

Theoretical Studies and Investigating of Selected Potent CDK2 Inhibitors as Anticancer Agents

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THEORETICAL STUDIES AND INVESTIGATION OF SELECTED POTENT CDK2 INHIBITORS AS ANTICANCER AGENTS

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ABSTRACT

In this study eight selected of the most potent cyclin dependent kinase 2 inhibitors in which targeting adenosine triphosphate-pocket site theoretically investigated to support literature information of frontier molecular orbitals, molecular electrostatic maps, and global chemical reactivity descriptors such as chemical hardness, chemical softness, chemical potential, electronegativity and electrophilicity of cyclin dependent kinase 2 inhibitors. Calculation and three-dimensional plotting were achieved through Gaussian 09W and Gausview 6 software's utilizing density functional theory quantum modeling applying both hybrids extended and not extended basis set. Crystal structure of CDK2 with inhibitors was obtained from protein data bank and visualized through PyMol Schrödinger software to assign polar and non-polar interactions of inhibitors with enzyme. A promising conclusion trend obtained in this research regarding to molecules that could have an inhibition activity toward the cyclin dependent kinase 2 enzymes. Our theoretical investigation emphasizes that, the anti-cancer activity has directly relationship with value of chemical hardness and chemical softness, where the most potent compounds was the pyrazolopyrimidine and imidazole pyrimidine and they have higher chemical hardness value and at the same time lower value of chemical softness compared with the rest of compounds.

Keywords DFT. GCRD. CDK2. Anti-cancer. ATP-competitive. FMO

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1. Introduction

Cyclin dependent kinases are class of serine / threonine protein kinase enzymes, which are in combination with their partners cyclin are key regulatory of cell division cycle, the primary function of such kinase enzymes is control process through cell cycle (CDK1 to CDK6) while CDK7-CDK17) implicated in transcription regulation [1].

As CDK's binds to the cyclins the partial active complexes formed then go further phosphorylation leading to active complexes which it regulates the cell development by means of passing cell through check points of cell cycle phases [2] as explained in figure 1 [3].

When mutation in check points through phases take place or deregulation by overexpression of CDK's in cell cycle, cells become abnormally and uncontrolled growth to form different type of tumors leading to cancer [4], CDK2 has an important role in cell division as shown in figure 1, when it binds to its partner cyclin E and the complex then phosphorylated, it driving the cell into the S-phase where DNA being synthesized, turn to late S-phase and it activated by phosphorylation CDK-cyclin A complex where the cell is preparing to become in G2 phase [5].

therefore CDK's become potent target in drug development and discovery over the last years [6], New generation of CDK-2 inhibitors targeting ATP binding site where it overcome the disadvantage of the first generation inhibitors such as low selectivity and potency [7], here we mention the most potent and selective CDK-2 ATP inhibitors (Table 1) [8].

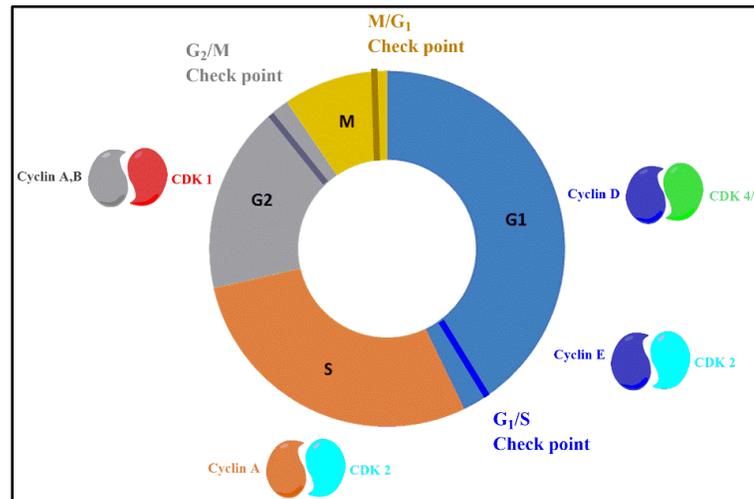
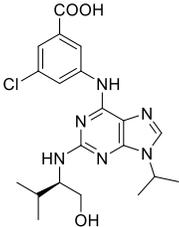
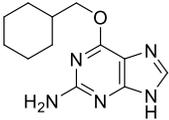
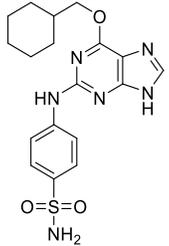
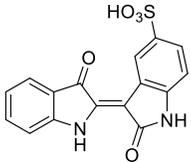
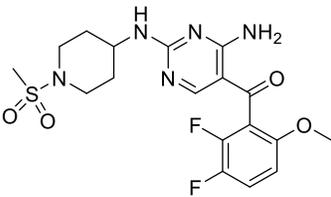
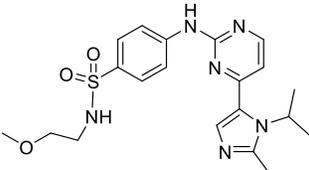
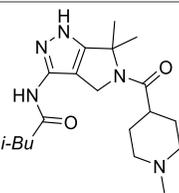


