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Recent Mechanistic Biological Insights in Chalcone Scaffold: A Masterpiece for Medicinal Chemistry

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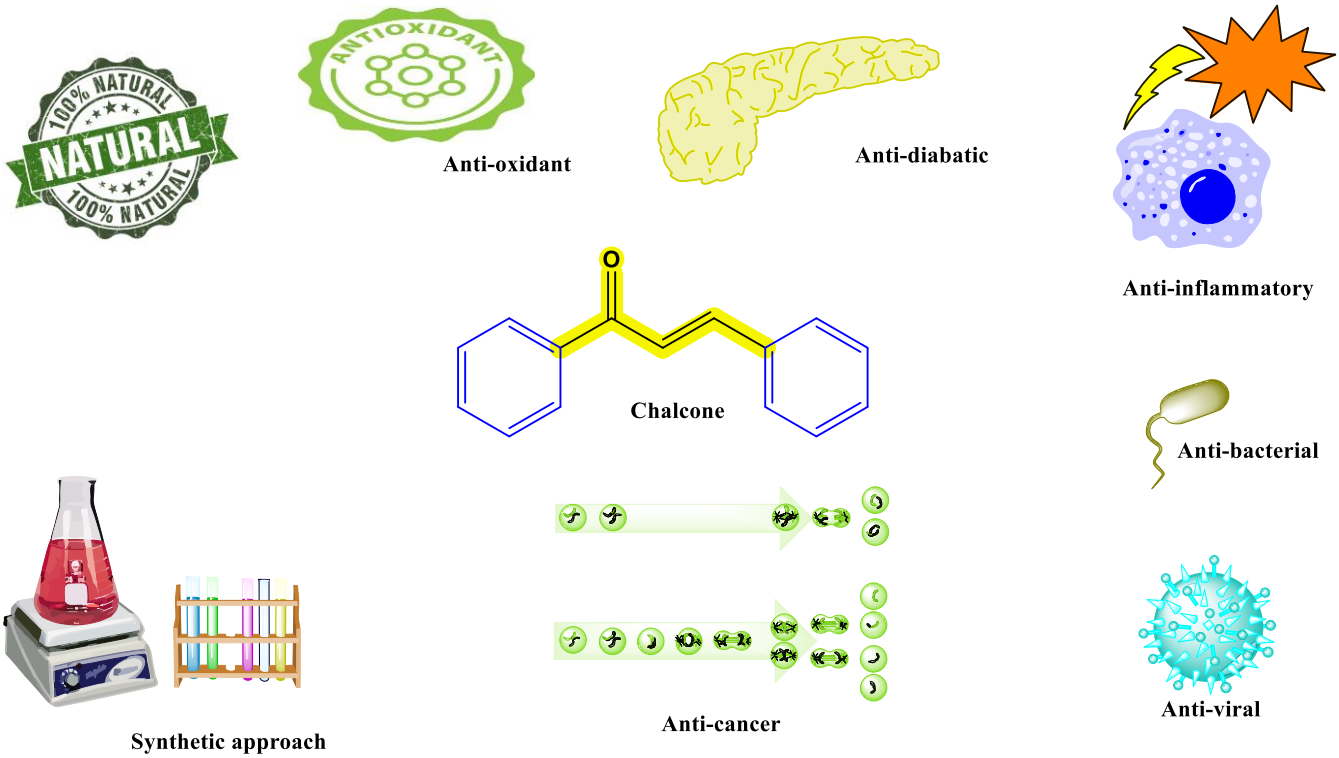
Abstract

In medicinal chemistry, privileged structures are frequently used as an effective template for finding new drugs. Chalcone is a typical simple compound that occurs in a wide variety of naturally occurring compounds. Chalcone derivatives are also prepared in large quantities due to their simple synthesis. These natural substances have demonstrated a wide range of intriguing biological behaviors with therapeutic potential for treating several diseases. The primary goal of this review is to provide comprehensive information on chalcone-based hybrids. Previous papers have reviewed their multitarget as well as broad-spectrum biological activities. However, some of these molecular targets are not supported by enough solid evidence. So, the most recent reports on the chalcone mechanisms of action were collected and discussed here.

