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Synthesis of new α-aminophosphonate derivatives incorporating benzimidazole, theophylline and adenine nucleobases using L-cysteine functionalized magnetic nanoparticles (LCMNP) as magnetic reusable catalyst: Evaluation of their anticancer properties

Foroogh Bahrami,[a] Farhad Panahi,[a] Fatemeh Daneshgar,[a] Reza Yousefi,[b] Mohammad Bagher Shahsavani[b] and Ali Khalafi-Nezhad*[a]*

A new class of structurally diverse α-aminophosphonate derivatives containing benzimidazole, theophylline and adenine heterocycles were synthesized using a simple and efficient strategy. This class of α-aminophosphonates was synthesized using the reaction of synthetic aldehydes containing nucleobases, amines and diethyl phosphonate using L-cysteine functionalized magnetic nanoparticles (LCMNP) as catalyst. The aldehyde derivatives containing benzimidazole, theophylline and adenine nucleobases were synthesized using the reaction of a bromo-substituted aldehyde drived from isovanillin and 4-hydroxy benzaldehyde. The LCMNP catalyst was found to be an efficient magnetic reusable catalyst for synthesis of this class of α-aminophosphonates under mild and clean conditions. This method is introduced as a suitable approach for the synthesis of new α-aminophosphonate derivatives containing nucleobases which has potential biological activity. As the anticancer properties of a selected group of thesesynthetic ligands were evaluated, they indicated poor activity comparted to cisplatin against Jurkat cancer cell line.

Introduction

α-Aminophosphonate derivatives have received considerable attentions in medicinal chemistry due to their widespread applications such as enzyme inhibition activity,[1] anticancer[2] and antibiotics[3] actions, pharmacological prperties,[4] and peptidomimetic utilizations.[5] This class of compounds can be hydrolyzed to α-aminophosphonic acids which there is several important biological active compounds based on this structure (for example Alafosfalin & Glyphosate).[6,7] Research on the synthesis of new derivatives of α-aminophosphonates is in progress. For example, recent studies shown that α-aminophosphonate derivatives showed anti-leishmanial activity.[8] There are attempts on the synthesis of new α-aminophosphonates derivatives and their applications.[9] In the recent years some of the α-aminophosphonate derivatives containing heterocycle moieties have been synthesized which shown interesting biological activities.[10] It seems that the existence of heterocyclic moieties in the structure of α-aminophosphonate molecule influenced the biological activity, significantly. The chemical structure of some of the biological active α-aminophosphonates incorporating heterocycle rings is shown in Figure 1. In the structure of these biological active compounds there is a heterocycle ring such as quinazoline, pyrazole, thiazol, pyridine and chromen which the existence of them in the structure of these molecules is very effective in their activity.[10]

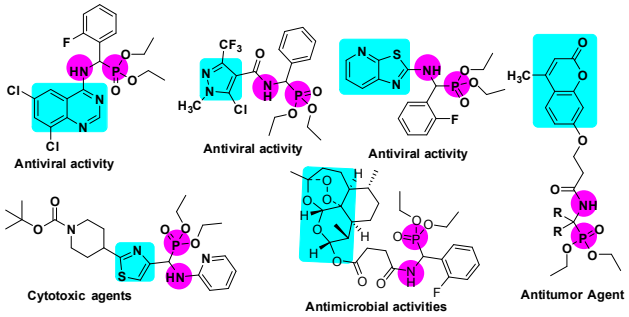

Figure 1 The chemical structure of some of the biological active α-aminophosphonates including heterocycle moieties

In continuation of our program on the utilization of nucleosides and carbohydrates in multicomponent reactions for one-pot synthesis of new compounds incorporating these fragments,[11] we would like to report the synthesis of new α-aminophosphonate derivatives containing benzimidazole,

[a] Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran
* Email: khalafi@susc.ac.ir; Panahi@shirazu.ac.ir
[b] Protein Chemistry Laboratory (PCL), Department of Biology, College of Sciences, Shiraz University, Shiraz 71454, Iran
Electronic Supplementary Information (ESI) available: Spectral data and copies of ^{1}H, ^{13}C NMR for synthesized compounds. See DOI: 10.1039/x0xx00000x

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theophylline and adenine heterocycles. These fragments are important due to a range of biological activities and medicinal applications associated with them. The existence of these heterocyclic moieties in the structure of many drugs obviously clarifies the important role of these heterocycles in medicinal chemistry. In many cases the presence of these nucleobases in the structure of biologically active compound enhanced the activity.[12-14]

For synthesis of these new α-aminophosphonate derivatives our previous strategy was used.[11d] Aldehyde derivatives incorporating desired heterocycle were synthesized and then it was used in a multicomponent reaction with amine and diethyl phosphonate which is known as Kabachnik–Fields reaction.[15] In order to obtain these compounds in high yield and clean conditions our previously catalyst system (L-cysteine functionalized magnetic nanoparticles, LCMNP) was used.[16] The LCMNP catalyst is a magnetic reusable and after finishing the reaction it was separated using an external magnetic field. Thus a clean and mild reaction condition will be available for synthesis of this class of compounds. The TEM and SEM images of LCMNP catalyst are shown in Figure 2 in order to illustrate the morphology and size of particles which are suitable for catalysis applications.

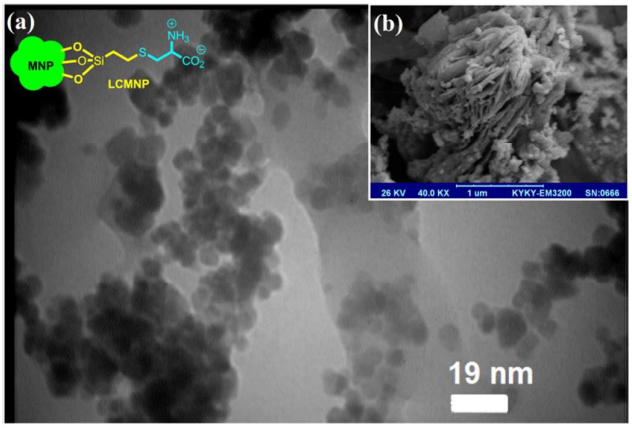
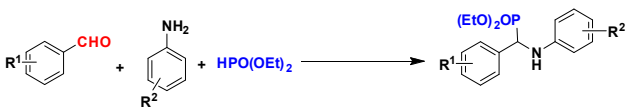


Figure 2 A TEM image of LCMNP catalyst (a). The average size of catalyst nanoparticles was approximately 10 nm. The black cores related to Fe_3O_4 and the white shells around them are attributed to the SiO_2 layer. A SEM image of LCMNP catalyst which shows the surface morphology of this material (b).

Results and discussion

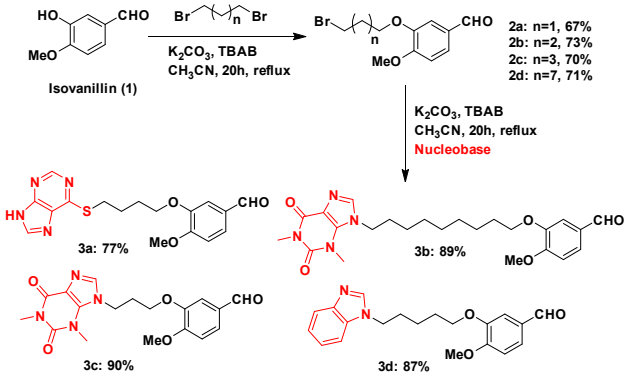
Synthesis of α-aminophosphonate derivatives

One of the methodologies for the synthesis of α-aminophosphonate has been known as Kabachnik–Fields reaction which is the nucleophilic addition of diethyl phosphonate to imines (in situ generated from amines and aldehydes) (Scheme 1).[17]



Scheme 1 One-pot three-component synthesis of α-aminophosphonates using reaction of amine, aldehyde and diethyl phosphonate

Our strategy in this study for the synthesis of α-aminophosphonate derivatives is the synthesis of aldehydes and use of them in the above reaction. Thus, we started our study with the synthesis of aldehyde derivatives containing benzimidazole and theophylline nucleobases. The approach for the synthesis of this class of aldehydes is shown in Scheme 2.



