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Research Article

DESIGN, SYNTHESIS AND MOLECULAR DOCKING STUDIES OF BENZOTHIAZOLE DERIVATIVES AS ANTI MICROBIAL AGENTS

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ABSTRACT

Objective: Microbial infections are becoming the most important issue for global health and economy. These infections are of communicable nature, which can range from common cold, cough, typhoid, malaria, cholera to even some severe disease conditions like Tb and AIDS. The researches carried out on benzothiazole moiety had established promising antimicrobial activities like antimalarial, antifungal, anti tubercular, antiviral as well as antitumor, analgesic and anti-inflammatory activities. The present study aimed to develop molecules with improved antimicrobial activity. The possible effective molecules were designed by incorporating the oxadiazole derivatives and Schiff bases into the benzothiazole moiety.

Methods: The benzothiazole compounds for synthesis was selected based on docking studies performed on Topoisomerase IVand Gyrase in bacteria and N-myristoyl transferase in fungi using Autodock. Molecules with better docking score was subjected to analysis by Lipinski's Rule of Five to determine drug likeness and further the toxicity profiling was performed, for a series of eight benzothiazole derivatives using Mol Inspiration Software and Discovery studio respectively. Further the compounds were synthesised.

Results: Among the eight benzothiazole derivatives 2{5[(1,3benzothiazol2ylsulfanyl)methyl]1,3,4oxa

diazol2yl}benzoicacid(OXA1),4{5[(1,3benzothiazol2ylsulfanyl)methyl]1,3,4oxadiazol2yl}aniline(OXA2),2(1,3benzothiazol2ylsulfanyl)*N*'[(*E*)(4hydroxy3methoxyphenyl)methylidene]acetohydrazide(S2),2(1,3benzothiazol2ylsulfanyl)*N*'[(*E*)(2hydroxyphenyl)methylidene]acetohydrazide(S3)and2(1,3benzothiazol-2-ylsulfanyl)-*N*'[(*E*)furan2ylmethylidene]acetohydrazide (S5) were found to have highest docking score, lesser toxicity profile and gave good yield which were further characterized. Antibacterial and antifungal activity of the synthesized derivatives was done in comparison with ciprofloxacin and ketoconazole as standard to discover the potency of synthesized derivatives.

Conclusion: Both Schiff bases and oxadiazole derivatives showed good antimicrobial activity. The docking results for antimicrobial activity were found to be comparable with the wet lab results.

Keywords: Benzothiazole moiety, 1, 3, 4 oxadiazole, Schiff bases, Antimicrobial activity, Molecular docking.

INTRODUCTION

Benzothiazole is an aromatic heterocyclic compound with the chemical formula C_7H_5NS. They represent an extensive group of compounds having a thiazole fused with benzene ring [1]. It is a proved fact that heterocyclic compounds containing nitrogen and sulphur possess potential pharmacological activities. Benzothiazole is usually prepared by ring closure of *o*-aminothiophenols with acid chlorides. Due to the immense importance in pharmaceutical utilities, the synthesis of derivative compounds is of considerable interests [2]. The benzothiazole moiety is established to have diverse chemical reactivity and biological spectrum of activity [3]. Benzothiazole with oxadiazole group and Schiff bases were reported to possess various pharmacological activity of clinical importance. Oxadiazole derivatives are well known to have a number of biological activities especially antimicrobial, anti-inflammatory and anti-convulsant. In the present work oxadiazoles incorporated with benzothiazole have been synthesized, expecting wide spectrum of biodynamic properties having potent clinical significance [4]. Schiff bases are currently been applied for the treatment of a number of disease condition. Though extensive research work has been reported on benzothiazole with Schiff base, relatively very little is known about the substituted benzothiazole with Schiff base [5]. Initial step of the research was the insilico screening for possible potential molecule, the molecular docking is frequently used to predict the binding orientation of drug candidates to their protein targets, to predict the affinity and activity. Docking is an important process in the rational design of drugs. In the present study we use microwave as well as conventional methods for the synthesis of molecules with substituted benzothiazole derivatives. The use of microwave irradiation is an established tool in organic synthesis for achieving better selectivity, rate enhancement and reduction of thermal degradation of by products [6]. The benzothiazole derivatives are the fastest growing antimicrobial class in terms of global revenue, increasingly being used in both the hospital and community sectors to treat broad range of infections. At the beginning of this century, neither the causative agents nor the active ingredients, which is used to cure the infections, could be identified. The scientific practice of organic chemistry and the rational application of microbiology resulted in the birth of various antimicrobial substances. This observation prompted us to design, synthesis and study the activity of benzthiazole as potential antimicrobial agents [8].

