or exclusive reaction product under certain reaction conditions.

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Although the synthesis methodologies were first applied for obtaining the basic skeleton of natural flavones or aurones (in which rings A and B are benzene rings), some of these methods were successfully extended also to obtain new bioactive flavonoidic analogues of natural compounds or flavones/aurones hybrids, through structural modulations at the level of A, B or C rings, with the aim of obtaining new bioisosters with improved biological functions. All structural modulations are keeping the aromatic character of A and B rings, essential for their biological activity.

Structural modulations made on ring A of flavones and aurones consist in grafting different electron withdrawing (halogen atoms, cian, nitro) or electron donating substituents such as hydroxy, methoxy or acyloxy groups. Bulkier substituents such as pyperidine, directly connected to A ring or through a linker, benzyloxy, benzylamino, isopentyloxy, benzylaminomethylene are also introduced at different positions of A ring of some reported flavonoidic analogues with anticancer / antimicrobial activity, exemplified below.

Structural modulations at aromatic B ring include the introduction of various electron withdrawing (halogen atoms, carbamoyl, trifluoromethyl groups) or electron donating substituents (hydroxy, methoxy, benzyloxy, alkyl, acylamino, alkylamino, dialkylamino, other multifunctionalized residues such as amino acid residues). Other structural modifications are based on the replacement of B ring with other pentaatomic or hexaatomic aromatic heterocycles such as thiazole, pyrazole, thiophene and pyridine, alone or linked/condensed with other (hetero)aromatic rings in order to obtain extended π conjugated aromatic systems such as 2-phenylthiazole, thiazolo[3,2-b]-1,2,4-triazole, 1,3-diphenylpyrazole, 3-naphtyl-1-phenylpyrazole and quinoline.

The structural changes at the level of C ring of flavones and aurones were less investigated. The most frequently reported changes include the derivatisation of the hydroxy group of hydroxyflavones, by alkylation or acylation. Recent attempts were made to obtain azaaurones, compounds which contain nitrogen as heteroatom in the C ring, instead of oxygen. It was found that the replacement of intracyclic oxygen of aurones with nitrogen is beneficial for the selective cytotoxicity against some multidrug resistant cancer cells such as the resistant cancer cell line P-glycoprotein-overexpressing human doxorubicin resistant uterine sarcoma cells (MES-SA/Dx5) [3].

2. Biological activity of flavones, flavonols and aurones

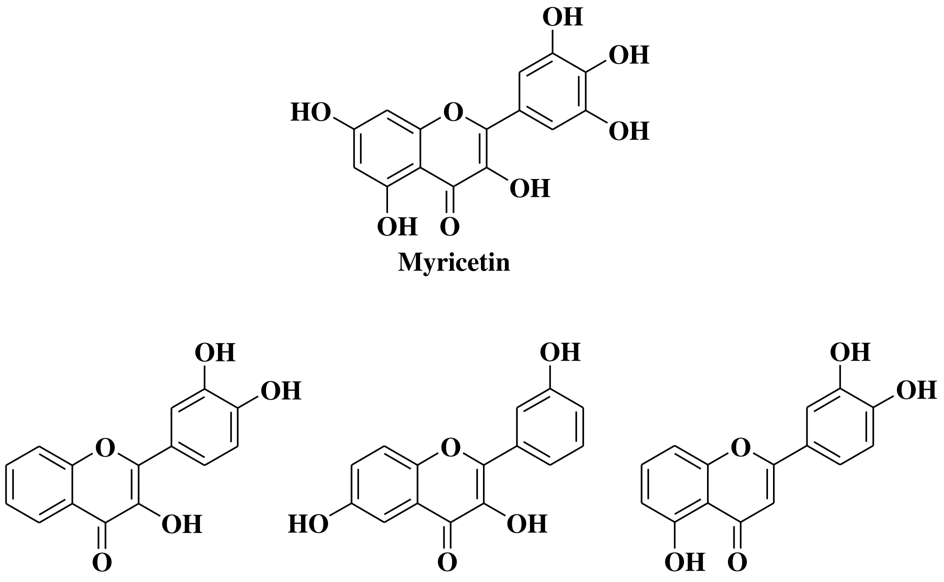
2.1. Anticancer activity

The antitumor activity of flavones is most often due to their ability to target certain key-structures that lead to cell cycle arrest and apoptosis of tumour cells. Thus, flavones can inhibit certain enzymes responsible for tumorigenesis, which were normally involved in the regulation of the cell cycle, but whose function was deregulated under pathological conditions, for example protein kinase C (PKC) [4], cyclin-dependent kinases (CDK) [5], casein kinases (CK) [6], PIM-1 kinases [7], death-associated protein kinase 1 (DAPK-1), tyrosin kinases [8]. Some flavones can inhibit the polymerization of tubulin, thus preventing the formation of microtubules [9]. All this results in the cell cycle arrest, most often in the G2/M phase. Flavones can also activate certain enzymes that cause tumour cell apoptosis, such as caspases [10,11].

The potential of flavones to act on multiple anticancer targets or by synergic mechanisms of action make them promising candidates for the development of new multitarget acting therapeutic agents.

In several cases, in particular for natural products, the anticancer activity of flavones and aurones is closely related to their antioxidant activity. Myricetin (Figure 2), a natural flavone with polyphenolic structure, presents good antioxidant properties by acting as a scavenger for reactive oxygen species and by enhancing the activity of glutathione-S transferase [12]. Myricetin presents also great antitumor properties, acting on multiple anticancer targets such as PKC, CK2, PIM-1, DAPK1, the molecular mechanisms of action being recently elucidated [13]. Myricetin proved to be effective also in preventing mutagenesis induced by different carcinogenic compounds.

The anticancer activity of flavones could be correlated with their antioxidant activity, but it is not a mandatory rule in all cases. Grigalius I. and Petrikaite V. studied the relationship between the anticancer and antioxidant activity of trihydroxyflavones. The antioxidant activity was evaluated by the DPPH (2,2-diphenyl-1-picrylhydrazyl) method, and the anticancer activity by the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) method, performed on three different types of human cancer cell lines: lung (A549), breast (MCF-7) and brain epithelium (U87). Based on the calculation of the Pearson coefficient (r), a moderate correlation was revealed between the two biological properties [14]. It was found that the substituents on the phenyl ring (B ring) are the most important for the antioxidant activity of trihydroxyflavones. Thus, the most potent antioxidants have the o-dihydroxy group (catechol) in ring B, which are involved in binding hydroxy, peroxyl and peroxynitrile radicals [14] (Figure 2). However, hydroxyflavone **2** does not possess this structural feature, but it presents the best anticancer activity, thus speculating the existence of other mechanisms of action for the anticancer activity in this case, besides the neutralizing effect of free radicals.


Myricetin

1 **2** **3**

Figure 2. Polyphenolic flavones with anticancer and antioxidant activity[14].

The structural elements of flavones capable of blocking different serine-threonine kinases involved in the cell cycle were studied by Zhao *et al*. The structure-activity relationship studies were realised for PKC, CK-2, PIM-1 kinase, DAPK-1 and CDK. It was found that the hydroxy groups grafted on rings A, B and C are acting as H-bond donors/acceptors in the interaction with PKC, PIM-1, DAPK-1 and CDK [15]. For the inhibition of CK-2, it was found that the presence of halogen atoms (Br, Cl) at positions 6 and 8 of A ring and respectively hydroxy group only in position 4 of ring B are beneficial. The carbonyl group in position 4 of the benzochromen-4-one ring act as H-bond acceptor in the interaction with various amino acid residues from CK-2, CDK si PIM-1. The benzene ring (B ring) interacts by ◎-◎ stacking with Fen113 of CK-2 and by this mechanism it also blocks the ATP binding site of these enzymes. The benzene ring (B ring) can also make van der Waals interactions with certain hydrophobic residues from CDK-9 and PIM-1 and in this way, it makes an additional contact with these enzymes without blocking the binding of ATP. It was also observed that changing the position of the phenyl ring from 2 to 3, specific to isoflavones, leads to the loss of activity [15].

Flavopiridol (Table 1, line 1) is a semisynthetic flavone that is currently in clinical trials as anticancer agent for the treatment of acute myeloid leukemia. This compound act by inhibiting kinases CDK-1, -2, -4, -6 and -7, competitive with ATP. At the same time, flavopiridol significantly inhibits kinases CDK-9 non-competitive with ATP [8,15]. Flavopiridol inhibits also the activity of positive transcription elongation factor (P-TEFb), a cyclin-dependent kinase controlling elongation by RNA polymerase II [16].

The anticancer activity of flavopiridol is due to the presence of chromone moiety, which is bioisosteric with the purine ring of ATP and binds competitively to the ATP binding pocket of CDK.

The benzene ring (ring B) provides an additional contact with the enzyme, as it occupies different regions from ATP and participates in van der Waals-type interactions with other amino acid units [15]. Other important elements for the inhibition of kinase activity by flavopiridol are the hydroxy group at C-7, the hydroxy group at C-5 and the carbonyl group at C-4, the nitrogen atom and the hydroxy group from the piperidine, all these functional groups being involved in the formation of hydrogen bonds with CDK [15].

Starting from the structures of two natural products with anticancer activity with different mechanisms of action, 3,5,4'-trimethoxystilbene and 5,6,7-trimethoxyflavone, Hassan A.H.E. *et al.* synthesized new antiproliferative compounds by combining the two pharmacophore moieties in the same molecule by replacing the vinylene residue in stilbene with the amide group. The most active compounds are presented in Table 1, lines 2-4.

Flavone-stylbene hybrids in which the nitrogen atom of the amide linker is attached to the flavone moiety proved to be more citotoxic than the corresponding compounds with the opposite amide linker configuration. Trimethoxylated flavone-stylbene hybrids showed superior activity compared to dimethoxylated flavone-stylbene hybrids on hematologic, colorectal, central nervous system, ovarian, renal, and breast cancer cell lines. On lung cancer cell lines, the dimethoxylated derivatives were generally more active than the trimethoxylated ones. Most of the tested hybrid compounds showed selective activity, showing no cytotoxicity on normal cells. Their anticancer mechanism of action consists in inducing apoptosis and inhibiting cell proliferation [17].

In continuation of these researches, Hassan *et al.* synthesized a series of trimethoxyflavone-based aryl-amides, starting from the structures of already approved arylamide-type medicinal compounds (imatinib, masitinib) and replacing the bulky aromatic entity in their structure with 5,6,7-trimethoxyflavone and 5-hydroxy-6,7-dimethoxyflavone. The formation of the amide bond was carried out in the 3' and 4' positions on the B ring of the flavone, using 3'-amino and 4'-amino precursors coupled with various acyl chlorides, respectively using 3'-carboxyl precursors condensed with arylamines [18].

Two flavones presented good broad-spectrum anticancer activity by triggering cell cycle arrest in G1 phase (Table 1, line 5). These compounds could represent hit compounds for the design of new more potent inhibitors of STE20/GCK-IV kinase family members including HGK, TNIK and MINK1 kinases. It was found that the presence of the carbonyl of amide linker attached to flavone moiety is beneficial for the anticancer activity of the tested flavone-based aryl-amides. Reversing the attachment mode of the amide linker led to a significant decrease in anticancer activity [18].

A series of dimethoxyflavonols and trimethoxyflavonols derivatives were obtained by alkylation of the hydroxy group at position 3 of cromen-4-one ring (C ring) (Figure 3). The compounds were investigated for their anticancer activity on both androgen-sensitive (LNCaP) and androgen-insensitive (PC-3 and DU145) prostate cancer cell lines [19].

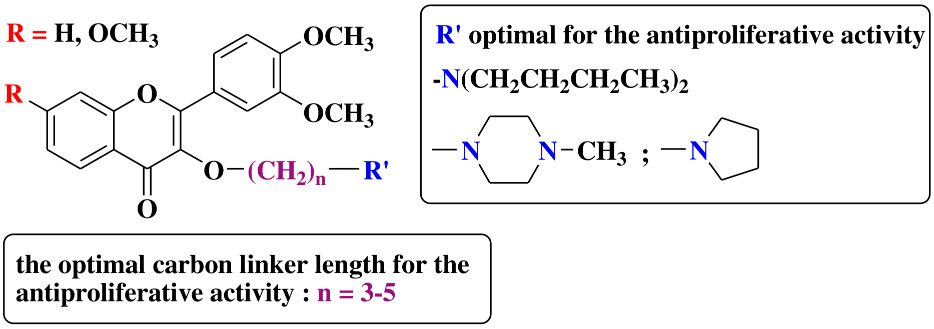


Figure 3. 3-O-Substituted flavonols as anti-prostate cancer agents. Structure-activity relationship study [19].

It was found that the alkylation of the hydroxy group in position 3 generally increased the antiproliferative activity of the compounds. The presence of an amino group linked to the hydroxy group at position 3 of flavonols through a 3- to 5-carbon linker is beneficial for the antiproliferative activity against the three human prostate cancer cell lines, with tumour-selectivity. 1-Methylpiperazine, pyrrolidine and dibutylamine groups proved to be beneficial for the improvement of the anti-cancer activity of the tested compounds. The most promising derivative in terms of selectivity, anticancer activity and biodisponibility contains a dibutyl amino group linked to the hydroxy by a 3-carbon linker (Table 1, line 6). The bioavailability of the tested compounds was superior to that of fisetin [19].

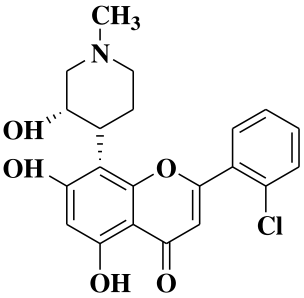
Starting from a series of differently substituted chalcones, Pontes *et al.* synthesized a series of chromene-chalcone hybrid compounds in order to test their anticancer activity on breast cancer cell lines. The most active compound is depicted in Table 1, line 7. The mechanism of action involves the inhibition of cell migration and induction of apoptosis, by determining cell cycle arrest in G2/M phase. Moreover, this compound proved to alter tubulin polymerization, representing a promising new *microtubule*-destabilizing agent. It was found that the presence of the halogen atoms grafted on the basic skeleton of chromene-chalcone hybrids is beneficial for the antitumor activity. Brominated compounds presented superior activity to chlorinated and fluorinated compounds. The evaluated compounds presented selective cytotoxicity on cancer cell lines compared to non-cancerous cell lines. The corresponding chalcones generally presented lower IC_{50} values than chromenes for both cell lines tested [9].

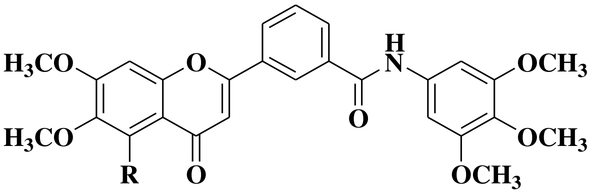
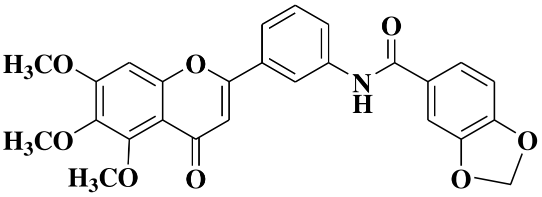
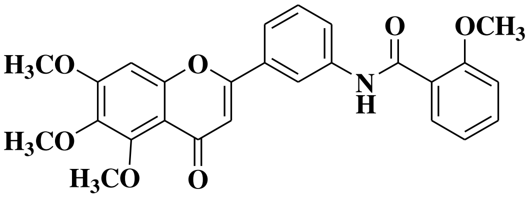
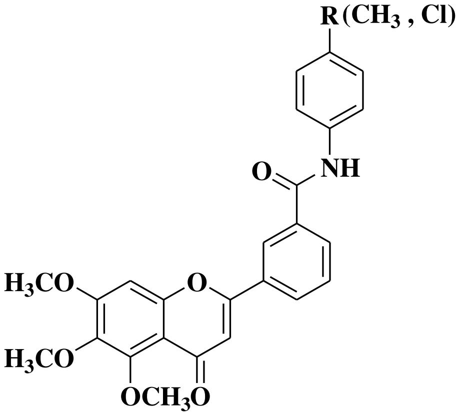
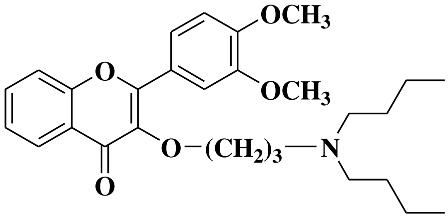
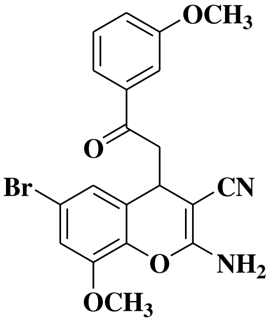
Natural and synthetic aurones possess a broad variety of biological activities, including antiproliferative activity against different cancer cell lines. The anticancer activity of aurones is due to their ability to interact with different key antitumor molecular targets: inhibition of serine/threonine cyclin-dependent kinases (CDK 1 and 2) [20] inhibition of topoisomerase II◎ [21], inhibition of sphingosine kinase (SphK) [22] and interfering the microtubule assembly [23]. In some cases, it was found that the anticancer activity of aurones is strongly related to their antioxidant activity [24].

Several aurones proved to modulate the activity of ATP-dependent efflux pumps, such as P-glycoprotein [25] and breast cancer resistance protein (BCRP/ABCG2) [26]. By this mechanism, aurones can potentiate the effect of simultaneously administered anticancer chemotherapeutics by blocking multidrug resistance mechanisms of tumor cells.

In our research group, a series of aurones analogues were synthesized by replacing the B ring (phenyl) with the 2-arylthiazole system in order to obtain compounds with superior anticancer activity, being aware of the anticancer potential of thiazole derivatives. Two aurone analogues were active against cancer cell lines resistant to currently used chemotherapeutics, such as multidrug-resistant leukemia cell lines and breast cancer cell lines, both showing cytotoxic activities superior to doxorubicin (Table 1, lines 14,15) [27]. Other recently reported examples of synthetic aurones with antitumor activity are illustrated in Table 1, lines 16-24.

Table 1. Synthetic analogues of flavones and aurones with antitumour properties.

