Formulation Development and Analysis
http://www.vensel.org/index.php/fda

Synthesis, spectral and crystal studies of 2-(4,6-diamino pyrimidin-2-ylthio)-N-m/p-tolyl/3,4-dimethylacetamides

Ajay Kumar Timiri
Vishnu Nayak Badavath
Barij Nayan Sinha
Venkatesan Jayaprakash

Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra 835215, India.

Selvarasu Subasri
Vijayan Vishwanathan
Devadasan Velmurugan

Centre of Advanced Study in Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai 600025, India

Corresponding author:
Venkatesan Jayaprakash (VJ):
Tel: +91-9470137264;
Email: drvenkatesanj@gmail.com

Submitted on: Mar 31, 2015
Revised on: Jul 16, 2015
Accepted on: Jul 28, 2015
DOI: 10.14805/fda.201511.7-14

Abstract: *Heterocyclic molecules always have a demand in medicinal chemistry research. Pyrimidines are interesting and important scaffold for study of biological importance as many essential biomolecules have pyrimidine structure embedded. Pyrimidines are also reported as inhibitors for biological activities like antibacterial, antifungal, anticancer, antiviral, a few to mention. Here we present the synthesis and X-ray crystal structure of the 2-(4,6-diaminopyrimidin-2-ylthio)-N-phenylacetamide derivatives. 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 IIIa crystallizes in the monoclinic P21/c space group with four molecules in the unit cell (a=22.857 Å, b=7.4305 Å, c=8.3686 Å, α=90°, β=93.454°, γ=90° and Z=4). The compound IIIb crystallizes in the orthorhombic Pbca space group with eight molecules in the unit cell (a=18.2022 Å, b=7.5132 Å, c=20.0233 Å, α=90°, β=90°, γ=90° and Z=8). The compound IIIc crystallizes in the monoclinic P21/c space group with four molecules in the unit cell (a=24.254 Å, b=7.3424 Å, c=8.4257 Å, α=90°, β=93.282°, γ=90° and Z=4).*

Keywords: *Heterocycles; Diaminopyrimidine; Crystal structure; Acetamide; Antiviral*

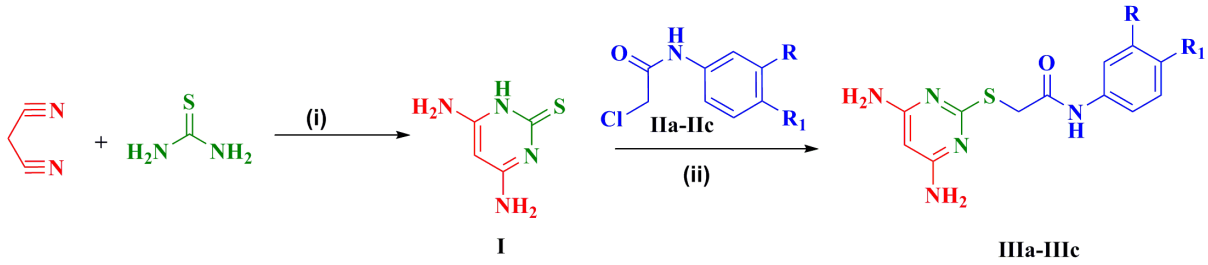
1. Introduction

Heterocyclic chemistry is a vast area with one of the most complex, widely distributed and hugely developing areas of organic chemistry, which covers a high degree of structural diversity and proven to be broadly and economically useful as therapeutic agents (1). It is one of the most valuable sources of novel compounds with diverse biological activity, mainly because of the unique ability of the resulting compounds to mimic the structure of peptides and to bind reversibly to proteins. One of the major chemical scaffolds of such heterocyclic chemistry is pyrimidine moiety. Compounds containing Pyrimidine nucleus are widely distributed in nature (2). Many biological molecules like folic acid (3), vitamin-B1(thiamine) (4), nucleic acid bases (Thymine (5), Uracil (6) & Cytosine (7)) has pyrimidine nucleus. Apart from wide availability in biological system, pyrimidine systems also have wide spectrum of biological activities like antimalarial (8), anti-cancer (9, 10), anti-bacterial (11, 12), anti-fungal (13), antiviral (14-16), anti-tubercular (17, 18), anthelminthic (19), anti-inflammatory (20), central nervous system depressants (21), antihistaminic (22, 23), metabolic electrolyte, antihypertensive agents (24), vasodilatory (25), for various liver disorders (26), antileprotic agent (27), respiratory tract and ear infections (28), urinary tract infections (29, 30) and parkinsonism (31). In search for antiviral agents against DENV, few 2-(4,6-diaminopyrimidin-2-ylthio)-N-m/p-tolyl/3,4-dimethylacetamides have been synthesized for targeting NS2B/NS3 protease. The compounds have been synthesized and X-Ray crystallographic data have been submitted to CCDC (CCDC 1038062, CCDC 1038089 and CCDC 1038090).

