Supporting Information for

Seven-membered Ring Nucleobases as Inhibitors of Human Cytidine Deaminase and APOBEC3A

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1. Enzymes used in the current study

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hA3A                MEASPASGPRHLMDPHIFTSNFNNG---IGRHKTYLCYEVERLDNGTSVKMDQHRGFLHN
A3A-E72A            MEASPASGPRHLMDPHIFTSNFNNG---IGRHKTYLCYEVERLDNGTSVKMDQHRGFLHN
hA3BCTD             --------------PDTFTFNFNNDPLVLRRRQTYLCYEVERLDNGTWVLMDQHMGFLCN
A3BCTDQMΔL3AL1      ------EILRYLMDPDTFTSNFNNG---IGRHKTYLCYEVERLDNGTSVKMDQHMGFLCN
hA3A                QAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQEN
A3A-E72A            QAKNLLCGFYGRHAALRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQEN
hA3BCTD             EAKNLLCGFYGRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQEN
A3BCTDQMΔL3AL1      E--------SGRHAELRFLDLVPSLQLDPAQIYRVTWFISWSPCFSWGCAGEVRAFLQEN
hA3A                THVRLRIFAARIYDY-DPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPW
A3A-E72A            THVRLRIFAARIYDY-DPLYKEALQMLRDAGAQVSIMTYDEFKHCWDTFVDHQGCPFQPW
hA3BCTD             THVRLRIFAARIYDY-DPLYKEALQMLRDAGAQVSIMTYDEFEYCWDTFVYRQGCPFQPW
A3BCTDQMΔL3AL1      THVRLRIKAARIYDY-DPLYKEALQMLRDAGAQVSIMTYDEFEYCWDTFVYRQGCPFQPW
hA3A                DGLDEHSQALSGRLRAILQNQGN
A3A-E72A            DGLDEHSQALSGRLRAILQNQGN
hA3BCTD             DGLEEHSQALSGRLRAILQNQGN
A3BCTDQMΔL3AL1      DGLEEHSQALSGRLRAILQ----
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Figure S1. Amino acid sequences of human A3A (hA3A), hA3B$_{CTD}$ in comparison with the enzymes used in this work. A3B$_{CTD}$ is the C-terminal domain of A3B. A3B$_{CTD}$-QM-ΔL3-AL1swap (loop 1 swapped with A3A); A3A-E72A-active site glutamate mutated to alanine.

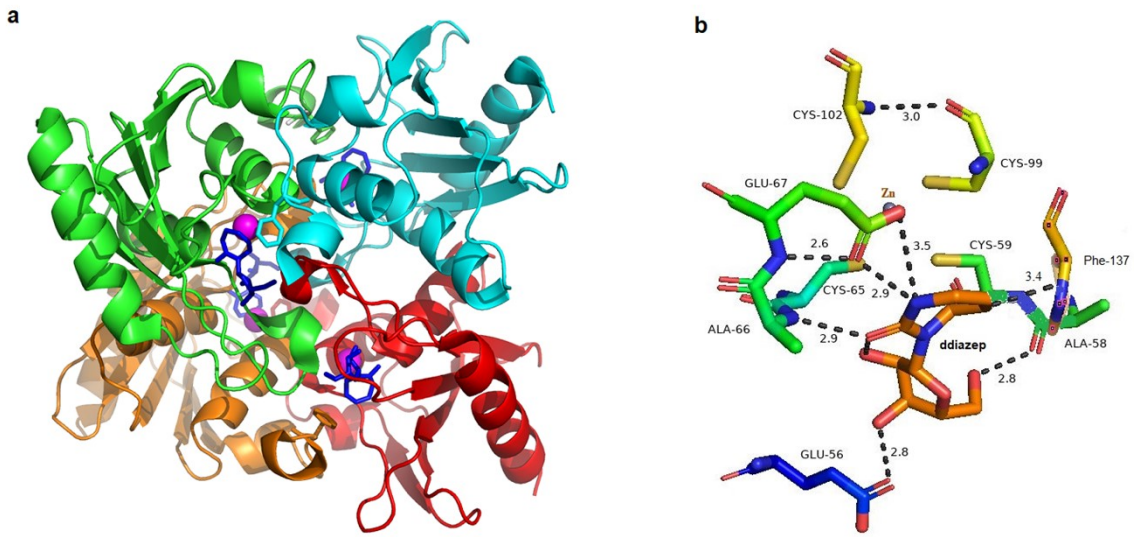


Figure S2. Crystal structure of a ribose form of diazepinone riboside that has been co-crystallised with hCDA.

a) Ribbon diagram of hCDA and ddiazep co-crystal, where ddiazep is depicted as blue sticks. b) Important interactions ddiazep (orange sticks) makes with the amino acid residues (light blue sticks) in hCDA (PDB ID: 1MQ0). The structures are rendered in PyMol (2.5). The Zn^{2+}-bound H_2O/OH^- sits just 2.9 Å from ddiazep N3 non-hydrogen-bonding conformation, 3.0 Å from C4 and 3.3 and 3.6 Å from C5 and C6 (the olefinic carbon atoms), This positioning of the olefinic bond away from the nucleophilic H_2O/OH^- explains why this bond is not hydrolysed. The ring is positioned with N3-H, although hydrogen-bonded to key general acid-base residue Glu67, pointing into the helix 66-76 with unfavourable dipole interaction. The hydrogen bonds between the inhibitor O5 atom and O-Ala58 and HN-Tyr60 are intermolecular, not intramolecular.

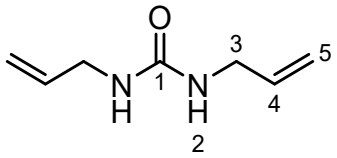
2. General synthetic information

All reactions were performed in oven-dried glassware under an atmosphere of dry argon or nitrogen unless otherwise noted. Moisture-sensitive reactions were carried out using standard syringe septum techniques and under an inert atmosphere of argon or nitrogen. All solvents and reagents were purified by standard techniques unless otherwise noted. Solvents for filtration, transfers, and chromatography were certified ACS grade. Evaporation of solvents was carried out under reduced pressure on a rotary vacuum evaporator below 40 ^{o}C. "Brine" refers to a saturated solution of sodium chloride in water. ^{1}H (500 or 700 MHz), ^{13}C (125.8 or 176.1 MHz), ^{31}P (202.5 MHz) NMR spectra were recorded on Bruker Avance 500- and 700-MHz spectrometers. Chemical shifts of organic compounds are reported in parts per million (ppm) downfield from tetramethylsilane. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (double of doublets), dt (double of triplets), ddd (doublet of doublet of doublets), t (triplet), q (quartet), m (multiplet). Coupling constants are reported in Hertz (Hz). The assignments of signals were done using 2D homonuclear ^{1}H-^{1}H COSY, NOESY and heteronuclear ^{1}H-^{13}C HMQC or HSQC, and HMBC spectra. NMR spectra were processed in TopSpin. High-resolution electrospray mass spectra were recorded on a Thermo Fisher Scientific Q Exactive Focus Hybrid Quadrupole-Orbitrap mass spectrometer. Ions generated by ESI were detected in positive ion mode for small molecules and negative ion mode for oligonucleotides. Total ion count (TIC) was recorded in centroid mode over the *m*/*z* range of 100-3,000 and analyzed using Thermo Fisher Xcalibur Qual Browser. Analytical thin layer chromatography (TLC) was performed on MERCK precoated silica gel 60-F254 (0.5-mm) aluminum plates. Visualisation of the spots on TLC plates was achieved either by exposure to UV light or by dipping the plates into aqueous $KMnO_4$ and heating with a heat gun. Silica gel column chromatography was performed using silica gel 60 (40–63 μm). Oligonucleotide syntheses were carried out on a MerMade-4 DNA/RNA synthesiser (BioAutomation) on a 5 μmol scale using standard manufacturer's protocol for unmodified nucleotides.

3. Experimental section

3.1. Synthesis of 1,3-diazepinone

3.1.1. Synthesis of diallyl urea (2)[3]



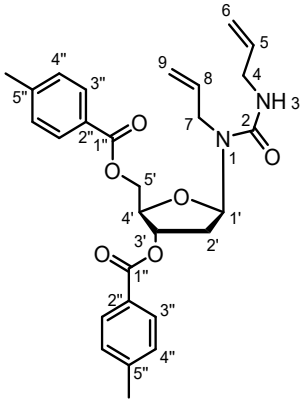
To a stirring solution of allylamine (1.00 g, 17.51 mmol) in dry THF (15 mL), *N*,*N*-disuccinimidyl carbonate (2.25 g, 8.86 mmol) was added at r.t. and the mixture was stirred at r.t. for 2 hr under argon. After consumption of the starting amine (TLC analysis, R_f = 0.35, 50% EtOAc in hexane), solvent was evaporated *in vacuo.* The crude product was purified by column chromatography over silica gel eluting with 0-50% EtOAc in hexane to afford the desired product as a white solid (R_f = 0.29, 50% EtOAc in hexane; yield 0.95 g, 77%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84-5.76 (m, 2H, H-4); 5.85 (bs, 2H, NH); 5.14 (dd, 2H, J = 17.2, 1.6 Hz, H-5a); 5.04 (dd, 2H, J = 10.3, 1.6 Hz, H-5b); 3.75-3.72 (m, 4H, H-3).

^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 158.7 (C2); 135.6 (2C, C4); 115.6 (2C, C5); 43.0 (2C, C3).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_7H_{13}N_2O$ 141.1028; found 141.1021.

3.1.2. Synthesis of 1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]diallylurea (3)



To the solution of diallyl urea **2** (2.00 g, 14.28 mmol) in benzene (30 mL), Et_3N (4.77 mL, 34.22 mmol) and trimethylsilyl chloride (4.35 mL, 40.45 mmol) were sequentially added at r.t. under argon. The reaction mixture was stirred overnight, and then filtered over sintered funnel. Solvents were evaporated *in vacuo* to afford silyl protected diallyl urea derivative. To the solution of silyl-protected diallyl urea (2.50 g, 8.78 mmol) in dichloroethane (60 mL), freshly

distilled $SnCl_4$ (3.36 mL, 28.71 mmol) and Hoffer's chlorosugar (3.36 g, 8.64 mmol) were sequentially added at −35 °C. Reaction mixture was stirred for 1.5 h at −35 °C and after the consumption of starting silylated diallyl amine, pyridine (10 mL) and H_2O (50 mL) were added and reaction mixture was stirred at r.t. for 1 h followed by addition of H_2O (100 mL). The resulting mixture was extracted with DCM (4 × 100 mL), combined organic layers were dried over Na_2SO_4, filtered and the combined organic fractions were evaporated *in vacuo*. The crude product was purified by flash chromatography on silica eluting with 0-30% EtOAc in hexane to afford the product as a foam (R_f = 0.38, 30% EtOAc in hexane; yield 2.00 g, 47%, β/α = 9:1).

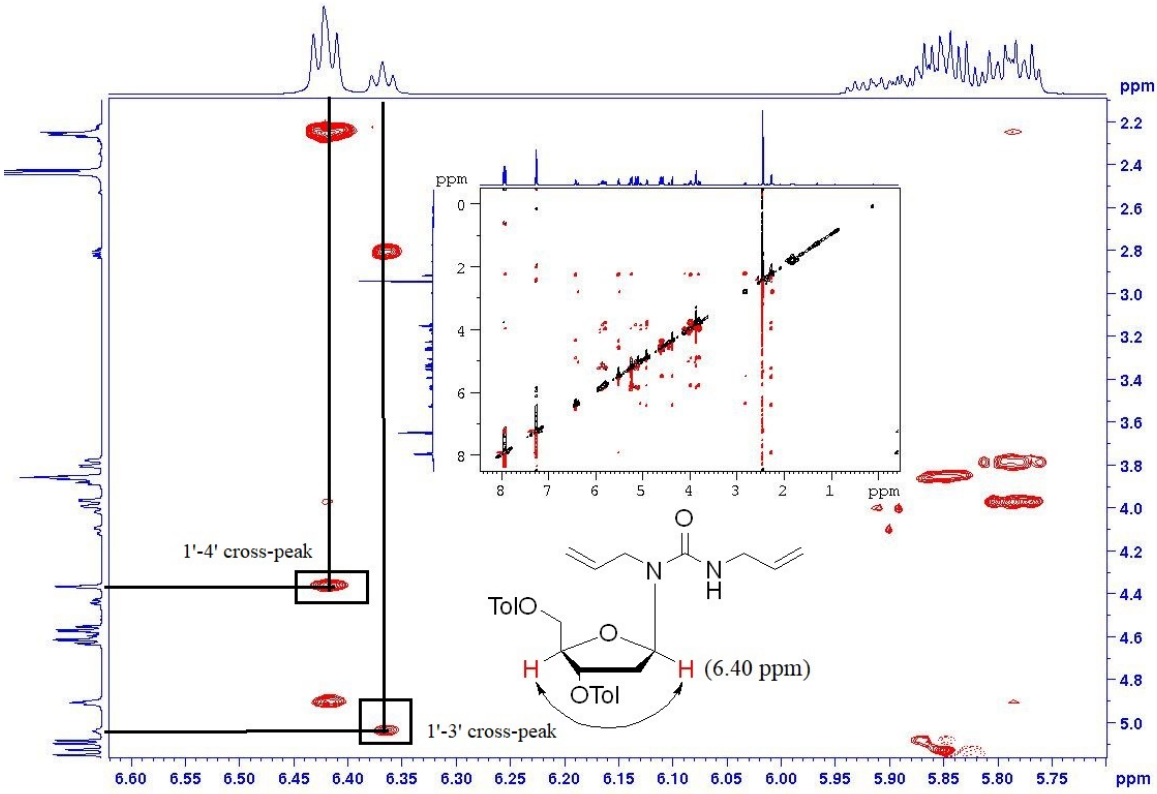


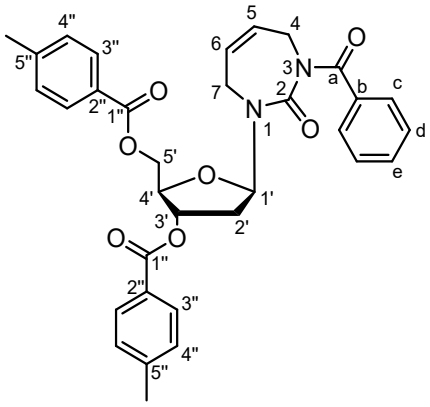
Figure S3. NOESY Spectrum of compound **3**. The spectrum shows the cross-peak between 1'-and 4'-protons of the major isomer of compound **3** through space, confirming it as a β-nucleoside and the cross-peak between 1'- and 3'- protons in the minor α-anomer.

The signals of only one major β-anomer were assigned in ^1H and ^{13}C NMR.

^1H NMR (500 MHz, $CDCl_3$) δ 7.93-7.89 (m, 4H, H-3"); 7.26-7.21 (m, 4H, H-4"); 6.42 (dd, 1H, J = 8.7, 6.9 Hz, H-1'); 5.87-5.76 (m, 2H, H-5, H-8); 5.50 (dt, 1H, J = 8.7, 6.9 Hz, H-3'); 5.26-5.22 (m, 2H, H-9); 5.14-5.12 (m, 1H, H-6a); 5.09-5.08 (m, 1H, H-6b); 4.90 (t, 1H, J = 5.3 Hz, H-3); 4.61 (dd, 1H, J = 11.9, 3.5 Hz, H-5'a); 4.55 (dd, 1H, J = 11.9, 3.6 Hz, H-5'b); 4.36 (m, 1H, H-4'); 3.99-3.95 (m, 1H, H-4a); 3.86-3.84 (m, 2H, H-7), 3.80-3.77 (m, 1H, H-4b); 2.43 (2s, 6H, CH_3); 2.26-2.24 (m, 2H, H-2').

$^{13}C\{^{1}H\}$ NMR (125.7 MHz, $CDCl_3$) δ 166.22 (C1"); 166.16 (C1"); 157.9 (C2); 144.3 (C5"); 144.0 (C5"); 135.2 (C2"); 135.0 (C2"); 129.8 (2C, C3"); 129.6 (2C, C3"); 129.2 (4C, C4"); 126.9 (C2"); 126.7 (C2"); 116.5 (C9); 115.6 (C6); 85.6 (C1'); 80.3 (C4'); 75.1 (C3'); 64.7 (C5'); 44.3 (C4); 43.1 (C7); 35.2 (C2'); 21.72, 21.69 (2C, CH_3).

3.1.3. Synthesis of 3-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-1-benzoyl-1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (5)



To a stirring solution of compound **3** (4.00 g, 8.12 mmol) in pyridine (100 mL) at 0 °C, Et_3N (4.80 mL, 34.50 mmol) and benzoyl chloride (2.83 mL, 24.38 mmol) were added sequentially, and the reaction mixture was allowed to stir overnight under r.t. After the consumption of starting nucleoside by observing TLC, pyridine was evaporated *in vacuo.* The residue was resuspended in 100 mL ethyl acetate, washed with brine (2 × 10 mL), the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel eluting with 0-30% EtOAc in hexane to afford the desired product as a foam (R_f = 0.42, 30% EtOAc in hexane; yield 4.00 g, 83%).

To a solution of the benzoyl-protected compound **4** (1.80 g, 3.02 mmol), in dry dichloromethane was added GreenCat™ (0.24 g, 10 mol%) and refluxed for 2 hr. After the consumption of the starting material, solvent was evaporated *in vacuo* and the crude product was purified by silica gel column chromatography eluting with 0-40% EtOAc in hexane to yield the desired product **5** as a foam (R_f = 0.39, 40% EtOAc in hexane; yield 0.70 g, β/α = 9:1, 41%). The material was resuspended and washed with methanol to afford pure β-anomer in > 99% purity (0.59 g, 34%).

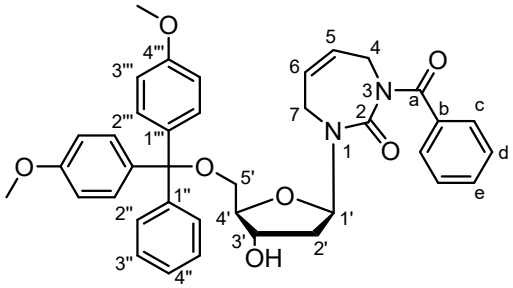
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H, H-3"); 7.89-7.86 (m, 2H, H-3"); 7.56-7.53 (m, 2H, H-c); 7.47-7.44 (m, 1H, H-e); 7.40-7.35 (m, 2H, H-d); 7.31-7.27 (m, 2H, H-4"); 7.23-7.20 (m, 2H, H-4"); 6.19 (dd, 1H, J = 9.3, 5.3 Hz, H-1'); 5.82-5.76 (m, 1H, H-5); 5.70-5.65 (m, 1H, H-6); 5.55 (m, 1H, H3'); 4.74 (dd, 1H, J = 15.4, 12.1 Hz, H-5'a); 4.68-4.62 (m, 1H, H7);

4.57 (dd, 1H, J = 15.6, 12.1 Hz, H-5'b); 4.35 (td, 1H, J = 3.3, 2.5 Hz, H-4'); 4.30-4.23 (m, 1H, H-7); 4.08 (dd, 1H, J = 19.2, 16.9 Hz, H-4); 3.96 (dd, 1H, J = 21.9, 16.9 Hz, H-4); 2.44, 2.40 (2s, 6H, CH_3); 2.31 (ddd, 1H, J = 16.0, 6.7, 5.3 Hz, H-2'b); 2.18 (ddd, 1H, J = 15.4, 9.3, 6.7 Hz, H-2'a).

$^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$) δ 171.0 (Ca); 166.22, 166.19 (2C, C1''); 159.7 (C2); 144.5, 144.4 (2C, C5''); 135.2 (C2''); 131.6 (Ce); 129.9, 129.7 (4C, C3''); 129.5, 129.3 (4C, C4''); 128.6 (2C, Cd); 128.3 (C5); 127.4 (2C, Cc); 127.0, 126.5 (2C, C1''); 124.0 (C6); 85.6 (C1'); 81.5 (C4'); 74.9 (C3'); 64.3 (C5'); 43.3 (C7); 39.3 (C4); 35.4 (C2'); 21.84, 21.81 (2C, CH_3).

HRMS (ESI) m/z: $[M+Na]^+$ Calcd for $C_{33}H_{32}N_2NaO_7$ 591.2107; found 591.2097.

3.1.4. Synthesis of 1-[2-deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl]-3-benzoyl-1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (6)



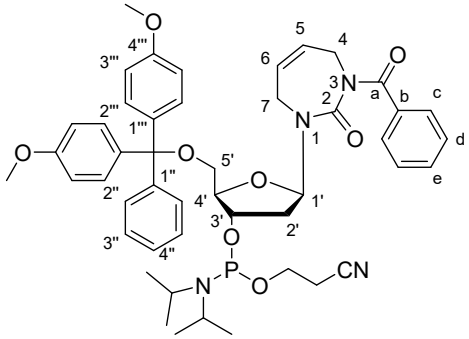
To a stirring solution of compound **5** (4.00 g, 7.04 mmol) in 400 mL methanol 40 mL of 30% aq. ammonia solution was added and the mixture kept stirring for 3 days. After the disappearance of the starting material, volatiles were removed by rotary vacuum evaporator and residue was co-evaporated again with 100 mL water to remove formed methyl toluate and then the residue was freeze dried from water (50 mL) to get the deprotected nucleoside (2.25 g, R_f = 0.45, 40% MeOH in DCM). This partially deprotected nucleoside was used without further purification to protect it 5'-end with DMT. To a stirring solution of the product (2.00 g, 6.02 mmol) in dry pyridine (40 mL) at 0 °C, 4,4'-dimethoxytrityl chloride (3.72 g, 11.00 mmol) was added, and mixture was stirred at r.t. overnight. Pyridine was evaporated *in vacuo*. The residue was dissolved in 50 mL ethyl acetate and washed with brine (2 × 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The crude product was purified by column chromatography over silica gel (packed in 10% Et_3N in DCM then washed with DCM) and compound was eluted with 0-20% acetone in DCM to afford the desired product **6** as a foam (3.13 g, 82%; R_f = 0.40, 20% acetone in DCM).

^1H NMR (500 MHz, $CDCl_3$) δ 7.57-7.54 (m, 2H, H-c); 7.46-7.42 (m, 3H, H-2'', H-e); 7.40-7.36 (m, 2H, H-d); 7.34-7.30 (m, 6H, H-3''', H-3''); 7.27-7.24 (m, 1H, H-4''); 6.87-6.83 (m, 4H,

H-3'''); 6.05 (app t, 1H, *J* = 7.05 Hz, H-1'); 5.79-5.75 (m, 1H, H-5); 5.70-5.66 (m, 1H, H-6); 4.62-4.55 (m, 1H, H-7); 4.43 (td, 1H, *J* = 4.8, 2.8 Hz, H-4'); 4.40-4.34 (m, 1H, H-7); 4.12 (dd, 1H, *J* = 19.4, 16.8 Hz, H-4); 3.96 (dd, 1H, *J* = 21.7, 16.8 Hz, H-4); 3.87 (td, 1H, *J* = 3.8, 2.2 Hz, H-3'); 3.80 (s, 6H, OCH_3); 3.40-3.31 (m, 2H, H-5'); 2.05 (dd, 2H, *J* = 6.9, 5.2 Hz, H-2').

$^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$) δ 170.8 (Ca); 159.3 (C2); 158.7 (2C, C4'''); 144.7 (C1''); 135.82, 135.81 (2C, C1'''); 135.3 (Cb); 131.5 (Ce); 130.21, 130.19 (4C, C2'''); 128.5 (2C, C3''); 128.3 (2C, C2''); 128.05 (C5); 128.02 (2C, Cd); 127.4 (2C, Cc); 127.1 (C4''); 124.3 (C6); 113.3 (4C, C3'''); 86.6 (*C*-Ar_3); 85.4 (C1'); 84.7 (C4'); 72.5 (C3'); 63.8 (C5'); 55.4 (2C, O*C*H_3); 43.2 (C7); 39.7 (C4); 38.4 (C2').

3.1.5. Synthesis of 1-[3-*O*-(*N*,*N*-di*iso*propylamino-2-cyanoethoxyphosphanyl)-2-deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl]-3-benzoyl-1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (7)



To a stirring solution of 5'-*O*-DMT protected compound **6** (0.20 g, 0.32 mmol) in dry DCM (10 mL) under argon at r.t., were added Et_3N (0.07 mL, 0.50 mmol) followed by 2-cyanoethyl *N*,*N*-di*iso*propyl chlorophosphoramidite (0.09 g, 0.38 mmol). After the disappearance of the starting material (TLC analysis, 10 min), the reaction mixture was washed with saturated sodium bicarbonate solution (2 × 5 mL) followed by brine (5 mL). The organic layer was passed through the column with anhydrous sodium sulphate and evaporated *in vacuo*. The crude product was purified by column chromatography over silica gel (column packed in Et_3N (10%) in DCM and then washed with DCM) eluting with DCM/acetone (9:1) to give the desired product as a white foam (R_f = 0.45, 10% acetone in DCM; yield 0.22 g, 82%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.62-7.59 (m, 2H, H-c); 7.51-7.46 (m, 3H, H-2'', H-e); 7.45-7.41 (m, 2H, H-d); 7.38-7.31 (m, 6H, H-2''', H-3''); 7.29-7.26 (m, 1H, H-4''); 6.87-6.83 (m, 4H, H-3'''); 6.10 (app t, 1H, *J* = 7.5 Hz, H-1'); 5.83-5.79 (m, 1H, H-5); 5.74-5.68 (m, 1H, H-6); 4.68- 4.63 (m, 1H, H-7); 4.62-4.57 (m, 1H, H-4'); 4.46-4.35 (m, 1H, H-7); 4.25-4.15 (m, 1H, H-4); 4.13-4.08 (m, 1H, H-4); 4.05, 4.02 (2td, 1H, *J* = 3.5, 1.8 Hz, H-3'); 3.82, 3.83 (2s, 6H, OCH_3); 3.75-3.67 (m, 1H, NC*H*CH_3); 3.66-3.60 (m, 1H, NC*H*CH_3); 3.58-3.51 (m, 2H, 2H,

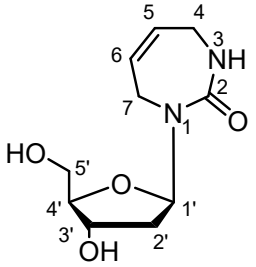
C*H*$_2$CH$_2$CN); 3.47, 3.43 (2dd, 1H, *J* = 10.4, 2.9 Hz, H-5'a); 3.31-3.26 (m, 1H, H-5'b); 2.60, 2.40 (2t, 2H, *J* = 7.5 Hz, CH$_2$C*H*$_2$CN); 2.27-2.10 (m, 2H, H-2'); 1.28-1.21 (m, 2H, CHC*H*$_3$); 1.19-1.13 (m, 8H, CHC*H*$_3$); 1.07-1.03 (m, 2H, CHC*H*$_3$).

^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 170.9, 170.8 (Ca); 159.42, 159.39 (C2); 158.74, 158.72 (2C, C4'''); 144.75, 144.73 (C1''); 135.9, 135.8 (2C, C1'''); 135.4 (Cb); 131.5 (Ce); 130.29, 130.26, 130.24 (4C, C2'''); 128.56, 128.53 (2C, C2''); 128.39, 128.34 (2C, Cd); 128.1 (C5); 128.0 (2C, C3''); 127.5 (2C, Cc); 127.12; 127.08 (C4''); 124.46, 124.42 (C6); 117.7, 117.5 (*C*N); 113.3 (4C, C3'''); 86.50, 86.49 (*C*Ar$_3$); 85.51, 85.46 (C1'); 84.45, 84.42, 84.23, 84.18 (C4'); 73.8, 73.7, 73.3, 73.2 (C3'); 63.2, 63.1 (C5'); 58.30, 58.26, 58.16, 58.11 (2C, *C*CH$_3$); 55.39, 55.37 (2C, O*C*H$_3$); 43.4, 43.3 (*C*H$_2$CH$_2$CN); 43.22, 43.17 (C7); 39.7, 39.6 (C4); 37.60, 37.56 (C2'); 24.74, 24.68, 24.64, 24.60, 24.58, 24.54 (4C, NCH*C*H$_3$); 20.54, 20.48, 20.32, 20.26 (CH$_2$*C*H$_2$CN).

^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$ ref. 85% H_3PO_4) δ 148.5, 148.3 in ~1:1 ratio.

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{47}H_{56}N_4O_8P$ 835.3836; found 835.3836.

3.1.6. Synthesis of 1-[2-deoxy-β-D-*erythro*-pentofuranosyl]-1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (8)



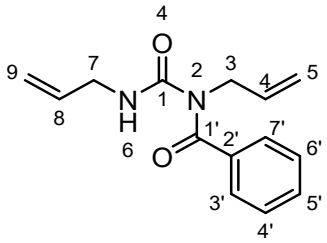
To a stirring solution of compound **5** (4.00 g, 7.04 mmol) in 400 mL methanol was added 40 mL of 30% aq. ammonia solution and kept stirring for 3 days. After the disappearance of the starting material, volatiles were removed by rotary vacuum evaporator and the residue was co-evaporated again with 100 mL water to remove formed methyl toluate and then freeze dried from water (50 mL) to get the compound 1-[2-deoxy-β-D-*erythro*-pentofuranosyl]-3-benzoyl-1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (2.25 g; R_f= 0.45, 40% MeOH in DCM). To 500 mg (1.50 mmol) of this product 3 mL of 30% aq. NH_3 solution was added, and the mixture was kept at r.t. for 15 min. After the disappearance of the starting material as evidenced by TLC, ammonia was evaporated *in vacuo.* The crude product was purified by preparative TLC using 20% MeOH in DCM as eluent. The compound **8** was visualised by UV, the band was scraped from the plate and eluted with methanol. The organic layer was evaporated to afford the required product as a foam (R_f= 0.42, 30% MeOH in DCM; yield: 0.20 g, 58%).

^{1}H NMR (500 MHz, D_2O) δ 6.97 (dd, 1H, J = 8.51, 6.62 Hz, H-1'); 5.93- 5.86 (m, 2H, H-5 and H-6); 4.36-4.32 (m, 1H, H-3'); 3.86- 3.75 (m, 4H, H-3 and H-7); 3.75- 3.67 (m, 2H, H-5'); 2.20 (ddd, 1H, J = 15.1, 8.2, 7.3 Hz, H-2'b); 2.03 (ddd, 1H, J = 15.1, 6.6, 3.2 Hz, H-2'a).

^{13}C{^{1}H} NMR (125.7 MHz, D_2O) δ 166.0 (C2); 128.0 (C5); 127.1 (C6); 86.4 (C4'); 84.7 (C1'); 70.9 (C3'); 68.4 (C5'); 66.5 (C7); 40.3 (C4); 36.1 (C2').

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{10}H_{16}N_2O_4Na$ 251.1008; found 251.0990.

3.1.7. Synthesis of *N*-allyl-*N*-(allylcarbamoyl)benzamide (10)



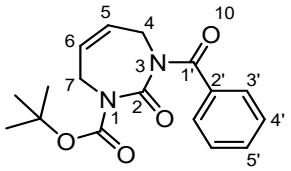
To a stirring solution of diallyl urea **2** (2.00 g, 14.27 mmol) in pyridine (50 mL) at 0 °C, Et_3N (5.96 mL, 42.84 mmol) and benzoyl chloride (4.95 mL, 42.64 mmol) were added sequentially, and the reaction mixture was allowed to stir overnight at r.t. After the consumption of the starting material by TLC monitoring, pyridine was evaporated *in vacuo.* The residue was resuspended in 50 mL ethyl acetate, washed with brine (2 × 10 mL), organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel eluting with 0-30% EtOAc in hexane to afford the desired product **10** as a foam (R_f = 0.38, 30% EtOAc in hexane; yield 2.98g, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (1H, NH); 7.48-7.45 (m, 1H, H-5'); 7.44-7.40 (m, 4H, H-3', H-4'); 5.96-5.88 (m, 1H, H-8); 5.84-5.76 (m, 1H, H-4); 5.26 (dd, 1H, J = 17.0, 1.3 Hz, H-9a); 5.16 (dd, 1H, J = 10.3, 1.3 Hz, H-9b); 5.11 (dd, 1H, J = 10.4, 1.3 Hz, H-5b); 4.96 (d, 1H, J = 17.3, 1.3 Hz, H-5a); 4.33-4.29 (m, 2H, H-3); 4.01-3.97 (m, 2H, H-7).

^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 175.2 (C1'); 154.5 (C1); 136.2 (C2'); 133.98 (C8); 133.95 (C4); 133.7 (C5'); 130.5 (C6'); 130.2 (C7'); 128.5 (2C, C3'); 126.1 (2C, C4'); 116.5 (C5); 116.2 (C9); 49.1 (C3); 43.0 (C7).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{16}N_2O_2Na$ 267.1109; found 267.1098.

3.1.8. Synthesis of 1-(*tert*-butyloxycarbonyl)-3-benzoyl-1,3,4,7-tetrahydro-2*H*-1,3-diazepine-2-one (12)



To a stirring solution of compound **10** (4.00 g, 16.37 mmol) in 100 mL of dry THF at 0 °C was added Et_3N (3.00 mL, 21.56 mmol), DMAP (0.10 g, 0.82 mmol), and stirred at the same temperature for 0.5 h, then di-*tert*-butyl dicarbonate (5.70 mL, 24.81 mmol) was added dropwise. The reaction mixture was refluxed overnight under argon. The reaction mixture was diluted with EtOAc (90 mL) and washed with water (3 ×10 mL). The organic layer was washed with brine (2 ×10 mL), dried over anhydrous sodium sulphate, filtered, concentrated *in vacuo,* and purified by silica gel column chromatography (10% EtOAc in hexane) to afford the desired compound **11** as an oil (R_f = 0.42, 10% EtOAc in hexane; yield: 4.60 g, 82%).

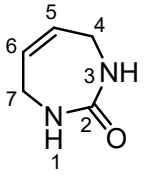
To a solution of the compound **11** (4.00 g, 11.61 mmol), in dry DCM (100 mL) was added GreenCat™ (0.91 g, 10 mol%) and the reaction mixture was refluxed for 2 hr. After the consumption of the starting material, solvent was evaporated *in vacuo* and the crude product was purified by silica gel column chromatography eluting with 0-40% EtOAc in hexane to yield the desired product as a foam (R_f = 0.40, 30% EtOAc in hexane; yield: 2.65 g, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61-7.57 (m, 2H, H-3'); 7.52-7.49 (m, 1H, H-5'); 7.45-7.41 (m, 2H, H-4'); 5.90 (s, 2H, H-5 and H-6); 4.61-4.55 (m, 4H, H-4 and H-7); 1.48 (s, 9H, CH_3).

^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 171.2 (C1'); 157.3 (C2'); 131.8 (C5'); 128.5 (2C, C3'); 127.6 (2C, C4'); 126.3 (C5); 126.1 (C6); 83.5 (*C*CH_3); 43.8 (C7); 42.3 (C4); 28.0 (3C, CH_3).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{20}N_2O_4Na$ 339.1321; found 339.1305.

3.1.9. Synthesis of 1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (14)



To a stirring solution of compound **12** (2.0 g, 6.32 mmol) in methanol (100 mL) was added 10 mL of 30% aq. ammonia. After stirring at r.t. for 10 min, the starting material was completely consumed as evidenced by TLC. The volatiles were evaporated *in vacuo* and the residue was dissolved in 20 mL DCM. Trifluoroacetic acid (10 mL) was added at r.t., and kept

stirring for 10 min. The reaction mixture was concentrated *in vacuo* and co-evaporated several times with DCM. The crude product was purified by silica gel column chromatography, eluting with 0-10% MeOH in DCM to afford the desired product as an off-white solid (R_f = 0.29, 10% MeOH in DCM; yield: 0.90 g, 86.8%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 5.99 (bs, 2H, NH); 5.77 (s, 2H, H-5, H-6); 3.53 (s, 4H, H-4, H-7).

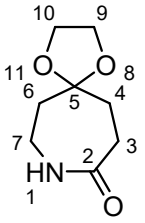
^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 164.9 (C2); 127.8 (2C, C4, C7); 40.8 (2C, C5, C6).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_5H_9N_2O$ 113.0715; found 113.0709.

3.2. Synthesis of 3-deaza-1,3-diazepinone derivatives

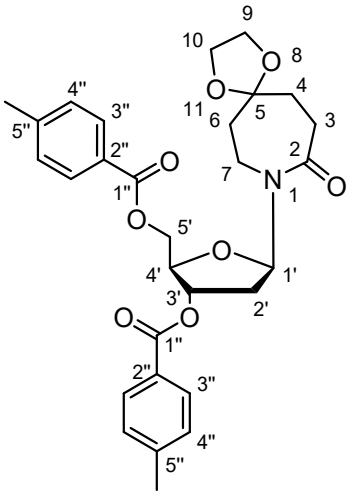
3.2.1. Synthesis of 1,4-dioxa-8-azaspiro[4.6]undecan-9-one (17)

Synthesis of compound **17** was done from commercially available compound **16** using reported procedure and the ^{1}H NMR matched the spectrum reported in the literature (yield 8.00 g, 73%).[1]



^{1}H NMR (500 MHz, DMSO-d_6) δ 7.51 (s, 1H, NH); 3.89, 3.88 (2s, 4H, H-9, H-10); 3.09-3.05 (m, 2H, H-7); 2.30-2.26 (m, 2H, H-3); 1.70-1.66 (m, 2H, H-4); 1.65-1.63 (m, 2H, H-6).

3.2.2. Synthesis of 8-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-1,4-dioxa-8-azaspiro[4.6]undecan-9-one (18)

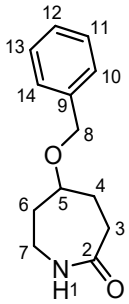


To a solution of compound **17** (7.50 g, 43.81 mmol) in 250 mL of 1,4-dioxane was added K-^{t}BuO (5.80 g, 51.69 mmol) followed by Hoffer's chlorosugar (14.00 g, 36.00 mmol) and the solution was stirred at r.t. for 2 hr. After the consumption of the starting materials as observed by TLC, the reaction mixture was diluted with EtOAc (100 mL) and washed with water (20 mL). Organic layer was separated, dried over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography over silica gel eluting with 0-30% EtOAc in hexane to afford the desired **18** as a foam (R_f = 0.35, 30% EtOAc in hexane, yield 14.50 g, 63%, with purity over 99% for the β-nucleoside as determined by ^{1}H NMR).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91-7.89 (m, 4H, H-3''); 7.36-7.34 (m, 4H, H-4''); 6.37 (dd, 1H, J = 9.4, 5.7 Hz, H-1'); 5.50 (app dt, 1H, J = 6.6, 2.2 Hz, H-3'); 4.59 (dd, 1H, J = 11.8, 4.1 Hz, H-5'a); 4.45 (dd, 1H, J = 11.8, 4.8 Hz, H-5'b); 4.31-4.29 (m, 1H, H-4'); 3.90-3.85 (m, 2H, H-9); 3.83-3.77 (m, 2H, H-10); 3.31-3.19 (m, 2H, H-7); 2.48-2.42 (m, 2H, H-3); 2.39 (s, 6H, CH_3); 2.30-2.23 (m, 1H, H-2'a); 2.17 (ddd, 1H, J = 14.1, 5.6, 1.7 Hz, H-2'b), 1.73-1.65 (m, 2H, H-4); 1.53 (t, 2H, J = 5.0 Hz, H-6).

^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 175.1 (C2); 165.9 (C1''); 165.8 (C1''); 144.5 (C5''); 144.4 (C5''); 129.84 (4C, C3''); 129.79, 129.72 (4C, C4''); 127.1 (C2''); 127.0 (C2''); 108.6 (C5); 83.3 (C1'); 80.3 (C4'); 75.5 ; 64.6 (C5'); 64.43 (C9); 64.41 (C10); 39.0 (C6); 37.1 (C7); 34.3 (C2'); 33.0 (C4); 32.2 (C3); 21.65, 21.61 (2C, CH_3).

3.2.3. Synthesis of 5-benzyloxyazepan-2-one (21)



Synthesis of compound **21** was performed from compound **16** (10.0 g, 64.03 mmol) by the reported procedures (overall yield 7.60 g, 54% over 5 steps).[1, 2]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H, H-10, H-11, H-13, H-14); 7.30-7.25 (m, 1H, H-12); 6.69 (s, 1H, NH); 4.55, 4.51 (2d, 2H, J = 11.90 Hz, H-8); 3.70-3.68 (m, 1H, H-5); 3.56-3.50 (m, 1H, H-7); 3.01-2.95 (m, 1H, H7); 2.84-2.79 (m, 1H, H-4); 2.24-2.19 (m, 1H, H-4); 1.97-1.90 (m, 2H, H-6); 1.87-1.80 (m, 2H, H-3).

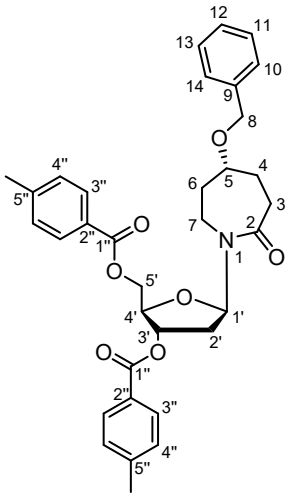
^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 179.0 (C2); 138.6 (C9); 128.5 (2C, C10, C14); 127.7 (C12); 127.5 (2C, C11, C13); 75.9 (C5); 70.2 (C8); 37.2 (C7); 34.6 (C3); 30.1 (C4); 27.8 (C6).

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{18}NO_2$ 220.1338; found 220.1331.

3.2.4. Synthesis of 1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-(*R*)-5-benzyloxyazepan-2-one (22*R*) and 1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-(*S*)-5-benzyloxyazepan-2-one (22*S*)

To a solution of the compound **21** (7.50 g, 34.20 mmol) in 250 mL of 1,4-dioxane was added K-^{t}BuO (5.80 g, 51.69 mmol) followed by Hoffer's chlorosugar (14.00 g, 36.00 mmol) and the solution was stirred at r.t. for 2 hr. After the consumption of the starting materials as

observed by TLC, the reaction mixture was diluted with EtOAc (100 mL) and washed with water. The organic layer was separated, dried over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography over silica gel eluting with 0-30% EtOAc in hexane to afford the desired pure isomers as foams (8.50 g, 47% of *R* isomer, R_f = 0.45, 30% EtOAc in hexane, and 4.30 g, 24% of *S* isomer, R_f = 0.42, 30% EtOAc in hexane, with purity over 99% as β-nucleosides as determined by ^{1}H NMR).

