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(54) **ENA NUCLEIC ACID DRUGS MODIFYING
SPLICING IN MRNA PRECURSOR**

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C07H 21/02 (2006.01)

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536/28.1

(57) **ABSTRACT**

Oligonucleotides having a nucleotide sequence complementary to nucleotide numbers such as 2571-2607, 2578-2592, 2571-2592, 2573-2592, 2578-2596, 2578-2601 or 2575-2592 of the dystrophin cDNA (Gene Bank accession No. NM_004006.1) and therapeutic agents for muscular dystrophy comprising such oligonucleotides.

FIG. 1

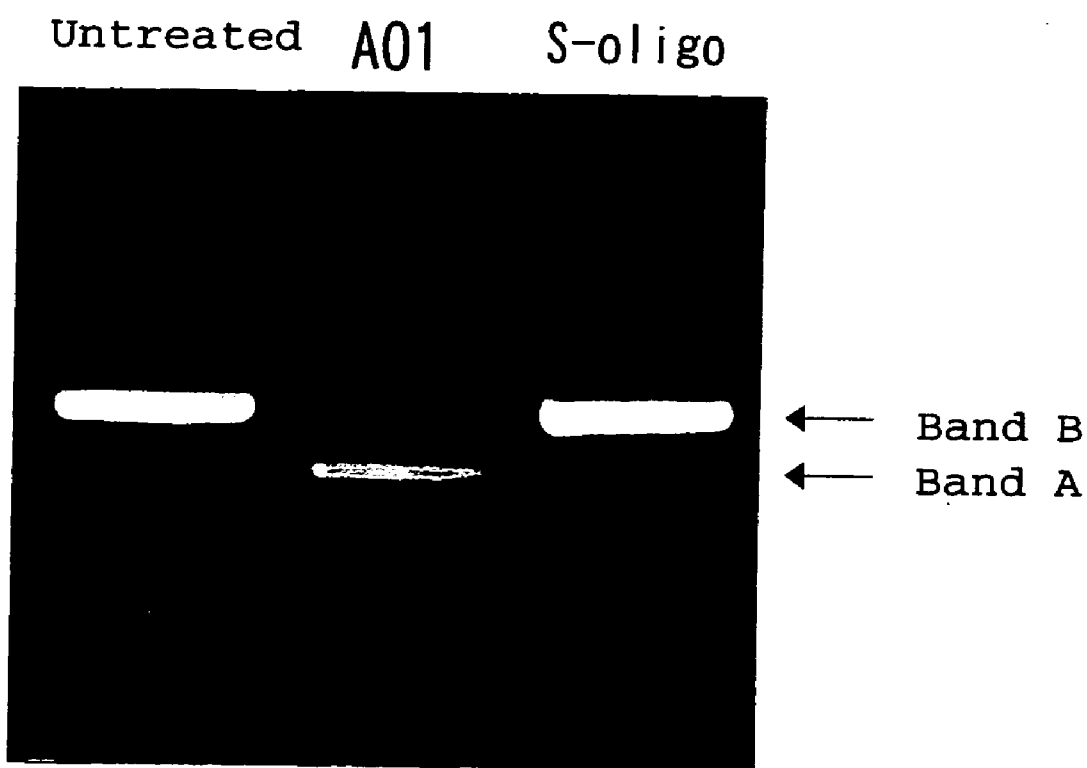


FIG. 2

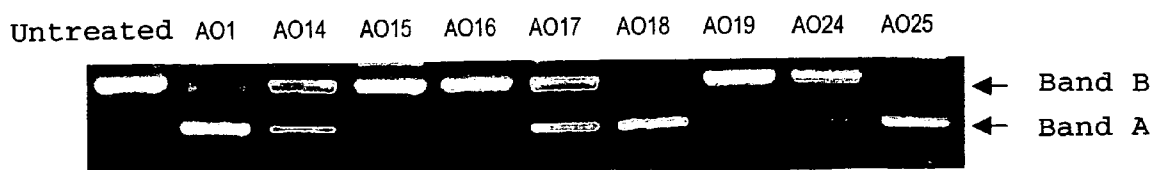


FIG. 3

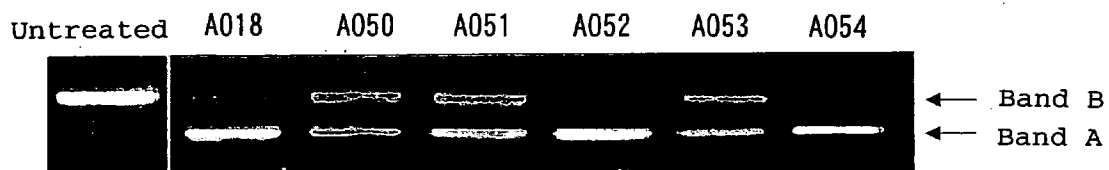


FIG. 4



FIG. 5

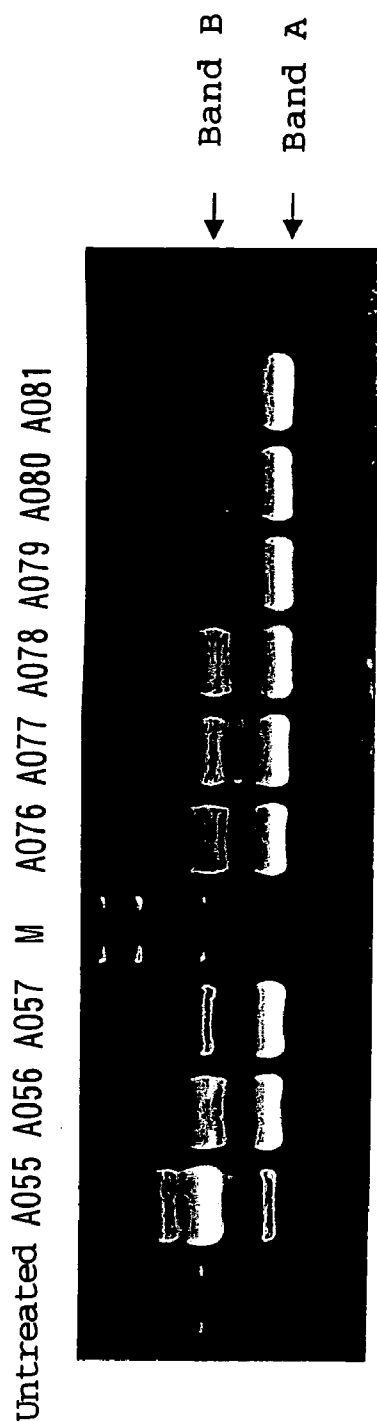


FIG. 6

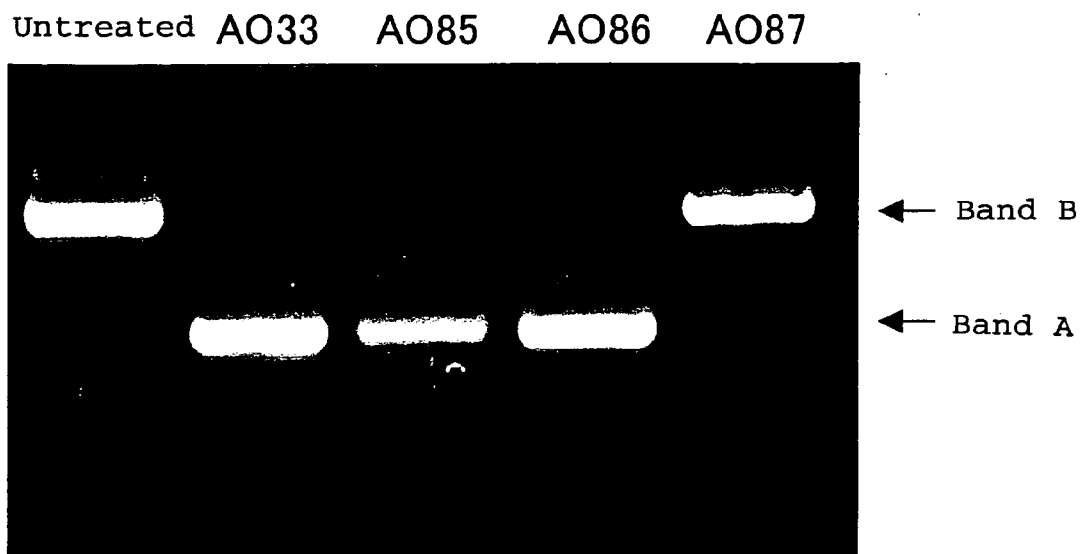


FIG. 7

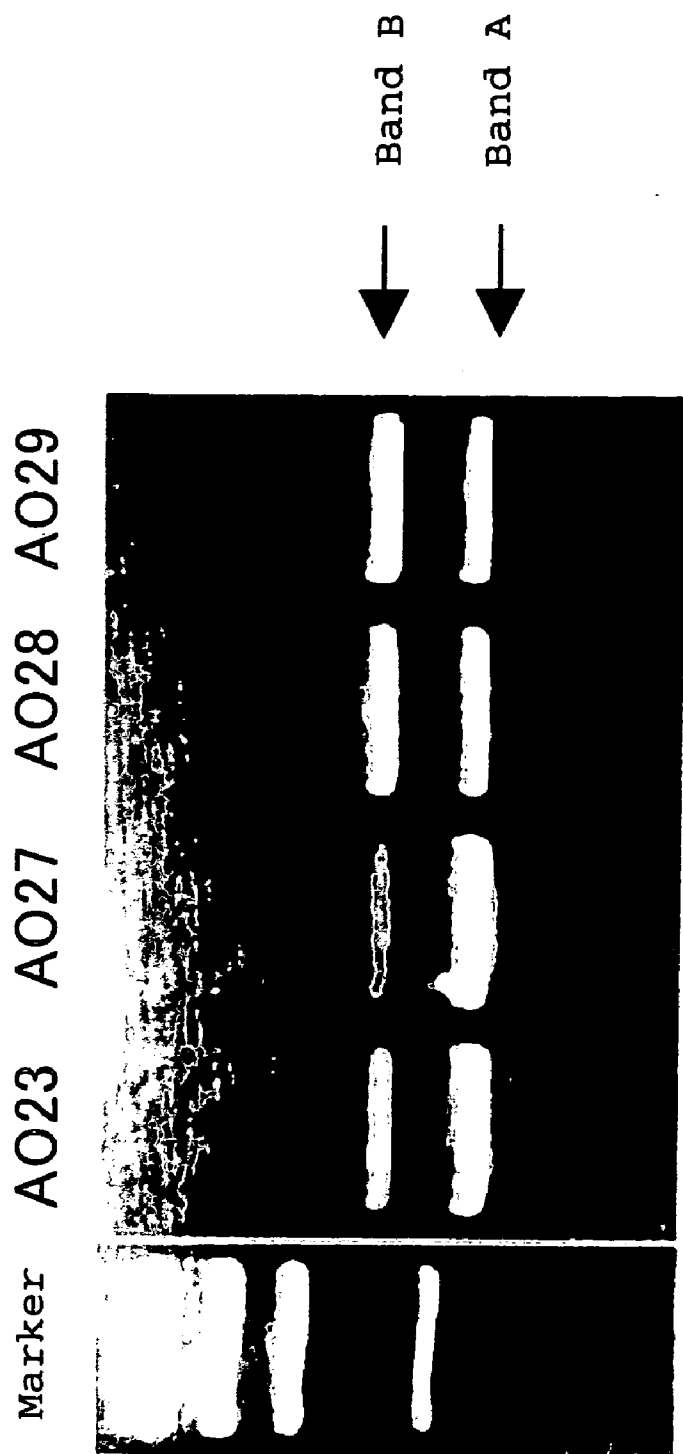


FIG. 8

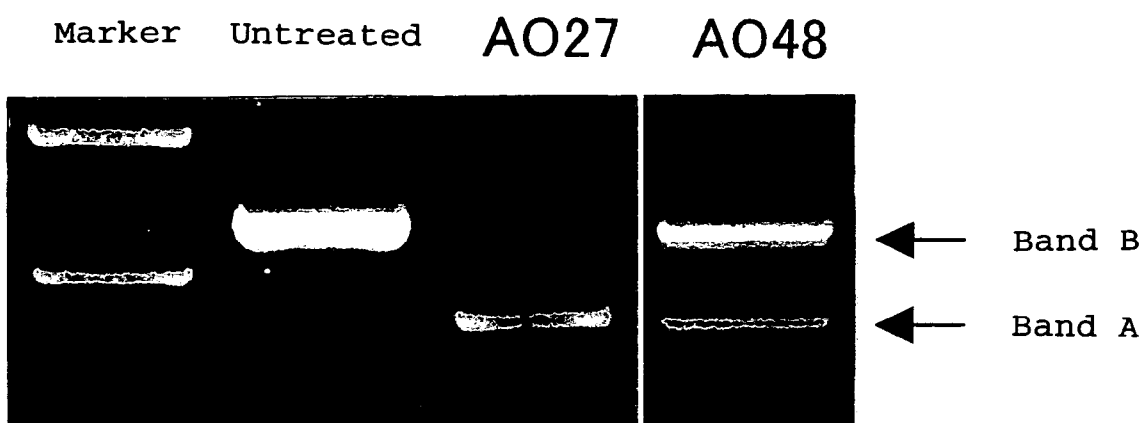


FIG. 9

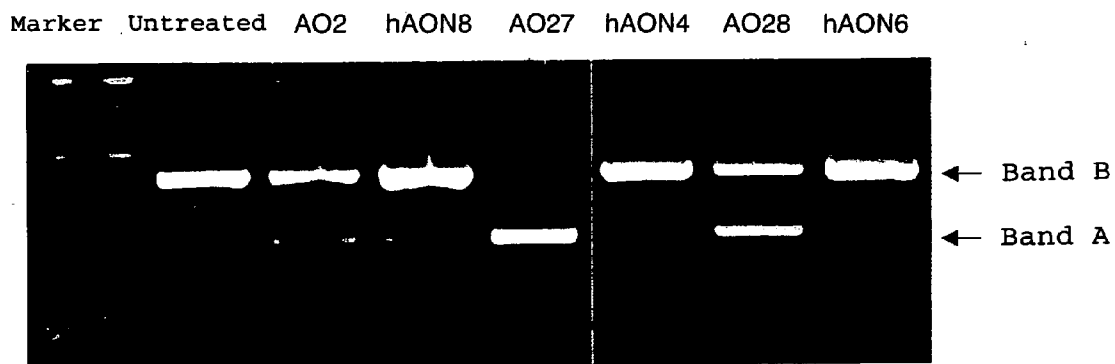


FIG. 10

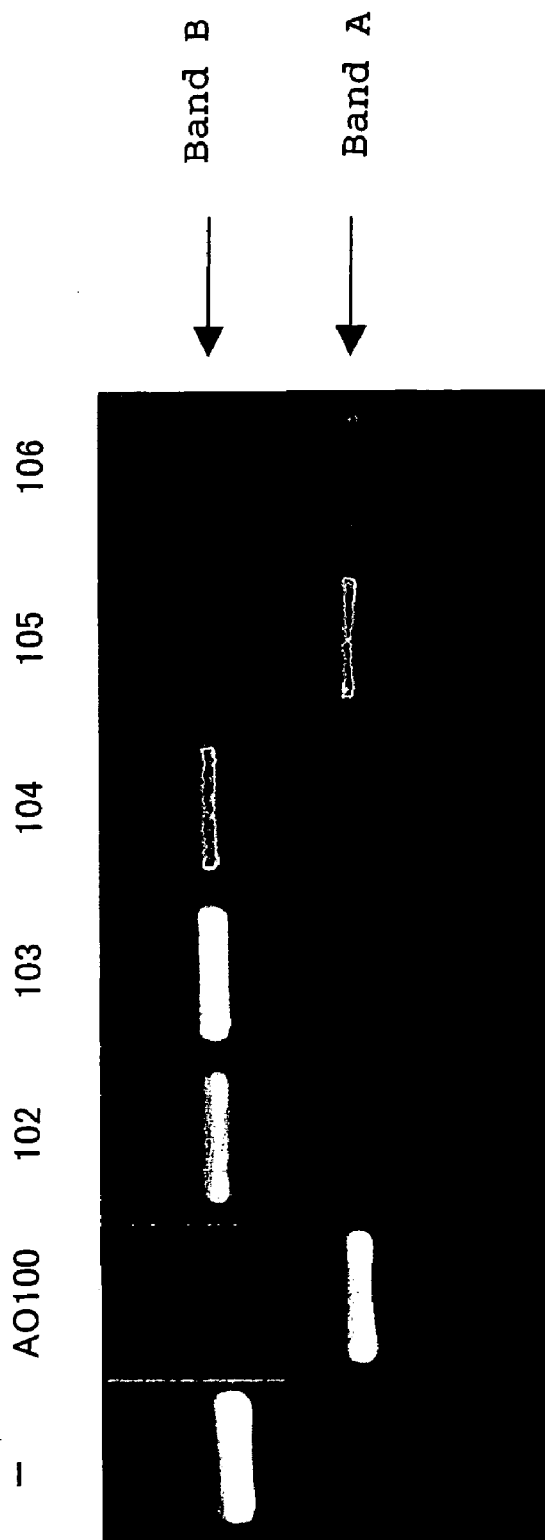


FIG. 11

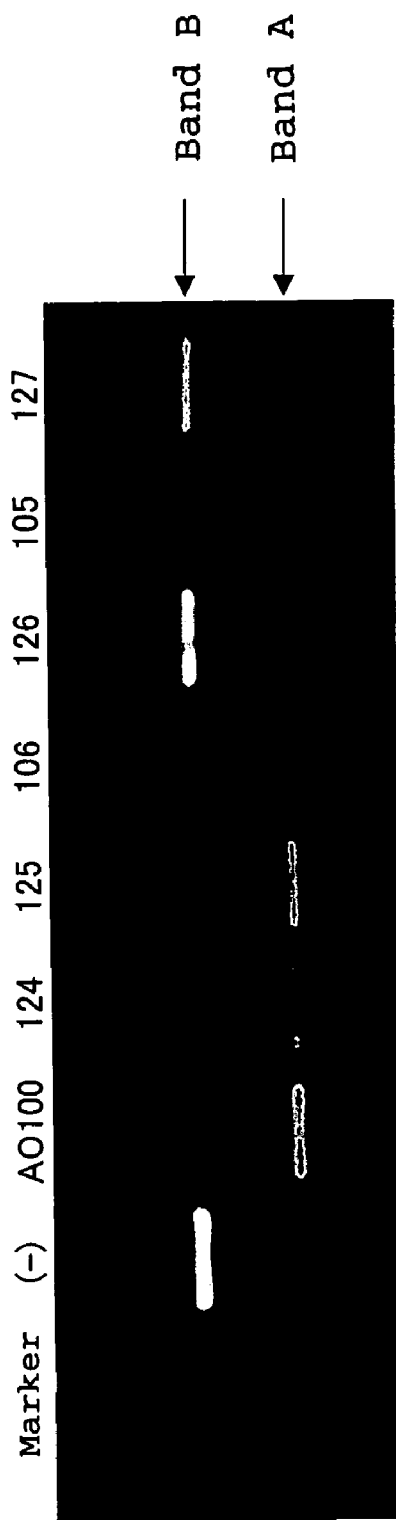


FIG. 12

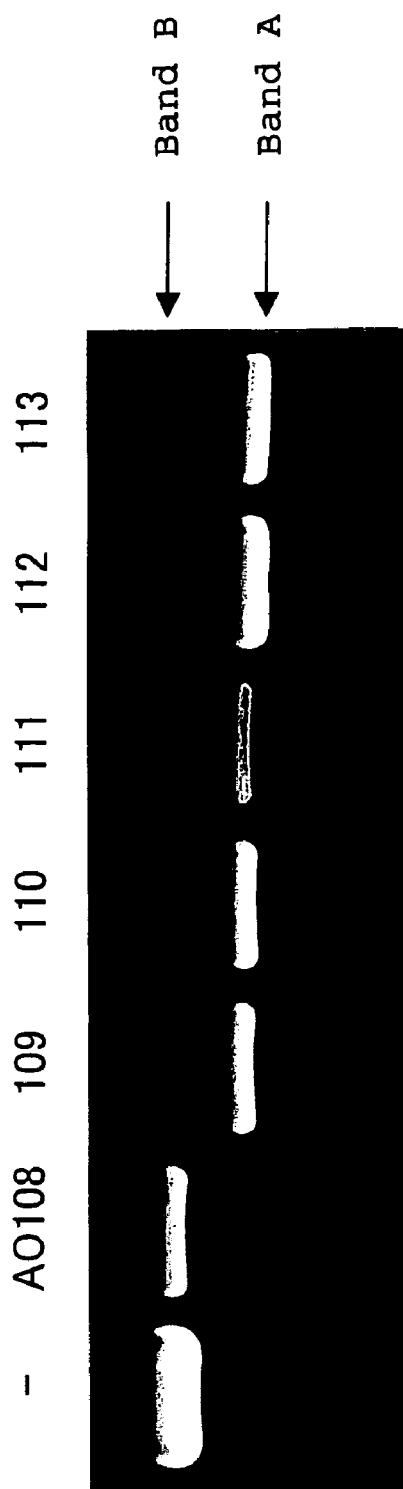


FIG. 13

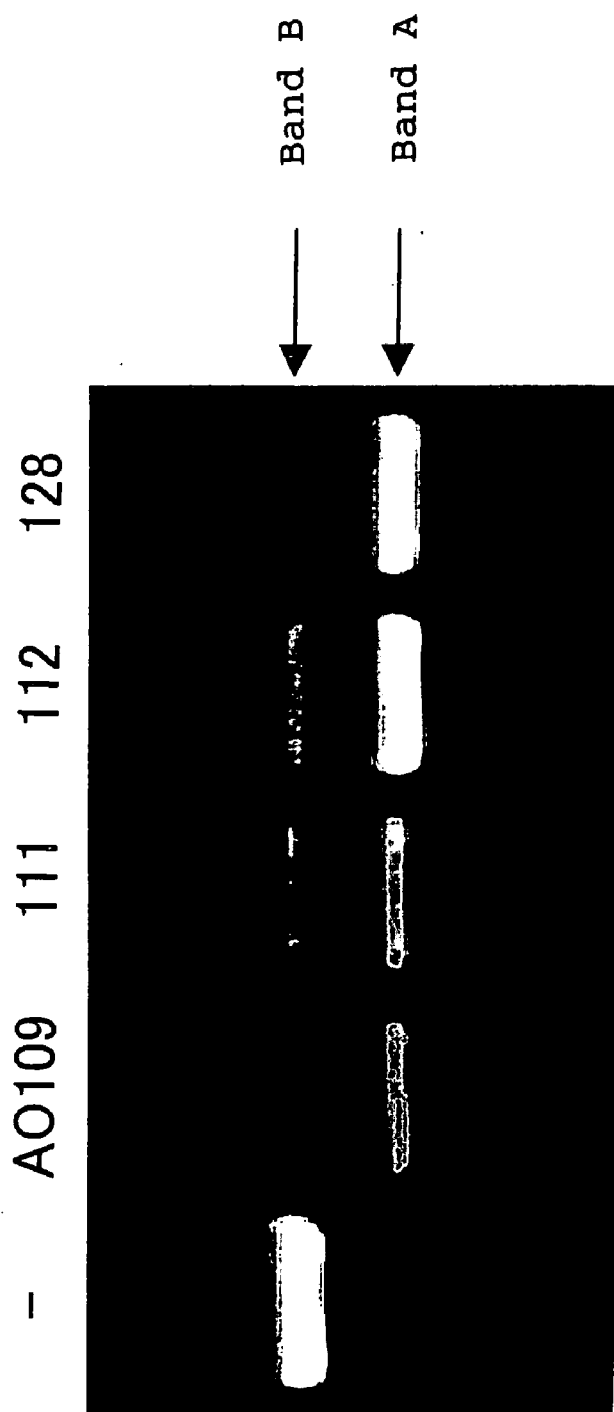


FIG. 14

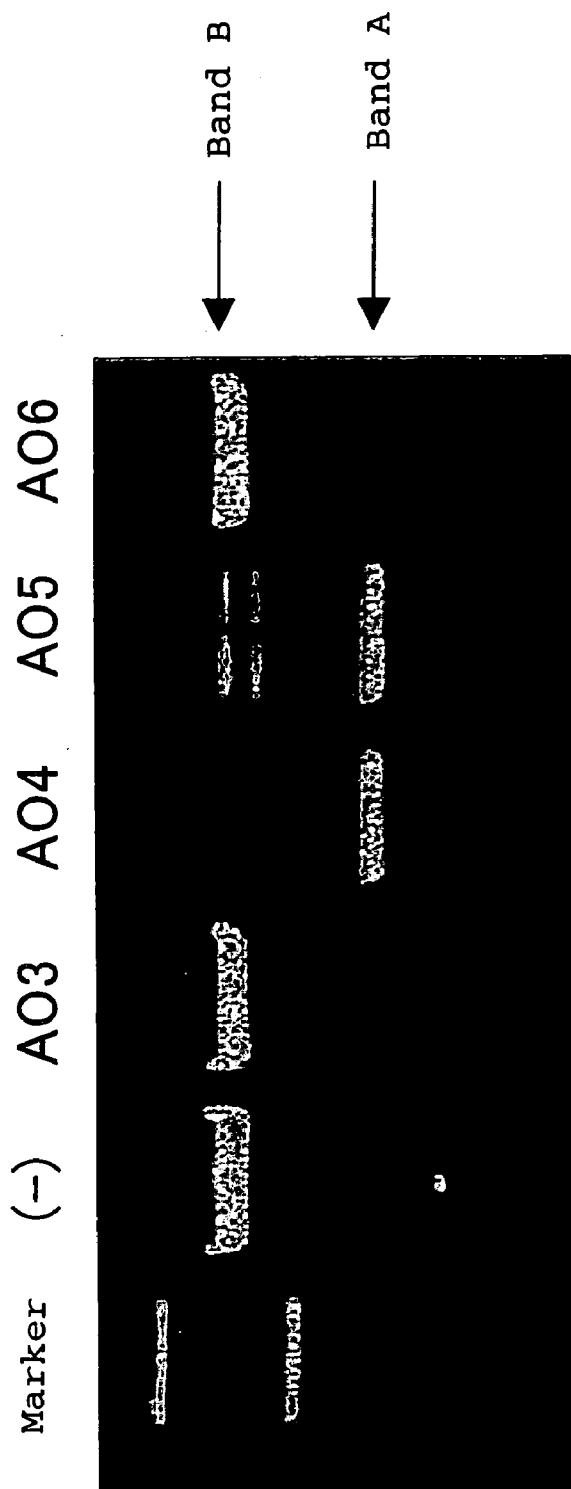


FIG. 15

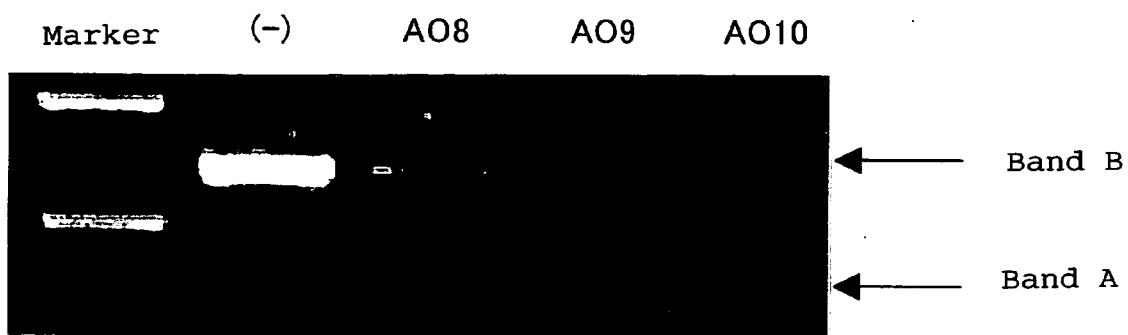


FIG. 16

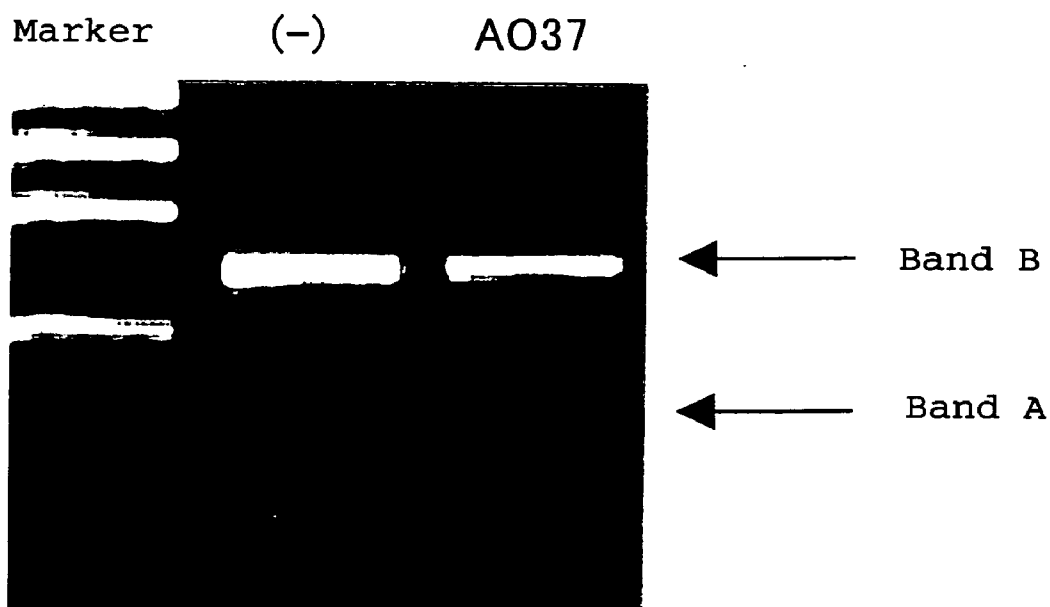


FIG. 17

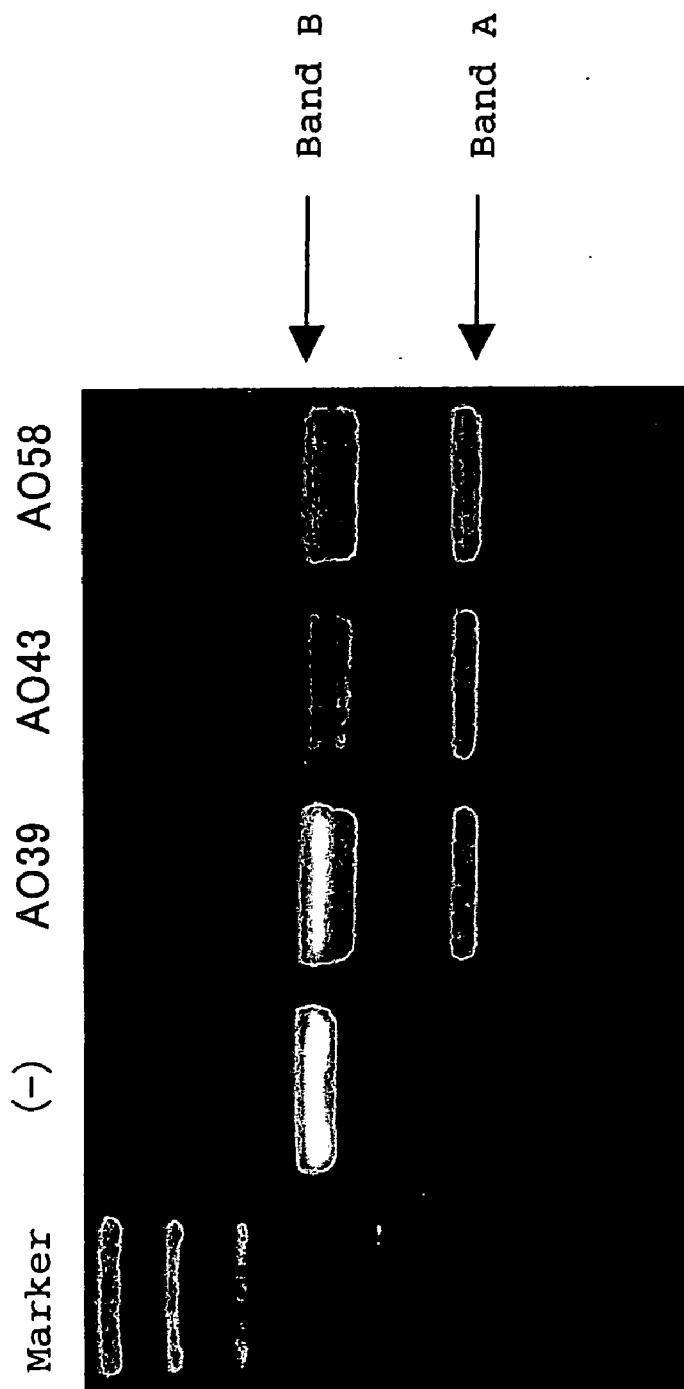


FIG. 18

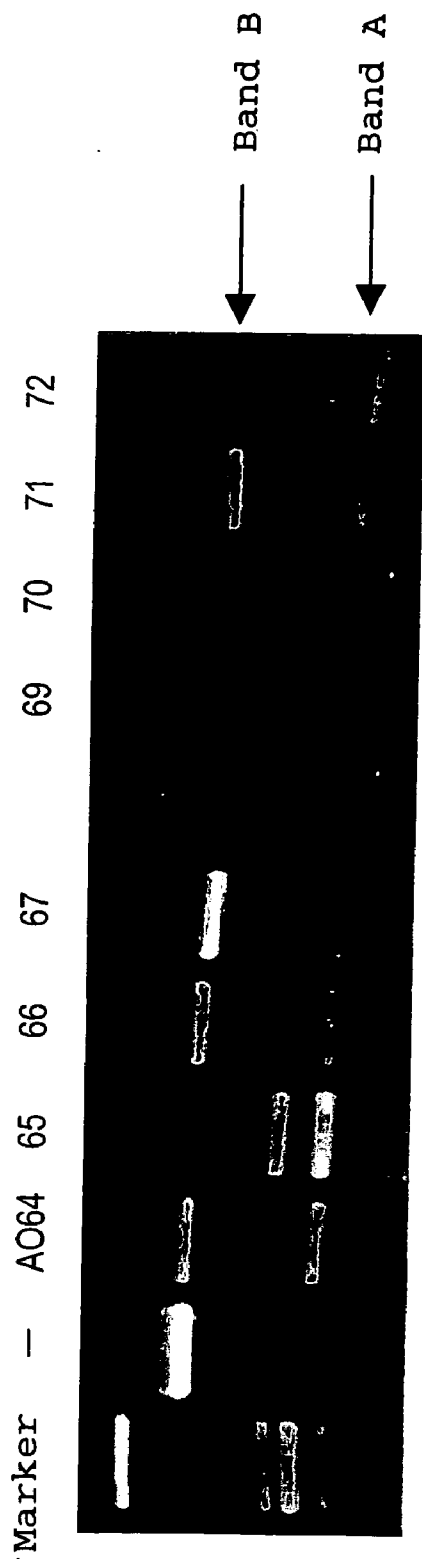


FIG. 19

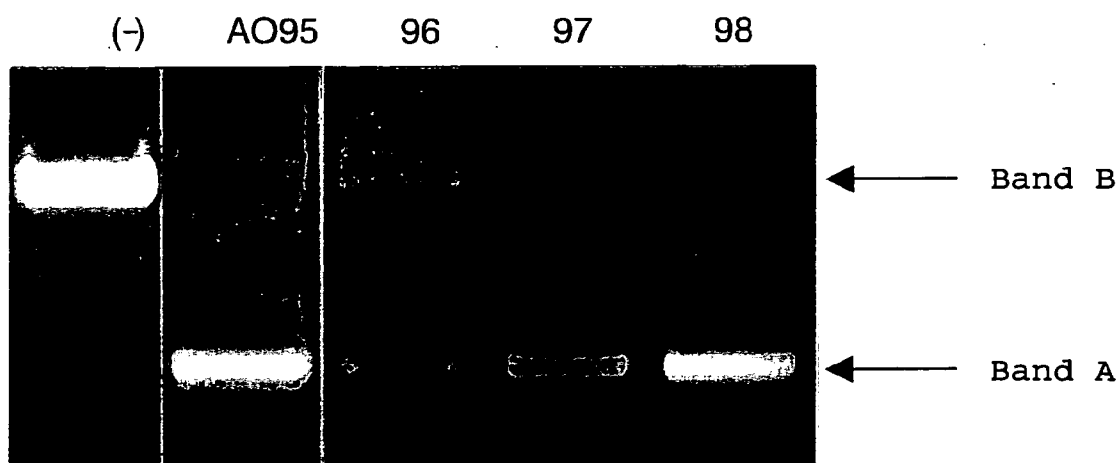


FIG. 20

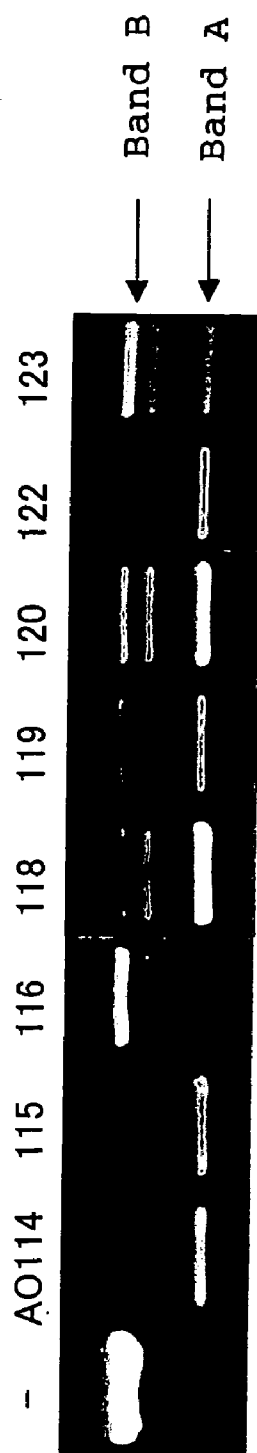


FIG. 21

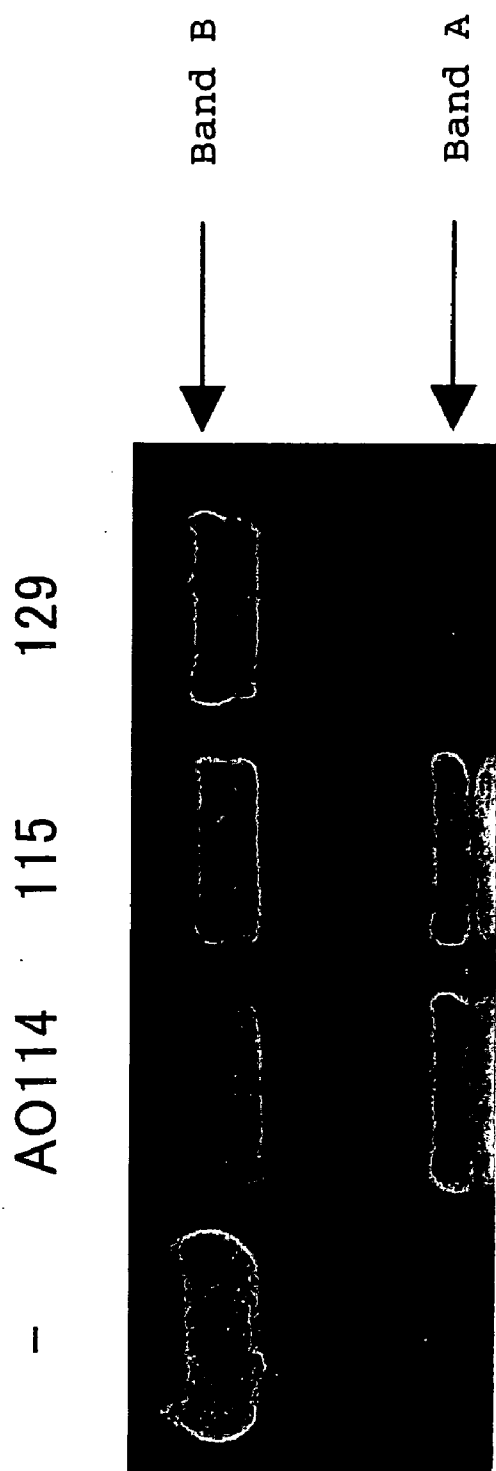
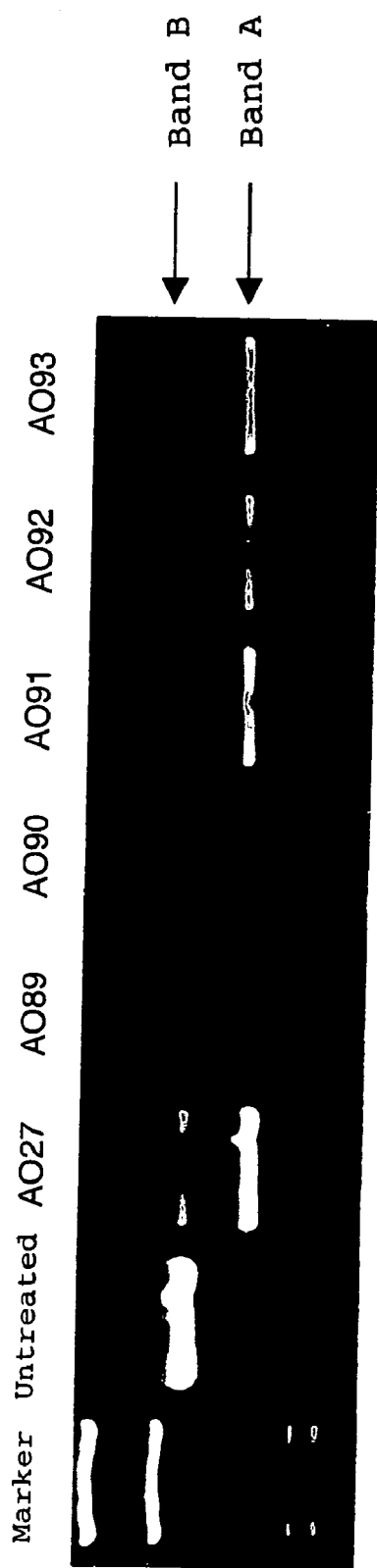


FIG. 22



ENA NUCLEIC ACID DRUGS MODIFYING SPLICING IN MRNA PRECURSOR

TECHNICAL FIELD

[0001] The present invention relates to ENA nucleic acid pharmaceuticals capable of modifying splicing of mRNA precursors. More specifically, the present invention relates to antisense oligonucleotide compounds to splicing enhancer sequences within exon 19, 41, 45, 46, 44, 50, 55, 51 or 53 of the dystrophin gene, as well as therapeutic agents for muscular dystrophy comprising the compounds.

BACKGROUND ART

[0002] Muscular dystrophy, which is a genetic muscular disease, is roughly classified into Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). DMD is the most frequently occurring genetic muscular disease and occurs at a ratio of 1 per 3,500 male births. DMD patients show symptoms of weakening of muscles in their childhood; thereafter, muscular atrophy progresses consistently and results in death at the age of around 20. Currently, there is no effective therapeutic for DMD. Development of therapeutics is strongly demanded by DMD patients throughout the world. BMD in many cases occurs in adulthood and most of the patients are capable of normal survival though slight weakening of muscles is observed. Mutations of deletions in the dystrophin gene have been identified in $\frac{2}{3}$ of DMD and BMD cases. The progress of clinical symptoms in DMD or BMD patients is predictable depending on whether such deletions disrupt the translational reading frame of mRNA or maintain that reading frame (Monaco A. P. et al., *Genomics* 1988: 2:90-95). Although molecular biological understanding of DMD has been thus deepened, no effective method for treating DMD has been established yet.

[0003] When DMD patients have a frame shift mutation, dystrophin protein disappears completely from patients' skeletal muscles. On the other hand, dystrophin protein is produced from in-frame mRNA in BMD patient-derived muscle tissues, though the protein is incomplete. As a method for treating DMD, there is known a method in which an out-frame mutation (the reading frame of amino acids is shifted) is converted to an in-frame mutation (the reading frame is maintained) by modifying dystrophin mRNA (Matsuo M., *Brain Dev* 1996; 18:167-172). Recently, it has been reported that the mdx mouse synthesized a deletion-containing dystrophin as a result of induction of exon skipping with an oligonucleotide complementary to the splicing consensus sequence of the dystrophin gene (Wilton S. D. et al., *Neuromusc Disord* 1999: 9:330-338; Mann C. J. et al., *Proc Natl Acad Sci USA* 2001: 98:42-47). In these studies, exon skipping is induced using as a target the splicing consensus sequence located on the border between two exons.

[0004] It is asserted that splicing is regulated by splicing enhancer sequences (SESs). In fact, it has been demonstrated that by disrupting the SES within exon 19 of the dystrophin gene with an antisense oligonucleotide complementary thereto, complete skipping of exon 19 occurs in normal lymphoblastoid cells (Takeshima Y. et al., *J Clin Invest* 1995: 95:515-520; Pramono Z. A. et al., *Biochem Biophys Res Commun* 1996: 226:445-449).

[0005] It has been also reported that by introducing an oligonucleotide complementary to the SES within exon 19

of the dystrophin gene to thereby induce exon skipping, a deletion-containing dystrophin was successfully produced in muscular cells derived from DMD patients carrying exon 20 deletion (Takeshima Y. et al., *Brain & Development* 2001: 23:788-790; Japanese Unexamined Patent Publication No. H11-140930; Japanese Unexamined Patent Publication No. 2002-10790). This indicates that repairing of the reading frame shift by inducing exon 19 skipping with an antisense oligonucleotide complementary to the SES within exon 19 of the dystrophin gene results in production of a dystrophin protein whose function is partially restored; and thus it is possible to change DMD to BMD. If it is possible to convert DMD, a severe myoatrophy, to slight BMD, prolonging patients' lives can be expected.

[0006] At present, oligonucleotide analogues having stable and excellent antisense activity are being developed (Japanese Unexamined Patent Publication No. 2000-297097).

[0007] It is an object of the present invention to provide therapeutics with broader applicable range and higher efficacy, by improving antisense oligonucleotides to the SES within exon 19, 41, 45, 46, 44, 50, 55, 51 or 53 of the dystrophin gene.

DISCLOSURE OF THE INVENTION

[0008] As a result of extensive and intensive researches toward the achievement of the above-described object, the present inventors have succeeded in designing and synthesizing those nucleotide sequences and antisense oligonucleotide compounds which have higher exon skipping effect on exon 19, 41, 45, 46, 44, 50, 55, 51 or 53 of the dystrophin gene. Thus, the present invention has been achieved.

[0009] The present invention may be summarized as follows.

[0010] [1] An oligonucleotide having the nucleotide sequence as shown in any one of SEQ ID NOS: 2-6, 10-22, 30-78, 87 or 88 in the SEQUENCE LISTING, or a pharmacologically acceptable salt thereof.

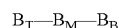
[0011] [2] The oligonucleotide of [1] above or a pharmacologically acceptable salt thereof, wherein at least one of the sugars and/or the phosphates constituting the oligonucleotide is modified.

[0012] [3] The oligonucleotide of [2] above or a pharmacologically acceptable salt thereof, wherein the sugar constituting the oligonucleotide is D-ribofuranose and the modification of the sugar is modification of the hydroxyl group at position 2' of D-ribofuranose.

[0013] [4] The oligonucleotide of [3] above or a pharmacologically acceptable salt thereof, wherein the modification of the sugar is 2'-O-alkylation and/or 2'-O,4'-C-alkylation of the D-ribofuranose.

[0014] [5] The oligonucleotide of [2] above or a pharmacologically acceptable salt thereof, wherein the modification of the phosphate is thioation of the phosphate group.

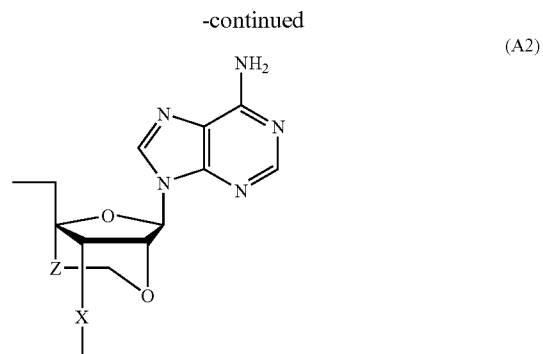
[0015] [6] A compound represented by the following general formula (I) or a pharmacologically acceptable salt thereof:



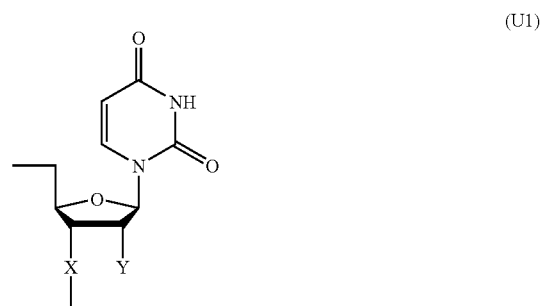
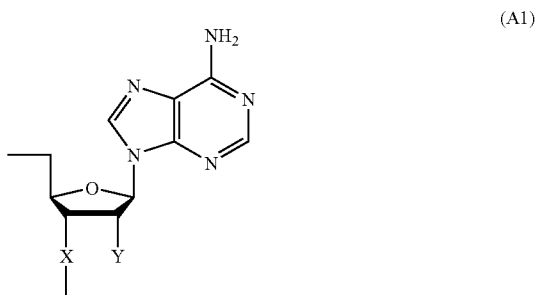
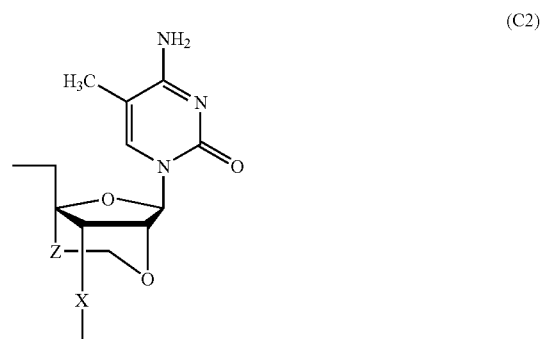
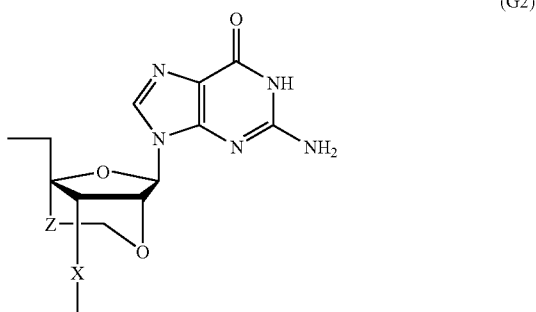
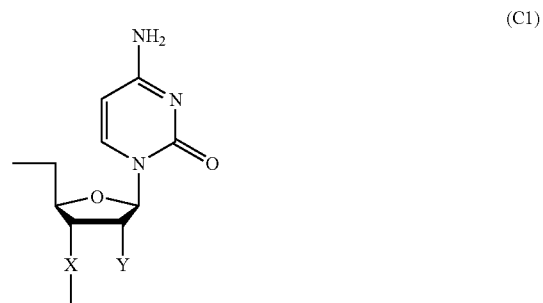
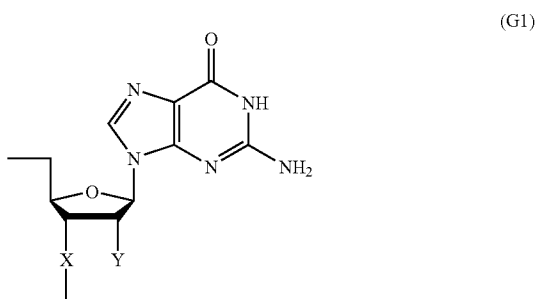
(I)

[0016] where B_T is a group represented by any one of the following (1a) to (1k):

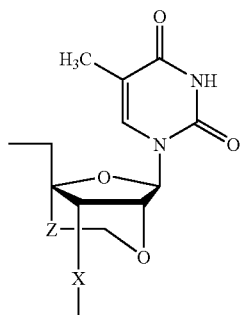
- HO—, (1a)
- HO-Bt, (1b)
- HO-Bc-Bt, (1c)
- HO-Bg-Bc-Bt, (1d)
- HO-Ba-Bg-Bc-Bt, (1e)
- HO-Bg-Ba-Bg-Bc-Bt, (1f)
- HO-Bt-Bg-Ba-Bg-Bc-Bt, (1g)
- HO-Bc-Bt-Bg-Ba-Bg-Bc-Bt, (1h)
- HO-Bc-Bc-Bt-Bg-Ba-Bg-Bc-Bt, or (1j)
- HO-Bg-Bc-Bc-Bt-Bg-Ba-Bg-Bc-Bt; (1k)



[0017] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

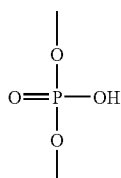


-continued

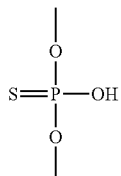


(T2)

[0018] where X is individually and independently a group represented by the following formula (X1) or (X2):



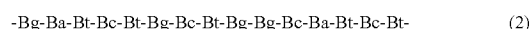
(X1)



(X2)

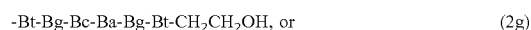
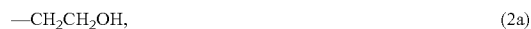
[0019] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0020] B_M is a group represented by the following formula (2):



[0021] where Bg, Ba, Bt and Bc are as defined above;

[0022] B_B is a group represented by any one of the following (2a) to (2h):



[0023] where Bg, Ba, Bt and Bc are as defined above;

[0024] provided that at least one of the nucleosides constituting the compound represented by formula (I) has 2'-O,4'-C-alkylene group.

[0025] [7] The compound according to claim 6 which is selected from the group consisting of the following compounds (i) to (vi), or a pharmacologically acceptable salt thereof:

[0026] (i) a compound where B_T is a group represented by (1k) and B_B is a group represented by (2h),

[0027] (ii) a compound where B_T is a group represented by (1a) and B_B is a group represented by (2a),

[0028] (iii) a compound where B_T is a group represented by (1a) and B_B is a group represented by (2h),

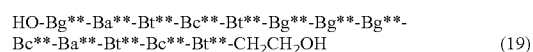
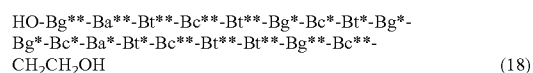
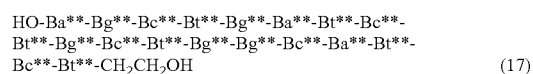
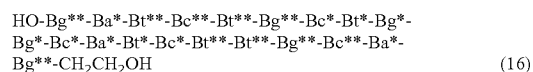
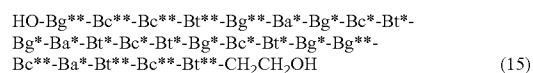
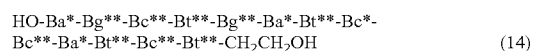
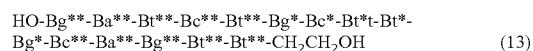
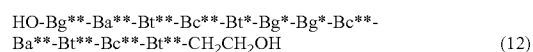
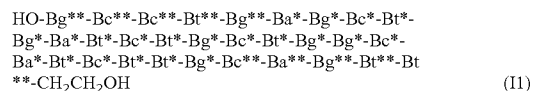
[0029] (iv) a compound where B_T is a group represented by (1e) and B_B is a group represented by (2a),

[0030] (v) a compound where B_T is a group represented by (1k) and B_B is a group represented by (2a),

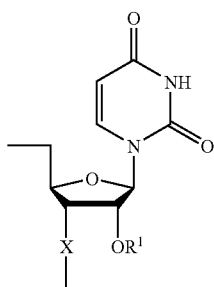
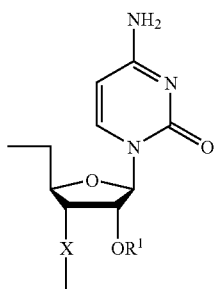
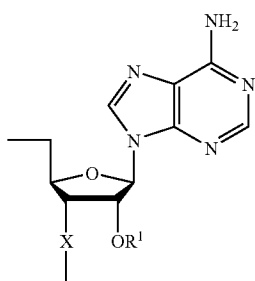
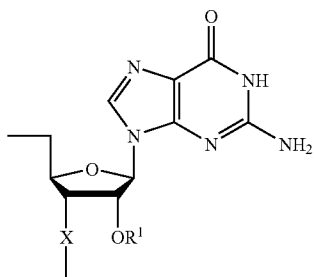
[0031] (vi) a compound where B_T is a group represented by (1a) and B_B is a group represented by (2f), and

[0032] (vii) a compound where B_T is a group represented by (1a) and B_B is a group represented by (2d).

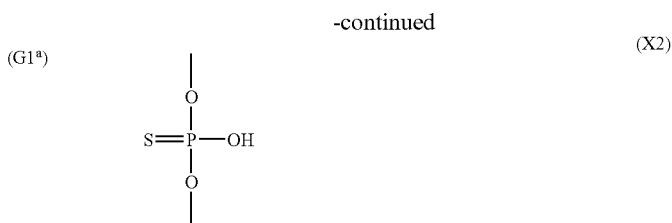
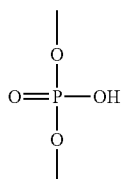
[0033] [8] The compound of [6] above which is selected from the group consisting of the following compounds (I1) to (I7), or a pharmacologically acceptable salt thereof:



[0034] where Bg* is a group represented by the following formula (G1^a), Ba* is a group represented by the following formula (A1^a); Bc* is a group represented by the following formula (C1^a); Bt* is a group represented by the following formula (U1^a); Bg** is a group represented by formula (G2); Ba** is a group represented by formula (A2); Bc** is a group represented by formula (C2); and Bt** is a group represented by formula (T2):



[0035] where X is individually and independently a group represented by the following formula (X1) or (X2):



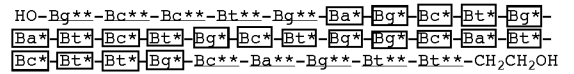
[0036] and R¹ is individually and independently an alkyl group with 1-6 carbon atoms.)

(A1^a) [0037] [9] The compound of [8] above where X in formulas (G1^a), (A1^a), (C1^a) and (U1^a) is a group represented by formula (X2) and X in formulas (G2), (A2), (C2) and (T2) is a group represented by formula (X1), or a pharmacologically acceptable salt thereof.

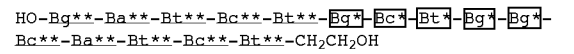
[0038] [10] The compound of [8] above where X in all the formulas (G1^a), (A1^a), (C1^a), (U1^a), (G2), (A2), (C2) and (T2) is a group represented by formula (X2), or a pharmacologically acceptable salt thereof.

(C1^a) [0039] [11] The compound of [8] above which is represented by any one of the following formulas (I1-a), (I2-a), (I3-a), (I4-a), (I5-a), (I6-a), (I7-a), (I8-a) and (I9-a), or a pharmacologically acceptable salt thereof:

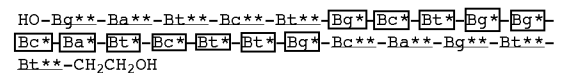
(I1-a)



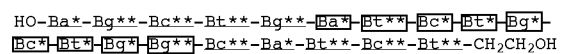
(I2-a)



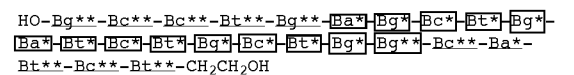
(I3-a)



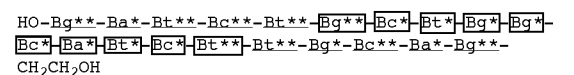
(I4-a)



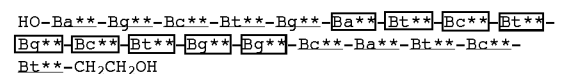
(I5-a)



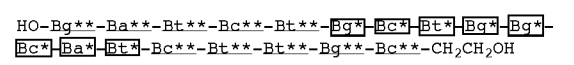
(I6-a)



(I7-a)

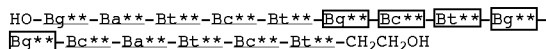


(I8-a)



-continued

(I9-a)



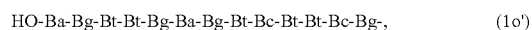
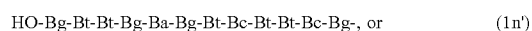
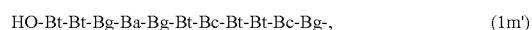
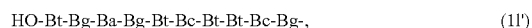
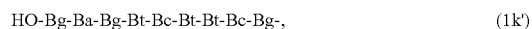
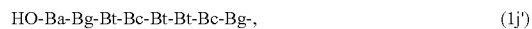
[0040] where Bg* is a group represented by formula (G1^a); Ba* is a group represented by formula (A1^a); Bc* is a group represented by formula (C1^a); Bt* is a group represented by formula (U1^a); Bg** is a group represented by formula (G2); Ba** is a group represented by formula (A2); Bc** is a group represented by formula (C2); Bt** is a group represented by formula (T2); and in individual formulas, at least one of Bg*, Ba*, Bc*, Bt*, Bg**, Ba**, Bc** and Bt** has a group represented by formula (X2) as X and all of Bg*, Bg**, Ba**, Bc** and Bt** have a group represented by (X1) as X.

[0041] [12] The compound of any one of [6] to [11] above where Y in formulas (G1), (A1), (C1) and (U1) is a methoxy group and Z in formulas (G2), (A2), (C2) and (T2) is an ethylene group, or a pharmacologically acceptable salt thereof.

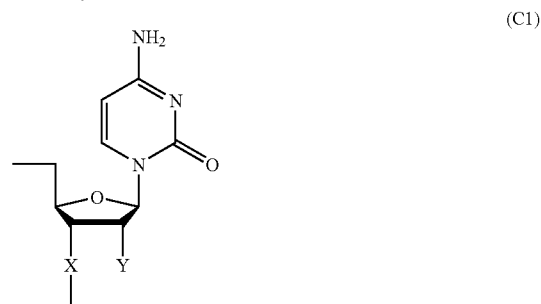
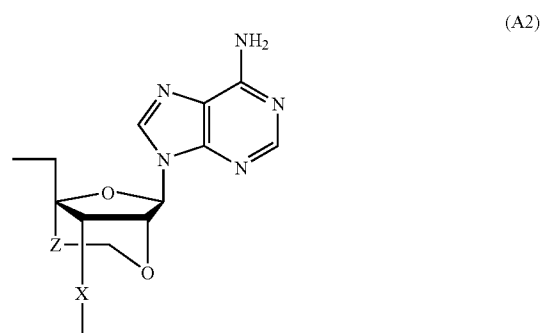
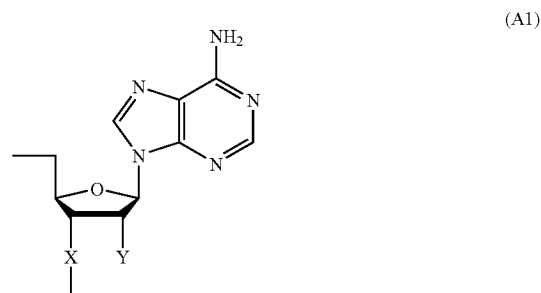
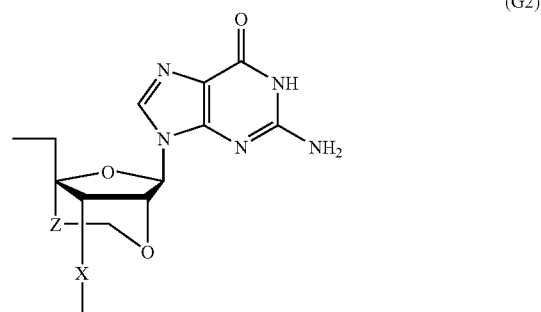
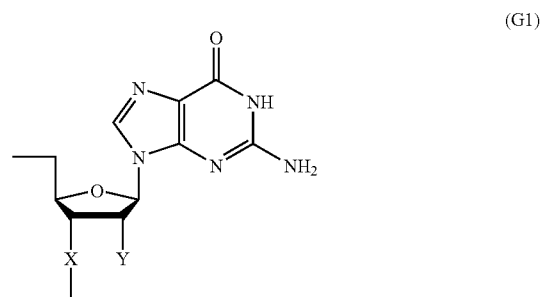
[0042] [13] A compound represented by the following general formula (I') or a pharmacologically acceptable salt thereof:



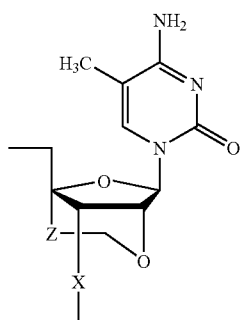
[0043] where B_{T1} is a group represented by any one of the following (1a') to (1o')



[0044] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



-continued



(C2)

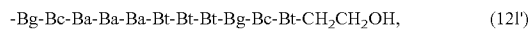
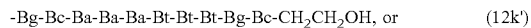
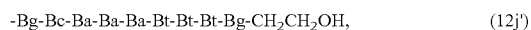
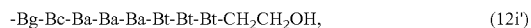
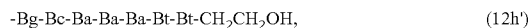
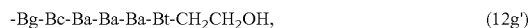
[0046] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0047] $B_{M'1}$ is a group represented by the following formula (1'):



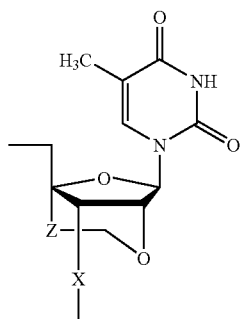
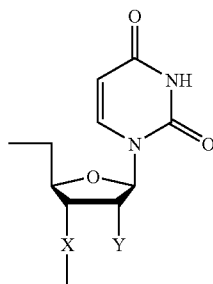
[0048] where Bg, Ba, Bt and Bc are as defined above;

[0049] $B_{B'1}$ is a group represented by any one of the following (12a') to (12l'):

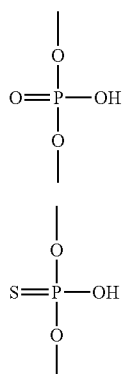


(U1)

(T2)



[0045] where X is individually and independently a group represented by the following formula (X1) or (X2):



(X1)

(X2)

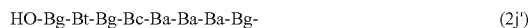
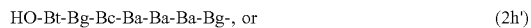
[0050] where Bg, Ba, Bt and Bc are as defined above;

[0051] provided that at least one of the nucleosides constituting the compound represented by formula (I') has 2'-O,4'-C-alkylene group.

