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Design, synthesis, docking studies, and antibiotic evaluation (*in vitro*) of some novel triphenylamine chalcones and their analogues

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ABSTRACT

Background: Antibiotic resistance has risen as a result of a variety of conditions, prompting researchers to look for new compounds that can combat multidrug-resistant organisms. Over the last two decades, chalcones have been proved to be attractive moieties in drug discovery. Various substituted acetophenones, propiophenones, and 4-(diphenylamino) benzaldehyde were combined, using the aldol condensation reaction to obtained eight novel triphenylamine chalcones. The compound's antimicrobial properties were investigated (*in vitro*). With the nonmutant X-ray target receptor (PDB: 5VBU), molecular docking experiments were also carried out to analyze the most favorable conformation and find the orientation that maximizes interaction and minimizes energy.

Results: Eight novel triphenylamine chalcones were successfully synthesized and recrystallized using ethanol; the percentage yield of the compounds was between 30% and 92%. The activity against different pathogens revealed that all synthesized compounds showed marked antimicrobial activity against the tested microorganisms. Compound **1b** showed the highest zone of inhibition (ZOI) against *Aspergillus niger*, measuring 30 mm. The minimum inhibitory concentration (MIC) results revealed that compounds **1a–1d**, and **2d** had the lowest MIC and inhibited *A. niger* growth at 12.5 g/ml. All the synthesized compounds showed a minimum bactericidal/fungicidal concentration (MBC/MFC) effect against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Candida albicans*, and *A. niger* at 50 µg/ml. The docking studies of the synthesized chalcones with the binding site of the target receptor reveal that the binding affinity of the synthesized chalcones was in the range of −11.2 to −9.4 kcal/mol, and showed the highest binding score compared to that of the standard drugs (fluconazole and ciproflaxacin), with docking scores of −7.9 and −7.3 kcal/mol, respectively.

Conclusion: The investigation reveals that compound **1b** showed the highest ZOI of 30 mm, least MIC, and MBC/MFC of 12.5 and 50 µg/ml, respectively, against *A. niger*, therefore displaying better antifungal potential as compared to the rest of the compounds. The outcome of the docking analysis revealed that compound **2a** showed a better binding affinity of −11.2 kcal/mol, which is higher than the remaining compounds and the control drugs (fluconazole and ciproflaxacin). Therefore, compounds **1b** and **2a**, which showed better antifungal and highest binding affinity, could be potential candidates in drug design.

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1. Background

The chemistry of chalcones has generated a bustle of research around the globe. The synthesis, chemical reactions, and biological applications of these compounds have captivated the attention of researchers (Kumara et al., 2017; Singh et al., 2014). Chalcones are characterized by a conjugated double bond on both benzene rings and a totally delocalized π-electron system (Maidur and Patil, 2018), which is dependent on the presence of other auxochromes. β-phenyl-α-benzoylethylene is another name for chalcones (Ugwu et al., 2015). Chalcones are abundantly found in spices, tea, fruits, and vegetables as one of the principal classes of natural products (Kumar et al., 2021). Claisen–Schmidt condensation of acetophenones with benzaldehydes is the most prevalent and efficient methods for producing chalcones. The yields are typically excellent, and reaction takes place at a lower temperature. The duration for reaction varies from 3 to 20 hours, depending on the substitution pattern and the solvent/base system utilized (Adnan et al., 2020; Bukhari et al., 2013).

Chalcones have proven to be biologically active; some substituted derivatives, including heterocyclic analogs, have been found to exhibit strong biological characteristics that have been shown to inhibit microorganism development (Frazier, 2020). Some chalcone derivatives have proven to be poisonous to mammals (Gomes et al., 2009) and insects (Singh et al., 2019), as well as inhibit enzymes (Agilandeshwari et al., 2016) and herbaceous plants (Mahapatra et al., 2019). They possess anti-inflammatory (Rashid et al., 2019; Ugwu et al., 2015), antifungal (Singh et al., 2019), antioxidant (Kumar et al., 2020; Singh et al., 2019; Vagish et al., 2021), anti-ulcer (Ugwu et al., 2015), antimalarial (Reeta et al., 2019), antituberculosis (Matos et al., 2014), antitumor (Ugwu et al., 2015), anti-helmintic (Matos et al., 2014), antispasmodic (Ugwu et al., 2015), antibacterial (Singh et al., 2019), and antineoplastic activities (Ugwu et al., 2015). These are just a few of the many biological activities linked to chalcones. Antimalarial action has been found for quinoline-based chalcones (Karaman et al., 2010; Martelli et al., 2019; Tomar et al., 2010; Ugwu et al., 2015).

