Synthesis and Antitumor Activities of Benzofuran[3,2-*d*]pyrimidine Derivatives

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Benzofuran[3,2-*d*]pyrimidine derivatives have good biological activity. This paper reported the synthesis of six compounds of benzofuran[3,2-*d*]pyrimidine derivatives. Their structures were confirmed by EI-MS, ¹H NMR, ¹³C NMR and single crystal X-ray diffraction analysis. The single crystal of 2-chloro-4-(*N,N*-diethyl-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine was obtained by recrystallization from chloroform solution. It crystallized in the monoclinic system, P2₁/c space group. The target compounds were screened *in vitro* anticancer activity using human lung cancer cell line A549 cells and human leukemia cell line K562 cells.

Keywords: Benzofuran[3,2-*d*]pyrimidine, Derivatives, Antitumor activities, Crystal structure, Synthesis.

INTRODUCTION

Epidermal growth factor receptor tyrosine kinase¹⁻³ (EGFR-TK) has recently been reported as a new target for studying antitumor activities. Its phosphorylation plays an important role in regulating tumor growth and metastasis. High expression of epidermal growth factor receptor has been associated with many types of tumor cell malignant proliferation. The study on inhibition of EGFR-TK has become a hot area of research. There is a variety of tyrosine kinase inhibitors in development state, wherein the most common is quinazoline⁴, pyrrolo-pyrimidine⁵⁻⁶, thienopyrimidine⁷ and pyridopyrimidine⁴ compounds. Benzofuran [3,2-*d*]pyrimidine structure similar with those compounds, theoretically promote the compounds should also have a good biological activity.

Benzofuran[3,2-*d*]pyrimidine **1** (MP-470, SuperGen Inc.)⁸ is a novel multitarget tyrosine kinase inhibitor currently in Phase I clinical trials, while compound **2** (Fig. 1) and its analogues were found to be histamine H₄ modulators⁹. In order to find high biologically active compound, we reported the synthesis of six compounds of benzofuran[3,2-*d*]pyrimidine derivatives in this paper. Those compound structures were confirmed by EI-MS, ¹H NMR, ¹³C NMR analysis and in addition, 2-chloro-4-(*N,N*-diethyl-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine was confirmed by single crystal X-ray diffraction analysis.

EXPERIMENTAL

Target product was synthesized following the procedure (Scheme-I). The raw materials 3-amino-5-nitro-2-benzofuran acid ethyl ester¹⁰ was prepared according to literature methods. Other reagents were AR grade and were used without further purification. The ¹H NMR spectrum was recorded on Bruker AV500 NMR spectrometer, CDCl₃ and DMSO were used as the solvent, tetramethylsilane (TMS) was used as an internal standard.

Synthesis of 8-nitro-benzofuran[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2**):** 3-Amino-5-nitro-2-benzofuran acid ethyl ester (20 g, 80 mmol) and urea (28.8 g, 480 mmol) were ground to a fine powder and then heated at 220 °C for 1.5 h. After cooling to room temperature, hot water was added to the reaction mixture for 0.5 h and the crude product was washed with hot water, after filtration, then, the solid was crystallized from DMSO, yielding 48 % white solid: m.p. >350 °C; EI-

Fig. 1. Benzofuran[3,2-*d*]pyrimidine

(i): urea, 220 °C; (ii): POCl₃, DMF; (iii): R-NH₂, ultrasonic

Scheme-I: Synthesis of compound TM

MS (*m/z*): 247[M⁺], 204, 156, 148, 102, 75; ¹H NMR (500 MHz, DMSO-*d*₆): δ ppm 12.03 (s, 1H, N-H), 11.57 (s, 1H, N-H), 8.92 (s, 1H, Ar-H), 8.42 (d, 1H, *J* = 8 Hz, Ar-H), 7.96 (d, 1H, *J* = 8 Hz, Ar-H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ ppm 158.4, 155.2, 151.5, 144.5, 134.0, 133.6, 125.3, 119.1, 118.8, 114.7.