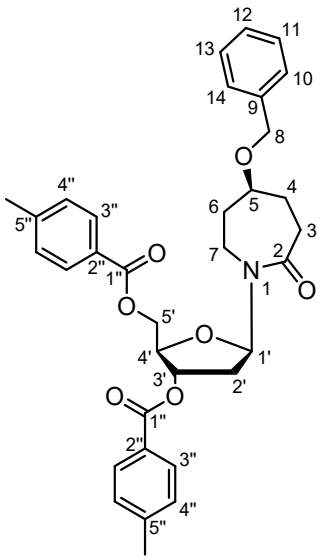


1-[2-Deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-(*R*)-5-benzyloxyazepan-2-one (**22*R***):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94-7.92 (m, 4H, H-10, H-11, H-13, H-14); 7.35-7.32 (m, 2H, H-3"); 7.29-7.27 (m, 3H, H-3", H-12); 7.26-7.23 (m, 4H, H-4"); 6.58 (dd, 1H, *J* = 9.6, 5.4 Hz, H-1'); 5.52-5.50 (m, 1H, H-3'); 4.66 (dd, 1H, *J* = 11.9, 3.5 Hz, H-5'); 4.53 (dd, 1H, *J* = 11.9, 3.9 Hz, H-5'); 4.47, 4.43 (2d, 2H, *J* = 11.9 Hz, H-8); 4.34 (td, 1H, *J* = 3.5, 1.4 Hz, H-4'); 3.63 (bs, 1H, H-5); 3.61-3.58 (m, 1H, H-7); 3.14 (dd, 1H, *J* = 15.7, 7.4 Hz, H-7); 2.94 (t, 1H, *J* = 12.7 Hz, H-3); 2.42 (s, 3H, CH_3); 2.41 (s, 3H, CH_3); 2.33-2.28 (m, 1H, H-2'a); 2.27-2.23 (m, 1H, H-3); 2.18-2.12 (m, 1H, H-2'b); 1.97-1.94 (m, 1H, H-6); 1.85-1.75 (m, 2H, H-6, H-4); 1.60-1.55 (m, 1H, H-4).

^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 176.5 (C2); 166.31 (C1"); 166.25 (C1"); 144.4 (C5"); 144.1 (C5"); 138.6 (C9); 129.9, 129.7 (4C, C3"); 129.4, 129.3 (4C, C4"); 128.5 (2C, C11, C13); 127.7 (C12); 127.4 (2C, C10, C14); 127.1, 126.7 (2C, C2"); 83.4 (C1'); 80.7, (C4'); 75.2 (C3'); 74.8 (C5); 69.9 (C8); 64.6 (C5'); 36.2 (C7); 34.9 (C2'); 34.0 (C6); 31.3 (C3); 28.1 (C4); 21.8 (2C, C6").

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{34}H_{37}NO_7Na$ 594.2468; found 594.2466.



1-[2-Deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-(*S*)-5-benzyloxyazepan-2-one (**22*S***):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94-7.93 (m, 4H, H-11, H-12, H-14, H-15); 7.35-7.33 (m, 2H, H-3''); 7.29-7.24 (m, 7H, H-3'', H-4'', H-13); 6.59 (dd, 1H, J = 9.5, 5.5 Hz, H1'); 5.54-5.52 (m, 1H, H-3'); 4.73 (dd, 1H, J = 11.9, 3.3 Hz, H-5'); 4.51 (dd, 1H, J = 11.9, 3.7 Hz, H-5'); 4.45, 4.41 (2d, 2H, J = 11.8 Hz, H-8); 4.32 (td, 1H, J = 3.1, 1.9 Hz, H-3'); 3.63-3.60 (m, 1H, H-5); 3.56-3.52 (m, 1H, H-7); 3.08-3.05 (m, 1H, H-7); 2.88-2.85 (m, 1H, H-3); 2.41 (s, 3H, CH_3); 2.41 (s, 3H,CH_3); 2.34-2.31 (m, 1H, H-3); 2.28-2.25 (m, 1H, H-2'a); 2.18-2.14 (m, 1H, H-2'b); 1.93-1.87 (m, 2H, H-4); 1.73-1.67 (m, 2H, H-6).

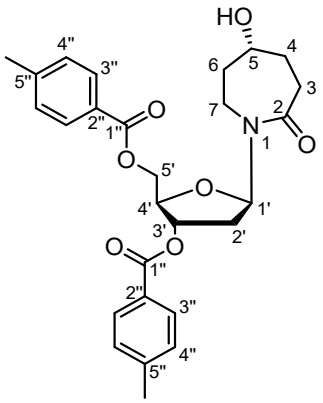
^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 176.3 (C2); 166.3 (C1''); 166.2 (C1''); 144.4 (C5''); 144.2 (C5''); 138.6 (C10); 129.9, 129.7 (4C, C3''); 129.4, 129.3 (4C, C4''); 128.5 (2C, C11, C13); 127.8 (C12); 127.5 (2C, C10, C14); 127.1, 126.7 (2C, C2''); 83.7 (C1'); 81.0, (C4'); 75.1 (C3'); 74.5 (C5); 70.0 (C8); 64.4 (C5'); 36.3 (C7); 34.8 (C2'); 34.1 (C6); 31.5 (C3); 28.2 (C4); 21.83, 21.79 (2C, C6'').

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{34}H_{37}NO_7Na$ 594.2468; found 594.2464.

3.2.5. Synthesis of 1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-(*R*)-5-hydroxyazepan-2-one (23*R*) and 1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-(*S*)-5-hydroxyazepan-2-one (23*S*)

The mixture of the benzylated substrate **22*R*** or **22*S*** (5.00 g, 8.75 mmol) with 10% Pd/C (0.5 g) in abs. EtOH (100 mL) was prepared and two vacuum/H_2 cycles were applied to replace air from the flask and fill it with hydrogen. The suspension was stirred at room temperature under hydrogen pressure (balloon) for 6 h. The reaction mixture was filtered through celite pad,

and washed 2 × 50 mL EtOH, the filtrate was concentrated *in vacuo* to provide the crude product. It was purified by column chromatography over silica gel eluting with 0-10% MeOH in DCM to afford the pure product as a foam.



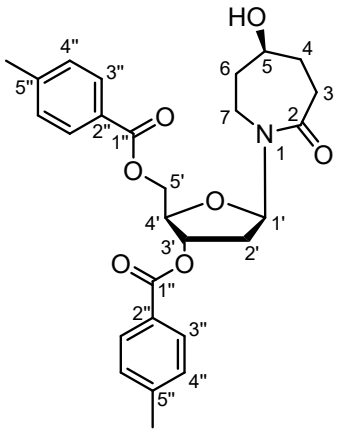
1-[2-Deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-(*R*)-5-hydroxyazepan-2-one (**23*R***):

Yield: 3.90 g, 93%.

R_f = 0.47 in 10% MeOH in DCM.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.90 (m, 4H, H-3"); 7.25-7.22 (m, 4H, H-4"); 6.57 (dd, 1H, J = 9.6, 5.4 Hz, H-1'); 5.52-5.50 (m, 1H, H-3'); 4.65 (dd, 1H, J = 11.9, 3.4 Hz, H-5'a); 4.52 (dd, 1H, J = 11.9, 3.8 Hz, H-5'b); 4.33 (td, J = 3.0, 1.60 Hz, H-4'); 3.93 (bs, 1H, H-5); 3.55 (dd, 1H, J = 15.5, 9.1 Hz, H-7); 3.12 (dd, 1H, J = 15.5, 8.1 Hz, H-7); 2.87-2.82 (m, 1H, H-3); 2.41 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 2.34-2.29 (m, 1H, H-4); 2.25 (dd, 1H, J = 13.8, 5.2 Hz, H-2'a); 2.17-2.11 (m, 1H, H-2'b); 1.92 (t, 1H, J = 12.2 Hz, H-3); 1.79-1.76 (m, 1H, H-4); 1.74-1.68 (m, 1H, H-6); 1.64-1.58 (m, 1H, H-6).

^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 176.2 (C2); 166.33 (C1"); 166.25 (C1"); 144.5 (C5"); 144.2 (C5"); 129.9, 129.7 (4C, C3"); 129.4, 129.3 (4C, C4"); 127.0, 126.7 (2C, C2"); 83.5 (C1'); 80.8 (C4'); 75.1 (C3'); 69.3 (C5); 64.6 (C5'); 37.3 (C6); 36.4 (C7); 35.0 (C2'); 31.4 (C3); 21.9, 21.8 (2C, 2 × CH_3).



1-[2-Deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-(*S*)-5-hydroxyazepan-2-one (**23*S***):

Yield: 3.70 g, 88%.

R_f = 0.46 in 10% MeOH in DCM.

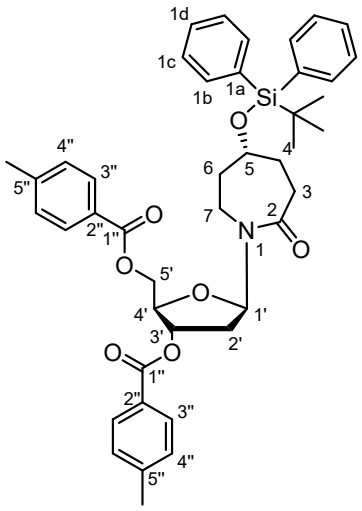
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.90 (m, 4H, H-3''), 7.25-7.23 (m, 4H, H-4''), 6.57 (dd, 1H, J = 9.5, 5.5 Hz, H-1'), 5.52-5.50 (m, 1H, H-3'), 4.67 (dd, 1H, J = 11.9, 3.3 Hz, H-5'a), 4.51 (dd, 1H, J = 11.9, 3.8 Hz, H-5'b), 4.31 (td, 1H, J = 3.2, 1.7 Hz, H-4'), 3.96-3.92 (m, 1H, H-5), 3.54 (dd, 1H, J = 15.5, 9.0 Hz, H-7), 3.08 (dd, 1H, J = 15.5, 8.3 Hz, H-7), 2.81 (t, 1H, J =12.4 Hz, H-3), 2.41 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.37-2.33 (m, 1H, H-4), 2.26 (dd, 1H, , 13.6, 5.2 Hz, H-2'a), 2.19-2.13 (m, 1H, H-2'b), 1.94 (t, 1H, J = 12.1 Hz, H-3), 1.84-1.78 (m, 2H, H-6), 1.75-1.69 (m, 1H, H-4), 1.53-1.47 (m, 1H, H-6).

^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 176.0 (C2), 166.34 (C1''), 166.26 (C1''), 144.5 (C5''), 144.3 (C5''), 129.9, 129.7 (4C, C3''), 129.5, 129.4 (4C, C4''), 127.0, 126.7 (2C, C2''), 83.6 (C1'), 80.9, (C4'), 75.1 (C3'), 69.3 (C5), 64.5 (C5'), 37.2 (C6), 36.3 (C7), 34.8 (C2'), 31.5 (2C, C3, C4), 21.84, 21.82 (2C, 2 × CH_3).

3.2.6. Synthesis of 1-{2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl}-[(*tert*-butyldiphenylsilyl)-(*R*)-5-oxy]azepan-2-one (25*R*) and 1-{2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl}-[(*tert*-butyldiphenylsilyl)-(*S*)-5-oxy]azepan-2-one (25*S*)

To a stirring solution of **23*R*** or **23*S*** (1.80 g, 3.74 mmol) in dry DCM (100 mL) at 0 °C was added imidazole (1.00 g, 14.68 mmol) followed by TBDPS chloride (1.46 mL, 5.61 mmol) dropwise. After the addition, the reaction mixture was slowly brought to room temperature and continued stirring overnight. The reaction was monitored by TLC, after consumption of the starting material, 100 mL DCM was added to the reaction mixture and washed with water (20 mL) followed by brine (10 mL). The organic layer was separated, dried over anhydrous sodium

sulphate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel eluting with 0-30% EtOAc in hexane to afford the product **25** as a foam.



1-[2-deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-[(*tert*-butyldiphenylsilyl)-(*R*)-5-oxy]azepan-2-one (**25*R***):

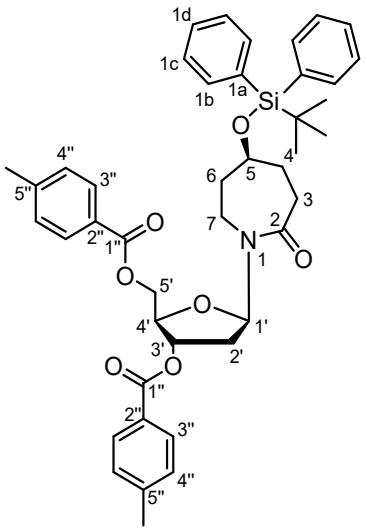
Yield: 2.30 g, 85%.

R_f = 0.40 in 30% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93-7.89 (m, 4H, H-1c); 7.61-7.58 (m, 4H, H-1b); 7.44-7.40 (m, 2H, H-1d); 7.37-7.32 (m, 4H, H-3''); 7.25-7.18 (m, 4H, H-4''); 6.58 (dd, 1H, J = 9.6, 5.32 Hz, H-1'); 5.50 (dt, 1H, J = 3.4, 2.6 Hz H-3'); 4.67 (dd, 1H, J = 11.9, 3.4 Hz, H-5'a); 4.56 (dd, 1H, J = 9.5, 5.5 Hz, H-5'b); 4.35 (td, 1H, J = 3.3, 1.8 Hz, H-4'); 4.00 (s, 1H, H-5); 3.76 (td, 1H, J = 14.6, 5.3 Hz, H-7); 3.17-3.08 (m, 2H, H-7, H-3); 2.41 (2s, 6H, CH_3); 2.24 (dd, 1H, J = 14.2, 8.5 Hz, H-3); 2.20 (dd, 1H, J = 14.6, 6.7 Hz, H-2'a); 2.10 (ddd, 1H, J = 16.3, 9.6, 6.7 Hz, H-2'b); 1.78-1.73 (m, 1H, H-4); 1.65-1.59 (m, 2H, H-6, H-4); 1.39 (t, 1H, J = 11.0 Hz, H-6); 1.04 (s, 9H, CH_3).

^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 176.4 (C2); 166.4 (1a); 166.2 (1a); 144.4 (C5''); 144.2 (C5''); 135.7 (2C, 1b); 134.1 (2C, 1b); 133.9 (C1''); 130.0, 129.7 (4C, 1c); 129.4, 129.3 (4C, C4''); 127.8, 126.8 (4C, C3''); 127.1, 126.7 (2C, 1d); 83.8 (C1'); 80.9, (C4'); 75.2 (C3'); 69.3 (C5); 64.5 (C5'); 37.5 (C6); 35.9 (C7); 34.9 (C2'); 31.3 (C3); 31.1 (C4); 27.1 (3C, C*CH$_3$*); 21.85, 21.82 (2C, C6'''); 19.4 (*C*CH$_3$).

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{43}H_{50}NO_7Si$ 720.3357; found 720.3340.



1-[2-Deoxy-3,5-di-*O*-(4-methylbenzoyl)-β-D-*erythro*-pentofuranosyl]-[(*tert*-butyldiphenylsilyl)-(*S*)-5-oxy]azepan-2-one (**25*S***):

Yield: 2.10 g, 78%.

R_f = 0.42 in 30% EtOAc in hexane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94-7.91 (m, 4H, H-c); 7.59-7.54 (m, 4H, H-b); 7.44-7.40 (m, 2H, H-d); 7.35-7.32 (m, 4H, H-3''); 7.25-7.20 (m, 4H, H-4''); 6.57 (dd, 1H, J = 9.3, 5.6 Hz, H-1'); 5.54-5.52 (m, 1H, H-3'); 4.67 (dd, 1H, J = 11.9, 3.2 Hz, H-5'a); 4.48 (dd, 1H, J = 11.9, 3.5 Hz, H-5'b); 4.29 (dt, 1H, J = 3.4, 2.0 Hz, H-4'); 3.94 (s, 1H, H-5); 3.67-3.62 (m, 1H, H-7); 3.08-3.03 (m, 1H, H-7); 2.96 (bs, 1H, H-3); 2.41 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 2.28 (dd, 1H, J = 13.9, 5.6 Hz, H-2'a); 2.27 (m, 1H, H-3); 2.25-2.17 (m, 2H, H-2'b); 1.72- 1.68 (m, 2H, H-4); 1.61-1.52 (m, 2H, H-6); 1.03 (s, 9H, CH_3).

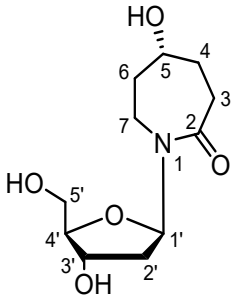
^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 176.38 (C2); 166.36, 166.21 (2C, C1''); 144.42, 144.22 (2C, C5''); 135.77, 135.74 (4C, C1b); 134.08, 133.87 (2C, C1a); 129.95, 129.66 (4C, C1c); 129.41, 129.34 (4C, C4''); 127.80, 126.79 (4C, C3''); 127.05, 126.74 (2C, C1d); 83.78 (1C, C1'); 80.93 (1C, C4'); 75.20 (1C, C3'); 69.31 (C1, C5); 64.48 (1C, C5'); 37.47 (1C, C6); 35.94 (1C, C7); 34.93 (1C, C2'); 31.25 (1C, C3); 31.11 (1C, C4); 27.10 (3C, C-*CH$_3$*); 21.85, 21.82 (2C, C6'''); 19.36 (1C, *C*-CH_3).

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{43}H_{50}NO_7Si$ 720.3357; found 720.3350.

3.2.7. Synthesis of 1-[2-deoxy-β-D-*erythro*-pentofuranosyl]-(*R*)-5-hydroxyazepan-2-one (24*R*) and 1-[2-deoxy-β-D-*erythro*-pentofuranosyl]-(*S*)-5-hydroxyazepan-2-one (24*S*)

Toluoyl-protected 2'-deoxynucleoside **23*R*** or **23*S*** (6.10 g, 12.67 mmol) was dissolved in MeOH (500 mL), and aq. ammonia (30%, 50 mL) was added in one portion. Reaction mixture

was stirred at room temperature for 3 days. Volatiles were evaporated *in vacuo*, co-evaporated with H_2O (2 × 200 mL), MeOH (200 mL) several times to get the desired product.



1-[2-Deoxy-β-D-*erythro*-pentofuranosyl]-(*R*)-5-hydroxyazepan-2-one (**24*R***):

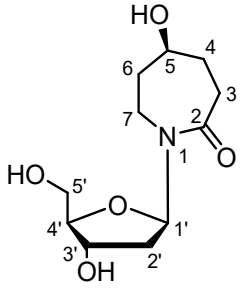
Yield: 2.25 g, 72%.

R_f = 0.35 in 30% MeOH in DCM.

^{1}H NMR (500 MHz, D_2O) δ 6.33 (dd, 1H, J = 8.0, 5.9 Hz, H-1'); 4.30-4.34 (m, 1H, H-3'); 4.01-3.95 (m, 1H, H-5); 3.88 (td, 1H, J = 4.0, 2.1 Hz, H-4'); 3.76 (dd, 1H, J = 12.2, 3.7 Hz, H-5'a); 3.69 (dd, 1H, J = 12.2, 5.4 Hz, H-5'b); 3.58 (dd, 1H, J = 15.8, 8.5 Hz, H-7); 3.30 (dd, 1H, J = 15.8, 9.0 Hz, H-7); 2.71 (t, 1H, J = 10.8 Hz, H-3); 2.48-2.41 (m, 1H, H-3); 2.18-2.12 (m, 1H, H-4); 2.07-2.04 (m, 1H, H-2'a); 2.03-1.95 (m, 3H, H-2'b, H4); 1.69-1.57 (m, 2H, H-6).

^{13}C{^{1}H} NMR (125.7 MHz, D_2O) δ 179.2 (C2); 85.2 (C4'); 83.6 (C1'); 71.0 (C3'); 69.5 (C5); 61.7 (C5'); 37.5 (C7); 35.9 (C6); 35.7 (C2'); 31.1 (C3); 30.0 (C4).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{19}NO_5Na$ 268.1161; found 268.1150.



1-[2-Deoxy-β-D-*erythro*-pentofuranosyl]-(*S*)-5-hydroxyazepan-2-one (**24*S***):

Yield: 2.46 g, 79%.

R_f = 0.35 in 30% MeOH in DCM.

^{1}H NMR (500 MHz, D_2O) δ 6.33 (dd, 1H, J = 8.5, 6.3 Hz, H-1'); 4.37-4.34 (m, 1H, H-3'); 3.98-3.94 (m, 1H, H-5); 3.89 (td, 1H, J = 4.3, 2.2 Hz, H-4'); 3.75 (dd, 1H, J = 12.3, 4.0 Hz, H-5'a); 3.68 (dd, 1H, J = 12.3, 5.6 Hz, H-5'b); 3.59 (dd, 1H, J = 15.9, 8.0 Hz, H-7); 3.27 (dd, 1H,

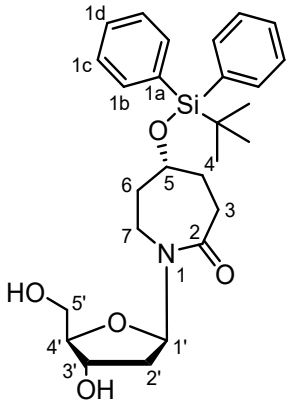
J = 15.9, 9.8 Hz, H-7); 2.67-2.51 (m, 2H, H-3); 2.21-2.15 (m, 1H, H-4); 2.08-1.98 (m, 2H, H-2'); 1.63-1.48 (m, 3H, H4, H-6).

$^{13}C\{^{1}H\}$ NMR (125.7 MHz, D_2O) δ 179.2 (C2); 85.1 (C4'); 83.4 (C1'); 71.1 (C3'); 70.0 (C5); 61.7 (C5'); 37.5 (C7); 35.74 (C6); 35.70 (C2'); 31.3 (C3); 30.2 (C4).

HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{19}NO_5Na$ 268.1161; found 268.1151.

3.2.8. Synthesis of 1-[2-deoxy-β-D-*erythro*-pentofuranosyl]-(*R*)-5-[(*tert*-butyldiphenylsilyl)-oxy]azepan-2-one (26*R*) and 1-[-2-deoxy-β-D-*erythro*-pentofuranosyl]-(*S*)-5-[(*tert*-butyldiphenylsilyl)-oxy]azepan-2-one (26*S*)

Compound **25*R*** or **25*S*** (1.20 g, 1.67 mmol) was dissolved in MeOH (100 mL) and aq. ammonia (30%, 15 mL) was added in one portion. Reaction mixture was stirred at room temperature for 3 days, evaporated all the volatiles, co-evaporated with H_2O (2 × 100 mL), MeOH (100 mL) several times to get **26*R*** or **26*S*** as a pure compound.



1-[2-Deoxy-β-D-*erythro*-pentofuranosyl]-(*R*)-5-[(*tert*-butyldiphenylsilyl)-oxy]azepan-2-one (**26*R***):

Yield: 0.72 g, 89%.

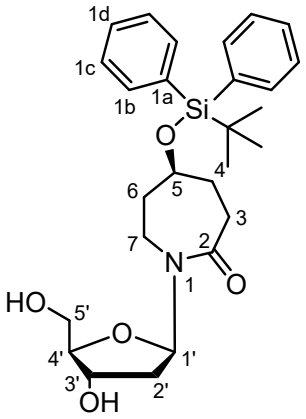
R_f = 0.40 in 20% MeOH in DCM.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.62 (m, 4H, H-1b); 7.44-7.41 (m, 2H, H-1d); 7.38-7.36 (m, 4H, H-1c); 6.27 (dd, 1H, *J* = 8.2, 6.5 Hz, H-1'); 4.32-4.29 (m, 1H, H-3'); 4.05 (s, 1H, H-5); 3.82 (td, 1H, *J* = 3.8, 2.8 Hz, H-4'); 3.81-3.79 (m, 1H, H-7); 3.76 (dd, 1H, *J* = 11.6, 3.8 Hz, H-5'a); 3.70 (dd, 1H, *J* = 11.6, 4.1, H-5'b); 3.50 (s, 1H, 3'-OH); 3.10 (d, *J* = 7.0Hz, 1H, H-7); 3.17 (d, *J* = 6.8 Hz, 1H, H-3); 2.93 (s, 1H, 5'-OH); 2.20 (dd, 1H, *J* = 14.1, 8.5 Hz, H-3); 2.05-1.99 (m, 1H, H-2'a); 1.96- 1.92 (ddd, *J* = 13.3, 6.1, 2.9 Hz, 1H, H-2'b); 1.78-1.72 (m, 2H, H-6, H-4); 1.63 (t, 1H, *J* = 13.2 Hz, H-4); 1.49 (m, 1H, H-6); 1.07 (s, 9H, CH_3).

$^{13}C\{^{1}H\}$ NMR (125.7 MHz, $CDCl_3$) δ 177.3 (C2); 135.82 (2C, C1b); 135.80 (2C, C1b); 134.0 (C1a); 133.9 (C1a); 129.97 (C1d); 129.95 (C1d); 127.8 (4C, C1c); 85.4 (C4'); 84.4 (C1');

72.0 (C3'); 69.2 (C5); 63.1 (C5'); 37.5 (H7); 37. 4 (C6); 37.0 (C2'); 31.1 (C3); 31.0 (C4); 27.1 (3C, C*CH*$_3$); 19.4 (*C*CH$_3$).

HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_{27}H_{38}NO_5Si$ 484.2519; found 484.2514.



1-[2-Deoxy-β-D-*erythro*-pentofuranosyl]-(*S*)-5-[(*tert*-butyldiphenylsilyl)-oxy]azepan-2-one (**26*S***):

Yield: 0.65 g, 80%.

R_f = 0.42 in 20% MeOH in DCM.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.61 (m, 4H, H-1b); 7.44-7.41 (m, 2H, H-1d); 7.38-7.35 (m, 4H, H-1c); 6.27 (dd, 1H, *J* = 7.8, 6.4 Hz, H-1'); 4.31-4.28 (m, 1H, H-3'); 4.00 (s, 1H, H-5); 3.79 (td, 1H, *J* = 4.1, 2.8 Hz, H-4'); 3.76-3.72 (m, 1H, H-7); 3.70 (dd, 1H, *J* = 11.4, 3.3 Hz, H-5'a); 3.64 (dd, 1H, *J* = 11.4, 4.1 Hz, H-5'b); 3.59 (s, 1H, 3'-OH); 3.03 (dd, 1H, *J* = 15.6, 6.9 Hz, H-7); 3.01-2.95 (m, 1H, H-3); 2.93 (s, 1H, 5'-OH); 2.23-2.18 (m, 1H, H-3); 2.10-2.04 (m, 1H, H-2'a); 2.0 (ddd, 1H, *J* = 13.6, 6.3, 3.2 Hz, H-2'b); 1.74-1.61 (m, 4H, H-6, H-4); 1.07 (s, 9H, CH_3).

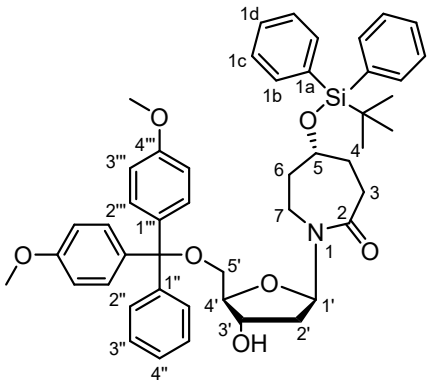
^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 176.9 (C2); 135.80 (2C, C1b); 135.79 (2C, C1b); 133.98 (C1a); 133.97 (C1a); 129.97 (C1d); 129.95 (C1d); 127.8 (4C, C1c); 85.5 (C4'); 84.8 (C1'); 72.0 (C3'); 69.7 (C5); 63.6 (C5'); 37.8 (H7); 37.5 (C2'); 37.3 (C6); 31.3 (C3); 31.2 (C4); 27.1 (3C, C*C*H3); 19.4 (*C*CH$_3$).

HRMS (ESI) *m/z*: [M+H]$^+$ Calcd for $C_{27}H_{38}NO_5Si$ 484.2519; found 484.2517.

3.2.9. Synthesis of 1-{2-deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl}-(*R*)-5-[(*tert*-butyldiphenylsilyl)oxy]azepan-2-one (27*R*) and 1-{2-deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl}-(*S*)-5-[(*tert*-butyldiphenylsilyl)oxy]azepan-2-one (27*S*)

To a stirring solution of a nucleoside **26*R*** or **26*S*** (0.40 g, 0. mmol) in dry pyridine (10 mL), 4,4'-*O*-dimethoxytrityl chloride (0.39 g, 1.15 mmol) was added at 0 °C and the mixture was

stirred at r.t. overnight under argon. After consumption of the starting nucleoside, water (1 mL) was added. Solvents were evaporated *in vacuo* and the residue was dissolved in 50 mL DCM and washed with brine (2 × 10 mL). Organic layer was dried over anhydrous sodium sulphate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography over silica gel (packed in 10% Et_3N in DCM and washed with DCM) and eluted with 0-5% MeOH in DCM to afford the desired product as a foam.



1-[2-Deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl]-(*R*)-5-[(*tert*-butyldiphenylsilyl)oxy]azepan-2-one (**27*R***):

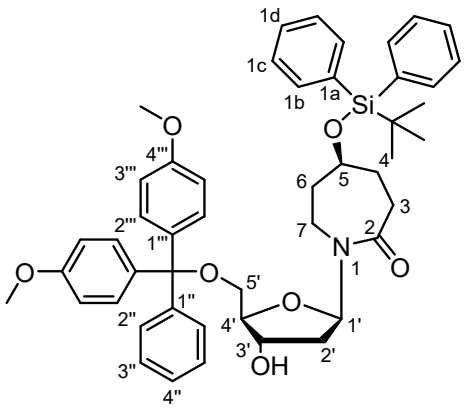
Yield: 0.58 g, 86%.

R_f = 0.45 in 5% MeOH in DCM.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.61 (m, 2H, H-b); 7.57-7.55 (m, 2H, H-b); 7.44-7.40 (m, 3H, H-1d, H-4"); 7.37-7.29 (m, 7H, H-1c, H-2", H-2'''); 7.27-7.19 (m, 5H, H-1c, H-2'''); 6.84- 6.81 (m, 4H, H-3'''); 6.51 (dd, 1H, J = 8.1, 6.6 Hz, H-1'); 4.38-4.36 (m, 1H, H-3'); 4.01 (s, 1H, H-5); 3.89 (td, 1H, J = 3.9, 2.2 Hz, H-4'); 3.78 (s, 6H, OCH_3); 3.32 (m, 2H, H-5'); 3.12 (bs, 1H, H-4); 2.81 (m, 2H, H-7); 2.23 (dd, 1H, J = 14.0, 8.6 Hz, H-4); 2.03-1.96 (m, 2H, H-2'); 1.80-1.74 (m, 1H, H-3); 1.71-1.63 (m, 2H, H-6, H-3); 1.48-1.40 (m, 1H, H-6); 1.03 (s, 9H, CH_3).

^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 176.7 (C2); 158.9 (2C, C4'''); 144.8 (C1"); 135.9 (2C, C1a); 135.77, 135.75 (4C, C1b); 134.0, 133.9 (2C, C1'''); 130.2 (4C, C2'''); 129.91, 129.86 (2C, C2"); 128.3, 128.0 (2C, C1d); 127.79, 127.77 (4C, C1c); 127.0 (2C, C4"); 113.3 (4C, C3'''); 86.6 (CAr$_3$); 84.4 (C4'); 83.1 (C1'); 73.2 (C3'); 69.2 (C5); 64.3 (C5'); 55.3 (2C, OCH_3); 46.2 (C7); 37.8 (C6); 31.2 (C3); 31.0 (C4); 27.1 (3C, CCH_3); 19.4 (CCH_3).

HRMS (ESI) *m*/*z*: [M+Na]$^+$ Calcd for $C_{48}H_{55}NNaO_7Si$ 808.3645; found 808.3640.



1-[2-Deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl]-(*S*)-5-[(*tert*-butyldiphenylsilyl)oxy]azepan-2-one (**27*S***):

Yield: 0.53 g, 81%.

R_f = 0.45 in 5% MeOH in DCM.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.61 (m, 2H, H-1b); 7.58-7.57 (m, 2H, H-1b); 7.44-7.39 (m, 3H, H-1d, H-2''); 7.38-7.34 (m, 3H, H-2'', H-1c); 7.31-7.28 (m, 6H, H-2''', H-3''); 7.25-7.18 (m, 3H, H4'', H-1c); 6.82-6.79 (m, 4H, H-3'''); 6.48 (dd, 1H, J = 8.1, 6.6 Hz, H-1'); 4.40 (m, 1H, H-3'); 4.00 (s, 1H, H-5); 3.85 (td, 1H, J = 3.5, 2.2 Hz, H-4'); 3.78 (2s, 6H, OCH_3); 3.33-3.25 (m, 2H, H-5'); 3.20-3.17 (m, 1H, H-4); 2.99 (bs, 1H, H-4); 2.78 (m, 2H, H-7); 2.28-2.23 (m, 1H, H-6); 2.13- 2.07 (m, 2H, H2'); 1.78-1.73 (m, 1H, H-3); 1.66-1.62 (m, 2H, H-6, H-3); 1.08 (s, 9H, CH_3).

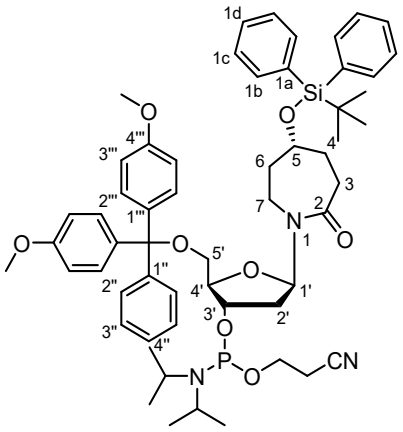
^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 176.3 (C2); 158.7 (2C, C4'''); 145.0 (C1''); 135.9 (2C, C1a); 135.79, 135.77 (4C, C1b); 134.01, 133.96 (2C, C1'''); 130.2 (4C, C2'''); 129.92, 129.88 (2C, C2''); 128.15, 127.96 (2C, C1d); 127.98, 127.8 (4C, C1c); 127.0 (C4''); 113.3 (4C, C3'''); 86.4 (*C*Ar$_3$); 84.3 (C4'); 83.5 (C1'); 73.0 (C3'); 69.8 (C5); 63.9 (C5'); 55.3 (2C, OCH_3); 46.2 (C7); 38.1 (C6); 31.3 (C3); 31.2 (C4); 27.1 (3C, C*C*H$_3$); 19.4 (*C*CH$_3$).

HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $C_{48}H_{55}NNaO_7Si$ 808.3645; found 808.3633.

3.2.10. Synthesis of 1-{3-*O*-(*N*,*N*-di*iso*propylamino-2-cyanoethoxyphosphanyl)-2-deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl}-(*R*)-5-[(*tert*-butyldiphenylsilyl)oxy]azepan-2-one (28*R*) and 1-{3-*O*-(*N*,*N*-di*iso*propylamino-2-cyanoethoxyphosphanyl)-2-deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl}-(*R*)-5-[(*tert*-butyldiphenylsilyl)oxy]azepan-2-one (28*S*)

To a stirring solution of the compound **27*R*** or **27*S*** (0.40 g, 0.51 mmol) in dry DCM (10 mL) under argon at r.t. were added Et_3N (0.12 ml, 0.86 mmol) followed by 2-cyanoethyl-*N*,*N*-di*iso*propyl chlorophosphoramidite (0.17 g, 0.72 mmol). After the disappearance of the starting

material on TLC in 20 min the reaction mixture was washed with saturated sodium bicarbonate solution (2 × 5 mL) followed by brine (5 mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and the combined fractions were evaporated *in vacuo*. The crude product was purified by column chromatography over silica gel (60-120 mesh, packed in Et_3N (10%) in DCM and washed with DCM) and eluted with DCM/acetone (9:1) to give a white foam.



1-[3-*O*-(*N*,*N*-di*iso*propylamino-2-cyanoethoxyphosphanyl)-2-deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl]-(*R*)-5-[(*tert*-butyldiphenylsilyl)oxy]azepan-2-one (**28*R***):

Yield: 0.45 g, 90%.

R_f = 0.40 in 10% acetone in DCM.

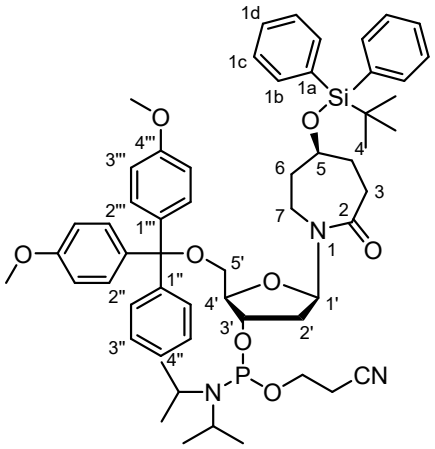
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.59-7.55 (m, 2H, H-1b); 7.51-7.48 (m, 2H, H-1b); 7.45-7.41 (m, 1H, H-4''); 7.40-7.35 (m, 6H, H-2'' H-1c); 7.29-7.19 (m, 8H, H-2''', H-3'', H-1d); 6.88-6.83 (m, 4H, H-3'''); 6.25 (dd, 1H, J = 8.45, 6.10 Hz, H-1'); 4.44-4.38 (m, 1H, H-3'); 3.98-4.02 (m, 1H, H-5); 3.92-3.85 (m, 1H, H-4'); 3.70 (s, 6H, OCH_3); 3.62-3.57 (m, 2H, CH_2CH$_2$CN); 3.57-3.55 (m, 1H, H-7); 3.54-3.43 (m, 2H, NCHCH$_3$); 3.29 (bs, 1H, H-4); 3.19-3.09 (m, 2H, H-5'); 2.73, 2.62 (2t, J = 5.9 Hz, CH$_2$CH_2CN); 2.21-2.15 (m, 1H, H-7); 2.08-2.10 (m, 1H, H-2'a); 1.97-1.86 (m, 1H, H-2'b); 1.69-1.59 (m, 2H, H-3); 1.58-1.52 (m, 2H, H-6); 1.19-1.06 (m, 12H, NCHCH_3); 0.96 (s, 9H, CH$_3$).

^{13}C{^{1}H} NMR (125.7 MHz, DMSO-d_6) δ 174.9 (C2); 158.12, 158.08 (2C, C4'''); 144.6 (C1''); 135.5, 135.3 (2C, C1a); 135.14, 135.09 (4C, C1b); 133.5, 133.2 (2C, C1'''); 129.84, 129.81, 129.7 (4C, C2'''); 129.60, 129.56 (2C, C2''); 127.78, 127.72 (2C, C1d); 127.98, 127.78 (4C, C1c); 126.7 (C4''); 118.9, 118.7 (CN); 113.1 (4C, C3'''); 85.65, 85.63 (1C, CAr$_3$); 82.7, 82.4 (C4'); 82.3 (C1'); 73.8 (C3'); 70.0 (C5); 63.3 (C5'); 58.4, 58.3, 58.22, 58.16 (2C, CCH$_3$); 55.0 (2C, OCH$_3$); 44.7, 44.51 (CH$_2$CH$_2$CN); 42.54, 42.47, 42.44 (2C, NCHCH$_3$); 37.0 (C6);

36.19 (C2'); 36.18 (C7); 30.7 (C4); 36.0 (C3); 26.7 (3C, C-*C*H_3); 24.32, 24.29, 24.23, 24.17, 24.10 (NCH*C*H_3); 19.8, 19.7 (CH_2*C*H_2CN).

$^{31}P\{^1H\}$ NMR (202.5 MHz, DMSO-d_6, ref. 85% H_3PO_4) δ 147.1, 146.6 in ~1:1 ratio.

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{57}H_{72}N_3O_8PSi$ 986.4905; found 985.5869.



1-[3-*O*-(*N*,*N*-di*iso*propylamino-2-cyanoethoxyphosphanyl)-2-deoxy-5-*O*-(4,4'-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl]-(*S*)-5-[(*tert*-butyldiphenylsilyl)oxy]azepan-2-one (**28*S***)

Yield: 0.43 g, 86%.

R_f = 0.41 in 10% acetone in DCM.

^1H NMR (500 MHz, DMSO-d_6) δ 7.57-7.55 (m, 2H, H-1b); 7.53-7.51 (m, 2H, H-1b); 7.45-7.41 (m, 1H, H-4''); 7.40-7.30 (m, 7H, H-2'', H-1c, H-1d); 7.25-7.17 (m, 6H, H-2''', H-3''); 6.85-6.81 (m, 4H, H-3'''); 6.23 (dd, 1H, *J* = 8.0, 6.0 Hz, H-1'); 4.44-4.38 (m, 1H, H-3'); 3.95 (bs, 1H, H-5); 3.87-3.81 (m, 1H, H-4'); 3.70 (s, 6H, OCH_3); 3.61-3.57 (m, 2H, C$H_2$$CH_2$CN); 3.56-3.44 (m, 2H, NC$H$$CH_3$); 3.18-3.11 (m, 2H, H-5'); 3.10-3.05 (1H, H-4); 2.75, 2.70 (bs, 1H, H-7); 2.62 (2t, *J* = 5.8 Hz, CH_2CH_2CN); 2.28-2.23 (1H, H-7); 2.14-2.08 (m, 1H, H-2'a); 2.03-1.92 (m, 1H, H-2'b); 1.73-1.68 (m, 1H, H-3); 1.64-1.57 (m, 2H, H-6, H-3); 1.54-1.47 (m, 1H, H-6); 1.12-1.08 (m, 9H, NCHCH_3); 1.00 (s, 9H, CH_3); 0.97, 0.96 (2s, NCHCH_3).

