Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2018, 7 (3): 496-500

(International Peer Reviewed Journal)

Structural Characterization and Docking Studies of (Z)-N-Phenyl Benzo Hydrazonoyl Chloride Derivative as Promising Antimicrobial *Acinetobacter Baumannii* Penicillin-Binding Protein Target

G. V. Ashok Reddy[1], C. S. Dileep[2], Shamantha Kumar[3], B. Vrushabendra[4], Chandra[5], N. Srikantamurthy[4] and B. H. Doreswamy[3*]

1. Department of Physics, Nitte Meenakshi Institute of Technology, Yelahanka, Bangalore 560 064, **INDIA**
2. Department of Physics, Vidyavardhaka College of Engineering, Gokulum, Mysore 570 002, **INDIA**
3. Department of Physics, SJB Institute of Technology, Kengeri, Bangalore 560 060, **INDIA**
4. Department of Chemistry, Vidyavardhaka College of Engineering, Gokulum, Mysore 570 002, **INDIA**
5. Department of Physics, The National Institute of Engineering (NIE), Mysore 570 008, **INDIA**

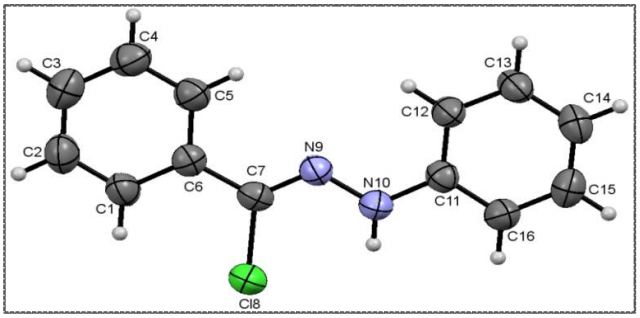
Email: dorephy@gmail.com

Accepted on 16th April, 2018

ABSTRACT

*Computer-aided prediction of interaction of benzohydrazonoyl chloride derivatives with protein target was carried out using open source program Auto Dock. Overall findings of the executed investigations highlight these compounds as very promising potent, broad spectrum antiviral agents. Molecular docking studies showed that the tested compound induced good fitting and forming different hydrogen bonds with the amino acid residues at the active sites of antimicrobial acinetobacter baumannii penicillin-binding target. A moderately high-yield synthesized compound (Z)-N-phenyl benzohydrazonoyl chloride (**4a**) was characterized and structure was confirmed by X-ray diffraction studies. The molecule crystallizes in orthorhombic under the space group Pcab, with cell parameters a = 7.606(1)Å, b = 11.8817(16)Å, c = 25.219(3)Å and Z=8. Crystal structure stabilized by an N10-H10...Cl8 and C1-H1...Cl8 intramolecular hydrogen bonds.*

Graphical Abstract



ORTEP of the molecule (4a) with thermal ellipsoids drawn at 50% probability

Keywords: Crystal structure, Docking study, Antimicrobial target, C-H..Cl and N-H..Cl interaction.

INTRODUCTION

Hydrazonoyl chloride also called α-chlorobenzaldehyde phenylhydrazone ($C_{13}H_{11}N_2Cl$) has developed as an imperative class of organic building block and it was first developed by Fisher in 19th century. It is considered as an important starting material to build five membered hetero molecules via nitrile imine which is the intermediate used in the 1, 3-dipolar cycloaddition reactions [**1-4**]. Due to these versatile applications hydrazonoyl chloride fascinated by much science and technological fields which are functioning towards generation of many useful materials to meet the demand of many societal problems. Two well-known convenient methods to obtain hydrazonoyl chloride are; chlorination of benzaldehyde phenylhydrazone and treating phosphorus pentachloride with N'-benzoyl-N-phenylhydrazine. Apart from these two methods, we have another simplest method to obtain hydrazonoyl chloride by treating N'-benzoyl-N-phenylhydrazine with triphenylphosphine followed by carbon tetrachloride in acetonitrile medium [**5**].