MATERIALS AND METHODS

In Silico Molecular Modelling

- Protein preparation

After conducting adequate literature review Topoisomerase IV (PDB entry code 3LPS), Gyrase (PDB entry code 3TTZ) in bacteria and N-myristoyl transferase (PDB entry code 1IYL) in fungi were selected as the target for the present study. The crystal structures of the above targets were obtained from Protein Data Bank and saved in standard 3D coordinate format.

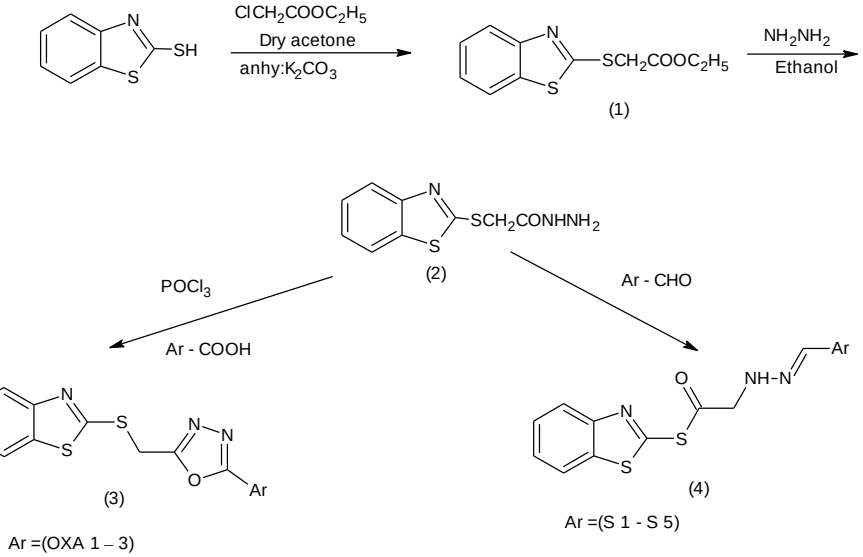
- Ligand preparation

Ligand preparation was done by drawing the structures using ChemSketch and further conversion to 3D pdb format using CORINA. Analysis of Lipinski rule of 5 was carried out by molinspiration program followed by determination of toxicity profile. Protein visualization was done by loading the structure in SWISS PDB Viewer. Further the Energy Minimization was performed by CHIRON software. Docking simulations were performed with AutoDock4 using Lamarckian genetic algorithm. The grid maps of docking studies were calculated using AutoGrid4 included in the Autodock4 tools. The number of docking runs was set to 50. Both Autogrid and Autodock computations were performed on Cygwin. Hydrogen bonding and hydrophobic interactions between docked ligands and macromolecule targets were analyzed using ADT (Version 1.50).

Chemistry

Scheme

The Oxadiazole derivatives and Schiff base analogues of benzothiazole were synthesized according to the given Scheme.



Experimental

All the chemicals and reagents used were of analytical grade and were procured from Loba chemicals.

Preparation of ethyl 2-(benzothiazolylthio) acetate (1)

Conventional synthesis

Dissolved the 2-Mercaptobenzothiazole (2.0 mol) in methanol and ethyl chloro acetate (2.0 mol) was added dropwise in presence of K_2CO_3 (8 g) in the mixture with stirring. The resulted mixture was refluxed for 10 hours and the reaction mixture poured into ice cold water and neutralized with dil HCl. The semisolid thus obtained was washed several times with water and left in water for 72 hours. The crystals formed were filtered, washed thoroughly with water and dried. It was recrystallised from chloroform [9].

Microwave synthesis

Mercaptobenzothiazole (0.01 mol, 1.67 g) and ethylchloroacetate (0.01 mol, 1.22ml) in dry acetone (4 ml) in the presence of anhydrous K_2CO_3 (1 g) were placed in a round bottom flask and microwave irradiated (300 W, 61-62 ^{o} C) for 4.0 min. Upon completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature and the treated with cold water. The separated solid was filtered, washed with water and recrystallized from chloroform.

