World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Original Article

Synthesis, docking and anti-oxidant activity of Zn (II) complexes of oximes

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Received: 08-07-2015 / Revised: 25-07-2015 / Accepted: 27-07-2015

ABSTRACT

Zinc complexes have been prepared by reacting metal chloride with ortho chlorobenzaldehyde oxime, para dimethyl aminobenzaldehyde oxime and Vanillin oxime. Docking study has been carried out for prepared complexes by using autodock software against Biotin Carboxylase (3JZI) as a target protein. The antioxidant activity have been studied and compared with their ligands against ascorbic acid as standard by DPPH assay method which gave significant results of activity.

Key words: Synthesis, Transition metal complex, Oximes, Antioxidant, DPPH assay, docking

INTRODUCTION

Synthesis of various Oximes and their complexes with transition metals are reported in the literature[1-9] and found to be active as antibacterial[1-6], anti-oxidant[7], antitubercular[8], antileprotic[10], antiviral[11], antimalarial[12] and active against certain kind of tumours[13, 14]. In continuation of our previous work regarding anti-microbial activity of transition metal complexes with Oximes derivatives[15], in the present paper synthesis, characterization, docking and antioxidant activity of Zn(II) complexes with ortho chlorobenzaldehyde oxime and para dimethyl amino benzaldehyde oxime and Vanillin oxime are reported , docking and difference in antioxidant activity between the free ligands and complexes were studied.

EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. IR spectra were recorded in KBr on Perkin-Elmer spectrometer. All compounds gave satisfactory analysis. Ortho chlorobenzaldehyde, para dimethyl amino benzaldehyde, Vanillin and Zinc chloride were obtained from sigma- Aldrich Ltd and used without further purification. The docking study of synthesized compounds and free ligands were carried out by using autodock software. Biotin carboxylase (3JZI) was selected as a target protein. All compounds were tested for their antioxidant activity against Ascorbic acid as standard at concentrations of 50,100,150 and 200µg/ml by DPPH

General method of synthesis of Ortho chlorobenzaldehyde oxime (1), Para dimethylamino benzaldehyde oxime (2), Vanillin oxime (3): Ortho chlorobenzaldehyde, Para dimethyl aminobenzaldehyde, Vanillin (0.02 mole) in 15mL ethanol was added to aqueous solution of hydroxylamine hydrochloride (0.08 mole) and sodium acetate (0.1 mole), the mixture was heated at 80-90 ºC for 10 minutes and then left to cool, the precipitate was collected and purified by crystallization from ethanol to give compounds (**1-3**) as crystals, yields 92.2, 82.9, 88.2%, respectively. (Fig-1,3and 5)

General method of synthesis of Complexes Ortho chlorobenzaldehyde oxime, Para dimethyl amino benzaldehyde oxime, Vanillin oxime with Zinc (II) (1a, 2a, 3a): Ortho chlorobenzaldehyde oxime, Paradimethyl aminobenzaldehyde oxime, Vanillin oxime (0.02 Mole) was dissolved in 15mL ethanol and was added to dissolved zinc chloride (0.001) in 15mL ethanol. The mixture was heated at 60ºC for 2 h and then left to cool. The precipitate was collected and purified by crystallization from ethanol to give compounds (**1a-3a**) as crystals,

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yields 82.2, 72.8, 78.2%, respectively. (Fig-2, 4 and 6)

Docking studies of Complexes and free ligands into active sites of Biotin carboxylase (3JZI): Biotin carboxylase (3JZI) was retrieved from the Protein Data Bank (PDB). It is repository for the 3D structural data of large biological molecules such as protein and nucleic acid. It is widely distributed in nature and has important function in fatty acids, cholesterol, and amino acid metabolism, gluconeogenesis, insulin secretion and other cellular processes. It functions as a cofactor that aids in the transfer of CO_2 groups to various target macromolecules. After obtaining PDB id (3JZI), the possible binding sites were searched using computed atlas of surface topography of proteins. These include pockets located on protein surfaces and voids buried in the interior of protein. The inhibitors against the active site of proteins. It is a computational technique. The samples conformation of small molecules in protein binding sites, Scoring functions are used to asses which of these conformations best the protein binding sites. The inhibitor and target protein was geometrically optimized and docked using docking Eigen Autodock-vina and Autodock-4.

In vitro antioxidant activity of free ligands (1-3) and their metal complexes (1a-3a): The invitro anti-oxidant activity of free ligands (**1-3**) and their metal complexes (**1a-3a**) were carried out by DPPH assay method. The free ligand and metal complexes 1ml each was added to 3ml 0.1millimole of methanolic DPPH solution at different concentration (50, 100, 150 and 200 µg/ml). Then the mixtures were vigorously shaken and left to stand for 30 minutes under subdued light. The absorbance was measured at 517nm in a UV Spectrometer. The lower absorbance of the reaction mixture indicates higher free radical scavenging activity. Ascorbic acid, which is a good anti-oxidant, was taken as standard in this study. For control, DPPH solution 3ml was mixed with methanol and used for the measuring the absorbance value. The decrease in the absorbance of DPPH solution on addition of test samples in relation to the control was used to calculate the anti-oxidant activity in terms of percentage inhibition of DPPH radicals. The capability of scavenging DPPH radical [Percentage free radical Scavenging Activity (%RSA)]

DPPH scavenging activity (%) =1-Ab. of the Sample X 100/Absorbance of the control

Oximes (**1-3**) were prepared from ortho chlorobenzaldehyde, para dimethyl aminobenzaldehyde and vanillin which have a good crystalline yield. The reaction of ortho chlorobenzaldehyde, para dimethyl aminobenzaldehyde and vanillin with hydroxylamine HCl in methanol gave a white crystal in high yield. In the complexes(**1a-3a**), the reaction of ortho chlorobenzaldehyde oxime with Zinc chloride gave pale brown crystals (**1a**).The reaction of para dimethyl aminobenzaldehyde oxime with Zinc chloride gave dark brown crystals (**2a**) and the reaction of vanillin oxime Zinc chloride gave fine brown crystals (**3a**). All the compounds are stable at room temperature and insoluble in water. Some physical properties, analytical and spectral data of the compounds are summarized in the table1.