Entry	**Chemical structure**	**Cancer cell lines against the tested compounds present cytotoxic activity**	**Ref.**
1	 **Flavopiridol**	- acute myeloid leukemia cells	[28]
2		**R = OCH_3**	[17]

		- cell lines of hematologic cancers RPMI8226, CCRFCEM, HL60(TB), K562, MOLT4, SR - non-small-cell lung cancer (NSCLC) A549, HOP62, HOP92, H226, H23, H460, H522 - breast cancer cells MCF7, HS578T, BT549, MDAMB468 **R = OH** - ovarian cancer cell lines OVCAR3, OVCAR8, ADRRES - breast cancer cells MCF7, HS578T, BT549, MDAMB468	
3		- cell lines of hematologic cancers RPMI8226, CCRFCEM, HL60(TB), K562, MOLT4, SR. - *non-small-cell lung cancer* cell lines (NSCLC) HOP92, H322M, H460, H522	[17]
4		- - cell lines of hematologic cancers RPMI8226, CCRFCEM, HL60(TB), K562, MOLT4 - *non-small-cell lung cancer* cell lines (NSCLC) A549, HOP92 H322M, H522	[17]
5		- large spectra antitumour activity: melanoma, hematologic, renal, colon, lung, brain, ovarian, breast and prostate cancer cell lines	[18]
6		- androgen-sensitive (LNCaP) - androgen-insensitive (PC-3 and DU145) prostate cancer cell lines.	[19]
7		- breast cancer cell lines MCF-7, Hs578T, with tumor selectivity compared to non-cancer cell lines MCF-10A	[9]

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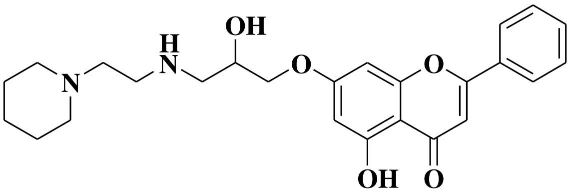
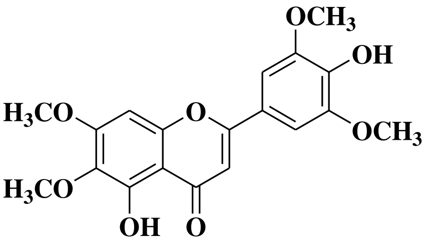
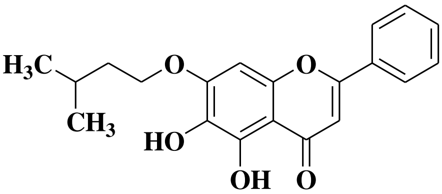
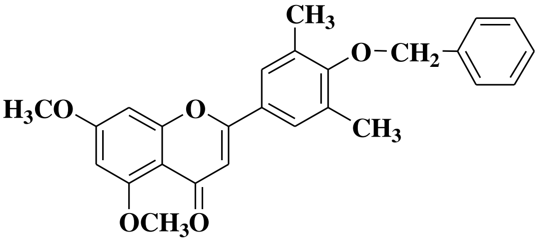
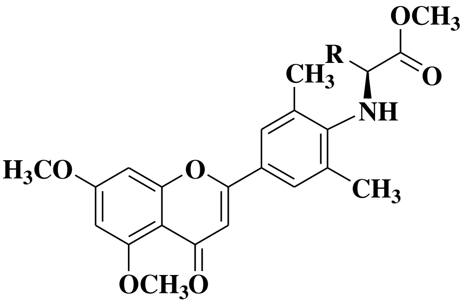
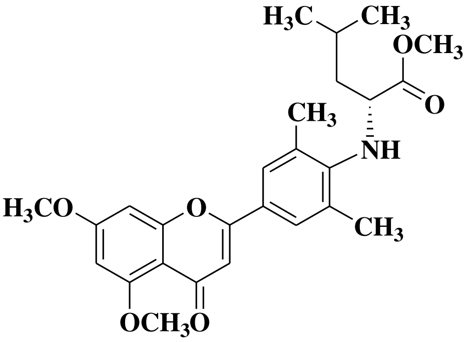
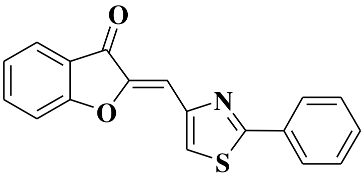
8		- AR negative castration-resistant prostate cancer cell line (CRPC) as topoisomerase II catalytic inhibitor and by intercalating and binding to the DNA minor groove - sensitizes AR-positive CRPC cells to enzalutamide and taxanes	[29]
9		- human pancreas adenocarcinoma ascites metastasis Aspc-1 cancer cell lines	[30]
10		- MCF-7 breast cancer cells and yeasts expressing human caspase-7	[11]
11		- human erythroleukemia cell line HEL prostate cancer cell line PC3	[31]
12	 **R = *iso*-C_4H_9, *sec*-C_4H_9, *iso*-C_3H_7, BocHN$(CH_2)_4$**	- human erythroleukemia cell line HEL prostate cancer cell line PC3	[31]
13		- human erythroleukemia cell line HEL prostate cancer cell line PC3	[31]
14		- leukemia cell line, doxorubicin-resistant phenotype CEM/ADR5000	[27]

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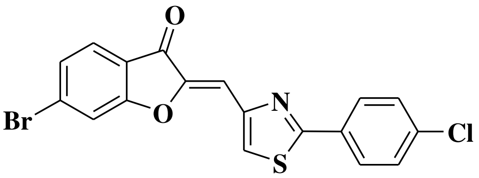
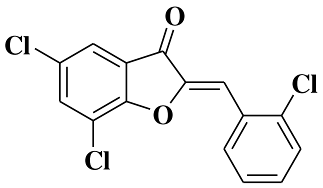
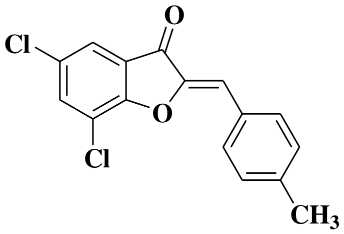
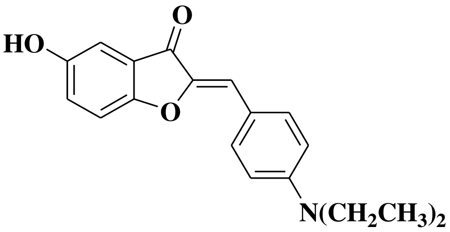
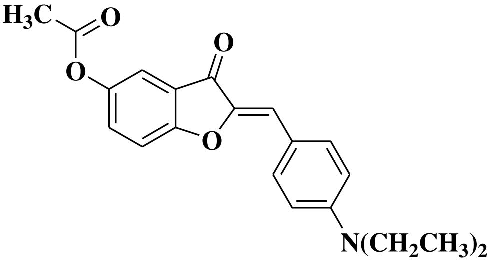
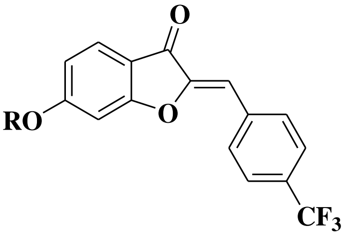
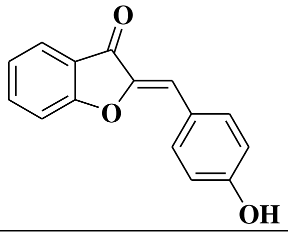
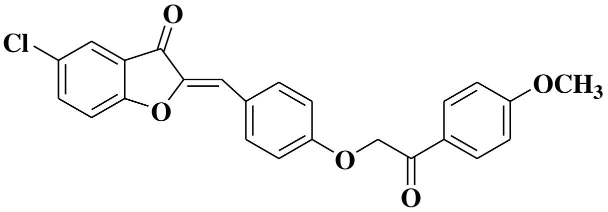
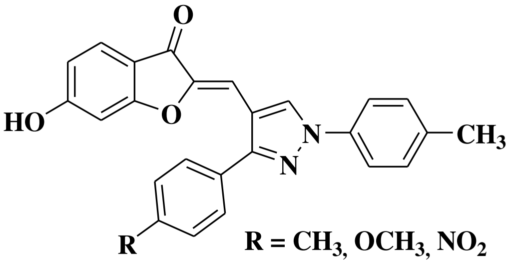
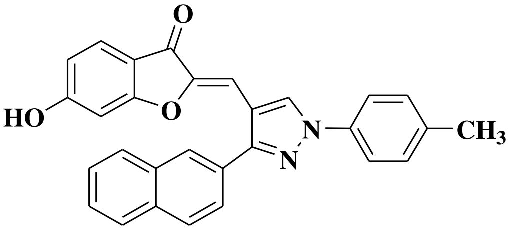
15		- breast adenocarcinoma cell line, resistant phenotype MDA-MB231/BCRP	[27]
16		- human colorectal cancer cell line HCT 116 - human chronic myelogenous leukemia cell line K562 - hormone-dependent breast cancer cell line MCF-7	[32]
17		- human chronic myelogenous leukemia cell line K562	[32]
18		- inhibition of in vitro angiogenesis of HUVEC (human umbilical vein endothelial cells) proliferation, motility and tube formation - anti-proliferative and anti-invasive activities against A549 (non-small cell lung cancer cell line) and MCF-7 (breast cancer cell line)	[33]
19		- inhibition of in vitro angiogenesis of HUVEC (human umbilical vein endothelial cells) proliferation, motility and tube formation - anti-proliferative and anti-invasive activities against A549 (non-small cell lung cancer cell line) and MCF-7 (breast cancer cell line)	[33]
20	 R = H, CH_3, C_2H_5, CH_2-CH=CH_2, C_6H_5-CH_2, n-C_7H_{15}	- leucocythemia cell line HL-60 - colorectal adenocarcinoma cell line HT-29	[34]

21		- human oral squamous carcinoma cell lines Ca9-22 (derived from gingival tissue), HSC-2 and HSC-4 (derived from tongue), with tumor-specificity in comparison to oral normal cells	[35]
22		- leukemia cell lines MOLT-4 and SR	[36]
23		- gastric cancer cell line CRL-1739	[37]
24		- gastric cancer cell line CRL-1739	[37]

2.2. *Antibacterial and antifungal activity*

Bacterial and fungal resistance to existing antibiotics is a worldwide health issue, particularly affecting the immunocompromised patients. Without effective antimicrobial agents, several medical procedures could endanger the patient lives by increasing the risk of microbial infections. The basic structure of natural flavones and aurones have inspired researchers to develop new antimicrobial agents with improved bioavailability and also antibacterial and antifungal properties.

Ashok D. *et al* synthesised new flavonols analogues bearing the extended heteroaromatic system 1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl instead of phenyl ring (B ring) and containing various substituents on the benzochromone system. The synthesised flavonol derivatives were screened for their antimicrobial activity against several fungal strains (*Aspergillus niger, Penicillium italicum, Fusarium oxysporum*) and bacterial strains (*Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Bacillus subtilis*). Four of the tested compounds (Table 2, lines 1-4) proved to have good antimicrobial activity and represent hit compounds for the design of new antifungal and/or antibacterial therapeutic agents [38].

In order to obtain new flavones analogues with antibacterial activity, Lv *et al.* synthesized a series of flavone Mannich base derivatives, by applying the Mannich reaction between primary amines, natural flavones as components with mobile hydrogen and formaldehyde as carbonyl component. The natural flavones used as precursors were baicalein, luteolin, quercetol, apigenin and kaempferol. The derivatization was performed at position 8 of the benzochromone moiety by applying the Mannich reaction. The antibacterial activity of the obtained flavone Mannich bases was evaluated for two Gram-positive bacteria (*Staphylococcus aureus* and *Listeria monocytogenes*), respectively for two Gram-negative bacteria (*Escherichia coli* and *Salmonella gallinarium*), and novobiocin and ciprofloxacin were used as standards. The structures of the most active compounds are represented in Table 2, lines 5,6. It was found that these compounds exhibit potent inhibition

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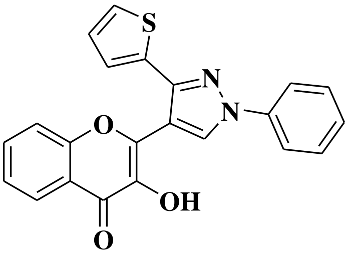
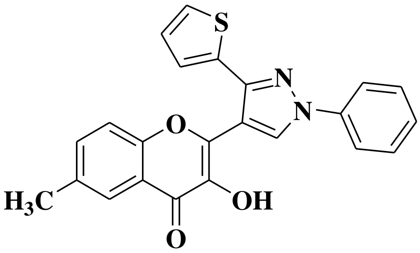
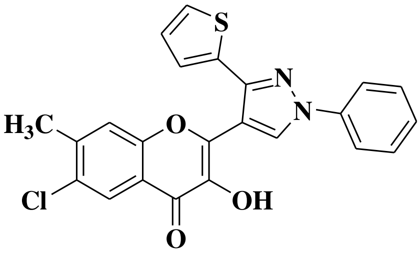
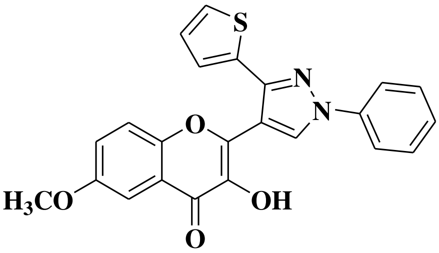
against topoisomerase II and topoisomerase IV isolated from *E. coli*, by performing *in vitro* experiments and *in silico* molecular docking studies [39].

New hydroxyflavone derivatives containing the dimethylamino group grafted at position 4 of the benzene ring (B ring) were synthesised and evaluated for their antifungal activity against *Acremonium strictum*, *Penicillium expansum* and *Aspergillus flavus*. Four of the tested compounds presented very good antifungal activities against some tested fungal strains (Table 2, lines 7-10) [40].

New quinoline-based aurone analogues were synthesised and evaluated for their antibacterial, antifungal and anti-biofilm activity. Compounds mentioned in Table 2, lines 11-13 presented the most significant antibacterial and antifungal activities and some of them proved to be also good anti-biofilm agents [41].

Table 2. Synthetic analogues of flavones and aurones with antimicrobial (antibacterial/ antifungal/ antiviral) properties.

Entry	Chemical structure	Cancer cell lines against the tested compounds present cytotoxic activity	Ref.
1		**Antifungal activity:** *Aspergillus niger* *Penicillium italicum* *Fusarium oxysporum*	[38]
2		**Antibacterial activity:** *Staphylococcus aureus* *Pseudomonas aeruginosa* *Escherichia coli*	[38]
3		**Antibacterial activity:** *Staphylococcus aureus* *Bacillus subtilis* *Escherichia coli* **Antifungal activity:** *Aspergillus niger* *Penicillium italicum* *Fusarium oxysporum*	[38]
4		**Antibacterial activity:** *Staphylococcus aureus* *Bacillus subtilis* *Escherichia coli* **Antifungal activity:** *Aspergillus niger* *Penicillium italicum* *Fusarium oxysporum*	[38]

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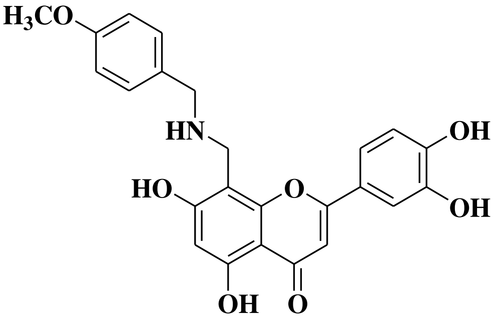
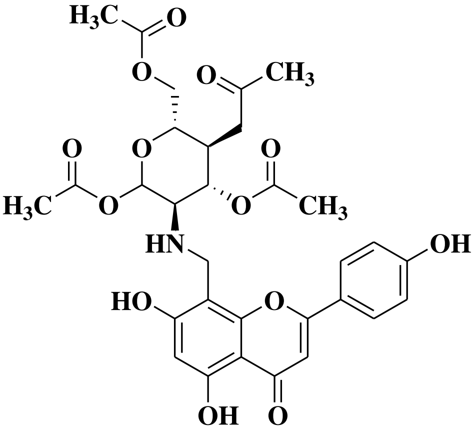
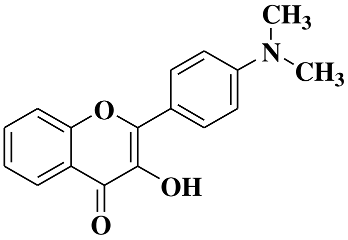
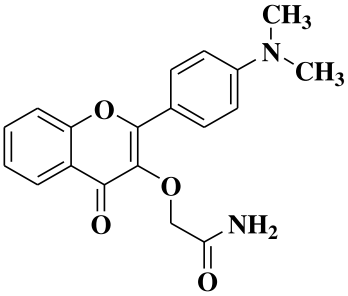
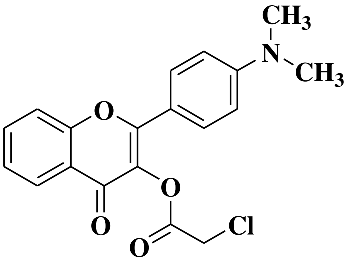
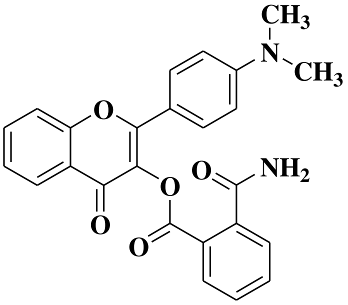
5		**Antibacterial activity:** *Staphylococcus aureus* *Escherichia coli* *Salmonella gallinarum*	[39]
6		**Antibacterial activity:** *Staphylococcus aureus* *Escherichia coli* *Salmonella gallinarum* *Listeria monocytogenes*	[39]
7		**Antifungal activity:** *Acremonium strictum* *Penicillium expansum* *Aspergillus flavus*	[40]
8		**Antifungal activity:** *Acremonium strictum* *Penicillium expansum* *Aspergillus flavus (moderate inhibition)*	[40]
9		**Antifungal activity:** *Acremonium strictum*	[40]
10		**Antifungal activity:** *Acremonium strictum*	[40]

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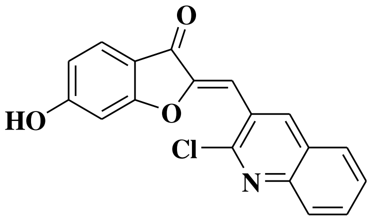
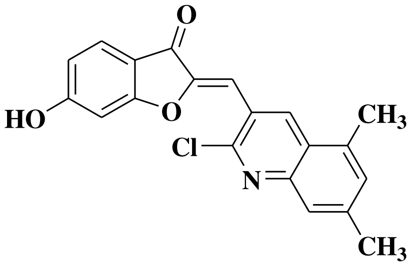
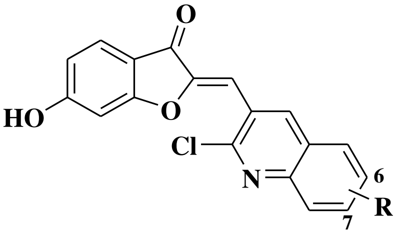
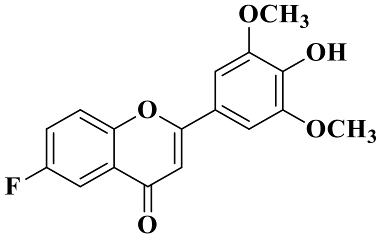
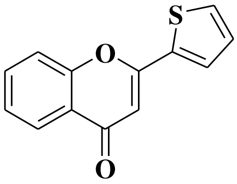
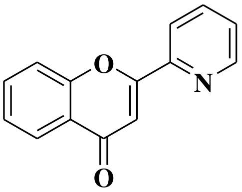
11		**Antibacterial activity:** *Staphylococcus aureus* *Bacillus subtilis* **Antifungal activity:** *Mycobacterium smegmatis* *Fusarium oxysporum*	[41]
12		**Antibacterial and antibiofilm activity:** *Staphylococcus aureus* *Bacillus subtilis* **Antifungal activity:** *Mycobacterium smegmatis* *Fusarium oxysporum* *Candida albicans*	[41]
13		**Antibacterial (R=6-OCH_3, 7-Cl) and anti-biofilm (R=6-OCH_3) activity:** *Staphylococcus aureus* *Bacillus subtilis* *Klebsiella pneumoniae* **Antifungal activity (R=7-Cl):** *Candida albicans*	[41]
14		**Antiviral activity against human *cytomegalovirus***	[42]
15		**Antiviral activity** against *Chikungunya Virus*	[43]
16		**Antiviral activity** against *Chikungunya Virus*	[43]

2.3. Antiviral activity

Viral infections represent a global health issue with many implications throughout history such the appearance of new mutant viral strains and the emergence of pandemics. Specific aspects of modernization, such as rapid air transit and urbanization, have accelerated the emergence and spread of viruses. Antiviral therapy is necessary when vaccination does not bring the expected results or in the case of infections for which vaccination has not been implemented. In the research of new molecules with antiviral potential, flavones are also included, with some important results and positive prospects for the future.

