CINEFORUM
ISSN: 0009-7039
Vol. 65. No. 4, 2025

Solvent-Free Mechanochemical Synthesis, Characterization, and Enzyme Inhibitory Evaluation of Novel Chalcone Derivatives

Dr. Swati[1]
[1]Assistant Professor, Department of Chemistry, Baba Mastnath University,
Asthal Bohar 124021 Rohtak, Haryana
shswati2@gmail.com
Komal[2]
[2]Research Scholar, Department of Chemistry, Baba Mastnath University,
Asthal Bohar 124021 Rohtak, Haryana
dhingrakomal05@gnmail.com

Abstract

This type of compound with α,β-unsaturated ketone structure has an extensive structural diversity and broad bioactivity, and is an important class of compound in drug discovery, such as chalcones [2]. This study reports on the synthesis of eight new chalcone derivatives (NC-1 through NC-8), which were obtained via a solvent-free mechanochemical Claisen–Schmidt condensation method in keeping with principles of green chemistry. Under seal condition, the synthesis was performed via mechanical oxidation of acetophenones with various substituents and aromatic aldehydes in solid state with potassium hydroxide as base catalyst. It has removed the cumbersome factor of organic solvents, minimized the time for the reaction and provided the desired products in considerable yields.

The chalcone derivatives synthesized appeared as crystalline solids which isolated on workup and characterized on the basis of percentage yield, TLC behavior, and melting point determination for purity and structural integrity. As shown, the yields were moderate to high, illustrating the efficiency of the mechanochemical method. The effect of ABA and ABA derivatives via aromatic substitution on coupled physicochemical properties was revealed through changes in Rf values and melting points.

Chalcones were synthesized and evaluated their inhibitory activity against two enzymes, α-amylase and trypsin, by in-vitro enzymatic studies. All of the compounds were inhibitory to some measurable degree, and the differences were ascribed to electronic and steric effects of the substituents on the aromatic rings. That is to say that the presence of electron-withdrawing and halogen substituents in the chalcones generally produced stronger inhibition on the enzymes. These results demonstrate the potential of this pathway-mediated strategy to be employed for mechanochemically synthesized scaffolds to for enzyme inhibition and medicinal chemistry direction.

Keywords: Chalcones; Mechanochemical synthesis; Solvent-free method; Enzyme inhibition; Structure-activity relationship

INTRODUCTION

A tribute to Chalcone, structurally defined as 1,3-diphenyl-2-propen-1-one, which is an important kind of α,β-unsaturated ketones: because its chemical structure are relatively changeable. Chalcones attract the attention of the great researchers not only for their

characteristic structure but also, and even more so, their peculiarly extensive spectrum of biological efficacy. The percolation system of conjugated enone and benzene ring serves as a privileged pharmacophore, chalcones can engage in hydrogen bonding, π-π stacking, hydrophobic interactions and covalent Michael-type interactions with a rich variety of biological targets [1]. This is as shown by years of research into chalcone derivatives: they are have featured in dozens of experiments and gone head-to-head, often surpassing traditional drugs or natural products on quality and effectiveness. Even among those that failed to oust established medicines, however, there have undoubtedly been some noteworthy successes against all expectations [2-4].In recent years, increasing attention has been devoted to developing environmentally friendly and green strategies for synthesizing chalcones. Conventional solvent-based Claisen condensation reactions, although efficient, demand long working time and use a great deal of solvent, with environmental costs higher than other methods [5]. To address these problems, routes that minimize the amount of solvent employed or do not require any solvents at all-delivery grinding, microwave syntheses and melt techniqus have all been widely explored and proven to considerably reduce energy consumption and waste production compared with traditional techniques [6,7]. While the greensuitability of these methods conforms to present-day requirements for sustainability, they also place new limitation s on substrate reactivity and on the physiochemical properties of substances to be treated [8].

