Journal of Kufa for Chemical Sciences
ISSN(P) :2077-2351 ISSN(E): 3006-3280
Journal Homepage:
https://journal.uokufa.edu.iq/index.php/jkcs/index

Review Article

Chalcone Promising Bioactive Structure in Medicinal Chemistry: A Review

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Abstract

In medicinal chemistry, privilege structures are essential and useful templates for the creation of new drugs. The chalcone scaffold stands out as one of the most basic yet important of these structures in this regard. Its unique structural features—the α,β-unsaturated carbonyl system and a fully delocalized π-electron system—as well as its simplicity of chemical synthesis and great amenability to substitution, make it logical to do extensive research on it. Because of these characteristics, it has a relatively low redox potential, which increases the possibility that it will take part in biological electron transfer reactions. The purpose of this review is to offer a thorough and critical analysis in order to assess the therapeutic potential of chalcone and its derivatives. A wide range of biological activities, including strong antibacterial, antifungal, anti-inflammatory, and anticancer properties, have been shown for these compounds. In particular, the review aims to examine the structure-activity relationship (SAR), with a focus on the reactive α,β-unsaturated keto function and its connection to the antibacterial mechanism. By looking at these various functions, this study aims to evaluate the advancements made thus far and pinpoint the present obstacles and research gaps required to fully realize chalcone's promise as a potent treatment for a variety of illnesses.

Keywords: Chalcone, Biological activity, structure-activity relationship (SAR),α,β-unsaturated ketone, Medicinal Chemistry, Therapeutic Potential.

1. Overview

A crucial component of every drug development plan is molecular diversity. The needed components can be produced naturally or chemically. Natural products still contain unidentified chemotypes (such as pharmacophores and molecular scaffolds). offer numerous structural components for the field of pharmaceutical chemistry. As a result, natural products are consistently considered to be highly important sources of inspiration for the creation of novel medications. Due to their special qualities, such as efficient molecular interactions with the targeted biological receptors for pharmacological effects, scientists have recently concentrated on smaller fragments, or scaffolds (~300 Da). In fragment-based drug design (FBDD), these characteristics are essential. Flavonoids have remarkable qualities. Chalcones, flavanones, flavones, isoflavones, aurones, neoflavones, and biflavones are among the several kinds of flavonoids.

Three carbon units make up the α,β-unsaturated system that forms the structural basis of chalcones. 1,3-diphenylprop-2-en-1-one is the name given to them (Figure 1), and extensive study has been conducted on their hydrophobic/hydrophilic properties, particularly when it comes to infectious and non-infectious diseases[1], [2]

Chalcones are found in both cis and trans forms, with the trans isomer having greater thermodynamic stability. The biological features of chalcones have been found to include anti-inflammatory[3] , anti-viral[4] , anticancer[5] , antimicrobial [6] , antioxidant[7] , antidiabetic [8],anti-Parkinson's [9], and anti-nociceptive properties[10](Figure 2). Following a thorough review of the literature, it was discovered that numerous scientific advancements have helped to clarify the bioactivities of chalcones.

The nature of chalcone chemistry is diverse. Adding heterocyclic moieties to the chalcones' structural framework increases their bioactivity, which is already known to occur in heterocyclic rings. Numerous research projects have been undertaken in recent years. Synthesized and evaluated a number of chalcone analogs, chalcones with heterocyclic rings, including quinoline [11], pyridine [5], pyrrole [12], indole [13], pyrazole [14], benzofuran [15], coumarin [16], isoxazole [17], benzimidazole [18], and azulene [19], are described in the literature. Chalcone analogues based on metallocene, including ruthenocenyl and ferrocenyl derivatives, have also been reported [20]. Chalcones have optical applications, including fluorescent probes [20]. In light of this context, an attempt was made to assemble an overview of

chalcone medicinal uses; their structure-activity relationship (SAR) investigations are covered in this review.

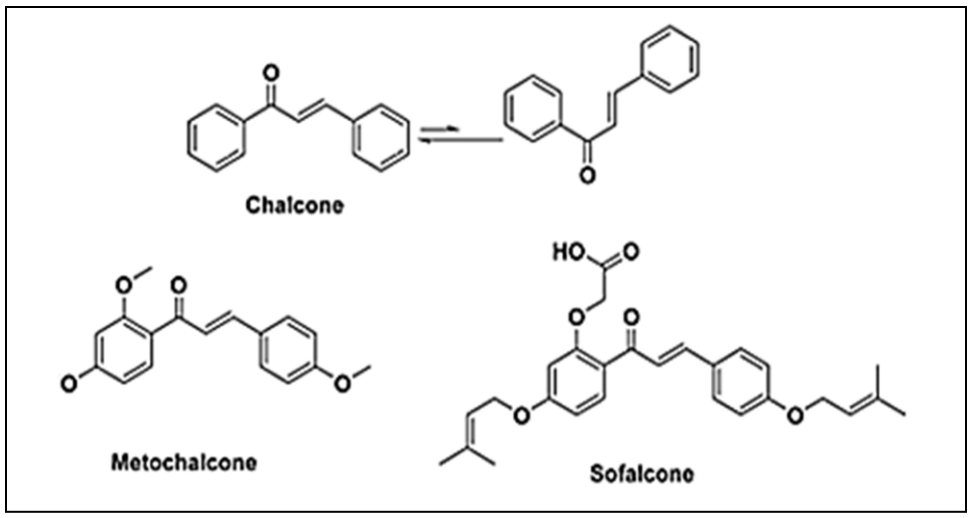


Figure 1: Two clinically authorised chalcone-based medicines and their structures

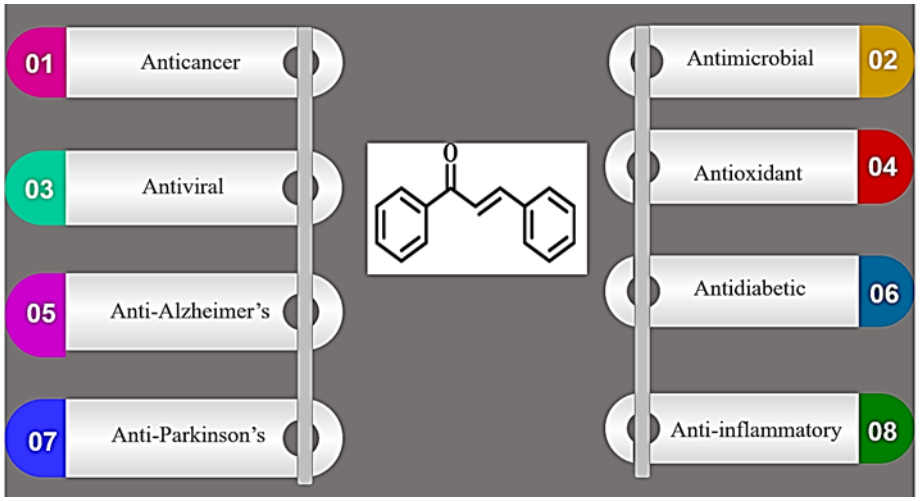


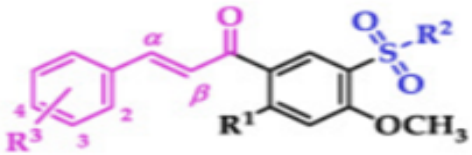
Figure 2: Shows the structure of chalcone and its bioactivity.

Coronaviruses have impacted millions globally. Shigella bacterial infections pose a considerable threat in developing nations, with mortality rates from diseases like malaria and tuberculosis increasing. The infections usually resist the many medications used to treat these diseases [1]. The field of synthetic and pharmaceutical organic chemistry has made major advances in recent years.

Consequently, the following subsections discuss the bioactivity of chalcones, which are regarded to be possible treatments for a variety of ailments.

1-1 Antitubercular Inaction

Pulmonary tuberculosis is the sixth leading cause of death worldwide. Pyrazinamide, streptomycin, and rifampicin are some of the drugs used to treat it.[1]. Numerous investigations have been undertaken on chalcone analogs to test their anti-tubercular activity, and chalcones with substantial anti-tubercular activity have been described. In vitro, all new sulfonamide hybrids were tested for antituberculosis activity against Mycobacterium bovis BCG (ATCC 35734) and H37Rv (ATCC 27294) strains using the agar dilution spot culture growth inhibition assay. After testing at 10 mg/L, compounds that showed inhibition were evaluated at 5, 1, 0.5, 0.1, and 0.01 mg/L. Positive control: isoniazid. Table 1 shows the minimal inhibitory concentrations (MICs) for each compound. The α,β-unsaturated carbonyl system proved to be a significant pharmacophore unit; among the tested compounds, only chalcones showed inhibitory effects (9.0 to 29**µM**), whereas sulfonamides, pyrazolines, and carbothioamides were inactive. Derivatives of isoniazid showed the strongest antitubercular action. The inhibitory activity was increased by the substituents 4-H, 4-OCH3, 3,4,5-(OCH3)3, and 3,4-OCH2O. 5, 7, and 8, which were isolated from chloride (R1 = OCH3), were the most active chalcones; they showed MIC values of 11 ~M, 9.0 ~M, and 9.8 ~M against Mycobacterium tuberculosis H37Rv, and 5 and 7 showed MIC values of 11 ~M and 9.0 ~M against Mycobacterium bovis BCG, respectively.[21].



