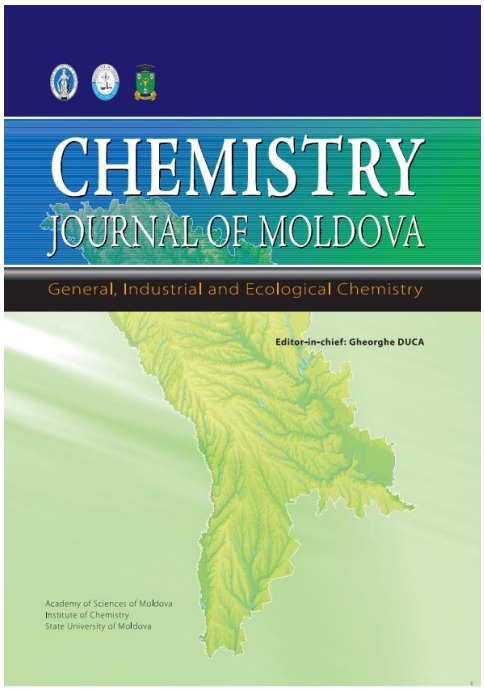

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AROMATIC METHYL KETONES IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE CHALCONES

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AROMATIC METHYL KETONES IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE CHALCONES

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Abstract. This review will primarily focus on recent methods employed for the synthesis of a diverse array of chalcones with broad-ranging biological activities, with a particular emphasis on the past five years. The utilization of aromatic methyl ketones and their derivatives as starting materials for the synthesis of various heterocyclic compounds, such as chalcones, pyrazolines, dioxolanes, aminothiazoles, and more, holds significant importance in the field of synthetic organic chemistry. The synthesized heterocyclic compounds can serve as valuable subjects for testing to assess their biological activity.

Keywords: acetophenone, vinyl-1,2,4-triazole, tetrazole-pyrazoline hybrid, Claisen-Schmidt condensation, chromenol.

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List of abbreviations and notations:

HCT-116	Colon cancer
PC-3	Prostate cancer
MCF-7	Breast cancer
r.t.	Room temperature
MIC	Minimum inhibitory concentration
NMR	Nuclear magnetic resonance
DMF	*N*,*N*-dimethylformamide
A-549	Lung cancer
A-375	Melanoma
EtOH	Ethanol
Et_3N	Triethylamine
SW480	Colon carcinoma
SOD2	Superoxide dismutase 2
DCM	Dichloromethane
ACN	Acetonitrile
*Pf*3D7	Plasmodium falciparum parasite
EDCI	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
HOBt	1*H*-1,2,3-Benzotriazol-1-ol
MBC	Minimum bactericidal concentration
WHO	World Health Organization

Introduction

Group of compounds showing promise in the development of novel medications is represented by chalcones. In nature, chalcones play an active physiological role in plants. They are susceptible to relatively facile oxidation and reduction reactions, and their redox potential indicates that chalcones are directly involved in the metabolic processes of plants. However, beyond their participation in metabolism, chalcones also serve other functions in plants, such as protective roles.

Despite the structural diversity and biological properties of natural chalcones, methods for their isolation from plant raw materials are often labor-intensive. The introduction of various substituents into the aromatic rings of chalcones allows the investigation of the relationship between their structure and properties, as well as the synthesis of pharmacologically active compounds with desired effects.

The primary objective of this review is to focus on advancing the synthesis of novel chalcones and to explore their *in vitro* activities against a range of cell lines. This comprehensive review holds significance in the field as it paves the way for identifying promising candidates for the development of novel drugs targeting drug-resistant bacterial strains.

It is particularly noteworthy that the reaction between 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanones and substituted benzaldehydes yields 1,3-diphenyl-2-(1*H*-1,2,4-triazol-1-yl)prop-2-en-1-ones. These can be formally considered as chalcones with a 1,2,4-triazole fragment at the second position. In this case, the methylene component is represented by the CH_2 group in the original phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone. Under similar conditions, when salicylaldehydes were used, hybrid molecules containing chromenol and 1,2,4-triazole were synthesized [1-3].

This review is dedicated to the synthesis methods of various substituted chalcones and hybrid molecules containing tetrazole,

1,2,4-triazole, and chromenol fragments. Additionally, the biological activity of the obtained compounds was examined.

Background

Synthesis of different chalcone derivatives

Chalcones, 1,3-diaryl-2-propen-2-ones, belong to the class of *α,β*-unsaturated ketones characterized by the presence of two aromatic or heteroaromatic rings, denoted as rings **A** and **B**, connected by three carbon atoms forming the *α,β*-unsaturated carbonyl system [4-6]. The simplest representative of the chalcone series is 1,3-diaryl-2-propen-2-one, that exists as *trans* (*E*)-chalcone and *cis* (*Z*)-chalcone isomers, with the *trans* isomer being thermodynamically more stable as shown in Figure 1 [7].

Chalcones are of significant interest to synthetic chemists due to the accessibility of starting materials, ease of synthesis, and their utility as valuable synthetic intermediates. They find application in the synthesis of various heterocyclic compounds and pharmaceuticals, owing to the high pharmacological activity exhibited by both synthetic and natural chalcones.

The presence of two electrophilic centres, the carbonyl group, and a carbon atom in the *β*-position, renders these compounds highly reactive. The distinct nature of these electrophilic centres significantly influences their high regioselectivity in reactions with mono- and binucleophiles. This property sets *α,β*-unsaturated carbonyl compounds apart from other ambident electrophiles, such as *β*-diketones.

Chalcones, due to their high reactivity, are attracting attention as precursors for the synthesis of various classes of organic compounds, including heterocyclic ones. The presence of different substituents in rings **A** and **B** provides a wide array of these compounds with diverse biological properties.

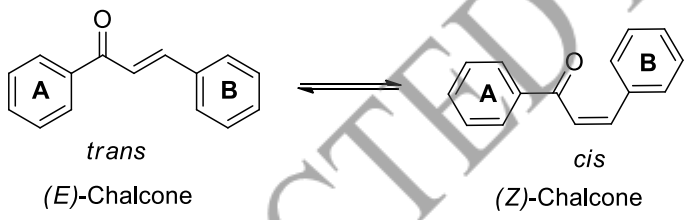


Figure 1. Isomers of *trans* (E)-chalcone and *cis* (Z)-chalcone.

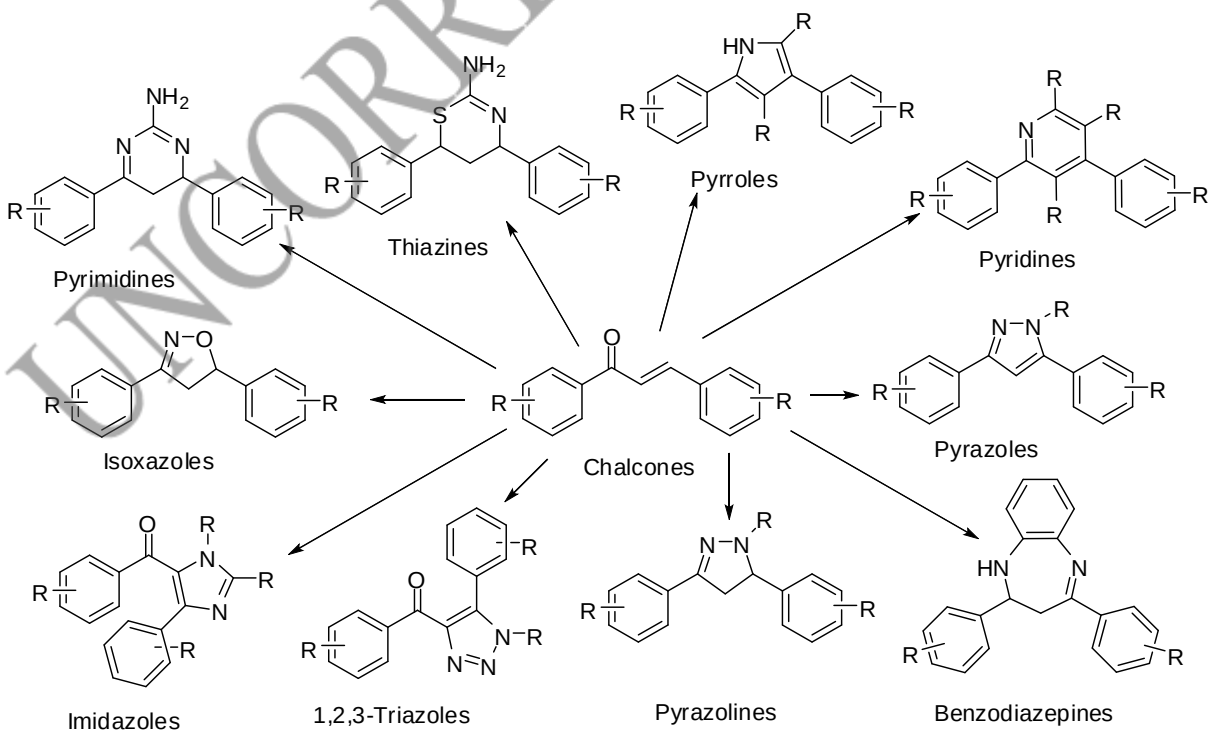


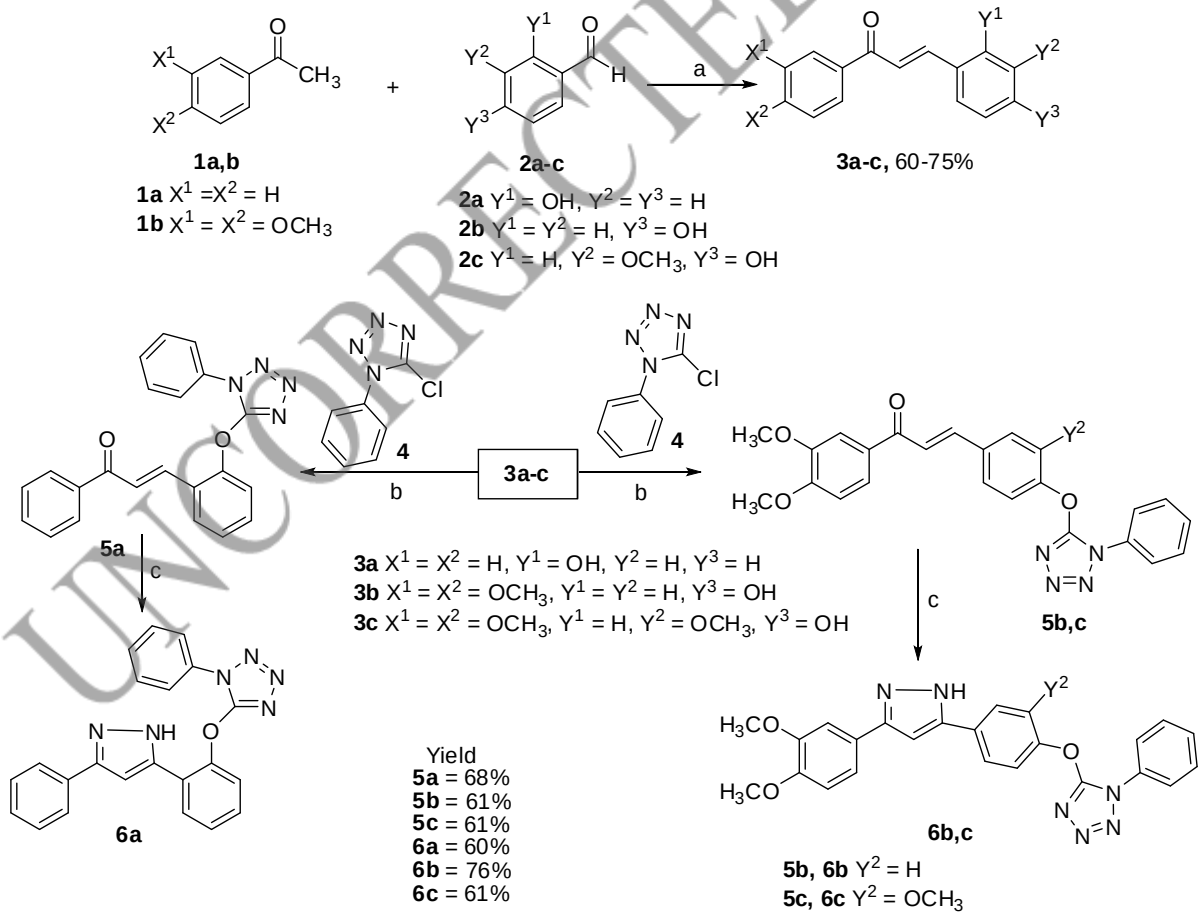
Figure 2. Compounds synthesized from chalcones.

When substituted chalcones interact with binucleophiles, various N, O, S-heterocyclic biologically active compounds can be obtained (Figure 2), such as pyrimidines and their derivatives [8-11], thiazines [12], pyridines [13,14], isoxazoles [15,16], pyrroles [17], pyrazoles [18], imidazoles [16,20], 1,2,3-triazoles [21-23], benzodiazepines [24-26] and pyrazolines [27,28].

