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Synthesis of Bromo Aniline derivatives and an insilico approach against HSP90 chaperone

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***Abstract*---**Heterocyclic compounds are occupied in a huge variety of drugs which are widely distributed in nature and essential to life; Aniline has its remarkable influence in products that have been used by humans in day to day life. Its derivatives have made a remarkable trend over drug synthesis and this work shows the synthesis, characterization of some Bromo aniline derivatives and their action against the *insilico* docking studies against 4,5 Diaryl Isoxazole Hsp90 Chaperone Inhibitors a potential skin cancer therapeutic agent (2VCJ).

***Keywords*---**aniline, Bromo aniline derivatives**,** skin cancer, molecular docking studies.

Introduction

Heterocycles are an extraordinarily important class of compounds, making up more than half of all known organic compounds. They have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals[1]. Due to the broad application the review on aniline has attracted the attention of many researchers. It has increased its attention after the use of aniline as a byproduct in the synthesis of many chemicals. Therefore this work gives a broad view on aniline, its derivatives and their applications in various fields[2]. It covers the importance of Bromo substituted aniline derivatives. Molecular chaperones are proteins which play a key role in the conformational maturation, stability and function of other "client" protein substrates within the cell.[3-4] Hsp90 is important for stabilization and trafficking of tyrosine and serine/threonine kinases that are activated in response to genotoxic stress, including those that are essential for survival of cancer cells Some Hsp90 inhibitors are currently in phase I/II clinical trials in combination with IR or chemotherapeutic agents[5-7]

Here, in present study, we have performed the molecular docking study of ten derivatives of Bromo aniline molecules, such as 5a - 5j against 4,5 Diaryl Isoxazole Hsp90 Chaperone (2VCJ) .[8]

Chemistry

The general schematic representation describing the routes of syntheses is furnished in the Scheme with two steps. Chalcone (a) were prepared by the condensation reaction of Benzaldehyde with respective ketones (Acetone/ Acetohenone) in the presence of sodium hydroxide in Water/ ethanol medium stirred for 4hrs. Dibromo/Tetrabromo chalcone(c) are synthesized by stirring Chalcone with liquid Bromine in the presence of Glacial acitic acid in chloroform in an ice bath medium for 1Hr. Further the Dibromo/Tetrabromo chalcone were stirred with 2-Chloro aniline in the presence of sodium hydroxide in an ethanol medium for 2-3 Hrs to obtain the product Bromo aniline derivative (5 a-j). All the synthesized compounds were characterized by analytical and spectral (Mass, IR, 1H and NMR) data. The physical and analytical data of the compounds (5a-j) are presented in Table 1 and 2.

Figure 1: Schematic diagram

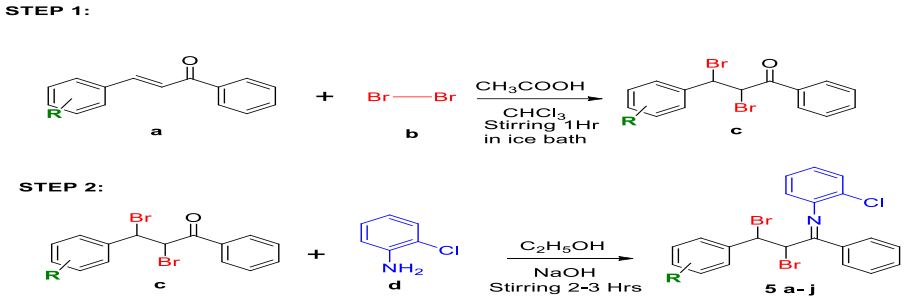


Table 1 : Physical data of Compounds (5a-j)

Compound	Compound Name	Reaction Time (hrs)	Yield (%)	Melting point^{0}C	Mass(m/z)
5a	2-chloro-N-(1,2,4,5-tetrabromo-1,5-diphenylpentan-3-ylidene)aniline	2	92	413-414	664.78
5b	2-chloro-N-(2,3-dibromo-3-(2,6-dichloro-4-methylphenyl)-1-phenylpropylidene)aniline	3	89	410-411	560.87
5c	2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(2,6-dichloro-4-methylphenyl)pentan-3-ylidene)aniline	3	88	630-631	830.65
5d	2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(2-chloro-4-methylphenyl)pentan-3-	2	90	545-546	760.73

	ylidene)aniline				
5e	2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(2,4-dimethylphenyl)pentan-3-ylidene)aniline	2	89	508-509	718.84
5f	2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(4-bromo-2-nitrophenyl)pentan-3-ylidene)aniline	3	86	507-508	910.57
5g	2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(4-methoxyphenyl)pentan-3-ylidene)aniline	2	85	504-505	722.80
5h	2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(3,4,5-trimethoxyphenyl)pentan-3-ylidene)aniline	2	86	689-690	842.85
5i	2-chloro-N-(1,2,4,5-tetrabromo-1,5-di(pyridin-3-yl)pentan-3-ylidene)aniline	3	87	534-535	664.77
5j	2-chloro-N-(1,2,4,5-tetrabromo-1,5-di(thiophen-3-yl)pentan-3-ylidene)aniline	3	89	540-541	674.69