$^{13}C\{^1H\}$ NMR (125.7 MHz, DMSO-d_6) δ 174.6 (C2); 158.1 (2C, C4'''); 144.7 (C1''); 135.4 (2C, C1a); 135.2, 135.1 (4C, C1b); 133.44, 133.40 (2C, C1'''); 129.85, 129.82, 129.69 (4C, C2'''); 127.79 (2C, C1d); 127.74 (4C, C1c); 129.68, 129.63 (2C, C2''); 127.5 (C4''); 118.7 (*C*N); 113.1 (4C, C3'''); 85.6 (*C*Ar_3); 82.6 (C4'); 82.3 (C1'); 73.8 (C3'); 70.0 (C5); 63.3 (C5'); 58.4, 58.3, 58.22, 58.16 (N*C*$H_2$$CH_2$CN); 55.0 (2C, OCH_3); 44.66, 44.51, (*C*$H_2$$CH_2$CN); 42.55, 42.48, (2C, N*C*HCH_3); 37.0 (C6); 36.2 (C7); 36.0 (C3); 30.7 (C4); 26.8 (3C, C*C*H3); 24.35, 24.29, 24.25, 24.19, 24.11 (4C, NCH*C*H_3); 19.8 (CH_2*C*H_2CN).

$^{31}P\{^{1}H\}$ NMR (202.5 MHz, DMSO-d_6, ref. 85% H_3PO_4) δ 147.2, 146.7 in ~1:1 ratio.

HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $C_{57}H_{72}N_3O_8PSi$ 986.4905; found 985.5860.

3.3. X-Ray data collection and analysis for compounds 22S and 22R

Single-crystal X-ray diffraction data for 1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-(*S*)-5-benzyloxyazepan-2-one (**22S**) and its diastereomer 1-[2-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-β-D-erythro-pentofuranosyl]-(*R*)-5-benzyloxyazepan-2-one (**22R**) were collected on a Rigaku Spider/Rapide image plate with Cu Kα radiation generated by a Rigaku MM007 microfocus X-ray generator and monochromated and focused with Rigaku VariMax-HF Confocal optical system at 150 K and 293 K, respectively. Absolute configuration was determined from anomalous dispersion (Flack parameters: −0.02(9) and −0.2(3), respectively) and confirmed by known stereochemistry of the 2-deoxy-D-ribose group. Both structures are in space group *C*2, but the axially more convenient *I*2 setting was used for the latter structure. By virtue of low temperature, (**22S**) is more precise, with final R_1 (observed data) of 0.0536 and w*R*2 (all data) of 0.1481 for 381 parameters, 4471 unique data and 1 restraint. Corresponding values for (**22R**), which also suffered from looser packing of molecules and disorder of toluoyl and benzyl groups that necessitated geometric restraints, are 0.0693, 0.2414, 380, 4270 and 187.

3.4. Oligonucleotide synthesis and purification

Oligonucleotides were prepared on a MerMade-4 DNA/RNA synthesizer (BioAutomation) on a 5 μmol scale using standard manufacturer's protocol. Coupling times of modified phosphoramidites were increased from 2 to 10 min. The final detritylated oligos were cleaved from the solid support and deprotected at r.t. using conc. NH_4OH. The deprotected oligos in solution were freeze-dried and dry pellets were dissolved in milli-Q water (1 mL) and purified by reverse-phase HPLC on 250/4.6 mm, 5 μm, 300 Å C18 column (Thermo Fisher Scientific) in a gradient of CH_3CN (0→20% for 20 min, 1.3 mL/min) in 0.1 M TEAA buffer (pH 7.0) with a detection at 260 nm. For the deprotection of the TBDPS protecting group in oligos, the dry pellets were suspended in 100 μL $Et_3N{\cdot}3HF$, and the mixture was kept at 22 °C for 30 min. The reaction mixture was quenched by the addition of 2 M TEAA buffer (pH 7.0) and oligos were purified by reverse-phase HPLC on 250/4.6 mm, 5 μm, 300 Å C18 column (Thermo Fisher Scientific) in a gradient of CH_3CN (0→20% for 20 min, 1.3 mL/min) in 0.1 M TEAA buffer (pH 7.0) with a detection at 260 nm. Oligonucleotides were freeze-dried, pellets were dissolved in milli-Q water (1.5 mL) and desalted by reverse-phase HPLC on 100/10 mm, 5μm, 300 Å C18 column (Phenomenex) in a gradient of CH_3CN (0→80% for 15 min, 5 mL/min) in milli-Q water with detection at 260 nm. Pure products were quantified by measuring absorbance at 260 nm, analysed by ESI-MS and concentrated by freeze-drying.

Table S1. List of oligos synthesised.

Name	DNA sequence, 5'→3'	ε_{260} ($L \cdot mol^{-1} \cdot cm^{-1}$)	Retention time (min)[a)]	ESI-MS [Da] found/calculated
7-mer dZ-linear	TTTT**dZ**AT	84800	14.2	2045.3722/2045.3675
9-mer dDiAzep	ATTT-**dDiAzep-**ATTT	83000	15.9	2679.4839/2678.5024
7-mer *R*-dAzep-OH	TTTT-***R*-dAzep-OH-**AT	58900	14.9	2078.3888/2078.4141
7-mer *S*-dAzep-OH	TTTT-***S*-dAzep-OH-**AT	58900	14.8	2078.3824/2078.4141
dDiAzep-hairpin	TGCGCTT-**dDiAzep-**GCGCT	110400	14.3	3916.6466/3916.6907
***S*-dAzep-OH-**hairpin	TGCGCTT-***S*-dAzep-OH-**GCGCT	110400	14.0	3934.6458/3933.7059
FdZ-hairpin	$(GC)_2$TT **FdZ** $(GC)_2$	110400	14.7	3311.50/3310.60

a) Reverse-phase HPLC on 250/4.6 mm, 5 µm, 300 Å C18 column (Thermo Fisher Scientific) in a gradient of CH_3CN (0→20% for 20 min, 1.3 mL/min) in 0.1 M TEAA buffer (pH 7.0) with a detection at 260 nm.

3.5. Quantitative evaluation of hCDA inhibitors

Kinetic analysis of dC deamination by hCDA (27 nM, Sigma-Aldrich, now Merck) was performed using Cary 300Bio UV-vis spectrophotomer with temperature controller (Varian) by recording absorbance at 286 nm of dC (1.5-2.0 mM) in 50 mM Na^+/K^+ phosphate buffer (pH 7.4) supplemented with 100 mM NaCl and 1 mM TCEP at 25 °C. Quartz cuvette with 1 mm pathlength was used.

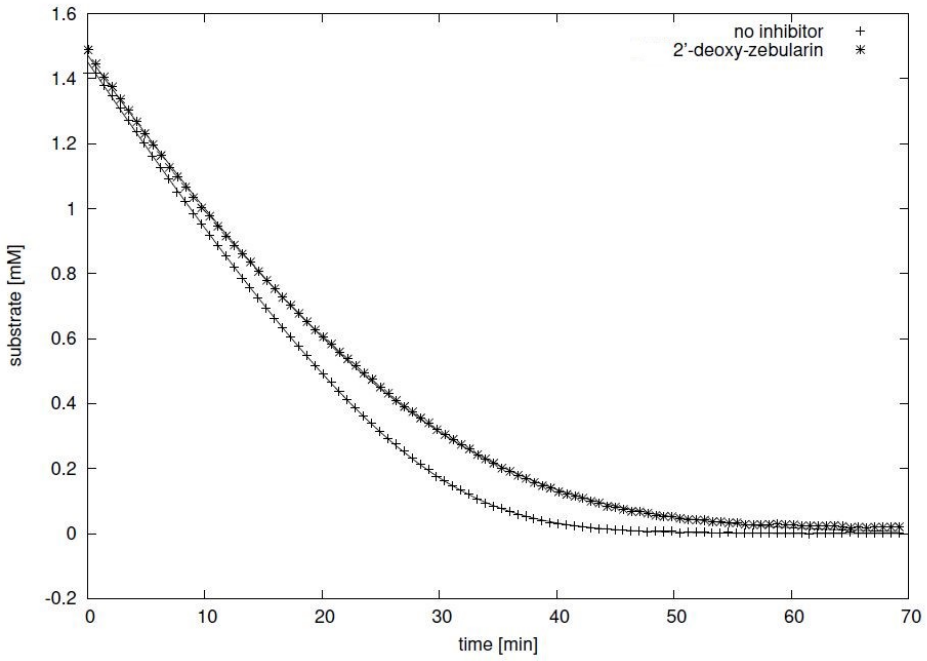


Figure S4. Cytidine deaminase-catalysed deamination of 2'-deoxycytidine.

UV-Vis spectroscopy at 286 nm of a 2 mM solution of 2'-deoxycytidine in the presence of 27 nM hCDA. The uninhibited deamination (pluses) and the reaction inhibited by the addition of 5 μM dZ start at about the same speed. However, as the reaction progresses, the inhibited reaction becomes slower, as its observed apparent K_m is larger than that in the uninhibited case. To be able to visualise the fitted curves, only every 5th data point is plotted.

The data were then fitted to the integrated Michaelis Menten equation:

$$[mm]_t = K_m W\left(\frac{c}{K_m}.e^{\frac{c - V_{max}t}{K_m}}\right) + d$$

where W is Lambert's W function, $[mm]_t$ the current substrate concentration with respect to the time t, $[S]_0$ is the initial substrate concentration, V_{max} and K_m^{obs} are the Michaelis-Menten

constants (K_m^{obs} is a real K_m if the inhibitor is absent) and t is the time, c the initial substrate concentration, and d a baseline correction parameter.

Two exemplary curves of enzyme-catalysed deamination are shown **Figure S4**. One reaction as control has only substrate and enzyme, while the second reaction contains 5 µM of 2'-deoxyzebularine (dZ). For each inhibitor, several time-course reactions were recorded for different inhibitor concentrations. To get an average K_i value, the observed K_m^{obs} values were plotted versus the inhibitor concentration [I] (**Figure S5** and **Figure S6**). A linear fit of this data (observed K_m^{obs} versus [I] as $y = a+bx$) has the noninhibited CDA K_m as y-axis intersection.

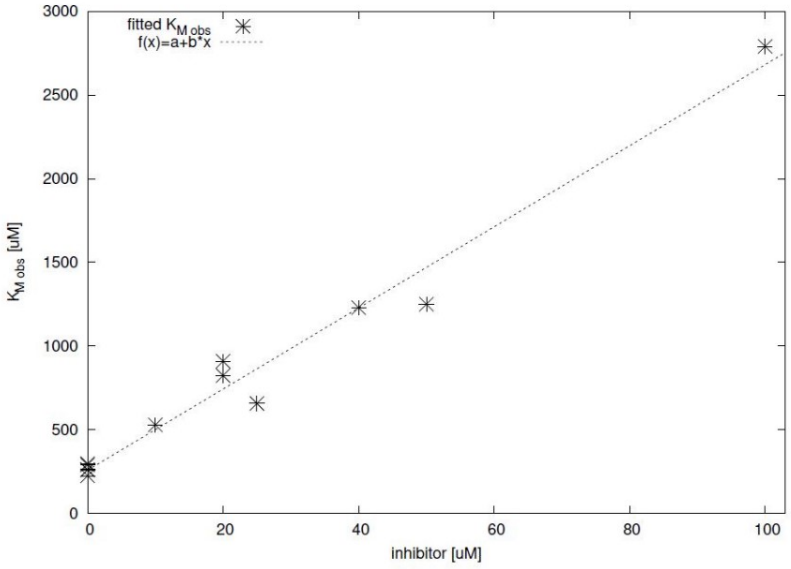


Figure S5. Plot of fitted K_m^{obs} values vs dZ concentration at pH 7.4.

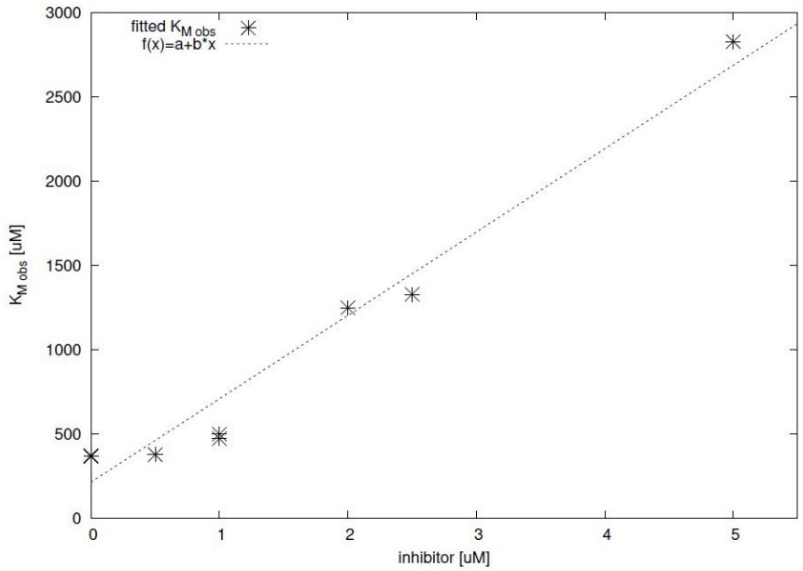


Figure S6. Plot of fitted K_m^{obs} values vs concentration of **dDiAzep** at pH 7.4.

3.6. Qualitative evaluation of linear inhibitors of $A3B_{CTD}$-catalysed deamination using ^1H NMR assay

Competitive inhibition of the synthesised oligonucleotides was performed by a similar procedure reported by us previously.[4-6] Data acquisitions were done on a 700-MHz Bruker NMR spectrometer equipped with a 1.7 mm cryoprobe at 293 K. A series of ^1H NMR spectra was recorded using 400 μM of a standard 7-mer oligonucleotide substrate 5'-T_4CAT, inhibitor at concentrations specified in Figure 5 in the main text, 300 nM of $A3B_{CTD}$-QM-ΔL3-AL1swap in a buffer containing 50 mM sodium phosphate (pH 6.0), 100 mM NaCl, 2.5 mM β-mercaptoethanol, 50 μM TSP. The H-5 proton doublet signal of the cytosine, which appears at 5.88 ppm (J = 7.7 Hz), was baselined and integrated. The signal of TSP at 0 ppm was used as an internal standard to determine the concentration of the substrate and its conversion during the reaction to the product, for which the signal appears at 5.71 ppm (J = 8.3 Hz). The area of the integrated signal was converted to substrate concentration and plotted versus reaction time. Linear regression was used to fit the data to determine the initial speed of the reaction.

3.7. Evaluation of modified hairpins as inhibitors of His_6-A3A-catalysed deamination of dC-hairpin using Lambert's W function

Time-resolved ^1H NMR kinetics were measured in 50 mM K^+/Na^+ phosphate buffer (pH 7.4) supplemented with 100 mM NaCl, 1 mM TCEP, 100 μM sodium trimethylsilylpropanesulfonate (DSS) and 10% D_2O. Substrate (dC-hairpin, TGCGCTTCGCGCT, underlined C is deaminated) was at 500 μM concentration. Reaction was performed in the presence of 140 nM of His_6-A3A at 293 K. The course of the reaction was followed by ^1H NMR until the substrate was consumed (28 hours). Subsequently the amount of substrate or product at each time point was calculated by integrating the decreasing substrate peak at 7.752 ppm (singlet) or the increasing product peak at 5.726 ppm (doublet) and calibrated by the area of DSS standard peak at 0.0 ppm. Using the known concentration of the standard, the peak was converted to a corresponding substrate concentration. The time at which each spectrum was recorded as a difference to the first spectrum was used as the time passed. The product or substrate concentration *versus* the time of reaction was plotted and fitted using the integrated form of the Michaelis-Menten equation:

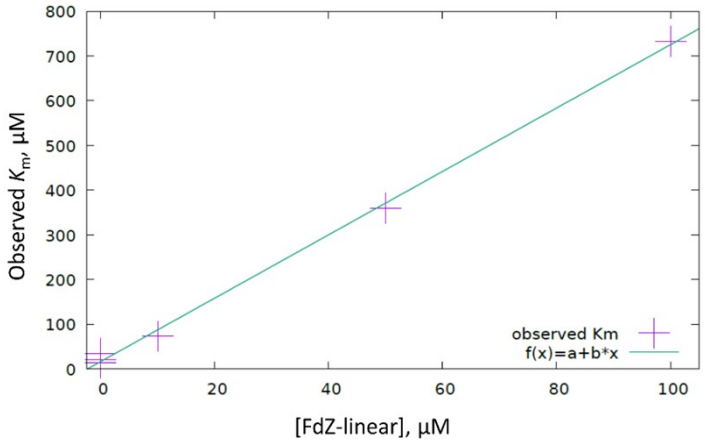
$$[S]_t = K_m\, W\left(\frac{[S]_0}{K_m} \cdot e^{\frac{[S]_0 - V_{max}\, t}{K_m}}\right)$$

where W is Lambert's W function, $[S]_t$ is the substrate concentration at specific time, $[S]_0$ is the initial substrate concentration, V_{max} and K_m are the Michaelis-Menten constants and t is

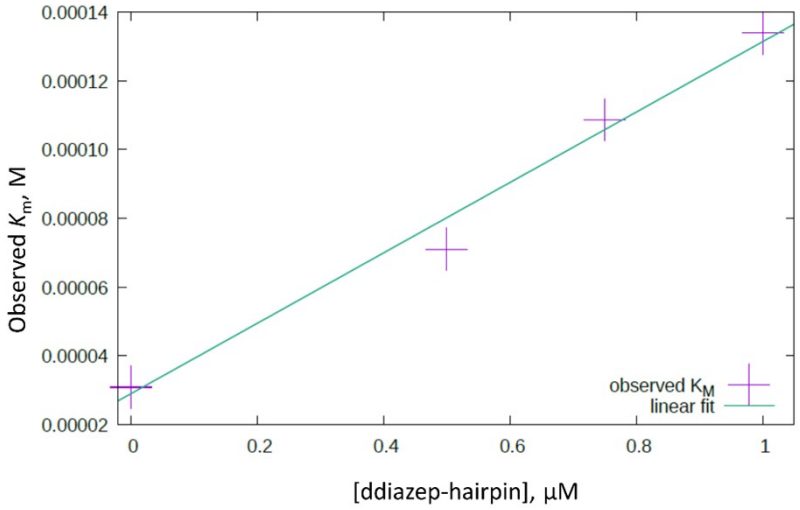
the time. The two Michaelis Menten constants, the initial substrate concentration and an offset which corrects for the integration baseline in the NMR spectra were fitted using Lambert's W function in Gnuplot.

By varying the concentration of an inhibitor, the plots of observed K_m versus inhibitor concentration were obtained (**Figure S7**) and K_i values were calculated. This allowed determination of K_m of the substrate (21 ± 10 μM in **Figure S7**A, B and 33 ± 7 μM in **Figure S7**C) and K_i of inhibitors (Table 3 in the main text).

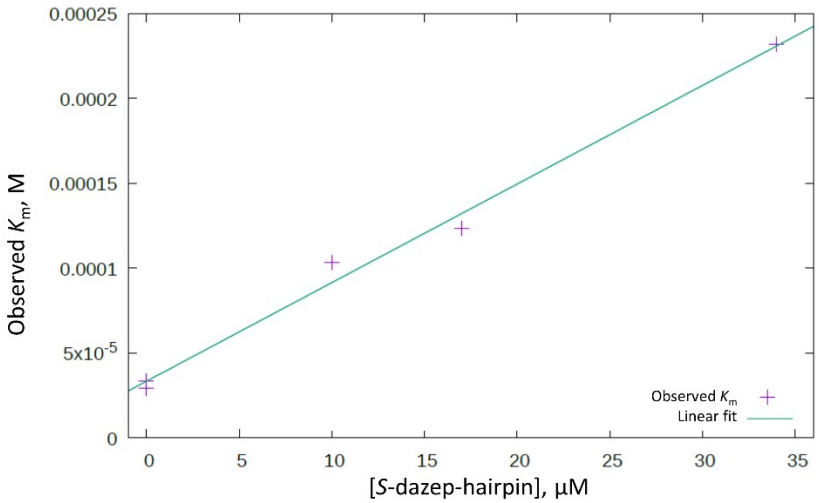
A)



B)



C)



D)

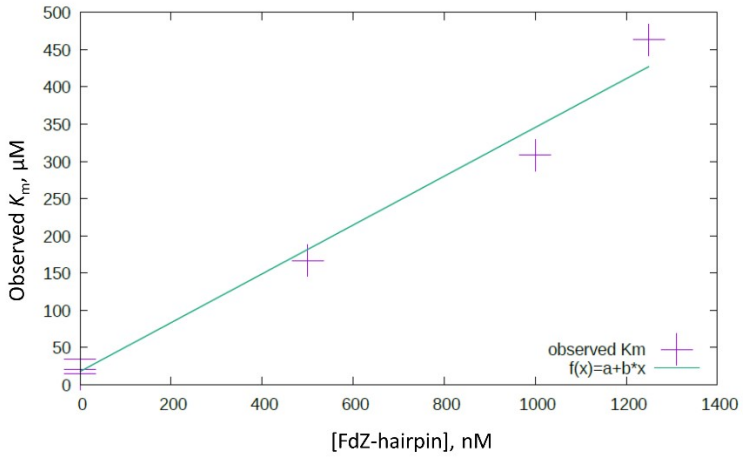


Figure S7. Observed K_m values of His_6-A3A catalysed deamination of dC-hairpin versus concentrations of **FdZ**-linear (A), **dDiAzep**-hairpin (B), ***S*-dAzep-OH**-hairpin (C), and **FdZ**-hairpin (D)and the linear fit of the data (solid line).

4. References:

(1) Tarkin-Tas, E.; Mathias, L. J. (2010) Synthesis and Ring-Opening Polymerization of 5-Azepane-2-one Ethylene Ketal: A New Route to Functional Aliphatic Polyamides, *Macromolecules 43*, 968-974.

(2) Schunk, S.; Linz, K.; Frormann, S.; Hinze, C.; Oberbörsch, S.; Sundermann, B.; Zemolka, S.; Englberger, W.; Germann, T.; Christoph, T. (2014) Discovery of spiro [cyclohexane-dihydropyrano [3, 4-b] indole]-amines as potent NOP and opioid receptor agonists, *ACS Med. Chem. Lett. 5*, 851-856.

(3) Perveen, S.; Abdul Hai, S. M.; Khan, R. A.; Khan, K. M.; Afza, N.; Sarfaraz, T. B. (2005) Expeditious Method for Synthesis of Symmetrical 1, 3-Disubstituted Ureas and Thioureas, *Synth. Commun. 35*, 1663-1674.

(4) Kvach, M. V.; Barzak, F. M.; Harjes, S.; Schares, H. A.; Jameson, G. B.; Ayoub, A. M.; Moorthy, R.; Aihara, H.; Harris, R. S.; Filichev, V. V. (2018) Inhibiting APOBEC3 Activity with Single-Stranded DNA Containing 2′-Deoxyzebularine Analogues, *Biochemistry 58*, 391-400.

(5) Kvach, M. V.; Barzak, F. M.; Harjes, S.; Schares, H. A.; Kurup, H. M.; Jones, K. F.; Sutton, L.; Donahue, J.; D'Aquila, R. T.; Jameson, G. B. (2020) Differential Inhibition of APOBEC3 DNA-Mutator Isozymes by Fluoro-and Non-Fluoro-Substituted 2′-Deoxyzebularine Embedded in Single-Stranded DNA, *ChemBioChem 21*, 1028.

(6) Barzak, F. M.; Harjes, S.; Kvach, M. V.; Kurup, H. M.; Jameson, G. B.; Filichev, V. V.; Harjes, E. (2019) Selective inhibition of APOBEC3 enzymes by single-stranded DNAs containing 2′-deoxyzebularine, *Org. Biomol. Chem. 17*, 9435-9441.

5. Experimental data for compounds synthesized

^{1}H NMR (500 MHz, $CDCl_3$)

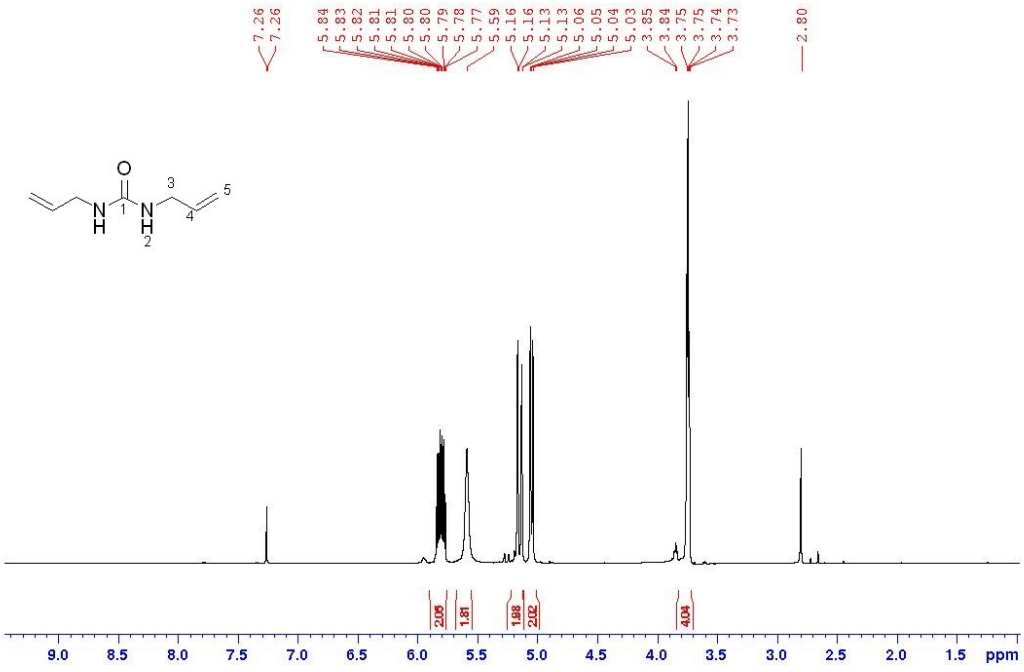


Figure S8. ^{1}H NMR spectrum of compound **2**.

^{13}C NMR (125.7 MHz, $CDCl_3$)

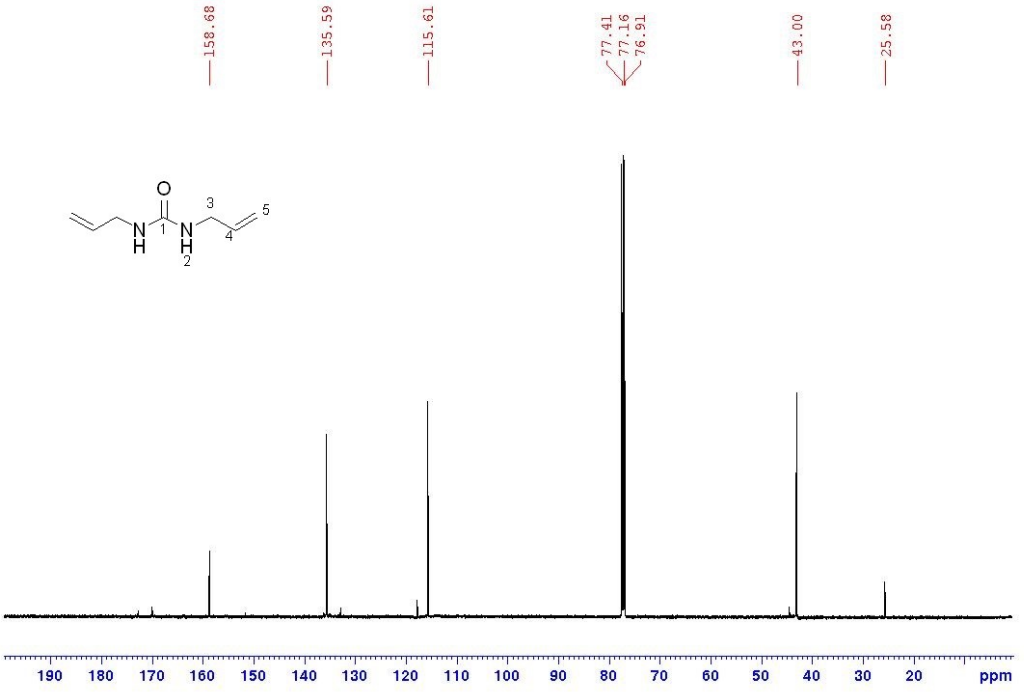


Figure S9. ^{13}C NMR spectrum of compound **2**.

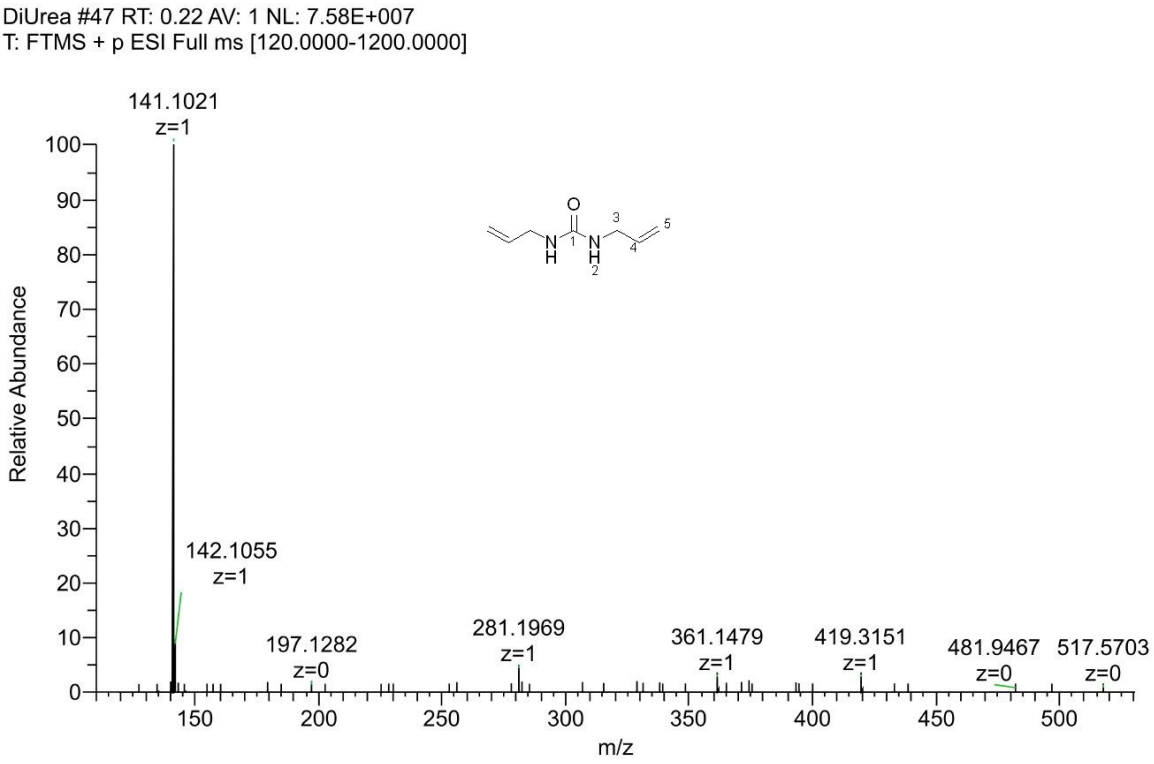


Figure S10. HRMS (ESI) of compound **2**.

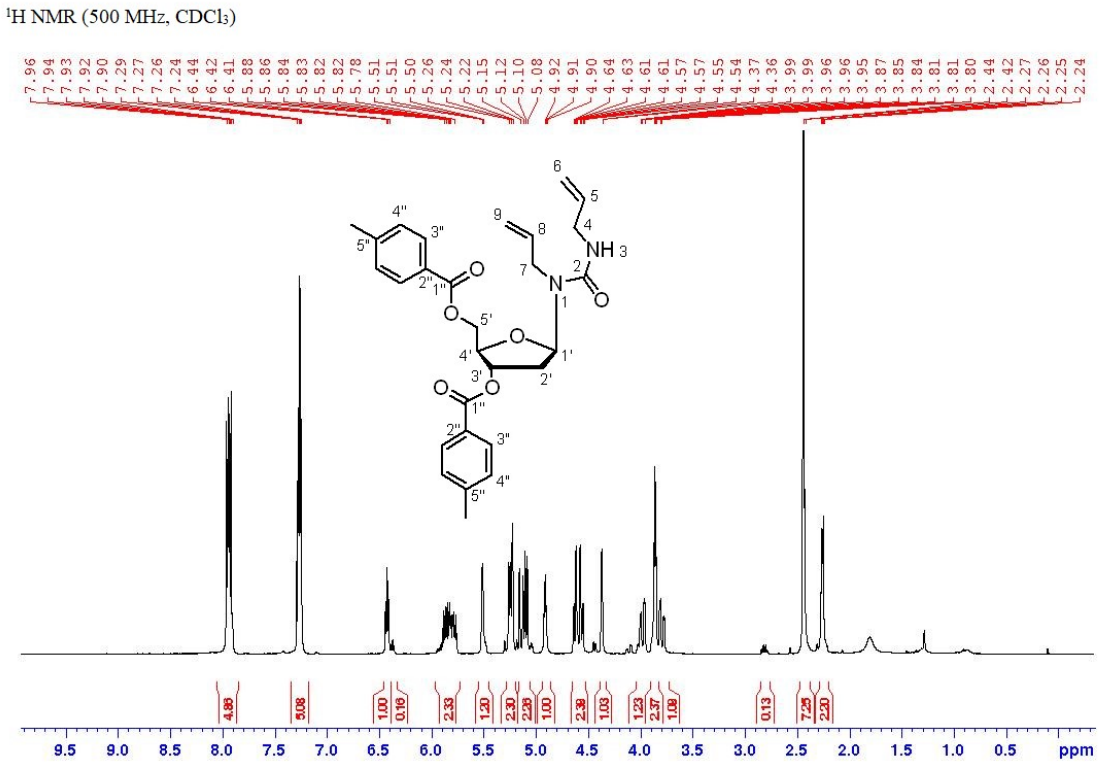


Figure S11. ^{1}H NMR spectrum of compound **3**.

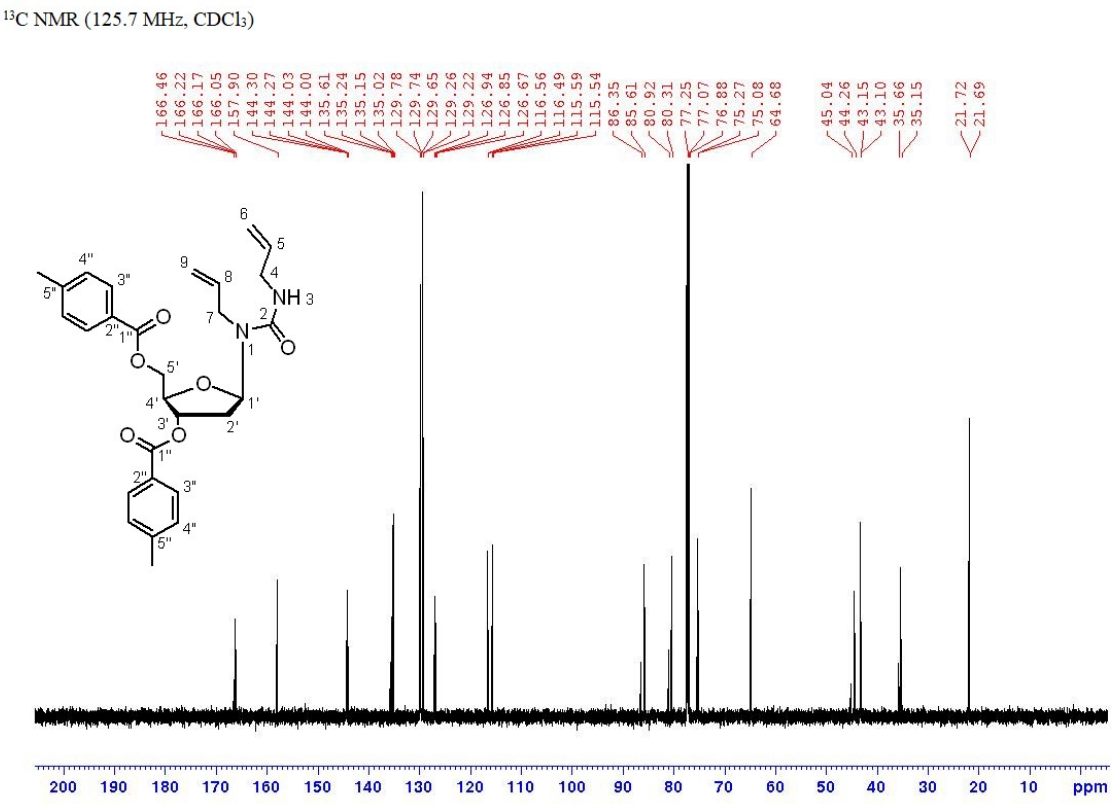


Figure S12. ^{13}C NMR spectrum of compound **3**.

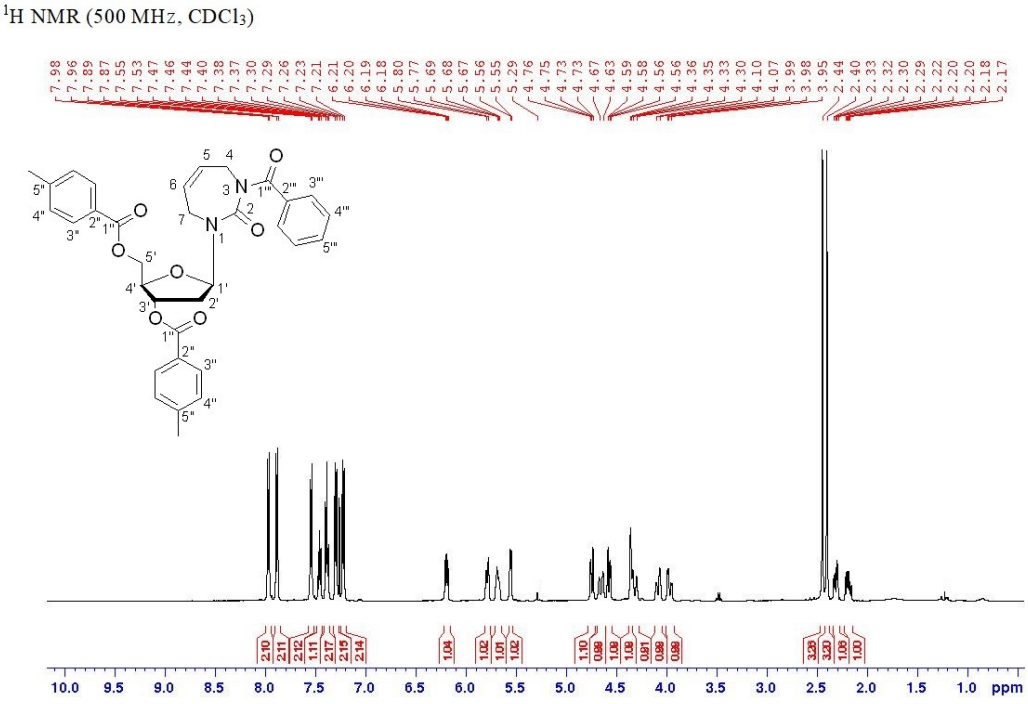


Figure S13. ^{1}H NMR spectrum of compound **5**.

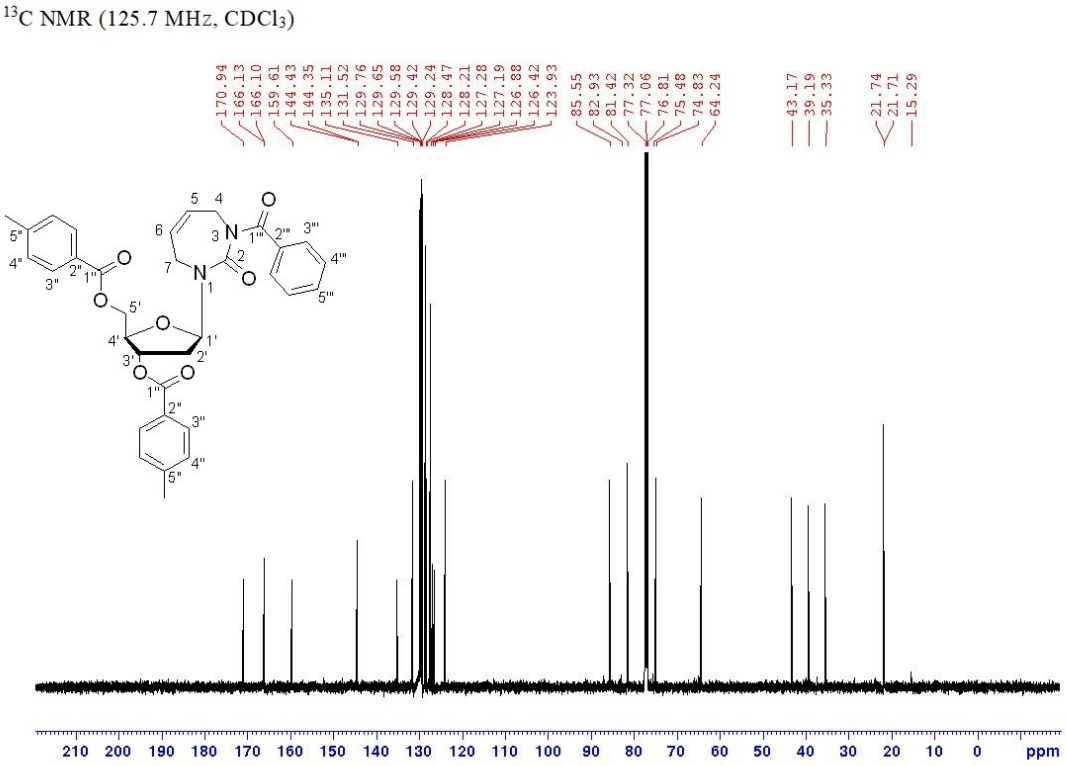


Figure S14. ^{13}C NMR spectrum of compound **5**.

