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HALOGEN-CONTAINING CHALCONES AS VERSATILE BIOACTIVE AGENTS: A REVIEW

Konul Shahverdiyeva, Samira Ismayilova, Alakbar Huseynzada, Ulviyya Hasanova, Niftali Yusubov, Valeh Ismayilov
Baku State University, Baku, Azerbaijan

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Along with the increase in the world population, the number and types of various diseases are also showing an increasing trend. This creates an important need to design and test a large number of drug molecules for the treatment of diseases. Throughout history, compounds existing in nature have been widely used for the treatment of diseases. Chalcones are widely distributed in nature in various plants and have been intensively used in medicine due to their biological activities, such as antibacterial, anti-inflammatory, and antioxidant. Despite the simplicity of the structure of these molecules and the ease of the synthesis process, their biological activities are significantly broad. Thus, as a result of the development of synthesis methods and biological studies, the structure of chalcones distributed in nature has been studied in depth, new chalcone derivatives have been synthesised based on these structures, and as a result of biological studies, it has been found that new chalcone derivatives, especially halogen-bearing chalcone molecules, exhibit a wide spectrum of biological activity. According to the results of recent studies, bromine and chlorine-containing chalcone molecules exhibit better anticancer, antifungal, and antibacterial activity compared to existing antibiotics and drugs. This article is devoted to a review of recent scientific research works on the synthesis and biological studies of new derivatives of chalcones, mainly halogen derivatives.

Keywords: halogen derivatives of chalcones; bioactivity; structure-activity relationship

INTRODUCTION

Microorganisms are developing resistance to conventional antimicrobial agents available in clinical practice, and there is a need to search for more active, effective, less toxic and cost-effective alternatives to existing drugs. Many studies have been conducted to investigate the therapeutic properties of chalcones and their various derivatives [1-3]. Chalcones, which are secondary metabolites of edible or medicinal plants, are included in the flavonoid family. Chalcones, which are 1,3-diphenyl-2-propen-1-ones, are based on two aryl moieties linked through an α,β-unsaturated carbonyl group [4]. These compounds are mainly polyphenolic compounds that range in colour from yellow to orange and contribute significantly to the pigmentation of the crown of some plants. Chalcones, which are naturally found in fruits, spices, teas and soy-based foods, have attracted much attention due to their potentially beneficial properties.

E-mail address: konulshahverdiyeva8@gmail.com

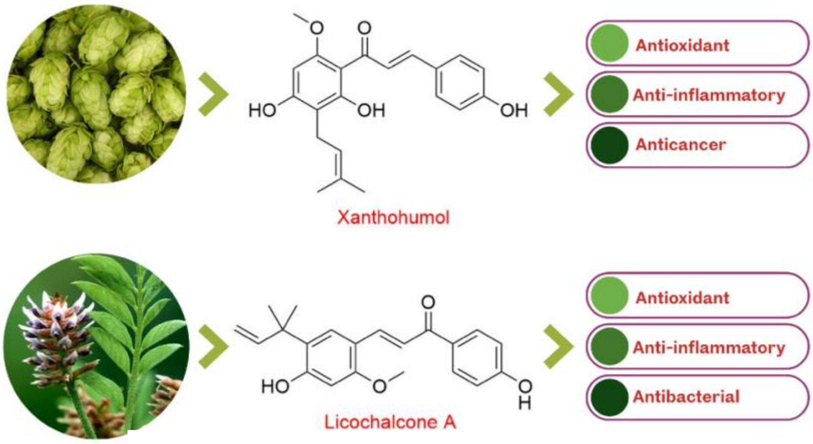


Figure 1. Naturally occurring chalcones

In addition, these molecules are present in natural products as pheromones, plant allelochemicals and insect hormones [5,6]. Chalcones can participate in many chemical reactions and are also used to synthesize heterocyclic compounds. A wide variety of chalcone derivatives can be synthesized by reacting aromatic aldehydes with aryl ketones in the presence of appropriate amounts of condensing agents [7]. A significant portion of medicinal chemistry research in the 21st century has focused on both natural and synthetic chalcones, as they possess diverse pharmacological potential, including antibacterial, [8,10] anti-inflammatory, [11-13] analgesic, [14,15] anticholinergic, [16] antiplatelet, [17] antiulcer, [18] antioxidant, [19,20] antimalarial, [21] anticancer, [22,23] antiviral, [24,27] anti-leshmanial, [28] antidiabetic, [29,30] immunomodulatory, [31,32] aldose reductase inhibition, [33] estrogenic, [34]. Chalcones are highly attractive molecules due to their simple structure, ease of synthesis, and promising biological applications. Several modifications of the chromophore of chalcones have been reported, including hydroxyl, methoxy, and amino groups as substituents with promising anticancer and antimicrobial activities [35-37]. The introduction of a chlorine atom into the chalcone structure can enhance its bioactivity, including antibacterial properties [38-40]. When a chlorine atom is introduced into the B ring of 2′-hydroxychalcone, it enhances its antituberculosis activity against Mycobacterium tuberculosis H37Rv strain [40]. In view of the above, this review aims to provide a comprehensive overview of recent research efforts devoted to the synthesis and biological activity of halogen-bearing chalcones, highlighting their potential as versatile compounds for the development of novel bioactive agents.

