(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 November 2017 (30.11.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/205879 A2

(51) International Patent Classification:
A61K 48/00 (2006.01) *C07F 9/6533* (2006.01)

(21) International Application Number:
PCT/US2017/040311

(22) International Filing Date:
30 June 2017 (30.06.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/340,953	24 May 2016 (24.05.2016)	US
62/341,049	24 May 2016 (24.05.2016)	US
62/357,153	30 June 2016 (30.06.2016)	US
62/357,134	30 June 2016 (30.06.2016)	US
62/508,256	18 May 2017 (18.05.2017)	US

(71) Applicant: **SAREPTA THERAPEUTICS, INC.** [US/US]; 215 First Street, Cambridge, MA 02139 (US).

(72) Inventors: **CAI, Bao**; c/o Sarepta Therapeutics, Inc., 215 First Street, Cambridge, MA 02142 (US). **MARTINI, Mitchell**; c/o Sarepta Therapeutics, Inc., 215 First Street, Cambridge, MA 02142 (US). **THOMAS, Katie**; c/o Sarepta Therapeutics, Inc., 215 First Street, Cambridge, MA 02142 (US). **SHIMABUKU, Ross**; c/o Sarepta Therapeutics, Inc., 215 First Street, Cambridge, MA 02142 (US).

(74) Agent: **TRINQUE, Brian, C.** et al.; Lathrop & Gage, LLP, 28 State Street, Boston, MA 02109 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*
— *with information concerning request for restoration of the right of priority in respect of one or more priority claims (Rules 26bis.3 and 48.2(b)(vii))*

(54) Title: PROCESSES FOR PREPARING PHOSPHORODIAMIDATE MORPHOLINO OLIGOMERS

(57) Abstract: Provided herein are processes for preparing an oligomer (e.g., a morpholino oligomer). The synthetic processes described herein may be advantageous to scaling up oligomer synthesis while maintaining overall yield and purity of a synthesized oligomer.

WO 2017/205879 A2

PROCESSES FOR PREPARING PHOSPHORODIAMIDATE MORPHOLINO OLIGOMERS

RELATED APPLICATIONS

This patent application claims the benefit of U.S. Provisional Patent Application Serial No. 62/508,256, filed May 18, 2017, U.S. Provisional Patent Application Serial No. 62/341,049, filed May 24, 2016, U.S. Provisional Patent Application Serial No. 62/340,953, filed May 24, 2016, U.S. Provisional Patent Application Serial No. 62/357,134, filed June 30, 2016, and U.S. Provisional Patent Application Serial No. 62/357,153, filed June 30, 2016. The entire contents of the above-referenced provisional patent applications are incorporated herein by reference.

BACKGROUND

Antisense technology provides a means for modulating the expression of one or more specific gene products, including alternative splice products, and is uniquely useful in a number of therapeutic, diagnostic, and research applications. The principle behind antisense technology is that an antisense compound, e.g., an oligonucleotide, which hybridizes to a target nucleic acid, modulates gene expression activities such as transcription, splicing or translation through any one of a number of antisense mechanisms. The sequence specificity of antisense compounds makes them attractive as tools for target validation and gene functionalization, as well as therapeutics to selectively modulate the expression of genes involved in disease.

Duchenne muscular dystrophy (DMD) is caused by a defect in the expression of the protein dystrophin. The gene encoding the protein contains 79 exons spread out over more than 2 million nucleotides of DNA. Any exonic mutation that changes the reading frame of the exon, or introduces a stop codon, or is characterized by removal of an entire out of frame exon or exons, or duplications of one or more exons, has the potential to disrupt production of functional dystrophin, resulting in DMD.

Recent clinical trials testing the safety and efficacy of splice switching oligonucleotides (SSOs) for the treatment of DMD are based on SSO technology to induce alternative splicing of pre-mRNAs by steric blockade of the spliceosome (Cirak *et al.*, 2011; Goemans *et al.*, 2011; Kinali *et al.*, 2009; van Deutekom *et al.*, 2007). However, despite these successes, the pharmacological options available for treating DMD are limited.

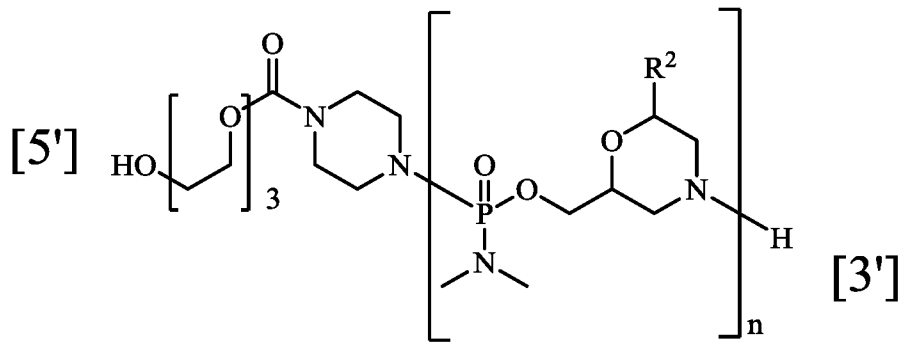
Casimersen is a phosphorodiamidate morpholino oligomer (PMO) designed to skip exon 45 of the human dystrophin gene in patients with DMD who are amendable to exon 45 skipping to restore the read frame and produce a functional shorter form of the dystrophin protein.

Although significant progress has been made in the field of antisense technology, there remains a need in the art for methods of preparing phosphorodiamidate morpholino oligomers with improved antisense or antigene performance.

SUMMARY

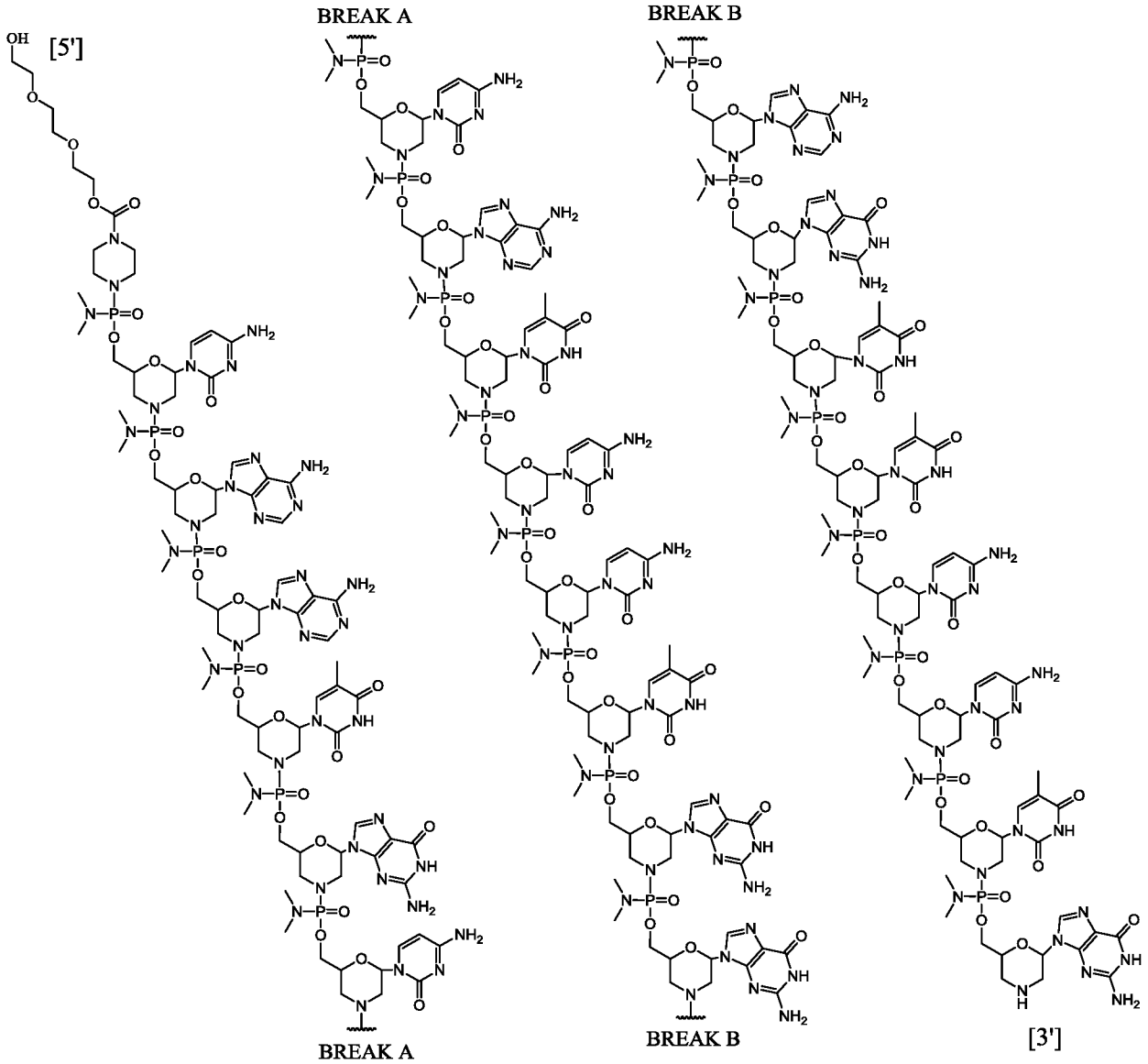
Provided herein are processes for preparing phosphorodiamidate morpholino oligomers (PMOs). The synthetic processes described herein allow for a scaled-up PMO synthesis while maintaining overall yield and purity of a synthesized PMO.

Accordingly, in one aspect, provided herein is a process for preparing an oligomeric compound of Formula (A):



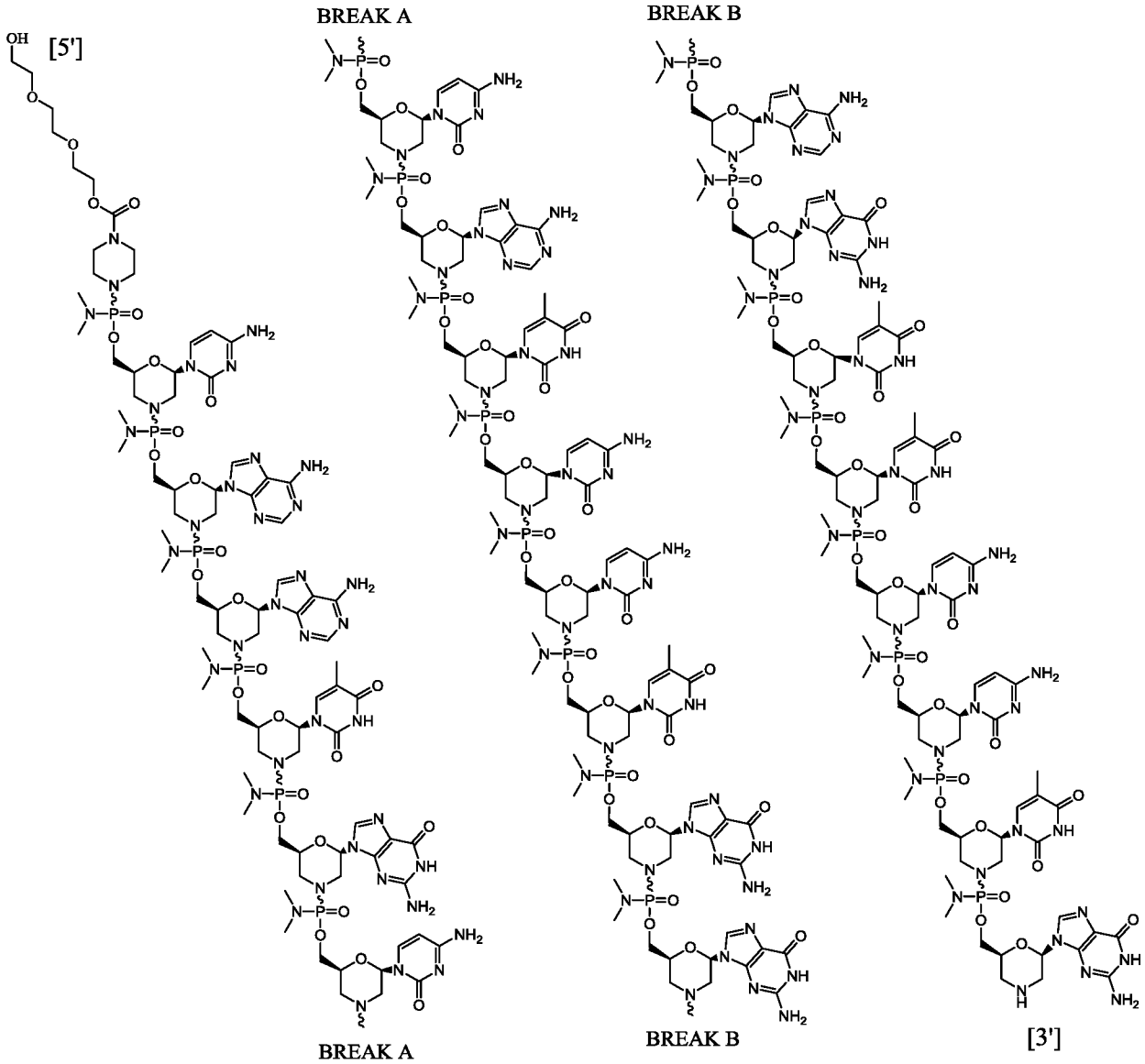
(A).

In certain embodiments, provided herein is a process for preparing an oligomeric compound of Formula (C):



(C).

In yet another embodiment, the oligomeric compound of the disclosure including, for example, some embodiments of an oligomeric compound of Formula (C), is an oligomeric compound of Formula (XII):



(XII).

For clarity, the structural formulas including, for example, oligomeric compound of Formula (C) and Casimersen depicted by Formula (XII), are a continuous structural formula from 5' to 3', and, for the convenience of depicting the entire formula in a compact form in the above structural formulas, Applicants have included various illustration breaks labeled "BREAK A" and "BREAK B." As would be understood by the skilled artisan, for example, each indication of "BREAK A" shows a continuation of the illustration of the structural formula at these points. The skilled artisan understands that the same is true for each instance of "BREAK B" in the structural formulas above including Casimersen. None of the illustration breaks, however, are intended to indicate, nor would the skilled artisan understand them to mean, an actual discontinuation of the structural formulas above including Casimersen.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 and Fig. 2 show representative analytical high performance liquid chromatography (HPLC) chromatogram of a synthesized and deprotected casimersen (SRP-4045) crude drug substance (see Example 4).

Fig. 3 and Fig. 4 show a representative analytical HPLC chromatogram of a purified casimersen drug substance solution (see Example 5).

Fig. 5 and Fig. 6 show a representative analytical HPLC chromatogram of a desalted and lyophilized casimersen drug substance (see Example 5).

DETAILED DESCRIPTION

Provided herein are processes for preparing a morpholino oligomer. The morpholino oligomer described herein displays stronger affinity for DNA and RNA without compromising sequence selectivity, relative to native or unmodified oligonucleotides. In some embodiments, the morpholino oligomer of the disclosure minimizes or prevents cleavage by RNase H. In some embodiments, the morpholino oligomer of the disclosure does not activate RNase H.

The processes described herein are advantageous in an industrial-scale process and can be applied to preparing quantities of a morpholino oligomer in high yield and scale (e.g., about 1 kg, about 1-10 kg, about 2-10 kg, about 5-20 kg, about 10-20 kg, or about 10-50 kg).

Definitions

Listed below are definitions of various terms used to describe this disclosure. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

"Base-protected" or "base protection" refers to protection of the base-pairing groups, e.g., purine or pyrimidine bases, on the morpholino subunits with protecting groups suitable to prevent reaction or interference of the base-pairing groups during stepwise oligomer synthesis. An example of a base-protected morpholino subunit is the activated C subunit Compound (C) having a CBZ protecting group on the cytosine amino group depicted below.

An "activated phosphoramidate group" is typically a chlorophosphoramidate group, having substitution at nitrogen which is desired in the eventual phosphorodiamidate linkage in the oligomer. An example is (dimethylamino)chlorophosphoramidate, i.e., –O-P(=O)(NMe_2)Cl.

The term "support-bound" refers to a chemical entity that is covalently linked to a support-medium.

The term "support-medium" refers to any material including, for example, any particle, bead, or surface, upon which an oligomer can be attached or synthesized upon, or can be modified for attachment or synthesis of an oligomer. Representative substrates include, but are not limited to, inorganic supports and organic supports such as glass and modified or functionalized glass, plastics (including acrylics, polystyrene and copolymers of styrene and other materials, polypropylene, polyethylene, polybutylene, polyurethanes, TEFLON, etc.), polysaccharides, nylon or nitrocellulose, ceramics, resins, silica or silica-based materials including silicon and modified silicon, carbon, metals, inorganic glasses, plastics, optical fiber bundles, and a variety of other polymers. Particularly useful support-medium and solid surfaces for some embodiments are located within a flow cell apparatus. In some embodiments of the processes described herein, the support-medium comprises polystyrene with 1% crosslinked divinylbenzene.

In some embodiments, representative support-medium comprise at least one reactive site for attachment or synthesis of an oligomer. For example, in some embodiments, a support-medium of the disclosure comprises one or more terminal amino or hydroxyl groups capable of forming a chemical bond with an incoming subunit or other activated group for attaching or synthesizing an oligomer.

Some representative support-medium that are amenable to the processes described herein include, but are not limited to, the following: controlled pore glass (CPG); oxalyl-controlled pore glass (see, e.g., Alul, et al., *Nucleic Acids Research* 1991, 19, 1527); silica-containing particles, such as porous glass beads and silica gel such as that formed by the reaction of trichloro-[3-(4-chloromethyl)phenyl]propylsilane and porous glass beads (see Parr and Grohmann, *Angew. Chem. Internatl. Ed.* 1972, 11, 314, sold under the trademark "PORASIL E" by Waters Associates, Framingham, Mass., USA); a mono ester of 1,4-dihydroxymethylbenzene and silica (see Bayer and Jung, *Tetrahedron Lett.,* 1970, 4503, sold under the trademark "BIOPAK" by Waters Associates); TENTAGEL (see, e.g., Wright, et al., *Tetrahedron Lett.* 1993, 34, 3373); cross-linked styrene/divinylbenzene copolymer beaded matrix, or POROS, a copolymer of polystyrene/divinylbenzene (available from Perseptive Biosystems); soluble support-medium such as polyethylene glycol PEG's (see Bonora et al., *Organic Process Research & Development*, 2000, 4, 225–231); PEPS support, which is a polyethylene (PE) film with pendant long-chain polystyrene (PS) grafts (see Berg, et al., *J. Am. Chem. Soc.,*1989, 111, 8024 and International Patent Application WO

1990/02749); copolymers of dimethylacrylamide cross-linked with N,N′-bisacryloylethylenediamine, including a known amount of N-tertbutoxycarbonyl-beta-alanyl-N′-acryloylhexamethylenediamine (see Atherton, et al., *J. Am. Chem. Soc.,* 1975, 97, 6584, *Bioorg. Chem.* 1979, 8, 351, and J. C. S. Perkin I 538 (1981)); glass particles coated with a hydrophobic cross-linked styrene polymer (see Scott, et al., *J. Chrom. Sci.,* 1971, 9, 577); fluorinated ethylene polymer onto which has been grafted polystyrene (see Kent and Merrifield, *Israel J. Chem.* 1978, 17, 243, and van Rietschoten in *Peptides* 1974, Y. Wolman, Ed., Wiley and Sons, New York, 1975, pp. 113–116); hydroxypropylacrylate-coated polypropylene membranes (Daniels, et al., *Tetrahedron Lett.* 1989, 4345); acrylic acid-grafted polyethylene-rods (Geysen, et al., *Proc. Natl. Acad. Sci. USA,* 1984, 81, 3998); a "tea bag" containing traditionally-used polymer beads (Houghten, *Proc. Natl. Acad. Sci. USA,* 1985, 82, 5131); and combinations thereof.

The term "flow cell apparatus" refers to a chamber comprising a surface (e.g., solid surface) across which one or more fluid reagents (e.g., liquid or gas) can be flowed.

The term "deblocking agent" refers to a composition (e.g., a solution) comprising a chemical acid or combination of chemical acids for removing protecting groups. Exemplary chemical acids used in deblocking agents include halogenated acids, e.g., chloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, and trifluoroacetic acid. In some embodiments, a deblocking agent removes one or more trityl groups from, for example, an oligomer, a support-bound oligomer, a support-bound subunit, or other protected nitrogen or oxygen moiety.

The terms "halogen" and "halo" refer to an atom selected from the group consisting of fluorine, chlorine, bromine, and iodine.

The term "capping agent" refers to a composition (e.g., a solution) comprising an acid anhydride (e.g., benzoic anhydride, acetic anhydride, phenoxyacetic anhydride, and the like) useful for blocking a reactive cite of, for example, a support-medium forming a chemical bond with an incoming subunit or other activated group.

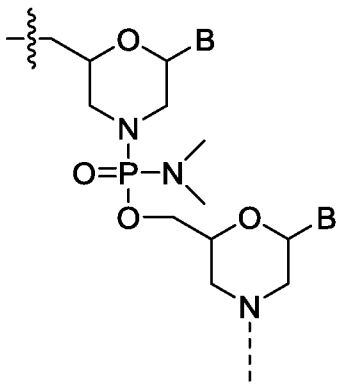
The term "cleavage agent" refers to a composition (e.g., a liquid solution or gaseous mixture) comprising a chemical base (e.g., ammonia or 1,8-diazabicycloundec-7-ene) or a combination of chemical bases useful for cleaving, for example, a support-bound oligomer from a support-medium.

The term "deprotecting agent" refers to a composition (e.g., a liquid solution or gaseous mixture) comprising a chemical base (e.g., ammonia, 1,8-diazabicycloundec-7-ene or potassium carbonate) or a combination of chemical bases useful for removing protecting

groups. For example, a deprotecting agent, in some embodiments, can remove the base protection from, for example, a morpholino subunit, morpholino subunits of a morpholino oligomer, or support-bound versions thereof.

The term "solvent" refers to a component of a solution or mixture in which a solute is dissolved. Solvents may be inorganic or organic (e.g., acetic acid, acetone, acetonitrile, acetyl acetone, 2-aminoethanol, aniline, anisole, benzene, benzonitrile, benzyl alcohol, 1-butanol, 2-butanol, i-butanol, 2-butanone, t-butyl alcohol, carbon disulfide, carbon tetrachloride, chlorobenzene, chloroform, cyclohexane, cyclohexanol, cyclohexanone, di-n-butylphthalate, 1,1-dichloroethane, 1,2-dichloroethane, diethylamine, diethylene glycol, diglyme, dimethoxyethane (glyme), N,N-dimethylaniline, dimethylformamide, dimethylphthalate, dimethylsulfoxide, dioxane, ethanol, ether, ethyl acetate, ethyl acetoacetate, ethyl benzoate, ethylene glycol, glycerin, heptane, 1-heptanol, hexane, 1-hexanol, methanol, methyl acetate, methyl t-butyl ether, methylene chloride, 1-octanol, pentane, 1-pentanol, 2-pentanol, 3-pentanol, 2-pentanone, 3-pentanone, 1-propanol, 2-propanol, pyridine, tetrahydrofuran, toluene, water, p-xylene).

The terms "morpholino," "morpholino oligomer," or "PMO" (phosphoramidate- or phosphorodiamidate morpholino oligomer) refer to a phosphorodiamidate morpholino oligomer of the following general structure:

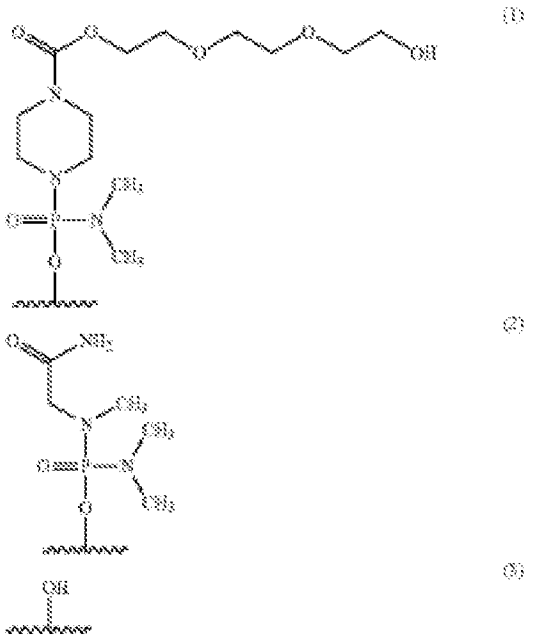


B = nucleobase

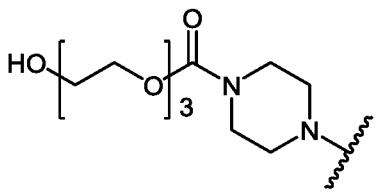
and as described in Figure 2 of Summerton, J., et al., *Antisense & Nucleic Acid Drug Development*, 7: 187-195 (1997). Morpholinos as described herein are intended to cover all stereoisomers and configurations of the foregoing general structure. The synthesis, structures, and binding characteristics of morpholino oligomers are detailed in U.S. Patent Nos. 5,698,685, 5,217,866, 5,142,047, 5,034,506, 5,166,315, 5,521,063, 5,506,337, 8,076,476, and 8,299,206, all of which are incorporated herein by reference.

In certain embodiments, a morpholino is conjugated at the 5' or 3' end of the oligomer

with a "tail" moiety to increase its stability and/or solubility. Exemplary tails include:



The term "EG3 tail" refers to triethylene glycol moieties conjugated to the oligomer, e.g., at its 3'- or 5'-end. For example, in some embodiments, "EG3 tail" conjugated to the 3' end of an oligomer can be of the structure:



The terms "about" or "approximately" are generally understood by persons knowledgeable in the relevant subject area, but in certain circumstances can mean within ±10%, or within ±5%, of a given value or range.

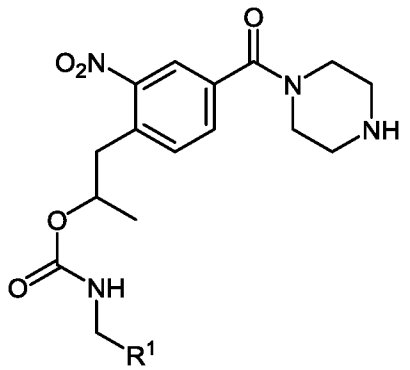
Processes for Preparing Morpholino Oligomers

Synthesis is generally performed, as described herein, on a support-medium. In general a first synthon (e.g. a monomer, such as a morpholino subunit) is first attached to a support-medium, and the oligomer is then synthesized by sequentially coupling subunits to the support-bound synthon. This iterative elongation eventually results in a final oligomeric compound. Suitable support-media can be soluble or insoluble, or may possess variable solubility in different solvents to allow the growing support-bound polymer to be either in or out of solution as desired. Traditional support-media are for the most part insoluble and are routinely placed in reaction vessels while reagents and solvents react with and/or wash the

growing chain until the oligomer has reached the target length, after which it is cleaved from the support, and, if necessary, further worked up to produce the final polymeric compound. More recent approaches have introduced soluble supports including soluble polymer supports to allow precipitating and dissolving the iteratively synthesized product at desired points in the synthesis (Gravert et al., *Chem. Rev.*, 1997, 97,489–510).

Provided herein are processes for preparing morpholino oligomers).

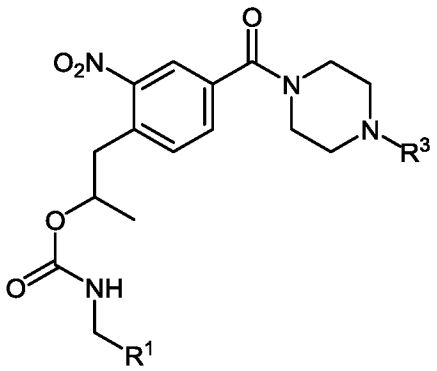
Thus, in one aspect, provided herein is a process for preparing a compound of Formula (II):



(II);

wherein R^1 is a support-medium;

wherein the process comprises contacting a compound of Formula (A1):

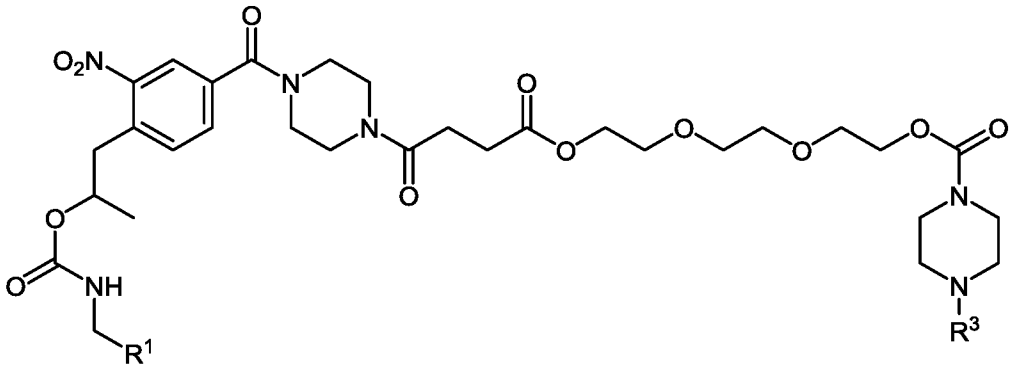


(A1);

wherein R^1 is a support-medium and R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

with a deblocking agent to form the compound of Formula (II).

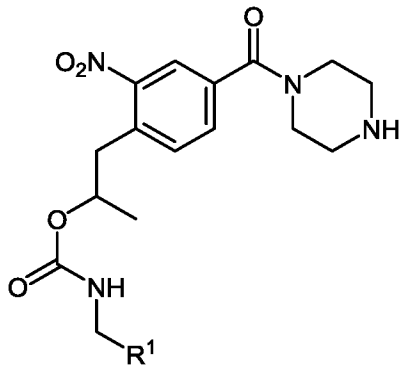
In another aspect, provided herein is a process for preparing a compound of Formula (A3):



(A3);

wherein R^1 is a support-medium, and R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

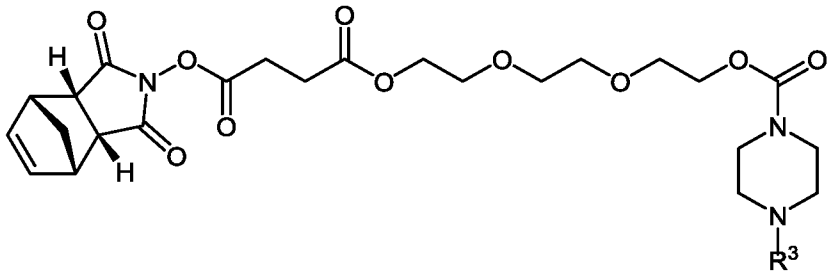
wherein the process comprises contacting a compound of Formula (II):



(II);

wherein R^1 is a support-medium;

with a compound of Formula (A2):

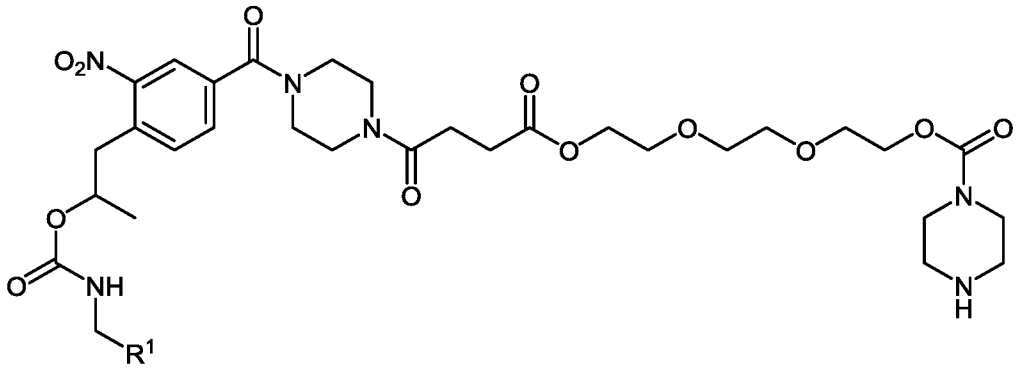


(A2);

wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

to form the compound of Formula (A3).

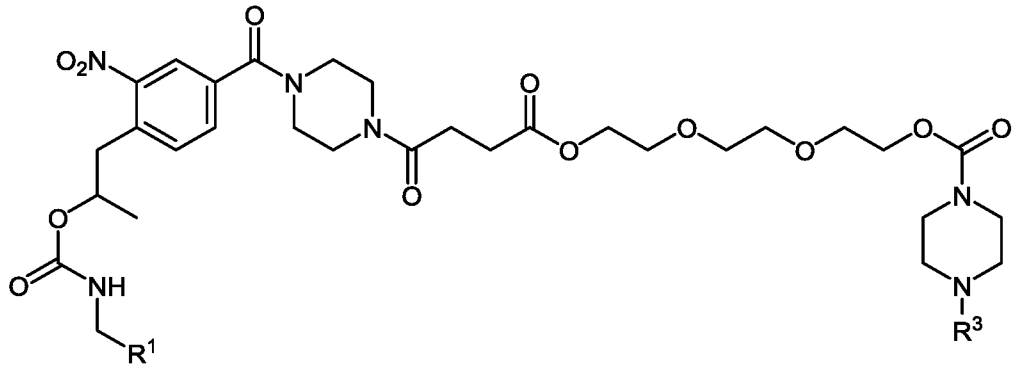
In still another aspect, provided herein is a process for preparing a compound of Formula (IV):



(IV);

wherein R^1 is a support-medium;

wherein the process comprises contacting a compound of Formula (A3):

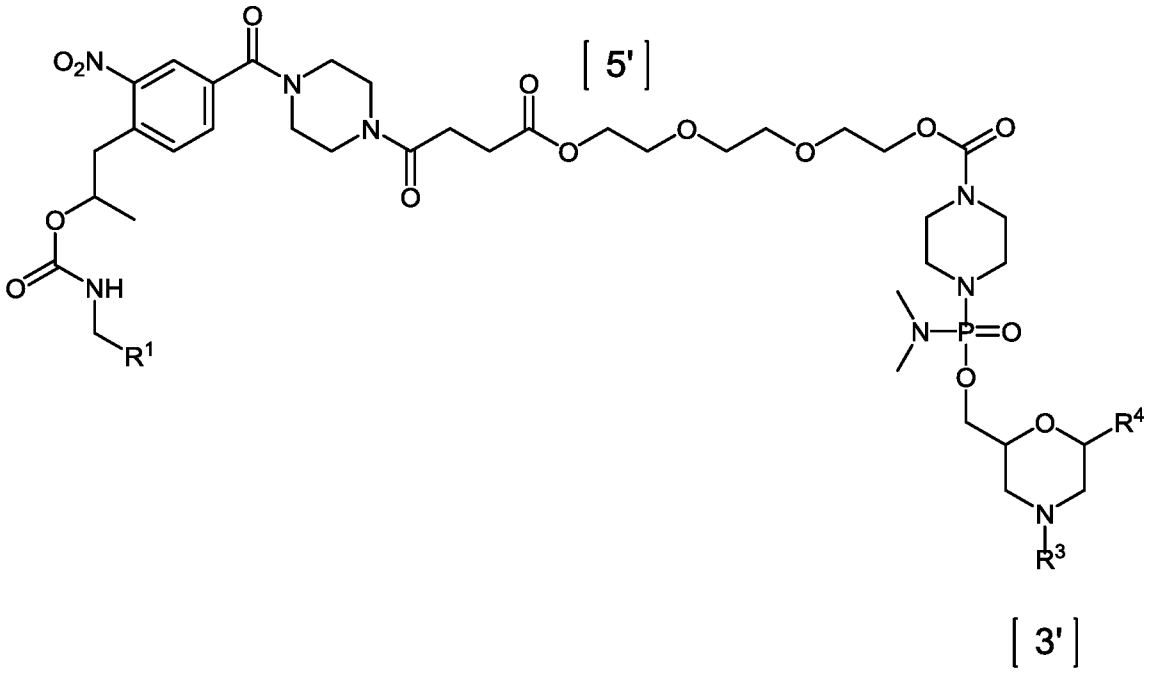


(A3);

wherein R^1 is a support-medium, and R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

with a deblocking agent to form a compound of Formula (IV).

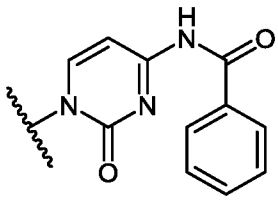
In yet another aspect, provided herein is a process for preparing a compound of Formula (A5):

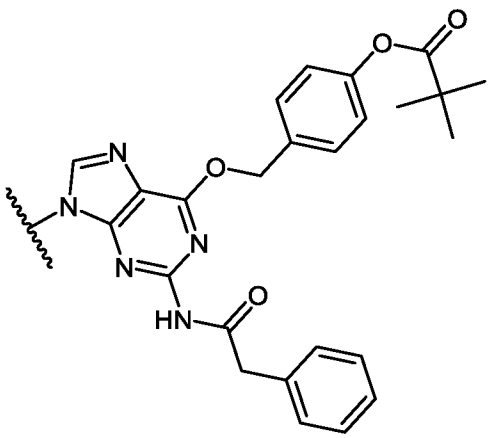


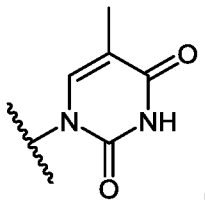
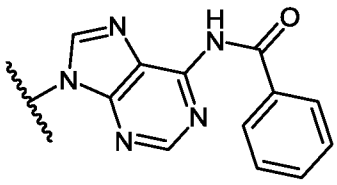
(A5);

wherein R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

R^4 is selected from the group consisting of:


(PC),


(DPG),


(T),

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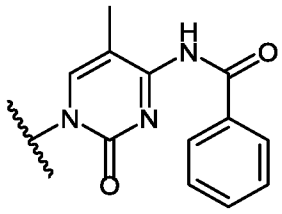
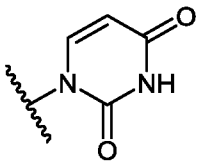
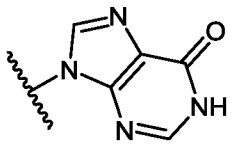
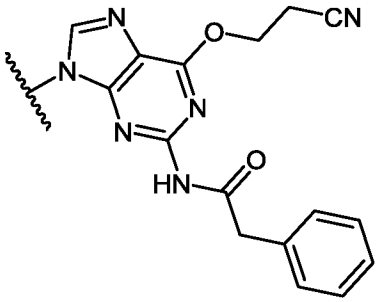
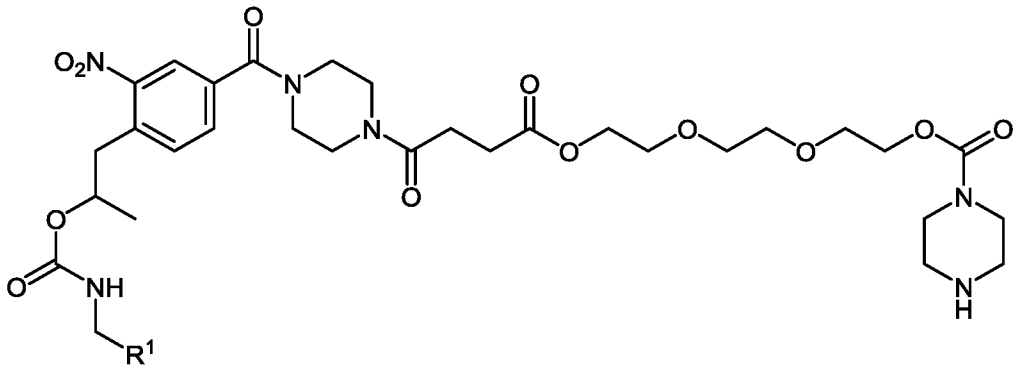

(P5mC),

(U),

(I), and

(PG);

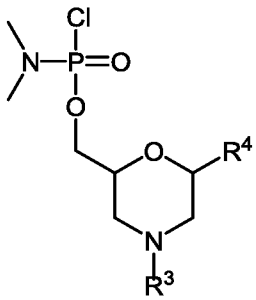
wherein the process comprises contacting a compound of Formula (IV):



(IV);

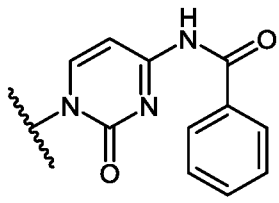
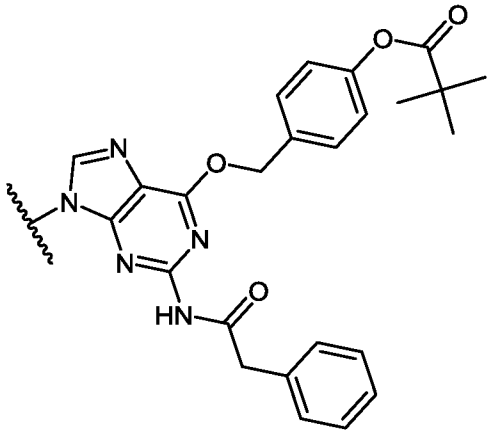
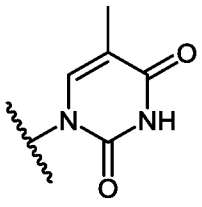
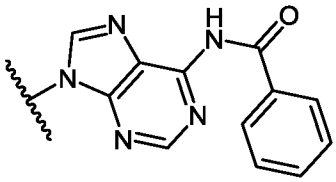
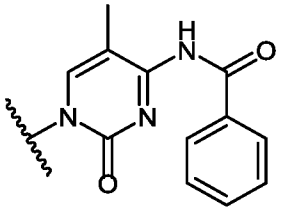
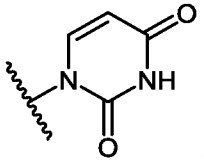
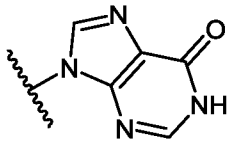
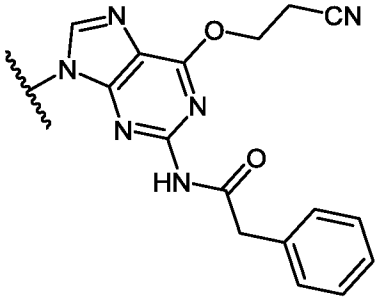
wherein R^1 is a support-medium;

with a compound of Formula (A4):



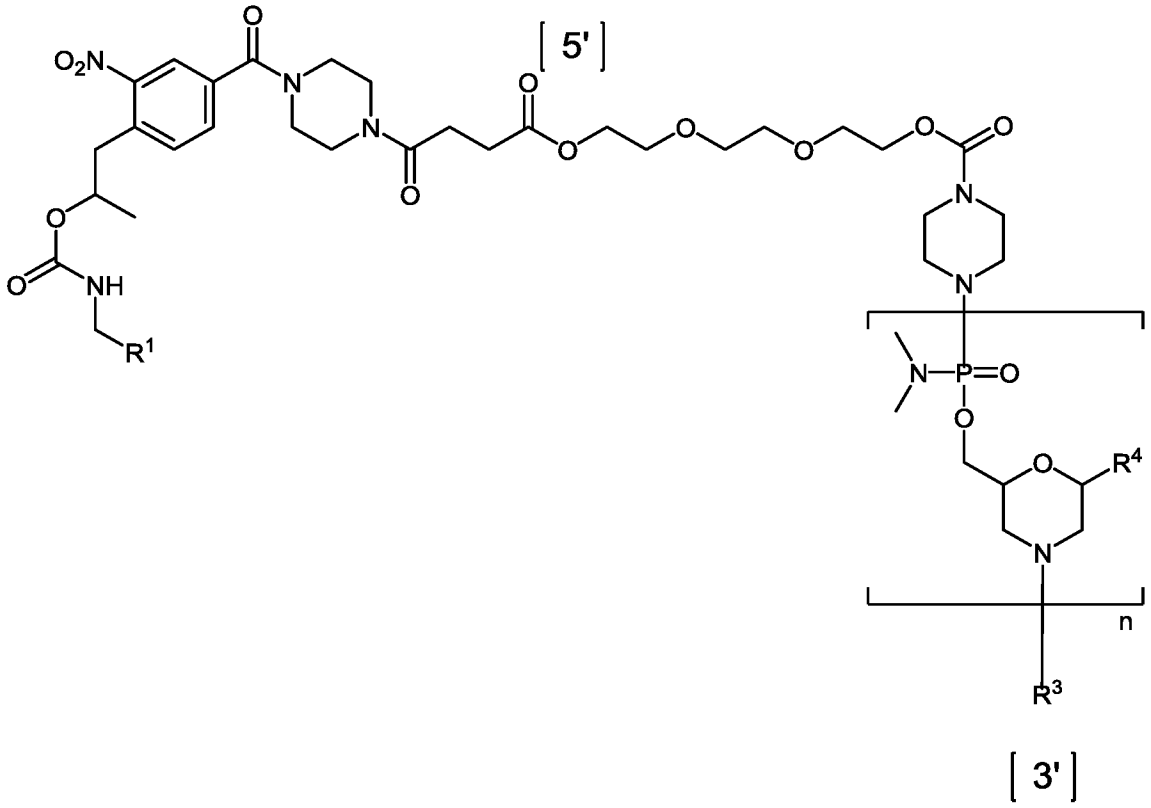
(A4);

wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is selected from the group consisting of:


(PC),

(DPG),

(T),

(PA),

(P5mC),

(U),

(I), and

(PG),

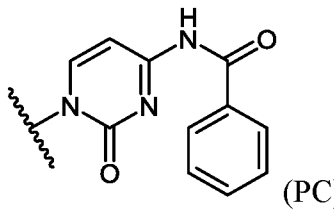
to form a compound of Formula (A5).

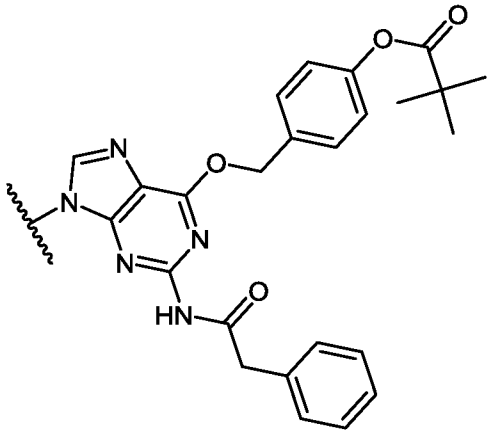
In another aspect, provided herein is a process for preparing a compound of Formula (A9):

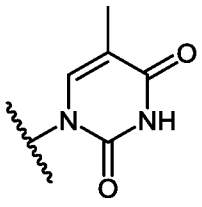


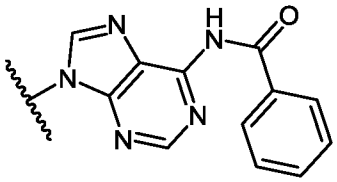
(A9);

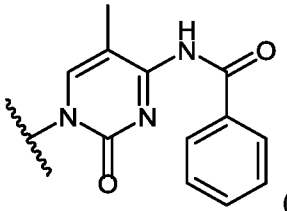
wherein n is an integer from 10 to 40, R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is, independently for each occurrence, selected from the group consisting of:

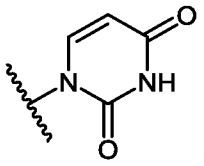

(PC),

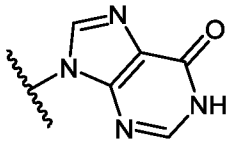

(DPG),

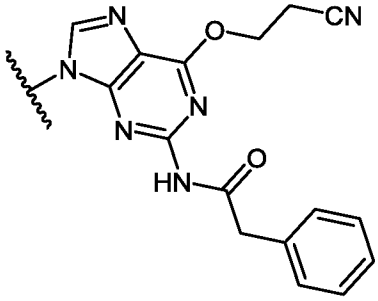

(T),


(PA),


(P5mC),

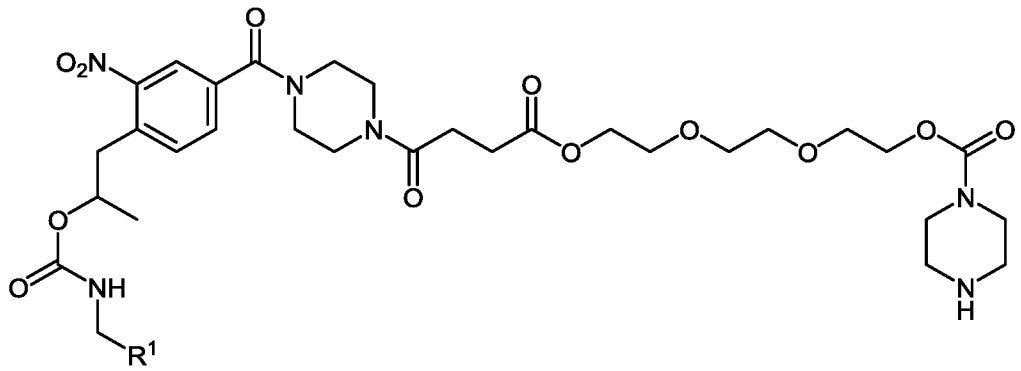

(U),


(I), and


(PG); and

wherein the process comprises the sequential steps of:

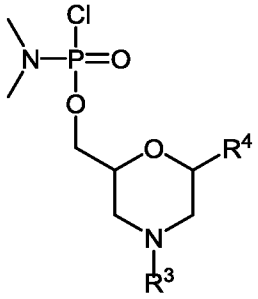
(a) contacting a compound of Formula (IV):



(IV);

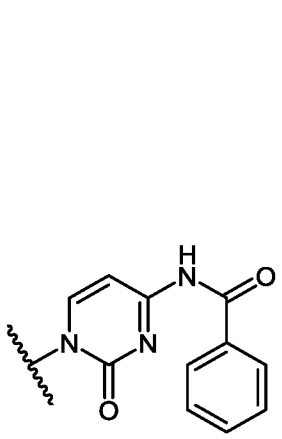
wherein R^1 is a support-medium;

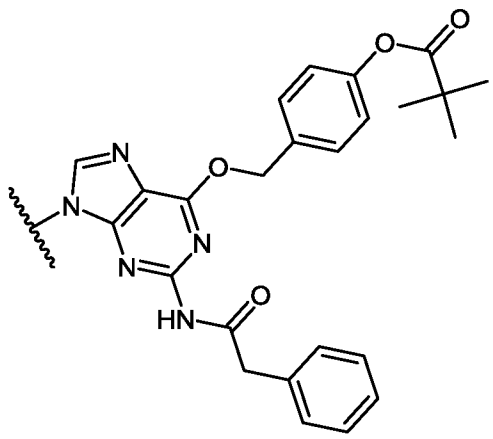
with a compound of Formula (A4):

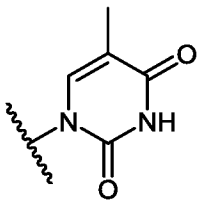


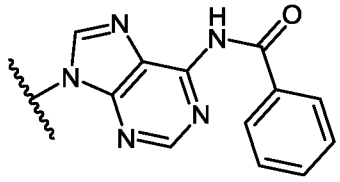
(A4);

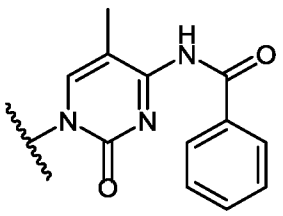
wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is selected from the group consisting of:

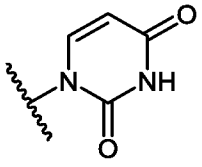
 (PC),

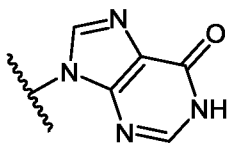
 (DPG),

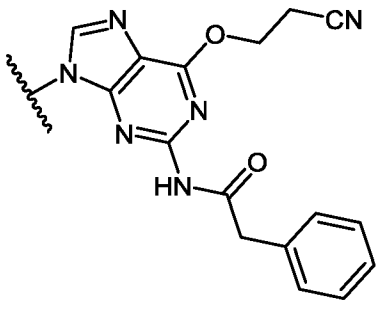
 (T),

 (PA),

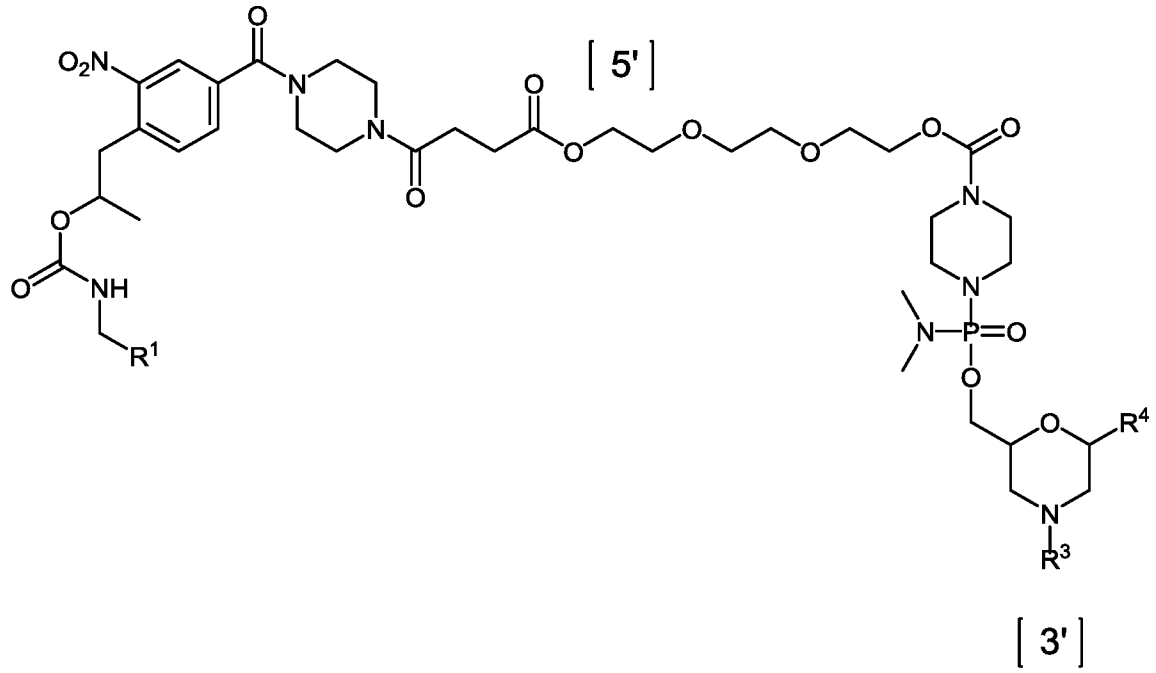
 (P5mC),

 (U),

 (I), and

 (PG),

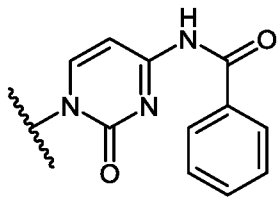
to form a compound of Formula (A5):

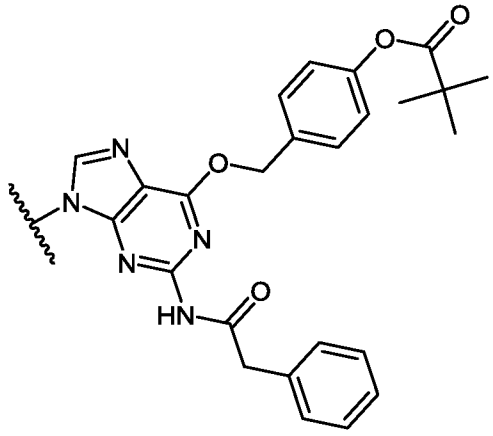


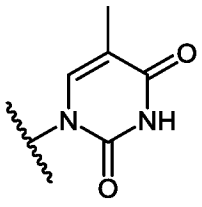
(A5);

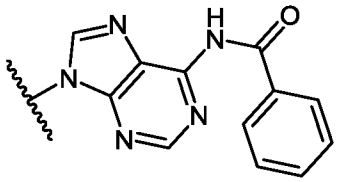
wherein R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

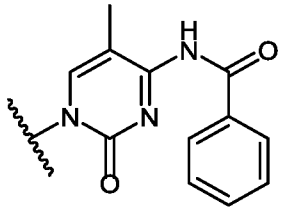
R^4 is selected from the group consisting of:

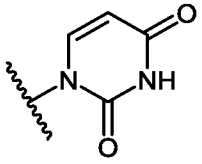

(PC),

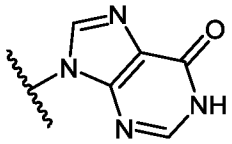

(DPG),

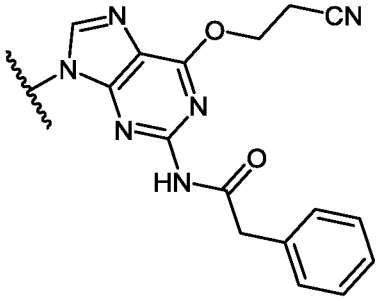

(T),


(PA),


(P5mC),


(U),

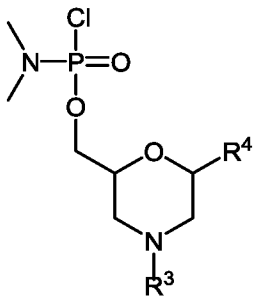

(I), and


(PG); and

(b) performing n-1 iterations of the sequential steps of:

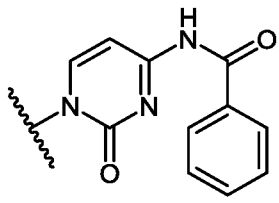
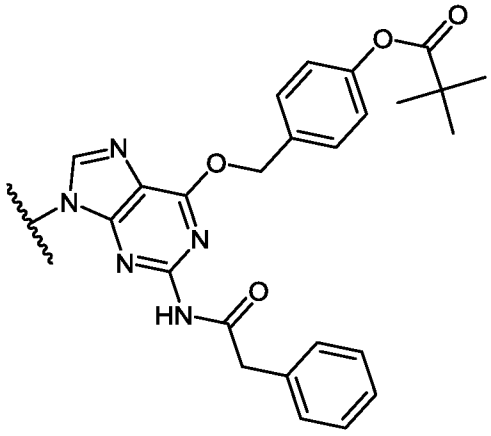
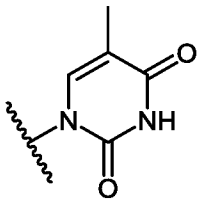
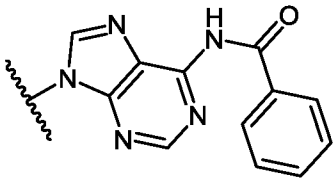
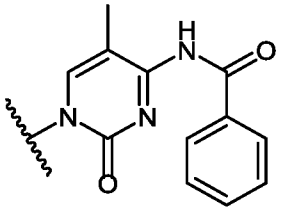
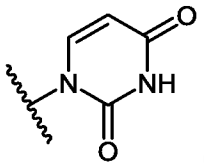
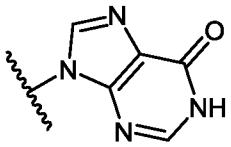
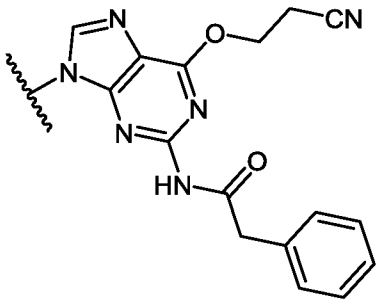
(b1) contacting the product formed by the immediately prior step with a deblocking agent; and

(b2) contacting the compound formed by the immediately prior step with a compound of Formula (A8):



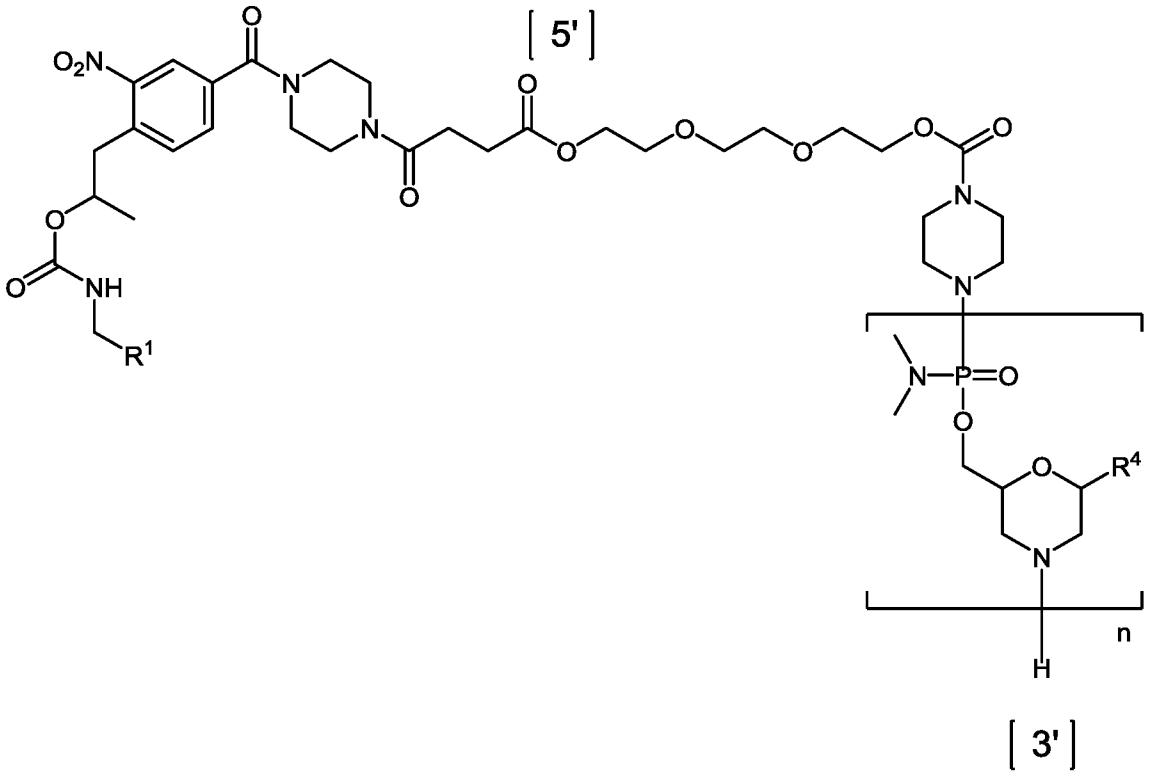
(A8);

wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is selected from the group consisting of:


(PC),

(DPG),

(T),

(PA),

(P5mC),

(U),

(I), and

(PG),

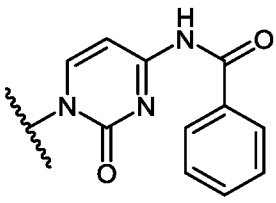
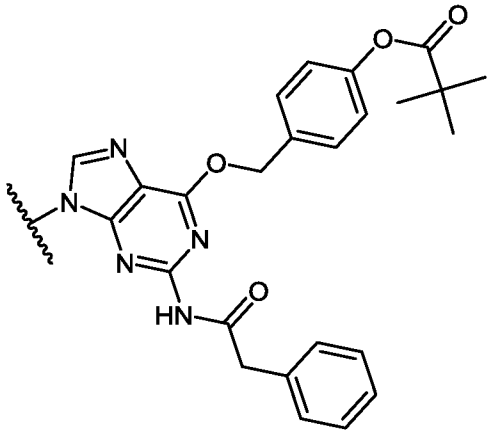
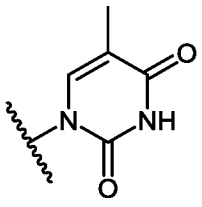
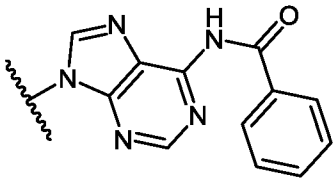
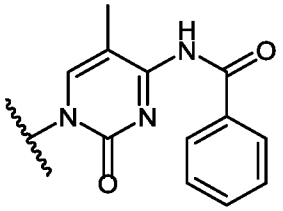
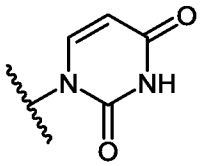
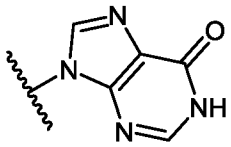
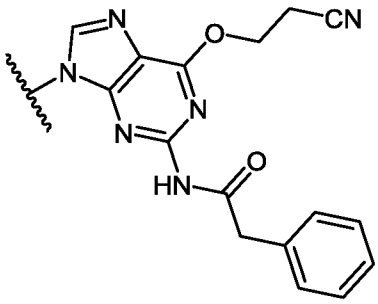
to form a compound of Formula (A9).

