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Synthesis, Crystal Structure and Interaction with Bovine Serum Albumin (BSA) of Two α-Aminophosphonic Acids Derivatives

Wei Huang[1] and Wen-Ling Wang[1*]

[1]School of Pharmacy, Yancheng Teachers' University, Yancheng, 224051, People's Republic of China.

Authors' contributions

This work was carried out in collaboration between both authors. Author WH synthesis the compound 1 & 2, performed the statistical analysis and wrote the first draft of the manuscript. Author WW designed the study, managed the analyses of the study and revised the manuscript. Both authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Two α-amino-phosphonate derivatives (***1*** & ***2***) were synthesized and their compositions and structures were characterized by Elemental Analysis (EA), FT-IR Spectrascopy (FT-IR), Electrospray Ionization Mass Spectrometry (ESI-MS), Nuclear Magnetic Resonance (NMR, ^{1}H, ^{13}C and ^{31}P) and X-ray crystallography. Compound ***1*** & ***2*** were crystallized in monoclinic system with the space group P2(1)/n and P2(1)/c, respectively. The interaction effects of two α-aminophosphonate derivatives (*1* & *2*) with BSA were investigated and the binding constants were 1.07×10^{4} M^{-1}, 1.68×10^{4} M^{-1}, respectively. Besides, the values of n were indicated that 1:1 complex was formed between BSA and 1&2.

Keywords: α-amino-phosphonate derivatives; characterizations; crystal structure; interaction; BSA.

**Corresponding author: E-mail: wangwenl2018@163.com;*

ABBREVIATIONS

1, *Diethyl (4-chlorophenylamino) (4-fluorophenyl) methylphosphonate ($C_{17}H_{20}ClFNO_3P$)*
2, *Diethyl (4-nitrophenylamino) (4-hydroxyphenyl) methylphosphonate ($C_{17}H_{21}N_2O_6P$)*

1. INTRODUCTION

The formation of phosphorus-carbon bond has been received intense interest in recent years because the bond plays important role in a wide of biological properties and is able to function as a-aminocarboxylic acid surrogates [1-4]. It is reported that α-aminophosphonates could act as herbicides [5] or antibacterial [6], antiviral [7] and antitumor agents [8]. The potential of α-aminophosphonates as enzyme inhibitors pharmacological agents has also been established [9-15]. Our previous studies have showed that some α-aminophosphonates could potently inhibit PTP1B and TCPTP with lower cytotoxicity [16]. Do the α-aminophosphonate derivatives interact with BSA and lead to the antiproliferation and apoptosis of tumor cells?

Bovine serum albumin (BSA) is the most important carrier protein in the living body and the most abundant carrier protein in the plasma. Therefore, studying the interaction between drugs and BSA could provide a basis for drugs design and development [17-18]. BSA contains a variety of coordination groups and could bind to a number of both endogenous and exogenous compounds. Therefore, BSA could store and transport certain drugs and small bioactive small molecules. Therefore, target BSA for the design of drug have been paid to special attention.

In this paper, two new α-aminophosphonate derivatives ***(1 & 2)*** with similar structure as the reported compound [16,19,20] are synthesized and characterized (Scheme 1 and Supplementary Information). Structural identification of the compound 1 & 2 were confirmed by IR, EAs ^{1}H-NMR, ^{31}P-NMR, ESI-MS spectroscopy and X-ray single crystal diffraction (Supplementary Information Fig. S1-S8). The interaction with BSA were investigated.

2. EXPERIMENTAL

2.1 Materials and Instrumentation

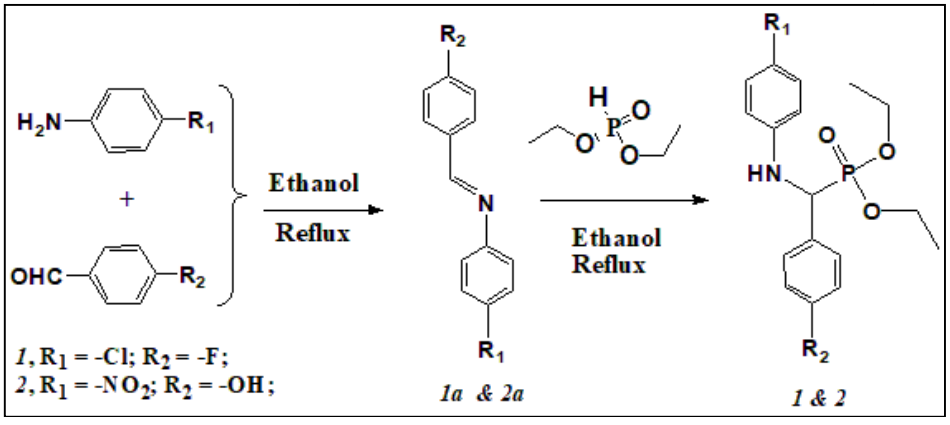
All the materials and instrumentations were purchased from commercial and used without further purification. Details information of materials and instrumentations were given in the Supplementary Material.

