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In-Silico Approach of 7-Azaindole Derivatives as Inhibitors of Bromodomain and Insulin Growth Factor Receptors for the Treatment of Diabetes-Related Cancer

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ABSTRACT

Several 7-azaindole derivatives were designed for its dual targeted inhibition towards 1K3A and 4HY3. Drug likeness, ADME studies, virtual toxicity studies and molecular docking studies were carried out using Accelrys drug discovery studio 3.5. All the compounds were found to follow Lipinski rule of 5. Molecular docking was performed for 21 designed ligands against 1K3A and 4HY3 receptors. Some of the designed compounds possess good binding affinity towards 1K3A and 4HY3. The 21 designed 7-azaindole derivatives were then docked against 1K3A (Insulin growth factor) and 4HY3 (bromodomain) receptors .The compounds were found to be having good interaction with amino acids such as VAL 215, GLY 105, LYS 325, ASP 164, LYS 1138, LEU 1143 . The compound **3a**4-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)benzene-1,2-diol,**4a** 5-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)benzene-1,3-diol and **20a** 2-(2-iodophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine having hydroxyl- and Iodo- substitution possess dual inhibition towards bromodomain and insulin growth factor receptor. Hence, these derivatives could be effective as a dual target in drug discovery for the cancer treatment.

1. INTRODUCTION

Cancer is a disease that can damage cellular mechanism of almost all parts of the body when they get exposed to it, cancer cells may or may not invade to its neighboring normal cells. Due to lack of knowledge in early detection and insufficient target oriented treatment, till now it is very difficult to cure the cancer. There are several treatment available for the cancer like Chemotherapy, Gene Therapy, Laser Therapy, Angiogenesis Blockers, Biotherapies, Bone Marrow Transplants and Stem Cell Therapy. Among the others types of treatment, triple therapy including tumor surgery and platinum based chemotherapy are considered to be the most efficient with the dose of bevacizumab and also the chalcones because of its maximum target site are available with several pathways.[1]

The insulin-like growth factors (IGFs) are mitogens that play a pivotal role in regulating cell proliferation, differentiation and apoptosis. A number of epidemiologic studies have shown that high circulating levels of a potent mitogen, insulin-like growth factor (IGF)-1, are associated with increased risk for several common cancers, including those of the breast, prostate, lung and colorectum.[2] the IGF system has two complex regulated growth factor (IGF-1 and IGF-2), the three receptor (IGF-IR, IGF-IIR, and insulin receptor, IR), six high affinity binding protein (IGFBP-1 to 6), a low affinity group of IGFBP proteases (kallikreins, cathepsins, and metallo-proteinase matrix, MMPs), and multiple low-affinity IGFBP-related proteins (IGFBP-rP 1 to 10) [3, 4] the binding if IGF-1 and IGF-2 to their respective receptor contributed to a deeper understanding of this complex mechanism. Its directs the activation of (1) Ras-Raf-mitogen activated protein kinases (MAPK) signaling and (2) phosphatidylinositol-4,5 bisphosphate 3-kinase (PI3K) AKT by which the IGF axis regulates cellular metabolism, homeostasis of the tissue and eventually, cell survival.[5,6] Several studies have shown that the effects of insulin/ IGF system on cancer cell activity during tumor progression is primarily through control of the epithelial- mesenchymal transition (EMT) program to achieve the malignant phenotypes.[7-10]

The insulin / IGF system is also involved in the metabolism of cancer cells, cancer drug resist ance, and cancerstem cell(CSC) phenotypes.[11,12] which emphasize the importance of this mec hanism in the cancer growth and progression monitoring networks. BRDs considered as the first identified protein that is coded with the D. melanogaster brahama gene which consist of 110 amino acid act as modulator throughout evolution using various transcriptional co-

regulators, chromatin modifying enzymes including nuclear scaffold proteins and directly bind to histone residue of acetylated lysine via NF-kappa B subunit RelA.[13]

BET bromodomain family members are implicated in many cancers including leukemia, lymphoma, multiple myeloma and C-MYC-driven cancers. BRD-containing proteins are frequently dysregulated in cancer; they participate in gene fusions that generate diverse, frequently oncogenic proteins, and many cancer-causing mutations.[14]

