INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Research Article

Design, Synthesis, Biological Evaluation And *In-Silico* Studies Of Nitrogen Containing Aryl Scaffolds As Antioxidant Agents

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ARTICLE INFO

Published: 20 Oct 2024
Keywords:
Nitrogen scaffolds, Antioxidant Activity, In-silico Docking.
DOI:
10.5281/zenodo.13957212

ABSTRACT

Research on the development of antioxidant drugs containing heterocyclic scaffolds, such as pyrimidine, benzothiazole, indole and an aryl moiety like aniline were shown a significant class in a medical field to treatise various ailments to our mankind. Furthermore, it has been established that these derivatives have a number of antioxidant properties. Nitrogen scaffolds play a responsive role in the treatment of infections. In the present inquiry, we brought together several aspects of twelve nitrogen containing aryl-heterocyclic derivatives (AB1-AB3, BT1-BT3, IC1-IC3, AN1-AN3) altered at the ortho, meta, and para-positions of the ring by various functional groups, and their in-silico activity was assessed towards Antioxidant (1KXM) inhibition. The efficacy of synthesized derivatives was evaluated using DPPH Radical Scavenging Method. The spectral characterization of the test compounds are analyzed.

INTRODUCTION

Antioxidants are chemicals that stop the oxidation of other molecules from harming cells. Numerous human diseases, including cellular necrosis, CVS disease, cancer, neurological disorder, Parkinson's dementia, Alzheimer's disease, inflammatory disease, etc., are greatly influenced by oxidative stress. Compounds containing hydroxyl groups at the para position of the aromatic ring confer a better radical scavenging activity compared to those with hydroxyl groups in other positions [1]. 2-Aminopyrimidine has great importance as pyrimidine is widely spread in living organisms. Gabriel and Colman first isolated pyrimidine in 1899. 2-Aminopyrimidine and its derivatives have a broad spectrum of biological activities. A large number of heterocyclic compounds derived from chalcone group have been reported as active biological entities, where 2-aminopyrimidine play a vital role owing to their wide range of therapeutic activities [2]. 2-Aminobenzothiazole moiety is

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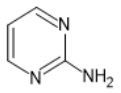
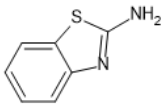
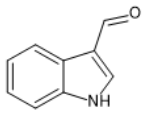
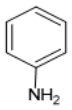
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

present in various bioactive molecules such as imaging agents for antitumor, antimicrobial, antifungal, orexin receptor antagonist and the Gram positive selective antibacterial. Benzothiazoles, which have benzene and thiazole rings, are utilized in numerous medicines worldwide. Chemical compounds like benzothiazoles and their heterocyclic derivatives have several biological impacts [3]. Indole-3-carboxaldehyde is an essential scaffold and intermediates enabling the generation of numerous synthetic and natural substances with therapeutical impacts, especially those retaining antitumor, antidepressant, antimicrobial, antiviral, anthelmintic and inhibitory effects on transcription and DNA replication as well as their muscle relaxant properties [4]. Aniline is an organic compound consisting of a phenyl group attached to an amino group, it is the simplest aromatic amine. Industrially significant commodity chemical, as well as a versatile starting material for fine chemical synthesis. In recent years, macrocyclization is a promising strategy in modern drug design, as it can minimize the entropic loss associated with the ligand adopting a favorable conformation, which may lead to a gain of potency and selectivity. "Schiff bases" emerged with the 1864 report of German scientist Hugo Schiff [5]. Drug discovery, drug design, testing, and development constitute the extensive and intricate steps involved in sketching a pharmacological molecule. A specific type of software called docking programs is often used in drug design. These programs facilitate in the binding of ligands, or small molecules, to proteins, or larger molecules with biological significance [6]. Thus, by keeping this above idea in our mind we had synthesized certain Novel Schiff bases containing the following Heteroaryl scaffolds viz., 2-aminopyrimidine, 2-aminobenzothiazole, Indole-3-carboxadehyde & aniline.

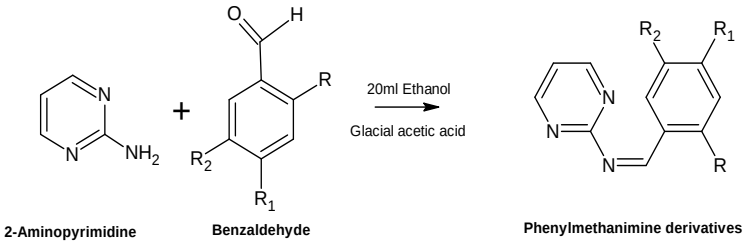
			
2-Aminopyrimidine	2-Aminobenzothiazole	Indole-3-carboxaldehyde	Aniline

In this study we aim for the docking studies of the synthesized compounds using PyRx tools.

EXPERIMENTAL

MATERIALS AND METHODS

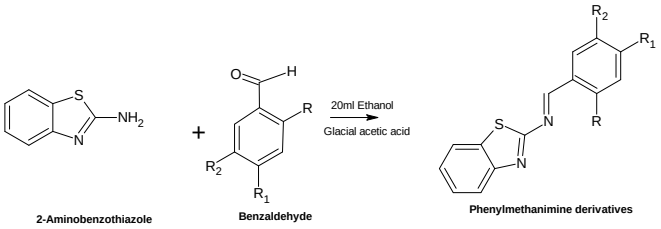
2-aminopyrimidine, 2-aminobenzothiazole, Indole-3-Carboxaldehyde and aniline were acquired from Sigma -Aldrich USA. Melting points of all the synthesized were determined by open capillary tube methods and values were uncorrected. The 2-aminopyrimidine derivatives [AB1-AB3] (Fig.2.1), 2-aminobenzothiazole derivatives [BT1-BT3] (Fig.2.2), Indole-3-carboxaldehyde derivatives [IC1-IC3] (Fig.2.3) and Aniline derivatives [AN1-AN3] (Fig.2.4), are synthesized.



