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Synthesis, Spectral Characterization, Antimicrobial Evaluation and Molecular Docking Studies of Some Novel Ethanone Derivatives Comprising Tetrazole and Piperazine Nuclei

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ABSTRACT

*In the present work, a new series of novel heterocyclic compounds containing both tetrazole and piperazine nuclei together namely 1-(1-aryl-1H-tetrazol-5-yl)-2-(piperazin-1-yl)ethanones (**4-10**) were synthesized by the treatment of respective 2-chloro-1-(1-aryl-1H-tetrazol-5-yl)ethanones (**3**) with piperazine in acetonitrile for 6h. The synthesized novel tetrazole substituted piperazine derivatives were evaluated for their antimicrobial activity using serial dilution method. The structures of the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectral data and Elemental analysis. Evaluation of antimicrobial activity shows that several compounds exhibits good activity when compared with the reference drug candidates and thus could be promising new lead molecules. The molecular docking studies have widened the scope of developing a new class of antimicrobial agents.*

Keywords: Tetrazole; piperazine; synthesis; antimicrobial activity; molecular docking.

INTRODUCTION

The emergence and spread of antimicrobial resistance have become one of the most serious public health concerns across the world. The search for new antimicrobial compounds is a challenging task as bacteria are continuously developing resistance to antimicrobial compounds; however, infections due to such bacterial strains are infrequent although potentially fatal [1-3]. In antimycotic pharmacotherapy, azoles have maintained a key role in the treatment of fungal infections and today the azole scaffold is still considered a viable lead structure for the synthesis of more efficacious and broad spectrum antifungal agents [4]. Tetrazoles are medicinally important heterocycles incorporated in a large number of drugs. Tetrazole and its derivatives possess very interesting pharmacological and biological properties and are reported to exhibit a variety of biological activities [5-18]. Development of the tetrazole chemistry has been largely associated with ring flexibility, stability which provides easily to different binding modes and toxicity decreasing properties [19]. In recent years, a number of publications and patents on the preparation, properties and applications of tetrazole derivatives, which are members of well-known azoles, have been increased with respect to other heterocyclic systems. In antifungal chemotherapy; ketoconazole,

itraconazole, fluconazole and miconazole which are well-known azole antifungals proved to be important drugs for combating fungal infections and currently remain the drug of choice in the treatment [20]. A number of remarkable studies have been reported that newly synthesized tetrazole derivatives had higher anticandidal activity than standard antifungal drugs, and this result was attributed to the isosteric properties of tetrazoles [21].

Piperazines are a broad class of chemical compounds with many important pharmacological properties in today's drug discovery. Piperazine moiety certainly deserves the molecule's backbone with versatile binding properties representing potent and selective ligands for a range of different biological targets in medicinal chemistry. Thus, piperazine is considered as honored scaffold. These compounds have remarkable pharmacological activities like antipsychotic, antimalarial, anticonvulsant, antiarrhythmic, antioxidant, dopamine transporter [22], antibacterial [23], D2/D4 antagonist, MC4Receptor [24] and HIV-protease inhibitor [25, 26] and cytotoxic activities [27]. Slight change in the substitution pattern in piperazine nucleus causes distinguishable differences in their pharmacological activities [28]. It is known that clinically useful drugs such as amoxapine, meclizine, trazodone, niaprazine, olanzapine and nefazodone having a piperazine moiety exhibit strong antimicrobial activity (**Figure 1**).

