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Design, Synthesis and Biological Evaluation of Novel Phenothiazines for Cancer Exploring through Anti-Oxidant and Anti-Inflammatory Activities

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Abstract **Original Research Article**

Cancer is defined as development of number of abnormal cells by uncontrollable cell division leads to the tissue detriment. It has the ability to spread throughout the body. Cancer is second-leading disease to cause the death in the world. Now-a-days survival rate for cancer may increase through the treatment. In this study, the cancer is treated by exploring the anti-oxidant and anti-inflammatory activity of novel Phenothiazines. Because anti-oxidants play a vital role in treatment of cancer by reducing the oxidative stress, abnormal cell division reduction, decrease in DNA damage, and reduced mutagenesis. As we know that NSAIDS (anti-inflammatory drugs) can help in prevention of cancer by inhibiting COX enzyme, increasing apoptosis, reducing cell migration, increasing chemo-sensitivity. Through this study we proved the anti-oxidant and anti-inflammatory activity of newly synthesized phenothiazine derivatives, followed by anti-cancer activity in addition with *in-silico* molecular docking studies to explore the exact mechanism of action of phenothiazine in cancer treatment.

Keywords: Phenothiazines, anti-oxidant, anti-inflammatory, anti-cancer activity, docking studies.

1. INTRODUCTION

Cancer is defined as development of number of abnormal cells by uncontrollable cell division leads to the tissue detriment. It can spread throughout the body. Cancer is second-leading disease to cause the death in the world. Now-a-days survival rate for cancer may increase through the treatment. In this study, the cancer is treated by exploring the anti-oxidant and anti-inflammatory activity of novel Phenothiazines.

This study focuses on the repurposing of phenothiazine derivatives in cancer therapy. Many reported studies suggest that anti-oxidants may reduce the oxidative stress by neutralizing the unstable atoms (free radicals) which can damage DNA andcause cancer. Anti-oxidants protectnon-cancerous cellsand can prevent chemoresistance to improve response to the drugs chemotherapy. Anti-oxidants can also reduce abnormal cell division, and mutagenesis. So, anti-oxidants may helpful for the cancer treatment.

Anti-inflammatory drugs plays major role in cancer treatment by reducing the inflammation which is main factor for the development and progression of tumor. These drugs also help to penetrate the immune cells in to the cancer cell to destroy them. They can protect the DNA from damage and repair the damaged DNA. These drugs can increase the apoptosis of cancer cells, reduce cell migration, and sensitize the cancer cells for cytotoxic drugs chemotherapy. NSAIDS are the well-known anti-inflammatory drugs suppress the genes which are activated during the inflammation and progression of cancer. They act by inhibiting the cyclooxygenase enzyme in turn leads to down regulation of VEGF (Vascular Endothelial Growth Factor) and inhibition of PI3K/Akt signaling pathway.

According to structure activity relationship modifications in Phenothiazine nucleus influence the extent of activity. Novel Phenothiazine derivatives were designed by modifying the angular attachments by substituting with different halogen derivatives. In this study we try to prove the exact mechanism of action of

novel phenothiazine derivatives through molecular docking studies. *In-silico* molecular docking studies may helpful for the development of more potent derivatives by reducing the time and cost for drug discovery process.

2. EXPERIMNTAL

2.1 INSTRUMENTS

All chemicals were purchased from Empire scientific chemical companies for synthesis. The melting point was observed in open glass capillaries on the mettle FP51 melting point apparatus. The IR spectrum peaks provide insight into the probable structure of the corresponding IR region ranges between 4000-666 cm-1. Quanta radiation from this spectrum region corresponds to energy difference between various vibrational levels of molecules. The compounds were recorded on BRUKER FTIR-8400S spectrophotometer shows different vibrational levels of molecules. The 1H NMR and 13C NMR spectra enable us to know different chemical and magnetic environments corresponding to protons and carbons in molecule. The samples were analysed on BRUKER 100MHz spectrometer.

2.2 General synthesis

Step :1 General procedure for the preparation of 7,8or9 substituted aniline Aldehyde derivative- Equimolar amount of substituted aniline was added to a chlorobenzaldehyde in 20 ml of DMF and 0.1 percent of potassium hydroxide solution and the reaction mixture was heated under refluxed at about 800C temperature, for 2 h. TLC indicated the end of reaction. The mixture was cooled by addition of a water /ice mixture. The solid was filtered I excellent yield.

Step:2 General procedure for the preparation of 7,8or9 substituted 10H phenothiazine 1 benzaldehyde derivative -II -Equimolar amount of 7,8or9 substituted Aniline benzaldehyde was added to a solution of sulphur powder and iodine in 5ml of ethanol. Reaction mixture was heated under reflux with stirring for about 2 h and poured into ice/water mixture. the precipitation was filtered and washed with cold water.

2.3 2-nitro-10,10a-dihydro-4aH-phenothiazine-9-carbaldehyde (PTZ-1)- A mixture of chlorobenzaldehyde 14.05gms and 2-nitro aniline 13.81gms in 20ml of KOH and 20 ml of Di methyl formamide was added by stirring, thus mixture was heated under reflex condenser for 2 hrs, then the mixture was cooled by addition of ice. The residue was filtered and dried. 7,8or9 substituted aniline Aldehyde derivative was formed. To the 7,8or9 substituted aniline Aldehyde derivative was added to a solution or sulphur 3.2 gms and iodine 1.26 gms in 5 -10 ml of ethanol by stirring. the mixture was heated under reflex condenser for 2 hrs. the mixture is poured in a ice /water. The residue is filtered and dried at room temperature. 2-nitro-10,10a-dihydro-4aH-phenothiazine-9-carbaldehyde PTZ-1was formed, percentage yield:63%.1H NMR (400Hz, DMSO), PTZ-1δ6.5(CHO), δ2.0, δ6.0(N-H), ,1C13 PTZ-1δ113(C-N). (C=O), δ2.0, δ6.0(C-S), Mass Spectroscopy(m/z): 250.503, IR: C-H (alkane)-2937.29, C-H (aromatic)-837, C=C (aromatic)-2149.33, C= O (ester)-, C=O (acid)-1707.4, C=O (amide)-,N-H(s)-1590.44, N-O(B)-1490, S-H(S)-2563.06, C-F(B):1330, C-C(S):746.37 ,C=N(B):1635.6 ,C=S(S):1184.05, C=S(B):1333.50 Interaction Residues: APG:73, TYR:409, TYR:472, PHE:480, ASN:575, LYS:501Estimated of free energy binding: -8.9kcal/mol.

2.4 3-nitro-10,10a-dihydro-4a*H*-phenothiazine-9-carbaldehyde (PTZ-2)- A mixture of chlorobenzaldehyde 14.05gms and 3-nitro aniline 13.81gms in 20ml of KOH and 20 ml of Di methyl formamide was added by stirring, thus mixture was heated under reflex condenser for 2 hrs, then the mixture was cooled by addition of ice. the residue was filtered and dried. 7,8or9 substituted aniline Aldehyde derivative was formed. To the 7,8or9 substituted aniline Aldehyde derivative was added to a solution or sulphur 3.2 gms and iodine 1.26 gms in 5 -10 ml of ethanol by stirring. the mixture was heated under reflex condenser for 2 hrs. the mixture is poured in a ice /water. The residue is filtered and dried at room temperature. 3-nitro-10,10a-dihydro-4a*H*-phenothiazine-9-carbaldehyde PTZ-2 yield-63, 1H NMR (400Hz, DMSO), PTZ-2 δ6.5(CHO), δ2.0, δ6.0(N-H),1C13 PTZ-2 δ6.5(C=O), δ2.0, δ6.0(C-N)Mass spectroscopy m/z: 248.504 IR: , C-H (aromatic)-849, C=C (aromatic)-1653.59, C=O (ester)-1592.91, C=O(acid)-1711.75,C=O (amide)-1695.03, N-H(s)-1592.44,N-O(B)-1592.1,,C-F(B):1488, C- C(S):746.37, C=N(B):1635.6, C=S(S):1184.05, C=S(B):11283. Interaction Residues: ASN;493, PHE;480, LYS;501, TYR;472 Estimated of free energy binding: -8.9kcal/mol.

2.5 4-chloro-10,10a-dihydro4a*H*-phenothiazine-9carbaldehyde (PTZ-3)- A mixture of chlorobenzaldehyde 14.05gms and 4-chloro aniline 13.81gms in 20ml of KOH and 20 ml of Di methyl formamide was added by stirring, thus mixture was heated under reflex condenser for 2 hrs, then the mixture was cooled by addition of ice. The residue was filtered and dried. 7,8or9 substituted aniline Aldehyde derivative was formed. To the 7,8or9 substituted aniline Aldehyde derivative was added to a solution or sulphur 3.2 gms and iodine 1.26 gms in 5 -10 ml of ethanol by stirring. the mixture was heated under reflex condenser for 2 hrs.the mixture is poured in a ice /water. The residue is filtered and dried at room temperature.4-chloro-10,10a-dihydro4a*H*-phenothiazine 9 carbaldehyde yield-85%. 1H NMR (400Hz, DMSO), PTZ-3 sδ5.5, CHOδ3.0 N-Hδ6. 1C13 PTZ-3 sδ5.5, C=Oδ3.0 N-Hδ6.0, Mass Spectroscopy m/z:158.446 , IR: C-H (alkane)-2937.29, C-H (aromatic)-837, C=C (aromatic)-2149.33, C= O (ester)-, C=O (acid)-1707.4, C=O(amide)-1085.27,N-H(s)-1649.92,N-O(B)-1592.88,C-F(B):1396.60, C C(S):799.6, C=N(B):1685.6, C=S(S):1192.32, C=S(B):1396 Interaction Residues: ALA;411, TYR;472,

PHE;480; ASN;575 Estimated of free energy binding: -8.6kcal/mol.

