Asian Journal of Chemistry; Vol. 26, No. 23 (2014), 7911-7914

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16723

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

YONG-ZHONG LU[1,2], QIAN-JUN ZHANG[1,*], YUN-QIAN ZHANG[1] and YING-CHUN ZHAO[1]

[1]College of Chemistry and Chemical Engineering, Guizhou University, Guiyang 550025, P.R. China
[2]School of Pharmaceutical Engineering, Guizhou Institute of Technology, Guiyang 550003, P.R. China

*Corresponding author: Tel: +86 851 8292313, E-mail: qianjunzhang@126.com

Received: 20 November 2013; *Accepted*: 27 December 2013; *Published online*: 15 November 2014; AJC-16262

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. There structures were confirmed by EI-MS, ^{1}H NMR, ^{13}C 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, $P2_1/c$ 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 kinase[1-3] (EGFR-TK) has recently been reported as a new target for studying antitumor activities. It's phosphorylation plays an important role in regulating tumor growth and metastasis. High expression of epidermal growth factor receptor has been associated with many type of tumor cell malignant proliferation. The study on inhibition of EGFR-TK has became a hot area of research. There is a variety of tyrosine kinase inhibitors are in development state, wherein the most common is quinazoline[4], pyrrolopyrimidine[5-6], thienopyrimidine[7] and pyridopyrimidine[4] compounds. Benzofuran [3,2-*d*]pyrimidine structure similar with those compounds, theoretically promote the compounds should also have a good biological activity.

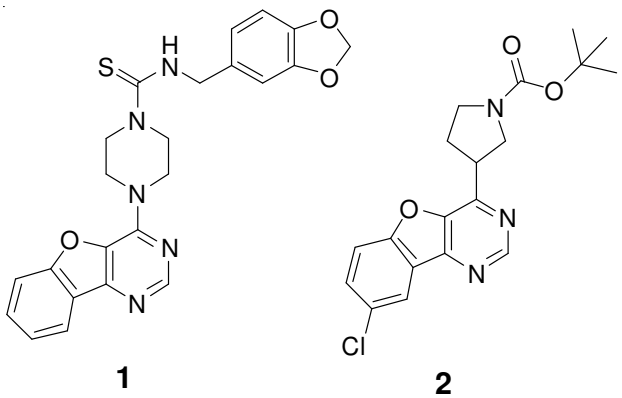


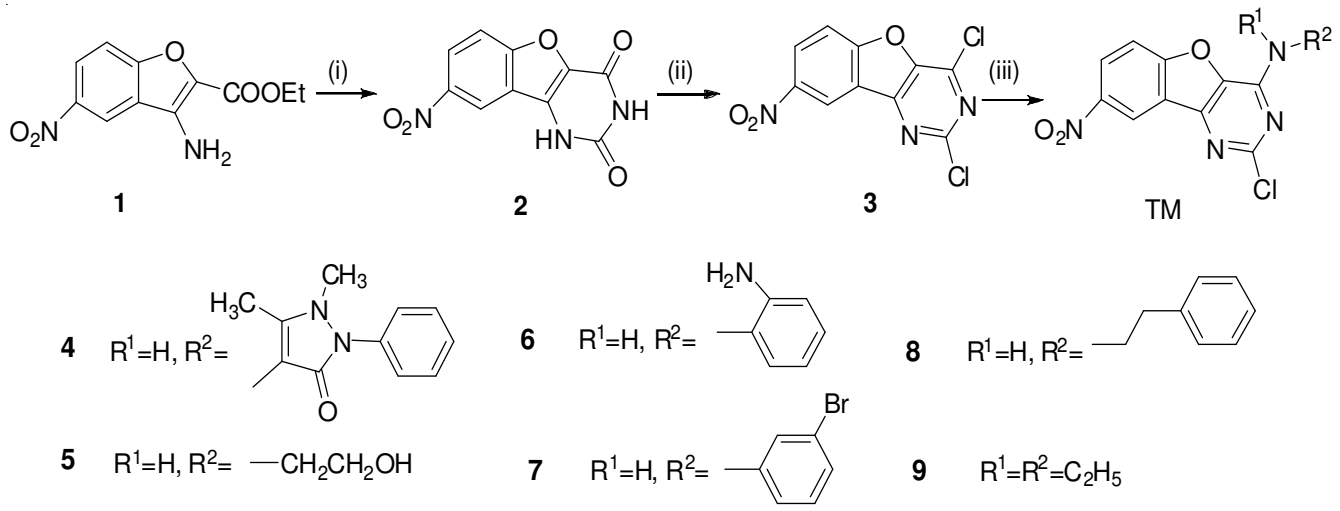
Fig. 1. Benzofuran[3,2-*d*]pyrimidine

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 H_4 modulators[9]. In order to find high biological 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, ^{1}H NMR, ^{13}C 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 ester[10] was prepared according to literature methods. Other reagents were AR grade and were used without further purification. The ^{1}H NMR spectrum was recorded on Bruker AV500 NMR spectrometer, $CDCl_3$ 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(1H,3H)-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-



