

(19)
(12)

(KR)
(A)

(51) 。 Int. Cl. ⁷
C07H 19/10

$$\begin{pmatrix} 11 \\ 43 \end{pmatrix}$$

2001 - 0071673
2001 07 31

(21)	10 - 2000 - 7014949
(22)	2000 12 28
	2000 12 28
(86)	PCT/US1999/14774
(86)	1999 06 29

(87)

WO 2000/00501
2000 01 06

(가)

AP ARIPO : 가

EA :

EP :

OA OAPI :

(30)	09/107,716	1998 06 30	(US)
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(71)

, 55113, , 2665

(72)

55110,	,12590
06457,	,4203

(74)

1

(54) -

4

() HIV d4T
 , HIV
 , R₁ , R₂ () , Y

1

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

AIDS

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

3' - 3' - (Zidovudine; AZT) AZT -
 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 (TK) -
 d4T
 (McGuigan et al., 1996 J. Med. Chem. 39:1748).

(electron - withdrawing) 가 d4T 가

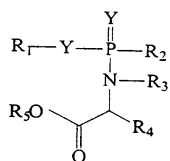
4T 2',3' - - 2'.3' - (, HIV HIV . d , - HIV 가 , , HIV

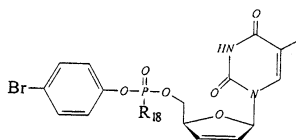
TK - CEM T - d4T (PBMNC) HIV , d4T - 5' - () RTMDR - 1, HIV - 1 AZT - NNI - HIV - 2 , AZT PBMNC TK - CEM T - HIV - 2 , AZT NNI - RTMDR - 1 HIV - 2 3dT - 5' - (d4T AZT PBMNC TK - CEM T - d4T AZT 가 , d4T AZT

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

가 HIV 가 HIV

, d4T AZT 가





d4T

Antiviral Res., 1992, 17:311
 N - THF d4T 가
 , d4T Mansuri, et al., 1989 J. Med. Chem. 32, 461
 , d4T McGuigan, et al.,

d4T 가 , d4T AZT
 (sustained release drugs)
 , , HIV / HIV

1 d4T
 2a 2b 가 가 가
 2c 가 A - d4T (elution) (2
 : X="H("), 3: X="OCH₃ () 4: X="Br(")).

2d 가
 3 TK - CEM 2 - 4 가
 pmol 4 CEM (lysate) . A - d4T - MP 680

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 - 1

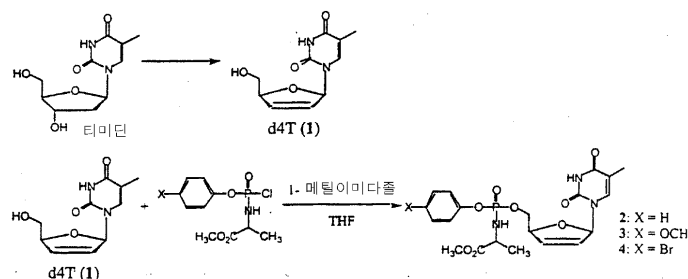
5a 5b (

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 /

(diastereomer)

HPLC

C18 4 × 250 mm L
96%

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

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

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

3: TK - CEM 2 - 4
 TK - 2 - 4 , 1 × 10⁶ CEM 가 3 2 - 4(100
 μ M) , , HLPC 가 , d4T
 CEM 4 CEM 2 3
 (680 pmol/10⁶ < 50 pmol/10⁶ ; 3).

CEM RPMI, 10% 1% / . 10⁶ /m
 I 가 37 3 100 μ M . PBS
 , 60% 0.5 ml 가 . - 20 , , 15,
 000 × g 10 . 100 μℓ HPLC . HP
 LC (quarternary) , (degausser), (diodearray)
 (HP) 1100
 . 250 × 4.6 mm Sulpelco LC - DB C18
 , 10 mM (pH 3.7) .
 10 5 35% 1 ml/ 5 35% , 20
 35 100% . 270 nm . A - d4T - MP 680 pmol
 8.7 4 CEM

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

[1]

		PBMNC			CEM		
화합물	X	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

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

4: MDR

4 AZT

HIV - MDR

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

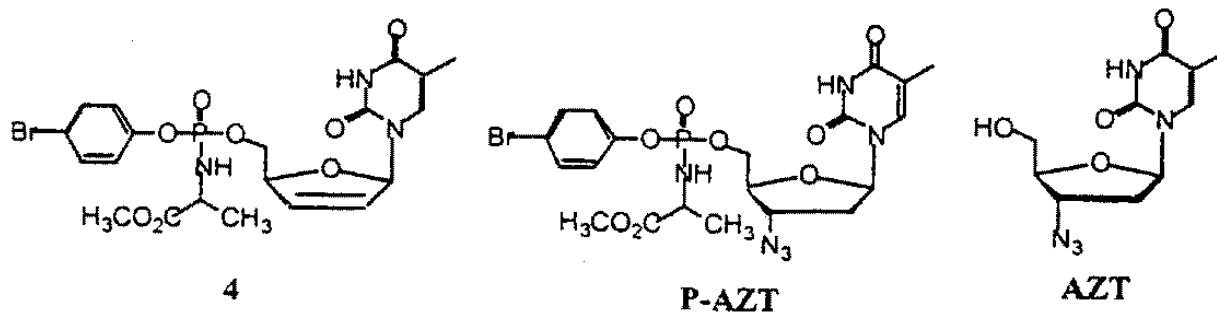
))

AZT - 5' - [p -
4

2 , 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

, 3' - (3dT)

- HIV

가 2 , 3dT(5)

d4T(1) (Mansuri, et al., 1989 J. Med. Chem. 32:461 - 466). (1)

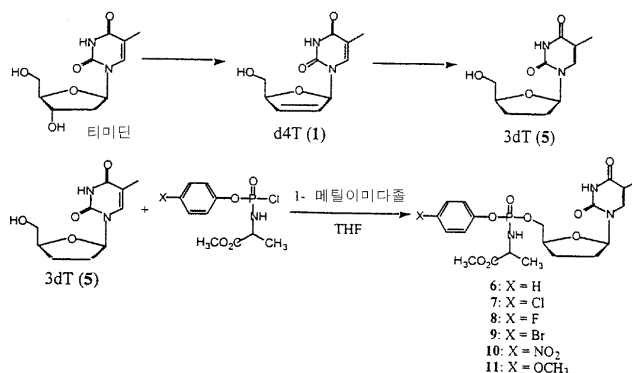
가(hydrogena

tion) H₂ 5% Pd/C

85% 3dT(5)

가 McGuigan et al., 1992 Antiviral. Res. 17:311 - 321

, 6 - 11 2



2. 가 , 1 M HCl, (org
anic phase) MgSO₄ , (NO₂
5% (vacuo))
가 THF 3dT 1 -
(gum)
12 , (org
6 - 11
가 . HPLC 1 ml/ 70:30 /
C18 4 × 250 mm LiChrospher HPLC 96%
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); ^{13}C NMR(CDCl_3) 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; ^{31}P NMR(CDCl_3) 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(CDCl_3) 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); ^{13}C NMR(CDCl_3) 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; ^{31}P NMR(CDCl_3) 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(CDCl_3) 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); ^{13}C NMR(CDCl_3) 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; ^{31}P NMR(CDCl_3) 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(CDCl_3) 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); ^{13}C NMR(CDCl_3) 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* ; ^{31}P NMR(CDCl_3) 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

CEM T - 3dT HIV - 1 6 - 11 d4T TK - Zarling et al., 1990; Erice et al., 1993; Uckun et al., 1998).

3dT (3). , 3dT TK - CEM T - 6 - 11 IC₅₀ [RT] 3dT (1.2 - 3.1 0.7, 3) IC₅₀ [RT] , , (prodrug) , , d4T TK - , d4T

TK - (McGuigan et al., 1996a). d4T AZT (McGuigan et al., 1993, 1996a), 3dT C₅₀ [RT] , TK - HIV - 1 3dT (3).

6 - 11 (PBMNC) TK - CEM T - , 3dT , d4T TK (McGuigan et al., 1996 Bioorg. Med. Chem. Lett. 6:1183 - 1186).

