Innovations

Synthesis, Insilico Studies, Pharmacophore Modelling, HOMO - LUMO Gap Analysis, for New 1, 2,3Triazole Appended Piperazine with Anti-Oxidant Activity

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Abstract: Aim*: Our aim is to grow new potent 1,2,3triazole appended piperazine which could find the Anti-oxidant activity.* ***Materials & methods:****In-silico design of novel analogues were carried out for fifteen compounds using Auto Dock Vina by using pdb id:* ***(PDB id: 1XLY)****and compared with standard drug ascorbic acid. Similarly Pharmagist software will be used to analyse 'parmacophore properties, which is responsible for a particular biological interaction.Guassian, Smarten, and Mastroessoftwares will be used to find out the HOMO-LUMO gaps which is used for examining the kinetic stability. The compounds which have better pharmacophore properties which have greater than 1.5 fitness and larger HOMO-LUMO gaps with highest docking score has been selected for the synthesis. We blend a gathering of mixtures containing 1,2,3 - Triazole subordinates collaborating with piperazine related with various primary aromatic amines (Table 1) and to evaluate their anti-oxidant activity. Five compounds which have highest docking score (Table2) better pharmacophore properties, and larger HOMO-LUMO gaps (Table 3& Table 4) were blended (Table-5) and their Designs were explained with FTIR ,1H NMR,13C NMR, MASS and essential investigation****, Conclusion****: Anti- oxidant activity was seen in the blended mixtures by utilizing DPPH technique, among this mixtures B1,B5, B11 shows huge enemy of oxidant action and compound B7 &B15 shows apparent enemy of oxidant activity(Table-6).*

Keywords*: Benzotriazole, Homo-Lumo Studies, Pharmacophore, Docking studies.*

Introduction:

The new improvement in the data on free radicals and responsive oxygen species (ROS) in science is making a clinical surprise that ensures some other season of prosperity and disease management.[1]Ironicly oxygen, a part crucial for life,[2]under unambiguous conditions malevolently influences the human body.[3]most of the potentially damaging effects of oxygen are a direct result of the turn of events and development of different manufactured blends, known as ROS, which will generally give oxygen to various substances. Free radicals and anti-oxidant agents have become regularly elaborate terms in present day discussions of disease mechanisms[4]. 1, 2, and 3 triazolesderivatives are crucial since they might be used to mix various heterocyclic compounds with various natural functions, including antimicrobial.[5,6,7,8,9] Anti-oxidant,[10,11,12,13,14]. Anti-tuberculosis [15,16,17,18,19,20,21] Anti-fungal [22] , Anticancer [23,24,25,26,27,28],activities.

Thus, in view of the above biological activity of 1,2,3-triazole derivatives and hybridized pharmacophore systems, we took the challenge to chalk out a synthetic path for better efficacy in terms of their antioxidant activity. Accordingly, we synthesized a series 1,23triazole-piperazine derivatives and evaluated their anti-oxidant activity. On account of their significance in industry, agribusiness, and organic movement, We assemble a set of mixtures 1,2,3-triazole with piperazine linked to many significant aromatic amines (Table 1).

1. **Experiment Section:**

Materials And Methods:

We purchased the synthetic chemicals from Vasa Manufactured Substances in Malleshwaram, Bangalore. Utilizing KBr pellets, ABB Bomem FTLA 2000-102 FTIR spectra were kept in the 400-4000 cm-1 territory. "The NMR spectra of the 1H and 13C were recorded utilizing BrukerAvance 300 (300 MHz) and Bruker 600 MHz.TMS is utilized as the interior benchmark, and the compound movements are given in parts per million (ppm) at 300 and 75 MHz exclusively.

Preparation Of 1,2,3Triazole Appended Piperazine:

Synthesis of The 0.01 gram of benzotriazole, 0.008 gram of Piperzine, and 0.6 ml of chlorobenzaldehydewere added in round bottomed flask (RBF) and dissolved in ethanol . Keep the above mixture forrefluxing up to 8 hours. After 8 hours remove the mixture and filter it..The product was kept fordryingin hot airoven at temperature120-160 degreeCelsiusfor5 minutes.

Synthesis of substitutedtriazole and piperazine derivatives Compounds (B1-B15):

The above product as weighedupto0.29grams and dissolved with ethanolin RBF. 0.1 gram of 5 different primary amines and 0.2 ml of formaldehyde were added and kept for refluxing for 8 hours. After refluxing, the product was taken out carefully and filtered.

Table-01: Amines used in Designing the compounds.

2.Biological Activity:

Invitro anti-oxidant activity:

In-vitro antioxidant activity

The combined mixtures will be evaluated for invitro cell reinforcement action. The anti-oxidant of all blended mixtures will be decided to use

1. DPPH radical scavenging activity

DPPH Method:

Preparation of the reagent – 3.96 DPPH was accurately weighed and dissolved in 50 ml of methanol. Preparation of the test and standard solutions- Stock solutions of 2000 ug/ml of the synthesized compounds and ascorbic acid were prepared in methanol. These solutions were serially diluted with methanol to obtain the required concentrations. The antioxidant activity of the test compounds and standards were assessed using 96 well micro titre plate. Absorbance of solvent containing the same amount of methanol and DPPD radical solution was measured as well.

$$\text{Scavenging (\%)} = \frac{\text{Absorbance} - \text{Absorbance (Sample)}}{\text{Absorbance}} \times 100$$

