

(19)
(12)

(KR)
(B1)

(51) . Int. Cl. 6 (45) 2003 03 29
A61K 9/00 (11) 10 - 0378443
A61K 31/70 (24) 2003 03 19

(21) 10 - 1999 - 7007113 (65) 2000 - 0070848
(22) 1999 08 06 (43) 2000 11 25
1999 08 06
(86) PCT/US1998/02701 (87) WO 1998/34593
(86) 1998 02 06 (87) 1998 08 13

(30) 08/797,472 1997 02 06 (US)

(73) (27703) 4222 470

(72)	(:27608)	1330
	(:27511)	200
	(:27713)	5815
	(:27607)	3101

(74)

(54)

], $\alpha^{32}P$ -UTP, 5' - [CTP], 5' - [ATP] 5' - [UTP]

, , , (), 가 ;

08/797,402 (1997 2 6)

가 , 1) , 2)
, 3) , 4) , 5)
(ocular pressure) 2
() ,

4 " " 가

가 1
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,
, , 가 . . . 가 . . . , ()
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(lacrimal system) 가
,
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가
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I. Plast. Reconstr. Surg., 8, 13(1992)).

1 (PANDO) , , ,
2 (SANDO) 2
, Ophthal. Plast. Reconstr. Surg., 8, 237(1992)).
20% , 1

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(
 catheter) , , 가
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 5062831 (1991); . . . , 5021043 (1991) 5169386 (1992)). ,
 (silastic) 가 (. . . , A
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 1065(1995); . . . , 5345948 (1994)).
 가 (. . . , Ophthal. Plas. Reconstr. Sur
 g., 12, 32(1996)).

	5'	-	(UTP)	5'	-	(ATP)
P2Y ₂						P2Y ₂
가	UTP	ATP		5,292,498		
	UTP		UTP	P2Y ₂	P2Y ₄	
가			ATP			(
Lett. 264, 130 - 34(1990); idem, J. Physiol. 447, 103 - 18(1992);						, J. Physiol. 449, 31
?)						, Inv. Ophthalmol. Vis. Sc.
97)).		P2Y ₂	/	P2Y ₄
가						-
가						,
			UTP			

가 (KCS),
(腺) (UTP) P2Y₂ P2Y₄ ()

2 1 - 4

3 1, 2, 3 4

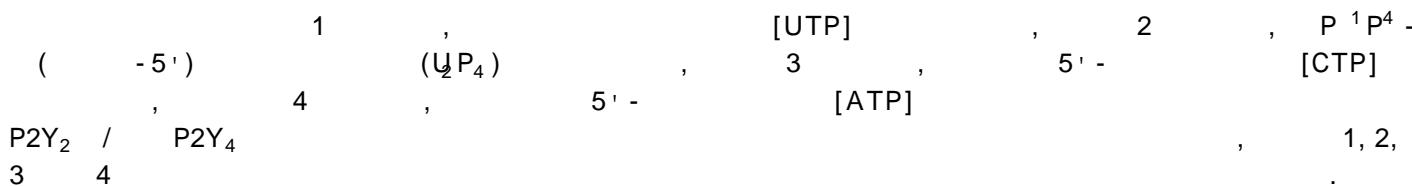
1 2

DN

5' - (UTP)가

UTP가
가 - (,)

가 , , . 가



1

[1]()

Np ₂ N	Np ₂ N'	Np ₃ N	Np ₃ N'	Np ₄ N	Np ₄ N'
Ap ₂ A(4,1)	Ap ₂ NAD(6)Ap ₂ TAD(6)	Up ₃ U(1)Ap ₃ A	Ap ₃ T(20)m ⁷	Up ₄ U(2,3)Ap ₄ A(1,4,29)	Ap ₄ U(3)Ap ₄ C(3)Ap ₄ G(3)G
Gp ₂ G(5,1)	Ap ₂ C - NAD(6)Ap ₂ C - P	(1,4,29)Xp ₃ X(Gp ₃ G(5)m ^{2,2} ,	Cp ₄ C(3)Gp ₄ G(1,5)Xp ₄ X	p ₄ U(3)Gp ₄ C(3)Up ₄ C(3)Ap ₄
m ⁷ Gp ₂ m ⁷	AD(6)Ap ₂ BAD(6)m ⁷ G	1)m ⁷ Gp ₃ m ⁷ G(⁷ Gp ₃ G(5)m ² ,	(1)Dp ₄ D(15)eAp ₄ eA(7)	T(20)m ⁷ Gp ₄ G(5)m ^{2,7} Gp ₄ G
G(5)	p ₂ G(5)Up ₂ U(43)	5)Gp ₃ G(1)	⁷ Gp ₃ G(5)	m ⁷ Gp ₄ m ⁷ G(5)	(5)m ^{2,2,7} Gp ₄ G(5)