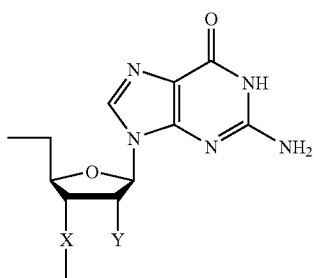
[0052] [14] A compound represented by the following general formula (II') or a pharmacologically acceptable salt thereof:



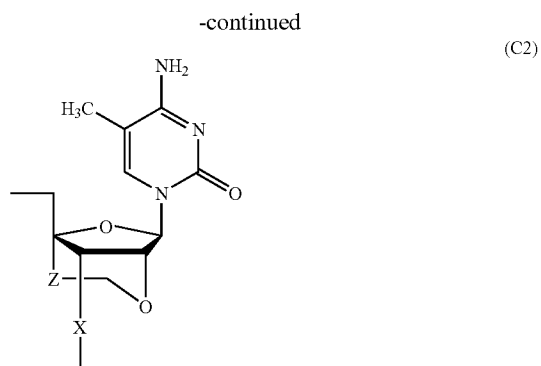
[0053] where $B_{T'2}$ is a group represented by any one of the following (2a') to (2j'):



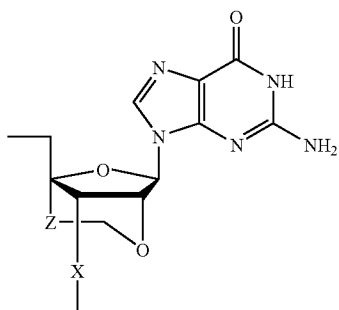
[0054] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



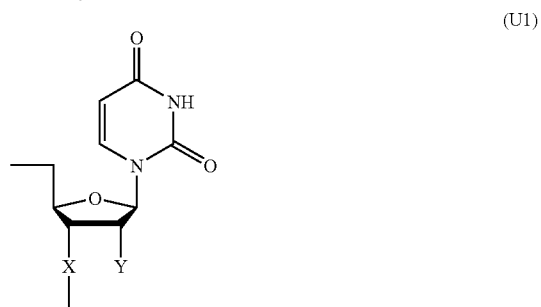
(G1)



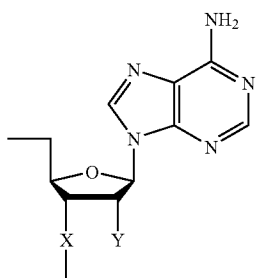
(G2)



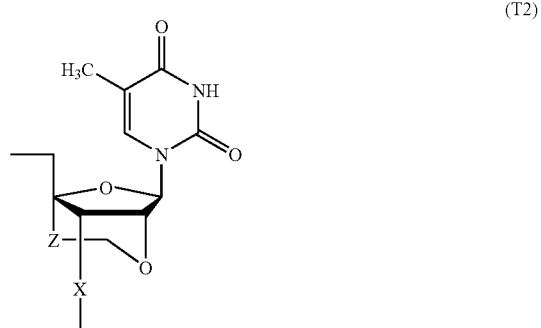
(A1)



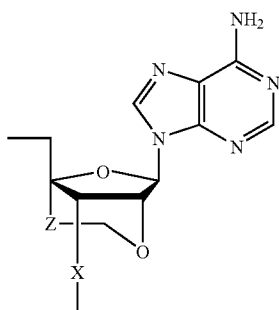
(U1)



(A2)



(T2)



(C1)

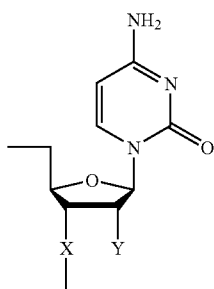
[0055] where X is individually and independently a group represented by the following formula (X1) or (X2):



(X1)



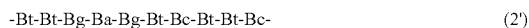
(X2)



[0056] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6

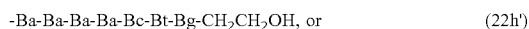
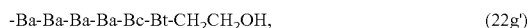
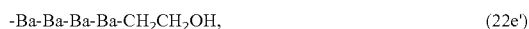
carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0057] B_{M2} is a group represented by the following formula (2'):



[0058] where Bg, Ba, Bt and Bc are as defined above;

[0059] B_{B2} is a group represented by any one of the following (22a') to (22i'):



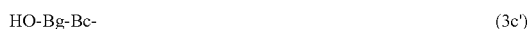
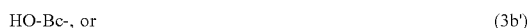
[0060] where Bg, Ba, Bt and Bc are as defined above;

[0061] provided that at least one of the nucleosides constituting the compound represented by formula (II') has 2'-O,4'-C-alkylene group.

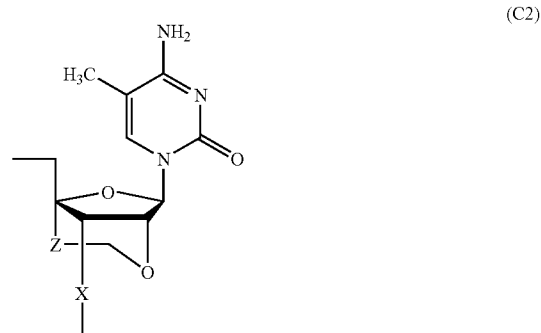
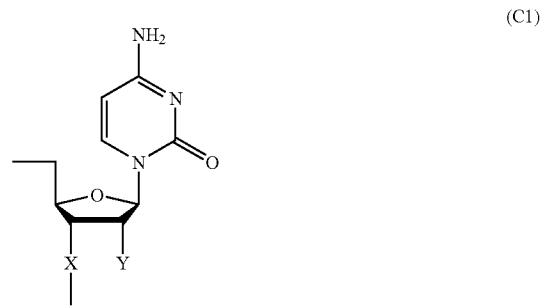
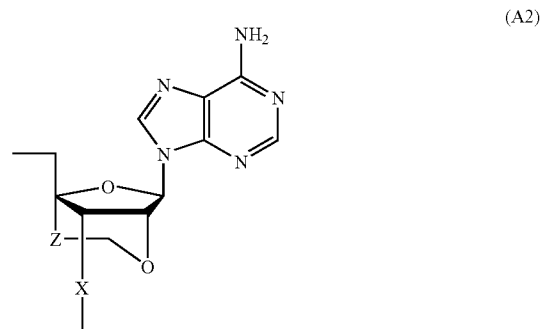
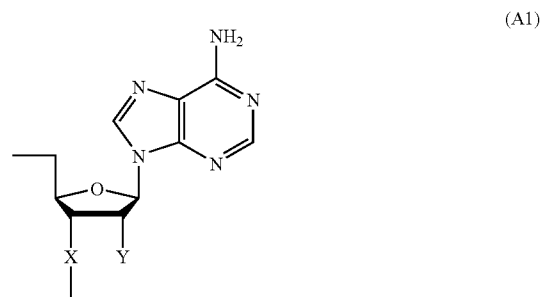
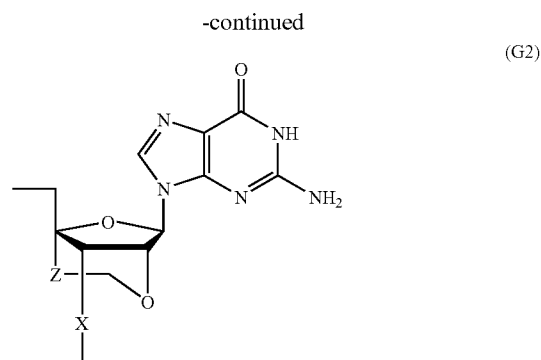
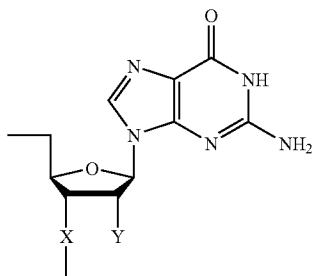
[0062] [15] A compound represented by the following general formula (III') or a pharmacologically acceptable salt thereof:



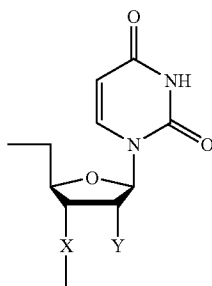
[0063] where B_{T3} is a group represented by any one of the following (3a') to (3c'):



[0064] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



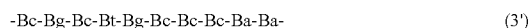
-continued



(U1)

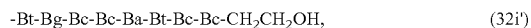
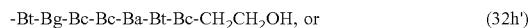
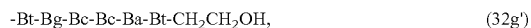
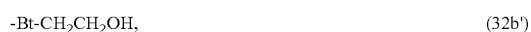
[0066] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0067] $B_{M'3}$ is a group represented by the following formula (3'):



[0068] where Bg, Ba, Bt and Bc are as described above;

[0069] $B_{B'3}$ is a group represented by any one of the following (32a') to (32i'):



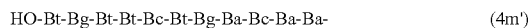
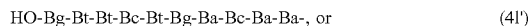
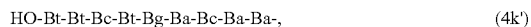
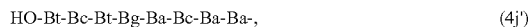
[0070] where Bg, Ba, Bt and Bc are as described above;

[0071] provided that at least one of the nucleosides constituting the compound represented by formula (III') has 2'-O,4'-C-alkylene group.

[0072] [16] A compound represented by the following general formula (IV') or a pharmacologically acceptable salt thereof:

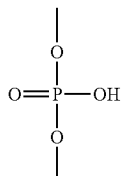


[0073] where $B_{T'4}$ is a group represented by any one of the following (4a') to (4m'):

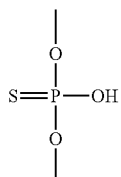


[0074] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

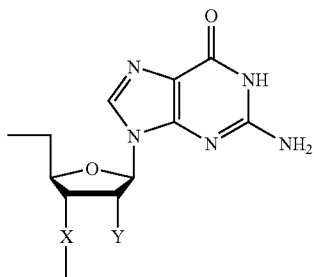
[0065] where X is individually and independently a group represented by the following formula (X1) or (X2):



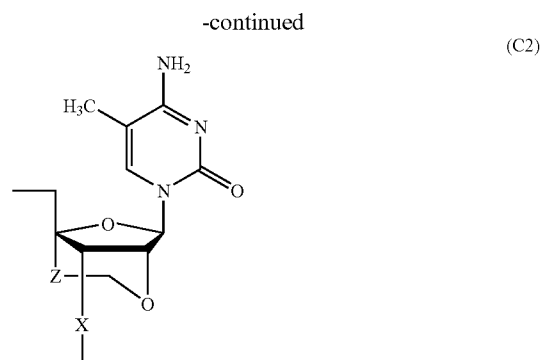
(X1)



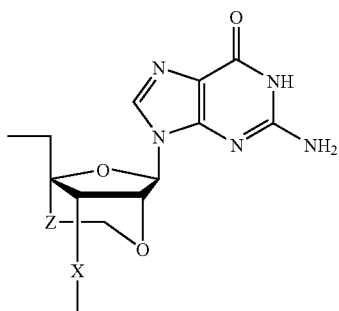
(X2)



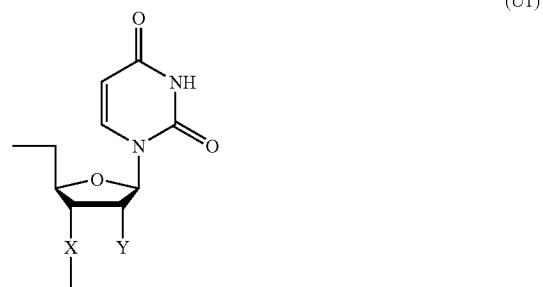
(G1)



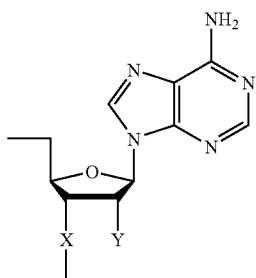
(C2)



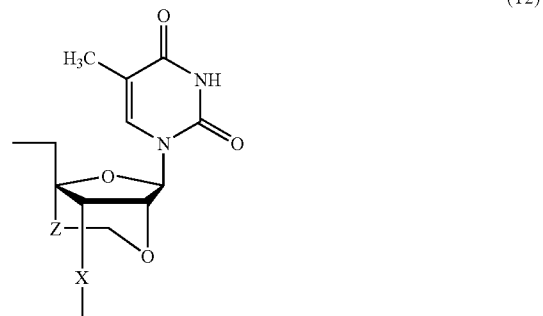
(G2)



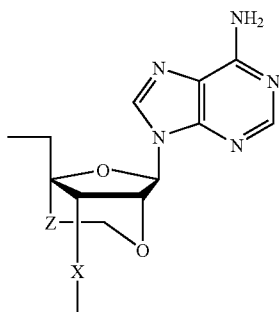
(U1)



(A1)



(T2)



(A2)

[0075] where X is individually and independently a group represented by the following formula (X1) or (X2):

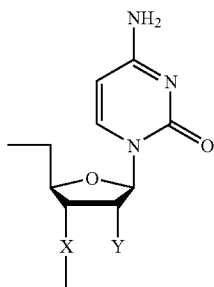


(X1)

(C1)



(X2)



[0076] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6

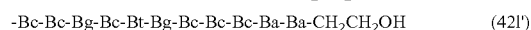
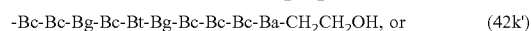
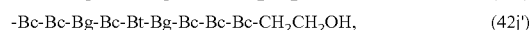
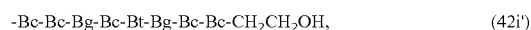
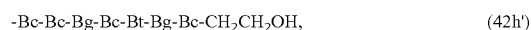
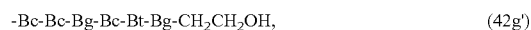
carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0077] B_{M^4} is a group represented by the following formula (4'):



[0078] where Bg, Ba, Bt and Bc are as described above;

[0079] B_{B^4} is a group represented by any one of the following (42a') to (42l'):



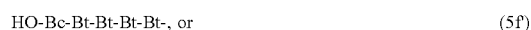
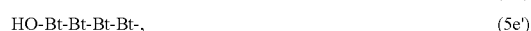
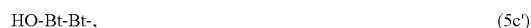
[0080] where Bg, Ba, Bt and Bc are as described above;

[0081] provided that at least one of the nucleosides constituting the compound represented by formula (IV') has 2'-O,4'-C-alkylene group.

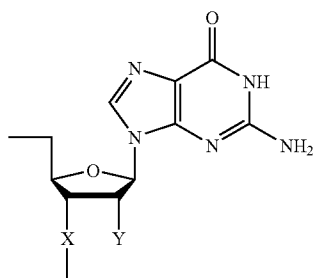
[0082] [17] A compound represented by the following general formula (V') or a pharmacologically acceptable salt thereof:



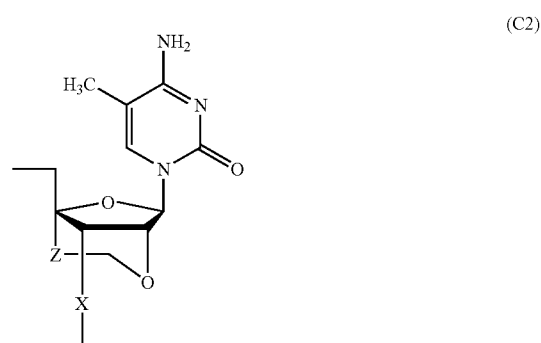
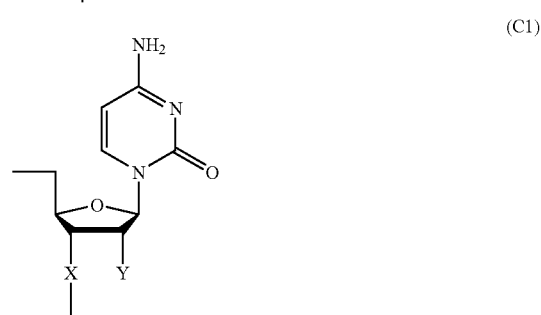
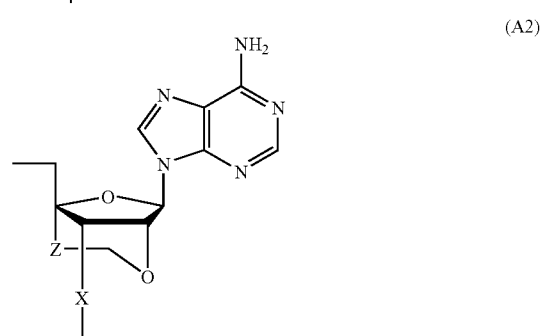
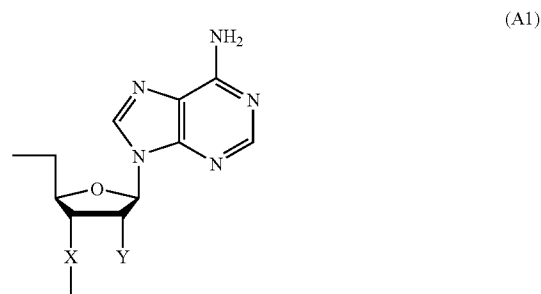
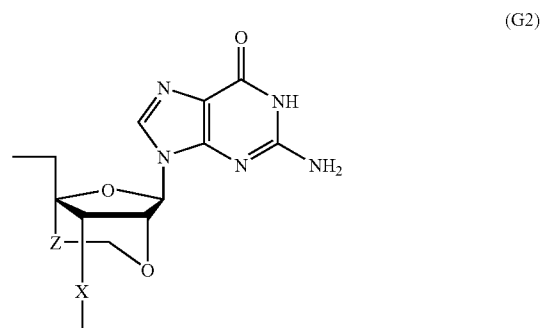
[0083] where B_{T^5} is a group represented by any one of the following (5a') to (5g'):



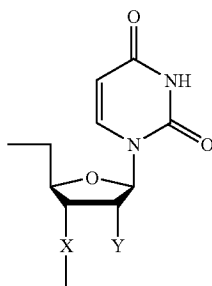
[0084] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



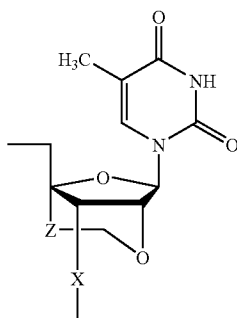
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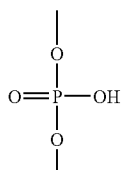


(U1)

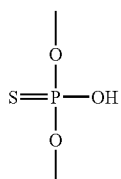


(T2)

[0085] where X is individually and independently a group represented by the following formula (X1) or (X2):



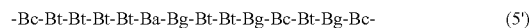
(X1)



(X2)

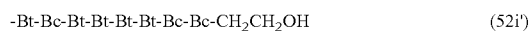
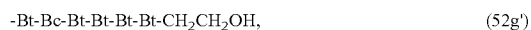
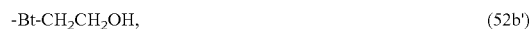
[0086] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0087] $B_{M'5}$ is a group represented by the following formula (5'):



[0088] where Bg, Ba, Bt and Bc are as described above;

[0089] $B_{B'5}$ is a group represented by any one of the following (52a') to (52i'):



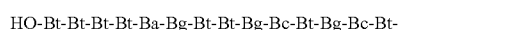
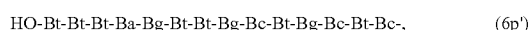
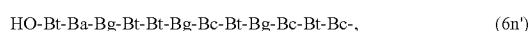
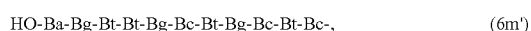
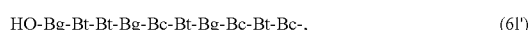
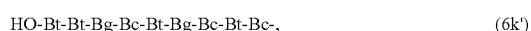
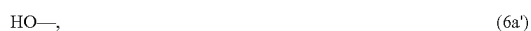
[0090] where Bg, Ba, Bt and Bc are as described above;

[0091] provided that at least one of the nucleosides constituting the compound represented by formula (V') has 2'-O,4'-C-alkylene group.

[0092] [18] A compound represented by the following general formula (VI') or a pharmacologically acceptable salt thereof:

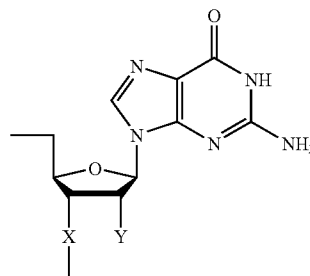


[0093] where $B_{T'6}$ is a group represented by any one of the following (6a') to (6r'):

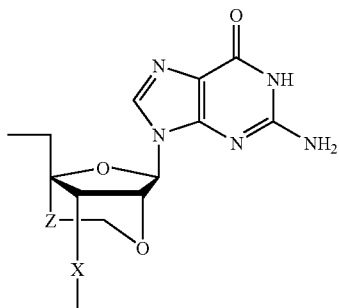


[0094] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

(G1)

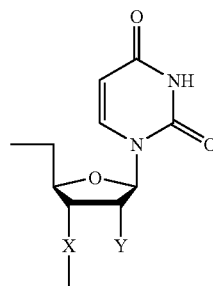


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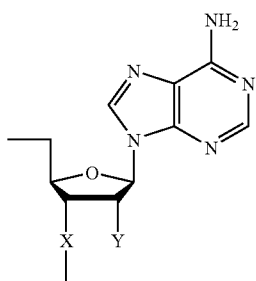


(G2)

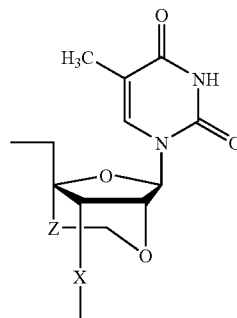
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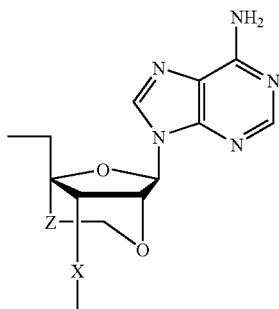
(U1)



(A1)

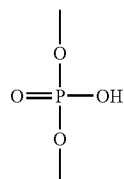


(T2)



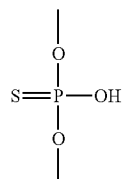
(A2)

[0095] where X is individually and independently a group represented by the following formula (X1) or (X2):



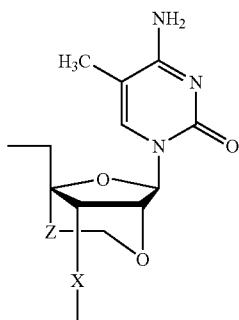
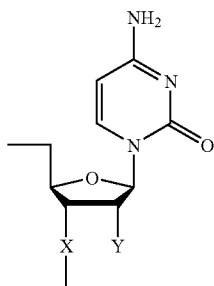
(X1)

(C1)



(X2)

(C2)



[0096] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0097] B_{M'6} is a group represented by the following formula (6'):



[0098] where Bg, Ba, Bt and Bc are as described above;

[0099] B_{B'6} is a group represented by any one of the following (62a') to (62m'):

- CH₂CH₂OH, (62a')
- Ba-CH₂CH₂OH, (62b')
- Ba-Bg-CH₂CH₂OH, (62c')
- Ba-Bg-Bg-CH₂CH₂OH, (62d')
- Ba-Bg-Bg-Bt-CH₂CH₂OH, (62e')
- Ba-Bg-Bg-Bt-Bt-CH₂CH₂OH, (62f')
- Ba-Bg-Bg-Bt-Bt-Bc-CH₂CH₂OH, (62g')
- Ba-Bg-Bg-Bt-Bt-Bc-Ba-CH₂CH₂OH, (62h')
- Ba-Bg-Bg-Bt-Bt-Bc-Ba-Ba-CH₂CH₂OH, (62i')
- Ba-Bg-Bg-Bt-Bt-Bc-Ba-Ba-Bg-CH₂CH₂OH, (62j')
- Ba-Bg-Bg-Bt-Bt-Bc-Ba-Ba-Bg-Bt-CH₂CH₂OH, (62k')
- Ba-Bg-Bg-Bt-Bt-Bc-Ba-Ba-Bg-Bt-Bg-CH₂CH₂OH, (62l')
- or
- Ba-Bg-Bg-Bt-Bt-Bc-Ba-Ba-Bg-Bt-Bg-CH₂CH₂OH (62m')

[0100] where Bg, Ba, Bt and Bc are as described above;

[0101] provided that at least one of the nucleosides constituting the compound represented by formula (VI') has 2'-O,4'-C-alkylene group.

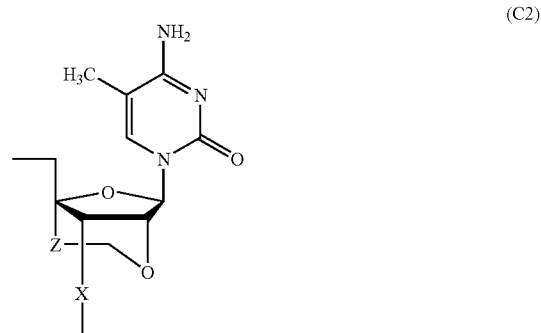
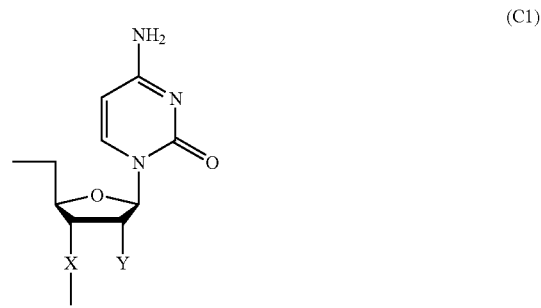
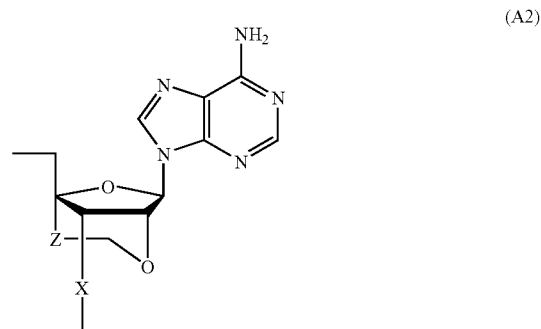
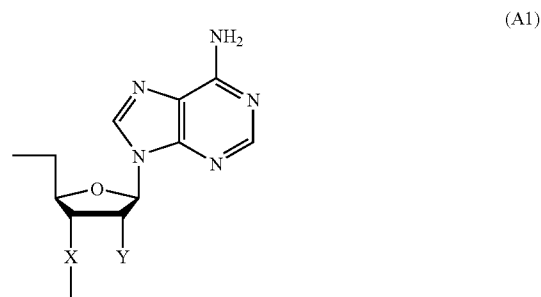
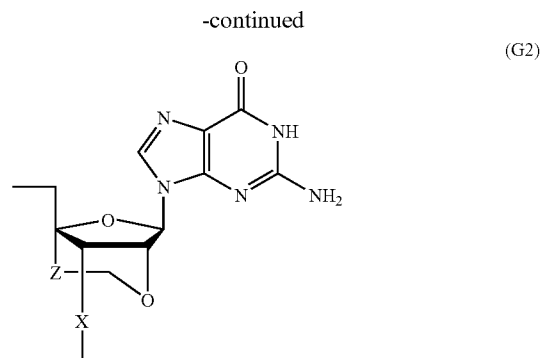
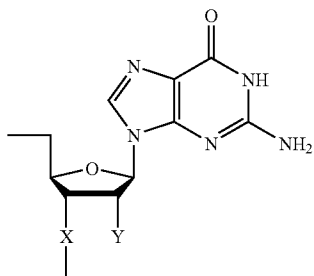
[0102] [19] A compound represented by the following general formula (VII') or a pharmacologically acceptable salt thereof:



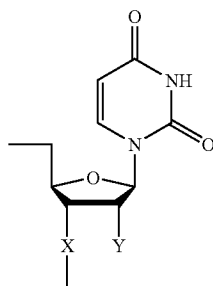
[0103] where B_{T7} is a group represented by any one of the following (7a') to (7f'):

- HO-, (7a')
- HO-Bt-, (7b')
- HO-Ba-Bt-, (7c')
- HO-Bt-Ba-Bt-, (7d')
- HO-Bt-Bt-Ba-Bt-, or (7e')
- HO-Bg-Bt-Bt-Ba-Bt- (7f')

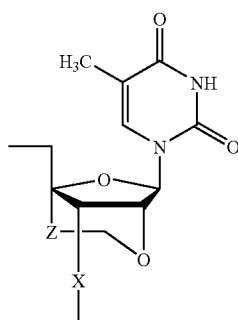
[0104] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



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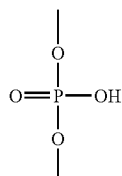


(U1)

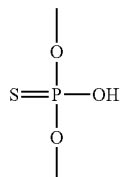


(T2)

[0105] where X is individually and independently a group represented by the following formula (X1) or (X2):



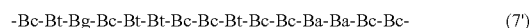
(X1)



(X2)

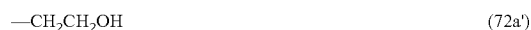
[0106] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0107] B_{M7} is a group represented by the following formula (7'):



[0108] where Bg, Ba, Bt and Bc are as described above;

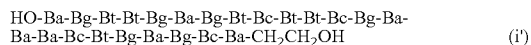
[0109] B_{B7} is a group represented by the following (72a'):



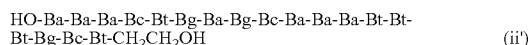
[0110] provided that at least one of the nucleosides constituting the compound represented by formula (VII') has 2'-O,4'-C-alkylene group.

[0111] [20] The compound of any one of [13] to [19] above which is selected from the group consisting of the following compounds (i') to (xiii'), or a pharmacologically acceptable salt thereof:

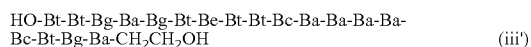
[0112] (i') a compound represented by the following formula (i'):



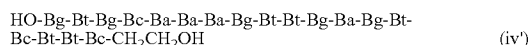
[0113] (ii') a compound represented by the following formula (ii'):



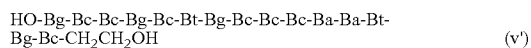
[0114] (iii') a compound represented by the following formula (iii'):



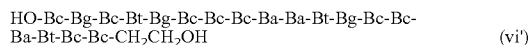
[0115] (iv') a compound represented by the following formula (iv'):



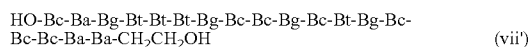
[0116] (v') a compound represented by the following formula (v'):



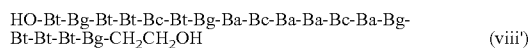
[0117] (vi') a compound represented by the following formula (vi'):



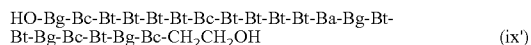
[0118] (vii') a compound represented by the following formula (vii'):



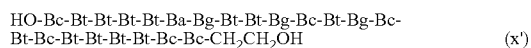
[0119] (viii') a compound represented by the following formula (viii'):



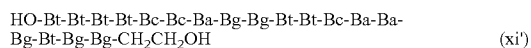
[0120] (ix') a compound represented by the following formula (ix'):



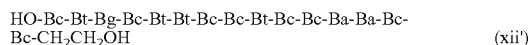
[0121] (x') a compound represented by the following formula (x'):



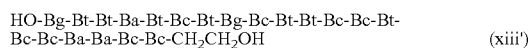
[0122] (xi') a compound represented by the following formula (xi'):



[0123] (xii') a compound represented by the following formula (xii'):

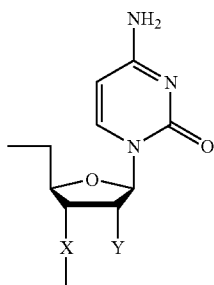
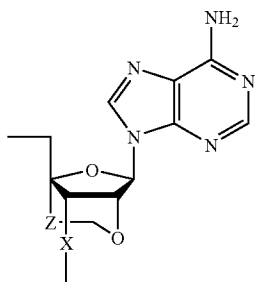
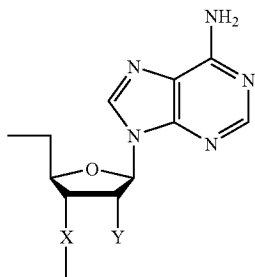
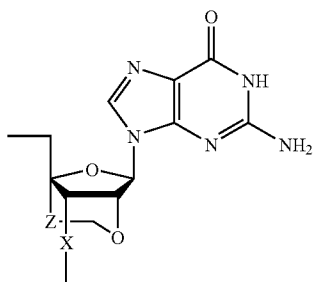
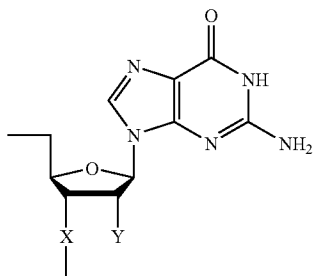


(xiii') a compound represented by the following formula (xiii'):

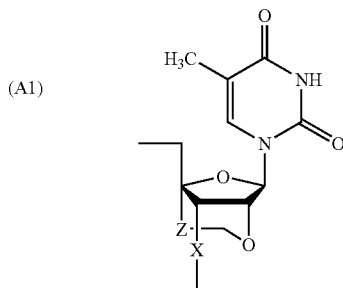
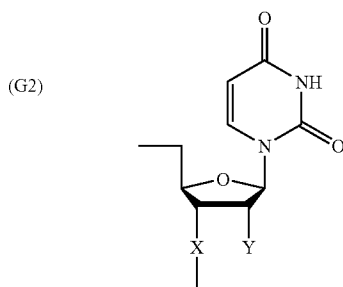
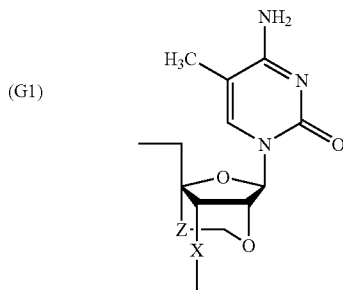


[0124] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the

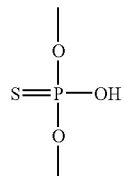
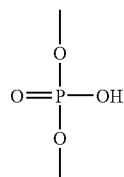
following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



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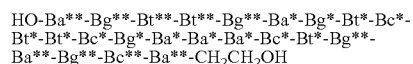


[0125] where X is individually and independently a group represented by the following formula (X1) or (X2):

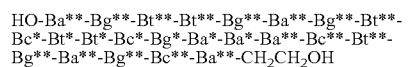


[0126] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms.

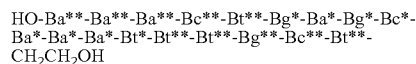
[0127] [21] The compound of any one of [13] to [20] above which is represented by any one of the following compounds (I'1) to (I'20), or a pharmacologically acceptable salt thereof:



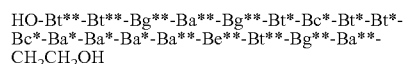
(I'1)



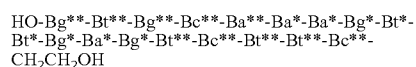
(I'2)



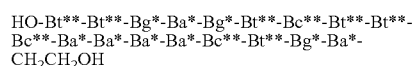
(I'3)



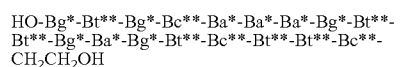
(I'4)



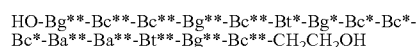
(I'5)



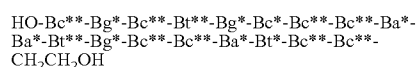
(I'6)



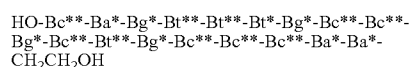
(I'7)



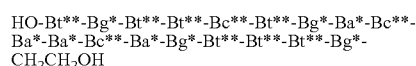
(I'8)



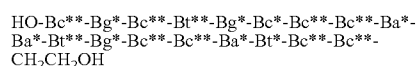
(I'9)



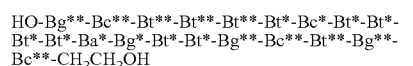
(I'10)



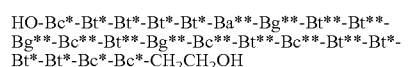
(I'11)



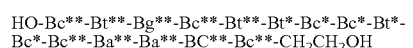
(I'12)



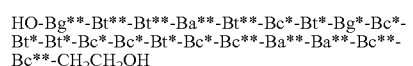
(I'13)



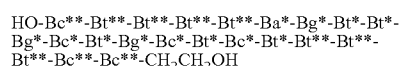
(I'14)



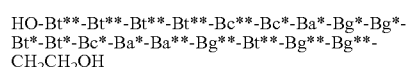
(I'15)



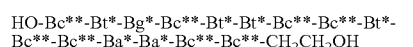
(I'16)



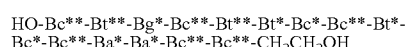
(I'17)



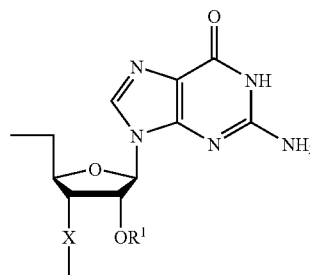
(I'18)



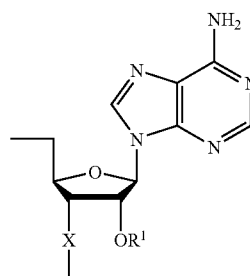
(I'19)



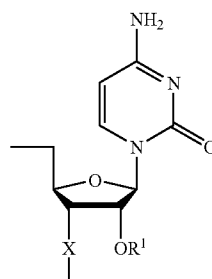
(I'20)



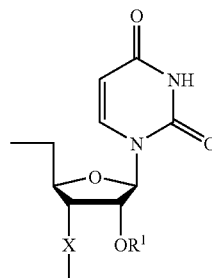
(G1^a)



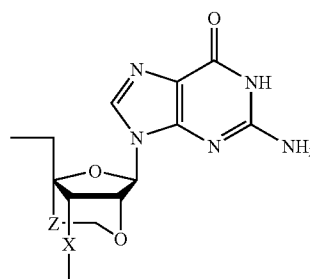
(A1^a)



(C1^a)



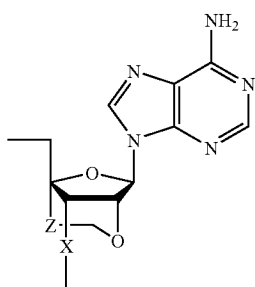
(U1^a)



(G2)

[0128] where Bg* is a group represented by the following formula (G1^a); Ba* is a group represented by the following formula (A1^a); Bc* is a group represented by the following formula (C1^a); Bt* is a group represented by the following formula (U1^a); Bg** is a group represented by the following formula (G2); Ba** is a group represented by the following formula (A2); Bc** is a group represented by the following formula (C2); and Bt** is a group represented by the following formula (T2):

-continued

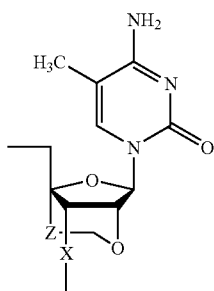


(A2)

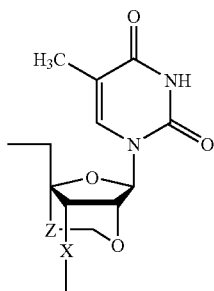
[0131] [22] The compound of [21] above where X in formulas (G1^a), (A1^a), (C1^a) and (U1^a) is a group represented by formula (X2) and X in formulas (G2), (A2), (C2) and (T2) is a group represented by formula (X1), or a pharmacologically acceptable salt thereof.

[0132] [23] The compound of [21] above where X in all the formulas (G1^a), (A1^a), (C1^a), (U1^a), (G2), (A2), (C2) and (T2) is a group represented by formula (X2), or a pharmacologically acceptable salt thereof.

[0133] [24] The compound of [21] above which is represented by any one of the following formulas (I'1-a) to (I'20-b), or a pharmacologically acceptable salt thereof:

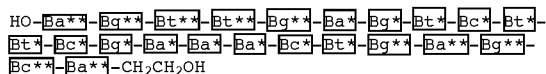


(C2)

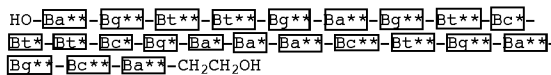


(T2)

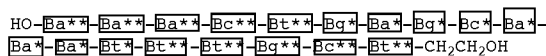
(I'1-a)



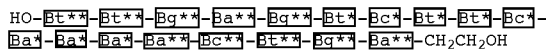
(I'2-a)



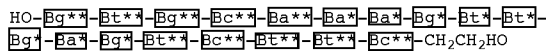
(I'3-a)



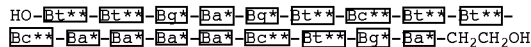
(I'4-a)



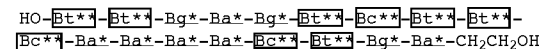
(I'5-a)



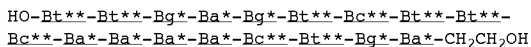
(I'6-a)



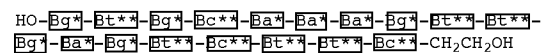
(I'6-b)



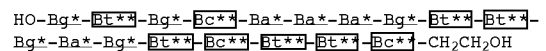
(I'6-c)



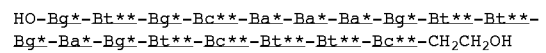
(I'7-a)



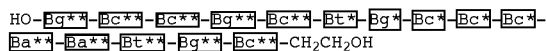
(I'7-b)



(I'7-c)



(I'8-a)

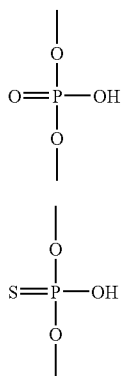


(I'9-a)



[0129] where X is individually and independently a group represented by the following formula (X1) or (X2); R¹ is individually and independently an alkyl group with 1-6 carbon atoms;

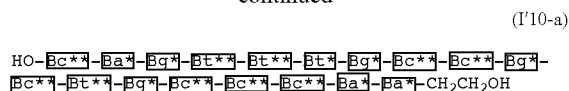
[0130] and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms:



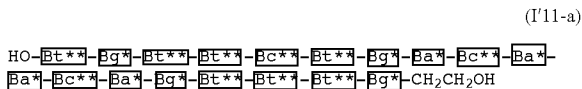
(X1)

(X2)

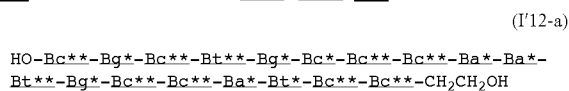
-continued



(I'10-a)



(I'11-a)



(I'12-a)

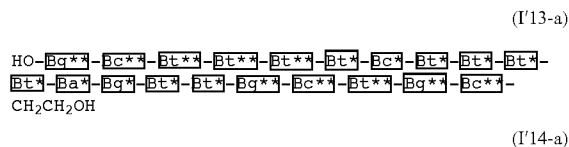
individual formulas, at least one of Bg^* , Ba^* , Bc^* , Bt^* , Bg^{**} , Ba^{**} , Bc^{**} and Bt^{**} has a group represented by formula (X2) as X and all of Bc^* , Bg^* , Ba^{**} , Bc^{**} and Bt^{**} have a group represented by (X1) as X.

[0135] [25] The compound of any one of [13] to [24] above where Y in formulas (G1), (A1), (C1) and (U1) is a methoxy group and Z in formulas (G2), (A2), (C2) and (T2) is an ethylene group, or a pharmacologically acceptable salt thereof.

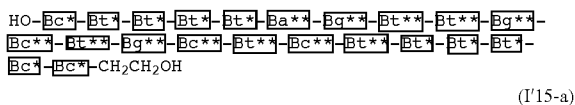
[0136] [26] A compound represented by the following general formula (I'') or a pharmacologically acceptable salt thereof:



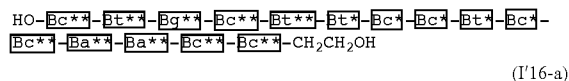
[0137] where B_{T-1} is a group represented by any one of the following (1a'') to (1m''):



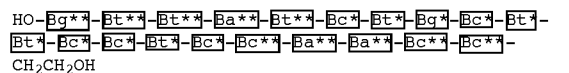
(I'14-a)



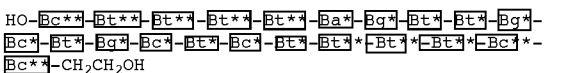
(I'15-a)



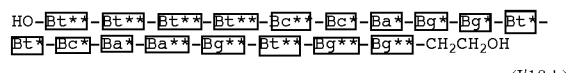
(I'16-a)



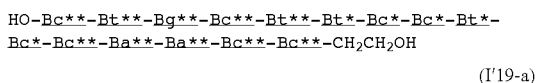
(I'17-a)



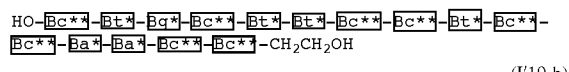
(I'18-a)



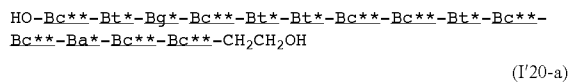
(I'18-b)



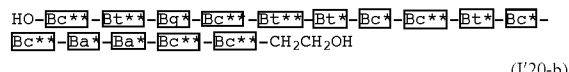
(I'19-a)



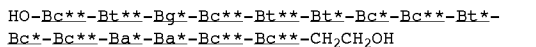
(I'19-b)



(I'20-a)



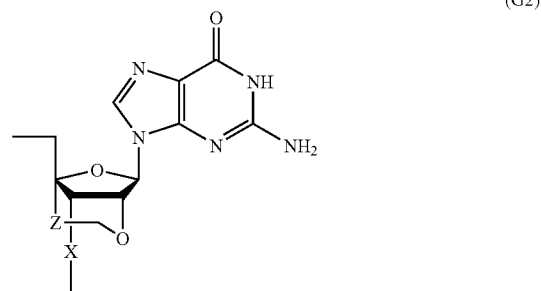
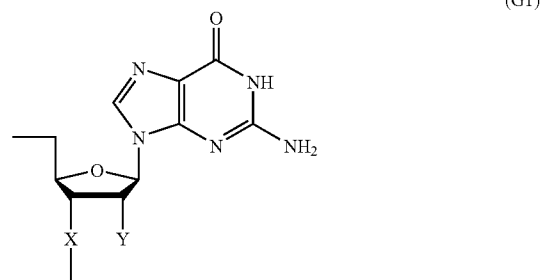
(I'20-b)



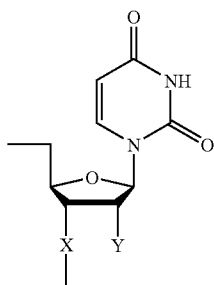
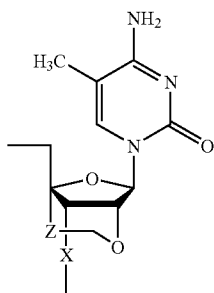
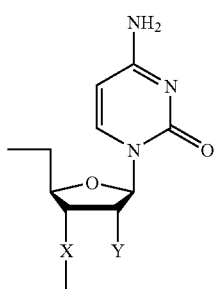
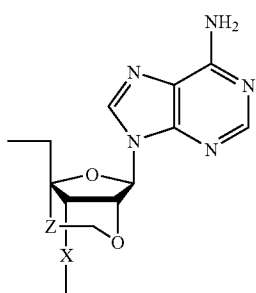
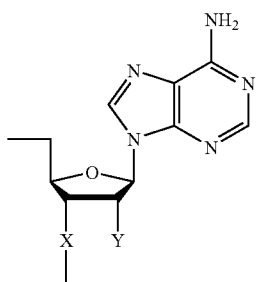
[0134] where Bg^* is a group represented by formula (G1^a), Ba^* is a group represented by formula (A1^a); Bc^* is a group represented by formula (C1^a); Bt^* is a group represented by formula (U1^a); Bg^{**} is a group represented by formula (G2); Ba^{**} is a group represented by formula (A2); Bc^{**} is a group represented by formula (C2); Bt^{**} is a group represented by formula (T2); and in

- HO—, (1a'')
- HO-Bt-, (1b'')
- HO-Bt-Bt-, (1c'')
- HO-Bt-Bt-Bt-, (1d'')
- HO-Ba-Bt-Bt-Bt-, (1e'')
- HO-Bt-Ba-Bt-Bt-Bt-, (1f'')
- HO-Bg-Bt-Ba-Bt-Bt-Bt-, (1g'')
- HO-Bt-Bg-Bt-Ba-Bt-Bt-Bt-, (1h'')
- HO-Bt-Bt-Bg-Bt-Ba-Bt-Bt-Bt-, (1i'')
- HO-Bt-Bt-Bt-Bg-Bt-Ba-Bt-Bt-Bt-, (1j'')
- HO-Ba-Bt-Bt-Bt-Bg-Bt-Ba-Bt-Bt-Bt-, (1k'')
- HO-Bc-Ba-Bt-Bt-Bt-Bg-Bt-Ba-Bt-Bt-Bt-, or (1l'')
- HO-Bc-Bc-Ba-Bt-Bt-Bt-Bg-Bt-Ba-Bt-Bt-Bt-, (1m'')

[0138] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

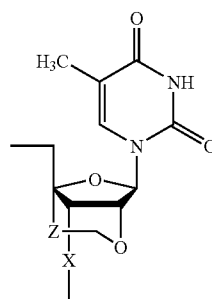


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-continued

(A1)

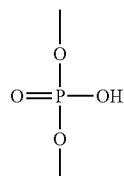


(T2)

(A2)

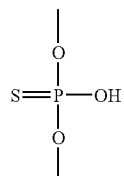
[0139] where X is individually and independently a group represented by the following formula (X1) or (X2):

(X1)



(C1)

(X2)



(C2)

[0140] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0141] B_{M''1} is a group represented by the following formula (1''):

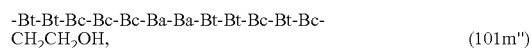
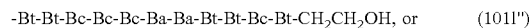


[0142] where Bg, Ba, Bt and Bc are as defined above;

[0143] B_{B''1} is a group represented by any one of the following (101a'') to (101k''):

(U1)

- CH₂CH₂OH, (101a'')
- Bt-CH₂CH₂OH, (101b'')
- Bt-Bt-CH₂CH₂OH, (101c'')
- Bt-Bt-Bc-CH₂CH₂OH, (101d'')
- Bt-Bt-Bc-Bc-CH₂CH₂OH, (101e'')
- Bt-Bt-Bc-Bc-Bc-CH₂CH₂OH, (101f'')
- Bt-Bt-Bc-Bc-Bc-Ba-CH₂CH₂OH, (101g'')
- Bt-Bt-Bc-Bc-Bc-Ba-Ba-CH₂CH₂OH, (101h'')
- Bt-Bt-Bc-Bc-Bc-Ba-Ba-Bt-CH₂CH₂OH, (101i'')
- Bt-Bt-Bc-Bc-Bc-Ba-Ba-Bt-Bt-CH₂CH₂OH, (101j'')
- Bt-Bt-Bc-Bc-Bc-Ba-Ba-Bt-Bt-Bc-CH₂CH₂OH, (101k'')



[0144] where Bg, Ba, Bt and Bc are as defined above;

[0145] provided that at least one of the nucleosides constituting the compound represented by formula (I'') has 2''-O,4''-C-alkylene group.

[0146] [27] A compound represented by the following general formula (II'') or a pharmacologically acceptable salt thereof:

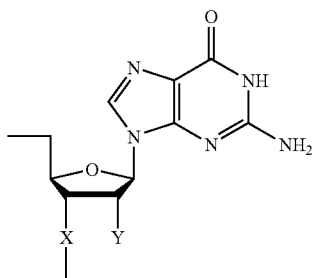


[0147] where B_{T''2} is a group represented by any one of the following (2a'') to (2g''):

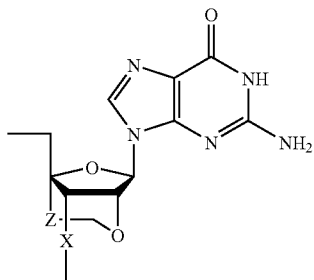


[0148] where Bg is a group represented by the following formula (G1) or (G2);

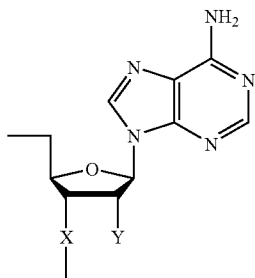
[0149] Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



(G1)

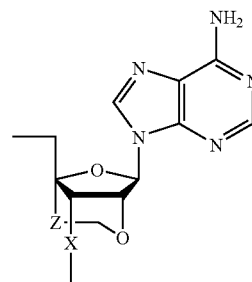


(G2)

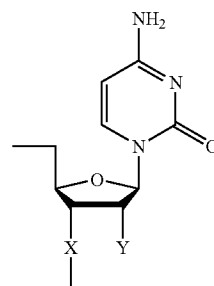


(A1)

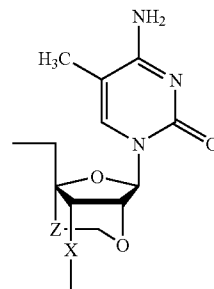
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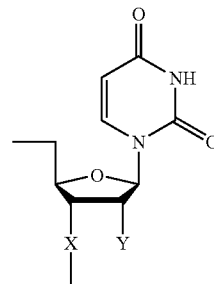
(A2)



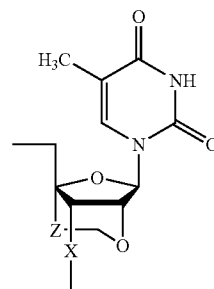
(C1)



(C2)



(U1)



(T2)

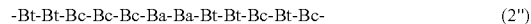
[0150] where X is individually and independently a group represented by the following formula (X1) or (X2):



[0151] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and

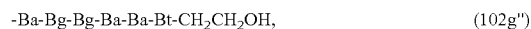
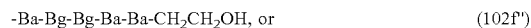
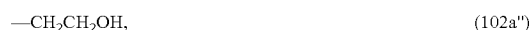
[0152] Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0153] $B_{M''2}$ is a group represented by the following formula (2''):



[0154] where Bg, Ba, Bt and Bc are as defined above;

[0155] $B_{B''2}$ is a group represented by any one of the following (102a'') to (102g''):



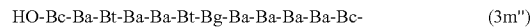
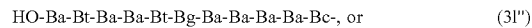
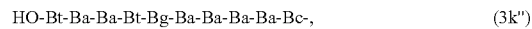
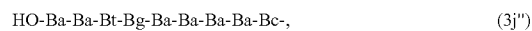
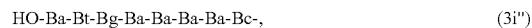
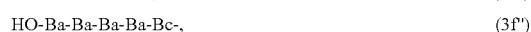
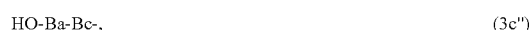
[0156] where Bg, Ba, Bt and Bc are as defined above;

[0157] provided that at least one of the nucleosides constituting the compound represented by formula (II'') has 2''-O,4''-C-alkylene group.

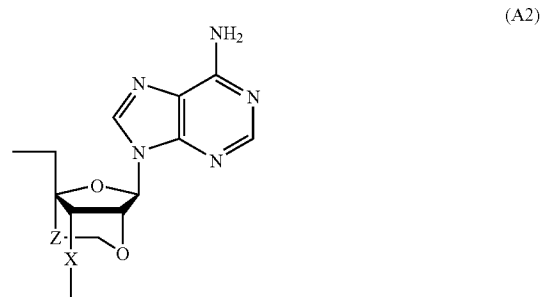
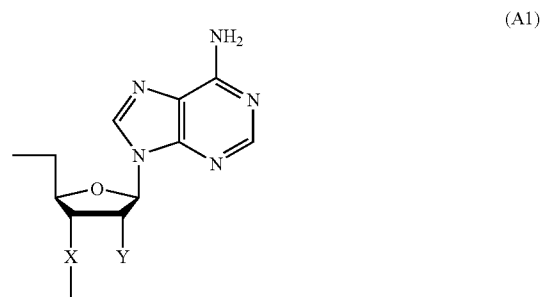
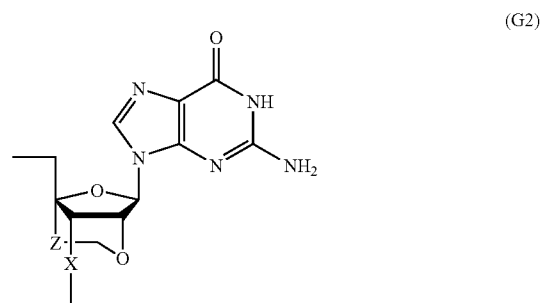
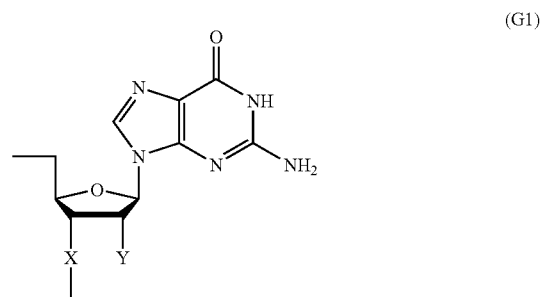
[0158] [28] A compound represented by the following general formula (III'') or a pharmacologically acceptable salt thereof:



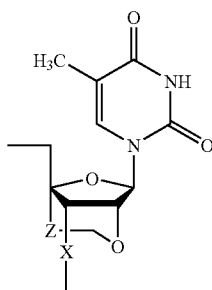
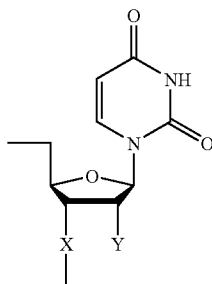
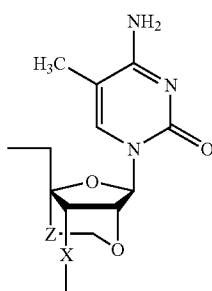
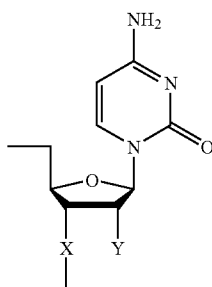
[0159] where $B_{T''3}$ is a group represented by any one of the following (3a'') to (3m''):



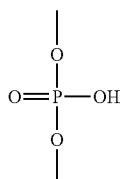
[0160] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



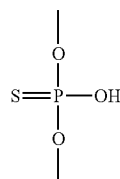
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[0161] where X is individually and independently a group represented by the following formula (X1) or (X2):



(C1) -continued



(X2)

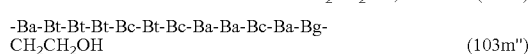
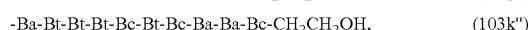
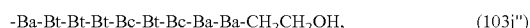
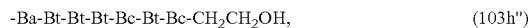
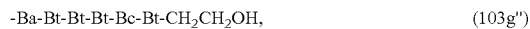
[0162] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0163] $B_{M''3}$ is a group represented by the following formula (3''):



[0164] where Bg, Ba, Bt and Bc are as defined above;

[0165] $B_{B''3}$ is a group represented by any one of the following (103a'') to (103m''):



(U1)

(T2)

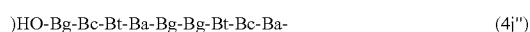
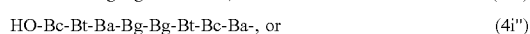
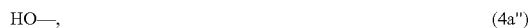
[0166] where Bg, Ba, Bt and Bc are as defined above;

[0167] provided that at least one of the nucleosides constituting the compound represented by formula (III'') has 2''-O,4''-C-alkylene group.

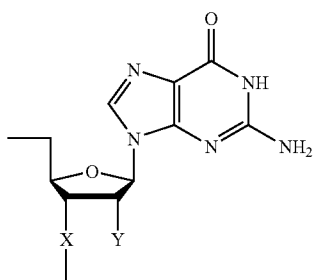
[0168] [29] A compound represented by the following general formula (IV'') or a pharmacologically acceptable salt thereof:



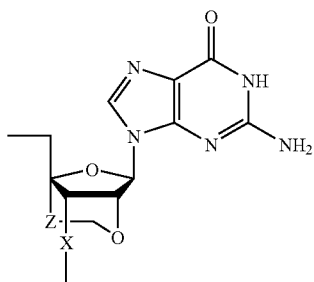
where $B_{T''4}$ is a group represented by any one of the following (4a'') to (4j''):



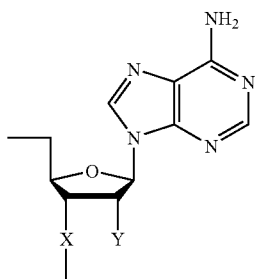
[0169] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



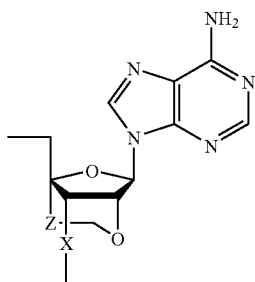
(G1)



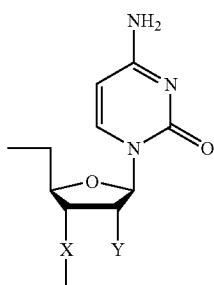
(G2)



(A1)

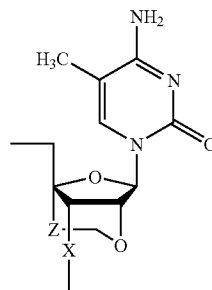


(A2)

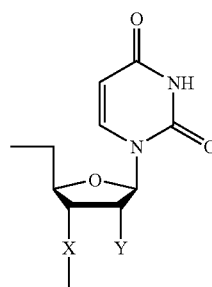


(C1)

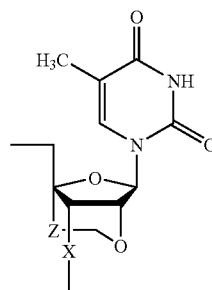
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(C2)

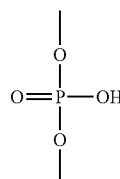


(U1)

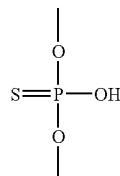


(T2)

[0170] where X is individually and independently a group represented by the following formula (X1) or (X2):



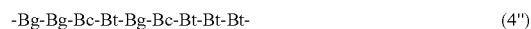
(X1)



(X2)

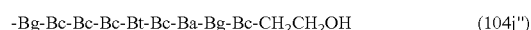
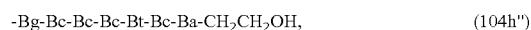
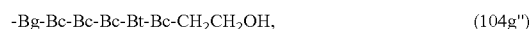
[0171] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0172] $B_{M''4}$ is a group represented by the following formula (4''):



[0173] where Bg, Ba, Bt and Bc are as defined above;

[0174] $B_{B''4}$ is a group represented by any one of the following (104a'') to (104j''):



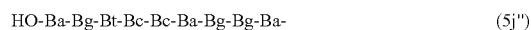
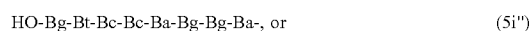
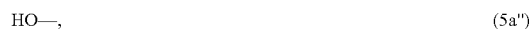
[0175] where Bg, Ba, Bt and Bc are as defined above;

[0176] provided that at least one of the nucleosides constituting the compound represented by formula (IV'') has 2''-O,4''-C-alkylene group.

