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Molecular docking, synthesis and study of substituted 1-Methyl-6-Oxo-2-[(2z)-2-(3-Oxo-4-Phenylazetidin-2-Ylidene)Hydrazinyl]-4-Phenyl-1,6-dihydropyrimidine-5-carbonitrile derivatives

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***Abstract*---**Synthesis of Substituted 2-[(2-chloro-4-oxo-3-phenylazetidin-1-yl)amino]-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile(6a-r) and 1-methyl-6-oxo-2-[(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)amino]-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (7a-o)Derivatives was completed using aromatic aldehyde, ethylcyanoacetate and thiourea in absolute ethanol as per the standard procedure.The completion of reactionmonitored by TLC and structure were confirmed by spectroscopic method viz FT-IR and 1H NMR and elemental analysis.The affinity of synthesized compounds with CDK4 protein was predicted by molecular docking studies. The docking results showed that compound 6l, 6p and 6r has highest affinity with CDK4 protein with minimum energy with good hydrogen bonding interaction.

***Keywords*---**carbonitrile derivatives, molecular docking, CDK4 proteins.

Introduction

Cancer is one of the most dangerous, rapid propagating diseases in current days with quite high mortality rate even in the well developed countries. The condition is even worst in the non-developed countries for the reasons like lack of availability of quality drugs due to poorness and sometimes lack of knowledge.[1]higher range of the cancers i.e 90–95% are caused due to behavioural factors and alternate lifestyle while 5–10% is inherited genetically. Numerous factors such as tobacco, diet, obesity, infections, ionizing and non-ionizing ultraviolet radiations, stress, lack of physical activity, and environmental pollutants which leads to cancers.[2]In tobacco smoke fifty known carcinogens are present, which containing polycyclic aromatic hydrocarbons and nitrosamines. In worldwide one fifth cancer death are due to tobacco.[3]

Diet, obesity and physical inactivity are other factors which leads to around 30–35% of cancer deaths. Approximately 14-20% of various cancer deathsare related to excess body weight in the United States. Physical inactivity affects the body weight and gives negative effects on endocrine and immune systems so it enhances cancer risk. Eating too much diet and Diets with lesser fruits, whole grains, and vegetables and also red meats are associated with various cancers.[4] In worldwide approximately 18% of cancer deaths are due to infectious diseases and it is different in region like 25% in Africa and 10% in developed world. Virus is one another major part for development of cancer various viruses such as human papillomavirus causes and develops cervical carcinoma, Epstein–Barr virus causes and develops B-cell lympho-proliferative disease and nasopharyngeal carcinoma. Hepatocellular carcinoma caused by hepatitis B and hepatitis C viruses and T-cell leukemia's caused by human T-cell leukemia virus-1.[2] Genetic mutation carriers are one another factor for cancer incidence and an inherited mutation in genes BRCA1 and BRCA2 which develops breast and ovarian cancer.[5]

Chronic myeloid or myelogenousleukemia (CML) is an uncommon cause of cancer-related mortality in the United States, with an estimated 8,430 new cases and 1,090 deaths anticipated in 2018.[6] CML is associated with the presence of the Philadelphia chromosome, a translocation between chromosomes 9 and 22 in humans, shows a fusion between the 5' end of the BCR gene and the 3' end of the ABL1 gene. In 1960 the Philadelphia chromosome was discovered, but the molecular genetic features were not understood until more recently. In the 1980s it was discovered that the Philadephia chromosome resulted in the BCR-ABL1 fusion gene.[7] In 2001, Imitinab comes over prior approval, CML was treated using interferon-alpha or bone marrow transplant. So, imatinib which is ABL1 kinase inhibitors have become the most common treatments for CML.