2.2 X-ray Crystallographic Studies

Single crystals of compound ***1 & 2*** were mounted on glass fibers for data collection. Detailed information were given in the Supplementary Material.

2.3 Synthesis of α-aminophosphonates

From Scheme 1, α-aminophosphonates ***1 & 2*** were prepared by the early reported methods with certain modified [16,19,20]. First, 20 mmol of aromatic amine and 20 mmol of aromatic benzaldehyde derivative were added to a 20 mL of C_2H_5OH and allowed to react for 2h. Schiff



Scheme 1. Synthesis of *1 & 2* in two-step by Pudovik reaction

Bases were obtained after being cooled to room temperature (Yield: 1a 84.2%, 2a 79.8%); Second, 22 mmol of diethyl phosphonate diluted in 10 mL of C_2H_5OH was added into 20 mmol Schiff base compounds in 20 mL of C_2H_5OH. Left the mixture refluxed for another 15-18 h with constant stirring. Yellow solids of 1 or 2 were obtained. The yellow block crystal ***(1 & 2)*** were collected after a week from C_2H_5OH ***(1)*** and C_2H_5OH/H_2O***(2).***

Diethyl (4-chlorophenylamino) (4-fluorophenyl) methylphosphonate *(1)*

Yield: 2.92 g, 38.4%. Colorless crystals were obtained from ethanol. EAs: calcd/found (%) for $C_{17}H_{20}ClFNO_3P$(***1***): C 54.92/54.88, H 5.42/6.04, N 3.77/3.77. IR(cm^{-1}): 3290 *v*(O-H, N-H), 2982 v(C_α-H), 1221 v(P=O), 1053 and 1025 v(P-O-C), 973 (C-P). ^{31}P NMR (D_2O/ethanol, ppm): δ 24.774. ^{1}H NMR(CD_3OD, ppm): δ 0.949-1.116(t, 6H, $2CH_3$), 4.811(m, 2H, -OCH_2-), 5.200 (s, 1H, Ar-NHR), 6.518-7.794 (m, 8H, aromatic H). Exact mass for ***1***: 371.0853, ESI-MS: [***1***-H]$^-$ (m/z, 370.0984).

Diethyl (4-nitrophenylamino) (4-hydroxyphenyl) methylphosphonate *(2)*

Yield: 2.24 g, 30%. Colorless crystals were obtained from ethanol/H_2O. EAs: calcd/found(%) for $C_{17}H_{21}N_2O_6P$: C 53.69/53.74, H 5.57/5.94, N 7.37/7.37. IR(cm^{-1}): 3422 and 3318 v(O-H, N-H), 2983 v(C_α-H), 1220 v(P=O), 1056 and 1016 v(P-O-C), 970 v(C-P). ^{31}P NMR(D_2O/ethanol, ppm): δ 22.283. ^{1}H-NMR(DMSO, ppm): δ 0.949-1.116 (t, 6H, 2-CH_3), 6.518-7.794 (m, 8H, aromatic H), 5.11(m, 2H, -OCH_2-), 5.11 (s, 1H, NH-), 4.811 (d, 1H, -CH-). Exact mass for ***2***: 380.1137, ESI-MS: [***2***+H]$^+$ (m/z, 381.1121).

3. RESULTS AND DISCUSSION

3.1 Crystal Structure of *1 & 2*

The Crystal structures of ***1*** & ***2*** were experimented to grow in different organic solvents or mix-solvents and the suitable crystals were obtained. Crystallographic data and hydrogen bonds are listed in Table 1 and Table S1 (shown in Supplementary information).

1 & ***2*** were monoclinic system with the space group P 21/n, P2 (1)/c, respectively. From Fig.1&2, two -O-CH_2CH_3 groups, one C_α atom, and a double bond O atom to form the tetrahedral geometries of P atoms. Besides, C_α atoms were responsible for the existence of optically activity, similar to the early report [16,19,20].

