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(12)

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2001 07 31

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(86) 1999 06 29

(87) WO 2000/00501
(87) 2000 01 06

(30) 09/107,716 1998 06 30 (US)

(71)

, 55113, , 2665

(72)

, , .
, 55110, ,12590
,
, 06457, ,4203

(74)

(54) -

4

1

, , , (HIV) , , HIV
 $2',3' -$ - $2',3' -$ (, " d4T")

AIDS

(reverse transcriptase: RT) . HIV
 가 . , HIV RT , HIV RT ,
 (" ddN") 5' 가 . RT 2',3' -
 . , AZT d4T ddN - HIV

3' - 3' - (Zidovudine; AZT) AZT -
 - , 2',3' -
 2',3' - (d4T) d4T -
 (Balzarini et al., 1989, J. Biol. Chem. 264:61
 27; McGuigan et al., 1996, J. Med. Chem. 39:1748). 1

ddN , McGuigan et al.
AZT (McGuigan et al., 1993 J. Med. Chem. 36:1048; McGuigan et al., 1992 Antiviral Res. 17:311) d4T (McGuigan et al., 1996 J. Med. Chem. 39:1748; McGuigan et al., 1996 Bioorg. Med. Chem. Lett. 6:1183)

가
(McGuian et al., 1996 J. Med. Chem. 39:1748).
d4T
(TK) -

(electron - withdrawing)

가

d4T

가

2',3' - , , , IIIV IIIV . d

47

HIV

- HIV

가

HIV

d

, - HIV d4T
 TK - CEM T - , (PBMNC) HIV
 , d4T , d4T - 5' - () RTMDR - 1, HIV - 1 AZT -
 NNI - HIV - 2 . , AZT
 TK - CEM T - PBMNC
 - HIV , AZT NNI - RTMDR - 1 HIV - 2
 d4T AZT , 3dT 3dT - 5' - () 3dT PBMNC TK - CEM T - d4T AZT . 가
 , d4T AZT

) HIV (, TK -) AZT - 5' - () HIV

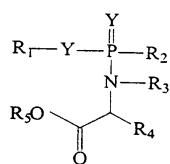
가

HIV

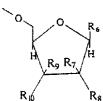
가

HIV

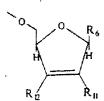
, , d4T AZT
가



$$[\quad , Y \quad , \quad , \quad , R_1 \quad , \quad , R_2]$$



(ID)



(III)

$$\{ \text{R}_6, \text{R}_7, \text{R}_8, \text{R}_9, \text{R}_{10}, \text{R}_{11}, \text{R}_{12}, \text{R}_{13}, \text{R}_{14}, \text{R}_{15}, \text{R}_{16} \}$$

$$R_3, \quad , \quad , \quad , R_4 \quad R_3 \quad R_4 \\ , R_5, \quad , \quad , \quad .]$$

" " ,
" , (, , , ,), NO₂,
" ,

$$" " R_{17} C(O) - (\quad , R_{17} \quad , \quad)$$

$$- \text{NO}_2, - \text{NR}_{13} \text{R}_{14} - \text{N}(\text{OR}_{15})\text{R}_{16} (\text{R}_{13}, \text{R}_{14}, \text{R}_{15} \text{R}_{16})$$

$$\text{R}_5) \text{R}_{16} \left(\text{R}_{13}, \text{R}_{14}, \text{R}_{15}, \text{R}_{16} \right)$$

" "

" "

"

,

, 5a 5b

NO₂

가

. 가

d4T

가

44

(Br, Cl, F, I)

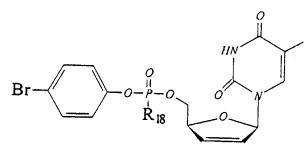
NO₂

71

6

$$\text{NHCH}(\text{CH}_3)\text{COOCH}_3$$

1



d4T

d4T

, d4T
Mansuri, et al., 1989 J. Med. Chem. 32, 461

Antiviral Res., 1992, 17:311

N -

THF

d4T

가

McGuigan, et al.,

d4T

가

, d4T
(sustained release drugs)

, , HIV / HIV

AZT

1 d4T

2a 2b

가 가

가

2c
: X="H("), 3: X="OCH₃ ()
A - d4T (elution) (2

2d

가

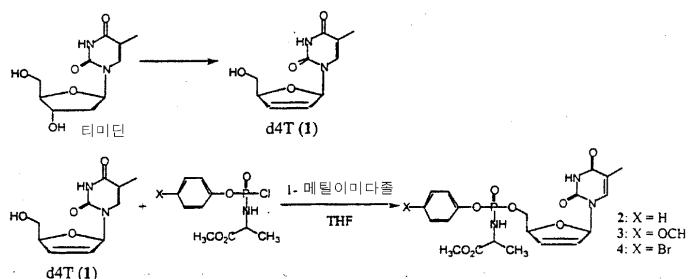
3 TK - CEM 2 - 4 4 A - d4T - MP 680
pmol CEM (lysate)4a - 4f 6c(4a) 7c(4b) , 6c(4c) 7c(4d) PBMNC
TK - CEM T - HTLV B - HIV , 6c(4e) 7c(4f) HIV - 1
(HTLV B), HIV - 2 RTMDR - 15a 5b
)

1: d4T

d4T Mansuri et al., 1989 J. Med. Chem. 32, 461

가 McGuigan et al., 1992 Antiviral Res., 17, 311

2 - 4 1



1:

가 THF

d4T 1 -

가

5 - 6

가

iChrospher
¹³C NMR1 ml/
HPLC

70:30 /

HPLC

C18 4 x 250 mm L
96%

(diastereomer)

화합물 2 : yield: 81%; IR (Neat): 3222, 2985, 2954, 1743, 1693, 1593, 1491, 1456, 1213, 1153, 1039, 931, 769 cm⁻¹; ¹H NMR (CDCl₃) δ 9.30 (br s, 1H), 7.30-7.10 (m, 6H), 6.85-6.82 (m, 1H), 6.36-6.26 (m, 1H), 5.91-5.85 (m, 1H), 5.00 (br m, 1H), 4.19-3.68 (m, 4H), 3.72, 3.71 (s, 3H), 1.83, 1.80 (d, 3H), 1.38-1.25 (m, 3H); ¹³C NMR (CDCl₃) δ 173.9, 163.7, 150.7, 149.7, 135.7*, 133.2*, 129.6*, 127.3*, 125.0*, 120.0, 111.1, 89.6*, 84.5*, 66.9*, 52.5*, 50.0*, 20.9 and 12.3; ³¹P

NMR (CDCl₃) δ 2.66, 3.20; MALDI-TOF mass m/e 487.9 (M+Na); HPLC retention time: 5.54 & 5.85 minutes.

화합물 3: yield: 92%; IR (Neat): 3223, 3072, 2999, 2953, 2837, 1743, 1693, 1506, 1443, 1207, 1153, 1111, 1034, 937, 837 and 756 cm⁻¹; ¹H NMR (CDCl₃) δ 9.40 (br s, 1H), 7.30-7.00 (m, 5H), 6.83-6.81 (m, 1H), 6.37-6.27 (m, 1H), 5.91-5.86 (m, 1H), 5.00 (br m, 1H), 4.40-4.30 (m, 2H), 4.20-4.10 (m, 2H), 3.95-3.93 (s, 3H), 3.82-3.80 (s, 3H), 1.85-1.81 (s, 3H) and 1.39-1.29 (m, 3H); ¹³C NMR (CDCl₃) δ 174.0, 163.9, 156.6, 150.8, 143.5, 135.8*, 133.3*, 127.4*, 121.2*, 114.5, 111.2, 89.7*, 84.5, 66.9*, 55.5, 52.5, 50.6*, 20.9, and 12.3; ³¹P NMR (CDCl₃) δ 3.82, 3.20; MALDI-TOF mass m/e 518.2 (M+Na); HPLC retention time: 5.83 & 6.26 minutes.

화합물 4: yield: 83%; IR (Neat): 3203, 3070, 2954, 2887, 2248, 1743, 1693, 1485, 1221, 1153, 1038, 912, 835, 733 cm⁻¹; ¹H NMR (CDCl₃) δ 9.60-9.58 (br s, 1H), 7.45-7.42 (m, 2H), 7.30-7.09 (m, 4H), 6.37-6.27 (m, 1H), 5.93-5.88 (m, 1H), 5.04-5.01 (br m, 1H), 4.35-4.33 (m, 2H), 4.27-3.98 (m, 2H), 3.71-3.70 (s, 3H), 1.85-1.81 (s, 3H), 1.37-1.31 (m, 3H); ¹³C NMR (CDCl₃) δ 173.7, 163.8, 150.8, 149.7*, 135.6*, 133.1*, 127.4*, 121.9*, 118.0, 111.2*, 89.7*, 84.4*, 67.8*, 52.5, 50.0*, 20.7, and 12.3; ³¹P NMR (CDCl₃) δ 3.41, 2.78; MALDI-TOF mass m/e 567.1 (M+Na); HPLC retention time: 12.04 & 12.72 minutes.

2: 2 - 4 가

2a 2b B(1) , 2 - 4 , 0.002 N NaOH . 가 , 가 A - d4T - MP HPLC . Lichrospher (C18) LC 70:30(/) . HP 2c . (isocratic)

가 2c 2 4(Tris - HCl
1 mM) 37 2 Tris - HCl (pH 7.4) 100 U
가 , . 15,000 × g , 0.1 ml
50 pmol HPLC A - d4T - MP 가
4 0.1 ml A - d4T - MP 1.4 nmol 2

2a 2b , - 1 (1, a b) 가 d4T
 가 가 . B(2a 2b)
 가 가 (1 A B). C 가 가
 D A - d4T - MP E
 가 , - d4T - (A - d4T - MP)
 0.002 N NaOH , 가 2, (OCH₃) 3
 4 (= "d4T - 5' - [p -]" d4T - pBPMAP)

2c , 4 - OCH₃ 4 3 2 가 가 (2d) . , 4 2 가

3: TK - CEM 2 - 4
 TK - μM 2 - 4, HLPC, 1 \times 10⁶ CEM, 가 3, 2 - 4(100 d4T
 . , , , , 4, CEM, < 50 pmol/10⁶, ; 3).
 CEM RPMI, 10% 1% / 10⁶ /m
 | 가 37 3 100 μM , , , , , , PBS
 , 60% 0.5 ml 가 . - 20, , , 15,
 000 \times g 10 100 μl HPLC, . HP
 LC (quaternary), (degausser), (diodearray)
 (HP) 1100
 . 250 \times 4.6 mm Sulpelco LC - DB C18
 . , 10 mM (pH 3.7)
 10 5 35%, 1 ml/, , , , , , 20
 35 100% , 5 35%
 . 270 nm A - d4T - MP 680 pmol
 . 8.7 4 CEM

가 , 4 - HIV 가 .
 d4T(1) 2 - 4 TK - C
 EM T - HIV (Zarling, et al., 1990 Nature 347:92, Erice et al., 19
 93 Antimicrob. Agents Chemother. 37:835; Uckun et al., 1998 Antimicrob. Agents Chemother. 42:383).
 p24 RT
 Zarling, Erice Uckun
 (microculture tetrazolium assay: MTA)

1 HIV - 1 HIV - 1 , d4T , HIV -
 가 d4T TK - CEM , d4T p24
 1 IC₅₀ 18 nM, TK - CEM 556 nM , RT
 IC₅₀ 40 nM 2355 nM 가 (1). 가
 CEM d4T , 4(d4T - 5' - [p -
]) d4T p24 12.6 (IC₅₀ : 44 nM 556 nM), RT
 41.3 (IC₅₀ : 57 nM 2355 nM)(1).

