RESEARCH ARTICLE

Crystal structure analysis, Molecular Docking and Interaction Studies of 2,4-diamino-6-nitro-5-(p-tolyl)-7,8,9,10-tetrahydro-5H-pyrimido[1,2-a][1,8]naphthyridine-3-carbonitrile N,N-dimethylformamide monosolvate

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ABSTRACT: The crystal structure of 2,4-diamino-6-nitro-5-(p-tolyl)-7,8,9,10-tetrahydro-5H-pyrimido[1,2-a][1,8]naphthyridine-3-carbonitrile N,N-dimethylformamide monosolvate were studied. The compound crystallizes in Triclinic P-1space group with unit cell parameters at 296(2) K as follows: a = 8.6179(4) Å, b =10.3807(5) Å, c =13.0700(5) Å, α =68.369(2)°, β= 75.273(3)°and γ = 77.969(3)°.Crystal data were collected using BRUKER SMART APEX II CCD X-ray diffractometer. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares procedures to the final R_1 of 0.087using SHELXL programs. The molecular structure is characterized by an intramolecular N-H…O hydrogen bond, which generates an S(6) ring motif. In the crystal, molecules are linked via N-H…O hydrogen bonds, forming infinite bands lying parallel to (110) and composed of alternate $R^2_2(12)$ graph-set ring motifs. These naphthyridine compounds play a significant role in binding with the Influenza virus enzyme.

KEYWORDS: Pyrimidine, Naphthyridine, Carbonitrile, Dimethylformamide and crystal structure.

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1. INTRODUCTION

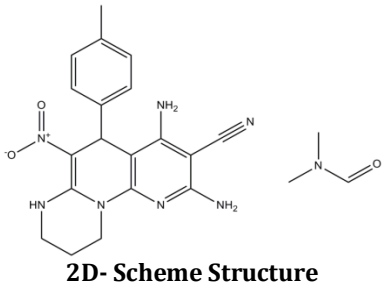
Naphthyridine derivatives play an important role in pharmaceuticals, agrochemicals, dyes, photographic materials and in corrosion inhibition and have many biological applications [1,2,3]. Naphthalene derivatives has been identified as new range of potent antimicrobials effective against wide range of human pathogens and have diverse and interesting antibiotic properties with minimum toxicity [4,5].The crystal structures of this compound is determined using X-ray crystallography were taken as inhibitors against the receptor of Influenza virus enzyme. Basic information of naphthyridine derivative have more biological information to act as drug, Influenza virus receptor selected as a targeted protein for molecular docking studies using the Autodock program.

2. X-RAY STRUCTURE DETERMINATION

Single crystal of the compound suitable for x-ray diffraction was obtained by slow evaporation method. Three dimensional intensity data were collected on a Bruker [6] SMART APEX CCD Diffractometer using graphite monochromatized Mo-Kα radiation (λ= 0.71073 Å) at Department of chemistry, IIT, Chennai, India. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares procedures using the SHELXL programs [7]. All the non-hydrogen atoms were refined using isotropic and later anisotropic thermal parameters. The hydrogen atoms were included in the structure factor calculation at idealized positions by using a riding model, but not refined. Images were created with ORTEP-3 [8].The crystallographic data for the compound are listed in Table 1.

3. SYNTHESIS OF THE COMPOUND

A dried 10 ml round bottom flask was charged with nitroketene-S,S-acetal (1.0 mmol), 1, 3-diaminopropane (1.0mmol), 4-methylbezaldehyde (1.2mmol), 2-aminoprop-1-ene-1, 1,3-tricarbonitrile (1.0mmol) and piperdine (0.25mmol) was added to the reaction mixture in EtOH under reflux condition for 2 hour. After completion of the reaction monitored by TLC, the reaction mixture was filtered to afford the crude product, which was further washed with 2 ml of EtOH to give pure product. Further the pure product was recrystallized from DMSO-d_6.Colorless block-like crystals of the title compounds, suitable for X-ray diffraction analysis, were obtained by slow evaporation of solutions in ethanol.



2D- Scheme Structure

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4. DOCKING PROCEDURE

Docking calculations were carried out using AutoDock tools, Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Docking calculations were carried out on influenza virus protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools [9].

Affinity (grid) maps of 60×60×60 Å grid points and 0.375 Å spacing were generated using the Autogrid program [9]. AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively.

Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method [10]. Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

The protein structures were downloaded from protein data bank (PDB) and the ligand structures drawn cannot be used as such for docking. Hence the protein and ligand(s) preparation must precede the use of the protocol.

