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Design, synthesis, docking studies and antibiotic evaluation (in vitro) of some novel (*E*)-4-(3-(diphenylamino)phenyl)-1-(4-methoxyphenyl)-2-methylbut-3-en-1-one 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 obtain eight novel triphenylamine chalcones. The compound's antimicrobial properties were investigated (in vitro). With the non-mutant X-ray Human cytochrome P450 21A2 Hydroxyprogesterone retrieved from Protein Data Bank (PDB: 5VBU), molecular docking experiments were also carried out to analyse the most favourable conformation and find the orientation that maximizes interaction and minimize energy.

Results: Eight novel triphenylamine chalcones were successfully synthesized and recrystallized using ethanol, the percentage yield of the compounds were between 30 and 92%. The activity against different pathogens revealed that, all synthesized compounds showed marked antimicrobial activity against the tested microorganisms. (*E*)-3-(4-(diphenylamino)phenyl)-1-(3'-nitrophenyl)prop-2-en-1-one (1b) showed the highest zone of inhibition against *Aspergillus niger*, measuring 30 mm. The minimum inhibitory concentration (MIC) results revealed that (*E*)-1-(4'-bromophenyl)-3-(4-(diphenylamino)phenyl)prop-2-en-1-one (1a), (*E*)-3-(4-(diphenylamino)phenyl)-1-(3'-nitrophenyl)prop-2-en-1-one (1b), (*E*)-1-(4'-chlorophenyl)-3-(4-(diphenylamino)phenyl)prop-2-en-1-one (1c), (*E*)-3-(4-(diphenylamino)phenyl)-1-(4'-fluorophenyl)prop-2-en-1-one (1d) and (*E*)-4-(3-(diphenylamino)phenyl)-1-(4-fluorophenyl)-2-methylbut-3-en-1-one (2d) had the lowest MIC and inhibit *Aspergillus niger* growth at 12.5 µg/ml. All the synthesized compounds showed minimum bactericidal concentration and minimum fungicidal concentration (MBC/MFC) effect against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Candida albicans* and *Aspergillus niger* at 50 µg/ml. The docking studies of the synthesized chalcones with the binding site of the Human cytochrome P450 21A2 Hydroxyprogesterone (PDB: 5VBU) reveal that the binding affinity of the synthesized chalcones was in the range

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of -11.2 to -9.4 kcal/mol and showed 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.

Conclusions: The investigation reveals that compound 1b showed the highest ZOI of 30 mm, least MIC and MBC/MFC of 12.5 and 50 $\mu\text{g/ml}$ against *Aspergillus niger*, respectively. Therefore, displayed better antifungal potential as compared to the rest of the compounds. The outcome of the docking analysis revealed that (*E*)-4-(3-(diphenylamino)phenyl)-1-(4'-hydroxyphenyl)-2-methylbut-3-en-1-one (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).

Keywords: Chalcones, Triphenylamine, Claisen–Schmidt condensation, Antimicrobial activity, Molecular docking, Binding affinity

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 (Singh et al. 2014; Kumara et al. 2017). 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 -benzoyl-ethylene 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 lower temperature. The duration for reaction varies from 3 to 20 h depending on the substitution pattern and the solvent/base system utilized, (Bukhari et al. 2012; Adnan et al. 2020).

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

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 (Walters et al. 1998; Bajorath, 2002; Jorgensen, 2004). Molecular docking investigations have become important tools in the search for new drug candidates (Langer and Hoffmann, 2001). This technique represents atomic level interface with target protein, allowing us to define small molecule behaviour 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).

Human cytochrome P450 21A2 Hydroxyprogesterone (PDB: 5VBU) is the major steroid 21-hydroxylase, converting progesterone to 11-deoxycorticosterone and 17 α -hydroxyprogesterone to 11-deoxycortisol. Deficiency of this enzyme is involved in approximately 95% cases of human congenital adrenal hyperplasia, a disorder of adrenal steroidogenesis, Pradeep et al. (2015). To our knowledge, there is no report on synthesis, antibiotic evaluation and molecular docking studies of triphenylamine chalcones. Hence, present research intended to synthesize, screen antimicrobial potential and study the molecular docking of novel triphenylamine chalcones.

