https://doi.org/10.31925/farmacia.2021.5.1 **REVIEW**

HETEROCYCLES 49. SYNTHESIS, CHEMICAL BEHAVIOUR AND BIOLOGICAL PROPERTIES OF HETEROCYCLIC CHALCONES. REVIEW FROM OUR RESEARCH

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Abstract

The synthesis of the natural products analogues has performed a remarkable expansion in recent years, as natural structures have inspired researchers to develop new potential therapeutic agents with improved pharmacological and pharmacokinetic profiles. This review provides an overview on the synthesis, chemical behaviour and biological properties of some already synthesized heterocyclic chalcones bearing thiazole, indole and pyridine moieties. The attention is directed to the reactivity of the α,β-unsaturated ketone system which provides access to new heterocyclic compounds. The structures of chalcones and their cyclisation products that have shown encouraging *in vitro* antitumour and antifungal properties are highlighted.

Rezumat

Sinteza analogilor produșilor naturali a cunoscut o expansiune remarcabilă în ultima vreme, deoarece structurile naturale au inspirat cercetătorii să dezvolte noi potențiali agenți terapeutici cu profiluri farmacologice și farmacocinetice îmbunătățite. Acest studiu de literatură oferă o imagine de ansamblu asupra sintezei, comportamentului chimic și proprietăților biologice ale unor calcone heterociclice deja sintetizate care conțin în structura lor nucleele tiazol, indol și piridină. Atenția este îndreptată asupra reactivității sistemului carbonilic α,β-nesaturat, care oferă acces la noi structuri heterociclice. Sunt evidențiate structurile calconelor și ale produșilor lor de ciclizare, care au demonstrat proprietăți antitumorale și antifungice *in vitro* încurajatoare.

Keywords: thiazole**,** chalcone, flavone, flavanone, aurone

Introduction

Chalcones, 1,3-diaryl-propen-1-ones, constitute one of the important groups of natural products with great medicinal value, due to their vast biological potential and also to their unique chemical behaviour, which make possible their cyclisation in different reaction conditions to flavonoid products and other heterocyclic compounds. Therefore, chalcones are offering access to a large panel of bioactive compounds.

The remarkable biological potential of natural chalcones and flavonoids [1] encouraged the research towards the synthesis of new analogues as promising candidates in the therapy of various diseases, such as cancer [2], microbial infections [3] and inflammatory diseases [4].

At present, there are several main directions for the design of new chalcone analogues of medicinal interest. In a first attempt, the 1,3-diphenyl-propen-1-one system is preserved and different electron donating or electron accepting substituents are grafted on the two benzene rings [5]. The replacement of one or both benzene rings with various heteroaromatic systems and the study of their reciprocal influence for the global pharmacological effect is a current concern for the design of new biologically active heterochalcones [6].

The transformation of chalcones into flavonoid compounds (flavones, flavanones, aurones), under various reaction conditions, provides access to new synthetic analogues of flavonoids with improved functions [7].

Moreover, chalcones are versatile metal ion ligands due to the α,β-unsaturated carbonyl bridge, either to the (hetero)aromatic rings, as well as due to certain heteroatoms with free pairs of electrons and favourable positions for complexation. The anticancer activity of several ruthenocenyl chalcones was recently reported [8].

Heterocyclic ring systems containing nitrogen and/or sulphur such as thiazole, indole and pyridine are recognized for their biological potential and their

presence in the structure of biologically active compounds proved to be crucial for their pharmacological properties. Thiazole is of particular interest in medicinal chemistry, being found a central core in the structure of many therapeutical agents and new drug candidates. The spectrum of biological activities of thiazole derivatives includes antibacterial [9], antiviral [10], anticancer [11], analgesic [12], anti-inflammatory [13], anticonvulsant [14] and antifungal [14] properties.

Considering that assembling two pharmacophore units in one molecular scaffold is a well-established approach to the synthesis of more effective drugs, many chalcones containing thiazole, indole or pyridine moieties have been synthesized in our research group starting from the corresponding heterocyclic aldehydes and methyl-ketones, by applying a versatile reaction pathway, the Claisen-Schmidt condensation. This review aims to present the advances in the research field of heterocyclic chalcones and derivatives containing thiazole, indole and pyridine moieties, respectively the main synthetic routes for their synthesis as well as their pharmacological properties.

Synthesis of thiazole chalcones by Claisen-Schmidt condensation

The Claisen-Schmidt condensation is the principal method for the synthesis of chalcones starting from aromatic aldehydes and acetophenones. Considering the fact that aldehydes are the main precursors in obtaining chalcones *via* Claisen-Schmidt condensation, we found it necessary to discuss first the synthesis of thiazole aldehydes, the more so as the synthesis of these compounds is quite difficult to achieve. The most advantageous method consists in converting halogenomethyl thiazoles into the corresponding thiazole carbaldehydes by applying the Sommelet reaction. This method is preferred because the 4-halogenomethylthiazoles used as precursors are readily obtainable by Hantzsch synthesis, starting from 1,3-dichloroacetone and different thiobenzamides.

Synthesis of 2-aryl-1,3-thiazole-4-carbaldehydes via Sommelet reaction

The Sommelet reaction, named after the researcher who developed it for the first time, Professor Marcel Sommelet, consists in the transformation of a halomethyl group into a formyl group. The method is based on the reaction of the halomethyl derivative with hexamethylenetetramine (urotropine, $C_6H_{12}N_4$), resulting the corresponding urotropinium salt, which by treatment with a solution of acetic acid 50% is transformed into the corresponding aldehyde. The reaction is applicable especially in the aromatic and heteroaromatic series and less in the aliphatic series.

Several reaction mechanisms were proposed for the Sommelet reaction, generally based on an oxidation-reduction step, which involves the transfer of a hydride ion from the carbon atom bound to the amine group (*H*-CH-NH_2) to the azomethinium cation $[CH_2{=}N{<}]^+$. Angyal *et al*. assumed that the transfer of the hydride ion occurs inter-molecularly, from the carbon atom bound to the amine group (*H*-CH-NH_2) to the N-protonated Schiff base formed in the reaction mixture [15, 16, 17] as follows (Figure 1).

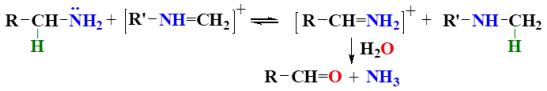


Figure 1.
The Sommelet reaction mechanism proposed by Angyal *et al*. [15, 16, 17]

According to the mechanism proposed by Le Henaff *et al*., the hydride ion is transferred intra-molecularly (Figure 2) [18]. The proposed mechanism involves an intramolecular rearrangement with the formation of a carbenium cation, stabilized by the formation of the azomethinium cation.

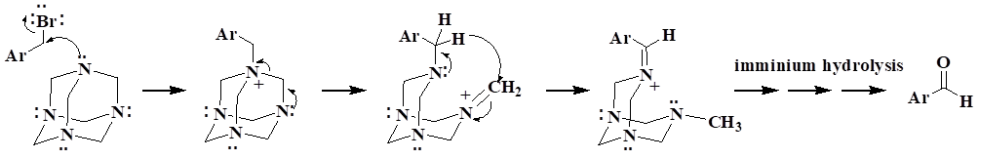


Figure 2.
The Sommelet reaction mechanism proposed by Le Henaff *et al*. [18]

Simiti *et al.* applied the Sommelet reaction in the series of 2-aryl-4-halomethylthiazoles containing different electron donating and electron withdrawing groups, in order to investigate the influence of the substituents and their position for the reactivity in the Sommelet reaction (Figure 3) [19, 20]. As it can be observed, the extended π-π conjugation of the 2-phenylthiazole system allows the transmission of the electronic effect of a substituent to the reaction centre and, consequently, it can influence the reactivity of the investigated compounds in the Sommelet reaction. The obtained results confirmed that the nature of the substituents grafted on the aromatic system significantly influence the Sommelet reaction yield.