1-8

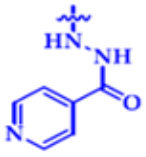
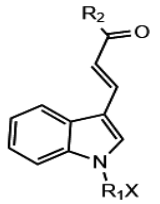
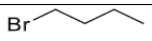
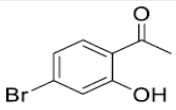
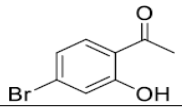
Compound	R^1	R^2	R^3	R^4
1			4-H	
2			3,4-OCH_2-O-	
3			4-H	
4	-H		4-OCH_3	----
5			4-H	
6	-OCH_3		4-OCH_3	----
7			3,4,5-$(OCH_3)_3$	
8			3,4-OCH_2-O-	

Table 1 shows anti-TB and cytotoxic action for compounds (1-8)

Compound	MIC Against *M. bovis* BCG (μM)	MIC Against *M. tuberculosis* $H_{37}Rv$ (μM)	Cytotoxicity IC_{50} on Vero Cell Line (μM)	Selectivity Index (SI) (SI = IC_{50}/MIC)
1	>29	29	1.06 ± 1.21	0.04
2	>25	25	1.70 ± 1.74	0.07
3	>23	23	6.32 ± 0.82	0.28
4	>21	21	2.19 ± 0.68	0.10
5	11	11	6.05 ± 1.39	0.28
6	>20	20	1.00 ± 1.20	0.05
7	9.0	9.0	0.26 ± 0.69	0.03
8	20	9.8	2.55 ± 0.93	0.26
Isoniazid	0.36	0.36	nd	

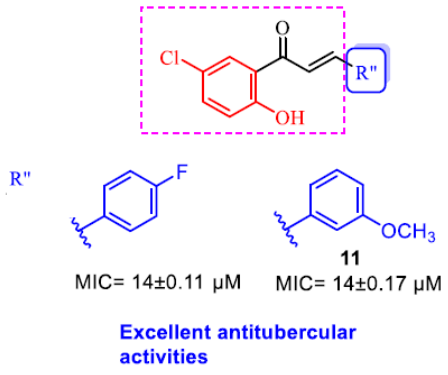
A series of N-alkylated indole chalcone derivatives was synthesized, docked, and tested for their ability to inhibit the H37Rv strain of Mycobacterium TB ATCC 27294. Among them, two compounds showed anti-tubercular activity: (E)-1-(4-bromo-2-hydroxyphenyl)-3-(1-butyl-1H-indol-3-yl)prop-2-en-1-one (S1R1) and (E)-1-(4-bromo-2-hydroxyphenyl)-3-(1-pentyl-1H-indol-3-yl)prop-2-en-1-one (S1R2). The activity is linked to both the existence of electron-withdrawing groups in N-alkylation of indole chalcone derivatives and their ability to bind metal atoms required for mycobacteria. Docking studies were conducted to comprehend the binding of N-alkylated indole chalcones. Compound S1R1 displayed binding mechanisms similar to FAS-II inhibitors like INH.[22]



S.no	Compound code	R1	R2
1	S1R 1		
2	S1R 2		

S.no	Compound codes	MIC value (µg/mL)
1	S1R 1	04
2	S1R 2	06

In another study, MABA assays were used to assess the synthesized chalcones' antitubercular properties. The analogs 1 (MIC = 14 ± 0.11 mM) and 2 (MIC = 14 ± 0.17 mM) with fluorine and methoxy groups at para and meta locations, respectively, were 1.8 times more active than conventional pyrazinamide (MIC = 25.34 ± 0.22 mM) [23]



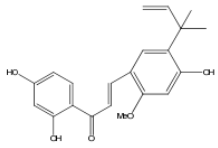
Compounds having a phenyl ring modified with an electron-donating methoxy substituent at the meta location and an electron-withdrawing fluorine atom at the para location exhibit antitubercular activity that is higher than that of the common medication pyrazinamide .

The ketovinyl bridge and the 2'-hydroxyphenyl-5'-chlorophenyl ring are promising for antitubercular action.

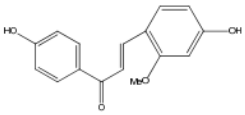
Fig.3: An overview of chalcones' anti-tubercular and structure-activity connections

1-2 Antiviral Activity

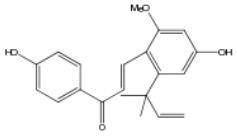
licochalcone G, A, echinantin, 5-prenylbutein, D, isoliquiritigenin, licoagrochalcone A, and C. These compounds inhibit influenza virus NAs. Prenylated 5-prenylbutein, a C-5 hydroxy derivative of licoagrochalcone A (IC50 25.87 + 2.03 µg mL), showed lower activity than echinantin and isoliquiritigenin (IC50 5.80 ± 0.30 and 8.41 ± 0.39 µg mL, respectively). The Humulus lupulus chalcone xanthohumol suppresses HIV-1 individually. Xanthohumol inhibits HIV-1 p24 antigen and RT production with EC50 values of 1:28 and 1:35 µg mL-1. Also effective against HSV-1, HSV-2, BVDV, and CMV is xanthohumol. Licochalcones A and B and 3,3',4,4'-tetrahydroxy-2-methoxy chalcone decreased TPA-induced HIV promoter activation but not Luc activity in pCMVLuc-transfected cells. Chalcones may have inhibited HIV transcription by binding to protein factors. Cardamonin suppressed HIV-1 PR activity by 75.1% at an IC50 of 31 µg mL. Glycycoumarin, glycyrin, glycyrol, liquiritigenin, isoliquiritigenin, licochalcone A, and glabridin are HCV-antiviral.[24]



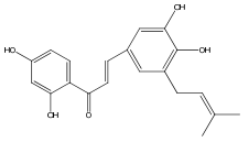
Licochalcone G



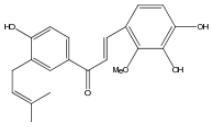
Echinantin



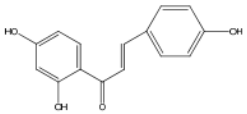
licoagrochalcone A



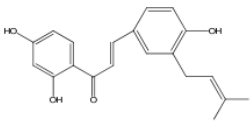
5-prenylbutein



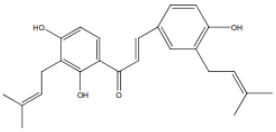
licochalcone D



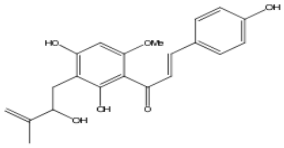
Isoliquiritigenin



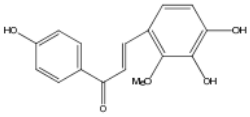
licoagrochalcone A



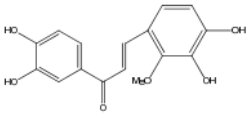
kanzonol C



Xanthohumol



Licochalcone A



Licochalcone B

Fig 4: Chalcone derivatives with Antiviral Activity

1-3 Anticancer activity

Certain chalcones, both synthetic and natural, have been demonstrated to have antioxidant characteristics and to be effective against tumor cells by inhibiting the production of superoxide. Millepachine (A), an anticancer chalcone. Licochalcone A (B), another anticancer chalcone found in Glycyrrhiza inflata, has been shown to be toxic to B16 melanoma cells and L1210 leukemia. One naturally occurring chalcone, butein (D), works to inhibit the growth of numerous human cancers, including osteosarcoma, breast cancer, colon cancer, and hepatic stellate cells; another naturally occurring chalcone, a new compound from the chalcone (C), improved the survival rate of mice injected with L1210 leukaemia at doses ranging from 2.65 to 5.0 mg/kg.[25]

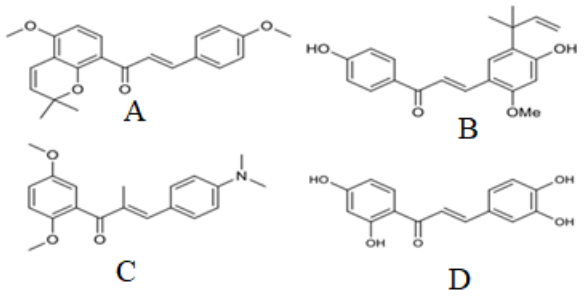


Fig. 5:Chalcone derivatives with anticancer activity

The anticancer activity of recently developed chalcone-sulfonamide hybrids was tested against 60 cancer cell lines. Compounds 1 and 2 were studied further, and 1 demonstrated significant GI50 values against melanoma and leukemia (LOX IMVI and K-562, respectively). A novel chalcone derivative, specifically the 3(DPP-23-loaded NP), was produced and evaluated on the MCF-7 and MDA-MB-231 cell lines. The accumulation of fluorescein isothiocyanate in MDA-MB-231 cells was observed to diminish cell viability and provided an effective drug delivery route. A number of thiophene-based chalcone derivatives were developed and tested for their in vitro anticancer activity using a panel comprising MCF-7, MDA-MB-453, PC-3, and A549 cell lines. The potency of novel compounds was compared to that of the reference medication, cisplatin. Compound 4 was found to be the most effective in the MTT assay, inducing dose-dependent apoptosis in A549 cells. N-substituted benzimidazole-chalcone derivatives featuring an alkyl chain and a five- or six-membered nitrogen ring exhibit enhanced cytotoxicity against MCF-7 and OVCAR-3 cell lines associated with ovarian cancer. Compound 5 performed better than the other chemicals when compared to the reference, cisplatin. Chalcone derivatives were synthesized, and their IC50 values were determined using MCF-7

and Hs578T cell lines. The compounds containing halogen substituents (especially bromine), 6, 7, and 8, exhibited much higher activity than those with methyl or hydroxyl groups. According to the findings, the most promising compound among all created compounds was compound 9 . The MTT was used to show that chalcones 10 and 11 have potential anticancer activity against MCF-7, MDA-MB-231, and Ishikawa cells. Several chalcone analogs were developed, and their antineoplastic activity was tested against lung cancer cell lines (NCI-H460, A549, and H1975). Studies on the Structure-Activity Relationship (SAR) show that the presence of an α, β-unsaturated ketone moiety in a molecule increases its anticancer activity in vitro. Compound 12 had a considerable antiproliferative effect on all cell lines evaluated. Furthermore, it has a greater safety profile in vivo and inhibits NCI-H460 cells in a time- and concentration-dependent manner by controlling ROS to induce caspase-3-mediated apoptosis. Zingiberaceae plants contain cardamonin, a botanochalcone (CRD, 13), which is a well-known compound with promising pharmacological effects. Preclinical pharmacokinetic studies in vivo and in vitro were conducted to assess the potential for cancer prevention and treatment. The findings revealed that CRD binds to mouse and rat plasma proteins at a small level. It disperses widely in mice, has a short average residence time, and has a high clearance rate [26].

