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Synthesis and *In-vitro* / *silico* Evaluation of Fluorinated Chalcones

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ABSTRACT

The methodologies detail the steps for synthesising a series of chalcones using a protic solvent and 4-fluoro-3-methylacetophenone (FMAA) along with substituted benzaldehydes. In the current investigation, we synthesized chalcone and tested *In-silico* and *In-vitro* evaluation. They have tested *In-vitro* studies for antimicrobial and antifungal activity using the disc-diffusion method. The *In-silico* analysis of all synthesized derivatives showed a strong binding affinity to the target microorganism proteins, with some compounds displaying the best binding affinity, according to *In-vitro* research. When compound 1C interacted with the protein Glutaredoxin, it had a-5.43 Kcal/mol affinity. The best binding energies with the proteins UDP-3-O-[3-hydroxymyristoyl] N-acetyl glucosamine deacetylase, DNA gyrase, and dihydrofolate reductase were demonstrated by compound 1D, which has -6.3 Kcal/mol, -5.62 Kcal/mol, and -6.55 Kcal/mol, respectively.

Keywords: 4-Fluoro-3-methylacetophenone, *In-vitro*, and *In-silico*, Ultrasonic synthesis, Grinding technique, Solvent-free synthesis.

INTRODUCTION

The shikimate route produces chalcones, phenolic phytochemicals of the flavonoid class. Flavonoids can trace their biosynthesis back to chalcones. In chemical terms, chalcones are usually alkenones that consist of two rings of ketones joined by a three-carbon bond. This class may also include dihydrochalcones and other saturated ketones[1]. These ketones have a three-carbon alkenone unit rather than an alkenone unit. One or more phenolic hydroxyl groups, along with phenyl and geranyl substituents, are present on the aromatic rings, and other distinguishing features are found in naturally occurring chalcones. Some 3,000 chalcones have been identified in nature[2], and many of these have been shown to modulate and protect cells through interactions with other biomolecules. Cytotoxic, anti-inflammatory, anticancer, antioxidant,

and antimitotic effects of chalcones and their derivatives have been the subject of multiple articles and patents[3]. Chalcone derivatives have been extensively studied for their bioactivities and bioinspired syntheses because of their medicinal potential and structural simplicity[4]. The natural product containing chalcone scaffold with a medicinal application. Chalcones enjoy a privileged status in medicinal chemistry because of their natural abundance and relative simplicity in synthetic chemistry. Many scientists have generated synthetic chalcones since the nineteenth century. Kostanecki and Tambor[5] were the first to synthesize chalcones by treating o-acetoxychalcone dibromides with an alcoholic alkali. Modern methods of synthesizing chalcones[6-8] involve forming the core chalcone nucleus from two aromatic ring molecules, like benzaldehyde and acetophenone, by combining an alkaline base with a polar solvent. Many researchers synthesize chalcone in unique ways such as ultrasonic, microwave, solvent-free, grinding, etc.[9-12]. These techniques are very important today because they reduce energy, avoid hazardous reagents, and environmental risks, reduce wastewater pollution, protect biological life, save the environment, and save time.

Herein, we report the efficient strategy for the synthesis of a series of structurally interesting chalcone derivatives. A base-catalyzed condensation of FMAA with benzaldehydes to synthesize a series of chalcone derivatives in chemical, ultrasonic, and solvent-free grinding methods. The structural features regulating the interaction of produced derivatives with an identified receptor were also elucidated using molecular docking techniques.

EXPERIMENTAL

MATERIAL AND METHODS

All synthetic chemical reagents and solvents used in this study were of the highest purity and obtained from reliable suppliers. Borosilicate labware was used, an 8 x 8 x 6 cm Grinding bowl, and a pestle made of Ceramic material used for grinding purposes. For sonication use an ultrasonic 6.5 lit bath. Open capillary tubes were used to determine the uncorrected melting points of the synthesized compounds. Thin-layer chromatography (TLC) with silica gel as the stationary phase and a mixture of petroleum ether and ethyl acetate as the mobile phase was employed to monitor the reaction progress and product formation. Each spot was visualized under ultraviolet light. The IR spectra were recorded using a Brucker FT-IR spectrometer, and the ^{1}H NMR spectra were obtained with a 400 MHz Brucker spectrometer.

The general procedure of compound 1a-j

The synthesis involved the use of FMAA along with substituted aromatic benzaldehydes in the presence of a base and alcohol as the solvent, we present an efficient procedure for synthesizing a sequence of chalcones **(1a-j)**. The typical pathway of a synthetic reaction is shown in Figure 1 below.