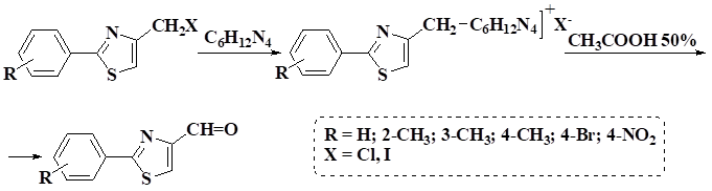


Figure 3.
The Sommelet reaction in the series of 2-aryl-4-halomethylthiazoles [19, 20]

Moreover, it was found that the success of the Sommelet reaction depends on the position of the halomethyl group grafted on the π-excessive heterocyclic systems. Considering the mechanism proposed by Le Henaff, it can be observed that the electron density at the carbon atom linked to the halomethyl group plays an essential role in reaction course. In the case of 4-chloromethyl-2-phenylthiazole ring system, the electron density in position 4 of the thiazole ring is very close to the electron density of the carbon atom from the benzene ring.

The Sommelet reaction was applied in the series of 2-aryl-4-chloromethylthiazoles substituted in position 5 of the thiazole ring with halogen atoms, in order to investigate if the electronic effects and the steric hindrance of the halogen atom could influence the Sommelet reaction course (Figure 4). The Sommelet reaction was performed directly, by refluxing the chloromethyl derivatives with urotropine in 50% acetic acid, and indirectly, by isolating the urotropinium salt followed by hydrolysis in 50% acetic acid, at reflux. Only the indirect procedure afforded the corresponding aldehydes, accompanied by side products. The best results were obtained by using 75% acetic acid in the hydrolysis step. This different behaviour in the Sommelet reaction of 5-bromine-substituted thiazole derivatives can be explained by the electronic effects of the bromine on the reaction centre [21].

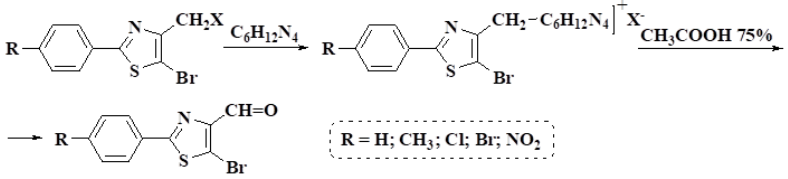


Figure 4.
The Sommelet reaction in the series of 2-aryl-5-bromo-4-halomethylthiazoles [21]

In further studies, the Sommelet reaction was applied for a series of 2-arylthiazoles bearing the halomethyl group grafted in the 5th position of the thiazole ring, where the electron density is higher compared with the 4th position. The corresponding thiazole-5-carbaldehydes were obtained with good yields, when the indirect Sommelet reaction was applied, with the isolation of the urotropinium salts followed by hydrolysis in 50% acetic acid. The results were unsatisfactory when the Sommelet reaction was applied directly, in a single step, without separating the urotropinium salts (Figure 5) [22].

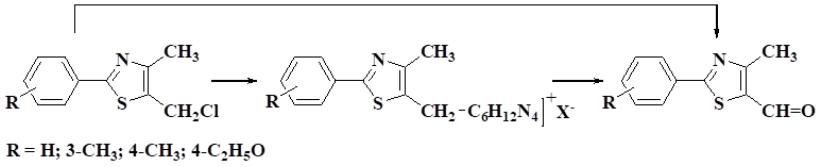


Figure 5.
The Sommelet reaction in the series of 2-aryl-5-halomethylthiazoles [22]

The performed experiments led to the conclusion that the Sommelet reaction cannot be applied in the electron deficient positions, such as in the case of the 2nd position of the thiazole ring, but it can be applied in the 4th and 5th positions of the thiazole ring, where the electron density is very close or higher than in the case of benzene.

The Sommelet reaction was successfully extended in the series of bis-thiazoles, compounds presenting an extended π-π conjugation between the benzene ring and the two thiazole rings [23], as well as in the 2-aryl-4-chloromethyloxazole series, in this case, the π-excessive character being higher in comparison with the 2-arylthiazole series (Figure 6) [24].

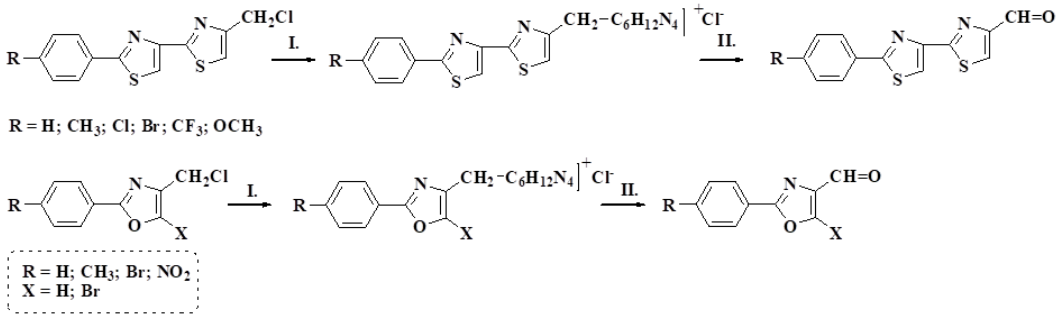


Figure 6.

The Sommelet reaction in the series of bis-thiazoles and 2-aryl-4-chloromethyloxazoles

Reaction conditions: **I.** hexamethylenetetramine/chloroforme; **II.** hexamethylenetetramine, CH_3COOH 50% [23, 24]

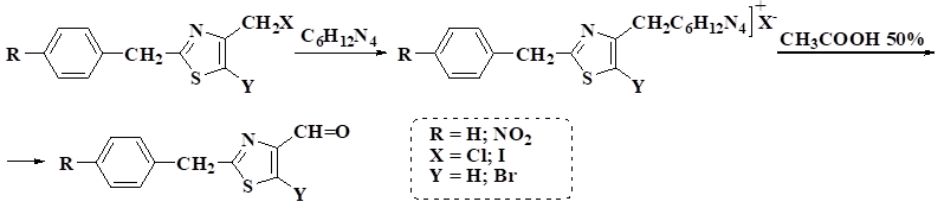


Figure 7.

The Sommelet reaction in the series of 2-benzyl-4-halomethyl-thiazoles [25, 26]

The Sommelet reaction was investigated, by the same research group, in the 2-benzyl-4-halomethyl-thiazole series (Figure 7) [25, 26]. The corresponding aldehydes were successfully obtained, suggesting that the interruption of the conjugation between the two aromatic rings does not affect the effectiveness of the Sommelet reaction. Good results were also obtained in the case when a bulky substituent (the bromine atom) was present in the 5th position of the thiazole ring.

The Sommelet reaction was further applied in the series of 2-anilino-4-chloromethylthiazoles and their N-acetyl derivatives [27, 28]. Although the nitrogen electrons from the amine function are delocalized in both directions, by p-π conjugation, the electron density remains higher in the 4th and the 5th positions of the thiazole ring. The corresponding thiazole-4-carbaldehyde derivatives were obtained in good yields *via* Sommelet reaction starting from the corresponding N-acetyl derivatives (Figure 8). Good yields were obtained even if in the 5th position of the thiazole ring was grafted a bulky substituent, the bromine.