In a study conducted by Abd ElMonaem, H.S. *et al*. [29], the synthesis of novel hybrids incorporating the tetrazole moiety with various chalcone derivatives was described. The researchers performed a reaction involving these chalcones and hydrazine hydrate to yield tetrazole-pyrazoline hybrids. Subsequently, all the newly synthesized hybrids underwent testing against three cancer cell lines: colon cancer (HCT-116), prostate cancer (PC-3), and breast cancer (MCF-7).

Chalcone derivatives **3a-c** were prepared *via* Claisen-Schmidt condensation of substituted acetophenone derivatives **1a** or **1b** with the corresponding hydroxybenzaldehydes **2a-c** in the presence of ethanolic NaOH (2.5%) (Scheme 1). The desired tetrazole-containing hybrids **5a-c** were obtained *via* the Williamson ether synthesis by reacting 5-chloro-1- phenyl-1*H*-tetrazole (**4**) with the prepared hydroxychalcone derivatives **3a-c** at room temperature for 24 hours, while stirring in DMF and in the presence of anhydrous K_2CO_3. Compounds **6a-c** were prepared by reacting *α,β*-unsaturated ketones **5a-c** with an excess of hydrazine hydrate (95%) in ethanol, at reflux temperature.

Compound 3-methoxy-4-((1-phenyl-1*H*-tetrazol-5-yl)oxy) benzaldehyde (**7**) was obtained by the reaction of O- alkylation of 4-hydroxy-3-methoxybenzaldehyde (vanilline) (**2b**) with 5-chloro-1-phenyl-1*H*-tetrazole (**4**) in DMF in the presence of anhydrous K_2CO_3.

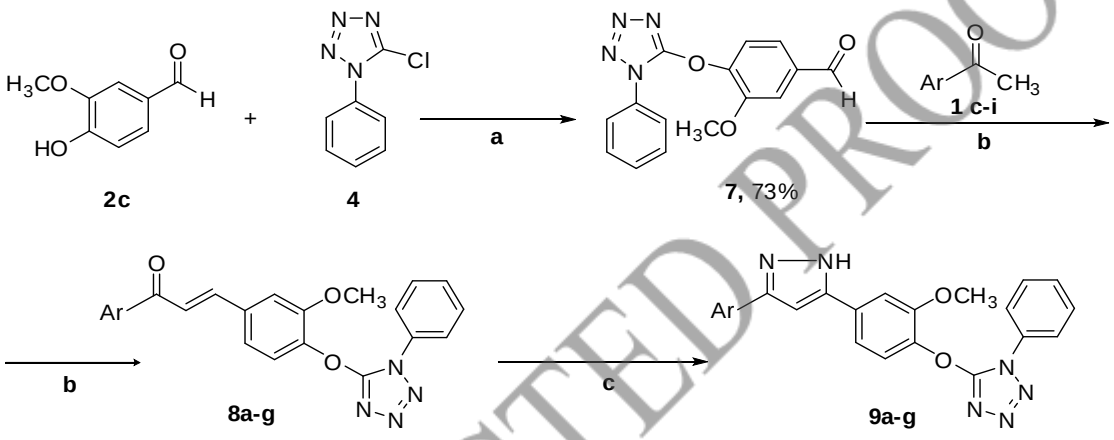


Reagents and conditions: (a) 2.5% NaOH, C_2H_5OH, r.t.; (b) K_2CO_3, DMF, 24 h, r.t.; (c) $NH_2NH_2 \cdot H_2O$, C_2H_5OH, reflux, 10-15 h.

Scheme 1. Synthesis of novel hybrids incorporating the tetrazole moiety with various chalcone derivatives [29].

Compound **7** was then reacted with substituted acetophenones **1c-g**, 2-acetylthiophene (**1h**) or 2-acetylfuran (**1i**) in the ethanolic solution of NaOH (2.5%) followed by acidification with HCl to obtained *α,β*-unsaturated carbonyl compounds **8a-g**. Nucleophilic cycloaddition reaction of compounds **8a-g** with hydrazine monohydrate (95%) in ethanol gave the corresponding pyrazolines **9a-g** (Scheme 2).

The starting compound 1-(4-((1-phenyl-1*H*-tetrazol-5-yl)oxy)phenyl)ethan-1-one (**10**) was prepared similar to compound **4**. Claisen-Schmidt condensation of differently substituted benzaldehydes **2d-i** with compound **10** was carried out in ethanolic NaOH (2.5%). After acidification with HCl were obtained the target compounds 1-(4-((1-phenyl-1*H*-tetrazol-5-yl)oxy)phenyl)-3-(un)substituted phenylprop-2-en-1-ones **11a-i**. The pyrazoline compounds **12a-i** were prepared by reacting *α,β*-unsaturated ketones **11a-i** with hydrazine monohydrate (95%) by refluxing in ethanol (Scheme 3).



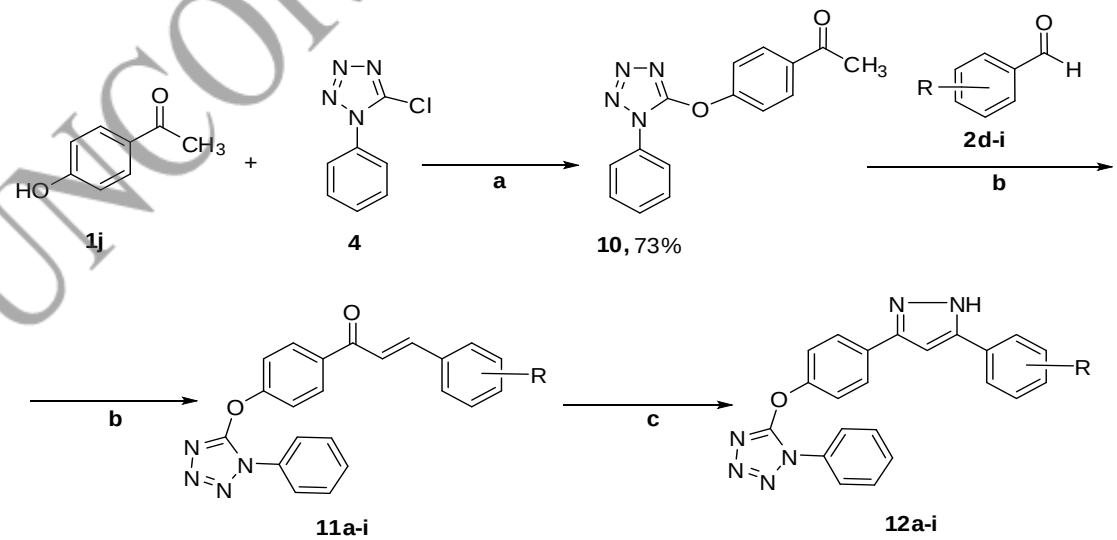
1c, 8a-9a: Ar= 2-OCH_3-C_6H_5 65%, 70%
1d, 8b-9b: Ar= 4-CH_3-C_6H_5 69%, 66%
1e, 8c-9c: Ar= 4-Cl-C_6H_5 82%, 69%
1f, 8d-9d: Ar= 4-Br-C_6H_5 62%, 64%
1g, 8e-9e: Ar= 4-F-C_6H_5 78%, 77%

1h, 8f-9f: Ar = 68%, 62%

1i, 8g-9g: Ar = 73%, 61%

Reagents and conditions: (a) K_2CO_3, DMF, 24 h, r.t.; (b) 2.5% NaOH, C_2H_5OH, 2 h; (c) $NH_2NH_2 \cdot H_2O$, C_2H_5OH, reflux, 10-15 h.

Scheme 2. Synthesis of compounds 8a-g and 9a-g [29].



2d, 11a-12a: R= H, 71%, 61%
2e, 11b-12b: R= 3,4-$(OCH_3)_2$, 69%, 63%
2f, 11c-12c: R= 3,4,5-$(OCH_3)_3$, 61%, 63%
2g, 11d-12d: R= 4-Cl, 85%, 62%
2h, 11e-12e: R= 2-Br, 81%, 71%

2i, 11f-12f: R= 4-Br, 77%, 60%
2j, 11g-12g: R= 4-F, 89%, 65%
2k,11h-12h: R= 2-NO_2, 79%, 64%
2l, 11i-12i: R= 4-$N(CH_3)_2$, 77%, 59%

Reagents and conditions: (a) K_2CO_3, DMF, 24 h, r.t.; (b) 2.5% NaOH, C_2H_5OH, 2 h; (c) $NH_2NH_2 \cdot H_2O$, C_2H_5OH, reflux, 10-15 h

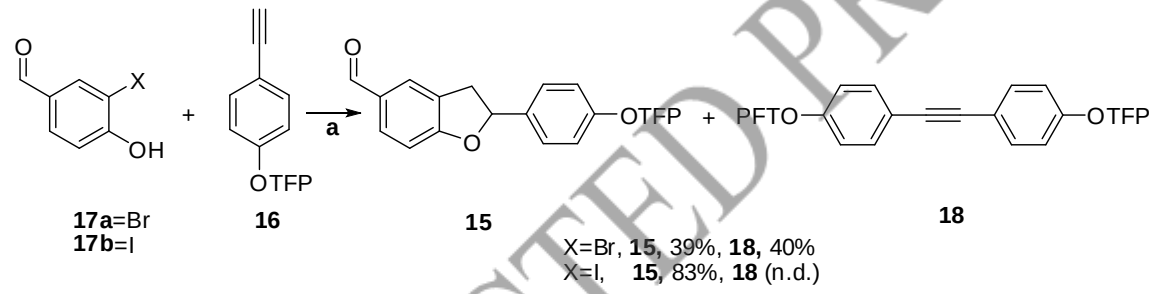
Scheme 3. Synthesis of compounds 11a-i and 12a-i [29].

The structures of the synthesized compounds were confirmed by physical methods, (m.p., elemental analyses, IR spectra, ^{1}H NMR and ^{13}C NMR spectra, GS-MS). The purities of the compounds were checked by thin layer chromatography (TLC).

Chalcone compounds **5a-c, 8a, 8c, 8e-g** showed considerable antiproliferative activities, with IC_{50} values better than, or comparable to, that of the reference drugs, cisplatin, and 5-FU, against HCT-116 and PC-3 cell lines with high selectivity towards cancer cell lines.

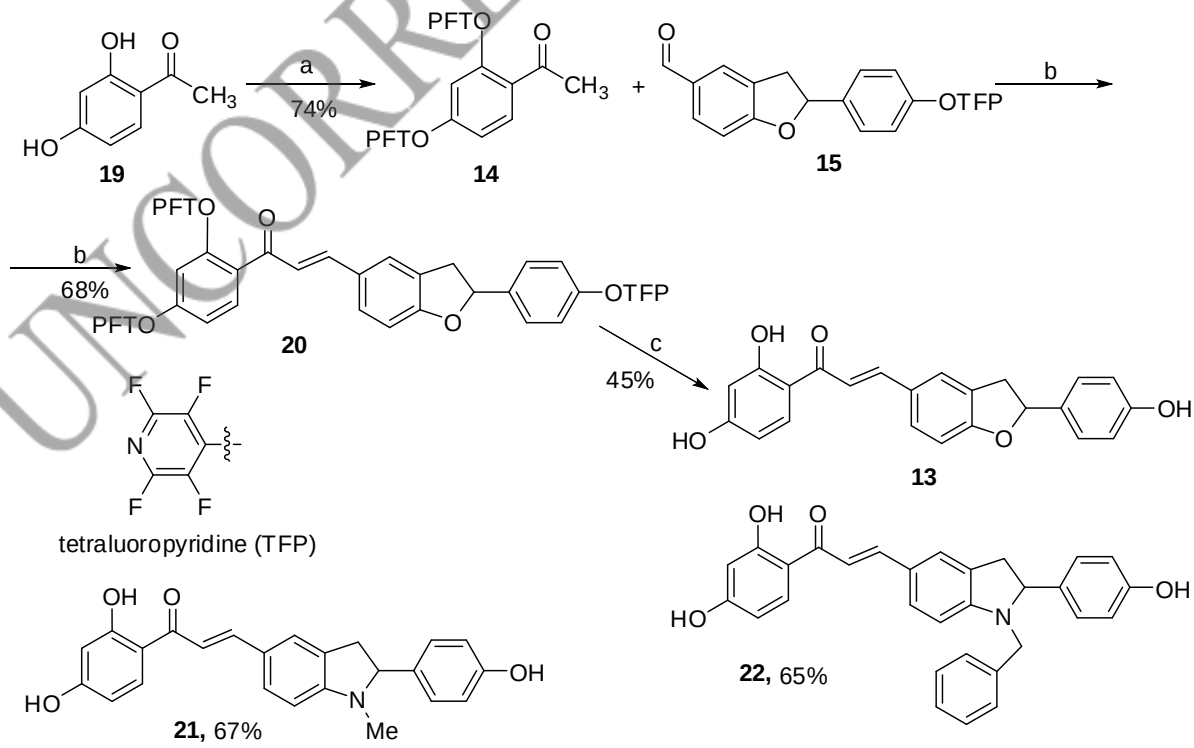
Pozzetti, L. *et al*. have developed and optimized total synthesis of the natural chalcone lophirone E (**13**) and of analogues containing heterocyclic B-rings, as anti-leishmanial agents [30]. Their synthetic investigations revealed the utility and limitations of the TFP O-protecting group for the synthesis of chalcone derivatives and allowed the synthesis number of analogues for early SAR (structure–activity relationship) investigation.

