Accepted Manuscript

Title: Synthesis and structure-activity relationships study of α-aminophosphonate derivatives containing a quinoline moiety

Authors: Xi-Feng Zhu, Jing Zhang, Shuo Sun, Yan-Chun Guo, Shu-Xia Cao, Yu-Fen Zhao

PII: S1001-8417(17)30068-2
DOI: http://dx.doi.org/doi:10.1016/j.cclet.2017.02.012
Reference: CCLET 3985

To appear in: *Chinese Chemical Letters*

Received date: 17-2-2017
Accepted date: 17-2-2017

Please cite this article as: Xi-Feng Zhu, Jing Zhang, Shuo Sun, Yan-Chun Guo, Shu-Xia Cao, Yu-Fen Zhao, Synthesis and structure-activity relationships study of α-aminophosphonate derivatives containing a quinoline moiety, Chinese Chemical Letters http://dx.doi.org/10.1016/j.cclet.2017.02.012

Original article

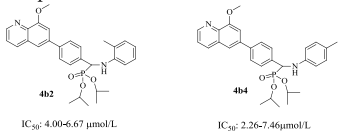
Synthesis and structure-activity relationships study of α-aminophosphonate derivatives containing a quinoline moiety

Xi-Feng Zhu[a], Jing Zhang[a], Shuo Sun[b], Yan-Chun Guo[a, *], Shu-Xia Cao[a,*], Yu-Fen Zhao [a,c]

[a] *The College of Chemistry and Molecular Engineering, the Key Laboratory of Chemical Biology and Organic Chemistry of Henan Province, Zhengzhou University, Zhengzhou 450001, China*
[b] *Department of Chemistry, International College of Zhengzhou University, Zhengzhou University, Zhengzhou 450001, China*
[c] *Department of Chemistry, College of Chemistry and Chemical Engineering, the Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen 361005, China*

∗ Corresponding authors.
E-mail addresses*: ycguo@zzu.edu.cn (Y.-C. Guo); csx@zzu.edu.cn (S.-X. Cao)*

Graphical absrtract



Two series of α-aminophosphonate derivatives containing a quinoline moiety have been designed, synthesized and evaluated for cytotoxic activity against Eca109 and Huh7 cancer cell lines *in vitro*. Among them, compounds **4b2** and **4b4** were found to be more active than Sunitinib against both of two cancer cell lines.

ABSTRACT
Two series of α-aminophosphonate derivatives containing a quinoline moiety have been designed and synthesized by introducing bioactive quinoline scaffold to α-aminophosphonate. The *in vitro* cytotoxic activities of target compounds were first investigated against two human cancer cell lines including Eca109 and Huh7 by MTT assay. Results revealed that most of target compounds exhibited moderate to high antitumor activities against the tested cancer cell lines and some demonstrated more potent inhibitory activities compared with Sunitinib. Among them, compounds **4b2** and **4b4** containing methyl-substituted aniline group were found to be more active than Sunitinib against both of two cancer cell lines, with IC_{50} in the range of 2.26 μmol/L-7.46 μmol/L.

Keywords: Quinoline, α-Aminophosphonate , Synthesis, Antitumor activity, In vitro.

1. Introduction

Cancer has become an important public health concern and a significant cause of death in the human population [1]. Cancer incidence and mortality have been increasing in China, making cancer the leading cause of death since 2010 and a major public health problem in the country [2]. Lung cancer was the leading cause of death in China followed by liver cancer, stomach cancer, esophageal cancer and colorectal cancer [3]. Despite many efforts to fight against cancer, the successful treatment of certain tumor types continues to be a challenge owing to their aggressiveness, the mechanisms of malignant cell metastasis, chemoresistance, and the lack of selectivity of some drugs [4]. Therefore, the development of novel anticancer agents with high efficacy and minimal side effects by synthesizing small and simple molecules is indispensable.