Table-1: Analytical and spectral data of the free ligands(1-3) and its metal complexes(1a-3a)

Compounds No.	Compounds Colour	m.p (ºC)	Key IR band, cm^{-1}	Molecular formula	Mol.wt	%yield
1	white	92-94	1623(C=N), 3210(O-H), 3301(C-H aromatic)	C_7H_6NOCl	156.5	92.2
2	white	50-52	1593(C=N), 3190(O-H), 1107(C-N), 3302(C-H aromatic)	$C_9H_{12}N_2O$	164.0	82.9
3	white	108-110	1625(C=N), 2920(O-H), 2962.48(OCH3), 3310(C-H aromatic)	$C_8H_9NO_3$	167.0	88.2
1a	Pale brown	190-192	1613(C=N), 3152(O-H), 3293(C-H aromatic)	$C_{14}H_{10}N_2O_2Cl_2Zn$	374.5	82.2
2a	Dark brown	76-78	1539(C=N), 3172.3(O-H), 979(C-N), 3286(C-H aromatic)	$C_{18}H_{22}N_4O_2Zn$	391.8	72.8
3a	Brown	216-218	1529(C=N), 2905(O-H), 2955(OCH3), 3325(C-H aromatic)	$C_{18}H_{20}N_2O_4Zn$	393.7	78.2

The IR spectra of free ligands (**1-3**) show broad bands 3210, 3190 and 2920 cm^{-1}, which corresponds to (O-H) of oximes. The IR spectrum of all the complexes (**1a-3a**) shows downshift in (O-H) of oximes by about 15-58cm^{-1}. These may be due to co-ordinate bond formation through oxygen of hydroxyl group [16]. The IR spectral of ligands (**1-3**) show bands at 1623, 1593 and 1625, which may be due to (C=N) of oximes. The IR spectra of all the complexes (**1a-3a**) shows downshift (C=N) of oximes by 10-96cm^{-1}. These may be due to co-ordinate bond formation through nitrogen of oximino group [17-18]. Molecular modeling (docking) study was carried out for ligands (**1-3**) and their transition metal complexes with Zn (II) (**1a-3a**). The target protein and inhibitors were geometrically optimized. The 3D structures of a target protein receptor molecule usually a protein, chemical compounds potential affinity toward site are rationally designed with aid of computational methods. All 6 compounds were docked against active site of target proteins. Out of 6 inhibitors analyze all 3 complexes (**1a-3a**) showed higher binding energy -6.09 kgcal/mole, -6.66 kgcal/mole, -4.86 kgcal/mole respectively against the target proteins. The binding energy of all the inhibitors was show in table-2. Figs 7-9 represent the docked structure of ligands and figs 10-12 represents the docked structure of complexes of the inhibitors to that of target protein.

Table 2: Energy Minimization Table of free ligands (1-3) and its metal complexes (1a-3a)

Compounds Code	Hydrogen bond interaction	H bond length (Aº)	Auto docking Score
1	Leu 199 : O	2.987	-3.71
2	Gln 99 : O	2.745	-5.17
3	Asp 17 : O	2.839	-4.8
1a	Leu 95 : O	2.938	-6.09
2a	Gln 254 : O	2.088	-6.66
3a	Leu 18 : O Asp 17 : N	2.766 2.644	-4.86

The Table-3 describes the molecular properties of the free ligand (**1-3**) and its transition metal complexes with Zinc (**1a-3a**). All complexes satisfy all the criteria of Lipinski rule of five [19-20].

Table 3: Molecular properties of free ligands (1-3) and its metal complexes (1a-3a)

Compounds Code	Mi log p	TPSA	n atoms	n ON	n OHNH	n violations	n rotb	Volume
1	2.986	32.592	10	2	1	0	1	128.858
2	2.458	35.830	12	3	1	0	2	161.228
3	1.695	62.054	12	4	2	0	2	148.885
1a	-4.261	36.916	21	4	0	0	2	270.948
2a	-4.856	43.312	25	6	0	0	4	335.688
3a	-5.356	95.840	25	8	2	0	4	311.044

The complexation of biologically important metal [Zn (II)] with Oximes and free ligands were further exploded with the evaluation of the anti-oxidant activity[21-22]. The ligands (**1-3**) each (50,100,150 and 200µg/ml) and the metal complexes (**1a-3a**) each (50,100,150 and 200µg/ml) were evaluated for invitro antioxidant activity against ascorbic acid as standard by DPPH assay method (Table-4). All the ligands / complexes exhibited appreciable in vitro activity against the tested strains. The metal complexes (**1a-3a)** show good antioxidant activity (Fig 13-15). These results indicate that the increases in the size of the transition metal complex with Oximes possess significant anti-oxidant activity.

Table- 4: Invitro anti-oxidant activity of ligands (1-3) and its metal complexes (1a-3a)

Compounds code	% Anti-oxidant activity			
Standard (Ascorbic acid)	50µg/ml	100µg/ml	150µg/ml	200µg/ml
	62.4	69.36	71.32	79.3
1	95.03	95.41	96.18	98.09
1a	95.80	95.80	96.18	98.09
2	89.31	94.65	94.65	97.32
2a	92.36	96.94	96.94	98.47
3	93.01	93.89	94.65	98.47
3a	93.89	94.65	95.41	98.47

Fig-1: Synthesis of Compound 1(O-chlorobenzaldehyde oxime)

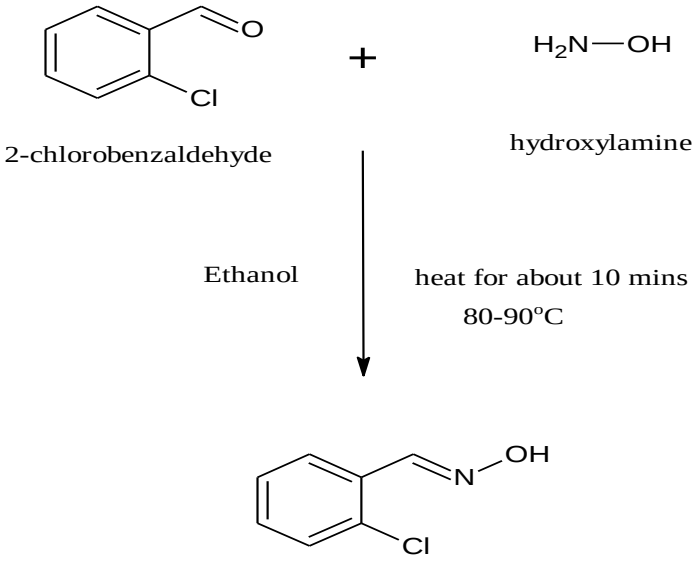


Fig-2: Synthesis of metal complex of O-chloro benzaldehyde oxime (1a)