Methods

All reagents and solvents used in this research were obtained from Sigma-Aldrich (Germany). These were used as obtained without further purification. These include 4-Chloroacetophenone,

4-(Diphenylamino)benzaldehyde, 4-Bromoacetophenone, 3-Nitroacetophenone, 4-Fluoroacetophenone, 4-Hydroxypropiofenone, 2-Bromopropiofenone, 4-Methoxypropiofenone, 4-Fluoropropiofenone, 10% NaOH and Ethanol.

Synthesis of the novel triphenylamine chalcones analogues (1a–d, 2a–d)

To 25 ml ethanol taken in 100 ml round bottomed flask equipped with a magnetic stirrer, were transferred equimolar quantities of 4-(diphenylamino)benzaldehyde (0.4 g, 1.5 mmol) and substituted acetophenones/propiofenone (0.4 g, 2 mmol) and stirred for 30 min. A solution of sodium hydroxide (10 mL, 10%) was added dropwise while stirring. The temperature for the reaction was maintained between 20 and 24 °C using cold water bath for 4–5 h. The progress and completion of the reaction were monitored using thin-layer chromatographic technique (TLC). On completion, the reaction mixture was placed in a refrigerator for 10 h. Formation of precipitate was observed, which was filtered, washed severally with water (100 ml), dried in air and purify by recrystallization from ethanol (30 ml) to obtained a triphenylamine chalcone, (1a–d, 2a–d). Hongtian et al. (2019). Table 1 shows the structures of the synthesized triphenylamine chalcones and their percentage yields (Schemes 1, 2).

The synthesis of the target novel triphenylamine chalcones was achieved via the conventional Claisen–Schmidt condensation reaction, where different equimolar substituted acetophenones/propiofenones and 4-(Diphenylamino) benzaldehyde in the presence of NaOH (10%) were stirred. This reaction was originated by the abstraction of proton from the alpha-carbon of the acetophenones/propiofenones 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/propiofenones to the aldehydic or carbonyl carbon of 4-(Diphenylamino) benzaldehyde to which form 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.

Antimicrobial evaluation

The synthesized triphenylamine chalcones were screened for antimicrobial properties, against some selected clinical isolates, which include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans*, *Salmonella typhi*, *Aspergillus Niger*, *Escherichia coli* and Methicilin Resistant *Staphylococcus aureus* (MRSA).

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).

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).

Minimum bactericidal/fungicidal concentration (MBC/MFC)

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

Molecular docking studies

Molecular Docking Analysis for eight (8) ligands (novel triphenylamine chalcones analogues) and controls (Fluconazole and Ciproflaxacin) was carried out to examine the most favourable interaction and identify the orientation which maximizes interactions and minimizes energy with the target receptor (PDB: 5VBU) (www.rcsb.org) (Fig. 1).

Preparation of the receptor

The three-dimensional structure of 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.

