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Designing and Molecular Modeling Studies on Novel Bisindole-imidazopyridine Against Adrenocarcinoma

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ABSTRACT

Adrenocarcinoma is an uncontrolled growth of epithelial cells originating in the ducts or breast lobules. EGFR or Epidermal growth factor receptor is a transmembrane protein with cytoplasmic kinase activity that transduces important growth factor signaling from the extracellular milieu to the cell. 45 bisindole-imdazopyridine analogues were obtained from the literature. Free-wilson QSAR studies were erformed on the given data set. Compounds were designed on the basis of QSAR studies. Further, Molecular docking studies were performed on the designed compounds to check the binding affinity on the protein. After that Drug-likeliness and ADMET studies were performed on the selected molecules. The results revealed that the selected analogues can be used against the treatment of adrenocarcinoma.

Keywords: Adrenocarcinoma, bisindole-imidazopyridine, QSAR, Molecular Docking, ADME studies.

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INTRODUCTION

Carcinomas are a complex form of human tumors (approximately 80% of all noncutaneous malignancies) and the most dangerous and common carcinoma is adenocarcinoma. Glandular or secretory epithelium containing any organ, and the most frequent sites including lungs, kidney, gastrointestinal tract, breast, and prostate can be affected by adenocarcinoma. Carcinomas like breast carcinoma is a group of malignant epithelial tumor characterized by the invasion of adjacent tissue and a marked tendancy to metastasize to distant sites. This is critical, as the WHO world cancer report indicates that by 2020, global cancer rate increase by 50% to 15 million [1,2].

The mutation and over expression of the epidermal growth factor receptor (EGFR) are associated with the development of a variety of cancers. EGFR is a protein that is present on the surface of both normal cells and cancer cells such as lung cancer cells. In the United States, an EGFR mutation is present in roughly 15 percent of people with lung cancer, in people of Eastern Asian descent though this number increases to 35 to 50 percent.[3] Mutations are more common in women than in men (42% versus 14%), in patients who have never smoked than in patients who have smoked (51% versus 10%), and in patients with adenocarcinoma than in those with other histologies (40% versus 3%).[4] EGFR mutations were generally assumed to give rise to spontaneous kinase activation, eliminating the dependence of the cancer mutants on dimerisation for activation[5]

45 bis-indole-imidazopyridine analogues were obtained from the literature. Bis-indole-imidazopyridine nucleus is present in many natural products isolated from marine sources with broad spectrum of biological activities.[6]

MATERIALS AND METHDS

QSAR studies:

QSAR is performed to co-relate biological properties with different substituents in a nucleus. A new series of bisindole-imidazopyridine analogues (45 molecules) were taken from literature survey. Free-wilson QSAR studies were performed on the given data set transferred to VALSTAT program and the best QSAR model was selected for study. Compounds were designed on the basis of QSAR studies.[7]

Molecular Docking:

Molecular docking is performed to study ligand protein interactions and predict the biological properties of

molecules. There are 20 bisindole-imidazopyridine analogues A1-A20 (screened by QSAR analysis), were designed. The software used in structure designing of molecules are ChemDraw and Chem3D.[8] Protein used for the docking study was PDB code : 5HIB, which is EGFR kinase domain mutant "TMLR" with a pyrazolopyrimidine inhibitor obtained from RCSB PDB.[9] Software used for docking studies was Autodock docking 4.2.6. Autodock score was generated by default calculation setting in software for all analogues. H-bond interactions were observed at autodock software after docking studies.[10]

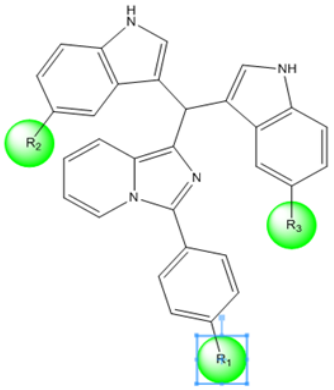
ADME Studies:

Absorption, distribution, metabolism and excretion, all pharmacokinetic properties of selected 5 analogues were performed to co-relate pharmacokinetic properties with pharmacodynamic properties of analogues. [11, 12]

RESULT AND DISCUSSION

QSAR Analysis:

Free-Wilson analysis performed on all analogues A1-A20 and best model generated by VALSTAT program was selected. According to the results obtained, the electron withdrawing groups such as methoxy group are most active substituent at R1, R2 and R3 positions. This study helped in the designing of molecules with more effective biological activity.



