SUPPORING INFORMATION

Synthesis and Anti-HBV Activity of Carbocyclic Nucleoside Hybrids with Salient Features of Entecavir and Aristeromycin

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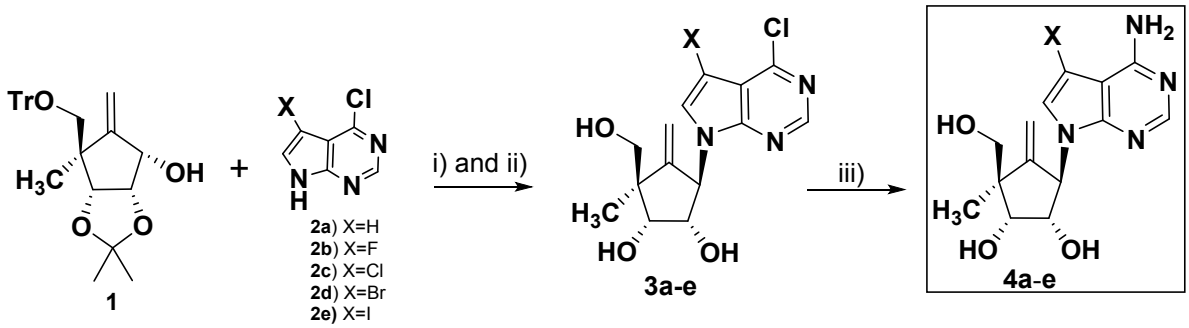
Experimental Section:

The ^{1}H and ^{13}C NMR spectroscopic data were recorded at 300 MHz or 400 MHz and 75 MHz or 100 MHz on a Varian NMR spectrometer with $CDCl_3$, DMSO-d_6 or CD_3OD as a solvent and in some cases TMS as internal standard (δ = 0). Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm. All coupling constants (*J* values) were expressed in Hertz (Hz). Multiplicities are stated as follows: singlet (s), doublet (d), double doublet (dd), triplet (t), and multiplet (m). Glassware for moisture-sensitive reactions was carried out under an atmosphere of argon. Melting points were recorded on a BUCHI (B-540) apparatus and are uncorrected. High-resolution mass spectra were recorded on a Thermo Q Exactive (resolution = 1, 40, 000 FWHM) under electrospray ionization (ESI) and are reported to four decimal places. Specific optical rotation measurements were carried out on a *JASCO* P-2000 digital polarimeter at 20 ^{o}C equipped with a PMT detector using the sodium line at 589 nm, and 2 mL (100 mm path length) cell. UV spectra were recorded on a Thermo Scientific Evolution 201 and 220 UV-Visible Spectrophotometers.



Scheme 1: Synthesis of **4a-e**. Reagents and conditions: **i**) PPh_3, DIAD, THF, 10 °C-rt, 1 h; **ii**) TFA:H_2O (8:2 ratio), rt, 30 min; **iii)** NH_3 in MeOH, 100 °C, sealed tube, 24 h.

General procedure for the synthesis of 3a-e: To a stirring solution of **1** (0.54 mmol), appropriate **2a-e** (0.71 mmol) and Ph_3P (1.36 mmol) in 5 ml dry THF was added DIAD (1.50 mmol) drop wise at 5-10 °C under argon atmosphere, stirring continued at rt for 1 h. Completion of reaction was monitored by TLC, volatiles were removed under reduced pressure. 10 mL TFA: water (8:2 ratio) was added to the crude at rt and stirred for 30 min. Up on consumption of starting material, the volatiles were removed under reduced pressure. The crude residue was partitioned between sat. $NaHCO_3$ solution (10 mL) and EtOAc (3 x 25 mL). The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (100-200 mesh), eluting up to 5% MeOH in CH_2Cl_2.

(1S,2R,3R,5R)-5-(4-Chloro-7H-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (3a): Purified yield: 45.4% (in two steps), off white solid, (TLC: R_f 0.3, 7% MeOH in CH_2Cl_2); $[\alpha]_D^{25}$: +21.6 (c = 0.25, MeOH); UV (MeOH) λ_{max}: 273.25 nm; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.21 (s, 3H), 3.52 (d, J = 11.2 Hz, 1H), 3.69 (d, J = 11.2 Hz, 1H), 4.03 (d, J = 4.4 Hz, 1H), 4.51 (d, J = 2.8 Hz, 1H), 4.77 (dd, J = 4.4 and 9.6 Hz, 1H), 5.07 (d, J = 3.2 Hz, 1H), 5.68–5.71 (m, 1H), 6.71 (d, J = 3.6 Hz, 1H), 7.64 (d, J = 3.6 Hz, 1H), 8.53 (s, 1H); MS-ESI (m/z): $[M+1]^+$ 309.97.

(1S,2R,3R,5R)-5-(4-Chloro-5-fluoro-7H-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (3b): Purified yield: 52% (in two steps), pale yellow solid, (TLC: R_f 0.3, 7% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: +6.4 (c = 0.25, DMSO); UV (MeOH) λ_{max}: 273.25 nm; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.19 (s, 3H), 3.51 (d, J = 11.1 Hz, 1H), 3.65 (d, J = 10.8 Hz, 1H), 4.00 (d, J = 4.5 Hz, 1H), 4.57 (d, J = 2.7 Hz, 1H), 4.65 (dd, J = 4.5 and 10.2 Hz, 1H), 5.09 (d, J = 3.0 Hz, 1H), 5.75–5.78 (m, 1H), 7.50 (d, J = 2.1 Hz, 1H), 8.55 (s, 1H); MS-ESI (*m*/*z*): $[M+1]^+$ 327.85.

(1S,2R,3R,5R)-5-(4,5-Dichloro-7H-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (3c): Purified yield: 65.6% (in two steps), off white

solid, (TLC: R_f 0.3, 7% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: –3.39 (c = 0.25, DMSO); UV (MeOH) λ_{max}: 273.25 nm; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.20 (s, 3H), 3.52 (d, J = 10.4 Hz, 1H), 3.66 (d, J = 11.6 Hz, 1H), 4.01 (d, J = 4.4 Hz, 1H), 4.56 (d, J = 2.4 Hz, 1H), 4.69 (dd, J = 4.8 and 10.0 Hz, 1H), 5.09 (d, J = 3.2 Hz, 1H), 5.74–5.78 (m, 1H), 7.71 (s, 1H), 8.56 (s, 1H); MS-ESI (m/z): $[M+1]^+$ 343.89.

(1S,2R,3R,5R)-5-(5-Bromo-4-chloro-7H-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (3d): Purified yield: 70.7% (in two steps), off white solid, (TLC: R_f 0.3, 7% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: +7.66 (c = 0.25, DMSO); UV (MeOH) λ_{max}: 273.25 nm; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.20 (s, 3H), 3.52 (d, J = 10.8 Hz, 1H), 3.67 (d, J = 11.2 Hz, 1H), 4.01 (d, J = 4.8 Hz, 1H), 4.56 (d, J = 2.8 Hz, 1H), 4.71 (dd, J = 4.8 and 10.4 Hz, 1H), 5.09 (d, J = 3.6 Hz, 1H), 5.74–5.78 (m, 1H), 7.77 (s, 1H), 8.56 (s, 1H); MS-ESI (m/z): $[M+1]^+$ 387.83 and $[M+2]^+$ 389.81.

(1S,2R,3R,5R)-5-(4-Chloro-5-iodo-7H-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (3e): Purified yield: 84.2% (in two steps), off white solid, (TLC: R_f 0.3, 7% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: + 8.99 (c = 0.25, DMSO); UV (MeOH) λ_{max}: 272.25 nm; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.19 (s, 3H), 3.52 (d, J = 10.8 Hz, 1H), 3.67 (d, J = 10.8 Hz, 1H), 4.01 (d, J = 4.4 Hz, 1H), 4.54 (d, J = 2.8 Hz, 1H), 4.72 (dd, J = 4.4 and 10.0 Hz, 1H), 5.08 (d, J = 2.8 Hz, 1H), 5.72–5.76 (m, 1H), 7.83 (s, 1H), 8.54 (s, 1H); MS-ESI (m/z): $[M+1]^+$ 435.80.

General procedure for the synthesis of 4a-e: A screw-cap vial equipped with a magnetic bar was charged with NH_3 in methanol (7M, 7 ml) and appropriate **3a-e** (0.80 mmol) was added. The vial was sealed and heated to 100 °C with stirring for 24 h. The reaction mixture was concentrated under reduced pressure and crude was purified by flash chromatography on silica gel (230-400 mesh, elution gradient 0-9% MeOH in CH_2Cl_2).

(1*S*,2*R*,3*R*,5*R*)-5-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (4a): Purified yield: 78%, off white solid, (TLC: R_f 0.2, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: +2.73 (c = 0.25, DMSO); mp: 210-220 °C; UV (MeOH) λ_{max}: 274.25 nm; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.19 (s, 3H), 3.51 (d, J = 10.8 Hz, 1H), 3.66 (d, J = 10.8 Hz, 1H), 4.01 (d, J = 5.2 Hz, 1H), 4.55 (d, J = 3.2 Hz, 1H), 4.73 (dd, J = 4.4 and 9.6 Hz, 1H), 5.07 (d, J = 3.2 Hz, 1H), 5.50–5.53 (m, 1H), 6.70 (d, J = 3.2 Hz, 1H), 7.27 (d, J = 3.2 Hz, 1H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.9, 49.2, 62.7, 69.2, 73.5, 74.3, 99.8, 102.0, 107.8, 123.8, 148.3, 149.5, 155.0, 155.3; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{14}H_{19}N_4O_3$ $[M+H]^+$: 291.1457, found: 291.1422.

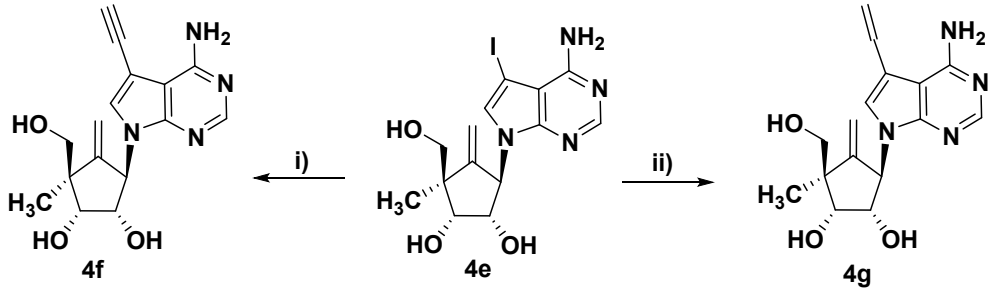
(1*S*,2*R*,3*R*,5*R*)-5-(4-Amino-5-fluoro-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (4b): Purified yield: 55%, off white solid, (TLC: Rf 0.2, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: –6.43 (c = 0.25, DMSO); mp: 243–247 °C; UV (MeOH) λ_{max}: 280.25 nm; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.18 (s, 3H), 3.50 (d, J = 10.8 Hz, 1H), 3.63 (d, J = 10.8 Hz, 1H), 3.98 (d, J = 4.8 Hz, 1H), 4.59 (d, J = 3.2 Hz, 1H), 4.63 (dd, J = 4.5 and 9.6 Hz, 1H),

5.07 (d, J = 3.3 Hz, 1H), 5.47–5.51 (m, 1H), 7.00 (d, J = 2.1 Hz, 1H), 8.02 (s, 1H); ^{19}F NMR (376 MHz, DMSO-d_6) δ : –168.25; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.9, 49.1, 62.0, 69.1, 73.4, 74.2, 91.9, 105.2, 107.8, 140.3, 146.4, 152.3, 154.2, 155.7; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{14}H_{18}FN_4O_3$ $[M+H]^+$: 309.1285, found: 309.1325.

(1*S*,2*R*,3*R*,5*R*)-5-(4-Amino-5-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin -7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (4c): Purified yield: 80%, off white solid, (TLC: Rf 0.2, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: –30.41 (c = 0.25, DMSO); mp: 226–229 °C; UV (MeOH) λ_{max}: 281.25 nm; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.18 (s, 3H), 3.51 (d, J = 11.1 Hz, 1H), 3.65 (d, J = 10.8 Hz, 1H), 3.99 (d, J = 4.8 Hz, 1H), 4.59 (d, J = 2.7 Hz, 1H), 4.68 (dd, J = 4.8 and 9.9 Hz, 1H), 5.08 (d, J = 3.0 Hz, 1H), 5.46–5.51 (m, 1H), 7.24 (s, 1H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.9, 49.2, 62.4, 69.1, 73.5, 74.2, 99.4, 101.4, 107.9, 120.0, 149.6, 152.2, 154.7, 156.7; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{14}H_{18}ClN_4O_3$ $[M+H]^+$: 325.0989, found: 325.1031.

(1*S*,2*R*,3*R*,5*R*)-5-(4-Amino-5-bromo-7*H*-pyrrolo[2,3-*d*] pyrimidin -7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (4d): Purified yield: 75%, off white solid, (TLC: Rf 0.2, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: +6.14 (c = 0.25, DMSO); mp: 228–232 °C; UV (MeOH) λ_{max}: 283.25 nm; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.18 (s, 3H), 3.51 (d, J = 11.1 Hz, 1H), 3.65 (d, J = 11.1 Hz, 1H), 3.98 (d, J = 4.5 Hz, 1H), 4.58 (d, J = 2.7 Hz, 1H), 4.69 (dd, J = 4.8 and 9.9 Hz, 1H), 5.08 (d, J = 2.7 Hz, 1H), 5.48–5.51 (m, 1H), 7.30 (s, 1H), 8.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.9, 49.2, 62.5, 69.1, 73.5, 74.2, 85.4, 100.6, 107.9, 122.5, 150.0, 152.0, 154.7, 156.8; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{14}H_{18}BrN_4O_3$ $[M+H]^+$: 369.0484, found: 369.0522.

(1*S*,2*R*,3*R*,5*R*)-5-(4-Amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (4e): Purified yield: 80%, off white solid, (TLC: Rf 0.2, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: +1.92 (c = 0.25, DMSO); mp: 227–228 °C; UV (MeOH) λ_{max}: 290.25 nm; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.17 (s, 3H); 3.51 (d, J = 11.1 Hz, 1H), 3.65 (d, J = 10.8 Hz, 1H), 3.99 (d, J = 4.8 Hz, 1H), 4.57 (d, J = 2.4 Hz, 1H), 4.70 (dd, J = 4.8 and 9.9 Hz, 1H), 5.07 (d, J = 3.0 Hz, 1H), 5.40–5.50 (m, 1H), 7.37 (s, 1H), 8.04 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.9, 49.2, 50.4, 62.6, 69.2, 73.6, 74.3, 102.8, 107.9, 127.9, 150.7, 151.6, 154.8, 157.1; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{14}H_{18}IN_4O_3$ $[M+H]^+$: 417.0345, found: 417.0377.



Scheme 2. Synthesis of 7-ethynyl/vinyl derivatives (**4f-g**). Reagents and conditions: **i**) a) Trimethylsilylacetylene, CuI, Et_3N, $Pd(PPh_3)_4$, DMF, 50 °C, 3 h; b) K_2CO_3, MeOH, rt, 30 min; **ii**) Tri-*n*-butyl vinyl tin, $Pd(PPh_3)_4$, DMF, 110 °C, 3 h.