The plane of the arylamine and benzaldehyde derivatives form a dihedral angle of 88.44 (0.19)° and 81.84 (0.10)°, respectively. When the -CH_2CH_3 bonded to P was substituted by hydroxy group, the dihedral angle between the 2-hydroxyphenyl and pyridine rings is 54.9 (1)° [21]. The bond lengths of C_α-P and P=O were almost comparable to the similar structures [16,19,20,22]. There were a lot of weak interactions exited in compound ***1*** & ***2***, such as N-H···O, O-H···O, C-H···O, C-H···π and N-O···π, resulting in stabilization in the structures(shown in Figs. 4-5).

Table 1. Crystallographic data for 1 & 2

Complex	***1***	***2***		***1***	***2***
Empirical formula	$C_{34}H_{40}Cl_2F_2N_2O_6P_2$	$C_{17}H_{21}N_2O_6P$	*a*(Å)	13.4882(7)	12.2302(5)
CCDC	1405042	1405038	b(Å)	18.1802(8)	8.5754(3)
Formula weight	743.52	380.33	c(Å)	16.1967(8)	17.8559(7)
Temperature	296(2) K	296(2) K	*α*(°)	90	90
Wavelength	0.71073 A	0.71073 A	*β*(°)	98.244(2)	100.193(2)
Crystal system	monoclinic	monoclinic	*γ*(°)	90	90
space group	P2(1)/n	P2(1)/c	V(Å^3)	3930.7(3)	1843.15(12)
Z	4	4	R_{int}	0.0299	0.0297
D_{calc}(g cm^{-3})	1.256	1.371	R_1, wR_2[*I*>	0.1479	0.0912
F(000)	1552	800	2σ(*I*)]	0.4145	0.2378
Goodness of fit	1.324	1.111	R_1,wR_2(all	0.1939	0.1093
Completeness (%)	99.1	98.1	data)	0.4610	0.2648
Reflections collect	26371	14955	Reflections unique	6864	4153