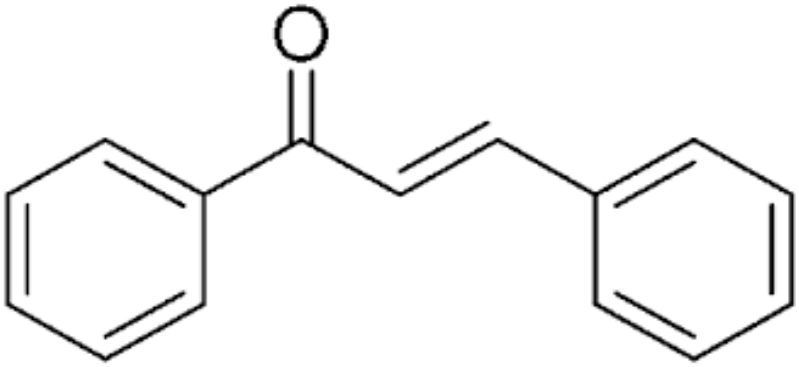

Figure 1: General chalcone structure

Incorporating halogen atoms into the structure of chalcone presents a very effective strategy for increasing its biological activity. The halogen atoms: chlorine, bromine, fluorine or iodine, not only change electronic distribution and increase lipophilicity but also can make halogen bonding with active sites in many enzymes possible [9, 10]. Recent researches have shown that network organizations containing halogen atoms behave in different manners than those without them, and in particular may inhibit enzymes more profoundly than their strength as free or unmodified molecules would suggest, spaning a chemical cock-and-bull story of achievement. Examination of these relationships has become an important field called a structure–activity relationship (SAR) study [23,24]. However, these substitutions of chalcone have some adverse effects on synthetic efficiency, notably for those reactions which take place in green and do not make use of solvents-stauration should be limited due to steric hindrance [8, 9].

Although there is an increasing body of evidence supporting the pharmacological significance chalcones, compounds with low isolated yields often fail to undergo detailed biological assays. This may lead to a publication bias due to low isolable yield, and it also means we are unable to develop an understanding of the structure and reactivity boundaries involved in green synthesis [13]. Recent studies underlined that low-yield chalcone derivatives nonetheless still possess significant biological and enzyme inhibitory activity--calling for comprehensive evaluation strategies that take into account both synthetic feasibility and biological relevance [1,14].

Using metabolic and proteolytic enzymes as the main research subjects for enzyme inhibition studies can provide an important criterion for judging the pharmaceutical action of chalcone derivatives. α-Amylase inhibition has long been associated with anti-diabetic activity and control over postprandial hyperglycemia, while trypsin inhibition is associated with anti-inflammatory and protease-modulating effects [15,16]. Such assays, together with molecular docking and computational modeling methods, enable us to correlate experimental inhibitory data against predicted modes of binding and thus make it possible for rational interpretation of SAR results as well as actual lead optimization [17,18].

Materials and Method

The synthesis of chalcone derivatives is not possible without acetophenones and aromatic aldehydes, all of which were obtained from normal commercial sources and used without further purification. The base catalyst in this reaction was potassium hydroxide (KOH) of analytical grade. Using silica gel 60 F_{254} precoated thin layer chromatographic plates, the development and purity of a product were monitored throughout a reaction. Work-up and purification steps required the use of ethanol and distilled water.

The chalcone derivatives (NC-1 to NC-8) were synthesized using a solvent-free mechanochemical Claisen-Schmidt condensation. Equal amounts (0.01 mol) of acetophenone and the corresponding aromaticaldehyde were placed together in a clean mortar and stirred in one dry, powdered form with 0.01 mol potassium hydroxide as catalyst. Stirring was continued for 30-40 minutes in one direction with a pestle at room temperature until an even paste was obtained. Mechanical grinding provided sufficient activation energy to facilitate carbon-carbon bond formation without the use of organic solvents. Reaction progress was semi-continuously monitored by TLC using n-hexane:ethyl acetate (7:3) as a mobile phase. Upon completion of the reaction, the mixture was added slowly to crushed ice with agitation, yielding a precipitated chalcone product. The solid was collected by vacuum filtration, thoroughly washed with cold dist. water to remove any residual alkali, further washed with cold ethanol and finally dried in air at room temperature. Final purification was achieved by recrystallization from ethanol to give the pure chalcone derivatives.

The synthesis of the chalcone derivatives was confirmed by yield, TLC behavior, and melting point determination. Percentage yield was calculated on the basis of the weight obtained for the pure product. By means of TLC analysis completion and purity of the reaction could be confirmed, with Rf values being recorded. Melting points were determined using the open capillary method and are reported as uncorrected values. In-vitro enzymatic evaluation was

carried out to assess α-amylase and trypsin inhibitory activity. α-Amylase inhibition was determined using the DNSA method to measure the reduction in maltose production at 540 nm, while trypsin inhibition was measured with casein as the substrate and absorbance recorded at 280 nm at the conclusion of the reaction. Enzyme activities were expressed as percentage inhibitions against a given concentration.