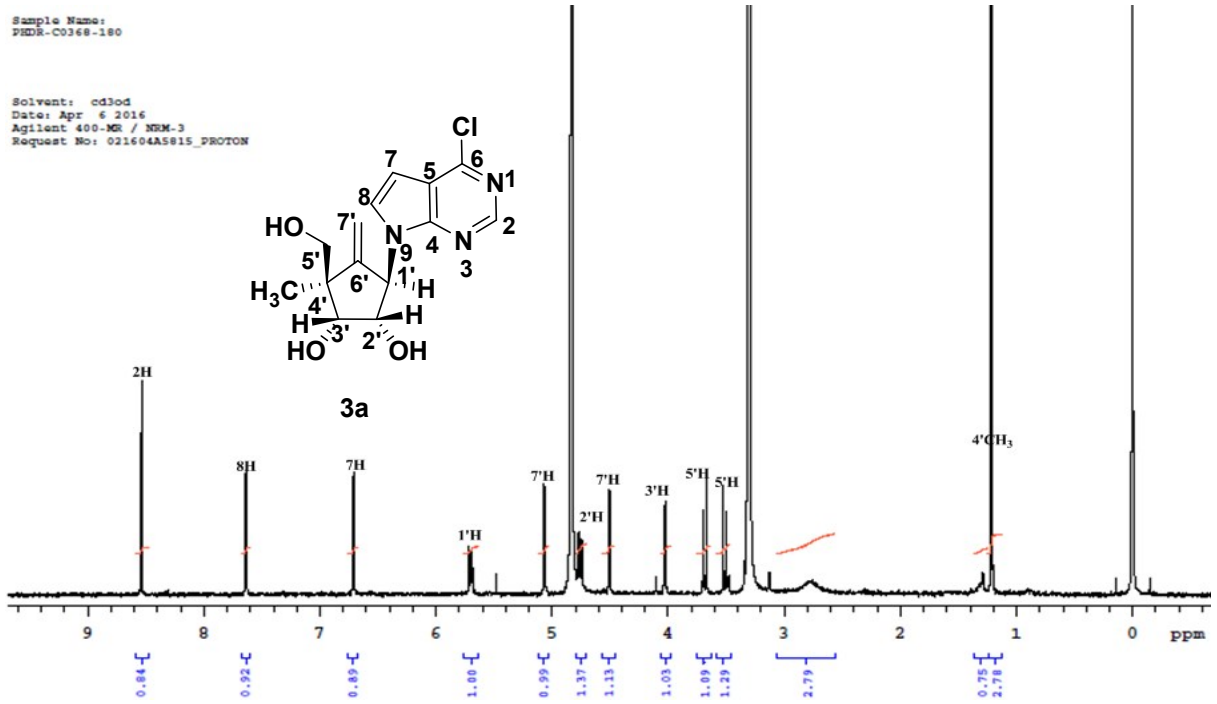
Procedure for the synthesis of 4f: A suspension of **4e** (0.60 mmol), trimethylsilyl acetylene (3.0 mmol), CuI (0.06 mmol), Et_3N (3.0 mmol) and $(PPh_3)_4Pd$ (0.06 mmol) in DMF was stirred at 50 °C under sealed condition for 3 h. The reaction mixture was concentrated under reduced pressure and crude was purified by silica gel (100-200 mesh) column chromatography, elution gradient 0-6% MeOH in CH_2Cl_2 to afford trimethylsilyl protected compound. The deprotection was carried out by stirring in methanol and K_2CO_3 (3.0 mmol) at rt for 30 min. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel (230-400 mesh), eluting gradient 0-7% MeOH in CH_2Cl_2.

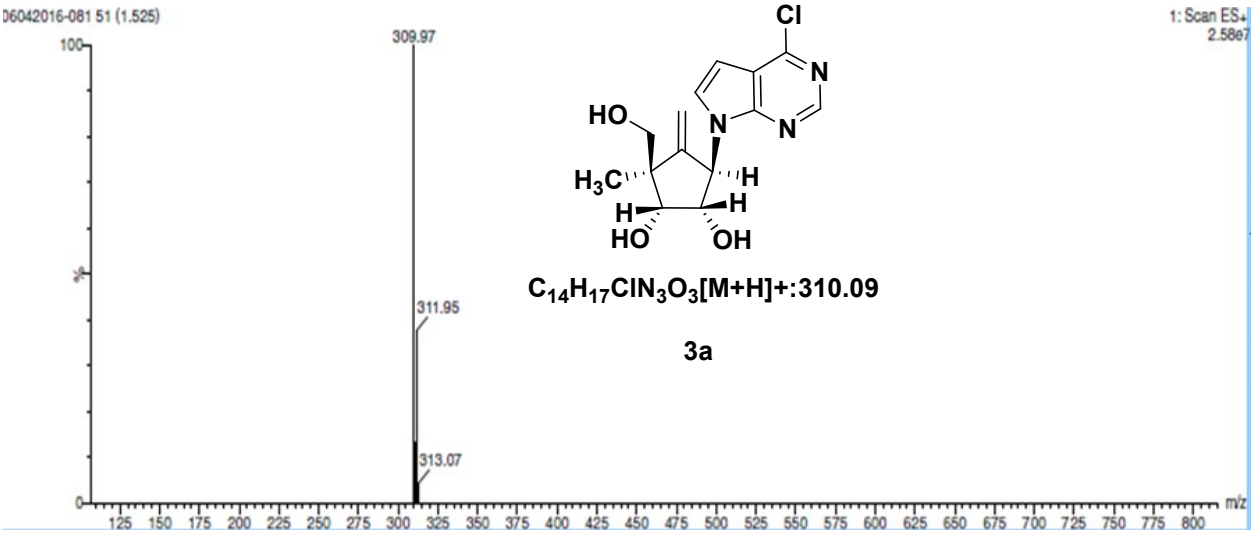
(1*S*,2*R*,3*R*,5*R*)-5-(4-Amino-5-ethynyl-7*H*-pyrrolo[2,3-*d*]pyrimid in-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (4f): Purified yield: 62%, off white solid. (TLC: Rf 0.1, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: –2.17 (c = 0.25, DMSO); mp: 183-187 °C; UV (MeOH) λ_{max}: 283.25 nm; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.18 (s, 3H), 3.51 (d, J = 10.8 Hz, 1H), 3.66 (d, J = 10.8 Hz, 1H), 3.70 (s, 1H), 3.99 (d, J = 4.4 Hz, 1H), 4.58 (d, J = 2.8 Hz, 1H), 4.72 (dd, J = 4.4 and 10.0 Hz, 1H), 5.08 (d, J = 3.2 Hz, 1H), 5.48–5.44 (m, 1H), 7.48 (s, 1H), 8.06 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.9, 49.3, 62.8, 69.2, 73.5, 74.2, 77.7, 82.7, 93.0, 102.1, 108.0, 128.5, 150.0, 152.4, 154.8, 157.4; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{16}H_{19}N_4O_3$ $[M+H]^+$: 315.1457, found: 315.1418.

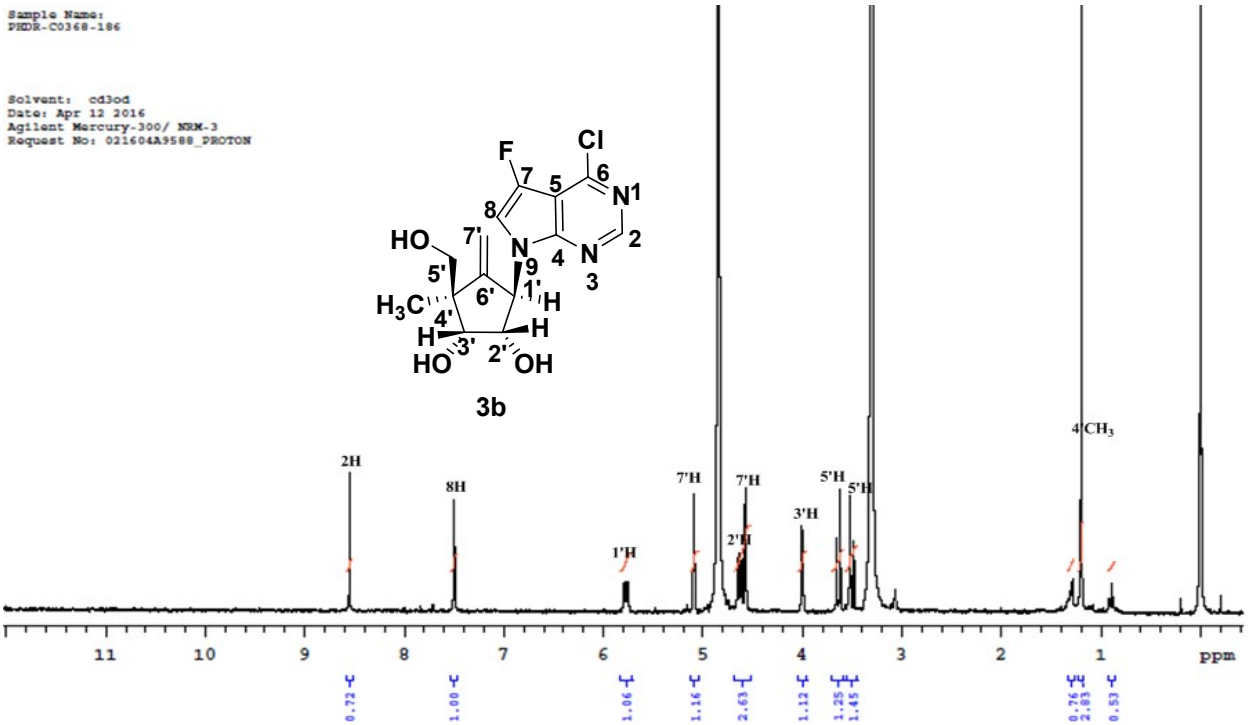
Procedure for the synthesis of 4g: To a suspension of **4e** (0.6 mmol), $Pd(PPh_3)_4$ (0.06 mmol) in anhydrous DMF under argon atmosphere, tri-*n*-butyl(vinyl)tin (1.8 mmol) was added. The resulting mixture was heated at 110 °C for 3 h under sealed condition. Upon completion of reaction, concentrated the volatile under reduced pressure and crude was purified by flash chromatography on silica gel (230-400 mesh), elution gradient 0-7% MeOH in CH_2Cl_2.

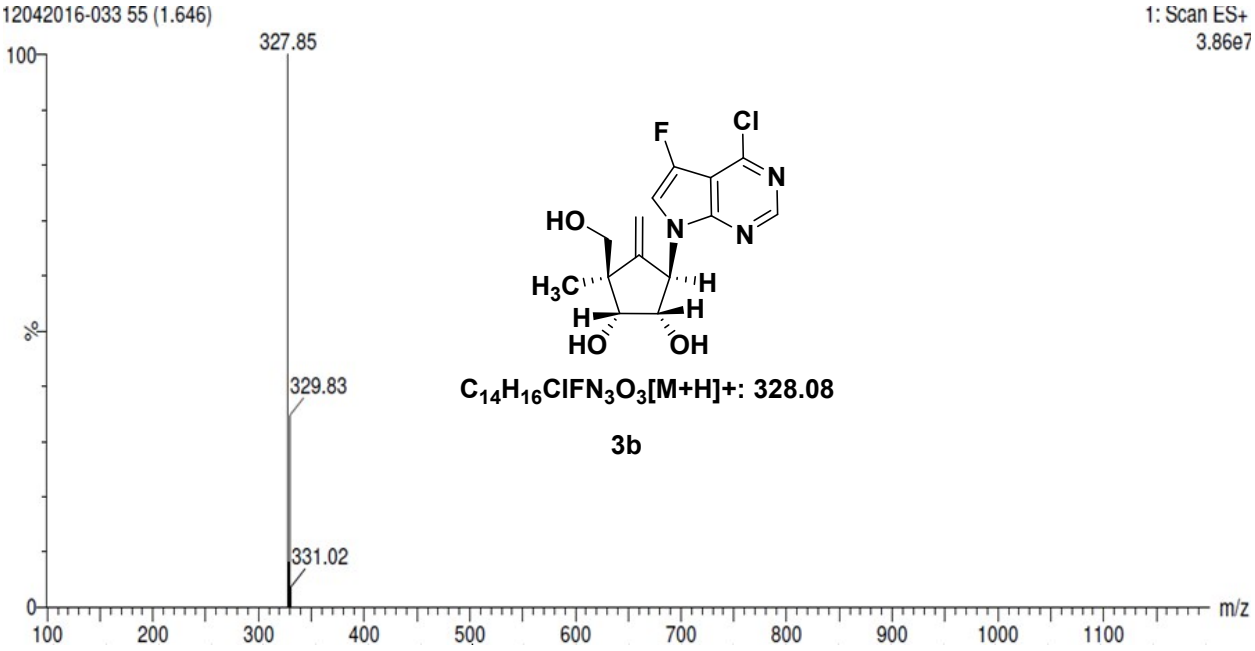
(1*S*,2*R*,3*R*,5*R*)-5-(4-Amino-5-vinyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-3-(hydroxymethyl)-3-methyl-4-methylenecyclopentane-1,2-diol (4g): Purified yield: 60%, off white solid, (TLC: Rf 0.1, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$: –14.28 (c = 0.25, DMSO); mp: 194–198 °C; UV (MeOH) λ_{max}: 294.25 nm; ^{1}H NMR (300 MHz, CD_3OD) δ: 1.19 (s, 3H), 3.52 (d, J = 11.1 Hz, 1H), 3.67 (d, J = 11.1 Hz, 1H), 4.00 (d, J = 4.8 Hz, 1H), 4.57 (d, J = 2.7 Hz, 1H), 4.78 (dd, J = 4.8 and 9.9 Hz, 1H), 5.07 (d, J = 3.3 Hz, 1H), 5.24 (dd, J = 1.5 and 10.8 Hz, 1H), 5.44–5.48 (m, 1H), 5.58 (dd, J = 1.8 and 17.4 Hz, 1H), 7.05 (dd, J = 10.8 and 11.1 Hz, 1H), 7.35 (s, 1H), 8.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 18.9, 49.2, 62.3, 69.2, 73.5, 74.1, 100.2, 107.7, 112.1, 113.3, 120.0, 129.2, 151.1, 155.0, 157.5; HRMS (ESI-Orbitrap) m/z: Exact mass calculated for $C_{16}H_{21}N_4O_3$ $[M+H]^+$: 317.1614, found: 317.1575.