RESULTS AND DISCUSSION

Chalcones are compounds containing an α,β-unsaturated ketone system, which causes them to behave as pharmacophore compounds and exhibit a number of biological activities such as anticancer, anti-inflammatory, antiviral, antibacterial, antifungal, etc.[41]

The addition of various groups to the structure of chalcones also affects their bioactivity. A number of groups, especially halogen functional groups, regulate the electron distribution throughout the molecule, increasing membrane permeability and making the binding to biological targets more effective. Due to their large size and electronegativity, Cl and Br atoms help to bind to the active centers through halogen bonds and hydrophobic interactions. Changes in the inhibitory activity of the substance can also be observed depending on the position of the halogen on the ring. It is noticeable in literature that more para-substituted derivatives show higher effects. [42]

New halogenated chalcone derivatives were introduced by Chlupacova et al. The synthesized bioactive substances, which contain electron-withdrawing groups in the aromatic ring, have a number of inhibitory properties. Chalcone 1 (Figure 2) showed a positive effect on ciprofloxacin by inhibiting Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhimurium, and Klebsiella aerogenes.

İn case of the comparison with its corresponding flavone, the antifungal properties of the chalcone 2 (Figure 3) showed more satisfactory results against Tricophyton longifusus, Microsporum canis, and Aspergillus flavus than the corresponding flavone.

Compound 3 (Figure 4) surpassed ketoconazole in its antifungal activity against dermatophytes with a minimum inhibitory concentration of 0.5-25 μg/mL. [43]

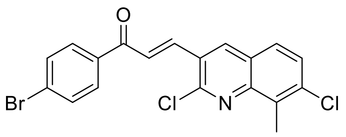


Figure 2. Chalcone 1

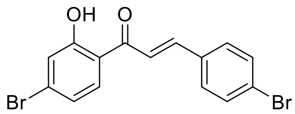


Figure 3. Chalcone 2

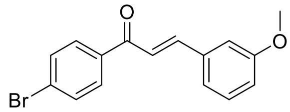


Figure 4. Chalcone 3

Bischalcone derivatives were prepared by Burmaoglu and his group from the reaction of 1,1-(2-hydroxy-4,6-dimethoxy-1,3-phenylene)bis (ethan-1-one) (2) with benzaldehydes.The general structure of the reactions obtained with the participation of an aqueous solution of potassium hydroxide. The cytotoxicity of these novel compounds was tested utilization of MTT analysis of pulmonary carcinoma. IC_{50} analysis indicated that the bischalcone derivative (Figure 5) had a marked cytotoxic effect on A-549 and Caco-2 cancer cell lines. [44]

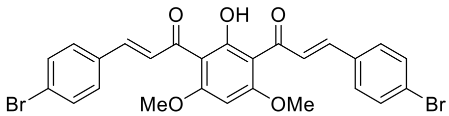


Figure 5. Bischalcone derivative

Flavone compound (Figure 7) was synthesized from brominated chalcone (Figure 6) in the presence of NaOH. The compound showed pronounced cytotoxic activity against A-549 and Caco-2 cancer cell lines. Flow cytometry analysis showed that it induced cell cycle arrest mainly in S and G_2/M phases. Western blot results supported these findings and showed increased expression of p53 and p27 proteins. Furthermore, fluorescence microscopy confirmed that compound 6 induced apoptosis in a concentration-dependent manner, indicating its potential as a promising anticancer agent. [45]

