BIOINFORMATION
Discovery at the interface of physical and biological sciences

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Volume 10(5)

Molecular docking studies of benzimidazopyrimidine and coumarin substituted benzimidazopyrimidine derivatives: As potential human Aurora A kinase inhibitors

Chandra[1], Kallimeledoddi B Puttaraju[2], Sankanahally Srinivasshetty Mahesh[3], Kalegowda Shivashankar[2], Neratur Krishnappagowda Lokanath[1] & Mahendra Madegowda[1]*

[1]Department of Studies in Physics, Manasagangotri, University of Mysore, Mysore- 570006, India; [2]P. G. Department of Chemistry, Central College Campus, Bangalore University, Bangalore- 560001, India; [3]Department of Physics, Acharya Institute of Technology, Bangalore- 560090, India; Mahendra Madegowda – Email: mahendra@physics.uni-mysore.ac.in; Phone: +91-9964330328; *Corresponding author

Received April 20, 2014; Accepted May 04, 2014; Published May 20, 2014

Abstract:
Protein kinases are important drug targets in human cancers, inflammation and metabolic diseases. Docking studies was performed for all the benzimidazopyrimidine and coumarin substituted benzimidazopyridimine derivatives with human Aurora A kinase target (3FDN) employing flexible ligand docking approach by using AutoDock 4.2. All the compounds were found to have minimum binding energy ranging from -6.26 to -9.29 kJ/mol. Among the molecules tested for docking study, 10-(6-Bromo-2-oxo-2H-chromen-4-ylmethyl)-2-isopropyl-10H-benzo[4,5]imidazo[1,2-a]pyrimidin-4-one (2k) showed minimum binding energy (-9.29 kJ/mol) with ligand efficiency of -0.31. All the ligands were docked deeply within the binding pocket region of 3FDN showing hydrogen bonds with Ala 213 and Asn 261. The docking study results showed that these derivatives are excellent inhibitor of human Aurora A kinase target; and also all these docked compounds have good inhibition constant, vdW + Hbond + desolv energy with best RMSD value.

Key Words: Benzimidazopyrimidine and coumarin substituted benzimidazopyridimine derivatives, Single crystal structure, Aurora A, Docking studies.

Background:
Benzimidazopyrimidine belonging to the fused heterocyclic system have three nitrogen atoms. The most prominent benzimidazole moiety in nature is N-ribosyl -dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12} **[1].** Literature survey revealed that benzimidazole derivatives play a vital role in biological activities such as antifungal, kinase inhibitor, anti-hepatitis-C-virus, antidepressant and anticancer **[2-8].** Also, heterocycles containing an imidazolone moiety exhibits various biological activities such as antibacterial and antifungal activities **[9-11].** Coumarins are an important class of widely distributed heterocyclic natural products exhibiting several biological properties. 4-Amino-3-(2-methylbenzyl)coumarin derivatives **[12]** exhibited potent estrogenic activity on the estrogen receptor positive (ER^+) human MCF-7 breast cancer cell line. Benzothiazolyl coumarin acetamide derivatives **[13]** exhibited strong *in vitro* anti-HIV effect against the wild-type HIV-1 cell

line. The *in vitro* antioxidant activities of 4-schiff bases-7-benzyloxy coumarin derivatives **[14]** revealed that DPPH and $ABTS^{+}$ radical scavenging activities were better than that of the commercial antioxidant BHT.

Human protein kinases are attractive targets for the development of new therapeutics because of their involvement in processes associated with the progression of cancers and metabolic diseases **[15, 16].** Aurora kinase family of serine/threonine kinase regulates some important events during mitosis. They play key roles in centrosome maturation and separation, mitotic spindle assembly and chromosome segregation **[17].** The Aurora kinase A is commonly overexpressed in many tumor cell lines and human primary tumours **[18]**. In addition, Aurora A has the ability to transport cell lines that are capable of forming tumours in mice **[19].** The role of Aurora A in the cell cycle and tumorogenesis suggested that the inhibition of the kinase activity have remarkable value for the development of small molecular therapeutics for cancer treatment. Based on the current success of Aurora kinase inhibitors in the development of kinase-based cancer therapy, we have initiated a virtual screening program for the identification of Aurora kinase inhibitors.

In our previous paper **[20]**, we have reported the synthesis, *in vitro* antimicrobial and anticancer activities of novel coumarin substituted dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-ones. In continuation to this, we study herewith, the crystal structure (2g) and molecular docking studies of benzimidazopyrimidine and coumarin substituted benzimidazopyridimine derivatives with human Aurora A kinase target to evaluate their potential value for the treatment of cancers.