Philadelphia chromosome should be found in other types of leukemias but presence of a BCR-ABL1 fusion geneis an absolute diagnostic method for CML, so it is present in all cases. Pyrimidine are6 membered heterocyclic compound made up of carbon and nitrogen. In nature it is available in various form and building block of essential biomolecule like vitamin, liposachharides. Most valuable compound of the nature is DNA and RNA made from various nucleotides containing pyrimidine nitrogenousbaeses. Since 1884 various synthetic drug molecules are used for the treatment of various disease due to structural

similarities with these endogenous molecule.[8]Synthesis of dihydropyrimidine has great importance as these derivative are used as antiviral, anti-infective, antibacterial, anticancer, antioxidant, anti-proliferative drugs. Pyrimidine heterocycle is important in many medicinal agents with diverse activity especially anticancer because it inhibits kinase activity and also act on cell cycle by apoptosis[9].

Materials and Methods

In medicinal chemistry several types of chemical compounds are available with diversity of medicinal activity. In the biology fundamental biomolecule in the lifecycle of every living things are nucleic acids and pyrimidine are building block of these biomolecules. Apart from this pyrimidine heterocyclic is strange in the drug discovery because of its diversity of action viz antifungal, antiviral, anti-diabetic, anticancer, antibacterial, antidiuretic, anti-inflammatory activities.

Molecular Docking

Discovery Studio 2019 Software, molecular docking analysis was carried out using the C-Docker protocol. Roscovitine-complexed X-ray crystallographic enzyme (CDK2) substrate (was downloaded from the protein database (http://www. rcsb. org/-pdb)) (PDB ID: 2A4L). The structures of the enzymes were checked for missing atoms, bonds, contacts, and cleaned. The enzyme structure was reinforced with hydrogen atoms. Manually deleted water molecules and bound ligand. The receptor was prepared by a protein preparation wizard in Macromolecules Tools. Missing loops of lengths less than or equal to the Maximal Loop Length are inserted and initially refined using Modeler. Further refinement was done using CHARMm minimization. The structures of compounds were sketched using Chem3D 18.1 and MM2 minimization was done. Ligands were loaded in Discovery Studio and full minimization was carried out using CHARMm force field and steepest Descent algorithm with 2000 iterations, RMS Gradient 0.01, Nonbond List radius 18.0 Å. The binding site was defined by selecting the co-crystal ligand. CDOCKER protocol was carried out for docking studies. The "-CDOCKER_ENERGY" and "-CDOCKER_INTERACTION_ENERGY" was used as an indicator for the quality of molecular docking. The high positive value of those indicators presented a good interaction between the ligand and the receptor.

Validation of the docking protocol

By performing the RMSD calculation between the docked pose and the crystal structure, we validated the adopted docking protocol to confirm the reliability of the chosen docking system.

Result and Discussion

Molecular docking studies

Using the CDOCKER algorithm, detailed intermolecular interaction was analyzed between the ligands and protein. The targeted protein's 3D structural details were collected with an entry code PDB ID 2A4L from the PDB Databank. The inhibitors

were docked to the targeted protein's active site and binding energies were measured. This showed that 6r, 6l and 6p compounds showed higher docking scores compared to those in the series. Compound 6r exhibited one H-bonding interaction between the nitrogen of Cyanide group of pyrimidine at 5th position with LYS89 (1.80 Å) and four Pi-Alkyl bond with LEU134, ILE10, VAL18 and ALA144 (4.47, 4.46, 5.29, 5.04 Å respectively) one carbon-hydrogen bond with LEU83 (2.73 Å), one Pi-Donor Hydrogen Bond interaction with GLU12 (3.18 Å) and one Pi-Anion interaction with Asp145 (4.00 Å) as shown in (Fig. 1). As depicted in Fig. 2, compound 6l exhibited five H-bonding interaction with ASP86, GLU12, LYS89, HIS84 (2.04, 2.03, 1.81, 3.08 Å respectively) and LEU83 (2.81, 2.26, 1.92 Å), two pi-Alkyl interaction with ILE10, LEU134 (5.0, 4.66 Å) and two carbon-hydrogen bond with GLY13, GLY11 (2.75, 2.40 Å). Compound 6p exhibited four Hydrogen bond interaction with THR14, LYS33, ILE10, LEU83 (2.63, 1.86,2.79, 2.31 Å respectively), three pi-Alkyl interaction with ALA31, VAL18, LEU134 (5.19, 4.75, 4.94 Å respectively), four carbon-hydrogen bond with GLY13, ASP145, PHE82, LYS89 (2.35, 2.5, 2.68,2.89 Å) as shown in (Fig. 3)