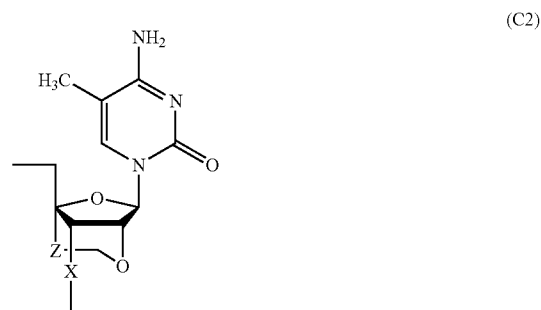
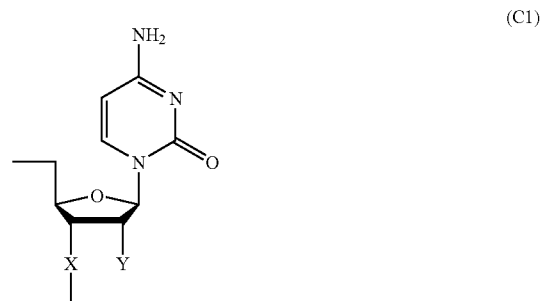
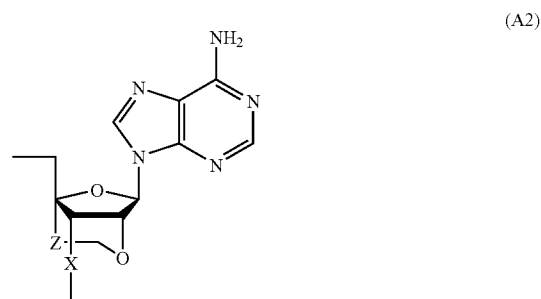
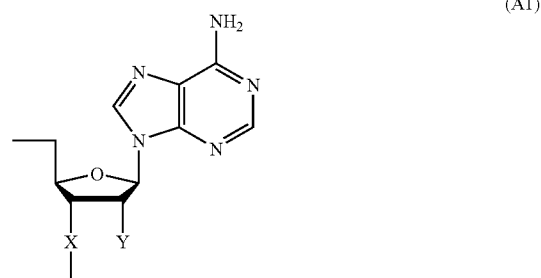
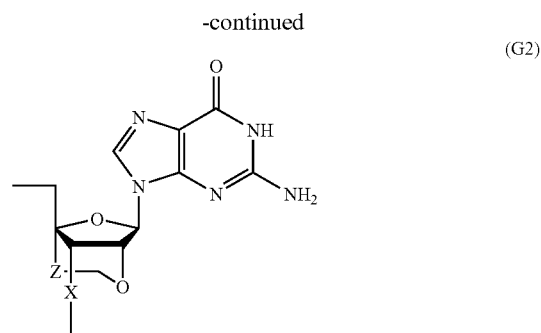
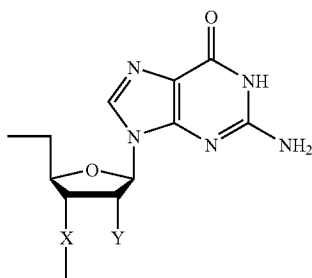
[0177] [30] A compound represented by the following general formula (V'') or a pharmacologically acceptable salt thereof:



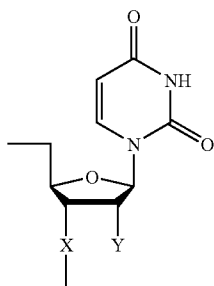
[0178] where $B_{T''5}$ is a group represented by any one of the following (5a'') to (5j''):



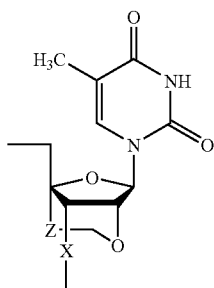
[0179] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



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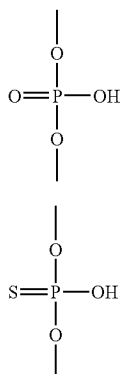


(U1)



(T2)

[0180] where X is individually and independently a group represented by the following formula (X1) or (X2):

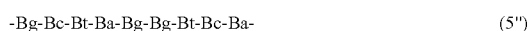


(X1)

(X2)

[0181] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0182] B_{M''5} is a group represented by the following formula (5''):



[0183] where Bg, Ba, Bt and Bc are as defined above;

[0184] B_{B''5} is a group represented by any one of the following (105a'') to (105j''):

- CH₂CH₂OH, (105a'')
- Bg-CH₂CH₂OH, (105b'')
- Bg-Bg-CH₂CH₂OH, (105c'')
- Bg-Bg-Bc-CH₂CH₂OH, (105d'')

- Bg-Bg-Bc-Bt-CH₂CH₂OH, (105e'')
- Bg-Bg-Bc-Bt-Bg-CH₂CH₂OH, (105f'')
- Bg-Bg-Bc-Bt-Bg-Bc-CH₂CH₂OH, (105g'')
- Bg-Bg-Bc-Bt-Bg-Bc-Bt-CH₂CH₂OH, (105h'')
- Bg-Bg-Bc-Bt-Bg-Bc-Bt-Bt-CH₂CH₂OH, or (105i'')
- Bg-Bg-Bc-Bt-Bg-Bc-Bt-Bt-Bt-CH₂CH₂OH (105j'')

[0185] where Bg, Ba, Bt and Bc are as defined above;

[0186] provided that at least one of the nucleosides constituting the compound represented by formula (V'') has 2''-O,4''-C-alkylene group.

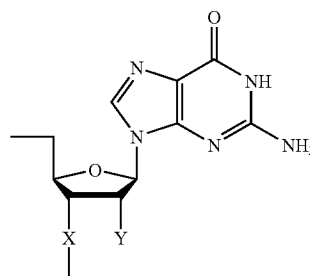
[0187] [31] A compound represented by the following general formula (VI'') or a pharmacologically acceptable salt thereof:



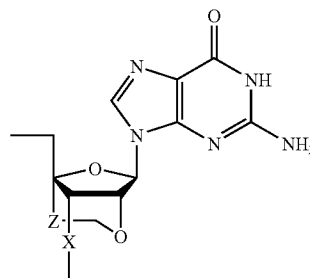
[0188] where B_{T''6} is a group represented by any one of the following (6a'') to (6j''):

- HO-, (6a'')
- HO-Ba-, (6b'')
- HO-Ba-Ba-, (6c'')
- HO-Ba-Ba-Ba-, (6d'')
- HO-Bc-Ba-Ba-Ba-, (6e'')
- HO-Bc-Bc-Ba-Ba-Ba-, (6f'')
- HO-Bt-Bc-Bc-Ba-Ba-Ba-, (6g'')
- HO-Bt-Bt-Bc-Bc-Ba-Ba-Ba-, (6h'')
- HO-Bc-Bt-Bt-Bc-Bc-Ba-Ba-Ba-, or (6i'')
- HO-Bt-Bc-Bt-Bt-Bc-Bc-Ba-Ba-Ba- (6j'')

[0189] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

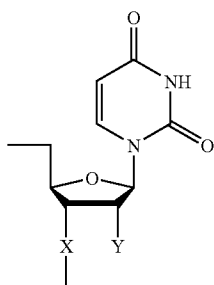
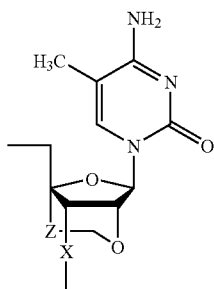
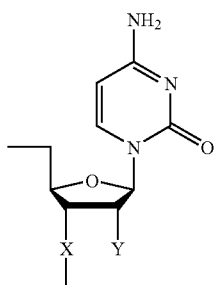
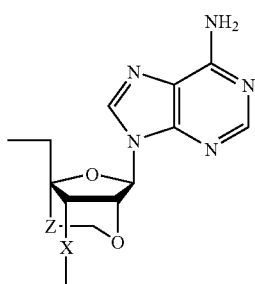
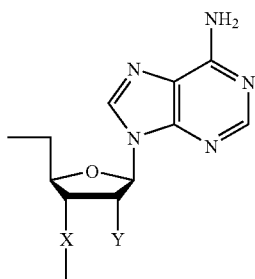


(G1)



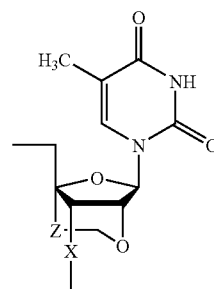
(G2)

-continued



-continued

(A1)

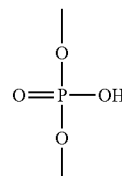


(T2)

(A2)

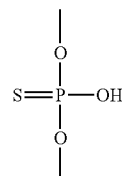
[0190] where X is individually and independently a group represented by the following formula (X1) or (X2):

(X1)



(X2)

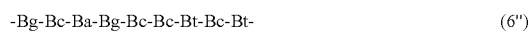
(C1)



[0191] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

(C2)

[0192] $B_{M''6}$ is a group represented by the following formula (6''):

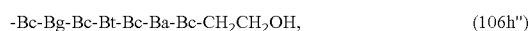
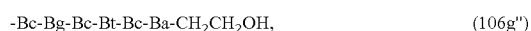


[0193] where Bg, Ba, Bt and Bc are as defined above;

[0194] $B_{B''6}$ is a group represented by any one of the following (106a'') to (106j''):



(U1)



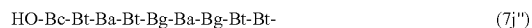
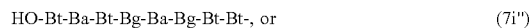
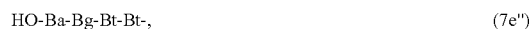
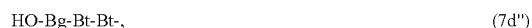
[0195] where Bg, Ba, Bt and Bc are as defined above;

[0196] provided that at least one of the nucleosides constituting the compound represented by formula (VI'') has 2''-O,4''-C-alkylene group.

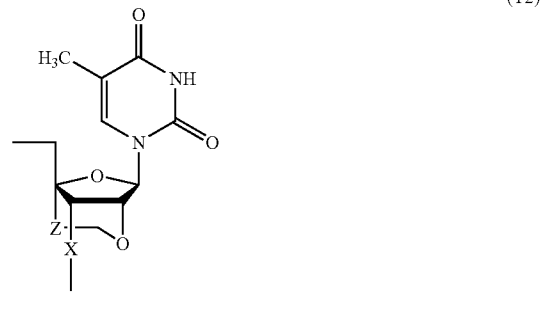
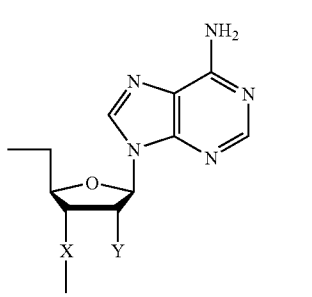
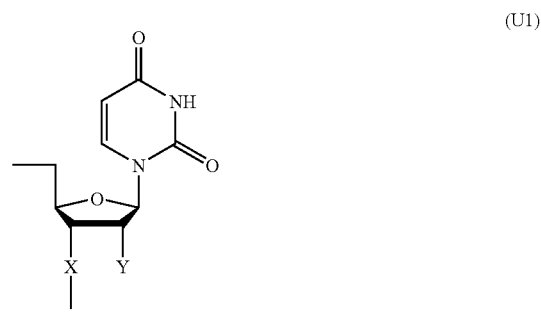
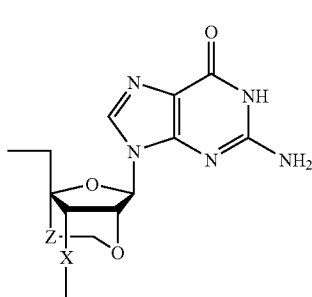
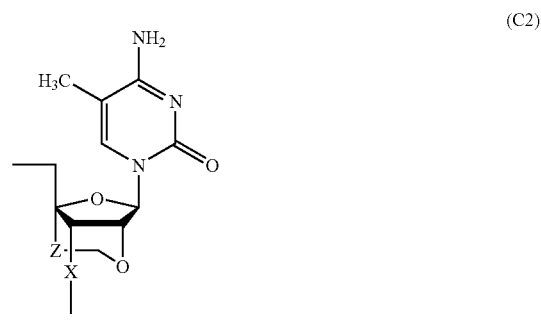
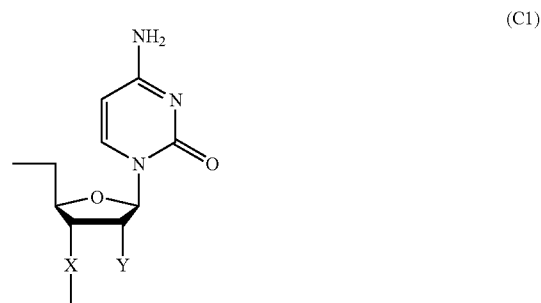
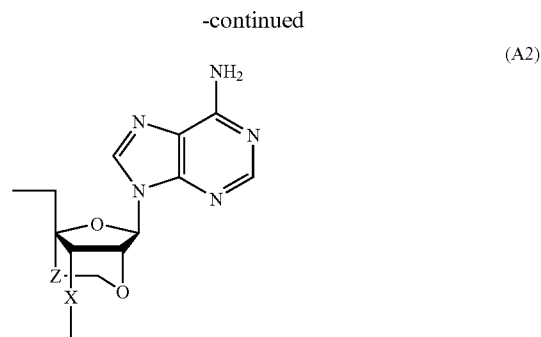
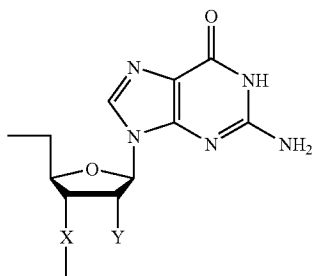
[0197] [32] A compound represented by the following general formula (VII^h) or a pharmacologically acceptable salt thereof:



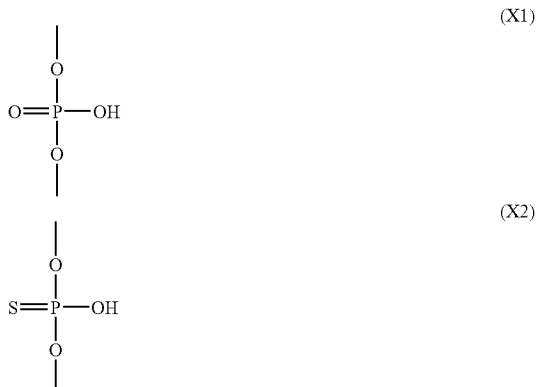
[0198] where $B_{T^{n7}}$ is a group represented by any one of the following (7a^h) to (7j^h):



[0199] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

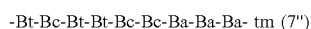


[0200] where X is individually and independently a group represented by the following formula (X1) or (X2):



[0201] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0202] B_{Mⁿ7} is a group represented by the following formula (7ⁿ):



[0203] where Bg, Ba, Bt and Bc are as defined above;

[0204] B_{Bⁿ7} is a group represented by any one of the following (107aⁿ) to (107jⁿ):

- CH₂CH₂OH, (107aⁿ)
- Bg-CH₂CH₂OH, (107bⁿ)
- Bg-Bc-CH₂CH₂OH, (107cⁿ)
- Bg-Bc-Ba-CH₂CH₂OH, (107dⁿ)
- Bg-Bc-Ba-Bg-CH₂CH₂OH, (107eⁿ)
- Bg-Bc-Ba-Bg-Bc-CH₂CH₂OH, (107fⁿ)
- Bg-Bc-Ba-Bg-Bc-Bc-CH₂CH₂OH, (107gⁿ)
- Bg-Bc-Ba-Bg-Bc-Bc-Bt-CH₂CH₂OH, (107hⁿ)
- Bg-Bc-Ba-Bg-Bc-Bc-Bt-Bc-CH₂CH₂OH, or (107iⁿ)
- Bg-Bc-Ba-Bg-Bc-Bc-Bt-Bc-Bt-CH₂CH₂OH (107jⁿ)

[0205] where Bg, Ba, Bt and Bc are as defined above;

[0206] provided that at least one of the nucleosides constituting the compound represented by formula (VIIⁿ) has 2ⁿ-O,4ⁿ-C-alkylene group.

[0207] [33] A compound represented by the following general formula (VIIIⁿ) or a pharmacologically acceptable salt thereof:

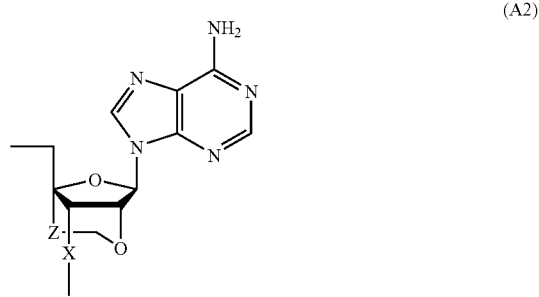
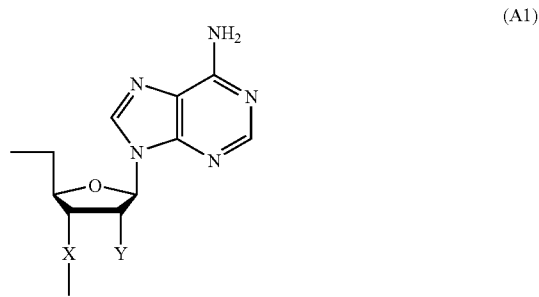
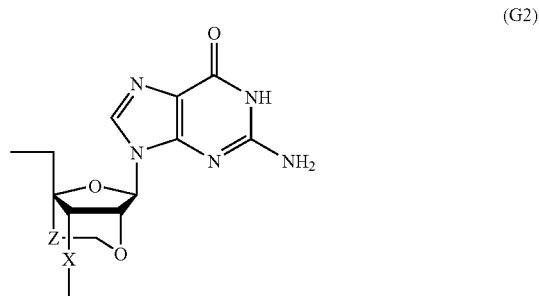
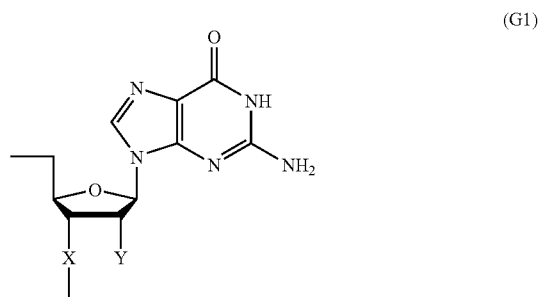


[0208] where B_{Tⁿ8} is a group represented by any one of the following (8aⁿ) to (8nⁿ):

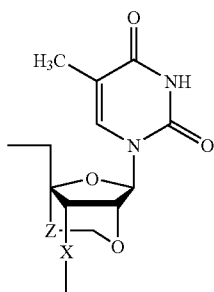
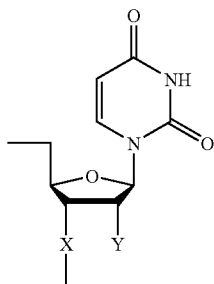
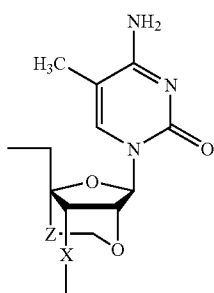
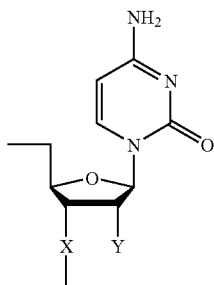
- HO-, (8aⁿ)
- HO-Bc-, (8bⁿ)
- HO-Bt-Bc-, (8cⁿ)
- HO-Ba-Bt-Bc-, (8dⁿ)
- HO-Bc-Ba-Bt-Bc-, (8eⁿ)
- HO-Bt-Bc-Ba-Bt-Bc-, (8fⁿ)

- HO-Bt-Bt-Bc-Ba-Bt-Bc-, (8gⁿ)
- HO-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8hⁿ)
- HO-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8iⁿ)
- HO-Bt-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8jⁿ)
- HO-Bt-Bt-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8kⁿ)
- HO-Ba-Bt-Bt-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8lⁿ)
- HO-Bc-Ba-Bt-Bt-Bg-Bt-Bt-Bc-Ba-Bt-Bc-, or (8mⁿ)
- HO-Bc-Bc-Ba-Bt-Bt-Bg-Bt-Bt-Bc-Ba-Bt-Bc- (8nⁿ)

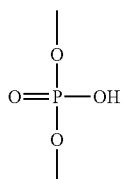
[0209] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



-continued



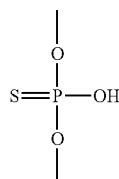
[0210] where X is individually and independently a group represented by the following formula (X1) or (X2):



(X1)

-continued

(C1)



(X2)

[0211] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

(C2)

[0212] B_{M''8} is a group represented by the following formula (8''):



[0213] where Bg, Ba, Bt and Bc are as defined above;

[0214] B_{B''8} is a group represented by any one of the following (108a'') to (108n''):

- CH₂CH₂OH, (108a'')
- Bt-CH₂CH₂OH, (108b'')
- Bt-Bt-CH₂CH₂OH, (108c'')
- Bt-Bt-Bt-CH₂CH₂OH, (108d'')
- Bt-Bt-Bt-Bt-CH₂CH₂OH, (108e'')
- Bt-Bt-Bt-Bt-Ba-CH₂CH₂OH, (108f'')
- Bt-Bt-Bt-Bt-Ba-Bc-CH₂CH₂OH, (108g'')
- Bt-Bt-Bt-Bt-Ba-Bc-Bt-CH₂CH₂OH, (108h'')
- Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-CH₂CH₂OH, (108i'')
- Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-CH₂CH₂OH, (108j'')
- Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-Bc-CH₂CH₂OH, (108k'')
- Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-Bc-Bt-CH₂CH₂OH, (108l'')
- Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-Bc-Bt-Bt-CH₂CH₂OH, (108m'')
- or
- Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-Bc-Bt-Bt-Bg-CH₂CH₂OH (108n'')

(U1)

(T2)

[0215] where Bg, Ba, Bt and Bc are as defined above;

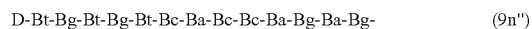
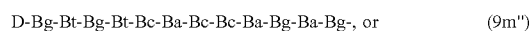
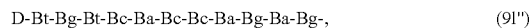
[0216] provided that at least one of the nucleosides constituting the compound represented by formula (VIII'') has 2''-O,4''-C-alkylene group.

[0217] [34] A compound represented by the following general formula (IX'') or a pharmacologically acceptable salt thereof:

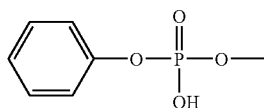


[0218] where B_{T''9} is a group represented by any one of the following (9a'') to (9n''):

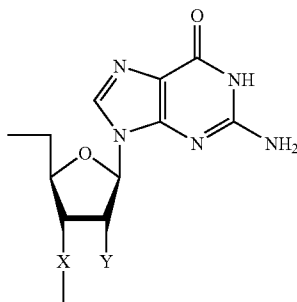
- D-, (9a'')
- D-Bg-, (9b'')
- D-Ba-Bg-, (9c'')
- D-Bg-Ba-Bg-, (9d'')
- D-Ba-Bg-Ba-Bg-, (9e'')
- D-Bc-Ba-Bg-Ba-Bg-, (9f'')
- D-Bc-Bc-Ba-Bg-Ba-Bg-, (9g'')
- D-Ba-Bc-Bc-Ba-Bg-Ba-Bg-, (9h'')
- D-Bc-Ba-Bc-Bc-Ba-Bg-Ba-Bg-, (9i'')
- D-Bt-Bc-Ba-Bc-Bc-Ba-Bg-Ba-Bg-, (9j'')
- D-Bg-Bt-Bc-Ba-Bc-Bc-Ba-Bg-Ba-Bg-, (9k'')



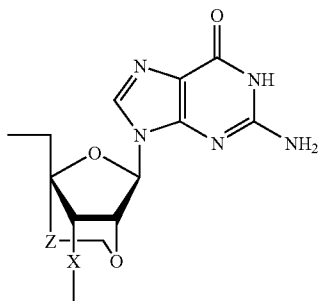
[0219] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); Bt is a group represented by the following formula (U1) or (T2); and D is HO— or Ph- wherein Ph- is a group represented by the following first formula:



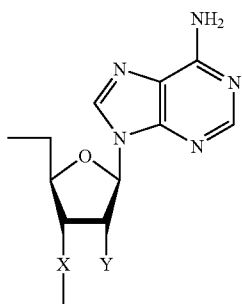
(G1)



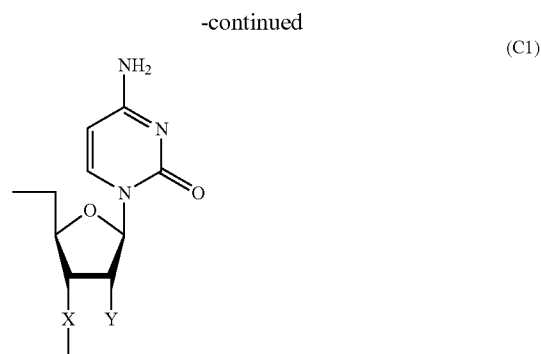
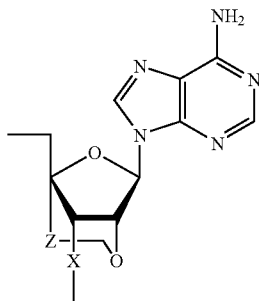
(G2)



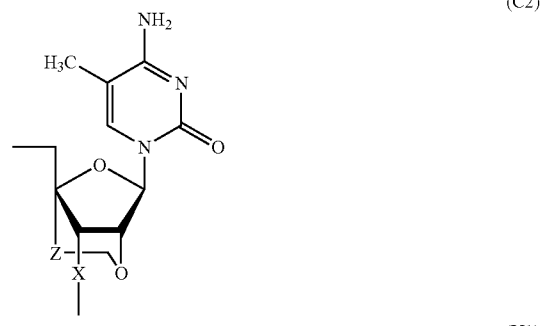
(A1)



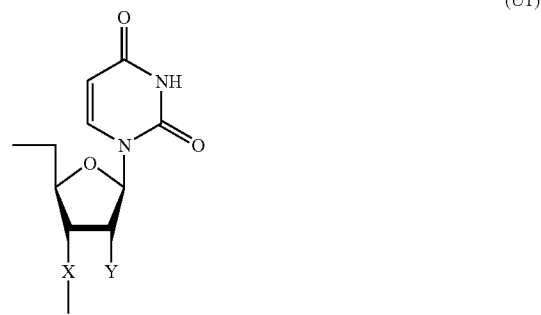
(A2)



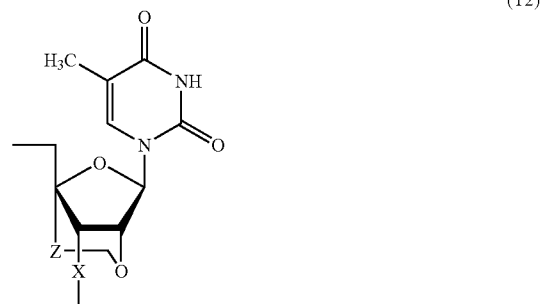
(C1)



(C2)

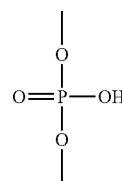


(U1)



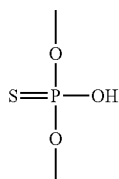
(T2)

[0220] where X is individually and independently a group represented by the following formula (X1) or (X2):

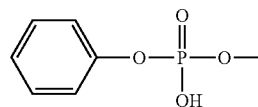


(X1)

-continued



(X2)



(G1)

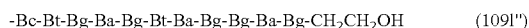
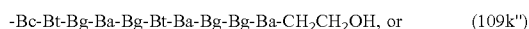
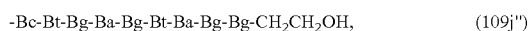
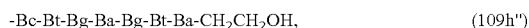
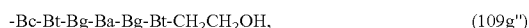
[0221] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0222] $B_{M''9}$ is a group represented by the following formula (9''):



[0223] where Bg, Ba, Bt and Bc are as defined above;

[0224] $B_{B''9}$ is a group represented by any one of the following (109a'') to (109l''):



[0225] where Bg, Ba, Bt and Bc are as defined above;

[0226] provided that at least one of the nucleosides constituting the compound represented by formula (IX'') has 2''-O,4''-C-alkylene group.

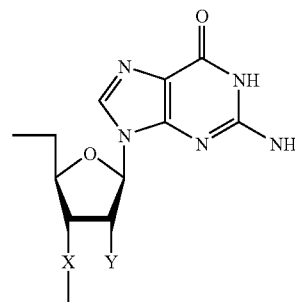
[0227] [35] A compound represented by the following general formula (X'') or a pharmacologically acceptable salt thereof:



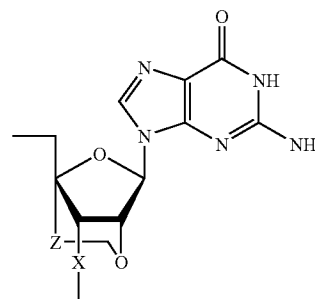
[0228] where $B_{T''10}$ is a group represented by any one of the following (10a'') to (10e''):



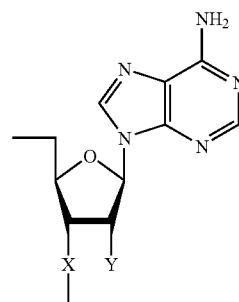
[0229] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); Bt is a group represented by the following formula (U1) or (T2); and D is HO— or Ph— wherein Ph— is a group represented by the following first formula:



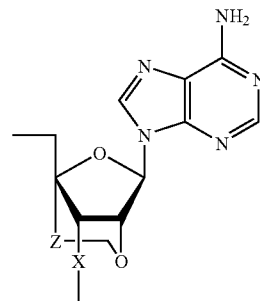
(G2)



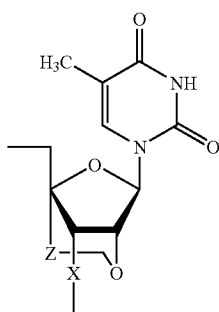
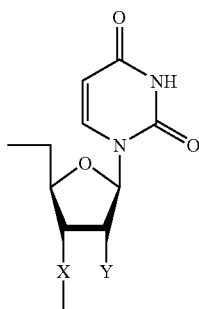
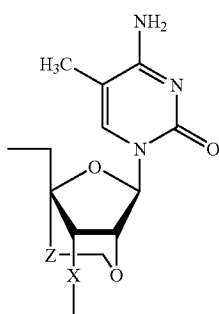
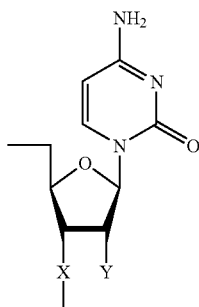
(A1)



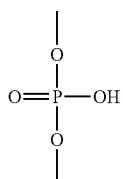
(A2)



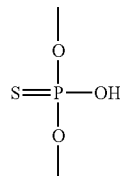
-continued



[0230] where X is individually and independently a group represented by the following formula (X1) or (X2):



(C1)



(C2)

(U1)

(T2)

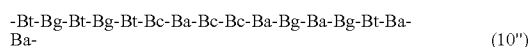
(X1)

-continued

(X2)

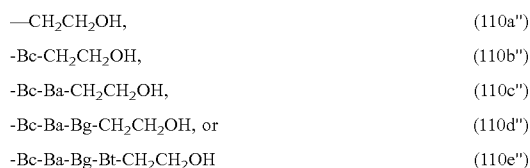
[0231] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0232] B_{M''10} is a group represented by the following formula (10''):



[0233] where Bg, Ba, Bt and Bc are as defined above;

[0234] B_{B''10} is a group represented by any one of the following (110a'') to (110e''):



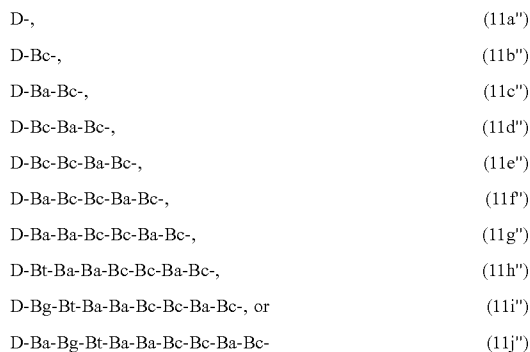
[0235] where Bg, Ba, Bt and Bc are as defined above;

[0236] provided that at least one of the nucleosides constituting the compound represented by formula (X'') has 2''-O,4''-C-alkylene group.

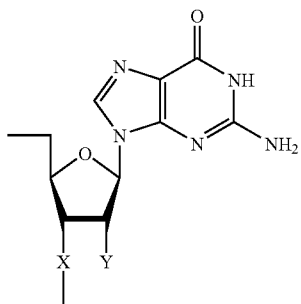
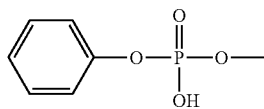
[0237] [36] A compound represented by the following general formula (XI'') or a pharmacologically acceptable salt thereof:



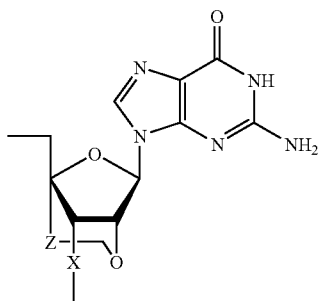
[0238] where B_{T''11} is a group represented by any one of the following (11a'') to (11j''):



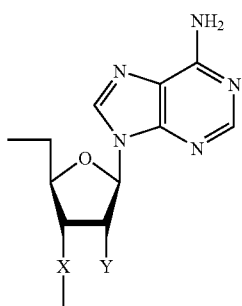
[0239] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); Bt is a group represented by the following formula (U1) or (T2); and D is HO— or Ph- wherein Ph- is a group represented by the following first formula:



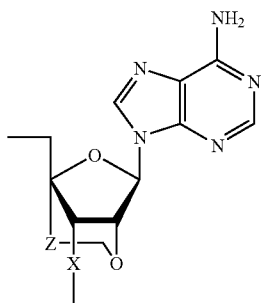
(G1)



(G2)

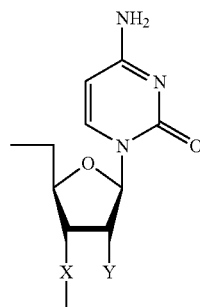


(A1)

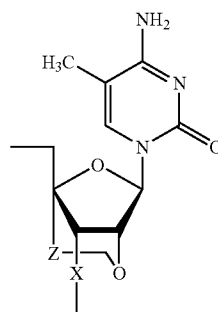


(A2)

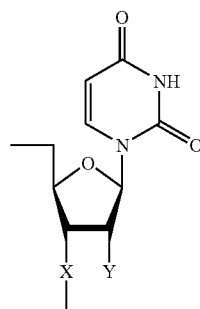
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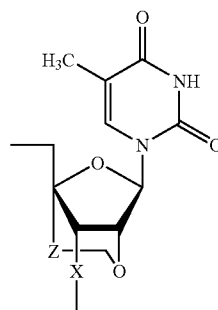
(C1)



(C2)

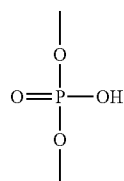


(U1)



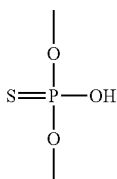
(T2)

[0240] where X is individually and independently a group represented by the following formula (X1) or (X2):



(X1)

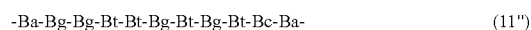
-continued



(X2)

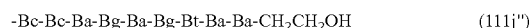
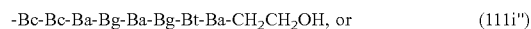
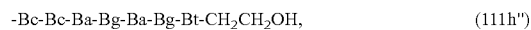
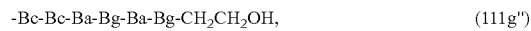
[0241] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0242] $B_{M''11}$ is a group represented by the following formula (11''):



[0243] where Bg, Ba, Bt and Bc are as defined above;

[0244] $B_{B''11}$ is a group represented by any one of the following (111a'') to (111j''):



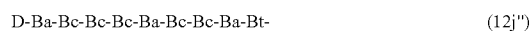
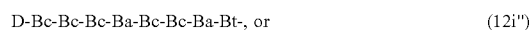
[0245] where Bg, Ba, Bt and Bc are as defined above;

[0246] provided that at least one of the nucleosides constituting the compound represented by formula (XI'') has 2''-O,4''-C-alkylene group.

[0247] [37] A compound represented by the following general formula (XII'') or a pharmacologically acceptable salt thereof:

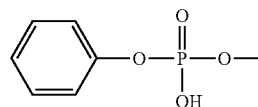


[0248] where $B_{T''12}$ is a group represented by any one of the following (12a'') to (12j''):

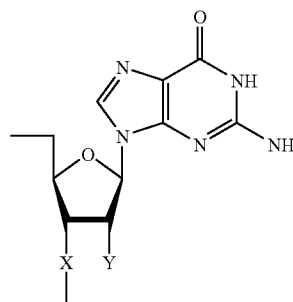


[0249] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); Bt is a group

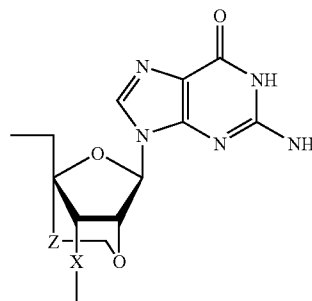
represented by the following formula (U1) or (T2); and D is HO— or Ph- wherein Ph- is a group represented by the following first formula:



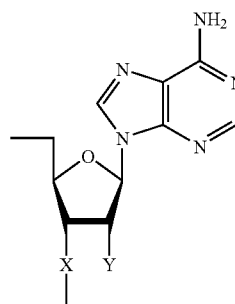
(G1)



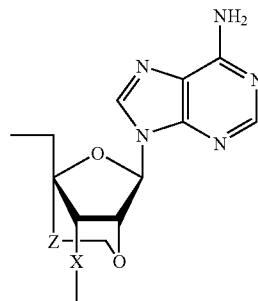
(G2)



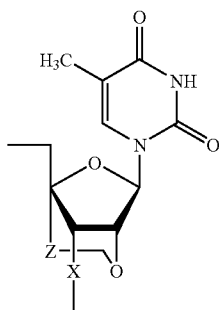
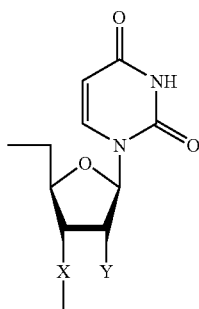
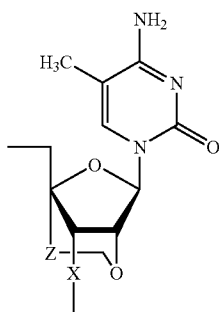
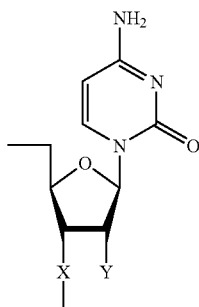
(A1)



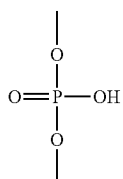
(A2)



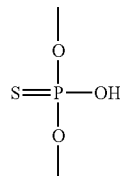
-continued



[0250] where X is individually and independently a group represented by the following formula (X1) or (X2):



(C1)



(X2)

(C2)

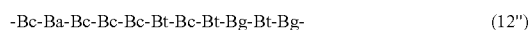
(U1)

(T2)

-continued

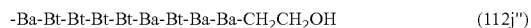
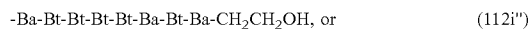
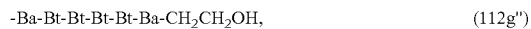
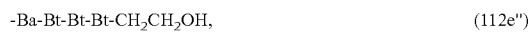
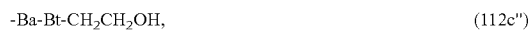
[0251] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0252] $B_{M''12}$ is a group represented by the following formula (12''):



[0253] where Bg, Ba, Bt and Bc are as defined above;

[0254] $B_{B''12}$ is a group represented by any one of the following (112a'')-(112j''):



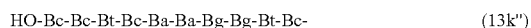
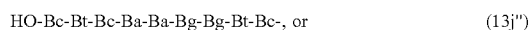
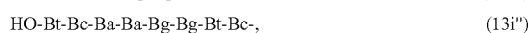
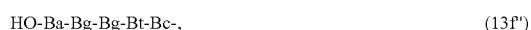
[0255] where Bg, Ba, Bt and Bc are as defined above;

[0256] provided that at least one of the nucleosides constituting the compound represented by formula (XII'') has 2''-O,4''-C-alkylene group.

[0257] [38] A compound represented by the following general formula (XIII'') or a pharmacologically acceptable salt thereof:

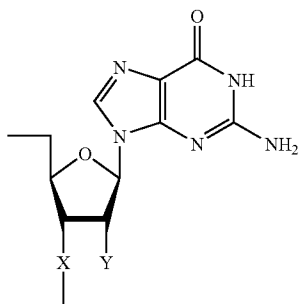


[0258] where $B_{T''13}$ is a group represented by any one of the following (13a'') to (13k''):

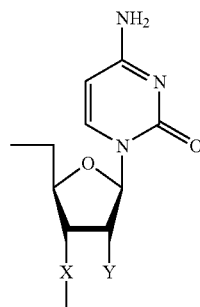


[0259] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented

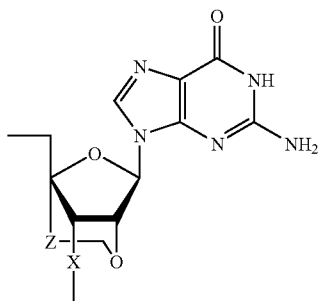
by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



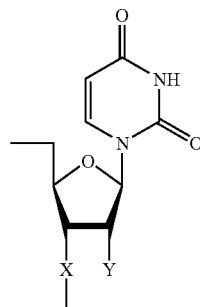
(G1)



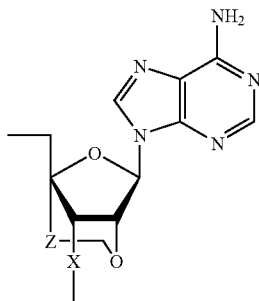
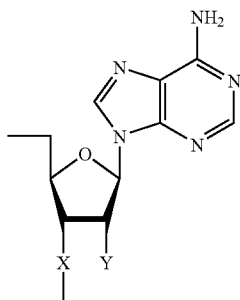
(G2)



(A1)



(A2)



-continued

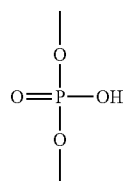
(C1)

(C2)

(U1)

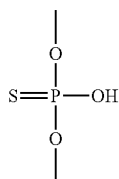
(T2)

[0260] where X is individually and independently a group represented by the following formula (X1) or (X2):



(X1)

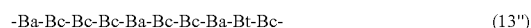
-continued



(X2)

[0261] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0262] $B_{M^{13}}$ is a group represented by the following formula (13''):



[0263] where Bg, Ba, Bt and Bc are as defined above;

[0264] $B_{B^{13}}$ is a group represented by the following formula (113a''):

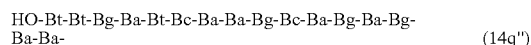
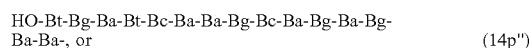
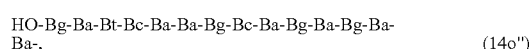
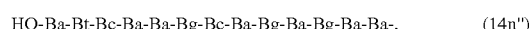
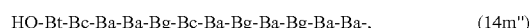
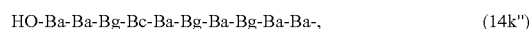
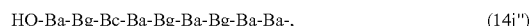
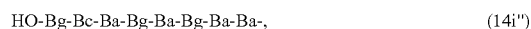
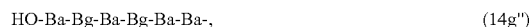
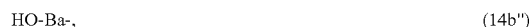
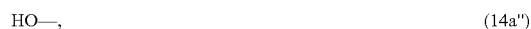


[0265] provided that at least one of the nucleosides constituting the compound represented by formula (XIII'') has 2''-O,4''-C-alkylene group.

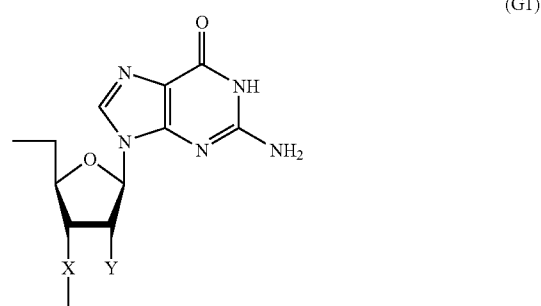
[0266] [39] A compound represented by the following general formula (XIV'') or a pharmacologically acceptable salt thereof:



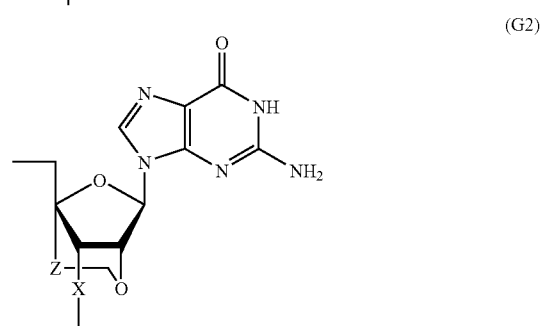
where $B_{T^{14}}$ is a group represented by any one of the following (14a'') to (14q''):



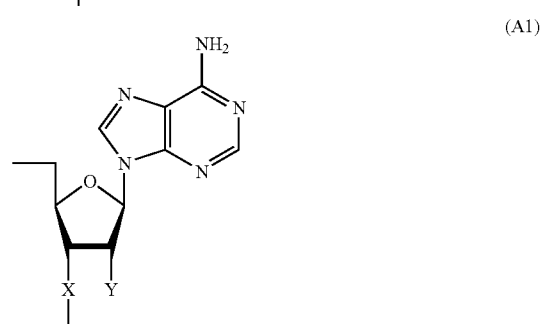
[0267] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



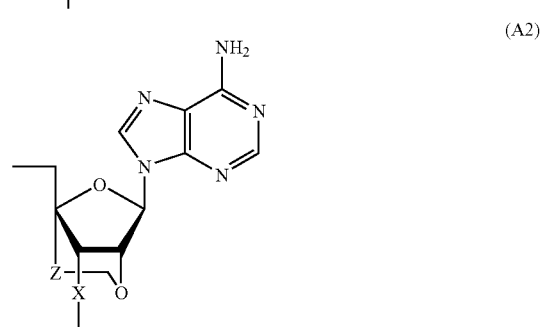
(G1)



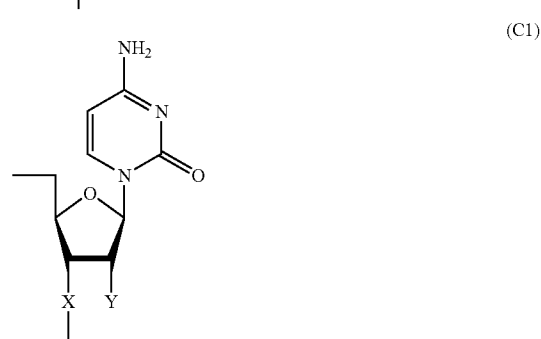
(G2)



(A1)

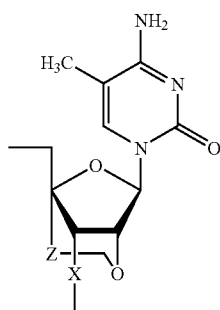


(A2)



(C1)

-continued



(C2)

carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0270] $B_{M''14}$ is a group represented by the following formula (14''):

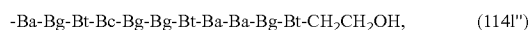
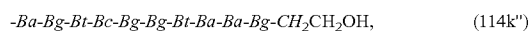
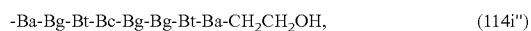
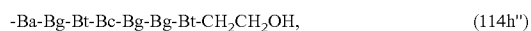
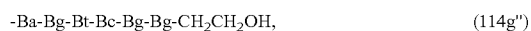


[0271] where Bg, Ba, Bt and Bc are as defined above;

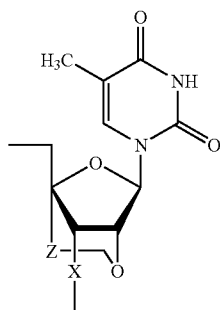
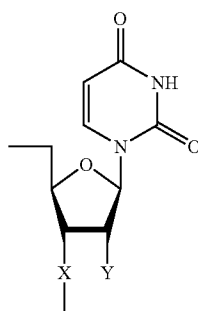
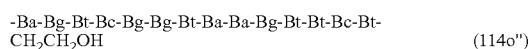
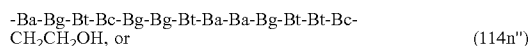
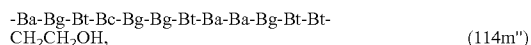
[0272] $B_{B''14}$ is a group represented by any one of the following (114a'') to (114o''):



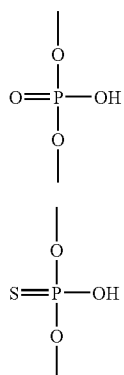
(U1)



(T2)



[0268] where X is individually and independently a group represented by the following formula (X1) or (X2):

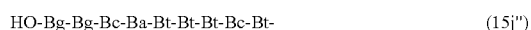
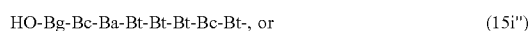


(X1)

(X2)

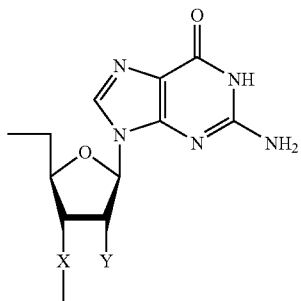


[0276] where $B_{T''15}$ is a group represented by any one of the following (15a'') to (15j''):

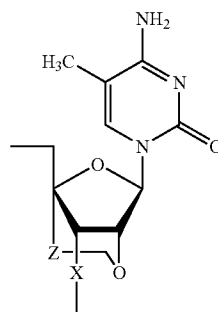


[0277] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

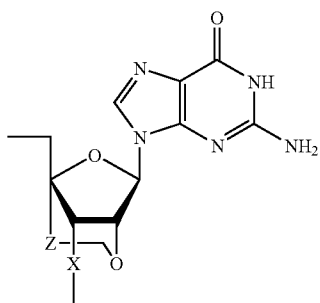
[0269] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6



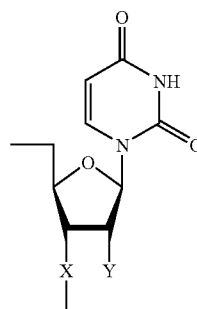
(G1)



(G2)

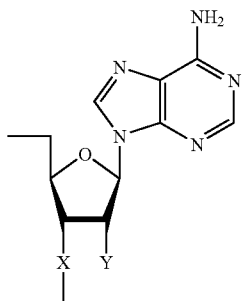


(A1)

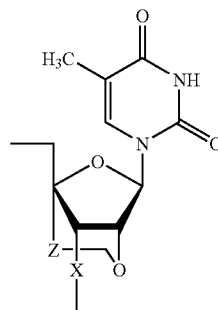


(C2)

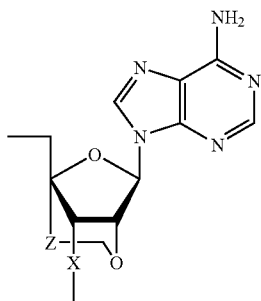
(U1)



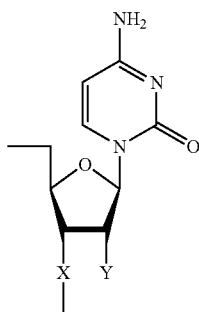
(A2)



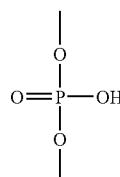
(T2)



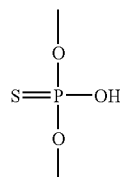
(C1)



[0278] where X is individually and independently a group represented by the following formula (X1) or (X2):



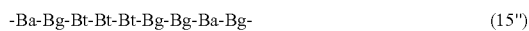
(X1)



(X2)

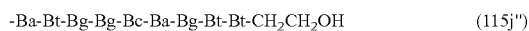
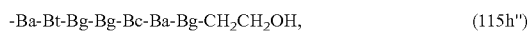
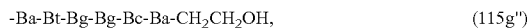
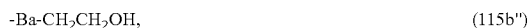
[0279] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0280] $B_{M''15}$ is a group represented by the following formula (15''):



[0281] where Bg, Ba, Bt and Bc are as defined above;

[0282] $B_{B''15}$ is a group represented by any one of the following (115a'') to (115j''):



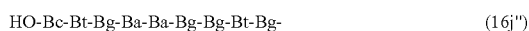
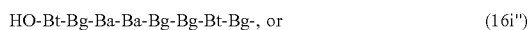
[0283] where Bg, Ba, Bt and Bc are as defined above;

[0284] provided that at least one of the nucleosides constituting the compound represented by formula (XV'') has 2''-O,4''-C-alkylene group.

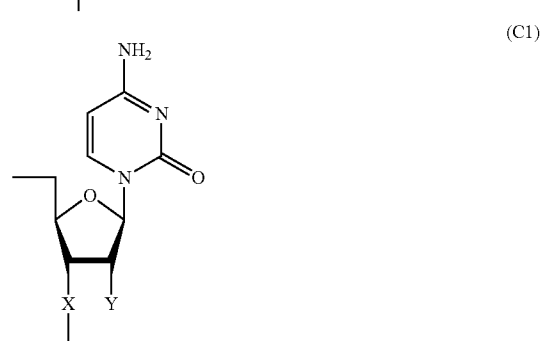
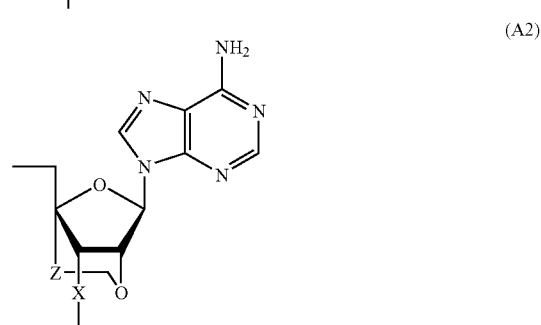
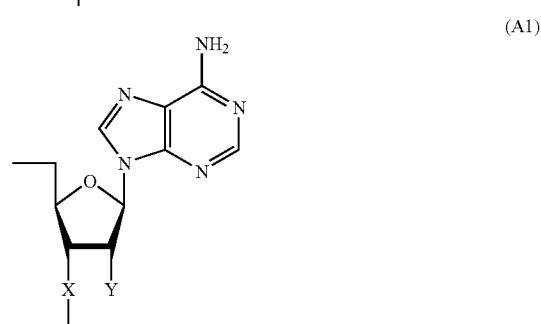
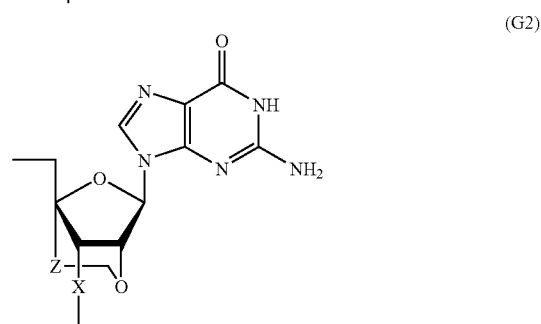
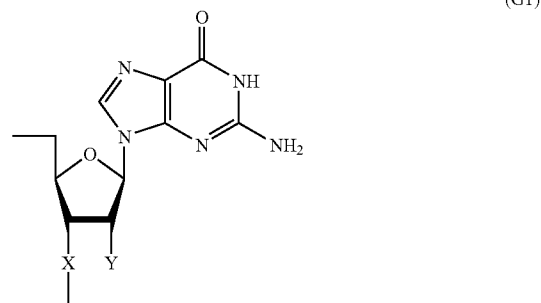
[0285] [41] A compound represented by the following general formula (XVI'') or a pharmacologically acceptable salt thereof:



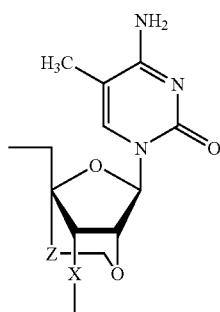
[0286] where $B_{T''16}$ is a group represented by any one of the following (15a'') to (15j''):



[0287] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



-continued



(C2)

[0289] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0290] $B_{M^{*}16}$ is a group represented by the following formula (16''):

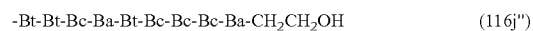
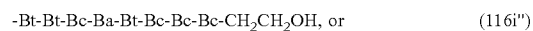
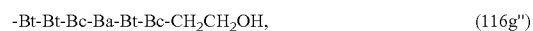


[0291] where Bg, Ba, Bt and Bc are as defined above;

[0292] $B_{B^{*}16}$ is a group represented by any one of the following (116a'') to (116j''):



(U1)



(T2)

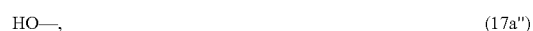
[0293] where Bg, Ba, Bt and Bc are as defined above;

[0294] provided that at least one of the nucleosides constituting the compound represented by formula (XVI'') has 2''-O,4''-C-alkylene group.

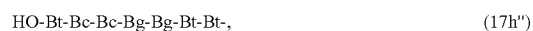
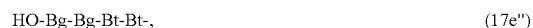
[0295] [42] A compound represented by the following general formula (XVII'') or a pharmacologically acceptable salt thereof:



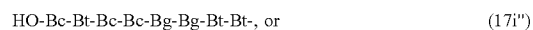
[0296] where $B_{T^{*}17}$ is a group represented by any one of the following (17a'') to (17j''):



(X1)

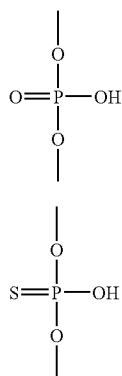


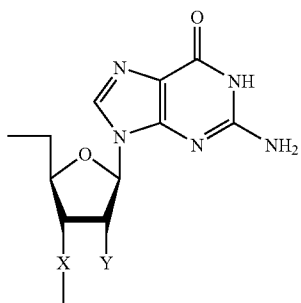
(X2)



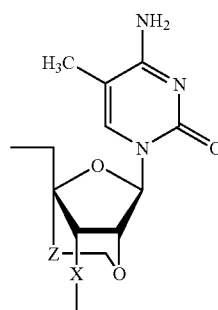
[0297] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

[0288] where X is individually and independently a group represented by the following formula (X1) or (X2):

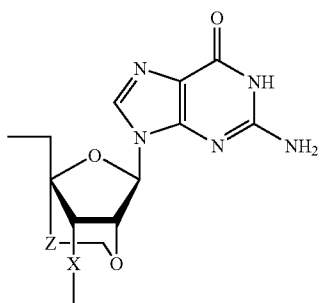




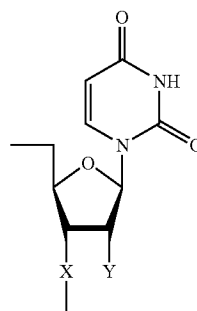
(G1)



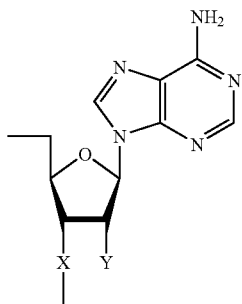
(G2)



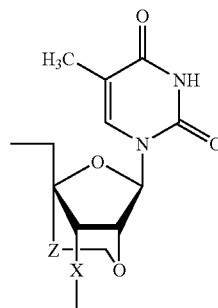
(A1)



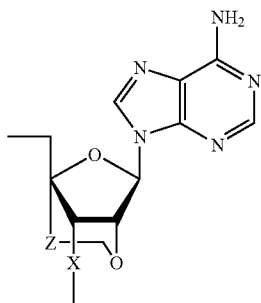
(U1)



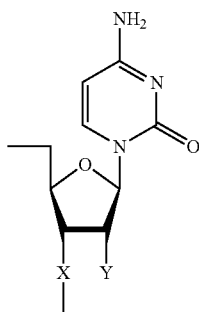
(A2)



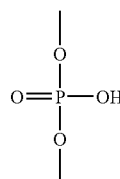
(T2)



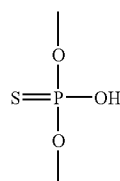
(C1)



[0298] where X is individually and independently a group represented by the following formula (X1) or (X2):



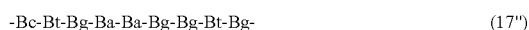
(X1)



(X2)

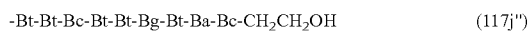
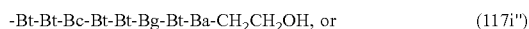
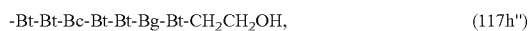
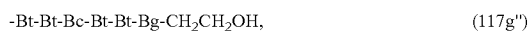
[0299] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0300] $B_{M''17}$ is a group represented by the following formula (17''):



[0301] where Bg, Ba, Bt and Bc are as defined above;

[0302] $B_{B''17}$ is a group represented by any one of the following (117a'') to (117j''):



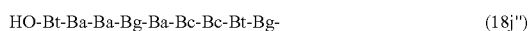
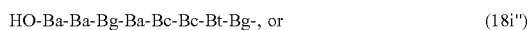
[0303] where Bg, Ba, Bt and Bc are as defined above;

[0304] provided that at least one of the nucleosides constituting the compound represented by formula (XVII'') has 2''-O,4''-C-alkylene group.

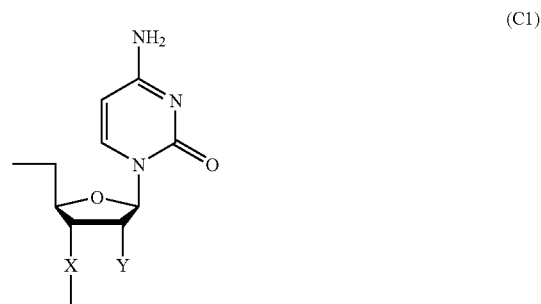
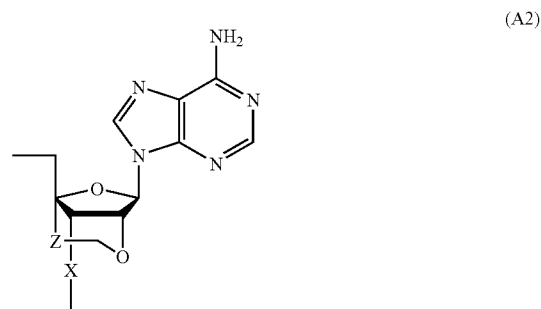
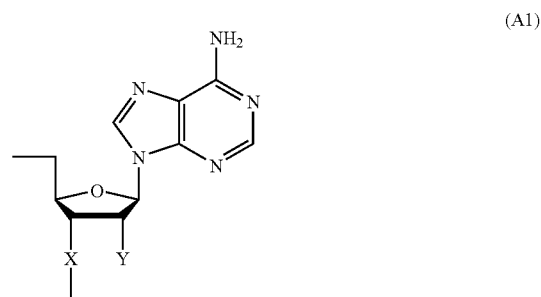
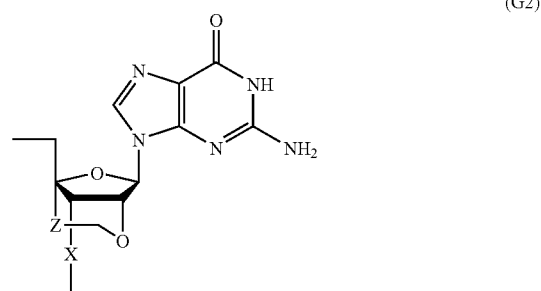
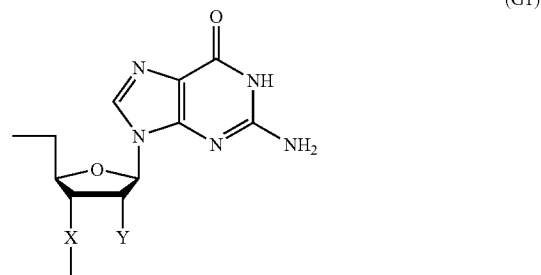
[0305] [43] A compound represented by the following general formula (XVIII'') or a pharmacologically acceptable salt thereof:



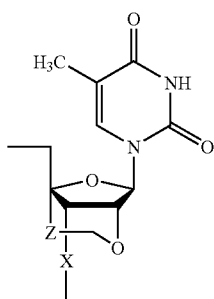
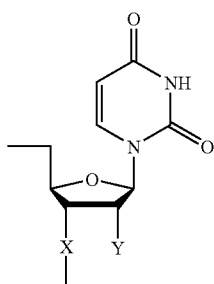
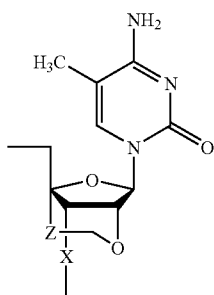
[0306] where $B_{T''18}$ is a group represented by any one of the following (18a'') to (18j''):



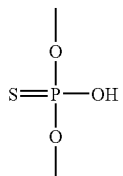
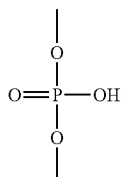
[0307] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



-continued



[0308] where X is individually and independently a group represented by the following formula (X1) or (X2):



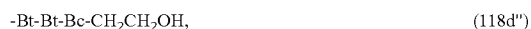
[0309] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

(C2) [0310] $B_{M^{*}18}$ is a group represented by the following formula (18''):

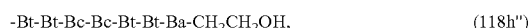


[0311] where Bg, Ba, Bt and Bc are as defined above;

[0312] $B_{B^{*}18}$ is a group represented by any one of the following (118a'') to (118j''):



(U1) -Bt-Bt-Bc-Bc-Bt-CH₂CH₂OH, (118f'')



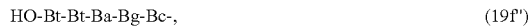
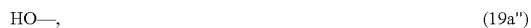
[0313] where Bg, Ba, Bt and Bc are as defined above;

[0314] provided that at least one of the nucleosides constituting the compound represented by formula (XVIII'') has 2''-O,4''-C-alkylene group.

