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Anti-inflammatory Pyrazole Derivatives as Aurora Kinase Inhibitors-Molecular Docking and ADMET Studies

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ABSTRACT

In our earlier research we have synthesized series of substituted 3,5-diphenyl-4,5-dihydro-pyrazole-1-carbothioic acid benzylideneamide derivatives and evaluated for their anti-inflammatory activity. In the recent years, pyrazole derivatives are proved for their varied pharmacological effects ranging from antimicrobial activity to anti-cancer effects. In this study, we have hypothesized the efficiency of our earlier synthesized anti-inflammatory diphenyl-pyrazole derivatives for their potential in inhibition of Aurora kinase protein, through molecular docking studies. Molecular docking simulation studies are performed using Glide XP module of Schrodinger Suite and ligand binding energies are also calculated. Molecular docking studies of the selected compounds against Aurora kinase revealed superior docking scores ranging from -8.273 (compound 8) to -5.641 (compound 2) and also provided insight of binding conformations of the ligands in Aurora kinase protein environment. Additionally, molecular property and Absorption, Distribution, Metabolism and Excretion (ADME) predictor analysis is also performed for the dataset ligands, which further provided the probable explanation for the binding potentials.

Keywords: Aurora Kinase, Pyrazole, Molecular docking, Binding energy, ADME

INTRODUCTION

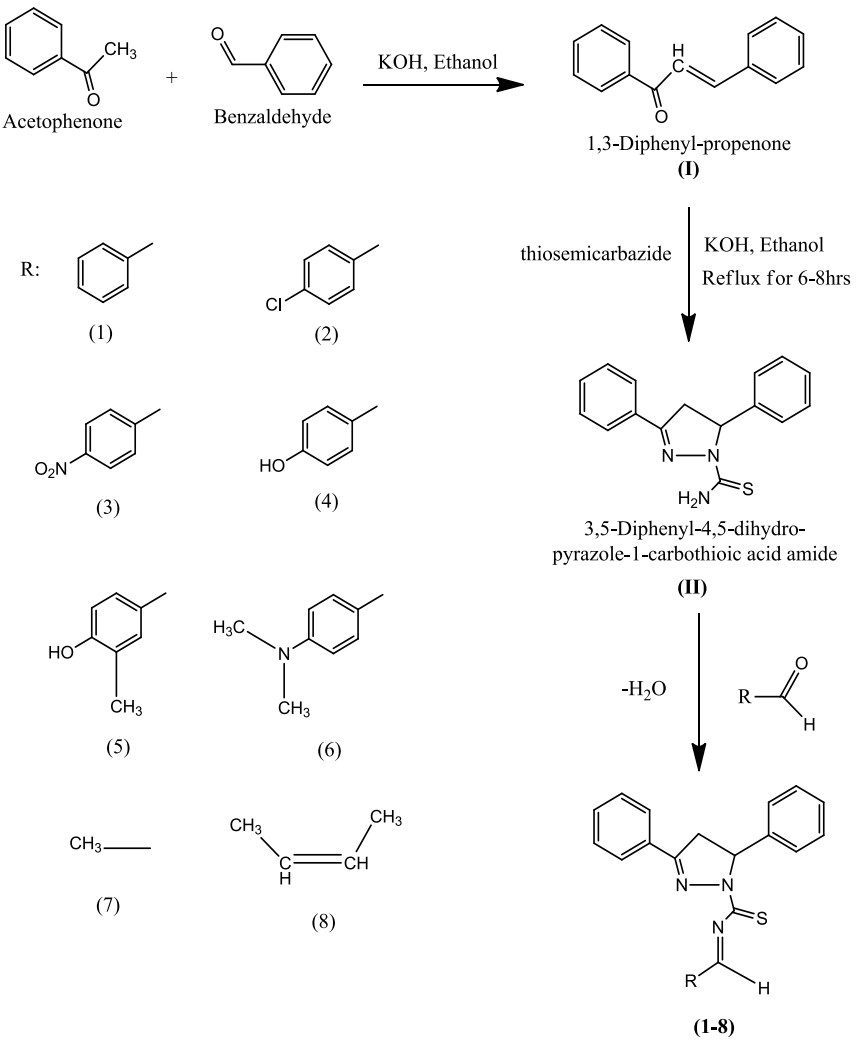
Pyrazole nucleus is a 1,2-diazole organic compounds in which derivatization majorly occur at either as N-substitution or as C-substitution, resulting in distinct variety of compounds (2). Pyrazole derivatives possess diverse pharmacological/biological activities including antitumor [1], antibacterial [2], antifungal [3], antiviral [4], antiparasitic [5], antitubercular [6] and insecticidal agents [7]. Some of these compounds have also anti-inflammatory [8], antidiabetic [9], anesthetics [10], and analgesic [11] properties. The N-substituted pyrazoles derivatives exhibited vivid anticancer activity in various oncological interests including antileukemic [12], antiproliferative [13], etc., Anticancer molecular mechanistic insights of these compounds revealed interaction/inhibition with variety of cellular proteins such as Cyclin Dependent Kinase (CDK) [14], aurora kinase (A,B,C) [15,16]. During the years, pyrazoles are proved to be potent Aurora kinase inhibitors (IC_{50}=0.16 ± 0.03 μM)) [17].