2.6 3-chloro-4-fluoro-10, dihydro-4aH-phenothiazine-carbaldehyde (PTZ-3)-A mixture of chlorobenzaldehyde 14.05gms and 3-chloro4-fluoro aniline 13.81gms in 20ml of KOH and 20 ml of Di methyl formamide was added by stirring, thus mixture was heated under reflex condenser for 2 hrs, then the mixture was cooled by addition of ice The residue was filtered and dried. 7,8or9 substituted aniline Aldehyde derivative was formed.

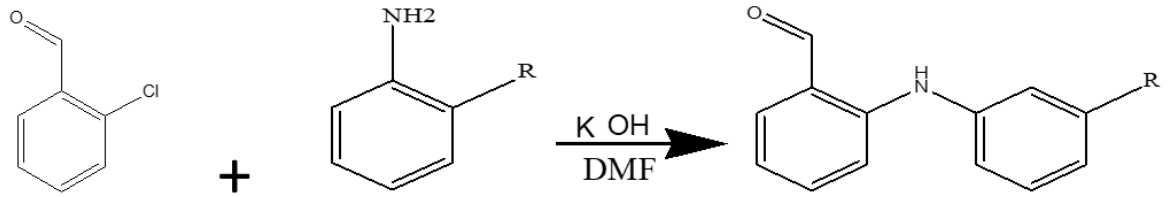
To the 7,8or9 substituted aniline Aldehyde derivative was added to a solution or sulphur 3.2 gms and iodine 1.26 gms in 5 -10 ml of ethanol by stirring. the mixture was heated under reflex condenser for 2 hrs. The mixture is poured in a ice /water. The residue is filtered and dried at room temperature3-chloro-4-fluoro-10, dihydro-4aH-phenothiazine-carbaldehyde (PTZ-3), yield-80% .1H NMR (400Hz, DMSO), PTZ-4 CHO δ 6.0, N-H δ6.6 .1C13 PTZ-4 (C=O) δ 6.0, (C-N) δ6.6 .IR: C-H (alkane)-297521, C-H (aromatic)-826.65, C=C (aromatic)-1675.18, C= O (ester)-1585.60, C=O (acid)-1740.9, C=O (amide)-1725.13, N-H(s)-1644.8,N-O(B)-1585.60,C-F(B):1356.53,C-C(S):782.29,C=S(S):1185.71,C=S(B):1356Spectroscopy m/z: 1185Interaction Residues: TYR;472, ASN;575, PHE;480Estimated of free energy binding: -8.7kcal/mol.

2.7 4-fluoro-10,10a-dihydro4a*H*-phenothiazine9carbaldehyde (PTZ -4)- A mixture of chlorobenzaldehyde 14.05gms and 3-chloro4-fluoro aniline 13.81gms in 20ml of KOH and 20 ml of Di methyl formamide was added by stirring, thus mixture was heated under reflex condenser for 2 hrs, then the mixture was cooled by addition of ice .the residue was filtered and dried. 7,8or9 substituted aniline Aldehyde derivative was formed.

To the 7,8or9 substituted aniline Aldehyde derivative was added to a solution or sulphur 3.2 gms and iodine 1.26 gms in 5 -10 ml of ethanol by stirring. the mixture was heated under reflex condenser for 2 hrs.the mixture is poured in a ice /water. The residue is filtered and dried at room temperature4-fluoro-10,10a-dihydro4a*H*-phenothiazine9carbaldehyde (PTZ -4) yield-89, 1H NMR (400Hz, DMSO), \PTZ-5 sδ5.5, CHOδ3.0 N-Hδ6.0,1C13 PPTZ-5 (sδ5.5, C=Oδ3.0 C-Nδ6.0). IR: C-H (alkane)-2909.68, C-H:830.34,C-.C (aromatic):2170.98, C=C (aromatic)-1587.08, C= O (ester)-1726.50, C=O (acid)-1695.46, C=O (amide)-1637.12, N-H(s)-1695.46, N-O(B)-1511.25, C-F(B):1361.89, C-C(S):776.88, C=N(B):1683.6, C=S(S):1183.77, C=S(B):1361.89. Mass Spectroscopy m/z: 202.346, Interaction Residues: PHE;480, ALA;411, ASN;575Estimated of free energy binding: -8.6kcal/mol.

3. REACTION SCHEME General Scheme for the Synthesis of the Compounds

STEP-1



STEP-2

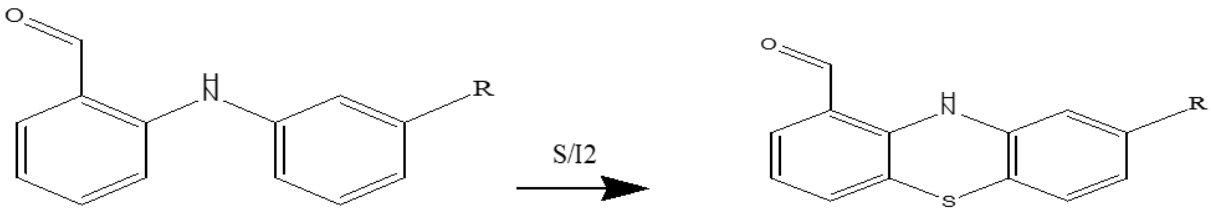


Table-1: List of synthesized compounds with their IUPAC names

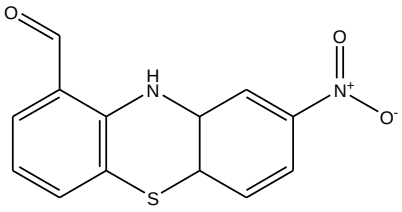
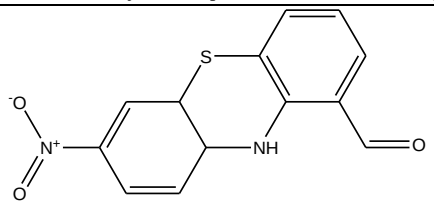
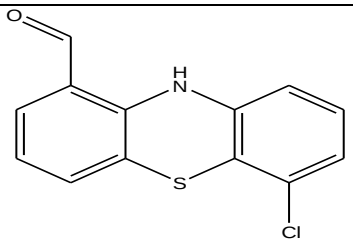
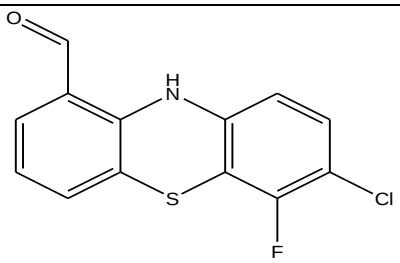
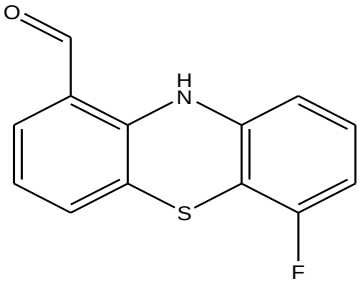
S.N	Compound	Structure	Molecular formula	Molecular weight	Melting point	% yield
1	PTZ-I	 2-nitro-10,10adihydro4aH-phenothiazine-9carbaldehyde	$C_{12}H_8N_2O_2S$	244.26	95-98	69
2	PTZ-II	 3-nitro-10,10adihydro4aH-phenothiazine-9carbaldehyde	$C_{12}H_8N_2O_2S$	244.27	97-99	63
3	PTZ-III	 4-chloro10,10a-dihydro4a*H*-phenothiazine-9carbaldehyde	$C_{12}H_8CINS$	233.72	95-98	85
4	PTZ-IV	 3chloro4fluoro10dihydro4aHphenothiazinecarbaldehyde	$C_{13}H_9CIFNOS$	281.73	98-110	80
5	PTZ-V	 4-fluoro-10,10a-dihydro4a*H*phenothiazine9carbaldehyde	$C_{13}H_{10}FNOS$	247.29	95-120	89

Table-2: IR data for synthesized compounds

Compound code	C-H (alkane)	C-H (arom atic)	C=C (alkene)	C=C (aromatic)	C=O (ester)	C=O (acid)	C=O (amide)	N-H (Stretch ing)	N-O (Bend ing)	S-H (Stret ching)	C-F (Bend ing)	C-C (Stre tchin g)	C=N(Ben ding)	C=S (Stretc hing)	C=S (Bend ing)
PTZ-I	2937.29	839.47	1655.69	2149.33	—	1707.4	—	1590.44	1590.44	2563.06	1330.50	746.37	1635.6	1184.05	1333.50
PTZ-II	—	849.78	1653.59	1592.91	1734.4	1711.75	1695.03	1617.61	1592.1	—	1488.32	785.63	1668..8	1183.19	1246.46
PTZ-III	—	823.26	1669.54	1592.88	1712.5	1712.51	1085.57	1649.72	1592.88	—	1396.60	799.86	1685.5	1192.32	1396.60
PTZ-IV	2975.21	826.65	1671.18	1585.60	1740.9	1725.23	1691.74	1644.8	1585.60	2553.16	1356.53	782.29	___	1185.71	1356.53
PTZ-V	2909.68	830.34	2170.98	1587.08	1749.7	1726.50	1695.46	1637.12	1695.46	2522.15	1361.89	776.88	1653.6	1183.77	1361.89