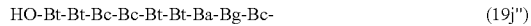
(T2) [0315] [44] A compound represented by the following general formula (XIX'') or a pharmacologically acceptable salt thereof:



[0316] where $B_{T^{*}19}$ is a group represented by any one of the following (19a'') to (19j''):

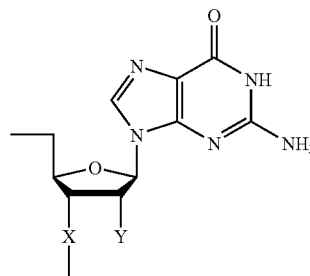


(X1) HO-Bt-Bc-Bc-Bt-Bt-Ba-Bg-Bc-, or (19i'')

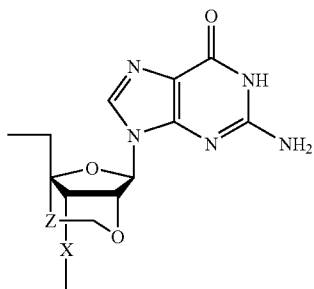


[0317] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

(G1)

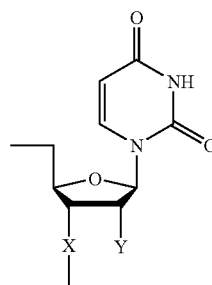


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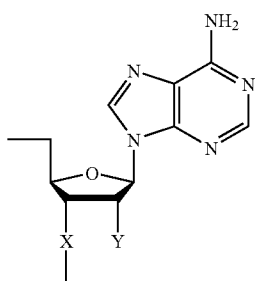


(G2)

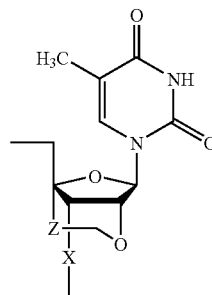
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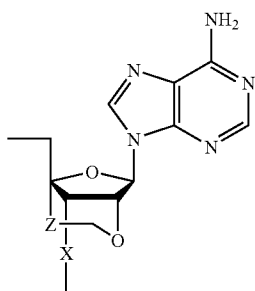
(U1)



(A1)

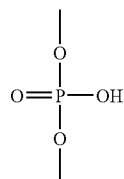


(T2)

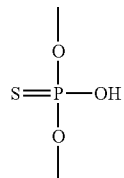


(A2)

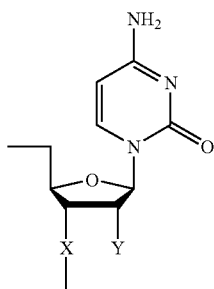
[0318] where X is individually and independently a group represented by the following formula (X1) or (X2):



(X1)



(X2)



(C1)

[0319] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0320] B_{M''19} is a group represented by the following formula (19''):

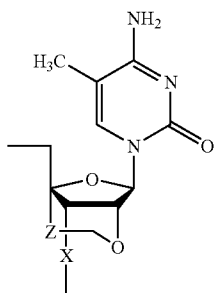
(C2)



[0321] where Bg, Ba, Bt and Bc are as defined above;

[0322] B_{B''19} is a group represented by any one of the following (119a'') to (119j''):

- CH₂CH₂OH, (119a'')
- Bt-CH₂CH₂OH, (119b'')
- Bt-Bt-CH₂CH₂OH, (119c'')
- Bt-Bt-Bg-CH₂CH₂OH, (119d'')
- Bt-Bt-Bg-Bt-CH₂CH₂OH, (119e'')
- Bt-Bt-Bg-Bt-Bg-CH₂CH₂OH, (119f'')



- Bt-Bt-Bg-Bt-Bg-Bt-CH₂CH₂OH, (119g")
- Bt-Bt-Bg-Bt-Bg-Bt-Bt-CH₂CH₂OH, (119h")
- Bt-Bt-Bg-Bt-Bg-Bt-Bt-Bg-CH₂CH₂OH, or (119i")
- Bt-Bt-Bg-Bt-Bg-Bt-Bt-Bg-Ba-CH₂CH₂OH (119j")

[0323] where Bg, Ba, Bt and Bc are as defined above;

[0324] provided that at least one of the nucleosides constituting the compound represented by formula (XIX") has 2"-O,4"-C-alkylene group.

[0325] [45] A compound represented by the following general formula (XX") or a pharmacologically acceptable salt thereof:

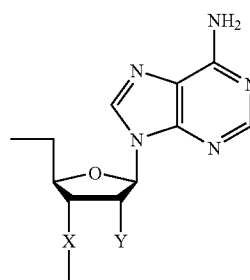


[0326] where B_{T"20} is a group represented by any one of the following (20a") to (20j"):

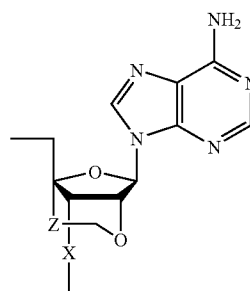
- HO-, (20a")
- HO-Bc-, (20b")
- HO-Bt-Bc-, (20c")
- HO-Bt-Bt-Bc-, (20d")
- HO-Bc-Bt-Bt-Bc-, (20e")
- HO-Bg-Bc-Bt-Bt-Bc-, (20f")
- HO-Ba-Bg-Bc-Bt-Bt-Bc-, (20g")
- HO-Bc-Ba-Bg-Bc-Bt-Bt-Bc-, (20h")
- HO-Bt-Bc-Ba-Bg-Bc-Bt-Bt-Bc-, or (20i")
- HO-Bc-Bt-Bc-Ba-Bg-Bc-Bt-Bt-Bc- (20j")

[0327] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):

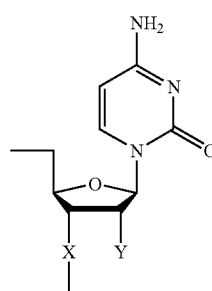
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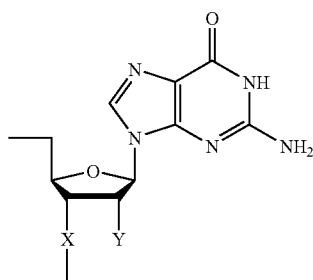
(A1)



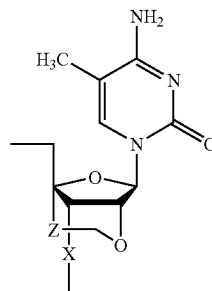
(A2)



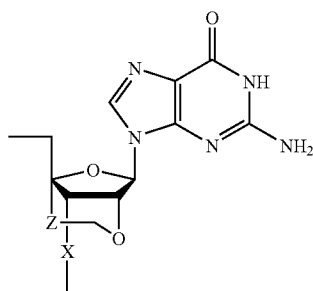
(C1)



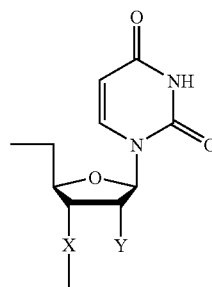
(G1)



(C2)

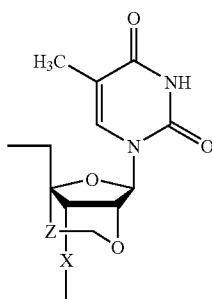


(G2)



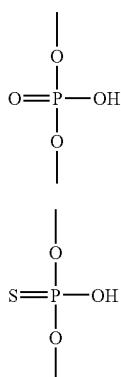
(U1)

-continued



(T2)

[0328] where X is individually and independently a group represented by the following formula (X1) or (X2):



(X1)

(X2)

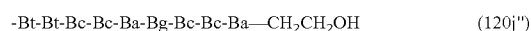
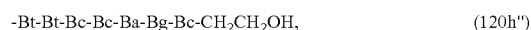
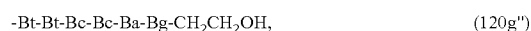
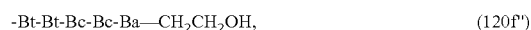
[0329] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0330] $B_{M''20}$ is a group represented by the following formula (20''):



[0331] where Bg, Ba, Bt and Bc are as defined above;

[0332] $B_{B''20}$ is a group represented by any one of the following (120a'') to (120j''):



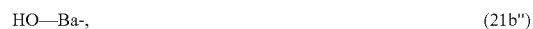
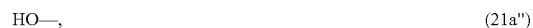
[0333] where Bg, Ba, Bt and Bc are as defined above;

[0334] provided that at least one of the nucleosides constituting the compound represented by formula (XX'') has 2''-O,4''-C-alkylene group.

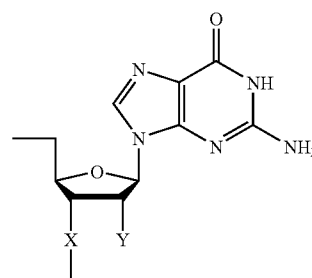
[0335] [46] A compound represented by the following general formula (XXI'') or a pharmacologically acceptable salt thereof:



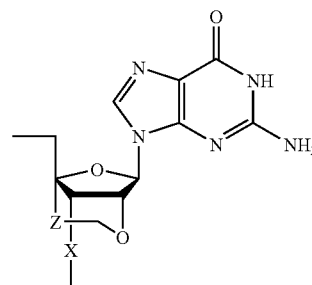
[0336] where $B_{T''21}$ is a group represented by any one of the following (21a'') to (21e''):



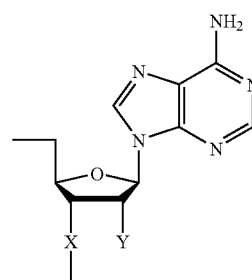
[0337] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); and Bt is a group represented by the following formula (U1) or (T2):



(G1)

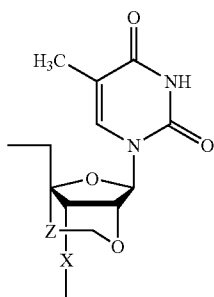
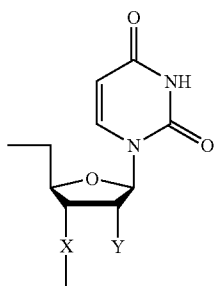
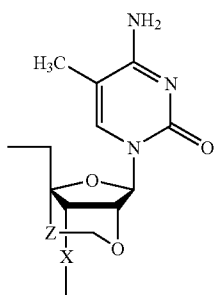
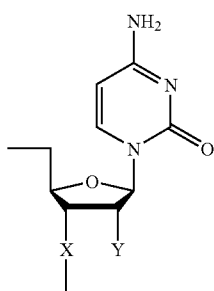
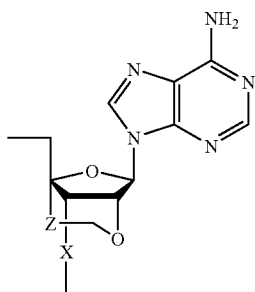


(G2)



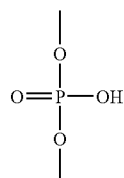
(A1)

-continued



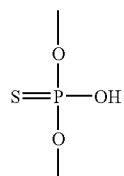
[0338] where X is individually and independently a group represented by the following formula (X1) or (X2):

(A2)



(X1)

(C1)

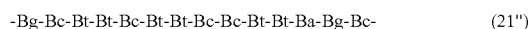


(X2)

[0339] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

[0340] $B_{M''21}$ is a group represented by the following formula (21''):

(C2)



[0341] where Bg, Ba, Bt and Bc are as defined above;

[0342] $B_{B''21}$ is a group represented by any one of the following (121a'') to (121e''):



(U1)

[0343] where Bg, Ba, Bt and Bc are as defined above;

[0344] provided that at least one of the nucleosides constituting the compound represented by formula (XXI'') has 2''-O,4''-C-alkylene group.

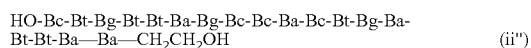
[0345] [47] The compound of any one of [26] to [46] above which is selected from the group consisting of the following compounds (i'') to (xlix''), or a pharmacologically acceptable salt thereof:

[0346] (i'') a compound represented by the following formula (i''):

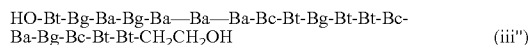
(T2)



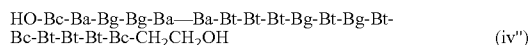
[0347] (ii'') a compound represented by the following formula (ii''):



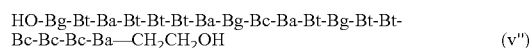
[0348] (iii'') a compound represented by the following formula (iii''):



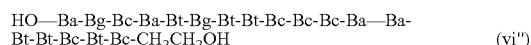
[0349] (iv'') a compound represented by the following formula (iv''):



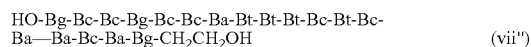
[0350] (v^{''}) a compound represented by the following formula (v^{''}):



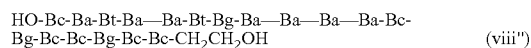
[0351] (vi^{''}) a compound represented by the following formula (vi^{''}):



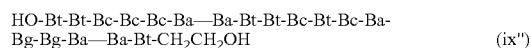
[0352] (vii^{''}) a compound represented by the following formula (vii^{''}):



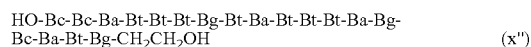
[0353] (viii^{''}) a compound represented by the following formula (viii^{''}):



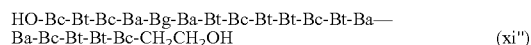
[0354] (ix^{''}) a compound represented by the following formula (ix^{''}):



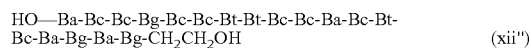
[0355] (x^{''}) a compound represented by the following formula (x^{''}):



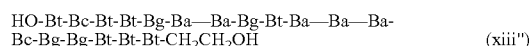
[0356] (xi^{''}) a compound represented by the following formula (xi^{''}):



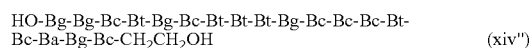
[0357] (xii^{''}) a compound represented by the following formula (xii^{''}):



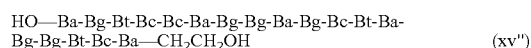
[0358] (xiii^{''}) a compound represented by the following formula (xiii^{''}):



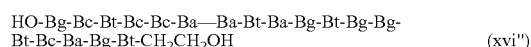
[0359] (xiv^{''}) a compound represented by the following formula (xiv^{''}):



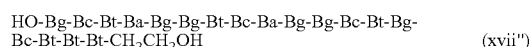
[0360] (xv^{''}) a compound represented by the following formula (xv^{''}):



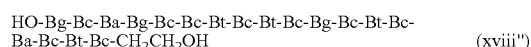
[0361] (xvi^{''}) a compound represented by the following formula (xvi^{''}):



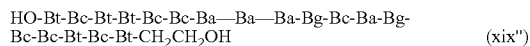
[0362] (xvii^{''}) a compound represented by the following formula (xvii^{''}):



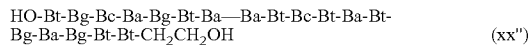
[0363] (xviii^{''}) a compound represented by the following formula (xviii^{''}):



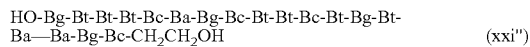
[0364] (xix^{''}) a compound represented by the following formula (xix^{''}):



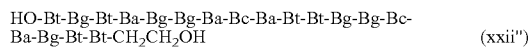
[0365] (xx^{''}) a compound represented by the following formula (xx^{''}):



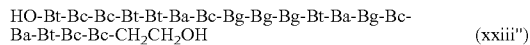
[0366] (xxi^{''}) a compound represented by the following formula (xxi^{''}):



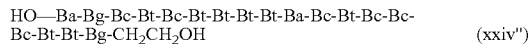
[0367] (xxii^{''}) a compound represented by the following formula (xxii^{''}):



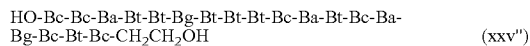
[0368] (xxiii^{''}) a compound represented by the following formula (xxiii^{''}):



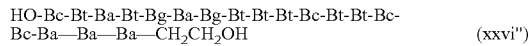
[0369] (xxiv^{''}) a compound represented by the following formula (xxiv^{''}):



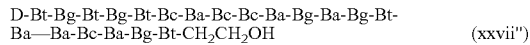
[0370] (xxv^{''}) a compound represented by the following formula (xxv^{''}):



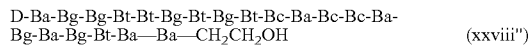
[0371] (xxvi^{''}) a compound represented by the following formula (xxvi^{''}):



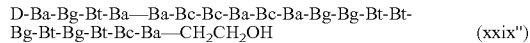
[0372] (xxvii^{''}) a compound represented by the following formula (xxvii^{''}):



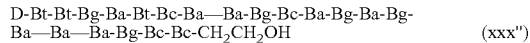
[0373] (xxviii^{''}) a compound represented by the following formula (xxviii^{''}):



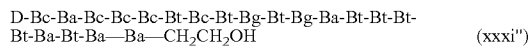
[0374] (xxix^{''}) a compound represented by the following formula (xxix^{''}):



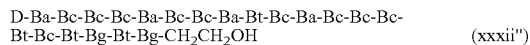
[0375] (xxx^{''}) a compound represented by the following formula (xxx^{''}):



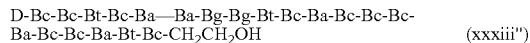
[0376] (xxx^{''}i) a compound represented by the following formula (xxx^{''}i):



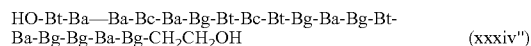
[0377] (xxx^{''}ii) a compound represented by the following formula (xxx^{''}ii):



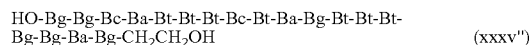
[0378] (xxx^{''}iii) a compound represented by the following formula (xxx^{''}iii):



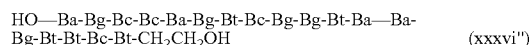
[0379] (xxxiv") a compound represented by the following formula (xxxiv"):



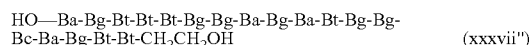
[0380] (xxxv") a compound represented by the following formula (xxxv"):



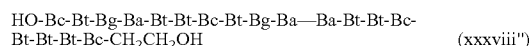
[0381] (xxxvi") a compound represented by the following formula (xxxvi"):



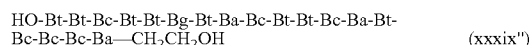
[0382] (xxxvii") a compound represented by the following formula (xxxvii"):



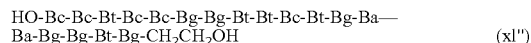
[0383] (xxxviii") a compound represented by the following formula (xxxviii"):



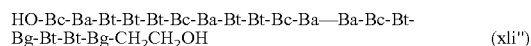
[0384] (xxxix") a compound represented by the following formula (xxxix"):



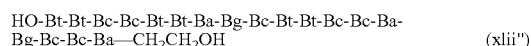
[0385] (xl") a compound represented by the following formula (xl"):



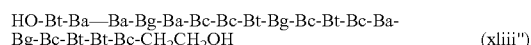
[0386] (xli") a compound represented by the following formula (xli"):



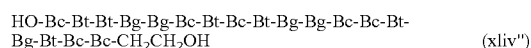
[0387] (xlii") a compound represented by the following formula (xlii"):



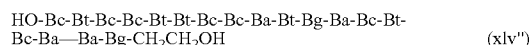
[0388] (xliii") a compound represented by the following formula (xliii"):



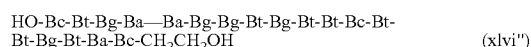
[0389] (xliv") a compound represented by the following formula (xliv"):



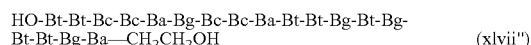
[0390] (xlv") a compound represented by the following formula (xlv"):



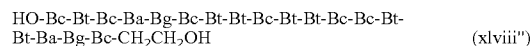
[0391] (xlvi") a compound represented by the following formula (xlvi"):



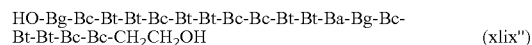
[0392] (xlvii") a compound represented by the following formula (xlvii"):



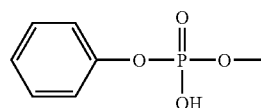
[0393] (xlviii") a compound represented by the following formula (xlviii"):



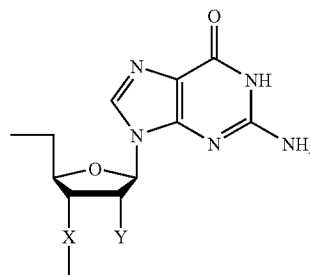
[0394] (xlix") a compound represented by the following formula (xlix"):



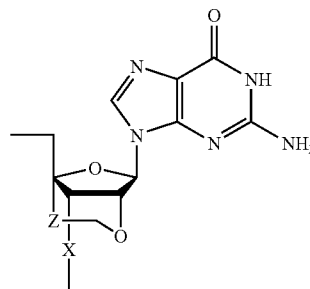
[0395] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented by the following formula (C1) or (C2); Bt is a group represented by the following formula (U1) or (T2); and D is HO— or Ph- wherein Ph- is a group represented by the following first formula:



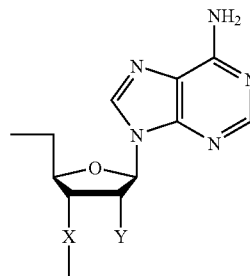
(G1)



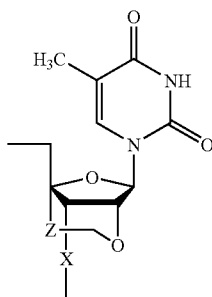
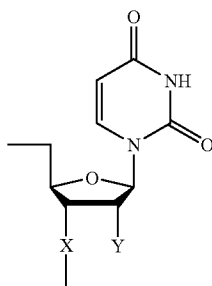
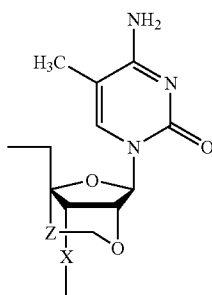
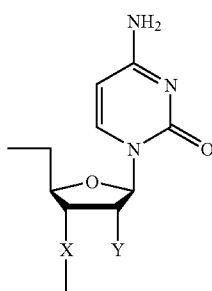
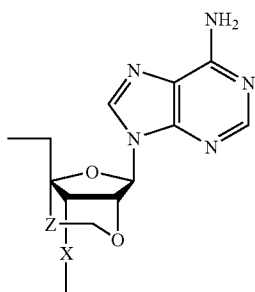
(G2)



(A1)

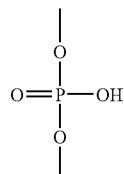


-continued



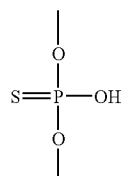
[0396] where X is individually and independently a group represented by the following formula (X1) or (X2):

(A2)



(X1)

(C1)



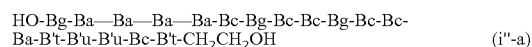
(X2)

[0397] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms.

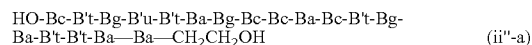
[0398] [48] The compound of any one of [26] to [46] above which is selected from the group consisting of the following compounds (i''-a) to (li''-a), or a pharmacologically acceptable salt thereof:

(C2)

[0399] (i''-a) a compound represented by the following formula (i''-a):

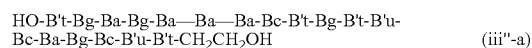


[0400] (ii''-a) a compound represented by the following formula (ii''-a):

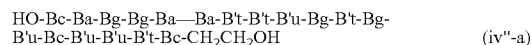


(U1)

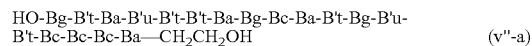
[0401] (iii''-a) a compound represented by the following formula (iii''-a):



[0402] (iv''-a) a compound represented by the following formula (iv''-a):

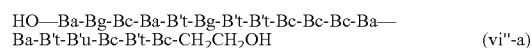


[0403] (v''-a) a compound represented by the following formula (v''-a):

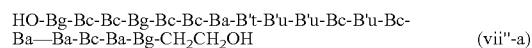


(T2)

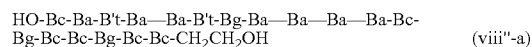
[0404] (vi''-a) a compound represented by the following formula (vi''-a):



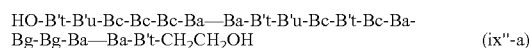
[0405] (vii''-a) a compound represented by the following formula (vii''-a):



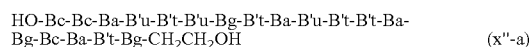
[0406] (viii''-a) a compound represented by the following formula (viii''-a):



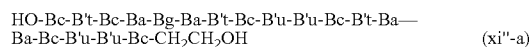
[0407] (ix"-a) a compound represented by the following formula (ix"-a):



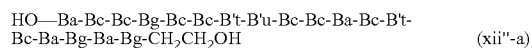
[0408] (x"-a) a compound represented by the following formula (x"-a):



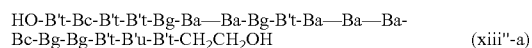
[0409] (xi"-a) a compound represented by the following formula (xi"-a):



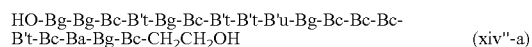
[0410] (xii"-a) a compound represented by the following formula (xii"-a):



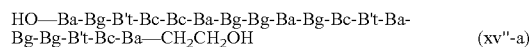
[0411] (xiii"-a) a compound represented by the following formula (xiii"-a):



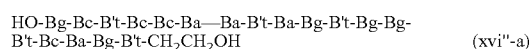
[0412] (xiv"-a) a compound represented by the following formula (xiv"-a):



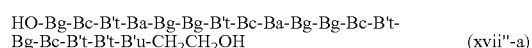
[0413] (xv"-a) a compound represented by the following formula (xv"-a):



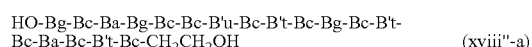
[0414] (xvi"-a) a compound represented by the following formula (xvi"-a):



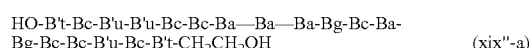
[0415] (xvii"-a) a compound represented by the following formula (xvii"-a):



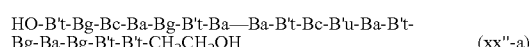
[0416] (xviii"-a) a compound represented by the following formula (xviii"-a):



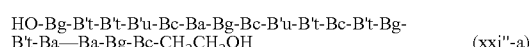
[0417] (xix"-a) a compound represented by the following formula (xix"-a):



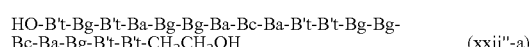
[0418] (xx"-a) a compound represented by the following formula (xx"-a):



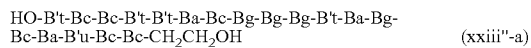
[0419] (xxi"-a) a compound represented by the following formula (xxi"-a):



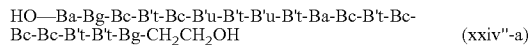
[0420] (xxii"-a) a compound represented by the following formula (xxii"-a):



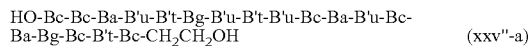
[0421] (xxiii"-a) a compound represented by the following formula (xxiii"-a):



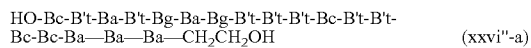
[0422] (xxiv"-a) a compound represented by the following formula (xxiv"-a):



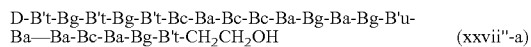
[0423] (xxv"-a) a compound represented by the following formula (xxv"-a):



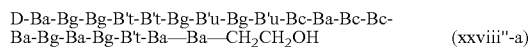
[0424] (xxvi"-a) a compound represented by the following formula (xxvi"-a):



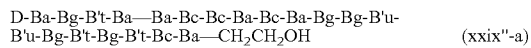
[0425] (xxvii"-a) a compound represented by the following formula (xxvii"-a):



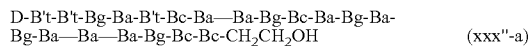
[0426] (xxviii"-a) a compound represented by the following formula (xxviii"-a):



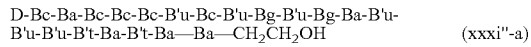
[0427] (xxix"-a) a compound represented by the following formula (xxix"-a):



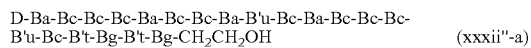
[0428] (xxx"-a) a compound represented by the following formula (xxx"-a):



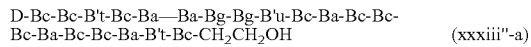
[0429] (xxxii"-a) a compound represented by the following formula (xxxii"-a):



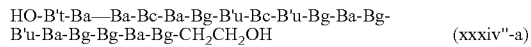
[0430] (xxxiii"-a) a compound represented by the following formula (xxxiii"-a):



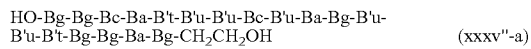
[0431] (xxxiiii"-a) a compound represented by the following formula (xxxiiii"-a):



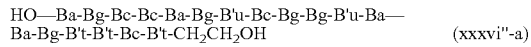
[0432] (xxxv"-a) a compound represented by the following formula (xxxv"-a):



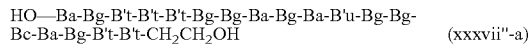
[0433] (xxxvi"-a) a compound represented by the following formula (xxxvi"-a):



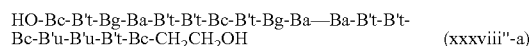
[0434] (xxxvii"-a) a compound represented by the following formula (xxxvii"-a):



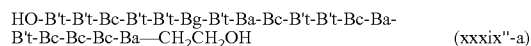
[0435] (xxxviii"-a) a compound represented by the following formula (xxxviii"-a):



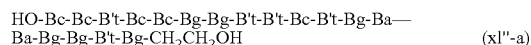
[0436] (xxxviii"-a) a compound represented by the following formula (xxxviii"-a):



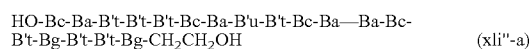
[0437] (xxxix"-a) a compound represented by the following formula (xxxix"-a):



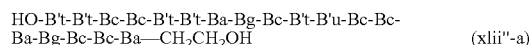
[0438] (xli"-a) a compound represented by the following formula (xli"-a):



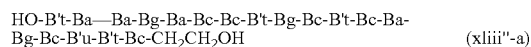
[0439] (xlii"-a) a compound represented by the following formula (xlii"-a):



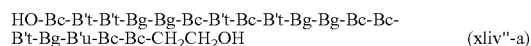
[0440] (xliii"-a) a compound represented by the following formula (xliii"-a):



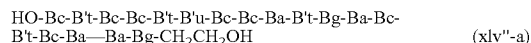
[0441] (xliv"-a) a compound represented by the following formula (xliv"-a):



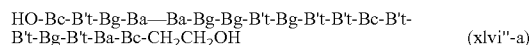
[0442] (xlv"-a) a compound represented by the following formula (xlv"-a):



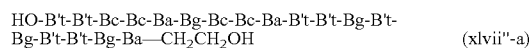
[0443] (xlvi"-a) a compound represented by the following formula (xlvi"-a):



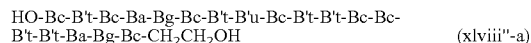
[0444] (xlvii"-a) a compound represented by the following formula (xlvii"-a):



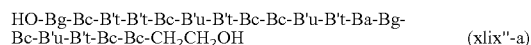
[0445] (xlviii"-a) a compound represented by the following formula (xlviii"-a):



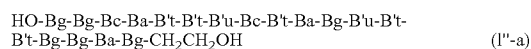
[0446] (xlix"-a) a compound represented by the following formula (xlix"-a):



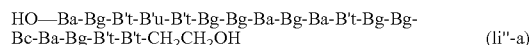
[0447] (l"-a) a compound represented by the following formula (l"-a):



[0448] (li"-a) a compound represented by the following formula (li"-a):

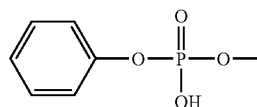


[0449] (lii"-a) a compound represented by the following formula (lii"-a):

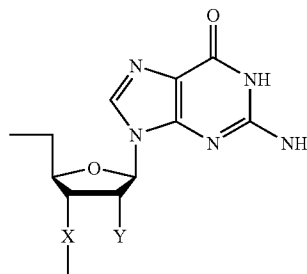


[0450] where Bg is a group represented by the following formula (G1) or (G2); Ba is a group represented by the following formula (A1) or (A2); Bc is a group represented

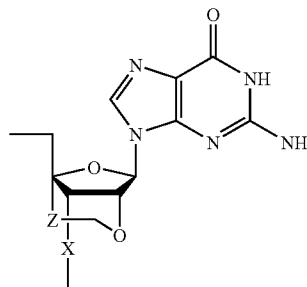
by the following formula (C1) or (C2); B't is a group represented by the following formula (T2); B'u is a formula represented by the following formula (U1); and D is HO— or Ph- wherein Ph- is a group represented by the following first formula:



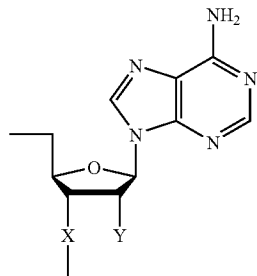
(G1)



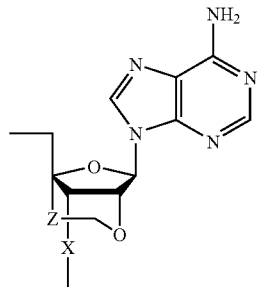
(G2)



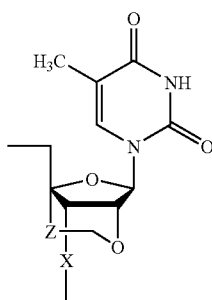
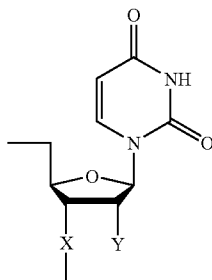
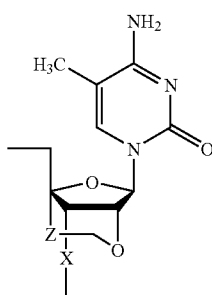
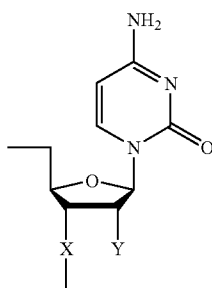
(A1)



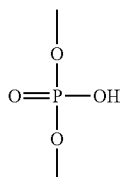
(A2)



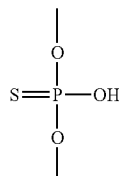
-continued



[0451] where X is individually and independently a group represented by the following formula (X1) or (X2):



(C1) -continued



(X2)

(C1)

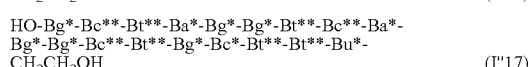
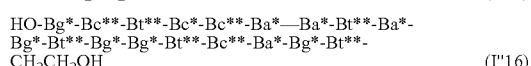
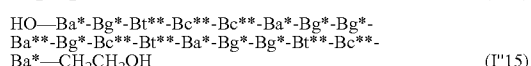
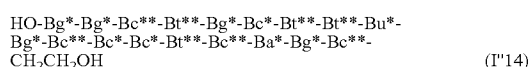
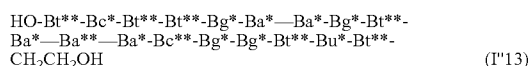
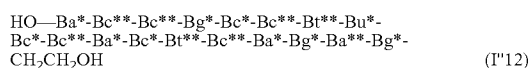
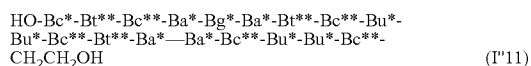
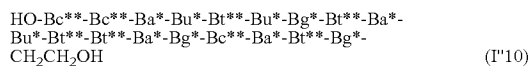
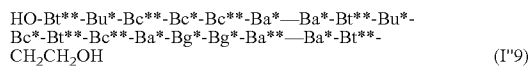
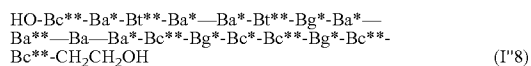
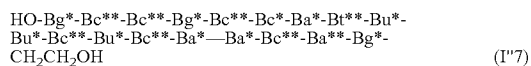
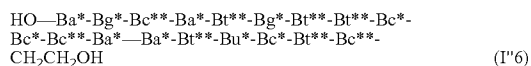
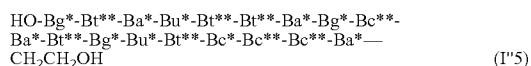
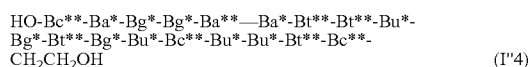
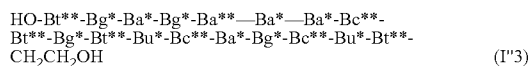
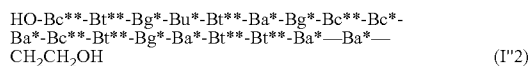
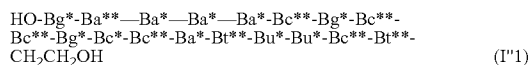
(C2)

(U1)

(T2)

[0452] Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms.

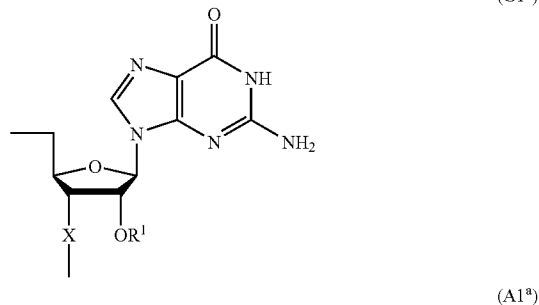
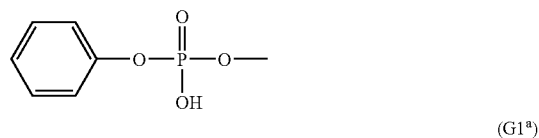
[0453] [49] The compound of any one of [26] to [48] above which is represented by any one of the following formulas (I'1) to (I'51), or a pharmacologically acceptable salt thereof:



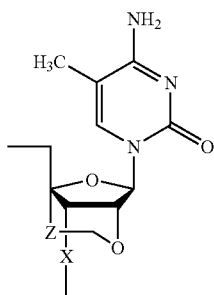
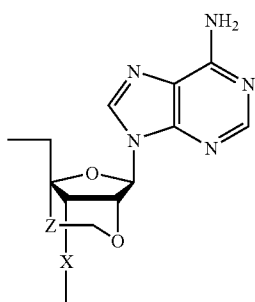
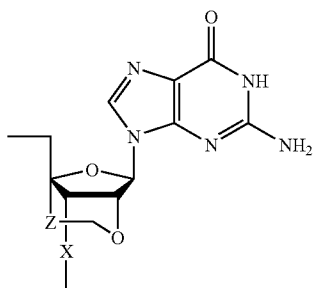
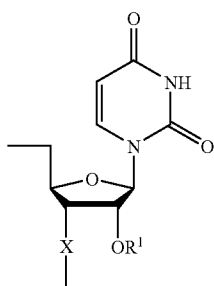
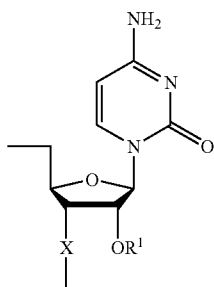
- (I'18) HO-Bg*-Bc**-Ba*-Bg*-Bc**-Bc**-Bu*-Bc*-Bt**-Bc*-Bg*-Bc**-Bt**
CH₂CH₂OH
- (I'19) HO-Bt**
Ba*-Bg*-Bc**-Ba*-Bg*-Bc**-Bc**-Bu*-Bc**-Bt**
CH₂CH₂OH
- (I'20) HO-Bt**
Bc**-Bu*-Ba*-Bt**
CH₂CH₂OH
- (I'21) HO-Bg*-Bt**
Bt**
CH₂CH₂OH
- (I'22) HO-Bt**
Bt**
CH₂CH₂OH
- (I'23) HO-Bt**
Bc**
CH₂CH₂OH
- (I'24) HO—Ba*
Ba*-Bc*-Bt**
CH₂CH₂OH
- (I'25) HO-Bc**
Bc**
CH₂CH₂OH
- (I'26) HO-Bc*
Bt**
CH₂CH₂OH
- (I'27) Ph-Bt**
Ba*-Bg*-Bu*
CH₂CH₂OH
- (I'28) Ph-Ba**
Ba**
CH₂CH₂OH
- (I'29) Ph-Ba**
Bc**
CH₂CH₂OH
- (I'30) Ph-Bt**
Bc**
CH₂CH₂OH
- (I'31) Ph-Bc**
Bu*
CH₂CH₂OH
- (I'32) Ph-Ba**
Bc**
CH₂CH₂OH
- (I'33) Ph-Bc**
Bu*
CH₂CH₂OH
- (I'34) HO-Bt**
Bu*
CH₂CH₂OH
- (I'35) HO-Bg**
Bu*
CH₂CH₂OH
- (I'36) HO—Ba**
Bt**
CH₂CH₂OH
- (I'37) HO—Ba**
Bg*
CH₂CH₂OH
- (I'38) HO-Bc**
Ba*
CH₂CH₂OH
- (I'39) HO-Bt**
Bt**
CH₂CH₂OH
- (I'40) HO-Bc**
Bt**
CH₂CH₂OH
- (I'41) HO-Bc**
Bc**
CH₂CH₂OH

- (I'42) HO-Bt**
Bt**
CH₂CH₂OH
- (I'43) HO-Bt**
Bc**
CH₂CH₂OH
- (I'44) HO-Bc**
Bg*
CH₂CH₂OH
- (I'45) HO-Bc**
Ba*
CH₂CH₂OH
- (I'46) HO-Bc**
Bt**
CH₂CH₂OH
- (I'47) HO-Bt**
Bt**
CH₂CH₂OH
- (I'48) HO-Bc**
Bt**
CH₂CH₂OH
- (I'49) HO-Bg*
Bu*
CH₂CH₂OH
- (I'50) HO-Bg*
Ba*
CH₂CH₂OH
- (I'51) HO—Ba**
Bg*
CH₂CH₂OH

[0454] where Bg* is a group represented by the following formula (G1^a), Ba* is a group represented by the following formula (A1^a); Bc* is a group represented by the following formula (C1^a); Bu* is a group represented by the following formula (U1^a); Bg** is a group represented by the following formula (G2); Ba** is a group represented by the following formula (A2); Bc** is a group represented by the following formula (C2); Bt** is a group represented by the following formula (T2); and Ph is a group represented by the following first formula:

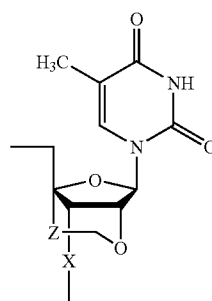


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-continued

(C1^a)

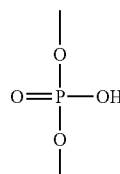


(T2)

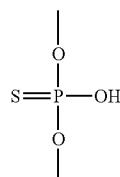
(U1^a)

[0455] where X is individually and independently a group represented by the following formula (X1) or (X2); R¹ is individually and independently an alkyl group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms:

(X1)



(G2)



(X2)

(A2)

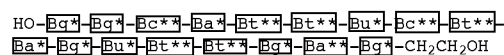
[0456] [50] The compound of [49] above where X in formulas (G1^a), (A1^a), (C1^a) and (U1^a) is a group represented by formula (X2) and X in formulas (G2), (A2), (C2) and (T2) is a group represented by formula (X1), or a pharmacologically acceptable salt thereof.

[0457] [51] The compound of [49] above where X in all the formulas (G1^a), (A1^a), (C1^a), (U1^a), (G2), (A2), (C2) and (T2) is a group represented by formula (X2), or a pharmacologically acceptable salt thereof.

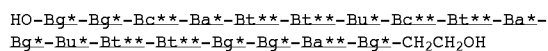
[0458] [52] The compound of [49] above which is represented by any one of the following formulas (I''50-a) to (I''51-b), or a salt thereof:

(C2)

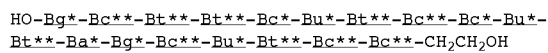
(I''50-a)



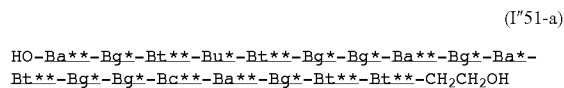
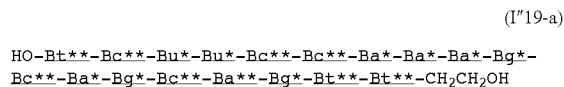
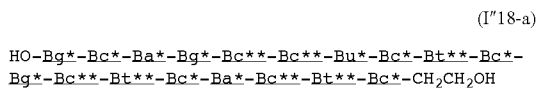
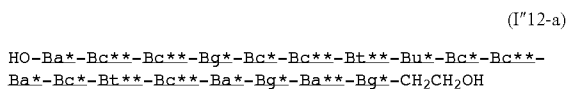
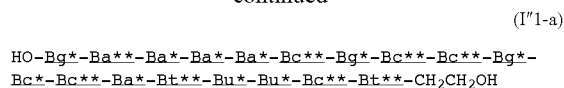
(I''50-b)



(I''49-a)



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[0459] where Bg* is a group represented by formula (G1^a), Ba* is a group represented by formula (A1^a); Bc* is a group represented by formula (C1^a); Bu* is a group represented by formula (U1^a); Bg** is a group represented by formula (G2); Ba** is a group represented by formula (A2); Bc** is a group represented by formula (C2); Bt** is a group represented by formula (T2); and in individual formulas, at least one of Bg*, Ba*, Bc*, Bu*, Bg**, Ba**, Bc** and Bt** has a group represented by formula (X2) as X and all of Bc*, Bg**, Ba**, Bc** and Bt**, Bt**, Bg**, Ba**, Bc** and Bt** have a group represented by formula (X1) as X.

[0460] [53] The compound of any one of [26] to [52] above where Y in formulas (G1), (A1), (C1) and (U1) is a methoxy group and Z in formulas (G2), (A2), (C2) and (T2) is an ethylene group, or a pharmacologically acceptable salt thereof.

[0461] [54] A therapeutic agent for muscular dystrophy, comprising the oligonucleotide of [1] above or a pharmacologically acceptable salt thereof, or the compound of any one of [6], [13] to [19] and [26] to [46] or a pharmacologically acceptable salt thereof.

[0462] [55] The therapeutic agent of [54] above, which is an agent for treating Duchenne muscular dystrophy.

[0463] [56] The therapeutic agent of [54] above, whose target of treatment is those patients in which the total number of the amino acids in the open reading frame of the dystrophin gene will be a multiple of 3 when exon 19, 41, 45, 46, 44, 50, 55, 51 or 53 of the dystrophin gene has been skipped.

[0464] The term "oligonucleotide" used in the present invention encompasses not only oligo DNA or oligo RNA, but also an oligonucleotide in which at least one D-ribofuranose constituting the oligonucleotide is 2'-O-alkylated; an oligonucleotide in which at least one D-ribofuranose constituting the oligonucleotide is 2'-O,4'-C-alkylenated; an

oligonucleotide in which at least one phosphate constituting the oligonucleotide is thioated; or a combination thereof. Such oligonucleotides in which at least one D-ribofuranose constituting the oligonucleotides is 2'-O-alkylated or 2'-O, 4'-C-alkylenated have high binding strength to RNA and high resistance to nuclease. Thus, they are expected to produce higher therapeutic effect than natural nucleotides (i.e. oligo DNA or oligo RNA). Further, an oligonucleotide in which at least one phosphate constituting the oligonucleotide is thioated also has high resistance to nuclease and, thus, is expected to produce higher therapeutic effect than natural nucleotides (i.e. oligo DNA or oligo RNA). An oligonucleotide comprising both the modified sugar and the modified phosphate as described above has still higher resistance to nuclease and, thus, is expected to produce still higher therapeutic effect.

[0465] With respect to the oligonucleotide of the present invention, examples of the modification of sugar include, but are not limited to, 2'-O-alkylation (e.g. 2'-O-methylation, 2'-O-aminoethylation, 2'-O-propylation, 2'-O-allylation, 2'-O-methoxyethylation, 2'-O-butylation, 2'-O-pentylation, or 2'-O-propargylation) of D-ribofuranose; 2'-O,4'-C-alkylation (e.g. 2'-O,4'-C-ethylenation, 2'-O,4'-C-methylenation, 2'-O,4'-C-propylenation, 2'-O,4'-C-tetramethylation, or 2'-O,4'-C-pentamethylation) of D-ribofuranose; 3'-deoxy-3'-amino-2'-deoxy-D-ribofuranose; and 3'-deoxy-3'-amino-2'-deoxy-2'-fluoro-D-ribofuranose.

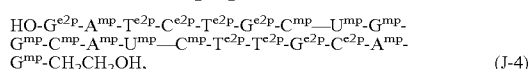
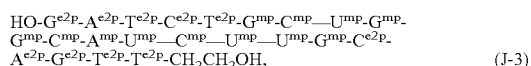
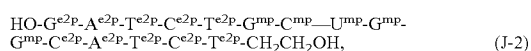
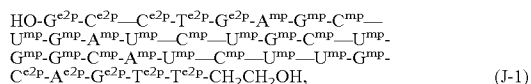
[0466] With respect to the oligonucleotide of the present invention, examples of the modification of phosphate include, but are not limited to, phosphorothioate, methylphosphonate, methylthiophosphonate, phosphorodithioate and phosphoroamidate.

[0467] With respect to Y in formulas (G1), (A1), (C1) and (U1), examples of the alkoxy group with 1-6 carbon atoms include, but are not limited to, methoxy group, aminoethoxy group, propoxy group, allyloxy group, methoxyethoxy group, butoxy group, pentyloxy group, and propargyloxy group.

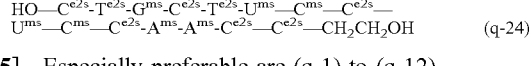
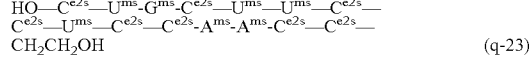
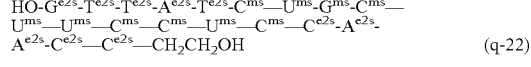
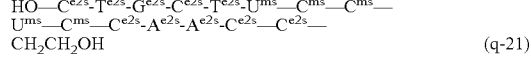
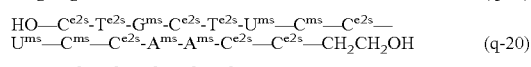
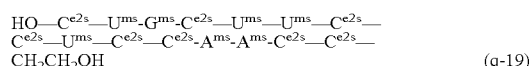
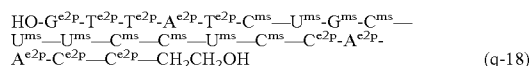
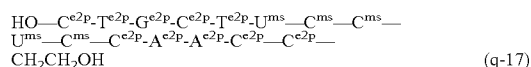
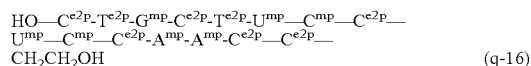
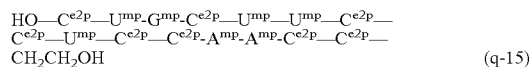
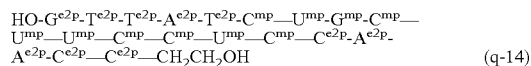
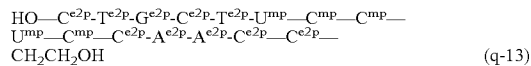
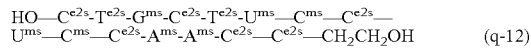
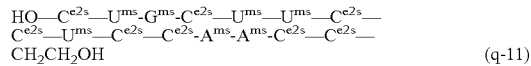
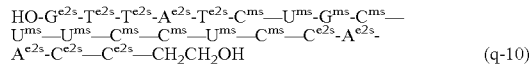
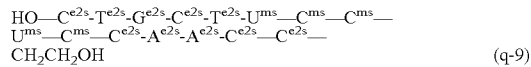
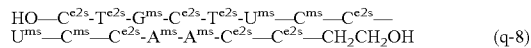
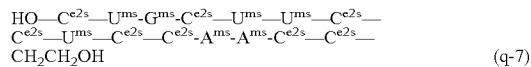
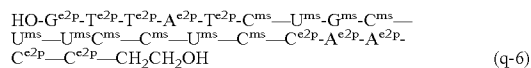
[0468] With respect to Z in formulas (G2), (A2), (C2) and (T2), examples of the alkylene group with 1-5 carbon atoms include, but are not limited to, methylene group, ethylene group, propylene group, tetramethylene group and pentamethylene group.

[0469] With respect to R¹ in formulas (G1^a), (A1^a), (C1^a) and (U1^a), examples of the alkyl group with 1-6 carbon atoms include, but are not limited to, methyl group, aminoethyl group, propyl group, allyl group, methoxyethyl group, butyl group, pentyl group and propargyl group.

[0470] Preferable examples of the compound represented by general formula (I) include the following compounds.

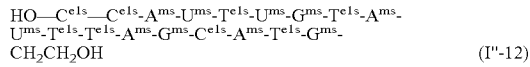
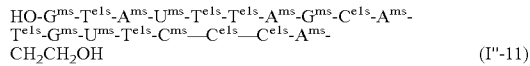
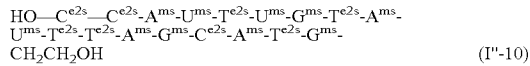
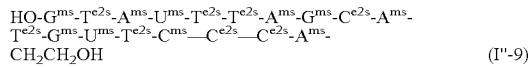
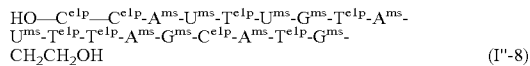
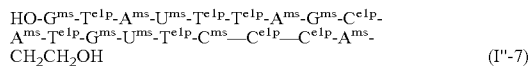
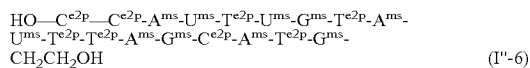
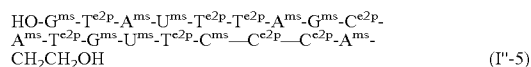
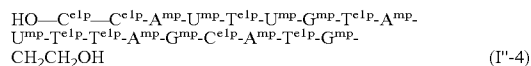
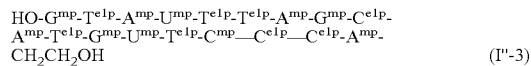
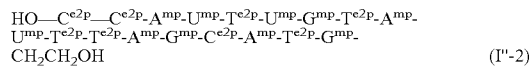
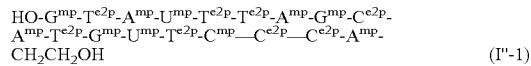


- (J-5) HO-A^{mp}.G^{mp}.C^{e2p}.T^{e2p}.G^{e2p}.A^{mp}.T^{e2p}.C^{mp}_U^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.G^{e2p}.C^{e2p}.A^{mp}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-6) HO-G^{e2p}.C^{e2p}_C^{e2p}.T^{e2p}.G^{e2p}.A^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.G^{e2p}.C^{e2p}.A^{mp}.T^{e2p}.C^{e2p}.CH₂CH₂OH,
- (J-7) HO-A^{e2p}.G^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.C^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-8) HO-A^{ms}.G^{e2s}.C^{e2s}.T^{e2s}.G^{e2s}.A^{ms}.T^{e2s}.C^{ms}_U^{ms}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{e2s}.C^{e2s}.A^{ms}.T^{e2s}.C^{e2s}.T^{e2s}.CH₂CH₂OH,
- (J-9) HO-A^{ms}.G^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.A^{ms}.T^{e2p}.C^{ms}_U^{ms}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{e2p}.C^{e2p}.A^{ms}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-10) HO-A^{mp}.G^{mp}.C^{e2p}.T^{e2p}.G^{mp}.A^{mp}.T^{e2p}.C^{e2p}.T^{e2p}.G^{mp}.C^{e2p}.T^{e2p}.G^{mp}.C^{e2p}.A^{mp}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-11) HO-A^{ms}.G^{ms}.C^{e2s}.T^{e2s}.G^{ms}.A^{ms}.T^{e2s}.C^{e2s}.T^{e2s}.G^{ms}.C^{e2s}.T^{e2s}.G^{ms}.C^{e2s}.A^{ms}.T^{e2s}.C^{e2s}.T^{e2s}.CH₂CH₂OH,
- (J-12) HO-A^{ms}.G^{ms}.C^{e2p}.T^{e2p}.G^{ms}.A^{ms}.T^{e2p}.C^{e2p}.T^{e2p}.G^{ms}.C^{e2p}.T^{e2p}.G^{ms}.C^{e2p}.A^{ms}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-13) HO-G^{e1p}.C^{e1p}_C^{e1p}.T^{e1p}.G^{e1p}.A^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.G^{mp}.C^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{e1p}.A^{e1p}.G^{e1p}.T^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-14) HO-G^{e1p}.A^{e1p}.T^{e1p}.C^{e1p}.T^{e1p}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.C^{e1p}.A^{e1p}.T^{e1p}.C^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-15) HO-G^{e1p}.A^{e1p}.T^{e1p}.C^{e1p}.T^{e1p}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.C^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{e1p}.A^{e1p}.G^{e1p}.T^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-16) HO-G^{e1p}.A^{mp}.T^{e1p}.C^{e1p}.T^{e1p}.G^{e1p}.C^{mp}_U^{mp}.G^{mp}.C^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{e1p}.A^{e1p}.G^{e1p}.T^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-17) HO-A^{mp}.G^{e1p}.C^{e1p}.T^{e1p}.G^{e1p}.A^{mp}.T^{e1p}.C^{mp}_U^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.G^{e1p}.C^{e1p}.A^{mp}.T^{e1p}.C^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-18) HO-G^{e1p}.C^{e1p}_C^{e1p}.T^{e1p}.G^{e1p}.A^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.G^{e1p}.C^{e1p}.A^{mp}.T^{e1p}.C^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-19) HO-A^{e1p}.G^{e1p}.C^{e1p}.T^{e1p}.G^{e1p}.A^{e1p}.T^{e1p}.C^{e1p}.T^{e1p}.G^{e1p}.C^{e1p}.T^{e1p}.G^{e1p}.C^{e1p}.A^{e1p}.T^{e1p}.C^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-20) HO-A^{ms}.G^{e1s}.C^{e1s}.T^{e1s}.G^{e1s}.A^{ms}.T^{e1s}.C^{ms}_U^{ms}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{e1s}.C^{e1s}.A^{ms}.T^{e1s}.C^{e1s}.T^{e1s}.CH₂CH₂OH,
- (J-21) HO-A^{ms}.G^{e1p}.C^{e1p}.T^{e1p}.G^{e1p}.A^{ms}.T^{e1p}.C^{ms}_U^{ms}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{e1p}.C^{e1p}.A^{ms}.T^{e1p}.C^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-22) HO-A^{mp}.G^{mp}.C^{e1p}.T^{e1p}.G^{mp}.A^{mp}.T^{e1p}.C^{e1p}.T^{e1p}.G^{mp}.C^{e1p}.T^{e1p}.G^{mp}.C^{e1p}.A^{mp}.T^{e1p}.C^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-23) HO-A^{ms}.G^{ms}.C^{e1s}.T^{e1s}.G^{ms}.A^{ms}.T^{e1s}.C^{e1s}.T^{e1s}.G^{ms}.C^{e1s}.T^{e1s}.G^{ms}.C^{e1s}.A^{ms}.T^{e1s}.C^{e1s}.T^{e1s}.CH₂CH₂OH,
- (J-24) HO-A^{ms}.G^{ms}.C^{e1p}.T^{e1p}.G^{ms}.A^{ms}.T^{e1p}.C^{e1p}.T^{e1p}.G^{ms}.C^{e1p}.T^{e1p}.G^{ms}.C^{e1p}.A^{ms}.T^{e1p}.C^{e1p}.T^{e1p}.CH₂CH₂OH,
- (J-25) HO-G^{e2p}.C^{e2p}_C^{e2p}.T^{e2p}.G^{e2p}.A^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.C^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{e2p}.A^{e2p}.G^{e2p}.T^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-26) HO-G^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.C^{mp}.C^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-27) HO-G^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.C^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{e2p}.A^{e2p}.G^{e2p}.T^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-28) HO-G^{e2p}.A^{mp}.T^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.C^{mp}_U^{mp}.G^{mp}.C^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{e2p}.T^{e2p}.C^{e2p}.A^{mp}.G^{mp}.CH₂CH₂OH,
- (J-29) HO-A^{mp}.G^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.A^{mp}.T^{e2p}.C^{mp}_U^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.G^{e2p}.C^{e2p}.A^{mp}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-30) HO-G^{e2p}.C^{e2p}_C^{e2p}.T^{e2p}.G^{e2p}.A^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.A^{mp}.U^{mp}_C^{mp}_U^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.G^{e2p}.C^{e2p}.A^{mp}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-31) HO-A^{e2p}.G^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.C^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-32) HO-A^{ms}.G^{e2s}.C^{e2s}.T^{e2s}.G^{e2s}.A^{ms}.T^{e2s}.C^{ms}_U^{ms}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{e2s}.C^{e2s}.A^{ms}.T^{e2s}.C^{e2s}.T^{e2s}.CH₂CH₂OH,
- (J-33) HO-A^{ms}.G^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.A^{ms}.T^{e2p}.C^{ms}_U^{ms}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{e2p}.C^{e2p}.A^{ms}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-34) HO-A^{mp}.G^{mp}.C^{e2p}.T^{e2p}.G^{mp}.A^{mp}.T^{e2p}.C^{e2p}.T^{e2p}.G^{mp}.C^{e2p}.T^{e2p}.G^{mp}.C^{e2p}.A^{mp}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-35) HO-A^{ms}.G^{mp}.C^{e2s}.T^{e2s}.G^{ms}.A^{ms}.T^{e2s}.C^{e2s}.T^{e2s}.G^{ms}.C^{e2s}.T^{e2s}.G^{ms}.G^{ms}.C^{e2s}.A^{ms}.T^{e2s}.C^{e2s}.T^{e2s}.CH₂CH₂OH,
- (J-36) HO-A^{ms}.G^{ms}.C^{e2p}.T^{e2p}.G^{ms}.A^{ms}.T^{e2p}.C^{e2p}.T^{e2p}.G^{ms}.C^{e2p}.T^{e2p}.G^{ms}.G^{ms}.C^{e2p}.A^{ms}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-37) HO-A^{mp}.G^{e1p}.C^{e2p}.T^{e2p}.G^{e1p}.A^{mp}.T^{e2p}.C^{mp}_U^{mp}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.G^{e1p}.C^{e2p}.A^{mp}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-38) HO-A^{ms}.G^{e1s}.C^{e2s}.T^{e2s}.G^{e1s}.A^{ms}.T^{e2s}.C^{ms}_U^{ms}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{e1s}.C^{e2s}.A^{ms}.T^{e2s}.C^{e2s}.T^{e2s}.CH₂CH₂OH,
- (J-39) HO-A^{ms}.G^{e1p}.C^{e2p}.T^{e2p}.G^{e1p}.A^{ms}.T^{e2p}.C^{ms}_U^{ms}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{e1p}.C^{e2p}.A^{ms}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH,
- (J-40) HO-A^{mp}.G^{mp}.C^{e1p}.T^{e1p}.G^{mp}.A^{mp}.T^{e2p}.C^{e1p}.T^{e2p}.G^{mp}.C^{e1p}.T^{e2p}.G^{mp}.C^{e2p}.A^{mp}.T^{e2p}.C^{e1p}.T^{e2p}.CH₂CH₂OH,
- (J-41) HO-A^{ms}.G^{ms}.C^{e1s}.T^{e2s}.G^{ms}.A^{ms}.T^{e2s}.C^{e1s}.T^{e2s}.G^{ms}.C^{e1s}.T^{e2s}.G^{ms}.G^{ms}.C^{e2s}.A^{ms}.T^{e2s}.C^{e1s}.T^{e2s}.CH₂CH₂OH,
- (J-42) HO-A^{ms}.G^{ms}.C^{e1p}.T^{e2p}.G^{ms}.A^{ms}.T^{e2p}.C^{e1p}.T^{e2p}.G^{ms}.C^{e1p}.T^{e2p}.G^{ms}.C^{e1p}.A^{ms}.T^{e2p}.C^{e1p}.T^{e2p}.CH₂CH₂OH,
- (J-43) HO-A^{mp}.G^{mp}.C^{mp}.T^{e2p}.G^{mp}.A^{mp}.T^{e2p}.C^{mp}.T^{e2p}.G^{mp}.C^{mp}.T^{e2p}.G^{mp}.C^{mp}.A^{mp}.T^{e2p}.C^{mp}.T^{e2p}.CH₂CH₂OH,
- (J-44) HO-A^{ms}.G^{ms}.C^{ms}.T^{e2s}.G^{ms}.A^{ms}.T^{e2s}.C^{ms}.T^{e2s}.G^{ms}.C^{ms}.T^{e2s}.G^{ms}.G^{ms}.C^{ms}.A^{ms}.T^{e2s}.C^{ms}.T^{e2s}.CH₂CH₂OH,
- (J-45) HO-A^{ms}.G^{ms}.C^{ms}.T^{e2p}.G^{ms}.A^{ms}.T^{e2p}.C^{ms}.T^{e2p}.G^{ms}.C^{ms}.T^{e2p}.G^{ms}.C^{ms}.G^{ms}.C^{ms}.A^{ms}.T^{e2p}.C^{ms}.T^{e2p}.CH₂CH₂OH,
- (J-46) HO-G^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.C^{mp}.A^{mp}_U^{mp}_C^{e2p}.T^{e2p}.T^{e2p}.G^{e2p}.C^{e2p}_CH₂CH₂OH
- (J-47) HO-G^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.G^{e2p}.C^{e2p}_U^{e2p}.G^{e2p}.G^{e2p}.C^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.CH₂CH₂OH
- (J-48) HO-G^{e1p}.A^{e1p}.T^{e1p}.C^{e1p}.T^{e1p}.G^{mp}.C^{mp}_U^{mp}.G^{mp}.C^{mp}.A^{mp}.U^{mp}_C^{e1p}.T^{e1p}.T^{e1p}.G^{e1p}.C^{e1p}_CH₂CH₂OH
- (J-49) HO-G^{e1p}.A^{e1p}.T^{e1p}.C^{e1p}.T^{e1p}.G^{e1p}.C^{e1p}_U^{e1p}.G^{e1p}.G^{e1p}.C^{e1p}.A^{e1p}.T^{e1p}.C^{e1p}.T^{e1p}.CH₂CH₂OH
- (J-50) HO-G^{e2p}.A^{e2p}.T^{e2p}.C^{e2p}.T^{e2p}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{ms}.C^{ms}.A^{ms}.U^{ms}_C^{e2p}.T^{e2p}.T^{e2p}.G^{e2p}.C^{e2p}_CH₂CH₂OH
- (J-51) HO-G^{e2s}.A^{e2s}.T^{e2s}.C^{e2s}.T^{e2s}.G^{e2s}.C^{e2s}_U^{e2s}.G^{e2s}.G^{e2s}.C^{e2s}.A^{e2s}.T^{e2s}.C^{e2s}.T^{e2s}.CH₂CH₂OH
- (J-52) HO-G^{e1p}.A^{e1p}.T^{e1p}.C^{e1p}.T^{e1p}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{ms}.C^{ms}.A^{ms}.U^{ms}_C^{e1p}.T^{e1p}.T^{e1p}.G^{e1p}.C^{e1p}_CH₂CH₂OH
- (J-53) HO-G^{e1s}.A^{e1s}.T^{e1s}.C^{e1s}.T^{e1s}.G^{e1s}.C^{e1s}_U^{e1s}.G^{e1s}.G^{e1s}.C^{e1s}.A^{e1s}.T^{e1s}.C^{e1s}.T^{e1s}.CH₂CH₂OH
- (J-54) HO-G^{e2s}.A^{e2s}.T^{e2s}.C^{e2s}.T^{e2s}.G^{ms}.C^{ms}_U^{ms}.G^{ms}.G^{ms}.C^{ms}.A^{ms}.U^{ms}_C^{e2s}.T^{e2s}.T^{e2s}.G^{e2s}.C^{e2s}_CH₂CH₂OH



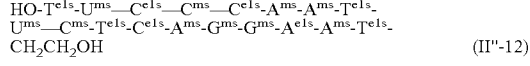
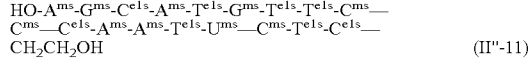
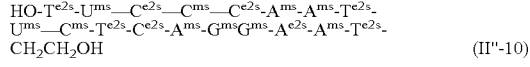
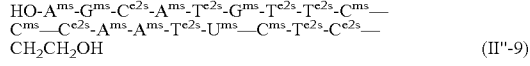
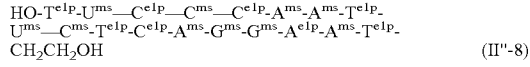
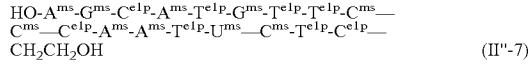
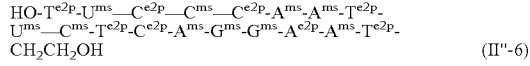
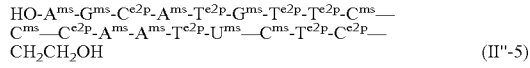
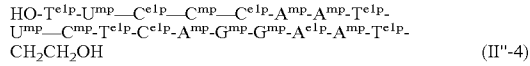
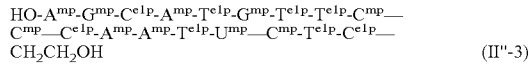
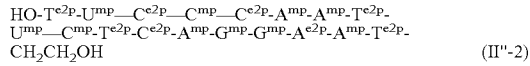
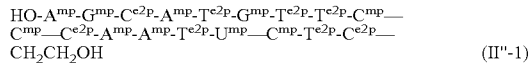
[0485] Especially preferable are (q-1) to (q-12).