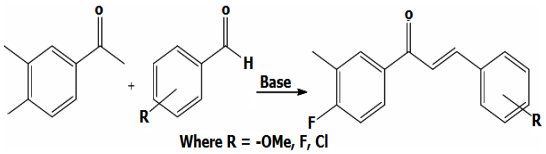
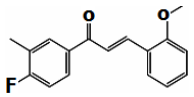
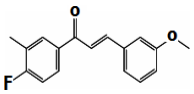
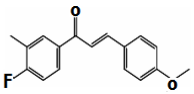
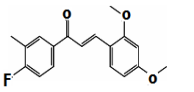
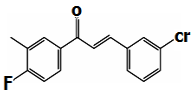
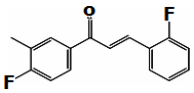
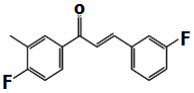
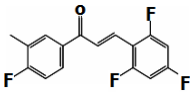
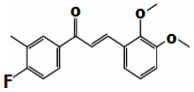
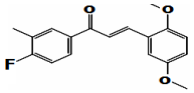


Fig. 1. Reaction scheme of compound 1a-j

Chemical: Chalcones are prepared through the Claisen-Schmidt condensation reaction. A solution was produced in 5 mL of ethanol with 1.31 mmol of FMAA and 1.31 mmol of substituted benzaldehydes. The solution was then supplemented with NaOH (1.97 mmol). Until the reaction was verified by TLC, the mixture was stirred at room temperature. The chalcone was then filtered out after the mixture was neutralized with diluted HCl at 0°C. The crude chalcone was refined by recrystallization in alcohol to yield (1a-j).

Ultra-sonication: Added 1.31 mmol of FMAA, 1.31 mmol of substituted benzaldehydes, and 1.97 mmol of NaOH in a test tube. The resulting mixture was brought to room temperature and subjected to ultrasonic agitation until complete conversion to the product **(1a-j)** was confirmed by TLC. Once the reaction was complete, the solid chalcones **(1a-j)** were obtained by cooling the interacting components in an ice bath and neutralizing them by dil. HCl. The chalcone is recrystallized from alcohol.

The listed chalcones (1a-j) were synthesized using the method mentioned above.

Comp (1a-j)	Product	Yield	Description
a		79.38 %	White solid
b		81.00 %	Off-white solid
c		84.63 %	Off-white solid
d		74.00 %	Off-white solid
e		73.91 %	White solid
f		70.60 %	Light yellow solid
g		73.31 %	Yellow solid
h		75.68 %	Off-white solid
i		80.00 %	White solid
j		87.50 %	Off-white solid

Grinding: In a clean Grinding bowl and pestle 1.31 mmol of FMAA, 1.31 mmol of substituted benzaldehydes, and 1.97 mmol of NaOH at room temperature. Grind the mixture for several minutes, the solid product was observed which was checked in TLC. Once confirmed the complete absence of acetophenone the solid chalcones **(1a-j)** were obtained by cooling the interacting components in an ice bath and neutralizing by dil. HCl. The chalcone is recrystallized from alcohol.

Spectral data of synthesis compound (1a-j)

(E)-1-(4-fluoro-3-methylphenyl)-3-(2-methoxyphenyl) prop-2-en-1-one,

White solid, yield 79.38%; m.p. 155°C. FT-IR (KBr) cm^{-1}: 3023, 2972, 2929, 1659, 1590, 1243, 1146, 738, 681. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.385, 3.944, 6.964, 6.964-8.164.

(E)-1-(4-fluoro-3-methylphenyl)-3-(3-methoxyphenyl) prop-2-en-1-one,

Off-white solid, yield 81.0%; m.p. 157°C. FT-IR (KBr) cm^{-1}: 3029, 2973, 2929, 1660, 1591, 1250, 1146, 740, 623. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.386, 3.950, 6.968, 7.012-8.166.

(E)-1-(4-fluoro-3-methylphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one,

Off-white solid, yield 84.63%; m.p. 155°C. FT-IR (KBr) cm^{-1}: 3027, 2974, 2922, 1660, 1585, 1250, 1153, 751, 683. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.366-2.540, 3.858, 7.043-7.063, 7.314-8.166.

(E)-3-(2,4-dimethoxyphenyl)-1-(4-fluoro-3-methylphenyl)prop-2-en-1-one,

Off-White solid, yield 74.0%; m.p. 159°C. FT-IR (KBr) cm^{-1}: 3012, 2968, 2939, 1649, 1592, 1256, 1144, 761/715. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.365, 3.968-3.944, 6.921, 7.087-7.914.

(E)-3-(3-chlorophenyl)-1-(4-fluoro-3-methylphenyl) prop-2-en-1-one,

White solid, yield 73.91%; m.p. 156°C. FT-IR (KBr) cm^{-1}: 3025, 2971, 2927, 1662, 1594, 1241, 738, 688. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.368, 7.120, 7.142-7.923.

(E)-1-(4-fluoro-3-methylphenyl)-3-(2-fluorophenyl) prop-2-en-1-one,

Light yellow solid, yield 70.60%; m.p. 157°C. FT-IR (KBr) cm^{-1}: 3065, 2978, 2924, 1657, 1586, 1235, 752, 625. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.393, 7.122-7.144, 7.166-7.944.