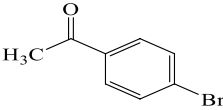
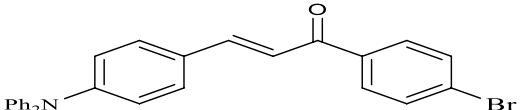
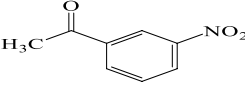
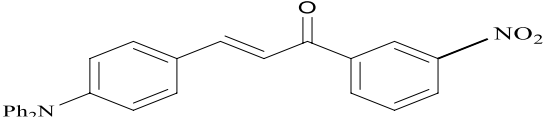
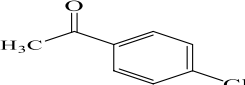
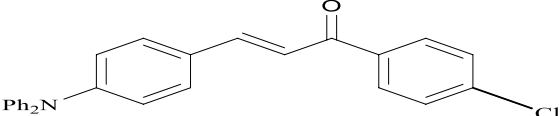
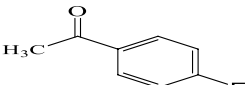
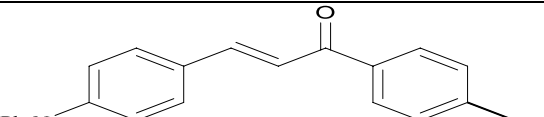
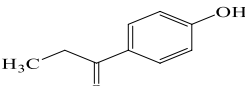
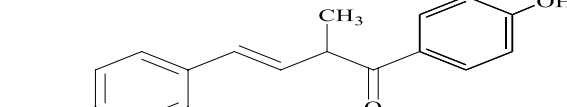
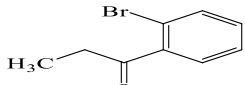
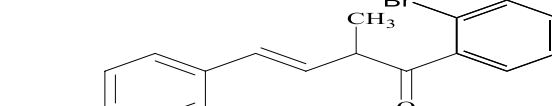
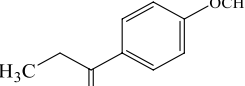
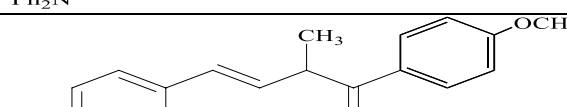
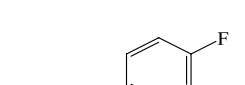
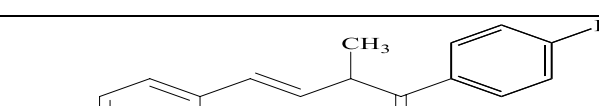
Preparation of ligand

All the eight (8) ligands (triphenylamine chalcones analogues) and controls (Fluconazole and Ciproflaxacin) studied were designed and synthesized as mentioned earlier. ChemDraw ultra 8.0 software was used to generate the two-dimensional structures of the synthesized chalcones (Li et al. 2004). Spartan software (Spartan'20 v.1.1 /2020) was used to convert the 2D structures to 3D. Geometrical optimization using the AM1 semi-empirical method was performed on all the compounds using the Spartan software and saved as pdb files. Polar hydrogens were added before computing Gasteiger charges, using the BIOVIA DiscoveryStudio2021.