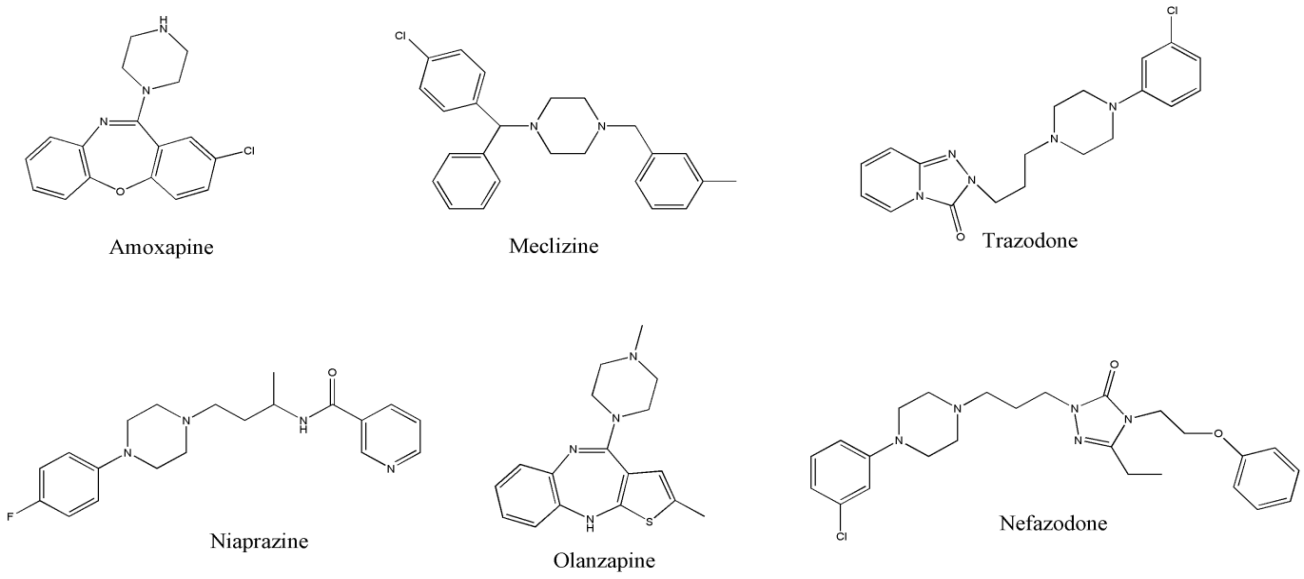


Figure 1. Biologically active piperazine containing drugs

In view of these observations, we planned to synthesize a system, which combines both bioactive tetrazole and piperazine components together to give a new series of novel 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone derivatives (**4-10**) to be responsible for the antimicrobial activity.

MATERIALS AND METHODS

Chemistry: All the reactions routinely monitored by thin layer chromatography (TLC). All the reported melting points were taken in open capillaries and were uncorrected. Infrared (IR) spectra were recorded in KBr (pellet forms) on a Thermo Nicolet-Avatar-330 Fourier Transform Infrared (FT-IR) spectrophotometer and only noteworthy absorption values (cm^{-1}) were listed. ^{1}H and ^{13}C NMR (nuclear magnetic resonance) were recorded with Bruker AMX-400 spectrometer at 400 and 100 MHz respectively. NMR spectra were obtained in DMSO-d_6 solutions and are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. Mass spectrometry is recorded with Applied Biosystem mass

spectrometer. Elemental analyses (C, H and N) were performed using the Thermo Scientific Flash 2000 organic elemental analyzer. Merck silica gel (100-200 mesh) was used for column chromatography.

General procedure for synthesis of 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone (4-10): A 100 mL RB flask was charged with 2-chloro-1-(1-aryl-1*H*-tetrazol-5-yl) ethanone (1 mmol), piperazine (1.2 mmol) and triethylamine (0.1 mmol) in acetonitrile (25 mL). The reaction mixture was stirred for 6 hrs at room temperature. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was quenched with crushed ice and the solid was filtered, washed with water and dried under vacuum to get novel 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone. Finally the crude product was purified through column chromatography. The yield and melting point of the newly synthesized compounds (**4-10**) are shown in **Table 1**.

Table -1 Physical data for the newly synthesized compounds **4-10**

Compound	X	Yield (%)	Mp (°C)
4	H	79	180-182
5	CH_3	72	158-162
6	OCH_3	70	170-172
7	Cl	80	192-194
8	Br	70	172-176
9	F	77	169-172
10	NO_2	78	165-168

1-(1-phenyl-1H -tetrazol-5-yl)-2-(piperazin-1-yl)ethanone (4): IR (KBr) ν_{max} (cm^{-1}): 3428 (-NH), 1690 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.43 (4H, s, CH_2), 2.70-2.71(4H, d, CH_2), 3.16 (2H, s, CH_2), 7.07-7.11 (1H, t, CH), 7.33-7.35 (2H, d, *J* = 8 Hz, CH), 7.50-7.52 (2H, d, *J* = 8 Hz, CH), 9.1 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): *δ* 45.19, 53.45, 61.27, 119.6, 123.8, 137.3, 150.2 and 172.5. MS (*m/z*): 272 (M^+). For $C_{13}H_{16}N_6O$ calculated: 57.34% C, 5.92% H and 30. 86% N; Found: 56.54% C, 5.79% H and 30.75% N.

