Nucleoside and nucleotide analogues by catalyst free Huisgen nitrile oxide–alkyne 1,3-dipolar cycloaddition†

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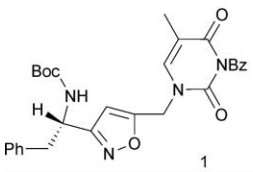
An efficient, catalyst free, 1,3-dipolar cycloaddition strategy to conjugate nucleosides and nucleotides with isoxazoles under atmospheric conditions and in an aqueous environment is reported. The protocol involves chloramine-T as a practical reagent to induce *in situ* nitrile oxide formation and the alkyne partner is attached to the sugar residue or the nucleobase. The reactions are regiospecific, fast and high yielding.

Introduction

In the last 20 years or so non natural nucleic acid and nucleoside analogues have demonstrated significant clinical value as anti-cancer and antiviral compounds and many structural variations involving changes to the nucleobase and, or the ribofuranose moiety have been explored.[1-4] In parallel, the isoxazole ring has been identified as attractive in terms of its hydrolytic stability, its potential for π-stacking and H-bonding and due to its sharing the isosteric character of the amide and ester bond.[5,6] It is well recognised that the activities of different segments within a molecule can act in concert or confer new attributes on the molecule, and in this context the synthesis and bioactivity of isoxazole, isoxazoline and isoxazolidine modified nucleosides has received much attention. Several families of analogues have been explored, many involve heterocyclic replacement of the nucleoside ribose[7-11] whilst others fall into the class of C^5-modified pyrimidine nucleoside drugs,[12,13] and others examine the influence of an N^3-tethered heterocycle,[8,14] finally, isoxazoles have been introduced both directly and remotely to the 4′-ribose carbon.[15,16] Two significant nucleoside derivatives include the N^1-tethered isoxazole **1** which has potent activity against the Polio virus[7] and the N^3-ligated isoxazoline **2** which displays potent anti-HIV activity.[14] Further interesting applications of heterocyclic modifications within nucleotide and oligonucleotide chemistry include isoxazole or isoxazoline replacement of the nucleotide phosphodiester linkage[17,18] and the recently reported nitrile oxide click modification of DNA by cycloaddition to alkynes[19] and strained alkenes.[20] In this context we wish to report an efficient synthetic approach to the preparation of sugar ($C^{3'}$-*O*-) and nucleobase (N^3-) tethered isoxazole thymidines. The key reaction, a nitrile oxide–alkyne click cycloaddition, proceeds selectively and in high yield under mild reaction conditions. That the protocol is free from copper is significant for broader applications as it removes the need to manage potentially problematic redox interference chemistry; thus, it presents a complementary approach to the azide–alkyne cycloaddition which has been highly successful in generation of nucleoside, nucleotide and oligonucleotide conjugates.[21]



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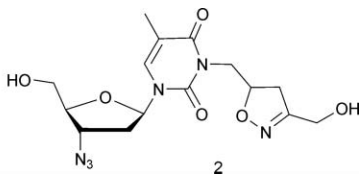

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The preparation of isoxazole modified nucleosides by selection of an isoxazole carboxylic acid as one component of the Ugi reaction[16] or by cyclisation approaches[22] represents alternatives to the commonly employed 1,3-dipolar cycloaddition route. The latter approach has been demonstrated with the nucleoside bearing either the alkyne moiety or the nitrile oxide precursor; both ribose[15,17] and nucleobase[13] modified oximes have served as nitrile oxide precursors, whilst the alkyne functionality is more commonly found on the base unit[7,8,12] than on the sugar.[22] In the reports to date NaOCl, NCS or NBS have been selected as the dipole generating agents, generally the reactions are of 10–24 h duration and yields vary from fair to good. In one recent example a solid phase approach was demonstrated,[8] though more generally the cycloadditions are reported in solution with THF or CH_2Cl_2 as reaction solvent.

We have recently shown solid phase nitrile oxide click cycloaddition chemistry to be successful for the preparation of isoxazole modified DNA[19] and for generating 2′-OMe ribonucleoside and ribonucleotide analogues by [3+2]-cycloaddition to 2′-*O*-propargyl substrates.[23] In this paper we further demonstrate the utility of this reaction in the solution phase synthesis of sugar ($C^{3'}$-*O*) and nucleobase (N^3-) tethered isoxazoles.

Results and discussion

Nucleoside chemistry is delicate due to the numerous reactive sites and the first step in the synthetic sequence required selective protection of the 5′-OH of thymidine, thus, the already known **4**[24] was prepared from thymidine **3** in good yield. Introduction of the $C^{3'}$-*O*-propargyl group proceeded by nucleophilic displacement. Propargyl bromide was selected as the alkylating agent and NaH as the base. It was necessary to exercise caution during the addition of the bromide and, to ensure regioselective formation of **5**, a

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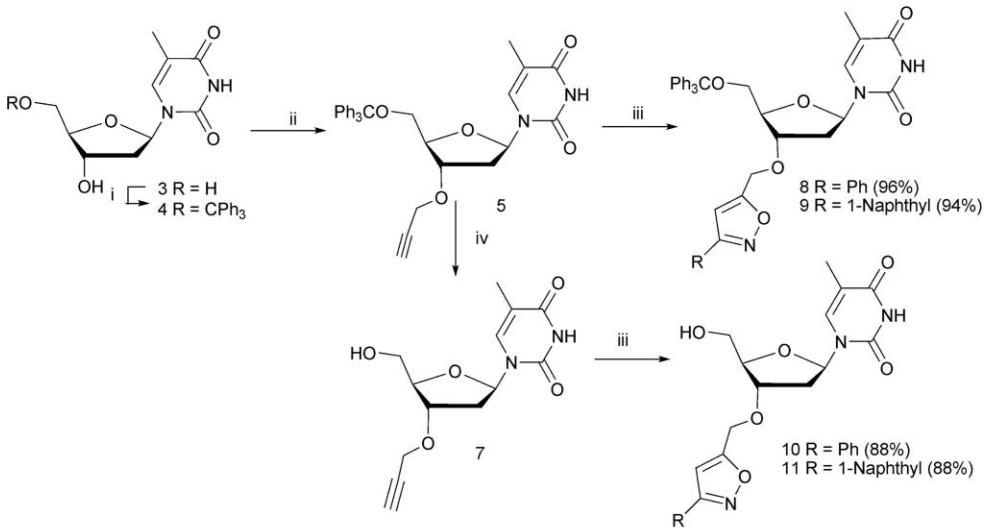


i. Anh. pyridine, Ph_3CCl, Ar, 0.5 h, 100 °C (86%); ii. Anh THF, NaH, Ar, rt, 1 h; then 0 °C, $CHCCH_2Br$, 17 h, rt (93%); iii. RCHNOH, Chloramine T, $NaHCO_3$, EtOH, 1h, rt; iv.DCA, CH_2Cl_2, rt, 0.5 h (96%)