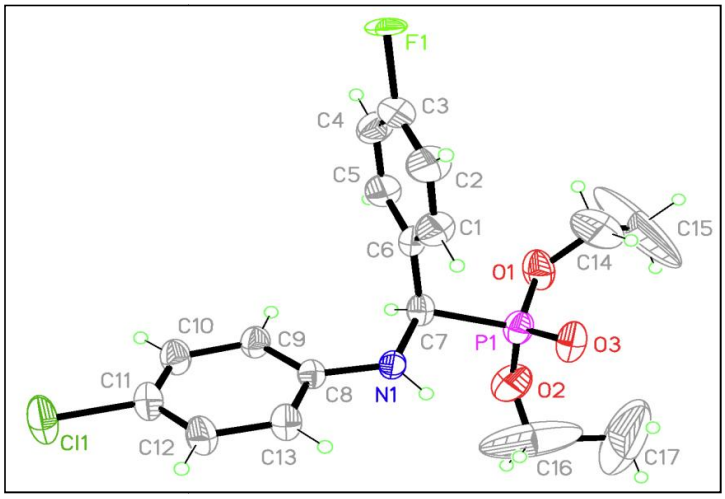


Fig. 1. X-ray structure of the *1* with a 30% probability of thermal ellipsoids

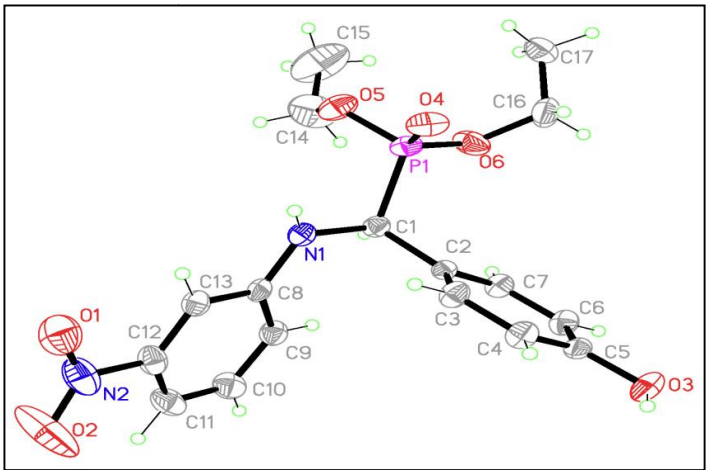


Fig. 2. X-ray structure of the *2* with a 30% probability of thermal ellipsoids

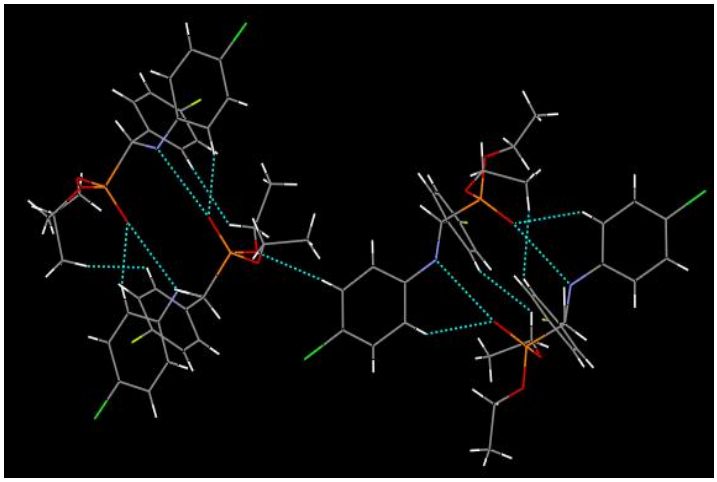


Fig. 3. Hydrogen bonding network for *1*

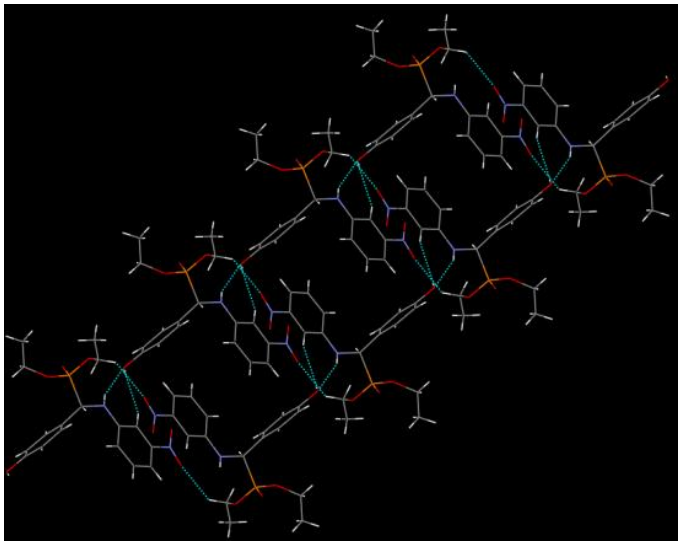


Fig. 4. Hydrogen bonding network for *2*

3.2 BSA Interaction with Compound *1* & *2*

As showed in Fig.5 & 6, with the increasing amount of conpound **1** and compound **2**, the fluorescence intensity of BSA at 336 nm regularly decreased. The results indicated that compound **1**& **2** could interact with BSA result in the fluorescence intensity quenching. Followed by the equation of Stern -Volmer, $F_0/F=1+k_q\tau_0[Q]=1+K_{sv}[Q]$ [23].(where F_0 and F are the fluorescence intensity of BSA before and after difference amount of **1**&**2** were added, respectively. K_q, reaction rate constant, K_{sv}, Kinetic quenching constant, τ_0, about 10^{-8}s), we could find that the values of k_q for **1**&**2** were 2.2×10^{13} $L\cdot mol^{-1}\cdot s^{-1}$ and $2.8\times10^{13}L\cdot mol^{-1}\cdot s^{-1}$, respectively. The k_q values were higher than the maximum scatter collision-quenching, which told us that the interaction between **1**&**2** and BSA were static quenching, indicating the static quenching mechanism was existed [24].

For static quenching, the binding constant and stoichiometry between BSA and **1**&**2** were calculated by the equation [25]