Table-3: ^{1}H-NMR spectral data for synthesized compounds

Compound Code	Nature of Protein	Aromatic Proton	CHO-H	N-H	S-H	Total no. of Protons
PTZ-I	No of proton δValueppm	6 6.5-8.0	1 2.0-2.6	1 5.0-9.0	-	8
PTZ-II	No of proton δValueppm	6 6-8	1 2.8-3.0	1 5.5-8.0	-	8
PTZ-III	No of proton δValueppm	6 5.5-8	1 3.0-3.5	1 6.0-7.6	-	8
PTZ-IV	No of proton δValueppm	5 5.6-7	1 4.0-4.5	1 6.6-7.0	-	7
PTZ-V	No of proton δValueppm	6 6.0-7.0	1 1.5-4	1 7.0-8.0	-	8

Table-3.1: C-NMR spectral data for synthesized compounds

compound code	Nature of protein	aromatic carbon	C-N	C=O	C-S	Total no. of protons
PTZ-I	No of proton δValueppm	9 113.12	1 152.14	1 39.95	1 14.2	12
PTZ-II	No of proton δValueppm	9 112.15	1 161.25	1 39.51	1 28.2	12
PTZ-III	No of proton δValueppm	9 115.02	1 162.45	1 33.45	1 28.3	12
PTZ-IV	No of proton δValueppm	10 116.71	1 160.22	1 38.12	1 16.2	13
PTZ-V	No of proton δValueppm	10 112.3	1 150.4	1 30.15	1 14.2	13

BIOLOGICAL SCREENING:

Table-4: **Analysis of molecular docking**

S.No	Compound code	Docking score
1	PTZ-I	-8.9kcal/mol
2	PTZ-II	-8.9kcal/mol
3	PTZ-III	-8.6kcal/mol
4	PTZ-IV	-8.7kcal/mol

5	PTZ-V	-8.6kcal/mol
6	ASPIRIN	-7.2kcal/mol

Table-5: Electronic properties- Mulliken charges

Atom	charge
C (1)	0.302846
C (2)	-0.298885
C (3)	-0.016195
C (4)	-0.116317
C (5)	-0.127964
C (6)	-0.136589
N (7)	-0.666559
C (8)	-0.021606
S (9)	0.389213
C (10)	-0.398432
C (11)	-0.126978
C (12)	0.256463
C (13)	-0.088983
C (14)	-0.113315
N (15)	0.035632
O (16)	-0.244300
O (17)	-0.253843
C (18)	0.141860
O (19)	-0.406723
H (20)	0.148315
H (21)	0.183887
H (22)	0.141411
H (23)	0.320414
H (24)	0.199655
H (25)	0.208490
H (26)	0.214348
H (27)	0.161827
H (28)	0.200550
H (29)	0.111776

Table-6: ***In-vitro*** **Analysis of Anti-cancer Activity**

S.NO	Compound code	nameof drug concentration	initial weight(gm)	Weight at		Drainradial length		No. of Seeds germinated		% of seed germination	
				T0(gms)	T48(gms)	T0(cm)	T48(cm)	T0	T48	T0	T48
1	**PTZ-I**	100µg/ml	1.52	3.52	3.98	0.89	0.98	9	11	45%	55%
		200µg/ml	1.55	3.92	4.68	0.85	0.91	8	11	40%	55%
		300µg/ml	1.54	3.12	4.02	0.84	0.95	9	10	45%	50%
		400µg/ml	1.56	3.35	3.46	0.85	0.94	9	11	40%	50%
		500µg/ml	1.58	3.16	3.55	0.84	0.96	8	10	45%	55%
2	**PTZ-II**	100µg/ml	1.56	3.82	4.72	1.02	1.18	10	11	50%	55%
		200µg/ml	1.56	3.64	4.32	0.52	0.58	7	9	35%	45%
		300µg/ml	1.54	3.42	4.12	0.58	0.62	6	8	30%	40%
		400µg/ml	1.54	3.44	4.15	0.57	0.54	8	8	35%	45%
		500µg/ml	1.57	3.55	4.20	0.54	0.60	7	7	30%	40%
3	**PTZ-III**	100µg/ml	1.56	3.52	4.32	1.05	0.98	9	11	45%	40%
		200µg/ml	1.54	3.54	4.21	0.82	0.97	9	9	40%	55%
		300µg/ml	1.55	3.4648	4.39	0.91	1.02	8	8	40%	55%
		400µg/ml	1.55	3.55	4.40	0.95	1.05	7	8	40%	45%
		500µg/ml	1.59	3.48	4.48	0.95	1.04	8	8	45%	55%

4	**PTZ-IV**	100µg/ml	1.52	2.73	3.93	1.32	0.82	10	11	50%	50%
		200µg/ml8	1.54	3.07	4.02	1.25	0.91	11	11	55%	60%
		300µg/ml	1.54	3.13	4.29	1.12	0.82	9	10	45%	65%
		400µg/ml	1.52	3.15	4.18	1.10	0.84	8	10	45%	60%
		500µg/ml	1.55	3.25	4.12	1.08	0.88	9	11	55%	50%
5	**PTZ-V**	100µg/ml	1.55	3.09	3.99	0.98	0.91	10	12	50%	55%
		200µg/ml	1.52	3.22	4.02	1.06	1.32	8	13	40%	60%
		300µg/ml	1.52	3.13	4.29	1.12	1.25	9	11	45%	55%
		400µg/ml	1.56	3.18	4.08	1.16	1.12	8	11	50%	55%
		500µg/ml	1.53	3.23	4.33	1.14	1.26	8	10	55%	50%
6	**standard**	100µg/ml	1.56	3.42	4.32	0.52	0.58	7	9	35%	45%
		200µg/ml	1.54	3.64	4.12	0.58	0.61	6	8	45%	40%
		300µg/ml	1.56	3.42	4.02	0.61	1.05	7	9	30%	55%
		400µg/ml	1.53	3.44	4.99	0.50	1.00	6	9	30%	55%
		500µg/ml	1.54	3.68	4.06	0.66	0.8	7	8	35%	50%

Table-7: ***In-vitro*** **Analysis of Anti-inflammatory Activity**

S.No	Name of the Compounds	Absorbance Value (Mean)	% Inhibition
1	PTZ-I	1.564	50.9
2	PTZ-II	1.904	92.1
3	PTZ-III	1.826	57.9
4	PTZ-IV	1.753	56.2
5	PTZ-V	1.650	53.4
6	STANDARD	0.142	89.5
7	CONTROL	0.265	0

Table-8: ***In-vitro*** **Analysis of Anti-oxidant Activity**

S.No	Name of the Compounds	Absorbance Value (Mean)	% Inhibition
1	PTZ-I	0.3040	59.0
2	PTZ-II	0.2208	70.2
3	PTZ-III	0.4726	36.4
4	PTZ-IV	0.4934	33.5
5	PTZ-V	0.1402	81.1
6	Standard	0.7678	86.4
7	control	0.5665	0

4. RESULTS

Compounds synthesized were screened for anti-Cancer activity. The length of the used Mung beans are measured at regular intervals. Among all the screened compounds PTZ-3&PTZ-4 had shown potent activity compared to standard. Compounds synthesized were screened for Anti-inflammatory activity using inhibition of albumin denaturation and then turbidity was measure at 240nm. Among all the screened compounds PTZ-II had shown the potent a activity compared to standard. Compounds synthesized were screened for Anti-oxidant activity among all the screened compounds PTZ-V had shown the potent a activity compared to standard. Perform the molecular docking studies for anti-Cancer activity using AutoDock Software, kDM5 is collected from protein data bank.