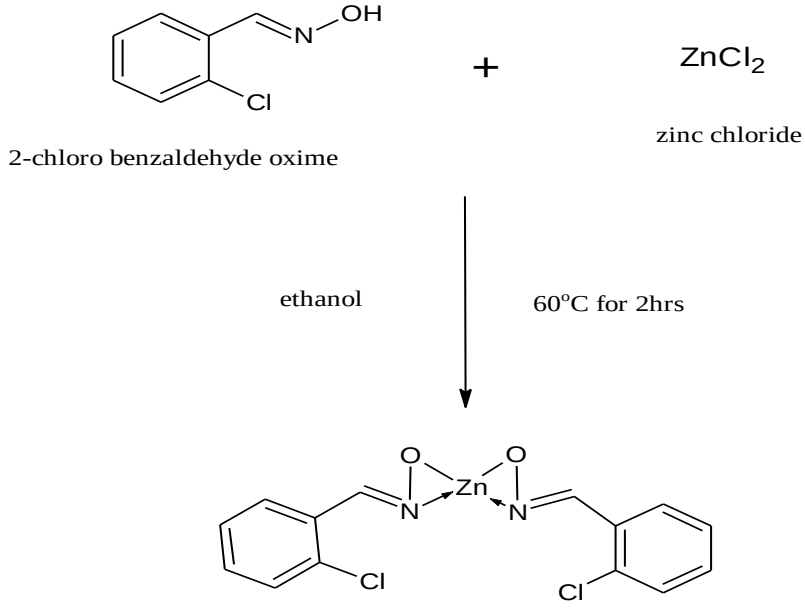


Fig-3: Synthesis of Compound 2 (P-dimethyl aminobenzaldehyde oxime)

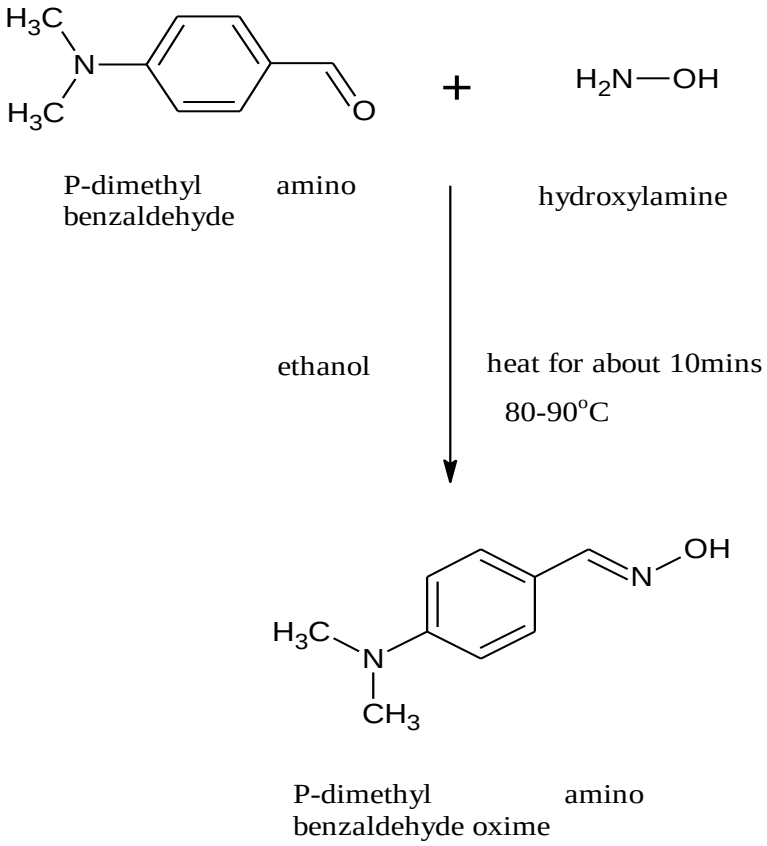


Fig-4: Synthesis of metal complex of P-dimethyl aminobenzaldehyde oxime (2a)

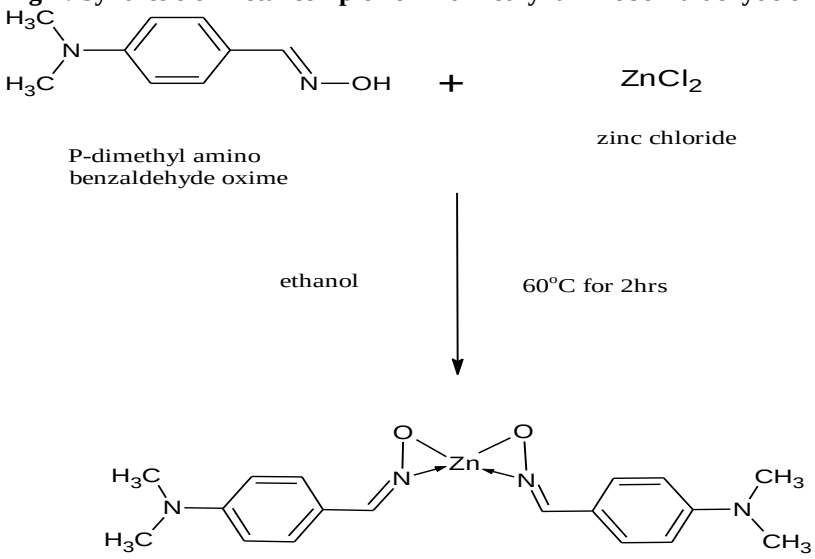


Fig-5: Synthesis of Compound 3 (Vanillin oxime)