Ever since their finding, hydrazonoyl chloride engrossed many chemists due to its wide variety of applications in the synthetic chemistry of Nitrogen containing molecules [**6**]. Hence, hydrazonoyl chloride is widely considered as an important intermediate for the synthesis of biologically active hetero cycles in the history of heterocyclic chemistry [**7**]. In addition, these intermediates have provided very unique and interesting potent moieties which are widely applicable in many fields including pharmaceutical and industrial fields like in the synthesis of bis-pyrroles, pyrazoles, isoxazolines, fused cyclohepta pyrimidines, hydrazides, triazoles, thiazoles and thiadiazoles. Comprehensive literature survey provided the importance of hydrazonoyl chloride as intermediate to prepare nitrogenous compounds with biological efficacy such as antimicrobial, antitumor, anticancer and anti-HCV activities [**8-14**].

The present scenario in synthetic chemistry has been focused on designing new molecules by the lead hybridization-based synthesis of different pharmacophore fragments in a single molecule with improved biological efficacy. To validate and specify the target protein for the antimicrobial activity of synthesized acinetobacter baumannii penicillin-binding protein was selected and downloaded from the Protein Data Bank.

MATERIALS AND METHODS

Docking studies and Crystal structure determination: Molecular docking of obtained compound (4a) was performed using the open source software AutoDock. Protein target selected from the collection of experimentally determined 3D-structures of biological macromolecules database PDB. The docking poses in AutoDock are ranked according to their docking scores and the lowest binding energy of macromolecule ligand complex has been considered to be the best. Finally, both the ranked list of docked ligand and their corresponding binding poses were analyzed. The docking study with acinetobacter baumannii penicillin binding protein target using AutoDock 4.2 which proved H-bond interaction and strong binding affinity.

Table 1. The dock score results of the ligand (4a) with antimicrobial target (3UDI)

Compound	Binding Energy(kJ mol^{-1})	Ligand Efficiency	Inhibition Constant	vdW+H-bond+desolv energy	No. of H-bonds	Bonding residues	Bond Length (Å)
4a	-6.2	-0.39	28.54	-7.37	1	3UDI:A:ILE661:HN	2.196

The compound (Z)-N-phenyl benzo hydrazonoyl chloride derivative was characterized and structure was confirmed by single crystal X-ray diffraction studies. X-ray intensity data were collected on a Bruker Proteum2 CCD diffractometer using CuK α radiation. Raw data was processed and reduced by using APEX2 and SAINT [**10**]. The structure was solved by direct methods and refined by full-matrix least squares method on F^2 using SHELXS and SHELXL programs,

respectively [**11-18**]. The X-ray structure of (Z)-N-phenyl benzo hydrazonoyl chloride derivative was used for the docking studies. A summary of docking results and crystallographic data for molecule (**4a**) are given in table 1and table 2a and 2b, respectively.

Table 2a. Crystal data and structure refinement for **4a**

Empirical formula	$C_{13}H_{11}ClN_2$
Formula weight	230.69
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	orthorhombic, *Pcab*
Unit cell dimensions	a = 7.606(1) Å, b = 11.8817(16) Å c = 25.219(3) Å
Volume	2279.1(5) $Å^3$
Z, Calculated density	8, 1.345 Mg m^{3-1}
F_{000}	960
Crystal size	0.22 x 0.20 x 0.18 mm
Theta range for data collection	3.28 to 27.48°.
Limiting indices	-7≤ h≤ 7, -11≤ k≤ 12, -30≤ l≤ 30
Reflections collected / unique	2570 / 1937 [R(int) = 0.0192]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1937 / 0 /145
Goodness-of-fit on F^2	1.068
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.1150
R indices (all data)	R1 = 0.0619, wR2 = 0.1285
Largest diff. peak and hole	0.196 and -0.41 e.$Å^{-3}$

Table 2b. Bond lengths [Å], angles [°] and Torsion angles [^{0}] for 4a.