[1]

화합물	X	PBMNC			CEM		
		IC ₅₀ [p24]	IC ₅₀ [RT]	IC ₅₀ [MTA]	IC ₅₀ [p24]	IC ₅₀ [RT]	IC ₅₀ [MTA]
1 (= d4T)		0.018	0.040	>10	0.556	2.355	>10
2	H	ND	ND	>10	0.145	0.133	>10
3	-OCH ₃	0.033	0.033	>10	0.106	0.320	>10
4	Br	0.022	0.042	>10	0.044	0.057	>10

MTA 10,000 nM
 CEM , 3 4가
 (IC₅₀ : 33 nM 42 nM),
 3 HIV - TK - CEM RT 4 5.6 (IC₅₀ -
 : 320 nM 57 nM). , , , , d4T -
 HIV , , , , d4T
 4T , , , , d4T

4: MDR

4 AZT

HIV - MDR

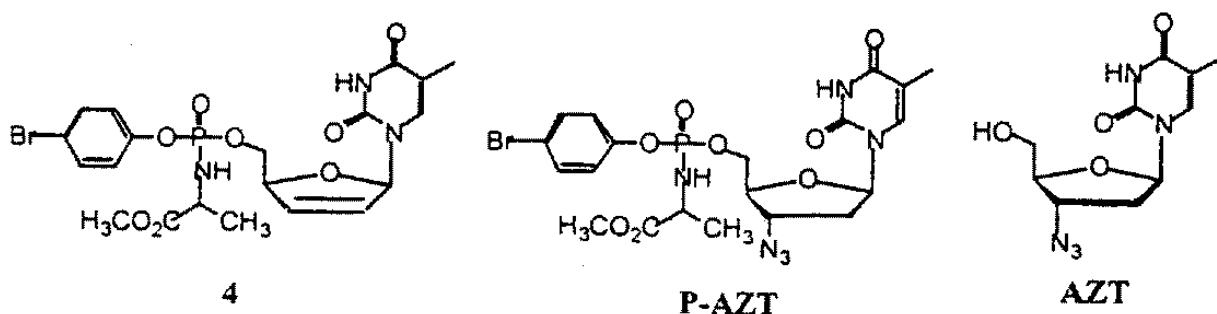
4(d4T - 5' - [p -
] (P - AZT) AZT

])

AZT - 5' - [p -
42 , P - AZT AZT IC₅₀ 1.5 2.0 nM
0.02 nM) AZT(2.0 nM) 100

4 (

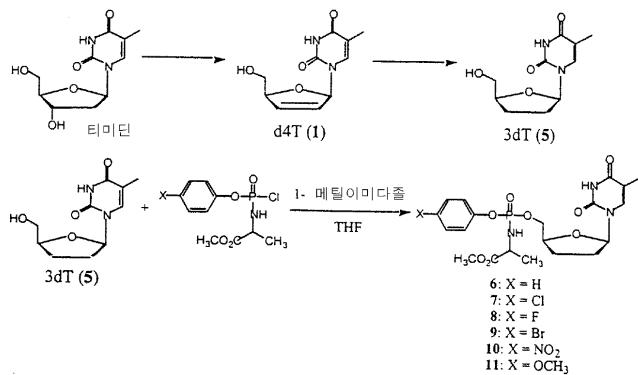
[2]



	HIV-2	HIV-MDR
화합물	IC ₅₀ [RT]	IC ₅₀ [RT]
4	0.4	0.02
P-AZT	3.9	1.5
AZT	2.4	2.0

5: 3dT

가 , 3' - - (3dT) - HIV
 d4T(1) 2 , 3dT(5)
 tion) H₂ 5% Pd/C (Mansuri, et al., 1989 J. Med. Chem. 32:461 - 466). (1) 가(hydrogena
 , 6 - 11 2 McGuigan et al., 1992 Antiviral. Res. 17:311 - 321



2.

가	12	가 THF (NO ₂ (vacuo))	3dT	1 - (gum)	(org
anic phase)	MgSO ₄	,	,	,	6 - 11
5%					

가	HPLC	1 ml/	70:30 /	HPLC	96%
C18 4 × 250 mm LiChrospher
13 C NMR					

화합물 5: yield: 85%; ¹H NMR(CDCl₃) δ 11.1 (br s, 1H), 7.82 (s, 1H), 5.97-5.94 (m, 1H), 5.10 (br s, 1H), 4.05-3.95 (m, 1H), 3.72-3.52 (m, 2H), 2.30-1.86 (m, 4H), 1.77 (s, 3H); ¹³C NMR(CDCl₃) δ 163.9, 150.4, 136.4, 108.7, 84.8, 81.4, 62.2, 31.8, 25.1, and 12.5.

화합물 6: yield: 96%; IR (neat): 3211, 2955, 2821, 1689, 1491, 1265, 1211, 1153, 1043 and 933 cm⁻¹; ¹H NMR(CDCl₃) δ 10.1 (br s, 1H), 7.47 (s, 1H), 7.32-7.12 (m, 5H), 6.14-6.08 (m, 1H), 4.41-4.21 (m, 4H), 4.05-4.00 (m, 1H), 3.70, 3.69 (s, 3H), 2.37-2.32 (m, 1H), 2.05-1.89 (m, 7H), 1.38-1.35 (dd, 3H); ¹³C NMR(CDCl₃) δ 173.6*, 163.8, 150.3, 150.1*, 135.2, 129.4*, 124.7, 119.8*, 110.5*, 85.7*, 78.3*, 67.2*, 52.3, 50.1*, 31.6*, 25.4*, 20.7*, and 12.4*; ³¹P NMR(CDCl₃) δ 2.82 & 3.11; MS (MALDI-TOF): 490.4 (M+Na); HPLC retention time = 6.86, 7.35 minutes.

화합물 7: yield: 96%; IR (neat): 3217, 2954, 2821, 1743, 1689, 1489, 1265, 1217, 1153, 1092, 1012, 926 & 837 cm⁻¹; ¹H NMR(CDCl₃) δ 9.40 (br s, 1H), 7.43-7.41 (m, 1H), 7.30-7.14 (m, 4H), 6.13-6.07 (m, 1H), 4.39-4.00 (m, 5H), 3.71, 3.70 (s, 3H), 2.38-2.36 (m, 2H), 2.09-1.89 (m, 5H), 1.39-1.36 (dd, 3H); ¹³C NMR(CDCl₃) δ 173.6*, 163.7, 150.2, 148.8*, 135.3, 129.5-129.0, 121.5-121.3, 116.3, 110.6, 86.0*, 78.4*, 67.7*, 52.6*, 50.2*, 31.8*, 25.4*, 20.9* and 12.5; ³¹P NMR(CDCl₃) δ 2.87 & 3.09; MS (MALDI-TOF): 524.9 (M+Na); HPLC retention time = 14.05, 14.89 minutes.

화합물 8: Viscous oil, yield: 96%; λ_{max} : 223 (ϵ 3338) and 269 (ϵ 4695) nm; IR (neat): 3211, 2955, 1743, 1693, 1500, 1569, 1265, 1197, 1153, 1045, 923 & 843 cm⁻¹; ¹H NMR(CDCl₃) δ 9.40 (br s, 1H), 7.45-7.43 (d, 1H), 7.19-7.01 (m, 4H),

6.14-6.06 (m, 1H), 4.39-3.97 (m, 5H), 3.71, 3.70 (s, 3H), 2.38-1.89 (m, 7H), 1.39-1.35 (t, 3H); ¹³C NMR(CDCl₃) δ 173.6*, 163.7, 150.2, 150.1*, 135.3, 121.5*, 116.3*, 110.6*, 85.9*, 78.4*, 67.7*, 52.6, 50.2*, 31.8*, 25.6*, 20.9*, and 12.5; ³¹P NMR(CDCl₃) δ 3.13 & 3.37; MS (MALDI-TOF): 508.2 (M+Na); HPLC retention time = 8.38, 8.80 minutes.

화합물 9: yield: 83%; IR (neat): 3211, 2954, 1743, 1689, 1485, 1265, 1217, 1153, 1010, 923 & 833 cm⁻¹; ¹H NMR(CDCl₃) δ 9.82 (br s, 1H), 7.45-7.41 (m, 3H), 7.15-7.11 (m, 2H), 6.14-6.06 (m, 1H), 4.39-4.00 (m, 5H), 3.71, 3.70 (s, 3H), 2.38-1.89 (m, 7H), 1.39-1.35 (dd, 3H); ¹³C NMR(CDCl₃) δ 173.6*, 163.8, 150.3, 148.5*, 135.2, 132.6*, 121.8*, 117.7, 110.6*, 85.9*, 78.3*, 67.2*, 52.5, 50.2*, 31.6*, 25.6*, 20.8*, and 12.5; ³¹P NMR(CDCl₃) δ 2.83 & 3.05; MS (MALDI-TOF): 570.0 (M+2+Na); HPLC retention time = 15.50, 16.57 minutes.

화합물 10: yield, 87%; IR (neat): 3203, 2955, 1743, 1684, 1593, 1522, 1348, 1265, 1153, 1101, 920 & 860 cm⁻¹; ¹H NMR(CDCl₃) δ 9.51 (br s, 1H), 8.24-8.21 (m, 2H), 7.42-7.37 (m, 3H), 6.13-6.08 (m, 1H), 4.39-4.03 (m, 5H), 3.72, 3.71 (s, 3H), 2.38-1.89 (m, 7H), 1.41-1.38 (dd, 3H); ¹³C NMR(CDCl₃) δ 173.4*, 163.7, 155.2*, 150.2, 144.4, 135.3, 125.9-125.4, 120.6*, 115.4, 110.6*, 86.1*, 78.4*, 68.1*, 52.7, 50.2*, 31.7*, 25.8*, 20.9* and 12.5; ³¹P NMR(CDCl₃) δ 2.60 & 2.81; MS (MALDI-TOF): 535.0 (M+Na); HPLC retention time = 8.12, 10.14 minutes.

화합물 11: yield, 100%; IR (neat): 3209, 2954, 1743, 1506, 1468, 1265, 1207, 1153, 1036, 937 & 835 cm⁻¹; ¹H NMR(CDCl₃) δ 9.89 (br s, 1H), 7.49-7.47 (m, 1H), 7.16-7.11 (m, 2H), 6.84-6.80 (m, 2H), 6.15-6.09 (m, 1H), 4.39-4.02 (m, 5H), 3.77, 3.76 (s, 3H), 3.74, 3.73 (s, 3H), 2.38-1.89 (m, 7H), 1.38-1.33 (t, 3H); ¹³C NMR(CDCl₃) δ 173.7*, 163.9, 156.3, 150.3, 143.7*, 135.2, 120.7*, 114.3*, 110.5, 85.7*, 78.4*, 67.3*, 55.4, 52.4, 50.1*, 31.8*, 25.4*, 20.8* and 12.4*; ³¹P NMR(CDCl₃) δ 3.27 & 3.52; MS (MALDI-TOF): 521.3 (M+1+Na); HPLC retention time = 7.15, 7.66 minutes.