Due to the continued resistance and resurgence of pathogens against available antibiotics, the constant search for potentially novel drug candidates has emerged. Simultaneously, researchers developed the concepts of protein purification and crystallography, allowing researchers to learn more about the protein and ligand interactions. Today, computational methodologies are pervading many facets of drug development (Bajorath, 2002; Jorgensen, 2004; Walters et al., 1998). Molecular docking investigations have become important tools in the search for new drugs candidates (Langer and Hoffmann, 2001). This technique represents the atomic level interface with target proteins, allowing us to define small molecule behavior in target protein binding sites (McConkey et al., 2002). The process also determines the ligand structure, location, and orientation within the binding site, as well as the binding affinity (Kitchen et al., 2004; Prabhudeva et al., 2019). To our knowledge, there is no report on synthesis, antibiotic evaluation, and molecular docking studies of triphenylamine chalcones. Hence, the present research intended to design, synthesize, screen antimicrobial potential, and study the molecular docking of novel triphenylamine chalcones.

2. Methods

Reagents and solvents used in this research were obtained from Sigma-Aldrich (Germany). These were used as obtained without further purification.

2.1. Synthesis of the novel triphenylamine chalcones analogs (1a–d, 2a–d)

To a 100 ml round-bottom flask, equipped with a magnetic stirrer, dissolved in 25 ml ethanol, equimolar quantities of 4-(diphenylamino)benzaldehyde (0.4 g, 1.5 mmol) and substituted acetophenones/propiophenone (0.4 g, 2 mmol) were transferred and stirred for 30 minutes. A solution of sodium hydroxide (10 ml, 10%) was added dropwise while stirring. The temperature for the reaction was maintained between 20°C and 24°C using cold water bath for 4–5 hours. The progress and completion of the reaction was monitored using the thin-layer chromatographic technique. On completion, the reaction mixture was placed in a refrigerator for 10 hours. Formation of a precipitate was observed, which was filtered, washed several times with water (100 ml), dried in air, and purified by recrystallization from ethanol (30 ml) to obtain a triphenylamine chalcone (1a–d, 2a–d) (Table 1) (Hongtian et al., 2019; Schemes 1 and 2).

2.2. Chemistry

The synthesis of the target novel triphenylamine chalcones was achieved via the conventional Claisen–Schmidt condensation reaction, where different equimolar substituted acetophenones/propiophenones and 4-(diphenylamino)benzaldehyde in the presence of NaOH (10%) were stirred. This reaction was

originated by the abstraction of protons from the alpha-carbon of the acetophenones/propiophenones to generate the resonance stabilized enolate ion by the base. The second stage was the nucleophilic attack on the electron-deficient carbonyl carbon of 4-(diphenylamino)benzaldehyde, which results in the formation of a new C–C bond. This connects the alpha-carbon of the acetophenones/propiophenones to the aldehydic or carbonyl carbon of 4-(diphenylamino)benzaldehyde, which forms an intermediate. The reaction was completed by protonation and deprotonation by the hydroxyl ion of the base to form the targeted α,β-unsaturated triphenylamine chalcone.

2.3. Antimicrobial evaluation

The synthesized triphenylamine chalcones were screened for antimicrobial properties, against some selected clinical isolates, which included *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans*, *Salmonella typhi*, *Aspergillus niger*, *Escherichia coli*, and methicillin resistant *S. aureus* (MRSA).

2.3.1. Zone of inhibition (ZOI)

The ZOI of the synthesized triphenylamine chalcones was carried out according to the procedure as described by Karou et al. (2006).

2.3.2. Minimum inhibitory concentration (MIC)

The MIC of the synthesized triphenylamine chalcones was determined by using the broth dilution method as reported by Bruton et al. (2007).

2.3.3. Minimum bactericidal/fungicidal concentration (MBC/MFC)

The MBC/MFC of the synthesized triphenylamine chalcones were determined according to the procedure, as described by the Clinical and Laboratory Standard Institute (CLSI, 2015).

2.4. Molecular docking studies

Molecular docking analysis for eight ligands (novel triphenylamine chalcones analogs) and controls (fluconazole and ciproflaxacin) was carried out to examine the most favorable interaction and identify the orientation which maximizes interactions and minimizes energy with the target receptor (PDB: 5VBU) (www.rcsb.org) (Fig. 1).

2.4.1. Preparation of the receptor

The three-dimensional structure of the target receptor (Fig. 1) retrieved from the PDB was prepared by removing the water molecules and other heteroatoms, before minimization for the docking study. Discovery Studio Visualizer software v.21.1.0.20298 was used for the preparation. The treated target receptor (Fig. 2) was saved in pdb file format and transferred to Pyrx software for docking.