2-(piperazin-1-yl)-1-(1-p-tolyl-1H-tetrazol-5-yl)ethanone (5): IR (KBr) ν_{max} (cm^{-1}): 3404 (-NH), 1688 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.26 (3H, s, CH_3), 2.42 (4H, s, CH_2), 2.70 (4H, s, CH_2), 3.15 (2H, s, CH_2), 7.12-7.14 (2H, d, *J* = 8 Hz, CH), 7.38-7.40 (2H, d, *J* = 8 Hz, CH), 9.1 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz,): *δ* 20.35, 45.43, 53.72, 61.36, 119.6, 129.3, 132.7, 150.1 and 172.5. MS (*m/z*): 286 (M^+). For $C_{14}H_{18}N_6O$ calculated: 58.73% C, 6.34% H and 29.35% N; Found: 58.44% C, 6.23% H and 29.75% N.

1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone (6): IR (KBr) ν_{max} (cm^{-1}): 3419 (-NH), 1690 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.42 (4H, s, CH_2), 2.70 (4H, s, CH_2), 3.15 (2H, s, CH_2), 3.73 (3H, s, OCH_3), 6.89-6.91 (2H, d, *J* = 8 Hz, CH), 7.41-7.43 (2H, d, *J* = 8 Hz, CH), 9.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz,): *δ* 45.42, 52.36, 53.75, 55.14, 61.36, 114.0, 121.4, 130.3, 155.6 and 172.4. MS (*m/z*): 302 (M^+). For $C_{14}H_{18}N_6O_2$ calculated: 55.62% C, 6.00% H and 27.80% N; Found: 55.47% C, 5.68% H and 27.64% N.

1-(1-(4-chlorophenyl)-1H-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone (7): IR (KBr) ν_{max} (cm^{-1}): 3460 (-NH), 1679 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.30 (4H, s, CH_2), 2.76 (4H, s, CH_2), 3.20 (2H, s, CH_2), 7.57-7.59 (2H, d, *J* = 8 Hz, CH), 7.68-7.70 (2H, d, *J* = 8 Hz, CH), 9.01 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz,): *δ* 45.43, 53.72, 61.36, 121.6, 130.1, 150.2, 155.7 and 168.5. MS (*m/z*): 306 (M^+).

For $C_{13}H_{15}ClN_6O$ calculated: 50.90% C, 4.93% H and 27.40% N; Found: 50.77% C, 4.85% H and 27.24% N.

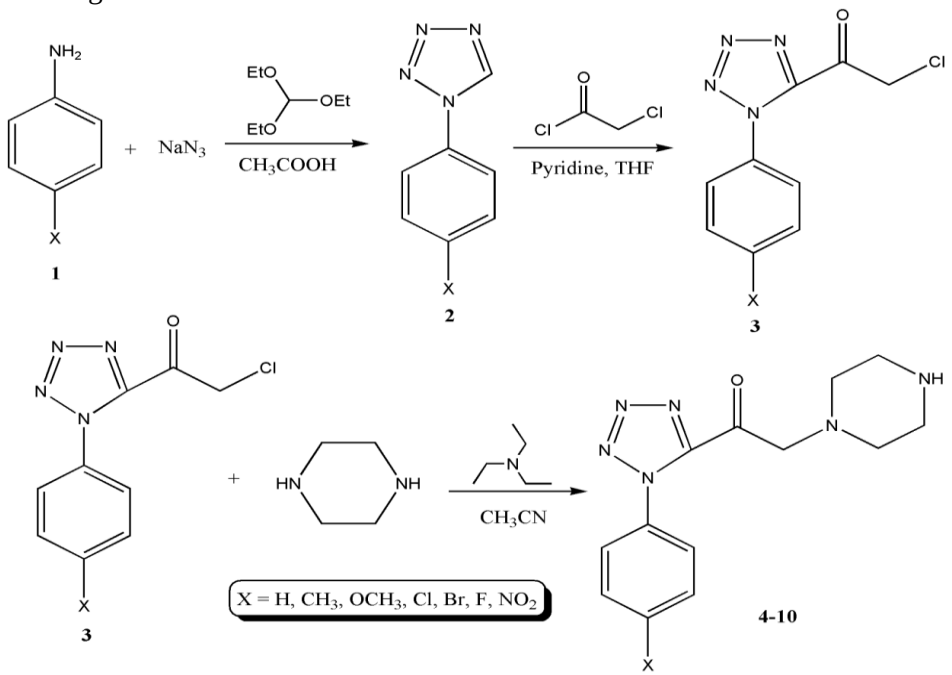
1-(1-(4-bromophenyl)-1H-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone (8) : IR (KBr) ν_{max} (cm^{-1}): 3445 (-NH), 1690 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.20 (4H, s, CH_2), 2.70 (4H, s, CH_2), 3.16 (2H, s, CH_2), 7.43 (4H, s, CH), 9.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz,): *δ* 45.43, 53.75, 62.02, 117.0, 121.78, 132.0, 136.2, 149.8 and 172.0. MS (*m/z*): 351 (M^+). For $C_{13}H_{15}BrN_6O$ calculated: 44.46% C, 4.30% H and 23.93% N; Found: 44.21% C, 4.15% H and 22.62% N.