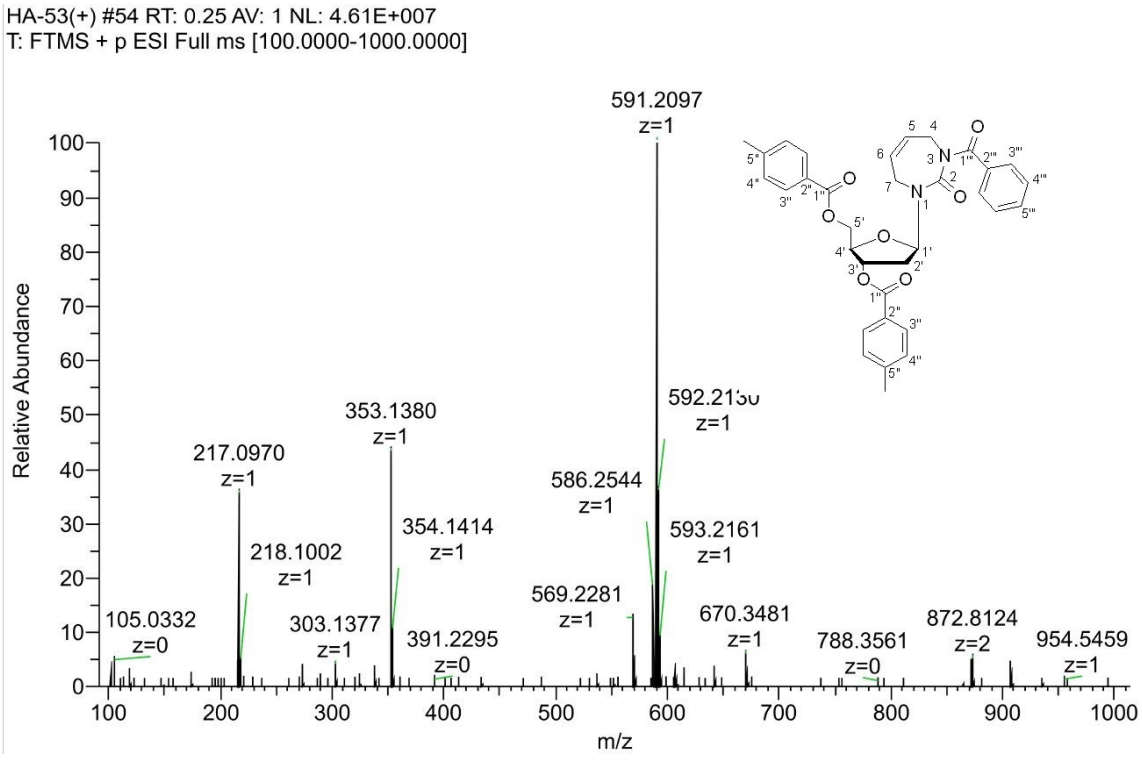


Figure S15. HRMS (ESI) of compound **5**.

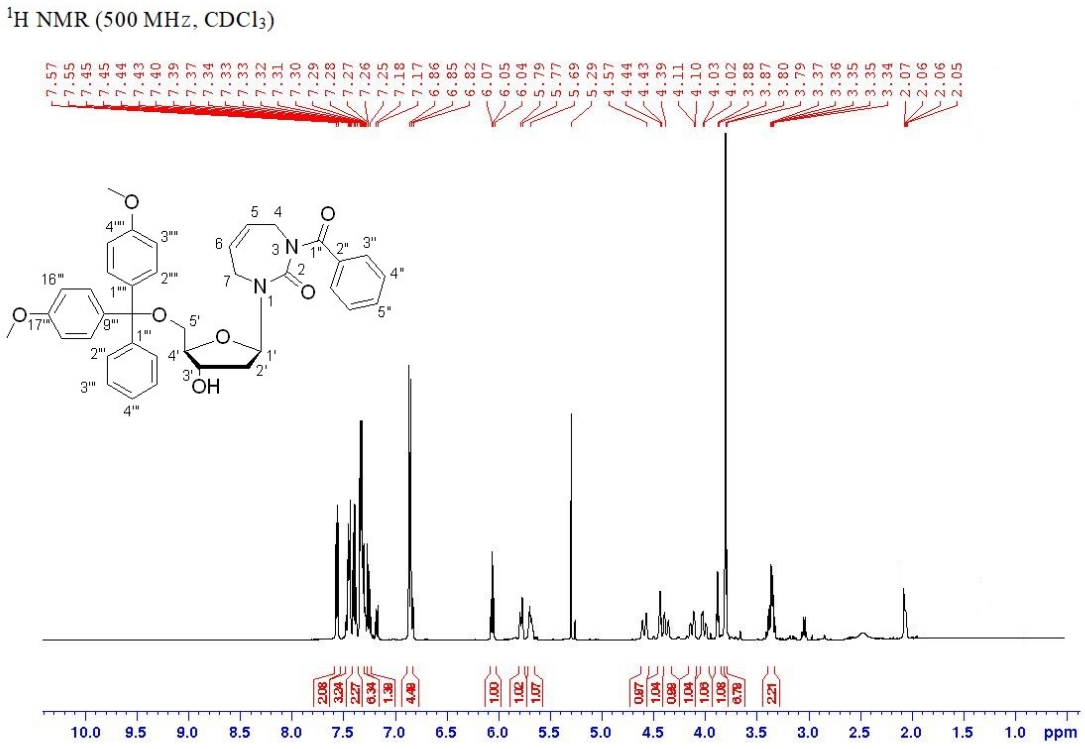


Figure S16. ^{1}H NMR spectrum of compound **6**.

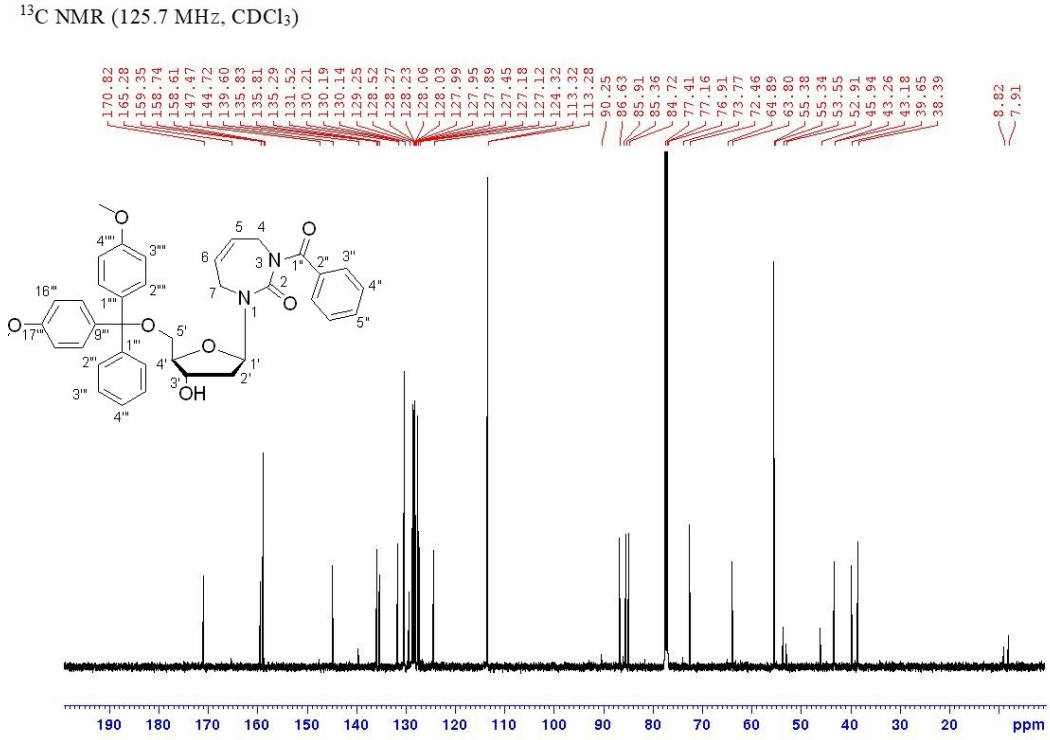


Figure S17. ^{13}C NMR spectrum of compound **6**.

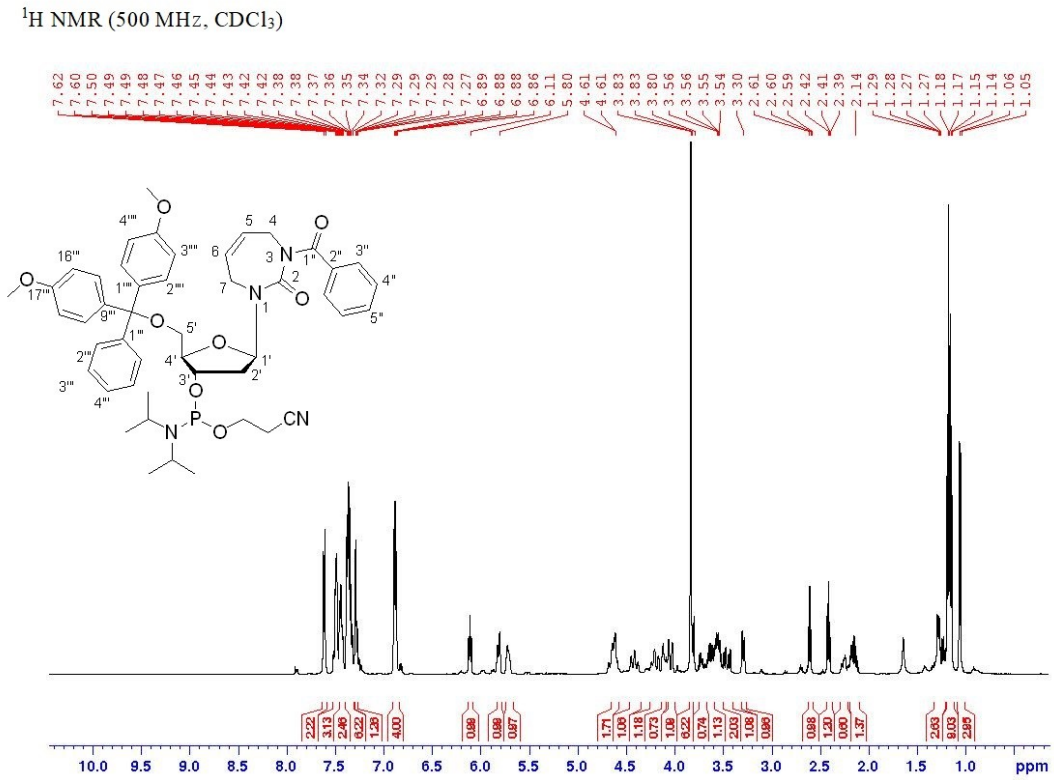


Figure S18. ^{1}H NMR spectrum of compound **7**.

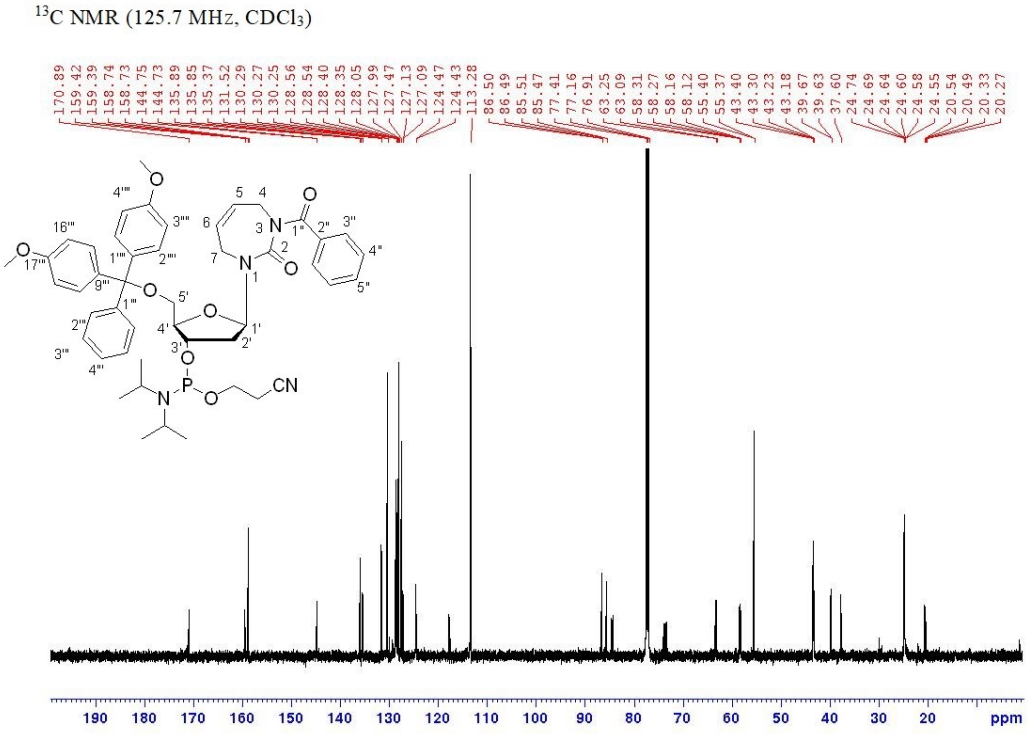


Figure S19. ^{13}C NMR spectrum of compound **7**.

^{31}P NMR (202.5 MHz, $CDCl_3$)

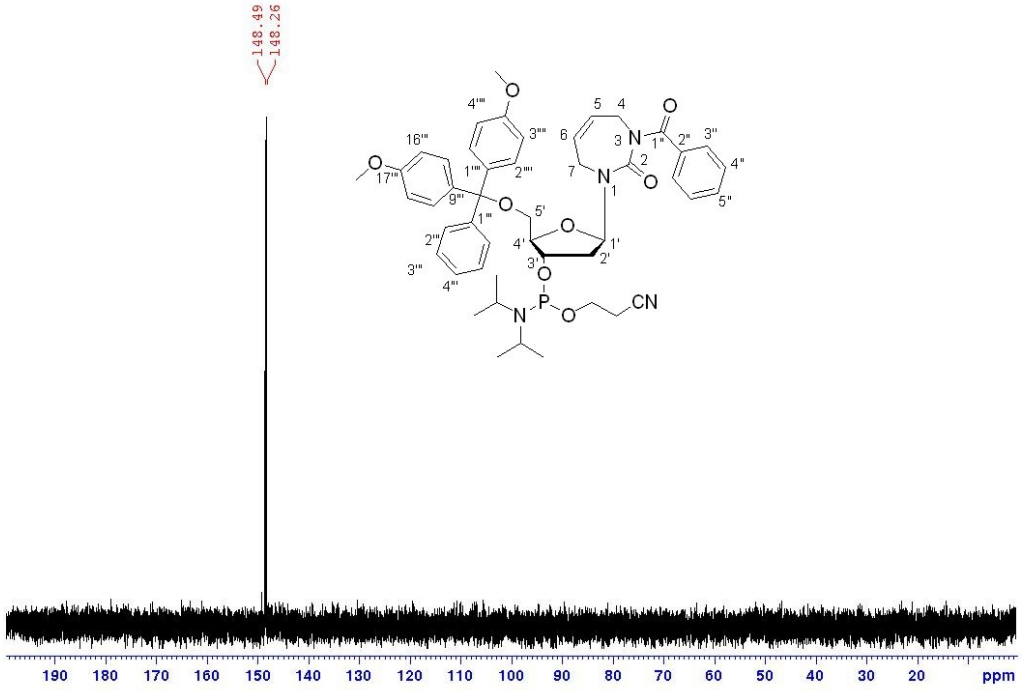


Figure S20. ^{31}P NMR spectrum of compound **7**.

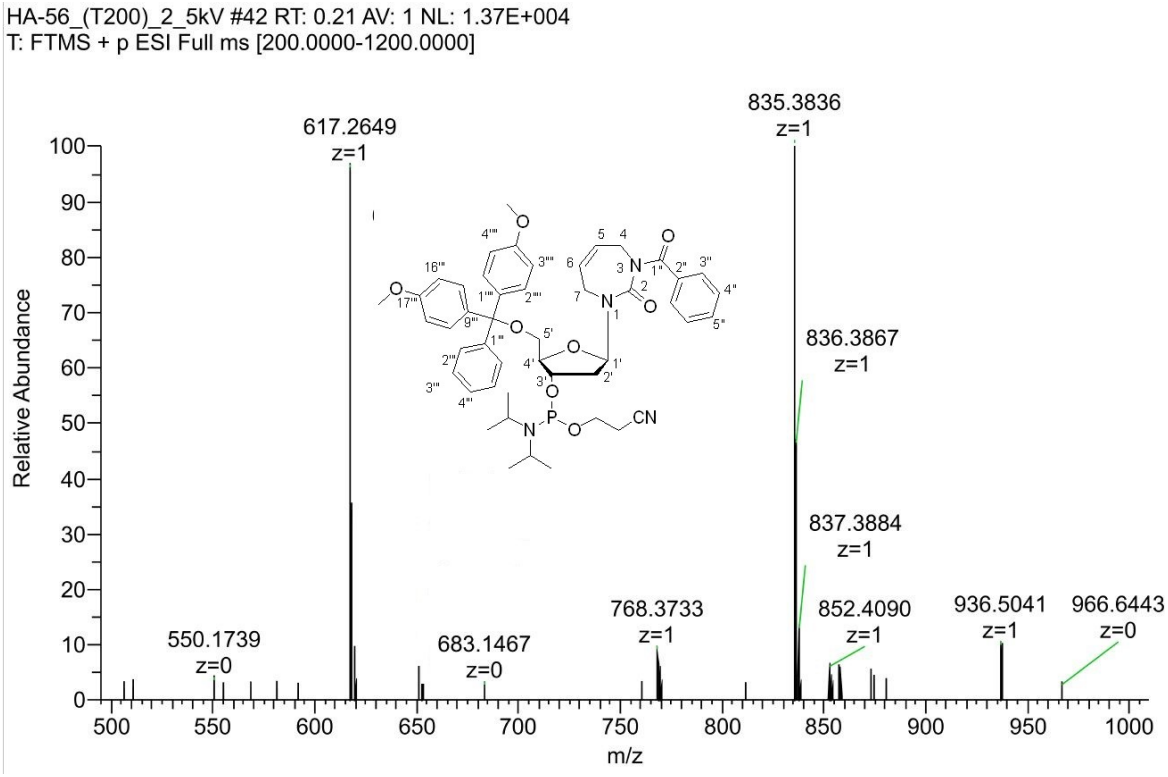


Figure S21. HRMS (ESI) of compound **7**.

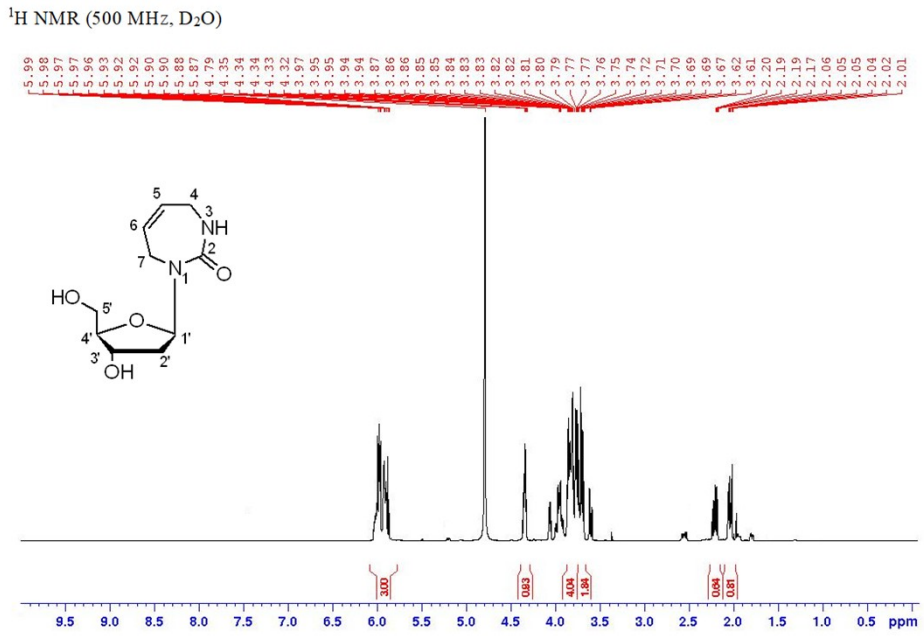


Figure S22. ^{1}H NMR spectrum of compound **8**.

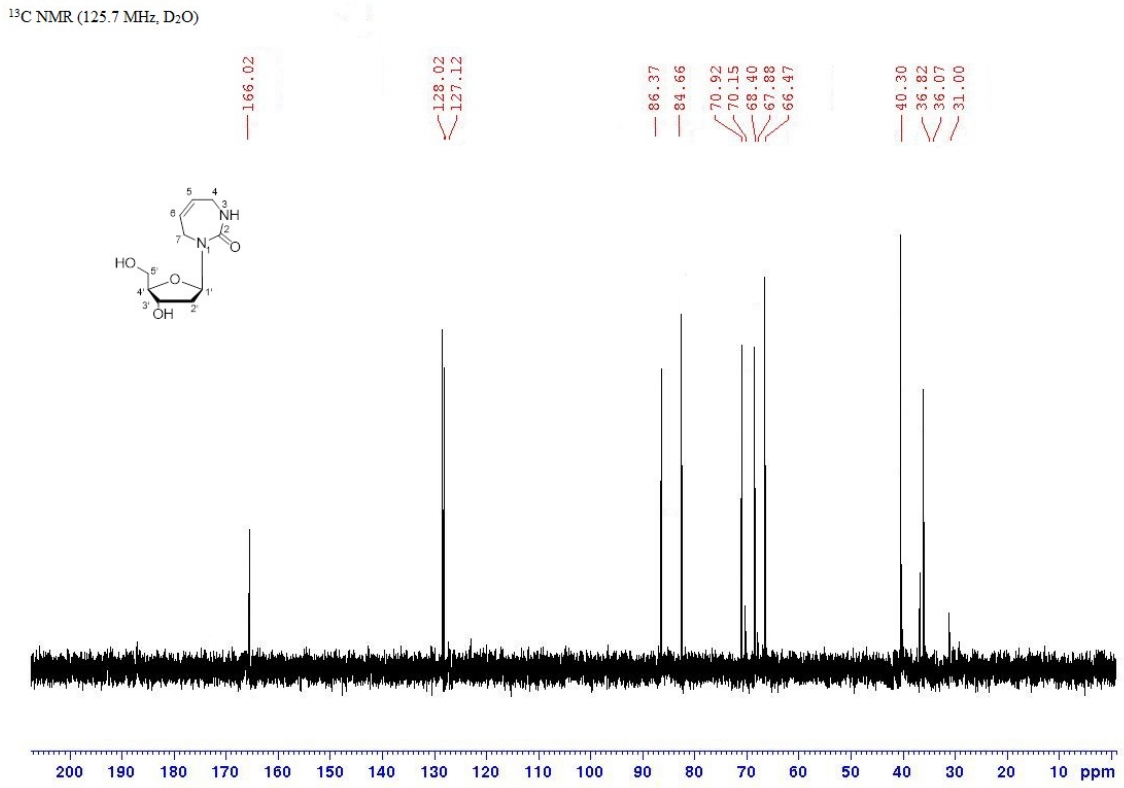


Figure S23. ^{13}C NMR spectrum of compound **8**.

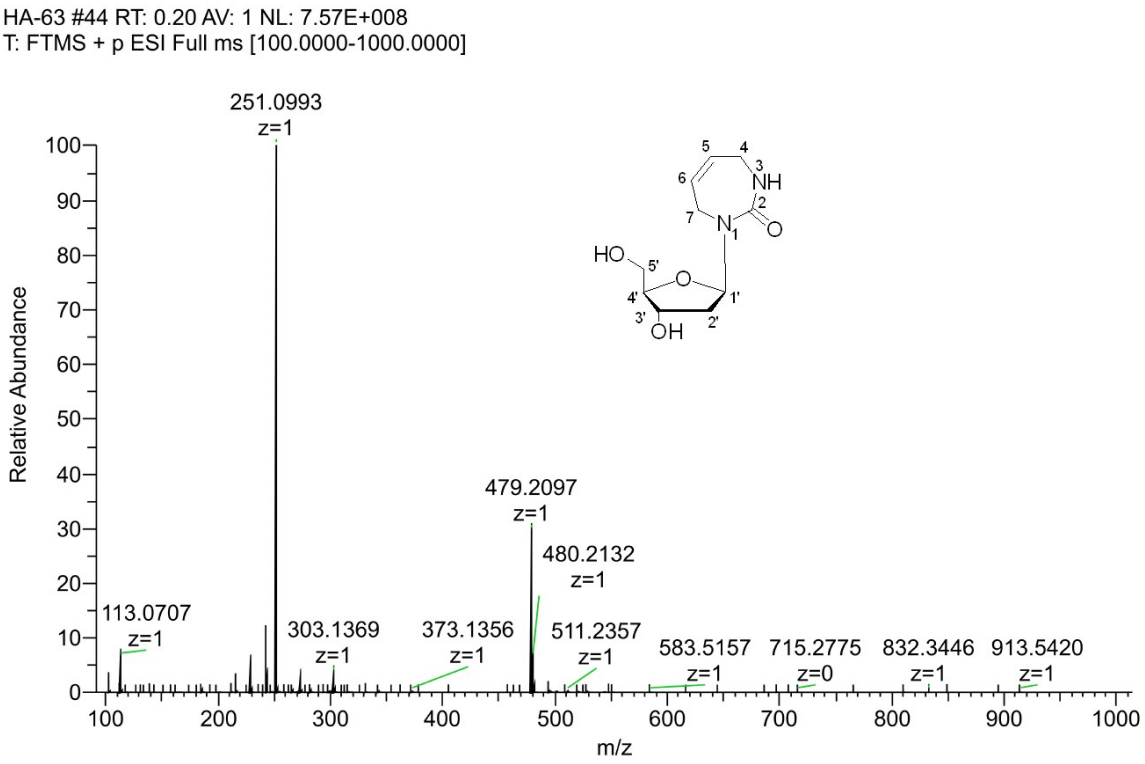


Figure S24. HRMS (ESI) spectrum of compound **8**.

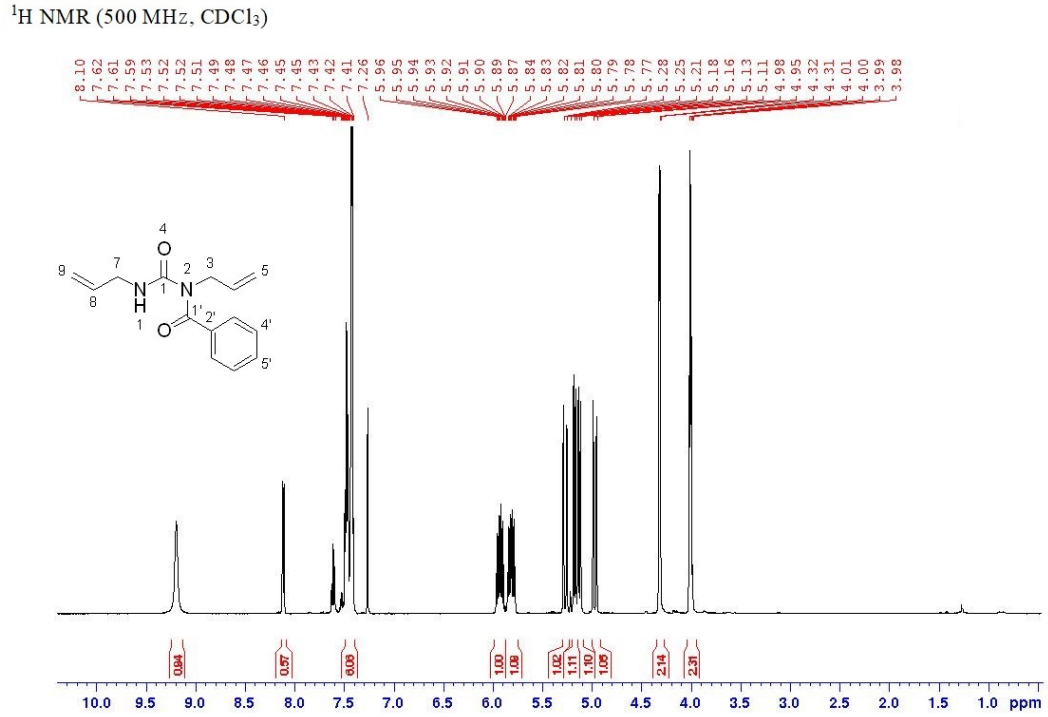


Figure S25. ^{1}H NMR spectrum of compound **10**.

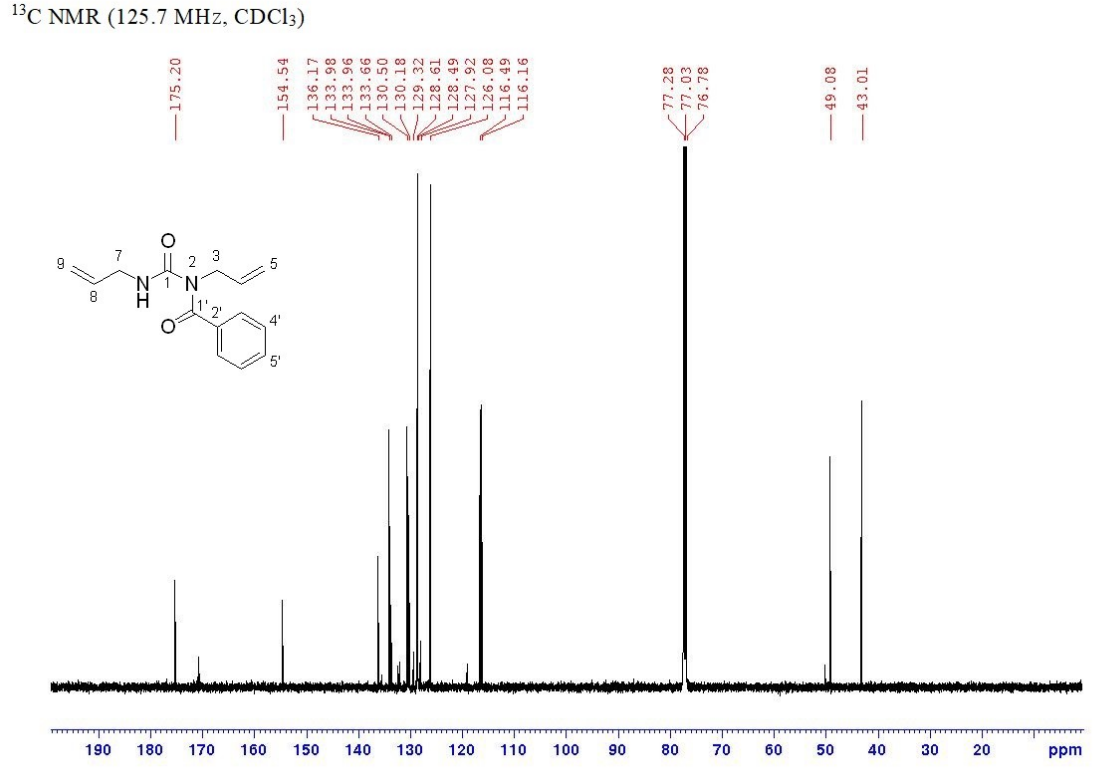


Figure S26. ^{13}C NMR spectrum of compound **10**.

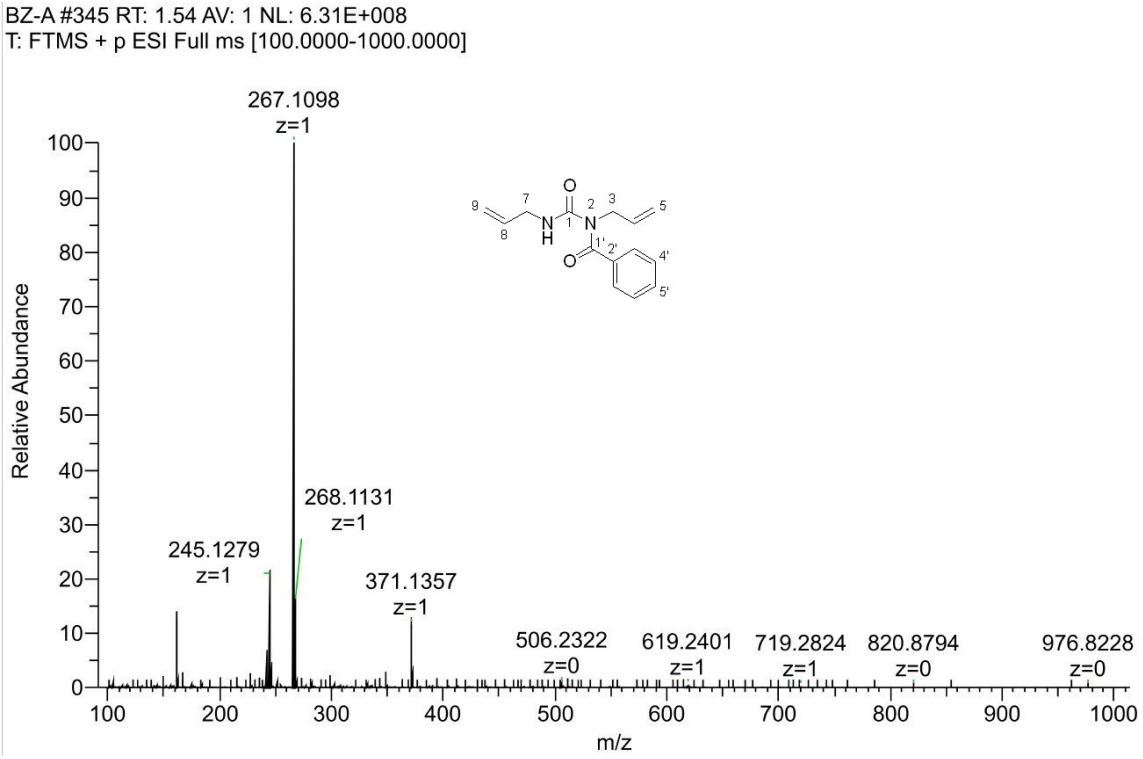


Figure S27. HRMS (ESI) of compound **10**.

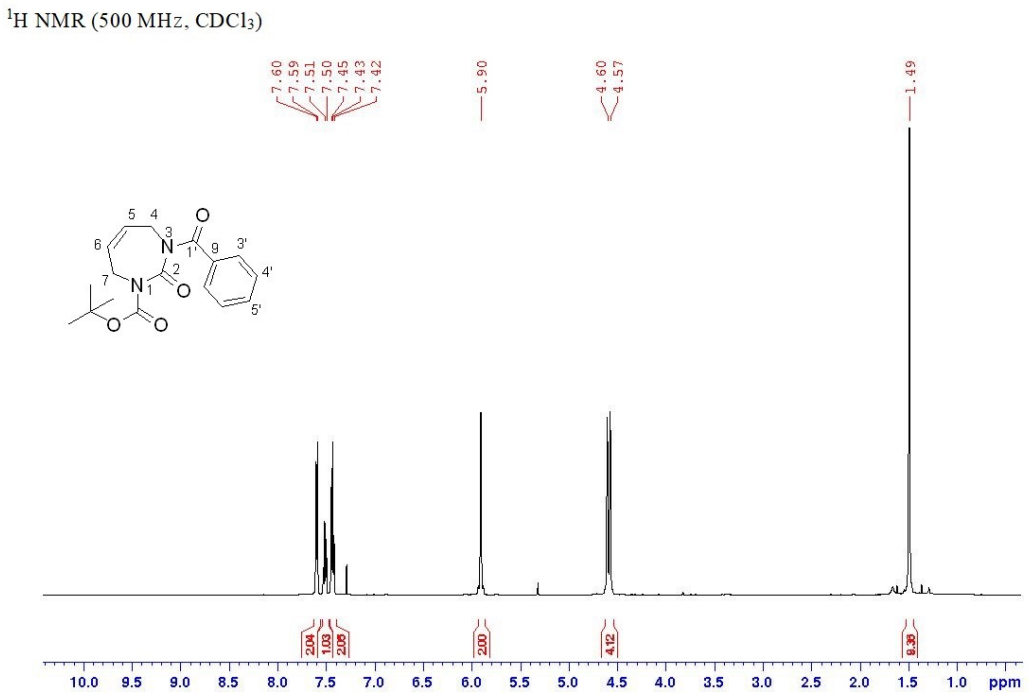


Figure S28. ^{1}H NMR spectrum of compound **12**.

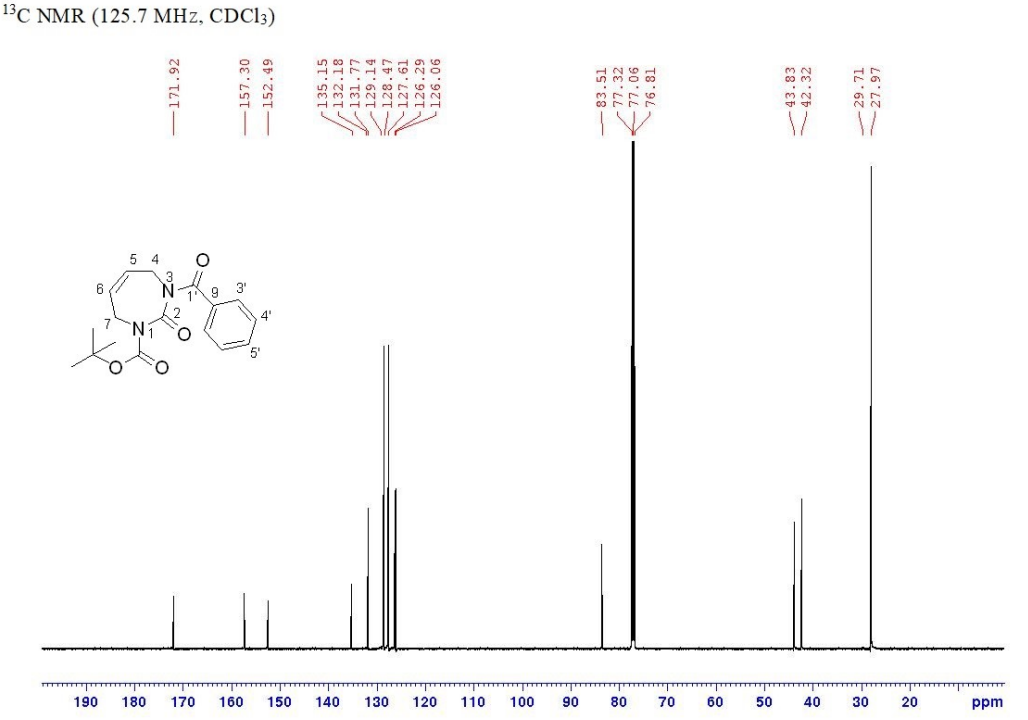


Figure S29. ^{13}C NMR spectrum of compound **12**.

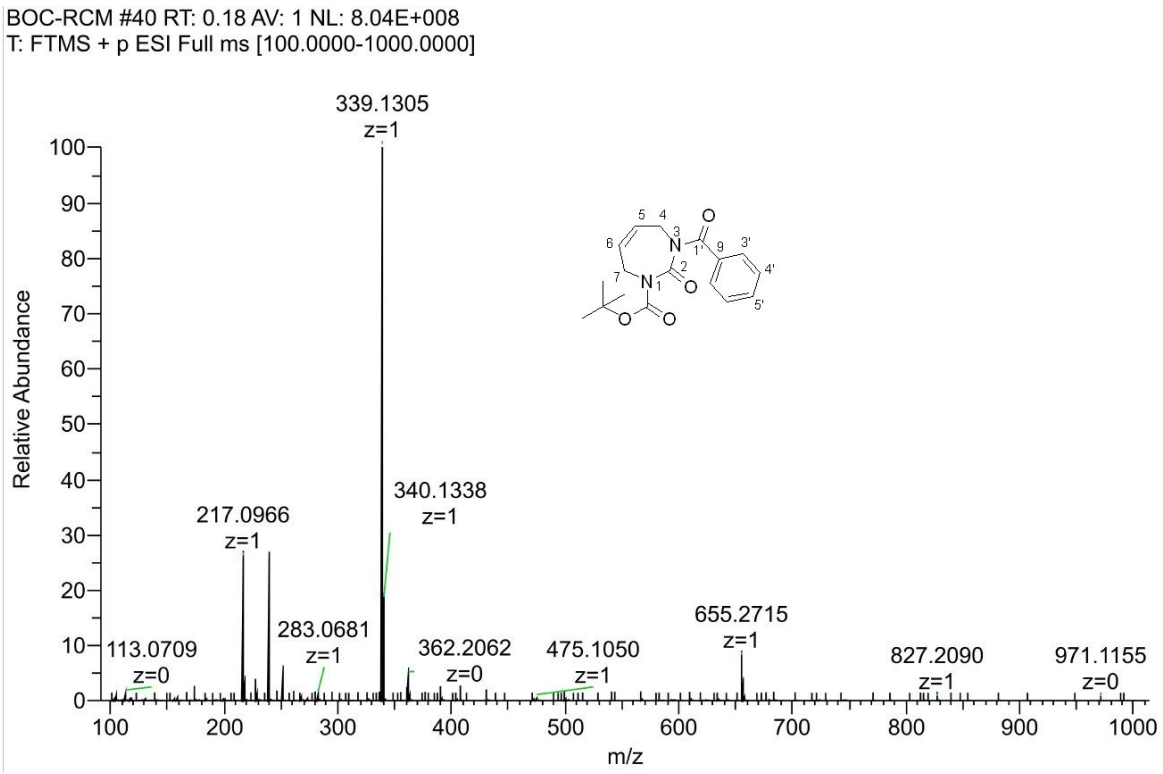


Figure S30. HRMS (ESI) of compound **12**.