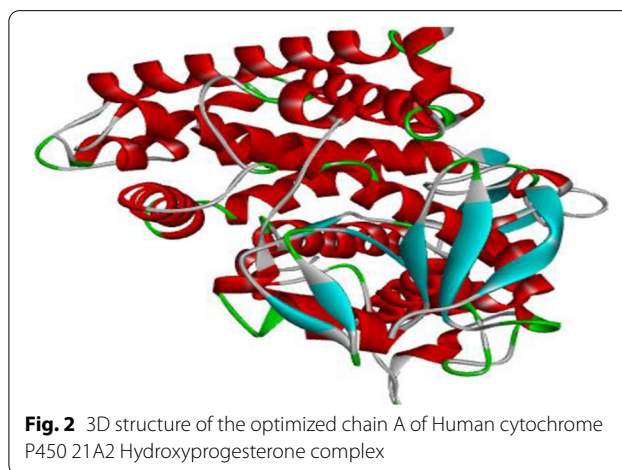
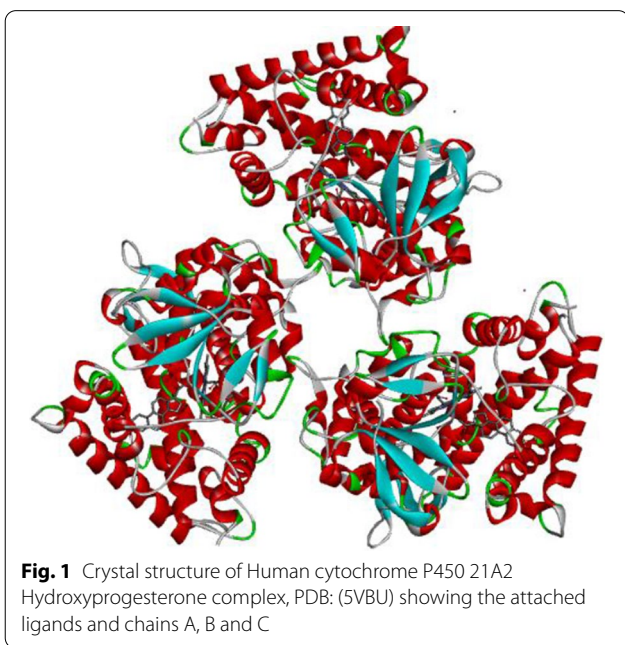
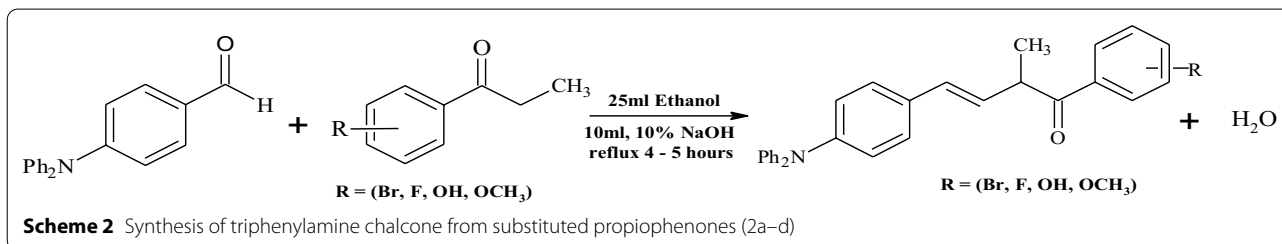
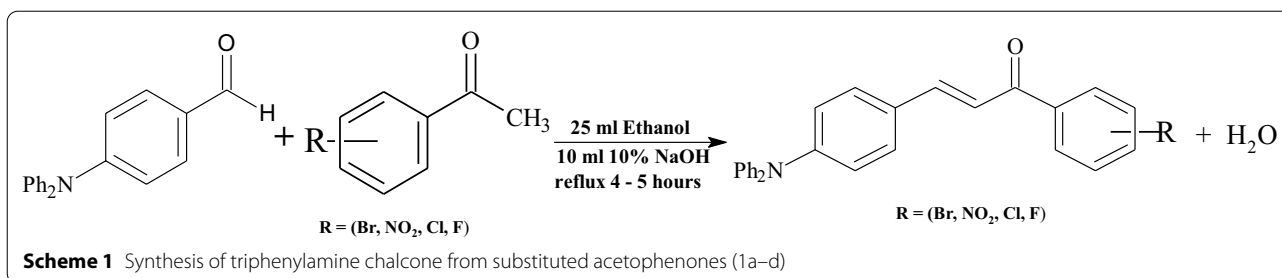
Molecular docking

PyRx virtual screening software was used to study the ligand-receptor interactions between the target receptor (PDB: 5VBU) and the eight (8) synthesized ligands (novel triphenylamine chalcones analogues) and

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

(1a): (*E*)-1-(4'-bromophenyl)-3-(4-(diphenylamino)phenyl)prop-2-en-1-one(1b): (*E*)-3-(4-(diphenylamino)phenyl)-1-(3'-nitrophenyl)prop-2-en-1-one(1c): (*E*)-1-(4'-chlorophenyl)-3-(4-(diphenylamino)phenyl)prop-2-en-1-one(1d): (*E*)-3-(4-(diphenylamino)phenyl)-1-(4'-fluorophenyl)prop-2-en-1-one(2a): (*E*)-4-(3-(diphenylamino)phenyl)-1-(4'-hydroxyphenyl)-2-methylbut-3-en-1-one(2b): (*E*)-1-(2'-bromophenyl)-4-(3-(diphenylamino)phenyl)-2-methylbut-3-en-1-one(2c): (*E*)-4-(3-(diphenylamino)phenyl)-1-(4'-methoxyphenyl)-2-methylbut-3-en-1-one(2d): (*E*)-4-(3-(diphenylamino)phenyl)-1-(4'-fluorophenyl)-2-methylbut-3-en-1-one



controls (Fluconazole and Ciproflaxacin), while Discovery studio visualizer software was employed in visualizing and analysing the docking results.