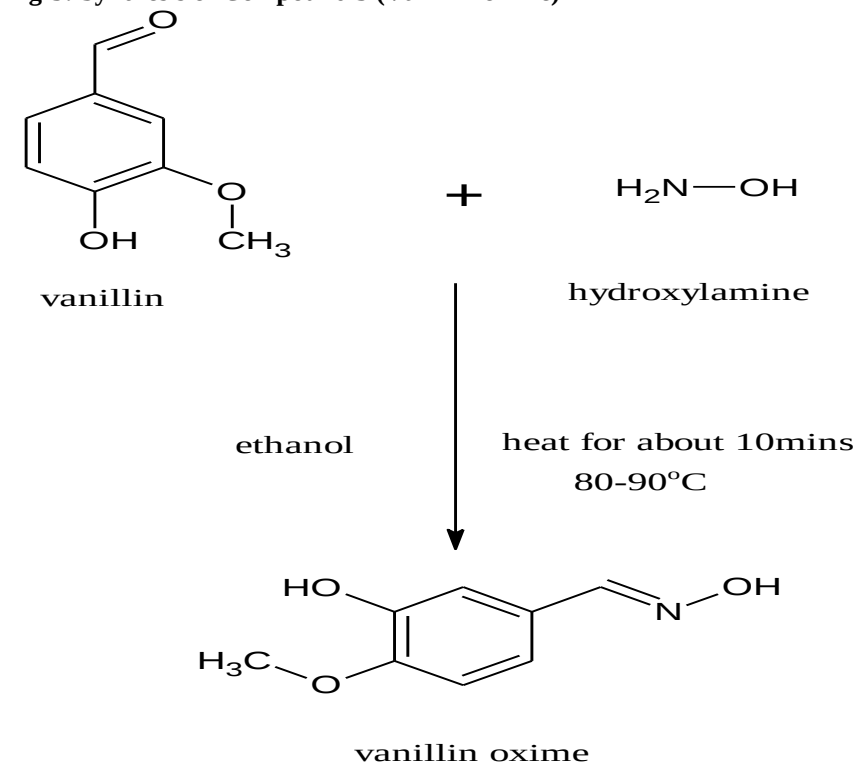


Fig-6: Synthesis of metal complex of vanillin oxime (3a)

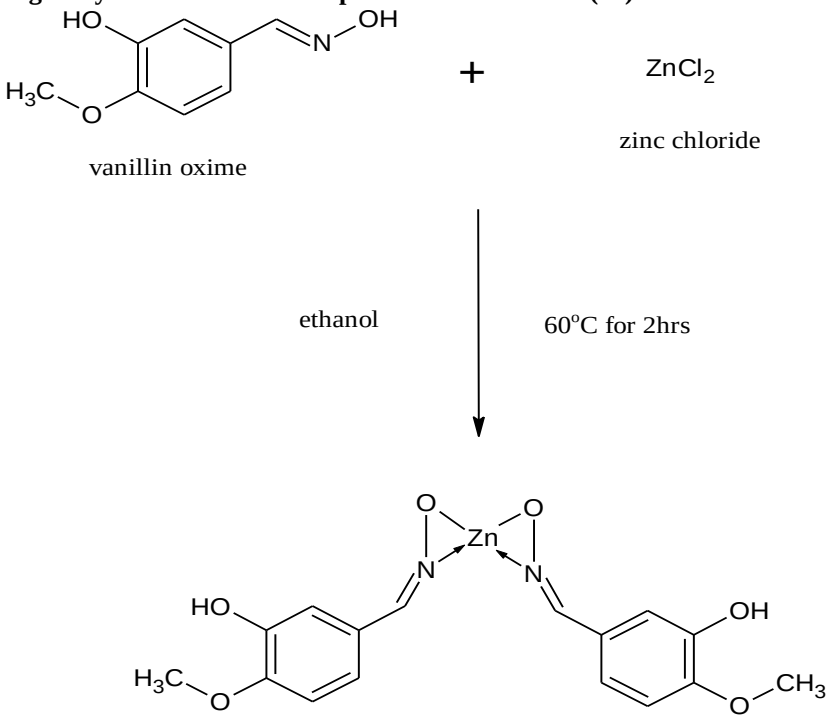


Fig-7: Docking structure of free legand (compound 1):

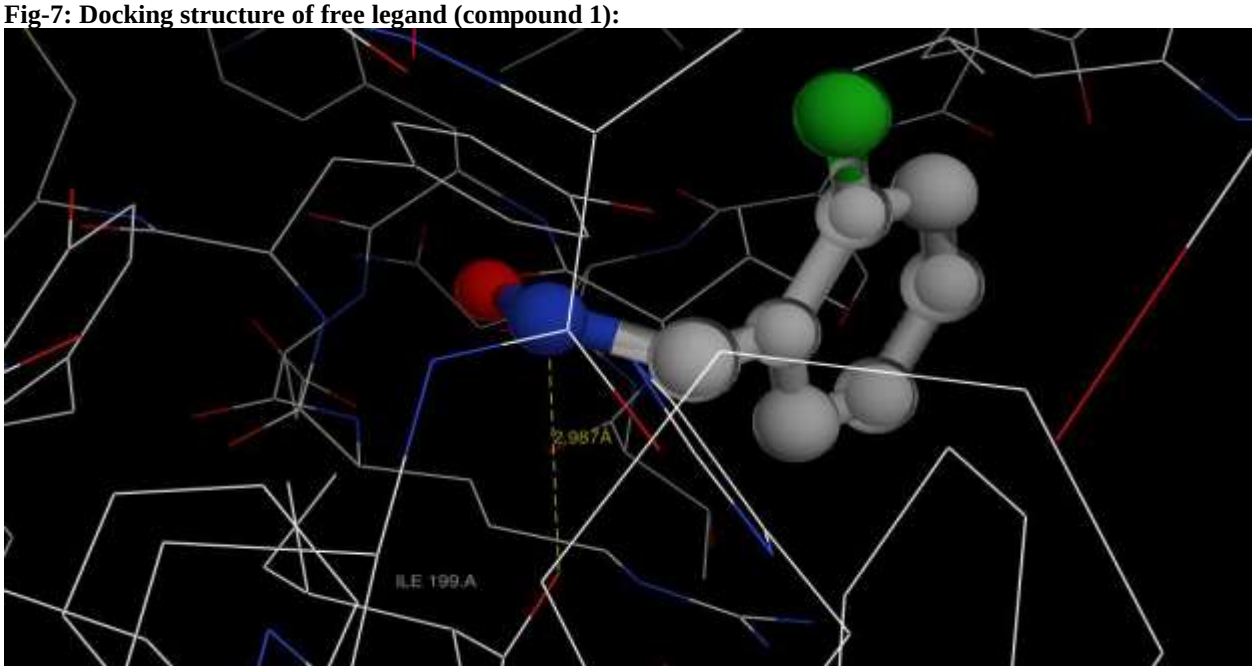


Fig-8: Docking structure of free legand (compound 2):