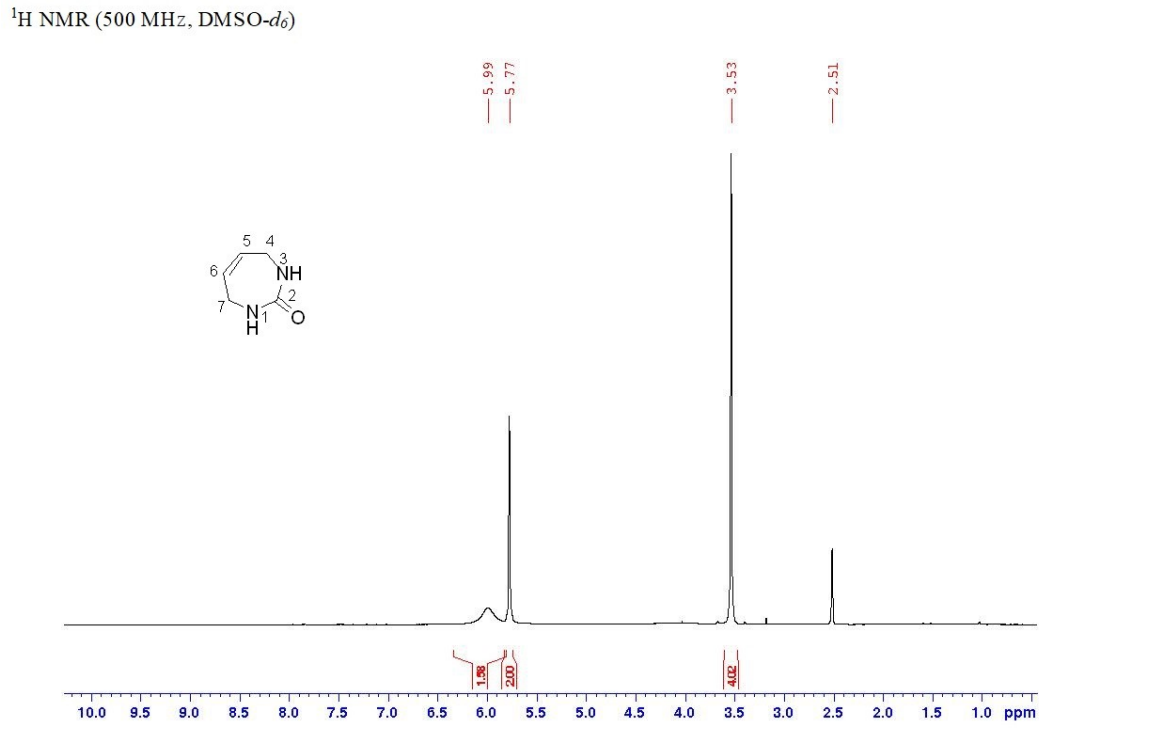


Figure S31. ^{1}H NMR spectrum of compound **14**.

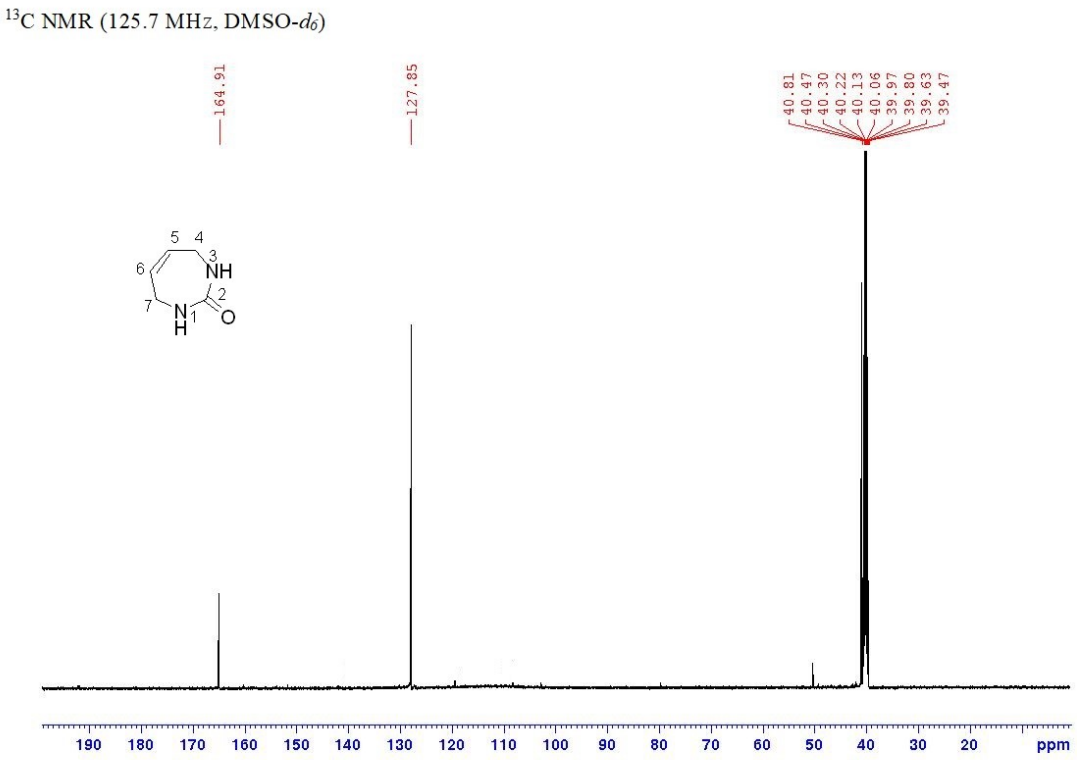


Figure S32. ^{13}C NMR spectrum of compound **14**.

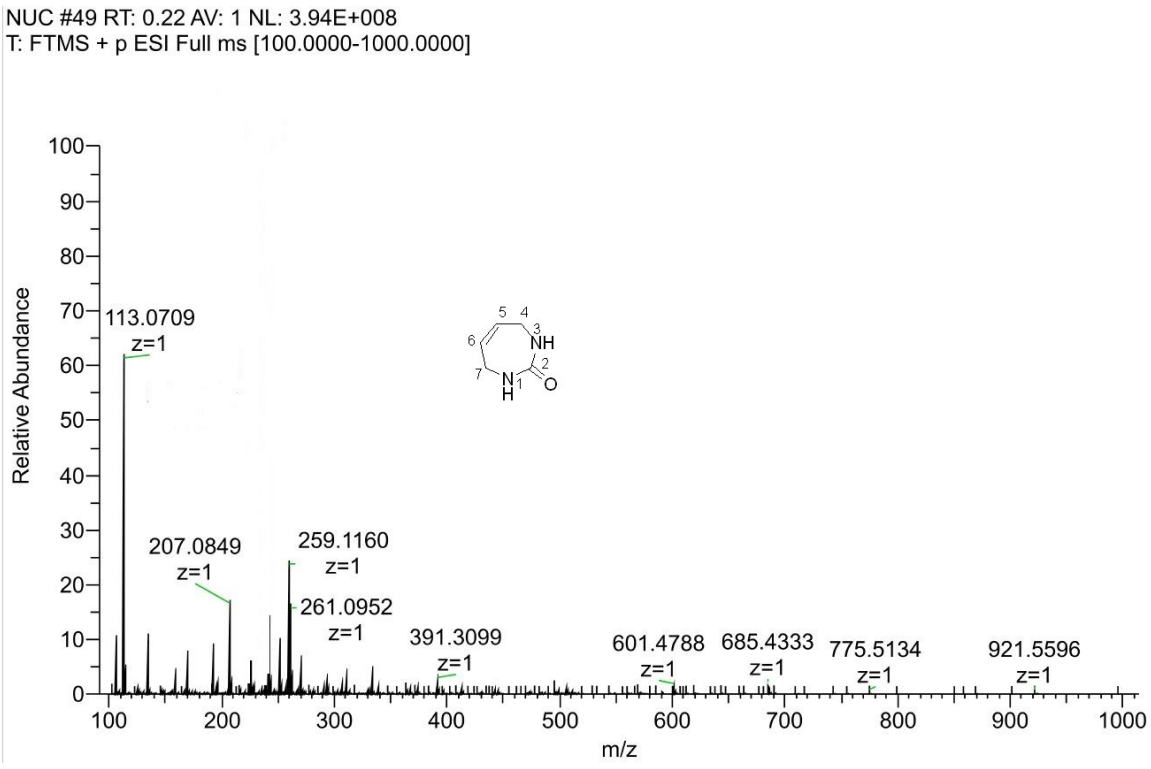


Figure S33. HRMS (ESI) of compound **14**.

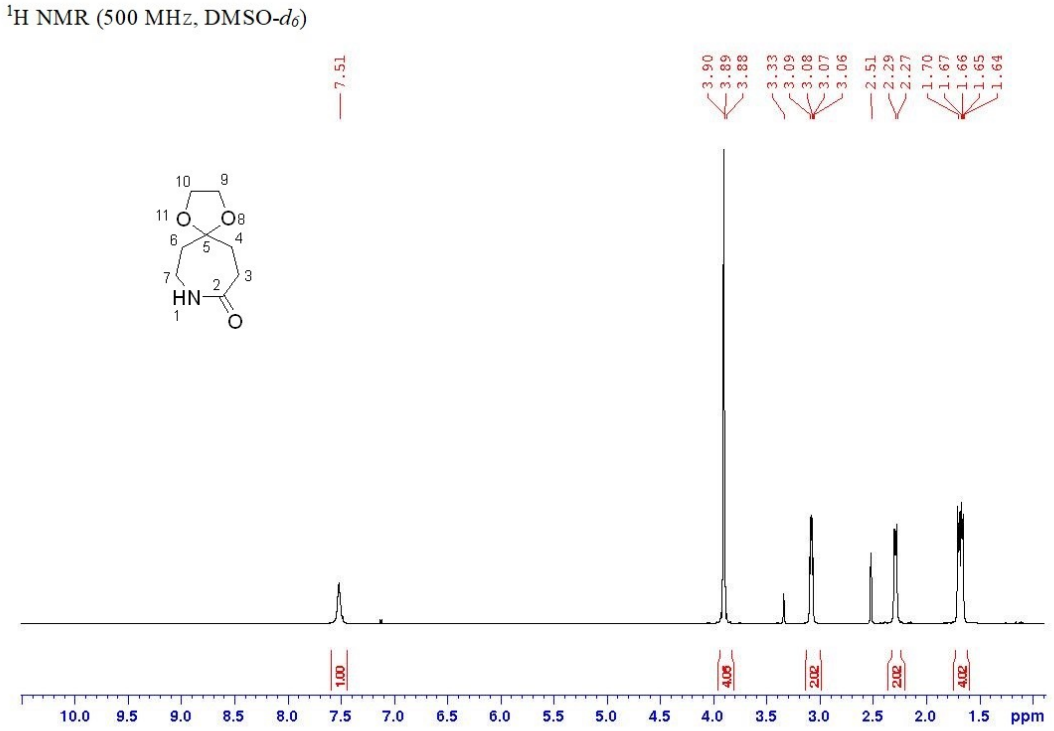


Figure S34. ^{1}H NMR spectrum of compound **17**.

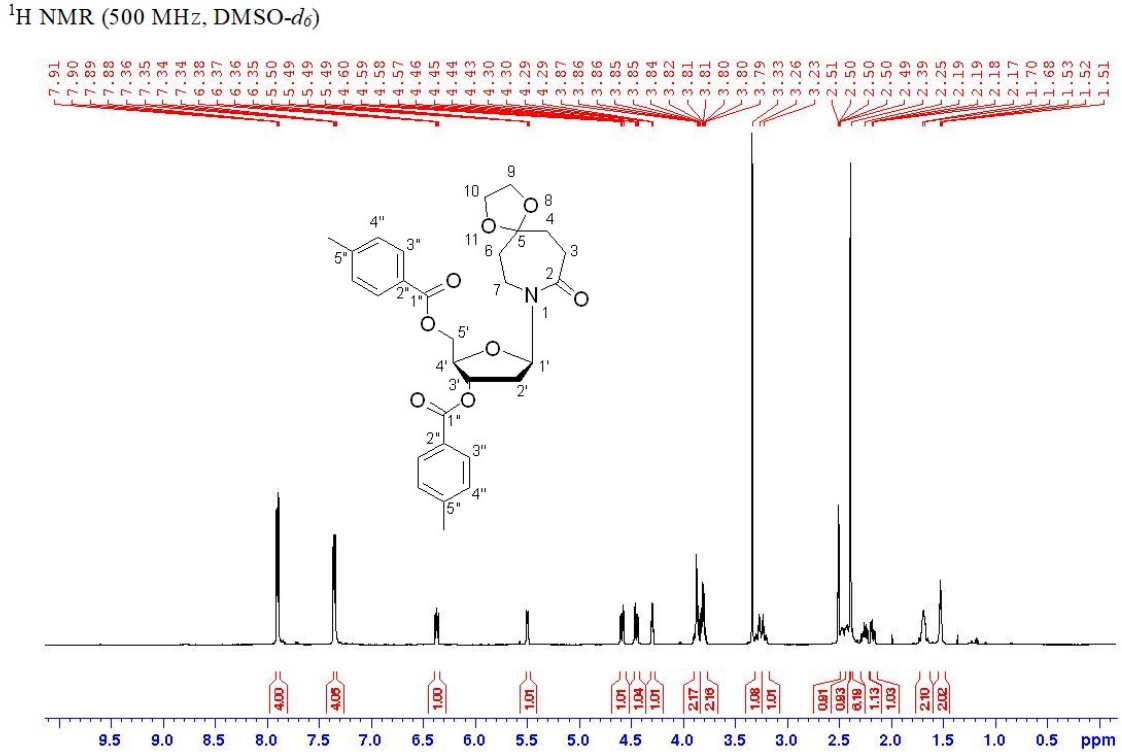


Figure S35. ^{1}H NMR spectrum of compound **18**.

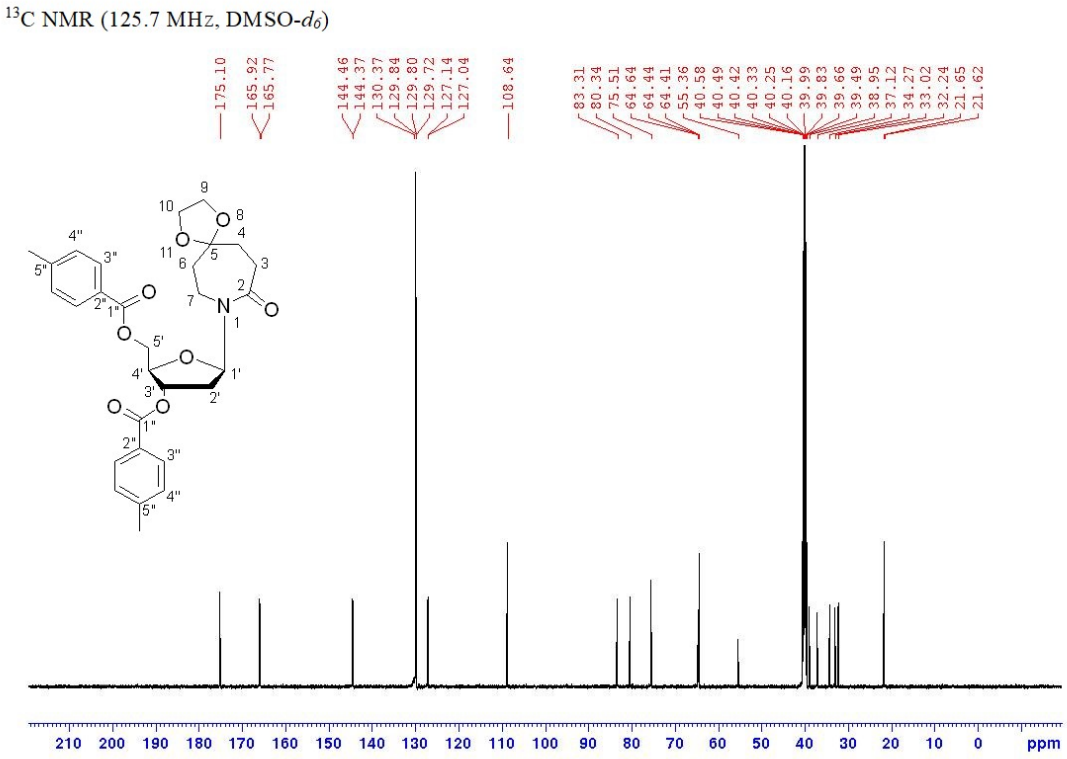


Figure S36. ^{13}C NMR spectrum of compound **18**.

^{1}H NMR (500 MHz, $CDCl_3$)

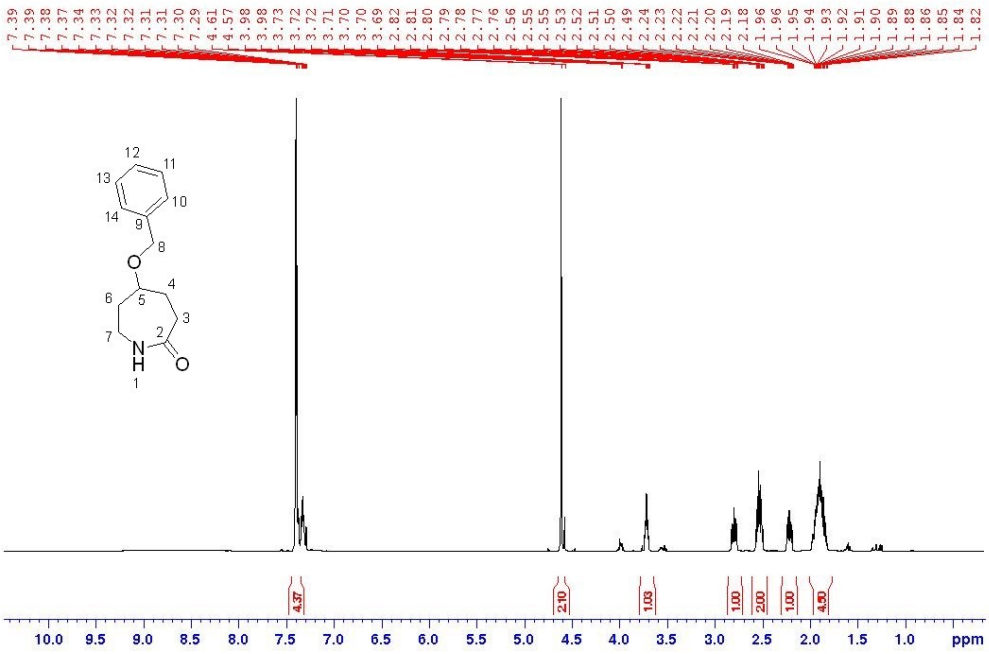


Figure S37. ^{1}H NMR spectrum of compound **21**.

^{13}C NMR (125.7 MHz, $CDCl_3$)

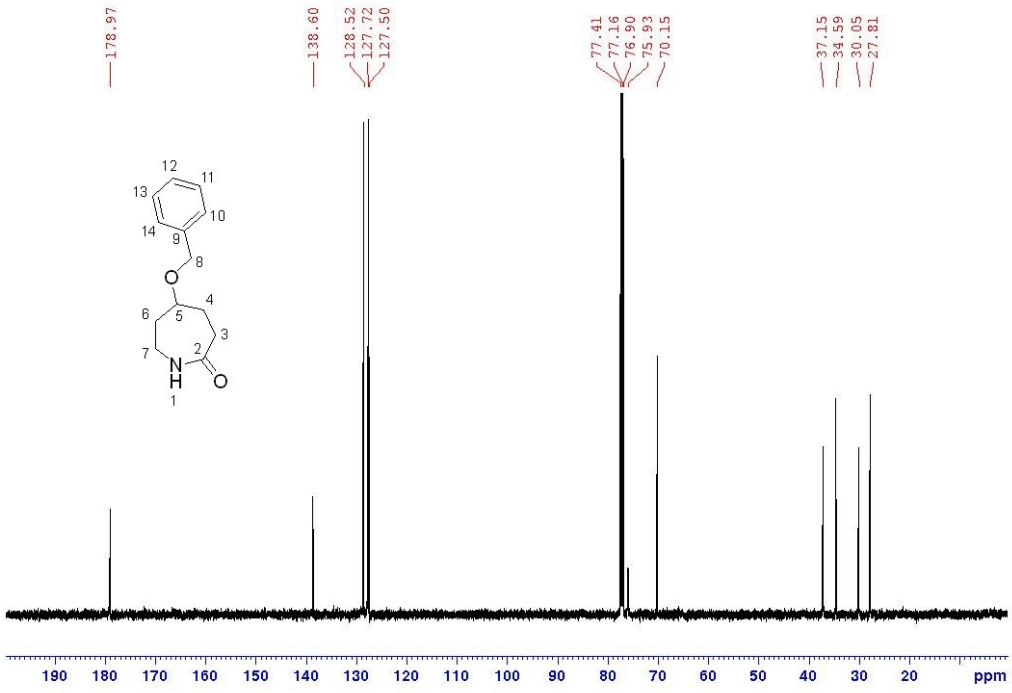


Figure S38. ^{13}C NMR spectrum of compound **21**.

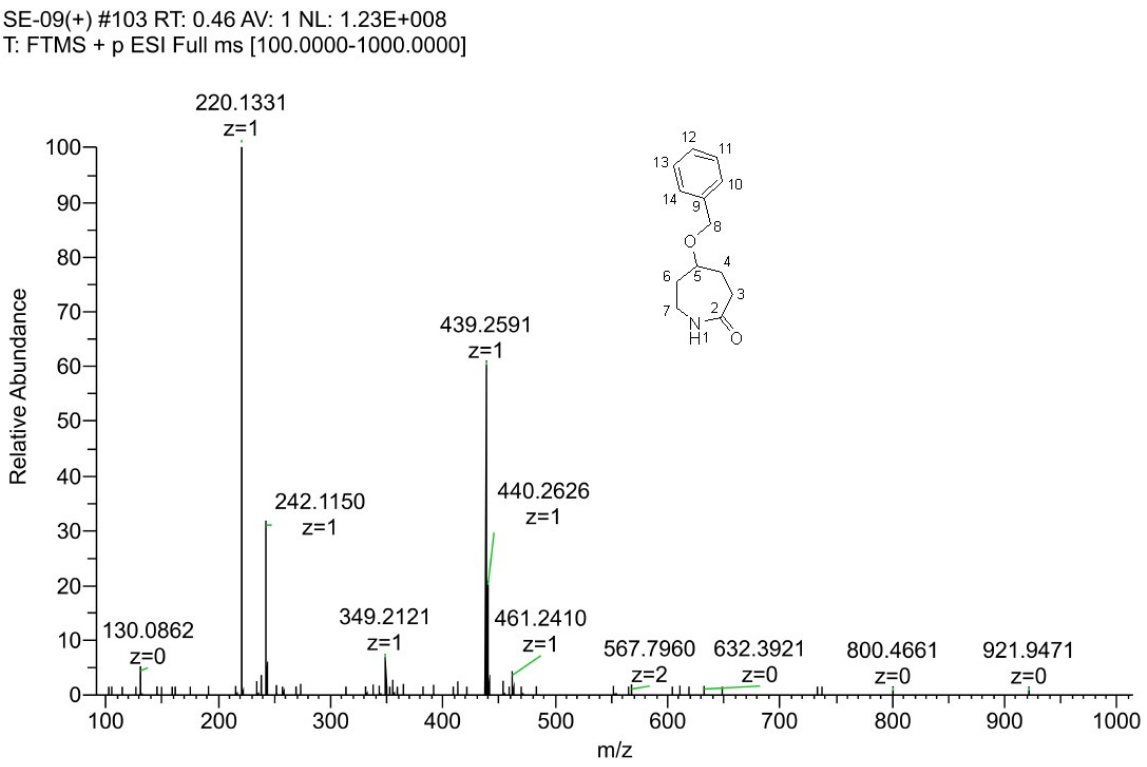


Figure S39. HRMS (ESI) of compound **21**.

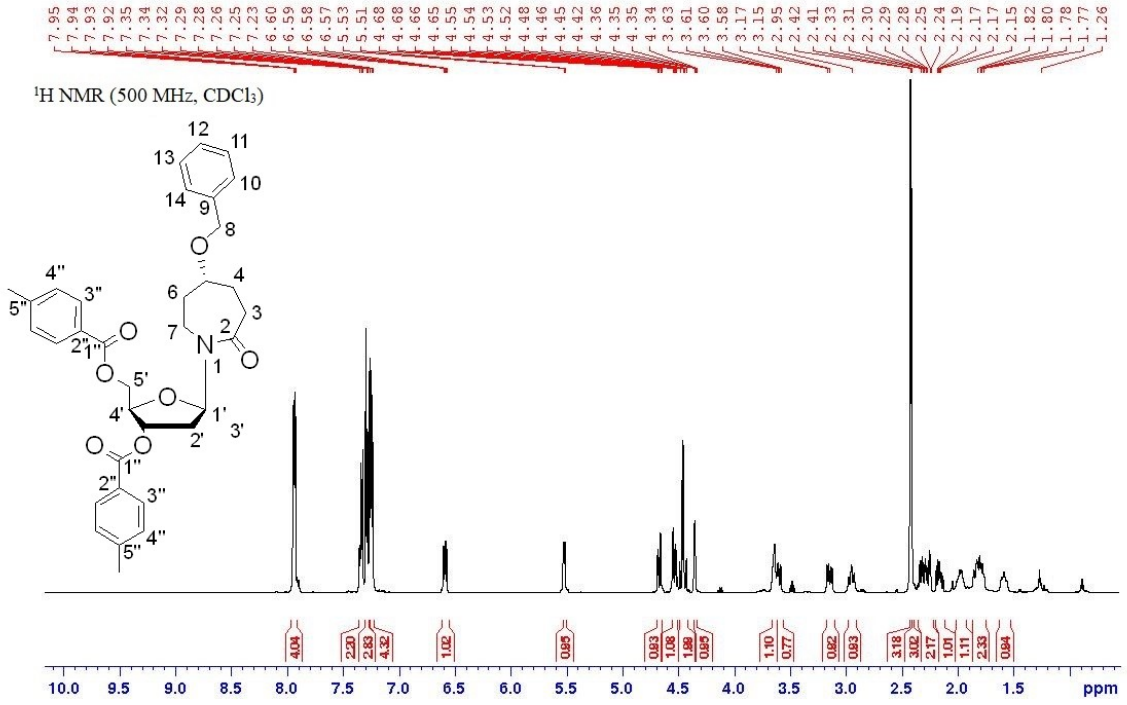


Figure S40. ^{1}H NMR spectrum of compound **22*R***.

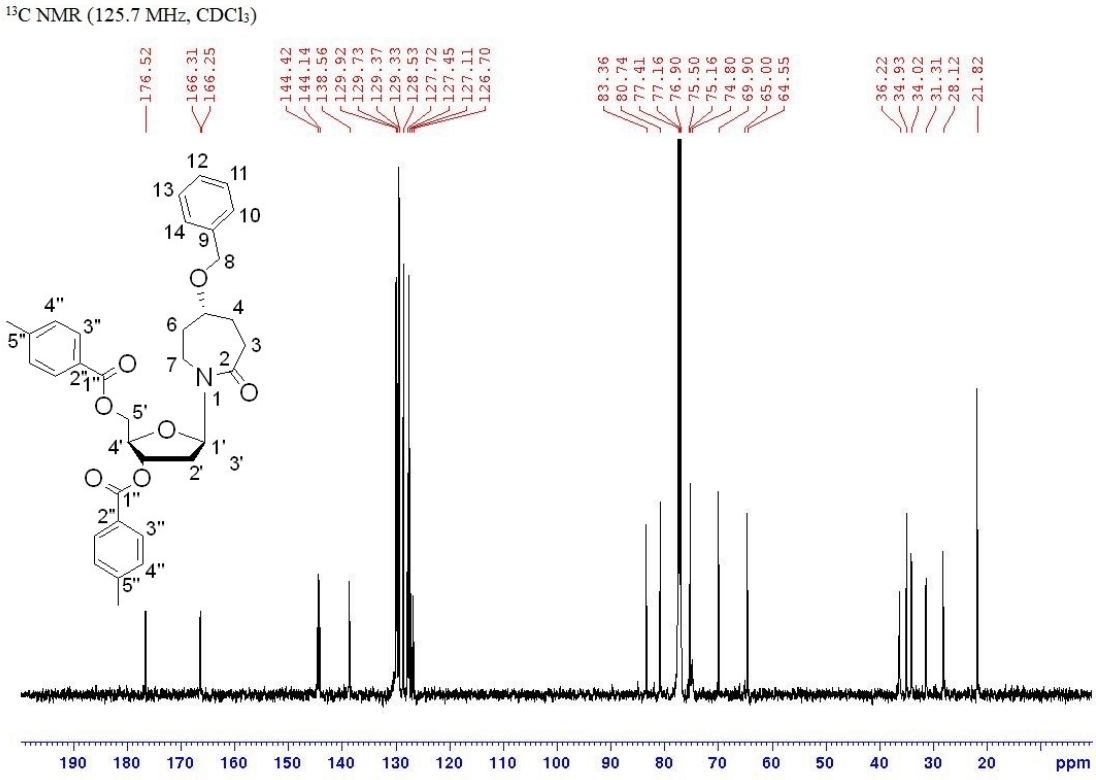


Figure S41. ^{13}C NMR spectrum of compound **22*R***.

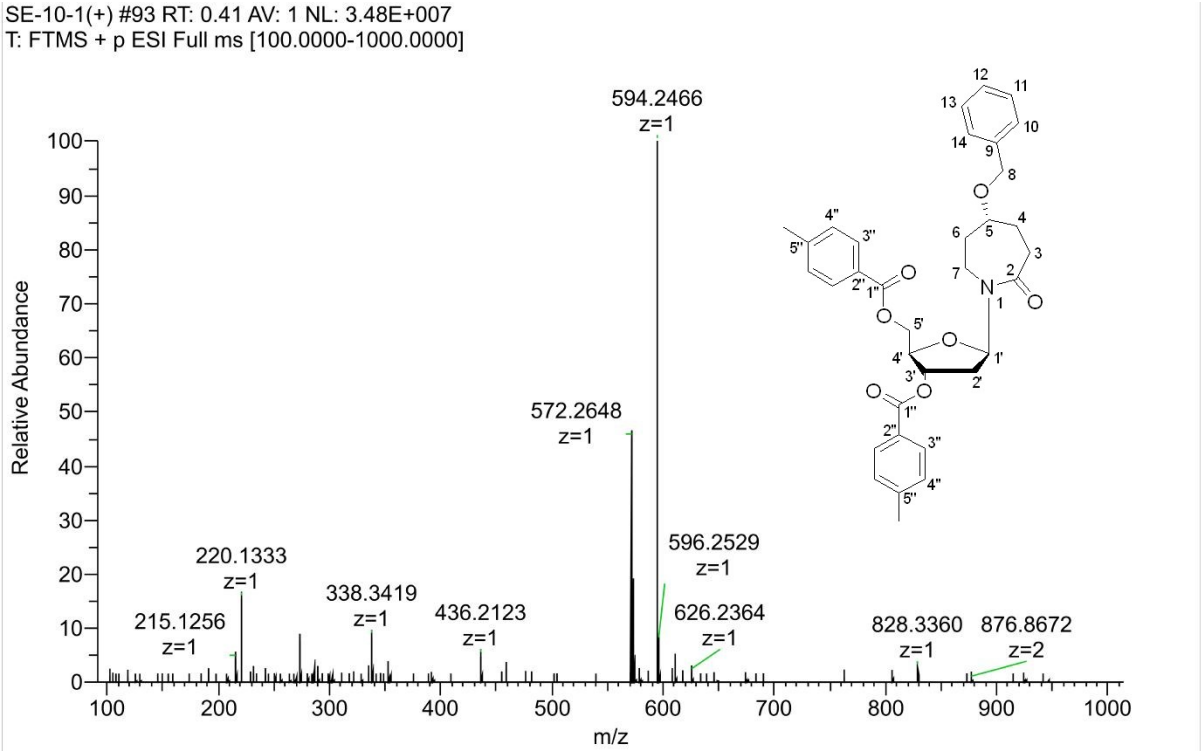


Figure S42. HRMS (ESI) of compound **22*R***.

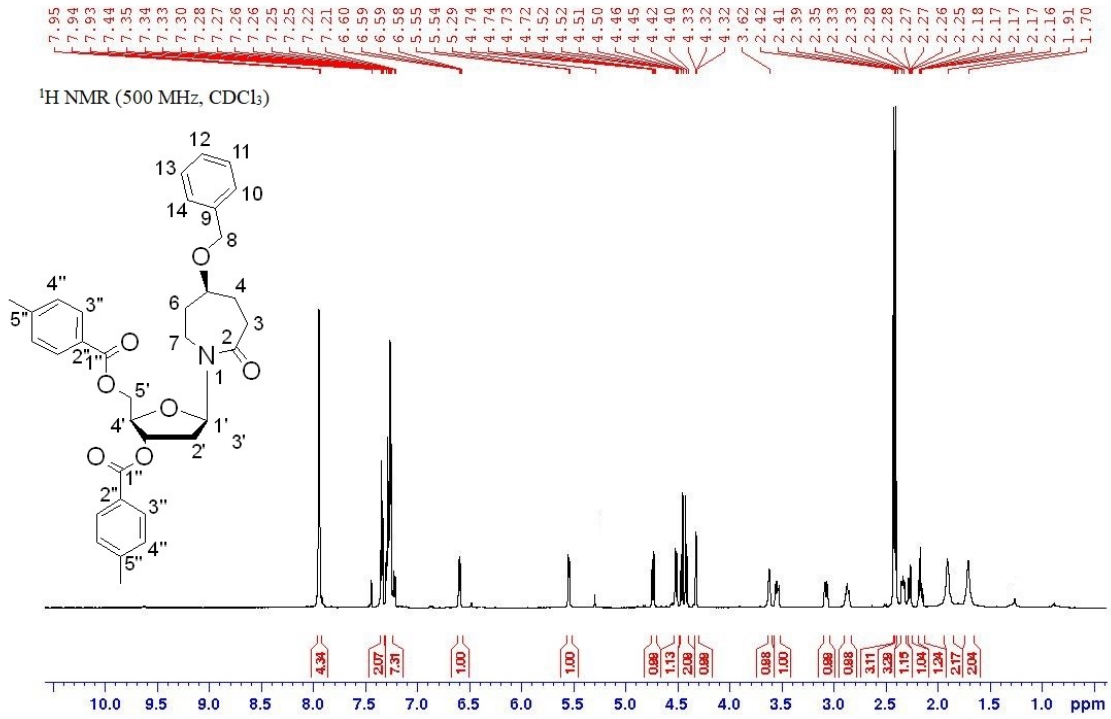


Figure S43. ^{1}H NMR spectrum of compound **22*S***.

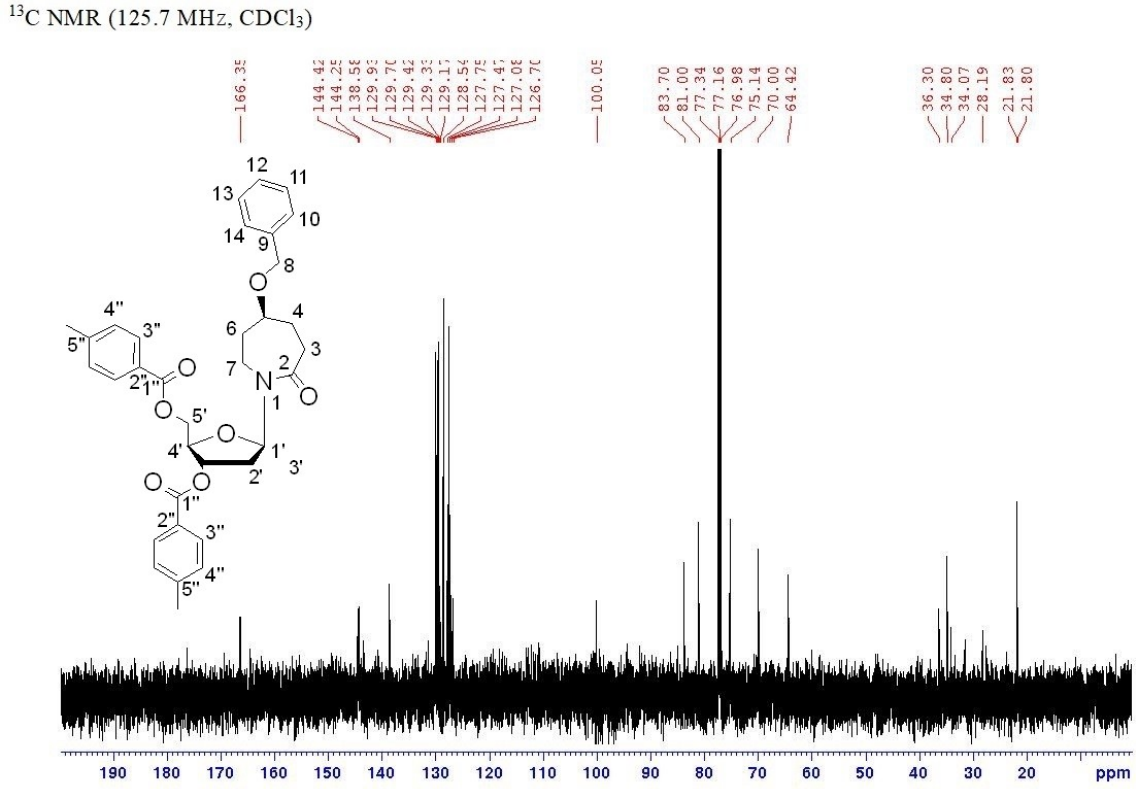


Figure S44. ^{13}C NMR spectrum of compound **22*S***.

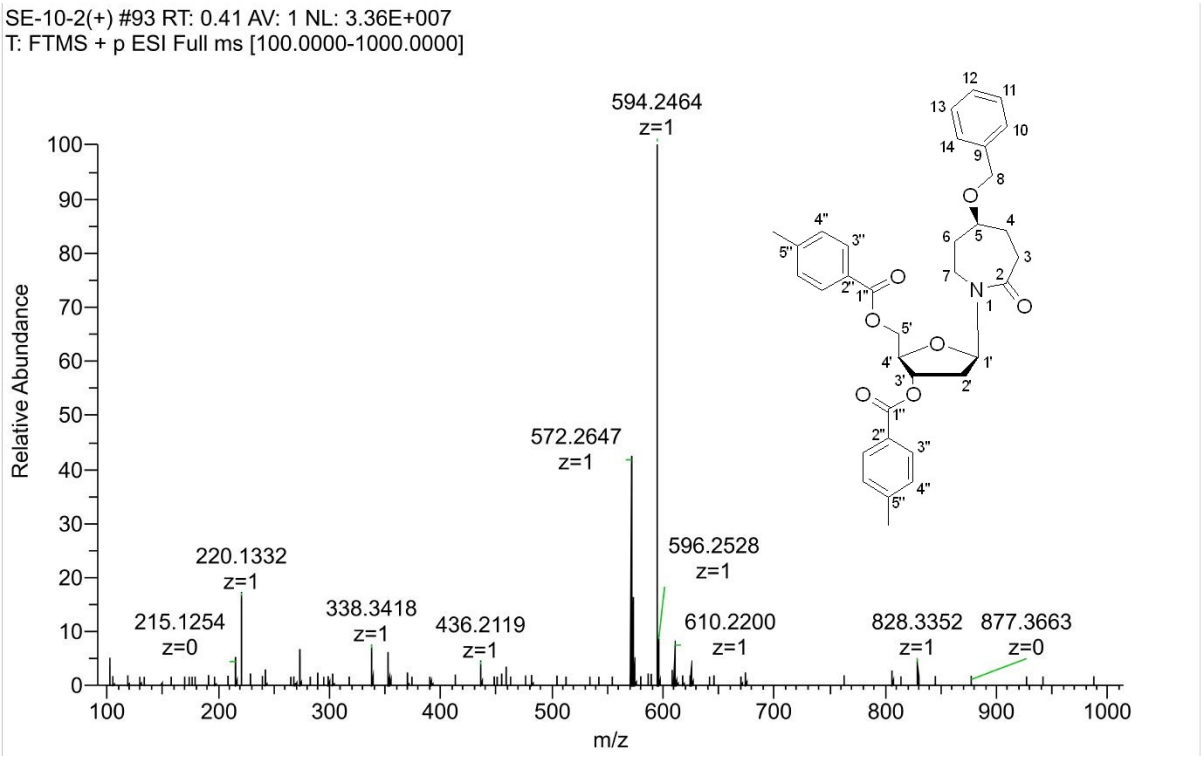


Figure S45. HRMS (ESI) of compound **22*S***.

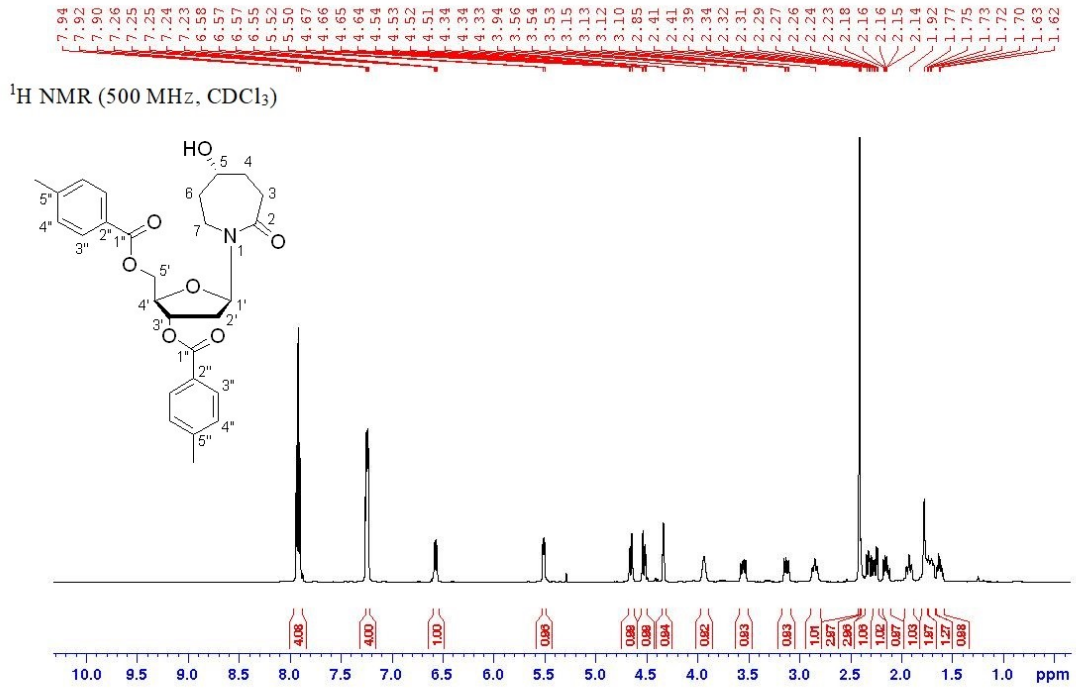


Figure S46. ^{1}H NMR spectrum of compound **23*R***.