In the current investigation, we have hypothesized the inhibitory potentials of the anti-inflammatory pyrazole derivatives which were earlier designed and developed in our laboratory against Aurora Kinase protein [18]. In order to evaluate our hypothesis we have performed molecular docking studies to the data set compounds along with calculation of ligand binding energies. Additionally, we have also performed predictor analysis of molecular properties and ADME scores of the data set ligands.

MATERIALS AND METHODS

Dataset ligands and ligand optimization

Anti-inflammatory activity possessing pyrazole derivatives which were earlier developed in our laboratory were selected (Scheme 1) [18]. 2D structures of the compounds were converted to 3D using potential algorithms and application of high efficient force fields. Initial geometrical optimization and energy minimization of molecules were performed by using the Ligprep tool of Schrodinger suite [19]. Various ionization states were generated using Ligprep module using a special program EPIK along with various possible conformers and tautomers.



Scheme 1: Synthesis of diphenyl pyrazole derivatives

Molecular properties of the processed ligands were studied by using Qikprop module. Qikprop module also predicts ADME profiles like blockage of Human Ether-a-go-go-related Gene (hERG) K^+ channels, apparent Caco-2 cell permeability, brain/blood partition coefficient, apparent Madin-Darby canine kidney (MDCK) cell permeability, skin permeability, binding to human serum albumin, and human oral absorption of the given set of ligands [20].

Molecular docking studies

The digital structure of the Aurora-A kinase protein was retrieved from the Protein databank website with PDB Id: 1MQ4 and the structure was optimized by deleting unbound water molecules which are over 1 Å, adding hydrogen atoms to satisfy the valences, adding missing amino acids to stabilize side chains and energy of the whole structure was minimized using OPLS-2005 force field using Protein Preparation Wizard tool of Schrodinger Suite [21].

Thus structurally optimized protein structure was used to examine protein-ligand interactions of the dataset ligands using Glide Xp docking protocol. Initially, a 3D grid was established to the binding pocket (active site) of the protein, into which all the dataset ligands were docked into. Binding interactions and efficiency of the binding were calculated in terms of Glide Score, which is a combination of hydrophilic, hydrophobic, metal binding groups, Van der Waals energy, freezing rotatable bonds and polar interactions with receptor [22]. GScore=0.065x Van der Waals energy+0.130x Coulomb energy+Lipophilic term (Hydrophobic interactions)+H bonding+Metal binding+BuryP (Penalty for buried polar groups)+RotB (Penalty for freezing rotatable bonds)+Site (Polar interactions in the active site)

Post docking calculations

Prime MM/GBSA (molecular mechanics based generalized Born/surface area) module of Schrodinger suite was used to calculate the binding energies of the docked complexes, which is a combination of OPLS molecular mechanics energies (EMM), an SGB solvation model for polar solvation (GSGB), and a non-polar solvation term (GNP) containing non-polar solvent accessible surface area and Vander Waals interactions. In this, docking results were rescored through an energy function with a well-defined description of binding contributions. The total free energy of binding is then expressed in the form below mentioned Equation [22]:

$$\Delta G_{bind} = G_{complex} - (G_{protein} + G_{ligand})$$

Where, ΔG_{bind} is ligand binding energy.