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

μM , RT
50%
t al., 1989 J. Med. Chem. 32:461).

50%(IC₅₀ [RT])⁹ MTA(IC₅₀ [MTA])
(Mansuri et

[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).

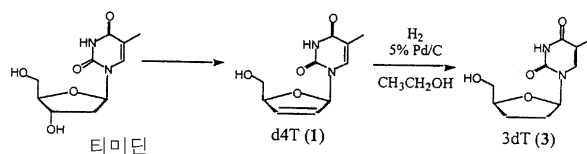
7: d4T, AZT 3dT - HIV

1 , d4T(1) (Mansuri et
al., 1989). H₂ 5% Pd/C (1) 가 85% 3dT(3) (1).

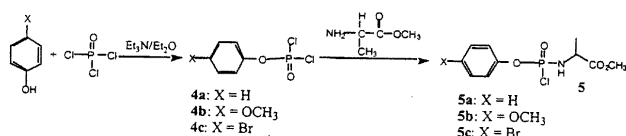
AZT(2) (5a, 5b 5c) ddN (Chu et al., U.S. Patent No. 4,841,039).
 2)(McGuigan et al., 1992), 4a, 4b, 5a, 5b, 7a 7b 4c 5c

d4T(1), AZT(2) 3dT(3) 3
 (McGuigan et al., 1992).
 (5)가 THF ddN(1,2 3) 1 - 가
 , 1 M HCl, MgSO₄

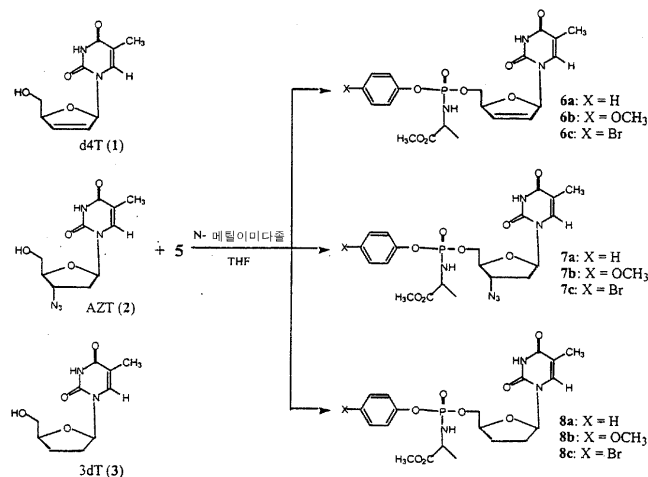
도식 1. d4T와 3dT의 합성



도식 2. 페닐메톡시알라닐 포스포로클로리데이트의 합성



도식 3. ddN의 페닐메톡시알라닐포스페이트 유도체의 합성



p -

4c

McGuigan et al., 1993
 0 mmol) (10.65 ml) , Et₂O (165 ml) p - (13.20 g; 76.3
 O (83 ml) (8.5 ml; 91.2 mmol) 0 3 Et₂
 , 2 가 ,
 , Et₂O (2 × 50 ml) Et₂O
 4c , (bp. 110 - 115 /2 mm H
 g) 4c(14.05 g; 63.5%) . 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
 mmol) - 70 3 CH₂Cl₂ (180 ml) (8.80 ml; 63.14
 4c(8.69 g; 29.97 mmol) L - CH₂Cl₂ (250 ml) p -
 mmol) (4.19 g; 30.02
 . Et₂O (300 ml) 가 ,
 . 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 (CDCl_3) 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); ^{13}C NMR(CDCl_3) 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; ^{31}P NMR(CDCl_3) δ 2.66, 3.20; MALDI-TOF mass m/e 487.9 ($\text{M}+\text{Na}$); 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(CDCl_3) 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); ^{13}C NMR(CDCl_3) 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; ^{31}P NMR(CDCl_3) δ 3.82, 3.20; MALDI-TOF mass m/e 518.2 ($\text{M}+\text{Na}$); 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(CDCl_3) 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); ^{13}C NMR(CDCl_3) 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; ^{31}P NMR(CDCl_3) δ 3.41, 2.78; MALDI-TOF mass m/e 567.1 ($\text{M}+\text{Na}$); 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, CDCl_3) δ 8.69 (1H, br, 3-NH), 7.45 (2H, d, $J=9.0\text{Hz}$, 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⁺, ⁷⁹Br).

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+1+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

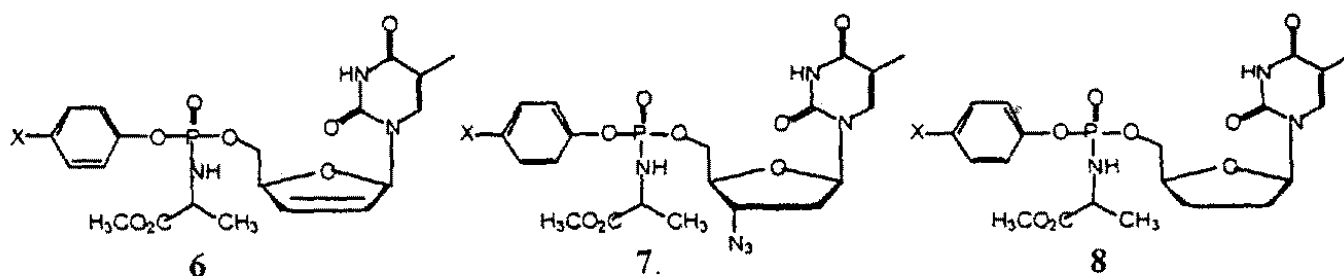
(IC₅₀ [RT]) 50%
 AZT - HIV - 1(: HTLV_B) - , AZT - NNI - HIV - 1(: RTMD
 R - 1) - (by Dr. Brendan Larder, NIH AIDS Research and Reference Reagent Program, DIV, SIDS, NIAID, N
 IH; cat. # 2529) HTLV_B - TK - CEM T - HIV - 2(; CBL - 20) -
 (PBMNC) 가 . RT
 (,) RT 50% (CC₅₀ [M
 TA]) 2,3 - (2 - - 4 - - 5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

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

d4T - V - 1, HIV - 1 TK - PBMNC CEM, d4T . HI
 IC_{50} PBMNC 40 nM, TK - CEM 2400 nM (4 RT 4a - 4f).
 60 6c(d4T - 5' - [p -]) d4T RT
 (4).
 , MTA 10,000 nM PBMNC CEM
 (IC_{50} : 30 nM 40 nM)(4), 6b 6c가
 M RT 6c 5 6b HIV TK - CE
 (IC_{50} : 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 IC_{50} PBMNC 3 nM, TK - CEM 2
 00 nM . d4T , AZT HIV - 1
 TK - CEM T - AZT
 , AZT - 5' - () 7c TK - CEM
 HIV , AZT 5 (IC_{50} [RT] : 0.04 μ M 0.2 μ M).
 MTA 10,000 nM PBMNC CEM
 .
 8a - c 3dT(3) PBMNC TK - CEM T - HIV - 1
 d4T(1) . 3dT TK - CEM T -
 d4T (4). , 8a - c
 IC_{50} [RT] 3dT(1.2 - 3.1 0.7, 4) IC_{50} [RT] , , (prodrug)
 , , 가 TK - - . d
 4T, AZT 3dT , TK - HIV - 1
 IC_{50} [RT] , TK - PBMNC TK - CEM T -
 3dT djT (4 4a - 4f). 8a - c TK
 , 3dT TK

[4 - 1]

정상의 말초 혈액 단핵구세포(PBMNC)와 TK-결핍 CEM T-세포에서
d4T, AZT 및 3dT의 페닐메톡시알라니닐포스페이트 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]