Table 2: Elemental Analysis

Elements	C	H	N	S	O	Br	Cl
Compound							
5a	41.64	2.73	2.11	-	-	48.17	5.34
5b	47.14	2.88	2.5	-	-	28.51	18.97
5c	36.21	2.19	1.69	-	-	38.54	21.38
5d	39.49	2.65	1.84	-	-	42.03	13.99
5e	45.07	3.64	1.95	-	-	44.42	4.93
5f	30.32	1.55	4.16	-	7.02	52.61	3.89
5g	41.5	3.06	1.94	-	4.42	44.18	4.9
5h	41.29	3.58	1.66	-	11.38	37.89	4.2
5i	37.9	2.42	6.31	-	-	48.03	5.33
5j	33.78	2.09	2.07	9.49	-	47.31	5.25

Experimental section

2-chloro-N-(1,2,4,5-tetrabromo-1,5-diphenylpentan-3-ylidene)aniline (5a)

Yield-92%,m.p-413-414^0 C, ^{1}H NMR- δ 4.21-4.23 (d,Bromides proton), 5.29-5.31 (d,conjugated ethylene proton),6.77-6.78(d,ethylene proton) ,7.15-7.71(m,aromatic proton), ^{13}C NMR- δ39.57-40.25(methylbromide),44.19-44.49(methyl carbon),128.50,128.75,130.65, 130.67, 137.54,138.50,139.85 (aromatic carbons), 164.53(CN carbon), IR(KBR)-679.7,752.2,1475.0,1299.9,2802.7, cm^{-1}, Mass (m/z)- 664.78.

2-chloro-N-(2,3-dibromo-3-(2,6-dichloro-4-methylphenyl)-1-phenylpropylidene)aniline (5b)

Yield-89%,m.p-410-411^0 C, ^{1}H NMR- δ 4.52 (d,Bromides proton), 5.29 (d,conjugated ethylene proton),6.77-6.78(d,ethylene proton) ,7.26-7.91(m,aromatic proton),2.34(s,methyl proton) 13C ^{13}C NMR - δ34.8-45.6(methyl bromide),20.3(methyl carbon),127.2,128.8,131.0,134.0,135.6,141.4,143.2 (aromatic carbons), 164.6(CN carbon), IR(KBR)- 678.7,754.5,1480.9,1289.6,2813.2, cm-^{1}, Mass (m/z)- 560.87.

2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(2,6-dichloro-4-methylphenyl)pentan-3-ylidene)aniline (5c)

Yield-88%,m.p-630-631^0 C, ^{1}H NMR- δ 4.51 (s,Bromides proton), 5.31 (s,conjugated ethylene proton),3.77-3.82(d,chlorides proton) ,7.26-7.49(m,aromatic proton),2.34,2.36(d,methyl proton) ^{13}C NMR - δ34.5-(methylbromide),39.3(methyl chloride)20.3(methylcarbon),135.6127.8,128.1,128.6,131.2,134.8,138.6 (aromatic carbons), 164.3(CN carbon), IR(KBR)-692.5,592.3,1493.8,1284.9,1598.3,2844.9cm-^{1}Mass (m/z)- 830.65.

2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(2-chloro-4-methylphenyl)pentan-3-ylidene)aniline (5d)

Yield-90%,m.p-545-546^0 C, ^{1}H NMR- δ 4.32(d,Bromides proton), 5.29 (s,conjugated ethylene proton),3.69-3.78(d,chlorides proton) ,7.28-7.39(m,aromatic proton),2.31,2.32(d, methyl proton) ^{13}C NMR - δ34.9- (methyl bromide),38.6(methyl chloride)20.9(methylcarbon),127.2,127.8,128.3,128.9,130.9,134.5,137.6 (aromatic carbons), 164.4(CN carbon), IR(KBR)-689.8,591.8,1494.1,1285.3,1597.7,2846.2cm^{-1}, Mass (m/z)- 760.73

2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(2,4-dimethylphenyl)pentan-3-ylidene)aniline (5e)

Yield-89%,m.p-508-509^0 C, ^{1}H NMR- δ 4.28,4.32(d,Bromides proton), 5.29 (s,conjugated ethylene proton), 3.68(s,chlorides proton) ,7.27-7.41(m,aromatic proton),2.42,2.32(d, methyl proton) ^{13}C NMR - δ34.9- (methyl bromide),37.9(methyl chloride)21.4(methylcarbon),127.2,127.8,128.3,128.9,130.8,134.4,137.6 (aromatic carbons), 164.0(CN carbon), IR(KBR)-689.7,591.9,149.3.1,1285.4,1596.7,2833.4 Cm^{-1}, Mass (m/z)- 718.84