2-Aminopyrimidine Benzaldehyde Phenylmethanimine derivatives

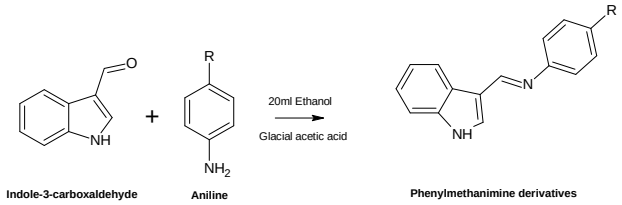
Compound Code	R	R_1	R_2
AB_1	H	Cl	H
AB_2	Cl	H	NO_2
AB_3	H	NO_2	H

Figure 1: - Scheme for the Synthesis of 2-aminopyrimidine derivatives



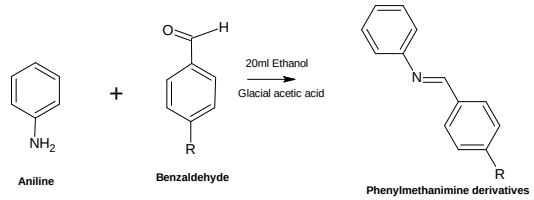
Compound Code	R	R_1	R_2
BT_1	H	Cl	H
BT_2	Cl	H	NO_2
BT_3	H	NO_2	H

Figure 2: - Scheme for the Synthesis of 2-aminobenzothiazole derivatives



Compound Code	R
IC_1	Cl
IC_2	NO_2
IC_3	H

Figure 3: - Scheme for the Synthesis of Indole-3-carboxaldehyde derivatives



Compound Code	R
AN_1	Cl
AN_2	NO_2
AN_3	H

Figure 4: - Scheme for the Synthesis of Aniline derivatives

ANTIOXIDANT ACTIVITY

PRINCIPLE

Antioxidants are the compounds capable to either delay or inhibit the oxidation processes which occur under the influence of atmospheric oxygen or reactive oxygen species. DPPH free scavenging method is based on reduction of DPPH in ethanol in presence of hydrogen donation due to the formation of non-radical form DPPH.

PROCEDURE

The antioxidant activity of sample is determined by DPPH scavenging assay method. A solution of

DPPH was prepared by dissolving 12.5mg of DPPH in 50ml ethanol. The absorbance of stock solution was diluted with ethanol to an absorbance of 0.98 different concentrations (20, 40, 60,80,100µg/ml) of sample was prepared in ethanol, then added to 1ml of DPPH solution.

This reaction mixture was incubated at 37°C darkness for 20-30min. The absorbance was determined at 517nm. Ascorbic acid was used as standard.

MOLECULAR DOCKING METHODOLOGY

In the current molecular simulation study, PyRx Software was used to constitute a ligand-based computer modeling program for forecasting binding energy of the selected compound [7]. The structures of all synthesized compounds are produced using Chemsketch software (http://www.acdlabs.com/resources/freeware).

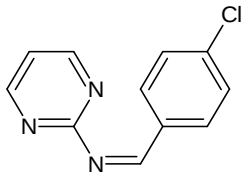
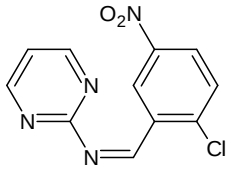
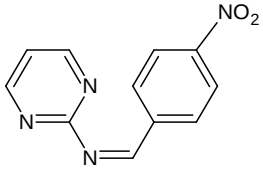
Chem3D pro 8.0 was utilized to optimize the structures and to minimize energy. Molecular docking was performed out using the optimized compounds.

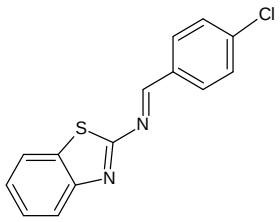
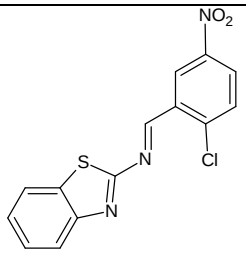
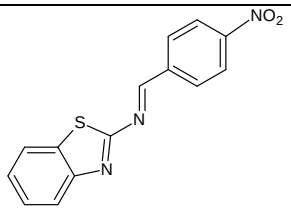
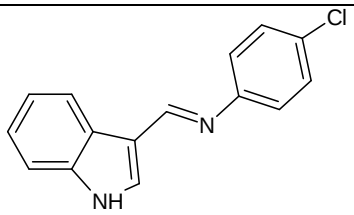
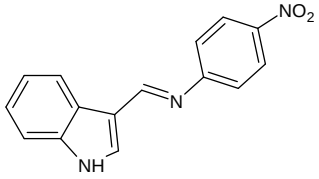
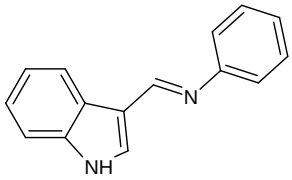
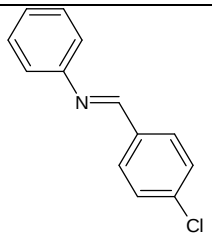
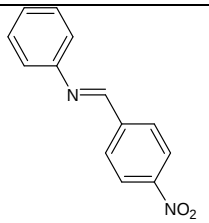
A. **PREPARATION OF GRID AND DOCKING PARAMETERS**

The 3D structure of the molecular target was taken from Protein Data Bank (PDB) (www.rcsb.org). Loading the molecules in to PyRx workspace. Converting the pdb file to pdbqt files. Select the protein and ligand by simply clicking and run vina. Select vina search space. Enclose the labels within grid box. The active sites were selected using grid boxes around the bound cocrystal ligands, which was like this: number of grid points (60×60×60), center (xyz coordinates) and the grid point spacing was 0.375 Å. In order to correlate the test compounds for their respective activity and to examine their in-silico interaction, they were docked into the active site. Click forward button to start vina calculations. Once the calculations are done, results will be populated by giving binding affinity (Kcal/mol) values. Docking study was performed using PyRx Software and Discovery Studio is utilized for visualization.