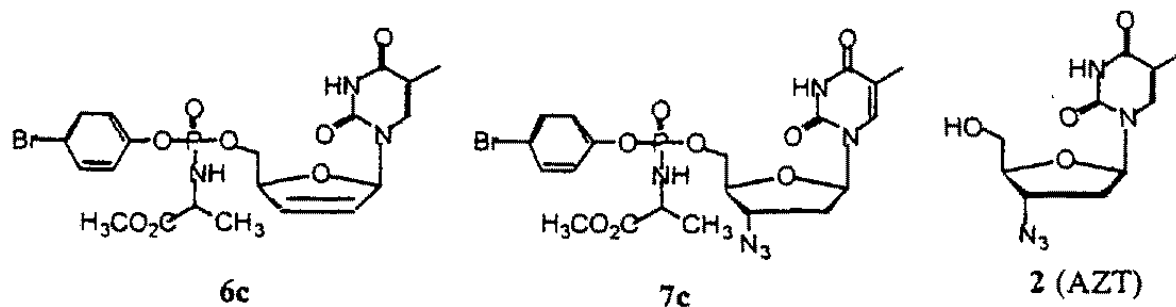
		PBMNC		CEM	
화합물	X	IC ₅₀ [RT]	IC ₅₀ [MTA]	IC ₅₀ [RT]	IC ₅₀ [MTA]
8b	OMe	1.3	>10	19.7	>10
8c	Br	1.2	>10	22.8	>10
1 (d4T)	-	0.04	>10	2.4	>10
2 (AZT)	-	0.003	>10	0.2	>10
3 (3dT)	-	0.7	>10	91.2	>10

HIV - 2 RTMDR - 1 d4T - 5' - () AZT - 5' - ()

6c 7c PBMNC RTMDR - 1, HIV - 1 AZT - NNI - HIV - 2 HIV
 AZT(2)
) RTMDR - 1 HIV - 2 6c, d4T - 5' - ()
 AZT 7c AZT(2) 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, RT

50%(IC₅₀ [RT])

6a, 6b, 6c, TK-, CEM, d4T(1), d4T - (4).
(6a, 6b, 6c) HIV-1 PBMNC, d4T(1), d4T - 5' - [p - 6c] 6c가 TK -
CEM 가 - HIV 가 (2), TK - CEM T -
d4T (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 (IC₅₀ : 40 nM 2
00 nM). 3dT (4),
8c 가 가 (, 2 B C).
, 8c 8a 1 가 (, 2 A B)가 3dT
, 8a, 8b 8c가
가 (2). 3dT
, d4T
3dT HIV TK- CEM T -
- HIV

가

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

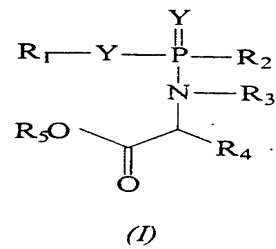
가

(57)

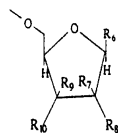
1.

HIV

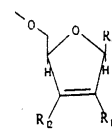
HIV



[, Y ,

 R_1 R_2 

(II)



(III)

{ , R_6 ,

$\text{R}_7, \text{R}_8, \text{R}_9, \text{R}_{10}, \text{R}_{11}, \text{R}_{12}$, , , , - NO_2 , - NR_{13} R_{14} - $\text{N}(\text{OR}_{15})\text{R}_{16}$
 (, $\text{R}_{13}, \text{R}_{14}, \text{R}_{15}, \text{R}_{16}$, , .) . }

R_3 , , ,

R_4 ,

R_3 R_4 ,

R_5 , , .]

2.

1 , Y HIV HIV .

3.

1 , R_1 HIV HIV .

4.

1 , R_6 , HIV HIV .

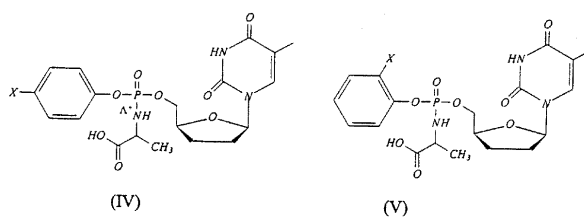
5.

1 , R_4 HIV HIV .

6.

HIV

HIV



(, X .)

7.

6 , X NO_2 HIV HIV .

8.

7 , X HIV HIV .

9.

8

,

HIV

HIV

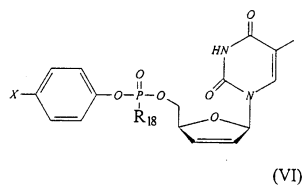
.

10.

HIV

HIV

.



(, X

, R₁₈

.)

11.

10

,

R₁₈- NHCH(CH₃)COOCH₃

HIV

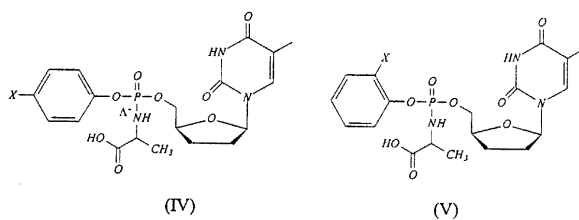
HIV

.

12.

HIV

.



(, X

.)

13.

12

,

X

NO₂

HIV

.

14.

13

,

X

HIV

.

15.

14

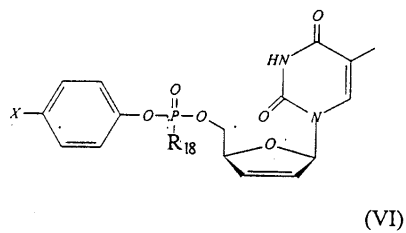
,

HIV

.

16.

HIV



(VI)

(, X , R₂ .)

17.

16 , R₁₈ - NHCH(CH₃)COOCH₃

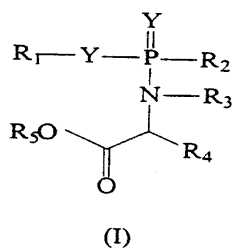
HIV

18.

HIV

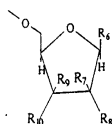
가

HIV

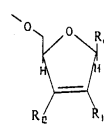


(I)

[, Y ,

R₁ ,R₂ ,

(II)



(III)

{ , R₆ ,

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

R_3 , , ,

R_4 ,

R_3 R_4 ,

R_5 , , .]

19.

18 , Y HIV .

20.

18 , R_1 HIV .

21.

18 , R_6 , HIV .

22.

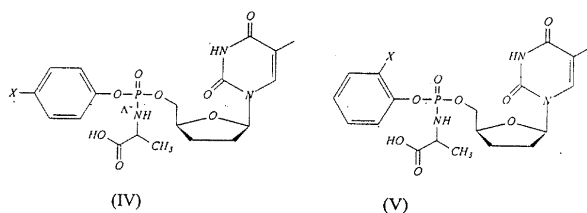
18 , R_4 HIV .

23.

HIV

가

HIV



(, X .)

24.

23 , X NO_2 HIV .

25.

24 , X HIV .

26.

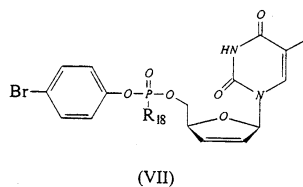
25 , HIV .

27.

HIV

HIV

가



(, R_{18} .)

28.

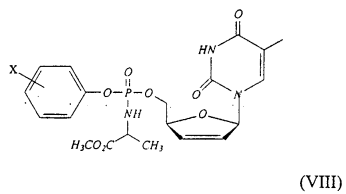
27 , R_{18} - $\text{NHCH}(\text{CH}_3)\text{COOCH}_3$ HIV .

29.