2.4.2. Preparation of the ligand

All the eight ligands (triphenylamine chalcones analogs) and controls (fluconazole and ciproflaxacin) studied were designed and synthesized as mentioned earlier. ChemDraw ultra 8.0 software was used to

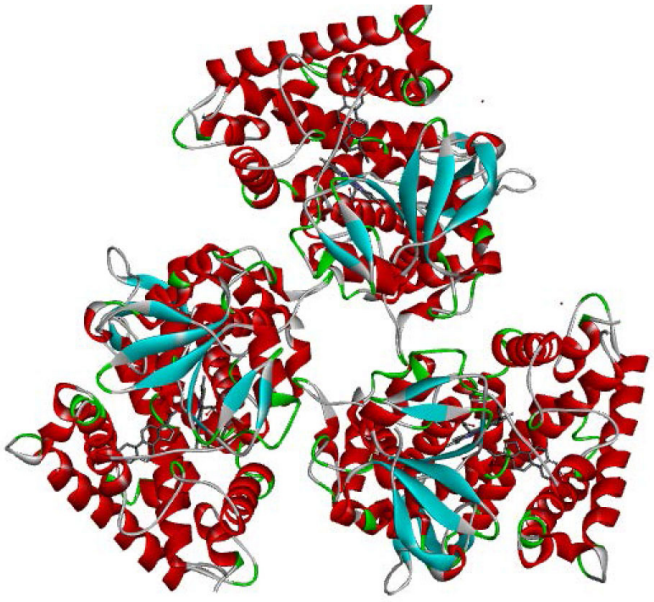


Figure 1. Crystal structure of human cytochrome P450 21A2 hydroxyprogesterone complex (PDB: 5VBU) showing the attached ligands and chains A, B, and C (Chumxue et al., 2017).

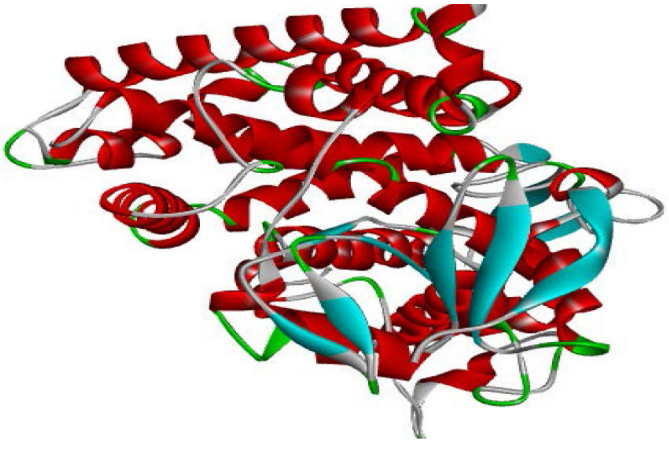


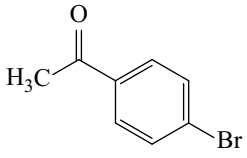
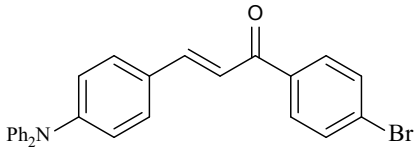
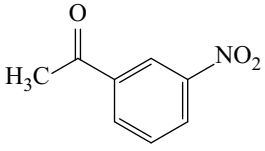
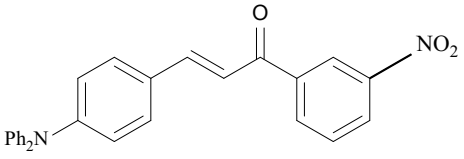
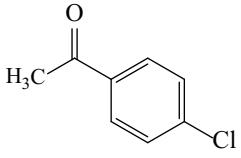
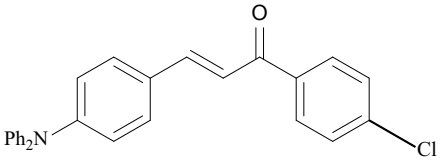
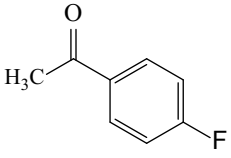
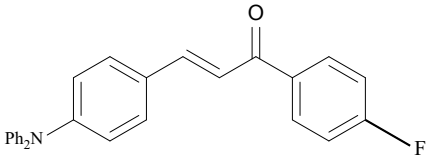
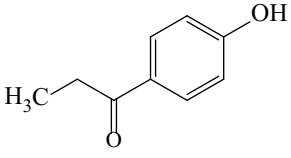
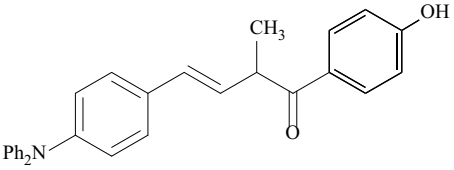
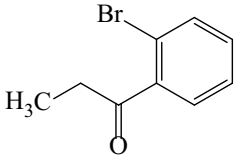
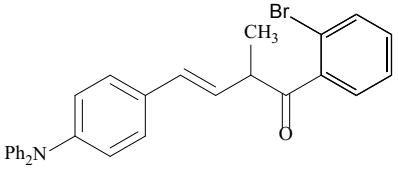
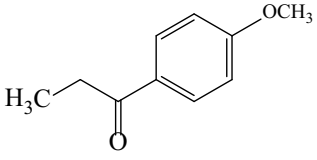
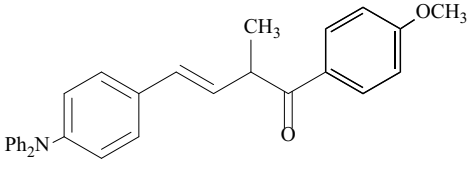
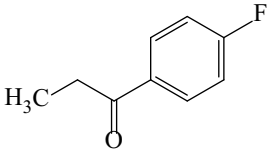
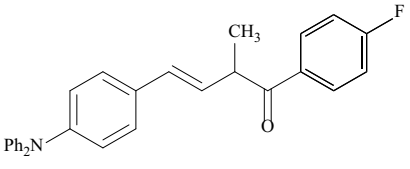
Figure 2. 3D structure of the optimized chain A of human cytochrome P450 21A2 hydroxyprogesterone complex.