5. RESULTS AND DISCUSSION

The symmetric unit of the title compound is shown in Fig. 1. The 4H-pyrido [1,2-a]pyrimidine ring has a flat-boat conformation, making dihedral angle of 15.8(2)°. The Pyridine ring mean plane of the methyl phenyl moiety, with a dihedral angle of 80.4(1)°. The dimethylformamide groups assume a twisted conformation, as can be seen from the torsion angle C21-N8-C22-O3 = -9.1° (-) Syn-Periplanar conformation for this group. Atoms N2 and O4 deviated from the respective two phenyl rings by -0.016(4) Å and 0.008(4) Å, respectively.

The molecular structure is characterized by an intramolecular N-H…O hydrogen bond, which generates an S(6) ring motif. In the crystal, molecules are linked via N-H…O hydrogen bonds, forming infinite bands lying parallel to (110) and composed of alternate $R^2_2(12)$ graph-set ring motifs. The crystal structure is further stabilized by C-H…π interactions, forming chains a three-dimensional structure. The chains are linked by slipped parallel π …π interactions, involving inversion related methylphenyl and pyridine, forming slabs parallel to the bc plane Cg4-Cg4^1 = 3.903Å, inter-planar distance = -3.5087(15) Å, slippage = 1.708 Å Cg4 is the centroid of ring (C2-C3-C4-C6-C7-C8). The selected bond lengths and angles are listed in table 3.

The naphthyridines (Scheme 1) consist of those diazanaphthalenes which have one nitrogen atom in each ring neither of which occupies a bridgehead position. The naphthyridines and their derivatives exhibit various types of biological activity, and the organic chemistry has been frequently reviewed [11-13]. The preparation of the ligands can be found in the references to their metal complexes.

Basic information of naphthyridine derivative have more biological information to act as drug, Influenza virus receptor selected as a targeted protein for molecular docking studies using the Autodock program. The docking scores and interaction energies are calculated for each compound (Table 4).

Hydrogen bonding interaction diagram shows that the naphthyridine compound (ST8) (Fig.4) have more number of hydrogen bonding interactions as an evidence from the docking score and it's compared that of the co-crystallized molecule with Influenza virus protein. The docking score and interactions are compared with the co-crystal ligand of influenza virus protein. Molecular docking studies identify this compound (ST8) have good binding capability to the active site amino acids of SER324 at a distances of 3.1 and 3.3Å, HIS357 at a distances of 3.1Å and LYS339 at a distances of 3.3 and 2.8Å to Influenza virus receptor. End of the result, it can be concluded that the size and flexibility of naphthyridine compound play a significant role in binding with the Influenza virus enzyme.

Table 1: Crystal data and structure refinement of the titled compound

Compound	Parameters
Empirical formula	C_{22} H_{26} N_8 O_3
Formula weight	827.92
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 8.6179(4)Å alpha = 68.369(2)° b = 10.3807(5)Å beta = 75.273(3)° c = 13.0700(5)Å gamma = 77.969(3)°
Volume	1042.60(8)Å^3
Z, Calculated density	1, 1.319Mg/m^3
Absorption coefficient	0.092mm^{-1}

F(000)	436
Crystal size	25 x 30 x 20 mm
Theta range for data collection	2.128 to 24.993deg.
Limiting indices	-10<=h<=10, -12<=k<=12, -15<=l<=15
Reflections collected / unique	18880 / 3643 [R(int) = 0.0324]
Completeness to theta = 25.00	100.00%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3643 / 37 / 318
Goodness-of-fit on F^2	1.064
Final R indices [I>2sigma(I)]	**R1 = 0.0877**, wR2 = 0.2609
R indices (all data)	R1 = 0.1126, wR2 = 0.2939
Largest diff. peak and hole	0.927 and -0.502e. $Å^{-3}$

Table 2: Hydrogen-bonds geometry [Å]

Distance (Å)				Angle (º)
D—H...A	**D—H**	**H...A**	**D...A**	**D—H...A**
C8-H8...O1[i]	0.98	2.40	3.165(5)	134
C17-H17A...O1[ii]	0.97	2.57	3.286(7)	130
N2-H2B...N3[iii]	0.906	2.23	3.114(5)	166
N2-H2A...O1[i]	0.901	2.28	3.151(4)	162

Symmetry codes: i) -x+1,-y+1,-z+1; ii) -x+2,-y+1,-z+1; iii) -x,-y+1,-z+2

Table 3: Selected Bond lengths (Å) and Bond angles (º)