1-(1-(4-fluorophenyl)-1H-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone (9) : IR (KBr) ν_{max} (cm^{-1}): 3438 (-NH), 1692 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.60-2.61 (4H, d, CH_2), 2.94-2.96 (4H, d, CH_2), 3.17 (2H, s, CH_2), 6.69-6.71 (2H, d, *J* = 8 Hz, CH), 7.11-7.13 (2H, d, *J* = 8 Hz, CH), 9.20 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz,): *δ* 53.75, 62.12, 66.72, 117.0, 121.7, 132.0, 136.2, 149.8 and 182.0. MS (*m/z*): 290 (M^+). For $C_{13}H_{15}FN_6O$ calculated: 53.79% C, 5.21% H and 28.95% N; Found: 50.67% C, 5.12% H and 28.79% N.

1-(1-(4-nitrophenyl)-1H-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone (10) : IR (KBr) ν_{max} (cm^{-1}): 3444 (-NH), 1679 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.21 (4H, s, CH_2), 2.70 (4H, s, CH_2), 3.11 (2H, s, CH_2), 7.41-7.43 (2H, d, *J* = 8 Hz, CH), 8.11-8.13 (2H, d, *J* = 8 Hz, CH), 9.30 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz,): *δ* 55.16, 63.02, 121.6, 130.1, 150.2, 155.7 and 168.5. MS (*m/z*): 317 (M^+). For $C_{13}H_{15}N_7O_3$ calculated: 49.21% C, 4.76% H and 30.90% N; Found: 49.01% C, 4.66% H and 29.89% N.

RESULTS AND DISCUSSION

Chemistry: The new 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone derivatives (**4-10**) were synthesized according to **Scheme 1**.



Scheme 1. Scheme for the synthesis of 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone derivatives (**4-10**)

Reaction of aryl anilines with sodium azide and triethylorthoformate in acetic acid resulted in the formation of tetrazole compounds (**2**). Compounds (**2**) on further reaction with chloroacetylchloride resulted in the formation of 2-chloro-1-(1-aryl-1*H*-tetrazol-5-yl)ethanones (**3**). Compounds (**3**) on further reaction with piperazine in acetonitrile yields novel 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl) ethanones (**4-10**). All the synthesized compounds were characterized using IR, ^{1}H NMR, ^{13}C NMR, Elemental analysis and mass spectral studies.

In order to assign the IR and NMR spectral values, 1-(1-phenyl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone **4** has been chosen as representative compound. The FT-IR spectrum of compound **4** showed characteristic absorptions at 3428 cm^{-1} due to N-H stretching vibrations of the piperazine group. The band at 1690 cm^{-1} is due to the presence of the carbonyl group stretching frequency. The absorption frequency at 2925-2854 $cm^{-1}$is assigned to the aromatic C-H stretching vibration. The absorption band at 1209 cm^{-1} is consistent with the C-N stretching vibration. The observed NH, C=O, C-H, and C-N stretching vibrational bands are supporting evidence for the formation of synthesized compound **4**. In the ^{1}H NMR spectrum of compound **4**, two singlets observed at 2.43 and 2.71, are due to the methylene protons of the piperazine ring. The singlet at 3.16 ppm is assigned to the CH_2 protons of ethanone moiety. The aromatic protons appeared as a multiplet in the range of 7.07-7.52 ppm. The NH proton of piperazine ring appeared at 9.16 ppm. In the ^{13}C NMR spectrum of compound **4,** two signals are observed at 45.1 and 53.4 ppm. Out of which, the signal at 45.1 ppm is due to the methylene carbon of the piperazine ring attached to NH $[HN(CH_2)_2]$ and the other signal at 53.4 ppm is unambiguously assigned to the methylene carbon of the piperazine ring attached to N$[N(CH_2)_2]$.The ^{13}C resonance observed at 61.2 ppm is assigned to the methylene carbon of ethanone moiety. Aromatic carbons are observed in the range of 119.6-128.9 ppm. The aromatic *ipso* carbon and the tetrazole *ipso* carbon are observed at 137.3 and 150.2 ppm respectively. The remaining ^{13}C signal at 172.5 ppm is due to the carbonyl carbon.