Keywords

Chalcone; Biological activity; Anti-inflammatory; Anti-bacterial; Anti-fungal; Anti-cancer; EGFR kinase.



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1. Introduction

Chalcone is an aromatic ketone that serves as the central core of several important biological compounds. Chalcones are precursors of the abundant flavonoids and isoflavonoids found in plants [1]. Chalcones are a structurally diverse group of flavonoids that easily cyclize to form flavonoid structures, which is an isomeric key step in the skeletal variation of chalcones. Due to the open-chain framework as well as the feature of skeletal alteration to create a new category of organic molecules such as azachalcones, meicinal chemists have been drawn to the chemistry of chalcones [2]. Various therapeutic effects are displayed by chalcone derivatives (**Fig. 1**) such as antioxidants [3], antihypertensive [1], anti-inflammatory [4], antimalarial [5], antiviral [6], anti-bacterial [7] and anticancer [8] activities. Chalcone has both trans (E) and cis (Z) isomers according to stereochemistry, but the Z conformer is more unstable because of the steric effects of ring A with a carbonyl group **fig 2**. The electrophilic, α,β-unsaturated carbonyl system and two aromatic rings are continuously conjugated in chalcones. Their low redox potential, reactivity, electron transfer reactions, and more importantly, their promising biological activities, may all be due to continuous conjugation in chalcone skeleton. Chalcones are an interesting class of substances with meaningful therapeutic potential for treating a number of diseases.

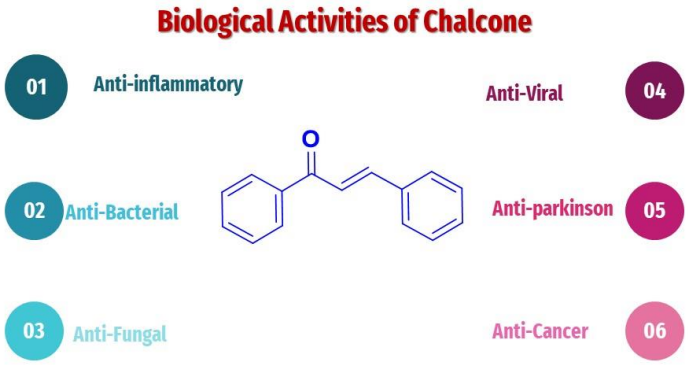


Fig.1 General biological activities of Chalcone.

2. Chemistry of chalcone

Chalcone is known by its commonly accepted consistent IUPAC name, 1,3-diphenyl-2-propen-1-one, which is also known as phenyl styryl ketone [9]. The numbering of positions between the flavonoid structure and the chalcone nucleus differs significantly. The aryl rings are known as rings A and B in chalcone, with ring A being labelled with primed numbers but ring B being designated with non-primed numbers as shown in **Fig. 2**. However, they can also arise as dihydrochalcones, dimers (bichalcones), and glycosides. In general, naturally present chalcones are common with substitutions like hydroxyl, methyl, and phenyl groups. Additionally, **Fig. 2** shows the numbering scheme used to distinguish the positions of the fused ring phenyl substituents, such as the furano and pyrano groups. Chalcones have drawn a lot of attention from researchers for decades because they are the foundation of numerous biologically intriguing compounds. Bichalcones have two chalcone molecules in a single structure, including rhuschalcone from *Rhus pyroides* [10]. Dihydrochalcones are a category of compounds with a reduced α,β-unsaturated double bond, such as the fleminchalcones from *Flemingia philippinensis* [11]. Although chalcone mimics have a similar α,β-unsaturated ketone system or fused configurations derived from chalcones by specific biosynthesis pathways, they (such as piperlongumines) are not structurally related to traditional chalcones [12]. It might not be possible to count all the natural chalcones. **Table 1** lists representative classical chalcones, bichalcones, dihydrochalcones, chalcone mimics, and fused chalcones that have been isolated recently from natural sources along with their potential biological activities. Variations of group substitution and a simple synthesis for the design of new drugs, chalcones are frequently used as templates in medicinal chemistry. Chalcones were typically synthesized through condensation reactions with the aid of acid or base catalysis**.** The Claisen-Schmidt reaction is the organic chemistry reaction that people are most familiar with. Acetophenones and aldehydes undergo condensation in the existence of acid or base catalysts in polar solvents at 50-70 °C for several hours in this reaction to create chalcone derivatives [13]. Chalcone from an aldol product through the dehydration of an enolate mechanism is produced in the presence of a base, whereas an acid catalyzed reaction produces the product from an enol mechanism. NaOH, KOH, and NaH are the common base reagents utilized for this condensation. moreover, grinding method is another green friendly method for chalcone synthesis [14]. The grinding process is very straightforward, safe for the environment, solvent-free, and important for its rapid reaction times and quantitative yields. Using a pestle and an open mortar, different chalcones were made by grinding up a mixture of the appropriate methyl ketones, aldehydes, and sodium hydroxide. The technique of microwave irradiation is now widely used in organic synthesis. Because it reduces reaction time, byproducts, solvent evaporation, and high yields. So, this method has more benefits than other conventional methods in synthesis of chalcones [15]. The process of creating new chemical entities through the fusion of two different chemotypes is known as molecular hybridization. This is a substitute to combination chemotherapy, which involves combining two or more medications with distinct modes of action [16]. A high risk of drug interactions exists with simple combination chemotherapy [17]. Chalcones are understood to be a special scaffold that allows for the incorporation of various compounds or pharmacophores with a variety of activities. Hybrid molecules are chosen for other purposes besides the biological activities for multitargeting mechanisms, such as enhancing solubility and oral bioavailability.

