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Synthesis of AZT-Phosphonate, Phosphonothioate and Phosphonoselenoate

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Abstract: Phosphonate, phosphonothioate and phosphonoselenoate derivatives of AZT were synthesized in an expeditious way and high yields.

Keywords: AZT, phosphonate, phosphonothioate, phosphonoselenoate, hydrogenphosphonate.

In search for therapeutically improved inhibitors of HIV, a wide variety of sugar-modified nucleosides have been developed and found to possess potential bioactivity. One of them is 3′-azido-3′-deoxythymidine (AZT) **1**, which was the first clinically approved drug against HIV infection, despite its undesirable side reactions such as bone marrow suppression and the emergence of resistant HIV variants[1]. In order to reduce its toxicity and increase the anti-HIV activity, a lot of works have been reported to develop the novel, more efficacious and more selective derivatives of AZT[2]. 5′-hydrogenphosphonate of AZT is one of the most significant compounds, which is much less toxicity than AZT and now it is in the processing of clinical trial[3]. Here we will report the synthesis of phosphonate, phosphonothioate and phosphonoselenoate derivatives of AZT with two AZT molecular units.

At first, AZT **1** was synthesized using a two-step protocol route in 76.8% overall yield[4]. In the previous paper[6], we have described an expeditious route to synthesize symmetry H-phosphonates using transesterificaton reaction between corresponding alcohol and phenyl phosphite (DPP) in almost quantitatively yields. DPP is a commercial available and inexpensive phosphorylation reagent. Using this methodology, DPP (1 mmol) in 2 mL anhydrous pyridine was added to AZT (2 mmol) in 3 ml anhydrous pyridine in 5 min at room temperature. The obtained solution was stirred for additional 2 hours. Then, the symmetry H-phosphonate **2** (δp *ca.* 10.64 ppm) was obtained in almost quantitatively yield as shown in ^{31}P NMR spectroscopy. The H-phosphonate **2** was not separated and was oxidized directly using I_2 in pyridine/H_2O (49:1), sulfur (S_8) or selenium respectively. After silicon gel chromatography purification (CH_2Cl_2:CH_3OH:Et_3N=100:10:1), the targeted phosphonate **3a**, Phosphonothioate **3b** and phosphonoselenoate **3c** derivatives of AZT were obtained as foam in 91%,

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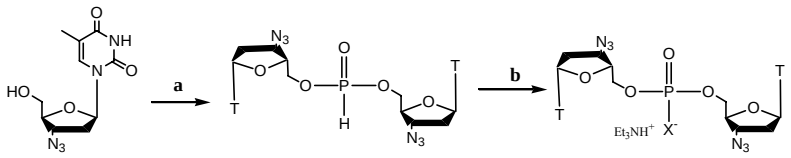
95% and 89% yield , respectively[7].

In conclusion, phosphonate **3a**, phosphonothioate **3b** and phosphonoselenoate **3c** derivatives of AZT were synthesized in an expeditious way and in high yields.

Scheme 1



Reagents and reaction conditions: (a) diphenyl phosphite (0.5 eq.), pyridine, RT, 2 hours; (b) I_2 in pyridine/H_2O (49:1)(2eq., 30min.), sulfur (S_8, 2eq., 30min) or selenium (2eq., 12 hours), respectively, at RT.

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7. Spectral data of **5a**: ^{31}P NMR (121 MHz, CD_3OD, δppm): 0.53; ^{1}H NMR (500 MHz, CD_3OD, δppm): 7.68 (s, 2H, H-6), 6.19 (t, 2H, J1', 2'=6.5 Hz, H-1'), 4.72 (br, 2H, NH-3), 4.43 (m, 2H, H-3'), 4.10 (m, 4H, H-5'), 4.03 (m, 2H, H-4′), 3.19 (q, 6H, J=7.5 Hz, N(CH_2CH_3)$_3$), 2.46 (m, 2H, H-2′a), 2.36 (m, 2H, H-2b′), 1.30 (t, 9H, J=7.5 Hz, N(CH2CH_3)$_3$); ^{13}C NMR (125 MHz, CD_3OD, δppm): 166.3 (C-4), 152.2 (C-2), 137.3 (C-6), 112 (C-5), 85.9 (C-1'), 84.4 (C-4'), 66.3 (C-5', $^{2}J_{P-C}$ =5.4 Hz), 62.3 (C-3'), 47.7 (N(CH_2CH_3)$_3$) 37.8 (C-2'), 12.6 (CH3), 9.2 (N(CH_2CH_3)$_3$); ESI-MS(-): *m/z* 595 (M-H)$^+$; **5b**: ^{31}P NMR (121 MHz, CD_3OD, δppm): 59.21, ESI-MS(-): *m/z* 611 (M-H)$^+$; **5c**: ^{31}P NMR (121 MHz, CD_3OD, δppm): 53.23 (J_{p-Se}=810Hz), ESI-MS (-): *m/z* 659 (M-H)$^+$; the ^{1}H NMR and ^{13}C NMR spectral data of **5b** and **5c** are very similar with **5a**.

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