Research Article

Design, Synthesis and Evaluation of Chalcones: An Isosteric Approach

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Received: 03-03-2025; **Revised:** 28-05-2025; **Accepted:** 05-06-2025; **Published online:** 15-06-2025.

ABSTRACT

This study explores the bioisosteric replacement of the ring system in chalcones to enhance their biological activity. The target chalcone derivatives were synthesized using the conventional Claisen-Schmidt reaction. The reaction yielded products in good amounts, confirming its efficiency. The synthesized chalcones were then evaluated for their potential activity using an in silico approach. PASS prediction software (Way2Dryg) was employed to predict the pharmacological properties of the chalcones. The in silico results provides valuable insights into the predicted biological activities of the chalcones. The study reveals that structural modification through bioisosteric replacement can significantly influence the biological activity of chalcones. These findings offer a promising approach for the development of bioactive chalcone derivatives. Overall, this study demonstrates the potential of bioisosteric modification in enhancing the bioactivity of chalcones.

Keywords: PASS prediction, Claisen-Schmidt reaction.

INTRODUCTION

Bioisosterism: The concept of bioisosterism, introduced by Langmuir in 1919, involves substituting atoms or groups in biologically active molecules with others that share similar physicochemical properties. This concept was later expanded by Grimm in 1925 through the Hydride Displacement Law, and in 1932, Erlenmeyer et al. broadened it to include elements, molecules, or ions with similar valence electrons[1]. Hinsberg applied isosterism to entire molecules, introducing "ring equivalents" in aromatic systems. In the 1950s, Friedman and Thornber coined the term bioisosteres, defining them as compounds that share structural similarities and exhibit biological activity[4]. Thornber expanded this in 1979 to include groups, subunits, or molecules with similar properties and biological effects.

Chalcones: Chalcones are flavonoid-related aromatic compounds, known for their α, β-unsaturated carbonyl group, which gives them unique chemical reactivity. Found in various plants, chalcones are considered secondary metabolites and contribute to the plant's defense mechanisms[2]. They are notable for their broad pharmacological activities, including antiproliferative, antibacterial, antiviral, antifungal, and antileishmanial effects. This makes them promising candidates for cancer therapies, infection treatments, and addressing neglected tropical diseases like leishmaniasis[3]. Chalcones also serve as precursors in the synthesis of biologically active heterocycles, expanding their potential for drug development[5]. Their diverse applications make chalcones an ongoing area of research in medicinal chemistry and drug design.

MATERIALS AND METHODS

Part i: General procedure for the synthesis of Chalcone

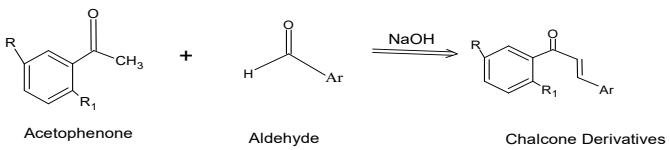
Step 1:

Required quantity of hydroxyl acetophenone [0.01 mole] was taken in dry mortar and required quantity of sodium hydroxide was added and triturated to form a smooth paste. Followed by addition of aromatic aldehyde [0.01 mole] in small quantities with continuous trituration, until the product is formed. The progress of the reaction was monitored by TLC using n-hexane in required ratios as solvent system.

Step 2:

The mixture was added to ice cold water. It is mixed well and the excess of sodium hydroxide was neutralized by adding sufficient quantity of dilute hydrochloric acid. The precipitate of chalcone was collected by filtration.

REACTION:



Acetophenone Aldehyde Chalcone Derivatives

R1= OH, R = CH_3 Ar = Benzene, Furan

Part ii: Purification

The impure synthesized compound is dissolved in absolute ethanol and boiled it. Activated charcoal is added and heating is continued until 70% of the solvent evaporates. The resulting solution is filtered off to remove insoluble

materials and kept it aside for 24 hrs. to induce crystallization.

Part iii: Characterization

1. TLC

Rf value of all the synthesized series of derivatives AB (1-4) is determined by using n-hexane and ethylacetate as solvent system in required ratios and TLC sheets (Merck 60F) and the Rf values obtained for each compound was shown below in table 1.

2. Melting Point

Melting point of the synthesized series of derivatives AB (1-4) were recorded by open capillary tube method and the values obtained for each compound was shown below in table.

3. FTIR Spectroscopy

IR spectra of all the synthesized series of compounds AB (1-4) were recorded using FTIR (84000s-shimadzu) and the spectrum obtained for each compound is attached with this followed by experimental data.

RESULT AND DISCUSSION

All the chalcones were evaluated for different activities by taking pass prediction score using Way-2-Drug software.

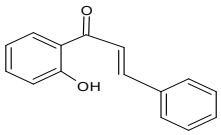
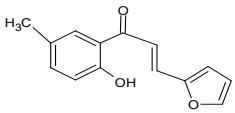
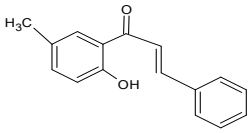
Pass Prediction

Pass prediction, or prediction of activity spectra for substances, is a web- based tool that estimates a chemical compound's biological activity.