[2]

Np ₅ N	Np ₅ N'	Np ₆ N	Np ₆ N'	Np ₈ N
Ap ₅ A(4)	Ap ₅ T(20)	Ap ₆ A(4)	Ap ₆ T(20)	Ap ₈ A(4)

[3]

AppZppA	DppZppD	ApZppZpA	ApSpZpSpA
Z	Z	Z	Z
CH ₂ (8)CH ₂ CH ₂ (8)CHF(8)CF ₂ (8)	CH ₂ (15)CH ₂ CH ₂ (15)CHF(15)CF ₂ (15)	CH ₂ (8)CH ₂ CH ₂ (8)CHF(8)CF ₂ (8)	CHF(8)CF ₂ (8)
CHCl(8)CCl ₂ (8)	CHCl(15)CCl ₂ (15)	CHCl(8)CCl ₂ (8)	O(8)

A = eA =

U = m⁷G = 7 -G = m^{2,7}G = 2,7 -T = m^{2,2,7}G = 2,2,7 -

X = NAD =

TAD = C - NAD = C -

BAD = C - PAD = C -

D = 2,6 - N =

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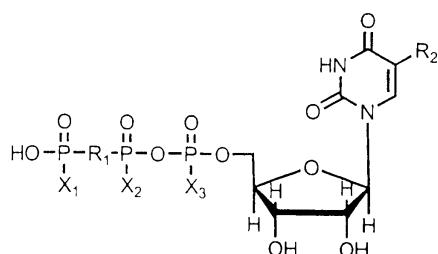
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UTP

1

.

1



(1 ,

X₁, X₂ X₃ O⁻ S⁻ , X₂ X₃ O⁻ ,R₁ O, , (, ,) , R₁

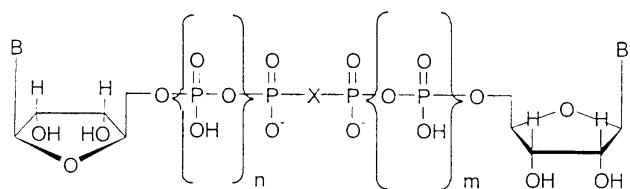
R₂ H Br , R₂ H

)

1 5' - (UTP) 5' - O - (3' -) (U
TP S)

2

2



(2 :

X , , ;

n = 0 1;

m = 0 1;

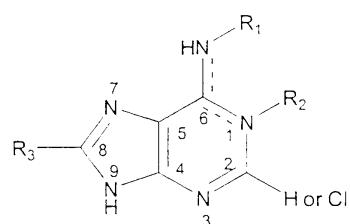
n+m = 0, 1 2;

B B' 9 - 1 -)

B B' 가 , N - 1 , D - , L - , X 가 m+n 3 4 .
. D - . 가

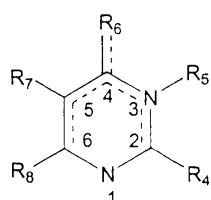
B B' 9 - 1 - 2a , m+n 2b
B B' 가 , N - 1 , D - , L - , D - , L - X 가 .
. D - . 3 4 .
. D - . 가

2a



1 - ; 1, N6 - (4 -
; 8 - , 6 - HNR ; 8 - HNR R
; (C₁₋₆) ; ; ([6 -]) - , - - ()
, ,) , , ,
, , - () , ,
- (,) C₁₋₄ , .
가 , B B' , 1 - , 2b .

