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R E S E A E C H A R T I C L E

In-Silico Design & Lead Optimization of Pyrazolo Quinazolines Derivatives using Docking, Virtual Screening Techniques

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A B S T R A C T

The pyrazolo quinazolines ring systems bearing various substituents at the C-3 position are widely distributed in nature. Luteolin is a flavanoid derivative, has been reported to have anti cancer, anti fungal, and other bacteriostatic activities. The broad spectrum of pharmacological activity in individual pyrazolo quinazolines indicates that this series of compounds is of an undoubted. Selection of protein is performed and 1GII is confirmed as best fit protein for CDK inhibitor. Ligands library is prepared based on the active pharmacophore. Virtual screening is performed and all the ligands are found to be with acceptable binding energy. ADMET predictions are performed and ligands with Toxicity, mutagencity, tumorogencity, irritant nature and ligands beyond Lipinski "Rule of five" are removed from the ligand library. The remaining ligands further screened by docking studies and binding energy and inhibition energy are calculated.

Keywords: Pyrazoles, Quinazolines, Ligands, Docking

A R T I C L E I N F O

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1. Introduction

In nature's collection of biologically active heterocyclic, benzofuran derivatives constitute a major group. The pyrazolo quinazolines ring systems bearing various substituents at the C-3 position are widely distributed in nature. Luteolin is a flavanoid derivative, has been reported to have anti cancer, anti fungal, and other bacteriostatic activities[1,2,3]. The broad spectrum of pharmacological activity in individual pyrazolo quinazolines indicates that

this series of compounds is of an undoubted. In silico advances in the recent trends has grabbed a wide range of tools for the optimization of lead molecules. Which reduces a lot of researcher's expenses, the tools like docking studies, virtual screening and ADME predictors are been used to optimize the lead molecules.(4) Cyclin Dependent Kinase (CDK) plays a vital role in control cell cycle progression from one phase to another, however, mutational changes in these molecules lead to the perturbed cell cycle leading to uncontrolled cellular proliferations. In human mutations CDK –II is responsible for cancers. (5) CDK-II is prominent protein found in major tumors, so CDK-II protein inhibitor is being opted for in silico screening of the lead benzofuranones

2. Materials and Methods

Selection of protein: CDK is the most abundantly found in tumor cell generation. So, CDK inhibitor has been selected for Docking the lead molecules, the protein database was searched in the portal http://www.rcsb.org, the protein was searched from a group and 1GII protein was found with species of Homosapiens with X-ray method was used in determination of the protein, with lowest resolution of 2.00A^{o} and validated for the Domain completeness.

Preparation of Protein:

The selected protein 1GII has been was explored in Auto dock 4.0, the bonds and atoms in the protein are optimized, missing hydrogen's are added, non polar center between the hydrogen's where merged and all the histidine hydrogen's are protonated with +1charge. Kollaman and gastegier charges were added to the protein. All the missing atoms are repaired and charges are applied to the protein.

Design of Ligands: The basic pyrazolo quinazolines was designed with modifications in the R^1, R^2, R^3, and R^4 of the molecule given below in figure: 1.

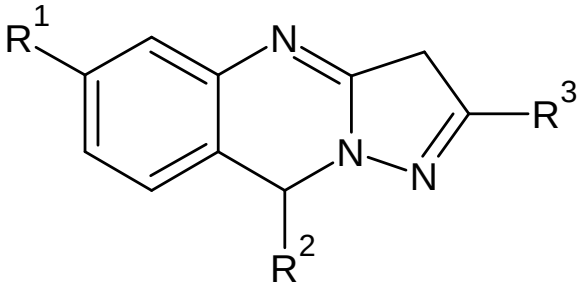

Figure 1

Table 1

R^1	CH_3,C2H5,NO2,CL , BR	5COMBINATIONS
R^2	NHCH3,NHC2H5, NHnC3H7,NHiC3 H7,NHC6H5,NC2 H6,NC4H10	7COMBINATIONS
R^3	NHCH3,NHC2H5, NHnC3H7,NHiC3 H7,NHC6H5,NC2 H6,NC4H10	7COMBINATIONS