2. SCHEME:

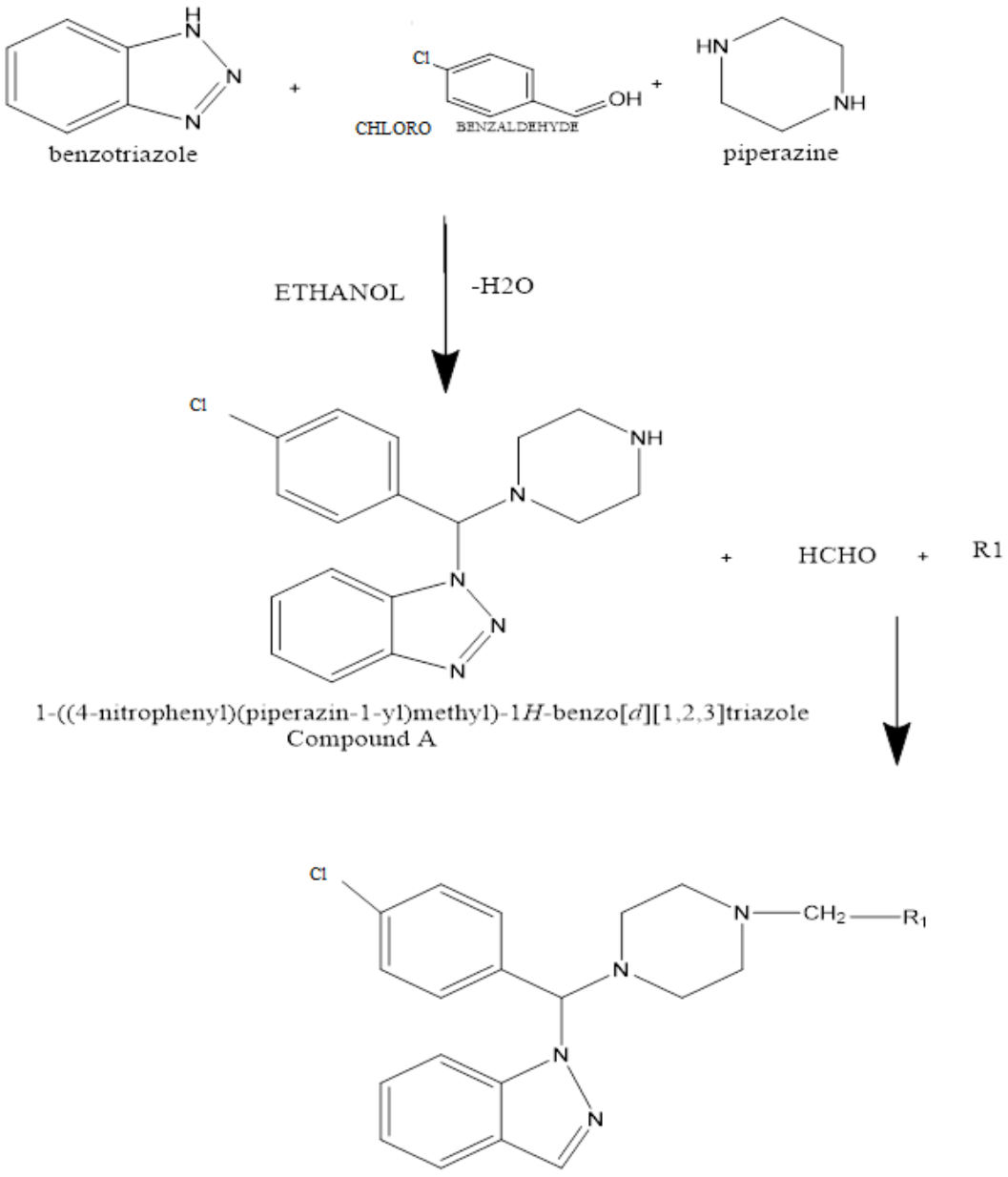

benzotriazole
CHLORO BENZALDEHYDE
piperazine
ETHANOL
-H2O
1-((4-nitrophenyl)(piperazin-1-yl)methyl)-1H-benzo[d][1,2,3]triazole
Compound A
HCHO
R1

Table:1

Sl No	Compounds	R1
1	B1	Aniline
2	B2	Ortho Anisidine
3	B3	Meta Anisidine
4	B4	Para Anisidine
5	B5	4-Chloro aniline
6	B6	2-Chloro aniline
7	B7	4-Bromo aniline
8	B8	2-Bromo aniline
9	B9	2-Nitro aniline
10	B10	3-Nitro aniline
11	B11	4-Nitro aniline
12	B12	2,4,Dimethyl aniline
13	B13	2,6 Dimethyl aniline
14	B14	Ortho toluidine
15	B15	Para toluidine

4. Molecular Docking, Pharmacophore & Homo Lumo Studies:

These compounds will be further evaluated computationally for their Molecular modelling ,Pharmacophore and HOMO-LUMO gap analysis.Using AutodockVina in the Pyrex programme, the ligands were docked to the active site **(PDB id: 1XLY**). If the docking procedure was successful, it was also feasible to reconstruct the complexes (ligand-receptor) using the Chimaera programme, enabling further research. The complexes' interactions were investigated using Discovery Studio Visualizer and pyMOL. By using Pharma gist software pharmacophore modelling can be performed and Gaussian, smarten, maestros soft wares can be utilized to find homo lumo gaps. Pharmacophore-based techniques are nowadays an important part of many computer-aided drug design workflows and have been successfully applied for tasks such as virtual screening, lead optimization and de novo design. Referance ligand that is cocrystal structure will be taken from online PDB protein and finding best fitting molecule, Cocrystal structure should have ligand height, fitting protein, binding pocket.The fifteen derivatives are subjected to these 6 pharmacaphore features (A2,

A4, A1,R15, R16, H5).It should have minimum 3 matching sites so it resembles that it had 50% of matching cocrystal ligand.