Initially, the authors screened for optimization of the one-pot Sonogashira coupling-intramolecular cyclization to key synthon **15**. To improve the yield of compound **15**, they used the iodinated derivative **17b** that was more reactive, giving the desired product in 83% yield with no Glaser homocoupling by-product **18** (Scheme 4)**.**



Reagents and conditions: (a) $Pd(PPh_3)_4$, PPh_3, degassed Et_3N, CuI, 90°C, 12 h.

Scheme 4. Synthesis of key synthon 15 [30].



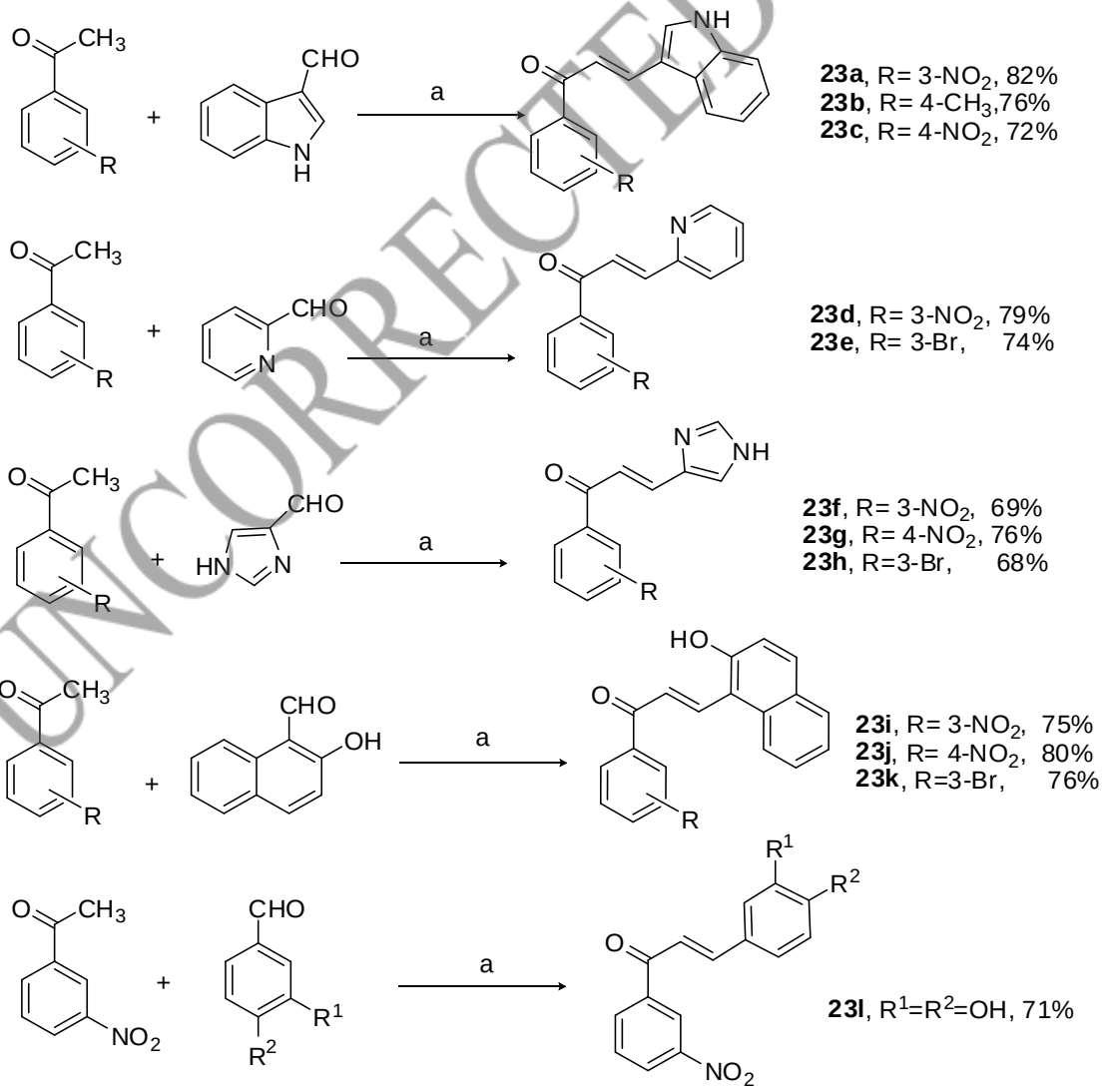
Reagents and conditions: (a) pentafluoropyridine, K_2CO_3, ACN, 25°C, 12 h;
(b) trimethylsilyl trifluoromethanesulfonate, triethylamine, DCM, -20°C to 25°C, 12 h;
(c) methylthioglycolate, KF, 18-C-6, ACN/H_2O, 25°C, 12 h.

Scheme 5. Synthesis of 1-(2,4-dihydroxyphenyl)-3-(2-(4-hydroxyphenyl)-1-methylindolin-5-yl)prop-2-en-1-one (21) and 3-(1-benzyl-2-(4-hydroxyphenyl)indolin-5-yl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one (22) [30].

After that authors started to the evaluation of the best reaction conditions for the condensation between the aromatic aldehyde **15** and the acetophenone derivative **14**, which was obtained upon the protection of commercially available 2,4,-dihydroxyatophenone (**19**). It was observed that alkaline conditions were unsuitable for this reaction, possibly due to the limited reactivity of the electron-rich heteroaromatic aldehyde towards the enolate of **14**. Consequently, our focus shifted towards exploring Lewis acid-promoted conditions. Treatment of a mixture of **14** and **15** with trimethylsilyltrifluoromethanesulfonate (TMSOTf) in the presence of Et_3N at -20°C resulted in the desired compound **20** being obtained in a yield of 68%. The final deprotection step was carried out by careful and slow addition of methyl thioglycolate to a solution of the chalcone, potassium fluoride, and 18-crown-6 (Scheme 5).

The article describes the synthesis of 10 compounds using various aromatic aldehydes. All substances were investigated for their activity against *Leishmania infantum* promastigotes disclosing derivatives **13** and **21, 22** as those endowed with the most interesting activities (IC_{50}= 15.3, 27.2, 15.9 μM, respectively). SAR investigations highlighted the potential of this class of compounds as antiparasitic hits, which made this study worthy of further investigation.

Rizwan, A. *et al*. prepared twelve β-chalcone derivatives **23a-l** using different substituted aldehydes in basic condition by Claisene-Schmidt condensation reaction [31]. Antimicrobial properties of the synthesized chalcone derivatives (Scheme 6) were evaluated against different bacterial strains *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella enterica, Staphylococcus pneumoniae* and *Enterococcus faecalis* by disc diffusion method.



Reagents and conditions: (a) 2.5% NaOH, C_2H_5OH, reflux.

Scheme 6. Synthesis of chalcone derivatives 23a-l [31].

The pharmacological testing of chalcones **23a-l** showed that chalcone **23b** has promising potential against tested bacterial strains. Chalcone **23b** showed significant binding towards Ct-DNA with intrinsic binding constant K_b= 1.75x10^4 M^{-1}. Antioxidant activity was also carried out to evaluate the antioxidant activity of the chalcone derivative **23b** by DPPH and H_2O_2 assay. The antibacterial activity of chalcone derivatives was compared with Ciprofloxacin as a reference drug. So, this study could be considered useful for the investigation of new antimicrobial agents.

In the ongoing study, Babu, A. and Selvaraju, K. have reported their findings pertaining to the synthesis and characterization of five newly developed chalcone derivatives **28a-e** [32]. These chalcones were synthesized through the condensation of variously substituted acetophenones with differently substituted benzaldehydes.

Compound *N*-(3-acetylphenyl)-2-chloroacetamide (**26**), was synthesized through the reaction between 3-aminoacetophenone (**24**) and chloroacetylchloride (**25**) in glacial acetic acid at 25-30°C. Subsequently, compound **26** underwent a reaction with *N*-(4-hydroxyphenyl)acetamide in DMF, utilizing potassium carbonate as a catalyst. For the synthesis of the substituted chalcones **28a-e**, equimolar quantities of 2-(4-acetamidophenoxy)-*N*-(3-acetylphenyl)acetamide and the respective substituted benzaldehyde or furfuraldehyde were mixed in an ethanol medium. To this mixture, a 20% sodium hydroxide (NaOH) aqueous solution was added, and the reaction mixture was vigorously stirred for a duration of 24 hours (Scheme 7).

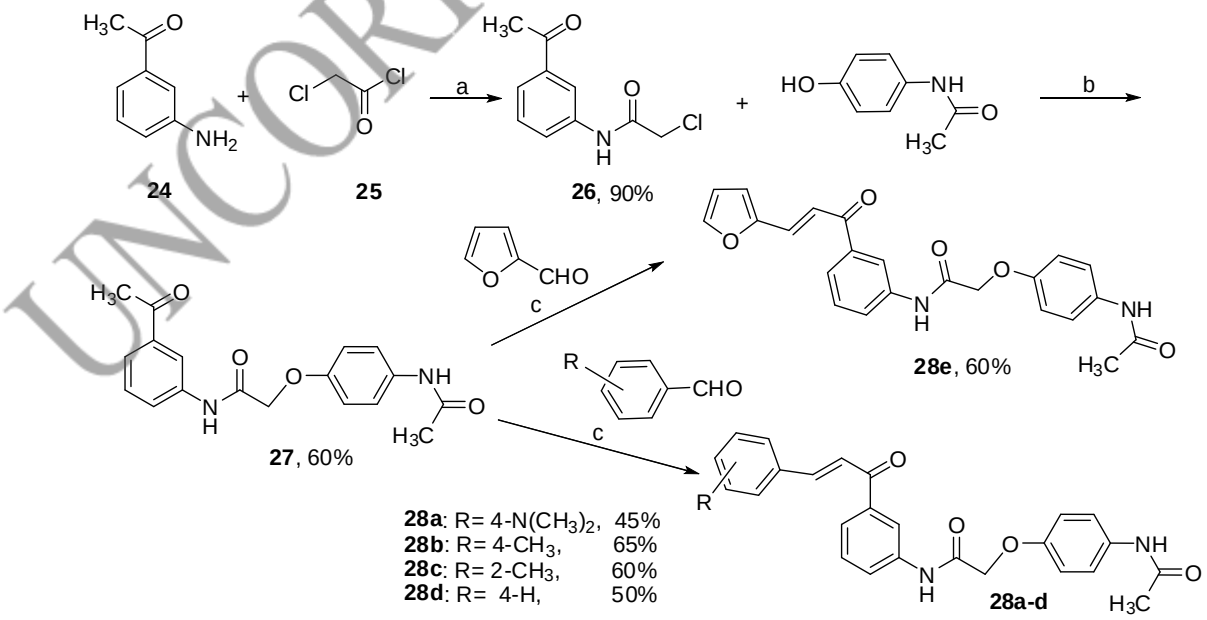
The synthesized chalcones have been utilized in antibacterial research. Compound **28e** exhibited remarkable activity, whereas compounds **28a, 28b, 28c,** and **28d** displayed good to reasonable activity against *E. coli*, *S. aureus*, *K. pneumonia, and B. subtilis* at both concentrations, *i.e*., 100 µg/mL and 200 µg/mL (Table 1).

Table 1

Antibacterial activity of chalcones 28a-e.

Compound	*Zone of Inhibition (mm)*							
	S. aereus		*B. subtilis*		*E. coli*		*K. pneumonia*	
	100µg	*200µg*	*100µg*	*200µg*	*100µg*	*200µg*	*100µg*	*200µg*
28a	-	-	10	14	9	15	-	-
28b	9	13	8	12	10	14	7	9
28c	-	12	-	11	-	9	-	-
28d	9	14	-	14	11	13	-	12
28e	10	15	10	13	9	14	-	-
Streptomycin (10µg)	24	23	25	17				

-Not active



Reagents and conditions: (a) chloroacetylchloride, glacial acetic acid, 25-30°C, 30 min; (b) K_2CO_3, DMF, 3 h, reflux; (c) 20% NaOH, C_2H_5OH, 24 h, r.t.

Scheme 7. Synthesis of chalcones 28a-e [**32**].

The antibacterial activity of all compounds was assessed using the disc diffusion technique. Antimicrobial activity was also evaluated *in vitro* against *E. coli, S. aureus, K. pneumonia, B. subtilis*, and compared to Streptomycin (10 μg) as the standard drug (Table 1).

The synthesized chalcones were screened for antifungal activity using Fluconazole (15 μg) and Clotrimazole (15 μg) as standards. *In vitro* antifungal activity was tested against *C. albicans* and *A. niger*. Compounds **28a**, **28c**, and **28d** exhibited good activity against both *C. albicans* and *A. niger*, while compounds **28a** and **28e** demonstrated moderate activity against both organisms (Table 2).