RESULTS AND DISCUSSION

Table 1: Synthesized Test compounds

Sr No.	COMPOUND CODE	STRUCTURE	NAME
1.	AB_1		(*Z*)-1-(4-chlorophenyl)-*N*-(pyrimidin-2-yl)methanimine
2.	AB_2		(*Z*)-1-(2-chloro-5-nitrophenyl)-*N*-(pyrimidin-2-yl)methanimine
3.	AB_3		(*Z*)-1-(4-nitrophenyl)-*N*-(pyrimidin-2-yl)methanimine

4.	BT_1		(*E*)-*N*-(1,3-benzothiazol-2-yl)-1-(4-chlorophenyl)methanimine
5.	BT_2		(*E*)-*N*-(1,3-benzothiazol-2-yl)-1-(2-chloro-5-nitrophenyl)methanimine
6.	BT_3		(*E*)-*N*-(1,3-benzothiazol-2-yl)-1-(4-nitrophenyl)methanimine
7.	IC_1		(*E*)-*N*-(4-chlorophenyl)-1-(1*H*-indol-3-yl)methanimine
8.	IC_2		(*E*)-1-(1*H*-indol-3-yl)-*N*-(4-nitrophenyl)methanimine
9.	IC_3		(*E*)-1-(1*H*-indol-3-yl)-*N*-phenyl methanimine
10.	AN_1		(*E*)-1-(4-chlorophenyl) -*N*-phenylmethanimine
11.	AN_2		(*E*)-1-(4-nitrophenyl) -*N*-phenylmethanimine

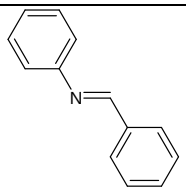
12.	AN_3		(*E*)-*N*,1-diphenylmethanimine

Table 2: Physiochemical properties of Test compounds

Compound Code	Molecular Formula	Molar Refractivity (cm^3)	Molar Volume (cm^3)	Melting Point (°C)	Density (g/cm^3)	R_f Value	Colour
AB_1	$C_{11}H_8ClN_3$	61.90 ± 0.5	176.0 ± 7.0	58	1.23 ± 0.1	0.235	Off White
AB_2	$C_{11}H_7ClN_4O_2$	67.56 ± 0.5	181.5 ± 7.0	62	1.44 ± 0.1	0.719	Cream
AB_3	$C_{11}H_8N_4O_2$	62.96 ± 0.5	172.1 ± 7.0	55-57	1.32 ± 0.1	0.326	White
BT_1	$C_{14}H_9ClN_2S$	77.93 ± 0.5	205.7 ± 7.0	115	1.32 ± 0.1	0.147	Cream
BT_2	$C_{14}H_8ClN_3O_2S$	83.59 ± 0.5	211.0 ± 7.0	131	1.50 ± 0.1	0.366	Light Brown
BT_3	$C_{14}H_9N_3O_2S$	78.99 ± 0.5	201.7 ± 7.0	120	1.40 ± 0.1	0.214	Cream
IC_1	$C_{15}H_{11}ClN_2$	74.73 ± 0.5	207.2 ± 7.0	101	1.22 ± 0.1	0.236	Pale Yellow
IC_2	$C_{15}H_{11}N_3O_2$	75.79 ± 0.5	203.3 ± 7.0	58-62	1.30 ± 0.1	0.357	Light Yellow
IC_3	$C_{15}H_{12}N_2$	70.13 ± 0.5	197.9 ± 7.0	93.2	1.11 ± 0.1	0.262	Yellow
AN_1	$C_{13}H_{10}Cl\ N$	65.01 ± 0.5	198.8 ± 7.0	125	1.08 ± 0.1	0.435	Light Brown
AN_2	$C_{13}H_{10}N_2\ O_2$	66.07 ± 0.5	194.9 ± 7.0	109	1.16 ± 0.1	0.324	Off White
AN_3	$C_{13}H_{11}N$	60.41 ± 0.5	189.5 ± 7.0	137	0.95 ± 0.1	0.462	Cream

DOCKING RESULTS OF ANTIOXIDANT ACTIVITY

The newly synthesized nitrogen containing aryl-heterocyclic derivatives were subjected to docking using PDB:1KXM (Antioxidant) with the aid of PyRx software. The docking results were shown in Table 5.14. In which Compound BT2 and AB2 shows maximum binding affinity of -9.7 and -8.7, Compound AN1 and AN2 shows minimum binding affinity of -7.5 and -7.6 against antioxidant protein (PDB ID: 1KXM) when compared with the standard drug Ascorbic acid.

