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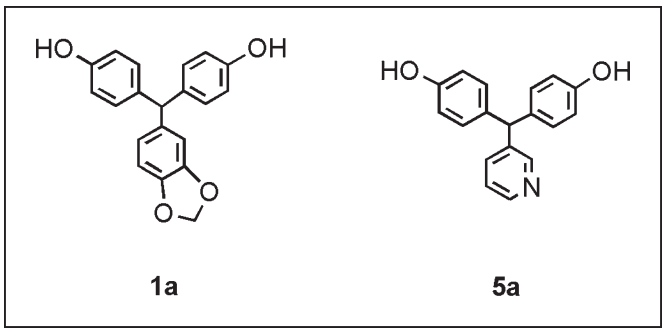

Some molecular modifications were attempted to find antiviral active compounds in the class of triarylmethanes against herpes simplex virus type 1 (HSV-1). All the synthesized compounds were evaluated for antiviral activity with HSV-1 by a plaque reduction assay. Some of the compounds showed significant antiviral activities.

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INTRODUCTION

In our synthetic studies on antiviral compounds, we found that some triarylmethane derivatives showed significant activity against herpes simplex virus type 1 (HSV-1) in a plaque reduction assay [1–3]. Most of the compounds, which were synthesized previously, showed a wide range of activities against the HSV-1 virus. Molecular modifications of this class of compounds seemed interesting, and we therefore carried out further synthetic investigation and evaluation of this new class of derivatives.

In this series, we recently reported that the triarylmethane scaffold derivative **1a** showed a higher level of antiviral activity (EC_{50} = 2.1 μM) and lower cytotoxicity (IC_{50} = 79.3 μM) than those of the corresponding 4,4′-dihydroxytriphenylmethane derivative **2**, showing antiviral activity (EC_{50} = 5.5 μM, IC_{50} = 38.1 μM) [1]. Compound **1a** is composed of a heterocyclic methylenedioxy group instead of the 4-methoxyphenyl group in **2**. Phosphorylated aciclovir and many nucleoside phosphates have also shown significant antiviral activity [4–6]. A methane-based symmetrical tri-indolemethane **3** for enhancement of chemically induced HL-60 cell differentiation has recently been reported [7]. The corresponding tri-indolemethyl cation (turbomycin A) was isolated from soil microbial DNA, and it exhibited broad antibiotic activity against gram-negative and gram-positive organisms [8]. Therefore, the alteration of a phenyl ring to other heterocycles or the introduction of phosphoryl ester functionalities into the products has attracted our attention as a potential approach to find new antiviral active compounds.

We describe here, the preparation of some new heteroaryl (pyridine or pyrrole ring)-substituted triarylmethane derivatives. For the purpose of structural comparison nonheterocyclic 4,4′,4″-trihydroxytriphenylmethane **4a** was chosen. We also attempted the transformation of hydroxyl groups of products to phosphoryl ester functionalities. Results of plaque reduction assays to assess the anti-HSV-1 activities of these compounds are also presented.

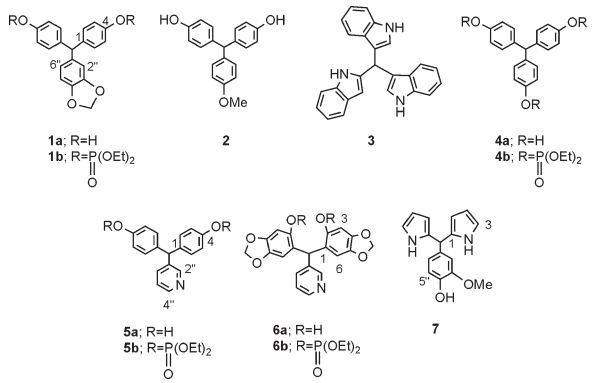
RESULTS AND DISCUSSION

Chemistry. We have already reported [1] the procedure for synthesis of compound **1a** by condensation of phenol and aldehyde using various Brønsted acids. The reaction of phenol and aldehyde (piperonal) with sulfuric acid in the shade for **1a** improved the yield to 93%.