Fig 1 CDK's cell cycle regulation

Table 1 Most potent CDK2-inhibitors

Inhibitor name / family	Chemical structure	IC ₅₀ against CDK2	Reference
Purvalanol B Purine / Adenine		CDK 2-A 0.006 μM	[9]
NU2058 Purine / guanine		17 μM	[10]
NU6102 Purine / guanine		0.006 μM	[11]
CYP51 Indole Indirubin-5-sulphonate		CDK 2-A 0.035 μM	[12]
R547 Aminopyrimidine		0.003 μM	[7]
Pyrazolopyrimidine		CDK 2-A 0.001 μM	[13]
Imidazole pyrimidine		0.001 μM	[14]
PHA-793887 Pyrroazole		0.008 μM	[15]

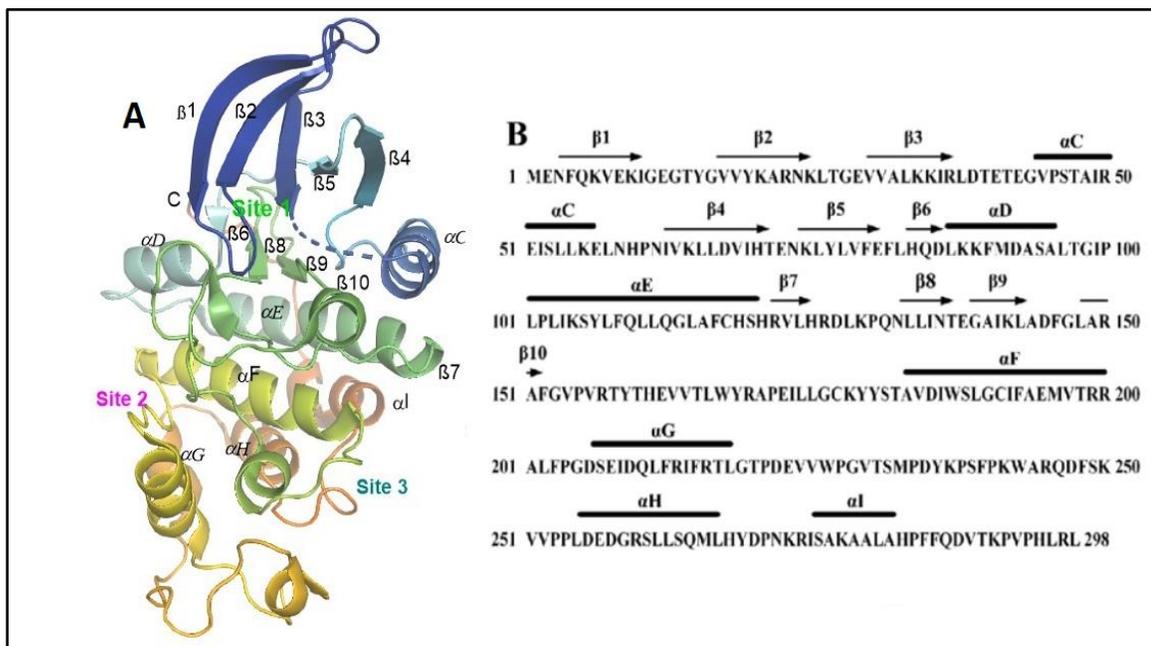


Fig 2 A CDK2 secondary structure (PDB ID: 4EK3), B CDK2 primary structure

CDK2 has three sites in which binds to inhibitors, site I represent ATP binding pocket as shown in figure 2, precisely $\beta 1$, $\beta 2$, $\beta 3$, $\beta 6$, $\beta 8$, $\beta 9$ while site II and site III are noncompetitive binding sites, in this study we focus on ATP competitive bind site for their conservation after bind to small molecule inhibitors such as inhibitors in table 1 [16].

Density functional theory it's a quantum mechanical modeling method where it's applications has a great significance in targeting drug discovery studies especially invention of new anti-cancer agents [17], [18], [19]. Interrupting of DFT calculations aid in create a comprehensive picture about physical and chemical properties such as stability and reactivity toward electrophiles or nucleophiles as well as build a molecular electrostatic map that represents the electropositive and electronegative sites over the chemical structure, polarity, reactivity descriptors etc.

There are different theoretical studies such as electronegativity equalization principle (EEP), maximum hardness principle, minimum polarizability principle (MPP) that utilize DFT calculations specifically using energy values of frontier molecular orbitals; highest occupied molecular orbital HOMO and lowest unoccupied molecular orbital LUMO, to specify global and local reactivity descriptors such as chemical hardness, softness, chemical potential, electrophilicity, electronegativity, Fukui function and local softness [20].

In 1934 Koopman's assign the values of ionization potential I and electron affinity A as the negative value of HOMO and LUMO energy respectively in his theorem (equation 1 and 2) [21]

$$I = -E_{HOMO} \quad eq 1$$

$$A = -E_{LUMO} \quad eq 2$$

The stability and reactivity of the chemical molecules are usually could be assigned from the values of chemical hardness and softness regarding to the Pearson theorem "maximum hardness principle" [22], where chemical hardness η measure resistance of the molecule to charge transfer intramolecularly and it could be obtained mathematically by subtraction of ionization potential from electron affinity equation 3, in contrast the chemical softness S is ability of the molecule system to react and mathematically obtained from the reciprocal of the chemical hardness equation 4 [23].

$$\eta = I - A \quad eq 3$$

$$S = \frac{1}{\eta} \quad eq 4$$

Chemical potential μ is used to measure the propensity of the electrons to escape from the system in an equilibrium state, equation 5.

