2 8 < 6 | } &; 9 w 9 Y J ÖËÄ † þ ¥ ! 9 a † î # F h ý Ÿ

邱晓敏, 刘 嘉, 冯继禄, 牛春娟, 李 科(, (S 3; ex, T eXT e eX. 0 T 4 T 1 , 140 200433)

K 1 " ¥ Z E (PMEA), 4 0l .; , ,9 e 1F. , lX, D .j 3) ,e Z 8 < 6 | } &; w ,1P4K 0 9 TM)r DM9 0 0 . 0 0 . 4 0l 4 IR, ^{1}H NMR D 4 T Z : (7 1a 1e0 0 . 4 T)E.j . 3= HBsAg HBeAg0 3= HBV DNA46T Z T 1 el ² T 10(DM9 0 0 . ;1 9 0 0 . 3= HBsAg HBeAg46T 3B0 e PMEA, 0 0 . 1e3= HBV DNA46T e PMEAT , ,: , 4bT T 4 ², PMEAe Z 8 < 6 | } &; w F HBV DNA 46T 9Z9 , 3= HBsAg HBeAg46T .G(1 o M ;0 T 0 9 ;6 , (. ; 3=e (9 , 46T Ï ms Ë | R914 ÓDS½' A Óc I | 1006- 0111(2010) 04- 0299- 05

Studies on synthesis and antiviral activities of a novel acyclic nucleoside phospho nates analogues on HBV

QIU Xiaomin, LIU Jia, FENG Jilu, NIU Chun juan, LI Ke (Department of Medical Chemistry, School of Pharmacy, Second Military Medical University, Shanghai 200433, China)

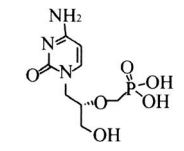
[Abstract] Objective To study of design and synthesis of the novel acyclic nucleoside phosphonates analogues and study their activities of inhibiting HBV. **Methods** Based on the chemical structure of PMEA, and according to the theory of bioisostere, a 8 aza 6 thiophenyl group was introduced and a series of title compounds were synthesized. All of them were confirmed by IR, ^{1}H NMR and MS. Preliminary pharmacological test of compounds 1a 1e was made on HBV. **Results** Ten compounds were synthesized. The test results show the inhibitory rate of 1a 1e compounds on HBsAg and HBeAg is higher than PMEA. The inhibitory rate of compound 1e on HBV DNA is correspond with PMEA. **Conclusion** The PMEA derivatives with a 8 aza 6 thiophenyl group have high activity on inhibiting HBsAg, HBeAg and HBV DNA.

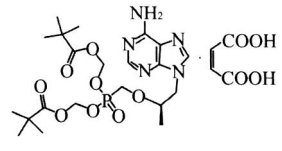
[Keywords] acyclic nucleoside phosphonates; chemical synthesis; PMEA; Anti hepatitis B virus activity

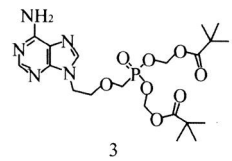
1 - ý

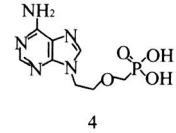
¤ Ÿ Y ~ É ^ B Õ ® Y ~ É h ý (HBV) e ZT,) T 4 : T : 1 T 4R9 [1], DMZ51 e , 3= 9 , eX. : (n1 0 E63 eX. 0 E63 eX. 6 : 0 T 4 0l(3 (. e 0 0 E60 3h0 0 E6[2] e[: e 3 , e 0 0 E63 1 . 3) (, l . 1 T eX. e e)M,u:)T e T (e ,, 1 1 lMe eX1Y4 , T 9 ,3) (, Tw 1 ,f T : , DXeXT 0 (, T [3]

lL 1980D Z) (b T] 3h0 0 E63. e 3=9 , l e e 3 , 3h0 0 E6r 0 . (acyclic nucleoside phospho nates, ANP) e 9 . 3=9 , 0 E63 1 . , : eLe[l[Tu0 e e 3(eX9I D lr 141 e e :)T 9 . , 9 , (Z , 9 eX. . T((n (. (cidofovir, 1) .KD (. ( ) 1 @2(Tenofovir disoproxil fumarate, 2) 6 , (. @2[3] (adefovir dipivoxil, 3)


