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Synthesis of α-Aminoalkyl Phosphonate Derivatives of Resveratrol as Potential Antitumour Agents

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Several α-aminoalkyl phosphonate derivatives of resveratrol were first prepared by partial synthesis from resveratrol. Antitumour activities of the synthesized compounds were determined against a human nasopharyngeal epidermoid tumour cell line KB and a human normal cell line L02 in vitro. The results indicated that these compounds showed good cytotoxic activity against KB but weak cytotoxic activity against L02. Compounds **5c** and **5d** showed significant cytotoxic activity against KB, with median inhibition concentration (IC_{50}) values of 0.4 μM and 0.9 μM, respectively. On the basis of the biological results, the structure–activity relationship is discussed concisely. The potent antitumour activities shown by **5c** and **5d** make these resveratrol phosphonate derivatives of great interest for further investigations.

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Introduction

Resveratrol, a naturally occurring phytoalexin (*trans*-3,5,4′-trihydroxy-*trans*-stilbene) present in grapes, berries, peanuts, and red wine,[1,2] has been suggested as a potential cancer chemopreventive agent based on its striking inhibitory effects on cellular events associated with cancer initiation, promotion, and progression.[3] Extensive data in human cell cultures indicate that resveratrol exhibits activity against a wide variety of cancer cells such as hepatoma,[4,5] gastric cancer,[6] leukemia,[7] lung cancer,[8] prostate cancer,[9] breast cancer,[10] skin cancer,[11,12] and so on. The simplicity of resveratrol, associated with its interesting anticancer activity, offers promise for the rational design of new chemotherapeutic agents, and efforts have recently been devoted regarding a detailed study on the structure–activity relationships (SAR) of this type of substituted stilbene derivatives.[13,14] We have been exploring the antitumour properties of a series of methoxylated resveratrol derivatives modified by the introduction of lipophilic chains in the C2 position of the molecule.[15] Among them, several compounds exhibited similar activity to 5-fluorouracil (5-FU), an anticancer drug.

Many α-aminophosphonate derivatives have been reported to possess antitumour activities.[16,17] It is known that phosphorus substituents regulate important biological functions and that molecular modifications involving the introduction of organophosphorus functionalities could increase their biological activity.[18–20]

Enlightened by these positive results and in continuation of our work, we were encouraged to design and synthesize a series of α-aminoalkyl phosphonate derivatives of resveratrol for antitumour evaluation and SAR analysis. In the present work, we describe the effective synthesis, and in vitro cytotoxic activities against a human nasopharyngeal epidermoid tumour cell line KB of eight new α-aminoalkyl phosphonate derivatives of resveratrol and their SAR.

Results and Discussion

Chemistry

In a previous study on resveratrol, we prepared a series of methoxylated resveratrol derivatives modified in the C2 position.[15] To explore more potent antitumour agents, phosphonate was introduced into the structure of resveratrol.

The preparation of resveratrol analogues is outlined in Scheme 1. Treatment of resveratrol with $(CH_3)_2SO_4$ in 10% NaOH solution under nitrogen afforded compound **2**. Vilsmeier formylation of compound **2** by treatment with a slight excess of $POCl_3$ in DMF at 0°C yielded aldehyde compound **3**. Then, condensation reaction of compound **3** with a series of amines afforded the Schiff bases, which were treated with diethyl phosphite and 4-methylbenzenesulfonic acid (TsOH) to afford the targeted compounds (Scheme 1 and Fig. 1).

Biological Activity

All of the compounds were tested for cytotoxic activity against a human nasopharyngeal epidermoid tumour cell line KB and a human normal cell line L02. The results are summarized in Table 1. The results showed that most of the compounds exhibited good cytotoxic activity against KB but weak cytotoxic activity against L02. In our previous study,[15] compound **3** showed the most potent cytotoxic activity. In the present study, as expected, most of the α-aminoalkyl phosphonate derivatives of resveratrol exhibited better activity than compound **3**. This result indicated the introduction of the phosphonate group was able to significantly improve the activity of resveratrol derivatives. Among these phosphonate compounds, compounds **5c**, **5d**, **5e**, **5f**, except