Electronegativity χ it's an important physical description of the atoms in molecules, where it defined as "the power of an atom in a molecule to attract electrons to itself" and it's the negative value of the chemical potential equation 5.

$$\mu = \frac{I+A}{2} = -\chi \quad \text{eq 5}$$

Another important chemical reactivity descriptors is the electrophilicity ω in which measures how much energy of the system need to become stable after accepting an additional electrons, it determined by dividing the square of chemical potential μ by 2 fold chemical hardness equation 6 [24].

$$\omega = \frac{\mu^2}{2\eta} \quad \text{eq 6}$$

Gazques and coworkers in 2007 they define two new reactivity descriptors electron donating ω^- and electron accepting power ω^+ where they describe ability of the chemical system to donate or accept small fraction of the charge [25] equation 7 and 8 respectively.

$$\omega^- = \frac{(3I+A)^2}{16(I-A)} \quad \text{eq 7}$$

$$\omega^+ = \frac{(I+3A)^2}{16(I-A)} \quad \text{eq 8}$$

Due to lack in information and the relation between strong binding of CDK2 inhibitors previously mentioned and the reactivity descriptors in this study 8 selected of the most potent CDK2 inhibitors will be theoretically investigated by global chemical reactivity descriptors, molecular electrostatic potential maps and HOMO-LUMO plotting and energy orbitals anticipating and make a relationship between the reactivity parameters and physio-chemical properties and the selectivity, potency of the inhibitors toward CDK2 kinase enzyme.

The aim of this study is to support the theoretical literature with chemical reactivity descriptors of the most potent CDK2 inhibitors under clinical studies further to build a good visualization about design new CDK2 targeting anti-cancer agent that would have drug like characteristic, selectivity, and potency.

2. Methods

All DFT calculation of 10 potent CDK2 inhibitors was performed using Gaussian 09W and Gausview 6 full software packages [26,27], energy mode at gas phase ground state Becke, three parameters, Lee-Yang-Parr “B3LYP” hybrid basis set [28] at 6-31G and 6-311++ G (d,p) level of theory to study the effect of extended basis set on the calculations [29]. Gaussian output CHK point file of each basis set was analyzed by Gausview 6 to obtain HOMO, LUMO orbitals and energies with restricted wave function, transparent molecular electrostatic potential maps were performed by applying total density cube with SCF density matrix, ESP mapping surface. Crystal structure of CDK2 with each inhibitor was downloaded as pse extension file type and visualized using Schrödinger software PyMol 2.5 python license windows version.

3. Results and discussion

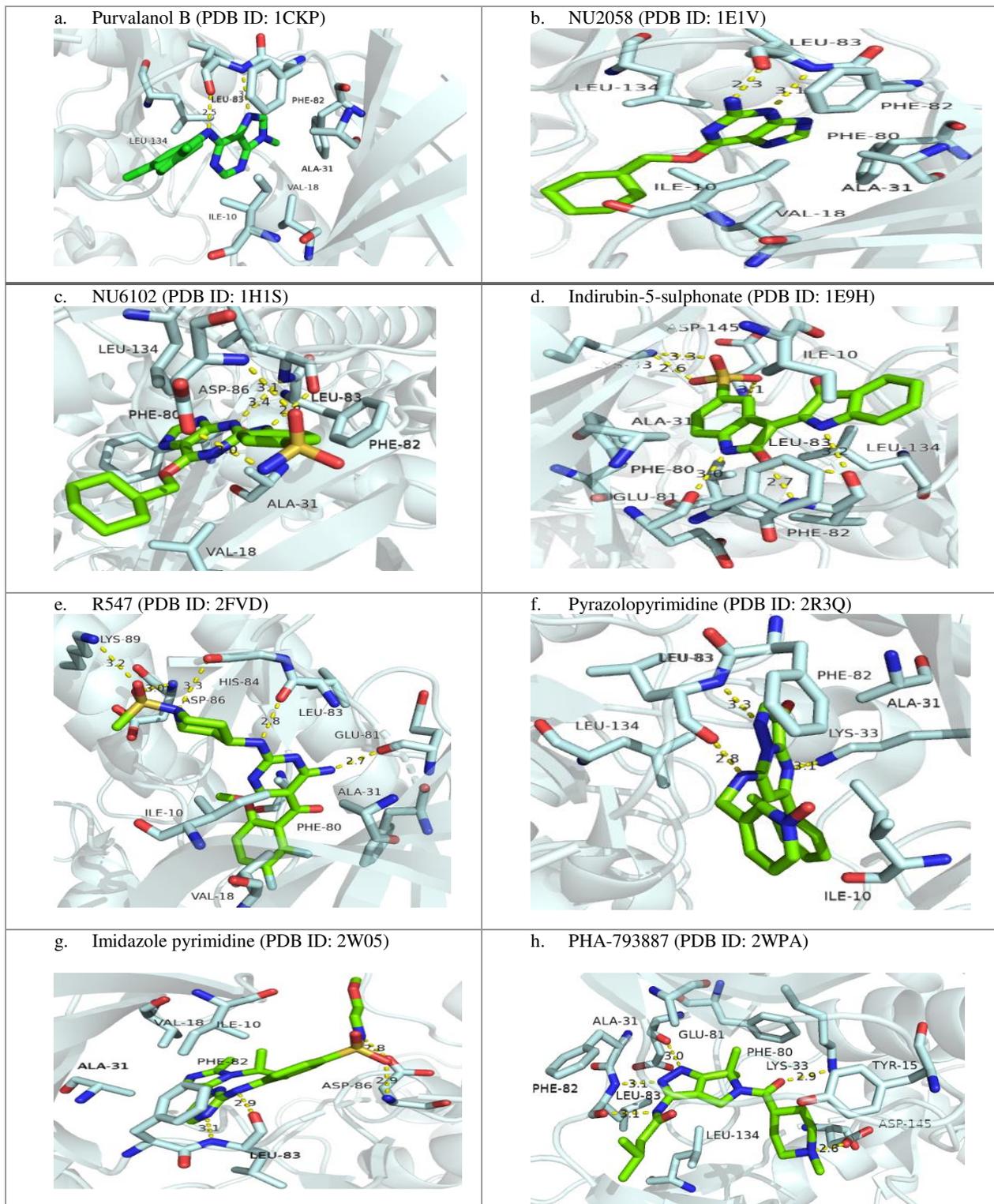
CDK2-ATP competitive inhibitor interactions

