Research Article

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Novel Imidazole 2-Amino Pyrimidine Derivatives: *In silico* Studies, Evaluation of Their Anti-Cancer Activity Against Human-CDK2

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ABSTRACT

In drug discovery process the identification of lead compounds by virtual screening is a novel approach. From the literature it is understood that imidazoles and pyrimidines have gained much importance among the medicinal chemists because of their flexible structure and varied pharmacological activities. In present study imidazole and 2-amino pyrimidine derivatives were designed, subjected to the structure based virtual screenings in order to find the novel anticancer agents against human CDK2 protein. The molecular properties and molecular toxicity prediction was done using various online softwares like Molinspiration, Molsoft, OSIRIS, pkCSM along with bioactivity properties. The derivatives which exhibited drug like property were further subjected to molecular docking studies using Autodock Vina. Hits are identified, the basic pharmacophoric features responsible for the anticancer activity were predicted. Based on docking results the compound 24, which exhibited highest binding interaction with receptor will be further synthesized and can be novel lead for the development of anticancer agents.

Keywords: Virtual Screening, Autodock Vina, pkCSM, Anticancer Activity, Human CDK2

1. Introduction

Tumors are the leading cause of death. Currently many anticancer agents are available but have to compromise with their intolerance, side effects, site specific target, etc. Cyclin dependent kinase-2 and/or cell division protein kinase-2 is an enzyme in humans encoded by CDK2 gene. The activity of cyclin dependent kinase-2 is restricted to G1-S phase of the cell cycle and play a very important role in tumor development. CDK2 acts as check points and are associated with regulatory subunits of complex such as cyclin E or A, that binds to the G1 phase. On other hand imidazole is one such scaffold having potential to overcome the disadvantages associated with current anticancer therapy [1]. Imidazole and pyrimidine are a class of heterocyclic compounds with a variety of interesting and varied pharmacological actions such as antiparasitic [2], antiprotozoal [3], antileishmanial [4], antioxidant [5], anticancer [6-11], anti-inflammatory [12, 13], anti-fungal [14-16], herbicidal [17], insecticidal [18], antiviral [19, 20] and antihypertensive activity [21]. Yi-Zhe Wu et al. [22], synthesized a series of 3H-imidazole[4,5-c]pyridine derivatives as CDK2 inhibitors and concluded that among the series the compound 5b exhibited the highest CDK2 inhibition with a IC 50 value of 21 nM can be a novel target for development of targeted anticancer agents. Al-Warhi et al. [23] synthesized imidazole/benzimidazole thio-arylethanone derivatives as CDK2 inhibitors and concluded that among the series, the compound 10e displayed the greatest *in vitro* potency against CDK2 with a IC_{50} values of 0.62 µM with acceptable pharmacokinetic properties and thus can be a potential lead to be develop as anticancer agent. Singh et al. [24] synthesized a series of 3-pyrimidineylazaindole derivatives and reported that among the series the compound 8a, was not only potent against CDK2, but also proved druglike properties with the hydrogen bond interaction at the active site of CDK receptor with Asp-145, Leu-83, Lys-33, Glu-51 and Glu-81. Diao PC et al. [25] designed novel pyrimidine fused benzthiazole derivatives against CDK2, and concluded that the compound 9a possessed the highest CDK2 inhibition activity than standard with a IC_{50} value of 15.4 nM. Also the docking studies revealed that the hydrogen bond interactions were important to inhibit the enzyme CDK2 with active site interactions at Asp-86, Leu-83, Lys-33. Wang et al. [26] synthesized a series of novel pyrimidine derivatives against CDK2, and concluded that among the series the compound 10a was the most potent compound with a IC_{50} value of 45.8µM, further the compound showed the hydrogen bond interactions with the active site of receptor CDK at Leu-83, Gln-131 and hydrophobic interaction with Asp-86. Ajani H et al. [27], synthesized a series of imidazole pyrimidine derivatives and evaluated their anticancer activity against CDK2 and concluded that the compound 3j was active compounds among the series with a IC_{50} value of 1.3 µM, also the ligands showed the hydrogen bond interactions with active site of protein at Lys33, Glu51, Asp145, indicating that hydrogen bonding is essential to inhibit the CDK2 activity. Also a number of fused pyrimidine and imidazole derivative are under clinical trials against CDK2 like AZD5438 (phase-1 clinical trial completed), AT7519 (phase-2 clinical trial completed), R547 (phase-1 clinical trial completed), Milcicib (Phase-2 clinical trial), Dinaciclib (Phase 3 clinical trial) and drugs like PHA-793887 and rosocovitine were terminated from the clinical trial, due to dose related severe hepatotoxicity and limited potency. The data for the above clinical trial drugs can be obtained from https://clinicaltrials.gov and https://www.selleckchem.com/CDK.html. Based on the above literature findings it is endeavoured that a combination of imidazole and 2-amino pyrimidine can be a fruitful outcome for the design and development of the targeted CDK2 inhibitors. The imidazole is linked to 2-amino pyrimidine and substituted at 4th-position with various electron donating and accepting groups on 2-amino pyrimidine to form various substituted imidazole-pyrimidine derivatives as represented in the Table 1. Also to avoid the wastage of chemicals, time and money involved in direct synthesis, prior physicochemical properties were predicted using various online softwares and molecules docking studies performed help to find potent compound among the designed molecules. The designed derivatives were docked using Autodock VINA software (Flexible docking) against the protein human cyclin dependent kinase-2 complexed with the CDK4 Inhibitor (1GII). The designed compounds which show the highest binding affinity with protein target can be act as promising lead to develop the novel potent anticancer agents.