Heteroaryl-substituted triarylmethane derivatives **5a** or **7** containing pyridine or pyrrole rings were easily synthesized in excellent yield by the reaction of phenol and nicotinaldehyde or the reaction of pyrrole and vanillin using trifluoroacetic acid (TFA) as a Brønsted acid. For compound **6a**, the reaction of bromomagnesium phenolate of sesamol with nicotinaldehyde at a reaction

Table 1

Physical data of triarylmethane derivatives (**1** and **4–7**)



Compound	mp (°C) (Recryst solvent) Appearance	Formula	Analysis (%) Calcd (Found) C	H	N	Formula, HR-MS *m/z* Calcd (Found)	IR (cm^{-1}) (KBr)
1b	Pale yellow oil	$C_{28}H_{34}O_{10}P_2$ · $1.5H_2O$	54.28 (54.36	6.02 6.29	0.00 0.00)	$C_{28}H_{35}O_{10}P_2$ $(M + H)^+$ 593.1705 (593.1705)	3490 (OH) 1275 (P=O) 1030 (P—O)
4b	Pale yellow oil	$C_{31}H_{43}O_{12}P_3$ · $2.5H_2O$	49.94 (49.95	6.49 6.43	0.00 0.00)	$C_{31}H_{44}O_{12}P_3$ $(M + H)^+$ 701.2046 (701.2046)	3500 (OH) 1270 (P=O) 1025 (P—O)
5a	239–244 (CH_3CN-H_2O) colorless powder	$C_{18}H_{15}NO_2$ · $0.2H_2O$	76.96 (77.03	5.53 5.56	4.99 5.16)	$C_{18}H_{16}NO_2$ $(M + H)^+$ 278.1181 (278.1182)	3240 (OH) 1260 (C—O) 1105 (C—O)
5b	Pale yellow viscous solid[a]	$C_{26}H_{33}NO_8P_2$ · $0.3H_2O$	56.28 (56.27	6.10 6.18	2.52 2.50)	$C_{26}H_{34}NO_8P_2$ $(M + H)^+$ 550.1760 (550.1757)	3500 (OH) 1275 (P=O) 1030 (P—O)
6b	Yellow oil	$C_{28}H_{33}NO_{12}P_2$ · $0.8H_2O$	51.59 (51.63	5.35 5.34	2.15 2.11)	$C_{28}H_{34}NO_{12}P_2$ $(M + H)^+$ 638.1556 (638.1557)	3495 (OH) 1275 (P=O) 1025 (P—O)
7	117-120 (*iso*-PrOH) pale purple crystals	$C_{16}H_{16}N_2O_2$	71.62 (71.64	6.01 6.09	10.44 10.43)	$C_{16}H_{16}N_2O_2$ (M^+) 268.1212 (268.1214)	3420 (OH) 3320 (NH) 1230 (C—O)

[a] Consistent and correct mp could not be obtained because this compound is a viscous material.

temperature of 30°C and a long reaction time (2 d) gave an excellent result (84% yield).

The phosphorylation of hydroxyl groups of tri- or dihydroxytriarylmethanes **1a** and **4–6b** gave tris- or bis- phosphoryl esters (**1b** and **4–6a**) by the reported procedures [9,10]. Thus, the phosphorylation of hydroxygroups was accomplished by a slight excess of $(EtO)_2POH$ in the presence of Et_3N in CCl_4 from 0°C to room temperature overnight to give the products **1b** and **4–6b** in 11–89% yields. Compounds **5b** and **6b** were obtained under the conditions of a slight excess of $(EtO)_2POCl$ in the presence of NaH at room temperature for 1 h in 43% and 66% yields, respectively. In both methods, the yields of phosphorylated products depend on the solubility of the starting tri- or dihydroxytriarylmethanes. In fact, the addition of THF or DMF to improve the solubility of the reaction solvent resulted in better yields of the corresponding phosphorylated products (see experimental).

All of the structures of the new compounds synthesized were determined by using spectroscopic data and elemental analyses, and the signal assignments were confirmed by 2D-NMR analyses (Tables 1 and 2).