Synthesis of 2,4-dichloro-8-nitro-benzofuran[3,2-*d*]-pyrimidine (3): Compound 2 (4.9 g, 20 mmol) was dissolved in POCl₃ (30 mL). Then added a few drops of DMF and refluxed for 10 h. After cooling to room temperature, then the reaction solution was added to a stirred beaker containing crushed ice. The crude product was washed with water after filtration, then, the solid was crystallized from chloroform-isopropanol, yielding 62 % colorless crystals: m.p. 214-217 °C; EI-MS (*m/z*): 283[M⁺], 253, 237, 225, 148, 112, 87, 69, 57; ¹H NMR (500 MHz, CDCl₃): δ ppm 9.18 (d, 1H, *J* = 2.3 Hz, Ar-H), 8.71 (dd, 1H, *J* = 2.3, 9.2 Hz, Ar-H), 7.92 (d, 1H, *J* = 9.2 Hz, Ar-H); ¹³C NMR (125 MHz, CDCl₃): δ ppm 160.9, 154.9, 152.7, 145.4, 145.3, 144.9, 128.3, 121.6, 119.9, 114.4.

Synthesis of 2-chloro-4-(N-antipyrene-4-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine (4): Compound 3 (142 mg, 0.5 mmol) was dissolved in dichloromethane (5 mL) at a 50 mL round bottom flask, then, added 4-aminoantipyrene (122 mg, 0.6 mmol) and triethylamine (0.1 mL, 0.7 mmol). Ultrasound treatment 9 h. Then evaporated and washed with water, the residue was crystallized from chloroform, yielding 81 % light yellow crystals: m.p. 260-263 °C; EI-MS (*m/z*): 450[M⁺], 340, 83, 56, 42; ¹H NMR (400 MHz, CDCl₃): δ ppm 10.59 (s, 1H, N-H), 8.91 (d, 1H, *J* = 2 Hz, Ar-H), 8.48 (dd, 1H, *J* = 2.4, 8.8 Hz, Ar-H), 7.54-7.59 (m, 4H, Ar-H), 7.40-7.45 (m, 2H, Ar-H), 3.28 (s, 3H, N-CH₃), 2.20 (s, 3H, C-CH₃); ¹³C NMR (125 MHz, CDCl₃): δ ppm 162.8, 159.1, 154.9, 152.0, 148.9, 146.7, 144.7, 135.6, 134.3, 129.7, 127.9, 125.6, 125.1, 121.8, 118.5, 113.3, 107.4, 35.8, 12.3.

Synthesis of 2-chloro-4-(N-ethanol-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine (5): Compound 3 (142 mg, 0.5 mmol) was dissolved in dichloromethane (5 mL) at a 50 mL round bottom flask, then, added 2-aminoethanol (37 mg, 0.6 mmol) and triethylamine (0.1 mL, 0.7 mmol). Ultrasound

treatment for 3 h. Then evaporated and washed with water, yielding 96 % white solid: m.p. 213-214 °C; EI-MS (*m/z*): 308[M⁺], 277, 264, 231, 195, 167, 139, 30; ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 8.82 (d, 1H, *J* = 2.4 Hz, Ar-H), 8.52 (dd, 1H, *J* = 2.4, 8.8 Hz, Ar-H), 8.04 (d, 1H, *J* = 9.2 Hz, Ar-H), 7.84 (brs, 1H, -OH), 4.85 (s, 1H, N-H), 3.59 (q, 4H, *J* = 7.5 Hz, -CH₂-CH₂-); ¹³C NMR (125 MHz, DMSO-*d*₆): δ ppm 159, 154.9, 150.7, 145.8, 144.7, 136.7, 125.9, 122.6, 117.8, 114.5, 59.5, 58.