Bromodomain-containing protein 4 (BRD4) is a chromatin reader proteins, which includes BET family like BRD2, BRD3, BRD4 and BRDT, Among all, the most challenging BET family proteins is BRD4 that get interacted with Nacetyl lysine residues on histones and nuclear proteins via two conserved N-terminal.[15-18] BRD4 get interacted with acetylated chromatin protein to discrete the function of genomic region and to regulate mediator complex such as pTEFb via RNApol II, elongation and transcription mechanism.[19-20] several acetylated transcription factors get involved such as RelA, ERα, p53, and TWIST to maintain the oncogenic gene expression in cancer.[21-22] In healthy body, BRD4 protein required to maintain the chromatin stability, controls and regulate the cell cycling transition from M phase to G1 phase via through the recruitment of P-TEFb mediator complex.

The *in vivo* study indicate the defects in cell differentiation and organogenesis of heterozygous Brd4+/- as the null animal die in utero therefore, for the normal cell cycling progression and development, the BRD4 is most required.[23] The epigenetic modification does not change the sequence of nucleotide but reversible change and heritable alter to the DNA of a cell. Several epigenetic mechanism are get involved in maintaining normal cellular homeostasis and normal gene expression via through changes in CpG island methylation patterns and histone modifications The dysregulation of proteins lead to disease pathogenesis via through the interaction with modified DNA macro-molecular complexes.[24,25] Most of the anticancer drugs are monotargeted towards cancer. Use of dual targeting strategies and applying pharmacophore group of different active compounds could be useful for the design of most successful drugs.[26] the rational behind the work is to find out the best selective designed 7-azaindole derivative molecules toward the inhibition of dual target recptor.

2. MATERIALS AND METHOD:

Docking program requires three computation steps to carry out docking study these are as follows:

(1) Preparation of the receptor

(2) Preparation of the ligand

(3) Setup of the parameters of the docking program

The following subsections describe these three steps in detail.

2.1. RECEPTOR PREPARATION:

The three dimensional structure of BRD4 (PDB CODE-4HY3) were obtained from PDB. (http://www.rcsb.org/pdb/home/home.do). RCSB is a single, global archive for information about the 3D structure of macromolecules such as protein, DNA and their complexes, as determined by X-ray crystallography, NMR spectroscopy and cryoelectron microscopy.[27]

2.2. LIGAND PREPARATION:

The 7-azaindole derivative compound were designed with help of chemdraw and the ligand were loaded into Accelrys drug discovery studio 3.5. To predict the ligand molecular properties e.g. a log P value, hydrogen bond donors and hydrogen acceptors, surface area and molecular weight, absorption, distribution, metabolism (ADME) and analyses for solubility, intestinal absorption excretion and toxicity.

High throughput screening approaches and virtual screening were used for the identification of lead compounds. The compound datasets were screened effectively in the initial stages for ADMET to decrease cost and clinical failures of new drugs. [27]

2.3. DRUGS LIKENESS EVALUATION:

Drug likeness properties of the compound were predicted with the help of Lipinski drug filter using Accelrys drug discovery studio 3.5. The prediction of Lipinski rule gives us concept regarding the proper use of commercial drug. [27]

2.4. ADME DESCRIPTORS:

Absorption, distribution, metabolism and excretion is an important parameter used to know the pharmacokinetic properties of the drugs, as well as the degree of hepatotoxicity and plasma protein binding (PPB) aqueous solubility, blood brain barrier (BBB) and CYP2D2 that tells us the simple concept of the proper use of drugs. [27]

2.5. MOLECULAR SIMULATION STUDIES:

Chemistry at Harvard Molecular Mechanics (CHARMM) force field is a flexible molecular mechanics and dynamics program that are used in drug Accelrys drug discovery studio 3.5. For ligand minimization and protein minimization, broad range calculations such as calculation of geometries, interaction and conformation energies, local minima, barriers to rotation, free energy time-dependent dynamic behavior, and simulations. [27]

2.6. TARGET PROTEIN AND ACTIVE SITE PREDICTION:

The various literature surveys were taken into consideration for the evaluation of protein and the active sites.