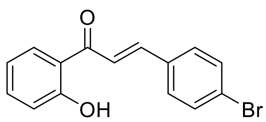


Figure 6. Brominated chalcone derivative

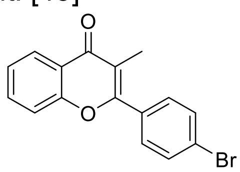


Figure 7. Brominated flavone derivative

Chalcone derivatives prepared in the presence of 4-hydroxyacetophenone and halogenated benzaldehydes and their Mannich bases are substances with protective activity containing halogen groups in their structures, as presented by Yamali and his group. Cellular toxicity of chalcones was evaluated against oral cells and cell lines. The number of cells were examined by MTT method. Among these substances, 3-(4-bromophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (Figure 8) was investigated for its cytotoxicity potential and selective toxicity, and PSE values were measured. The studies conducted showed that chalcone has a satisfactory effect against oral cancer cells (HCS-2, HCS-3, and HCS-4) with a CC50 of 5.7 μM, while its toxic effect against normal cells is quite low at 40 μM. [46]

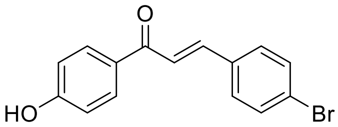


Figure 8. 3-(4-bromophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one

2-aminopyrimidine derivatives and homocyclic pyrimidine derivatives (Figure 9) were prepared in a two-step process. Compounds 9 were initially obtained by condensation of chalcone precursors with guanidine nitrate in ethanolic NaOH. Compounds 10 were obtained in 75–85% yield by reacting the resulting amino-substituted pyrimidines with 4-chloro-2,6-dimethylquinoline in the presence of anhydrous potassium carbonate and tetrahydrofuran. The halogen (Cl, Br, and F) and methoxy groups in the aromatic ring, which enhance their interaction with biological targets and overall efficacy, primarily contribute to the significant antibacterial activity of both pyrimidines.[47]

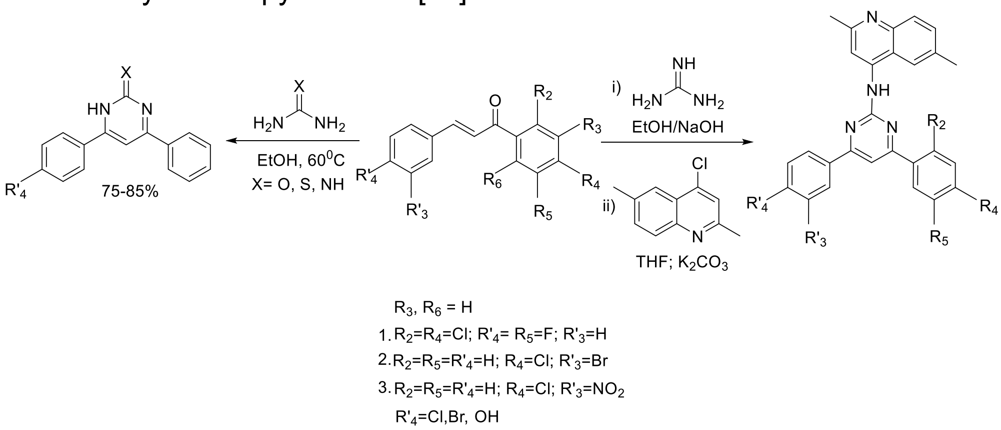


Figure 9. Synthesis procedure of 2-aminopyrimidine derivatives and homocyclic pyrimidine derivatives

A series of 2-hydroxy-3-nitrochalcones substituted with 5-methyl, 5-bromo, and 5-chloro were prepared. The compounds were then evaluated for their ability to inhibit α-glucosidase and α-amylase activity in vitro using enzymatic assays. Compared with the antidiabetic drug acarbose, most of the tested compounds showed greater inhibitory potency against α-glucosidase. Compared with the anticancer drug curcumin, chalcones showed a dual inhibitory effect on both enzymes without cytotoxicity against Raw-264.7 macrophage cells (mouse). [48]

Sun and colleagues conducted antiviral studies on a novel chalcone derivative. New compound (Figure 10), a chalcone derivative bearing an oxygen bridge and a 4-bromophenyl substituent at position 5, exhibited moderate antiviral activity against tobacco mosaic virus (TMV) in vivo. Its viral inactivation rate (63.1 ± 7.6%) was higher than its therapeutic (37.4 ± 4.6%) and protective (42.9 ± 7.7%) effects. This suggests that it focuses on direct virus inactivation.[49]