2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(4-bromo-2-nitrophenyl)pentan-3-ylidene)aniline (5f)

Yield-86%,m.p-507-508^0 C, NMR- δ 4.31,4.35(d,Bromides proton), 5.32 (s,conjugated ethylene proton), 7.28-7.53(m,aromatic proton), ^{13}C NMR - δ35.1-(methyl bromide),38.2(methyl chloride)21.2(methylcarbon), 128.50,128.75,130.65, 130.67, 137.54,138.50,139.85 (aromatic carbons),

164.2(CN carbon), IR(KBR)- 692.5,592.3,1493.8,1284.9,1539.4,1596.7,2852.3cm^{-1}, Mass (m/e)- 910.57.

2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(4-methoxyphenyl)pentan-3-ylidene)aniline (5g)

Yield-85%,m.p-504-505^{0}C , ^{1}H NMR- δ 2.1-2.7(s,methylene proton),3.6-3.9 (s,methoxy proton), 4.6-5.8 (d,bromide proton),6.05-6.65(d,ethylene proton) ,6.91-8.109m,aromatic proton) , ^{13}C NMR-δ δ39.57-40.25(methylbromide), 55.40(methyl carbon),61.69(methoxy carbon),127.53,127.92,128.24,128.51,128.96,129.03,129.85,130.45,130.87,133.30,134.83 (aromatic carbons), 160.5(CN carbon),IR(KBR)- 2830.2,1654.8,1589.2,1268.0,1604.3,672.0 cm^{-1}, Mass (m/z)- 722.80.

2-chloro-N-(1,2,4,5-tetrabromo-1,5-bis(3,4,5-trimethoxyphenyl)pentan-3-ylidene)aniline (5h)

Yield-86%,m.p-689-690^0 C, ^{1}H NMR- δ 3.8 (s, methoxy proton), 4.52-5.1 (d, bromide proton),6.03-6.52(d, ethylene proton) ,6.52-7.49 (m, aromatic proton) , ^{13}C NMR-δ 40.0-45.3(methyl bromide),106.4(ethyl carbon),56.1(methoxy carbon),127.8,128.1,128.6,129.03,132.6,139.4 (aromatic carbons), 164.5(CN carbon),IR(KBR)- 2830.2,1654.8,1589.2,1268.0,1604.3,672.0 cm^{-1}, Mass (m/z)- 842.85.

2-chloro-N-(1,2,4,5-tetrabromo-1,5-di(pyridin-3-yl)pentan-3-ylidene)aniline (5i)

Yield-87%,m.p-534-535^0 C, ^{1}H NMR- δ 4.52,5.29 (H-Br proton),6.05-6.75(d,ethylene proton) ,7.25-7.67(m,aromatic proton),^{13}C NMR-δ40.0-44.7(d,methylbromide),127.66,127.89,128.13,128.56,128.78,129.48,129.90,130.57, (aromatic carbons), 157.20(CN carbon), IR(KBR)- 2830.8,1654,1604,870 cm^{-1}, Mass (m/e)- 664.77.

2-chloro-N-(1,2,4,5-tetrabromo-1,5-di(thiophen-3-yl)pentan-3-ylidene)aniline (5j)

Yield-89%,m.p-540-541^0 C, ^{1}H NMR- δ 4.5-5.1 (d,ethylene proton),6.74-6.75(d,ethylene proton) ,6.85-7.90(m,aromatic proton),^{13}C NMR-δ126.1,127.6,128.1,128.6,130.1,137.5,139.0(aromatic carbons), 164.5(CN carbon), 121.3(CS carbon), IR(KBR)- 2833.4,1596.7, 1654,1604,870 cm^{-1}, Mass (m/e)- 674.69