2. Results and discussion

2.1. Synthesis and characterization of the compounds

Diaminopyrimidine is an important class of chemical scaffold to constitute variety of biological activities. Compounds **IIIa-IIIc** were synthesized according to the reaction outlined in **Scheme 1**. The reaction involves nucleophillic substitution bimolecular (SN^2) reaction mechanism. Where in, nucleophillic sulfide anion attacks on N-benzyl-2-chloroacetamide and removes the chloride to form the desired compound.



Scheme 1. Reaction conditions: (i) Ethanol, Sodium metal, Reflux, 5h (ii) Ethanol, KOH, Reflux 2-2.5 h

The byproduct hydrochloric acid and the remaining excess potassium hydroxide are soluble in water so they are removed by filtration. Structure of compounds synthesized are presented in Table 1.

Table 1. Compounds synthesized

Compound	R	R_1
IIIa	$-CH_3$	-H
IIIb	-H	$-CH_3$
IIIc	$-CH_3$	$-CH_3$

2.2. X-Ray structure determination

Refer Table 2. for crystal data and refinement.

Table 2. Crystal data and structure refinement of compounds **IIIa-IIIc**

Parameters	IIIa	IIIb	IIIc
Empirical formula	$C_{13}H_{15}N_5OS$	$C_{13}H_{15}N_5OS$	$C_{14}H_{17}N_5OS$
Formula weight	289.36	289.36	303.39
Temperature (K)	293(2)	293(2)	293(2)
Wavelength(Å)	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	P 21/c	P b c a	P 21/c
Unit cell dimensions	a= 22.857(2) Å b=7.430(7) Å c= 8.368(9) Å β=93.45(7) °	a=18.202(2) Å b=7.513(6) Å c= 20.023(2) Å	a=24.254(3) Å b=7.342(8) c=8.425(1) Å β=93.28(5) °
Volume ($Å^3$)	1418.7(3)	2738.3(4)	1498.0(3)
Z, Cal.density (Mg m^{-3})	4, 1.355	8, 1.404	4, 1.345
Absorption coefficient (mm^{-1})	0.232	0.240	0.223
F(000)	608	1216	640
Crystal size (mm)	0.30 x 0.25 x 0.20	0.25 x 0.15 x 0.20	0.25 x 0.25 x 0.20
Theta range for data collection (°)	1.79 to 28.33	2.03 to 28.49	0.84 to 28.51
Limiting indices	-30<=h<=30, -8<=k<=9, -11<=l<=9	-24<=h<=23, -10<=k<=10, -20<=l<=26	-32<=h<=30, -9<=k<=9, -11<=l<=11
Reflections collected / unique	11858/3488 [R(int)=0.0576]	14633/3450 [R(int)=0.0575]	14204/3776 [R(int)=0.0753]
Max. and min. transmission	0.9551 and 0.9338	0.9536 and 0.9315	0.9568 and 0.9362
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	3488/0/182	3450/0/182	3776/0/192
Goodness-of-fit on F^2	1.011	1.03	1.045
Final R indices [I>2 σ (I)]	R1 = 0.0925, wR2 = 0.2623	R1 = 0.0489, wR2 = 0.1218	R1 = 0.0707, wR2 = 0.1681
R indices (all data)	R1 = 0.1273, wR2 = 0.2859	R1 = 0.0817, wR2 = 0.1426	R1 = 0.1508, wR2 = 0.2119
Largest difference peak and hole (e. $Å^{-3}$)	0.959 and -0.441	0.365 and -0.277	0.531 and -0.300

*Compound **IIIa** [2-((4,6-diaminopyrimidin-2-yl)thio)-N-(m-tolyl)acetamide]*

The ORTEP diagram of the compound C_{13} H_{15} N_5 O_1 S_1 drawn at 30% probability level is shown in Fig 1. The pyrimidine ring (N3/N4/C10-C13) and phenyl ring (C2-C7) make a dihedral angle of 55.8 (2) °. The amino group of nitrogens N1 and N2 attached with pyrimidine ring deviate by 0.0705 Å and -0.0386 Å, respectively. The methyl group of C1 atom attached with the phenyl ring deviates by -0.0377 Å. The diaminopyrimidine group is almost planar with maximum deviation of -0.045 Å for N3 atom. Thio-acetamide group connects the diaminopyrimidine and methylphenyl group in axial orientation which can be seen from the torsion angle N5/C8/C9/S1= -80.5°.