Thesynthesized molecule have these properties,so it is said to be more fitting. Here (R) represents Ring structure,(A) represents acceptor,(D) represents Donar and (H) represents Hydrophobic interaction.The larger a compounds HOMO-LUMO gap,the more stable the compound,gap tell us at what wavelength the compound can absorb.HOMO energy is firmly connected with reactivity to electrophilic assault, being the most elevated energy orbital containing electrons. LUMO energy is firmly connected with reactivity to nucleophilic assault. Since it is least energy orbital that can acknowledge electrons. The scaffolds which show better docking score, minimum 3 matching site of pharmacophore and larger HOMO-LUMO gaps will be taken up as the lead molecule for further synthesis.

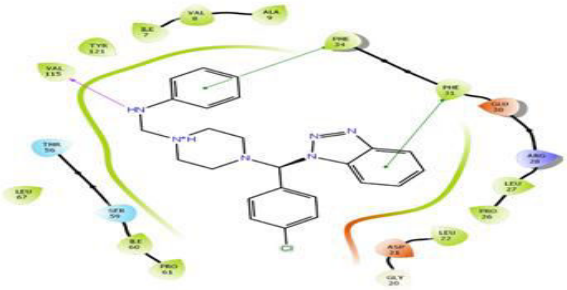
Docking and Gliding Score:

Table-02

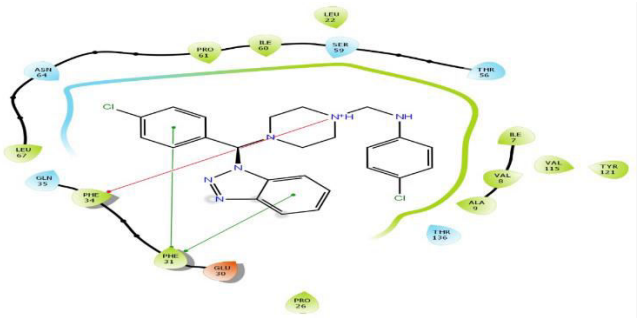
Compounds	**Docking score**	**Interaction of amino acids**
Compound B1	-7.097	Tyr,met,ile,leu
Compound B2	-6.121	Glu,Ser,asp, Leu, Phe
Compound B3	-5.342	Val,Ala, Leu, Asp, Cys
Compound B4	-4.564	Arg,Lys,Phe,Val,Trp
Compound B5	-7.206	val, Asp, Tyr, Leu, Phe
Compound B6	-4.523	Val,Ala, Leu, Asp, Cys
Compound B7	-7.416	Phe, Leu, Tyr
Compound B8	-5.689	Thr,Asp,Phe, Gly, Val
Compound B9	-5.231	Thr,Asp,Phe,Val
Compound B10	-6.234	Ala, Tyr, Val
Compound B11	-6.696	Gly, Val, Tyr, Ala,pro
Compound B12	-5.232	Val,Ala,Ser,Leu,Thr,Gly
Compound B13	-4.432	Thr,Asp,Phe,Val,Lys,Leu,The,Arg
Compound B14	-5.642	Arg,Glu,Phe,Glu,Gly,Lys,Ser
Compound B15	-7.972	Phe,Asp, Val, Tyr
Standard Ascorbic acid	-4.922	Gly, Val, Tyr, Ala.

Figure1:Docking in an active site of human DHFR
(PDB id: 1XLY)