1
cidofovir


2
tenofovir dioproxil fumarate


3
adefovir dipivoxil


4
adefovir

Holy, [4]e 1982D 9: ,)E PMEA (adefovir, 4) , 0 9 4A(9 Zy, 3=e T (e 9 , 46T , , 1 , PMEA 3= HBsAg HBeAg46T ZTT 4) , 9 Z)T 9 4 9 , HBsAg HBeAgl0 e) 4 , ,)C . , (eX, 4G)4 (e 1Ye e[, , 1U T , : Z T 9 , 1F. 3 e (0 , (h T

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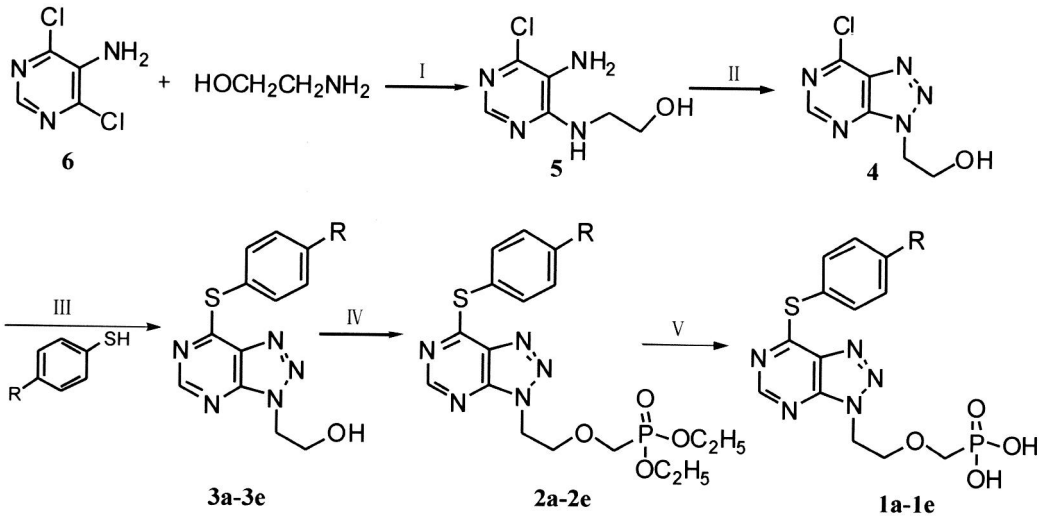
T € e º (1983), D , 1 1 T 4 1F
Y ß T € . Tel (021) 81871237, E mail proflkk@ sina com.

Starrett, [5] 1992D 9:,)E 6 , (. @2 (3), 4 0l 3 e: (7 3) (, , 9 1F , HBV DXeX: (eX. e 10mg/d, 4G)4 e 2002 D 9:, 9I) 0 FDA D lr e e:)T) T e T (e 6 , (. @21 6 , (. , Z5eX, Z5eX9 (T 1 9I@2) 1 4 1 (,f e 3 , 6 , (. 4 Z) 4) 0 Z 1HT 0 ,3 e 9 T eL)c 1 0 4Ne 3=9 , l e . T: T e[, (T , , , 6 , (. e, 1F. , 9N T 4 e PMEA4 0l. 4. ,I , 3 e 1F. , lX, D .j e 3 , (7 PMEA 0 T 4 0l 0c4 , 4 4. 8. .Te lX (CH) .K0 9 , e lX (N)4A4 N6 Ê¼ (NH).K0 9 7 4. (SH)e, 1F. , e Z 8 < 6 | } &; , 1P4K9 0 9)E 10(. 4 . Tx9:, , 2 (8 < 6 | } & ; p 9H w 9)e es 4. 4%4. r 1 /(Se @20 0. 0 T 4 0l 4 IR, ^{1}H NMR D 4 T Z: DM9 0 0 . , 0 9) T Z. 11 1