Synthesis of 2-chloro-4-(N-*o*-amino-phenyl-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine (6): Compound 3 (142 mg, 0.5 mmol) was dissolved in dichloromethane (5 mL) at a 50 mL round bottom flask, then, added 1,2-diaminobenzene (65 mg, 0.6 mmol) and triethylamine (0.1 mL, 0.7 mmol). Ultrasound treatment 3 h. Then evaporated and washed with water, the residue was crystallized from DMF, yielding 68 % light yellow solid: m.p. 253-255 °C; EI-MS (*m/z*): 355[M⁺], 320, 274, 118, 65; ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 9.99 (s, 1H, N-H), 8.89 (d, 1H, *J* = 1.6 Hz, Ar-H), 8.55 (d, 1H, *J* = 8.8 Hz, Ar-H), 8.04 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.12 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.05 (t, 1H, *J* = 7.6 Hz, Ar-H), 6.78 (d, 1H, *J* = 8 Hz, Ar-H), 6.60 (t, 1H, *J* = 7.4 Hz, Ar-H), 5.10 (s, 2H, NH₂); ¹³C NMR (125 MHz, DMSO-*d*₆): δ ppm 159.2, 154.7, 150.3, 145.2, 144.9, 137.2, 128.4, 128.3, 126.2, 122.7, 121.8, 118.2, 116.3, 116.1, 114.6.

Synthesis of 2-chloro-4-(N-*m*-bromophenyl-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine (7): Compound 3 (142 mg, 0.5 mmol) was dissolved in dichloromethane (5 mL) at a 50 mL round bottom flask, then, added 1-amino-3-bromobenzene (103 mg, 0.6 mmol) and triethylamine (0.1 mL, 0.7 mmol). Ultrasound treatment for 6 h. Then evaporated and washed with water, the residue was crystallized from ethyl acetate, yielding 62 % light yellow crystals: m.p. 191-193 °C; EI-MS (*m/z*): 420[M⁺], 383, 373, 339, 293, 155, 116, 102, 75; ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 10.91 (s, 1H, N-H), 8.94 (d, 1H, *J* = 2.4 Hz, Ar-H), 8.60 (dd, 1H, *J* = 2.4, 9.2 Hz, Ar-H), 8.11-8.16 (m, 2H, Ar-H), 7.85 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.35-7.42 (m, 2H, Ar-H); ¹³C NMR (125 MHz, DMSO-*d*₆): δ ppm

159.1, 154.9, 150.5, 145.9, 145.1, 144.8, 137.1, 128.6, 128.2, 126.5, 122.7, 121.8, 118.2, 116.7, 116.2, 114.6.

Synthesis of 2-chloro-4-(*N*-phenylethylamine)-8-nitro-benzofuran[3,2-*d*]pyrimidine (8): Compound **3** (142 mg, 0.5 mmol) was dissolved in dichloromethane (5 mL) in a 50 mL round bottom flask, then, added phenethylamine (73 mg, 0.6 mmol) and triethylamine (0.1 mL, 0.7 mmol). Ultrasound treatment for 1.5 h. Then evaporated and washed with water, yielding 96 % light yellow solid: m.p. 249-250 °C; EI-MS (m/z): 368[M⁺], 277, 264, 231, 139, 104, 91; ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 8.82 (d, 1H, *J* = 2.0Hz, Ar-H), 8.52 (dd, 1H, *J* = 2.4, 9.2Hz, Ar-H), 8.04 (d, 1H, *J* = 9.2Hz, Ar-H), 7.90 (s, 1H, N-H), 7.21-7.36 (m, 5H, Ar-H), 2.85-3.05 (m, 4H, -CH₂-CH₂-); ¹³C NMR (125 MHz, DMSO-*d*₆): δ ppm 159.1, 154.9, 150.6, 146.1, 144.8, 139.6, 129.2, 127.3, 126.8, 126.0, 122.8, 121.6, 118.1, 114.6, 42.4, 33.5.

