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Synthesis and Crystal structure of Benzofuro[3,2-d]pyrimidine Derivative

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The single crystal of N^8,N^8-dibenzyl-N^4-(3-bromophenyl)benzofuro[3,2-d]pyrimidine-4,8-diamine was obtained by recrystallization from pure ethanol solution. The structure was confirmed by ^{1}H NMR, ^{13}C NMR and single crystal X-ray diffraction analysis. The cell unit parameters that crystallized in the triclinic system, space group P-1 including a = 9.5792 (10) Å, b = 10.3148 (10) Å, c = 17.11324 (17) Å, α = 104.102 (4)º, β = 106.038 (4)º, γ = 95.381 (4)º. V = 1554.2 (3) Å^3, Z = 2, M_r = 627.56, D_c = 1.341 g/cm^3, $F_{(000)}$ = 652, R = 0.0602, wR = 0.2031 for 5442 reflections with I > 2σ(I). The crystal of the compound was stabilized a 2D supramolecular layer structure through the interactions between the hydrogen bonds and the C-H···π.

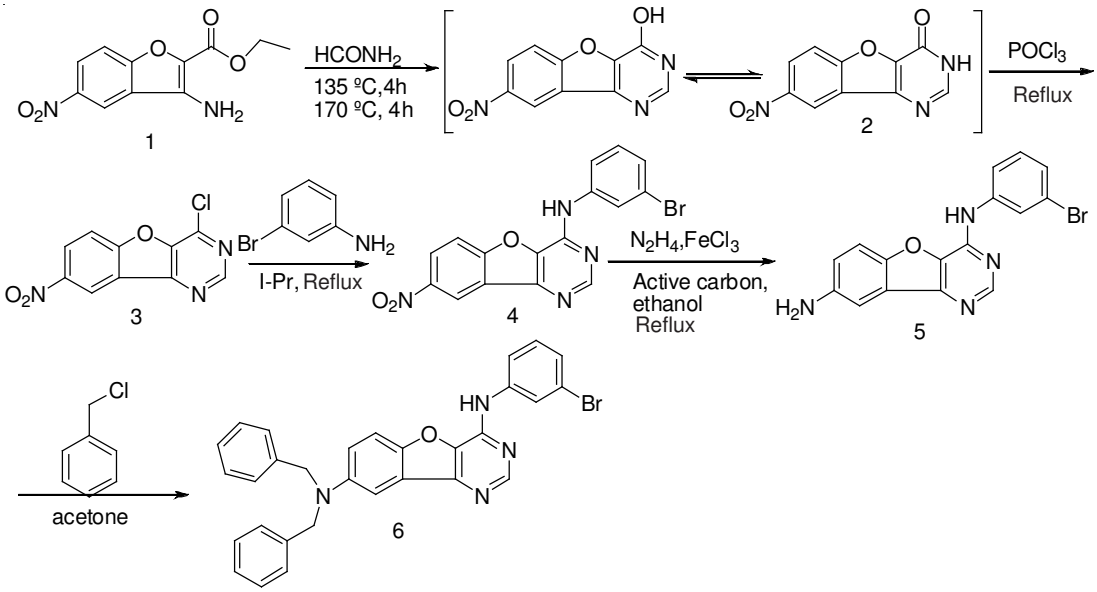
Key Words: Crystal structure, N-8-Benzyl-N-(3-bromophenyl)-N-8-phenethyl-benzofuro[3,2-d]pyrimidine-4,8-diamine, Synthesis.

INTRODUCTION

Benzofuro[3,2-d]pyrimidine derivatives displayed a broad spectrum of bioactivity, such as antiinflammatory[1], antifungal[2], antitumor[3], anticancer[4], inhibitors of platelet aggregation[5]. In recent years, the kinds of compounds had devoted a considerable attention in synthetic organic chemistry as well as in modern pharmaceutical chemistry. In this study, the synthesis and crystal structure of a new benzofuro[3,2-d]pyrimidine derivative were presented by ^{1}H NMR, ^{13}C NMR and single crystal X-ray diffraction analysis, which provide related materials developing the benzofuro[3,2-d]pyrimidine derivatives.

EXPERIMENTAL

Compound **6** was synthesized from the procedure (**Scheme-I**). 3-Amino-5-nitro-2-benzofuran acid ethyl ester was prepared according to the methods of the literature[6]. Other



Scheme-I: Synthesis of compound **6**

reagents were AR grade. The ^{1}H NMR spectrum was recorded on Bruker AV500 NMR spectrometer. DMSO-d_6 was used as the solvent, tetramethylsilane (TMS) as an internal standard.