In yet another aspect, provided herein is a process for preparing a compound of Formula (A10):

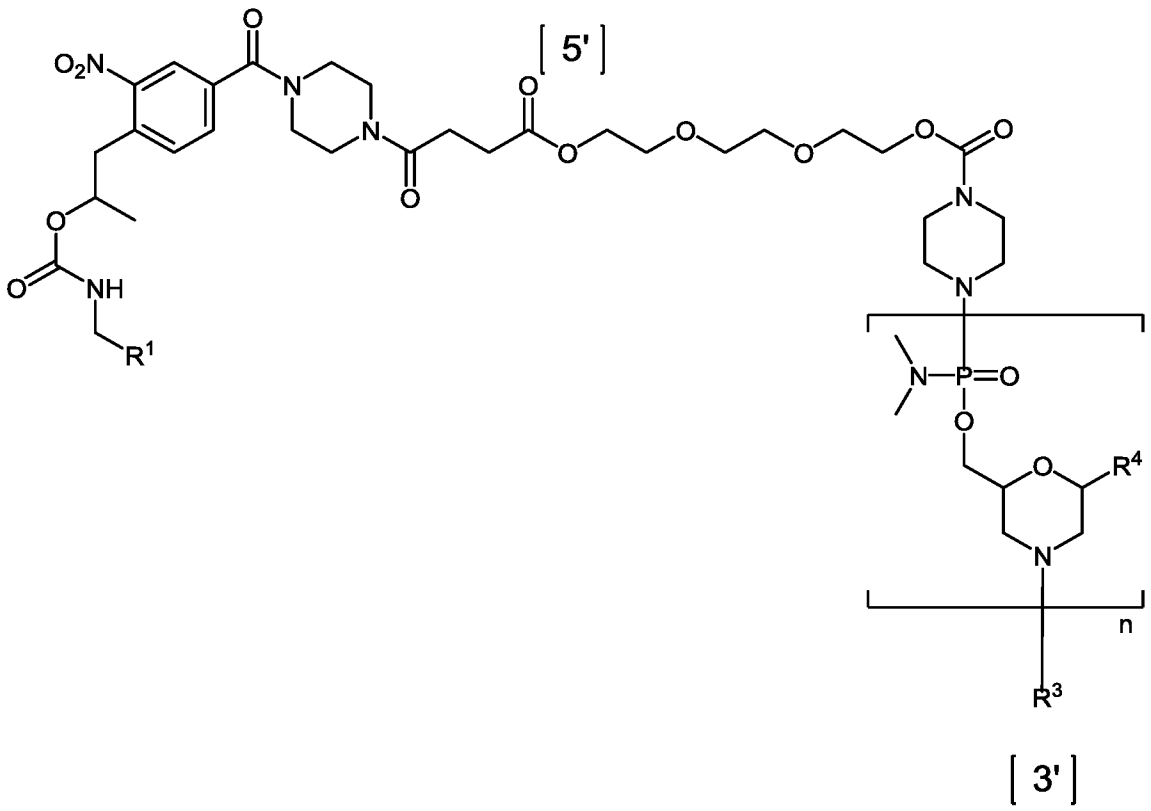


(A10);

wherein n is an integer from 10 to 40, R^1 is a support-medium, and R^4 is, independently for each occurrence, selected from the group consisting of:

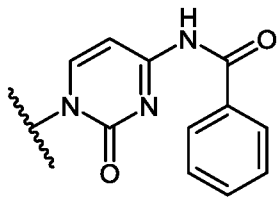
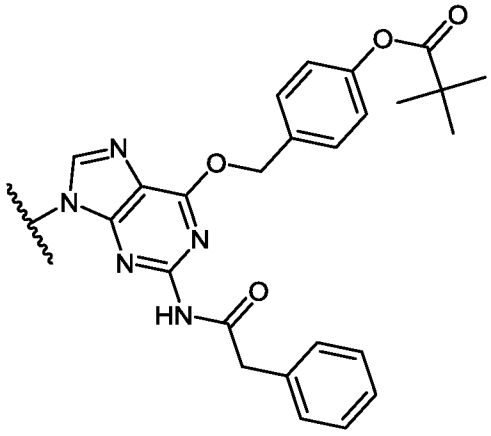
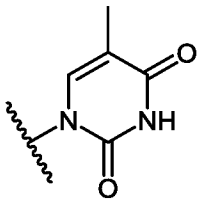
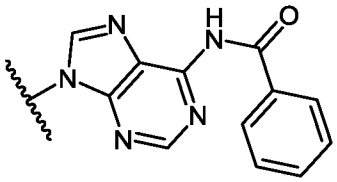
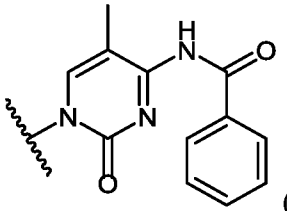
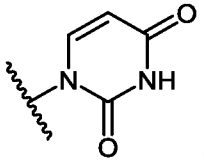
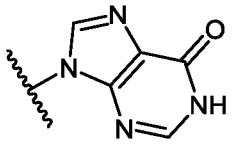
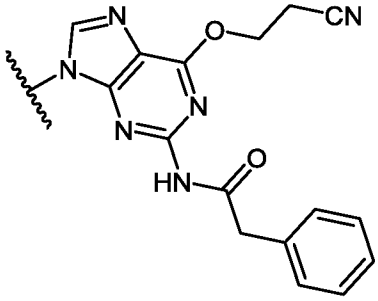

(PC),

(DPG),

(T),

(PA),

(P5mC),

(U),

(I), and

(PG);

wherein the process comprises contacting a compound of Formula (A9):



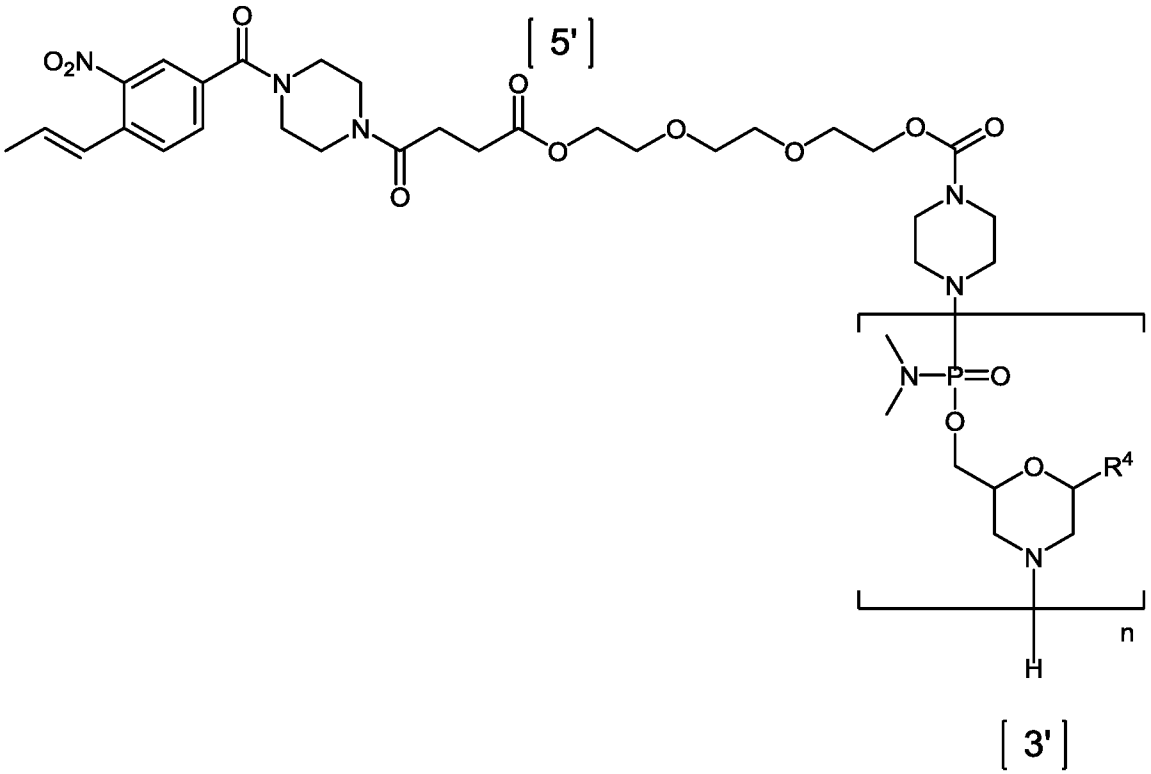
(A9);

wherein n is an integer from 10 to 40, R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is, independently for each occurrence, selected from the group consisting of:


(PC),

(DPG),

(T),

(PA),

(P5mC),

(U),

(I), and

(PG); and

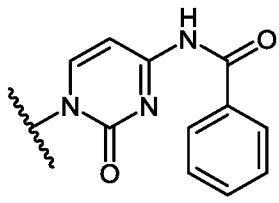
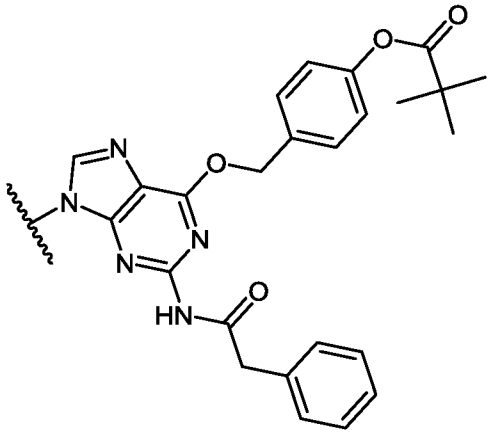
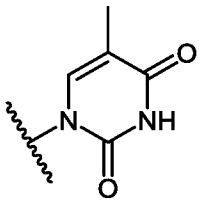
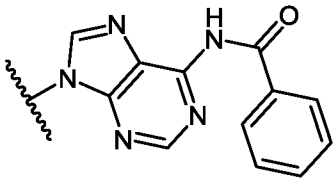
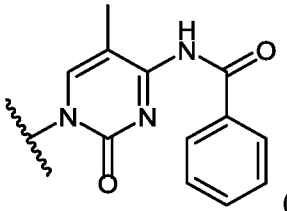
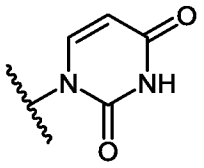
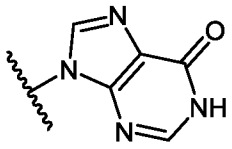
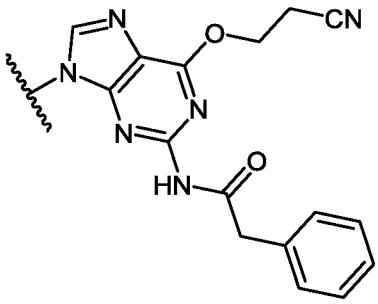
with a deblocking agent to form a compound of Formula (A10).

In still another aspect, provided herein is a process for preparing a compound of Formula (A11):

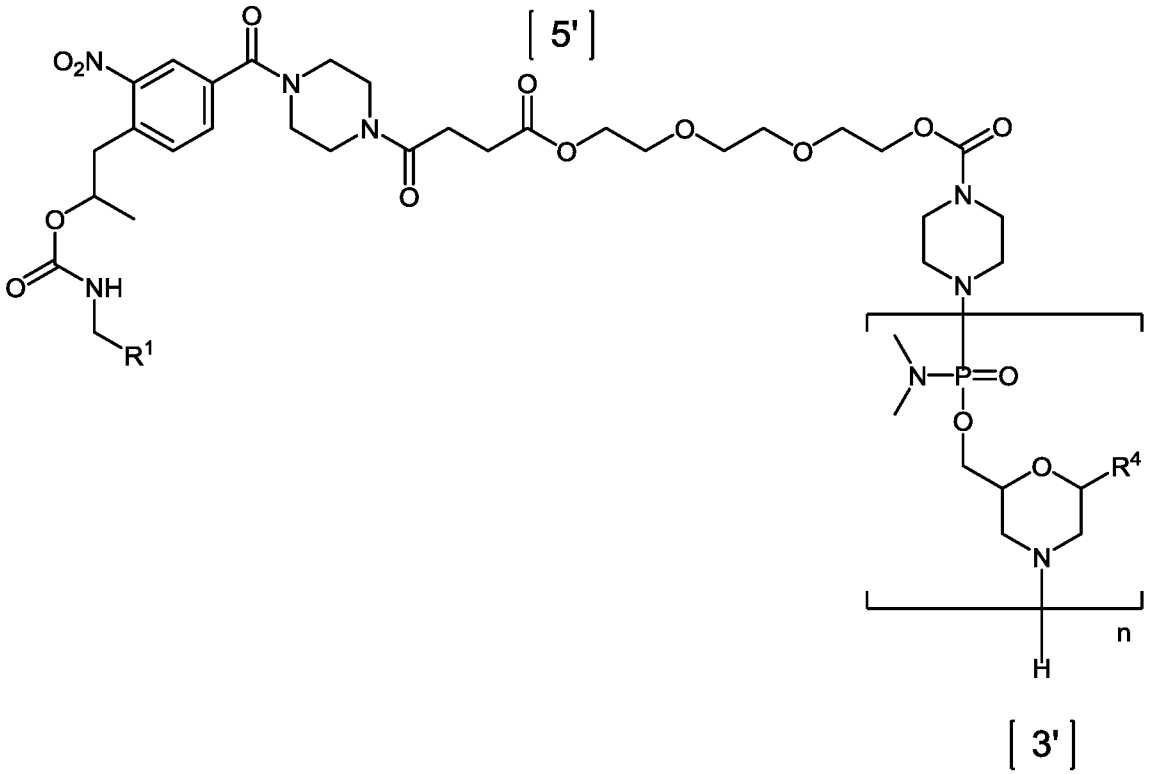


(A11);

wherein n is an integer from 10 to 40, and R^4 is, for each occurrence independently selected from the group consisting of:

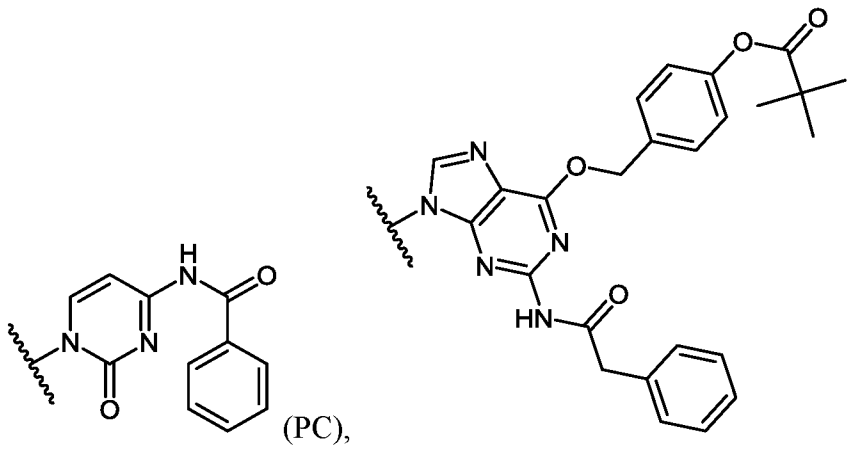

(PC),

(DPG),

(T),

(PA),

(P5mC),

(U),

(I), and

(PG); and

wherein the process comprises contacting the compound of Formula (A10):

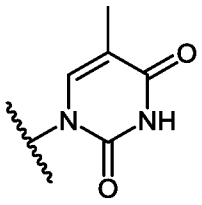


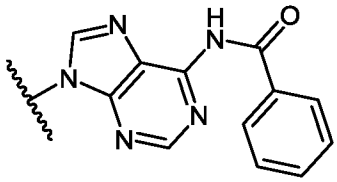
(A10);

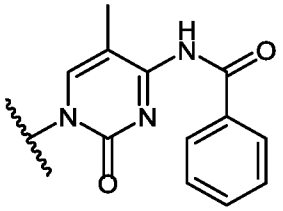
wherein n is an integer from 10 to 40, R^1 is a support-medium, and R^4 is, independently for each occurrence, selected from the group consisting of:

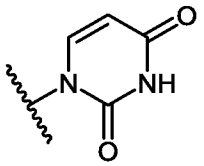

(PC),

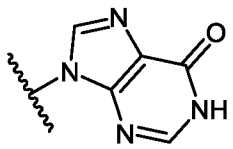
(DPG),

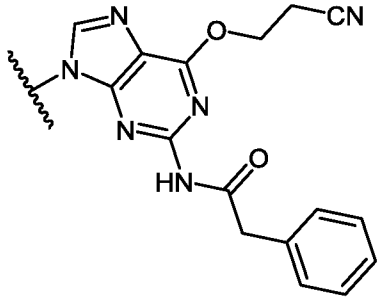

(T),


(PA),


(P5mC),

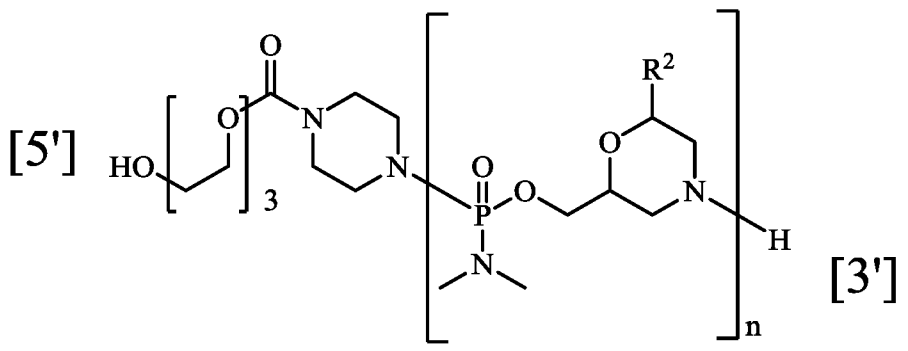

(U),


(I), and


(PG);

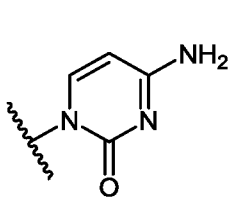
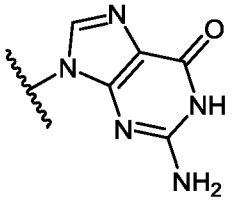
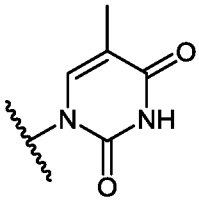
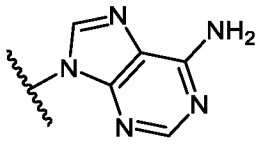
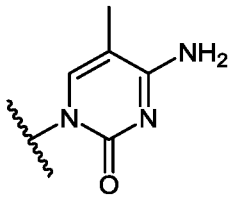
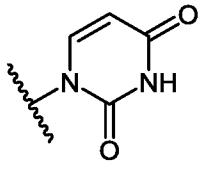
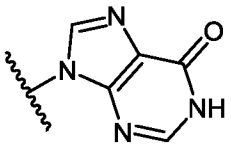
with a cleaving agent to form a compound of Formula (A11).

In another aspect, provided herein is a process for preparing an oligomeric compound of Formula (A):

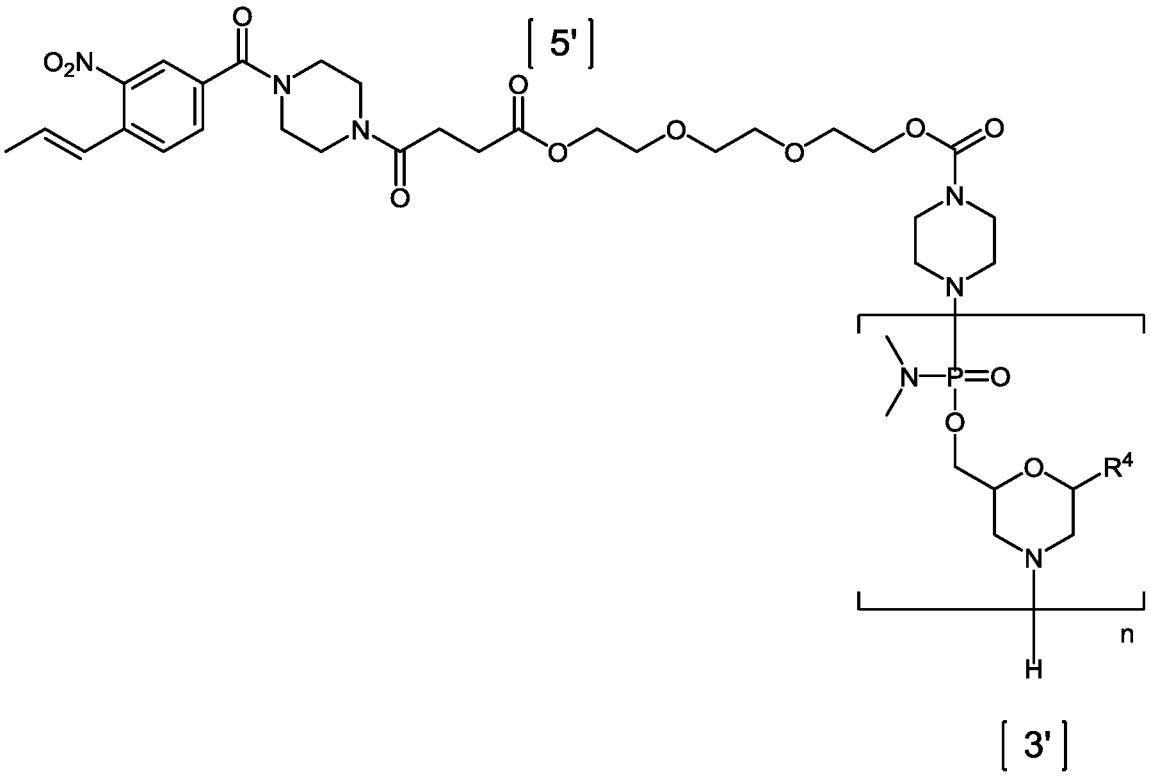


(A);

wherein n is an integer from 10 to 40, and each R^2 is, independently for each occurrence, selected from the group consisting of:

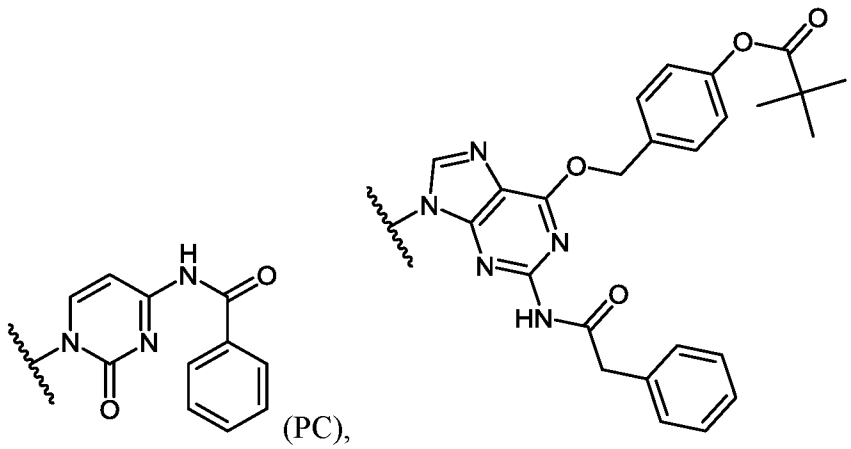

(C),

(G),

(T),

(A),

(5mC),

(U), and

(I);

wherein the process comprises contacting a compound of Formula (A11):

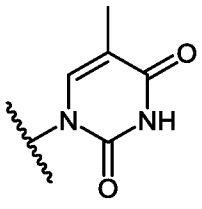


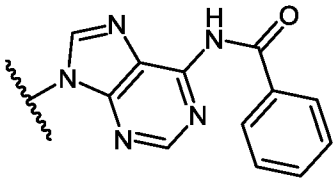
(A11);

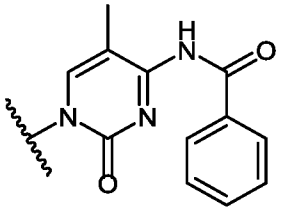
wherein n is an integer from 10 to 40, and R^4 is, independently for each occurrence, selected from the group consisting of:

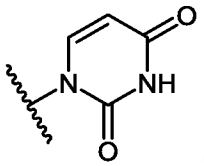

(PC),

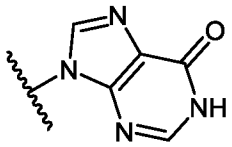
(DPG),

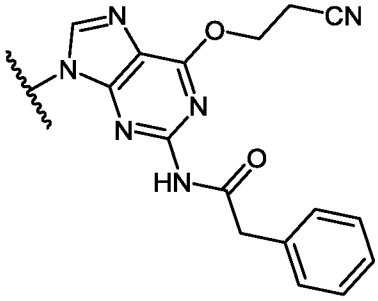

(T),


(PA),


(P5mC),

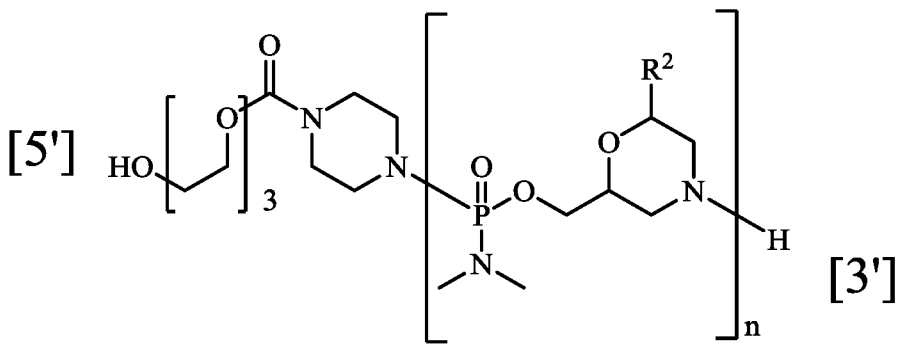

(U),


(I), and


(PG); and

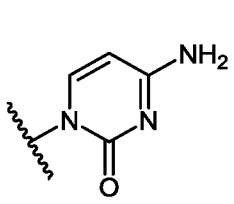
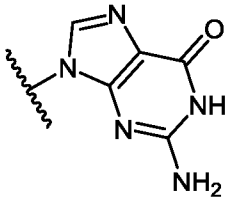
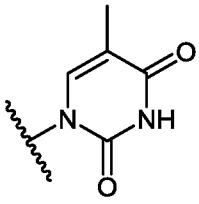
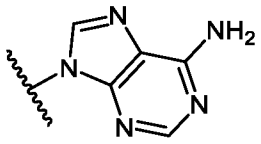
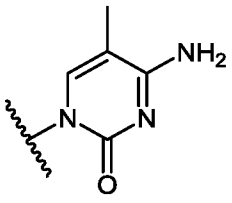
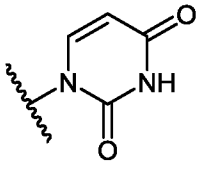
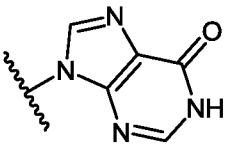
with a deprotecting agent to form the oligomeric compound of Formula (A).

In another aspect, provided herein is a process for preparing an oligomeric compound of Formula (A):


[5'] [3']

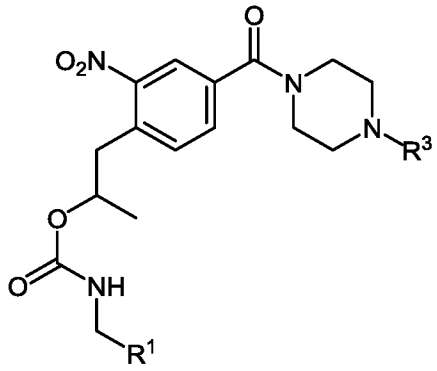
(A);

wherein n is an integer from 10 to 40, and each R^2 is, independently for each occurrence, selected from the group consisting of:


(C),

(G),

(T),

(A),

(5mC),

(U), and

(I),

wherein the process comprises the sequential steps of:

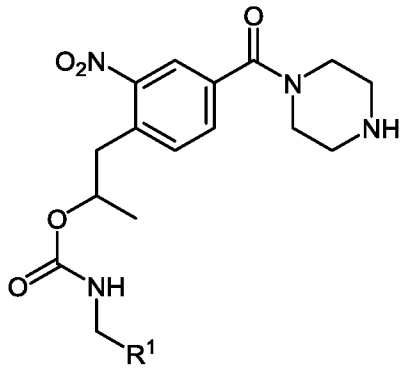
(a) contacting a compound of Formula (A1):



(A1);

wherein R^1 is a support-medium and R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

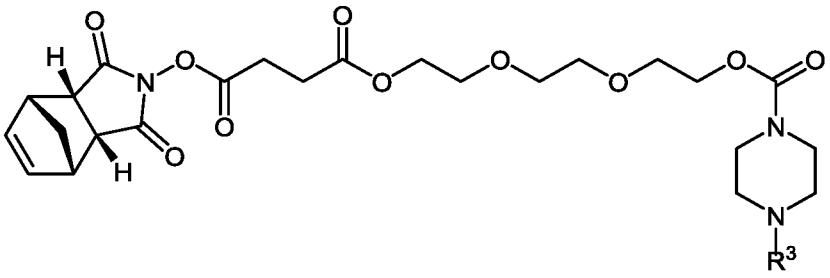
with a deblocking agent to form the compound of Formula (II):



(II);

wherein R^1 is a support-medium;

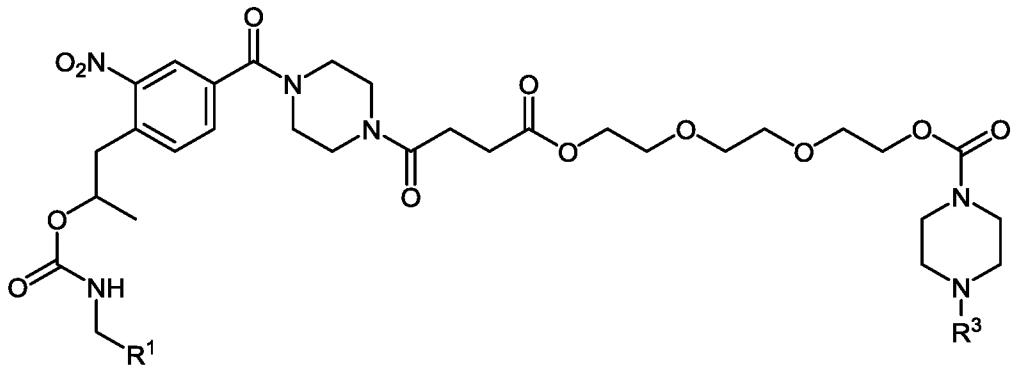
(b) contacting the compound of Formula (II) with a compound of Formula (A2):



(A2);

wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

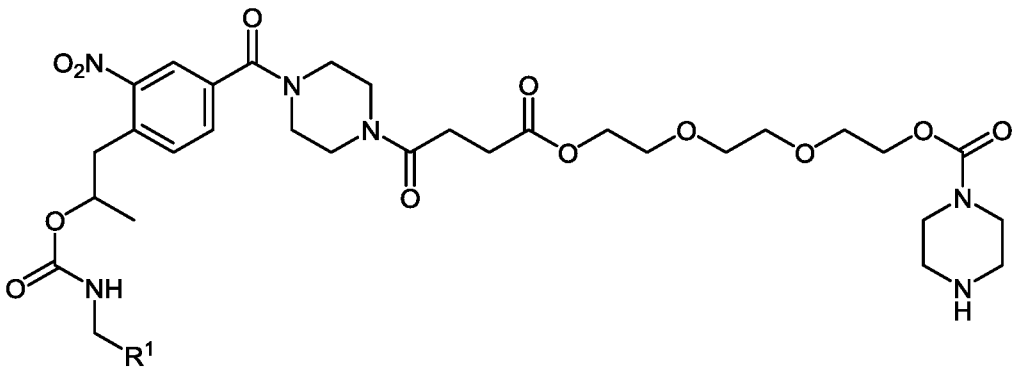
to form a compound of Formula (A3):



(A3);

wherein R^1 is a support-medium, and R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

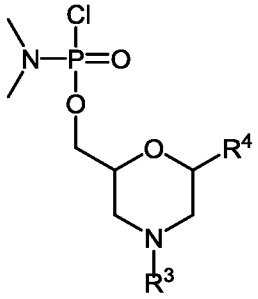
(c) contacting the compound of Formula (A3) with a deblocking agent to form a compound of Formula (IV):



(IV);

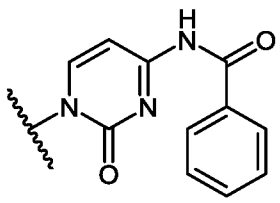
wherein R^1 is a support-medium;

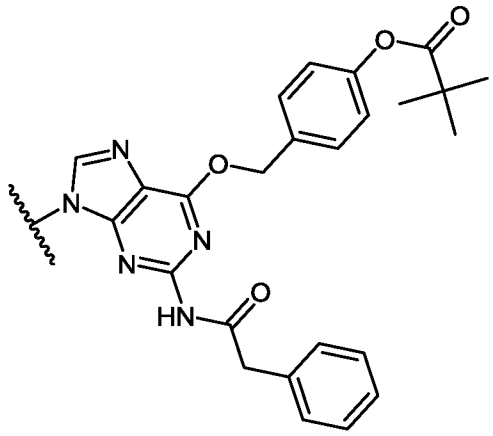
(d) contacting the compound of Formula (IV) with a compound of Formula (A4):

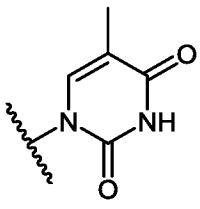


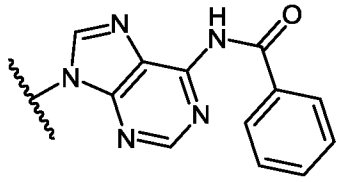
(A4);

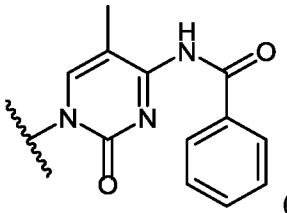
wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is selected from the group consisting of:

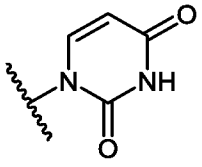
 (PC),

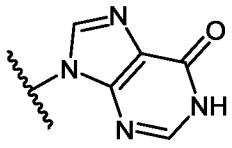
 (DPG),

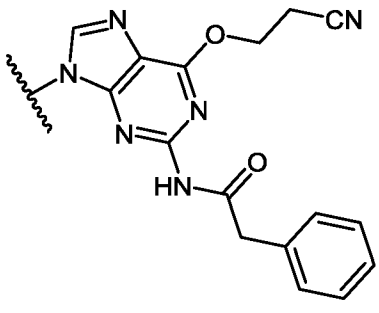
 (T),

 (PA),

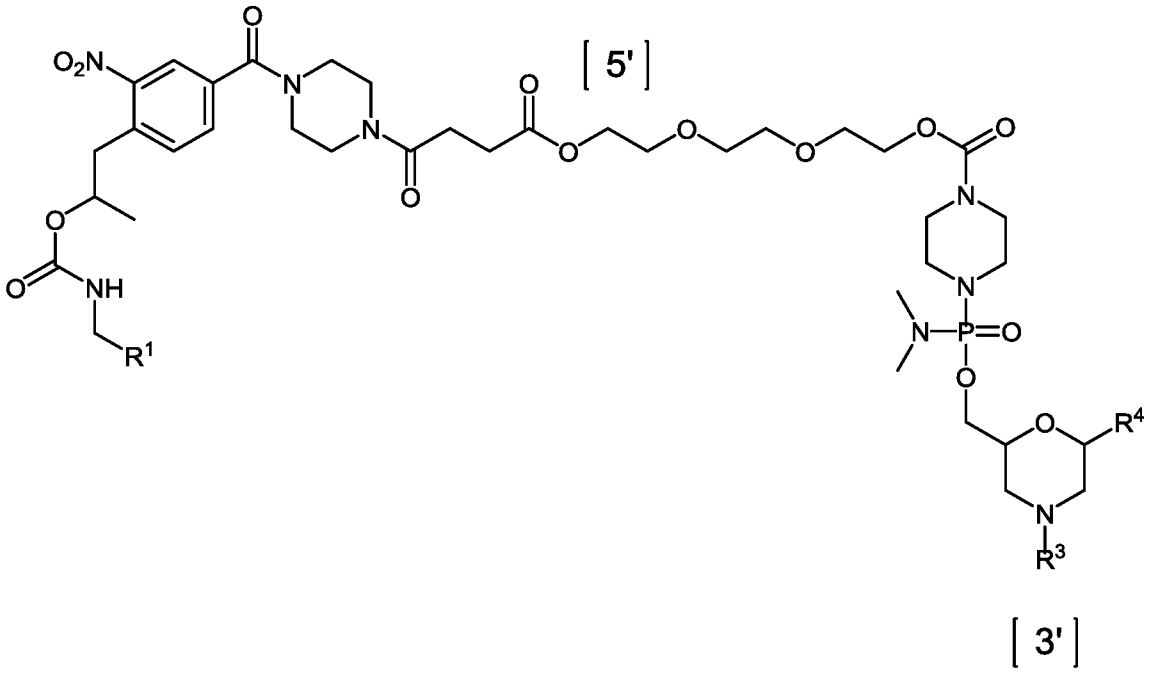
 (P5mC),

 (U),

 (I), and

 (PG),

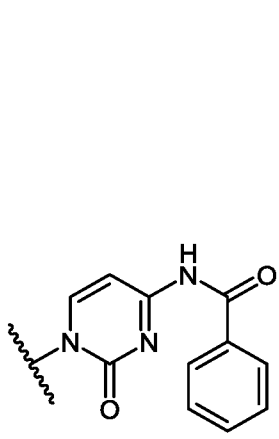
to form a compound of Formula (A5):

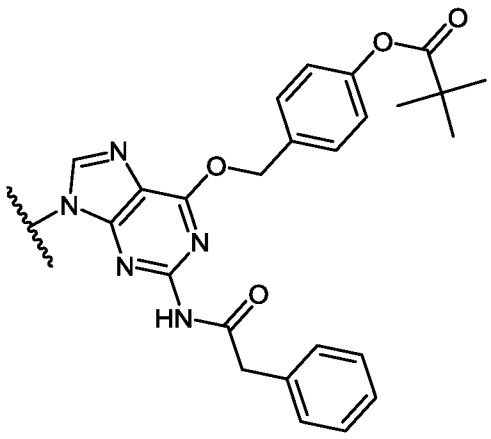


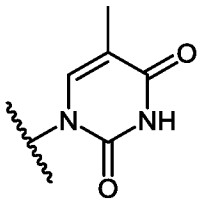
(A5);

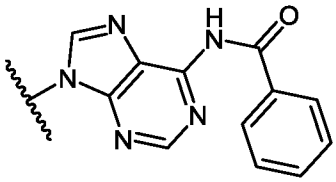
wherein R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

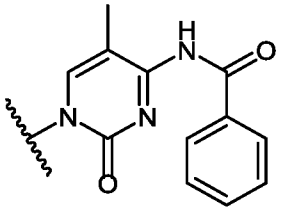
R^4 is selected from the group consisting of:

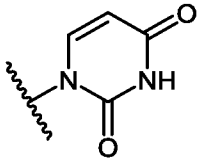

(PC),

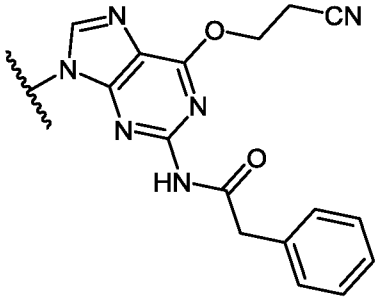

(DPG),

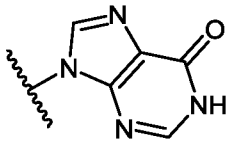

(T),


(PA),


(P5mC),


(U),

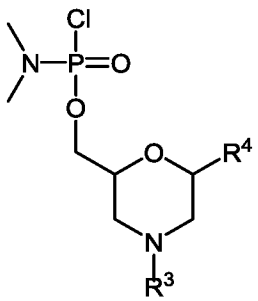

(PG);


(I), and

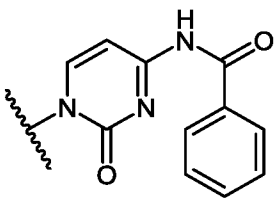
(e) performing n-1 iterations of the sequential steps of:

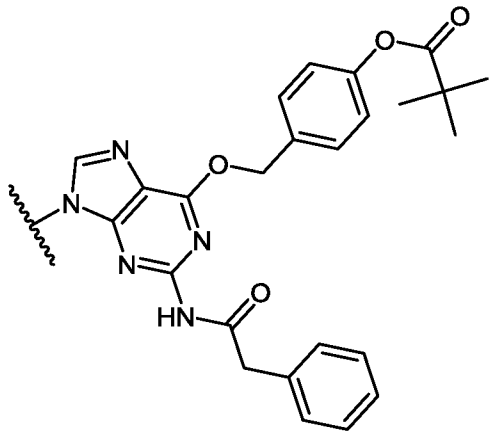
(e1) contacting the product formed by the immediately prior step with a deblocking agent; and

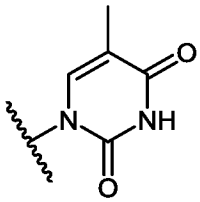
(e2) contacting the compound formed by the immediately prior step with a compound of Formula (A8):

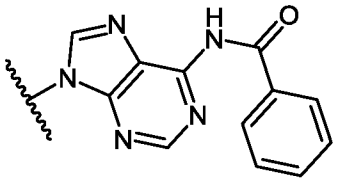

(A8);

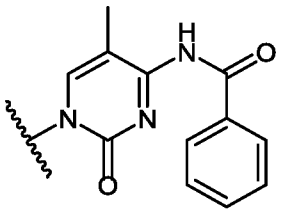
wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is, independently for each compound of Formula (A8), selected from the group consisting of:

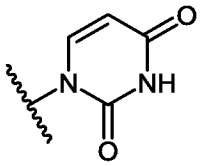

(PC),

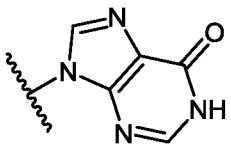

(DPG),

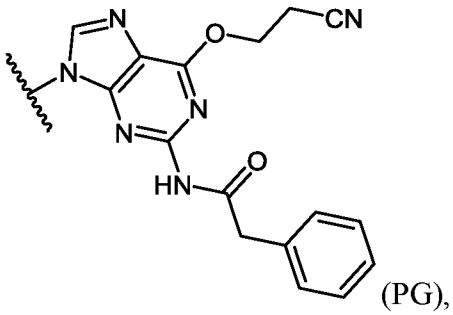

(T),


(PA),

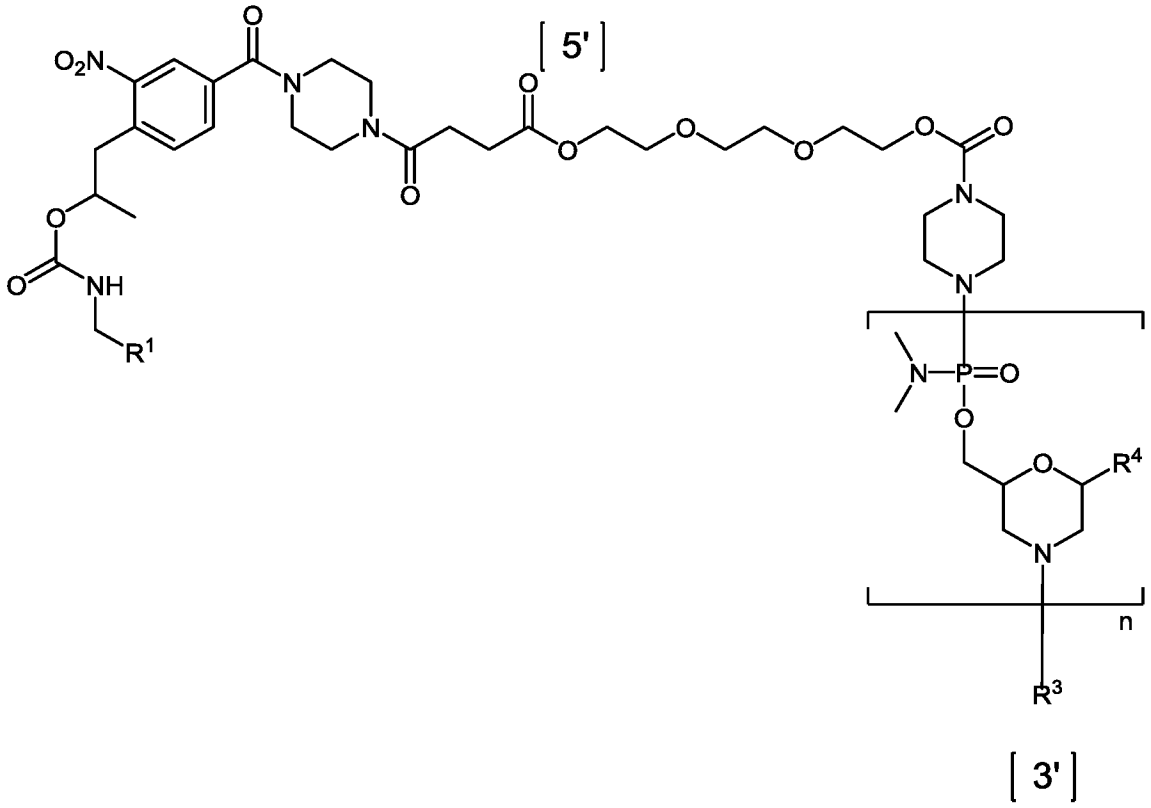

(P5mC),


(U),


(I), and

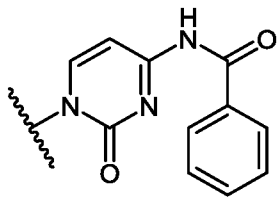
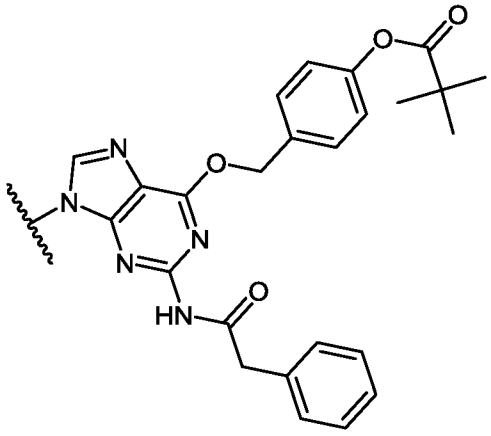
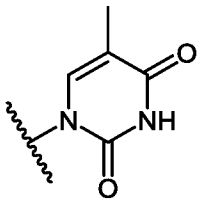
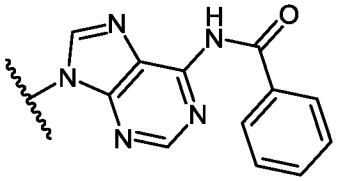
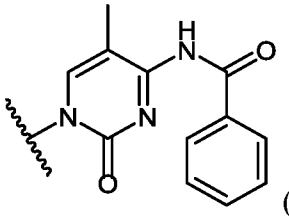
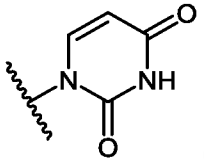
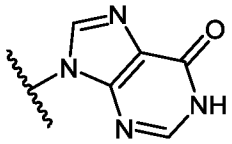
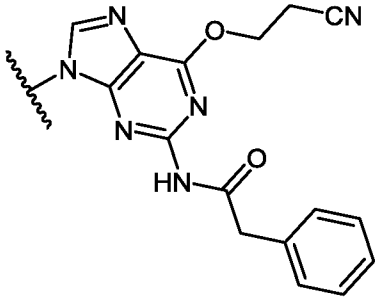

(PG),

to form a compound of Formula (A9):

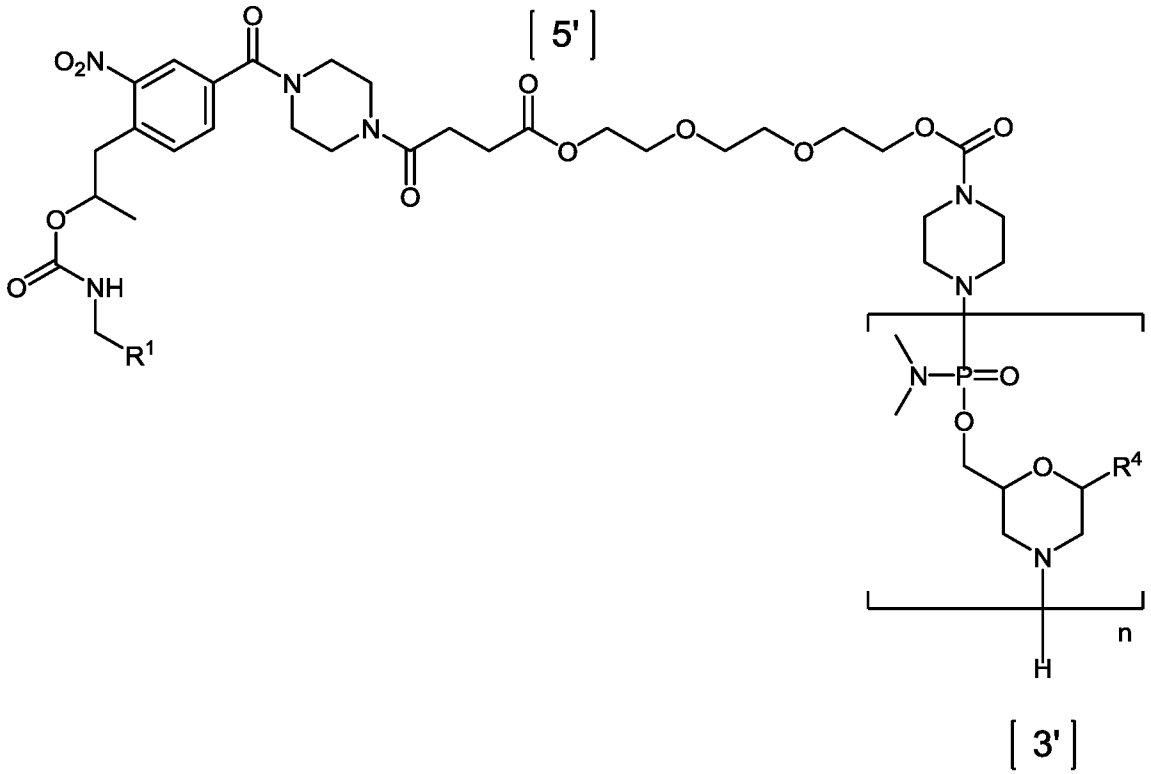


(A9);

wherein n is an integer from 10 to 40, R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is, independently for each occurrence, selected from the group consisting of:

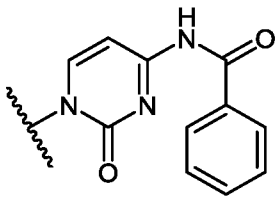

(PC),

(DPG),

(T),

(PA),

(P5mC),

(U),

(I), and

(PG); and

(f) contacting the compound of Formula (A9) with a deblocking agent to form a compound of Formula (A10):

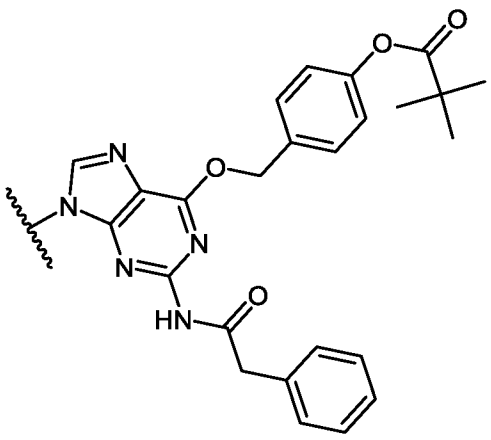


(A10);

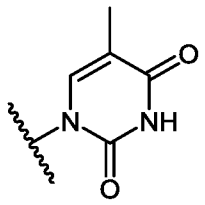
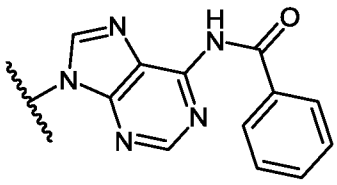
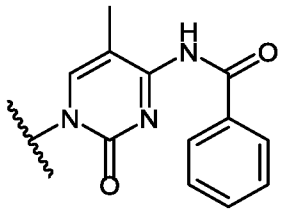
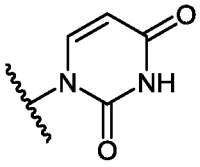
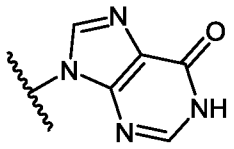
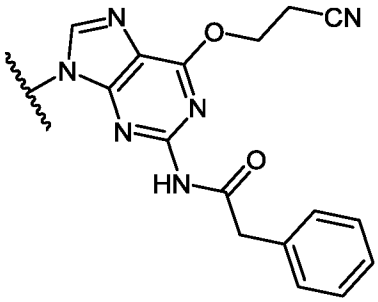
wherein n is an integer from 10 to 40, R^1 is a support-medium, and R^4 is, independently for each occurrence, selected from the group consisting of:



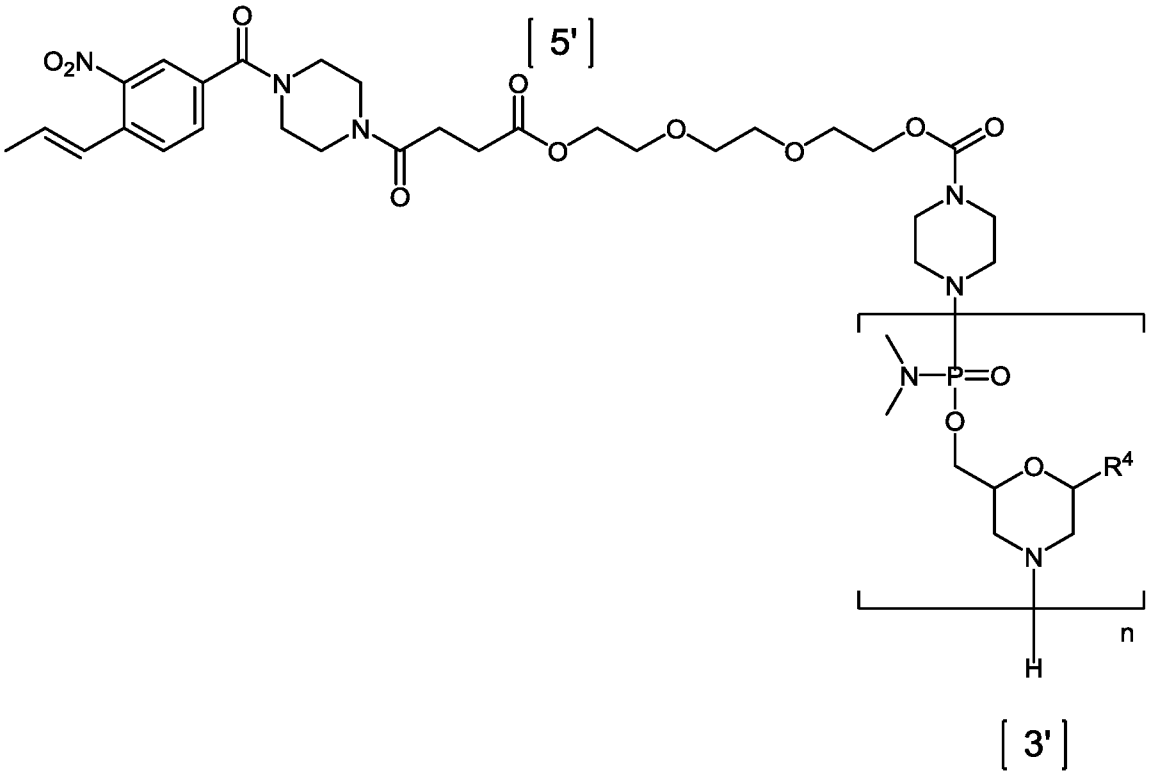
(PC),



(DPG),

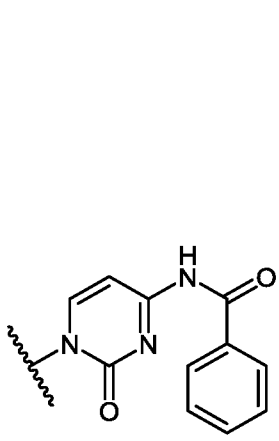
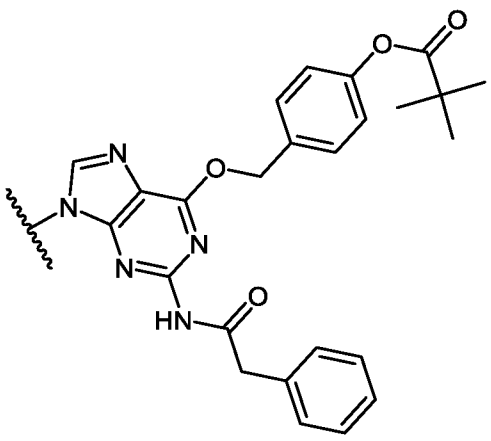
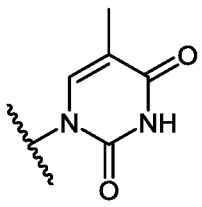
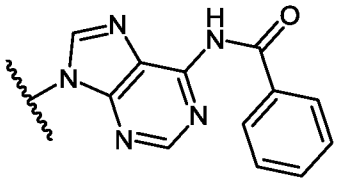
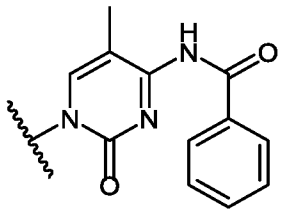
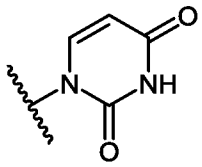
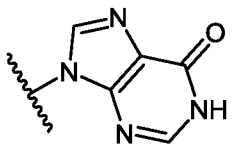
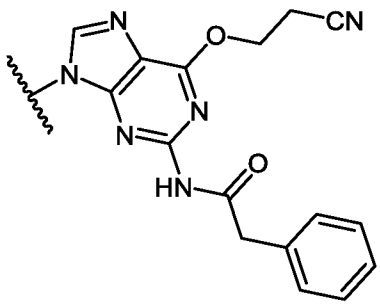

(T),

(PA),

(P5mC),

(U),

(I), and

(PG);

(g) contacting the compound of Formula (A10) with a cleaving agent to form a compound of Formula (A11):



(A11);

wherein n is an integer from 10 to 40, and R^4 is, independently for each occurrence, selected from the group consisting of:


(PC),

(DPG),

(T),

(PA),

(P5mC),

(U),

(I), and

(PG); and

(h) contacting the compound of Formula (A11) with a deprotecting agent to form the oligomeric compound of Formula (A).

In one embodiment, step (d) or step (e2) further comprises contacting the compound of Formula (IV) or the compound formed by the immediately prior step, respectively, with a capping agent.

In another embodiment, each step is performed in the presence of at least one solvent.

In yet another embodiment, the deblocking agent used in each step is a solution comprising a halogenated acid.

In still another embodiment, the deblocking agent used in each step is cyanoacetic acid.

In another embodiment, the halogenated acid is selected from the group consisting of chloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, and trifluoroacetic acid.

In another embodiment, the halogenated acid is trifluoroacetic acid.

In yet another embodiment, at least one of steps (a), (c), (e1), and (f) further comprise the step of contacting the deblocked compound of each step with a neutralization agent.

In still another embodiment, each of steps (a), (c), (e1), and (f) further comprise the step of contacting the deblocked compound of each step with a neutralization agent.

In another embodiment, the neutralization agent is in a solution comprising dichloromethane and isopropyl alcohol.

In yet another embodiment, the neutralization agent is a monoalkyl, dialkyl, or trialkyl amine.

In still another embodiment, the neutralization agent is N,N-diisopropylethylamine.

In another embodiment, the deblocking agent used in each step is a solution comprising 4-cyanopyridine, dichloromethane, trifluoroacetic acid, trifluoroethanol, and water.

In yet another embodiment, the capping agent is in a solution comprising ethylmorpholine and methylpyrrolidinone.

In still another embodiment, the capping agent is an acid anhydride.

In another embodiment, the acid anhydride is benzoic anhydride.

In another embodiment, the compounds of Formula (A4) and Formula (A8) are each, independently, in a solution comprising ethylmorpholine and dimethylimidazolidinone.

In another embodiment, the cleavage agent comprises dithiothreitol and 1,8-diazabicyclo[5.4.0]undec-7-ene.

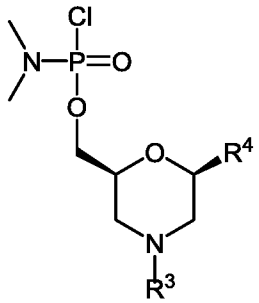
In still another embodiment, the cleavage agent is in a solution comprising N-methyl-2-pyrrolidone.

In yet another embodiment, the deprotecting agent comprises NH_3.

In still another embodiment, the deprotecting agent is in an aqueous solution.

In yet another embodiment, the support-medium comprises polystyrene with 1% crosslinked divinylbenzene.

In another embodiment, the compound of Formula (A4) is of Formula (A4a):

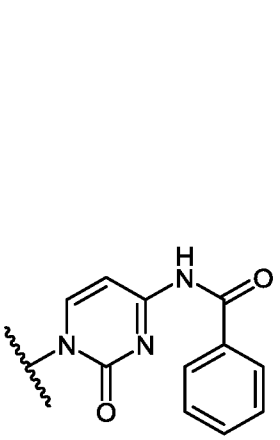


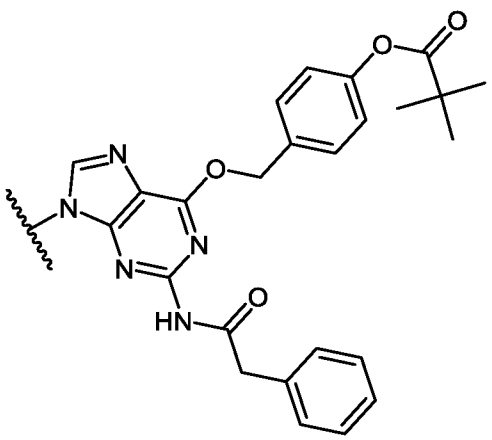
(A4a);

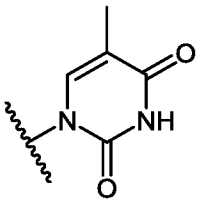
wherein:

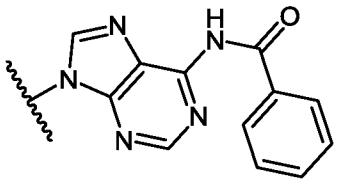
R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

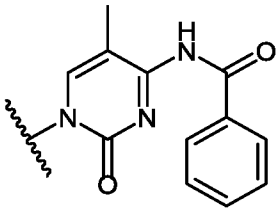
R^4 is selected from:

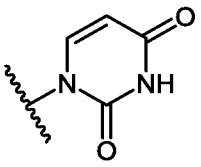

(PC),

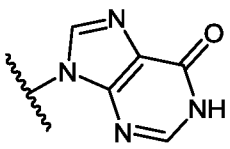

(DPG),

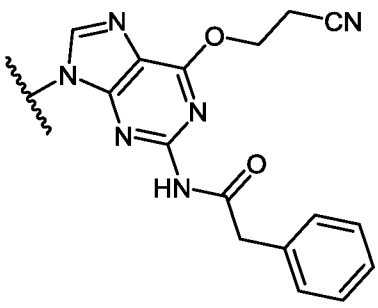

(T),


(PA),

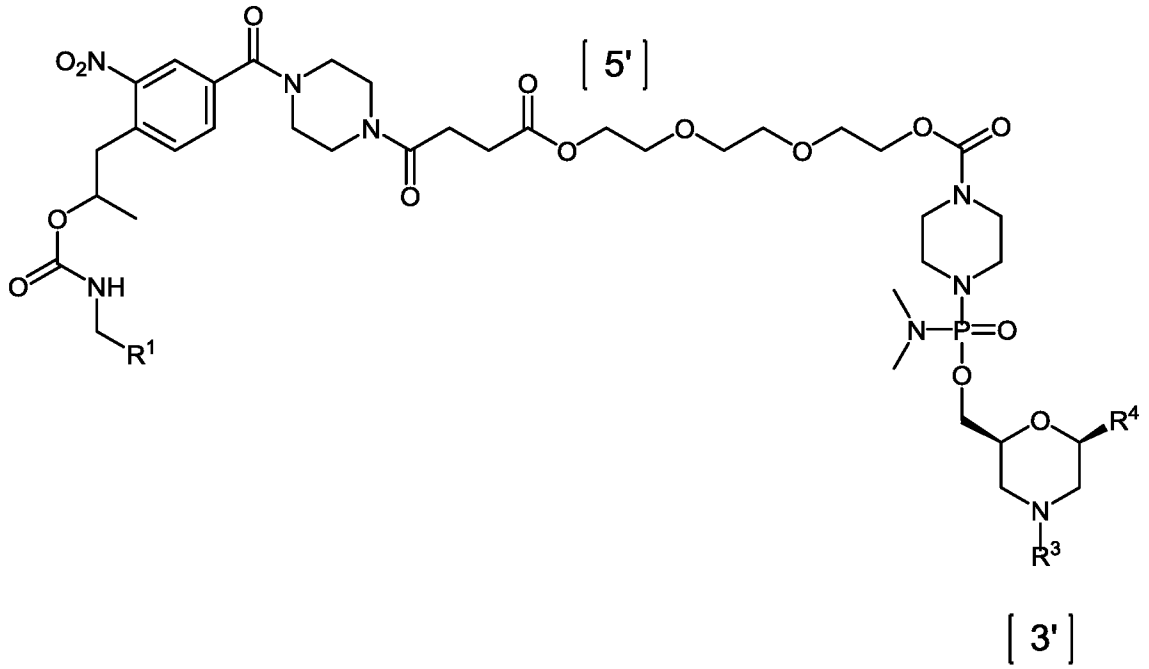

(P5mC),


(U),


(I), and


(PG).

In another embodiment, the compound of Formula (A5) is of Formula (A5a):



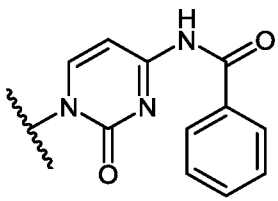
(A5a);

wherein:

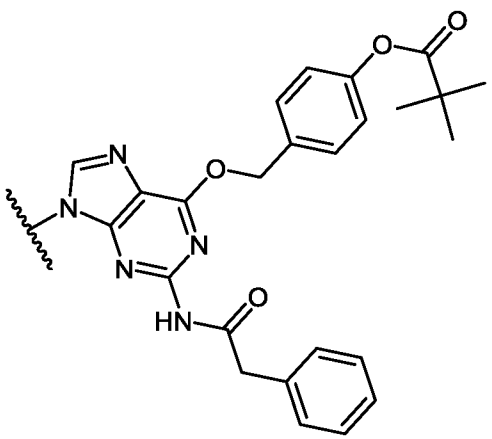
R^1 is a support-medium,

R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

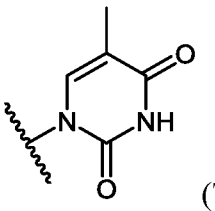
R^4 is selected from:



(PC),



(DPG),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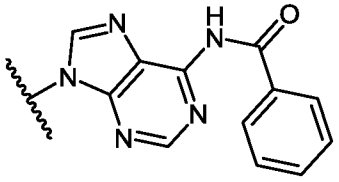
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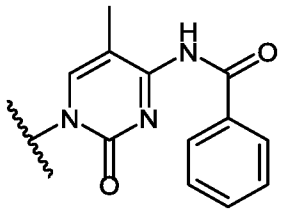
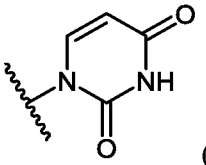

(P5mC),

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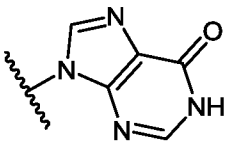
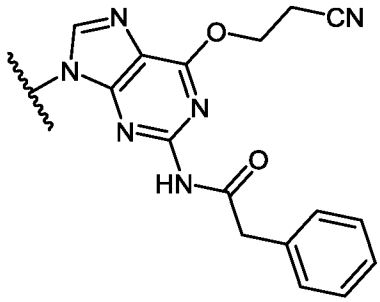
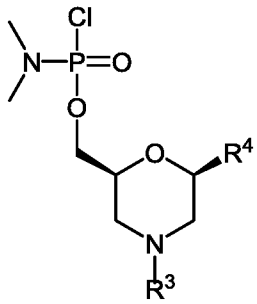

(I), and

(PG).

In yet another embodiment, the compound of Formula (A8) is of Formula (A8a):

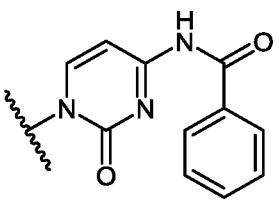


(A8a);

wherein:

R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

R^4 is, independently at each occurrence of the compound of Formula (A8a), selected from the group consisting of: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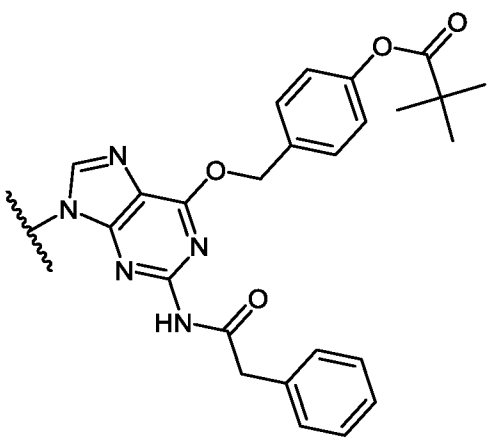
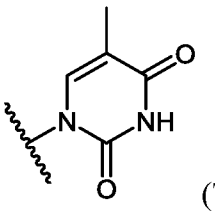
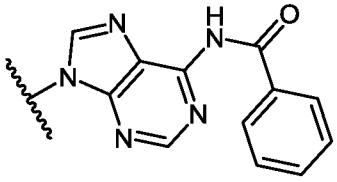
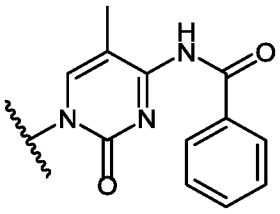
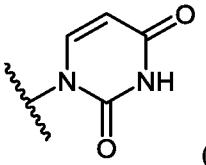
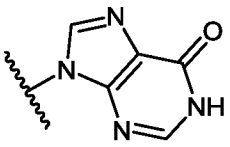
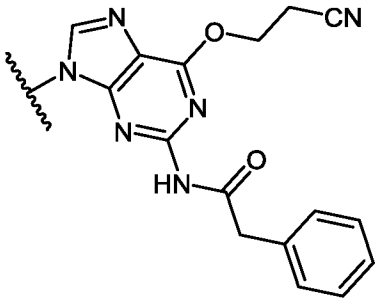
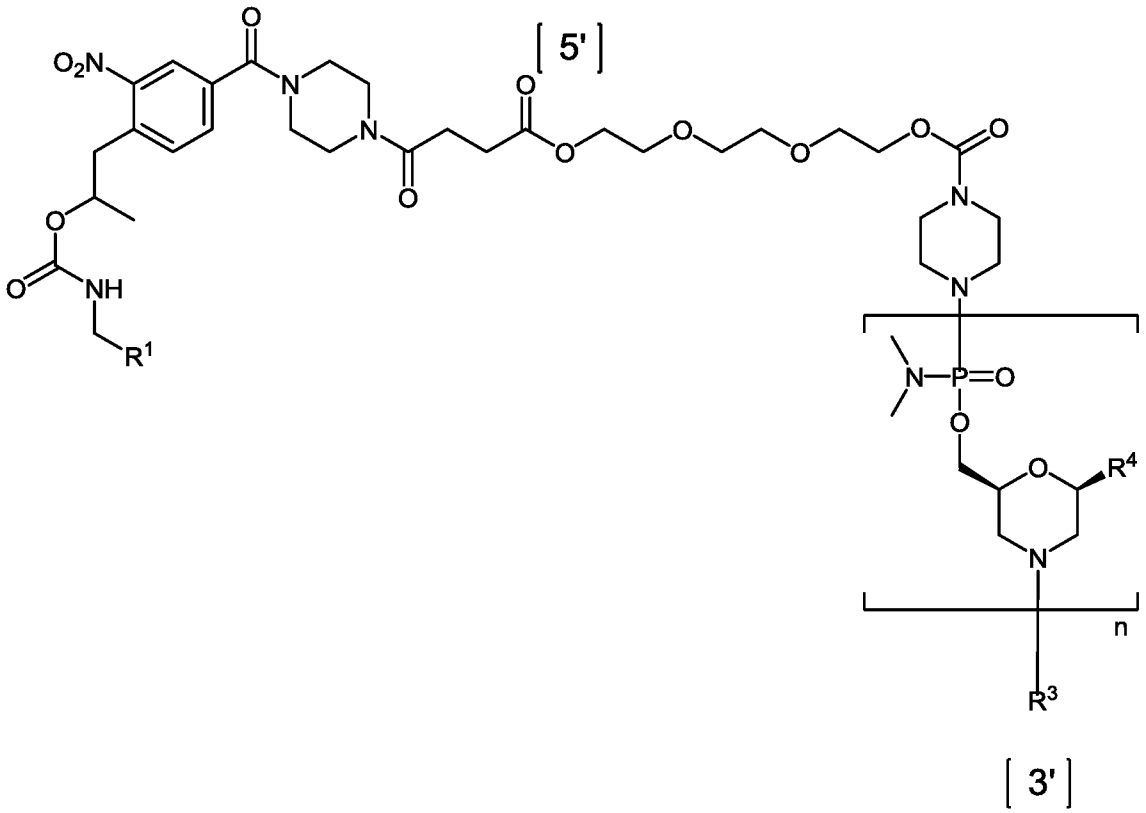

(DPG),


(T),

(PA),

(P5mC),

(U),

(I), and

(PG).