(E)-1-(4-fluoro-3-methylphenyl)-3-(3-fluorophenyl) prop-2-en-1-one

Yellow solid, yield 73.31%; m.p. 159°C. FT-IR (KBr) cm^{-1}: 3042, 2981, 2922, 1659, 1583, 1219, 756, 624. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.377, 7.112-7.151, 7.156-7.934.

(E)-1-(4-fluoro-3-methylphenyl)-3-(2,4,6-trifluorophenyl) prop-2-en-1-one,

Off-whit solid, yield 75.68%; m.p. 163°C. FT-IR (KBr) cm^{-1}: 3057, 2933, 2919, 1664, 1587, 1245, 739. ^1H NMR (400 MHz, $CDCl_3$, δ ppm): 2.383, 7.032-7.120, 7.142-7.928.

E)-3-(2,3-dimethoxyphenyl)-1-(4-fluoro-3-methylphenyl)prop-2-en-1-one,

White solid, yield 80.00%; m.p. 161°C. FT-IR (KBr) cm^{-1}: 3012, 2936, 2833, 1615, 1584, 1262,

1150, 745, 686. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.326, 3.798-3.889, 7.086, 7.342-8.183.

(E)-3-(2,5-dimethoxyphenyl)-1-(4-fluoro-3-methylphenyl) prop-2-en-1-one,

Off-White solid, yield 87.50%; m.p. 159°C. FT-IR (KBr) cm^{-1}: 3010, 2935, 2838, 1612, 1589, 1264, 1148, 747, 686. ^{1}H NMR (400 MHz, $CDCl_3$,δ ppm): 2.326-2.379, 3.798-3.889, 7.086, 7.331-8.162.

Disc-Diffusion Study

We evaluated the antibacterial activity of the azomethine compound using the disc diffusion method[13]. We used 6-millimeter discs made from Whatman filter paper no.1. The 500 g/mL concentration of chalcones solution was prepared. To cultivate the bacteria, 20 mL of sterile growth media was poured into each sterile petri dish, covered, and placed in the refrigerator to solidify. After incubating the broth cultures of microorganisms for 16 h, we performed disc diffusion studies[14–15]. After sterilization and inoculation, the sample, control, and standard discs were air-dried at room temperature to eliminate any residual solvent that might affect the results. For bacteria, the zone of inhibition appears after 24 h of incubation at 37°C on plates that were chilled for 1 h to increase the rate of chemical diffusion from the test disc into the agar plate[16].

***In-silico* (Molecular Docking) Study**

The docking and virtual screening were performed as per the established protocol from our lab that is published elsewhere[17-21]. To further understand how the synthesized compounds interact with pathogenic microbial species at the molecular level, molecular docking experiments were conducted. The PyRx domain took advantage of Open Babel to bring in ligand molecules in SDF format for energy reduction with the UFF Force field. The Python Prescription 0.8 (PyRx) package, of which AutoDock 4.2 is a component, was used.[22] On an affinity grid with 50 points at each of the three X, Y, and Z coordinates and a spacing of 0.375A, the Autogrid program was employed to encompass the entire active site. We employed a Lamarckian genetic algorithm to perform the conformational search for the optimal binding pose. The three-dimensional receptor-ligand interaction and two-dimensional chemical interaction structures were shown using the Biovia Discovery Studio17.1.0[23]. Three bacteria and one fungus were used in the in-silico assessment of the antifungal and antibacterial activity. *E. coli* glutaredoxin (PDB ID: 1GRX) and Pseudomonas aeruginosa UDP-3-O-((R)-3-hydroxymyristoyl)-N-acetyl glucosamine deacetylase (PDB ID: 3P3E) were two of the *Gram-negative* bacteria targets. *Staphylococcus aureus* DNA gyrase (PDB ID: 3G75) and dihydrofolate reductase (PDB ID: 1AI9) were chosen as targets for *Gram-positive* bacteria and fungi, respectively. The three-dimensional structures of the ligand-coated targets were obtained from the Protein Data Bank (http://www.rcsb.org). The most effective compounds against Candida albicans, according to an in vitro investigation, were 1a, 1c, and 1d, which also showed strong binding affinity in an in-silico study. Similar antibacterial and antifungal studies were conducted, and Table 1 shows their binding affinities.

RESULTS AND DISCUSSION

Chemistry

Chalcones **(1a-j)** were synthesized by reacting FMAA with aromatic benzaldehydes in the presence of dilute alkali[24]. The chalcones derivatives of the FMAA moiety illustrated in Fig. 1 were synthesized from FMAA and substituted benzaldehydes at an equimolar concentration in the presence of the basic catalyst sodium hydroxide. All chalcone compounds are non-hygroscopic, insoluble in water, and resistant to various organic solvents, making them stable at room temperature. All prepared organic compounds had structures confirmed by UV-Visible, IR, and NMR spectrum data. The freshly synthesized azomethines were discovered to have maxima in the wavelength range of 275-440 nm (λ_{max}).