RESULTS AND DISCUSSION

Predicted molecular properties and ADME profile

Various molecular properties such as Molecular weight, dipole, volume, Solvent Accessible Surface Area (SASA), hydrophobic component of SASA (FOSA), hydrophilic component of SASA (FISA), π (carbon and attached hydrogen) component of the SASA (PISA), and weakly polar component of the SASA (halogens, P, and S) (WPSA) have been determined using Qikprop module (Table 1). Molecular weight of all the compounds are within the normal range of 135-700 Da. Parameters such as dipole, SASA, FOSA, FISA, WPSA, and volume are also within the normal range for all the compounds. However, for compounds 1-4, π component of the SASA was found to be beyond the recommended range. This could be majorly due to the availability of additional phenyl group creating the resonance effect.

Table 1: Predicted molecular properties of the dataset ligands and the recommended range of the values

Molecule	Molecular weight	Dipole	SASA	FOSA	FISA	PISA	WPSA	Volume
1	369.483	9.918	653.622	47.287	15.436	520.758	70.141	1191.476
2	403.928	9.042	705.228	47.138	16.107	499.808	142.176	1256.608
3	414.481	9.819	691.1	47.366	112.741	460.875	70.118	1263.553
4	385.483	10.387	665.487	47.328	70.14	477.893	70.126	1213.81
5	399.509	9.519	693.924	130.879	60.715	432.213	70.117	1269.937
6	412.551	11.298	730.249	202.116	17.063	440.947	70.123	1341.622
7	307.412	9.381	584.281	133.993	16.034	364.542	69.712	1023.916
8	333.45	9.9	649.854	183.105	13.78	382.666	70.303	1143.29

Recommended range: Molecular weight (130-725), dipole (1-12.5), SASA-Solvent accessible surface area (300-1000), FOSA-Hydrophobic component of SASA (0-750), FISA-Hydrophilic component of SASA (7-330), PISA -π (carbon and attached hydrogen) component of the SASA (0.0-450.0), WPSA-Weakly polar component of the SASA (halogens, P, and S) (0.0-175.0), volume (500-2000).

Predicted ADME parameters include partition co-efficient, predicted aqueous solubility (QPlogS), probability of CNS effects, blockage of HERG K^+ channels (QPlogHERG), apparent Caco-2 cell permeability (QPPCaco), brain/blood partition coefficient (QPlogBB), apparent MDCK cell permeability (QPPMDCK), skin permeability (QPlogKp), binding to human serum albumin (QPlogKhsa) and human oral absorption of the given set of ligands (Table 2). All the compounds possessed higher human oral absorption levels (96%-100%). Other than compound 2 and 7, all the compounds resulted in low to inactive effect towards CNS. Partition coefficient of compound 2 (6.561) is slightly higher than the recommended (-2.0-6.5), whereas, compound 2, 5, and 6 were found to be have predicted water solubility beyond recommended range. All the compounds were reported to have extremely good apparent Caco-2 cell permeability (> 500), and with moderate potential to cross through blood-brain-barrier (-0.629-0.563).