Bond	Length (Å)	Bond	Angle (°)
C(1)-C(2)	1.525(7)	C(7)-C(2)-C(3)	118.0(4)
C(2)-C(7)	1.365(8)	C(7)-C(2)-C(1)	122.2(5)
C(2)-C(3)	1.391(7)	C(3)-C(2)-C(1)	119.8(6)
C(3)-C(4)	1.389(6)	C(4)-C(3)-C(2)	120.4(5)
C(4)-C(5)	1.375(5)	C(5)-C(4)-C(3)	121.5(4)
C(5)-C(6)	1.392(6)	C(4)-C(5)-C(6)	117.6(4)
C(5)-C(8)	1.517(5)	C(4)-C(5)-C(8)	121.9(3)
C(6)-C(7)	1.382(7)	C(6)-C(5)-C(8)	120.4(4)
C(8)-C(15)	1.495(5)	C(7)-C(6)-C(5)	120.6(4)
C(8)-C(9)	1.519(5)	C(2)-C(7)-C(6)	121.8(5)
C(9)-C(13)	1.370(5)	C(15)-C(8)-C(5)	113.0(3)
C(9)-C(10)	1.411(5)	C(15)-C(8)-C(9)	108.9(3)
C(10)-N(2)	1.354(5)	C(5)-C(8)-C(9)	111.4(3)
C(10)-C(11)	1.410(5)	C(13)-C(9)-C(10)	117.2(3)
C(11)-C(12)	1.400(5)	C(13)-C(9)-C(8)	120.5(3)
C(11)-C(19)	1.418(5)	C(10)-C(9)-C(8)	122.2(3)
C(12)-N(5)	1.331(5)	N(2)-C(10)-C(11)	120.7(3)
C(12)-N(4)	1.356(5)	N(2)-C(10)-C(9)	122.1(3)
C(13)-N(5)	1.337(5)	C(11)-C(10)-C(9)	117.1(3)
C(13)-N(6)	1.408(5)	C(12)-C(11)-C(10)	119.7(3)
C(14)-N(7)	1.325(5)	C(12)-C(11)-C(19)	119.0(3)

Table 4 Docking score and hydrogen bond interaction of Thiophene compound ligand (ST8) with the receptor molecules

Compound	Score	Hydrogen Bond Interaction	Distance (Å)
ST8	-7.4	LYS339 N...N-O N...N-O HIS357 N...H-O SER324 O-H...O O-H...O	 3.3 2.8 3.1 3.1 3.3
COCRY	-5.8	ASN444 O-H...N O-H...O LYS412 O-H...O GLU407 O-H...O ASP408 N-H...O N...H-O	 3.5 3.3 3.1 2.8 3.3 3.2

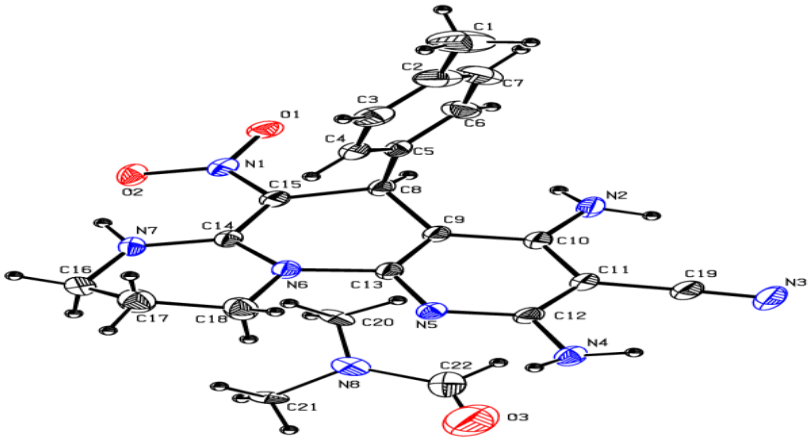

Fig.1.The molecular structure of the title compound, with the atom-numbering scheme. The displacement ellipsoids are drawn at 30% probability level. H atoms are shown as spheres of arbitrary radius.