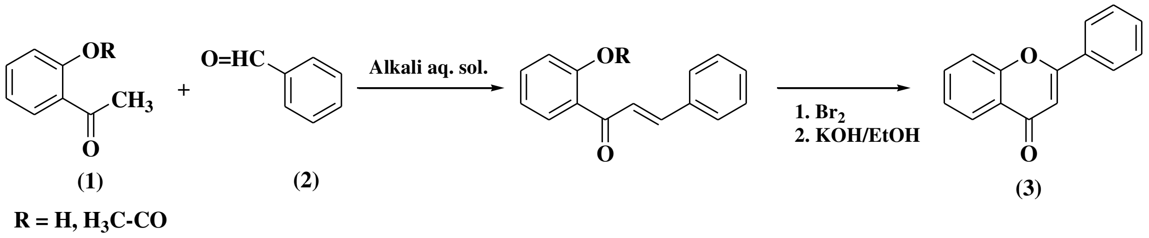
Starting from tricin, 4',5,7-trihydroxy-3',5'-dimethoxyflavone, a flavone derivative with activity against cytomegalovirus (CMV), Fujimoto *et al*. modulated its structure, by grafting a fluorine atom on the benzochromen-4-one ring. Thus, two compounds were obtained, 6-F-tricin and 7-F-tricin whose antiviral activity was measured against cytomegalovirus, replicated on embryonic lung cell cultures. Compared to ganciclovir, 6-F-tricin showed a much stronger action against cytomegalovirus (Table 2, line 14). Moreover, it was observed that 6-F-tricin did not produce cytotoxicity on the used embryonic cells. Substitution with fluorine is beneficial for increasing the affinity for target proteins, in this case for CDK9 (cyclin-dependent kinase 9) [42].

The antiviral potential of flavones has also been demonstrated against tropical diseases, such as Chikungunya fever. Badavath *et al.* synthesized nineteen flavones in order to evaluate their antiviral activity against Chikungunya virus replication. Two compounds showed activity at concentrations below 1 µg/mL (Table 2, lines 15,16). It was observed that the more potent compounds are possessing heterocycles (thiophen-2-yl and pyridyn-2-yl) in position 2 of the benzochromen-4-one, instead of the benzene ring (B ring). By molecular docking studies it was deduced that these compounds act by inhibiting the Chikungunya virus protease [43].

3. Chemical synthesis of flavones

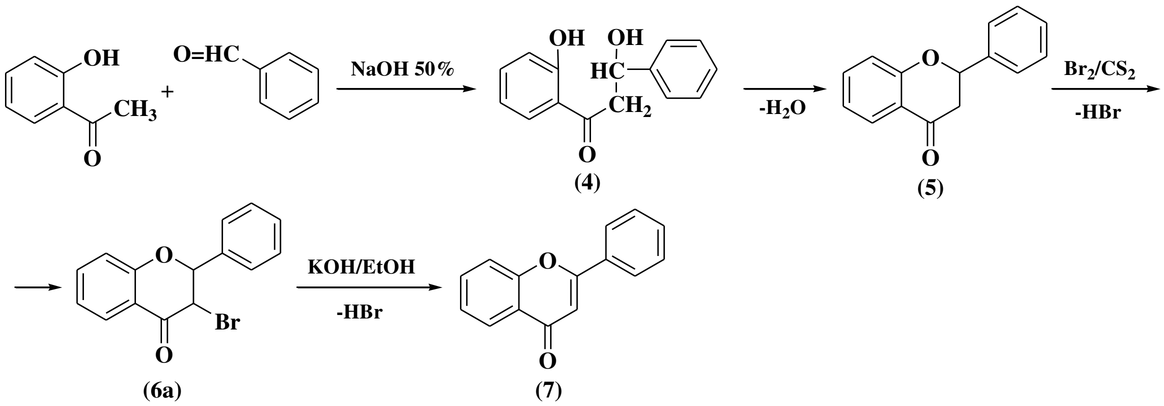
3.1. Von Kostanecki method

Stanislaus von Kostanecki's method was established in 1898-1899 and is considered one of the earliest methods of synthesis for flavones. It uses *o*-hydroxyacetophenone (or *o*-acetoxyacetophenone) **(1)** and benzaldehyde **(2)** as precursors to form 2′-hydroxychalcone (or 2′-acetoxychalcone), through a Claisen-Schmidt condensation. In the next step, the obtained chalcone is converted to flavone **(3)**, through bromination followed by a dehydrobromination reaction in alkali alcoholic solution (Scheme 1).



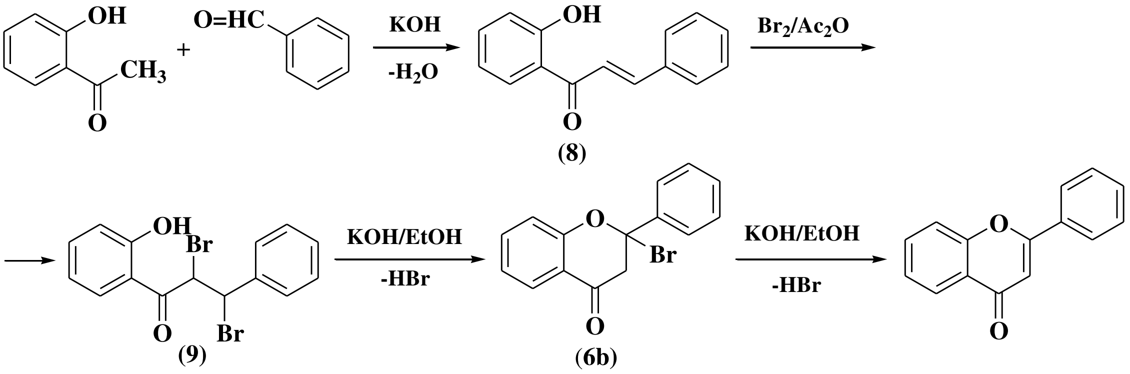
Scheme 1. von Kostanecki method for obtaining flavones.

Table 4. between the two compounds would form and then, by cyclization, a flavanone **(5)** is formed. This flavanone is next subjected to nuclear bromination with bromine in carbon disulfide, resulting a 3-bromoflavanone **(6a)** [44] and, ultimately, the brominated intermediate suffers a dehydrobromination reaction, thus resulting a flavone (Scheme 2) [45,46].



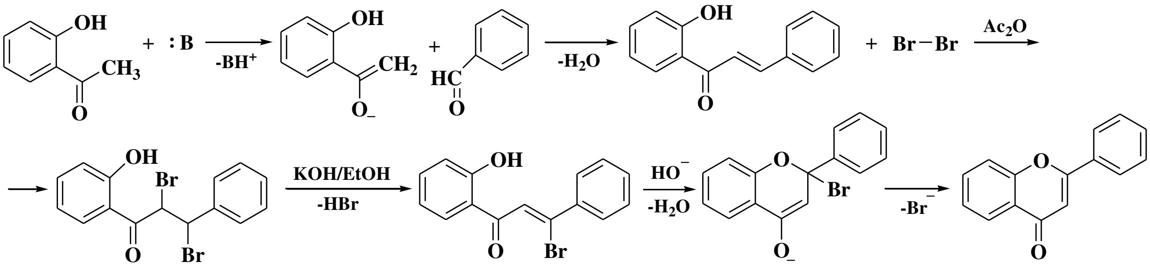
Scheme 2. von Kostanecki method according to collaboration with Levi and Tambor.

However, according to von Kostanecki's collaboration with Emilewicz and Tambor (also known as Emilewicz-von Kostanecki cyclization), the chalcone **(8)** is formed and then brominated, forming a chalcone dibromide **(9)**. This brominated compound is cyclized through the elimination of one bromine atom, resulting a 2-bromoflavanone **(6b)** and, finally, the flavone after eliminating the second atom (Scheme 3) [2,46].



Scheme 3. Emilewicz-von Kostanecki cyclization reaction steps.

The proposed mechanism debuts with a Claisen-Schmidt condensation, resulting a chalcone. Further, the chalcone is subjected to bromation on the C=C bond, with formation of a chalcone dibromide. Next step is the dehydrohalogenation reaction, coupled with cyclization, resulting a 2-bromoflavanone intermediate and then the flavone (Scheme 4) [2].



Scheme 4. Emilewicz-von Kostanecki mechanism (adapted from Kshatriya *et. al.*) [2].

The limitations of the von Kostanecki method are the possibility of nuclear bromination and the tendency to form 2-benzylidene-coumaran-3-ones **(10)** (benzalcoumaranones or aurones [47]) (Scheme 5) instead of flavones, when trying to synthesize natural flavones either with 5,7-disubstitution pattern or with a 4′- or 5′-alkoxy substituent or containing phloroglucinol moiety. Von Kostanecki obtained better results when used methyl ether derivates [48–50]. Hutchins and Wheeler observed that treating the chalcone dibromides with potassium cyanide in ethanolic solution or heating above the melting point will convert them back into flavones [50]. The same reagent converts benzalcoumaranones back to flavones (Scheme 5). The quantity of ethanolic potassium cyanide influences the reaction's outcome. In the case of 2-*p*-alkoxybenzylidenecoumaran-3-ones, refluxing with an excess of reagent will cause the ring expansion of the aurone and form 4′-alkoxyflavones, while treating the chalcone dibromide with an insufficient quantity of ethanolic potassium cyanide would produce 2-benzylidene-coumaran-3-one, instead of flavone [51].

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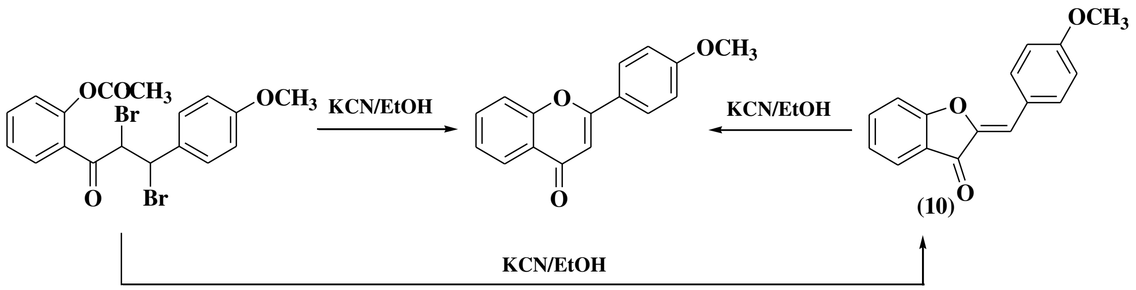
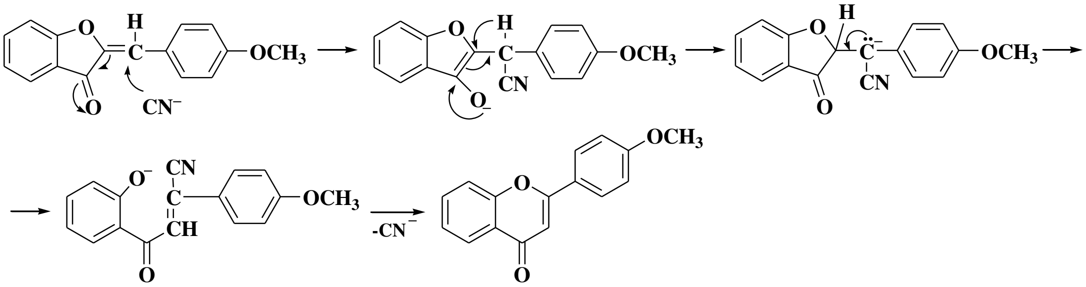


Scheme 5. Hutchins and Wheeler method to convert chalcone dibromides and aurones to flavones using ethanolic potassium cyanide (image adapted from Fitzgerald *et. al*) [51].

The possible mechanism of obtaining flavones from aurones using ethanolic potassium cyanide debuts with the nucleophilic attack by cyanide anion on the methine carbon, followed by hydrogen transfer and carbanion formation. The carbanion's electrons migrate, recreating the double bond, and preparing the ring expansion. Conjugation and nucleophilic attack by the newly-formed oxygen anion lead to the expulsion of cyanide anion, a good nucleofuge, and ring closure (Scheme 6) [51].



Scheme 6. Possible mechanism for converting aurones to flavones using ethanolic potassium cyanide (image adapted from Fitzgerald *et. al.*) [51].

However, it has been established that aurone formation may be avoided by providing milder conditions for the dehydrohalogenation reaction [46]. Donnelly and Doran have observed that the quantity of flavone increases with the decrease of base concentration [52]. von Auwers and Anschutz have shown that 4′-alkoxyflavones can be obtained by doing the cyclization reaction in cold alcohol, rather than hot alcohol which generates aurones [46,53].

Zemplén and Bognár made an improvement of the von Kostanecki method and demonstrated that nuclear bromination could be avoided by submitting acetates of hydroxyflavanones to bromination in absolute chloroform and in the presence of UV light. The obtained intermediate was a 3-bromoflavanone, which can be easily dehydrobrominated, thus resulting a flavone. This method is suitable for obtaining 3-hydroxyflavones [44,48].

Improvements in the direct dehydrogenation of chalcones and flavanones were made by using selenium dioxide as oxidative reagent [48,54].

A new method by von Kostanecki was established in 1904, in collaboration with Szabránski. This method is used for obtaining 3-hydroxyflavones from flavanones, via isonitrosoflavanones. The flavanone is nitrosated with pentylnitrite and hydrochloric acid. The isonitrosoflavanone is converted to 3-hydroxyflavone by adding diluted sulphuric acid and eliminating hydroxylamine (Scheme 7) [55].

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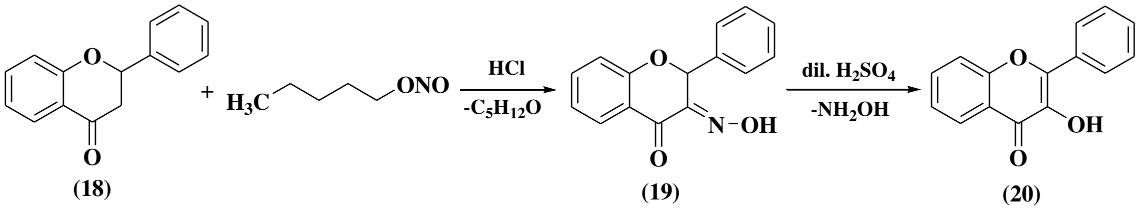
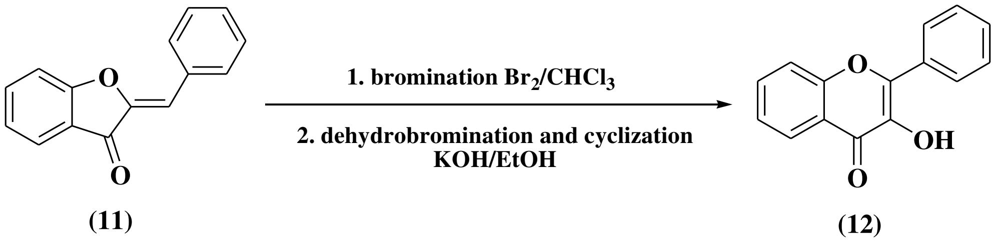


Scheme 7. von Kostanecki-Szabránski method for obtaining 3-hydroxyflavones.

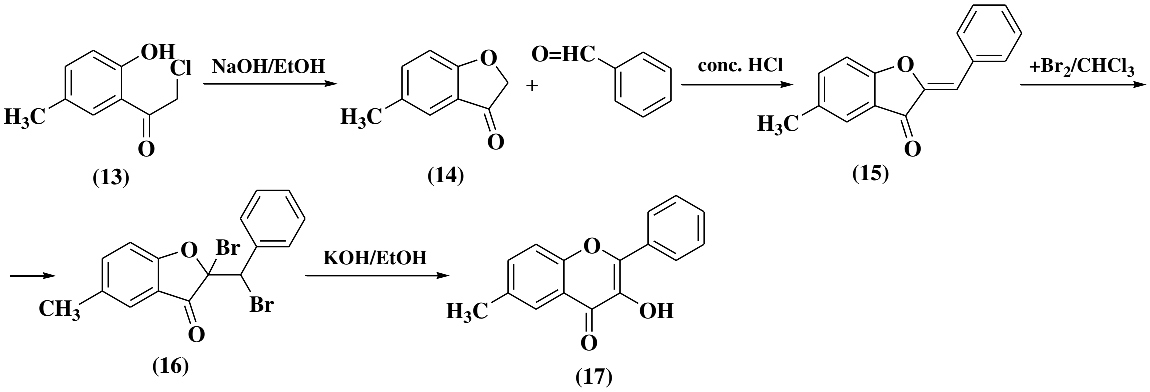
3.2. Von Auwers-Müller method

Karl von Auwers's method was first established in 1908, in collaboration with Müller and it consists in the conversion of aurones **11** into 3-hydroxyflavones **12** (Scheme 8) by bromuration in chloroform, followed by dehydrohalogenation with ring rearrangement, by the action of potassium hydroxide in ethanolic solution (Scheme 9) [2,56].



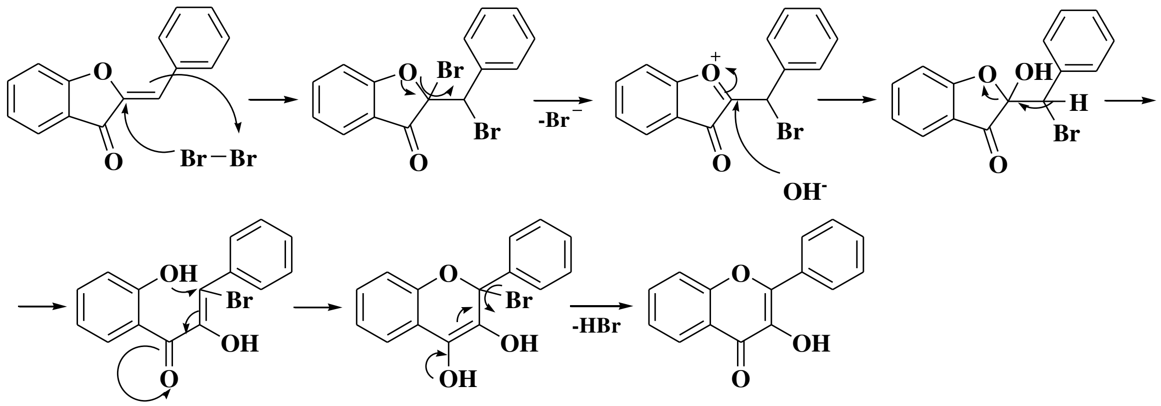
Scheme 8. The von Auwers-Müller method of obtaining 3-hydroxyflavones.