Table 3: Docking Results of test compounds against Antioxidant protein (PDB ID: 1KXM)

SI NO.	COMPOUND CODE	Binding Affinity (kcal/mol)
1	AB_1	-8.2
2	AB_2	**-8.7**
3	AB_3	-8.0
4	BT_1	-8.3
5	BT_2	**-9.7**
6	BT_3	-8.6
7	IC_1	-8.5
8	IC_2	-7.9
9	IC_3	-8.2
10	AN_1	-7.5
11	AN_2	-7.6
12	AN_3	-8.2

13	Ascorbic Acid	-5.7

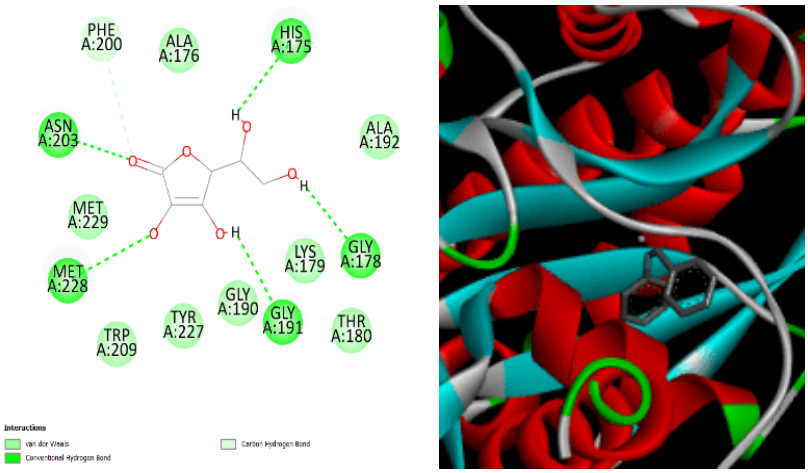


Figure 1: Binding Surface and 2D ligand interaction diagram of Standard (Ascorbic acid)

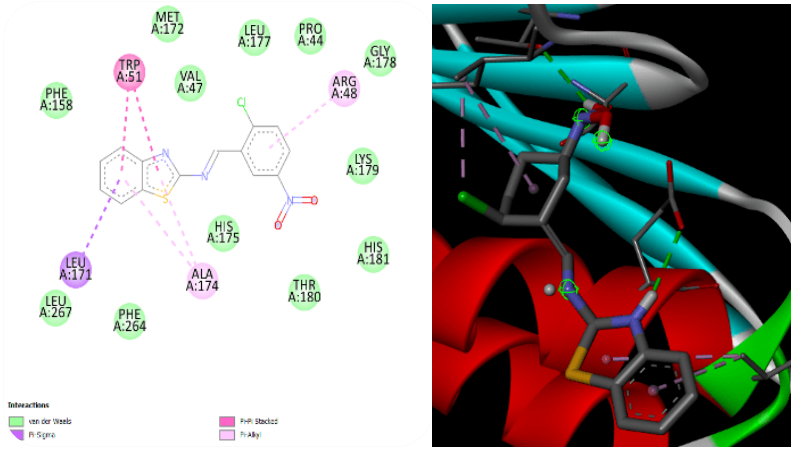


Figure 2: Binding Surface and 2D ligand interaction diagram of Compound BT2

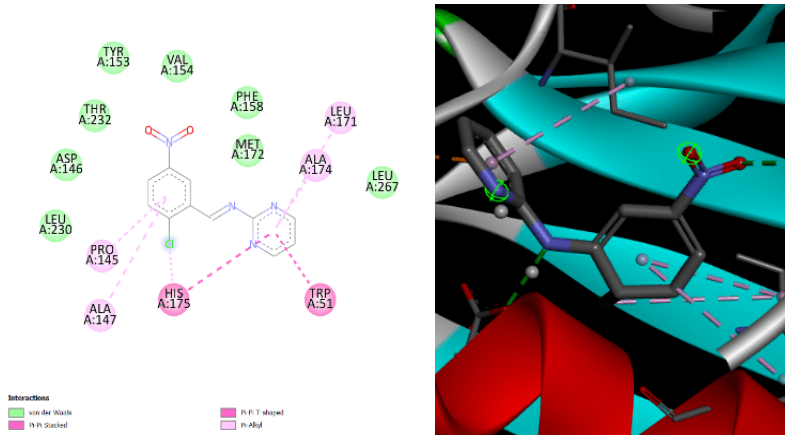


Figure 3: Binding Surface and 2D ligand interaction diagram of Compound AB2.

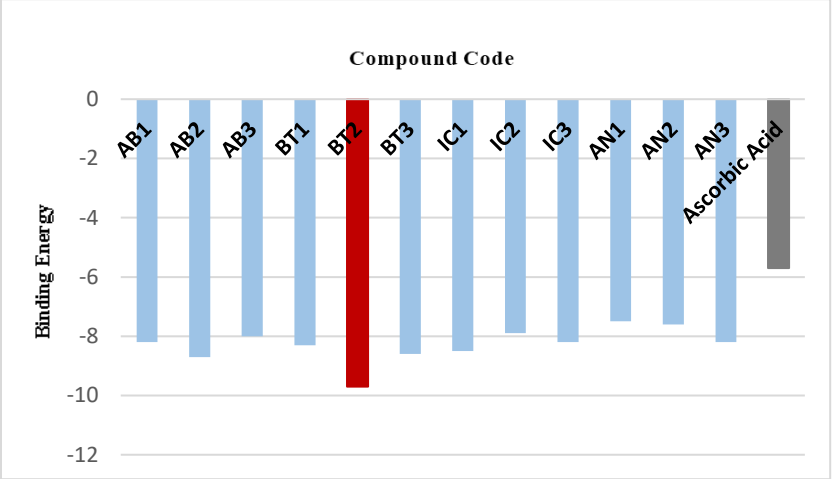


Figure 4: Histogram of Docking results of test compounds on Antioxidant activity

ANTIOXIDANT STUDIES (DPPH Radical Scavenging Method)

The newly synthesized compounds were screened for their invitro antioxidant activity by DPPH radical scavenging activity. The compounds were tested at various concentrations (0.2, 0.4, 0.6, 0.8, 1.0 µg/mL) and the Q(%) values had been determined for each compound and compared with control as well as standard antioxidants. l-ascorbic acid (AA) was used as the standard antioxidants. In DPPH radical scavenging activity assay, the purple chromogen radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) is reduced by antioxidant/reducing compounds to the corresponding pale-yellow hydrazine. The scavenging capacity is generally evaluated in organic media by monitoring the absorbance decrease at 515– 528nm until the absorbance remains constant or by electron spin resonance. DPPH radical is reduced by antioxidants and causing absorbance decrease at 515nm is the principle of measurement of this assay.