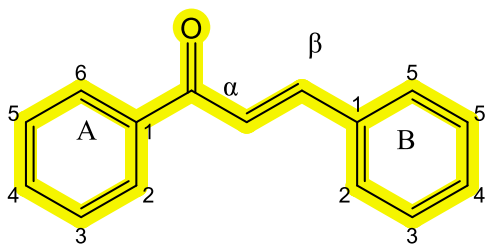
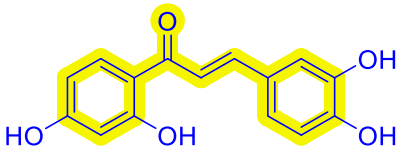
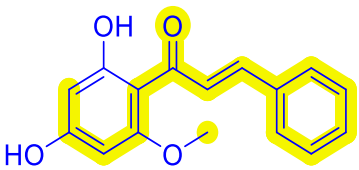
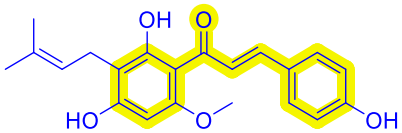
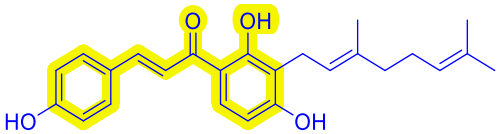
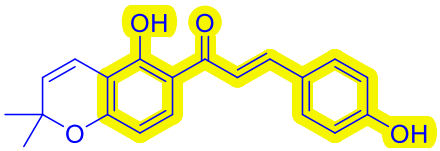
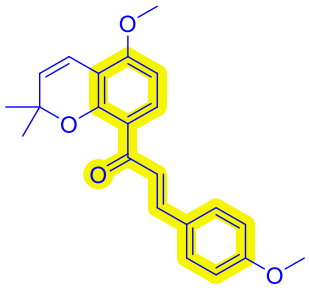


Fig.2 General structure& numbering system of Chalcone.

Table 1 Selected natural chalcone occurring molecules and their biological activities.

No.	Name	Chemical structure	Biological activity	Ref
1	**Butein**		Anti-Cancer	[65]
2	**Cardamonin**		Anti-Cancer	[66]
3	**Xanthohumol**		Anti-HIV	[67]
4	**Xanthoangelol**		Anti-Cancer	[68]
5	**Isobavachromene**		Anti-diabetic	[69]
6	**Millepachine**		Antineoplastic	[70]

3. Biological aspects of chalcone

Due to their small configurations and Michael acceptor characteristics, which make them reactive to various biological molecules and enable them to bind with them rapidly, chalcones exhibit a wide range of biological activities. The biological effects of chalcones include neuroprotective effects, anti-inflammatory effects, anti-bacterial effects, anti-tuberculosis effects, antidiabetic effects, antioxidant effects, antimicrobial effects, antiviral effects, and antimalarial effects [18-27]. The mechanisms of action of these chalcone molecules have been the subject of tremendous effort. Previous papers have reviewed their multitarget as well as broad-spectrum biological activities. However, some of these molecular targets are not supported by enough solid evidence. So, the most recent reports on the chalcone mechanisms of action were collected and discussed here.

