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Synthesis, Molecular Docking Study, and Adme Properties of 1, 2, 3-Triazole Derivatives.

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ABSTRACT:
In-silico design of novel analogues were carried out using Auto Dock Vina,Swiss ADME software will be used to analyse 'Lipinski Rule of Five' and drug likeness properties. Three derivatives which obeyed rule of five and having desired physico-chemical properties and highest docking score were synthesized (PDB code: 2K35).The synthesis has been carried out in single step process to determine their anti-microbial activity.Antimicrobialactivity was observed in the different compounds by disc diffusion method, among this the compound S-B shows significant anti-microbial activity and compound S-A and S-Calso shows appreciable anti-microbial activity.Thesynthesized compoundswere structurally elucidated using FTIR ,1H NMR, and elemental analysis. Furthermore modification of triazole-based compounds at different positions to generate new molecules with potent antitumor, antioxidant, and antimicrobial activities will be described in future.

Keywords: Benzotriazole,Benzene,Antimicrobial,Organisms

I. INTRODUCTION:

Triazoles and their derivatives are of great importance in medicinal chemistry and can be used for the synthesis of numerous heterocyclic compounds with different biological activities such as. anti-microbial[1,7] , anti-tumor [2] anti-tuberculosis [3] , anti-inflammatory[4] , analgesic[5] ,Anti-Lung cancer[6]anti-HIV-1 [8], cytotoxic [9], antihistaminic [10], anti-proliferative [11,12,13,14,15]. anti- oxidant [16,17,18,19]. activities and also inhibitors of glycogen synthase kinase-3 [20], antagonists of GABA receptors [21,22], agonists of muscarine receptors [23], neuroleptic [24].Thus, the design and synthesis of novel triazole derivatives are the prospective direction of medicinal chemistry for the scientists working in this field .The struggle against infectiousdiseases has become a never-ending process as microorganisms undergo rapid genetic changesand develop resistance to numerous medicines and therapeutic agents for many diseases fasterthan new treatments are become accessible. Because of their widespread application in industryand agriculture, the triazole class has sparked a lot of interest in recent decades. Furthermore, triazole can be found in a variety of naturalgoods, metabolic products of fungus and primitive marine creatures etc. Because of their importance in industry, agriculture, andbiological activity, the coordination chemistry of triazole and benzotriazole derivatives wasinvestigated. The above statement inspired our interest to synthesize a group of compounds containing 1,2,3Triazole derivatives associated with various primary aromatic amines (table-1) moiety and to evaluate their antimicrobial potency (table-7).Insilico design were carried out using soft ware Auto Dock Vina(table-2) (fig 1-10), Three derivatives which have highest docking score were synthesized (table-3) and elucidated with FTIR ,1H NMR, (table-4 & 5)and elemental analysis.Antimicrobialactivity was observed in the synthesized compounds byusing disc diffusion method, among this compound S-B shows significant anti-microbial activity and compound S-A and S- Calso shows appreciable anti-microbial activity.ADME properties and drug-likeness prediction carried out using Swiss ADME(table-8)

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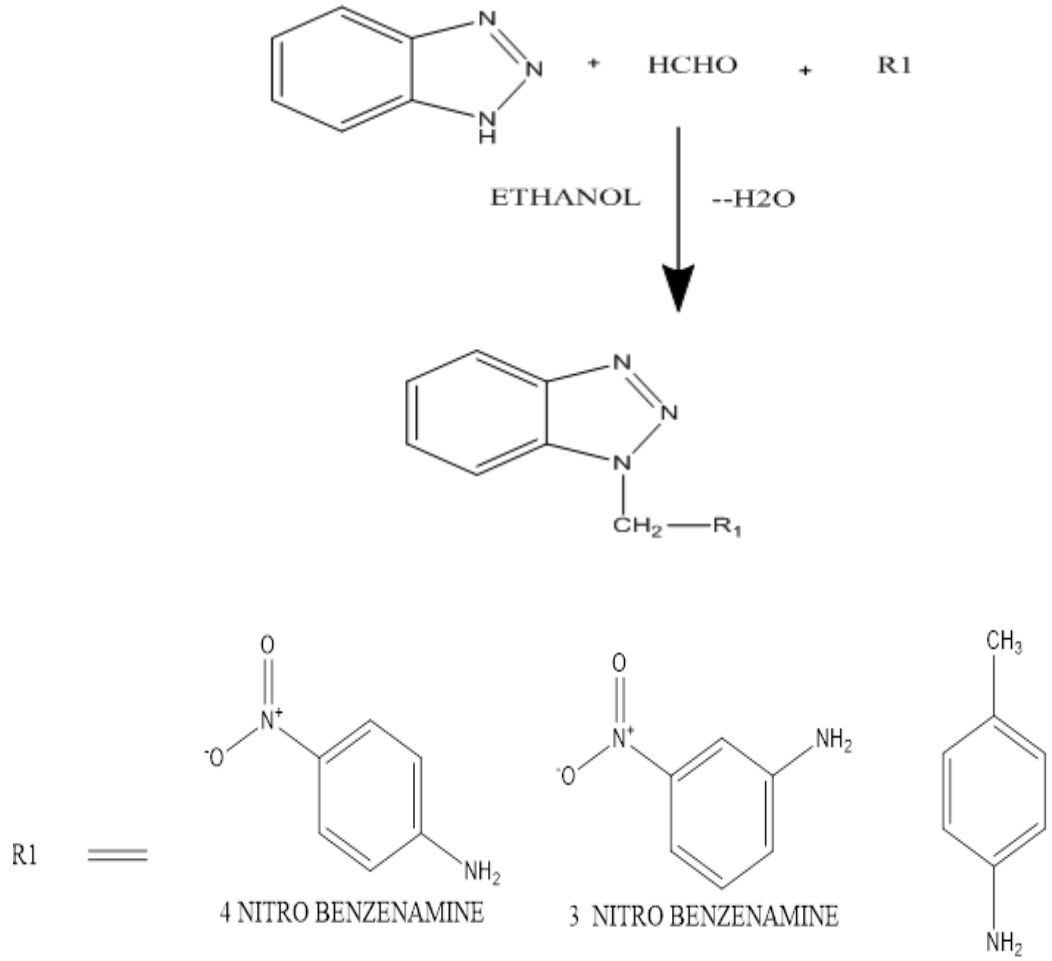
Experimental Work:



MOLECULAR DOCKING

Before the docking analysis,ligands were prepared from the optimized Compounds and saved in pdb file format using spartan,14 .The 3D Compound of Hydramacin-1 protein was downloaded from the protein bank (with pdb ID:2K35).The enzyme was prepared with help of discovery studio visualizer for the docking analysis. In the course of the preparation, hydrogen was added. water molecule, heteroatoms and co-ligands were eliminated from the crystal Compound saved in pbd file.

The docking of the ligands to the active site was achieved with the help of pyrexsoftware using Autodockvina. After successful docking protocol, reformation of the complexes (ligand-receptor) for further investigation was also achieved utilizing chimera softwa re. Discovery studio visualizer and pyMOL were used to investigate the interactions of the complexes.

Table-01

Sl No	Compounds	R1
1	S-A	4-Nitobenzenamine
2	S-B	3-Nitobenzenamine
3	S-C	P-Toludine

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4	S-D	2-Chloroaniline
5	S-E	4-Chloroaniline
6	S-F	O-Toludine
7	S-G	P-Toludine
8	S-H	P-Anisidine
9	S-I	4-Bromo Aniline
10	S-J	O-Anisidine

Docking And Glide Score Of 2k35(Table-02)

SlNo	Compounds	2K35	Interaction of amino acids
1.	S-A	-5.9	ARG,THR,TRP
2.	S-B	-6.5	ARG,THR,GLU,TRP
3.	S-C	-5.8	ARG,THR,TRP
4.	S-D	-5.5	THR,ARG,TRP
5.	S-E	-5.4	THR,ARG,TRP
6.	S-F	-5.5	ARG,THR,TRP
7.	S-G	-5.5	ARG,THR,TRP
8.	S-H	-5.2	GLY,ASN,THR,ASN,TRP,ARG
9.	S-I	-5.1	TRP,ARG,LYS,THR
10.	S-J	-5.5	ARG,THR,TRP