N-heterocyclic compounds are very crucial in drug design [5-7]. Compounds containing quinoline rings are extensively found in several classes of natural and synthetic biologically active compounds [8-10]. Quinoline-bearing structures are well-known due to their broad biological activities [11], such as anticancer [12], antifungal [13], antibacterial [14], antitubercular [15] and antimalarial [16] that have been used in traditional medicine as a remedy. Recently, quinoline-based azolyalkylquinolines bearing different azole groups, such as benzothiazole (SRA-HX-1), tetrazole (SRA-HX-2), and 1,2,4-triazole (SRAHX-3), have been synthesized and reported as potent antitumor agents for breast cancer cells *in vitro* [17]. 8-Hydroxyquinoline derivative (8-hydroxy-2-quinolinecarbaldehyde) has been reported to possess strong antitumor activities against human cancer cell lines and hepatocellular carcinoma Hep3B [18]. Moreover, a novel quinoline derivative **83b1** (8-(4-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydro-2-methylquin-oline, has shown to inhibit cancer growth in human esophageal squamous cell carcinoma.[19].The structure of the quinoline derivative is depicted in Fig. 1.

α-Aminophosphonic acids and their corresponding α-amino phosphonates have received much attention in organic and medicinal chemistry because of their pharmacological properties and clinical applications [20-22]. Some of them have been used as potent enzyme inhibitors, antimicrobial, antitumor, antioxidant and antiviral agents [23-28]. It was reported that introduction of

aminophosphonate group to pharmacy core is able to improve the antitumor activity and many aminophosphonate derivatives have demonstrated potent inhibitory activities against human tumors [29,30].

Existing thieno[2,3-d]pyrimidine in one *α*-amino phosphonate molecule can exhibit valuable anti-tumor activity [31]. These special scaffold compounds strongly provoked our interest to continuously explore this kind of compounds. Based on this strategy, we lead to the proposal to incorporate quinoline scaffold into the *α*-aminophosphonate. Then two series of *α*-aminophosphonate derivatives containing a quinoline moiety were synthesized (Scheme 1). The *in vitro* cytotoxic activities of target compounds were tested against esophageal cancer (Eca109) and hepatocellular carcinoma (Huh7) by MTT method. This represents the first report about the synthesis and *in vitro* antitumor activity evaluation of α-aminophosphonate derivatives containing a quinoline moiety.

2. Results and discussion

As shown in Table 1, the results of preliminary bioassay reveal that most of target compounds exhibited moderate to strong antitumor activity against human cancer cell lines Eca109 and Huh7 cells. Some of them demonstrated more potent antitumor activities than the reference drug. Sunitinib (SU) is a multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenic activity. Recently, Sunitinib has been used to treat solid cancers, such as renal cell carcinoma, gastrointestinal stromal tumors, neuroendocrine tumors in several Phase II/III trials, lung cancer, pancreatic cancer, chondrosarcoma, esophageal cancer, bladder cancer, glioma, aggressive fbromatosis, and also showed potential efficacy in progression-free survival and overall survival [32]. Furthermore, research shows that Sunitinib has same antitumor activity in hepatocellular carcinoma [33]. So Sunitinib was selected as the positive control.

In Eca109 assay, compounds **4a1**, **4a2**, **4a5**, **4a7**, **4a12**, **4a13**, **4b1** and **4b8** exhibited preferable cytotoxic activity than the Sunitinib (IC_{50} = 16.54 μmol/L), implying favorable inhibition activities of these compounds on Eca109 cell. Besides, compounds **4a3**, **4a4**, **4b2**, **4b3**, **4b4** and **4b7** were approximately 2-3 times potent than Sunitinib. Interestingly, compound **4a11**, the most promising compound, showed significant inhibitory preference to Eca109 with IC_{50} value of 3.41 μmol/L, about 5 times more potent than Sunitinib. In Huh7 assay, compounds **4a3**, **4a4**, **4a7**, **4b2**, **4b3**, **4b4** and **4b8** showed potent antitumor activity. Especially, compounds **4b2** and **4b4** (IC_{50} = 2.26 μmol/L -4.00 μmol/L) showed more potent activity against Huh7 than Sunitinib (IC_{50} = 5.27 μmol/L). Among all the target compounds, it is worth noting that compounds **4b2** and **4b4** which possess methyl-substituted aniline group were found to be more active than Sunitinib against both of two cancer cell lines, with IC_{50} in the range of 2.26 μmol/L-7.46 μmol/L.