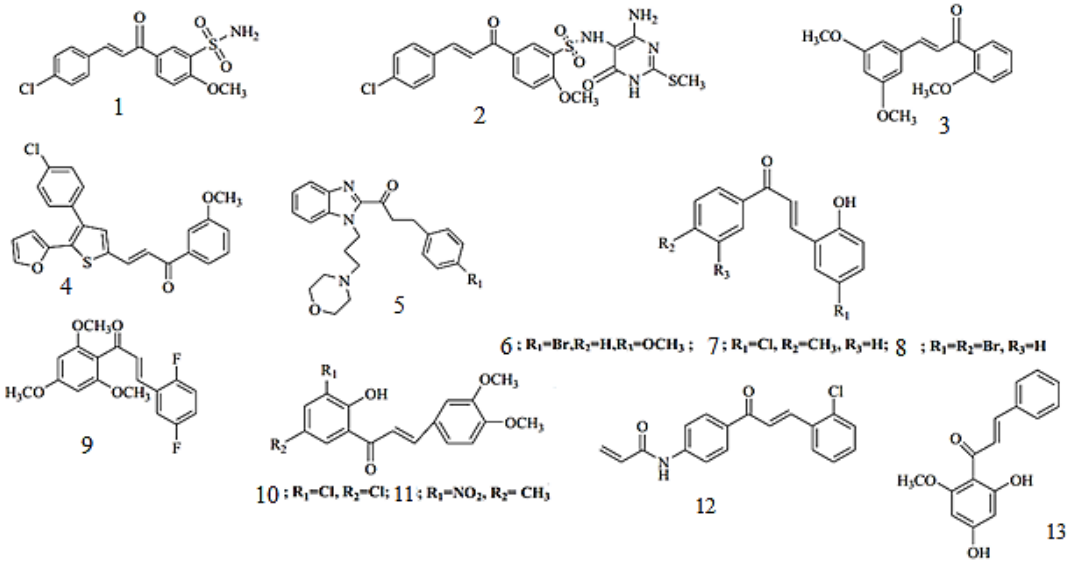
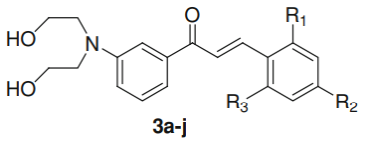


Fig. 6: The chalcone hybrids' structures were evaluated for their potential as anticancer drugs.

1-4 Antimicrobial activity

Novel 3-[N, N-Bis(2-hydroxyethyl)-amino]-chalcone compounds 3a-j were synthesised and tested in vitro for antibacterial effects on Gram-positive bacteria

such as S. aureus as well as B. subtilis, Gram-negative microbes P. aeruginosa, E. coli, and S. typhi, and antifungal effects against C. albicans. Table 1 displays preliminary biological screening findings for all newly synthesised chalcones against the microorganisms indicated above. Except for 3b, 3c, 3h, and 3i, the majority of chalcones had moderate antibacterial activity against Gram-positive bacteria (S. aureus and B. subtilis) and Gram-negative pathogens (P. aeruginosa, S. typhi, and E. coli). Compounds 3d and 3e demonstrated no activity against B. subtilis. Furthermore, 3e showed no activity against E. coli or P. aeruginosa. Surprisingly, all of the chalcones had moderate to good antifungal activity (C. albicans). Compound 3f, which contains 2-F in the B ring, was extremely effective against C. albicans and S. typhi, with MIC values of 32 and 64 µg/mL, respectively. This chemical is also capable of blocking the growth of other microbes. Compounds 3g and 3j, which contained 4-F and 2-SO3H in the B ring, demonstrated good antifungal activity against C. albicans with a MIC value of 32 µg/mL, while compounds 3e and 3d had reduced effectiveness against all of the tested microorganisms. A compound with no B-ring substituents, compound 3a, showed moderate to strong antibacterial and effective antifungal properties[27]



3a-j

3a: $R_1 = R_2 = R_3 = H$ **3b:** $R_1 = R_3 = H$; $R_2 = Cl$ **3c:** $R_1 = R_2 = H$; $R_3 = Cl$

3d: $R_1 = R_2 = Cl$; $R_3 = H$ **3e:** $R_1 = R_3 = H$; $R_2 = Br$ **3f:** $R_1 = F$; $R_2 = R_3 = H$

3g: $R_1 = R_3 = H$; $R_2 = F$ **3h:** $R_1 = R_3 = H$; $R_2 = N(CH_3)_2$

3i: $R_1 = R_3 = H$; $R_2 = NO_2$ **3j :** $R_2 = R_3 = H$; $R_1 = SO_3H$

Fig.7: Chalcone compounds 3a-j

Table 2: Antimicrobial properties [a] of the recently produced chalcones [a] (Cchalcones= 25 mg/ml)

Compounds	Fungi	Gram-positive bacteria		Gram-negative bacteria		
	C. albicans	*B. subtilis*	*S. aureus*	*P. aeruginosa*	*S. typhi*	*E. coli*
3a	+++	++	++	++	++	++
3b	+	–	–	–	–	–
3c	+	++	–	–	–	–
3d	+++	–	++	++	++	–
3e	+	–	++	–	++	–
3f	+++	++	++	++	++	++
3g	+++	++	++	++	++	++
3h	+	–	–	–	–	–
3i	+	–	–	–	–	–
3j	+++	++	++	++	+ +	++

Values were averages from duplicate experiments. [a]Plate-hole diffusion experiments were used to evaluate activity [a], with values representing the diameter of growth inhibition zones around the holes.

The measurement of the inhibition zones

+++ >10 mm, ++ 8–10 mm, + 6–8 mm, – <6 mm

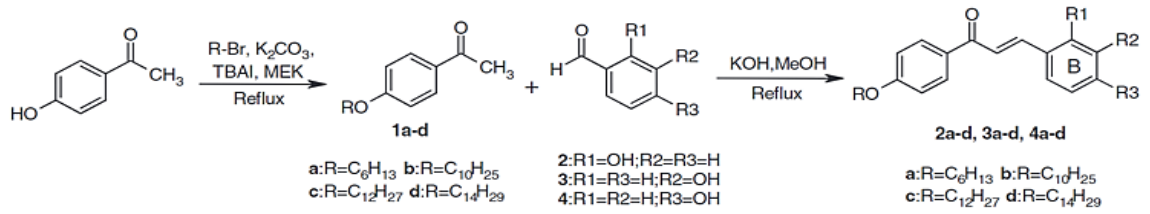
Table 3: Minimum inhibitory concentration (MIC) values for the antibacterial activity of the investigated substances

Compounds	MIC(ug mL^{-1})					
	Fungi	Gram-positive bacteria		Gram- negative bacteria		
	C. albicans	*S. aureus*	*B. subtilis*	*P. aeruginosa*	*S. typhi*	*E. coli*
3a	32	64	128	128	64	128
3d	128	128	Nt[a]	>128	128	Nt
3e	128	128	Nt	Nt	128	Nt
3f	32	128	128	128	64	128
3g	32	128	128	128	128	>128
3j	32	128	128	128	128	>128
Ciprofloxacin[b]	2.00	0.25	0.125	2.00	16	0.125

The minimal inhibitory concentrations of the evaluated substances were determined using the broth tube method; the values represent the average of duplicate experiments.

[a] NT was not subjected to testing. [b] Ciprofloxacin was utilised as a control

A separate study conducted antimicrobial tests on chalcone derivatives containing hydroxyl groups in ortho, meta, or para positions, with varying lengths of alkyl groups, against wild-type Escherichia coli American Type Culture Collection 8739 to assess the influence of the hydroxyl and alkyl groups in the synthesized chalcones. All synthesised compounds exhibited significant antibacterial activity. The optimal inhibition was ascertained by the placement of the hydroxyl group and the length of the alkyl chains. The presence of hydroxyl groups at the meta position of C6 alkyl chains yielded the highest antibacterial activity. The presence of alkyl chains, alongside hydroxyl groups, enhanced antibacterial activity, exhibiting a concentration-dependent inhibitory effect. Nonetheless, the inhibitory activity diminished with increasing chain length.[28]



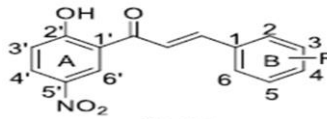
Scheme 1: Synthesis of chalcone compounds

Table 4: The MIC for chemicals 2a–d, 3a–d, and 4a–d.