Scheme 2 The synthetic approach for the synthesis of aldehydes with benzimidazole and theophylline moiety started from isovanillin

Isovanillin (**1**)[18] was used as the starting material and it was reacted with different dibromides in order to synthesis aldehydes **2a-d**. These compounds were synthesized in gram scale in good yields. Then, aldehydes **2** were reacted with *9H*-purine-6-thiol, theophylline and benzimidazole and aldehydes **3a-d** were produced. Aldehyde **3a** is containing an adenine moiety with a 4 carbon atom chain connected to isovanillin aldehyde. Two aldehydes were synthesized using theophylline with different spacer (**3b** & **3c**). An aldehyde incorporating benzimidazole ring (**3d**) was also synthesized with a 5 carbon chain spacer.

After synthesize and characterization of aldehydes (**3a-d**) we checked different conditions to find an appreciate procedure for conversion of the synthetic aldehydes to the corresponding α-aminophosphonate. For optimization study the reaction of isovanillin, *p*-toluidine and diethyl phosphonate was selected as model reaction. The results of optimization studies are shown in Table 1.

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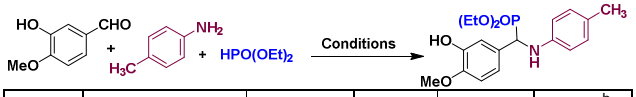
Table 1 Optimized reaction conditions for synthesis of α-aminophosphonate derivatives using LCMNP catalyst[a]

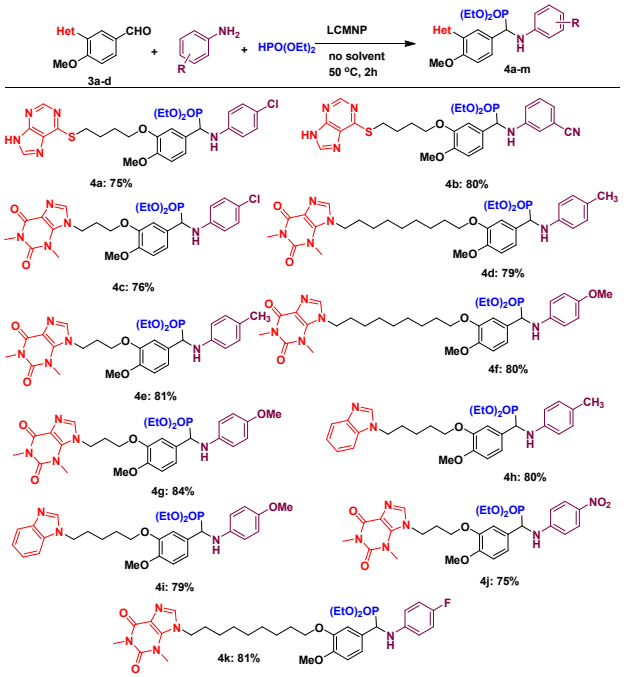


Entry	Catalyst (mol%)	Solvent	T (°C)	Time (h)	Yield[b] (%)
1	none	neat	80	24	60
2	none	neat	rt	24	45
3	$Mg(ClO_4)_2$ (5)	neat	80	6	73
4	$InCl_3$ (15)	neat	rt	20	65
5	$ZrOCl_2$ (10)	neat	rt	5	71
6	L-proline (5)	neat	50	10	55
7	LPMNP (5)	neat	50	10	72
8	LCMNP (8.5)	neat	rt	5	85
9	**LCMNP (8.5)**	**neat**	**50**	**2**	**92**
10	LCMNP (8.5)	EtOH	50	5	75
11	LCMNP (8.5)	CH_3CN	50	5	78
12	LCMNP (8.5)	Toluene	50	12	55
13	LCMNP (8.5)	DMF	50	6	71
14	LCMNP (12)	neat	50	2	93
15	LCMNP (5)	neat	50	6	87

[a] Reaction conditions: isovanillin (1.0 mmol), *p*-toluidine (1.0 mmol), diethyl phosphonate (1.2 mmol), solvent (3 mL) and LCMNP (0.05 g, 8.5 mol%). [b] Isolated yield.

As shown in Table 1 under catalyst- and solvent-free conditions about 45-60 % of product was produced (entries 1 & 2). We decided to use from reported catalyst systems in the literature to improve the reaction yield. In the presence of $Mg(ClO_4)_2$ at 80 °C about 73% of product was observed (Table 1, entry 3).[17b] By use of other Lewis acids such as $InCl_3$[19] and $ZrOCl_2$[20] no significant improvement in reaction yield related to $Mg(ClO_4)_2$ was detected (Table 1, entries 4 & 5). By using L-proline as catalyst at 50 °C only 55% of product was isolated from the reaction mixture (Table 1, entry 6). Since, the most problems associated with these catalyst systems was the separation of them from the reaction mixture which resulted in the decreasing of reaction yield we decided to use from magnetic reusable catalyst. By use of the magnetic reusable catalyst systems it is possible to separate the catalyst from the reaction mixture after completion of the reaction using an external magnetic field.[21] We used from our previous reported catalyst system LPMNP,[22] which is a L-proline-supported magnetic nanoparticles catalyst system and about 72% of product was obtained after 10h at 50 °C (Table 1, entry 7). In the presence of LCMNP catalyst at rt and under neat conditions about 85% of product was observed (Table 1, entry 8). At higher temperature of 50 °C the reaction yield was increased to 92% (Table 1, entry 9). The solvent conditions were also checked and no superiority was observed in comparison with solvent-less conditions (Table 1, entries 10-13). The catalyst loading was optimized and 8.5 mol% of catalyst was found to be optimal (Table 1, entries 14 & 15).

Thus the conditions showed in Table 1 entry 4 was applied in the synthesis of α-aminophosphonate from the synthetic aldehydes (**3a-d**). The method was efficient for the synthesis of new α-aminophosphonates using synthetic aldehydes. Consequently, a set of α-aminophosphonate derivatives containing adenine, theophylline and benzimidazole heterocycles were synthesized in good to excellent yields (Scheme 3).



Scheme 3 Synthesis of new α-aminophosphonate derivatives containing adenine, theophylline and benzimidazole heterocycles. Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), diethyl phosphonate (1.2 mmol), LCMNP (0.05 g, 8.5 mol%).

As shown in scheme 4, by selection of different amines it is possible to synthesize diverse derivatives of this class of α-aminophosphonates in good to excellent yields using LCMNP catalyst. Both amines with electron-donating and electron withdrawing groups were used and all of the products were obtained in high yields. Thus the used methodology in this study is suitable for synthesis of α-aminophosphonates bearing these heterocycles.

In order to increase the diversity of synthetic aminophosphonates further, other aldehydes were synthesized starting from 4-hydeoxy benzaldehyde (Scheme 4).

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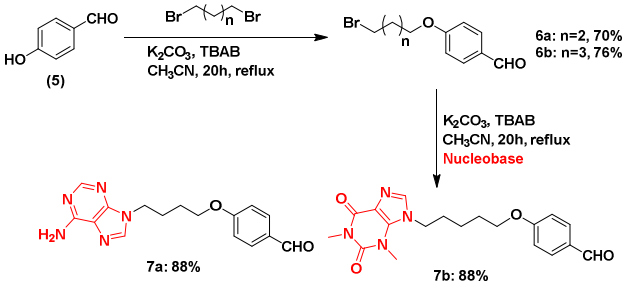


Scheme 4 Synthesis of new theophylline and adenine based aldehydes

The synthesized aldehydes **7a** and **7b** were converted to α-aminophosphonates derivatives using optimized reaction conditions and compounds **8a-d** were obtained in good isolated yield (Figure 3).