2b



(2b :

R_4 , , , , , C_{1-6} , C_{1-6}

$$R_5 \rightarrow \dots \rightarrow C_{1-6} \rightarrow \dots \rightarrow C_{1-5} \rightarrow \dots \rightarrow$$

R₆ , , , , , C₁₋₆ , C₁₋₅ , N³
,

$R_7, \dots, (C_{2-6}, C_{2-3}, R_6 - R_7, N, O; R_8)$

2b , 2 - 6 - 가
R₄, R₆ R₇ 가 -

2a 2b

1 8 1 4

2 8

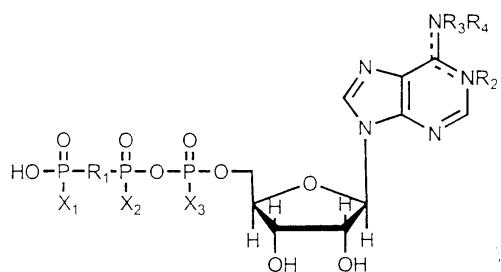
2 6

, C₁₋₄, C₁₋₄, C₇₋₁₂

ATP

3

3

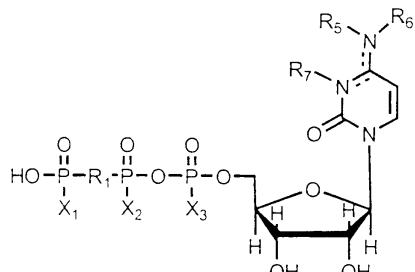


(3 :

R₁, X₁, X₂ X₃ 1 ,R₂ 가 R₃ R₄ H , N - 1 C - 6() ,R₂ 가 O R₃ R₄ H , N - 1 C - 6(1 -) ,N - 1 R₃, R₄ R₂ - CH=CH - , N - 6 C - 6(1,N6 -) 가 N - 6

CTP 4 :

4



(4 :

$$R_1, X_1, X_2, X_3 \quad \quad \quad 1 \quad \quad \quad ,$$

$$10^{-1} \text{ Moles/} \text{,} \quad 10^{-6} \quad 10^{-1} \text{ Moles/} \text{,} \quad , \quad 10^{-7}$$

6 , 1 0.25mg/Ml 50mg/Ml 100mg . UTP() . UTP , 2

1, 3 4 , Sigma Chemical Compan
 y(PO Box 14508, St. Louis, MO 63178) 가 . 2 P. Zamecnik
 (Proc. Natl. Acad. Sci. USA 89, 838 - 42(1981); K. Ng. L. E. Orgel, Nucleic Acids Res.15(8), 3572 -
 80(1977)

가

(mineral

oil) (white petroleum)

가
가
가
1 5

(nasal spray)

가

/

1, 2, 3 4

가

가 가

가

가

가

1

12 , (Sprague - Dawley) (Charles River Laboratories, Wilmington, MA)
 (1300mg/kg) , (106.5mM NaCl, 26.1mM NaHCO₃, 18.7mM
 KCl, 1.0mM MgCl₂, 0.5mM NaH₂PO₄, 1.1mM CaCl₂ 10mM HEPES pH 7.45) 1% (lidoca
 ine) 20 μL 10

4 (Karnovsky) (2.5% 2%
 , pH 4) 1 (Clonetics Corp, San D
 iego, CA) , 3μm 6
 (Alcian Blue) (pH 5) (periodic acid) - (AB - PAS)
 160 () 가
 (masked fashion) , , 가
 (0.16mm²) , , 가 ()
 , , , , ,
 D. Dartt , Exp. Eye Res., 63, 27(1996)

2

(vitrogen) 37 30 3 μM Fura - 2/AM
 NaCl , ,
 Fura - 2 , , [Ca²⁺]_i 25

, [Ca²⁺]_i , Zeiss Axiovert 1M 35
 (SPEX Industries, Inc., Edison, NJ) , ,
 , 340nm 380nm (> 450nm) (3 - 5μm)

가 , 1.5 × 10⁻⁴ M 10⁻³ M MnCl₂ NaCl
 /AM , 340nm/380nm (340/380nm) Fura - 2
 R_s - R_x] (, R_o R_s 가 Ca²⁺ Ca²⁺ : [Ca²⁺]_i = K_d [(R_x - R_o)/(-
 (J. Biol. Chem. 260, 3440 - 3450(1985)) Ca²⁺)] , G. Grynkiewicz [Ca²⁺]_i
 +]_i R_x K_d K_d / (F_o/F_s) , K_d Fura - 2
 25 K_d = 1.57 × 10⁻⁷ M , F_o F_s 380nm Ca²⁺ Ca²⁺
 R. Boucher 5,292,498