^{1}H and ^{13}C NMR Copies:



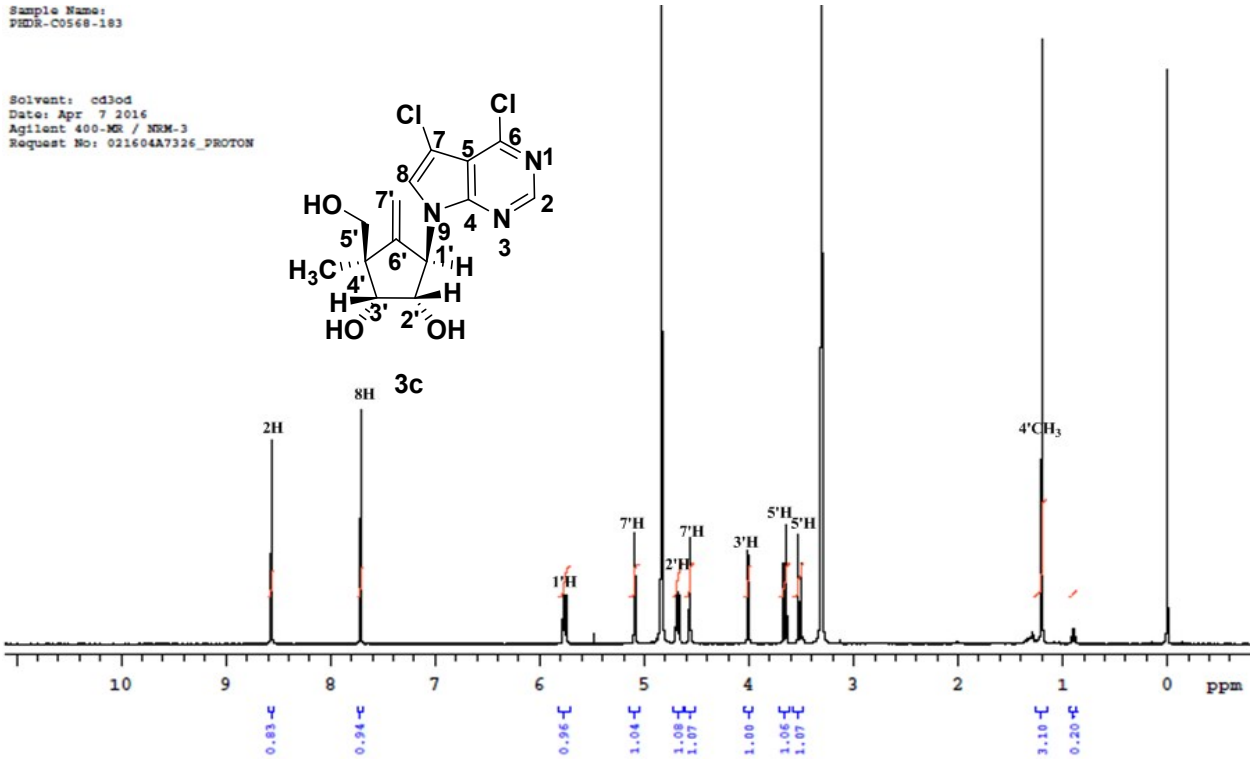


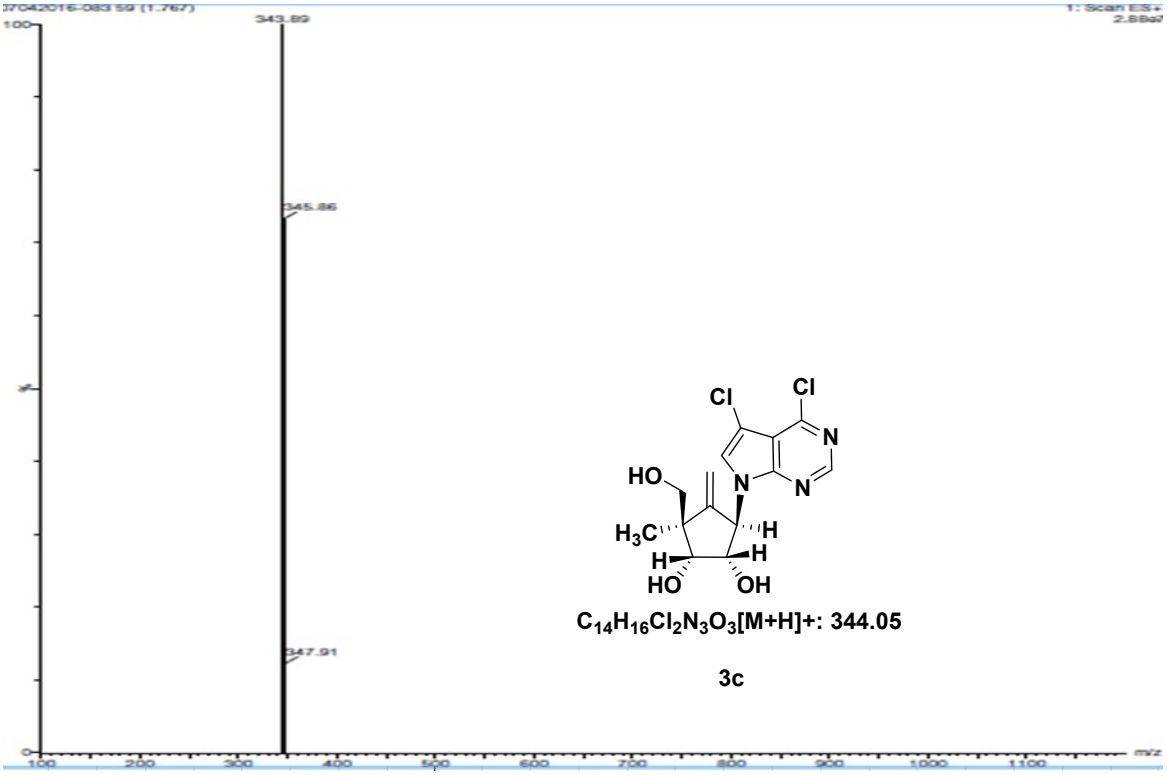




$C_{14}H_{16}ClFN_3O_3[M+H]^+$: 328.08

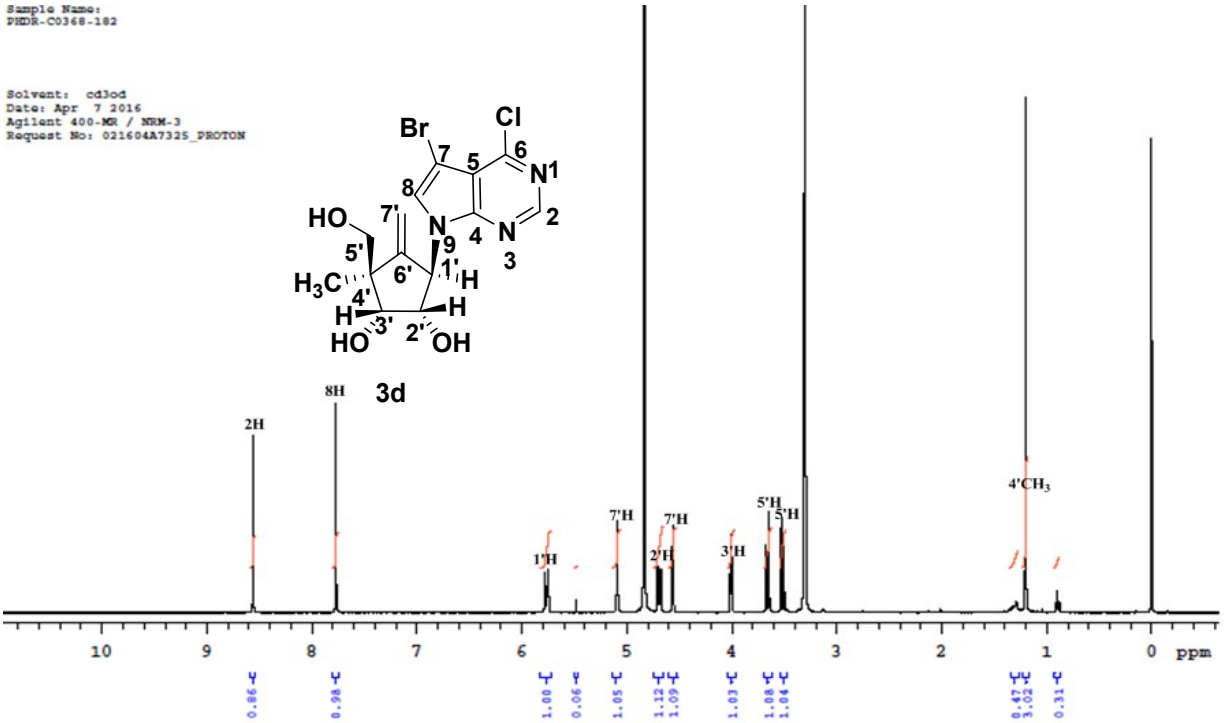
3b

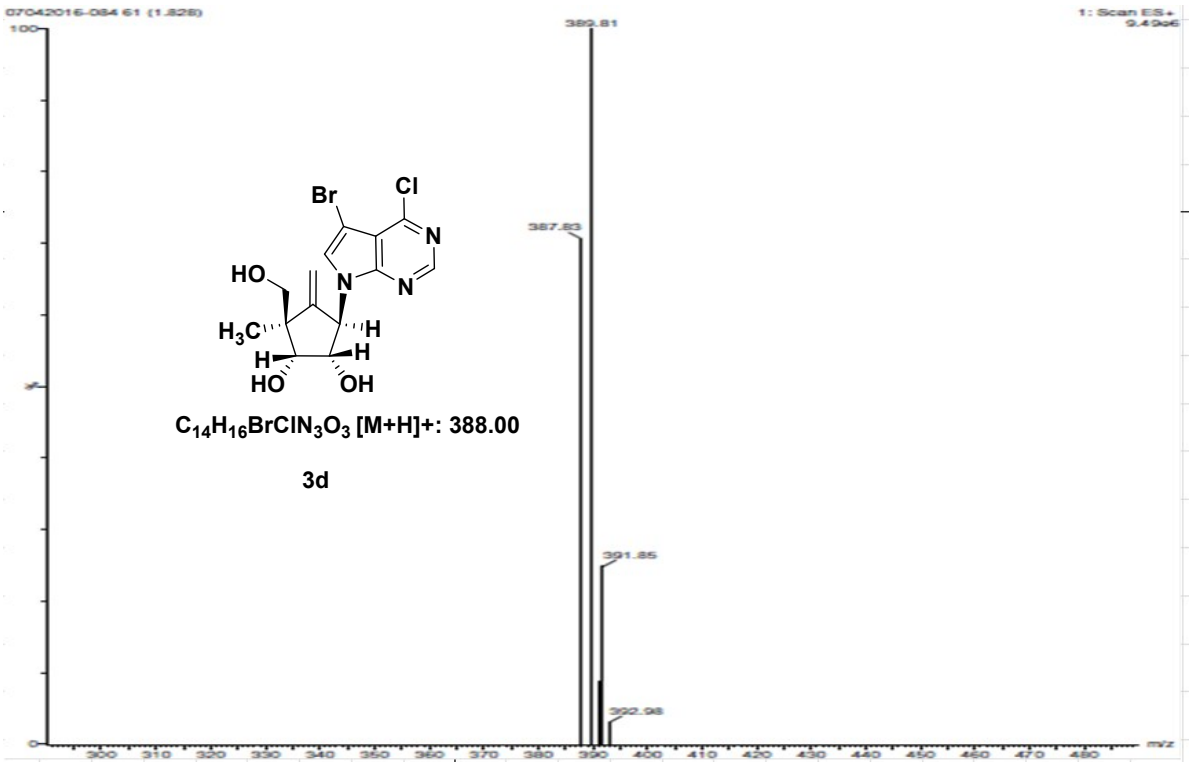




$C_{14}H_{16}Cl_2N_3O_3[M+H]^+$: 344.05

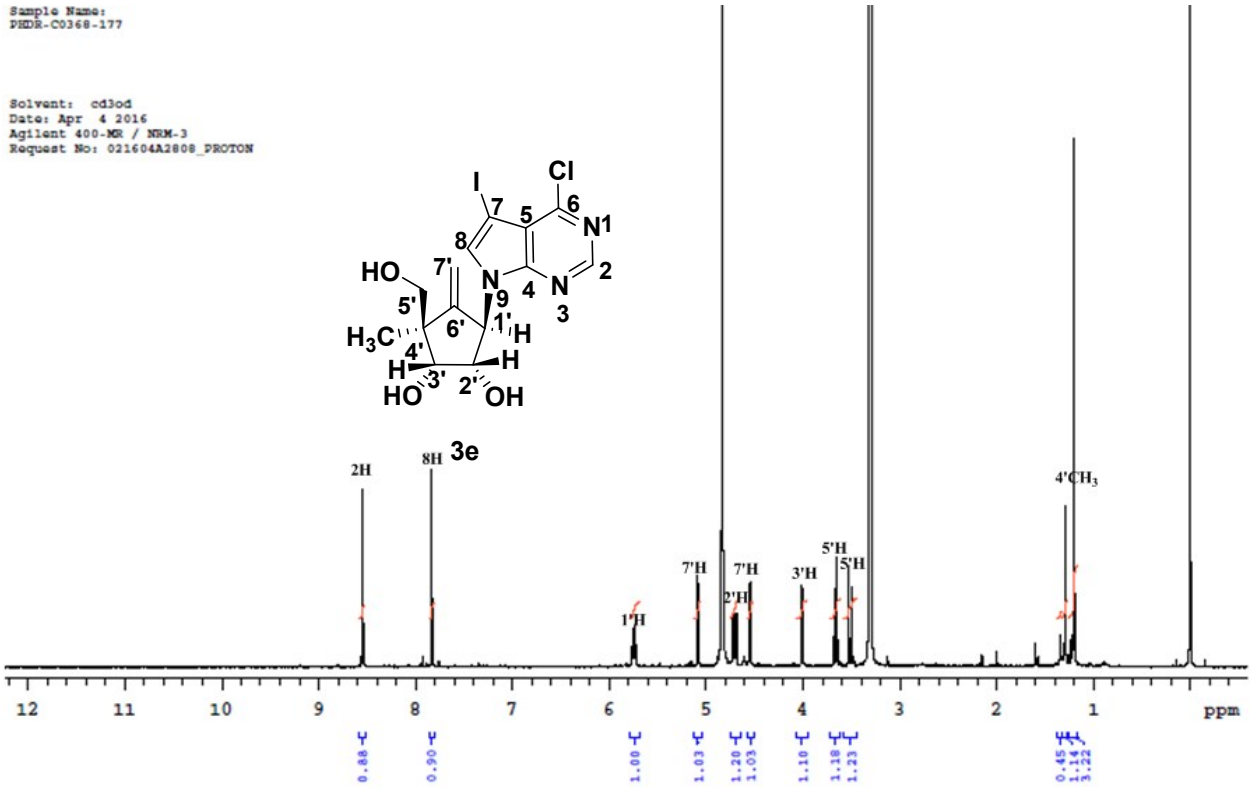
3c

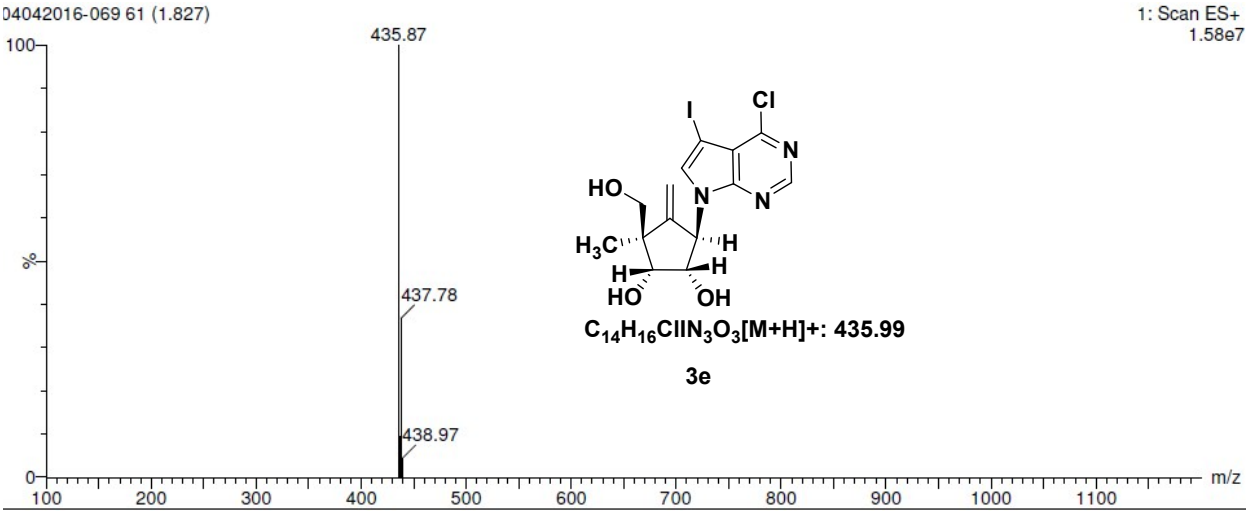




$C_{14}H_{16}BrClN_3O_3$ [M+H]+: 388.00

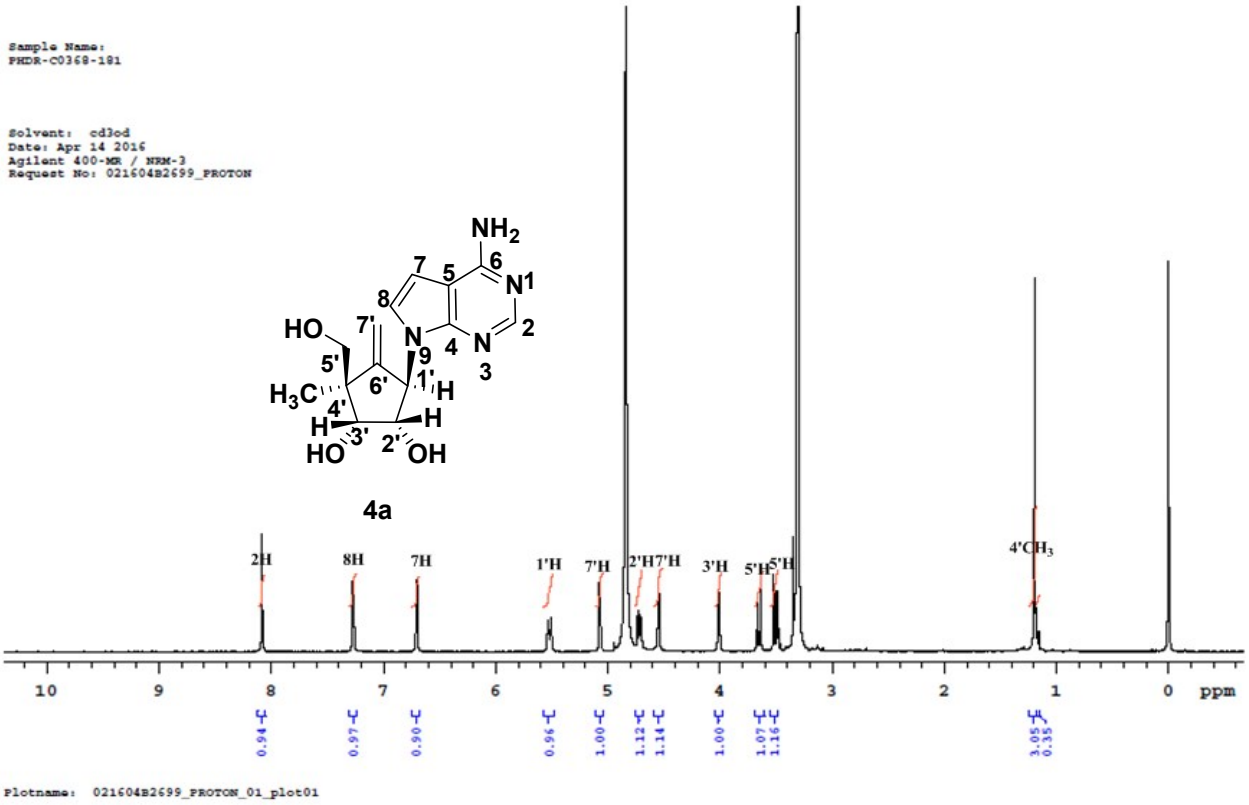
3d

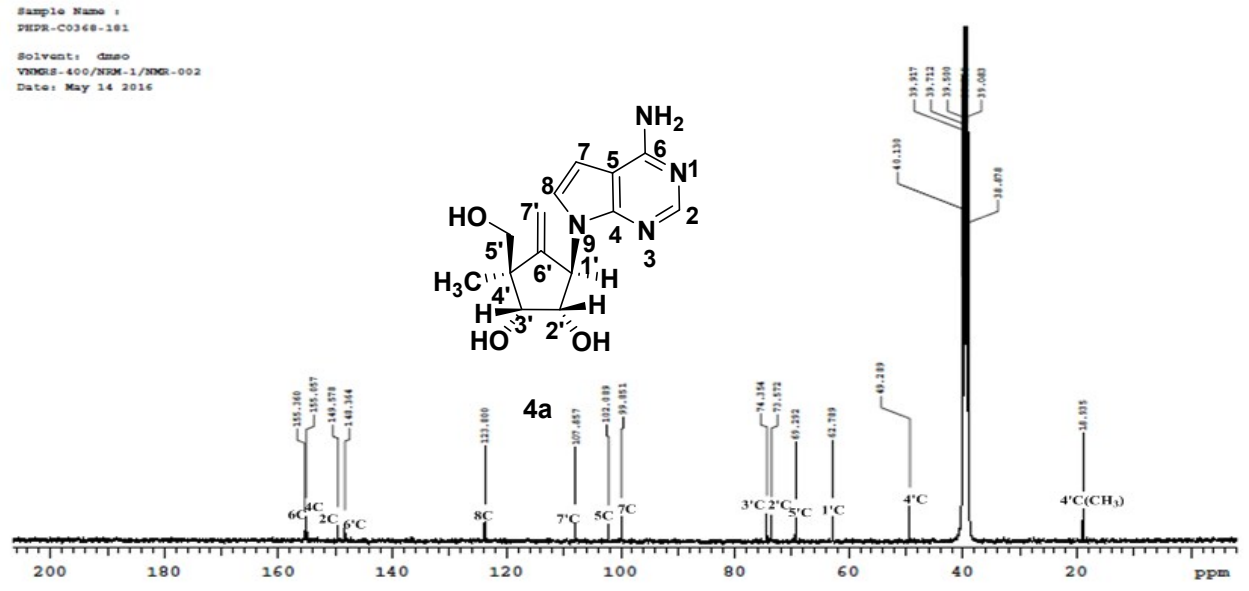


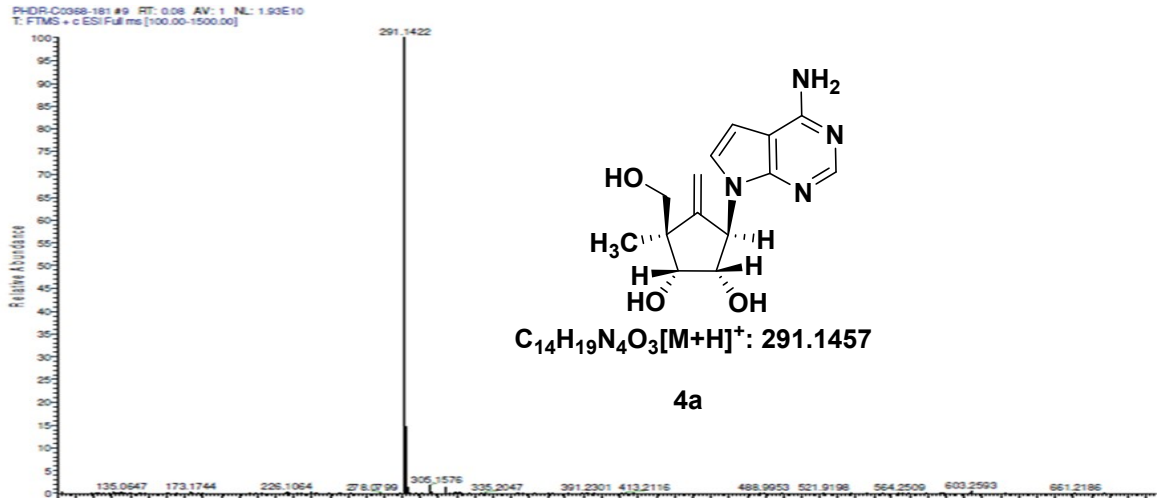


$C_{14}H_{16}ClIN_3O_3[M+H]^+$: 435.99

3e

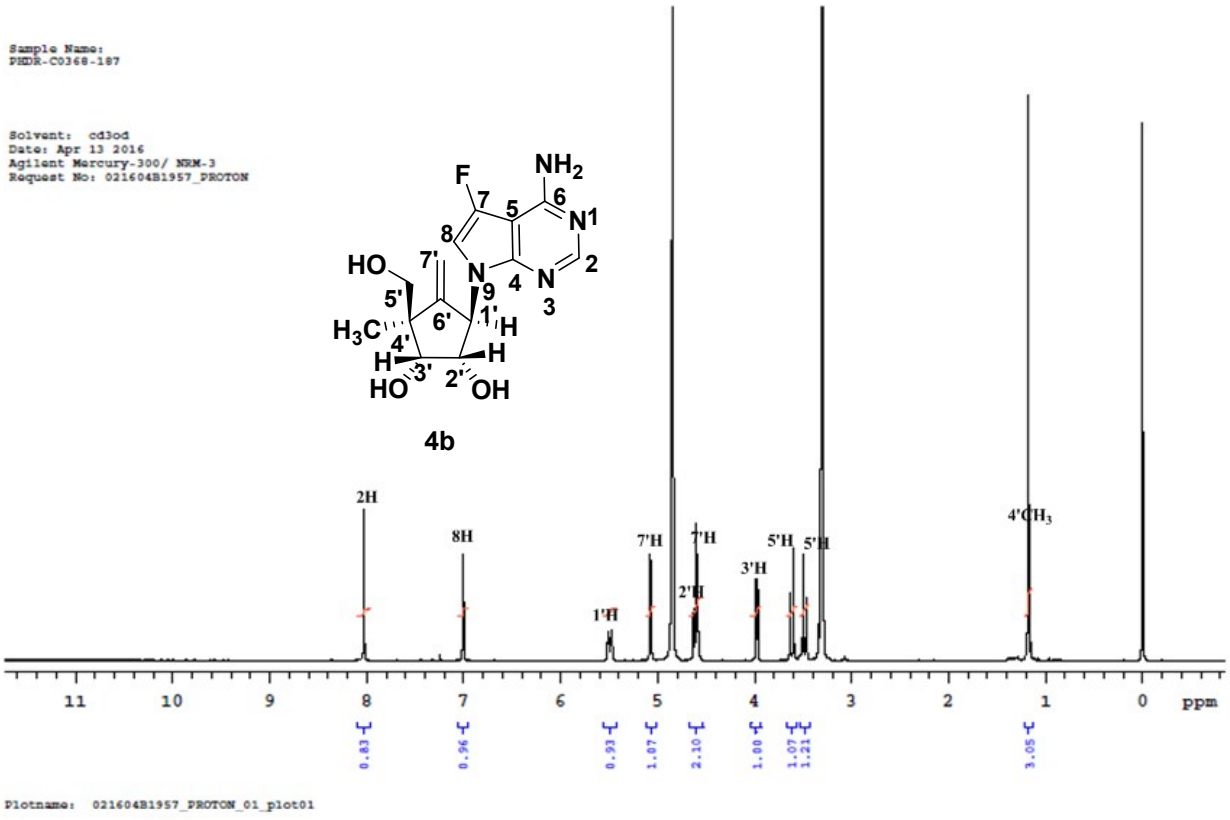

Sample Name:
PHDR-C0368-181
Solvent: cd3od
Date: Apr 14 2016
Agilent 400-MR / NRM-3
Request No: 021604B2699_PROTON
4a
2H
8H
7H
1'H
7'H
2'H
7'H
3'H
5'H
5'H
4'CH3
ppm