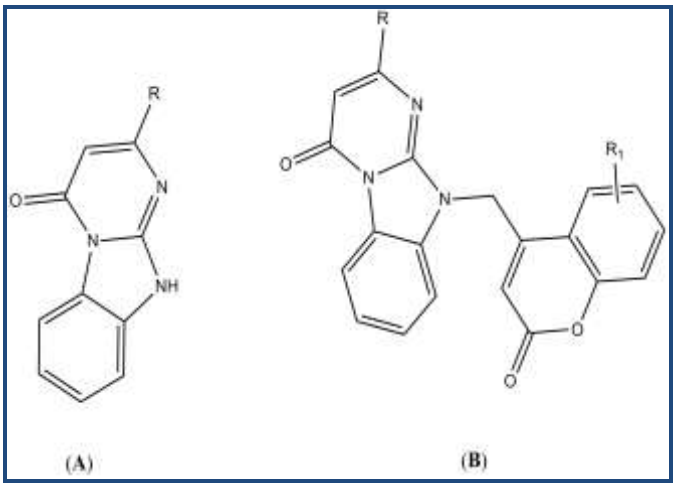

Figure 1: Structure of **(A)** Bennzimidazopyrimidine **(B)** Coumarin substituted benzimidazopyridimine derivatives.

Methodology:

Preparation of ligands

The 2D structures (.mol) of all the thirteen compounds as tabulated in **Table 1 (see supplementary material)** were drawn and the structure was analyzed by using ChemDraw Ultra 12.0. All the compounds (2a-2k) are converted to 3D structure (.pdb) using Openbable software tool. The 3D coordinates (.pdb) of each molecule were loaded on to Dundee PRODRG server for energy minimization **[21].** The structure of the benzimidazopyridimine and coumarin substituted benzimidazopyridimines are shown in **Figure 1.**

Preparation of macromolecule

The protein target, which is retrieved from the RCSB Protein Data Bank (PDB code 3FDN) serves as docking receptor **[22].** All the bound ligands and water molecules were removed from the active site of the receptor. For docking target, crucial amino acids of the active site were identified using data in pdbsum as shown in **Figure 2 [23**].

X-ray structure determination

A single crystal of the compound (2g) with dimensions of 0.30 × 0.25 × 0.20 mm was chosen for X-ray diffraction studies. The data were collected on a Bruker SMART APEX II X-ray diffractometer with graphite monochromated MoKα radiation, operating at 50 kV and 30 mA. Raw data was processed and reduced by using APEX2 and SAINT **[24].** The structure was solved by direct methods using SHELXS-97 **[25].** All non-hydrogen atoms were revealed in the first Fourier map itself. Full-matrix least squares refinement was carried out using SHELXL-97 **[25].** Anisotropic refinement of non-hydrogen atoms was started at this stage. Subsequent refinements were carried out with anisotropic thermal parameters for non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms which were placed at chemically acceptable positions. CCDC- 990917 contains the supplementary crystallographic data of molecule 2g **[26].** The X-ray structure of this compound (2g) was used for the docking studies.

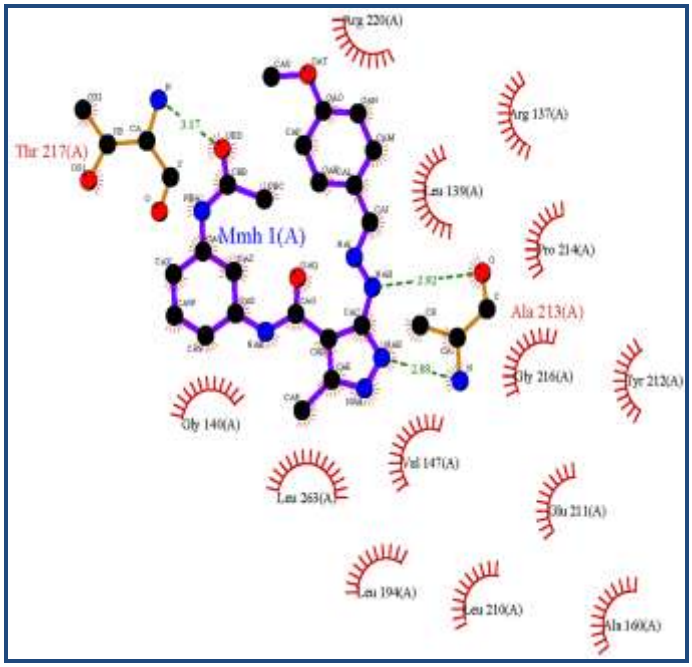

Figure 2: Ligplot results of Aurora A (3FDN), showing the binding of ligand Mmh 1(A) with amino acid residues present in an active site pocket.