Figure 2: ^{13}C NMR Spectrum

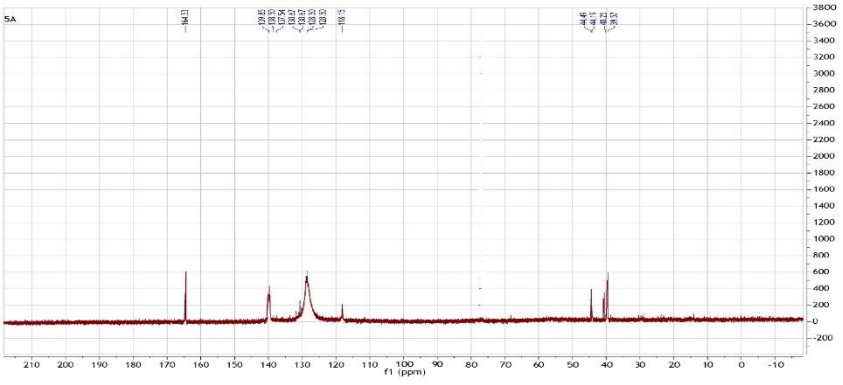


Figure 3 1H NMR Spectrum

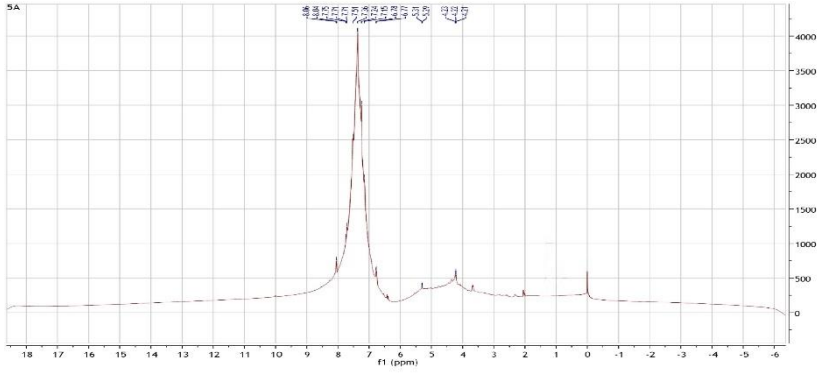


Figure 4 Mass Spectrum

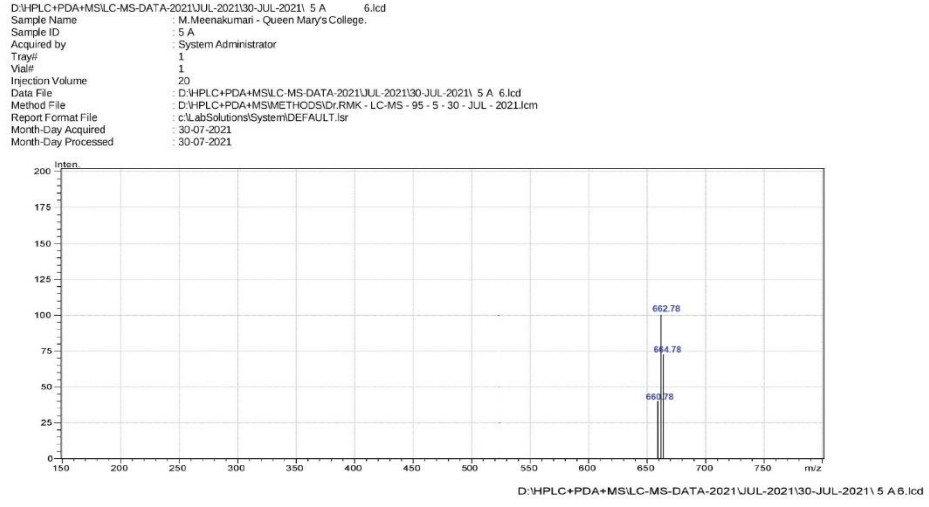
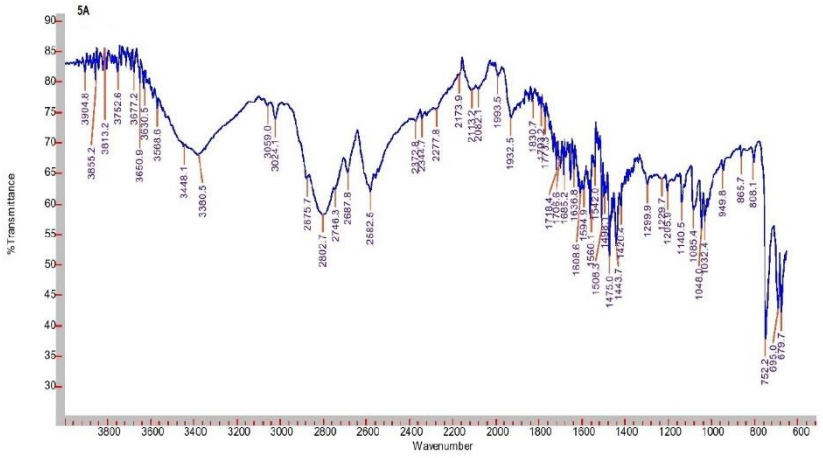


Figure 5 IR Spectrum



Molecular docking studies
Computational section
Docking Studies

The docking studies of the above 10 compounds with protein have been carried out by application of LIGAND DOCKING in the module GLIDE of SCHRODINGER software. By this tool prediction of best binding interaction between the ligand and the protein were done. Creating an output directory for every work is a must while working in Schrodinger. Before initiating the ligand preparation, the structures have to be converted into maestro format (.mae format) from .sdf format. The structures of the 10 compounds have been drawn with the help of the, CHEMDRAW ULTRA 12.0 tool. Each structure has been imported into the MAESTRO12.1 from the project table and are then exported from the .sdf format to the .mae format. The Computational studies were carried out using Schrodinger Maestero software and the Admet properties were carried out using the tool Schrodinger Qikprop and verified for the standards of Pfizer rule of 5 and Ghose filter rule for bioavailability (Table 3)[9-12].