m 1 " S Ä † þ ¥ † î ^ L

a: R= CH_3; b: R= Br c: R= F; d: R= Cl; e: R= $CH(CH_3)_2$

I Na_2CO_3/CH_3CN; II $NaNO_2/CH_3COOH$; III NaH/DMF; IV NaH/DMF / $PTsCH_2POO(OC_2H_5)_2$/HoAc; V $Si(CH_3)_3Br/CH_2Cl_2$

2 L † s

¶ Ä¨ RY 2T Z , e 9 , ;0 ,Y0D: Bruker AC 300PT e Za9 , , TMS. DS9 ; CDCl$_3$ 4A DMSO . Z 4G, TMS. DS9 : D 9 e Q TOF Micro YA019 : D e 9 , ;0 . 0dD 9 e Bruker Bector22T 0 . 0d D e , KBrT D : 9 T, :@0w4 H (10~ 40 μM) 144 T 9)9 9 T, :@ HSGF 254T 0w4 6 144 T , Z , 0 ek0 (9 1F9 1 e 1 4G3B. (T, ,[4g1 4G

2 1 2 (5氨基 6氯嘧啶 4氨基)乙醇 (5)的制备 5¼ 4, 6 = o } J 6 (20 g, 0 122mol) .T 1 Dg (51. 7g, 0. 488 mol) e ,b 6 (89. 5 g, 0. 146mol)0 e r 150 m,14=Z 0)z 24 h, D 1 , 0Rj ,4=1 T. 1 ,0) ,) 9 e lL3 1 TPZ , , 1 4M) 9 ,9 . : 4 4 ,, 20. 13 g6 Z: l: 0Rj 5, 1) : 95. 13% ^{1}H NMR (300 MHz, DMSO): δ7. 71 (s, 1H, 2' = CH), 6. 90 (s, 1H, NH), 5. 50 (s, 2H, NH_2), 4. 78 (s, 1H, OH), 3. 53 (t, 2H, *J* = 4. 5Hz, NCH_2), 3. 34~ 3. 46 (m, 2H, CH_2OH)

2 2 2 (7氯 3H [1, 2, 3]三氮唑 [4, 5 d]嘌呤 3基)乙醇 (4)的制备 5(10 g, 0. 053mol), 9 , 1 (2 65 mol, 147 ml), 1 (147 ml), CH_2Cl_2 (295 ml), 9 e 3 Z: 0℃, 3a)f 4 6 TU , 4=e 3 , T T 1 DgZ ew (4 0 g, 0. 058 mol), , 9j, 0℃ 30 min, 1. 4 6 2 h, 4: (9 , e 1 e @2 200 ml×6, E Z 1 T , 0 9 e 4TT , 9. 0 1%T 1 TPe[, ,. 1)d 1) (:J , 0) , D 1 , e ew, 4=Z 11)4 4%9H, D 1 , : 9 T, (e 1 e @2/1=e) = 2∶ 1), 0 Z 0R.j 4, 7. 1 g 1) : 67. 4% ^{1}H NMR (300 MHz, CDCl$_3$): δ8. 93 (s, 1H, 2' = CH), 4. 90 (t, 2H, *J* = 5. 1Hz, NCH_2), 3. 34~ 3. 46 (t, 2H, *J* = 5. 1Hz, CH_2OH)