The antitumor data also indicate that the substituents of phosphonate have no apparent influence on antitumor activity to Eca109 and Huh7 cells. For example, when R was Ph and R´ was Et, compound **4a2** exhibited good antitumor activities against Eca109 and Huh7 cells, with IC_{50} values of 11.18, 10.78 μmol/L, respectively. The inhibitory activity of compound **4b2**, where the phosphonate was substituted by *i*-Pr, was litter higher than that of **4a2** against Eca109 and Huh7 with IC_{50} values of 6.67, 4.00 μmol/L, respectively. The same trend was observed for compounds **4a3**/**4b3**, **4a4**/**4b4** and **4a8**/**4b8** against Eca109 and Huh7 cells. While compound **4a5** with 3-F (R) and Et (R´) showed antitumor activity against Huh7 with IC_{50} values of 11.94 μmol/L. Compound **4b5** with 3-F (R) and *i*-Pr (R´) had a lower activity (IC_{50} = 14.4 μmol/L) than that of **4a5**. This also applied to compounds **4a11**/**4b11**, **4a12**/**4b12** against Eca 109 and Huh7 cells.

Different substituents on the phenyl ring had a great influence in antitumor activity. Compound **4a1** and **4b1** with unsubstituted aryl ring exhibited good antitumor activities against Eca109 and Huh7 cells, with IC_{50} values of 12.68, 17.93 and 14.38, 10.18 μmol/L, respectively. Compounds **4a2**-**4a4** and **4b2**-**4b4** containing methyl-substituted aniline group showed more potent antitumor activities against the tested cancer cell lines with IC_{50} in the range of 2.26-11.18 μmol/L. Compounds **4a7**, **4b7** and **4b8** with 3-chlorophenyl and 4-chlorophenyl moiety showed enhanced inhibitory activity against Eca109 and Huh7 cells, as well as compounds **4a11**, **4b11** and **4a12** with 3-nitrophenyl and 4-nitrophenyl moiety. Besides, *meta*-substituted derivatives showed more potent activity than *para*-substituted derivatives (**4a7** *vs.* **4a8**, **4a11** *vs.* **4a12**, **4b11** *vs.* **4b12**). These results indicated that methyl-, chloro- and nitro-substituent at the phenyl ring is favorable for activity. However, compounds **4a6**, **4b5** and **4b6** with 3-fluoro phenyl and 4-fluoro phenyl moiety had less cytotoxic activity against Eca109 and Huh7 cells. The antitumor activities of compounds **4a9**, **4a10**, **4b9** and **4b10** with 3-methoxyl phenyl and 4-methoxyl phenyl moiety were decreased dramatically. These results indicated that methoxyl at the phenyl ring are unfavorable. When aromatic amine group was substituted by benzylamine or 2-aminopyridine, the target compounds **4a13, 4a14**, **4b13** and **4b14** had less or inconspicuous cytotoxic activity. The bioactive assay implied that the substitutions on the phenyl ring significantly affect the antitumor activity of the target compounds.

3. Conclusion

In summary, two series of *α*-aminophosphonate derivatives containing a quinoline moiety were synthesized efficiently and their cytotoxic activities against two human cancer cell lines including Eca109 and Huh7 were evaluated for the first time. Moreover, based on experimental results, the structure-activity relationship was analyzed. Biological assays revealed that the substitutions on the phenyl ring influenced the antitumor activity remarkably, while the substitutes of phosphonate had no apparent influence on the antitumor activity. Among them, compound **4a11** showed excellent inhibitory activity to Eca109, approximately 5-fold more active than Sunitinib. Additionally, compounds **4b2** and **4b4** containing methyl-substituted aniline group were the most efficient against both of

the tested cancer cell lines. All the above results demonstrated that these compounds could be promising lead compounds of novel antitumor drugs. Further studies will focus on structural optimization and precise mechanism of action of these compounds.