Totally a library of 5x 7 = 35 ligands are designed

Table 2: Virtual screening results

S.No	Ligand	Target	Binding Energy	Info
1	1_uff_E=457.23	1GII	-8.8	Vina
2	5_uff_E=384.06	1GII	-8.7	Vina
3	33_uff_E=448.64	1GII	-8.7	Vina
4	31_uff_E=392.45	1GII	-8.7	Vina
5	28_uff_E=310.95	1GII	-8.7	Vina
6	17_uff_E=348.63	1GII	-8.7	Vina
7	18_uff_E=429.07	1GII	-8.6	Vina
8	25_uff_E=444.80	1GII	-8.6	Vina
9	24_uff_E=375.92	1GII	-8.6	Vina
10	14_uff_E=309.53	1GII	-8.6	Vina
11	4_uff_E=444.46	1GII	-8.6	Vina
12	11_uff_E=419.69	1GII	-8.5	Vina
13	9_uff_E=366.55	1GII	-8.5	Vina
14	8_uff_E=366.07	1GII	-8.5	Vina
15	15_uff_E=307.64	1GII	-8.5	Vina
16	12_uff_E=400.40	1GII	-8.5	Vina
17	22_uff_E=435.66	1GII	-8.5	Vina
18	27_uff_E=392.53	1GII	-8.5	Vina
19	29_uff_E=433.51	1GII	-8.5	Vina
20	26_uff_E=346.60	1GII	-8.5	Vina
21	23_uff_E=325.89	1GII	-8.5	Vina
22	30_uff_E=355.13	1GII	-8.5	Vina
23	32_uff_E=375.89	1GII	-8.5	Vina
24	16_uff_E=354.28	1GII	-8.5	Vina
25	3_uff_E=470.95	1GII	-8.5	Vina
26	10_uff_E=338.53	1GII	-8.4	Vina
27	2_uff_E=344.48	1GII	-8.4	Vina
28	6_uff_E=414.51	1GII	-8.4	Vina
29	7_uff_E=429.81	1GII	-8.4	Vina
30	35_uff_E=423.65	1GII	-8.4	Vina
31	20_uff_E=395.51	1GII	-8.4	Vina
32	13_uff_E=388.81	1GII	-8.4	Vina
33	19_uff_E=409.05	1GII	-8.4	Vina
34	21_uff_E=436.69	1GII	-8.4	Vina
35	35_uff_E=441.25	1GII	-8.4	Vina

3. Results and Discussions

Preparation of Ligands:

The above combinations of ligands were drawn with Chemsketch open source software obtained from http://www.acdlabs.com, as (.mol) file in 2D structural format. Then the ligands are under gone for energy optimization and converted (.pdb) 3D structural format by using Discovery studio visualiser 4.0 from http://accelrys.com and the angular forces between the bonds of ligands are minimized.

Virtual screening:

The optimized protein is then explored in virtual screening software and then ligand databank of the group is also linked and quantitative optimization is performed. Then computational parameters like autogrid, autovina, autodock are applied, protein is fixed in the grid box and Virtual screening is performed.

ADMET Profile Prediction of Ligands

Ligands are preliminary are studied for Adsorption, Distribution, Metabolism, Elimination, and Toxicity for search for best fit ligands. Lipinski rule of 5 is the best fit parameter for prediction of ADMET of ligands, Lipinski rule of 5 paramaetrs Log p (≤5), Molecular weight (≤500daltons), Hydrogen acceptors (≤5) and hydrogen acceptors (≤5). Molecules violate these parameters are found to be with poor bioavailability parameters. Data warrior of OSIRIS software is utilized for the prediction of the above parameters and the best fit results are listed below.

Docking studies: The best fit ligands from primary filtration by virtual screening and docking are then subjected to secondary Insilco studies (Docking).

Protein and Ligand Preparation:

Auto dock 4.0 open source software is utilized for the docking studies. The optimized protein file (1GII) is explored in the auto dock 4.0, then optimized ligand is fit in it and 3D structural energy is minimized, torrisions of the ligands are verified, adjusted and ligand is stored as (.pdbqt) parameter.

Grid Allignment:

The protein (1GII) is explored in 3D space and grid box is fixed on the macromolecule protein and grid adjusted such that all binding pockets are aligned in the grid, and other parameters are fixed and grid parameter file (.gpf) is prepared.

Docking parameters:

The macromolecule and ligand are exposed then genetic algorithm search, auto dock 4.2 parameters are fixed. Lamirikan genetic algorithm for docking (.dpf) is prepared.

Docking:

The prepared grid parameter file is then docked over with standard grid path database and grid log file (.glg) is prepared. The docking parameter file is then docked with comparison to the standard docking path file and docking score are obtained.