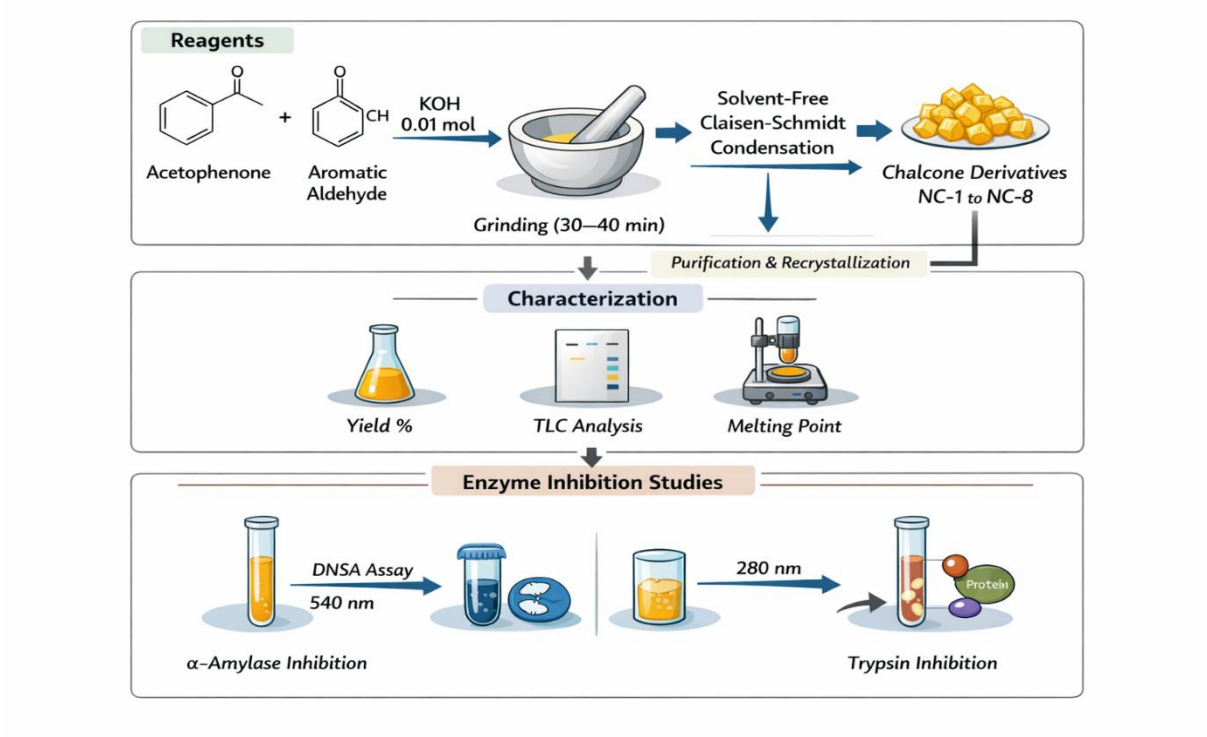

Figure 2: Scheme of methodology for study

RESULTS

The 8 novel chalcone derivatives NC-1 to NC-8 were synthesized by a solvent-free mechanochemical Claisen–Schmidt condensation. The reactions proceeded efficiently in ambient conditions, yielding crystalline products that could be easily taken from the benchtop after a simple work-up and recrystallization. The use of a solvent-free grinding method minimized solvent usage and sped up the formation with good yields, demonstrating how this Green Chemistry strategy is practical.

To confirm purity and structural integrity, the synthesized chalcones were characterized by the percentage yield, thin layer chromatography (TLC) behaviour and their melting point analysis. In addition, the bioactivity of synthesized compounds was evaluated through in-vitro, enzyme inhibition studies against α-amylase and trypsin enzymes. These enzymes were chosen because they are involved in metabolic and proteolytic processes-making them important objec tives for biology.

This result shows that differences in aromatic substitution significantly affects both the physicochemical properties and enzyme inhibitory activity observed. The difference between yield, Rf values, melting points and percent inhibition by different chalcones is a reflection of electronic and spatial effects that are felt in this molecule. Following are the results in detail,

starting with yield analysis to prove purity expected from a synthesis product, then TLC behaviours and melting point characteristics before concluding on a discussion of bioactivity.