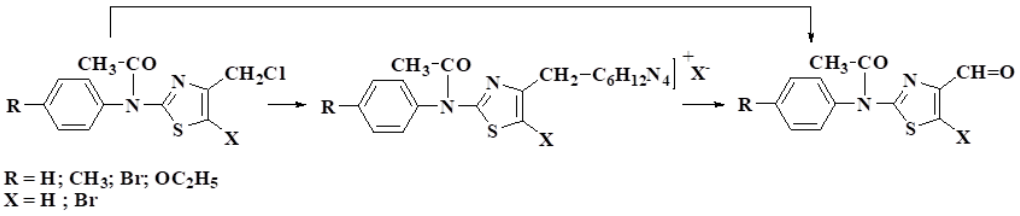


Figure 8.

The Sommelet reaction in the series of N-acetyl-2-anilino-4 chloromethylthiazoles [27, 28]

In order to confirm the influence of the electron density at the carbon linked to the halomethyl group for the Sommelet reaction, the reaction was investigated in the series of 2-anilino-5-chloromethyl-1,3,4-thiadiazoles and their N-acetyl derivatives, based on the supposition that the nitrogen electrons from the amine function (electron donating group) could theoretically compensate the electron deficit from the 5nd position of 1,3,4-thiadiazole. The Sommelet reaction was unsuccessful in this case, because the electron density in the 5th position of the 1,3,4-thiadiazole remains low, even if in the 2nd position is present an electron donating group [29, 30].

In the same research group, the Sommelet reaction was applied for the first time in a condensed heterocyclic system, the thiazolo[3,2-b][1,2,4]triazole ring. Taking into account that the reactivity of the halomethyl group in 6th position of the 2-aryl-thiazolo-[3,2-b][1,2,4]triazole system is comparable to that of the halomethyl group in 4th position of the 2-aryl-thiazole ring system, the Sommelet reaction was applied in the series of 2-aryl-6-halomethyl-thiazolo-[3,2-b][1,2,4]triazoles (Figure 9) [31, 32].

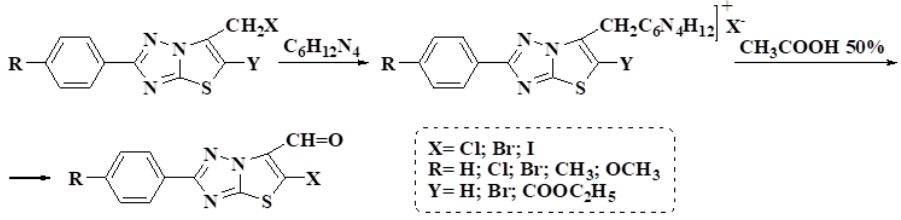


Figure 9.
The Sommelet reaction in the series of thiazolo[3,2-b][1,2,4]triazoles [31, 32]

It was found that the substituents grafted in the 5th position of the thiazolo[3,2-b][1,2,4]triazole ring (Y) influenced the reactivity of the halomethyl group in the Sommelet reaction. When the 5th position of the heteroaromatic ring is free (Y = H), the corresponding aldehydes are obtained with poor yields. When an electron-withdrawing group is grafted in the 5th position (Br, $COOC_2H_5$), the corresponding aldehydes are obtained with better yields, thus suggesting that the Sommelet reaction is favoured by the electronic effects of these substituents [32].

Concerning the nature of the halogen atom from the halomethyl group (CH_2X), no differences regarding the reactivity during the Sommelet reaction were observed. In all cases, the urotropinium salts were obtained in 70 - 80% yields and the hydrolysis step occurred with 20 - 40% yields.

The presented reported data are showing that the Sommelet reaction represents a synthetically convenient and very useful procedure for converting a halomethyl group into a formyl group, which can be successfully applied in the series of oxazoles, thiazoles, as well as in the series of heterocyclic compounds with fused rings, such as thiazolo[3,2-b][1,2,4]triazole.

It is important to note that the Sommelet reaction cannot be applied for introducing the formyl group in electron deficient positions, such as the 2nd position of the thiazole ring, or the 2nd and 5th position of the 1,3,4-thiadiazole ring. The reactive positions are those in which the electron density is at least as high as in the case of benzene: the 4th and 5th positions of the thiazole/oxazole ring, and respectively the 5th and 6th positions of the thiazolo[3,2-b][1,2,4]triazole ring.

Synthesis of chalcones by Claisen-Schmidt condensation

The Claisen-Schmidt condensation is a carbon-carbon bond forming reaction that most often refers to the condensation of an aromatic aldehyde or ketone and an enolizable ketone, in the presence of a basic catalyst. Compared to aldehydes, the carbonyl group from ketone is less reactive toward nucleophilic addition. In the presence of a basic catalyst, the enolisable ketone is transformed into enolates, which can perform a nucleophilic attack on the carbonyl group of aldehydes, with the formation of a new carbon-carbon bond. If the formed β-hydroxycarbonyl compound still has a reactive α hydrogen, a dehydration reaction will rapidly undergo, resulting the corresponding α,β-unsaturated ketone. The synthesis of chalcones by condensation of aldehydes with enolisable ketones can be performed also in acid catalysis, in the presence of protic acids or Lewis acids [33].

Being aware of the biological potential of the thiazole ring, Simiti *et al*. decided to extend the Claisen-Schmidt condensation in the thiazole series, for the synthesis of new chalcones bearing the thiazole core (Figure 10) [34].

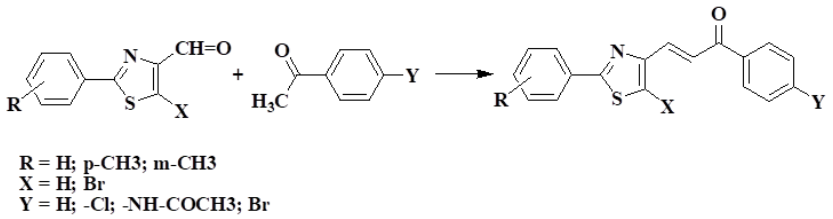


Figure 10.
Synthesis of thiazole chalcones [34]

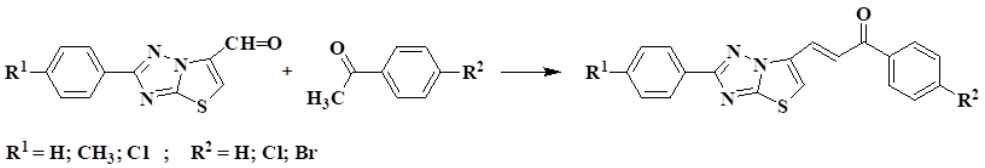


Figure 11.
Synthesis of thiazolo[3,2-b][1,2,4]triazole chalcones by Claisen-Schmidt condensation [35]

The Claisen-Schmidt condensation was further applied in the thiazolo[3,2-b][1,2,4]triazole heterochalcones series. A series of 2-aryl-thiazolo[3,2-b][1,2,4]triazole-5-carbaldehydes were condensed with a series of acetophenones in basic catalysis, affording the corresponding heterochalcones in good yields (Figure 11) [35].

In continuation of this research, new heterochalcones were synthesized by Claisen-Schmidt condensation of thiazole and thiazolo[3,2b]-[1,2,4]triazole aldehydes with *ortho*- and *para*-hydroxy-acetophenone (Figure 12) [36].

With the aim of obtaining new α-bromo-heterochalcones, the condensation of 2-aryl-thiazol-4-carbaldehydes and 2-aryl-thiazolo[3,2-b][1,2,4]triazol-5-carbaldehydes with 2-bromoacetophenone was studied. In the presence of potassium hydroxide, sodium hydroxide or other weaker bases (sodium carbonate or pyridine), no halogenated reaction products were obtained [24]. By performing a detailed study regarding the condensation of 2-phenyl-thiazol-4-carbaldehyde with 2-bromo-acetophenone in basic catalysis, it was found that a mixture of epoxy-ketone, α-diketone and 3-hydroxy-furane derivative was formed, instead of the expected halogenated product, the α-bromo-heterochalcone (Figure 13) [37].