Biological activities

Antiviral activities. The anti-HSV-1 activities of the synthesized compounds were estimated by using plaque reduction assays in Vero cells [11]. The results of the assays are summarized in Table 3 together with the data for the original compounds **1a** [1] and **6a** [1].

Substitution with a pyridine ring (compound **5a**) resulted in antiviral activity (EC_{50} = 6.8 μM, IC_{50} =

Table 2

^{13}C- and ^{1}H-NMR data of triarylmethane derivatives (**1** and **4**—**7**) (δ ppm, *J* Hz).[a]

	1b		**4b**		**5a**		**5b**		**6b**		**7**	
Position	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	140.41		140.07		133.60		139.05		123.89 d (8.3)		125.48	
2	130.42	7.04 d (8.5)	130.48	7.02 d (8.85)	129.66	6.89 d (8.5)	130.40	7.04 d (8.7)	142.79 d (7.2)			
3	119.77 d (5.2)	7.13 d (8.5)	119.87 d (4.1)	7.13 dd (8.85, 1.1)	115.08	6.70 d (8.5)	120.11 d (5.2)	7.16 d (8.7)	102.18	7.01 s	108.29	6.61–6.64 m[b]
4	149.24 d (7.2)		149.37 d (3.2)		155.65		149.63 d (7.2)		144.65 or 147.27		98.49	5.98 t (2.9)
5	119.77 d (5.2)	7.13 d (8.5)	119.87 d (4.1)	7.13 dd (8.85, 1.1)	115.08	6.70 d (8.5)	120.11 d (5.2)	7.16 d (8.7)	147.27 or 144.65		97.81	5.72–5.74 m
6	130.42	7.04 d (8.5)	130.48	7.02 d (8.85)	129.66	6.89 d (8.5)	130.40	7.04 d (8.7)	109.11	6.24 s		
OH						9.24 s						
—CH <	55.05	5.40 s	54.75	5.46 s	51.69	5.41 s	53.02	5.50 s	41.47	6.12 s	35.45	5.30 s
1″	137.34		140.07		140.32		138.98		140.91		127.00	
2″	109.71	6.55 d (1.8)	130.48	7.02 d (8.85)	149.94	8.33 d (1.8)	150.53	8.40 br s	149.20	8.57 s	103.96	6.75 d (2.1)
3″	147.77		119.87 d (4.1)	7.13 dd (8.85, 1.1)							139.19	
4″	146.18		149.37 d (3.2)		147.06	8.39 dm (4.9)	147.86	8.48 br d (3.7)	146.88	8.56 dd (5.5)	136.47	
5″	108.03	6.71 d (7.9)	119.87 d (4.1)	7.13 dd (8.85, 1.1)	123.20	7.30 dd (7.9, 4.9)	123.34	7.23 m	124.88	7.44 dd (7.9, 5.5)	106.29	6.70 d (8.2)
6″	122.37	6.52 ddd (7.9, 1.8, 0.6)	130.48	7.02 d (8.85)	136.01	7.43 dm (7.9)	136.65	7.37 m	140.20	7.68 d (7.9)	112.58	6.61–6.64 m[b]
—OCH_2O—	100.96	5.92 s							101.94	5.95 s		
	P—O—CH_2CH_3; 16.00 d (7.2) (CH_3), 64.60 d (6.2) (CH_2).	P—O—CH_2CH_3; 1.35 dt (7.0, 1.2) (CH_3), 4.21 ddq (8.2, 7.0, 2.7) (CH_2).	P—O—CH_2CH_3; 16.04 d (7.3) (CH_3), 64.55 d (6.2) (CH_2).	P—O—CH_2CH_3; 1.35 dt (7.0, 0.9) (CH_3), 4.21 ddq (8.2, 7.0, 2.7) (CH_2).			P—O—CH_2CH_3; 16.04 d (7.2) (CH_3), 64.57 d (6.2) (CH_2)	P—O—CH_2CH_3; 1.35 dt (7.0, 0.9) (CH_3), 4.22 ddq (8.2, 7.0, 2.7) (CH_2)	P—O—CH_2CH_3; 16.03 and 16.08 d (5.2) (CH_3), 64.88 and 64.92 d (11.3) (CH_2)	P—O—CH_2CH_3; 1.22 and 1.27 dt (7.0, 0.9) (CH_3), 4.03 m (CH_2)	OMe; 46.84	OMe; 3.72 s