Scheme 1

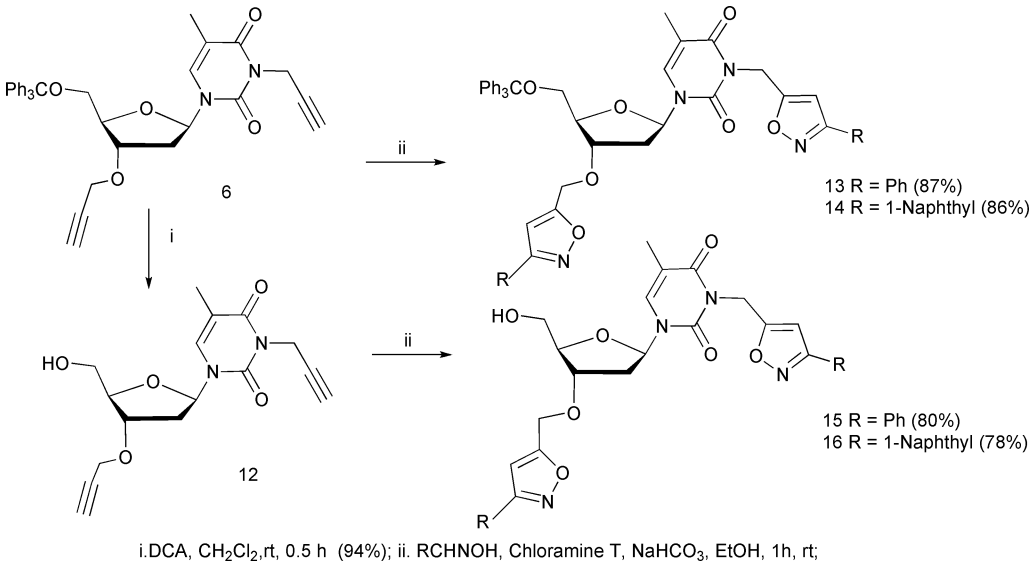
solution of this reagent in THF was added dropwise at 0 °C; without this precaution the *C*$^{3'}$-*O*, *N*^{3}-bisalkylated product **6** was found as a side product, Scheme 1. Most of the antiviral nucleoside analogues have 5′-hydroxyl groups for kinase phosphorylation, however, some 5′-tritylated derivatives have demonstrated inhibition of thymidine phosphorylase and angiogenesis.[25] Thus, it was deemed important to explore the cycloaddition reaction with the 5′-OH group both protected and unprotected, accordingly, DCA (dichloroacetic acid) mediated detritylation of **5** furnished the known **7**.[26]

With the desired thymidine dipolarophiles **5** and **7** to hand the concept that chloramine-T mediated nitrile oxide–alkyne cycloaddition chemistry offers a tool to prepare nucleoside derivatives was tested. Aromatic appendages are interesting for biological activity, accordingly benzaldehyde oxime and 1-naphthaldehyde oxime were selected as the nitrile oxide precursors. The choice of chloramine-T as the dipole generating agent[27] facilitates a move away from CH_2Cl_2 or THF and aqueous ethanolic $NaHCO_3$ was the solvent of choice. The 5′-protected thymidine **5** was first examined. The reaction components were simply mixed together in aqueous ethanolic sodium hydrogen carbonate at room temperature. The reaction was very fast, reaching completion simply upon stirring for 1 h under atmospheric conditions and following purification **8** and **9** were isolated in 96% and 94% yield respectively. The reaction was equally successful with the 5′-deprotected substrate **7**, and the adducts from cycloaddition to benzonitrile oxide and 1-naphthonitrile oxide, **10** and **11** respectively, were both obtained in 88%, Scheme 1.

The structural elucidation of the cycloadducts was made on the basis of their NMR spectra. In all four cases an examination of the ^{1}H NMR spectra of the crude reaction products was suggestive of a high yielding, regiospecific formation of a 3,5-disubstituted isoxazole. A singlet resonance in the region 6.52–6.62 ppm, diagnostic for the 4-*H* proton of the isoxazole ring, confirms the regiochemistry of the reaction; the expected position for the regioisomeric 3,4-disubstituted isoxazole would be ~1 ppm further downfield.[28] The regioselectivity of the reaction is also supported by the presence of only one signal representing the OCH_2-isoxazole methylene protons. These protons present as AB doublets at ~4.6 ppm whilst in the starting propargylated thymidines the corresponding protons appeared ~0.5 ppm upfield as part of a multiplet signal together with the resonance of the 4′-proton.

The *C*$^{3'}$-*O*-,*N*^{3}-bispropargyl modified thymidine **6** was prepared in good yield from **4** following deprotonation with NaH (6 eq.) and alkylation with propargyl bromide (3 eq.). The successful formation of the diynyl nucleoside was evident from the appearance of two triplet resonances in the ^{1}H NMR spectrum at 2.41 and 2.17 ppm, diagnostic of the inequivalent alkyne protons; the adjacent methylene protons appeared as doublets at 4.25 (OCH_2) and 4.77 (NCH_2) ppm respectively. Both the 5′-tritylated diynyl **6** and its 5′-hydroxy parent **12** succumbed to the nitrile oxide click cycloaddition protocol described above. Thus, the aryl nitrile oxides generated from reaction of benzaldehyde oxime or 1-naphthaldehyde oxime with chloramine-T reacted, in turn, with **6** or **12** under atmospheric conditions, at ambient temperature in ethanolic sodium hydrogen carbonate. No compromise in regioselectivity was noted in formation of the double cycloaddition products **13** through **16** which were isolated in 78–87% yield, Scheme 2. Once again ^{1}H NMR spectral evidence supports formation of the 3,5-disubstituted isoxazoles; in all cases, concomitant with cycloaddition was the disappearance of the alkyne proton resonances and a downfield shift (~0.5 ppm) in the position of the both the NCH_2 and the OCH_2methylene protons. No other regioisomer could be found amongst the crude products.