ANTIOXIDANT ACTIVITY OF STANDARD: ASCORBIC ACID

Table 4: Antioxidant activity of standard (Ascorbic acid)

CONCENTRATION (µg/mL)	ABSORBANCE	Q(%)
0.2	0.731	20.5434
0.4	0.864	6.0869
0.6	0.872	5.2174
0.8	0.878	4.5652
1.0	0.891	3.1521

ANTIOXIDANT ACTIVITY OF TEST COMPOUND AB2

Table 5: Antioxidant activity of test compound AB

CONCENTRATION (µg/mL)	ABSORBANCE	Q(%)
0.2	0.421	54.2391
0.4	0.445	51.6304
0.6	0.430	53.2608
0.8	0.477	48.1521
1.0	0.474	48.4782

ANTIOXIDANT ACTIVITY OF TEST COMPOUND BT2

Table 6: Antioxidant activity of test compound BT2

CONCENTRATION (µg/mL)	ABSORBANCE	Q(%)
0.2	0.478	48.0434
0.4	0.454	50.6521
0.6	0.463	49.6739
0.8	0.487	47.0652
1.0	0.475	48.3695

ANTIOXIDANT ACTIVITY OF TEST COMPOUND IC2

Table 7: Antioxidant activity of test compound IC2

CONCENTRATION (µg/mL)	ABSORBANCE	Q(%)
0.2	0.421	54.2391
0.4	0.463	49.6739
0.6	0.487	47.0652
0.8	0.475	48.3695
1.0	0.474	48.4782

ANTIOXIDANT ACTIVITY OF TEST COMPOUND AN2

Table 8: Antioxidant activity of test compound AN2

CONCENTRATION (µg/mL)	ABSORBANCE	Q(%)
0.2	0.454	50.6521
0.4	0.463	49.6739
0.6	0.487	47.0652
0.8	0.477	48.1521
1.0	0.474	48.4782

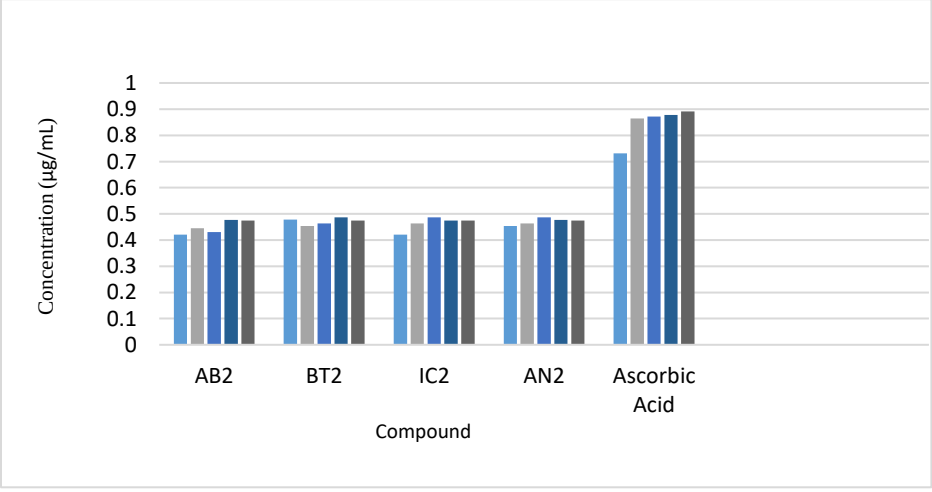


Figure 5: Graphical representation of Antioxidant activity results

SPECTRAL CHARACTERIZATION

Table 9: Absorbance of tested compounds obtained from UV spectroscopy

Compound Code	Wavelength (nm)	Absorbance
AB_1	237	2.1
AB_2	206	2.5
BT_1	261.4	0.79
BT_2	232.2	0.62
IC_1	248	3.21
IC_2	243	0.852
IC_3	372	0.89
AN_1	237.5	2.9
AN_2	208.5	0.74
AN_3	248	0.735