Preparation of 2-(benzo[d]thiazol-2-ylthio) acetohydrazide (2)

Conventional synthesis

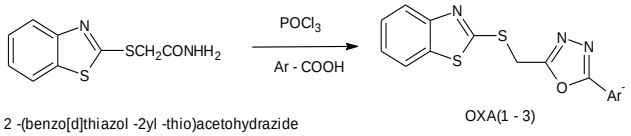
Ethyl 2-(benzothiazolylthio) acetate (1), (0.01 mol, 2.53 g) and hydrazine hydrate (0.01 mol, 0.9 ml) in ethanol (20 ml) were refluxed for about 5 hour on a steam bath. After cooling the resulting solid was filtered, dried and recrystallized from ethanol to obtain compound.

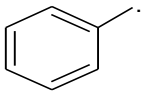
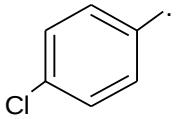
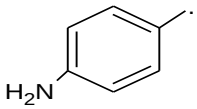
Microwave synthesis

Ethyl 2-(benzothiazolylthio)acetate (0.01 mol,2.53 g) and hydrazine hydrate (0.01 mol, 0.9 ml) in ethanol (20 ml) were placed in a round bottom flask and microwave irradiated (350 W, 76-78 ^{o}C) for 3.5 min. After completion of the reaction (monitored by TLC.), the mixture was cooled and the resulting solid was filtered, dried and recrystallized from ethanol.

Preparation of oxadiazole derivatives

Reaction



S. No	Ar
OXA1	
OXA2	
OXA3	

Conventional synthesis

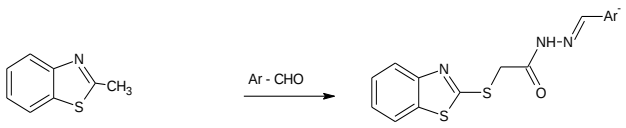
A mixture of hydrazide (1g, 0.01 mol), appropriate aromatic acid (benzoic, 4-chloro benzoic and 4-amino benzoic acid) (0.02 mol) and phosphoryl chloride (10 ml) was refluxed on a water-bath for 6-8h. After cooling to room temperature, it was poured onto crushed ice with stirring. The solid thus obtained was filtered, washed with water and crystallized from methanol [10].

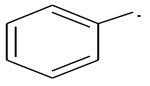
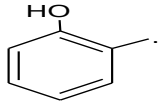
Microwave synthesis

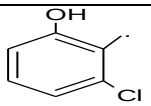
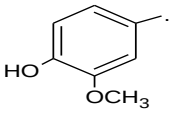
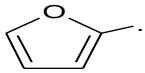
A mixture of hydrazide (0.0025 mole, 0.738g) and aromatic acid (0.0025mole, 0.305g) was refluxed in the presence of $POCl_3$ (5ml) for 45 minutes in a microwave at a temperature of 80-85^{0} C.

Preparation of Schiff bases

Reaction



S. No:	Ar
S1	
S2	

S3	
S4	
S5	

Conventional synthesis

A mixture of compound (0.01 mol, 2.39 g) and aromatic aldehyde (0.01 mol,1.51 g) (Benzaldehyde, furfural, vanillin,salicylaldehyde, 5-chloro salicylaldehyde) and 2-3 drops of glacial acetic acid in ethanol (25ml) was refluxed on a water bath for about 6 hrs. The solvent was removed and residue recrystallized from ethanol [11].

Microwave synthesis

A mixture of compound (0.01 mol, 2.39 g), aromatic aldehyde (0.01 mol, 1.51 g) and 2-3 drops of glacial acetic acid in ethanol (20 ml) were placed in a round bottom flask and microwave irradiated (400 W, 76-78 ^{o}C) for 3 min . After completion of the reaction (monitored by TLC), the solvent was removed and residue recrystallized from ethanol.