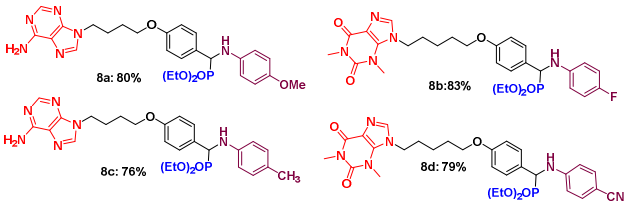
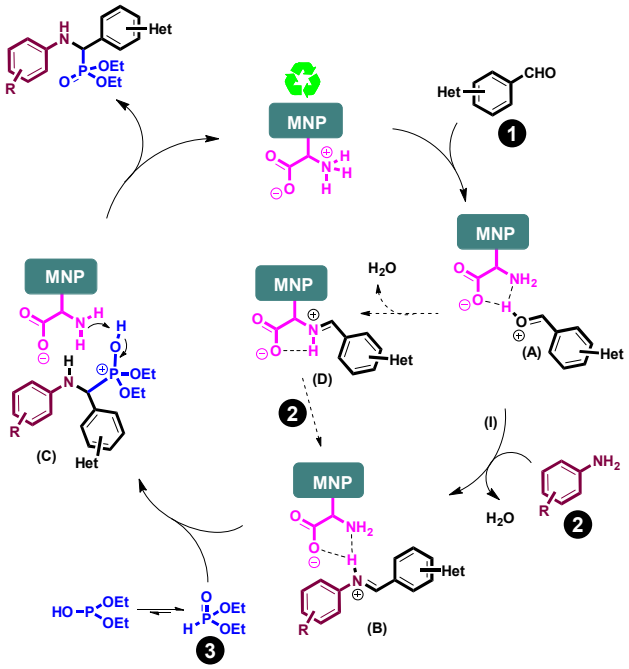


Figure 3 The chemical structure of synthesized α-aminophosphonate derivatives. Reaction conditions: aldehyde (1.0 mmol), amine (1.0 mmol), diethyl phosphonate (1.2 mmol), LCMNP (0.05 g, 8.5 mol%).

It is clear that this methodology is applicable for synthesize of diverse α-aminophosphonate derivatives using the selection of a hydroxy substituted aldehyde to react with a dibromide in order to synthesize a bromo-substituted aldehyde. Nucleophilic addition of a nucleobase to the bromo-substituted aldehyde resulted in the production of nucleobase functionalized aldehyde which can be undergo in the reaction with amine and diethyl phosphonate for synthesize of desirable α-aminophosphonate. This strategy is efficient for the synthesis of adenine derivatives such as **4a**, **4b**, **8a** and **8c** which may be important in medicinal chemistry because there are a range of biological active adenine-based phosphonate compounds.[19] The LCMNP catalyst facilitates the mild conditions that suitable for efficient and clean synthesis of this class of compounds. Since the LCMNP catalyst is magnetic reusable it is possible the separation from the catalyst from the reaction mixture using an external magnetic field after completion of the reaction. This situation caused that the synthetic compounds obtained in more comfortable conditions with less impurity.

A reaction mechanism was proposed as shown in Scheme 5 based on primary amino acid catalysis[24] and previous reported pathways for Kabachnik–Fields reaction in the literatures.[25] Aldehyde group can activate by amino acid functionality on the surface of magnetic nanoparticles in LCMNP catalyst (**A**).[26] The amine component reacted with the activated aldehyde in order to form imine intermediate (B).[27] Addition of diethyl phosphonate to the formed imine resulted in the production of intermediate **C**, which after deprotonation process catalyzed by LCMNP catalyst produces the final product.[28] Also, in another path (dash line), the amino group of amino acid moiety can react with aldehyde to form imine intermediate **D** which in the following is converted to imine **B** due to the high stability of imine **B** related to **D**.



Scheme 5. Proposed mechanism for reaction.

Anticancer activity of some synthetic ligands (8b, 8c, 4c, 4i)

Since the α-aminophosphonate derivatives have been already indicated to possess anticancer activity,[29] this feature was evaluated for a selected group of the synthetic ligands including **8b**, **8c**, **4c** and **4i**. In this study the synthetic ligands were tested for their anticancer activity against Jurkat cancer cell line, as the cells were incubated with the ligands for 24 h. The cytotoxic activity was measured by MTT assay as described in the experimental section. The synthetic ligands as indicated in Figure 4, demonstrated a dose-dependent anticancer activity against this cell line. Also, our results (Figure 4 and Table 2) suggest poor anticancer properties for these ligands compared to cisplatin.

Table 2 The IC_{50} values of the synthetic ligands after incubation with Jurkat cancer cells line for 24 h

Ligands	Cisplatin	**8b**	**8c**	**4c**	**4i**
IC_{50} (μM)	74.08 (± 1.3)[a]	286.27 (± 8.7)	299.18 (± 7.3)	324.01 (± 4.3)	327.43 (± 3.8)

[a] Standard deviation.

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Moreover, all the synthetic ligands indicated approximately similar anticancer activities, suggesting that different substitutions on the main molecular scaffold did not modulate their biological activity to the significant levels.

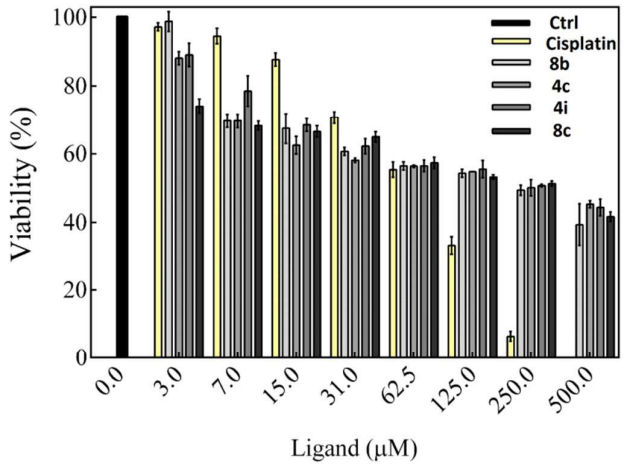

Figure 4 The growth suppression activity of the synthetic ligands against Jurkat cancer cell line. The tumor cells were incubated with varying concentrations of each ligand, ranging from 0 to 500 μM for 24 h. The growth inhibitory activity was assessed using MTT assay.[30] Also Cisplatin was used as a positive control.

Conclusions

In conclusion, we introduced a synthetic methodology for the synthesis of a new class of α-aminophosphonate derivatives incorporating benzimidazole, theophylline and adenine heterocycles in a three-step process. For this purpose, isovanillin or 4-hydroxybenzaldehyde was used as simple and cheap starting materials toward synthesis of structurally complex nucleobase derived aldehydes. Subsequently, the synthetic aldehydes undergoes in a multicomponent reaction with amines and diethyl phosphonate in the presence of LCMNP catalyst for one-pot synthesis of α-aminophosphonate derivatives incorporating these heterocycles. The LCMNP catalyst promotes this reaction under mild and environmentally being conditions to obtain desired products in high yields. The anticancer activities of some ligands (**8c**, **8b**, **4c**, **4i**) were evaluated and the results show that they have poor activity against Jurkat cancer cell line. The biological activities of the synthesized α-aminophosphonates are under evaluation and will be reported in due course.

Experimental section

General. Chemicals were purchased from Merck and Aldrich chemical companies. All the chemicals and solvents were used as received without purification. For recording ^{1}H NMR and ^{13}C NMR spectra we used a Bruker (250 MHz) Advance DRX, and samples were dissolved in pure deuterated DMSO-d_6 or $CDCl_3$ solvents with tetramethylsilane (TMS) as internal standard. FT-IR spectroscopy (Shimadzu FT-IR 8300 spectrophotometer) was employed for characterization of the compounds. The scanning electron micrography (SEM) images for the catalyst were obtained by SEM instrumentation (SEM, XL-30 FEG SEM, Philips, at 20 kV). Transmission electron microscopy (TEM) images were obtained using a TEM apparatus (CM-10-Philips, 100 kV) for the characterization of the LCMNP catalyst. Melting points were determined in open capillary tubes in Barnstead Electrothermal 9100 BZ circulating oil melting point apparatus. The reaction monitoring was accomplished by TLC on silica gel PolyGram SILG/UV254 plates.

Synthesis of α-aminophosphonates

Synthesis of aldehydes 3a-d, 7a & 7b. In double-necked round-bottom flask (100 mL) equipped with a condenser, a mixture consisting of isovanillin/4-hydroxy benzaldehyde (0.02 mol, 2.44 g), dibromoalkane (0.06 mol), K_2CO_3 (2.76 g, 0.02 mol), and a catalytic amount of TBAB (0.1 g) in MeCN (50 mL) was refluxed for 20 h. After cooling and solvent evaporation, the resulting foam was dissolved in $CHCl_3$ (150 mL) and washed with water (3 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography on silica gel [eluting with a mixture of *n*-hexane and EtOAc (10:1)].