[a] **1** and **4–6b** were measured in $CDCl_3$; **5a** and **7** were measured in DMSO-d_6 and CD_3OD, respectively.
[b] Two signals coincided.

Table 3

Antiviral activity (EC_{50}) and cytotoxicity (IC_{50}) against HSV-1.

	EC_{50} (μM)	I C_{50} (μM)	IC_{50}/EC_{50}
1a[a]	2.1	79.3	38.2
1b	>16	21.3	<1.3
4a	22.6	127	5.6
4b	8.6	19.8	2.3
5a	6.8	54.1	7.9
5b	>36	39.6	<1.1
6a[a]	7.3	>135	>18.5
6b	49.1	87.6	1.8
7	>150	190	<1.3

[a] The data of the compounds from [1].

54.1 μM) similar to that of compound **6a** (EC_{50} = 7.3 μM, IC_{50} > 135 μM) previously reported [1]; however, its cytotoxicity was increased to that of 2,2′-dihydroxytriarylmethane **6a**. The introduction of two pyrrole rings with an N—H group (compound **7**) resulted in no significant antiviral activity at a concentration of 150 μM. Thus, two hydroxyl groups on the triphenylmethane scaffold might be necessary to show significant antiviral potency.

The phosphorylation of hydroxyl groups of **1a**, **5a**, and **6a** resulted in increased cytotoxicity in both transformations into **1b**, **5b**, and **6b**, respectively. Transformation of nonheterocyclic derivative **4a** into **4b** also showed a similar tendency. Phosphorylated triphenylmethane derivative **4b** showed a higher level of antiviral activity than that of original compound **4a**, but antiviral activities of both heteroaryl-substituted derivatives **5b** and **6b** were lower than those of the corresponding **5a** and **6a**, respectively. With reference to the phosphorylated hetero-ring substituted derivative **1b**, its antiviral activity was also lower than that of the corresponding nonphosphorylated original compound **1a**. Compounds synthesized in this study showed inhibitory concentrations (EC_{50}) ranging from 6.8 to > 150 μM. Among these compounds, we found that **5a** has the highest level of activity against HSV-1 (EC_{50} = 6.8 μM), but its selectivity index was 7.9.

In this study on modification of triarylmethanes by alteration of heteroaryl rings and transformation into phosphorylated derivatives, unfortunately, we could not find more potent antiviral compounds than the 4,4′-dihydroxytriarylmethane **1a** reported previously [1]. Throughout this work, however, it is notable that compounds **5a** and **6a** containing a heteroaryl group (pyridine) showed higher levels of antiviral activity than that of C_3 symmetrical 4,4′,4″-trihydroxytriphenylmethane **4a** (EC_{50} = 22.6 μM), and the C_3 symmetry structure of both compounds (a prochiral symmetrical molecule) was destroyed by introducing a different heteroaryl ring in the molecule. To elucidate these phenomena, further molecular modifications of triarylmethanes and evaluation of their activity against HSV-1 are underway.