Synthesis of 2-chloro-4-(*N,N*-diethyl-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine (9): Compound **3** (142 mg, 0.5 mmol) was dissolved in dichloromethane (5 mL) at a 50 mL round bottom flask, then, added diethylamine (44 mg, 0.6 mmol) and triethylamine (0.1 mL, 0.7 mmol). Ultrasound treatment 3 h. Then evaporated and washed with water, the residue was crystallized from chloroform, yielding 84 % light yellow crystals: m.p. 194-196 °C; EI-MS (m/z): 320[M⁺], 305, 291, 277, 245, 231, 168, 139, 72, 44; ¹H NMR (500 MHz, CDCl₃): δ ppm 9.01 (d, 1H, *J* = 2.5 Hz, Ar-H), 8.47 (dd, 1H, *J* = 2.8, 9.2Hz, Ar-H), 7.71 (d, 1H, *J* = 9.2Hz, Ar-H), 3.81-3.95 (m, 4H, N-CH₂-), 1.34-1.41 (m, 6H, -CH₃); ¹³C NMR (125 MHz, CDCl₃): δ ppm 158.9, 154.8, 150.7, 145.7, 144.7, 136.6, 125.9, 122.5, 117.8, 114.5, 58.3, 12.3.

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 0.18 mm × 0.13 mm × 0.11 mm. The reflections were collected by ϕ and ω scans technique in the range of $0.890 \leq \theta \leq 25.99^\circ$ from which 1231 [$I > 2\sigma(I)$] reflection were corrected for Lorentz and polarization factors. The structure was solved by direct method using SHELXS-97¹¹ 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

Fig. 2 shows the molecular structure of 2-chloro-4-(*N,N*-diethyl-amino)-8-nitro- benzofuran[3,2-*d*]pyrimidine. It crystallizes in the monoclinic system with P21/c space group with unit cell parameters: *a* = 13.230 (7) Å, *b* = 8.142 (5) Å, *c* = 14.487 (9) Å, α = 90°, β = 108.525 (18)°, γ = 90°. *V* = 1479.7 (15) Å³, *Z* = 4, *Mr* = 320.73, *D_c* = 1.440 g/cm³, μ = 0.277 mm⁻¹, *F* (000) = 664. The selected bond lengths and bond angles are listed in Table-1. The benzofuran ring (C2-C3-C4-C5-C6-C1-O1-C7-C8) and the pyrimidine ring (C7-C8-N2-C9-N3-C10) of 2-chloro-4-(*N,N*-diethyl-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine is tend to coplanar. The crystal were stabilized by C(9)-Cl(1)...Cg(3) (Cg(3): C1-C2-C3-C4-C5-C6, Symmetry code: 2-*x*, -*y*, -*z*) interaction and π - π Stacking. These interaction were formed between adjacent molecules resulting in a 2D supramolecular chain structures.

Fig. 2. Molecular structure of 2-chloro-4-(*N,N*-diethyl-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine

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

O2-N1	1.246(14)	N4-C12	1.481(14)	N3-C10-N4	118.4(8)
O1-C7	1.373(8)	N3-C9	1.283(9)	O1-C7-C10	126.2(6)
O3-N1	1.226(11)	N3-C10	1.367(7)	N2-C8-C2	128.5(6)
O1-C1	1.368(12)	C1-C2	1.416(8)	O1-C7-C8	113.6(7)
N4-C10	1.325(10)	C7-C8	1.367(9)	N1-C4-C3	117.4(7)
N4-C11	1.482(9)	Cl(1)-C9	1.733(7)	C2-C2-C8	135.6(5)

The *in vitro* antitumor activity data of the target compounds were listed in Tables 2 and 3. The screening tested using doxorubicin as positive control and the screening model using human lung cancer cell line A549 cells and human leukemia cell line K562 cells. The A549 cell model selection method using SRB assay and K562 cell model selection method was MTT assay.

