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The Synthesis of Distamycin Analog Containing Phosphonyl Group

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The Synthesis of Distamycin Analog Containing Phosphonyl Group

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In order to obtain high biological activity compound, a series of distamycin analog containing phosphonyl group were synthesized by chloroform reaction and coupling reaction using DCC/HOBT as promoting additives.

Keywords Biological activity; DNA; distamycin; polyamides

INTRODUCTION

Many research efforts have been aimed at targeting specific sequences in DNA with synthetic ligands with the idea of designing both drugs

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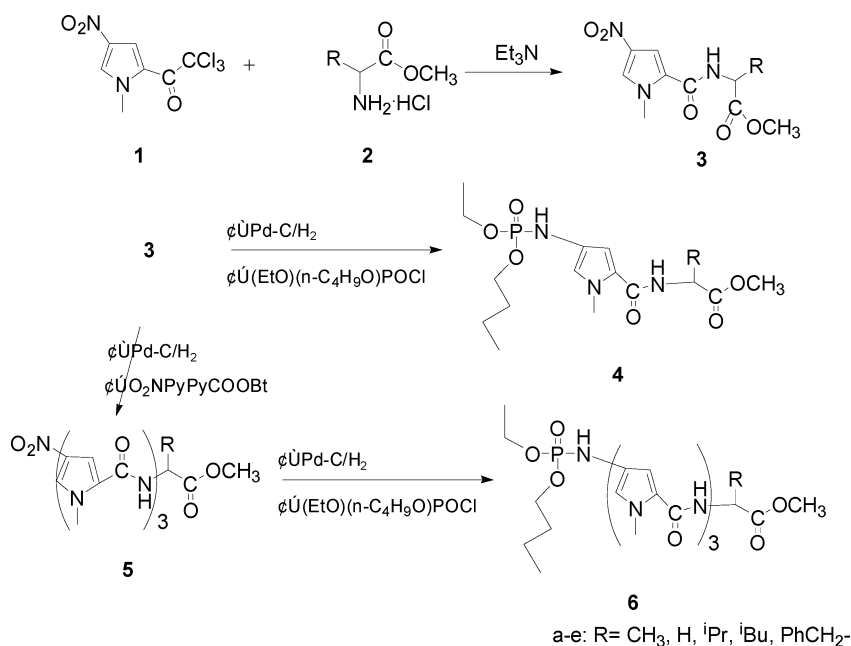
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and molecular probes for DNA polymorphism.¹ Recently, the natural product distamycin, netropsin and their analog have attracted considerable attention on the part of synthetic and biological chemists because they recognize and bind in the minor groove of predetermined DNA sequences with high affinity and specificity.² Since these polyamides can permeate living cell membranes, they have the potential to control specific gene expression.³ Therefore, these polyamides are one of the most widely studied class of agents characterized by high level of sequence specificity and they are still an interesting class of DNA ligands which demonstrate to possess several biological activities.²⁻³

Our group found some amino acid containing phosphonyl group had good biological activity.⁴ In order to obtain high biological activity compound, a series of polyamides containing phosphonyl group are synthesized. The synthetic route is shown in Scheme 1.

RESULTS AND DISCUSSION

The compounds **4** and **6** are our targeted molecule, which consist of phosphoryl group, polyamides and amino acid methyl ester. Compounds **3** are synthesized using chloroform reaction. In this step, the choice of



SCHEME 1 Synthetic route of title compounds.

solvent is important. The hydrochloric acid salt of amino acid methyl ester is diffuent in water or methol. But in these solvents, compound 1 will be transfer to relevant carboxylic acid (NO_2PyCOOH) or ester ($\text{NO}_2\text{PyCOOMe}$). Compared to DMF and acetone, chloroform is best solvent for this reaction. After Et_3N is added, the hydrochloric acid salt of amino acid methyl ester can well solved in chloroform at ultrasonic.

In the synthesis of compounds 4, TLC is needed to monitor the progress of the hydrogenation. After this step is finished, phosphorochloridic acid alkyl ester is dropwised into it. The coupling reaction finished in 24 h and compounds 4 can be easily obtained by column chromatography.