Spectral Characterisation

The infra red spectra of the synthesized compounds were recorded using SHIMADZU - FTIR (IR AFFINITY 1) spectrometer using potassium bromide pellet technique. ^{1}HNMR of synthesized compounds were taken using BRUKER SPECTROSPIN - 400 MHz spectrometer using tetra methyl silane (TMS) as an internal standard. ^{1}HNMR spectra were recorded with DMSO (d_6) as solvent and the chemical shift were expressed as delta values related to TMS as ppm. Mass spectra of the samples were recorded on MSMS-QP 5050 SHIMADZU instrument.

OXA1*(2-{5-[(1,3-benzothiazol-2-ylsulfanyl)methyl]-1,3,4-oxadiazol-2-yl}benzoicacid)*

IR KBr cm-^{1}3066(C-H aromatic stretching), 1577(C=C stretching in benzene ring), 1685(C=N aromatic stretching), 1180(C-O-C stretching) HNMR(400MHzDMSO) δ(ppm)7.959(d,*J*=7.2Hz,1H),7.63 (t,*J*=7.4Hz,2H),7.51(t,*J*=7.6Hz1H),3.385(s,S- CH2, 1H) ESI MS (m/z, relative abundance) 326[(M+H)$^{+}$,5.8]

OXA2 *(4-{5-[1,3-benzothiazol-2ylsulfanyl)methyl]-1,3,4-oxadiazol-2-yl}aniline)*

IR KBr cm^{-1} 3217(C-H aromatic stretching), 1512(C=C stretching in benzene ring), 1597(C=N aromatic stretching), 1182(C-O-C stretching), 3338(N-H stretching).

HNMR(400MHzDMSO)δ(ppm)7.9337.690(m,Ar-4H), 7.614(d, *J*=8.4Hz.Ar-H), 7.512-7.186(m,Ar-2H),6.64(d *J*=7.2Hz,Ar-H), 6.55(d *J*=8.4Hz,Ar-2H), 3.507(s,NH2,1H)

OXA3*(2-({[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}sulfanyl)-1,3-benzothiazole)*

IR KBr cm^{-1} 2837(C-H aromatic stretching), 1593(C=C stretching in benzene ring), 1683(C=N aromatic stretching), 1089(C-O- C stretching, 682 (C-Cl stretching) H NMR (400MHz DMSO) δ (ppm) 7.956-7.935(m,Ar-4H).7.585-7.564(m,Ar-4H), 3.364(s,S-CH2,1H)

S1*(2-(1,3-benzothiazol-2-ylsulfanyl)-N'-[(E)-phenylmethylidine]acetohydrazide)*

IR KBr cm^{-1} 3055(C-H stretching in aromatic ring), 1674(C=O of amide), 1620(C=N of aromatic ring), 1456(C=C of aromatic ring) HNMR (400MHz DMSO) δ (ppm) 8.729(s, C=ONH,1H),7.907-7.842(m,Ar-4H),7.327 7.310(m, Ar-5H), 3.368 (s, S CH2,1H)

S2*(2-(1,3-benzothiazol-2-ylsulfanyl)-N'-[(E)-(4-hydroxy-3-methoxyphenyl) methylidene] acetohydrazide)*

IR KBr cm^{-1} 3022(C-H stretching in aromatic ring), 1670(C=O of amide), 1593(C=N of aromatic ring), 630(C-S stretching)1460(C=C of aromatic ring), 2850(O-CH3 group) HNMR(400MHzDMSOδppm11.607(s,C=ONH,1H),11.595(s,N=CH,1H),8.02(t,*J*=7.45ArH),7.29(d,*J*=1.6Hz,ArH),7.28(d,*J*=10.4Hz,ArH),7.09(t,*J*=7.2Hz,ArH),6.9(d,*J*=8Hz,Ar- H), 4.676(s,S-CH2,1H),4.267(s, O- H,1H),3.356(s,O-CH3,1H ESI MS (m/z, relative abundance) 372[(M-H)$^{+}$, 95.4]

S3*(2-(1,3-benzothiazol-2-ylsulfanyl)-N'-[(E)-(2-hydroxyphenyl) methylidene] acetohydrazide)*