2 3 2 (7 4取代苯硫酚基) 3H [1, 2, 3]三氮唑 [4, 5 d]嘧啶 3基)乙醇 (3a~ 3e)的制备

2 3 1 (4 1 g, 0. 033 mol)Z 4 e DMF (20 ml): , 4=Z NaH (1. 3 g, 0. 033 mol), 4 6 1 h, 4=0 0 . 4 (5. 0 g, 0. 025 mol), DMFZ ew, , 9j, 4 6 24 h, Z Z 100 ml 1 : , 1F9 ,)4 T l: 0R.j , 4 6 , 0) , 1 TP, e) TP, , , . 0 Z 0R.j 1 Z m6m: 4, 4 , 2 4 g6 Z 0R.j 2 (7 (4 J &

) 3H [1, 2, 3]Z , mt [4, 5 d]m m%3)e ,b (3a), 1) : 65. 4% mp: 229. 3 ~ 230. 4 ℃. ^{1}H NMR (500 MHz, DMSO d$_6$): δ12. 7 (s, 1H, CH$_2$OH) 8. 20 (s, 1H, 2' = CH), 7. 06 ~ 7. 21(m, 4H, PhH), 4. 68(t, 2H, *J* = 6. 5Hz, NCH$_2$), 3. 52 (t, 2H, *J* = 6. 5Hz, CH$_2$OH), 2. 36(s, 3H, CH$_3$)

2. 3. 2 2 (7 (4 – i6 9H)d (4.) 3H [1, 2, 3[Z , mt [4, 5 d]m m%3)e ,b (3b) 3a: 9P((/ , , , 0 Z 0R.j 3b, 1) : 64. 0% mp: 249. 3 ~ 249. 9 ℃ ^{1}H NMR (300 MHz, DMSO d$_6$): δ12. 7 (brs, 1H, CH$_2$OH), 8. 22 (s, 1H, 2' = CH), 7. 43 ~ 7. 46(d, 2H, *J* = 9Hz, PhH), 7. 24 ~ 7. 27(d, *J* = 9Hz 2H, PhH), 4. 72 (t, 2H, *J* = 6. 6Hz, NCH$_2$), 3. 61 (t, 2H, *J* = 6. 3Hz, CH$_2$OH)

2. 3. 3 2 (7 (4 —& ; p) 3H [1, 2, 3]Z , mt [4, 5 d]m m%3)e ,b (3c) 3a: 9P((/ , , 6 Z 0R.j 3c, 1) : 53. 9% mp: 200. 6 ~ 201. 4 ℃ ^{1}H NMR (300 MHz, DMSO d$_6$): δ12. 7(s, 1H, CH$_2$OH) 8. 22 (s, 1H, 2' = CH), 7. 34 ~ 7. 39 (m, 2H, PhH), 7. 08 ~ 7. 14 (m, 2H, PhH), 4. 69 (t, 2H, *J* = 6. 3Hz, NCH$_2$), 3. 54 (t, 2H, *J* = 6. 3Hz, CH$_2$OH)

2. 3. 4 2 (7 (4 o & ; p) 3H [1, 2, 3]Z , mt [4, 5 d]m m%3)e ,b (3d) 3a: 9P((/ , , 6 Z 0R.j 3d, 1) : 55. 3% mp: 207 ~ 209 ℃ ^{1}H NMR (300 MHz, DMSO d$_6$): δ12. 7 (brs, 1H, CH$_2$OH), 8. 21 (s, 1H, 2' = CH), 7. 32 (s, 4H, PhH), 4. 71(t, 2H, *J* = 6. 3 Hz, NCH$_2$), 3. 59 (t, 2H, *J* = 6. 3 Hz, CH$_2$OH)