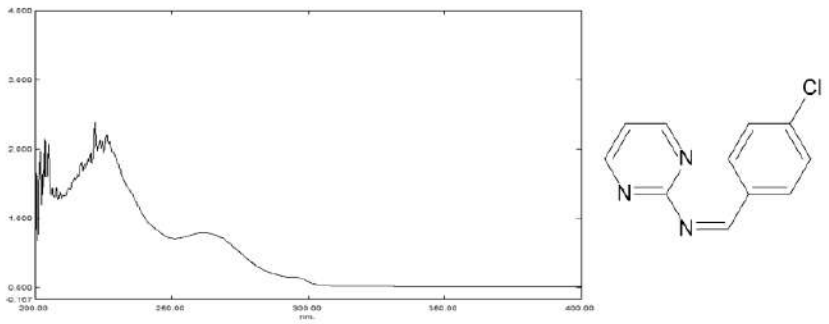


Figure 6: UV Spectra of compound AB1

Table 10: Results of Spectral Characterization

Compound Code	FT-IR	^{1}H-NMR & ^{13}C-NMR	ES-MS
AB_1	1051, 1286, 1594, 1697, 2926, 3105.	^{1}H-NMR-δ ppm: 7.214-8.330 (m, 14H, Ar-H), 2.16 (s, 2H, NH). ^{13}C-NMR-δ ppm: 172.5, 171.9, 158.7, 112.8, 35.2, 32.8, 22.9, 22.8, 13.5.	217.65
AB_2	1247, 1533, 1632, 2696, 3115.	^{1}H-NMR-δ ppm: 9.125 (s,1H, NH), 8.379 (d, J= 8.3Hz, 2H, Ar-H), 7.702 (s, 1H, NH), 7.680 (d, J= 8.1Hz, 2H, Ar-H), 5.740 (s, 1H, CH). ^{13}C-NMR-δ ppm: 15.29, 62.70, 77.42, 98.27, 121.28, 123.88, 125.97, 129.45, 132.11, 147.13, 154.20.	199.21
AB_3	1275, 1508, 1560, 1680, 2733,3241.	^{1}H-NMR-δ ppm: 4.68 (1H, NH), 2.92 (3Hz, 2H, CH_2), 1.90 (m, 13H, CH_2CH_3), 0.95 (t, 7.3Hz, 3H, CH_3). ^{13}C-NMR-δ ppm: 172.6, 171.8, 158.6, 113.1, 31.8, 22.7, 14.5, 13.6.	228.21
BT_1	1384, 1517, 1585, 1635, 2850, 3057.	^{1}H-NMR-δ ppm: 8.079 (s,1H, NH), 8.059 (d, J= 8.3Hz, 2H, Ar-H), 7.591 (s, 1H, NH), 7.452 (d, J= 8.1Hz, 2H, Ar-H), 6.690 (s, 1H, CH), 1.254 (s, 2H, CH_2). ^{13}C-NMR-δ ppm: 29.79, 76.79, 77.43, 118.33, 121.15, 122.67, 126.40,	310.79

		129.75, 131.41, 139.39, 150.04, 170.54.	
BT_2	1348, 1529, 1608, 1622, 2852, 3236.	^{1}H-NMR-δ ppm: 8.962 (s,1H, NH), 8.298 (d, 2H, Ar-H), 7.631 (s, 1H, NH), 7.052 (d, 2H, Ar-H), 1.233 (s, 2H, CH_2). ^{13}C-NMR-δ ppm: 32.79, 79.21, 95.43, 123.33, 123.65, 125.97, 128.89, 129.75, 133.91, 139.96, 156.04, 189.32.	292.35
BT_3	1365, 1533, 1627, 1654, 2865, 3124.	^{1}H-NMR-δ ppm: 8.231 (s,1H, NH), 8.165 (d, J= 8.3H_Z, 2H, Ar-H), 7.183 (s, 1H, NH), 7.602 (d, J= 8.1H_Z, 2H, Ar-H), 6.687 (s, 1H, CH), 1.268 (s, 2H, CH_2). ^{13}C-NMR-δ ppm: 27.79, 78.79, 76.43, 115.33, 128.15, 124.67, 122.40, 125.75, 138.41, 133.39, 154.04, 179.54.	321.35
IC_1	1298, 1514, 1635, 2702, 3481.	^{1}H-NMR-δ ppm:10.24 (s, 1H, NH), 7.659 (s, 2H, Ar-H), 7.591 (s, 1H, NH), 7.472 (d, J= 8.1H_Z, 2H, Ar-H), 6.990 (s, 1H, CH), 1.964 (s, 2H, CH_2). ^{13}C-NMR-δ ppm:160.1, 149.1, 135.5, 130.8, 127.3, 126.1, 122.2, 119.2, 111.2.	276.35
IC_2	1285, 1570, 1678, 2734, 3205.	^{1}H-NMR-δ ppm: 10.174 (s, 1H, NH), 7.341 (s, 2H, Ar-H), 7.624 (s, 1H, NH), 7.831 (d, J= 8.1H_Z, 2H, Ar-H), 7.01 (s, 1H, CH), 1.654 (s, 2H, CH_2). ^{13}C-NMR-δ ppm:147.1, 132.8, 130.2, 127.5, 126.9, 123.7, 122.1, 119.8, 112.0, 111.8, 102.3.	294.73
IC_3	1240, 1282, 1683, 2671, 3361.	^{1}H-NMR-δ ppm: 10.156 (s, 1H, NH), 7.812 (s, 2H, Ar-H), 7.177 (s, 1H, NH), 7.523 (d, J= 8.1H_Z, 2H, Ar-H), 6.647 (s, 1H, CH), 1.247 (s, 2H, CH_2). ^{13}C-NMR-δ ppm:155.1, 132.8, 130.2, 123.7, 121.8, 118.6, 113.5, 111.2, 103.7.	276.28
AN_1	1350, 1527, 1591, 1629, 2856, 3109.	^{1}H-NMR-δ ppm: 8.39 (s, 1H, NH), 7.621 (s, 2H, Ar-H), 8.12 (s, 1H, NH), 7.534 (d, J= 8.1H_Z, 2H, Ar-H), 7.141 (s, 1H, CH), 1.532 (s, 2H, CH_2). ^{13}C-NMR-δ ppm:130.2, 122.4, 127.5, 154.1, 163.1, 140.9, 123.5, 150.4.	305.28
AN_2	1286, 1575, 1625, 2887, 3248.	^{1}H-NMR-δ ppm: 8.19 (s, 1H, NH), 7.657 (s, 2H, Ar-H), 8.226 (s, 1H, NH), 7.673 (d, J= 8.1H_Z, 2H, Ar-H), 6.892 (s, 1H, CH), 1.075 (s, 2H, CH_2). ^{13}C-NMR-δ ppm:130.1, 122.3, 127.3, 153.2, 160.1, 139.9, 121.2, 150.7.	260.28