$$\lg\frac{F_0-F}{F}=\lg K_A+n\lg[Q]$$

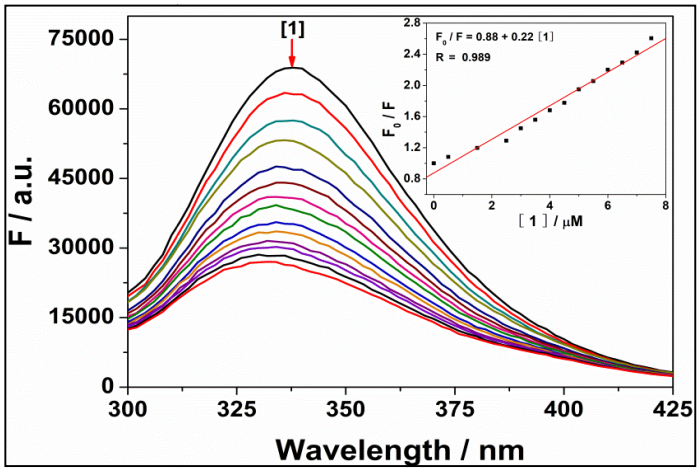


Fig. 5. The Fluorescence spectrum of BSA with different concentrations of compound 1 were added. Inset: Stern-Volmer plots for the concentration of compound 1 with the fluorescence intensity

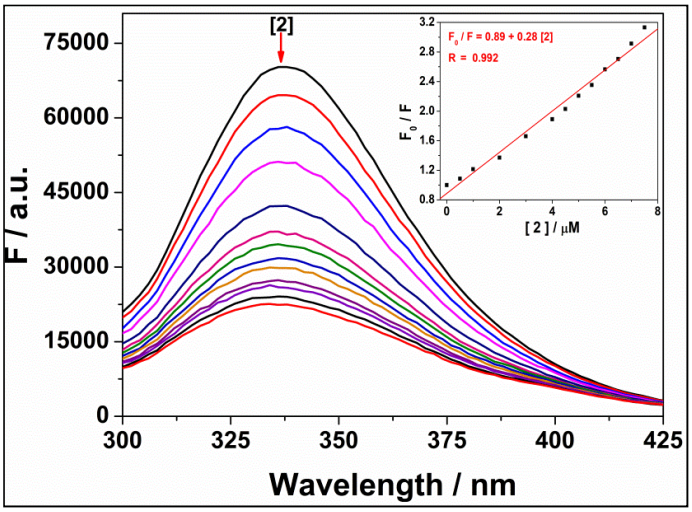


Fig. 6. The Fluorescence spectrum of BSA with different concentrations of compound 2 were added. Inset: Stern-Volmer plots for the concentration of compound 2 with the fluorescence intensity

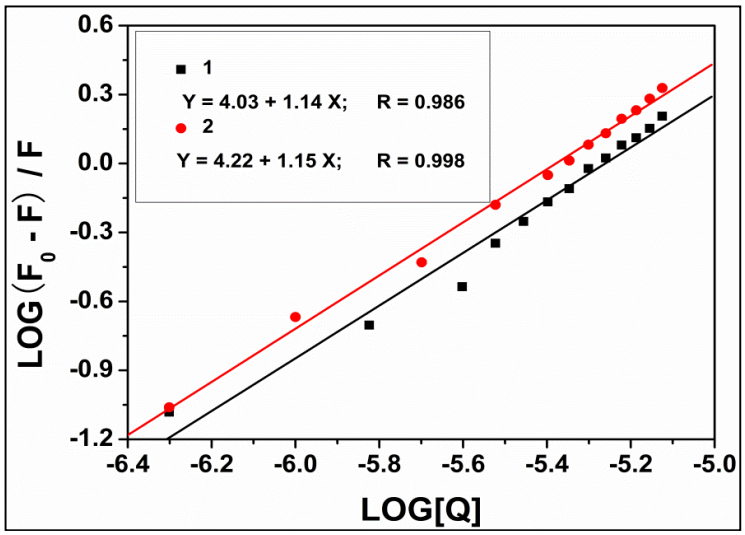


Fig. 7. Plot of log[(F_0-F)/F] vs. log[Q] (Q stand for compound 1 and compound 2)

From the slope and the intercept of the line of log (F_0 - F)/F vs. log [Q], the value of n and K_A could be obtained (Fig. 7). Table 1 showed that a higher binding constants was found by **2** with BSA than **1**. As the reported results, the values of n were nearly 1, indicated that the formation of 1:1 complex were obtained between BSA and ***1&2***.