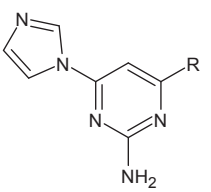
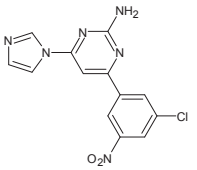
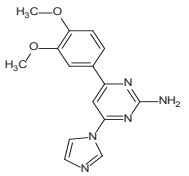
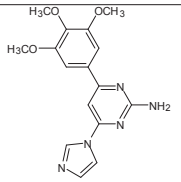
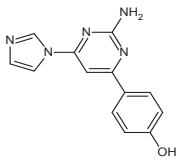
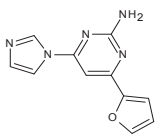
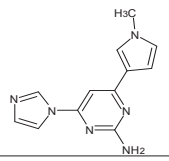
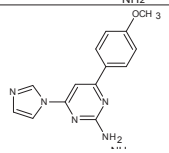
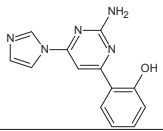
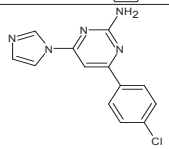


Figure 1. General structure of designed imidazole 2-amino pyrimidine derivatives

Table 1. Structure and IUPAC names of the designed imidazole 2-amino pyrimidine derivatives

Compd	Structure	IUPAC name
1		4-(3-chloro-5-nitrophenyl)-6-(1H-imidazol-1-yl)pyrimidin-2-amine
2		4-(3,4-dimethoxyphenyl)-6-(1H-imidazol-1-yl)pyrimidin-2-amine
3		4-(1H-imidazol-1-yl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine
4		4-[2-amino-6-(1H-imidazol-1-yl)pyrimidin-4-yl]phenol
5		4-(furan-2-yl)-6-(1H-imidazol-1-yl)pyrimidin-2-amine
6		4-(1H-imidazol-1-yl)-6-(1-methyl-1H-pyrrol-2-yl)pyrimidin-2-amine
7		4-(1H-imidazol-1-yl)-6-(4-methoxyphenyl)pyrimidin-2-ami
8		2-[2-amino-6-(1H-imidazol-1-yl)pyrimidin-4-yl]phenol
9		4-(4-chlorophenyl)-6-(1H-imidazol-1-yl)pyrimidin-2-amine

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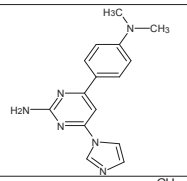
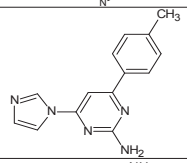
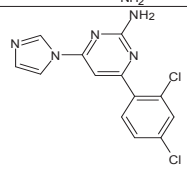
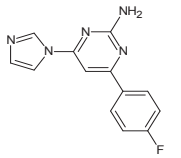
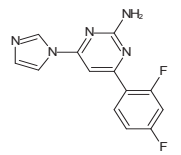
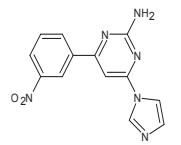
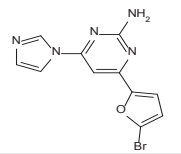
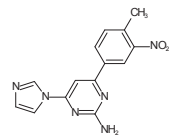
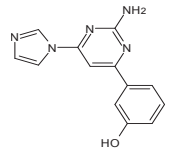
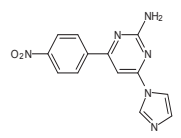
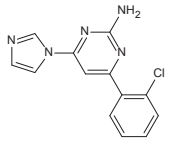
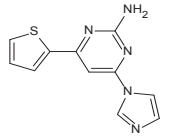
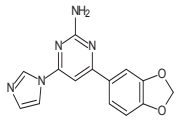
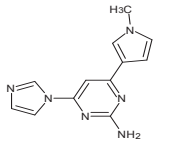
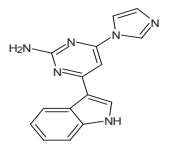
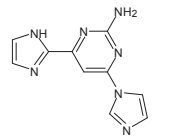
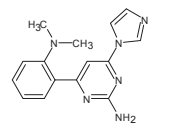
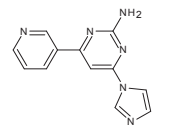
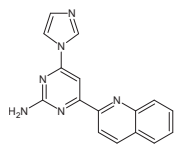
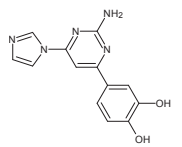
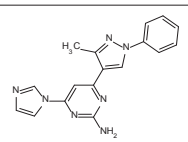
10		4-[4-(dimethylamino)phenyl]-6-(1H-imidazol-1-yl)pyrimidin-2-amine
11		4-(1H-imidazol-1-yl)-6-(4-methylphenyl)pyrimidin-2-amine
12		4-(2,4-dichlorophenyl)-6-(1H-imidazol-1-yl)pyrimidin-2-amine
13		4-(4-fluorophenyl)-6-(1H-imidazol-1-yl)pyrimidin-2-amine
14		4-(2,4-difluorophenyl)-6-(1H-imidazol-1-yl)pyrimidin-2-amine
15		4-(1H-imidazol-1-yl)-6-(3-nitrophenyl)pyrimidin-2-amine
16		4-(5-bromofuran-2-yl)-6-(1H-imidazol-1-yl)pyrimidin-2-amine
17		4-(1H-imidazol-1-yl)-6-(4-methyl-3-nitrophenyl) pyrimidin-2-amine
18		3-[2-amino-6-(1H-imidazol-1-yl)pyrimidin-4-yl]phenol
19		4-(1H-imidazol-1-yl)-6-(4-nitrophenyl)pyrimidin-2-amine