Originally, the aurone used by von Auwers and Müller was 2-benzyliden-5-methylcoumaranone **15**, obtained from 5-methylcoumaranone **14** previously synthesized by Stoermer and Bartsch [57]. Von Auwers and Müller synthesised coumaranone **15** starting from *o*-chloracetyl-*p*-cresol **(13)** (Scheme 9) [56]. This is supposed to a cyclodehydrohalogenation by the action of sodium hydroxide in ethanol, while heating. The obtained coumaranone **14,** by condensation with benzaldehyde, is converted into the aurone **15**, which adds bromine to the ethylene bond. The obtained dibromo derivative **16** is transformed by dehydrobromination and recyclisation, under the action of potassium hydroxide, in ethanol, while heating, into 3-hydroxyflavone **17** [56].



Scheme 9. Original von Auwers synthesis using 4-methylcoumaranone.

The mechanism of von Auwers synthesis is presented in Scheme 10. It debuts with bromination of aurone on the double bond, resulting a 1,2-dibrominated compound. Following substitution of bromine by nucleophilic attack of hydroxide anion results an *α,β*-unsaturated ketone, which yields hydroxyflavone through cyclodebromination [2].

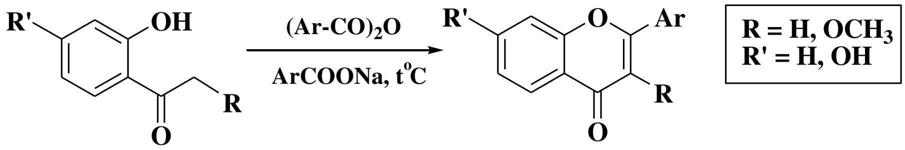


Scheme 10. Mechanism of von Auwers synthesis.

As much as this method tried to bring improvements to von Kostanecki's one, it also had limited applicability for obtaining naturally 3-hydroxyflavones. To improve the outcome of this method, they suggested chlorination instead of bromination. This resulted in a trichlorinated derivate that would convert into a chlorinated hydroxyflavone, which has one chlorine atom at position 5 or 7. However, any attempt to eliminate the last chlorine atom failed. 3-Hydroxyflavones could be obtained from aurones in better yields only if the splitting of coumaranone ring would take place easier than the dehydrohalogenation. They concluded that the presence of chlorine, methoxy and methyl groups in position 5 of coumaranone ring facilitates the formation of 3-hydroxyflavone, while methoxy and methyl groups in *meta* position and two methoxy groups on the aldehyde make it more difficult [58,59].

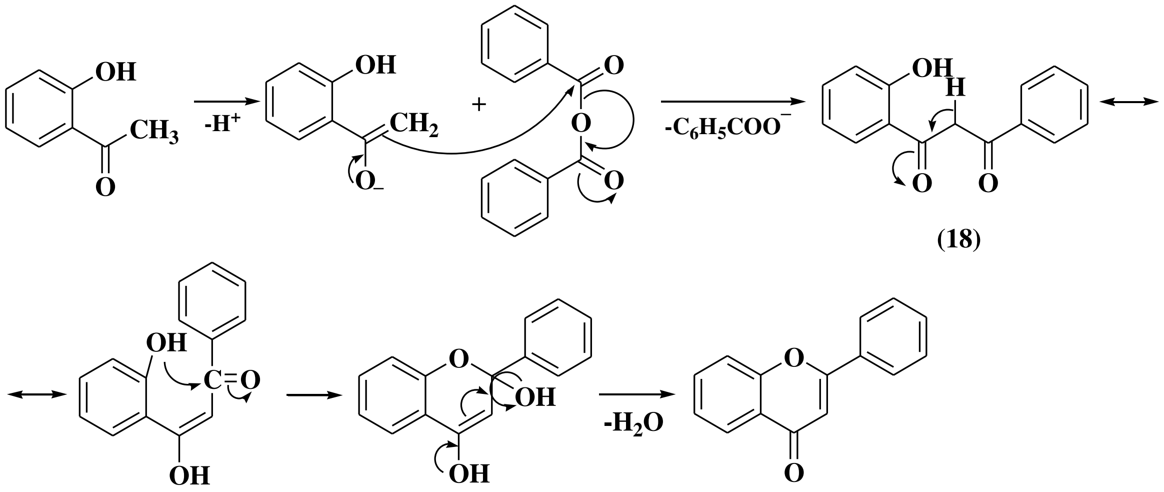
3.3. Allan-Robinson method

The Allan-Robinson method was first set up in 1924 and converts 2-hydroxyacetophenones to flavones by treatment with anhydrides of aromatic carboxylic acids and the sodium salts of the corresponding carboxylic acids, while heating (Scheme 11). The first attempt of this procedure consisted in converting ω-methoxyresacetophenone (Scheme 11: R′=OH, R=OCH_3) into 7-hydroxy-3-methoxyflavone, using benzoic anhydride and sodium benzoate (Ar = C_6H_5). This method was further extended by using various 2-hydroxyacetophenone derivatives and aromatic anhydrides as starting materials [60].



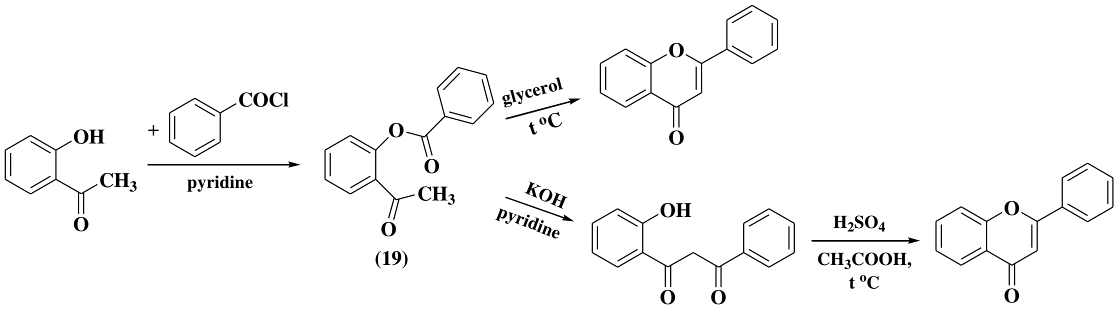
Scheme 11. Allan-Robinson method for obtaining flavones.

In the first step of the reaction mechanism, the enolic tautomer of 2-hydroxyacetophenone performs a nucleophilic attack to the carbonyl group of the anhydride, resulting a 1,3-diketone compound (*o*-hidroxydibenzoylmethane) **(18)**. The basic conditions, provided by the sodium salt, transform the intermediate into a flavone, by enolisation followed by intramolecular cyclocondensation (Scheme 12) [2].



Scheme 12. General reaction mechanism of the Allan-Robinson method for the synthesis of flavones.

An alternative to the reaction conditions of this method was proposed by Wheeler. This modification implies that 2-hydroxyacetophenone is turned into 2-benzoyloxyacetophenone **(19)**, with benzoyl chloride and pyridine. The newly obtained acetophenone can be converted into flavone, either by using glycerol and heating or glacial acetic acid and concentrated sulfuric acid while heating (Scheme 13) [61].



Scheme 13. Wheeler's alternative reaction conditions.

Unlike the previous presented methods, this one can be used for synthesizing more complex structures, making the Allan-Robinson method suitable for obtaining natural flavones and 3-hydroxyflavones. It was used for obtaining a large variety of natural compounds including fisetin, quercitin [62], datiscetin [63], myricetin, methylgalangin [64], limocitrol, limocitrin, spinacitrin [65], kaempferol [66], axillarin [67] and jaceidin [68].

3.4. Baker-Verkataraman method

This method was established after the individual work of Baker and Verkataraman in 1933. It is used to obtain flavones from *o*-acyloxyacetophenones (**20**). These precursors are first converted into *o*-hydroxydibenzoylmethane **(21)** derivatives, by heating in benzene or toluene with anhydrous potassium carbonate. Then, using cold concentrated sulfuric acid, the o-hydroxydibenzoylmethane derivatives (**21**) are cyclized into flavones [2,69] (Scheme 14).

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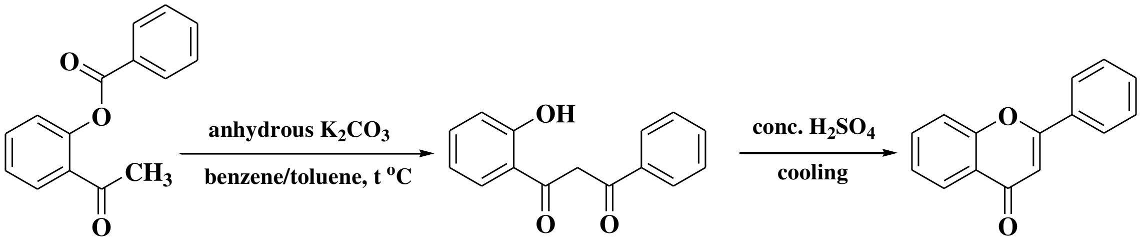
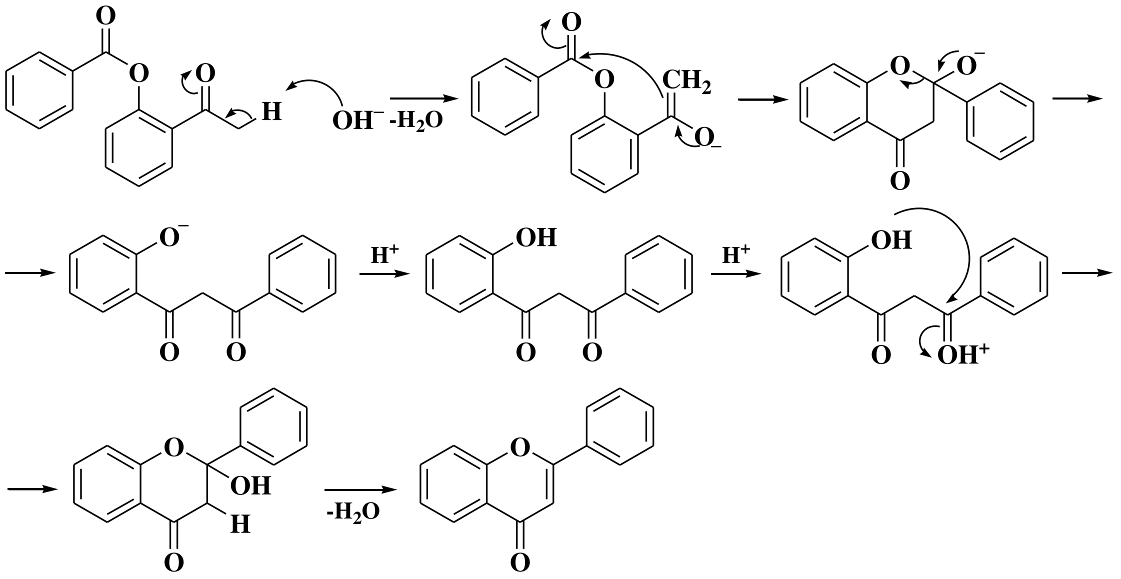


(20) **(21)**

Scheme 14. The Baker-Venkataraman method.

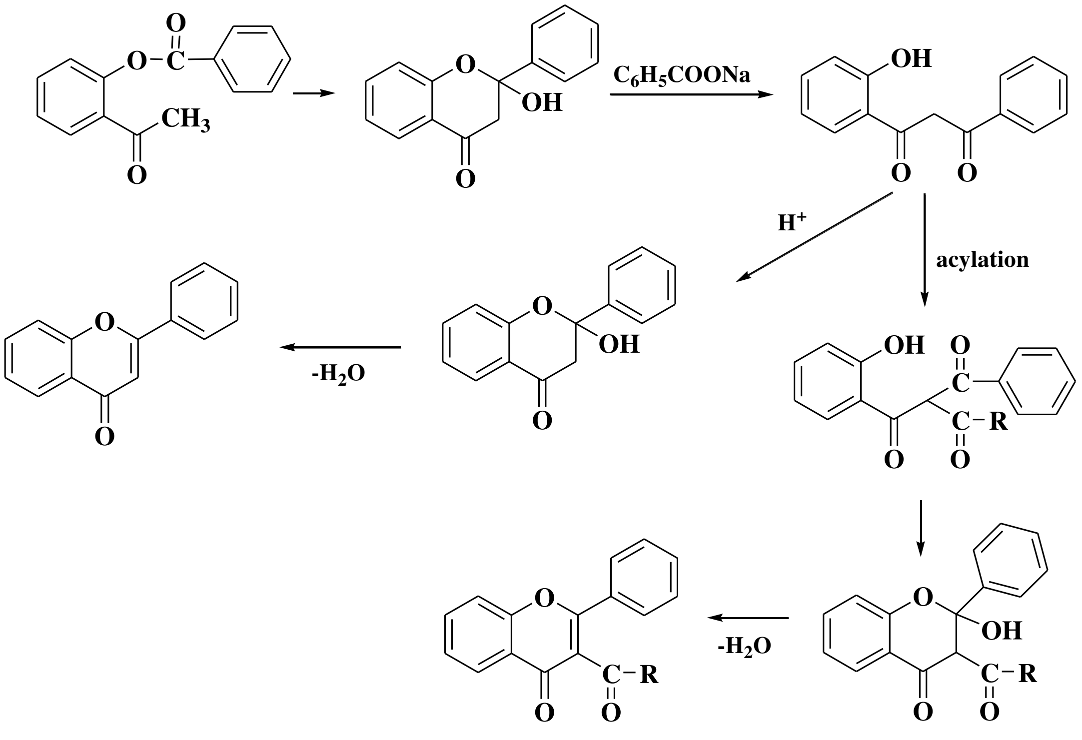
Verkataraman first used this method to obtain *α*-naphtoflavone from 2-acetyl-1-naphthyl benzoate, by heating with sodium benzoate and benzoic anhydride [70,71]. Mahal and Verkataraman obtained the diketone derivative by treatement with $NaNH_2$ in ether at room temperature. Further cyclisation to the corresponding *α*-naphtoflavone was performed with concentrated sulfuric acid in ethanol, at reflux. [72].

According to the mechanism, this method debuts with an intramolecular Claisen condensation between acetophenone and an ester group grafted on the aromatic ring, in *orto* (an *o*-acyloxyacetophenone), which can also be interpreted as an acyl group transfer. This is followed by cyclocondensation in acidic conditions, via a 2-hydroxyflavanone intermediate (Scheme 15) [2,73].



Scheme 15. The mechanism of Baker-Verkataraman method.

Baker found out that under the action of sodium salts of carboxylic acids, this method could yield 3-acylflavones. Instead of doing a cyclocondensation, the *o*-hydroxybenzoylmethane can be acylated on the methylene carbon, resulting a triacylmethane derivative. Next, this derivate is cyclized to 2-hydroxy-3-acylflavanone and then dehydrated, resulting a 3-acylflavone **(22)** (Scheme 16) [69].



(22)

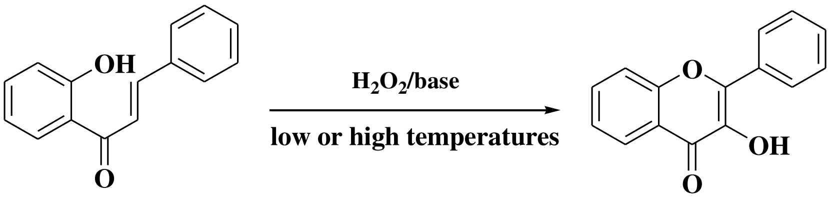
Scheme 16. Synthesis of 3-acylflavones.

However, the conventional method could not produce large yields of flavones [73]. Cramer and Elschnig discovered that the best catalyst is sodium ethoxide [74]. Ares *et al.* suggested using potassium tert-butoxide for the diketone intermediate synthesis, obtaining higher yields [75]. Jain *et al.* used benzoyl chloride in benzene, under phase transfer-catalysis conditions, with *n*-tetrabutylamonium hydrogen sulphate, obtaining *o*-hydroxydibenzoylmethane. Further treatment with *p*-toluenesulphonic acid yielded to flavones with good results [76]. A modification to this method permits the synthesis of hydroxyflavones with phloroglucinol units, by heating the 2-hydroxyacetophenones with aqueous 5% potassium carbonate and followed by treatment with acetic acid [77]. Song and Ahn proposed the usage of tetrabutylammonium fluoride as phase transfer catalyst for the condensation of dibenzoylmethanes, also obtaining good yields [78]. Another useful reaction condition for cyclocondensation was discovered by Stanek and Stodulski and uses N-triflylphosphoramide, an organocatalyst, which is active in mild reaction conditions [79]. By using microwave irradiation, Pinto *et al.* managed to obtain 3-aroyl-5-hydroxyflavones from 2,6-diaroyloxyacetophenones [80]. Same results were obtained with shorter reaction time, by using ethyl ammonium nitrate, a recyclable ionic liquid, under microwave irradiation [81].

By cyclisation of dibenzoylmethanes with $CuBr_2$, 3-bromoflavones are formed, which can be converted into 3-aminoflavones [82]. Other reported catalysts useful for converting dibenzoylmethanes into flavones are: $FeCl_3$ in dichloromethane [83]; $CuCl_2$ under microwave irradiation [84]; Cobalt(bis(salicylideniminato-3-propyl)hydroxide, a six coordinate cobalt Schiff base complex [85]; montmorillonite K 10 Clay, under microwave irradiation (clay-catalyzed synthesis) [86]; amberlyst 15, a cation-exchange resin, under reflux in isopropyl alcohol [87]; solid supported catalysts like mesoporous titania/tungstophosphoric acid composites TiO_2/ $H_3PW_{12}O_{40}$ at reflux [88], trifluoromethanesulfonic acid in toluene at reflux [89], Wells-Dawson heteropolyacid in toluene at reflux, or solvent free [90], molybdophosphoric and molybdosilicic Keggin heteropolyacids in acetonitrile at reflux [91], silica gel supported $NaHSO_4$ in toluene at reflux [92].