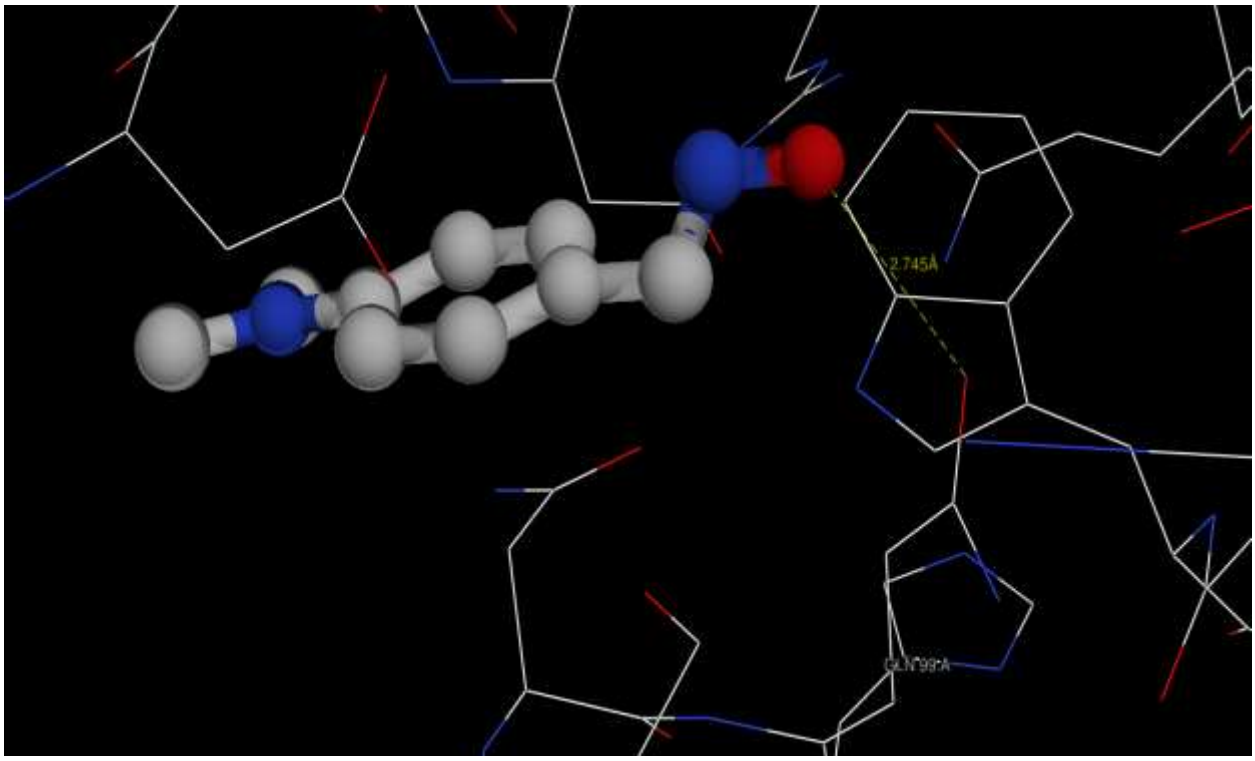


Fig-9: Docking structure of free legand (compound 3):

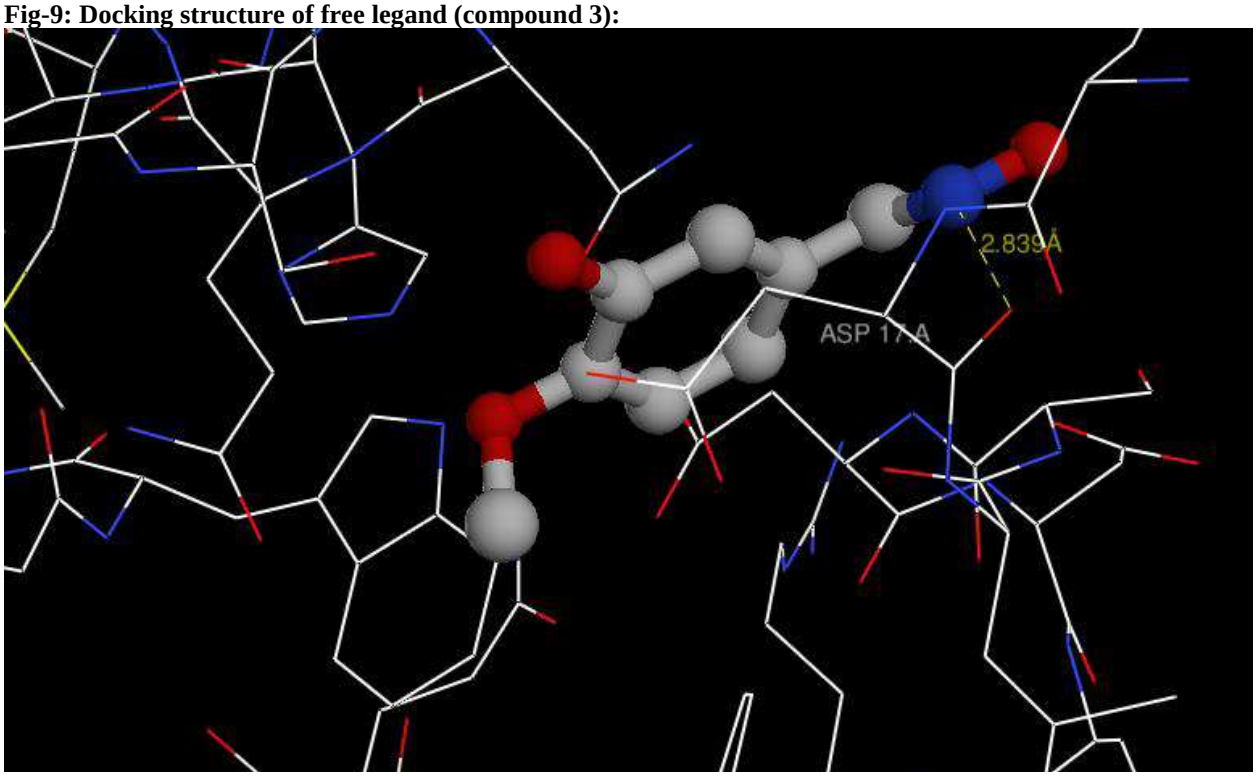


Fig-10: Docking structure of the metal complex (Compound 1a)