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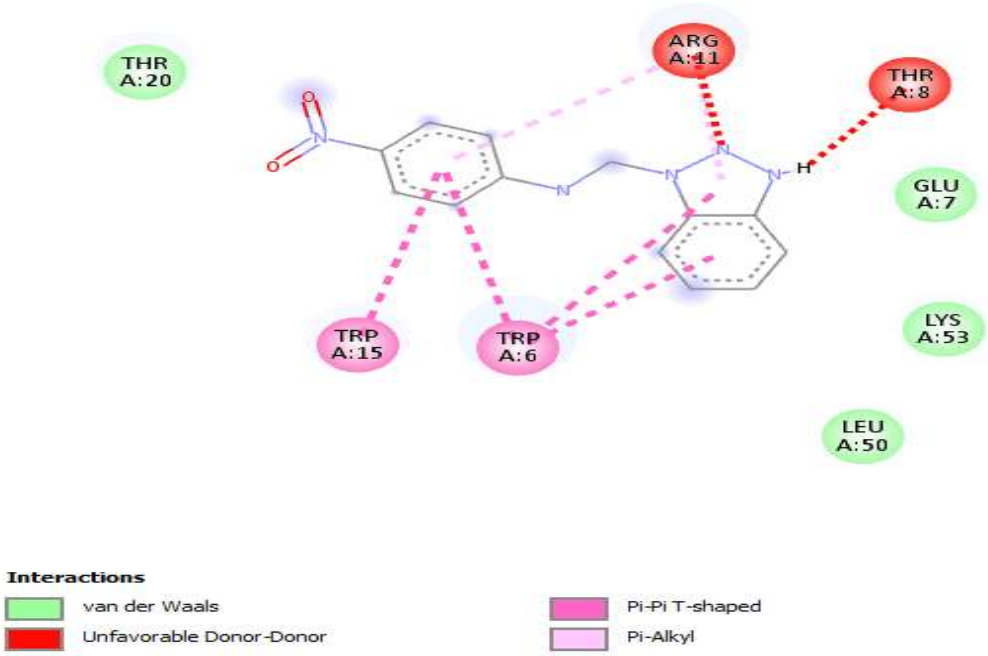
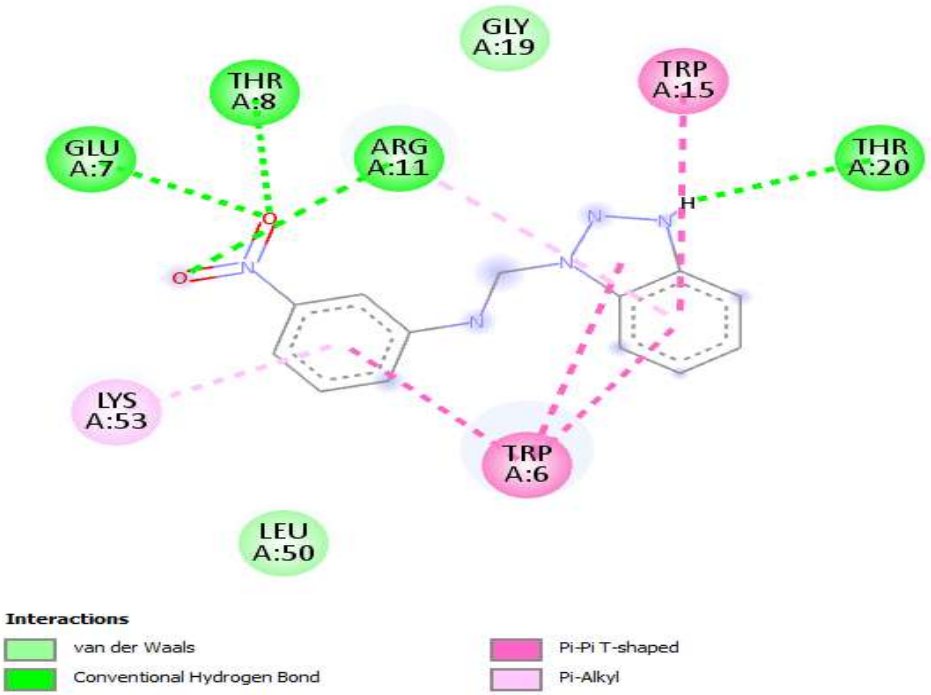


S-A (fig 1)



S-B (fig 2)