To show compatibility with the nucleotide phosphodiester backbone **20** was prepared by coupling of the alkynyl alcohol **17**[19] to the 5′-Dmt protected thymidine phosphoramidite **18**. Following oxidation and work-up, the protecting group was removed from **19** by treatment with DCA and **20** was obtained in 53% yield over the two steps, Scheme 3. Analysis by ^{31}P, ^{13}C and ^{1}H NMR spectroscopy together with HRMS data confirmed the expected



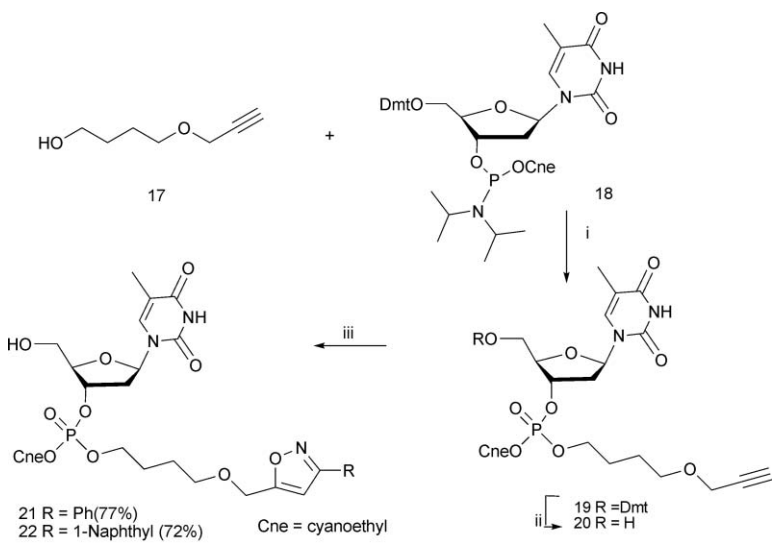
Scheme 2

structure. In particular a resonance at δ –2.6 ppm is diagnostic for the P(v) nucleus; proton and ^{13}C assignments were supported by 2D-COSY experiments.

The nucleotide **20** subjected to the cycloaddition protocol under the same conditions as described above for the nucleoside substrates. Thus the phenyl and naphthyl substituted isoxazole derivitized nucleotides **21** and **22** were obtained in 77% and 72% yield respectively following reaction with the appropriate oxime and chloramine-T in ethanolic $NaHCO_3$ (rt, 1 h), Scheme 3. Characterisation of the cycloadducts was made on the basis of their NMR spectral data. In both cases a singlet resonance in the region 6.58–6.59 ppm, diagnostic for the 4-*H* proton of the isoxazole ring confirms formation of a 3,5-disubstituted isoxazole, further confirmation of the regiochemistry of the reaction is supported by the appearance of the OCH_2 isoxazole protons as AB doublets at ~4.7 ppm.

Conclusion

In conclusion nitrile oxide–alkyne click cycloaddition chemistry offers a robust route to novel isoxazole conjugated nucleosides or nucleotides with either 5′-trityl protection or with a free 5′-OH available for additional structural elaboration. The ability to incorporate an isoxazole nucleus in the design of new thymidine receptor agonists is potentially very valuable and the significance of the current work lies in the demonstration of a high yielding chloramine-T protocol for rapid, catalyst free nucleoside and nucleotide elaboration under very mild conditions *viz* room



Scheme 3

temperature, atmospheric conditions and an aqueous environment. The synthetic utility of the nitrile oxide reaction, which reaches completion in 60 min at rt, compares favourably with the observed copper catalysed formation of triazole linked dithymidines which whilst complete within 3 min under microwave activation (80 °C, 300 W),[29] requires 24 h to reach ~40% completion at rt.[30]

Experimental

Analytical TLC was performed on precoated (250 μm) silica gel 60 F-254 plates from Merck. All plates were visualized by UV irradiation, and/or staining with 5% H_2SO_4 in ethanol, followed by heating. Flash chromatography grade silica gel 60 (230-400 mesh) was obtained from Merck. Mass analysis was performed on a LC/TOF-MS instrument. The LC was a model 1200 Series (Agilent Corp, Santa Clara, CA), injection volume was 10 μL, the column was an Agilent Eclipse XBD-C18 (Agilent), 5-micron with a mobile phase of A = ACN with 0.1% formic acid and B = 0.1% formic acid in water. The gradient was 5% to 100% A over 15 min at a flow rate of 0.5 mL min^{-1}. The LC/TOF-MS was a model 6210 Time-Of-Flight LC/MS (Agilent Corp, Santa Clara, CA) with an electrospray source positive and negative (ESI ±), capilary 3,500 V, nebuliser spray 30 psig, drying gas 5 L min^{-1}, source temperature 325 °C. The fragmentor was used at 175 V. Reference masses (Agilent solution) were 121.050873, 149.02332, 322.048121, 922.009798, 1221.990633, 1521.971475, and 2421.91399 *m/z*. The NMR spectra were obtained for ^1H at 300 MHz, for ^{13}C at 75 MHz and for ^{31}P at 121 MHz on a Bruker instrument at 25 °C. All samples for NMR were prepared in $CDCl_3$. Chemical shifts are reported in ppm downfield from TMS as standard and coupling constants are reported in hertz. Chemical agents were purchased from Aldrich Chemical Company unless otherwise noted.

3′-*O*-(2-Propynyl)-5′-*O*-(triphenylmethyl)thymidine 5

To a solution of 5′-*O*-trityl-3′-*O*-propargylthymidine **4** (100 mg, 0.206 mmol) in anhydrous THF (4 mL) at 0 °C was added slowly, under argon, anhydrous sodium hydride (13 mg, 0.516 mmol) and the mixture was stirred at RT for 1 h. The reaction mixture was cooled to 0 °C prior to the addition, drop by drop, of a solution of propargyl bromide (0.206 mmol) in THF (1 mL). The mixture was allowed to slowly warm to RT and stirred for a further 17 h. The reaction was quenched by addition of water. The product was isolated following extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using dichloromethane and acetone (95 : 5) as eluant to give the title compound as an off-white foam (93%).

