Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2018, 7 (1): 189-194

(International Peer Reviewed Journal)

Structure and Molecular Modeling Studies of 1,3-Diphenyl-1*H*-Pyrazole Derivative as Potential Human Kinase Inhibitor

B. G.Devika[1], Shamantha Kumar[2], Chandra[3], N. Srikantamurthy[4], Shridevi D. Doddaramappa[5] and B. H. Doreswamy[2*]

1. Department of Physics, SJM Institute of Technology, Chitradurga 577 501, **INDIA**
2. Department of Physics, SJB Institute of Technology, Kengeri, Bangalore 560 060, **INDIA**
3. Department of Physics, The National Institute of Engineering (NIE), Mysore 570 008, **INDIA**
4. Department of Chemistry, Vidyavardhaka College of Engineering, Gokulum, Mysore 570 002, **INDIA**
5. Department of Studies in Chemistry, Manasagangotri, University of Mysore, Mysore-570006, **INDIA**

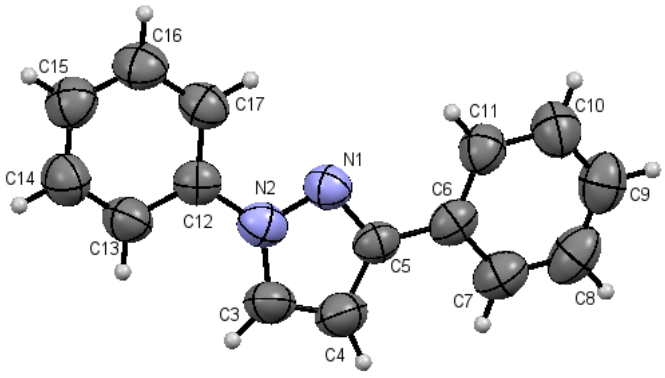
Email: dorephy@gmail.com

Accepted on 13th January 2018, Published online on 27th January 2018

ABSTRACT

*Molecular modeling was performed for 1,3-diphenyl-1H-pyrazole (**2a**) derivative with Aurora A (3FDN) inhibitor employing flexible ligand docking method by using Auto Dock. The title molecule found to be minimum binding energy-6.31 kJmol^{-1} with ligand efficiency of -0.37. The molecular modeling results showed that pyrazole derivative (**2a**) with Aurora A inhibitor are good inhibition constant, vdW + Hbond + desolv energy with best RMSD value. The compound 1,3-diphenyl-1H-pyrazole derivative (**2a**) was characterized and structure was confirmed by X-ray diffraction studies. The molecule crystallizes in monoclinic under the space group $P2_1/c$, with cell parameters a = 5.619(2)Å, b = 9.362(4)Å, c = 22.553(10)Å, β = 95.429(7)º and Z=4. Crystal structure stabilized by anC11-H11...N1 and C17-H17...N1 intramolecular hydrogen bonds.*

Graphical Abstract:



ORTEP of the molecule-pyrazole derivative with thermal ellipsoids drawn at 50% probability

Keywords: Docking study, Aurora A inhibitor, crystal structure, C-H…N interaction.

INTRODUCTION

Pyrazole ring is a pervasive motif in biologically active compounds. This is due to their wide spectrum of biological activity and easy preparation. Therefore, it is an important template in combinatorial as well as medicinal chemistry. In fact, some of the pyrazole derivatives like Celecoxib (COX-2 inhibitor), Viagra (phosphodiesterase inhibitor), Rimonabant (anorectic antiobesity drug), Lonazolac (non-steroidal anti-inflammatory drug) etc., are now widely used in the market as therapeutic agents [1-2].

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[3-4]. Particularly, Aurora kinase family of serine/threonine kinase regulates some important events during mitosis. Also, Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of pain and inflammation. Currently used NSAIDs suffer from limitations in their therapeutic uses, since they cause gastrointestinal and renal side effects, which are inseparable from their pharmacological activities. The discovery of a second isoform cyclooxygenase (cyclooxygenase-2) which is over expressed in inflammatory cells and the central nervous system, developing anti-inflammatory and analgesic agents that lack the gastrointestinal side effects of currently available nonsteroidal anti-inflammatory drugs [5]. Cyclooxygenase-2 is an inducible enzyme which is induced in response to the release of several pro inflammatory mediators [6-8].