2.7. MOLECULAR DOCKING:

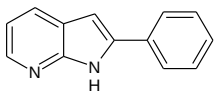
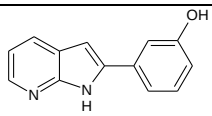
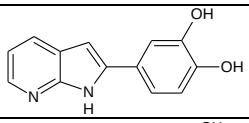
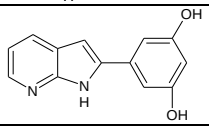
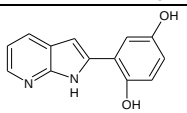
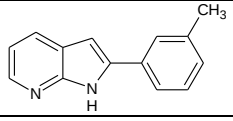
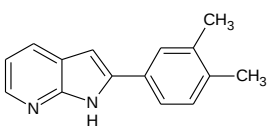
To carry out docking study, Accelrys drug discovery studio 3.5 are used. In this study, ligand were designed using chemsketch/chemdraw and protein were downloaded from protein data bank (PDB) with the link (http://www.rcsb.org/pdb/home/home.do). E.g. to download bromodomain protein 4HY3 is the PDB code. Hydrogen were added to interact with amino acid present in the particular protein which is seen in 2D structure. To add the hydrogen click on chemistry then hydrogen add. Both the ligand and protein should prepared. Ligand were prepared on clicking small molecule followed by prepare ligand and then ligand minimization were done. Protein preparation were done on clicking macromolecules then prepare protein followed by full minimization of protein once both the ligand and protein were prepared the click on receptor ligand interaction, List will be display, click on define and editing binding sites, click on receptor cavities click on docking ligand (C-Docker), Box will appear (In parameter value), Input receptor = 4hy3, Input ligand = add all the ligand. Click on run. [27]

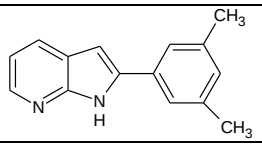
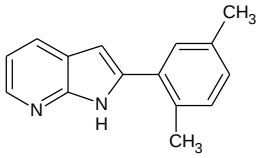
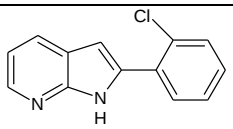
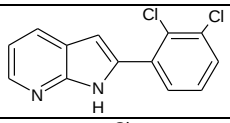
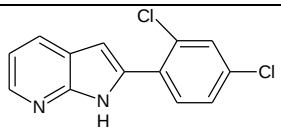
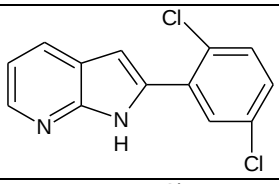
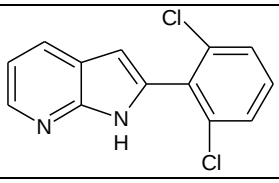
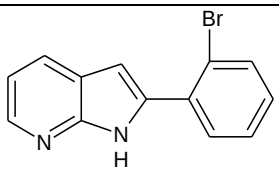
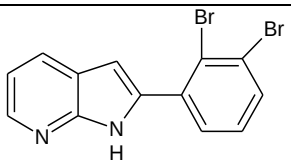
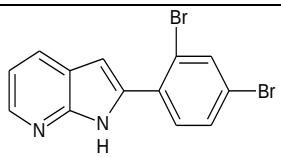
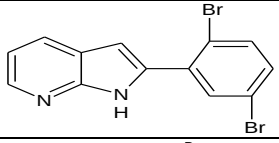
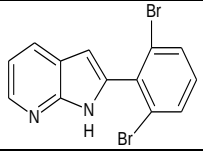
3.0 RESULTS AND DISCUSSION:

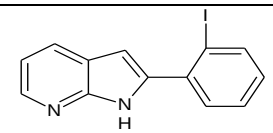
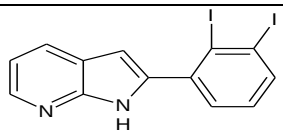
3.1. Drug Likeness: [27]

The 7-azaindole derivative designed compound having good number of hydrogen bond acceptor and donor. The hydrogen bond donor ranges from 1 to 3 whereas acceptor having 1 to 3. The compound were designed to enhanced the binding with the receptor by means of hydrogen bonding, all the 7-azaindole derivative designed compound follow the Lipinski rule of 5 and increases the drug likeness properties that are mention in **Table 1** polar surface areas were taken into considered to know the amount of drug to permeate through cell membrane. All pyrimidine derivatives designed compound are within the permissible limit and having no bioavailability problem.