3.1. Characteristics of chalcone derivatives that have anti-inflammatory activity

It is still crucial to create new substances that have an improved safety profile and anti-inflammatory-analgesic activity. Long-term NSAID use has been linked to renal and gastric adverse drug reactions (ADRs), which are caused by NSAID ability to inhibit the cyclooxygenase 1 (COX-1) enzyme. Several chalcone derivatives have been found to have therapeutic potential as NSAIDS, according to the literature [28, 29]. In addition to these drugs, Asmaa H.H. Ahmed et al. designed & synthesized novel chalcone / pyrazole hybrids **(1-3) fig.3** and tested them for anti-inflammatory activity [30]. Hybrid **1** showed strong inhibitory activity against COX-2 (IC_{50} = 5.13 µM) and COX-1 (IC_{50} = 33.46 µM and SI = 6.49) compared to celecoxib (IC_{50} = 0.204 µM and SI = 175.49). It revealed mild selectivity against COX-2 over COX-1. In comparison to celecoxib, compound **1** had low or negligible cardiovascular toxicity. Interestingly, hybrid **1** was

the most effective inhibitor of NO release that may be likened to its capacity to prevent and suppress the mRNA upregulation of iNOS. Also, compound **1** demonstrated promising inhibition activity against 5-LOX.

A.M. Hayallah et al. designed and synthesized novel 2′-hydroxychalcone-triazole hybrids (**4-6**) **fig.4** as potent anti-inflammatory agents. With an IC_{50} value of 0.037 µM and a selectivity index of 359.46, molecule **4** demonstrated the highest inhibitory activity against COX-2 in terms of anti-inflammatory activity compared to celecoxib (IC_{50} = 0.052 µM) [31].

3.2. Anti-Viral activity of chalcone derivatives.

One of the coronavirus families that appeared by the end of 2019 is SARS-CoV-2. It spread around the world and infected the respiratory system. G.E.D.A. Abuo-Rahma et al. synthesized a novel series of Ciprofloxacin- chalcone hybrid **7** (**fig. 5)** and screened their potential inhibitory activity against SARS- CoV-2 protease [32]. With an EC_{50} of 3.93 nmol/L, the novel chalcone significantly reduced viral load replication. The virus capacity to form plaques was inhibited to 86.8%. The necessity of including a substitution in the parent drug was demonstrated by the docking study into the SARS- CoV-2 M pro active site. ciprofloxacin antiviral activity was improved by a substitution at the C-7 position (hybrid **7),** it had several significant interactions within the active site; the carbonyl oxygen in the amide spacer formed two hydrogen bonds with Gly143 and Cys145. The evaluation of the drug-likeness characteristics also suggested that the chalcone might have acceptable ADMET properties.

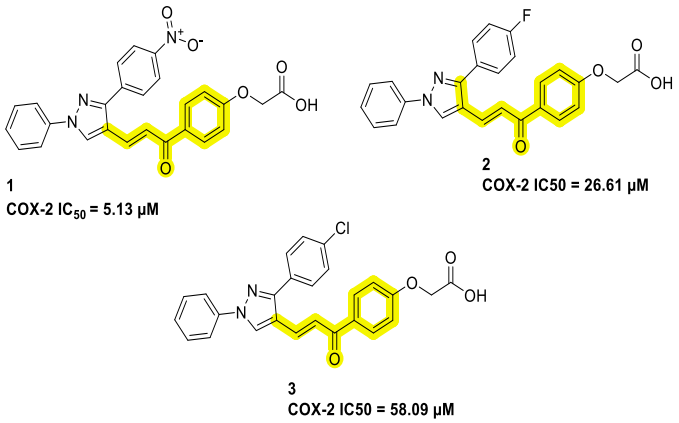


Fig.3 Selected structures of novel chalcone / pyrazole hybrids with anti-inflammatory activity.