R_f 0.31 (DCM, Acetone, 95 : 5); ^1H NMR: δ 8.88 (1H, br s, NH), 7.58 (1H, s, H6), 7.50–7.18 (15H, m, Ph), 6.37–6.30 (1H, m, H1′), 4.56–4.49 (1H, m, H3′), 4.19–4.11 (3H, m, H4′, OCH_2), 3.47 (1H, dd, ^2J 10.6, ^3J 3.0, H5′), 3.38 (1H, dd, ^2J 10.6, ^3J 3.0, H5′), 2.58–2.47 (1H, m, H2′), 2.41 (1H, t, ^4J 2.4, C≡CH), 2.29–2.19 (1H, m, H2′), 1.49 (3H, s, CH_3); ^{13}C NMR: δ 163.7 (C_2), 150.3 (C_4), 143.4 (ArC), 135.4 (C_6), 128.7 (ArC), 128.1 (ArC), 127.4 (ArC), 111.2 (C_5), 87.5 (CPh_3), 84.8 ($C_{1'}$), 83.8 ($C_{4'}$), 79.1 (*C*≡CH), 78.5 ($C_{3'}$), 75.1 (*C*H≡C), 63.6 ($C_{5'}$), 53.4 (OCH_2), 37.8 ($C_{2'}$), 11.9 (CH_3); HRMS (ESI): *m/z* $C_{32}H_{30}N_2NaO_5$ requires 545.2047 $[M+Na]^+$, found 545.2052 (0.96 ppm).

General procedure for the nitrile oxide–alkyne cycloaddition

To a round bottomed flask containing the oxime (2 eq. for the monoalkynes **5**, **7** and **19** or 3 eq. for the bisalkynes **6** and **12**) and chloramine-T monohydrate (2.5 eq. for the mono- or 3.5 eq. for the bisalkynes) in 4% aqueous sodium hydrogen carbonate (2 mL per 0.1 mmol of oxime) and ethanol (1 mL per 0.1 mmol oxime) was added the propargylated thymidine. The mixture was stirred for 1 h at RT after which analysis by TLC indicated complete reaction. The product was isolated following extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to afford the crude products which were purified as described below.

3′-*O*-[(3-Phenylisoxazol-5-yl)methyl]-5′-*O*-(triphenylmethyl)thymidine 8

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and acetone (97 : 3), to give the title compound as an off-white solid, (96%).

R_f 0.46 (DCM, Acetone, 95 : 5); ^1H NMR: δ 8.78 (1H, br s, NH), 7.83–7.18 (21H, m, H6, Ph), 6.52 (1H, s, CH=CO iso), 6.41–6.34 (1H, m, H1′), 4.65 (1H, d, ^2J 13.9, OCH_2), 4.58 (1H, d, ^2J 13.9, OCH_2), 4.38–4.32 (1H, m, H3′), 4.21–4.16 (1H, m, H4′), 3.50 (1H, dd, ^2J 10.6, ^3J 3.3, H5′), 3.35 (1H, dd, ^2J 10.6, ^3J 2.7, H5′), 2.59–2.49 (1H, m, H2′), 2.31–2.18 (1H, m, H2′), 1.52 (3H, s, CH_3); ^{13}C NMR: δ 169.0 (C=N iso), 163.7 (C_2), 162.5 (*C*O=CH iso), 150.3 (C_4), 143.2 (ArC), 135.3 (C_6), 130.2 (ArC), 129.0 (ArC), 128.7 (ArC), 128.6 (ArC), 128.1 (ArC), 127.5 (ArC), 126.9 (ArC), 111.4 (C_5), 101.3 (*C*H=CO iso), 87.6 (CPh_3), 84.8 ($C_{1'}$), 83.8 ($C_{4'}$), 80.1 ($C_{3'}$), 63.8 ($C_{5'}$), 62.2 (OCH_2), 37.8 ($C_{2'}$), 11.9 (CH_3); HRMS (ESI): *m/z* $C_{39}H_{35}N_3NaO_6$ requires 664.2418 $[M+Na]^+$, found 664.2398 (–3.07 ppm).

3′-*O*-[3-[(1-Naphthyl)isoxazol-5-yl]methyl]-5′-*O*-(triphenylmethyl)thymidine 9

The crude product was purified by flash column chromatography over silica gel using dichloromethane and acetone (95 : 5) as eluant to give the title compound as an off-white solid (94%).

R_f 0.21 (DCM, Acetone, 95 : 5); ^1H NMR: δ 8.41 (1H, br s, NH), 8.38–7.17 (23H, m, H6, Ph, Naph), 6.53 (1H, s, CH=CO iso), 6.42–6.35 (1H, m, H1′), 4.73 (1H, d, ^2J 13.6, OCH_2), 4.65 (1H, d, ^2J 13.6, OCH_2), 4.45–4.38 (1H, m, H3′), 4.24–4.17 (1H, m, H4′), 3.52 (1H, dd, ^2J 10.7, ^3J 3.3, H5′), 3.37 (1H, dd, ^2J 10.6, ^3J 3.0, H5′), 2.65–2.51 (1H, m, H2′), 2.34–2.21 (1H, m, H2′), 1.52 (3H, s, CH_3); ^{13}C NMR: δ 168.3 (C=N iso), 163.4 (C_2), 162.6 (*C*O=CH iso), 150.2 (C_4), 143.2 (ArC), 135.3 (C_6), [133.8, 130.9, 130.4, 128.6, 128.5, 128.1, 127.9, 127.5, 127.1, 126.5, 126.3, 125.6, 125.2] (ArC), 111.3 (C_5), 104.6 (*C*H=CO iso), 87.6 (CPh_3), 84.8 ($C_{1'}$), 83.8 ($C_{4'}$), 80.2 ($C_{3'}$), 63.8 ($C_{5'}$), 62.3 (OCH_2), 37.9 ($C_{2'}$), 11.9 (CH_3); HRMS (ESI): *m/z* $C_{43}H_{38}N_3O_6$ requires 692.2755 $[M+H]^+$, found 692.2741 (–2.1 ppm).