20		4-(2-chlorophenyl)-6-(1H-imidazol-1-yl)pyrimidin-2-amine
21		4-(1H-imidazol-1-yl)-6-(thiophen-2-yl)pyrimidin-2-amine
22		4-(2H-1,3-benzodioxol-5-yl)-6-(1H-imidazol-1-yl) pyrimidin-2-amine
23		4-(1H-imidazol-1-yl)-6-(1-methyl-1H-pyrrol-3-yl) pyrimidin-2-amine
24		4-(1H-imidazol-1-yl)-6-(1H-indol-3-yl)pyrimidin-2-amine
25		4-(1H-imidazol-1-yl)-6-(1H-imidazol-2-yl)pyrimidin-2-amine
26		4-[2-(dimethylamino)phenyl]-6-(1H-imidazol-1-yl) pyrimidin-2-amine
27		4-(1H-imidazol-1-yl)-6-(pyridin-3-yl)pyrimidin-2-amine
28		4-(1H-imidazol-1-yl)-6-(quinolin-2-yl)pyrimidin-2-amine
29		4-[2-amino-6-(1H-imidazol-1-yl)pyrimidin-4-yl]benzene-1,2-diol
30		4-(1H-imidazol-1-yl)-6-(3-methyl-1-phenyl-1H-pyrazol-4-yl)pyrimidin-2-amine

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2. Material and Methods

2.1. Molecular property prediction, bioactivity prediction and ADMET properties

In silico studies involves the simulation of molecules on a computer and are used to find the ADMET parameters of a large data to optimize the lead molecules by comparing their ADMET properties and screening the drug candidates. Properties predicted mainly includes hydrophobicity, molecular size, flexibility and presence of various pharmacophoric features which influence the behavior of molecules in a living organism, including oral bioavailability. The softwares that were used to calculate the molecular properties include Molsoft [28], Molinspiration [29], pkCSM [30], OSIRIS [31], to evaluate the drug likeness and toxicity of the designed compounds. Molsoft a very robust and fast online tool that determines the chemical properties of compounds based on fragmentation method, which involves splitting up of a molecule into a set of linear or non-linear fragments of different sizes and representation levels and counting the number of occurrences of each chemical pattern found. Then a partial least squares (PLS) regression model will be built and optimized for a particular property to be calculated like molecular formula, molecular weight, number of hydrogen bond acceptors, number of hydrogen bond donors, octanol/water partition coefficient, water solubility, polar surface area, volume, number of stereo centers and drug likeness model score. Molinspiration is an independent online research tool that uses modern Cheminformatics techniques that helps to calculate molecular properties required for drug design and QSAR studies like Lipinski rule of five, molecular volume and total number of atoms present in a molecule along with finding the bioactivity of designed compounds against GPCR ligand activity, ion channel modulator activity, kinase inhibition activity and nuclear receptor activity. pkCSM is another online tool which is used to predict the ADMET parameters. New drug development is a challenging task, involving time, money, labor and one of the drawback for drugs to reach market is their poor pharmacokinetic and toxicity properties. The computational software pkCSM, minimizes this risk of developing unfruitful drugs and instead helps in development of more effective and safe drugs. An immensely important property of drug molecules is their teratogenic effect that can be easily identified by using online OSIRIS property explorer, which is an integral part of Actelion's in house substance. The results for a particular compound are displayed in color codes. The red color is an indication of high risks undesired effects like mutagenicity, while the green color indicates drug confirm behavior and is safe to be considered.

2.2. Docking studies

Molecular docking is a method that finds the best orientation of a ligand with the particular receptor of interest [32, 33]. Molecular docking along with scoring function is used to screen huge databases [34] for finding out potential drug candidates *in silico*, which in turn targets the protein of interest [35]. The molecular docking tool used in the study was Autodock Vina. In the optimization of docking study of Vina, a variety of stochastic global optimization approaches were explored, including genetic algorithms [36, 37]. RMSD value for native ligand was found to be 0.5. A receptor grid was generated around the protein active site where the ligands bind, to get precise scoring of a particular ligand poses. The dock score energies [38] of analogs, further clarify the design of potential drug candidates. The docking was performed by using Autodock Vina software, installed on an Intel Core Processor (i5-3317U CPU @ 1.70 GHz) with 6 GB RAM and Windows 7 with 64-bit Operating System. The protein target (Human cyclin dependent kinase-2) was downloaded from protein data bank (PDB ID: 1GII) rcbs [39]. Around the co-crystallized ligand a grid was generated. By using MGL Tools & Pharmit the coordinates (x = 5.129, y = 8.593, z = 25.667) were generated to have an interactive exploration of chemical space (http://pharmit.csb.pitt.edu/). Docking was performed, after the pdbqt files for both target & ligands were prepared and docking was performed in the absence of water molecules for all 31 molecules (30+1 standard drug). By using discovery studio, the molecules were visualized for the interactions with the active site on amino acids [40].

