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X-ray crystal structure of N-benzyl-2-(4,6-diaminopyrimidin-2-ylthio)-acetamide

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Abstract: N-benzyl-2-(4,6-diaminopyrimidin-2-ylthio)-acetamide, was synthesized by the reaction of 4,6-diamino-pyrimidine-2-thiol with 2-chloro-N-benzyl acetamide in the presence of potassium hydroxide under reflux conditions and crystallized. X-ray diffraction intensity data were collected at room temperature (293k) on a Bruker axs SMART APEXII single crystal X-ray diffractometer equipped with graphite monochromatic Mo *Kα* (λ=0.71073 Å) radiation and CCD detector. The compound crystallizes in the monoclinic $P2_1/n$ space group with four molecules in the unit cell (a=8.5657(5) Å, b=9.3203(5) Å, c=18.2134(10) Å, α=90°, β=91.540(4) °, γ=90° and Z=4). The three dimensional molecular structure of this compound was determined by X-ray crystallography using SHELXS97 and later refined by SHELXL97 to a final R-value 4.3%. In the crystal, the molecular structure is stabilized by intramolecular N—H...S, C—H...N and C—H...O hydrogen bonds and the packing is stabilized by intermolecular N—H...N and N—H...O hydrogen bonds.

Keywords: Acetamide; crystal structure; 4,6-diamino pyrimidine; hydrogen bond; molecular dynamics

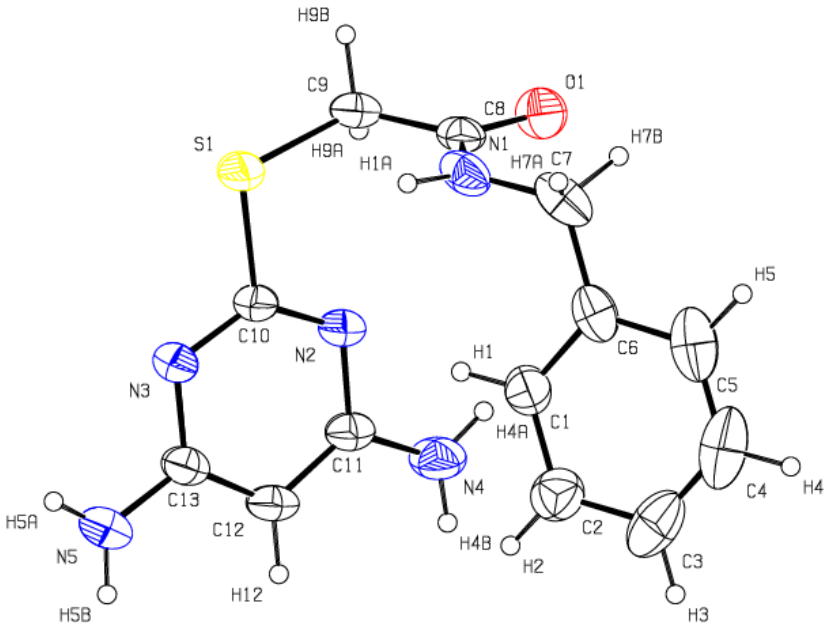

Figure 1. ORTEP diagram of N-benzy-2-(4,6-diaminopyrimidin-2-ylthio)-acetamide drawn at 30% probability.

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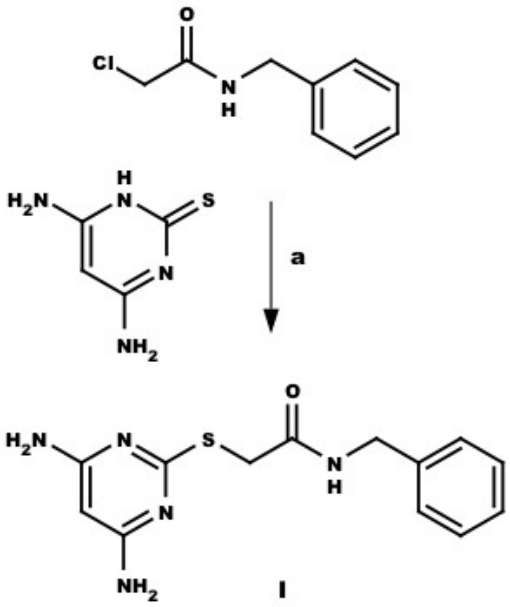
1. Introduction