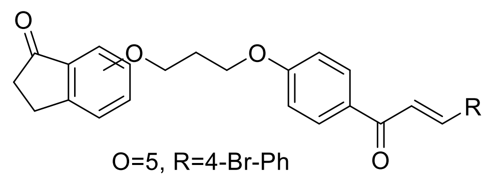
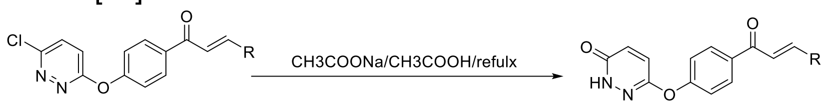


Figure 10. 4-bromophenyl substituted novel chalcone

Chen et al. synthesized pyridazine-based halogenated chalcones. (Figure 11) The antibacterial properties of these chalcones were tested against Xanthomonas axonopodis pv. citri (Xac), Pseudomonas syringae pv. actinidiae (Psa), and Xanthomonas oryzae pv. oryzae (Xoo). The compounds at concentrations of 50 and 100 μg/mL showed different effects against the bacteria. Compound C showed high and significant effects against Xac and Xoo, respectively, at 100 μg/mL. B′ showed a stable inhibition pattern against all tested pathogens, with 29.72 ± 6.62% for Xac, 14.77 ± 0.89% for Psa, and 35.66 ± 1.31% for Xoo at 100 μg/mL. A′ showed moderate effects compared to the others, while compounds A and B showed weak but significant effects.[50]

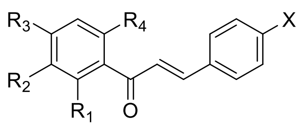


A. R=4-F-C6H4
B. R=4-Cl-C6H4
C. R=4-Br-C6H4

A'. R=4-F-C6H4
B'. R=4-Cl-C6H4

Figure 11. Pyridazine-based halogenated chalcones

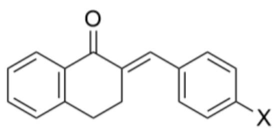
To evaluate the potential of the biological activity of synthesized halogenated derivatives of trimethoxychalcone (Figure 12), their inhibitory effect on key enzymes, such as MAO-A, MAO-B, AChE, BChE, and BACE-1, was studied by Vishal and his group. Compounds A and B showed the strongest inhibitory activity against MAO-A and MAO-B enzymes. Both derivatives showed good selectivity over MAO-B, with SI values of 15.1 and 31.1, respectively, which means that they performed better than the reference inhibitor Toloxatone. In addition, both showed moderate activity against AChe and BChe enzymes, while compound A was significantly more effective against BACE-1. The results obtained make these novel chalcone derivatives suitable for the design of neurotherapeutic multifunctional reagents.[51]



A. R1=OCH3, R2=OCH3, R3=OCH3, R4=H, X=Cl
B. R1=OCH3, R2=OCH3, R3=OCH3, R4=H, X=Br
C. R1=OCH3, R2=OCH3, R3=OCH3, R4=H, X=I

