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Review Article

Exploring The Therapeutic Potential of Chalcone Derivatives: A Review of Biological Activities

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A B S T R A C T

This article provides an overview of chalcones, focusing on their role in drug discovery. Chalcones are naturally occurring compounds with a β-unsaturated carbonyl aromatic ketone structure, commonly found in plants as precursors to flavonoids and isoflavones. The review emphasizes the potential of chalcone analogues in drug design, highlighting how structural modifications can enhance pharmacological activity and reduce toxicity. It categorizes the biological activities of chalcone derivatives, such as antidiabetic, antibacterial, anti-inflammatory, and neuroleptic effects. The article also explores the structure-activity relationship (SAR) and the mechanisms behind these effects, aiming to guide future research for developing safer and more effective drugs. Overall, chalcones are presented as versatile scaffolds for designing new therapeutic agents.

Keywords: Chalcone, Drug discovery, Drug design, Chalcone analogues, SAR

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INTRODUCTION

DOCKING

Molecular docking is a computational method used to predict the optimal orientation of a ligand when it binds to a target protein, forming a stable complex. This technique is widely used in structure-based drug design, as it helps determine how small molecules, such as potential drug candidates, interact with their target proteins. Understanding these interactions is crucial for assessing the strength and stability of the binding, which directly impacts drug effectiveness.

Key aspects of molecular docking include:

1. Binding Orientation: The method predicts the most favorable position of the ligand relative to the protein's binding site. The correct orientation is essential for successful interactions, influencing the biological activity of the ligand.
2. Energy Minimization: The goal of docking is to minimize the overall free energy of the system, achieving a stable configuration where both the ligand and protein are optimally aligned. This typically involves refining the structures of both components to reach an energetically favourable state.

Two Main Approaches:

- Surface Matching: This method treats the ligand and protein as complementary surfaces and attempts to fit them together, much like pieces of a puzzle. It's primarily used for predicting docking poses based on shape compatibility.
- Interaction Energy Calculations: This approach calculates the energy of various ligand-protein configurations, helping to identify the most energetically favorable binding mode based on their interactions.

Applications: Docking is widely used for:

- Estimating binding affinity: By evaluating the energy associated with different docking poses, researchers can predict how strongly a ligand will bind to the protein.

- Drug discovery: It assists in identifying potential drug candidates by screening compounds for their ability to bind to target proteins.
- Understanding biochemical interactions: Docking is valuable for studying enzyme mechanisms, protein functions, and other molecular processes.

In summary, molecular docking is a vital tool in drug development and molecular biology, enabling the prediction of protein-ligand interactions and guiding the design of effective therapeutic molecules.[1,2]

CHALCONE

Chalcones are flavonoid-type phenolic phytochemicals, biosynthesized via the shikimate pathway. They are α,β-unsaturated ketones with aromatic rings linked through a three-carbon alkenone unit. They have phenolic hydroxyl functionalities and prenyl and geranyl substitutions. There are thousands of naturally occurring chalcones, many of which have antidiabetic, anticancer, anti inflammatory, antibacterial effects, making them potential therapeutic interventions.[3]

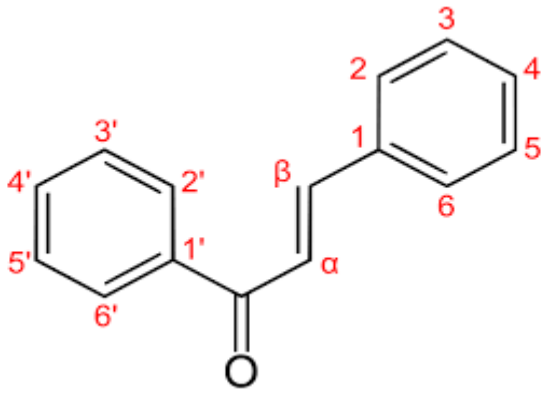


Figure: 1 Chalcone

Table: 1 Physical properties of Chalcone

IUPAC Name	Trans-1,3-diaryl-2-propen-1-one
Molecular formula	$C_{15}H_{12}O$
Molar mass	208.26 g mol^{-1}
Exact mass	208.088815
Density	1.071g/mol^{3}