General procedure for deprotection of 5′-trityl thymidine derivatives

The tritylated thymidine was stirred for 0.5 h at RT in a solution of DCA 3.5% in DCM (1 mL/0.1 mmol). The reaction mixture was washed with a saturated solution of sodium hydrogen carbonate until the aqueous layer became neutral. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to afford the crude products which were purified as described below.

3′-*O*-(2-Propynyl)thymidine 7[25]

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and methanol (0 to 5%), to give the title compound as an off-white foam (96%).

R_f 0.18 (DCM, MeOH, 95 : 5); ^{1}H NMR: δ 9.45 (1H, br s, NH), 7.44 (1H, s, H6), 6.12 (1H, t, ^3J 6.6, H1′), 4.46–4.38 (1H, m, H3′), 4.29–4.09 (3H, m, H4′, OCH_2), 3.95 (1H, dd, ^2J 12.1, ^3J 2.7, H5′), 3.82 (1H, dd, ^2J 12.1, ^3J 3.0, H5′), 3.58 (1H, br s, OH), 2.49 (1H, t, ^4J 2.4, C≡CH), 2.46-2.30 (2H, m, H2′), 1.90 (3H, s, CH_3); HRMS (ESI): *m/z* $C_{13}H_{16}N_2NaO_5$ requires 280.1148 $[M+Na]^+$, found 280.1178 (2.61 ppm).

3′-*O*-[(3-Phenylisoxazol-5-yl)methyl]thymidine 10

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and methanol (95 : 5), to give the title compound as an off-white solid (88%).

^{1}H NMR: δ 8.55 (1H, br s, NH), 7.81–7.78 (2H, m, ArH), 7.46–7.44 (3H, m, ArH), 7.38 (1H, s, H6), 6.59 (1H, s, CH=CO iso)), 6.13 (1H, t, *J* 7.2, H1′), 4.72 (1H, d, ^2J 13.8, OCH_2), 4.66 (1H, d, ^2J 13.8, OCH_2), 4.40–4.37 (1H, m, H3′), 4.15 (1H d, *J* 2.7, H4′), 3.92 (1H dd, ^2J 11.7, ^3J 2.7, H5′), 3.80 (1H dd, ^2J 11.7, ^3J 3.0, H5′), 2.41–2.37 (2H, m, H2′), 1.89 (3H, s, CH_3); ^{13}C NMR: δ 170.0 (C=N iso), 163.3 (C_2), 162.1 (*C*O=CH iso), 150.5 (C_4), 136.0 (C_6), 130.0–126.6 (ArH), 109.9 (C_5), 101.2 (*C*H=CO iso), 85.0 ($C_{1'}$), 85.8 ($C_{4'}$), 80.3 ($C_{3'}$), 62.1 ($C_{5'}$), 61.7 (OCH_2), 36.9 ($C_{2'}$), 11.6 (CH_3); HRMS (ESI): *m/z* $C_{20}H_{22}N_3O_6$ requires 400.1509 $[M+Na]^+$, found 400.1494 (1.16 ppm).

3′-*O*-[3-[(1-Naphthyl)isoxazol-5-yl]methyl]thymidine 11

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and methanol (95 : 5), to give the title compound as an off-white solid (88%).

R_f 0.24 (DCM, MeOH, 95 : 5); ^{1}H NMR: δ 8.39–8.32 (1H, m, ArH), 7.99–7.89 (2H, m, ArH), 7.72–7.67 (1H, m, ArH), 7.60–7.50 (3H, m, ArH), 7.38 (1H, s, H6), 6.62 (1H, s, CH=CO iso), 6.14 (1H, t, ^3J 9.9, H1′), 4.78 (1H, d, ^2J 13.9, OCH_2), 4.73 (1H, d, ^2J 13.9, OCH_2), 4.49–4.41 (1H, m, H3′), 4.23–4.16 (1H, m, H4′), 3.96 (1H, dd, ^2J 12.5, ^3J 3.3, H5′), 3.83 (1H, dd, ^2J 12.4, ^3J 2.7, H5′), 2.49–2.40 (2H, m, H2′), 1.92 (3H, s, CH_3); ^{13}C NMR: δ 168.3 (C=N iso), 163.5 (C_2), 162.7 (*C*O=CH iso), 150.3 (C_4), 137.0 (C_6), [133.8, 130.9, 130.4, 128.6, 127.9, 127.2, 126.4, 125.5, 125.2] (ArC), 111.4 (C_5), 104.8 (*C*H=CO iso), 87.5 ($C_{1'}$), 85.0 ($C_{4'}$), 80.0 ($C_{3'}$), 62.7 ($C_{5'}$), 62.5 (OCH_2), 37.0 ($C_{2'}$), 12.5 (CH_3); HRMS (ESI): *m/z* $C_{24}H_{23}KN_3O_6$ requires 488.1218 $[M+K]^+$, found 488.1221 (0.58 ppm).

3-(2-Propynyl)-3′-*O*-(2-propynyl)-5′-*O*-(triphenylmethyl)thymidine 6

To a solution of 5′-*O*-trityl-3′-*O*-propargylthymidine **4** (195 mg, 0.402 mmol) in anhydrous THF (4 mL) at 0 °C was added slowly, under argon, anhydrous sodium hydride (58 mg, 2.415 mmol) and the mixture was stirred at RT for 1 h. Propargyl bromide (1.40 mL, 1.335 mmol) was added drop by drop and the mixture was stirred for 17 h at RT. The reaction was quenched by addition of water. The product was isolated following extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using dichloromethane and acetone (0 to 2%) as eluant to give the title compound as an off-white foam (77%).