Purine / Adenine analogues purvalanol B show good inhibition activity against CDK2, in fact table 2 A represent interactions whether polar or non-polar, where the two nitrogen atoms on purine ring made H-bonding with carbonyl and amino groups of Leu-83 residue. While amino acids with hydrophobic side chain like Leu-134, Ile-10, Val-18, Ala-31, Phe-82 make a hydrophobic interaction with purvalanol [9]. Second purine derivative is NU2058, where the amino group at position 2 and nitrogen atom of purine ring making two hydrogen bonding with carbonyl and amino group of Leu-83 residue while Leu-134, Phe-82, Phe-80, Ala-31, Val-18, Ile-10 making hydrophobic interactions as they close to inhibitor (Table 2 B) [10]. Addition of benzene sulfonamide on amino group at position 2 of purine ring allowing the ligand to make another 2 hydrogen bonds additionally on that Leu-83 at oxygen atom of sulfonate group with amino group of Asp-86 and amino group of sulfonamide with carbonyl of the same backbone residue [11]. Indirubin-5-sulphonate is indole-based structure show potent inhibition activity with IC₅₀ 0.035 μ M against CDK2-cyclin A complex, by studying it's interactions with CDK2 it turned out that indirubin-5-sulphonate create at sulfonate group, 3 hydrogen bonding with amino groups of Lys-33 and Asp-145, and at NH-CO-N of indirubin a network hydrogen bonding interaction with carbonyl and amino groups of Leu-83 and with carbonyl group of Glu-81 backbone residues respectively, Ile-10, Leu-134, Phe-82, Phe-80, Ala-31 non-polar side chain backbone residues get closer to indirubin inhibitor and making hydrophobic interactions as presented in table 3-D [12]. Next CDK2 ATP-pocket inhibitor is R547, aminopyrimidine is the chemical structure and it is forming 5 hydrogen bonding, two at sulfonyl group with amino groups of Lys-89 and Asp-86, at nitrogen atom of piperidine ring with hydroxyl group on His-84, at amine groups 6 and 2-positions substituted on pyrimidine ring with carbonyl Leu-83 and Glu-81 respectively, non-polar interactions of R547 could be concluded with Ile-10, Val-18, Phe-80, Ala-31 at hydrophobic side chain of most closer residues table 2 E [7]. Pyrazolopyrimidine inhibitor with IC₅₀ value around 0.001 μ M against CDK2-cyclin A which is great

inhibition activity, polar interactions of this agent indeed at different nitrogen atoms at 1, 7, positions and substituted position 4 of pyrimidine ring with amino group of Lys-33, Leu-83 and carbonyl group of Leu-83 respectively, however the hydrophobic interactions included non-polar side chain of Leu-134, Ile-10, Ala-31, Phe-82 amino acid residues at ATP-binding pocket on CDK2 table 2 F [13]. Imidazole pyrimidine inhibitor invented by AstraZenca pharmaceuticals- research team exhibit a great activity against CDK2 with IC_{50} 0.001 μ M and after analyzing complex co-structure of ligand and CDK2 using PyMol software it deduced that the hydrogen bonds could be formed at two places in the structure, the first place is on nitrogen atom of pyrimidine ring and amino group at position 2 with amino and carbonyl groups of Leu-83 respectively, the second place is sulfonyl and amino group para-substituted on phenyl ring with amino and carbonyl of Asp-86 backbone residue. Hydrophobic attractions as previously inhibitors on the same site ATP-pocket the competitive inhibitor site with non-polar side chain of the following amino acid residues, Val-18, Ile-10, Ala-31, Phe-82 table 2 G [14]. Considerable activity exhibited by PHA-793887 against CDK2 and the interactions presented in table 2 H, polar interaction (hydrogen bonding) of this inhibitor after analyzing the complex co-structure of CDK2 with PHA-793887 appear at 3 sites, nitrogen atoms at pyrazole ring on positions 1,2 and 9 with carbonyl of Glu-81, amino and carbonyl of Leu-83 respectively, on the other hand a set of amino acids residues making hydrophobic attraction toward carbon atom skeleton of PHA-793887 such as Phe-82, Ala-31, Leu-134, Phe-80, Tyr-15 [15].

The molecular visualization interaction of inhibitor-enzyme interaction could be concluded as follows, molecules have functional group contain N,O atoms can make a hydrogen bonding interaction especially with Leu-83, and molecules which have hydrophobic carbon residue it could making hydrophobic attraction with non-polar side chain residues at ATP-pocket site on CDK2 enzyme, consequently molecule with this features that expected to have inhibition activity against CDK2 allowing it to be anti-cancer agent.