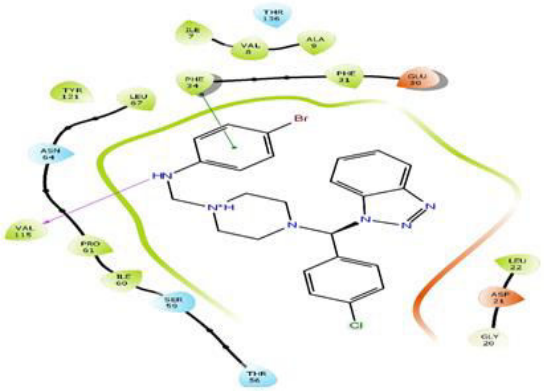
Compound B1



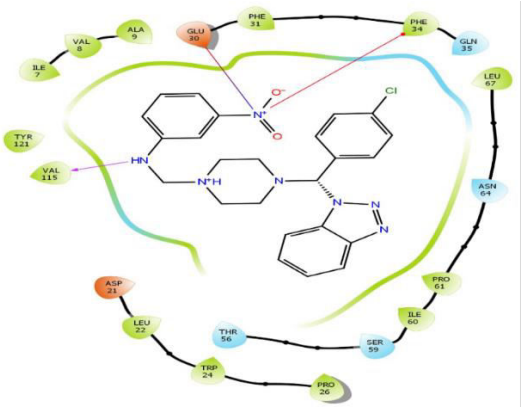
Compound B5



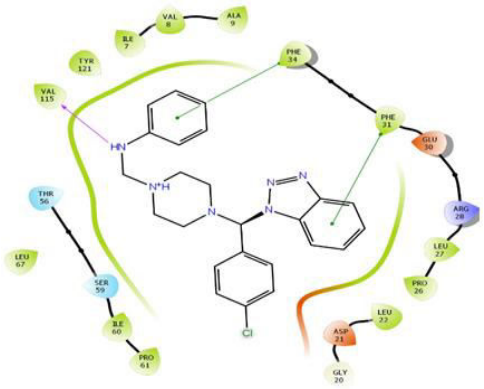
Compound B7



Compound B11



Compound B15
STD Ascorbic acid

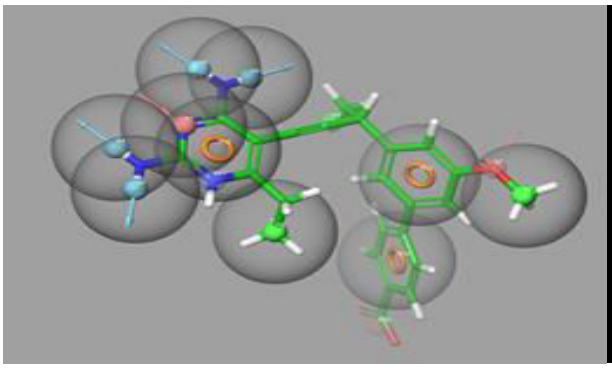


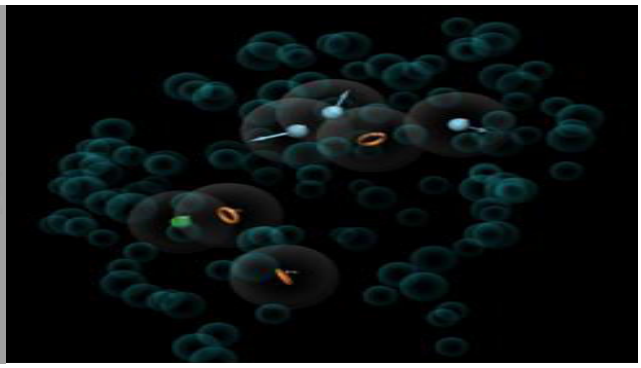
Pharmacophore Modelling:

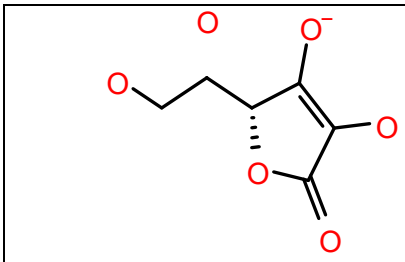
TABLE-03

Sl no	Compounds	Matching ligand site	Fitness
1.	Compound B1	D(-) D(3) H(-) R(8) R(9) R(7)	1.172
2.	Compound B2	D(-) D(4) H(-) R(10) R(8) R(11)	1.218
3.	Compound B3	D(4) D(-) H(-) R(10) R(11) R(9)	1.05
4.	Compound B4	D(-) D(4) H(-) R(10) R(11) R(9)	1.158
5.	Compound B5	D(-) D(-) H(5) R(9) R(10) R(7)	0.619
6.	Compound B6	D(-) D(3) H(-) R(9) R(7) R(10)	1.24
7.	Compound B7	D(-) D(-) H(-) R(10) R(7) R(9)	1.585
8.	Compound B8	D(-) D(3) H(-) R(10) R(9) R(7)	1.348
9.	Compound B9	D(-) D(3) H(-) R(9) R(6) R(8)	1.335
10.	Compound B10	D(3) D(-) H(-) R(9) R(8) R(7)	1.153
11.	Compound B11	D(3) D(-) H(-) R(9) R(8) R(7)	1.147
12.	Compound B12	D(-) D(-) H(4) R(11) R(10) R(8)	1.197

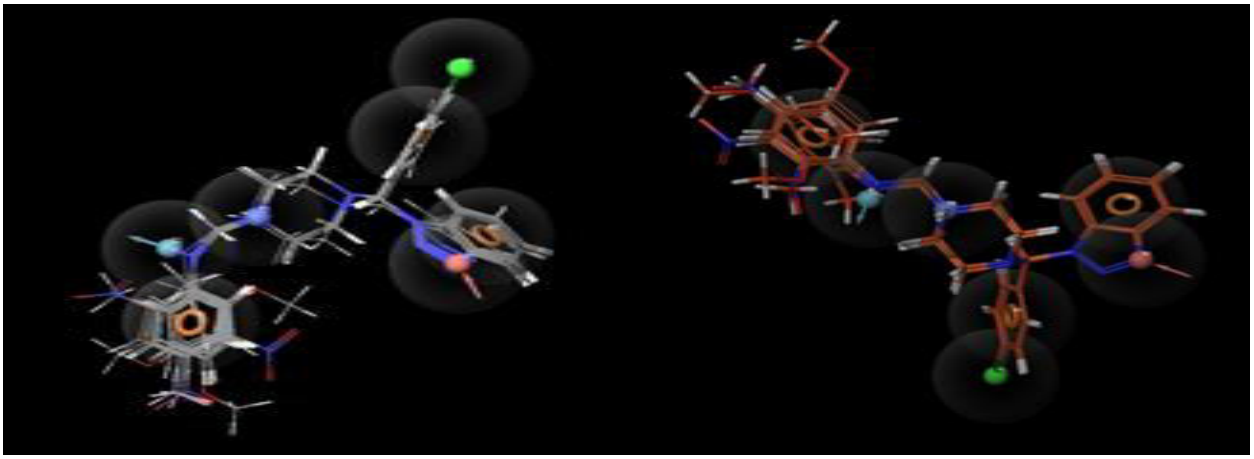
13.	Compound B13	D(-) D(3) H(4) R(-) R(8) R(10)	1.214
14.	Compound B14	D(-) D(-) H(4) R(10) R(9) R(7)	1.206
15.	Compound B15	D(3) D(-) H(-) R(10) R(9) R(8)	1.427
16.	*Standard Ascorbic acid*	D(-) D(3) H(-) R(-) R(9) R(-)	0.531