Chemistry of Chalcone

Chalcone (1,3-diphenylprop-2-en-1-one) is a medicinally preferred scaffold in which a three-carbon α, β-unsaturated carbonyl bridge connects the two aromatic nuclei. Important ligands are chalcones and flavanones because they undergo isomeric interconversion when exposed to acid or base. The molecule's carbonyl oxygen and/or other heteroatom(s) serve as electron donors to help the metal ion form a complex. A wide range of biological activities have been described for numerous natural and (semi-)synthetic chalcones in the literature. Clinical usage of certain chalcone-based medications has also been authorized.[3,4]

Synthesis of Chalcone

Chalcones are synthesized by Claisen–Schmidt condensation, which involves cross aldol condensation of appropriate aldehydes and ketones by base catalysed or acid catalysed reactions followed by dehydration.[4]

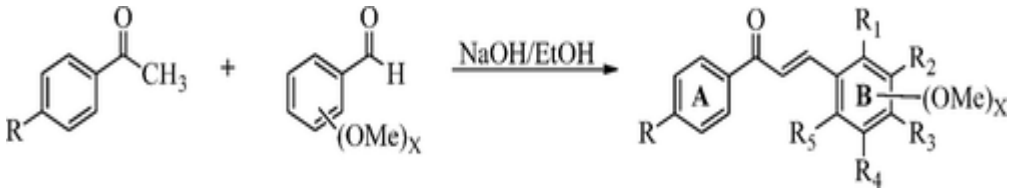


Figure: 2 Synthesis of Chalcone

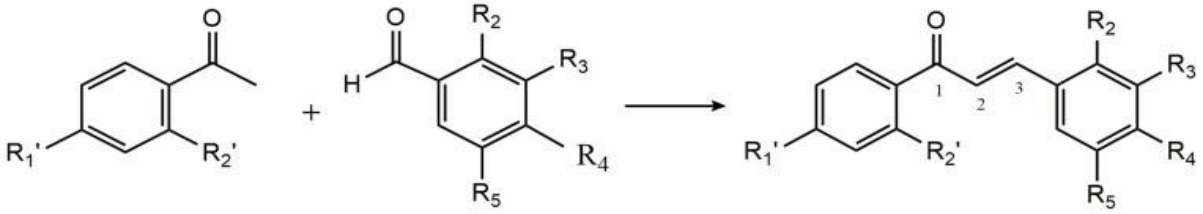
PHARMACOLOGICAL ACTIVITIES

Anti-diabetic activity

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia due to defects in insulin secretion and action. The global prevalence of diabetes has increased over the past three decades, necessitating the development of new interventions. Chalcones, secondary metabolites of plants, have been used in traditional medicine due to their anti-diabetic properties. These compounds act on various therapeutic targets, including DPP-4, GLUT4, SGLT2, and PTP1B. Chalcones have significant structural features, with hydroxyl, prenyl, and geranyl groups enhancing their activity.[5]

Synthesis of Chalcones

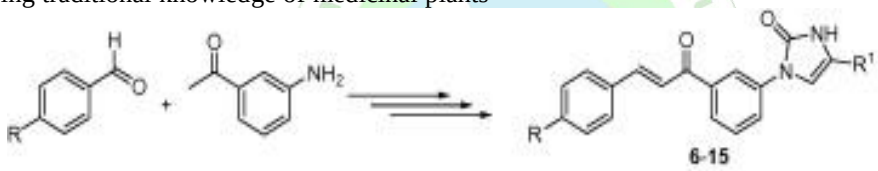
The synthesis of all the chalcone derivatives was achieved using Claisen–Schmidt condensation reaction (Scheme 1).For each reaction, equimolar quantities of benzaldehyde derivatives (13 mmol) and acetophenone derivatives (13 mmol) were dissolved in 65 mL absolute ethanol in a 250 mL round-bottom flask equipped with a magnetic stirrer. Then, 60% aq. NaOH (40 mL) was added dropwise and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC every 2 h using n-hexane: ethyl acetate (3:1) as mobile phase. After completion of the reaction, the mixture was neutralized with 2M HCl and then allowed to cool in an ice bath, whereby a yellow precipitate was formed. The reaction mixture was filtered using a vacuum system, and the resulting solid was then washed with cold water, dried and eluted over silica gel packed column chromatography using the same solvent system to get the target chalcone derivative.