Plotname: 021604B2699_PROTON_01_plot01


Sample Name :
PHDR-C0368-181
Solvent: dmso
VNMRS-400/NRM-1/NMR-002
Date: May 14 2016
4a
6C
4C
2C
5'C
8C
7'C
5C
7C
3'C
2'C
5'C
1'C
4'C
4'C(CH3)
ppm

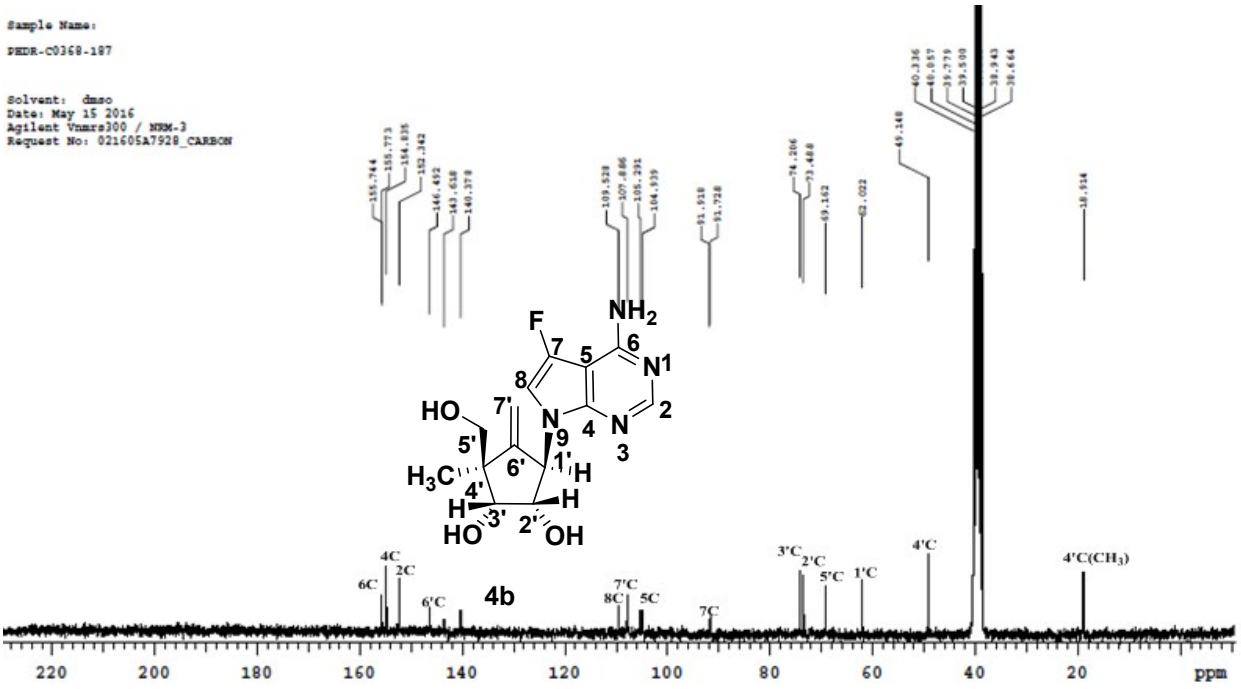


$C_{14}H_{19}N_4O_3[M+H]^+$: 291.1457

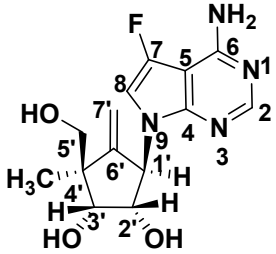
4a



4b



C0368-187

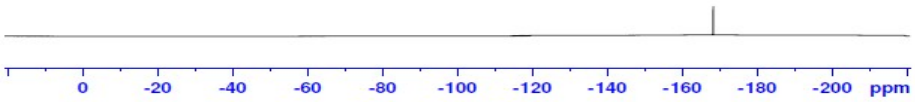


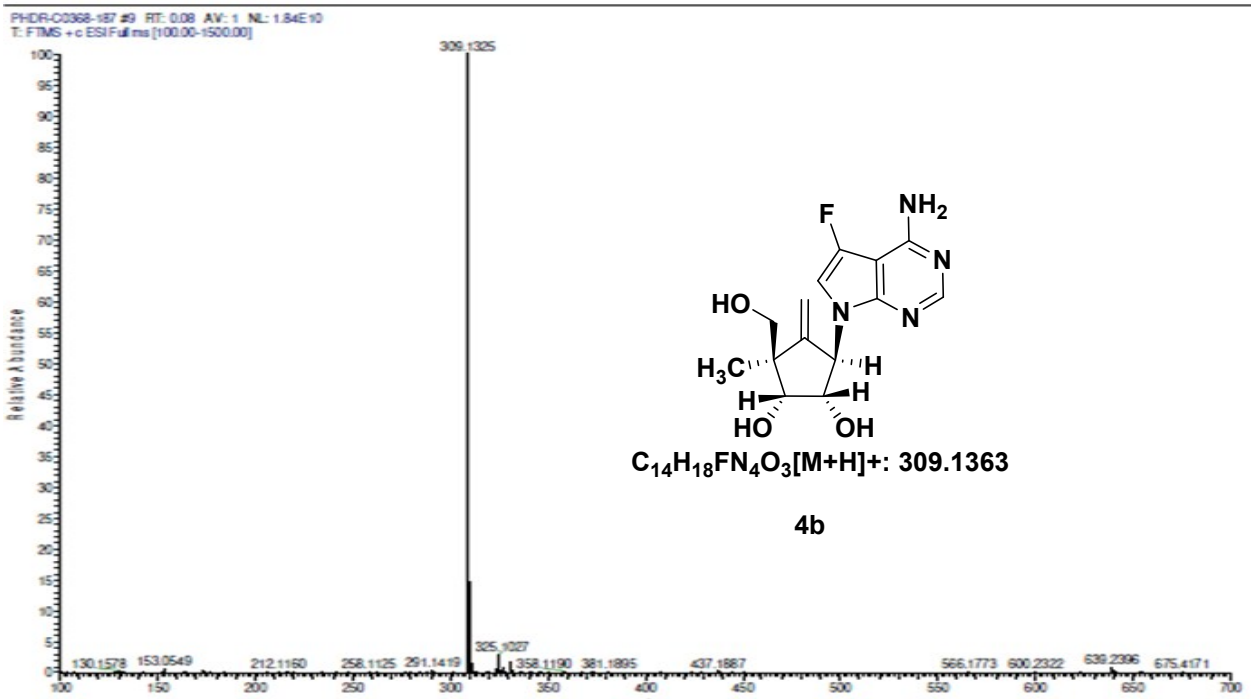
4b

Current Data Parameters
NAME 021809m3914-C0368-187
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 20180917
Time 12.11 h
INSTRUM CAB AV4 400 MHZ BASIC
PROBHD Z116098_0700 (
PULPROG zg
TD 131072
SOLVENT DMSO
NS 64
DS 4
SWH 90909.094 Hz
FIDRES 1.387163 Hz
AQ 0.7208960 sec
RG 101
DW 5.500 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
SFO1 376.1869302 MHz
NUC1 19F
P1 18.00 usec
PLW1 24.36100006 W

