

(74)

•

•

(54)

], 가 5' - [CTP], 5' - [ATP] 5' - [UTP]

08/797,402 (1997 2 6) .

가
가,
3 8
(KCS),
(腺)

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

4 " " . 가 .

가 1 . (, CLAO Journal 22(2), 141 - 45(1996)).

가 () .

가 , 가 , (, Cornea 9(1), S48 - 550(1990)). 3 - - 1 - (IB MX) 4,753,945 (4,868,154).

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가 . 가 . (, Ophthal., 95, 1447(1988); , Ophthal. Plas. Reconstr. Surg., 9, 43(1993); , Ophtha I. Plast. Reconstr. Surg., 8, 13(1992)).

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, 5' - (UTP) 5' - (ATP) P2Y₂ P2Y₂ . UTP ATP 5,292,498 가 UTP UTP P2Y₂ P2Y₄ . P2 가 ATP (, Febs Lett. 264, 130 - 34(1990); idem, J. Physiol. 447, 103 - 18(1992); , J. Physiol. 449, 31 3 - 31(1992); , Eur J. Physiol. 429, 578(1995); , Inv. Ophthal. Vis. Sc i. 38(4)(1997)). P2Y₂ / P2Y₄ 가 가 UTP

가 , (KCS), , (腺) , (UTP) P2Y₂ P2Y₄ 가 () .

,
DN ,

[UTP] , P¹P⁴ - (- 5') [U₂P₄]
[CTP] 5' - [ATP] , U
P2Y₂ / P2Y₄
TP, U₂P₄, CTP ATP

2

1 - 4

3

1, 2, 3 4

가

(KCS),

(腺)

1 2

DN ,

5' - (UTP)가

UTP가
가 (,) ,

" " ;
; NX₄⁺ (X C₁₋₄)
가 가

(- 5') 1 , [UTP] , 2 , P¹ P⁴ -
 (U₂ P₄) 3 , 5' - [CTP]
 4 , 5' - [ATP]
 P₂Y₂ / P₂Y₄ , 1, 2,
 3 4 .

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 = m⁷ G = 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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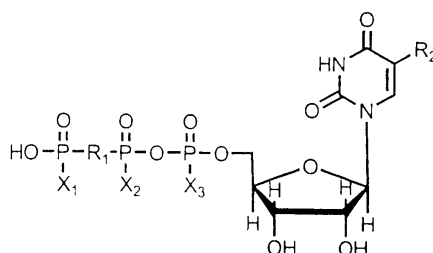
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UTP 1 .

1



(1 ,

$X_1, X_2, X_3, O^-, S^-, X_2, X_3, O^-$,

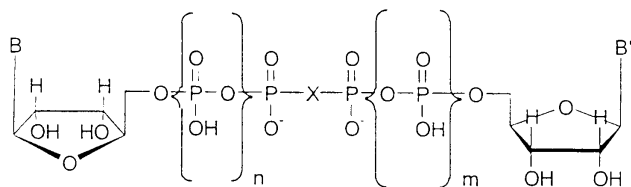
$R_1, O,$, (,) , R_1

R_2 H Br, R_2 H)

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

2 .

2



(2 :

X , , ;

$n = 0$ 1;

$m = 0$ 1;

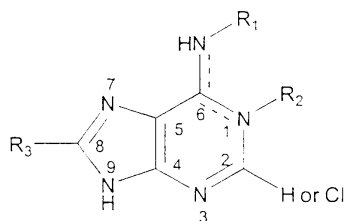
$n+m = 0, 1$ 2;

B B' 9- 1-)

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

B B' 9- 1- 2a 2b . B B'가 , N-1 , D- , L- D- L- X가 3 4 . D- 가 .

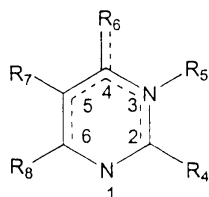
2a



C_{1-6} - C_{1-4} ; N_6 - (4 - 5 -) ; 6 -
 , 6 - HNR' 8 - HNR' R'
 (C_{1-6}) ; ([6 -]) -, - - (
 ,) ,
 , - () ,
 ,
 - (,) C_{1-4} .

가, B, B', 1 - , 2b .