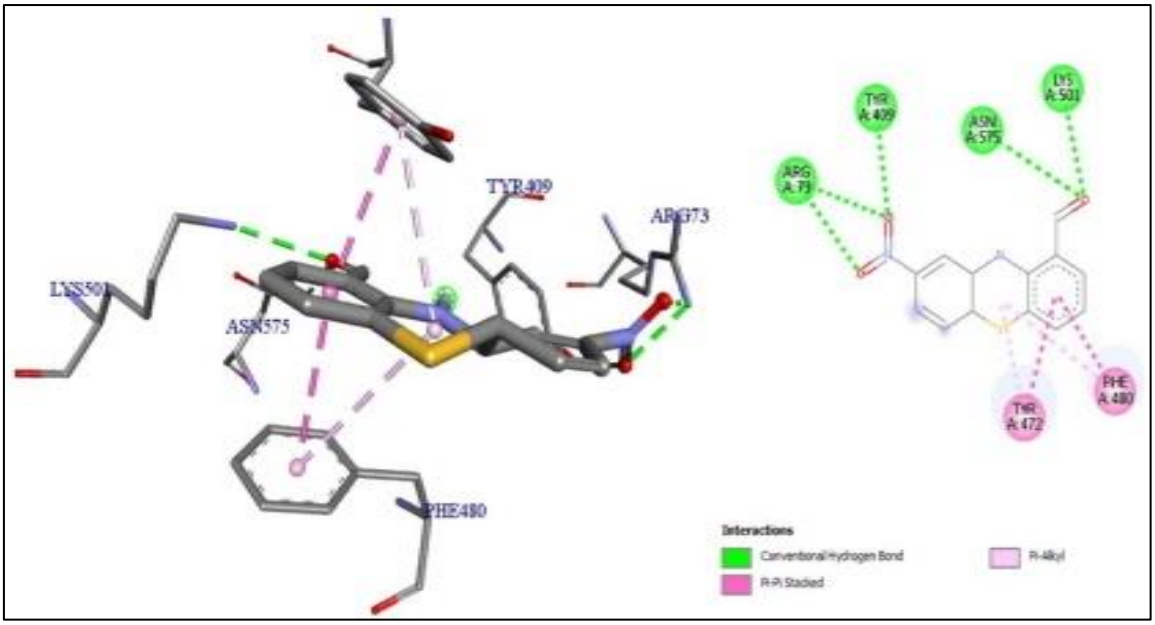


Figure-1: PTZ-1

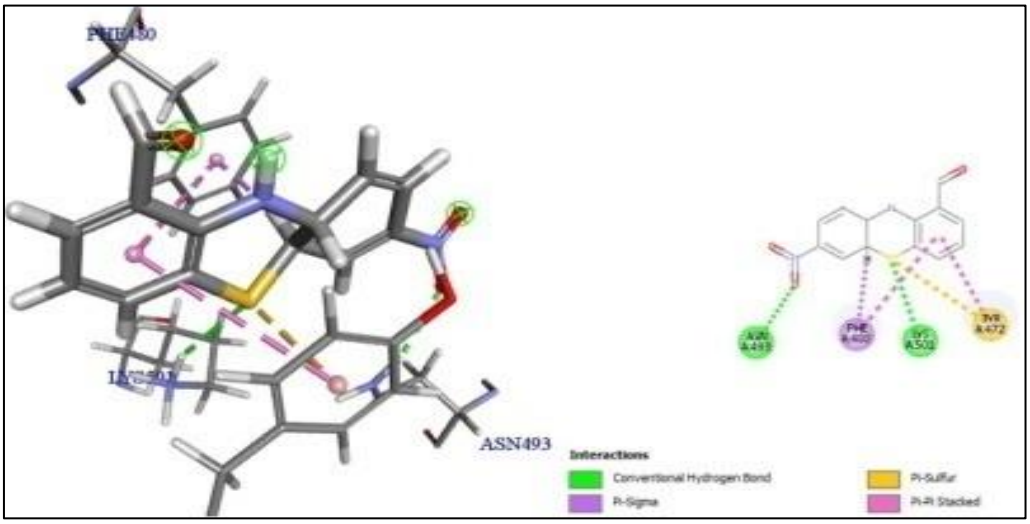


Figure-2: PTZ-2

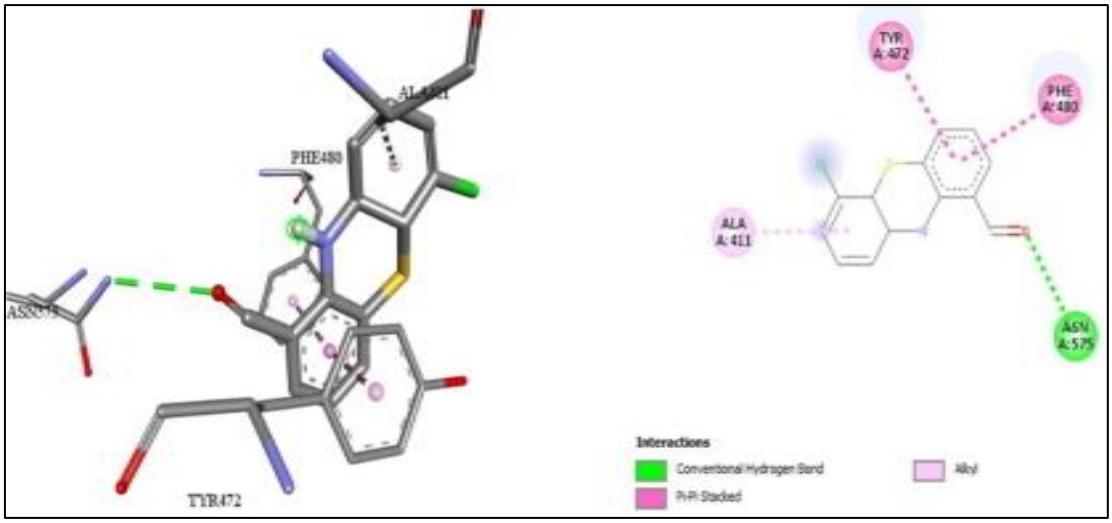


Figure-3: PTZ-3

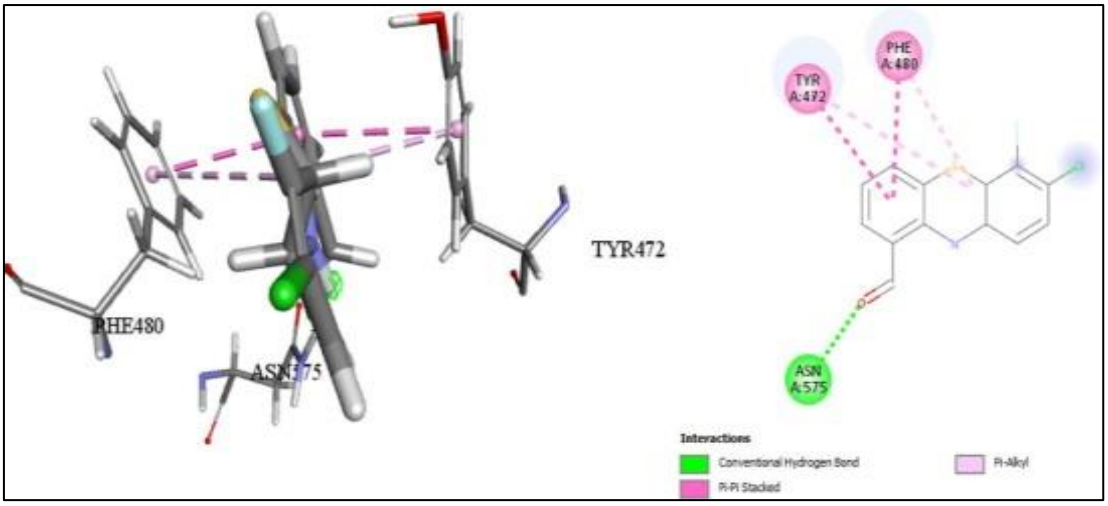


Figure-4: PTZ-4

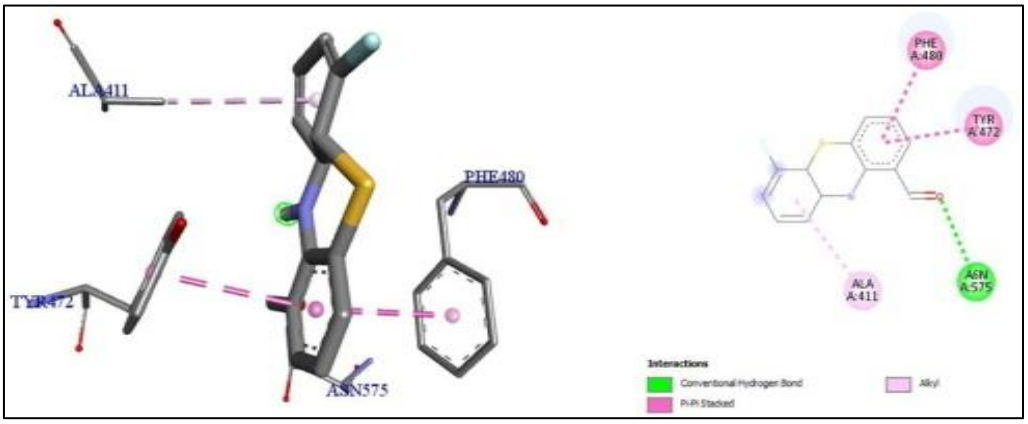


Figure-5: PTZ-5

IR Spectral Studies:

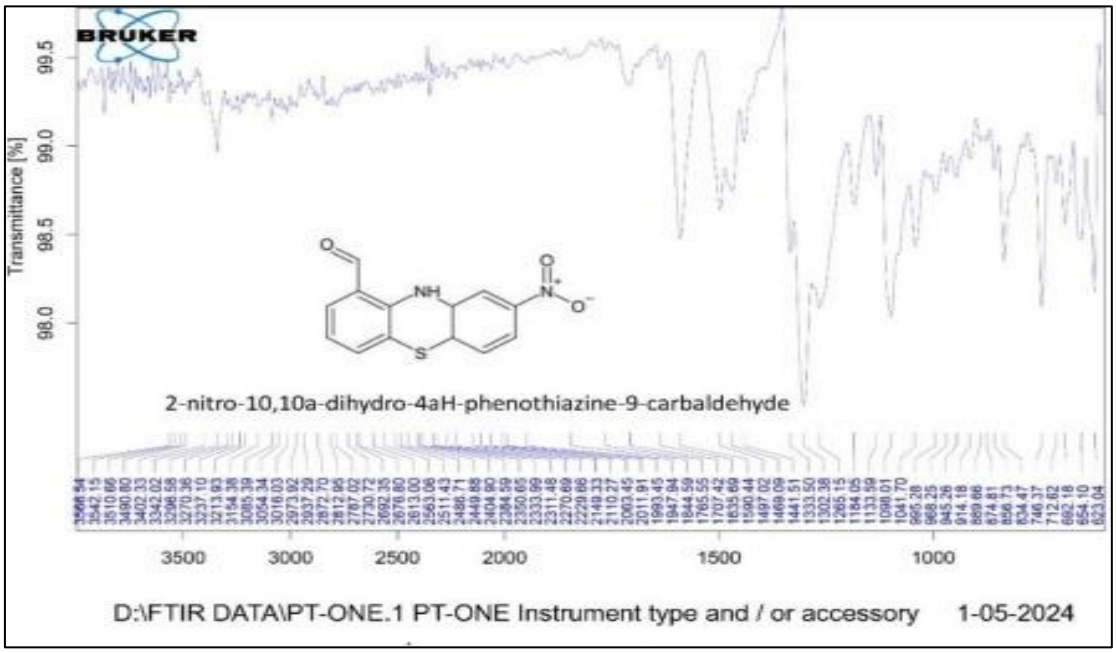


Figure-6: IR Spectroscopy for PTZ-1

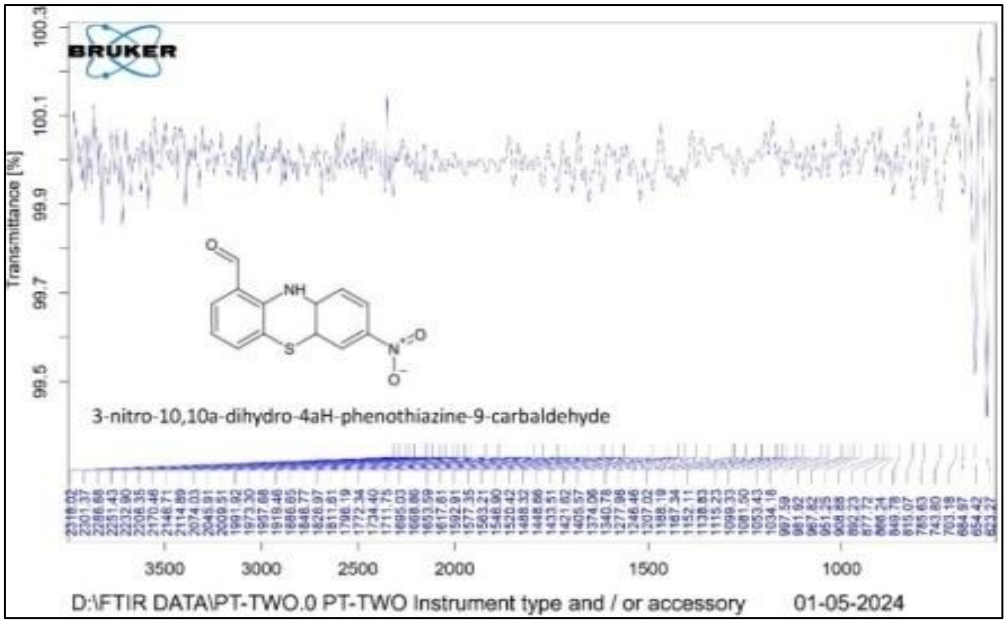


Figure-7: IR Spectroscopy for PTZ-2

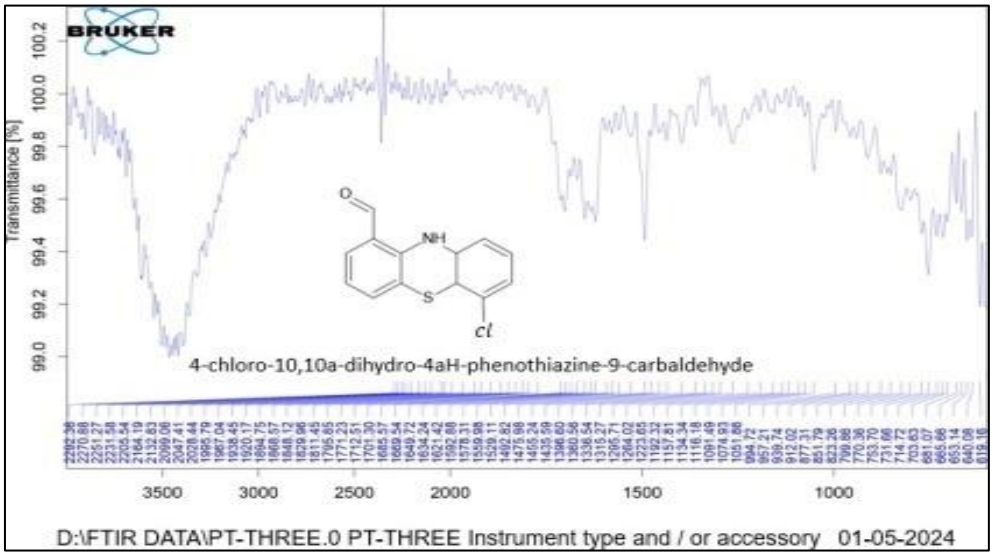


Figure-8: IR Spectroscopy for PTZ-3

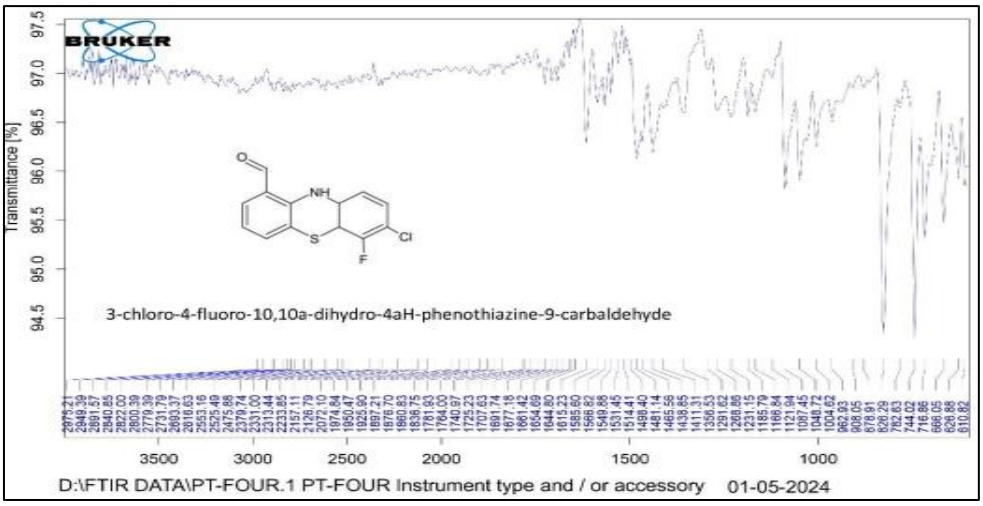


Figure-9: IR Spectroscopy for PTZ-4

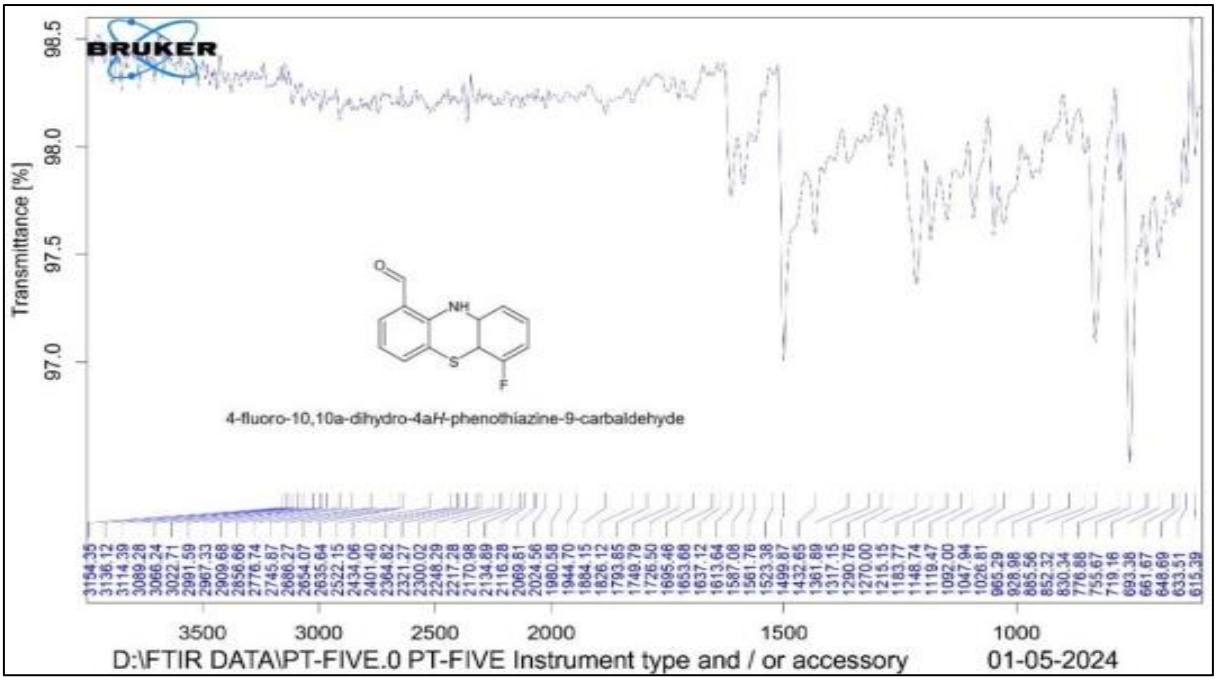


Figure-10: IR Spectroscopy for PTZ-5

NMR spectral studies

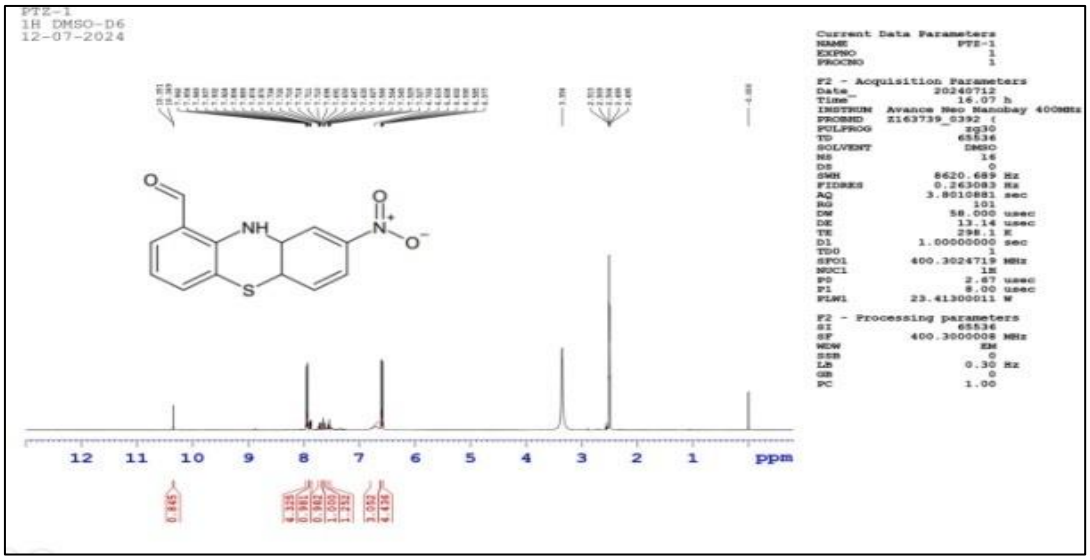


Figure-11: ^{1}H NMR Spectroscopy for PTZ-1

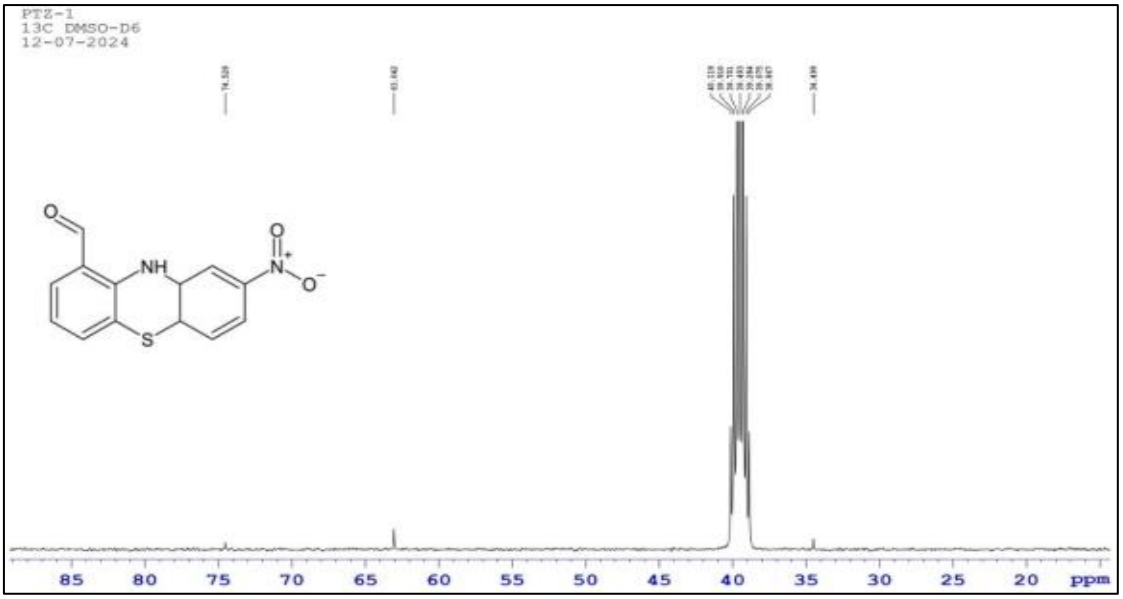


Figure-12: C NMR Spectroscopy for PTZ-1

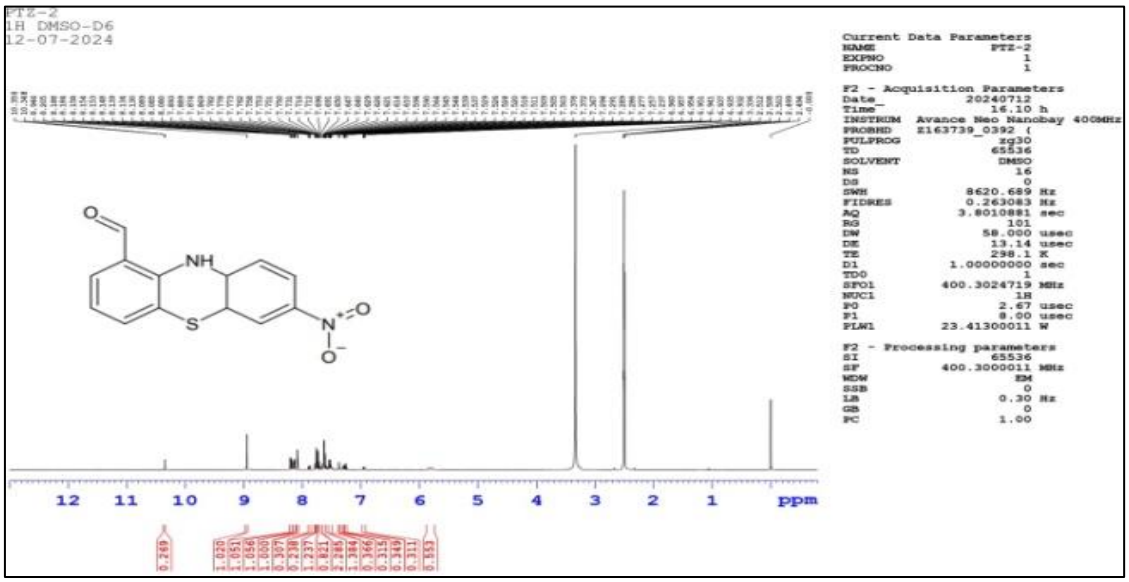


Figure-13: ^{1}H NMR Spectroscopy for PTZ-2

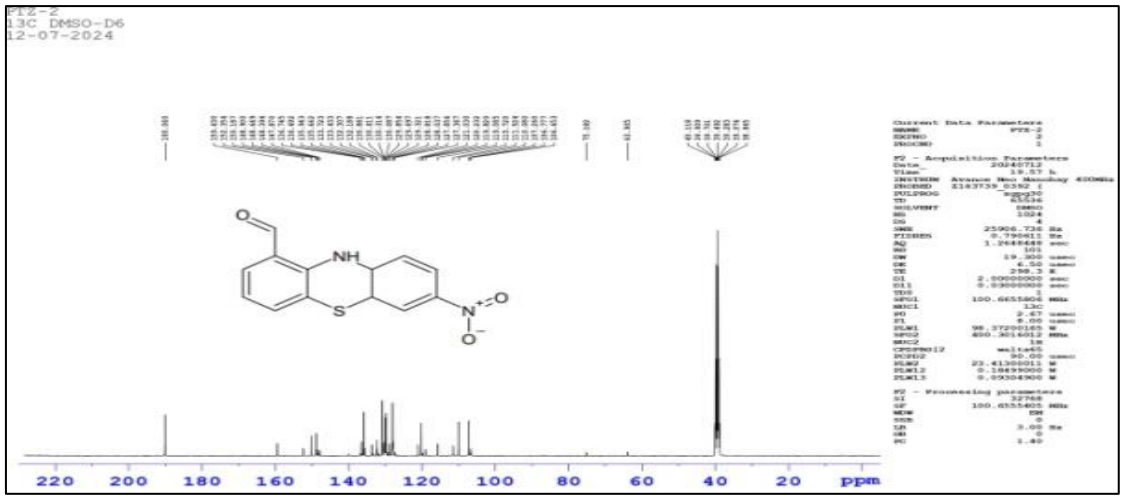


Figure-14: C NMR Spectroscopy for PTZ-2

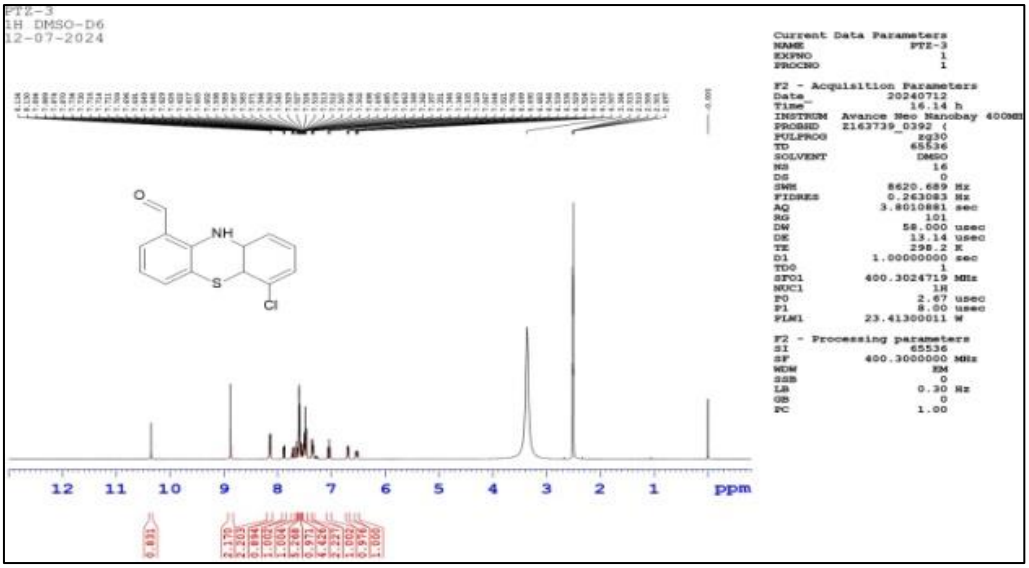


Figure-15: ^{1}H NMR Spectroscopy for PTZ-3

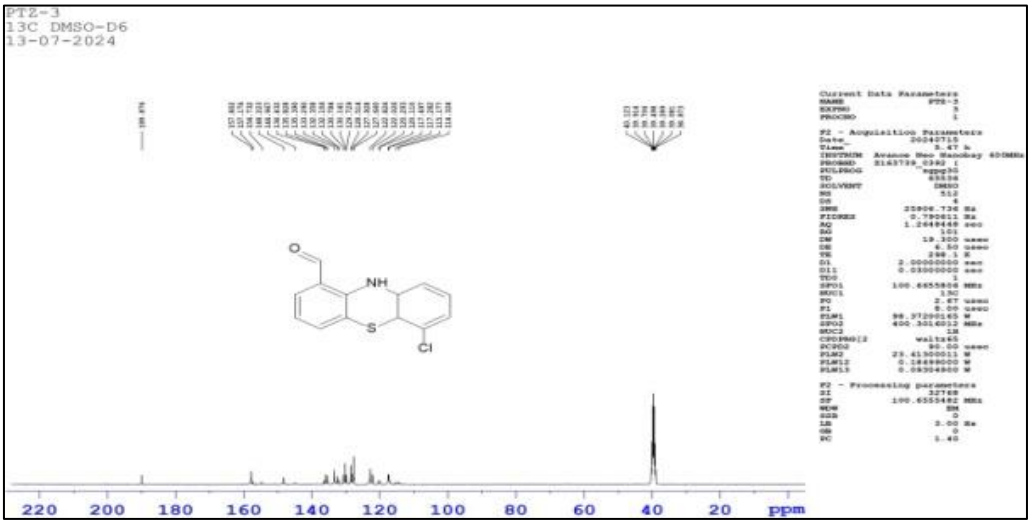