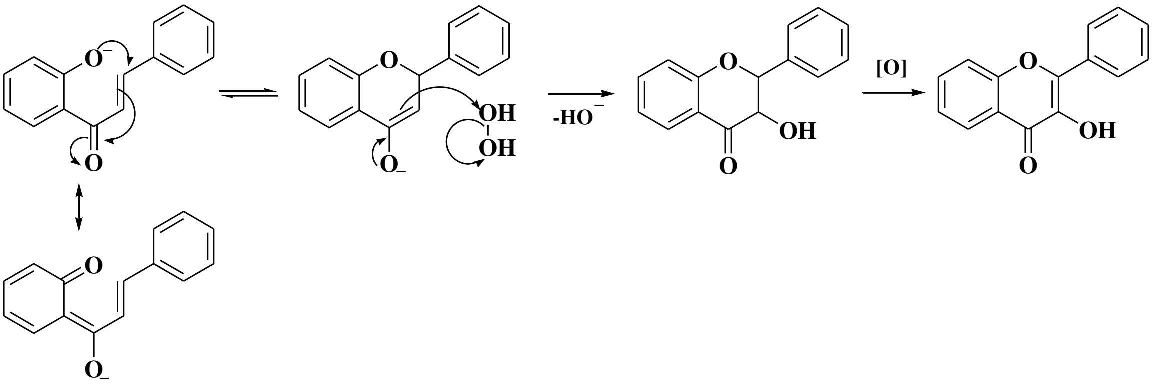
3.5. Algar-Flynn-Oyamada method

This method represents the collaboration between Algar and Flynn and the individual work of Oyamada from 1934-1935. It can be used for obtaining 3-hydroxyflavones from 2-hydroxychalcones by means of hydrogen peroxide in aqueous sodium hydroxide solution and cooling [93]. Algar and Flynn used this method with hot potassium hydroxide alcoholic solution, both with good yields (Scheme 17) [94].



Scheme 17. The Algar-Flynn-Oyamada method.

The mechanism suffered many alterations along the time. At first, Algar and Flynn were not able to isolate the intermediates. They proposed the transitory formation of an ethylene peroxide in the first stage of oxidation [94]. Oyamada considers the existence of a flavanone intermediate, with the flavanonol being formed by the electrophilic attack of hydrogen peroxide on position 3 of the flavanone anion [93,95]. Dean and Podimuang demonstrated that no epoxides were formed as intermediates for obtaining 3-hydroxyflavones. They argued that a β-position attack by the hydroperoxide anion would be difficult for phenolic chalcones, due to the internal electronic inactivation (see mesomere structure) and due to the basic conditions that turn them into anions, creating electrostatic repulsion of the hydrogen peroxide (Scheme 18) [96].



Scheme 18. The mechanism of Algar-Flynn-Oyamada method proposed by Dean and Podimuang.

Starting from *o*-hydroxychalcones, by means of epoxides as intermediates, two cyclization products can theoretically be formed: aurones, if the attack takes place in the ◎ position, and respectively flavonols (*via* flavanones), if the attack takes place in the ◎ position (Scheme 19). When 6'-substituted-2'-hydroxychalcones were used as precursors, it was found that the cyclization takes place preferentially by ◎ attack, with the formation of aurones as majority reaction products. This is due to the fact that the substituent grafted in the 6′-position of the chalcone displaces the keto group from the plane of the aromatic ring. This causes a steric inhibition of resonance from the 2′-oxygen anion and determine activation the ◎-carbon [59].

Adams and Main argued that it is not excluded that epoxides are precursors and intermediates in the formation of flavonols, by ◎-attack. They demonstrated that by treating an epoxide at various pHs in aqueous acetonitrile solution and room temperature, led to small amounts of the β-cyclization product, a flavonol derivative [97,98].

Dean and Podimuang's theory was also challenged by Serdiuk *et al.* They concluded that epoxides are indeed intermediates in this method, by analyzing the thermodynamic characteristics

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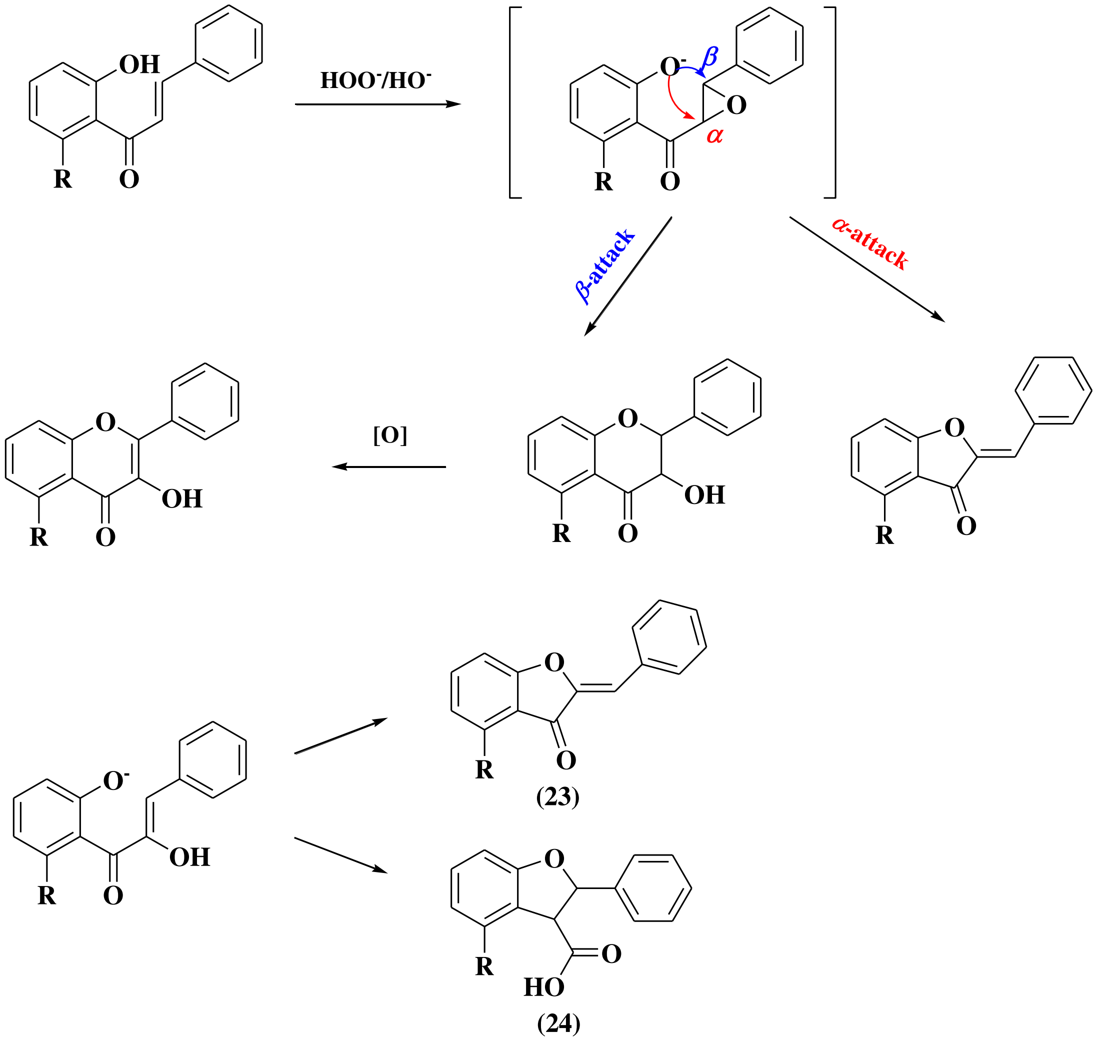
of the intermediate reactions and finding out that the reactions of chalcones in anionic form with the hydroperoxide anion are energetically favorable [95]. However, Bhattacharyya and Hatua demonstrated through the density functional theory that epoxidation is unlikely because of the electrostatic interaction of the hydroperoxide anion with the conjugated double bond, although an epoxide intermediate could still be formed at high temperatures and converted into aurone, supporting Dean and Podimuang's work [99].

The major limitation of the Algar-Flynn-Oyamada method consists in the fact that it cannot be applied for the synthesis of 3-hydroxyflavones by cyclisation of the corresponding 6′-substituted *o*-hydroxychalcones because in this case the cyclization takes place preferentially by ◎ attack [100]. Also, besides 3-hydroxyflavones, aurones can be easily obtained through *α*-cyclization and sometimes even 2-benzyl-2-hydroxydihydrobenzofuran-3-ones **(23)** and 2-arylbenzofuran-3-carboxylic acids **(24)** are formed [98,101] (Scheme 19).



Scheme 19. Algar-Flynn-Oyamada reaction products. Aurone formation happens in higher yields when a 6'-substituted chalcone is used.

A couple of modifications for this method exist: Na_2CO_3 and H_2O_2 in methanol and water for obtaining 5′-substituted-3-hydroxyflavones [102], phase transfer catalysis (tetrabutylammonium bromide, iodide or hydrogensulphate, benzyltriphenylphosphonium chloride, ethyltriphenylphosphonium iodide, propyltriphenylphosphonium iodide or bromide) [103], direct synthesis, starting from acetophenone and aldehyde, without isolating the chalcone intermediate, known as one-pot synthesis [38,104–107].

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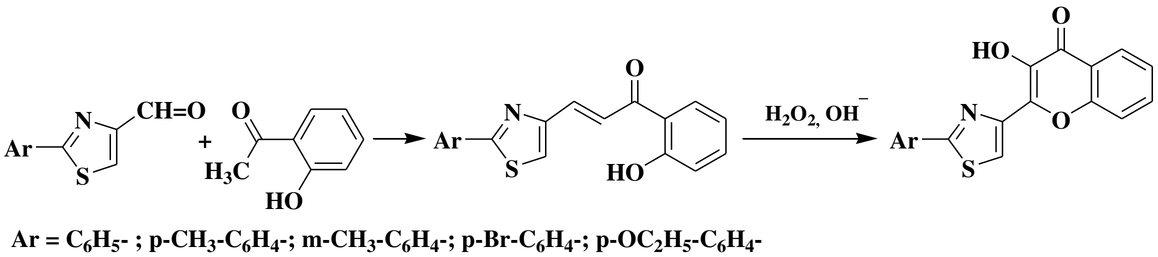
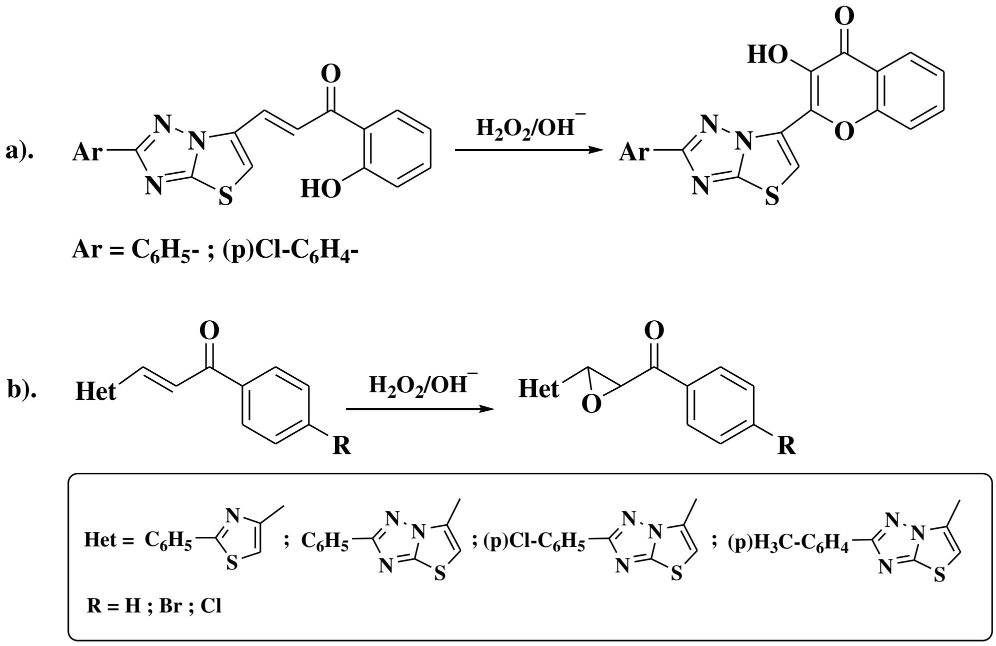
The oxidative cyclisation with H_2O_2/OH^- of *o*-hydroxychalcones was successfully extended in our research group for the synthesis of new analogues of hydroxyflavones containing the 2-phenylthiazole moiety instead of the benzene ring B of the basic skeleton of natural flavones. In a first step, the thiazole *o*-hydroxy-heterochalcones were obtained in 75 - 82% yields by the condensation of *o*-hydroxyacetophenone with different 2-arylthiazol-4-yl carbaldehydes (Scheme 20). Their epoxidation with hydrogen peroxide followed by oxidative cyclisation afforded the corresponding 2-arylthiazole hydroxyflavones in 65 - 71% yields [108].



Scheme 20. Synthesis of new thiazole hydroxychromones by oxidative cyclisation of thiazole *o*-hydroxy chalcones [108].

The cyclisation pathway of thiazole and thiazolo[3,2b][1,2,4]triazole hetero-chalcones with hydrogen peroxide in basic media (NaOH) was investigated by V. Zaharia *et al.* By treatment with hydrogen peroxide of *o*-hydroxy-heterochalcones in basic media, the corresponding hydroxy-chromones were obtained (Scheme 21 a)). The unhydroxylated heterochalcones afforded in the same reaction conditions the corresponding epoxy-ketones (Scheme 21 b))[109].



Scheme 21. a). Synthesis of thiazolo[3,2-b][1,2,4]triazole hydroxychromones by cyclisation of *o*-hydroxychalcones. **b).** Synthesis of thiazole and thiazolo[3,2-b][1,2,4]triazole epoxyketones [109].

3.6. Claisen-Schmidt method

This method was established in 1962 and consists of two steps. The first step is a Claisen-Schmidt condensation between an acetophenone and benzaldehyde derivates, in basic medium, resulting chalcones. Second step represents the oxidative cyclization of chalcones, which can be achieved with a large variety of conditions and catalysts [2] (Scheme 22).

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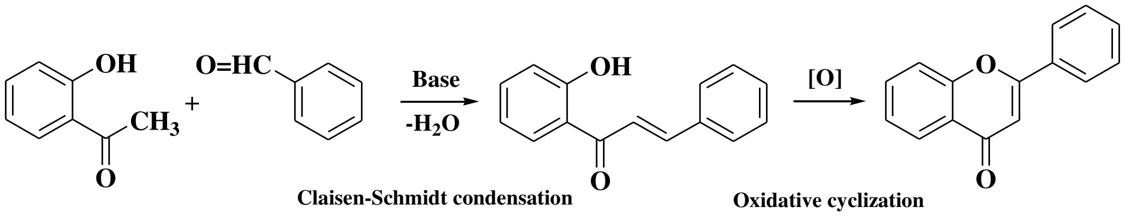
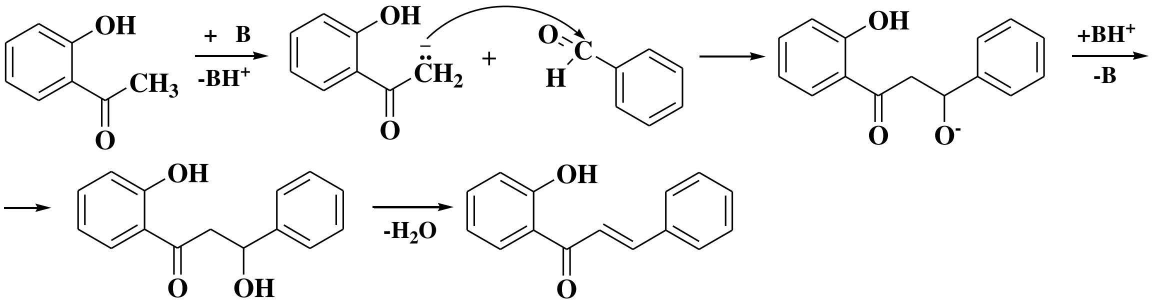


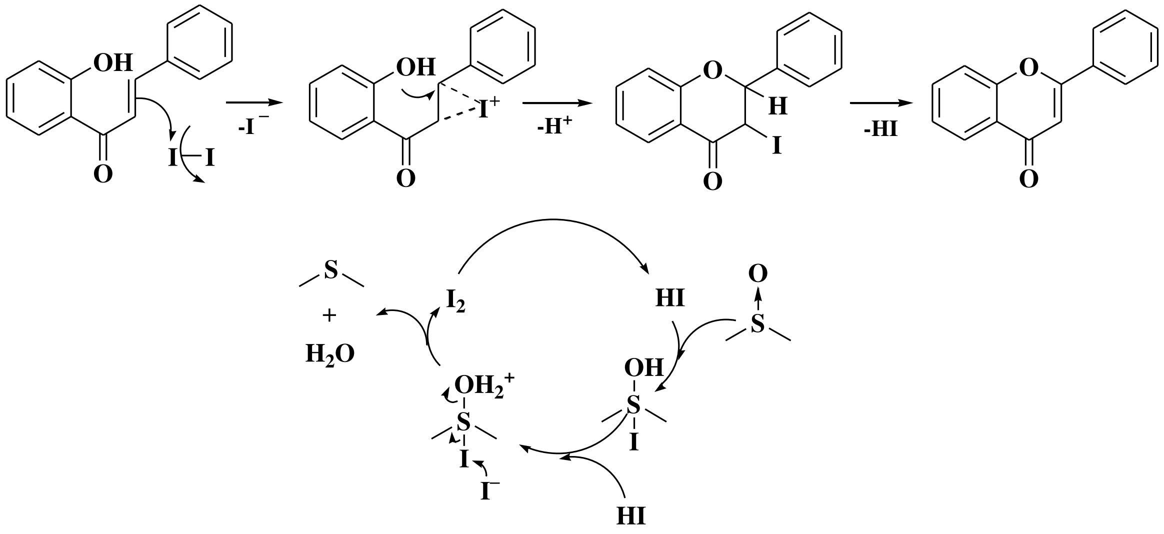
Scheme 22. The Claisen-Schmidt method.

The mechanism of condensation debuts with the formation of an anion of the acetophenone, under basic conditions. The base extracts a proton from the carbon in α-position. This is followed by a nucleophilic attack of the anion on the carbonyl group of benzaldehyde, thus resulting the chalcone [110] (Scheme 23).



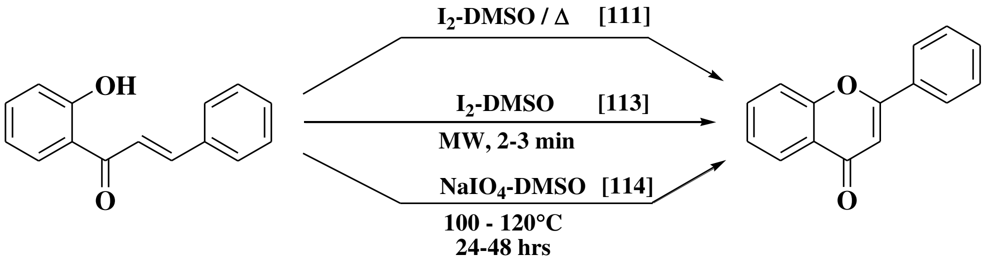
Scheme 23. The mechanism of Claisen-Schmidt condensation.

The cyclization can be realized by many methods, first starting with iodine in hot dimethylsulfoxide (I_2/DMSO, Δ). Patonay *et al.* observed that this method is suitable for a large variety of substituents, including electron-donating and electron-withdrawing, sensitive to oxidation and protecting groups. Thus, it can be considered a general method of cyclization for obtaining flavones from 2′-hydroxychalcones [111]. The mechanism involves the formation of a iodonium cation by the interaction of I_2 with the *o*-hydroxycalcone, followed by cyclisation by nucleophilic attack of the *o*-hydroxy group. Further elimination of hydroiodic acid afford the corresponding flavones. The solvent DMSO is important in this reaction because it acts as a co-oxidant and regenerates iodine [112] (Scheme 24).