3. Results and Discussion

3.1. Molecular property results

The predicted properties by using Molsoft application of molecules (1-30) are showed in the Table 2. While the Table 3, represents properties calculated using Molinspiration, which also predicts the drug-likeness and bioactivity properties as well. From the

Table 2. Represents the calculated properties of imidazole pyrimidine derivatives using molsoft software

Compd	No.of HBA[a]	No.of HBD[b]	Mol Log P[c]	Mol Log S[d]	Mol PSA[e]	Mol Vol.[f]	No. of Stereocenters[g]	DLMS[h]
1.	5	2	2.54	-3.31	84.27	249.20	0	-0.49
2.	5	2	0.62	-1.28	66.45	270.18	0	-0.07
3.	6	2	-0.21	-0.70	74.17	302.02	0	-0.18
4.	4	3	1.91	-1.41	68.81	217.46	0	-0.15
5.	4	2	1.47	-1.37	59.00	197.41	0	-0.72
6.	3	2	0.19	-0.36	55.47	217.79	0	-0.47
7.	4	2	1.53	-1.59	58.74	238.75	0	-0.20
8.	4	2	2.41	-2.46	67.74	218.00	0	-0.26
9.	3	2	3.07	-3.28	51.19	224.10	0	-0.11
10.	3	2	2.54	-2.64	54.00	256.46	0	-0.40
11.	3	2	2.92	-3.12	51.19	227.85	0	-0.38
12.	3	2	3.38	-4.09	51.19	239.42	0	-0.05
13.	3	2	2.54	-2.64	51.19	212.82	0	-0.27
14.	3	2	2.48	-2.81	51.19	217.69	0	-0.22
15.	5	2	2.30	-2.35	84.57	231.97	0	-0.69
16.	4	2	2.13	-2.39	60.12	209.06	0	-0.54
17.	5	2	2.66	-2.90	84.27	252.60	0	-0.56
18.	4	3	2.00	-1.20	68.81	217.53	0	-0.24
19.	5	2	2.40	-2.60	84.57	231.90	0	-0.66
20.	3	2	2.67	-3.56	51.19	222.15	0	-0.26
21.	4	2	2.00	-1.74	52.21	201.79	0	-0.41
22.	5	2	2.31	-2.56	68.31	246.74	0	-0.56
23.	3	2	0.92	-0.60	55.47	217.79	0	-0.47
24.	3	3	2.47	-2.97	61.06	245.77	0	-1.03
25.	4	3	0.40	-1.48	71.65	188.21	0	-0.63
26.	3	2	2.58	-2.89	53.70	256.49	0	-0.44
27.	4	2	1.02	-0.53	60.71	202.39	0	-0.35
28.	4	2	2.47	-3.00	59.52	250.82	0	-0.58
29.	5	4	1.43	-0.98	84.29	230.18	0	0.10
30.	4	2	2.31	-2.46	65.90	284.09	0	-0.20
DB04186	3	2	2.20	-2.86	58.35	306.50	1	0.32

a. No. of hydrogen bond acceptors; b. No. of hydrogen bond donars; c. Molecular octanol/water partition coefficient; d. water solubility; e. Molecular Polar Surface Area; f. Molecular Volume; g. No. of stereocenters; h. Druglikeness Score

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Table 3: Represents the Molinspiration properties of the designed imidazole pyrimidine (1-30) derivatives

Com.	LogP[a]	TPSA[b]	nAtoms[c]	M.wt[d]	Non[e]	nOHNH[f]	n-Viol[g]	Nrotb[h]	M.Vol.[i]
1	2.15	115.46	22	316.71	8	2	0	3	247.92
2	1.23	88.10	22	297.32	7	2	0	4	2621.2
3	1.22	97.33	24	327.34	8	2	0	5	287.68
4	1.10	89.86	19	253.26	6	3	0	2	219.06
5	0.53	82.77	17	227.23	6	2	0	2	192.62
6	0.45	74.75	18	240.27	6	2	0	2	212.97
7	1.64	78.87	20	267.29	6	2	0	3	236.59
8	1.32	89.86	19	253.26	6	2	0	2	219.06
9	2.26	69.63	19	271.71	5	2	0	2	224.58
10	1.69	72.87	21	280.33	6	2	0	3	256.95
11	2.03	69.63	19	251.29	5	2	0	2	227.61
12	2.87	69.63	20	306.16	5	2	0	2	238.12
13	1.75	69.63	19	255.26	5	2	0	2	215.98
14	1.84	69.63	20	273.25	5	2	0	2	220.91
15	1.52	115.46	21	282.26	8	2	0	3	234.38
16	1.66	82.77	18	306.12	6	2	0	2	210.50
17	1.92	115.46	22	296.29	8	2	0	3	250.94
18	1.08	89.86	19	253.26	6	3	0	2	219.06
19	1.54	115.46	21	282.26	8	2	0	3	234.38
20	2.21	69.63	19	271.71	5	2	0	2	224.58
21	1.37	69.63	17	243.29	5	2	0	2	201.76
22	1.48	88.10	21	281.27	7	2	0	2	234.98
23	0.49	74.57	18	240.27	6	2	0	2	212.97
24	1.74	85.42	21	276.30	6	3	0	2	240.03
25	-0.11	98.32	17	227.23	7	3	0	2	191.88
26	1.64	72.87	21	280.33	6	2	0	3	256.95
27	0.51	82.53	18	238.25	6	2	0	2	206.89
28	1.69	82.53	22	288.31	6	2	0	2	250.88
29	0.62	110.09	20	269.26	7	4	0	2	227.08
30	1.46	87.46	24	317.36	7	2	0	3	280.23
DB04186	1.81	74.33	23	308.34	6	2	0	2	272.40