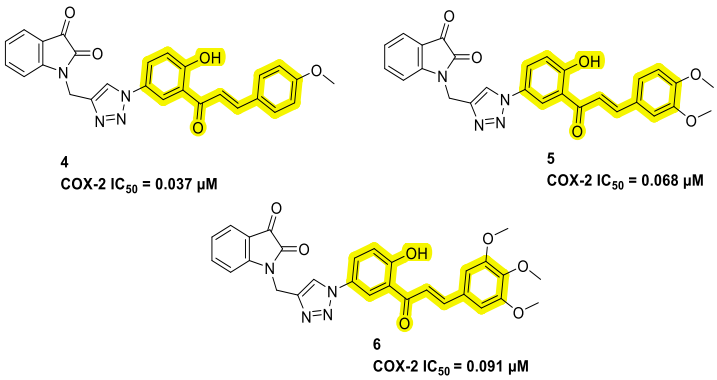


Fig.4 Novel 2′-hydroxychalcone-triazole hybrids as anti-inflammatory activity.

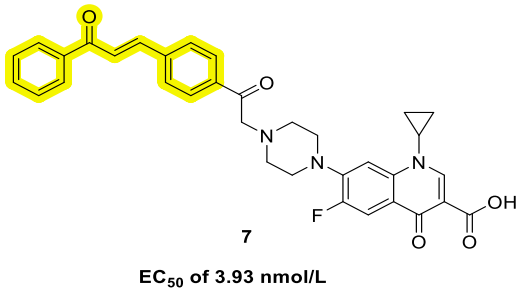


Fig.5 Novel Ciprofloxacin- chalcone hybrid as anti-viral activity.

3.3. Antifungal activity of chalcone derivatives

Due to an increase in immunodeficient patients, organ transplantation, tracheal intubation, and endoscopic techniques, invasive fungal infections have recently increased dramatically [33]. Additionally, a major factor in this rise has been the widespread use of corticosteroids, immune suppressants, and broad-spectrum antibiotics. The escalating rate of drug resistance has lagged behind the clinical discovery of novel antifungal agents [34]. As a consequence, efforts are being made to use drug combinations to prevent the growth of fungi that develop drug resistance. Antifungal drug combinations were nevertheless restricted because of their high costs and negative health effects [35]. Antifungal agents like azoles can be kept on the market for longer by altering the structure of antimicrobial drugs that have encountered microbial resistance. Regarding the structural modification of parent compounds, it has been acknowledged that researchers are approaching the finish line with the current investments in chemotherapeutics. As a result, it is necessary to introduce new candidates with unique chemical properties from those already available in the market. The most prevalent yeast that may result in invasive fungal infections is Candida species, especially Candida albicans [36]. However, it has also been demonstrated that fluconazole increases infections caused by Candida glabrata, C. tropicalis, and C. parapsilosis. Fluconazole has been shown to decrease the incidence of candidaemia and reduce infections caused by Candida albicans. In particular, Candida parapsilosis accounted for 21.9% of the cases [37]. A series of difluoro phenyl pyrazole chalcone derivatives (**8, Fig. 6**) were reported by S. Y. Jadhavn et al. against several human pathogenic fungi, showing promising antifungal activity at MIC of 25 g/mL against *T. harzianum* [38].

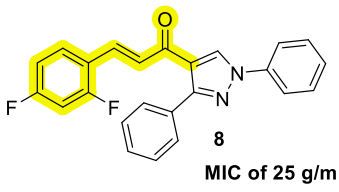


Fig.6 Novel difluoro phenyl pyrazole chalcone hybrid as anti-fungal activity.