Compound	MIC (ppm)	Compound	MIC (ppm)	Compound	MIC (ppm)
2a	109.8	**3a**	104.0	**4a**	111.9
2b	126.0	**3b**	129.8	**4b**	138.9
2c	132.1	**3c**	131.5	**4c**	143.3
2d	152.3	**3d**	156.5	**4d**	163.8

The escalating threat of drug-resistant microorganisms underscores the urgent necessity for novel antimicrobial agents. In response, considerable scientific effort has been directed toward developing innovative ideas and solutions to address this challenge. Chalcones, noted for their extensive biological activity, have become compelling candidates for combating drug resistance. The synthesis of a series of 2′-Hydroxychalcones (5a, 5b, 5c, and 5d), including diverse electron-withdrawing and electron-donating groups, was achieved using Claisen-Schmidt condensation. The analysis of the synthesised compounds revealed their significant potential as

antibacterial and antibiofilm agents. Compounds 5a and 5d exhibited significant antibacterial efficacy against multidrug-resistant bacteria, including E. coli, P. aeruginosa, K. pneumoniae, and S. aureus, surpassing the reference drug Ciprofloxacin (30 µg/mL) and other synthetic agents. Compound 5d exhibited a notable 19.5 mm inhibitory zone against K. pneumoniae. Compared to Ciprofloxacin (30 µg/mL), 5a (30 µg) and 5d (50 µg) demonstrated significant biofilm suppression efficacy ($P < 0.05$). The synthesised chalcones 5a-5d were subjected to docking using PachDock molecular docking software to assess their inhibitory potential on Glucosamine-6-phosphate (GlcN-6-P) synthase. The findings indicated that ligand 5a had a strong binding affinity for the target, achieving a score of 4238 and an ACE value of -160.89 kcal/mol, signifying antibacterial efficacy. These findings underscore the potential of chalcones, particularly 5a and 5d, as promising candidates for the formulation of innovative antimicrobial agents aimed at combating drug-resistant bacteria and biofilm formation [29].



5a-5d
(yield= 61-72%)

(5a), R= 4-F
(5b), R= 4-Cl
(5c), R= 4-Br
(5d), R= 4-OCH$_3$

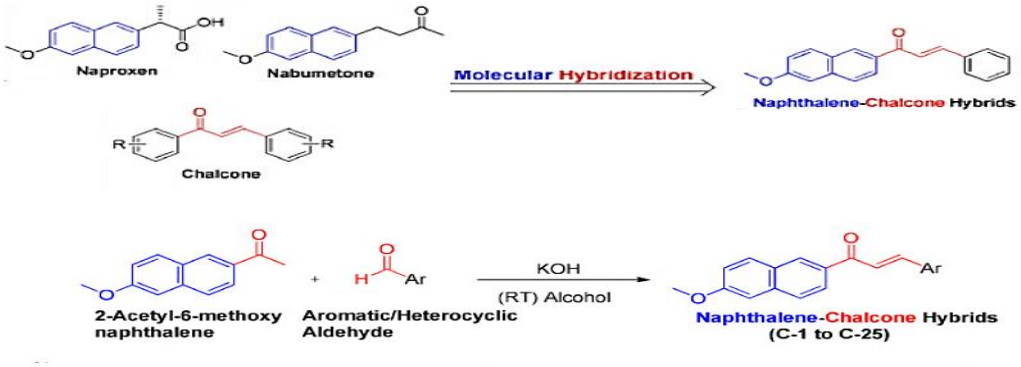
Table 5: Antimicrobial activity of products (5a-5d).

Sr. No.	Conc.	*E. Coli*	*P. aeruginosa*	*S. Aureus*	*K. pneumoniae*	Substituent Properties
	µg/mL	Diameter of zone of inhibition in (mm)				
5a	30	15	16	12	13	**A Ring:** Electron-donating and withdrawing group
	50	21	28	29	21	**B ring:** Electron withdrawing
5b	30	=	=	=	-	**A Ring:** Electron-donating and withdrawing group
	50	16	17	23	12	**B ring:** Electron withdrawing
5c	30	=	-	=	=	**A Ring:** Electron-donating and withdrawing group
	50	=	=	=	=	**B ring:** Electron withdrawing
5d	30	13	14	10	12	**A Ring:** Electron-donating and withdrawing group
	50	22	29	28	19.5	**B ring:** Electron donating group
Cipro.	30	21	28	28	20	

1-5 Anti-inflammatory activity

Antiviral, antibacterial, antimalarial, antitumor, antifungal, and anticancer activities are only a few of the many biological effects observed in chalcone compounds. The

anti-inflammatory effects in vivo of naphthalene-chalcone hybrids C1–C25 that were previously synthesised from 2-Acetyl-6-Methoxy Naphthalene. We used established spectroscopic techniques to characterise all synthesised chalcones (C1-C25) and assessed them for in vivo anti-inflammatory activities. In-silico docking methods were used to target COX-1 (PDB ID: 1EQH) and COX-2 (PDB ID: 1PXX) proteins using the 'Molegro Virtual Docker' docking tool. Molecular docking studies on chalcones (C1–C25) showed that compound C-24 outperformed the standard flurbiprofen (-115.259 kcal/mol) on the COX-1 target, with a docking score of -117.495 kcal/mol. By using 'QikProp, 2022' to forecast theoretical ADME, we were able to gain a better understanding of pharmacokinetics and found that all substances exhibited satisfactory pharmacokinetic properties. [30].



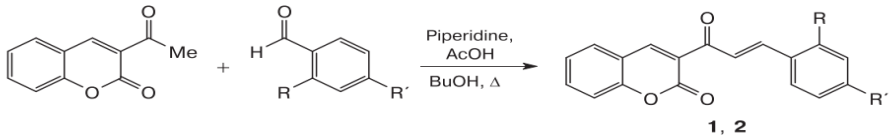
Ar = (**C-1**) 4-methoxyphenyl ; 3,4-dimethoxyphenyl (**C-2**); 3,4,5-trimethoxyphenyl (**C-3**); 2,4,5-trimethoxyphenyl (**C-4**); 4-methylphenyl (**C-5**); 2-hydroxyphenyl (**C-6**); 3-hydroxyphenyl (**C-7**); 4-hydroxyphenyl (**C-8**); 3-nitrophenyl (**C-9**); 4-nitrophenyl (**C-10**); 2-nitrophenyl (**C-11**); 4-pyridinyl (**C-12**); 3-pyridinyl (**C-13**); 2-pyridinyl (**C-14**); 9-anthracenyl (**C-15**); 2-phenyl (**C-16**); 2-chlorophenyl (**C-17**); 4-chlorophenyl (**C-18**); 2,4-dichlorophenyl (**C-19**); 4-fluorophenyl (**C-20**); 2-fluorophenyl (**C-21**); 2,4-difluorophenyl (**C-22**); 4-bromophenyl (**C-23**); 3-bromophenyl (**C-24**); 4-dimethylaminophenyl (**C-25**).

Scheme 2. Synthesis of Naphthalene-Chalcones Hybrids

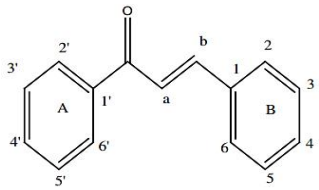
1-6- Antioxidant activity

Novel hydroxy derivatives of chalcones were synthesized, and antioxidant activity was tested. The in silico technique anticipated that these compounds would have strong antioxidant capabilities. Compounds 1–3 demonstrated extended antioxidant activity in vitro against peroxide oxidation of oleic acid and lipids from tilapia liver homogenate. The chalcone dihydroxy derivative showed the highest efficiency in oleic acid oxidation, possibly due to the presence of two hydroxy groups and a chromene moiety. Compound 3 demonstrated the highest efficiency in liver lipid oxidation, likely due to the sterically hindered phenolic moiety, which improves structural stability. In vitro experiments validated the antioxidant and radical scavenging properties predicted in silico for novel hydroxy derivatives of chalcones. The acquired results show the necessity for further in vitro and in vivo

research to identify the most effective antioxidants from the produced hydroxy derivatives of chalcones for practical applications[31] .

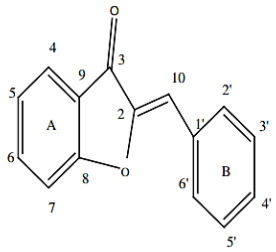


Chalcones and aurones exhibit significant antioxidant effects. They are recognised for inhibiting the tyrosinase enzyme, which plays a role in melanin synthesis. A variety of substituted chalcones and aurones have been synthesised and assessed for their antioxidant capabilities. The docking analysis of this series of compounds was conducted on the crystal structure of Bacillus megaterium tyrosinase, utilising VlifeMDS 3.0 software. The antioxidant activity data derived from four methodologies—DPPH free radical scavenging assay, iron chelating assay, reducing power assay, and hydrogen peroxide scavenging assay—indicate that the activity is enhanced by the presence of a dimethylamino group at position 4/4′ of ring B, as demonstrated by the notable activities of SB7 and SB8 in the context of chalcones and aurones, respectively. The diminished activity of SB4 and SB5 in DPPH scavenging and reducing power assays may be ascribed to the presence of a chloro group on the B-ring. Moreover, both chalcones and aurones are enhanced by the presence of a hydroxyl group on the A-ring, preferably at position 5/5′.[32] .