Bond lengths [Å] and angles [°]				Torsion angles [^{0}]	
Atoms	**Length**	**Atoms**	**Length**	**Atoms**	**Length**
Cl8-C7	1.7639(17)	C2-C1-C6	120.63(19)	C7- N9-N10-C11	-170.21(15)
N9-N10	1.349(2)	C1-C2-C3	120.8(2)	N10-N9-C7-Cl8	-0.2(2)
N9-C7	1.267(2)	C2-C3-C4	119.24(19)	N10-N9-C7-C6	179.47(15)
N10-C11	1.402(2)	C3-C4-C5	120.6(2)	N9-N10-C11-C12	-6.3(2)
C1-C2	1.381(3)	C4-C5-C6	120.51(19)	N9-N10-C11-C16	174.41(16)
C1-C6	1.391(3)	C1-C6-C5	118.16(17)	C6-C1-C2-C3	1.4(3)
C2-C3	1.370(3)	Cl-C6-C7	122.59(16)	C2-C1-C6-C5	0.1(3)
C3-C4	1.380(3)	C5-C6-C7	119.23(16)	C2-C1-C6-C7	178.14(18)
C4-C5	1.381(3)	Cl8-C7-N9	120.30(14)	C1-C2-C3-C4	-1.4(3)
C5-C6	1.394(3)	Cl8-C7-C6	117.09(12)	C2-C3-C4-C5	0.1(3)
C6-C7	1.466(2)	N9-C7-C6	122.62(15)	C3-C4-C5-C6	1.4(3)
C11-C16	1.386(3)	C11-C16-C15	119.74(18)	C4-C5-C6-C1	-1.5(3)
C11-C12	1.386(3)	N10-C11-C12	121.68(16)	C4-C5-C6-C7	-179.56(18)
C12-C13	1.385(3)	C12-C11-C16	120.12(16)	C1-C6- C7-Cl8	5.3(2)
C13-C14	1.382(3)	N10-C11-C16	118.20(15)	C1-C6-C7-N9	-174.34(17)
C14-C15	1.378(3)	C11-C12-C13	119.27(17)	C5-C6-C7-Cl8	-176.67(14)
C15-C16	1.383(3)	C12-C13-C14	120.98(19)	C5-C6-C7-N9	3.7(3)
N10-N9-C7	120.98(15)	C13-C14-C15	119.17(18)	N10-C11-C12-C13	-179.87(18)
N9-N10-C11	119.57(14)	--	--	C16-C11-C12-C13	-0.6(3)
--	--	--	--	N10-C11-C16-C15	-180.00(19)
--	--	--	--	C12-C11-C16-C15	0.7(3)
--	--	--	--	C11-C12-C13-C14	0.1(3)
--	--	--	--	C12-C13-C14-C15	0.4(3)

RESULTS AND DISCUSSION

The molecular docking was performed and analyzed using AutoDock 4.2. A Lamarckian genetic algorithm method implemented in the program suite was employed to identify appropriate binding modes and conformation of the ligand molecules. The compound(Z)-N-phenyl benzo hydrazonoyl

chloride found to have minimum binding energy of-6.2 kJ mol^{-1} with antimicrobial acinetobacter baumannii penicillin-binding target (PDB Code: 3UDI) with ligand efficiency of -0.39 (as shown in figure 3). Also, compound (Z)-N-phenyl benzo hydrazonoyl chloride was found to show hydrogen bond interaction with active site amino acid residues ILE661 at a distance of 2.196 Å **(**as shown in figure 4**)**.