There were two elements in the synthesis of compound 5. One is the qualitative reduction of the nitro group of 3 to an amino group. The termination of hydrogenation in time is very important. Although the hydrogenation is fulfilled almost quantitatively, the amino products are rather unstable. To achieve the optimum result, TLC are employed to monitor the progress of the hydrogenation. The other one is the preparation of an active ester of the carboxyl component. Adding excess of DCC facilitated the formation of the active ester. In this step, methanol and ethanol are better solvent than other solvent.

Similar to the synthesis of 5, TLC is needed to monitor the progress of the hydrogenation in the syntheisis of 6. However, alcohol can not used as solvent in this step due to the alcoholysis of phosphorochloridic acid alkyl ester. After compared to other solvent, CH_2Cl_2 and acetic acid ethyl ester are good solvent for this step.

^1H NMR, IR, and ESI-MS spectra of the obtained compounds are recorded. Compounds 3 and 4 exhibit one N-Me signal and one O-Me signal, which appears a single peak at ca. 3.9 and 3.8, respectively. ^{31}P NMR and ^1H - ^{31}P HMQC spectra of the obtained compounds 4 also are recorded. From the ^{31}P NMR, a single peak is observed arround 3.9 ppm. There are two kind of amide signals appears at ca. 5.0 and ca. 6.2 ppm in ^1H NMR. The peak observed at $\delta = 5$ ppm assign to the H atom on P-NH bond, due to its interaction with P resonance at $\delta = 3.9$ ppm. Compounds 5 and 6 exhibit three N-Me signals and one O-Me, all of them appears at ca. 4.18 ppm. ESI mass spectra for all compounds showed both $[\text{M}+\text{H}]^+$ and $[\text{M}+\text{Na}]^+$ ion.

CONCLUSION

In conclusion, we developed a good route for the synthesis of distamycin analog containing phosphonyl group. The significant feature of this procedure is that there is no need of protecting and deprotecting amino

group. The reactions are convenient and efficient. The biological activity of compounds **4** and **6** are currently being examined.

EXPERIMENTAL

General

^1H NMR and ^{31}P NMR spectra were measured by using a Bruker AC-P400 spectrometer with TMS and 85% H_3PO_4 as the internal and external reference respectively and with CDCl_3 or DMSO as the solvent. IR spectra was recorded as KBr pellets on a BRUCK spectrometer. Mass spectra was acquired in positive ion mode using a Bruker ESQUIRE-LCTM ion trap spectrometer equipped with a gas nebulizer probe, capable of analyzing ions up to m/z 20000. Solvents were purified and dried by standard procedures. Compounds **1** and **2** were synthesized according to Refs,^{5,6} respectively.

The Synthesis of Compound **3**

To a solution of compound **2c** 1.010 g (5.0 mmol) in 20 ml of CH_2Cl_2 was added Et_3N (0.8 mL). After stirred 1/2 h and filtrated, the active amino acid solution was obtained. Separately, a solution of compound **1** 1.3110 g (4.8 mmol) in 5 ml of CH_2Cl_2 was dropped to the active amino acid solution, followed by stirring 24 h. Then the mixture solution was concentrated in vacuo. Column chromatography of the residue (eluant with CHCl_3 and MeOH 40:1) provided light yellow power of compound **3c** in 70%.

3a. Yield: 83%; m.p. 147–148°C; ^1H NMR (400MHz, CDCl_3): 7.56 (d, 1H, $J = 1.4\text{Hz}$), 7.16 (d, 1H, $J = 1.7\text{Hz}$), 6.48 (d, 1H, $J = 6.4\text{Hz}$) (-NH), 4.68 (m, 1H) (-CH), 3.98 (s, 3H), 3.80 (s, 3H), 1.50 (d, 3H, $J = 7.1\text{Hz}$) (- CH_3); IR ν/cm^{-1} : 3354, 3125, 2966, 1720, 1665, 1526, 1373, 1314, 1212, 750; ESI-MS: 255.8 $[\text{M}+\text{H}]^+$, 277.8 $[\text{M}+\text{Na}]^+$.