EXPERIMENTAL

Melting points were determined using a micro melting point apparatus (Yanagimoto MP-S3) without correction. IR spectra were measured by a Shimadzu FTIR-8100 IR spectrophotometer. Low- and high-resolution mass spectra (LR-MS and HR-MS) were obtained by a JEOL JMS HX-110 double-focusing model equipped with a FAB ion source interfaced with a JEOL JMA-DA 7000 data system. ^{1}H- and ^{13}C-NMR spectra were obtained by JEOL JNM A-500. Chemical shifts were expressed in δ ppm downfield from an internal tetramethylsilane signal for ^{1}H-NMR and the carbon signal of the corresponding solvent [$CDCl_3$ (77.00 ppm), CD_3OD (39.50 ppm), and dimethyl sulfoxide (DMSO)-d_6 (39.50 ppm)] for ^{13}C-NMR. Microanalyses were performed with a Yanaco MT-6 CHN corder. Routine monitoring of reactions was carried out using precoated Kieselgel $60F_{254}$ plates (E. Merck). Centrifugal or flash column chromatography was performed on silica gel (Able-Biott or Fuji Silysia FL60B, respectively) with a UV detector. Preparation of compounds (**1a** [1], **4a** [1], and **6a** [4]) have already been reported. Commercially available starting materials including **4a** were used without further purification.

4,4′-(1,3-Benzodioxol-5-ylmethylene)bisphenol (1a) [1]. To a solution of phenol (755 mg, 8.0 mmol) and 3,4-methylenedioxybenzaldehyde (600 mg, 4.0 mmol) in AcOH (2.3 mL) was added conc. H_2SO_4 (0.43 mL, 8.0 mmol). In the shade, the solution was stirred for 20 h at room temperature. The reaction mixture was poured into ice water (50 mL) and extracted from AcOEt (100 mL × 3). The organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the residue was purified by centrifugal chromatography on silica gel (1% EtOH/CH_2Cl_2) to give **1a** (1.192 g, 3.7 mmol, 93% yield). Recrystallization from water/*iso*PrOH gave pale reddish crystals.

General procedure of phosphorylation for preparation of 4,4′-(1,3-benzodioxol-5-ylmethylene)bisphenylphosphoric acid tetraethyl ester (1b). This compound was prepared according to the method reported by Huffman *et al*. [9]. Thus, diethyl phosphite (3.6 mmol) was added to a stirred solution of **1a** (1.5 mmol) in CCl_4 (5 mL) at 0°C, followed by the addition of Et_3N (4.2 mmol) dropwise. The reaction mixture was stirred overnight at 0°C to room temperature for 18 h. After dilution with CH_2Cl_2, the resulting mixture was washed with water, 10% aqueous HCl, and brine and then dried over $MgSO_4$. After filtration and evaporation, the residue was purified by centrifugal chromatography (SiO_2: 30–40% AcOEt in *n*-hexane), which gave **1b** (0.281 mmol, 19% yield) as a pale yellow oil.

4,4′,4″-Methylidynetriphenyl-phosphoric acid hexaethyl ester (4b). In a manner similar to that for the preparation of **1b**, after reaction of **4a** (2.0 mmol) in CCl_4 (3 mL), diethyl phosphite (7.4 mmol) and Et_3N (8.2 mmol) at temperatures in the range of 0°C to room temperature for 17 h, purification by flash chromatography (SiO_2: 2–10% EtOH in CH_2Cl_2) gave **4b** (1.78 mmol, 89% yield) as a pale yellow oil.

4,4′-(3-Pyridinylmethylene)bisphenol (5a). A mixture of phenol (941 mg, 10.0 mmol) and nicotinaldehyde (536 mg, 5.0 mmol) and TFA (3.85 mL, 50 mmol) was stirred in the shade at room temperature for 20 h. After evaporation, purification by centrifugal chromatography (50–70% AcOEt in *n*-hexane) gave **5a** (1.380 g, 5.0 mmol) as a colorless solid quantitatively. Recrystallization from CH_3CN—H_2O gave an analytically pure colorless powder **5a**.

4,4′-(3-Pyridinylmethylene)bisphenylphosphoric acid tetraethyl ester (5b)

[Method A]. In a manner similar to that for the preparation of **1b**, after the reaction of **5a** (1.0 mmol) in CCl_4 (3 mL), diethyl phosphate (3.7 mmol), and Et_3N (4.1 mmol) in the range of 0°C to room temperature for 18 h, purification by centrifugal chromatography (SiO_2: 3–5% EtOH in CH_2Cl_2) gave **5b** (0.281 mmol, 11% yield) as a pale yellow viscous solid.