HIV

HIV

가

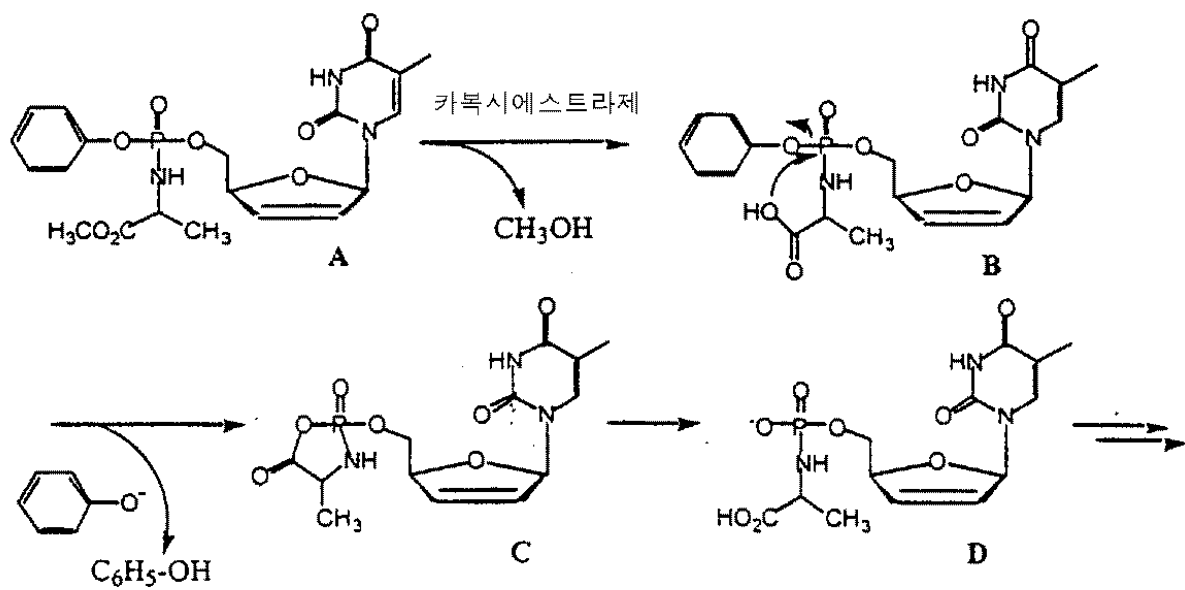


(, X .)

30.

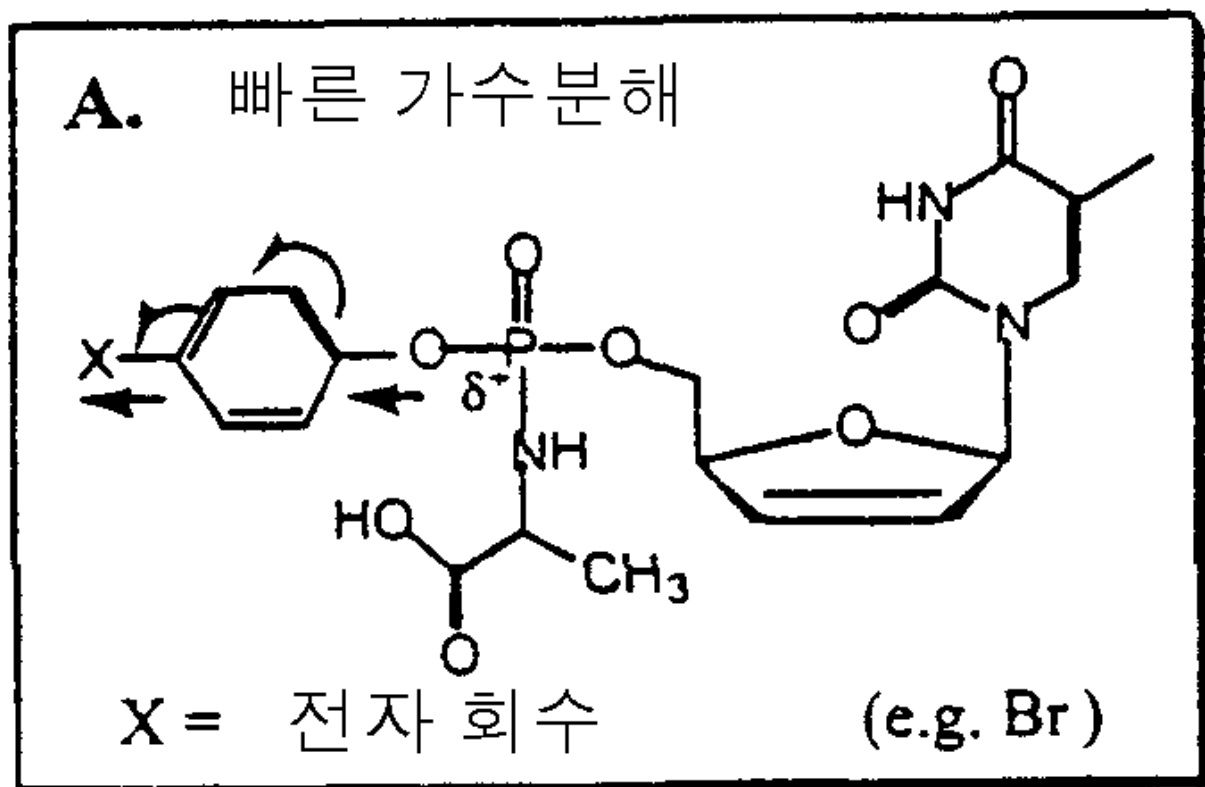
29 , X NO_2 HIV .