AN_3	1321, 1591, 1685, 2673, 3093.	^{1}H-NMR-δ ppm: 8.67 (s, 1H, NH), 7.659 (s, 2H, Ar-H), 8.18 (s, 1H, NH), 7.583 (d, J= 8.1H_Z, 2H, Ar-H), 6.196 (s, 1H, CH), 1.857 (s, 2H, CH_2). ^{13}C-NMR-δ ppm:128.5, 162.8, 129.0, 131.1, 130.8, 123.7, 153.8, 160.5.	231.15

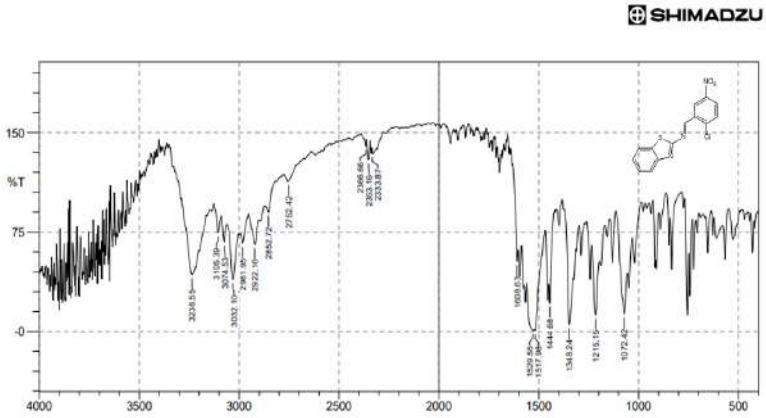


Figure 7: IR Spectra of Compound BT2

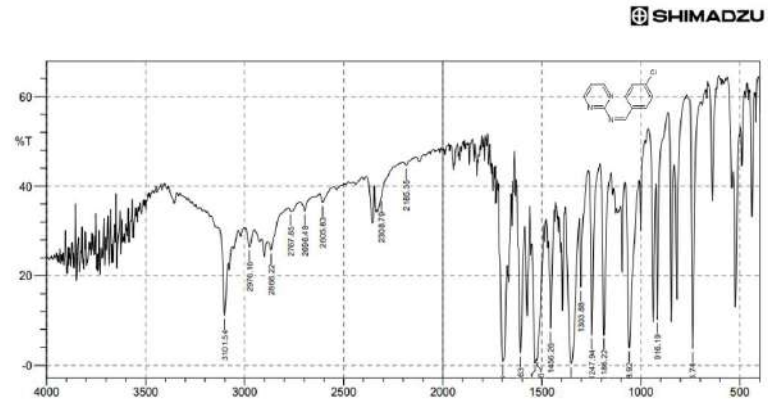


Figure 8: IR Spectra of Compound AB1

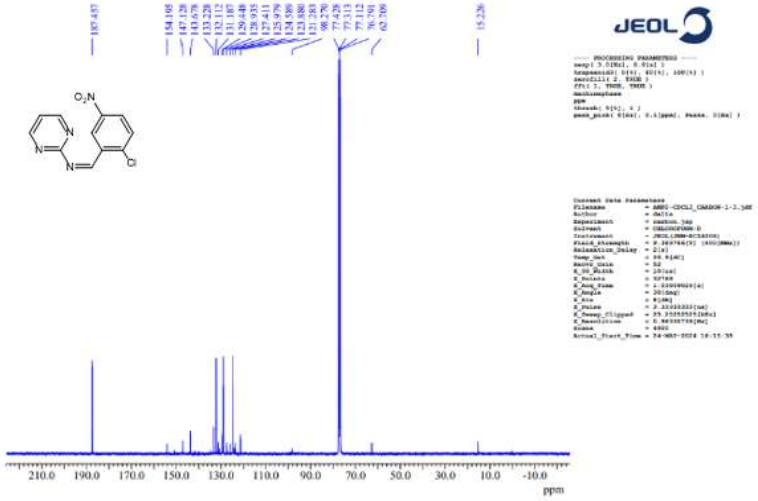


Figure 9: 13C NMR Spectra of Compound AB2

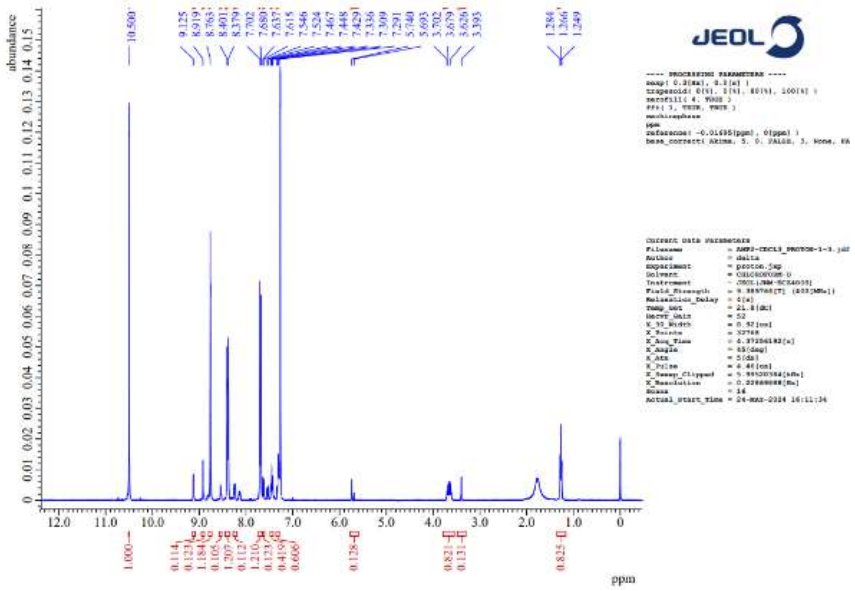


Figure 10: 1H NMR Spectra of Compound AB2