a.LogP-Octonol/Water Partition Coefficient; b. Tpsa-Total Polar Surface Area; c. No. of atoms; d. Molecular Weight; e. No. of Hydrogen Acceptors; f.No. Of Hydrogen Donors; g. no. of violations
h.No. of Rotatable Bonds; i. MV-Molecular Volume

above results it is clear that all the compounds accepted Lipinski rule indicating that they show good oral absorption theoretically. While the bioactivity results of the designed (1-30) compounds are represented in Table 4. All the compounds displayed good activity when compared to standard against GPRCP Ligands, kinase inhibitor and enzyme inhibitor. The compounds displayed highest enzyme inhibition activity with a bioactivity score range of 0.20-0.87 when compared to standard with 0.08, which indicates that these drugs can be developed as potent enzyme inhibitors.

From the pkCSM studies performed (Table 5) for compounds (1-30) indicates that all the compounds

Table 4: Represents the bioactivity of the designed imidazole 2-amino pyrimidine derivatives (1-30)

Compd	GPCRL[a]	ICM[b]	KI[c]	NRL[d]	PI[e]	EI[f]
1	0.14	0.04	0.62	-0.29	-0.38	0.35
2	0.26	0.04	0.78	-0.22	-0.23	0.46
3	0.24	0.02	0.72	-0.26	-0.19	0.41
4	0.32	0.22	0.85	-0.14	-0.26	0.64
5	0.14	-0.14	0.48	-0.76	-0.69	0.44
6	0.28	0.13	0.94	-0.20	-0.46	0.73
7	0.24	0.05	0.75	-0.28	-0.29	0.49
8	0.28	0.13	0.80	-0.21	-0.30	0.56
9	0.27	0.16	0.77	-0.35	-0.33	0.53
10	0.32	0.11	0.83	-0.20	-0.20	0.50
11	0.21	0.06	0.73	-0.36	-0.35	0.49
12	0.34	0.16	0.80	-0.27	-0.23	0.48
13	0.28	0.14	0.83	-0.29	-0.31	0.55
14	0.33	0.24	0.92	-0.23	-0.24	0.56
15	0.13	0.06	0.65	-0.34	-0.34	0.41
16	0.15	-0.21	0.29	-1.26	-0.77	0.20
17	0.09	-0.01	0.59	-0.31	-0.36	0.31
18	0.32	0.22	0.88	-0.13	-0.27	0.65
19	0.13	0.07	0.62	-0.34	-0.34	0.39
20	0.30	0.15	0.18	-0.32	-0.28	0.51
21	0.02	-0.04	0.71	-0.70	-0.56	0.49
22	0.30	0.04	0.76	-0.29	-0.24	0.51
23	0.38	0.16	1.14	-0.22	-0.56	0.77
24	0.45	0.27	1.14	-0.06	-0.27	0.71
25	0.56	0.47	1.12	-0.64	-0.14	0.87
26	0.26	0.14	0.80	-0.37	-0.26	0.50
27	0.31	0.28	0.98	-0.41	-0.28	0.71
28	0.40	0.19	0.92	-0.15	-0.12	0.59
29	0.33	0.20	0.87	-0.12	-0.23	0.63
30	0.28	-0.18	0.67	-0.46	-0.29	0.21
DB04186	0.28	0.03	0.68	-0.47	0.15	0.08

a.GPRCP-G protein-couples receptor ligand; b.ICM-Ion channel modulator; c. KI-Kinase inhibitor; d. NRL-Nuclear receptor ligand; e. PI-Protease inhibitor; f. EI-Enzyme inhibitor

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Table 5. Represents the pkCSM of the designed imidazole 2-amino pyrimidine (1-30)