3

KCS

8
 (KSC) , , 8 , KCS (J. Gilbard
 , Ophthalmol 96, 677(1978)) 0.1 - 0.4 μ L
 . UTP 3.0mmol
 4 UTP 1 (10 μ L) 4
 , , ,
 . 20 ,
 (D. Dartt , Exp. Eye Res. 67, 27(1996)). 0.1 - 0.4 μ L

UTP 가 , KCS

J.P. Gilbard. Arch. Ophthalmol. 112, 1614(1994)

4

U_2P_4 (P^1, P^4 - (),) , U_2P_4 GLP 가
 . U_2P_4 가 Draize 가
 , (2 - 2.5kg)가 Elevage Scientifiq
 ue des Dombes(Chantillon sur Charlaronne, France) 가

5.0% NaCl 5.0% U_2P_4
 50 μ L (20 5) , 0, 1, 2 3 Drai
 ze ,
 5.0% U_2P_4 (0 - 4 가 1). () , U_2P_4

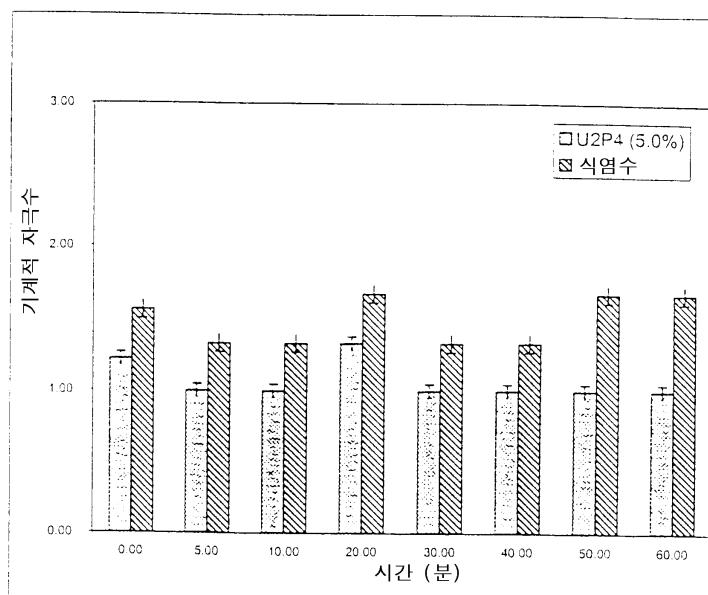
5

U_2P_4 (P^1, P^4 - (),) , U_2P_4 GLP 가

, (2 - 2.5kg)가 Elevage Scientif
 ique des Dombes(Chantillon sur Charlaronne, France) 가

NaCl

5.0% U_2P_4 가 50 μL (20 5)
5, 10, 20, 30, 40, 50 60 Cochet 가 .
가 .



도 1. 5.0% U_2P_4 를 5회 접적한후 기록되는 안검반사를 유도하는데 필요한 기계적 자극수는 도 1에 나타나 있다. 식염수(좌측 눈)에 비해, U_2P_4 는 각막 마취효과를 전혀 나타내지 않았다.