Table 3. Qikprop Results of the compounds

Title	Rotatable bonds	mol MW	donor HB	accpt HB	QP logPo/w	Qplog HERG	QP PCaco	Qp logBB	QPP MDCK	QP logKp	PercentHuman OralAbsorption
5A	8	663.471	0	1	8.784	-6.737	8759.8	0.528	10000	0.874	100
5B	6	560.542	0	1	8.163	-5.916	8191.4	0.622	10000	0.2	100
5C	8	829.305	0	1	10.338	-5.858	8514.5	0.812	10000	0.09	100
5D	8	760.415	0	1	9.674	-5.466	8577	0.702	10000	0.074	100
5E	8	719.578	0	1	9.792	-6.193	9550.3	0.528	10000	0.331	100
5F	10	911.258	0	3	8.47	-5.65	1023.6	-0.204	10000	-1.412	100
5G	10	723.523	0	2.5	8.593	-5.943	8619.7	0.39	10000	0.483	100
5H	14	843.628	0	5.5	9.174	-6.207	9756.9	0.171	10000	0.561	100
5I	8	665.446	0	4	6.683	-6.324	2597.1	-0.009	10000	-0.404	100
5J	8	675.515	0	1	8.676	-5.888	8759.5	0.808	10000	0.37	100

Ligand and protein preparation

Ligand Preparation

Ligand Preparation (LigPrep) is an application where we generate a simple 2D structure to 3D structure which includes the generation of the tautomeric, stereochemical and ionization variations. LigPrep helps in generating an accurate 3D molecular model. The important characteristic of LigPrep application is the energy minimization with optimized potentials for liquid simulations-2005 (OPLS_2005) as the applied force field which filters customized ligands which can thus be used for further computational analysis. All the 10 ligands have been minimized using Schrödinger suite. The output folder for LigPrep will be displayed as out.maegz [12].

Impact Minimization

The output folder of LigPrep is used as the input folder for impact minimization. The impact minimization is performed with IMPACT module in which a tool called minimization. Among many conformers obtained in LigPrep, the conformer with least potential energy were minimized with impact minimization under the applied OPLS_2005 force field. The significance of impact minimization is to observe the Lennard Jones Energy, which should be in negative [13].

Protein Preparation

The protein was retrieved from PDB (http://www.pdb.org) with the PDB id 2VCJ. The ProPrep was processed with the help of the protein preparation wizard from the workflows option of the Schrodinger suite. The force field applied for preparation of protein is optimized potentials for liquid simulations-2005 (OPLS_2005). The water molecules, hetero atoms, residues were deleted while one of the chains is retained along with H-bond. The active site of the protein is identified by the help of PDBCASTp and Q-site finder [14].

Grid Generation

The receptor-grid is generated with glide module. Grid generation represents the physical properties like volume of the receptor (specifically the active site) that is needed for carrying out the ligand-docking process. Import the output file of the protein preparation; also define the receptor, active site, the positional constraints, and then monitor the generation of the grid calculation. The generated receptor grid is used for the comparative docking studies conducted in ligand docking procedure[15].

Docking

The docking has been carried out by the application LIGAND DOCKING which is present in the module GLIDE12.1 version in the extra precision (XP) mode for clear and accurate details along with Epik state penalties to docking score. Select the selected entries for the ligand to be docked. Also load the output file of the grid generated. The output files of impact minimization of all the compounds are

taken as the input files for the docking process. The docking of each compound along with the grid will be carried out which generates conformational changes with respect to the active site of the protein(PDB ID- 2VCJ). The glide scores or docking scores will be displayed in a text document. Thus, the ligand which has the least glide score will be considered to have the best docked pose or best glide score.