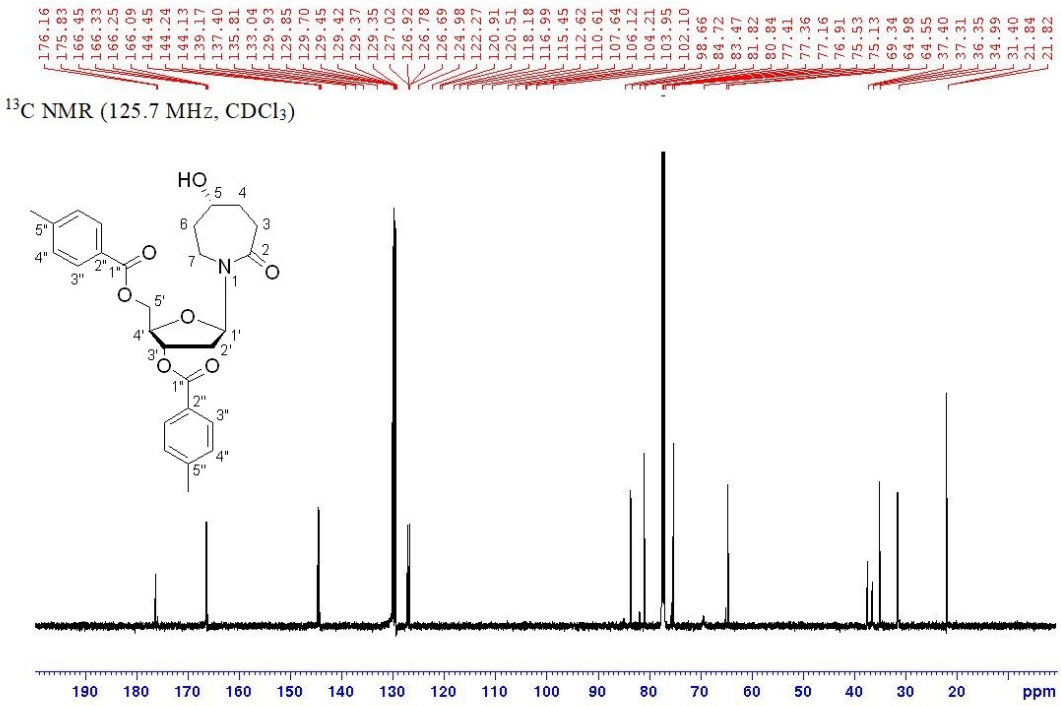


Figure S47. ^{13}C NMR spectrum of compound **23*R***.

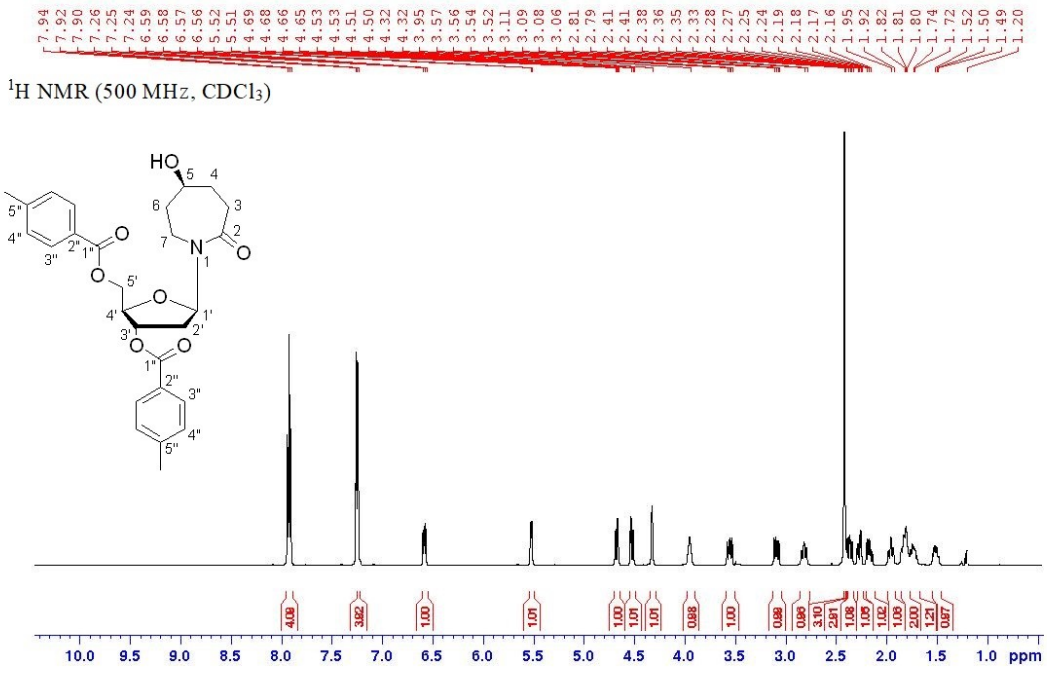


Figure S48. ^{1}H NMR spectrum of compound **23*S***.

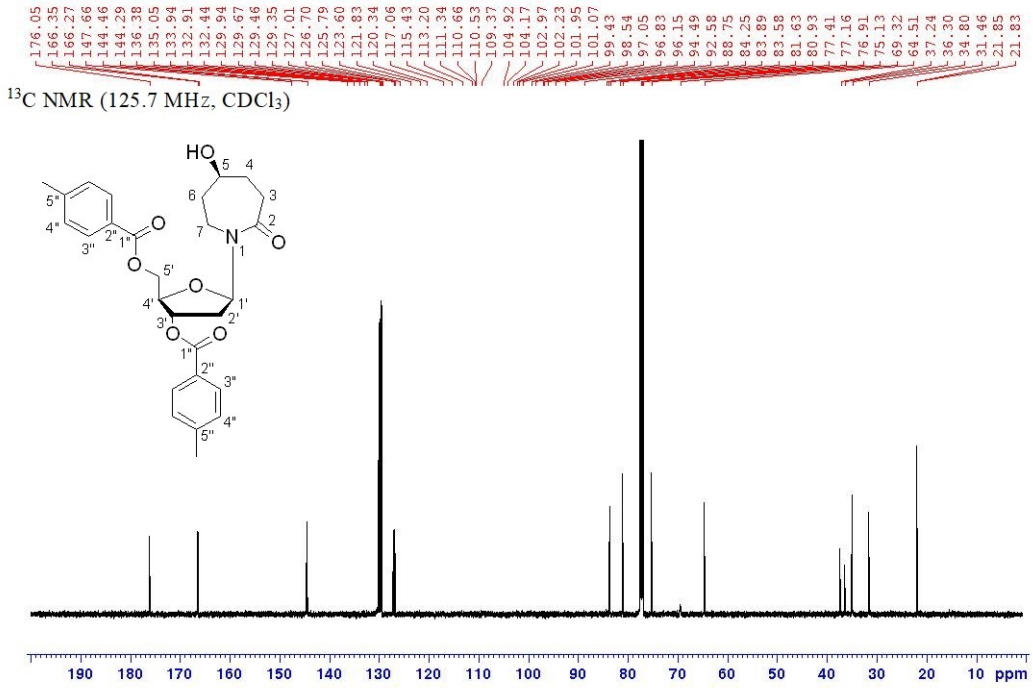


Figure S49. ^{13}C NMR spectrum of compound **23*S***.

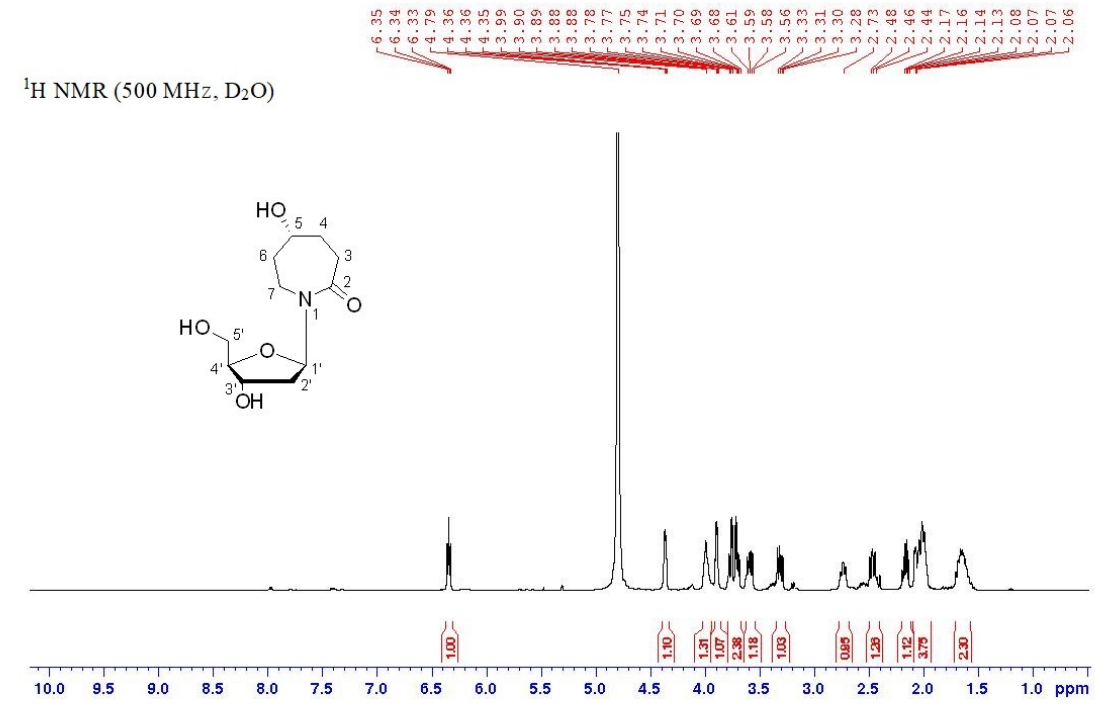


Figure S50. ^{1}H NMR spectrum of compound **24*R***.

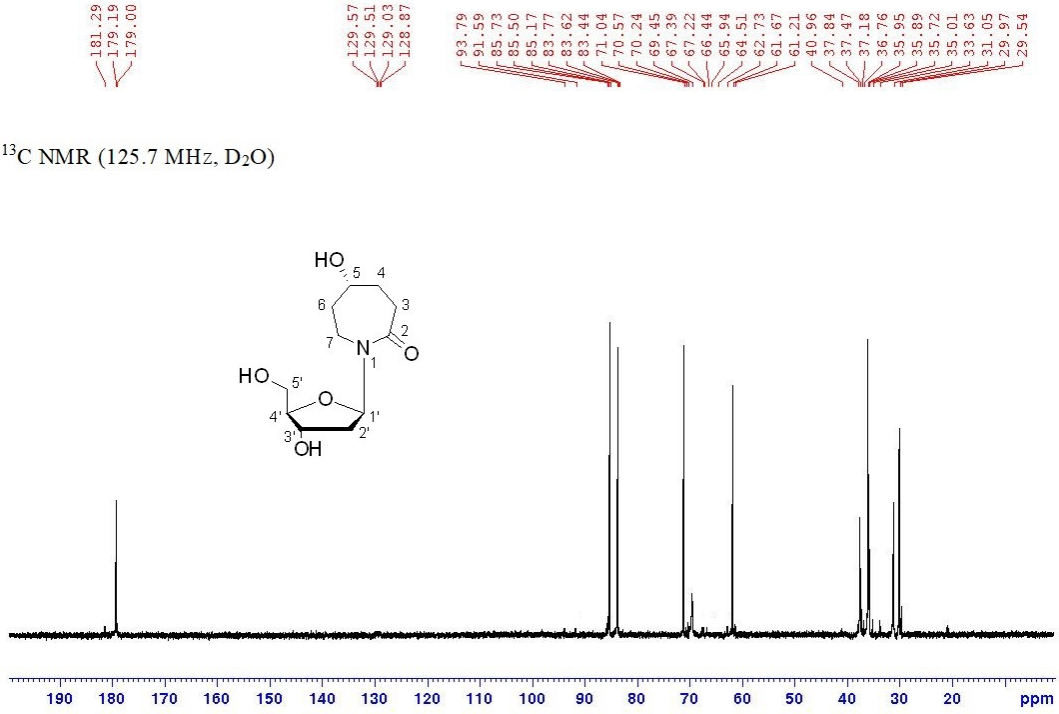


Figure S51. ^{13}C NMR spectrum of compound **24*R***.

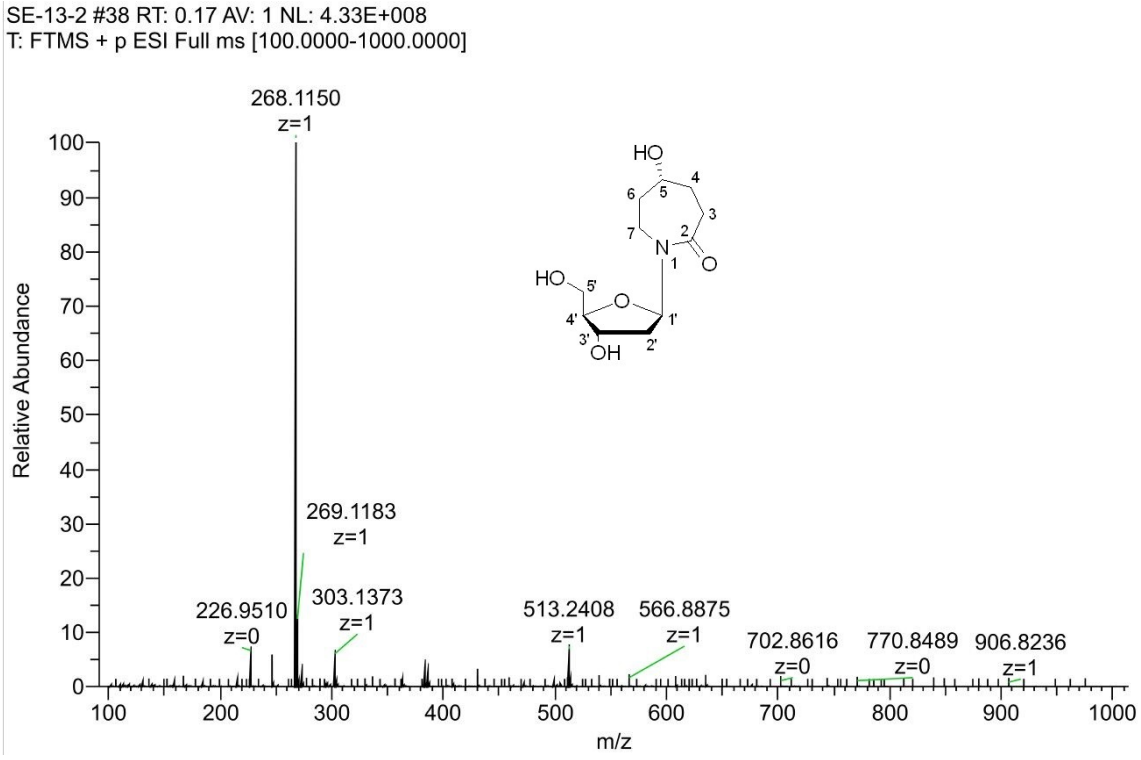


Figure S52. HRMS (ESI) of compound **24*R*.**

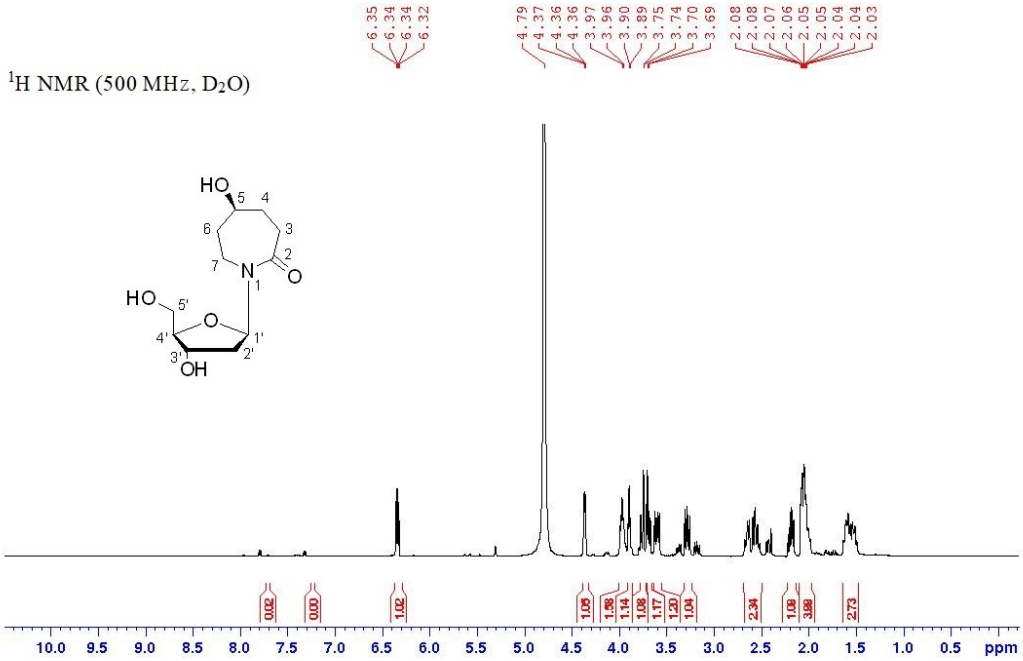


Figure S53. ^{1}H NMR spectrum of compound **24*S*.**

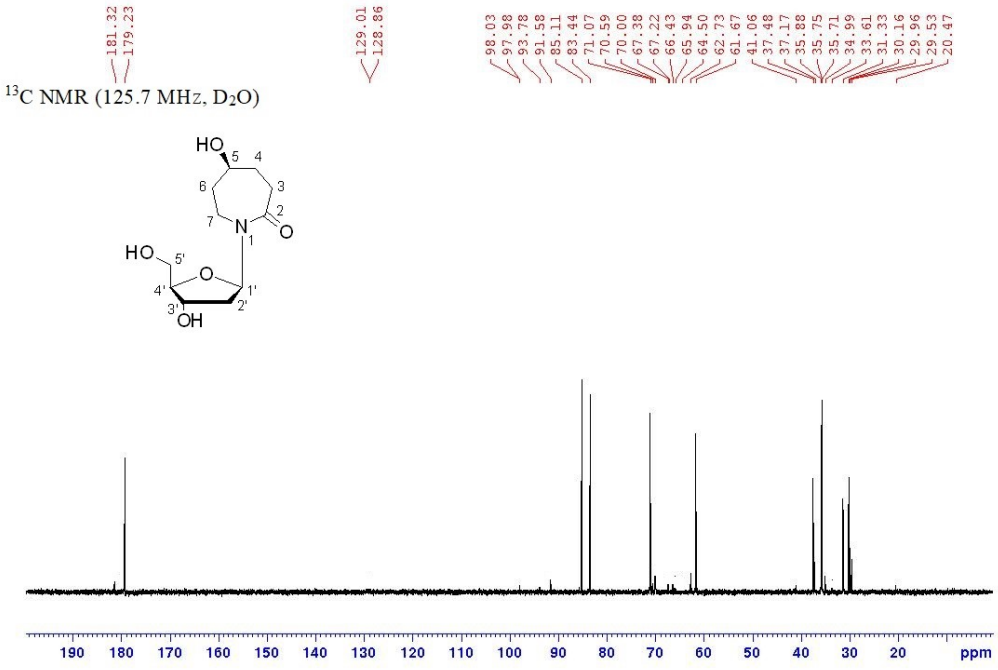


Figure S54. ^{13}C NMR spectrum of compound **24*S***.

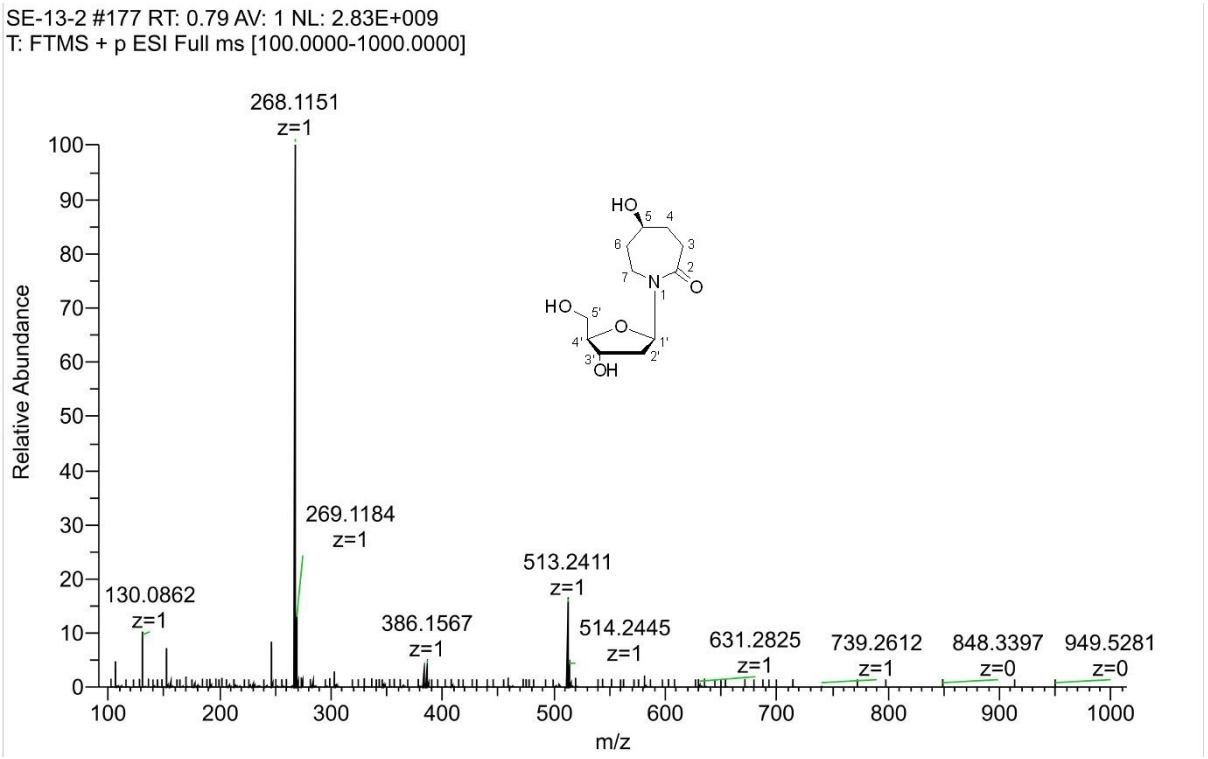


Figure S55. HRMS (ESI) of compound **24*S***.

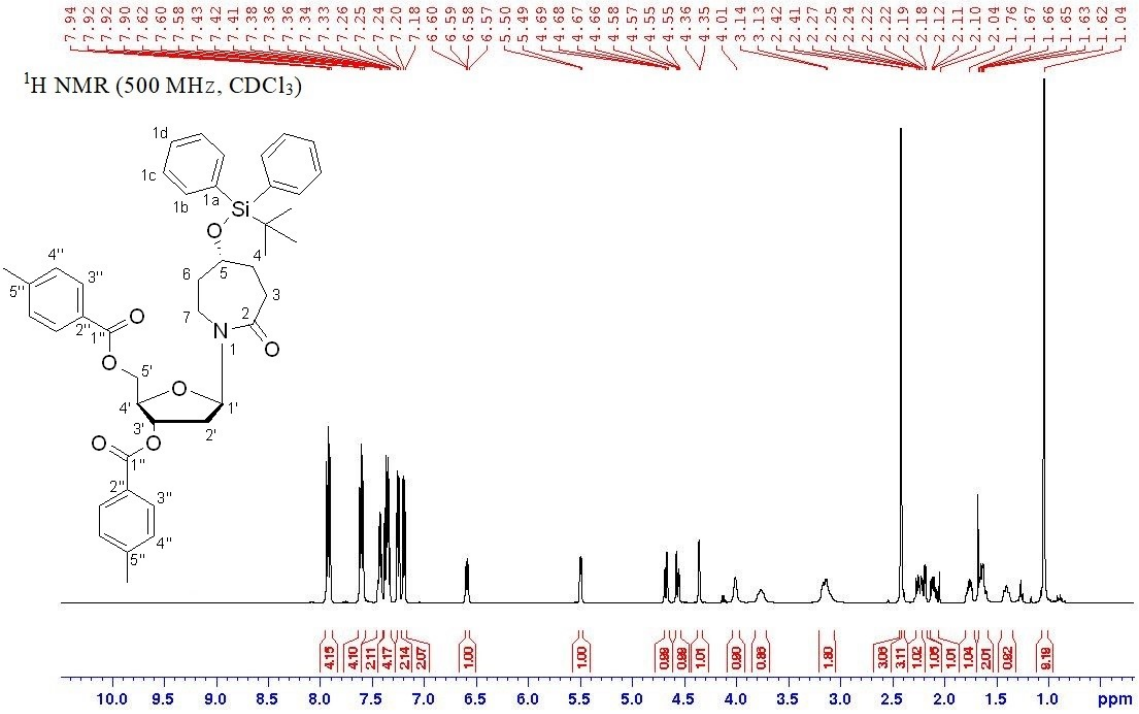


Figure S56. ^{1}H NMR spectrum of compound **25*R***.

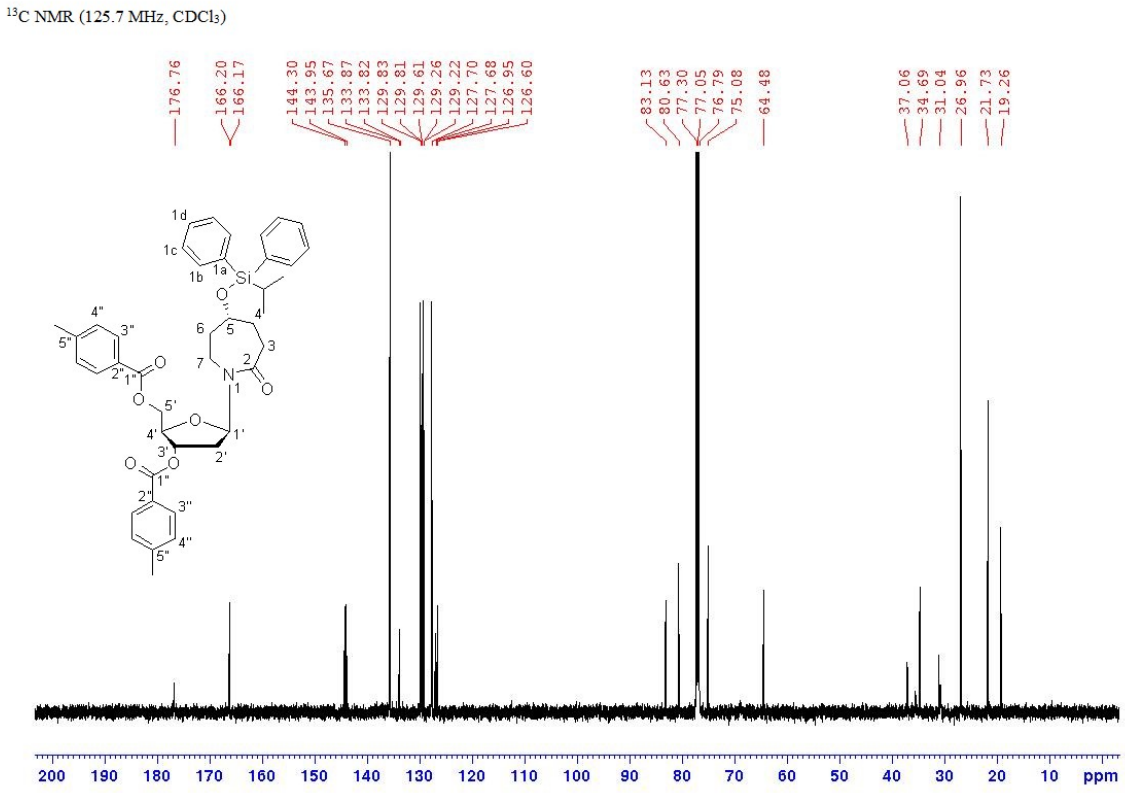


Figure S57. ^{13}C NMR spectrum of compound **25*R***.

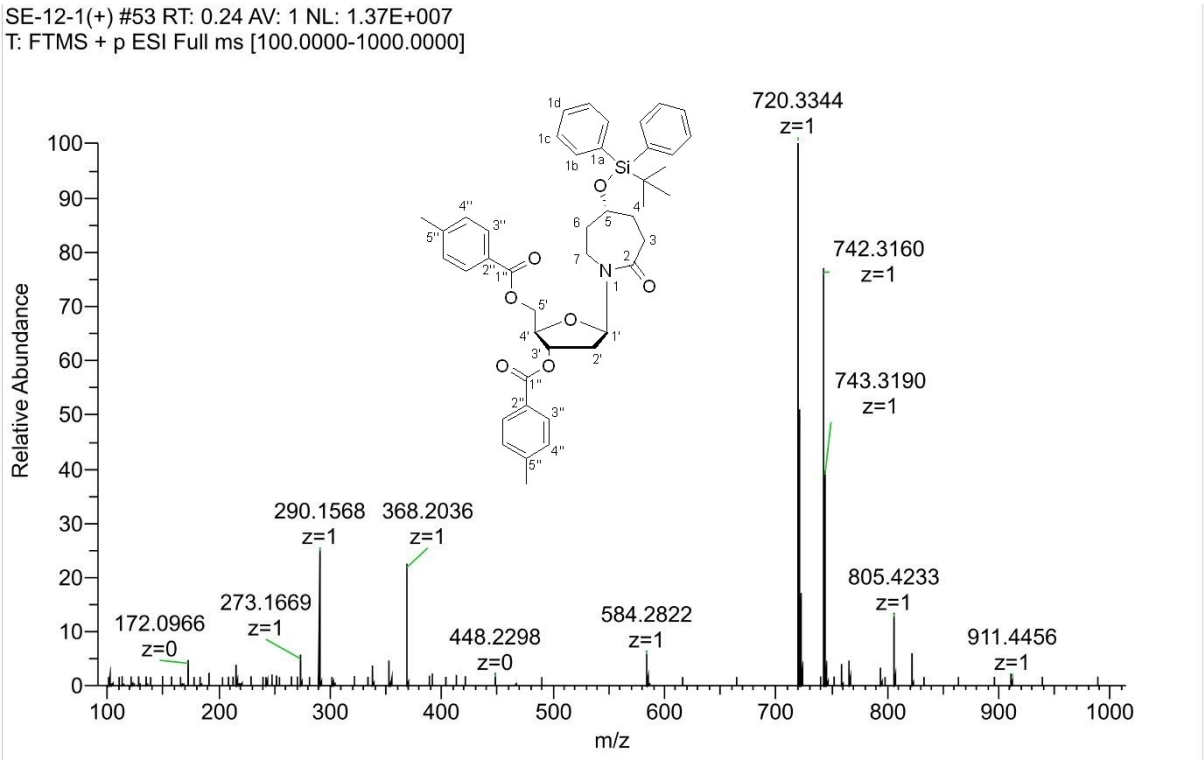


Figure S58. HRMS (ESI) of compound **25*R***.

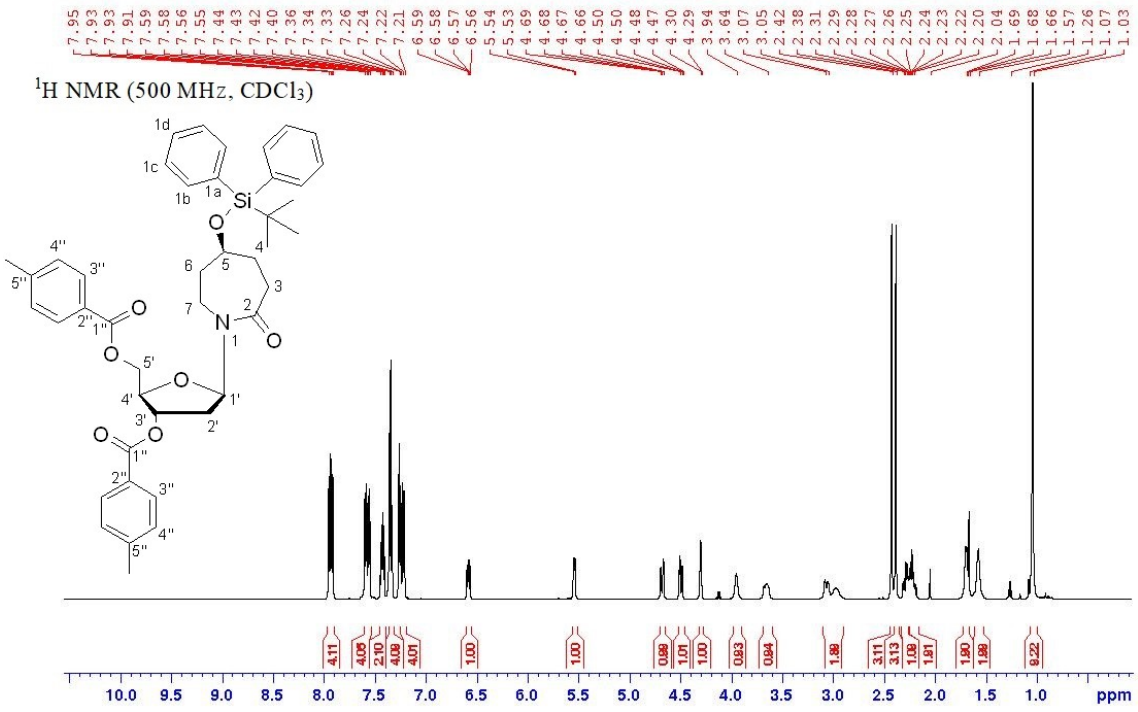


Figure S59. ^{1}H NMR spectrum of compound **25*S***.

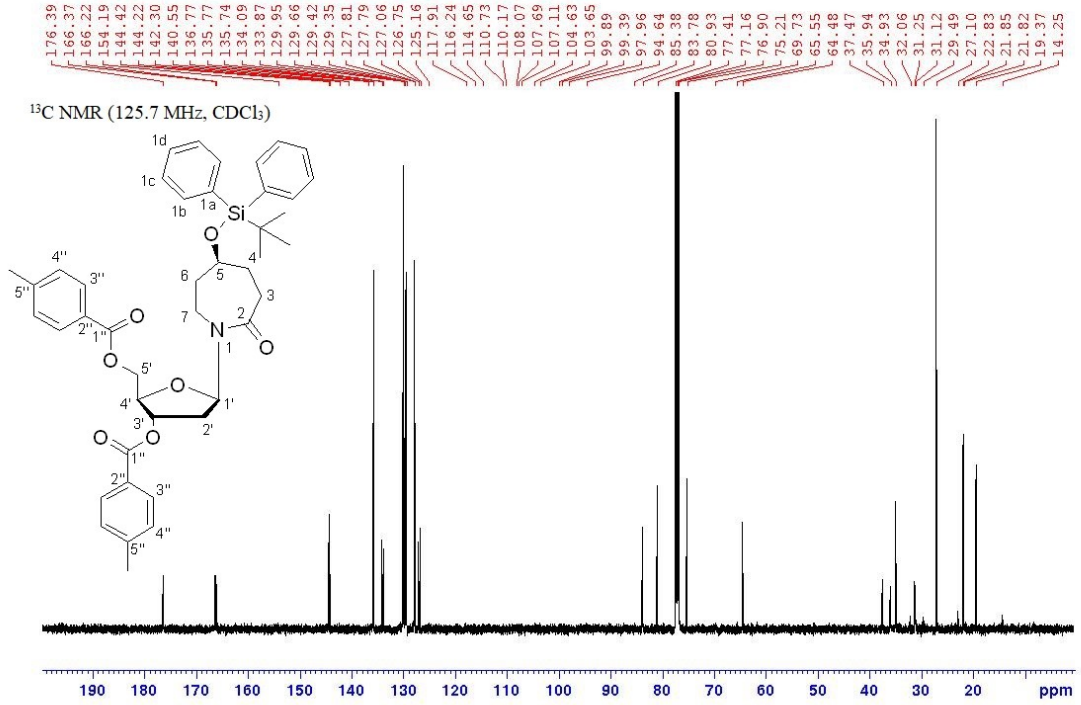


Figure S60. ^{13}C NMR spectrum of compound **25*S***.

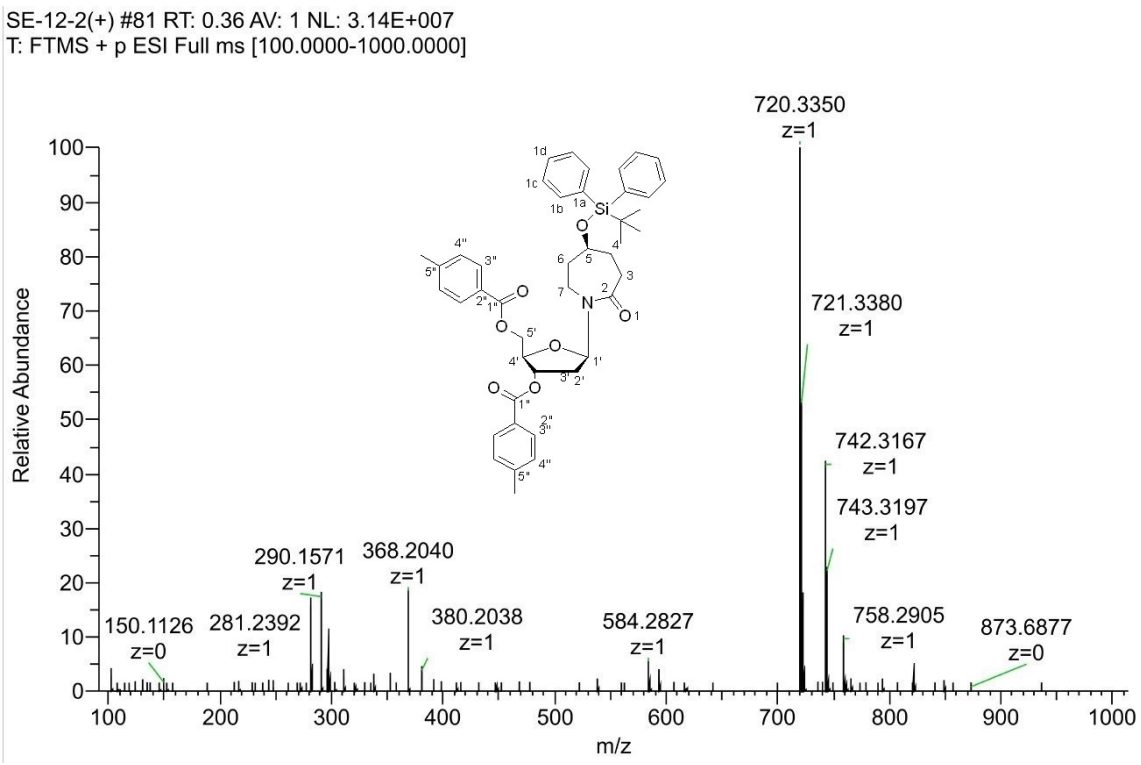


Figure S61. HRMS (ESI) of compound **25*S***.

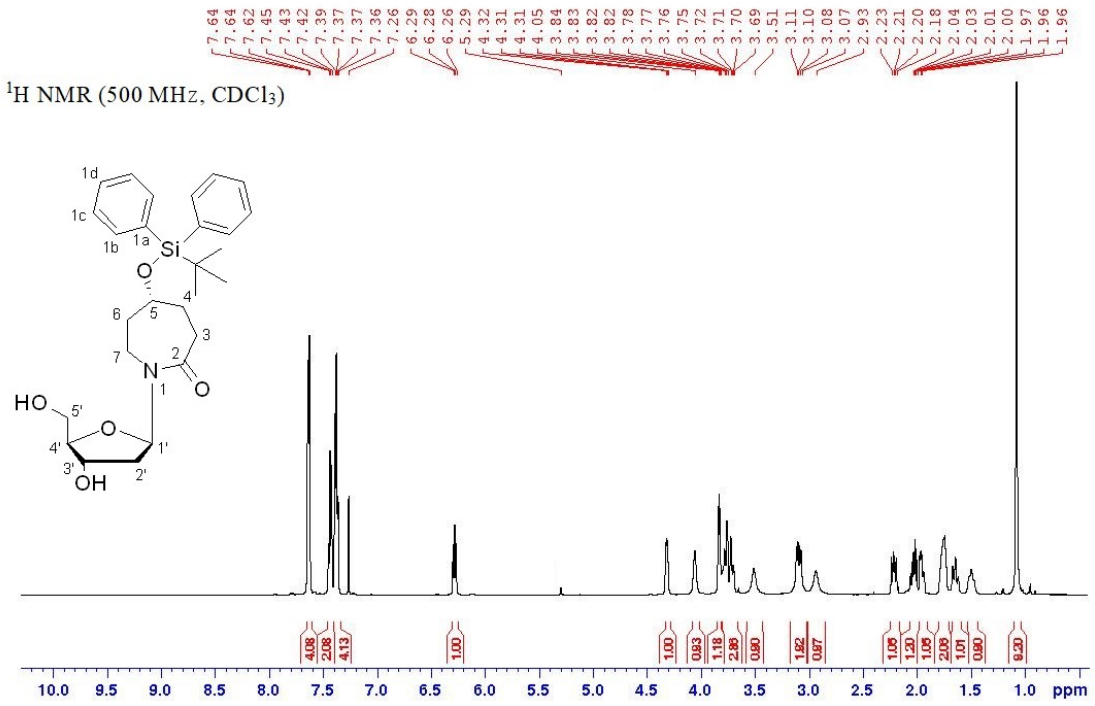


Figure S62. ^{1}H NMR spectrum of compound **26*R***.