Results

Results of antimicrobial studies

See Tables 2, 3 and 4.

Results of molecular studies

See Figs. 3, 4, 5, 6, 7 and 8, Tables 5 and 6.

Discussion

Antimicrobial studies

All the synthesized compounds were shown to possess remarkable activities against the tested microbes, by showing a significant zone of inhibitions relative to that of the standard drugs used as shown in Table 2. Compound 1b showed prominent zone of inhibition of 30 mm against *Aspergillus niger*, while compounds 1a, 2d, 1c, 2b and 2c showed zone of inhibitions of 25 mm, 23 mm, 22 mm and 21 mm also, against *Aspergillus niger*. Compounds 1c, 1d, 2a, 2b and 2c each showed zone of inhibition of 20 mm against *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Candida albicans* and *Aspergillus niger*. While, compounds 1a, 1b and 2a showed the lowest zone of inhibition of 13 mm each against *Candida albicans*, *Staphylococcus aureus*

Table 2 Zone of inhibition (mm) for the synthesized triphenylamine chalcones and standard controls against test microbes

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

Key; (–): Not determined, *Cip* ciprofloxacin, *Flu* fluconazole

Table 3 Minimum Inhibitory Concentrations (MIC) ($\mu\text{g/ml}$) for the synthesized triphenylamine chalcones against the test microbes

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

Table 4 Minimum Bactericidal/Fungicidal Concentrations (MBC/MFC) ($\mu\text{g/ml}$) of the synthesized triphenylamine chalcones against the test microbes

Test Organisms	Triphenylamine chalcones							
	1a	1b	1c	1d	2a	2b	2c	2d
<i>E. coli</i>	–	–	–	50	–	100	100	–
<i>P. aeruginosa</i>	–	100	100	100	–	100	50	100
<i>S. typhi</i>	–	–	100	–	–	–	–	100
<i>S. aureus</i>	–	–	–	100	–	–	–	–
<i>B. subtilis</i>	–	100	100	50	100	50	50	100
MRSA	–	–	100	100	–	100	–	100
<i>C. albicans</i>	100	100	50	100	100	50	50	100
<i>A. niger</i>	50	50	50	50	50	50	50	50

Key; (–): No MBC/MFC

and *Escherichia coli*. Thus, compounds 1a, 1b, 1c and 1d showed zone of inhibitions (25 mm, 30 mm and 23 mm) greater than the standard drugs (Fluconazole and ciprofloxacin) against *Aspergillus niger* Singh et al. (2019).

Table 3 presents the results of the MIC and showed that compounds 1a, 1b, 1c, 1d and 2d possess the least MIC and inhibit the growth of *Aspergillus niger* at 12.5 $\mu\text{g/ml}$. While compounds 1b, 1c, 1d, 2a, 2b, 2c and 2d inhibit the growth of *Candida albicans*, *Bacillus*