3-(3-Bromopropoxy)-4-methoxybenzaldehyde (2a). Yield: 67% (3.7 g), white crystals, mp 58-59 °C.IR (KBr): ν =3093, 2948, 2800, 1674, 1730, 1589, 1437, 665 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 1.97-2.00 (m, 2H), 3.40- 3.45 (m, 2H), 3.86(s, 3H), 4-4.05 (m, 2H), 6.90 (d, *J* = 10.0 Hz, 1H), 7.30 (d, *J* = 2.5 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 9.76 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$/TMS): δ (ppm) = 29.8, 32.0, 56.0, 66.4, 110.7, 110.7, 126.9, 129.9, 148.6, 154.7, 190.7. Anal. Calcd for $C_{11}H_{13}BrO_3$(273.13): C, 48.37; H, 4.80. Found: C, 48.28; H, 4.74.

3-(4-Bromobutoxy)-4-methoxybenzaldehyde (2b). Yield: 73% (4.12 g), white crystals, mp 59-60 °C. IR (KBr): ν = 3090, 2947, 2790, 1681, 1730, 1523, 1388, 1263, 1174, 740 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 1.98-2.04 (m, 4H), 3.44-3.49 (m, 2H), 3.90 (s, 3H), 4.04-4.08 (m, 2H), 6.93 (d, *J* = 7.5 Hz, 1H), 7.25-7.43 (m, 2H), 9.79 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$/TMS): δ (ppm) = 27.6, 29.4, 33.3, 56.1, 67.9, 110.3, 110.6, 126.9, 130.0, 148.8, 154.8, 190.8. Anal. Calcd for $C_{12}H_{15}BrO_3$ (387.15): C, 50.19; H, 5.27. Found: C, 50.11; H, 5.22.

3-((5-Bromopentyl)oxy)-4-methoxybenzaldehyde (2c). Yield: 70% (4.2 g), white crystals, mp 61-62 °C. IR (KBr): ν =3090, 2943, 2784, 1685, 1733, 1523, 1387, 1267, 1175, 743 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 1.54-1.64 (m, 2H), 1.78-1.95 (m, 4H), 3.38 (t, *J* = 7.5 Hz, 2H), 3.88 (s, 3H), 3.99-4.04 (m, 2H), 6.92 (d, *J* = 5.0 Hz, 1H), 7.33 (s, 1H), 7.40 (d, *J* = 2.5 Hz, 1H), 9.75 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ (ppm) = 24.2, 27.6, 35.0, 36.3, 55.8, 68.0, 110.5, 111.3, 125.8, 129.5, 148.3, 153.2, 191.3. Anal. Calcd for $C_{13}H_{17}BrO_3$ (301.18): C, 51.84; H, 5.69. Found: C, 51.75; H, 5.63.

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3-((9-Bromononyl)oxy)-4-methoxybenzaldehyde (2d). Yield: 71% (5.07 g), yellow oil. IR (KBr, neat): ν = 3078, 2854, 2723, 1681, 1725, 1589, 1434, 1184, 748 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$/TMS): δ(ppm) = 1.19-1.35 (m, 10H), 1.74-1.79 (m, 4H), 3.29-3.34 (m, 2H), 3.86 (s, 3H), 3.98 (t, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 10.0 Hz, 1H), 7.25-7.26 (m, 1H), 9.76 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ (ppm) = 27.5, 28.0, 28.1, 28.5, 28.6, 28.8, 32.2, 34.7, 55.7, 68.1, 110.3, 111.1, 125.5, 129.5, 148.4, 154.2, 190.9. Anal. Calcd for$C_{17}H_{25}BrO_3$ (357.29): C, 57.15; H, 7.05. Found: C, 57.07; H, 6.98.

4-(4-Bromobutoxy)benzaldehyde (6a). Yield: 70% (3.6 g), yellow oil. IR (KBr, neat): ν = 2939, 2831, 2738, 1697, 1512, 1465, 648 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 1.21 (s, 2H), 2.26-2.30 (m. 2H), 3.53-3.56 (m, 2H), 4-4.1 (m, 2H), 7.12-7.14 (m, 1H), 7.34-7.40 (m, 3H), 9.90 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$/TMS): δ (ppm) = 27.2, 29.2, 33.3, 67.2, 114.0, 114.7, 129.8, 131.5, 131.9, 163.8, 190.7. Anal. Calcd for $C_{11}H_{13}BrO_2$ (257.13): C, 51.38; H, 5.10. Found: C, 51.31; H, 5.03.

4-((5-Bromopentyl)oxy)benzaldehyde (6b). Yield: 76% (4.12 g), white crystals, mp 60-61 °C. IR (KBr): ν = 3155, 2920, 2795, 1690, 1735, 1450, 1518, 665 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 0.53 (d, *J* = 2.5 Hz, 2H), 0.91 (d, *J* = 5.0 Hz, 2H), 1.63-1.65 (m, 2H), 3.06-3.14 (m, 2H), 3.66-3.70(m, 2H), 6.78-6.83 (m, 1H), 7.01-7.02 (m, 1H), 7.07-7.10 (m, 2H), 9.61 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$/TMS): δ (ppm) = 28.4, 29.7, 31.9, 33.2, 65.6, 114.1, 114.7, 130.0, 132.0, 135.6, 163.6, 190.8. Anal. Calcd for $C_{12}H_{15}BrO$ (271.15): C, 53.16; H, 5.58. Found: C, 53.07; H, 5.51.

Synthesis of theophylline, benzimidazole and adenine-based aldehyde. In a double-necked round-bottom flask (100 mL) equipped with a condenser, a mixture consisting of nucleobase (0.01 mol), bromo-substituted aldehyde (0.012 mol), K_2CO_3 (1.38 g, 0.01 mol), and a catalytic amount of TBAB (0.1 g) in MeCN (50 mL) was refluxed for 20 h. After cooling and solvent evaporation, the resulting foam was dissolved in $CHCl_3$ (150 mL) and washed with water (3 × 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography on silica gel [eluting with a mixture of *n*-hexane and EtOAc (1:1)].

3-(4-((*9H*-purin-6-yl)thio)butoxy)-4-methoxybenzaldehyde(3a). Yield: 77% (2.79 g), white crystals, mp 101-102 °C. IR (KBr): ν = 3471, 2947, 2746, 1735, 1513, 1272, 1134 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 1.71-2.15 (m, 4H), 3.46-3.51 (m, 2H), 3.94 (s, 3H), 4.38-4.43 (m, 2H), 6.94-6.99 (m, 1H), 7.26 (s, 1H), 7.34-7.47 (m, 2H), 8.14 (s, 1H), 8.68 (s, 1H), 9.83 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 25.4, 27.9, 30.8, 56.9, 75.2, 111.3, 111.6, 126.0, 129.2, 134.6, 145.8, 147.4, 153.9, 155.1, 163.5, 164.9, 191.3. Anal. Calcd for $C_{17}H_{18}N_4O_3S$ (358.42): C, 56.97; H, 5.06; N, 15.63; S, 8.94. Found: C, 56.88; H, 5.00; N, 15.56; S, 8.88.

3-((9-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)nonyl)oxy)-4-methoxybenzaldehyde (3b). Yield: 89% (4.1 g), white crystals, mp 120-121 °C. IR (KBr):ν = 3215, 2850, 2367, 1672, 1640, 1737, 1566, 1350, 1155 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 1.25-1.43 (m, 10H), 1.82-1.86 (m, 4H), 3.40 (s, 3H), 3.58 (s, 3H), 3.94 (s, 3H), 4.03-4.08 (m, 2H), 4.27 (t, *J* = 7.5 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 7.26 (s, 1H), 7.38-7.45(m, 1H), 9.83 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 22.6, 25.3, 26.1, 28.2, 28.3, 28.4, 28.6, 29.6, 30.0, 46.1, 55.8, 68, 111.3, 111.3, 116.0, 124.0, 135.0, 140.3, 142.3, 148.3, 150.3, 155.4, 159.8, 191.3. Anal. Calcd for $C_{24}H_{32}N_4O_5$ (456.54): C, 63.14; H, 7.07; N, 12.27. Found: C, 63.06; H, 7.01; N, 12.18.