IR KBr cm^{-1} 3028(C-H stretching in aromatic ring), 1681(C=O of amide), 1622(C=N of aromatic ring), 1489(C=C of aromatic ring), 3176(OH stretching), 3028(N-H stretching) HNMR(400MHzDMSO)δ(ppm)12.072(s,C=ONH,1H),11.692(s,N=CH, 1H),7.84(d,*J*=7.848Hz,Ar- H),7.70(d, *J*=6.8Hz,Ar-H),7.55(t, *J*=4Hz,Ar-H),6.925-6.906(m, Ar 2H),6.87(t,*J*=13.4Hz,Ar-2H),4.682(s,S-CH2,1H)3.355(s,OH,1H) ESI MS (m/z, relative abundance) 342[(M-H)$^{+}$ 100]

S4*(2-(1,3-benzothiazol-2-ylsulfanyl)-N'-[(E)-(2-chloro-6-hydroxyphenyl) methylidene] acetohydrazide*

IR KBr cm^{-1} 3041(C-H stretching in aromatic ring), 1737(C=O of amide), 1645(C=N of aromatic ring), 1425(C=C of aromatic ring), 3284(N-H stretching), 750(C-Cl) HNMR(400MHzDMSO)δ(ppm)9.439(s,C=ONH,1H),8.959(s,N=CH,1H),8.025(d,*J*=8Hz,Ar- H),7.83(t, *J*=7.4Hz,Ar- H),7.782(d, *J*=2.4Hz,Ar-H),7.67(d, *J*=8Hz,Ar H),7.37(t, *J*=7.2Hz,Ar-2H),7.326-7.245(m,Ar-2H),7.015(d,*J*=8.8Hz,Ar-H),4.314(s,S CH2,1H)3.370(s,OH,1H).

S5 *(2-(1,3-benzothiazol-2-ylsulfanyl)-N'-[(E)-furan-2-methylidene]acetohydrazide*

IR KBr cm^{-1} 3057(C-H stretching in aromatic ring), 1735(C=O of amide), 1678(C=N of aromatic ring), 1458(C=C of aromatic ring), 3176(OH stretching),3190 (C-H stretching in Furan), 3190(N-H stretching) HNMR(400MHzDMSO)δ(ppm)11.80(s,C=ONH,1H) ,11.716(s,N=CH,1H),8.040, 8.012(m,Ar-4H),7.863-7.818(m,Ar-4H),4.644(s,S-CH2,1H) ESI MS (m/z, relative abundance) 316[(M+H)$^{+}$, 100]

RESULTS

Insilico Molecular Docking

On analysing the docking score obtained from insilico docking studies, the compounds OXA1, OXA2, S2, S3 and S5 gave comparatively good interaction with the selected targets. Docking images are shown in Fig 1,2,3. Docking sores of 8 compounds are shown in Table 1. From all the three microbial targets taken for this study all the ligands showed good binding against topoisomerase target. On analysing with Lipinski's Rule of Five, compounds showed mi LogP ≤ 5, n rot b ≤ 5, M.W ≤ 500, nOHNH ≤ 5, n ON ≤ 10. All synthesized compounds did not show any violations of rules (n-violations = 0) i.e., they obeyed 'Lipinski rule of 5. ADMET studies were also carried out using Discovery studio to determine their hepatotoxicity, solubility, absorption, penetration to BBB and plasma protein binding.