Diaminopyrimidines are an important class of six membered heterocyclics with many applications. Some derivatives of diaminopyrimidines are reported to have anticancer activity, selectively inhibiting c-Fms kinase of M-CSF-dependent myeloid leukemia cells;[1] other pyrimidine derivatives are immunosuppressants,[2] H4 receptor antagonists,[3] hair growth stimulators,[4] antibacterials,[5] potential antimicrobial agents,[6] potential anti-AIDS agents,[7] antiviral[8] and anti dermatic agents.[9] In addition to these activities, 2,4-diamino-5-cyano-6-[2-(phosphonomethoxy)ethoxy]pyrimidine derivatives have anti-retro viral activity;[10] and 2,4-diamino pyrimidines have *in vivo* anti-trypanosoma brucei activity.[11] 2,4-diamino-6-(thioarylmethyl)pyrido[2,3-d]pyrimidine derivatives,[12] 2,4-diamino-5-(2'-arylpropagyl)pyrimidine derivatives,[13] 2,4-diamino-5-substituted-furo[2,3-d]pyrimidine and 2-amino-4-oxo-6-substituted-pyrrolo[2,3-d]pyrimidines[14] have DHFR inhibition activity. In search for antiviral agents against DENV, N-benzyl-2-(4,6-diaminopyrimidin-2-ylthio)acetamide has been designed and synthesized for targeting NS2B-NS3 protease. The compound has been crystallized and X-ray crystallographic data has been submitted to CDCC (CCDC 999396). **Figure 1** shows the Oak Ridge Thermal Ellipsoidal Plot (ORTEP)[15] of N-benzyl-2-(4,6-diaminopyrimidin-2-ylthio)acetamide.

2. Results and Discussion

As a part of a program of ongoing research in search for small molecule heterocyclics as inhibitors against DENV-protease, a diaminopyrimidine has been synthesized and subjected to X-ray crystallographic study. 2-(4,6-diaminopyrimidin-2-ylthio)-N-benzylacetamide was synthesized according to the reaction outlined in **Scheme 1**. The reaction involves a nucleophillic substitution bimolecular (SN^2) reaction mechanism. The biproduct hydrochloric acid is soluble in water, which is removed by filtration.



Scheme 1. Reagents and conditions: (a) KOH, EtOH, reflux, 2h

X-ray diffraction intensity data were collected at room temperature (293k) on a Bruker axs SMART APEXII single crystal X-ray diffractometer equipped with graphite monochromated Mo *Kα* (λ=0.71073 Å) radiation and CCD detector. A crystal of dimensions 0.30 x 0.25 x 0.20 mm^3 was mounted on a glass fiber using cyanoacrylate adhesive. The unit cell parameters were determined from 36 frames measured (0.5° phi-scan) from three different crystallographic zones using the method of difference vectors. The intensity data were collected with an average four-fold redundancy per reflection and optimum resolution (0.75 Å). The intensity data collection, frames integration, Lorentz and polarization corrections and decay correction were carried out using *SAINT-NT* (version 7.06a) software.[16] An empirical absorption correction (multi-scan) was performed using the *SADABS* program.[16] The compound crystallizes in the monoclinic $P2_1/n$ space group with four molecules in the unit cell.

The crystal structure was solved by direct methods using *SHELXS-97* and refined by full-matrix least-squares using *SHELXL-97.*[17] The molecular geometry was calculated using PARST.[18] The hydrogen atoms were placed in calculated positions with C—H = 0.93 Å to 0.96 Å, refined in the riding model with fixed isotropic displacement parameters: U_{iso} (H) = $1.5U_{eq}$(C) for methyl group and U_{iso} (H) = $1.2U_{eq}$(C) for other groups. The dihedral angle between the phenyl ring and the pyrimidine ring is 48.09(1)°. Molecular dynamics simulation studies [see Supporting information] carried out for 15ns reveals the variation of this angle in the range 0-54°. The amine group N4 and N5 attached with the pyrimidine ring deviate by −0.0230 (2)Å and 0.0120 (2)Å, respectively. Both pyrimidine ring and phenyl ring are essentially planar with a maximum deviation of 0.0069 (2) Å and 0.0010 (2) Å, respectively. The molecule adopts an extended conformation, which is evident from torsion angle (C7—N1—C8—C9=179.1 (1) °) (additional information is provided in Supporting information).