title	ascorbic acid.mol
docking score	-4.922
MMGBSA dG Bind	-3.03



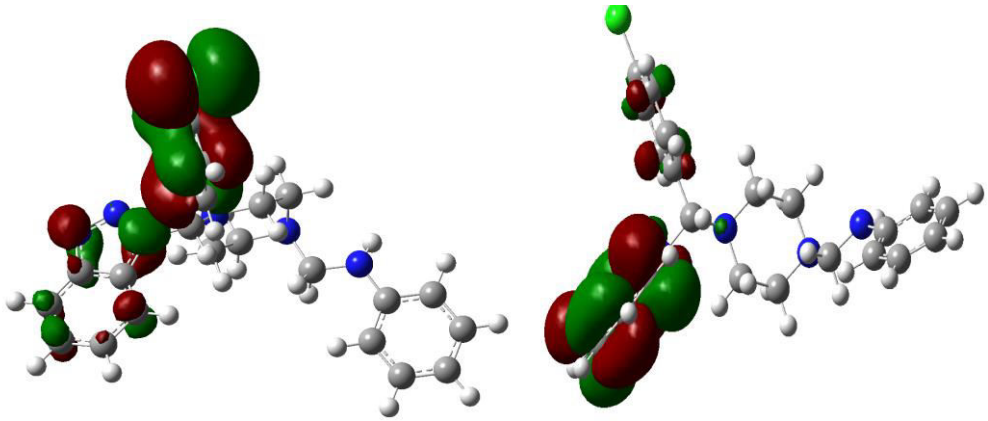
HOMO LUMO GAP ANALYSIS:

Table-04

Sl no	Compounds	HOMO	LUMO
1.	Compound B1	-0.29433	-0.17836
2.	Compound B2	-0.29234	-0.17835
3.	Compound B3	-0.29432	-0.17835
4.	Compound B4	-0.28511	-0.17835
5.	Compound B5	-0.27739	-0.17836
6.	Compound B6	-0.28353	-0.17835
7.	Compound B7	-0.29431	-0.17835
8.	Compound B8	-0.29430	-0.17835
9.	Compound B9	-0.29421	-0.20242
10.	Compound B10	-0.29431	-0.20885
11.	Compound B11	-0.029433	-0.19779
12.	Compound B12	-0.29432	-0.17836
13.	Compound B13	-0.29434	-0.17836
14.	Compound B14	-0.29433	-0.17835
15.	Compound B15	-0.29432	-0.17836
16.	*Standard Ascorbic acid*	-0.34408	-0.12473