Table 1: Drug likeness[27]

Compound structure	Compound code	Number of H-bond (donor)	Number of H-Bond (acceptor)	A log P	Molecular weight	Molecular fractional polar surface area
	**1a**	1	1	2.98	194.23	0.15
	**2a**	2	2	2.73	210.23	0.24
	**3a**	3	3	2.49	226.23	0.32
	**4a**	3	3	2.49	226.23	0.32
	**5a**	3	3	2.49	226.23	0.32
	**6a**	1	1	3.46	208.25	0.14
	**7a**	1	1	3.95	222.28	0.12

	**8a**	1	1	3.95	222.28	0.12
	**9a**	1	1	3.95	222.28	0.12
	**10a**	1	1	3.64	228.67	0.13
	**11a**	1	1	4.31	263.12	0.12
	**12a**	1	1	4.31	263.12	0.12
	**13a**	1	1	4.31	263.12	0.12
	**14a**	1	1	4.31	263.12	0.12
	**15a**	1	1	3.73	273.12	0.13
	**16a**	1	1	4.47	352.02	0.11
	**17a**	1	1	4.47	352.02	0.11
	**18a**	1	1	4.47	352.02	0.11
	**19a**	1	1	4.47	352.02	0.11

	**20a**	1	1	3.56	320.12	0.12
	**21a**	1	1	4.13	446.02	0.10

3.2. ADME INVESTIGATION:

Accelrys drug discovery studio 3.5. was used to calculate in silico ADME parameters. They were calculated to avoid failure of the drug in the final stages of discovery process. All the designed 21 compounds possessed aqueous solubility level in the range of 2 (−6.0 < log (molar solubility) <−4.0) and 3 (−4.0 < log (molar solubility) <−2.0) which indicates that the designed compounds possessed low to good aqueous solubility.The blood brain barrier (BBB) level were in the range of 0-2 indicating that the designed compounds possessed very high to medium penetration level.The level of CYP2D6 is 1 which indicate the inhibition and hepatotoxic is less than 1 indicating the compound is non- toxic. All these compound indicate that the designed compounds could be druggable and hence it was further processed for docking studies. The details of the ADME investigation were specified in **Table 2.** [27]

Table 2: ADME investigation of the designed compounds[27]

Compound code	Aqueous solubility Level	BBB Level	CYP2D6	Hepatotoxicity Level	PPB Level
1a	2	1	-3.86	0.09	0.13
2a	3	2	-3.87	0.15	0.02
3a	3	2	-4.06	0.08	0.00
4a	3	2	-3.66	0.01	0.00
5a	3	2	-4.16	0.08	0.00
6a	2	1	-3.12	0.19	0.36
7a	2	1	-2.86	0.12	0.11
8a	2	1	-3.66	0.08	0.01
9a	2	1	-3.16	0.12	0.11
10a	2	1	-1.30	8.56	0.01
11a	2	0	-0.93	1.31	0.01
12a	2	0	-0.30	0.03	0.01
13a	2	0	-1.13	0.03	0.01
14a	2	0	-1.23	1.31	0.17
15a	2	1	-3.21	0.26	0.33
16a	2	0	-2.39	0.21	0.28
17a	2	0	-2.56	0.03	0.05
18a	2	0	-2.56	0.03	0.05
19a	2	0	-2.39	0.21	0.28
20a	2	1	-3.12	0.25	0.31
21a	2	1	-3.25	0.09	0.12

3.3. VIRTUAL TOXICITY STUDIES:

TOPKAT predicts endpoint of toxicity based on chemical structure in Accelrys drug discovery studio 3.5. including NTP carcinogenicity (female Rat, Male Rat), Ames Mutagenicity, Rat Oral LD_{50}, Skin irritation and development of toxicity shown in **Table 3:** The various model were computed and recorded that satisfied all the validation criteria for the query compound that are show in the table number 3. The mutagenicity predict the drug's potential to cause human cell to mutate, which is based on Ames research carcinogenicity assay and estimate the

compound potential to cause normal human cell to get cancer, the toxicity studies was carried out for both the male and female rat to reduce the time and cost in the clinical trial. The skin irritation test support the topical use of particular compound predicted to be non-toxic, if it ranges from 0 to 0.29 and if it ranges from 0.3 to 0.69 the compound is indeterminate, the compound having ranges from >0.7 and <1 is toxic. If the discriminant score is negative then probability of causing cancer is 0 or non-carcinogenicity in case, the discriminant score is positive the probability to getting cancer is high. [27]

Table 3a: Toxicity Studies [27]