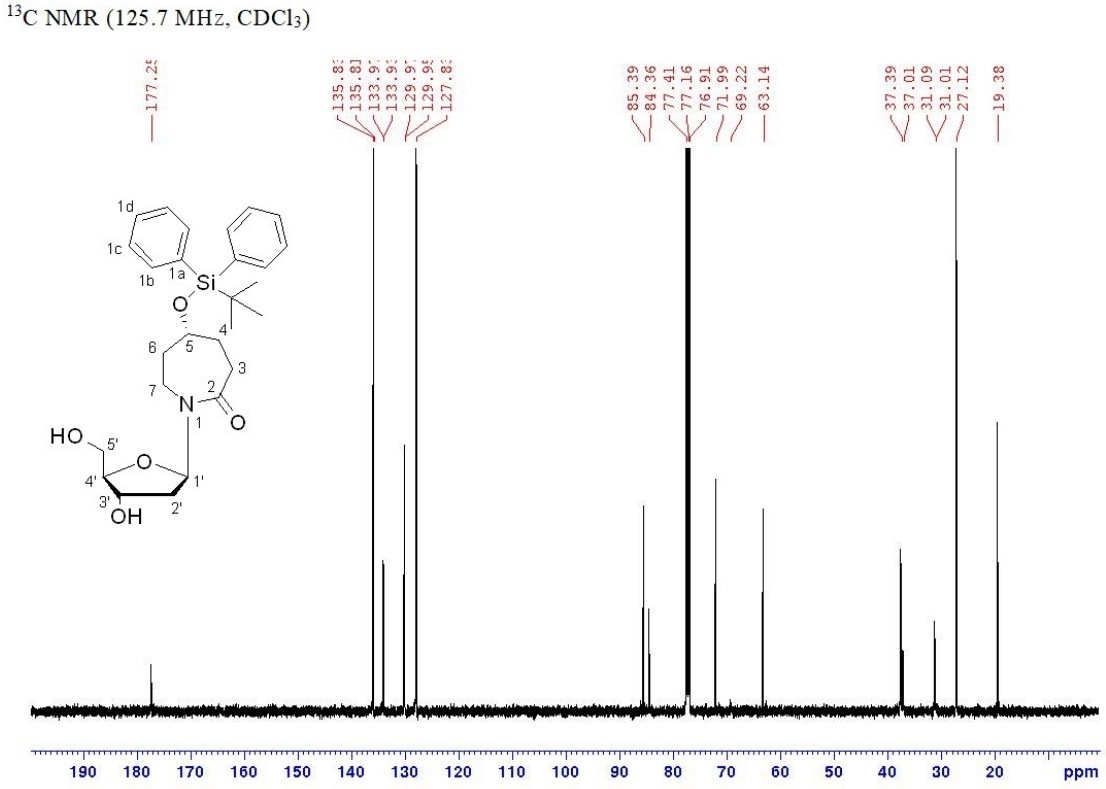


Figure S63. ^{13}C NMR spectrum of compound **26*R***.

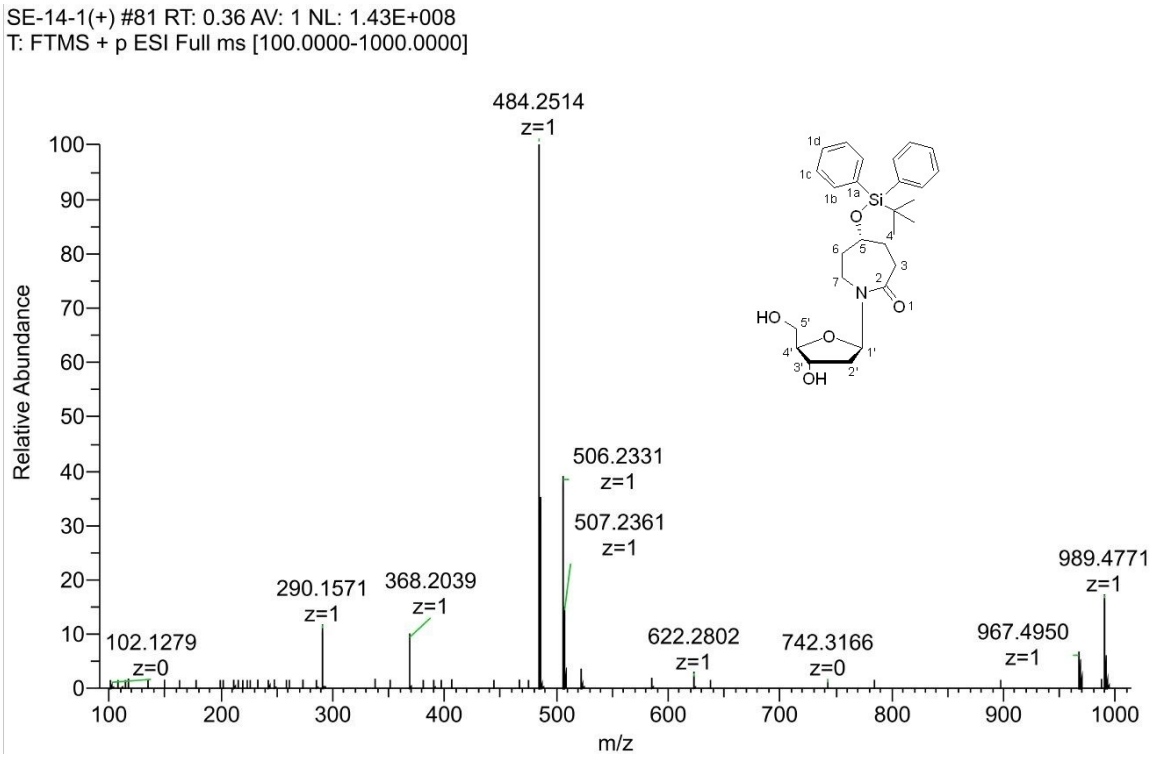


Figure S64. HRMS (ESI) of compound **26*R***.

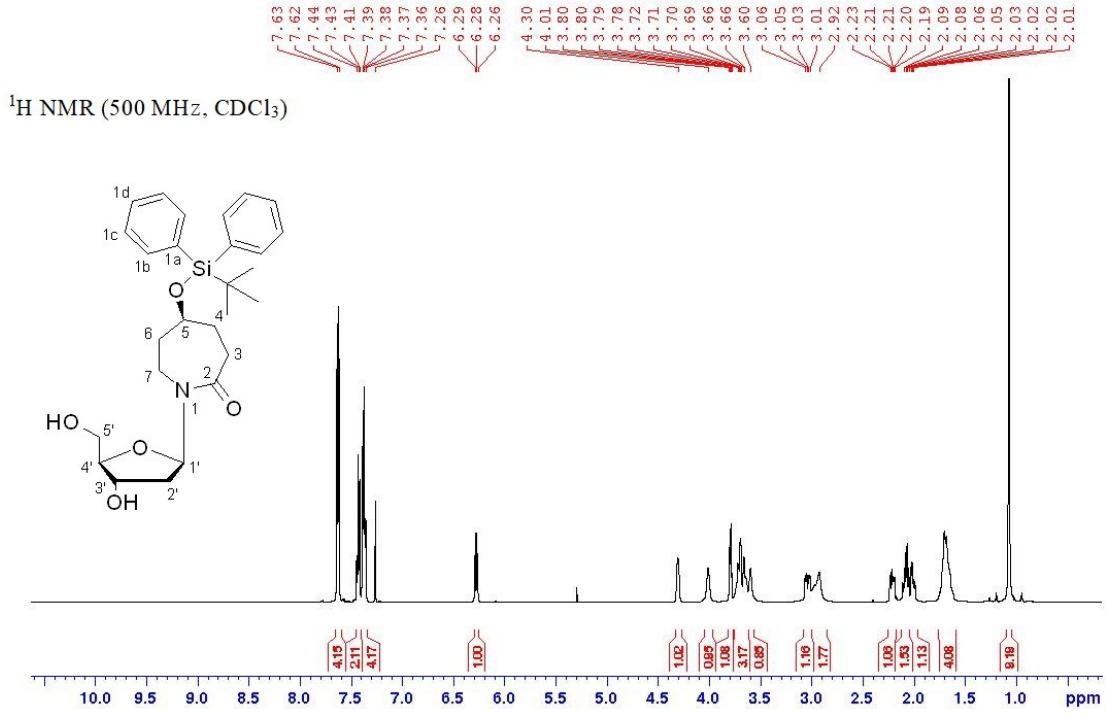


Figure S65. ^{1}H NMR spectrum of compound **26*S***.

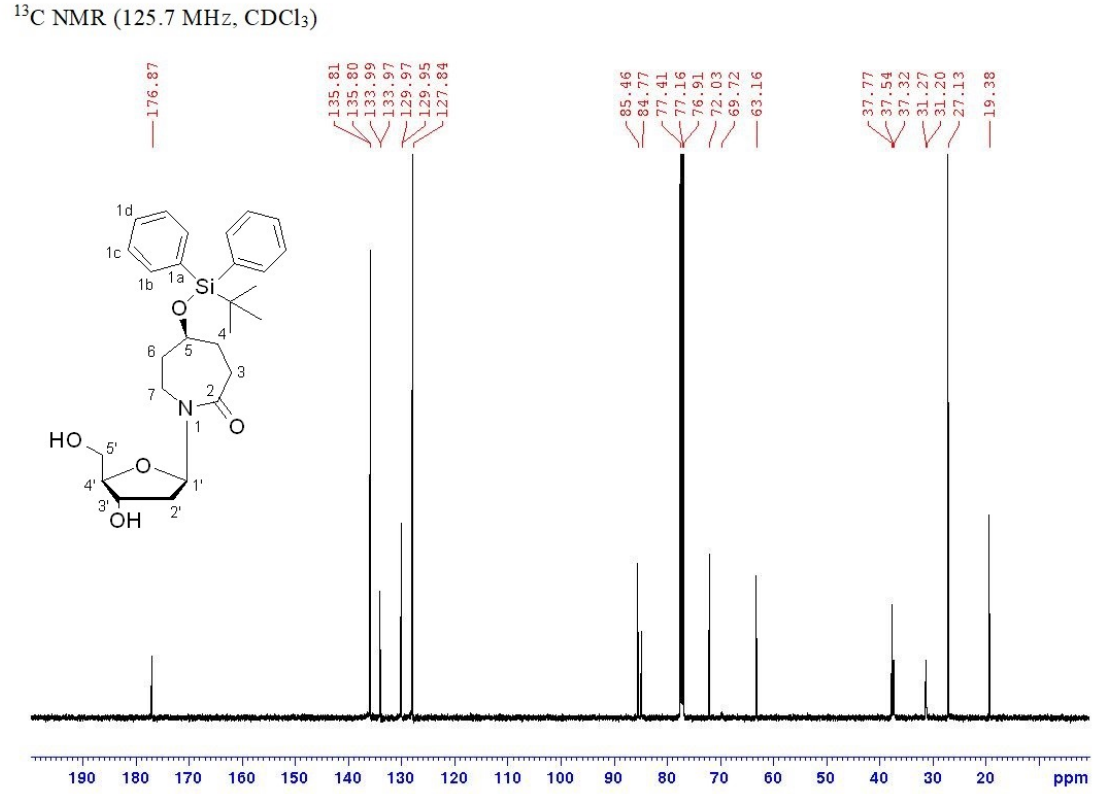


Figure S66. ^{13}C NMR spectrum of compound **26*S***.

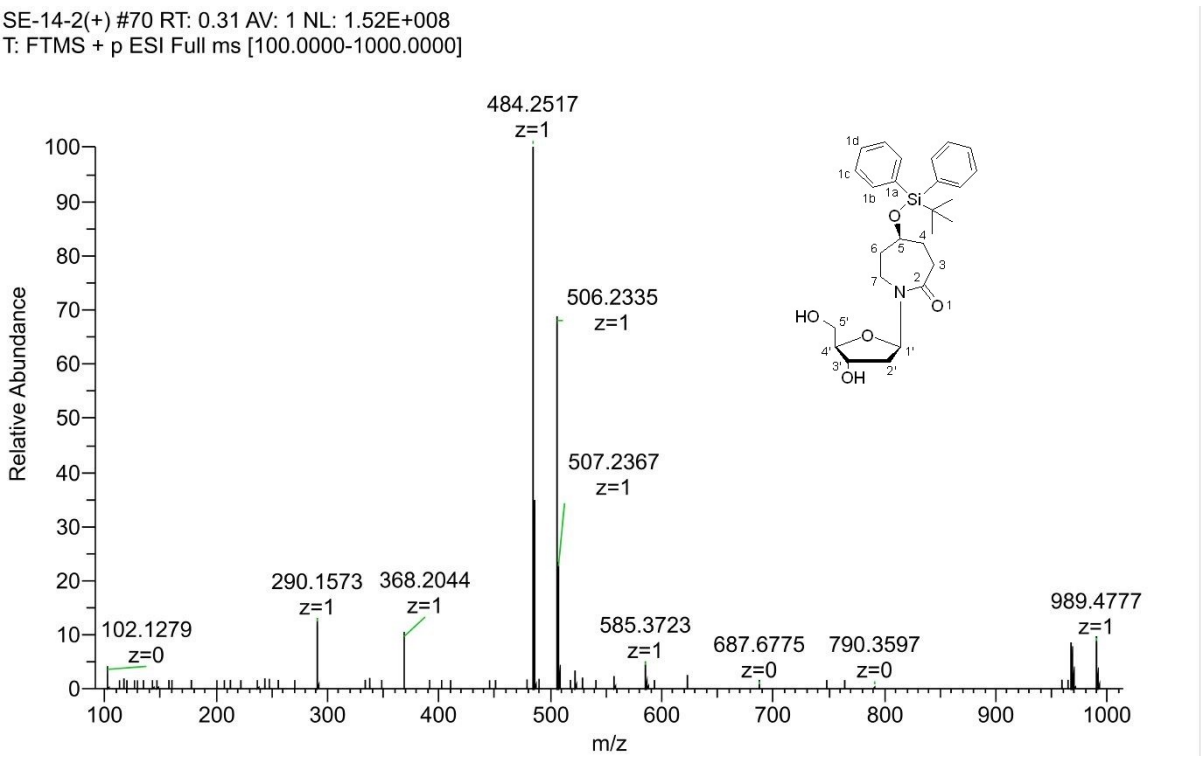


Figure S67. HRMS (ESI) of compound **26*S***.

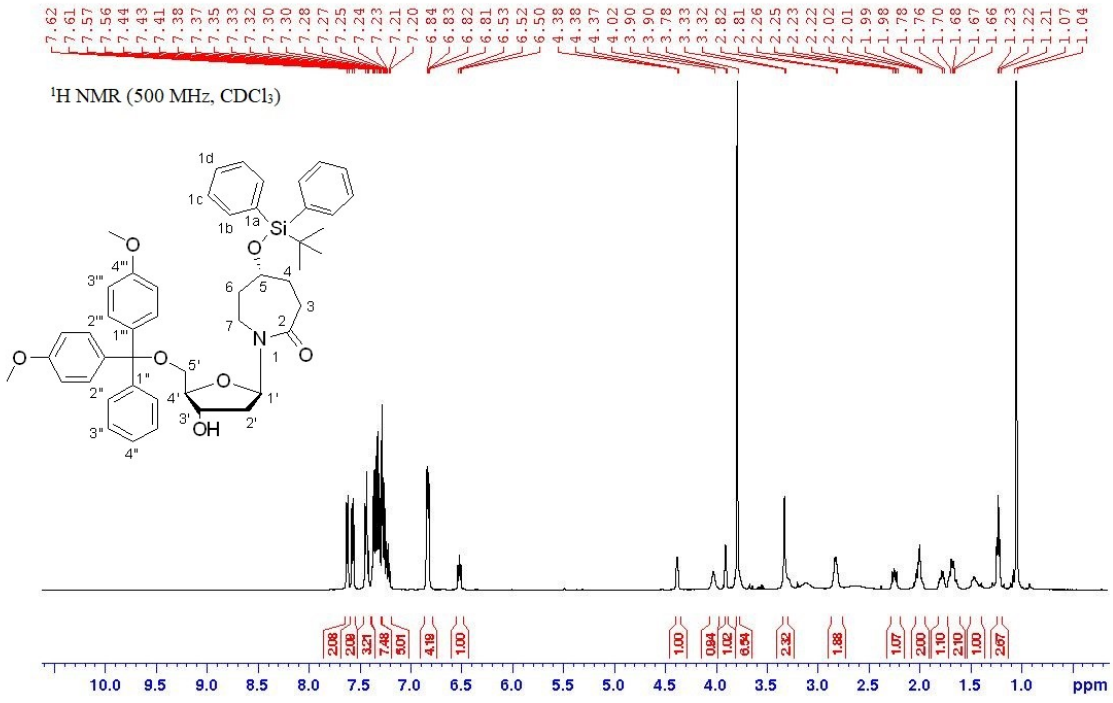


Figure S68. ^{1}H NMR spectrum of compound **27*R***.

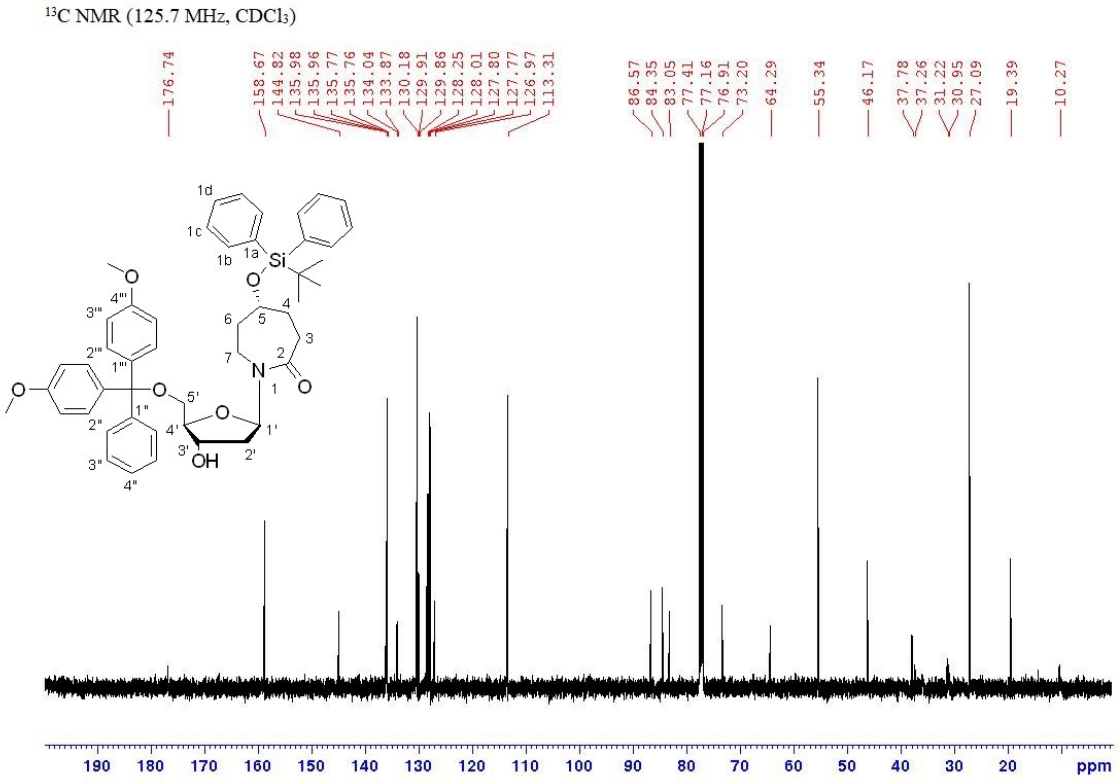


Figure S69.[13]C NMR spectrum of compound **27*R***.

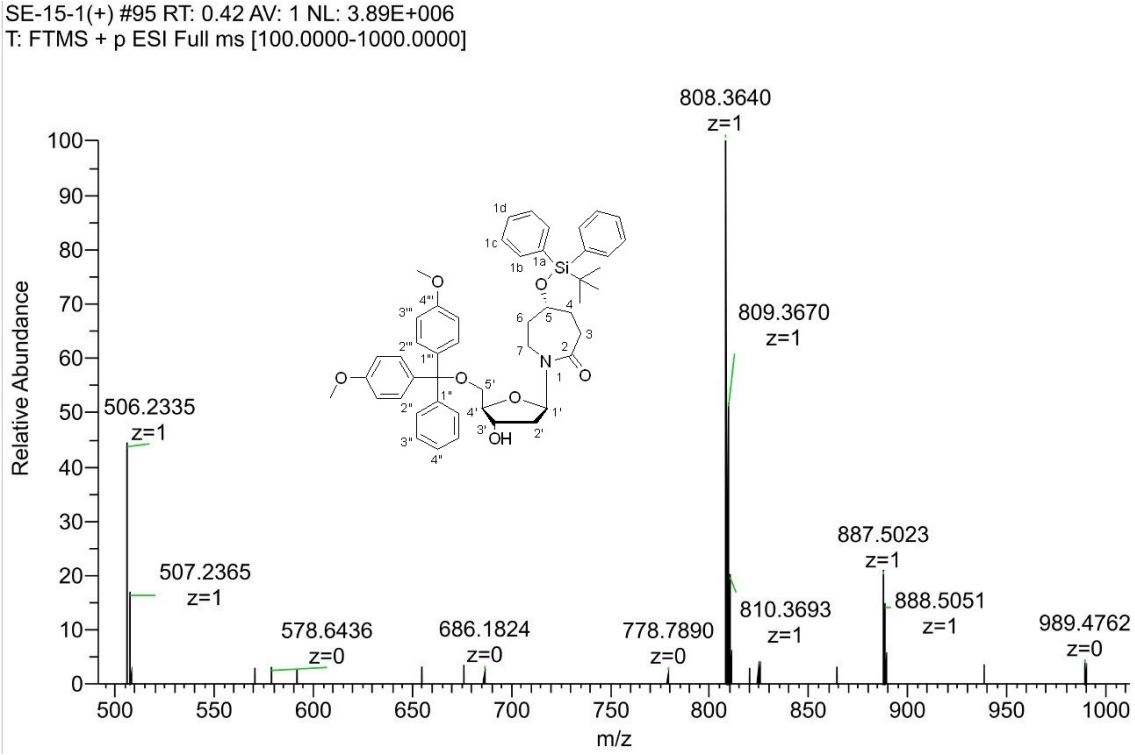


Figure S70. HRMS (ESI) of compound **27*R***.

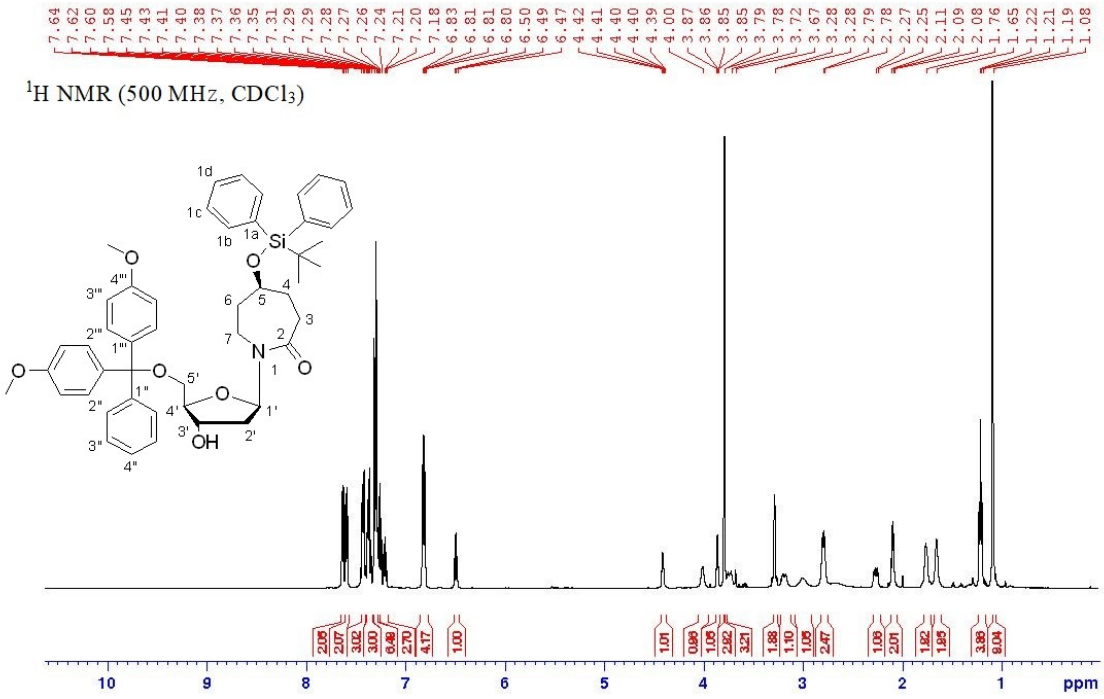


Figure S71. ^{1}H NMR spectrum of compound **27*S***.

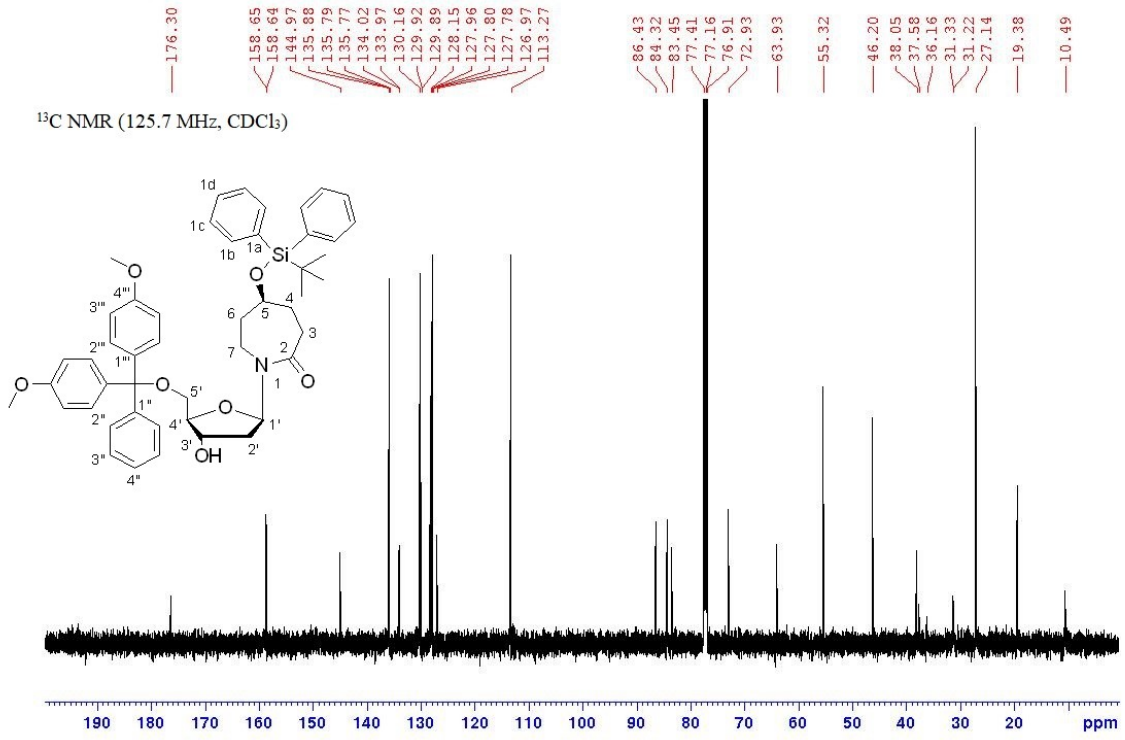


Figure S72. ^{13}C NMR spectrum of compound **27*S***.

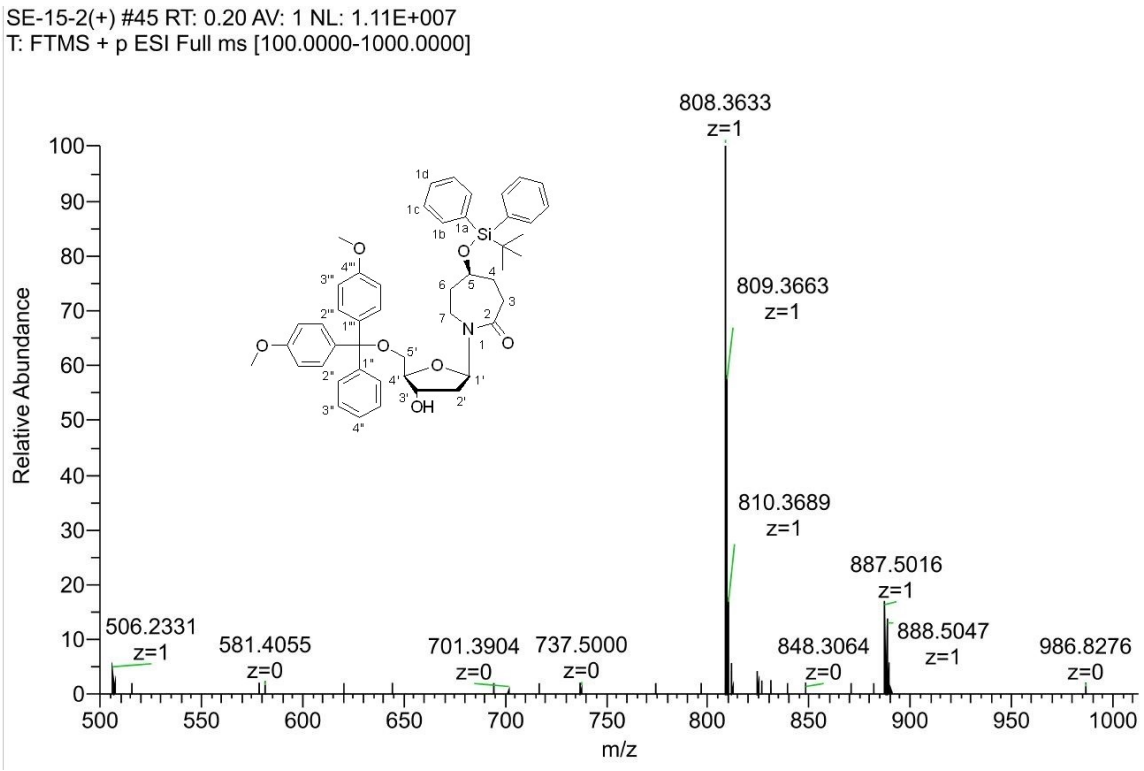


Figure S73. HRMS (ESI) of compound **27*S***.

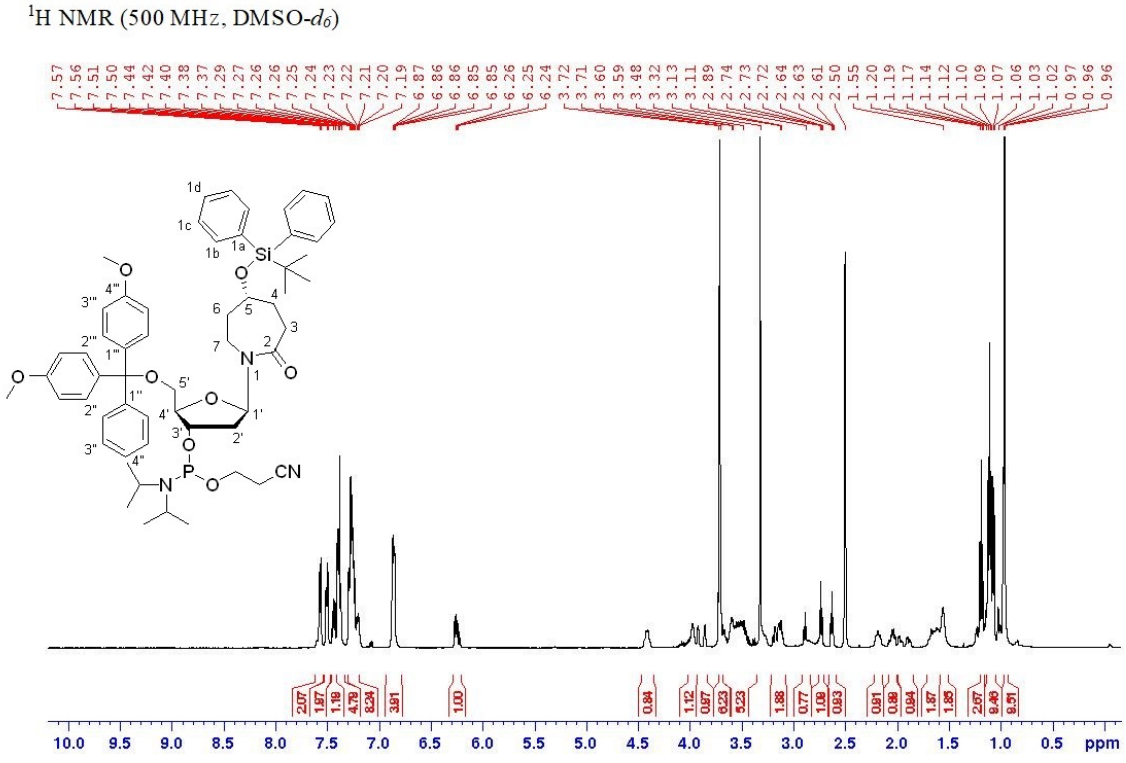


Figure S74. ^{1}H NMR spectrum of compound **28*R***.

^{13}C NMR (125.7 MHz, DMSO-d_6)

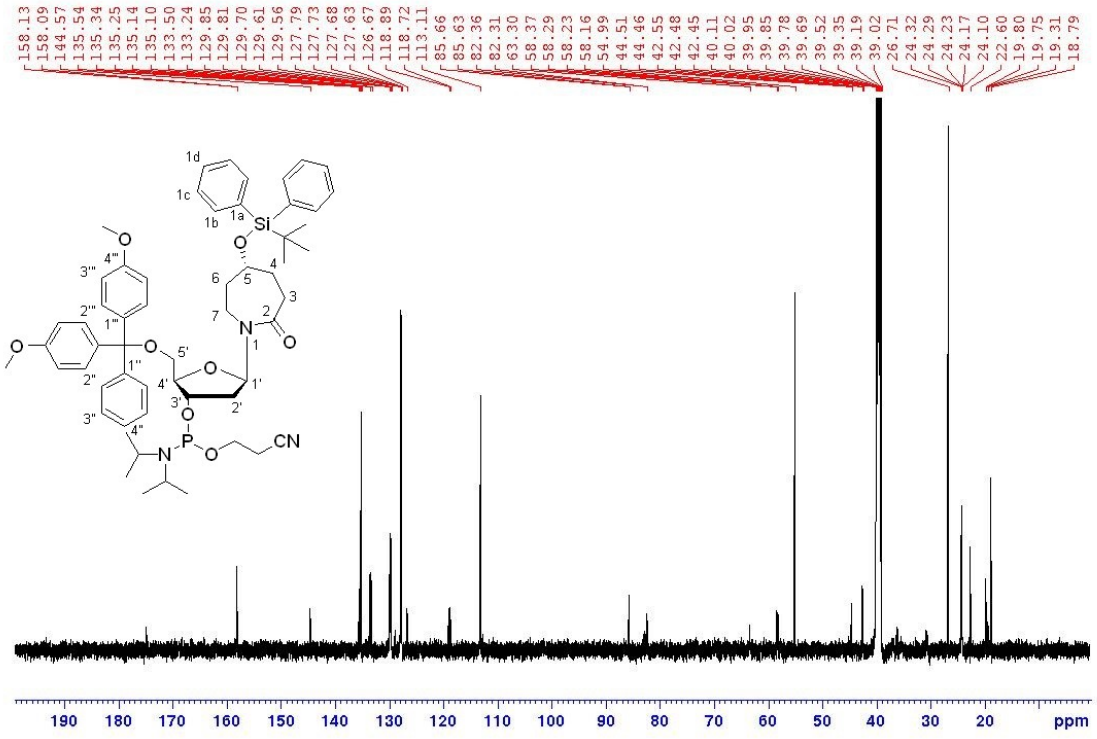


Figure S75. ^{13}C NMR spectrum of compound **28*R***.

^{31}P NMR (202.5 MHz, DMSO-d_6)

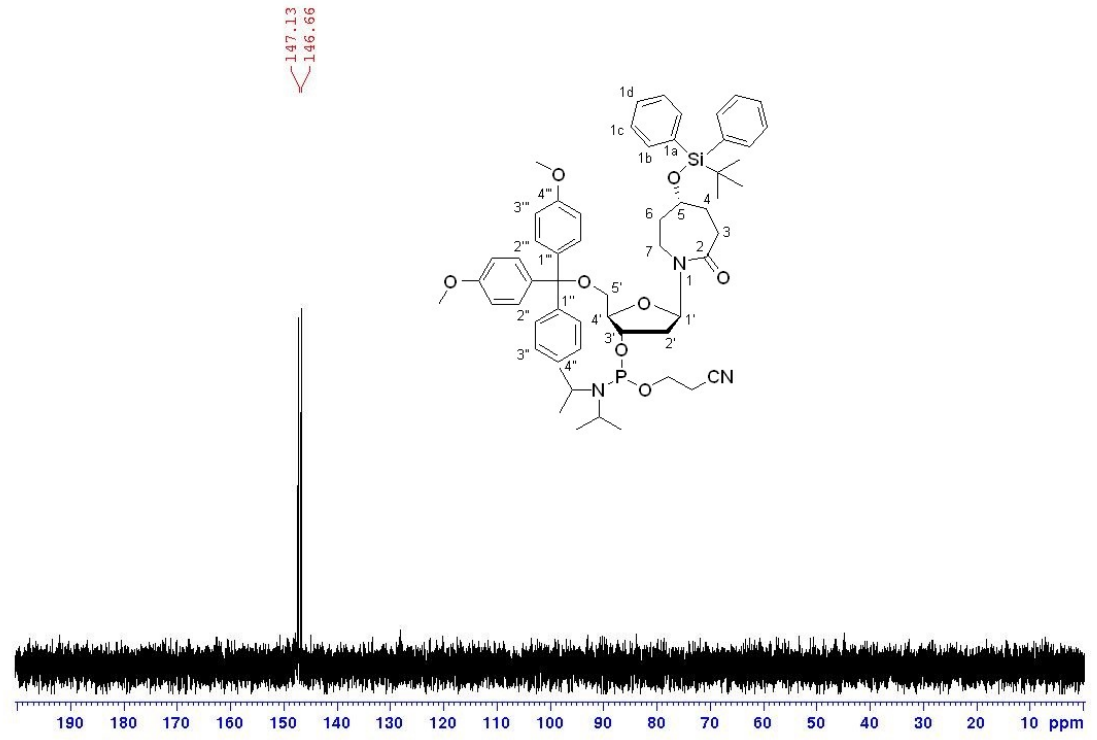


Figure S76. ^{31}P NMR spectrum of compound **28*R***.

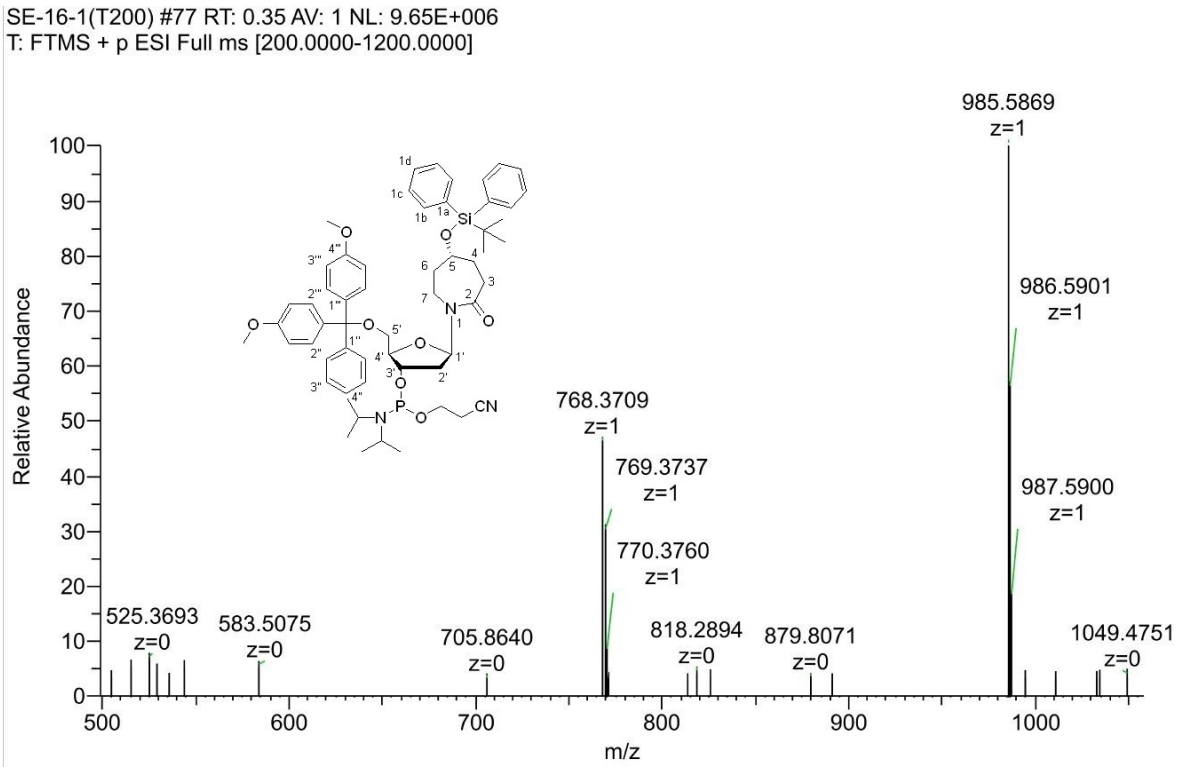


Figure S77. HRMS (ESI) of compound **28*R***.