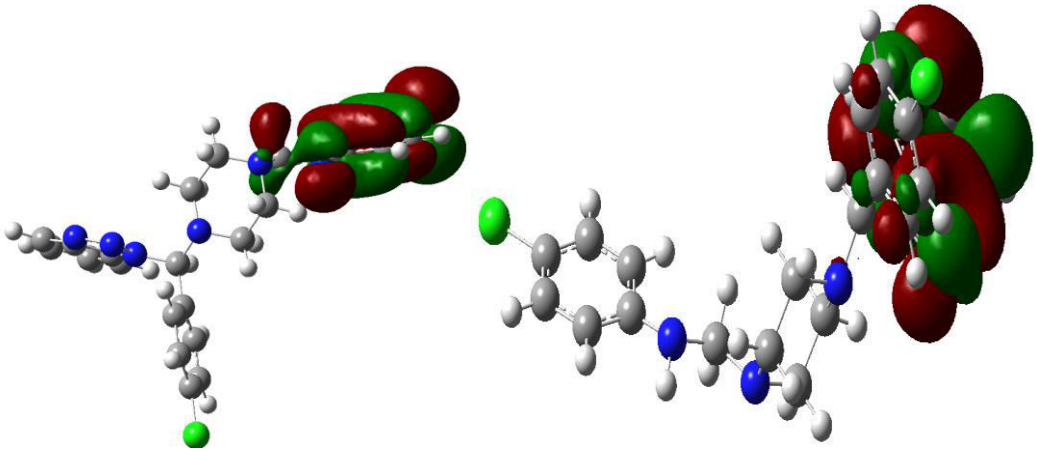
Compound:B1

Homo **Lumo**



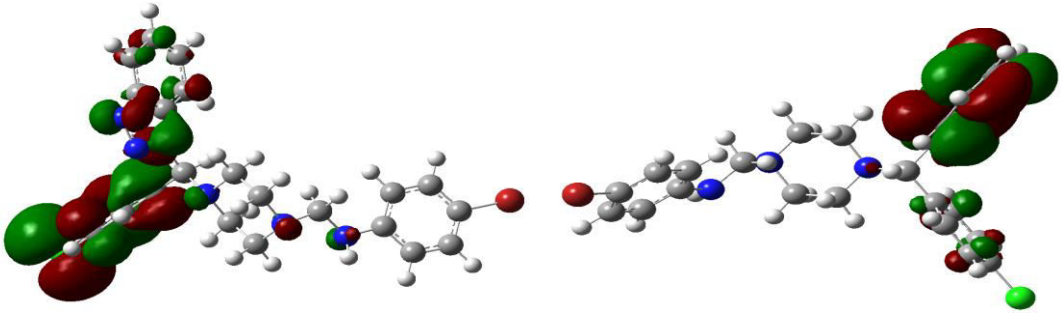
Compound:B5

Homo **Lumo**



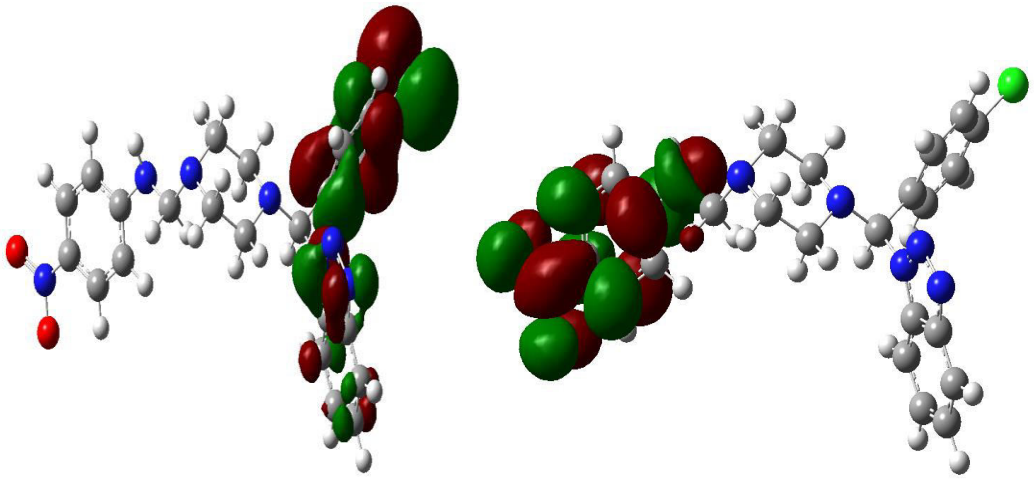
Compound :B7

Homo **Lumo**



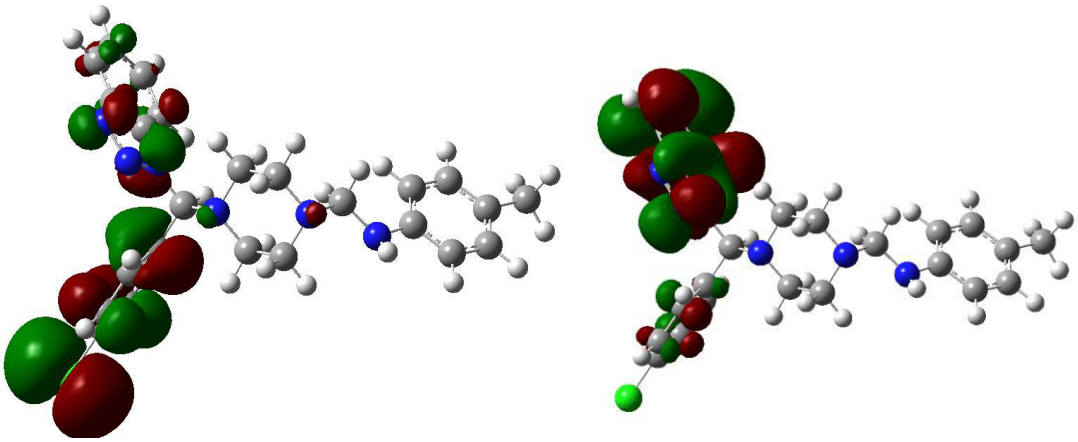
Compound :B11

Homo **Lumo**



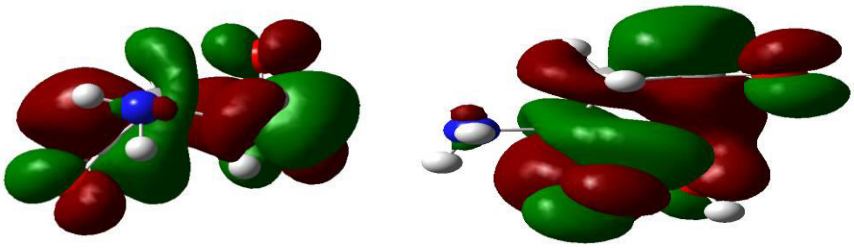
Compound :B15

Homo **Lumo**



STD Ascorbic Acid

Homo **Lumo**



5. Result and Discussion:

The structural details of the produced chemicals were clarified by using FTIR, 1H NMR, 13C NMR, and MASS. The spectra of the substances that were synthesised are listed below.