generate the two-dimensional structures of the synthesized chalcones (Li et al., 2004). Spartan software was used to convert the 2D structures to 3D. Geometrical optimization using the AM1 semi-empirical method was carried out on all the compounds using the Spartan software and saved as pdb files. Polar hydrogens were added before computing the Gasteiger charges.

2.4.3. Molecular docking

PyRx virtual screening software was used to study the ligand–receptor interactions between the

Table 1. Synthesized triphenylamine chalcones and their percentage yields (%).

Compounds code	R	Triphenylamine chalcone	Yield
1a			70
1b			92
1c			57
1d			60
2a			55
2b			30
2c			52
2d			54

target receptor (PDB: 5VBU) and the eight synthesized ligands (novel triphenylamine chalcones analogs) and controls (fluconazole and ciproflaxacin), while the Discovery Studio Visualizer software was employed in visualizing and analyzing the docking results.

3. Results

3.1. Results of antimicrobial studies

3.2. Results of molecular studies

4. Discussion

4.1. Antimicrobial studies

All the synthesized compounds were shown to possess remarkable activities against the tested microbes by showing significant ZOIs (Table 2) relative to that of the standard drugs used. Compound **1b** showed a prominent ZOI of 30 mm against *A. niger*, while compounds **1a**, **2d**, **1c**, **2b**, and **2c** showed ZOI of 25, 23, 22, and 21 mm also, against *A. niger*. Compounds **1c**, **1d**, **2a**–**2c** each showed ZOI of 20 mm against *B. subtilis*, *P. aeruginosa*, *C. albicans*, and *A. niger*, while compounds **1a**, **1b**, and **2a** showed the lowest ZOI of 13 mm each against *C. albicans*, *S. aureus*, and *E. coli.* Thus, compounds **1a**–**1d** showed ZOI (25, 30, and 23 mm) greater than the standard drugs (fluconozole and ciprofloxacin) against *A. niger*.

The results of the MIC (Table 3) showed that compounds **1a**–**1d**, and **2d** possess the least MIC and inhibit the growth of *A. niger* at 12.5 µg/ml, while compounds **1b**–**1d**, **2a**–**2d** inhibit the growth of *C. albicans*, *B. subtilis*, MRSA, *E. coli*, *P. aeruginosa*, and *A. niger* at 25 µg/ml. At 50 µg/ml, the growth of *P. aeruginosa*, *B. subtilis*, *C. albicans*, MRSA, *S. typhi*, *S. aureus*, and *E. coli* was inhibited by compounds **1a**–**1d**, **2a**–**2d**. Compounds **1a**–**1d**, **2a**–**2d** inhibit the growth of *E. coli*, *P. aeruginosa*, *S. typhi*, *S. aureus*, *B. subtilis*, and MRSA at 100 µg/ml.

The results of MBC/MFC (Table 4) showed that compounds **1a**–**1d**, **2a**–**2d** completely killed *E. coli*, *P. aeruginosa*, *B. subtilis*, *C. albicans*, and *A. niger* at 50 µg/

Table 2. ZOI (mm) for the synthesized triphenylamine chalcones and standard controls against test microbes.