3-(3-(1, 3-dimethyl-2, 6-dioxo-1, 2, 3, 6-tetrahydro-9H-purin-9-yl) propoxy)-4-methoxybenzaldehyde (3c). Yield 90% (3.4g), white crystals, mp 114-115°C. IR (KBr): ν = 3217, 2365, 1673, 1640, 1735, 1566, 1350, 1150 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 2.63(t, *J* = 5.0 Hz, 2H), 3.50 (s, 3H), 3.74 (s, 3H), 4.15 (s, 3H), 4.34-4.39 (m, 2H), 4.72-4.77 (m, 2H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.65 (s, 1H), 7.87(d, *J* = 10.0 Hz, 1H), 8.36 (s, 1H), 10.13 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 27.4, 29.3, 29.3, 43.9, 55.8, 65.5, 110.6, 111.3, 117.2, 126.1, 132.5, 134.7, 142.4, 149.7, 160.6, 166.1, 169.5, 191.2. Anal. Calcd for $C_{18}H_{20}N_4O_5$ (372.38): C, 58.06; H, 5.41; N, 15.05. Found: C, 57.95; H, 5.36; N, 15.01.

3-((5-(*1H*-Benzo[d]imidazol-1-yl)pentyl)oxy)-4-methoxybenzaldehyde (3d). Yield 87% (2.94 g), mp110-111 °C. IR (KBr): ν = 3125, 2910, 2815, 1690, 1737, 1450, 1581, 1256, 1115 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 1.57 (t, *J* = 7.5 Hz, 2H), 1.87-2.01(m, 4H), 3.91(s, 3H), 4.03-4.08 (m, 2H), 4.20 (t, *J* = 7.5 Hz, 2H), 6.90 (d, *J* = 7.5 Hz, 1H), 7.26- 7.36 (m, 2H), 7.37 (d, *J* = 2.5 Hz, 2H), 7.44 (t, *J* = 2.5 Hz, 2H), 7.90 (s, 1H), 9.82 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 22.7, 28.0, 29.0, 43.9, 55.8, 68, 110.3, 111.3, 119.3, 121.2, 122.1, 125.8, 126.4, 130.4, 140.6, 143.9, 148.2, 149.9, 155.6, 191.3. Anal. Calcd for $C_{20}H_{22}N_2O_3$ (338.41): C, 70.99; H, 6.55; N, 8.28. Found: C, 70.91; H, 6.50; N, 8.23.

4-(4-(6-amino-9H-purin-9-yl)butoxy)benzaldehyde (7a). Yield: 88% (2.74g), white crystals, mp118-119°C. IR (KBr): ν = 3290, 2931, 2877, 1666, 1737, 1450, 1581, 1264, 1164 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 1.66-1.71 (m, 2H), 1.93-1.98 (m, 2H), 4.02-4.07 (m, 2H), 4.17-4.22 (m, 2H), 7.17 (s, 2H), 7.37 (s, 1H), 7.46- 7.49 (m, 2H), 7.75 (s, 1H), 8.13 (d, *J* = 7.5 Hz, 2H), 9.94 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 25.6, 26.1, 42.5, 67.1, 113.5, 121.3, 122.3, 126.7, 130.2, 137.5, 140.8, 149.4, 152.3, 155.8, 158.9, 192.9. Anal. Calcd for $C_{16}H_{17}N_5O_2$ (311.14): C, 61.72; H, 5.50; N, 22.49. Found: C, 61.66; H, 5.43; N, 22.42.

4-((5-(**1,3-dimethyl-2,6-dioxo-1,2,3, 6-tetrahydro-9H-purin-9yl)pentyl)oxy)benzaldehyde (7b).** Yield 88% (3.26g), mp 116-117°C. IR (KBr): ν = 3217, 2854, 2360, 1672, 1640, 1735, 1590, 1350, 1150 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$/TMS): δ (ppm) = 2.25-2.30 (m, 4H), 2.47-2.49 (m, 2H), 3.40 (s, 3H), 3.58 (s, 3H), 4.03-4.08 (m, 2H), 4.27 (t, *J* = 7.5 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 2H), 7.81 (d, *J* = 7.5Hz, 2H), 8.05 (s, 1H), 9.85 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 22.8, 27.4, 28.0, 29.3, 34.5, 47.4, 65.2, 114.7, 116.6, 122.4, 122.7, 123.5, 131.6, 134.4, 140.0, 142.5, 153.5, 161.0, 191.2. Anal. Calcd for $C_{19}H_{22}N_4O_4$ (370.16): C, 61.61; H, 5.99; N, 15.13. Found: C,61.54; H, 5.93; N, 15.08.

Synthesis of α-Aminophosphonates: Aldehyde (1 mmol), amine (1 mmol), diethylphosphite (1.2 mmol) and LCMNP catalyst (0.05 g, 8.5 mol%) were mixed and stirred at 50 °C for 2 h. The progress of the reaction was monitored by TLC

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(eluent: EtOAc: *n*-hexane, 1:1). After completion of the reaction the LCMNP catalyst was isolated from the reaction mixture using an external magnetic field to remain the crude product in reaction vessel. To obtain high purity of the synthetic α-aminophosphonates the column chromatography was used.

Diethyl((3-(4-((9H-purin-6-yl)thio)butoxy)-4-methoxyphenyl)((4-chlorophenyl)amino)methyl)phosphonate (4a). Yield 75% (4.53g), IR (KBr, neat): ν = 3425, 2252, 2129, 1651, 1246, 1026, 825, 736 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 0.98- 1.04 (m, 6H), 1.84-1.89 (m, 4H), 2.70(d, *J* = 2.5 Hz, 2H), 3.66 (s, 3H), 3.97-4.04 (m, 6H), 4.89 (d, *J* = 30.0 Hz, 1H), 6.46 (s, 1H), 6.77 (d, *J* = 5.0 Hz, 4H), 6.98 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 2.5 Hz, 1H), 7.92 (s, 1H), 8.48 (s, 1H), 8.67(s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 15.9, 16.0, 16.1, 25.9, 27.7, 54.5, 55.3, 62.3, 67.8, 78.6, 110.5, 111.3, 113.6, 114.9, 120.0, 125.8, 128.2, 128.5, 129.5, 144.6, 146.3, 147.3, 148.3, 151.2, 155.7, 159.2, 164.7. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 27.74. MS: m/z 605 (21, M^+). Anal. Calcd for $C_{27}H_{33}ClN_5O_5PS$ (605.16): C, 53.51; H, 5.49; N, 11.56; S, 5.29. Found: C, 53.44; H, 5.43; N, 11.51; S, 5.22.

Diethyl((3-(4-((3H-imidazo[4,5-b]pyridin-7-yl)thio)butoxy)-4-methoxyphenyl)((3-cyanophenyl)amino)methyl)phosphonate (4b). Yield 80% (4.76g), IR (KBr, neat): ν = 3423, 2254, 2129, 1651, 1244, 1026, 825, 736 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 1.39- 1.44 (m, 6H), 1.53 (d, *J* = 5.0 Hz, 4H), 2.45 (s, 2H), 4.09 (s, 3H), 4.22-4.40 (m, 6H), 5.48 (d, *J* = 10.0 Hz, 1H), 6.16 (s, 1H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 2.5 Hz, 4H), 8.38 (s, 1H), 8.88 (s, 1H), 9.06 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): δ (ppm) = 15.9, 15.9, 16.2,25.9, 27.7, 54.5, 55.3, 62.1, 64.2, 75.5, 108.6, 111.3, 113.6, 114.9, 118.9, 120.0, 125.9, 128.2, 128.5, 144.6, 146.1, 146.3, 148.3, 151.3, 155.7, 159.3, 159.7. MS: m/z 638 (15, M^+). Anal. Calcd for $C_{28}H_{36}N_5O_5PS$ (595.20): C, 57.42; H, 6.20; N, 11.96; S, 5.47. Found: C, 57.36; H, 6.16; N, 11.92; S, 5.41.

Diethyl (((4-chlorophenyl)amino)(3-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)propoxy)-4-methoxyphenyl)methyl)phosphonate (4c). Yield 76% (4.71g), IR (KBr, neat): 3433, 2931, 2129, 1651, 1246, 1026, 817, 715 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 1.01 (t, *J* = 7.5 Hz, 6H), 2.06- 2.23 (m, 2H), 2.87 (s, 3H), 3.19 (s, 3H), 3.40 (s, 3H), 3.74 (s, 3H), 3.78-3.87 (m, 6H), 4.00 (t, *J* = 7.5 Hz, 2H), 4.38 (s, 1H), 4.82 (d, *J* = 20.0 Hz, 1H), 6.57-6.66 (m, 2H), 6.76-6.89 (m, 2H), 7 (d, *J* = 7.5 Hz, 2H), 7.09 (s, 1H), 8 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 13.8, 20.0, 27.4, 29.3, 29.6, 43.7, 50.1, 55.4, 62.2, 65.6, 66.6, 110.6, 111.5, 114.2, 114.9, 120.0, 121.1, 125.4, 126.5, 128.2, 128.5, 142.4, 146.3, 147.1, 148.4, 150.9, 150.9, 154.3. MS: m/z 620 (20, M^+). Anal. Calcd for $C_{28}H_{35}ClN_5O_7P$ (620.04): C, 54.24; H, 5.69; N, 11.30. Found: C, 54.13; H, 5.61; N, 11.22.