Compd	HIA (%)[a]	log Papp (10^{-6}Cm/S)[b]	log Kp[c]	log L/kg[d]	log BB[e]	H-Tox[f]
1	90.352	1.261	-2.735	0.17	-1.56	H-tox
2	97.453	1.466	-2.735	0.27	-1.009	H-tox
3	86.544	1.116	-2.735	0.342	-1.209	H-tox
4	93.808	1.451	-2.735	-0.301	-1.002	H-tox
5	98.505	1.324	-2.735	0.466	-1.049	H-tox
6	88.846	1.351	-2.735	0.548	-0.862	H-tox
7	95.744	1.393	-2.735	0.287	-0.829	H-tox
8	93.655	1.419	-2.735	0.299	-0.921	H-tox
9	94.439	1.529	-2.735	0.296	-1.044	Non-toxic
10	95.904	1.468	-2.735	0.456	-0.719	H-tox
11	95.269	1.348	-2.735	0.417	-0.49	H-tox
12	92.809	1.525	-2.735	0.321	-1.212	Non-toxic
13	95.619	0.441	-2.735	0.011	0.446	H-tox
14	94.69	1.428	-2.735	0.201	-1.277	H-tox
15	93.559	1.254	-2.735	-0.094	-1.096	Non-toxic
16	96.625	1.361	-2.735	0.475	-1.225	H-tox
17	93.529	0.349	-2.735	0.327	-1.046	H-tox
18	94.423	1.465	-2.735	0.363	-0.969	H-tox
19	93.599	1.249	-2.735	-0.079	-1.096	Non-toxic
20	94.546	1.529	-2.735	0.31	-1.027	Non-toxic
21	92.173	1.21	-2.735	0.006	0.781	Non-toxic
22	96.564	1.496	-2.735	0.214	-1.271	H-tox
23	88.846	1.351	-2.735	0.548	-0.862	H-tox
24	91.573	1.186	-2.735	-0.185	-0.526	H-tox
25	80.045	-0.147	-2.735	0.015	-1.292	H-tox
26	96.063	1.46	-2.735	0.457	0.715	H-tox
27	70.564	1.304	-2.735	0.363	-1.049	H-tox
28	96.195	1.367	-2.735	0.018	-0.988	Non-toxic
29	90.208	-0.243	-2.735	0.306	-1.413	H-tox
30	98.147	1.345	-2.735	0.083	-1.07	H-tox
DB01486	91.156	0.874	-3.044	0.224	-0.921	H-tox

a. HIA (%)-Human intestinal absorption; b. log Papp- In Vitro Caco-2 Cell Permeability; c. log Kp- In vitro Skin Permeability; d. log L/kg- In vitro VDss (human); e. log BB- In vitro blood brain barrier permeability; f. H-Tox - Hepatotoxicity

showed significant permeation and absorption against Caco-2 monolayer of cell and human intestine absorption (HIA%) respectively indicating that the drugs can be orally administered. On the other hand the teratogenic property evaluated by Osiris (Table 6), indicates that except the compounds 1, 10, 15, 17, 19, 23, 24 and 30, the rest of the compounds are devoid of teratogenic properties and can be the safe inhibitors.

3.2. Docking results

Docking studies of the designed (1-30) imidazole linked 2-amino pyrimidine derivative with their binding energies and interaction sites is shown in Table 7. By using CASTp, the potential active site amino acids of 1GII complex were predicted. Figure 2 & 3, shows the 2D and 3D structure of protein human cyclin dependent kinase-2 complexed with the CDK4 Inhibitor (1GII). The Figure 4 & 5, represents the interaction of compound 24, with pro-

Table 6: Represents the toxicity properties of the designed imidazole 2-amino pyrimidine derivatives calculated using OSIRIS software

Compd	c Log P	Solu.	Druglikeness	Drug score	M	T	I	R
1	1.94	-5.15	-7.77	0.10				
2	2.46	-3.99	3.74	0.91				
3	2.39	-4.01	5.21	0.91				
4	2.26	-3.66	1.67	0.87				
5	1.83	-3.31	1.27	0.86				
6	1.55	-2.33	3.60	0.95				
7	2.53	-3.97	1.61	0.86				
8	2.26	-3.66	1.31	0.85				
9	3.21	-4.69	2.59	0.87				
10	2.50	-3.99	0.62	0.46				
11	2.95	-4.30	0.01	0.69				
12	3.81	-5.43	2.83	0.82				
13	2.70	-4.27	0.78	0.78				
14	2.80	-4.58	0.15	0.71				
15	1.34	-4.42	-3.94	0.17				
16	2.65	-3.90	-0.57	0.62				
17	1.68	-4.76	-7.35	0.10				
18	2.26	-3.66	1.57	0.86				
19	1.34	-4.42	-8.91	0.17				
20	3.21	-4.69	2.00	0.85				
21	2.62	-3.88	3.46	0.92				
22	2.71	-4.67	1.81	0.86				
23	1.46	-2.64	2.71	0.56				
24	2.64	-4.48	2.87	0.54				
25	0.75	-2.83	2.00	0.92				
26	2.50	-3.99	3.10	0.91				
27	1.60	-3.16	2.36	0.92				
28	3.01	-4.35	1.39	0.82				
29	1.91	-3.36	2.59	0.92				
30	2.71	-3.34	4.38	0.54				
DB01486	2.35	-3.71	5.11	0.92				

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Table 7. Docking interactions of human cyclin dependent kinase 2 (1GII) & ligands (1-30)