R_f 0.58 (DCM, Acetone, 98 : 2); ^{1}H NMR: δ 7.62 (1H, s, H6), 7.50–7.20 (15H, m, Ph), 6.42–6.34 (1H, m, H1′), 4.77 (2H, d, ^4J 2.4, NCH_2), 4.58–4.49 (1H, m, H3′), 4.25–4.07 (3H, m, H4′, OCH_2), 3.47 (1H, dd, ^2J 10.7, ^3J 3.0, H5′), 3.38 (1H, dd, ^2J 10.7, ^3J 3.0, H5′), 2.61–2.50 (1H, m, H2′), 2.41 (1H, t, ^4J 2.4, $OCH_2C{\equiv}CH$), 2.32–2.19 (1H, m, H2′), 2.17 (1H, t, ^4J 2.4, $NCH_2C{\equiv}CH$), 1.51 (3H, s, CH_3); ^{13}C NMR: δ 162.5 (C_2), 150.2 (C_4), 143.3 (ArC), 133.9 (C_6), [128.7, 128.9, 128.7, 128.1, 127.9, 127.5, 127.1] (ArC), 110.1 (C_5), 87.5 (CPh_3), 85.5 ($C_{1'}$), 83.8 ($C_{4'}$), 79.1 ($OCH_2C{\equiv}CH$), 78.3 ($NCH_2C{\equiv}CH$, $C_{3'}$), 75.1 ($OCH_2C{\equiv}CH$), 70.6 ($NCH_2C{\equiv}CH$), 63.6 ($C_{5'}$), 56.7 (OCH_2), 37.9 ($C_{2'}$), 30.4 (NCH_2),12.6 (CH_3); HRMS (ESI): *m/z* $C_{35}H_{33}N_2O_5$ requires 561.2384 $[M+H]^+$, found 561.2402 (3.23 ppm).

3-[(3-Phenylisoxazol-5-yl)methyl]-3′-*O*-[(3-phenylisoxazol-5-yl)methyl]-5′-*O*-(triphenylmethyl)thymidine 13

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and acetone (0 to 2%), to give the title compound as an off-white solid (87%).

R_f 0.70 (DCM, Acetone, 98 : 2); ^{1}H NMR: δ 7.81–7.73 (5H, m, ArH), 7.62 (1H, s, H6), 7.49–7.20 (20H, m, ArH), 6.57 (1H, s, CH=CO iso), 6.51 (1H, s, CH=CO iso), 6.44–6.37 (1H, m, H1′), 5.31 (2H, m, NCH_2), 4.65 (1H, d, ^2J 13.6, OCH_2), 4.58 (1H, d, ^2J 13.6, OCH_2), 4.40–4.33 (1H, m, H3′), 4.21–4.15 (1H, m, H4′), 3.51 (1H, dd, ^2J 10.9, ^3J 3.3, H5′), 3.35 (1H, dd, ^2J 10.7, ^3J 2.7, H5′), 2.61–2.52 (1H, m, H2′), 2.32–2.20 (1H, m, H2′), 1.54 (3H, s, CH_3); ^{13}C NMR: δ 169.0 (C=N iso), 167.7 (C=N iso), 162.7 (C_2), 162.5 (2 × *C*O=CH iso), 150.5 (C_4), 143.2 (ArC), 134.0 (C_6), [130.2, 129.3, 129.0, 128.8, 128.7, 128.6, 128.1, 127.5, 126.9] (ArC), 110.6 (C_5), 101.3 (2 × *C*H=CO iso), 87.6 (CPh_3), 85.6 ($C_{1'}$), 83.9 ($C_{4'}$), 80.0 ($C_{3'}$), 63.7 ($C_{5'}$), 62.3 (OCH_2), 38.0 ($C_{2'}$), 36.2 (NCH_2), 12.6 (CH_3); HRMS (ESI): *m/z* $C_{49}H_{42}N_4O_7$ requires 798.3048 $[M^*]^+$, found 798.3105 (7.16 ppm).

3-[3-[(Naphthyl)isoxazol-5-yl]methyl]-3′-*O*-[3-[(naphthyl)isoxazol-5-yl]methyl]-5′-*O*-(triphenylmethyl)thymidine 14

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and acetone (0 to 2%), to give the title compound as an off-white solid (86%).

R_f 0.58 (DCM, Acetone, 98 : 2); ^{1}H NMR: δ 8.43–8.29 (2H, m, ArH), 7.99–7.84 (4H, m, ArH), 7.70–7.17 (24H, m, H6, ArH), 6.59 (1H, s, CH=CO iso), 6.52 (1H, s, CH=CO iso), 6.49–6.42 (1H, m, H1′), 5.38 (2H, s, NCH_2), 4.72 (1H, d, ^2J 13.4, OCH_2), 4.64

(1H, d, ^2J 13.4, OCH_2), 4.49–4.39 (1H, m, H3′), 4.26–4.18 (1H, m, H4′), 3.54 (1H, dd, ^2J 10.7, ^3J 3.0, H5′), 3.38 (1H, dd, ^2J 10.7, ^3J 2.7, H5′), 2.67–2.56 (1H, m, H2′), 2.38–2.26 (1H, m, H2′), 1.56 (3H, s, CH_3); ^{13}C NMR: δ 168.3 (C=N iso), 167.1 (C=N iso), 162.7 (C_2), 162.6 (2 × *C*O=CH iso), 150.5 (C_4), 143.3 (ArC), 134.1 (C_6), [133.8, 131.0, 113.4, 130.2, 128.8, 128.6, 128.5, 128.4, 128.1, 127.9, 127.5, 127.2, 127.0, 126.8, 126.5, 126.4, 126.2, 125.8, 125.6, 125.2, 125.1] (ArC), 110.6 (C_5), 104.7 (2 × *C*H=CO iso), 87.6 (CPh_3), 85.6 ($C_{1'}$), 83.9 ($C_{4'}$), 80.1 ($C_{3'}$), 63.7 ($C_{5'}$), 62.3 (OCH_2), 38.0 ($C_{2'}$), 36.4 (NCH_2), 12.6 (CH_3); HRMS (ESI): *m/z* $C_{57}H_{46}N_4NaO_7$ requires 921.3259 $[M+Na]^+$, found 921.3282 (2.52 ppm).

3-(2-Propynyl)-3′-*O*-(2-propynyl)thymidine 12

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and methanol (0 to 5%), to give the title compound as a off-white foam (94%).