[Method B]. According to the method reported by Asaad *et al* [10], NaH (60% in oil, 10 mmol) was added to a stirred solution of **5a** (1.0 mmol) in dry THF-CH_2Cl_2 (1, 3 mL) at room temperature under an N_2 atmosphere. After stirring for 0.5 h, diethyl chlorophosphate (3.0 mmol) in dry CH_2Cl_2 (2 mL) was added to the reaction mixture dropwise for 20 min and then stirred for more 1 h. The reaction mixture was then poured into a saturated $NaHCO_3$ solution (40 mL) and extracted with CH_2Cl_2 (30 mL × 2), and its organic layer was washed with water, dried over $MgSO_4$, and evaporated. The resulting products were purified by centrifugal chromatography (SiO_2: 5% EtOH in CH_2Cl_2) to give **5b** (0.432 mmol, 43% yield).

6,6′-(3-Pyridinylmethylene)bis-1,3-benzodioxol-5-ol (6a) [1]. Under N_2 atmosphere, a solution of sesamol (2.76 g, 20.0 mmol) in dry ether (Et_2O; 50 mL) was added dropwise to a solution of 3 M EtMgBr (6.7 mL, 20 mmol) in dry Et_2O (60 mL) with stirring at room temperature, and the mixture was kept for 10 min, then the solvent was removed in vacuo. After addition of dry CH_2Cl_2 (300 mL) to the residue, a solution of nicotinaldehyde (536 mg, 5.0 mmol) in dry CH_2Cl_2 (50 mL) was added with stirring under N_2 atmosphere. The resulting mixture was sonicated at 30°C for 2 days. The reaction was quenched with saturated aqueous NH_4Cl (100 mL), and the mixture was extracted with AcOEt (100 mL × 3). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the solid. The residue was recrystallized from MeOH to give **6a** as a pale green powder (1.53 g, 4.2 mmol) in 84% yield.

Preparation of 6,6′-(3-pyridinylmethylene)bis-1,3-benzodioxol-5-ylphosphoric acid tetraethyl ester (6b)

[Method A]. In a manner similar to that of the preparation of **1b**, after reaction of **6a** (1.0 mmol) in CCl_4 (3 mL), diethyl phosphite (3.7 mmol), and Et_3N (4.1 mmol) at temperatures in the range of 0°C to room temperature for 18 h, purification by centrifugal chromatography (SiO_2: 3–5% EtOH in CH_2Cl_2) gave **6b** (0.505 mmol, 51% yield) as a yellow oil.

[Method B]. In a manner similar to that for the preparation of **5b**, after the reaction of **6a** (1.0 mmol) in dry THF-CH_2Cl_2-DMF (3, 3, 2 mL) and 60% NaH (2.6 mmol) with diethyl chlorophosphate (2.4 mmol) in dry CH_2Cl_2 (2 mL) for 1.5 h, the reaction mixture was poured into a saturated $NaHCO_3$ solution (50 mL) and extracted with AcOEt (40 mL × 3). Centrifugal chromatography (SiO_2: 70–100% AcOEt in *n*-hexane) gave **6b** (0.663 mmol, 66% yield) as a yellow oil.

2,2′-[(4-Hydroxy-3-methoxy-phenyl)methylene]bis-1*H*-pyrrol (7). A mixture of pyrrole (16.4 mL, 240 mmol) and vanillin (912 mg, 6.0 mmol) and TFA (94 μL, 1.2 mmol) was stirred in the shade at room temperature for 20 h. After evaporation, purification by flash chromatography (5% AcOEt in $CHCl_3$) gave **7** (1.288 g, 4.8 mmol) as a colorless solid in 80% yield. Recrystallization from *iso*-PrOH gave analytically pure pale violet crystals **7**.

Antiviral activity assay and cytotoxicity of target compounds. The antiviral activities of synthesized compounds were measured using a plaque reduction assay [11] as described in our previous article [1]. Results of antiviral activity (EC_{50}) and cytotoxicity values (IC_{50}) with Vero cells are summarized in Table 3.

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