[0486] Preferable examples of the compound represented by general formula (I') include the following compounds.



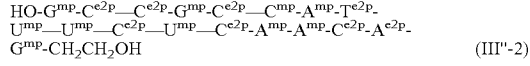
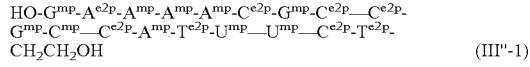
[0487] Especially preferable are (I''-1), (I''-2), (I''-9) and (I''-10).

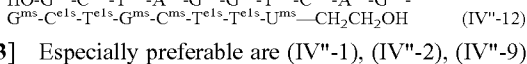
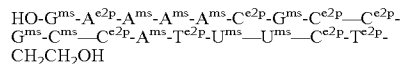
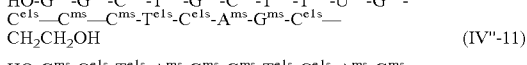
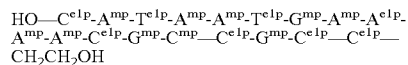
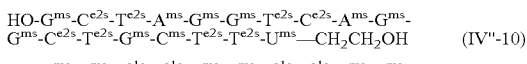
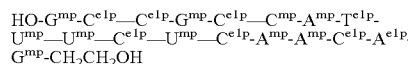
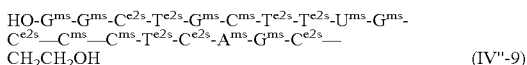
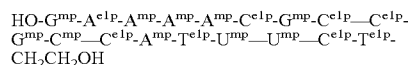
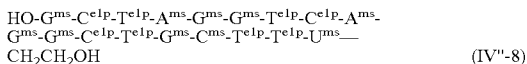
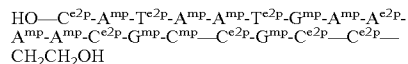
[0488] Preferable examples of the compound represented by general formula (II') include the following compounds.



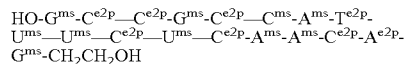
[0489] Especially preferable are (II''-1), (II''-2), (II''-9) and (II''-10).

[0490] Preferable examples of the compound represented by general formula (III'') include the following compounds.

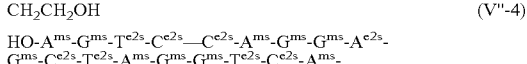
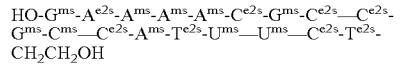
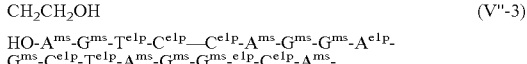
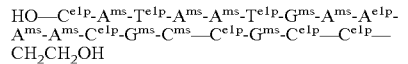
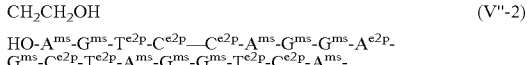
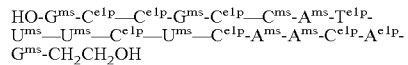
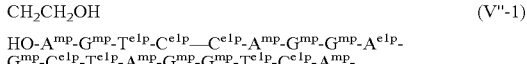
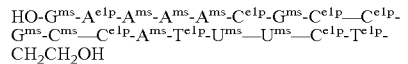
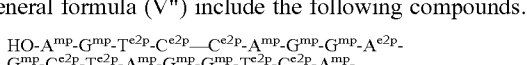
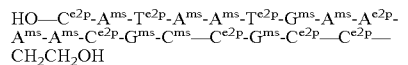




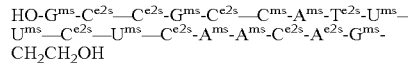
[0493] Especially preferable are (IV"-1), (IV"-2), (IV"-9) and (IV"-10).



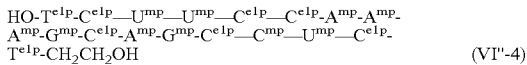
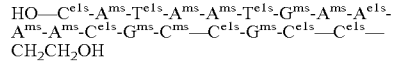
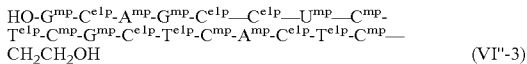
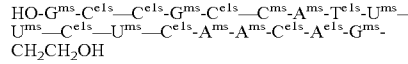
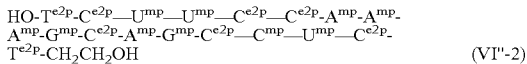
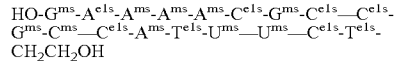
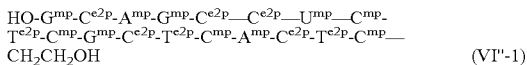
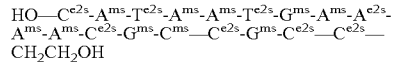
[0494] Preferable examples of the compound represented by general formula (V") include the following compounds.



[0495] Especially preferable are (V"-1) and (V"-5).

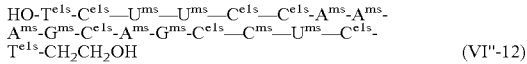
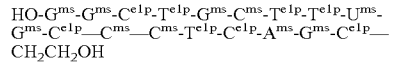
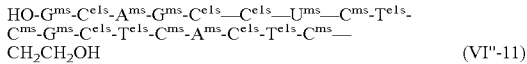
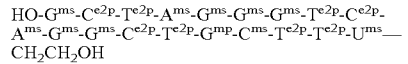
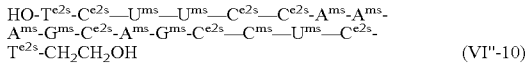
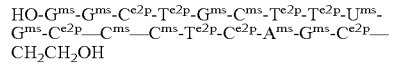
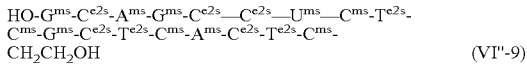
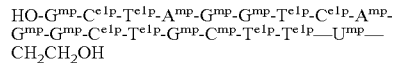
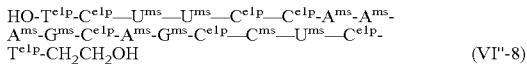
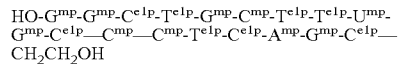
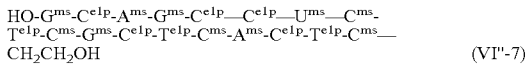
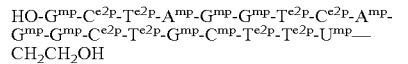
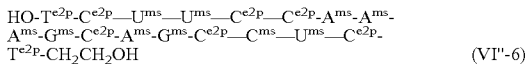
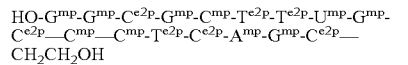
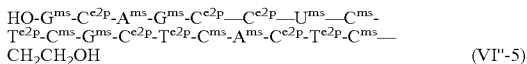


[0496] Preferable examples of the compound represented by general formula (VI") include the following compounds.



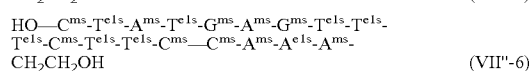
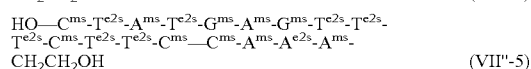
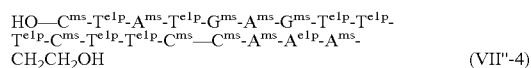
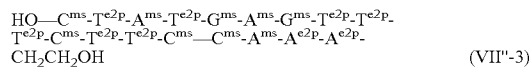
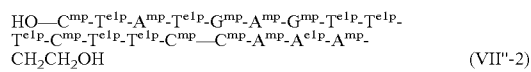
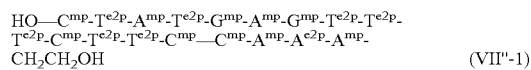
[0491] Especially preferable are (III"-1), (III"-2), (III"-3), (III"-13), (III"-14) and (III"-15).

[0492] Preferable examples of the compound represented by general formula (IV") include the following compounds.



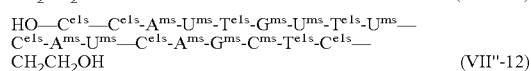
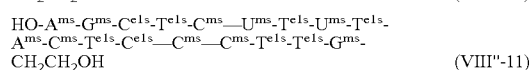
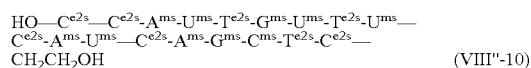
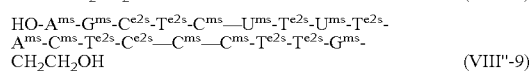
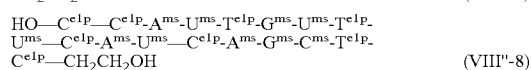
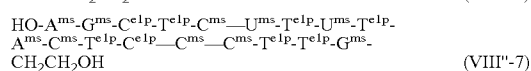
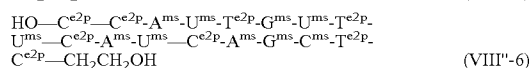
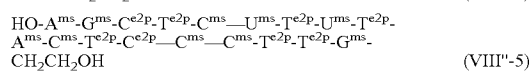
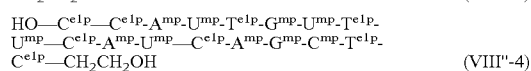
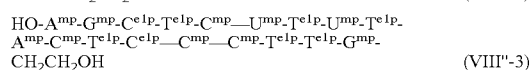
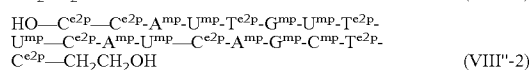
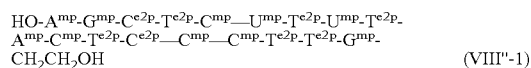
[0497] Especially preferable are (VI"-1), (VI"-2), (VI"-9) and (VI"-10).

[0498] Preferable examples of the compound represented by general formula (VII") include the following compounds.



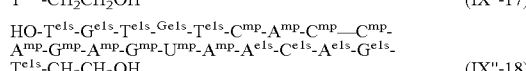
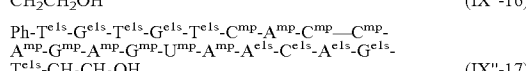
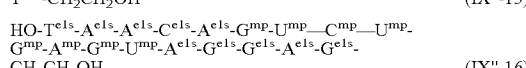
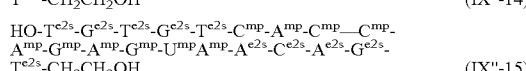
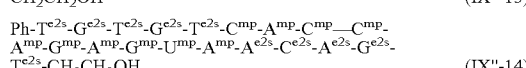
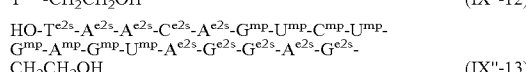
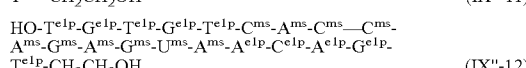
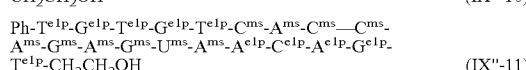
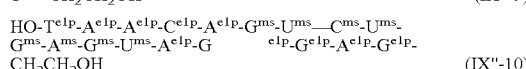
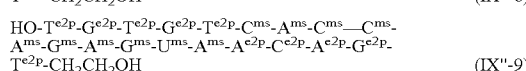
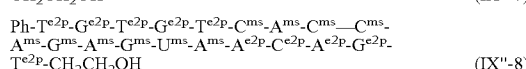
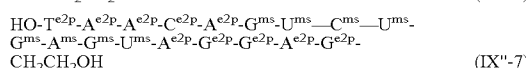
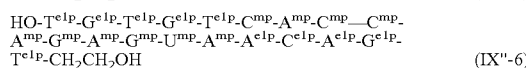
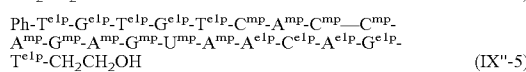
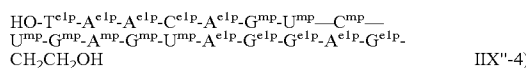
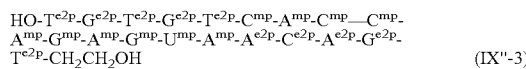
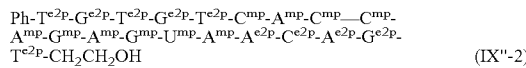
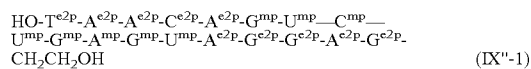
[0499] Especially preferable are (VII"-1) and (VII"-5).

[0500] Preferable examples of the compound represented by general formula (VIII") include the following compounds.



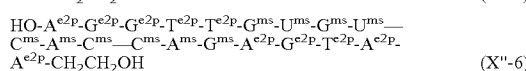
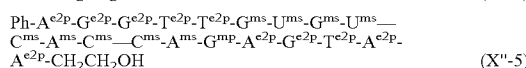
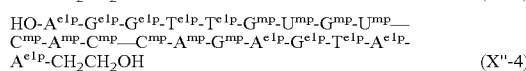
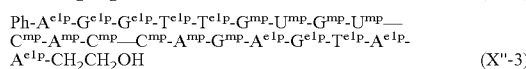
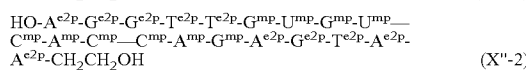
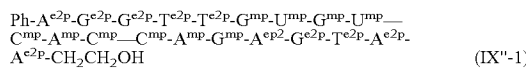
[0501] Especially preferable are (VIII"-1), (VIII"-2), (VIII"-9) and (VIII"-10).

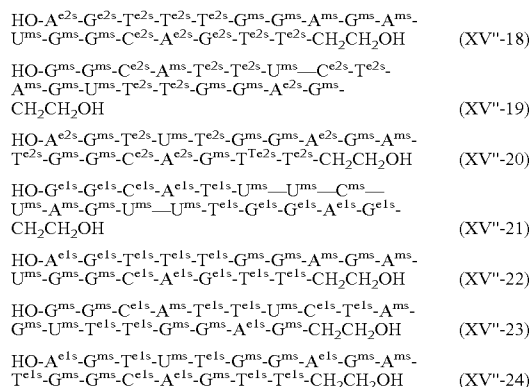
[0502] Preferable examples of the compound represented by general formula (IX") include the following compounds.



[0503] Especially preferable are (IX"-1), (IX"-2), (IX"-3), (IX"-13), (IX"-14) and (IX"-15).

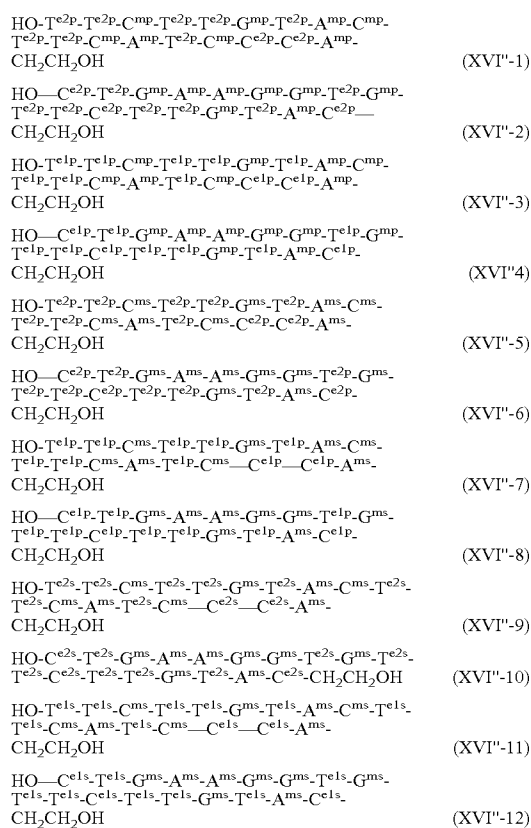
[0504] Preferable examples of the compound represented by general formula (X") include the following compounds.





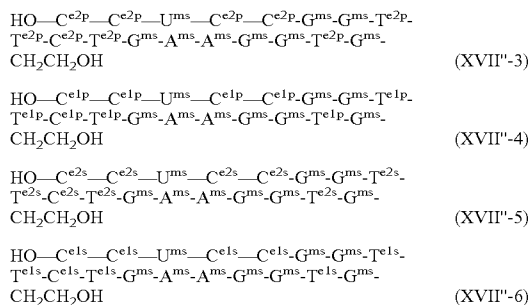
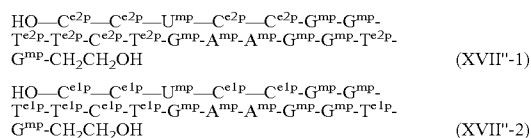
[0515] Especially preferable are (XV"-1), (XV"-2), (XV"-3), (XV"-4), (XV"-17), (XV"-18), (XV"-19) and (XV"-20).

[0516] Preferable examples of the compound represented by general formula (XVI") include the following compounds.



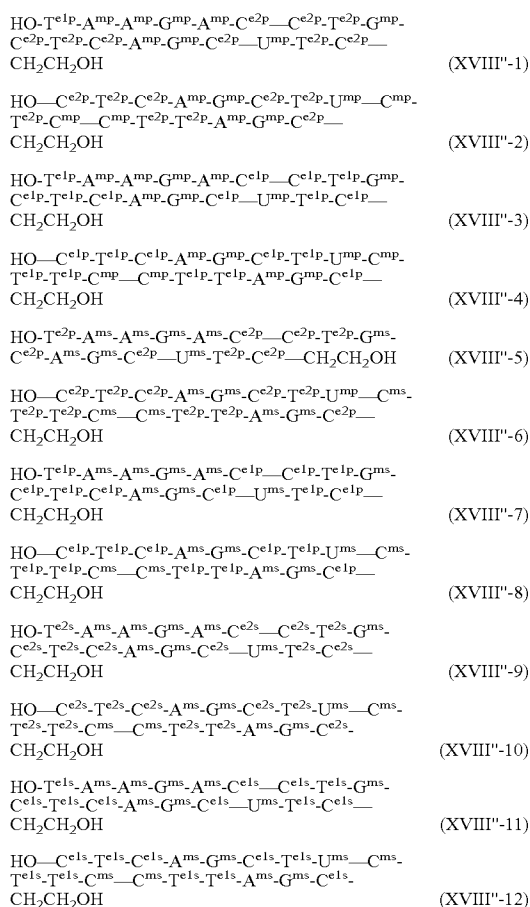
[0517] Especially preferable are (XVI"-1), (XVI"-2), (XVI"-9) and (XVI"-10).

[0518] Preferable examples of the compound represented by general formula (XVII") include the following compounds.



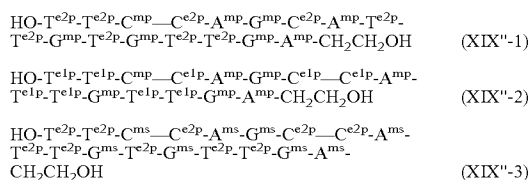
[0519] Especially preferable are (XVII"-1) and (XVII"-5).

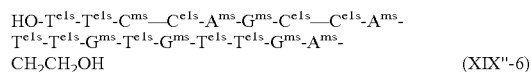
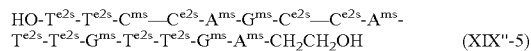
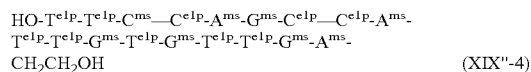
[0520] Preferable examples of the compound represented by general formula (XVIII") include the following compounds.



[0521] Especially preferable are (XVIII"-1), (XVIII"-2), (XVIII"-9) and (XVIII"-10).

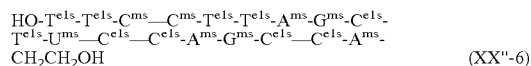
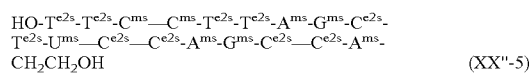
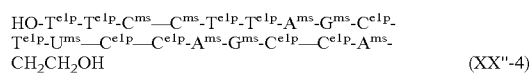
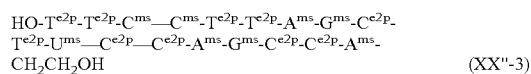
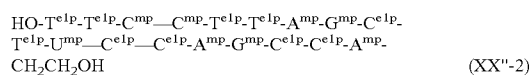
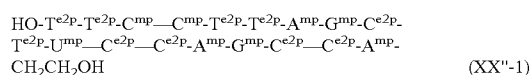
[0522] Preferable examples of the compound represented by general formula (XIX") include the following compounds.





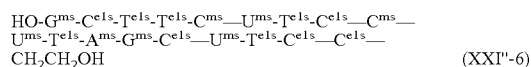
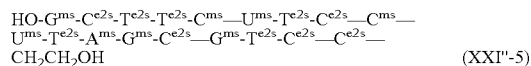
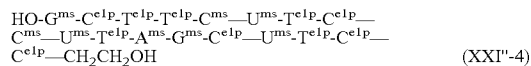
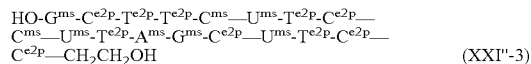
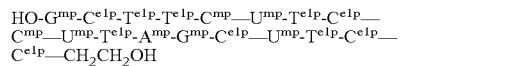
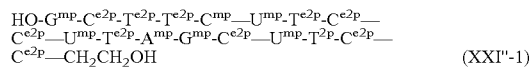
[0523] Especially preferable are (XIX''-1) and (XIX''-5).

[0524] Preferable examples of the compound represented by general formula (XX'') include the following compounds.



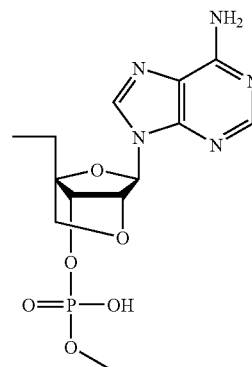
[0525] Especially preferable are (XX''-1) and (XX''-5).

[0526] Preferable examples of the compound represented by general formula (XXI'') include the following compounds.

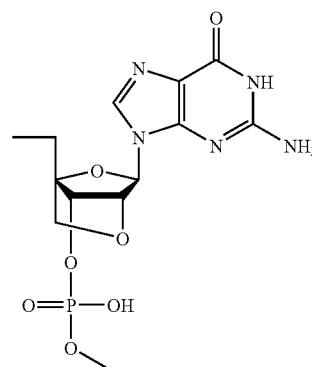


[0527] Especially preferable are (XXI''-1) and (XXI''-5).

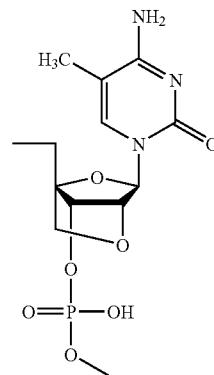
[0528] In the present specification, A^{e1p}, G^{e1p}, C^{e1p}, T^{e1p}, A^{e2p}, G^{e2p}, C^{e2p}, T^{e2p}, A^{mp}, G^{mp}, C^{mp}, U^{mp}, A^{e1s}, G^{e1s}, C^{e1s}, T^{e1s}, A^{e2s}, G^{e2s}, C^{e2s}, T^{e2s}, A^{ms}, G^{ms}, C^{ms}, U^{ms} and Ph are groups having the following structures, respectively.



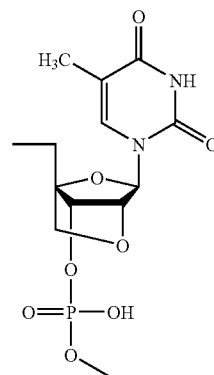
(A^{e1p})



(G^{e1p})

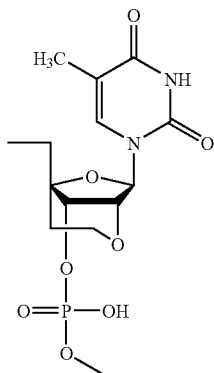
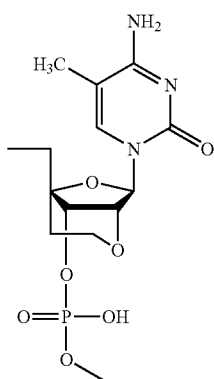
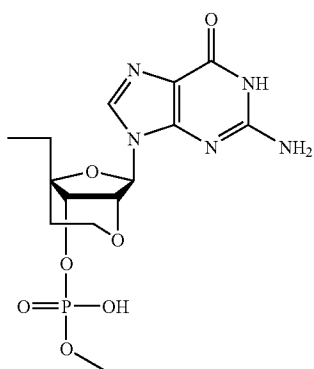
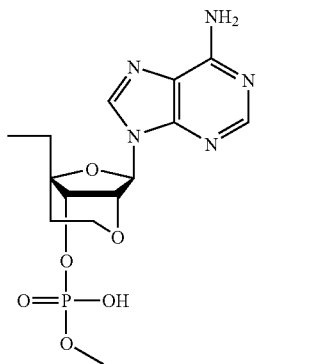


(C^{e1p})



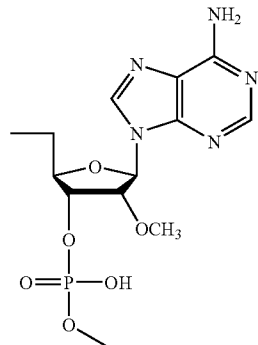
(T^{e1p})

-continued



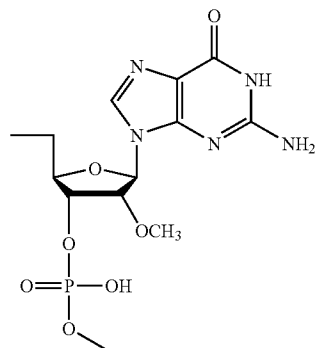
-continued

(A^{e2P})



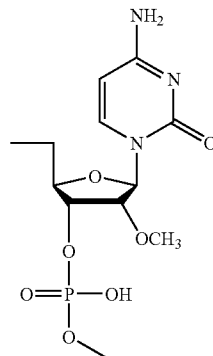
(A^{mp})

(G^{e2P})



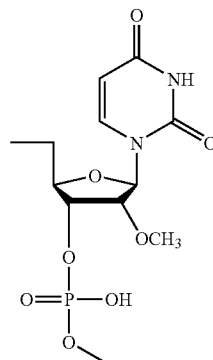
(G^{mp})

(C^{e2P})



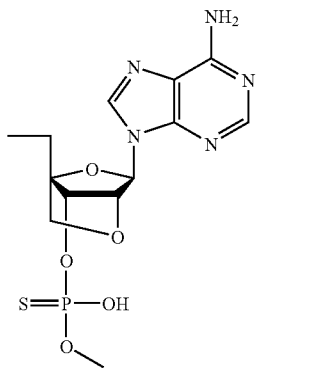
(C^{mp})

(U^{e2P})



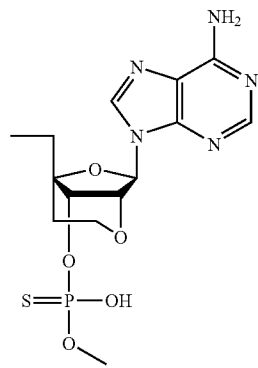
(U^{mp})

-continued

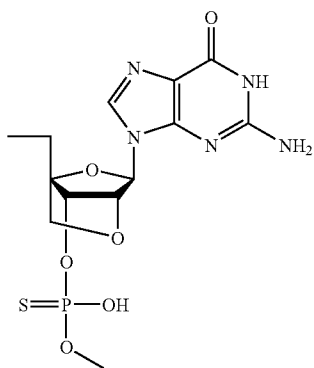


(A^{e1s})

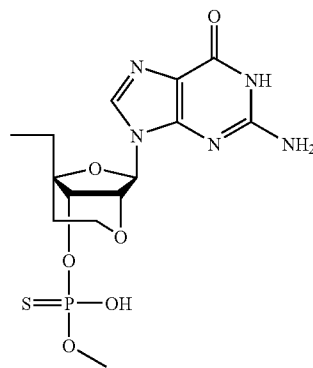
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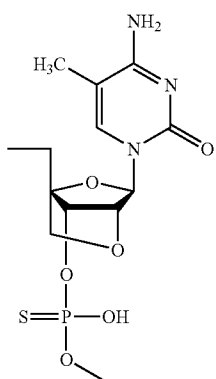
(A^{e2s})



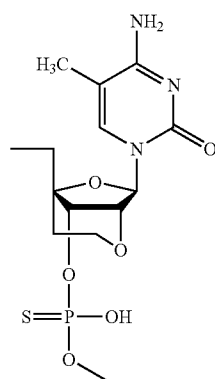
(G^{e1s})



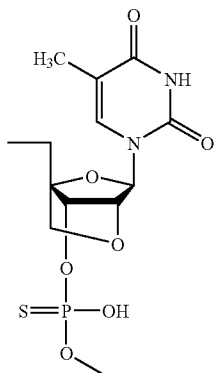
(G^{e2s})



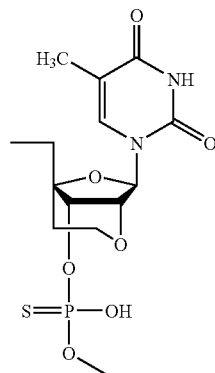
(C^{e1s})



(C^{e2s})

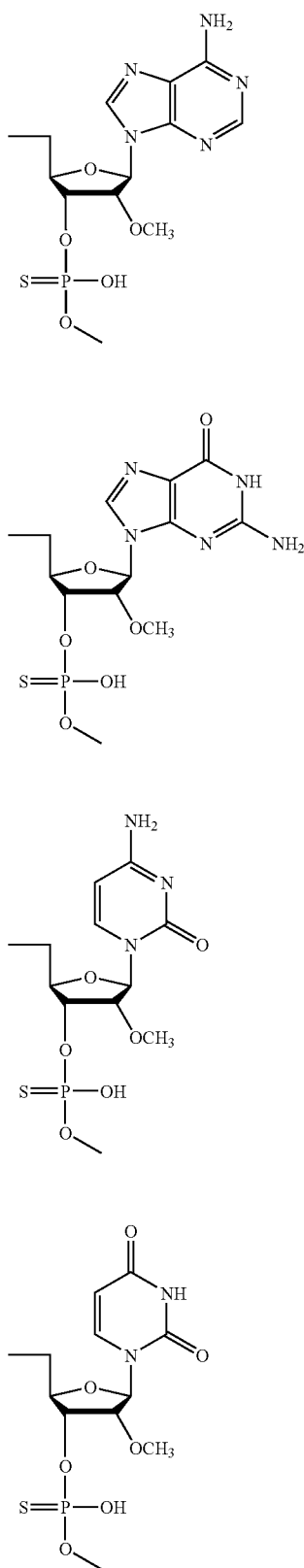


(T^{e1s})

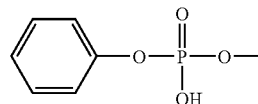


(T^{e2s})

-continued



-continued

(A^{ms})

(Ph)

(G^{ms})(C^{ms})(U^{ms})

[0529] The term “pharmacologically acceptable salt thereof” used in the present specification refers to salts of the oligonucleotide of the invention (e.g. oligonucleotide having the nucleotide sequence as shown in any one of SEQ ID NOS: 1-6, 10-22, 30-78, 87 or 88) or salts of those compounds represented by general formulas (I), (I') to (VII') and (I'') to (XXI''). Examples of such salts include metal salts such as alkali metal salts (e.g. sodium salts, potassium salts, lithium salts), alkaline earth metal salts (e.g. calcium salts, magnesium salts), aluminium salts, iron salts, zinc salts, copper salts, nickel salts, cobalt salts and the like; amine salts such as inorganic salts (e.g. ammonium salts), organic salts [e.g. t-octylamine salts, dibenzylamine salts, morpholine salts, glucosamine salts, phenylglycine alkyl ester salts, ethylenediamine salts, N-methylglucamine salts, guanidine salts, diethylamine salts, triethylamine salts, dicyclohexylamine salts; N',N'-dibenzylethylenediamine salts, chlorprocaine salts, procaine salts, diethanolamine salts, N-benzylphenethylamine salts, piperazine salts, tetramethylammonium salts, tris(hydroxymethyl)aminomethane salts] and the like; inorganic acid salts such as halogenated hydroacid salts (e.g. hydrofluorates, hydrochlorides, hydrobromates, hydriodates), nitrates, perchlorates, sulfates, phosphates and the like; organic acid salts such as lower alkane sulfonates (e.g. methanesulfonates, trifluoromethanesulfonates, ethanesulfonates), aryl sulfonates (e.g. benzenesulfonates, p-toluenesulfonates), acetates, malates, fumarates, succinates, citrates, tartrates, oxalates, maleates and the like; and amino acid salts (e.g. glycine salts, lysine salts, arginine salts, ornithine salts, glutamates, aspartates). These salts may be prepared according to known methods.

[0530] It should be noted that compounds represented by general formulas (I), (I') to (VII') and (I'') to (XXI'') may occur as hydrates and that such hydrates are also included in the present invention.

[0531] The oligonucleotide of the invention, the compounds represented by general formulas (I), (I') to (VII') and (I'') to (XXI'') (hereinafter, referred to as the “compound of the invention”) and pharmacologically acceptable salts thereof are effective as pharmaceuticals for treating muscular dystrophy.

[0532] The compound of the invention may be synthesized based on the method described in the literature (Nucleic Acids Research, 12: 4539 (1984)) using a commercial synthesizer (e.g. PerkinElmer Model 392 employing the phosphoroamidite method). As to the phosphoroamidite reagents used in the synthesis, commercial reagents are available for natural nucleosides and 2'-O-methylnucleosides (i.e. 2'-O-methylguanosine, 2'-O-methyladenosine, 2'-O-methylcytosine and 2'-O-methyluridine). As to 2'-O-alkyl-guanosine, -adenosine, -cytosine and -uridine where the alkyl group has 2-6 carbon atoms, they may be synthesized or purchased as described below.

[0533] 2'-O-aminoethyl-guanosine, -adenosine, -cytosine and -uridine may be synthesized according to Blommers et al., *Biochemistry* (1998), 37: 17714-17725.

[0534] 2'-O-propyl-guanosine, -adenosine, -cytosine and -uridine may be synthesized according to Lesnik, E. A. et al., *Biochemistry* (1993), 32: 7832-7838.

[0535] 2'-O-allyl-guanosine, -adenosine, -cytosine and -uridine are commercially available.

[0536] 2'-O-methoxyethyl-guanosine, -adenosine, -cytosine and -uridine may be synthesized according to U.S. Pat. No. 6,261,840 or Martin, P., *Helv. Chim. Acta.* (1995) 78: 486-504.

[0537] 2'-O-butyl-guanosine, -adenosine, -cytosine and -uridine may be synthesized according to Lesnik, E. A. et al., *Biochemistry* (1993), 32: 7832-7838.

[0538] 2'-O-pentyl-guanosine, -adenosine, -cytosine and -uridine may be synthesized according to Lesnik, E. A. et al., *Biochemistry* (1993), 32: 7832-7838.

[0539] 2'-O-propargyl-guanosine, -adenosine, -cytosine and -uridine are commercially available.

[0540] 2'-O,4'-C-methylene-guanosine, -adenosine, 5-methyl-cytosine and -thymidine may be synthesized according to the method described in WO99/14226. 2'-O,4'-C-alkylene-guanosine and -adenosine where the alkylene group has 2-5 carbon atoms, 5-methyl-cytosine and -thymidine may be synthesized according to the method described in WO00/47599.

[0541] In the thioation of phosphate groups, thioate derivatives may be obtained based on the methods described in *Tetrahedron Letters*, 32, 3005 (1991) and *J. Am. Chem. Soc.*, 112, 1253 (1990), using sulfur and a reagent such as tetraethylthiuram disulfide (TETD; Applied Biosystems) or Beaucage reagent (Glen Research) which reacts with a trivalent phosphate to form a thioate.

[0542] With respect to the controlled pore glass (DPG) used in the synthesizer, use of a modified CPG (described in Example 12b of Japanese Unexamined Patent Publication No. H7-87982) allows synthesis of oligonucleotides to which 2-hydroxyethylphosphate group is attached at the 3' end. Further, use of 3'-amino-Modifier C3 CPG, 3'-amino-Modifier C7 CPG; Glyceryl CPG (Glen Research), 3'-specer C3 SynBase CPG 1000 or 3'-specer C9 SynBase CPG 1000 (Link Technologies) allows synthesis of oligonucleotides to which a hydroxyalkylphosphate group or aminoalkylphosphate group is attached at the 3' end.

[0543] The compounds of the present invention and pharmacologically acceptable salts thereof have an effect of inducing skipping of exon 19, 41, 45, 46, 44, 50, 55, 51 or 53 of the dystrophin gene. The compounds of the invention represented by general formulas (I), (I') to (VII') and (II") to (XXI") and pharmacologically acceptable salts thereof have high binding strength to RNA and high resistance to nuclease. Therefore, the compounds of the invention and pharmacologically acceptable salts thereof are useful as pharmaceuticals for treating muscular dystrophy.

[0544] When the compound of the invention or a pharmacologically acceptable salt thereof is used as a therapeutic for muscular dystrophy, the compound or a pharmacologically acceptable salt or ester thereof may be administered by

itself. Alternatively, the compound or a pharmacologically acceptable salt or ester thereof may be mixed with appropriate pharmacologically acceptable excipients or diluents, prepared into tablets, capsules, granules, powders, syrups, etc. and administered orally; or prepared into injections, suppositories, patches, external medicines, etc. and administered parenterally.

[0545] These formulations may be prepared by well-known methods using additives such as excipients [organic excipients e.g. sugar derivatives (such as lactose, white sugar, glucose, mannitol and sorbitol), starch derivatives (such as corn starch, potato starch, a starch and dextrin), cellulose derivatives (such as crystalline cellulose), gum arabic, dextran, pullulan and the like; and inorganic excipients e.g. silicate derivatives (such as light silicic acid anhydride, synthetic aluminium silicate, calcium silicate and magnesium aluminate metasilicate), phosphates (such as calcium hydrogenphosphate), carbonates (such as calcium carbonate), sulfates (such as calcium sulfate) and the like], lubricants (e.g. metal salts of stearic acid such as stearic acid, calcium stearate, and magnesium stearate; talc; colloidal silica; waxes such as bees wax and spermaceti; boric acid; adipic acid; sulfates such as sodium sulfate; glycol; fumaric acid; sodium benzoate; DL leucine; lauryl sulfates such as sodium lauryl sulfate and magnesium lauryl sulfate; silicic acid materials such as silicic acid anhydride and silicic acid hydrate; above-mentioned starch derivatives), binders (e.g. hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, macrogol, compounds enumerated above as excipients), disintegrants (e.g. cellulose derivatives such as low-substituted hydroxypropylcellulose, carboxymethylcellulose, calcium carboxymethylcellulose, internally crosslinked sodium carboxymethylcellulose; chemically modified starches/celluloses such as carboxymethyl starch, sodium carboxymethyl starch, crosslinked polyvinylpyrrolidone), emulsifiers (e.g. colloidal clay such as bentonite, Veegum; metal hydroxides such as magnesium hydroxide, aluminium hydroxide; anionic surfactants such as sodium lauryl sulfate, calcium stearate; cationic surfactants such as benzalkonium chloride; nonionic surfactants such as polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid esters, sucrose fatty acid ester), stabilizers (e.g. paroxybenzoic acid esters such as methyl paraben, propyl paraben; alcohols such as chlorobutanol, benzyl alcohol, phenylethyl alcohol; benzalkonium chloride; phenols such as phenol, cresol; thimerosal; dehydroacetic acid; sorbic acid), flavoring/aromatic agents (e.g. conventionally used sweeteners, acidifiers, aromatics, etc.) or diluents.

[0546] The therapeutic agent of the present invention comprises preferably 0.05-5 gmoles/ml of the compound of the invention or a pharmacologically acceptable salt thereof, 0.02-10% w/v of carbohydrates or polyhydric alcohols, and 0.01-0.4% w/v of pharmacologically acceptable surfactants. More preferable range for the content of the compound of the invention or a pharmacologically acceptable salt thereof is 0.1-1 μ moles/ml.

[0547] For the above carbohydrates, monosaccharides and/or disaccharides are especially preferable. Examples of these carbohydrates and polyhydric alcohols include, but are not limited to, glucose, galactose, mannose, lactose, maltose, mannitol and sorbitol. These may be used alone or in combination.

[0548] Preferable examples of surfactants include, but are not limited to, polyoxyethylene sorbitan mono- to tri-esters, alkyl phenyl polyoxyethylene, sodium taurocholate, sodium cholate and polyhydric alcohol esters. Especially preferable are polyoxyethylene sorbitan mono- to tri-esters, where especially preferable esters are oleates, laurates, stearates and palmitates. These surfactants may be used alone or in combination.

[0549] More preferably, the therapeutic agent of the invention comprises 0.03-0.09 M of pharmacologically acceptable neutral salt, e.g. sodium chloride, potassium chloride and/or calcium chloride.

[0550] Still more preferably, the therapeutic agent of the invention may comprise 0.002-0.05 M of pharmacologically acceptable buffer. Examples of preferable buffers include sodium citrate, sodium glycinate, sodium phosphate and tris(hydroxymethyl)aminomethane. These buffers may be used alone or in combination.

[0551] The above-described therapeutic agent of the invention may be supplied in the state of solution. However, considering the storing of the therapeutic agent for some period of time, usually, it is preferable to lyophilize the therapeutic agent for the purpose of stabilizing the antisense oligonucleotide and thereby preventing the lowering of its therapeutic effect. The lyophilized therapeutic agent may be reconstructed with a dissolving liquid (e.g. distilled water for injection) at the time of use, and used in the state of solution. Thus, the therapeutic agent of the invention encompasses such a lyophilized therapeutic agent to be reconstructed with a dissolving liquid at the time of use so that individual components fall under specific concentration ranges. In order to enhance the solubility of the lyophilized product, the therapeutic agent may further contain albumin or amino acids such as glycine.

[0552] When the compound of the invention or a pharmacologically acceptable salt thereof is administered to humans, for example, the compound or salt may be administered orally or intravenously at a dose of about 0.1-100 mg/kg body weight per day, preferably 1-50 mg/kg body weight per day for adult patients once a day or divided into several portions. The dose and the number of times of administration may be appropriately changed depending on the type of disease, conditions, the age of the patient, the route of administration, etc.

[0553] Administration of the compound of the invention or a pharmacologically acceptable salt thereof to DMD patients may be performed, for example, as described below. Briefly, the compound of the invention or a pharmacologically acceptable salt thereof may be prepared by methods well-known to those skilled in the art, sterilized by conventional methods and then formulated into, for example, an injection solution with a concentration of 1200 µg/ml. This solution is, for example, drip-fed to the patient intravenously in the form of infusion so that the antisense oligonucleotide is administered to the patient at a dose of, for example, 20 mg/kg body weight. Such administration may be repeated, for example, 4 times at intervals of 2 weeks. Then, while confirming the therapeutic effect using indicators such as expression of dystrophin protein in muscle biopsy tissues, serum creatine kinase levels and clinical symptoms, this treatment is repeated appropriately. If therapeutic effect is recognized and yet no definite side effect is observed, this

treatment is continued; in principle, the administration is continued throughout life time.

[0554] The present specification includes the contents disclosed in the specifications and/or drawings of the Japanese Patent Applications No. 2002-340857 and No. 2003-204381 based on which the present application claims priority.

BRIEF DESCRIPTION OF THE DRAWINGS

[0555] FIG. 1 is a photograph of electrophoresis showing the results of amplification of exons 17-20 by RT-PCR using RNAs extracted from muscular cells transfected with the compound of Example 1 (AO1) and from untreated muscular cells.

[0556] FIG. 2 a photograph of electrophoresis showing the results of amplification of exons 17-20 by RT-PCR using RNAs extracted from muscular cells transfected with any one of the compounds of Examples 1-7 (AO1, AO14, AO15, AO16, AO18, AO19 and AO25), 13 (AO17) and 14 (AO24) and from untreated muscular cells.

[0557] FIG. 3 a photograph of electrophoresis showing the results of amplification of exons 17-20 by RT-PCR using RNAs extracted from muscular cells transfected with any one of the compounds of Examples 5 (AO18) and 8-12 (AO50, AO51, AO52, AO53 and AO54) and from untreated muscular cells.

[0558] FIG. 4 shows the effects of the compounds of Examples 15-19 (AO20, AO26, AO55, AO56 and AO57) on exon 41 skipping.

[0559] FIG. 5 shows the effects of the compounds of Examples 17-25 (AO55, AO56, AO57, AO76, AO77, AO78, AO79, AO80 and AO81) on exon 41 skipping.

[0560] FIG. 6 shows the effects of the compounds of Examples 26-29 (AO33, AO85, AO86 and AO87) on exon 45 skipping.

[0561] FIG. 7 shows the effects of the compounds of Examples 32-35 (AO23, AO27, AO28 and AO29) on exon 46 skipping.

[0562] FIG. 8 shows the effects of the compounds of Examples 33 and 36 (AO27 and AO48) on exon 46 skipping.

[0563] FIG. 9 shows the effects of the compounds of Examples 31, 33 and 34 and the compounds of Reference Examples 1-3 (AO2, AO27 and AO28; hAON4, hAON6 and hAON8) on exon 46 skipping.

[0564] FIG. 10 shows the effects of the compounds of Examples 42-47 (AO100, AO102, AO103, AO104, AO105 and AO106) on exon 44 skipping.

[0565] FIG. 11 shows the effects of the compounds of Examples 42, 62, 63, 47, 64, 46 and 65 (AO100, AO124, AO125, AO106, AO126, AO105 and AO127) on exon 44 skipping.

[0566] FIG. 12 shows the effects of the compounds of Examples 48-53 (AO108, AO109, AO110, AO111, AO112 and AO113) on exon 50 skipping.

[0567] FIG. 13 shows the effects of the compounds of Examples 49, 51, 52 and 66 (AO109, AO111, AO112 and AO128) on exon 50 skipping.

[0568] FIG. 14 shows the effects of the compounds of Examples 68-71 (AO3, AO4, AO5 and AO6) on exon 51 skipping.

[0569] FIG. 15 shows the effects of the compounds of Examples 72-74 (AO8, AO9 and AO10) on exon 51 skipping.

[0570] FIG. 16 shows the effect of the compound of Example 75 (AO37) on exon 51 skipping.

[0571] FIG. 17 shows the effects of the compounds of Examples 76-78 (AO39, AO43 and AO58) on exon 51 skipping.

[0572] FIG. 18 shows the effects of the compounds of Examples 79-86 (AO64, AO65, AO66, AO67, AO69, AO70, AO71 and AO72) on exon 53 skipping.

[0573] FIG. 19 shows the effects of the compounds of Examples 87-90 (AO95, AO96, AO97 and AO98) on exon 53 skipping.

[0574] FIG. 20 shows the effects of the compounds of Examples 54-61 (AO114, AO115, AO116, AO118, AO119, AO120, AO122 and AO123) on exon 55 skipping.

[0575] FIG. 21 shows the effects of the compounds of Examples 54, 55 and 67 (AO114, AO115 and AO129) on exon 55 skipping.

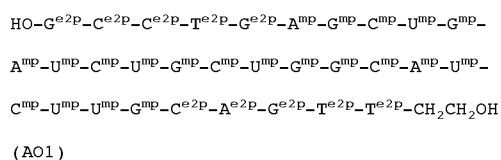
[0576] FIG. 22 shows the effects of the compounds of Examples 33, 37, 38, 39, 40 and 41 (AO27, AO89, AO90, AO91, AO92 and AO93) on exon 46 skipping.

BEST MODES FOR CARRYING OUT THE INVENTION

[0577] Hereinbelow, the present invention will be described specifically with reference to the following Examples. These Examples are provided only for the purpose of illustration, and they are not intended to limit the present invention.

EXAMPLE 1

[0578] Synthesis of



[0579] The subject compound was synthesized with an automated nucleic acid synthesizer (PerkinElmer ABI model 394 DNA/RNA synthesizer) at a 40 nmol scale. The concentrations of solvents, reagents and phosphoroamidites at individual synthesis cycles were the same as used in the synthesis of natural oligonucleotides. The solvents, reagents and phosphoroamidites of 2'-O-methylnucleoside (adenosine form: product No. 27-1822-41; guanosine form: product No. 27-1826-41; cytosine form: product No. 27-1823-02; uridine form: product No. 27-1825-42) were products from Amersham Pharmacia. As non-natural phosphoroamidites, those compounds disclosed in Example 14 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-6-N-benzoyladenine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite), Example 27 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-2-N-isobutylguanosine-3'-O-(2-cyanoethyl N,N-diisopropyl)phospho-

amidite), Example 22 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-4-N-benzoyl-5-methylcytosine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite), and Example 9 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-5-methyluridine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite) of Japanese Unexamined Patent Publication No. 2000-297097 were used. The subject compound was synthesized on a modified control pore glass (CPG) (disclosed in Example 12b of Japanese Unexamined Patent Publication No. H7-87982) as a solid support. However, the time period for condensation of amidites was 15 min.

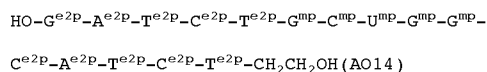
[0580] The protected oligonucleotide analogue having the sequence of interest was treated with concentrated aqueous ammonia to thereby cut out the oligomer from the support and, at the same time, remove the protective cyanoethyl groups on phosphorus atoms and the protective groups on nucleic acid bases. The solvent was distilled off under reduced pressure, and the resultant residue was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.06 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 9.61 min. (0.393 A₂₆₀ units) (λ_{max} (H₂O)=260 nm)

[0581] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 10628.04; measured value: 10626.86).

[0582] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2571-2607 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 2

[0583] Synthesis of



[0584] The compound of Example 2 having a sequence of interest was synthesized in the same manner as in Example 1. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.64 min was collected. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA),

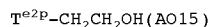
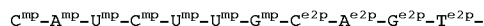
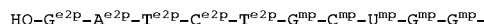
pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 4.58 min. (0.806 A₂₆₀ units) (λ_{max} (H₂O)=261 nm)

[0585] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 5281.60; measured value: 5281.40).

[0586] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2592 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 3

[0587] Synthesis of



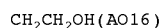
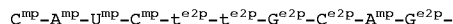
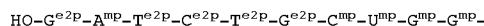
[0588] The compound of Example 3 having a sequence of interest was synthesized in the same manner as in Example 1. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.47 min was collected. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15% 60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.38 min. (15.05 A₂₆₀ units) (λ_{max} (H₂O)=259 nm)

[0589] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 7609.08; measured value: 7609.43).

[0590] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2571-2592 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 4

[0591] Synthesis of



[0592] The compound of Example 4 having a sequence of interest was synthesized in the same manner as in Example 1. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→55% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.23 min was collected. When

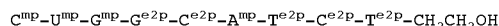
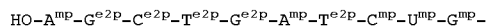
analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.34 min. (6.13 A₂₆₀ units) (λ_{max} (H₂O)=259.4 nm)

[0593] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6968.69; measured value: 6969.14).

[0594] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2573-2592 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 5

[0595] Synthesis of



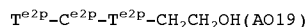
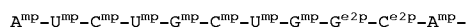
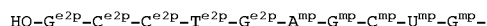
[0596] The compound of Example 5 having a sequence of interest was synthesized in the same manner as in Example 1. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.39 min was collected. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15% 60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.22 min. (6.88 A₂₆₀ units) (λ_{max} (H₂O)=261 nm)

[0597] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6623.48; measured value: 6623.68).

[0598] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2596 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 6

[0599] Synthesis of



[0600] The compound of Example 6 having a sequence of interest was synthesized in the same manner as in Example 1. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine

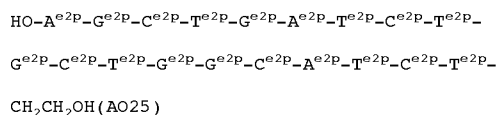
acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.10 min was collected. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.07 min. (6.98 A₂₆₀ units) (λ_{max} (H₂O)=259 nm)

[0601] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 8300.57; measured value: 8300.14).

[0602] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2601 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 7

[0603] Synthesis of



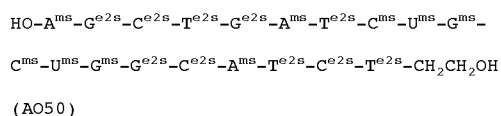
[0604] The compound of Example 7 having a sequence of interest was synthesized in the same manner as in Example 1. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 4.71 min was collected. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.75 min. (5.26 A₂₆₀ units) (λ_{max} (H₂O)=261 nm)

[0605] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6787.68; measured value: 6786.90).

[0606] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2596 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 8

[0607] Synthesis of



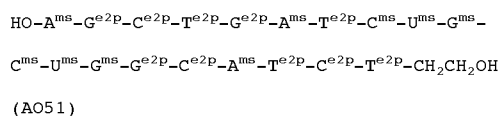
[0608] The compound of Example 5 having a sequence of interest was synthesized in the same manner as in Example

1 except for using a program for 1 μmol scale [installed in the automated nucleic acid synthesizer (PerkinElmer ABI model 394 DNA/RNA synthesizer)]. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/acetonitrile-pyridine (9:1 v/v mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→55% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 10.57 min was collected. When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B→20 80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 7.38 min. (49.06 A₂₆₀ units) (X_{max} (H₂O)=261 nm) The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6928.74; measured value: 6928.73).

[0609] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2596 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 9

[0610] Synthesis of



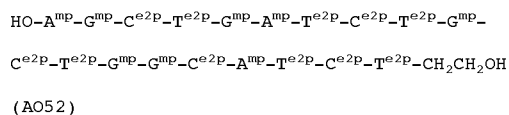
[0611] The compound of Example 5 having a sequence of interest was synthesized in the same manner as in Example 8 using a program for 1 μmol scale. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.20 min was collected. When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 4.48 min. (30.78 A₂₆₀ units) (λ_{max} (H₂O)=260 nm)

[0612] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6768.08; measured value: 6768.06).

[0613] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2596 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 10

[0614] Synthesis of



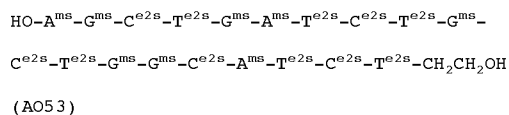
[0615] The compound of Example 5 having a sequence of interest was synthesized in the same manner as in Example 1. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.32 min was collected. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 25%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.51 min. (1.67 A₂₆₀ units) (λ_{max} (H₂O)=261 nm)

[0616] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6691.60; measured value: 6691.37).

[0617] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2596 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 11

[0618] Synthesis of



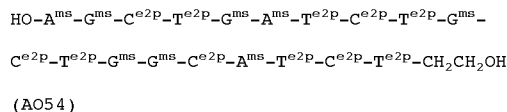
[0619] The compound of Example 5 having a sequence of interest was synthesized in the same manner as in Example 8 using a program for 1 pmol scale. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→50% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 10.59 min was collected. When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 6.61 min. (36.63 A₂₆₀ units) (λ_{max} (H₂O)=263 nm)

[0620] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6996.86; measured value: 6996.80).

[0621] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2596 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 12

[0622] Synthesis of



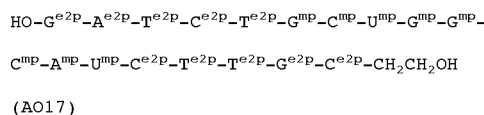
[0623] The compound of Example 5 having a sequence of interest was synthesized in the same manner as in Example 8 using a program for 1 ptmol scale. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.02 min was collected. When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 4.51 min. (44.20 A₂₆₀ units) (λ_{max} (H₂O)=260 nm)

[0624] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6820.13; measured value: 6820.12).

[0625] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2596 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 13

[0626] Synthesis of



[0627] The compound of Example 13 having a sequence of interest was synthesized in the same manner as in Example 1. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 8.32 min was collected. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%- 65% (10 min, linear gradient);

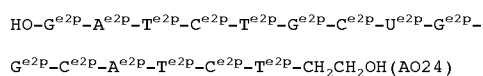
60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.14 min. (5.91 A₂₆₀ units) (λ_{max} (H₂O)=260 nm)

[0628] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6280.24; measured value: 6279.98).

[0629] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2575-2592 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 14

[0630] Synthesis of



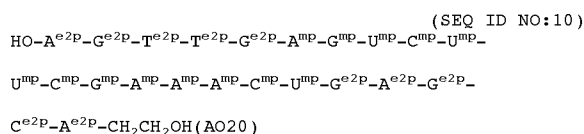
[0631] The compound of Example 14 having a sequence of interest was synthesized in the same manner as in Example 1. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→55% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.80 min was collected. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→65% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.89 min. (11.30 A₂₆₀ units) (λ_{max} (H₂O)=261 nm)

[0632] The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 5369.71; measured value: 5369.20).

[0633] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 2578-2592 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 15

[0634] Synthesis of



[0635] The subject compound was synthesized with an automated nucleic acid synthesizer (PerkinElmer ABI model 394 DNA/RNA synthesizer) using a 40 nmol DNA program. The concentrations of solvents, reagents and phosphoroamidites at individual synthesis cycles were the same as used in the synthesis of natural oligonucleotides. The solvents, reagents and phosphoroamidites of 2'-O-methylnucleoside (adenosine form: product No. 27-1822-41; guanosine form: product No. 27-1826-41; cytidine form: product No. 27-1823-02; uridine form: product No. 27-1825-42) were

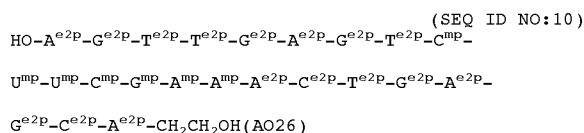
products from Amersham Pharmacia. As non-natural phosphoroamidites, those compounds disclosed in Example 28 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-6-N-benzoyladenosine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite), Example 41 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-N-isobutylguanosine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite), Example 36 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-4-N-benzoyl-5-methylcytidine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite), and Example 23 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-5-methyluridine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite) of Japanese Unexamined Patent Publication No. 2000-297097 were used. The subject compound was synthesized using approx. 0.25 μmol of a modified control pore glass (CPG) (disclosed in Example 12b of Japanese Unexamined Patent Publication No. H7-87982) as a solid support. However, the time period for condensation of amidites was 15 min.

[0636] The protected oligonucleotide analogue having the sequence of interest was treated with concentrated aqueous ammonia to thereby cut out the oligomer from the support and, at the same time, remove the protective cyanoethyl groups on phosphorus atoms and the protective groups on nucleic acid bases. The solvent was distilled off under reduced pressure, and the resultant residue was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→55% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.29 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (0.473 A₂₆₀ units) (λ_{max} (H₂O)=259 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 10%→65% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.62 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 7980.34).

[0637] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6133-6155 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 16

[0638] Synthesis of



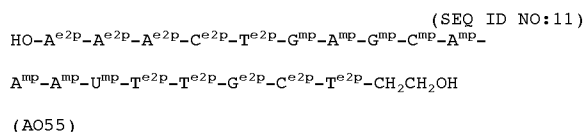
[0639] The compound of Example 16 having a sequence of interest was synthesized in the same manner as the

compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 9.76 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (7.93 A₂₆₀ units) (λ_{max} (H₂O)=259 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→70% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.03 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 8094.48; measured value: 8093.74).

[0640] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6133-6155 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 17

[0641] Synthesis of

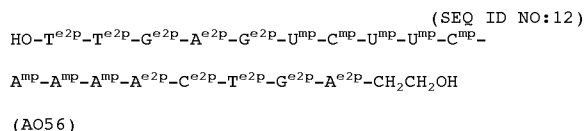


[0642] The compound of Example 17 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→38% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 9.00 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (9.50 A₂₆₀ units) (λ_{max} (H₂O)=259 nm). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr; gradient: solution B 10→40% (10 min, linear gradient); 60° C.; 2 ml/min], the subject compound was eluted at 6.14 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6350.31; measured value: 6350.07).

[0643] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6125-6142 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 18

[0644] Synthesis of

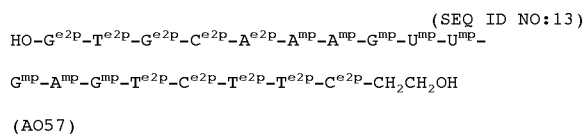


[0645] The compound of Example 18 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→38% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.44 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (11.15 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.38 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6254.21; measured value: 6254.15).

[0646] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6136-6153 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 19

[0647] Synthesis of



[0648] The compound of Example 19 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA),

pH 7.0; solution B: acetonitrile B %: 10%→38% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 8.06 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (9.60 A₂₆₀ units) (λ_{max} (H₂O)=258 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.73 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6328.29; measured value: 6327.91).

[0649] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6144-6161 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 20

[0650] Synthesis of

(SEQ ID NO: 12)
 HO-T^{e2p}-T^{e2p}-G^{mp}-A^{mp}-G^{mp}-T^{e2p}-C^{e2p}-T^{e2p}-T^{e2p}-C^{e2p}-
 A^{mp}-A^{mp}-A^{mp}-A^{mp}-C^{e2p}-T^{e2p}-G^{mp}-A^{mp}-CH₂CH₂OH (AO76)

[0651] The compound of Example 20 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.30 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (13.64 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 10.0 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6456.94; measured value: 6456.59).

[0652] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6136-6153 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 21

[0653] Synthesis of

(SEQ ID NO: 12)
 HO-T^{e2p}-T^{e2p}-G^{ms}-A^{ms}-G^{ms}-T^{e2p}-C^{e2p}-T^{e2p}-T^{e2p}-C^{e2p}-
 A^{ms}-A^{ms}-A^{ms}-A^{ms}-C^{e2p}-T^{e2p}-G^{ms}-A^{ms}-CH₂CH₂OH (AO77)

[0654] The compound of Example 21 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 v/v mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.81 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (5.26 A₂₆₀ units) (λ_{max} (H₂O)=262 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 10.0 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6456.94; measured value: 6456.59).