In our previous paper [9], we have reported a simple and efficient synthesis of substituted pyrazoles. In view of the therapeutical and pharmaceutical importance of the pyrazole derivatives, in continuation to this, we study herewith, the detailed structure and molecular modeling ofpyrazole derivative (2a) as potential Aurora A inhibitor (3FDN) to improve the therapeutic potency and to reduce the classical side effects.

MATERIALS AND METHODS

Crystal structure determination: Automated docking was used to assess the appropriate binding orientations and conformations of the ligand molecules with different protein inhibitors. The results of molecular modeling study comprised of the binding energy, inhibition constant, hydrogen bond interaction energy, vander Waals forces and ligand efficiency. The lowest binding energy of macromolecule ligand complex has been considered to be the best. The details of dock score results of the pyrazole derivative with Aurora A inhibitor (3FDN) are given in Table 2.

The compound 1,3-diphenyl-1H-pyrazole derivative was characterized and structure was confirmed by single crystal X-ray diffraction studies. The data were collected on a Bruker SMART APEX II X-ray diffractometer with graphite monochromated MoKα radiation. Raw data was processed and reduced by using APEX2 and SAINT [10]. The structure was solved by direct methods and full-matrix least squares refinement was carried out using SHELXS-97/SHELXL-97, respectively [11-13]. The X-ray structure of 1,3-diphenyl-1*H*-pyrazole derivative was used for the docking studies. A summary of docking results and crystallographic data for molecule (**2a**) are given in table 1and table2, respectively. ORTEP of the molecule (2a) with thermal ellipsoids drawn at 50% probability, packing diagram of the molecule (2a),Docking of molecule (2a) in the active site pocket of Aurora A, Enfolding of molecule (2a) in the active site pocket of 3FDN are shown in Figs 1-4.

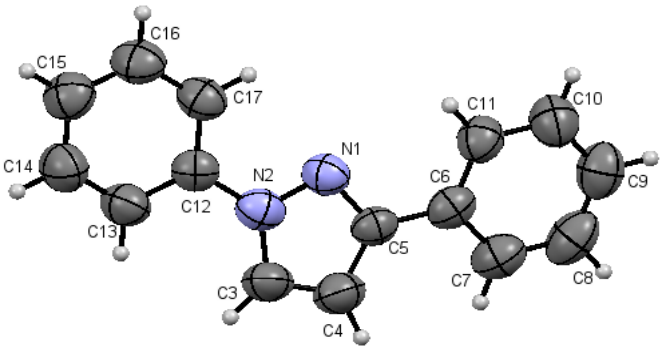


Figure 1. ORTEP of the molecule (2a) with thermal ellipsoids drawn at 50% probability

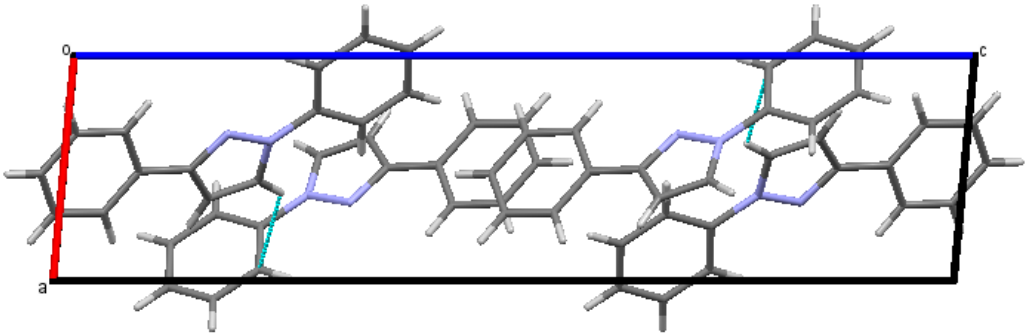


Figure 2. Packing diagram of the molecule (2a)