1,3-diaryl-2-propen-1-ones (Chalcones)

S no.	Compounds	R_1	R_2	R_3	R_4	R_5
SB1	2′,5′-Dihydroxy-3,4-dimethoxy chalcone	H	OH	H	OCH_3	OCH_3
SB2	2′,4′-Dihydroxy-4-dimethylamino chalcone	OH	H	H	H	$N(CH_3)_2$
SB5	2′,4′-Dihydroxy-4-chloro chalcone	OH	H	H	H	Cl
SB7	2′,5′-Dihydroxy-4-dimethylamino chalcone	H	OH	H	H	$N(CH_3)_2$
SB10	2′,4′-Dihydroxy-3,4-dimethoxy chalcone	OH	H	H	OCH_3	OCH_3



2-benzylidenebenzofuran-3-(2H)-ones

(Aurones)

S no.	Compounds	R_1	R_2	R_3	R_4	R_5
SB3	6-Hydroxy-4′-dimethylamino aurone	OH	H	H	H	$N(CH_3)_2$
SB4	6-Hydroxy-4′-chloro aurone	OH	H	H	H	Cl
SB6	5-Hydroxy-3′,4′-dimethoxy aurone	H	OH	H	OCH_3	OCH_3
SB8	5-Hydroxy-4′-dimethylamino aurone	H	OH	H	H	$N(CH_3)_2$
SB9	6-Hydroxy-3′,4′-dimethoxy aurone	OH	H	H	OCH_3	OCH_3

Table 6: Antioxidant activity of aurones and substituted chalcone derivatives

Compound no.	DPPH scavenging ability IC_{50} µg/ml ± SD	H_2O_2 scavenging ability IC_{50} µg/ml ± SD	Iron chelating activity assay IC_{50} µg/ml ± SD	Reducing power IC_{50} µg/ml ± SD
SB1	132.22 ± 0.7	89.59 ± 1.8	159.22 ± 1.02	111.79 ± 0.69
SB2	65.8 ± 0.7	135.88 ± 0.53	140.16 ± 1.08	53.6 ± 1.1
SB3	109.92 ± 1.02	193.91 ± 0.36	179.33 ± 0.31	70.1 ± 2.2
SB4	266.12 ± 0.49	178.13 ± 0.36	179.18 ± 0.74	188.31 ± 0.31
SB5	264.95 ± 1.6	129.02 ± 0.85	159.97 ± 0.29	155.87 ± 0.68
SB6	222.19 ± 0.7	206.57 ± 0.19	185.05 ± 1.2	151.43 ± 0.25
SB7	24.32 ± 0.87	153.85 ± 2.1	90.81 ± 0.86	47.79 ± 1.3
SB8	243 ± 0.13	174.07 ± 1.9	149.98 ± 0.51	64.16 ± 1.2
SB9	173.29 ± 0.94	248.16 ± 0.76	213.83 ± 0.68	168.23 ± 0.83
SB10	35.2 ± 1.5	70.1 ± 0.92	166.73 ± 2.5	134.45 ± 0.34
Ascorbic acid	98.77 ± 0.53	445.92 ± 1.4	126.12 ± 0.5	53.24 ± 0.72

Table 7: Dock score for aurone and substituted chalcone derivatives

Compound no.	Compounds	Dock score (kcal/mol)
SB1	2′,5′-Dihydroxy-3,4-dimethoxy chalcone	−5.35
SB2	2′,4′-Dihydroxy-4-dimethylamino chalcone	−25.62
SB3	6-Hydroxy-4′-dimethylamino aurone	−42.23
SB4	6-Hydroxy-4′-chloro aurone	−40.89
SB5	2′,4′-Dihydroxy-4-chloro chalcone	−40.19
SB6	5-Hydroxy-3′,4′-dimethoxy aurone	−34.43
SB7	2′,5′-Dihydroxy-4-dimethylamino chalcone	−31.95
SB8	5-Hydroxy-4′-dimethylamino aurone	−91.39
SB9	6-Hydroxy-3′,4′-dimethoxy aurone	−31.82
SB10	2′,4′-Dihydroxy-3,4-dimethoxy chalcone	−16.91
Standard	NDGA (Nordihydroguaiaretic acid)	−41.88

1-7-Antiulcer activity

The antiulcer efficacy of novel quinoline-chalcone hybrids was investigated. Eight compounds were identified as efficacious in ulcer models in Sprague Dawley rats. The antisecretory and cytoprotective properties of these hybrids were examined to elucidate their mode of action. The active hybrids increased mucin levels and inhibited erosions in a pyloric ligated ulcer model. Furthermore, they markedly increased gastric PGE2 concentrations in an aspirin-induced ulcer model. Supplementary assessments, encompassing in vitro metabolic stability and in vivo pharmacokinetics, identified compound 6 as an orally bioactive and safe candidate, warranting further investigation for it development as an antiulcer drug.[33]

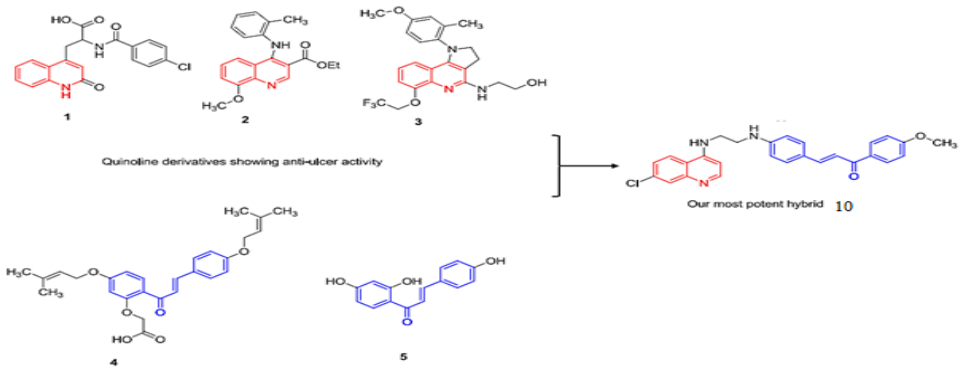
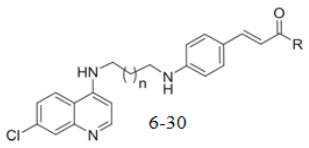
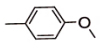
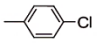
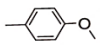
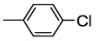
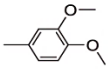
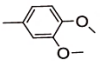
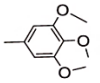


Figure 8: Shows the chemical structures of quinoline and chalcones with substantial antiulcer action.

Table 8:Substituted quinoline-chalcone hybrids.



Comp.no	n	R	Comp.no	n	R	Comp.no	n	R
6	0		15	1		24	1	
7	1		16	0		25	0	
8	0		17	1		26	1	
9	1		18	1		27	0	
10	0		19	0		28	1	
11	1		20	1		29	0	
12	0		21	0		30	1	
13	1		22	1				
14	0		23	0				

As shown in Table 9, the ulcer index (UI) of rats with cold restraint-induced stomach ulcers was affected by hybrid compounds as well as the reference drug omeprazole. One-way ANOVA and Dunnett's Multiple Comparison Test were used to conduct the statistical study. Out of six participants in each group, *P < 0.05 and **P < 0.01 were determined in comparison to the control.

Table 9.

CRU Model					
Comp. no	Ulcer index (UI)			Mean ulcer score	% Protection index (PI)
	(12.5 mg/ kg. p.o.)	(25 mg/ kg. p.o.)	(50 mg/ kg. p.o.)	(25 mg/kg. p.o.)	(25 mg/kg. p.o.)
Control	12	12	12	20 ± 1.44	0
6	12	9	9	15 ± 2.51	25
7	9	6	4.5	10 ± 3.65	50*
8	12	12	12	20 ± 1.60	0
9	12	5.7	9	9.6 ± 2.50	52*
10	9	6	4.5	10 ± 3.05	50*
11	12	12	12	20 ± 2.70	0
12	12	12	12	20 ± 1.11	0
13	12	12	12	20 ± 2.09	0
14	12	12	12	20 ± 2.31	0
15	9	3	3	05 ± 4.91	75**
16	12	9	9	15 ± 2.50	25
17	12	6	12	10 ± 2.51	50*
18	12	9	9	15 ± 3.50	25
19	12	6	9	10 ± 4.66	50*
20	12	9	12	15 ± 3.01	25
21	12	6	6	10 ± 3.46	50*
22	9	9	9	15 ± 2.50	25
23	9	6	6	10 ± 3.66	50*
24	12	12	12	20 ± 2.51	0
25	12	12	12	20 ± 1.50	0
26	9	6	6	10 ± 1.44	50*
27	12	9	9	15 ± 2.00	25
Omeprazole (10 mg/kg, p.o)	12	9	9	15 ± 2.66	25
		2.7		4.5 ± 2.50	77.5**

1-8-Neuroprotective activity

Thiamine hydrochloride (VB1) was used for the first time as a catalyst in the metal-free Claisen-Schmidt condensation synthesis of chalcones. This ecologically friendly technique offers various advantages, including a broad range of functional

group tolerance, a high product yield, and the catalyst's recoverability. Furthermore, this novel process allows for the production of the pharmaceutically significant compound 2′,4′-dihydroxy-6′-methoxy-3′,5′-dimethylchalcone (3f) and its derivatives. Additionally, 3f and its derivatives underwent in vitro testing to evaluate their potential neuroprotective efficacy against apoptosis induced by oxygen-glucose deprivation/reoxygenation (OGD/R) in SH-SY5Y cell lines. The majority of the compounds exhibited neuroprotective effects, with one of the synthesised chalcones (3s), incorporating a prenyl moiety, demonstrating the highest efficacy by reducing the expression levels of cleaved caspase-3, cleaved caspase-9, Bax, and p53 proteins.[34].