Docking Images

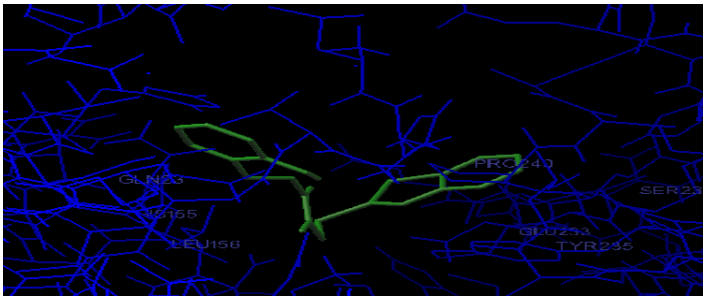


Fig. 1: S3 Bound To Topoisomeraseiv Docking Score: - 7.52

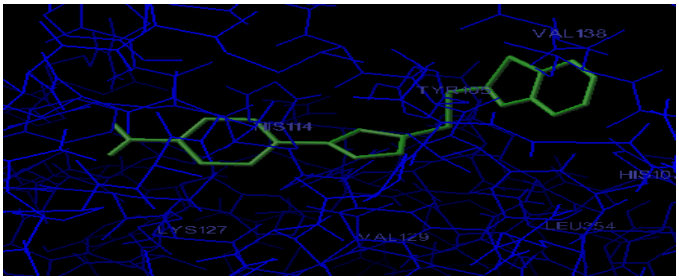


Fig. 2: OXA3 Bound To Gyrase.Docking Score:-5.42

The purified compounds were identified / characterized by following methods Physical Data and Melting Point Determination, Thin Layer Chromatography in (Table 2) Infra Red Spectroscopy, Nuclear Magnetic Resonance Spectroscopy, Mass Spectroscopy. Benzothiazole substituted with Schiff bases showed peaks at 3055 (C-H stretching in aromatic ring), 1674(C=O of amide), 1620(C=N of aromatic ring), 1456(C=C of aromatic ring), 2850(O-CH3 group), 750(C- Cl), 3176(OH stretching) by disappearance of NHNH2 peak.

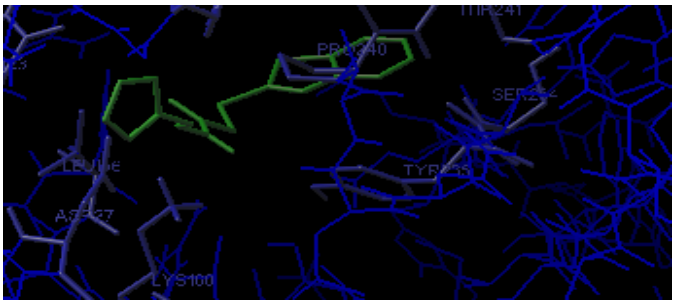


Fig. 3: S5 Bound To N-myristoyltransferase.Docking Score:-6.43

Oxadiazole derivatives showed singlet peak at 3.364-3.385 ppm in S-CH2. For Schiff bases the singlet peak was obtained at S-CH2 in (3-4 ppm), C=ONH (8-11 ppm) and N=CH (8-11 ppm). From mass spectra, the molecular weight of the derivatives OXA1, S2, S3 and S5 were found to be 325.41 373.45, 343.43 and 317.39 respectively. The compounds OXA1, S3 and S5 showed M+H peak and 4OH showed M-H peak.

Table 1: Docking score of 8 compounds

S. No.	Comp:Code	Topoisomerase IV	Gyrase	N-Myristoyl Transferase
1	OXA1	-6.95	-6.15	-6.34
2	OXA2	-7.23	-6.55	-6.71
3	OXA3	-6.38	-5.42	-6.19
4	S1	-6.23	-5.70	-6.03
5	S2	-8.05	-6.86	-7.70
6	S3	-7.52	-6.83	-7.31
7	S4	-6.50	-5.00	-5.93
8	S5	-7.26	-6.30	-6.43

Table 2: Physical data of compounds

Comp. Code	Mol: formula	M.W(g)	M.P(^{0}C)	% yield	TLC solvent	TLC
BT1	$C_{11}H_{11}NO_2S_2$	253.3	59	71%	Petether:Ethylacetate(1:1)	0.63
BT2	$C_9H_9N_3OS_2$	239.3	192	70%	Chloroform: methanol (9:1)	0.65
OXA1	$C_{16}H_{13}N_3OS_2$	325.4	112	68%	Ethylacetate:acetone (9:1)	0.72
OXA2	$C_{16}H_{12}N_4OS_2$	340.4	213	55%	Ethylacetate:acetone (9:1)	0.69
OXA3	$C_{16}H_{10}ClN_3OS_2$	359.8	156	58%	Ethylacetate: acetone (9:1)	0.76
S1	$C_{16}H_{13}N_3OS_2$	327.4	132	63%	Hexane:ethylacetate (3:7)	0.66
S2	$C_{17}H_{15}N_3O_3S_2$	373.4	120	64%	Hexane:ethylacetate (3:7)	0.65
S3	$C_{16}H_{13}N_3O_2S_2$	343.4	147	72%	Hexane:ethylacetate (3:7)	0.69
S4	$C_{16}H_{12}ClN_3O_2S_2$	377.8	118	66%	Hexane:ethylacetate (3:7)	0.63
S5	$C_{14}H_{11}N_3O_2S_2$	317.3	114	73%	Hexane:ethylacetate (3:7)	0.68

Antimicrobial Activity

The antimicrobial activity of all the synthesized compounds (OXA1-3, S1-S5) were examined against Gram-positive (*Staphylococcus aureus)* and Gram-negative (*Escherichia coli*) and fungal strain *(Candida albicans)* organisms by measuring zones of inhibition in Table 3. The antimicrobial activity was performed by Agar diffusion method at different concentrations 2µl,5µl,10µl,15µl,20µl and 25µl.(Fig 4).