Figure-16: C NMR Spectroscopy for PTZ-3

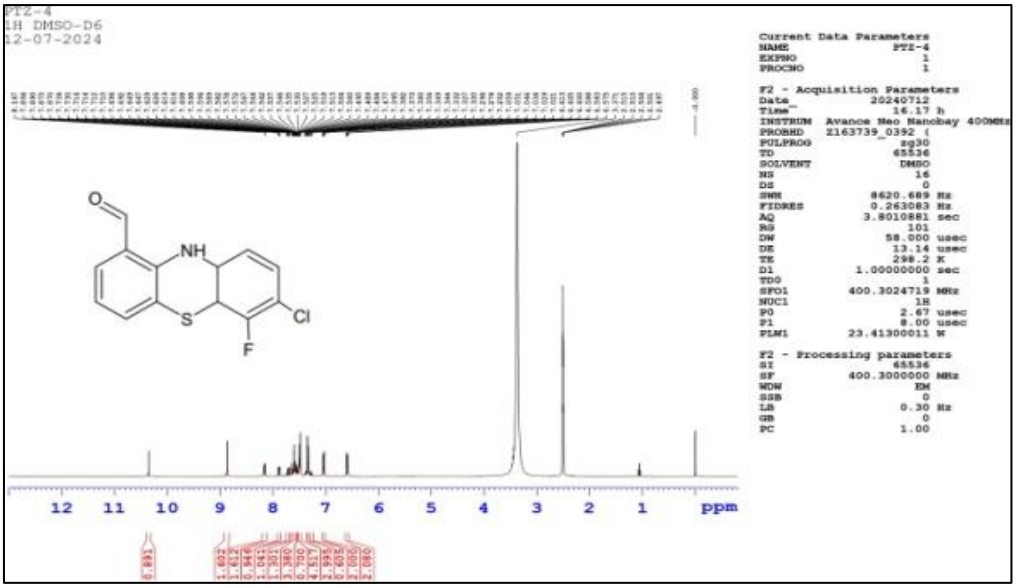


Figure-17: ^{1}H NMR Spectroscopy for PTZ-4

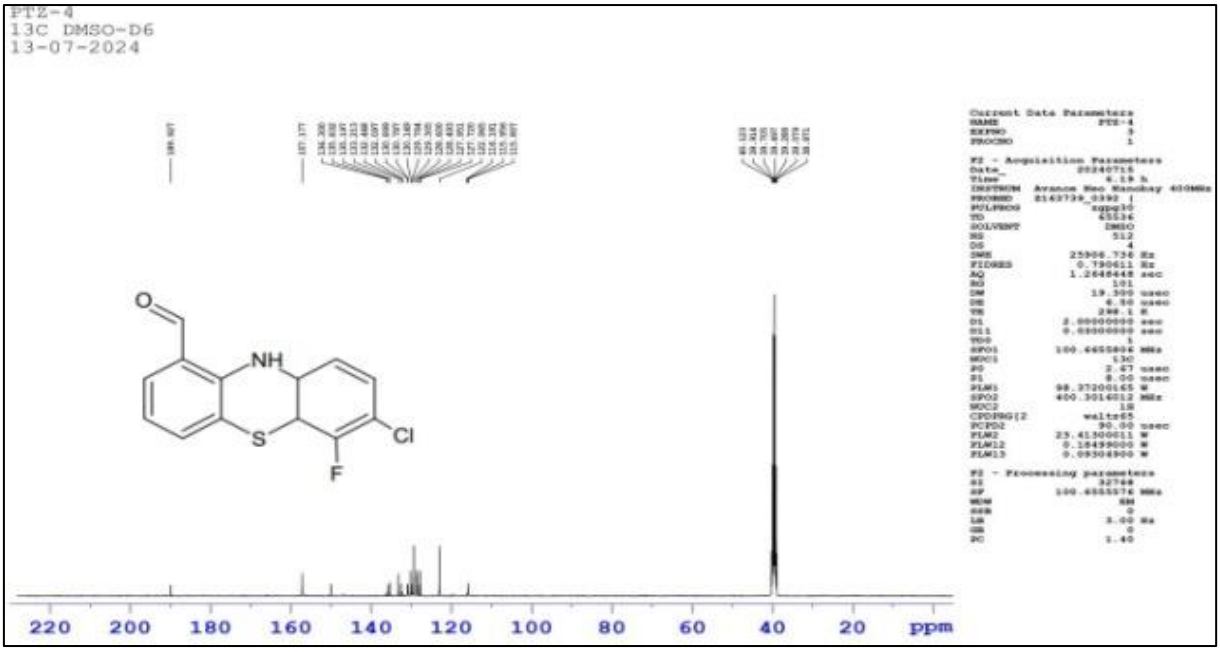


Figure-18: C NMR Spectroscopy for PTZ-4

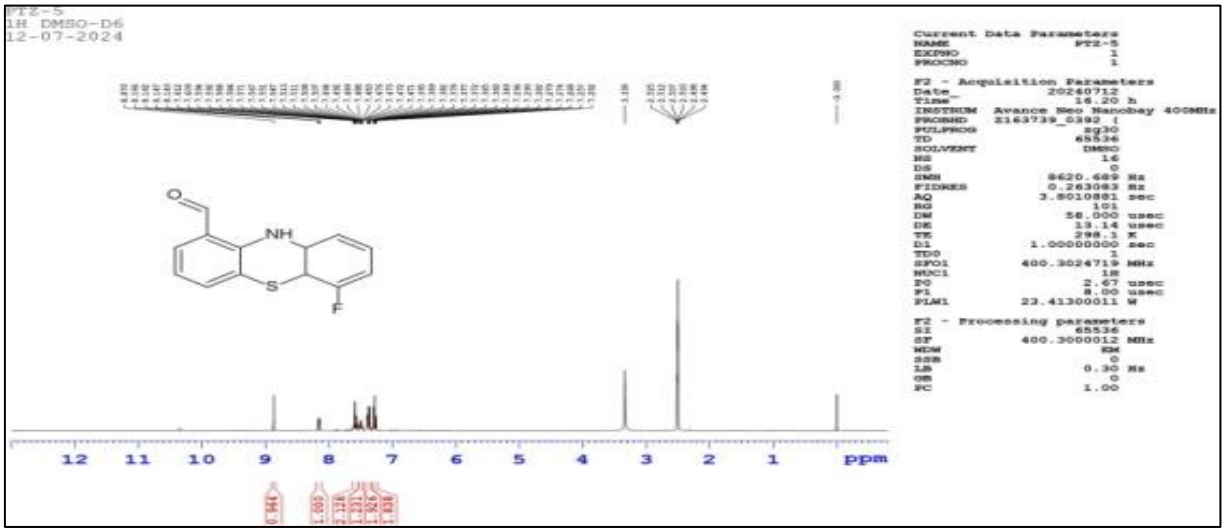


Figure-19: ^{1}H NMR Spectroscopy for PTZ-5

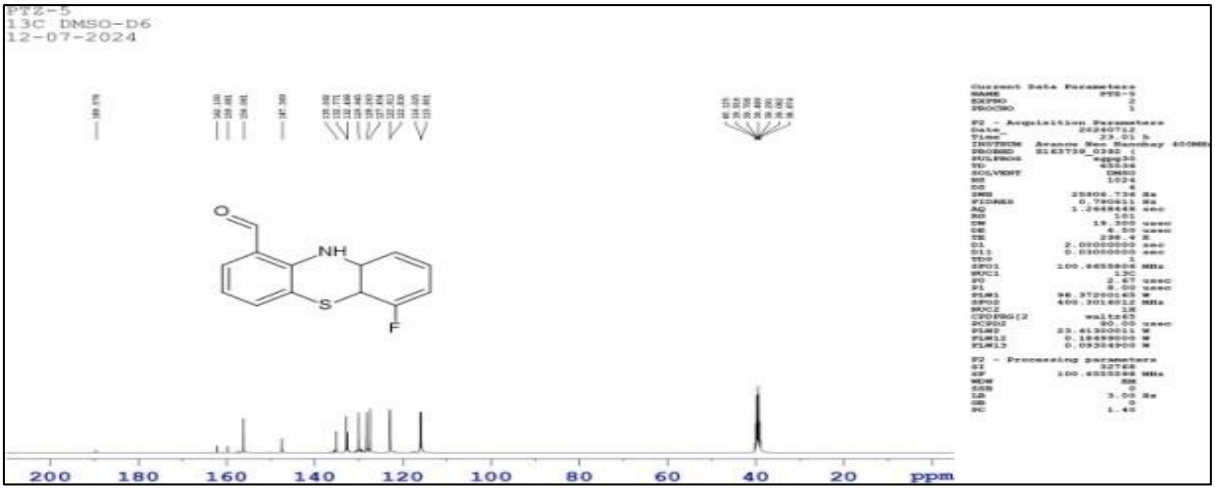
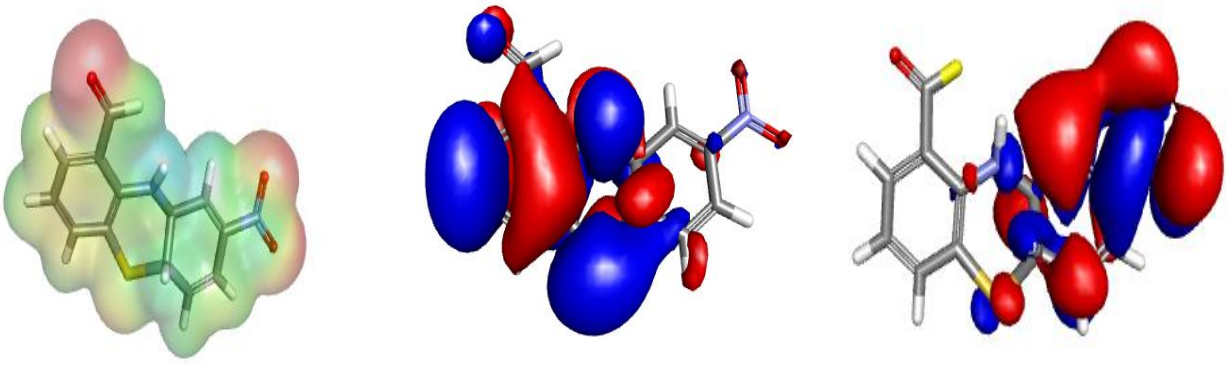


Figure-20: C NMR Spectroscopy for PTZ-5

HOMO LUMO Results:



HOMO = -0.22290Ha = -6.065eV

LUMO = -0.12589Ha = -3.426eV

Band Gap Energy (Ha) = 0.0884351= 2.406 eV

Figure-21 DFT Energy calculations

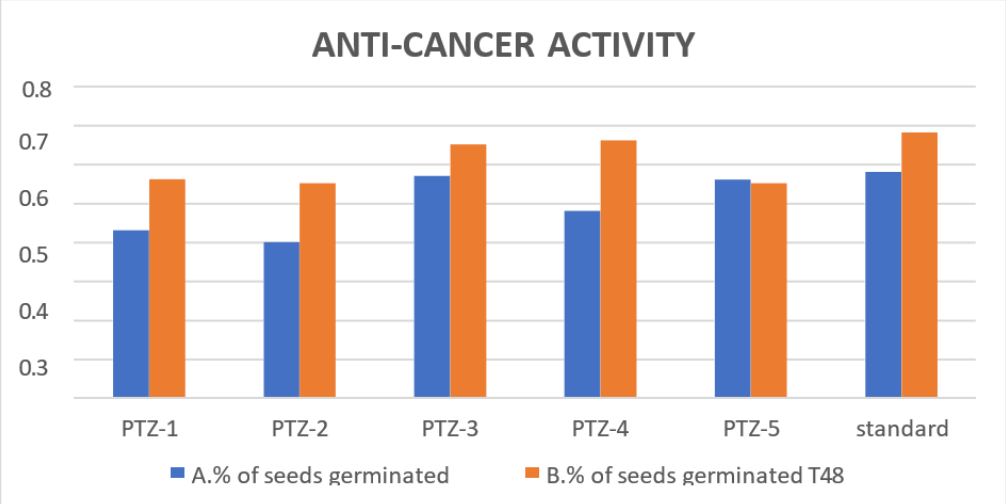


Figure-22: *In-Vitro* Anti-cancer activity

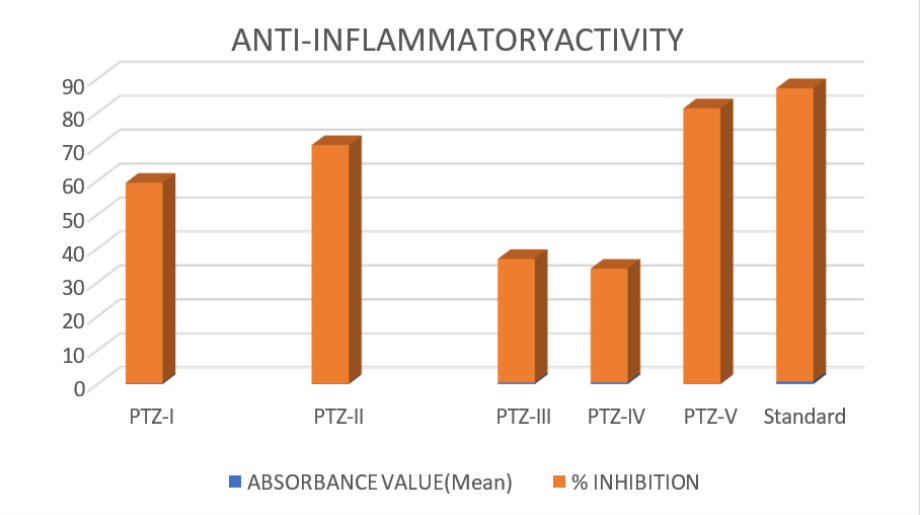


Figure-23: *In-Vitro* Anti-Inflammatory activity

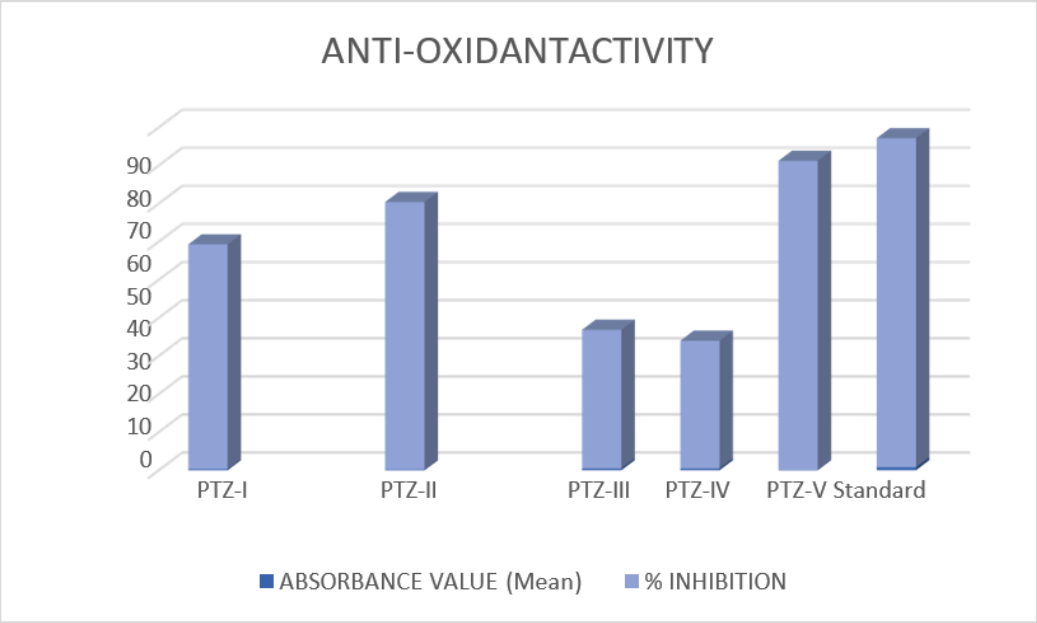


Figure-24: *In-Vitro* Anti-Oxidant activity

5. DISCUSSION