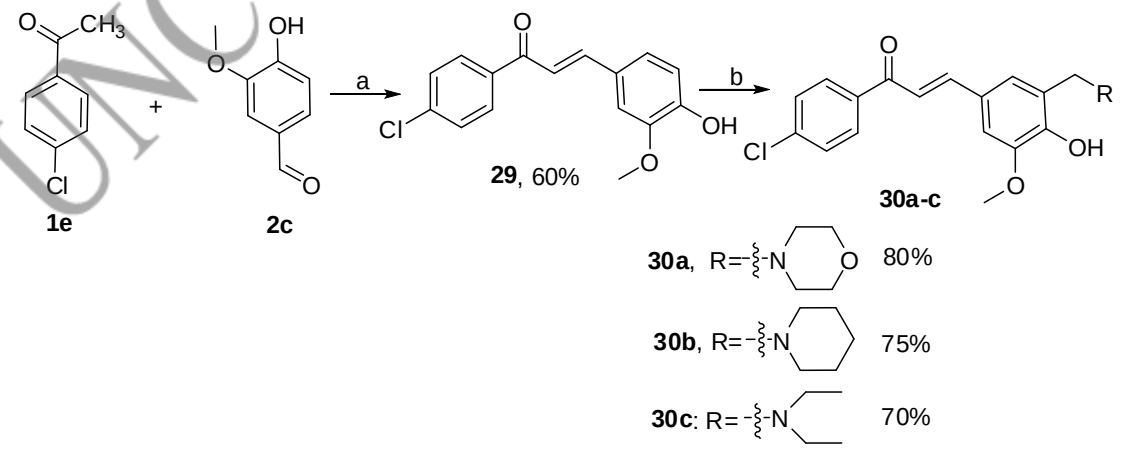
The inhibition zones for the chalcones against these organisms were measured in (mm) and are presented in Tables 1 and 2.

According to the Global Malaria Programme (GMP) [33], led by the WHO which is responsible for coordinating WHO's global efforts to control and eliminate malaria and is guided by the "Global technical strategy for malaria 2016–2030" adopted by the World Health Assembly in May 2015 and updated in 2021, malaria is one of the diseases requiring constant monitoring. According to the World Health Organization's estimates, in 2021, 619 000 people worldwide died from malaria, compared to 625 000 in the first year of the pandemic. The increasing resistance suggests a high prevalence of resistance of the *Plasmodium malaria* parasite to the introduced drugs. The development of new antimalarial drugs [34] is necessary to overcome the parasite's resistance, and thus, reduce the number of malaria infection cases.

Syahri, J. *et al*. synthesized three novel chalcone derivatives **30a-c** incorporating amine groups and assessed their antimalarial potential [35]. The synthesis of chalcone **29** has been previously documented [34]. The synthesis of aminoalkylated chalcone derivatives, namely **30a–c**, was carried out *via* the Mannich reaction. Initially, chalcone **29** (10 mmol) was dissolved in ethanol (75 mL) until a homogeneous solution was achieved. Subsequently, 10 mmol of 37% formaldehyde solution and 10 mmol of secondary amines (morpholine for **30a**, piperidine for **30b**, and diethylamine for **30c**) were added while stirring at room temperature (Scheme 8)**.**

Antifungal activity of chalcones 28a-e.

Compound	*Zone of Inhibition (mm)*			
	C.albicans		*A.niger*	
	100μg	*200μg*	*100μg*	*200μg*
28a	13	15	9	13
28b	9	14	10	12
28c	12	16	11	13
28d	14	18	8	12
28e	11	14	12	14
Fluconazole (15 μg)	-		27	
Clotrimazole (15μg)	22		-	



Reagents and conditions: (a) 60% NaOH, ethanol, stir at r.t. overnight; (b) Secondary amine (R), formaldehyde, ethanol, stir for 20 h.

Scheme 8. Synthesis of aminoalkylated chalcone derivatives 30a-c [35].

The *in vitro* evaluation of the antimalarial activity of chalcone **29** and its aminoalkylated derivatives **30a-c** was conducted against the chloroquine-sensitive *P. falciparum* (Pf3D7) strain. The data presented in Table 3 clearly indicates a noteworthy enhancement in antimalarial activity upon the introduction of secondary amines to the chalcone compound.

Table 3

An *in vitro* antimalarial activity (IC_{50}) against *Pf*3D7.

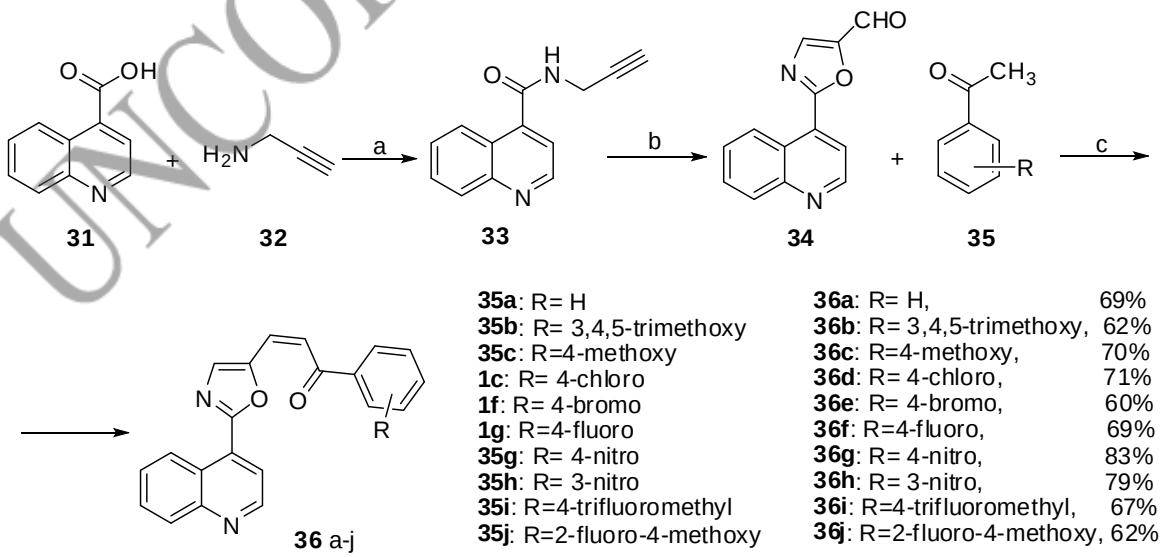
Compound	IC_{50} *(μM)*
29	25.84 ± 0.412
30a	0.62 ± 0.299
30b	0.54 ± 0.649
30c	1.12 ± 0.369
Chloroquine	+0.06 ± 0.387

Chalcone **29**, lacking a secondary amine group, exhibited an IC_{50} value of 25.84 μM. However, the incorporation of diethylamine (**30c**) resulted in a significant improvement in antimalarial activity, with an IC_{50} of 1.12 μM. Similarly, the substitution of piperidine (**30b**) and the inclusion of a morpholine group (**30a**) demonstrated superior antimalarial activity, with IC_{50} values of 0.54 and 0.62 μM, respectively. These findings underscore the pivotal role played by the amine group in enhancing antimalarial activity.

The research illustrates that the incorporation of secondary amine groups, such as morpholine, piperidine, and diethylamine, led to a significant enhancement in the antimalarial activity of chalcone derivatives, transitioning from moderate (25.84 μM) to strong activity (0.54–1.12 μM). Molecular docking of **30b** further supports these findings by revealing interactions between the amine groups within the chalcone compound and the SER111 and SER108 amino acid residues of the PfDHFR-TS protein. Consequently, secondary amine groups prove to be pivotal in the development of promising new candidate antimalarial drugs.

Venkatakrishna, M. has successfully synthesized a novel series of chalcone-tethered quinoline derivatives [36]. Furthermore, these newly synthesized compounds were subjected to testing against three human cancer cell lines: MCF-7 (breast), A-549 (lung), and A375 (melanoma).

The synthesis of these chalcone-tethered quinoline derivatives **36a-j** is outlined in (Scheme 9). Commercially available quinoline-4-carboxylic acid (**31**) was coupled with propargyl amine (**32**) in CH_2Cl_2, employing EDCI and HOBt at room temperature for 12 hours to yield *N*-(prop-2-ynyl)quinoline-4-carboxamide (**33**). Subsequently, amide **33** was cyclized in the presence of $Hg(ClO_4)_2$ and $(NH_4)_2Ce(NO_3)$ in CH_3CN medium at room temperature for 1 hour, resulting in the formation of 2-(quinolin-4-yl)oxazole-5-carbaldehyde (**34**) in good yield. Finally, aldehyde and **34** was reacted with various substituted acetophenones **35a-c, 1c, 1f, 1g** and **35g-j** in the presence of a catalytic amount of piperidine in ethanol medium under reflux conditions to obtain pure chalcone compounds **36a-j**.



35a: R= H
35b: R= 3,4,5-trimethoxy
35c: R=4-methoxy
1c: R= 4-chloro
1f: R= 4-bromo
1g: R=4-fluoro
35g: R= 4-nitro
35h: R= 3-nitro
35i: R=4-trifluoromethyl
35j: R=2-fluoro-4-methoxy

36a: R= H, 69%
36b: R= 3,4,5-trimethoxy, 62%
36c: R=4-methoxy, 70%
36d: R= 4-chloro, 71%
36e: R= 4-bromo, 60%
36f: R=4-fluoro, 69%
36g: R= 4-nitro, 83%
36h: R= 3-nitro, 79%
36i: R=4-trifluoromethyl, 67%
36j: R=2-fluoro-4-methoxy, 62%

Reagents and conditions: (a) DCM, EDCI, HOBt, r.t., 12 h; (b) $Hg(ClO_4)_2$, $(NH_4)_2Ce(NO_3)$, ACN, r.t., 12 h; (c) piperidine, C_2H_5OH, reflux, 6 h.

Scheme 9. Synthesis of chalcone-tethered quinoline derivatives 36a-j [36].

All the newly synthesized compounds **36a-j** underwent evaluation for their *in vitro* anticancer activity against three human cancer cell lines: MCF-7, A-549 and A375 through the utilization of the MTT assay. Adriamycin was employed as the control drug, and the results are quantified in IC_{50} values (μM), as presented in Table 4. These newly synthesized compounds **36a-j** demonstrated a range of activity from moderate to robust against all the tested cell lines. Particularly noteworthy are compounds **36b, 36d, 36e, 36g, 36h**, and **36j,** which exhibited more potent activity compared to the positive control, Adriamycin.

Table 4

Anticancer activity of target compounds 36a-j in IC_{50} μM.

Compound	*MCF-7*	*A-549*	*A375*
36a	3.78	8.56	-
36b	0.89	0.25	1.55
36c	2.65	3.77	4.67
36d	0.56	0.18	7.56
36e	0.77	0.80	1.92
36f	2.18	6.38	7.23
36g	1.90	0.11	0.34
36h	0.62	1.78	1.23
36i	4.99	5.10	-
36j	0.33	1.28	3.18
Adriamycin	2.02	2.18	5.51

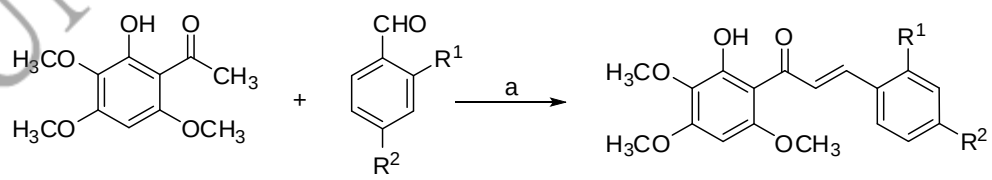
As a result of the growing resistance of bacteria, the effectiveness of antibiotics currently employed in clinical practice diminishes progressively [37]. Multiple mechanisms of resistance can concurrently exist within the same bacterial strain, thereby rendering these multidrug-resistant strains a critical public health concern.

Multidrug-resistant bacteria instigate a plethora of infections worldwide, leading to approximately 700 000 fatalities annually. The development of novel technologies capable of reversing bacterial resistance has become imperative to sustain effective clinical treatment for infections. Consequently, synthetic compounds that exhibit direct antibiotic activity or work in tandem with conventional antibiotics can prove to be highly valuable.

Sampaio de Freitas, T., *et al.* synthesized four chalcones **39a-d** and conducted a comprehensive investigation into their biological activity [38]. Additionally, they examined the combined effects of these chalcones when used in conjunction with the antibiotics gentamicin and ciprofloxacin. Furthermore, their study explored the influence of the position and nature of substituents within the **B** ring of the chalcone compounds, with the potential to exert a direct antibacterial effect.

The chalcones **39a-d** were synthesized *via* a Claisen–Schmidt condensation reaction under basic conditions. Specifically, 2-hydroxy-3,4,6-trimethoxyacetophenone **37** (4 mmol) and benzaldehydes **38** (4 mmol) were combined in a 50 mL flask. Subsequently, 10 mL of a 50% ethanolic NaOH solution was added to the mixture. The reaction mixture was stirred for 48 hours at room temperature, with TLC monitoring using *n*-hexane:ethyl acetate (2:1) as the solvent system. After 48 hours, the reaction mixture was neutralized with a 10% dilute HCl solution, followed by the addition of ice water. The resulting precipitate was then filtered under reduced pressure, washed with cold water, and subjected to recrystallization from ethanol (Scheme 10).

The position and type of substituents in the **B** ring of chalcones exert a significant influence on their direct antibacterial activity. Furthermore, the positioning and quantity of substituents play a pivotal role in determining the reversibility of bacterial resistance, particularly concerning the mechanisms involving efflux pumps.