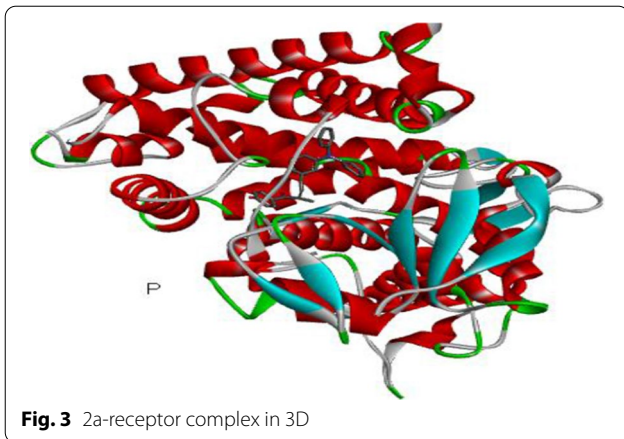


Fig. 3 2a-receptor complex in 3D

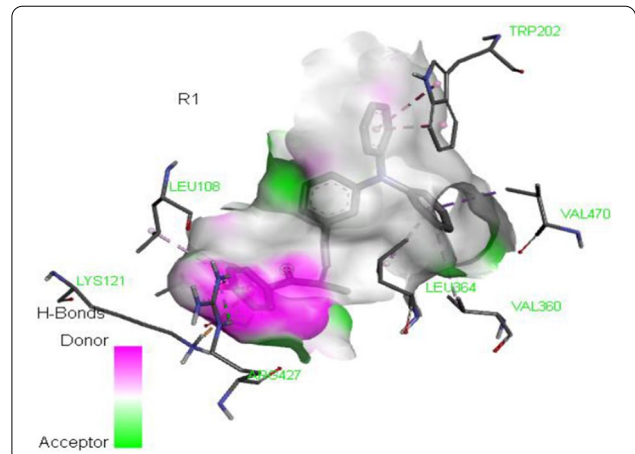


Fig. 6 2a-receptor complex in 3D, showing hydrogen bonding

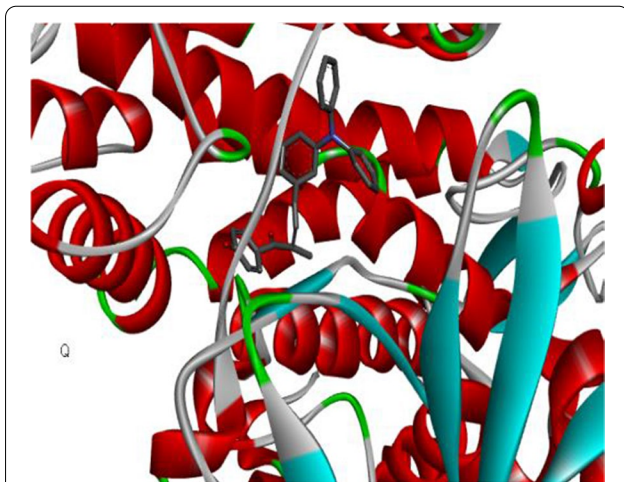


Fig. 4 Expanded 2a-receptor complex in 3D

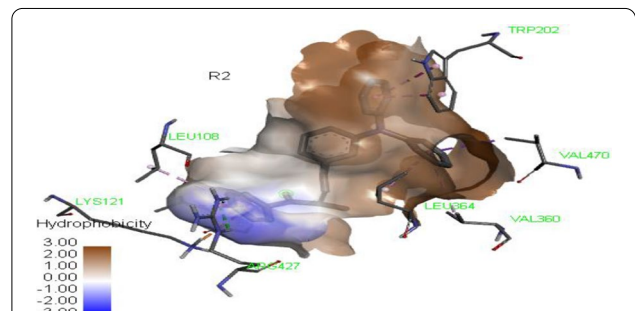


Fig. 7 2a-receptor complex in 3D, showing hydrophobic interactions

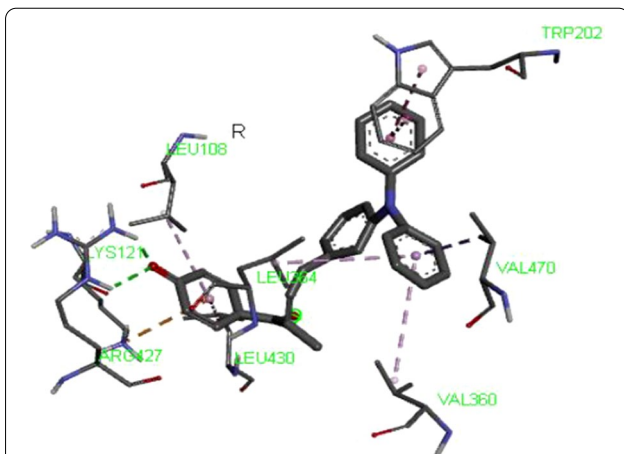


Fig. 5 2a-receptor complex showing different interactions in 3D

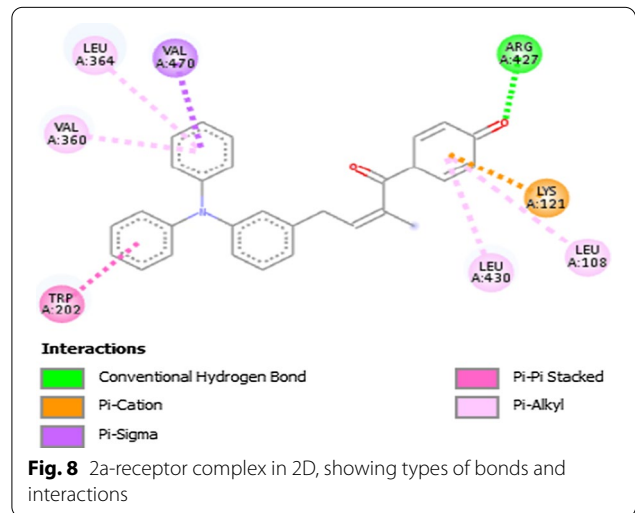


Fig. 8 2a-receptor complex in 2D, showing types of bonds and interactions

subtilis, MRSA, *Escherichia coli*, *Pseudomonas aeruginosa* and *Aspergillus niger* at 25 µg/ml. At 50 µg/ml, the growth of *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Candida albicans*, MRSA, *Salmonella typhi*,

Table 5 Binding Energy results of the synthesized triphenylamine chalcones with 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
Ciproflaxacin	-7.3

Staphylococcus aureus and *Escherichia coli* were inhibited by compounds 1a, 1b, 1c, 1d, 2a, 2b, 2c and 2d. Compounds 1a, 1b, 1c, 1d, 2a, 2b, 2c and 2d inhibit the growth of *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus aureus*, *Bacillus subtilis* and MRSA at 100 µg/ml.