Synthesis of 8-nitrobenfuro[3,2-d]pyrimidin-4(3*H*)-one (2): 152 mL of formamide was added to 3-amino-5-nitro-2-benzofuran acid ethyl ester (20.1 g, 80.3 mmol) in a stirred three-necked flask at room temperature. The mixture was stirred in 135 ºC for 4 h and then in 170 ºC for 4 h. After the material were run out, the mixture was pooled into a beaker with water (400 mL) added at room temperature and then separated out the residue, yielding 74.8 % white solid: m.p. 220-225 ºC; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.25-8.28 (d, *J* = 9.20 Hz, 1H, Ar-H), 8.70-8.72 (dd, *J* = 2.30 Hz, 1H, Ar-H), 9.05-9.06 (d, *J* = 2.30 Hz , 1H, Ar-H), 9.19 (s, 1H, pyrimidine-H).

Synthesis of 4-chloro-8-nitrobenzofu[3,2-d]pyrimidine (3): $POCl_3$ (4.1 mL) was added dropwise to 8-nitrobenfuro[3,2-d]pyrimidin-4(3*H*)-one (0.5 g, 2.16 mmol), The mixture was boiled for 12 h. After evaporation of $POCl_3$, the residue was dissolved in water and the sediment of compound **3** was filtered and dried in the air. The compound **3** was obtained in 74 % yielding as white crystal: m.p. 195-200 ºC; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 8.25-8.28 (d, *J* = 9.20 Hz, 1H, Ar-H), 8.70-8.72 (dd, *J* = 2.30 Hz, 1H, ArH), 9.05-9.06 (d, *J* = 2.30 Hz, 1H, Ar-H), 9.19 (s, 1H, pyrimidine-H).

Synthesis of N-(3-bromophenyl)-8-nitrbenzofuro[3,2-d]-pyrimidin-4-amine (4): A mixture of 4-chloro-8-nitro-benzofu[3,2-d]pyrimidine (0.18 g, 0.72 mmol) and 3-bromoaniline (0.15 g, 0.88 mmol) were refluxed in 10 mL propan-2-ol for 8 h. After evaporation of propan-2-ol, the residue was dissolved in ethanol and then sediment of compound **4** was filtered and dried in the air. The compound **4** was obtained in 80 % yielding as yellow solid: m.p. 259-262 ºC; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.30-7.32 (d, *J* = 8.00 Hz, 1H, Ar-H), 7.35-7.38 (t, *J* = 8.00 Hz, 1H, Ar-H), 7.90-7.92 (d, *J* = 9.15 Hz 1H, Ar-H), 8.11-8.13 (d, *J* = 9.15 Hz 1H ,Ar-H), 8.30 (s, 1H, Ar-H), 8.61-8.59 (q, *J* = 9.13 Hz, 1H, Ar-H), 8.82 (s, 1H, Ar-H), 8.90 (s, 1H, pyrimidine-H), 10.60 (s, 1H, N-H).

Synthesis of N^4-(3-bromophenyl)benzofuro[3,2-d]-pyrimidine-4,8-diamine (5): A mixture of N-(3-bromophenyl)-8-nitrbenzofuro[3,2-d]pyrimidin-4-amine (0.50 g, 1.3 mmol), $FeCl_3$ (0.13 g, 0.8 mmol) and active carbon (0.10 g) in 10 mL ethanol was refluxed and then 80 % $N_2H_4{\cdot}H_2O$ was added dropwise to the mixture with continuous stirred. The mixture was boiled for 12 h and then used suction filter to get mixed solution and evaporated to remove solvent. The compound **5** was obtained in 81 % yielding as white solid. m.p. 242-245; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 5.30(s, 2H, N-H), 7.00-7.02 (q, *J* = 2.30 Hz, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 7.23-7.25 (d, *J* = 8.60 Hz, 1H, Ar-H), 7.31-7.34 (t, *J* = 8.00 Hz, 1H, Ar-H), 7.52-7.53 (d, *J* = 9.15 Hz, 1H, Ar-H), 7.90-7.92 (d, *J* = 9.20 Hz, 1H, Ar-H), 8.33 (s, 1H, Ar-H), 8.64 (s, 1H, pyrimidine-H), 10.12 (s, 1H, N-H).