FT-IR Spectra

The experimental section summarizes the infrared frequencies displayed by the benzaldehyde substituents of FFMAA derivatives. A band of moderate intensity, corresponding to the aromatic ν(C-H) frequency range, was seen for FMAA derivatives. The novel chalcones with an aromatic ($-CH_3$) group showed poor broadband in the 2922-2968 cm^{-1} range[25]. Bands at 2939–2981 cm^{-1} in the FTIR spectra of the newly discovered derivatives are associated with the -CH= stretching vibration. The (C=O) group is responsible for a prominent band in the infrared spectra of all chalcones compounds, centered at 1649-1664 cm^{-1} [26-27]. The aromatic ν(C=C) vibrations are responsible for the medium intensity band between 1583 and 1594 cm^{-1}. In the spectra, we observed the (C-F) band around 1219-1256 cm^{-1} in derivatives of FMAA with benzaldehyde substituents. Compounds 1a-1d, 1i,

and 1j included the -OCH_3 group on the aromatic ring, which caused the appearance of the medium intensity band at 1144-1153 cm^{-1} [28]. C-Cl stretching vibration explains the band's appearance at 1241 cm^{-1} in compound 1e.

^{1}H-NMR Spectra

In the ^{1}H-NMR spectra of compound 1a-j, the methyl group protons are assigned to two singlets at 2.36-2.39 ppm. All of the synthesized chalcones exhibited two doublets in the range 6.90-7.12 and 6.92-7.14 ppm in their ^{1}H NMR spectra[29], corresponding to typical coupling constants (J) of 15.3 and 15.1 Hz, respectively, confirming their production. The aromatic proton of synthesized new chalcones has a multiplet peak at 6.96-8.16 ppm integrating[30]. For compounds 1a-1d, 1i, and 1j, a singlet peak at 3.94-3.97 ppm for three protons may be attributed to -OCH_3.

Antibacterial activity

The bacterial strains were used in the disc diffusion method of antimicrobial tests. Table 1 presents the minimum inhibitory concentrations (MICs) of the chalcone derivatives for the four different bacterial strains. Three of the 10 heterocyclic chalcones tested showed substantial activity against *E. coli* MCC 2412. The conventional medication was effective against *Bacillus subtilis* MCC 2010 MCC 2080, compounds **1a-j**, which have fluoro substituents on the phenyl ring, demonstrated even more pronounced activity. Pseudomonas aeruginosa MCC 2080 was resistant to the reference medication and all compounds except those with a phenyl moiety **(1a-j)**. This compound's antimicrobial effectiveness against *Pseudomonas aeruginosa* MCC 2080 indicated its promise to treat drug-resistant bacteria. Some compounds with fluoro or bromo substituents were effective against the bacteria, whereas others were only moderately or ineffective[31-34]. Compound 1d exhibits significant activity against bacteria due to its meta and para substituent methoxy groups. Compound 1c exhibits a similar effect on antibacterial activity against Pseudomonas aeruginosa MCC 2080 due to its para methoxy group.

Table 1: Antimicrobial activities of compounds 1a-j

Compound (1a-j)	Antimicrobial action (inhibition zone)			
	S. aureus (MCC2408)	*B. subtilis* (MCC2010)	*E. coli* (MCC2412)	*P. aeruginosa* (MCC2080)
a	6	9	0	8
b	9	11	6	7
c	6	6	9	22
d	24	23	24	6
e	6	8	8	0
f	7	0	6	7
g	6	8	7	10
h	9	7	6	0
i	6	6	9	10
j	7	8	16	7
Streptomycin	7	6	10	18

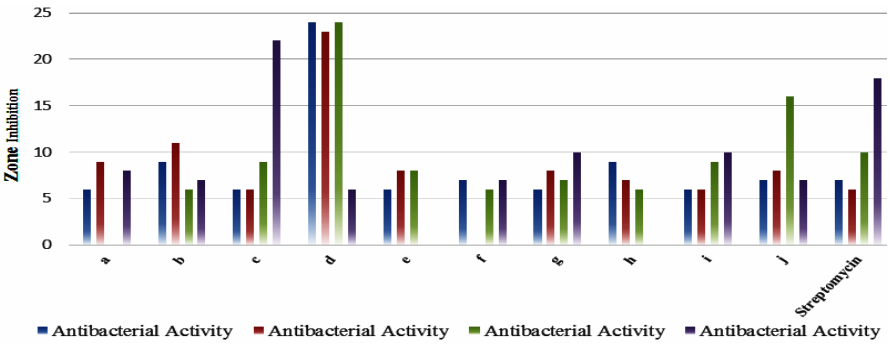


Fig. 2. Antimicrobial activity of compounds 1a-j

Antifungal activity

In this work, *C. albicans* (MCC1439) and *S. cerevisiae* (MCC1033) were subjected to a MIC of 50 g/mL of fluconazole. Based on the results presented in Table 2, all compounds examined possessed a fungicidal potential superior to the reference medication, with a MIC of 54 g/mL against fungus.