3b. Yield: 84%; m.p. 153–154°C; ^1H NMR : 7.58 (d, 1H, $J = 1.7\text{Hz}$), 7.18 (d, 1H, $J = 1.9\text{Hz}$), 6.49 (br, 1H,) (-NH), 4.17 (d, 2H, $J = 5.3\text{Hz}$) (- CH_2), 3.98 (S, 3H), 3.82 (S, 3H); IR ν/cm^{-1} : 3399, 3135, 2958, 1724, 1665, 1520, 1324, 1231, 755; 241.5; ESI-MS: $[\text{M}+\text{H}]^+$, 263.3 $[\text{M}+\text{Na}]^+$,

3c. Yield: 70%; m.p. 96–97°C; ^1H NMR: 7.57 (d, 1H, $J = 2.0\text{Hz}$), 7.18 (d, 1H, $J = 2.0\text{Hz}$), 6.43 (d, 1H, $J = 8.4\text{Hz}$) (-NH), 4.64 (m, 1H) (-CH), 3.97 (S, 3H), 3.79 (S, 3H), 2.25 (m, 1H) (-CH), 1.0 (d, 3H, $J = 9.6\text{Hz}$), 0.98 (d, 3H, $J = 10\text{Hz}$); IR ν/cm^{-1} : 3367, 3138, 2945, 1747, 1645, 1522, 1315, 752; ESI-MS: 284.6 $[\text{M}+\text{H}]^+$, 306.6 $[\text{M}+\text{Na}]^+$.

3d. Yield: 87%; m.p. 99–100°C; ^1H NMR: 7.56 (d, 1H, $J = 1.6\text{ Hz}$), 7.16 (d, 1H, $J = 1.8\text{ Hz}$), 6.41 (d, 1H, $J = 8.1\text{ Hz}$) (-NH), 4.68 (m, 1H) (-CH), 3.96 (s, 3H), 3.78 (s, 3H), 1.97 (m, 1H), 1.48 (m, 1H), 1.26 (m, 1H), 0.96 (m, 6H, 2-CH₃); IR ν/cm^{-1} : 3312, 3130, 2953, 1742, 1642, 1527, 1313, 1207, 754; ESI-MS: 298.6 $[\text{M}+\text{H}]^+$, 320.6 $[\text{M}+\text{Na}]^+$.

3e. Yield: 66%; m.p. 118–119°C; ^1H NMR: 7.54 (s, 1H), 7.30 (m, 3H) (ph-H), 7.13 (m, 2H) (ph-H), 6.99 (d, 1H, $J = 2.0\text{ Hz}$), 6.30 (d, 1H, $J = 7.6\text{ Hz}$) (-NH), 4.97 (m, 1H) (-CH), 3.95 (s, 3H), 3.77 (s, 3H), 3.21 (m, 2H) (-CH₂-ph); IR ν/cm^{-1} : 3344, 3131, 1738, 1635, 1527, 1403, 1313, 751; ESI-MS: 330.1 $[\text{M}-\text{H}]^-$.

The Synthesis of Compound 4

To a solution of compound **3** (0.31 mmol) in 15 ml of CH₂Cl₂ was added Pd/C catalyst (10%), and the mixture was stirred under a slight positive pressure of H₂ at room temperature for 18 h. The catalyst was removed by filtration through Celite and the filtrate was added 1 ml Et₃N. The solution was cooled to -10°C and 0.2 ml (EtO)(n-C₄H₉O)POCl was dropped. The result solution was stirred for 24 h at this temperature. After filtrated and concentrated in vacuo, a yellow oil was obtained. Purification by column chromatography (CHCl₃:CHOH = 20:1), compound **4** was obtained in oil.

4a. ^1H NMR (400 MHz, CDCl₃): δ 6.50 (s, 1H), 6.35 (s, 1H), 6.34 (d, 1H), 5.13 (d, 1H, $J = 10.4\text{ Hz}$), 4.67 (m, 1H) (-CH), 4.08 (m, 4H) (2-OCH₂), 3.84 (s, 3H), 3.75 (s, 3H), 1.66 (m, 2H) (-CH₂), 1.47 (d, 3H, $J = 7.2\text{ Hz}$) (-CH₃), 1.37 (m, 5H) (-CH₂-CH₃), 0.92 (t, 3H, $J = 7.4\text{ Hz}$) (-CH₃); ^{31}P NMR: 3.96; IR ν/cm^{-1} : 3272, 2959, 1743, 1648, 1526, 1457, 1206, 1024; ESI-MS: 390.3 $[\text{M}+\text{H}]^+$, 412.3 $[\text{M}+\text{Na}]$.