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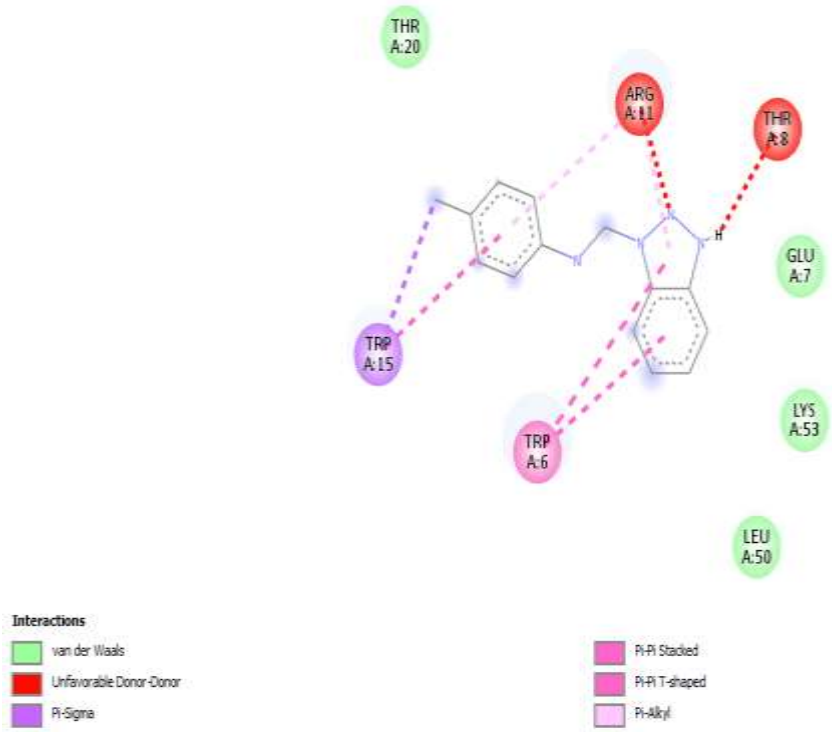
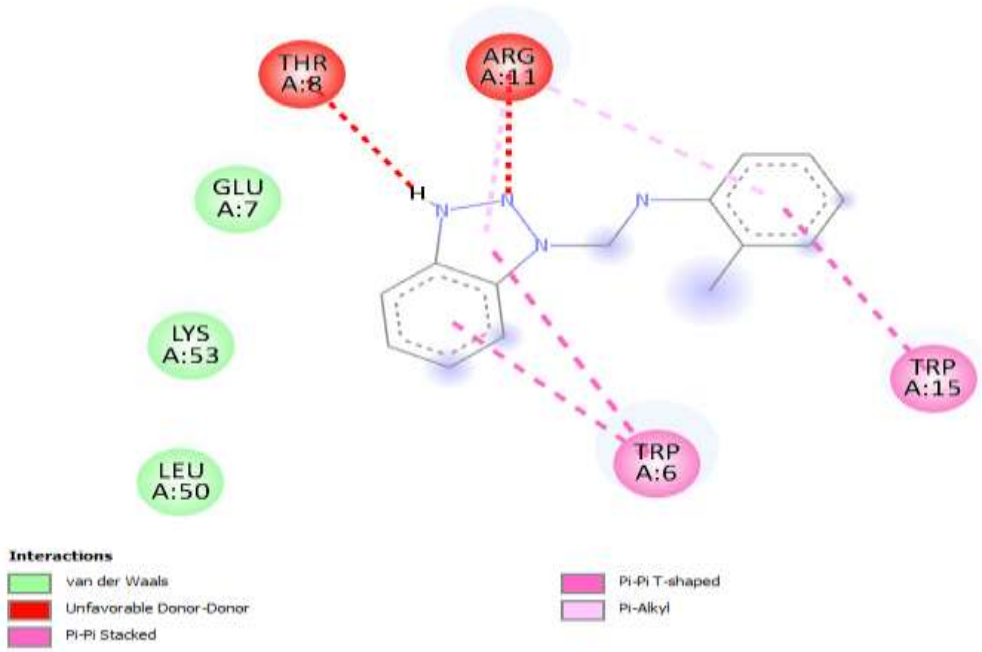


S-C (fig 3)



S-D (fig 4)

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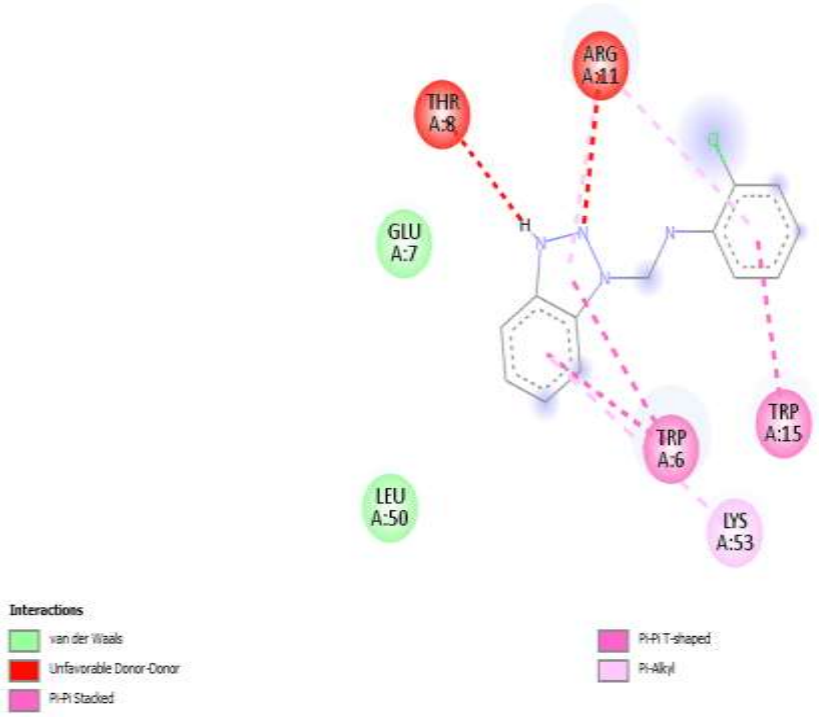
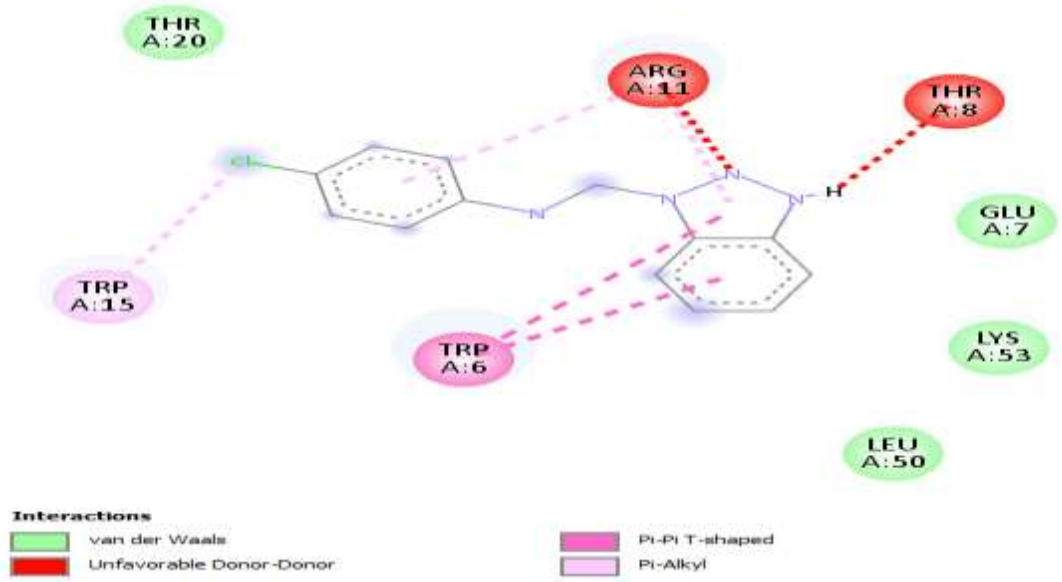