6: 3dT 6 - 11

3dT	6 - 11	d4T	TK -	(Zarling et al., 1990; Erice et al., 1993; Uckun et al., 1998).
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3dT (3). IC ₅₀ [RT] TK -	3dT , , (prodrug)	TK - - -	CEM T - 6 - 11 IC ₅₀ [RT]	d4T , , , d4T - -	TK - d4T d4T	TK - (McGuigan et al., 1996a). d4T AZT (McGuigan et al., 1993, 1996a), 3dT	TK - HIV - 1 3dT
---	----------------------------	----------------	--	----------------------------------	--------------------	--	------------------------

6 - 11 TK - . d4T - HIV	(PBMNC) TK - TK -	CEM T - TK - TK -	TK - TK -	,
(PBMNC) TK - CEM T - 3 - (6				(M

cGuigan et al., 1996 Bioorg. Med. Chem. Lett. 6:1183 - 1186).

μ M , RT
50%
50%(IC_{50} [RT])⁹ MTA(IC_{50} [MTA])
(Mansuri e t al., 1989 J. Med. Chem. 32:461).

[3]

		PBMNC		CEM	
화합물	X	IC ₅₀ [RT]	IC ₅₀ [MTA]	IC ₅₀ [RT]	IC ₅₀ [MTA]
6	H	2.1	>100	7.5	>100
7	Cl	2.1	>100	21.9	>100
8	F	3.1	>100	32.7	>100
9	Br	1.2	>100	22.8	>100
10	NO ₂	2.0	>100	22.6	>100
11	OMe	1.3	>100	19.7	>100
3dT	-	0.7	>100	91.2	>100
d4T	-	0.004	>100	2.335	>100

5a 5b , 1 3dT
 B D 가 .
 7 - 10 가 가 (2a 2b). ,
 6 11
 - 1 가 (1 A B) 가 3dT
 가 . , 7 - 10
 가

(McIntee et al., 1997 J. Med. Chem. 40:3323 - 3331).

7: d4T, AZT 3dT - HIV

al., 1989). H₂ 5% Pd/C (1) 가 85% 3dT(3) (1).

AZT(2)

(5a, 5b 5c)

ddN

(Chu et al., U.S. Patent No. 4,841,039).

2)(McGuigan et al., 1992),

4a, 4b, 5a, 5b, 7a 7b

4c 5c

()

d4T(1), AZT(2) 3dT(3)

(McGuigan et al., 1992).

(5) 가 THF

ddN(1,2

3)

1 -

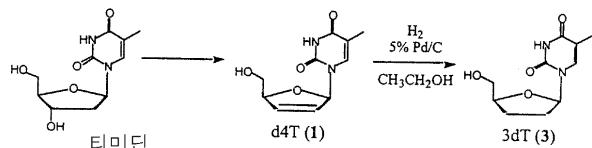
가

, 1 M HCl,

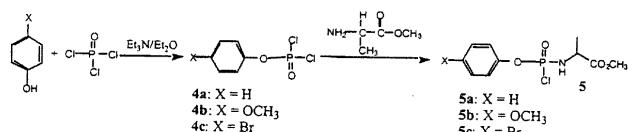
MgSO₄

3

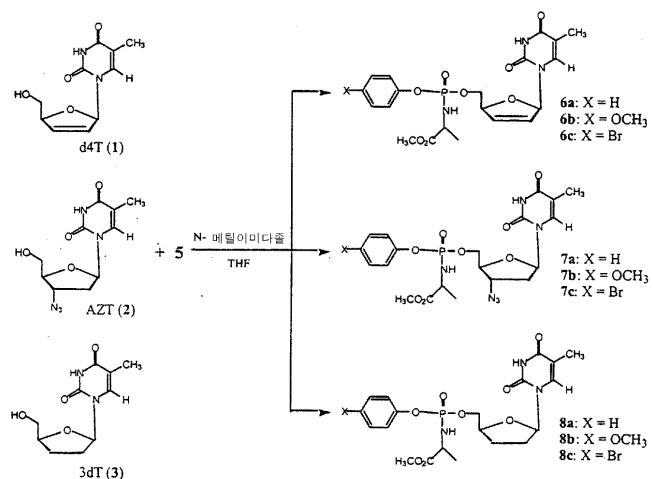
도식 1. d4T와 3dT의 합성



도식 2. 페닐메톡시알라니닐포스포로글로리데이트의 합성



도식 3. ddN의 페닐메톡시알라니닐포스페이트 유도체의 합성



p -

4c

McGuigan et al., 1993
 0 mmol) , Et₂O (165 ml) p - (13.20 g; 76.3
 O (83 ml) (10.65 ml) 0 3 Et₂
 , , , , ,
 , 2 가 Et₂O (2 × 50 ml) Et₂O
 g) 4c(14.05 g; 63.5%) , (bp. 110 - 115 /2 mm H
 1 IR(neat) 3095, 1481, 1303, 1187, 948, 829 cm⁻¹

¹H NMR (300 MHz, CDCl₃) δ 7.50 (2H, d, J=9.0 Hz), 7.15 (2H, d, J=9.0 Hz).
 GC/MS (m/e) 290 (M⁺), 254 (M⁺ - Cl), 173 (M⁺ - POCl₂, ⁸¹Br), 171 (M⁺ - POCl₂,
⁷⁹Br), 156 (M⁺ - PO₂Cl₂, ⁸¹Br), 154 (M⁺ - PO₂Cl₂, ⁷⁹Br).

p - 5C
 McGuigan et al CH₂Cl₂ (180 ml) (8.80 ml; 63.14
 mmol) - 70 3 CH₂Cl₂ (250 ml) p -
 4c(8.69 g; 29.97 mmol) L - (4.19 g; 30.02
 mmol) , , ,
 , , , Et₂O (300 ml) Et₂O (2 × 60 ml) Et₂O
 , , , 5c(10.7 g)

IR (Neat) 3212,
 2989, 2952, 1747, 1483, 1270, 1209, 1147, 927, 831, 757cm⁻¹. ¹H NMR (300 MHz,
 CDCl₃) δ 8.70 (1H, br, Ala-NH), 7.48 (2H, d, J=9.0Hz, aryl H), 7.16 (2H, d,
 J=9.0Hz, aryl H), 3.79 & 3.77 (3H, s & s, -OCH₃), 1.51 & 1.40 (3H, d & d, Ala-CH₃).
 MS (CI, m/e) 357.9 (M⁺, ⁸¹Br), 355.9 (M⁺, ⁷⁹Br), 322.0 (M⁺ - Cl, ⁸¹Br), 320.0 (M⁺ -
 Cl, ⁷⁹Br), 297.9 (M⁺ - COOCH₃, ⁸¹Br), 295.9 (M⁺ - COOCH₃, ⁷⁹Br), 184.0 (M⁺ -
 BrC₆H₄O).

AZT(1), d4T(2) 3dT(3)

HPLC 1 ml/ 70:30 / C18 4 × 250 mm LiChrospher
 . . HPLC 96% ¹³C NMR

화합물 6a: yield: 81%; IR (Neat): 3222, 2985, 2954, 1743, 1693, 1593, 1491, 1456, 1213, 1153, 1039, 931, 769 cm⁻¹; ¹H NMR (CDCl₃) δ 9.30 (br s, 1H), 7.30-7.10 (m, 6H), 6.85-6.82 (m, 1H), 6.36-6.26 (m, 1H), 5.91-5.85 (m, 1H), 5.00 (br m, 1H), 4.19-3.68 (m, 4H), 3.72, 3.71 (s, 3H), 1.83, 1.80 (d, 3H), 1.38-1.25 (m, 3H); ¹³C NMR (CDCl₃) δ 173.9, 163.7, 150.7, 149.7, 135.7*, 133.2*, 129.6*, 127.3*, 125.0*, 120.0, 111.1, 89.6*, 84.5*, 66.9*, 52.5*, 50.0*, 20.9 and 12.3; ³¹P NMR (CDCl₃) δ 2.66, 3.20; MALDI-TOF mass m/e 487.9 (M+Na); HPLC retention time: 5.54 & 5.85 minute.

화합물 6b: yield: 92%; IR (Neat): 3223, 3072, 2999, 2953, 2837, 1743, 1693, 1506, 1443, 1207, 1153, 1111, 1034, 937, 837 and 756 cm⁻¹; ¹H NMR (CDCl₃) δ 9.40 (br s, 1H), 7.30-7.00 (m, 5H), 6.83-6.81 (m, 1H), 6.37-6.27 (m, 1H), 5.91-5.86 (m, 1H), 5.00 (br m, 1H), 4.40-4.30 (m, 2H), 4.20-4.10 (m, 2H), 3.95-3.93 (s, 3H), 3.82-3.80 (s, 3H), 1.85-1.81 (s, 3H) and 1.39-1.29 (m, 3H); ¹³C NMR (CDCl₃) δ 174.0, 163.9, 156.6, 150.8, 143.5, 135.8*, 133.3*, 127.4*, 121.2*, 114.5, 111.2, 89.7*, 84.5, 66.9*, 55.5, 52.5, 50.6*, 20.9, and 12.3; ³¹P NMR (CDCl₃) δ 3.82, 3.20; MALDI-TOF mass m/e 518.2 (M+Na); HPLC retention time: 5.83 & 6.26 minute.

화합물 6c: yield: 83%; IR (Neat): 3203, 3070, 2954, 2887, 2248, 1743, 1693, 1485, 1221, 1153, 1038, 912, 835, 733 cm⁻¹; ¹H NMR (CDCl₃) δ 9.60-9.58 (br s, 1H), 7.45-7.42 (m, 2H), 7.30-7.09 (m, 4H), 6.37-6.27 (m, 1H), 5.93-5.88 (m, 1H), 5.04-5.01 (br m, 1H), 4.35-4.33 (m, 2H), 4.27-3.98 (m, 2H), 3.71-3.70 (s, 3H), 1.85-1.81 (s, 3H), 1.37-1.31 (m, 3H); ¹³C NMR (CDCl₃) δ 173.7, 163.8, 150.8, 149.7*, 135.6*, 133.1*, 127.4*, 121.9*, 118.0, 111.2*, 89.7*, 84.4*, 67.8*, 52.5, 50.0*, 20.7, and 12.3; ³¹P NMR (CDCl₃) δ 3.41, 2.78; MALDI-TOF mass m/e 567.1 (M+Na); HPLC retention time: 12.04 & 12.72 minute.

화합물 7c: yield: 95%; IR (Neat) 3205.7, 3066.3, 2954.5, 2109.8, 1745.3, 1691.3, 1484.9, 1270.9, 1153.2, 1010.5 and 926.1 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 8.69 (1H, br, 3-NH), 7.45 (2H, d, J=9.0 Hz, aryl H), 7.34 & 7.32 (1H, s & s, vinyl

H), 7.11 (2H, d, J=9.0 Hz, aryl H), 6.18 & 6.13 (1H, t & t, J = 6.6 & 6.6 Hz, H at C-1'), 4.44-3.77 (6H, m, H at C-3', 4' & 5', Ala-NH and Ala-CH), 3.73 & 3.72 (3H, s & s, -COOCH₃), 2.51-2.20 (2H, m, H at C-2'), 2.18 (3H, s, -CH₃ at C-5), 1.39 & 1.36 (3H, d & d, Ala-CH₃). ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 163.6, 150.1, 149.2, 149.1, 135.2, 132.4, 121.6, 117.8, 111.1, 85.0, 84.7, 81.9, 81.8, 65.5, 60.1, 59.9, 52.4, 50.0, 49.9, 36.9, 20.6, 20.5, 12.2. MS (CI, m/e) 589.1 (M⁺, ⁸¹Br) and 587.1 (M⁺, ⁷⁵Br).