The crystal packing is shown in **Figure 2**. In the crystal, the molecular structure is stabilized by intramolecular N—H...S, C—H...N and C—H...O hydrogen bonds and the packing is stabilized by intermolecular N—H...N and N—H…O hydrogen bonds (**Figure 3**.). N5—H5A...N3 hydrogen bonds stabilize the crystal packing forming $R_2^2(8)$ dimers. The molecular graphics diagram (**Figure 3**.) ORTEP-3 was drawn using PLATON.[15, 19]

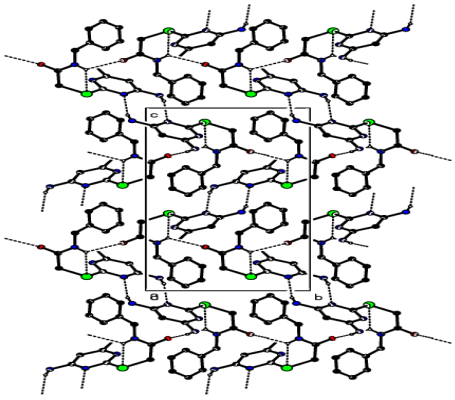


Figure 2. Crystal packing diagram

Crystallographic data are listed in **Table 1**, selected bond lengths, bond angles and hydrogen bond data are listed in **Tables 2**, **3** and **4** respectively.

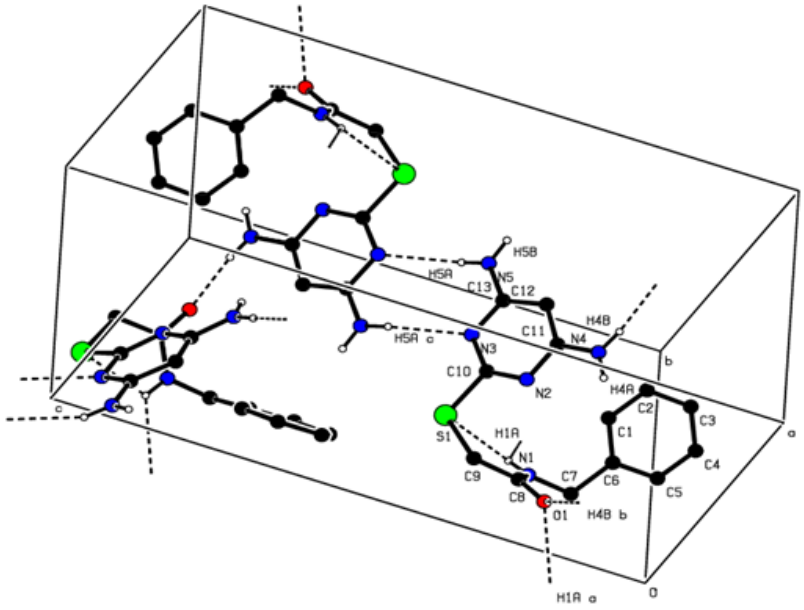


Figure 3. Inter and intramolecular hydrogen bonds

Table 1. Crystal data and structure refinement

Parameters	Compound I
Empirical formula	C_{13} H_{15} N_5 O S
Formula weight	289.36
Temperature (K)	293(2)
Wavelength(Å)	0.71073
Crystal system	Monoclinic
Spacegroup	P 21/n
Unit cell dimensions	a=8.5657(5)Å, b=9.3203(5)Å, c = 18.2134(10)Å and β = 91.540(4)°.
Volume (A^3)	1453.54 (14)
Z, Calculated density	4,1.322 Mg/m^3
F(000)	608
Crystal size	0.30 x 0.25 x 0.20 mm^3
Theta range for data collection	2.24 to 28.36°
Limiting indices	-11<=h<=11, -12<=k<=12, -22<=l<=24
Reflections collected / unique	13701 / 3597 [R(int) = 0.0203]
Completeness to theta	98.8 %
Max. and min. transmission	0.9562 and 0.9353
Refinement method	Full-matrixleast-squares on F^2
Data / restraints / parameters	3597 / 0 / 181
Goodness-of-fit on F^2	1.008
Final R indices [I>2σ(I)]	R1 = 0.0426, wR2 = 0.1134
R indices (all data)	R1 = 0.0603, wR2 = 0.1282
Largest difference peak and hole	0.206e $Å^{-3}$ and -0.233e $Å^{-3}$

Table 2. Selected Bond lengths [Å]

Bond	Bond length[Å]
C(1)- C(6)	1.371(2)
C(1)- C(2)	1.378(3)
C(2)- C(3)	1.371(3)
C(3)- C(4)	1.358(4)
C(4)- C(5)	1.364(4)
C(5)- C(6)	1.377(3)
C(6)- C(7)	1.507(3)
C(7)- N(1)	1.440(3)
C(8)- O(1)	1.226(2)
C(8)- N(1)	1.325(2)
C(8)- C(9)	1.503(3)
C(9)- S(1)	1.798(2)
C(10)- N(2)	1.315(2)
C(10)- N(3)	1.327(2)
C(10)- S(1)	1.769(2)
C(11)- N(4)	1.344(2)
C(11)- N(2)	1.358(2)
C(11)- C(12)	1.388(2)
C(12)- C(13)	1.384(2)
C(13)- N(5)	1.349(2)
C(13)- N(3)	1.356(2)