Molecular docking

The molecular docking was performed and analyzed using AutoDock 4.2. A Lamarkian genetic algorithm method implemented in the program suite was employed to identify appropriate binding modes and conformation of the ligand molecules. Gasteiger charges were added and the rotatable

bonds were set by the AutoDock tools and all torsions were allowed to rotate. Polar hydrogen atoms were added and Kollaman charges were assigned to the protein using AutoDock tools (ADT). The grid map was centered at the active site pocket of the protein by Autogrid. The grid map which was centered at the following residues of the protein (Thr 217, Arg 220, Arg 137, Leu 139, Pro 214, Ala 213, Gly 216, Tyr 212, Gly 140, Leu 263, Val 147, Glu 211, Leu 194, Leu 210, Ala 160) were predicted from the ligplot **(Figure 2).** In all the cases, we have used grid maps with a grid box size of 55×55×55 Å^3 points with a grid-point spacing of 0.375 Å. During docking, centre grid parameters were specified for x, y and z axis as -2.0, -32.0 and 7.0, respectively. The Lamarckian genetic algorithm, the pseudo-Solis and Wets methods were applied for minimization using default parameters. Binding energy, torsional energy, intermolecular energy, number of H-bonds and RMS value were recorded in each ligand bound conformations. The details of dock score results of the different benzimidazopyrimidine derivatives are given in **Table 2 (see supplementary material).**

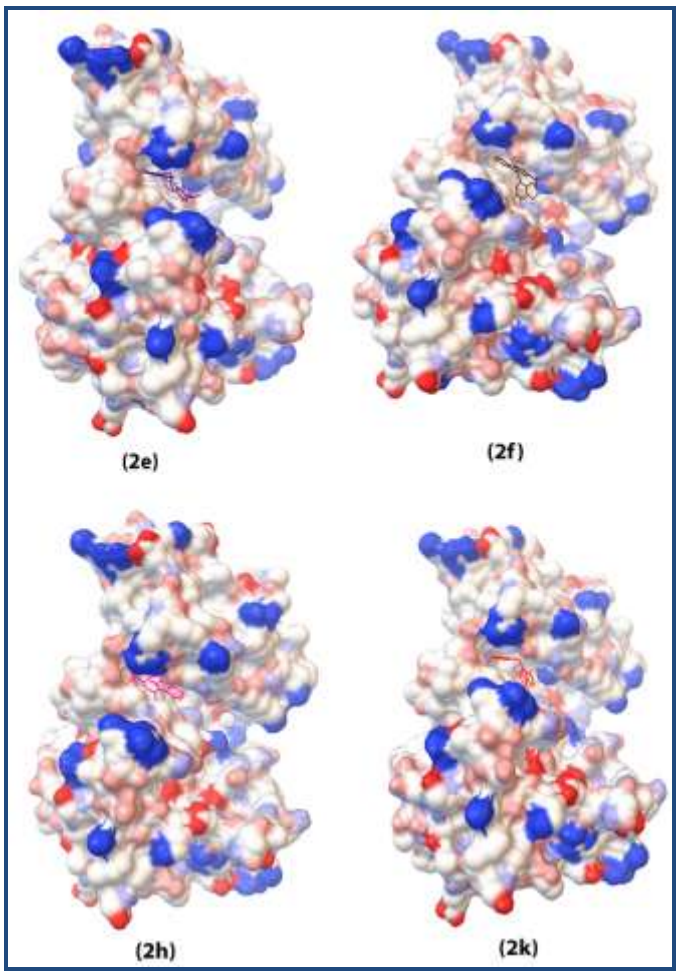

Figure 3: Enfolding of molecules 2e, 2f, 2h and 2k in the active site pocket

Results & Discussion:

The crystal structure analysis showed that the compound (2g) crystallizes in monoclinic system under the space group $P2_1/n$ with cell parameters, a = 9.3819(12) Å, b = 8.0471(10) Å, c = 26.808(4) Å, β = 93.592(7)° and Z=4. The crystal structure was solved by direct methods and refined by full-matrix least squares on F^2 to a final residual value of R1 = 0.0486. Automated docking was used to assess the binding modes and conformation of the ligand molecules. Docking studies was performed for all the benzimidazopyrimidine and coumarin substituted benzimidazopyridimine derivatives. In docking study, all the compounds were found to have minimum binding energy ranging from -6.26 to -9.29 kJ/mol. Among the docked molecules, 2h, 2i, 2j and 2k revealed minimum binding energy of -8.8, -9.1, -8.9 and -9.29 kJ/mol, with ligand efficiency of -0.29, -0.29, -0.3 and -0.31, respectively. These molecules were completely wrapped by active site amino acid residues at the active site pocket region (as shown in **Figure 3).**