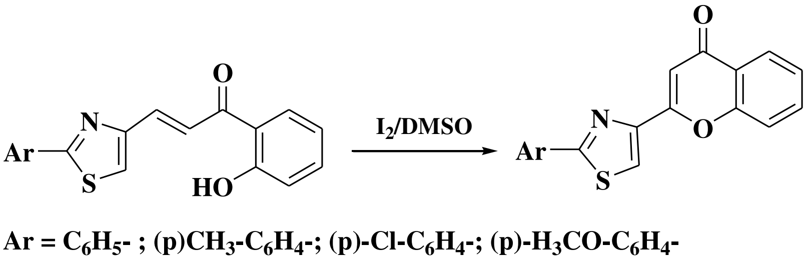
Scheme 24. Mechanism of oxidative cyclization of *o*-hydroxychalcones with I_2/DMSO. Role of DMSO in regeneration of iodine (mechanism adapted from Masesane) [112].

By using microwave irradiation, the time of reaction is greatly reduced to approximatively 3 minutes [113]. However, this method is limited in the case of 2′-hydroxychalcones with a phloroglucinol oxygenation pattern, resulting complex mixtures. Hans and Grover extended the applicability of iodine as an oxidant agent, by using instead sodium periodate in hot dimethylsulfoxide ($NaIO_4$/DMSO, Δ), managing to smoothly convert phloroglucinol-derived chalcones into corresponding flavones [114] (Scheme 25).



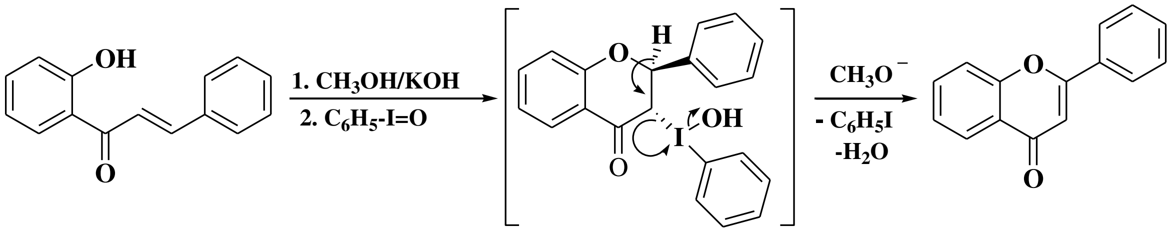
Scheme 25. Oxidative cyclisation using I_2 or $NaIO_4$ in DMSO.

In order to extend the general method of cyclisation of *o*-hydroxychalcones with iodine in dimethyl sulfoxide, our research group investigated this method using as precursors a series of 2-arylthiazole *o*-hydroxychalcones. A similar chemical behaviour was observed in this case, the corresponding 2-arylthiazole flavones being obtained with 32-55% yields (Scheme 26) [115].



Scheme 26. Cyclisation of 2-arylthiazole *o*-hydroxychalcones with iodine in dimethyl sulfoxide [116].

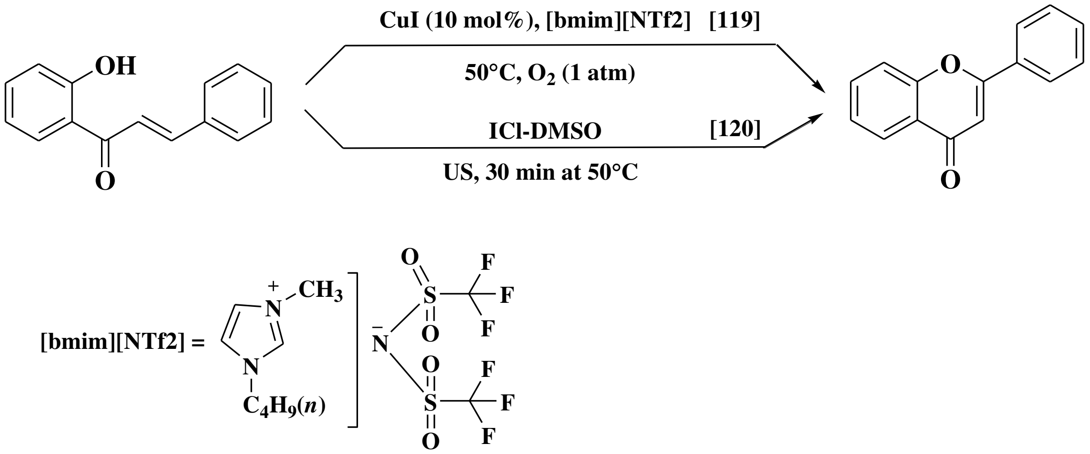
Another method capable of cyclizing this chalcones was established by Litkei *et al.*, who used iodosobenzene diacetate (phenyliodine(III) diacetate, PIDA), a hypervalent iodine reagent, which forms iodosylbenzene *in situ* [117] (Scheme 27). The same reagent was used for obtaining prenylated flavones, which are abundant in nature, from prenylated 2′-hydroxychalcones [118].



Scheme 27. Oxidative cyclization using hypervalent iodine reagent.

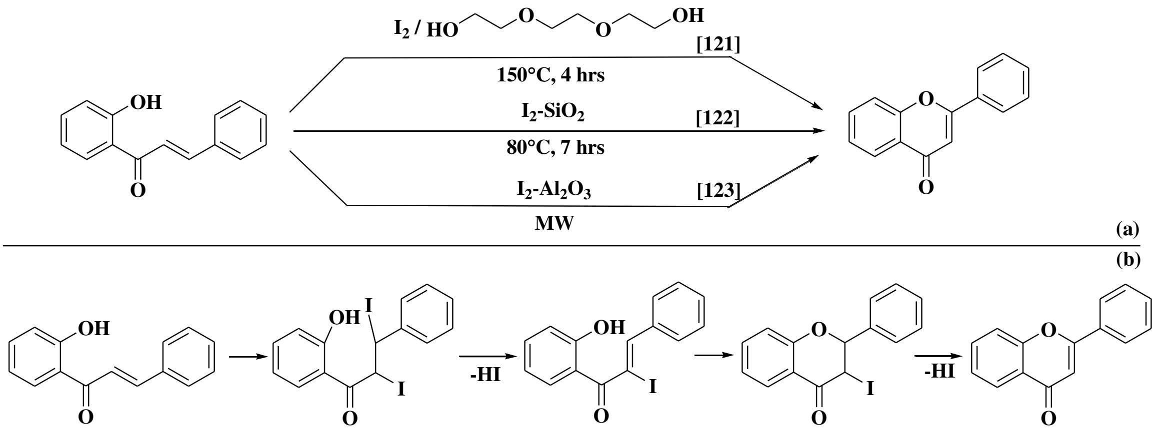
The usage of ionic liquids for this oxidative cyclization was described in the literature. Du *et al.* developed a new method assisted by Cu(I) iodide, mediated by the ionic liquid [bmim][NTf2] (1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide) at low temperature. The reaction mechanism has not been fully elucidated, but the results so far reveal that a flavanone is formed intermediately. Flavanone seems to be dehydrogenated to the corresponding flavone in the same reaction conditions [119]. Lahyani and Trabelsi reported the oxidative cyclisation of *o*-

hydroxychalcones with iodine monochloride in dimethylsulfoxide (ICl-DMSO), under ultrasounds. The method presents the advantages of ultrasound processes such as mild conditions, high yields and eco-friendliness. The mechanism is similar with the one from oxidative cyclization with I_2-DMSO [120] (Scheme 28).



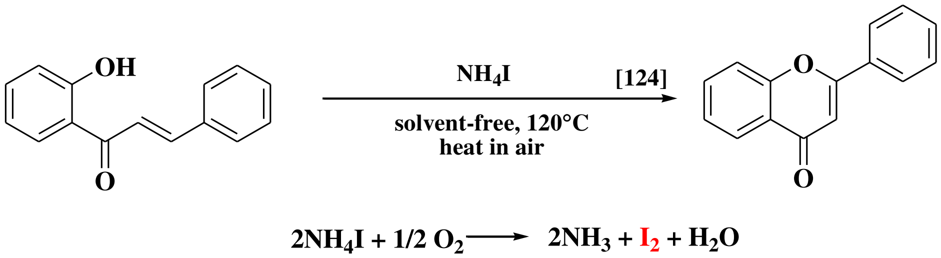
Scheme 28. Oxidative cyclization of orth-hydroxychalcone with CuI in ionic liquid, respectively with ICl in DMSO, under ultrasounds.

Heating 2′-hydroxychalcones with iodine in triethylene glycol is also a good and inexpensive method. While the mechanism is not fully understood, the authors proposed a pathway which involves the iodination of chalcone, resulting chalcone diiodides, similar with the chalcone dihalides from the von Kostanecki's method. Cyclization is the result of dehydrohalogenation, resulting a 3-iodoflavanone, which yields flavone after the β-elimination of a second hydroiodic acid molecule [121]. The usage of iodine on silica gel (I_2-SiO_2) was reported by Babu *et al.* with favorable results and less harmful effects towards environment [122]. Another solid supported catalyst, iodine on neutral alumina (I_2-Al_2O_3), was reported by Sarda *et al.*, with short reaction time, simple conditions and very good yields [123] (Scheme 29).



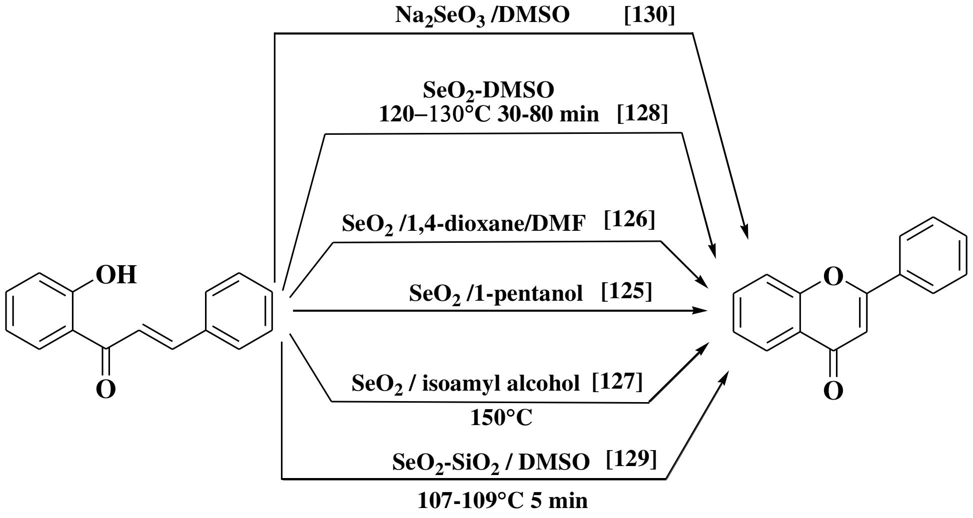
Scheme 29. (a) Oxidative cyclization with iodine in triethylene glycol and solid supports (silica gel and alumina). **(b)** The proposed pathway for oxidation with molecular iodine (adapted from Miyake *et al.* [121]).

An alternative to the toxicity and corrosiveness of iodine was proposed by Kulkarni *et al.*, who used ammonium iodide, on exposure to air and solvent-free conditions, which generated *in situ* iodine and cyclized 2′-hydroxychalcone in high yields [124] (Scheme 30).



Scheme 30. Oxidative cyclization using NH_4I in solvent-free conditions.

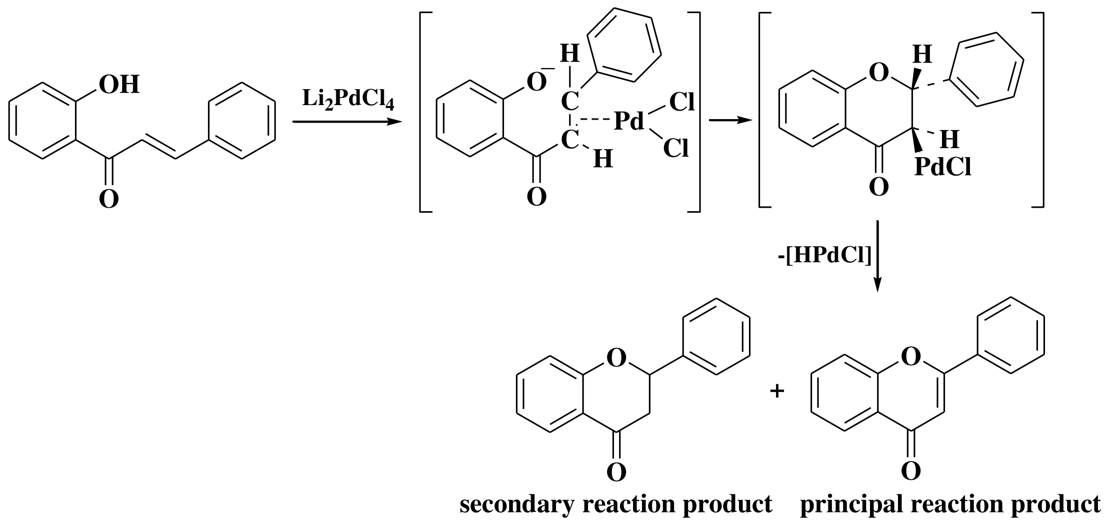
Selenium dioxide is another catalyst used for cyclization. It can be combined with various solvents, like pentan-1-ol [125], but with low yields [114]; dioxane [126]; isoamyl alcohol with prolonged heating, formation of side products and low yields [127]. Dimethylsulfoxide was also used with good yields [128], but in order to diminish the high toxicity of DMSO, Gupta *et al.* managed to use selenium dioxide and traces of solvent over silica gel, under microwave irradiation with very good results [129]. Similar with I_2/DMSO, SeO_2/DMSO is also problematic for chalcones with phloroglucinol oxygenation pattern [114]. However, selenium dioxide is volatile and hazardous. Lamba and Makrandi proposed using sodium selenite (Na_2SeO_3), which is less volatile and found out that it acts as a proper dehydrogenating agent in DMSO [130] (Scheme 31).



Scheme 31. Oxidative cyclization using selenium-based catalysts in different solvents and conditions.

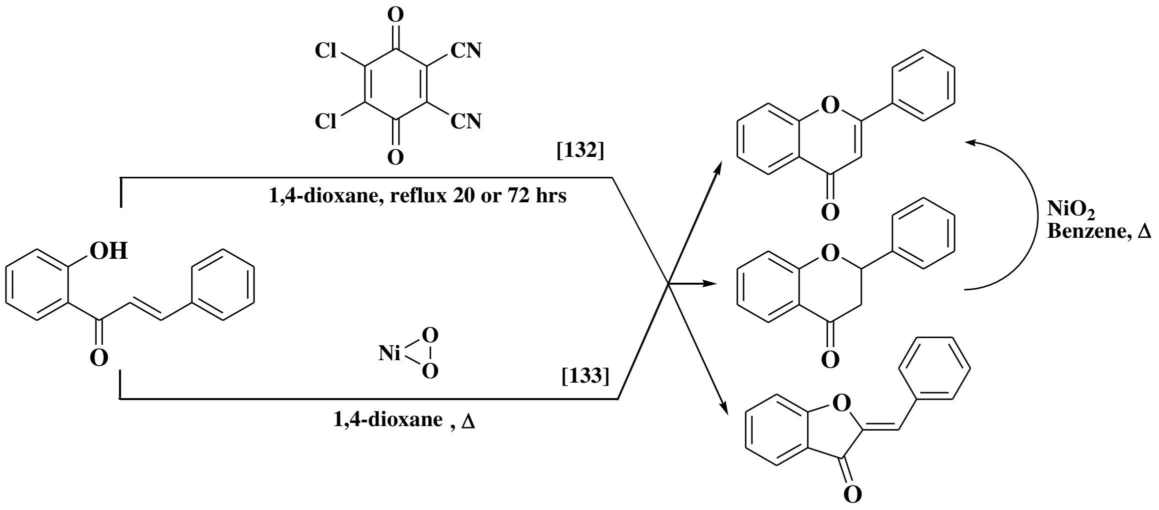
In our research group, the oxidative cyclisation of 2-arylthiazole *o*-hydroxychalcones with selenium dioxide in *n*-butanol was investigated. In this case, the corresponding flavones and hydroxyflavones were formed, in different molar ratios (Scheme 40) [27].

Palladium was also experimented on as a catalyst. Kasahara *et al.* used lithium chloropalladite (Li_2PdCl_4) and palladium(II) acetate, $(CH_3COO)_2Pd$), for obtaining flavones. The reaction was described as a phenoxypalladation, followed by the elimination of palladium (II) hydride (HPdX). This method also yielded small amounts of flavanone [131] (Scheme 32).



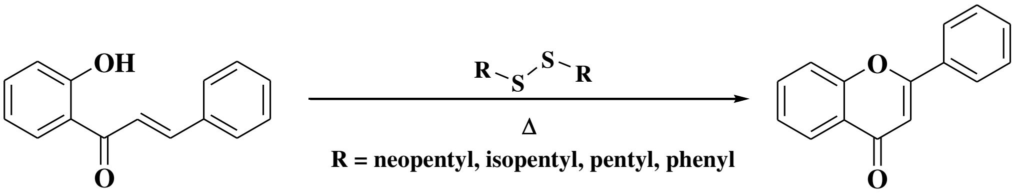
Scheme 32. Oxidative cyclization with palladium(II) salts.

Cyclodehydrogenation with DDQ (2,3-dichloro-5,6-dicyano-p-benzoquinone) was proposed by Imafuku *et al.* Their method uses dioxane as solvent and results in a mixture of flavones, flavanones and aurones, with low yields [132]. Another agent that acts in a similar manner is nickel peroxide (NiO_2) in dioxane, yielding a similar mixture. However, flavanones can be dehydrogenated to flavones, under the action of NiO_2 in benzene as solvent [133] (Scheme 33).



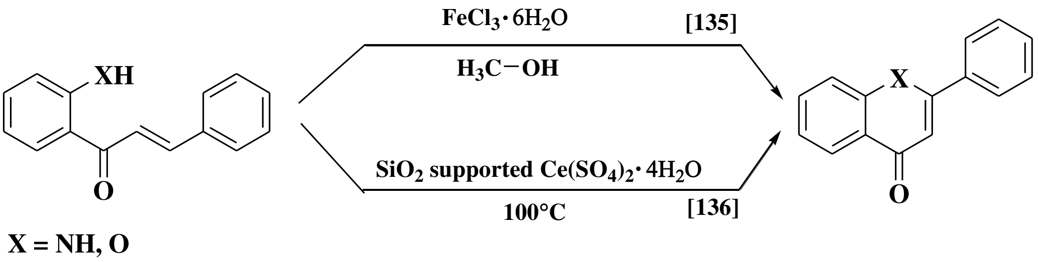
Scheme 33. Oxidative cyclization using DDQ and nickel peroxide.

Disulfides are also a good choice for cyclodehydrogenation. Hoshino *et al.* used four disulfides: dineopentyl disulfide, diisopentyl disulfide, dipentyl disulfide and diphenyl disulfide, the later giving the best yields. The disadvantages of this method include the very high temperatures (260-290ºC) and very low yields when electron-withdrawing groups (NO_2) were present [134] (Scheme 34).