2. 3. 5 2 (7 (4 s d & ; p) 3H [1, 2, 3]Z , mt [4, 5 d]m m%3)e ,b (3e) 3a: 9P((/ , , 6 Z 0R.j 3e, 1) : 75. 8% mp: 207. 3 ~ 209 1 ℃ ^{1}H NMR (300 MHz, DMSO d$_6$): δ12. 7 (s, 1H, CH$_2$OH), 8. 21 (s, 1H, 2' = CH), 7. 09 ~ 7. 22(m, 4H, *J* = 8. 1Hz, PhH), 4. 69 (t, 2H, *J* = 6. 3 Hz, NCH$_2$), 3. 53 (t, 2H, *J* = 6. 3 Hz, CH$_2$OH), 2. 77 ~ 2. 86[m, 1H, CH(CH$_3$)$_2$], 1. 16 [d, *J* = 6. 9Hz, 6H, CH(CH$_3$)$_2$]

2. 4 二乙基(2 (7 (4取代苯硫酚基) 3H [1, 2, 3] 三氮唑[4, 5 d]嘧啶 3基)乙氧基)甲基膦酸酯(2a ~ 2e)的合成 3a (1 g, 0. 003 5 mol), DMF 4 m], NaH (0. 42 g, 0. 010 4 mol), 4 6 1 h, 4=((S e 4.)c 1 @2)4%4. 4 J & Ü Ö (3. 34 g, 0. 010 4 mol), DMFZ ew, , 9j, 4 6 6 h, 9 1 e 3 Z TU, 4=9 , 1 (0. 62 g, 0. 010 4 mol), D 1 , 3 Z , (S) 4% T. 1 1 TP, (S) 4% 15 m] × 3, E Z 1 T , 0 9 e 4TT , . 1)d 1) (:J , 0) , D 1 , , 0 Z e ew, : 9 T, : () (: = 100 : 1), , . Z e ew, 3 Z , 6 Z 0Rj (Se 4. (2 (7 (4 J & ; p) 3H [1, 2, 3]Z , mt [4, 5 d]m m%3)e es4.)4%4. r 1 @2(2a), 1) : 46. 6% mp: 89. 1 ~ 90. 9 ℃ ^{1}H NMR (500 MHz, DMSO d$_6$): δ8. 20(s, 1H, 2' = CH), 7. 32(m, 2H, *J* = 5. 0 Hz, PhH), 7. 12 (d, 2H, *J* = 5. 0 Hz, PhH), 4. 71 (t, 2H, *J* = 7. 0 Hz, NCH$_2$), 4. 49 (d, 2H, *J* = 10 Hz, OCH$_2$P), 4. 18 ~ 4. 22 (m, 4H, CH$_2$CH$_3$), 3. 46 (t, 2H, *J* = 7. 0 Hz, CH$_2$O), 2. 32 (s, 3H, CH$_3$), 1. 33 (t, *J* = 7. 0 Hz, CH$_2$CH$_3$) IR (cm^{-1}): 3 093. 11, 3 044. 58 (Ph, C = H), 2 992. 00, 2 926. 38 (CH$_2$), 1 942. 80 (Ph, C = C), 1 713. 79(P = O), 1 584. 06(C = N), 1 557. 99, (C N)

. (/ : 9P0 0 . 2b ~ 2e

2. 5 (2 (7 (4取代苯硫酚基) 3H [1, 2, 3]三氮唑[4, 5 d]嘧啶 3基)乙氧基)甲基膦酸(1a ~ 1e) 的合成 2 a (0. 4 g, 0. 9 mmol) Z 4 e (S) 4% : , 4=Z Z 4%4. i6 0w. (0. 49 g, 3. 2 mmol), 0)z , (e . Z , D 1 , , 6 0R.j , 4=Z 1 , T, , f 6 Z 0R .j , 0) , : 4 4 , (:J 0 , 0 0 . (2 (7 (4 J & ; p) 3H [1, 2, 3]Z , mt [4, 5 d]m m%3)e es4.)4%4. r 1 (1a) 1) 57. 0% mp: 196. 1 ~ 197. 3 ℃. ^{1}H NMR (500 MHz, DMSO d$_6$): δ11. 5 (brs, 2H, OH), 8. 49 (s, 1H, 2' = CH), 7. 23(d, *J* = 5Hz 2H, PhH), 7. 10(d, *J* = 5Hz 2H , PhH), 4. 67 (t, 2H, *J* = 6. 5Hz, NCH$_2$), 4. 20 (d, 2H, *J* = 12. 5Hz, OCH$_2$P), 3. 51(t, 2H, *J* = 6. 5Hz, CH$_2$O), 2. 24(s, 3H, CH$_3$) IR (cm^{-1}): 3 421. 40 (OH), 3189. 68, 3037. 24(Ph, C = H), 2993. 70, 2 916. 70(CH$_2$), 1 698. 14(P = O), 1 578. 69(C = N), 1 557. 29, (C N)