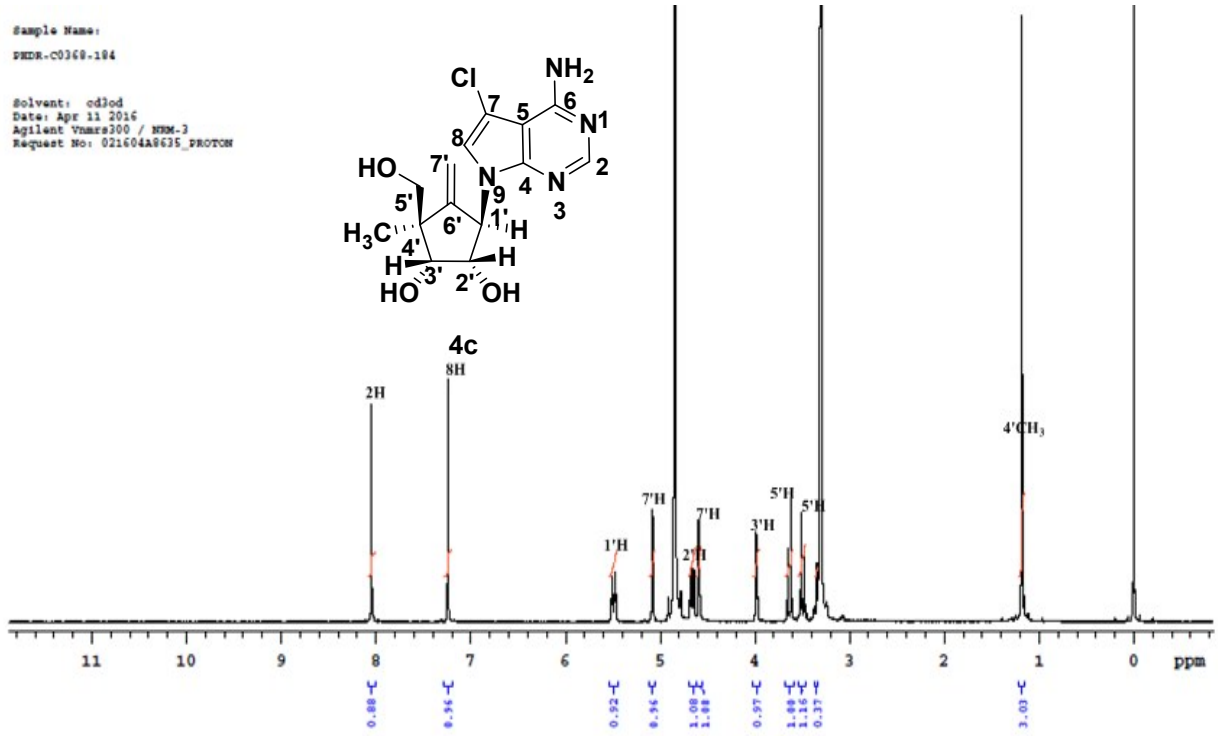
F2 - Processing parameters
SI 65536
SF 376.2245526 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.00

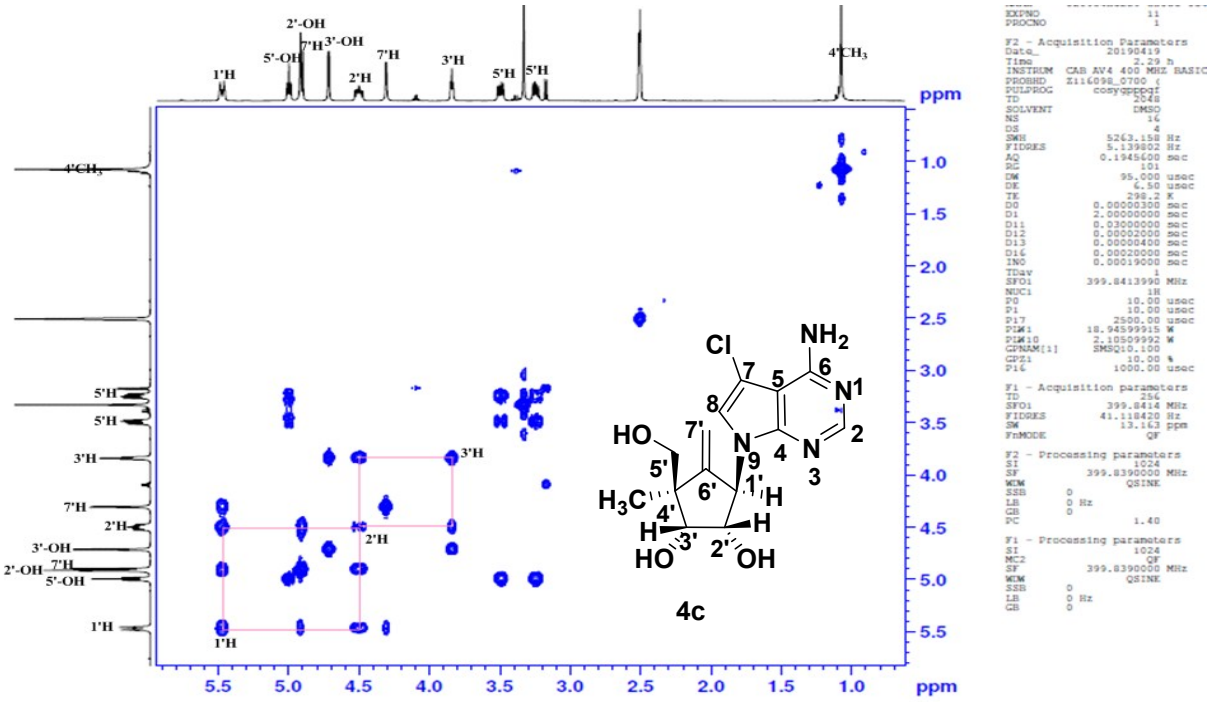


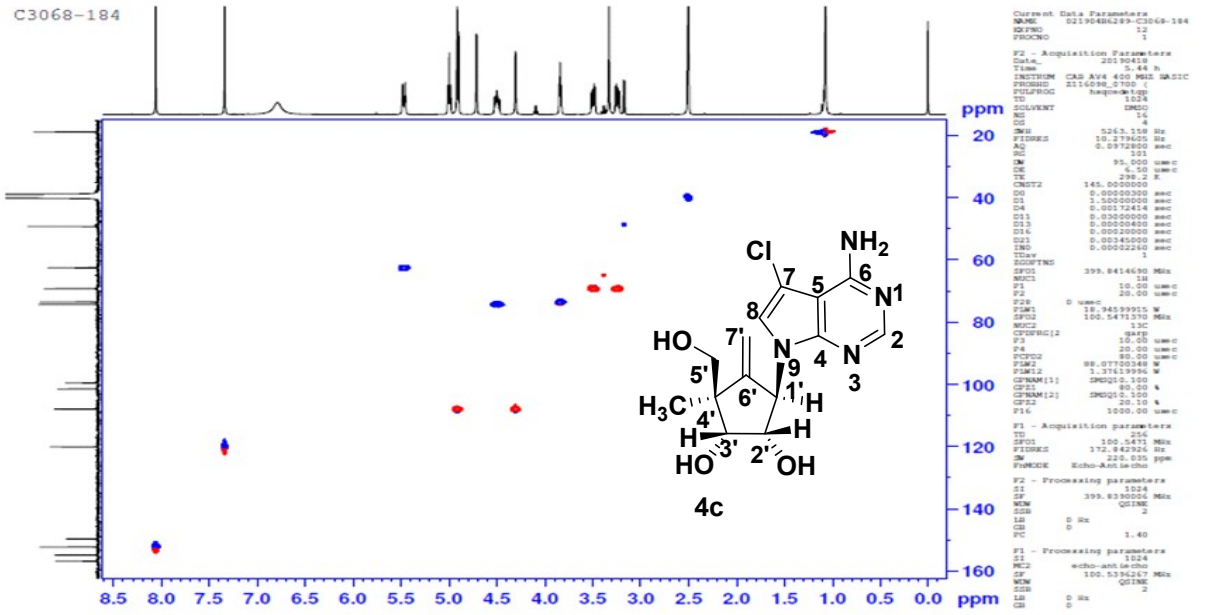


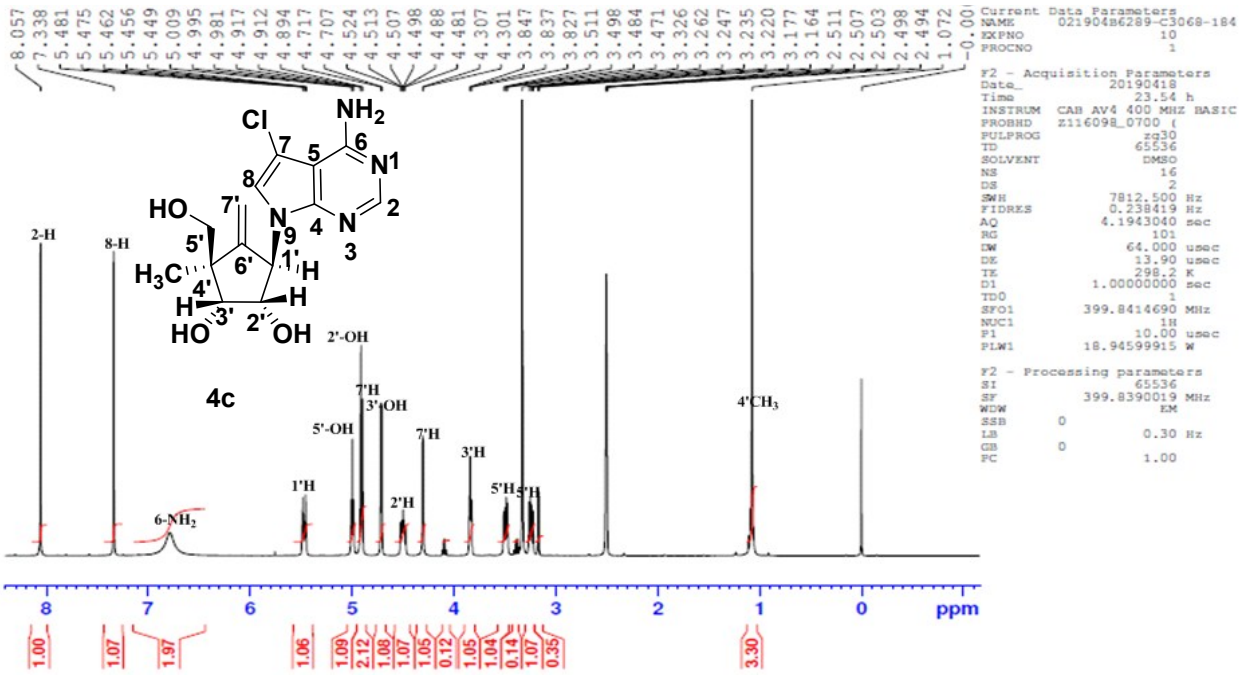
$C_{14}H_{18}FN_4O_3[M+H]^+$: 309.1363

4b

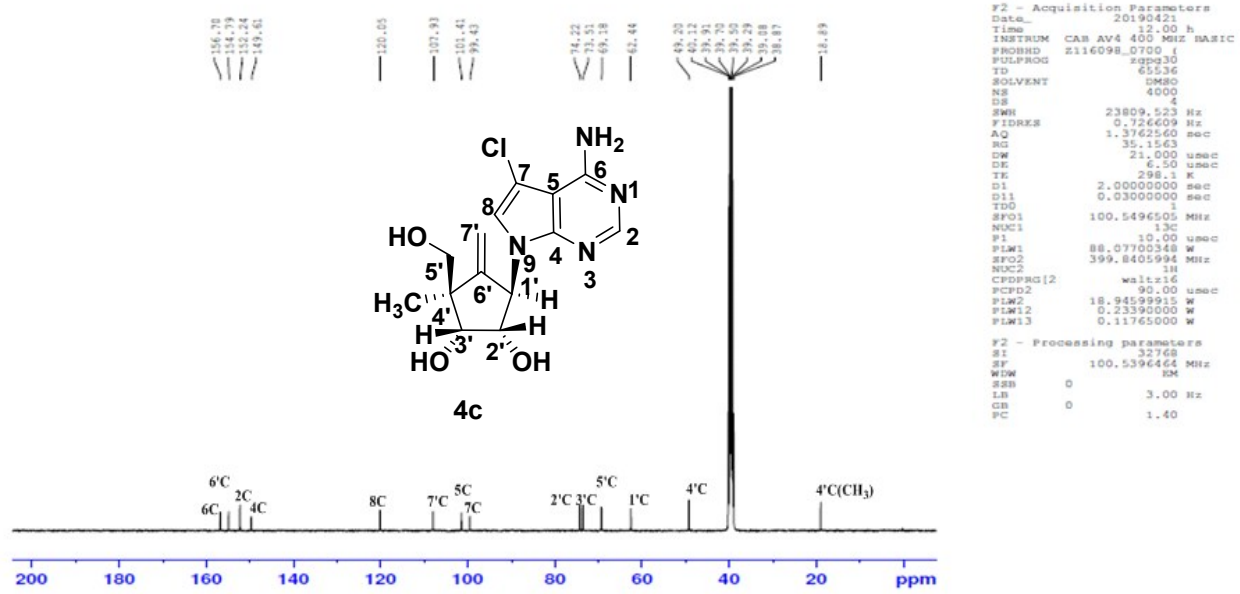



2'-OH
7'H
3'-OH
5'-OH
1'H
2'H
7'H
3'H
5'H
5'H
4'CH3
ppm
4'CH3
5'H
5'H
3'H
7'H
2'H
3'-OH
2'-OH
7'H
5'-OH
1'H
3'H
2'H
1'H
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
Cl
NH2
HO
N
H3C
H
OH
4c