Result and Discussion

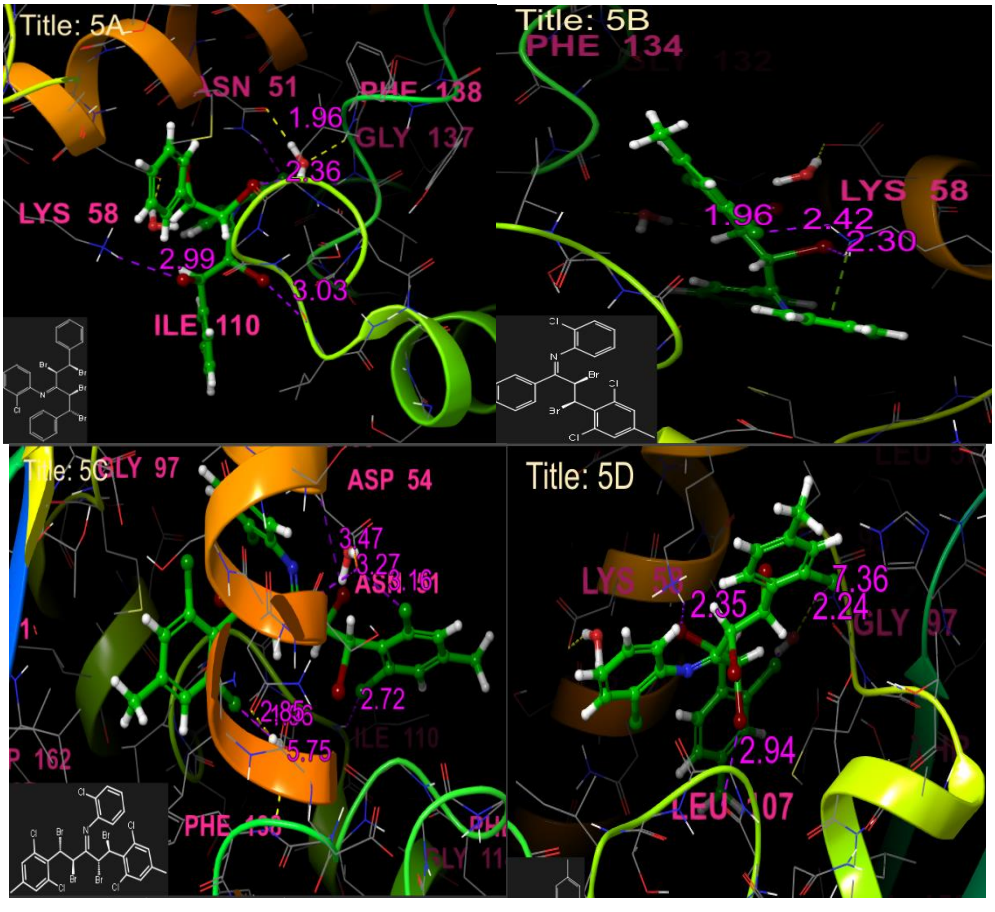
Molecular docking is a tool used in computer aided structure based rational drug design. It is designed to predict how a small molecule binds to a target protein with known 3D structure, and binding energies determined. Also the position of the ligand in the hosts binding site can be visualized. It is helpful for developing better drug with improved activity. The docking score is measure of strength of the non-covalent interaction or binding affinity between two molecules after they have been docked[16-18]. In calculating the docking score, the small organic molecule or ligand is considered as a rigid structure and its interactions with protein receptors are recorded and expressed in terms of energy associated with such interactions. In calculations of the Glide energy value, the conformational, orientational, and positional space of the docked ligand are taken into consideration [19-20]. Thus, the Glide energy value is obtained with torsionally flexible energy optimization where the ligand is a flexible entity and all its possible geometrical orientations are considered. Hence, the Glide energy value is a more reliable, enhanced, and realistic approach to investigate the docking process. Both docking score or docking and Glide energy are free energy values and expressed in kcal mol−1. All the synthesized compounds exhibited good Glide energy and docking scores towards the receptor active pocket, and bind to the active site of the amino acid residue with H-bonding (Table 4). Compound 5a showed the highest docking score and a lower Glide energy. Compound 5a can be considered to be the best docked ligand with the highest docking score and lowest Glide energy. Compounds 5b,5c,5d,5e,5f,5g,5h,5i,5j have moderate docking scores and Glide energies. In this study compound 5a showed the shortest hydrogen bonding distance of 1.96 Å,2.36 Å,1.96 Å,3.03 Å, 2.99Å with the amino acid likely due to presence of the more electronegative atom. Docking score results shown in table 4and interaction of the compounds shown figure 6.