In still another embodiment, the compound of formula (A9) is of Formula (A9a):



(A9a);

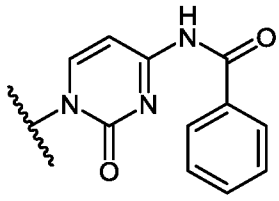
wherein:

n is an integer from 10 to 40,

R^1 is a support-medium,

R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

R^4 is, independently for each occurrence, selected from the group consisting of: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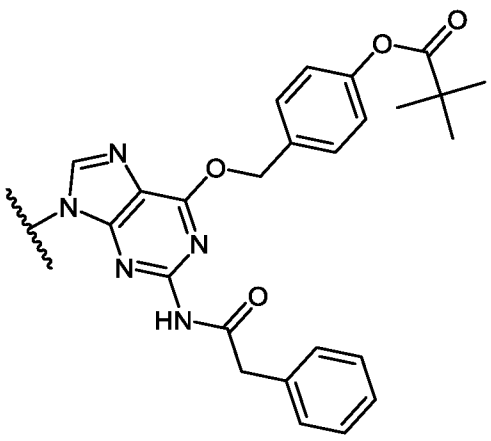
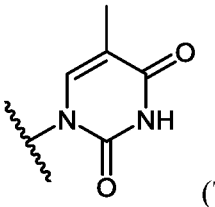
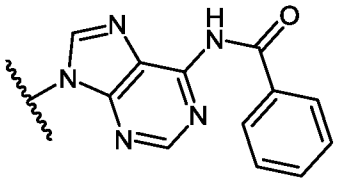
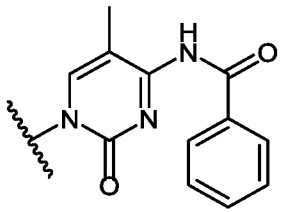
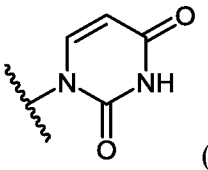
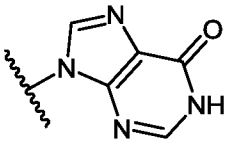
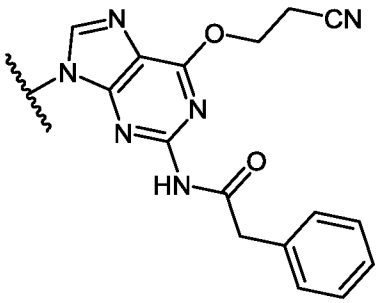
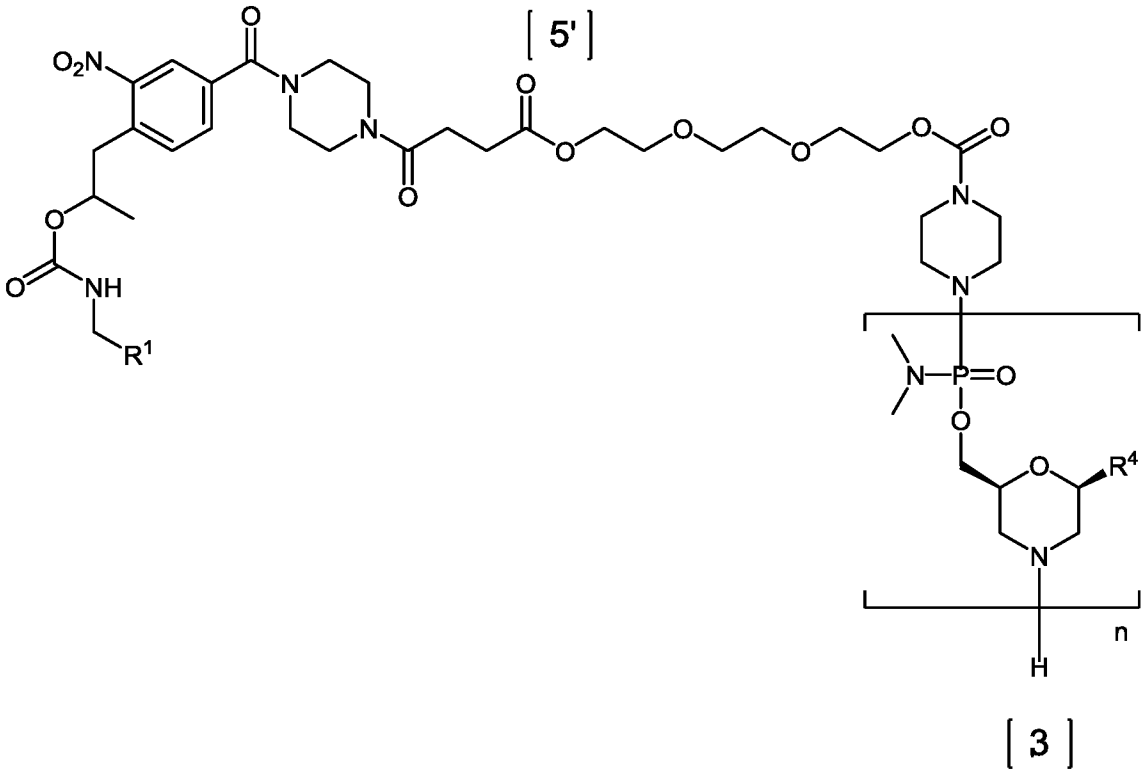

(DPG),

(T),

(PA),

(P5mC),

(U),

(I), and

(PG).

In another embodiment, the compound of Formula (A10) is of Formula (A10a):



[5']

[3]

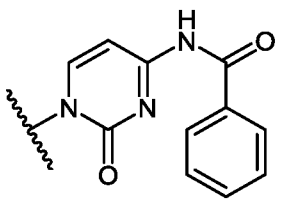
(A10a);

wherein:

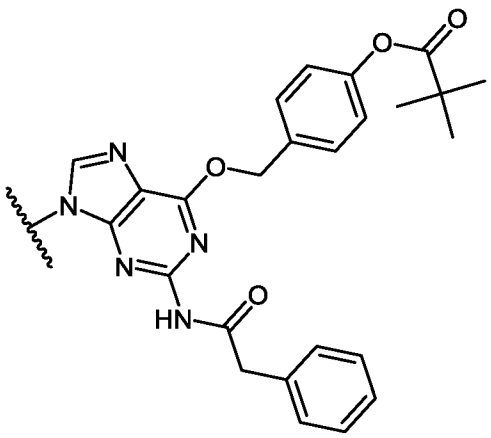
n is an integer from 10 to 40,

R^1 is a support-medium, and

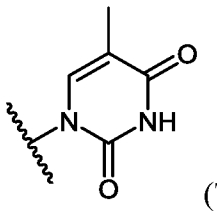
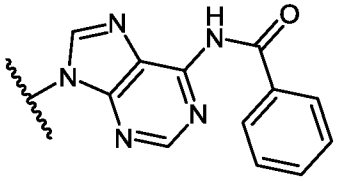
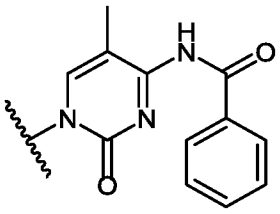
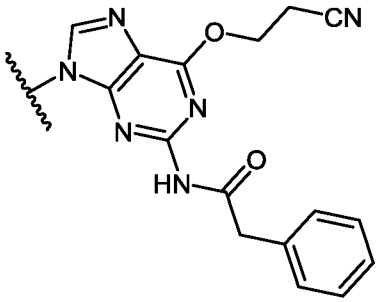
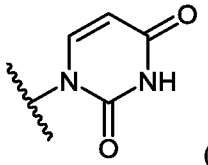
R^4 is, independently for each occurrence, selected from the group consisting of:



(PC),



(DPG),


(T),

(PA),

(P5mC),


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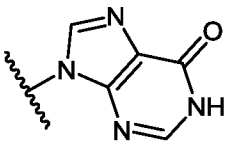
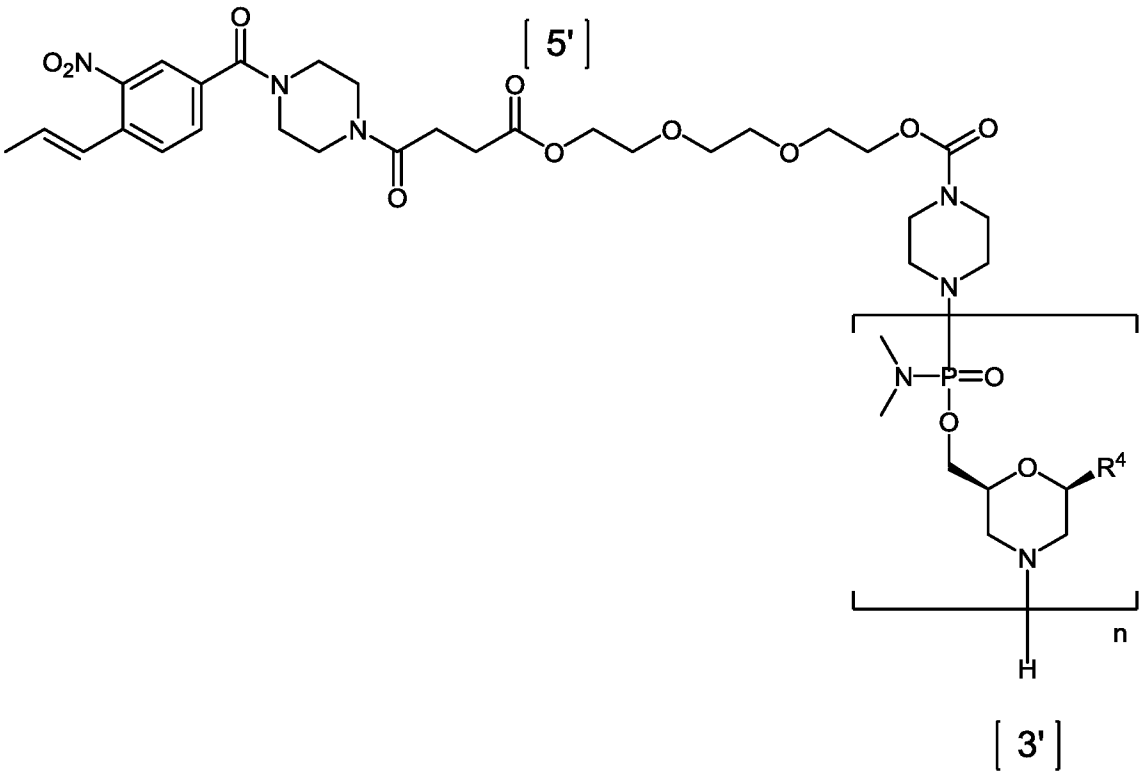

(I), and
(PG).

In another embodiment, the compound of Formula (A11) is of Formula (A11a):

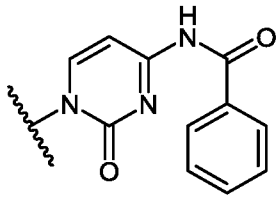


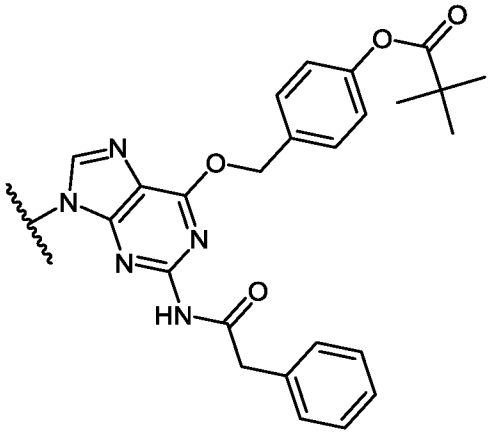
(A11a);

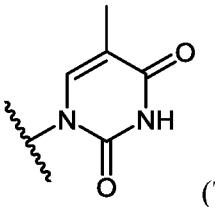
wherein:

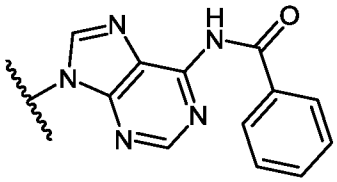
n is an integer from 10 to 40, and

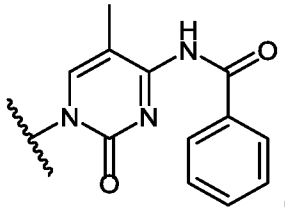
R^4 is, independently for each occurrence, selected from the group consisting of:

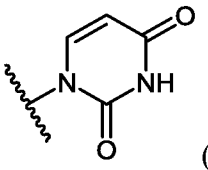

(PC),

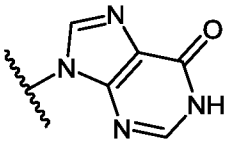

(DPG),

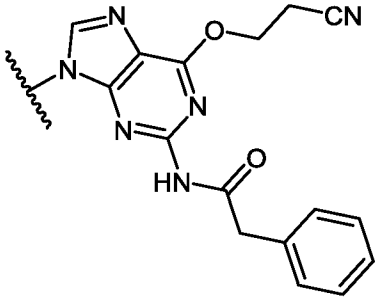

(T),


(PA),


(P5mC),


(U),

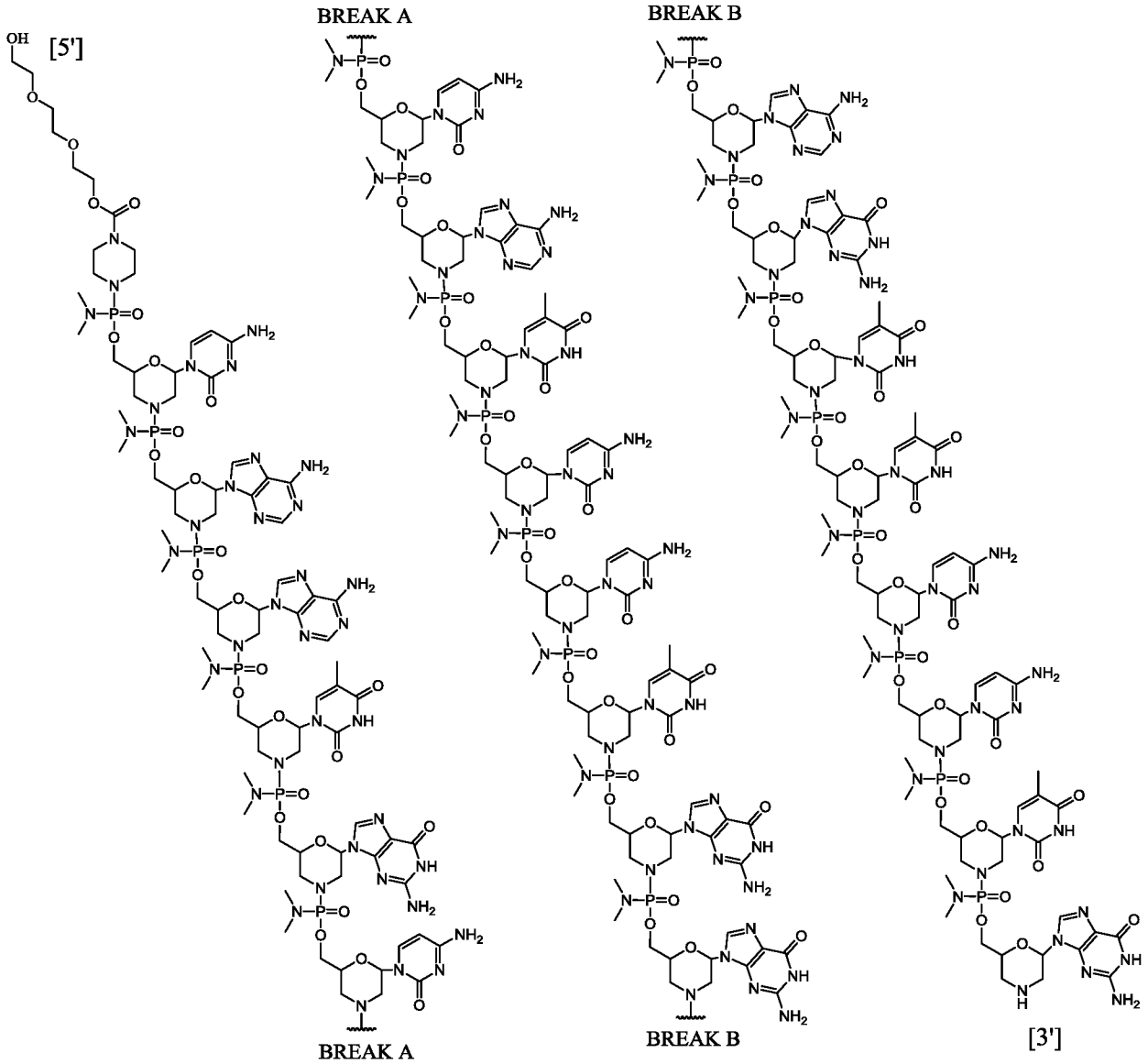

(I), and


(PG).

In an embodiment of the oligomeric compound of Formula (A), n is 22, and R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	C	11	C	21	T
2	A	12	T	22	G
3	A	13	G		
4	T	14	G		
5	G	15	A		
6	C	16	G		
7	C	17	T		
8	A	18	T		
9	T	19	C		
10	C	20	C		

wherein the oligomeric compound of Formula (A) is a compound of Formula (C):

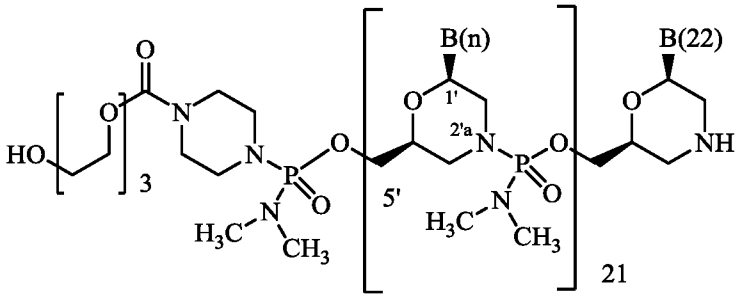


(C)

or a pharmaceutically acceptable salt thereof.

"Casimersen," formerly known by its code name "SPR-4045," is a PMO having the base sequence 5'-CAATGCCATCCTGGAGTTCCTG-3' (SEQ ID NO:1). Casimersen is registered under CAS Registry Number 1422958-19-7. Chemical names include: all-P-ambo-[P,2',3'-trideoxy-P-(dimethylamino)-2',3'-imino-2',3'-seco](2'a→5')(C-A-A-T-G-C-C-A-T-C-C-T-G-G-A-G-T-T-C-C-T-G) 5'-[4-({2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}carbonyl)-N,N-dimethylpiperazine-1-phosphonamidate].

Casimersen has the following chemical structure:

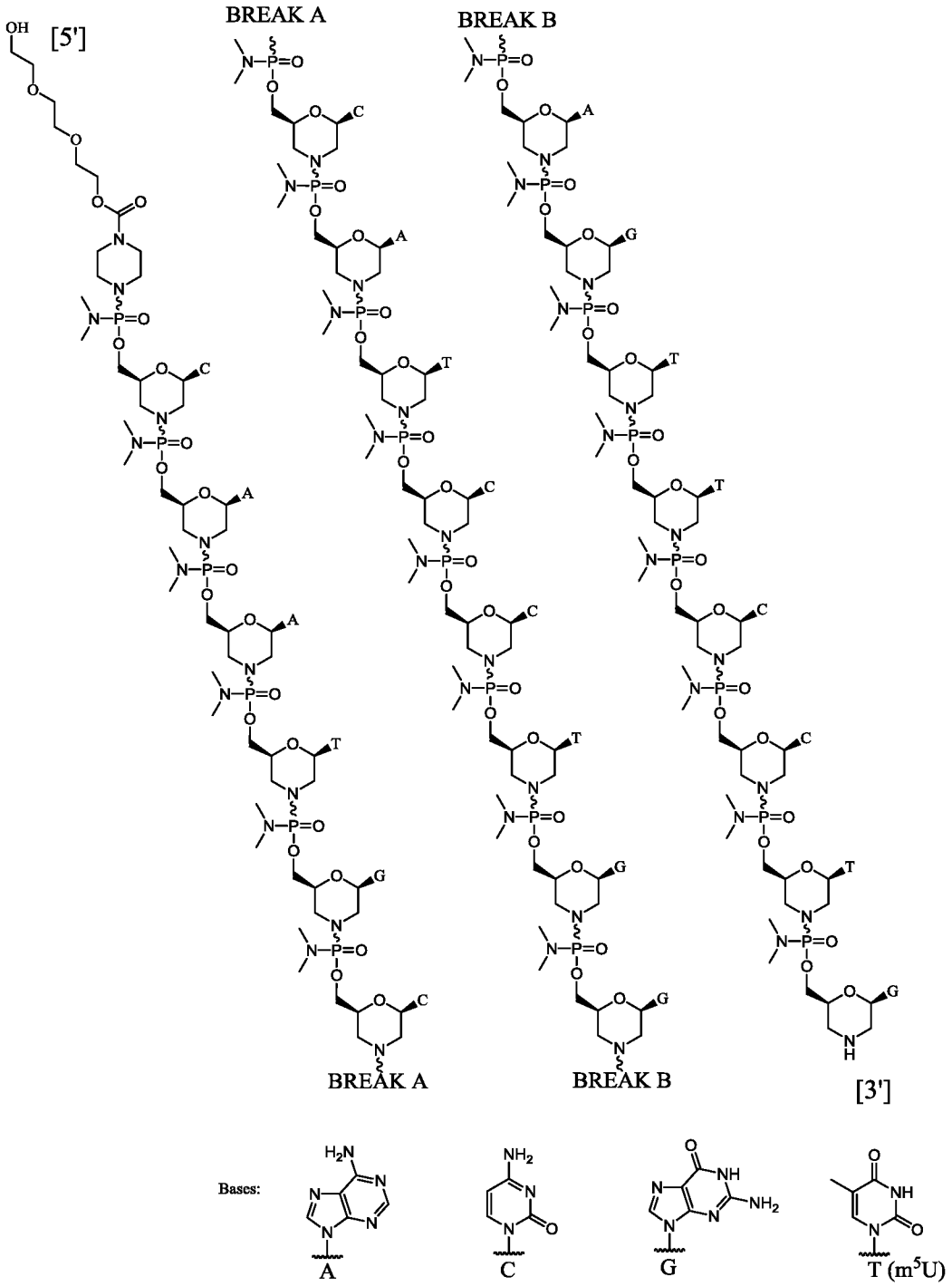


n = 1 - 21

B(1-22):

C-A-A-T-G-C-C-A-T-C-C-T-G-G-A-G-T-T-C-C-T-G

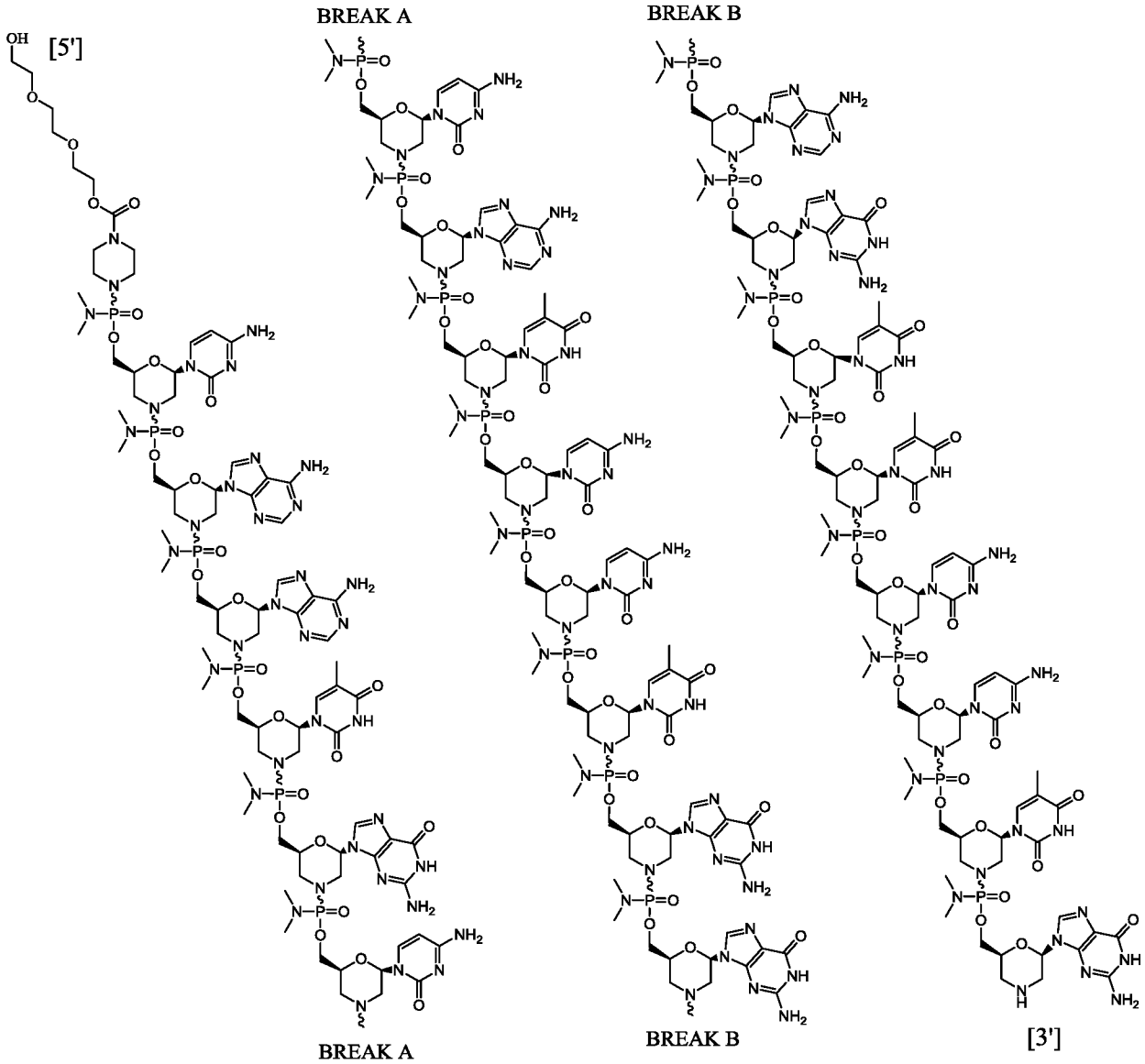
and also is represented by the following chemical structure:



The sequence of bases from the 5' end to the 3' end is:

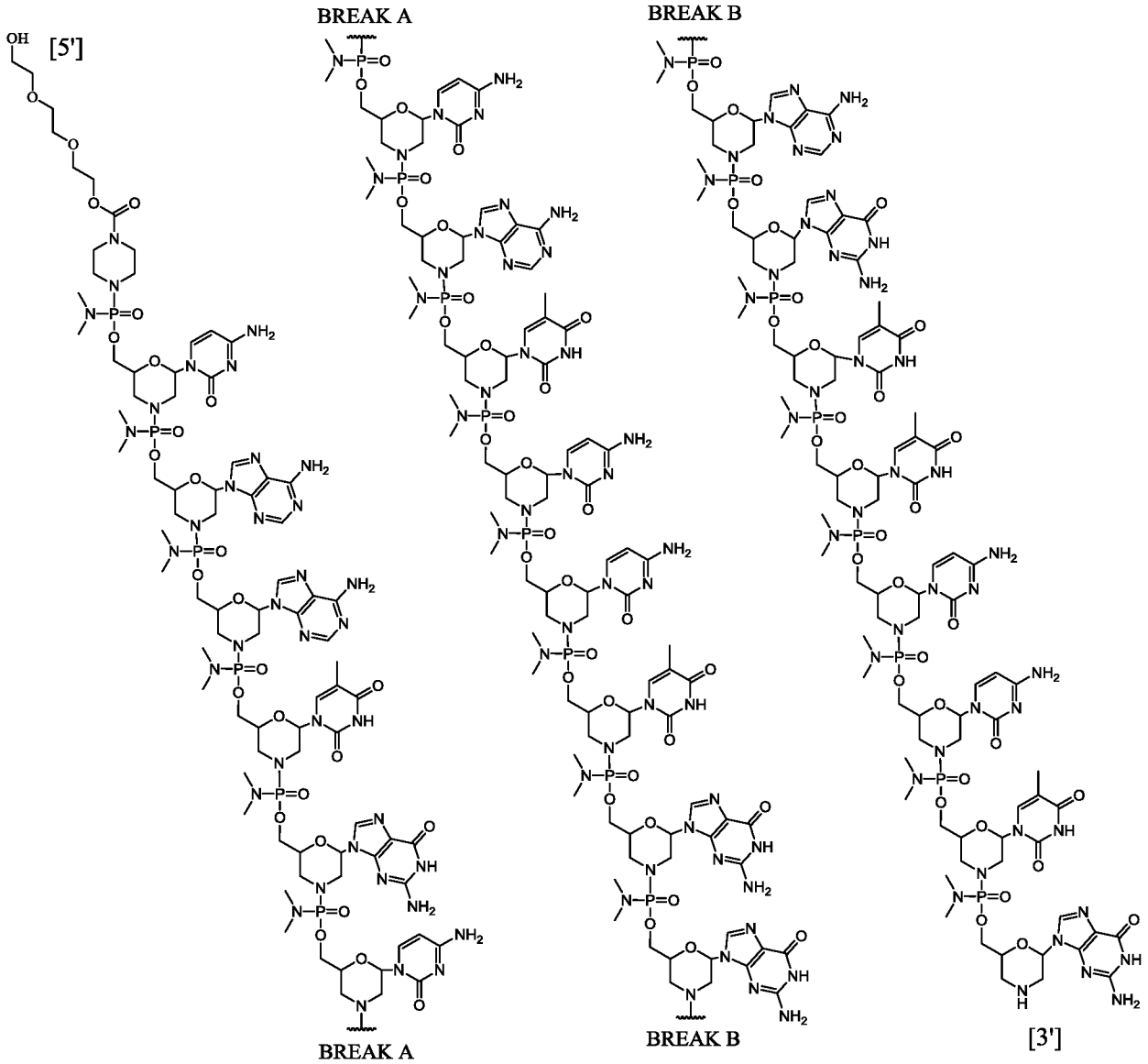
CAATGCCATCCTGGAGTTCCTG

Casimersen can also be depicted by the structure of Formula (XII):



(XII).

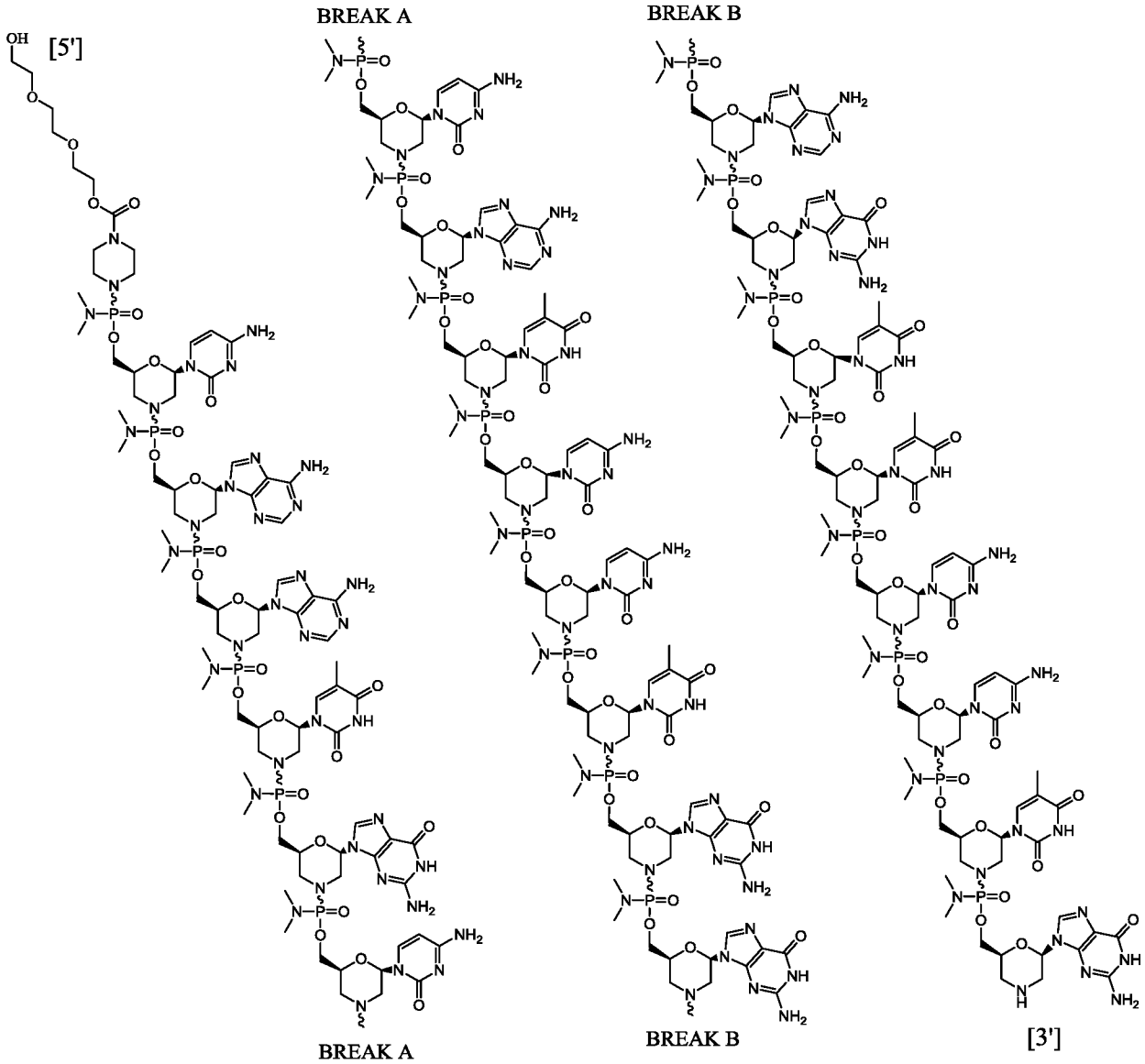
Thus, in one embodiment of the process described above, the oligomeric compound of Formula (A) is a compound of Formula (C):



(C),

or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the oligomeric compound of Formula (C) is an oligomeric compound of Formula (XII):



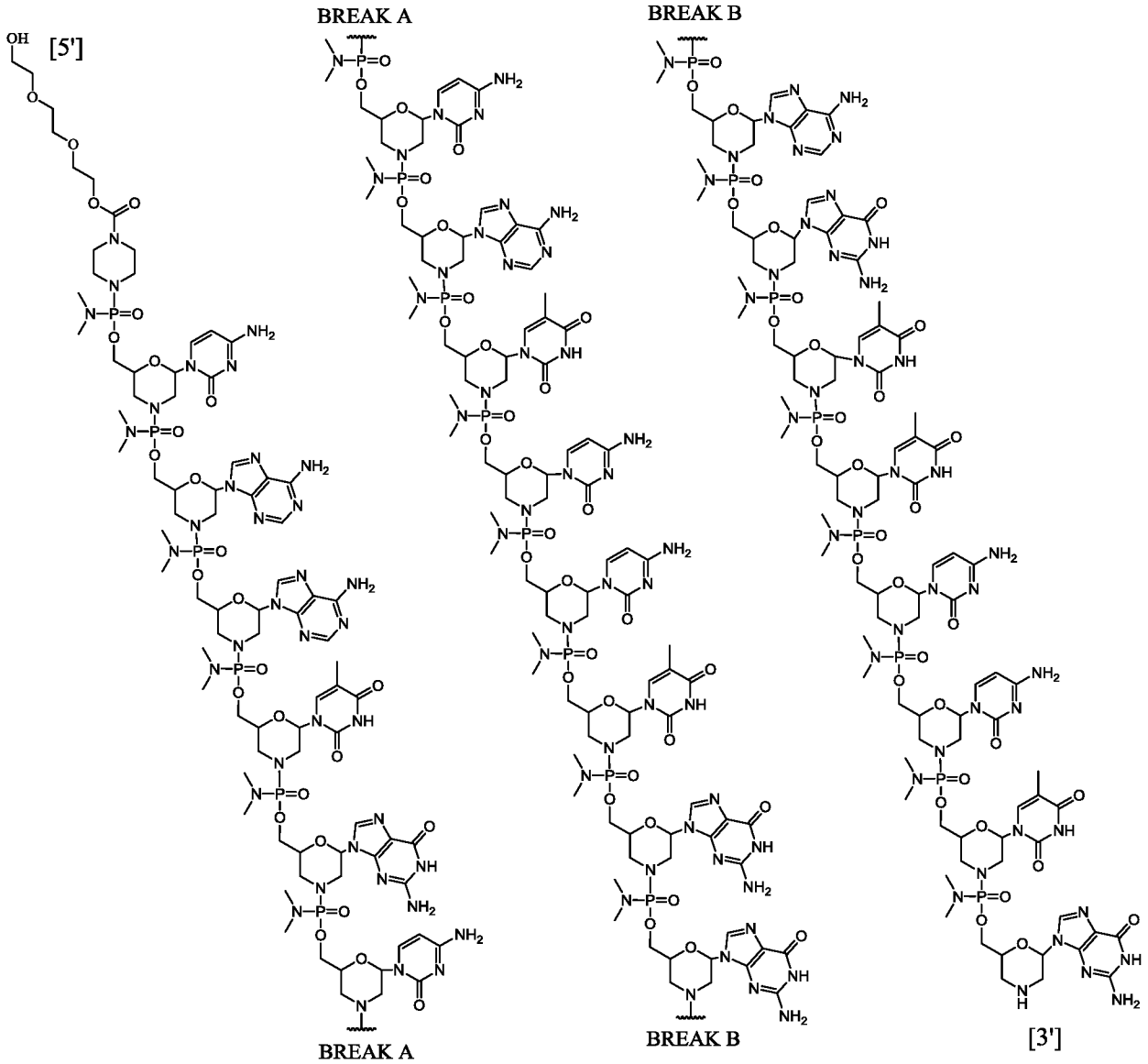
(XII),

or a pharmaceutically acceptable salt thereof.

Processes for Preparing Casimersen

Provided herein are processes for preparing Casimersen.

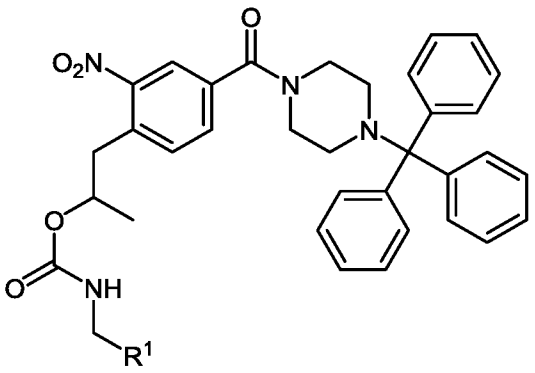
In another aspect, provided herein is a process for preparing an oligomeric compound of Formula (C):



(C);

wherein the process comprises the sequential steps of:

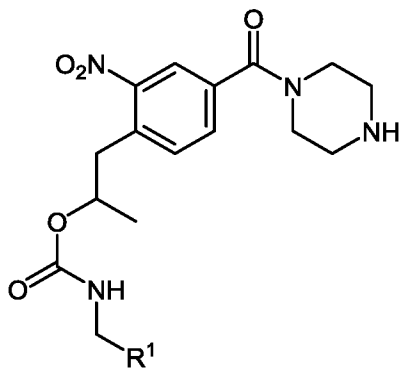
(a) contacting a compound of Formula (I):



(I);

wherein R^1 is a support-medium,

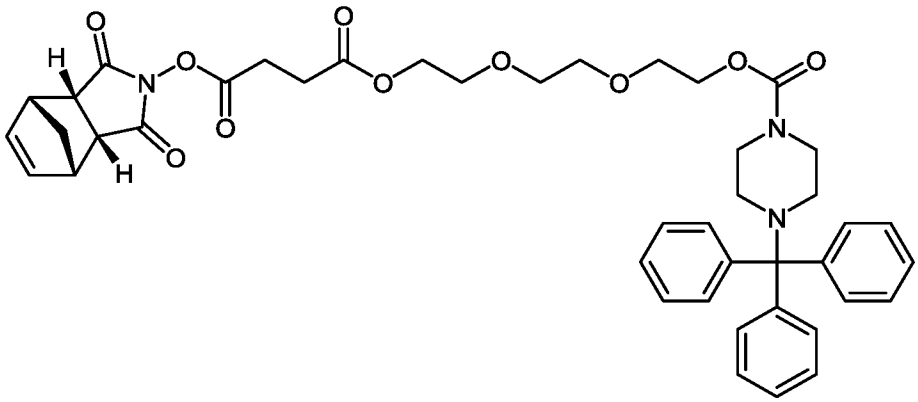
with a deblocking agent to form the compound of Formula (II):



(II);

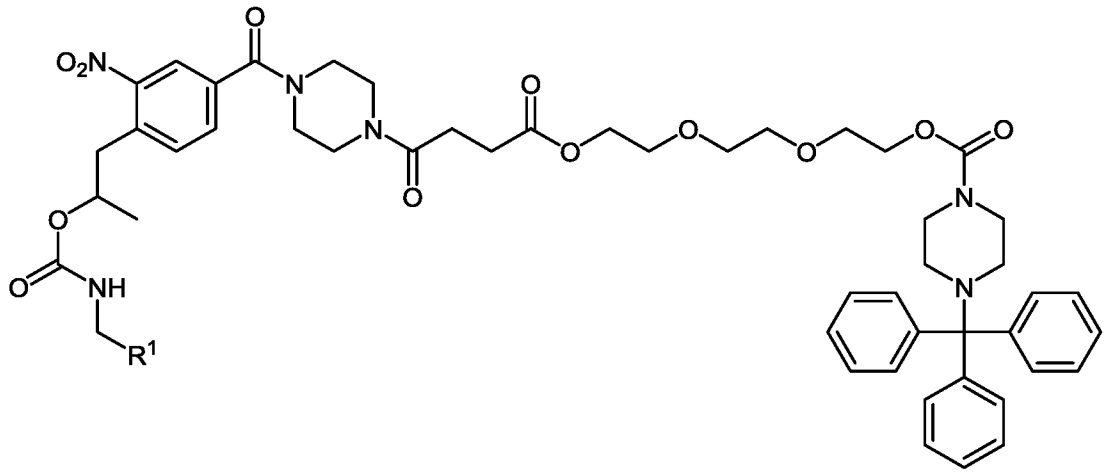
wherein R^1 is a support-medium;

(b) contacting the compound of Formula (II) with compound (B):



(B);

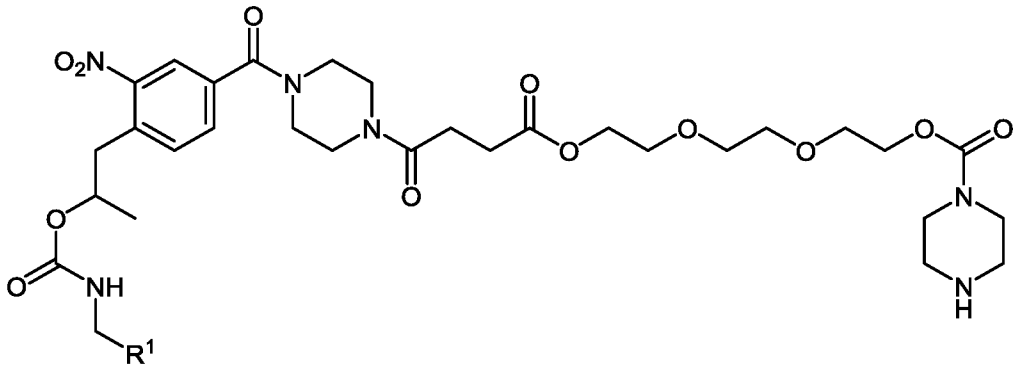
to form a compound of Formula (III):



(III);

wherein R^1 is a support-medium;

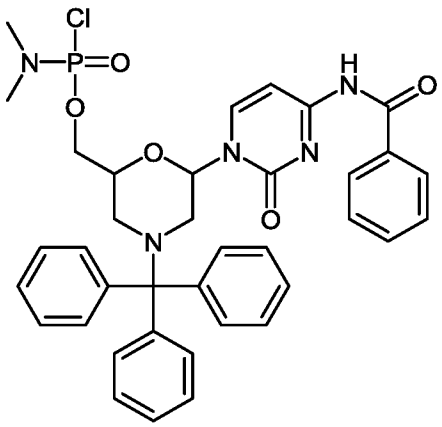
(c) contacting the compound of Formula (III) with a deblocking agent to form a compound of Formula (IV):



(IV);

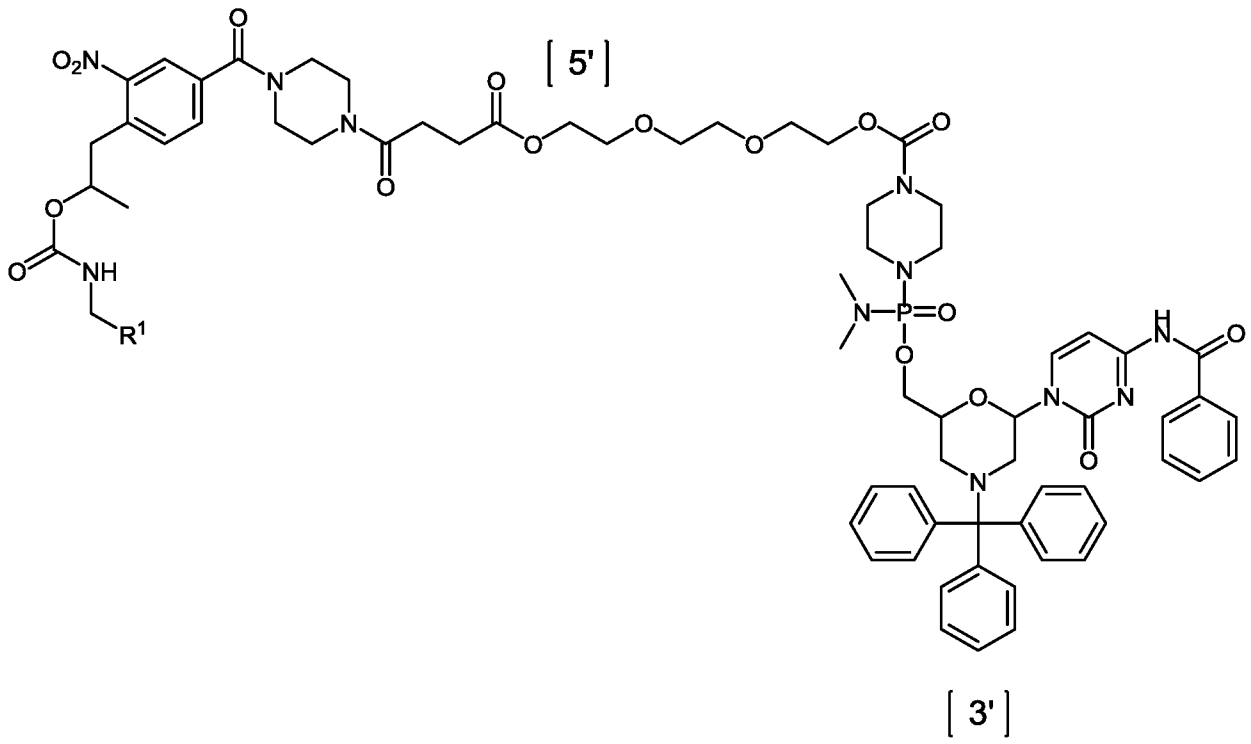
wherein R^1 is a support-medium;

(d) contacting the compound of Formula (IV) with a compound of Formula (D):



(D);

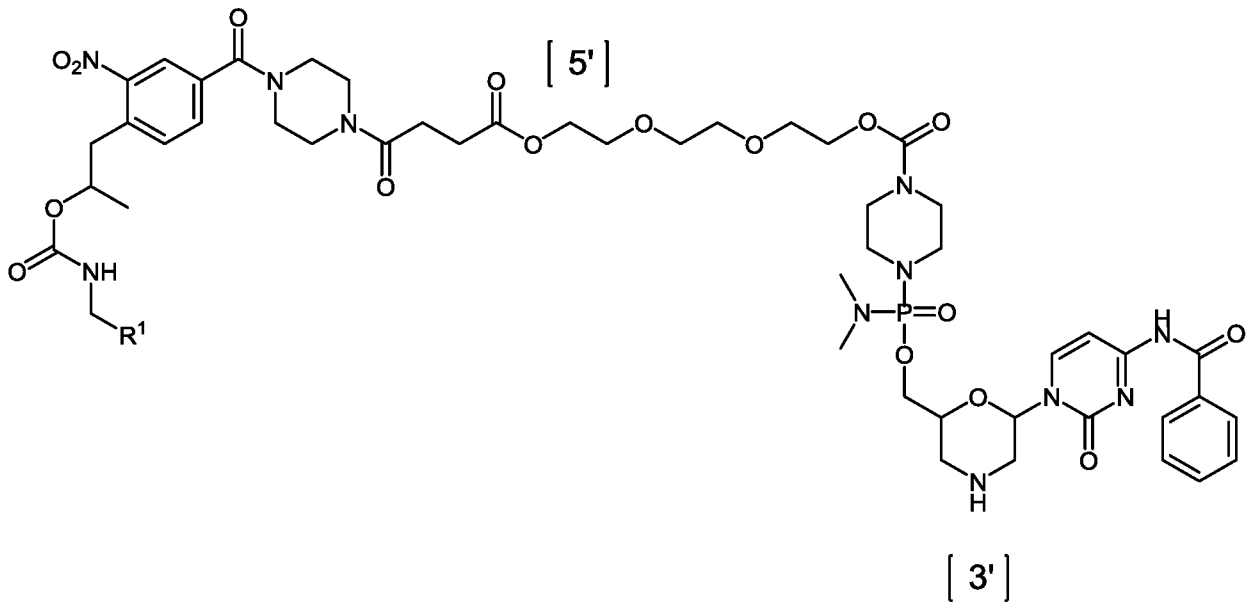
to form a compound of Formula (V):



(V);

wherein R^1 is a support-medium;

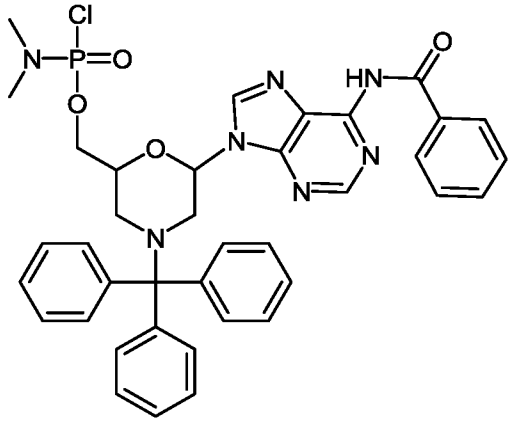
(e) contacting the compound of Formula (V) with a deblocking agent to form a compound of Formula (VI):



(VI);

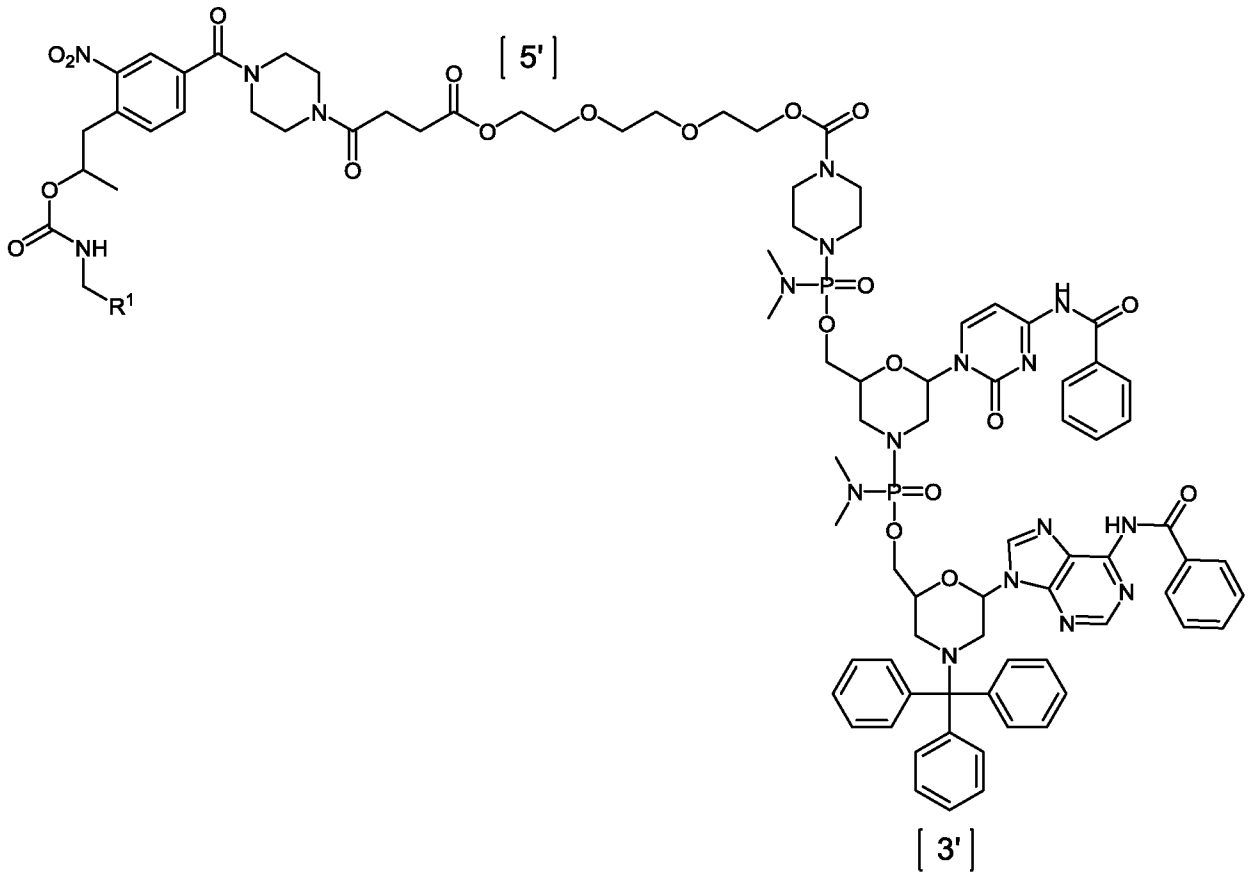
wherein R^1 is a support-medium;

(f) contacting the compound of Formula (VI) with a compound of Formula (F):



(F);

to form a compound of Formula (VII):



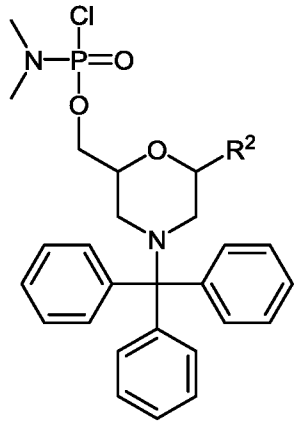
(VII);

wherein R^1 is a support-medium;

(g) performing 20 iterations of the sequential steps of:

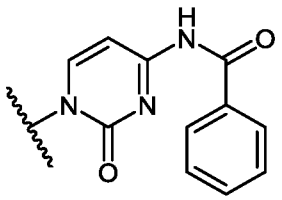
(g1) contacting the product formed by the immediately prior step with a deblocking agent; and

(g2) contacting the compound formed by the immediately prior step with a compound of Formula (VIII):

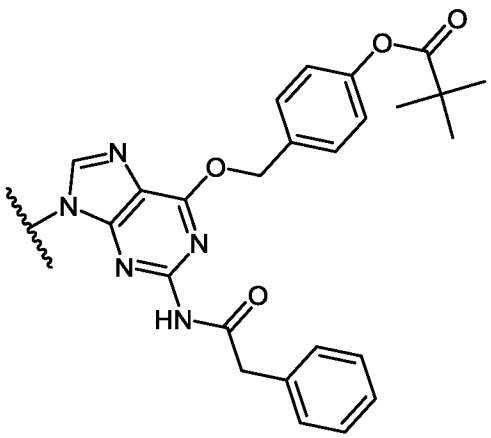


(VIII);

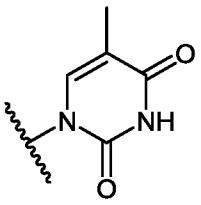
wherein R^2 is, independently for each compound of Formula (VIII), selected from the group consisting of:



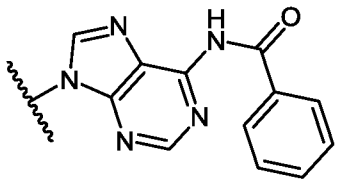
(PC),



(DPG),



(T), and



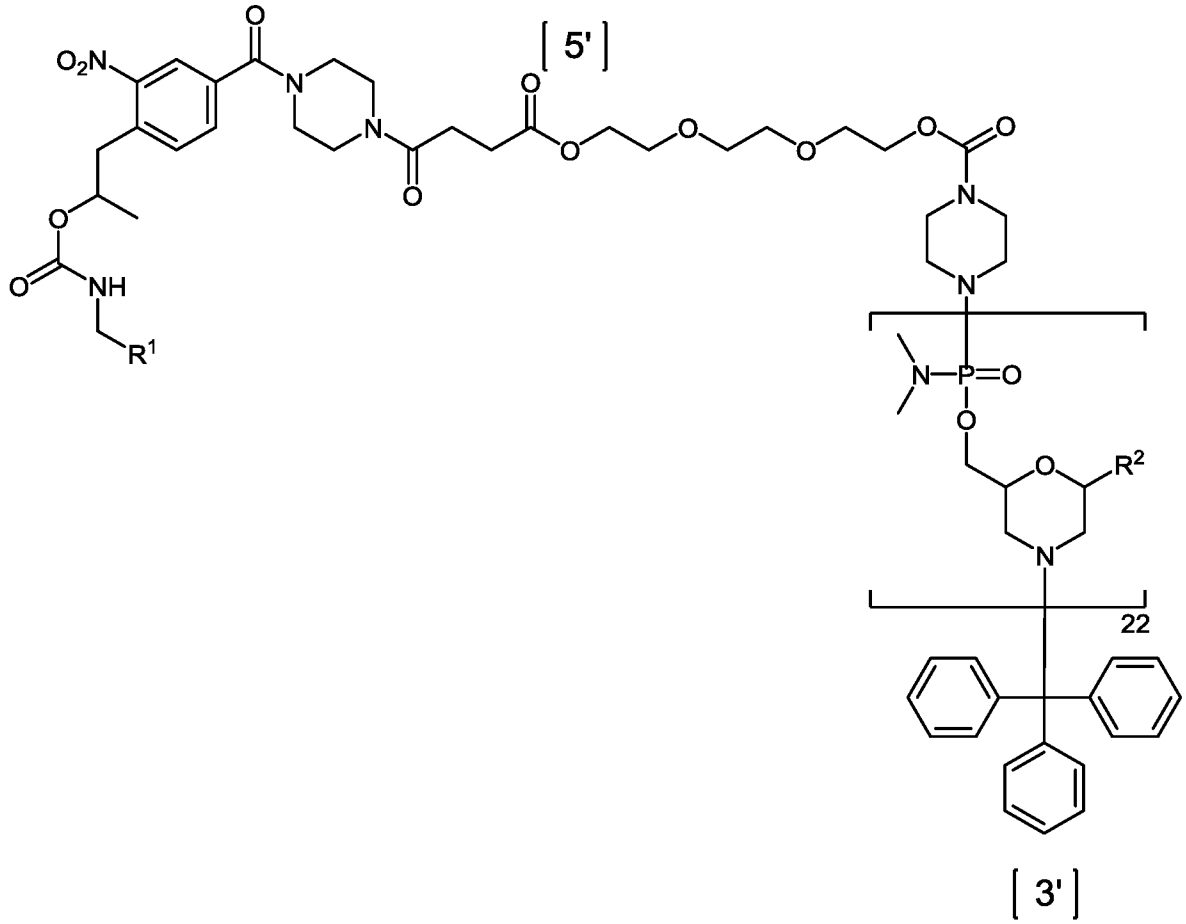
(PA),

wherein, for each iteration from 1 to 20, R^2 is:

Iteration No.	R^2	Iteration No.	R^2
1	PA	11	DPG
2	T	12	DPG
3	DPG	13	PA
4	PC	14	DPG
5	PC	15	T
6	PA	16	T
7	T	17	PC

8	PC	18	PC
9	PC	19	T
10	T	20	DPG

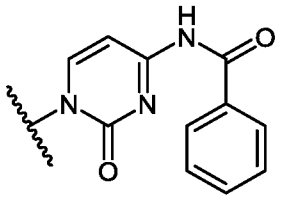
to form a compound of Formula (IX):

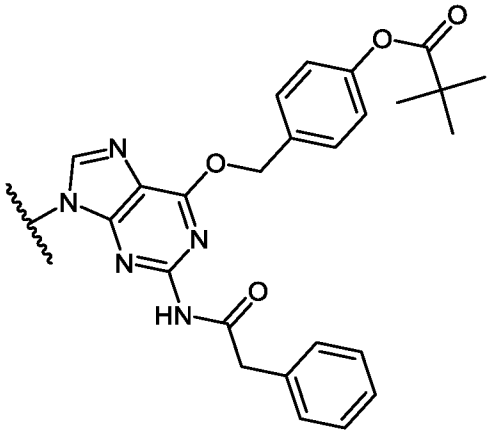


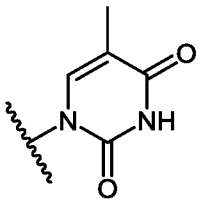
(IX);

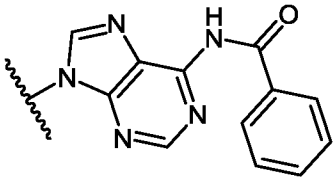
wherein R^1 is a support-medium,

wherein R^2 is, independently for each occurrence, selected from the group consisting of:


(PC),


(DPG),

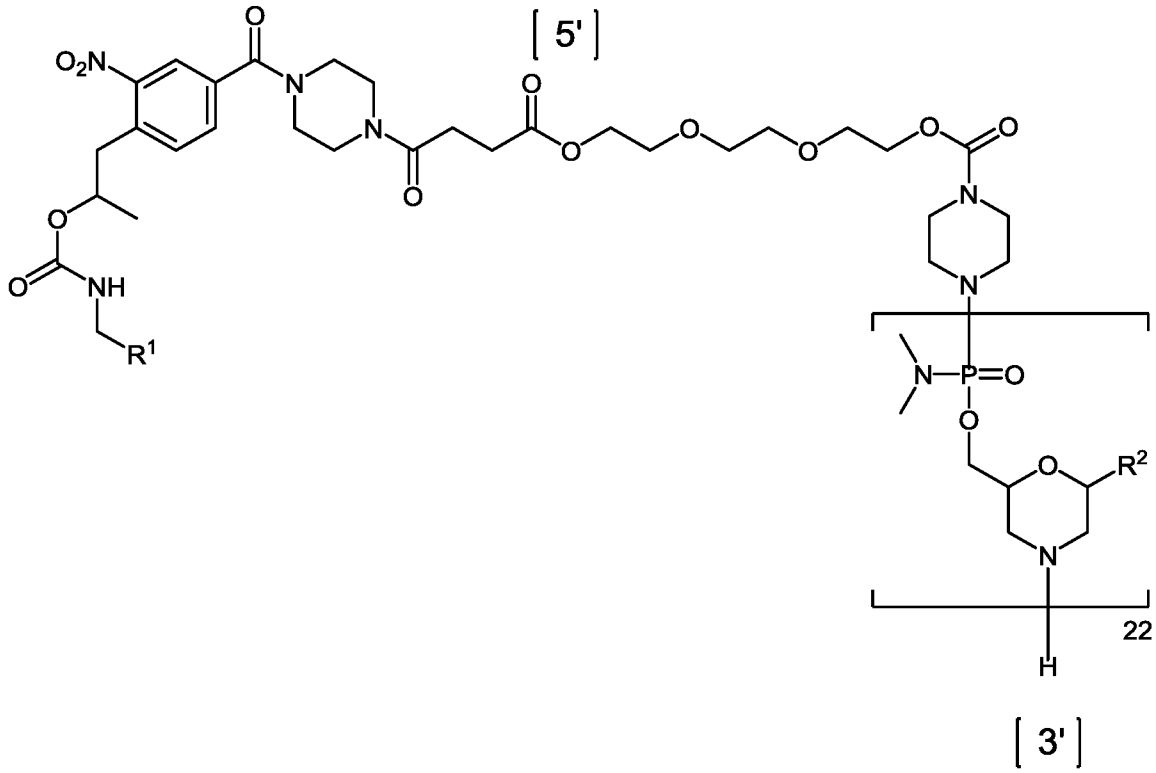

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

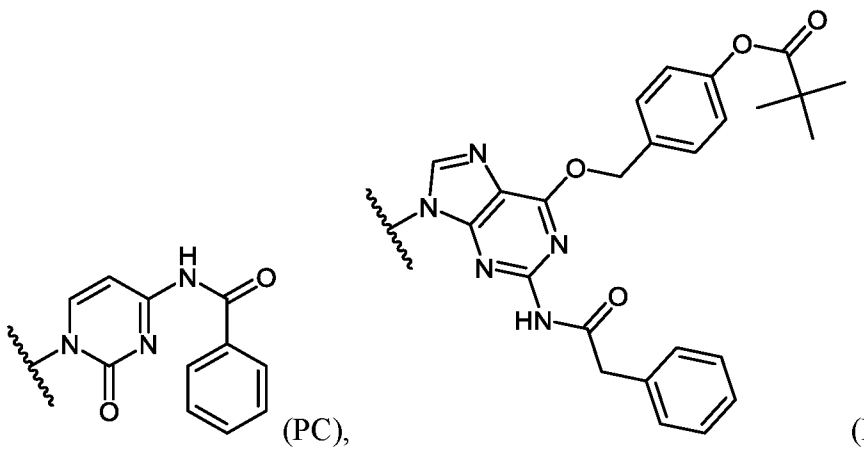
(h) contacting the compound of Formula (IX) with a deblocking agent to form a compound of Formula (X):



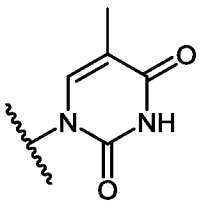
(X);

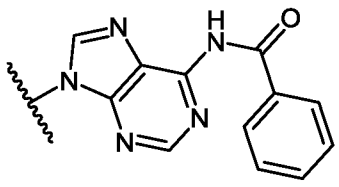
wherein R^1 is a support-medium,

wherein R^2 is, independently for each occurrence, selected from the group consisting of:


(PC),

(DPG),

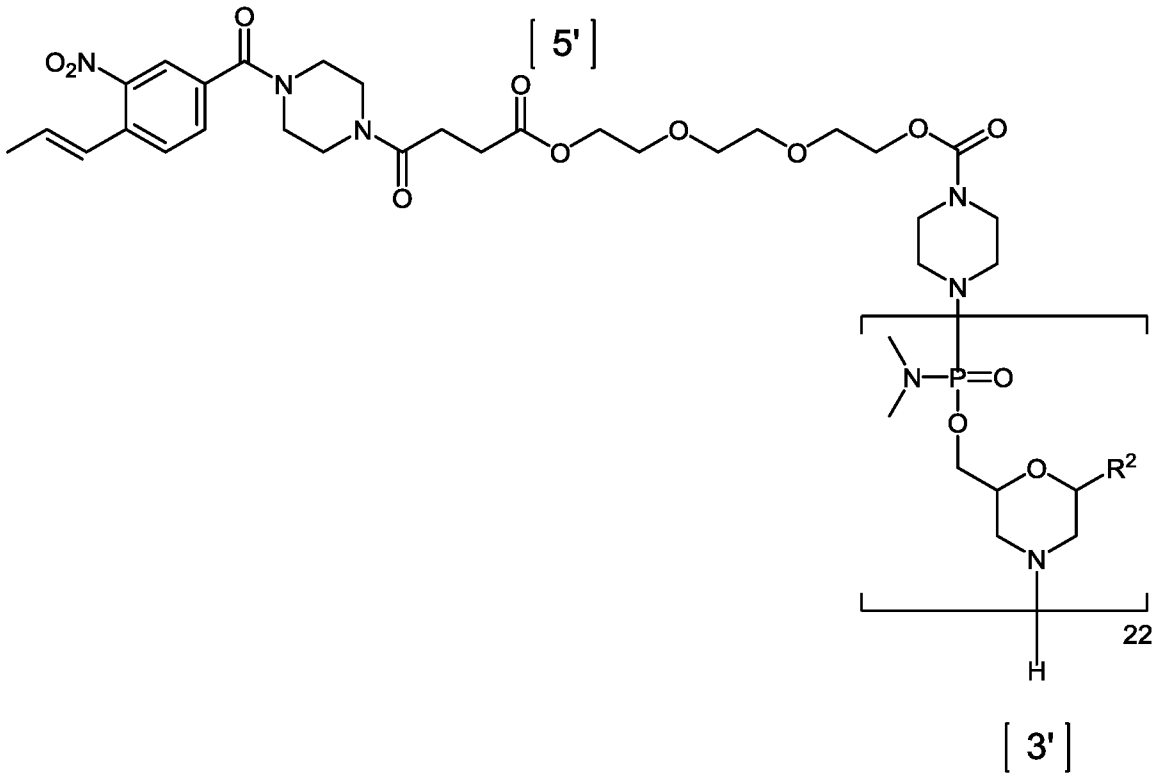

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

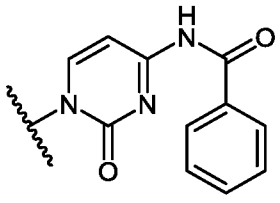
Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

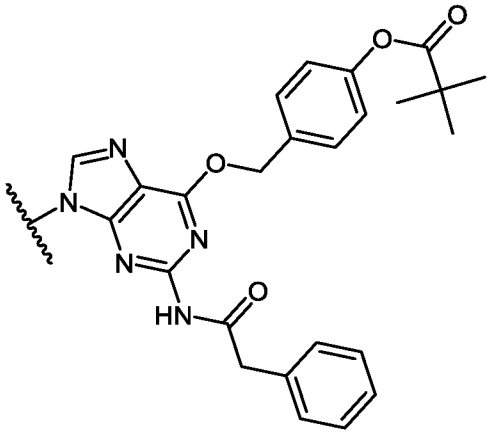
(i) contacting the compound of Formula (X) with a cleaving agent to form a compound of Formula (XI):

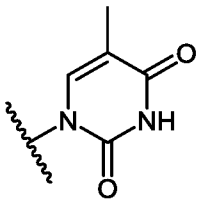


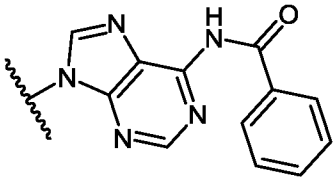
(XI),

wherein R^2 is, independently for each occurrence, selected from the group consisting of:


(PC),


(DPG),


(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

and

(j) contacting the compound of Formula (XI) with a deprotecting agent to form the oligomeric compound of Formula (C).