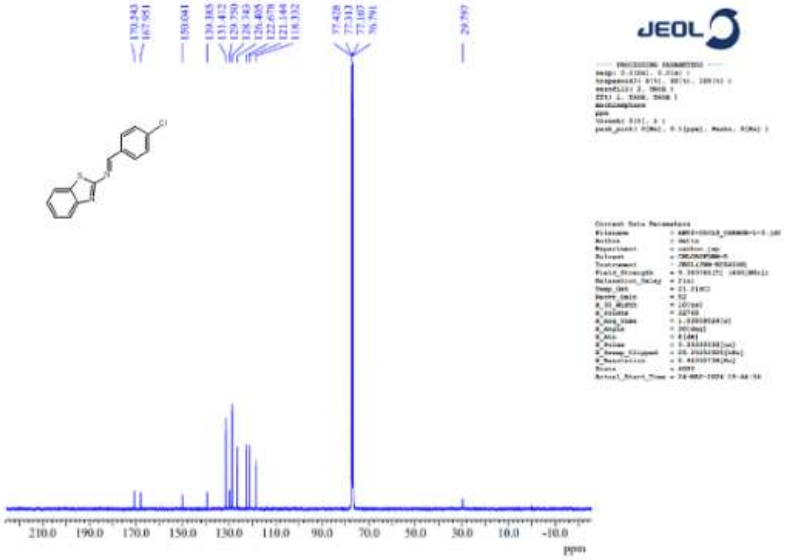


Figure 11: 13C NMR Spectra of Compound BT1

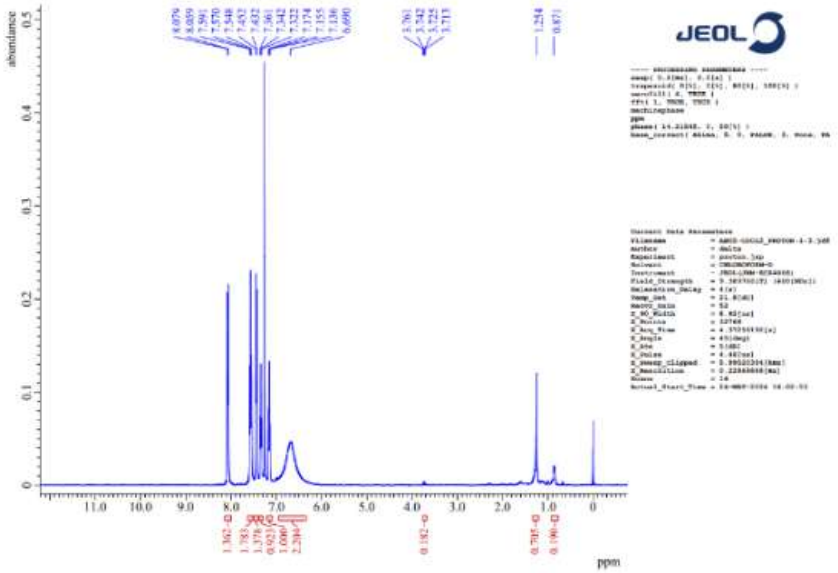


Figure 12: 1H NMR Spectra of Compound BT1

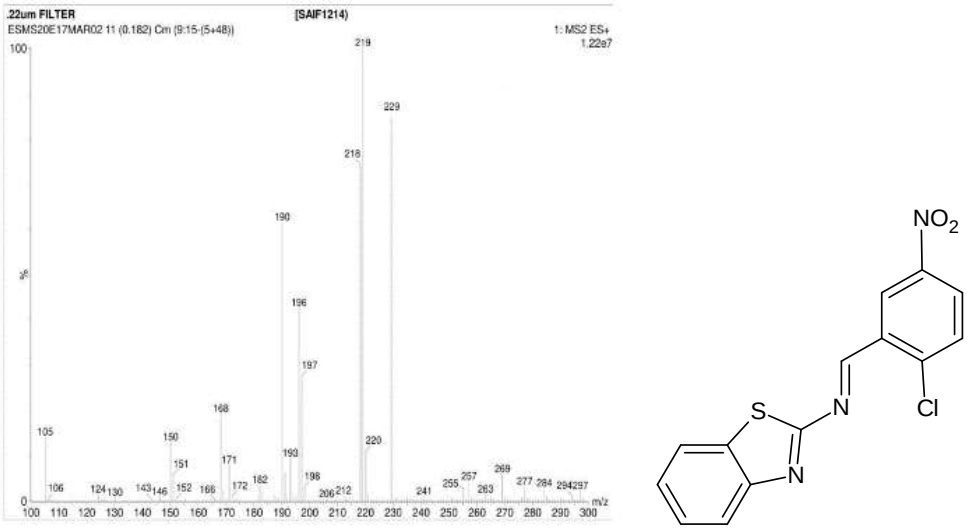


Figure 13: Mass Spectra of Compound BT2

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HOW TO CITE: Aswini Sasidharan , Baskar Lakshmanan, R. Sudharsan , Design, Synthesis, Biological Evaluation And *In-Silico* Studies Of Nitrogen Containing Aryl Scaffolds As Antioxidant Agents, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 10, 1130-1144. https://doi.org/10.5281/zenodo.13957212