Diethyl ((3-((9-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)nonyl)oxy)-4-methoxyphenyl)(p-tolylamino)methyl)phosphonate (4d). Yield 79% (5.4g), IR (KBr, neat): 3433, 2931, 2129, 1715, 1651, 1246, 1026, 817, 715 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 1.00-1.05 (m, 6H), 1.16-1.23 (m, 10H), 1.61-1.66 (m, 2H), 1.72 (d, *J* = 10.0 Hz, 2H), 2.05 (s, 3H), 2.71 (s, 3H), 3.20 (s, 3H), 3.39 (s, 3H), 3.84-3.89 (m, 4H), 4.01 (t, *J* = 7.5 Hz, 2H), 4.17-4.22 (m, 2H), 4.84 (d, *J* = 25.0 Hz, 1H), 6.65 (d, *J* = 10.0 Hz, 2H), 6.76-6.84 (m, 2H), 6.90-6.98 (m, 2H), 7.1 (s, 1H), 7.93 (s, 1H), 8.05 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 16.0, 16.2, 19.9, 25.3, 25.5, 27.4, 27.7, 28.3, 28.5, 28.7, 29.3, 30.1, 46.1,55.3, 61.4, 61.9, 62.3, 68, 105.8, 111.3, 113.7, 116.5, 120.6, 125.2, 128.9, 129.4, 133.9, 136.5, 142.3, 145.0, 147.4, 148.3, 151.7, 153.9, 154.2. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 28.26. MS: m/z 683 (9, M^+). Anal. Calcd for $C_{35}H_{50}N_5O_7P$ (683.34): C, 61.48; H, 7.37; N, 10.24. Found: C, 61.39; H, 7.31; N, 10.17.

Diethyl ((3-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)propoxy)-4-methoxyphenyl)(p-tolylamino)methyl)phosphonate (4e). Yield: 81% (4.85g), IR (KBr, neat): 3433, 2932, 2129, 1715, 1651, 1246, 1026, 814, 712 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 0.98-1.04 (m, 6H), 1.12-1.19 (m, 2H), 2.71 (s, 3H), 2.87 (s, 3H), 3.19 (s, 3H), 3.40 (s, 3H), 3.84 (t, *J* = 7.5 Hz, 4H), 4 (t, *J* = 7.5 Hz, 2H), 4.38 (t, *J* = 5.0 Hz, 2H), 4.82 (d, *J* = 30 Hz, 1H), 6.60-6.66 (m, 2H), 6.77 (d, *J* = 7.5 Hz, 2H), 6.83-6.89 (m, 1H), 7 (d, *J* = 7.5 Hz, 1H), 7.09 (s, 1H), 7.93 (s, 1H), 8 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 16.2, 19.9, 27.4, 27.4, 29.3, 29.6, 43.7, 52.4, 54.9, 55.4, 55.4, 65.5, 106.0, 111.4, 113.7, 121.1, 125.2, 127.2, 129.0, 129.0, 134.4, 142.4, 142.4, 144.6, 147.0, 148.4, 148.4, 150.9, 154.3. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 23.20. MS: m/z 599 (18, M^+). Anal. Calcd for $C_{29}H_{38}N_5O_7P$ (599.25): C, 58.09; H, 6.39; N, 11.68. Found: C, 58.01; H, 6.33; N, 11.60.

Diethyl ((3-((9-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)nonyl)oxy)-4-methoxyphenyl)((4-methoxyphenyl)amino)methyl)phosphonate (4f). Yield 80% (5.59g), IR (KBr, neat): 3434, 2931, 2129, 1715, 1651, 1246, 1026, 815, 712 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 0.99-1.06 (m, 6H), 1.15-1.23 (m, 10H), 1.48 (t, *J* = 7.5 Hz, 2H), 1.80 (t, *J* = 7.5 Hz, 2H), 2.48 (s, 3H), 2.71 (s, 3H), 2.87 (s, 3H), 3.21 (s, 3H), 3.53 (d, *J* = 10.0 Hz, 4H), 3.99-4.04 (m, 2H), 4.20 (t, *J* = 7.5 Hz, 2H), 4.80 (d, *J* = 20.0 Hz, 1H), 6.57-6.61 (m, 3H), 6.68-6.72 (m, 2H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 10.0 Hz, 1H), 7.09 (s, 1H), 7.93 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 25.3, 26.1, 27.4, 28.3, 28.5, 29.3, 30.1, 30.6, 31.2, 34.8, 35.7, 46.1, 51.8, 55.0, 55.3, 59.6, 62.3, 68.0, 111.2, 114.1, 114.8, 119.0, 122.9, 130.2, 131.4, 133.8, 134.0, 140.5, 142.3, 146.3, 150.2, 152.8, 154.2, 155.3, 162.2. MS: m/z 699 (23, M^+). Anal. Calcd. For $C_{35}H_{50}N_5O_8P$ (699.34): C, 60.07; H, 7.20; N, 10.01. Found: C, 59.94; H, 7.11; N, 9.92.

Diethyl ((3-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)propoxy)-4-methoxyphenyl)((4-methoxyphenyl)amino)methyl)phosphonate (4g). Yield: 84% (5.16g), IR (KBr, neat): 3433, 2931, 2129, 1715, 1651, 1246, 1026, 814, 712 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 0.97-1.02 (m, 6H), 2.22-2.27 (m, 2H), 3.14 (s, 3H), 3.39 (s, 3H), 3.55 (s, 3H), 3.66 (s, 3H), 3.83 (d, *J* = 22.5 Hz, 4H), 3.98 (d, *J* = 7.5 Hz, 2H), 4.37 (s, 2H), 4.78 (d, *J* = 25.0 Hz, 1H), 6.58 (d, *J* = 10.0 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 10.0 Hz, 1H), 7.29 (s, 1H), 7.50 (s, 1H), 8 (s. 1H), 8.48 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 16.0, 16.2, 19.9, 27.4, 29.3, 29.6, 43.7, 52.4, 54.9,

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55.4, 62.0, 65.5, 106.0, 111.6, 113.7, 114.1, 120.3, 125.2, 126.1, 129.0, 133.4, 134.1, 142.4, 143.7, 144.6, 146.1, 148.4, 150.9, 152.5. MS: m/z 615 (8, M^+). Anal. Calcd for $C_{29}H_{38}N_5O_8P$ (615.25): C, 56.58; H, 6.22; N, 11.38. Found: C, 56.58; H, 6.22; N, 11.38.

Diethyl ((2-(4-(*1H*-benzo[d]imidazol-1-yl)butoxy)-4-methoxyphenyl)(p-tolylamino)methyl)phosphonate (4h). Yield: 80% (4.41g). IR (KBr, neat): 3125, 2910, 2815, 1450, 1581, 1256, 1115, 814, 712 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ(ppm)= 0.98- 1.04 (m, 6H), 1.12-1.19 (m, 4H), 2.04 (s, 3H), 3.48-3.54 (m, 2H), 3.65 (s, 3H), 3.84-3.88 (m, 4H), 3.98-4.03 (m, 2H), 4.24 (t, *J* = 7.5 Hz, 2H), 4.88 (d, *J* = 10.0 Hz, 1H), 6.65 (d, *J* = 10.0 Hz, 1H), 6.75-6.84 (m, 4H), 6.95-6.99 (m, 1H), 7.09-7.18 (m, 1H), 7.20-7.23 (m, 2H), 7.57-7.62 (m,2H), 7.93 (s, 1H), 8.23 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 19.9, 22.7, 26.1, 28.0, 29.0, 31.2, 44.2, 54.9, 55.3, 62.0, 62.3, 67.9, 110.7, 111.3, 113.7, 118.7, 120.6, 122.0, 122.6, 125.2, 128.9, 129.0, 134.8, 141.5, 143.6, 144.7, 145.0, 147.4, 147.4, 148.1, 148.2. MS: m/z 551 (14, M^+). Anal. Calcd for $C_{31}H_{40}N_3O_5P$ (551.25): C, 65.83; H, 7.13; N, 7.43. Found: C, 65.74; H, 7.06; N, 7.37.