2b



(2b :

$$R_4, \quad , \quad , \quad , \quad , \quad C_{1-6}, \quad C_{1-6}, \quad ,$$
$$R_5, C_{1-6}, C_{1-5}, \dots;$$
$$R_6 \quad , \quad , \quad , \quad , \quad C_{1-6} \quad , \quad C_{1-5} \quad , \quad N^3$$
[illegible]
$$R_8 = \left(\begin{array}{cccccccc} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ & & 1 & 1 & 1 & 1 & 1 & 1 \\ & & & 1 & 1 & 1 & 1 & 1 \\ & & & & 1 & 1 & 1 & 1 \\ & & & & & 1 & 1 & 1 \\ & & & & & & 1 & 1 \\ & & & & & & & 1 \end{array} \right)$$

2b, 2 - 6 - 가 ; R_4, R_6 R_7 가 - .

2a 2b

1 8 , 1 4

2 8

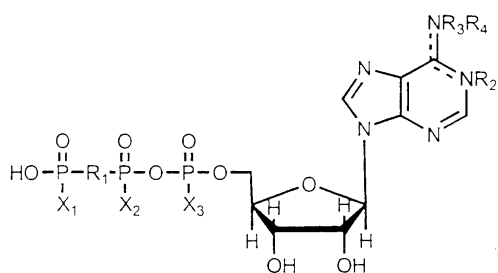
2 6

, C₁₋₄, C₁₋₄, C₇₋₁₂C₁₋₄

ATP

3

3



(3 :

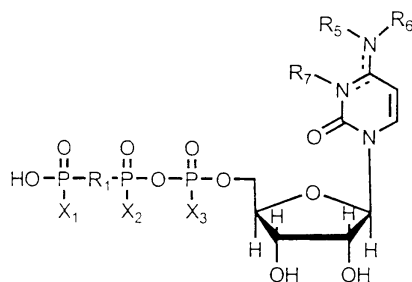
R₁, X₁, X₂ X₃ 1 ,R₂가 R₃ R₄ H , N - 1 C - 6() ,R₂가 O R₃ R₄ H , N - 1 C - 6(1 -) ,

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 1 ,

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

R_5, R_6, R_7 - CH=CH - , 4 - 5 - N - 4 C
- 4(3, N⁴ -) N - 3 N - 4)

1, 2, 3 4 D - ,
, L - , D - L - . D - 가

;
NX₄⁺ (, X C₁₋₄) 가
가

;
(pump - catheter)
Ocuser() System (Alza Corp., Pa
lo Alto, CA) 가
가
가

10⁻¹ Moles/ , 10⁻⁶ 10⁻¹ Moles/ , 10⁻⁷

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

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), , , , , .

(nasal spray) / 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 가 가 ()
 D. Dartt , Exp. Eye Res., 63, 27(1996)

2

(vitrogen) 37 30 3 μ M Fura - 2/AM
 NaCl , [Ca²⁺]_i 25
 Fura - 2 ,
 , [Ca²⁺]_i , Zeiss Axiovert IM 35
 (SPEX Industries, Inc., Edison, NJ) ,
 , 340nm 380nm(> 450nm)
 (3 - 5μm)

가 , 1.5 × 10⁻⁴ M 10⁻³ M MnCl₂ NaCl
 (340/380nm) Fura - 2
 /AM , 340nm/380nm , [Ca²⁺]_i = K[(R_x - R_o)/(-
 R_s - R_x)](, R_o R_s가 Ca²⁺) , G. Grynkiewicz
 (J. Biol. Chem. 260, 3440 - 3450(1985)) [Ca²⁺
⁺]_i . R_x . K 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

(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 0.1 - 0.4 μ L . 20 (D. Dartt , Exp. Eye Res. 67, 27(1996)).

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

4

U_2P_4 (P^1 , P^4 - (),) , U_2P_4 GLP 가 . U₂P₄가 Draize 가 .

, (2 - 2.5kg)가 Elevage Scientifi que des Dombes(Chantillon sur Charlaronne, France) 가

NaCl 5.0% U_2P_4 50 μ L (20 5) , 0, 1, 2 3 Draize ze , ,

5.0% U_2P_4 (0 - 4 가 1). , , U_2P_4 (2).