S-E (fig 5)



S-F (fig 6)

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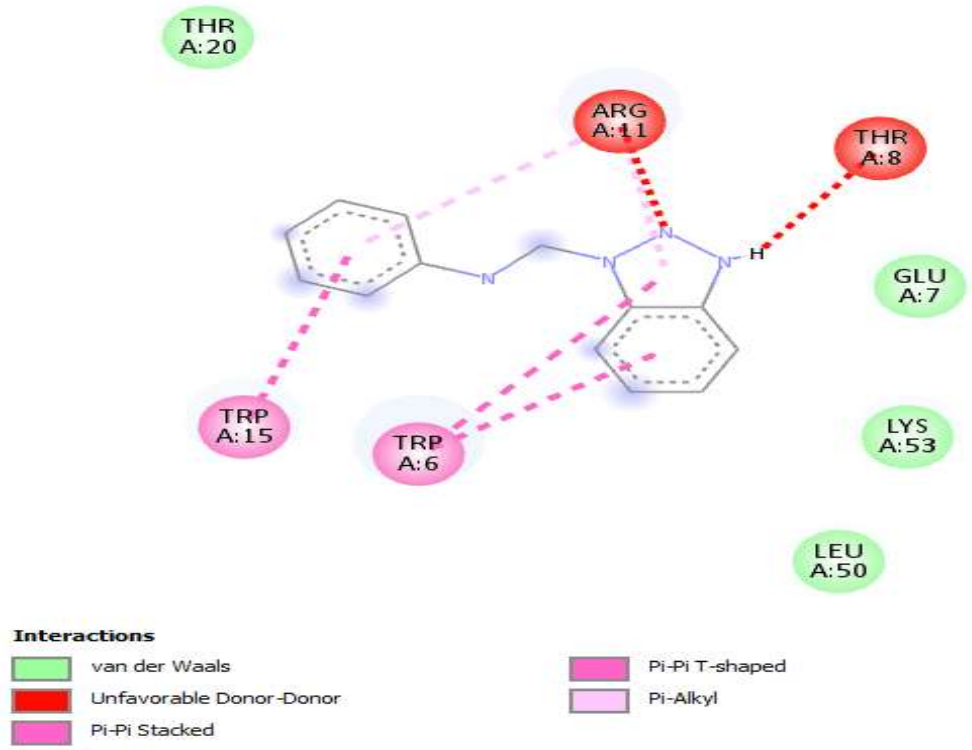
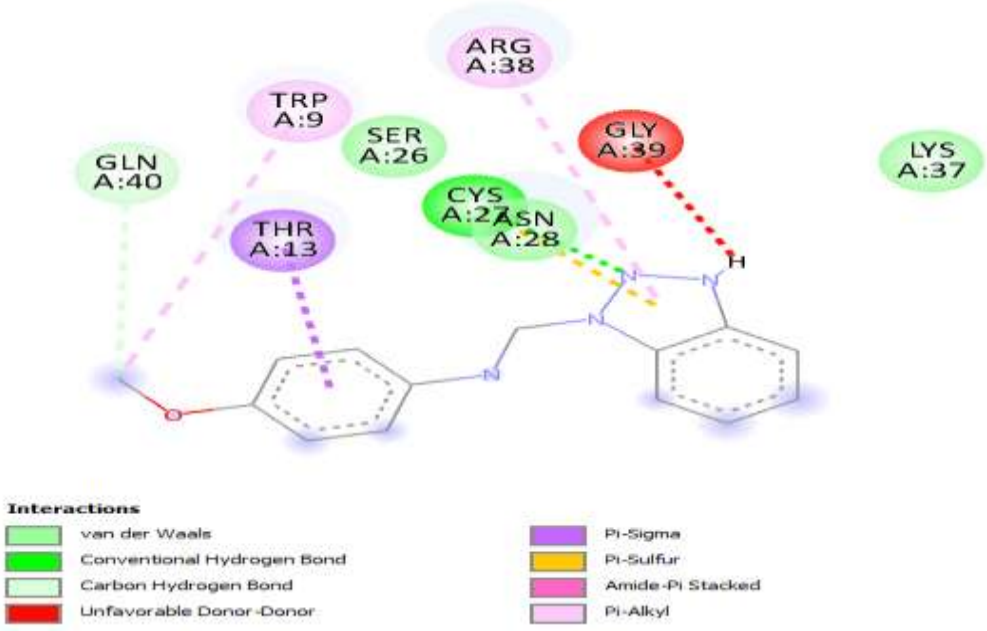