(i): urea, 220 ℃; (ii): $POCl_3$, DMF; (iii): R-NH_2, ultrasonic

Scheme-I: Sythesis of compound TM

MS (*m/z*): 247[M^+], 204, 156, 148, 102, 75; ^{1}H 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**); ^{13}C 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 $POCl_3$ (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; ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 9.18 (d, 1H, *J* = 2.3Hz, Ar-**H**), 8.71 (dd, 1H, *J* = 2.3, 9.2Hz, Ar-**H**), 7.92 (d, 1H, *J* = 9.2Hz, Ar-**H**); ^{13}C NMR (125 MHz, $CDCl_3$): 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-antipyrine-4-amino)-8-nitro-benzofuran[3,2-d]pyrimidine (4): Compound **3** (142 mg, 0.5 mmol) was dissolved in dichloromethane (5mL) at a 50 mL round bottom flask, then, added 4-aminoantipyrine (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; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.59 (s, 1H, N-**H**), 8.91 (d, 1H, *J* = 2 Hz, Ar-**H**), 8.48 (dd, 1H, *J* = 2.4, 8.8Hz, Ar-**H**), 7.54-7.59 (m, 4H, Ar-**H**), 7.40-7.45 (m, 2H, Ar-**H**), 3.28 (s, 3H, N-C**H**$_3$), 2.20 (s, 3H, C-C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 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; ^{1}H NMR (400 MHz, DMSO- d_6): δ ppm 8.82 (d, 1H, *J* = 2.4Hz, Ar-H), 8.52 (dd, 1H, *J* = 2.4, 8.8Hz, Ar-**H**), 8.04 (d, 1H, J = 9.2Hz, Ar-**H**), 7.84 (brs, 1H, -O**H**), 4.85 (s, 1H, N-**H**), 3.59 (q, 4H, *J* = 7.5Hz, **-CH$_2$-CH$_2$-**); ^{13}C 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; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 9.99 (s, 1H, N-**H**), 8.89 (d, 1H, *J* = 1.6Hz, Ar-**H**), 8.55 (d, 1H, *J* = 8.8Hz, Ar-**H**), 8.04 (d, 1H, J = 8.4Hz, Ar-**H**), 7.12 (d, 1H, *J* = 7.6Hz, Ar-**H**), 7.05 (t, 1H, *J* = 7.6Hz, Ar-**H**), 6.78 (d, 1H, *J* = 8Hz, Ar-**H**), 6.60 (t, 1H, *J* = 7.4Hz, Ar-**H**), 5.10 (s, 2H, NH_2); ^{13}C 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-bromo-benzene (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; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 10.91 (s, 1H, N-**H**), 8.94 (d, 1H, *J* = 2.4Hz, Ar-**H**), 8.60 (dd, 1H, *J* = 2.4, 9.2Hz, Ar-**H**), 8.11-8.16 (m, 2H, Ar-**H**), 7.85 (d, 1H, *J* = 7.6Hz, Ar-**H**), 7.35-7.42 (m, 2H, Ar-**H**); ^{13}C 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; ^{1}H 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, **-CH_2-CH_2-**); ^{13}C 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; ^{1}H NMR (500 MHz, $CDCl_3$): 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-C**H**2-), 1.34-1.41 (m, 6H, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 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$_\alpha$ radiation (λ = 0.71073Å) 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 ≤ θ ≤ 25.99º from which 1231 [I >2σ(I)] reflection were corrected for Lorentz and polarization factors. The structure was solved by direct method using SHELXS-97[11] 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) Å^3, Z = 4, Mr = 320.73, Dc = 1.440 g/cm^3, 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*]py- rimidine 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.

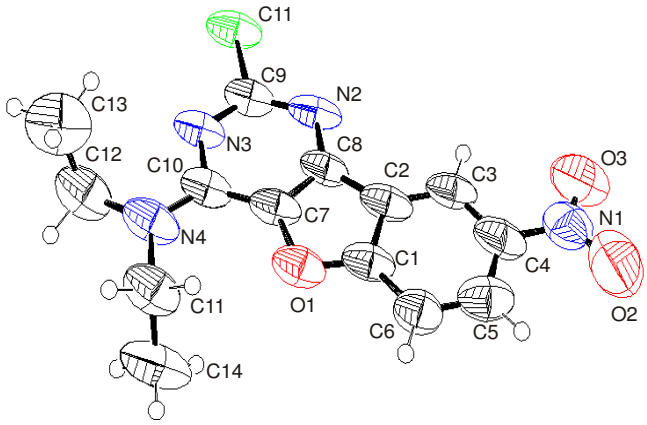


Fig. 2. Molecular structure of 2-chloro-4-(*N*,*N*-diethyl-amino)-8-nitro-benzofuran[3,2-*d*]pyrimidine