The results of MBC/MFC showed that compounds 1a, 1b, 1c, 1d, 2a, 2b, 2c and 2d completely killed *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Candida albicans* and *Aspergillus niger* at 50 µg/ml, while a concentration of 100 µg/ml was required by compounds 1a, 1b, 1c, 1d, 2a, 2b, 2c and 2d to completely kill *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, MRSA, *Staphylococcus aureus*, *Bacillus subtilis* and *Candida albicans* as shown in Table 4.

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 relation of the novel triphenylamine chalcone analogues and human cytochrome P450 21A2 Hydroxyprogesterone complex.

Table 5 shows 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 (8) ligands (novel triphenylamine chalcones analogues) showed 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. The interaction of the ligand/ triphenylamine chalcone (2a) with the target receptor (PDB: 5VBU) is shown in Figs. 3, 4 and 5. The interaction 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, LEU430) as shown in Figs. 6

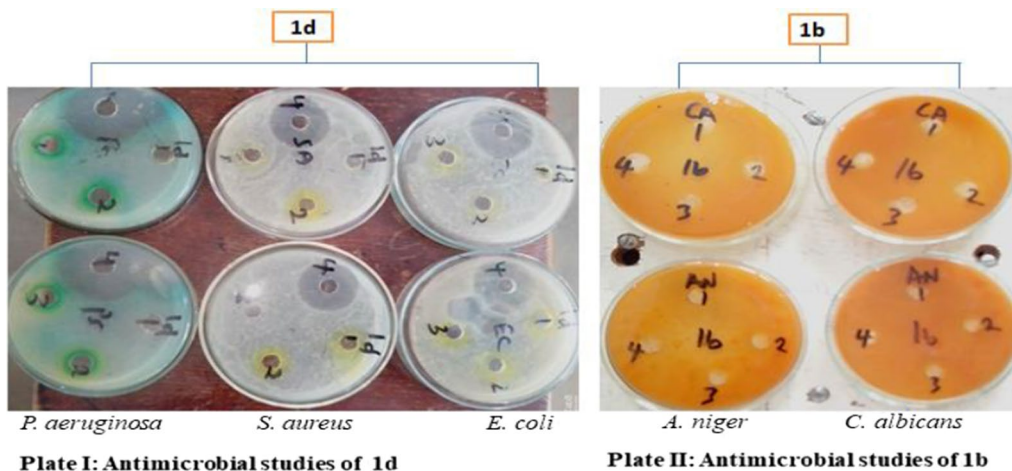


Table 6 Amino acid-interaction, bond distance and type of ligand-receptor interaction