In an embodiment, step (d), step (f), step (g2), or combinations thereof further comprises contacting the compound of Formula (IV), Formula (VI), or the compound formed by the immediately prior step, respectively, with a capping agent.

In certain embodiments, each of step (d), step (f) and step (g2) further comprises contacting the compound of Formula (IV), Formula (VI), or the compound formed by the immediately prior step, respectively, with a capping agent.

In another embodiment, each step is performed in the presence of at least one solvent.

In yet another embodiment, the deblocking agent used in each step is a solution comprising a halogenated acid.

In still another embodiment, the deblocking agent used in each step is cyanoacetic acid.

In another embodiment, the halogenated acid is selected from the group consisting of chloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, and trifluoroacetic acid.

In yet another embodiment, the halogenated acid is trifluoroacetic acid.

In still another embodiment, at least one of steps (c), (e), and (g1) further comprise the step of contacting the deblocked compound of each step with a neutralization agent.

In another embodiment, each of steps (c), (e), and (g1) further comprise the step of contacting the deblocked compound of each step with a neutralization agent.

In yet another embodiment, the neutralization agent is in a solution comprising dichloromethane and isopropyl alcohol.

In still another embodiment, the neutralization agent is a monoalkyl, dialkyl, or trialkyl amine.

In another embodiment, the neutralization agent is N,N-diisopropylethylamine.

In yet another embodiment, the deblocking agent used in each step is a solution comprising 4-cyanopyridine, dichloromethane, trifluoroacetic acid, trifluoroethanol, and water.

In still another embodiment, the capping agent is in a solution comprising ethylmorpholine and methylpyrrolidinone.

In another embodiment, the capping agent is an acid anhydride.

In yet another embodiment, the acid anhydride is benzoic anhydride.

In still another embodiment, the compound of Formula (VIII), Formula (D), and Formula (F) are each, independently, in a solution comprising ethylmorpholine and dimethylimidazolidinone.

In another embodiment, the cleavage agent comprises dithiothreitol and 1,8-diazabicyclo[5.4.0]undec-7-ene.

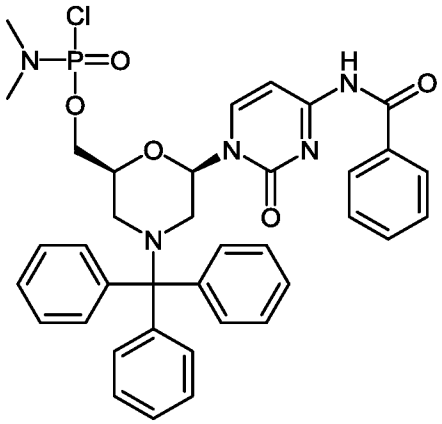
In yet another embodiment, the cleavage agent is in a solution comprising N-methyl-2-pyrrolidone.

In still another embodiment, the deprotecting agent comprises NH_3.

In another embodiment, the deprotecting agent is in an aqueous solution.

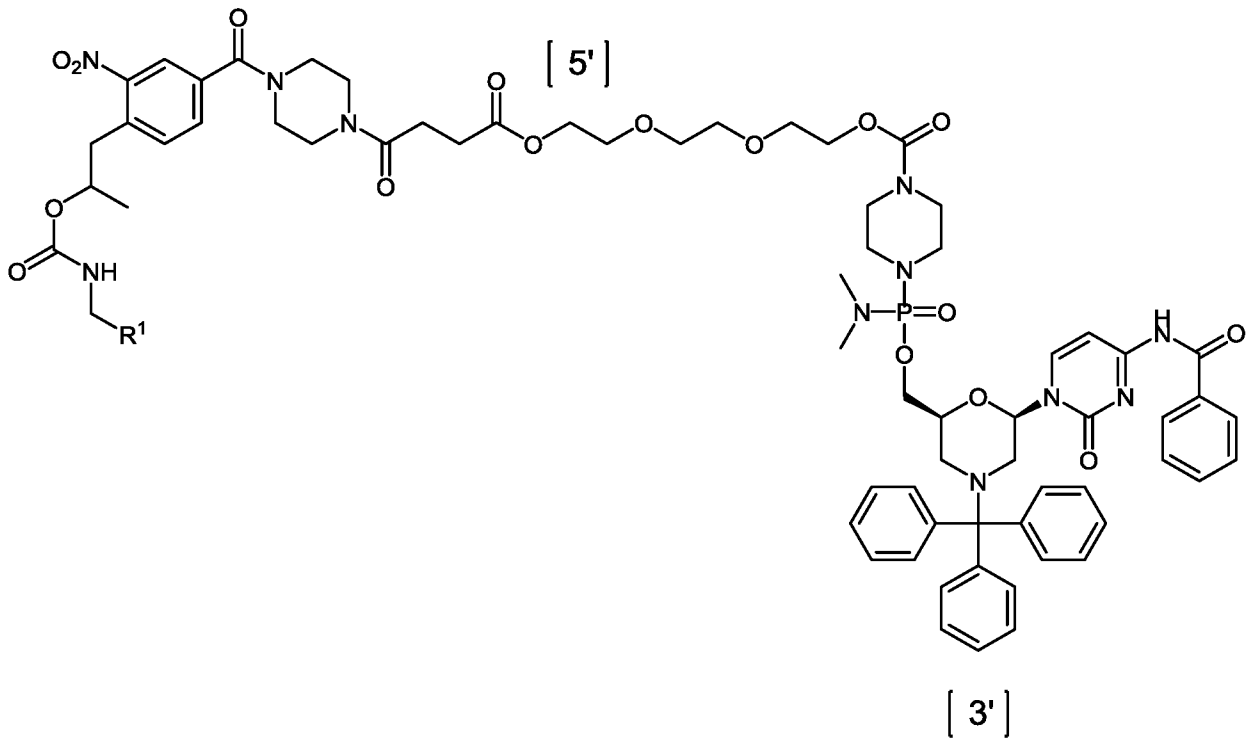
In yet another embodiment, the support-medium comprises polystyrene with 1% crosslinked divinylbenzene.

In another embodiment, the compound of Formula (D) is of Formula (D1):



(D1).

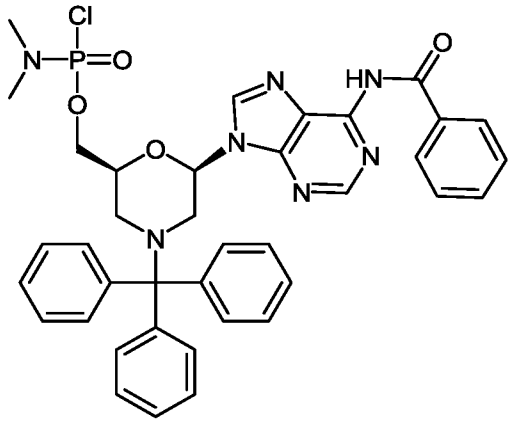
In another embodiment, the compound of Formula (V) is of Formula (Va):



(Va),

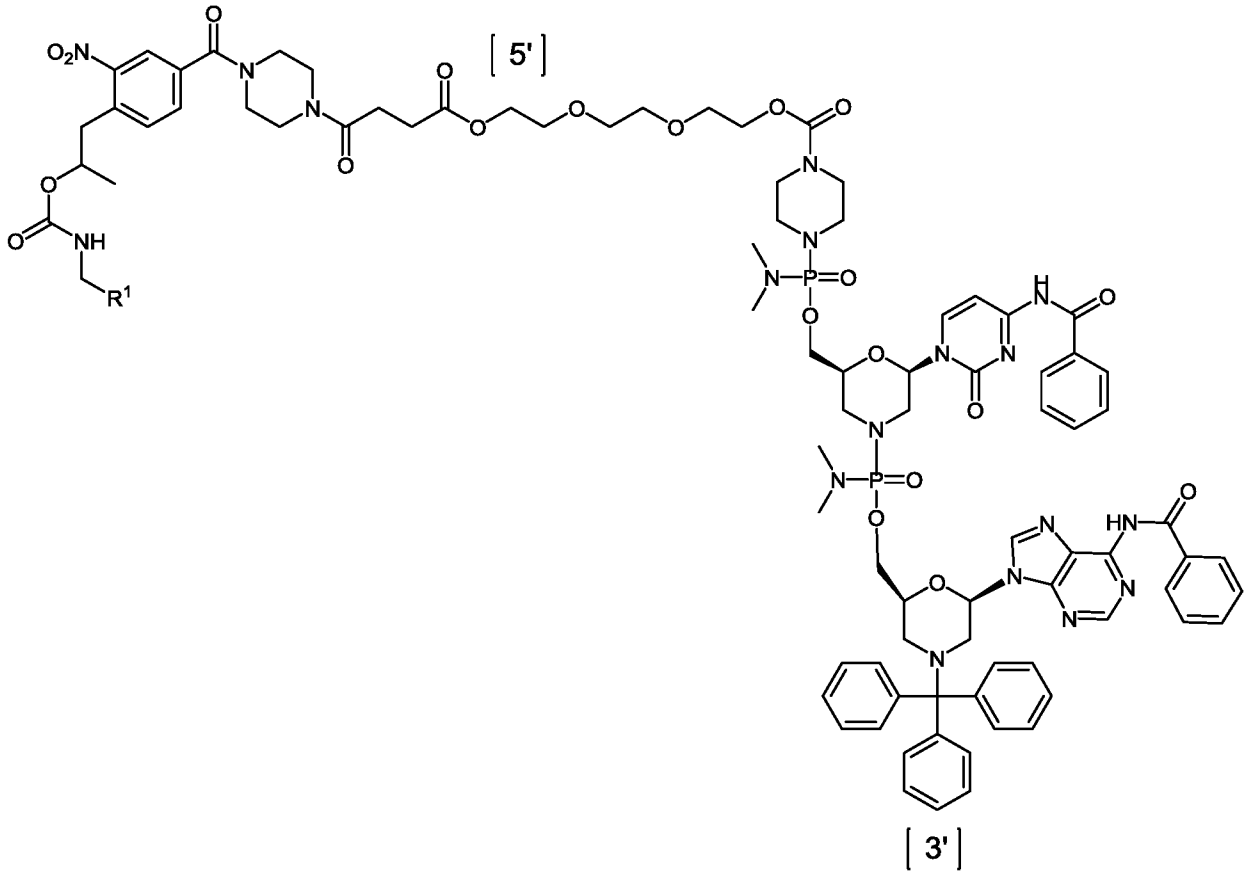
wherein R^1 is a support-medium.

In another embodiment, the compound of Formula (F) is of Formula (F1):



(F1).

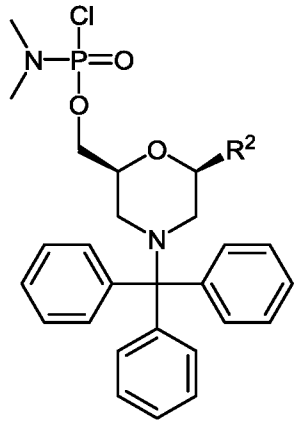
In another embodiment, the compound of Formula (VII) is of Formula (VIIa):



(VIIa),

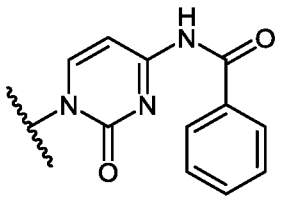
wherein R^1 is a support-medium.

In another embodiment, the compound of Formula (VIII) is of Formula (VIIIa):

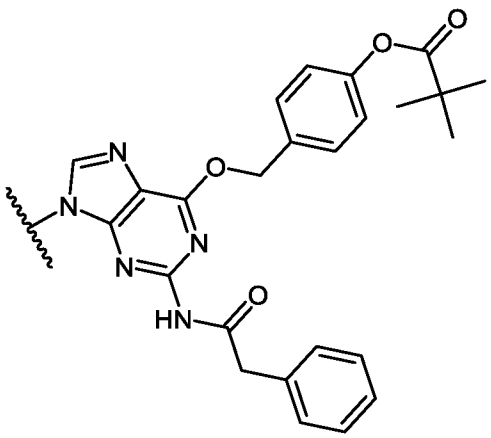


(VIIIa);

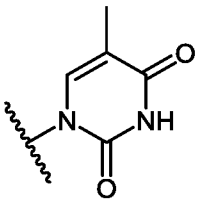
wherein R^2 is, independently for each compound of Formula (VIIIa), selected from the group consisting of:



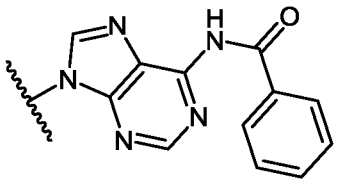
(PC),



(DPG),

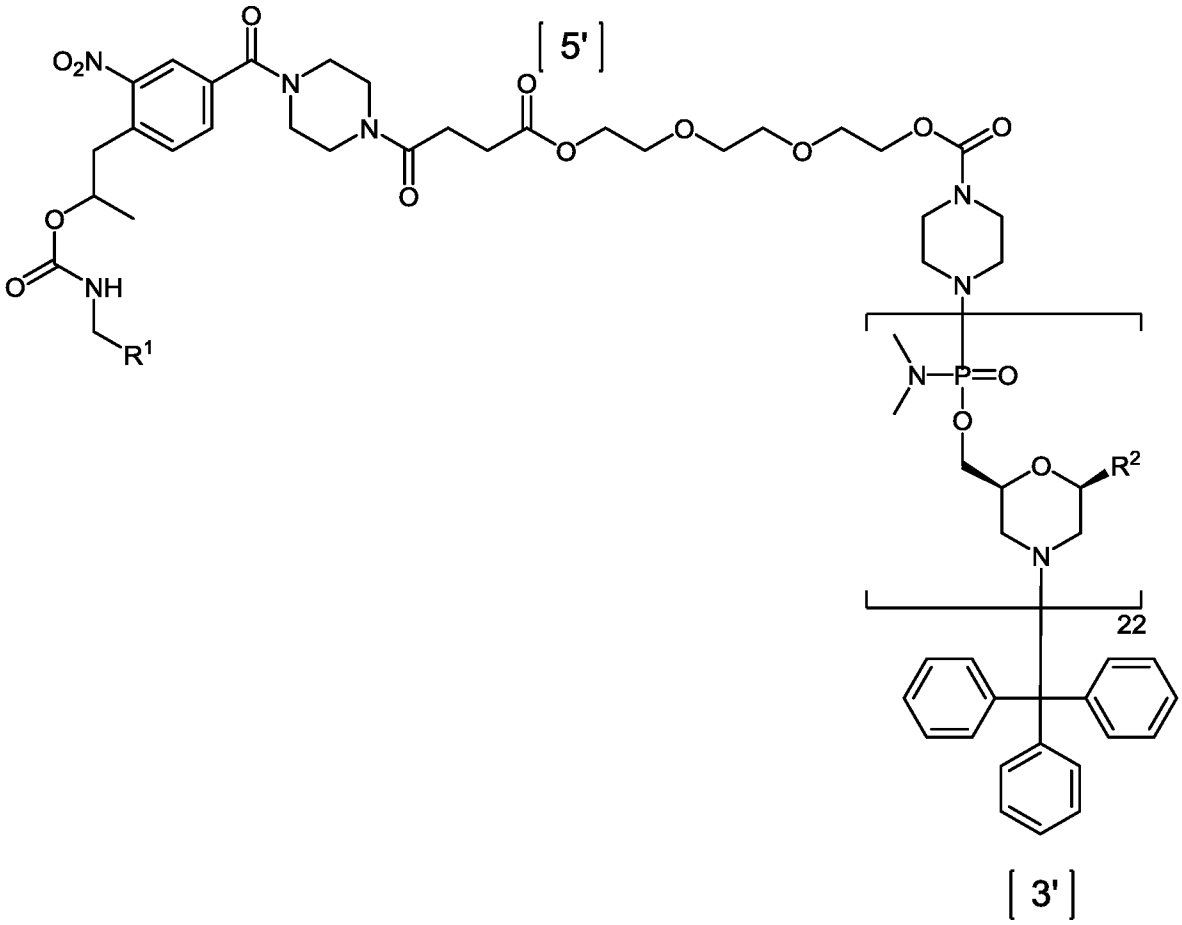


(T), and



(PA).

In another embodiment, the compound of Formula (IX) is of Formula (IXa):

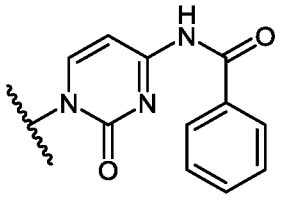


(IXa),

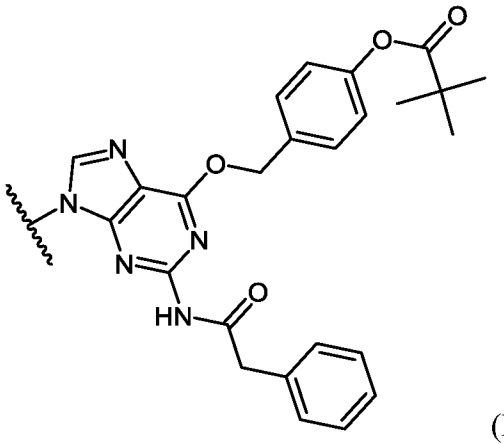
or a pharmaceutically acceptable salt thereof, wherein

R^1 is a support-medium, and

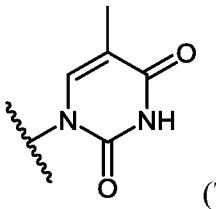
R^2 is, independently at each occurrence, selected from the group consisting of:



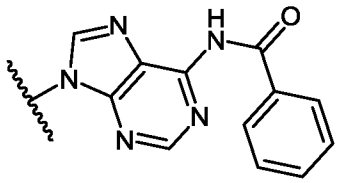
(PC),



(DPG),



(T), and

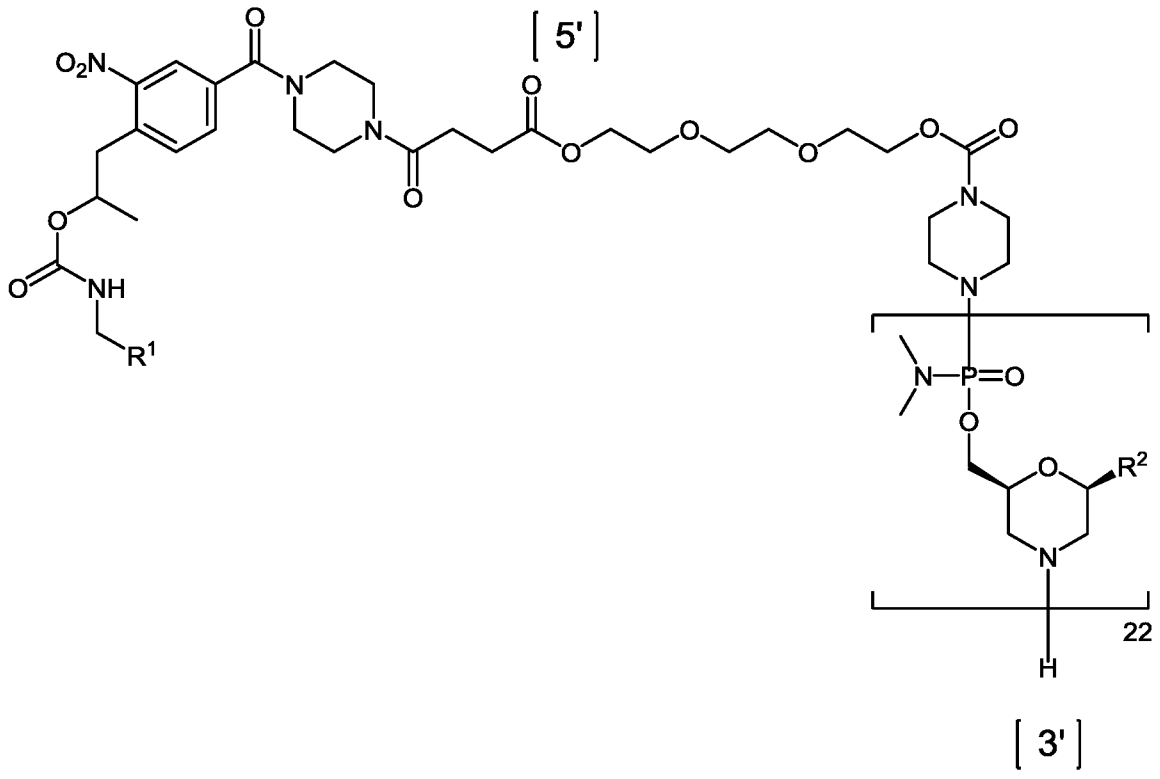


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

In another embodiment, the compound of Formula (X) is of Formula (Xa):

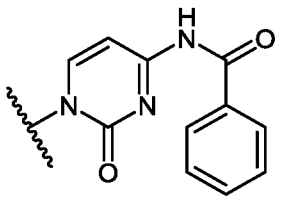


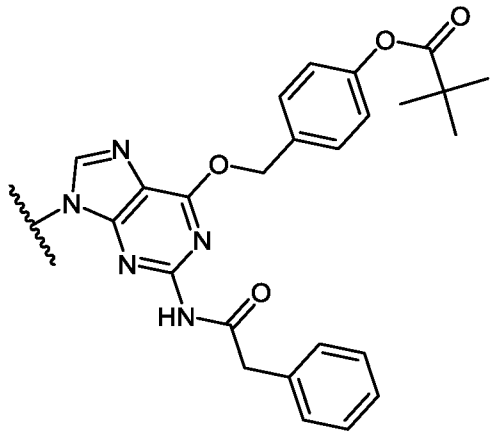
(Xa),

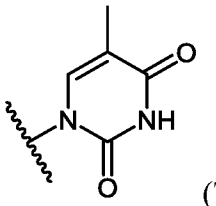
or a pharmaceutically acceptable salt thereof, wherein

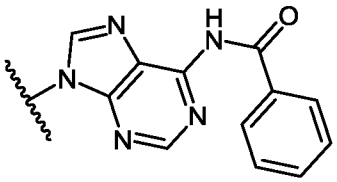
R^1 is a support-medium, and

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),

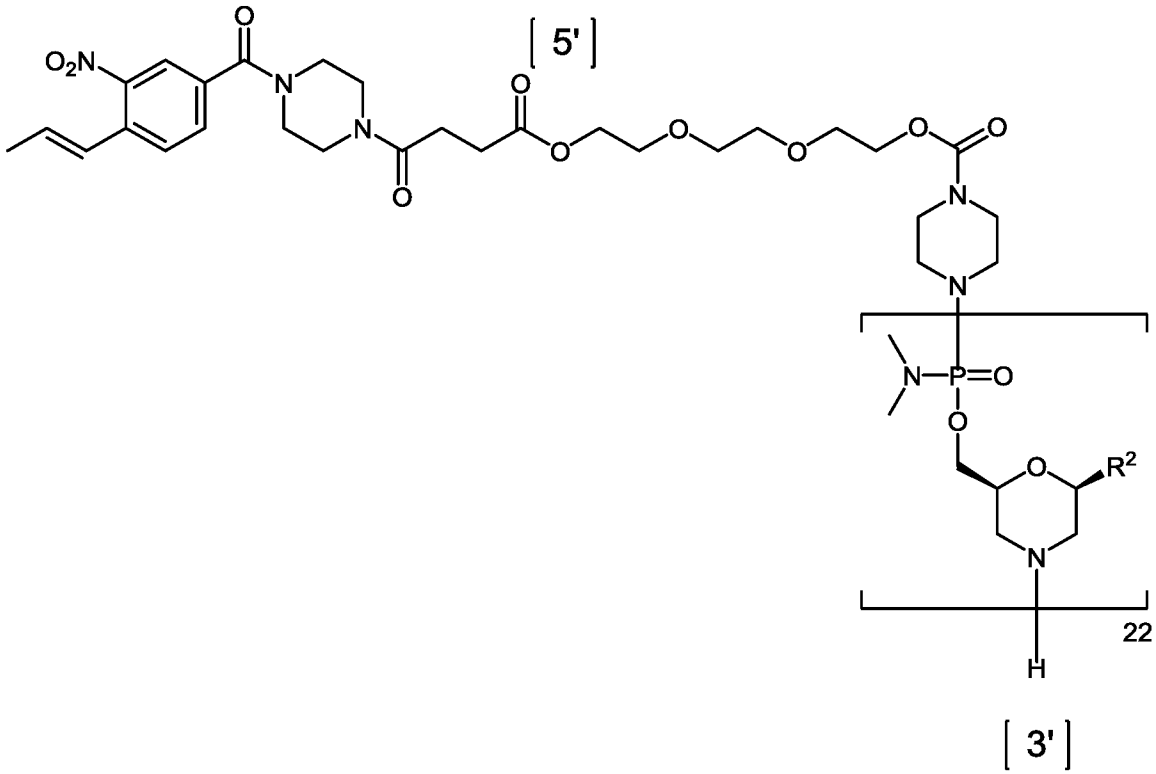

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

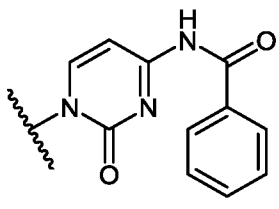
In another embodiment, the compound of Formula (XI) is of Formula (XIa):



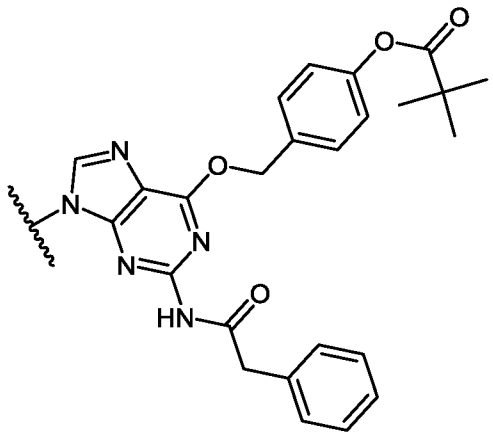
(XIa),

or a pharmaceutically acceptable salt thereof, wherein:

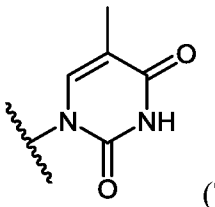
R^2 is, independently at each occurrence, selected from the group consisting of:



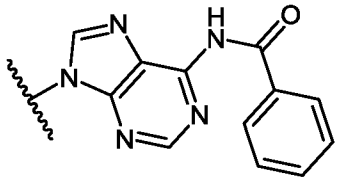
(PC),



(DPG),



(T), and

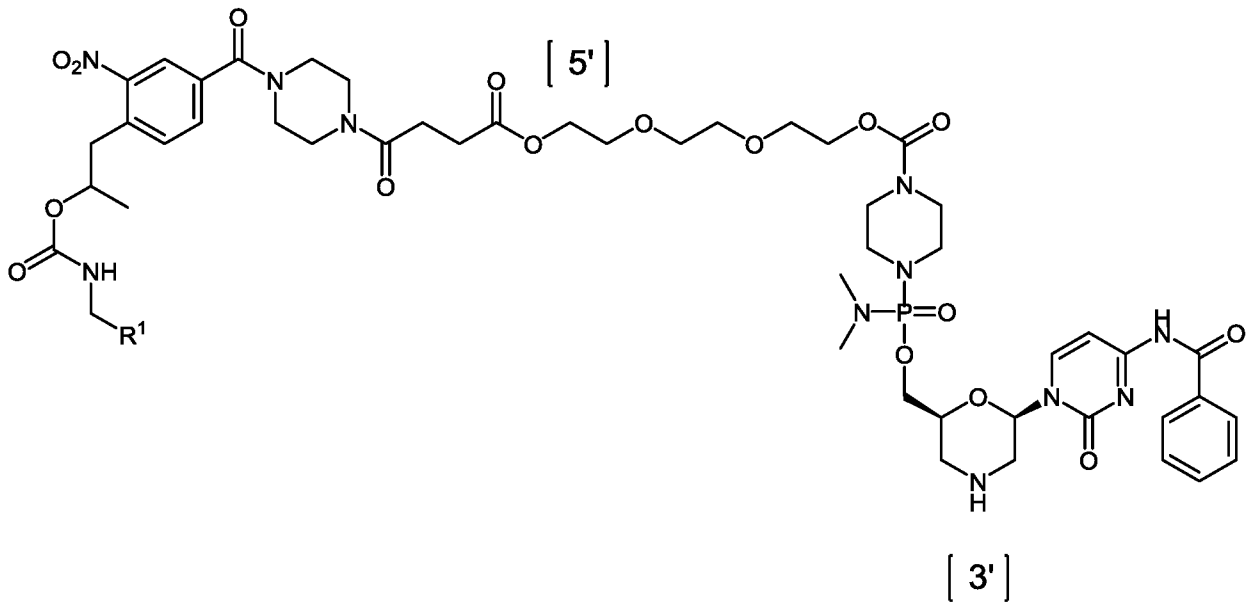


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

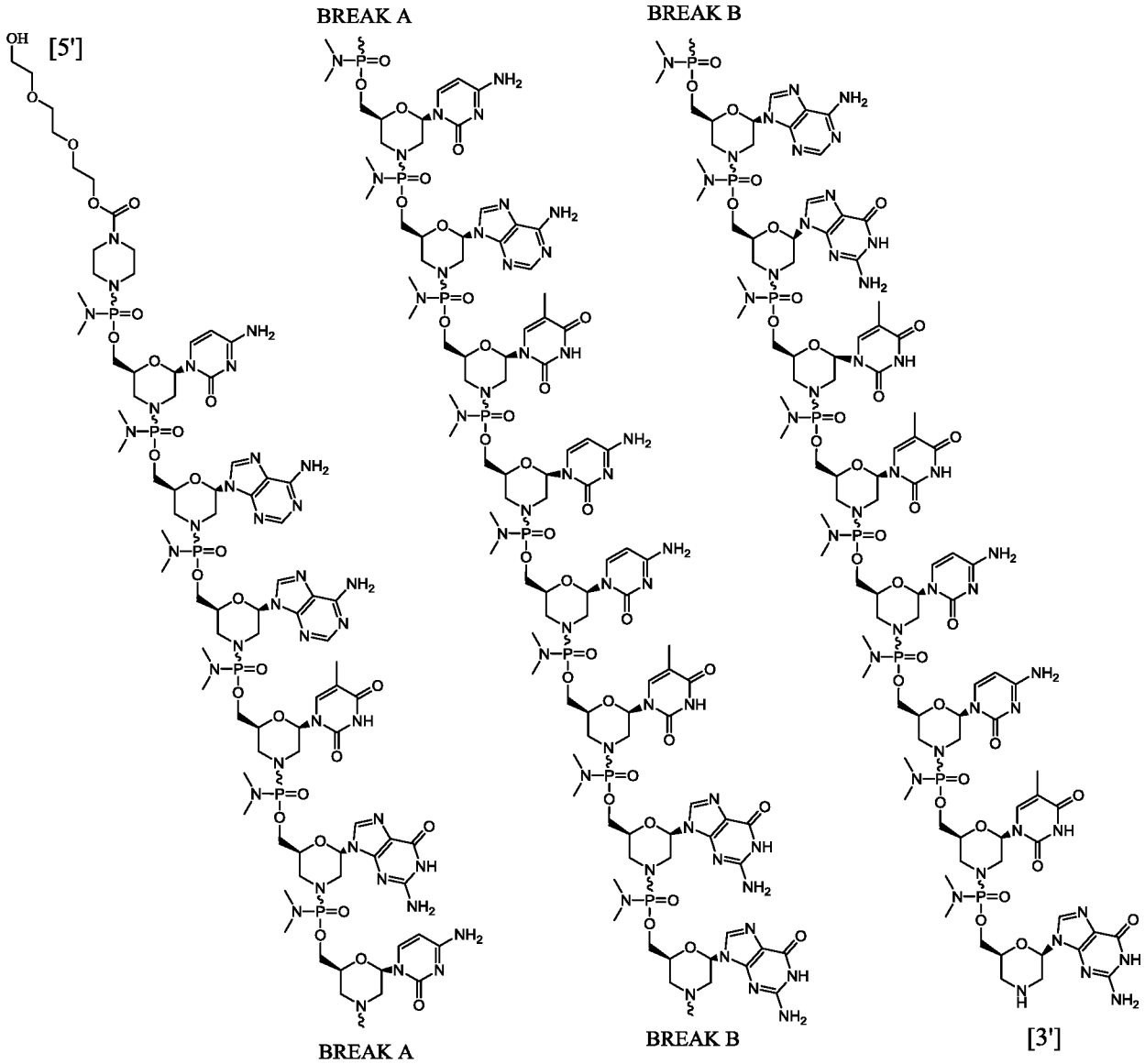
In another embodiment, the compound of Formula (VI) is of Formula (VIa):



(VIa);

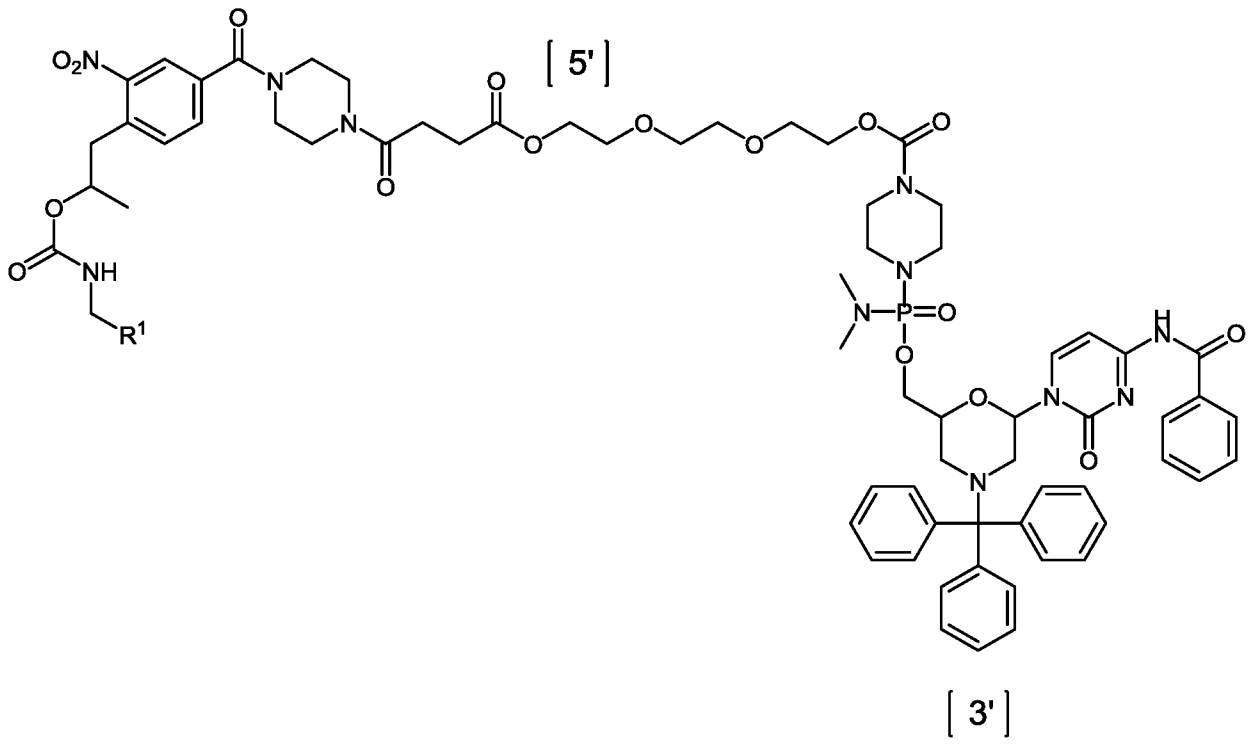
wherein R^1 is a support-medium.

In still another embodiment, the oligomeric compound of Formula (C) is an oligomeric compound of Formula (XII):



(XII).

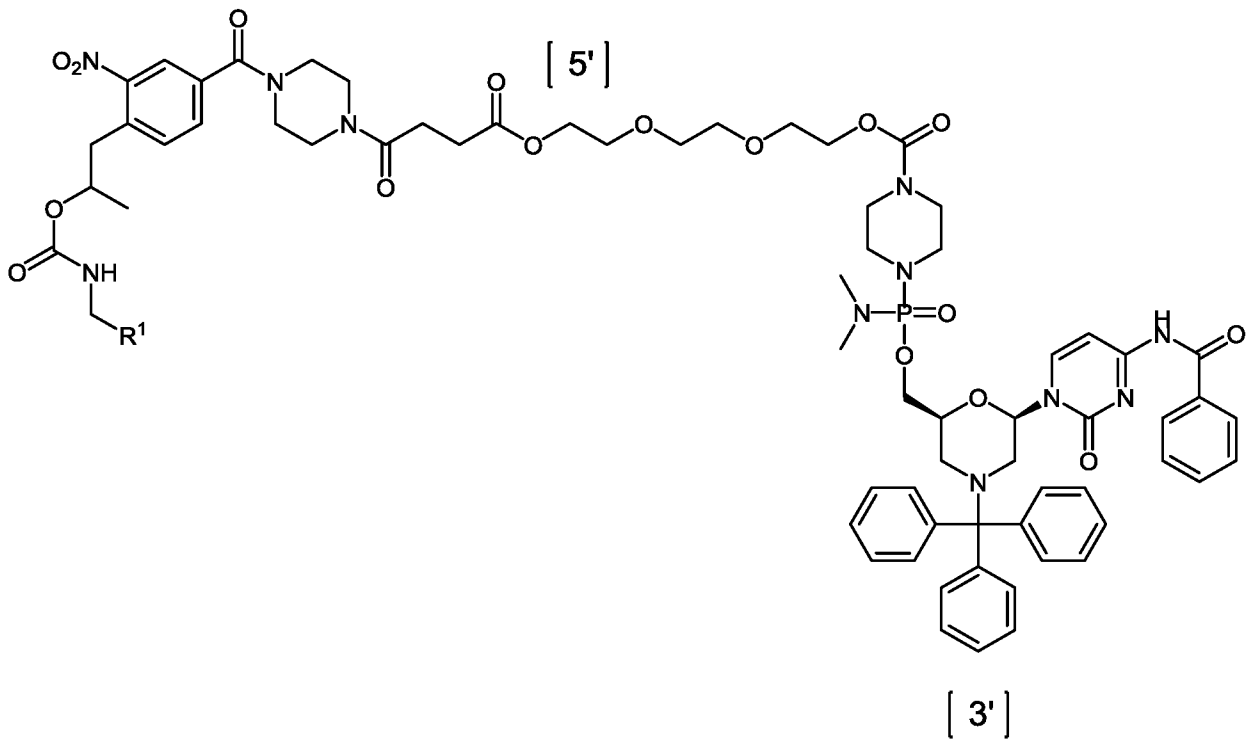
In another aspect, provided herein is a compound of Formula (V):



(V);

or a pharmaceutically acceptable salt thereof, wherein R^1 is a support-medium.

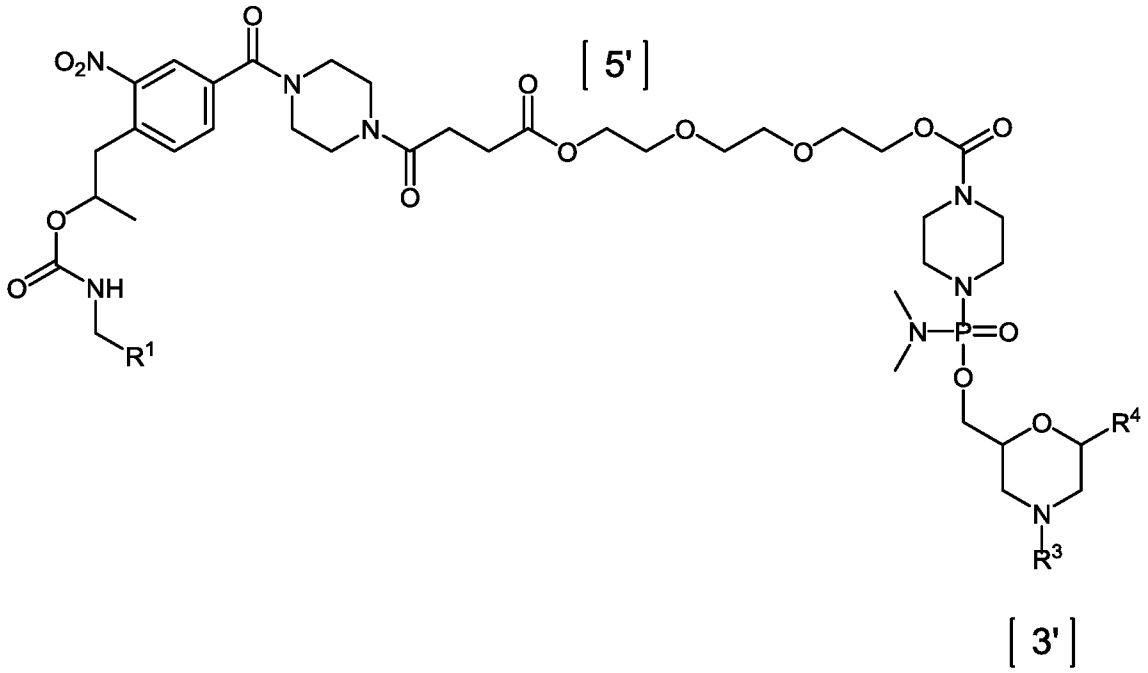
In one embodiment, the compound of Formula (V) is of Formula (Va):



(Va),

or a pharmaceutically acceptable salt thereof, wherein R^1 is a support-medium.

In another aspect, provided herein is a compound of Formula (A5):

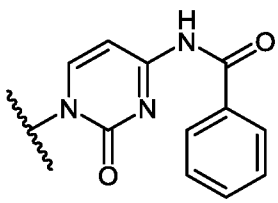


[5']

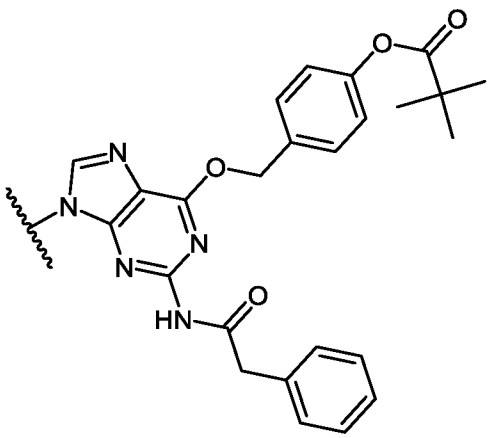
[3']

(A5);

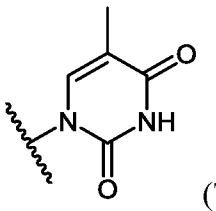
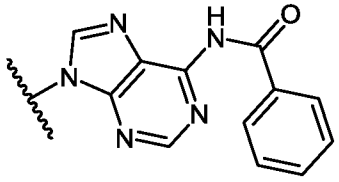
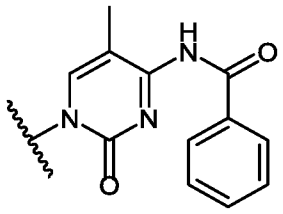
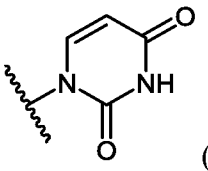
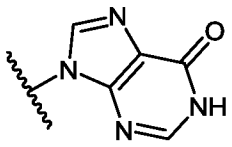
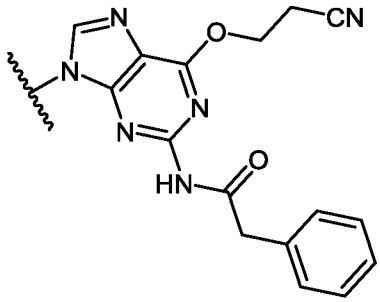
or a pharmaceutically acceptable salt thereof, wherein R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is selected from:



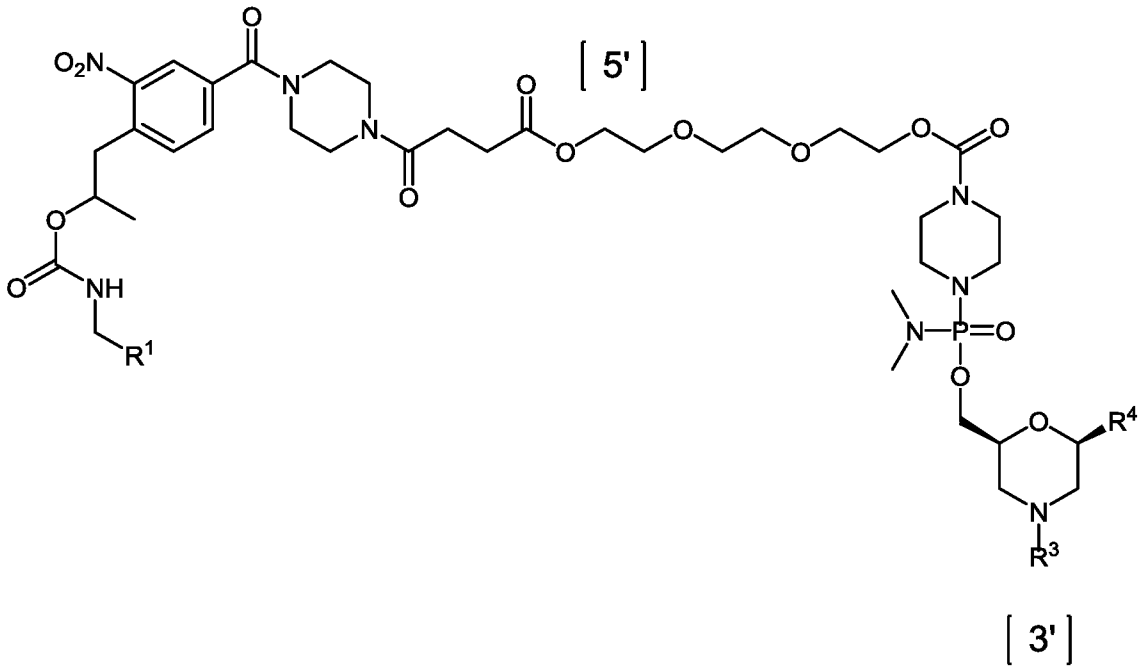
(PC),



(DPG),

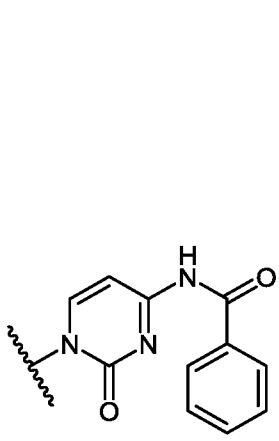
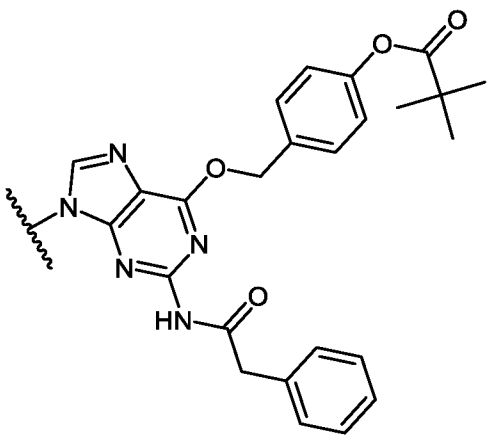
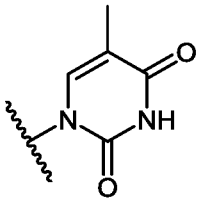
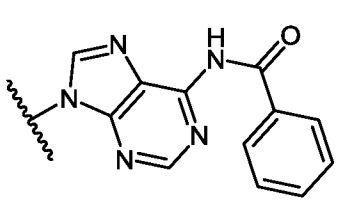
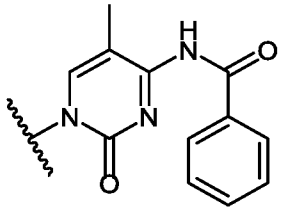
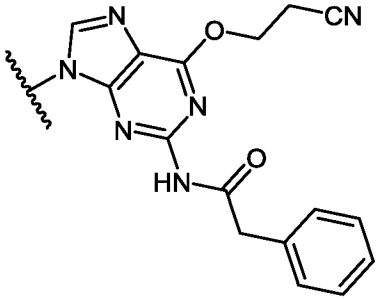
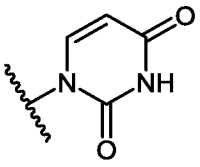
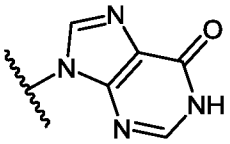

(T),

(PA),

(P5mC),

(U),

(I), and

(PG).

In one embodiment, the compound of Formula (A5) is of Formula (A5a):

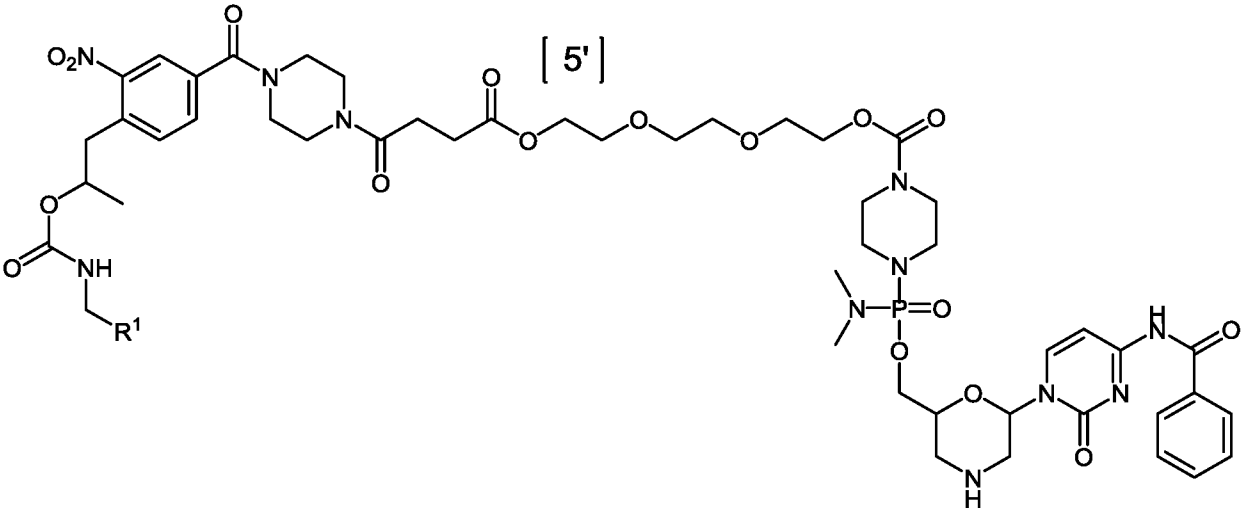


(A5a);

or a pharmaceutically acceptable salt thereof, wherein R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is selected from:


(PC),

(DPG),

(T),

(PA),

(P5mC),


(U),

(I), and
(PG).

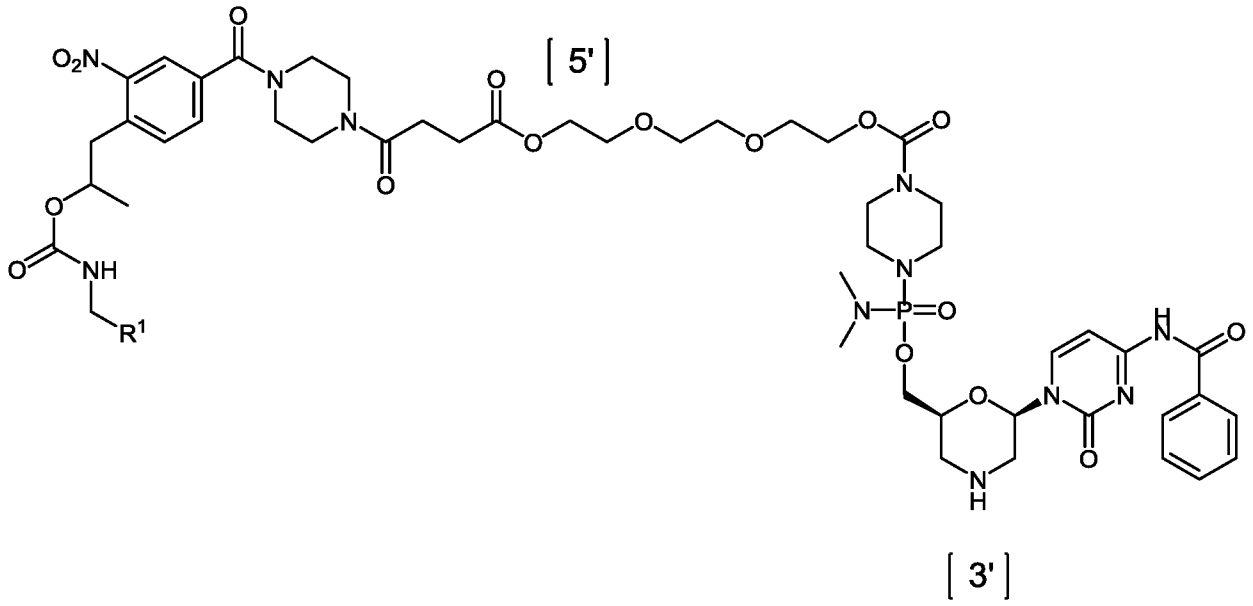
In another aspect, provided herein is a compound of Formula (VI):



(VI);

or a pharmaceutically acceptable salt thereof, wherein R^1 is a support-medium.

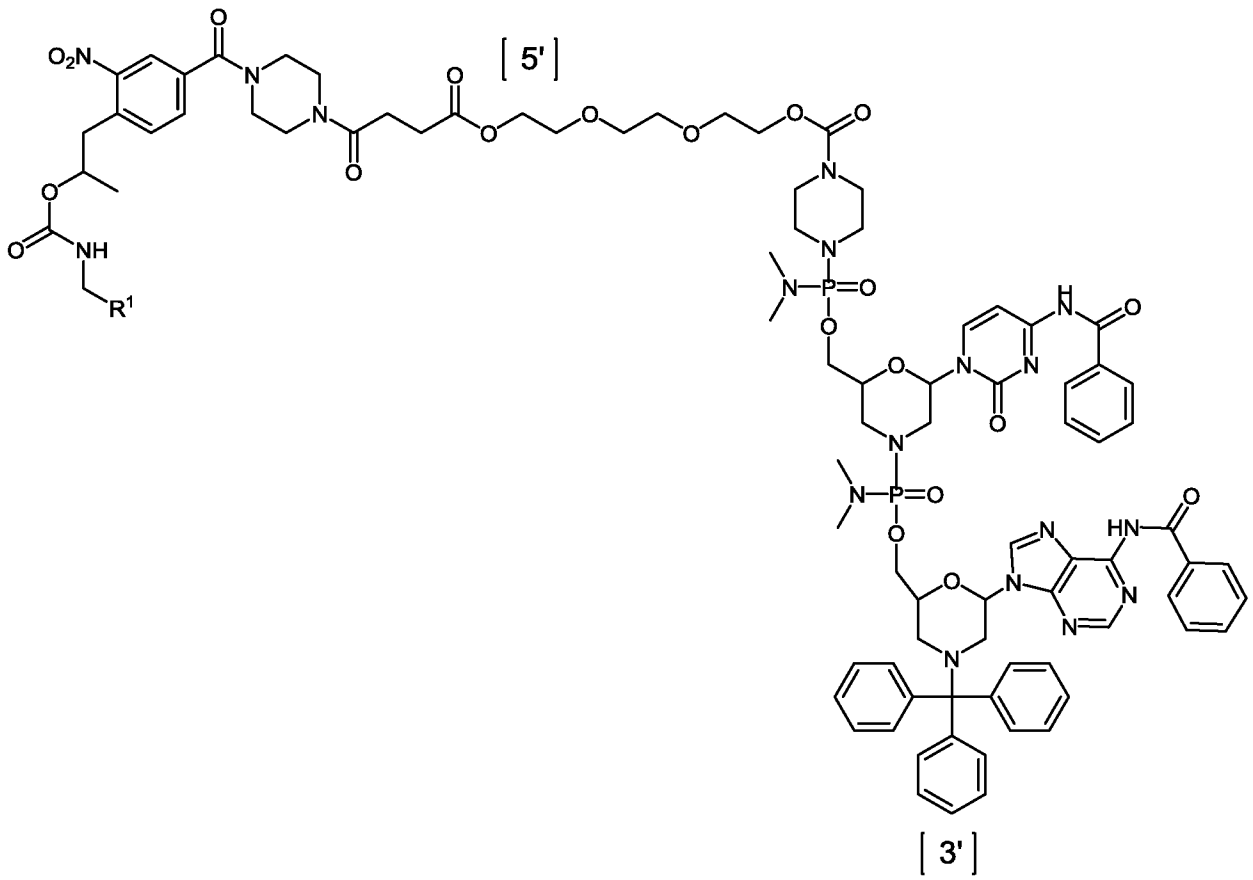
In one embodiment, the compound of Formula (VI) is of Formula (VIa):



(VIa);

or a pharmaceutically acceptable salt thereof, wherein R^1 is a support-medium.

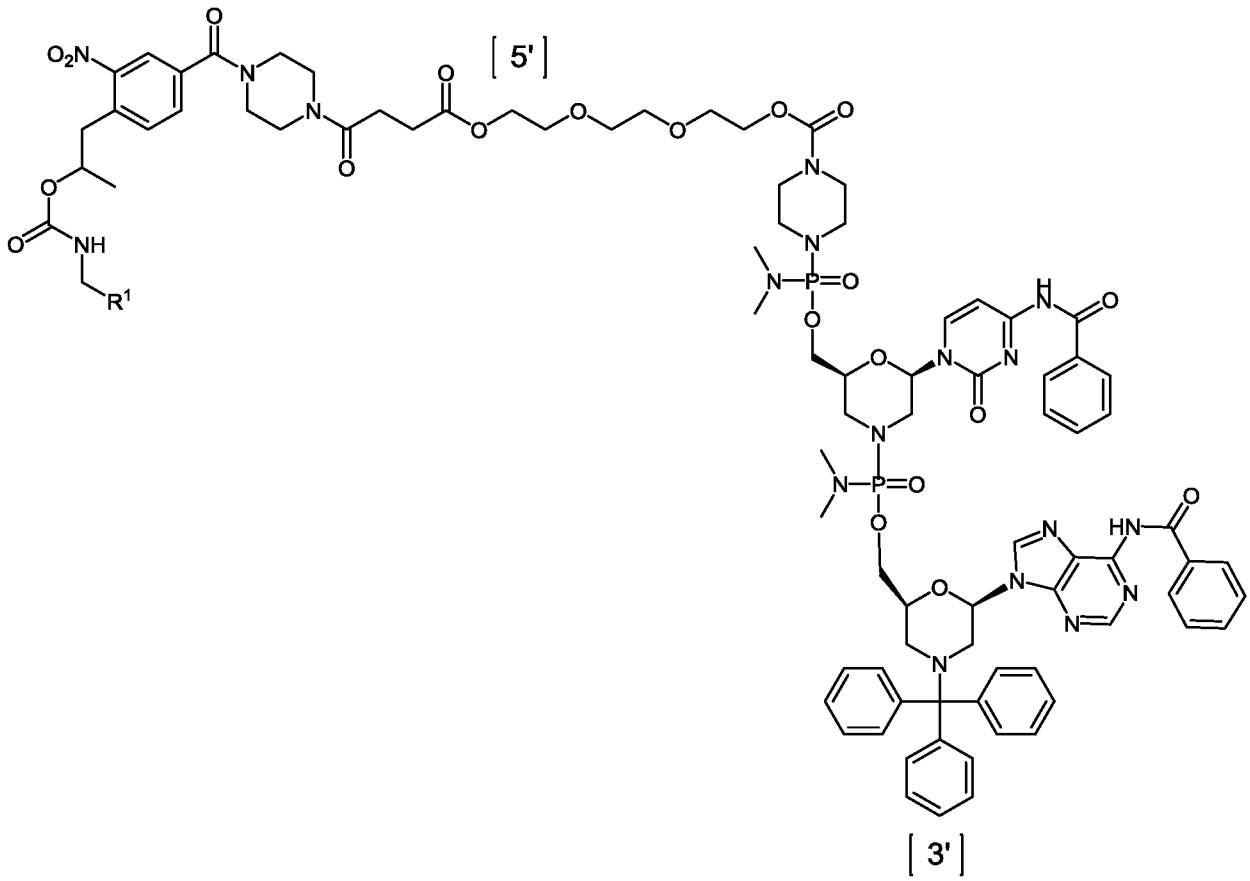
In another aspect, provided herein is a compound of Formula (VII):



(VII);

or a pharmaceutically acceptable salt thereof, wherein R^1 is a support-medium.

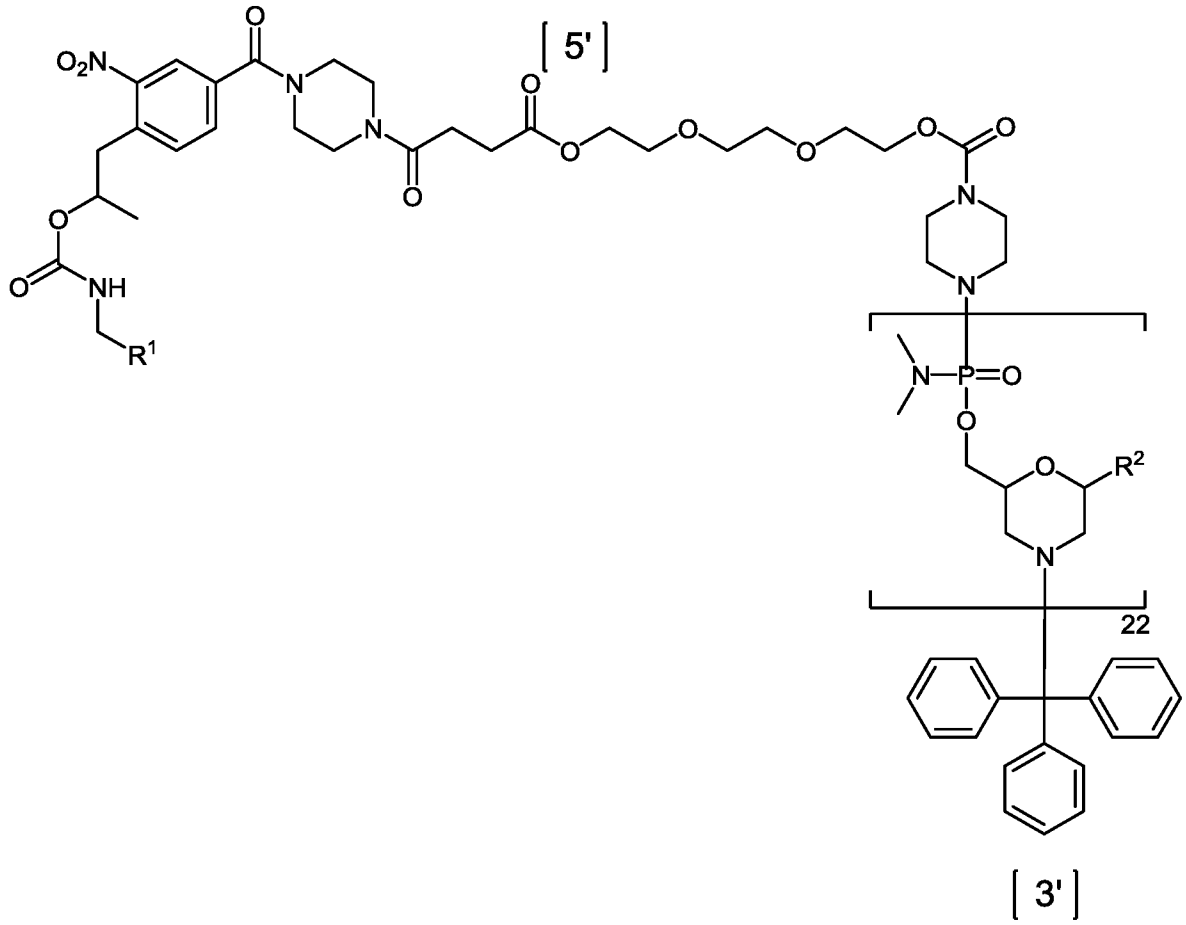
In one embodiment, the compound of Formula (VII) is of Formula (VIIa):



(VIIa);

or a pharmaceutically acceptable salt thereof, wherein R^1 is a support-medium.