5

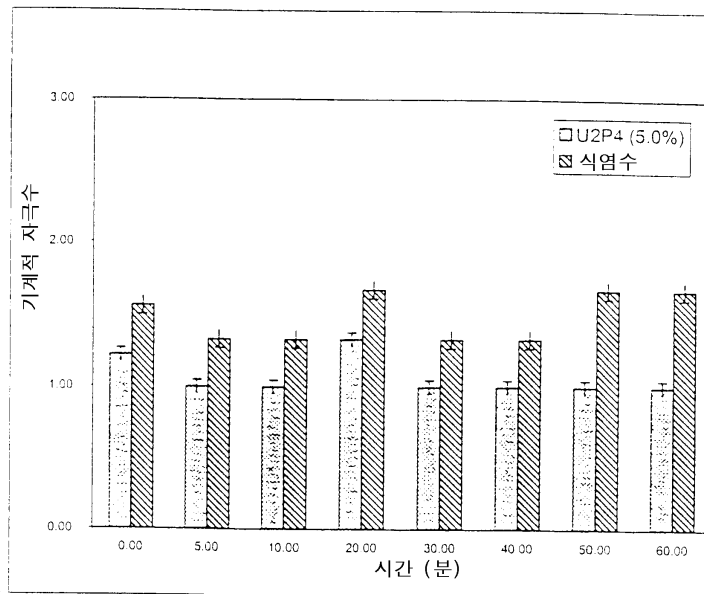
U_2P_4 (P^1 , P^4 - (),) , U_2P_4 GLP 가 .

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

NaCl

5.0% U_2P_4 가 50 μ L (20 5)
5, 10, 20, 30, 40, 50 60 Cochet 가

가 U_2P_4 5.0%
(1).



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

6

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

(2 - 2.5kg)가 Elevage Scientifique d
es Dombes(Chantillon sur Charlaronne, France) 가