Scheme 1 Reagents and conditions: 60% aq. NaOH, Ethanol

Anti-cancer activity

Cancer, a complex disease, is a major global health concern. Various treatments, including surgery, chemotherapy, and radiotherapy, are used to combat it. However, multidrug resistance and side effects pose challenges. Phytochemicals like chalcones, which are inexpensive, readily available, and nontoxic, can target key cancer-inducing molecular reactions. Scientists are using traditional knowledge of medicinal plants and marine natural products to create new, powerful antitumor drugs. Chalcone compounds have a chemical scaffold that can be modified to alter their biological activities. Hybridization with other anticancer pharmacophores can overcome drug resistance and improve therapeutic specificity. This review focuses on the medicinal chemistry strategies used for the design and development of anticancer chalcones.[6,7]

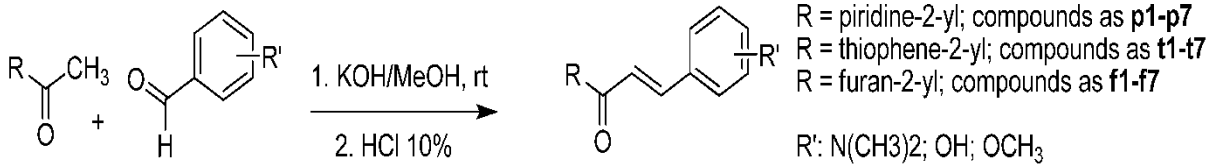


6-15

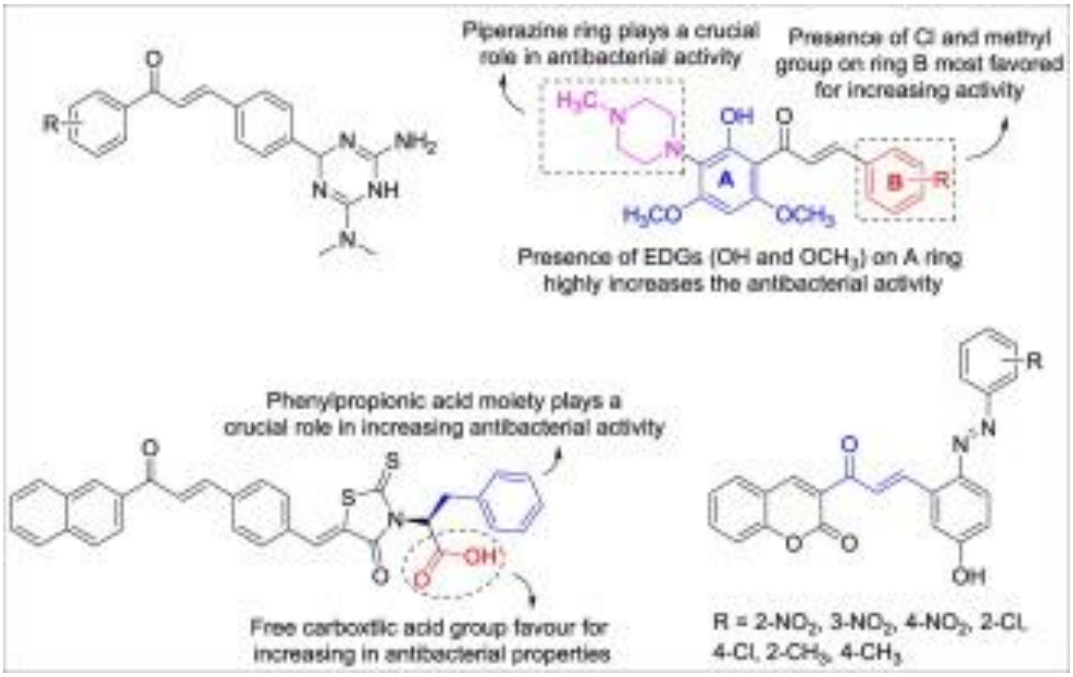
6: R = 4-OH-3-OMe; R^1 = Phenyl
7: R = 4-OH-3-OMe; R^1 = 4 -methoxy phenyl
8: R = 4-OH-3-OMe; R^1 = 4 -chloro phenyl
9: R = 3-OH; R^1 = phenyl
10: R = 3-OH; R^1 = 4 -chloro phenyl
11: R = 3,4,5-(MeO)3; R^1 = phenyl
12: R = 3,4,5-(MeO)3; R^1 = 4 -methoxy phenyl
13: R = 3,4,5-(MeO)3; R^1 = 3,4,5 -trimethoxy phenyl
14: R = 3,4,5-(MeO)3; R^1 = 4 chloro phenyl
15: R = 3-OH; R^1 = naphthyl