[0655] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6136-6153 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 22

[0656] Synthesis of

(SEQ ID NO: 12)
 HO-T^{e2s}-T^{e2s}-G^{ms}-A^{ms}-G^{ms}-T^{e2s}-C^{e2s}-T^{e2s}-T^{e2s}-C^{e2s}-
 A^{ms}-A^{ms}-A^{ms}-A^{ms}-C^{e2s}-T^{e2s}-G^{ms}-A^{ms}-CH₂CH₂OH (AO78)

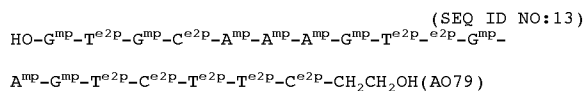
[0657] The compound of Example 22 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 v/v mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH

7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.75 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (15.04 A₂₆₀ units) (Bmax (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethyl amine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%) 80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 10.2 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6601.53; measured value: 6601.11).

[0658] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6136-6153 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 23

[0659] Synthesis of

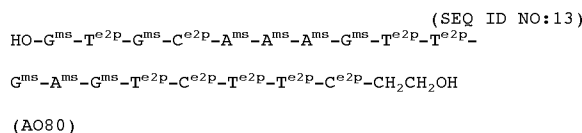


[0660] The compound of Example 23 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.95 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (11.73 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.52 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6344.33; measured value: 6344.28).

[0661] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6144-6161 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 24

[0662] Synthesis of

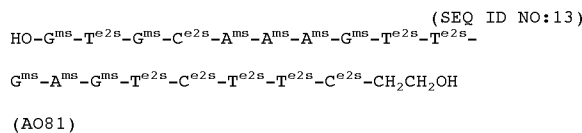


[0663] The compound of Example 24 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 v/v mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.55 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (15.27 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.71 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6488.93; measured value: 6489.03).

[0664] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6144-6161 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 25

[0665] Synthesis of



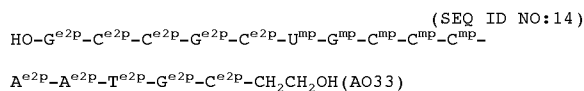
[0666] The compound of Example 25 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC

[Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.10 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (17.01 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 9.12 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6633.53; measured value: 6633.51).

[0667] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6144-6161 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 26

[0668] Synthesis of

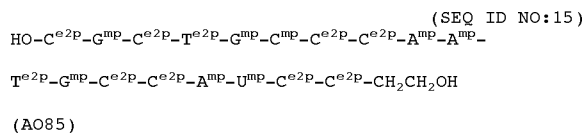


[0669] The compound of Example 26 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.36 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (12.70 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.92 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 5250.59; measured value: 5250.61).

[0670] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6696-6710 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 27

[0671] Synthesis of

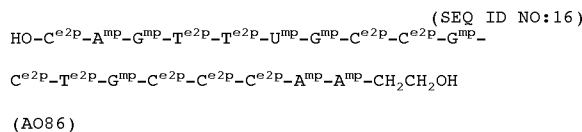


[0672] The compound of Example 27 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.32 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (7.93 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.63 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6263.34; measured value: 6263.40).

[0673] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6691-6708 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 28

[0674] Synthesis of



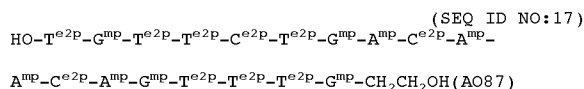
[0675] The compound of Example 28 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA),

pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.10 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (9.01 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.27 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6304.35; measured value: 6304.47).

[0676] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6699-6716 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 29

[0677] Synthesis of

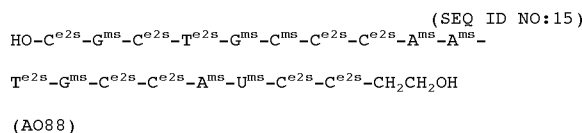


[0678] The compound of Example 29 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.63 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (8.65 A₂₆₀ units) (λ_{max} (H₂O)=259 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.06 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6331.33; measured value: 6331.14).

[0679] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6710-6727 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 30

[0680] Synthesis of

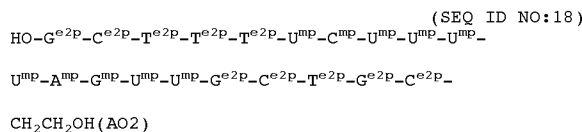


[0681] The compound of Example 30 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.57 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (12.02 A₂₆₀ units) (λ_{max} (H₂O)=262 nm). When analyzed by ion exchange [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr; gradient: solution B 20→60% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 7.11 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6552.54; measured value: 6553.12).

[0682] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6691-6708 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 31

[0683] Synthesis of



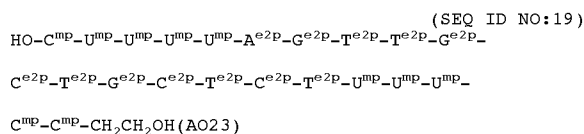
[0684] The compound of Example 31 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction

eluted at 6.13 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (3.91 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 10%→50% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 9.95 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6859.54; measured value: 6858.95).

[0685] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6973-6992 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 32

[0686] Synthesis of

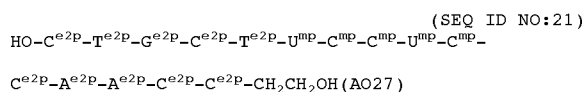


[0687] The compound of Example 32 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.60 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (3.56 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→65% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 9.31 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 7496.97; measured value: 7496.53).

[0688] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6965-6986 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 33

[0689] Synthesis of

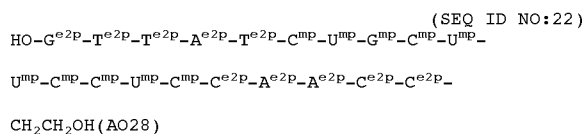


[0690] The compound of Example 33 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→55% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.76 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (6.29 A₂₆₀ units) (λ_{max} (H₂O)=265 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→65% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.27 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 5160.54; measured value: 5159.90).

[0691] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6921-6935 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 34

[0692] Synthesis of



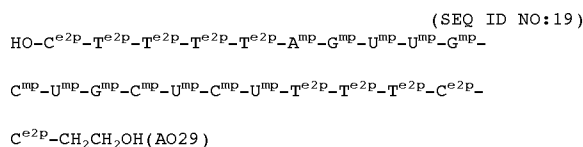
[0693] The compound of Example 34 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.04 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of

water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (5.83 A₂₆₀ units) (λ_{max} (H₂O)=263 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→65% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.16 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6808.57; measured value: 6809.21).

[0694] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6921-6940 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 35

[0695] Synthesis of

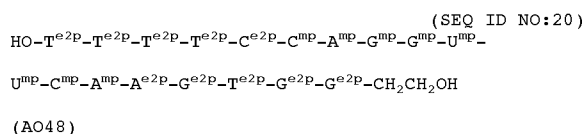


[0696] The compound of Example 35 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.34 min was collected. (1.83 A₂₆₀ units) (λ_{max} (H₂O)=261 nm) After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→65% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.45 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 7501.00; measured value: 7500.93).

[0697] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6965-6986 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 36

[0698] Synthesis of

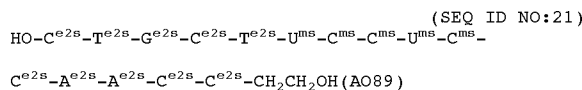


[0699] The compound of Example 36 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.55 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (19.88 A₂₆₀ units) (λ_{max} (H₂O)=259 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.72 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6291.22; measured value: 6290.99).

[0700] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6953-6970 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 37

[0701] Synthesis of



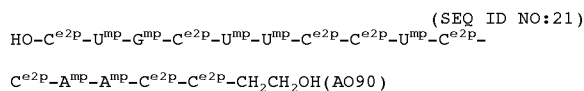
[0702] The compound of Example 37 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthine hydride/ acetonitrile-pyridine (9:1 v/v mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.56 min was collected. After the solvent was distilled off

under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (5.42 A₂₆₀ units) (λ_{max} (H₂O)=267 nm). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-SPW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→60% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 6.10 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 5401.54; measured value: 5401.12).

[0703] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6921-6935 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 38

[0704] Synthesis of

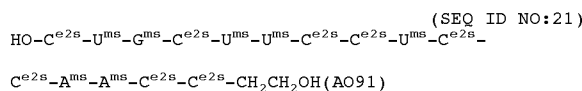


[0705] The compound of Example 38 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→38% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.05 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (11.86 A₂₆₀ units) (λ_{max} (H₂O)=266 nm). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 5→25% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 8.50 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 5150.55; measured value: 5150.69).

[0706] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6921-6935 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 39

[0707] Synthesis of

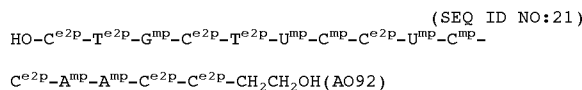


[0708] The compound of Example 39 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 v/v mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.21 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (10.77 A₂₆₀ units) (λ_{max} (H₂O)=266 nm). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→60% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 6.12 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 5391.55; measured value: 5391.76).

[0709] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6921-6935 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 40

[0710] Synthesis of



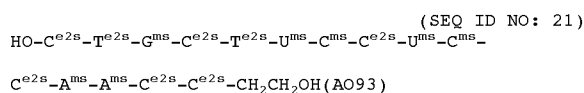
[0711] The compound of Example 40 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→38% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.48 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left

for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (10.64 A_{260} units) (λ_{max} (H_2O)=266 nm). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 5→25% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 5.71 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 5150.55; measured value: 5150.62).

[0712] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6921-6935 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 41

[0713] Synthesis of



[0714] The compound of Example 41 having a sequence of interest was synthesized in the same manner as the compound of Example 15 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 v/v mixture) for 15 min, instead of the oxidation step with iodine- H_2O . After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 m/min; 254 nm]. The fraction eluted at 7.22 min was collected. (12.77 A_{260} units) (λ_{max} (H_2O)=267 nm)

[0715] After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest. When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→60% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 6.42 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 5391.55; measured value: 5391.64).

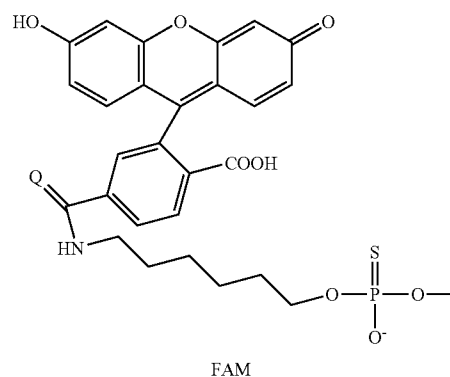
[0716] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6921-6935 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

REFERENCE EXAMPLE 1

Synthesis of hAON4

[0717] hAON4 [FAM-CUG CUU CCU CCA ACC (SEQ ID NO: 23); all the nucleotides are 2'-O-methylnucleotide and linked with each other by a phosphorothioate bond] which is disclosed in a document (van Deutekom, J. C. T. et al. (2001) Hum. Mol. Genet. 10, 1547-1554) and known as an oligonucleotide that induces exon 46 skipping was synthesized according to the above document.

[0718] FAM is a fluorescence group with the following structure.



REFERENCE EXAMPLE 2

Synthesis of hAON6

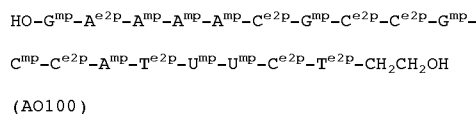
[0719] hAON6 [FAM-GUU AUC UGC UUC CUC CAA CC (SEQ ID NO: 24); all the nucleotides are 2'-O-methylnucleotide and linked with each other by a phosphorothioate bond] which is disclosed in a document (van Deutekom, J. C. T. et al. (2001) Hum. Mol. Genet. 10, 1547-1554) and known as an oligonucleotide that induces exon 46 skipping was synthesized according to the above document.

REFERENCE EXAMPLE 3

[0720] hAON8 [FAM-GCU UUU CUU UUA GUU GCU GC (SEQ ID NO: 25); all the nucleotides are 2'-O-methylnucleotide and linked with each other by a phosphorothioate bond] which is disclosed in a document (van Deutekom, J. C. T. et al. (2001) Hum. Mol. Genet. 10, 1547-1554) and known as an oligonucleotide that induces exon 46 skipping was synthesized according to the above document.

EXAMPLE 42

[0721] Synthesis of



[0722] The subject compound was synthesized with an automated nucleic acid synthesizer (PerkinElmer ABI model 394 DNA/RNA synthesizer) at a 40 nmol scale. The con-

centrations of solvents, reagents and phosphoroamidites at individual synthesis cycles were the same as used in the synthesis of natural oligonucleotides. The solvents, reagents and phosphoroamidites of 2'-O-methylnucleoside (adenosine form: product No. 27-1822-41; guanosine form: product No. 27-1826-41; cytidine form: product No. 27-1823-02; uridine form: product No. 27-1825-42) were products from Amersham Pharmacia. As non-natural phosphoroamidites, those compounds disclosed in Example 55 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-6-N-benzoyladenine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite), Example 68 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-N-isobutylguanidine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite), Example 63 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-4-N-benzoyl-5-methylcytidine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite), and Example 50 (5'-O-dimethoxytrityl-2'-O,4'-C-ethylene-5-methyluridine-3'-O-(2-cyanoethyl N,N-diisopropyl)phosphoroamidite) of Japanese Unexamined Patent Publication No. 2000-297097 were used. The subject compound was synthesized on a modified control pore glass (CPG) (disclosed in Example 12b of Japanese Unexamined Patent Publication No. H7-87982) as a solid support. However, the time period for condensation of amidites was 15 min.

[0723] The protected oligonucleotide analogue having the sequence of interest was treated with concentrated aqueous ammonia to thereby cut out the oligomer from the support and, at the same time, remove the protective cyanoethyl groups on phosphorus atoms and the protective groups on nucleic acid bases. The solvent was distilled off under reduced pressure, and the resultant residue was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.55 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (1.40 A₂₆₀ units) (λ_{max} (H₂O)=264 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.40 min. The compound was identified by

HO-C^{e2p}-T^{e2p}-G^{mp}-U^{mp}-T^{e2p}-A^{mp}-G^{mp}-C^{e2p}-C^{mp}-A^{mp}-

C^{e2p}-T^{e2p}-G^{mp}-A^{mp}-T^{e2p}-T^{e2p}-A^{mp}-A^{mp}-CH₂CH₂OH

(AO102)

[0724] negative ion ESI mass spectrometric analysis (calculated value: 6246.28; measured value: 6245.68).

[0725] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6555-6572 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 43

[0726] Synthesis of

[0727] The compound of Example 43 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.76 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (14.2 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.42 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6262.27; measured value: 6261.87).

[0728] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6591-6608 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 44

[0729] Synthesis of

HO-T^{e2p}-G^{mp}-A^{mp}-G^{mp}-A^{e2p}-A^{mp}-A^{mp}-C^{e2p}-T^{e2p}-G^{mp}-

T^{e2p}-U^{mp}-C^{e2p}-A^{mp}-G^{mp}-C^{e2p}-U^{mp}-T^{e2p}-CH₂CH₂OH

(AO103)

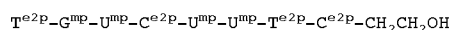
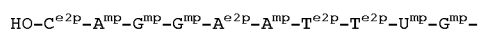
[0730] The compound of Example 44 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 8.12 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (0.204 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethyl-

amine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.84 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6288.27; measured value: 6288.16).

[0731] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6609-6626 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 45

[0732] Synthesis of



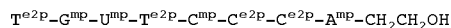
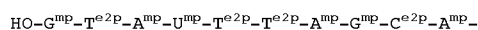
(AO104)

[0733] The compound of Example 45 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.46 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (3.73 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.20 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6242.19; measured value: 6241.47).

[0734] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6627-6644 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 45

[0735] Synthesis of



(AO105)

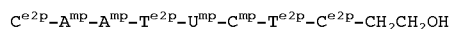
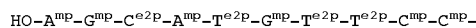
[0736] The compound of Example 46 having a sequence of interest was synthesized in the same manner as the

compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.11 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (14.8 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.04 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6239.23; measured value: 6238.90).

[0737] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6650-6667 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 47

[0738] Synthesis of



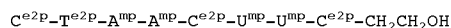
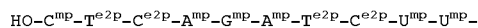
(AO106)

[0739] The compound of Example 47 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.51 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (6.97 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.22 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6198.22; measured value: 6197.87).

[0740] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6644-6661 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 48

[0741] Synthesis of



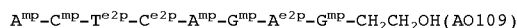
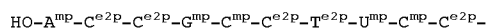
(AO108)

[0742] The compound of Example 48 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.74 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (4.91 A₂₆₀ units) (λ_{max} (H₂O)=263 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.94 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6159.18; measured value: 6159.35).

[0743] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7447-7464 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 49

[0744] Synthesis of



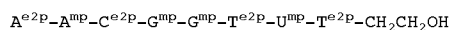
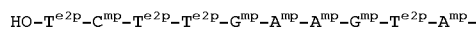
[0745] The compound of Example 49 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.72 min was collected. After the solvent was

distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (3.30 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.53 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6221.27; measured value: 6220.43).

[0746] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7465-7482 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 50

[0747] Synthesis of



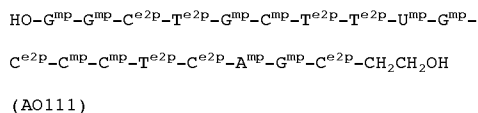
(AO110)

[0748] The compound of Example 50 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.18 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (3.92 A₂₆₀ units) (λ_{max} (H₂O)=258 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.66 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6289.26; measured value: 6288.99).

[0749] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7483-7500 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 51

[0750] Synthesis of

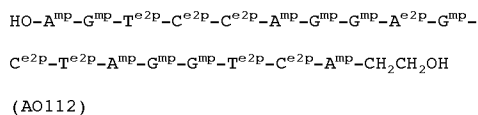


[0751] The compound of Example 51 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.91 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (9.48 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 4.81 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6245.24; measured value: 6244.86).

[0752] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7501-7518 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 52

[0753] Synthesis of



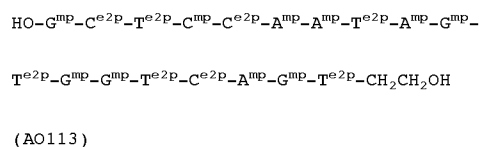
[0754] The compound of Example 52 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.00 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of

water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (0.200 A₂₆₀ units) (λ_{max} (H₂O)=253 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 4.33 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6365.37; measured value: 6365.99).

[0755] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7519-7536 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 53

[0756] Synthesis of

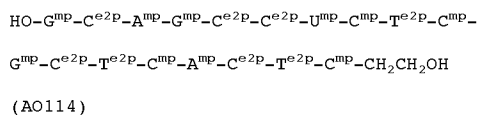


[0757] The compound of Example 53 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.22 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (4.96 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 4.96 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6317.31; measured value: 6317.06).

[0758] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7534-7551 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 54

[0759] Synthesis of

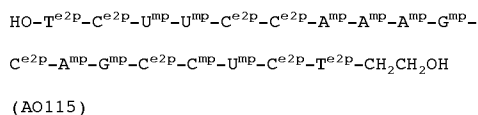


[0760] The compound of Example 54 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.13 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (2.02 A₂₆₀ units) (λ_{max} (H₂O)=267 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.89 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6188.23; measured value: 6187.79).

[0761] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8275-8292 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 55

[0762] Synthesis of



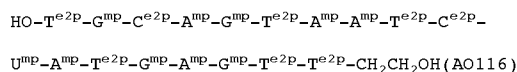
[0763] The compound of Example 55 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.08 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby

obtain the compound of interest (2.68 A₂₆₀ units) (λ_{max} (H₂O)=262 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.85 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6197.24; measured value: 6196.74).

[0764] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8284-8301 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 56

[0765] Synthesis of

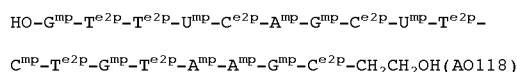


[0766] The compound of Example 56 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.02 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (13.40 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.55 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6303.28; measured value: 6302.90).

[0767] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8302-8319 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 57

[0768] Synthesis of



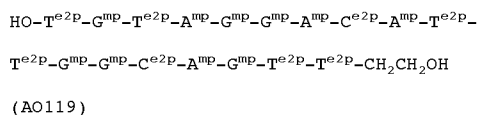
[0769] The compound of Example 57 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase

HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.69 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (8.16 A₂₆₀ units) (λ_{max} (H₂O)=261 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.69 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6255.23; measured value: 6254.64).

[0770] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8356-8373 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 58

[0771] Synthesis of

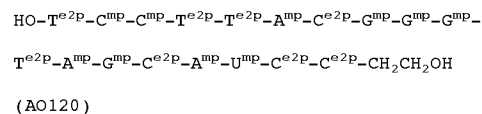


[0772] The compound of Example 58 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.62 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (8.06 A₂₆₀ units) (λ_{max} (H₂O)=259 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.72 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6358.32; measured value: 6357.91).

[0773] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8374-8391 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 59

[0774] Synthesis of

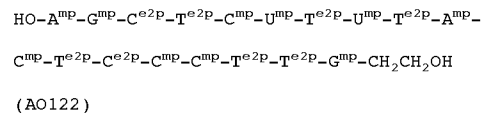


[0775] The compound of Example 59 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.14 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (0.459 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.09 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6253.26; measured value: 6253.06).

[0776] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8392-8409 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 60

[0777] Synthesis of



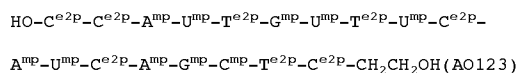
[0778] The compound of Example 60 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction

eluted at 6.13 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (7.93 A₂₆₀ units) (λ_{\max} (H₂O)=263 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.55 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6152.14; measured value: 6151.48).

[0779] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8428-8445 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 61

[0780] Synthesis of

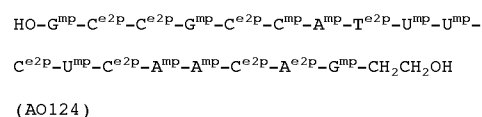


[0781] The compound of Example 61 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.71 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (9.66 A₂₆₀ units) (λ_{\max} (H₂O)=263 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.69 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6175.18; measured value: 6174.65).

[0782] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8441-8458 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 62

[0783] Synthesis of



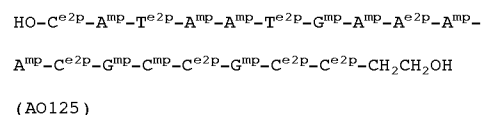
[0784] The compound of Example 62 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.59 min was collected. (12.70 A₂₆₀ units).

[0785] After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest. When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.13 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6222.25; measured value: 6222.24).

[0786] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6549-6566 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 63

[0787] Synthesis of



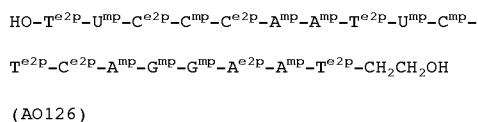
[0788] The compound of Example 63 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.68 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the

solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (11.74 A_{260} units). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.41 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6292.36; measured value: 6292.55).

[0789] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6561-6578 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 64

[0790] Synthesis of

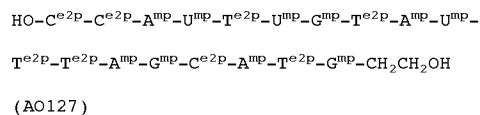


[0791] The compound of Example 64 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.91 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (13.31 A_{260} units). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.25 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6208.22; measured value: 6208.15).

[0792] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6638-6655 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 65

[0793] Synthesis of

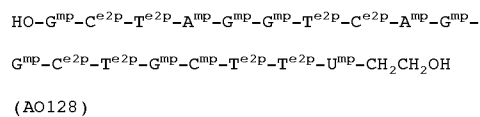


[0794] The compound of Example 65 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.49 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (11.38 A_{260} units). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.24 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6240.22; measured value: 6239.82).

[0795] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6656-6673 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 66

[0796] Synthesis of



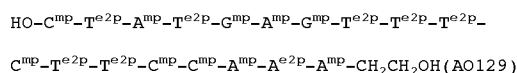
[0797] The compound of Example 66 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.61 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby

obtain the compound of interest (1.11 A₂₆₀ units). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.59 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6310.27; measured value: 6310.33).

[0798] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7510-7527 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 67

[0799] Synthesis of



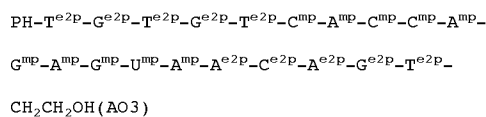
[0800] The compound of Example 67 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.83 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (2.21 A₂₆₀ units). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.70 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6209.21; measured value: 6209.06).

[0801] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8293-8310 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

(EXON 51)

EXAMPLE 68

[0802] Synthesis of

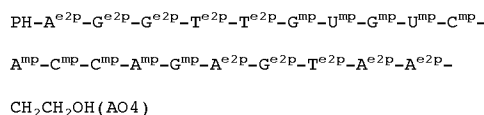


[0803] The compound of Example 68 having a sequence of interest was synthesized in the same manner as in Example 42, except that phenyl 2-cyanoethyl N,N-diisopropylphosphoramidite (Hotoda, H. et al. Nucleosides & Nucleotides 15, 531-538, (1996)) was used in the final condensation to introduce phenylphosphate on the 5' terminal side. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.24 min was collected. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4. OHV 25). The solvent was distilled off to thereby obtain the compound of interest (1.21 A₂₆₀ units) ($\lambda_{\text{max}}(\text{H}_2\text{O})=259$ nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.79 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6240.22; measured value: 6239.82).

[0804] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7565-7584 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 69

[0805] Synthesis of



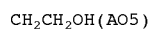
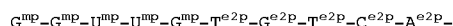
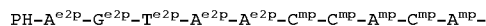
[0806] The compound of Example 69 having a sequence of interest was synthesized in the same manner as in Example 42, except that phenyl 2-cyanoethyl N,N-diisopropylphosphoramidite (Hotoda, H. et al. Nucleosides & Nucleotides 15, 531-538, (1996)) was used in the final condensation to introduce phenylphosphate on the 5' terminal side. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.23 min was collected. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (2.67 A₂₆₀ units) ($\lambda_{\text{max}}(\text{H}_2\text{O})=259$ nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.45

min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 7153.77; measured value: 7152.95).

[0807] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7569-7588 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 70

[0808] Synthesis of

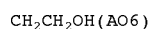
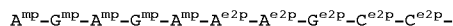
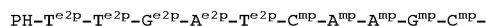


[0809] The compound of Example 70 having a sequence of interest was synthesized in the same manner as in Example 42, except that phenyl 2-cyanoethyl N,N-diisopropylphosphoramidite (Hotoda, H. et al. Nucleosides & Nucleotides 15, 531-538, (1996)) was used in the final condensation to introduce phenylphosphate on the 5' terminal side. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 4.71 min was collected. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (0.836 A₂₆₀ units) (λ_{max} (H₂O)=259 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.56 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 7127.78; measured value: 7127.27).

[0810] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7578-7597 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 71

[0811] Synthesis of



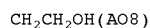
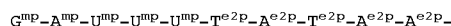
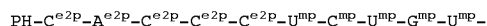
[0812] The compound of Example 71 having a sequence of interest was synthesized in the same manner as in Example 42, except that phenyl 2-cyanoethyl N,N-diisopropylphosphoramidite (Hotoda, H. et al. Nucleosides & Nucleotides 15, 531-538, (1996)) was used in the final conden-

sation to introduce phenylphosphate on the 5' terminal side. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.79 min was collected. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (2.04 A₂₆₀ units) (λ_{max} (H₂O)=258 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.81 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 7187.88; measured value: 7187.41).

[0813] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7698-7717 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 72

[0814] Synthesis of

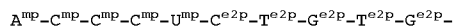
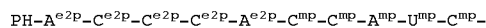


[0815] The compound of Example 72 having a sequence of interest was synthesized in the same manner as in Example 42, except that phenyl 2-cyanoethyl N,N-diisopropylphosphoramidite (Hotoda, H. et al. Nucleosides & Nucleotides 15, 531-538, (1996)) was used in the final condensation to introduce phenylphosphate on the 5' terminal side. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→13% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.20 min was collected. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (2.64 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.07 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 7014.69; measured value: 7014.45).

[0816] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7719-7738 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 73

[0817] Synthesis of



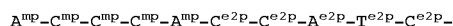
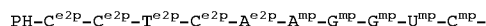
CH₂CH₂OH (A09)

[0818] The compound of Example 73 having a sequence of interest was synthesized in the same manner as in Example 42, except that phenyl 2-cyanoethyl N,N-diisopropylphosphoramidite (Hotoda, H. et al. Nucleosides & Nucleotides 15, 531-538, (1996)) was used in the final condensation to introduce phenylphosphate on the 5' terminal side. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.74 min was collected. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (3.08 A₂₆₀ units) (λ_{max} (H₂O)=265 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.20 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6986.72; measured value: 6986.81).

[0819] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7728-7747 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 74

[0820] Synthesis of



CH₂CH₂OH (A010)

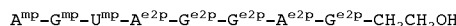
[0821] The compound of Example 74 having a sequence of interest was synthesized in the same manner as in Example 42, except that phenyl 2-cyanoethyl N,N-diisopropylphosphoramidite (Hotoda, H. et al. Nucleosides & Nucleotides 15, 531-538, (1996)) was used in the final condensation to introduce phenylphosphate on the 5' terminal side. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm);

solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.62 min was collected. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (3.31 A₂₆₀ units) (λ_{max} (H₂O)=266 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 5%→15% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.46 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 7037.82; measured value: 7036.73).

[0822] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7738-7757 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 75

[0823] Synthesis of



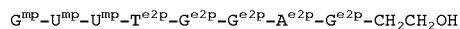
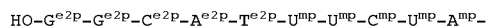
(A037)

[0824] The compound of Example 75 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.64 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (17.9 A₂₆₀ units) (λ_{max} (H₂O)=257 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 9.03 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6344.26; measured value: 6343.66).

[0825] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7554-7571 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 76

[0826] Synthesis of



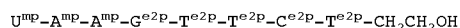
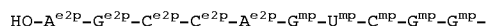
(AO39)

[0827] The compound of Example 76 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.82 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (17.5 A₂₆₀ units) (λ_{max} (H₂O)=259 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.51 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6289.17; measured value: 6289.10).

[0828] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7612-7629 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 77

[0829] Synthesis of



(AO43)

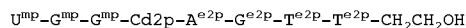
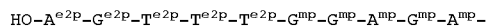
[0830] The compound of Example 77 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction

eluted at 6.76 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (6.57 A₂₆₀ units) (λ_{max} (H₂O)=258 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.90 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6313.28; measured value: 6313.15).

[0831] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7684-7701 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 78

[0832] Synthesis of



(AO58)

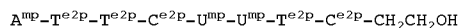
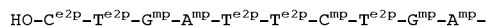
[0833] The compound of Example 78 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→38% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.62 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (10.7 A₂₆₀ units) (λ_{max} (H₂O)=258 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 4.80 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6313.28; measured value: 6313.15).

[0834] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7603-7620 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

(EXON 53)

EXAMPLE 79

[0835] Synthesis of



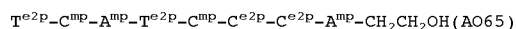
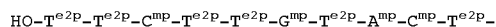
(AO64)

[0836] The compound of Example 79 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.06 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (9.08 A₂₆₀ units) (λ_{max} (H₂O)=263 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.62 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6229.23; measured value: 6229.27).

[0837] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7907-7924 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 80

[0838] Synthesis of



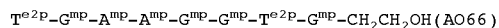
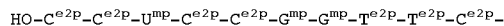
[0839] The compound of Example 80 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min,

linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.16 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (7.19 A₂₆₀ units) (λ_{max} (H₂O)=264 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.98 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6188.22; measured value: 6288.69).

[0840] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7925-7942 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 81

[0841] Synthesis of

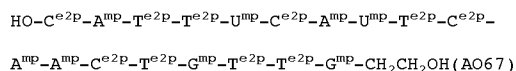


[0842] The compound of Example 81 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.01 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (10.7 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.80 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6335.32; measured value: 6334.97).

[0843] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7943-7960 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 82

[0844] Synthesis of

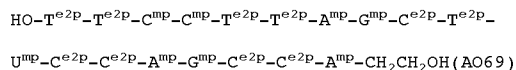


[0845] The compound of Example 82 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.36 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (13.8 A₂₆₀ units) (λ_{max} (H₂O)=260 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 6.70 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6252.27; measured value: 6252.37).

[0846] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7961-7978 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 83

[0847] Synthesis of



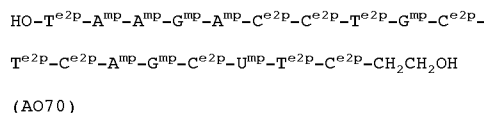
[0848] The compound of Example 42 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.10 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (8.12 A₂₆₀ units) (λ_{max}

(H₂O)=264 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.02 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6226.27; measured value: 6226.10).

[0849] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7997-8014 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 84

[0850] Synthesis of

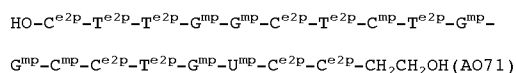


[0851] The compound of Example 84 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.27 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (12.2 A₂₆₀ units) (λ_{max} (H₂O)=262 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.57 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6289.29; measured value: 6289.34).

[0852] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8015-8032 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 85

[0853] Synthesis of

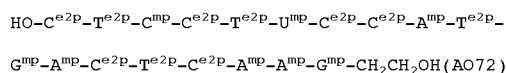


[0854] The compound of Example 85 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.65 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (10.6 A₂₆₀ units) (λ_{max} (H₂O)=262 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→80% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 5.68 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6274.27; measured value: 6274.42).

[0855] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8033-8050 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 86

[0856] Synthesis of

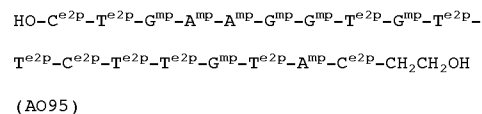


[0857] The compound of Example 86 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→46% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.09 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (10.1 A₂₆₀ units) (λ_{max} (H₂O)=264 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 20%→60% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.33 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6249.31; measured value: 6249.21).

[0858] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8051-8068 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 87

[0859] Synthesis of

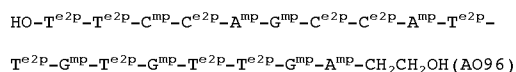


[0860] The compound of Example 87 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.22 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (10.6 A₂₆₀ units) (λ_{max} (H₂O)=259 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.31 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6347.33; measured value: 6347.50).

[0861] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7934-7951 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 88

[0862] Synthesis of



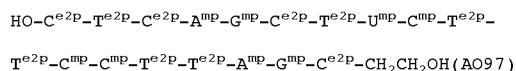
[0863] The compound of Example 88 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.09 min was collected. After the solvent was

distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (12.8 A_{260} units) (λ_{max} (H_2O)=262 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 8.60 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6307.31; measured value: 6307.34).

[0864] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7988-8005 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 89

[0865] Synthesis of

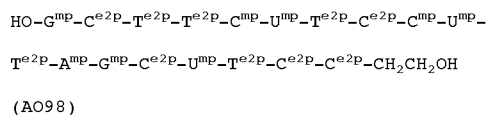


[0866] The compound of Example 89 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.74 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (10.7 A_{260} units) (λ_{max} (H_2O)=265 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254nm], the subject compound was eluted at 8.00 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6203.23; measured value: 6203.08).

[0867] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8006-8023 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 90

[0868] Synthesis of

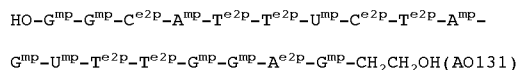


[0869] The compound of Example 90 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 5.35 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (9.81 A_{260} units) (λ_{max} (H_2O)=265 nm). When analyzed by reversed phase HPLC [column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: 25% acetonitrile, 0.1 M TEAA B %: 15%→100% (10 min, linear gradient); 60° C.; 2 ml/min; 254 nm], the subject compound was eluted at 7.06 min. The compound was identified by negative ion ESI mass spectrometric analysis (calculated value: 6180.19; measured value: 6180.27).

[0870] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8002-8019 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 91

[0871] Synthesis of



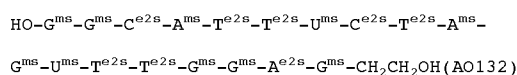
[0872] The compound of Example 91 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.27 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product

No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (1.80 A₂₆₀ units). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: 1solution B 15→60% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 4.89 min.

[0873] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7612-7629 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 92

[0874] Synthesis of

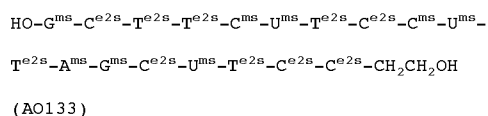


[0875] The compound of Example 92 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.47 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (15.1 A₂₆₀ units). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 8.46 min.

[0876] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7612-7629 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 93

[0877] Synthesis of



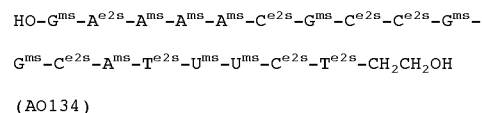
[0878] The compound of Example 93 having a sequence of interest was synthesized in the same manner as the

compound of Example 42 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.65 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (15.1 A₂₆₀ units). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20-80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 6.47 min.

[0879] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8002-8019 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 94

[0880] Synthesis of

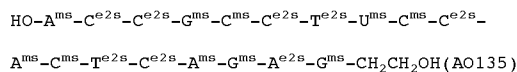


[0881] The compound of Example 94 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.51 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (6.65 A₂₆₀ units). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 7.46 min.

[0882] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 6555-6572 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 95

[0883] Synthesis of

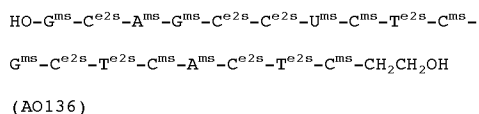


[0884] The compound of Example 95 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.87 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (9.06 A₂₆₀ units). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 6.92 min.

[0885] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7465-7482 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 96

[0886] Synthesis of



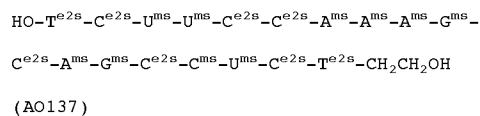
[0887] The compound of Example 96 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% aceto-

nitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.24 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (11.2 A₂₆₀ units). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 6.66 min.

[0888] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8275-8292 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 97

[0889] Synthesis of

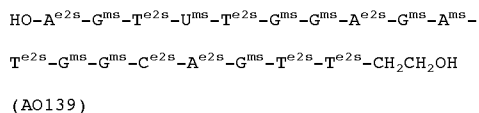


[0890] The compound of Example 97 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.40 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (9.46 A₂₆₀ units). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 6.82 min.

[0891] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 8284-8301 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 98

[0892] Synthesis of

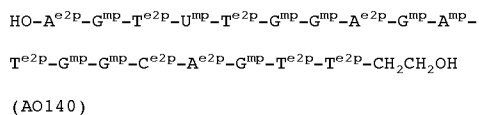


[0893] The compound of Example 98 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. However, the portion with a phosphorothioate bond was sulfurized by treating with a mixed solution of 0.02 M xanthane hydride/ acetonitrile-pyridine (9:1 mixture) for 15 min, instead of the oxidation step with iodine-H₂O. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 7.08 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (12.9 A₂₆₀ units). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 20→80% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 6.92 min.

[0894] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7603-7620 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

EXAMPLE 99

[0895] Synthesis of



[0896] The compound of Example 99 having a sequence of interest was synthesized in the same manner as the compound of Example 42 was synthesized. After deprotection, the resultant product was purified by reversed phase HPLC [Shimadzu model LC-10VP; column: Merck, Chromolith Performance RP-18e (4.6×100 mm); solution A: 5% acetonitrile, 0.1 M aqueous triethylamine acetate (TEAA), pH 7.0; solution B: acetonitrile B %: 10%→45% (8 min, linear gradient); 60° C.; 2 ml/min; 254 nm]. The fraction eluted at 6.47 min was collected. After the solvent was distilled off under reduced pressure, 80% aqueous acetic acid solution was added to the residue, which was then left for 20 min to remove the DMTr group. After distilling off the solvent, the resultant residue was dissolved in 0.5 ml of

water and filtered with Ultrafree-MC (Millipore: product No. UFC4 OHV 25). The solvent was distilled off to thereby obtain the compound of interest (3.54 A₂₆₀ units). When analyzed by ion exchange HPLC [column: Tosoh TSK-gel DEAE-5PW (7.5×75 mm); solution A: 20% acetonitrile; solution B: 20% acetonitrile, 67 mM phosphate buffer (pH 6.8), 1.5 M KBr, gradient: solution B 10→50% (10 min, linear gradient); 40° C.; 2 ml/min], the subject compound was eluted at 5.54 min.

[0897] The nucleotide sequence of the subject compound is complementary to the nucleotides Nos. 7603-7620 of dystrophin cDNA (Gene Bank accession No. NM_004006.1).

TEST EXAMPLE 1

Method of Analysis of the Exon Skipping Induction Ability by Antisense ENA

Preparation of Primary Culture of Myoblast Cells

[0898] A primary culture of myoblast cells was established as described below.

[0899] 1. Muscle tissue samples taken from the rectus muscle of the thigh of Duchenne muscular dystrophy patients were cut into fine pieces and washed with PBS twice.

[0900] 2. The muscle tissue from 1 above was treated with Difco Bacto™ tripton 250 at 37° C. for 30 min to thereby obtain free cells enzymatically.

[0901] 3. The free cells from 2 above were washed with DMEM (containing 20% FBS) twice.

[0902] 4. The cells from 3 above were suspended in DMEM (containing 20% FBS and 4% ultrosor G).

[0903] 5. The suspension cells from 4 were passed through a mesh (Becton Dickinson: cell strainer 35-2360) to recover only free cells.

[0904] 6. The recovered cells from 5 above were seeded on gelatin-coated dishes.

[0905] 7. The cells were cultured at 37° C. in an atmosphere of 5% CO₂ in air.

Induction of Differentiation

[0906] Differentiation of muscular cells was induced as described below.

[0907] 1. Cultured cells obtained above were seeded on 6-well plates (gelatin coated). When cells became confluent, the medium was exchanged with DMEM (containing 2% horse serum (HS)).

[0908] 2. After a 4 day cultivation, the cells were transfected with the compounds prepared in Examples (ENAs) as described below.

ENA Transfection

[0909] Myoblast cells were transfected with the compounds prepared in Examples (ENAs) as described below.

[0910] 1. 200 pmol of each of the compounds prepared in Examples (10 μg/20 μl milliQ) was dissolved in 100 μl of Opti-MEM (GIBCO-BRL).

[0911] 2. 6 μ l of Plus reagent (GIBCO-BRL) was added to the solution from 1 above, which was then left at room temperature for 15 min.

[0912] 3. In another tube, 8 μ l of Lipofectamine (GIBCO-BRL) was dissolved in 100 μ l of Opti-MEM.

[0913] 4. After completion of the treatment of 2 above, the solution from 3 above was added to the solution from 2 above. The resultant solution was left at room temperature for another 15 min.

[0914] 5. Myoblast cells 4 days after the start of the induction of differentiation were washed with PBS once. Then, 800 μ l of Opti-MEM was added thereto.

[0915] 6. After completion of the treatment of 4 above, the treated solution was added to the cells from 5 above.

[0916] 7. The cells from 6 above were cultured at 37° C. in an atmosphere of 5% CO₂ in air for 3 hr. Then, 500 μ l of DMEM (containing 6% HS) was added to each well.

[0917] 8. Cells were cultured further.

RNA Extraction

[0918] RNA was extracted as described below.

[0919] 1. ENA-transfected cells were cultured for 2 days and then washed with PBS once. To these cells, 500 μ l of ISOGEN (Nippon Gene) was added.

[0920] 2. The cells were left at room temperature for 5 min, followed by recovery of ISOGEN in each well into tubes.

[0921] 3. RNA was extracted according to the protocol of ISOGEN (Nippon Gene).

[0922] 4. Finally, RNA was dissolved in 20 μ l of DEP.W.

Reverse Transcription

[0923] Reverse transcription was performed as described below.

[0924] 1. To 2 μ l of RNA, DEP.W (sterilized water treated with diethylpyrocarbonate) was added to make a 6 μ l solution.

[0925] 2. To the solution from 1 above, 2 μ l of random hexamer (Invitrogen: 3 μ g/ μ l product was diluted to 20-fold before use) was added.

[0926] 3. The resultant solution was heated at 65° for 10 min.

[0927] 4. Then, the solution was cooled on ice for 2 min.

[0928] 5. To the above reaction solution, the following was added:

MMLV-reverse transcriptase (Invitrogen: 200 U/ μ l)	1 μ l
Human placenta ribonuclease inhibitor (Takara: 40 U/ μ l)	1 μ l
DTT (attached to MMLV-reverse transcriptase)	1 μ l
Buffer (attached to MMLV-reverse transcriptase)	4 μ l
dNTPs (attached to Takara Ex Taq)	5 μ l

[0929] 6. The resultant solution was kept at 37° C. for 1 hr, and then heated at 95° C. for 5 min.

[0930] 7. After the reaction, the solution was stored at -80° C.

PCR Reaction

[0931] PCR reaction was performed as described below.

[0932] 1. The following components were mixed and then heated at 94° C. for 4 min.

Reverse transcription product	3 μ l
Forward primer (10 pmol/ μ l)	1 μ l
Reverse primer (10 pmol/ μ l)	1 μ l
dNTP (attached to TAKARA Ex Taq)	2 μ l
Buffer (attached to TAKARA Ex Taq)	2 μ l
Ex Taq (TAKARA)	0.1 μ l
Sterilized water	11 μ l

[0933] 2. After the above-mentioned treatment at 94° C. for 4 min, 35 cycles of 94° C. for 1 min/60° C. for 1 min/72° C. for 3 min were performed.

[0934] 3. Then, the reaction solution was heated at 72° C. for 7 min.

[0935] The nucleotide sequences of the forward and reverse primers used in the PCR reaction are as described below.

Forward primer: (SEQ ID NO:8)
GCA TGC TCA AGA GGA ACT TCC (exon 17)

Reverse primer: (SEQ ID NO:9)
TAG CAA CTG GCA GAA TTC GAT (exon 20)

[0936] 3. The PCR product was analyzed by 2% agarose gel electrophoresis.

[0937] The resultant gel was stained with ethidium bromide. The resultant band (A) (where exon 19 was skipped) and band (B) (where exon 19 was not skipped) were visualized with a gel photographing device (Printgraph Model AE-6911FXFD; ATTO) and quantitatively determined with ATTO Densitograph ver.4.1 for the Macintosh. The values obtained were put into the formula $A/(A+B) \times 100$ to obtain skipping efficiency (%).

[0938] 5. The band where skipping had occurred was cut out, and the PCR product was subcloned into pT7 Blue-T vector (Novagen), followed by sequencing reaction with Thermo Sequenase™ II dye terminator cycle sequencing kit (Amersham Pharmacia Biotech) and confirmation of the nucleotide sequence with ABI PRISM 310 Genetic Analyzer (Applied Biosystems). The reaction procedures were according to the manual attached to the kit.

[Results]

[0939] As shown in FIG. 1 and Table 1, the compound of Example 1 showed more efficient exon 19 skipping than 31 mer-phosphorothioate oligonucleotide (S-oligo) disclosed in Y. Takeshima et al., Brain & Development (2001) 23, 788-790, which has the same nucleotide sequence as that of the compound of Example 1. Further, as shown in FIGS. 2 and 3 and Tables 2 and 3, the compounds of Examples 2-14 also showed more efficient skipping than S-oligo.

TABLE 1

Oligonucleotide	Skipping (%)
S-oligo	2
AO1 Example 1	80

[0940]

TABLE 2

Oligonucleotide	Skipping (%)
AO1 Example 1	88
AO14 Example 2	29
AO15 Example 3	3
AO16 Example 4	4
AO18 Example 5	92
AO19 Example 6	5
AO25 Example 7	83
AO17 Example 13	39
AO24 Example 14	14

[0941]

TABLE 3

Oligonucleotide	Skipping (%)
AO18 Example 5	90
AO50 Example 8	53
AO51 Example 9	55
AO52 Example 10	97
AO53 Example 11	55
AO54 Example 12	91

TEST EXAMPLE 2

Method of Analysis of the Exon Skipping Induction Ability by Antisense ENA

Preparation of Primary Culture of Myoblast Cells

[0942] A primary culture of myoblast cells was established as described below.

[0943] 1. Muscle tissue samples taken from the rectus muscle of the thigh of Duchenne muscular dystrophy patients were cut into fine pieces and washed with PBS twice.

[0944] 2. The muscle tissue from 1 above was treated with Difco Bacto™ tripton 250 (5% solution in PBS) at 37° C. for 30 min to thereby obtain free cells enzymatically.

[0945] 3. The free cells from 2 above were washed with DMEM (containing 20% FBS) twice.

[0946] 4. The cells from 3 above were suspended in DMEM (containing 20% FBS and 4% ultrosor G).

[0947] 5. The suspension cells from 4 were passed through a mesh (Becton Dickinson: cell strainer 35-2360) to recover only free cells.

[0948] 6. The recovered cells from 5 above were seeded on gelatin-coated dishes.

[0949] 7. The cells were cultured at 37° C. in an atmosphere of 5% CO₂ in air.

Induction of Differentiation

[0950] Differentiation of muscular cells was induced as described below.

[0951] 1. Cultured cells obtained above were seeded on 6-well plates (gelatin coated). When cells became confluent, the medium was exchanged with DMEM (containing 2% horse serum (HS)).

[0952] 2. After a 4 day cultivation, the cells were transfected with the compounds prepared in Examples (ENAs) as described below.

ENA Transfection

[0953] Myoblast cells were transfected with the compounds prepared in Examples (ENAs) as described below.

[0954] 1. 200 pmol of each of the compounds prepared in Examples (10 µg/20 [µl milliQ]) was dissolved in 100 µl of Opti-MEM (GIBCO-BRL).

[0955] 2. 6 µl of Plus reagent (GIBCO-BRL) was added to the solution from 1 above, which was then left at room temperature for 15 min.

[0956] 3. In another tube, 8 µl of Lipofectamine (GIBCO-BRL) was dissolved in 100 µl of Opti-MEM.

[0957] 4. After completion of the treatment of 2 above, the solution from 3 above was added to the solution from 2 above. The resultant solution was left at room temperature for another 15 min.

[0958] 5. Myoblast cells 4 days after the start of the induction of differentiation were washed with PBS once. Then, 800 µl of Opti-MEM was added thereto.

[0959] 6. After completion of the treatment of 4 above, the treated solution was added to the cells from 5 above.

[0960] 7. The cells from 6 above were cultured at 37° C. in an atmosphere of 5% CO₂ in air for 3 hr. Then, 500 µl of DMEM (containing 6% HS) was added to each well.

[0961] 8. Cells were cultured further.

RNA Extraction

[0962] RNA was extracted as described below.

[0963] 1. ENA-transfected cells were cultured for 2 days and then washed with PBS once. To these cells, 500 µl of ISOGEN (Nippon Gene) was added.

[0964] 2. The cells were left at room temperature for 5 min, followed by recovery of ISOGEN in each well into tubes.

[0965] 3. RNA was extracted according to the protocol of ISOGEN (Nippon Gene).

[0966] 4. Finally, RNA was dissolved in 20 µl of DEPW.

Reverse Transcription

[0967] Reverse transcription was performed as described below.

[0968] 1. To 2 µg of RNA, DEPW (sterilized water treated with diethylpyrocarbonate) was added to make a 6 µl solution.

[0969] 2. To the solution from 1 above, 2 μ l of random hexamer (Invitrogen: 3 μ g/ μ l product was diluted to 20-fold before use) was added.

[0970] 3. The resultant solution was heated at 65° for 10 min.

[0971] 4. Then, the solution was cooled on ice for 2 min.

[0972] 5. To the above reaction solution, the following was added:

MMLV-reverse transcriptase (Invitrogen: 200 U/ μ l)	1 μ l
Human placenta ribonuclease inhibitor (Takara: 40 U/ μ l)	1 μ l
DTT (attached to MMLV-reverse transcriptase)	1 μ l
Buffer (attached to MMLV-reverse transcriptase)	4 μ l
dNTPs (attached to Takara Ex Taq)	5 μ l

[0973] 6. The resultant solution was kept at 37° C. for 1 hr, and then heated at 95° C. for 5 min.

[0974] 7. After the reaction, the solution was stored at -80° C.

PCR Reaction

[0975] PCR reaction was performed as described below.

[0976] 1. The following components were mixed and then heated at 94° C. for 4 min.

Reverse transcription product	3 μ l
Forward primer (10 pmol/ μ l)	1 μ l
Reverse primer (10 pmol/ μ l)	1 μ l
dNTP (attached to TAKARA Ex Taq)	2 μ l
Buffer (attached to TAKARA Ex Taq)	2 μ l
Ex Taq (TAKARA)	0.1 μ l
Sterilized water	11 μ l

[0977] 2. After the above-mentioned treatment at 94° C. for 4 min, 35 cycles of 94° C. for 1 min/60° C. for 1 min/72° C. for 3 min were performed.

[0978] 3. Then, the reaction solution was heated at 72° C. for 7 min.

[0979] The nucleotide sequences of the forward and reverse primers used in the PCR for detecting exon 41 skipping were as described below.

Forward primer: (SEQ ID NO:26)
5'-GGT ATC AGT ACA AGA GGC AGG CTG-3' (exon 40)

Reverse primer: (SEQ ID NO:27)
5'-CAC TTC TAA TAG GGC TTG TG-3' (exon 42)

[0980] The nucleotide sequences of the forward and reverse primers used in the PCR for detecting exon 45 and exon 46 skipping were as described below.

Forward primer: (SEQ ID NO:28)
5'-GCT GAA CAG TTT CTC AGA AAG ACA CAA-3' (exon 44)

Reverse primer: (SEQ ID NO:29)
5'-TCC ACT GGA GAT TTG TCT GC-3' (exon 47)

[0981] 4. The PCR product was analyzed by 2% agarose gel electrophoresis.

[0982] The resultant gel was stained with ethidium bromide. The resultant band (A) (where an exon was skipped) and band (B) (where an exon was not skipped) were visualized with a gel photographing device (Printgraph Model AE-6911 FXFD; ATTO) and quantitatively determined with ATTO Densitograph ver.4.1 for the Macintosh. The values obtained were put into the formula $A/(A+B) \times 100$ to obtain skipping efficiency (%).

[0983] 5. The band where skipping had occurred was cut out, and the PCR product was subcloned into pT7 Blue-T vector (Novagen), followed by sequencing reaction with Thermo Sequenase™ II dye terminator cycle sequencing kit (Amersham Pharmacia Biotec) and confirmation of the nucleotide sequence with ABI PRISM 310 Genetic Analyzer (Applied Biosystems). The reaction procedures were according to the manual attached to the kit.

[Results]

[0984] The results of exon 41 skipping are shown in FIGS. 4 and 5. Exon 41 skipping occurred when the compounds of Examples 15 to 25 were used.

[0985] The results of exon 45 skipping are shown in FIG. 6. Exon 45 skipping occurred when the compounds of Examples 26 to 29 were used.

[0986] The results of exon 46 skipping are shown in FIGS. 7, 8 and 9. Exon 45 skipping occurred when the compounds of Examples 31 to 36 were used. Further, compared to the compound of Reference Example 1 disclosed in van Deutekom, J. C. T. et al. (2001) Hum. Mol. Genet. 10, 1547-1554, the compound of Example 33 having the same nucleotide sequence showed more efficient exon 46 skipping. Compared to the compound of Reference Example 2 disclosed in van Deutekom, J. C. T. et al. (2001) Hum. Mol. Genet. 10, 1547-1554, the compound of Example 34 having the same nucleotide sequence also showed more efficient exon 46 skipping. Further, compared to the compound of Reference Example 2 disclosed in van Deutekom, J. C. T. et al. (2001) Hum. Mol. Genet. 10, 1547-1554, the compound of Example 34 having the same nucleotide sequence also showed more efficient exon 46 skipping. Further, compared to the compound of Reference Example 2 disclosed in van Deutekom, J. C. T. et al. (2001) Hum. Mol. Genet. 10, 1547-1554, the compound of Example 31 having the same nucleotide sequence also showed more efficient exon 46 skipping.

[0987] FIG. 22 shows the results of exon 46 skipping. Exon 46 skipping occurred when the compounds of Examples 33 and 37-41 were used.

TEST EXAMPLE 3

Method of Analysis of the Exon Skipping Induction Ability by Antisense ENA

Preparation of Primary Culture of Myoblast Cells

[0988] A primary culture of myoblast cells was established as described below.

[0989] 1. Muscle tissue samples taken from the rectus muscle of the thigh of Duchenne muscular dystrophy patients were cut into fine pieces and washed with PBS twice.

[0990] 2. The muscle tissue from 1 above was treated with Difco Bacto™ tripton 250 (5% solution in PBS) at 37° C. for 30 min to thereby obtain free cells enzymatically.

[0991] 3. The free cells from 2 above were washed with DMEM (containing 20% FBS) twice.

[0992] 4. The cells from 3 above were suspended in DMEM (containing 20% FBS and 4% ultrosor G).

[0993] 5. The suspension cells from 4 were passed through a mesh (Becton Dickinson: cell strainer 35-2360) to recover only free cells.

[0994] 6. The recovered cells from 5 above were seeded on gelatin-coated dishes.

[0995] 7. The cells were cultured at 37° C. in an atmosphere of 5% CO₂ in air.

Induction of Differentiation

[0996] Differentiation of muscular cells was induced as described below.

[0997] 1. Cultured cells obtained above were seeded on 6-well plates (gelatin coated). When cells became confluent, the medium was exchanged with DMEM (containing 2% horse serum (HS)).

[0998] 2. After a 4 day cultivation, the cells were transfected with the compounds prepared in Examples (ENAs) as described below.

ENA Transfection

[0999] Myoblast cells were transfected with the compounds prepared in Examples (ENAs) as described below.

[1000] 1. 200 pmol of each of the compounds prepared in Examples (10 µg/20 µl milliQ) was dissolved in 100 µl of Opti-MEM (GIBCO-BRL).

[1001] 2. 6 µl of Plus reagent (GIBCO-BRL) was added to the solution from 1 above, which was then left at room temperature for 15 min.

[1002] 3. In another tube, 8 µl of Lipofectamine (GIBCO-BRL) was dissolved in 100 µl of Opti-MEM.

[1003] 4. After completion of the treatment of 2 above, the solution from 3 above was added to the solution from 2 above. The resultant solution was left at room temperature for another 15 min.

[1004] 5. Myoblast cells 4 days after the start of the induction of differentiation were washed with PBS once. Then, 800 µl of Opti-MEM was added thereto.

[1005] 6. After completion of the treatment of 4 above, the treated solution was added to the cells from 5 above.

[1006] 7. The cells from 6 above were cultured at 37° C. in an atmosphere of 5% CO₂ in air for 3 hr. Then, 500 µl of DMEM (containing 6% HS) was added to each well.

[1007] 8. Cells were cultured further.

RNA Extraction

[1008] RNA was extracted as described below.

[1009] 1. ENA-transfected cells were cultured for 2 days and then washed with PBS once. To these cells, 500 µl of ISOGEN (Nippon Gene) was added.

[1010] 2. The cells were left at room temperature for 5 min, followed by recovery of ISOGEN in each well into tubes.

[1011] 3. RNA was extracted according to the protocol of ISOGEN (Nippon Gene).

[1012] 4. Finally, RNA was dissolved in 20 µl of DEPW.

Reverse Transcription

[1013] Reverse transcription was performed as described below.

[1014] 1. To 2 µg of RNA, DEPW (sterilized water treated with diethylpyrocarbonate) was added to make a 6 µl solution.

[1015] 2. To the solution from 1 above, 2 µl of random hexamer (Invitrogen: 3 µg/µl product was diluted to 20-fold before use) was added.

[1016] 3. The resultant solution was heated at 65° for 10 min.

[1017] 4. Then, the solution was cooled on ice for 2 min.

[1018] 5. To the above reaction solution, the following was added:

MMLV-reverse transcriptase (Invitrogen: 200 U/µl)	1 µl
Human placenta ribonuclease inhibitor (Takara: 40 U/µl)	1 µl
DTT (attached to MMLV-reverse transcriptase)	1 µl
Buffer (attached to MMLV-reverse transcriptase)	4 µl
dNTPs (attached to Takara Ex Taq)	5 µl

[1019] 6. The resultant solution was kept at 37° C. for 1 hr, and then heated at 95° C. for 5 min.

[1020] 7. After the reaction, the solution was stored at -80° C.

PCR Reaction

[1021] PCR reaction was performed as described below.

[1022] 1. The following components were mixed and then heated at 94° C. for 4 min.

Reverse transcription product	3 µl
Forward primer (10 pmol/µl)	1 µl
Reverse primer (10 pmol/µl)	1 µl
dNTP (attached to TAKARA Ex Taq)	2 µl

-continued

Buffer (attached to TAKARA Ex Taq)	2 μ l
Ex Taq (TAKARA)	0.1 μ l
Sterilized water	11 μ l

[1023] 2. After the above-mentioned treatment at 94° C. for 4 min, 35 cycles of 94° C. for 1 min/60° C. for 1 min/72° C. for 3 min were performed.

[1024] 3. Then, the reaction solution was heated at 72° C. for 7 min.

[1025] The nucleotide sequences of the forward and reverse primers used in the PCR reactions for detecting the skipping of exons 44, 50, 51, 53 and 55 are as described below.

Exon 44:
 Forward: (SEQ ID NO:79)
 5'-TAGTCTACAACAAAGCTCAGGT-3' (exon 43)

Reverse: (SEQ ID NO:80)
 5'-CTTCCCAGTTGCATTCAAT-3' (exon 45)

Exons 50 and 51:
 Forward: (SEQ ID NO:81)
 5'-CAAGGAGAAATTGAAGCTCAA-3' (exon 48)

Reverse: (SEQ ID NO:82)
 5'-CGATCCGTAATGATTGTTCTAGC-3' (exon 52)

Exon 53:
 Forward: (SEQ ID NO:83)
 5'-TGGACAGAACTTACCGACTGG-3' (exon 51)

Reverse: (SEQ ID NO:84)
 5'-GGCGGAGGTCTTTGGCCAAC-3' (exon 54)

Exon 55:
 Forward: (SEQ ID NO:85)
 5'-AAGGATTCAACACAATGGCTGG-3' (exon 53)

Reverse: (SEQ ID NO:86)
 5'-GTAACAGGACTGCATCATCG-3' (exon 56)

[1026] 3. The PCR product was analyzed by 2% agarose gel electrophoresis.

[1027] The resultant gel was stained with ethidium bromide. The resultant band (A) (where an exon was skipped) and band (B) (where an exon was not skipped) were visualized with a gel photographing device (Printgraph Model AE-6911FXFD; ATTO) and quantitatively determined with ATTO Densitograph ver.4.1 for the Macintosh. The values obtained were put into the formula $A/(A+B) \times 100$ to obtain skipping efficiency (%).

[1028] 5. The band where skipping had occurred was cut out, and the PCR product was subcloned into pT7 Blue-T vector (Novagen), followed by sequencing reaction with Thermo Sequenase™ II dye terminator cycle sequencing kit (Amersham Pharmacia Biotech) and confirmation of the

nucleotide sequence with ABI PRISM 310 Genetic Analyzer (Applied Biosystems). The reaction procedures were according to the manual attached to the kit.

[Results]

[1029] FIGS. 10 and 11 show examples of exon 44 skipping induced by compounds A0100, AO102-106 and AO124-127. As shown in these Figures, exon 44 skipping was observed when these compounds were used.

[1030] FIGS. 12 and 13 show examples of exon 50 skipping induced by compounds AO108-113 and AO128. In FIG. 13, assay was performed under conditions that the concentration of the compounds was 40 pmol/ml. As shown in these Figures, exon 50 skipping was observed when these compounds were used.

[1031] FIGS. 14, 15, 16 and 17 shows examples of exon 51 skipping induced by compounds A03-6, AO8-10, AO37, AO39, AO43 and AO58. As shown in these Figures, exon 51 skipping was observed when these compounds were used.

[1032] FIGS. 18 and 19 show examples of exon 53 skipping induced by compounds A064-67, AO69-72 and AO95-98. As shown in these Figures, exon 53 skipping was observed when these compounds were used.

[1033] FIGS. 20 and 21 show examples of exon 44 skipping induced by compounds A0114-116, AO118-120, AO122, AO123 and AO129. In FIG. 21, assay was performed under conditions that the concentration of the compounds was 100 pmol/ml. As shown in these Figures, exon 44 skipping was observed when these compounds were used.

FORMULATION EXAMPLE 1

[1034] According to the following prescription, necessary amounts of base components are mixed and dissolved. To this solution, any one of the compounds of Examples 1 to 99 or a salt thereof is dissolved to prepare a solution of a specific volume. The resultant solution is filtered with a membrane filter 0.22 μ m in pore size to thereby obtain a preparation for intravenous administration.

Any one of the compounds of Examples 1 to 99 or a salt thereof	500 mg
Sodium chloride	8.6 g
Potassium chloride	0.3 g
Calcium chloride	0.33 g
Distilled water for injection	to give a total volume of 1000 ml

FORMULATION EXAMPLE 2

[1035] According to the following prescription, necessary amounts of base components are mixed and dissolved. To this solution, any one of the compounds of Examples 1 to 99 or a salt thereof is dissolved to prepare a solution of a specific volume. The resultant solution is filtered with a filter 15 nm in pore size (PLANOVE 15: Asahi Kasei) to thereby obtain a preparation for intravenous administration.