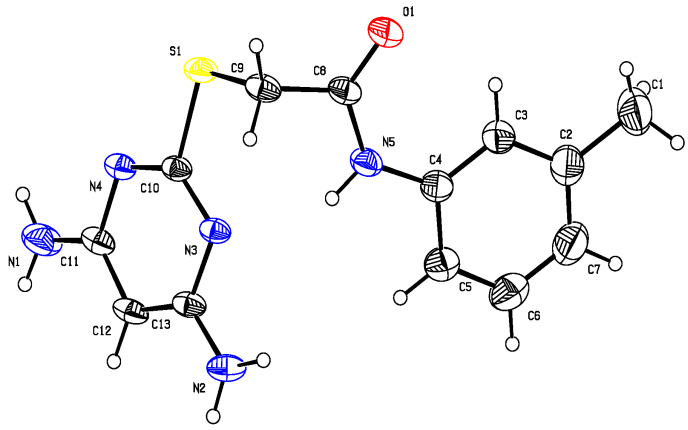


Fig. 1. ORTEP diagram of Compound **IIIa**. Displacement ellipsoids are drawn at the 30% probability level.

The molecular structure is stabilized by intramolecular & intermolecular interactions of type N—H...N, N—H...O, C—H...O and C—H...N types of hydrogen bonds. The hydrogen bond geometry of compound IIIa was given in Table 3. In the crystal packing N—H...N type of intermolecular interaction shows R_2^2 (8) dimer formation and also N—H...N intramolecular interaction stabilizes the molecular structure. The crystal packing of the compound is viewed down b axis. The crystal packing diagram of Compound IIIa is in Fig 2.

Table 3. Hydrogen –bond geometry (Å) for compound **IIIa**

D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	D-H...A [°]
N5—H5A...N3^{i}	0.86	2.23	2.9933(3)	149
C3—H3...O1^{i}	0.93	2.30	2.9029(3)	122
C9—H9B...N3^{i}	0.97	2.51	2.9162(3)	105
N1—H1D...N4^{ii}	0.86	2.30	3.1432(3)	168
N2—H2A...O1^{iii}	0.86	2.22	2.9702(3)	146

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

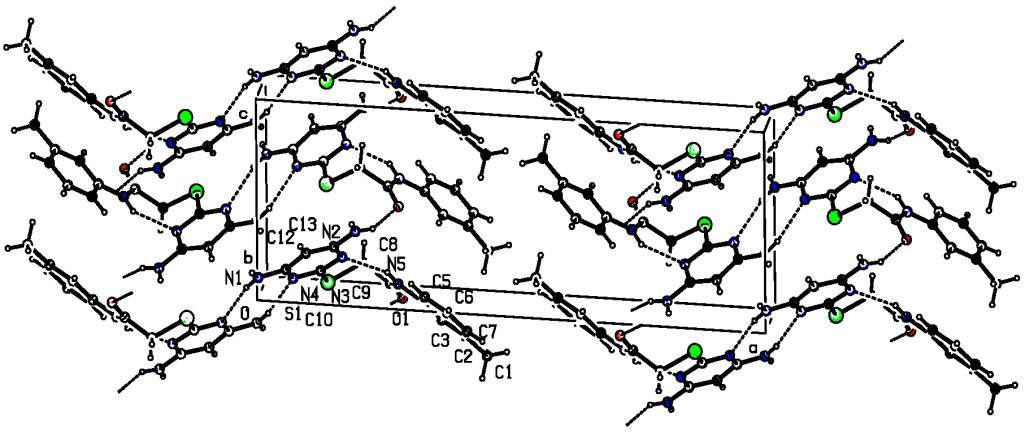


Fig. 2. Crystal packing diagram of compound **IIIa**

*Compound **IIIb** [2-((4,6-diaminopyrimidin-2-yl)thio)-N-(p-tolyl)acetamide]*

The ORTEP diagram of the compound C_{13} H_{15} N_5 O_1 S_1 drawn at 30% probability level is shown in Fig 3. The pyrimidine ring (N3/N4/C10-C13) and phenyl ring (C2-C7) make a dihedral angle of 42.35 (1) °. The amino group of nitrogens N1 and N2 attached with pyrimidine ring deviate by 0.0644 Å and 0.1141 Å, respectively. The methyl group of C1 atom attached with the phenyl ring deviates by 0.0313 Å. The diaminopyrimidine group is almost planar with maximum deviation of -0.082 Å for C12 atom. Thio-acetamide group connects the diaminopyrimidine and methylphenyl group in axial orientation which can be seen from the torsion angle N5/C8/C9/S1= -79.3°.