1



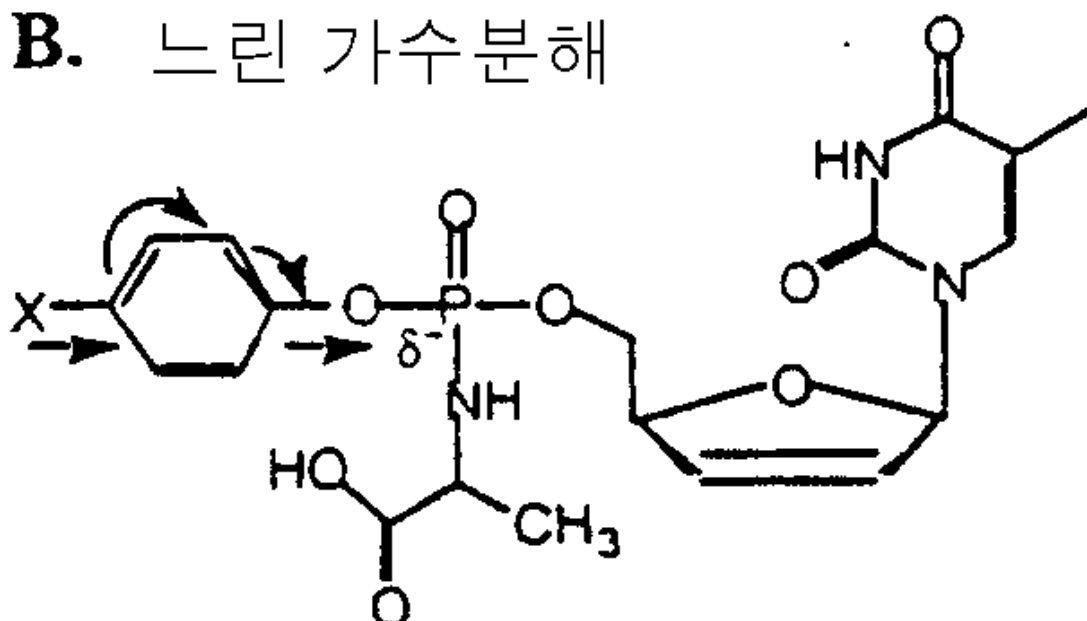
문헌에 제공된 d4T의 아릴포스페이트 유도체의 대사 경로

2a



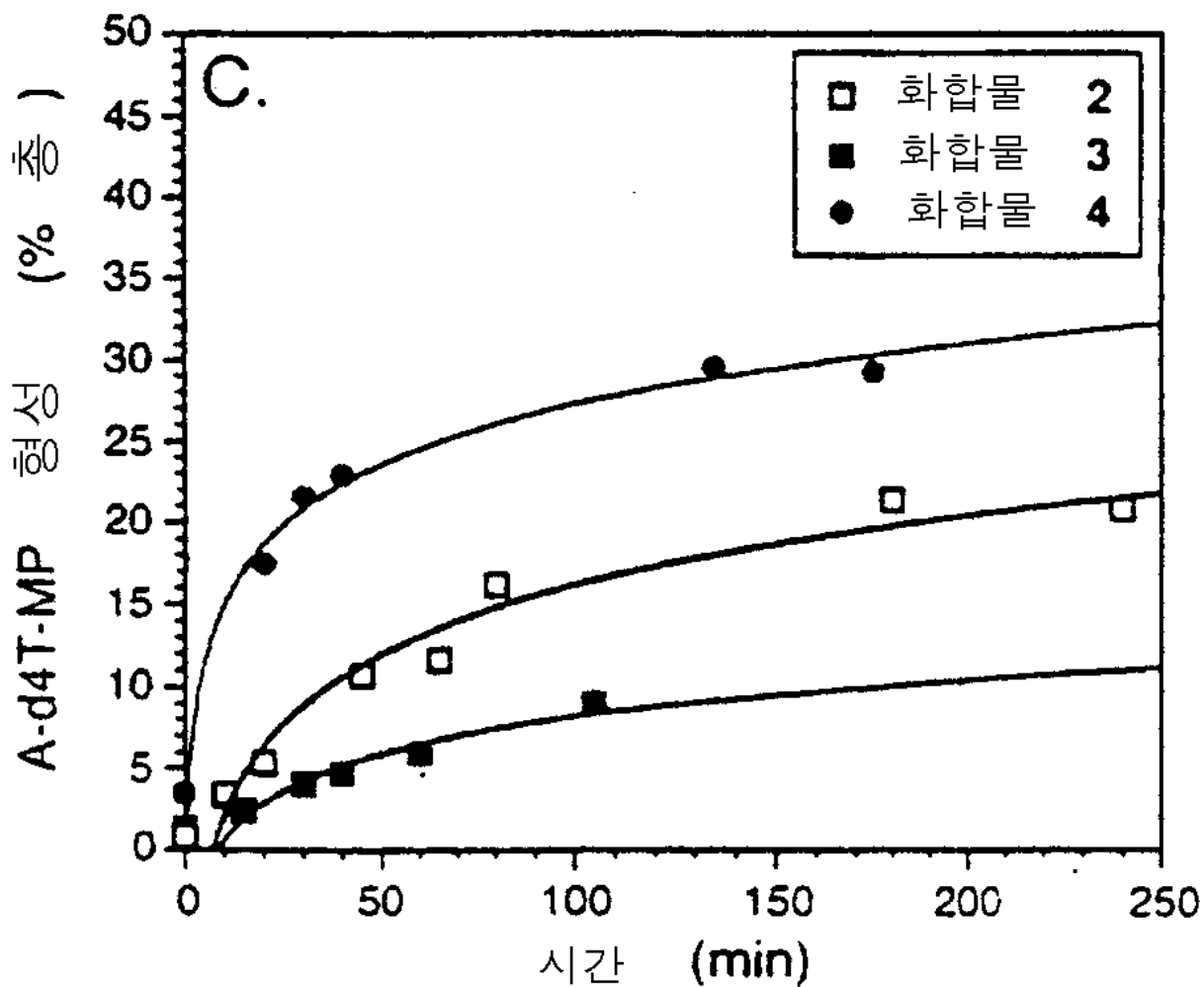
2b

B. 느린 가수분해

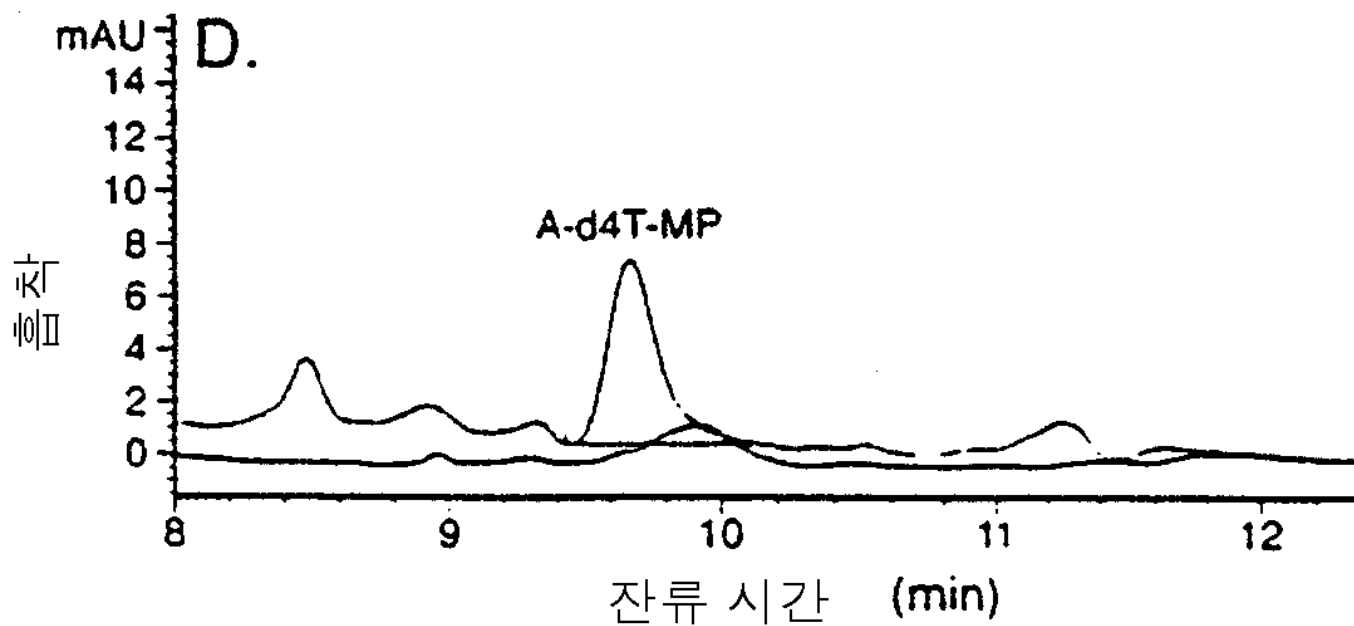


X = 전자 제공 (e.g. OCH_3)