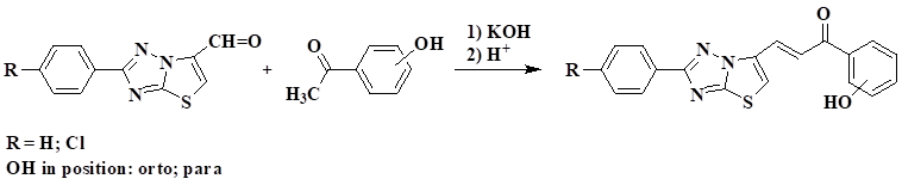


Figure 12.
Synthesis of thiazolo[3,2-b][1,2,4]triazole chalcones [36]

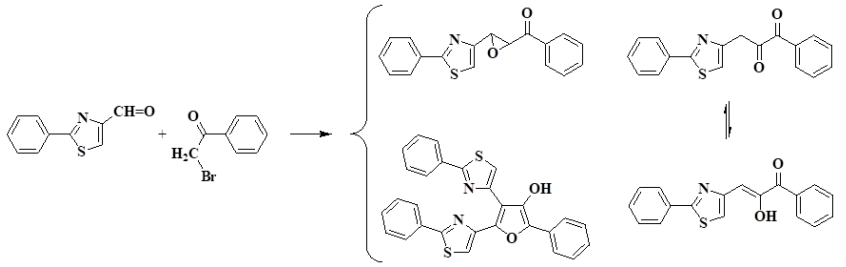


Figure 13.
Reaction of 2-phenylthiazole-4-carbaldehyde with 2-bromo-acetophenone [37]

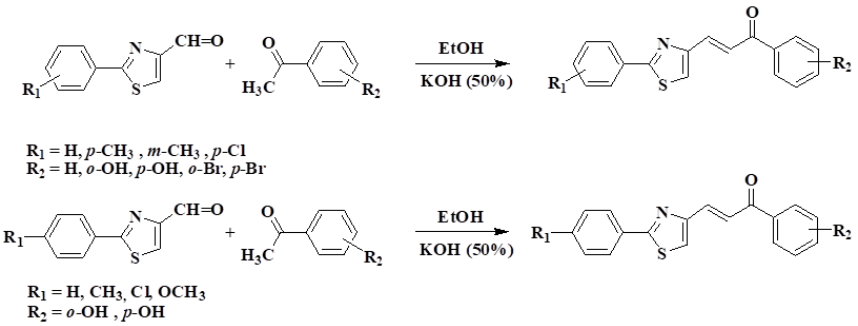


Figure 14.
Synthesis of 2-arylthiazole chalcones by Claisen-Schmidt condensation [38, 40]

The Claisen-Schmidt condensation was further extended in the series of 2-arylthiazole-4-carbaldehydes bearing electron-donating or electron-withdrawing substituents on the 2-phenylthiazole system [38, 39, 40]. First, their base-catalyzed condensation with acetophenone and monosubstituted acetophenones such as *ortho*-/*para*-bromacetophenone and *ortho*-/*para*-hydroxy-acetophenone was applied for the synthesis of the corresponding 2-arylthiazole chalcones (Figure 14) [38, 40].

Considering that *ortho*-hydroxychalcones are the principal precursors for accessing various flavonoidic derivatives such as flavones, flavanones and aurones by cyclisation in different reaction conditions, the research was further oriented towards the synthesis of new thiazole *ortho*-hydroxychalcones, by Claisen-Schmidt condensation of 2-arylthiazole-4-carbaldehydes with different *ortho*- and *para*-disubstituted or tri-substituted acetophenones (Figure 15) [39].

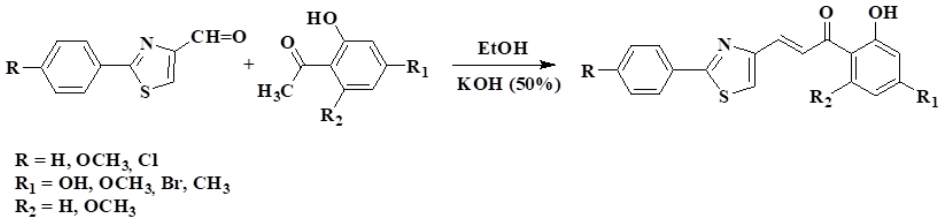


Figure 15.
Synthesis of *ortho*-hydroxychalcones by Claisen-Schmidt condensation [39]

Chemical behaviour of chalcones

Chalcones are central core structures for a variety of natural products, bioprecursors of flavonoids. Furthermore, chalcones are key intermediates for various classes of compounds with biological potential, such as: flavones, flavanones, aurones, pyrazolines, pyrazoles, epoxydes etc.

A series of 2-arylthiazol-4-yl carbaldehydes were used in the Claisen-Schmidt condensation with acetophenone and other acetophenones substituted in the *para* position with Cl, Br and acetamido group. The obtained chalcones were treated with phenylhydrazine and *p*-Br-phenylhydrazine, resulting in the corresponding 1-aryl-pyrazolines substituted with thiazole in position 5. By treatment with MnO_2 in $CHCl_3$, the pyrazolines were transformed into the corresponding pyrazoles (Figure 16) [34].

A series of *ortho*-hydroxy-heterochalcones were obtained in 75 - 82% yields by the condensation of *ortho*-hydroxyacetophenone with some 2-arylthiazol-4-yl carbaldehydes (Figure 17). Their epoxidation with hydrogen peroxide followed by oxidative cyclisation afforded the 2-(2-arylthiazol-4-yl)-3-hydroxychromones in 65 - 71% yields [41].

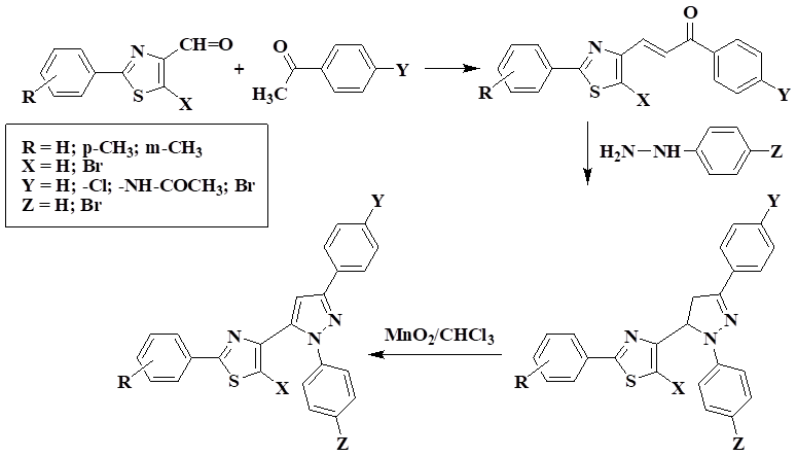


Figure 16.
Synthesis of thiazole chalcones and their use as intermediates for obtaining pyrazolines and pyrazoles [34]

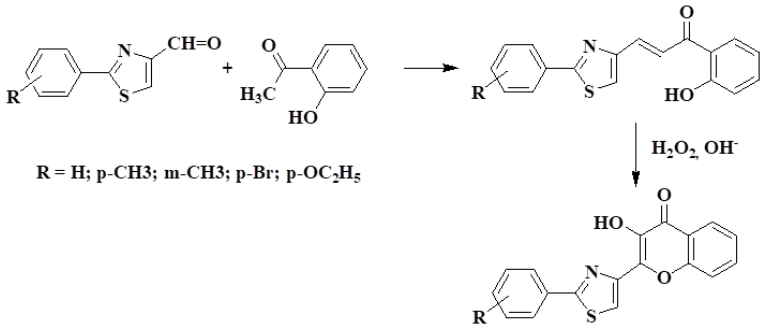


Figure 17.
Synthesis of thiazole *ortho*-hydroxy chalcones and their cyclisation to hydroxychromones [41]

In further studies, the reactivity of *ortho*-hydroxy-heterochalcones derived from thiazole was studied in the condensation with different nitrogen-nucleophiles, such as hydrazine and phenylhydrazine and it was found that different cyclisation products are formed, depending on the nitrogen-nucleophile partner [42].