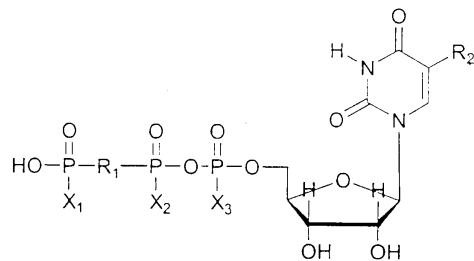
NaCl

50 μ L). 1, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168, 175, 182, 189, 196, 203, 210, 217, 224, 231, 238, 245, 252, 259, 266, 273, 280, 287, 294, 301, 308, 315, 322, 329, 336, 343, 350, 357, 364, 371, 378, 385, 392, 399, 406, 413, 420, 427, 434, 441, 448, 455, 462, 469, 476, 483, 490, 497, 504, 511, 518, 525, 532, 539, 546, 553, 560, 567, 574, 581, 588, 595, 602, 609, 616, 623, 630, 637, 644, 651, 658, 665, 672, 679, 686, 693, 700, 707, 714, 721, 728, 735, 742, 749, 756, 763, 770, 777, 784, 791, 798, 805, 812, 819, 826, 833, 840, 847, 854, 861, 868, 875, 882, 889, 896, 903, 910, 917, 924, 931, 938, 945, 952, 959, 966, 973, 980, 987, 994, 1001, 1008, 1015, 1022, 1029, 1036, 1043, 1050, 1057, 1064, 1071, 1078, 1085, 1092, 1099, 1106, 1113, 1120, 1127, 1134, 1141, 1148, 1155, 1162, 1169, 1176, 1183, 1190, 1197, 1204, 1211, 1218, 1225, 1232, 1239, 1246, 1253, 1260, 1267, 1274, 1281, 1288, 1295, 1302, 1309, 1316, 1323, 1330, 1337, 1344, 1351, 1358, 1365, 1372, 1379, 1386, 1393, 1400, 1407, 1414, 1421, 1428, 1435, 1442, 1449, 1456, 1463, 1470, 1477, 1484, 1491, 1498, 1505, 1512, 1519, 1526, 1533, 1540, 1547, 1554, 1561, 1568, 1575, 1582, 1589, 1596, 1603, 1610, 1617, 1624, 1631, 1638, 1645, 1652, 1659, 1666, 1673, 1680, 1687, 1694, 1701, 1708, 1715, 1722, 1729, 1736, 1743, 1750, 1757, 1764, 1771, 1778, 1785, 1792, 1799, 1806, 1813, 1820, 1827, 1834, 1841, 1848, 1855, 1862, 1869, 1876, 1883, 1890, 1897, 1904, 1911, 1918, 1925, 1932, 1939, 1946, 1953, 1960, 1967, 1974, 1981, 1988, 1995, 2002, 2009, 2016, 2023, 2030, 2037, 2044, 2051, 2058, 2065, 2072, 2079, 2086, 2093, 2100, 2107, 2114, 2121, 2128, 2135, 2142, 2149, 2156, 2163, 2170, 2177, 2184, 2191, 2198, 2205, 2212, 2219, 2226, 2233, 2240, 2247, 2254, 2261, 2268, 2275, 2282, 2289, 2296, 2303, 2310, 2317, 2324, 2331, 2338, 2345, 2352, 2359, 2366, 2373, 2380, 2387, 2394, 2401, 2408, 2415, 2422, 2429, 2436, 2443, 2450, 2457, 2464, 2471, 2478, 2485, 2492, 2499, 2506, 2513, 2520, 2527, 2534, 2541, 2548, 2555, 2562, 2569, 2576, 2583, 2590, 2597, 2604, 2611, 2618, 2625, 2632, 2639, 2646, 2653, 2660, 2667, 2674, 2681, 2688, 2695, 2702, 2709, 2716, 2723, 2730, 2737, 2744, 2751, 2758, 2765, 2772, 2779, 2786, 2793, 2800, 2807, 2814, 2821, 2828, 2835, 2842, 2849, 2856, 2863, 2870, 2877, 2884, 2891, 2898, 2905, 2912, 2919, 2926, 2933, 2940, 2947, 2954, 2961, 2968, 2975, 2982, 2989, 2996, 3003, 3010, 3017, 3024, 3031, 3038, 3045, 3052, 3059, 3066, 3073, 3080, 3087, 3094, 3101, 3108, 3115, 3122, 3129, 3136, 3143, 3150, 3157, 3164, 3171, 3178, 3185, 3192, 3199, 3206, 3213, 3220, 3227, 3234, 3241, 3248, 3255, 3262, 3269, 3276, 3283, 3290, 3297, 3304, 3311, 3318, 3325, 3332, 3339, 3346, 3353, 3360, 3367, 3374, 3381, 3388, 3395, 3402, 3409, 3416, 3423, 3430, 3437, 3444, 3451, 3458, 3465, 3472, 3479, 3486, 3493, 3500, 3507, 3514, 3521, 3528, 3535, 3542, 3549, 3556, 3563, 3570, 3577, 3584, 3591, 3598, 3605, 3612, 3619, 3626, 3633, 3640, 3647, 3654, 3661, 3668, 3675, 3682, 3689, 3696, 3703, 3710, 3717, 3724, 3731, 3738, 3745, 3752, 3759, 3766, 3773, 3780, 3787, 3794, 3801, 3808, 3815, 3822, 3829, 3836, 3843, 3850, 3857, 3864, 3871, 3878, 3885, 3892, 3899, 3906, 3913, 3920, 3927, 3934, 3941, 3948, 3955, 3962, 3969, 3976, 3983, 3990, 3997, 4004, 4011, 4018, 4025, 4032, 4039, 4046, 4053, 4060, 4067, 4074, 4081, 4088, 4095, 4102, 4109, 4116, 4123, 4130, 4137, 4144, 4151, 4158, 4165, 4172, 4179, 4186, 4193, 4200, 4207, 4214, 4221, 4228, 4235, 4242, 4249, 4256, 4263, 4270, 4277, 4284, 4291, 4298, 4305, 4312, 4319, 4326, 4333, 4340, 4347, 4354, 4361, 4368, 4375, 4382, 4389, 4396, 4403, 4410, 4417, 4424, 4431, 4438, 4445, 4452, 4459, 4466, 4473, 4480, 4487, 4494, 4501, 4508, 4515, 4522, 4529, 4536, 4543, 4550, 4557, 4564, 4571, 4578, 4585, 4592, 4599, 4606, 4613, 4620, 4627, 4634, 4641, 4648, 4655, 4662, 4669, 4676, 4683, 4690, 4697, 4704, 4711, 4718, 4725, 4732, 4739, 4746, 4753, 4760, 4767, 4774, 4781, 4788, 4795, 4802, 4809, 4816, 4823, 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5992, 5999, 6006, 6013, 6020, 6027, 6034, 6041, 6048, 6055, 6062, 6069, 6076, 6083, 6090, 6097, 6104, 6111, 6118, 6125, 6132, 6139, 6146, 6153, 6160, 6167, 6174, 6181, 6188, 6195, 6202, 6209, 6216, 6223, 6230, 6237, 6244, 6251, 6258, 6265, 6272, 6279, 6286, 6293, 6300, 6307, 6314, 6321, 6328, 6335, 6342, 6349, 6356, 6363, 6370, 6377, 6384, 6391, 6398, 6405, 6412, 6419, 6426, 6433, 6440, 6447, 6454, 6461, 6468, 6475, 6482, 6489, 6496, 6503, 6510, 6517, 6524, 6531, 6538, 6545, 6552, 6559, 6566, 6573, 6580, 6587, 6594, 6601, 6608, 6615, 6622, 6629, 6636, 6643, 6650, 6657, 6664, 6671, 6678, 6685, 6692, 6699, 6706, 6713, 6720, 6727, 6734, 6741, 6748, 6755, 6762, 6769, 6776, 6783, 6790, 6797, 6804, 6811, 6818, 6825, 6832, 6839, 6846, 6853, 6860, 6867, 6874, 6881, 6888, 6895, 6902, 6909, 6916, 6923, 6930, 6937, 6944, 6951, 6958, 6965, 6972, 6979, 6986, 6993, 7000, 7007, 7014, 7021, 7028, 7035, 7042, 7049, 7056, 7063, 7070, 7077, 7084, 7091, 7098, 7105, 7112, 7119, 7126, 7133, 7140, 7147, 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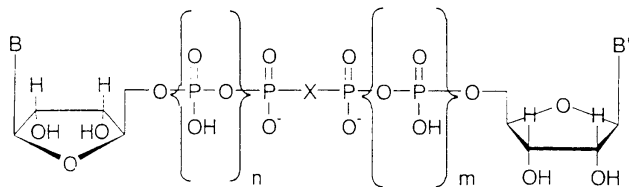
(1)