Diethyl ((3-((5-(1H-benzo[d]imidazol-1-yl)pentyl)oxy)-4-methoxyphenyl)((4-methoxyphenyl)amino)methyl)phosphonate (4i). Yield: 79 % (4.59g), IR (KBr, neat): 3123, 2910, 2815, 1453, 1581, 1256, 1115, 813, 712 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ(ppm)= 1.00 (t, *J* = 7.5 Hz, 6H), 1.13-1.17 (m, 4H), 1.82 (t, *J* = 7.5 Hz, 2H), 3.54 (s, 3H), 3.64 (s, 3H), 3.83-3.87 (m, 4H), 4.01 (t, *J* = 7.5 Hz, 2H), 4.21- 4.26 (m, 2H), 4.85 (d, *J* = 10.0 Hz, 1H), 6.56-6.61 (m, 2H), 6.70 (d, *J* = 10.0 Hz, 2H), 6.81 (d, *J* = 7.5 Hz, 2H), 6.96 (d, *J* =5.0Hz, 1H), 7.09 (s, 1H), 7.17-7.23 (m, 2H), 7.57-7.64 (m, 2H), 7.92 (s, 1H), 8.21 (s, 1H), . ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 16, 16.3, 22.7, 28, 29.1, 43.9, 53, 55, 55.3, 61.9, 62, 67.9, 110.3, 111,3, 113.4, 114.1, 114.8, 119.3, 120.7, 121.3, 122.1, 123.9, 129, 133.7, 141, 141.2, 143.2, 143.9, 147.4, 148.2, 151.2. MS: m/z 581 (11, M^+). Anal. Calcd for $C_{31}H_{40}N_3O_6P$ (581.27): C, 64.01; H, 6.93; N, 7.22. Found: C, 63.92; H, 6.87; N, 7.17.

Diethyl ((3-(3-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)propoxy)-4-methoxyphenyl)((4-nitrophenyl)amino)methyl)phosphonate (4j). Yield 75% (4.72g), IR (KBr, neat): 3433, 2931, 2125, 1715, 1655, 1246, 1026, 817, 710 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm)= 1.11-1.16 (m, 6H), 2.23-2.28 (m, 2H), 3.18 (s, 3H), 3.40 (s, 3H), 3.69 (s, 3H), 3.85-3.91 (m, 4H), 3.98-4.03 (m, 2H), 4.37-4.42 (m, 2H), 5.20 (d, *J* = 10.0 Hz, 1H), 6.91 (d, *J* = 10.0 Hz, 2H), 7.06 (d, *J* = 7.5 Hz, 2H), 7.14 (s, 1H), 7.92 (d, *J* = 5.0 Hz, 2H), 8 (s, 1H), 8.13 (s, 1H).^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 18.3, 19.8, 24.3, 27.4, 29.3, 43.7, 55.4, 56.6, 62.3, 62.5, 65.5, 111.5, 112.1, 114.7, 122.2, 125.6, 125.8, 127.6, 129.9, 130.7, 135, 136.7, 141.1, 142.4, 147.1, 148.7, 150.8, 157.9. MS: m/z 630 (28, M^+). Anal. Calcd for $C_{28}H_{35}N_6O_9P$ (630.22): C, 53.33; H, 5.59; N, 13.33. Found: C, 53.25; H, 5.50; N, 13.23.

Diethyl ((3-((9-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)nonyl)oxy)-4-methoxyphenyl)((4-fluorophenyl)amino)methyl)phosphonate (4k). Yield: 81% (5.56g), IR (KBr, neat): 3433, 2933, 2123, 1715, 1655, 1246, 1026, 813, 710 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 1.14-1.22 (m, 6H), 1.66 -1.74 (m, 10H), 1.88 (d, *J* = 2.5 Hz, 2H), 2.26 (d, *J* = 5.0 Hz, 2H), 2.70 (s, 3H), 2.85 (s, 3H), 3.19 (s, 3H), 3.66-3.71 (m, 2H), 3.86-3.97 (m, 4H), 4.16-4.21 (m, 2H), 4.79 (d, *J* = 12.5 Hz, 1H), 6.88 (s, 1H), 6.98 (s, 1H), 7.08 (d, *J* = 5.0 Hz, 2H), 7.44 (d, *J* = 5.0 Hz, 2H), 7.92 (s, 1H), 8.05 (t, *J* = 2.5 Hz, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 15.9, 16.0, 20.9, 25.3, 25.5, 27.4, 28.2, 28.6, 28.7, 29.3, 30.0, 46.1, 55.4, 61.7, 67.6, 68.0, 70.2, 111.2, 115.0, 120.8, 122.7, 125.4, 128.0, 132.5, 134.2, 135.3, 135.7, 140.0, 142.3, 145.8, 150.9, 154.2, 155.1, 158.5. MS: m/z 687 (19, M^+). Anal. Calcd for $C_{34}H_{47}FN_5O_7P$ (687.32): C, 59.38; H, 6.89; N, 10.18. Found: C, 59.29; H, 6.81; N, 10.07.

Diethyl ((3-(4-(6-amino-9H-purin-9-yl) butoxy)-4-methoxyphenyl) ((4-methoxyphenyl) amino) methyl) phosphonate (8a). Yield: 80% (4.76g), IR (KBr, neat): ν = 3427, 2129, 1651, 1246, 1027, 815, 715 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 1.00-1.03 (m, 6H), 1.17 (t, *J* = 2.5 Hz, 2H), 1.89 (t, *J* = 2.5 Hz, 2H), 3.33 (s, 3H), 3.91 (t, *J* = 5.0 Hz, 4H), 4.00-4.04 (m, 2H), 4.14-4.18 (m, 2H), 4.81 (d, *J* = 12.5 Hz, 1H), 4.91 (d, *J* = 10.0 Hz, 2H), 6.57-6.62 (m, 2H), 6,68-6.72 (m, 2H), 7.05 (s, 2H), 7.17 (s, 2H), 7.50 (s, 1H), 7.91 (s, 1H), 8.13 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 15.9, 16.2, 25.8, 26.2, 42.6, 55.0, 62.0, 62.1, 62.4, 66.7, 110.8, 114.1, 114.6, 117.4, 120.7, 128.7, 133.4, 135.0, 137.2, 138.6, 140.7, 144.7, 149.4, 151.3, 152.3, 155.8, 158.2. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 23.22. MS: m/z 584 (16, M^+). Anal. Calcd for $C_{27}H_{35}N_6O_5P$ (584.25): C, 58.48; H, 6.36; N, 15.15. Found: C, 58.41; H, 6.30; N, 15.09.

Diethyl ((3-((5-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)pentyl)oxy)-4-methoxyphenyl)((4-fluorophenyl)amino)methyl)phosphonate (8b). Yield: 83 % (5.23g), IR (KBr, neat): 3433, 2931, 2129, 1715, 1651, 1246, 1026, 814, 712 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 0.83 (t, *J* = 7.5 Hz, 6H), 0.97-1.06 (m, 6H), 2.97 (s, 3H), 3.19 (s, 3H), 3.30-3.35 (m, 2H), 3.68 (d, *J* = 5.0 Hz, 2H), 3.79-3.85 (m 4H), 4.69 (d, *J* = 17.5 Hz, 1H), 6.60 (d, *J* = 10.0 Hz, 4H), 6.81 (d, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.74 (s, 1H), 7.82 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 18.5, 20.3, 27.4, 29.3, 30.6, 35.7, 43.6, 54.4, 62.0, 65.5, 67.8, 72.2, 113.8, 113.9, 114.3, 114.4, 114.7, 115.0, 128.5, 129.3, 131.6, 135.3, 140.9, 142.5, 148.4, 150.9, 152.8, 154.2, 162.2. MS: m/z 631 (25, M^+). Anal. Calcd for $C_{29}H_{37}FN_5O_6P$ (631.26): C, 57.90; H, 6.20; N, 11.64. Found: C, 57.90; H, 6.20; N, 11.64.