By treatment with hydrazine of *ortho*-hydroxyheterochalcones and *ortho*-acetoxyheterochalcones, the corresponding pyrazoline derivatives were obtained. When acetic acid was used as solvent, the acetylation of the NH group occurred simultaneosly with the cyclisation step, resulting the corresponding N-acetylated pyrazolines. The cyclisation with hydrazine, in ethanol as solvent, afforded the corresponding unacylated pyrazolines [42].

When phenylhydrazine was used as nitrogen-nucleophile, a different cyclisation pathway was observed, in the same reaction conditions, resulting the corresponding hydrazono-chromanes. The same hydrazono-chromanes were formed when the *ortho*-acetoxyheterochalcones were used in the cyclisation (Figure 18). The reactions were performed in acetic acid as solvent, and no acetylation of the NH group was observed, which can be explained by taking into consideration the lower N-nucleophilicity of the phenylhydrazine moiety, due to electronic effects [42].

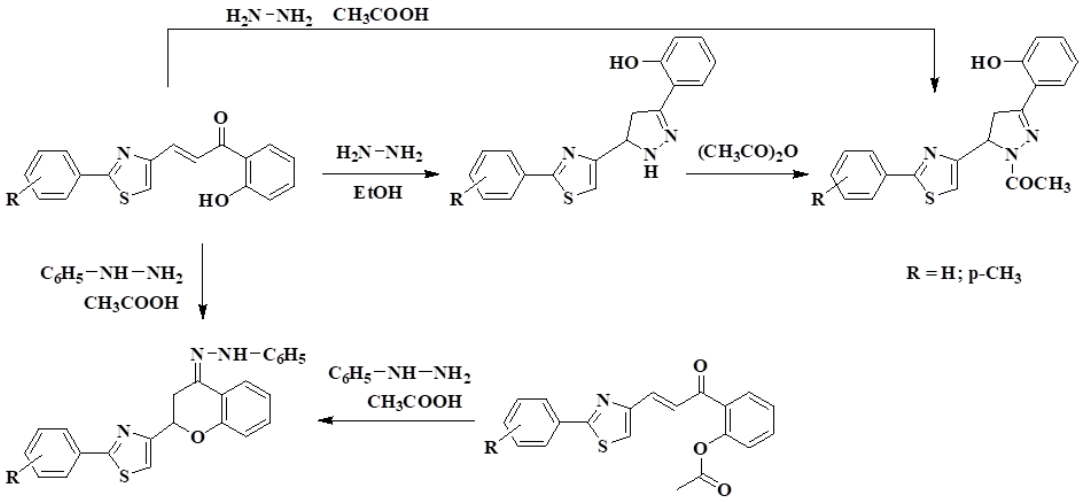


Figure 18.
Synthesis of thiazole pyrazolines and hydrazono-chromanes [42]

The chemical behaviour of previously synthesized thiazole and thiazolo[3,2b][1,2,4]triazole heterochalcones was investigated by V. Zaharia's group in order to obtain new cyclisation products. By treatment with hydrogen peroxide of *ortho*-hydroxyheterochalcones in basic media, the corresponding hydroxychromones were obtained (Figure 19), while the unhydroxylated heterochalcones previously obtained were transformed in the same conditions in epoxyketones (Figure 20) [36].

Moreover, thiazole and thiazolo[3,2-b][1,2,4]triazole pyrazolines and isoxazolines were obtained by the condensation of the heterochalcones with hydrazine and respectively with hydroxylamine (Figure 21) [36].

Ortho-hydroxychalcones are versatile precursors for a large panel of flavonoidic derivatives, such as flavones, flavanones and aurones, due to the reactivity of the α,β-unsaturated ketone function and also to the *ortho*-hydroxyl group, grafted in a sterically convenient position for cyclisation. Generally, the course of the cyclisation reaction depends to a large extent on the nature of the two aromatic/heteroaromatic systems bounded by the propenone chain, the nature of the existing substituents, as well as on the reaction conditions. Consequently, a detailed investigation of the products formed during cyclisation of 2-arylthiazole derived *ortho*-hydroxychalcones in different reaction conditions was found necessary for the investigation of the chemical behaviour of these chalcones.

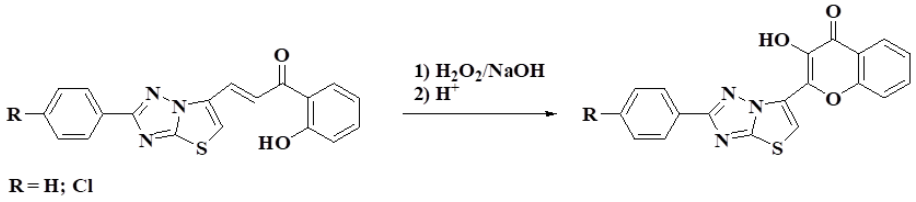


Figure 19.
Synthesis of thiazolo[3,2-b][1,2,4]triazole hydroxychromones by cyclisation of *ortho*-hydroxychalcones [36]

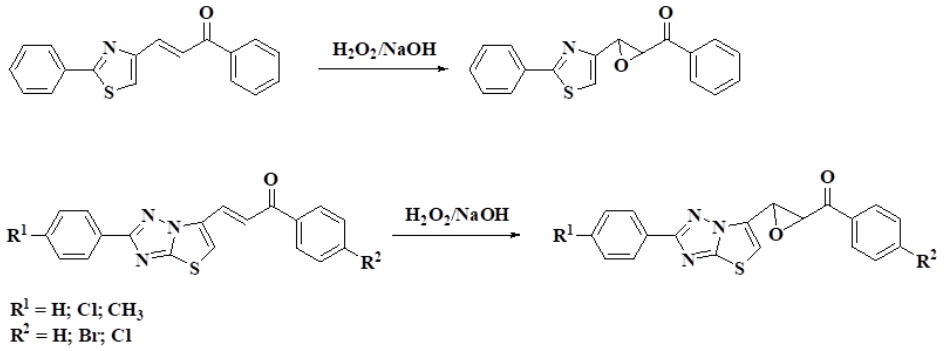


Figure 20.
Synthesis of thiazole and thiazolo[3,2-b][1,2,4]triazole epoxyketones [36]