Test organisms	Triphenylamine chalcones									
	1a	**1b**	**1c**	**1d**	**2a**	**2b**	**2c**	**2d**	**Cip**	**Flu**
E. coli	14	16	15	20	13	18	19	16	30	-
P. aeruginosa	15	18	18	18	16	18	20	19	40	-
S. typhi	16	14	17	16	16	13	15	18	26	-
S. aureus	13	15	14	18	13	13	15	15	28	-
B. subtilis	16	17	20	17	18	20	20	18	25	-
MRSA	14	16	19	15	16	17	16	19	30	-
C. albicans	17	13	20	13	16	20	20	18	-	20
A. niger	25	30	23	20	20	22	21	23	-	22

-: Not determined, Cip: ciprofloxacin, Flu: Fluconazole.

Table 3. MICs (µg/ml) for the synthesized triphenylamine chalcones against the test microbes.

Test organisms	Triphenylamine chalcones							
	1a	**1b**	**1c**	**1d**	**2a**	**2b**	**2c**	**2d**
E. coli	100	100	100	25	100	50	25	100
P. aeruginosa	100	50	50	50	100	25	25	25
S. typhi	100	100	50	100	100	100	100	50
S. aureus	100	100	100	50	100	100	100	100
B. subtilis	100	50	25	25	25	25	25	50
MRSA	100	50	25	50	100	50	50	25
C. albicans	50	25	25	50	50	25	25	50
A. niger	12.5	12.5	12.5	12.5	25	25	25	12.5

Table 4. MBC/MFCs (µg/ml) of the synthesized triphenylamine chalcones against the test microbes.

Test organisms	Triphenylamine chalcones							
	1a	**1b**	**1c**	**1d**	**2a**	**2b**	**2c**	**2d**
E. coli	-	-	-	50	-	100	100	-
P. aeruginosa	-	100	100	100	-	100	50	100
S. typhi	-	-	100	-	-	-	-	100
S. aureus	-	-	-	100	-	-	-	-
B. subtilis	-	100	100	50	100	50	50	100
MRSA	-	-	100	100	-	100	-	100
C. albicans	100	100	50	100	100	50	50	100
A. niger	50	50	50	50	50	50	50	50

-: No MBC/MFC.

ml, while a concentration of 100 µg/ml was required by compounds **1a**–**1d**, **2a**–**2d** to completely kill *E. coli*, *P. aeruginosa*, *S. typhi*, MRSA, *S. aureus*, *B. subtilis*, and *C. albicans*.

4.2. Molecular docking studies

Each ligand/chalcones was successively docked to the binding site of the receptor (PDB: 5VBU) in order understand the mode of interaction of the triphenylamine chalcones with the target receptor. The analysis of the docking investigations provided us with an insight into the interactional relationship of the novel triphenylamine chalcone analogs and human cytochrome P450 21A2 hydroxyprogestrerone complex.

Table 5 showed the results of the binding affinity of the synthesized triphenylamine chalcones/ligands, which ranges between −11.2 and −9.4 kcal/mol. Compound **2a** showed the highest docking score of −11.2 kcal/mol, followed by compounds/ligands **1b** and **2b** which showed the binding energy of −10.7 kcal/mol, while compounds **1c**, **2c**, **2d**, and **1a** showed the docking scores of −10.4, −10.3, −10.3, and −10.1, respectively. Compound/ligand **1d** showed the least binding score of −9.4. The eight ligands (novel triphenylamine chalcones analogs) showed the highest binding score compared to that of the standard ligand/compounds (fluconazole and ciproflaxacin), which showed the docking scores of −7.9 and −7.3 kcal/mol, respectively.

Ligand/triphenylamine chalcone **2a** showed the highest binding affinity (−11.2 kcal/mol) compared to other compounds. Discovery Studio Visualizer software was used to view and analyze the docking investigations. The interaction of the ligand/triphenylamine chalcone **(2a)** with the target receptor (PDB: 5BVU) is shown in Figures 3–5. The interaction

Table 5. Binding energy results of the synthesized triphenylamine chalcones with the target receptor (PDB: 5VBU).