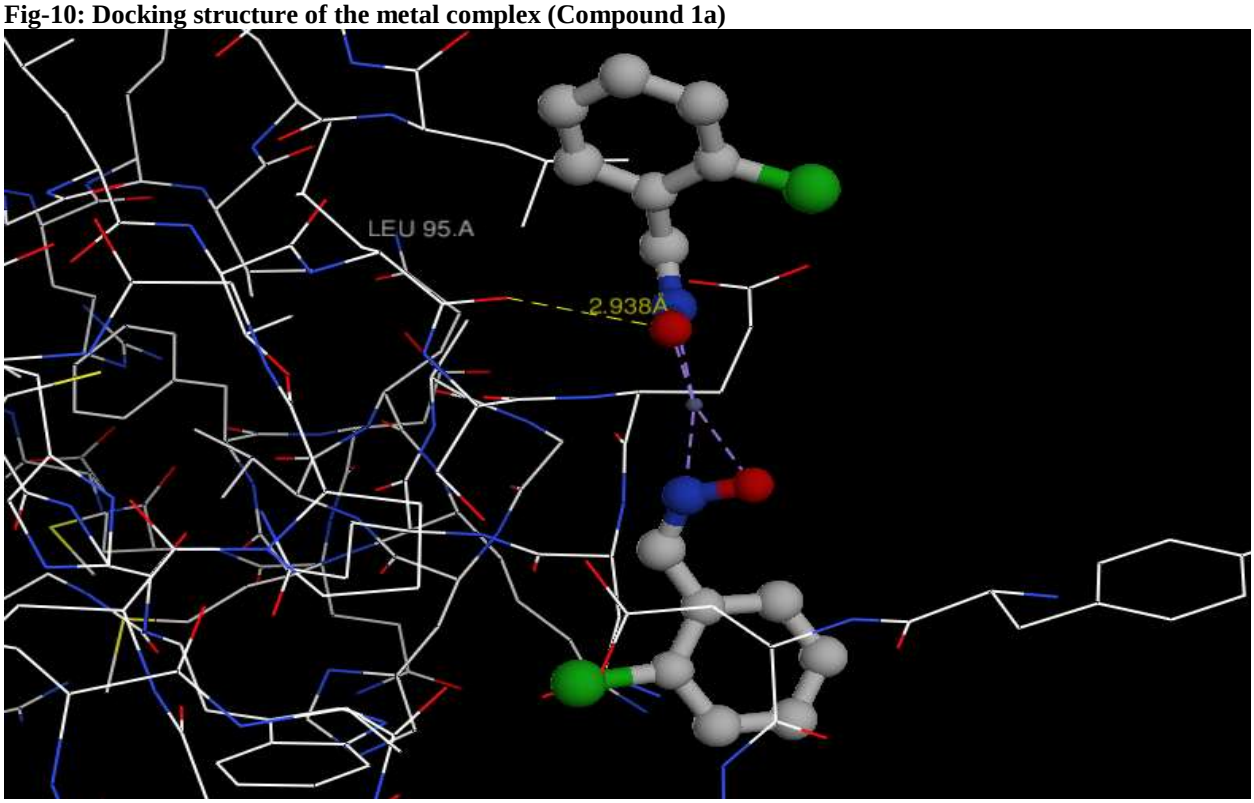


Fig-11: Docking structure of the metal complex (Compound 2a)

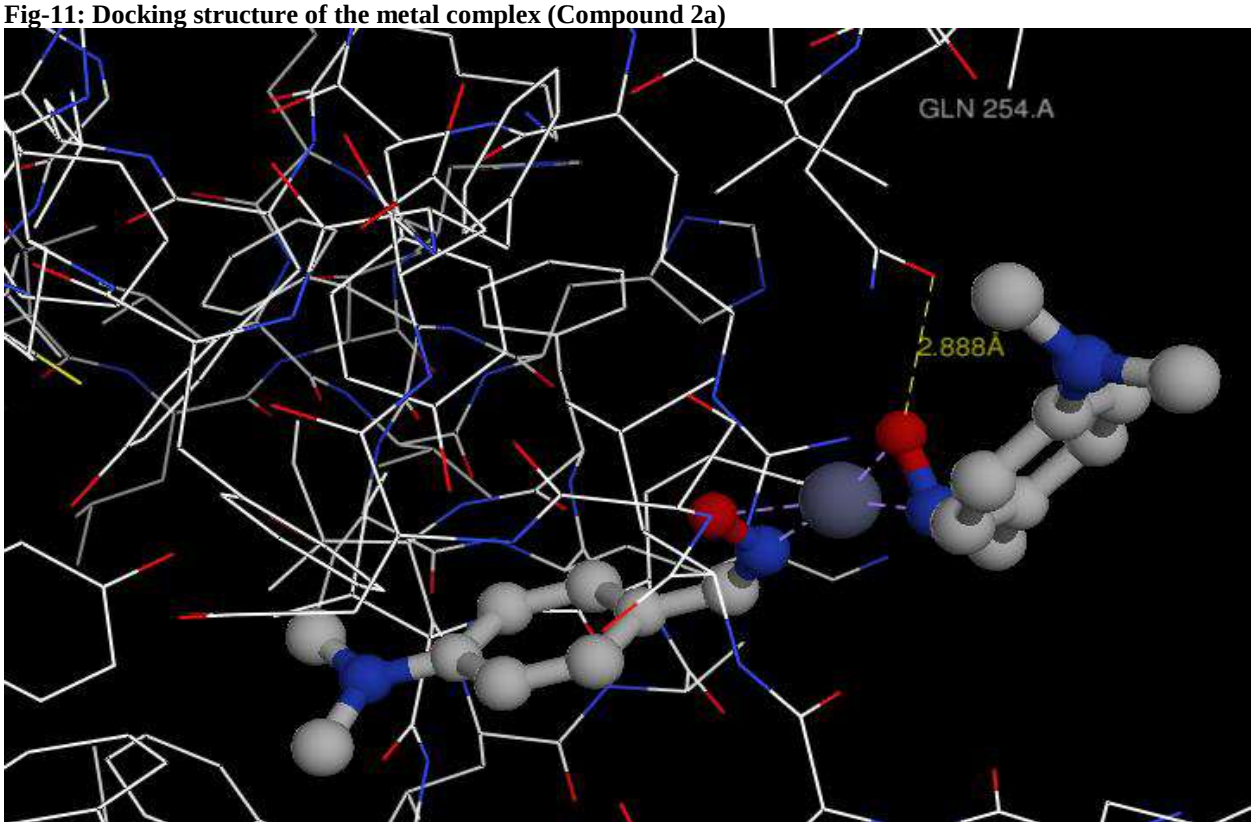


Fig-12: Docking structure of the metal complex (Compound 3a)