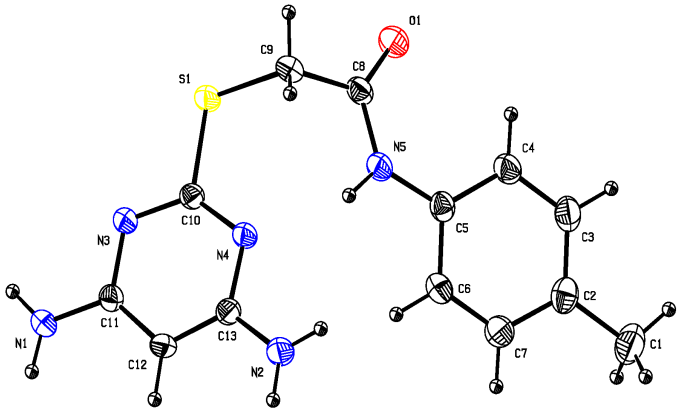


Fig. 3. ORTEP diagram of Compound **IIIb**. Displacement ellipsoids are drawn at the 30% probability level.

The molecular structure is stabilized by intramolecular & intermolecular interactions of type N—H...N, N—H...O, C—H...O and C—H...N types of hydrogen bonds. The hydrogen bond geometry of compound IIIb was given in Table 4. In the crystal packing N—H...N type of intermolecular interaction shows R_2^2 (8) dimer formation and also N—H...N intramolecular interaction stabilizes the molecular structure. The crystal packing of the compound is viewed down b axis. The crystal packing diagram of Compound IIIb is in Fig 4.

Table 4. Hydrogen bond geometry (Å) for compound **IIIb**

D-H…A	D-H (Å)	H…A (Å)	D…A (Å)	D-H…A [°]
N5—H5…N4^{i}	0.86	2.07	2.8679(2)	153
C4—H4…O1^{i}	0.93	2.47	2.9959(3)	116
C9—H9B…N4^{i}	0.97	2.60	2.9488(3)	101
N1—H1D…N3 ^{ii}	0.86	2.21	3.0338(3)	159
N2—H2B…O1^{iii}	0.86	2.18	2.9367(2)	147
C12—H12…O1^{iii}	0.93	2.48	3.1647(3)	131

Symmetry codes: i= x, y, z; ii= -x, 1-y, -z; iii= -½+x, y, ½-z

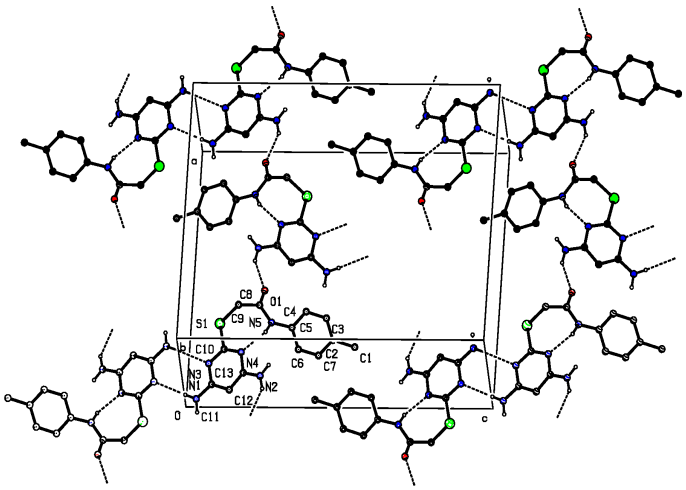


Fig. 4. Crystal packing diagram of compound **IIIb**

*Compound **IIIc** [2-((4,6-diaminopyrimidin-2-yl)thio)-N-(3,4-dimethylphenyl)acetamide]*

The ORTEP diagram of the compound C_{14} H_{17} N_5 O_1 S_1 drawn at 30% probability level is shown in Fig 5. The pyrimidine ring (N1/N2/C1-C4) and phenyl ring (C7-C12) make a dihedral angle of 54.18 °. The amino group of nitrogens N3 and N4 attached with pyrimidine ring deviate by 0.0760 Å and -0.0455 Å, respectively. The methyl groups C13 and C14 attached with the phenyl ring deviate by -0.0103 Å and -0.0390 Å respectively. The diaminopyrimidine group is almost planar with maximum deviation of -0.046 Å for N1 atom. Thio-acetamide group connects the diaminopyrimidine and dimethylphenyl group are in axial orientation which can be seen from the torsion angle S1/C5/C6/N5= -80.7(3)°.

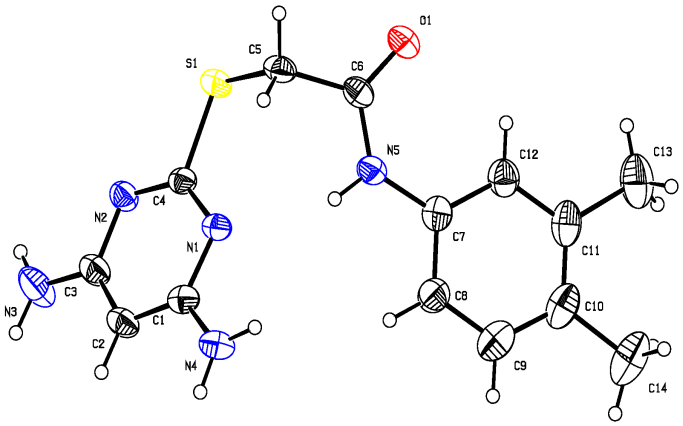


Fig. 5. ORTEP diagram of Compound **IIIc.** Displacement ellipsoids are drawn at the 30% probability level.