In another aspect, provided herein is a compound of Formula (IX):

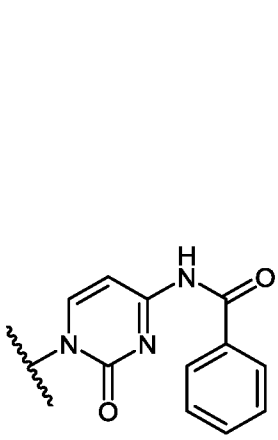


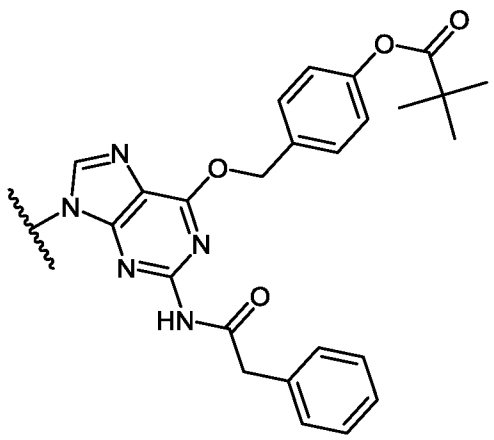
(IX),

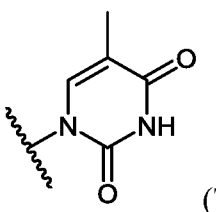
or a pharmaceutically acceptable salt thereof, wherein:

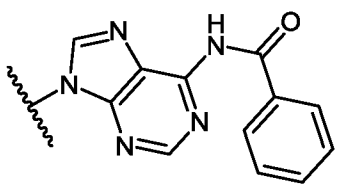
R^1 is a support-medium, and

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),

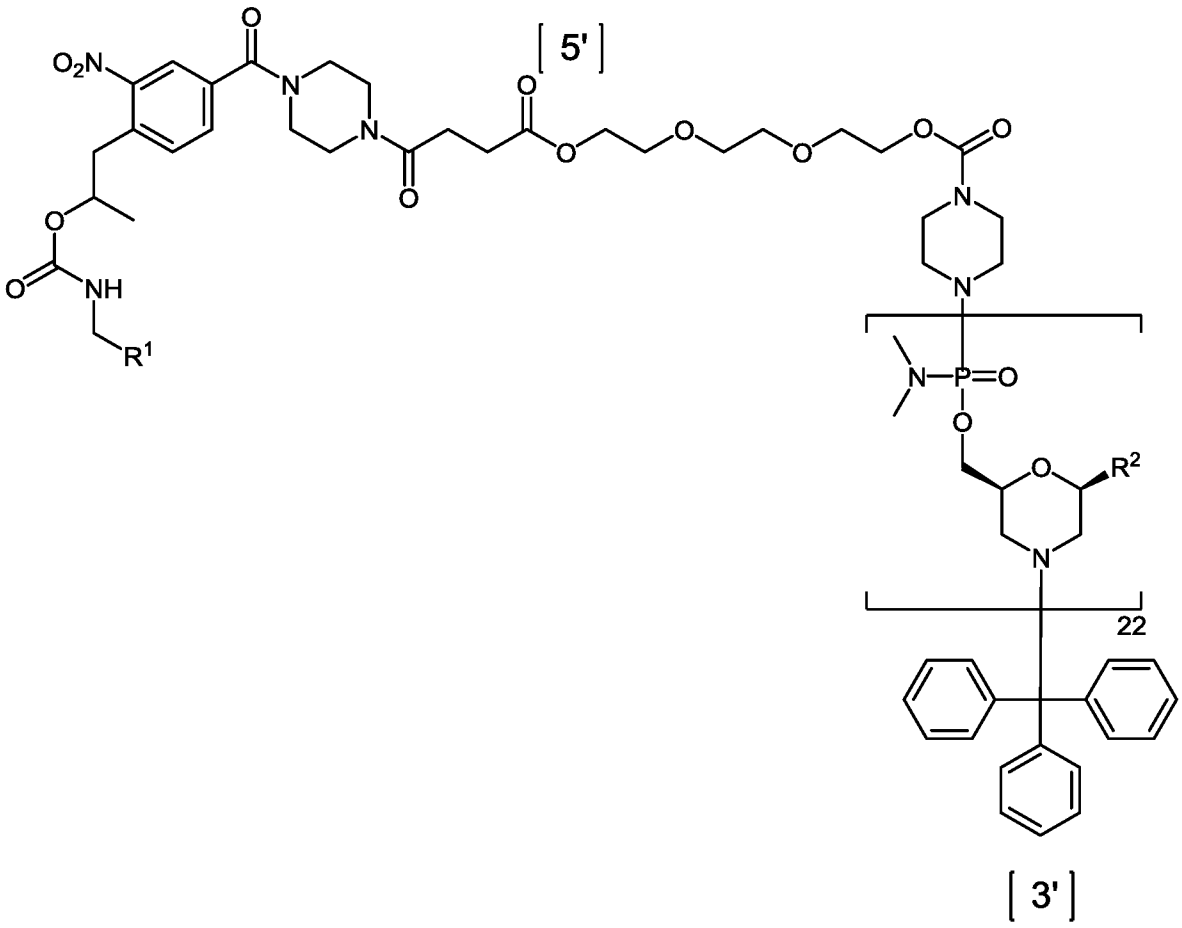

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

In one embodiment, the compound of Formula (IX) is of Formula (IXa):

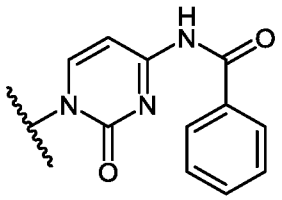


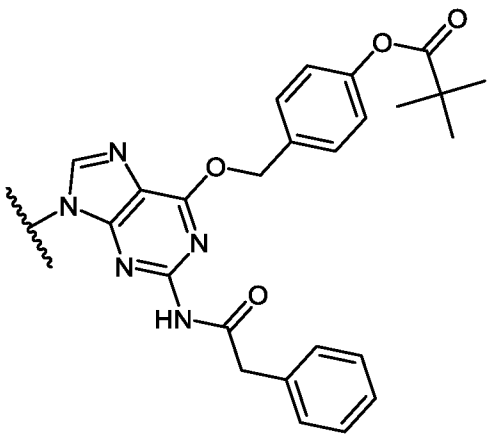
(IXa),

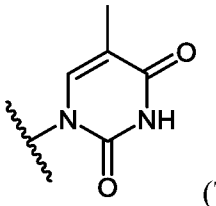
or a pharmaceutically acceptable salt thereof, wherein

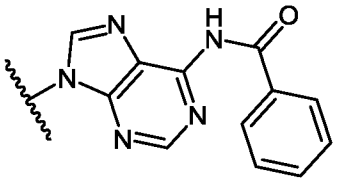
R^1 is a support-medium, and

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),

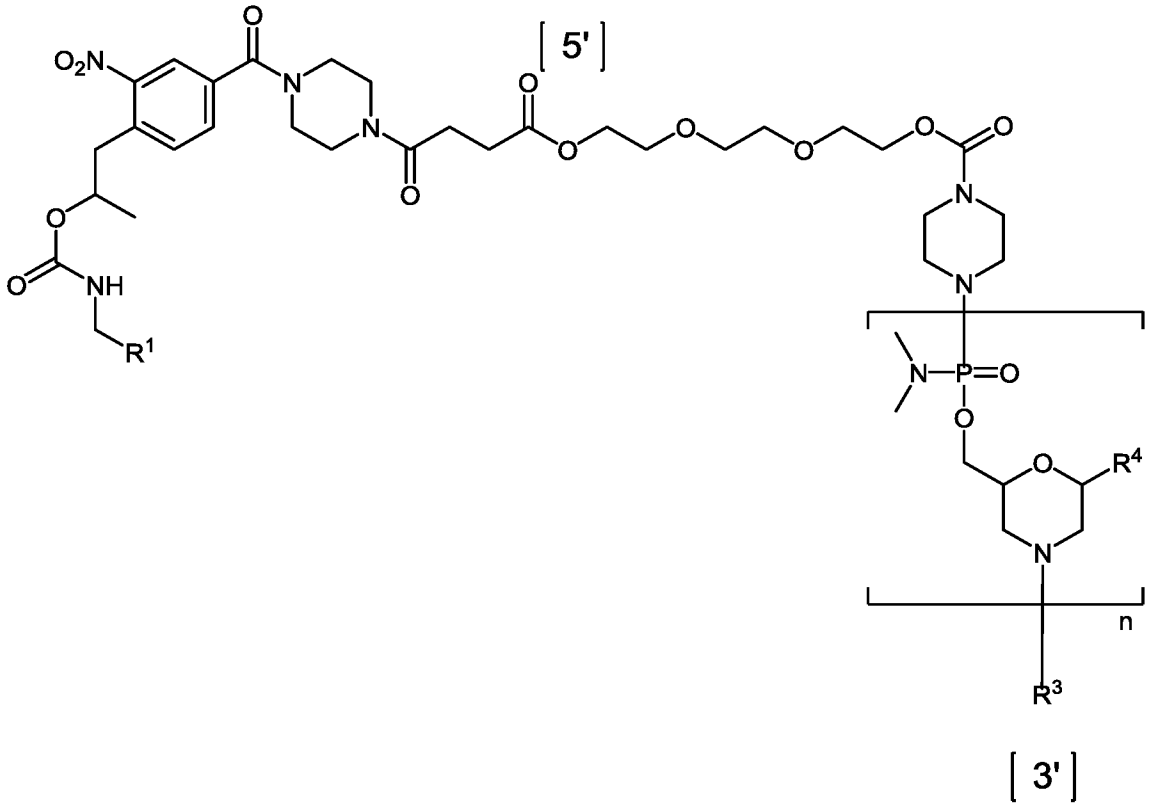

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

In another aspect, provided herein is a compound of Formula (A9):



(A9),

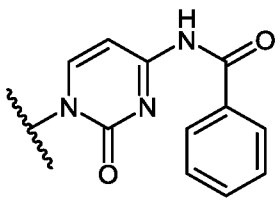
or a pharmaceutically acceptable salt thereof, wherein:

n is an integer from 10 to 40;

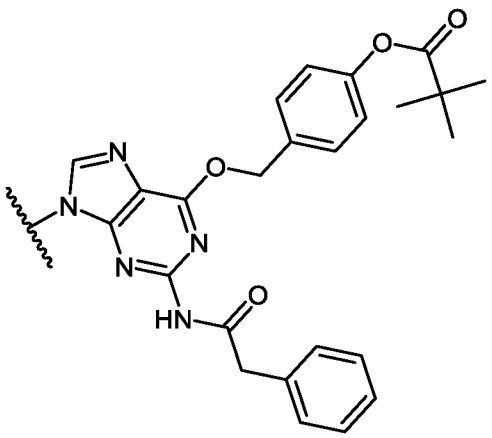
R^1 is a support-medium;

R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl; and

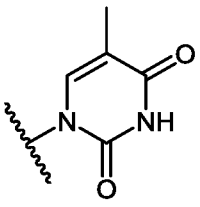
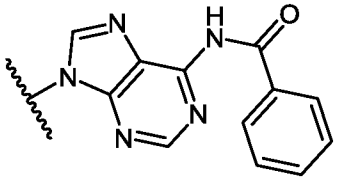
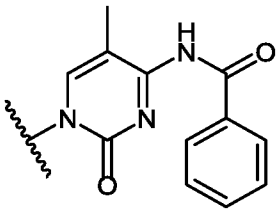
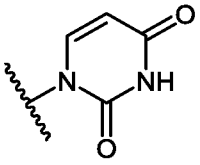
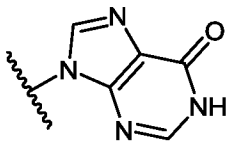
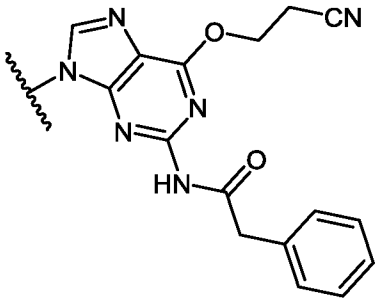
R^4 is, independently at each occurrence, selected from the group consisting of:



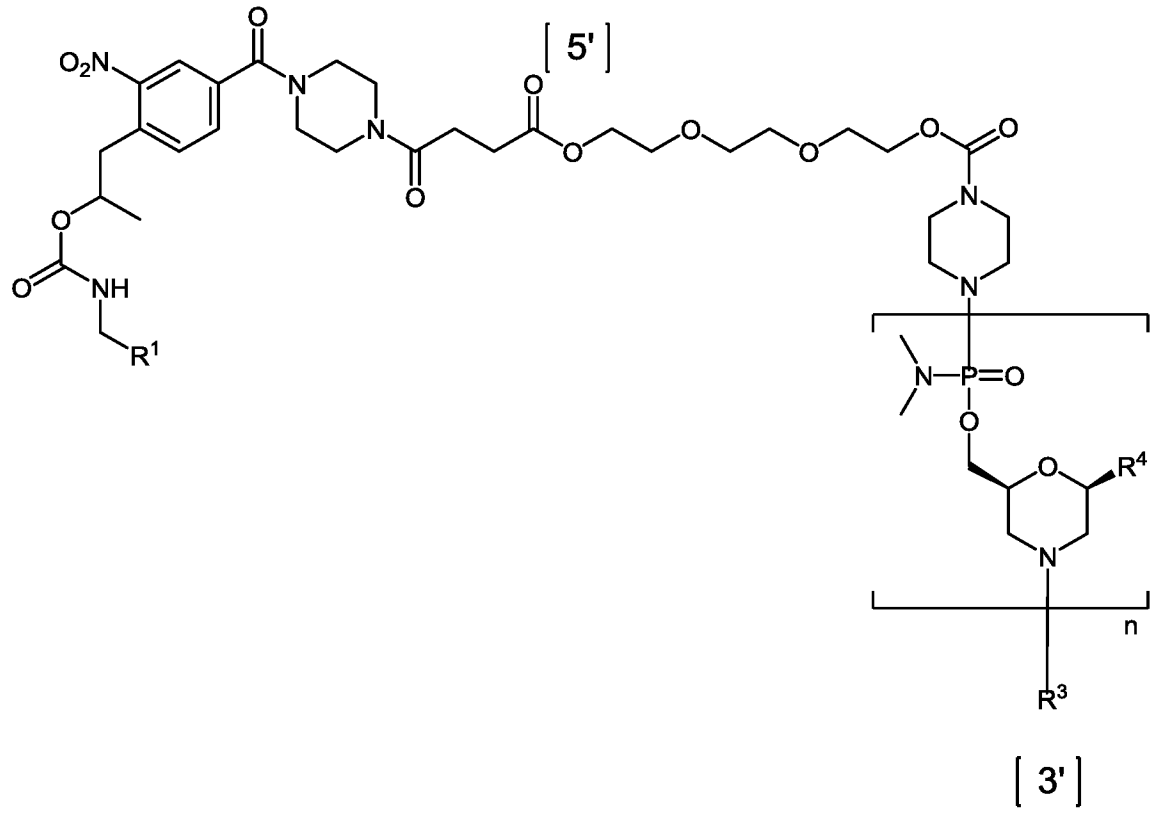
(PC),



(DPG),


(T),

(PA),

(P5mC),

(U),

(I), and

(PG).

In one embodiment, the compound of Formula (A9) is of Formula (A9a):



(A9a),

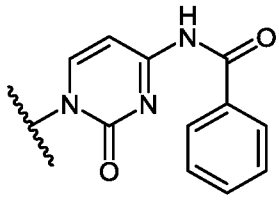
or a pharmaceutically acceptable salt thereof, wherein:

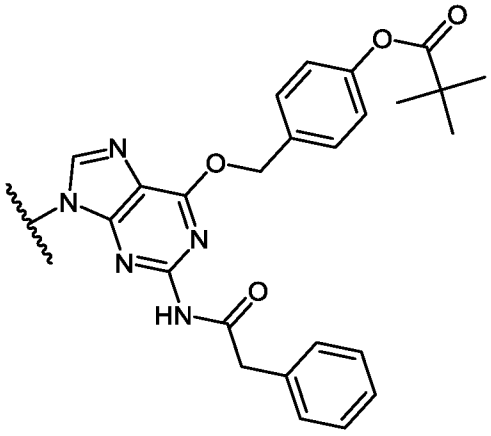
n is an integer from 10 to 40;

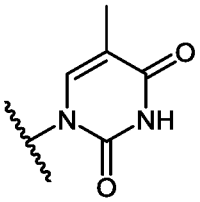
R^1 is a support-medium;

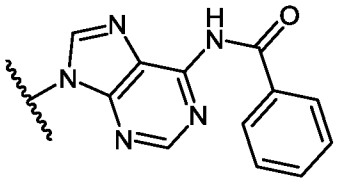
R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl; and

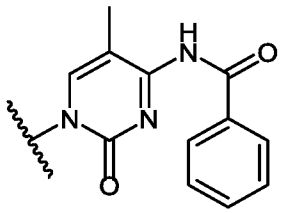
R^4 is, independently at each occurrence, selected from the group consisting of:

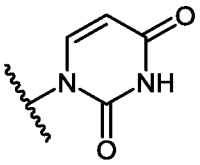

(PC),

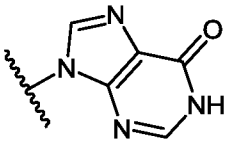

(DPG),

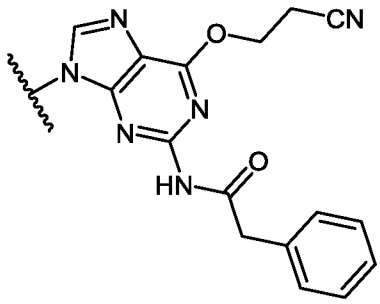

(T),


(PA),

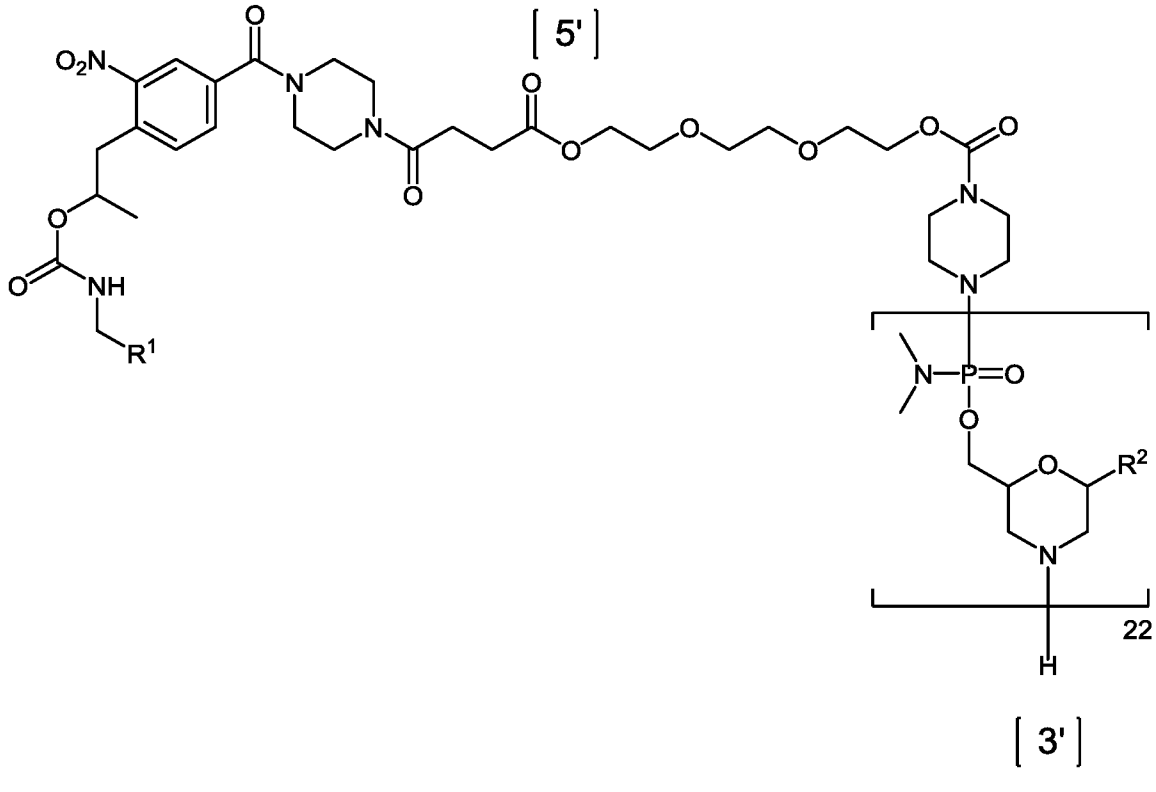

(P5mC),


(U),


(I), and


(PG).

In another aspect, provided herein is a compound of Formula (X):

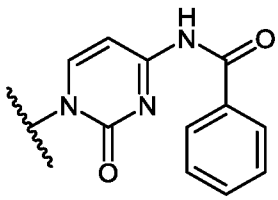


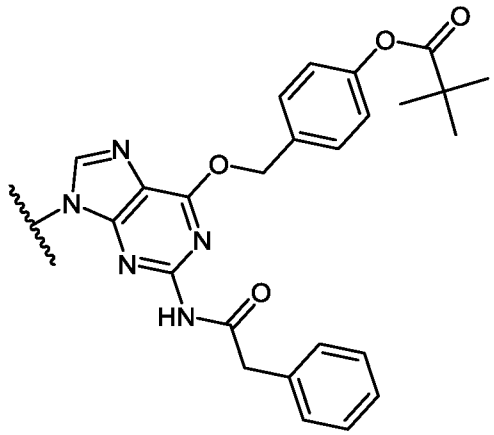
(X);

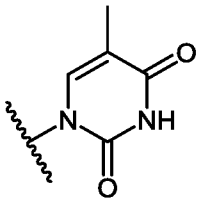
or a pharmaceutically acceptable salt thereof, wherein

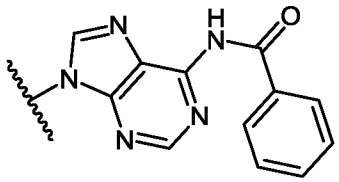
R^1 is a support-medium, and

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),

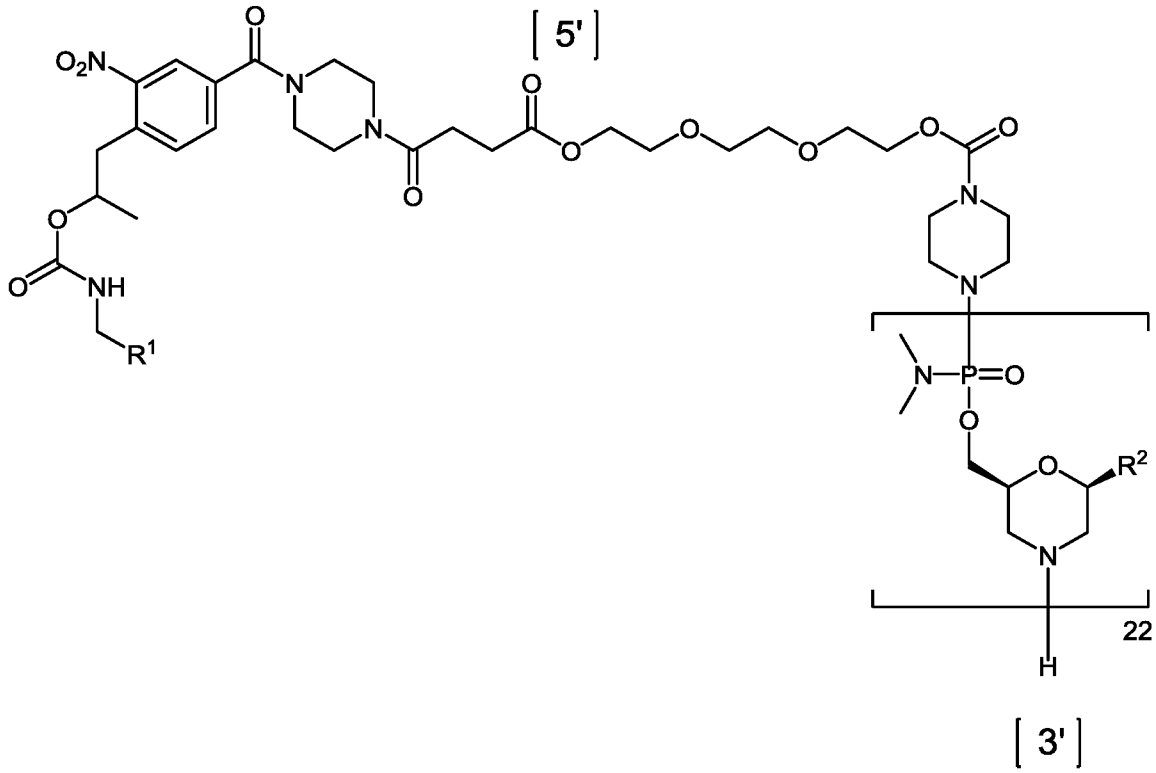

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

In one embodiment, the compound of Formula (X) is of Formula (Xa):

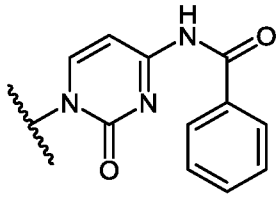


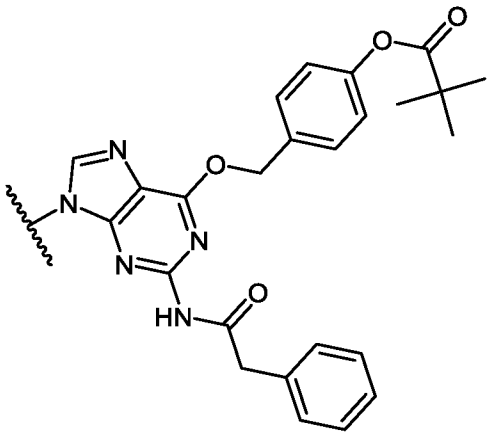
(Xa),

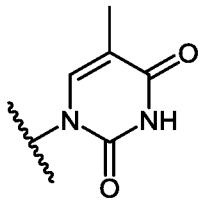
or a pharmaceutically acceptable salt thereof, wherein

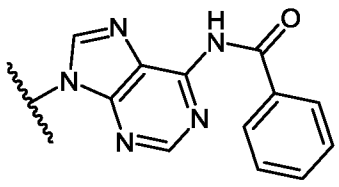
R^1 is a support-medium, and

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),

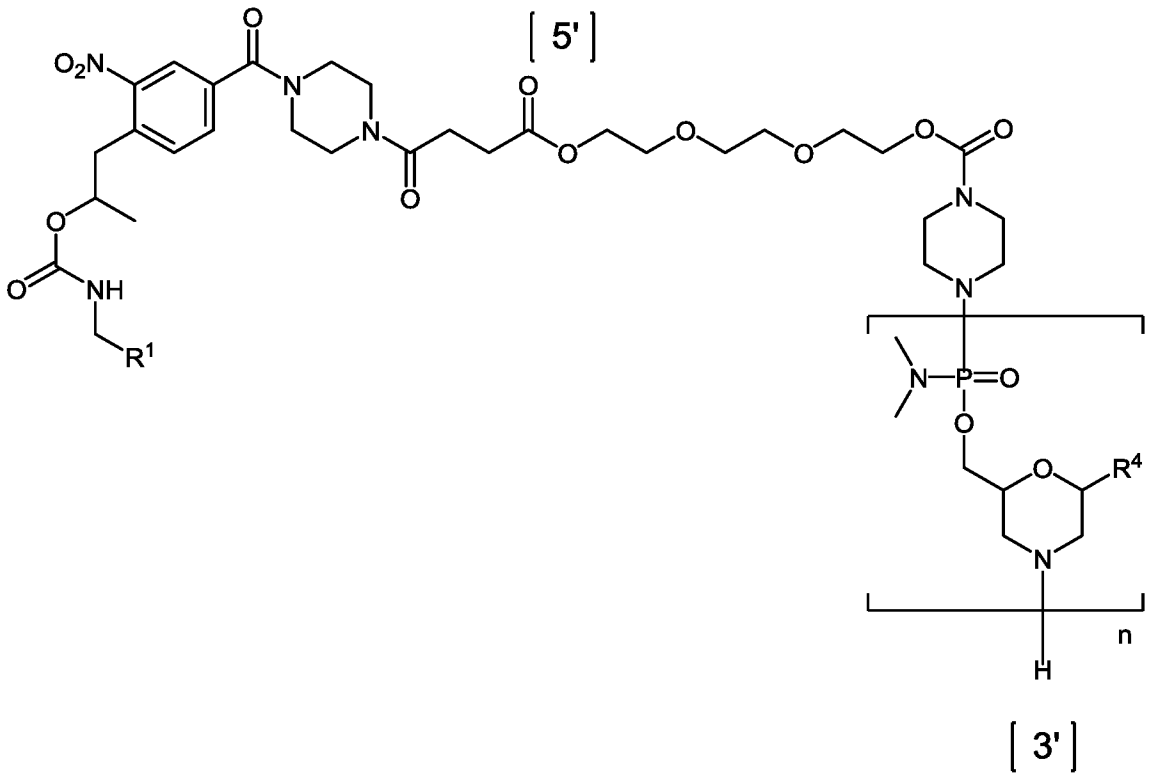

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

In another aspect, provided herein is a compound of Formula (A10):



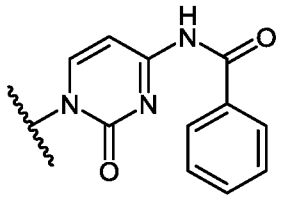
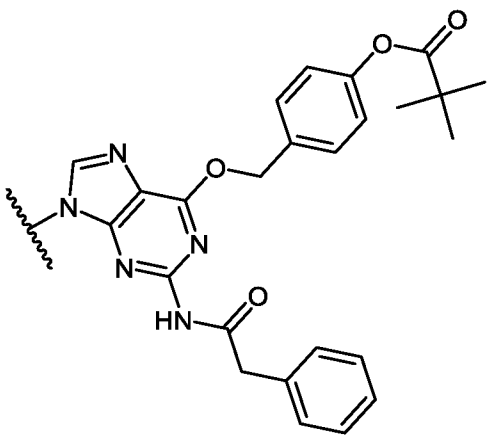
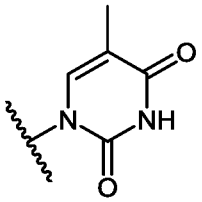
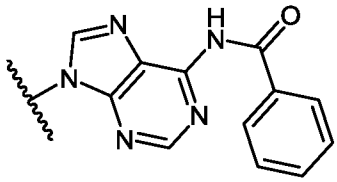
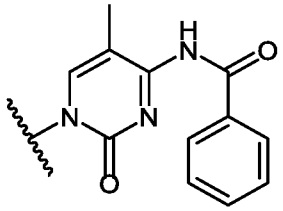
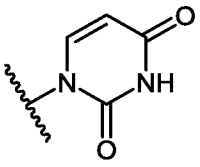
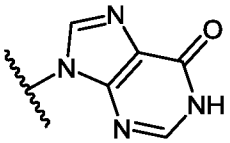
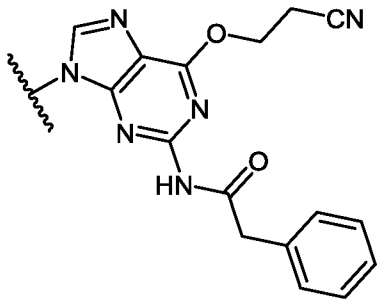
(A10),

or a pharmaceutically acceptable salt thereof, wherein:

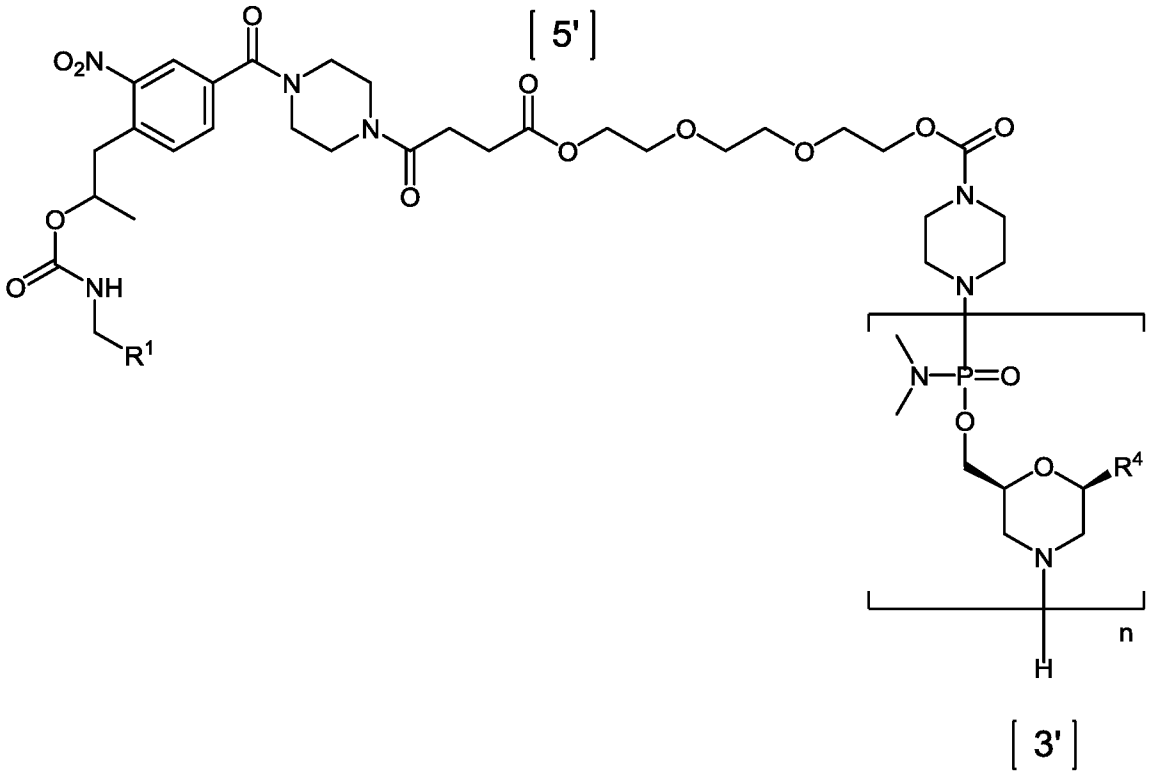
n is an integer from 10 to 40;

R^1 is a support-medium; and

R^4 is, independently at each occurrence, selected from the group consisting of:


(PC),

(DPG),

(T),

(PA),

(P5mC),

(U),

(I), and

(PG).

In one embodiment, the compound of Formula (A10) is of Formula (A10a):



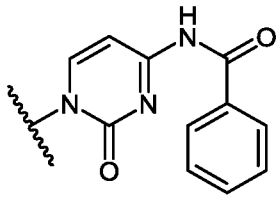
(A10a),

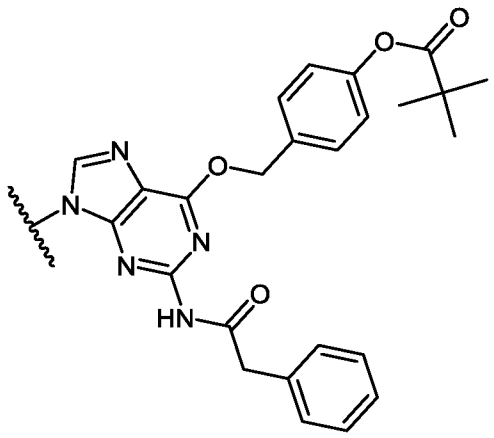
or a pharmaceutically acceptable salt thereof, wherein:

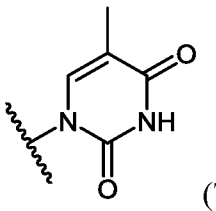
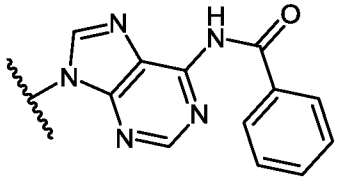
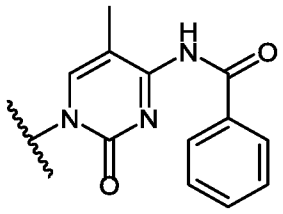
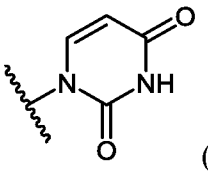
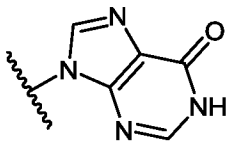
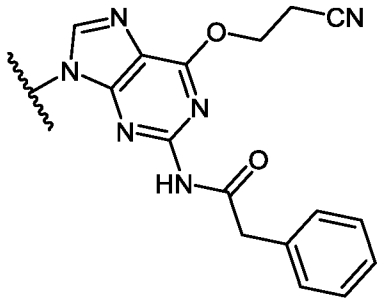
n is an integer from 10 to 40;

R^1 is a support-medium; and

R^4 is, independently at each occurrence, selected from the group consisting of:

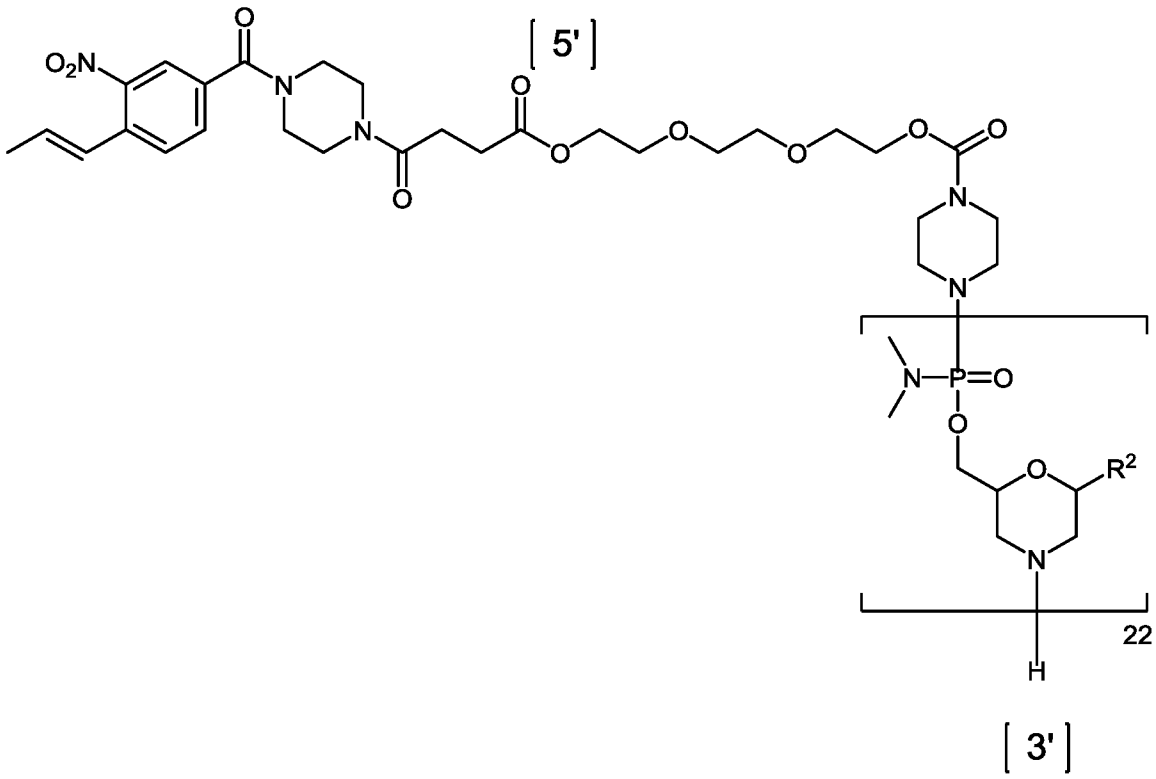

(PC),


(DPG),


(T),

(PA),

(P5mC),

(U),

(I), and

(PG).

In another embodiment of these compounds, the support-medium comprises polystyrene with 1% crosslinked divinylbenzene.

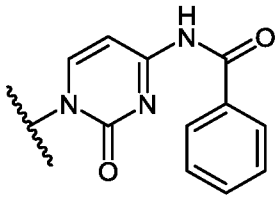
In another aspect, provided herein is a compound of Formula (XI):

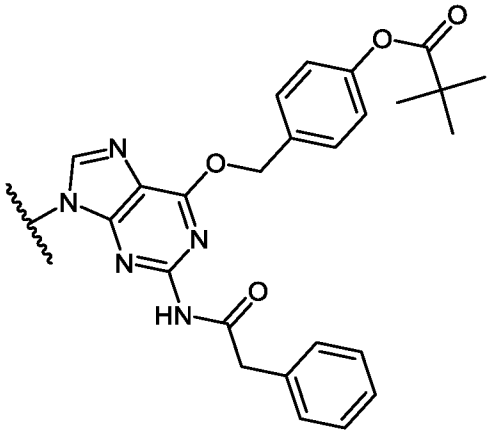


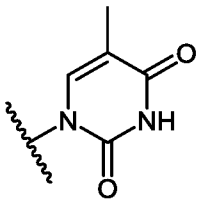
(XI),

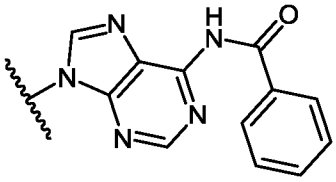
or a pharmaceutically acceptable salt thereof, wherein:

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),

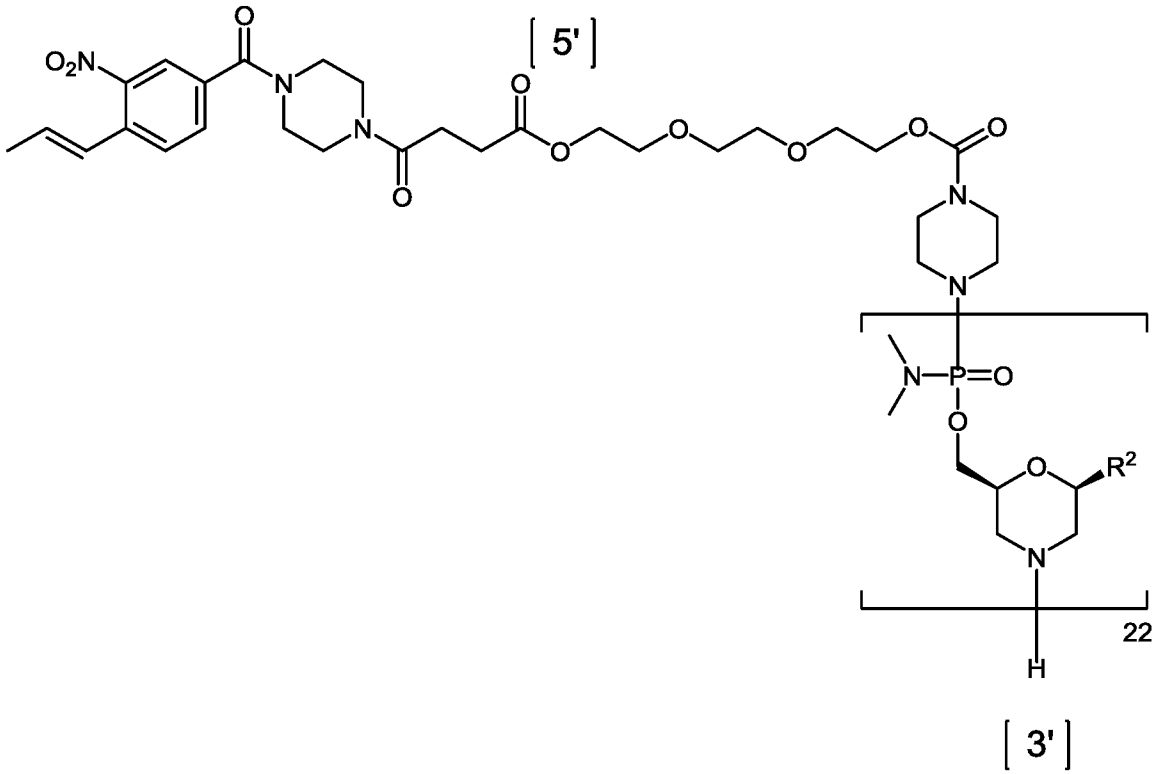

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

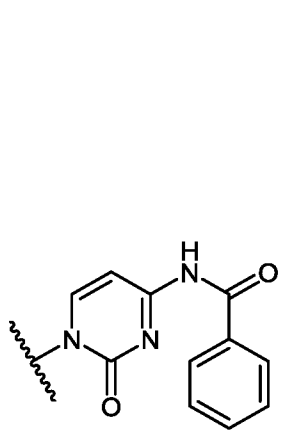
In one embodiment, the compound of Formula (XI) is of Formula (XIa):

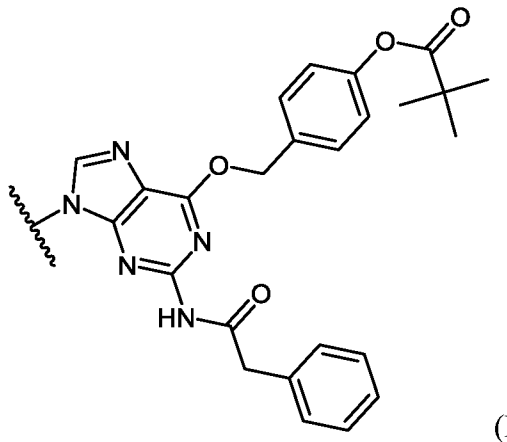


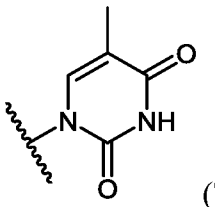
(XIa),

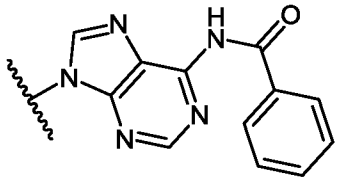
or a pharmaceutically acceptable salt thereof, wherein

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),

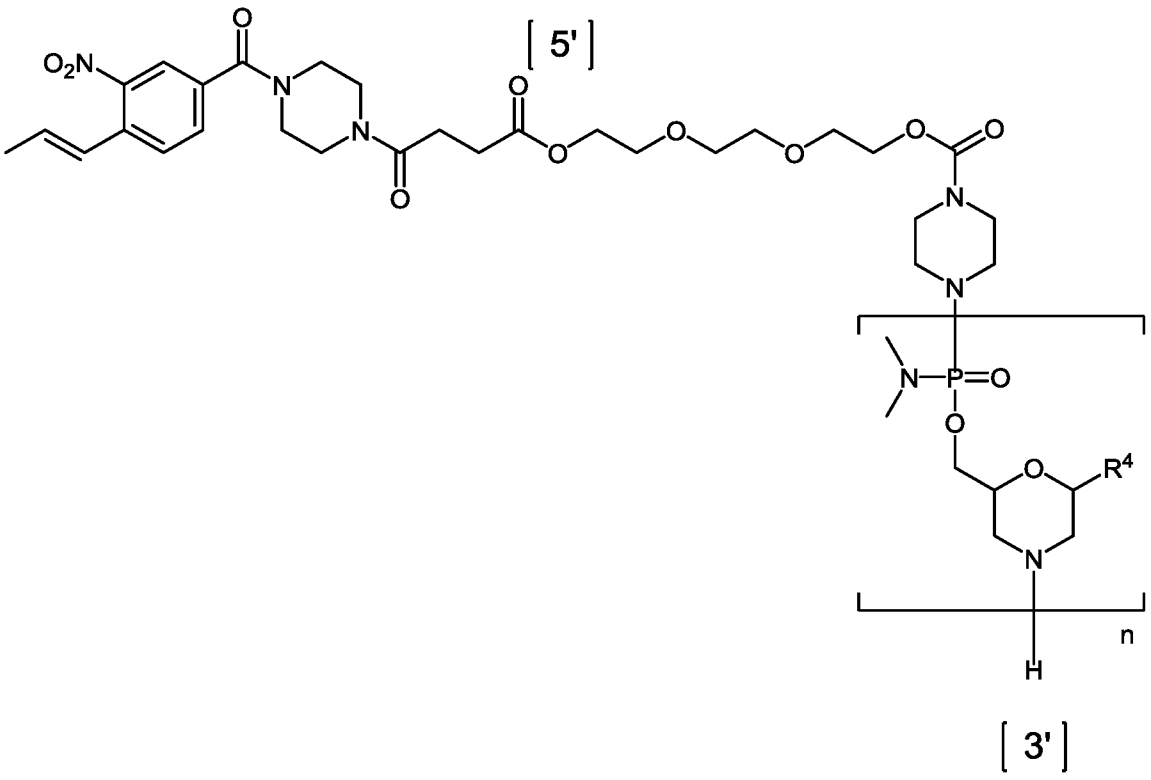

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

In another aspect, provided herein is a compound of Formula (A11):

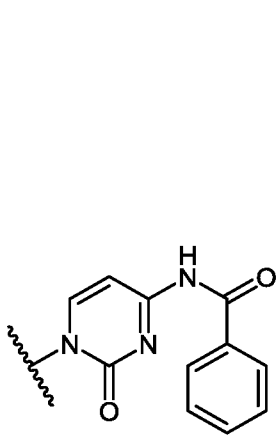


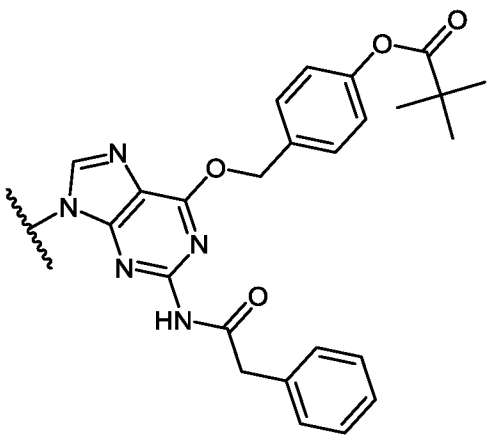
(A11),

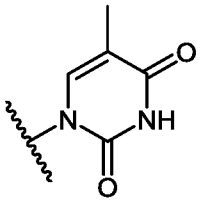
or a pharmaceutically acceptable salt thereof, wherein:

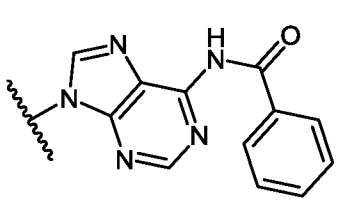
n is an integer from 10 to 40; and

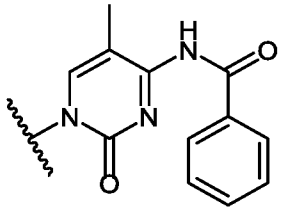
R^4 is, independently at each occurrence, selected from the group consisting of:

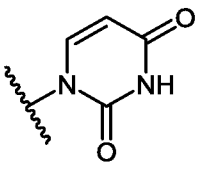

(PC),

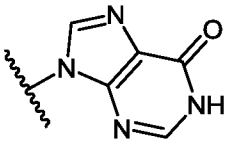

(DPG),

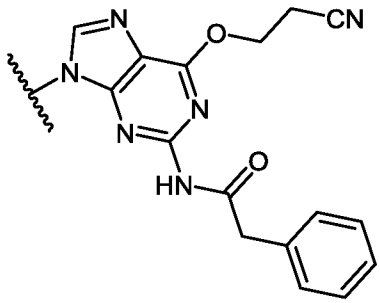

(T),


(PA),

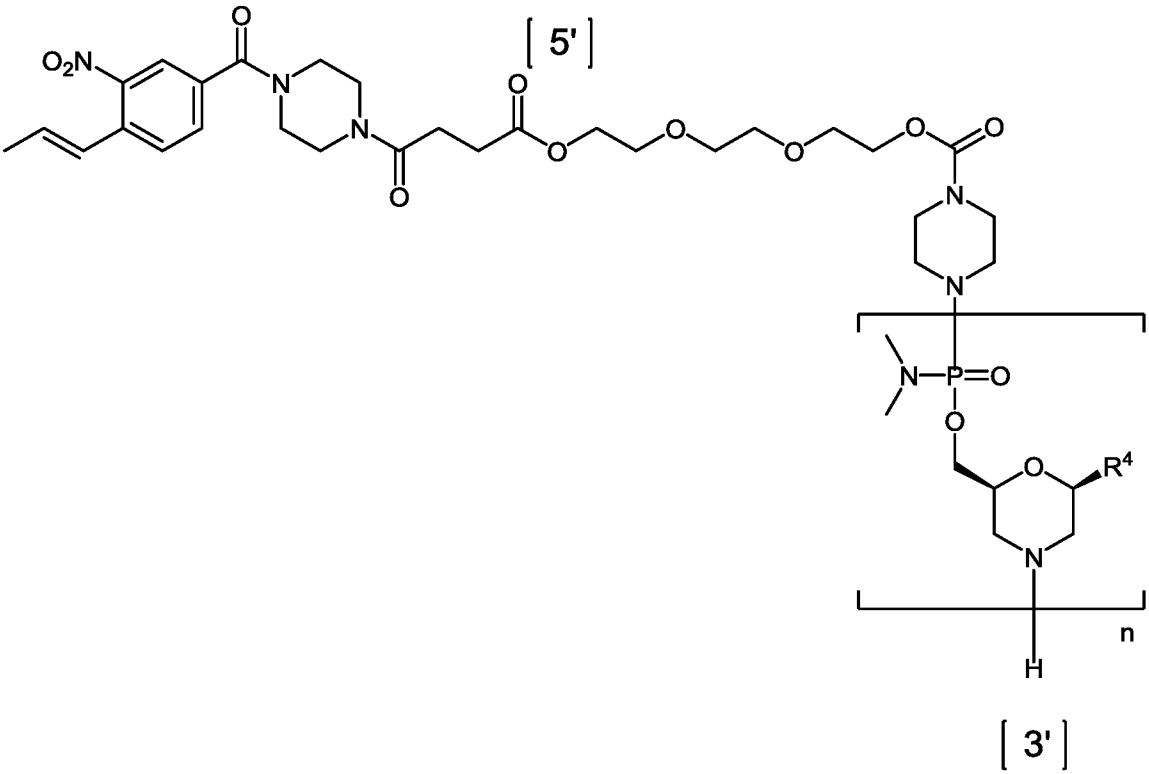

(P5mC),


(U),


(I), and


(PG).

In one embodiment, the compound of Formula (A11) is of formula (A11a):

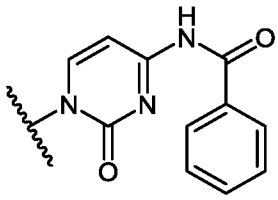


(A11a),

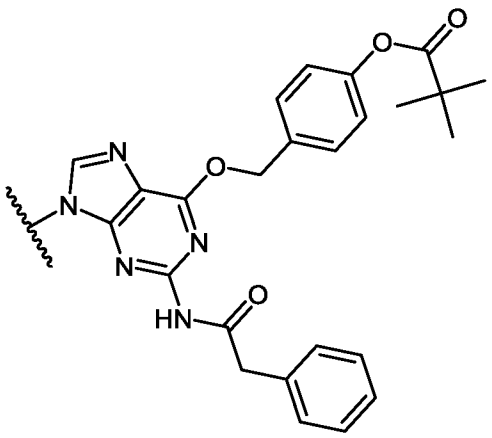
or a pharmaceutically acceptable salt thereof, wherein:

n is an integer from 10 to 40; and

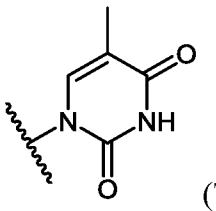
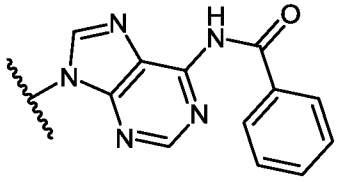
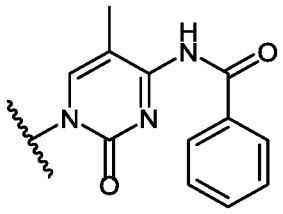
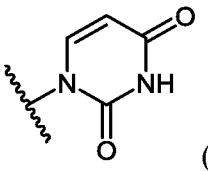
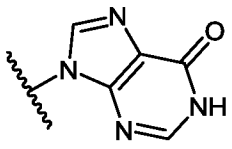
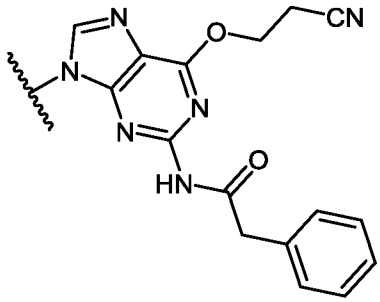
R^4 is, independently at each occurrence, selected from the group consisting of:



(PC),



(DPG),


(T),

(PA),

(P5mC),

(U),

(I), and

(PG).

Oligomers

Important properties of morpholino-based subunits include: 1) the ability to be linked in an oligomeric form by stable, uncharged or positively charged backbone linkages; 2) the ability to support a nucleotide base (e.g. adenine, cytosine, guanine, thymidine, uracil, 5-methyl-cytosine and hypoxanthine) such that the polymer formed can hybridize with a complementary-base target nucleic acid, including target RNA; 3) the ability of the oligomer to be actively or passively transported into mammalian cells; and 4) the ability of the oligomer and oligomer:RNA heteroduplex to resist RNAse and RNase H degradation, respectively.

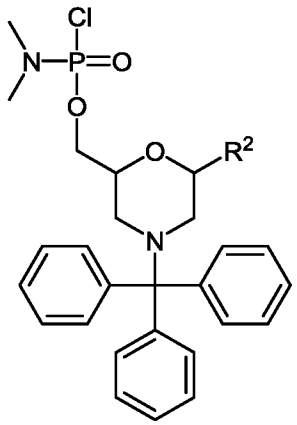
In some embodiments, the antisense oligomers contain base modifications or substitutions. For example, certain nucleo-bases may be selected to increase the binding affinity of the antisense oligomers described herein. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2°C, and may be incorporated into the antisense oligomers described herein. In one embodiment, at least one pyrimidine base of the oligomer comprises a 5-substituted pyrimidine base, wherein the pyrimidine base is selected from the group consisting of cytosine, thymine and uracil. In one embodiment, the 5-substituted pyrimidine base is 5-methylcytosine. In another embodiment, at least one purine base of the oligomer comprises hypoxanthine.

Morpholino-based oligomers (including antisense oligomers) are detailed, for example, in U.S. Patent Nos. 5,698,685, 5,217,866, 5,142,047, 5,034,506, 5,166,315, 5,185,444, 5,521,063, 5,506,337, 8,299,206, and 8, 076,476, International Patent Application Publication Nos. WO/2009/064471 and WO/2012/043730, and Summerton et al. (1997,

Antisense and Nucleic Acid Drug Development, 7, 187-195), each of which are hereby incorporated by reference in their entirety.

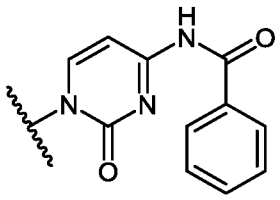
Oligomeric compounds of the disclosure may have asymmetric centers, chiral axes, and chiral planes (as described, for example, in: E. L. Eliel and S. H. Wilen, *Stereo-chemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190, and March, J., *Advanced Organic Chemistry*, 3d. Ed., Chap. 4, John Wiley & Sons, New York (1985)), and may occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers. Oligomeric compounds of the disclosure herein specifically mentioned, without any indication of its stereo-chemistry, are intended to represent all possible isomers and mixtures thereof.

Specifically, without wishing to be bound by any particular theory, oligomeric compounds of the disclosure are prepared, as discussed herein, from activated morpholino subunits including such non-limiting examples such as a compound of Formula (VIII):

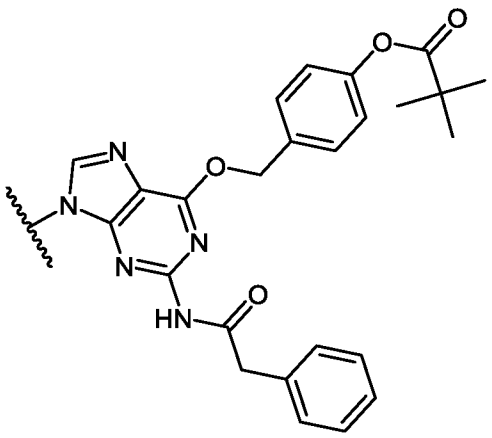


(VIII);

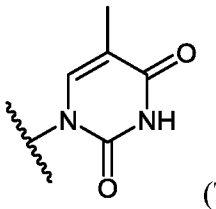
wherein R^2 is, independently for each compound of Formula (VIII), selected from the group consisting of:



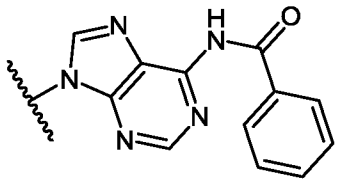
(PC),



(DPG),

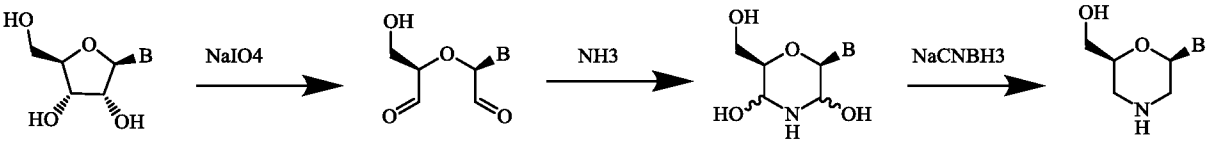


(T), and



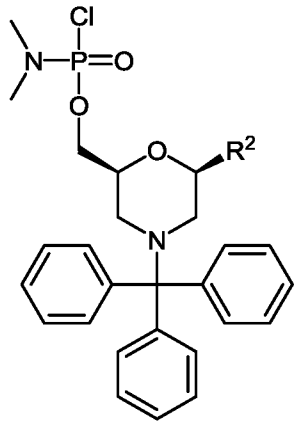
(PA).

Each of the above-mentioned compounds of Formula (VIII), may be prepared, for example, from the corresponding beta-D-ribofuranosyl as depicted below:



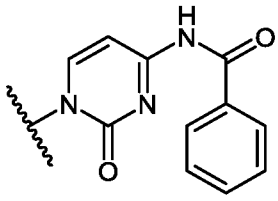
See Summerton et al., *Antisense & Nucleic Acid Drug Dev.* 7:187-195 (1997). Without being bound by any particular theory, the stereo chemistry of the two chiral carbons is retained under the synthetic conditions such that a number of possible stereo isomers of each morpholino subunit may be produced based on selection of, for example, an alpha-L-ribofuranosyl, alpha-D- ribofuranosyl, beta-L-ribofuranosyl, or beta-D-ribofuranosyl starting material.

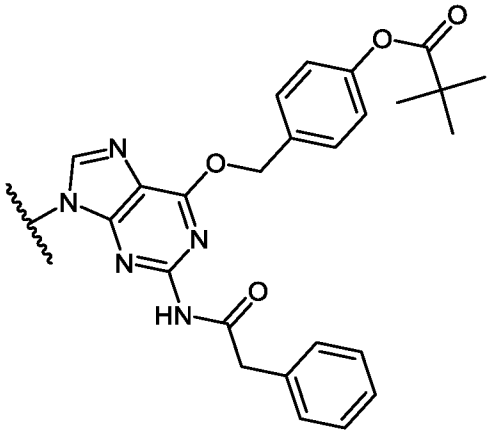
For example, in some embodiments, a compound of Formula (VIII) of the disclosure may be of Formula (VIIIa):

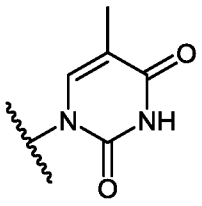


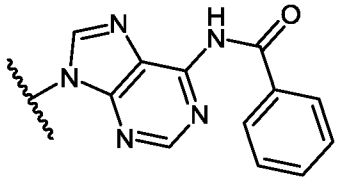
(VIIIa);

wherein R^2 is, independently for each compound of Formula (VIIIa), selected from the group consisting of:


(PC),


(DPG),


(T), and


(PA).

Without wishing to be bound by any particular theory, incorporation of 10 to 40 compounds of Formula (VIII), for example, into an oligomeric compound of the disclosure may result in numerous possible stereoisomers.

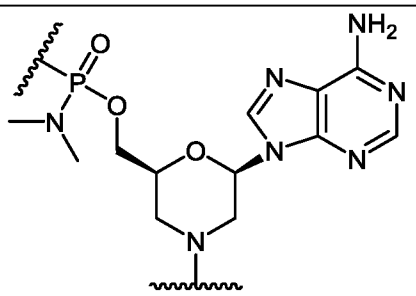
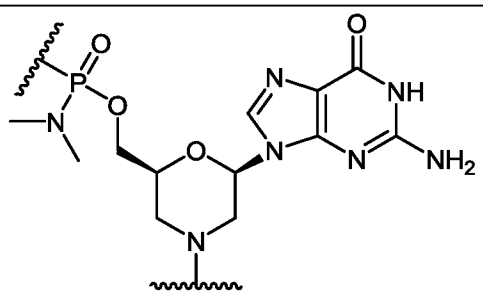
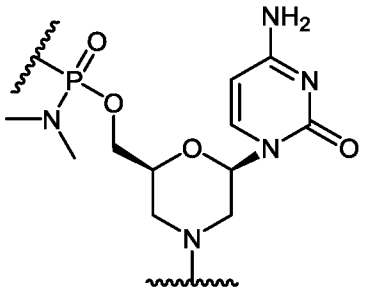
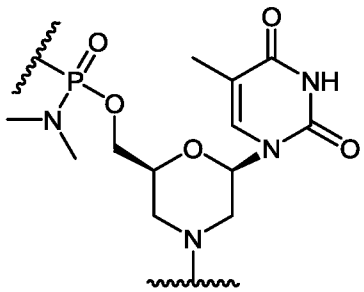
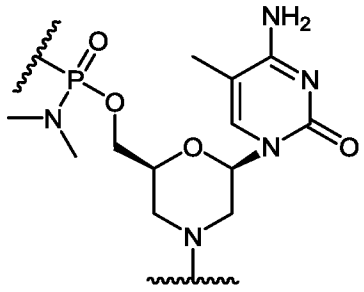
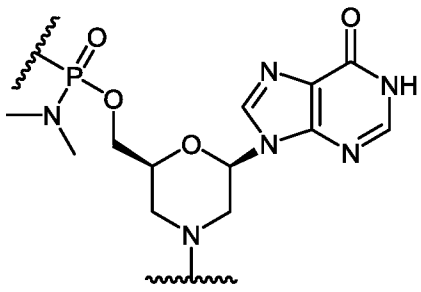
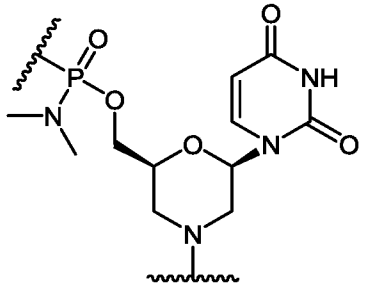
Without wishing to be bound by any particular theory, oligomeric compounds of the disclosure comprise one or more phosphorous-containing intersubunits, which create a chiral center at each phosphorus, each of which is designated as either an "Sp" or "Rp" configuration as understood in the art. Without wishing to be bound by any particular theory, this chirality creates stereoisomers, which have identical chemical composition but different three-dimensional arrangement of their atoms.