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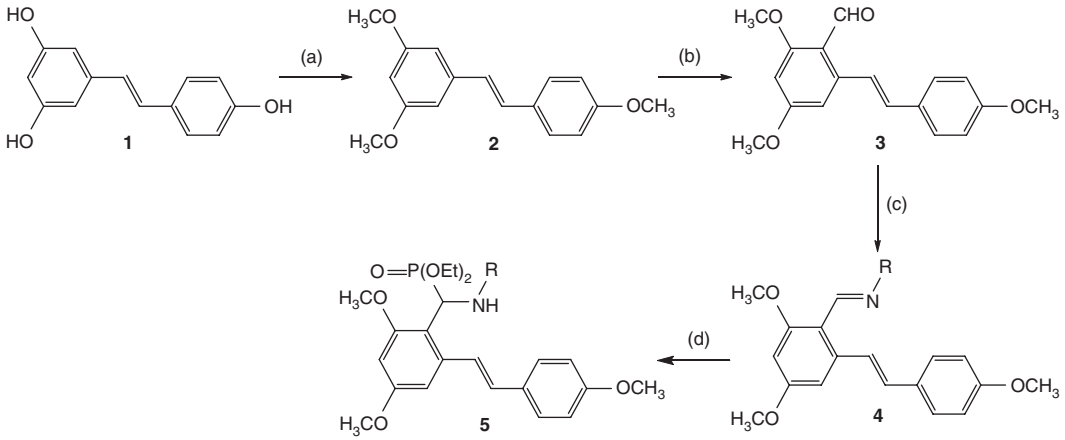

Scheme 1. Synthesis of the resveratrol analogues. Reagents and conditions: (a) $(CH_3)_2SO_4$, 10% NaOH, 0–40°C, 76% yield; (b) $POCl_3$, DMF, 0°C, 69% yield; (c) RNH_2, ethanol, reflux; (d) diethyl phosphite, 4-methylbenzenesulfonic acid (TsOH), ethanol, 80°C, 65–78% yield.

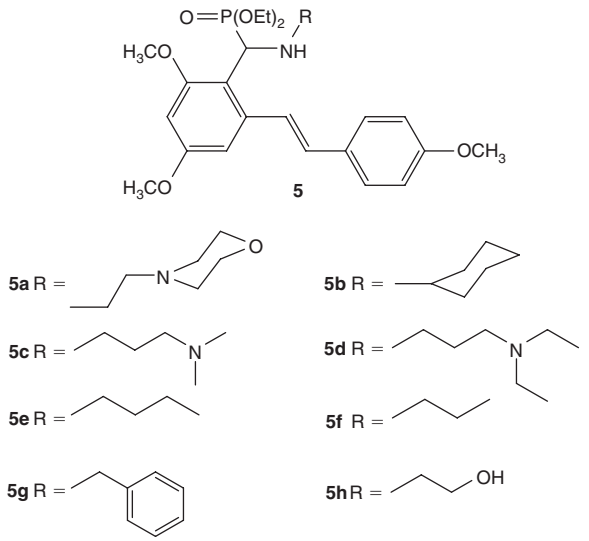

Fig. 1. Structures of **5a**–**5h**.

Table 1. Cytotoxic activity of synthesized compounds against a human nasopharyngeal epidermoid tumour cell line KB and a human normal cell line L02

IC_{50} = 50% inhibitory concentration represents the mean ± s.d. from dose–response curves of at least three experiments

Compound	KB (IC_{50} [μM])	L02 (IC_{50} [μM])
1	>80	>80
2	10.2 ± 0.5	46.5 ± 1.5
3	8.9 ± 0.3	43.7 ± 0.3
5a	3.2 ± 0.1	25.6 ± 2.1
5b	11.5 ± 0.2	63.4 ± 3.6
5c	0.4 ± 0.1	15.4 ± 0.5
5d	0.9 ± 0.1	26.9 ± 1.2
5e	5.2 ± 0.1	35.4 ± 2.3
5f	6.5 ± 0.1	39.5 ± 2.0
5g	12.1 ± 0.8	70.6 ± 3.2
5h	28.2 ± 2.2	>80
5-fluorouracil	13.4 ± 0.2	16.7 ± 0.4

for **5h**, containing straight side chains showed better activities against KB than compounds **5b** and **5g** containing ringed side chains. Compound **5a** containing a morpholine ring side chain also exhibited higher activity against KB than compounds **5b** and **5g**. Of all the compounds, **5c** and **5d**, bearing two nitrogen atoms in their side chains, showed activity 30- and 15-fold (median inhibition concentration (IC_{50}) = 0.4 μM and 0.9 μM, respectively) higher than 5-FU, an anticancer drug. In contrast, introduction of an OH group in the side chain decreased the inhibitory activity (IC_{50} value of compound **5h** = 28.2 μM); this may be due to the hydrophilicity of the OH group hindering the compound from permeating the cell membrane.