Any one of the compounds of Examples 1 to 99 or a salt thereof	100 mg
Sodium chloride	8.3 g
Potassium chloride	0.3 g
Calcium chloride	0.33 g
Sodium hydrogenphosphate · 12H ₂ O	1.8 g
1N HCl	appropriate amount (pH 7.4)
Distilled water for injection	to give a total volume of 1000 ml

FORMULATION EXAMPLE 3

[1036] According to the following prescription, necessary amounts of base components are mixed and dissolved. To this solution, any one of the compounds of Examples 1 to 99 or a salt thereof is dissolved to prepare a solution of a specific volume. The resultant solution is filtered with a filter 35 nm in pore size (PLANOVE 35: Asahi Kasei) to thereby obtain a preparation for intravenous administration.

Any one of the compounds of Examples 1 to 99 or a salt thereof	100 mg
Sodium chloride	8.3 g
Potassium chloride	0.3 g
Calcium chloride	0.33 g
Glucose	0.4 g
Sodium hydrogenphosphate · 12H ₂ O	1.8 g
1N HCl	appropriate amount (pH 7.4)
Distilled water for injection	to give a total volume of 1000 ml

[1037] All publications, patents and patent applications cited herein are incorporated herein by reference in their entirety.

INDUSTRIAL APPLICABILITY

[1038] The compounds of the present invention and pharmacologically acceptable salts thereof have an effect of inducing skipping of exon 19, 41, 45, 46, 44, 50, 55, 51 or 53 of the dystrophin gene and thus useful as pharmaceuticals for treating muscular dystrophy.

SEQUENCE LISTING FREE TEXT

[1039] SEQ ID NO: 1 shows the nucleotide sequence of the oligonucleotide prepared in Example 1 (AO1).

[1040] SEQ ID NO: 2 shows the nucleotide sequence of the oligonucleotides prepared in Examples 2 and 14 (AO14 and AO24).

[1041] SEQ ID NO: 3 shows the nucleotide sequence of the oligonucleotide prepared in Example 3 (AO15).

[1042] SEQ ID NO: 4 shows the nucleotide sequence of the oligonucleotide prepared in Example 5 (AO18) and the oligonucleotide prepared in Example 7 (AO25).

[1043] SEQ ID NO: 5 shows the nucleotide sequence of the oligonucleotide prepared in Example 6 (AO19).

[1044] SEQ ID NO: 6 shows the nucleotide sequence of the oligonucleotide prepared in Example 4 (AO16).

[1045] SEQ ID NO: 7 shows the nucleotide sequence of the oligonucleotide prepared in Example 13 (AO17).

[1046] SEQ ID NO: 8 shows the nucleotide sequence of the forward primer used in Test Example 1.

[1047] SEQ ID NO: 9 shows the nucleotide sequence of the reverse primer used in Test Examples 1.

[1048] SEQ ID NO: 10 shows the nucleotide sequence of the oligonucleotides prepared in Examples 15 and 16 (AO20 and AO26).

[1049] SEQ ID NO: 11 shows the nucleotide sequence of the oligonucleotide prepared in Example 17 (AO55).

[1050] SEQ ID NO: 12 shows the nucleotide sequence of the oligonucleotides prepared in Examples 18, 20, 21 and 22 (AO56, AO76, AO77 and AO78).

[1051] SEQ ID NO: 13 shows the nucleotide sequence of the oligonucleotides prepared in Examples 19, 23, 24 and 25 (AO57, AO79, AO80 and AO81) and the oligonucleotide prepared in Example 21 (AO25).

[1052] SEQ ID NO: 14 shows the nucleotide sequence of the oligonucleotide prepared in Example 26 (AO33).

[1053] SEQ ID NO: 15 shows the nucleotide sequence of the oligonucleotides prepared in Examples 27 and 30 (AO85 and SO88).

[1054] SEQ ID NO: 16 shows the nucleotide sequence of the oligonucleotide prepared in Example 28 (AO86).

[1055] SEQ ID NO: 17 shows the nucleotide sequence of the oligonucleotide prepared in Example 29 (AO87).

[1056] SEQ ID NO: 18 shows the nucleotide sequence of the oligonucleotide prepared in Example 31 (AO2).

[1057] SEQ ID NO: 19 shows the nucleotide sequence of the oligonucleotides prepared in Examples 32 and 35 (AO23 and AO29).

[1058] SEQ ID NO: 20 shows the nucleotide sequence of the oligonucleotide prepared in Example 36 (AO48).

[1059] SEQ ID NO: 21 shows the nucleotide sequence of the oligonucleotides prepared in Examples 33, 37, 38, 39, 40 and 41 (AO27, AO89, AO90, SO91, AO92 and AO93).

[1060] SEQ ID NO: 22 shows the nucleotide sequence of the oligonucleotide prepared in Example 34 (AO28).

[1061] SEQ ID NO: 23 shows the nucleotide sequence of the oligonucleotide prepared in Reference Example 1.

[1062] SEQ ID NO: 24 shows the nucleotide sequence of the oligonucleotide prepared in Reference Example 2.

[1063] SEQ ID NO: 25 shows the nucleotide sequence of the oligonucleotide prepared in Reference Example 3.

[1064] SEQ ID NO: 26 shows the nucleotide sequence of the forward primer (for the PCR reaction for detecting exon 41 skipping) used in Test Example 2.

[1065] SEQ ID NO: 27 shows the nucleotide sequence of the reverse primer (for the PCR reaction for detecting exon 41 skipping) used in Test Example 2.

[1066] SEQ ID NO: 28 shows the nucleotide sequence of the forward primer (for the PCR reaction for detecting exon 45 and exon 46 skipping) used in Test Example 2.

- [1067] SEQ ID NO: 29 shows the nucleotide sequence of the reverse primer (for the PCR reaction for detecting exon 45 and exon 46 skipping) used in Test Example 2.
- [1068] SEQ ID NO: 30 shows the nucleotide sequence of the oligonucleotides prepared in Examples 42 and 94 (AO100 and AO134).
- [1069] SEQ ID NO: 31 shows the nucleotide sequence of the oligonucleotide prepared in Example 43 (AO102).
- [1070] SEQ ID NO: 32 shows the nucleotide sequence of the oligonucleotide prepared in Example 44 (AO103).
- [1071] SEQ ID NO: 33 shows the nucleotide sequence of the oligonucleotide prepared in Example 45 (AO104).
- [1072] SEQ ID NO: 34 shows the nucleotide sequence of the oligonucleotide prepared in Example 46 (AO105).
- [1073] SEQ ID NO: 35 shows the nucleotide sequence of the oligonucleotide prepared in Example 47 (AO106).
- [1074] SEQ ID NO: 36 shows the nucleotide sequence of the oligonucleotide prepared in Example 62 (AO124).
- [1075] SEQ ID NO: 37 shows the nucleotide sequence of the oligonucleotide prepared in Example 63 (AO125).
- [1076] SEQ ID NO: 38 shows the nucleotide sequence of the oligonucleotide prepared in Example 64 (AO126).
- [1077] SEQ ID NO: 39 shows the nucleotide sequence of the oligonucleotide prepared in Example 65 (AO127).
- [1078] SEQ ID NO: 40 shows the nucleotide sequence of the oligonucleotide prepared in Example 48 (AO108).
- [1079] SEQ ID NO: 41 shows the nucleotide sequence of the oligonucleotides prepared in Examples 49 and 95 (AO109 and AO135).
- [1080] SEQ ID NO: 42 shows the nucleotide sequence of the oligonucleotide prepared in Example 50 (AO110).
- [1081] SEQ ID NO: 43 shows the nucleotide sequence of the oligonucleotide prepared in Example 51 (AO111).
- [1082] SEQ ID NO: 44 shows the nucleotide sequence of the oligonucleotide prepared in Example 52 (AO112).
- [1083] SEQ ID NO: 45 shows the nucleotide sequence of the oligonucleotide prepared in Example 53 (AO113).
- [1084] SEQ ID NO: 46 shows the nucleotide sequence of the oligonucleotide prepared in Example 66 (AO128).
- [1085] SEQ ID NO: 47 shows the nucleotide sequence of the oligonucleotides prepared in Examples 54 and 96 (AO114 and SO136).
- [1086] SEQ ID NO: 48 shows the nucleotide sequence of the oligonucleotides prepared in Example 55 and 97 (AO115 and AO137).
- [1087] SEQ ID NO: 49 shows the nucleotide sequence of the oligonucleotide prepared in Example 56 (AO116).
- [1088] SEQ ID NO: 50 shows the nucleotide sequence of the oligonucleotide prepared in Example 57 (AO118).
- [1089] SEQ ID NO: 51 shows the nucleotide sequence of the oligonucleotide prepared in Example 58 (AO119).
- [1090] SEQ ID NO: 52 shows the nucleotide sequence of the oligonucleotide prepared in Example 59 (AO120).
- [1091] SEQ ID NO: 53 shows the nucleotide sequence of the oligonucleotide prepared in Example 60 (AO122).
- [1092] SEQ ID NO: 54 shows the nucleotide sequence of the oligonucleotide prepared in Example 61 (AO123).
- [1093] SEQ ID NO: 55 shows the nucleotide sequence of the oligonucleotide prepared in Example 67 (AO129).
- [1094] SEQ ID NO: 56 shows the nucleotide sequence of the oligonucleotide prepared in Example 68 (AO3).
- [1095] SEQ ID NO: 57 shows the nucleotide sequence of the oligonucleotide prepared in Example 69 (AO4).
- [1096] SEQ ID NO: 58 shows the nucleotide sequence of the oligonucleotide prepared in Example 70 (AO5).
- [1097] SEQ ID NO: 59 shows the nucleotide sequence of the oligonucleotide prepared in Example 71 (AO6).
- [1098] SEQ ID NO: 60 shows the nucleotide sequence of the oligonucleotide prepared in Example 72 (AO8).
- [1099] SEQ ID NO: 61 shows the nucleotide sequence of the oligonucleotide prepared in Example 73 (AO9).
- [1100] SEQ ID NO: 62 shows the nucleotide sequence of the oligonucleotide prepared in Example 74 (AO10).
- [1101] SEQ ID NO: 63 shows the nucleotide sequence of the oligonucleotide prepared in Example 75 (AO37).
- [1102] SEQ ID NO: 64 shows the nucleotide sequence of the oligonucleotide prepared in Example 76 (AO39).
- [1103] SEQ ID NO: 65 shows the nucleotide sequence of the oligonucleotide prepared in Example 77 (AO43).
- [1104] SEQ ID NO: 66 shows the nucleotide sequence of the oligonucleotide prepared in Example 78 (AO58).
- [1105] SEQ ID NO: 67 shows the nucleotide sequence of the oligonucleotide prepared in Example 79 (AO64).
- [1106] SEQ ID NO: 68 shows the nucleotide sequence of the oligonucleotide prepared in Example 80 (AO65).
- [1107] SEQ ID NO: 69 shows the nucleotide sequence of the oligonucleotide prepared in Example 81 (AO66).
- [1108] SEQ ID NO: 70 shows the nucleotide sequence of the oligonucleotide prepared in Example 82 (AO67).
- [1109] SEQ ID NO: 71 shows the nucleotide sequence of the oligonucleotide prepared in Example 83 (AO69).
- [1110] SEQ ID NO: 72 shows the nucleotide sequence of the oligonucleotide prepared in Example 84 (AO70).
- [1111] SEQ ID NO: 73 shows the nucleotide sequence of the oligonucleotide prepared in Example 85 (AO71).
- [1112] SEQ ID NO: 74 shows the nucleotide sequence of the oligonucleotide prepared in Example 86 (AO72).
- [1113] SEQ ID NO: 75 shows the nucleotide sequence of the oligonucleotide prepared in Example 87 (AO95).
- [1114] SEQ ID NO: 76 shows the nucleotide sequence of the oligonucleotide prepared in Example 88 (AO96).
- [1115] SEQ ID NO: 77 shows the nucleotide sequence of the oligonucleotide prepared in Example 89 (AO97).
- [1116] SEQ ID NO: 78 shows the nucleotide sequence of the oligonucleotides prepared in Examples 90 and 93 (AO98 and AO133).

[1117] SEQ ID NO: 79 shows the nucleotide sequence of the forward primer (for the PCR reaction for detecting exon 44 skipping) used in Test Example 3.

[1118] SEQ ID NO: 80 shows the nucleotide sequence of the reverse primer (for the PCR reaction for detecting exon 44 skipping) used in Test Example 3.

[1119] SEQ ID NO: 81 shows the nucleotide sequence of the forward primer (for the PCR reaction for detecting exon 50 and exon 51 skipping) used in Test Example 3.

[1120] SEQ ID NO: 82 shows the nucleotide sequence of the reverse primer (for the PCR reaction for detecting exon 50 and exon 51 skipping) used in Test Example 3.

[1121] SEQ ID NO: 83 shows the nucleotide sequence of the forward primer (for the PCR reaction for detecting exon 53 skipping) used in Test Example 3.

[1122] SEQ ID NO: 84 shows the nucleotide sequence of the reverse primer (for the PCR reaction for detecting exon 53 skipping) used in Test Example 3.

[1123] SEQ ID NO: 85 shows the nucleotide sequence of the forward primer (for the PCR reaction for detecting exon 55 skipping) used in Test Example 3.

[1124] SEQ ID NO: 86 shows the nucleotide sequence of the reverse primer (for the PCR reaction for detecting exon 55 skipping) used in Test Example 3.

[1125] SEQ ID NO: 87 shows the nucleotide sequence of the oligonucleotides prepared in Example 91 and 92 (AO131 and AO132).

[1126] SEQ ID NO: 88 shows the nucleotide sequence of the oligonucleotides prepared in Example 98 and 99 (AO139 and AO140).

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caggaattug tgucuutc 18

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gctaggtcag gctgcttu 18

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agtutggaga tggcagtt

18

1.-59. (canceled)

60. A method of treating muscular dystrophy in a patient in need thereof, said method comprising administering to the patient an effective amount of a pharmaceutical composition comprising an antisense oligonucleotide compound capable of inducing skipping of any one of the exons of the dystrophin gene or a pharmacologically acceptable salt thereof, provided that at least one of the nucleotides constituting the compound has a 2'-O, 4'-C-alkylene group.

61. The method according to claim 60, wherein muscular dystrophy is Duchenne muscular dystrophy.

62. The method according to claim 61, wherein the total number of amino acids in the open reading frame of the dystrophin gene in the patient will be a multiple of 3 when exon 19, 41, 45, 46, 44, 50, 55, 51 or 53 of the dystrophin gene has been skipped.

63. An antisense oligonucleotide compound complementary to a nucleotide sequence in any one of the region of the nucleotides Nos. 6691-6727, 7554-7757, 6921-6992, 6555-6673, 7447-7551, 7907-8068, 8275-8458, 2571-2601 or 6125-6161 of dystrophin cDNA (Gene Bank accession No. NM_004006.1) or a pharmaceutically acceptable salt thereof, provided that at least one of the nucleotides constituting the compound complementary to a nucleotide sequence in the region of the nucleotides No. 2571-2601 of dystrophin cDNA (Gene Bank accession No. NM_004006.1) has a 2'-O, 4'-C-alkylene group.

64. The compound according to claim 63 or a pharmacologically acceptable salt thereof, having the nucleotide sequence as shown in any one of SEQ ID NOS: 15, 14, 16, 17, 64, 56-63, 65, 66, 87, 88, 18-22, 30-39, 40-46, 67-78, 47-55, 2-7 or 10-13.

65. The compound according to claim 63 or a pharmacologically acceptable salt thereof, wherein at least one of the sugars and/or the phosphates constituting the oligonucleotide is modified.

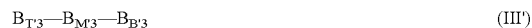
66. The compound according to claim 65 or a pharmacologically acceptable salt thereof, wherein the sugar constituting the oligonucleotide is D-ribofuranose and the modification of the sugar is modification of the hydroxyl group at position 2' of D-ribofuranose.

67. The compound according to claim 66 or a pharmacologically acceptable salt thereof, wherein the modification of the sugar is 2'-O-alkylation and/or 2'-O4'-C-alkylation of the D-ribofuranose.

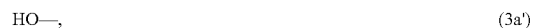
68. The compound according to claim 65 or a pharmacologically acceptable salt thereof, wherein the modification of the phosphate is thioation of the phosphate group.

69. The compound according to claim 63 which is represented by any one of formulae (III'), (IV'), (XV'), (IX''), (X''), (XI''), (XII''), (XIII''), (XIV''), (V') (VI') (VII') (I''), (II''), (III''), (IV''), (V''), (XVI''), (XVII''), (XVIII''), (XIX''), (XX''), (XXI''), (VI''), (VII''), (VIII''), (I), (I') and (II'), or a pharmacologically acceptable salt thereof,

wherein said formulae are defined as follows:

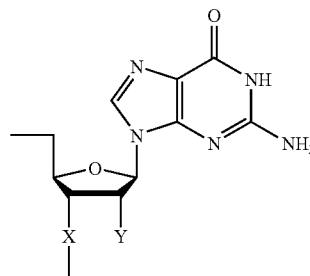


where B_{T_3} is a group represented by any one of (3a') to (3c'):

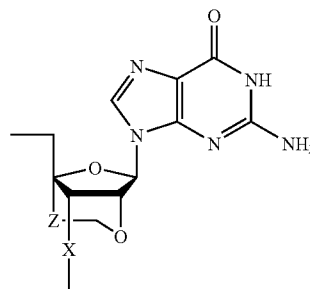


where Bg is a group represented by formula (G1) or (G2); and Bc is a group represented by formula (C1) or (C2):

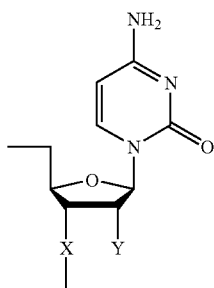
(G1)



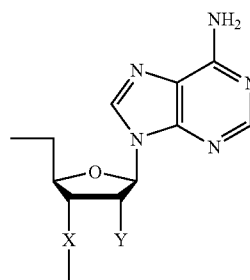
(G2)



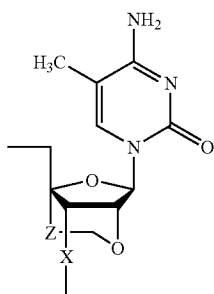
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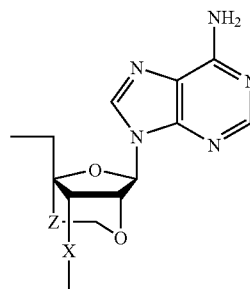
(C1)



(A1)

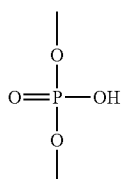


(C2)

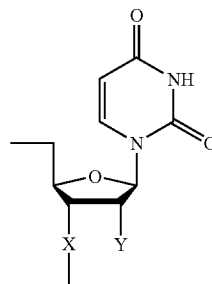


(A2)

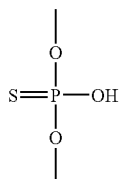
where X is individually and independently a group represented by formula (X1) or (X2):



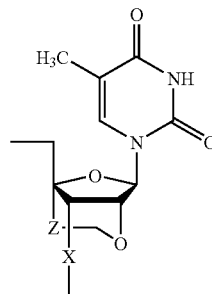
(X1)



(U1)



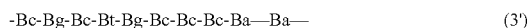
(X2)



(T2)

Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms;

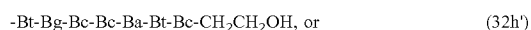
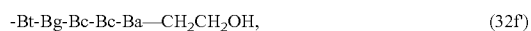
B_{M'3} is a group represented by formula (3'):



where Bg and Bc are as defined above; Ba is a group represented by formula (A1) or (A2); and Bt is a group represented by formula (U1) or (T2):

where X and Y are as defined above;

B_{B'3} is a group represented by any one of (32a') to (32i'):

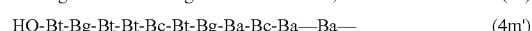
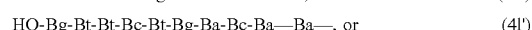
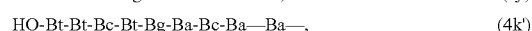
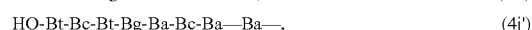
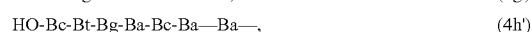
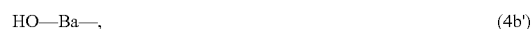


where Bg, Ba, Bt and Bc are as described above;

provided that at least one of the nucleosides constituting the compound represented by formula (III') has a 2'-O, 4'-C-alkylene group;



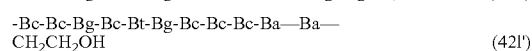
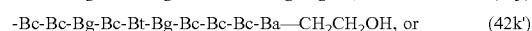
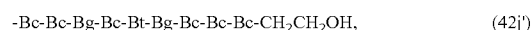
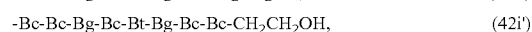
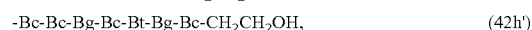
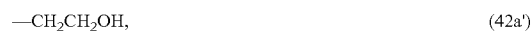
where $B_{T'4}$ is a group represented by any one of (4a') to (4m')



$B_{M'4}$ is a group represented by formula (4')



$B_{B'4}$ is a group represented by any one of (42a') to (42l')

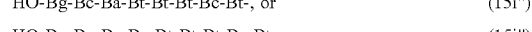


where Bg, Ba, Bt and Bc are as described above;

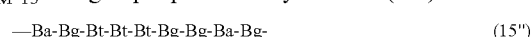
provided that at least one of the nucleosides constituting the compound represented by formula (IV') has a 2'-O, 4'-C-alkylene group;



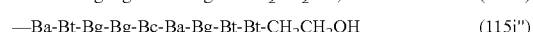
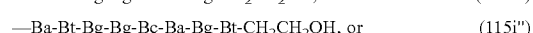
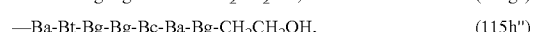
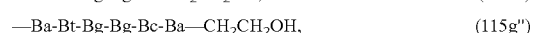
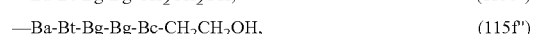
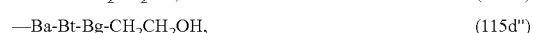
where $B_{T''15}$ is a group represented by any one of the following (15a'') to (15j'')



$B_{M''15}$ is a group represented by formula (15'')



$B_{B''15}$ is a group represented by any one of (115a'') to (115j'')

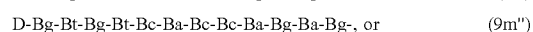
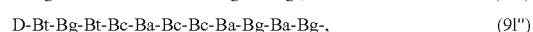
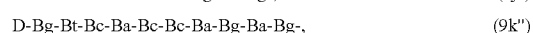
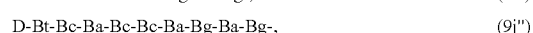


where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (XV'') has 2''-O, 4''-C-alkylene group;



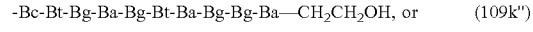
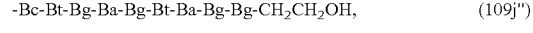
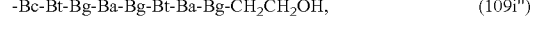
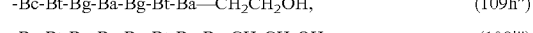
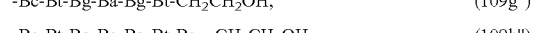
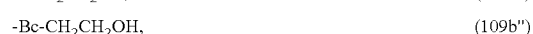
where $B_{T''9}$ is a group represented by any one of (9a'') to (9n'')



$B_{M''9}$ is a group represented by formula (9'')

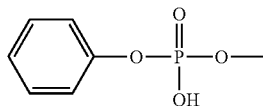


$B_{B''9}$ is a group represented by any one of (109a'') to (109l'')



where Bg, Ba, Bt and Bc are as defined above; and D is HO— or Ph—

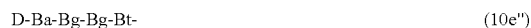
wherein Ph- is a group represented by formula:



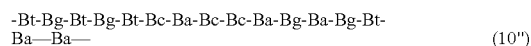
provided that at least one of the nucleosides constituting the compound represented by formula (IX^{''}) has 2''-O, 4''-C-alkylene group;



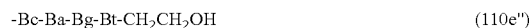
where $B_{T''10}$ is a group represented by any one of (10a'') to (10e''):



$B_{M''10}$ is a group represented by formula (10''):



$B_{B''10}$ is a group represented by any one of (110a'') to (110e''):

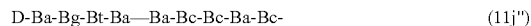
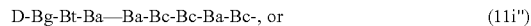


where Bg, Ba, Bt, Bc and D are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (X'') has 2''-O, 4''-C-alkylene group;



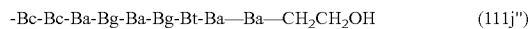
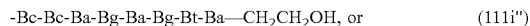
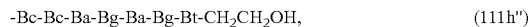
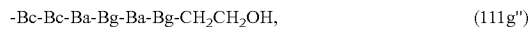
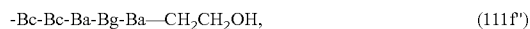
where $B_{T''11}$ is a group represented by any one of (11a'') to (11j''):



$B_{M''11}$ is a group represented by formula (11''):



$B_{B''11}$ is a group represented by any one of (111a'') to (111j''):

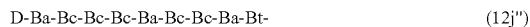
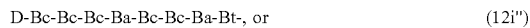
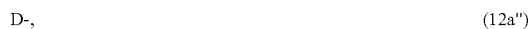


where Bg, Ba, Bt, Bc and D are as defined above;

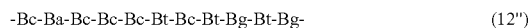
provided that at least one of the nucleosides constituting the compound represented by formula (XI'') has 2''-O, 4''-C-alkylene group;



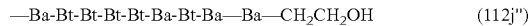
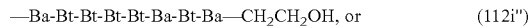
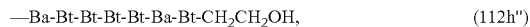
where $B_{T''12}$ is a group represented by any one of (12a'') to (12j''):



$B_{M''12}$ is a group represented by formula (12''):



$B_{B''12}$ is a group represented by any one of (112a'')~(112j''):

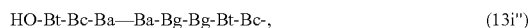


where Bg, Ba, Bt, Bc and D are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (XII'') has 2''-O, 4''-C-alkylene group;



where $B_{T''13}$ is a group represented by any one of (13a'') to (13k''):



HO-Bc-Bt-Bc-Ba—Ba-Bg-Bg-Bt-Bc-, or (13j'')

HO-Bc-Bc-Bt-Bc-Ba—Ba-Bg-Bg-Bt-Bc-, (13k'')

$B_{M^{13}}$ is a group represented by formula (13'')

—Ba-Bc-Bc-Bc-Ba-Bc-Bc-Ba-Bt-Bc- (13'')

where Bg, Ba, Bt and Bc are as defined above;

$B_{B^{13}}$ is a group represented by (113a'')

—CH₂CH₂OH (113a'')

provided that at least one of the nucleosides constituting the compound represented by formula (XIII'') has 2''-O, 4''-C-alkylene group;

$B_{T^{14}}—B_{M^{14}}—B_{B^{14}}$ (XIV'')

where $B_{T^{14}}$ is a group represented by any one of (14a'') to (14q'')

HO—, (14a'')

—HO—Ba—, (14b'')

HO—Ba—Ba—, (14c'')

HO-Bg-Ba—Ba—, (14d'')

HO—Ba-Bg-Ba—Ba—, (14e'')

HO-Bg-Ba-Bg-Ba—Ba—, (14f'')

HO—Ba-Bg-Ba-Bg-Ba—Ba—, (14g'')

HO-Bc-Ba-Bg-Ba-Bg-Ba—Ba—, (14h'')

HO-Bg-Bc-Ba-Bg-Ba-Bg-Ba—Ba—, (14i'')

HO—Ba-Bg-Bc-Ba-Bg-Ba-Bg-Ba—Ba—, (14j'')

HO—Ba—Ba-Bg-Bc-Ba-Bg-Ba-Bg-Ba—Ba—, (14k'')

HO-Bc-Ba—Ba-Bg-Bc-Ba-Bg-Ba-Bg-Ba—Ba—, (14l'')

HO-Bt-Bc-Ba—Ba-Bg-Bc-Ba-Bg-Ba-Bg-Ba—Ba—, (14m'')

HO—Ba-Bt-Bc-Ba—Ba-Bg-Bc-Ba-Bg-Ba-Bg-Ba—Ba—, (14n'')

HO-Bg-Ba-Bt-Bc-Ba—Ba-Bg-Bc-Ba-Bg-Ba-Bg-Ba—Ba—, (14o'')

HO-Bt-Bg-Ba-Bt-Bc-Ba—Ba-Bg-Bc-Ba-Bg-Ba-Bg-Ba—Ba—, or (14p'')

HO-Bt-Bt-Bg-Ba-Bt-Bc-Ba—Ba-Bg-Bc-Ba-Bg-Ba-Bg-Ba—Ba— (14q'')

$B_{M^{14}}$ is a group represented by formula (14'')

—Ba-Bg-Bc-Bc- (14'')

$B_{B^{14}}$ is a group represented by any one of (114a'') to (114o'')

—CH₂CH₂OH, (114a'')

—Ba—CH₂CH₂OH, (114b'')

—Ba-Bg-CH₂CH₂OH, (114c'')

—Ba-Bg-Bt-CH₂CH₂OH, (114d'')

—Ba-Bg-Bt-Bc-CH₂CH₂OH, (114e'')

—Ba-Bg-Bt-Bc-Bg-CH₂CH₂OH, (114f'')

—Ba-Bg-Bt-Bc-Bg-Bg-CH₂CH₂OH, (114g'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-CH₂CH₂OH, (114h'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-Ba—CH₂CH₂OH, (114i'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-Ba—Ba—CH₂CH₂OH, (114j'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-Ba—Ba-Bg-CH₂CH₂OH, (114k'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-Ba—Ba-Bg-Bt-CH₂CH₂OH, (114l'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-Ba—Ba-Bg-Bt-Bt-CH₂CH₂OH, (114m'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-Ba—Ba-Bg-Bt-Bt-CH₂CH₂OH, (114n'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-Ba—Ba-Bg-Bt-Bt-CH₂CH₂OH, (114o'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-Ba—Ba-Bg-Bt-Bt-Bc-CH₂CH₂OH, or (114n'')

—Ba-Bg-Bt-Bc-Bg-Bg-Bt-Ba—Ba-Bg-Bt-Bt-Bc-Bt-CH₂CH₂OH (114o'')

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (XIV'') has 2''-O, 4''-C-alkylene group;

$B_{T^{15}}—B_{M^{15}}—B_{B^{15}}$ (V')

where $B_{T^{15}}$ is a group represented by any one of (5a') to (5g')

HO—, (5a')

HO-Bt-, (5b')

HO-Bt-Bt-, (5c')

HO-Bt-Bt-Bt-, (5d')

HO-Bt-Bt-Bt-Bt-, (5e')

HO-Bc-Bt-Bt-Bt-Bt-, or (5f')

HO-Bg-Bc-Bt-Bt-Bt-Bt- (5g')

$B_{M^{15}}$ is a group represented by formula (5')

—Bc-Bt-Bt-Bt-Bt-Ba-Bg-Bt-Bt-Bg-Bc-Bt-Bg-Bc- (5')

$B_{B^{15}}$ is a group represented by any one of (52a') to (52i')

—CH₂CH₂OH, (52a')

—Bt-CH₂CH₂OH, (52b')

—Bt-Bc-CH₂CH₂OH, (52c')

—Bt-Bc-Bt-CH₂CH₂OH, (52d')

—Bt-Bc-Bt-Bt-CH₂CH₂OH, (52e')

—Bt-Bc-Bt-Bt-Bt-CH₂CH₂OH, (52f')

—Bt-Bc-Bt-Bt-Bt-Bt-CH₂CH₂OH, (52g')

—Bt-Bc-Bt-Bt-Bt-Bt-Bc-CH₂CH₂OH, or (52h')

—Bt-Bc-Bt-Bt-Bt-Bt-Bc-Bc-CH₂CH₂OH (52i')

where Bg, Ba, Bt and Bc are as described above;

provided that at least one of the nucleosides constituting the compound represented by formula (V') has a 2'-O, 4'-C-alkylene group;

$B_{T^{16}}—B_{M^{16}}—B_{B^{16}}$ (VI')

where $B_{T^{16}}$ is a group represented by any one of (6a') to (6r')

HO—, (6a')

HO-Bc-, (6b')

HO-Bt-Bc-, (6c')

HO-Bc-Bt-Bc-, (6d')

HO-Bg-Bc-Bt-Bc-, (6e')

HO-Bt-Bg-Bc-Bt-Bc-, (6f')

HO-Bc-Bt-Bg-Bc-Bt-Bc-, (6g')

HO-Bg-Bc-Bt-Bg-Bc-Bt-Bc-, (6h')

HO-Bt-Bg-Bc-Bt-Bg-Bc-Bt-Bc-, (6j')

HO-Bt-Bt-Bg-Bc-Bt-Bg-Bc-Bt-Bc-, (6k')

HO-Bg-Bt-Bt-Bg-Bc-Bt-Bg-Bc-Bt-Bc-, (6l')

HO—Ba-Bg-Bt-Bt-Bg-Bc-Bt-Bg-Bc-Bt-Bc-, (6m')

HO-Bt-Ba-Bg-Bt-Bt-Bg-Bc-Bt-Bg-Bc-Bt-Bc-, (6n')

HO-Bt-Bt-Ba-Bg-Bt-Bt-Bg-Bc-Bt-Bg-Bc-Bt-Bc-, (6o')

HO-Bt-Bt-Bt-Ba-Bg-Bt-Bt-Bg-Bc-Bt-Bg-Bc-Bt-Bc-, (6p')

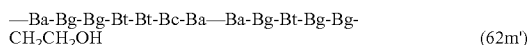
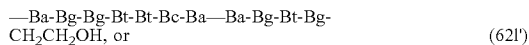
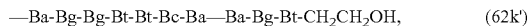
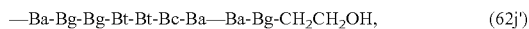
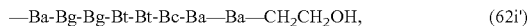
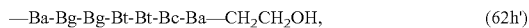
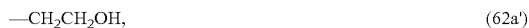
HO-Bt-Bt-Bt-Bt-Ba-Bg-Bt-Bt-Bg-Bc-Bt-Bg-Bc-Bt-Bc-, or (6q')

HO-Bc-Bt-Bt-Bt-Bt-Ba-Bg-Bt-Bt-Bg-Bc-Bt-Bg-Bc-Bt-Bc- (6r')

$B_{M'6}$ is a group represented by formula (6'):



$B_{B'6}$ is a group represented by any one of (62a') to (62m'):

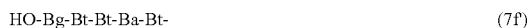


where Bg, Ba, Bt and Bc are as described above;

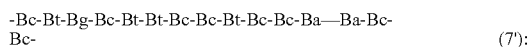
provided that at least one of the nucleosides constituting the compound represented by formula (VI') has a 2'-O, 'C-alkylene group;



where $B_{T'7}$ is a group represented by any one of (7a') to (7f'):



$B_{M'7}$ is a group represented by formula (7'):



where Bg, Ba, Bt and Bc are as described above;

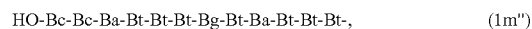
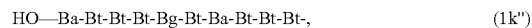
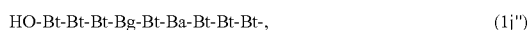
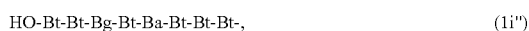
$B_{B'7}$ is a group represented by (72a'):



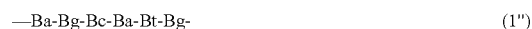
provided that at least one of the nucleosides constituting the compound represented by formula (VII') has a 2'-O, 4'-C-alkylene group;



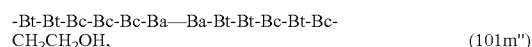
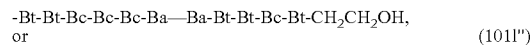
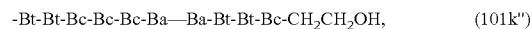
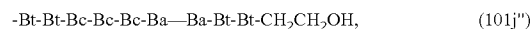
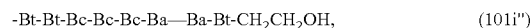
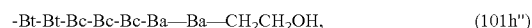
where $B_{T''1}$ is a group represented by any one of (1a'') to (1m''):



$B_{M''1}$ is a group represented by formula (1''):



$B_{B''1}$ is a group represented by any one of (101a'') to (101m''):



where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides, constituting the compound represented by formula (I'') has 2''-O, 4''-C-alkylene group;



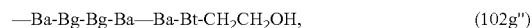
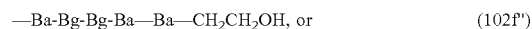
where $B_{T''2}$ is a group represented by any one of (2a'') to (2g''):



$B_{M''2}$ is a group represented by formula (2''):



$B_{B''2}$ is a group represented by any one of (102a'') to (102g''):



where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (II'') has 2''-O, 4''-C-alkylene group;



where $B_{T''3}$ is a group represented by any one of (3a'') to (3m''):

HO—,	(3a'')
HO-Bc—,	(3b'')
HO—Ba-Bc—,	(3c'')
HO—Ba—Ba-Bc—,	(3d'')
HO—Ba—Ba—Ba-Bc—,	(3e'')
HO—Ba—Ba—Ba—Ba-Bc—,	(3f'')
HO-Bg-Ba—Ba—Ba—Ba-Bc—,	(3g'')
HO-Bt-Bg-Ba—Ba—Ba—Ba-Bc—,	(3h'')
HO—Ba-Bt-Bg-Ba—Ba—Ba—Ba-Bc—,	(3i'')
HO—Ba—Ba-Bt-Bg-Ba—Ba—Ba—Ba-Bc—,	(3j'')
HO-Bt-Ba—Ba-Bt-Bg-Ba—Ba—Ba—Ba-Bc—,	(3k'')
HO—Ba-Bt-Ba—Ba-Bt-Bg-Ba—Ba—Ba—Ba-Bc—,	(3l'')
HO-Bc-Ba-Bt-Ba—Ba-Bt-Bg-Ba—Ba—Ba—Ba-Bc—,	(3m'')

$B_{M''3}$ is a group represented by formula (3''):

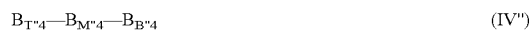


$B_{B''3}$ is a group represented by any one of (103a'') to (103m''):

—CH ₂ CH ₂ OH,	(103a'')
—Ba—CH ₂ CH ₂ OH,	(103b'')
—Ba-Bt-CH ₂ CH ₂ OH,	(103c'')
—Ba-Bt-Bt-CH ₂ CH ₂ OH,	(103d'')
—Ba-Bt-Bt-Bt-CH ₂ CH ₂ OH,	(103e'')
—Ba-Bt-Bt-Bt-Bc-CH ₂ CH ₂ OH,	(103f'')
—Ba-Bt-Bt-Bt-Bc-Bt-CH ₂ CH ₂ OH,	(103g'')
—Ba-Bt-Bt-Bt-Bc-Bt-Bc-CH ₂ CH ₂ OH,	(103h'')
—Ba-Bt-Bt-Bt-Bc-Bt-Bc-Ba—CH ₂ CH ₂ OH,	(103i'')
—Ba-Bt-Bt-Bt-Bc-Bt-Bc-Ba—Ba—CH ₂ CH ₂ OH,	(103j'')
—Ba-Bt-Bt-Bt-Bc-Bt-Bc-Ba—Ba-Bc-CH ₂ CH ₂ OH,	(103k'')
—Ba-Bt-Bt-Bt-Bc-Bt-Bc-Ba—Ba-Bc-Ba—CH ₂ CH ₂ OH, or	(103l'')
—Ba-Bt-Bt-Bt-Bc-Bt-Bc-Ba—Ba-Bc-Ba-Bg-CH ₂ CH ₂ OH	(103m'')

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (III'') has 2''-O, 4''-C-alkylene group;



where $B_{T''4}$ is a group represented by any one of (4a'') to (4j''):

HO—,	(4a'')
HO—Ba—,	(4b'')
HO-Bc-Ba—,	(4c'')
HO-Bt-Bc-Ba—,	(4d'')
HO-Bg-Bt-Bc-Ba—,	(4e'')
HO-Bg-Bg-Bt-Bc-Ba—,	(4f'')
HO—Ba-Bg-Bg-Bt-Bc-Ba—,	(4g'')
HO-Bt-Ba-Bg-Bg-Bt-Bc-Ba—,	(4h'')
HO-Bc-Bt-Ba-Bg-Bg-Bt-Bc-Ba—,	(4i'')
HO-Bg-Bc-Bt-Ba-Bg-Bg-Bt-Bc-Ba—	(4j'')

$B_{M''4}$ is a group represented by formula (4''):



$B_{B''4}$ is a group represented by any one of (104a'') to (104j''):

—CH ₂ CH ₂ OH,	(104a'')
—Bg-CH ₂ CH ₂ OH,	(104b'')
—Bg-Bc-CH ₂ CH ₂ OH,	(104c'')
—Bg-Bc-Bc-CH ₂ CH ₂ OH,	(104d'')
—Bg-Bc-Bc-Bc-CH ₂ CH ₂ OH,	(104e'')
—Bg-Bc-Bc-Bc-Bt-CH ₂ CH ₂ OH,	(104f'')
—Bg-Bc-Bc-Bc-Bt-Bc-CH ₂ CH ₂ OH,	(104g'')
—Bg-Bc-Bc-Bc-Bt-Bc-Ba—CH ₂ CH ₂ OH,	(104h'')
—Bg-Bc-Bc-Bc-Bt-Bc-Ba-Bg-CH ₂ CH ₂ OH, or	(104i'')
—Bg-Bc-Bc-Bc-Bt-Bc-Ba-Bg-Bc-CH ₂ CH ₂ OH	(104j'')

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (IV'') has 2''-O, 4''-C-alkylene group;



where $B_{T''5}$ is a group represented by any one of (5a'') to (5j''):

HO—,	(5a'')
HO—Ba—,	(5b'')
HO-Bg-Ba—,	(5c'')
HO-Bg-Bg-Ba—,	(5d'')
HO—Ba-Bg-Bg-Ba—,	(5e'')
HO-Bc-Ba-Bg-Bg-Ba—,	(5f'')
HO-Bc-Bc-Ba-Bg-Bg-Ba—,	(5g'')
HO-Bt-Bc-Bc-Ba-Bg-Bg-Ba—,	(5h'')
HO-Bg-Bt-Bc-Bc-Ba-Bg-Bg-Ba—, or	(5i'')
HO—Ba-Bg-Bt-Bc-Bc-Ba-Bg-Bg-Ba—	(5j'')

$B_{M''5}$ is a group represented by formula (5''):



$B_{B''5}$ is a group represented by any one of (105a'') to (105j''):

—CH ₂ CH ₂ OH,	(105a'')
—Bg-CH ₂ CH ₂ OH,	(105b'')
—Bg-Bg-CH ₂ CH ₂ OH,	(105c'')
—Bg-Bg-Bc-CH ₂ CH ₂ OH,	(105d'')
—Bg-Bg-Bc-Bt-CH ₂ CH ₂ OH,	(105e'')
—Bg-Bg-Bc-Bt-Bg-CH ₂ CH ₂ OH,	(105f'')
—Bg-Bg-Bc-Bt-Bg-Bc-CH ₂ CH ₂ OH,	(105g'')
—Bg-Bg-Bc-Bt-Bg-Bc-Bt-CH ₂ CH ₂ OH,	(105h'')
—Bg-Bg-Bc-Bt-Bg-Bc-Bt-Bt-CH ₂ CH ₂ OH, or	(105i'')
—Bg-Bg-Bc-Bt-Bg-Bc-Bt-Bt-Bt-CH ₂ CH ₂ OH	(105j'')

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (V'') has 2''-O, 4''-C-alkylene group;



where $B_{T''16}$ is a group represented by any one of (16a'') to (16j''):

HO—,	(16a'')
HO-Bg—,	(16b'')
HO-Bt-Bg—,	(16c'')

HO-Bg-Bt-Bg-,	(16d")
HO-Bg-Bg-Bt-Bg-,	(16e")
HO—Ba-Bg-Bg-Bt-Bg-,	(16f")
HO—Ba—Ba-Bg-Bg-Bt-Bg-,	(16g")
HO-Bg-Ba—Ba-Bg-Bg-Bt-Bg-,	(16h")
HO-Bt-Bg-Ba—Ba-Bg-Bg-Bt-Bg-, or	(16i")
HO-Bc-Bt-Bg-Ba—Ba-Bg-Bg-Bt-Bg-	(16j")

$B_{M^{16}}$ is a group represented by formula (16")

-Bt-Bt-Bc-Bt-Bt-Bg-Bt-Ba-Bc-	(16")
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$B_{B^{16}}$ is a group represented by any one of (116a") to (116j"):

—CH ₂ CH ₂ OH,	(116a")
-Bt-CH ₂ CH ₂ OH,	(116b")
-Bt-Bt-CH ₂ CH ₂ OH,	(116c")
-Bt-Bt-Bc-CH ₂ CH ₂ OH,	(116d")
-Bt-Bt-Bc-Ba—CH ₂ CH ₂ OH,	(116e")
-Bt-Bt-Bc-Ba-Bt-CH ₂ CH ₂ OH,	(116f")
-Bt-Bt-Bc-Ba-Bt-Bc-CH ₂ CH ₂ OH,	(116g")
-Bt-Bt-Bc-Ba-Bt-Bc-Bc-CH ₂ CH ₂ OH,	(116h")
-Bt-Bt-Bc-Ba-Bt-Bc-Bc-Bc-CH ₂ CH ₂ OH, or	(116i")
-Bt-Bt-Bc-Ba-Bt-Bc-Bc-Bc-Ba—CH ₂ CH ₂ OH	(116j")

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (XVI") has 2"-O, 4"-C-alkylene group;

$B_{T^{17}}—B_{M^{17}}—B_{B^{17}}$	(XVII")
------------------------------------	---------

where $B_{T^{17}}$ is a group represented by any one of (17a") to (17j"):

HO—,	(17a")
HO-Bt-,	(17b")
HO-Bt-Bt-,	(17c")
HO-Bg-Bt-Bt-,	(17d")
HO-Bg-Bg-Bt-Bt-,	(17e")
HO-Bc-Bg-Bg-Bt-Bt-,	(17f")
HO-Bc-Bc-Bg-Bg-Bt-Bt-,	(17g")
HO-Bt-Bc-Bc-Bg-Bg-Bt-Bt-,	(17h")
HO-Bc-Bt-Bc-Bc-Bg-Bg-Bt-Bt-, or	(17i")
HO-Bc-Bc-Bt-Bc-Bc-Bg-Bg-Bt-Bt-	(17j")

$B_{M^{17}}$ is a group represented by formula (17"):

-Bc-Bt-Bg-Ba—Ba-Bg-Bg-Bt-Bg-	(17")
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$B_{B^{17}}$ is a group represented by any one of (117a") to (117j"):

—CH ₂ CH ₂ OH,	(117a")
-Bt-CH ₂ CH ₂ OH,	(117b")
-Bt-Bt-CH ₂ CH ₂ OH,	(117c")
-Bt-Bt-Bc-CH ₂ CH ₂ OH,	(117d")
-Bt-Bt-Bc-Bt-CH ₂ CH ₂ OH,	(117e")
-Bt-Bt-Bc-Bt-Bt-CH ₂ CH ₂ OH,	(117f")
-Bt-Bt-Bc-Bt-Bt-Bg-CH ₂ CH ₂ OH,	(117g")
-Bt-Bt-Bc-Bt-Bt-Bg-Bt-CH ₂ CH ₂ OH,	(117h")
-Bt-Bt-Bc-Bt-Bt-Bg-Bt-Ba—CH ₂ CH ₂ OH, or	(117i")
-Bt-Bt-Bc-Bt-Bt-Bg-Bt-Ba-Bc-CH ₂ CH ₂ OH	(117j")

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (XVII") has 2"-O, 4"-C-alkylene group;

$B_{T^{18}}—B_{M^{18}}—B_{B^{18}}$	(XVIII")
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where $B_{T^{18}}$ is a group represented by any one of (18a") to (18j"):

HO—,	(18a")
HO-Bg-,	(18b")
HO-Bt-Bg-,	(18c")
HO-Bc-Bt-Bg-,	(18d")
HO-Bc-Bc-Bt-Bg-,	(18e")
HO—Ba-Bc-Bc-Bt-Bg-,	(18f")
HO-Bg-Ba-Bc-Bc-Bt-Bg-,	(18g")
HO—Ba-Bg-Ba-Bc-Bc-Bt-Bg-,	(18h")
HO—Ba—Ba-Bg-Ba-Bc-Bc-Bt-Bg-, or	(18i")
HO-Bt-Ba—Ba-Bg-Ba-Bc-Bc-Bt-Bg-	(18j")

$B_{M^{18}}$ is a group represented by formula (18")

-Bc-Bt-Bc-Ba-Bg-Bc-Bt-Bt-Bc-	(18")
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$B_{B^{18}}$ is a group represented by any one of (118a") to (118j"):

—CH ₂ CH ₂ OH,	(118a")
-Bt-CH ₂ CH ₂ OH,	(118b")
-Bt-Bt-CH ₂ CH ₂ OH,	(118c")
-Bt-Bt-Bc-CH ₂ CH ₂ OH,	(118d")
-Bt-Bt-Bc-Bc-CH ₂ CH ₂ OH,	(118e")
-Bt-Bt-Bc-Bc-Bt-CH ₂ CH ₂ OH,	(118f")
-Bt-Bt-Bc-Bc-Bt-Bt-CH ₂ CH ₂ OH,	(118g")
-Bt-Bt-Bc-Bc-Bt-Bt-Ba—CH ₂ CH ₂ OH,	(118h")
-Bt-Bt-Bc-Bc-Bt-Bt-Ba-Bg-CH ₂ CH ₂ OH, or	(118i")
-Bt-Bt-Bc-Bc-Bt-Bt-Ba-Bg-Bc-CH ₂ CH ₂ OH	(118j")

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (XVIII") has 2"-O, 4"-C-alkylene group;

$B_{T^{19}}—B_{M^{19}}—B_{B^{19}}$	(XIX")
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where $B_{T^{19}}$ is a group represented by any one of (19a") to (19j"):

HO—,	(19a")
HO-Bc-,	(19b")
HO-Bg-Bc-,	(19c")
HO—Ba-Bg-Bc-,	(19d")
HO-Bt-Ba-Bg-Bc-,	(19e")
HO-Bt-Bt-Ba-Bg-Bc-,	(19f")
HO-Bc-Bt-Bt-Ba-Bg-Bc-,	(19g")
HO-Bc-Bc-Bt-Bt-Ba-Bg-Bc-,	(19h")
HO-Bt-Bc-Bc-Bt-Bt-Ba-Bg-Bc-, or	(19i")
HO-Bt-Bt-Bc-Bc-Bt-Bt-Ba-Bg-Bc-	(19j")

$B_{M^{19}}$ is a group represented by formula (19"):

-Bt-Bt-Bc-Bc-Ba-Bg-Bc-Bc-Ba—	(19")
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$B_{B^{19}}$ is a group represented by any one of (119a") to (119j"):

—CH ₂ CH ₂ OH,	(119a")
-Bt-CH ₂ CH ₂ OH,	(119b")

-Bt-Bt-CH ₂ CH ₂ OH,	(119c")
-Bt-Bt-Bg-CH ₂ CH ₂ OH,	(119d")
-Bt-Bt-Bg-Bt-CH ₂ CH ₂ OH,	(119e")
-Bt-Bt-Bg-Bt-Bg-CH ₂ CH ₂ OH,	(119f")
-Bt-Bt-Bg-Bt-Bg-Bt-CH ₂ CH ₂ OH,	(119g")
-Bt-Bt-Bg-Bt-Bg-Bt-Bt-CH ₂ CH ₂ OH,	(119h")
-Bt-Bt-Bg-Bt-Bg-Bt-Bt-Bg-CH ₂ CH ₂ OH, or	(119i")
-Bt-Bt-Bg-Bt-Bg-Bt-Bt-Bg-Ba-CH ₂ CH ₂ OH	(119j")

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (XIX") has 2"-O, 4"-C-alkylene group;



where B_{T''20} is a group represented by any one of (20a") to (20j"):

HO—,	(20a")
HO-Bc—,	(20b")
HO-Bt-Bc—,	(20c")
HO-Bt-Bt-Bc—,	(20d")
HO-Bc-Bt-Bt-Bc—,	(20e")
HO-Bg-Bc-Bt-Bt-Bc—,	(20f")
HO—Ba-Bg-Bc-Bt-Bt-Bc—,	(20g")
HO-Bc-Ba-Bg-Bc-Bt-Bt-Bc—,	(20h")
HO-Bt-Bc-Ba-Bg-Bc-Bt-Bt-Bc—, or	(20i")
HO-Bc-Bt-Bc-Ba-Bg-Bc-Bt-Bt-Bc—	(20j")

B_{M''20} is a group represented by formula (20"):



B_{B''20} is a group represented by any one of (120a") to (120j"):

—CH ₂ CH ₂ OH,	(120a")
-Bt-CH ₂ CH ₂ OH,	(120b")
-Bt-Bt-CH ₂ CH ₂ OH,	(120c")
-Bt-Bt-Bc-CH ₂ CH ₂ OH,	(120d")
-Bt-Bt-Bc-Bc-CH ₂ CH ₂ OH,	(120e")
-Bt-Bt-Bc-Bc-Ba—CH ₂ CH ₂ OH,	(120f")
-Bt-Bt-Bc-Bc-Ba-Bg-CH ₂ CH ₂ OH,	(120g")
-Bt-Bt-Bc-Bc-Ba-Bg-Bc-CH ₂ CH ₂ OH,	(120h")
-Bt-Bt-Bc-Bc-Ba-Bg-Bc-Bc-CH ₂ CH ₂ OH, or	(120i")
-Bt-Bt-Bc-Bc-Ba-Bg-Bc-Bc-Ba—CH ₂ CH ₂ OH	(120j")

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (XX") has 2"-O, 4"-C-alkylene group;



where B_{T''21} is a group represented by any one of (21a") to (21e"):

HO—,	(21a")
HO—Ba—,	(21b")
HO-Bc-Ba—,	(21c")
HO-Bt-Bc-Ba—, or	(21d")
HO-Bc-Bt-Bc-Ba—	(21e")

B_{M''21} is a group represented by formula (21"):



B_{B''21} is a group represented by any one of (121a") to (121e"):

—CH ₂ CH ₂ OH,	(121a")
-Bt-CH ₂ CH ₂ OH,	(121b")
-Bt-Bt-CH ₂ CH ₂ OH,	(121c")
-Bt-Bt-Bc-CH ₂ CH ₂ OH, or	(121d")
-Bt-Bt-Bc-Bc-CH ₂ CH ₂ OH	(121e")

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (XXI") has 2"-O, 4"-C-alkylene group;



where B_{T''6} is a group represented by any one of (6a") to (6j"):

HO—,	(6a")
HO—Ba—,	(6b")
HO—Ba—Ba—,	(6c")
HO—Ba—Ba—Ba—,	(6d")
HO-Bc-Ba—Ba—Ba—,	(6e")
HO-Bc-Bc-Ba—Ba—Ba—,	(6f")
HO-Bt-Bc-Bc-Ba—Ba—Ba—,	(6g")
HO-Bt-Bt-Bc-Bc-Ba—Ba—Ba—,	(6h")
HO-Bc-Bt-Bt-Bc-Bc-Ba—Ba—Ba—, or	(6i")
HO-Bt-Bc-Bt-Bt-Bc-Bc-Ba—Ba—Ba—	(6j")

B_{M''6} is a group represented by formula (6"):



B_{B''6} is a group represented by any one of (106a") to (106j"):

—CH ₂ CH ₂ OH,	(106a")
-Bc-CH ₂ CH ₂ OH,	(106b")
-Bc-Bg-CH ₂ CH ₂ OH,	(106c")
-Bc-Bg-Bc-CH ₂ CH ₂ OH,	(106d")
-Bc-Bg-Bc-Bt-CH ₂ CH ₂ OH,	(106e")
-Bc-Bg-Bc-Bt-Bc-CH ₂ CH ₂ OH,	(106f")
-Bc-Bg-Bc-Bt-Bc-Ba—CH ₂ CH ₂ OH,	(106g")
-Bc-Bg-Bc-Bt-Bc-Ba-Bc-CH ₂ CH ₂ OH,	(106h")
-Bc-Bg-Bc-Bt-Bc-Ba-Bc-Bt-CH ₂ CH ₂ OH, or	(106i")
-Bc-Bg-Bc-Bt-Bc-Ba-Bc-Bt-Bc-CH ₂ CH ₂ OH,	(106j")

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (VI") has 2"-O, 4"-C-alkylene group;



where B_{T''7} is a group represented by any one of (7a") to (7j"):

HO—,	(7a")
HO-Bt—,	(7b")
HO-Bt-Bt—,	(7c")
HO-Bg-Bt-Bt—,	(7d")
HO—Ba-Bg-Bt-Bt—,	(7e")
HO-Bg-Ba-Bg-Bt-Bt—,	(7f")
HO-Bt-Bg-Ba-Bg-Bt-Bt—,	(7g")
HO—Ba-Bt-Bg-Ba-Bg-Bt-Bt—,	(7h")

HO-Bt-Ba-Bt-Bg-Ba-Bg-Bt-Bt-, or (7i")

HO-Bc-Bt-Ba-Bt-Bg-Ba-Bg-Bt-Bt- (7j")

$B_{M^{n7}}$ is a group represented by formula (7"):

-Bt-Bc-Bt-Bt-Bc-Bc-Ba—Ba—Ba— (7")

$B_{B^{n7}}$ is a group represented by any one of (107a") to (107j"):

—CH₂CH₂OH, (107a")

-Bg-CH₂CH₂OH, (107b")

-Bg-Bc-CH₂CH₂OH, (107c")

-Bg-Bc-Ba—CH₂CH₂OH, (107d")

-Bg-Bc-Ba-Bg-CH₂CH₂OH, (107e")

-Bg-Bc-Ba-Bg-Bc-CH₂CH₂OH, (107f")

-Bg-Bc-Ba-Bg-Bc-Bc-CH₂CH₂OH, (107g")

-Bg-Bc-Ba-Bg-Bc-Bc-Bt-CH₂CH₂OH, (107h")

-Bg-Bc-Ba-Bg-Bc-Bc-Bt-CH₂CH₂OH, or (107i")

-Bg-Bc-Ba-Bg-Bc-Bc-Bt-Bt-CH₂CH₂OH (107j")

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (VII") has 2"-O, 4"-C-alkylene group;

$B_{T^s}—B_{M^s}—B_{B^s}$ (VIII")

where B_{T^s} is a group represented by any one of (8a") to (8n"):

HO—, (8a")

HO-Bc-, (8b")

HO-Bt-Bc-, (8c")

HO—Ba-Bt-Bc-, (8d")

HO-Bc-Ba-Bt-Bc-, (8e")

HO-Bt-Bc-Ba-Bt-Bc-, (8f")

HO-Bt-Bt-Bc-Ba-Bt-Bc-, (8g")

HO-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8h")

HO-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8i")

HO-Bt-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8j")

HO-Bt-Bt-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8k")

HO—Ba-Bt-Bt-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, (8l")

HO-Bc-Ba-Bt-Bt-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc-, or (8m")

HO-Bc-Bc-Ba-Bt-Bt-Bg-Bt-Bt-Bt-Bc-Ba-Bt-Bc- (8n")

$B_{M^{n8}}$ is a group represented by formula (8"):

—Ba-Bg-Bc-Bt-Bc- (8")

$B_{B^{n8}}$ is a group represented by any one of (108a") to (108n"):

—CH₂CH₂OH, (108a")

-Bt-CH₂CH₂OH, (108b")

-Bt-Bt-CH₂CH₂OH, (108c")

-Bt-Bt-Bt-CH₂CH₂OH, (108d")

-Bt-Bt-Bt-Bt-CH₂CH₂OH, (108e")

-Bt-Bt-Bt-Bt-Ba—CH₂CH₂OH, (108f")

-Bt-Bt-Bt-Bt-Ba-Bc-CH₂CH₂OH, (108g")

-Bt-Bt-Bt-Bt-Ba-Bc-Bt-CH₂CH₂OH, (108h")

-Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-CH₂CH₂OH, (108i")

-Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-CH₂CH₂OH, (108j")

-Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-Bc-CH₂CH₂OH, (108k")

-Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-Bc-Bt-CH₂CH₂OH, (108l")

-Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-Bc-Bt-Bt-CH₂CH₂OH, (108m")

or
-Bt-Bt-Bt-Bt-Ba-Bc-Bt-Bc-Bc-Bc-Bt-Bt-Bg-CH₂CH₂OH (108n")

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (VIII") has 2"-O, 4"-C-alkylene group;

$B_T—B_M—B_B$ (I)

where B_T is a group represented by any one of (1a) to (1k):

HO—, (1a)

HO-Bt-, (1b)

HO-Bc-Bt-, (1c)

HO-Bg-Bc-Bt-, (1d)

HO—Ba-Bg-Bc-Bt-, (1e)

HO-Bg-Ba-Bg-Bc-Bt-, (1f)

HO-Bt-Bg-Ba-Bg-Bc-Bt-, (1g)

HO-Bc-Bt-Bg-Ba-Bg-Bc-Bt-, (1h)

HO-Bc-Bc-Bt-Bg-Ba-Bg-Bc-Bt-, or (1j)

HO-Bg-Bc-Bc-Bt-Bg-Ba-Bg-Bc-Bt-, (1k)

B_M is a group represented by formula (2):

-Bg-Ba-Bt-Bc-Bt-Bg-Bc-Bt-Bg-Bg-Bc-Ba-Bt-Bc-Bt- (2)

where Bg, Ba, Bt and Bc are as defined above;

B_B is a group represented by any one of (2a) to (2h):

—CH₂CH₂OH, (2a)

-Bt-CH₂CH₂OH, (2b)

-Bt-Bg-CH₂CH₂OH, (2c)

-Bt-Bg-Bc-CH₂CH₂OH, (2d)

-Bt-Bg-Bc-Ba—CH₂CH₂OH, (2e)

-Bt-Bg-Bc-Ba-Bg-CH₂CH₂OH, (2f)

-Bt-Bg-Bc-Ba-Bg-Bt-CH₂CH₂OH, or (2g)

-Bt-Bg-Bc-Ba-Bg-Bt-Bt-CH₂CH₂OH (2h)

where Bg, Ba, Bt and Bc are as defined above;

provided that at least one of the nucleosides constituting the compound represented by formula (I) has a 2'-O, 4'-C-alkylene group;

$B_{T1}—B_{M1}—B_{B1}$ (I')

where B_{T1} is a group represented by any one of (1a') to (1o'):

HO—, (1a')

HO-Bg-, (1b')

HO-Bc-Bg-, (1c')

HO-Bt-Bc-Bg-, (1d')

HO-Bt-Bt-Bc-Bg-, (1e')

HO-Bc-Bt-Bt-Bc-Bg-, (1f')

HO-Bt-Bc-Bt-Bt-Bc-Bg-, (1g')

HO-Bg-Bt-Bc-Bt-Bt-Bc-Bg-, (1h')

HO—Ba-Bg-Bt-Bc-Bt-Bt-Bc-Bg-, (1j')

HO-Bg-Ba-Bg-Bt-Bc-Bt-Bt-Bc-Bg-, (1k')

HO-Bt-Bg-Ba-Bg-Bt-Bc-Bt-Bt-Bc-Bg-, (1l')

HO-Bt-Bt-Bg-Ba-Bg-Bt-Bc-Bt-Bt-Bc-Bg-, (1m')

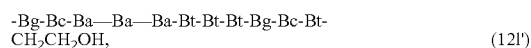
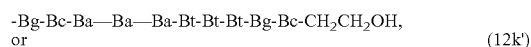
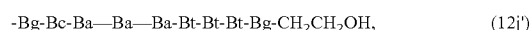
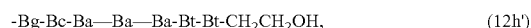
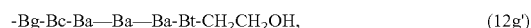
HO-Bg-Bt-Bt-Bg-Ba-Bg-Bt-Bc-Bt-Bt-Bc-Bg-, or (1n')

HO—Ba-Bg-Bt-Bt-Bg-Ba-Bg-Bt-Bc-Bt-Bt-Bc-Bg-, (1o')

B_{M1} is a group represented by formula (1'):



B_{B1} is a group represented by any one of (12a') to (12l'):

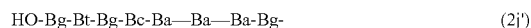
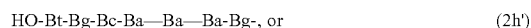


where Bg, Ba, Bt and Bc are as defined above;

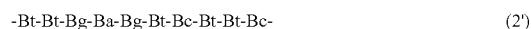
provided that at least one of the nucleosides constituting the compound represented by formula (I') has a 2'-O, 4'-C-alkylene group;



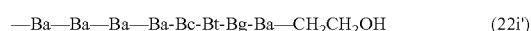
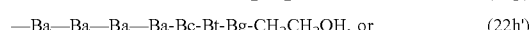
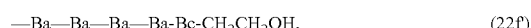
where B_{T2} is a group represented by any one of (2a') to (2j'):



B_{M2} is a group represented by formula (21'):



B_{B2} is a group represented by any one of (22a') to (22i'):

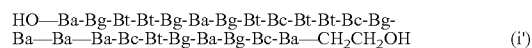


where Bg, Ba, Bt and Bc are as defined above;

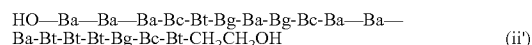
provided that at least one of the nucleosides constituting the compound represented by formula (II') has a 2'-O, 4'-C-alkylene group.