Table 2: Antifungal activities of compounds 1a-j

Compound (1a-j)	Antifungal Activity (zone of inhibition) *C. Albicans* (MCC1439)	*S. cerevisiae* (MCC1033)
a	7	0
b	6	0
c	7	8
d	8	0
e	6	8
f	8	11
g	9	6
h	7	8
i	6	7
j	0	12
Fluconazole	9	6

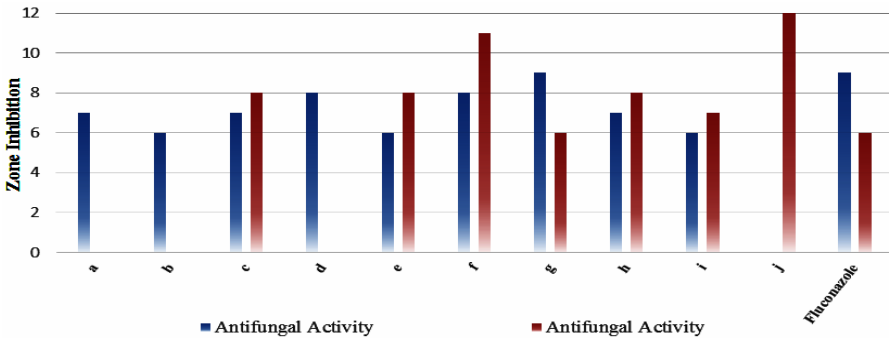


Fig. 3. Antifungal activity of compounds 1a-j

In-silico (Molecular Docking) study

Ten compounds **1a-j** were docked in bacterial and fungal proteins as mentioned above. To gain more insights about the compounds, interactions were studied in detail. As shown in Fig. 4, 3P3E interacts best with compound 1d. The compound forms hydrogen bonds with residues Thr190, Phe191; Van der Waals interactions with Leu18, Ser63, His78, Thr75 Asp241, His237, Phy160, Ile158, Lys261, Ser262, Gly263 and a Pi-alkyl interaction with residue His19. The second bacterial protein 3G75 shows the highest binding affinity for compound 1d as shown in Figure 5. It shows hydrogen bonding with residues Ser55, Asp54, Van der Waals interaction with Glu58, Ile102, Ser128, Val130, Leu103, Thr173, Val131, Glu50. The third bacterial protein 1GRX best interacts with the compound 1c as shown in Fig. 6. It forms a hydrogen bond with residues Thr73, Van der Waals interaction with Ser14, Gly57, Thr58, Ser9, Asp74, and a carbon-hydrogen bond Lys45. The antifungal protein 1AI9 shows the highest binding affinity with compound 1d as shown in Fig. 7. The compound forms a hydrogen bond with Ala11, Van der Waals interaction with Gly23, Tyr 21, Thr147, Gly20, Lys24, Glu32, Ile112, Tyr118, Gly114, Val10 and a pi stacked: Phe 36.

Table 3: The enthalpy of binding of the freshly produced chemicals (∆G)

Compounds (1a-j)	Fungi *C. albicans* (1AI9)	*Pseudomonas. a* (3P3E)	Bacteria *E.coli* (1GRX)	*Staphylococcus. a* (3G75)
a	-6.51	-6.54	-5.68	-5.99
b	-6.77	-6.22	-5.97	-5.55
c	-6.74	-6.17	-5.43	-5.65
d	-6.55	-6.30	-5.47	-5.62
e	-6.74	-6.39	-5.88	-5.8
f	-6.71	-6.08	-5.62	-5.41
g	-6.69	-6.29	-5.56	-5.96
h	-6.40	-5.60	-5.36	-5.24
i	-6.43	-6.38	-5.73	-6.72
j	-6.54	-6.50	-5.24	-6.08

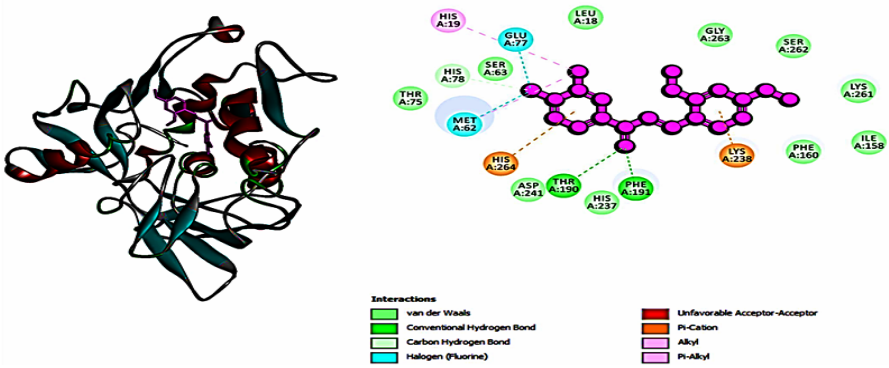


Fig. 4. The 3D and 2D images illustrate the binding interactions between compound 1d and the amino acids of 3P3E