Table 10: VB1[a] catalyzes the production of chalcones

Entry	Product	R^1	R^2	Time (h)	Yield [b] (%)
1 *	3a *	H	C_6H_5	10	82
2 *	3b *	4-Cl	C_6H_5	10	81
3 *	3c *	2-OH-4,5-(C_4H_8)	2-Furyl	14	71
4 *	3d *	2-OH-4,5-(C_4H_8)	2-Thienyl	14	73 [d]
5 *	3e *	2-OH-4,5-(C_4H_8)	3-Pyridyl	10	79
6 *	3f *	2,4-$(OH)_2$-6-OCH_3 -3,5-$(CH_3)_2$	C_6H_5	10	82
7 *	3g *	2,4-$(OH)_2$-6-OCH_3	C_6H_5	10	80
8 *	3h *	2,4-$(OH)_2$-6-OCH_3	3-$OCH_3C_6H_4$	10	83
9 *	3i *	2,4-$(OH)_2$-6-OCH_3	4-$OCH_3C_6H_4$	10	85
10 *	3j *	2,4-$(OH)_2$-6-OCH_3	3-OHC_6H_4	10	82
11 *	3k *	2,4-$(OH)_2$-6-OCH_3	4-OHC_6H_4	10	82
12 *	3l *	2,4-$(OH)_2$-6-OCH_3	3-ClC_6H_4	13	76
13 *	3m *	2,4-$(OH)_2$-6-OCH_3	4-ClC_6H_4	13	77
14 *	3n *	2-OH-4,6-$(OCH_3)_2$	4-OHC_6H_4	10	83
15 *	3o *	2-OH-4,6-$(OCH_3)_2$	3-$NO_2C_6H_4$	13	79
16 *	3p *	2-OH-4,6-$(OCH_3)_2$	4-$OCH_3C_6H_4$	10	83
17 *	3q *	2-OH-3,4,5-$(OCH_3)_3$	3,4-$(OCH_3)_2C_6H_3$	10	82
18 *	3r *	3,4,5-$(OCH_3)_3$	3,4-$(OCH_3)_2C_6H_3$	10	87
19 *	3s *	2-OH-4,6-$(OCH_3)_2$-3-$CH_2CHC(CH_3)_2$	3,4-(Methylenedioxy)C_6H_3	10	85
20 *	3t *	2-OH- 4,6-$(OCH_3)_2$-3-$CH_2CHC(CH_3)_2$	3,4,5-$(OCH_3)_3C_6H_2$	10	83

a) At reflux temperature, combine 1.0 mmol of 1, 2.0 mmol of 2, 2.5 mol% VB1, and 4.0 mL of EtOH-H2O (v/v = 1:1). b) Relative yields. c) The initial components did not undergo a complete reaction; 0.041 mmol of the initial components wererecovered. d) The initial material's yield after recovery

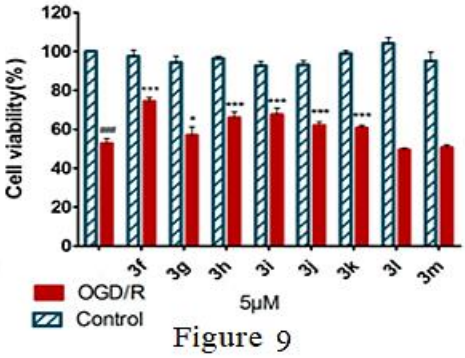


Figure 9

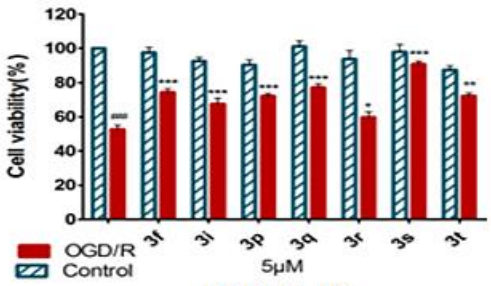


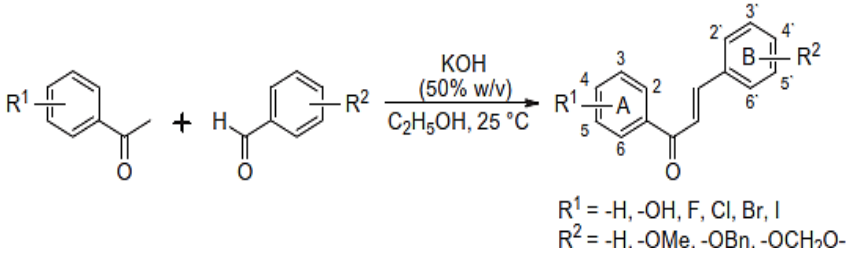
Figure 10

Figure 9: Effect of 3f-m on human neuronal SH-SY5Y cell viability. The cells were pretreated with varied dosages of 3f-m for 24 hours before OGD/R for 5.5 hours and reoxygenation for 4 hours. The data are presented as means ± SD (n = 3). ## $p < 0.001$ vs. control; * $p < 0.05$; *** 0.001 vs. OGD/R group.

Figure10: shows how derivatives 3p-t affect human neuronal SH-SY5Y cell survival. The cells were pretreated with various concentrations of 3p-t derivatives for 24 hours before OGD/R for 5.5 hours and reoxygenation for 4 hours. The data are presented as means ± SD (n = 3). *** $p < 0.001$ vs. OGD/R group; ### $p < 0.001$ vs. control group**.**

1-9- Anti-diabetic activity

The study investigated whether chalcones with electron-donating or electron-withdrawing substitutions had higher glucose absorption. Additionally, chalcone derivatives were synthesised in a single step with high purity and yield. The chalcones that had an iodo substitution at position 3 on the A-ring exhibited a similar level of activity (approximately 238 mg/dl). On the other hand, the chalcones that had chloro, bromo, iodo, and hydroxy substitutions at position 2 on the A-ring demonstrated the highest level of activity with glucose medium concentration (ranging from 210 to 236 mg/dl). This was in contrast to pioglitazone and rosiglitazone, which had respective concentrations of 230 and 263 mg/dl. [35]



	A-Ring				B-Ring			Glucose (mg/dl)[a]		A-Ring				B-Ring			Glucose (mg/dl)[a]
	2	3	4	5	3′	4′	5′			2	3	4	5	3′	4′	5′	
1a	H	H	H	H	H	H	H	253 ± 9.9	**3e**	H	H	F	H	OCH_3	H	H	285 ± 1.6
1b	H	H	H	H	H	OCH_3	H	261 ± 3.2	**4a**	Cl	H	H	H	H	OCH_3	H	234 ± 24.4
1c	H	H	H	H	OCH_3	H	H	261 ± 7.2	**4b**	H	Cl	H	H	H	H	H	291 ± 9.2
1d	H	H	H	H	OBn	H	H	285 ± 8.2	**4c**	H	Cl	H	H	H	OCH_3	H	287 ± 13.4
1e	H	H	H	H	H	OBn	H	274 ± 13.0	**4d**	H	Cl	H	H	OCH_3	H	H	255 ± 27.1
1f	H	H	H	H	H	OH	H	263 ± 5.6	**4e**	H	H	Cl	H	H	H	H	295 ± 8.8
1g	H	H	H	H	H	$-OCH_2O-$		252 ± 18.1	**4f**	H	H	Cl	H	H	OCH_3	H	293 ± 7.8
1h	OH	H	H	H	H	H	H	269 ± 11.0	**4g**	H	H	Cl	H	OCH_3	H	H	272 ± 22.4
1i	OH	H	H	H	H	OCH_3	H	283 ± 21.4	**5a**	Br	H	H	H	H	H	H	249 ± 20.8
1j	OH	H	H	H	OCH_3	H	H	264 ± 7.8	**5b**	Br	H	H	H	H	OCH_3	H	230 ± 8.7
1k	OH	H	H	H	OBn	H	H	256 ± 13.1	**5c**	Br	H	H	H	OCH_3	H	H	249 ± 5.2
1l	OH	H	H	H	H	OBn	H	260 ± 3.8	**5d**	H	Br	H	H	H	H	H	299 ± 7.3
1m	OH	H	H	H	H	OH	H	267 ± 3.4	**5e**	H	Br	H	H	H	OCH_3	H	248 ± 8.0
1n	OH	H	H	H	H	$-OCH_2O-$		279 ± 7.6	**5f**	H	Br	H	H	OCH_3	H	H	262 ± 2.2
1o	OH	H	OH	H	H	H	H	273 ± 2.9	**5g**	H	H	Br	H	H	H	H	295 ± 5.8
1p	OH	H	OH	H	H	OCH_3	H	248 ± 0.4	**5h**	H	H	Br	H	H	OCH_3	H	261 ± 12.7
1q	OH	H	OH	H	OCH_3	H	H	274 ± 12.1	**5i**	H	H	Br	H	OCH_3	H	H	257 ± 10.0
1r	OH	H	OH	H	OBn	H	H	283 ± 2.6	**6a**	I	H	H	H	H	H	H	223 ± 13.8
1s	OH	H	OH	H	H	OBn	H	249 ± 12.2	**6b**	I	H	H	H	H	OCH_3	H	210 ± 3.7
2a	OH	H	H	F	OCH_3	H	H	297 ± 9.3	**6c**	I	H	H	H	OCH_3	H	H	210 ± 2.0
2b	OH	H	H	Cl	H	H	H	236 ± 17.5	**6d**	I	H	H	H	H	OBn	H	249 ± 3.6
2c	OH	H	H	Cl	H	OCH_3	H	282 ± 16.4	**6e**	H	I	H	H	OBn	H	H	238 ± 1.1
2d	OH	H	H	Br	OCH_3	H	H	266 ± 23.3	**6f**	H	I	H	H	H	H	H	294 ± 7.3
2e	OH	H	H	Br	H	H	H	253 ± 7.8	**6g**	H	I	H	H	H	OCH_3	H	233 ± 3.5
2f	H	H	H	Br	H	OCH_3	H	254 ± 17.6	**6h**	H	I	H	H	OCH_3	H	H	246 ± 11.3
2g	OH	H	H	Br	OCH_3	H	H	260 ± 3.3	**6i**	H	H	I	H	H	H	H	292 ± 5.3
2h	OH	H	H	Br	H	OBn	H	256 ± 1.3	**6j**	H	H	I	H	H	OCH_3	H	299 ± 3.8
2i	OH	H	H	Br	OBn	H	H	252 ± 0.1	**6k**	H	H	I	H	OCH_3	H	H	274 ± 22.5
3a	F	H	H	H	H	OCH_3	H	259 ± .3	Control								310 ± 4.0
3b	F	H	H	H	OCH_3	H	H	285 ± 4.4	Insulin (3.2×10^{-7} M)								294 ± 6.3
3c	H	F	H	H	H	OCH_3	H	298 ± 15.5	Rosiglitazone[b]								263 ± 23.9
3d	H	F	H	H	OCH_3	H	H	282 ± 10.1	Pioglitazone[b]								230 ± 13.5

The data are N = 3 determinations' means ± SD.