Diethyl ((4-(4-(6-amino-9H-purin-9-yl)butoxy)phenyl)(*p*-tolylamino)methyl)phosphonate (8c). Yield: 76% (4.08g), IR (KBr, neat): ν = 3427, 2129, 1651, 1246, 1027, 817, 715 cm $^{-1}$. ^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 1.46- 1.51 (m, 6H), 1.60-1.65 (m, 2H), 2.24-2.29 (m, 2H), 2.36 (s, 3H), 4.13-4.27 (m, 4H), 4.31-4.39(m, 2H), 4.45-4.53(m, 2H), 5.32 (d, *J* = 10.0 Hz, 2H), 5.43 (d, *J* = 10.0 Hz, 1H), 7.12 (d, *J* = 5.0 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 10.0 Hz, 2H), 7.66 (s, 2H), 7.96 (s, 1H), 8.40 (s, 1H), 8.61 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 16.3, 16.5, 20.3, 26.2, 26.6, 43.1, 48.8, 58.0, 62.8, 67.0, 114.0, 115.1, 115.9, 125.6, 129.2, 129.4, 131.5, 132.8, 138.9, 141.5, 145, 145.2, 151.8, 151.9, 155.6, 156.1, 158.9. MS: m/z 538 (18, M^+). Anal. Calcd for $C_{27}H_{35}N_6O_4P$

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(538.25): C, 60.21; H, 6.55; N, 15.60. Found: C, 60.13; H, 6.48; N, 15.53.

Diethyl (((4-cyanophenyl)amino)(3-((5-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-9H-purin-9-yl)pentyl)oxy)-4-methoxyphenyl)methyl)phosphonate (8d). Yield 79 % (5.04g), IR (KBr, neat): 3433, 2931, 2129, 1715, 1655, 1243, 1026, 814, 712 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6/TMS): δ (ppm) = 1.55 (t, *J* = 7.5 Hz, 6H), 1.65-1.70 (m, 4H), 2.71-2.76 (m, 2H), 3.69 (s, 3H), 3.91 (s, 3H), 4.35-4.41 (m, 4H), 4.51-4.56 (m, 2H), 4.87-4.92 (m, 2H), 5.65 (d, *J* = 10.0 Hz, 1H), 7.34 (d, *J* = 10.0 Hz, 2H), 7.42 (d, *J* = 5.0 Hz, 2H), 7.67 (t, *J* = 5.0Hz, 2H), 7.92 (d, *J* = 7.5 Hz, 2H), 8.45 (s, 1H), 8.54 (s, 1H). ^{13}C NMR (62.5 MHz, DMSO-d_6/TMS): 15.9, 16.2, 27.4, 29.3, 29.5, 31.2, 34.8, 43.7, 53.6, 62.1, 62.2, 62.3, 106.0, 111.3, 113.9, 115.4, 118.3, 119.3, 119.8, 121.3, 127.9, 129.3, 129.7, 132.6, 142.5, 147.8, 148.4, 150.9, 154.2, 157.7. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ (ppm) = 22.38. MS: m/z 638 (22, M^+). Anal. Calcd for $C_{30}H_{37}N_6O_6P$ (638.26): C, 59.20; H, 6.13; N, 13.81. Found: C, 59.12; H, 6.06; N, 13.74.

Anticancer activity of the synthetic ligands

The growth inhibitory effect of the synthetic ligands (8c, 8b, 4c, 4i) toward Jurkat cancer cell line was measured, using 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay. Also, cisplatin was also used as a positive control.[31] The cancer cells were cultured in RPMI-1640 and the medium was supplemented with 10% FBS and 1% penicillin–streptomycin (100 mg/ml streptomycin and 100 U/ml penicillin) to control the growth of contaminating microorganisms. The cells were cultured in 96-well cell culture plates at a cell density of 2.5×10^4 cells/well, with varying concentrations of each synthetic ligand (0–500 µM). The cancer cells were kept at 37 °C in a humidified atmosphere of 5% CO_2 for 24 h. Four hours to the end of incubations, 25 µl of sterilized MTT solution (5 mg/ml in PBS) was added to each well containing fresh and cultured medium. At the end, the insoluble formazan produced was dissolved in a solution containing 10% SDS and 50% DMF (left for 1 h at 37 °C in dark conditions) and the optical density (OD) was read against reagent blank with multi well scanning spectrophotometer (ELISA reader, Bio-Tek's ELx808, USA), at a wavelength of 570 nm. The absorbance was a function of concentration of the converted MTT (yellow) to purple formazan. The OD values of study groups were divided by the OD values of untreated controls and presented as the percentage of control (as 100%). Also the values of IC_{50} (the concentrations required for 50% growth inhibition), after 24 h of incubation with these ligands were calculated from the dose-response curves.[30]

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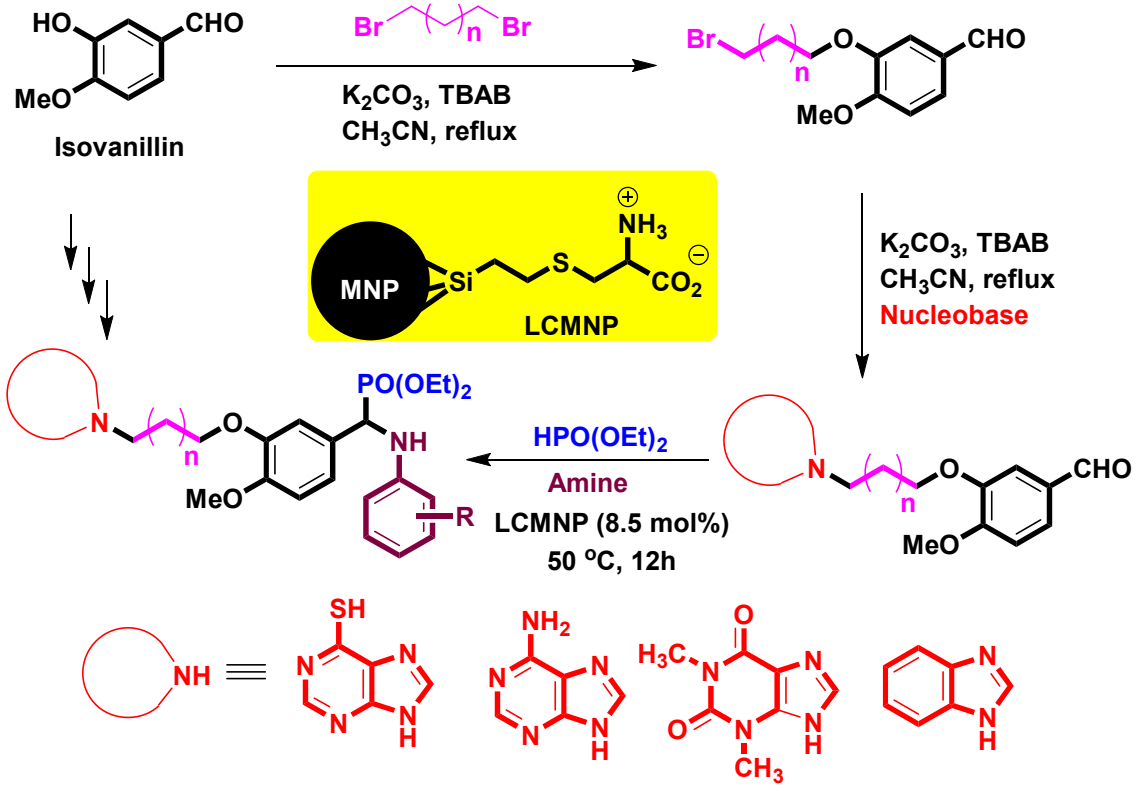
Synthesis of new α-aminophosphonate derivatives incorporating benzimidazole, theophylline and adenine nucleobases using L-cysteine functionalized magnetic nanoparticles (LCMNP) as magnetic reusable catalyst: Evaluation of their anticancer properties

Foroogh Bahrami,[a] Farhad Panahi,*[a] Fatemeh Daneshgar,[a] Reza Yousefi,[b] Mohammad Bagher Shahsavani[b] and Ali Khalafi-Nezhad*[a]

[a] *Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran*

** Email: khalafi@susc.ac.ir; Panahi@shirazu.ac.ir*

[b] *Protein Chemistry Laboratory (PCL), Department of Biology, College of Sciences, Shiraz University, Shiraz 71454, Iran*



A new class of α-aminophosphonate derivatives incorporating benzimidazole, theophylline and adenine nucleobases were synthesized in a three-step process and the anticancer activities of selected ligands were evaluated.