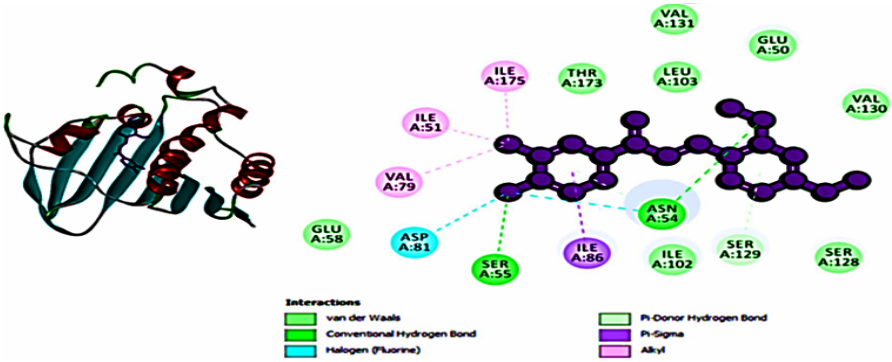


Fig. 5. Covalent interactions between chemical 1d and the amino acids in 3G75, are shown in 3D and 2D

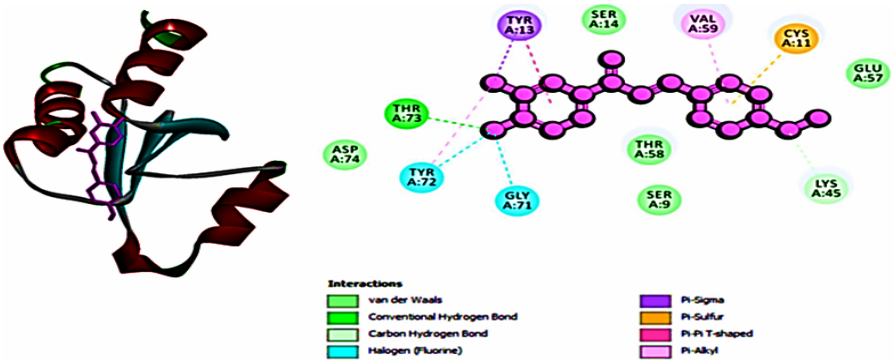


Fig. 6. Compound 1c's binding interactions with 1GRX's amino residues are depicted in 3D and 2D

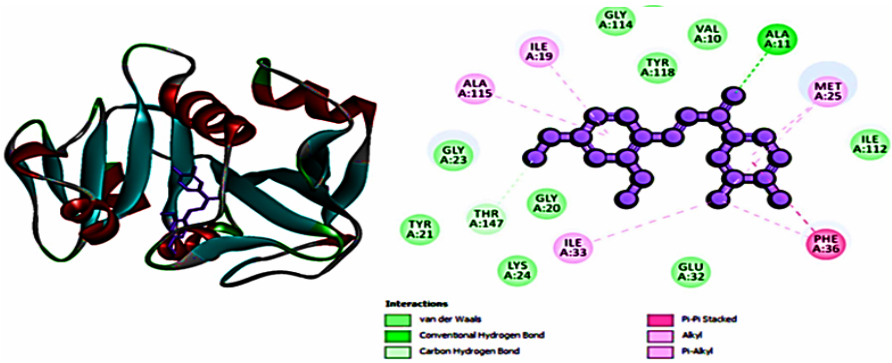


Fig. 7. Compound 1d's binding interactions with 1AI9's amino acids are depicted in 3D and 2D

CONCLUSION

This study discusses the synthesis, characterization, and antibacterial and antifungal properties of substituted benzaldehyde derivatives of FMAA. These compounds' structures were investigated using UV, ^{1}H NMR, and FT-IR spectrum spectroscopy. The process defined as a chemical route and ultrasonic, grinding, solvent-free reaction which delivers a suitable yield was used to synthesize these new chalcone derivatives. These methods are very significant in today's world because they save time, safeguard biological life, reduce wastewater pollution, and reduce energy and environmental dangers. Subsequently, the antibacterial effects of the fluorinated chalcones **(1a-j)** were evaluated against bacterial strains. These compounds exhibited superior antibacterial activity compared to streptomycin and demonstrated efficacy against a broad spectrum of bacteria. Based on their binding free energy, compounds 1c and 1d were recognized as promising candidates for the development of new antifungal and antibacterial agents. Our goal is to determine the mechanism of action of newly synthesized derivatives **(1a-j)** in the inhibition of 3P3E, 1GRX, 3G75, and 1AI9 through in vitro observation and structural analysis of the docked complex.

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Conflict of interest

The authors declare that they have no conflicts of interest.