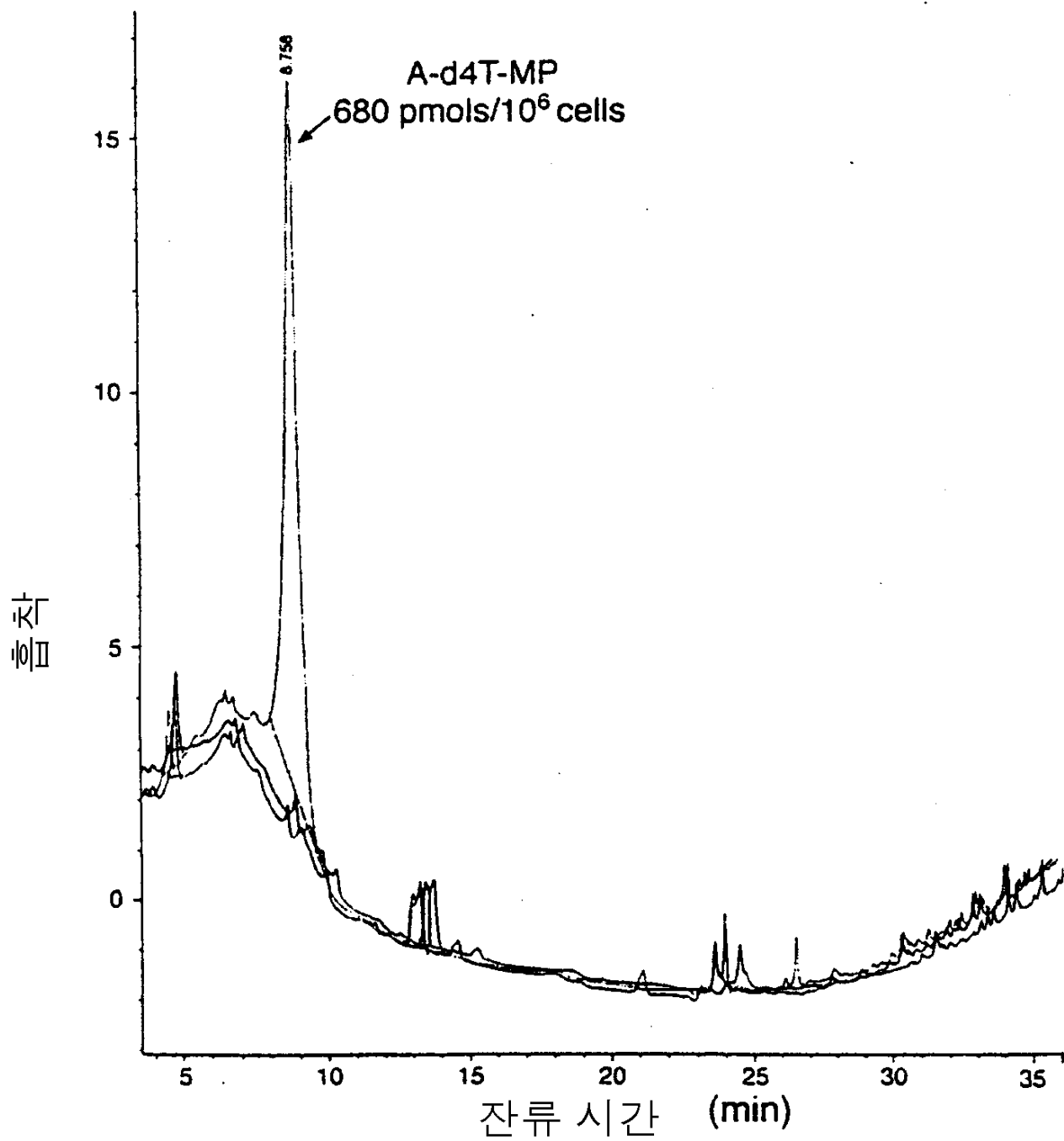
2c



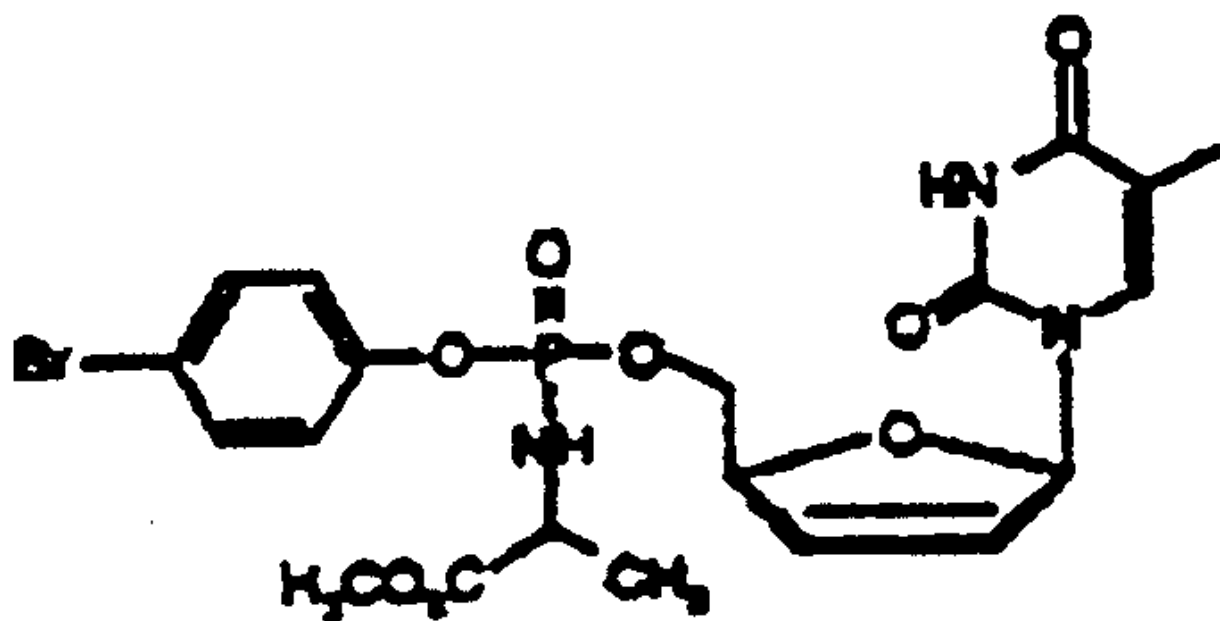
2d



3

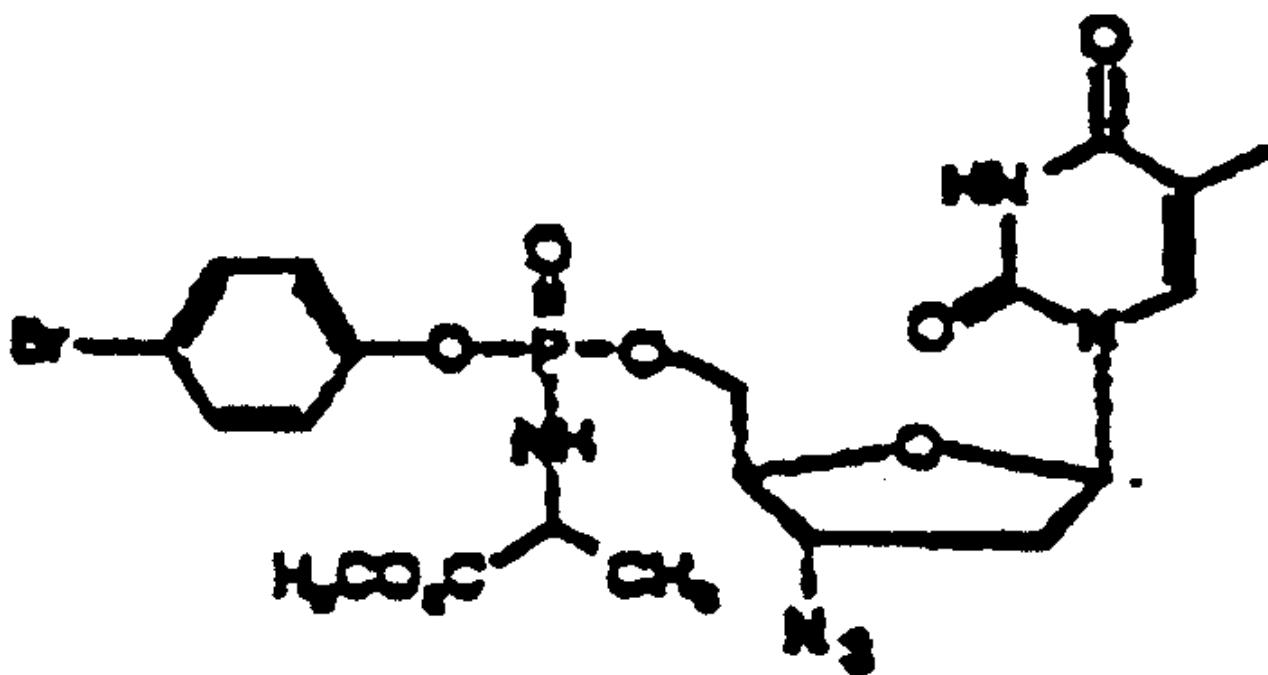