The green area represents the favourable substituents group positions

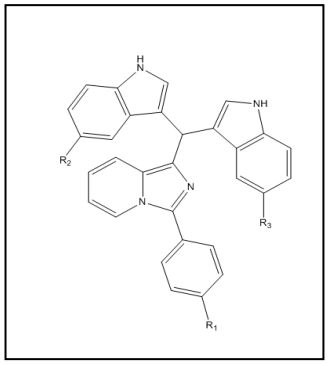
Table 1: QSAR Results

Parameter	Value
n	18
r	0.707822
r^2	0.501012
variance	0.02939
Std error	0.171434
F	53.7887
Q^2	0.922516

Biological activity = [4.89182(± 0.120595)] +35H [0.0918182(± 0.220959)] +35OMe [0.418182(± 0.288276)] +25OMe[0.451818(± 0.288276)]

Table 2: All analogues with substituents

Compound	R1	R2	R3	Compound	R1	R2	R3
A1	4H	5-H	5-H	**A11**	3,4-diOMe	5-Br	5-Br
A2	4H	5-OMe	5-OMe	**A12**	3,4-diOMe	5-CN	5-CN
A3	4H	5-Br	5-Br	**A13**	4-CF3	5-H	5-H
A4	4H	5-CN	5-CN	**A14**	4-CF3	5-OMe	5-OMe
A5	4OMe	5-H	5-H	**A15**	4-CF3	5-Br	5-Br
A6	4OMe	5-OMe	5-OMe	**A16**	4-CF3	5-CN	5-CN
A7	4OMe	5-Br	5-Br	**A17**	4-F	5-H	5-H
A8	4OMe	5-CN	5-CN	**A18**	4-F	5-OMe	5-OMe
A9	3,4-diOMe	5-H	5-H	**A19**	4-F	5-Br	5-Br
A10	3,4-diOMe	5-OMe	5-OMe	**A20**	4-F	5-CN	5-CN



Bis-indole-imidazopyridine moiety

Molecular Docking:

The Protein used, PDB code 5HIB, it was reported contains a co-crystallized ligand name 63M bind to active site with H-bond interaction with Lys745 and Met793. It was found that the scores obtained were higher than the co-crystallized ligand . The most active compound A13 having binding with Lys745 (fig 1.2).

Table 3: Docking results

Compound	Autodock Score
A15	-9.4
A3	-9.2
A2	-9
A13	-9
A14	-9
63M	-6.6

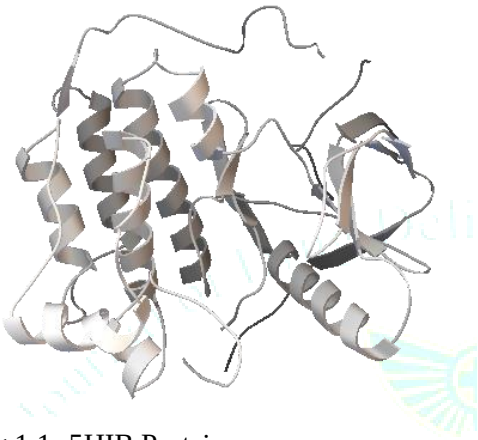


Fig 1.1- 5HIB Protein

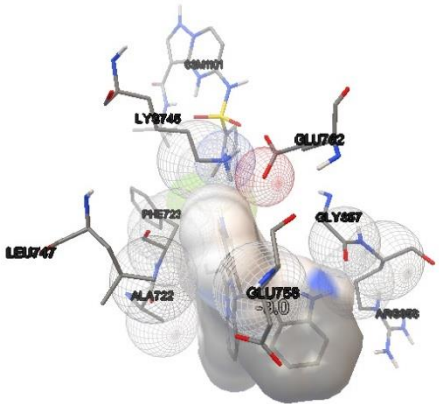


Fig 1.2- AnalogueA13 and protein interactions

ADME Studies :

TABLE 4 : ADME Parameters and results

Parameters	Results				
	A15	A3	A2	A13	A14
BBB	14.58	5.17962	0.17972	4.95409	0.578674
Buffer_solubility_mg_L	6.90151	9216.32	26.5598	75.401	8.41534
Caco2	55.4643	49.9737	56.4482	35.7488	40.6508
CYP_2C19_inhibition	Non	Non	Non	Non	Non
CYP_2C9_inhibition	Inhibitor	Non	Non	Non	Non
HIA	94.994747	95.53804	96.2376	95.5215	96.266776
MDCK	0.018101	0.156428	2.96545	0.0634228	0.0459559
Plasma_Protein_Binding	100	100	86.5571	100	89.559723
Pure water solubility mg/L	0.0001497	0.0932111	7.4954	0.640586	1.26297
Skin_Permeability	-2.47492	-3.13826	-3.69998	-2.33411	-2.68818
SKlogD_value	7.41626	4.6973	3.40234	5.00846	4.32502

CONCLUSION

The selected series of compounds on which QSAR and molecular docking studies were performed which resulted in identification of 5 potential compounds which can be used for further *in-vitro* and *in-vivo* studies, against the treatment of breast cancer.

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