Triphenylamine chalcones	Binding energy (kcal/mol)
1a	−10.1
1b	−10.7
1c	−10.4
1d	−9.4
2a	−11.2
2b	−10.7
2c	−10.3
2d	−10.3
Fluconazole	−7.9
Cifroplaxacin	−7.3

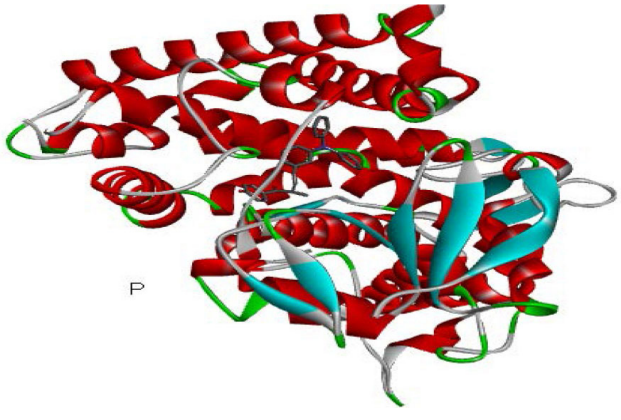


Figure 3. 2a-receptor complex in 3D.

was observed with one hydrogen, one electrostatic attraction, and six hydrophobic interactions (2.5449, 4.0569, 3.73562, 4.34337. 5.2863, 5.48907, 5.44454, and 5.35682 Å with ARG427, LYS121, VAL470, TRP202, VAL360, LEU364, LEU108, and LEU430), as

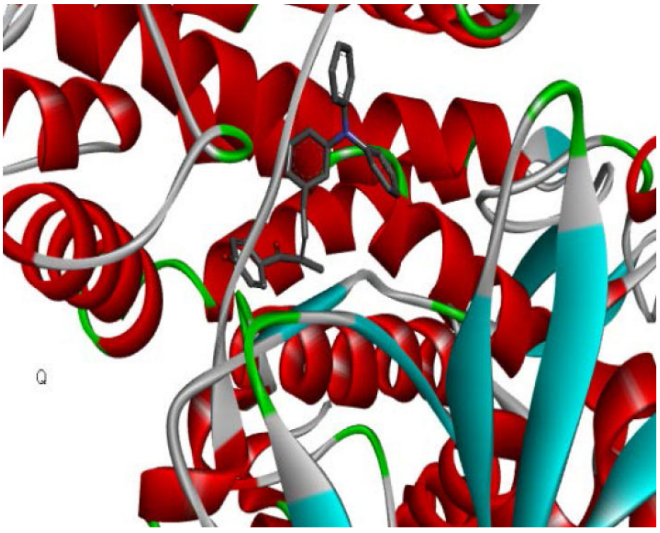


Figure 4. Expanded 2a-receptor complex in 3D.

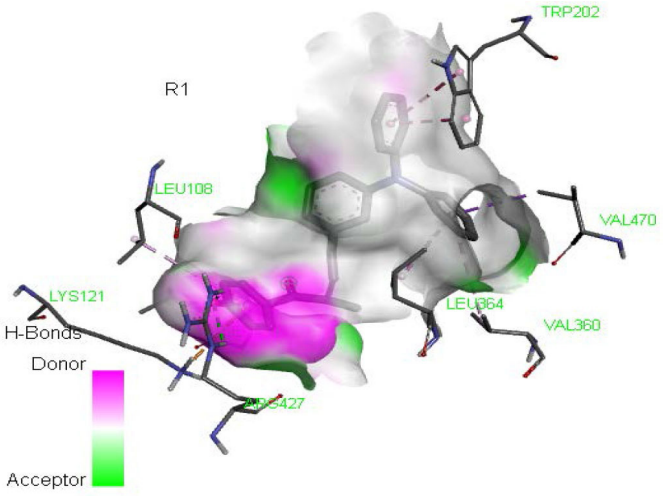


Figure 6. 2a-receptor complex in 3D showing hydrogen bonding.

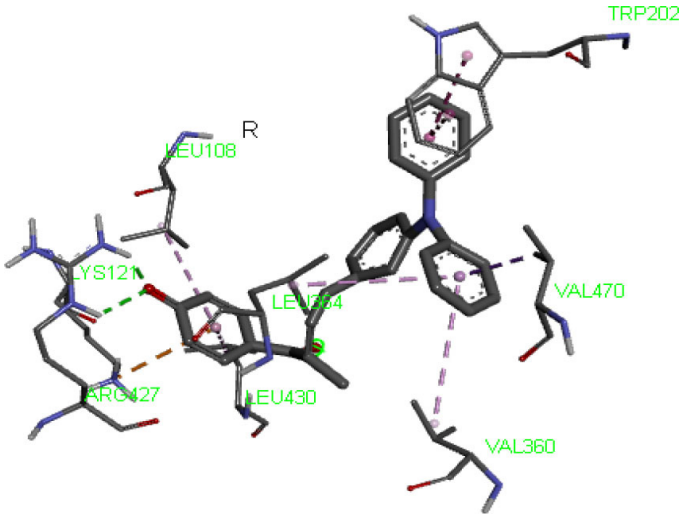


Figure 5. 2a-receptor complex showing different interactions in 3D.