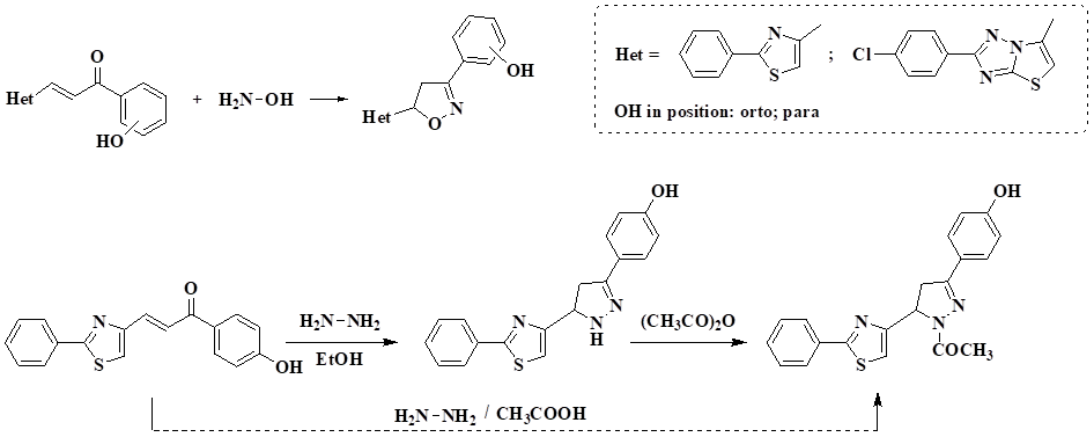


Figure 21.
Synthesis of thiazole and thiazolo[3,2-b][1,2,4]triazole pyrazolines and isoxazolines starting from the corresponding heterochalcones [36]

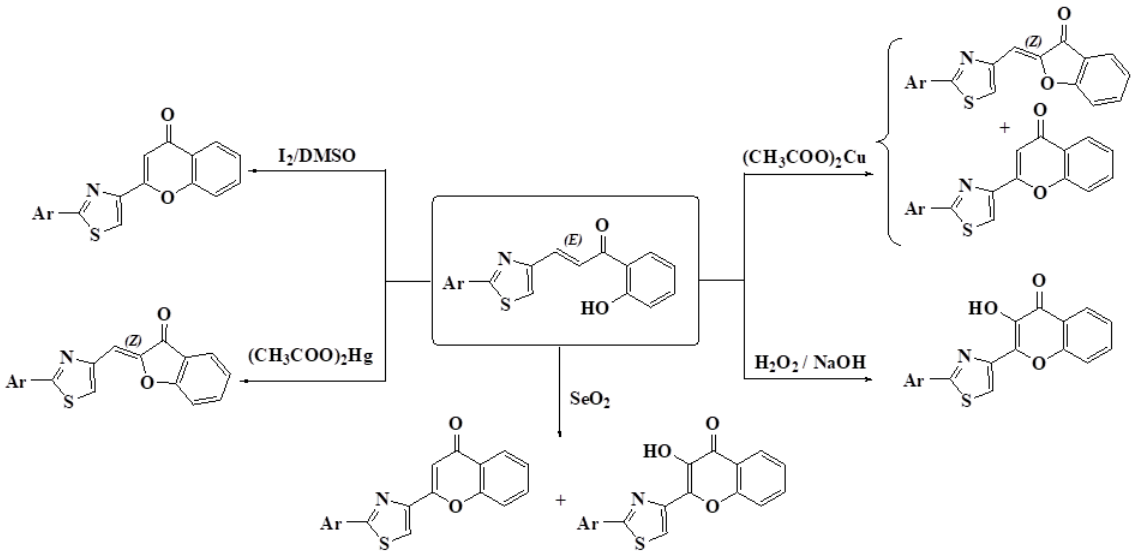


Figure 22.
Cyclisation products obtained by the oxidative cyclisation of 2-arylthiazole *ortho*-hydroxychalcones with different oxidizing agents [43]

It was found that the oxidative cyclisation of the 2-arylthiazole *ortho*-hydroxychalcones led to various reaction products, depending on the oxidizing agent that was used. When copper(II) acetate in dimethyl-sulfoxyde was used, the 2-phenylthiazole *ortho*-hydroxychalcone led to the formation of a mixture of aurone and the corresponding flavone in an approximate 1:1 molar ratio [43]. Hydroxyflavones were obtained when the oxidative cyclisation of 2-arylthiazole *ortho*-hydroxychalcones underwent with

hydrogen peroxide in alkaline catalysis [43] and flavones were obtained when the oxidative cyclisation of 2-arylthiazole *ortho*-hydroxychalcones was performed with iodine in dimethylsulfoxide [40, 43]. A mixture of flavones and hydroxyflavones was obtained when the oxidizing agent was selenium dioxide in *n*-butanol [43]. When the cyclisation of 2-phenylthiazole *ortho*-hydroxychalcone was performed with mercury(II) acetate in pyridine as solvent, the corresponding Z-aurone was obtained in good yields (80%) [43]. This method was further applied for the synthesis of new 2-arylthiazole aurones with Z configuration (70 - 86% yields), by oxidative cyclisation of the corresponding 2-arylthiazole *ortho*-hydroxychalcones (Figure 22) [43].

New 2-arylthiazole flavanones and flavones were obtained by cyclisation of the corresponding 2-aryl-thiazole *ortho*-hydroxychalcones, in different reaction conditions: flavanones were obtained with 40 - 55% yields by cyclisation in acidic catalysis (H_2SO_4 conc. in ethanol), and flavones were obtained with 32 - 55% yields by oxidative cyclisation with iodine in dimethylsulfoxide (Figure 23) [40]. Other reported cyclisation pathway towards 2-phenylthiazole flavanone consists in the cyclisation of the 2-phenylthiazole *ortho*-hydroxychalcone in acetic acid, or in the presence of sodium acetate, in methanol as solvent. A better yield was obtained when the cyclisation was performed in the presence of sodium acetate in methanol [44].

The chemical behaviour of 2-phenylthiazole *ortho*-methoxychalcones in cyclisation reactions was studied in order to obtain new epoxydes and flavones (Figure 24) [44]. In the synthesis of epoxydes, it was confirmed that the methoxyl group grafted on the benzoyl moiety is resistant in the presence of hydrogen peroxide and NaOH. By reflux with iodine in dimethylsulfoxyde, the *ortho*-methoxy-chalcones were cyclised to the corresponding flavones, this step involving the demethylation of the methoxyl group from the benzoyl moiety of chalcone [44].

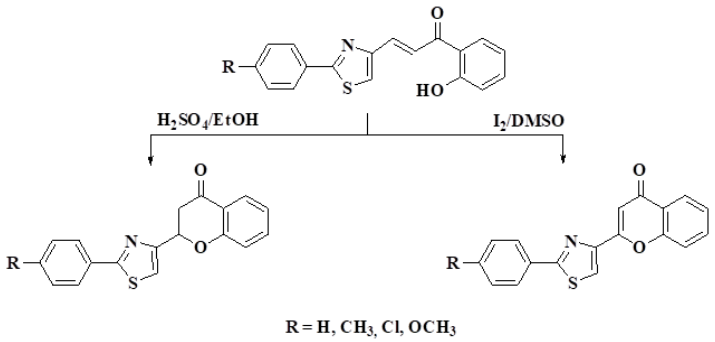


Figure 23.
Cyclisation products of 2-arylthiazole *ortho*-hydroxychalcones [40]

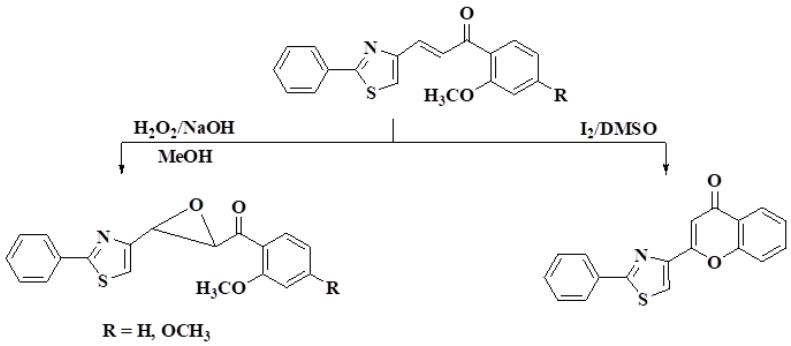


Figure 24.
Cyclisation products of 2-arylthiazole *ortho*-methoxychalcones [44]

Biological activity of the synthesized hetero-aromatic chalcones and their cyclisation products

A series of 2-aryl-thiazolo[3,2-b][1,2,4]triazole hetero-chalcones obtained as previously described by Claisen-Schmidt condensation of the corresponding aldehydes with acetophenones were evaluated for their anti-bacterial and antifungal activity (Figure 25). A good activity against *Candida albicans* was observed, the most active chalcones being those containing Br or Cl grafted on the phenyl rings [35].