Rosiglitazone and pioglitazone, two chalcone derivatives, were used at identical 30 mg/ml concentrations.

In another study, the antidiabetic potential of chalcones (designated JA1, JA2, and JA3) was assessed against alpha-glucosidase. The synthetic compounds' antidiabetic activity was assessed in a rat model using oral administration at dosages of 10 and 20 mg/kg body weight. Using commercially available kits, the levels of HDL, LDL, serum creatinine, alanine phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, total cholesterol, and triglycerides were measured. The molecule with the best inhibitory capability against alpha-glucosidase was JA3. When compared to acarbose on day 28, compound JA3 at the tested doses restored the blood glucose level in diabetic rats (caused by STZ) to nearly normal levels (126.88 and 119.13 mg/dl at 10 and 20 mg/kg body weight). When compared to the diabetic control group, substance JA3 normalized the blood biochemical markers in diabetic rats. The findings suggest that JA3 is a promising therapeutic candidate for antidiabetic purposes [36].

Table 11: Inhibition of alpha-glucosidase activity.

Sample	Glucosidase IC_{50} (µg/mL)
JA1	85.11±1.29
JA2	97.24±1.48
JA3	63.04±1.17
Acarbose	60.38±1.22

Indicated by mean ± SEM, n = 3.

Table 12: grams per deciliter of blood glucose.

Groups/dose (mg/kg)		Blood glucose level (mg/dL)				
		0min	30 min	60 min	90 min	120 min
Control		108.09 ± 4.30	181.35 ± 4.39$^{!!!}$	167.80 ± 4.21$^{!!!}$	143.21 ± 4.38$^{!!!}$	125.83 ± 3.98$^{!!!}$
JA1	**10**	106.21 ± 4.61	124.71 ± 4.04*	120.18 ± 4.71*	117.21 ± 4.91*	115.18 ± 4.72
	20	104.10 ± 4.82	118.19 ± 4.61**	115.41 ± 4.69**	115.30 ± 4.70**	113.31 ± 4.66
JA2	**10**	106.41 ± 4.79	131.29 ± 4.71*	126.09 ± 4.67*	122.91 ± 4.61*	120.67 ± 4.57
	20	105.19 ± 4.68	127.37 ± 4.87*	124.19 ± 4.70*	121.08 ± 4.77*	118.03 ± 4.81
JA3	**10**	108.11 ± 4.77	120.39 ± 4.67*	118.20 ± 4.61**	114.91 ± 4.91**	112.91 ± 4.71
	20	106.76 ± 4.82	116.98 ± 4.71**	114.21 ± 4.66**	113.21 ± 4.42**	109.70 ± 4.86*
Standard (Glibenclamide)	**0.5**	107.21 ± 4.76	111.51 ± 4.86**	109.76 ± 4.97***	107.31 ± 4.61***	105.12 ± 4.70*

All values are expressed as mean ± SEM, with n = 8. P values were determined through a one-way ANOVA followed by Dunnett's post hoc multiple comparison test to assess differences between the diabetic control group and the control group. A one-way ANOVA and Dunnett comparison were employed to analyse the diabetes control group against test samples and glibenclamide-treated groups, with significance levels set at *P<0.05, **P<0.01, and ***P<0.001.

Table 13: Blood glucose level (mg/dL) in rats with STZ-induced diabetes.

Groups/dose (mg/kg)		Blood glucose level (mg/dL)				
		Day 1	Day 7	Day 14	Day 21	Day 28
Normal control		110.65 ± 4.81	108.41 ± 4.66	110.08 ± 4.80	103.87 ± 4.81	105.62 ± 4.96
Diabetic control		428.22 ± 4.81$^{!!!}$	432.71 ± 4.96$^{!!!}$	443.20 ± 5.91$^{!!!}$	438.81 ± 4.94$^{!!!}$	428.67 ± 4.90$^{!!!}$
JA1	**10**	426.41 ± 4.69	314.71 ± 4.79*	235.69 ± 4.80*	181.12 ± 4.82*	152.67 ± 4.76*
	20	431.70 ± 5.10	301.39 ± 4.93*	219.41 ± 4.71*	159.03 ± 4.71**	134.89 ± 4.63**
JA2	**10**	433.91 ± 4.93	323.19 ± 4.68*	241.70 ± 4.84*	188.11 ± 4.81*	164.31 ± 4.77*
	20	428.22 ± 4.77	312.90 ± 4.71	229.91 ± 4.78*	162.40 ± 4.73**	142.60 ± 4.68**
JA3	**10**	437.41 ± 4.80	279.81 ± 4.67*	206.65 ± 4.89**	151.13 ± 4.80**	126.88 ± 4.90***
	20	431.62 ± 4.87	266.70 ± 4.80**	184.12 ± 4.83***	138.56 ± 4.69***	119.13 ± 4.71***
Standard (Glibenclamide)	**0.5**	434.88 ± 5.01	231.71 ± 4.71***	155.46 ± 4.71***	122.14 ± 4.61***	105.83 ± 4.67***

All values are expressed using Mean ± SEM, n = 8. A one-way ANOVA and Dunnett's post hoc multiple comparison test are used to compare the diabetic control group to the control group ($P < 0.001$). Diabetic control group vs test samples and glibenclamide-treated groups were compared using one-way ANOVA and Dunnett comparison (P-values < 0.05, **P-values < 0.01)

The anti-diabetic properties of chalcone and murucanine are widely recognized. The current study aims to rationally integrate the two scaffolds to create a hybrid molecule that will exhibit comparable or more pronounced activity compared to the marketed product and cumulatively produce higher pharmacological activity than its parents. Every one of the new Murrayanine-chalcone hybrids showed activity between 6.27 and 30.87%. The blood glucose level was effectively lowered (>18%) by molecules 3a, 3f, 3g, and 3h. The best anti-hyperglycemic effect was shown by chalcone 3g, which has two lipophilic substituents at meta locations in the B-ring (30.87% decrease in glucose level). Electrophilic halogen substituents at the para and meta locations showed better biological activity than those at the ortho position. However, this investigation does not allow for the definition of a particularly clear structure-activity-relationship (SAR). By modifying different anti-diabetic targets, the study created new opportunities for the use of natural scaffolds in hybrid form as anti-diabetic medicines[37]

3a-h

Table 14: Murrayanine-chalcone hybrids' (3a–h) in vivo anti-hyperglycemic potential in STZ rat models

Compound	R	% anti-hyperglycemic activity
3a	2-F	19.34
3b	4-F	13.51
3c	2-I	6.27
3d	4-I	9.33
3e	4-Br	18.17
3f	2-CF_3	21.29
3g	3,5-CF_3	30.87
3h	2,4-Cl; 5-F	26.74
Std.	-	38.49

Glibenclamide, the standard medication, is used as the control; 1% gum acacia

1-10- Antituberculosis activities

Several flavonoids, chalcones, and chemicals with chalcone-like structures were tested for their inhibitory efficacy against Mycobacterium TB H37Rv. Eight of these compounds demonstrated antimicrobial activity of more than 90% at a concentration of 12.5 mg/mL. Inhibition was observed for the chalcones (1-(2-hydroxyphenyl)-3-(3-chlorophenyl)-2-propen-1-one (22) and 1-(2-hydroxyphenyl)-3-(3-iodophenyl)-2-propen-1-one (37) at 90% and 92%, respectively. Chalcone structure (a heterocyclic ring replaced with 2-propen-1-one) 1-(4-fluorophenyl)-3-(pyridin-3-yl)-2-propen-1-one (48), 1-(3-hydroxyphenyl)-3-(phenanthren-9-yl)-2-propen-1-one (49), 1-(pyridin-3-yl)-3-(phenanthen-9-yl)-2-propen-1-one (50) and 1-(furan-2-yl)-3-phenyl-2-propen-1-one exhibited 98, 97, 96 and 96% inhibition, respectively. The lowest values that inhibited 99% of the inoculum were found to be 20.3, 31.5, 48.3, >35.7, 6.8, and 19.2 for the inoculum samples from 22, 37, 48, 49, 50, and 51, respectively. An aromatic ring with a hydrophobic substituent and another aromatic ring with a hydrogen-bonding group gave the chalcones and compounds with a chalcone-like structure their improved anti-TB activity. Higher geometric limitations are associated with flavones and flavanones as compared to chalcones. One possible explanation for the lower activity of flavones compared to chalcones is that their terminal aromatic rings are not all aligned on the same plane.[38].