. (/ : 9P0 0 . 1b ~ 1e DM9 0 0 . , 0 T 4 0l Z , 1) 4A0yD 1 3Z4 9 1

2. 6 药理实验

2. 6. 1 : 1 el 1Y(3Z1 1P 4K4G)4 l= D (0 e MEM D ePewD :

2. 6. 2 PMEA (, (S 3; ex, T eXT e eX. 0 T 4 T 1) 4 ℃

2. 6. 3 (HBV) DNA 3)Y l0 Z Z (6 TR9((HepG2), 2 2. 15 TR9((HepG2 2 2 2. 15TR9( )

2. 6. 4 MTT(/ 4 9 eMD (7 TR9(, , T , MTT(Aldrich)

2. 6. 5 HBV 3=e 4 9 (ELISA): 4 9 eMD (7 HBsAg0 HBeAg, e : l e

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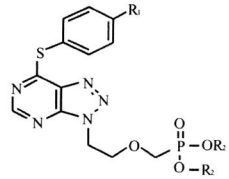

I |	R_1	R_2	mp(℃) ,)	(%)	^{1}H NMR(500 MHz, DMSO d) δ
1 a	CH_3	H	196 1~197 3	57 0	11 5 (brs, 2H, OH), 8 49 (s, 1H, 2' = CH), 7 23 (d, *J* = 5 Hz 2H, PhH), 7 10 (d, *J* = 5 Hz 2H, PhH), 4 67 (t, 2H, *J* = 6 5 Hz, NCH_2), 4 20 (d, 2H, *J* = 12 5 Hz, OCH_2P), 3 51 (t, 2H, *J* = 6 5 Hz, CH_2O), 2 24 (s, 3H, CH_3)
1 b	Br	H	209 8~210 9	67 4	11 5 (brs, 2H, OH), 8 44 (s, 1H, 2' = CH), 7 47 (d, 2H, PhH), 7 28 (d, 2H, PhH), 4 73 (t, 2H, *J* = 6 0 Hz, NCH_2), 4 35 (d, 2H, *J* = 12 3 Hz, OCH_2P), 3 60 (t, 2H, *J* = 6 0 Hz, CH_2O)
1 c	F	H	210 2~211 4	65 3	11 4 (brs, 2H, OH), 8 63 (s, 1H, 2' = CH), 7 37~7 42 (m, 2H, PhH), 7 13~7 19 (m, 2H, PhH), 4 68 (t, 2H, *J* = 6 3 Hz, NCH_2), 3 98 (d, 2H, *J* = 11 8 Hz, OCH_2P), 3 52~3 55 (m, 2H, CH_2O)
1 d	Cl	H	202 1~203 2	78 4	11 5 (brs, 2H, OH), 8 20 (s, 1H, 2' = CH), 7 26~7 34 (m, 4H, PhH), 4 71 (t, 2H, *J* = 7 0 Hz, NCH_2), 4 49 (d, 2H, *J* = 12 0 Hz, OCH_2P), 3 49~3 50 (t, 2H, *J* = 7 0 Hz, CH_2O)
1 e	$CH(Me)_2$	H	199 2~200 3	82 1	11 7 (brs, 2H, OH), 8 20 (s, 1H, 2' = CH), 7 36 (d, 2H, *J* = 6 3 Hz, PhH), 7 17 (d, 2H, *J* = 6 3 Hz, PhH), 4 71 (t, 2H, *J* = 12 Hz, NCH_2), 4 49 (d, 2H, *J* = 12 3 Hz, OCH_2P), 3 46 (t, 2H, *J* = 6 9 Hz, CH_2O), 2 84~2 93 (m, *J* = 6 9 Hz, 1H, $CH(CH_3)_2$), 1 24~1 26 (d, *J* = 6 9 Hz, 6H, $CH(CH_3)_2$)