$$U_2 P_4 (P^1, P^4 - (\quad \quad \quad), \quad \quad \quad) ,$$

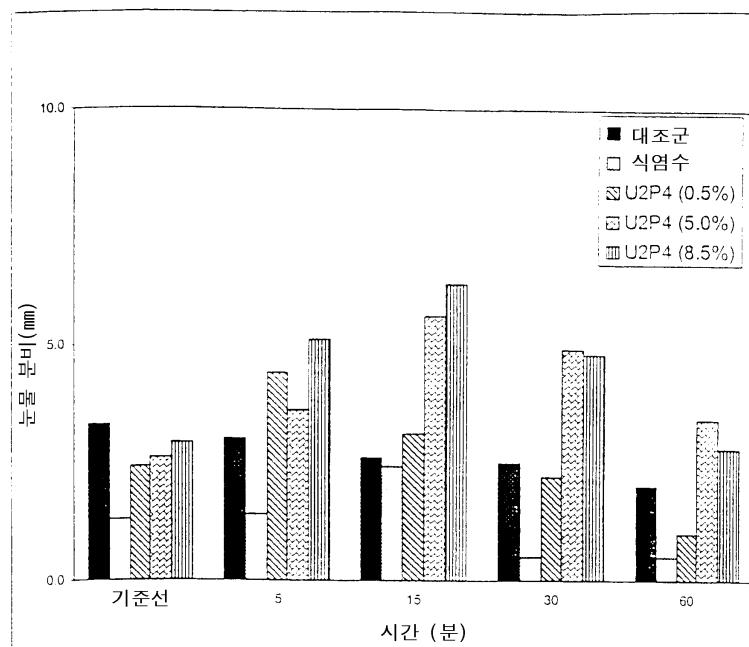
, (2 - 2)
es Dombes (Chantillon sur Charlaronne, France)

Elevage Scientifique d 가

NaCl

50 μ L). 1 , 7 , 14 8 14 5 0.5%, 5.0% 8.5% U_2P_4 (0, 5, 15, 30 60 Schirmer

U₂P₄ 60 가 .(2)



도 2. 토끼 눈에 세 농도의 U_2P_4 를 1회 투여한 후 60분 동안의 눈물분비회는 도 2에 나타나 있다.
식염수 대조군에 비해, 세 농도의 U_2P_4 모두 눈물분비를 증가시킨다.
상기 데이터는 8마리의 동물의 평균으로서 나타낸다.

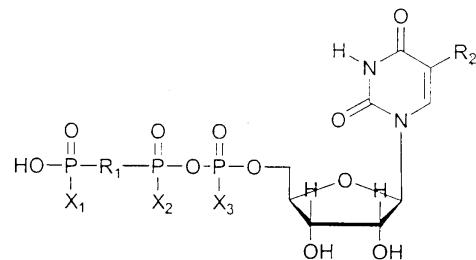
가

(57)

1.

가

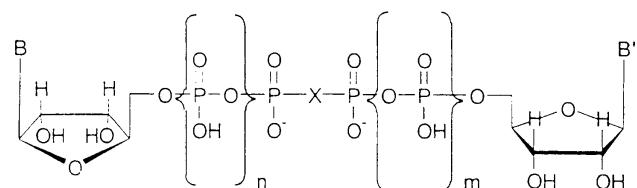
(1)



(1),

X₁, X₂, X₃ O⁻ S⁻ ,R₁ O, , , ,R₂ H Br)

(2)



(2),

X , , , , ;

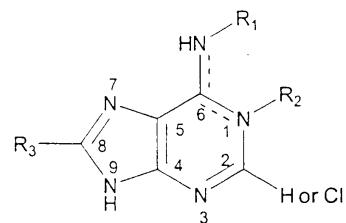
n = 0 1;

m = 0 1;

n + m = 0, 1 2 ;

B B' 9 - 1 - , 2a 2b
)

(2a)



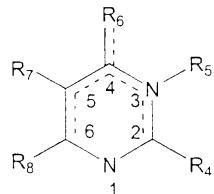
(2a , R₃ NHR' ;

8 - NHR' R₁ R' , , (moiety) (C₁₋₆) , C₁₋₆
 C₁₋₆ , - A()CONH() - , - A()NHCO() - (, A ,
 , ,) ;

$$R_2 \quad 0 \quad ;$$

R₁ R₂ 4' 5' 5)

(2b)



(2b ,

R_4 , , , , C_{6-10} , C_{1-6} , C_{1-6} (C_{1-6})
 $,$;

$$R_5, C_{1-6}, C_{1-6}, C_{6-10}, C_{1-5}, , , ,$$

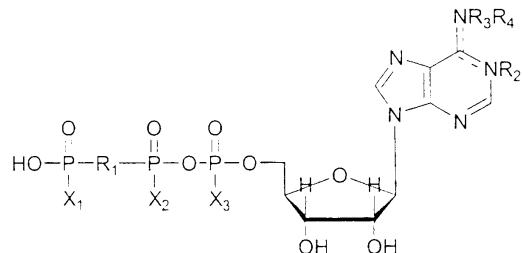
$$R_6, C_{6-10}, C_{6-10}, C_{1-6}, C_{1-5},$$

$$(C_{1-6}), (C_{1-6}),$$

$$N_3;$$

R₇ , , , , , C₁₋₆ C₆₋₁₀
 , (CF₃), C₂₋₆ C₂₋₃ , , , , , ,
), C₂₋₃ ; R₆ - R₇ R₆ N O 5 6 ,
 , R₇ ; ; R₈

(3)