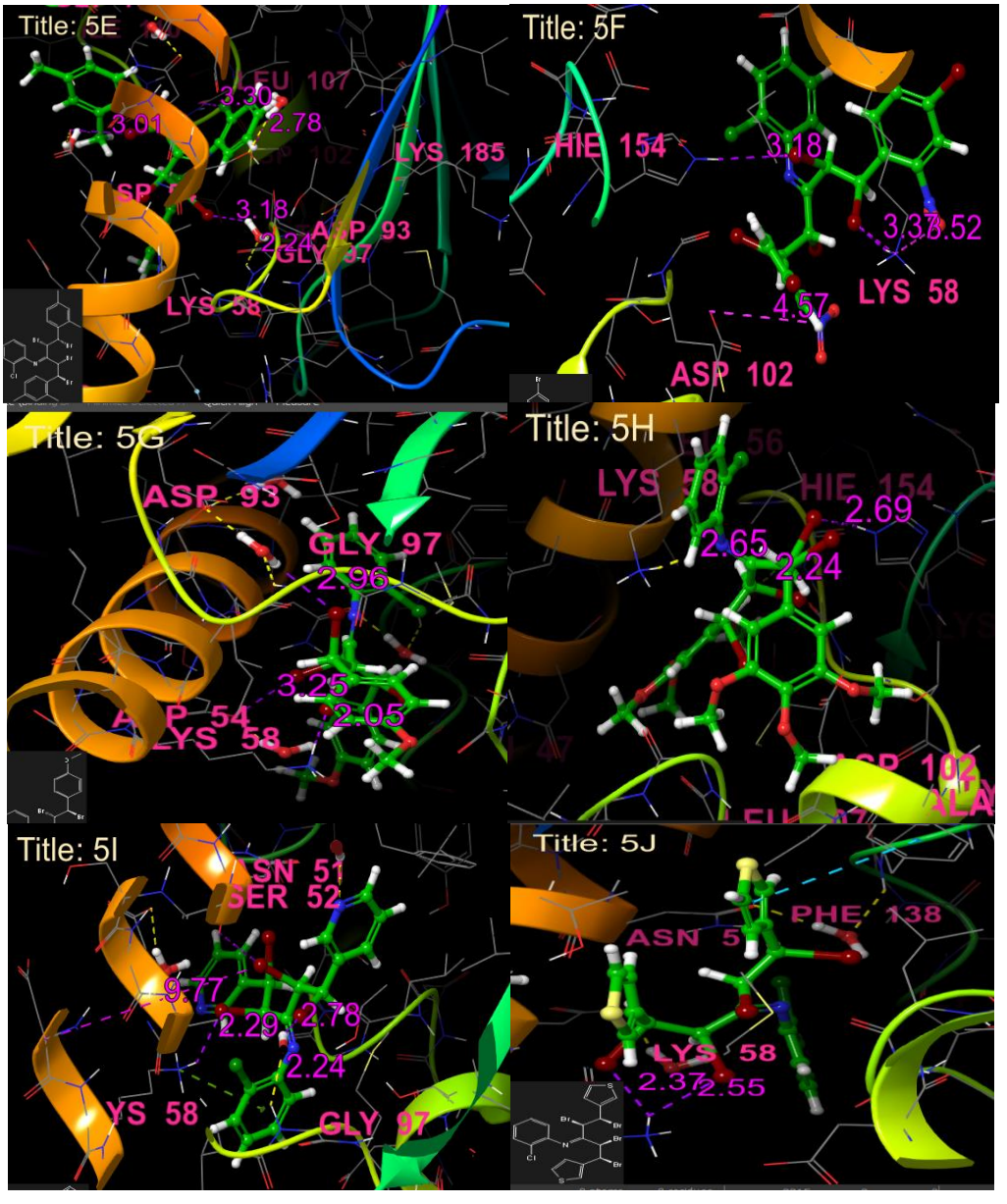
Table 4. Docking Results of the compounds

COMPOUNDS	DOCKING SCORE	GLIDE ENERGY	NO.OF RESIDUES	AMINO ACIDS	BOND LENGTH
5a	3.059	-42.702	5	ASN51,GLY137 PHE138,LYS58, ILE110	1.96,2.36, 1.96,3.03, 2.99
5b	-5.274	-37.395	2	LYS58,LYS58	1.96,2.42
5c	0.245	-27.446	6	GLY91,PHE138 ASP58,LYS58, ILE110,ASP54	3.47,3.27, 3.16,2.85, 5.75,2.72
5d	-1.938	-19.302	3	GLY97,LYS58, LEU107	2.35,2.24, 2.94
5e	-0.702	-28.076	3	ASP54,LEU107,	2.78,3.30,

				GLY97	3.18
5f	-1.613	-37.68	4	HIE154,ASP102, LYS58,LYS58	3.18,4.57, 3.37,3.52
5g	-2.875	-36.695	4	ASP54,GLY97, ASP93,LYS58	3.25,2.96, 2.84,2.05
5h	-2.349	-41.407	2	HIE154,LYS58	2.69,2.65
5i	-5.093	-49.48	4	GLY97,SER52, ASN51,LYS58	9.77,2.78, 2.29,2.24
5j	-4.07	-21.588	3	ASN51,ASP54, LYS58	2.45,2.37, 2.55

Figure 6: 3d interaction diagram of compounds 5a- 5j with 2VCJ





Cell line and culture

A431 cell line was obtained from National Centre for Cell Sciences, Pune (NCCS). The cells were maintained in DMEM supplemented with 10% FBS, penicillin (100 U/ml), and streptomycin (100 µg /ml) in a humidified atmosphere of 50 µg /ml CO_2 at 37 °C.

***In Vitro* assay for Anticancer activity: (MTT assay) (Mosmann, 1983)**

Cells (1 × 10^5/well) were plated in 24-well plates and incubated in 37^0C with 5% CO_2 condition. After the cell reaches the confluence, the various concentrations of the samples were added and incubated for 24hrs. After incubation, the sample was removed from the well and washed with phosphate-buffered saline (pH 7.4) or DMEM without serum. 100µl/well (5mg/ml) of 0.5% 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl--tetrazolium bromide (MTT) was added and incubated for 4 hours. After incubation, 1ml of DMSO was added in all the wells .The absorbance at 570nm was measured with UV- Spectrophotometer using DMSO as the blank. Measurements were performed and the concentration required for a 50% inhibition (IC50) was determined graphically. The % cell viability was calculated using the following formula:

% Cell viability = A570 of treated cells / A570 of control cells × 100

Graphs are plotted using the % of Cell Viability at Y-axis and concentration of the sample in X-axis. Cell control and sample control is included in each assay to compare the full cell viability assessments.