In the present study, Novel 9,10 phenothiazine derivatives were synthesized and characterized by TLC, IR, NMR and Mass spectroscopic data. All synthesized (PTZ-1to PTZ-5) were screened for Docking studies and also for *in-vitro* Anti Cancer, Anti-oxidant and Anti-Inflammatory. Molecular docking studies of title compounds for Anti Cancer Activity using Buffer and Aspirin as standard, (5ive) had shown the compounds PTZ-3, PTZ-4, PTZ-5, PTZ-1, PTZ-2 were potent compared to standard and other title compounds.

Evaluation of *in-vitro* anti-inflammatory activity was screened for synthesized compounds using Ibuprofen as standard and (COX-II) had shown the compounds PTZ-2, PTZ-3, PTZ-4, PTZ-5, PTZ-1 were potent compared to standard and other title compounds. Evaluation of in-vitro anti -oxidant activity was screened for synthesized compounds using ascorbic acid as standard. PTZ-5, PTZ-2, PTZ-1, PTZ-3, PTZ-4 had shown the significant activity.

6. CONCLUSION

From this study, it is concluded that 9,10 substituted phenothiazine derivatives incorporation of various halogenated compounds at 1,2&3 positions and cyclization with sulfur to the benzaldehyde would produce new compounds with potent biological activities like anti cancer, anti- inflammatory and anti-oxidant Activity. All the synthesized compounds would deserve for further advanced investigation and will be perform *in-vivo* studies for anti-cancer, anti-inflammatory and anti-oxidant.

LIST OF ABBREVATIONS

PTZ- Phenothiazine
NMR- Nuclear magnetic resonance
IR- Infrared spectroscopy
kDM5- Lysine-specific demethylase 5A
HOMO-Highest occupied molecular orbital
LUMO- Lowest unoccupied molecular orbital

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CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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