Compound Code	NTP carcinogenicity (female rat)	Computed probability	NTP carcinogenicity (male rat)	Computed probability
1a	-3.27	0.44	-0.73	0.58
2a	-4.89	0.39	-4.86	0.38
3a	-5.21	0.38	-0.81	0.58
4a	-2.04	0.47	-1.97	0.53
5a	-2.41	0.46	-3.78	0.44
6a	-3.38	0.43	-2.08	0.52
7a	0.52	0.52	0.38	0.62
8a	-2.18	0.46	-3.01	0.48
9a	0.63	0.52	-0.45	0.59
10a	-2.70	0.45	-2.92	0.48
11a	-2.90	0.45	-3.27	0.47
12a	-4.56	0.40	-3.37	0.46
13a	-4.68	0.40	-2.05	0.53
14a	-3.061	0.44	-3.19	0.47
15a	0.72	0.52	0.96	0.64
16a	0.77	0.52	0.20	0.62
17a	0.53	0.52	0.59	0.63
18a	0.41	0.52	0.23	0.62
19a	-0.33	0.50	-0.970	0.57
20a	-1.44	0.4	-0.74	0.58
21a	-1.34	0.48	-0.99	0.57

Table 3b: Toxicity Studies[27]

Compound Code	Ames mutagenicity	Development of Toxicity	Rat oral LD_{50}	Skin irritation	Computed probability
1a	1.59	-7.01	0.14	-0.25	0.97
2a	0.93	-5.75	0.10	-0.96	0.97
3a	0.41	-3.45	0.15	-1.13	0.96
4a	-0.86	-3.67	0.04	-1.90	0.94
5a	0.17	-3.81	0.19	-0.86	0.97
6a	1.53	-6.09	0.31	-0.25	0.97
7a	1.47	-5.67	0.11	-0.46	0.97
8a	0.79	-5.19	0.28	-0.23	0.97
9a	0.52	-4.90	0.24	-0.17	0.97
10a	-0.55	-5.25	0.20	-0.67	0.97
11a	-3.89	-4.74	0.05	-0.43	0.97
12a	-2.55	-4.62	0.09	-0.42	0.97
13a	-1.75	-4.70	0.07	-0.19	0.97
14a	-1.11	-4.45	0.08	-0.33	0.97
15a	-1.95	-4.69	0.29	-0.62	0.97
16a	-2.31	-4.49	0.08	-0.32	0.97
17a	-5.73	-3.45	0.32	-0.31	0.97
18a	-3.99	-3.29	0.24	-0.07	0.99
19a	-2.95	-4.17	0.13	-0.21	0.97
20a	-1.20	-4.38	0.25	-0.454	0.97
21a	-2.029	-3.588	0.07	-0.38	0.97

3.4. DOCKING STUDIES:

Docking studies of the designed 7-azaindole derivatives compounds were carried out to find out the best fit orientation of the molecule with the specified target. The designed compounds were docked with 1K3A and 4HY3 using Accelrys drug discovery studio 3.5. Discovery Studio 3.5. From the results obtained, it was observed that all the designed compounds exhibited good binding with the targets. CDOCKER interaction energy for all the compounds ranges from **-26.64 to -18.75** with 1K3A receptor and from **-26.22 to -20.63** with 4HY3 receptor. Most of the compounds interact with amino acids such as VAL 215, GLY 105, LYS 325, and ASP 164 with 4HY3. The compound which is having 3, 5-dihydroxy substituent was found to be having good interaction with bromodomain with a hydrogen bond distance of **2.09Å**. In 1K3A receptor LEU 1143, LYS 1138 were involved in the binding with the designed derivatives. The compound which possesses 3, 4-dihydroxy substitutions were found to be having good interaction with 1K3A as shown in **TABLE 4 & 5[27]**

Table 4: Docking results with 1K3A[27]

Compound code	CDOCKER interaction Energy (-)	H-bond distance (Å)	Interacting amino acids	Interaction Ligand-residue
1a	18.75	1.96	LYS 1138	Attached to N
2a	21.00	2.16	GLU1016	Attached to H
3a	26.64	2.16	LYS1138	Attached to O
4a	26.11	2.16	LYS1138 LEU1143 LEU1143	Attached to O Attached to H Attached to O
5a	23.20	2.63	ARG1012	Attached to O
6a	21.17	2.16	GLY1125	Attached to NH
7a	21.93	2.16	ARG1128	Attached to N
8a	21.47	2.16	GLY1125	Attached to NH
9a	21.15	-	-	-
10a	16.77	-	-	-
11a	24.14	-	-	-
12a	22.10	2.00	LYS 1138	Attached to N
13a	19.34	-	-	-
14a	24.87	2.16	GLU 1016	Attached to NH
15a	22.57	-	-	-