Table 2 Crystal structure of CDK2 complex with Inhibitors

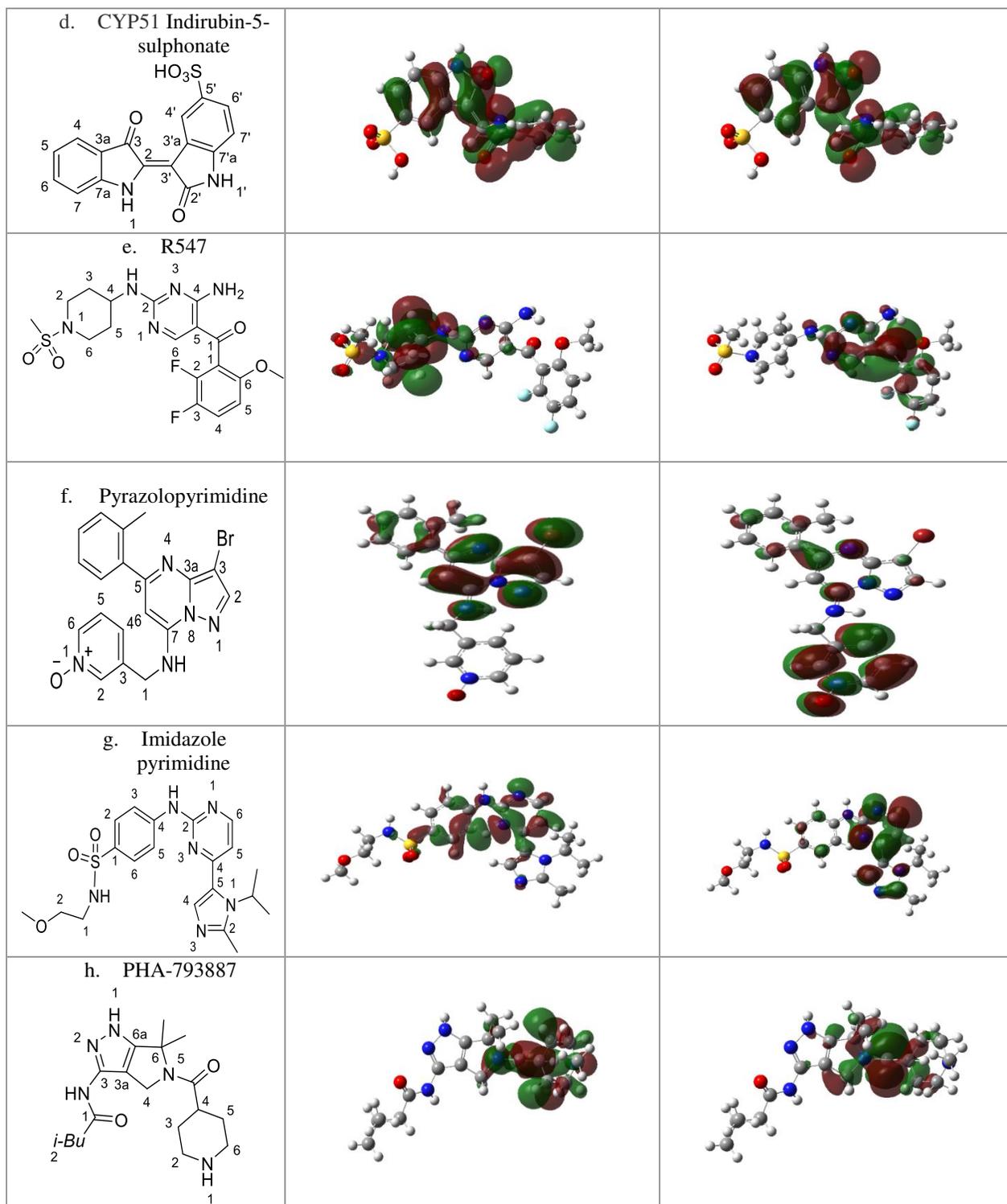


FMO HOMO-LUMO

Frontier molecular orbital of the inhibitors was obtained by means B3LYP method using 6-311G++(d,p) extended basis set including the polarization of d and p orbitals and double diffused on triple zeta function as to get more reliable results the orbitals 3D-diagrams illustrated in table 3. Red color represents the positive phase while the negative phase in green color. As quantum explanation of ligand-binding site (inhibitor-ATP competitive site) mechanism [30] HOMO orbital diagrams expressing the ability to donate electrons from the inhibitor to the binding site of CDK2 in our case ATP-competitive pocket site oppositely, the LUMO orbitals express the ability of the inhibitor to accept electrons from the binding site of the CDK2. Purvalanol B, CYP51 and PHA-793887 HOMO and LUMO orbitals appear similarly means that sites that trend to donate electron from HOMO to the enzyme binding site approximately the same sites on the molecules that trend to accept an electron from the binding site of the enzyme on LUMO orbitals of inhibitors table 3 A, D and H. The HOMO orbitals of NU2058 locate from 6-substitution position on pyrimidine ring to cyclohexanol ring, while the LUMO orbitals extends from 6-position of pyrimidine ring to the whole chemical structure table 3 B. Regarding to NU6102 inhibitor HOMO orbitals distributed over the all chemical structure accept cyclohexyl group but the LUMO orbitals confined at purine ring, amino group at position 2 oxygen atom at position 6 table 3 C. R547 HOMO-LUMO orbitals divided the structure equally where HOMO orbitals distributed from position to of pyrimidine to sulfonyl group whereas LUMO orbitals located from pyrimidine to substituted phenyl ring table 3 E. HOMO orbital surfaces of pyrazolopyrimidine inhibitor locate at the main scaffold with little at phenyl ring position 5 while LUMO locate at phenyl ring substituted with nitro group table 3 F. Lastly HOMO orbitals of imidazole pyrimidine inhibitor locate over structure from sulfonyl group to pyrimidine ring but the LUMO orbitals locate from pyrimidine to imidazole ring except its alkyl substituted table 3 G.