Synthesis of N^8,N^8-dibenzyl-N^4-(3-bromophenyl) benzofuro[3,2-d]pyrimidine-4,8-diamine (6): N^4-(3-Bromophenyl)benzofuro[3,2-d]pyrimidine-4,8-diamine (0.50 g, 1.4 mmol), potassium carbonate (0.39 g, 2.8 mmol) and benzyl chloride (0.36 g, 2.8 mmol) in 15 mL acetone was stirred at room temperature for 8 h and then 5 mL water was added, filtered to get yellow solid. Compound **6** was crystalli-zed from pure ethanol, yielding 60 % white crystals: m.p. 75 ºC; ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 5.47 (s, 4H, -CH_2-), 7.00-7.02 (q, *J* = 2.30 Hz, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 7.23-7.25 (d, *J* = 8.60 Hz, 1H, Ar-H), 7.31~7.34(t, *J* = 8.00 Hz, 1H, Ar-H), 7.35-7.36 (d, *J* = 8.43 Hz, 4H, Ar-H), 7.38-7.41 (m, 2H, Ar-H), 7.42 (m, 4H, Ar-H), 7.52-7.53 (d, *J* = 9.15 Hz, 1H, Ar-H), 7.90-7.92 (d, *J* = 9.20 Hz, 1H, Ar-H), 8.8.23 (s, 1H, Ar-H), 8.61 (s, 1H, pyrimidine-H), 10.13 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 55.29, 102.84, 113.19, 118.04, 121.80, 126.56, 127.33, 127.62, 127.92, 128.96, 129.10, 129.46, 131.00, 136.00, 138.02, 139.21, 144.80, 148.09, 148.56, 149.31, 152.79.

Crystal structure determination: The X-ray data were collected on a Bruker Apex-II CCD diffractometer using graphite monochromated MoK_α radiation (λ = 0.71073 Å) at 293(2) K with crystal size 0.20 mm × 0.21 mm × 0.22 mm. A total of 5442 (R_{int} = 0.043) independent reflections were collected by ϕ and ω scans technique in the range of $2.1 \le \theta \le 25.00^\circ$ from which 3420 [$I > 2\sigma(I)$] reflection were corrected for Lorentz and polarization factors. The structure was solved by direct method using SHELXS-97[7] and refined using a full-matrix least-squares procedure on F^2 in SHELXS-97. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added theoretically and refined with riding model.

RESULTS AND DISCUSSION

The result showed that the crystal contained an ethanol molecules by X-ray crystal structure esperiments (Fig. 1). It crystallizes in P-1 space group and triclinic crystal system. The selected bond lengths and bond angles are given in Table-1. N-C distances range from 1.328(6) to 1.456 (6) Å; the C15-N1-C17-C18 torsion angel of 88.7(5)º and the C17-N1-C24-C25 torsion angel of -111.7(4)º. The benzofuran [3,2-d]pyrimidine ring tends to coplanar.

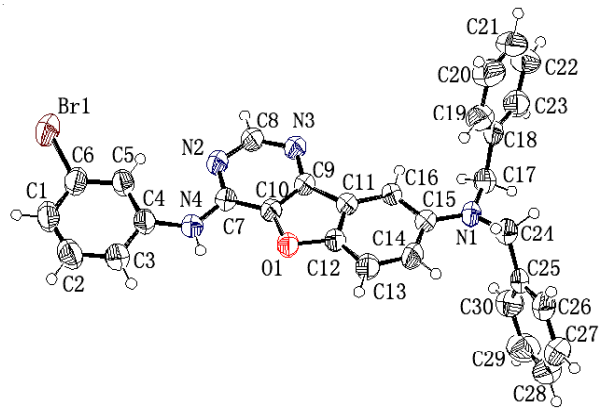


Fig. 1. Molecular structure of compound **6**

Fig. 2 shows the packing diagram of the compound **6**. The crystal was stabilized by C-H···N, C-H···O and N-H···O intermolecular and intramolecular hydrogen bonds and C-H···π interactions (Table-2). These interactions were formed between adjacent molecules resulting in a 2D supramolecular layer and it contained a layer of ethanol molecules between each layer of the molecule.

TABLE-1
SELECTED BOND DISTANCES (Å) AND ANGLES (º)

Br1-C6	1.889(5)	O1-C12	1.392(5)	C4-N4-C7	130.3(4)
N1-C17	1.444(6)	N2-C7	1.335(5)	Br1-C6-C5	118.8(4)
N3-C8	1.328(6)	N4-C4	1.404(5)	C10-O1-C12	104.5(3)
O1-C10	1.370(5)	N4-C7	1.359(6)	N2-C8-N3	128.7(4)
N1-C24	1.456(6)	C17-C18	1.521(6)	C17-N1-C24	117.3(4)
N3-C9	1.357(5)	C7-C10	1.389(5)	N2-C7-N7	122.9(3)