4a



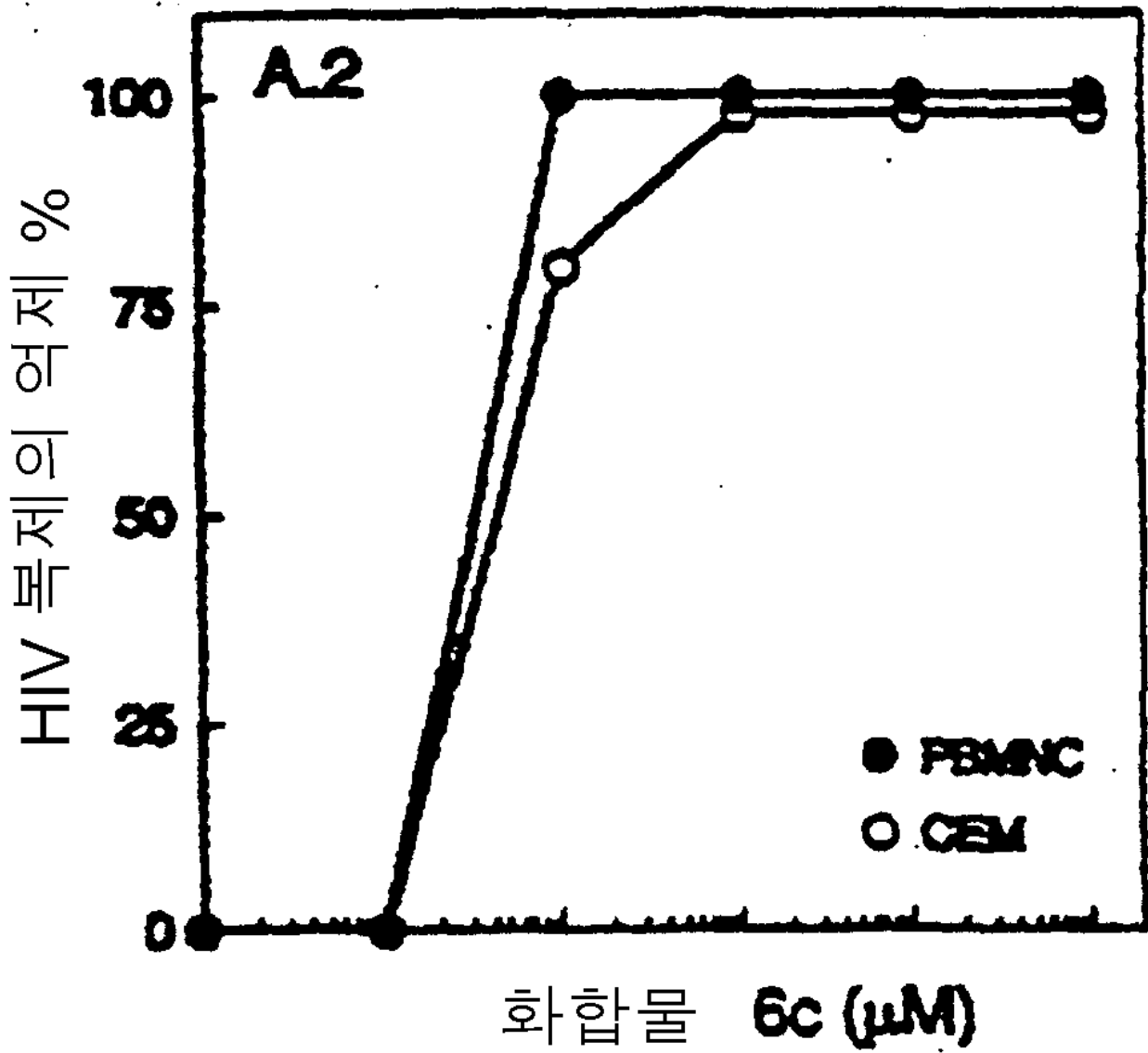
6c

4b

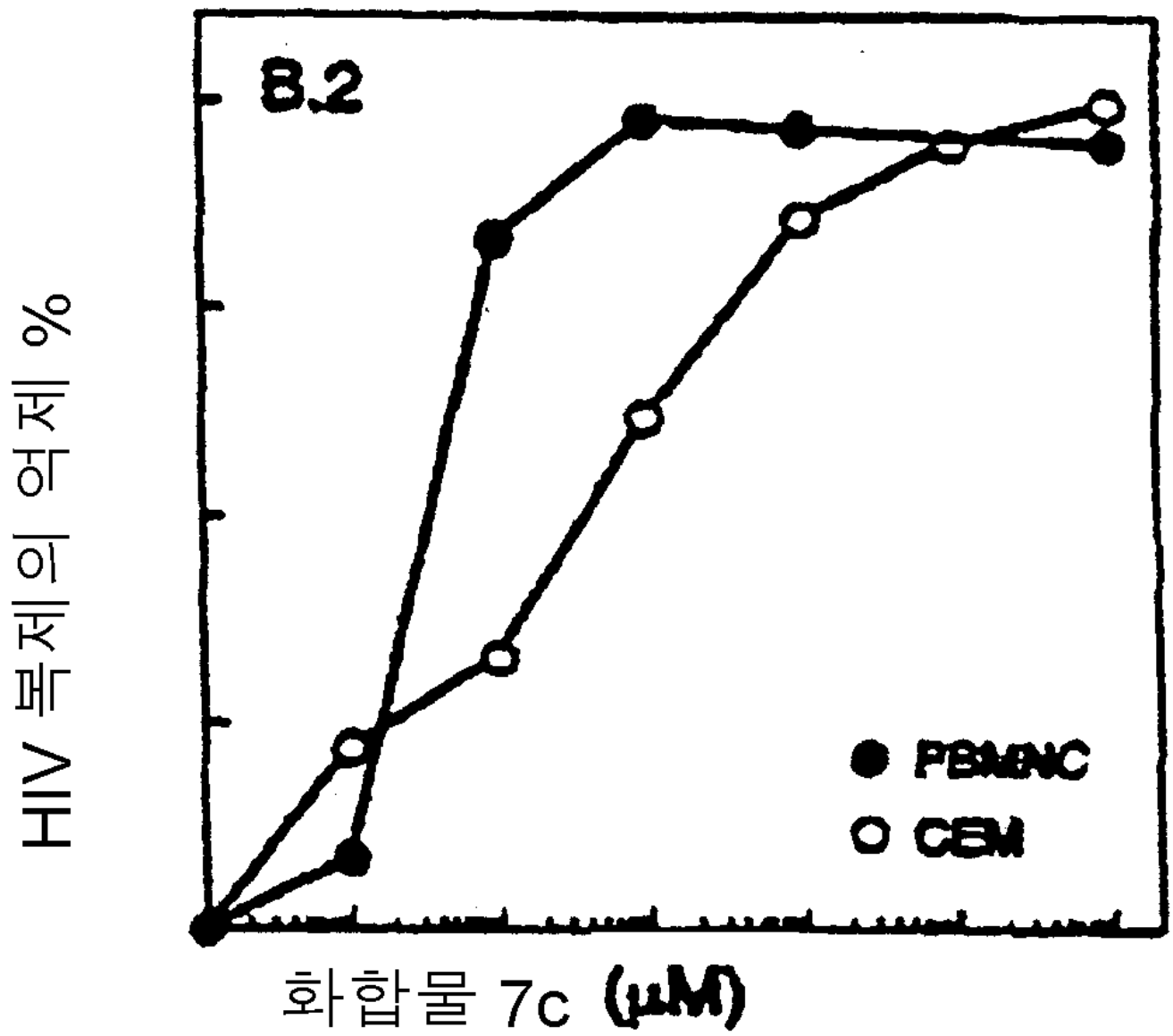


7c

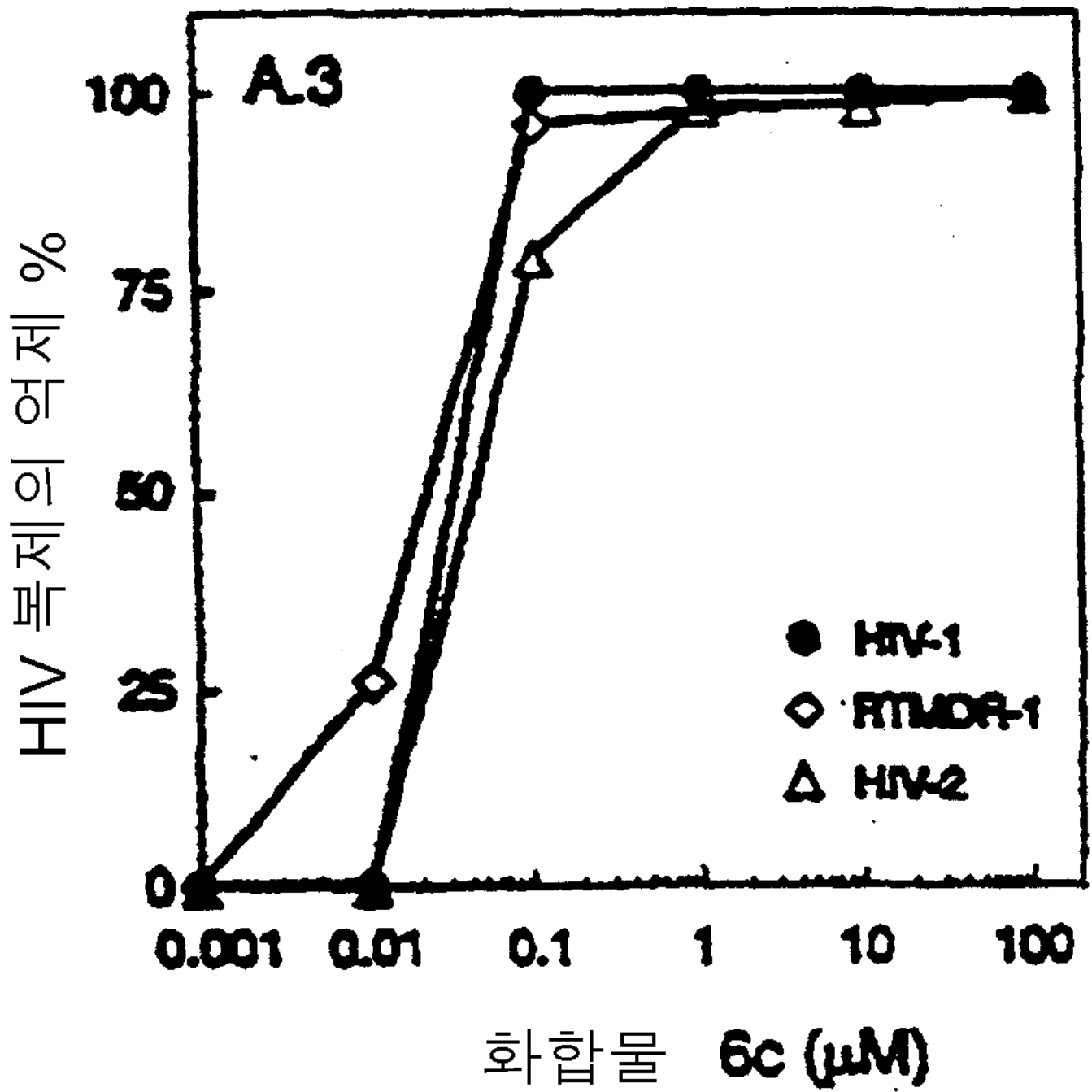