Table 5: Anticancer effect of Sample 5A *on* A431 cell line

S.No	Concentration (µg/ml)	Dilutions	Absorbance (O.D)	Cell Viability (%)
1	1000	Neat	0.150	14.56
2	500	1:1	0.206	20.00
3	250	1:2	0.261	25.33
4	125	1:4	0.317	30.77
5	62.5	1:8	0.373	36.21
6	31.2	1:16	0.432	41.94
7	15.6	1:32	0.488	47.37
8	7.8	1:64	0.545	52.91
9	Cell control	-	1.030	100

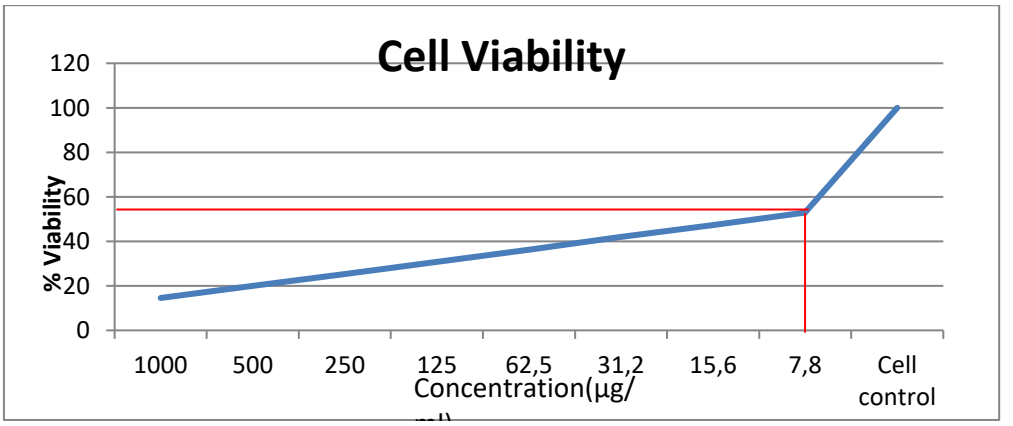
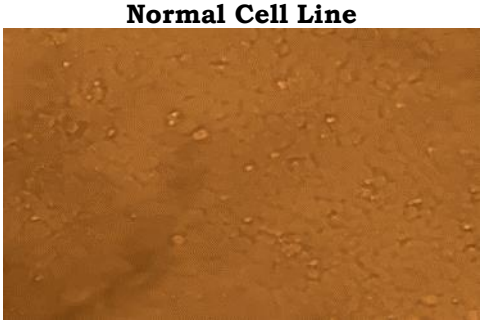
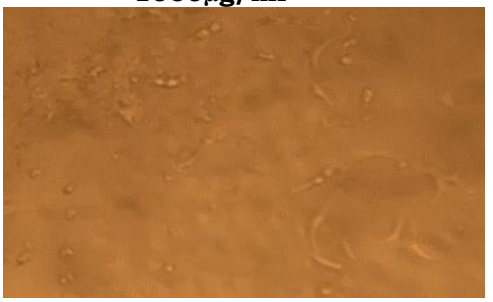


Figure 8: Anticancer effect of Sample 5A on *A431* cell line

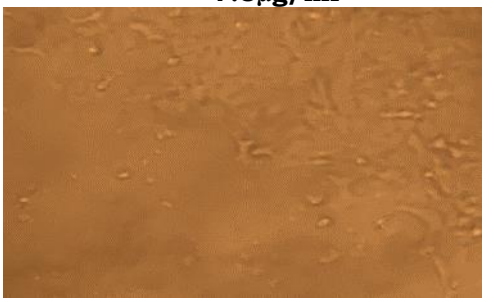
Normal Cell Line



1000µg/ml



7.8µg/ml



Conclusion

The synthesized compounds were characterized by ^{1}H NMR,^{13}C NMR,IR and Mass spectral analysis. The results obtained from the study confirmed the product Bromo aniline derivatives were formed. Henceforth viewing the characteristic properties, all the compounds have variety of biological activity viz., antimicrobial, anti fungal, anti-inflammatory and anticancer, etc. The acquired data states all Bromo aniline derivatives show high bio activity. Molecular docking studies of among all 10 compounds, 5a shows highly active for Skin cancer. And anti cancer effect is shown through cell line study .This may be utilized for further studies in designing a drug against Skin cancer according to provided data and studies.

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