3.4. Antibacterial properties of chalcone derivatives

Current research efforts in medicinal chemistry synthesis laboratories are concentrated on designing novel compounds with antibacterial activity. The World Health Organization (WHO) has warned that unless new medicines are developed

pressingly, resistant infections pose a serious threat to human health. Antibiotic resistance is increasing exponentially worldwide [39]. The Infectious Diseases Society of America was able to advance antibiotic research with the goal of developing ten new systemic antibiotics by 2020 [40]. Muhamad Mustafa et al. synthesized novel bioactive compounds in 2020 that depend on the hybrid of chalcone and azidosulfonamide (**9 Fig. 7**) to inhibit the growth of K. pneumonia [41]. The prepared compound may exert its activity by inhibiting the microbial DHPS enzyme, according to an in silico molecular docking analysis that showed the synthesised azidosulfonamide-chalcone successfully occupied the protein-binding site of the dihydropteroate synthase (DHPS). These findings offered crucial data for the potential development of antimicrobial compounds with greater potency.

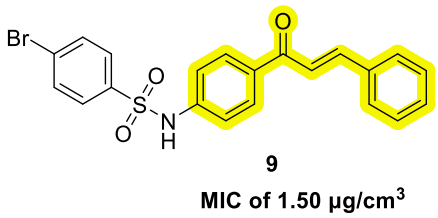


Fig.7 Novel chalcone azidosulfonamide hybrid as anti-bacterial activity.

3.5. Chalcone hybrids as potential therapeutic agent for Parkinson disease.

In Western Europe, there are 160 cases of Parkinson's disease (PD) for every 100,000 people, which affects 4% of people over the age of 80. Neurologists and practitioners will have a more difficult time managing Parkinson's disease as the population ages [42]. In the past decade, we have made progress in our understanding of the pathogenesis of Parkinson's disease thanks to the discovery of several gene mutations that have the potential to be contagious [43]. Levodopa plus a peripheral decarboxylase inhibitor were the standard of care for Parkinson's disease treatment for the past 40 years. In many ways, Levodopa plus a peripheral decarboxylase inhibitor still are the best combination treatment [44]. Levodopa is transported through the duodenum and proximal jejunum by the large neutral amino acid (LNAA) transport system. Levodopa is rapidly converted to dopamine in the GI tract by the enzyme L-amino acid decarboxylase (AADC), with only about 30% of a levodopa dose attempting to reach the systemic circulation [45]. The central and peripheral nervous systems contain monoamine oxidase (MAO), which hydrolyzes bioactive amines and is essential for the inactivation of neurotransmitters [46]. Inhibitors of the MAO-A and MAO-B isoenzymes, which have been identified, were used to cure neuropsychiatric and neurodegenerative disorders [47]. MAO-A inhibitors are also used to treat psychiatric conditions like depression because MAO-A is a protein that breaks down serotonin and noradrenaline in the central nervous system (CNS). Since MAO-B is a crucial enzyme in the central nervous system metabolism of dopamine and β-phenylethylamine, MAO-B inhibitors are used to cure neurodegenerative diseases, particularly Parkinson's disease [48, 49]. An elevation in striatal dopaminergic activity caused by the inhibition of dopamine metabolism justifies the use of specific MAO-B inhibitors in Parkinson disease [50]. A more logical justification for the use of MAO-B inhibitors in Parkinson's disease patients is the fact that hydrogen peroxide is produced as a byproduct of MAO catalysis [51]. It has been hypothesized that hydrogen peroxide produced in the brain by MAO-B may significantly contribute to Parkinson's disease neurodegeneration because hydrogen peroxide can result in oxidative damage. MAO-B inhibitors have subsequently been marketed as potential neuroprotective medications [52]. Several chalcone derivatives (**10–12, Fig. 8)** were recently synthesized and tested as monoamine oxidase inhibitors by Eman A. M. Beshr et al. [53] in 2022. Compound **10** showed the greatest MAO-B inhibition with an IC_{50} value of 0.067 µM, followed by compound **11** (IC_{50} = 0.118 µM), with MAO-B/ MAO-A values of 93.88 and >338.98, respectively, when compared to pargyline (IC_{50} = 0.140 µM) as the reference compound.