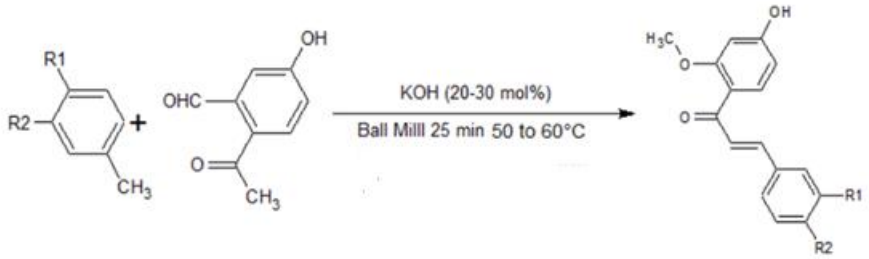

Figure 3: Scheme of reaction

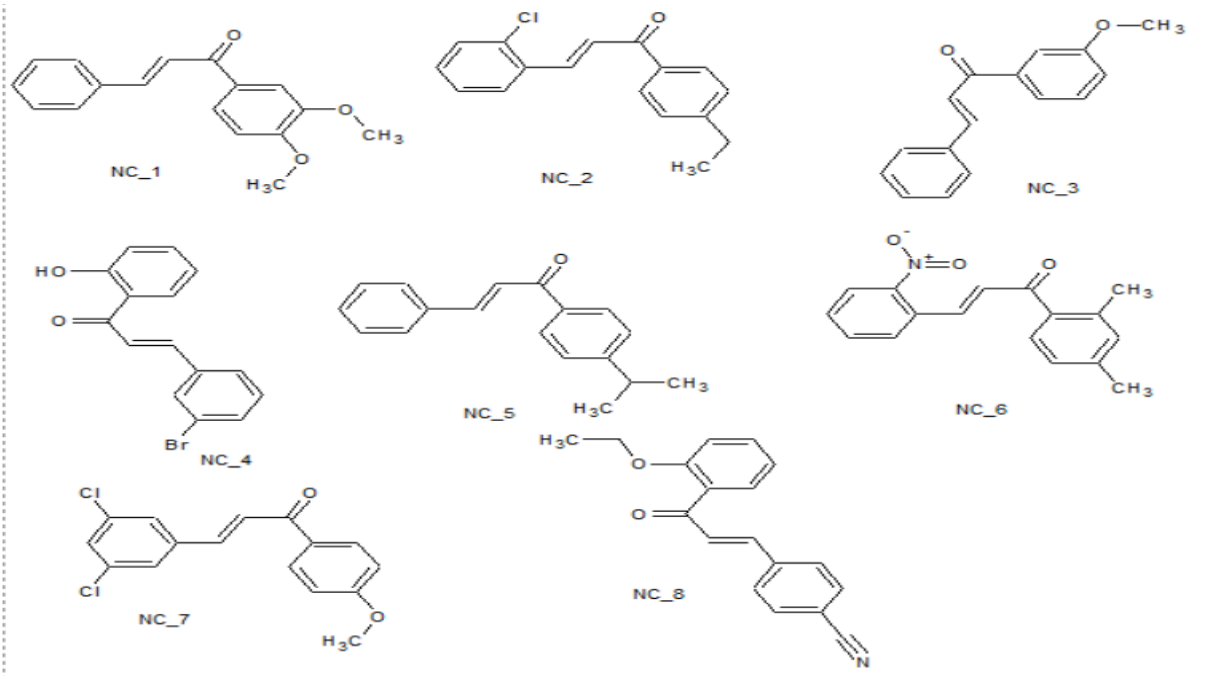

Figure 4: List of synthesized compounds

Table 1. Yield Summary of Halo-Substituted Chalcone Derivatives

Compound Code	Yield (%)
NC-1	82
NC-2	78
NC-3	85
NC-4	74
NC-5	80
NC-6	83
NC-7	76
NC-8	88

The isolated yields of the synthesized chalcone derivatives were found to vary between 74% and 88%, thus establishing the overall efficiency of the mechanochemical synthesis method. The chalcone derivatives with electron-withdrawing groups had higher yields, and this can be attributed to the increased electrophilicity of the compounds, thus making it easier for the condensation reaction to occur. However, the derivatives with bulkier alkyl groups had slightly lower yields, and this could be attributed to steric effects that may hinder solid-state molecular interactions during the grinding process. The overall high yields of all the derivatives establish the efficiency of the solvent-free mechanochemical method in the synthesis of chalcones with diverse structures.