Table 2: Predicted pharmacokinetic (ADME) profiles of compounds

Molecule	CNS	QPlog Po/w	QPlogS	QPlog HERG	QPP Caco	QPlog BB	QPP MDCK	QPlog Kp	QPlog Khsa	% Human oral absorption
1	1	5.891	-6.326	-6.741	7071.635	0.406	9926.864	0.319	0.879	100
2	2	6.561	-7.618	-7.175	6968.863	0.563	10000	0.232	1.069	100
3	0	5.13	-6.35	-6.677	844.845	-0.629	998.415	-1.59	0.779	96.411
4	0	5.259	-6.307	-6.612	2141.734	-0.189	2729.084	-0.745	0.826	100
5	0	5.624	-6.817	-6.55	2631.129	-0.111	3408.612	-0.732	0.976	100
6	1	6.279	-7.092	-6.781	6824.873	0.319	9550.782	0.103	1.005	100
7	2	4.609	-5.173	-5.846	6979.971	0.463	9735.071	-0.339	0.436	100
8	1	5.427	-6.256	-6.372	7332.069	0.416	10000	-0.137	0.74	100

Recommended range

CNS Predicted central nervous system activity on a –2 (inactive) to +2 (active) scale; QPlogP o/w: Predicted octanol/water partition coefficient (–2.0-6.5); QPlogS: Predicted aqueous solubility (-6.5-0.5); QPlogHERG: Predicted IC_{50} value for blockage of HERG K^+ channels (below-5); QPPCaco: Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells are a model for the gut-blood barrier (<25: poor, >500: great); QPlogBB: Predicted brain/blood partition coefficient (-3-1.2); QPPMDCK: Predicted apparent MDCK cell permeability in nm/s. MDCK cells are considered to be a good mimic for the blood-brain barrier (<25: poor, >500: great); QPlogKp: Predicted skin permeability, log Kp (–8.0- –1.0); QPlogKhsa: Prediction of binding to human serum albumin (–1.5-1.5); %Human-Oral Absorption (>80% is high, <25% is poor).

Molecular docking and binding energy calculations

Molecular docking studies were performed in order to find the possible protein ligand interactions of the dataset ligands which were earlier proved to have anti-inflammatory activity. Additionally, these also assisted in identifying the conformational changes of the ligand in the protein environment. About generates 100 different protein ligand complex conformations for each docked complex was generated through Glide XP module. Based on the EModel energy, only one was displayed in the result. Glide dock sores of the dataset ligands were shown in Table 3 along with the interaction amino acids and number of amino acids.

Among the docked ligands, compound 5 reported highest dock score of -8.273 with Emodel energy of -68.911 Kcal/mol. Compound 5 possessed 2 hydrogen bonds, each with Glutamine 211 and Alanine 213 amino acids at bond distances of 2.01 Å and 2.07 Å, respectively (Figures 1 and 2).

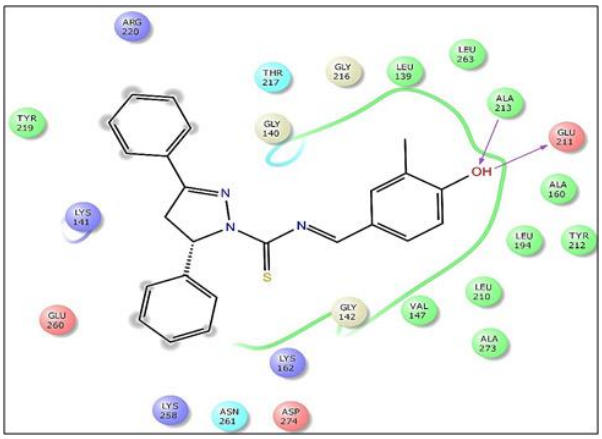


Figure 1: Binding interactions of compound 5 at kinase domain of Aurora kinase protein