APPLICATIONS

Antibacterial activity: The *in vitro* antibacterial activity of the newly synthesized compounds **4-10** was determined by serial dilution method. All the synthesized Compounds, **4-10** were assessed to elicit their antibacterial activity *in vitro* against *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhi*, *Vibrio cholerae*, *Escherichia coli* and *Klebsiella pneumoniae*. The antibacterial potency of the synthesized compounds was compared with Ciprofloxacin using their minimum inhibitory concentration (MIC) by serial dilution method; the values are summarized in **Table 2**.

Table -2 *In vitro* antibacterial activities of **4-10** against clinically isolated bacterial strains

Compound	Minimum inhibitory concentration (MIC) in µg/mL					
	S. aureus	*B. subtilis*	*S. typhi*	*V. cholerae*	*E. coli*	*K. pneumonia*
4	100	50	100	-	100	100
5	50	100	-	100	50	50
6	100	50	100	50	25	100
7	12.5	12.5	25	25	100	-
8	100	100	100	-	50	100
9	25	12.5	50	25	12.5	50
10	50	12.5	50	100	50	-
Ciprofloxacin	12.5	12.5	25	25	12.5	25

'—' no inhibition even at a higher concentration of 200 µg mL^{-1}

Close surveys of the MIC values indicate that all the compounds exhibited a varied range (12.5–200 µg mL^{-1}) of antibacterial activity against all the tested bacterial strains. The MIC values of compounds **7, 9** and **10** showed maximum inhibition activity (12.5 µg mL^{-1}) against *B. subtilis.* Among the various substituted compounds, compound **4** against *V. cholerae,* compound **5** against *S. typhi,* compound **7** against *K. pneumonia,* compound **8** against *V. cholerae* and compound **10** against *K. pneumonia* did not show any activity even at maximum concentration (200 µg/mL). Electron withdrawing substituents like chloro, fluoro and nitro substituted compounds **7**, **9** and **10** exerted excellent antibacterial activities. Fluorination increases the lipophilicity due to strong electron withdrawing capability of fluorine. Moreover, fluorine substitution was commonly used in contemporary medicinal chemistry to improve metabolic stability, bioavailability and protein ligand interactions.

Antifungal activity: In order to extend the antimicrobial evaluation, the antifungal screening was also done, which revealed that the synthesized compounds (**4-10**) showed good inhibition against various tested fungal strains viz., *Aspergillus flavus, Aspergillus niger, Candida albicans, Mucor, Candida 6* and *Rhizopus*. Here, Fluconazole was used as standard drug. The results indicate that among the tested compounds, compound **9** showed maximum inhibition activity (6.25 µg/mL) against *C. albicans.* Among the various substituted compounds, compound **4** and **8** against *Mucor,* compound **5** against *A. flavus* and compound **5** and **7** against *Rhizopus* did not show any activity even at maximum concentration (200 µg mL^{-1}). However, the introduction of halogen functionality at *para* position of phenyl groups in compound **7, 8** and **9** registered moderate inhibition potency against all the tested fungal organisms with MIC ranging from 6.25 - 100 µg mL^{-1}. The fluoro substituted compound **9** shows maximum antifungal potency against *C. albicans*. A modification of *para* proton (compound **4**) by chloro, fluoro and nitro group i.e., compounds 7, **9** and **10** shows moderate activity against the entire tested fungal strains but registered high inhibition against *C. albicans* (6.25-25µg mL^{-1}). Results of antifungal studies have been presented in **Table 3**.

Table -3 *In vitro* antifungal activities of **4-10** against clinically isolated fungal strains

Compound	Minimum inhibitory concentration (MIC) in µg/mL					
	A. flavus	*A. niger*	*C. albicans*	*Mucor*	*Candida 6*	*Rhizopus*
4	50	50	50	-	50	100
5	-	100	25	100	100	-
6	50	50	50	100	50	50
7	50	50	25	50	25	-
8	100	100	50	-	50	100
9	50	25	6.25	25	12.5	50
10	25	100	12.5	50	25	50
Fluconazole	12.5	25	12.5	25	25	50

'—' no inhibition even at a higher concentration of 200 µg/mL

Molecular docking studies: Molecular docking studies were conducted in order to validate the obtained pharmacological data and to provide understandable evidence for the observed antimicrobial activity of all synthesized compounds. Molecular docking study is a well-established technique to determine the interaction of two molecules and find the best orientation of ligand would form a complex with overall minimum energy. In our research group now a days we are using this docking program to check the *in silico* activities of the newly synthesized bioactive molecules [29, 30]. Molecular modeling study was carried out using docking program DOCK SERVER (www.dockingserver.com). All the newly synthesized

compounds **(4-10)** were docked with *alpha-amylase complexed with maltopentaose* of *B. subtilis* at ten different orientations. The structure of the protein mentioned above [PDB: **1BAG**] was retrieved from the Protein Data Bank [www.rcsb.org (DOI: 10.2210/pdb1bag/pdb)] and further modified for docking calculations. The ligand molecules were drawn and analysed using Chem Draw Ultra 8.0. **3D**, coordinates were prepared using dock server. Based on the *in vitro* antimicrobial studies, it is worthwhile to do *in silico* studies;it supports the *invitro* activity.