Without wishing to be bound by any particular theory, the configuration of each phosphorous intersubunit linkage occurs randomly during synthesis of, for example, oligomeric compounds of the disclosure. Without wishing to be bound by any particular theory, the synthesis process generates an exponentially large number of stereoisomers of an oligomeric compound of the disclosure because oligomeric compounds of the disclosure are comprised of numerous phosphorous intersubunit linkages – with each phosphorous intersubunit linkage having a random chiral configuration. Specifically, without wishing to be bound by any particular theory, each intersubunit linkage of an additional morpholino subunit doubles the number of stereoisomers of the product, so that a conventional preparation of an oligomeric compound of the disclosure is in fact a highly heterogeneous mixtures of 2^N stereoisomers, where N represents the number of phosphorous intersubunit linkages.

Thus, unless otherwise indicated, all such isomers, including diastereomeric and enantiomeric mixtures, and pure enantiomers and diastereomers are included such as, for example, when one or more bonds from one or more stereo center is indicated by "-" or "~~" or an equivalent as would be understood in the art.

Table 1 depicts various embodiments of morpholino subunits provided in the processes described herein.

Table 1: Various embodiments of morpholino subunits.

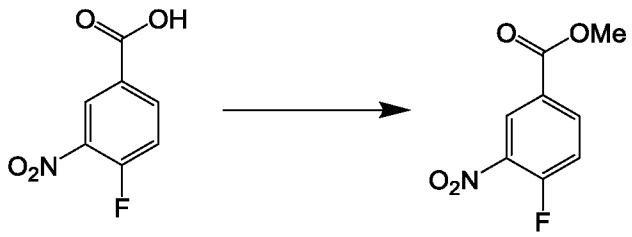
A = 	G = 
C = 	T = 
5-Me-C = 	I = 
U = 	

EXAMPLES

Examples have been set forth below for the purpose of illustration and to describe certain specific embodiments of the disclosure. However, the scope of the claims is not to be in any way limited by the examples set forth herein. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations or methods of the disclosure may be made without departing from the spirit of the disclosure and the scope of the appended claims. Definitions of the variables in the structures in the schemes herein are commensurate with those of corresponding positions in the formulae presented herein.

Example 1: NCP2 Anchor Synthesis

1. Preparation of Methyl 4-Fluoro-3-Nitrobenzoate (**1**)

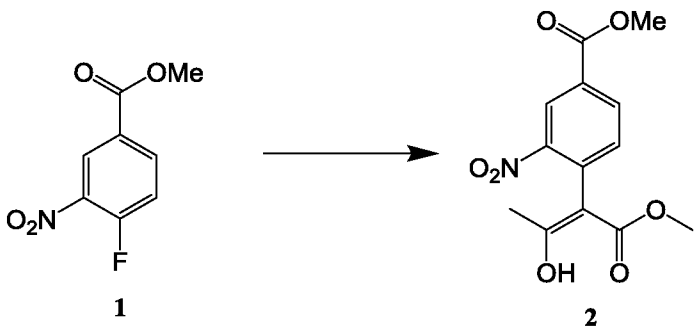


1

To a 100L flask was charged 12.7kg of 4-fluoro-3-nitrobenzoic acid was added 40kg of methanol and 2.82kg concentrated sulfuric acid. The mixture was stirred at reflux (65° C) for 36 hours. The reaction mixture was cooled to 0° C. Crystals formed at 38° C. The mixture was held at 0° C for 4 hrs then filtered under nitrogen. The 100L flask was washed and filter cake was washed with 10kg of methanol that had been cooled to 0° C. The solid filter cake was dried on the funnel for 1 hour, transferred to trays, and dried in a vacuum oven at room temperature to a constant weight of 13.695kg methyl 4-fluoro-3-nitrobenzoate (100% yield; HPLC 99%).

2. Preparation of 3-Nitro-4-(2-oxopropyl)benzoic Acid

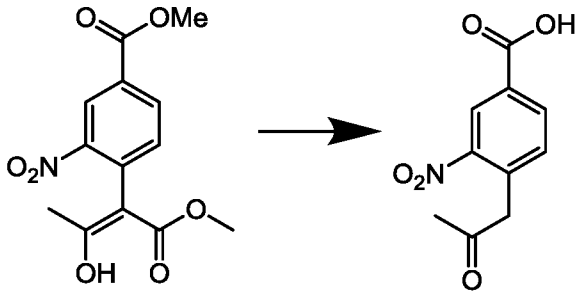
A. (Z)-Methyl 4-(3-Hydroxy-1-Methoxy-1-Oxobut-2-en-2-yl)-3-Nitrobenzoate (**2**)



1 2

To a 100L flask was charged 3.98kg of methyl 4-fluoro-3-nitrobenzoate (**1**) from the previous step 9.8kg DMF, 2.81kg methyl acetoacetate. The mixture was stirred and cooled to 0° C. To this was added 3.66kg DBU over about 4 hours while the temperature was maintained at or below 5° C. The mixture was stirred an additional 1 hour. To the reaction flask was added a solution of 8.15kg of citric acid in 37.5kg of purified water while the reaction temperature was maintained at or below 15° C. After the addition, the reaction mixture was stirred an addition 30 minutes then filtered under nitrogen. The wet filter cake was returned to the 100L flask along with 14.8kg of purified water. The slurry was stirred for 10 minutes then filtered. The wet cake was again returned to the 100L flask, slurried with 14.8kg of purified water for 10 minutes, and filtered to crude (Z)-methyl 4-(3-hydroxy-1-methoxy-1-oxobut-2-en-2-yl)-3-nitrobenzoate.

B. 3-Nitro-4-(2-oxopropyl)benzoic Acid

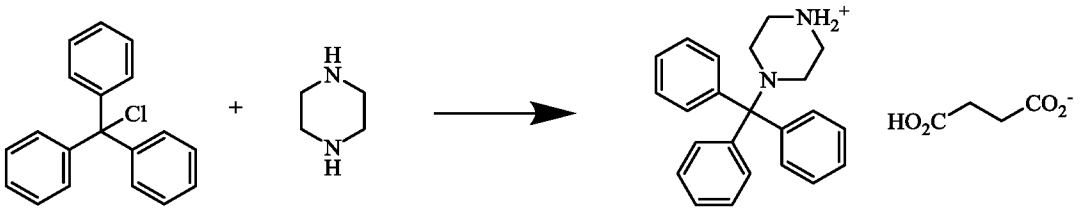


2 3

The crude (Z)-methyl 4-(3-hydroxy-1-methoxy-1-oxobut-2-en-2-yl)-3-nitrobenzoate was charged to a 100L reaction flask under nitrogen. To this was added 14.2kg 1,4-dioxane and the stirred. To the mixture was added a solution of 16.655kg concentrated HCl and 13.33kg purified water (6M HCl) over 2 hours while the temperature of the reaction mixture was maintained below 15° C. When the addition was complete, the reaction mixture was heated at reflux (80° C) for 24 hours, cooled to room temperature, and filtered under nitrogen. The solid filter cake was triturated with 14.8kg of purified water, filtered, triturated again with 14.8kg of purified water, and filtered. The solid was returned to the 100L flask with

39.9kg of DCM and refluxed with stirring for 1 hour. 1.5kg of purified water was added to dissolve the remaining solids. The bottom organic layer was split to a pre-warmed 72L flask, then returned to a clean dry 100L flask. The solution was cooled to 0° C, held for 1 hour, then filtered. The solid filter cake was washed twice each with a solution of 9.8kg DCM and 5kg heptane, then dried on the funnel. The solid was transferred to trays and dried to a constant weight of 1.855kg 3-Nitro-4-(2-oxopropyl)benzoic Acid. Overall yield 42% from compound **1.** HPLC 99.45%.

3. Preparation of N-Tritylpiperazine Succinate (NTP)

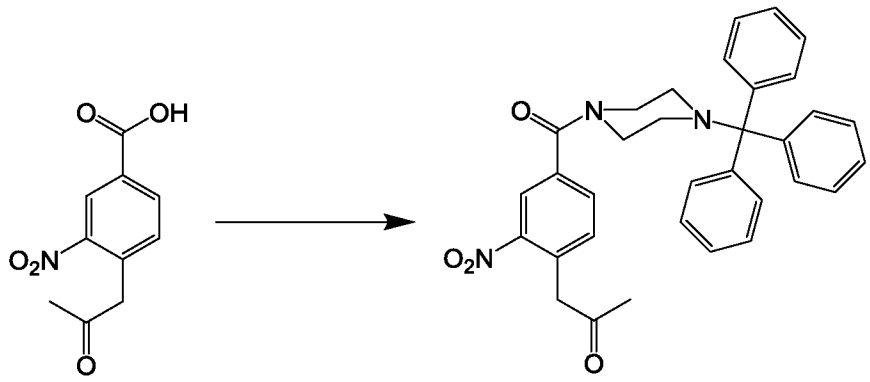


To a 72L jacketed flask was charged under nitrogen 1.805kg triphenylmethyl chloride and 8.3kg of toluene (TPC solution). The mixture was stirred until the solids dissolved. To a 100L jacketed reaction flask was added under nitrogen 5.61kg piperazine, 19.9kg toluene, and 3.72kg methanol. The mixture was stirred and cooled to 0° C. To this was slowly added in portions the TPC solution over 4 hours while the reaction temperature was maintained at or below 10° C. The mixture was stirred for 1.5 hours at 10° C, then allowed to warm to 14° C. 32.6kg of purified water was charged to the 72L flask, then transferred to the 100L flask while the internal batch temperature was maintained at 20+/-5° C. The layers were allowed to split and the bottom aqueous layer was separated and stored. The organic layer was extracted three times with 32kg of purified water each, and the aqueous layers were separated and combined with the stored aqueous solution.

The remaining organic layer was cooled to 18° C and a solution of 847g of succinic acid in 10.87kg of purified water was added slowly in portions to the organic layer. The mixture was stirred for 1.75 hours at 20+/-5° C. The mixture was filtered, and the solids were washed with 2kg TBME and 2kg of acetone then dried on the funnel. The filter cake was triturated twice with 5.7kg each of acetone and filtered and washed with 1kg of acetone between triturations. The solid was dried on the funnel, then transferred to trays and dried in a vacuum oven at room temperature to a constant weight of 2.32kg of NTP. Yield 80%.

4. Preparation of (4-(2-Hydroxypropyl)-3-NitrophenyI)(4-Tritylpiperazin-1-yl)Methanone

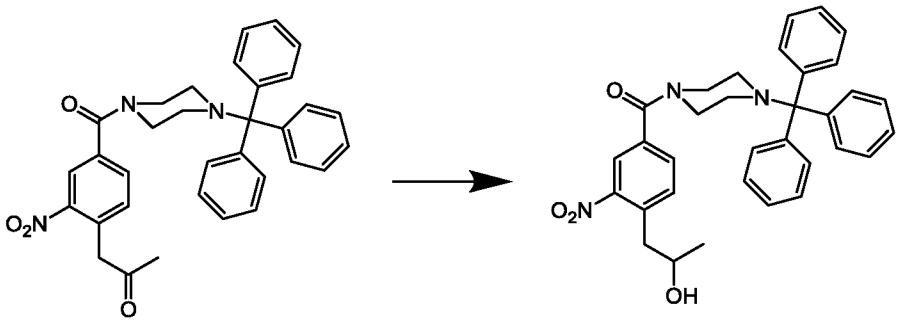
A. Preparation of 1-(2-Nitro-4(4-Tritylpiperazine-1-Carbonyl)Phenyl)Propan-2-one



3 4

To a 100L jacketed flask was charged under nitrogen 2kg of 3-Nitro-4-(2-oxopropyl)benzoic Acid (**3**), 18.3 kg DCM, 1.845kg N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC.HCl). The solution was stirred until a homogenous mixture was formed. 3.048kg of NTP was added over 30 minutes at room temperature and stirred for 8 hours. 5.44kg of purified water was added to the reaction mixture and stirred for 30 minutes. The layers were allowed to separate and the bottom organic layer containing the product was drained and stored. The aqueous layer was extracted twice with 5.65kg of DCM. The combined organic layers were washed with a solution of 1.08kg sodium chloride in 4.08kg purified water. The organic layers were dried over 1.068kg of sodium sulfate and filtered. The sodium sulfate was washed with 1.3kg of DCM. The combined organic layers were slurried with 252g of silica gel and filtered through a filter funnel containing a bed of 252g of silica gel. The silica gel bed was washed with 2kg of DCM. The combined organic layers were evaporated on a rotovap. 4.8kg of THF was added to the residue and then evaporated on the rotovap until 2.5 volumes of the crude 1-(2-nitro-4(4-tritylpiperazine-1-carbonyl)phenyl)propan-2-one in THF was reached.

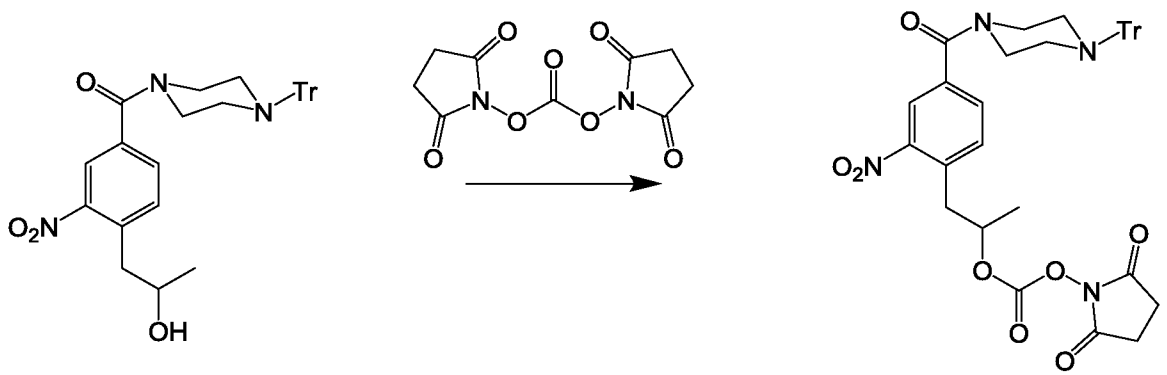
B. Preparation of (4-(2-Hydroxypropyl)-3-NitrophenyI)(4-Tritylpiperazin-1-yl)Methanone (**5**)



4 5

To a 100L jacketed flask was charged under nitrogen 3600g of **4** from the previous step and 9800g THF. The stirred solution was cooled to ≤5°C. The solution was diluted with 11525g ethanol and 194g of sodium borohydride was added over about 2 hours at ≤5° C. The reaction mixture was stirred an additional 2 hours at ≤5° C. The reaction was quenched with a solution of about 1.1kg ammonium chloride in about 3kg of water by slow addition to maintain the temperature at ≤10° C. The reaction mixture was stirred an additional 30 minutes, filtered to remove inorganics, and recharged to a 100L jacketed flask and extracted with 23kg of DCM. The organic layer was separated and the aqueous was twice more extracted with 4.7kg of DCM each. The combined organic layers were washed with a solution of about 800g of sodium chloride in about 3kg of water, then dried over 2.7kg of sodium sulfate. The suspension was filtered and the filter cake was washed with 2kg of DCM. The combined filtrates were concentrated to 2.0 volumes, diluted with about 360g of ethyl acetate, and evaporated. The crude product was loaded onto a silica gel column of 4kg of silica packed with DCM under nitrogen and eluted with 2.3kg ethyl acetate in 7.2kg of DCM. The combined fractions were evaporated and the residue was taken up in 11.7kg of toluene. The toluene solution was filtered and the filter cake was washed twice with 2kg of toluene each. The filter cake was dried to a constant weight of 2.275kg of compound **5** (46% yield from compound **3**) HPLC 96.99%.

5. Preparation of 2,5-Dioxopyrrolidin-1-yl(1-(2-Nitro-4-(4-triphenylmethylpiperazine-1 Carbonyl)Phenyl)Propan-2-yl) Carbonate (**NCP2 Anchor**)



5 **NCP2 Anchor**

To a 100L jacketed flask was charged under nitrogen 4.3kg of compound **5** (weight adjusted based on residual toluene by ^{1}H NMR; all reagents here after were scaled accordingly) and 12.7kg pyridine. To this was charged 3.160 kg of DSC (78.91 weight % by ^{1}H NMR) while the internal temperature was maintained at ≤35° C. The reaction mixture

was aged for about 22 hours at ambience then filtered. The filter cake was washed with 200g of pyridine. In two batches each comprising ½ the filtrate volume, filtrate wash charged slowly to a 100L jacketed flask containing a solution of about 11kg of citric acid in about 50 kg of water and stirred for 30 minutes to allow for solid precipitation. The solid was collected with a filter funnel, washed twice with 4.3kg of water per wash, and dried on the filter funnel under vacuum.

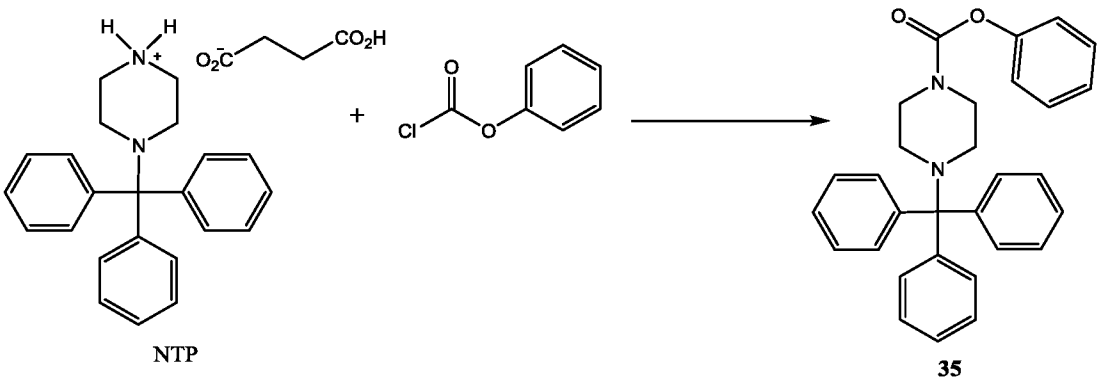
The combined solids were charged to a 100L jacketed flask and dissolved in 28kg of DCM and washed with a solution of 900g of potassium carbonate in 4.3kg of water. After 1 hour, the layers were allowed to separate and the aqueous layer was removed. The organic layer was washed with 10kg of water, separated, and dried over 3.5kg of sodium sulfate. The DCM was filtered, evaporated, and dried under vacuum to 6.16kg of **NCP2 Anchor** (114% yield).

Example 2: Anchor Loaded Resin Synthesis

To a 75L solid phase synthesis reactor was charged about 52L of NMP and 2600g of aminomethyl polystyrene resin. The resin was stirred in the NMP to swell for about 2 hours then drained. The resin was washed twice with about 39L DCM per wash, then twice with 39L Neutralization Solution per wash, then twice with 39L of DCM per wash. The NCP2 Anchor Solution was slowly added to the stirring resin solution, stirred for 24 hours at room temperature, and drained. The resin was washed four times with 39L of NMP per wash, and six times with 39L of DCM per wash. The resin was treated and stirred with ½ the DEDC Capping Solution for 30 minutes, drained, and was treated and stirred with the 2nd ½ of the DEDC Capping Solution for 30 minutes and drained. The resin was washed six times with 39L of DCM per wash then dried in an oven to constant weight of 3573.71g of Anchor Loaded Resin.

Example 3: Preparation of Activated EG3 Tail

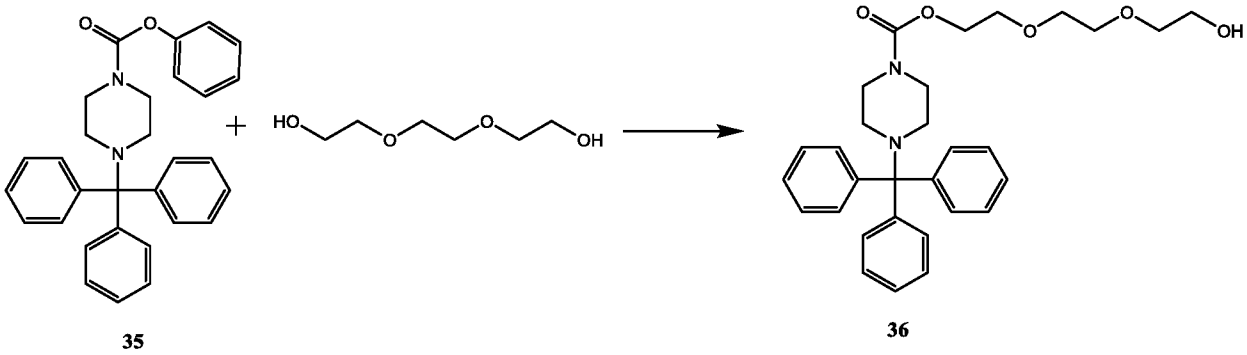
1. Preparation of Trityl Piperazine Phenyl Carbamate (**35**)



NTP 35

To a cooled suspension of NTP in dichloromethane (6 mL/g NTP) was added a solution of potassium carbonate (3.2 eq) in water (4 mL/g potassium carbonate). To this two-phase mixture was slowly added a solution of phenyl chloroformate (1.03 eq) in dichloromethane (2 g/g phenyl chloroformate). The reaction mixture was warmed to 20° C. Upon reaction completion (1-2 hr), the layers were separated. The organic layer was washed with water, and dried over anhydrous potassium carbonate. The product **35** was isolated by crystallization from acetonitrile. Yield=80%

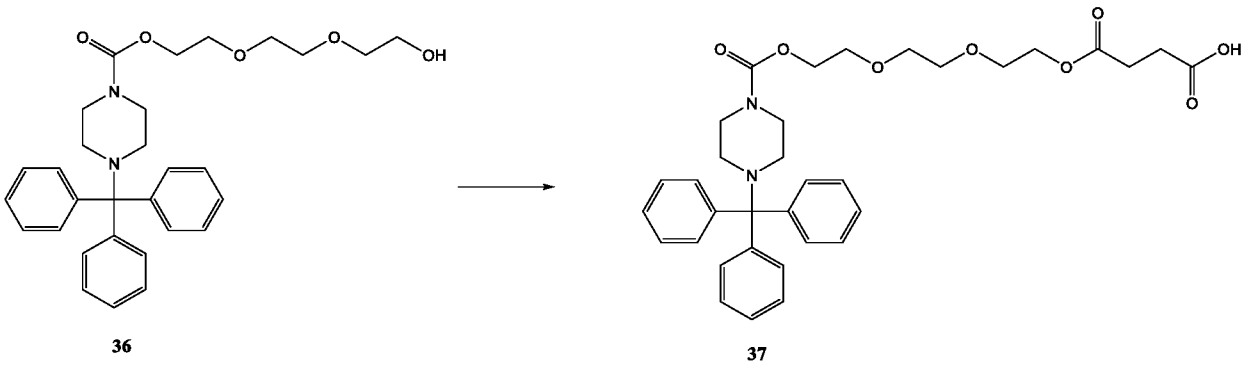
2. Preparation of Carbamate Alcohol (**36**)



35 36

Sodium hydride (1.2 eq) was suspended in 1-methyl-2-pyrrolidinone (32 mL/g sodium hydride). To this suspension were added triethylene glycol (10.0 eq) and compound **35** (1.0 eq). The resulting slurry was heated to 95° C. Upon reaction completion (1-2 hr), the mixture was cooled to 20° C. To this mixture was added 30% dichloromethane/methyl tert-butyl ether (v:v) and water. The product-containing organic layer was washed successively with aqueous NaOH, aqueous succinic acid, and saturated aqueous sodium chloride. The product **36** was isolated by crystallization from dichloromethane/methyl tert-butyl ether/heptane. Yield=90%.

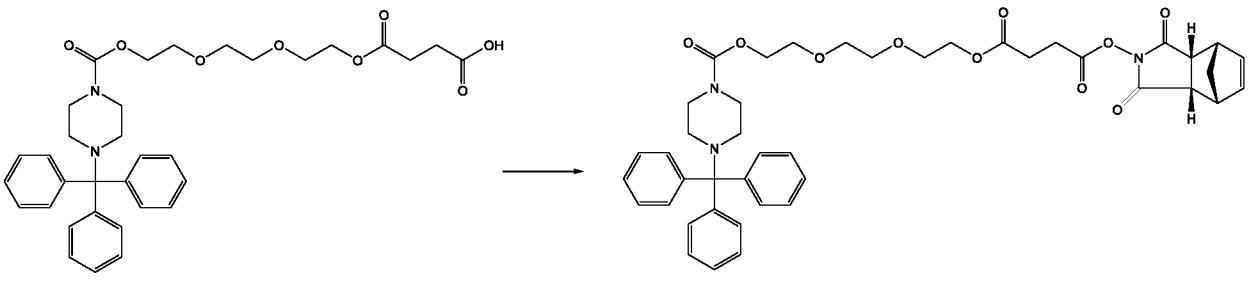
3. Preparation of EG3 Tail Acid (**37**)



36 37

To a solution of compound **36** in tetrahydrofuran (7 mL/g **36**) was added succinic anhydride (2.0 eq) and DMAP (0.5 eq). The mixture was heated to 50° C. Upon reaction completion (5 hr), the mixture was cooled to 20° C and adjusted to pH 8.5 with aqueous $NaHCO_3$. Methyl tert-butyl ether was added, and the product was extracted into the aqueous layer. Dichloromethane was added, and the mixture was adjusted to pH 3 with aqueous citric acid. The product-containing organic layer was washed with a mixture of pH=3 citrate buffer and saturated aqueous sodium chloride. This dichloromethane solution of **37** was used without isolation in the preparation of compound **38**.

4. Preparation of Activated EG3 Tail (**38**)



37 38

To the solution of compound **37** was added N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide (HONB) (1.02 eq), 4-dimethylaminopyridine (DMAP) (0.34 eq), and then 1-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC) (1.1 eq). The mixture was heated to 55° C. Upon reaction completion (4-5 hr), the mixture was cooled to 20° C and washed successively with 1:1 0.2 M citric acid/brine and brine. The dichloromethane solution underwent solvent exchange to acetone and then to N,N-dimethylformamide, and the product was isolated by precipitation from acetone/N,N-dimethylformamide into saturated aqueous sodium chloride. The crude product was reslurried several times in water to remove

residual N,N-dimethylformamide and salts. Yield=70% of Activated EG3 Tail **38** from compound **36**.

Example 4: 50L Solid-phase Synthesis of Casimersen [Oligomeric Compound (XII)] Crude Drug Substance

1. Materials

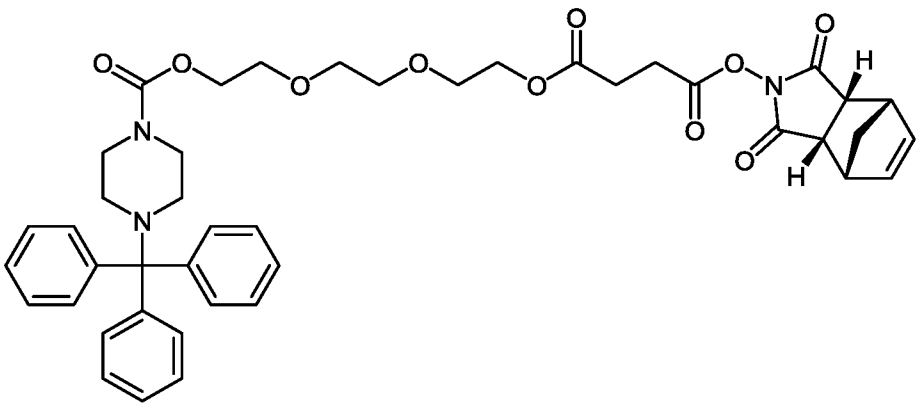
Table 2: Starting Materials

Material Name	Chemical Name	CAS Number	Chemical Formula	Molecular Weight
Activated A Subunit	Phosphoramidochloridic acid, *N*,*N*-dimethyl-,[6-[6-(benzoylamino)-9H-purin-9-yl]-4-(triphenylmethyl)-2-morpholinyl]methyl ester	1155373-30-0	$C_{38}H_{37}ClN_7O_4P$	722.2
Activated C Subunit	Phosphoramidochloridic acid, *N*,*N*-dimethyl-,[6-[4-(benzoylamino)-2-oxo-1(2H)-pyrimidinyl]-4-(triphenylmethyl)-2-morpholinyl]methyl ester	1155373-31-1	$C_{37}H_{37}ClN_5O_5P$	698.2
Activated DPG Subunit	Propanoic Acid, 2,2-dimethyl-,4-[[[9-[6-[[[chloro(dimethylamino)phosphinyl]oxy]methyl]-4-(triphenylmethyl)-2-morpholinyl]-2-[(2-phenylacetyl)amino]-9H-purin-6-yl]oxy]methyl]phenyl ester	1155309-89-9	$C_{51}H_{53}ClN_7O_7P$	942.2

Activated T Subunit	Phosphoramidochloridic acid, *N*,*N*-dimethyl-,[6-(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-pyrimidinyl)]-4-(triphenylmethyl)-2-morpholinyl]methyl ester	1155373-34-4	$C_{31}H_{34}ClN_4O_5P$	609.1
Activated EG3 Tail	Butanedioic acid, 1-[3aR,4S,7R,7aS)-1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-methano-2H-isoindol-2-yl] 4-[2-[2-[2-[[[4-(triphenylmethyl)-1-piperazinyl]carbonyl]oxy]ethoxy]ethoxy]ethyl] ester	1380600-06-5	$C_{43}H_{47}N_3O_{10}$	765.9

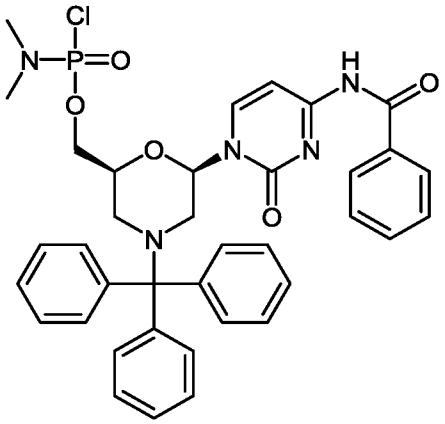
Chemical Structures of Starting Materials:

A. Activated EG3 Tail



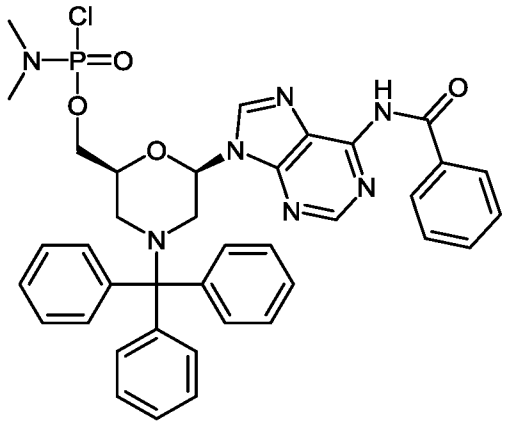
Compound (B)

B. Activated C Subunit (For preparation, see U.S. Patent No. 8,067,571)



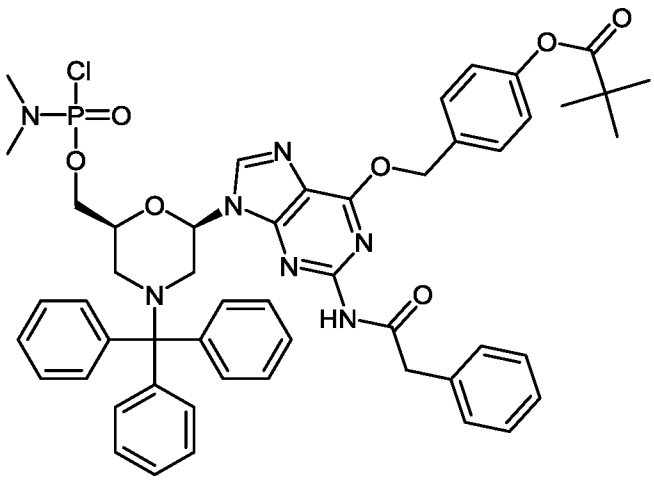
Compound of Formula (D1)

C. Activated A Subunit (For preparation, see U.S. Patent No. 8,067,571)



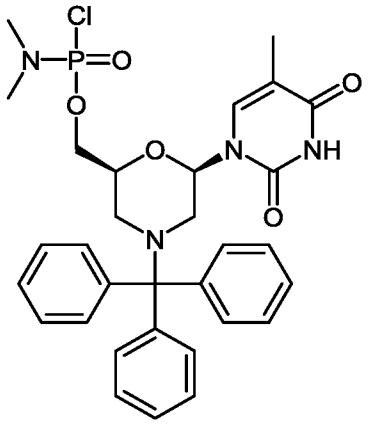
Compound of Formula (F1)

D. Activated DPG Subunit (For preparation, see WO 2009/064471)



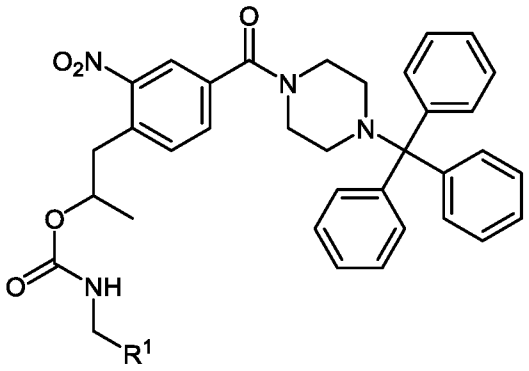
Compound (E1)

E. Activated T Subunit (For preparation, see WO 2013/082551)



Compound (G1)

F. Anchor Loaded Resin



Formula (I)

wherein

R^1 is a support-medium.

Table 3: Description of Solutions for Solid Phase Oligomer Synthesis of Casimersen Crude Drug Substance

Solution Name	Solution Composition
NCP2 Anchor Solution	37.5L NMP and 1292g NCP2 Anchor
DEDC Capping Solution	4.16L Diethyl Dicarbonate (DEDC), 3.64L NEM, and 33.8L DCM
CYTFA Solution	2.02 kg 4-cyanopyridine, 158 L DCM, 1.42 L TFA, 39 L TFE, and 2 L purified water
Neutralization Solution	35.3 L IPA, 7.5 L DIPEA, and 106.5 L DCM
Cleavage Solution	1,530.04 g DTT, 6.96 L NMP, and 2.98 L DBU

2. Synthesis of Casimersen Crude Drug Substance

A. Resin swelling

750 g of Anchor Loaded Resin and 10.5 L of NMP were charged to a 50 L silanized reactor and stirred for 3 hours. The NMP was drained and the Anchor Loaded Resin was washed twice with 5.5L each of DCM and twice with 5.5 L each of 30% TFE/DCM.

B. Cycle 0: EG3 Tail Coupling

The Anchor Loaded Resin was washed three times with 5.5 L each of 30% TFE/DCM and drained, washed with 5.5 L of CYFTA solution for 15 minutes and drained, and again washed with 5.5 L of CYTFA Solution for 15 minutes without draining to which 122 mL of 1:1 NEM/DCM was charged and the suspension stirred for 2 minutes and drained. The resin was washed once with 5.5L Neutralization Solution for 10 minutes and drained, twice with 5.5 L of Neutralization Solution for 5 minutes and drained, then twice with 5.5 L each of DCM and drained. A solution of 706.2 g of activated EG3 Tail (MW 765.85) and 234 mL of NEM in 3 L of DMI was charged to the resin and stirred for 3 hours at RT and drained. The resin was washed once with 5.5 L of Neutralization Solution for 10 minutes and drained, once with 5.5 L of Neutralization Solution for 5 minutes and drained, and once with 5.5 L of DCM and drained. A solution of 374.8 g of benzoic anhydride and 195 mL NEM in 2680 mL NMP was charged and stirred for 15 minutes and drained. The resin was washed once with 5.5 L of Neutralization Solution for 10 minutes and drained, once with 5.5 L of Neutralization Solution for 5 minutes and drained, and once with 5.5 L of DCM and drained and twice with 5.5 L each of 30% TFE/DCM. The resin was suspended in 5.5 L of 30% TFE/DCM and held for 14 hours.

C. Subunit Coupling Cycles 1-22

i. Pre-coupling treatments

Prior to each coupling cycle as described in **Table 4**, the resin was: 1) washed with 30% TFE/DCM; 2) a) treated with CYTFA Solution 15 minutes and drained, and b) treated with CYTFA solution for 15 minutes to which was added 1:1 NEM/DCM, stirred, and drained; 3) stirred three times with Neutralization Solution; and 4) washed twice with DCM. See **Table 4**.

ii. Post Coupling Treatments

After each subunit solution was drained as described in **Table 4**, the resin was: 1) washed with DCM; and 2) washed three times with 30% TFE/DCM. If the resin was held for

a time period prior to the next coupling cycle, the third TFE/DCM wash was not drained and the resin was retained in said TFE/DCM wash solution. See **Table 4**.

iii. Activated Subunit Coupling Cycles

The coupling cycles were performed as described in **Table 4**.

iv. Final IPA Washing

After the final coupling step was performed as described in **Table 4**, the resin was washed 8 times with 19.5 L each of IPA, and dried under vacuum at room temperature for about 63.5 hours to a dried weight of 4523 g.

D. Cleavage

The above resin bound Casimersen Crude Drug Substance was divided into two lots, each lot was treated as follows. Two 2261.5 g lots of resin were each: 1) stirred with 10L of NMP for 2hrs, then the NMP was drained; 2) washed tree times with 10L each of 30% TFE/DCM; 3) treated with 10L CYTFA Solution for 15 minutes; and 4) 10L of CYTFA Solution for 15 minutes to which 130ml 1:1 NEM/DCM was then added and stirred for 2 minutes and drained. The resin was treated three times with 10L each of Neutralization Solution, washed six times with 10L of DCM, and eight times with 10L each of NMP. The resin was treated with a Cleaving Solution of 1530.4g DTT and 2980 DBU in 6.96L NMP for 2 hours to detach the Casimersen Crude Drug Substance from the resin. The Cleaving Solution was drained and retained in a separate vessel. The reactor and resin were washed with 4.97L of NMP which was combined with the Cleaving Solution.

Table 4:

Cycle No.: Subunit (SU)	Pre-coupling Treatment				Coupling Cycle		Post-Coupling Treatment	
	1	2	3	4			1	2
	30% TFE/DCM Wash	CYTFA Solution[1]	Neutralization Solution	DCM Wash	Quantity SU (g) NEM (L) DMI (L)	RT Coupling Time (Hrs.)	DCM Wash	30% TFE/DCM Wash
1:C	5.5L	a) 5,5L b) 5.5L, 122ml	3x5.5L	5.5L	584g; 195 ml NEM; 3.2L DMI	5	5.5L	3x5.5L
2:A	7.0L	a) 7L b) 7L, 158ml	3x7L	2x7L	592.2g and 195ml	4.25	7L	3x7L

[1] ml indicates the amount of 1:1 NEM/DCM

Cycle No.: Subunit (SU)	Pre-coupling Treatment				Coupling Cycle		Post-Coupling Treatment	
	1	2	3	4			1	2
	30% TFE/DCM Wash	CYTFA Solution[1]	Neutralization Solution	DCM Wash	Quantity SU (g) NEM (L) DMI (L)	RT Coupling Time (Hrs.)	DCM Wash	30% TFE/DCM Wash
					NEM 3.2L DMI			
3:A	8L	a) 8L b) 8L, 182ml	3x8L	2x8L	592.2g; 195ml NEM; 3.4L DMI	4.25	8L	3x8L
4:T	9L	a) 9L b) 9L, 206ml	3x9L	2x9L	514.2g; 195ml NEM; 3.6L DMI	4.25	9L	3x9L
5:G	9.5L	a) 9.5L b) 9.5L, 220ml	3x9.5L	2x9.5L	755.5g; 195ml NEM; 3.4L DMI	4.25	9.5L	3x9.5L
6:C	10L	a) 10L b) 10L, 232ml	3x10L	2x10L	584.4g; 195ml NEM; 3.45L DMI	4.25	10L	3x10L
7:C	11L	a) 11L b) 11L, 256ml	3x11L	2x11L	584.5g; 195ml NEM; 3.57L DMI	4.25	11L	3x11L
8:A	11L	a) 11L b) 11L, 256ml	3x11L	2x11L	592.5g; 195ml NEM; 3.64L DMI	4.25	11L	3x11L
9:T	11.5L	a) 11.5L b) 11.5L 268ml	3x11.5L	2x 11.5L	514.5g; 195ml NEM; 3.72L DMI	4.25	11.5L	3x11.5L
10:C	12L	a) 12L b) 12L, 280ml	3x12L	2x12L	338.5g; 195ml NEM; 3.96L DMI	4.25	12L	3x12L

Cycle No.: Subunit (SU)	Pre-coupling Treatment				Coupling Cycle		Post-Coupling Treatment	
	1	2	3	4			1	2
	30% TFE/DCM Wash	CYTFA Solution[1]	Neutralization Solution	DCM Wash	Quantity SU (g) NEM (L) DMI (L)	RT Coupling Time (Hrs.)	DCM Wash	30% TFE/DCM Wash
11:C	13.5L	a) 13.5L b) 13.5L, 204ml	3x13.5L	2x 13.5L	770.4g; 253ml NEM; 4.02L DMI	4.25	13.5 L	3x13.5L
12:T	13.5L	a) 13.5L b) 13.5L, 204ml	3x13.5L	2x 13.5L	668.7g; 253ml NEM; 4.02L DMI	4.25	13.5 L	3x13.5L
13:DPG	14L	a) 14L b) 14L, 216ml	3x14L	2x14 L	982.3g; 253ml NEM; 4.02L DMI	4.25	14L	3x14L
14:DPG	14.5L	a) 14.5L b) 14.5L, 228ml	3x14.5L	2x 14.5L	982.3g; 253ml NEM; 4.1L DMI	4.25	14.5 L	3x14.5L
15:A	15.5L	a) 15.5L b) 15.5L, 254ml	3x15.5L	2x 15.5L	770.1g; 253ml NEM; 4.26L DMI	4.25	15.5 L	3x15.5L
16:DPG	15.5L	a) 15.5L b) 15.5L, 254ml	3x15.5L	2x 15.5L	982.4g; 253ml NEM; 4.26L DMI	4.25	15.5 L	3x15.5L
17:T	16L	a) 16L b) 16L, 366ml	3x16L	2x16 L	549.6g; 253ml NEM; 4.4L DMI	4.75	16L	3x16L
18:T	16.5L	a) 16.5L b) 16.5L, 378ml	3x16.5L	2x 16.5L	630.7g; 253ml NEM; 4.4L DMI	4.25	16.5 L	3x16.5L
19:C	16.5L	a) 16.5L b)	3x16.5L	2x 16.5L	770.4g; 253ml NEM;	4.25	16.5 L	3x16.5L

Cycle No.: Subunit (SU)	Pre-coupling Treatment				Coupling Cycle		Post-Coupling Treatment	
	1	2	3	4			1	2
	30% TFE/DCM Wash	CYTFA Solution[1]	Neutralization Solution	DCM Wash	Quantity SU (g) NEM (L) DMI (L)	RT Coupling Time (Hrs.)	DCM Wash	30% TFE/DCM Wash
		16.5L, 378ml			4.57L DMI			
20:C	17L	a) 17L b) 17L, 390ml	3x17L	2x17 L	770.4g; 253ml NEM; 4.57L DMI	4.75	17L	3x17L
21:T	17L	a) 17L b) 17L, 390ml	3x17L	2x17 L	776.4g; 311ml NEM; 4.72L DMI	4.25	17L	3x17L
22:DPG	17.5L	a) 17.5L b) 17.5L, 402ml	3x17.5L	2x 17.5L	1208.7g; 311ml NEM; 4.72L DMI	4.75	17.5 L	3x17.5L

E. Deprotection

The combined Cleaving Solution and NMP wash were transferred to a pressure vessel to which was added 39.8L of NH_4OH ($NH_3 \cdot H_2O$) that had been chilled to a temperature of -10° to -25° C in a freezer. The pressure vessel was sealed and heated to 45° C for 16hrs then allowed to cool to 25° C. This deprotection solution containing the Casimersen crude drug substance was diluted 3:1 with purified water prior to solvent removal. During solvent removal, the deprotection solution was pH adjusted to 3.0 with 2M phosphoric acid, then to pH 8.03 with NH_4OH. HPLC: C18 80.93% (**Fig. 1**) and SCX-10 84.4% (**Fig. 2**).

Example 5: Purification of Casimersen Crude Drug Substance

The deprotection solution from Example 4, part E, containing the Casimersen crude drug substance was loaded onto a column of ToyoPearl Super-Q 650S anion exchange resin (Tosoh Bioscience) and eluted with a gradient of 0-35% B over 17 column volume (Buffer A: 10 mM sodium hydroxide; Buffer B: 1 M sodium chloride in 10 mM sodium hydroxide) and fractions of acceptable purity (C18 and SCX HPLC) were pooled to a purified drug product solution. HPLC: 97.74% (**C18; Fig. 3**) 94.58% (SCX; **Fig. 4**).

The purified drug substance solution was desalted and lyophilized to 1477.82 g purified Casimersen drug substance. Yield 63.37%; HPLC: 96.045% (**Fig. 5**; C18) 96.346% (**Fig. 6**; SCX).

Table 5. Acronyms

Acronym	**Name**
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMI	1,3-Dimethyl-2-imidazolidinone
DTT	Dithiothreitol
IPA	Isopropyl alcohol
MW	Molecular weight
NEM	N-Ethylmorpholine
NMP	N-Methyl-2-pyrrolidone
RT	Room temperature
TFA	2,2,2-Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol

INCORPORATION BY REFERENCE

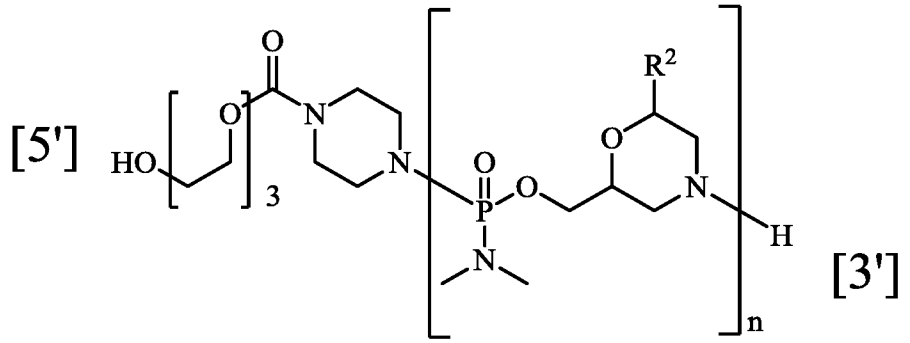
The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents of the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

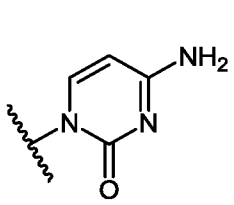
CLAIMS

1. A process for preparing an oligomeric compound of Formula (A):



(A);

wherein n is an integer from 10 to 40, and each R^2 is, independently for each occurrence, selected from the group consisting of:



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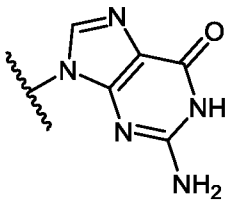

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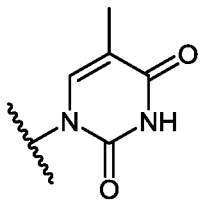

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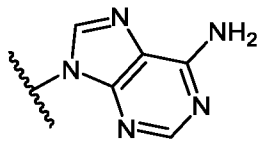

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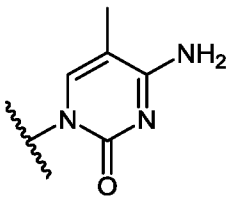

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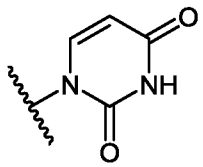

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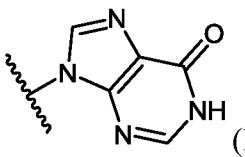
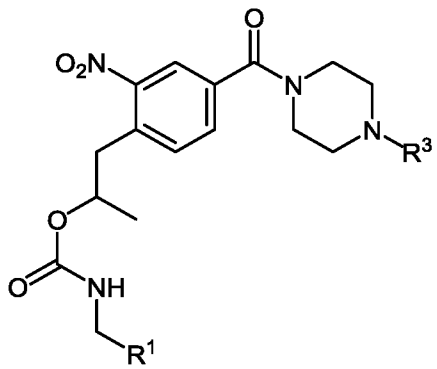


(I),

wherein the process comprises the sequential steps of:

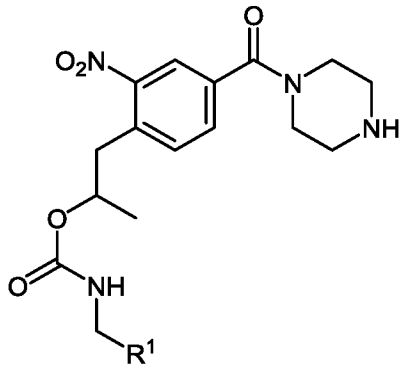
(a) contacting a compound of Formula (A1):



(A1);

wherein R^1 is a support-medium and R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

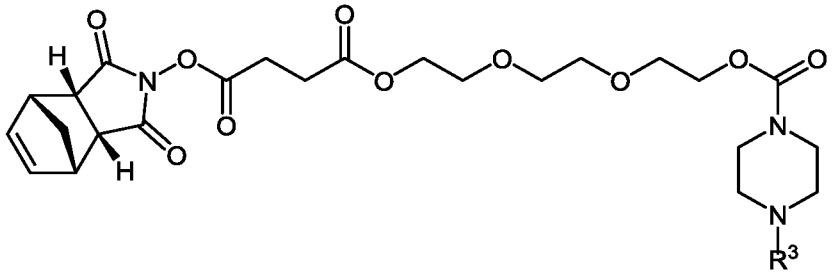
with a deblocking agent to form the compound of Formula (II):



(II);

wherein R^1 is a support-medium;

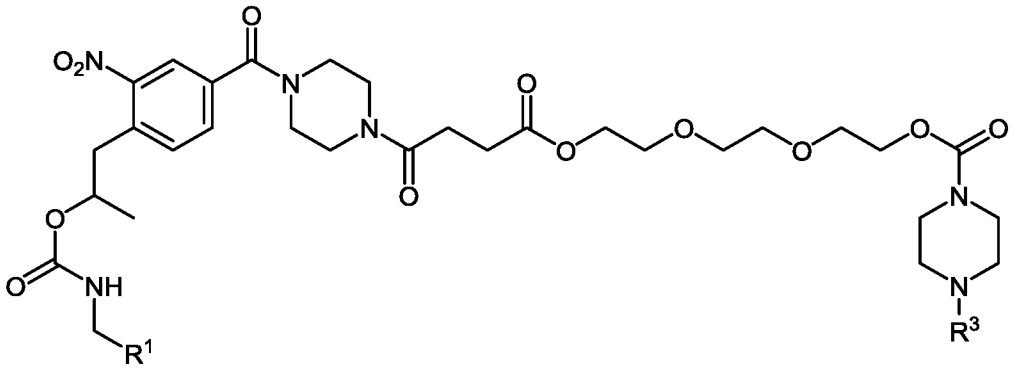
(b) contacting the compound of Formula (II) with a compound of Formula (A2):



(A2);

wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

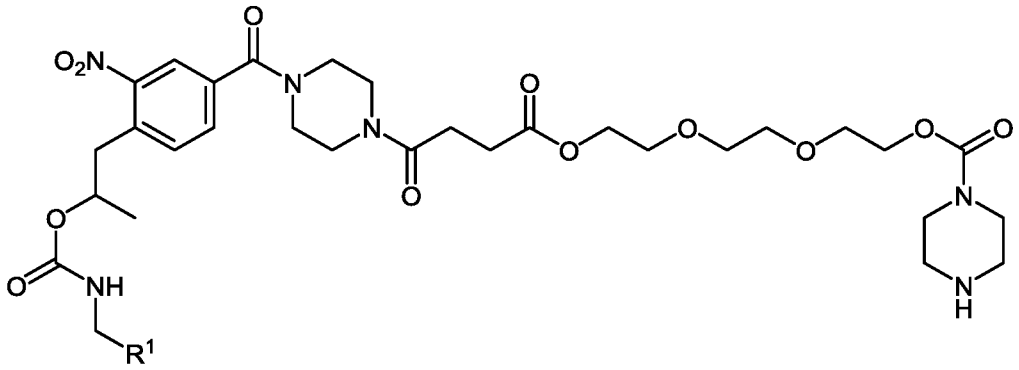
to form a compound of Formula (A3):



(A3);

wherein R^1 is a support-medium, and R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl;

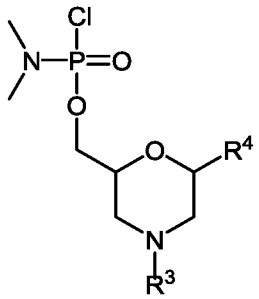
(c) contacting the compound of Formula (A3) with a deblocking agent to form a compound of Formula (IV):



(IV);

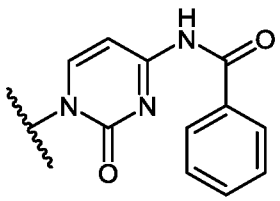
wherein R^1 is a support-medium;

(d) contacting the compound of Formula (IV) with a compound of Formula (A4):



(A4);

wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is selected from the group consisting of:



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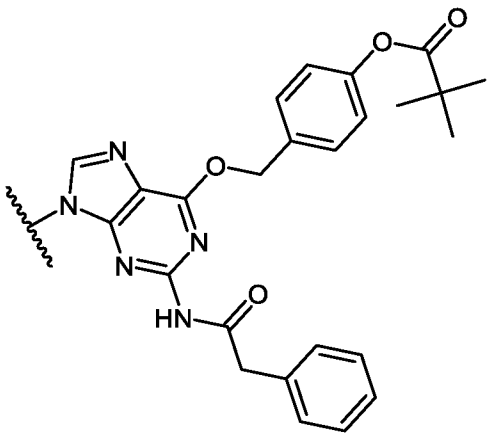

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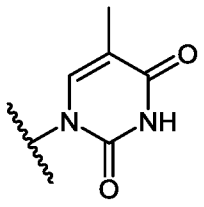
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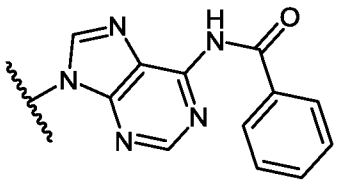
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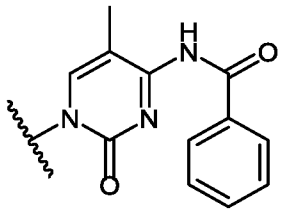
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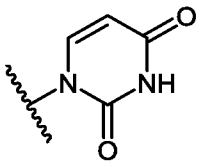
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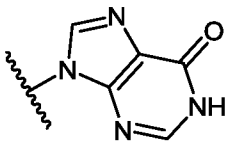
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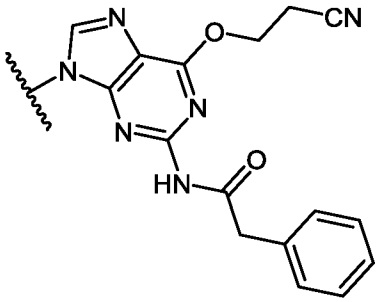
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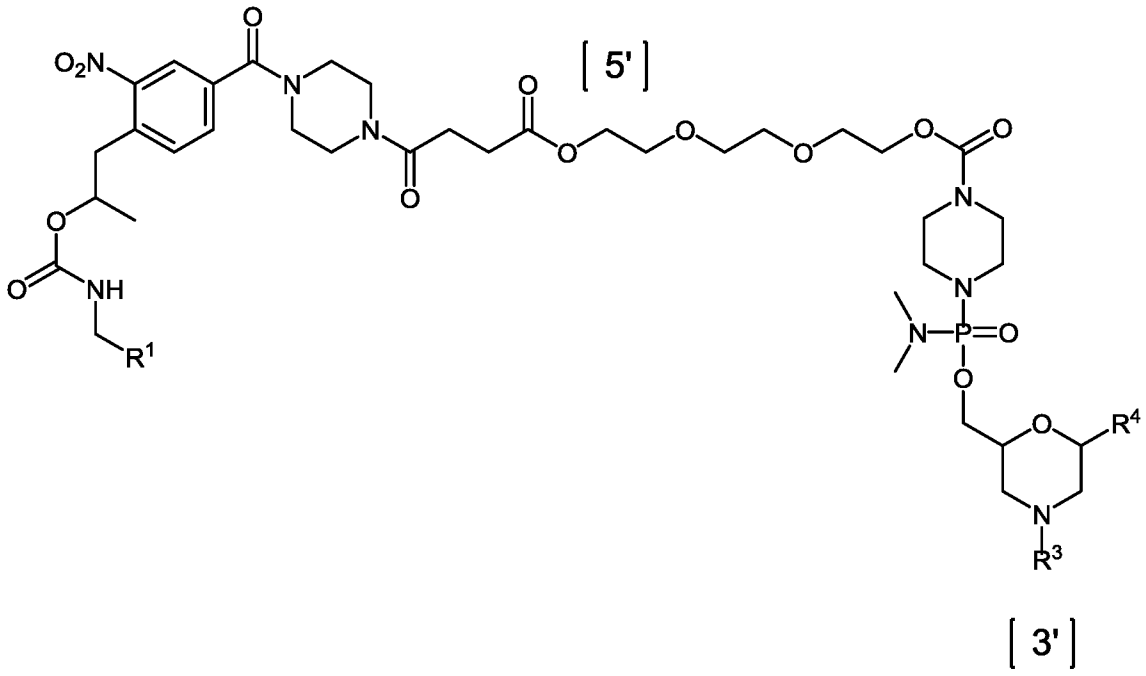
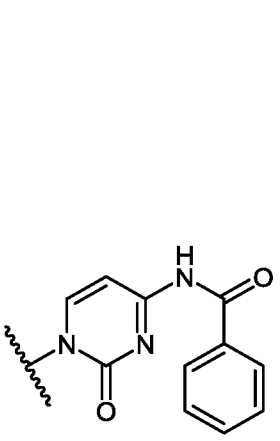
to form a compound of Formula (A5):

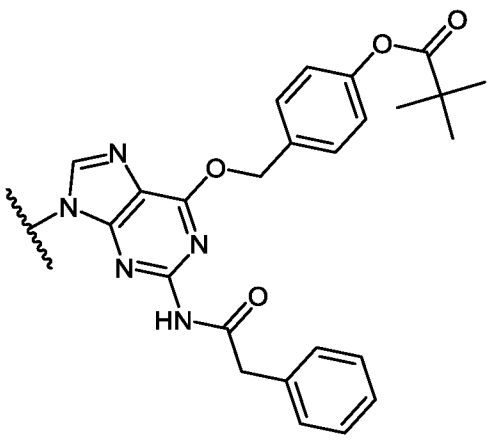


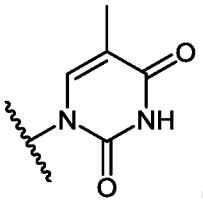
(A5);

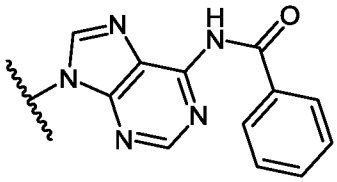
wherein R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

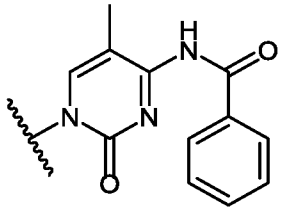
R^4 is selected from:

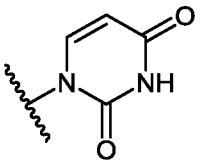

(PC),

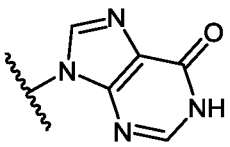

(DPG),

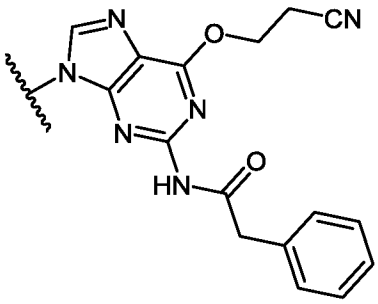

(T),


(PA),


(P5mC),


(U),

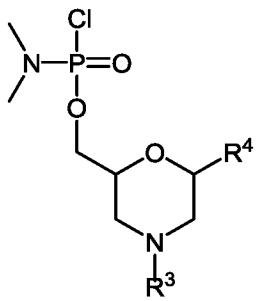

(I), and


(PG);

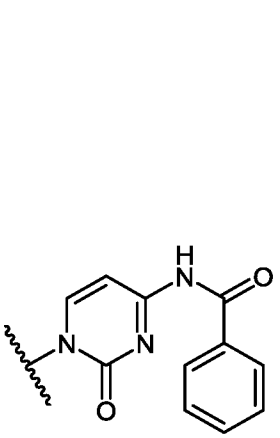
(e) performing n-1 iterations of the sequential steps of:

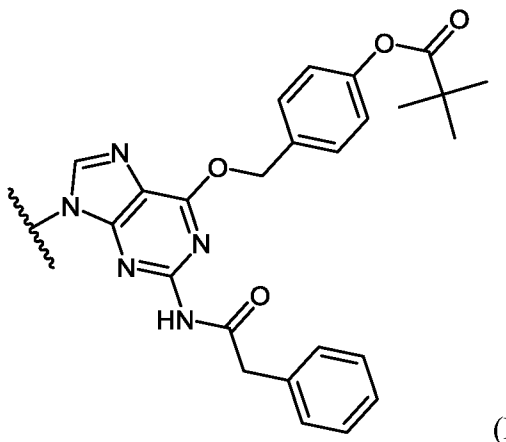
(e1) contacting the product formed by the immediately prior step with a deblocking agent; and

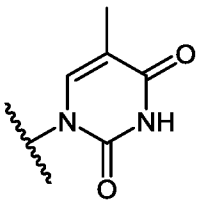
(e2) contacting the compound formed by the immediately prior step with a compound of Formula (A8):

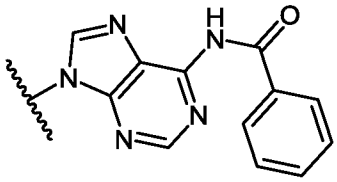

(A8);

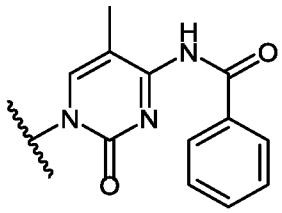
wherein R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is, independently for each compound of Formula (A8), selected from the group consisting of:

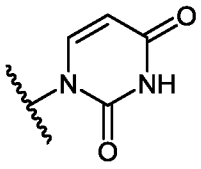

(PC),

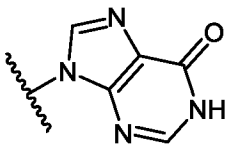

(DPG),

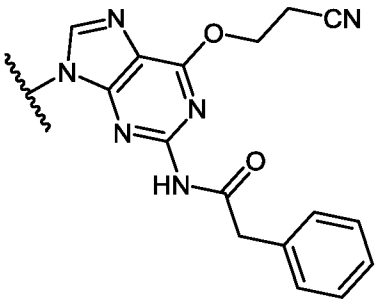

(T),


(PA),

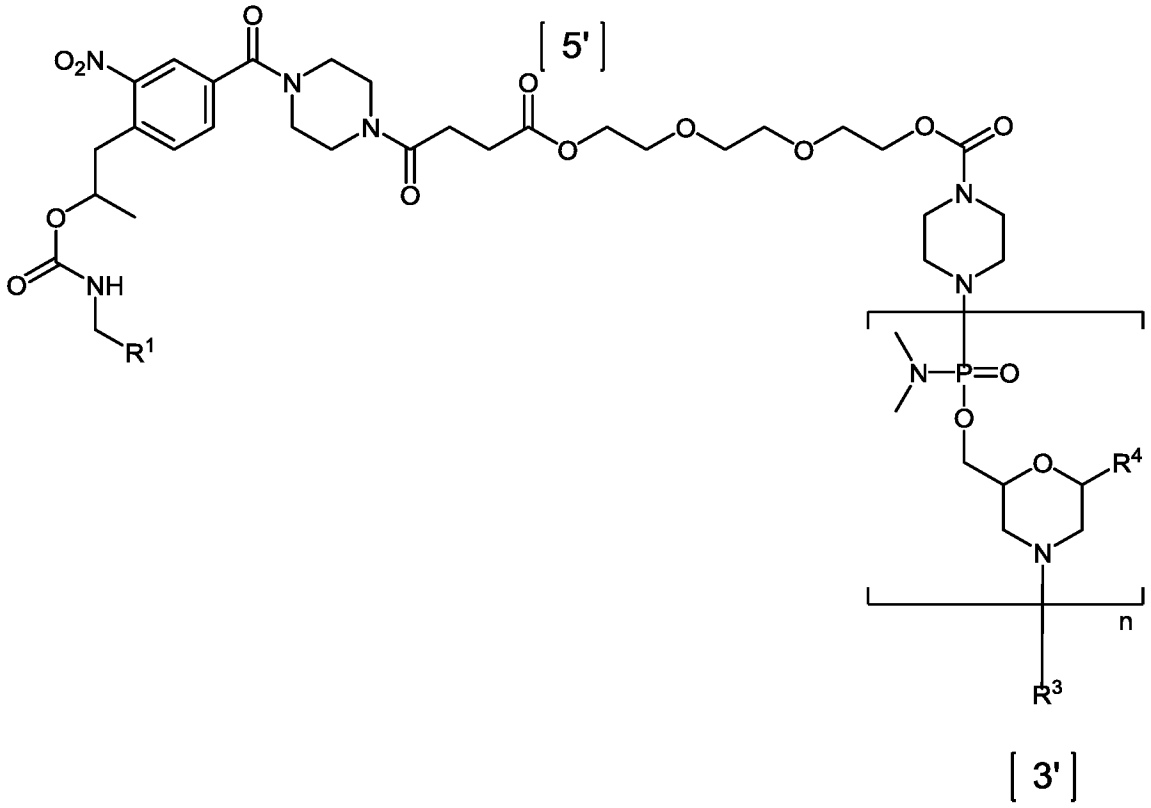

(P5mC),


(U),


(I), and

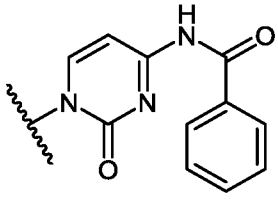

(PG),

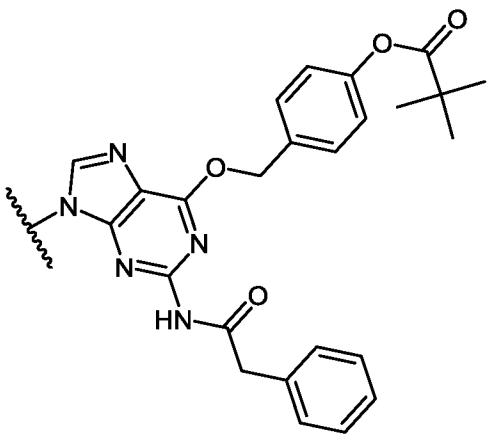
to form a compound of Formula (A9):

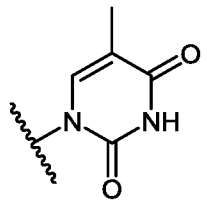
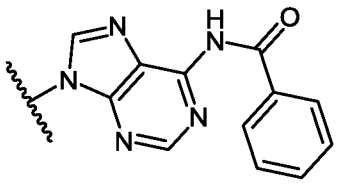
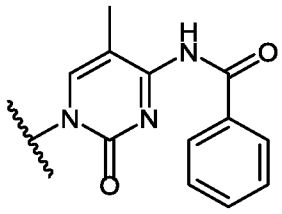
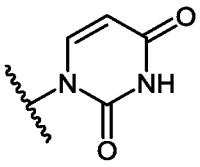
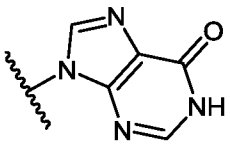
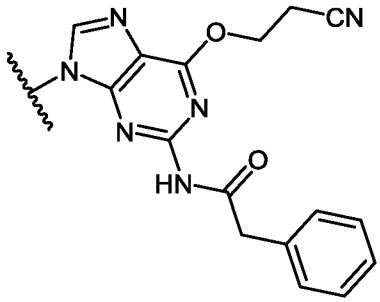