Table 3 Frontier molecular energy HOMO, LUMO orbital diagram

CDK2 inhibitor	HOMO	LUMO
<p>a. Purvalanol B</p>		
<p>b. NU2058</p>		
<p>c. NU6102</p>		

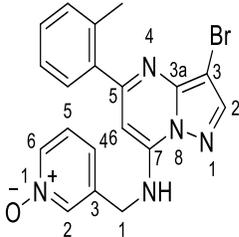
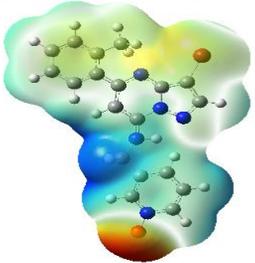
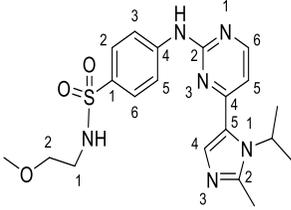
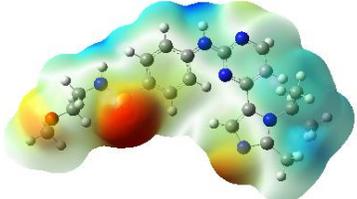
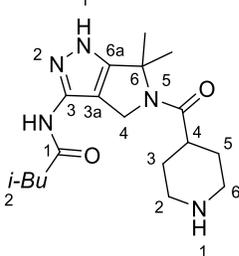
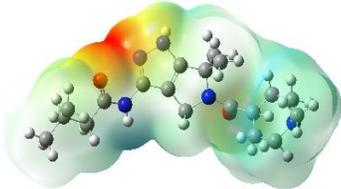


Molecular electrostatic potential maps

The molecular electrostatic maps of the inhibitors were done utilizing the extended basis set 6-311G++(d,p) consequently to recognize the distribution of the charge over the chemical structure to assign theoretically electrophilic and nucleophilic sites that will involve in the chemical reactions. The maps have different color range start from red, orange yellow, green to blue where the red color show electronegative potential (nucleophilic site reactive toward the electrophiles) and the blue color show electropositive potential (electrophilic site that reactive toward the nucleophiles). Table 4 show the MEP maps and electrophilic, nucleophilic sites of the selected inhibitors.

Table 4 Molecular electrostatic potential maps of CDK2 inhibitors

CDK2 inhibitor	MEP	Electrophilic sites	Nucleophilic sites
<p>Purvalanol B</p> <p>COOH</p>		<p>1. Hydrogen atoms of isopropyl group substituted at position 9</p>	<p>1. Nitrogen atom at 7 position</p> <p>2. Nitrogen atom at 2 position</p>
<p>NU2058</p>		<p>1. Nitrogen atoms of purine ring at 9,3, 2 and 1 position</p>	<p>1. Nitrogen atom at 7</p> <p>2. Oxygen substituted at 6 position.</p> <p>3. Cyclohexyl ring</p>
<p>NU6102</p>		<p>1. Hydrogen atom of amino group substituted on sulfonyl group</p> <p>2. Around the structure accept at nucleophile sites</p>	<p>1. Nitrogen atom at 7</p> <p>2. Oxygen atom substituted at 6</p> <p>3. Oxygen atoms of Sulfonyl group</p>
<p>CYP51</p> <p>Indirubin-5-sulphonate</p>		<p>1. Hydrogen atom of sulfonyl group</p> <p>2. Hydrogen atom of 1'</p> <p>3. Hydrogen atoms of carbons at 6',7 and 7a' positions</p> <p>4. Hydrogen atom at 3a position</p>	<p>1. Oxygen atom of carbonyl at 3 position</p> <p>2. Oxygen atom of carbonyl at position 2'</p> <p>3. Oxygen atoms of sulfonyl group</p>
<p>R547</p>		<p>1. Hydrogen atoms of methoxy group</p> <p>2. Hydrogen atom of phenyl ring at 5 and 4</p> <p>3. Piperidine ring</p>	<p>1. Nitrogen atom of Amino group, carbon at position 4 and nitrogen at position 3 of pyrimidine ring</p> <p>2. Oxygen atoms of sulfonyl group</p>