Anti-microbial activity

Antibiotic resistance is causing a surge in the search for new antibacterial agents. Chalcone-based compounds offer diverse pharmacological properties and structural diversity, making them valuable for drug discovery. The need for new antibacterial agents with increased strength, new targets, low cost, superior pharmacokinetic properties, and minimal side effects is urgent. Recent developments in medicinal chemistry explore these compounds' structure-activity relationships.[8]

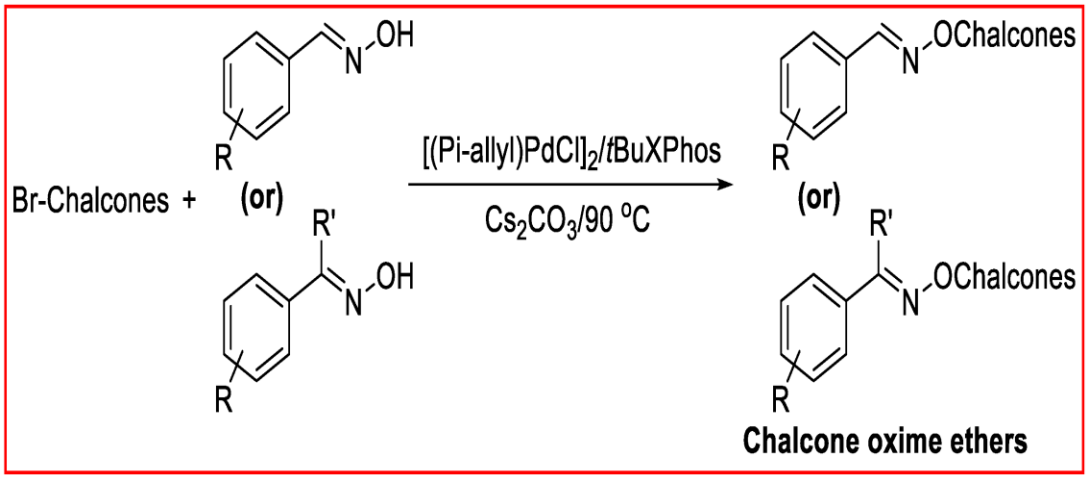


Reagents and Conditions: KOH (1.5 eq.), heteroaryl methyl ketone (1 eq.), substituted benzaldehydes (1 eq.); MeOH, room temperature; dilute HCl.



Neuroleptic activity

Alzheimer's disease (AD) is a major medical concern affecting 100 million patients within 30 years. Researchers are increasingly focusing on multitarget-drugs to manage the disease, recognizing its multifactorial nature. Monoamine oxidase (MAO)-A is used for depression and anxiety, while MAO-B targets AD and Parkinson's disease. Ladostigil, a multi-functional drug, combines rasagiline and ChE inhibitory activity. Chalcones, versatile scaffolds found in edible plants, have potent MAO-B inhibitory effects, with ethoxy and ethylacetohydroxamate functionalities conferring significant inhibitory effects.