4. Experimental

Commercial reagents and solvents were used as received without further purification unless otherwise specified. Toluene was freshly distilled over sodium with the use of diphenyl ketone as an indicator under nitrogen. High resolution mass spectra (HRMS) were obtained with a Q-Tof mass spectrometer using the ESI technique. NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. ^{1}H and ^{13}C chemical shifts were quoted in DMSO-d_6 with tetramethylsilane (TMS) as the internal standard, and ^{31}P chemical shifts were acquired in DMSO-d_6 with H_3PO_4 as the internal standard. Column chromatography was performed on silica gel 200-300 mesh.

The target compounds **4a1-4a14 and 4b1-4b14** were prepared as shown in Scheme 1. Compound **1** was synthesized according to well-established literature procedures [34]. Commercially available 4-bromo-2-methoxyaniline treated with glycerin in the presence of 3-nitrobenzenesulfonic acid with concentrated sulfuric acid to afford 6-bromo-8-methoxy-quinoline (**1**). Compound **1** then underwent Suzuki cross-coupling reaction with 4-formylphenylboronic acid in toluene, using $Pd(PPh_3)_4$ as a catalyst to give intermediate **2** with excellent yield. Various methods for the synthesis of α-aminophosphonates were reported. To our best knowledge, one pot Mannich-type process of carbonyl compounds, amines, and dialkyl phosphonate in the presence of a Lewis acid remains the most efficient, simple, general and high yielding method. Therefore, the reaction of intermediate **2** with diethyl or diisopropyl phosphonate and various substituted amines in the presence of $FeCl_3$ in absolute ethanol generated target compounds (**4a1**~**4a10** and **4b1**~**4b10**) with good yields (Pathway 1). Unfortunately, the scope of this reaction was limited and the target compounds (**4a11**~**4a14** and **4b11**~**4b14**) were obtained by the reaction of intermediate **2**, various amine with dialkyl phosphonate in anhydrous toluene by one pot synthesis without any catalyst (Pathway 2). All the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, IR and high resolution mass spectrometry, respectively (see Supporting information for structure characterization).

For preliminary screening of antitumor candidates, the cytotoxic activities of target compounds were evaluated against two human cancer cell lines Eca109 and Huh7 using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The cancer cell lines seeded into the 96-well plate (100 μL each well) were incubated at 37 ºC in a 5% CO_2 incubator. After 24 h, the target compounds at different concentrations were added to the culture medium and the cell cultures were continued for 72 h. The cultured cells were mixed with 10 μL 5 mg/mL of MTT solution and incubated for 4 h at 37 ºC. The formazan crystals were dissolved in 100 mL DMSO each well, and the absorbency at 570 nm and 630 nm (for the reference wavelength) was measured with microplate reader. Each experiment was performed at least three times. The results expressed as IC_{50} (inhibitory concentration 50%) were the averages of three determinations and calculated by using the GraphPad Prism 6.0 software. The results were illustrated in Table 1 with Sunitinib as the positive control.

Acknowledgment

We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (Nos. 21105091, 21172201).