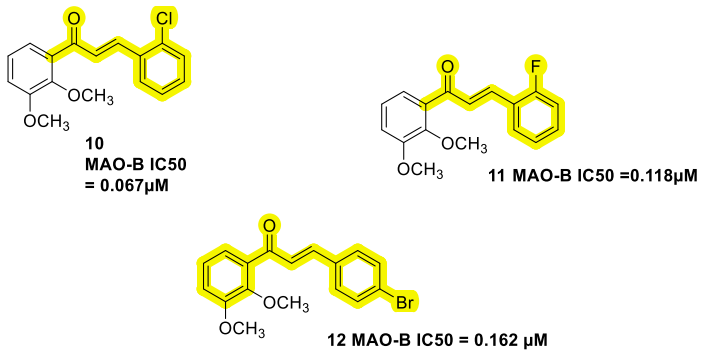


Fig.8 Novel chalcone hybrids against Parkinson.

3.6. Anticancer properties of chalcones

The WHO 2020 Global Cancer Statistics Report estimates that there will be 19.3 million new cases of cancer and 10 million deaths from cancer in 2020. New cancer therapies are therefore urgently required. Classical chemotherapy drugs cause DNA damage, which hastens the death of cancer cells1. They serve as the primary method of treatment for many cancers [54]. Contrarily, chemotherapy can damage normally dividing healthy cells, which may result in transitory side effects like nausea and hair loss [55]. Additionally, traditional chemotherapy may result in more mutations, which could result in the growth of additional cancers or the progression of treatment resistance in the initial tumor [56]. On the other hand, targeted therapies are created to block particular biochemical pathways in cancer cells that result in tumor cell death without harming DNA [57]. Enzymes called protein kinases catalyze the transfer of a phosphate group to a specific amino acid in a protein, altering the protein's functionality [58]. Tyrosine protein kinases, serine threonine protein kinases, and other common kinases are the most prevalent among the various subfamilies of protein kinases based on their substrate selectivity [59]. Protein kinases are significant cellular regulators that also regulate DNA damage repair, cell motility, apoptosis, and cell proliferation. Because they typically play a crucial role in signal transduction networks, protein kinases are significant targets for the investigation and development of novel anticancer agents [60]. Along with cell proliferation, apoptosis dysfunction, metastasis, and angiogenesis, the epidermal growth factor receptor (EGFR) has also been connected to tumor growth and progression [61]. As potential EGFR kinase inhibitors, Mohammed Abdel-Aziz et al. [62] published a set of new 1,3,4-oxadiazolechalcone/benzimidazole hybrids (**13-15, Fig. 9**) in 2022. The antiproliferative effects of the recently synthesized compounds were evaluated against a panel of four human cancer cell lines (A549, MCF7, Panc1, and HT29). When compared to doxorubicin, which has an IC_{50} range of 0.90 to 1.41 µM, compounds **13** to **15** showed promising antiproliferative

properties. Additionally, erlotinib was used as a reference drug to assess the inhibitory potency of these substances against the EGFR and BRAF kinases. Through molecular modelling studies, the modes of binding of the most effective hybrids to the EGFR ATP binding site were investigated.

Chalcone hybrids have drawn a lot of interest due to their strong proliferative activity. In order to create new antiproliferative candidates, Mohamed Hisham et al. [63] focused on the synthesis of a number of novel quinazoline-4-one/chalcone hybrids (**16–18, Fig. 10**). *In vitro* experiments examining the inhibitory effect on the epidermal growth factor receptor (EGFR) revealed that chalcone derivatives perform equally as reference drug erlotinib (IC_{50} = 0.05 µM). The IC_{50} values were 0.11 µM, 0.90 µM, and 0.56 µM, respectively.

In 2019, Hesham A.Abou-Zied et al. synthesized novel chalcone/ xanthine derivatives as hybrid molecules (**19-21, Fig. 11**). *In-vitro* studies of the inhibitory effect on the epidermal growth factor receptor (EGFR) revealed that chalcone hybrids were equipotent to reference drug staurosporine (IC_{50} = 0.4 µM). Hybrids **19**, **20**, and **21** had IC_{50} values of 0.5 µM, 0.3 µM, and 0.8 µM, respectively [64].