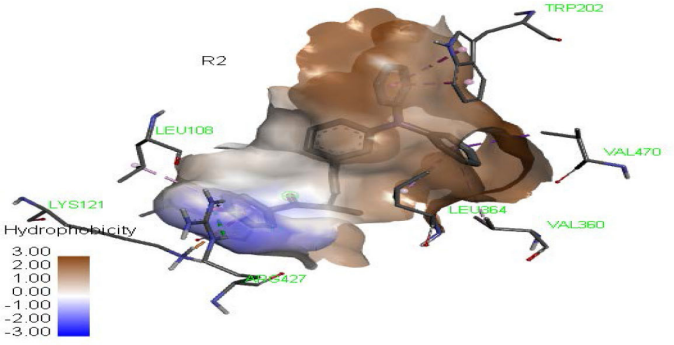


Figure 7. 2a-receptor complex in 3D showing hydrophobic interactions.

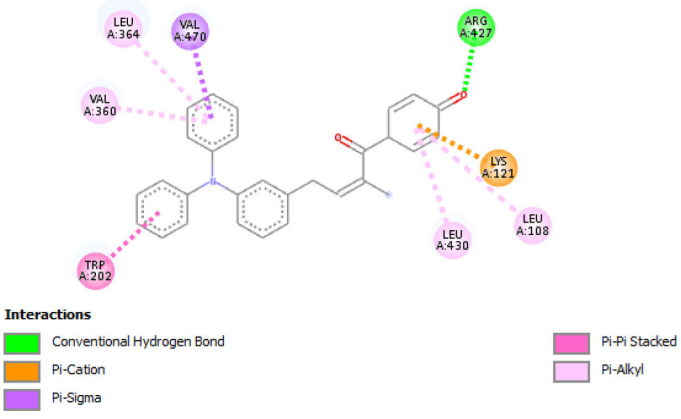
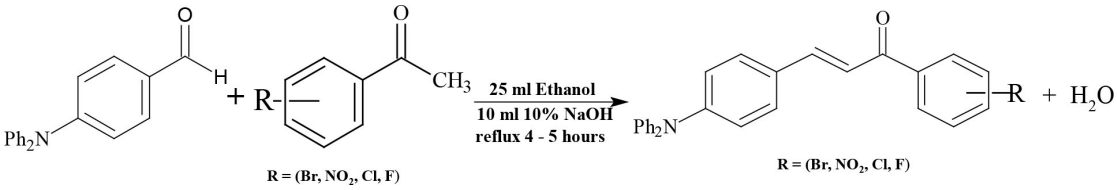
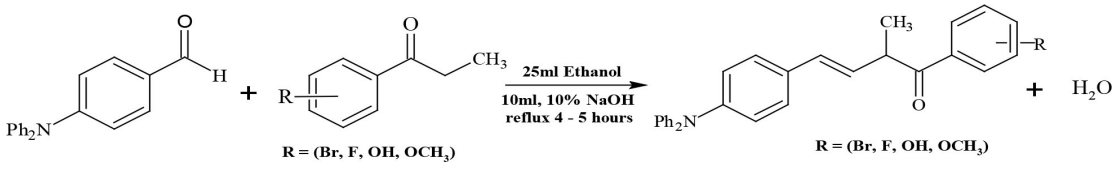


Figure 8. 2a-receptor complex in 2D showing types of bonds and interactions.

shown in Figures 6 and 7. The two-dimensional structural form of the ligand–receptor complex is shown in Figure 8. One hydrogen bond interaction with ARG427 was formed due to the presence of OH the triphenylamine chalcone/chalcone **(2a)**. The electrostatic interaction of the ligand/triphenylamine chalcone was detected with LYS121. Also, the hydrophobic interactions were noticed with VAL470, TRP202, VAL360, LEU364, LEU108, and LEU430 of the target receptor. The areas which represent both hydrogen bond and hydrophobic interactions between the target receptor and the ligand/triphenylamine chalcone are shown in Figures 6 and 7. Therefore, ligand/triphenylamine chalcone **(2a)** fit perfectly into the binding site of the receptor (PDB: 5VBU) (Table 6).



Scheme 1. Synthesis of triphenylamine chalcone from substituted acetophenones (1a–d).



Scheme 2. Synthesis of triphenylamine chalcones from substituted propiophenones (2a–d).

Table 6. Amino acid interaction, bond distance, and type of ligand–receptor interaction.