In silico studies revealed all the synthesized molecules showed good binding energy toward the target protein ranging from -8.06 to -7.92 kcal mol^{-1}. The docking results revealed that compound **5** showed minimum binding energy of -8.06 kcal mol^{-1}, which is due to dipole-dipole and hydrogen bond interaction with amino acids of targeted protein. It was observed that the most active compound of the series, i.e., compound **9** was predicted to be most active *in silico* too. The other compounds like **7** and **10** having significant antibacterial activity are also found to have good docking scores as shown in **Table 4**.

Table 4 Molecular docking results of the target molecules with *alpha-amylase complexed with maltopentaose* from *Bacillus subtilis* (PDB ID: **1BAG**)

Compound	Binding Energy (kcal/mol)	Docking Energy (kcal/mol)	Inhibition Constant (μM)	Intermolec. Energy (kcal/mol)
4	-7.98	-7.46	1.42	-9.24
5	-8.06	-6.99	1.23	-9.07
6	-7.36	-6.73	4.00	-8.84
7	-7.85	-7.02	1.77	-9.00
8	-7.94	-7.46	1.52	-9.48
9	-7.96	-7.16	1.45	-9.12
10	-7.92	-7.42	1.56	-9.48

The acting force of this binding mode is mainly depends on hydrogen bonding, electrostatic forces, van-der Waals forces and hydrophobic interaction due to non-polar residue interaction and water structure effect alteration [31]. Docked ligand molecule **4** with the secondary structure of *alpha-amylase complexed with maltopentaose* of *B. subtilis* in solid and ribbon model is depicted in **Figure 2**. The surface cavity with target molecule **4** at the active pocket of the protein structure is depicted in **Figure 3**. 2D plot of hydrogen bond forming amino acids with target ligand and HB plot of interacted residues in protein of *E. coli* with compound **4** is depicted in **figure 4 & 5** respectively.

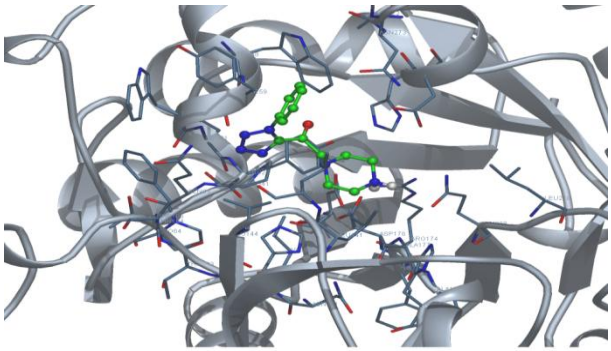


Figure 2. Docked ligand molecule **4** with the secondary structure of *alpha-amylase complexed with maltopentaose* in solid and ribbon model

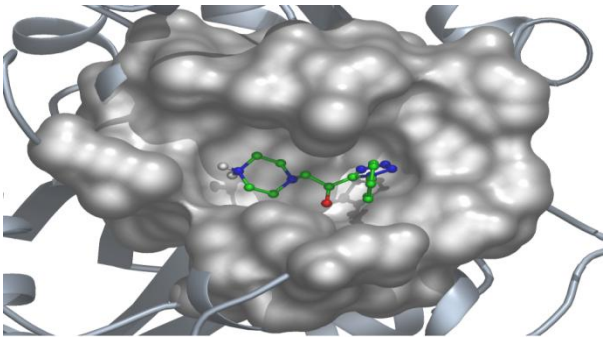


Figure 3. The surface cavity with target molecule **4** at the active pocket of the protein