화합물 8a: yield: 96%; IR (Neat): 3211, 2955, 2821, 1689, 1491, 1265, 1211, 1153, 1043 and 933 cm⁻¹; ¹H NMR(CDCl₃) δ 10.1 (br s, 1H), 7.47 (s, 1H), 7.32-7.12 (m, 5H), 6.14-6.08 (m, 1H), 4.41-4.21 (m, 4H), 4.05-4.00 (m, 1H), 3.70, 3.69 (s, 3H), 2.37-2.32 (m, 1H), 2.05-1.89 (m, 7H), 1.38-1.35 (dd, 3H); ¹³C NMR(CDCl₃) δ 173.6*, 163.8, 150.3, 150.1*, 135.2, 129.4*, 124.7, 119.8*, 110.5*, 85.7*, 78.3*, 67.2*, 52.3, 50.1*, 31.6*, 25.4*, 20.7*, and 12.4*; ³¹P NMR(CDCl₃) δ 2.82 & 3.11; MS (MALDI-TOF): 490.4 (M+Na); HPLC retention time = 6.86, 7.35 minute.

화합물 8b: yield, 100%; IR (Neat): 3209, 2954, 1743, 1506, 1468, 1265, 1207, 1153, 1036, 937 & 835 cm⁻¹; ¹H NMR(CDCl₃) δ 9.89 (br s, 1H), 7.49-7.47 (m, 1H), 7.16-7.11 (m, 2H), 6.84-6.80 (m, 2H), 6.15-6.09 (m, 1H), 4.39-4.02 (m, 5H), 3.77, 3.76 (s, 3H), 3.74, 3.73 (s, 3H), 2.38-1.89 (m, 7H), 1.38-1.33 (t, 3H); ¹³C NMR(CDCl₃) δ 173.7*, 163.9, 156.3, 150.3, 143.7*, 135.2, 120.7*, 114.3*, 110.5, 85.7*, 78.4*, 67.3*, 55.4, 52.4, 50.1*, 31.8*, 25.4*, 20.8* and 12.4*; ³¹P NMR(CDCl₃) δ 3.27 & 3.52; MS (MALDI-TOF): 521.3 (M+I+Na); HPLC retention time = 7.15, 7.66 minute.

화합물 8c: yield: 83%; IR (Neat): 3211, 2954, 1743, 1689, 1485, 1265, 1217, 1153, 1010, 923 & 833 cm⁻¹; ¹H NMR(CDCl₃) δ 9.82 (br s, 1H), 7.45-7.41 (m, 3H), 7.15-7.11 (m, 2H), 6.14-6.06 (m, 1H), 4.39-4.00 (m, 5H), 3.71, 3.70 (s, 3H), 2.38-1.89 (m, 7H), 1.39-1.35 (dd, 3H); ¹³C NMR(CDCl₃) δ 173.6*, 163.8, 150.3, 148.5*, 135.2, 132.6*, 121.8*, 117.7, 110.6*, 85.9*, 78.3*, 67.2*, 52.5, 50.2*, 31.6*, 25.6*, 20.8*, and 12.5; ³¹P NMR(CDCl₃) δ 2.83 & 3.05; MS (MALDI-TOF): 570.0

(M+2+Na); HPLC = "15.50," 16.57

- HIV

- HIV (IC₅₀ [RT]) 50%
AZT - HIV - 1(: HTLV B) - , AZT - NNI - HIV - 1(: RTMD R - 1) - (by Dr. Brendan Larder, NIH AIDS Research and Reference Reagent Program, DIV, SIDS, NIAID, N IH; cat. # 2529) HTLV B - TK - CEM T - HIV - 2(;CBL - 20) - RT
(PBMNC) が 50% (CC₅₀ [M TA]) 2,3 - (2 - - 4 - - 5 - -) - 5 - [(MTA)] - 2H - (Zarling et al., 1990; Erice et al., 1993, Uckun et al., 1998).

- HIV d4T - 5' - () AZT - 5' - ()

d4T - HIV - 1 PBMNC , d4T . d4T . HI
V - 1 d4T TK - CEM . d4T RT
IC₅₀ PBMNC 40 nM , TK - CEM 2400 nM (4 4a - 4f).
TK - CEM d4T ,
6c(d4T - 5' - [p -]) d4T RT
60 (4).

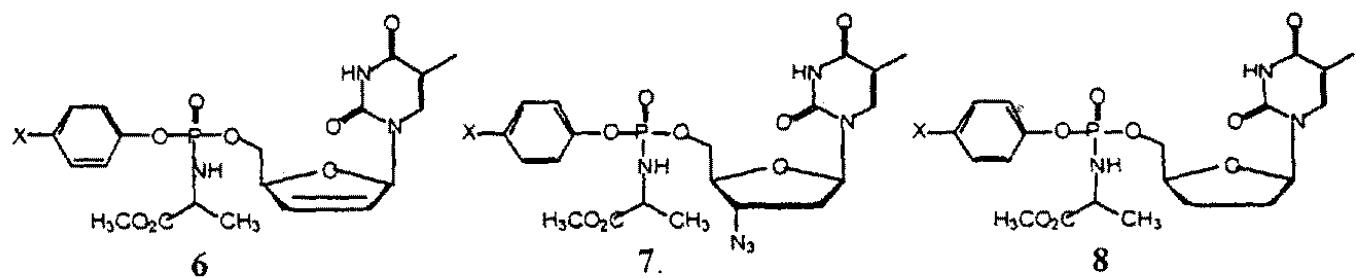
, MTA 10,000 nM PBMNC CEM
, 6b 6c† 6b HIV TK - CE
(IC₅₀ : 30 nM 40 nM) (4), 6c 5 (IC₅₀ : 300 nM 60 nM) (4).

7a, 7b, 7c AZT(2) PBMNC TK - CEM T - HIV
(4). RT ()
MTA) . HIV - 1 AZT(2) TK - CEM
, AZT RT IC₅₀ PBMNC 3 nM , TK - CEM 2
00 nM d4T , AZT AZT AZT ()
TK - CEM T - , AZT - 5' - () 7c TK - CEM HIV - 1
HIV , AZT 5 (IC₅₀ [RT] : 0.04 μM 0.2 μM).
MTA 10,000 nM PBMNC CEM

8a - c 3dT(3) PBMNC TK - CEM T - HIV - 1
d4T(1) 3dT TK - CEM T - 8a - c
d4T (4). (prodrug)
IC₅₀ [RT] 3dT(1.2 - 3.1 0.7, 4) IC₅₀ [RT] , , - d
, , , , ,
4T, AZT 3dT , TK - HIV - 1
IC₅₀ [RT] , TK -
3dT djT (4 4a - 4f). 8a - c PBMNC TK - CEM T -
, , 3dT TK

[4 - 1]

정상의 말초 혈액 단핵구세포(PBMNC)와 TK-결핍 CEM T-세포에서 d4T, AZT 및 3dT의 폐닐메톡시알라니닐포스페이트 유도체의 항-HIV 활성



화합물	X	PBMNC		CEM	
		IC ₅₀ [RT]	IC ₅₀ [MTA]	IC ₅₀ [RT]	IC ₅₀ [MTA]
6a	H	N.D.	N.D.	0.1	>10
6b	OCH ₃	0.03	>10	0.3	>10
6c	Br	0.04	>10	0.06	>10
7a	H	N.D.	N.D.	1.7	>10
7b	OMe	0.1	>10	4.1	>10
7c	Br	0.004	>10	0.04	>10
8a	H	2.1	>10	7.5	>10

[4 - 2]

화합물	X	PBMNC		CEM	
		IC ₅₀ [RT]	IC ₅₀ [MTA]	IC ₅₀ [RT]	IC ₅₀ [MTA]
8b	OMe	1.3	>10	19.7	>10
8c	Br	1.2	>10	22.8	>10
1 (d4T)	-	0.04	>10	2.4	>10
2 (AZT)	-	0.003	>10	0.2	>10
3 (3dT)	-	0.7	>10	91.2	>10

HIV - 2 RTMDR - 1

d4T - 5' - (

)

) AZT - 5' - (

6c 7c PBMNC RTMDR - 1, HIV - 1 AZT - NNI - HIV - 2 HIV

AZT(2)

) RTMDR - 1

d4T

6c, d4T - 5' - (

HIV - 2

7c

AZT(2)

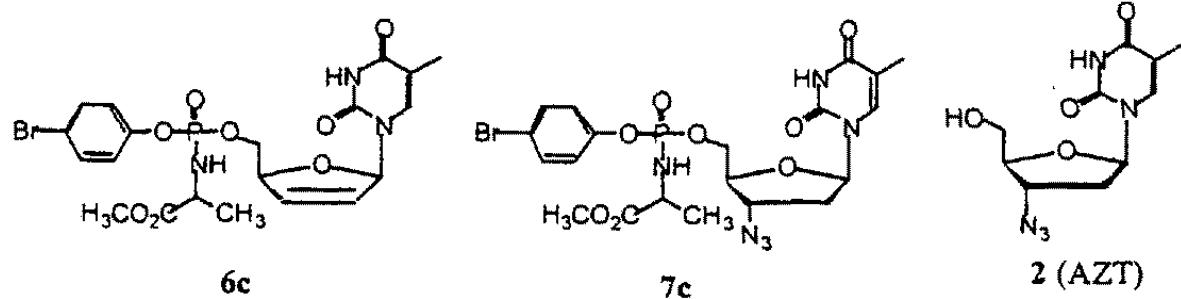
AZT

AZT

RTMDR - 1 HIV - 2

[5 - 1]

HIV-2 및 RTMDR-1 세포에서 유도 화합물 6c 및 7c의 항-HIV 활성



[5 - 2]

	HIV-2	RTMDR-1
화합물	IC ₅₀ [RT]	IC ₅₀ [RT]
6c	0.4	0.02
7c	3.9	1.5
2 (AZT)	2.4	2.0

 μM , RT50% (IC₅₀ [RT])

6a, 6b 6c TK - CEM
 (6a, 6b 6c) HIV - 1 PBMNC d4T(1)
 d4T , d4T - 5' - [p - , d4T -
 CEM 가 - HIV . 6c ,
 가 (2), TK - CEM T -
 d4T] 6c가 TK -
 (McIntee, et al., 1997, J.
 Med. Chem. 40:3233 - 3331).

TK - CEM AZT , 7c() > 7a() >
 7b() d4T , AZT
 (7a, 7b 7c) , 7c TK - CEM AZT
 00 nM). 3dT (4), (IC50 : 4₀ nM 2
 , 8c 8c 가 가 (, 2 B C).
 , - 1 가 (, 2 A B)가 3dT
 , 가 8b 8a, 8b 8c가
 , d4T , (2). 3dT
 3dT HIV TK - CEM T -
 - HIV

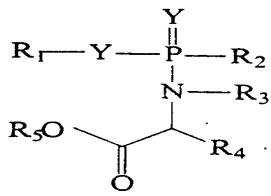
가

, d4T - 5' - [p -] 6c AZT - 5' - [p -
] 7c TK - CEM T - HIV
 - HIV . 가, d4T 6c RTMDR - 1, HIV - 1 AZT - NNI -
 HIV - 2 . d4T AZT
 , 3dT , 3dT - 5' - () PBMNC TK - CEM
 - HIV . 가 , d4T AZT
 TK - HIV . , 6c 7c
 HIV HIV

가

(57)

1.