37 **38a-d** **39a-d**

38a: R^1= F, R^2= H
38b: R^1= H, R^2= F
38c: R^1= H, R^2= Cl
38d: R^1= Cl, R^2= Cl

39a: R^1= F, R^2= H, 84%
39b: R^1= H, R^2= F, 69%
39c: R^1= H, R^2= Cl, 75%
39d: R^1= Cl, R^2= Cl, 74%

Reagents and conditions: (a) 50% NaOH, C_2H_5OH, r.t., 48 h.

Scheme 10. Synthesis of chalcones 39a-d [38].

Notably, chalcone **39b**, modified with a fluorine substitution at position 4 in the **B** ring, exhibited the most pronounced direct antibacterial effect. In contrast, chalcone **39d** demonstrated the most promising synergistic effect when employed alongside the tested antibiotics, particularly in the presence of chlorpromazine-sensitive efflux pumps.

The combination of a chlorine substitution at position 4 in the **B** ring showcased the most potent association for reversing bacterial resistance, underlining the importance of this specific substitution pattern

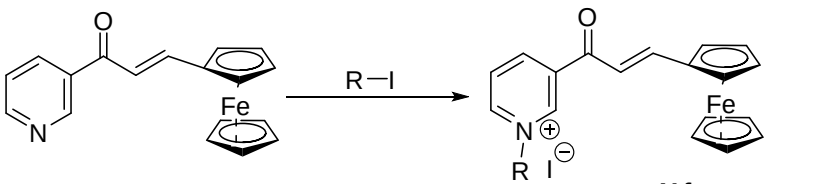
As mentioned earlier, the rapid spread of infections is associated with the development of bacterial resistance to drugs, such as methicillin-resistant *Staphylococcus aureus* (MRSA). It has quickly become a global concern as the infection spreads from healthcare facilities to the general population. Derivatives of ferrocenyl chalcones, which possess antimicrobial activity, have captured interest.

Henry, E. J., *et al.* conducted further research to assess the cytotoxicity of ferrocenyl chalcones [39]. Ten recently synthesized chalcones, in which ring **B** was replaced with a ferrocenyl fragment and ring **A** contained an increasing alkyl chain length from 1 to 10 carbon atoms, were used. To obtain ring **A** derivatives, salts were obtained using alkyl iodides (Scheme 11).

Using a twofold broth microdilution method, the minimum inhibitory concentration (MIC) of five out of the ten compounds was found to be lower against gram-positive organisms (MICs ranged from 0.008 mg/mL to 0.063 mg/mL) than against Gram-negative organisms (MICs= 0.125 mg/mL). These novel ferrocenyl chalcone compounds demonstrated effectiveness against three types of clinically isolated drug-resistant *S. aureus* strains, including MRSA, as well as against other non-resistant clinically isolated and laboratory-adapted Gram-positive bacteria. These same compounds inhibited the growth of non-resistant bacteria, potentially by blocking the cellular respiration of Gram-positive bacteria. The results suggest that these newly developed compounds could be significant antimicrobial agents in the treatment of infections caused by clinically resistant bacteria. The results regarding antimicrobial activity are presented [39].

In the pursuit of discovering novel antibacterial compounds, Shinde, R.A. and his research team synthesized a series of six chalcone derivatives bearing 1,4-benzodioxan-6-yl substitutions [40]. These compounds were prepared through the reaction of 1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)ethan-1-one (**42**) with aromatic aldehydes substituted with fluorine and chlorine **38b-d, 43a-b, d-f**. The synthesized products were comprehensively characterized using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques. Subsequently, these newly synthesized chalcones were subjected to *in vitro* antibacterial assays against both Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli* and *Proteus vulgaris*).

It's noteworthy that all chalcone derivatives (designated as **44a-f**) were successfully synthesized *via* the Claisen–Schmidt condensation reaction (Scheme 12). Among these compounds, **44e**, featuring a 2,6-dichlorobenzaldehyde moiety, exhibited the highest yield, with a remarkable 95% yield obtained. In contrast, compound **44b** yielded the lowest at 82%. This observation highlights an enhancement in yield when the fluorine substituent is replaced by a chlorine substituent.



40

41a, R=methyl
41b, R=ethyl
41c, R=propyl
41d, R=butyl
41e, R=pentyl
41f, R=hexyl
41g, R=heptyl
41h, R=octyl
41i, R=nonyl
41g, R=decyl

Reagents and conditions: ACN, R-I, reflux.

Scheme 11. Synthesis of ferrocenyl chalcones 41a-g [39].

In the process of screening chalcone compounds **44a-f** for their antibacterial properties, were employed both Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli* and *Proteus vulgaris*). To assess the antibacterial efficacy of the synthesized compounds, were utilized the well-established agar diffusion assay.

The synthesized chalcone compounds exhibited promising antibacterial activity against the tested bacterial strains. Notably, compounds **44a**, **44b**, **44e**, and **44f** displayed particularly robust antimicrobial activity. In antibacterial screening, author employed chloramphenicol as the standard reference drug and used DMSO as control. The outcomes of the antibacterial screening are displayed in (Table 5).

The review describes the synthesis of novel trimethoxyphenyl-derived chalcone-benzimidazolium salts. In total, 33 new hybrid substances were successfully synthesized [41]. These compounds were subjected to *in vitro* screening to evaluate their biological properties against five distinct human tumor cell lines.

Scheme 13 shows that the chalcone **47** was synthesized *via* a NaOH-catalyzed Claisen−Schmidt condensation between 4-hydroxyacetophenone (**45**) and 3,4,5-trimethoxy benzaldehyde (**46**) in 66% yield. The chalcone **47** was alkylated with 1,3-dibromopropane in the presence of NaH to afford compound **48** in 63% yield. The respective chalcone-benzimidazoles **49a-c** were obtained in the presence of K_2CO_3 in acetone with 66-75% yield. Finally, trimethoxyphenyl-derived chalcone-benzimidazolies salts (**50a-j, 51a-j,** and **52a-j**) were prepared with excellent yield (75−91%) by treating chalcone-benzimidazole hybrid **49a-c** with various alkyl bromides in acetone or toluene at 80°C. The detailed structures and yields of trimethoxyphenyl-derived chalcone-benzimidazolies salts are discussed in the review [41].

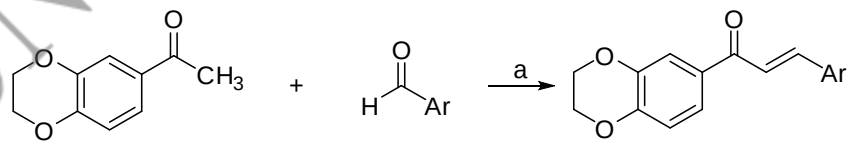
The cytotoxic potential of all newly synthesized hybrid compounds was assessed *in vitro* against a panel of human tumor cell lines. This panel encompassed leukemia (HL-60), myeloid liver carcinoma (SMMC-7721), lung carcinoma (A549), breast carcinoma (MCF-7), and colon carcinoma (SW480). Cisplatin (DDP) served as the reference drug for comparison. Based on the results of the biological tests, the following conclusions can be drawn.

Table 5

Antibacterial activity of the synthesized chalcone derivatives.

№	*Entry*	*E. coli*	*P. vulgaris*	*S. aureus*	*B. subtilis*
1	**44a**	+++	-	-	+++
2	**44b**	-	++	-	++
3	**44c**	-	-	-	-
4	**44d**	-	-	-	-
5	**44e**	++	++	+++	++
6	**44f**	++	+++	++	++
Control	**DMSO**	-	-	-	-
Standard	Chloramphenicol	++++	++++	++++	++++

Note: + = less than 5 mm; ++ = 5–10 mm; +++ = 10–15 mm; ++++ = more than 15 mm; - = No zone of inhibition.



42 **38b-d, 43 a-b,d-f** **44a-f**

43a,44a: Ar= 3-fluorophenyl, 86%
38b,44b: Ar= 4-fluorophenyl, 82%
38d,44c: Ar= 2,4-dichlorophenyl, 94%
43d,44d: Ar= 2,3-dichlorophenyl, 93%
43e,44e: Ar= 2,6-dichlorophenyl, 95%
43f,44f: Ar= 2-chlorophenyl, 92%

Reagents and conditions: (a) 30% NaOH, C_2H_5OH, r.t., 2 h.

Scheme 12. Synthesis of chalcones 43a-f [40].

Compounds **50f, 50j, 51f, 51i**, and **51j**, which feature a 5,6-dimethylbenzimidazole or 2-methyl-benzimidazole ring, along with a 2-naphthylmethyl substituent and a 4-methylbenzyl or 2-naphthylacyl substituent at position-3 of the benzimidazole ring, exhibited the highest potency among the derivatives. Notably, compounds **51f** and **51i** were the most potent among these derivatives, with IC_{50} values below 6.70 μM against all five human tumor cell lines. These values indicate a greater selectivity toward HL-60 and MCF-7 cell lines.

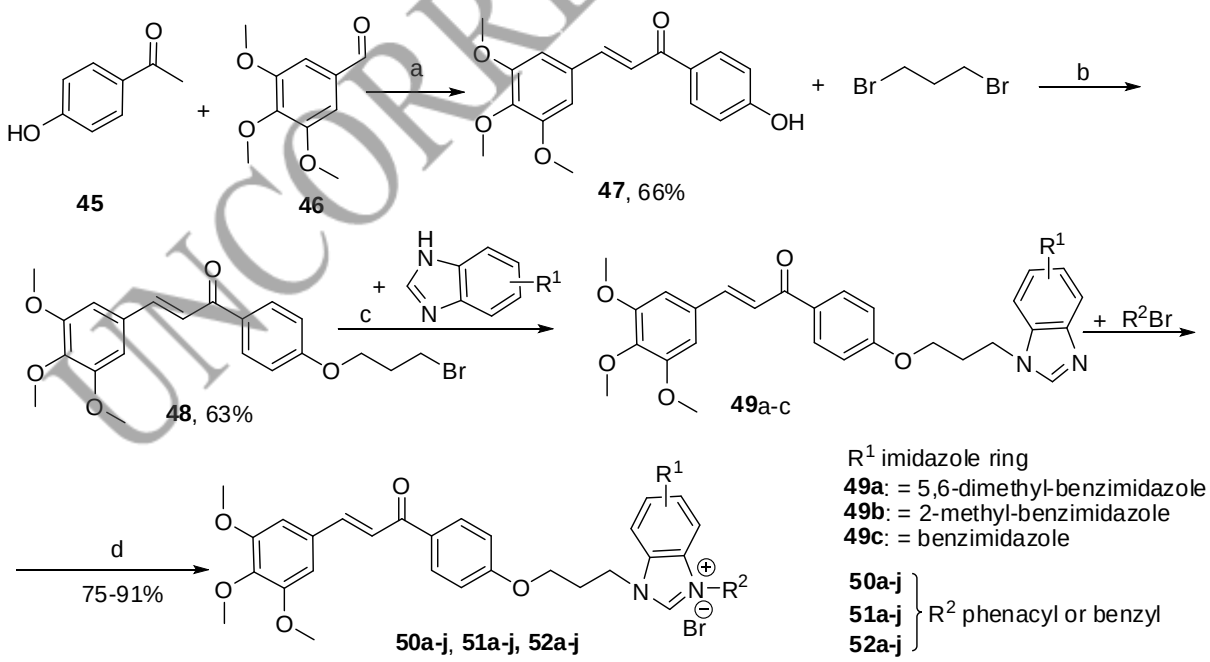
Compound **50f** demonstrated increased selectivity for HL-60, MCF-7, and SW-480 cell lines, with IC_{50} values that were 8.0-fold, 11.1-fold, and 5.8-fold lower than those of DDP (cisplatin), respectively. Further investigations into the antitumor mechanism of action revealed that compound **50f** induces cell-cycle G1 phase arrest and apoptosis in SMMC-7721 cells.

The trimethoxyphenyl-derived chalcone-benzimidazolium salts, specifically compounds **50f, 50j, 51f, 51i**, and **51j**, present promising leads for future structural modifications guided by the structure-activity relationship studies.

Neurodegenerative disorders are characterized by memory loss, cognitive decline, and structural brain changes. Two of the most prominent neurodegenerative diseases are Alzheimer's disease and Parkinson's disease. The urgent need for the development of novel neuroprotective agents to treat these conditions is underscored by their prevalence among the aging population worldwide.

In a recent study [42], researchers synthesized a new series of chalcone-triazole hybrids (designated as **58a-g**) and assessed their biological properties, including cytotoxicity, antioxidant activity, anti-apoptotic effects, and neuroprotection using SH-SY5Y cells. Notably, various natural and synthetic compounds, such as chalcones and 1,2,3-triazole analogs, have been reported to demonstrate neuroprotective effects [43-45]. Chalcone-based compounds have been extensively investigated with the aim of preventing neurodegenerative disorders [46].

1,2,3-Triazoles, as nitrogen heterocycles, are found in a diverse range of biologically active molecules due to their distinct properties [47]. They are capable of forming hydrogen bonds with numerous biomolecular targets, exhibit high stability against metabolic degradation, and have fewer undesired side effects. Several chalcone-triazole hybrids displaying various biological activities have been documented. The linkage of chalcone and 1,2,3-triazole units has resulted in hybrids with enhanced biological activities compared to their parent pharmacophoric units [48-54].