Validation and selection of the docking method

To determine the precision of the docking procedure, co-crystal ligand RMSD values were calculated. The lowest RMSD value results from the CDOCKER protocol combined with the CDK2 protein model (1.54 Å) (Fig. 4). Fig. (1) 3D Interaction of compound 6r at the binding site of the enzyme (PDB ID: 2A4L) (A) Interaction with Protein 2A4L, (C) Hydrophobic interaction, (D) Hydrogen bond interaction, (E) 2D Interaction of the compound 6r at the active site of the enzyme 2A4L.

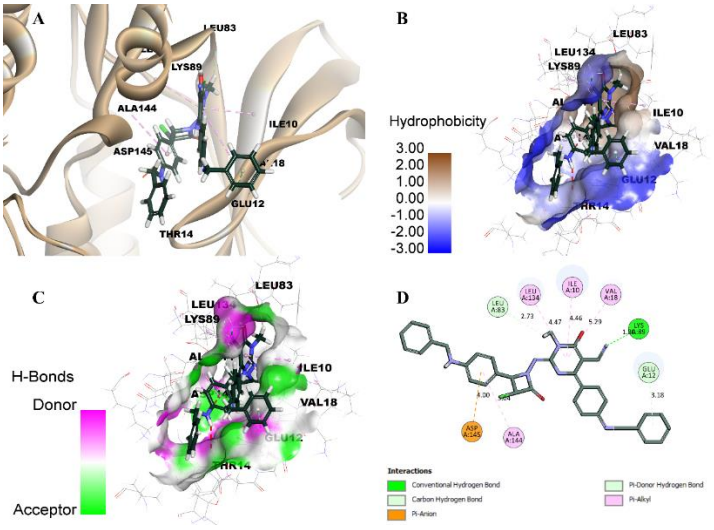


Fig. (2) 3D Interaction of compound 6l at the binding site of the enzyme (PDB ID: 2A4L) (A) Interaction with Protein 2A4L, (C) Hydrophobic interaction, (D) Hydrogen bond interaction, (E) 2D Interaction of the compound 6l at the active site of the enzyme 2A4L

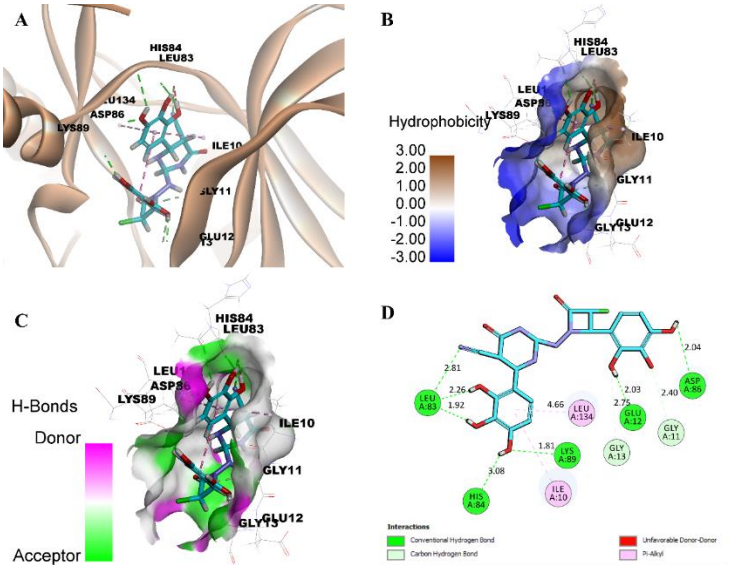
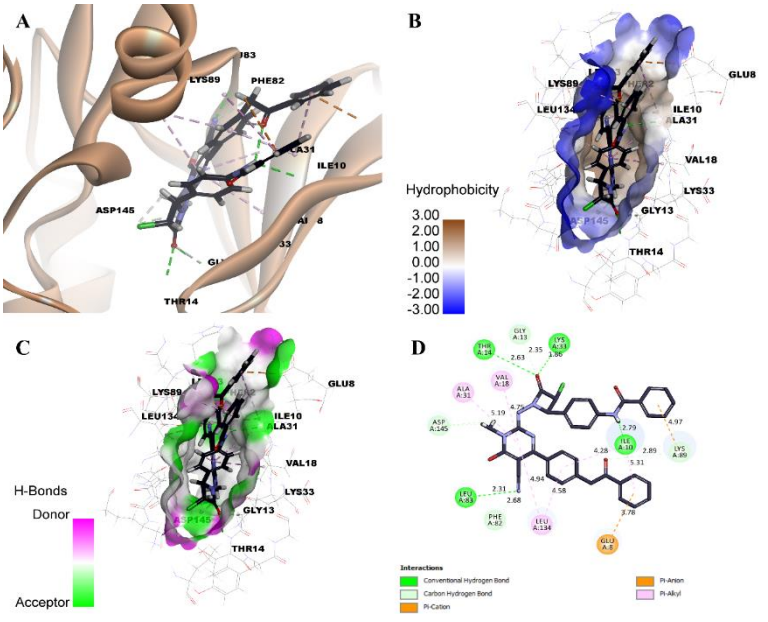