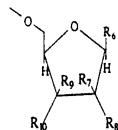


(D)

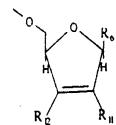
[, Y

R₁

R₂



(II)



(III)

{ , R₆

$R_7, R_8, R_9, R_{10}, R_{11}, R_{12}$, , , , - NO_2 , - $\text{NR}_{13}R_{14}$, - $\text{N}(\text{OR}_{15})R_{16}$
 $(\quad, R_{13}, R_{14}, R_{15}, R_{16}$, , , .) .} ,

R₃ , , , ,

R₄ , ,

R₃ R₄ , , , ,

R₅ , , , , .]

2.

1 , Y HIV HIV

3.

1 , R₁ HIV HIV

4.

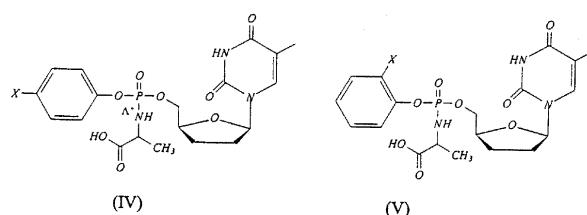
1 , R₆ , , HIV HIV

5.

1 , R₄ HIV HIV

6.

HIV HIV



(, X .)

7.

6 , X NO₂ HIV HIV

8.

7 , X HIV HIV

9.

8

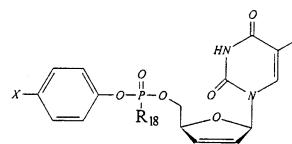
HIV

HIV

10.

HIV

HIV



(, X)

, R₁₈

.)

11.

10

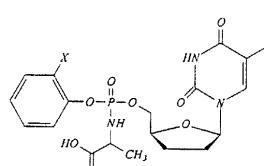
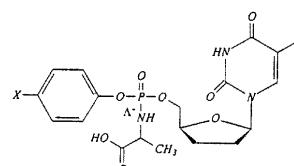
, R₁₈- NHCH(CH₃)COOCH₃

HIV

HIV

12.

HIV



(, X)

.)

13.

12

, X

NO₂

HIV

14.

13

, X

HIV

15.

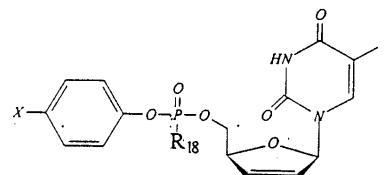
14

, X

HIV

16.

HIV



(VI)

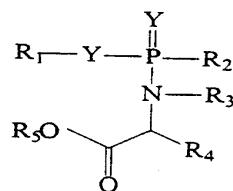
(, X , R₂ .)

17.

16 , R₁₈ - NHCH(CH₃)COOCH₃ HIV

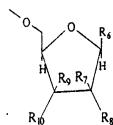
18.

HIV HIV 가

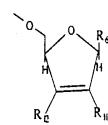


(I)

[, Y ,]

R₁R₂

(II)



(III)

{ , R₆ , }R₇, R₈, R₉, R₁₀, R₁₁, R₁₂ , , , , , - NO₂, - NR₁₃ R₁₄ , - N(OR₁₅)R₁₆
(, R₁₃, R₁₄, R₁₅, R₁₆ ,) . } ,

$$R_3, \quad , \quad , \quad ,$$

R₄

$$R_3 \quad R_4$$

19.

18 , Y HIV

20.

18 . . . R₁ HIV

21

18 β_e HIV

22

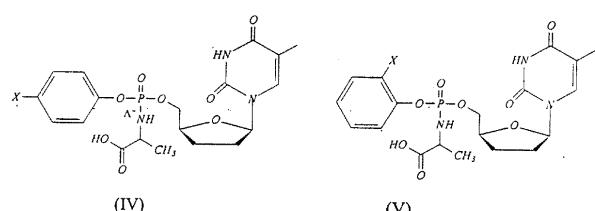
18 R. J. H. van der Veen et al. / Journal of Internal Medicine 2010; 267: 173–183

23

HIV

HIV

가



(\quad , X \quad)

24.

23 X NO₂ HIV

25.

24 . X HIV

26.

25

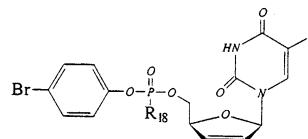
HIV

27.

HIV

가

HIV



(VII)

(, R_{18} .)

28.

27 , R_{18} - $\text{NHCH}(\text{CH}_3)\text{COOCH}_3$

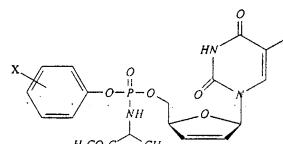
HIV

29.

HIV

가

HIV



(VIII)

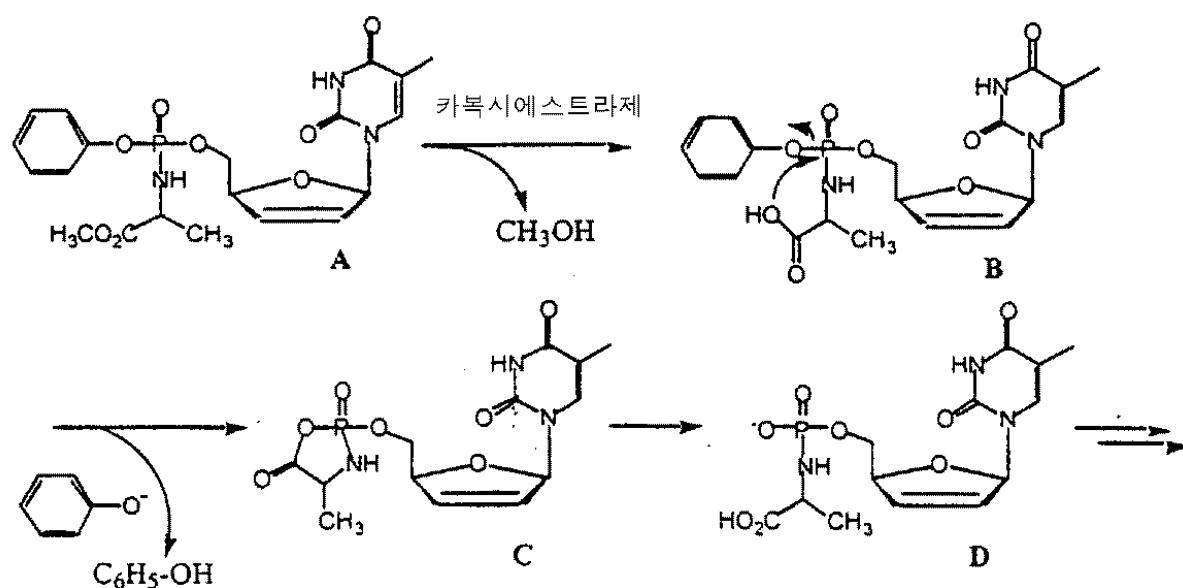
(, X .)

30.