Reagents and conditions: (a) 5% NaOH, C_2H_5OH/H_2O, r.t., 13 days; (b) DMF, NaH, r.t.; (c) K_2CO_3, acetone, 60°C, tube, 12-24 h; (d) acetone, toluene, tube, 80°C.

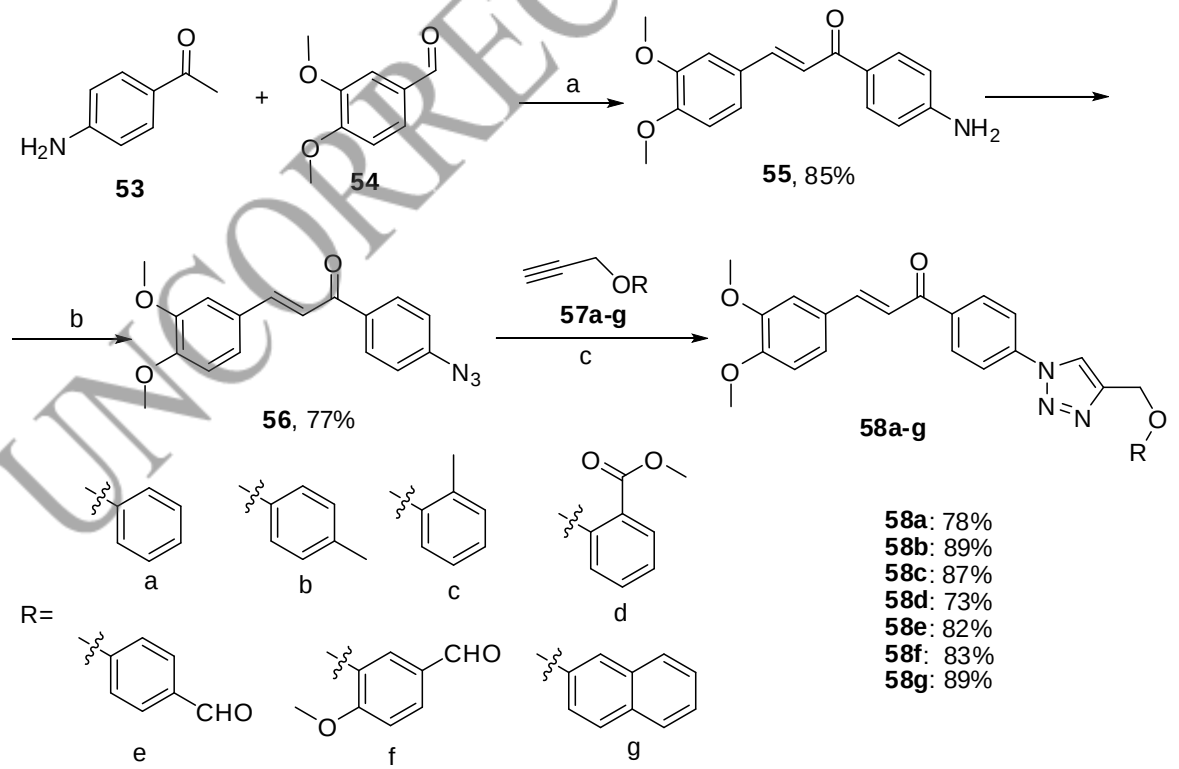
Scheme 13. Synthesis of trimethoxyphenyl-derived chalcone-benzimidazolies salts 50a-j, 51a-j, and 52a-j [41].

The synthesis of chalcone-triazole hybrids **58a-g** (as shown in Scheme 14) involved several key steps. Initially, the hybrids were prepared through the base-catalyzed Claisen-Schmidt condensation of 3,4-dimethoxybenzaldehyde **54** and 4-aminoacetophenone **53**. Subsequently, the aminochalcone **55** underwent a diazotization reaction using sodium nitrite and sodium azide in a mixture of glacial acetic acid and concentrated hydrochloric acid, yielding the azidochalcone **56**. In the final step, the Cu(II)-catalyzed azide-alkyne cycloaddition between the azido compound **56** and alkynes **57a-g** was carried out, resulting in the formation of the novel hybrids **58a-g** with good yields (ranging from 73% to 89%). The alkynes **57a-g** were obtained through the alkylation of the corresponding phenol derivatives with propargyl bromide [55].

The results of the study demonstrated that compounds **58a** and **58e** exhibited notable neuroprotective effects in neuronal cells subjected to oxidative stress-induced damage. Both compounds significantly enhanced neuronal cell morphology and substantially increased cell survival rates in the face of oxidative stress. Furthermore, compounds **58a** and **58e** effectively mitigated H_2O_2-induced mitochondrial dysfunction, as evidenced by the preservation of mitochondrial membrane potential, the attenuation of BAX protein levels, the elevation of BCL-2 protein levels within the mitochondria, and the upregulation of the mitochondrial antioxidant enzyme SOD2 [56].

Of particular interest, these compounds exerted their neuroprotective effects through the SIRT-FOXO3a signalling pathway, a mechanism reminiscent of the action of resveratrol. These findings strongly suggest that the chalcone-triazole derivatives, specifically **58a** and **58e**, hold promise as potential candidates for the development of disease-modifying therapies in the context of neurodegenerative disorders.

The academic interest in the study of chemical compounds containing 1,2,4-triazole fragments is motivated by their unique properties. In this heterocyclic compound, nitrogen atoms can serve as both hydrogen bond donors and acceptors at active centres within biological systems. Additionally, the structural 1,2,4-triazole fragment displays remarkable stability, resistant to both chemical reactions and metabolic degradation, making it a robust foundation for developing chemical compounds with enhanced properties.



Reagents and conditions: (a) 40% KOH, C_2H_5OH, r.t.; (b) HCl/CH_3COOH, 0°C, 15 min, then NaN_3, r.t. 30 min; (c) alkyne **57**, $CuSO_4 \times 5H_2O$, sodium ascorbate, *t*-$BuOH/H_2O$, r.t.

Scheme 14. Synthesis of chalcone-triazole hybrids 58a-g [42].

It is noteworthy that this structural fragment's capacity to improve ligand solubility impacts their biological activity. It's important to emphasize that the inclusion of the 1,2,4-triazole fragment in a molecule can significantly optimize the pharmacokinetic parameters of a drug, affecting processes such as absorption, distribution, metabolism, and excretion due to the polar nature of this fragment. These modifications can also influence the pharmacodynamic characteristics of the drug, further enriching its activity profile.

Hence, research on chemical compounds incorporating the 1,2,4-triazole fragment in their structure is of significant interest to the scientific community and offers promising applications in various fields related to medicine, biology, and chemistry.

As mentioned earlier, antibiotic resistance and the emergence of new viral infections [57] pose a substantial threat to public health, necessitating the urgent quest for new and improved antimicrobial, antiviral, and antifungal agents [58]. Compounds containing the 1,2,4-triazole ring in their structure exhibit diverse biological activities and are integral to numerous biologically active molecules with a wide range of effects, including antibacterial [59-61], analgesic [62], and more.

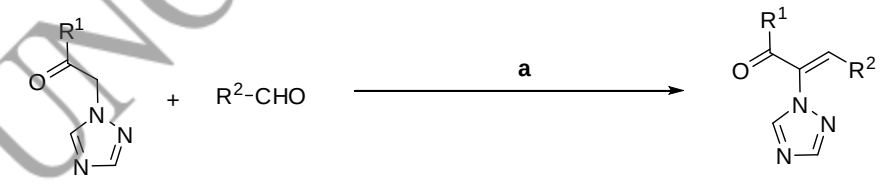
Drawing from the presented data, Stingaci E., *et al.* successfully synthesized a novel series of 1,2,4-triazole derivatives [63]. These vinyl-1,2,4-triazoles were prepared *via* the condensation of 1-phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanones with substituted benzaldehydes (Scheme 15).

All derivatives of vinyl-1,2,4-triazoles **60a-h** were effectively synthesized in benzene under reflux conditions, using a 1:1 mixture of piperidine and acetic acid as a catalyst.

The product yields varied from 42% for **60f** to 93% for **60b.** It is important to emphasize that under these specified conditions, all compounds were obtained with a high level of stereoselectivity, as confirmed by experimental data obtained using NOESY. These data indicate that the vinyl protons do not interact with the protons of the 1,2,4-triazole, allowing us to conclude that the obtained compounds correspond to the Z-isomer.

All the synthesized compounds exhibited notable antibacterial activity, with MIC and MBC values ranging from 0.0002 to 0.0069 mM. The antibacterial potency can be ranked as follows: **60h > 60f > 60g > 60c > 60a > 60e > 60b > 60d**. Compound **60h** emerged as the most active among all, with an MIC ranging from 0.0002 to 0.0033 mM and an MBC of 0.0004-0.0033 mM. Conversely, Compound **60d** displayed the lowest antibacterial potency, with MIC and MBC values at 0.0027-0.0054 mM, respectively.

The antibacterial effectiveness of the compounds against *B. subtilis* can be summarized as follows: **60h > 60f > 60g > 60c > 60b > 60e > 60d > 60a**, while against *P. fluorescens*: **60f > 60a > 60c > 60b > 60d > 60e > 60h > 60g**. The susceptibility of *Erwinia species* (*Erwinia amylovora, Erwinia carotovora*) to the synthesized compounds appeared to differ from that of *B. subtilis* and *P. fluorescens*, with rankings as follows: **60h > 60g > 60b > 60a > 60c > 60e = 60f > 60d** and **60h > 60a > 60c = 60d > 60e = 60f > 60b > 60g**. On the other hand, *Xanthomonas campestris* displayed entirely different responses to the tested compounds: **60h > 60c > 60a > 60e = 60f > 60d > 60b > 60g**.

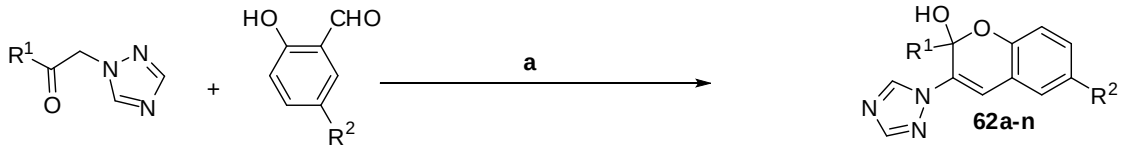


59a $R^1=C_6H_5$
59b R^1=4-Ph-C_6H_4
59c R^1=4-Cl-C_6H_4
59d R^1=2-naphtyl
59e R^1=2,4-Cl_2-C_6H_3
59h $R^1=Me_2CHCH_2$

60a $R^1=C_6H_5$, R^2=3-OH-C_6H_4 78%
60b R^1=4-Ph-C_6H_4, R^2=4-NMe_2-C_6H_4 93%
60c R^1=4-Cl-C_6H_4, R^2=2-OH,5-NO_2-C_6H_3 76%
60d R^1=2-naphtyl, R^2=4-NMe_2-C_6H_4 80%
60e R^1=2,4-Cl_2-C_6H_3, $R^2=C_6H_5$ 82%
60f R^1=2,4-Cl_2-C_6H_3, R^2=4-NO_2-C_6H_4 42%
60g R^1=2,4-Cl_2-C_6H_3, R^2=3,5-(^{t}Bu)$_2$-4-OH-C_6H_2 82%
60h $R^1=Me_2CHCH_2$, R^2=4-NO_2-C_6H_4 54%

Reagents and conditions: (a) piperidine/AcOH, 1:1, cat. C_6H_6, reflux.

Scheme 15. Synthesis of chalcone-1,2,4-triazole hybrids 60a-g [63].



59a R^1=C_6H_5
59e R^1=2,4-Cl_2-C_6H_3
59f R^1=2-Cl-C_6H_4
59g R^1=Me_3C
59i R^1=4-CH_3-C_6H_4

61a R^2=Br
61b R^2=Cl
61c R^2=H
61d R^2=NO_2
61e R^2=C_6H_5

62a R^1=C_6H_5, R^2=Br	65%
62b R^1=C_6H_5, R^2=Cl	43%
62c R^1=2-Cl-C_6H_4, R^2=H	71%
62d R^1=2-Cl-C_6H_4, R^2=Cl	53%
62e R^1=4-CH_3-C_6H_4, R^2=H	30%
62f R^1=2,4-Cl_2-C_6H_3, R^2=Cl	75%
62g R^1=2,4-Cl_2-C_6H_3, R^2=Br	89%
62h R^1=2,4-Cl_2-C_6H_3, R^2=NO_2	25%
62i R^1=2,4-Cl_2-C_6H_3, R^2=C_6H_5	40%
62j R^1=Me_3C, R^2=C_6H_5	67%
62k R^1=Me_3C, R^2=H	70%
62l R^1=Me_3C, R^2=NO_2	40%
62m R^1=Me_3C, R^2=Cl	56%
62n R^1=Me_3C, R^2=Br	70%

Reagents and conditions: (a) piperidine/AcOH, 1:1, cat. C_6H_6, reflux.

Scheme 16. Synthesis of chromenol-1,2,4-triazole hybrids 62a-n [66].