70. The compound according to claims 69 which is selected from the group consisting of compounds (i') to (xiii'), or a pharmacologically acceptable salt thereof:

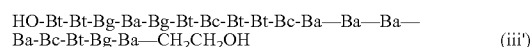
(i') a compound represented by formula (i'):



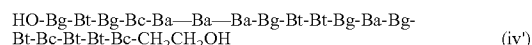
(ii') a compound represented by formula (ii'):



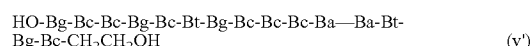
(iii') a compound represented by formula (iii'):



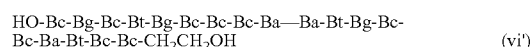
(iv') a compound represented by formula (iv'):



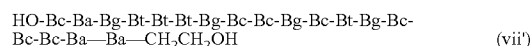
(v') a compound represented by formula (v'):



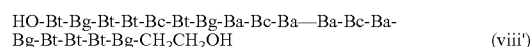
(vi') a compound represented by formula (vi'):



(vii') a compound represented by formula (vii'):



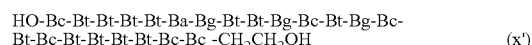
(viii') a compound represented by formula (viii'):



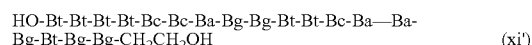
(ix') a compound represented by formula (ix'):



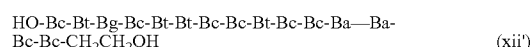
(x') a compound represented by formula (x'):



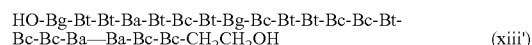
(xi') a compound represented by formula (xi'):



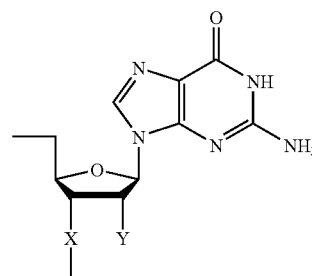
(xii') a compound represented by formula (xii'):



(xiii') a compound represented by formula (xiii'):

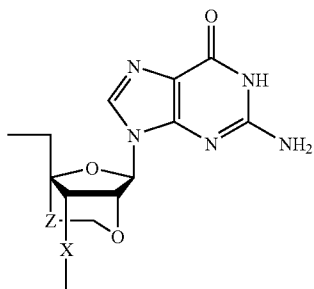


where Bg is a group represented by formula (G1) or (G2); Ba is a group represented by formula (A1) or (A2); Bc is a group represented by formula (C1) or (C2); and Bt is a group represented by formula (U1) or (T2):



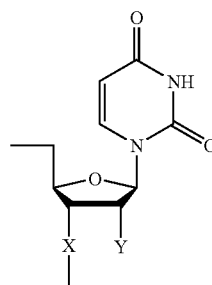
(G1)

-continued

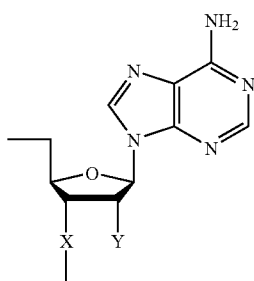


(G2)

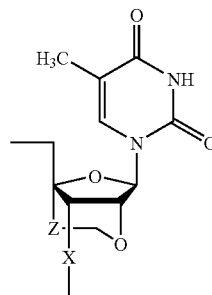
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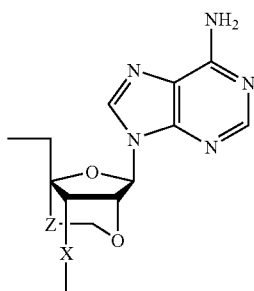
(U1)



(A1)

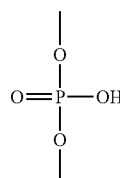


(T2)

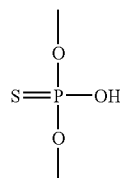


(A2)

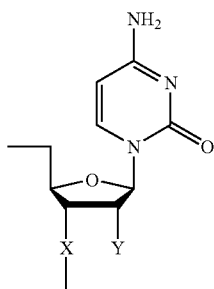
where X is individually and independently a group represented by formula (X1) or (X2):



(X1)

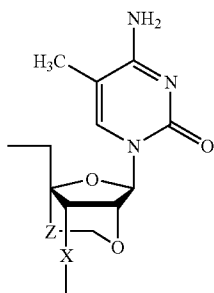


(X2)



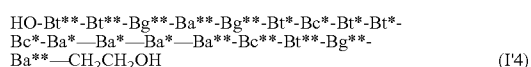
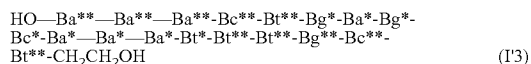
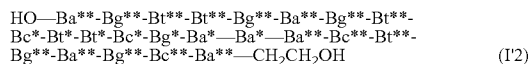
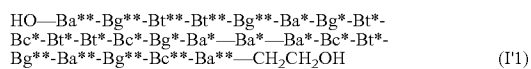
(C1)

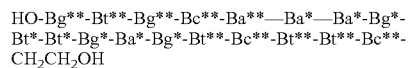
Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms.



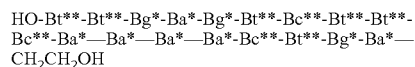
(C2)

71. The compound according to claim 69 which is represented by any one of compounds (I'1) to (I'20), or a pharmacologically acceptable salt thereof:

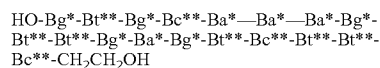




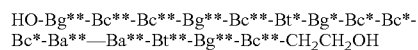
(I'5)



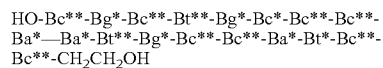
(I'6)



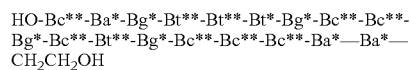
(I'7)



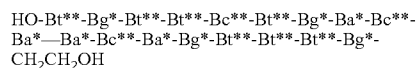
(I'8)



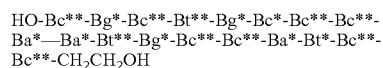
(I'9)



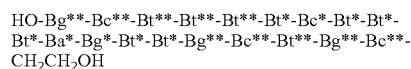
(I'10)



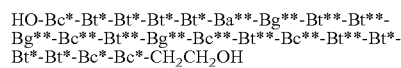
(I'11)



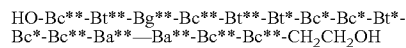
(I'12)



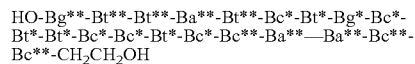
(I'13)



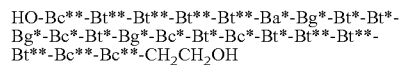
(I'14)



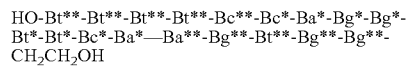
(I'15)



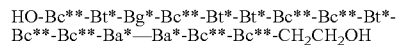
(I'16)



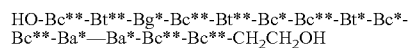
(I'17)



(I'18)

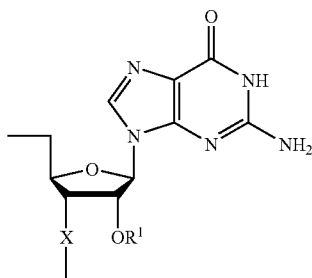


(I'19)



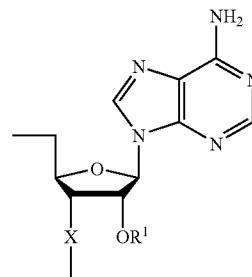
(I'20)

where Bg^{*} is a group represented by formula (G1^a); Ba^{*} is a group represented by formula (A1^a); Bc^{*} is a group represented by formula (C1^a); Bt^{*} is a group represented by formula (U1^a); Bg^{**} is a group represented by formula (G2); Ba^{**} is a group represented by formula (A2); Bc^{**} is a group represented by formula (C2); and Bt^{**} is a group represented by formula (T2):

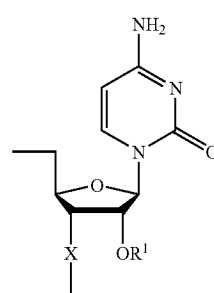


(G1^a)

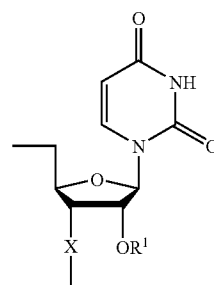
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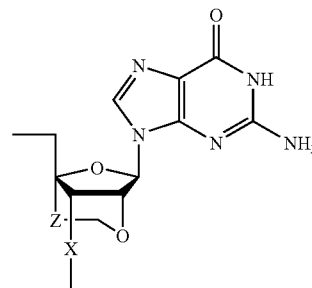
(A1^a)



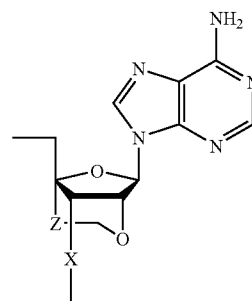
(C1^a)



(U1^a)

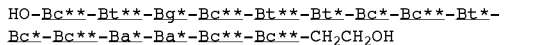
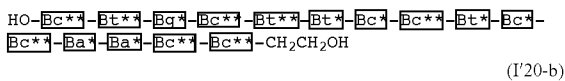
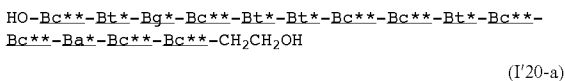
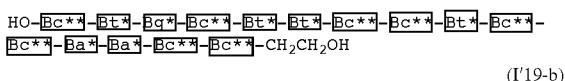
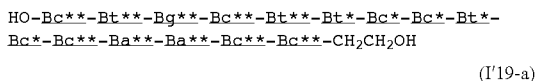
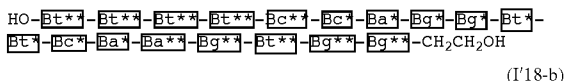
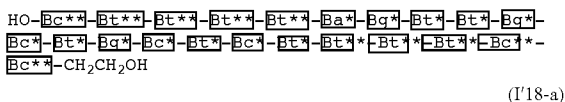
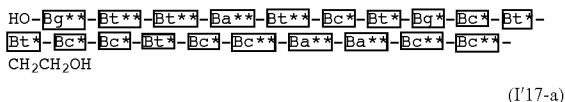
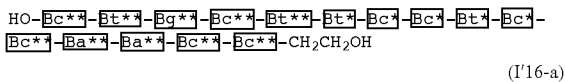
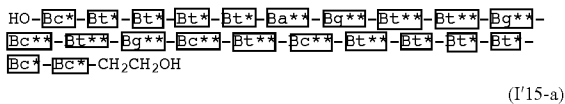
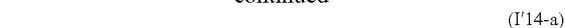


(G2)



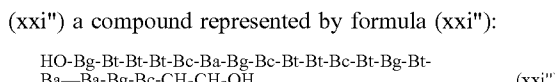
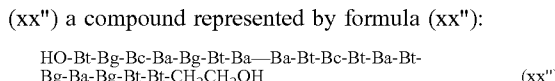
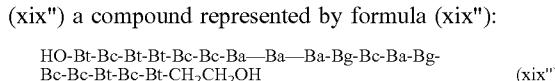
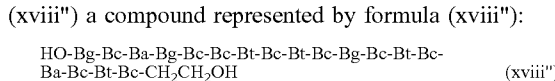
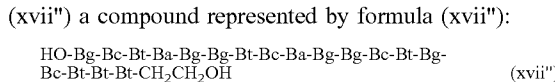
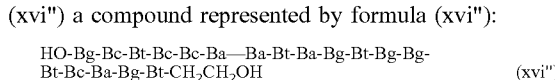
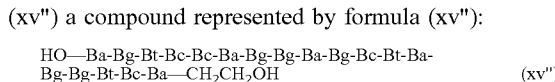
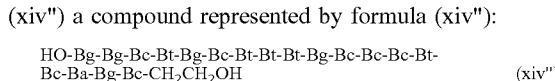
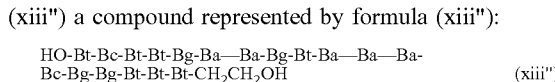
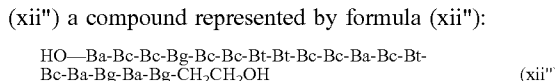
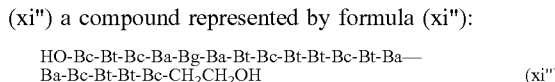
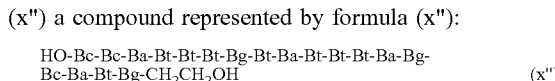
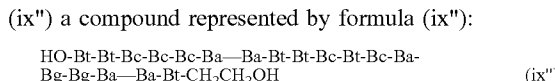
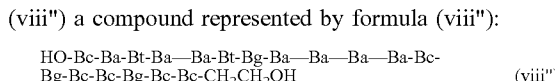
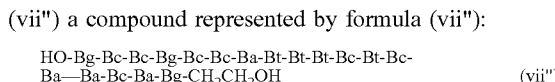
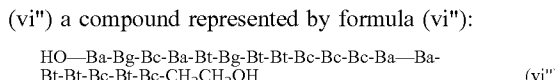
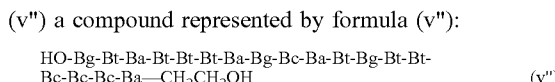
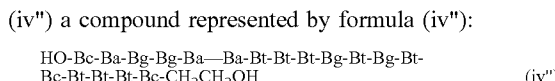
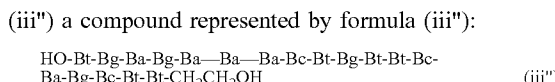
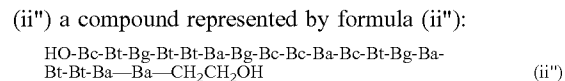
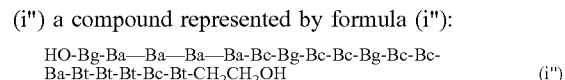
(A2)

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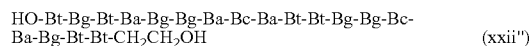


where Bg* is a group represented by formula (G1^a), Ba* is a group represented by formula (A1^a); Bc* is a group represented by formula (C1^a); Bt* is a group represented by formula (U1^a); Bg** is a group represented by formula (G2); Ba** is a group represented by formula (A2); Bc** is a group represented by formula (C2); Bt** is a group represented by formula (T2); and in individual formulas, at least one of Bg*, Ba*, Bc*, Bt*, Bg**, Ba**, Bc** and Bt** has a group represented by formula (X2) as X and all of Bc*, Bg*, Ba**, Bc** and Bt** have a group represented by (X1) as X.

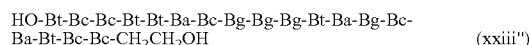
73. The compound according to claim 69 which is selected from the group consisting of compounds (i'') to (xlx''), or a pharmacologically acceptable salt thereof:



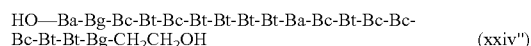
(xxii") a compound represented by formula (xxii"):



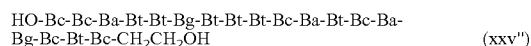
(xxiii") a compound represented by formula (xxiii"):



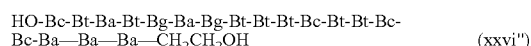
(xxiv") a compound represented by formula (xxiv"):



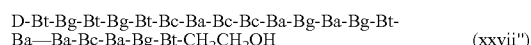
(xxv") a compound represented by formula (xxv"):



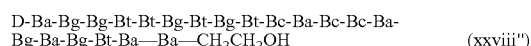
(xxvi") a compound represented by formula (xxvi"):



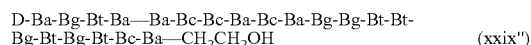
(xxvii") a compound represented by formula (xxvii"):



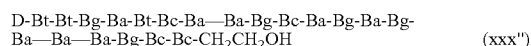
(xxviii") a compound represented by formula (xxviii"):



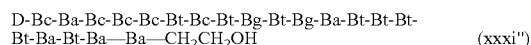
(xxix") a compound represented by formula (xxix"):



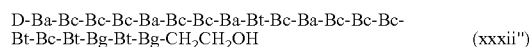
(xxx") a compound represented by formula (xxx"):



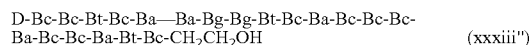
(xxxi") a compound represented by formula (xxxi"):



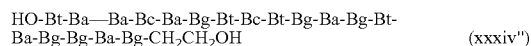
(xxxii") a compound represented by formula (xxxii"):



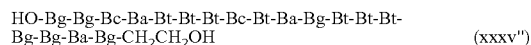
(xxxiii") a compound represented by formula (xxxiii"):



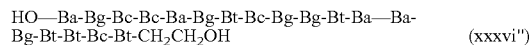
(xxxiv") a compound represented by formula (xxxiv"):



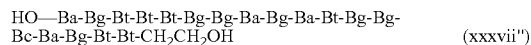
(xxxv") a compound represented by formula (xxxv"):



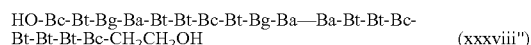
(xxxvi") a compound represented by formula (xxxvi"):



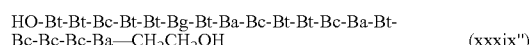
(xxxvii") a compound represented by formula (xxxvii"):



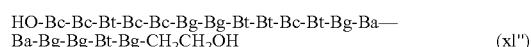
(xxxviii") a compound represented by formula (xxxviii"):



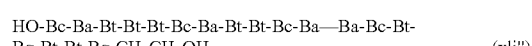
(xxxix") a compound represented by formula (xxxix"):



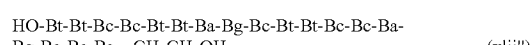
(xl") a compound represented by formula (xl"):



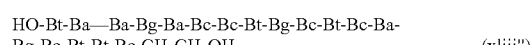
(xli") a compound represented by formula (xli"):



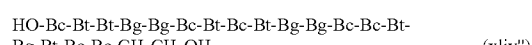
(xlii") a compound represented by formula (xlii"):



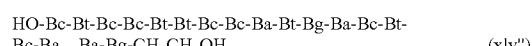
(xliii") a compound represented by formula (xliii"):



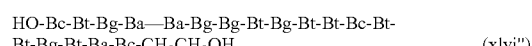
(xliv") a compound represented by formula (xliv"):



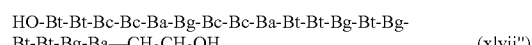
(xlv") a compound represented by formula (xlv"):



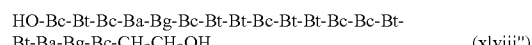
(xlvi") a compound represented by formula (xlvi"):



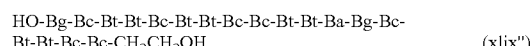
(xlvii") a compound represented by formula (xlvii"):



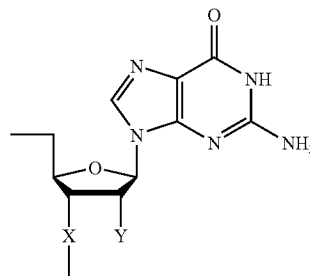
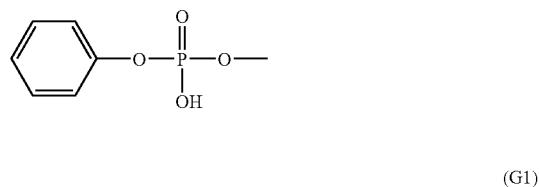
(xlviii") a compound represented by formula (xlviii"):



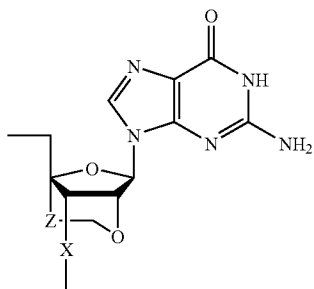
(xlix") a compound represented by formula (xlix"):



where Bg is a group represented by formula (G1) or (G2); Ba is a group represented by formula (A1) or (A2); Bc is a group represented by formula (C1) or (C2); Bt is a group represented by formula (U1) or (T2); and D is HO— or Ph- wherein Ph- is a group represented by first formula:

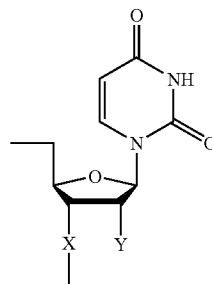


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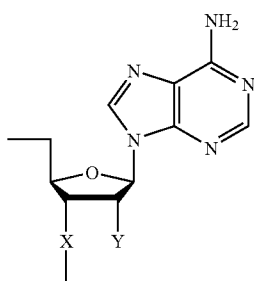


(G2)

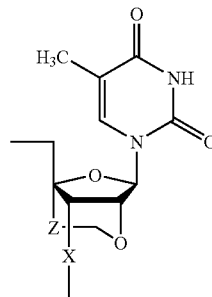
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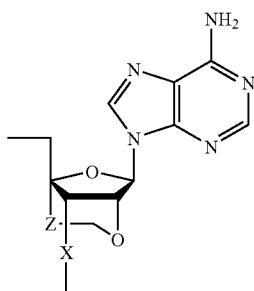
(U1)



(A1)

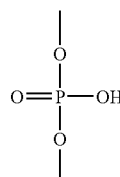


(T2)

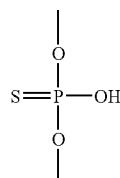


(A2)

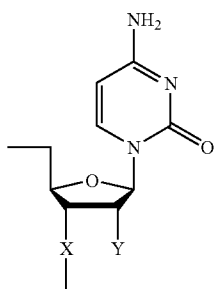
where X is individually and independently a group represented by formula (X1) or (X2):



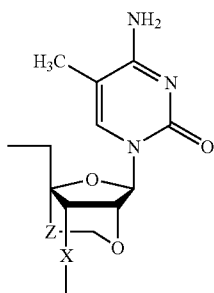
(X1)



(X2)



(C1)

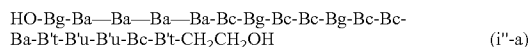


(C2)

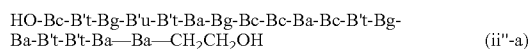
Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms.

74. The compound according to claim 69 which is selected from the group consisting of compounds (i''-a) to (ii''-a), or a pharmacologically acceptable salt thereof:

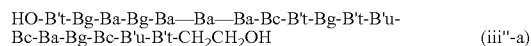
(i''-a) a compound represented by formula (i''-a):



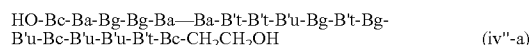
(ii''-a) a compound represented by formula (ii''-a):



(iii"-a) a compound represented by formula (iii"-a):



(iv"-a) a compound represented by formula (iv"-a):



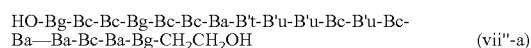
(v"-a) a compound represented by formula (v"-a):



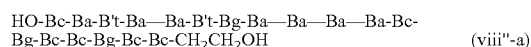
(vi"-a) a compound represented by formula (vi"-a):



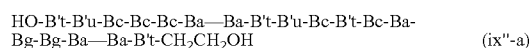
(vii"-a) a compound represented by formula (vii"-a):



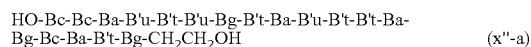
(viii"-a) a compound represented by formula (viii"-a):



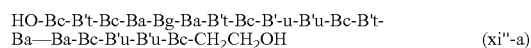
(ix"-a) a compound represented by formula (ix"-a):



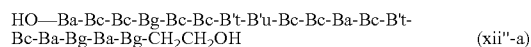
(x"-a) a compound represented by formula (x"-a):



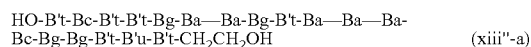
(xi"-a) a compound represented by formula (xi"-a):



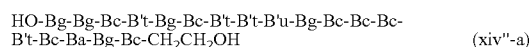
(xii"-a) a compound represented by formula (xii"-a):



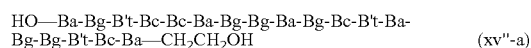
(xiii"-a) a compound represented by formula (xiii"-a):



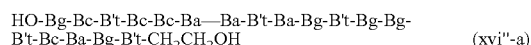
(xiv"-a) a compound represented by formula (xiv"-a):



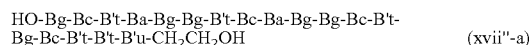
(xv"-a) a compound represented by formula (xv"-a):



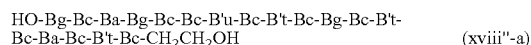
(xvi"-a) a compound represented by formula (xvi"-a):



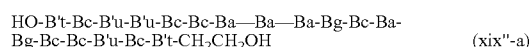
(xvii"-a) a compound represented by formula (xvii"-a):



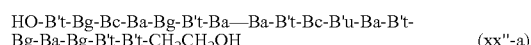
(xviii"-a) a compound represented by formula (xviii"-a):



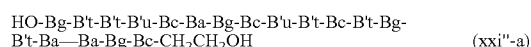
(xix"-a) a compound represented by formula (xix"-a):



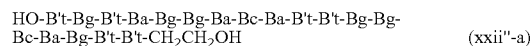
(xx"-a) a compound represented-by formula (xx"-a):



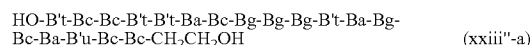
(xxi"-a) a compound represented by formula (xxi"-a):



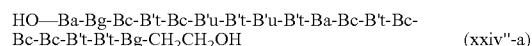
(xxii"-a) a compound represented by formula (xxii"-a):



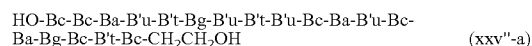
(xxiii"-a) a compound represented by formula (xxiii"-a):



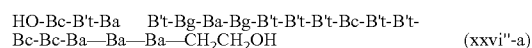
(xxiv"-a) a compound represented by formula (xxiv"-a):



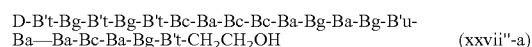
(xxv"-a) a compound represented by formula (xxv"-a):



(xxvi"-a) a compound represented by formula (xxvi"-a):



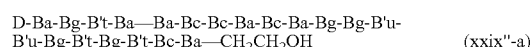
(xxvii"-a) a compound represented by formula (xxvii"-a):



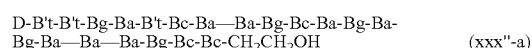
(xxviii"-a) a compound represented by formula (xxviii"-a):



(xxix"-a) a compound represented by formula (xxix"-a):



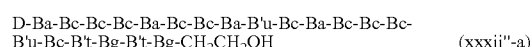
(xxx"-a) a compound represented by formula (xxx"-a):



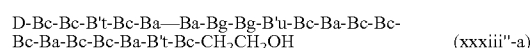
(xxxi"-a) a compound represented by formula (xxxi"-a):



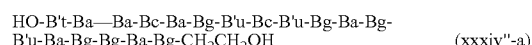
(xxxii"-a) a compound represented by formula (xxxii"-a):



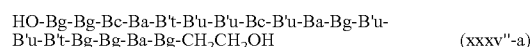
(xxxiii"-a) a compound represented by formula (xxxiii"-a):



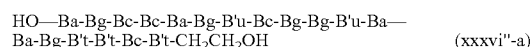
(xxxiv"-a) a compound represented by formula (xxxiv"-a):



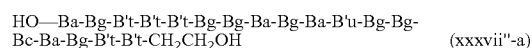
(xxxv"-a) a compound represented by formula (xxxv"-a):



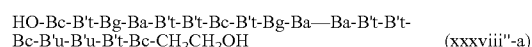
(xxxvi"-a) a compound represented by formula (xxxvi"-a):



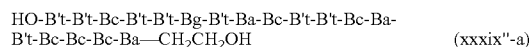
(xxxvii"-a) a compound represented by formula (xxxvii"-a):



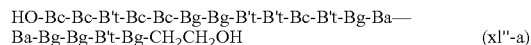
(xxxviii"-a) a compound represented by formula (xxxviii"-a):



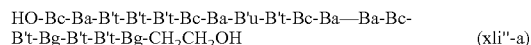
(xxxix"-a) a compound represented by formula (xxxix"-a):



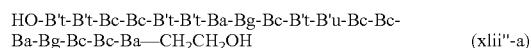
(xli"-a) a compound represented by formula (xli"-a):



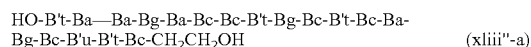
(xlii"-a) a compound represented by formula (xlii"-a):



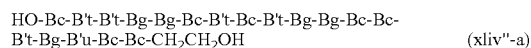
(xliii"-a) a compound represented by formula (xliii"-a):



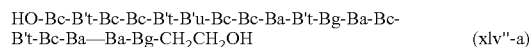
(xliv"-a) a compound represented by formula (xliv"-a):



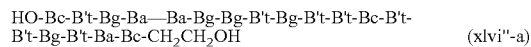
(xlv"-a) a compound represented by formula (xlv"-a):



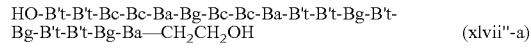
(xlvi"-a) a compound represented by formula (xlvi"-a):



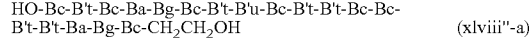
(xlvii"-a) a compound represented by formula (xlvii"-a):



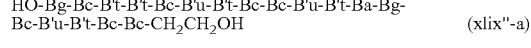
(xlviii"-a) a compound represented by formula (xlviii"-a):



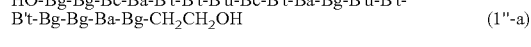
(xlix"-a) a compound represented by formula (xlix"-a):



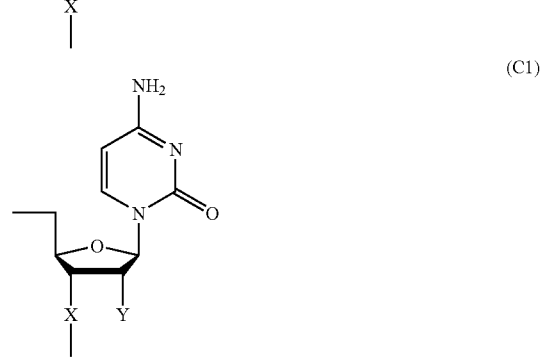
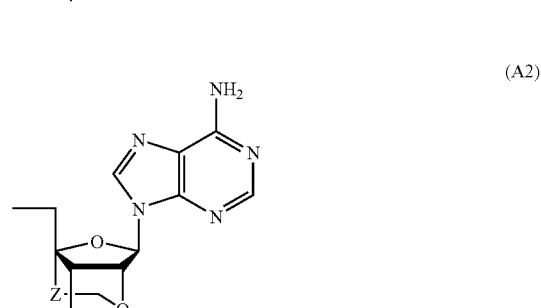
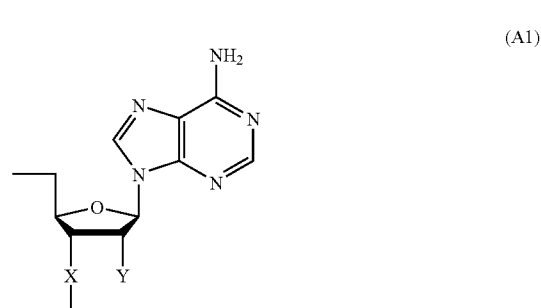
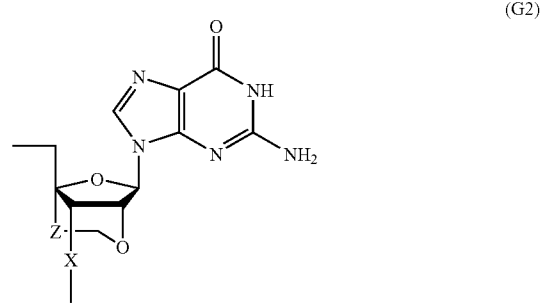
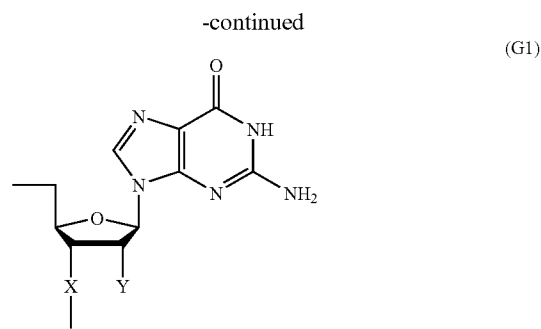
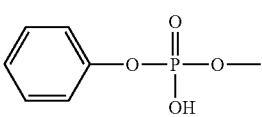
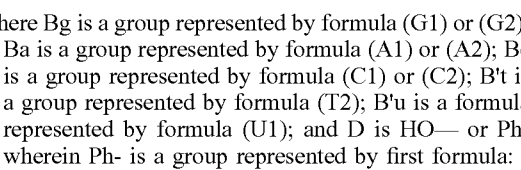
(1"-a) a compound represented by formula (1"-a):



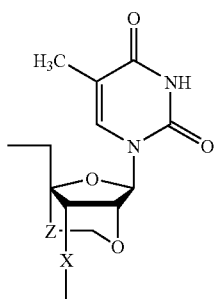
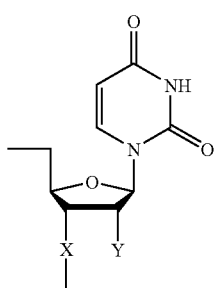
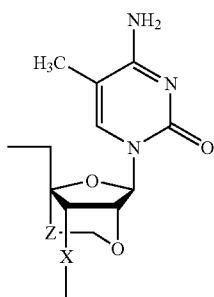
(1i"-a) a compound represented by formula (1i"-a):



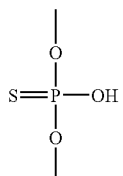
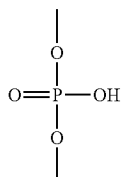
where Bg is a group represented by formula (G1) or (G2); Ba is a group represented by formula (A1) or (A2); Bc is a group represented by formula (C1) or (C2); B't is a group represented by formula (T2); B'u is a formula represented by formula (U1); and D is HO— or Ph— wherein Ph— is a group represented by first formula:



-continued



where X is individually and independently a group represented by formula (X1) or (X2):



Y is individually and independently a hydrogen atom, a hydroxyl group or an alkoxy group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms.

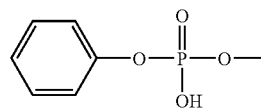
75. The compound according to claim 69 which is represented by any one of formulae (I¹) to (I⁵¹), or a pharmacologically acceptable salt thereof:

- (C2)
- (I¹) HO-Bg*-Ba**—Ba*—Ba*—Ba*—Ba*.Bc**-.Bg*-Bc**-.Bc**-.Bg*-Bc*.Bc**-.Ba*.Bt**-.Bu*.Bu1*-Bc**-.Bt**-.CH₂CH₂OH (I¹)
- (I²) HO-Bc**-.Bt**-.Bg*-Bu*.Bt**-.Ba*.Bg*-Bc**-.Bc*-Ba*.Bc**-.Bt**-.Bg*-Ba*.Bt**-.Bt**-.Ba*—Ba*—CH₂CH₂OH (I²)
- (I³) HO-Bt**-.Bg*-Ba*.Bg*-Ba**—Ba*—Ba*.Bc**-.Bt**-.Bg*-Bt**-.Bu*.Bc**-.Ba*.Bg*-Bc**-.Bu*.Bt**-.CH₂CH₂OH (I³)
- (I⁴) HO-Bc**-.Ba*.Bg*.Bg*-Ba**—Ba*.Bt**-.Bt**-.Bu*.Bg*-Bt**-.Bg*-Bu*.Bc**-.Bu*.Bu*.Bt**-.Bc**-.CH₂CH₂OH (I⁴)
- (U1)
- (I⁵) HO-Bg*-Bt**-.Ba*.Bu*.Bt**-.Bt**-.Ba*.Bg*-Bc**-.Ba*.Bt**-.Bg*-Bu*.Bt**-.Bc*.Bc**-.Bc**-.Ba*—CH₂CH₂OH (I⁵)
- (I⁶) HO—Ba*.Bg*.Bc**-.Ba*.Bt**-.Bg*-Bt**-.Bt**-.Bc*-Bc*.Bc**-.Ba*.Ba*.Bt**-.Bu*.Bc*.Bt**-.Bc**-.CH₂CH₂OH (I⁶)
- (I⁷) HO-Bg*.Bc**-.Bc**-.Bg*.Bc**-.Bc*.Ba*.Bt**-.Bu*.Bu*.Bc**-.Bu*.Bc**-.Ba*—Ba*.Bc**-.Ba**-.Bg*-CH₂CH₂OH (I⁷)
- (I⁸) HO-Bc**-.Ba*.Bt**-.Ba*—Ba*.Bt**-.Bg*-Ba*—Ba**—Ba*—Ba*.Bc**-.Bg*.Bc*.Bc**-.Bg*-Bc**-.Bc**-.CH₂CH₂OH (I⁸)
- (T2)
- (I⁹) HO-Bt**-.Bu*.Bc**-.Bc*.Bc**-.Ba*—Ba*.Bt**-.Bu*.Bc*-Bt**-.Bc**-.Ba*.Bg*-Bg*-Ba*—Ba*.Bt**-.CH₂CH₂OH (I⁹)
- (I¹⁰) HO-Bc**-.Bc**-.Ba*.Bu*.Bt**-.Bu*.Bg*-Bt**-.Ba*.Bu*.Bt**-.Bt**-.Ba*.Bg*-Bc**-.Ba*.Bt**-.Bg*-CH₂CH₂OH (I¹⁰)
- (I¹¹) HO-Bc*.Bt**-.Bc**-.Ba*.Bg*.Ba*.Bt**-.Bc**-.Bu*.Bu*.Bc**-.Ba*—Ba*.Bc**-.Bu*.Bu*.Bc**-.CH₂CH₂OH (I¹¹)
- (I¹²) HO—Ba*.Bc**-.Bc**-.Bg*.Bc*.Bc**-.Bt**-.Bu*.Bc*.Bc**-.Ba*.Bc*.Bt**-.Bc**-.Ba*.Bg*-Ba**-.Bg*-CH₂CH₂OH (I¹²)
- (I¹³) HO-Bt**-.Bc*.Bt**-.Bt**-.Bg*-Ba*—Ba*.Bg*-Bt**-.Ba*—Ba**—Ba*.Bc**-.Bg*.Bg*.Bt**-.Bu*.Bt**-.CH₂CH₂OH (I¹³)
- (I¹⁴) HO-Bg*.Bg*.Bc**-.Bt**-.Bg*.Bc*.Bt**-.Bt**-.Bu*.Bg*.Bc**-.Bc*.Bc*.Bt**-.Bc**-.Ba*.Bg*-Bc**-.CH₂CH₂OH (I¹⁴)
- (I¹⁵) HO—Ba*.Bg*-Bt**-.Bc**-.Bc**-.Ba*.Bg*-Bg*-Ba**-.Bg*-Bc**-.Bt**-.Ba*.Bg*-Bg*-Bt**-.Bc**-.Ba*—CH₂CH₂OH (I¹⁵)
- (X1)
- (I¹⁶) HO-Bg*.Bc**-.Bt**-.Bc*.Bc**-.Ba*—Ba*.Bt**-.Ba*.Bg*-Bt**-.Bg*.Bg*.Bt**-.Bc**-.Ba*.Bg*-Bt**-.CH₂CH₂OH (I¹⁶)
- (I¹⁷) HO-Bg*.Bc**-.Bt**-.Ba*.Bg*.Bg*-Bt**-.Bc**-.Ba*.Bg*-Bg*.Bt**-.Bg*.Bc*.Bt**-.Bu*.CH₂CH₂OH (I¹⁷)
- (I¹⁸) HO-Bg*.Bc**-.Ba*.Bg*.Bc**-.Bc**-.Bu*.Bc*.Bt**-.Bc*.Bg*.Bc**-.Bt**-.Bc*.Ba*.Bc**-.Bt**-.Bc*-CH₂CH₂OH (I¹⁸)
- (X2)
- (I¹⁹) HO-Bt**-.Bc**-.Bu*.Bu*.Bc**-.Bc**-.Ba*—Ba*—Ba*.Bg*.Bc*.Ba*.Bg*.Bc**-.Bc*.Bu*.Bc**-.Bt**-.CH₂CH₂OH (I¹⁹)
- (I²⁰) HO-Bt**-.Bg*.Bc**-.Ba*.Bg*.Bt**-.Ba*—Ba*.Bt**-.Bc**-.Bu*.Ba*.Bt**-.Bg*.Ba*.Bg*-Bt**-.Bt**-.CH₂CH₂OH (I²⁰)
- (I²¹) HO-Bg*.Bt**-.Bt**-.Bu*.Bc**-.Ba*.Bg*-Bc**-.Bu*.Bt**-.Bc*.Bg*-Bt**-.Ba*—Ba*.Bg*-Bc**-.CH₂CH₂OH (I²¹)
- (I²²) HO-Bt**-.Bg*-Bt**-.Ba*.Bg*-Bg*.Ba*.Bc**-.Ba*.Bt**-.Bt**-.Bg*.Bg*.Bc**-.Ba*.Bg*-Bt**-.Bt**-.CH₂CH₂OH (I²²)
- (I²³) HO-Bt**-.Bc*.Bc*.Bt**-.Bt**-.Ba*.Bc**-.Bg*-Bg*-Bt**-.Ba*.Bg*.Bc**-.Ba*.Bu*.Bc**-.Bc**-.CH₂CH₂OH (I²³)

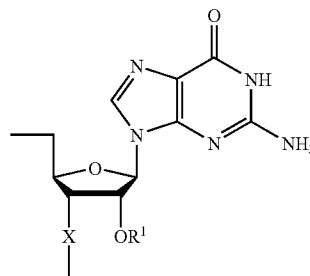
- (I²⁴) HO—Ba^{*}-Bg^{*}-Bc^{**}-Bt^{**}-Bc^{*}-Bu^{*}-Bt^{**}-Bu^{*}-Bt^{**}-Ba^{*}-Bc^{*}-Bt^{**}-Bc^{**}-Bc^{*}-Bc^{*}-Bt^{**}-Bt^{**}-Bg^{*}-CH₂CH₂OH
- (I²⁵) HO-Bc^{**}-Bc^{**}-Ba^{*}-Bu^{*}-Bt^{**}-Bg^{*}-Bu^{*}-Bt^{**}-Bu^{*}-Bc^{**}-Ba^{*}-Bu^{*}-Bc^{**}-Ba^{*}-Bg^{*}-Bc^{*}-Bt^{**}-Bc^{**}-CH₂CH₂OH
- (I²⁶) HO-Bc^{*}-Bt^{**}-Bt^{**}-Bg^{*}-Ba^{*}-Bg^{*}-Bt^{**}-Bt^{**}-Bt^{**}-Bc^{*}-Bt^{**}-Bt^{**}-Bc^{*}-Bc^{*}-Ba^{*}-Ba^{*}-Ba^{*}-CH₂CH₂OH
- (I²⁷) Ph-Bt^{**}-Bg^{**}-Bt^{**}-Bg^{**}-Bt^{**}-Bc^{*}-Ba^{*}-Bc^{*}-Bc^{*}-Ba^{*}-Bg^{*}-Ba^{*}-Bg^{*}-Bu^{*}-Ba^{*}-Ba^{*}-Bc^{**}-Ba^{*}-Bg^{**}-Bt^{**}-CH₂CH₂OH
- (I²⁸) Ph-Ba^{**}-Bg^{**}-Bg^{**}-Bt^{**}-Bt^{**}-Bg^{*}-Bu^{*}-Bg^{*}-Bu^{*}-Bc^{*}-Ba^{*}-Bc^{*}-Bc^{*}-Ba^{*}-Bg^{*}-Ba^{**}-Bg^{**}-Bt^{**}-Ba^{**}-Ba^{**}-CH₂CH₂OH
- (I²⁹) Ph-Ba^{**}-Bg^{**}-Bt^{**}-Ba^{**}-Ba^{**}-Bc^{*}-Bc^{*}-Ba^{*}-Bc^{*}-Ba^{*}-Bg^{*}-Bu^{*}-Bg^{*}-Bt^{**}-Bg^{**}-Bt^{**}-Bc^{**}-Ba^{**}-CH₂CH₂OH
- (I³⁰) Ph-Bt^{**}-Bt^{**}-Bg^{**}-Ba^{**}-Bt^{**}-Bc^{*}-Ba^{*}-Ba^{*}-Bg^{*}-Bc^{*}-Ba^{*}-Bg^{*}-Ba^{*}-Bg^{*}-Ba^{*}-Ba^{**}-Ba^{**}-Bg^{**}-Bc^{**}-Bc^{**}-CH₂CH₂OH
- (I³¹) Ph-Bc^{**}-Ba^{**}-Bc^{**}-Bc^{**}-Bc^{**}-Bc^{**}-Bu^{*}-Bc^{*}-Bu^{*}-Bg^{*}-Bu^{*}-Bg^{*}-Ba^{*}-Bu^{*}-Bt^{**}-Ba^{**}-Bt^{**}-Ba^{**}-Ba^{**}-CH₂CH₂OH
- (I³²) Ph-Ba^{**}-Bc^{**}-Bc^{**}-Bc^{**}-Ba^{**}-Bc^{*}-Bc^{*}-Ba^{*}-Bu^{*}-Bc^{*}-Ba^{*}-Bc^{*}-Bc^{*}-Bc^{*}-Bu^{*}-Bc^{**}-Bt^{**}-Bg^{**}-Bt^{**}-Bg^{**}-CH₂CH₂OH
- (I³³) Ph-Bc^{**}-Bc^{**}-Bt^{**}-Bc^{**}-Ba^{**}-Ba^{*}-Bg^{*}-Bg^{*}-Bu^{*}-Bc^{*}-Bc^{*}-Bc^{*}-Ba^{*}-Bc^{*}-Bc^{*}-Ba^{**}-Bt^{**}-Bc^{**}-CH₂CH₂OH
- (I³⁴) HO-Bt^{**}-Ba^{**}-Ba^{**}-Bc^{**}-Ba^{**}-Bg^{*}-Bu^{*}-Bc^{*}-Bu^{*}-Bg^{*}-Ba^{*}-Bg^{*}-Bu^{*}-Ba^{**}-Bg^{**}-Bg^{**}-Ba^{**}-Bg^{**}-CH₂CH₂OH
- (I³⁵) HO-Bg^{**}-Bg^{**}-Bc^{**}-Ba^{**}-Bt^{**}-Bu^{*}-Bu^{*}-Bc^{*}-Bu^{*}-Ba^{*}-Bg^{*}-Bu^{*}-Bt^{**}-Bg^{**}-Bg^{**}-Ba^{**}-Bg^{**}-CH₂CH₂OH
- (I³⁶) HO—Ba^{**}-Bg^{**}-Bc^{**}-Bc^{**}-Ba^{**}-Bg^{*}-Bu^{*}-Bc^{*}-Bg^{*}-Bg^{*}-Bu^{*}-Ba^{*}-Ba^{*}-Bg^{**}-Bt^{**}-Bt^{**}-Bc^{**}-Bt^{**}-CH₂CH₂OH
- (I³⁷) HO—Ba^{**}-Bg^{**}-Bt^{**}-Bt^{**}-Bt^{**}-Bg^{*}-Bg^{*}-Ba^{*}-Bg^{*}-Ba^{*}-Bu^{*}-Bg^{*}-Bc^{*}-Ba^{*}-Bg^{*}-Bt^{**}-Bt^{**}-CH₂CH₂OH
- (I³⁸) HO-Bc^{**}-Bt^{**}-Bg^{*}-Ba^{*}-Bt^{**}-Bt^{**}-Bc^{*}-Bt^{**}-Bg^{*}-Ba^{*}-Ba^{*}-Bt^{**}-Bc^{**}-Bc^{**}-Bu^{*}-Bu^{*}-Bt^{**}-Bc^{**}-CH₂CH₂OH
- (I³⁹) HO-Bt^{**}-Bt^{**}-Bc^{*}-Bt^{**}-Bt^{**}-Bg^{*}-Bt^{**}-Ba^{*}-Bc^{*}-Bt^{**}-Bt^{**}-Bc^{*}-Ba^{*}-Bt^{**}-Bc^{*}-Bc^{*}-Bc^{*}-Ba^{*}-CH₂CH₂OH
- (I⁴⁰) HO-Bc^{**}-Bc^{**}-Bu^{*}-Bc^{**}-Bc^{**}-Bg^{*}-Bg^{*}-Bt^{**}-Bt^{**}-Bc^{**}-Bc^{**}-Bt^{**}-Bg^{*}-Ba^{*}-Ba^{*}-Bg^{*}-Bg^{*}-Bt^{**}-Bg^{**}-CH₂CH₂OH
- (I⁴¹) HO-Bc^{**}-Ba^{*}-Bt^{**}-Bt^{**}-Bu^{*}-Bc^{**}-Ba^{*}-Bu^{*}-Bt^{**}-Bc^{**}-Ba^{*}-Ba^{*}-Bc^{**}-Bt^{**}-Bg^{*}-Bt^{**}-Bt^{**}-Bg^{*}-CH₂CH₂OH
- (I⁴²) HO-Bt^{**}-Bt^{**}-Bc^{*}-Bc^{*}-Bt^{**}-Bt^{**}-Ba^{*}-Bg^{*}-Bc^{**}-Bt^{**}-Bt^{**}-Bu^{*}-Bc^{*}-Bc^{**}-Ba^{*}-Bg^{*}-Bc^{**}-Ba^{*}-CH₂CH₂OH
- (I⁴³) HO-Bt^{**}-Ba^{*}-Ba^{*}-Bg^{*}-Ba^{*}-Bc^{**}-Bt^{**}-Bg^{*}-Bc^{**}-Bt^{**}-Bc^{**}-Bc^{**}-Ba^{*}-Bg^{*}-Bc^{**}-Bu^{*}-Bt^{**}-Bc^{*}-CH₂CH₂OH
- (I⁴⁴) HO-Bc^{**}-Bt^{**}-Bt^{**}-Bg^{*}-Bg^{*}-Bc^{**}-Bt^{**}-Bc^{*}-Bt^{**}-Bg^{*}-Bg^{*}-Bc^{**}-Bc^{**}-Bc^{**}-Bt^{**}-Bg^{*}-Bu^{*}-Bc^{**}-Bc^{**}-CH₂CH₂OH
- (I⁴⁵) HO-Bc^{**}-Bt^{**}-Bc^{*}-Bc^{**}-Bt^{**}-Bu^{*}-Bc^{**}-Bc^{**}-Ba^{*}-Bt^{**}-Bg^{*}-Ba^{*}-Bc^{**}-Bt^{**}-Bc^{*}-Ba^{*}-Ba^{*}-Bg^{*}-CH₂CH₂OH
- (I⁴⁶) HO-Bc^{**}-Bt^{**}-Bg^{*}-Ba^{*}-Ba^{*}-Bg^{*}-Bg^{*}-Bt^{**}-Bg^{*}-Bt^{**}-Bt^{**}-Bc^{**}-Bt^{**}-Bt^{**}-Bg^{*}-Bt^{**}-Bt^{**}-Ba^{*}-Bc^{**}-CH₂CH₂OH
- (I⁴⁷) HO-Bt^{**}-Bt^{**}-Bc^{*}-Bc^{**}-Ba^{*}-Bg^{*}-Bc^{**}-Bc^{**}-Ba^{*}-Bt^{**}-Bt^{**}-Bg^{*}-Bt^{**}-Bg^{*}-Bt^{**}-Bt^{**}-Bg^{*}-Ba^{*}-CH₂CH₂OH
- (I⁴⁸) HO-Bc^{**}-Bt^{**}-Bc^{**}-Ba^{*}-Bg^{*}-Bc^{**}-Bt^{**}-Bu^{*}-Bc^{*}-Bt^{**}-Bt^{**}-Bc^{*}-Bc^{**}-Bt^{**}-Bt^{**}-Ba^{*}-Bg^{*}-Bc^{**}-CH₂CH₂OH

- (I⁴⁹) HO-Bg^{*}-Bc^{**}-Bt^{**}-Bt^{**}-Bc^{*}-Bu^{*}-Bt^{**}-Bc^{**}-Bc^{*}-Bu^{*}-Bt^{**}-Ba^{*}-Bg^{*}-Bc^{**}-Bu^{*}-Bt^{**}-Bc^{**}-Bc^{**}-CH₂CH₂OH
- (I⁵⁰) HO-Bg^{*}-Bg^{*}-Bc^{**}-Ba^{*}-Bt^{**}-Bt^{**}-Bu^{*}-Bc^{**}-Bt^{**}-Ba^{*}-Bg^{*}-Bu^{*}-Bt^{**}-Bt^{**}-Bg^{*}-Bg^{*}-Ba^{*}-Bg^{*}-CH₂CH₂OH
- (I⁵¹) HO—Ba^{**}-Bg^{*}-Bt^{**}-Bu^{*}-Bt^{**}-Bg^{*}-Bg^{*}-Ba^{**}-Bg^{*}-Ba^{*}-Bt^{**}-Bg^{*}-Bc^{*}-Ba^{**}-Bg^{*}-Bt^{**}-Bt^{**}-CH₂CH₂OH

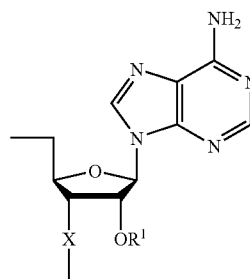
where Bg^{*} is a group represented by formula (G1^a), Ba^{*} is a group represented by formula (A1^a); Bc^{*} is a group represented by formula (C1^a); Bu^{*} is a group represented by formula (U1^a); Bg^{**} is a group represented by formula (G2); Ba^{**} is a group represented by formula (A2); Bc^{**} is a group represented by formula (C2); Bt^{**} is a group represented by formula (T2); and Ph- is a group represented by first formula:



(G1^a)

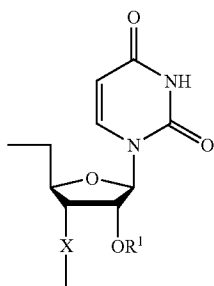


(A1^a)



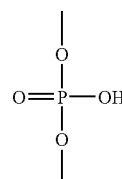
(C1^a)

-continued

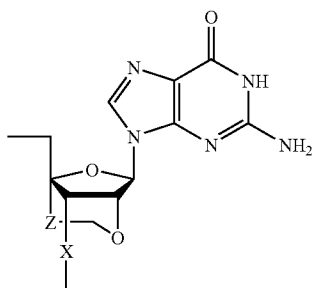


(U1^a)

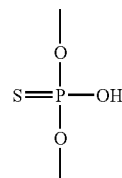
individually and independently an alkyl group with 1-6 carbon atoms; and Z is individually and independently a single bond or an alkylene group with 1-5 carbon atoms:



(X1)



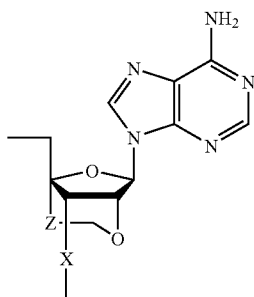
(G2)



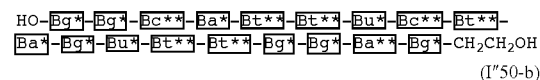
(X2)

76. The compound according to claim 75 which is represented by any one of formulae (I^{''}50-a) to (I^{''}51-b), or a salt thereof:

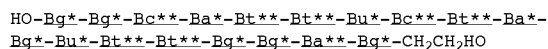
(A2)



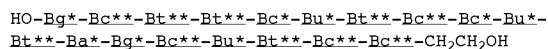
(I^{''}50-a)



(I^{''}50-b)

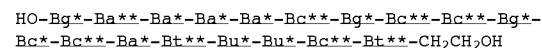


(I^{''}49-a)

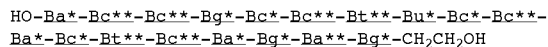


(C2)

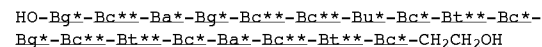
(I^{''}1-a)



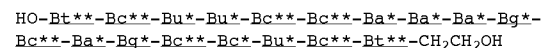
(I^{''}12-a)



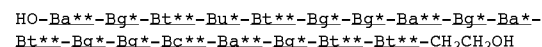
(I^{''}18-a)



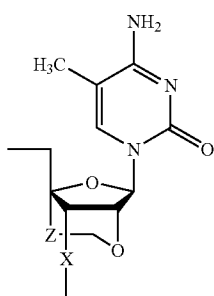
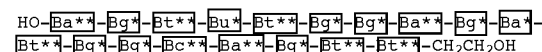
(I^{''}19-a)



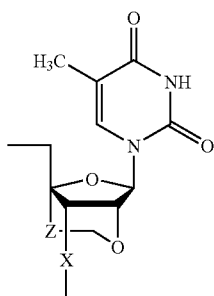
(I^{''}51-a)



(I^{''}51-b)



(T2)



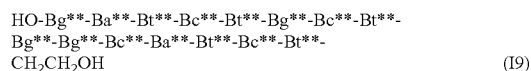
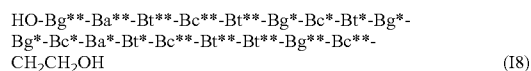
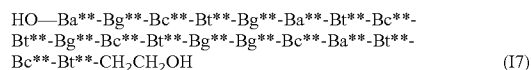
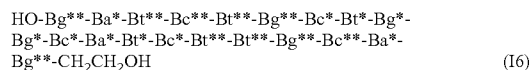
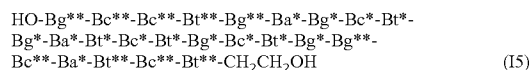
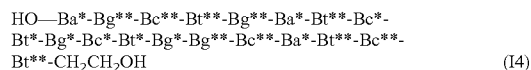
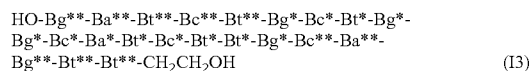
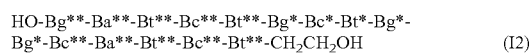
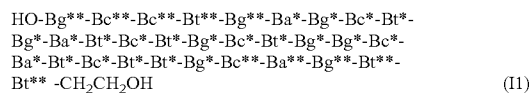
where X is individually and independently a group represented by the following formula (X1) or (X2); R¹ is

where Bg* is a group represented by formula (G1^a), Ba* is a group represented by formula (A1^a); Bc* is a group represented by formula (C1^a); Bu* is a group represented by formula (U1^a); Bg** is a group represented

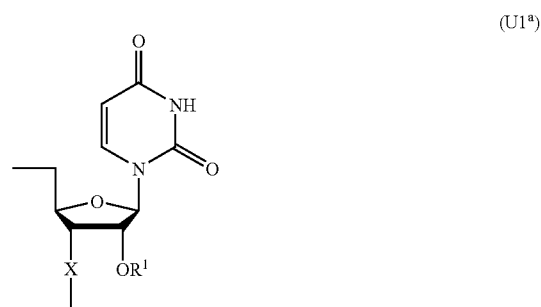
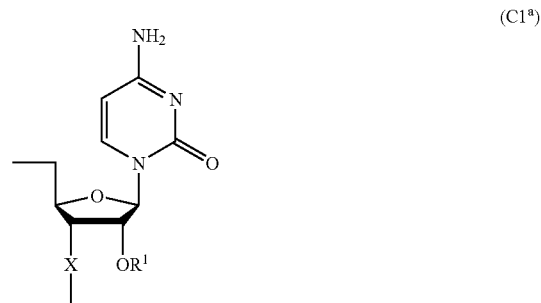
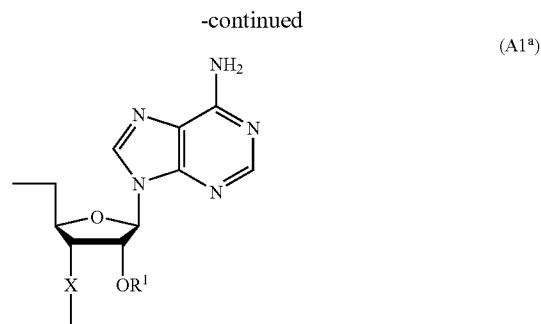
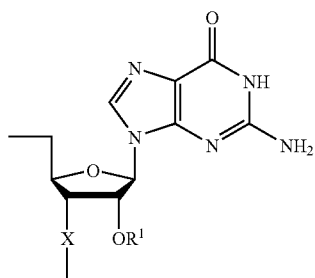
by formula (G2); Ba** is a group represented by formula (A2); Bc** is a group represented by formula (C2); and Bt** is a group represented by formula (T2);

in individual formulas, at least one of Bg*, Ba*, Bc*, Bu*, Bg**, Ba**, Bc** and Bt** has a group represented by formula (X2) as X and all of Bc*, Bg*, Ba**, Bc**, Bc**, Bc**, Bc**, Bc**, Bc** and Bt** have a group represented by formula (X1) as X.

77. The compound according to claim 69 which is selected from the group consisting of compounds (I1) to (I7), or a pharmacologically acceptable salt thereof:



where Bg* is a group represented by formula (G1^a), Ba* is a group represented by formula (A1^a); Bc* is a group represented by formula (U1^a); Bt* is a group represented by formula (G2); Ba** is a group represented by formula (A2); Bc** is a group represented by formula (C2); and Bt** is a group represented by formula (T2);



where X is individually and independently a group represented by formula (X1) or (X2):



and R¹ is individually and independently an alkyl group with 1-6 carbon atoms.

95. The compound according to claim 74 where X in all the formulae (G1^a), (A1^a), (C1^a), (U1^a), (G2), (A2), (C2), and (T2) is a group represented by formula (X2), or a pharmacologically acceptable salt thereof.

96. The compound according to claim 74 where Y in (G1), formulae (G1), (A1), (C1) and (U1) is a methoxy group and Z in formulae (G2), (A2), (C2) and (T2) is an ethylene group, or a pharmacologically acceptable salt thereof.

97. The compound according to claim 75 where X in formulas (G1^a), (A1^a), (C1^a) and (U1^a) is a group represented by formula (X2) and X in formulae (G2), (A2), (C2) and (T2) is a group represented by formula (X1), or a pharmacologically acceptable salt thereof.

98. The compound according to claim 75 where X in all the formulae (G1^a), (A1^a), (C1^a), (U1^a), (G2), (A2), (C2) and (T2) is a group represented by formula (X2), or a pharmacologically acceptable salt thereof.

99. The compound according to claim 75 where Y in formulae (G1), (A1), (C1) and (U1) is a methoxy group and Z in formulae (G2), (A2), (C2) and (T2) is an ethylene group, or a pharmacologically acceptable salt thereof.

100. The compound according to claim 76 where X in formulas (G1^a), (A1^a), (C1^a) and (U1^a) is a group represented by formula (X2) and X in formulae (G2), (A2), (C2) and (T2) is a group represented by formula (X1), or a pharmacologically acceptable salt thereof.

101. The compound according to claim 76 where X in all the formulae (G1^a), (A1^a), (C1^a), (U1^a), (G2), (A2), (C2) and (T2) is a group represented by formula (X2), or a pharmacologically acceptable salt thereof.

102. The compound according to claim 76 where Y in formulae (G1), (A1), (C1) and (U1) is a methoxy group and Z in formulae (G2), (A2), (C2) and (T2) is an ethylene group, or a pharmacologically acceptable salt thereof.

103. The compound according to claim 77 where X in formulas (G1^a), (A1^a), (C1^a) and (U1^a) is a group represented by formula (X2) and X in formulae (G2), (A2), (C2)

and (T2) is a group represented by formula (X1), or a pharmacologically acceptable salt thereof.

104. The compound according to claim 77 where X in all the formulae (G1^a), (A1^a), (C1^a), (U1^a), (G2), (A2), (C2) and (T2) is a group represented by formula (X2), or a pharmacologically acceptable salt thereof.

105. The compound according to claim 77 where Y in formulae (G1), (A1), (C1) and (U1) is a methoxy group and Z in formulae (G2), (A2), (C2) and (T2) is an ethylene group, or a pharmacologically acceptable salt thereof.

106. The compound according to claim 78 where X in formulas (G1^a), (A1^a), (C1^a) and (U1^a) is a group represented by formula (X2) and X in formulae (G2), (A2), (C2) and (T2) is a group represented by formula (X1), or a pharmacologically acceptable salt thereof.

107. The compound according to claim 78 where X in all the formulae (G1^a), (A1^a), (C1^a), (U1^a), (G2), (A2), (C2) and (T2) is a group represented by formula (X2), or a pharmacologically acceptable salt thereof.

108. The compound according to claim 78 where Y in formulae (G1), (A1), (C1) and (U1) is a methoxy group and Z in formulae (G2), (A2), (C2) and (T2) is an ethylene group, or a pharmacologically acceptable salt thereof.

109. A method of treating muscular dystrophy in a patient in need thereof, said method comprising administering to the patient an effective amount of a pharmaceutical composition comprising the compound of claim 63 or a pharmacologically acceptable salt thereof.

110. The method according to claim 109, wherein muscular dystrophy is Duchenne muscular dystrophy.

111. The method according to claim 110, wherein the total number of the amino acids in the open reading frame of the dystrophin gene in the patient will be a multiple of 3 when exon 19, 41, 45, 46, 44, 50, 55, 51 or 53 of the dystrophin gene has been skipped.

* * * * *