The molecular structure is stabilized by intramolecular & intermolecular interaction of type N—H...N, N—H...O, C—H...O and C—H...N types of hydrogen bonds. The hydrogen bond geometry of compound IIIc was given in Table 5. In the crystal packing N—H...N type of intermolecular interaction shows R_2^2 (8) dimer formation and also N—H...N intramolecular interaction stabilizes the molecular structure. The crystal packing of the compound is viewed down b axis. The crystal packing diagram of Compound IIIc is in Fig 6.

Table 5. Hydrogen –bond geometry (Å) for compound **IIIc**

D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	D-H...A [°]
N5—H5...N1^{i}	0.86	2.21	2.975(4)	149
C5—H5B...N1 ^{i}	0.97	2.49	2.898(4)	105
C12—H12...O1^{i}	0.93	2.32	2.920(5)	122
N3—H3A...N2^{ii}	0.86	2.30	3.145(5)	168
N4—H4B...O1^{iii}	0.86	2.22	2.981(4)	148

Symmetry codes: i= x, y, z; ii= -x, 1-y, -z; iii= x, ½-y, ½+z

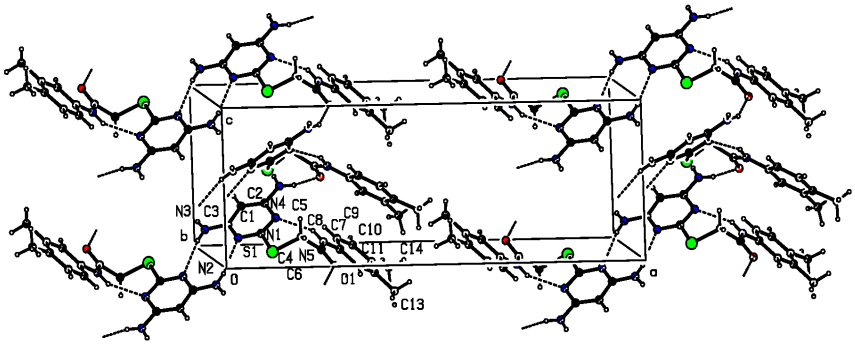


Fig. 6. Crystal packing diagram of compound **IIIc**

3. Experimental Procedure

Material & Equipments: Chemicals and solvents were of reagent grade and purchased from CDH/Merck/Sigma-Aldrich/Rankem. Completions of reaction were monitored on normal phase pre-coated silica with aluminum back TLC plates (Merck™ KGaA, Germany). Melting points were determined on an OPTIMELT automated system apparatus and are uncorrected. Intermediates were characterized by their FT-IR spectra (FTIR-8400S-Schimadzu).

3.1. Synthesis

3.1.1. Synthesis of 4,6-diamino-pyrimidine-2-thiol (I)

Thiourea (5 g, 65 mmol) and malanonitrile (4.3 g, 65 mmol) were added to a freshly prepared solution of sodium ethoxide (Na 1.5 g, 65 mmol, in Ethanol, 100 mL). The mixture was refluxed for 5 h, and then the precipitate was filtered off. The solid was dissolved in water (50 mL) and the pH adjusted around 7–8, the resulted precipitate was filtered, dried to give 4,6-diamino-2-thiol. The yield was 55%.

3.1.2. General procedure for synthesis of N-phenylacetamides (IIa-IIc)

To a solution of 9.16 mmol of aniline derivatives in acetic acid solution kept under ice bath, 11.0 mmol of chloroacetyl chloride was added dropwise. After the addition, the solution was stirred for 1-3 h, excess of chloroacetyl chloride solution was quenched with saturated sodium acetate solution. Acetanilide was filtered and washed thoroughly with ice cold water and dried. Yield is 78-95%.

3.1.3. General synthesis of 2-(4,6-diaminopyrimidin-2-ylthio)-N-phenylacetamide derivatives (IIIa-IIIc)

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 3.52 mmol of 2-chloro-N-phenylacetamide derivatives was added and refluxed for 2-2.5 h. When the end of reaction was observed by TLC, ethanol was evaporated in vaccuo and cold water was added to it and the precipitate was filtered and dried to give the 2-(4,6-diaminopyrimidin-2-ylthio)-N-phenylacetamide derivatives product is crystalline powder having a yield of 90-97%.