S-G (fig 7)



S-H (fig 8)

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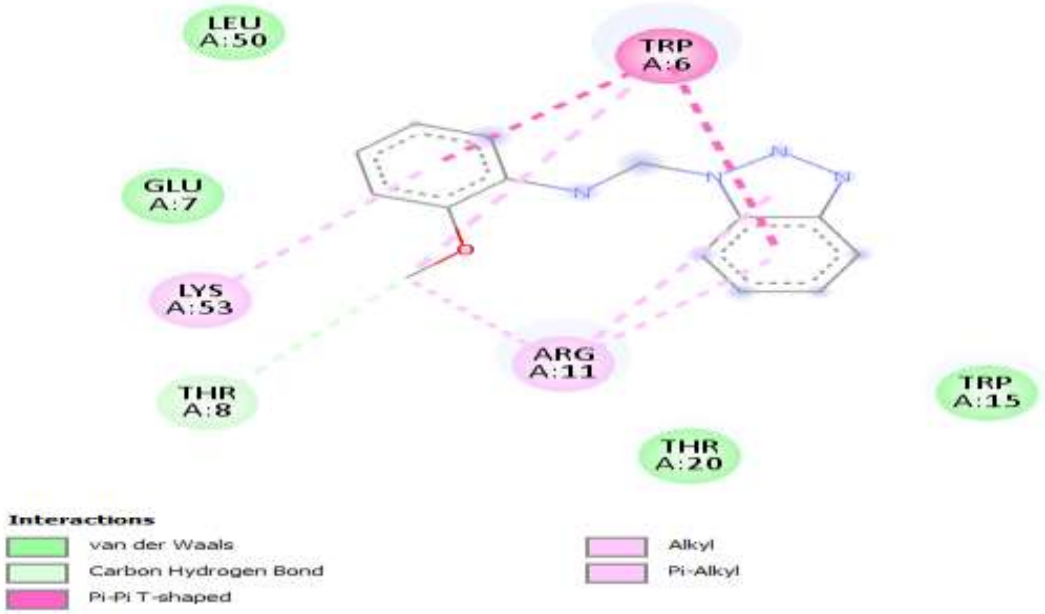
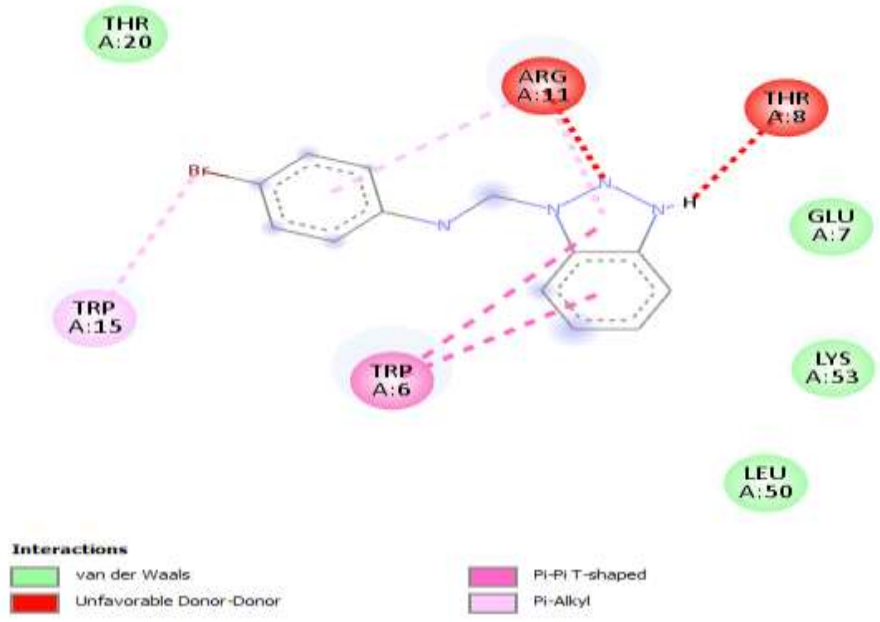