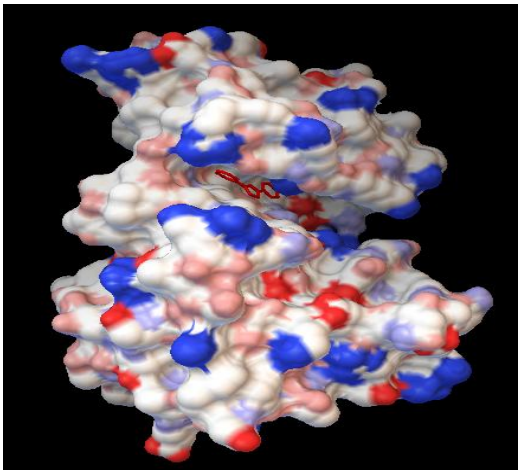


Figure 3. Docking of molecule (2a) in the active site pocket of Aurora A

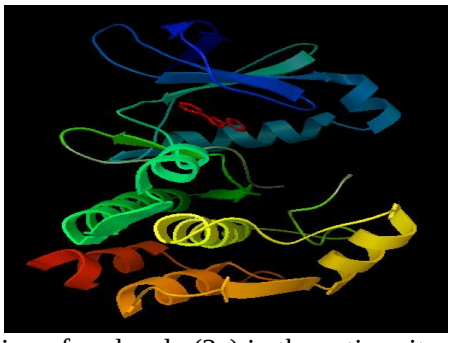


Figure 4. Enfolding of molecule (2a) in the active site pocket of 3FDN

Table 1. The dock score results of the ligand (2a) with protein Aurora A kinase target

Compound	**Binding Energy(kJ mol^{-1})**	**Ligand Efficiency**	**Inhibition Constant**	**vdW+H-bond+desolv energy**
2a	-6.31	-0.37	23.57	-6.87

Table 2. Crystal data and structure refinement for **2a**

Identification code	2a
Empirical formula	C_{15} H_{12} N_2
Formula weight	220.27
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 5.619(2) Å, b = 9.362(4) Å
	c = 22.553(8) Å, β = 95.429(7)°
Volume	1181.1(8) Å^3
Z, Calculated density	4, 1.239 Mg/m^3
Absorption coefficient	0.074 mm^{-1}
F_{000}	464
Crystal size	0.30 x 0.25 x 0.20 mm
Theta range for data collection	1.81 to 28.33°.
Limiting indices	-7≤ h≤ 7, -11≤ k≤ 12, -30≤ l≤ 30
Reflections collected / unique	13270 / 2863 [R(int) = 0.0222]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2863 / 0 / 154
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0502, wR2 = 0.1309
R indices (all data)	R1 = 0.0892, wR2 = 0.1534
Largest diff. peak and hole	0.196 and -0.41 e.Å^{-3}

The bond lengths and angles are presented in Tables 3, 4.

Table 3. Bond lengths [Å] and angles [°] for 2a

Atoms	Length	Atoms	Length
N(1)-C(5)	1.3412(19)	C(5)-N(1)-N(2)	105.40(13)
N(1)-N(2)	1.3533(18)	N(1)-N(2)-C(3)	110.84(14)
N(2)-C(3)	1.365(2)	N(1)-N(2)-C(12)	120.43(13)
N(2)-C(12)	1.434(2)	C(3)-N(2)-C(12)	128.73(14)
C(12)-C(17)	1.377(2)	C(17)-C(12)-C(13)	119.38(15)
C(12)-C(13)	1.378(2)	C(17)-C(12)-N(2)	120.52(14)
C(5)-C(4)	1.387(2)	C(13)-C(12)-N(2)	120.10(14)
C(5)-C(4)	1.447(2)	N(1)-C(5)-C(4)	110.10(14)
C(5)-C(6)	1.383(2)	N(1)-C(5)-C(6)	120.18(14)