Synthesis of N-((4-((1*H*-Benzo[*d*][1,2,3]triazole-1-yl)(4-chlorophenyl)methyl)piperazine-1-yl)methyl)aniline(Compound B1):Yellow colour, M.P 142°C ,Yield 83%,Mol Formula: C24H25ClN6,Mol Wt: 432.18, Elemental Analysis C,66.58;H,5.82,Cl8.19;N,19.41 . IR cm^{-1} (KBr): 550,820, and 3200 cm-1. ^{1}HNMR (500 MHz, $CDCl_3$): δ ppm (NH) 6.34 (CH2) 4.13,(CH)6.11 ppm,^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): (CH2)74.6,(CH)126.2(C)146.2 ppm, *m/z* %: 432.18 (Base peak) 433.23 $(M+1)^+$.

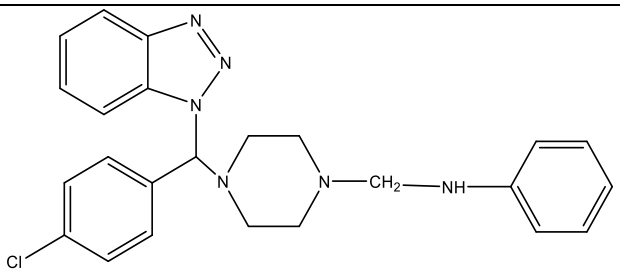
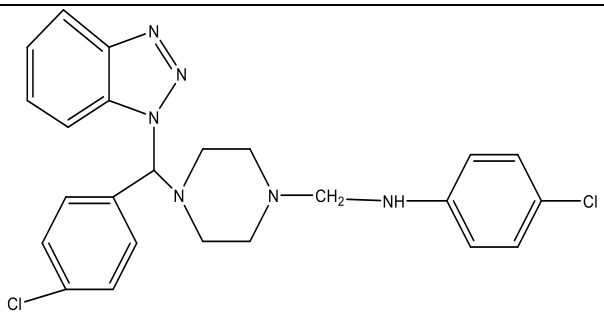
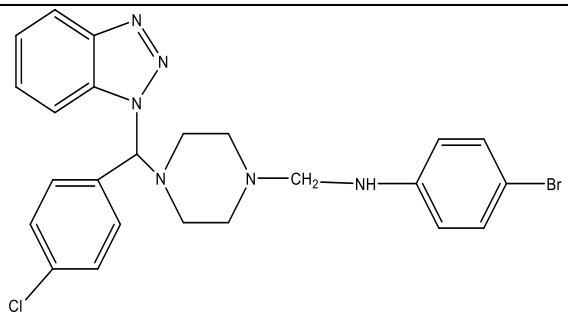
Synthesis of N-((4-((1*H*-Benzo[*d*][1,2,3]triazole-1-yl)(4-chlorophenyl)methyl)piperazine-1-yl)methyl)-4-chloroaniline(Compound B5): Whitish Yellow colour, M.P 158°C ,Yield 83%,Mol Formula: C24H24Cl2N6,Mol Wt: 466.14, Elemental Analysis C,61.67;H,5.18,Cl,15.17;N,17.98. IR cm^{-1} (KBr): 560,3320 and 3200 cm-1. ^{1}HNMR (500 MHz, $CDCl_3$): δ ppm (NH) 6.34 (CH2) 4.13,(CH)6.11 ppm,^{13}CNMR (125 MHz, DMSO-d_6, δ ppm): (CH2)74.6,(CH)126.2(C)130.4 ppm, *m/z*%: 466.14 (Base peak) 467.23 $(M+1)^+$.

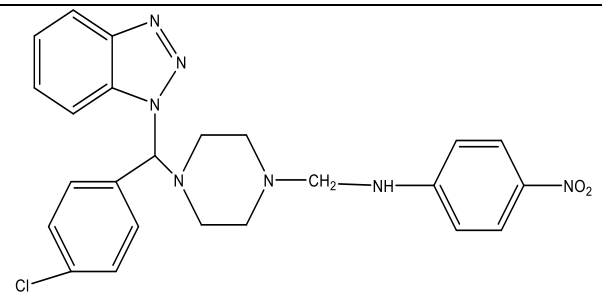
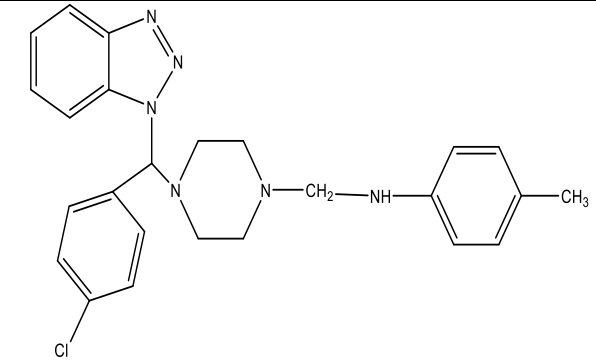
Synthesis of N-((4-((1*H*-Benzo[*d*][1,2,3]triazole-1-yl)(4-chlorophenyl)methyl)piperazine-1-yl)methyl)-4-bromoaniline(Compound B7): Yellowish colour, M.P 180°C ,Yield 83%,Mol Formula: C24H24BrClN6, MolWt:510.09,ElementalAnalysis C,56.32;H,4.73,Br,15.61,Cl,6.93;N,16.42. IR cm^{-1} (KBr): 530,3340 and 3250 cm-1. ^{1}HNMR (500 MHz, $CDCl_3$): δ ppm (NH) 6.34 (CH2) 4.13,(CH)6.11 ppm,^{13}CNMR (125 MHz, DMSO-d_6, δ ppm): (CH2)74.6,(CH)126.2(C)130.4 ppm, *m/z*%: 510.09 (Base peak) 511.12 $(M+1)^+$.