S-I (fig 9)



S-J (fig 10)

Planofthework

0.01Molof Benzotriazolewasdissolved inlittleamountof ethanolinRoundbottomflask. 0.05Molof formaldehydewaspipette and0.01 Molgmofpara-nitroaniline wasweighandmixedin aboveround bottom flask. Thewholemixturewasshakenwellandfixedintotheref luxcondenserandleaveforrefluxingforminimum 8 hour,Afterrefluxingproductwastakenoutcarefullyan dfilterwithdistilledwater. Afterfilterationprocessproductwaskeptfordryinginh otairovenattemperature120-160degreeCelsius

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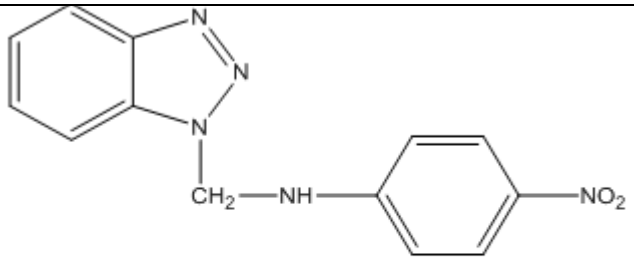
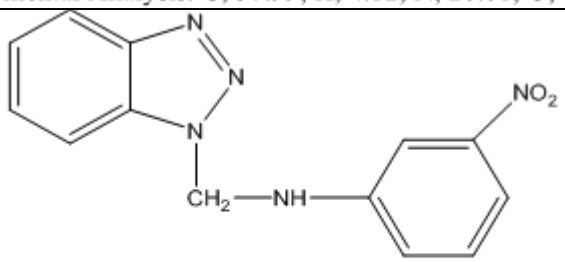
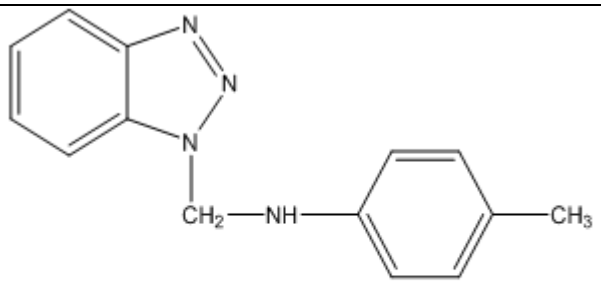
for5minute.

(Table-03)

SL.NO	STRUCTURE	M.P	YIELD
S- A	 *N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-4-nitroaniline Chemical Formula: $C_{13}H_{11}N_5O_2$ Molecular Weight: 269.26 Elemental Analysis: C, 57.99; H, 4.12; N, 26.01; O, 11.88	147	85%
S- B	 *N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-nitroaniline Chemical Formula: $C_{13}H_{11}N_5O_2$ Molecular Weight: 269.26 Elemental Analysis: C, 57.99; H, 4.12; N, 26.01; O, 11.88	44	87%
S-C	 *N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-4-methylaniline Chemical Formula: $C_{14}H_{14}N_4$ Molecular Weight: 238.29 Elemental Analysis: C, 70.57; H, 5.92; N, 23.51	68	83%

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IR SPECTRA FOR (S-A TO S-C) COMPOUND**(Table-04)**

S.no	Compound	Mol.Formula	IRspectraldataincm^{-1}
1.	S-A	$C_6H_6N_2O_2$	3370,3071,1962,1893,1652,1599,1449,1309,1264,1152,1045, 946,832,738,602,586,550,525 cm^4
2.	S-B	C_7H_9N	3304,3176,3093,2986,2916,2858,1863,1784,1668,1614,1506,1453,1362,1298,1148,1001,903,846,736,607,551,524cm^4
3.	S-C	$C_6H_6N_2O_2$	3282,3093,2968,1927,1680,1621,1522,1440,1336,1264,1210,1154,1011,946,854,754,733,668,571,539,530,513,502cm^4

NMR SPECTRA FOR (S-A TO S-C) COMPOUND**(Table-05)**

S.No.	Compond	Mol.formula	^{1}HNMR Spectral data delvalue
1.	S-A	$C_6H_6N_2O_2$	2.176,2.144,2.086,6.319,4.973,4.363,6.953, 6.971,6.865,6.886
2.	S-B	C_7H_9N	8.075, 8.052, 7.031, 7.008, 6.294, 8.057, 3.398,7.431
3.	S-C	$C_6H_6N_2O_2$	6.253, 6.271, 3.357, 7.713 , 7.381, 8.029, 8.049, 8.057

A. Antimicrobialactivity

The antibacterial activity of synthesized compounds S(A-C) was done by using disc diffusionmethodagainst that followingorganism as directed byEllen JBoron

E.coliATCC-750 -Gramnegative

TestSample:

S-A =

N-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-4-nitroaniline

S-B =

N-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-nitroaniline

S-C=

The test sample S(A-C) were used in concentration of 100mg/ml, using dimethyl sulfoxide assolvent and ciprofloxacin in concentration, 50mg/ml in a suitable solvent was used as a standardforEscherichiacoli.