The protein (3FDN) comprises of fifteen active site residues, which are promiscuous to the ligands. Out of which only two (Ala 213 and Asn 261) residues are directly interacting with the ligands. Most of the residues that are in close proximity to the inhibitor are hydrophobic in nature. All the ligands were docked deeply within the binding pocket region of 3FDN. The ligand molecules 2e, 2f, 2h and 2k were found to show hydrogen bond interaction with active site amino acid residues Ala 213 and Asn 261 at a distance of (1.923 and 2.203), (1.909 and 1.925), (2.234 and 1.928) and (2.024 and 2.104) Å, respectively **(Figure 4).** The ligands 2a, 2b, 2g and 2j showed only one hydrogen bond interaction with protein, where as ligand 2c and 2i has no interaction with the protein. The docking results for all ligand molecules against protein target showed minimum intermolecular energy, ligand efficiency, binding energy, inhibition constant and vdW + Hbond + desolv energy with best RMSD value. From this study, we have predicted ligands 2h, 2i, 2j and 2k may act as potential inhibitors of human Aurora A kinase enzyme.

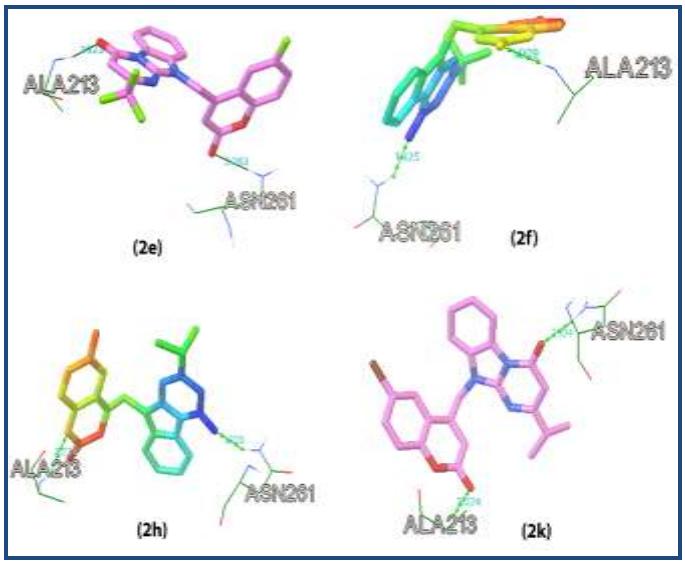

Figure 4: H-bond interaction of ligand molecules (2e, 2f, 2h and 2k) with 3FDN

Acknowledgement:

The author MM would like to thank UGC, New Delhi, Government of India, for awarding a project under the head F. No. 41-920/2012(SR) dated: 25-07-2012.

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Edited by P Kangueane
Citation: **Chandra *et al.*** Bioinformation 10(5): 288-292 (2014)

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Supplementary material:

Table 1: Different groups of benzimidazopyrimidine and coumarin substituted benzimidazopyrimidine derivatives

Compounds	R	R1
2a	ipr	-
2b	4-$CF_3C_6H_4$	-
2c	3-FC_6H_4	-
2d	CF_3	6- OCH_3
2e	CF_3	6-F
2f	CF_3	6-CH_3
2g	CF_3	6,8-($OCH_3)_2$
2h	*i*pr	6-F
2i	*i*pr	6-OCH_3
2j	*i*pr	6-Cl
2k	*i*pr	6-Br

Table 2: The dock score results of the different benzimidazopyrimidine and coumarin substituted benzimidazopyridimine derivatives

Compounds	Binding Energy (kJ mol^{-1})	Ligand Efficiency	Inhibition Constant	vdW+H-bond+desolv energy	No. of H-bonds	Bonding residues	Bond Length (Å)
2a	-6.26	-0.37	25.94	-6.55	1	3FDN:A:ALA213:HN	1.778
2b	-7.3	-0.3	4.47	-7.59	1	3FDN:A:ALA213:HN	1.959
2c	-7.28	-0.35	4.58	-7.48	-	-	-
2d	-8.03	-0.25	1.3	-9.23	2	3FDN:A:ALA213:HN	2.063
						3FDN:A:ASN261:HD22	2.064
2e	-8.13	-0.26	1.1	-8.89	2	3FDN:A:ALA213:HN	1.923
						3FDN:A:ASN261:HD22	2.203
2f	-8.39	-0.27	706.74	-9.33	2	3FDN:A:ALA213:HN	1.909
						3FDN:A:ASN261:HD22	1.925
2g	-8.67	-0.27	412.37	-9.49	1	3FDN:A:ALA213:HN	1.938
2h	-8.8	-0.29	354.57	-9.69	2	3FDN:A:ALA213:HN	2.234
						3FDN:A:ASN261:HD22	1.928
2i	-9.1	-0.29	214.1	-10.34	-	-	-
2j	-8.9	-0.3	301.24	-9.79	1	3FDN:A:ALA213:HN	2.18
2k	-9.29	-0.31	155.7	-10.23	2	3FDN:A:ALA213:HN	2.024
						3FDN:A:ASN261:HD22	2.104