Table 3: ADMET Profile Prediction Of Ligands

Molecule Name	cLogP	cLogS	H-Acceptors	H-Donors	Total Surface Area	Polar Surface Area	Druglikeness	LE from Molecule Name	LLE from Molecule Name	LELP from Molecule Name	Mutagenic	Tumorigenic	Reproductive Effective	Irritant
1	2.4351	-2.98	4	1	224	55.76	0.2867	0.64984	6.5649	3.7472	none	none	none	none
2	2.7108	-3.294	4	0	239	44.76	0.25055	0.5967	5.9882	4.543	none	none	none	none
3	3.1247	-3.62	3	0	236	35.53	0.21835	0.61539	5.3982	5.0776	none	none	none	none
4	3.1247	-3.62	3	0	220	35.53	0.21835	0.60637	5.2732	5.1532	none	none	none	none
5	3.5403	-3.779	3	0	239	35.53	0.024994	0.5694	4.7607	6.2176	none	none	none	none
6	2.1035	-3.352	4	1	222	61.55	0.42647	0.59365	6.1183	3.5433	none	none	none	none
7	1.8592	-3.736	5	0	244	81.35	-4.8386	0.53274	6.2957	3.4899	none	none	none	none
8	3.506	-4.11	3	0	234	35.53	-1.5395	0.58463	4.5909	5.9969	none	none	none	none
9	3.3868	-4.012	3	0	231	35.53	0.34327	0.58094	4.659	5.8299	none	none	none	none
10	2.7108	-3.294	4	0	234	44.76	0.25055	0.54875	5.2892	4.9399	none	none	none	none
11	2.3651	-2.998	5	1	241	64.99	0.2867	0.51992	5.5935	4.549	none	none	none	none
12	2.6408	-3.312	5	0	276	53.99	0.25055	0.49393	5.28	5.3465	none	none	none	none
13	3.0547	-3.638	4	0	265	44.76	0.21835	0.51518	4.8314	5.9294	none	none	none	none
17	3.436	-4.128	4	0	263	44.76	-1.5395	0.50757	4.3336	6.7696	none	none	none	none
18	3.3168	-4.03	4	0	260	44.76	0.34327	0.50594	4.4279	6.5557	none	none	none	none
19	2.4351	-2.98	4	1	221	55.76	0.2867	0.55751	5.2861	4.3678	none	none	none	none
21	2.3651	-2.998	5	1	244	64.99	0.2867	0.50157	5.3127	4.7154	none	none	none	none
22	2.779	-3.324	4	1	238	55.76	0.259	0.52526	4.8786	5.2907	none	none	none	none
28	3.1247	-3.62	3	0	235	35.53	0.21835	0.54535	4.4281	5.7297	none	none	none	none
30	3.0547	-3.638	4	0	245	44.76	0.21835	0.49145	4.4682	6.2157	none	none	none	none

Table 4: List of best fit molecules with docking score

S.NO	Molecule no	Binding energy	IC 50	IC 50 UNITS	No. of Confirmations
1	1	-9.53	103.7	NANO MOLAR	7
2	2	-9.34	141.87	NANO MOLAR	6
3	3	-9.21	176.58	NANO MOLAR	10

4	4	-9.05	232.38	NANO MOLAR	7
5	5	-8.29	840.64	NANO MOLAR	10
6	6	-8.26	888.6	NANO MOLAR	8
7	7	-8.22	936.1	NANO MOLAR	7
8	8	-8.22	946.25	NANO MOLAR	7
9	9	-8.19	996.33	NANO MOLAR	8
10	10	-8.13	1.09	MICRO MOLAR	9
11	11	-8.12	1.11	MICRO MOLAR	9
12	12	-8.1	1.15	MICRO MOLAR	10
13	13	-8.08	1.2	MICRO MOLAR	10
14	17	-8.07	1.22	MICRO MOLAR	10
15	18	-8.06	1.24	MICRO MOLAR	10
16	19	-8.04	1.27	MICRO MOLAR	9
17	21	-8.02	1.33	MICRO MOLAR	8
18	22	-8	1.39	MICRO MOLAR	9
19	28	-7.99	1.39	MICRO MOLAR	8
20	30	-7.99	1.39	MICRO MOLAR	9

4. Conclusion

Selection of protein is performed and 1GII is confirmed as best fit protein for CDK inhibitor. Ligands library is prepared based on the active pharmacophore. Virtual screening is performed and all the ligands are found to be with acceptable binding energy. ADMET predictions are performed and ligands with Toxicity, mutagencity, tumorogencity, irritant nature and ligands beyond Lipinski "Rule of five" are removed from the ligand library. The remaining ligands further screened by docking studies and binding energy and inhibition energy are calculated.

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