References

[1] A. Jemal, F. Bray, M.M. Center, et al., Global cancer statistics, CA Cancer J. Clin. 61 (2011) 69-90.
[2] China National Statistical Bureau, China Statistical Yearbook-2010, China Statistics Press, Beijing, China, 2010.
[3] W.Q. Chen, R.S. Zheng, H.M. Zeng, et al., Annual report on status of cancer in China, 2011, Chin. J. Cancer Res. 27 (2015) 2-12.
[4] G. Colombano, C. Travelli, U. Galli, et al., A novel potent nicotinamide phosphoribosyltransferase inhibitor synthesized via click chemistry, J. Med. Chem. 53 (2010) 616-623.
[5] V. Spanò, A. Montalbano, A. Carbone, et al., Synthesis of a new class of pyrrolo[3, 4-*h*]quinazolines with antimitotic activity, Eur. J. Med. Chem. 74 (2014) 340-357.
[6] R. Dua, S. Shrivastava, S.K. Sonwane, S.K. Srivastava, Pharmacological significance of synthetic heterocycles scaffold: a review, Adv. Biol. Res. 5 (2011) 120-144.
[7] P. Diana, A. Carbone, P. Barraja, et al., Synthesis and antitumor activity of 3-(2-phenyl-1, 3-thiazol-4-yl)-1 *H*-indoles and 3-(2-phenyl-1, 3-thiazol-4-yl)-1 *H*-7-azaindoles, ChemMedChem 6 (2011) 1300-1309.
[8] K.D. Thomas, A.V. Adhikari, N.S. Shetty, Design, synthesis and antimicrobial activities of some new quinoline derivatives carrying 1, 2, 3-triazole moiety, Eur. J. Med. Chem. 45 (2010) 3803-3810.
[9] P. Barraja, P. Diana, A. Montalbano, et al., Pyrrolo[3, 4-*h*]quinolinones a new class of photochemothera peutic agents, Bioorg. Med. Chem. 19 (2011) 2326-2341.
[10] K. Kaur, M. Jain, R.P. Reddy, R. Jain, Quinolines and structurally related heterocycles as antimalarials, Eur. J. Med. Chem. 45 (2010) 3245-3264.
[11] A. Marella, O.P. Tanwar, R. Saha, et al., Quinoline: a versatile heterocyclic, Saudi Pharm. J. 21 (2013) 1-12.
[12] O. Afzal, S. Kumar, M.R. Haider, et al., A review on anticancer potential of bioactive heterocycle quinoline, Eur. J. Med. Chem. 97 (2015) 871-910.
[13] R. Musiol, J. Jampilek, V. Buchta, et al., Antifungal properties of new series of quinoline derivatives, Bioorg. Med. Chem. 14 (2006) 3592-3598.
[14] P. Palit, P. Paira, A. Hazra, et al., Phase transfer catalyzed synthesis of bis-quinolines: antileishmanial activity in experimental visceral leishmaniasis and in vitro antibacterial evaluation, Eur. J. Med. Chem. 44 (2009) 845-853.
[15] R.S. Keri, S.A. Patil, Quinoline: a promising antitubercular target, Biomed Pharmacother. 68 (2014) 1161-1175.
[16] R.R. Soares, J.M.F.D. Silva, B.C. Carlos, et al., New quinoline derivatives demonstrate a promising antimalarial activity against *Plasmodium falciparum* in vitro and *Plasmodium berghei* in vivo, Bioorg. Med. Chem. Lett. 25 (2015) 2308-2313.