Thin-Layer Chromatography (TLC) Analysis

Table 2: TLC Rf Values of Synthesized Chalcones

Compound Code	Rf Value*
NC-1	0.56
NC-2	0.60
NC-3	0.52
NC-4	0.48
NC-5	0.62
NC-6	0.50
NC-7	0.54
NC-8	0.46

*Solvent system: n-hexane : ethyl acetate (7:3)

Thin Layer Chromatography was used to check the progress of the reaction and the purity of the synthesized chalcones. All the compounds gave a single, sharp spot on the TLC plate, which confirmed the successful transformation of the starting materials and their proper purification. The Rf values were dependent on the type of substituents present on the aromatic rings. The chalcones containing polar functional groups had lower Rf values because of increased interaction with the stationary phase, while the alkyl-substituted chalcones had higher Rf values.

Melting Point Analysis

Table 3: Melting Point Data of Synthesized Chalcones

Compound Code	Melting Point (°C)
NC-1	128–131
NC-2	121–124
NC-3	134–137
NC-4	142–145
NC-5	118–121
NC-6	146–149
NC-7	139–142
NC-8	151–154

The synthesized chalcones were assessed for their crystalline nature and purity by determining their melting points. All compounds showed narrow melting ranges with a high degree of

purity and less significant impurities. Electron-withdrawing or polar substituents in the chalcone molecules usually result in higher melting points, due to stronger forms of intermolecular interaction and/or better crystal packing. In contrast, the melting points of alkyl-substituted derivatives were relatively low. Melting point data corroborate the successful synthesis of chemically diverse chalcone derivatives.

In-Vitro Enzymatic Inhibition Studies

Table 4 Enzymatic Inhibition Activity of Synthesized Chalcones

Compound Code	α-Amylase Inhibition (%)	Trypsin Inhibition (%)
NC-1	31.4 ± 1.2	26.8 ± 1.0
NC-2	29.6 ± 1.1	24.3 ± 0.9
NC-3	35.2 ± 1.4	28.9 ± 1.2
NC-4	33.7 ± 1.3	27.5 ± 1.1
NC-5	30.8 ± 1.0	25.6 ± 0.8
NC-6	36.5 ± 1.5	30.1 ± 1.3
NC-7	32.4 ± 1.2	26.9 ± 1.0
NC-8	38.1 ± 1.6	31.4 ± 1.4

The synthesized chalcone derivatives have been evaluated for a quantitative finding for their α-amylase and trypsin inhibitory activity. Differences in inhibition percentages during a 48 h period corroborated the effect of varying site of substitution on aromatic rings on enzyme interaction. The increased inhibition of chalcones bearing a strong electron-withdrawing group for both enzymes indicates higher binding affinity. Derivatives with alkyl substitutions exhibited moderate inhibition levels. In general, the results reflect that the structural modification of the chalcone scaffold is an essential factor that contributes to the modulation of enzymatic activity, and accordingly, these kind of compounds are probably good candidates for more biological exploring.

DISCUSSION

We report the synthesis and physicochemical characterization of eight new chalcone derivatives (NC-1 to NC-8), which were prepared via a high-yielding mechanochemical Claisen–Schmidt condensation method under solvent-free conditions, and assess their in-vitro enzymatic inhibition potential. This discussion then overlaps these results with the classical and more recent literature to provide interpretations for the trends observed in terms of yield, purity, melting, and enzyme inhibition while focusing on substitution effects, non-covalent interactions, and enzyme–ligand binding.

Halogen bonding and other types of weak intermolecular interactions are quite relevant to the physiochemical properties and biological effect of small molecules. Directional halogen bonding is a stabilizing interaction that has been well established in biological systems, contributing to ligand specificity and binding strength [19]. The halogen-containing chalcone derivatives in current study had relatively higher melting points and enzyme inhibition compared with the relatives which may associated with stronger intermolecular interactions and the better binding complementarity due to halogen participation.

The possibility to modify the reaction pathways, to sieve the selectivity and also to provide the reaction with high efficiency as a solvent-free reaction has been shown by the mechanochemical synthesis [20,21]. All chalcone derivatives synthesized in the present study were obtained in even shorter reaction times than these screened via mechanochemistry, thus demonstrating the applicability of this technique beyond carbon-carbon bond-forming reactions. Differences in yield from NC-1 to NC-8 can be attributed to electronic and steric effects that influence the formation of the enolate and its subsequent condensation reaction, effects which have been shown to be particularly pronounced under solid-state reaction conditions [21].