Synthesis of 2-(4,6-diaminopyrimidin-2-ylthio)-N-m-tolylacetamide (IIIa)

Synthesis of **IIIa** was done as per the general procedure given above, refluxing 3.52 mmol of **IIa** with equimolar quantity of **I** and potassium hydroxide in ethanol for 2.5 h. 2-(4,6-diaminopyrimidin-2-ylthio)-N-(naphthalen-1-yl)acetamide product is a crystalline powder having a yield of 90%. M.p is 218-220^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3H, -C$\underline{H}_3$), 3.75 (s, 2H, -C$\underline{H}_2$-S-), 5.18 (s, 1H, =C$\underline{H}$-), 6.29 (s, 4H, -(N$\underline{H}_2$)$_2$), 6.84 (d, 1H, J=7.8 Hz, Ar-$\underline{H}$), 7.15 (t, 1H, J=7.8 Hz, Ar-$\underline{H}$), 7.33 (d, 1H, J=8.3 Hz, Ar-$\underline{H}$), 7.40 (s, 1H, Ar-$\underline{H}$), 10.16 (s, 1H, -N$\underline{H}$); IR (KBr): 3463, 3289, 3183, 2921, 1681, 1655, 1306 cm^{-1}

Synthesis of 2-(4,6-diaminopyrimidin-2-ylthio)-N-p-tolylacetamide (IIIb)

Synthesis of **IIIb** was done as per the general procedure given above taking 3.52 mmol of **IIb** with equimolar quantity of **I** and potassium hydroxide in ethanol for 2.1 h. 2-(4,6-diaminopyrimidin-2-ylthio)-N-(naphthalen-1-yl)acetamide product is a crystalline powder having a yield of 95%. M.p is 236-238^{0}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3H, -C$\underline{H}_3$), 3.74 (s, 2H, -C$\underline{H}_2$-S-), 5.17 (s, 1H, =C$\underline{H}$-), 6.27 (s, 4H, -(N$\underline{H}_2$)$_2$), 7.08 (d, 1H, J=7.8 Hz, Ar-$\underline{H}$), 7.43 (d, 2H J=8.3 Hz, Ar-$\underline{H}$), 10.11 (s, 1H, -N$\underline{H}$); IR (KBr): 3465, 3290, 3188, 2918, 1682, 1655, 1306 cm^{-1}

Synthesis of 2-(4,6-diaminopyrimidin-2-ylthio)-N-(3,4-dimethylphenyl)acetamide (IIIc)

Synthesis of **IIIc** was done as per the general procedure given above taking 3.52 mmol of **IIc** with equimolar quantity of **I** and potassium hydroxide in ethanol for 2 h. 2-(4,6-diaminopyrimidin-2-ylthio)-N-(naphthalen-1-yl)acetamide product is a crystalline powder having a yield of 97%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.13 (s, 6H, -C$\underline{H}_3$), 3.73 (s, 2H, -C$\underline{H}_2$-S-), 5.17 (s, 1H, =C$\underline{H}$-), 6.27 (s, 4H, -(N$\underline{H}_2$)$_2$), 7.01 (d, 1H, J=8.3 Hz, Ar-$\underline{H}$), 7.25 (dd, 1 H, J=8.1, 1.7 Hz, Ar-$\underline{H}$), 7.32 (s, 1H, Ar-$\underline{H}$), 10.00 (s, 1H, -N$\underline{H}$); M.p is 226-228^{0}C. IR (KBr): 3463, 3297, 3186, 1679, 1655, 1305 cm^{-1}

3.2. X-ray analysis

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 (32). An empirical absorption correction (multi-scan) was performed using the *SADABS* program (32). The crystal structure was solved by direct methods using *SHELXS-97*[33] and refined by full-matrix least-squares using *SHELXL-97* (33). Molecular geometry was calculated using PARST (34). All non-hydrogen atoms were refined using

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 the ORTEP-PLATON program (35, 36).

3.2.1. Refinement

The hydrogen atoms were placed in calculated positions with C—H = 0.93 Å to 0.97 Å and N—H = 0.86 Å, refined in the riding model with fixed isotropic displacement parameters: *U*iso(H) = 1.5*U*eq(C) for methyl groups and *U*iso(H) = 1.2*U*eq(C) for C aromatic. The methyl groups were allowed to rotate but not to tip.

4. Conclusion

Total of three novel compounds were synthesized using different acetanilide derivatives and 4,6-diaminopyrimidine in the presence of potassium hydroxide as base. The compounds were characterized by TLC, melting points, ^{1}H NMR and FT-IR spectrum. These three compounds were crystallized using methanol as solvent. X-ray crystal revealed that the molecular structures were stabilized by intramolecular and intermolecular interactions of N—H...N, N—H...O, C—H...O and C—H...N types of hydrogen bonds.