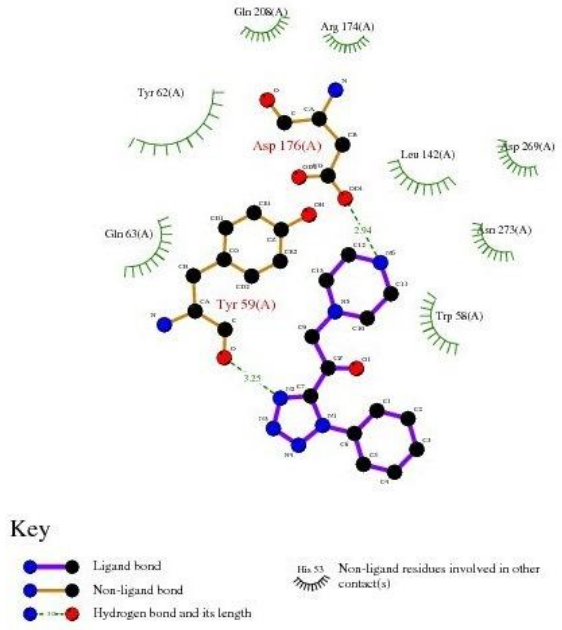


Figure 4. 2D plot of hydrogen bond forming amino acids with target ligand for compound **4**

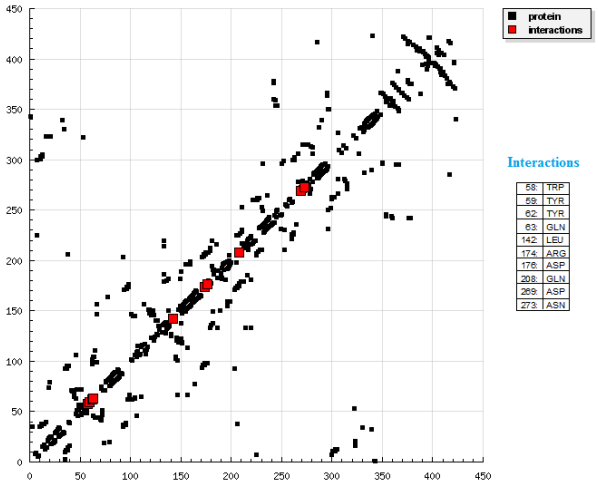


Figure 5. HB plot of interacted residues in protein with compound **4**

The *in vitro* antifungal MIC values are correlated well with binding energies obtained through molecular docking with *3,4-Dihydroxy-2-butanone 4-phosphate Synthase* (PDB: **1TKU**) of *C. albicans* [www.rcsb.org (DOI: 10.2210/pdb1tku/pdb)]. Docked ligand molecule **5** with the secondary protein structure of *3,4-Dihydroxy-2-butanone 4-phosphate Synthase* in solid and ribbon model is depicted in **Figure6**.The minimum fungal inhibition potency against*C. albicans* of compounds **9** (6.25 µg mL^{-1}) and **10** (12.5 µg ml^{-1}) showed excellent docking energies. Their binding energies are -7.26 and -7.18 kcal/mol respectively [**Table 5]**.

Table 5 Molecular docking results of the target molecules with *3,4-Dihydroxy-2-butanone 4-phosphate Synthase* from *Canida albicans* (PDB ID: **1TKU**)

Compound	Binding Energy (kcal/mol)	Docking Energy (kcal/mol)	Inhibition Constant (µM)	Intermolec. Energy (kcal/mol)
4	-7.03	-6.23	7.06	-8.15
5	-8.04	-7.45	1.28	-9.42
6	-6.78	-6.16	10.66	-8.53
7	-7.88	-6.91	1.68	-8.95
8	-7.78	-6.81	1.97	-8.73
9	-7.26	-6.37	4.80	-8.16
10	-7.18	-7.20	5.43	-9.06

From the comparative analysis, the above compounds **9** and **10** shows good *in vitro* antifungal activity which is further supported by their *in silico* analysis. The above mentioned compounds utilize their amino head group to interact with the crucial amino acid residues such as His 145, Glu 32 through hydrogen bonds. The surface cavity with target molecule **5** at the active pocket of the protein structure is depicted in **Figure 7**. 2D plot of hydrogen bond forming amino acids with target ligand and HB plot of interacted

residues in protein of *C. albicans* with compound **5** is depicted in **Figure 8 & 9** respectively. Therefore, it is pleasing to state that the docking studies have widened the scope of developing a new class of antimicrobial agents.