Ligand/compound	Protein interaction	Bond distance (Å)	Type of bond interaction
1a	TRP202	4.93594	Hydrophobic
	VAL101	4.97629	Hydrophobic
	VAL198	5.11692	Hydrophobic
	VAL360	5.2578	Hydrophobic
	CYS429	5.37315	Hydrophobic
	LEU430	5.13073	Hydrophobic
	LEU108	5.23057	Hydrophobic
	LEU110	5.32372	Hydrophobic
1b	ARG92	2.22588	Hydrogen bond
	ARG427	1.83408	Hydrogen bond
	LEU430	3.21564	Hydrogen bond
	VAL470	3.86767	Hydrophobic
	TRP202	3.83466	Hydrophobic
	TRP202	4.53881	Hydrophobic
	LEU108-SER109	5.28813	Hydrophobic
	VAL428-CYS429	5.18984	Hydrophobic
	LEU110	5.48518	Hydrophobic
	VAL360	5.10827	Hydrophobic
	LEU108	5.29357	Hydrophobic
	LEU430	5.0342	Hydrophobic
1c	VAL198	4.6017	Hydrophobic
	LEU227	5.18326	Hydrophobic
	CYS429	4.28371	Hydrophobic
	VAL360	4.8503	Hydrophobic
	ILE471	5.47831	Hydrophobic
	VAL101	5.41637	Hydrophobic
	ILE291	5.32346	Hydrophobic
	TRP202	4.24247	Hydrophobic
1d	LEU64	3.17822	Halogen
	PRO93	3.24979	Hydrophobic
	PRO95	3.67448	Hydrophobic
	VAL69	4.27875	Hydrophobic
	LEU40	4.96375	Hydrophobic
	VAL212	5.16423	Hydrophobic
	LEU362	4.85287	Hydrophobic
	ILE386	4.62883	Hydrophobic
	PRO365	5.40796	Hydrophobic
	VAL384	5.17048	Hydrophobic
	TYR98	4.2068	Hydrophobic

Continued

2a	ARG427	2.5449	Hydrogen bond
	LYS121	4.0569	Electrostatic
	VAL470	3.73562	Hydrophobic
	TRP202	4.34337	Hydrophobic
	VAL360	5.2863	Hydrophobic
	LEU364	5.48907	Hydrophobic
	LEU108	5.44454	Hydrophobic
	LEU430	5.35682	Hydrophobic
2b	LEU64	5.08451	Hydrophobic
	ILE386	4.65396	Hydrophobic
	PRO95	5.23623	Hydrophobic
	PRO365	4.89571	Hydrophobic
	LEU40	4.99849	Hydrophobic
	ILE209	5.41451	Hydrophobic
2c	ILE291	3.51114	Hydrophobic
	VAL101	4.15088	Hydrophobic
	VAL198	4.80089	Hydrophobic
	VAL360	5.35382	Hydrophobic
	LEU108	5.29535	Hydrophobic
	CYS429	5.47704	Hydrophobic
	LEU430	4.95443	Hydrophobic
2d	ARG234	2.91932	Hydrogen bond-halogen
	VAL360	3.43541	Hydrophobic
	CYS429	4.3062	Hydrophobic
	LEU199	5.46418	Hydrophobic
	ILE471	5.47336	Hydrophobic
	VAL101	4.66462	Hydrophobic
	ILE291	5.09895	Hydrophobic
Fluconazole	ASP288	2.18916	Hydrogen bond
	VAL470	2.64556	Hydrogen bond
	TRP202	4.34172	Hydrophobic
	LEU110	3.88479	Hydrophobic
Ciproflaxacin	SER469	2.57816	Hydrogen bond
	LEU40	2.33333	Hydrogen bond
	GLN42	2.66041	Hydrogen bond
	LEU40	4.92581	Hydrophobic
	LEU41	5.17388	Hydrophobic

5. Conclusion

The synthesis of eight novel triphenylamine chalcones was successively carried out via the conventional Claisen–Schmidt condensation reactions. The results of the antimicrobial screening of the synthesized chalcones as indicated by the ZOI showed that all the synthesized compounds possess remarkable activities against the tested microbes, by showing a significant ZOIs relative to that of the standard drugs used. Compound **1b** showed the highest ZOI of 30 mm, least MIC, and MBC/MFC of 12.5 and 50 µg/ml, respectively, against *A. niger*. The outcome of the docking studies revealed that compound **2a** showed marked docking score with binding affinity of −11.2 kcal/mol, which is higher relative to other compounds and the standard controls (fluconazole and ciproflaxacin). Therefore, compounds **1b** and **2a**, which showed better antifungal and highest binding affinity, could be potential candidates in drug design.

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