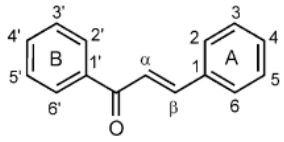
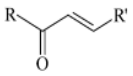


Table 15: Chalcones' anti-tuberculosis activity

Compd	B-ring 2′–	3′–	4′–	5′–	6′–	A-ring 2–	3–	4–	5–	Activity % inhibition at 12.5 mg/mL	MIC (μg/mL)
RMP											0.125–0.25
1	OH		OCH_3							78	[a]
2	OH				OCH_3			OCH_3		75	—
3	OH			Phenyl						68	—
4			NO_2					OCH_3		62	—
5	OH									61	—
6		OH					OCH_2	O		53	—
7	OH		OCH_3		OCH_3			OCH_3		40	—
8	OH					OCH_3				39	—
9	OH		OCH_3					OCH_3		32	—
10	OH						OH			18	—
11	OH						NH_2			11	—
12	OH			NH_2						6	—
13			NH_2							3	—
14	OH		EtO		EtO					0	—
15	OH		OCH_3		OH		OCH_3	OCH_3	OCH_3	0	—
16	OH			COOH				OCH_3		0	—
17	OH						$NHCOCH_3$			0	—
18		F						OCH_3		82	—
19	OH				F			OCH_3		66	—
20	OH		F					OCH_3		63	—
21	OH	F						OCH_3		45	—
22	OH						Cl			90	20.3
23	OH		Cl							89	—
24	OH			Cl						67	—
25	OH							Cl		67	—
26	OH		Cl					OCH_3		57	—
27	OH			Cl				OCH_3		20	—
28	OH					Br				83	—
29	OH	Br								79	—
30	OH							Br		70	—
31	OH			Br						68	—
32	OH		Br							57	—
33	OH		Br					OCH_3		25	—
34	OH			Br				OCH_3		23	—
35	OH		Br			NH_2				12	—
36	OH			Br		NH_2				8	—
37	OH						I			92	31.5
38		NH_2				I				88	—
39	OH			I						51	—
40	OH		OCH_3				I			47	—
41	OH					I				41	—
42	OH		I							21	—
43	OH							I		21	—
44	OH	I								0	—
45	OH			I				OCH_3		0	—
46	OH	I						OCH_3		0	—
47	OH			COOH			I			0	—

[a] 12.5 and unidentified.

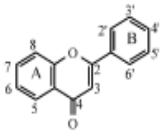
Table 16: Chalcone-like compounds' anti-tuberculosis activity



Compd	R	R′	Activity % inhibition at 12.5 μg/mL	MIC (μ/mL)
RMP				0.125–0.25
48	4-Fuorophenyl-	Pyridin-3-yl-	98	48.3
49	3-Hydroxyphenyl-	Phenanthren-9-yl-	97	31.5
50	Pyridin-3-yl-	Phenanthren-9-yl-	96	6.8
51	Furan-2-yl-	3-Phenyl-	96	19.2
52	Phenanthren-2-yl-	2-Aminopyridino-3-yl-	74	—[a]
53	3-Fluorenyl-	2-Aminopyridino-3-yl-	53	—
54	Pyridin-2-yl-	Pyridin-2-yl-	42	—
55	Naphthalen-1-yl-	Phenyl-	37	—
56	Pyridin-2-yl-	4-Dimethylaminophenyl-	16	—
57	4-Bromo-2-hydroxyphenyl-	Furan-2-yl-	17	—
58	Pyridin-4-yl-	Indol-2-yl-	12	—
59	2-Hydroxy-4-methoxyphenyl-	Furan-2-yl-	3	—
60	4-Aminophenyl-	2-Aminopyridin-3-yl-	7	—
61	Pyridin-4-yl-	4-Dimethylaminophenyl-	1	—
62	2-Hydroxy-5-methoxyphenyl-	Furan-2-yl-	0	—
63	4-Methoxyphenyl-	Pyridin-4-yl-	0	—
64	4-Methoxyphenyl-	Pyridin-3-yl-	0	—
65	2-Hydroxy-5-chlorophenyl-	2-Aminopyridin-3-yl-	0	—
66	4-Aminophenyl-	2-Aminopyridin-3-yl-	0	—
67	3-Hydroxynaphthalen-2-yl-	2-Aminopyridin-3-yl-	0	—
68	Furan-2-yl-	Pyridin-4-yl-	0	—
69	Pyridin-2-yl-	4-Methoxyphenyl-	0	—

[a] > 12.5 and not determined.

Table 17: Flavanones' anti-tuberculosis properties



Compd	3	5	6	7	8	3′	4′	5′	Activity% inhibition at 12.5 μg/mL
125		OCH_3			Br				87
126						Br			73
127	OH					Cl			63
128				Br					53
129				OCH_3			Cl		48
130			Cl						30
131			I						27
132	Br_2	OCH_3		OCH_3		OCH_3	OCH_3	OCH_3	16
133				I					9
134			Br						8
135				F					7
136		OCH_3		OCH_3		OCH_3	OCH_3	OCH_3	0
137			COOH				OCH_3		0
138			COOH						0
139				OCH_3		NO_2			0
140	Br_2								0
141				I			OCH_3		0
142	Br_2								0

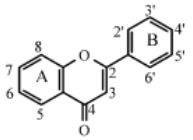


Table 18: Flavones' anti-tuberculosis properties

Compd	3	5	6	7	8	2′	3′	4′	Activity % inhibition at 12.5 μg/mL
70					Br				66
71					Cl				62
72	OH		I						64
73	OH						Br		60
74	OH			Cl					58
75	OH		Br						58
76	OH			Cl					52
77								I	51
78	OH			F				OCH_3	50
79	OAc			F				OCH_3	50
80	OH		Cl					OCH_3	48
81	OH							OCH_3	48
82	OCH_3		Br						44
83	OH				F				43
84	OH			I				OCH_3	43
85	OH								38
86								OCH_3	29
87	OH		F					OCH_3	29
88							NO_2	Cl	28
89	Br							OCH_3	28
90								Br	26
91	OH		Br					OCH_3	24
92						Br			23
93						I			22
94							I		22
95				I					20
96	Br			OCH_3				Cl	19
97								OH	18
98				F					15
99				Br					15
100			I					OCH_3	15
101	Br								13
102		OCH_3		OCH_3				OCH_3	12
103	Benzoyl			Benzoyl					12
104								Cl	7
105			F						7
106	OH				I			OCH_3	6
107					I				5
108			COOH					OCH_3	2
109						OH			1
110				OCH_3					0
111				F				OCH_3	0
112				OCH_3				OCH_3	0
113			F					OCH_3	0
114							Cl		0
115				Cl					0
116			Br						0
117			I						0
118		OCH_3		OCH_3	I			OCH_3	0
119		OCH_3		OCH_3			I	OCH_3	0
120	I								0
121				I				OCH_3	0
122	OH		COOH					OCH_3	0
123	Br	OCH_3		OCH_3				OCH_3	0
124		OCH_3		OCH_3				OH	0

Substituted quinolinyl chalcones and pyrimidines were produced and tested for antitubercular and antimalarial action against Mycobacterium tuberculosis H37RV and Plasmodium falciparum NF-54 strains, respectively. Comparing structure-activity relationships reveals distinct physicochemical and structural needs for these two activities. Compounds 22 and 23 exhibited antitubercular action at a minimum inhibitory concentration of 3.12 mg/mL and were nontoxic to VERO and MBMDM cell lines [39].

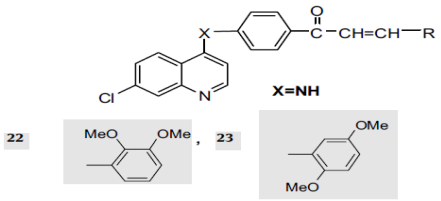


Table 19: Cytotoxicity of the VERO and MBMDM cell lines.

Compound No.	MIC (μg/mL)	VERO	MBMDM[a]
22	3.12	NT	NT
23	3.12	NT	NT
Pyrazinamide	50	NT	NT

[a] MBMDM: mouse bone marrow derived macrophages; NT: nontoxic.

Conclusions

In drug discovery, chalcones represent an essential structural backbone. They have strong biological activity against a variety of disorders (such as diabetes, cancer, inflammation, and other diseases). Heterocyclic rings are a crucial source of inspiration for creating new drugs because they frequently improve this activity by adding them to their structure. In one study with MICs ranging from 9.0 to 29μM, only chalcone analogs showed strong antitubercular action against Mycobacterium strains; compared compounds examined showed no activity. This demonstrates that the key pharmacophore for antitubercular action in chalcones is the α,β-unsaturated carbonyl system. Broad-spectrum antiviral activity is exhibited by natural chalcones, including licochalcones and xanthohumol, which suppress viruses such as influenza (by targeting NA), HIV-1, HSV-1/2, and CMV. They are therefore strong contenders for the creation of novel antiviral treatments. As essential candidates for the development of cancer drugs, chalcones, both natural (such as Licochalcone A and Butein) and synthetic, exhibit strong anticancer activity through a variety of mechanisms, such as preventing the production of superoxide and causing cytotoxicity against different tumor cells, including leukemia, breast cancer, and colon cancer. Through the inhibition of COX-1 and COX-2 enzymes, naphthalene-chalcone hybrids exhibit strong anti-inflammatory properties. In COX-1 molecular docking tests, certain synthetic drugs behaved better than the common medication flurbiprofen and showed acceptable pharmacokinetic (ADME) characteristics. In vitro confirmation of the strong antioxidant activity of novel hydroxy chalcone derivatives validates in silico predictions. The inclusion of hydroxyl groups and the chromene moiety increases this action, especially in preventing oleic acid and liver lipid oxidation. Therefore, more research is required to find useful uses for these potent antioxidants. New quinoline-chalcone hybrids have strong antiulcer properties via two pathways: improved cytoprotection (via raising mucin levels and stomach PGE 2) and antisecretory actions. The derivatives, in particular, some compounds showed strong in vitro neuroprotective efficacy. Strong glucose absorption activity (210–236 mg/dl) is demonstrated by synthesized chalcone derivatives, particularly those containing electron-withdrawing groups such as chloro, bromo, iodo, and hydroxy. They are positioned as attractive candidates for antidiabetic therapy because of their activity, which is on par with or possibly better than that of common medications like pioglitazone. Chalcones and structures resembling them exhibit strong antituberculosis properties (up to 99% inhibition). An aromatic ring with a

hydrophobic substituent and another with a hydrogen-bonding group are needed for this activity. Chalcones are thought to be preferable to flavones because of their structural flexibility, which permits non-coplanar aromatic rings, which are essential for bioactivity.

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