Fig. (3) 3D Interaction of compound 6p at the binding site of the enzyme (PDB ID: 2A4L) (A) Interaction with Protein 2A4L, (C) Hydrophobic interaction, (D) Hydrogen bond interaction, (E) 2D Interaction of the compound 6p at the active site of the enzyme 2A4L



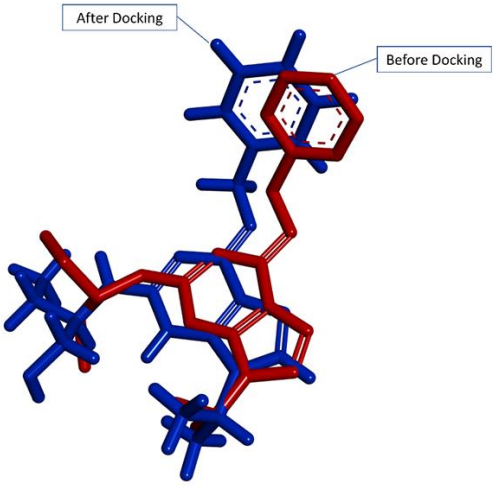


Fig. 4. RMSD of docked pose of Cocrystal ligand of 2A4L between before docking and after docking

Synthesis of 4-oxo-6-phenyl-2-sulfanyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(2)

The mixture of ethyl-cynoacetate (0.1 moles), thiourea (0.1 moles) and benzaldehyde(0.1 moles)was refluxed into round bottom flask in presence of 5.9g potassium carbonate (0.1 moles)for 8-12 hours. The completion of reaction was examined using TLC. The reaction mixture was poured into hot water and acidified with glacial acetic acid. The solid residue filtered and recrystallized using glacial acetic acid.

Synthesis of 3-methyl-2-(methylsulfanyl)-4-oxo-6-phenyl-1,2,3,4-tetrahydro-5-carbonitrile(3)

Reaction mixture containing Compound **2**(0.01moles), methyl iodide(0.01moles) and potassium carbonate was stirred in DMF at room temperature for 4-6 hours and poured into cold water. Finally neutralized with glacial acetic acid and filtered the solid residue by suction filtration. The solid residue filtered and recrystallized using glacial acetic acid.

Synthesis of 2-hydrazinyl-3-methyl-4-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(4)

The compound(2) was refluxed with hydrazine hydrate(0.01mole) in absolute ethanol for 5-6 hours.The reaction mixture poured into ice cold water and solid residue filtered and recrystallized using ethanol.

Synthesis of Compound (5a-r)

It was synthesized by heating the compound **4**(0.01mole) and various substituted aromatic aldehyde under reflux in presence of glacial acetic acid for 5-6 hours.

The reaction mixture poured into ice cold water and solid residue filtered and recrystallized using ethanol.