REFERENCES

1. Stompor, M.; Broda, D., & Bajek-Bil, A., Dihydrochalcones: Methods of acquisition and pharmacological properties—A first systematic review., *Molecules*., **2019**, *24*(24), 4468.
2. Wang, M.; Lin, L.; Lu, J. J., & Chen, X. Pharmacological review of isobavachalcone, a naturally occurring chalcone., *Pharmacological Research*., **2021**, *165*, 105483. https://doi.org/10.1016/j.phrs.2021. 105483
3. Nadia E.; Hrichi H.; Ruba A.; Wassila D.; Fatin, and Rania B (2022) Synthesis of Chalcones Derivatives and Their Biological Activities: A Review., *ACS Omega.,* **2022**, *7*, 27769–27786 https://doi.org/10.1021/acsomega.2c01779
4. Jasim, H. A.; Nahar, L.; Jasim, M. A.; Moore, S. A.; Ritchie, K. J., & Sarker, S. D. (2021). Chalcones: synthetic chemistry follows where nature leads., *Biomolecules.,* **2021**, *11*, 1203. https://doi.org/10.3390/biom11081203
5. Hutchins, W.A.; Wheeler, T.S. Chalcones: A new synthesis of chrysin, apigenin, and luteolin., *J. Chem. Soc*., **1939**, 91–94. doi:10.1039/JR9390000091
6. Farooq, S., & Ngaini, Z. Recent synthetic methodologies for chalcone synthesis (2013-2018)., *Current Organocatalysis*., **2019**, *6*(3), 184-192. DOI: 10.2174/2213337206666190306155140
7. Jung, J. C.; Lee, Y.; Min, D.; Jung, M., & Oh, S., Practical synthesis of chalcone derivatives and their biological activities., *Molecules*., **2017**, *22*(11), 1872. doi:10.3390/molecules22111872
8. Jin, C.; Liang, Y. J.; He, H.; & Fu, L. Synthesis and antitumor activity of novel chalcone derivatives., *Biomedicine & Pharmacotherapy*., **2013**, *67*(3), 215-217. doi: 10.1016/j.biopha.2010.12.010
9. Jarag K.; Pinjari D.; Pandit A.; Shankarling G., Synthesis of chalcone (3-(4-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one): Advantage of sonochemical method over conventional method., *Ultrasonics Sonochemistry.,* **2011**, *18*(2011) 617–623. doi: 10.1016/j.ultsonch.2010.09.010
10. Gupta R.; Gupta N.; Jain A.; (2010), Improved synthesis of chalcone and pyrazoline under ultrasonic irradiation. INDIAN J. CHEM., SEC B MARCH **2010**.
11. Zangade S.; Mokle S.; Vibhute A.; Vibhute Y.; An Efficient and Operationally Simple Synthesis of Some New Chalcones by Using Grinding Technique., *Chemi. Sci. J*., **2011**, 2011: CSJ-13
12. Rateb N M.; Zohdi H F.; (2009) Atom-Efficient, Solvent-Free, Green Synthesis of Chalcones by Grinding, Synthetic Communications1., **2009,** *39*, 2789–2794, http://dx.doi.org/10.1080/00397910802664244