Conclusions

In summary, we synthesized a series of α-aminoalkyl phosphonate derivatives of resveratrol and examined their cytotoxic activity against a human nasopharyngeal epidermoid tumour cell line KB. According to the above results, introduction of phosphonate was able to significantly improve the activity of resveratrol derivatives, probably because the phosphonate group makes the compounds transport through the cell membrane easily. Altogether, our findings might provide novel promising strategies to synthesize more potent antitumour agents derived from resveratrol.

Experimental

General

Resveratrol was bought from Xi'an Mingzhu Co., Xi'an, China. ^{1}H NMR spectra were recorded on a Bruker DRX 500 or DPX 300 model spectrometer in [D_6]DMSO. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million relative to residual solvent protons. Electrospray ionization-mass spectrometry spectra were recorded on a Mariner System 5304 Mass spectrometer. Melting points were obtained by using a Boetius micromelting point apparatus. Elemental analyses were performed on a CHN-O-Rapid instrument. Flash-column chromatography was performed on silica gel Merck Kieselgel 60 (230–400 mesh). TLC was performed on silica gel plates (GF_{254}, Merk); spots were detected visually by ultraviolet irradiation (254 nm).

Synthesis of trans-*3,4′,5-Trimethoxystilbene* ***2***

Dimethyl sulfate (4.9 mL) was dropped into a solution of 456 mg (2 mmol) of compound **1** in 5 mL of aq. NaOH (10%)

under an atmosphere of nitrogen while cooling with an ice/water bath, keeping the rate such that the temperature of the reaction solution was under 40°C. The mixture was stirred for 2 h, and extracted with 10 mL of EtOAc twice. The organic layer was washed with water, dried over Na_2SO_4, and evaporated under vacuum. Purification by silica gel (petroleum ether/dichloromethane, 1:1, $R_f = 0.25$) afforded compound **2** (colourless crystalline solid, 410 mg, 1.52 mmol, yield 76%), mp 54–56°C. ESI MS 271.3 $[M + H]^+$. δ_H ([D$_6$]DMSO) 3.77 (s, 9H), 6.39 (s, 1H), 6.74 (s, 2H), 6.94 (d, 2H, *J* 8.4), 7.02 (d, 1H, *J* 16.4), 7.21 (d, 1H, *J* 16.4), 7.53 (d, 2H, *J* 8.4). Calc. for $C_{17}H_{18}O_3$: C 75.53, H 6.71. Found: C 75.61, H 6.74%.

Synthesis of trans*-2-Formyl-3,4′,5-trimethoxystilbene* ***3***

To a solution of 270 mg (1 mmol) of compound **2** in 5 mL of DMF was added dropwise 200 μL (0.21 g, 1.0 mmol) of $POCl_3$ while cooling with an ice/water bath. The reaction mixture was stirred for 30 min at room temperature. The solution was added to a mixture of ice and water, and the yellow solution was extracted with three 10-mL portions of dichloromethane. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered, evaporated, and recrystallized from dichloromethane, and afforded compound **3** (yellow solid, 206 mg, 0.69 mmol, yield 69%), mp 108–109°C. ESI MS 299.3 $[M + H]^+$. δ_H ([D$_6$]DMSO) 3.78 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.63 (s, 1H), 6.91 (s, 1H), 6.97 (d, 2H, *J* 7.9), 7.21 (d, 1H, *J* 16.2), 7.50 (d, 2H, *J* 7.9), 7.95 (d, 1H, *J* 16.2), 10.41 (s, 1H). Calc. for $C_{18}H_{18}O_4$: C 72.74, H 6.08. Found: C 72.56, H 6.11%.

General Procedure for the Synthesis of ***5a–5h***

Compound **3** (1 mmol) was dissolved in 5 mL of ethanol, and amine was added to the solution. The reaction mixture was refluxed for 30 min. Then, 2 mmol of diethyl phosphite and 0.1 mmol of TsOH were added to the reaction solution, and stirred at 80°C for 4 h. The mixture was evaporated under vacuum, and added to 10 mL of water, and the solution was extracted with 5-mL portions of EtOAc twice. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by silica gel (petroleum spirits/ethyl acetate 3:1, R_f values ranged from 0.2 to 0.3) afforded pure products.