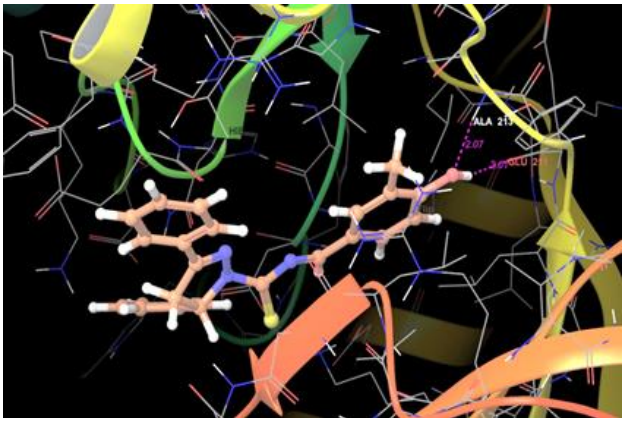


Figure 2: 2D Representation of binding interactions of compound 5 with Aurora kinase protein

Dock scores of all the compounds ranged from -8.273 (compound 5) to -5.641 (compound 2). Alanine 213 is the most commonly interacted amino acid with the data set ligands. Other amino acids include Glutamine 211 and Lysine 162 (compound 1). These constitute the kinase domain of Aurora-A kinase protein. Binding efficiency of compounds such as compound 8, 7, 6 and 2 is majorly contributed by hydrophobic and other Van Der Waals forces but not hydrogen bonding.

Multi-Ligand Bimolecular Association with Energetics (MBAE) consists of an automated mechanism that calculate the free energy of binding (FEB) of each docked complex. Total free energy of binding (binding energy) of each ligand is tabulated in Table 3. The total free energy of binding is the difference energy of the complex and ligand & protein which includes solvation energy, Vander wall's energy, electrostatic energy, valence energy, and constraint energy. Compound with highest dock score (compound 5) possessed the binding energy of -64.52 Kcal/mol, whereas compound 3 reported the highest binding energy of -77.11 Kcal/mol.

Table 3: Docking results and protein-ligand binding interactions of anti-inflammatory pyrazole derivatives Aurora kinase

Compound	Dock score	Emodel energy	No of H-bonds	Amino acids	H bond distance	Binding energy
5	-8.273	-68.911	2	GLU 211 ALA 213	2.01 2.07	-64.51724
8	-7.773	-53.978	0	-	-	-73.34981
7	-7.489	-44.635	0	-	-	-69.27386
1	-6.827	-67.463	1	LYS 162	2.68	-58.16287
4	-6.31	-69.561	1	ALA 213	2.27	-72.12781
6	-6.031	-51.706	0	-	-	-70.07951
3	-5.938	-63.606	1	ALA 213	2.21	-77.10874
2	-5.641	-61.8	0	-	-	-66.62178

CONCLUSION

In the current investigation, we have hypothesized the probable Aurora-A kinase inhibitory potentials of anti-inflammatory pyrazole derivatives and docking simulations were performed in order to identify binding efficiency and binding energy towards the Aurora kinase protein. Among all the tested dataset ligands, compound 5 has shown highest dock score (XP GScore) with better ADME profiles. Binding energies in the protein–ligand interactions explain how fit the ligand binds with target protein. Molecular docking studies of these anti-inflammatory pyrazole derivatives provided deeper insights in understanding the probable conformations of these tested ligands in the Aurora kinase protein environment.