- It uses a compounds structure to predict it's potential biological effects.
- PASS uses the structural formula of a substance as input.
- It predicts the likelihood of the substances belonging to the "Active" class (pa) and the "inactive" class (pi).
- It considers all activities with pa > pi to be probable.

All the chalcones were evaluated for different activities by taking pass prediction score using Way-2-Drug software.

Table 1: Rf values of compounds

SI.NO	Code	Structure	IUPAC Name	M.F	M.W	Melting Point	Rf Value
1.	A3		2-Hydroxy chalcone	$C_{15}H_{12}O_2$	224.29	98-100^{0}C	0.49
2.	B2		(2E)-3-(2-furyl)-1-(2hydroxy 5 methyl phenyl)-2-propene-1-one	$C_{14}H_{12}O_3$	228.247	96-100^{0}C	0.54
3.	B3		2-Hydroxy-5-methyl chalcone	$C_{16}H_{14}O_2$	238.286	96-100^{0}C	0.65

IR range of Test compound A3 was found to be C=O (1685.67), CH=CH (1604.37).

IR range of Test compound B2 was found to be C=O (1667.88), CH=CH (1653.54).

IR range of Test compound B3 was found to be C=O (1690.33), CH=CH (1653.49).

Table 2: Evaluation of different activties

Pa	Muco-Membranous protector	Anti-Inflammatory	Feruloyl esterase Inhibitor	Anti -infective	Anti-tubercular	Insulysin Inhibitor
A1	0,855	0,674	0,503	0,494	0,277	0,586
A2	0,714	0,583	0,634	0,736	0,736	0,864
A3	0,944	0,683	0,895	0,463	0,559	0,787
B1	0,847	0,688	0,712	0,494	0,289	0,548
B2	0,703	0,588	0,806	0,736	0,748	0,841
B3	0,940	0,717	0,937	0,463	0,572	0,771
C1	0,836	0,453	0,351	0,423	0,219	0,493
C2	0,515	0,413	0,362	0,358	0,239	0,433
C3	0,904	0,589	0,837	0,287	0,466	0,727

Mucomembraneous Protector Activity of series (A_1- A_3) the highest activity shown by A_3. In the second series (B_1-B_3) the highest activity shown by B_3. In the third (C_1-C_3) the highest activity shown by C_1. Among the A_3, B_3 and C_1 the higher most activity shown by A_3.

Anti-Inflammatory Protector Activity of series (A_1- A_3) the highest activity shown by A_3. In the second series (B_1-B_3) the highest activity shown by B_3. In the third (C_1-C_3) the highest activity shown by C_3. Among the A_3, B_3 and C_3 the higher most activity shown by B_3.

Feruloyl Esterase Inhibitor. Protector Activity of series (A_1-A_3) the highest activity shown by A_3. In the second series (B_1-B_3) the highest activity shown by B_3. In the third (C_1-C_3) the highest activity shown by C_3. . Among the A_3, B_3 and C_3 the higher most activity shown by B_3.

Anti-Infective Activity of series (A_1- A_3) the highest activity shown by A_2. In the second series (B_1-B_3) the highest activity shown by B_2. In the third (C_1-C_3) the highest activity shown by C_1. Among the A_2, B_2 and C_1 both (A_2, B_2) showing higher most activity.

Anti-Tubercular Activity of series (A_1- A_3) the highest activity shown by A_2. In the second series (B_1-B_3) the highest activity shown by B_2. In the third (C_1-C_3) the highest activity shown by C_3. Among the A_2, B_2 and C_3 the higher most activity shown by B_2.

Insulysin Inhibitor Activity of series (A_1- A_3) the highest activity shown by A_2. In the second series (B_1-B_3) the highest activity shown by B_2. In the third (C_1-C_3) the highest activity shown by C_3. Among the A_2, B_2 and C_3 the higher most activity shown by A_2.

Future Aspects:

This study can be used for,

- **Experimental Validation:** Further *in vitro* and *in vivo* studies are essential to validate the predicted biological activities of the synthesized chalcones.
- **Mechanistic Studies:** Investigating the underlying mechanisms of action of the modified chalcones to better understand their interactions at the molecular level.
- **Pharmacokinetics and Toxicology:** Detailed studies on ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles to assess the drug-likeness of the derivatives.
- **Broader Structural Exploration:** Exploring a wider variety of bioisosteric replacements to fine-tune biological activity and specificity.
- **Target-Specific Design:** Designing chalcone derivatives tailored to interact with specific molecular targets associated with diseases of interest.

CONCLUSION

In this study, a bioisosteric ring substitution was carried out to design structurally equivalent analogs. The test compounds were evaluated using a pass prediction model to predict their biological activity. Based on the prediction data, three compounds were selected for synthesis. Following synthesis, the structures were confirmed through characterization techniques. The confirmed compounds can be subjected to in vivo studies for further evaluation.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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