29 , X NO_2

HIV

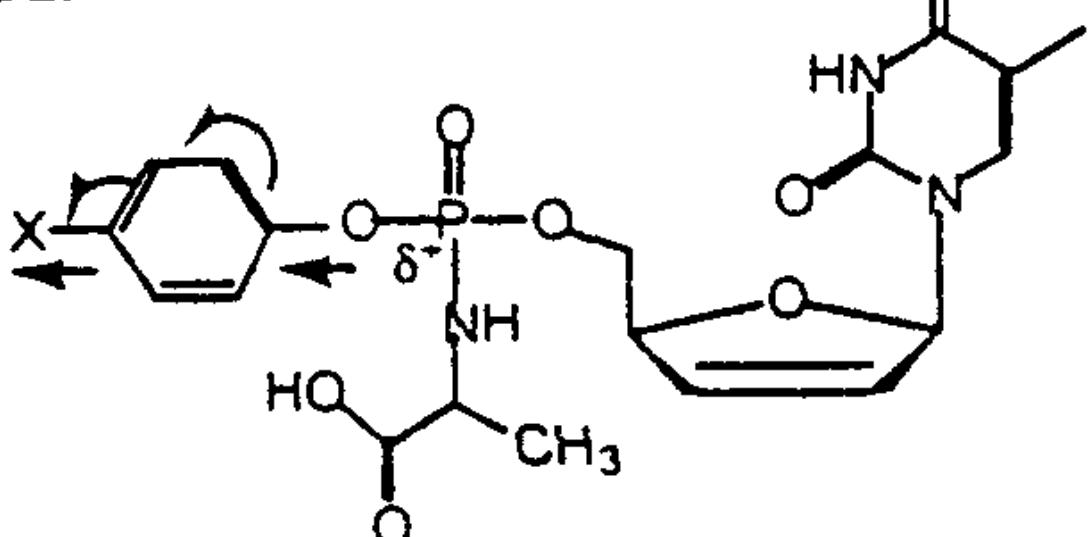
1



문헌에 제공된 d4T의 아릴포스페이트 유도체의 대사 경로

2a

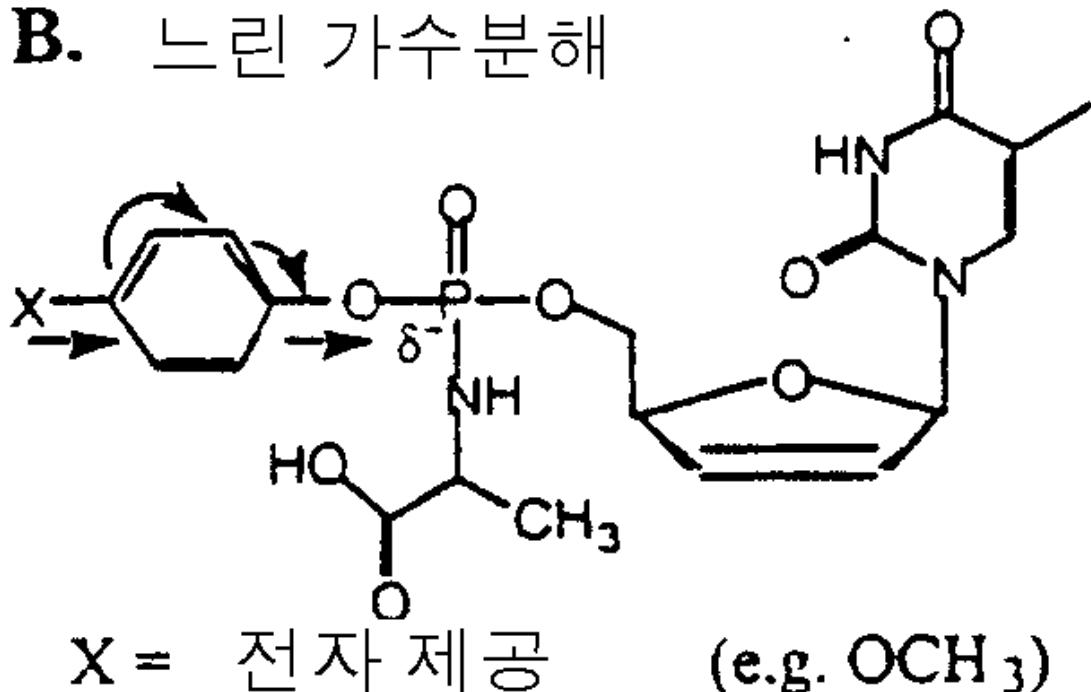
A. 빠른 가수분해



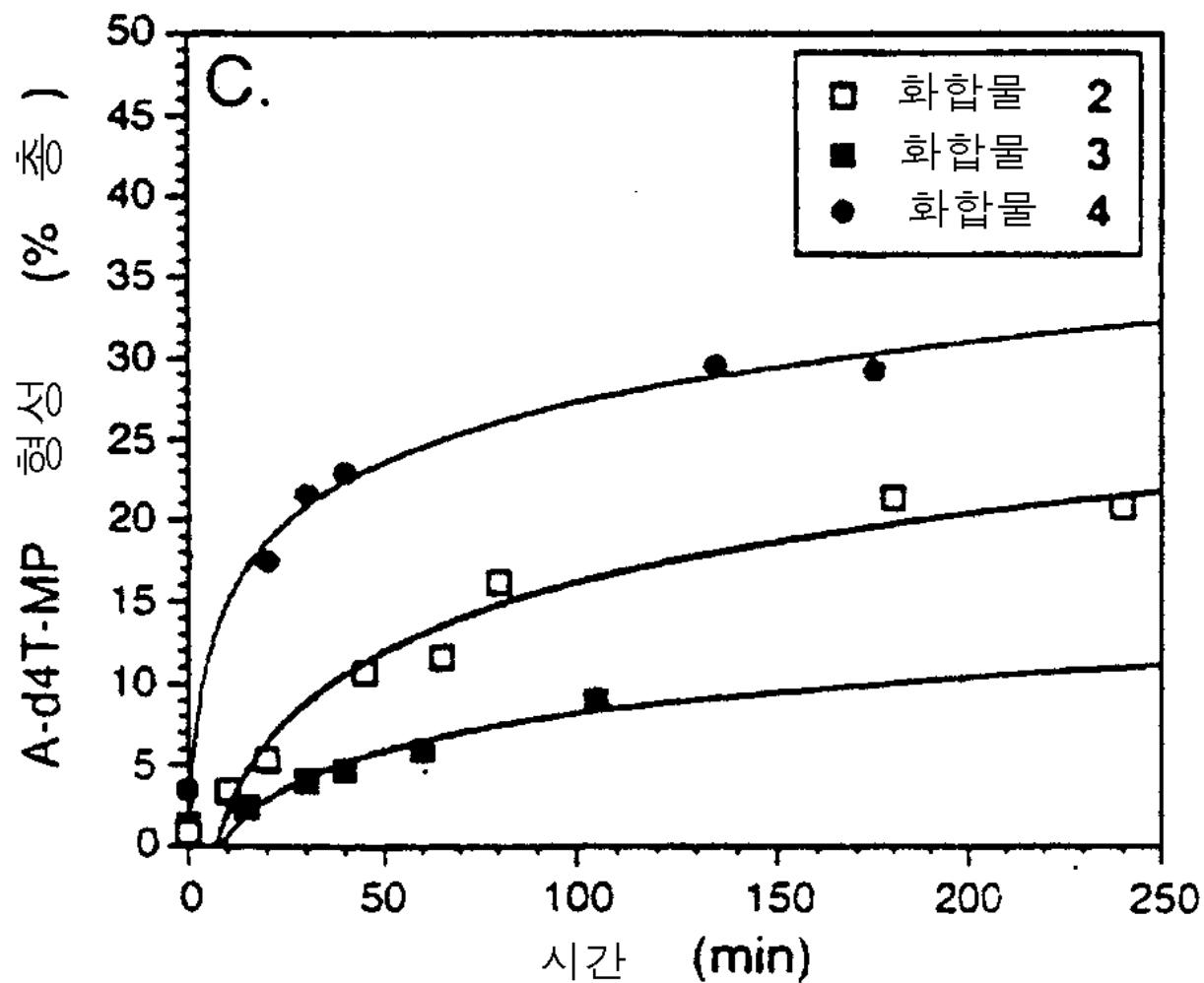
$X =$ 전자 회수

(e.g. Br)