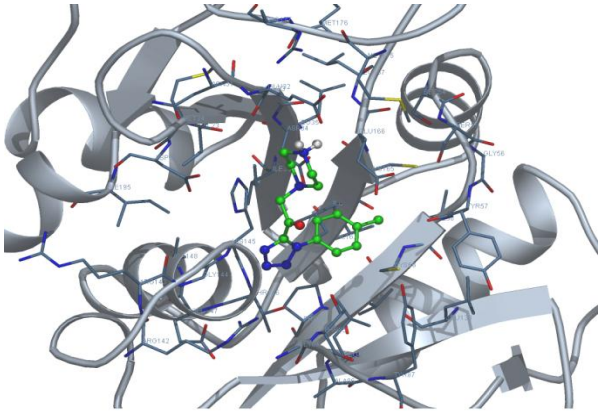


Figure 6. Docked ligand molecule **5** with the secondary structure of *3,4-Dihydroxy-2-butanone 4-phosphate Synthase* in solid and ribbon model

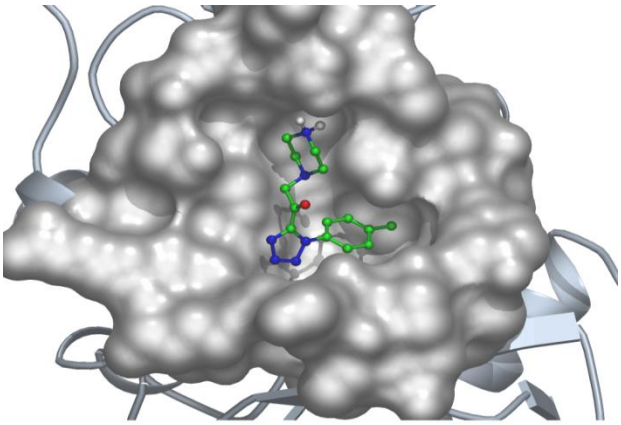


Figure 7. The surface cavity with target molecule **5** at the active pocket of the protein

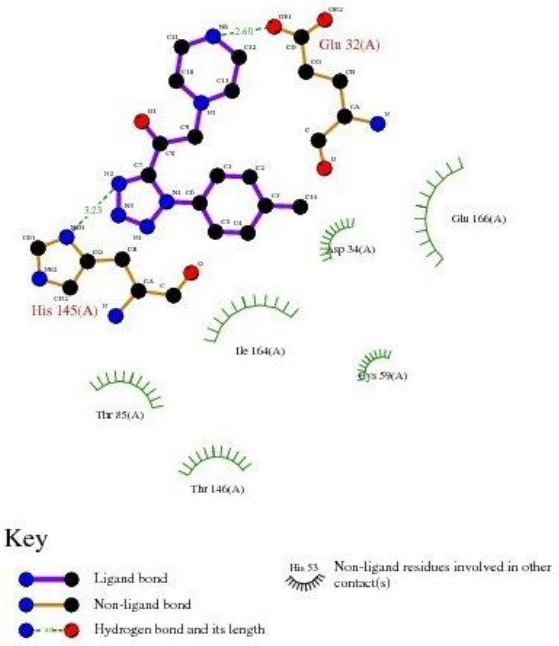


Figure 8. 2D plot of hydrogen bond forming amino acids with target ligand for compound **5**

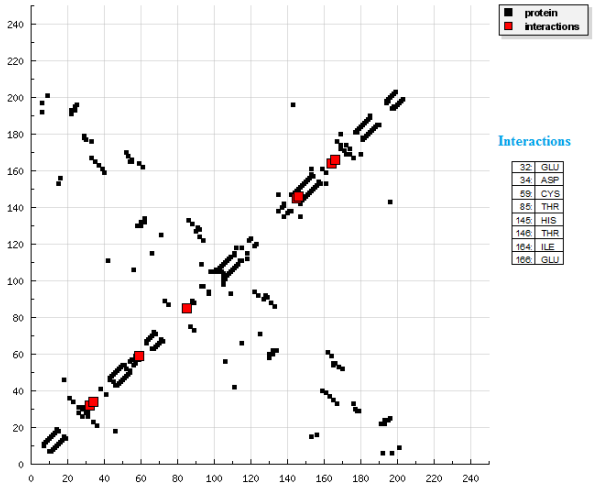


Figure 9. HB plot of interacted residues in protein with compound **5**

CONCLUSIONS

In conclusion, a series of novel 1-(1-aryl-1*H*-tetrazol-5-yl)-2-(piperazin-1-yl)ethanone derivatives were synthesized in good yields and their structures were characterized by their IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data. The synthesized compounds showed a wide range of potentially promising antibacterial and antifungal activities. Compounds **7, 9** and **10** showed significant antimicrobial activity against the tested bacterial and fungal strains. The docking study reveals that hydrophobic interactions played a major role in ligand receptor interactions. Finally, the results indicate that these new compounds could be considered as a new lead for further optimization.

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