(1 ,

 X_1, X_2, X_3 O^- S^- , R_1 O, , R_2 H Br)

(2)



(2 ,

 X , , , ; $n = 0$ 1; $m = 0$ 1; $n + m = 0, 1$ 2 ; B B')

9 -

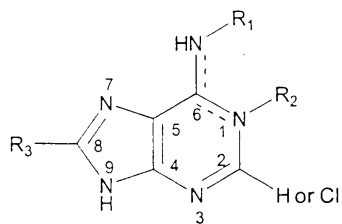
1 -

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2a

2b

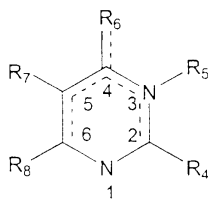
(2a)

(2a , R_3 NHR' ;

8 - NHR' R_1 R' , (moiety) (C_{1-6}) , C_{1-6} ,
 C_{1-6} , - A()CONH() - , - A()NHCO() - (, A ,
 , ,) ;

 R_2 O ; R_1 R_2 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 ;

R_7 , , , , C_{1-6} C_{6-10} , , , ,
 , (CF_3) , C_{2-6} , C_{2-3} , (R_6 N , O 5 6 ,
) , C_{2-3} ; $R_6 - R_7$ R_6 ; R_8 ,
 , R_7 ;

2.

1 , , , , , .

3.

1 ,

2 가 3 C_{1-6} C_{6-10} , 1 4

(moiety) , , ,

, C_{1-4} , C_{6-12} , C_{6-12} , , , ,

, C_{1-4} , , , ,

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4.

1 ,

B B' N - 1 , X가 3 4

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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
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14.

가
 2, 2a 2b , 4 5' - , 1 3 5' - 5' - ,
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15.

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22.

14

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10^{-7}

10^{-1} moles/

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23.

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

24.

14 ,
 (probing), .

25.

14 ,
 DNA , .

26.

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

27.

5' - , 5' - , 5' - , 2, 2a 2b , 5' - 가 ;
 ,
 0.25mg/Mℓ 50mg/Mℓ , .

28.

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

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' -) ,