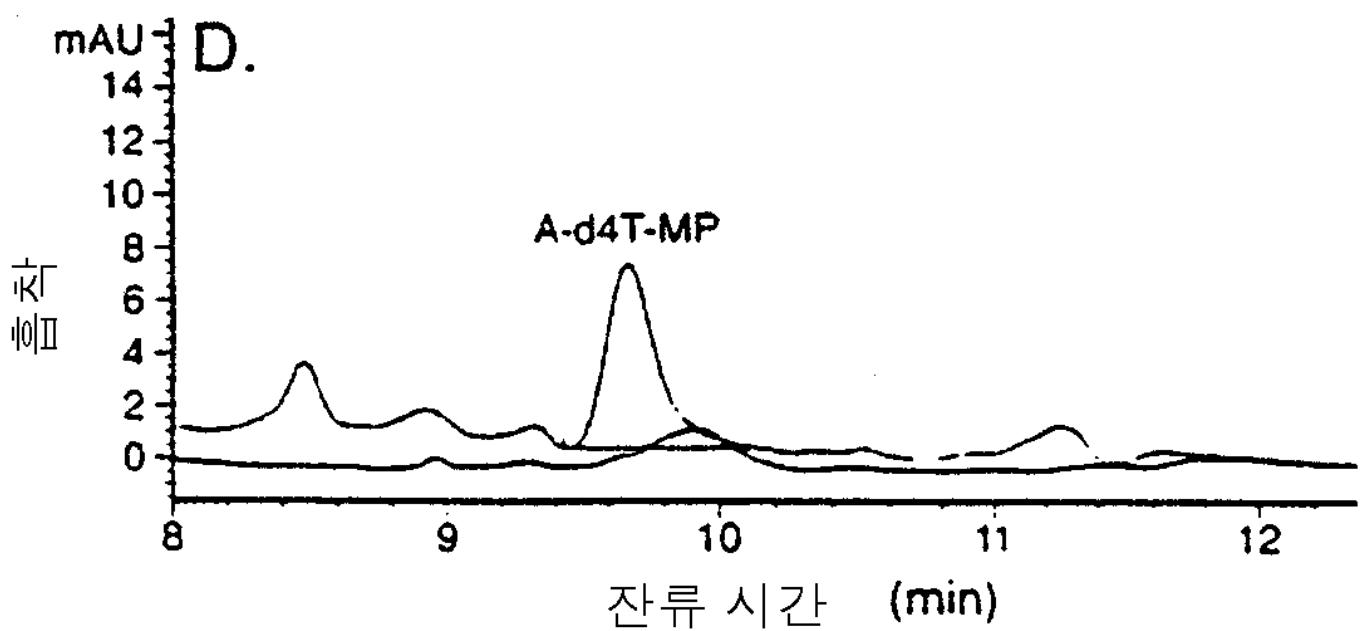
2b

B. 느린 가수분해

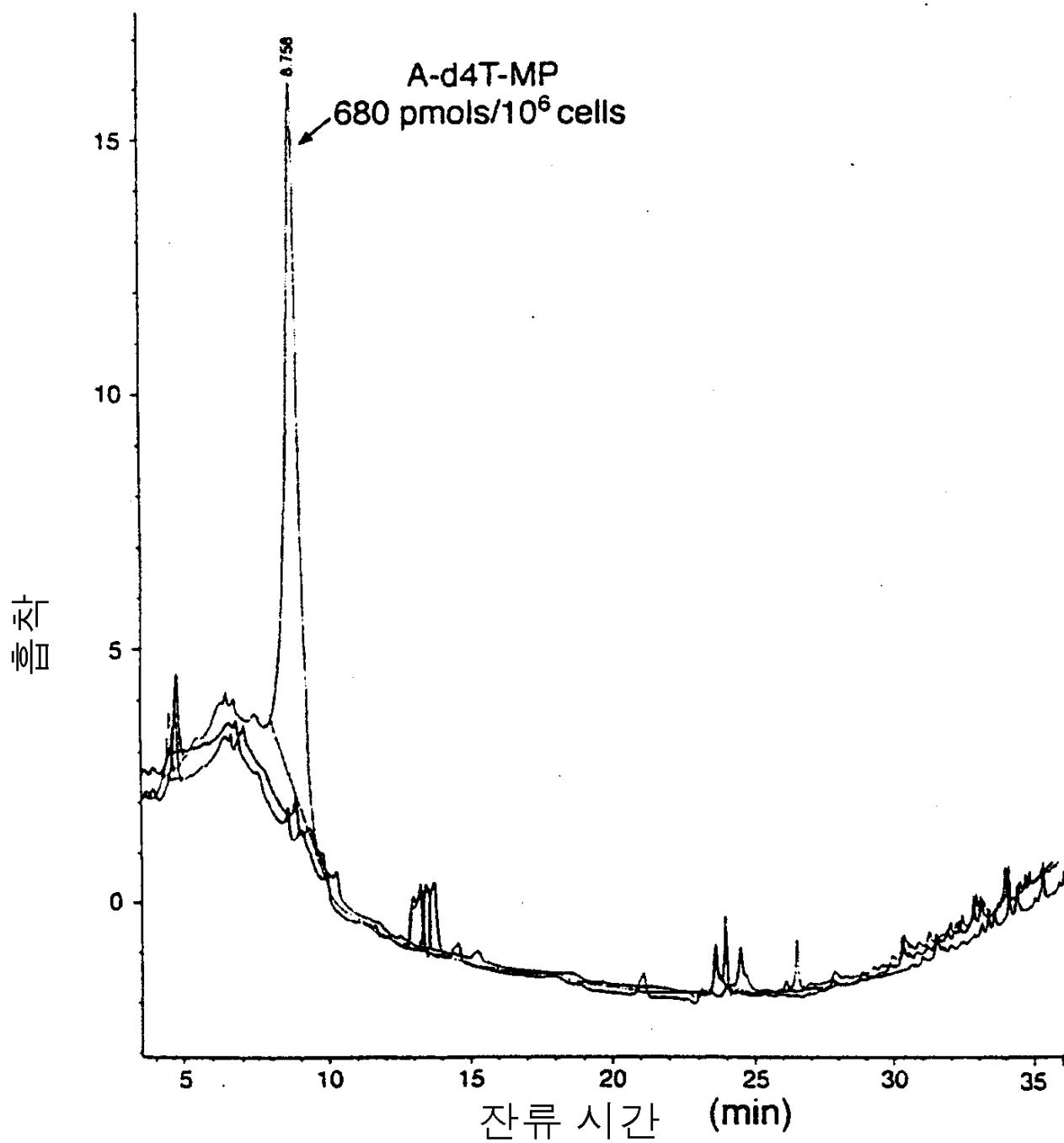
2c



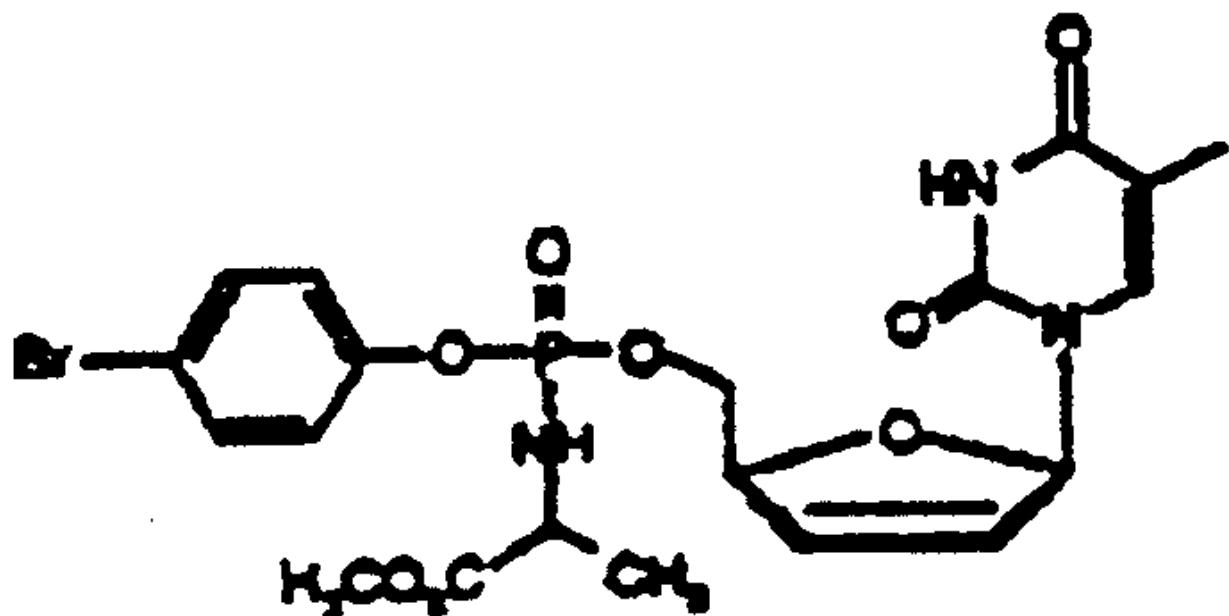
2d



3

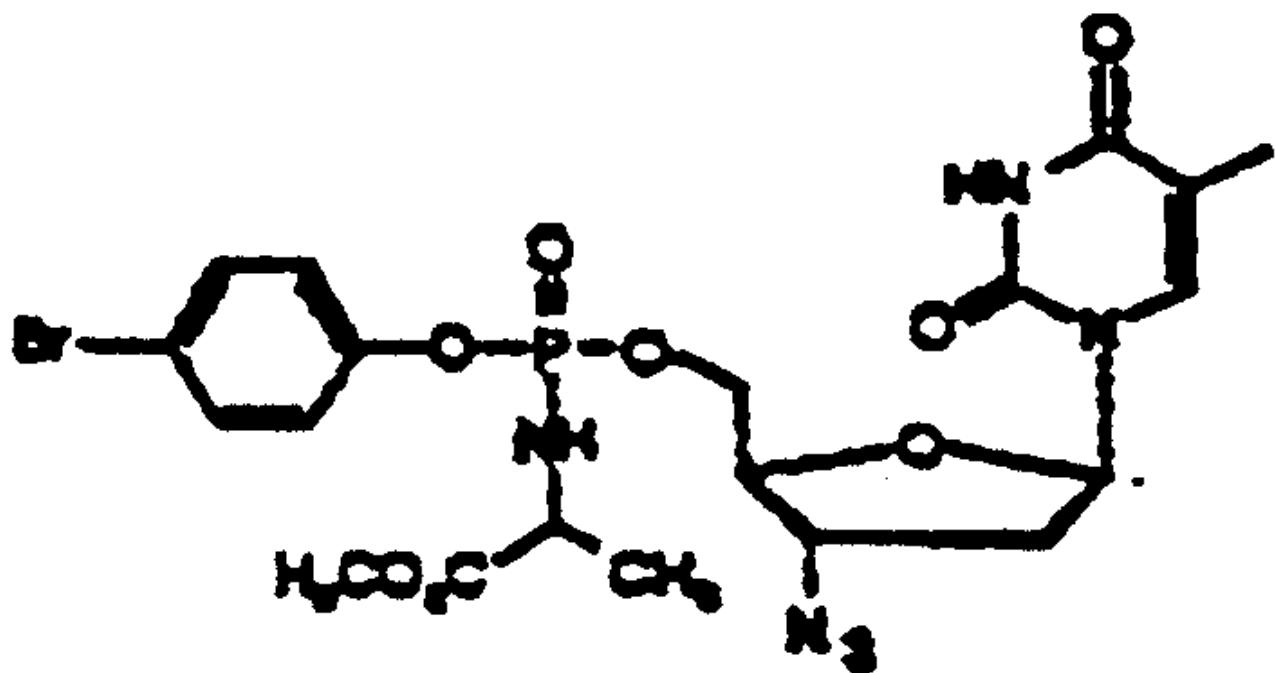


4a



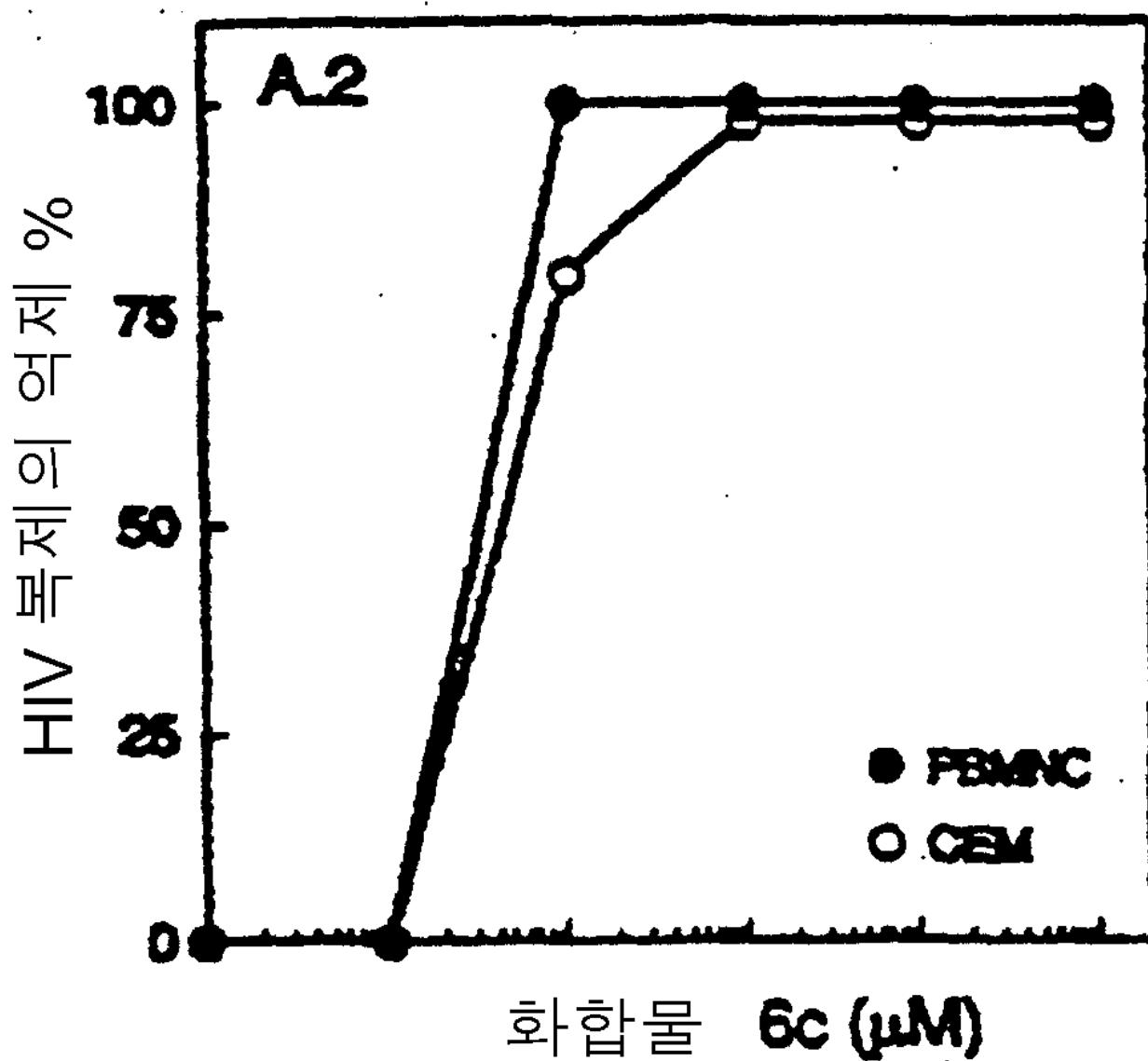
6c

4b

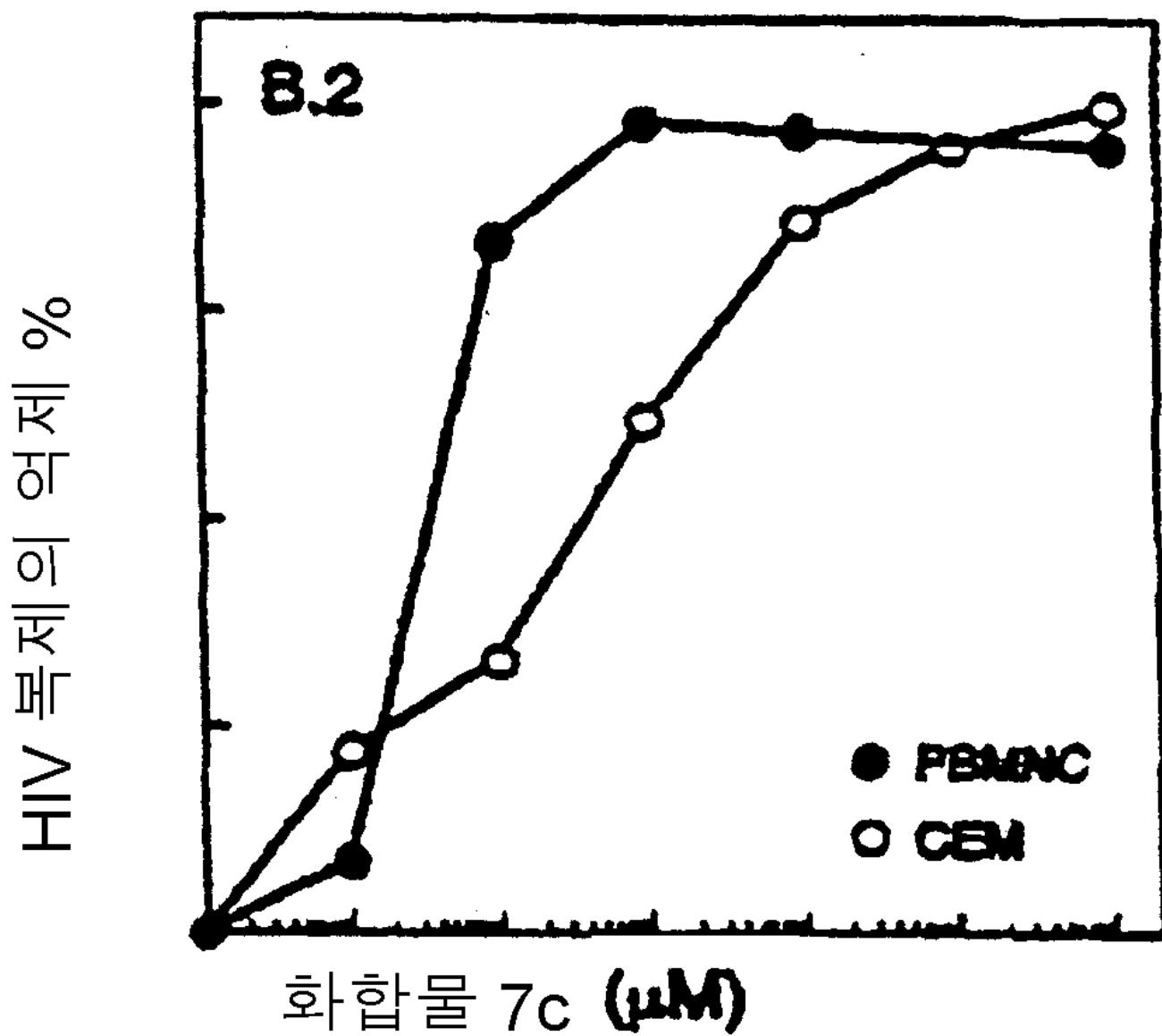