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	
1b	LEU110	5.32372	Hydrophobic	
	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	
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	

Table 6 (continued)

Ligand/compound	Protein interaction	Bond distance (Å)	Type of bond interaction
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

and 7. The two-dimensional structural form of the ligand-receptor complex is shown in Fig. 8. One hydrogen bond interaction with ARG427 was formed, due to the presence of OH group in 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 the both hydrogen bond and hydrophobic interactions between the target receptor and the ligand/triphenylamine chalcone are shown in Figs. 6 and 7. Therefore, ligand/triphenylamine chalcone (2a) fits perfectly into the binding site of the receptor (PDB: 5VBU). All type of interactions, amino acids and bond length are shown in Table 6.

Correlation of molecular docking studies and antimicrobial studies

The docking studies of the synthesized chalcones with the binding site of the Human cytochrome P450 21A2 Hydroxyprogesterone (PDB: 5VBU) reveal that the binding affinity of the synthesized chalcones was in the range of -11.2 to -9.4 kcal/mol and showed 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. Compound 2a displayed best docking score of -11.2 kcal/mol. The binding affinity, hydrogen bond and hydrophobic interactions of the synthesized chalcones and the standard controls (fluconazole and ciproflaxacin) are summarized in Tables 5 and 6. Compared to fluconazole, compound (1b) showed similar residual interactions (hydrophobic) profiles with amino acid residues TRP 202, LEU 110 and VAL 470, (1a) TRP 202 and LEU 110, (2a) VAL 470 and (1c) TRP 202. Similarly, compounds 1b, 1d and 2d showed Hydrophobic

interactions LEU 40, as shown by the standard drug ciproflaxacin. Therefore, the synthesized compounds showed similarities in the residual amino acid interactions with clinical drugs against the Human cytochrome P450 21A2 Hydroxyprogesterone enzyme. The docking investigations are in agreement with the in vitro antimicrobial assay results. Hence, compound 1b indicated higher antifungal potential by showing similarities in residual interactions with amino acids residue as shown by standard antifungal drug (fluconazole), while the antimicrobial investigation reveals that compound 1b showed the highest ZOI of 30 mm, least MIC and MBC/MFC of 12.5 and 50 $\mu\text{g/ml}$ against *Aspergillus niger*, respectively.

Conclusions

Synthesis of eight novel triphenylamine chalcones was successively carried out via the conventional Claisen–Schmidt condensation reactions, and the compounds were successfully characterized using FT-IR and NMR spectroscopic analyses. The results of the antimicrobial screening of the synthesized chalcones as indicated by zone of inhibition (ZOI) showed that all the synthesized compounds possess remarkable activities against the tested microbes, by showing a significant zone of inhibitions 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 $\mu\text{g/ml}$ against *Aspergillus 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.

Abbreviations

ZOI: Zone of inhibition; MIC: Minimum inhibitory concentration; MRSA: Methicillin resistant *Staphylococcus aureus*; MBC: Minimum bactericidal concentration; MFC: Minimum fungicidal concentration; mm: Millimetre; µg/ml: Microgram per mil; PDB: Protein data bank; kcal: Kilocalorie; mol: Mole; β: Beta; α: Alpha; mmol: Millimole; g: Gram; TLC: Thin layer chromatography; mL: Milli litre; DMSO: Dimethyl sulfoxide; °C: Degree Celsius; MHB: Mueller hinton broth; CFU: Number of colonies times dilution factor; 2D: Two dimensional; 3D: Three dimensional; rmsd: Root mean square deviation; TRP: Tryptophan; VAL: Valine; CYS: Cysteine; ARG: Arginine; LEU: Leucine; SER: Serine; ILE: Isoleucine; PRO: Proline.

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Authors' contributions

AT carried out the synthesis, the antimicrobial studies and the molecular docking studies and produces the manuscript. RG guides the synthesis and review the manuscript. ORAI guides the synthesis of the novel chalcones. JDH guides the synthesis, antimicrobial studies and the review of the manuscript. All authors read and approved the manuscript.

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