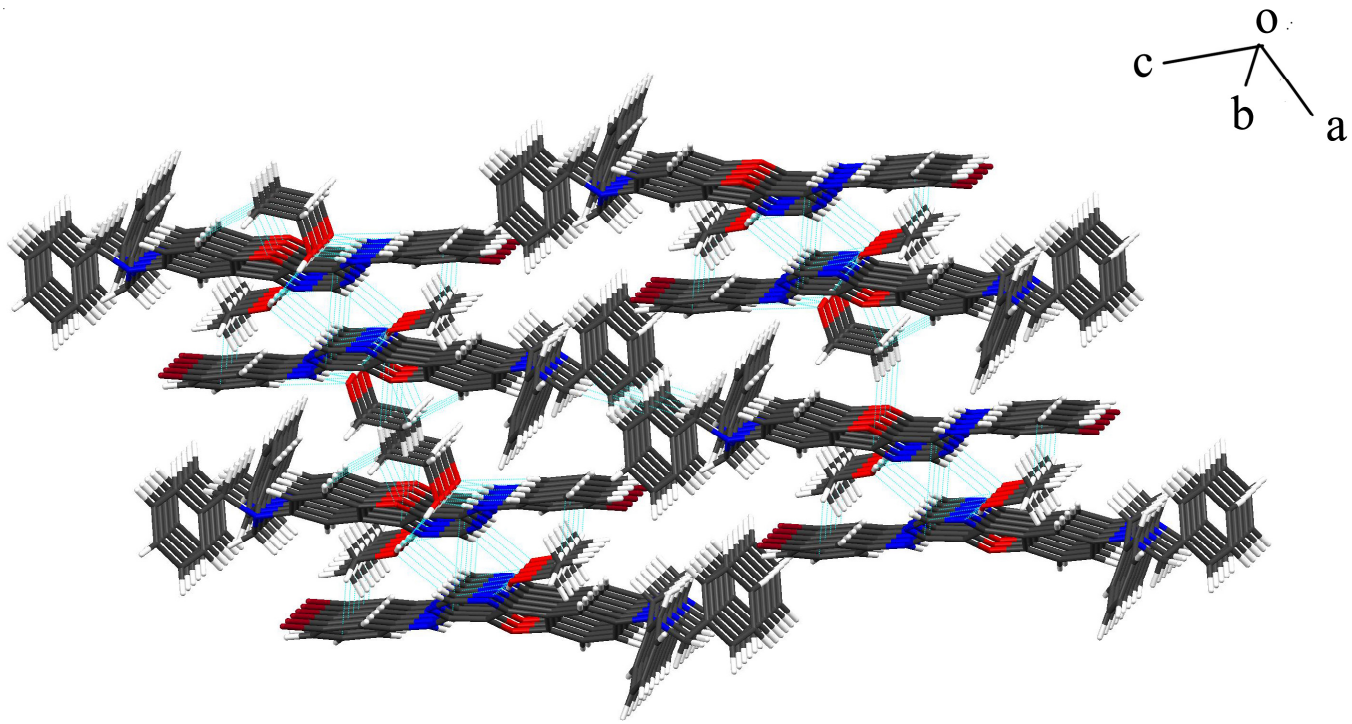


Fig. 2. Packing diagram of compound **6**

TABLE-2
HYDROGEN BOND AND C-H···C-H···π INTETACTIONS
DISTANCES (Å) AND ANGLES (º)

Type (D-H···A)	d(H···A)	∠(DHA)	d(D···A)	Symmetry code
O2-H2A···N3	2.02	168	2.823(5)	x, -1+y, z
O3-H3A···O2	1.97	176	2.787(5)	x, -1+y, z
N4-H122···O1	2.55(5)	105(4)	2.887(4)	x, -1+y, z
N4-H122···O3	2.09(4)	169(4)	2.917(6)	x, -1+y, z
C3-H3···O3	2.47	142	3.254(6)	x, -1+y, z
C5-H5···N2	2.31	123	2.922(6)	x, -1+y, z
C19-H19···N1	2.58	102	2.917(6)	x, -1+y, z
C30-H30···N1	2.60	101	2.918(6)	x, -1+y, z
C22-H22···Cg(6)	3.00	152	3.847(6)	x, 1+y, z
C27-H27···Cg(5)	2.97	137	3.701(6)	2-x, 1-y, -z
C32-H32B···Cg(4)	2.99	162	3.926(8)	2-x, 2-y, 1-z

Conclusion

A new benzofuran[3,2-d]pyrimidine derivative had been synthesized and characterized by ^{1}H NMR, ^{13}C NMR and X-ray diffraction analysis. It crystallized in the triclinic system with P-1 space group. X-ray crystal structure study shows the crystal contained ethanol molecules. The crystal of the compound was stabilized a 2D supramolecular layer structure through the interactions between the hydrogen bonds and the C-H···π.

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