Table 5: Docking results with 4HY3[27]

Compound code	CDOCKER interaction Energy(-)	H-bond distance in Å	Interacting amino acids	Interaction Ligand-residue
1a	21.69	-	-	-
2a	22.79	2.03	ASP 164	Attached to OH
3a	23.99	2.07	LYS 325 ASP164	Attached to OH Attached to OH
4a	26.22	2.09	VAL 215 GLY 105 LYS325 ASP164	Attached to OH Attached to OH Attached to N Attached to NH
5a	23.37	1.99	LYS 325 ASP 164	Attached to O Attached to H
6a	20.59	-	ASP 164 LYS 325	-
7a	19.44	2.09	LYS325 ASP164	Attached to NH Attached to N

Table 5: Docking results with 4HY3[27]

Compound code	CDOCKER interaction Energy(-)	H-bond distance in Å	Interacting amino acids	Interaction Ligand-residue
8a	21.46	2.00	-	Attached to N Attached to NH
9a	25.15	-	-	-
10a	22.58	-	-	-
11a	20.63	-	-	-
12a	20.413	-	-	-
13a	21.23	-	-	-
14a	21.48	-	-	-
15a	19.57	-	-	-
16a	24.56	-	-	-
17a	21.20	-	-	-
18a	21.17	-	LYS 325	-
19a	22.39	1.94	-	Attached to N
20a	27.73	-		-

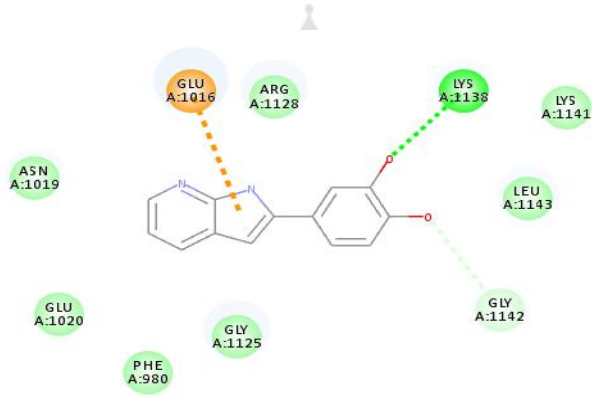


Figure 1: Binding interactions between 3a with 1K3A.