4c. ^1H NMR: 6.52 (s, 1H), 6.35 (s, 1H), 6.24 (d, 1H, $J = 8.8\text{ Hz}$) (-NH), 4.98 (d, 1H, $J = 10.4\text{ Hz}$), 4.64 (m, 1H) (-CH), 4.09 (m, 4H) (2-OCH₂), 3.84 (s, 3H), 3.76 (s, 3H), 2.22 (m, 1H) (-CH), 1.67 (m, 2H) (-CH₂), 1.37 (m, 5H) (-CH₂-CH₃), 0.94 (m, 9H) (3-CH₃); ^{31}P NMR: 3.91; IR ν/cm^{-1} : 3436, 3268, 2962, 1741, 1653, 1509, 1462, 1239, 1025; ESI-MS: 418.3 $[\text{M}+\text{H}]^+$, 440.3 $[\text{M}+\text{Na}]^+$.

4d. ^1H NMR: 6.50 (s, 1H), 6.34 (s, 1H), 6.12 (d, 1H, $J = 8.4\text{ Hz}$) (-NH), 4.83 (d, 1H, $J = 7.4\text{ Hz}$), 4.71 (m, 1H) (-CH), 4.12 (m, 4H) (2-OCH₂), 3.84 (s, 3H), 3.75 (s, 3H), 1.67 (m, 6H) (3-CH₂), 1.37 (m, 5H) (-CH₂-CH₃), 0.94 (m, 9H) (3-CH₃); ^{31}P NMR: 3.98; IR ν/cm^{-1} : 3423, 2959, 1741, 1652, 1581, 1526, 1440, 1204, 1025; ESI-MS: 432.4 $[\text{M}+\text{H}]^+$.

The Synthesis of Compound 5

To a solution of $\text{NO}_2\text{PyPyCOOH}$ (0.513 g, 1.7 mmol) in 18 ml of DMF was added HOBt (0.2254 g, 1.7 mmol) and DCC solution (0.4326 g, 2.1 mmol DCC in 3 ml CH_2Cl_2). The solution was stirred for 4 h at room temperature. After filtrated, the active ester solution was obtained.

Separately, a solution of compound **3a** 0.4271 g (1.7 mmol) in 20 ml of CH_3OH was mixed with Pd/C catalyst (10%), and the mixture was stirred under a slight positive pressure of H_2 at room temperature for 12 h. The catalyst was removed by filtration through Celite and the filtrate was added to the active ester. Then 1 ml Et_3N was added to the mixture solution, followed by stirring 24 h. The desiccator was removed by filtration, and the filtrate was concentrated in vacuo. Column chromatography of the residue (eluant with CHCl_3 and MeOH 20:1) provided compound **5a** 0.4589 g (0.92 mmol) in 54%.

5a. Yield: 54%; m.p. 142–144°C; ^1H NMR (400MHz, CDCl_3): δ 8.65 (s, 1H), 8.04 (s, 1H), 7.58 (s, 2H), 7.47 (s, 1H), 7.27 (s, 1H), 7.17 (s, 1H), 6.69 (s, 1H), 6.46 (s, 1H), 4.75 (d, 1H, $J = 8.8\text{Hz}$) (-CH), 4.03 (s, 3H), 3.90 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 1.52 (d, 3H, $J = 7.2\text{Hz}$) ($-\text{CH}_3$); IR ν/cm^{-1} : 3398, 3130, 2930, 1738, 1649, 1527, 1400, 1309, 1206, 1112, 812; ESI-MS: 497.7 $[\text{M}-\text{H}]^-$ 522.3 $[\text{M}+\text{Na}]^+$.