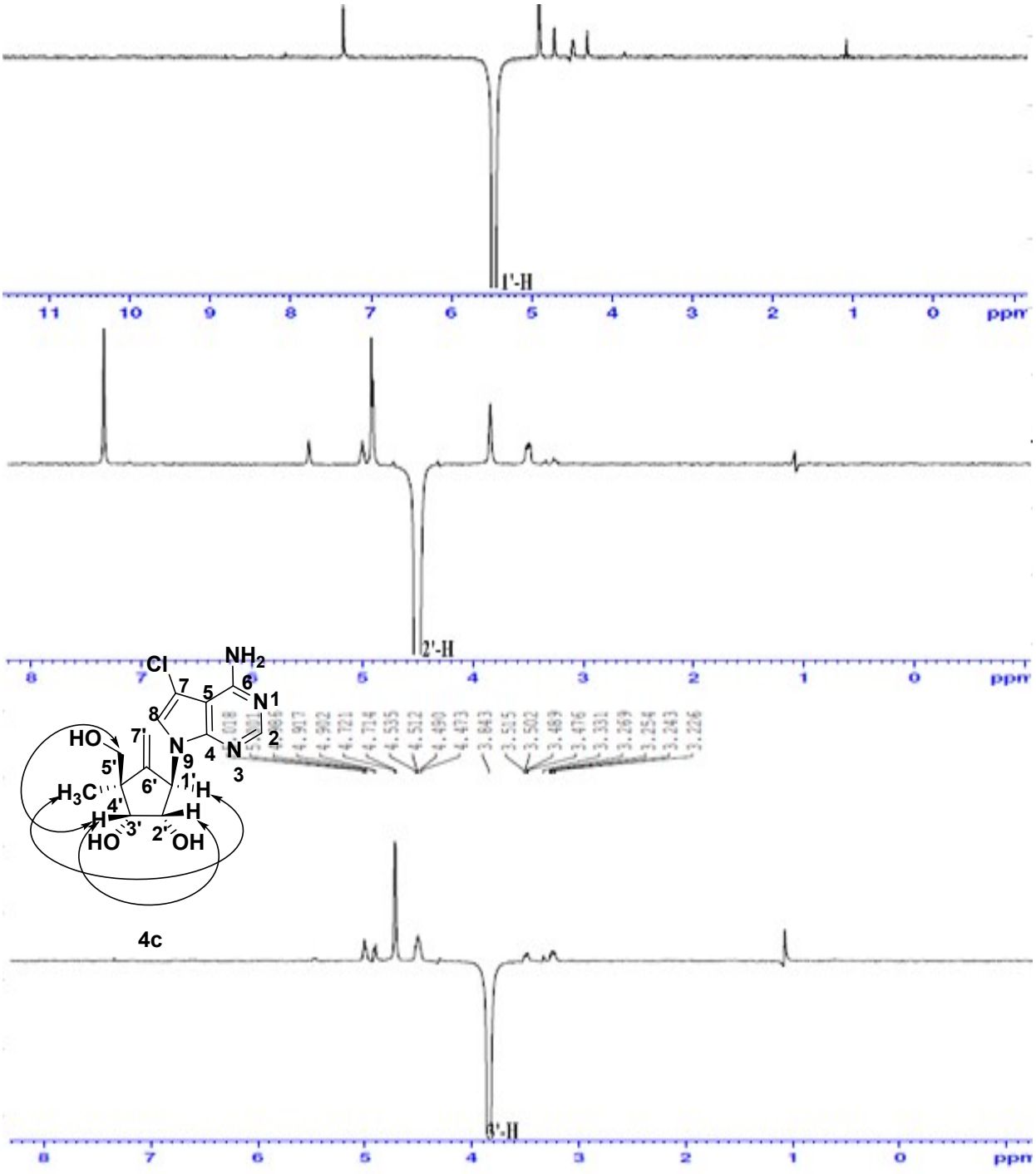

C3068-184
ppm
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
Cl
NH2
HO
N
H3C
H
OH
4c



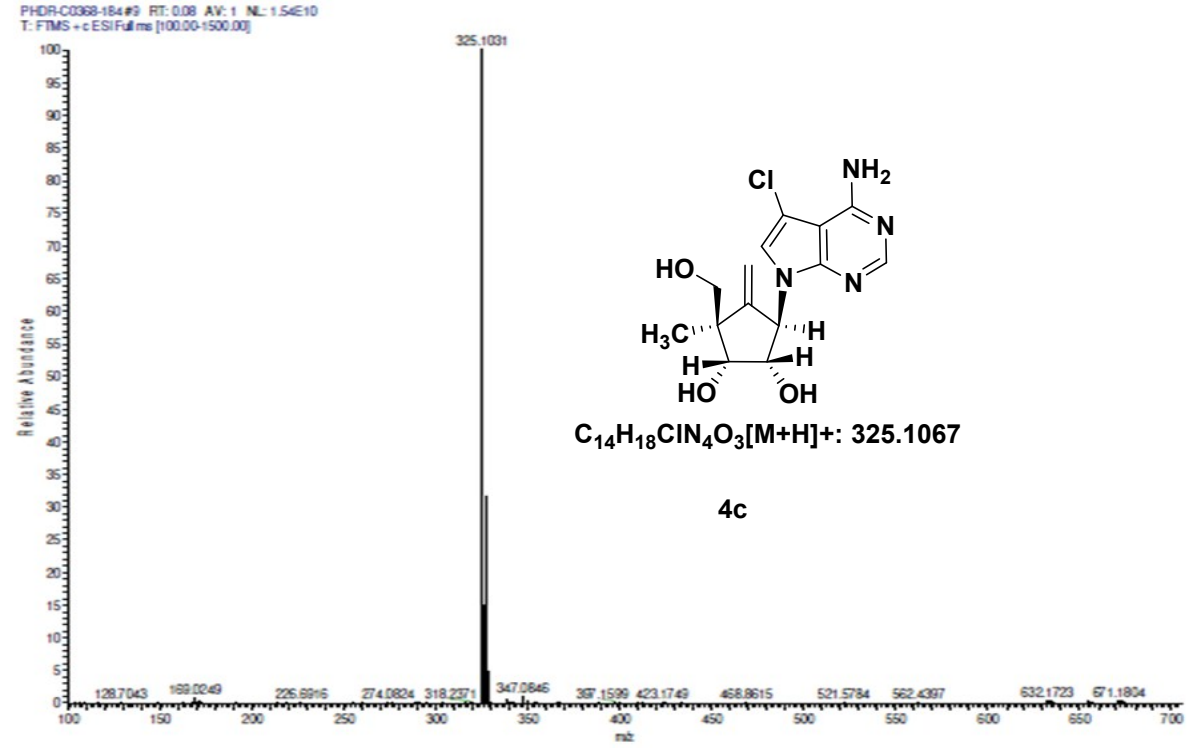

```
Current Data Parameters
NAME      021904B6289-C3068-184
EXPNO                        10
PROCNO                        1

F2 - Acquisition Parameters
Date_               20190418
Time                   23.54 h
INSTRUM   CAB AV4 400 MHZ BASIC
PROBHD    Z116098_0700 (
PULPROG                  zg30
TD                      65536
SOLVENT                 DMSO
NS                         16
DS                          2
SWH                  7812.500 Hz
FIDRES               0.238419 Hz
AQ                   4.1943040 sec
RG                        101
DW                     64.000 usec
DE                     13.90 usec
TE                     298.2 K
D1                1.00000000 sec
TD0                         1
SFO1             399.8414690 MHz
NUC1                       1H
P1                     10.00 usec
PLW1             18.94599915 W

F2 - Processing parameters
SI                      65536
SF               399.8390019 MHz
WDW                        EM
SSB                 0
LB                     0.30 Hz
GB                  0
PC                     1.00
```




```
Current Data Parameters
NAME      021904B6289-C3068-184
EXPNO                        17
PROCNO                        1

F2 - Acquisition Parameters
Date_               20190421
Time                   12.00 h
INSTRUM   CAB AV4 400 MHZ BASIC
PROBHD    Z116098_0700 (
PULPROG                zgpg30
TD                      65536
SOLVENT                 DMSO
NS                       4000
DS                          4
SWH                 23809.523 Hz
FIDRES               0.726609 Hz
AQ                   1.3762560 sec
RG                     35.1563
DW                     21.000 usec
DE                      6.50 usec
TE                     298.1 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                         1
SFO1            100.5496505 MHz
NUC1                       13C
P1                     10.00 usec
PLW1             88.07700348 W
SFO2             399.8405994 MHz
NUC2                       1H
CPDPRG[2              waltz16
PCPD2                  90.00 usec
PLW2             18.94599915 W
PLW12             0.23390000 W
PLW13             0.11765000 W

F2 - Processing parameters
SI                      32768
SF              100.5396464 MHz
WDW                        EM
SSB                 0
LB                     3.00 Hz
GB                  0
PC                     1.40
```

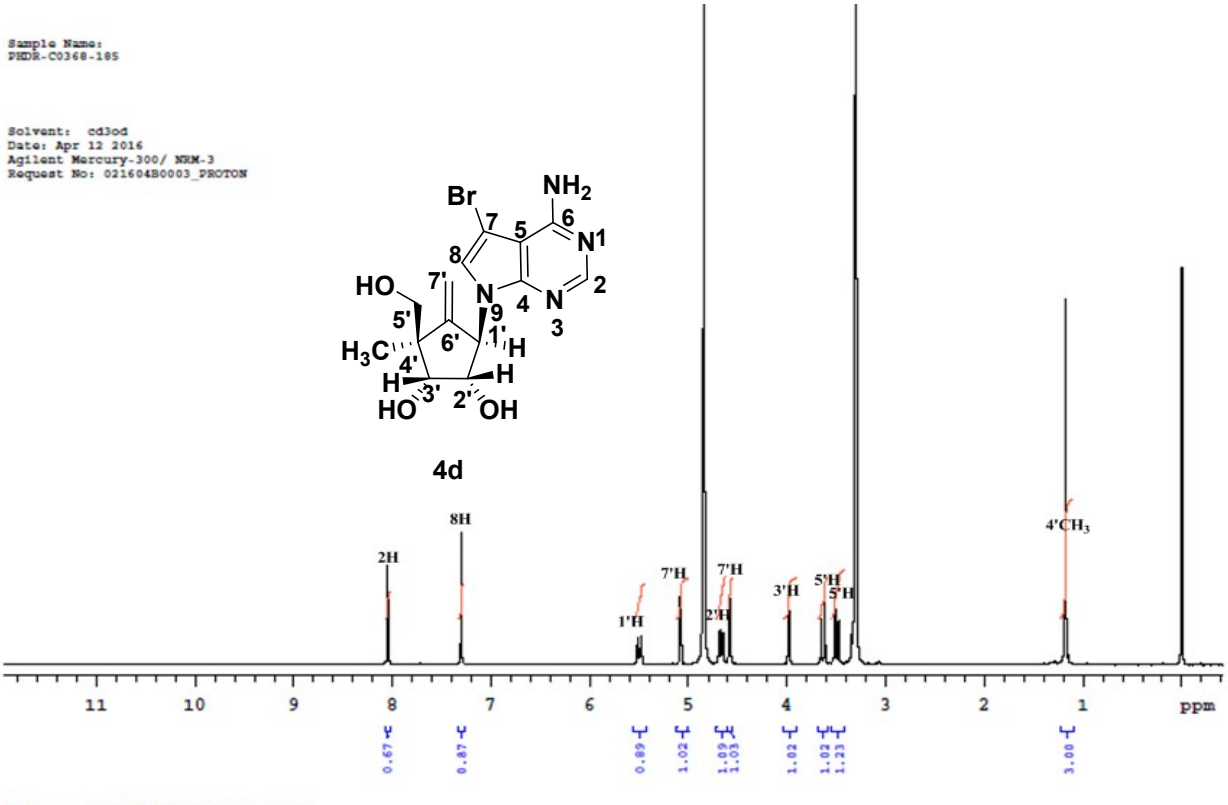


NOE correlation of the protons in **4c** (correlated protons has shown the increase in the intensity of the signal in the upper the line).