Enzyme inhibition and molecular docking studies on chalcone scaffolds have been well characterized. Two recent studies reported on various chalcone derivatives possessing heterocyclic scaffolds with appreciable enzyme inhibitory activity further supported by docking analysis suggesting substituent effects and electronic properties play a key role on the overall activity [22]. The enzyme inhibition results obtained have alluded such observations, particularly for chalcones bearing electron-withdrawing groups that show a better inhibition percentage.

Hybrid chalcone compounds remain an object of interest as their biological profiles are improved [6,7,8,9]. Hybrids based on chalcone have been described as selective aldose reductase inhibitors and demonstrate CHO cytotoxicity [23], highlighting the diverse range of possible enzyme targets for compounds based on the chalcone core. The moderate to high inhibition of enzymes observed for the present chalcone derivatives is consistent with their potential utility as lead scaffolds for further functionalization and hybridization.

Chalcone and pyrazoline derivatives have also been studied extensively as protein-protein inhibitors of transcription factors [24], suggesting that the scope of biological activity of chalcone-based molecules may extend beyond classical enzyme targets. Such results strengthen the importance of chalcones being multi-functional bioactive scaffolds and also substantiate the use of enzyme inhibition studies as early biological screening step.

While the present study was not concerned specifically with enzyme inhibition over cytotoxicity, it may be noted that previous reports dealing with structurally related heterocyclic compounds provide evidence that both the substitution pattern and linker design strongly influence biological effects [25]. These results highlight the importance of both steric and electronic factors in guiding the interpretation of enzyme inhibition data and in the prioritization of targets for further biological testing.

Furthermore, significant contribution to their biological activity in the antitubercular field was also observed from electronic modulation, such as electron-withdrawing substituents and aromatic substitutions in functionalized chalcone derivatives [26]. While this work did not include antitubercular screening, the inhibition trends on the enzymes vary with the presence of end functional groups and rank according to reports where structural heterogeneity increase interactions with biological targets.

Carbohydrate-processing enzymes including α-glucosidase and α-amylase are potential therapeutic targets for metabolic disorders. Recently, highly potent α-glucosidase inhibition was found with coumarin–chalcone hybrids and it was shown that activity is highly dependent

on aromatic substitution and noted electronic effects [27]. NC-1 to NC-8 exhibited similar trends in α-amylase inhibition suggesting a chalcone scaffold amenable to carbohydrate-digesting enzyme modulation.

Halogenated chalcone derivatives have been systematically screened for inhibition of metabolic enzymes and found that halogen substituents enhance binding affinity through hydrophobic interactions and halogen bonding [28]. The enhanced inhibition observed in the presence of halogen-substituted derivatives in this work thus validates these findings and provides further rationale for a preference that takes halogen incorporation for chalcone design to other HSPs.

Complete reviews on chalcone pharmacology emphasize the high diversity of biological activities found in these compounds as enzyme inhibitors [30], anticancer [31], anti-inflammatory [32], and antibacterial [33], but the structure–activity relationships (SAR) are essential in defining the potency and selectivity [29]. These results expand on this evidence by showing that small changes in aromatic substitution can exert large changes in inhibiting enzymes.

Additionally, in addition to metabolic enzymes, chalcones have also been found to inhibit bacterial virulence factors, thus disrupting the process leading to infection [30]. This broadens the therapeutic importance of chalcones by suggesting that inhibition of enzyme activity in vitro can lead to a variety of biological applications.

More recent studies of antiparasitic activity of chalcone derivatives show that both the positions of the aromatic substitutions and electronic effects are highly important in the biological activity [31]. The reproducibility of substitution-dependent activity over different biological targets validates the SAR trends found herestory.

In recent years, multi-target enzyme inhibition has arisen as an important strategy of contemporary medicinal chemistry. Reported chalcone hybrids also exhibit dual enzyme inhibitory activity, complemented by in-silico characterization and biological evaluation [32]. The moderate inhibition towards both α-amylase and trypsin obtained in the present work indicates that these chalcone derivatives probably have multi-target activity which must be continued in future years.

Investigations on chalcone derivatives have continuously shown that there is a satisfactory correlation between enzyme inhibition, docking scores, and anticancer activity in computational and experimental studies [33]. While none of the work performed here was computational analysis, the antimicrobial inhibition results make an excellent starting point for targeted in-silico exploration.

Chalcones with halogenated substituents have been additionally described as anti-inflammatory agents with good ADME features, further highlighting the most important part of the structure and the therapeutic value of halogen substitutions [34]. The inhibition patterns with these enzymes observed in the present study substantiates these findings and merit further biological profiling.