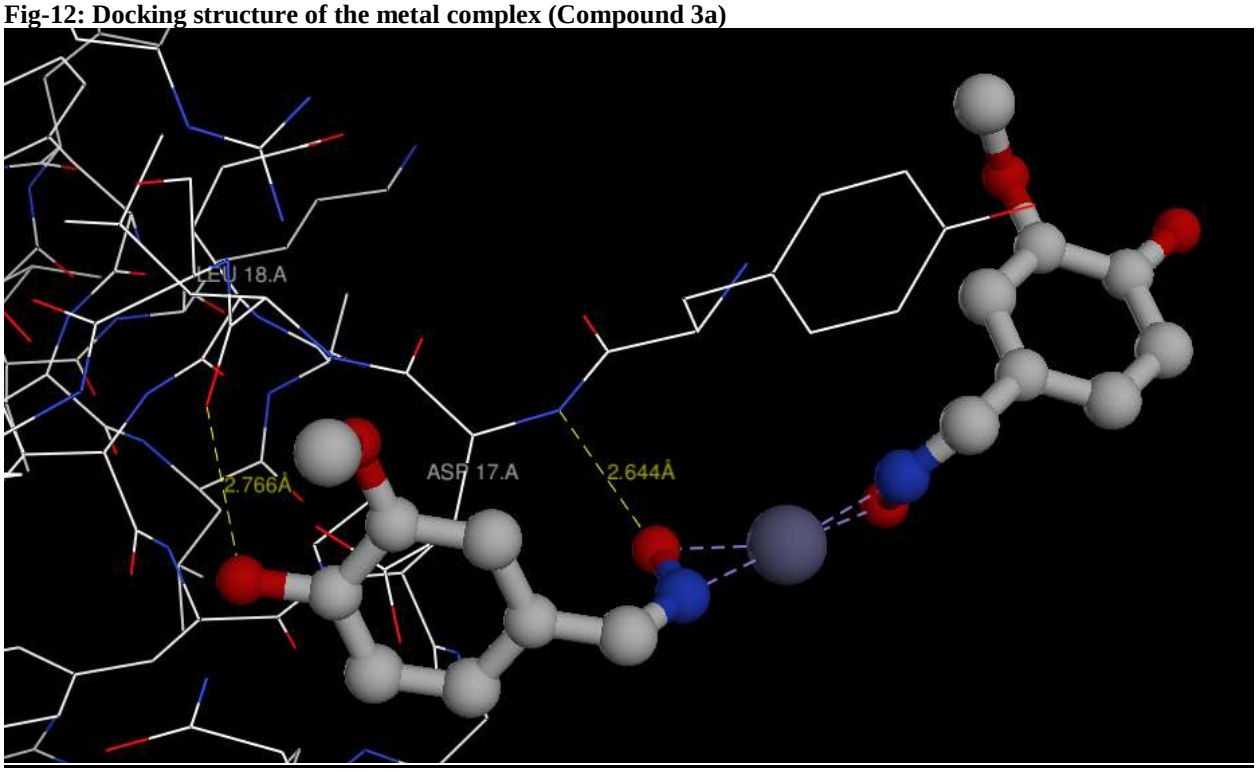
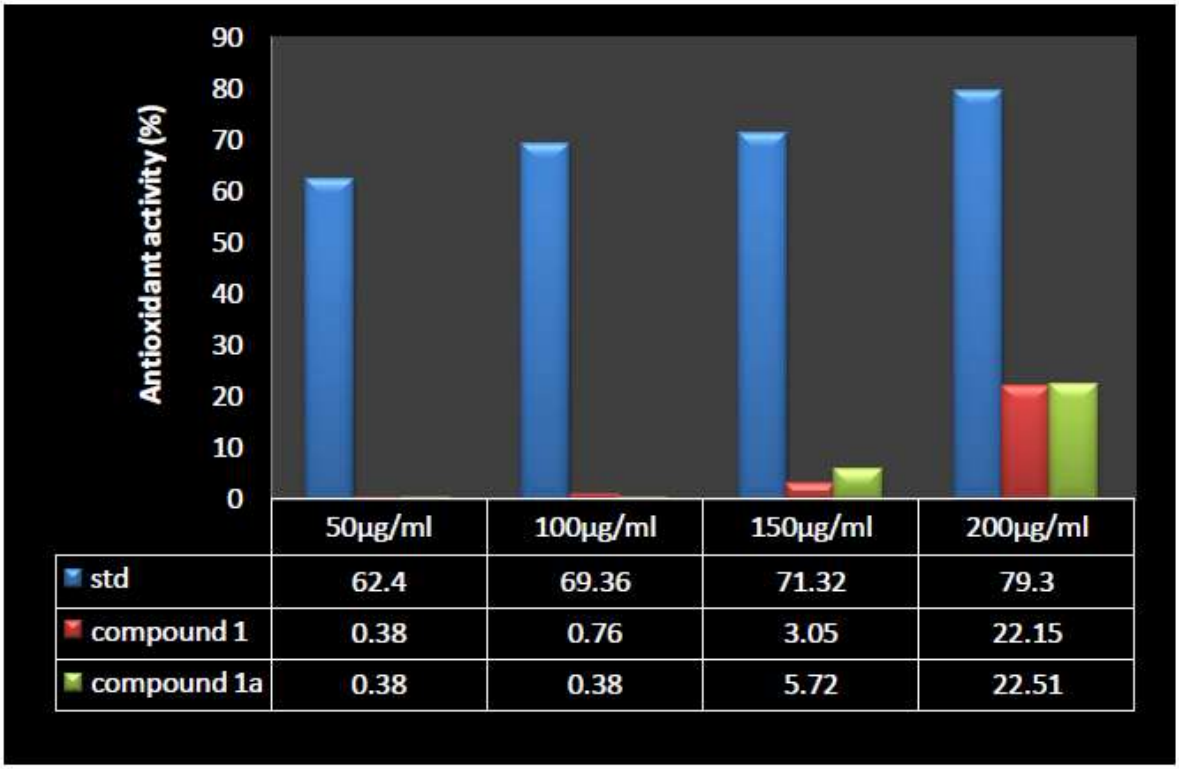
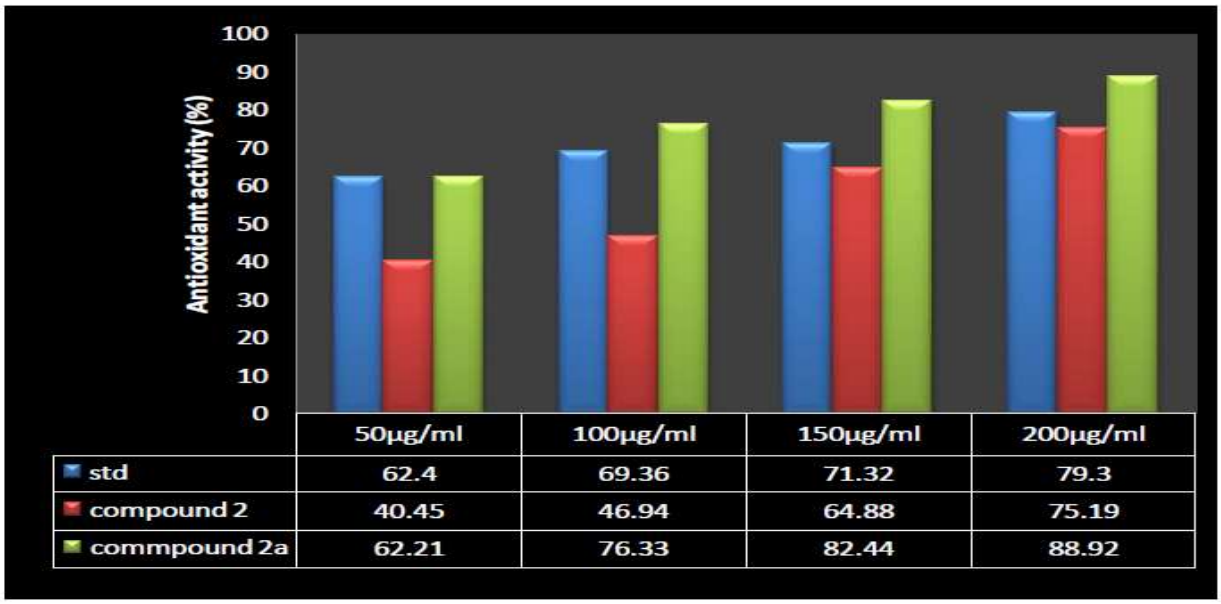