2 a	CH_3	C_2H_5	89 1~90 9	46 6	8 21 (s, 1H, 2' = CH), 7 32 (m, 2H, *J* = 5 0 Hz PhH), 7 12 (d, 2H, *J* = 5 0 Hz, PhH), 4 71 (t, 2H, *J* = 7 0 Hz, NCH_2), 4 49 (d, 2H, *J* = 10 Hz, OCH_2P), 4 18~4 22 (m, 4H, CH_2CH_3), 3 46 (t, 2H, *J* = 7 0 Hz, CH_2O), 2 32 (s, 3H, CH_3), 1 33 (t, 6H, *J* = 7 0 Hz, CH_2CH_3)
2 b	Br	C_2H_5	88 9~90 2	37 5	8 20 (s, 1H, 2' = CH), 7 41~7 45 (m, 2H, PhH), 6 98~7 05 (m, 2H, PhH), 4 71 (t, 2H, *J* = 6 9 Hz, NCH_2), 4 50 (d, 2H, *J* = 12 3 Hz, OCH_2P), 4 15~4 26 (m, 4H, CH_2CH_3), 3 45 (t, 2H, *J* = 6 9 Hz, CH_2O), 1 32 (t 6H, *J* = 6 9 Hz, CH_2CH_3)
2 c	F	C_2H_5	94 4~95 9	41 4	8 20 (s, 1H, 2' = CH), 7 41~7 45 (m, 2H, PhH), 7 26~7 28 (m, 2H, PhH), 4 73 (t, 2H, *J* = 7 2 Hz, NCH_2), 4 51 (d, 2H, *J* = 13 8 Hz, OCH_2P), 4 18~4 24 (m, 4H, CH_2CH_3), 3 51 (t, 2H, *J* = 6 9 Hz, CH_2O), 1 33 (t *J* = 6 9 Hz, 6H CH_2CH_3)
2 d	Cl	C_2H_5	76 1~77 5	44 7	8 21 (s, 1H, 2' = CH), 7 26~7 34 (m, 4H, PhH), 4 71 (t, 2H, *J* = 7 0 Hz NCH_2), 4 49 (d, 2H, *J* = 12 0 Hz, OCH_2P), 4 19~4 21 (m, 4H, CH_2CH_3), 3 49 (t, 2H, *J* = 7 0 Hz, CH_2O), 1 33 (t, 6H, *J* = 7 0 Hz, CH_2CH_3)
2 e	$CH(Me)_2$	C_2H_5	89 3~90 0	38 8	8 22 (s, 1H, 2' = CH), 7 41~7 45 (m, 2H, PhH), 7 26~7 28 (m, 2H, PhH), 4 73 (t, 2H, *J* = 7 2 Hz, NCH_2), 4 51 (d, 2H, *J* = 13 8 Hz, OCH_2P), 4 18~4 24 (m, 4H, CH_2CH_3), 3 51 (t, 2H, *J* = 6 9 Hz, CH_2O) 2 84~2 93 (m, 1H, *J* = 6 9 Hz, $CH(CH_3)_2$), 1 35 (t, 6H, *J* = 6 9 Hz, CH_2CH_3), 1 24 ~1 26 (d, 6H, *J* = 6 9 Hz, $CH(CH_3)_2$)