R_f 0.39 (DCM, MeOH, 95 : 5); ^{1}H NMR: δ 7.43 (1H, s, H6), 6.14 (1H, t, ^3J 7.5, H1′), 4.72 (2H, d, ^4J 2.4, NCH_2), 4.47–4.40 (1H, m, H3′), 4.28–4.05 (4H, m, H4, OCH_2, OH), 3.97 (1H, dd, ^2J 12.5, ^3J 2.7, H5′), 3.85 (1H, dd, ^2J 12.5, ^3J 3.0, H5′), 2.49 (1H, t, ^4J 2.4, $OCH_2C{\equiv}CH$), 2.47–2.36 (2H, m, H2′), 2.17 (1H, t, ^4J 2.4, $NCH_2C{\equiv}CH$), 1.96 (3H, s, CH_3);^{13}C NMR: δ 162.6 (C_2), 150.2 (C_4), 135.5 (C_6), 110.5 (C_5), 88.0 ($C_{1'}$), 84.9 ($C_{4'}$), 79.1 ($OCH_2C{\equiv}CH$), 78.4 ($C_{3'}$), 78.0 ($NCH_2C{\equiv}CH$), 75.2 ($OCH_2C{\equiv}CH$), 70.8 ($NCH_2C{\equiv}CH$), 62.6 ($C_{5'}$), 56.9 (OCH_2), 38.0 ($C_{2'}$), 30.5 (NCH_2),13.2 (CH_3); HRMS (ESI): *m/z* $C_{16}H_{18}KN_2O_5$ requires 357.0847 $[M+K]^+$, found 357.0853 (1.46 ppm).

3-[(3-Phenylisoxazol-5-yl)methyl]-3′-*O*-[(3-phenylisoxazol-5-yl)methyl]thymidine 15

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and methanol (98 : 2), to give the title compound as an off-white solid (80%).

R_f 0.35 (DCM, MeOH, 98 : 2); ^{1}H NMR: δ 7.78–7.64 (4H, m, ArH), 7.44–7.28 (7H, m, H6, ArH), 6.52 (1H, s, CH=CO iso), 6.49 (1H, s, CH=CO iso), 6.11 (1H, t, ^3J 7.7, H1′), 5.22 (2H, s, NCH_2), 4.63 (1H, d, ^2J 13.4, OCH_2), 4.58 (1H, d, ^2J 13.4, OCH_2), 4.36–4.28 (1H, m, H3′), 4.12–4.06 (1H, m, H4′), 3.88 (1H, dd, ^2J 11.6, ^3J 2.4, H5′), 3.74 (1H, br d, ^2J 11.5, H5′), 2.52–2.25 (3H, m, H2′, OH), 1.88 (3H, s, CH_3); ^{13}C NMR: δ 168.0 (C=N iso), 166.6 (C=N iso), 161.6 (C_2), 161.5 (2 × *C*O=CH iso), 149.5 (C_4), 134.3 (C_6), [129.2, 129.0, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.2, 126.5, 126.1, 125.8] (ArC), 109.4 (C_5), 100.6 (*C*H=CO iso), 100.4 (*C*H=CO iso), 86.8 ($C_{1'}$), 84.0 ($C_{4'}$), 78.7 ($C_{3'}$), 61.7 ($C_{5'}$), 61.4 (OCH_2), 36.2 ($C_{2'}$), 35.2 (NCH_2), 12.2 (CH_3); HRMS (ESI): *m/z* $C_{30}H_{29}N_4O_7$ requires 557.2031 $[M+H]^+$, found 557.2051 (3.71 ppm).

3-[3-[(Naphthyl)isoxazol-5-yl]methyl]-3′-*O*-[3-[(naphthyl)isoxazol-5-yl]methyl]thymidine 16

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and acetone (9 : 1), to give the title compound as an off-white solid (78%).

R_f 0.44 (DCM, MeOH, 95 : 5); ^{1}H NMR: δ 8.40–8.31 (2H, m, ArH), 7.99–7.83 (4H, m, ArH), 7.73–7.44 (9H, m, H6, ArH), 6.60 (1H, s, CH=CO iso), 6.58 (1H, s, CH=CO iso), 6.26–6.19 (1H, m, H1′), 5.37 (2H, s, NCH_2), 4.76 (1H, d, ^2J 13.6, OCH_2), 4.70 (1H, d, ^2J 13.6, OCH_2), 4.48–4.39 (1H, m, H3′), 4.22–4.14 (1H, m, H4′), 3.79–3.40 (2H, m, H5′), 2.68 (1H, s, OH), 2.54–2.33 (2H, m, H2′), 1.95 (3H, s, CH_3); ^{13}C NMR: δ 168.3 (C=N iso), 167.0 (C=N iso), 162.7 (C_2), 150.6 (C_4), 135.4 (2 × *C*O=CH iso), 133.8 (C_6), [131.0, 130.4, 130.2, 128.6, 128.4, 127.8, 127.2, 127.0, 126.7, 126.4, 126.2, 125.7, 125.5, 125.2, 125.1] (ArC), 110.4 (C_5), 104.8 (*C*H=CO iso), 104.7 (*C*H=CO iso), 87.8 ($C_{1'}$), 85.0 ($C_{4'}$), 79.9 ($C_{3'}$), 67.9 ($C_{5'}$), 62.5 (OCH_2), 37.3 ($C_{2'}$), 36.3 (NCH_2), 13.2 (CH_3); HRMS (ESI): *m/z* $C_{38}H_{33}N_4O_7$ requires 658.2375 $[M+H]^+$, found 658.2388 (1.84 ppm).

3′-Thymidylic acid, 2-cyanoethyl 4-(2-propynyl-1-yloxy)butyl ester 20

To a round bottom flask containing a solution of alkynyl alcohol **17**[19] (72 mg, 0.562 mmol) in dry acetonitrile (10 mL) was added, under argon, BMT (BMT = 5-benzylmercaptotetrazole, 215 mg, 1.119 mmol) followed by dT-CE phosphoramidite **18** (500 mg, 0.671 mmol). The mixture was stirred for 0.5 h at RT after which analysis by TLC (hexane–EtOAc, 1 : 1) indicated complete reaction. The mixture was cooled to 0 °C in order to add drop by drop the solution of iodine (0.1 M in THF/pyridine/H_2O 78 : 20 : 2/mL). The resulting mixture was stirred for 0.5 h at 0 °C, and after addition of ethyl acetate (20 mL), washed with a saturated solution of sodium thiosulfate. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product (551 mg) was dissolved in a solution of DCA 3.5% in DCM (10 mL), and was stirred for 0.5 h at RT. The reaction mixture was washed with a saturated solution of sodium hydrogen carbonate until the aqueous layer became neutral. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography over silica gel using dichloromethane and methanol (0 to 10%) as eluant to give the title compound as a yellow oil (53%).