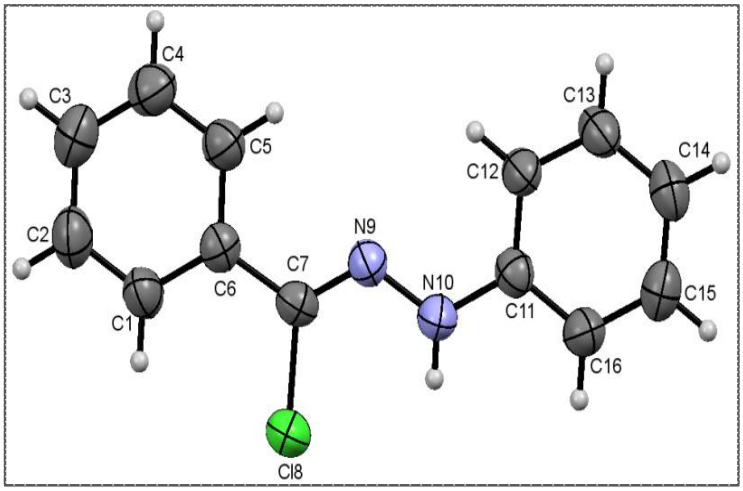


Figure 1. ORTEP of the molecule (4a) with thermal ellipsoids drawn at 50% probability

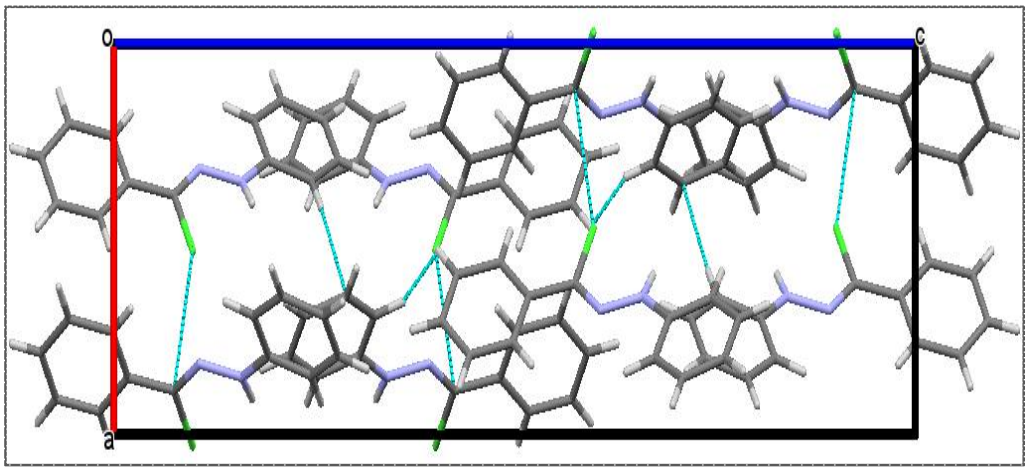


Figure 2. Packing diagram of the molecule (4a)

In the molecular structure of the title compound (Fig. 1), two thinly rings (C1-C6/C11-C16) is almost co-planar as indicated by the dihedral angle value of $13.15(10)^0$. The hydrazone moiety is anti-periplanar conformation (C11-N10-N9-C7) with respect to the phenyl ring (C11-C12-C13-C14-C15-C16), as indicated by the torsion angle values of $170.21(15)^0$. Also, benzene ring is present in syn-periplanar (C5/C6/C7/Cl8) conformation with respect to the chloride moiety, as indicated by the torsion angle value of $5.3(2)^0$. The crystal structure is stabilized by an N10-H10...Cl8 and C1-H1...Cl8 intramolecular hydrogen bonds, the packing diagram of the molecule as shown in figure 2.