The anti microbial drug Ciprofloxacin and ketoconazole was selected as standard drug at a concentration of 0.25mg.It was compared with the test sample. Nutrient agar was used as culture media for antibacterial activity studies and Sabouraud dextrose agar was used. Minimum inhibitory concentration was also calculated. (Table 4) It was found at 0.15mg/ml in antibacterial strains and 0.2mg/ml in antifungal strains and in accordance with the data obtained from antimicrobial activity, it was observed that all compounds with Schiff base derivatives exhibited good activity when compared to oxadiazole derivatives of benzothiazole, which was found to be equivalent to the docking results for the same. Activity was found to be better in ligands with electron donating substituent in the aromatic side chain e.g. hydroxyl group present at 2nd position (S3), amino group present at 4th position (OXA2), 3rd and hydroxyl group at 4th position (S2). Ligand (S5) with furan ring in the side chain also had shown comparably good antimicrobial activity with the standard.

Table 3: Antimicrobial activity-Zone of inhibition at 0.25 mg

Compound	Zone of inhibition(0.25 mg)(cm)		
	E.coli	S.aureus	C.albicans
OXA1	0.8	0.7	0.8
OXA2	0.9	0.8	0.8
S2	0.9	0.9	0.9
S3	0.9	0.8	0.8
S5	0.9	0.9	0.9
Ciprofloxacin	1.1	1.1	-
Ketoconazole	-	-	1.1

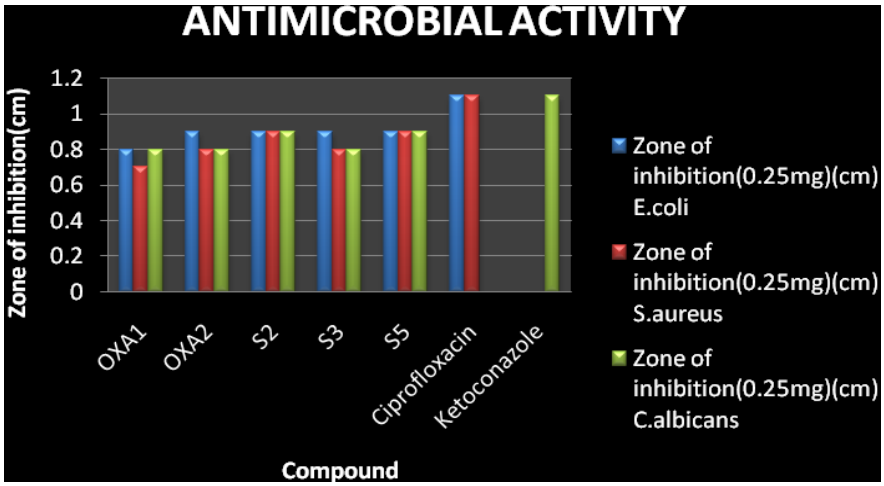


Fig. 4: Antimicrobialactivity- Zone of inhibition at 0.25mg

Table 4: Minimum inhibitory concentration of all samples at different organisms

Organism	Minimum Inhibitory Concentration(mg/ml)				
Sample	***Sample* OXA1**	***Sample* OXA2**	***Sample* S2**	***Sample* S3**	***Sample* S5**
E.coli	0.15	0.15	0.15	0.15	0.15
S.aureus	0.15	0.15	0.15	0.15	0.15
Candida albicans	0.2	0.2	0.2	0.2	0.2