4. CONCLUSION

In conclusion, our data indicate that the α-aminophosphonates derivatives *(**1&2**)* can bind to BSA and the fluorescence quenching mechanism of BSA with ***1&2*** were of static procedures. The binding constant of BSA and ***1&2*** were 1.07 × 10^4 M^{-1} and 1.68 × 10^4 M^{-1}, respectively. Besides, the values of n were manifested to reveal that the formation of 1:1 complex were obtained between BSA and ***1&2***.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Atherton FR, Hassall CH, Lambert RW. J. Med. Chem. 1986;29.
2. Baldwin C, Williams JM. J. Tetrahedron: Asymmetry. 1995;6:679.
3. a) Kaboudin B, Karimi M, Bioorg. Med. Chem. Lett. 2006;16:5324. b) Afarinkia K, Rees CW. Tetrahedron. 1990;46:7175. c) Moonen K, Laureyn I, Stevens CV. Chem. Rev. 2004;104:6177.
4. a) Allen MC, Fuhrer W, Tuck B, Wade R, Wood JMJ. Med. Chem. 1989;32:1652. b) Gancarz R, Wieczorek JS. Synthesis. 1978;625. c) Kaboudin B, Relat Elem. 2002;177:1749. d) Montchamp JL. J. Organomet. Chem. 2005;690:2388.
5. Reddy GCS, Annar SS, Rao KUM, Balakrishna A, Reddy CS. Pharm. Chem. 2010;2:177.
6. Pratt RF. Science. 1989;246:917.
7. Liu J, Yang S, Li X, Fan H, Bhadury P, Xu W, Wu J, Wan Z. Molecules. 2010;15: 5112.
8. a) Huang J, Chen R. Heteroat. Chem. 2008;480. b) Lavielle G, Hautefaye P, Schaeffer C, Boutin JA, Cudennec CA, Pierré A. J. Med. Chem. 1998;1991:34.
9. Onita N, Sisu I, Penescu M, Purcarea VL, Kurunczi L. Farmacia. 2010;58:531.
10. Holmes CP, Li XF, Pan YJ, Xu CD, Bhandari A, Moody CM, Miguel JA, Ferla SW, De Francisco MN, Frederick BT, Zhou SQ, Macher N, Jang L, Irvine JD, Grove JR. Bioorg. Med. Chem. Lett. 2008; 18:2719.
11. Wahhab A, Smil D, Ajamian A, Allan M, Chantigny Y, Therrien E, Nguyen N, Mankuc S, Leit S, Rahil J, Petschner AJ, Lu AH, Nicolescu A, Lefebvre S, Montcalm S, Fournel M, Yan TP, Li ZM, Besterman JM, Déziel R. Bioorg. Med. Chem. Lett. 2009;19:336.
12. Thérien M, Skorey K, Zamboni R, Li CS, Lau CK, LeRiche T, Truong VL, Waddleton D, Ramachandran C. Bioorg. Med. Chem. Lett. 2004;14:2319.
13. Shimbashi A, Tsuchiya A, Imoto M, Nishiyama S. Bioorg. Med. Chem. Lett. 2005;15:61.
14. Liu DG, Gao Y, Voigt JH, Lee K, Nicklaus MC, Wu L, Zhang ZY, Burke TR. Jr, Bioorg. Med. Chem. Lett. 2003;13:3005.
15. Arabaci G, Yi T, Fu H, Porter ME, Beebe KD, Pei D. Bioorg. Med. Chem. Lett. 2012; 12:3047.
16. Wang QM, Zhu ML, Zhu RT, Lu LP, Yuan CX, Xing S, Fu XQ, Mei YH, Hang QW. Eur. J. Med. Chem. 2012;49:354.
17. Li W, Ji YH, Li CX, Liu ZY, Li N, Fang L, Chang J, Tan J. World J Gastroenterolo. 2016;22:3758.
18. Cheng L, Bulmer C. A. Margaritis, Current drug delivery. 2015;12:351.
19. Wang QM, Gao W, Song JL, Liu Y, Qi H, Tang XH. J. Appl. Spectrosc. 2016;83(4): 703.
20. Wang QM, Yang L, Ding H, Chen XR, Wang H, Tang XH. Bioorg. Chem. 2016;69:132.
21. Rohovec J, Vojtíšek P, Lukeš I. Phosphorus Sulfur Silicon Relat. Elem. 1999;148:79.
22. Li MX, Zhu ML, Lu LP. Acta Cryst. 2008; E64:1178.
23. Sochor J, Dobes J, Krystofova O, Ruttkay-Nedecky B, Babula P, Pohanka M, Jurikova T, Zitka O, Adam V, Klejdus B, Kizek R. Int. J Electrochem. Sc. 2013; 8:8464.
24. Cory M, McKee DD, Kagan J, Henry DW, Allen Miller J. J. Am Chem. Soc. 1985;107: 528-536.
25. Scatchard G, Ann NY. Acad. Sci. 1949; 52:660-672.

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