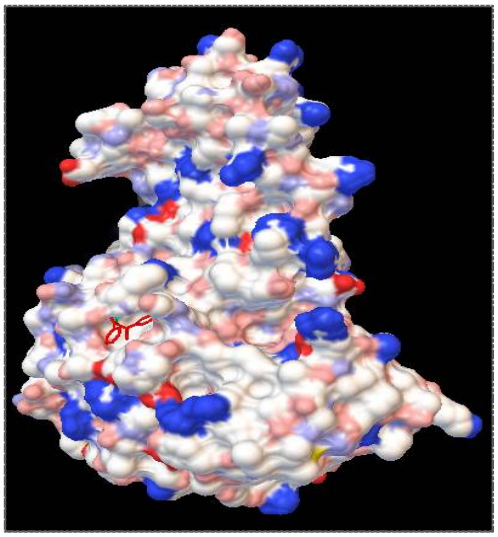


Figure 3. Docking of molecule (4a) in the active site (4a) pocket of Aurora A

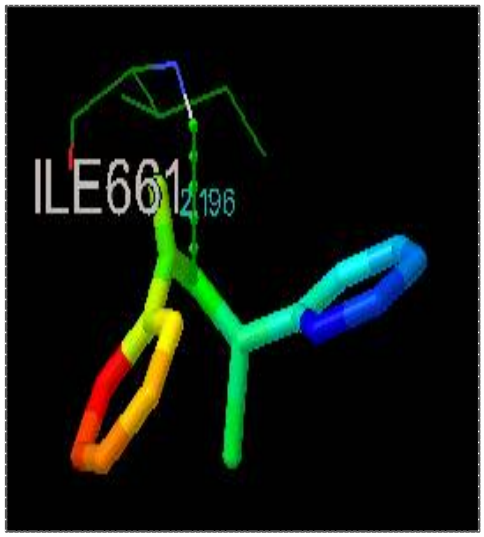


Figure 4. Hydrogen bond interaction of molecule in the active site pocket of 3FDN

ACKNOWLEDGMENTS

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

REFERENCES

[1]. A. S Shawali, C. J Parkanyi, *Heterocycl. Chem*., **1980**, 17, 833-854.
[2]. V. P. Himatkumar, A. V. Kavita, P. P. Sudhanshu, S. F. Peter, *Tetrahedron*, **1996**, 52, 661-668.
[3]. P. Caramella, P. Grunanger, In 1,3-Dipolar Cycloaddition Chemistry, Padwa, A., Ed.; Interscience: London, **1984**, vol. 1, p. 291;
[4]. R. Huisgen, R. Grashey, J. Sauer, In Chemistry of Alkenes; Patai, S., Ed.; Interscience: London, **1964**, p.806.
[5]. Peder Wolkoff, A New Method of Preparing Hydrazonyl Halides, *Can. J. Chem.*, **1975**, 53, 1333-1335.
[6]. A. S. Shawali, M. M. Edrees, Arkivoc, **2006**, 9, 292-365.
[7]. A. S. Shawali, M. A. Abdallah, *Adv Heterocycl. Chem*,. **2001**, 80, 277-338.
[8]. A. K. Nabila, *Molecules*, 2016, 21, 1-9.
[9]. Y. H Zaki, A. R. Sayed, S. A. Elroby, *Chemistry Central Journal*, **2016**, 10, 1-13.
[10]. A. Thoraya, M. A. Farghaly, A. Zeinab Muhammad, *Current Organic Synthesis*, **2016**, 13, 291-299.
[11]. Frantisek Sersen, Fridrich Gregan, Matus Pesko, Dana Dvoranova, Katarina Kraľova,Zuzana Matkovicova Juraj Gregan and Jana Donovalova, Molecules, **2015**, 20, 14139-14154.
[12]. T. A. Farghaly, S. M Gomha, A. R. Sayed, M. A Khedr, *Current Organic Synthesis*, **2016**, 13, 445-455.
[13]. Abdou, O. Abdelhamid, Zeineb H. Ismail, Marwa S. El Gendy and Moustafa M. Ghorab, *Journal of Phosphorus, Sulfur, and Silicon and the Related Elements*, **2007,** 182, 2409-2418.
[14]. Kamal M Dawood, Sobhi M. Gomha, *Journal of Heterocyclic Chemistry*, **2015**, 52, 1400-1405.
[15]. Bruker, APEX2, SAINT. Bruker AXS Inc, Madison, Wisconsin, USA **2009**.
[16]. G. M. Sheldrick, *Acta. Cryst.*, **2008,** A64, 112-122.
[17]. G. M. Sheldrick, *Acta Cryst.*, **2015**, C71, 3-8.
[18]. A. L. Spek, *Acta Cryst.* **2009,** D65, 148-155.