Table 3. Selected Bond angles [°]

Bond	Bond angle [°]
C(6)- C(1)- C(2)	121.2(2)
C(3)- C(2)- C(1)	120.3(2)
C(4)- C(3)- C(2)	118.8(3)
C(3)- C(4)- C(5)	120.8(2)
C(4)- C(5)- C(6)	121.6(3)
C(1)- C(6)- C(5)	117.2(2)
C(1)- C(6)- C(7)	122.9(2)
C(5)- C(6)- C(7)	119.7(2)
N(1)- C(7)- C(6)	114.6(2)
O(1)- C(8)- N(1)	121.5(2)
O(1)- C(8)- C(9)	118.8(2)
N(1)- C(8)- C(9)	119.4(1)
C(8)- C(9)- S(1)	118.0(1)
N(2)- C(10)- N(3)	130.1(1)
N(2)- C(10)- S(1)	118.1(1)
N(3)- C(10)- S(1)	111.6(1)
N(4)- C(11)- N(2)	115.3(1)
N(4)-C(11)-C(12)	123.3(1)
N(2)-C(11)-C(12)	121.3(2)
C(11)-C(12)-C(13)	117.9(1)
N(5)- C(13)- N(3)	115.1(2)
N(5)-C(13)-C(12)	123.2(1)
N(3)-C(13)-C(12)	121.6(1)
C(8)- N(1)- C(7)	122.1(1)
C(10)-N(2)-C(11)	114.6(1)
C(10)-N(3)-C(13)	114.3(1)
C(10)-S(1)-C(9)	101.4(8)

Table 4. Hydrogen Bonds

D—H...A	D —H (Å)	H...A (Å)	D...A (Å)	D—H...A [°]
N1—H1A...S1^{i}	0.86	2.63	3.064(2)	112
N1—H1A...O1^{ii}	0.86	2.59	3.173(2)	126
N4—H4B...O1^{iii}	0.86	1.96	2.816(2)	172
N5—H5A...N3^{iv}	0.86	2.34	3.145(2)	156
C1—H1...N1^{i}	0.93	2.53	2.870(2)	102
C7—H7B...O1^{i}	0.97	2.39	2.740(2)	100

Symmetry codes: i= x, y, z; ii= ½-x, ½+y, ½-z; iii= -½-x, ½+y, ½-z;iv= -x, 2-y, -z

3. Experimental

Materials and methods: Chemicals and solvents were of reagent grade and purchased from Sigma-Aldrich/Merck/CDH/Rankem. Completion of reactions was monitored on TLC plates (Merck). Intermediates were characterized by their FT-IR spectra (FTIR-8400S-Schimadzu). X-ray diffraction intensity data were collected on Bruker axs SMART APEXII single crystal X-ray diffractometer equipped with graphite monochromated Mo $K\alpha$ (λ=0.71073 Å) radiation and CCD detector.

3.1. Procedure for the synthesis of N-benzyl-2-(4,6-diaminopyrimidin-2-ylthiol)-acetamide

To a solution of 4,6-diamino-pyrimidine-2-thiol (0.5 g; 3.52 mmol) in 25 mL of ethanol in round bottom flask, potassium hydroxide (0.2g; 3.52 mmol) was added and refluxed for half an hour and to it 0.64g (3.52 mmol) of 2-chloro-N-benzyl acetamide was added and refluxed for 2hrs. When the end of reaction was observed by TLC, the precipitate was filtered, washed with cold water and dried to give 2-(4,6-diaminopyrimidin-2-ylthio)-N-benzylacetamide. Yield 92%. Mp 185-187 ^{0}C

3.2. Procedure for crystallization of N-benzyl-2-(4,6-diaminopyrimidin-2-ylthio)-acetamide

A single crystal suitable for X-ray diffraction was obtained by slow evaporation of a solution of the title compound in methanol at room temperature.

4. Conclusion

N-benzyl-2-(4,6-diaminopyrimidin-2-ylthio)-acetamide was synthesized and crystallized. The synthetic procedure and X-ray crystal structure are described. A molecular dynamics study indicates extensive variation in the dihedral angle between the phenyl ring and pyrimidine ring. Consequently the molecule can adopt many possible conformations as a biologically active therapeutics target, can make strong stacking interactions with aromatic residues and also has a great propensity for making intermolecular interactions. As diaminopyrimidines have antiviral activity, the synthesized compounds have been submitted for antiviral screening. The results of this study will be published at a later date.

Supplementary material

Crystallographic data (excluding structure factors) have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 999396 for N-benzyl-2-(4,6-diaminopyrimidin-2-ylthio)-acetamide.

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