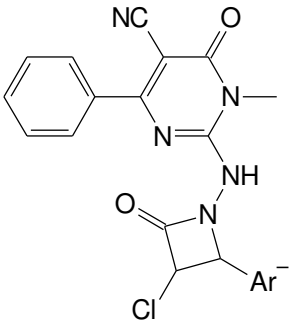
Synthesis of Compound (6a-r)

Thecompounds(5a-r) (0.002moles) and TEA (0.004moles) was dissolved into 4-dioxane(50ml), cooled and stirred for 15 to 20 minutes. To this solution chloroacetylchloride(0.004moles) added drop wise within 20 minutes. Resultant solution was stirred for 3 hours and then refluxed for 8 hours. The final mixture was concentrated and poured into ice cold water and solid was separated by suction and recrystallized with glacial acetic acid. Yield-65-78%

Synthesis of Compound (7a-o)

Thecompounds(5a-r) 0.01moles and thioglycolic acid(0.01moles) was stirred into glacial acetic acid refluxed for 12 hours. Reaction mixture was poured into ice cold water and solid residue was separated by suction filtration. The residue was recrystallized using absolute ethanol. Yield-70-85%

Scheme – 1



6a-r

5c = 2-{(2*Z*)-2-[(4-hydroxy-3-methoxyphenyl)methylidene]hydrazinyl}-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile, C20H17N5O3=375.38 IR= 2212cm^{-1}(CN), 1691cm^{-1}(CO), 1612cm^{-1}(C=N), 1472(C=C), NMR= δ 7.58, δ 7.74 and δ 7.90(Ar-H), δ 2.56(NH-N), δ 3.24(N-CH3).δ 3.71 (s, 3H, OCH3), 8.55 (s, 1H, Ar-H), 7.47 (d, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 12.18 (s, 1H, NH-N=C);

5e = 2-{(2*Z*)-2-[(2-amino-3,5-dibromophenyl)methylidene]hydrazinyl}-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile(C19H14Br2N6O=502.16), IR= 2254cm^{-1}(CN), 1686cm^{-1}(C=N), 1510 cm^{-1} (C=C), 3328 cm^{-1}(NH), 528 cm^{-1}(C-Br)8.63 (s, 1H, Ar-H), 7.31 (d, 2H, ArH), 7.34 (d, 2H, Ar-H), 7.06 (d, 1H, Ar-H), 7.10 (s, 1H,NH).

5f = 2-{(2*Z*)-2-[(3,5-dibromo-4-hydroxyphenyl)methylidene]hydrazinyl}-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile(C19H13Br2N5O2=518.16);

IR= 2263cm-1(CN), 3412 cm-1(OH), 541 cm-1(C-Br)8.45 (s, 1H, Ar-H), 7.12 (d, 2H, ArH), 7.42 (d, 2H, Ar-H), 7.11 (d, 1H, Ar-H), 7.18 (s, 1H,NH), 2.21(s CH3)

5g = 2-{(2*Z*)-2-[(4-bromo-3-nitrophenyl)methylidene]hydrazinyl}-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile(C19H13BrN6O3=453.23);

IR= 2208cm-1(CN), 3421 cm-1(NH), 543 cm-1(C-Br)8.23 (s, 1H, Ar-H), 7.65 (d, 2H, ArH), 7.08 (d, 2H, Ar-H), 7.12 (d, 1H, Ar-H), 7.04 (s, 1H,NH).

5l= 1-methyl-6-oxo-4-phenyl-2-{(2*Z*)-2-[(3,4,5-trihydroxyphenyl)methylidene]hydrazinyl}-1,6-dihydropyrimidine-5-carbonitrile(C19H15N5O4=377.35) IR= 2210cm-1(CN), 1632cm-1(C=N), 1540 cm-1 (C=C), 3422 cm-1(NH), 3640 cm-1(OH), 8.22 (s, 1H, Ar-H), 7.28 (d, 2H, ArH), 7.45 (d, 2H, Ar-H), 7.12 (d, 1H, Ar-H), 7.08 (s, 1H,NH).