<p>Pyrazolopyrimidine</p> 		<ol style="list-style-type: none"> 1. Hydrogen atom of carbon at position 1 2. Hydrogen atoms of carbon phenyl ring at 6 and 5 position 	<ol style="list-style-type: none"> 1. Oxygen atom of nitro group 2. Around the bromine atom
<p>Imidazole pyrimidine</p> 		<ol style="list-style-type: none"> 1. Hydrogen atom of amino substituted at carbon 2 of pyrimidine 2. Hydrogen atom substituent on sulfonyl group 3. Hydrogen atoms of isopropyl and methyl substituents of imidazole ring 	<ol style="list-style-type: none"> 1. Oxygen atoms of sulfonyl group 2. Oxygen atom of methoxy group 3. Nitrogen atom at 3 on imidazole ring
<p>PHA-793887</p> 		<ol style="list-style-type: none"> 1. Pyperidine ring 	<ol style="list-style-type: none"> 1. Nitrogen atom at position 2 of pyrazole ring 2. Oxygen atom of carbonyl at carbon atom 1

Global chemical reactivity descriptors

The global chemical reactivity descriptors were obtained using 6-31G and 6-311++G(p,d) basis set in eV unit as shown in table 5, the descriptors values show no difference between the basis set except increasing in electrophilicity ω , electron donating ω^- and electron accepting powers ω^+ except that the difference not observable consequently we will analyze result with extended basis set as it's more reliable. The values are arranged ascending in table 6. First parameter in GCRD is the chemical hardness from table 6 pyrazolopyrimidine inhibitor have maximum resistance to charge transfer intramolecularly unlike purvalanol B, chemical softness counter to hardness maximum ability for reaction and charge transfer among inhibitors is purvalanol B it's expected that due to its chemical structure show diversity of functional groups, another GCRD is the electronegativity and the chemical potential, as we mentioned previously they have the same value but different in mathematical sign where indirubin shows maximum ability to attract electrons to the molecule itself but minimum ability for PHA-793887 inhibitor. Electrophilicity parameters describes the reactivity by propensity the molecule to accept electrons (ω^-) or donating electrons (ω^+) and the net electrophilicity ($\Delta\omega^\pm$), Indirubin-5-sulphonate have maximum ability to donating an electron to binding site, theoretically which agrees with HOMO orbitals diagram by distributing over the chemical structure means that there are more than one sites could donate an electron. Also, MEP show for Indirubin-5-sulphonate molecule 4 electronegative sites with red color, it's interestingly that the same inhibitor shows the highest value which represent the propensity to accept an electron means that its chemical structure has a wide range of the electronic behavior in different chemical systems.

We can summarize the relation between inhibition activity against CDK2 enzyme and the GCRD which is the main idea to perform the study. All inhibitors have a convergent value of chemical softness, chemical hardness, and electronegativity descriptors with standard deviation 0.31, 0.57, 0.8 respectively. The electrophilicity, electron donating accepting powers, and net electrophilicity have far apart values with standard deviation 6.58, 6.78, 6.61 and 12.39 respectively and this is promising trend result that will help research groups in design an anti-cancer agent, however we can conclude that the chemical agent

have a chemical softness value around 0.51 eV, chemical hardness value around 1.27 eV and 3.94 eV value for electronegativity it's theoretically expected that to have inhibition activity against CDK2 enzyme.

Table 5 Global Chemical reactivity descriptors using two basis set 6-31G, 6-311++G (d,p)

CDK2 inhibitor	E _{HOMO}	E _{LUMO}	E _{gap}	η	S	χ	μ	ω	I	A	ω ⁻	ω ⁺	Δω±
Purvalanol B 6-31G	-3.081	-2.163	0.919	0.459	1.089	2.622	-2.622	7.484	3.081	2.163	8.853	6.072	14.925
Purvalanol B 6-311++G (d,p)	-3.545	-2.571	0.973	0.487	1.027	3.058	-3.058	9.608	3.545	2.571	11.198	8.436	19.635
NU2058 6-31G	-5.826	-2.734	3.091	1.546	0.323	4.280	-4.280	5.926	5.826	2.734	8.259	15.247	23.507
NU2058 6-311++G (d,p)	-6.136	-3.019	3.117	1.558	0.321	4.578	-4.578	6.724	6.136	3.019	9.207	17.919	27.126
NU6102 6-31G	-6.500	-2.715	3.785	1.893	0.264	4.608	-4.608	5.609	6.500	2.715	8.149	17.560	25.710
NU6102 6-311++G (d,p)	-6.674	-2.937	3.737	1.869	0.268	4.805	-4.805	6.178	6.674	2.937	8.815	19.552	28.367
Indirubin-5-sulphonate 6-31G	-5.242	-4.185	1.057	0.528	0.946	4.714	-4.714	21.028	5.242	4.185	23.451	21.198	44.649
Indirubin-5-sulphonate 6-311++G (d,p)	-5.556	-4.484	1.072	0.536	0.932	5.020	-5.020	23.500	5.556	4.484	26.077	24.204	50.281
R547 6-31G	-3.690	-1.911	1.779	0.890	0.562	2.800	-2.800	4.407	3.690	1.911	5.918	6.241	12.159
R547 6-311++G (d,p)	-3.984	-2.169	1.815	0.908	0.551	3.076	-3.076	5.214	3.984	2.169	6.865	7.758	14.623
Pyrazolopyrimidine 6-31G	-5.606	-1.555	4.050	2.025	0.247	3.580	-3.580	3.165	5.606	1.555	5.209	8.829	14.038
Pyrazolopyrimidine 6-311++G (d,p)	-5.891	-2.058	3.833	1.917	0.261	3.975	-3.975	4.121	5.891	2.058	6.348	11.965	18.313
Imidazole pyrimidine 6-31G	-5.688	-2.438	3.250	1.625	0.308	4.063	-4.063	5.078	5.688	2.438	7.313	13.256	20.569
Imidazole pyrimidine 6-311++G (d,p)	-5.877	-2.673	3.204	1.602	0.312	4.275	-4.275	5.704	5.877	2.673	8.042	15.089	23.131
PHA-793887 6-31G	-3.613	-0.925	2.687	1.344	0.372	2.269	-2.269	1.916	3.613	0.925	3.218	3.065	6.283
PHA-793887 6-311++G (d,p)	-4.020	-1.383	2.637	1.319	0.379	2.701	-2.701	2.767	4.020	1.383	4.282	4.992	9.274