Figure 12. Halogenated derivatives of trimethoxychalcone

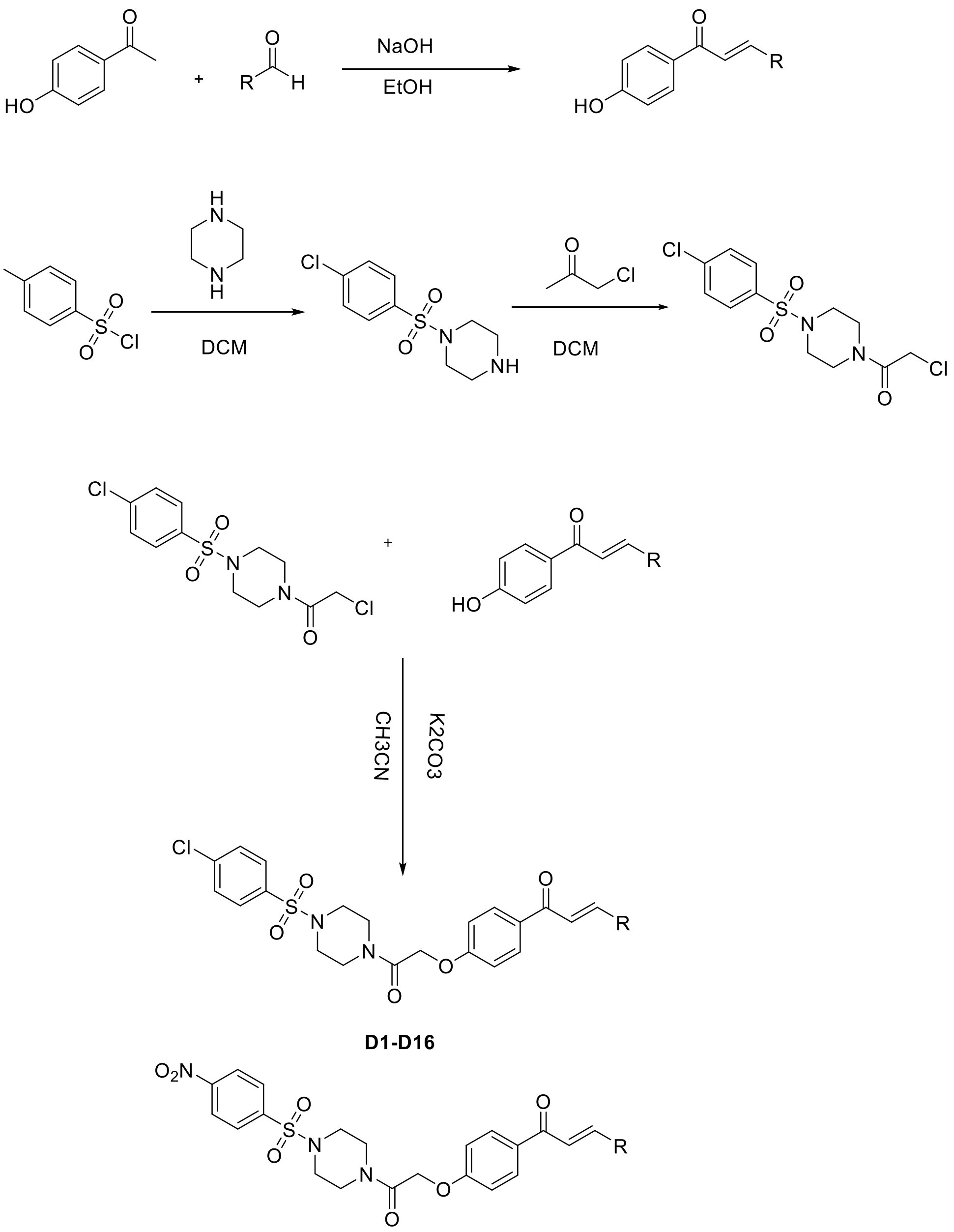
Novel 2-arylidene-3, 4-dihydronaphthalen-1(2H)-one derivatives (Figure 13) of chalcones were generated by Gupta et al., and their antifungal properties were investigated against C. albicans, A. niger. and M. gypseum. Chlorinated compound exhibited remarkable antifungal activity against M. gypseum with better inhibitor activity than ketoconazole. The brominated derivative of the significant chalcone showed average activity in comparison to the chlorinated one.[52]



X=F, Cl, Br

Figure 13. Novel 2-arylidene-3, 4-dihydronaphthalen-1(2H)-one derivatives

Antifungal activity of twenty chalcone derivatives (Figure 14) was obtained by Zhou and his team, investigated against several fungal species at 100 mg/ L using the mycelial growth rate method. The results were compared to the agricultural fungicide azoxystrobin. Fusarium oxysporum f. sp. cucumerinum, Colletotrichum capsici, Botrytis cinerea, Phytophthora parasitica, Fusarium moniliforme, R. solani, Alternaria brassicae, Colletotrichum gloeosporioides, Peronophythora litchii, and Fusarium graminearum were chosen as target yeasts. [53]



D1-D16

D17-D20

Figure 14. Synthesis procedure of 20 antifungal chalcone derivatives

According to the general results, the D2 compound has very high inhibition percentages against the most molds, especially R. solani and A brassicae. EC50 values for this chalcone derivative change between 0.3 and 38.5 mg/L, which corresponds to the best antifungal activity against the given species among 20 compounds. Additionally, D16 compound exhibited an overall strong impact against fungal pathogens. The inhibition percentage of D20 compound against R. solani was evaluated as 73.8, and against A. brassicae was 30.4.

CONCLUSION

The chemically facile synthesis and modification of chalcones is very convenient for the development of drug candidates with diverse functionalities. This review summarizes the synthesis and biological activity of halogen-bearing chalcone derivatives. The review shows the effect of the addition of halogen atoms, especially chlorine and bromine, to the chalcone molecule, as well as the location of the halogen atom in the molecule on the structure-activity relationship, as well as the role of these properties in biological activity and their effectiveness compared to existing drugs. The listed data will make a significant contribution to the synthesis of new chalcone derivatives and the study of their biological properties.

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