(A9);

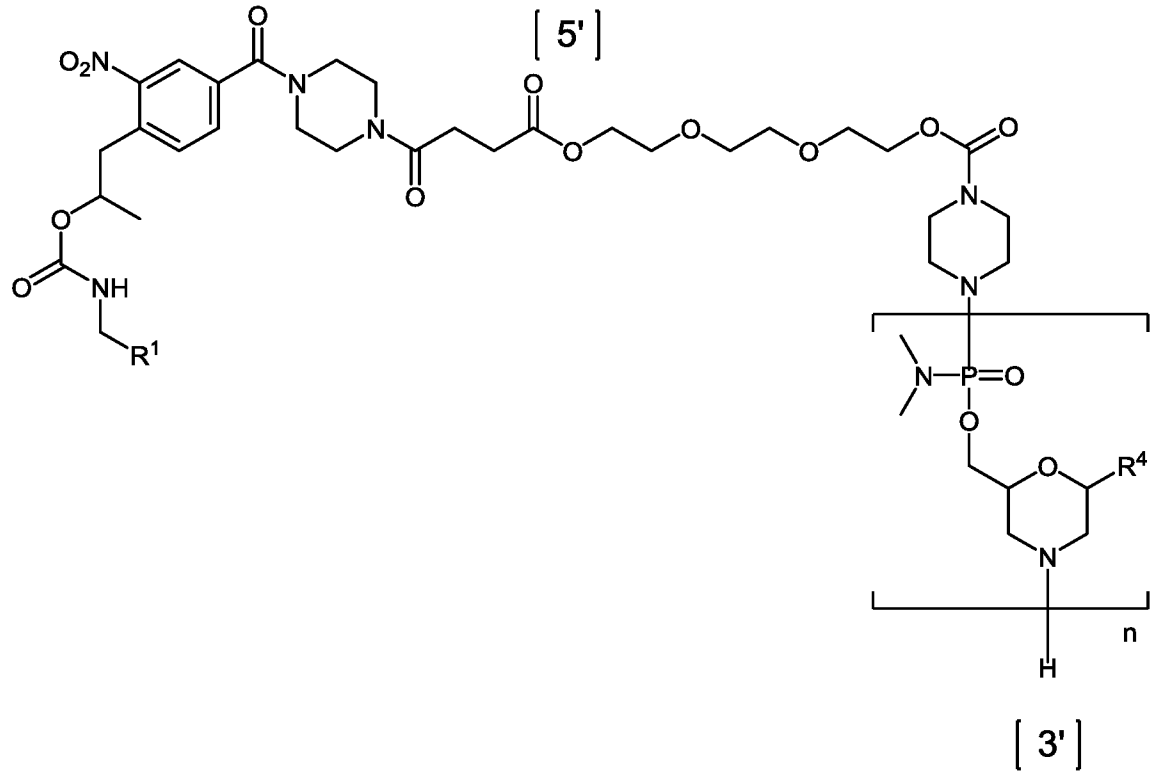
wherein n is an integer from 10 to 40, R^1 is a support-medium, R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and R^4 is, independently for each occurrence, selected from the group consisting of:


(PC),


(DPG),

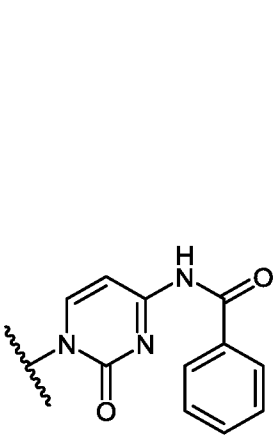

(T),

(PA),

(P5mC),

(U),

(I), and

(PG); and

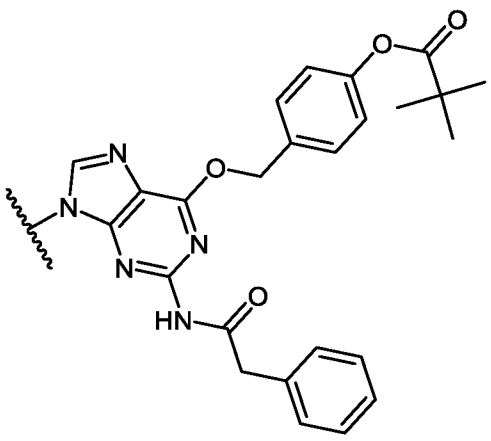
(f) contacting the compound of Formula (A9) with a deblocking agent to form a compound of Formula (A10):

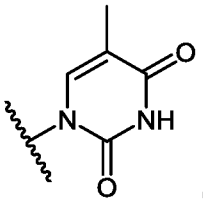


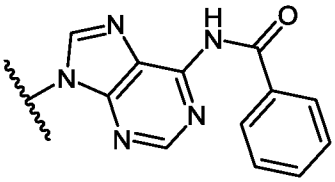
(A10);

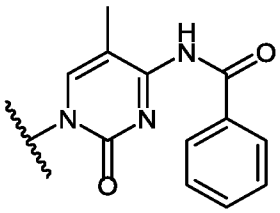
wherein n is an integer from 10 to 40, R^1 is a support-medium, and R^4 is, independently for each occurrence, selected from the group consisting of:

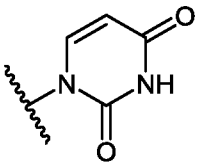

(PC),

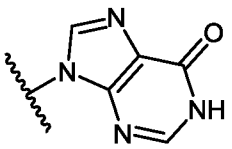

(DPG),

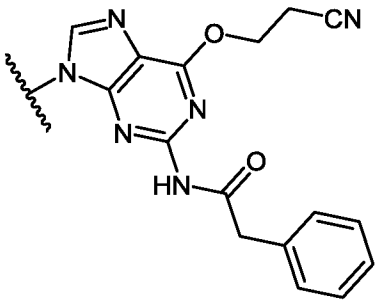

(T),


(PA),

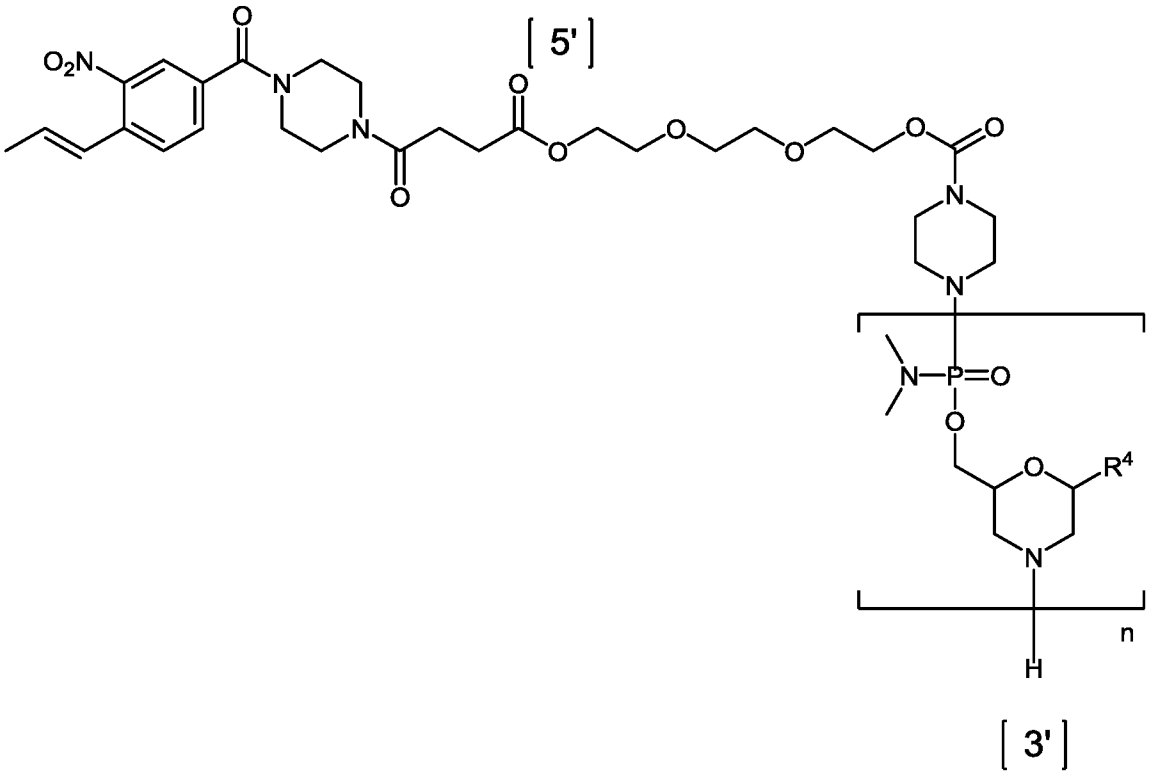

(P5mC),


(U),


(I), and

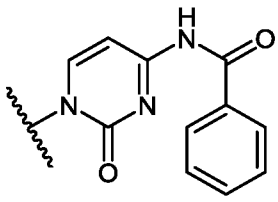

(PG);

(g) contacting the compound of Formula (A10) with a cleaving agent to form a compound of Formula (A11):

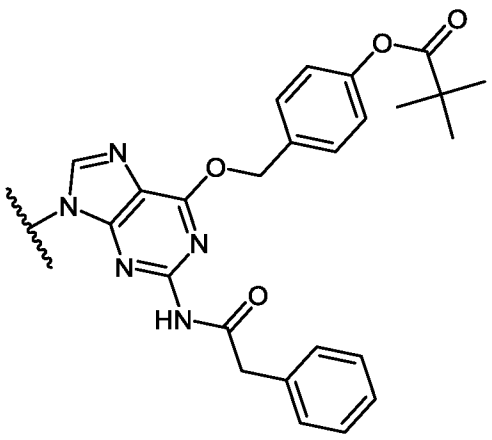


(A11);

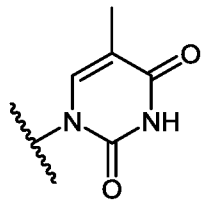
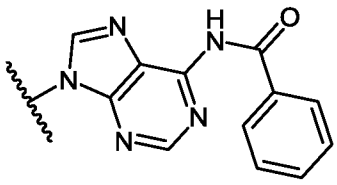
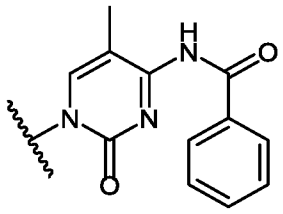
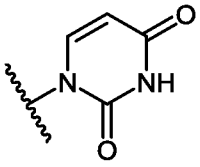
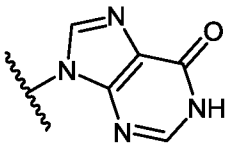
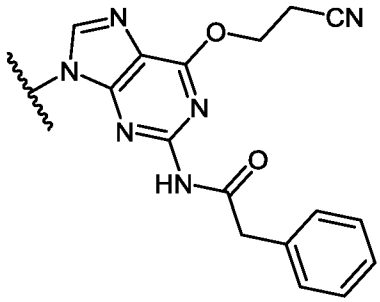
wherein n is an integer from 10 to 40, and R^4 is, independently for each occurrence, selected from the group consisting of:



(PC),

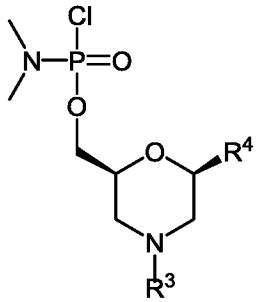


(DPG),


(T),

(PA),

(P5mC),

(U),

(I), and

(PG); and

(h) contacting the compound of Formula (A11) with a deprotecting agent to form the oligomeric compound of Formula (A).

2. The process of claim 1, wherein the compound of Formula (A4) is of Formula (A4a):

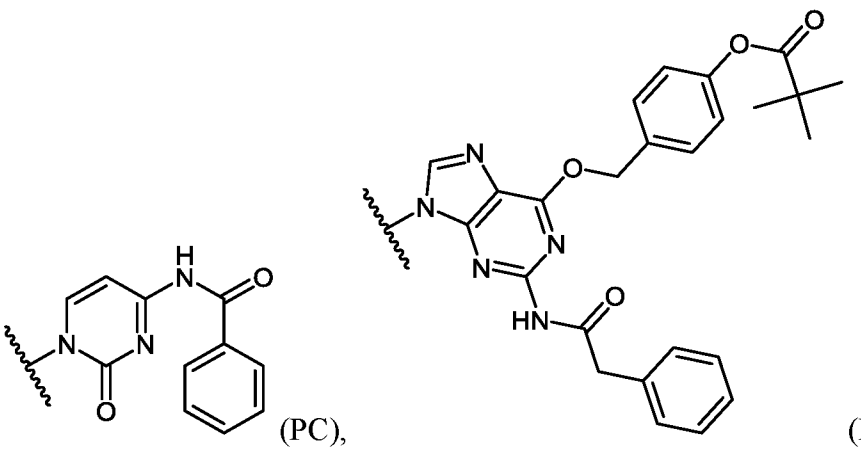


(A4a);

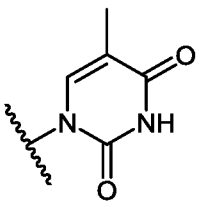
wherein:

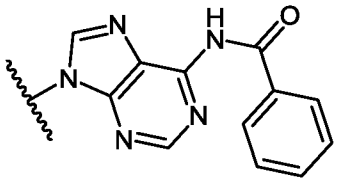
R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

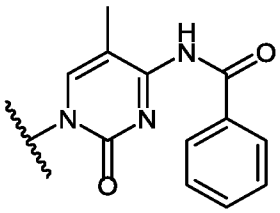
R^4 is selected from:

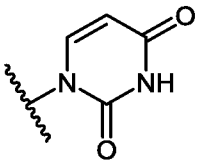

(PC),

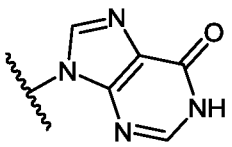
(DPG),

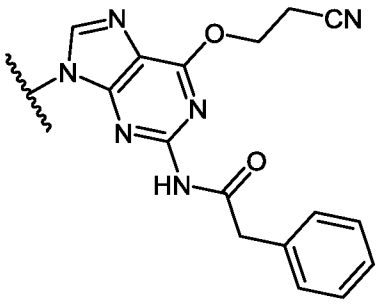

(T),


(PA),

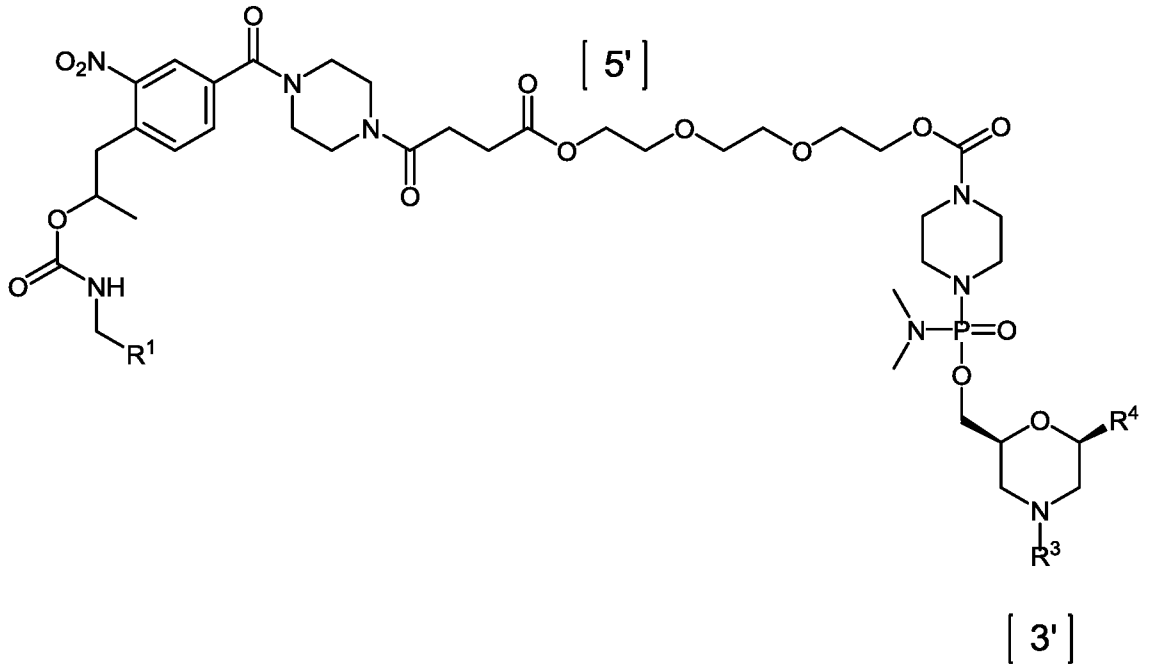

(P5mC),


(U),


(I), and


(PG).

3. The process of claim 1 or 2, wherein the compound of Formula (A5) is of Formula (A5a):



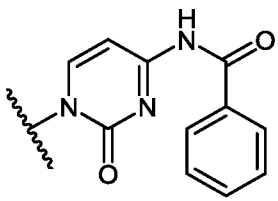
(A5a);

wherein:

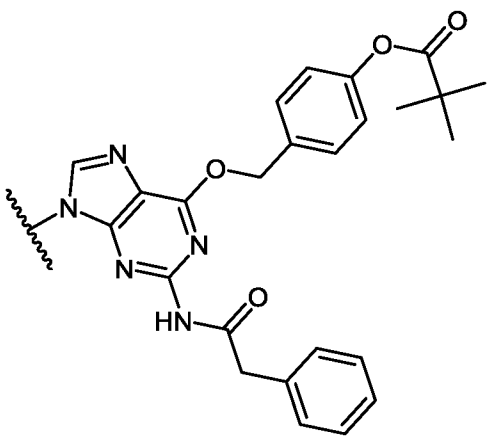
R^1 is a support-medium,

R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

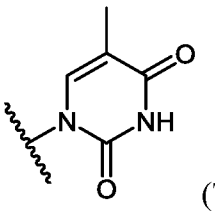
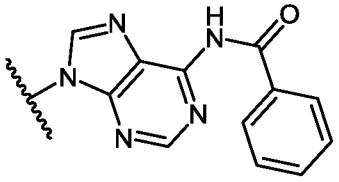
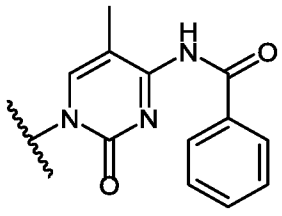
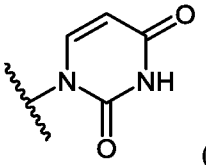
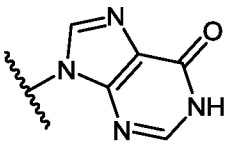
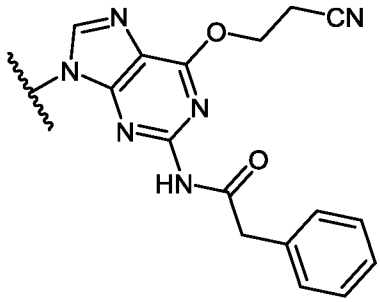
R^4 is selected from:



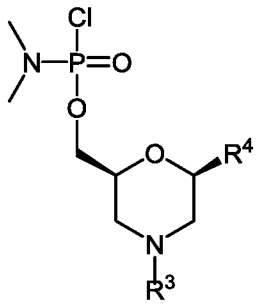
(PC),



(DPG),


(T),

(PA),

(P5mC),

(U),

(I), and

(PG).

4. The process of any one of claims 1-3, wherein the compound of Formula (A8) is of Formula (A8a):

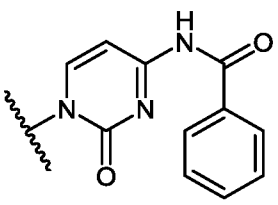
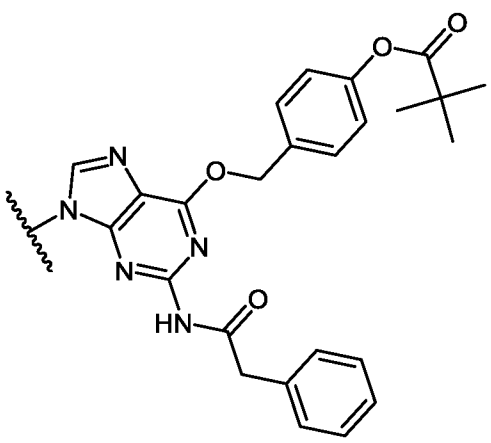


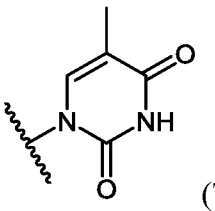
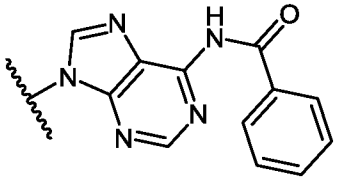
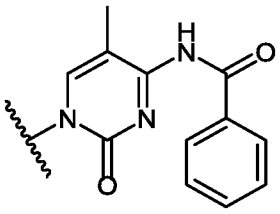
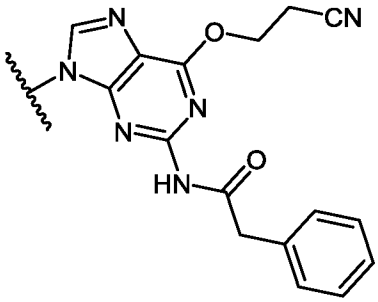
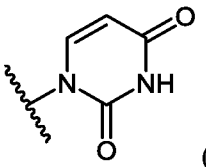
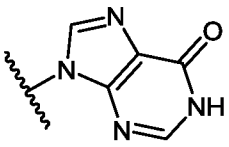
(A8a);

wherein:

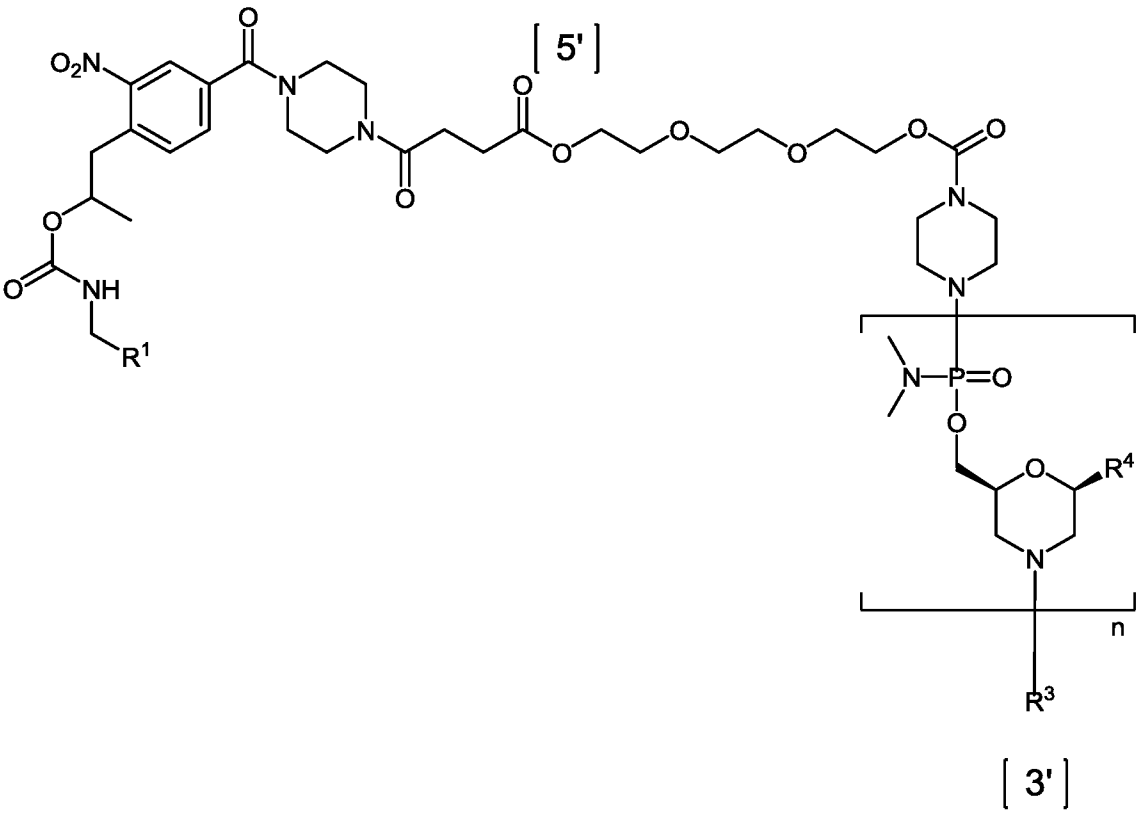
R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

R^4 is, independently at each occurrence of the compound of Formula (A8a), selected from the group consisting of:


(PC),

(DPG),


(T),

(PA),

(P5mC),


(U),

(I), and
(PG).

5. The process of any one of claims 1-4, wherein the compound of formula (A9) is of Formula (A9a):



(A9a);

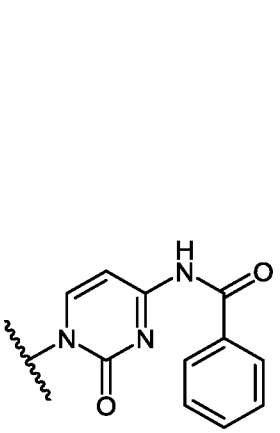
wherein:

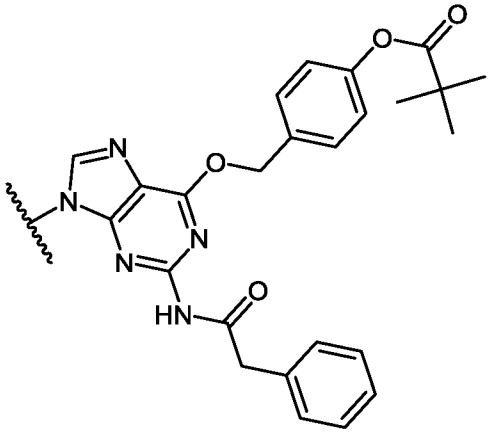
n is an integer from 10 to 40,

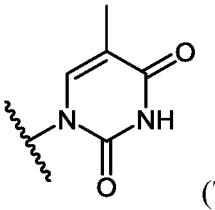
R^1 is a support-medium,

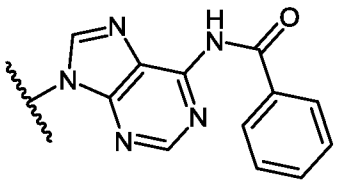
R^3 is selected from the group consisting of trityl, monomethoxytrityl, dimethoxytrityl and trimethoxytrityl, and

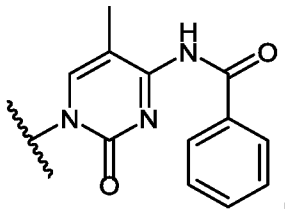
R^4 is, independently for each occurrence, selected from the group consisting of:

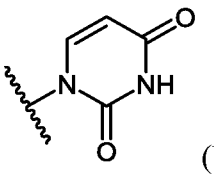

(PC),

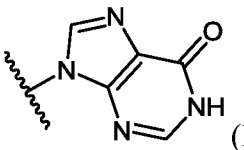

(DPG),

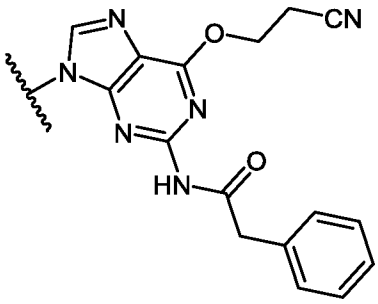

(T),


(PA),

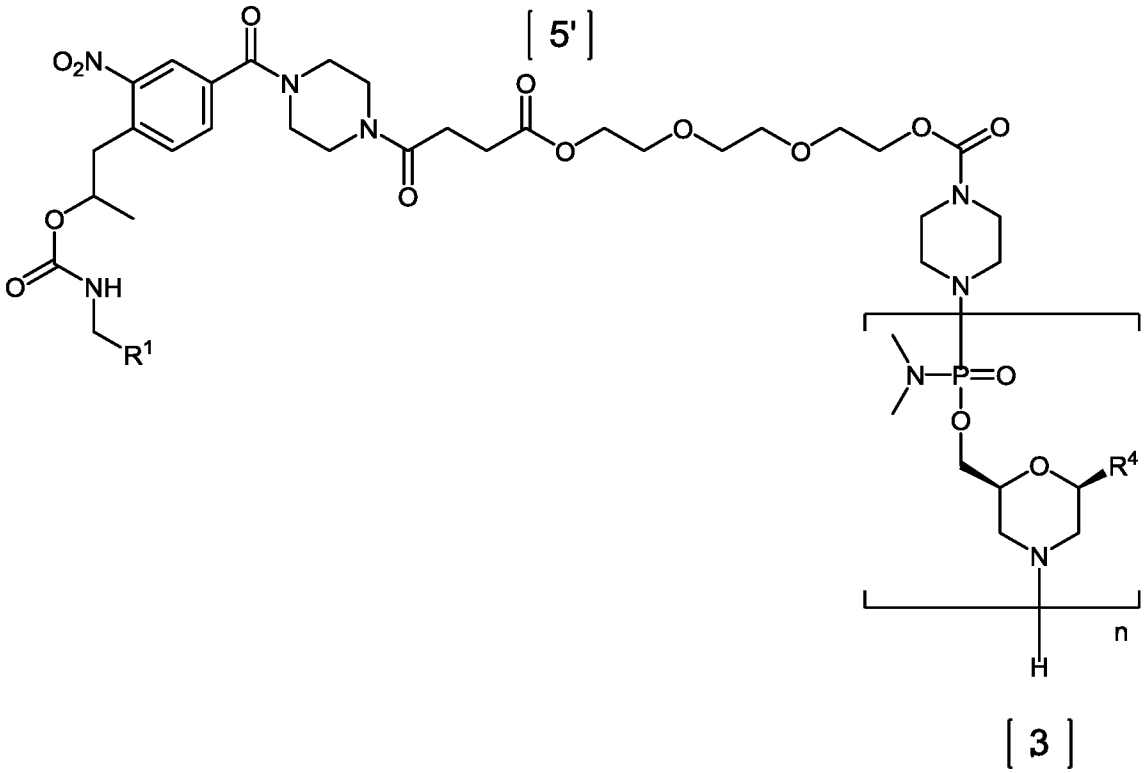

(P5mC),


(U),


(I), and


(PG).

6. The process of any one of claims 1-5, wherein the compound of Formula (A10) is of Formula (A10a):



[5']

[3]

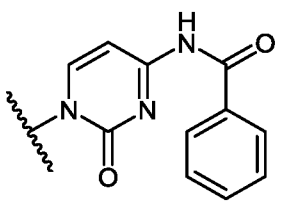
(A10a);

wherein:

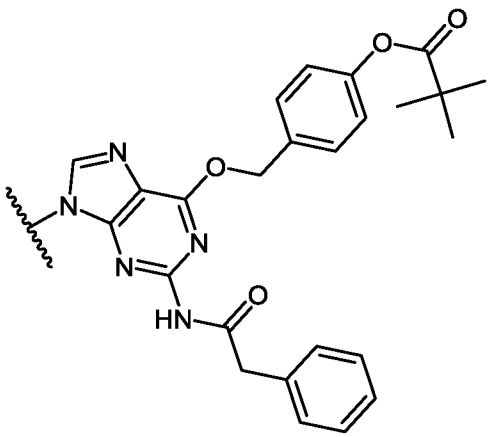
n is an integer from 10 to 40,

R^1 is a support-medium, and

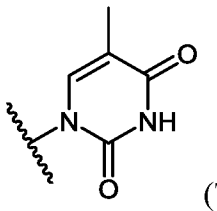
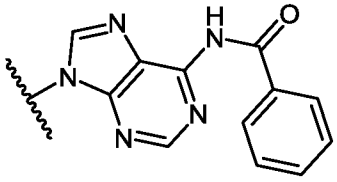
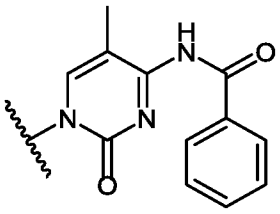
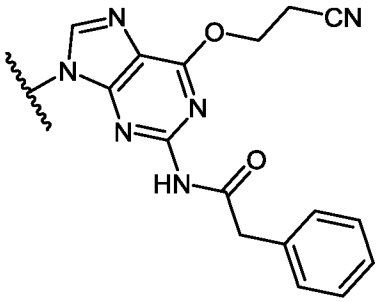
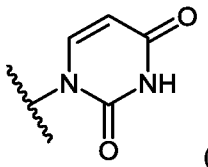
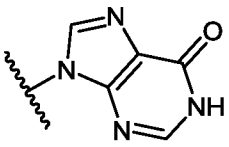
R^4 is, independently for each occurrence, selected from the group consisting of:



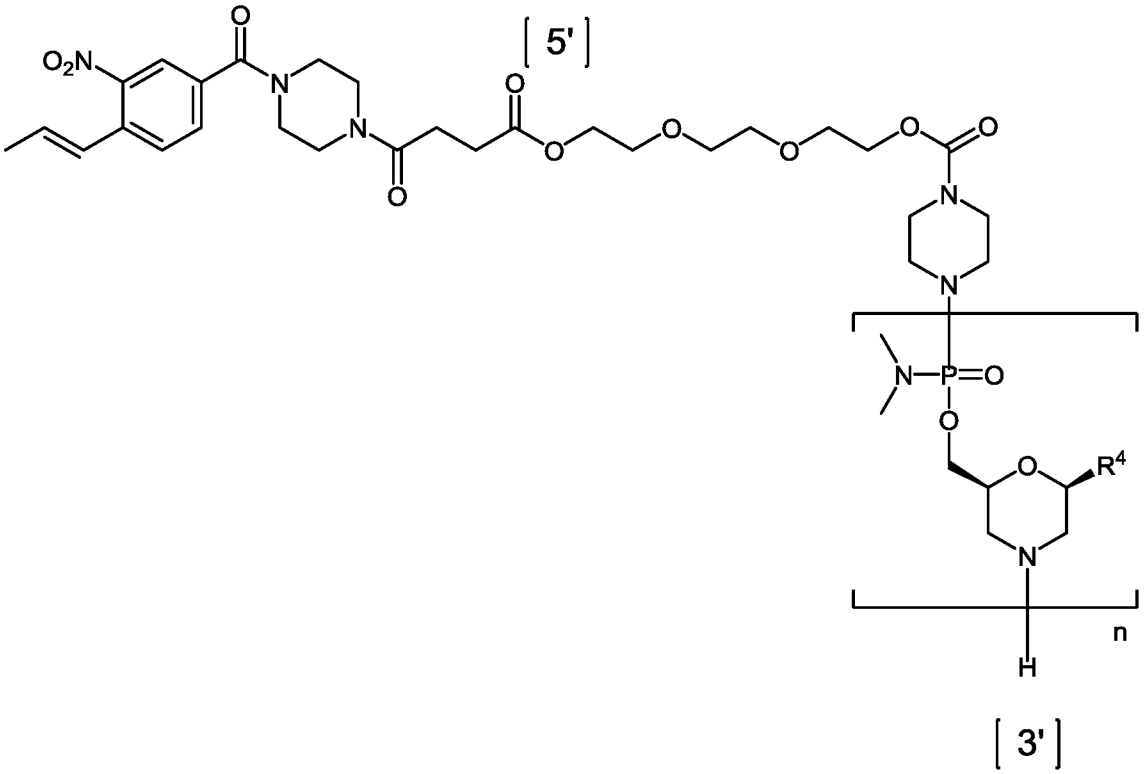
(PC),



(DPG),


(T),

(PA),

(P5mC),


(U),

(I), and
(PG).

7. The process of any one of claims 1-6, wherein the compound of Formula (A11) is of Formula (A11a):

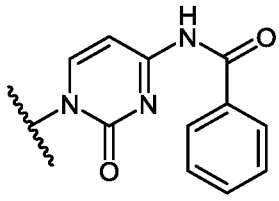
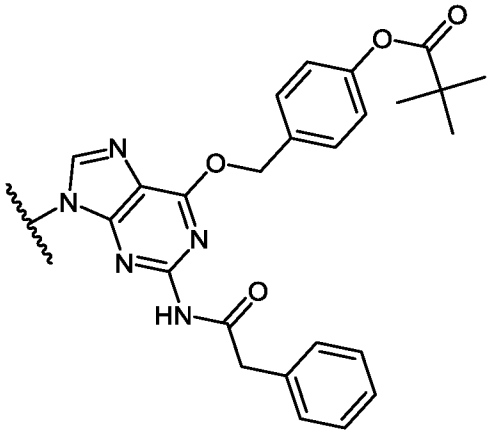
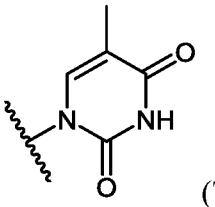
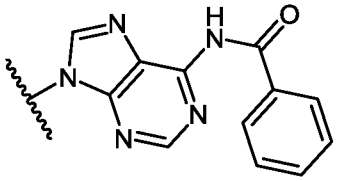
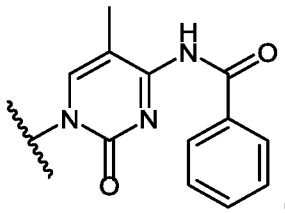
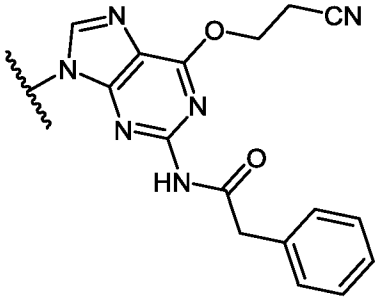
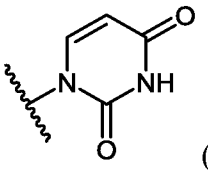
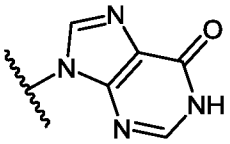


(A11a);

wherein:

n is an integer from 10 to 40, and

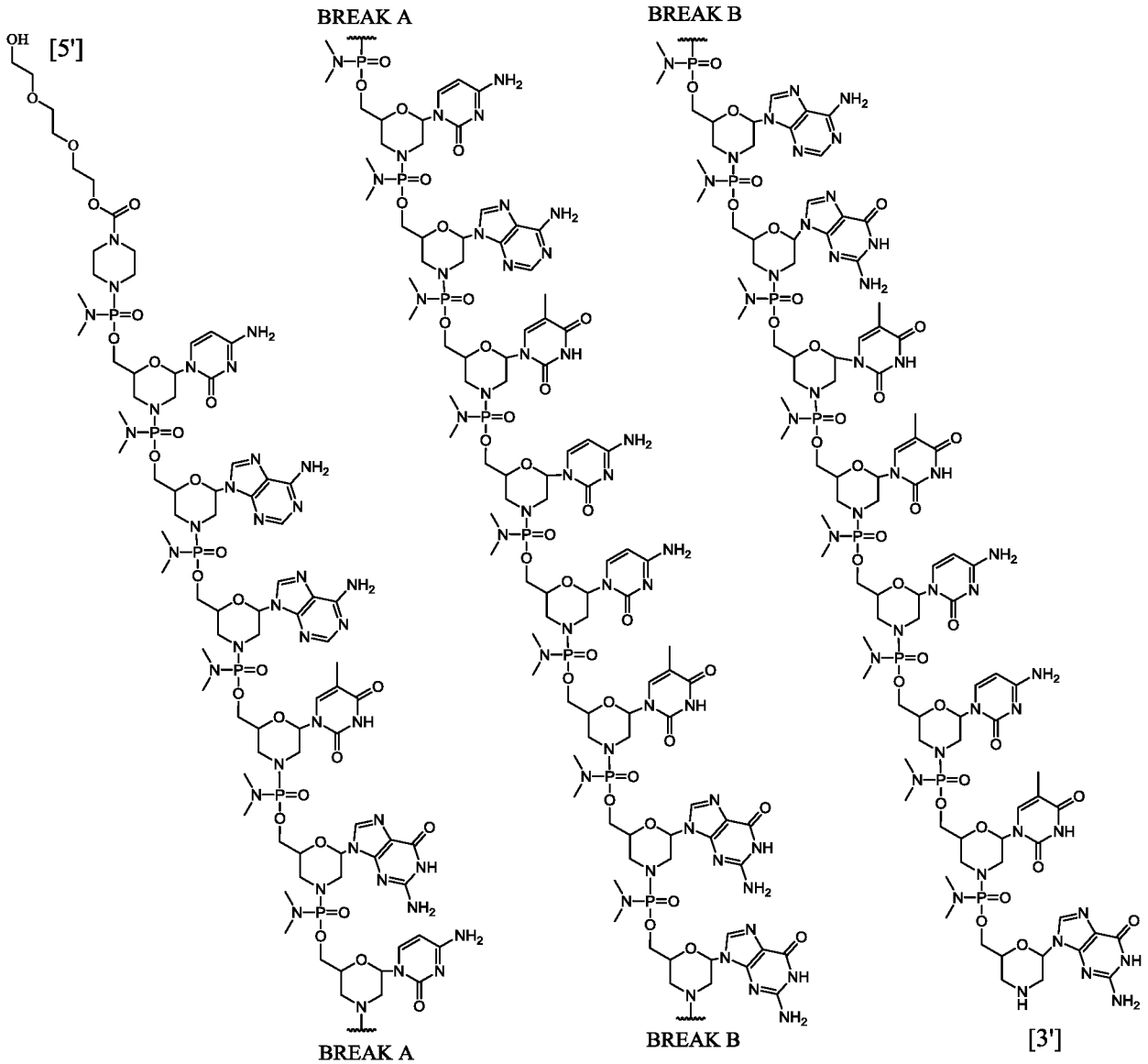
R^4 is, independently for each occurrence, selected from the group consisting of:


(PC),

(DPG),

(T),

(PA),

(P5mC),


(U),

(I), and
(PG).

5 8. The process of any one of claims 1-7, wherein for the oligomeric compound of Formula (A), n is 22, and R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	C	11	C	21	T
2	A	12	T	22	G
3	A	13	G		
4	T	14	G		
5	G	15	A		
6	C	16	G		
7	C	17	T		
8	A	18	T		
9	T	19	C		
10	C	20	C		

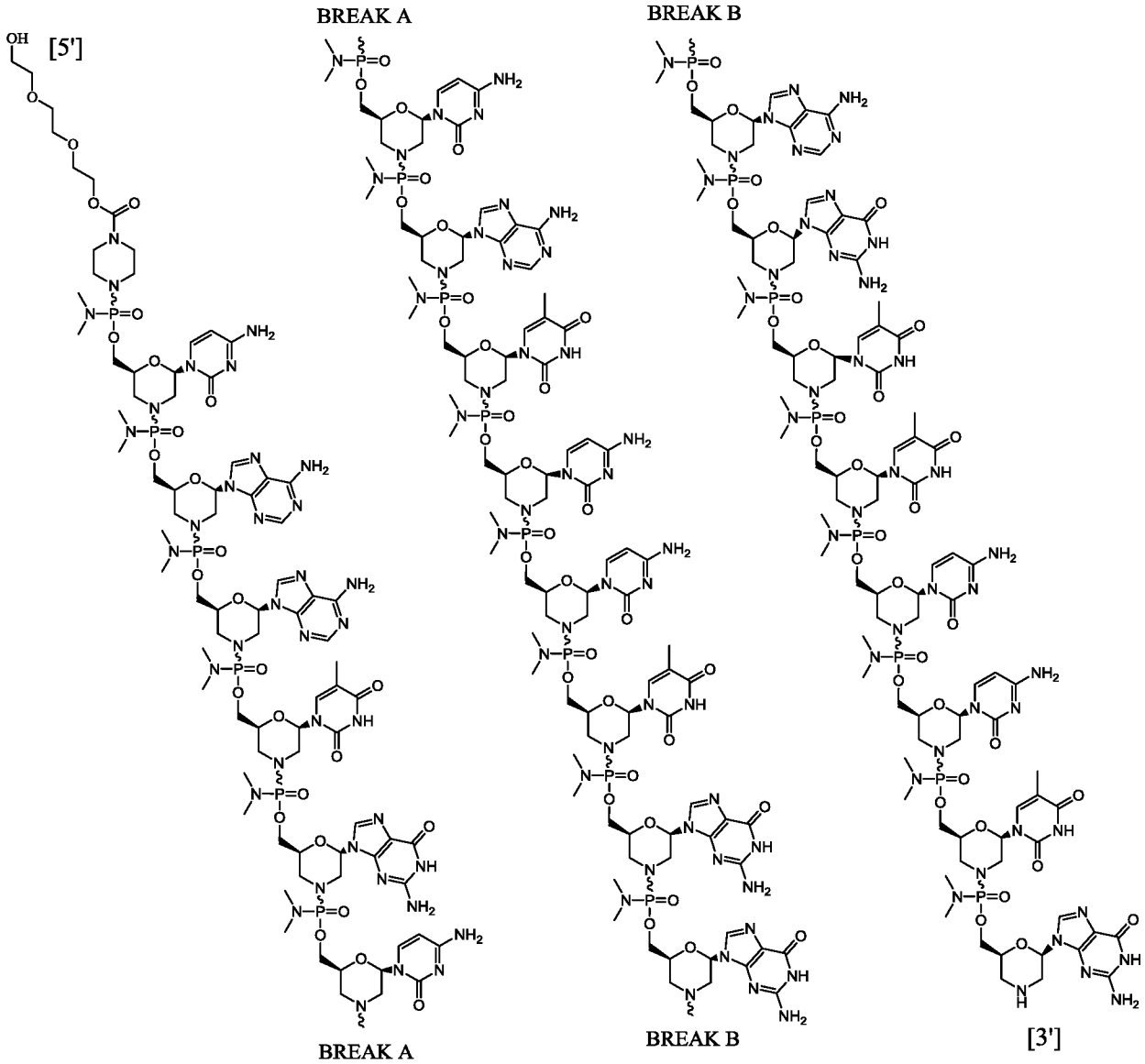
wherein the oligomeric compound of Formula (A) is a compound of Formula (C):



(C),

or a pharmaceutically acceptable salt thereof.

9. The process of any one of claims 1-8, wherein the oligomeric compound of Formula (C) is an oligomeric compound of Formula (XII):

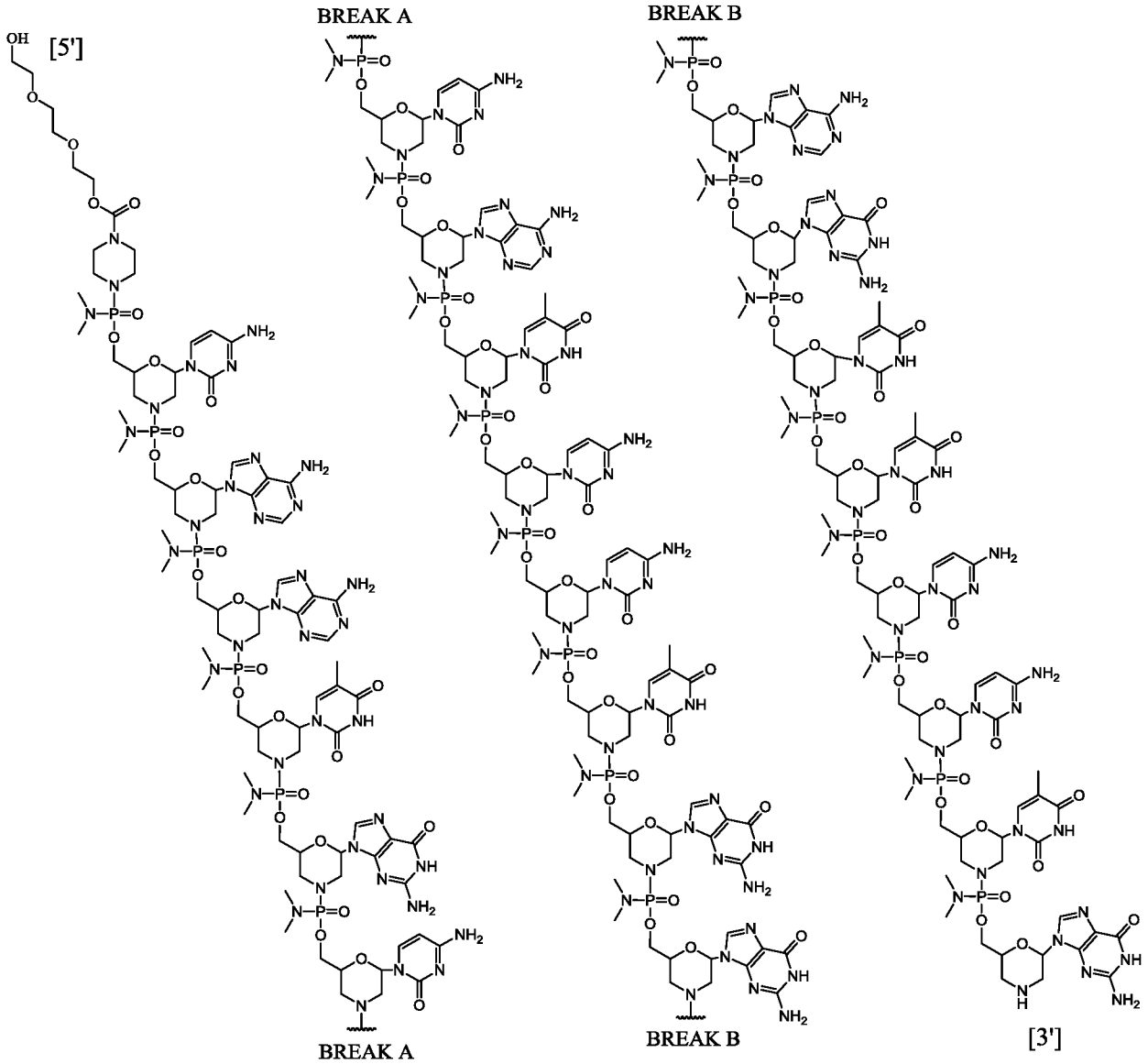


(XII),

or a pharmaceutically acceptable salt thereof.

10. The process of any one of claims 1-9, wherein R^3 is, at each occurrence, trityl.

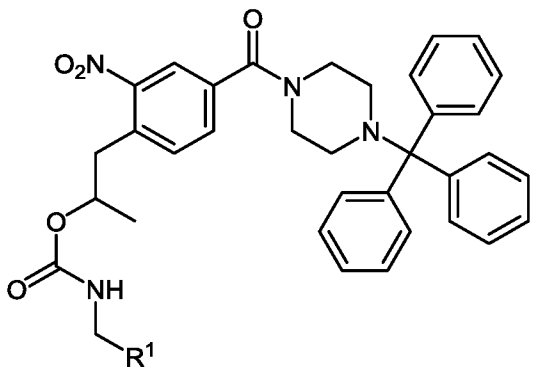
11. The process of claim 1, for preparing an oligomeric compound of Formula (C):



(C);

wherein the process comprises the sequential steps of:

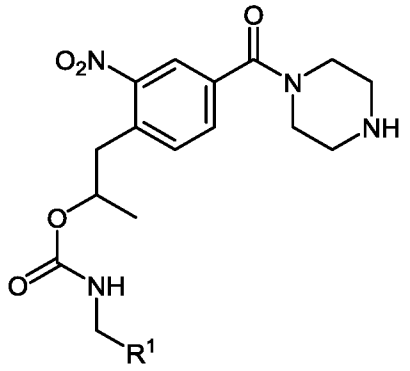
(a) contacting a compound of Formula (I):



(I);

wherein R^1 is a support-medium,

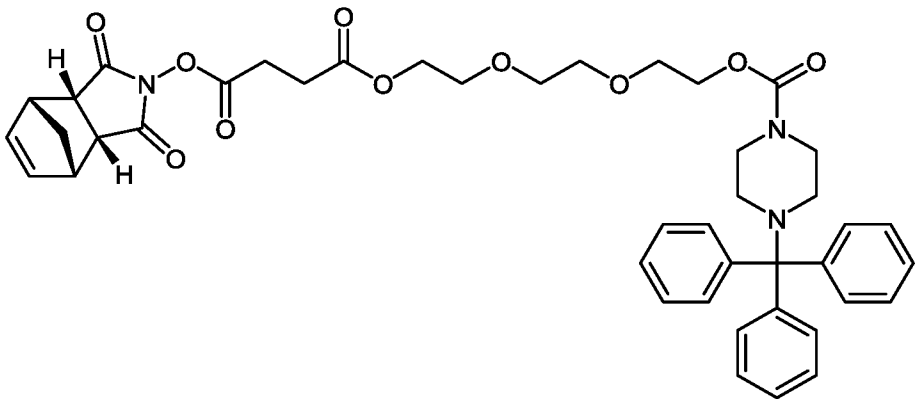
with a deblocking agent to form the compound of Formula (II):



(II);

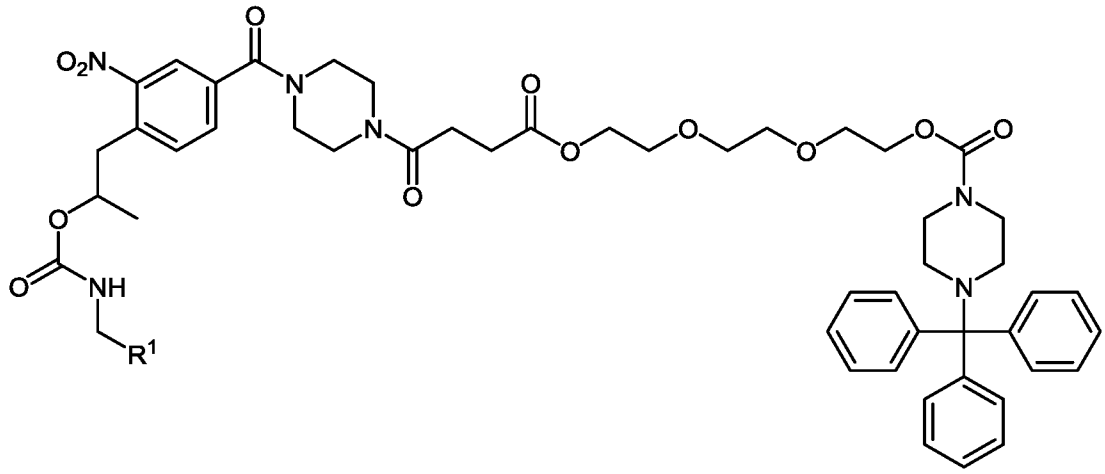
wherein R^1 is a support-medium;

(b) contacting the compound of Formula (II) with compound (B):



(B);

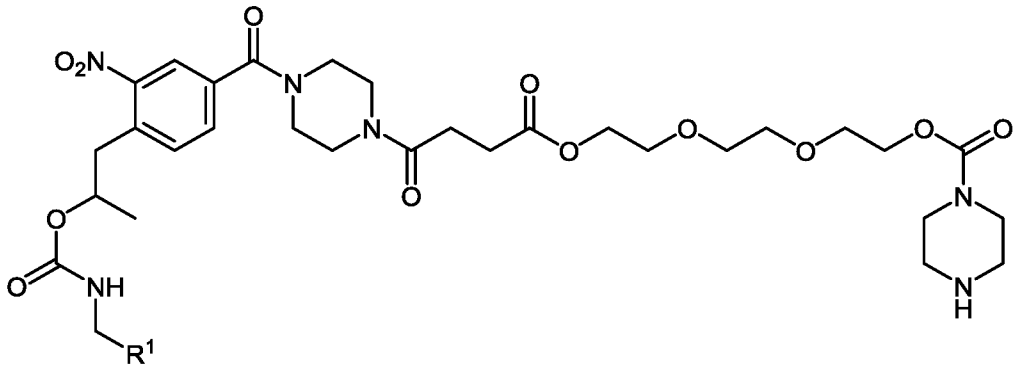
to form a compound of Formula (III):



(III);

wherein R^1 is a support-medium;

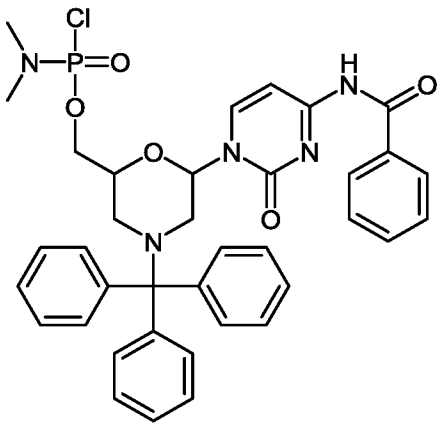
(c) contacting the compound of Formula (III) with a deblocking agent to form a compound of Formula (IV):



(IV);

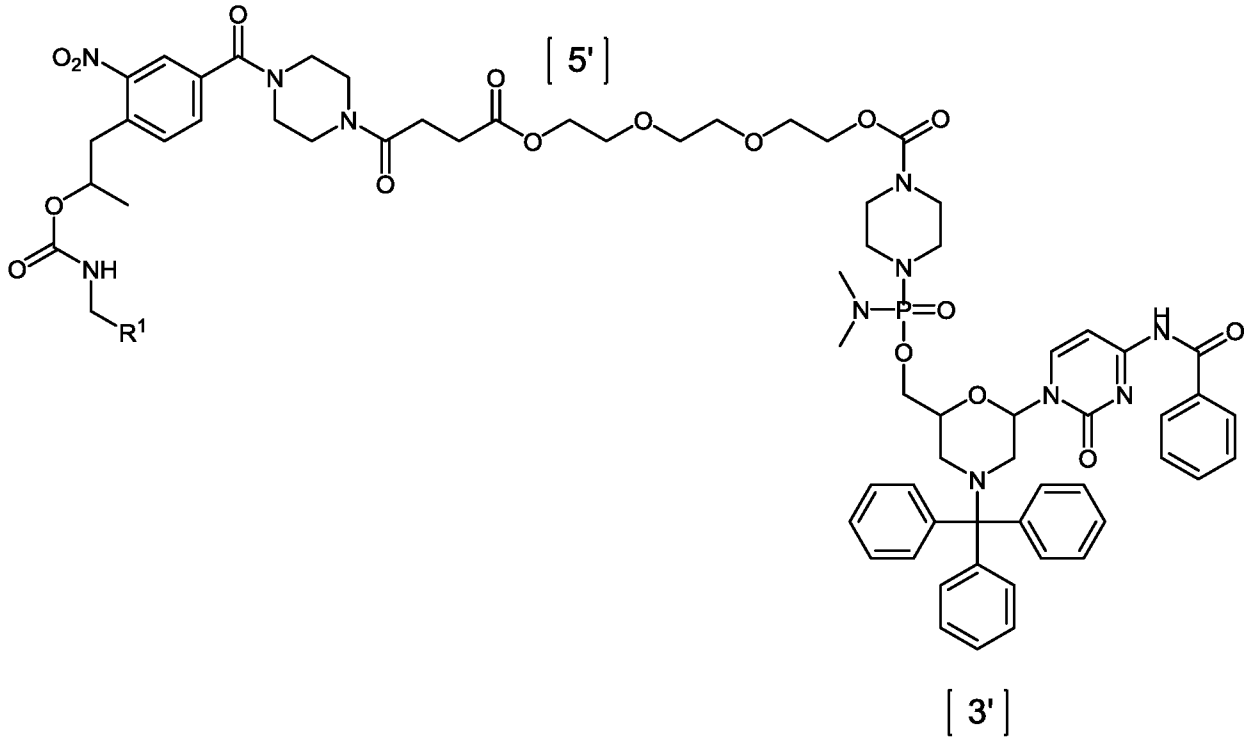
wherein R^1 is a support-medium;

(d) contacting the compound of Formula (IV) with a compound of Formula (D):



(D);

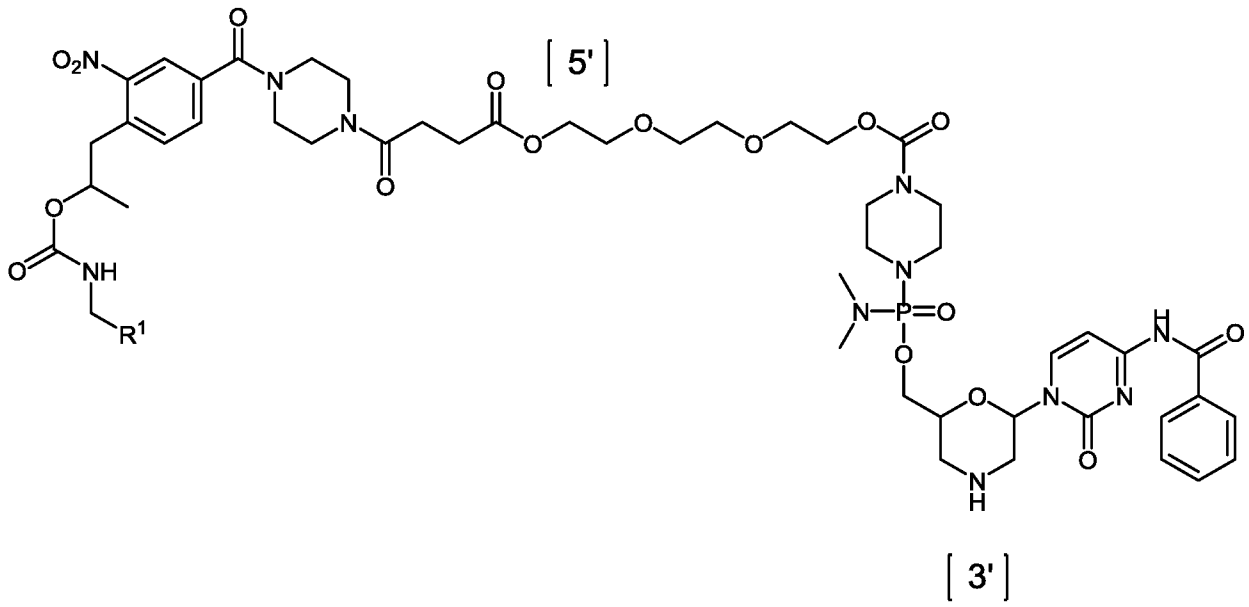
to form a compound of Formula (V):



(V);

wherein R^1 is a support-medium;

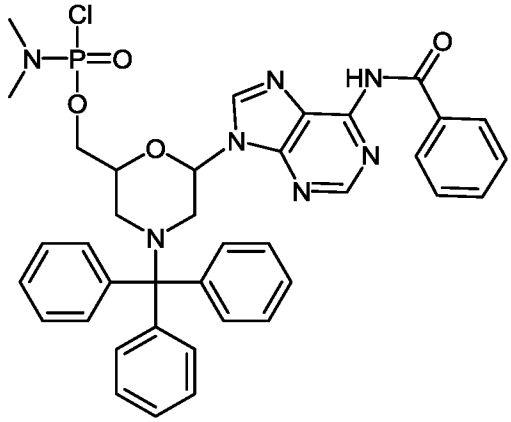
(e) contacting the compound of Formula (V) with a deblocking agent to form a compound of Formula (VI):



(VI);

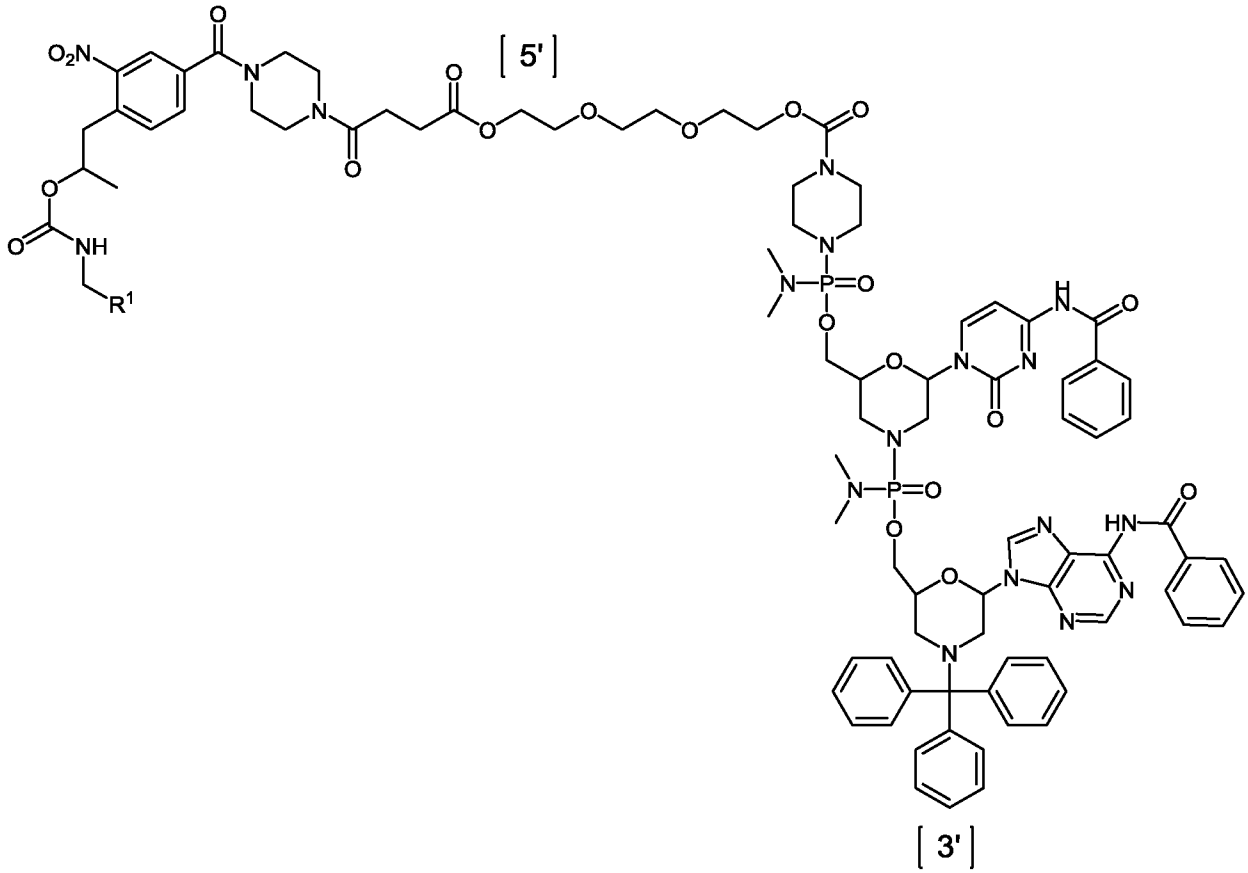
wherein R^1 is a support-medium;

(f) contacting the compound of Formula (VI) with compound of Formula (F):



(F);

to form a compound of Formula (VII):



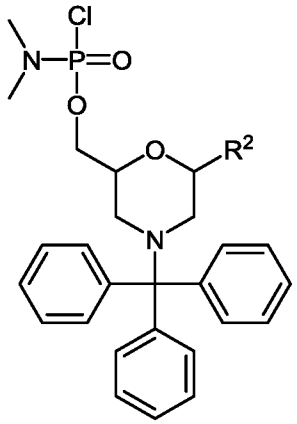
(VII);

wherein R^1 is a support-medium;

(g) performing 20 iterations of the sequential steps of:

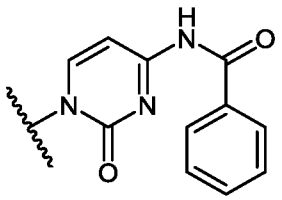
(g1) contacting the product formed by the immediately prior step with a deblocking agent; and

(g2) contacting the compound formed by the immediately prior step with a compound of Formula (VIII):

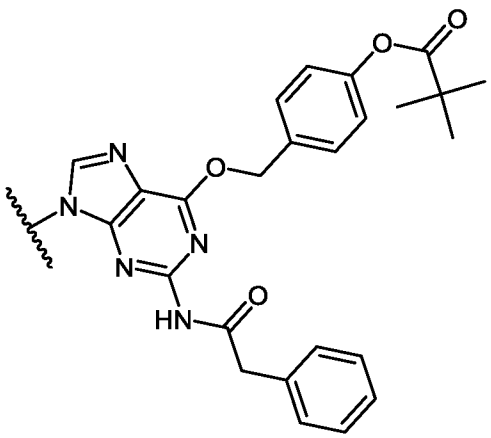


(VIII);