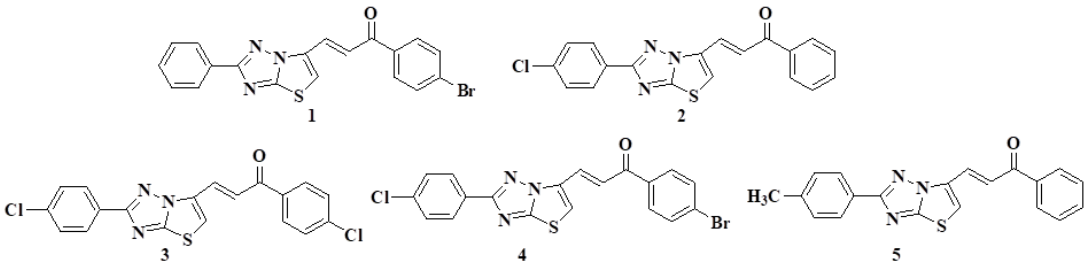


Figure 25.
Thiazolo[3,2-b][1,2,4]triazole chalcones with antifungal activity against *Candida albicans* [35]

The antitumor activity of chalcones is due to their ability to target certain structures with a key role in tumor genesis and cancer progression, most often proteins involved in cell cycle regulation and apoptosis.
According to literature data, there are several mechanisms by which chalcones cause apoptosis of tumour cells: the inhibition of the epidermal growth factor receptor (EGFR) [45], the induction of the expression of pro-apoptotic proteins, for example Bax protein [46]; inhibiting the expression of anti-apoptotic proteins, most commonly the Bcl-2 protein [46, 47]; the activation of several caspases [46] (e.g. caspase 3, caspase 8) and the increase of reactive oxygen species level which causes the loss of mitochondrial membrane potential [46, 48].
Chalcones present antiproliferative activity by inhibiting different enzymes involved in the cell cycle regulation, for example cyclin-dependent kinases [49]. Moreover, chalcones can prevent the formation of microtubules by binding to tubulin [48, 50]. All these facts conduct to cell cycle arrest, most often in the G2 / M phase [48, 51].
The ability of chalcones to interact with tubulin or some enzymes involved in the cell cycle is due to their potential to function as Michael acceptors in reaction with certain amino acid units in the structure of proteins, e.g. with cysteine [52] as well as other interactions with amino acid units, by hydrogen bonds or by π–π interactions between the aromatic units [8].
The interaction of chalcones with DNA is unlikely, due to the structural flexibility of the propenone chain. This fact can be considered a major advantage because it reduces the risk of mutagenic or genotoxic side effects of chalcones [53].
A series of thiazole chalcones were synthesized by Claisen-Schmidt condensation (Figure 14) and evaluated for their *in vitro* cytotoxic activity against three human cancer cell lines: prostate carcinoma (DU-145), hepatocellular carcinoma (Hep-G2) and human leukemia monocytic cell line (THP-1). The most active compounds were chalcones **6** and **7** (Table I, line 1 and 2) with IC_{50} values below 10 µM on both DU-145 and THP-1. They also showed 100% inhibition of DU-145 growth at 50 µM, highlighting their good cytotoxic activities [38].
New thiazole *ortho*-hydroxychalcones were synthesized by Claisen-Schmidt condensation of 2-arylthiazole-4-carbaldehydes and different *ortho*- and *para*-di-substituted acetophenones (Figure 15) [39]. Some of the synthesized *ortho*-hydroxychalcones showed significant antitumor activity with IC_{50} values below 10 µM against some of the tested tumour cell lines. The structures of the compounds that showed superior activity to the reference drug, doxorubicin, as well as their IC_{50} values on the corresponding cancer cell lines are presented in Table I, lines 3 - 10. Compounds **8**, **9** and **10** (Table I, lines 3, 4 and 5) showed these results against 5 out of the 9 tested cancer cell lines, compounds **11** and **12** (Table I, lines 6 and 7) against 7/9 cancer cell lines and compound **13** showed good anticancer activity against 8/9 cancer cell lines. Other compounds active on the leukemia cell lines are compounds **14** and **15** (Table I, lines 9 and 10).
A series of 3-indolyl-1-pyridyl-2-propenones were obtained with 68.8 - 91.8% yields by the Claisen-Schmidt condensation of various indol-3-carbaldehydes and 3-/4-acetylpyridine in anhydrous methanol, in the presence of pyperidine as basic catalyst (Figure 26). Two of the synthesized compounds, **16** and **17** showed good cytotoxic activity against the leukaemia cell lines CEM/ADR5000 (Table I, lines 11 and 12) [54].

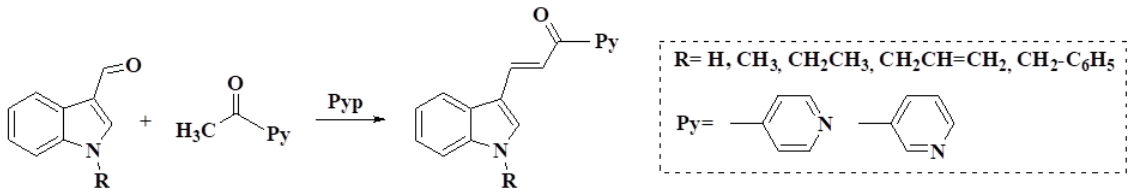


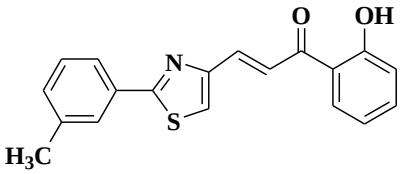
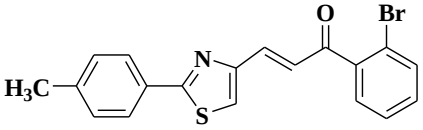
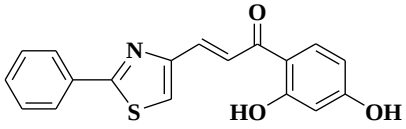
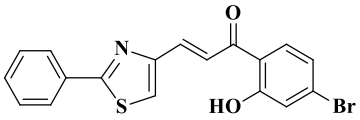
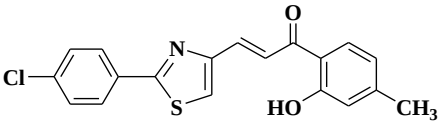
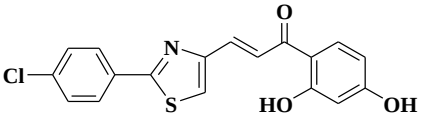
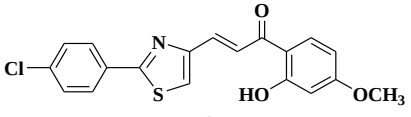
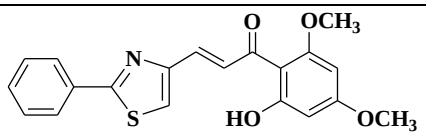
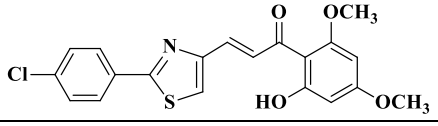
Figure 26.
Synthesis of 3-indolyl-1-pyridyl-2-propenones with anticancer properties [54]