Synthesis of N-((4-((1*H*-Benzo[*d*][1,2,3]triazole-1-yl)(4-chlorophenyl)methyl)piperazine-1-yl)methyl)-4-nitroaniline(Compound B11): Whitish Yellow colour, M.P 198°C ,Yield 83%,Mol Formula: C24H24ClN7O2, MolWt:477.95,ElementalAnalysis C,60.31;H,5.06,Cl,7.42;N,20.51,O,6.69. IR cm^{-1} (KBr): 540, 1550,3200 and 1700 cm-1. ^{1}HNMR (500 MHz, $CDCl_3$): δ ppm (NH) 6.94 (CH2) 4.13,(CH)6.11 ppm,^{13}CNMR (125 MHz, DMSO-d_6, δ ppm): (CH2)74.6,(CH)126.2(C)130.4 ppm, *m/z*%: 477.95 (Base peak) 478.17 $(M+1)^+$.

Synthesis of N-((4-((1*H*-Benzo[*d*][1,2,3]triazole-1-yl)(4-chlorophenyl)methyl)piperazine-1-yl)methyl)-4-methylaniline(Compound B15):Whitish Yellow colour, M.P 190°C ,Yield 83%,Mol Formula: C25H27ClN6, MolWt:446.20, ElementalAnalysis C,67.18;H,6.09,Cl,7.93;N,18.80. IR cm^{-1} (KBr): 520, 820, and 2830 cm-1. ^{1}HNMR (500 MHz, $CDCl_3$): δ ppm (NH) 6.94 (CH2) 4.13,(CH)6.11 ppm,^{13}CNMR (125 MHz, DMSO-d_6, δ ppm): (CH2)74.6,(CH)126.2(C)130.4 ppm, *m/z*%: 446.20 (Base peak) 447.20 $(M+1)^+$.

Table-05

Com	Structures	Yield(%	M.P(˚C)
B 1	 *N*-((4-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)(4-chlorophenyl)methyl)piperazin-1-yl)methyl)aniline	83	142
B5	 *N*-((4-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)(4-chlorophenyl)methyl)piperazin-1-yl)methyl)-4-chloroaniline	81	158
B7	 *N*-((4-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)(4-chlorophenyl)methyl)piperazin-1-yl)methyl)-4-bromoaniline	88	180

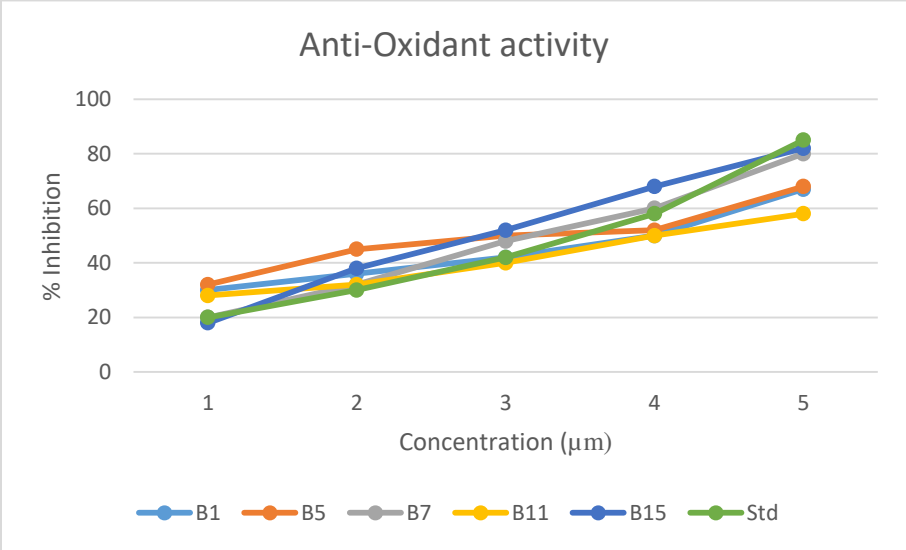
B11	 *N*-((4-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)(4-chlorophenyl)methyl)piperazin-1-yl)methyl)-4-nitroaniline	84	198
B15	 *N*-((4-((1*H*-benzo[*d*][1,2,3]triazol-1-yl)(4-chlorophenyl)methyl)piperazin-1-yl)methyl)-4-methylaniline	85	190

6.Anti-Oxidant Activity

The DPPH technique has been used to study the antioxidant activity of compounds B1,B5,B7,B11,B15. When compared to ascorbic acid (IC 50 = 6.1 μg/ml), B15 (IC 50 = 25.94 μg/ml) among the 10 compounds in the anti-oxidant activity showed superior antioxidant capabilities.

Table-06

Sl.No	Compound	% Inhibition	$IC_{50}\mu g/mL$
1	B1	64.19%	46.51
2	B5	60.81%	47.75
3	B7	80.44%	45.25
4	B11	55.44%	49.9
5	B15	83.63%	25.94
6	Ascorbic acid	55.12%	6.1



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