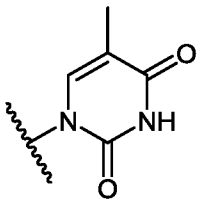
wherein R^2 is, independently for each compound of Formula (VIII), selected from the group consisting of:



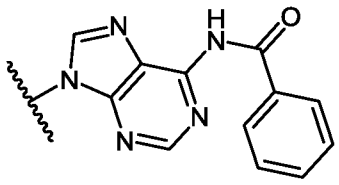
(PC),



(DPG),



(T), and

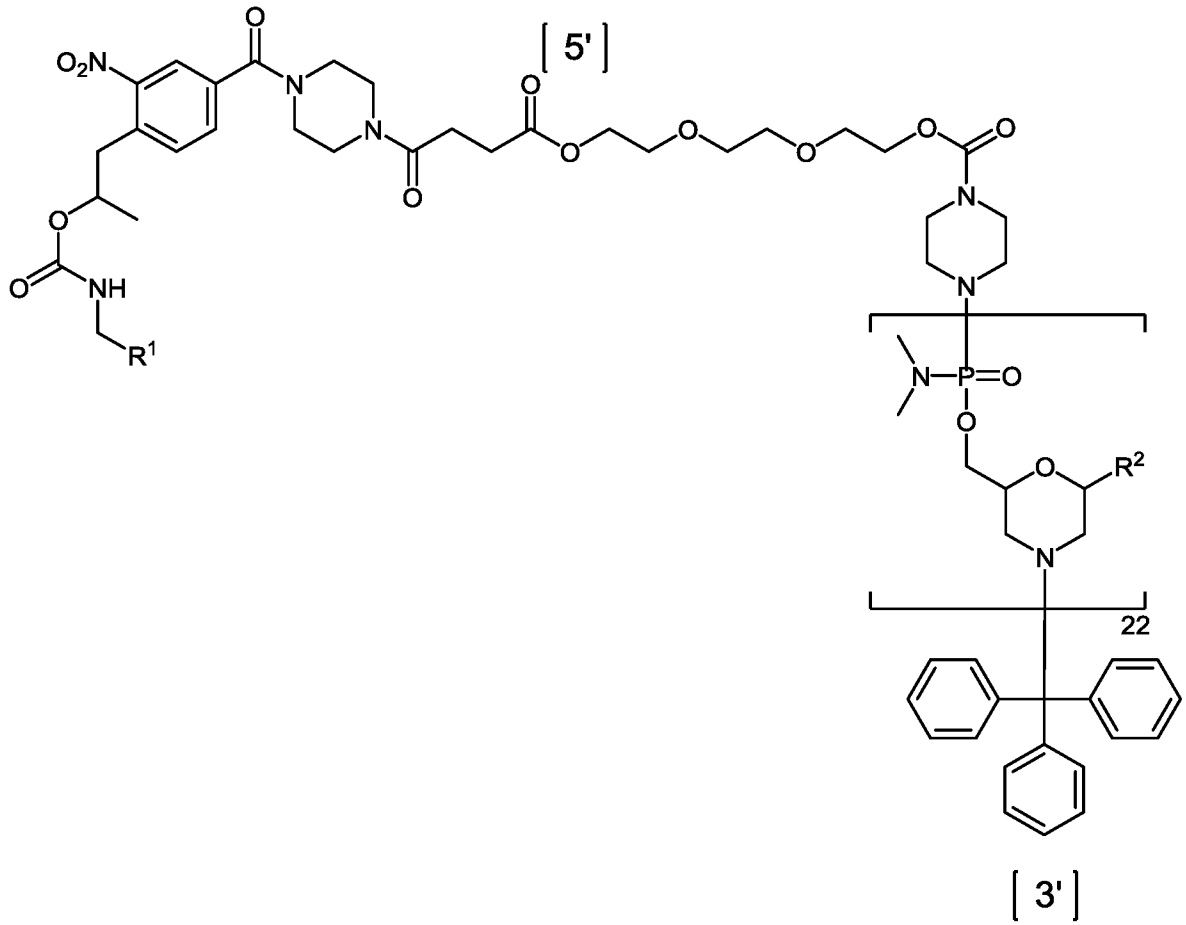


(PA),

wherein, for each iteration from 1 to 20, R^2 is:

Iteration No.	R^2	Iteration No.	R^2
1	PA	11	DPG
2	T	12	DPG
3	DPG	13	PA
4	PC	14	DPG
5	PC	15	T
6	PA	16	T
7	T	17	PC
8	PC	18	PC
9	PC	19	T
10	T	20	DPG

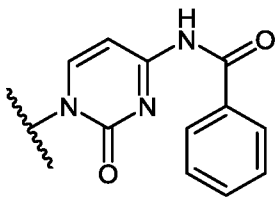
to form a compound of Formula (IX):

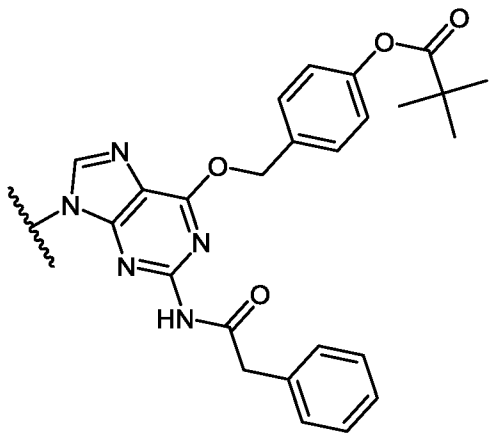


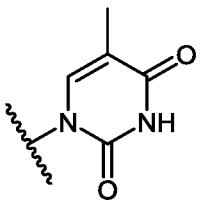
(IX);

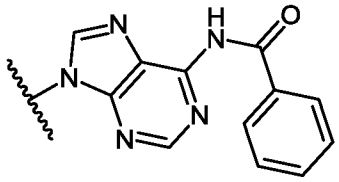
wherein R^1 is a support-medium,

wherein R^2 is, independently for each occurrence, selected from the group consisting of:


(PC),


(DPG),

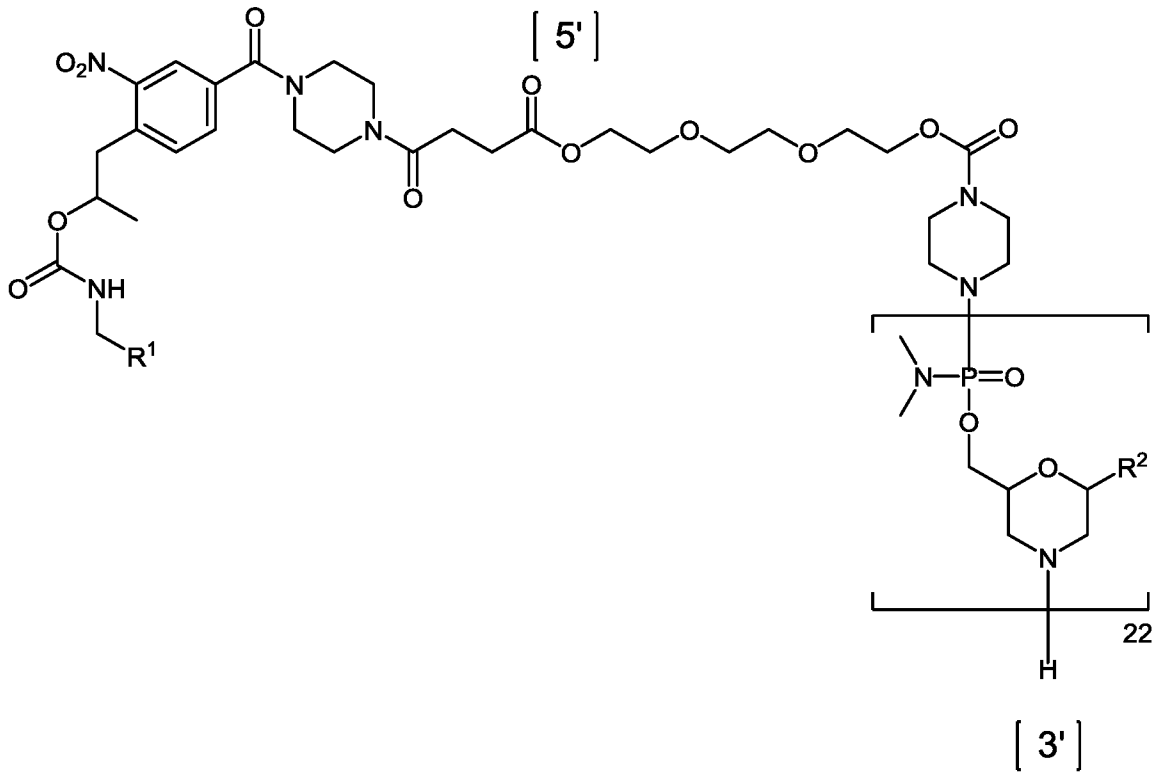

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

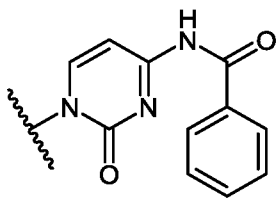
(h) contacting the compound of Formula (IX) with a deblocking agent to form a compound of Formula (X):

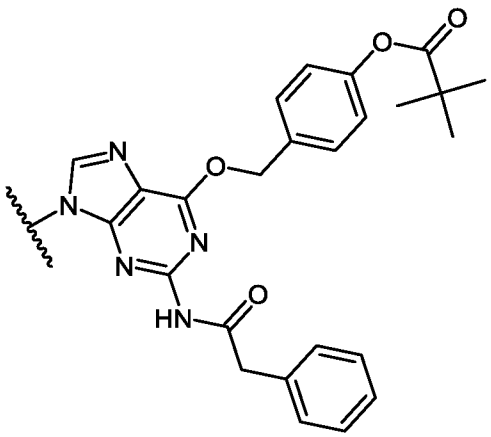


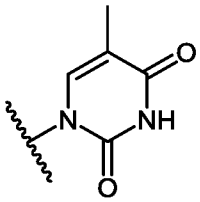
(X);

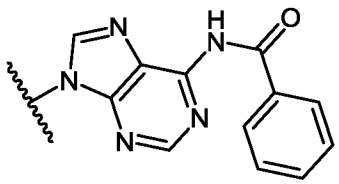
wherein R^1 is a support-medium,

wherein R^2 is, independently for each occurrence, selected from the group consisting of:


(PC),


(DPG),

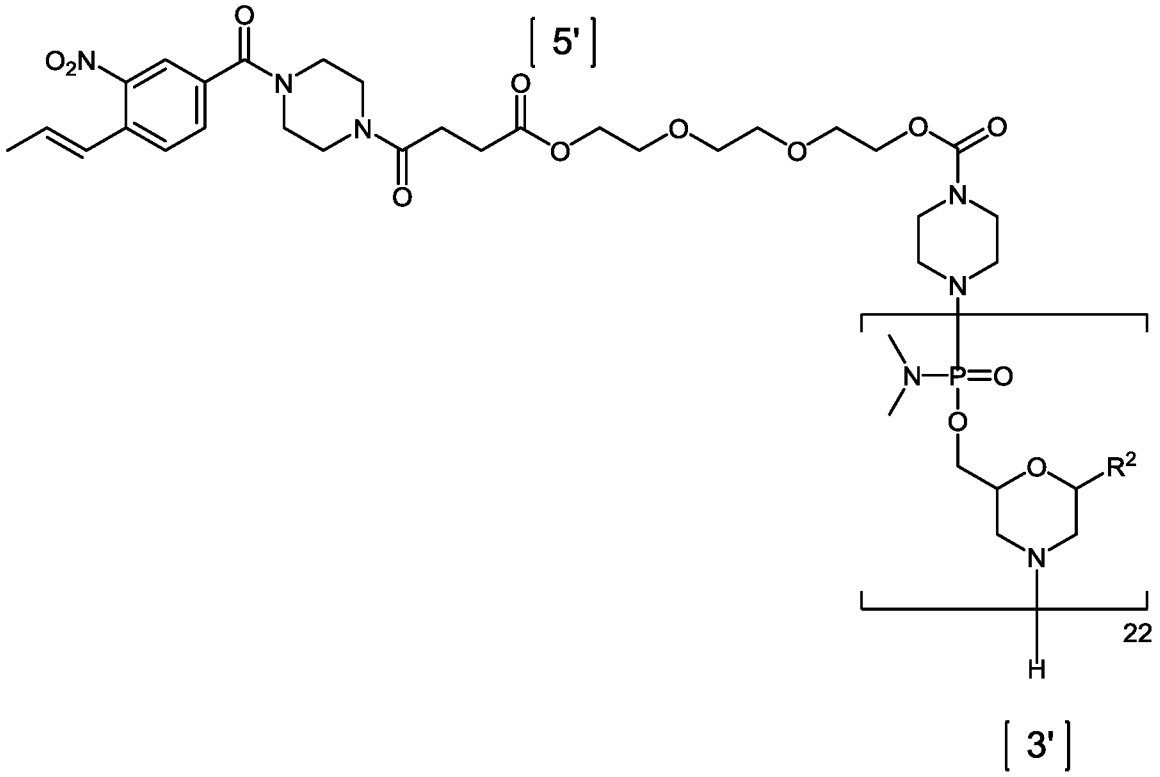

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

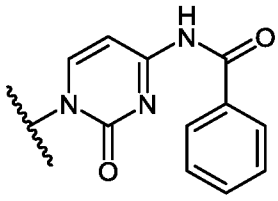
Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

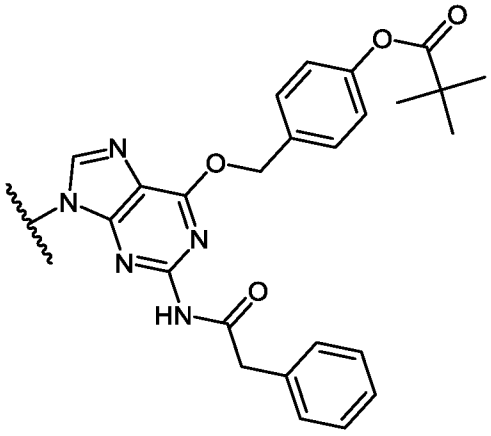
(i) contacting the compound of Formula (X) with a cleaving agent to form a compound of Formula (XI):

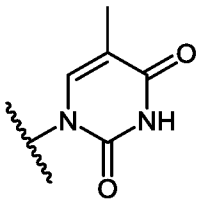


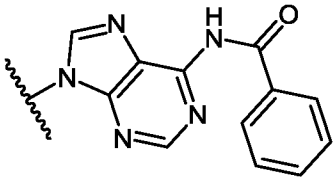
(XI),

wherein R^2 is, independently for each occurrence, selected from the group consisting of:


(PC),


(DPG),


(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

and

(j) contacting the compound of Formula (XI) with a deprotecting agent to form the oligomeric compound of Formula (C).

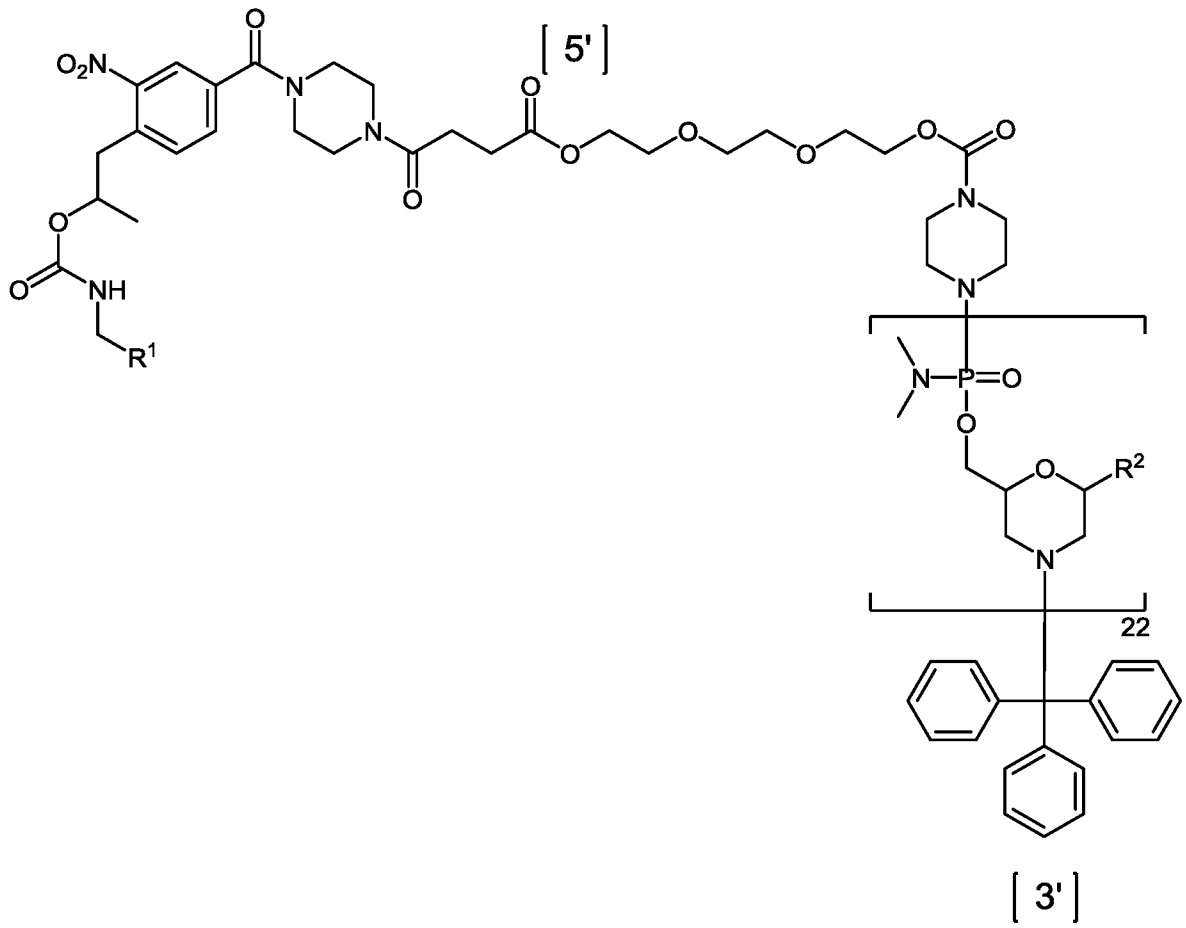
12. The process of any one of claims 1-11, wherein step (d), step (f) or step (g2) further comprises contacting the compound of Formula (IV), Formula (VI), or the compound formed by the immediately prior step, respectively, with a capping agent.

13. The process of any one of claims 1-12, wherein the deblocking agent used in each step is halogenated acid or cyanoacetic acid.

14. The process of claim 13, wherein the halogenated acid is selected from the group consisting of chloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, and trifluoroacetic acid.

15. The process of any one of claims 1-14, wherein the support-medium comprises a material selected from the group consisting of glass, modified or functionalized glass, plastics (including acrylics, polystyrene (e.g., polystyrene with 1% crosslinked divinylbenzene), copolymers of styrene and other materials, polypropylene, polyethylene, polybutylene, polyurethanes, and TEFLON), polysaccharides, nylon or nitrocellulose, ceramics, resins, silica or silica-based materials (including silicon and modified silicon), carbon, metals, and optical fiber bundles.

16. A compound of Formula (IX):

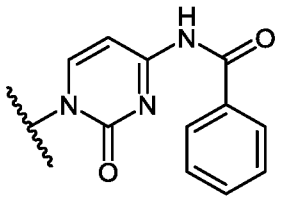


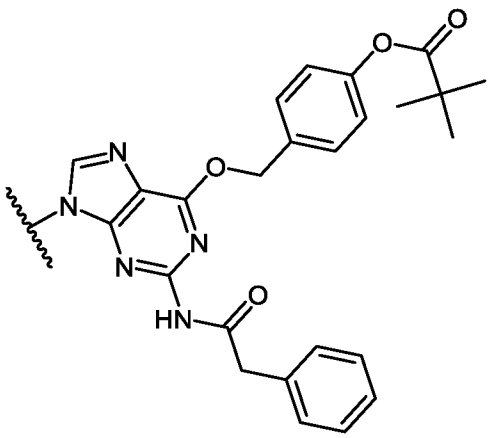
(IX),

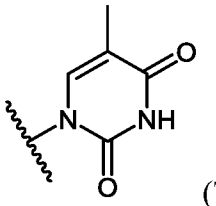
or a pharmaceutically acceptable salt thereof, wherein:

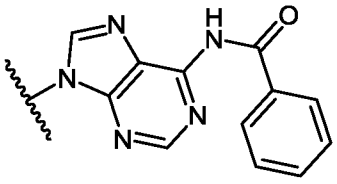
R^1 is a support-medium, and

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),

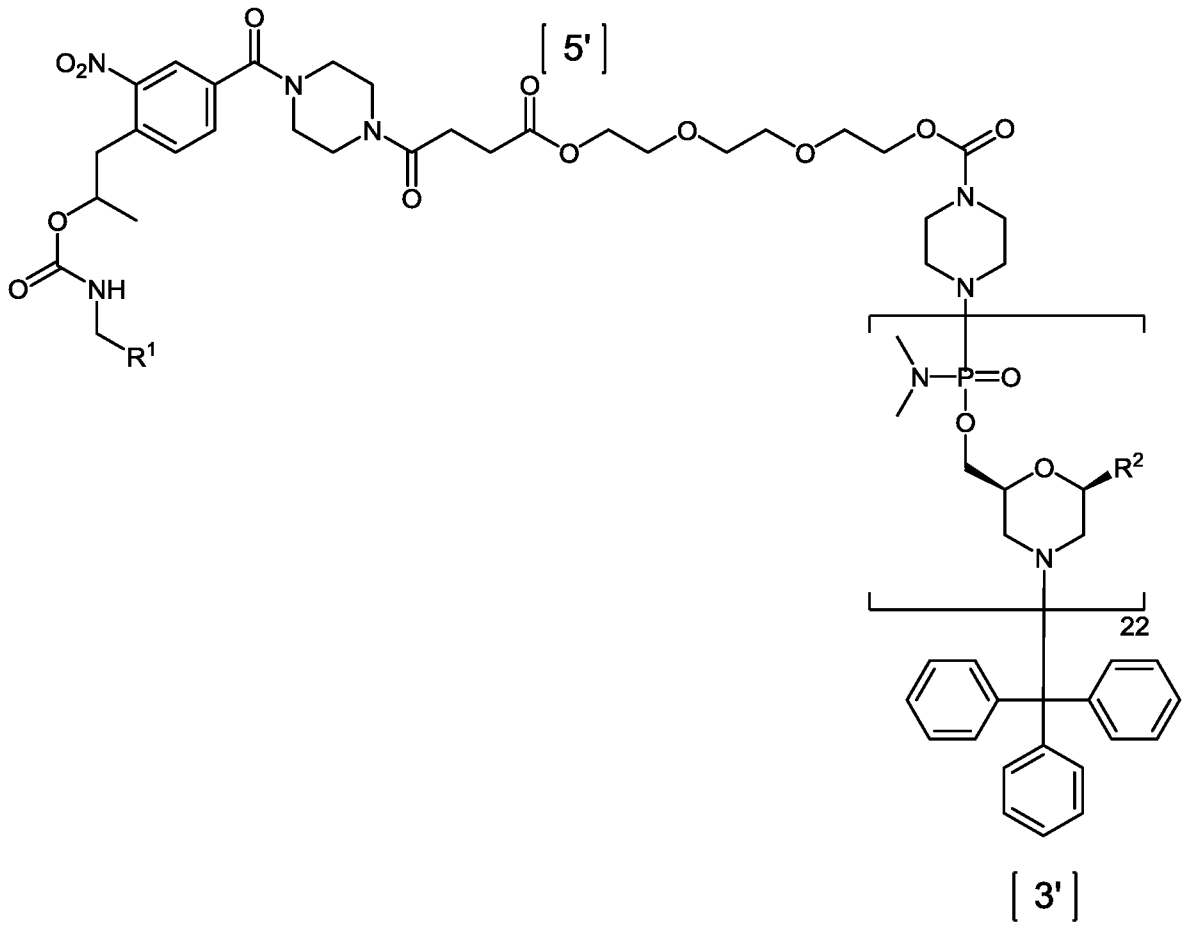

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

17. The compound of claim 16, wherein the compound of Formula (IX) is of Formula (IXa):

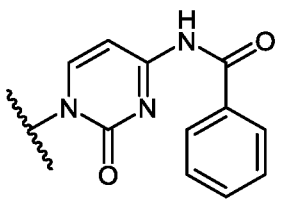


(IXa),

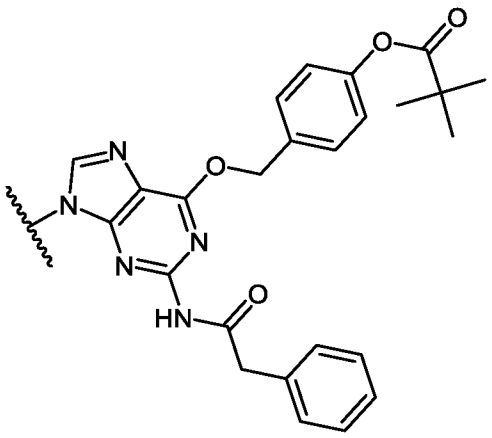
or a pharmaceutically acceptable salt thereof, wherein

R^1 is a support-medium, and

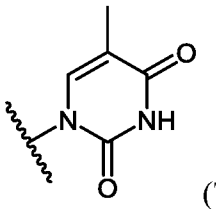
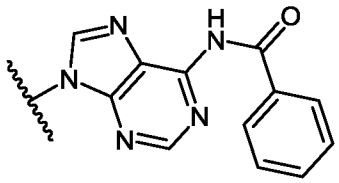
R^2 is, independently at each occurrence, selected from the group consisting of:



(PC),



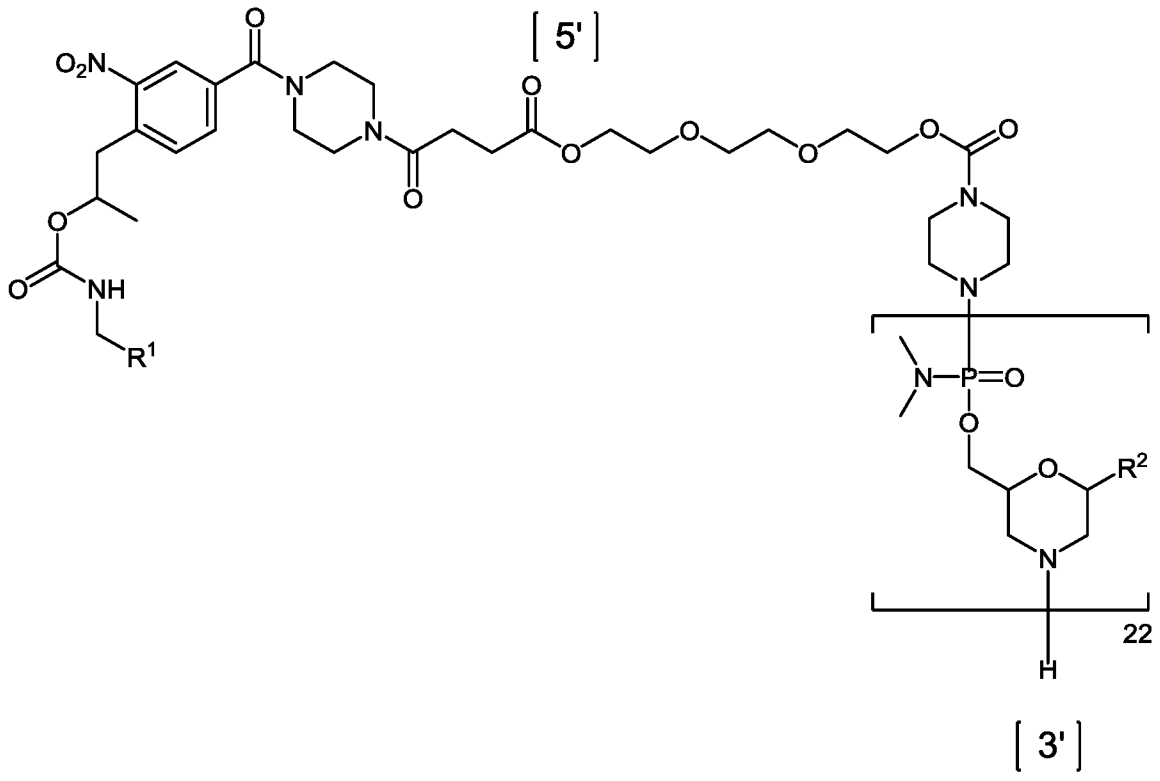
(DPG),


(T), and 
(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

18. A compound of Formula (X):

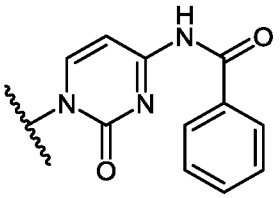


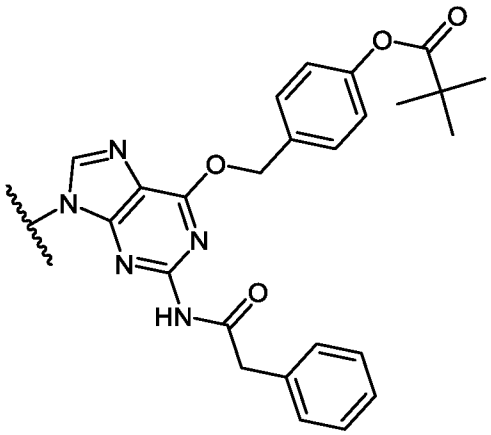
(X);

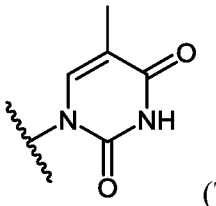
or a pharmaceutically acceptable salt thereof, wherein

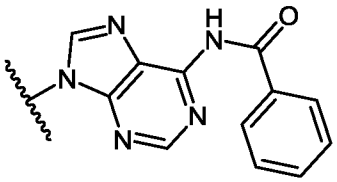
R^1 is a support-medium, and

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),

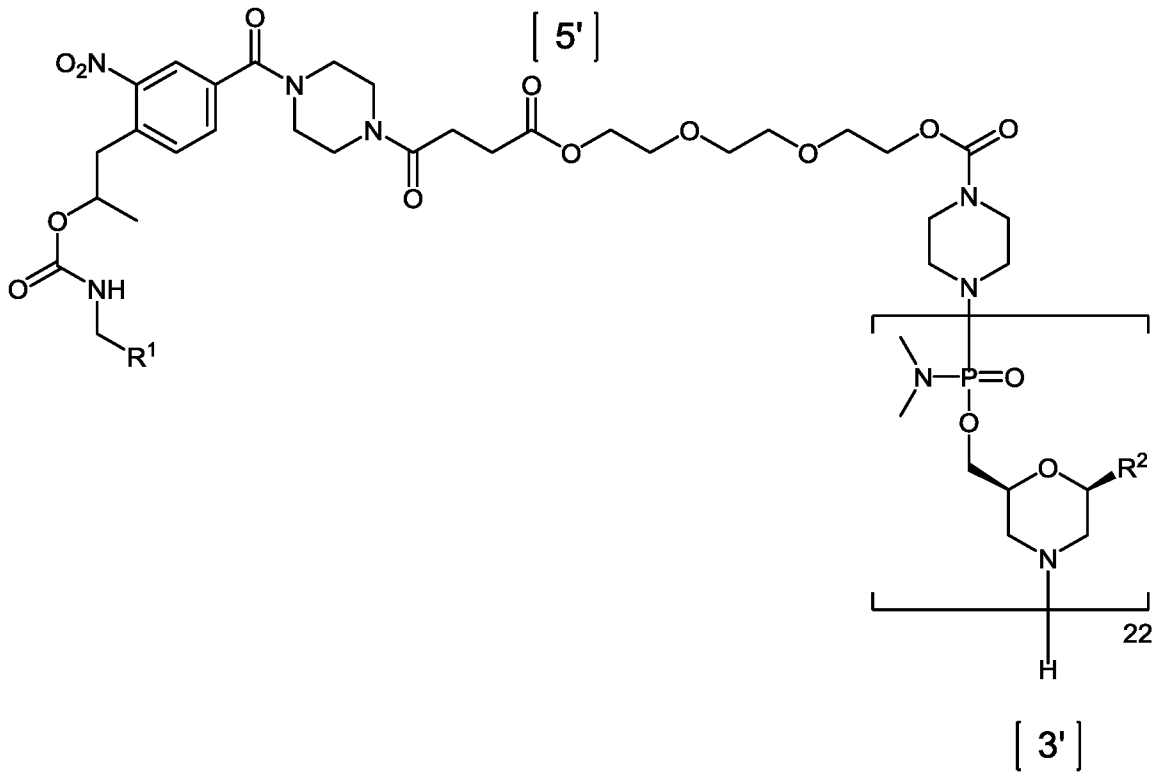

(T), and


(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

19. The compound of claim 70, wherein the compound of Formula (X) is of Formula (Xa):

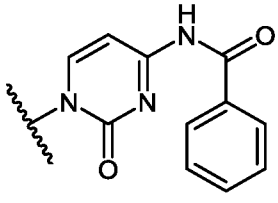


(Xa),

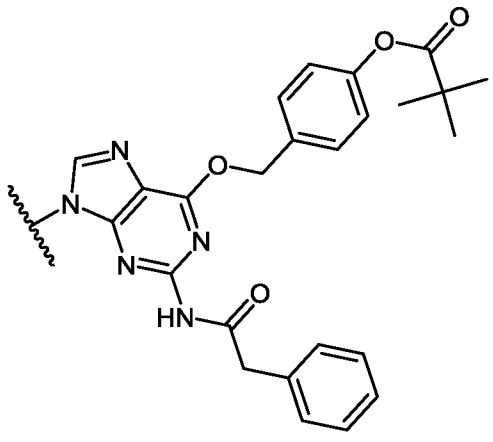
or a pharmaceutically acceptable salt thereof, wherein

R^1 is a support-medium, and

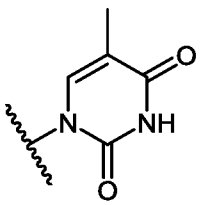
R^2 is, independently at each occurrence, selected from the group consisting of:



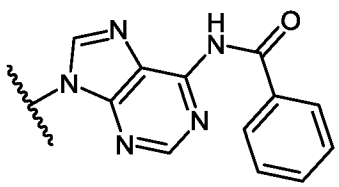
(PC),



(DPG),



(T), and



(PA), and

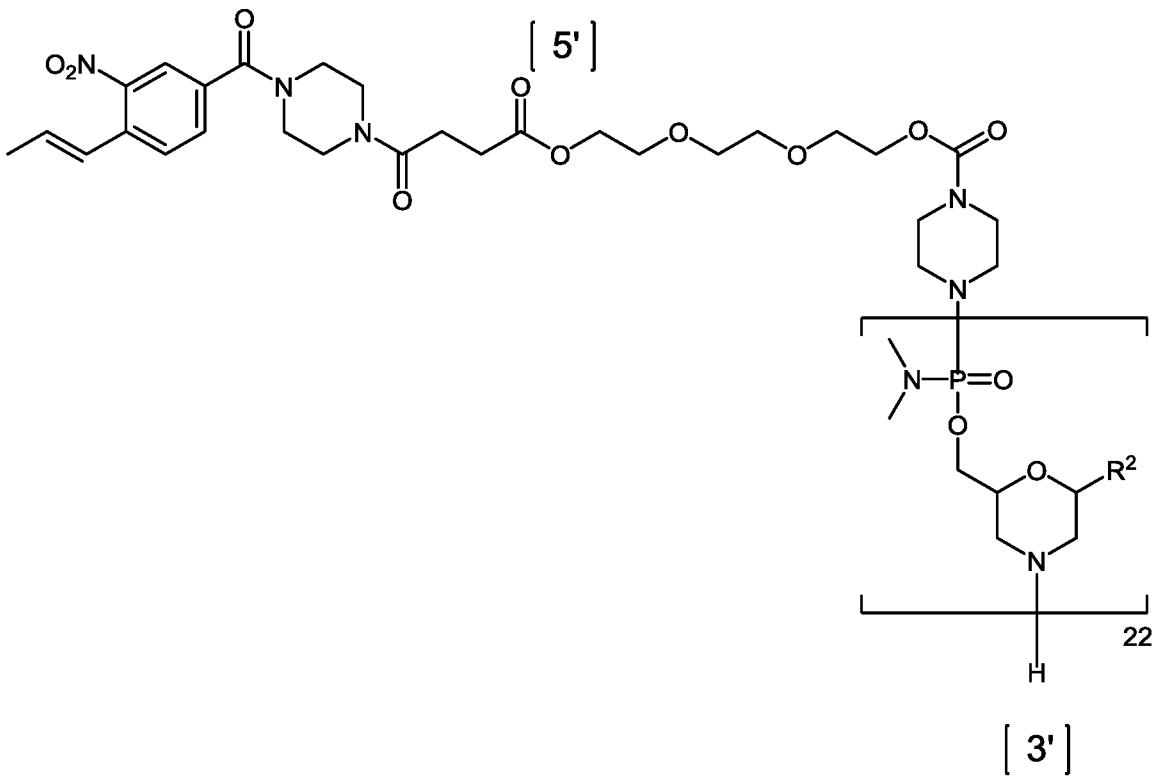
wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

.

20. The compound according to any one of claims 16-19, wherein the support-medium comprises polystyrene with 1% crosslinked divinylbenzene.

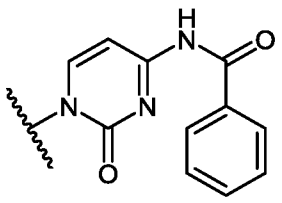
21. A compound of Formula (XI):

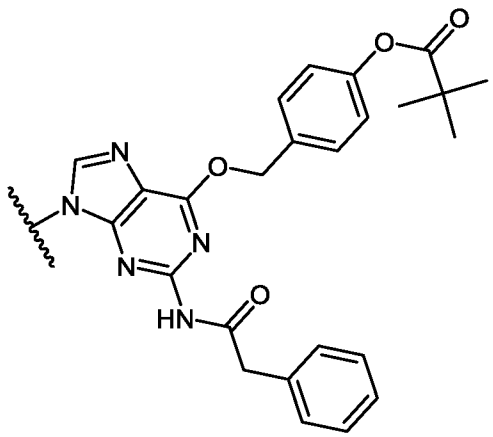


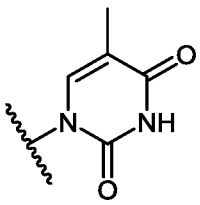
(XI),

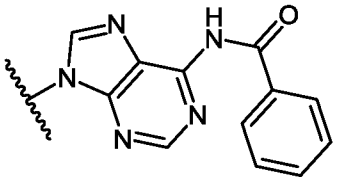
or a pharmaceutically acceptable salt thereof, wherein:

R^2 is, independently at each occurrence, selected from the group consisting of:


(PC),


(DPG),


(T), and

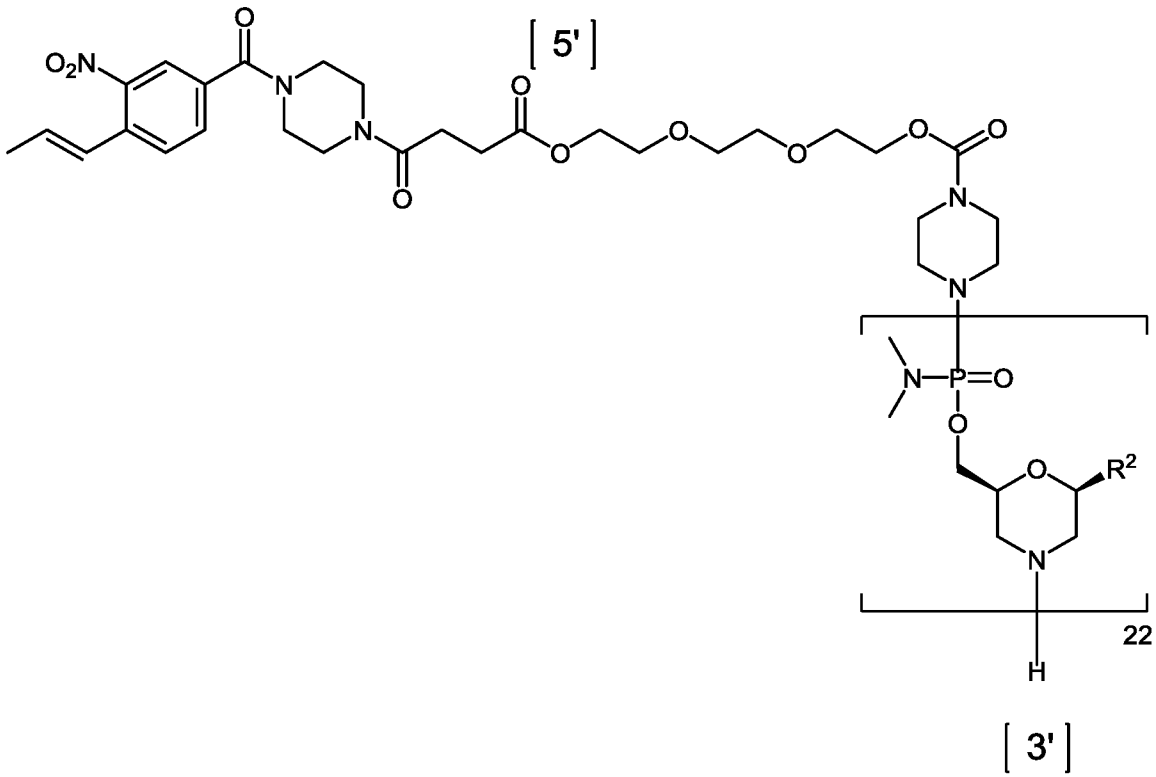

(PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

.

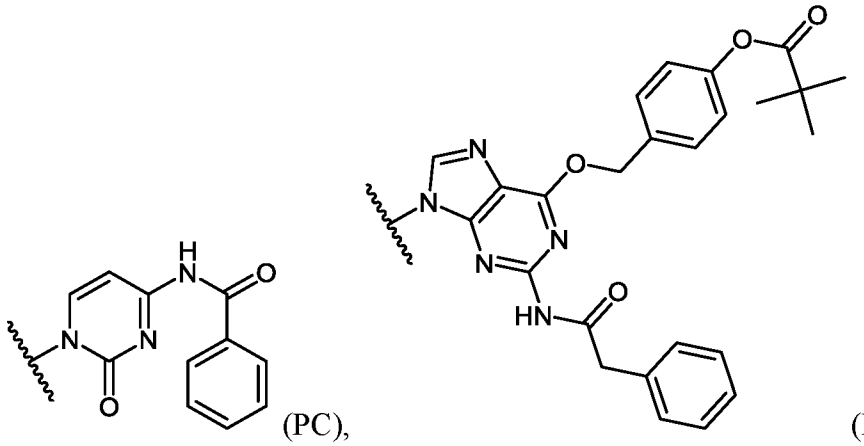
22. The compound of claim 21, wherein the compound of Formula (XI) is of Formula (XIa):



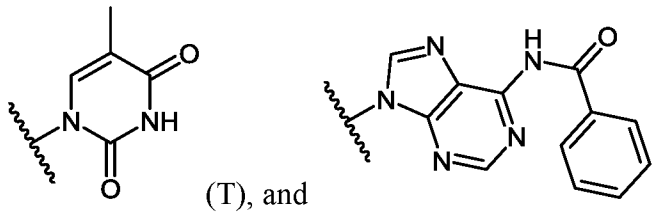
(XIa),

or a pharmaceutically acceptable salt thereof, wherein

R^2 is, independently at each occurrence, selected from the group consisting of:



(PC), (DPG),



(T), and (PA), and

wherein R^2 is at each position from 1 to 22 and 5' to 3':

Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2	Position No. 5' to 3'	R^2
1	PC	11	PC	21	T
2	PA	12	T	22	DPG
3	PA	13	DPG		
4	T	14	DPG		
5	DPG	15	PA		
6	PC	16	DPG		
7	PC	17	T		
8	PA	18	T		
9	T	19	PC		
10	PC	20	PC		

Fig. 1

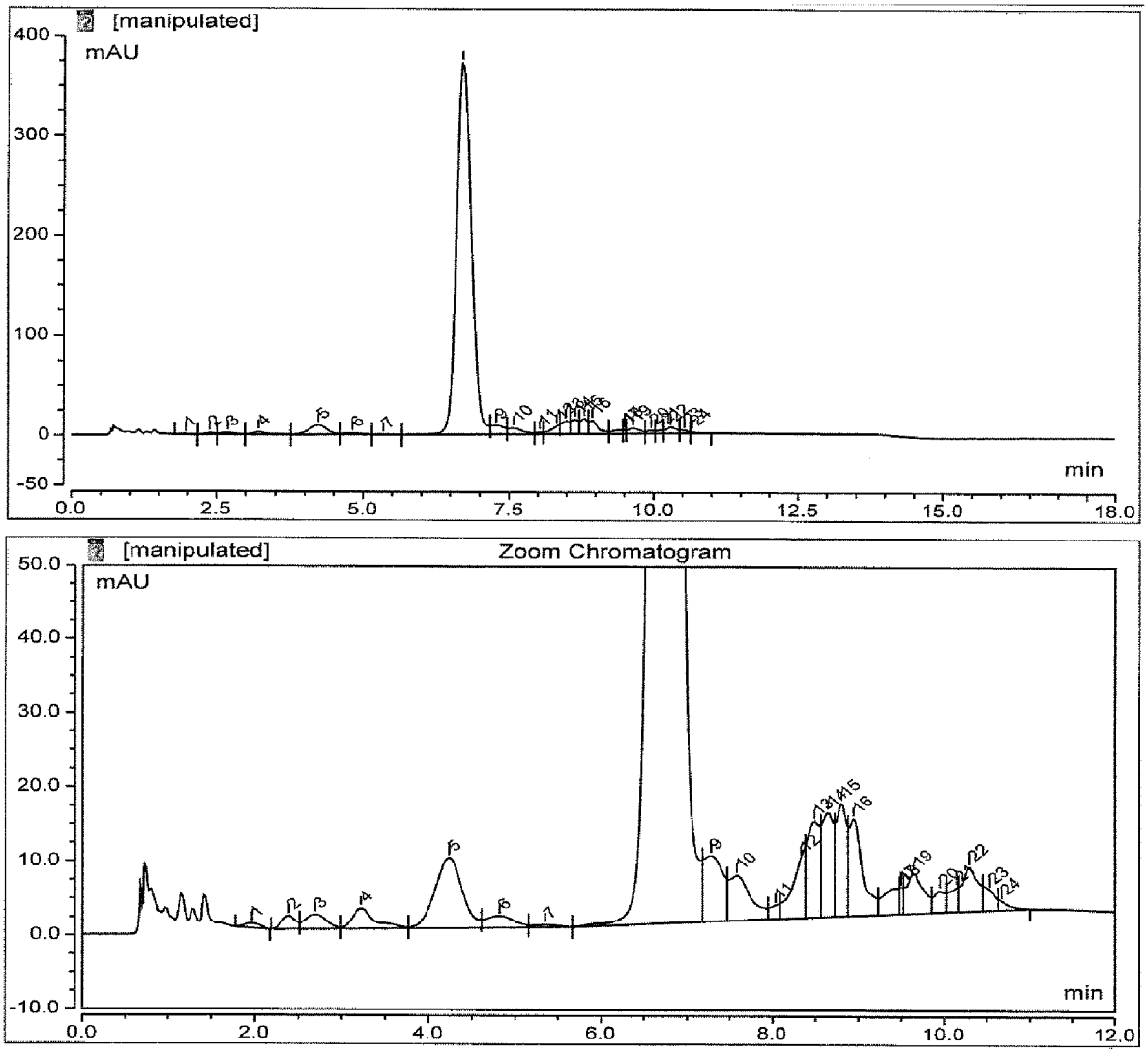
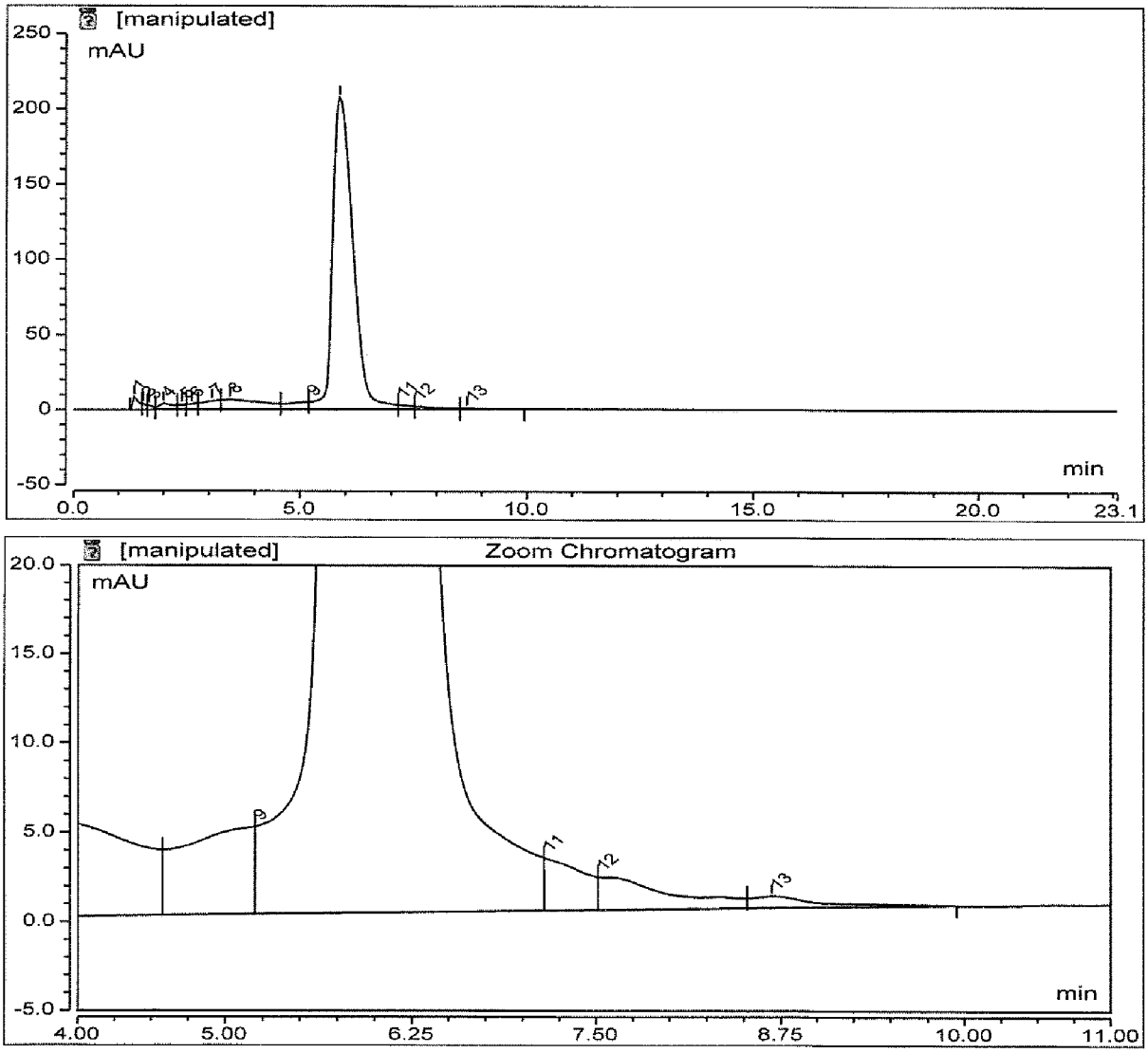

[manipulated]
mAU
400
300
200
100
0
-50
min
0.0
2.5
5.0
7.5
10.0
12.5
15.0
18.0
[manipulated]
Zoom Chromatogram
mAU
50.0
40.0
30.0
20.0
10.0
0.0
-10.0
min
0.0
2.0
4.0
6.0
8.0
10.0
12.0

Fig. 2


[manipulated]
mAU
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200
150
100
50
0
-50
min
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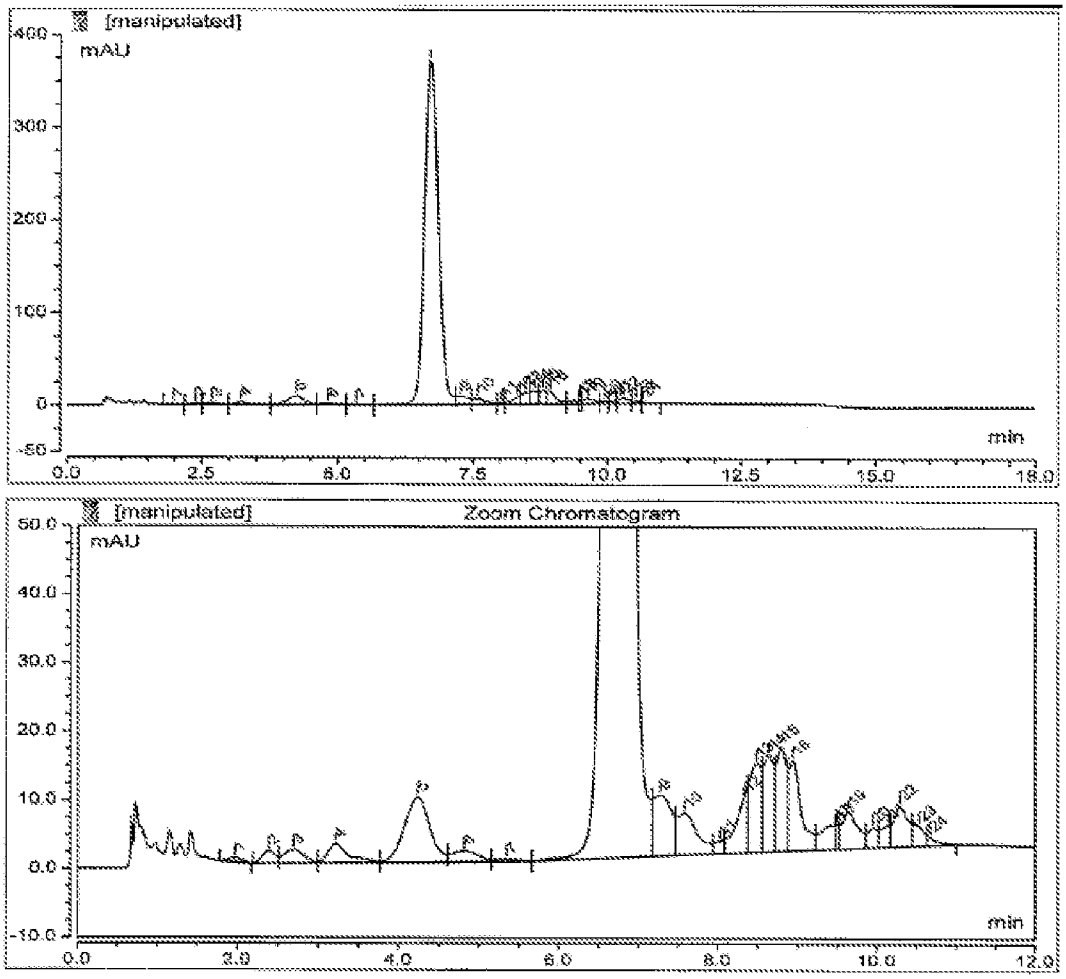
5.0
10.0
15.0
20.0
23.1
[manipulated]
Zoom Chromatogram
mAU
20.0
15.0
10.0
5.0
0.0
-5.0
min
4.00
5.00
6.25
7.50
8.75
10.00
11.00

Fig. 3


[manipulated]
mAU
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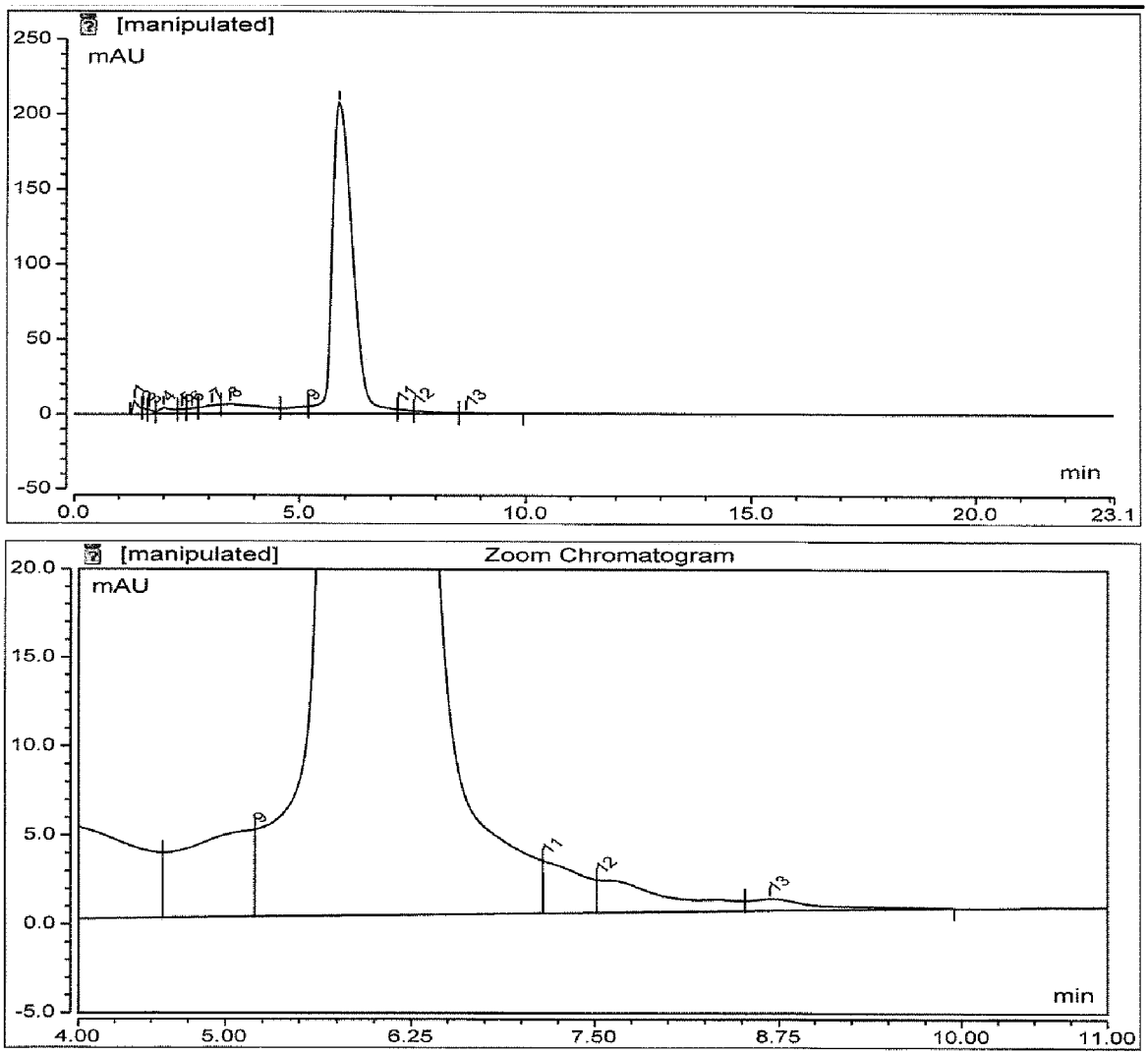
200
100
0
-50
min
0.0
2.5
5.0
7.5
10.0
12.5
15.0
18.0
[manipulated]
Zoom Chromatogram
mAU
50.0
40.0
30.0
20.0
10.0
0.0
-10.0
min
0.0
2.0
4.0
6.0
8.0
10.0
12.0

Fig. 4


[manipulated]
mAU
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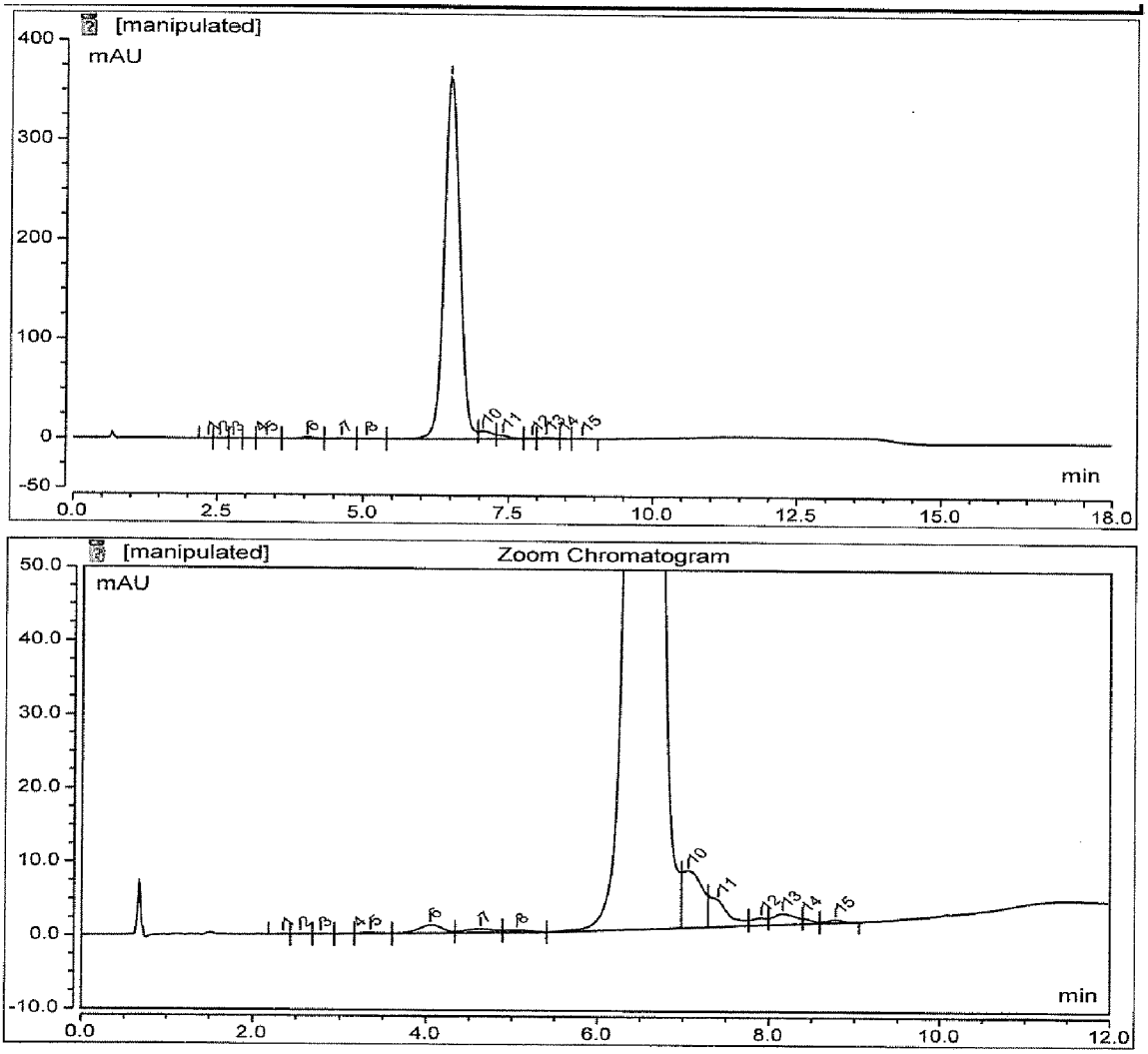
200
150
100
50
0
-50
min
0.0
5.0
10.0
15.0
20.0
23.1
[manipulated]
Zoom Chromatogram
mAU
20.0
15.0
10.0
5.0
0.0
-5.0
min
4.00
5.00
6.25
7.50
8.75
10.00
11.00

Fig. 5


[manipulated]
mAU
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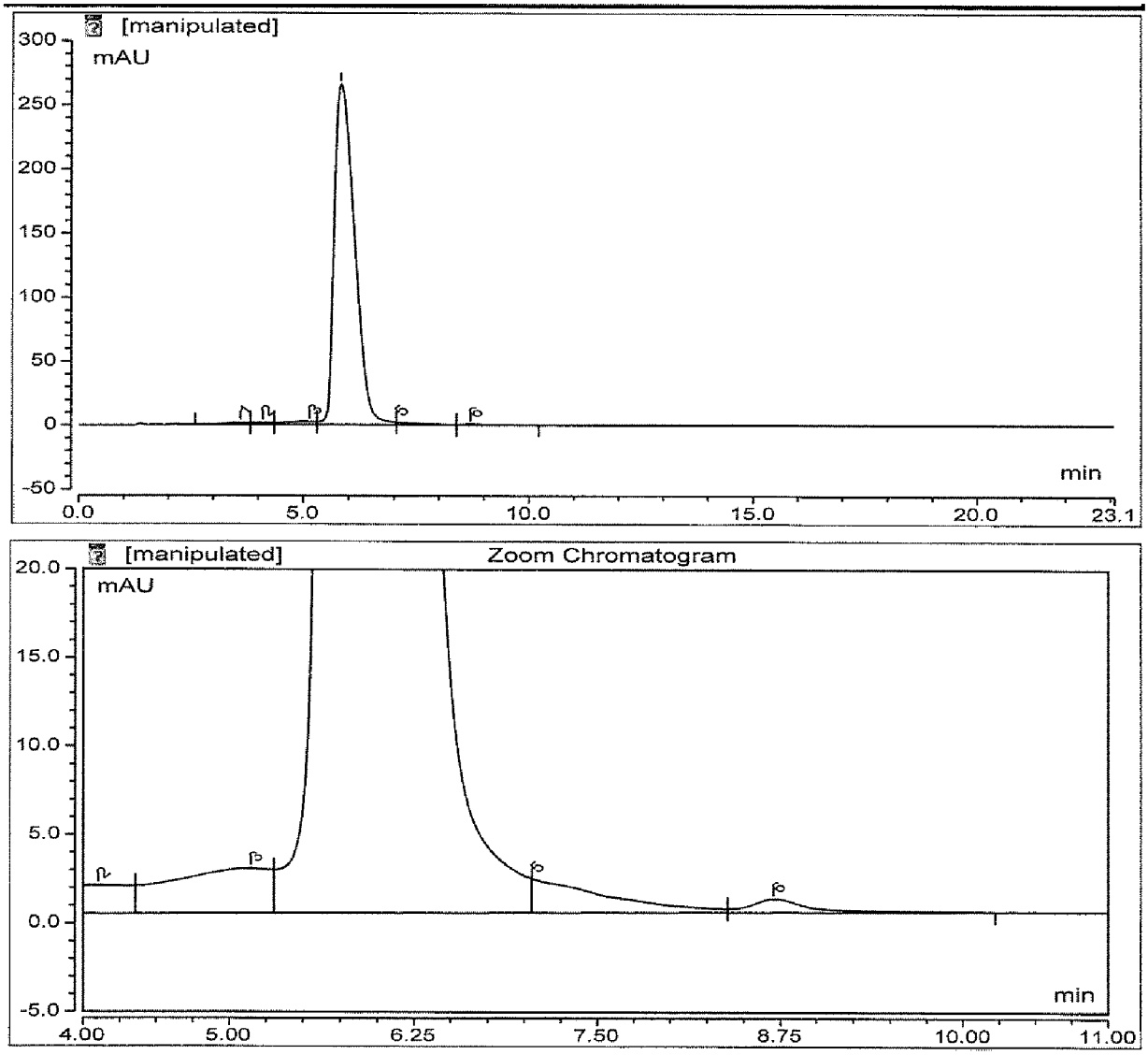
200
100
0
-50
min
0.0
2.5
5.0
7.5
10.0
12.5
15.0
18.0
[manipulated]
Zoom Chromatogram
mAU
50.0
40.0
30.0
20.0
10.0
0.0
-10.0
min
0.0
2.0
4.0
6.0
8.0
10.0
12.0

Fig. 6


[manipulated]
mAU
300
250
200
150
100
50
0
-50
min
0.0
5.0
10.0
15.0
20.0
23.1
[manipulated]
Zoom Chromatogram
mAU
20.0
15.0
10.0
5.0
0.0
-5.0
min
4.00
5.00
6.25
7.50
8.75
10.00
11.00