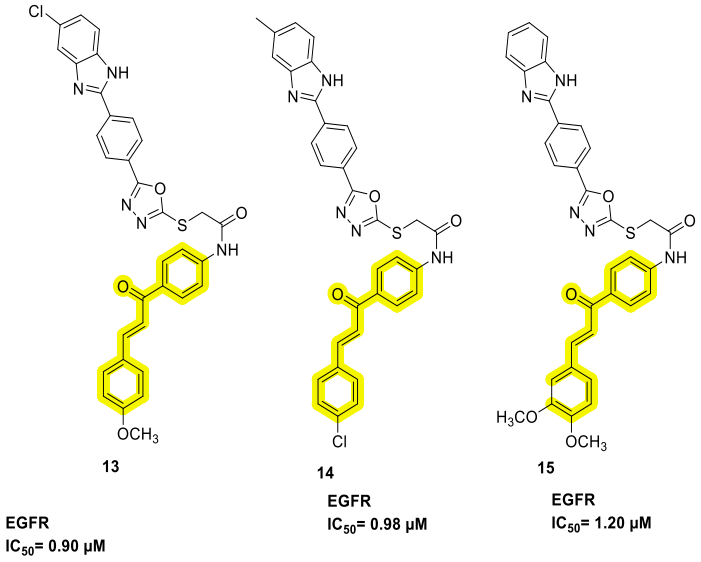


Fig.9 Novel 1,3,4-oxadiazolechalcone/benzimidazole hybrids as EGFR inhibitors.

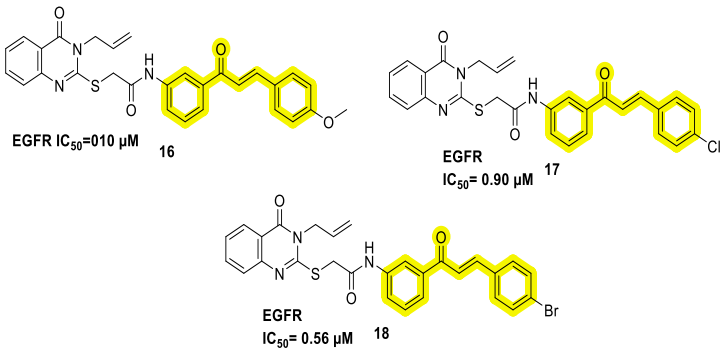


Fig.10 Novel quinazoline-4-one/chalcone hybrids as EGFR inhibitors.

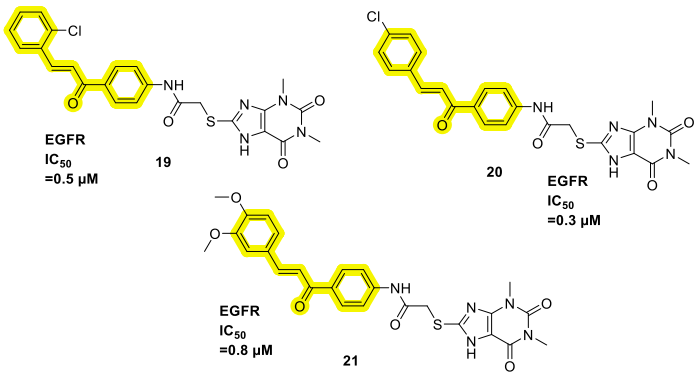


Fig.11 Novel chalcone- xanthine hybrids as EGFR inhibitors.

4. Conclusions

In medicinal chemistry, the effective strategy of using privileged structures for drug discovery has been widely adopted. By altering the central core structure and/or adding the side chains of the already-existing active compounds, they can quickly produce structurally novel chemotypes. Also, currently defined well-established synthetic protocols enable rapid expansion of the number of derivatives for biological uses. Finally, privileged structures are the cornerstone molecular frameworks, providing useful ligands for multiple targets through logical structural optimization. Chalcone is a common constituent of many naturally occurring substances, particularly those derived from plants. Chalcone derivatives have also been prepared in large quantities due to their simple synthesis. Because chalcone derivatives have demonstrated a variety of intriguing bioactivity with clinical activity against different diseases, chalcone is regarded as a privileged structure of considerable practical interest. In this review, we outlined the developments in chalcone hybrids over the previous five years as potential anti-inflammatory, anti-fungal, anti-bacterial, anti-Parkinson, and anticancer agents. In addition, we covered in this review, the mechanisms of action to lay out the course for developing and manufacturing novel chalcone hybrids with high efficacy and low toxicity.

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