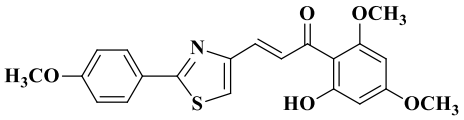
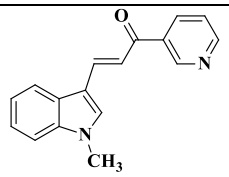
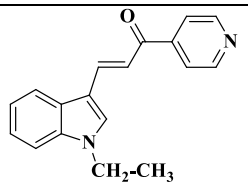
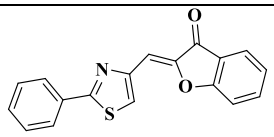
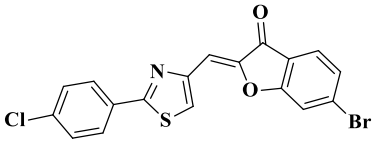
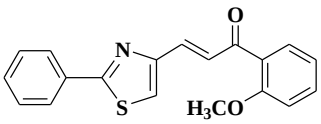
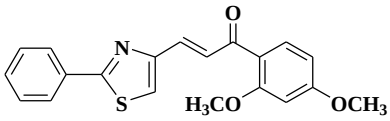
Concerning the antiproliferative activity of the thiazole aurones resulted from the oxidative cyclisation of the corresponding *ortho*-hydroxychalcones, the best results were observed for compounds **13** and **14** (Table I, lines 13 and 14) which displayed good cytotoxic activity against the leukemia cell lines CEM/ADR5000 and against the breast cancer cell lines MDA-MB231/ *BCRP* (Table I, lines 13 and 14) [43].

Thiazole methoxychalcones **20** and **21**, obtained by Claisen-Schmidt condensation of 2-phenylthiazole carbaldehyde with 2-methoxyacetophenone and respectively 2,4-dimethoxyacetophenone [44], showed good anticancer activity with IC_{50} values below 1 μM against several cancer cell lines such as human leukaemia, human colon carcinoma, glioblastoma and cervical cancer cells. The antiproliferative effect of the two compounds against these cancer cell lines proved to be superior to doxorubicin, which was the reference drug used in the experiments (Table I, lines 15 and 16) [44].

Table I

Thiazole chalcones and cyclisation products with antitumor activity

Nr. crt.	Compound	Tumour cell lines for which they have cytotoxicity (IC_{50} μM)
1	 **6**	Prostate carcinoma DU-145 (IC_{50} = 8.78 μM) Human leukaemia monocytic cell line THP-1 (IC_{50} = 10.63 μM) [38]
2	 **7**	Prostate carcinoma DU-145 (IC_{50} = 7.47 μM) Human leukaemia monocytic cell line THP-1 (IC_{50} = 9.51 μM) [38]
3	 **8**	Human leukaemia cell lines CEM/ADR5000 (IC_{50} = 4.38 μM) [39]
4	 **9**	Human colon carcinoma cell lines HCT116($p53^{-/-}$) (IC_{50} = 1.84 μM) [39]
5	 **10**	Human colon carcinoma cell line HCT116($p53^{-/-}$) (IC_{50} = 1.82 μM) [39]
6	 **11**	Human leukaemia cell lines CEM/ADR5000 (IC_{50} = 4.64 μM) Human colon carcinoma cell line HCT116($p53^{-/-}$) (IC_{50} = 3.10 μM) [39]
7	 **12**	Human leukaemia cell line CEM/ADR5000 (IC_{50} = 5.34 μM) [39]
8	 **13**	Human leukaemia cell line CEM/ADR5000 (IC_{50} = 3.46 μM) Human colon carcinoma cell line HCT116($p53^{-/-}$) (IC_{50} = 2.11 μM) [39]
9		Human leukaemia cell line CEM/ADR5000 (IC_{50} = 3.55 μM) [39]

Nr. crt.	Compound	Tumour cell lines for which they have cytotoxicity (IC_{50} µM)
	14	
10	 **15**	Human leukaemia cell line CEM/ADR5000 (IC_{50} = 2.72 µM) [39]
11	 **16**	Human leukaemia cell line CEM/ADR5000 (IC_{50} = 9.90 µM) [54]
12	 **17**	Human leukaemia cell lines CEM/ADR5000 (IC_{50} = 9.62 µM) [54]
13	 **18**	Human leukaemia cell line CEM/ADR5000 (IC_{50} = 5.85 µM) [43]
14	 **19**	Breast cancer cell line MDA-MB231/*BCRP* (IC_{50} = 5.43 µM) [43]
15	 **20**	Human leukaemia cell line CCRF-CEM (IC_{50} = 0.25 µM) and their MDR subline CEM/ADR5000 (IC_{50} = 0.47 µM) Human colon carcinoma cells HCT116($p53^{+/+}$) (IC_{50} = 0.87 µM) and HCT116($p53^{-/-}$) (IC_{50} = 0.62 µM) Glioblastoma cells MDR U87.ΔEGFR (IC_{50} = 0.75 µM) Cervical cancer cell line Caski (IC_{50} = 0.69 µM) [44]
16	 **21**	Cervical cancer cell line Caski (IC_{50} = 0.81 µM) [44]

Since the biological activity could be generally influenced by the lipophilicity of bioactive compounds, we considered necessary to also discuss the results regarding the lipophilicity evaluation of some of the previously synthesized thiazole chalcones and aurones with antitumor properties. Lipophilicity is an important molecular parameter because of its implication in the absorption, distribution, metabolization and elimination of bioactive compounds. Knowing the lipophilicity of potential bioactive molecules is very useful for the prediction studies of their pharmacological and pharmacokinetic properties.

The lipophilicity of some of the synthesized thiazole chalcones and thiazole aurones was evaluated by reversed-phase thin layer chromatography and by high performance liquid chromatography, in order to study the correlation between this parameter and the antitumor activity of these compounds. A good correlation was found between the experimental and computed lipophilicity parameters.

It was found that high lipophilicity of thiazole chalcones and aurones is not a mandatory requirement for good anticancer activity. For example, the most active thiazole chalcones, **9**, **10** and **13** presented a moderate lipophilicity, but even the least lipophilic ones, compound **8** for instance, showed good biological activity. The same conclusion was drawn in the case of the investigated aurones, where the most active aurone on the leukaemia resistant cancer cell lines, compound **18**, is a compound with moderate lipophilicity, and the most active aurone on the breast

adenocarcinoma cells, compound **19**, is the most lipophilic thiazole aurone [55].

Conclusions

The Sommelet reaction was developed as an efficient way to obtain thiazole aldehydes used as starting materials in the synthesis of thiazole chalcones, by a classical Claisen-Schmidt condensation with various substituted acetophenones. The reaction pathways and structures of some newly synthesized thiazole chalcones, as well as their chemical behaviour in various cyclisation reactions were presented, including thiazolotriazole heterochalcones, 2-arylthiazole chalcones, thiazolotriazole pyrazolines from chalcones moieties, arylthiazoyl pyrazolines from chalcones moieties, thiazole flavones, thiazole flavanones, thiazole hydroxy-flavones and thiazole aurones from *ortho*-hydroxy-chalcones. Containing both thiazole/indole/pyridine and chalcone moieties, heterocyclic chalcones were proven to have promising biological properties such as anticancer and antifungal activities.

The previously reported experimental research has shown that the therapeutic properties of chalcones, determined by the support molecule, can be influenced and shaped by the nature and position of the substituents in the molecule. The α,β-unsaturated ketone structure and the presence of different groups grafted on the aromatic moieties proved to be crucial for both the chemical behaviour and the therapeutic properties of chalcones.

Conflict of interest

The authors declare no conflict of interest.

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