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, ^{1}H NMR, ^{13}C 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^{-3}	50.12±2.52	Doxorubicin	1.00×10^{-5}	74.47±4.16
	1.00×10^{-4}	39.72±1.94		1.00×10^{-6}	51.09±0.38
	1.00×10^{-5}	30.32±3.43		8.00×10^{-7}	36.35±1.08
				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.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support from the Innovation Foundation of Guizhou University Graduate (No. 2010014) and the Foundation of Guizhou Province China (No. [2011]2067). The authors also gratefully acknowledge the financial support from the Science Foundation of Guizhou Institute of Technology (No. XJZK20130806).

REFERENCES

1. C. Carmi, E. Galvani, F. Vacondio, S. Rivara, A. Lodola, S. Russo, S. Aiello, F. Bordi, G. Costantino, A. Cavazzoni, R.R. Alfieri, A. Ardizzoni, P.G. Petronini and M. Mor, *J. Med. Chem*., **55**, 2251 (2012).
2. C.-H. Wu, M.S. Coumar, C.-Y. Chu, W.-H. Lin, Y.-R. Chen, C.-T. Chen, H.-Y. Shiao, S. Rafi, S.-Y. Wang, H. Hsu, C.-H. Chen, C.-Y. Chang, T.-Y. Chang, T.-W. Lien, M.-Y. Fang, K.-C. Yeh, C.-P. Chen, T.-K. Yeh, S.-H. Hsieh, J.T.-A. Hsu, C.-C. Liao, Y.-S. Chao and H.-P. Hsieh, *J. Med. Chem*., **53**, 7316 (2010).
3. A. Garofalo, L. Goossens, B. Baldeyrou, A. Lemoine, S. Ravez, P. Six, M.-H. David-Cordonnier, J.-P. Bonte, P. Depreux, A. Lansiaux and J.-F. Goossens, *J. Med. Chem*., **53**, 8089 (2010).
4. J.W. Wu, W.T. Chen, G.X. Xia, J. Zhang, J.A. Shao, B.Q. Tan, C.C. Zhang, W.W. Yu, Q.J. Weng, H.Y. Liu, M. Hu, H.L. Deng, Y. Hao, J.K. Shen and Y.P. Yu, *ACS Med. Chem. Lett*., **4**, 974 (2013).
5. S. Sogabe, Y. Kawakita, S. Igaki, H. Iwata, H. Miki, D.R. Cary, T. Takagi, S. Takagi, Y. Ohta and T. Ishikawa, *ACS Med. Chem. Lett*., **4**, 201 (2013).
6. R.A. Ward, M.J. Anderton, S. Ashton, P.A. Bethel, M. Box, S. Butterworth, N. Colclough, C.G. Chorley, C. Chuaqui, D.A.E. Cross, L.A. Dakin, J.É. Debreczeni, C. Eberlein, M.R.V. Finlay, G.B. Hill, M. Grist, T.C.M. Klinowska, C. Lane, S. Martin, J.P. Orme, P. Smith, F. Wang and M.J. Waring, *J. Med. Chem*., **56**, 7025 (2013).
7. D.P. Sutherlin, L. Bao, M. Berry, G. Castanedo, I. Chuckowree, J. Dotson, A. Folks, L. Friedman, R. Goldsmith, J. Gunzner, T. Heffron, J. Lesnick, C. Lewis, S. Mathieu, J. Murray, J. Nonomiya, J. Pang, N. Pegg, W.W. Prior, L. Rouge, L. Salphati, D. Sampath, Q. Tian, V. Tsui, N.C. Wan, S. Wang, B.Q. Wei, C. Wiesmann, P. Wu, B.-Y. Zhu and A. Olivero, *J. Med. Chem*., **54**, 7579 (2011).
8. L. H. Hurley, D. Mahadevan, H. Han, D. J. Bearss, H. Vankayalapati, S. Bashyam, R. M. Munoz, S. L. Warner, C. K. Della, D. D. Von Hoff, C. L. Grand, PCT Int. Appl. WO 2005/037825, (2005).
9. N. Harris, C. Higgs, S. Wren, H. J. Dyke, S. Price, S. Cramp, PCT Int. Appl. WO 2006/050965, (2006).
10. M.G. Liu, Y.G. Hu, G.P. Cheng, T. Xie and Z. Yang, *J. China Three Gorges Univ. (Nat. Sci.)*, **2**, 174 (2007).
11. G.M. Sheldrick, SHELXL-97 Program for the Solution and Refinement of Crystal structures, University of Göttingen, Germany (1997).