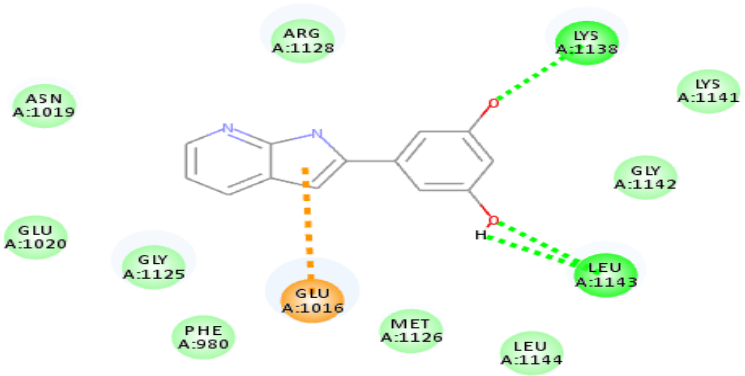


Figure 2: Binding interactions between 4a with 1K3A

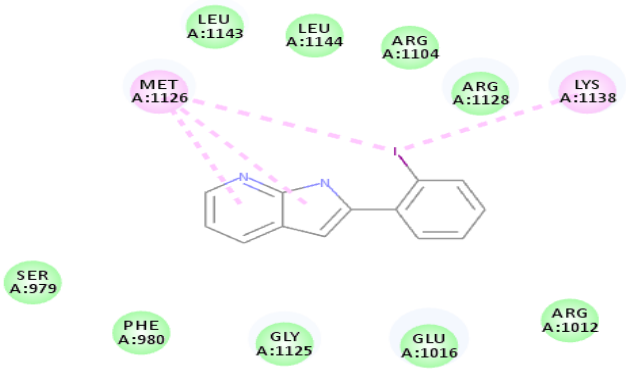


Figure 3: Binding interactions between 20a with 1K3A

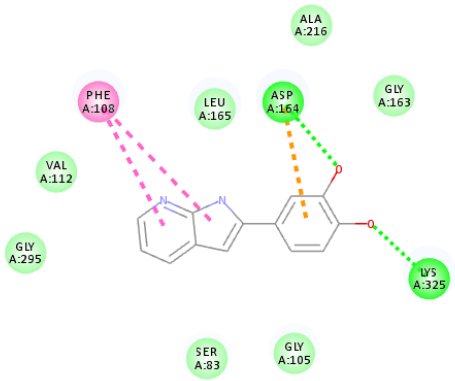


Figure 4: Binding interactions between 3a with 4HY3

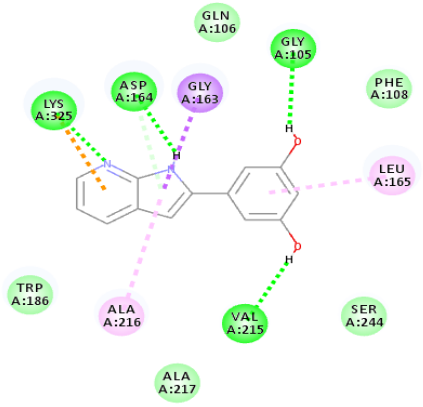


Figure 5: Binding interactions between 4a with 4HY3

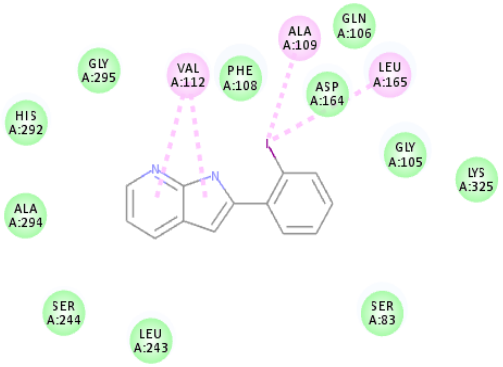


Figure 6: Binding interactions between 20a with 4HY3

4. CONCLUSION

In the present study twenty one 7-azaindole derivatives compound were designed and Drug Likeness, ADME studies, Virtual toxicity studies and molecular docking studies were carried out using Accelrys drug discovery studio 3.5. Most of the designed compounds possess 1 to 3 hydrogen donor and 1 to 3 hydrogen acceptor. All the compounds were found to follow Lipinski rule of 5 since it would increase drug likeness of the designed compounds. The aqueous solubility level ranges from 2-3 indicates that the designed compounds possessed low to good aqueous solubility. and The blood brain barrier (BBB) level were in the range of 0-2 indicating that the designed compounds possessed very high to medium penetration level.The level of CYP2D6 is 1 which indicate the inhibition and hepatotoxic is less than 1 indicating the compound is non- toxic. NTP Carcinogenicity Call (Female Rat, Male rat), Ames Mutagenicity, Rat Oral LD50, Skin Irritation, Developmental toxicity were virtually performed. From the discriminant score which was found to be negative, directly imply that the probability of causing cancer is 0 or the compound is non-carcinogenic. The 21 designed azaindole derivatives were then docked against 1K3A (Insulin growth factor) and 4HY3 (bromodomain) receptors The compounds were found to be having good interaction with amino acids such as VAL 215, GLY 105, LYS 325, ASP 164, LYS 1138, LEU 1143. Compound **3a**, **4a**, **14a** and **20a** were found to have maximum C-Docker interaction energy with 1K3A receptor. Compound **3a**, **4a**, **9a**, **16a** and **20a** were found to have maximum C-Docker interaction energy with 4HY3. From docking results it was concluded that the compound **3a** 4-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)benzene-1,2-diol, **4a** 5-(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)benzene-1,3-diol and **20a** 2-(2-iodophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine having hydroxyl substitution and Iodo substitution possess dual inhibition towards bromodomain and

insulin growth factor receptor and will be effective in the treatment diabetes related cancer. The significance of this work is to inhibits the over expression of bromodomain and insufficient insulin growth factor which is the major problem in both diabetes and also diabetes related cancer in the body. in order to inhibits we have designed the molecule in such a way that it will inhibits both the receptor respectively.

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