FORMULA:

PreparationofNutrient Agar:**(Table-06)**

PreparationofMedia:

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Ingridents	Range
Peptone	0.5%
Sodiumchloride	0.5%
Beefextract	0.5%
Agar	3.0%
Distilledwater	q.s
Phadjusted	7.2-7.4

Thenthe mediais distributedin 5mlquantityintoculturetubes andsterilized by autoclaving. Disc Diffusion Method:

To the sterile nutrient agar, suspension of Escherichia coli was added at 45 degree Celsius andtransferred to sterile petri dished and allowed to solidify. Sterile discs 5 mm in diameter (madefrom Whatmann filter paper sterilized in isopropyl alcohol) were dipped in solutions containingcompoundsamples, standard andblankwereplaced onsurfaceofagarplates.

The plates were left standing for one hour at room temperature as a period of pre incubationdiffusiontominimizetheeffectofvariationi ntimebetweentheapplicationsofdifferentsolutions.T hen the plates were incubated at 37 degree Celsius for 18 hours and observed for antibacterialactivity. The diameter of zone of inhibition were measured for plates in which the zone ofinhibitionwas observed.

II. RESULT AND DISCUSSION

Thetriazolederivativesweresynthesizedandscreened forAntimicrobialactivitiesandconfirmedbyIR and ^{1}H NMR.

S-A = *N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-4-nitroaniline

S-B = *N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-3-nitroaniline

S-C= *N*-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)methyl)-4-methylaniline

The melting point of all synthesized compounds were found in open capillary tubes and readingswere uncorrected. The elemental analysis was done and the result are mention in their particularsection.Thefoundvalues of theelements byelementalanalysis werecloserto calculated values.

ANTI-MICROBIALACTIVITY:

ANTI-BACTERIALACTIVITY:

Thesynthesizedcompoundswerescreenedfortheiranti bacterialactivityagainstEscherichiacoli. The result showed that the compoundS-B shows significant antibacterial activity andcompoundS-A& S-Chavingappreciableantibacterialactivitywhencompa redtostandardCiprofloxacin.

Table for Antimicrobial activity of compounds S(A-C)(Table-07)

S/N	Compounds	Antibacterial activity Zone of Inhibition(mm)
		Escherichiacoli
1	(Test) S-A	19
2	(Test) S-B	21
3	(Test) S-C	16
4	Standared (Ciprofloxacin)	31

ADMET STUDIES:(Table-08)

ADME properties and drug-likeness prediction of some selected anti-microbial agents among the data set was carried out using Swiss ADME a free web tool used in evaluating ADME properties and drug **-likeness of molecules.**

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Molecules	MW	HBD	HBA	GIABSORPTION	BBB permeant	Log K_p (skin permeation)	TPSA	Rule of Five
Acceptable range	130.0 - 725.0	0 - 6	2 - 20	HIGH-LOW	YES-NO	≤ 5	< 140Å²	Maximum is 4
S-A	269.26 g/mol	1	4	High	No	-5.94 cm/s	88.56 Å²	0
S-B	269.26 g/mol	1	4	High	No	-5.94 cm/s	88.56 Å²	0
S-C	238.29 g/mol	1	2	High	Yes	-5.38 cm/s	42.74 Å²	0
S-D	238.29 g/mol	1	2	High	Yes	-5.38 cm/s	42.74 Å²	0
S-E	258.71 g/mol	1	2	High	Yes	-5.31 cm/s	42.74 Å²	0
S-F	258.71 g/mol	1	2	High	Yes	-5.31 cm/s	42.74 Å²	0
S-G	224.26 g/mol	1	2	High	Yes	-5.55 cm/s	42.74 Å²	0
S-H	254.29 g/mol	1	3	High	Yes	-5.75 cm/s	51.97 Å²	0
S-I	254.29 g/mol	1	3	High	Yes	-5.75 cm/s	51.97 Å²	0
S-J	303.16 g/mol1	1	2	High	Yes	-5.54 cm/s	42.74 Å²	0

III. CONCLUSION:

According to data obtained from the present study, triazole derivatives were found to be an effective antimicrobial activity by disc diffusion methodwhen we compared to standard ciprofloxacin respectively. Based on the discussion above, these triazole analogs could be considered as useful templates for further development to obtain more potent antimicrobial activity.

Acknowledgement

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