DISCUSSION

In the present project, eight benzothiazole derivatives as shown in (table-6.1) were subjected to insilico docking studies. From the results obtained, the compounds with Schiff base as derivatives showed good binding interactions on the selected targets than oxadiazole derivatives. The Lipinski's rule of five was considered for evaluating the various properties of the compounds that would make it a possible orally active drug. Different parameters were studied of ADMET using Discovery studio such as absorption, penetration to the blood brain barrier, solubility, hepatotoxicity, plasma protein binding and metabolism. By means of m.p, TLC, IR, NMR and Mass analysis, the synthesized compounds purity were identified chemically characterised. The antimicrobial activity of compounds OXA1, OXA2, S2, S3, and S5 was carried out by Agar diffusion assay in *E.coli, S.aureus* and *C.albicans*. All the synthesized compounds OXA1, OXA2, S1, S2, and S3 were screened for antimicrobial activity at different concentrations 2 µl, 5µl, 10 µl and 15 µl, 20 µl, 25 µl. From the antimicrobial activity results, it was observed that all compounds with Schiff base as derivatives showed good activity when compared to oxadiazole derivatives of benzothiazole, which was found to be equivalent to the docking results for the same. Activity was found to be better in ligands with electron donating substituent in the aromatic side chain e.g, hydroxyl group present at 2nd position (S3), amino group present at 4th position (OXA2), methoxy group at 3rd and hydroxyl group at 4th position (S2). Ligand (S5) with furan ring in the side chain also had shown comparably good antimicrobial activity with the standard.

CONCLUSIONS

Drug discovery is a challenging process due to complexity of biological system. Synthesis of new molecules containing active moieties can be a promising approach to improve therapeutic properties. Eight different novel analogues were subjected to insilico molecular modelling. The binding mode of these compounds with different antimicrobial targets was found out using Autodock. The docking results for antimicrobial activity were comparative with the wet lab agar diffusion assay results. From the antimicrobial studies it reveals that compounds containing methoxy, hydroxyl, amino and furan substituents have good antifungal and antibacterial activity. All the 5 synthesised compounds show comparatively good antibacterial activity against gram –ve organism (*E.coli*) than gram +ve organism (S.aureus). All the 5 derivatives also proved to have good antifungal property. So Schiff base derivatives of benzothiazole can be considered as novel molecules with good antimicrobial properties. The novel ligands in this study can be used for further studies to develop molecules with advanced antimicrobial activity.

REFERENCES

1. Gilchrist TE: Heterocyclic Chemistry. 3. Longman; 1992.
2. Chaudhary P Recent advances in pharmacological activity of benzothiazole derivatives. International Journal of current pharmaceutical research 2010; 2(2): 170-176.
3. Yadav SK, Malipatil SM, Yadav SK Synthesis and biological evaluation of benzothiazole derivatives. IJDDHR 2010; 1(1): 42-43.

4. Nagaraj. 1, 3, 4 Oxadiazole: A potent drug candidate with various pharmacological activities. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3: 9-15.
5. Niazi S. Study of influence of linkers and substitutions on antimicrobial activity of some Schiff bases. Ijpps 2010; Vol 2: 108 – 112.
6. Hosam.A Saad. Microwave assisted synthesis of some new fused 1,2,4 triazines bearing thiophene moieties with expected pharmacological activity. Molecules 2011; 16:4937-4957.
7. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and application. Nature reviews. Drug discovery 2003; 3(11):935-949.
8. Levi SB, Drug Resistance: The New Apocalypse Trends. Microbiol. 1994; 2; 341-425.
9. Hemlata Kaur, Sunil Kumar, Indu Singh, K.K. Saxena, Ashok Kumar. Synthesis, characterization and biological activity of various substituted benzothiazole derivatives. Digest Journal of Nanosciences and Biostructures 2010; 5(1): 67 – 76.
10. Hamouly WS, Amin KM, Assaly SAEl, Meguid EAA: Synthesis and antitumor activity of some new 1,3,4-oxadiazole, pyrazole and pyrazolo[3,4-d]pyrimidine derivatives attached to 4-benzothiazol-2-yl phenyl moiety. Der Pharma Chemica 2011; 3 (6): 282-292.
11. K. G. Desai, J.P. Raval and K.R. Desai: Neat Reaction Technology for the Synthesis of 4-Oxo-thiazolidines Derived from 2-SH-Benzothiazole and Antimicrobial Screening of Some Synthesized 4-Thiazolidinones. Journal of the Iranian Chemical Society,September 2006; 3 (3): 233-241.