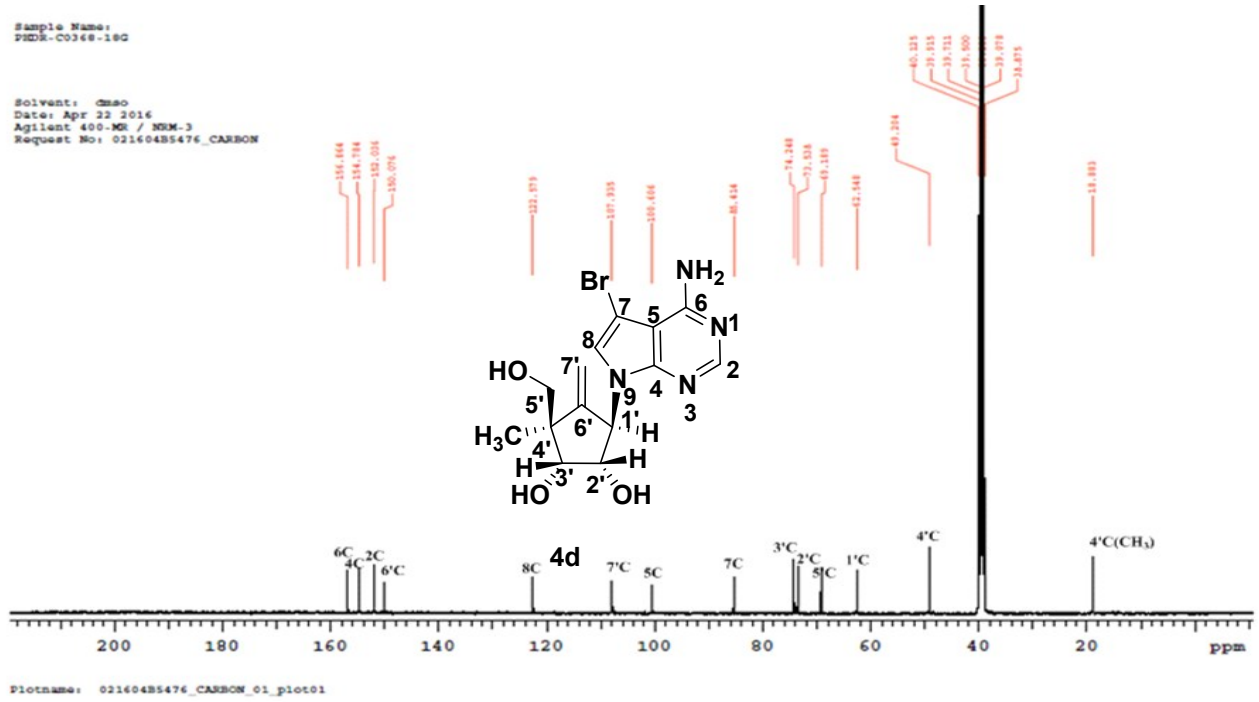


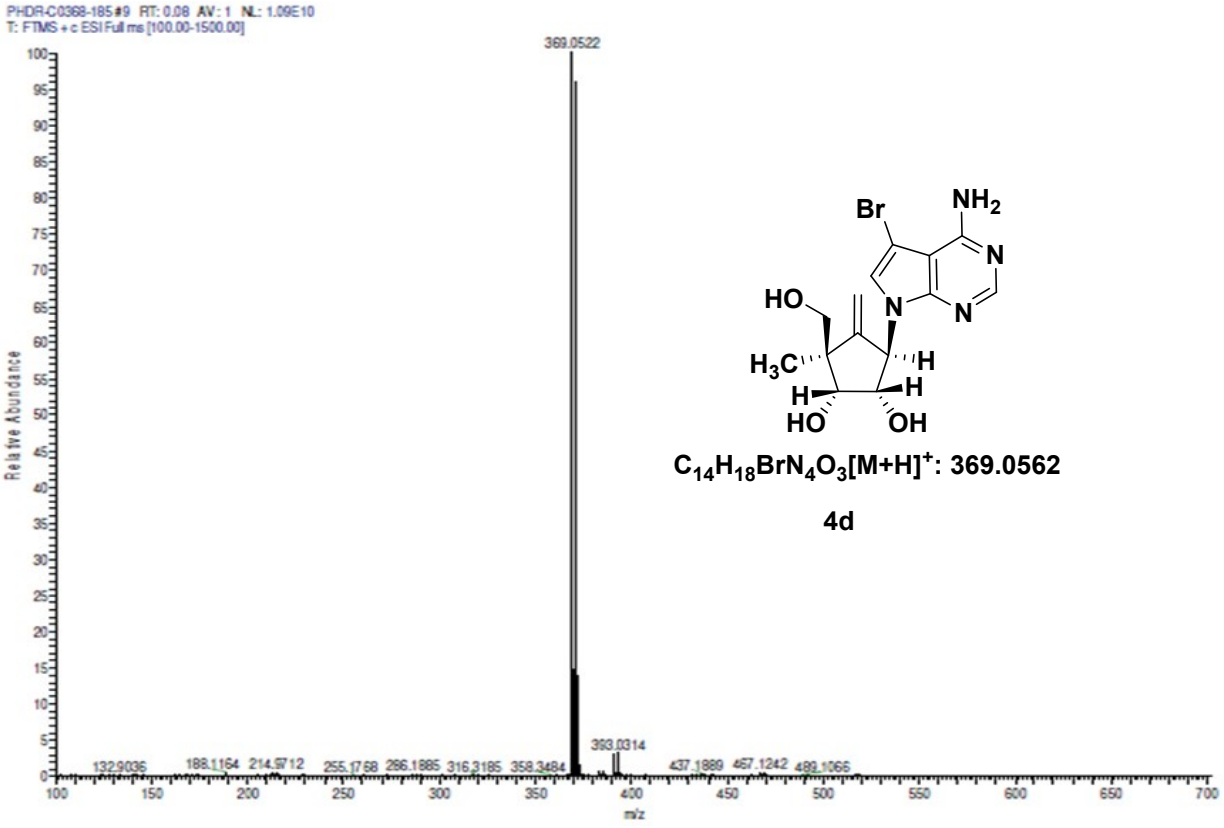
$C_{14}H_{18}ClN_4O_3[M+H]+$: 325.1067

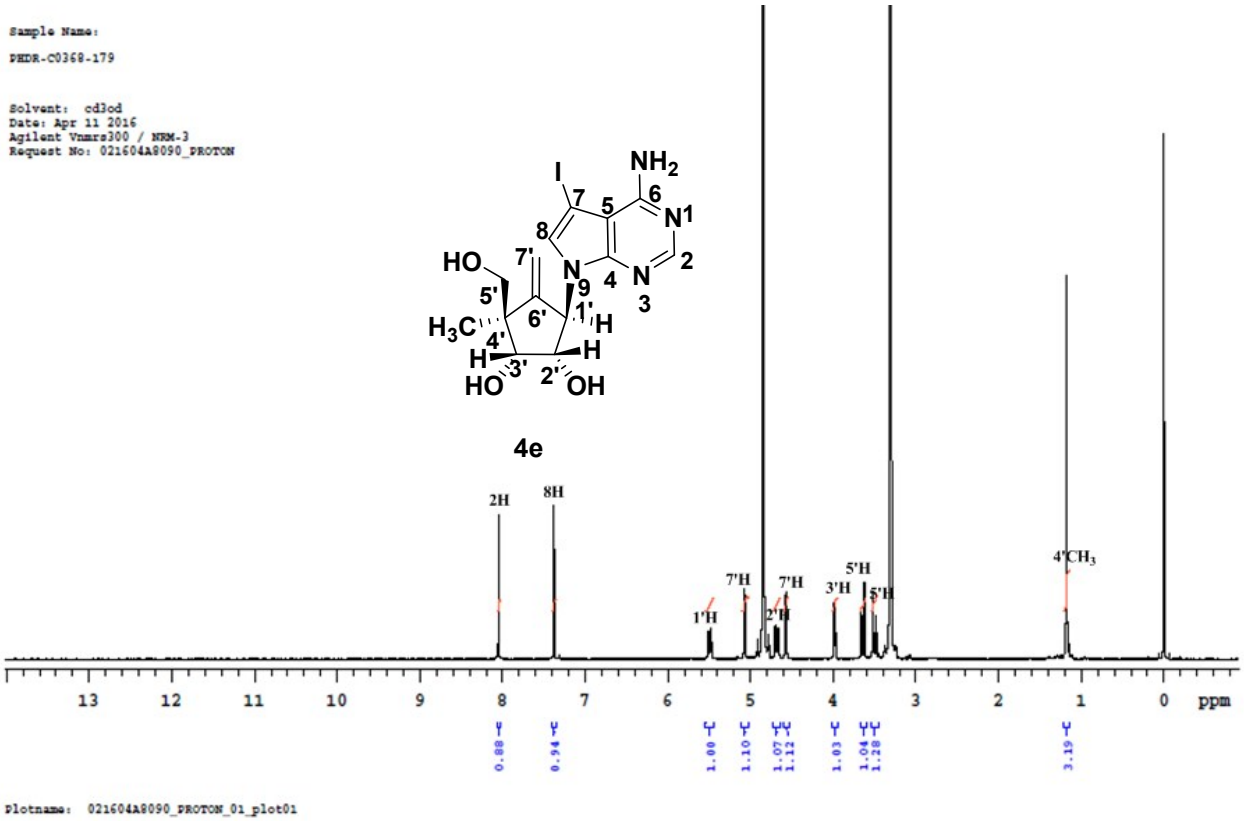
4c

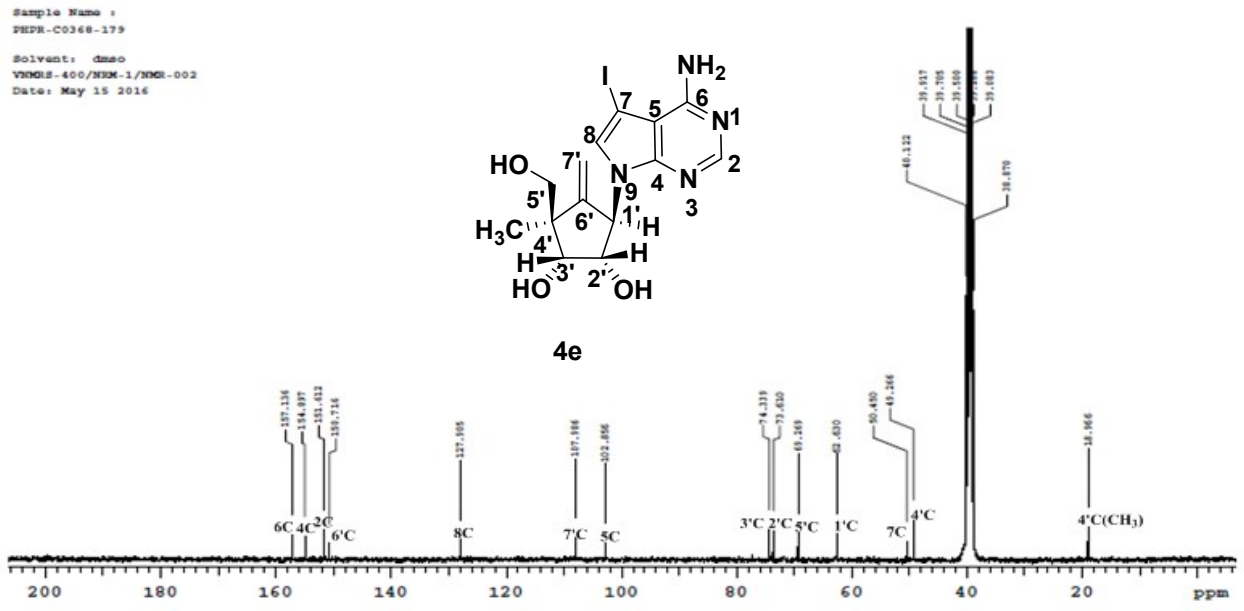


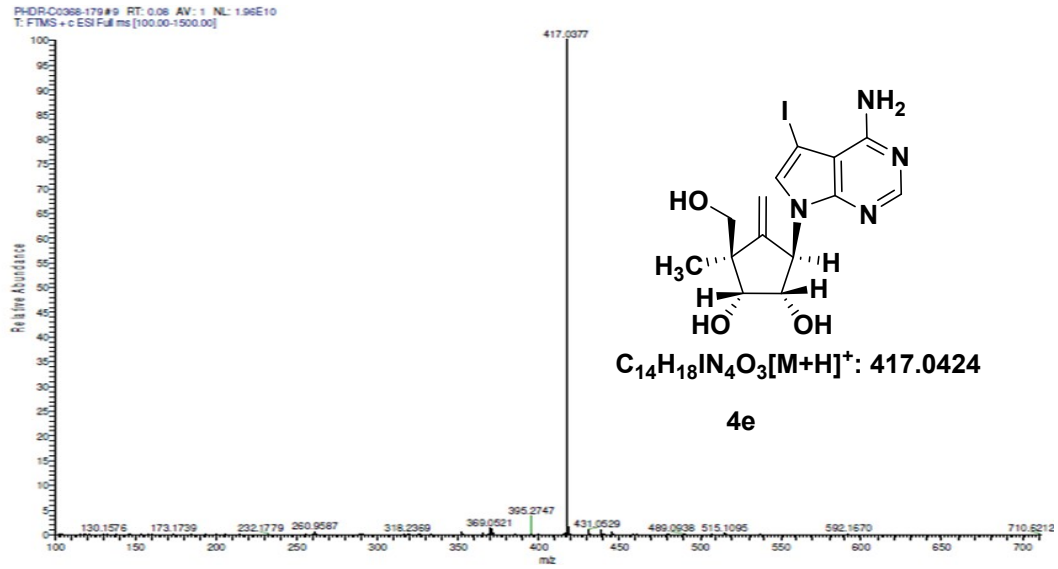
4d


Sample Name:
PHDR-C0368-18G
Solvent: cmso
Date: Apr 22 2016
Agilent 400-MR / NRM-3
Request No: 021604B5476_CARBON
Br
NH2
HO
H3C
HO
OH
4d
6C
4C
2C
6'C
8C
7'C
5C
7C
3'C
2'C
5'C
1'C
4'C
4'C(CH3)
200
180
160
140
120
100
80
60
40
20
ppm
Plotname: 021604B5476_CARBON_01_plot01


PHDR-C0368-185#9 RT: 0.08 AV: 1 NL: 1.09E10
T: FTMS + c ESI Full ms [100.00-1500.00]
369.0522
393.0314
132.9036
188.1164
214.9712
255.1768
286.1885
316.3185
358.3484
437.1889
467.1242
489.1066
Relative Abundance
m/z
Br
NH2
HO
H3C
HO
OH
C14H18BrN4O3[M+H]+: 369.0562
4d

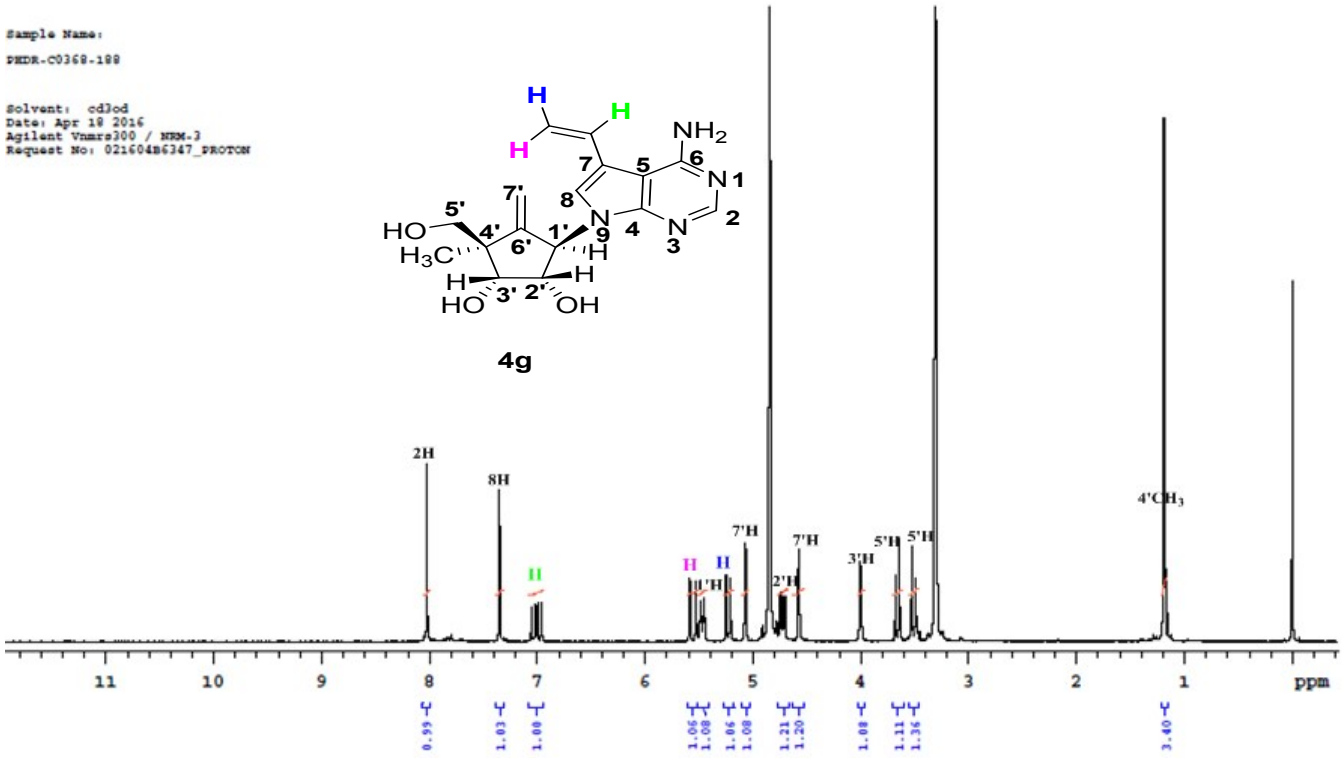

Sample Name:
PHDR-C0368-179
Solvent: cd3od
Date: Apr 11 2016
Agilent Vnmrs300 / NMM-3
Request No: 021604A8090_PROTON
4e
2H
8H
1'H
7'H
2'H
7'H
3'H
5'H
5'H
4'CH3
ppm
Plotname: 021604A8090_PROTON_01_plot01


Sample Name :
PHDR-C0368-179
Solvent: dmso
VNMRS-400/NMR-1/NMR-002
Date: May 15 2016
4e
6C
4C
2C
6'C
8C
7'C
5C
3'C
2'C
5'C
1'C
7C
4'C
4'C(CH3)
ppm