4c



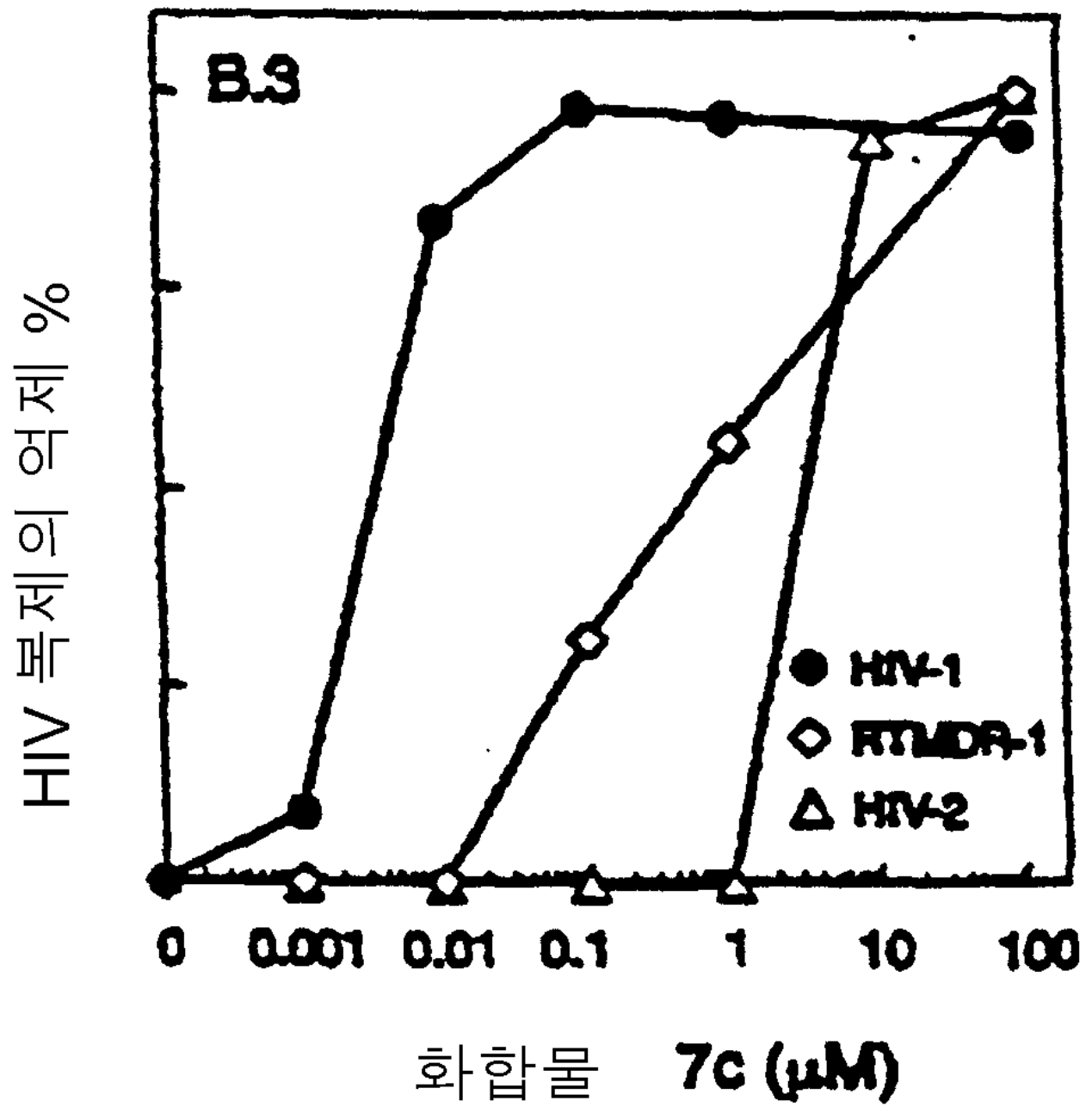
4d



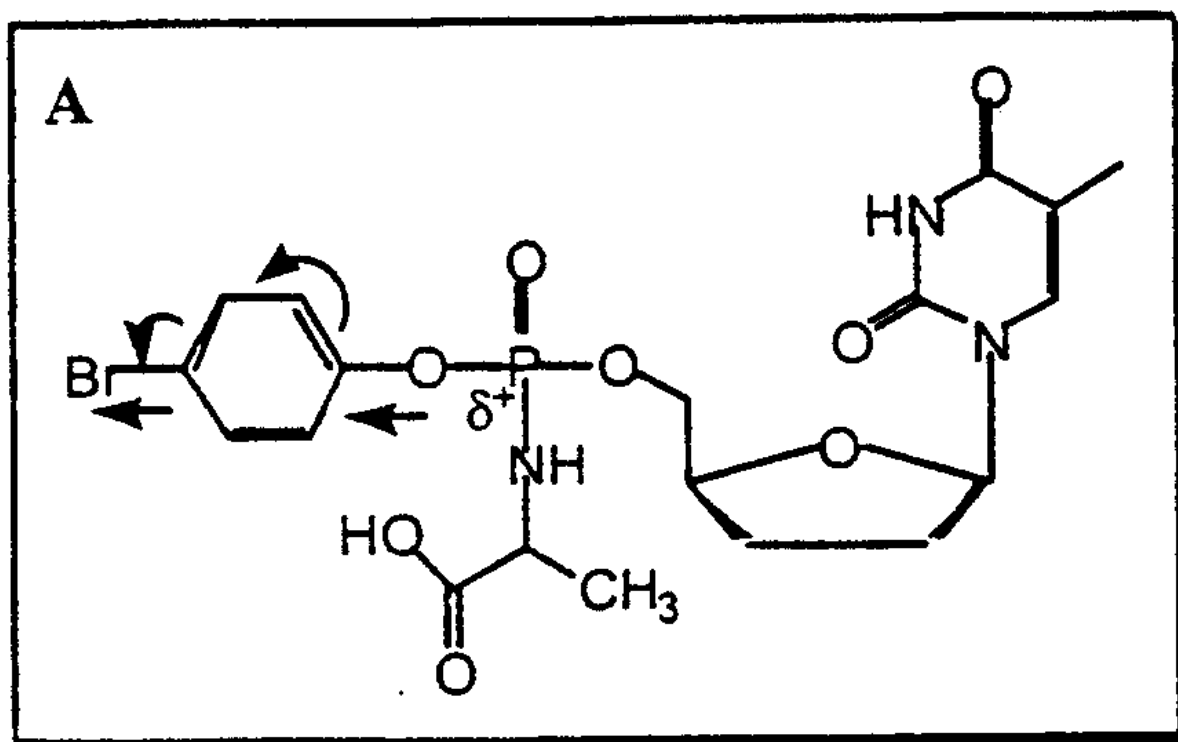
4e



4f



5a



5b