Compd	Binding Energy (K Cal/mol)	Hydrogen bond interactions	Hydrophobic Interactions
1	-8.1	VAL:40, GLN:88	VAL:18, ALA:101, ILE:10, PHE:37, LEU:91
2	8	VAL:40, HIS:41	ILE:10, LEU:91, ALA:101
3	-8	VAL:40, GLN:88	LEU:91, ALA:101, ILE:10, PHE:37
4	-7.5	GLY:13	ILE:10, VAL:18, LEU:91, HIS:39
5	-5.6	TYR:15, THR:14	ALA:106, ASP:84
6	-8	GLN:88	LEU:91, ILE:10, VAL:18, ALA:101
7	-7.9	GLN:88	LEU:91, PHE:37, VAL:18, ALA:101
8	-6.7	GLN:42, GLU:8, VAL:40	ILE:10, LEU:91, ALA:101, HIS:39
9	-7.8	VAL:40, HIS:41	LEU:91, ILE:10, PHE:37, VAL:18, ALA:101, LYS:33
10	-8.1	GLU:12, ASN:89, ASP:102, LYS:86	VAL:18, ILE:10, LEU:91, HIS:39
11	-8.7	ASP:102	VAL:18, ALA:101, LEU:91
12	-8.1	HIS:39, HIS:40, VAL:40	LEU:91, ILE:10, PHE:37, ALA:101
13	-7.2	GLN:88, ASP:102	ILE:10, LEU:91, ALA:101
14	-8.2	VAL:40, GLN:88, ASP:102	ILE:10, ALA:101, LEU:91
15	-7.6	ASP:102	ALA:101,VAL:18
16	-7.8	ASP:43	ALA:101,HIS:41,LEU:91,GLN:42, PHE:37
17	-7.9	VAL:40, ASP:102	LEU:91,ILE:10, ALA:101
18	-8.6	GLN:88	ILE:10, LEU:91, ALA:101, PHE:37
19	-8.3	---	ILE:10, GLU:12, GLY:11, LEU:91, ALA:101, VAL:18, HIS:39
20	-8.1	GLU:12, ASP:102	LEU:91, ALA:101
21	-6.3	LYS:9, ILE:10, GLN:42	THR:46, LEU:91
22	-8.5	VAL:40,ASP:43, GLU:12,ASP:102	ILE:10, HIS:39, LEU:91
23	-7	--	LEU:91, PHE:37, ALA:101
24	-9.2	GLU:12, VAL:40, ASP:102	ILE:10,VAL:18, LEU:91, HIS:39, ALA:101
25	-8	VAL:40	ILE:10, LEU:91, ALA:101, PHE:37
26	-6.5	GLU:12, ASP:102	VAL:18
27	-8.4	GLU:12	VAL:18, ILE:10, HIS:39, LEU:91
28	-6.7	VAL:40, ASP:102	ILE:10,VAL:18, LEU:91, ALA:101
29	-8.4	ASP:43	LEU:91, VAL:18, ALA:101, ASP:43, PHE:37
30	-7.6	VAL:40, GLN:8	ILE:10, LEU:91, HIS:39, VAL:18
DB01486	-10	VAL:40, LYS:33, HIS:39	VAL:18, LEU:91, ALA:101

VAL-Valine, ASP-Aspartic , GLN-Glutamine , LEU-Leucine, ILE-Isoleucine, HIS-Histidine , PHE-Phenylalanine , GLU-Glutamic acid , THR-Threonine

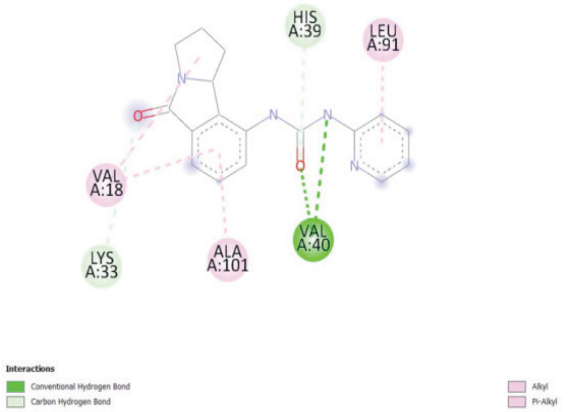

Figure 2. Shows structure of protein human cyclin dependent kinase 2 complexed with CDK4 inhibitor (DB04186).

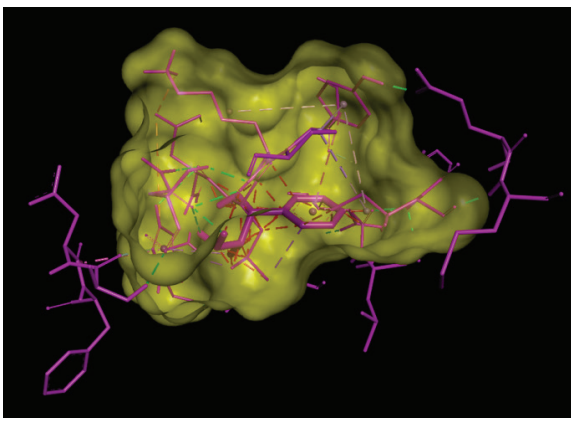

Figure 3. Represents the 3D dock pose of inhibitor into the receptor pocket (1GII)