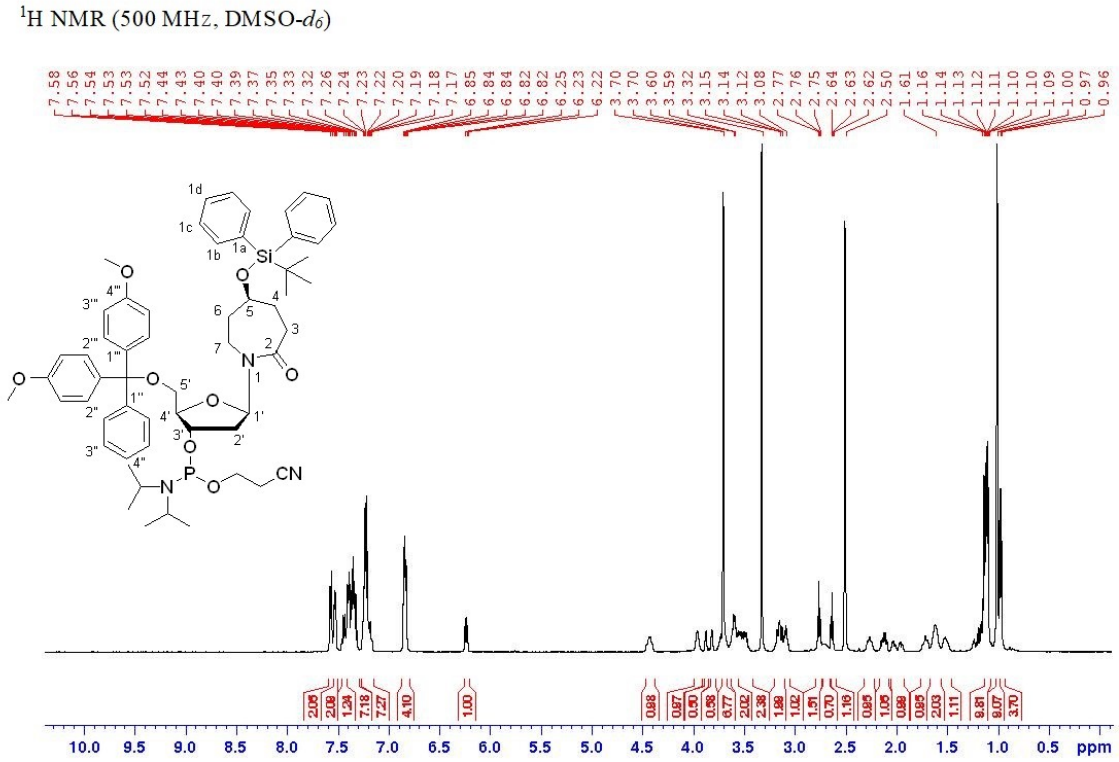


Figure S78. ^{1}H NMR spectrum of compound **28*S***.

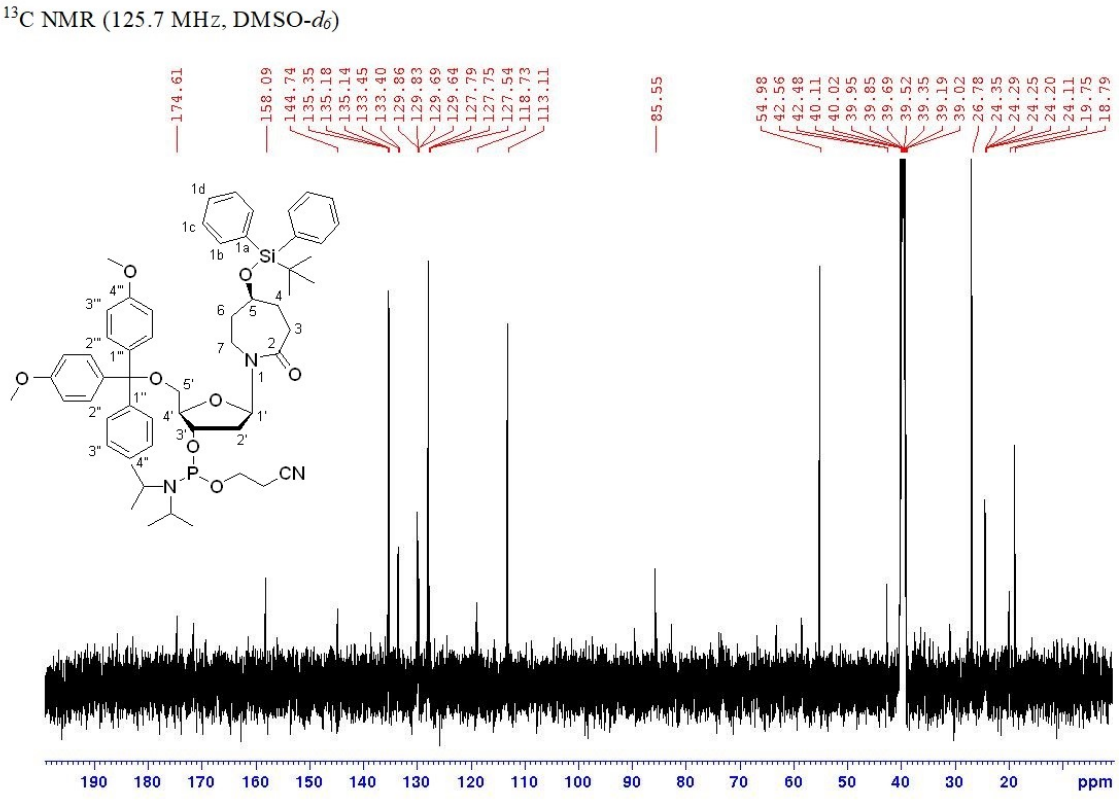


Figure S79. ^{13}C NMR spectrum of compound **28*S***.

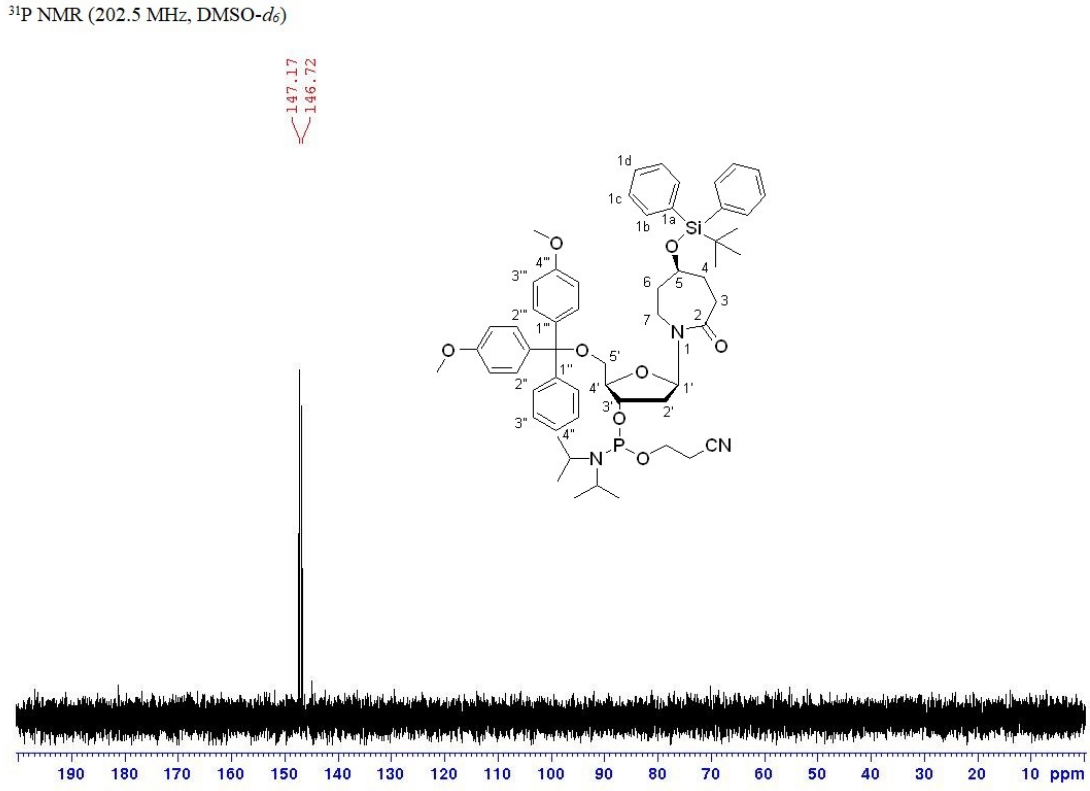


Figure S80. ^{31}P NMR spectrum of compound **28*S***.

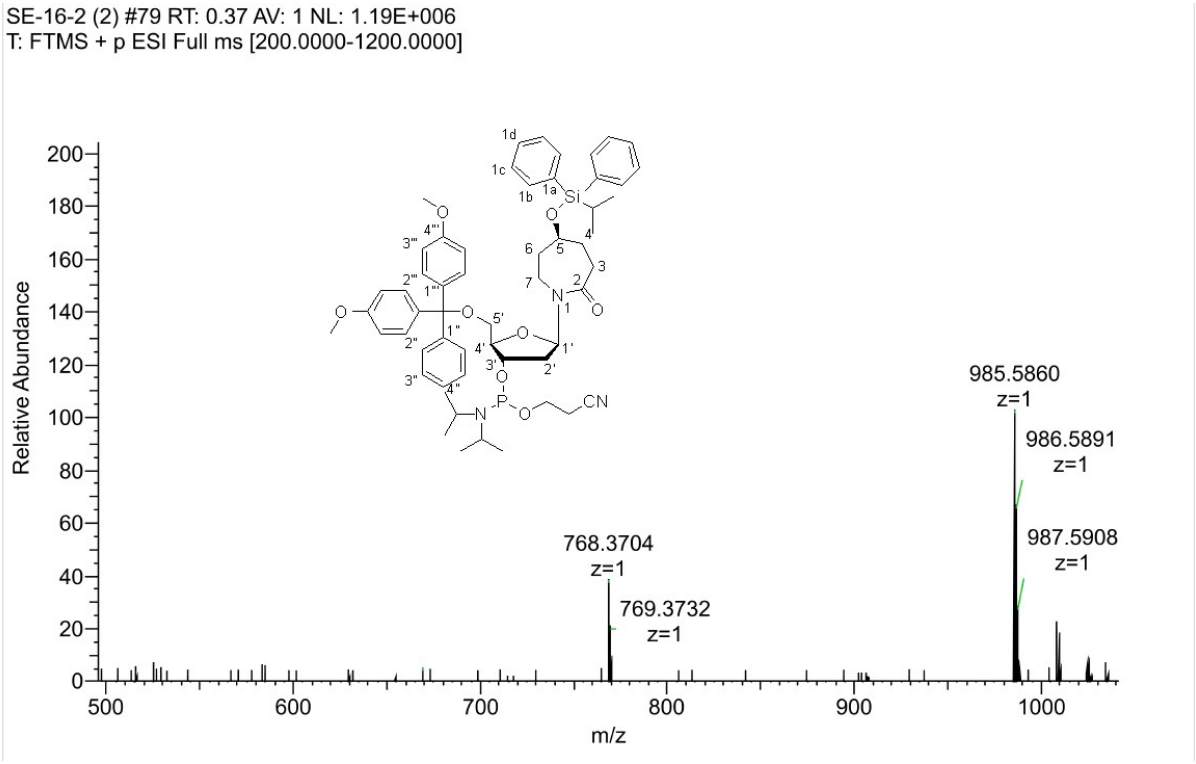


Figure S81. HRMS (ESI) of compound **28*S***.

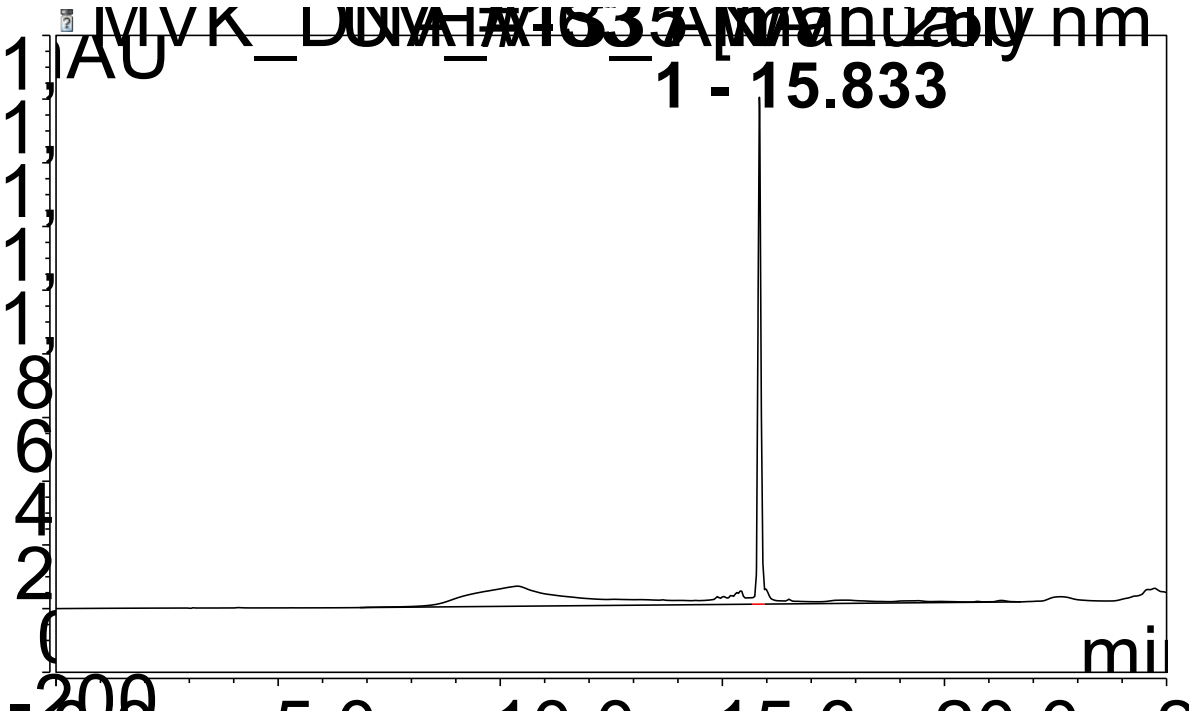


Figure S82. Reverse phase HPLC profile of 9-mer dDiAzep. Note that the broad peak at 10 min is an artefact of the buffer.

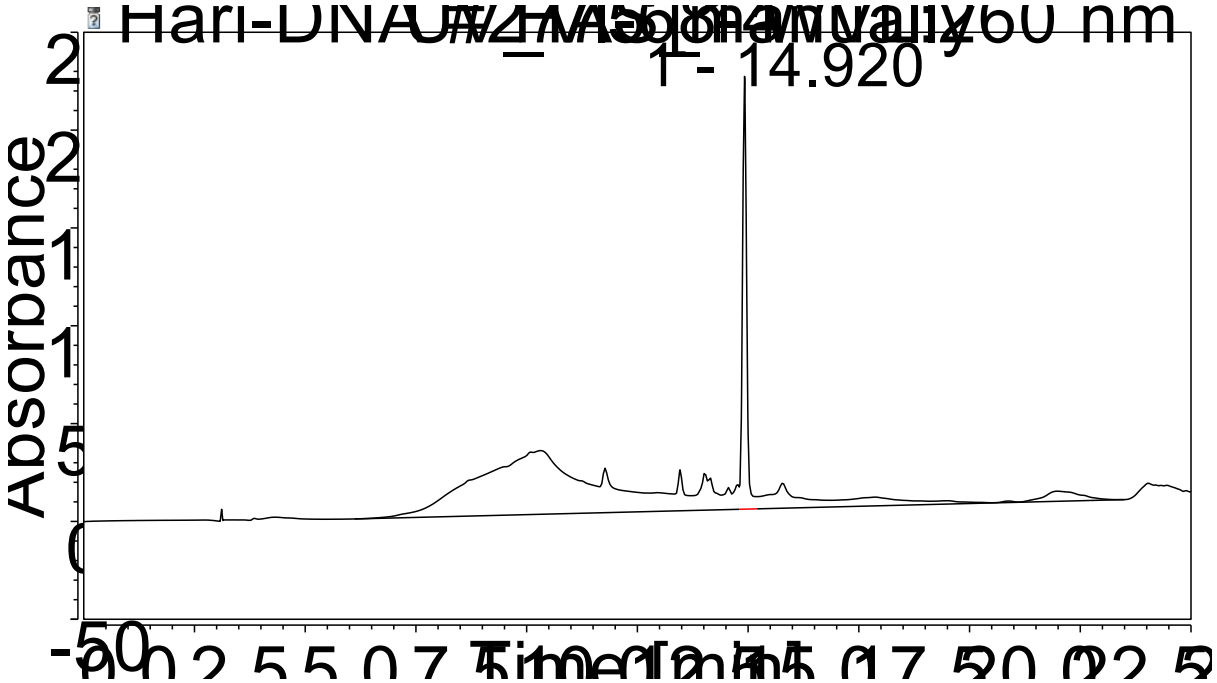


Figure S83. Reverse phase HPLC profile of 7-mer *R*-dAzep-OH. Note that the broad peak at 10 min is an artefact of the buffer.

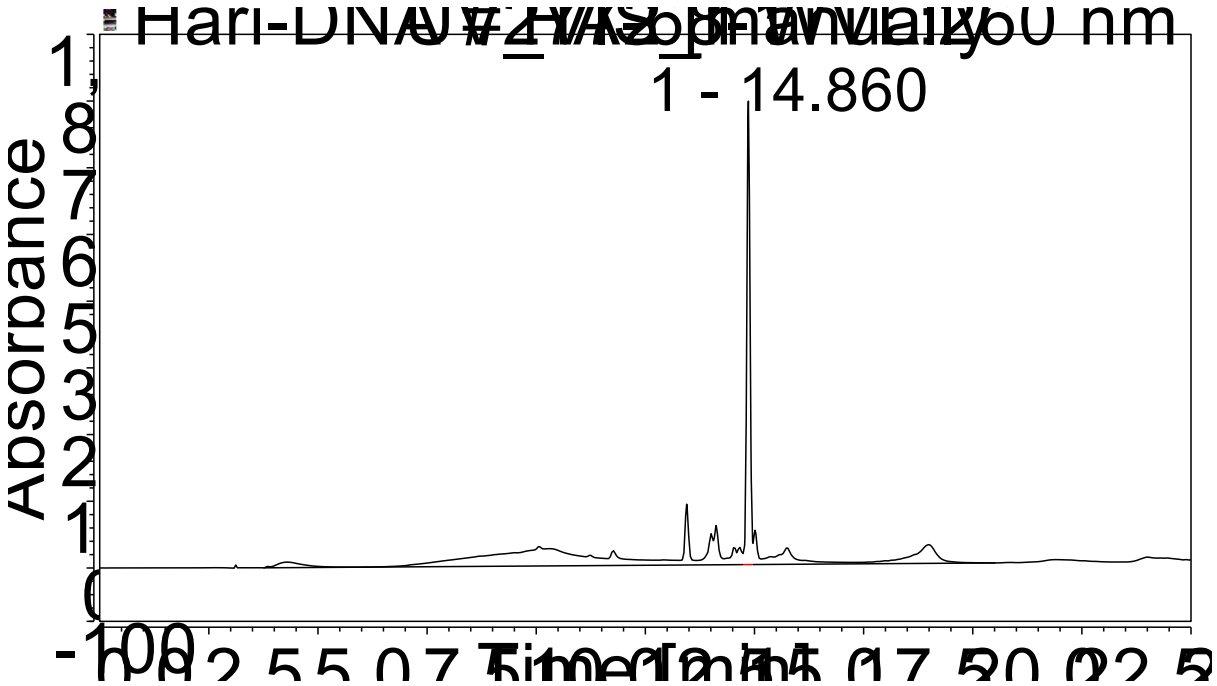


Figure S84. Reverse phase HPLC profile of 7-mer *S*-dAzep-OH. Note that the broad peak at 10 min is an artefact of the buffer.

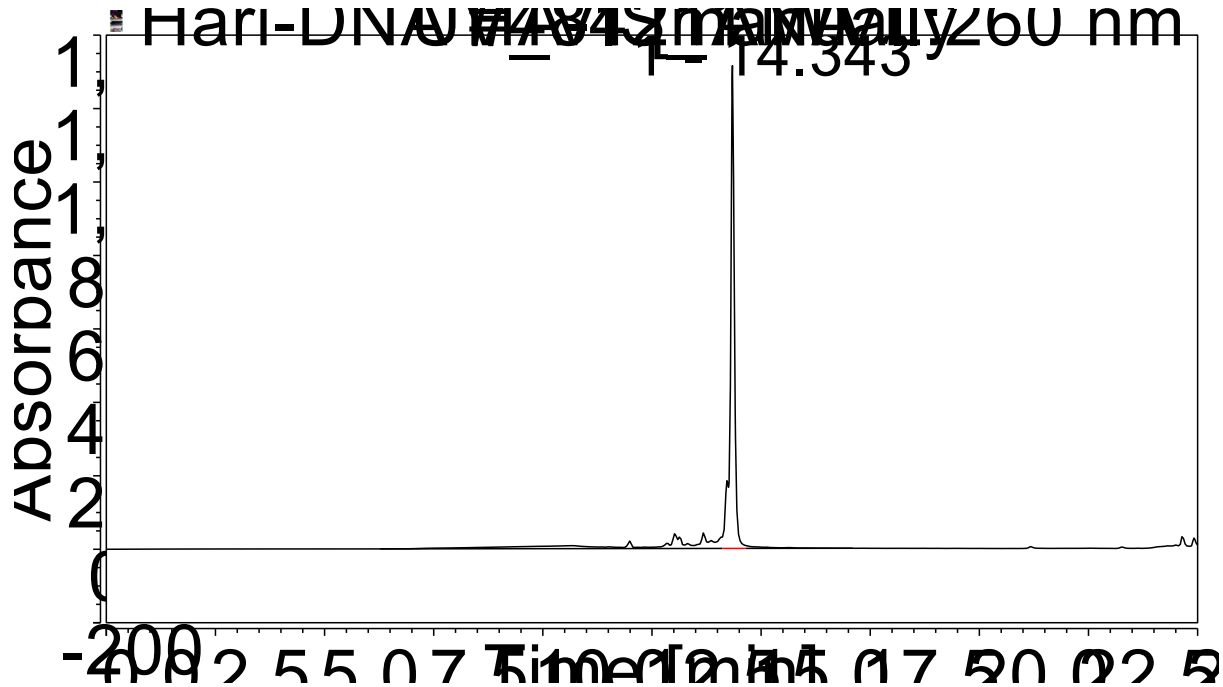


Figure S85. Reverse phase HPLC profile of **dDiAzep-hairpin**. Note that the broad peak at 10 min is an artefact of the buffer.

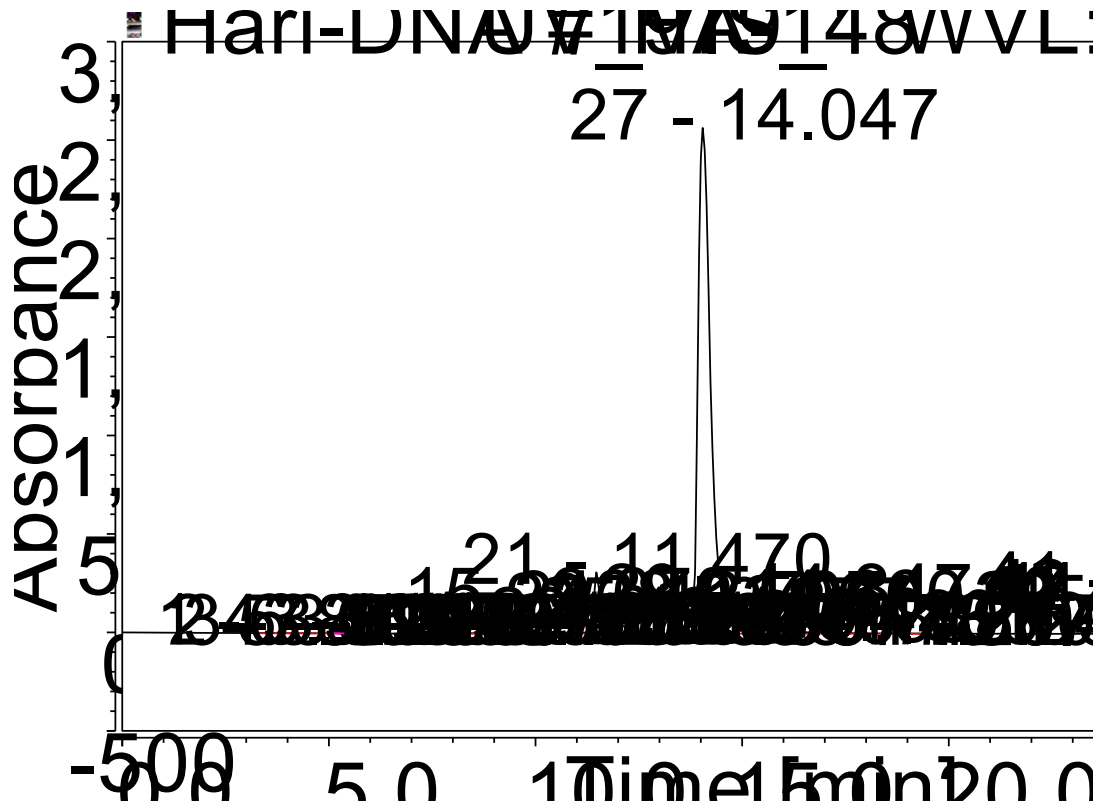


Figure S86. Reverse phase HPLC profile of ***S*-dAzep-OH-hairpin**. Note that the broad peak at 10 min is an artefact of the buffer.

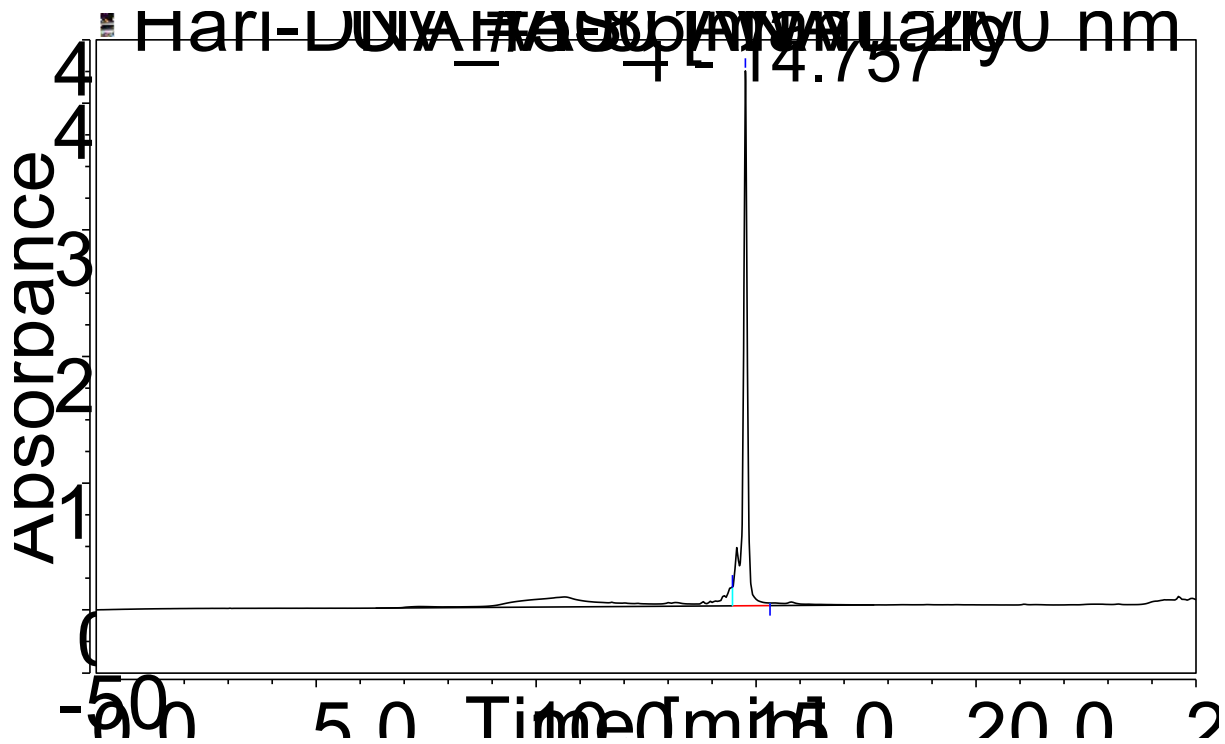


Figure S87. Reverse phase HPLC profile of **FdZ-hairpin**. Note that the broad peak at 10 min is an artefact of the buffer.

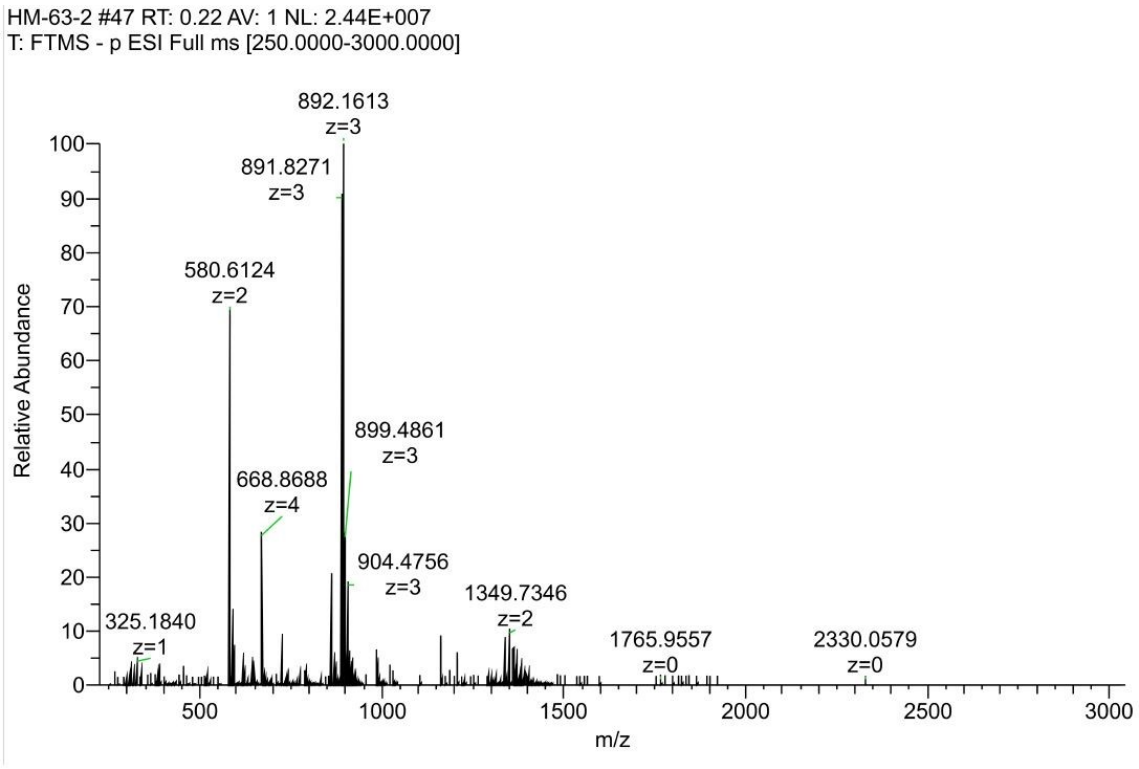


Figure S88. HRMS (ESI) of **9-mer dDiAzep.**

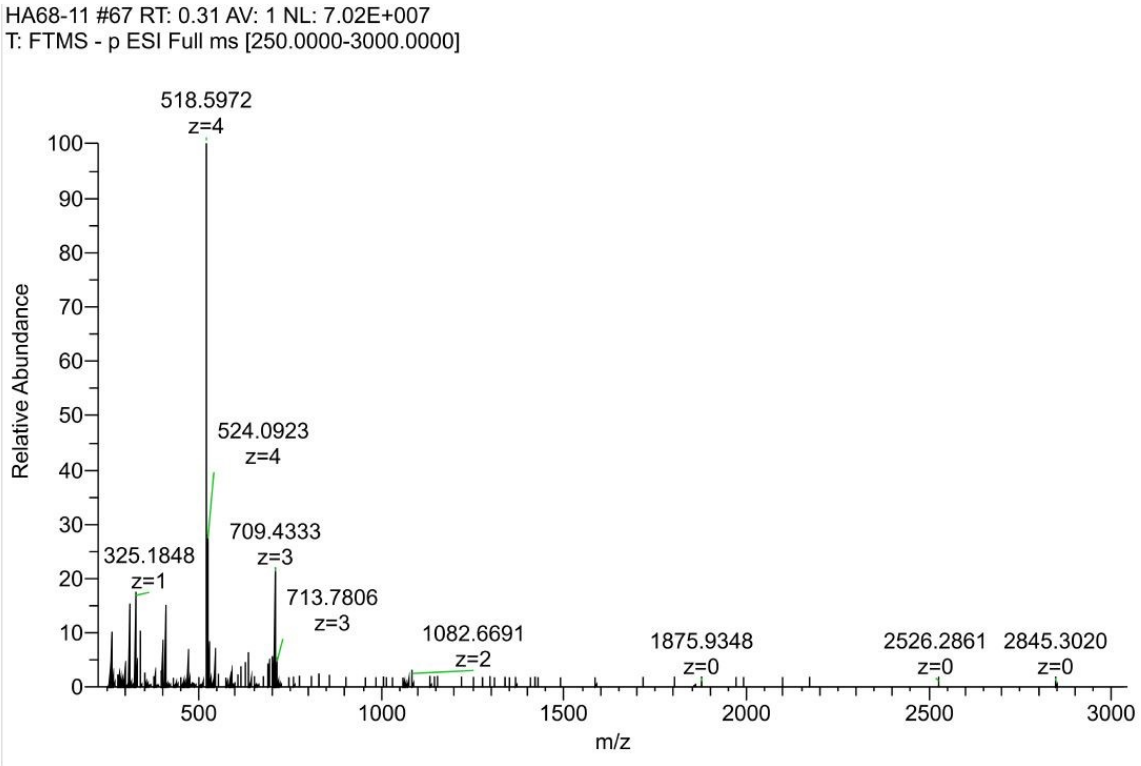


Figure S89. HRMS (ESI) of 7-mer ***R*-dAzep-OH.**

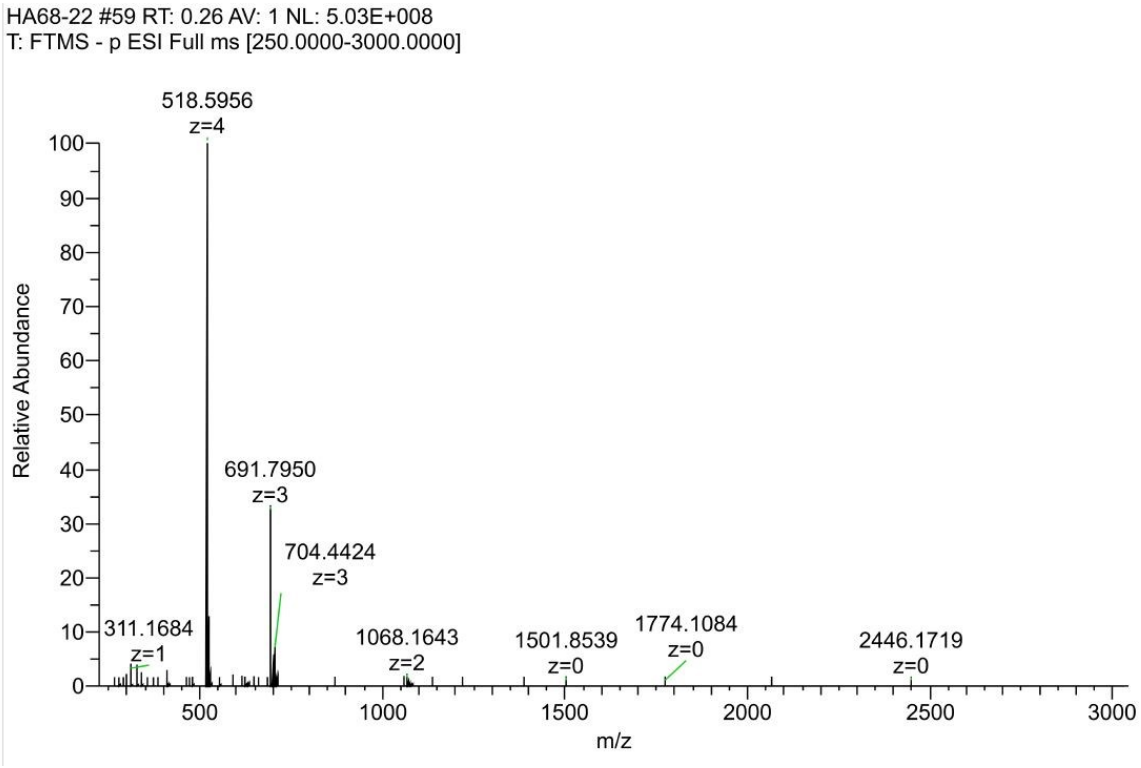


Figure S90. HRMS (ESI) of **7-mer *S*-dAzep-OH.**

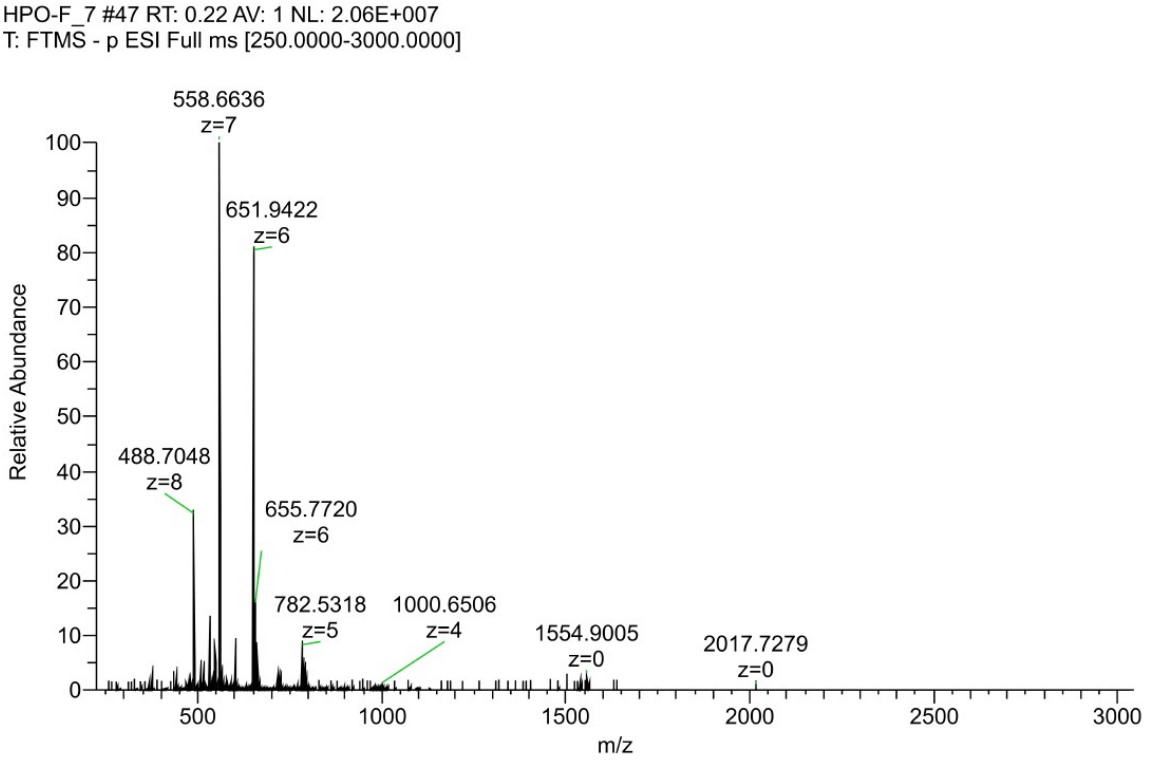


Figure S91. HRMS (ESI) of **dDiAzep-hairpin**.

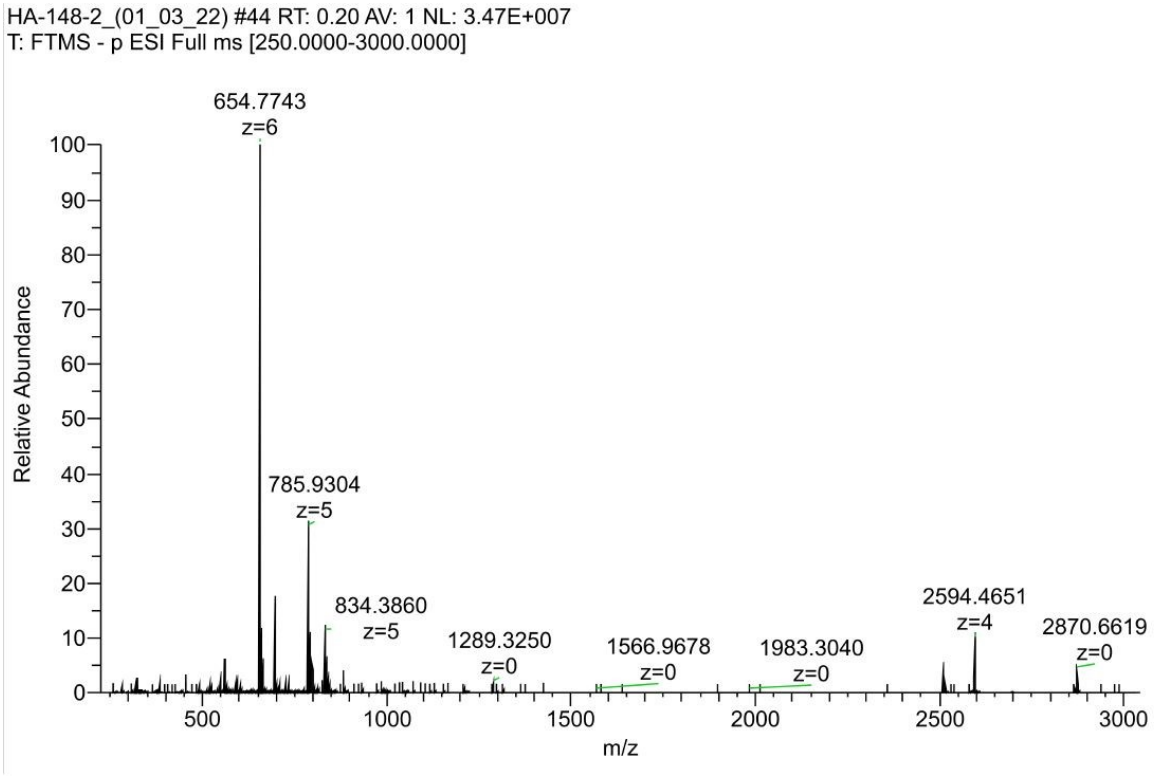


Figure S92. HRMS (ESI) of ***S*-dAzep-OH-hairpin**.

Figure S93. HRMS (ESI) of **FdZ**-hairpin.