*(*E*)-Diethyl 1-(*N*-Morpholinoethylamino)-1-[2-(4-methoxystyryl)-4,6-dimethoxyphenyl] methanephosphonate* ***5a***

White powder, yield 70%, mp 72–74°C. ESI MS 549.3 $[M + H]^+$. δ_H ([D$_6$]DMSO) 0.99 (t, 3H, *J* 7.0), 1.32 (t, 3H, *J* 7.0), 2.09–2.12 (m, 2H), 2.26–2.29 (m, 2H), 2.40–2.43 (m, 2H), 2.49–2.53 (m, 2H), 3.28–3.33 (m, 4H), 3.73 (q, 2H, *J* 7.0), 3.81 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.20 (q, 2H, *J* 7.0), 4.98 (d, 1H, *J* 26.8), 6.51 (s, 1H), 6.84 (s, 1H), 6.94 (d, 2H, *J* 8.4), 7.00 (d, 1H, *J* 16.4), 7.62 (d, 2H, *J* 8.4), 8.40 (d, 1H, *J* 16.4). Calc. for $C_{28}H_{41}N_2O_7P$: C 61.30, H 7.53, N 5.11. Found: C 61.38, H 7.58, N 5.06%.

*(*E*)-Diethyl 1-(*N*-Cyclohexylamino)-1-[2-(4-methoxystyryl)-4,6-dimethoxyphenyl] methanephosphonate* ***5b***

White powder, yield 78%, mp 65–67°C. ESI MS 518.3 $[M + H]^+$. δ_H ([D$_6$]DMSO) 0.99 (t, 3H, *J* 7.0), 1.01–1.15 (m, 4H), 1.17–1.20 (m, 2H), 1.32 (t, 3H, *J* 7.0), 1.47–1.51 (m, 2H), 1.60–1.63 (m, 2H), 1.72–1.76 (m, 1H), 3.72 (q, 2H, *J* 7.0), 3.81 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.98 (d, 1H, *J* 26.8), 5.12 (q, 2H, *J* 7.0), 6.52 (s, 1H), 6.73 (s, 1H), 6.92–6.96 (m, 3H), 7.57 (d, 2H, *J* 8.4), 8.48 (d, 1H, *J* 16.4). Calc. for $C_{28}H_{40}NO_6P$: C 64.97, H 7.99, N 2.71. Found: C 65.04, H 8.08, N 2.66%.

*(*E*)-Diethyl 1-[*N*-3-(Dimethylamino)propylamino]-1-[2-(4-methoxystyryl)-4,6-dimethoxyphenyl] methanephosphonate* ***5c***

White powder, yield 73%, mp 77–79°C. ESI MS 521.2 $[M + H]^+$. δ_H ([D$_6$]DMSO) 0.91 (t, 3H, *J* 7.0), 1.12–1.15 (m, 2H), 1.22 (t, 3H, *J* 7.0), 2.38–2.43 (m, 6H), 2.57–2.80 (m, 4H), 3.39–3.42 (m, 2H), 3.72–3.80 (m, 11H), 4.57 (d, 1H, *J* 26.8), 6.50 (s, 1H), 6.73 (s, 1H), 6.85–6.96 (m, 3H), 7.55 (d, 2H, *J* 8.4), 8.39 (d, 1H, *J* 16.4). Calc. for $C_{27}H_{41}N_2O_6P$: C 62.29, H 7.94, N 5.38. Found: C 62.18, H 7.81, N 5.26%.

*(*E*)-Diethyl 1-[*N*-3-(Diethylamino)propylamino]-1-[2-(4-methoxystyryl)-4,6-dimethoxyphenyl] methanephosphonate* ***5d***

White powder, yield 68%, mp 84–86°C. ESI MS 549.3 $[M + H]^+$. δ_H ([D$_6$]DMSO) 0.90–0.94 (m, 6H), 1.11–1.14 (m, 2H), 1.20–1.24 (m, 6H), 2.30–2.34 (m, 2H), 2.40–2.43 (m, 4H), 2.57–2.61 (m, 2H), 3.22–3.26 (m, 2H), 3.71 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 4.02–4.04 (m, 2H), 4.63 (d, 1H, *J* 26.8), 6.51 (s, 1H), 6.72 (s, 1H), 6.86–6.97 (m, 3H), 7.46 (d, 2H, *J* 8.4), 8.12 (d, 1H, *J* 16.4). Calc. for $C_{29}H_{45}N_2O_6P$: C 63.48, H 8.27, N 5.11. Found: C 63.44, H 8.12, N 5.23%.

*(*E*)-Diethyl 1-(*N*-Butylamino)-1-[2-(4-methoxystyryl)-4,6-dimethoxyphenyl] methanephosphonate* ***5e***

White powder, yield 65%, mp 63–65°C. ESI MS 492.3 $[M + H]^+$. δ_H ([D$_6$]DMSO) 0.79 (t, 3H, *J* 7.0), 0.93–0.98 (m, 3H), 1.18–1.36 (m, 7H), 2.25–2.30 (m, 2H), 3.63–3.68 (m, 2H), 3.77 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 4.07–4.10 (m, 2H), 4.82 (d, 1H, *J* 26.8), 6.50 (s, 1H), 6.76 (s, 1H), 6.93–6.99 (m, 3H), 7.51 (d, 2H, *J* 8.4), 8.15 (d, 1H, *J* 16.4). Calc. for $C_{26}H_{38}NO_6P$: C 63.53, H 7.79, N 2.85. Found: C 63.62, H 7.85, N 2.93%.