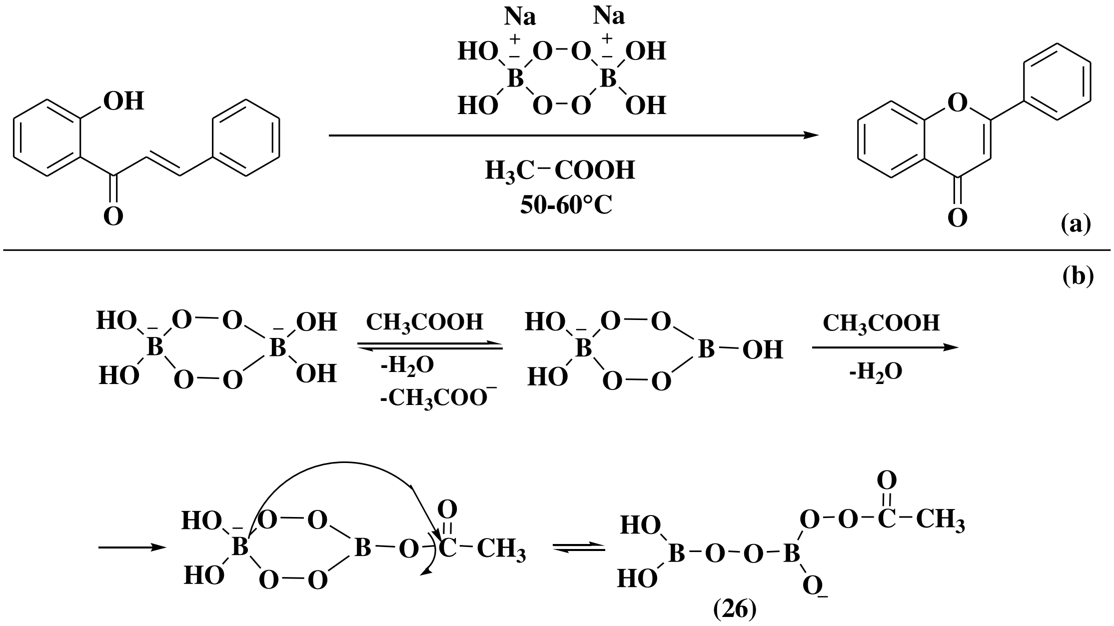
Scheme 34. Oxidative cyclization using organic disulfides.

Initially meant for obtaining quinolines from 2′-aminochalcones, using $FeCl_3 \cdot 6H_2O$ in methanol, Kumar and Perumal applied the same method on 2′-hydroxychalcones and obtained flavones with satisfactory results [135]. Similarly, Liu *et al.* used cerium sulphate tetrahydrate ($Ce(SO_4) \cdot 4H_2O$) on silica gel to obtain flavones from 2′-hydroxychalcones at 100ºC, aza-flavones and aza-flavanones from 2′-aminochalcones [136] (Scheme 35).



Scheme 35. Oxidative cyclization using $FeCl_3$ hexahydrate or $Ce(SO_4)_2$ tetrahydrate.

In addition to all the reagents previously mentioned, sodium perborate tetrahydrate (SPB) was proposed by Ganguly *et al.* They observed that depending on the solvent, this method could yield different products: warm acetic acid and SPB in excess yielded to flavones, while warm aqueous acetonitrile yielded to flavanones. For flavones, SPB and acetic acid generated peracetoxyboron anion species **(26)**, which oxidated the chalcones [137,138] (Scheme 36).



Scheme 36. (a) Oxidative cyclization using sodium perborate tetrahydrate (SPB). **(b)** The mechanism for generation of peracetoxyboron anionic species.

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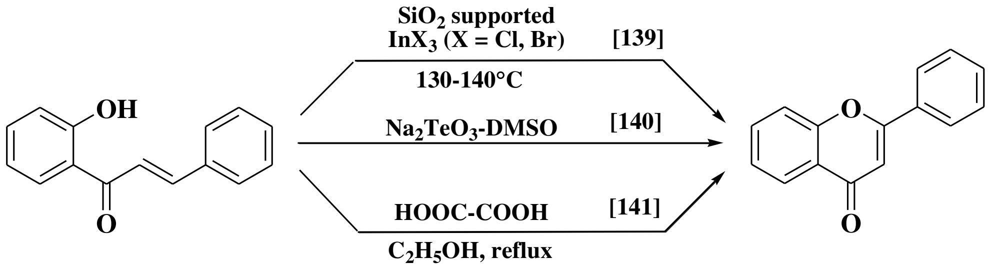
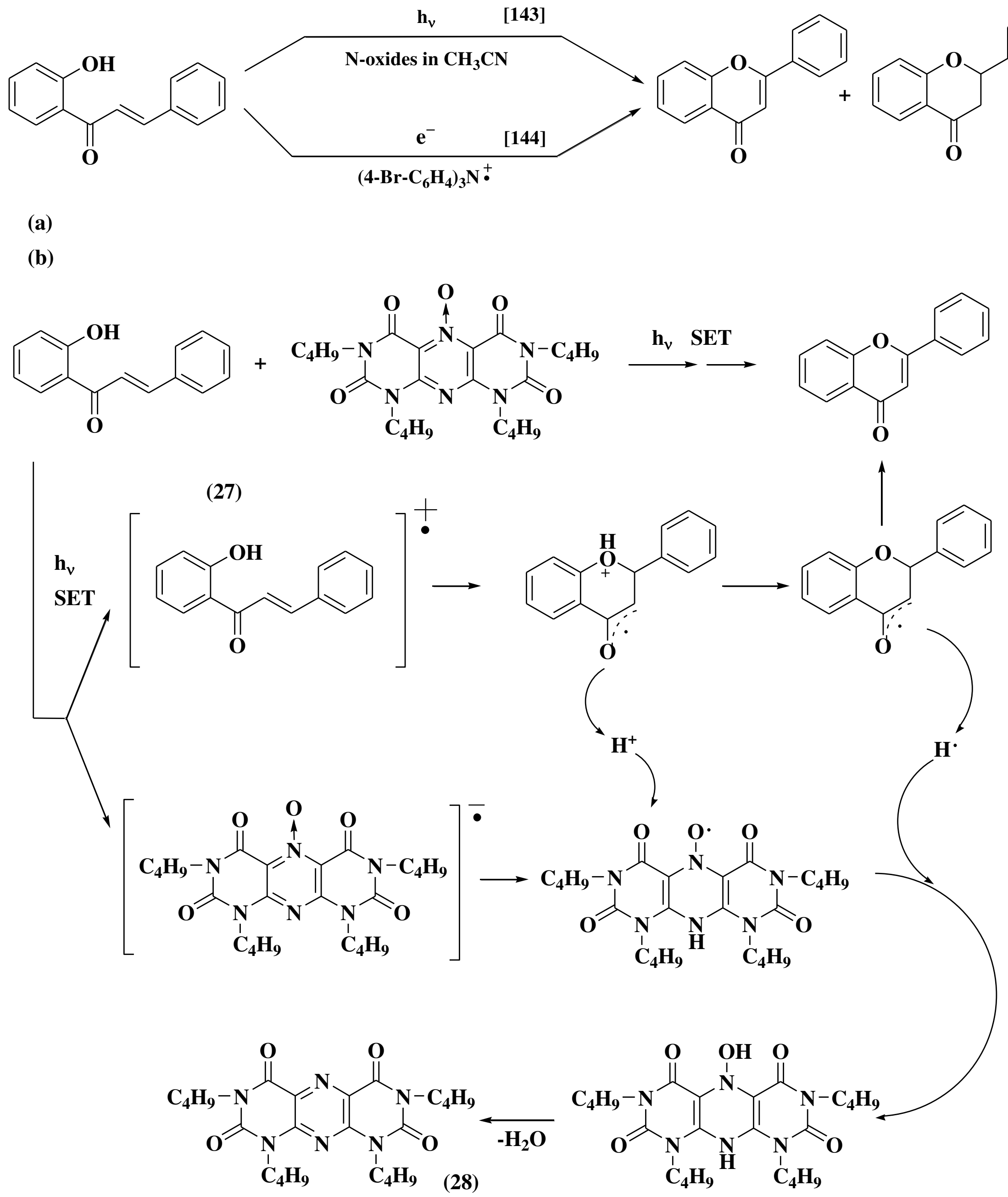
Other reagents include indium(III) halides ($InCl_3$ and $InBr_3$) on silica gel and solvent-free conditions, with higher yields when $InBr_3$ was used [139] or sodium tellurite in dimethylsulfoxide and anhydrous conditions (Na_2TeO_3-DMSO) [140]. The reaction mechanism was not completely elucidated. The supposed reported pathway for the oxidative cylisation with indium halides involves the formation of flavanone as intermediate, which is dehydrogenated in the same reaction conditions to the corresponding flavone [139]. Oxalic acid in ethanol reflux used by Zambare *et al.* proved to be a very useful and cheap method, with excellent yields over 90% [141] (Scheme 37).



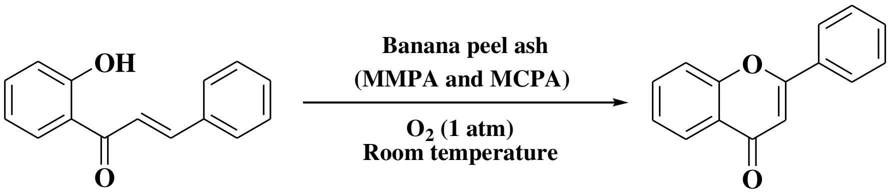
Scheme 37. (a) Oxidative cyclization of *o*-hydroxychalcones with indium(III) halides, sodium tellurite in DMSO and oxalic acid.

Photocyclization was another manner to perform this reaction. However, it yielded only flavanones and in low quantities [142]. By adding a heterocyclic N-oxide, pyrimido[5,4-g]pteridine N-oxide, Maki *et al.* managed to obtain flavones but still in unsatisfactory yields and only in a mixture with flavanones. The photoreaction involves a single electron transfer (SET) process from chalcone to N-oxide. Initially, the N-oxide is in a oxygenated form, pyrimido[5,4-g]pteridin-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone 5-oxide **(27)**, and as the mixture forms, it gets deoxygenated to pyrimido[5,4-g]pteridine **(28)** [143]. Electrochemistry found applications in this reaction too. Saničanin and Tabaković cyclized 2'-hydroxychalcones by generating electrochemically a cation radical of tris-(4-bromophenyl)amine, which acted as a homogenous electron-transfer reagent. This method creates a mixture of flavanones and flavones in moderate yields [144] (Scheme 38).

A different approach, by creating a totally non-hazardous medium was used by Tamuli *et al.* They used as catalyst a mixture of two agro-food wastes of *Musa sp.* 'Malbhog' peel ash (MMPA) and *Musa champa* Hort. ex Hook. F. peel ash (MCPA), which provided basic conditions for the cyclodehydrogenation, solvent-free and room temperature [145] (Scheme 39).



Scheme 38. (a) Oxidative cyclization using photo- and electrochemistry. (b) Mechanism of single electron transfer process (adapted from Maki *et al.* [143]).



Scheme 39. Oxidative cyclization using banana peel ash in open air and solvent-free conditions (adapted from Tamuli *et al.* [145]).

Among the reported methods for the cyclization of *o*-hydroxychalcones, in our research group we investigated the most promising ones, in order to obtain new flavonoid analogues containing the 2-arylthiazole moiety instead of the benzene ring B. Our aim was also to investigate the chemical behaviour of 2-arylthiazole *o*-hydroxychalcones in the cyclization reactions.

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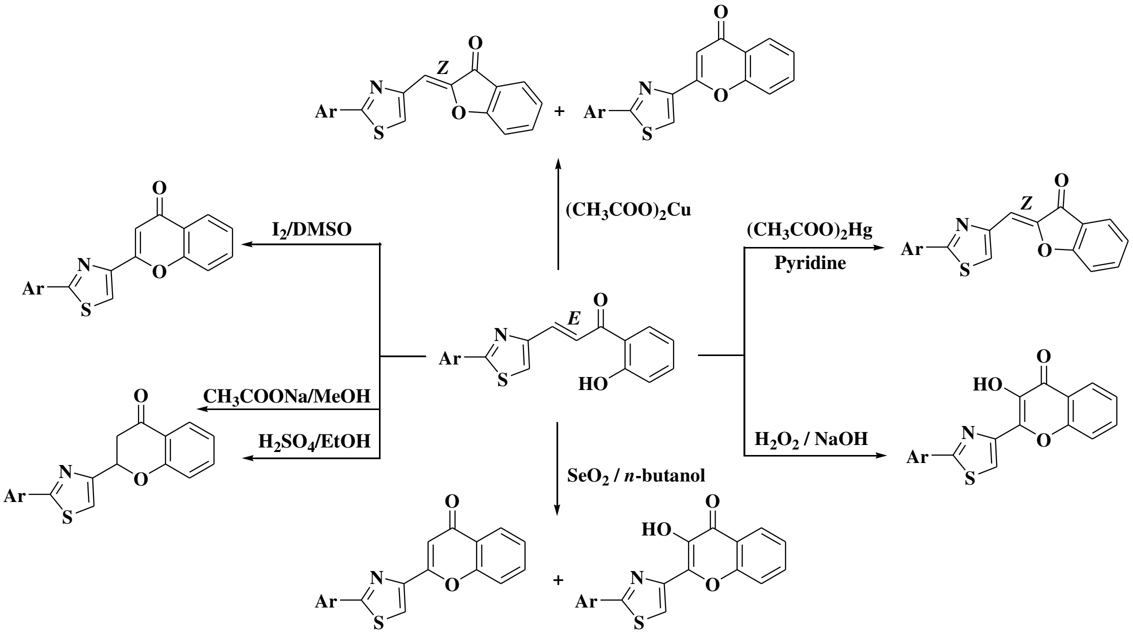
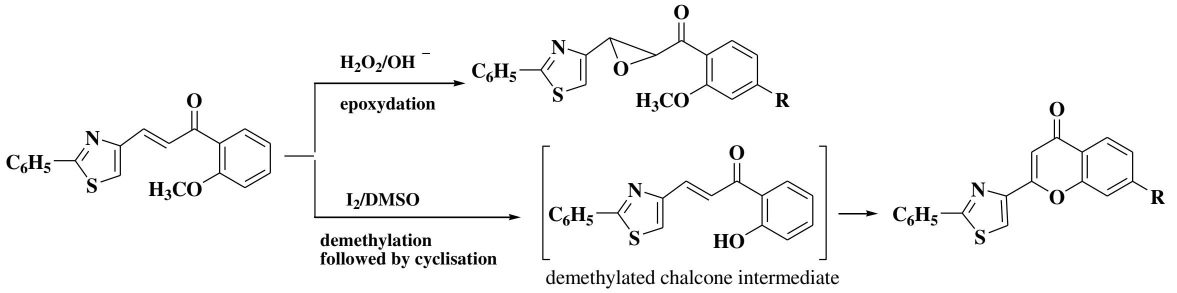
The oxidative cyclisation of the 2-arylthiazole *o*-hydroxychalcones afforded various reaction products, depending on the oxidizing agent. Flavanones were obtained with 40 - 55% yields by cyclisation of the corresponding 2-arylthiazole *o*-hydroxychalcones in acidic catalysis (H_2SO_4 conc. in ethanol) [116]. The cyclisation of 2-arylthiazole *o*-hydroxychalcones in the presence of sodium acetate, in methanol as solvent, afforded also the corresponding flavanones in good yields. With copper(II) acetate in dimethyl-sulfoxyde, resulted a mixture of aurone and the corresponding flavone in an approximate 1:1 molar ratio [27]. Hydroxyflavones were obtained by cyclisation of the same substrates with hydrogen peroxide in alkaline catalysis [27] and flavones were obtained when iodine in dimethylsulfoxide was used [27,116]. The cyclisation with selenium dioxide in *n*-butanol led to a mixture of flavones and hydroxyflavones [27]. The cyclisation with mercury(II) acetate in pyridine as solvent afforded the corresponding Z-aurones with 70-86% yields [27]. The cyclisation products and the reactions conditions are summarized in Scheme 40.



Scheme 40. Cyclisation products obtained by the oxidative cyclisation of 2-arylthiazole *o*-hydroxychalcones in different reaction conditions [27,116,146].

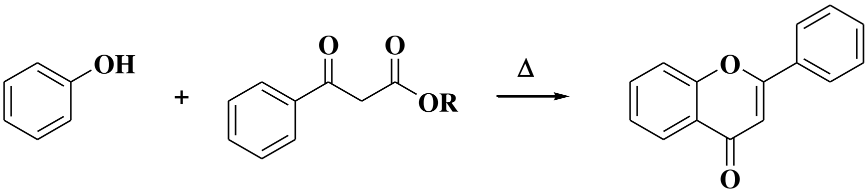
The cyclisation of *o*-methoxylated chalcones bearing the 2-arylthiazole moiety was further studied in similar reaction conditions. It was found that the reaction occurred differently, depending on the oxidizing agent and the reaction conditions. By treatment with iodine in dimethyl sulfoxide, at reflux, the corresponding flavones were formed. This fact indicates that the demethylation of the methoxy group of chalcone occurred, which allowed the cyclization to the corresponding flavone [146]. Instead, when hydrogen peroxide in NaOH was used as cyclization agent, the formation of the corresponding epoxides was observed, which can be explained by the fact that the methoxy group is resistant in these reaction conditions and therefore the cyclization to flavone cannot take place (Scheme 41) [146].



Scheme 41. Cyclisation products of 2-arylthiazole *o*-methoxychalcones [146].

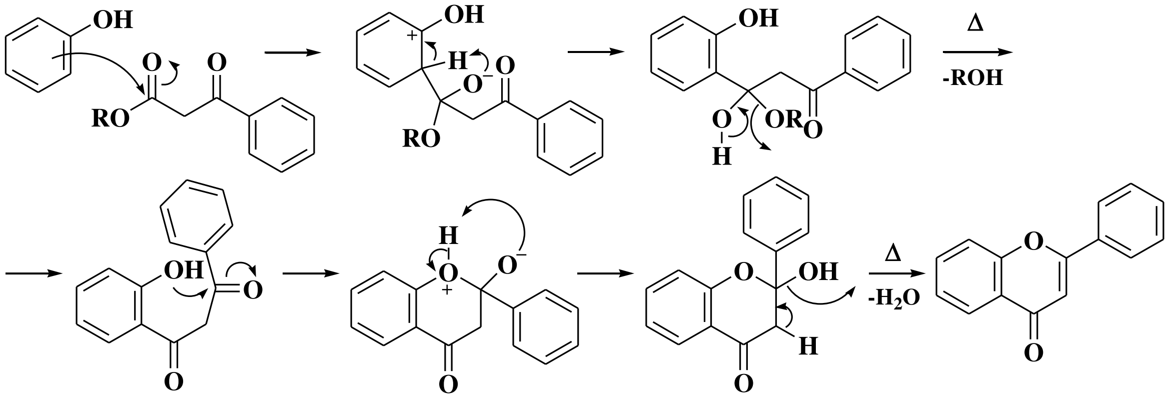
3.7. Mentzer method

The method is a synthesis of flavones based on the reaction between phenols (phenol, resorcinol or phloroglucinol) and *β*-ketoesters [115] (Scheme 42). It is based on the Pechmann reaction, used to obtain coumarins from phenol and ethyl acetoacetate [147]. Mentzer *et al.* obtained flavones from resorcinol and ethyl 2-benzylacetoacetate by heating up the mixture for 48 hours at 250ºC [148].