DMEM DePew (GIBCO), DePew.z 4= 10% 1 D T Z, G418 100 μg/ml (GIBCO), 0 03% 0P6 k 6, e 0 23% HePes, pH: 6 48 9 Z 1) 4 eMD 4= 0 2 ml DMSO, . Z Z 4 0 9 4= 3 79 ml 2% DMEM0), ,M3g, 0 eXD ePew, e 0 06% e, 6) 4 2 2 15TR9(Z 9, (TR9(T ew, 6 3×10^4 TR9(β D (0 4 : e 963 6, 2 d0 0 e 0 eXD ePew e TR9(l e 12 d0, TD14Z ewl ELISA 9, HBsAg HBeAg, e :), e TUTR9(e MIT (/ 9, eX . TR9(, T 1 el 4 0 4 9 2

2 6. 6 HBV 9, DNA e : l e 4 9 HepG2 2 2 15TR9(:@ 243 TR9(DeP6 : DeP 48 h

,4=Z 1 D 9 . D (0 0 eXD ePew, 4bT D eP 9 d () 3 d0 ewe[,), 1 4M14Z ew, e .e : (/ 4 T PCR 4 9 HBV e . : HBV 14e e . : 5' TgT CCT ggT TAT CgC Tgg 3' HBV TUe e . : 5' CAA ACg ggC AAC ATA CCT T 3' HBV e 0d.e : T)r : 5' (FAM) TgT gTC TgC ggC gTT TTA TCA T (TAMRA) 3' PCR: 95 ℃ 5 min; 95 ℃ 10 s; 60 ℃ 30 s, 40(T 0 4 0 4 9 2

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Ä † þ	CC_{50}(μg)[1]	AntiHBsAg		AntiHBeAg		AntiHBVDNA	
		IC_{50}(μg)[2]	SI[3]	IC_{50}(μg)	SI	IC_{50}(μg)	SI
1a	113.40	33.84	3.35	10.51	10.79	2.56	44.30
1b	244.40	34.25	7.14	16.23	15.06	3.80	54.32
1c	96.48	71.88	13.40	11.52	8.38	2.64	36.55
1d	167.91	37.13	4.52	11.14	15.07	4.24	39.60
1e	90.76	13.80	6.58	0.51	177.96	0.64	141.81
PMEA	540	305	1.77	286	1.89	0.517	1 400

[1]: 1 CC_{50}: 6 1 TR9(, T 1 T D (0; 2 IC_{50}; 6 1 e : D (0. 3 SI: T :G: 1 (SI= CC_{50} / IC_{50})

3),

3.1 3a3e1Y, 4 Z , 9Hjd(:@DgZ , :@TUe 9 1 e TU(e 1h, Z 0 4=Z T Th: 9P, : 4 .j 4, l ,o 9 1 1 . TU(e , 9) 0 , , : 4 4=. , 90 ℃ 16 h, 4N3 4.9N(e . Z

3.2 2a2e1Y, (e e : 4 .j 3a3e ((Se 4.)c 1 @2)4%4. 4 J &ÜÖ a) _ ¿ 1: 2 5: 2 59L3 .)p4 0

3.3 2a2f4 Z 4%4.i60w. 1 4 ,g3 0, , r 1 0 0 . ,Z 0 2a2e9 ,[0 4: 4 .)p(e ,:u9 . T, ,f 3 DG,T eL(, 4 pH: 9 3, , DM9 0 0 . 1a1e

3.4 5(r 1 0 0 . 4 T)E .j . 3= HBsAg HBeAg0 3= HBV DNA 46T Z T 1 el 1 9 0 0 . 3= HBsAg HBeAg46T 3B0 e PMEA, 0 0 . 1e3= HBV DNA 46T e PMEA T , ,: , 4bT T 4 4 0 Tw1 , PMEA e Z 8 < 6 | } & ; F HBV DNA 46T 9Z9 , 3= HBsAg HBeAg46T , e .G(

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