13. Kakanejadifard, A.; Azarbani, F.; Zabardasti, A.; Rezayat, A.; Ghasemian, M., & Kakanejadifard, S., Spectroscopy and solvatochromism studies along with antioxidant and antibacterial activities investigation of azo–azo-azomethine compounds 2-(2-hydroxyphenyl imino) methyl)-4-phenyldiazenyl) phenol. Spectrochimica Acta Part A., *Molecular and Biomolecular Spectroscopy*., **2014**, *124*, 153-158. http://dx.doi.org/10.1016/j.saa.2013.05.027
14. El-Gammal.; O. A.; Mohamed, F. S.; Rezk, G. N., & El-Bindary, A. A. Synthesis, characterization, catalytic, DNA binding, and antibacterial activities of Co(II), Ni(II), and Cu(II) complexes with new Schiff base ligand., *Journal of Molecular Liquids*., **2021**, *326*, 115223. https://doi.org/10.1016/j.molliq.2020.115223
15. Bakht J.; Shaheen S., & Shafi M. Antimicrobial potentials of Mentha longifolia by disc diffusion method., *Pakistan Journal of Pharmaceutical Sciences*., **2014**, *27*(4), 939-945.
16. Anagania B.; Singha J.; Bassina P.; Besrab G.; Benhama C.; Reddyc T.; Coxd J.; Goyala M Identification and validation of the mode of action of the chalcone anti-mycobacterial compounds., *The Cell Surface.,* **2020**, *6* (2020) 100041. https://doi.org/10.1016/j.tcsw.2020.100041
17. Meshram RJ.; Baladhye VB.; Gacche RN.; Karale BK.; Gaikar RB(2017). Pharmacophore mapping approach for drug target identification: chemical synthesis and in silico study on novel thiadiazole compounds., *Journal of clinical and diagnostic research: JCDR*., **2017,** *11*(5), KF01. DOI: 10.7860/JCDR/2017/22761.9925
18. Mogle PP.; Meshram RJ.; Hese SV.; Kamble RD.; Kamble SS.; Gacche RN.; Dawane BS (2016). Synthesis and molecular docking studies of a new series of bipyrazol-yl-thiazol-ylidene-hydrazinecarbothioamide derivatives as potential antitubercular agents., *MedChemComm.*, **2016**, *7*(7), 1405-20. DOI: 10.1039/x0xx00000x
19. Meshram RJ.; Jangle SN (2009). Molecular docking and binding energy studies on neuraminidase of h1n1 reveal possible answers to its resistance to oseltamivir., *IJDD*., **2009**, *1*, 34-39.
20. Sharbidre A.; Dhage P.; Duggal H.; Meshram R (2021). *In silico* investigation of Tridax procumbens phyto-constituents against SARS-CoV-2 infection., *Biointerface Res. Appl. Chem*., **2021**, *11*, 12120-48. https://doi.org/10.33263/BRIAC114.1212012148
21. Shaikh RU, Meshram RJ, Gacche RN. (2019). An investigation on in vitro anti-inflammatory and antiproliferative potential of isolated Labdane diterpenoids from Andrographis paniculata (Burm. f.) wall. Ex news: An important medicinal plant prescribed in Ayurveda., *European Journal of Integrative Medicine*., **2019,** *1*(32), 100983. doi.org/10.1016/j.eujim.2019.100983
22. Dallakyan, S.; Olson, A.J. Small-molecule library screening by docking with PyRx. Chemical Biology Humana Press, New York, NY **2015**, *1263*, 243-250, https://doi.org/10.1007/978-1-4939-2269-7_19.
23. Biovia, D.S.; Dsme, R. San Diego: Dassault Systèmes., **2017**.
24. Yadav, G. D., & Wagh, D. P. Claisen Schmidt Condensation using Green Catalytic Processes: A Critical Review., *Chemistry Select*., **2020**, *5*(29), 9059-9085. doi.org/10.1002/slct.202001737
25. Morar, M. I.; Fetea, F.; Rotar, A. M.; Nagy, M.; & Semeniuc, C. A. Characterization of essential oils extracted from different aromatic plants by FTIR spectroscopy., *Bull. UASVM Food Sci. Technol*., **2017**, *74*, 37-38. DOI: 10.15835/buasvmcn-fst:12634
26. Be, K. B.; Grabska, J.; Badzoka, J., & Huck, C. W., Spectra-structure correlations in NIR region of polymers from quantum chemical calculations. The cases of the aromatic ring, C= O, C N, and C-Cl functionalities. Spectrochimica Acta Part A: *Molecular and Biomolecular Spectroscopy*., **2021**, *262*, 120085. https://doi.org/10.1016/j.saa.2021.120085
27. Kosi ska, A. I., Nisiewicz, M. K., Nowicka, A. M., & Kasprzak, A., Electrochemical Recognition of Aromatic Species with Ferrocenylated 1, 3, 5 Triazine or 1, 3, 5 Triphenylbenzene Containing Highly Organized Molecules., *ChemPlusChem*., **2021**, *86*(6), 820-826. doi.org/10.1002/cplu.202100137

28. Khorrami, M. K.; Sadrara, M., & Mohammadi, M., Quality classification of gasoline samples based on their aliphatic to aromatic ratio and analysis of PONA content using genetic algorithm-based multivariate techniques and ATR-FTIR spectroscopy., *Infrared Physics & Technology.*, **2022**, *126*, 104354.
29. Van de Velde, F.; Knutsen, S. H.; Usov, A. I.; Rollema, H. S., & Cerezo, A. S. ^{1}H and ^{13}C high-resolution NMR spectroscopy of carrageenans: application in research and industry., *Trends in Food Science & Technology.*, **2002**, *13*(3), 73-92.
30. Mullen, C. A.; Strahan, G. D., & Boateng, A. A. Characterization of various fast-pyrolysis bio-oils by NMR spectroscopy., *Energy & Fuels.*, **2009**, *23*(5), 2707-2718. doi.10.1021/ef801048b.
31. Balouiri, M.; Sadiki, M., & Ibnsouda, S. K., Methods for in vitro evaluating antimicrobial activity: A review., *Journal of pharmaceutical analysis.*, **2016**, *6*(2), 71-79. http://dx.doi.org/10.1016/j.jpha.2015.11.005.
32. Ngamsurach, P., & Praipipat, P., Comparative antibacterial activities of Garcinia cowa and Piper sarmentosum extracts against *Staphylococcus aureus* and *Escherichia coli* with studying on disc diffusion assay, material characterizations, and batch experiments., *Heliyon.*, **2022,** *8*(11), e11704. https://doi.org/10.1016/j.heliyon.e11704
33. Doan, T. N., & Tran, D. T. Synthesis, antioxidant, and antimicrobial activities of a novel series of chalcones, pyrazolic chalcones, and allylic chalcones., *Pharmacology & Pharmacy.*, **2011**, *2*(04), 282. doi:10.4236/pp.2011.24036
34. Sharma, V.; Singh, G.; Kaur, H.; Saxena, A. K.; & Ishar, M. P. S. Synthesis of -ionone derived chalcones as potent antimicrobial agents., *Bioorganic & Medicinal Chemistry Letters.*, **2012**, *22*(20), 6343-6346. http://dx.doi.org/10.1016/j.bmcl.2012.08.084