Since then, a lot of studies have compared the anticancer activities of a range of novel chalcone derivatives including heterocyclic systems, indicating that alteration of the basic chalcone scaffolds allowed for a significant improvement in biological activity [35]. Moreover, these

reports provide additional support for the chalcone framework as a modular platform for drug development.

Chalcones have been identified as potential multifunctional therapeutic agents, including antioxidant and enzyme inhibitory properties, and new studies show that the synergy of experimental and computational data is essential for the characterization of the molecular mechanisms involved in a combination of biological activities [36] The current study contributes to this expanding field with systematic data on enzyme inhibition for informing future optimization.

CONCLUSION

It has been successfully accomplished the sustainable syntheses of eight novel chalcone derivatives by solven–free mechanochemical technique under Claisen–Schmidt condensation approach followed by the merits of green chemistry such as less amount of solvent (No solvent), simple operational procedure & improved product productivity. The chalcones were obtained in good yields and were characterized by TLC and melting point analysis for their purity and crystalline nature. Differences in the experimental physicochemical properties suggested the effect of aromatic substitution as the intermolecular interactions between molecules were altered. An in-vitro enzyme inhibition study demonstrated that all derivatives inhibited α-amylase and trypsin and that enhanced inhibition of chalcones with electron-withdrawing (or halogen) substituents was observed, suggesting the importance of electronic effects on enzyme–ligand interactions. The findings confirm that the chalcone scaffold can function as a generalizable template for enzyme inhibition and highlight that the mechanochemical approach can be used in future studies to rapidly develop bioactive compounds. In conclusion, these results provide a basis for further investigations, including kinetic studies, molecular docking, cytotoxicity evaluation, and structural optimizations, that plausibly continues in the area of chalcone derivatives as compound classes in medicinal chemistry and drug development.

REFERENCES

Elkanzi NAA, Hrichi H, Alolayan RA, Derafa W, Zahou FM, Bakr RB. Synthesis of chalcone derivatives and their biological activities: a review. ACS Omega. 2022;7(32):27769–27786.

Salehi B, Quispe C, Chamkhi I, et al. Pharmacological properties of chalcones: a review of preclinical studies. Front Pharmacol. 2021;11:592654.

Morsy NM, Hassan AS. Synthesis, reactions, and applications of chalcones: a review. Eur J Chem. 2022;13(2):241–252.

Adhikari S, Nath P, Deb VK, et al. Pharmacological potential of natural chalcones: recent studies and future perspectives. Front Pharmacol. 2025;16:1570385.

Dos Santos ATL, de Araújo-Neto JB, et al. Synthesis of chalcones and their antimicrobial and drug potentiating activities. Microb Pathog. 2023;180:106129.

Hernández JG, Bolm C. Altering product selectivity by mechanochemistry. J Org Chem. 2017;82(8):4007–4019.

Musatat AB, Atahan A, Ergün A, et al. Synthesis, enzyme inhibition, and molecular docking studies of a novel chalcone series. Biotechnol Appl Biochem. 2023;70(3):1357–1370.

Sheldon RA. The E-factor 25 years on: the rise of green chemistry and sustainability. Green Chem. 2017;19:18–43.

Wilcken R, Zimmermann MO, Lange A, et al. Halogen bonding in medicinal chemistry. J Med Chem. 2013;56(4):1363–1388.

Lu Y, Shi T, Wang Y, et al. Halogen bonding—A novel interaction for rational drug design. J Am Chem Soc. 2009;131(28):10370–10372.

Anil DA, Polat MF, Saglamtas R, et al. Enzyme inhibition profiles of novel halogenated chalcone derivatives. Comput Biol Chem. 2022;100:107748.

Iqtadar R, Naz A, Shah SAA, et al. New halogenated chalcones as anti-inflammatory agents. J Mol Struct. 2025;1326:141055.

Fanelli D. Negative results are disappearing from most disciplines and countries. Scientometrics. 2012;90:891–904.

Letulle C, Toublet FX, Pinon AHS, et al. Trimethoxylated chalcones with antiproliferative activity. Pharmaceuticals (Basel). 2024;17:1207.

Hu CM, Luo YX, Wang WJ, et al. Coumarin–chalcone derivatives as α-glucosidase inhibitors. Front Chem. 2022;10:926543.