[17] S. Rasoul-Amini, A. Khalaj, A. Shafiee, et al., Anti-tumor activity of new quinoline derivatives in human breast cancer T47D cells, Int. J. Cancer Res. 2 (2006) 102-108.
[18] S.H. Chan, C.H. Chui, S.W. Chan, et al., Synthesis of 8-ydroxyquinoline derivatives as novel antitumor agents, ACS Med. Chem. Lett. 4 (2013) 170-174.
[19] I.H.Y. Pun, D. Chan, S.H. Chan, et al., Anti-cancer effects of a novel quinoline derivative 83b1 on human esophageal squamous cell carcinoma (ESCC) through down-regulation of COX-2 mRNA and PGE2, Cancer Res. Treat. 18 (2016), doi: 10.4143/crt.2016.190.
[20] A. Mucha, P. Kafarski, Ł. Berlicki, Remarkable potential of the α-aminophosphonate/phosphinate structural motif in medicinal chemistry, J. Med. Chem. 54 (2011) 5955-5980.
[21] W. Han, P. Mayer, A.R. Ofial, Iron-catalyzed oxidative mono- and bis-phosphonation of *N*, *N*-dialkylanilines, Adv. Synth. Catal. 352 (2010) 1667-1676.
[22] P. Kafarski, B. Lejczak, Aminophosphonic acids of potential medical importance, Curr. Med. Chem. 1 (2001) 301-312.
[23] S.M. Agawane, J.M. Nagarkar, Nano ceria catalyzed synthesis of α-aminophosphonates under ultrasonication, Tetrahedron Lett. 52 (2011) 3499-3504.
[24] L. Pan, X.H. Liu, Y.X. Shi, B.L. Wang, S.H. Wang, Solvent- and catalyst-free synthesis and antifungal activities of α-aminophosphonate containing cyclopropane moiety, Chem. Res. Chin. Univ. 26 (2010) 389-393.
[25] S.A. Dake, D.S. Raut, K.R. Kharat, et al., Ionic liquid promoted synthesis, antibacterial and in vitro antiproliferative activity of novel α-aminophosphonate derivatives, Bioorg. Med. Chem. Lett. 21 (2011) 2527-2532.
[26] G.Y. Yao, M.Y. Ye, R.Z. Huang, et al., Synthesis and antitumor activities of novel rhein α-aminophosphonates conjugates, Bioorg. Med. Chem. Lett. 24 (2014) 501-507.
[27] G.S. Reddy, K.U.M. Rao, C.S. Sundar, et al., Neat synthesis and antioxidant activity of α-aminophosphonates, Arab. J. Chem. 7 (2014) 833-838.
[28] N. Gangwar, V.K. Kasana, Tartaric acid-catalyzed synthesis of α-aminophosphonates under solvent-free conditions, Synth. Commun. 41 (2011) 2800-2804.
[29] M.Y. Ye, G.Y. Yao, J.C. Wei, et al., Synthesis, cytotoxicity, DNA binding and apoptosis of rhein-phosphonate derivatives as antitumor agents, Int. J. Mol. Sci. 14 (2013) 9424-9439.
[30] X.C. Huang, M. Wang, Y.M. Pan, et al., Synthesis and antitumor activities of novel α-aminophosphonates dehydroabietic acid derivatives, Bioorg. Med. Chem. Lett. 23 (2013) 5283-5289.
[31] Y.C. Guo, J. Li, J.L. Ma, et al., Synthesis and antitumor activity of *α*-aminophosphonate derivatives containing thieno[2, 3-d]pyrimidines, Chin. Chem. Lett. 26 (2015) 755-758.
[32] S.K. Kim, W.P. Ding, L. Zhang, W. Tian, S.Y. Chen, Clinical response to sunitinib as a multitargeted tyrosine-kinase inhibitor (TKI) in solid cancers: a review of clinical trials, Onco Targets Ther. 7 (2014) 719-728.
[33] D. Koeberle, M. Montemurro, P. Samaras, et al., Continuous Sunitinib treatment in patients with advanced hepatocellular carcinoma: a Swiss group for clinical cancer research (SAKK) and Swiss association for the study of the liver (SASL) multicenter phase II trial (SAKK 77/06), Oncologist 15 (2010) 285-292.
[34] L.L. Zhang, E. Meggers, An extremely stable and orthogonal DNA base pair with a simplified three-carbon backbone, J. Am. Chem. Soc. 127 (2005) 74-75.