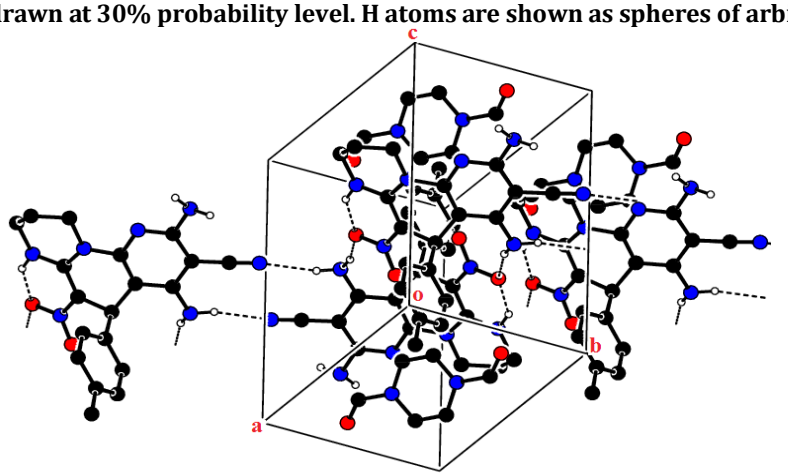

Fig.2. The crystal packing of the title compound, viewed along the *c*-axis, showing N-H...N hydrogen bonds resulting in the formation of $R^2_2(12)$ chains running parallel to the *b* axis

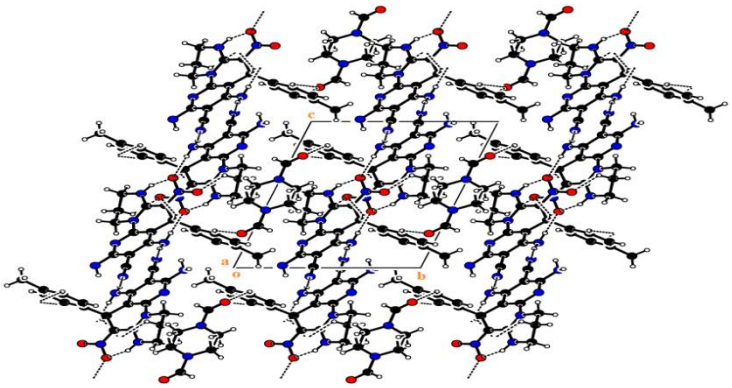

Fig. 3 A partial viewed along the *c* axis of the crystal packing of the title compound. Hydrogen bonds are shown as dashed lines (see Table 2 for details; H atoms not involved in hydrogen bonding have been omitted for clarity).

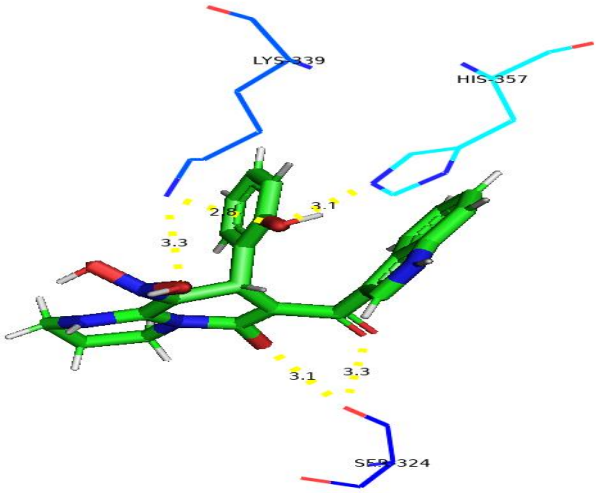

Fig. 4: The hydrogen bond interaction of the titled compound with the receptor molecule.

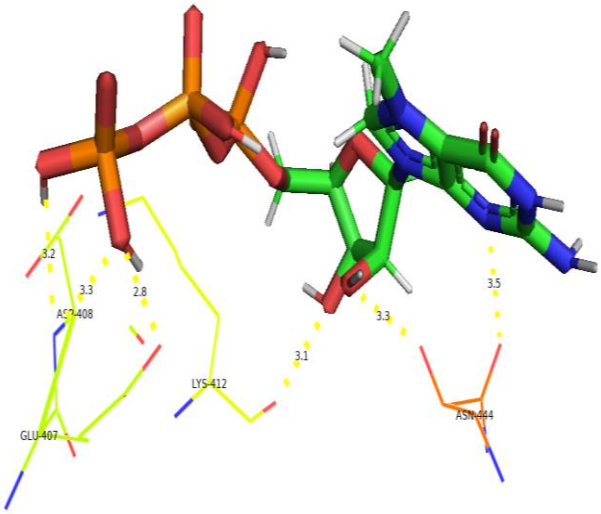

Fig. 5: The hydrogen bond interaction of the Co-crystal ligand with the receptor.

6. CONCLUSION

The crystal structure analysis of a novel naphthyridinecompound was studied using x-ray diffraction method. In the crystal, molecules are linked via C-H...O, N-H…N and N-H…O hydrogen bonds, formschains.The crystal packing is further stabilized by C---H...$\pi$and π---π intermolecular interactions.End of the result, it can be concluded that the size and flexibility of naphthyridine compound play a significant role in binding (ST8) with the Influenza virus enzyme.

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