Table 6 GCRD in eV unite

Reactivity descriptor	Ascending order	Value in eV
Chemical hardness η	Purvalanol B	0.487
	Indirubin-5-sulphnate	0.536
	R547	0.908
	PHA-793887	1.319
	NU2058	1.558
	Imidazole pyrimidine	1.602
	NU6102	1.869
Chemical softness S	Pyrazolopyrimidine	0.261
	NU6102	0.268
	Imidazole pyrimidine	0.312
	NU2058	0.321
	PHA-793887	0.379
	R547	0.551
	Indirubin-5-sulphnate	0.932
Electronegativity χ	Purvalanol B	1.027
	PHA-793887	2.701
	R547	3.076

	Pyrazolopyrimidine	3.975
	Imidazole pyrimidine	4.275
	NU2058	4.578
	NU6102	4.805
	Indirubin-5-sulphonate	5.020
Chemical potential μ	Indirubin-5-sulphonate	-5.020
	NU6102	-4.805
	NU2058	-4.578
	Imidazole pyrimidine	-4.275
	Pyrazolopyrimidine	-3.975
	R547	-3.076
	Purvalanol B	-3.058
	PHA-793887	-2.701
electrophilicity ω	PHA-793887	2.767
	Pyrazolopyrimidine	4.121
	R547	5.214
	Imidazole pyrimidine	5.704
	NU6102	6.178
	NU2058	6.724
	Purvalanol B	9.608
	Indirubin-5-sulphonate	23.500
Electron donating power ω^-	PHA-793887	4.282
	Pyrazolopyrimidine	6.348
	R547	6.865
	Imidazole pyrimidine	8.042
	NU6102	8.815
	NU2058	9.207
	Purvalanol B	11.198
	Indirubin-5-sulphonate	26.077
Electron accepting power ω^+	PHA-793887	4.992
	R547	7.758
	Purvalanol B	8.436
	Pyrazolopyrimidine	11.965
	Imidazole pyrimidine	15.089
	NU2058	17.919
	NU6102	19.552
	Indirubin-5-sulphonate	24.204
Net electrophilicity $\Delta\omega_{\pm}$	PHA-793887	3.545
	R547	3.984
	Pyrazolopyrimidine	4.020
	Purvalanol B	5.556
	Imidazole pyrimidine	5.877
	NU2058	5.891
	NU6102	6.136
	Indirubin-5-sulphonate	6.674
Ionization potential I	Purvalanol B	3.545
	R547	3.984
	PHA-793887	4.020
	Indirubin-5-sulphonate	5.556
	Imidazole pyrimidine	5.877
	Pyrazolopyrimidine	5.891

	NU2058	6.136
	NU6102	6.674
Electron affinity A	PHA-793887	1.383
	Pyrazolopyrimidine	2.058
	R547	2.169
	Purvalanol B	2.571
	Imidazole pyrimidine	2.673
	NU6102	2.937
	NU2058	3.019
	Indirubin-5-sulphonate	4.484

4. Conclusion

In this study 8 of potent CDK2 inhibitors was theoretically investigating through visualization the interaction with the CDK2 enzyme by ligand interaction PyMol software resulted in hydrogen bonding associated mainly with Leu-83, Glu 81 and Lys-33 while non-polar residues on CDK2 at ATP binding pocket site such as Leu-134, Ala-31, Phe-82, Val-18, Ile-10 and others make a hydrophobic interaction with the inhibitors. FMO diagrams results in purvalanol B, CYP51 and PHA-793887 show approximately same diagrams for HOMO and LUMO orbitals while other inhibitors show differences in the HOMO LUMO orbital diagrams, also the chemical compound have HOMO LUMO distribution over the chemical structure possess a relatively high value of electrophilicity descriptors. Molecular electrostatic maps show the nucleophilic and electrophilic sites in the chemical structure of the inhibitors presented in table 4. In analyzing and investigating the GCRD of the inhibitors we have reached a promising conclusion that the most important factors on the inhibition activity against CDK2 was chemical softness, hardness and electronegativity and we expected that any chemical molecule can make a hydrogen bonding and hydrophobic interactions along with possessing a 0.51 eV, 1.27 eV and 3.94 eV approximately values for chemical softness, chemical hardness and electronegativity it will have promising inhibition activity against the CDK2 enzyme which means that this is the start point in new strategy of develop a new potent anti-cancer agents by implement the theoretically expectation.

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5. Declarations

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No funding was received to assist with the preparation of this manuscript.

Conflict of interest

The authors served as employees of Philadelphia University during this project.

Availability of data and material

Data can be obtained through the corresponding author from email upon request.

Code availability

All PDB files used in this research were obtained from protein data bank. <https://www.rcsb.org/>

Author contribution

Mohammad Abunuwar: writing—original draft. Adnan Dahadha: writing—review.

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