TABLE-2
EFFECTS OF TARGET COMPOUNDS INHIBITION FOR A549

TM	Final conc. (mol L ⁻¹)	Inhibition (%)	TM	Final conc. (mol L ⁻¹)	Inhibition (%)
3	1.00×10 ⁻³	84.16±0.18	7	1.00×10 ⁻³	0
	1.00×10 ⁻⁴	90.94±0.23		1.00×10 ⁻⁴	0
	1.00×10 ⁻⁵	83.86±0.90		1.00×10 ⁻⁵	0
4	1.00×10 ⁻³	70.68±5.00	8	1.00×10 ⁻³	0
	1.00×10 ⁻⁴	26.06±2.24		1.00×10 ⁻⁴	16.00±0.25
	1.00×10 ⁻⁵	0		1.00×10 ⁻⁵	26.73±15.88
5	1.00×10 ⁻³	14.52±8.27	9	1.00×10 ⁻³	0
	1.00×10 ⁻⁴	0		1.00×10 ⁻⁴	3.16±0.12
	1.00×10 ⁻⁵	0		1.00×10 ⁻⁵	6.10±6.18
6	1.00×10 ⁻³	41.06±1.46	Doxo-rubicin	1.00×10 ⁻⁶	74.47±4.16
	1.00×10 ⁻⁴	44.05±3.18		5.00×10 ⁻⁷	51.09±0.38
	1.00×10 ⁻⁵	7.59±6.42		2.50×10 ⁻⁷	36.35±1.08
				1.25×10 ⁻⁷	27.04±0.99
				6.25×10 ⁻⁸	18.23±3.25

Conclusion

A new benzofuran[3,2-*d*]pyrimidine derivative has been synthesized and characterized by EI-MS, ¹H NMR, ¹³C NMR and X-ray diffraction analysis. 2-Chloro-4-(*N,N*-diethyl-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine crystallized in the monoclinic system with P21/c space group. The crystal packing were stabilized by C-Cl... π interaction and π - π stacking resulting in a 2D supramolecular chain structures. The target compounds were screened *in vitro* anticancer activity

TABLE-3
EFFECTS OF TARGET COMPOUNDS INHIBITION FOR K562

TM	Final conc. (mol L ⁻¹)	Inhibition (%)	TM	Final conc. (mol L ⁻¹)	Inhibition (%)
3	1.00×10 ⁻³	88.66±10.80	7	1.00×10 ⁻³	15.30±2.51
	1.00×10 ⁻⁴	100.00±3.25		1.00×10 ⁻⁴	0
	1.00×10 ⁻⁵	100.00±5.60		1.00×10 ⁻⁵	4.25±5.87
4	1.00×10 ⁻³	42.84±1.25	8	1.00×10 ⁻³	0
	1.00×10 ⁻⁴	43.53±0.40		1.00×10 ⁻⁴	0
	1.00×10 ⁻⁵	15.76±2.51		1.00×10 ⁻⁵	0
5	1.00×10 ⁻³	18.35±0.07	9	1.00×10 ⁻³	46.55±1.33
	1.00×10 ⁻⁴	16.52±0.64		1.00×10 ⁻⁴	14.76±1.09
	1.00×10 ⁻⁵	13.90±3.30		1.00×10 ⁻⁵	/
6				1.00×10 ⁻⁵	74.47±4.16
	1.00×10 ⁻³	50.12±2.52		1.00×10 ⁻⁶	51.09±0.38
	1.00×10 ⁻⁴	39.72±1.94	Doxorubicin	8.00×10 ⁻⁷	36.35±1.08
	1.00×10 ⁻⁵	30.32±3.43		4.00×10 ⁻⁷	27.04±0.99
				2.00×10 ⁻⁷	18.23±3.25

using human lung cancer cell line A549 cells and human leukemia cell line K562 cells. 2,4-dichloro-8-nitro-benzofuran[3,2-*d*]pyrimidine have a good antitumor activity, but other compounds were not obvious. The structure-activity relationship worthy to be studied further.

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