5b. Yield: 44%; m.p. 237–239°C; ^1H NMR: 10.30 (s, 1H), 9.99 (s, 1H), 8.43 (t, 1H), 8.17 (s, 1H), 7.59 (s, 1H), 7.28 (s, 1H), 7.25 (s, 1H), 7.04 (s, 1H), 6.94 (s, 1H), 3.96 (s, 3H), 3.92 (s, 2H) ($-\text{CH}_2$), 3.86 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H); IR ν/cm^{-1} : 3124, 2925, 1740, 1657, 1555, 1438, 1406, 1307, 810, 774, 747; ESI-MS: 484.2 $[\text{M}-\text{H}]^-$.

5c. Yield: 51%; m.p. 141–43°C; ^1H NMR: 8.69 (s, 1H), 7.52 (s, 1H), 7.60 (s, 1H), 7.42 (s, 1H), 7.38 (s, 1H), 7.18 (s, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 6.38 (s, 1H), 4.73 (m, 1H), (-CH), 4.04 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 3.75 (s, 3H), 2.25 (m, 1H) (-CH), 1.01 (d, 3H, $J = 7\text{Hz}$), 0.99 (d, 3H, $J = 7\text{Hz}$); IR ν/cm^{-1} : 3422, 3286, 3138, 3114, 2961, 1739, 1652, 1589, 1523, 1465, 1311; ESI-MS: 526.3 $[\text{M}-\text{H}]^-$ 550.3 $[\text{M}+\text{Na}]^+$.

5d⁷. Yield: 57%; m.p. 135–137°C; ^1H NMR: 10.31 (s, 1H), 9.98 (s, 1H), 8.32 (s, 1H), 8.20 (d, 1H, $J = 1.64\text{Hz}$), 7.60 (s, 1H), 7.28 (s, 1H), 7.23 (s, 1H), 7.05 (s, 2H), 4.43 (m, 1H) (-CH), 3.97 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.64 (s, 3H), 1.52 (m, 1H), 1.71 (m, 1H), 1.61 (m, 1H), 0.91 (d, 3H, $J = 4.9\text{Hz}$), 0.87 (d, 3H, $J = 6.4\text{Hz}$); IR ν/cm^{-1} : 3450, 3351, 3308, 3130, 2953, 1737, 1648, 1526, 1367, 1311, 1225; ESI-MS: 540.2 $[\text{M}-\text{H}]^-$ 542.3 $[\text{M}+\text{H}]^+$ 564.3 $[\text{M}+\text{Na}]^+$.

The Synthesis of Compound 6

To a solution of compound **4a** 0.1530 g (0.31 mmol) in 15 ml of CH_2Cl_2 was added Pd/C catalyst (10%), and the mixture was stirred under a slight positive pressure of H_2 at room temperature for 18 h. The catalyst was removed by filtration through Celite and the filtrate was added 1 ml Et_3N . The solution was cooled to -10°C and 0.2 ml $(\text{EtO})(n\text{-C}_4\text{H}_9\text{O})\text{POCl}$ was dropped. The result solution was stirred 24 h at this temperature. After filtrated and concentrated in vacuo, a yellow oil was obtained. Purification by column chromatography ($\text{CHCl}_3:\text{CHOH} = 20:1$), 0.0823 g (1.29 mmol) compound **6a** was obtained in 41% yield.

6a. ^1H NMR (400MHz, CDCl_3): δ 8.70 (s, 1H), 8.11 (s, 1H), 7.28 (m, 2H), 6.82 (s, 1H), 6.76 (s, 1H), 6.64 (d, 1H, $J = 7.3\text{Hz}$), 6.47 (s, 2H), 6.22 (d, 1H, $J = 9.3\text{Hz}$) (-NH), 4.70 (m, 1H) (-CH), 4.02 (m, 4H) (2- OCH_2), 3.92 (s, 3H), 3.87 (s, 6H), 3.74 (s, 3H), 1.58 (m, 2H) (- CH_2), 1.49 (d, 3H, $J = 7.1\text{Hz}$) (- CH_3), 1.29 (m, 5H) (- $\text{CH}_2\text{-CH}_3$), 0.84 (t, 3H, $J = 7.4\text{Hz}$) (- CH_3); ^{31}P NMR: -6.82; IR ν/cm^{-1} : 3285, 2956, 1738, 1643, 1529, 1463, 1256, 1022, 777; ESI-MS: 634.3 $[\text{M}+\text{H}]^+$, 656.3 $[\text{M}+\text{Na}]^+$.

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