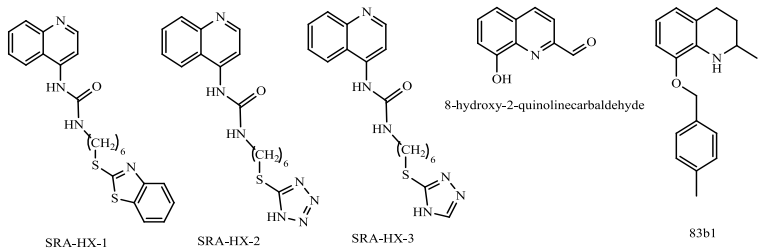
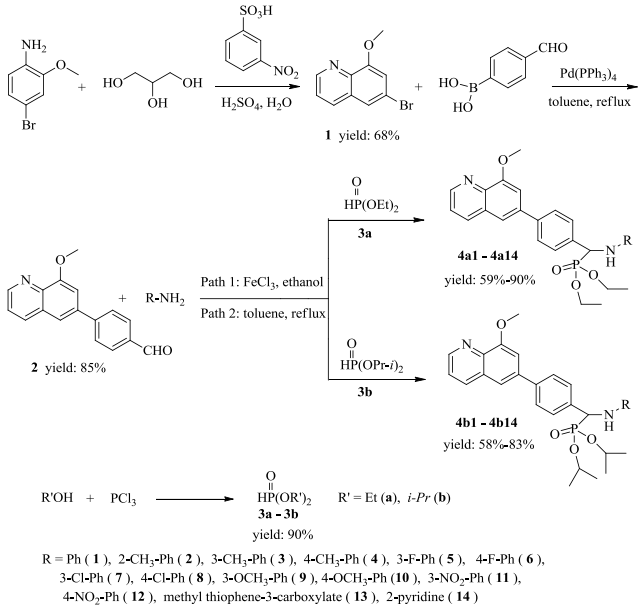


Fig 1 Quinoline derivatives



Scheme 1 The synthetic route for target compounds.

Table 1

The cytotoxic activity of target compounds against human cancer cell lines

Compd.	IC_{50} [a] (μmol/L)		Compd.	IC_{50} [a] (μmol/L)		Compd.	IC_{50} [a] (μmol/L)	
	Eca109 [b]	Huh7 [c]		Eca109 [b]	Huh7 [c]		Eca109 [b]	Huh7 [c]
4a1	12.68 ± 1.28	17.93 ± 1.08	**4b1**	14.38 ± 1.13	10.18 ± 1.06	**4a11**	3.41 ± 1.50	11.86 ±1.06
4a2	11.18 ± 1.25	10.78 ± 1.10	**4b2**	6.67± 1.24	4.00 ± 1.14	**4a12**	10.60 ± 1.18	11.70 ± 1.08
4a3	7.13± 1.23	8.28 ± 1.07	**4b3**	4.84 ± 1.28	6.65 ± 1.07	**4a13**	11.49 ± 1.34	12.43 ±1.10
4a4	9.03 ± 1.24	9.40± 1.09	**4b4**	7.46 ± 1.11	2.26 ± 1.20	**4a14**	75.38 ± 1.21	39.11
4a5	11.44 ± 1.18	11.94 ± 1.07	**4b5**	24.16 ± 1.15	14.40 ± 1.04	**4b11**	18.10 ± 1.13	12.43 ±1.07
4a6	27.72 ± 1.25	10.16 ± 1.17	**4b6**	27.56 ± 1.29	10.76 ± 1.04	**4b12**	62.92 ± 1.79	46.12
4a7	10.12 ± 1.23	5.46 ± 1.10	**4b7**	5.97 ± 1.19	10.31 ± 1.07	**4b13**	>50.00	82.77
4a8	57.79 ± 1.70	37.01 ± 1.21	**4b8**	11.37 ± 1.20	9.00 ± 1.05	**4b14**	91.58 ± 1.43	72.53
4a9	127.30 ± 1.94	77.79	**4b9**	>50.00	27.12	Sunitinib [d]	16.54 ± 1.17	5.27
4a10	125.40 ± 2.07	21.89 ± 1.10	**4b10**	>50.00	72.00			

[a] IC_{50}: Concentration which produces 50% inhibition of proliferation.

[b] Eca109: Esophageal cancer

[c] Huh7: Hepatocellular carcinoma

[d] Positive control, a small-molecule multi-targeted receptor tyrosine kinase inhibitor with activity against many human cancer cell lines.