7c

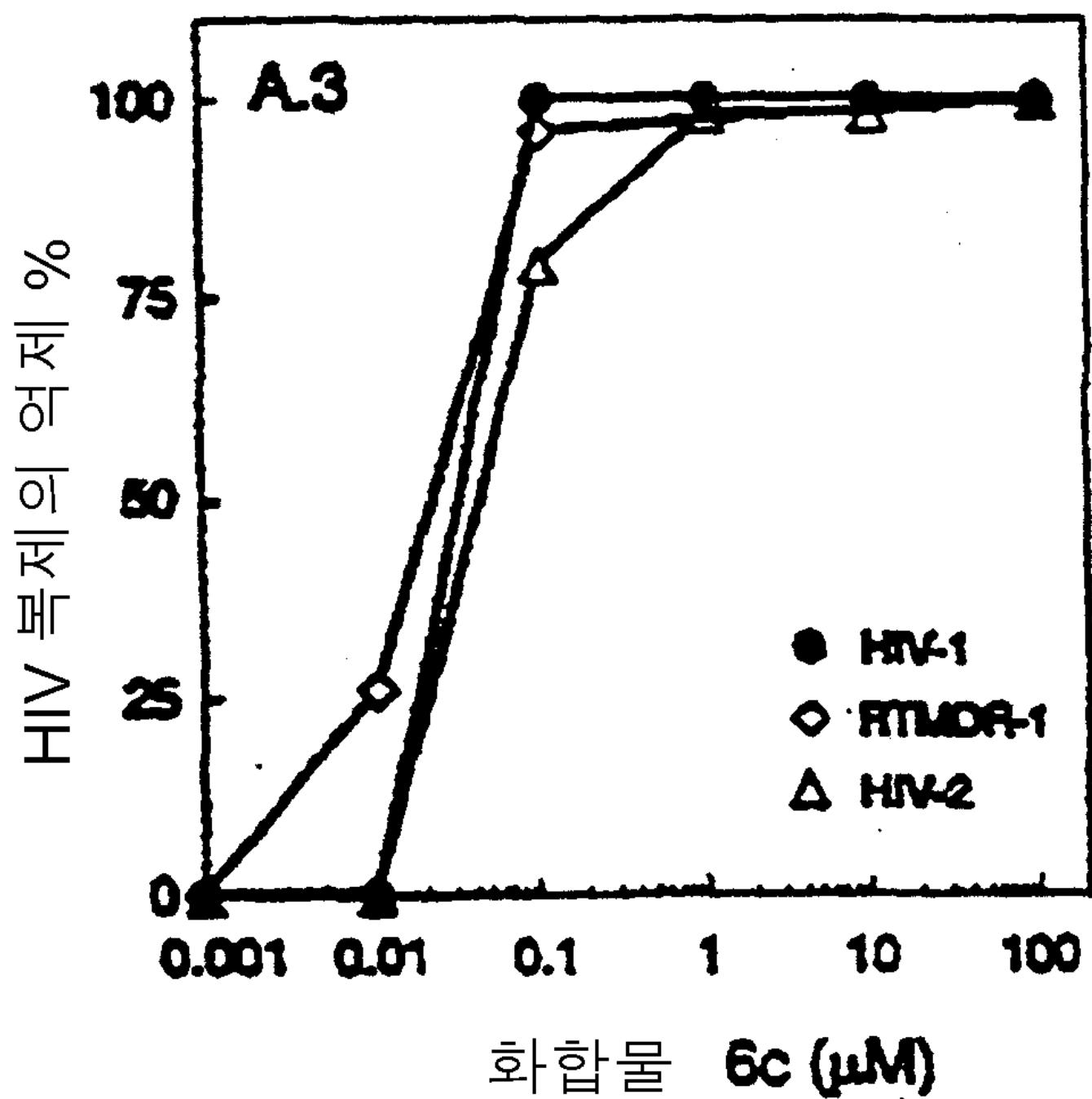
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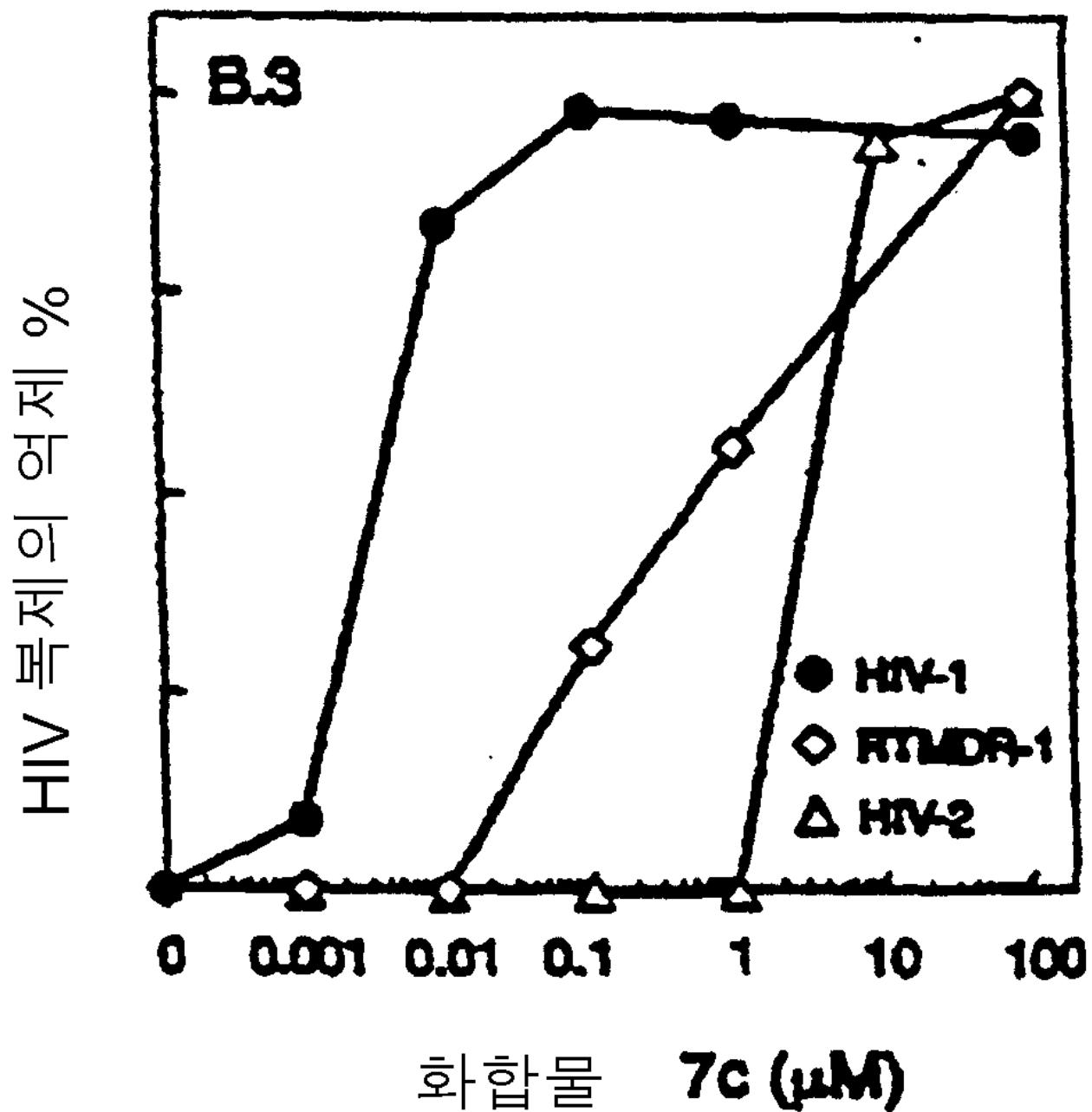
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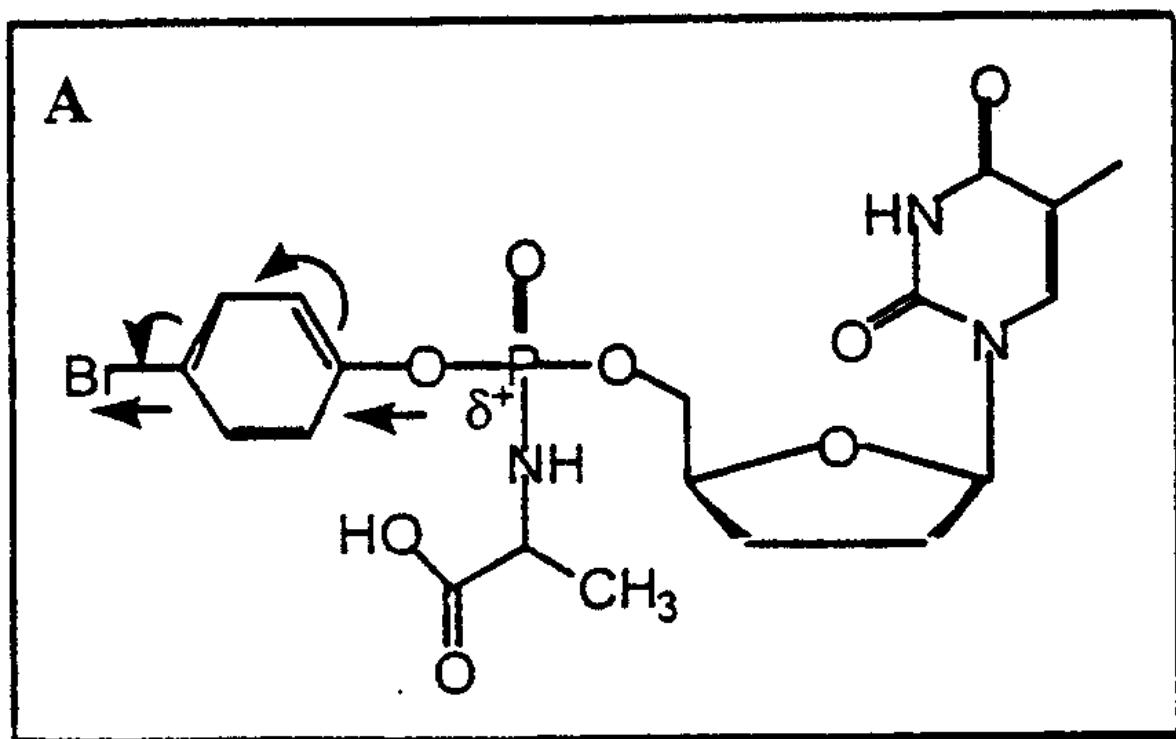
4e



4f



5a



5b