Scheme 1. Pd-catalyzed C–O cross-coupling reactions of bromo-chalcones with oximes.

Herein, we report the abilities of our previously synthesized chalcone ketoxime ethers to inhibit human MAOs (hMAOs) and AChE, kinetics, reversibility, and docking studies.[9]

Anti-inflammatory activity

Chalcone, a simple chemistry and easy-to-synthesize scaffold, has gained significant scientific interest in medicinal chemistry due to its potential to modulate molecular targets. Natural and synthetic chalcone derivatives have shown anti-inflammatory activity against various targets, including COX, LOX, IL, PGs, NOS, LTD4, NF-KB, ICAM-1, VCAM-1, MCP-1, and TLR4/MD-2. A comprehensive study from 1991 to 2016 aims to evaluate the antinociceptive and anti-inflammatory effects of different chalcone derivatives, which are commonly used to create selective COX-2 inhibitors. The study found that methylsulfonyl chalcone-derived compounds can be potent analgesic and anti-inflammatory if the proper substitutes bind with each phenyl ring at the para position. Further pharmacological and toxicological experiments could lead to novel drug development for managing pain and inflammation.

Effects of 8 chalcone-derived compounds on formalin induced paw edema in rat. Response represents the reduction of volume of inflamed paw; *p < 0.05, ** p < 0.01 significant difference compared with control group (n = 8); p-values: significance level for deviation of slope from zero; ND: Not determined due to no significant dose-response relationship.[10,11]

Compound	R1	R2	Dose (mg/kg)	Response (n) Mean ± SEM	Estimated ED50 Mean (95%Confidence Interval) p-value	p-value
Control			0	0.221 ± 0.018		
Celecoxib			10	0.218 ± 0.021	65.9 (29.2-148.5)	0.0078
			20	0.186 ± 0.027		
			40	0.088 ± 0.024 **		
			80	0.154 ± 0.019		
1	SO2Me	H	5	0.220 ± 0.015	26.2 (13.8-50.0)	0.0020
			10	0.148 ± 0.014 *		
			20	0.137 ± 0.015 *		
2	SO2Me	Me	5	0.170 ± 0.008	ND	0.0836
			10	0.156 ± 0.025		
			20	0.148 ± 0.014		
			40	0.128 ± 0.016 **		
3	SO2Me	F	10	0.204 ± 0.026	ND	0.1622
			20	0.210 ± 0.008		
			40	00.232 ± 0.052		
			100	0.246 ± 0.008		
4	SO2Me	Cl	20	0.254 ± 0.039	ND	0.5036
			40	0.218 ± 0.007		
			80	0.229 ± 0.023		
5	H	SO2Me	2.5	0.209 ± 0.013	40.4 (11.8-137.6)	0.0029
			5	0.164 ± 0.018		
			10	0.136 ± 0.010 *		
			20	0.144 ± 0.013 **		
6	Me	SO2Me	5	0.185 ± 0.021	ND	0.0840
			10	0.164 ± 0.019		
			20	0.175 ± 0.022		
			40	0.185 ± 0.026		
			80	0.112 ± 0.012 **		
7	F	SO2Me	2.5	0.216 ± 0.026	37.7 (6.9-204.4)	0.0339
			5	0.169 ± 0.032		
			10	0.164 ± 0.018		
			20	0.134 ± 0.024		
8	OMe	SO2Me	20	0.199 ± 0.028	ND	0.5036
			40	0.156 ± 0.026		
			80	0.133 ± 0.024		

CONCLUSION

Chalcones are a class of heterocyclic compounds displayed a wide range of biological activities. Therefore this nucleus was involved in the drug discovery and drug development processes.chalcone derivatives showed good biological activities such as Anti-diabetics, anti cancer, antibacterial, anti-inflammatory, neuroleptics etc. The present review is about the physical properties, synthesis of chalcone derivatives and focused on its biological outcomes.

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