Acknowledgments

We are pleased to acknowledge Department of Biotechnology (Govt. of India) for providing financial assistance through one of its INDO-GERMAN projects (BT/IN/GERMAN/15/DV/2010).

Supplementary Information

FT-IR spectrum, ^{1}H NMR spectrum and bond lengths, bond angles data of the compounds **IIIa-IIIc** are provided in the supplementary information. The crystallographic data of these three novel compounds were deposited with Cambridge Crystallographic Data Center allocated with deposit numbers CCDC 1038062, CCDC 1038089 and CCDC 1038090. A copy of data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK.

References

1. Quin LD, Tyrell JA. Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals: John Wiley & Sons; 2010.
2. Kappe CO. Biologically active dihydropyrimidones of the Biginelli-type—a literature survey. Eur J Med Chem. 2000;35(12):1043-52. http://dx.doi.org/10.1016/S0223-5234(00)01189-2
3. Waller CW, Hutchings BL, Mowat JH, Stokstad E, Boothe JH, Angier RB, et al. Synthesis of pteroylglutamic acid (liver L. casei factor) and pteroic acid. I. J Am Chem Soc. 1948;70(1):19-22. http://dx.doi.org/10.1021/ja01181a006
4. Chakravarty P, Suryanarayanan R. Characterization and structure analysis of thiamine hydrochloride methanol solvate. Cryst Growth Des. 2010;10(10):4414-20. http://dx.doi.org/10.1021/cg100522f
5. Ozeki K, Sakabe N, Tanaka J. The crystal structure of thymine. Acta Crystallogr B. 1969;25(6):1038-45. http://dx.doi.org/10.1107/S0567740869003505
6. Parry GS. The crystal structure of uracil. Acta Crystallogr. 1954;7(4):313-20. http://dx.doi.org/10.1107/S0365110X54000904
7. Barker D, Marsh R. The crystal structure of cytosine. Acta Crystallogr. 1964;17(12):1581-7. http://dx.doi.org/10.1107/S0365110X64003899
8. Agarwal A, Srivastava K, Puri S, Chauhan P. Synthesis of 2, 4, 6-trisubstituted pyrimidines as antimalarial agents. Bioorg Med Chem. 2005;13(15):4645-50. http://dx.doi.org/10.1016/j.bmc.2005.04.061
9. Zhang N, Ayral-Kaloustian S, Nguyen T, Afragola J, Hernandez R, Lucas J, et al. Synthesis and SAR of [1, 2, 4] triazolo [1, 5-a] pyrimidines, a class of anticancer agents with a unique mechanism of tubulin inhibition. J Med Chem. 2007;50(2):319-27. http://dx.doi.org/10.1021/jm060717i
10. Lukasik PM, Elabar S, Lam F, Shao H, Liu X, Abbas AY, et al. Synthesis and biological evaluation of imidazo [4, 5- *b*] pyridine and 4-heteroaryl-pyrimidine derivatives as anti-cancer agents. Eur J Med Chem. 2012;57:311-22. http://dx.doi.org/10.1016/j.ejmech.2012.09.034
11. Kumar R, Nair RR, Dhiman SS, Sharma J, Prakash O. Organoiodine (III)-mediated synthesis of 3-aryl/heteroaryl-5, 7-dimethyl-1, 2, 4-triazolo [4, 3-*c*] pyrimidines as antibacterial agents. Eur J Med Chem. 2009;44(5):2260-4. http://dx.doi.org/10.1016/j.ejmech.2008.06.004
12. Guerry P, Jolidon S, Masciadri R, Stalder H, Then R, inventors; WO 9616046 A2 19960530, assignee. Novel benzyl pyrimidines1996.
13. Devi N, Khuman C, Singh R, Singh L. Synthesis of pyrimido [4, 5-d] pyrimidines as antifungal agents. Indian J Heterocyc Chem. 1998;7(3):193-6.
14. Holý A, Votruba I, Masojídková M, Andrei G, Snoeck R, Naesens L, et al. 6-[2-(Phosphonomethoxy) alkoxy] pyrimidines with antiviral activity. J Med Chem. 2002;45(9):1918-29. http://dx.doi.org/10.1021/jm011095y
15. Qiu Y, Ptak R, Breitenbach J, Lin J, Cheng Y, Kern E, et al. (Z)-and (E)-2-(hydroxymethylcyclopropylidene)-methylpurines and pyrimidines as antiviral agents. Antiviral Chem Chemother. 1998;9(4):341-52.