5m= 2-{(2*Z*)-2-[(3-hydroxy-4-methoxyphenyl)methylidene]hydrazinyl}-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile(C20H17N5O3=375.38); IR= 2218cm-1(CN), 1598cm-1(CO), 1610cm-1(C=N), 1468(C=C), NMR= δ 7.88, δ 7.72 and δ 7.69(Ar-H), δ 2.78(NH-N), δ 3.11(N-CH3), 8.22 (s, 1H, Ar-H), 7.43 (d, 1H, Ar-H), 7.04 (d, 1H, Ar-H), 11.96 (s, 1H, NH-N=C);

5n= 2-{(2*Z*)-2-[(3-chloro-4-iodophenyl)methylidene]hydrazinyl}-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile(C19H13ClIN5O=489.69);

IR= 2220cm-1(CN), 1610cm-1(CO), 1524cm-1(C=N), 1491(C=C), NMR= δ 7.58, δ 7.68 and δ 7.88(Ar-H), δ 2.34(NH-N), δ 3.15(N-CH3), δ 574(C-Cl), 8.10 (s, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 7.26 (d, 1H, Ar-H), 11.92 (s, 1H, NH-N=C);

5o = 2-{(2*Z*)-2-[(4- phenylmorpholine)methylidene]hydrazinyl}-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile(C23H22N5O2=414.45);IR= 2272cm-1(CN), 1590cm-1(CO), 1512cm-1(C=N), 1455(C=C), 1034 cm-1(C-O-C), NMR= δ 7.74, δ 7.68 and δ 7.91(Ar-H), δ 2.10(NH-N), δ 3.12(N-CH3), 8.10 (s, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 7.26 (d, 1H, Ar-H), 11.92 (s, 1H, NH-N=C);

5p= 2-{(2*Z*)-2-[(4- phenylbenzamide)methylidene]hydrazinyl}-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile(C26H20N6O2=448.47); IR= 2245 cm-1(CN), 3345 cm-1(NH), 1576cm-1(CO), 1628cm-1(C=N), 1582cm-1 (C=C)), NMR= δ 7.88, δ 7.72 and δ 7.68(Ar-H), δ 2.08(NH-N), δ 3.11(N-CH3), 8.14 (s, 1H, Ar-H), 7.11 (d, 1H, Ar-H), 7.21 (d, 1H, Ar-H), 11.96 (s, 1H, NH-N=C);

5r= 2-{(2*Z*)-2-[(4- phenylbenzamide)methylidene]hydrazinyl}-1-methyl-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile(C26H22N6O=434.49);IR= 2212 cm-1(CN), 3352 cm-1(NH), 1554cm-1(CO), 1613cm-1(C=N), 1566cm-1 (C=C)), NMR= δ 7.91, δ 7.88 and δ 7.64(Ar-H), δ 2.02(NH-N), δ 3.08(N-CH3), δ 4.44 (d 2H NHCH2)8.11 (s, 1H, Ar-H), 7.02 (d, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 11.76 (s, 1H, NH-N=C);

6c= $C_{22}H_{18}ClN_5O_4$ (451.86) MP-258-260 °C; 1718.63 (C=O of β-lactum), 806.27(C-Cl bending) 4.97 (d,1H, CH-Cl ofazetidinone) 5.19 (d,1H, CH-Ar of azetidinone); 6e= $C_{21}H_{15}Br_2ClN_6O_2$ (578.64), MP- 292-294°C; 1712.63 (C=O of β-lactum),