*(*E*)-Diethyl 1-(*N*-Propylamino)-1-[2-(4-methoxystyryl)-4,6-dimethoxyphenyl] methanephosphonate* ***5f***

White powder, yield 76%, mp 59–61°C. ESI MS 478.3 $[M + H]^+$. δ_H ([D$_6$]DMSO) 0.68 (t, 3H, *J* 7.3), 0.97 (t, 3H, *J* 6.9), 1.15–1.30 (m, 5H), 2.22 (t, 2H, *J* 6.7), 3.70–3.71 (m, 2H), 3.75 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 4.03–4.10 (m, 2H), 4.86 (d, 1H, *J* 26.8), 6.53 (s, 1H), 6.77 (s, 1H), 6.95–7.01 (m, 3H), 7.53 (d, 2H, *J* 8.4), 8.18 (d, 1H, *J* 16.4). Calc. for $C_{25}H_{36}NO_6P$: C 62.88, H 7.60, N 2.93. Found: C 62.72, H 7.55, N 2.87%.

*(*E*)-Diethyl 1-(*N*-Benzylamino)-1-[2-(4-methoxystyryl)-4,6-dimethoxyphenyl] methanephosphonate* ***5g***

White powder, yield 68%, mp 92–94°C. ESI MS 526.4 $[M + H]^+$. δ_H ([D$_6$]DMSO) 0.94 (t, 3H, *J* 7.0), 1.23 (t, 3H, *J* 7.0), 3.64–3.68 (m, 4H), 3.77 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 4.04–4.06 (m, 2H), 4.84 (d, 1H, *J* 26.8), 6.50 (s, 1H), 6.56 (s, 1H), 6.80–6.81 (m, 1H), 6.82–6.88 (m, 2H), 6.90–6.92 (m, 2H), 7.19–7.21 (m, 2H), 7.35–7.37 (m, 2H), 7.51–7.52 (m, 1H), 8.24 (d, 1H, *J* 16.4). Calc. for $C_{29}H_{36}NO_6P$: C 66.27, H 6.90, N 2.67. Found: C 66.24, H 6.82, N 2.59%.

(E)-Diethyl 1-(N-2-Hydroxyethylamino)-1-[2-(4-methoxystyryl)-4,6-dimethoxyphenyl] methanephosphonate ***5h***

White powder, yield 72%, mp 115–117°C. ESI MS 480.3 $[M+H]^+$. δ_H ([D_6]DMSO) 0.73 (t, 3H, *J* 7.3), 0.98 (t, 3H, *J* 6.9), 2.72–2.76 (m, 2H), 3.61–3.63 (m, 2H), 3.71–3.75 (m, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 3.93 (s, 3H), 4.05–4.08 (m, 2H), 4.86 (d, 1H, *J* 26.8), 6.53 (s, 1H), 6.77 (s, 1H), 6.95–7.01 (m, 3H), 7.53 (d, 2H, *J* 8.4), 8.18 (d, 1H, *J* 16.4). Calc. for $C_{24}H_{34}NO_7P$: C 60.12, H 7.15, N 2.92. Found: C 60.24, H 7.22, N 2.98%.

Cytotoxicity Assay Against KB Cells

The cytotoxicity was evaluated as described elsewhere[21] with some modifications. Briefly, target tumour cells were grown to log phase in RPMI 1640 medium supplemented with 10% fetal bovine serum. After diluting to 2×10^4 cells mL^{-1} with the complete medium, 100 mL of the cell suspension obtained was added to each well of 96-well culture plates. The subsequent incubation was carried out at 37°C, 5% CO_2 atmosphere for 24 h before the cytotoxicity assessments. Tested samples at preset concentrations were added to six wells with 5-FU co-assayed as a positive reference. After a 48-h exposure period, 40 mL of phosphate buffered saline containing 2.5 mg mL^{-1} of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added to each well. Four hours later, the medium was replaced by 150 mL DMSO to solubilize the purple formazan crystals produced. The absorbance at 570 nm of each well was measured on an ELISA plate reader. The IC_{50} value was defined as the concentration at which 50% survival of cells occurred.

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