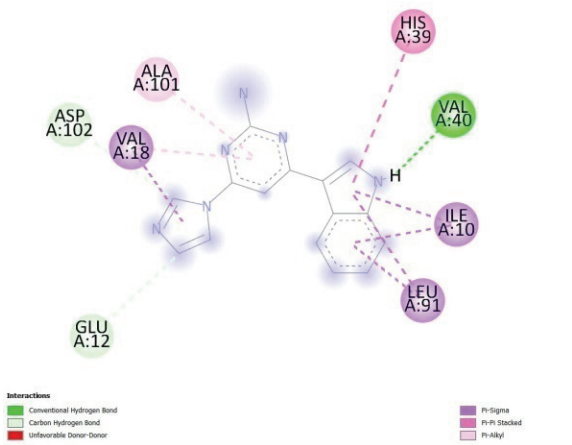

Figure 4. Represents 2D-Dock poses of compound 24 into human cyclin dependent kinase 2 protein (1GII) showing hydrogen bond interactions (Green dotted lines) and Hydrophobic interactions (Pink dotted lines).

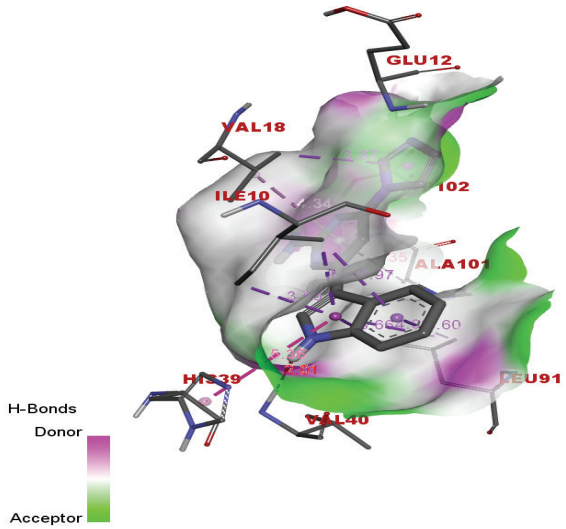

Figure 5. Represents 3D-Dock poses of compound 24 into human cyclin dependent kinase 2 protein

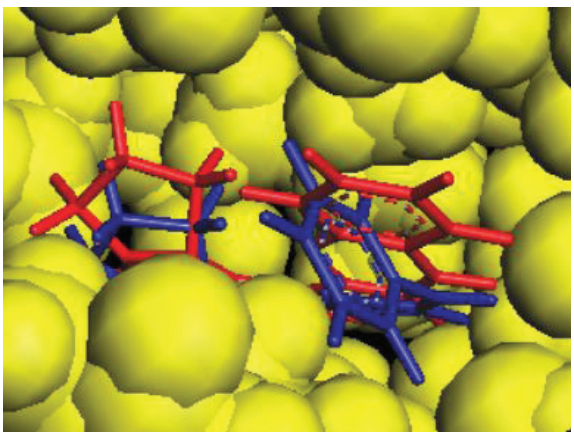

Figure 6. Represents the overlapped 3D structure of native and docked ligand, BLUE: CO-CRYSTALIZED LIGAND and RED: STANDARD LIGAND (**DB01486)**

tein active site on the receptor while the Figure 6, shows the overlapped structure of native and docked ligand. Out of the 30 designed inhibitors analyzed compound 24, showed the highest binding energy of -9.2 kcal/mol with three hydrogen bonding and five hydrophobic interactions with the targeted protein.

4. Conclusions

Based on literature a combination of imidazole linked to 2-amino pyrimidine with dithiocarbonates were designed and predicted for their molecular properties using various softwares like Molinspiration, Bioac-

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tivity properties, Molsoft, pkCSM and OSIRIS and these descriptors were useful in the general understanding of the chemical interactions with its target and helps in ascertaining the drug properties relevant to the drug design. The compounds were according to Lipinski rule, exhibiting good pharmacokinetic properties and except the compounds 9, 12, 15, 19, 20, 21 and 28, rest of the compounds exhibited the hepatotoxicity including the standard. While on other hand from Osiris data was clear that the compounds, except the compounds 1, 10, 15, 17, 19, 23, 24 and 30 were devoid of anyone of the teratogenic properties. Bioactivity properties of all the designed compounds were predicted and most of the compounds exhibited good bioactivity in comparison to standard. The docking studies of the designed molecules revealed that the compound 24 exhibited the highest binding energy of 9.2 kcal/mol with targetted CDK2 protein having -10 kcal/mol. The above insilico study indicates that the designed compounds (1-30) can be a possible lead for further developed into a potent anticancer agent as cycline dependant kinase-2 inhibitors (CDK2).

Conflict of interest

None.

Statement of Contribution of Researchers

Concept-H.S., Design-N.O; Supervision–H.S.; Resources-H.S.; Materials–Data Collection and/or Processing – P.K., S.M., M.S.S., .N.O.; Analysis and/or Interpretation –N.O., P.K., S.M., M.S.S.; Literature Search–P.K., S.M.; Writing–N.O., P.K., S.M., M. S.S., H.S.; Critical Reviews – H.S., S.J.T.)

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