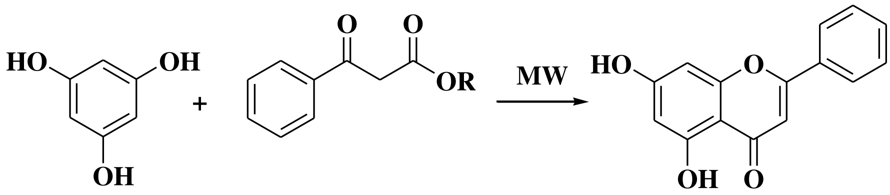
Scheme 42. The Mentzer method for the synthesis of flavones.

The mechanism involves a nucleophilic attack by the phenolic compound on the ketoester, resulting an arenium ion. Under heating, the intermediate eliminates ethanol and results *o*-hydroxydibenzoylmethane, a compound which is also available in the Baker-Verkataraman method, which cyclizes into flavone [115] (Scheme 43).



Scheme 43. The mechanism of Mentzer method (image adapted from Wang [115]).

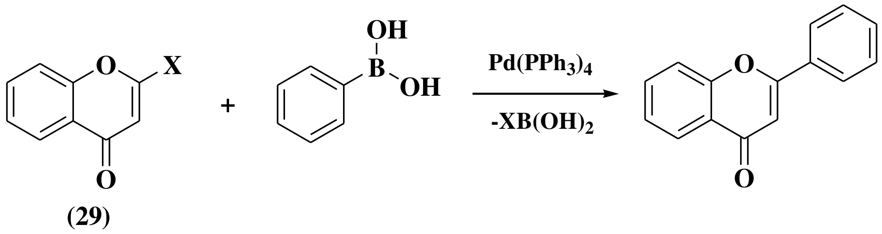
Seijas *et al.* developed a solvent-free modification of this method, which uses microwave irradiation instead of heating. The yields are good and the time of reaction is significantly reduced [149] (Scheme 44).



Scheme 44. A variation of Mentzer method using microwave irradiation (image adapted from Seijas *et al.* [149]).

3.8. Suzuki-Miyaura method

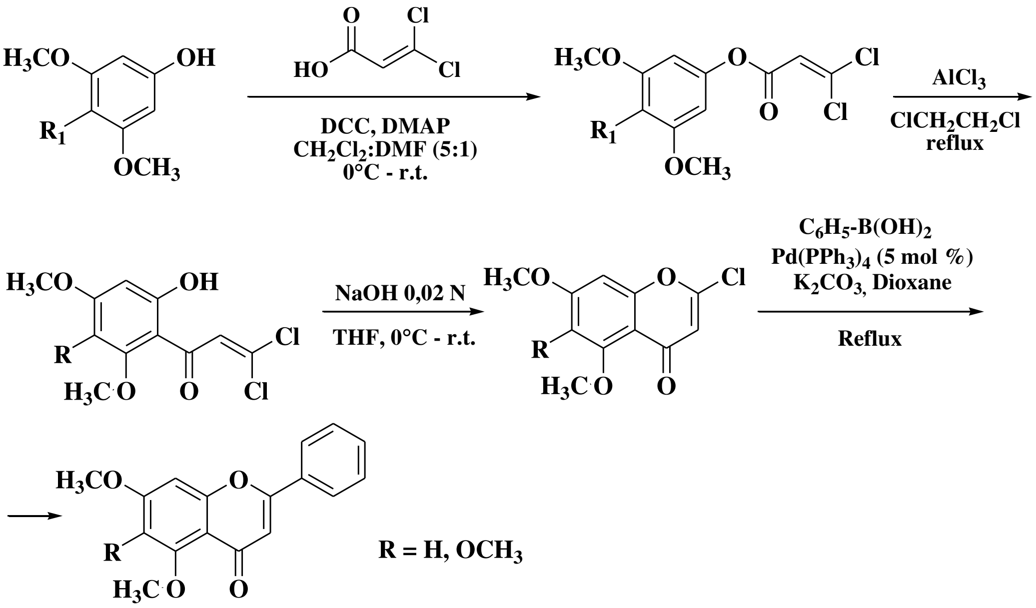
The Suzuki-Miyaura method is a cross-coupling reaction, based on the insertion of palladium in sp^2 hybridized C-X bonds and usage of various organoboron precursors, under mild conditions. In the case of flavones, 2-halochromones **(29)** are used as substrate, however they are difficult to obtain [150] (Scheme 45).



Scheme 45. The Suzuki-Miyaura method.

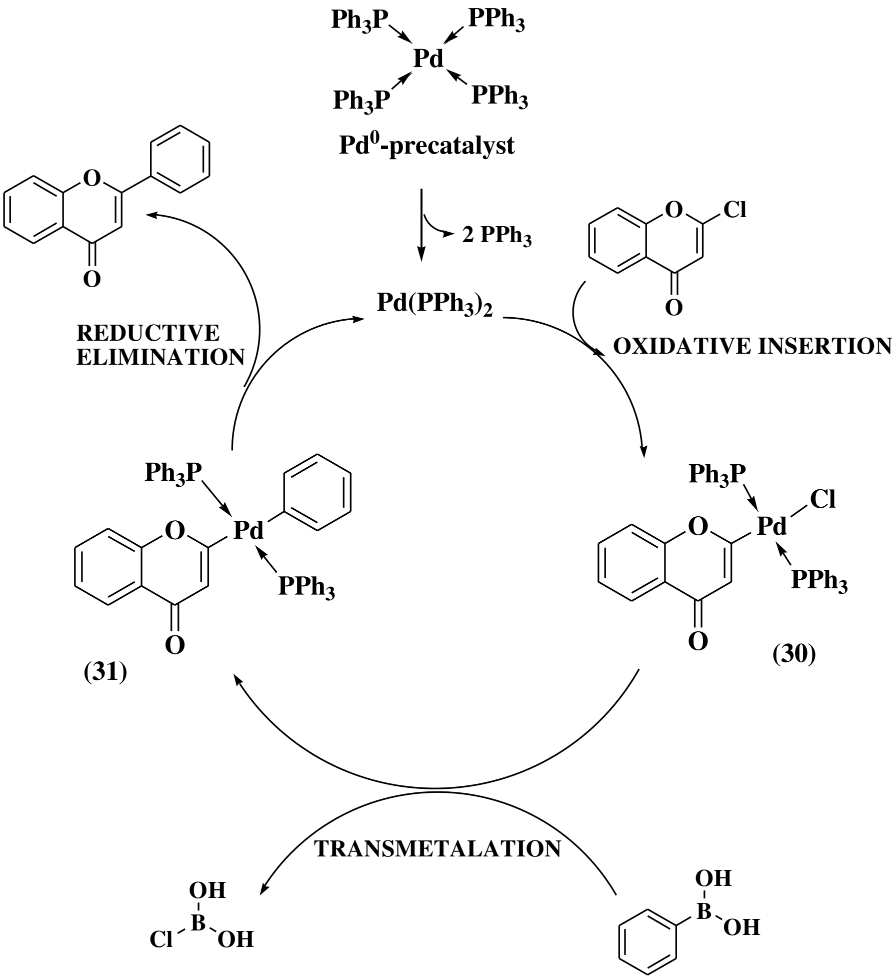
While this method is mostly used with 2-bromo- or 2-iodochromones, Kraus and Gupta demonstrated that these precursors yield to aurones, rather than flavones. By using 2-chlorochromone, they managed to obtain flavones in proper yields (68-74%).

Their synthesis starts with an esterification between a phenolic compound and 3,3-dichloroacrylic acid, resulting a dichloro acrylic ester. Further, this compound undergoes a Fries transposition, followed by cycloelimination in basic conditions, yielding 2-chlorochromone. Finally, it is coupled with arylboronic acids, which can replace the halogen atom from the chromone skeleton with the aryl rest of the boronic compound, thus resulting a flavone [151] (Scheme 46).



Scheme 46. The pathway of Suzuki-Miyaura method for obtaining substituted flavones (image adapted from Kraus and Gupta [151]).

The postulated mechanism of Suzuki-Miyaura method involves a catalytic cycle initiated by the formation of the active Pd^0 catalytic species Pd(PPh$_3$)$_2$. Further oxidative insertion of palladium to the 2-halogenochromone conducts to the organopalladium intermediate **30** (chromon-2-yl-palladium(II) chloride). In the transmetalation step, the chlorine atom is transferred to the boronic compound, resulting a chloroboronic acid and (chromon-2-yl)(phenyl)palladium **(31)**, which undergoes a reductive elimination, yielding the flavone and the active Pd^0 catalyst Pd(PPh$_3$)$_2$. [152] (Scheme 47).



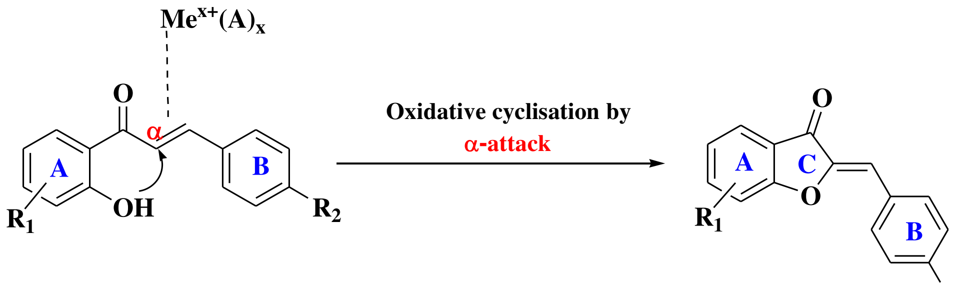
Scheme 47. Postulated mechanism for the Suzuki-Miyaura method.

4. Chemical synthesis of aurones

Among the reported methods for the synthesis of aurones, the most applied are those based on the oxidative cyclization of *o*-hydroxychalcones. These reactions are mediated by transitional metal salts Hg(CH$_3$COO)$_2$ [153], CuBr$_2$ [153,154] or Tl(NO$_3$)$_3$ [155], whose metal cation interacts with the double bond in chalcones, thus favoring the attack of the ortho hydroxy group on the alpha carbon (Scheme 48) [112].

Cyclization of *o*-hydroxychalcones with mercury(II) acetate afforded the best yields in aurones when the reaction was performed in pyridine [153] or dimethyl sulfoxide [156] as solvent, at reflux. In the case of cyclisation with cupric bromide, dimethyl sulfoxide proved to be the optimal solvent [153].

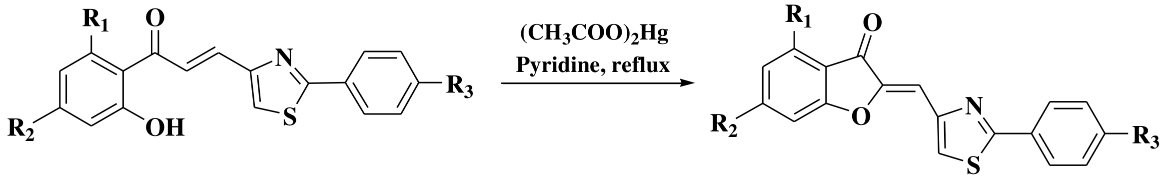
In the case of thallium nitrate mediated cyclisation, there are reported data indicating that the reaction course depends on the nature of the substituents on the B ring: only the electron-withdrawing groups (chlorine, formyl, methoxycarbonyl and nitro) grafted in the para position are favorable for the cyclization to aurones. In other cases, mixtures of aurones and isoflavones, or exclusively isoflavones are obtained [157].



$Me^{x+}(A)_x$: $Hg(CH_3COO)_2$, $CuBr_2$ or $Tl(NO_3)_3$

Scheme 48. Aurones synthesis by cyclisation of *o*-hydroxychalcones [153–155].

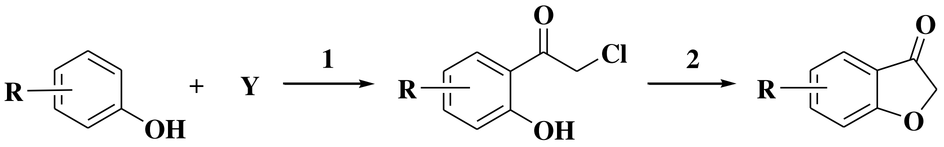
In our research group, a series of aurones analogues containing the 2-phenylthiazole aromatic system as B ring were synthesised in 70-86% yields, in Z configuration, by cyclisation of the corresponding *o*-hydroxychalcones, with mercury(II) acetate in pyridine at reflux (Scheme 49) [27].



$R_1 = H, OCH_3$ $R_2 = H, OCH_3, CH_3, Br$ $R_3 = H, OCH_3, Cl$

Scheme 49. Synthesis of aurones analogues containing the 2-phenylthiazole moiety [27].

Other chemical route towards aurones starts from substituted benzofuran-3-ones as precursors. Benzofuran-3-ones are synthesised in two steps. The first step consists in the introduction of a chloroacetyl group on the aromatic ring of the phenols, by applying a Hoesch-type reaction (with 2-chloronitriles in the presence of anhydrous $ZnCl_2$ and gaseous HCl) [158] or a Friedel-Crafts acylation (with alfa-halogenated acyl chlorides in the presence of $AlCl_3$) [33,159]. In the next step, an intramolecular Williamson-type reaction with ring closure is applied (Scheme 50) [33,158,159].



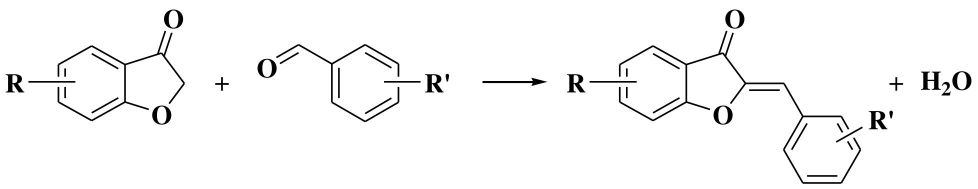
R=H, OH

For Y = $ClCH_2COCl$: 1. $AlCl_3$/ ethyl acetate ; 2. CH_3COONa/MeOH, reflux

For Y = $ClCH_2CN$: 1. $ZnCl_2$, HCl/diethylether ; 2. H_2O, reflux

Scheme 50. Synthesis of benzofuran-3-ones.

The condensation of benzofuran-3-ones with aromatic aldehydes affords the corresponding aurones. This step can be performed under acid catalysis with HCl conc./CH_3COOH [33], in basic catalysis with 50% KOH/Ethanol [158–160] or with Al_2O_3 as catalyst (Scheme 51) [160].

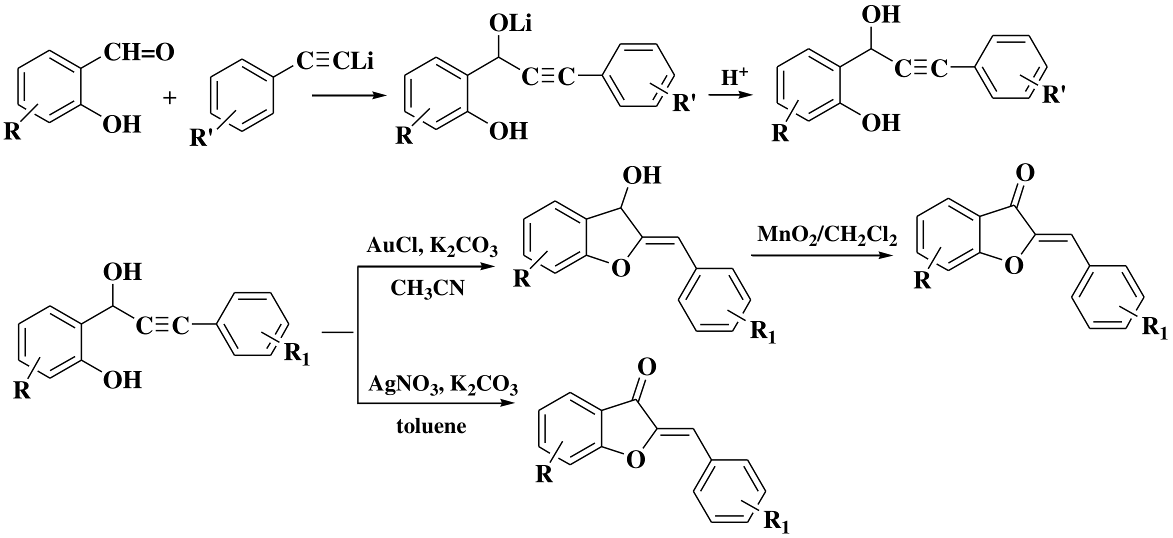


Scheme 51. Synthesis of aurones by condensation of aromatic aldehydes with benzofuran-3-ones.

Another reported method for the synthesis of aurones involves the cyclisation of hydroxypropynylphenol derivatives, obtained by alkynylation of salicylaldehyde derivatives with lithium arylacetylures (Scheme 52) [161,162].

Harkat et al. performed the cyclization of hydroxypropynylphenol derivatives in the presence of gold(I) chloride and potassium carbonate in acetonitrile. Further oxidation with MnO_2 of the intermediate secondary alcohol afforded the corresponding aurones (Scheme 52) [161].

Li S. *et al.* proposed a variant of cyclisation with $AgNO_3$. Ag^+ ions catalyze both the cyclocondensation reaction and the oxidation of the secondary alcohol to the corresponding aurone (Scheme 14) [162].



Scheme 52. Synthesis of aurones *via* hydroxypropynylphenol derivatives [161,162].

5. Conclusions

Flavones, flavonols and aurones are precious natural products from pharmacological point of view, that have inspired researchers over time to create new biologically active compounds, among which stand out anticancer and anti-infectious agents with benzochromon-4-one or benzofuran-3-one structure.

The polyphenolic structure of natural flavones and aurones determine a low stability to oxidants in solution and also generally decrease their bioavailability after oral administration, due to their low solubility, thus affecting their potential use as therapeutic agents. Consequently, structural modulations on aromatic rings A and B were reported for the design of new flavones / aurones analogues and both the improvement of therapeutic properties, pharmacokinetic profiles and the increase of stability must be taken into account.

The hybridation of the basic skeletons of flavones and aurones with other pharmacophore moieties led to obtaining new compounds with superior pharmacological profiles compared to their natural analogues.

The most applied route for the synthesis of flavones, hydroxyflavones and aurones consists in the cyclisation of *o*-hydroxychalcones. The cyclisation pathway occurs differently, depending either on the structure of the starting chalcone and also on the catalysts used and the reaction conditions.

Even if the presented methods for the synthesis of flavones and aurones generally refer to obtaining the basic skeleton for natural flavones and aurones, in which the aromatic moieties are benzene and benzochromon-4-one or benzofuran-3-one rings, these methods have also been successfully applied to obtain new synthetic analogues of flavones or aurones containing other aromatic moieties such as heteroaromatic systems.

The reported results presented in this review confirm that these general synthetic pathways have a great importance in the development of new flavones and aurones analogues with biological potential.

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