(3 ,

$$R_1, X_1, X_2, X_3 \quad 1$$

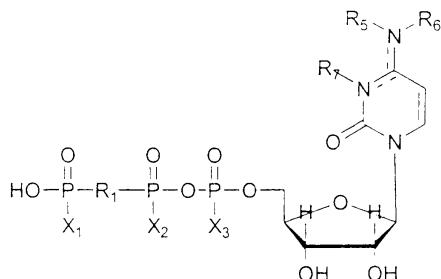
$$R_2 \text{ 가 } R_3 \quad R_4 \quad H \quad , N-1 \quad C-6(\quad) \quad ,$$

$$R_2 \geq 0 \quad R_3 \quad R_4 \quad H \quad , N-1 \quad C-6(\quad \quad \quad 1- \quad \quad)$$

$$R_3, R_4 \quad R_2 \quad -CH=CH- \quad , N-6 \quad C-6(I, N6- \quad) \quad \text{가} \quad N-6$$

$$N-1 \quad \quad \quad)$$

(4)



(4 ,

$$R_1, X_1, X_2, X_3 \quad 1 \quad ,$$

$$R_7 \quad R_5 \quad R_6 \quad H \quad , N - 3 \quad C - 4(\quad) \quad ,$$

$$(3, N^4 - R_5, R_6 R_7 - CH=CH - , N - 3 N - 4 4 - 5 -) N - 4 C - 4)$$

2.

1 ,

, , , , ,

3.

1 ,

2	3	C_{1-6}	C_{6-10}			1	4
가	,		(moiety)			,	,
	,	, C_{1-4}	, C_{6-12}	, C_{6-12}		,	,
	,	,	,	,		,	,
		C_{1-4}					

4.

1 ,

B B' N - 1 , X가 3 4

5.

1 ,

(moiety) D -

6.

1 ,

(moiety) L -

7.

1 ,

(moiety) D - L -

8.

1 ,

 $P^1, P^4 - (5' - P^2, P^3) -$

9.

1

,

$P^1, P^4 - (5' - P^2, P^3) -$

10.

1

,

$P^1, P^4 - (5' - P^2, P^3) -$

11.

1

,

$P^1, P^4 - (4 - 5') -$

12.

1

,

$P^1, P^4 - (3, N^4 - 5') -$

13.

1

,

1 10

14.

가

2, 2a 2b , 4 5' - , 1 3 5' - ,

가

15.

14

,

,

,

,

16.

15

,

-

,

17.

14

,

/

18.

17

,

19.

17

,

가

20.

17

,

21.

17

,

, , , , , , , ,

22.

14

,

 10^{-7} 10^{-1} moles/

23.

, 5' - , 5' - , 5' -
 , 2, 2a 2b ;
 , , , , ,
 , , , , ,

24.

14

(probing),

25.

14

DNA ,

26.

, 5' - , 5' - , 5' -
 , 1, 2 3 ;
 , , , , ,
 , , , , ,

27.

5' - , 5' - , 5' - , 2, 2a 2b
 , ;

0.25mg/Mℓ 50mg/Mℓ ,

28.

5' - , 5' - , 5' - , 2, 2a 2b
 , ;

1 100mg

29.

4 5' - , 1 3 5' - , 2, 2a 2b , 가

30.

5' - , 5' - , 5' - , 2, 2a 2b , ; 가 ;

0.25mg/Mℓ 50mg/Mℓ ,

31.

5' - , 5' - , 5' - , 2, 2a 2b , ; 가 ;

1 100mg

32.

1 ,

2, 2a 2b

33.

1 ,

P¹,P⁴ - (5' -)

34.

1 ,

P¹,P⁴ - (5' -) ,