534(C-Br), 768.61 (C-Cl bending) 4.88 (d,1H, CH-Cl ofazetidinone) 5.10 (d,1H, CH-Ar of azetidinone);6f= $C_{21}H_{14}Br_2ClN_5O_3$ (579.62), MP- 294-296 °C; 1735.22 (C=O of β-lactum), 528(C-Br), 3412(C-OH), 754.29(C-Cl bending) 4.92 (d,1H, CH-Cl ofazetidinone) 5.08 (d,1H, CH-Ar of azetidinone); 6g= $C_{21}H_{14}BrClN_6O_4$ (529.73), MP- 278-280°C, 1744.08 (C=O of β-lactum), 552 (C-Br), 3487(C-OH), 739.69(C-Cl bending) 4.96 (d,1H, CH-Cl ofazetidinone) 5.12 (d,1H, CH-Ar of azetidinone); 6l= $C_{21}H_{16}ClN_5O_5$ (453.83), MP- 266-368 °C; 1684.24 (C=O of β-lactum), 3512 (C-OH), 744.31(C-Cl bending) 4.91 (d,1H, CH-Cl ofazetidinone) 5.24 (d,1H, CH-Ar of azetidinone); 6m= $C_{22}H_{18}ClN_5O_4$ (451.86), MP- 260-262°C; 1624.81 (C=O of β-lactum), 3524 (C-OH), 765.21(C-Cl bending) 4.94 (d,1H, CH-Cl ofazetidinone) 5.18 (d,1H, CH-Ar of azetidinone); 6n= $C_{21}H_{14}Cl_2IN_5O_2$ (566.17), MP- 282-284°C; 1653.22 (C=O of β-lactum), 3496 (C-OH), 758.08(C-Cl bending) 4.88 (d,1H, CH-Cl ofazetidinone) 5.26 (d,1H, CH-Ar of azetidinone); 6o= $C_{25}H_{23}ClN_6O_3$ (490.94), MP-266-268°C; 1667.11 (C=O of β-lactum), 3498 (C-OH), 761.24(C-Cl bending) 4.89 (d,1H, CH-Cl ofazetidinone) 5.18 (d,1H, CH-Ar of azetidinone); 6p= $C_{28}H_{21}ClN_6O_3$ (524.95), MP-268-270°C; 1721.09 (C=O of β-lactum), 3511 (C-OH), 758.33(C-Cl bending) 4.91 (d,1H, CH-Cl ofazetidinone) 5.22 (d,1H, CH-Ar of azetidinone); 6r= $C_{28}H_{23}ClN_6O_2$ (510.97), MP-272-274°C; 1710.14 (C=O of β-lactum), 3514 (C-OH), 776.12(C-Cl bending) 4.90 (d,1H, CH-Cl of azetidinone) 5.09 (d,1H, CH-Ar of azetidinone).

ID	M.F	M.W	Ar	MP	Yield
6c	$C_{22}H_{18}ClN_5O_4$	451.86	-C6H3OHOCH3	258-260 °C	88.4%
6e	$C_{21}H_{15}Br_2ClN_6O_2$	578.64	-C6H2NH2Br2	292-294 °C	69.2%
6f	$C_{21}H_{14}Br_2ClN_5O_3$	579.62	- C6H2OHBr2	294-296 °C	71.6%
6g	$C_{21}H_{14}BrClN_6O_4$	529.73	- C6H3NO2Br	278-280 °C	79.3%
6l	$C_{21}H_{16}ClN_5O_5$	453.83	- C6H2OH3	266-368 °C	88.5%
6m	$C_{22}H_{18}ClN_5O_4$	451.86	- C6H3OHOCH3	260-262°C	73.9%
6n	$C_{21}H_{14}Cl_2IN_5O_2$	566.17	- C6H3ClI	282-284°C	49.8%
6o	$C_{25}H_{23}ClN_6O_3$	490.94	-C6H4C4H8NO	266-268°C	68.7%
6p	$C_{28}H_{21}ClN_6O_3$	524.95	-C13H10NO	268-270°C	64.8%
6r	$C_{28}H_{23}ClN_6O_2$	510.97	-C13H12N	272-274°C	85.2

Discussion

In this study, Protein Data Bank (PDB) and National centre for Biotechnology Information (NCBI) was used as chemical sources[10]. The software used for experiment that, ACD/Chemsketch Ultra 10.0 for draw series of dihydropyrimidine-thizolidine and dihydropyrimidine-azetidine derivatives structures and Autodock 4.0,Discovery studio or autodock 4.0 for docking studies[11].

Conclusion

According to exist literature and predicted analysis of the results from the our research of the docking, analytical, synthetic and computational study indicated that the designed novel dihydropyrimidine-thiazolidine and dihydropyrimidine-azetidine based –derivative have potent activation effect on CDK and tyrosine

kinase receptor as potential anticancer target as well as treatment of a number of life threading disease.

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