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REFERENCES

[1] E.C. Taylor, H.H. Patel, S. Gowravaram, R. Chaudhari, *Tetrahedron*., **1992**, 48, 8089-8100.
[2] A.A. Abdel-Rahman, A.E. Abdel-Megied, M.A. Hawata, E.R. Kasem, M.T. Shabaan, *Monatsh. Chem*., **2007**, 138(9), 889-897.
[3] E.M. Sharshira, N.M. Hamada, *Molecules*., **2011**, 16(9), 7736-7745.
[4] A.E. Rashad, A.H. Shamrokh, M.I. Hegab, H.M. Awad, *Acta Chim. Slov*., **2005**, 52, 429-434.
[5] A.E. Rashad, M.I. Hegab, R.E. Abdel-Megeid, J.A. Micky, F.M. Abdel-Megeid, *Bioorg. Med. Chem*., **2008**, 16(15), 7102-7106.
[6] B.A. Bhat, K.L. Dhar, S.C. Puri, A.K. Saxena, M. Shanmugavel, G.N. Qazi, *J. Med. Chem*., **2005**, 15(12), 3177-3180.
[7] M.L. Edwards, D.M. Stemerick, P.S. Sunkara, Chalcones, *J. Med. Chem*., **1990**, 33, 1948-1954.
[8] Y.B. Vibhute, M.A. Baseer, *Indian J. Chem*., **2003**, 42, 202-205.
[9] R.O. Clinton, A.J. Manson, F.W. Stonner, A.L. Beyler, G.O. Potts, A. Arnold, *J. Am. Chem. Soc*., **1959**, 81(6), 1513-1514.
[10] R. Kalirajan, S.U. Sivakumar, J.B. Gowramma, B. Suresh, *Int. J. Chem. Sci*., **2007**, 5, 73-80.
[11] G. Urmila, S. Vineeta, K. Vineeta, C. Sanjana, *Indian J Heterocycl Chem*., **2005**, 14, 265-266.
[12] G. Daidone, B. Maggio, D. Raffa, S. Plescia, D. Schillaci, M. Valeria Raimondi, *Farmaco*., **2004**, 59(5), 413-417.
[13] C. Fabio, P. Annalisa, N. Antonella, S. Silvia, B. Olga, R. Angelo, B. Francesco, B. Chiara, F. Paola, M. Giulia, M. Luisai, M. Fabrizio, B. Maurizio, *J. Med. Chem*., **2004**, 47(7), 1595-1598.
[14] V. Krystof, P. Cankar, I. Frysová, J. Slouka, G. Kontopidis, P. Dzubák, M. Hajdúch, J. Srovnal, W.F. de Azevedo, M. Orság, M. Paprskárová, J. Rolcík, A. Látr, P.M. Fischer, M. Strnad, *J. Med. Chem*., **2006**, 49(22), 6500-6509.
[15] C. Soncini, P. Carpinelli, L. Gianellini, D. Fancelli, P. Vianello, L. Rusconi, P. Storici, P. Zugnoni, E. Pesenti, V. Croci, R. Ceruti, M.L. Giorgini, P. Cappella, D. Ballinari, F. Sola, M. Varasi, R. Bravo, J. Moll, *Clin. Cancer Res*., **2006**, 12(13), 4080-4089.
[16] D. Fancelli, J. Moll, M. Varasi, R. Bravo, R. Artico, D. Berta, S. Bindi, A. Cameron, I. Candiani, P. Cappella, P. Carpinelli, W. Croci, B. Forte, M.L. Giorgini, J. Klapwijk, A. Marsiglio, E. Pesenti, M. Rocchetti, F. Roletto, D. Severino, C. Soncini, P. Storici, R. Tonani, P. Zugnoni, P. Vianello, *J. Med. Chem*., **2006**, 49(24), 7247-7251.
[17] X. Li, X. Lu, M. Xing, X.H. Yang, T.T. Zhao, H.B. Gong, H.L. Zhu, *Bioorg. Med. Chem. Lett*., **2012**, 22, 3589-3593.
[18] P. Harathi, V.S.S. Rajendra Prasad, D. Satyavati, S. Subramanian, V. Boya, P. Gali, *Asian J. Pharm. Clin. Res*., **2015**, 8, 83-87.
[19] Ligprep, Version 2.7, Schrodinger LLC, NY, USA, **2016**.
[20] D.R. Gade, P. Kunala, D. Raavi, P.K.R. Kunda, R.P. Velivela, *J. Recept. Sig. Transd*., **2014**. 35(2), 189-201.
[21] G.D. Reddy, K.N.V.P. Kumar, N. Duganath, R. Divya, K. Amitha, *Int. J. Drug Dev. Res*., **2012**, 4(3), 268-282.
[22] P. Chaitanya, G. Deepak Reddy, G. Varun, L.M. Srikanth, V. Prasad, A. Ravindranath, *Med. Chem.*, **2014**, 10(7), 711-723.