R_f 0.50 (DCM, MeOH, 95 : 5);^{1}H NMR: δ 9.71 (1H, br s, NH), 7.55 (1H, s, H6), 6.24 (1H, t, ^3J 7.2, H1′), 5.17 (1H, br s, H3′), 4.35–4.10 (7H, m, H4′, OCH_2 iso, 2 × $POCH_2$), 3.88 (1H, br s, H5′), 3.76 (1H, br s, OH), 3.56 (2H, t, ^3J 5.6, OCH_2CH_2), 2.82 (2H, t, ^3J 5.6, CH_2CN), 2.60–2.35 (3H, m, H2′, C≡CH), 1.90 (3H, s, CH_3), 1.86–1.63 (4H, m, $OCH_2CH_2CH_2CH_2O$);^{13}C NMR: δ 164.1(C_2), 150.6 (C_4), 136.5 (C_6), 116.7 (C≡N), 111.3 (C_5), 85.8 ($C_{1'}$), 85.7 ($C_{4'}$), 79.8 (*C*≡CH), 78.4 ($C_{3'}$), 74.5 (C≡*C*H), 69.2 (OCH_2CH_2), 68.7 ($POCH_2$), 62.3 ($POCH_2$), 61.8 ($C_{5'}$), 58.1 (OCH_2 iso), 38.5 ($C_{2'}$), 27.2 ($OCH_2CH_2CH_2CH_2O$), 25.4 ($OCH_2CH_2CH_2CH_2O$), 19.7 ($CH_2C{\equiv}N$), 12.5 (CH_3); ^{31}P NMR: δ –2.6; HRMS (ESI): *m/z* $C_{20}H_{28}KN_3O_9P$ requires 524.1195 $[M+K]^+$, found 524.1196 (0.27 ppm).

3′-Thymidylic acid, 2-cyanoethyl 4-[[(3-phenylisoxazole-5-yl)methyl]oxy]butyl ester 21

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and methanol (0 to 5%), to give the title compound as a yellow oil (77%).

R_f 0.54 (DCM, MeOH, 95 : 5); ^{1}H NMR: δ 9.45 (1H, br s, NH), 7.82-7.75 (2H, m, ArH), 7.51 (1H, s, H6), 7.48–7.41 (3H, m, ArH), 6.58 (1H, s, CH=CO iso), 6.22 (1H, t, ^3J 7.5, H1′), 5.19–5.12 (1H,

m, H3′), 4.63 (2H, m, OCH_2 iso), 4.33–4.11 (5H, m, H4′, 2 × $POCH_2$), 3.87 (2H, br s, H5′), 3.61 (2H, t, ^3J 6.0, $OC\underline{H}_2CH_2$), 2.78 (2H, t, ^3J 6.0, CH_2CN), 2.59–2.40 (2H, m, H2′), 2.17 (1H, br s, OH), 1.92–1.69 (7H, m, CH_3, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$);^{13}C NMR: δ 169.8 (C=N iso), 163.9(C_2), 162.5 (CO=CH), 150.5 (C_4), 136.5 (C_6), 130.2 (ArCH), 129.0 (ArCH), 128.8 (ArC), 126.8 (ArCH), 116.6 (C≡N), 111.3 (C_5), 101.2 (CH=CO iso), 86.0 ($C_{1'}$), 85.6 ($C_{4'}$), 78.4 ($C_{3'}$), 70.5 (OCH_2CH_2), 68.7 ($POCH_2$), 63.7 (OCH_2 iso), 62.2 ($POCH_2$), 62.0 ($C_{5'}$), 38.4 ($C_{2'}$), 27.2 ($OCH_2CH_2CH_2CH_2O$), 25.6 ($OCH_2CH_2CH_2CH_2O$), 19.8 (CH_2C≡N), 12.5 (CH_3); ^{31}P NMR: δ –2.5; HRMS (ESI): m/z $C_{27}H_{35}N_4O_{10}P$ requires 303.1040 $[M+2H]^{2+}$, found 303.1041 (0.46 ppm).

3′-Thymidylic acid, 2-cyanoethyl 4-[[3-[(1-naphthyl)isoxazole-5-yl]methyl]oxy]butyl ester 22

The crude product was purified by flash column chromatography over silica gel, eluting with dichloromethane and methanol (0 to 5%), to give the title compound as a yellow oil (72%).

R_f 0.57 (DCM, MeOH, 95 : 5); ^{1}H NMR: δ 8.91 (1H, br s, NH), 8.38–8.31 (1H, m, ArH), 7.99–7.88 (2H, m, ArH), 7.73–7.67 (1H, m, ArH), 7.59–7.50 (3H, m, ArH), 7.43 (1H, s, H6), 6.59 (1H, s, CH=CO iso), 6.19 (1H, t, ^3J 7.2, H1′), 5.19–5.11 (1H, m, H3′), 4.71 (2H, m, OCH_2 iso), 4.34–4.13 (5H, m, H4′, 2 × $POCH_2$), 3.88 (2H, br s, H5′), 3.67 (2H, t, ^3J 6.0, $OC\underline{H}_2CH_2$), 3.18 (1H, br s, OH), 2.77 (2H, t, ^3J 6.0, CH_2CN), 2.58–2.40 (2H, m, H2′), 1.95–1.70 (7H, m, CH_3, $OCH_2C\underline{H}_2C\underline{H}_2CH_2O$);^{13}C NMR: δ 169.1 (C=N iso), 163.6 (C_2), 162.6 (CO=CH), 150.4 (C_4), 136.5 (C_6), [130.9, 130.4, 128.6, 127.8, 127.1, 126.6, 126.4, 125.5, 125.2] (ArC), 116.6 (C≡N), 111.3 (C_5), 104.5 (CH=CO iso), 86.2 ($C_{1'}$), 85.6 ($C_{4'}$), 78.3 ($C_{3'}$), 70.6 (OCH_2CH_2), 68.6 ($POCH_2$), 63.7 (OCH_2 iso), 62.2 ($POCH_2$), 62.0 ($C_{5'}$), 38.4 ($C_{2'}$), 27.2 ($OCH_2CH_2CH_2CH_2O$), 25.6 ($OCH_2CH_2CH_2CH_2O$), 19.8 (CH_2C≡N), 12.5 (CH_3); ^{31}P NMR: δ –2.4; HRMS (ESI): m/z $C_{31}H_{37}N_4O_{10}P$ requires 328.1118 $[M+2H]^{2+}$, found 328.1119 (0.40 ppm).

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