Fig-13: Anti-Oxidant activity of Compound 1 &1a:-



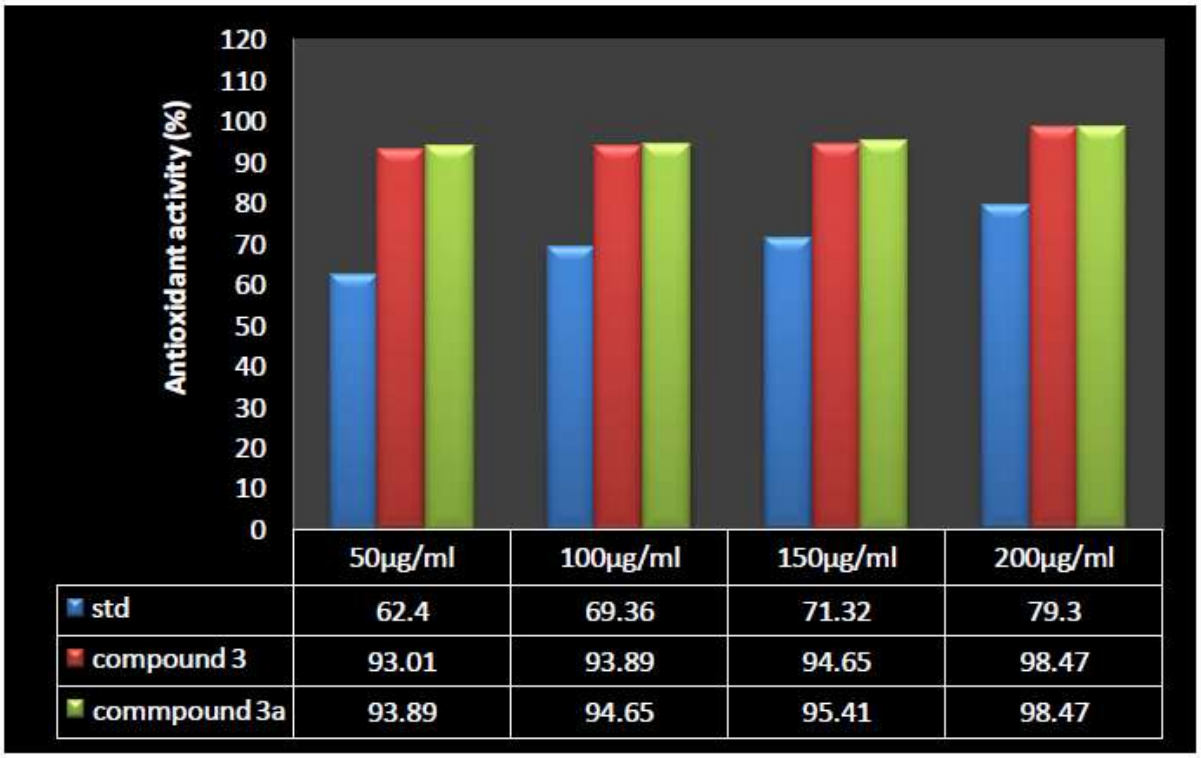
	50µg/ml	100µg/ml	150µg/ml	200µg/ml
std	62.4	69.36	71.32	79.3
compound 1	0.38	0.76	3.05	22.15
compound 1a	0.38	0.38	5.72	22.51

Fig-14: Anti-Oxidant activity of Compound 2 &2a:-



	50µg/ml	100µg/ml	150µg/ml	200µg/ml
std	62.4	69.36	71.32	79.3
compound 2	40.45	46.94	64.88	75.19
commpound 2a	62.21	76.33	82.44	88.92

Fig-15: Anti-Oxidant activity of Compound 3 &3a:-



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