Compounds **60f, 60g**, and **60h** exhibited very strong activity against *B. subtilis*, *Pseudomonas fluorescens, Erwinia amylovora*, and *Xanthomonas campestris*, with MIC and MBC values ranging from 0.0008 to 0.0017 mM. Additionally, compound **60f** displayed activity against *Erwinia carotovora* (MIC and MBC at 0.0013 mM). Compound **60h** demonstrated approximately six times higher activity against *Erwinia amylovora* compared to ampicillin, while compound **60g** showed nearly equivalent potency to ampicillin against *Pseudomonas fluorescens*. It's noteworthy to mention that, in general, the compounds exhibited higher efficacy against Gram-negative bacteria.

The antifungal activity was assessed against eight different fungal species: *Aspergillus fumigatus, A. versicolor, A. ochramensis, A. niger, Trichoderma viride, Penicillium funiculosum, P. ochrochloron, and P. verrucosum var. cyclopium*. Detailed results can be found in the article [63].

Earlier research has established the diverse biological activities exhibited by derivatives of 1,2,4-triazole [64,65]. Simultaneously, chromene derivatives are recognized for their broad range of biological activities. Building on this knowledge, Zveaghintseva, M., *et al*. synthesized 14 hybrid molecules containing both 1,2,4-triazole and chromenol fragments [66]. Subsequently, comprehensive biological tests for antifungal activity were conducted.

The reaction involving salicylic aldehydes **61a-e** with 1-(alkyl/aryl)-2-(1*H*-1,2,4-triazole-1-yl)ethanones **59a**, **59e**, **59f**, **59g** and **59i** in benzene, catalyzed by piperidine and acetic acid, yielded crystalline products **62a–n**. The yields of these products ranged from 25% to 75%, (Scheme 16).

The antifungal activity was assessed using a microdilution assay, with the reference drugs bifonazole and ketoconazole. The most impressive activity was observed for compound **62k**. Among the fungal species tested, *Trichoderma viride* exhibited the highest sensitivity, while *A. fumigatus* proved to be the most resistant. Notably, the majority of compounds, with the exceptions of **62e**, **62j**, and **62l**, demonstrated greater potency against *P.v.c* compared to ketoconazole for all tested fungi. Moreover, many of these compounds were even more effective than bifonazole against all the fungi examined. In particular, compound **62k** was identified as being 32 times more active than ketoconazole and 16 times more effective than bifonazole.

Conclusions

The data collected in this review underscores the substantial synthetic potential of chalcone derivatives in the construction of polyfunctional five- and six-membered heterocyclic compounds, specifically which exhibit notable biological activity. Furthermore, the pivotal role played by the Claisen-Schmidt reaction in chalcone synthesis highlights the remarkable progress achieved in exploring the biological properties of substituted chalcones. Consequently, it can be concluded that the investigation of chalcones holds significant importance within the realms of medical and

pharmaceutical science, owing to their broad spectrum of biological activities. This research may pave the way for the development of novel drugs and materials with useful properties.

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References

1. Fouad, S.A.; Hessein, S.A.; Abbas, S.Y.; Farrag, A.M.; Ammar, Y.A. Synthesis of chromen-2-one, pyrano[3,4-c]chromene and pyridino[3,4-c]chromene derivatives as potent antimicrobial agents. Croatica Chemica Acta, 2018, 91(1), pp. 99–107. DOI: https://doi.org/10.5562/cca3266
2. Prusty, J.S.; Kumar, A. Coumarins: Antifungal effectiveness and future therapeutic scope. Molecular Diversity, 2020, 24, pp. 1367–1383. DOI: https://doi.org/10.1007/s11030-019-09992-x
3. Youssef, M.S.K.; Abeed, A.A.O.; El-Emary, T.I. Synthesis and evaluation of chromene-based compounds containing pyrazole moiety as antimicrobial agents. Heterocyclic Communications, 2017, 23(1), pp. 55–64. DOI: https://doi.org/10.1515/hc-2016-0136
4. Liu, X.; Liu, X.; Xiong, Y. Synthesis of Chalcone Derivatives. Advances in Computer Science Research, 2016, 59, pp. 618–620. DOI: https://doi.org/10.2991/emcm-16.2017.118
5. Bukhari, S.N.A.; Jasamai, M.; Jantan, I. Synthesis and biological evaluation of chalcone derivatives (mini review). Mini Reviews in Medicinal Chemistry, 2012, 12(13), pp. 1394–1403 DOI: https://doi.org/10.2174/13895575112091394
6. Dhar, D.N. The chemistry of chalcones and related compounds. New York: Wiley, 1981, p. 285. ISBN: 978-0471080077
7. Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. Chalcone: A privileged structure in medicinal chemistry. Chemical Reviews, 2017, 117(12), pp. 7762–7810. DOI: https://doi.org/10.1021/acs.chemrev.7b00020
8. Kachroo, M.; Panda, R.; Yadav, Y. Synthesis and biological activities of some new pyrimidine derivatives from chalcones. Der Pharma Chemica, 2014, 6(2), pp. 352–359. ISSN 0975–413X. https://www.derpharmachemica.com/pharma-chemica/synthesis-and-biological-activities-of-some-new-pyrimidine-derivatives-from-chalcones.pdf
9. Sahoo, B.M.; Rajeswari, M.; Panda, J.; Binayani, S. Green expedient synthesis of pyrimidine derivatives via chalcones and evaluation of their anthelmintic activity. Indian Journal of Pharmaceutical Education and Research, 2017, 51(4S), pp. S700–S706. DOI: https://doi.org/10.5530/ijper.51.4s.101
10. Venkatesh, T.; Bodke, Y.D.; Joy, M.N.; Dhananjaya, B.L.; Venkataraman, S. Synthesis of some benzofuran derivatives containing pyrimidine moiety as potent antimicrobial agents. Iranian Journal of Pharmaceutical Research, 2018, 17(1), pp. 75–86. DOI: https://doi.org/10.22037/ijpr.2018.2181
11. Aswin, K.; Sheik Mansoor, S.; Logaiya, K.; Sudhan, S.P.N. Triphenylphosphine: an efficient catalyst for the synthesis of 4,6–diphenyl–3,4–dihydropyrimidine–2(1H)–thione under thermal conditions. Journal of King Saud University–Science, 2014, 26(12), pp. 141–148. DOI: http://dx.doi.org/10.1016/j.jksus.2013.05.004
12. Jayaseelan, D.; Ganapathi, M.; Guhanathan, S. Microwave–assisted synthesis of 4,6–diphenylsubstituted thiazine derivatives and its characterization. Organic Chemistry: An Indian Journal, 2015, 11(8), pp. 305–311. ISSN: 0974 – 7516. https://www.tsijournals.com/articles/microwave-assisted-synthesis-of-46-diphenyl-substituted-thiazinederivatives-and-its-characterisation.pdf
13. Huang, H.; Cai, J.; Tang, L.; Wang, Z.; Li, F.; Deng, G.-J. Metal–free assembly of polysubstituted pyridines from oximes and acroleins. The Journal of Organic Chemistry, 2016, 81(4), pp. 1499–1505. DOI: https://doi.org/10.1021/acs.joc.5b02624
14. Song, Z.; Huang, X.; Yi, W.; Zhang, W. One–pot reactions for modular synthesis of polysubstituted and fused pyridines. Organic Letters, 2016, 18(21), pp. 5640–5643. DOI: https://doi.org/10.1021/acs.orglett.6b02883
15. De Souza, A.A.N.; Xavier, V.F.; Coelho, G.S.; Sales Junior, P.A.; Romanha, A.J.; Murta, S.M.F.; Carneiro, C.M.; Taylor, J.G. Synthesis of 3,5–diarylisoxazole derivatives and evaluation of in vitro trypanocidal activity. Journal of the Brazilian Chemical Society, 2018, 29(2), pp. 269–277. DOI: https://doi.org/10.21577/0103-5053.20170137
16. Kalirajan, R.; Mohhamed Rafick, M.H.; Sankar, S.; Gowramma, B. Green synthesis of some novel chalcone and isoxazole substituted 9–anilino acridine derivatives and evaluation of their antimicrobial and larvicidal activities. Indian Journal of Chemistry, 2018, 57B, pp. 583–590. https://nopr.niscpr.res.in/bitstream/123456789/44176/1/IJCB%2057B%284%29%20583-590.pdf
17. Wang, Y.; Jiang, C–M.; Li, H–L.; He, F–S.; Luo, X.; Deng, W–P. Regioselective iodine–catalyzed construction of polysubstituted pyrroles from allenes and enamines. The Journal of Organic Chemistry, 2016, 81(18), pp. 8653–8658. DOI: https://doi.org/10.1021/acs.joc.6b01737
18. Ding, Y.; Zhang, T.; Chen, Q–Y.; Zhu, C. Visible–light photocatalytic aerobic annulation for the green synthesis of pyrazoles. Organic Letters, 2016, 18(17), pp. 4206–4209. DOI: https://doi.org/10.1021/acs.orglett.6b01867
19. Guchhait, S.K.; Hura, N.; Shah, A.P. Synthesis of polysubstituted 2–aminoimidazoles *via*

alkene–diamination of guanidine with conjugated *α*–bromoalkenones. The Journal of Organic Chemistry, 2017, 82(5), pp. 2745–2752. DOI: https://doi.org/10.1021/acs.joc.6b03021
20. Zhu, Y.; Li, C.; Zhang, J.; She, M.; Sun, W.; Wan, K.; Wang, Y.; Yin, B.; Liu, P.; Li, J. A facile $FeCl_3/I_2$–catalyzed aerobic oxidative coupling reaction: Synthesis of tetrasubstituted imidazoles from amidines and chalcones. Organic Letters, 2015, 17(15), pp. 3872–3875. DOI: https://doi.org/10.1021/acs.orglett.5b01854
21. Yang, L.; Wu, Y.; Yang, Y.; Wen, C.; Wan J–P. Catalyst–free synthesis of 4–acyl–NH–1,2,3–triazoles by water–mediated cycloaddition reactions of enaminones and tosyl azide. Beilstein Journal of Organic Chemistry, 2018, 14, pp. 2348–2353. DOI: https://doi.org/10.3762/bjoc.14.210
22. Wan, J–P.; Cao, S.; Liu, Y. Base–promoted synthesis of *N*–substituted 1,2,3–triazoles *via* enaminone–azide cycloaddition involving regitz diazo transfer. Organic Letters, 2016, 18(23), pp. 6034–6037. DOI: https://doi.org/10.1021/acs.orglett.6b02975
23. Singh, N.; Pandey, S.K.; Tripathi, R.P. Regioselective [3+2] cycloaddition of chalcones with a sugar azide: easy access to 1–(5–deoxy–D–xylofuranos–5–yl)–4,5–disubstituted–1H–1,2,3–triazoles. Carbohydrate Research, 2010, 345(12), pp. 1641–1648. DOI: https://doi.org/10.1016/j.carres.2010.04.019
24. Abd El-Sattar, N.E.A.; Badawy, E.H.K.; Abdel-Mottaleb, M.S.A. Synthesis of some pyrimidine, pyrazole, and pyridine derivatives and their reactivity descriptors. Journal of Chemistry, 2018, 11, pp. 1–11. DOI: https://doi.org/10.1155/2018/8795061
25. Shaikh, S.; Baseer, M.A. Synthesis and antimicrobial activities of some new 2,3–dihydro–1,5–benzodiazepine derivatives. International Journal of Pharmaceutical Sciences Research, 2013, 4(7), pp. 2717–2720. DOI: https://doi.org/10.13040/IJPSR.0975-8232.4(7).2717-20
26. El–Gaml, K.M. Application of chalcone in synthesis of new heterocycles containing 1,5–benzodiazepine derivatives. American Journal of Organic Chemistry, 2014, 4(1), pp. 14–19. DOI: https://doi.org/10.5923/j.ajoc.20140401.03
27. Nehra, B.; Rulhania, S.; Jaswal, S.; Kumar, B.; Singh, G.; Monga, V. Recent advancements in the development of bioactive pyrazoline derivatives. European Journal of Medicinal Chemistry, 2020, 112666. DOI: https://doi.org/10.1016/j.ejmech.2020.112666
28. Mantzanidou, M.; Pontiki, E.; Hadjipavlou–Litina, D. Pyrazoles and pyrazolines as anti–inflammatory agents. Molecules, 2021, 26(11), 3439, pp. 1–18. DOI: https://doi.org/10.3390/molecules26113439
29. Abd ElMonaem, H.S.; Abdel-Aziz, N.I.; Morsy, M.A.; Badria, F.A.; ElSenduny, F.; El-Ashmawy, M.B.; Moustafa, M.A. Synthesis, *in vitro* antiproliferative evaluation and molecular docking of new tetrazole–chalcone and tetrazole–pyrazoline hybrids. Journal of Applied Pharmaceutical Science, 2018, 8(5), pp. 075–087. DOI: https://doi.org/10.7324/JAPS.2018.8510
30. Pozzetti, L.; Ibba, R.; Rossi, S.; Taglialatela-Scafati, O.; Taramelli, D.; Basilico, N.; D'Alessandro, S.; Parapini, S.; Butini, S.; Campiani, G.; Gemma, S. Total synthesis of the natural chalcone Lophirone E, synthetic studies toward benzofuran and indole–based analogues, and investigation of anti–leishmanial activity. Molecules, 2022, 27(2), pp. 463–483. DOI: https://doi.org/10.3390/molecules27020463
31. Arif, R.; Rana, M.; Yasmeen, S.; Amaduddin; Khan, M.S.; Abid, M.; Khan, M.S.; Rahisuddin Facile synthesis of chalcone derivatives as antibacterial agents: synthesis, DNA binding, molecular docking, DFT and antioxidant studies. Journal of Molecular Structure, 2020, 1208, pp. 127905. DOI: https://doi.org/10.1016/j.molstruc.2020.127905
32. Kishore Babu, A.; Selvaraju, K. Synthesis and characterization of some novel chalcone derivatives. Rasayan Journal of Chemistry, 2018, 11(4), pp. 1501–1505. DOI: http://dx.doi.org/10.31788/RJC.2018.1144037
33. World Health Organization, Global Malaria Programme, 2021. https://www.who.int/teams/global-malaria-programme
34. Syahri, J.; Yuanita, E.; Nurohmah, B.A.; Wathon, M.H.; Syafri1, R.; Armunanto, R.; Purwono, B. Xanthone as antimalarial: QSAR analysis, synthesis, molecular docking and *in–vitro* antimalarial evaluation. Oriental Journal of Chemistry, 2017, 33(1), pp. 29–40. DOI: http://dx.doi.org/10.13005/ojc/330104
35. Syahri, J.; Nasution, H.; Nurohmah, B.A.; Purwono, B.; Yuanita, E. Novel aminoalkylated chalcone: synthesis, biological evaluation, and docking simulation as potent antimalarial agents. Journal of Applied Pharmaceutical Science, 2020, 10(6), pp. 001–005. DOI: http://doi.org/10.7324/JAPS.2020.10601
36. Manikala, V.; Rao, V.M. Synthesis and biological evaluation of chalcone tethered quinoline derivatives as anticancer agents. Chemical Data Collections, 2020, 28, p. 100423. DOI: https://doi.org/10.1016/j.cdc.2020.100423
37. Baquero, F.; Lanza, V.F.; Canton, R.; Coque, T.M. Public health evolutionary biology of antimicrobial resistance: priorities for intervention. Evolutionary Applications, 2014, 8(3), pp. 223–239. DOI: https://doi.org/10.1111/eva.12235
38. de Freitas, T.S.; Xavier, da C.J.; Pereira, R.L.S.; Rocha, J.E.; Muniz, D.F.; da Silva, P.T.; da Hora, J.P.; Dos Santos, H.S.; Bandeira, P.N.; Nogueira, C.E.S.; Teixeira, A.M.R.; Coutinho, H.D.M. Direct antibacterial and antibiotic resistance modulatory activity of chalcones synthesized from the natural product