C(6)-C(7)	1.367(7)	C(4)-C(5)-C(6)	129.71(15)
C(6)-C(11)	1.384(2)	C(7)-C(6)-C(11)	118.00(16)
C(17)-C(16)	1.378(2)	C(7)-C(6)-C(5)	121.72(16)
C(7)-C(8)	1.374(3)	C(11)-C(6)-C(5)	120.29(14)
C(11)-C(10)	1.378(2)	C(12)-C(17)-C(16)	119.62(16)
C(3)-C(4)	1.346(2)	C(8)-C(7)-C(6)	120.58(18)
C(13)-C(14)	1.365(2)	C(10)-C(11)-C(6)	120.64(16)
C(16)-C(15)	1.369(9)	C(4)-C(3)-N(2)	106.85(15)
C(14)-C(15)	1.368(2)	C(14)-C(13)-C(12)	120.16(17)
C(10)-C(9)	1.366(3)	C(15)-C(16)-C(17)	120.86(17)
C(9)-C(8)	1.362(3)	C(13)-C(14)-C(15)	120.92(18)

Table 4.Torsion angles [°] for 2a

C(5)-N(1)-N(2)-C(3)	0.06(17)
C(5)-N(1)-N(2)-C(12)	179.66(13)
N(2)-N(1)-C(5)-C(4)	-0.32(17)
N(2)-N(1)-C(5)-C(6)	-179.05(14)
N(1)-N(2)-C(3)-C(4)	0.23(18)
C(12)-N(2)-C(3)-C(4))	-179.33(15)
N(1)-N(2)-C(12)-C(13)	171.17(14)
N(1)-N(2)-C(12)-C(17)	-8.7(2)
C(3)-N(2)-C(12)-C(17)	170.84(16)
N(2)-C(3)-C(4)-C(5)	-0.42(19)
C(3)-C(4)-C(5)-N(1)	0.47(19)
N(1)-C(5)-C(6)-C(7)	-168.66(15)
N(1)-C(5)-C(6)-C(11)	11.6(2)
C(4)-C(5)-C(6)-C(7)	12.9(3)
C(4)-C(5)-C(6)-C(11)	-166.83(18)
C(5)-C(6)-C(7)-C(8)	-178.56(16)
C(11)-C(6)-C(7)-C(8)	1.2(3)
C(5)-C(6)-C(11)-C(10)	179.355(16)
C(7)-C(6)-C(11)-C(10)	-0.4(3)

RESULTS AND DISCUSSION

The binding interaction between macromolecule (3FDN) and ligand (**2a**) was done using AutoDock. Lamarckian genetic algorithm was used to study the docking calculation generated few poses for ligand molecules with the protein target. Polar hydrogen bond network was optimized and the systematic kollaman charges were added by means of a cluster-based approach. The compound1,3-diphenyl-1*H*-pyrazole found to have minimum binding energy of-6.31 kJmol^{-1} with Aurora Atarget (PDB Code: 3FDN) with ligand efficiency of -0.37. The molecule (2a) was completely wrapped by active site amino acid

residues at the active site pocket region as shown in Figure 3 and 4. In human protein kinase target more residues are closer to the ligand (2a) and arehydrophobic in nature.

In the molecular structure of the title compound (Fig. 1), pyrazole moiety (N1/N2/C3-C5) is almost same plane with the phenyl rings (C6-C11/C12-C17) as indicated by the dihedral angle values of 12.04(9)º and 8.91(9)º, respectively. Also, the dihedral angle between the two phenyl rings is 6.75(9) º. The pyrazole unit is present in anti-periplanar (N1/N2/C12/C13) and syn-periplanar (N1/C5/C6/C11) conformation with respect to the benzene rings, as indicated by the torsion angle values of 170.84(16)º and 11.6(2)º, respectively. There are no classical hydrogen bonds. The crystal structure is stabilized by an C11-H11...N1 and C17-H17...N1 intramolecular hydrogen bonds. The packing diagram of the molecule as shown in figure2.

APPLICATIONS

In view of the therapeutical and pharmaceutical importance of the pyrazole derivatives, studied the detailed structure and molecular modeling of pyrazole derivative (2a) as potential Aurora A inhibitor(3FDN) to improve the therapeutic potency and to reduce the classical side effects.

ACKNOWLEDGEMENTS

The authors would like to thank the SJB Institute of Technology, Bengaluru and National Institute of Engineering, Mysuru, for their support.

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AUTHOR ADDRESS

1. **B. H. Doreswamy**
Department of Physics,
SJB Institute of Technology,
Kengeri, Bangalore 560 060, India
Email: dorephy@gmail.com