http://dx.doi.org/10.1177/095632029800900406
16. De Clercq E. Therapeutic potential of phosphonylmethoxyalkylpurines and-pyrimidines as antiviral agents. Drugs Under Exp Clin Res. 1989;16(7):319-26.
17. Sharma M, Chaturvedi V, Manju Y, Bhatnagar S, Srivastava K, Puri S, et al. Substituted quinolinyl chalcones and quinolinyl pyrimidines as a new class of anti-infective agents. Eur J Med Chem. 2009;44(5):2081-91. http://dx.doi.org/10.1016/j.ejmech.2008.10.011
18. Patel R, Desai P, Desai K, Chikhalia K. Synthesis of pyrimidine based thiazolidinones and azetidinones: antimicrobial and antitubercular agents. Ind J Chem B. 2006;45(3):773. http://dx.doi.org/10.1002/chin.200628143
19. Rollo I. Drugs used in the chemotherapy of helminthiasis1980. Available from: http://www.popline.org/node/468309
20. Bekhit AA, Fahmy HT, Rostom SA, Baraka AM. Design and synthesis of some substituted 1*H*-pyrazolyl-thiazolo [4, 5-*d*] pyrimidines as anti-inflammatory–antimicrobial Agents. Eur J of Med Chem. 2003;38(1):27-36. http://dx.doi.org/10.1016/S0223-5234(02)00009-0
21. Kimura T, Ohno M, Ikeda M, Watanabe K, Kondo S, Ho I, et al., editors. Antianxiety effects of N3-phenacyluridine in mice. Nucl Acid Symp Ser; 1998: [London]: Information Retrieval Ltd., c1979-c2000.
22. Quintela J, Peinador C, Botana L, Estévez M, Riguera R. Synthesis and antihistaminic activity of 2-guanadino-3-cyanopyridines and pyrido [2, 3-*d*]-pyrimidines. Bioorg Med Chem. 1997;5(8):1543-53. http://dx.doi.org/10.1016/S0968-0896(97)00108-9
23. Shishoo CJ, Shirsath VS, Rathod IS, Yande VD. Design, synthesis and antihistaminic (H^1) activity of some condensed 3-aminopyrimidin-4 (3*H*)-ones. Eur J Med Chem. 2000;35(3):351-8. http://dx.doi.org/10.1016/S0223-5234(00)00128-8
24. Bennett LR, Blankley CJ, Fleming RW, Smith RD, Tessman DK. Antihypertensive activity of 6-arylpyrido [2, 3-d] pyrimidin-7-amine derivatives. J Med Chem. 1981;24(4):382-9. http://dx.doi.org/10.1021/jm00136a006
25. Kelton J, Hirsh J, editors. Bleeding associated with antithrombotic therapy. Semin Hematol; 1980.
26. Marchetti M, Puddu P, Caldarera C. Metabolic aspects oforotic acid fatty liver'. Nucleotide control mechanisms of lipid metabolism. Biochem J. 1964;92(1):46.
27. Nowak K, Suryło P. Leki przeciwtrądowe. Wiadomości Chem. 2006:257-78.
28. Periti P. Brodimoprim, a new bacterial dihydrofolate reductase inhibitor: a minireview. J Chemother. 1995;7(3):221-3. http://dx.doi.org/10.1179/joc.1995.7.3.221
29. Reuter M, Loenicker E, Reuter H. [Antibacterial treatment of urinary tract infections with co-tetroxazin (sterinor)]. Fortschritte der Medizin. 1981;99(17):654-8.
30. van Oosterom R, Hartman E, Hartman E. Pipemidic acid, a new treatment for recurrent urinary tract infection in small animals. Vet Quart. 1986;8(1):2-5. http://dx.doi.org/10.1080/01652176.1986.9694011
31. Sweet R, Wasterlain C, McDowell F. Piribedil, a dopamine agonist, in Parkinson's disease. Clin Pharmacol Ther. 1974;16(6):1077-82.
32. Bruker Inc A. APEX2 (Version 1.08), SAINT (Version 7.03), SADABS (Version 2.11), SHELXTL (Version 6.12). Bruker Advanced X-ray Solutions, Madison. 2004.
33. Sheldrick G. A short history of SHELX. Acta Crystallogr A. 2008;64(1):112-22. http://dx.doi.org/10.1107/S0108767307043930
34. Nardelli M. PARST95 - an update to PARST: a system of Fortran routines for calculating molecular structure parameters from the results of crystal structure analyses. J Appl Crystallogr. 1995;28(5):659. http://dx.doi.org/10.1107/S0021889895007138
35. Farrugia L. WinGX and ORTEP for Windows: an update. J Appl Crystallogr. 2012;45(4):849-54. http://dx.doi.org/10.1107/S0021889812029111
36. Spek A. Structure validation in chemical crystallography. Acta Crystallogr D. 2009;65(2):148-55. http://dx.doi.org/10.1107/S090744490804362X