2–hydroxy–3,4,6–trimethoxyacetophenone. FEMS Microbiology Letters, 2020, 367(15), pp. 1–8. DOI: https://doi.org/10.1093/femsle/fnaa124
39. Henry, E.J.; Bird, S.J.; Gowland, P.; Collins, M.; Cassella, J.P. Ferrocenyl chalcone derivatives as possible antimicrobial agents. The Journal of Antibiotics, 2020, 73, pp. 299–308. DOI: https://doi.org/10.1038/s41429–020–0280–y
40. Shinde, R.A.; Adole, V.A.; Jagdale, B.S.; Desale, B.S. Synthesis, antibacterial and computational studies of halo chalcone hybrids from 1–(2,3–Dihydrobenzo[b][1,4]dioxin–6–yl)ethan–1–one. Journal of the Indian Chemical Society, 2021, 98(4), pp. 100051. DOI: https://doi.org/10.1016/j.jics.2021.100051
41. Yang, J-L.; Ma, Y-H.; Li, Y-H.; Zhang, Y-P.; Tian, H-C.; Huang, Y-C.; Li, Y.; Chen, W.; Yang, L-J. Design, synthesis, and anticancer activity of novel trimethoxyphenyl–derived chalcone–benzimidazolium salts. American Chemical Society Omega, 2019, 4(23), pp. 20381–20393. DOI: https://doi.org/10.1021/acsomega.9b03077
42. Sooknual, P.; Pingaew, R.; Phopin, K.; Ruankham, W.; Prachayasittikul, S.; Ruchirawat, S.; Prachayasittikul, V. Synthesis and neuroprotective effects of novel chalcone–triazole hybrids. Bioorganic Chemistry, 2020, 105, p. 104384. DOI: https://doi.org/10.1016/j.bioorg.2020.104384
43. Gour, J.; Gatadi, S.; Pooladanda, V.; Mahammad Ghouse, S.; Malasala, S.; Madhavi, Y.V.; Godugu, C.; Nanduri, S. Facile synthesis of 1,2,3-triazole-fused Indolo- and Pyrrolo[1,4]diazepines, DNA-binding and evaluation of their anticancer activity. Bioorganic Chemistry, 2019, 93, p. 103306. DOI: https://doi.org/10.1016/j.bioorg.2019.103306
44. Yadav, P.; Lal, K.; Kumar, A.; Guru, S. K.; Jaglan, S.; Bhushan, S. Green synthesis and anticancer potential of chalcone linked-1,2,3-triazoles. European Journal of Medicinal Chemistry, 2017, 126, pp. 944–953. DOI: https://doi.org/10.1016/j.ejmech.2016.11.030
45. Lal, K.; Yadav, P.; Kumar, A.; Kumar, A.; Paul, A.K. Design, synthesis, characterization, antimicrobial evaluation and molecular modeling studies of some dehydroacetic acid-chalcone-1,2,3-triazole hybrids. Bioorganic Chemistry, 2018, 77, pp. 236–244. DOI: https://doi.org/10.1016/j.bioorg.2018.01.016
46. Zhang, X.; Rakesh, K.P.; Bukhari, S.N.A.; Balakrishna, M.; Manukumar, H.M.; Qin, H-L. Multi–targetable chalcone analogs to treat deadly Alzheimer's disease: current view and upcoming advice. Bioorganic Chemistry, 2018, 80, pp. 86–93. DOI: https://doi.org/10.1016/j.bioorg.2018.06.009
47. Santos, C.S.; de Oliveira, R.J.; de Oliveira, R.N.; Freitas, J.C.R. 1,2,3-Triazoles: general and key synthetic strategies. Arkivoc, 2020, 1, pp. 219–271. DOI: https://doi.org/10.24820/ark.5550190.p011.293
48. Rani, A.; Anand, A.; Kumar, K.; Kumar, V. Recent developments in biological aspects of chalcones: the odyssey continues. Expert Opinion on Drug Discovery, 2019, 14(3), pp. 249–288. DOI: https://doi.org/10.1080/17460441.2019.1573812
49. Singh, G.; Arora, A.; Kalra, P.; Maurya, I.K.; Ruizc, C.E.; Estebanc, M.A.; Sinha, S.; Goyal, K.; Sehgal, R. A strategic approach to the synthesis of ferrocene appended chalcone linked triazole allied organosilatranes: antibacterial, antifungal, antiparasitic and antioxidant studies. Bioorganic & Medicinal Chemistry, 2019, 27(1), pp. 188–195. DOI: https://doi.org/10.1016/j.bmc.2018.11.038
50. Singh, G.; Arora, A.; Mangat, S.S.; Rani, S.; Kaur, H.; Goyal, K.; Sehgal, K.; Maurya, I.K.; Tewari, R.; Choquesillo-Lazarte, D.; Sahoo, S.; Kaur, N. Design, synthesis and biological evaluation of chalconyl blended triazole allied organosilatranes as giardicidal and trichomonacidal agents. European Journal of Medicinal Chemistry, 2016, 108, pp. 287–300. DOI: https://doi.org/10.1016/j.ejmech.2015.11.029
51. Singh, P.; Anand, A.; Kumar, V. Recent developments in biological activities of chalcones: A mini review. European Journal of Medicinal Chemistry, 2014, 85, pp. 758–77. DOI: https://doi.org/10.1016/j.ejmech.2014.08.033
52. Yadav, P.; Lal, K.; Kumar, A.; Guru, S.K.; Jaglan, S.; Bhushan, S. Green synthesis and anticancer potential of chalcone linked–1,2,3–triazoles. European Journal of Medicinal Chemistry, 2017, 126, pp. 944–953. DOI: https://doi.org/10.1016/j.ejmech.2016.11.030
53. Lal, K.; Yadav, P.; Kumar, A.; Kumar, A.; Paul, A.K. Design, synthesis, characterization, antimicrobial evaluation and molecular modeling studies of some dehydroacetic acidchalcone–1,2,3–triazole hybrids. Bioorganic Chemistry, 2018, 77, pp. 236–244. DOI: https://doi.org/10.1016/j.bioorg.2018.01.016
54. Dheer, D.; Singh, V.; Shankar, R. Medicinal attributes of 1,2,3–triazoles: current developments. Bioorganic Chemistry, 2017, 71, pp. 30–54. DOI: https://doi.org/10.1016/j.bioorg.2017.01.010
55. Nemallapudi, B.R.; Guda, D.R.; Ummadi, N.; Avula, B.; Zyryanov, G.V.; Reddy, C.S.; Gundala, S. New methods for synthesis of 1,2,3-Triazoles: A Review. Polycyclic Aromatic Compounds, 2021, 42(6), pp. 1–19. DOI: https://doi.org/10.1080/10406638.2020.1866038
56. Flynn, J.M.; Melov, S. SOD2 in mitochondrial dysfunction and neurodegeneration. Free Radical Biology and Medicine, 2013, 62, pp. 4–12. DOI: https://doi.org/10.1016/j.freeradbiomed.2013.05.027
57. Duval, R.E.; Grare, M.; Demoré, B. Fight against antimicrobial resistance: we always need new antibacterials but for right bacteria. Molecules 2019, 24(17), pp. 3152–3160. DOI: https://doi.org/10.3390/molecules24173152
58. Al-Sa'doni, H.H.; Delmani, F.-A.; Al Balushi, A. M.; Al-Ahmad, A.H.; Alsawakhneh, S.O.; Al-Soud, Y.A. Synthesis and antibacterial activity of some new 1,2,4-triazole derivatives bearing

carbohydrazide moiety. European Journal of Chemistry, 2020, 11(2), pp. 113–119. DOI: https://doi.org/10.5155/eurjchem.11.2.113-119.1968
59. Strzelecka, M.; Świątek, P. 1,2,4-Triazoles as important antibacterial agents. Pharmaceuticals 2021, 14(3), pp. 224–251. DOI: https://doi.org/10.3390/ph14030224
60. Thomas, B.; Duval, R.E.; Fontanay, S.; Varbanov, M.; Boisbrun, M. Synthesis and antibacterial evaluation of bis-thiazolium, bis-imidazolium, and bis-triazolium derivatives. Methods and Applications of Medicinal Chemistry, 2019, 14(13), pp. 1232–1237. DOI: https://doi.org/10.1002/cmdc.201900151
61. Gao, F.; Wang, T.; Xiao, J.; Huang, G. Antibacterial activity study of 1,2,4-triazole derivatives. European Journal of Medicinal Chemistry, 2019, 173, pp. 274-281. DOI: https://doi.org/10.1016/j.ejmech.2019.04.043
62. Jeedi, N.M.; Bajji, S.; Ronad, P.M.; Nimbal, S.K.; Patil, S.B. Analgesic and anti-inflammatory investigation of 1,2,4- triazole derivatives in rats. Journal of Medical Pharmaceutical and allied Sciences, 2023,12(3), pp. 5850 – 5858. DOI: https://doi.org/10.55522/jmpas.V12I3.4666
63. Stingaci, E.; Zveaghinteva, M;, Pogrebnoi, S.; Lupascu, L.; Valica, V.; Uncu, L.;Smetanscaia, A.; Drumea, M.; Petrou, A.; Ciric, A.; Glamoclija, J.; Sokovic, M.; Kravtsov, V.; Geronikaki, A.; Macaev, F. New vinyl-1,2,4-triazole derivatives as antimicrobial agents: Synthesis, biological evaluation and molecular docking studies. Bioorganic & Medicinal Chemistry Letters. 2020, 30(17), 127368, pp. 1–12. DOI: https://doi.org/10.1016/j.bmcl.2020.127368
64. Jin, R.; Liu, J.; Zhang, G.; Li, J.; Zhang, S.; Guo, H. Design, synthesis, and antifungal activities of novel 1,2,4-triazole Schiff base derivatives. Chemistry and Biodiversity, 2018, 15(9), e1800263. DOI: https://doi.org/10.1002/cbdv.201800263
65. Gao, F.; Wang, T.; Xiao, J.; Huang, G. Antibacterial activity study of 1,2,4-triazole derivatives. European Journal of Medicinal Chemistry, 2019, 173, pp. 274–281. DOI: https://doi.org/10.1016/j.ejmech.2019.04.043
66. Zveaghintseva, M.; Stingaci, E.; Pogrebnoi, S.; Smetanscaia, A.; Valica, V.; Uncu, L.; Kravtsov, V.C.; Melenic, E.; Petrou, A.; Glamoclija, J.; Sokovic, M.; Carazo, A.; Mladenka, P.; Poroikov, V.; Geronikaki, A.; Macaev, F. Chromenol derivatives as novel antifungal agents: synthesis, in silico and *in vitro* evaluation. Molecules, 2021, 26(14), pp. 4304–4325. DOI: https://doi.org/10.3390/molecules26144304