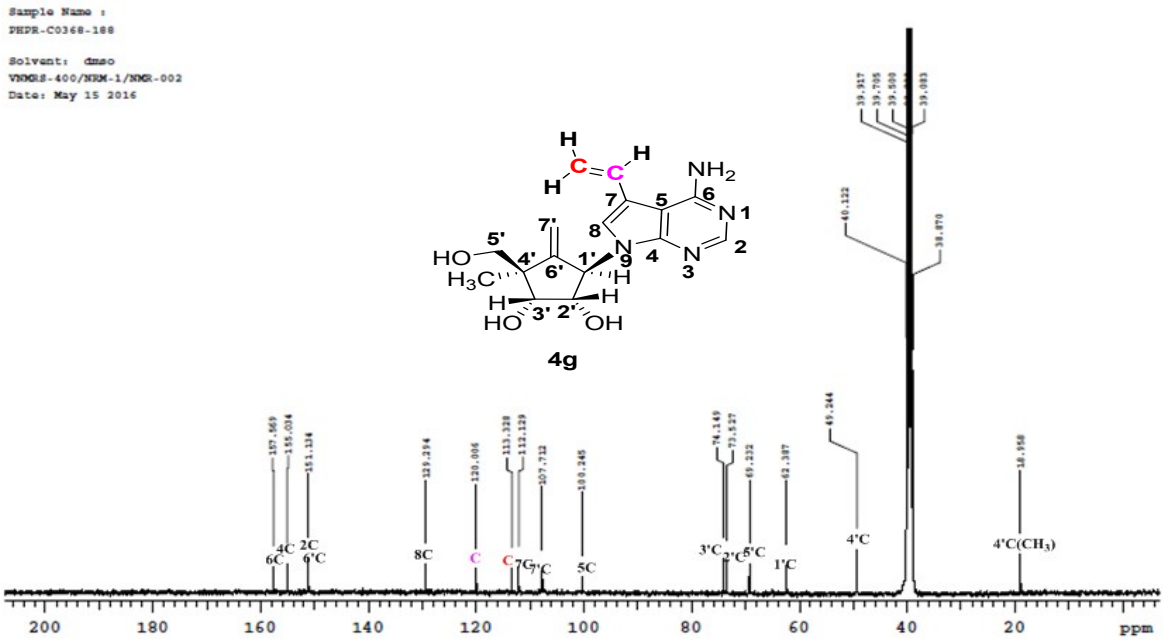


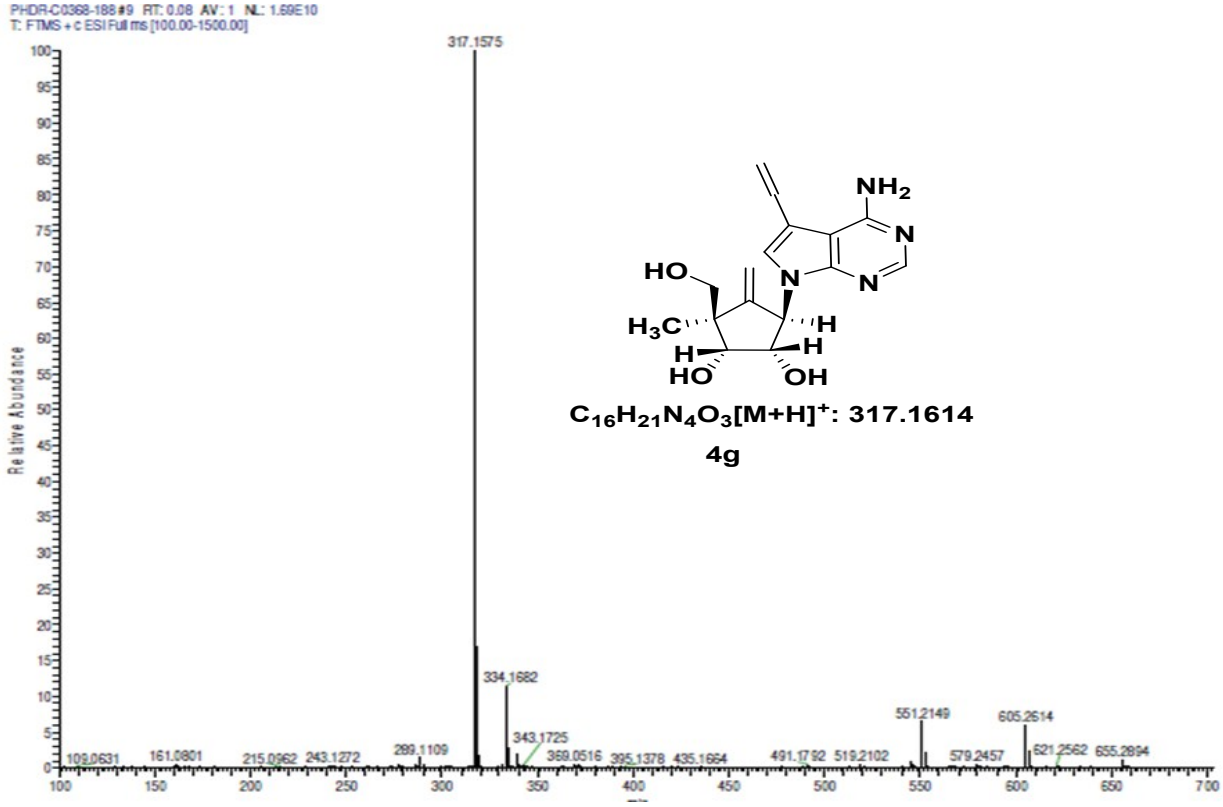
$C_{14}H_{18}IN_4O_3[M+H]^+$: 417.0424

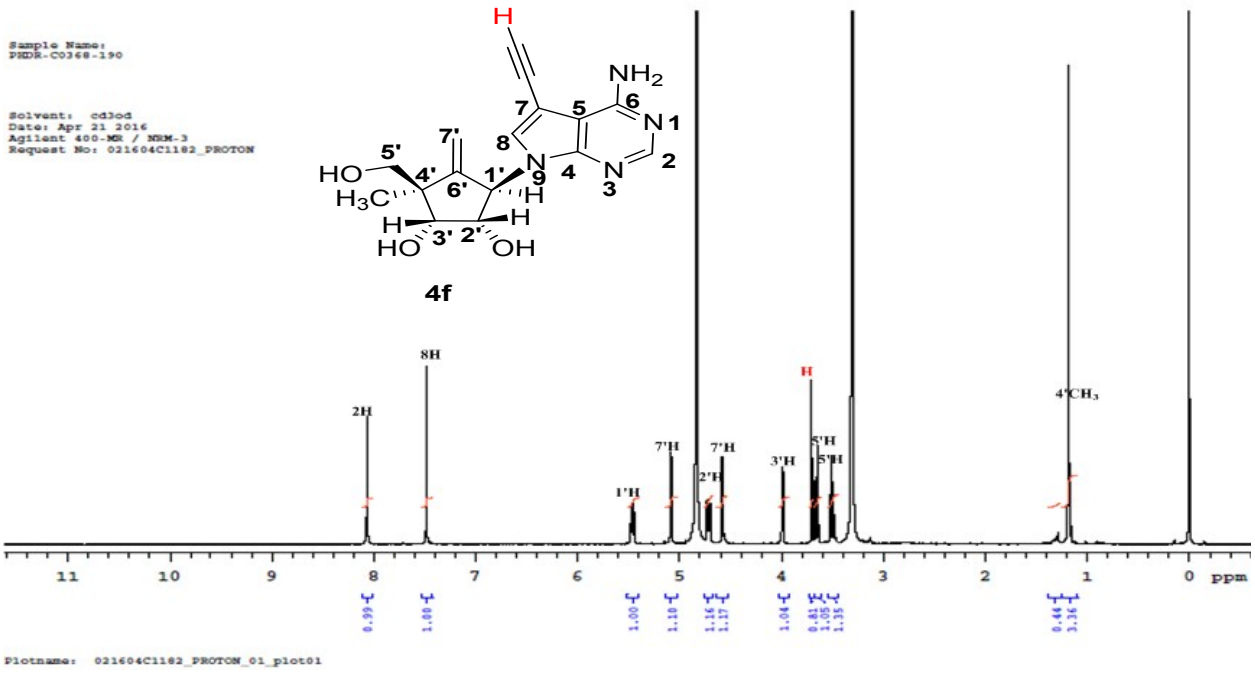
4e

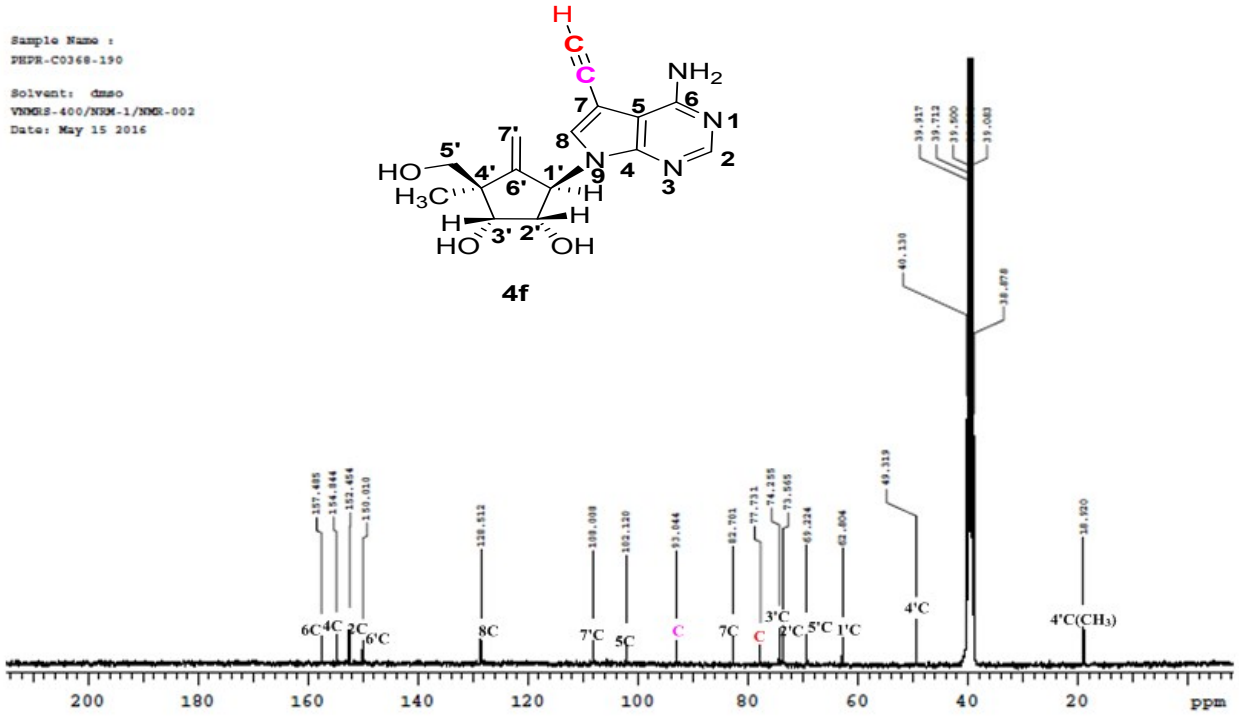


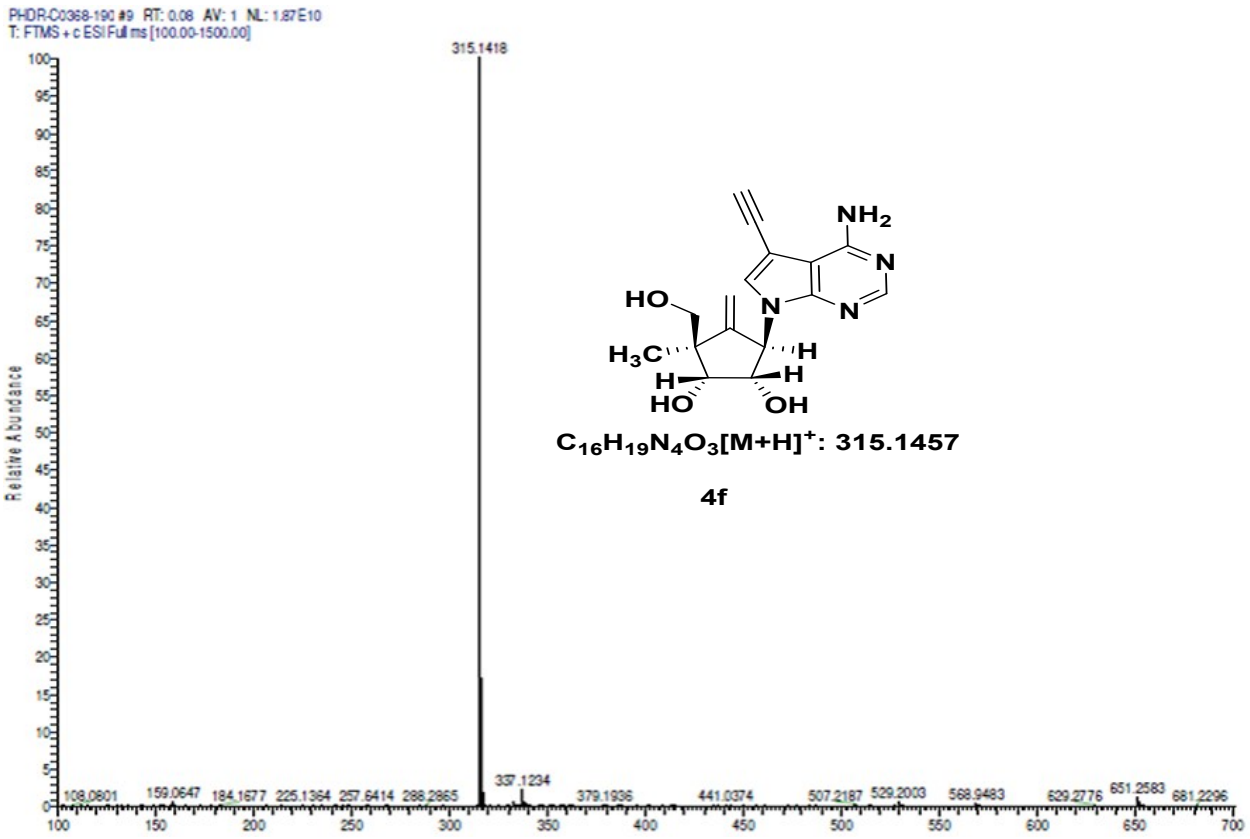
4g


Sample Name :
PHDR-C0368-188
Solvent: dmso
VNMRS-400/NMR-1/NMR-002
Date: May 15 2016
4g
4C 2C 6'C
8C
C
7C 7'C
5C
3'C 2'C 5'C
1'C
4'C
4'C(CH3)
200 180 160 140 120 100 80 60 40 20 ppm


PHDR-C0368-188 #9 RT: 0.08 AV: 1 NL: 1.69E10
T: FTMS + c ESI Full ms [100.00-1500.00]
Relative Abundance
317.1575
334.1682
343.1725
551.2149
605.2614
109.0631
161.0801
215.0962
243.1272
289.1109
369.0516
395.1378
435.1664
491.1792
519.2102
579.2457
621.2562
655.2894
C16H21N4O3[M+H]+: 317.1614
4g


Sample Name:
PKDR-C0368-190
Solvent: cd3od
Date: Apr 21 2016
Agilent 400-MR / NMM-3
Request No: 021604C1102_PROTON
4f
2H
8H
1'H
7'H
7'H
2'H
3'H
5'H
5'H
H
4'CH3
ppm
Plotname: 021604C1102_PROTON_01_plot01


Sample Name :
PKDR-C0368-190
Solvent: dmso
VNMRS-400/NMR-1/NMR-002
Date: May 15 2016
4f
6C
4C
2C
6'C
8C
7'C
5C
C
7C
C
3'C
2'C
5'C
1'C
4'C
4'C(CH3)
ppm



X-ray Crystal Structure Data of 4c:

$C_{14}H_{17}ClN_4O_3$ (M =324.7650 g/mol): monoclinic, space group P21 (no. 4),unit cell dimensions a =6.28(5) Å alpha = 90 °, b = 9.06 (10) Å beta = 90.1(6) °, c = 9.91 (6) Å gamma =90 °, V = 765.46(9) Å3, Z = 2, T = 293 K, Dcalc = 1.405 Mg/m3, Data completeness =1.84/1.00,Theta(max) = 26.370,R(reflections)=0.0352(2863), R2(reflections)=0.0985(3147), s = 0.952 and Npar = 222.