Ardiansah B, Rohman N, Nasution MAF, et al. Chalcone derivatives bearing triazole units as α-glucosidase inhibitors. Chem Pharm Bull (Tokyo). 2023;71(5):342–348.

Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening. Nat Rev Drug Discov. 2004;3(11):935–949.

Agbo EN, Maluleke BK, Gildenhuys S, et al. Biological evaluation and molecular docking studies of chalcone derivatives. Sci Rep. 2025;15:36575.

Auffinger P, Hays FA, Westhof E, Ho PS. Halogen bonds in biological molecules. *Proc Natl Acad Sci USA.* 2004;101(48):16789–16794. doi:10.1073/pnas.0407607101.

Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening. *Nat Rev Drug Discov.* 2004;3(11):935–949. doi:10.1038/nrd1549.

Hernández JG, Bolm C. Altering product selectivity by mechanochemistry. *J Org Chem.* 2017;82(8):4007–4019. doi:10.1021/acs.joc.6b02887.

Musatat AB, Atahan A, Ergün A, et al. Synthesis, enzyme inhibition, and molecular docking studies of a novel chalcone series bearing benzothiazole scaffold. *Biotechnol Appl Biochem.* 2023;70(3):1357–1370. doi:10.1002/bab.2445.

Guleç O, Duran HE, Arslan M, et al. Chalcone-inspired indole, carbazole, and phenothiazine hybrids as potent aldose reductase inhibitors with selective anticancer potential. *Bioorg Chem.* 2025;164:108861. doi:10.1016/j.bioorg.2025.108861.

Hwang SY, Jeon KH, Lee HJ, et al. Synthesis and biological assessment of chalcone and pyrazoline derivatives as novel inhibitors for ELF3–MED23 interaction. *eLife.* 2024;13:RP97051.

Alagoz MA, Ozdemir Z, Uysal M, et al. Synthesis, cytotoxicity and antiproliferative activity against AGS cells of new pyridazinone derivatives endowed with a piperazinyl linker. *Pharmaceuticals (Basel).* 2021;14:183.

Joshi S, Kawathekar NSS. Synthesis and biological evaluation of N-substituted indole chalcone derivatives as potent antitubercular agents. *Future J Pharm Sci.* 2025;11:113.

Hu CM, Luo YX, Wang WJ, et al. Synthesis and evaluation of coumarin–chalcone derivatives as α-glucosidase inhibitors. *Front Chem.* 2022;10:926543.

Anil DA, Polat MF, Saglamtas R, et al. Exploring enzyme inhibition profiles of novel halogenated chalcone derivatives on metabolic enzymes: synthesis, characterization and molecular modeling studies. *Comput Biol Chem.* 2022;100:107748.

Salehi B, Quispe C, Chamkhi I, et al. Pharmacological properties of chalcones: a review of preclinical studies including molecular mechanisms and clinical evidence. *Front Pharmacol.* 2021;11:592654.

Li H, Chen Y, Zhang B, et al. Inhibition of sortase A by chalcone prevents *Listeria monocytogenes* infection. *Biochem Pharmacol.* 2016;106:19–29.

Setshedi KJ, Beteck RM, Ilbeigi K, et al. Synthesis and in vitro biological activity of chalcone derivatives as potential antiparasitic agents. *Med Chem Res.* 2024;33:977–988.

Alici H, Topuz S, Demir K, et al. Synthesis, biological evaluation, and in silico characterization of novel imidazothiadiazole–chalcone hybrids as multi-target enzyme inhibitors. *Pharmaceuticals (Basel).* 2025;18:962.

Deka D, Chanda Das SR, Das T, et al. Chalcone derivatives: in silico design, molecular docking study and anticancer activity on MCF-7 cells. *In Silico Res Biomedicine.* 2025;1:100016.

Iqtadar R, Naz A, Shah SAA, et al. New halogenated chalcones as potential anti-inflammatory agents: a comprehensive in silico, in vitro, and in vivo study with ADME profiling. *J Mol Struct.* 2025;1326:141055.

Komirishetti D, Syed T, Mittapelli V. Synthesis and biological evaluation of chalcone derivatives of oxazole–pyrimidines as anticancer agents. *Results Chem.* 2025;15:102294.

Lokanath SM, Katagi MS, Bolakatti GS, et al. Exploring chalcone derivatives as multifunctional therapeutic agents: antioxidant potential, acetylcholinesterase inhibition and computational insights. *Drugs Drug Candidates.* 2025;4:16.