Fe(III)-Catalyzed synthesis of steroidal imidazoheterocycles as potent antiproliferative agents

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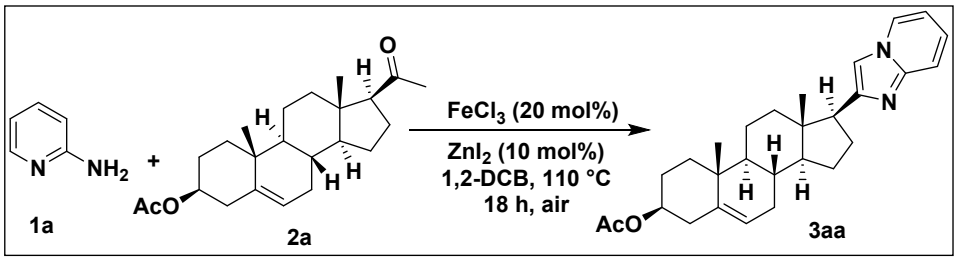
1. General Information:

NMR spectra were acquired on Bruker Avance 600, 500, 300 spectrometers at room temperature; the chemical shifts δ were measured in ppm relative to the solvent (^{1}H: $CDCl_3$, δ = 7.27 ppm; ^{13}C: $CDCl_3$, δ = 77.00 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; ddd, double double doublet. The coupling constants (*J*) are in Hertz. High-resolution and accurate mass spectra were obtained on Bruker microTOF-QTM ESI-TOF (Electrospray Ionization/Time of Flight) and Thermo Scientific* LTQ Orbitrap mass spectrometers. Melting points (mp) are uncorrected and were measured on a Boetius capillary melting point apparatus. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (silica gel 60 F254 aluminum supported plates); the visualization was accomplished with an UV lamp (365 nm) and using chemical staining with [$Ce(SO_4)_2/H_2SO_4$]. Column chromatography was performed on silica gel 60 (230-400 mesh, Merck). 2-Aminopyridines, 2-aminobenzothiazole, and steroids were commercially available and were used without purification. Iron salt (>97%, Lot SZBA0890 and >99.99%, Lot # MKBL0105V) was purchased from Sigma Aldrich. All reactions were carried out using freshly distilled and dry solvents. All reactions involving moisture sensitive reactants were executed using oven dried glassware.

2. Experimental procedures:

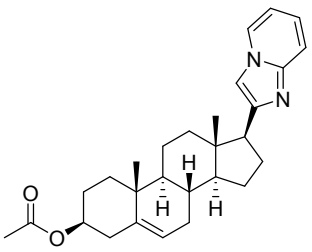
Typical experimental procedure for the synthesized compounds (3aa-3cb):



A mixture of 2-aminopyridine (0.24 mmol, 22.5 mg) (**1a**), pregnenolone acetate (**2a**) (0.2 mol, 71.7 mg) was taken in an oven dried reaction tube. Then 1,2-dichlorobenzene (2 mL) was added to it and stirred at room temperature for few seconds. Then zinc iodide (0.10 mmol, 7 mg) and iron(III) chloride (0.20 mmol, 6 mg) was added to it and stirred at 110 °C for 18 hours. After completion of the reaction (TLC) it was cooled to room temperature and extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4. The crude residue was

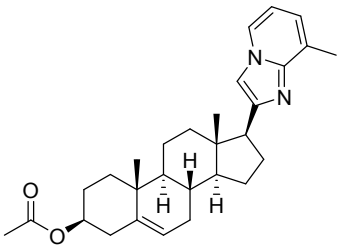
obtained after evaporating the solvent in vacuum and was purified by column chromatography on silica gel using a mixture petroleum ether and ethyl acetate (60:40) as an eluting solvent to afford the pure product (**3aa**) (69 mg, 81%) as a yellow solid.

3. Characterization data for the synthesized products:



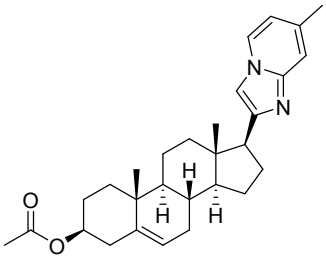
*17β-(Imidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (**3aa**)*:

Yield 69 mg (81%, 0.2 mmol); yellow solid; mp 156-158 °C; R_f = 0.06 (petroleum ether – EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 6.8 Hz, 1H, Ar), 7.58 (d, *J* = 9.0 Hz, 1H, Ar), 7.37 (s, 1H, Ar), 7.11 (dd, *J* = 6.8, 9.0 Hz, 1H, Ar), 6.72 (dd, *J* = 6.8, 6.8 Hz, 1H, Ar), 5.42 (m, 1H, 6-CH), 4.71 – 4.53 (m, 1H, 3α-CH), 2.88 (t, *J* = 9.8 Hz, 1H, 17α-CH), 2.43 – 2.07 (m, 5H), 2.05 (s, 3H, 3-$OCOCH_3$), 2.00 – 1.06 (m, 14H), 1.03 (s, 3H, 19-CH_3), 0.57 (s, 3H, 18-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 148.5, 144.8, 139.9, 125.2, 123.7, 122.6, 117.3, 111.7, 109.6, 74.0, 56.4, 50.9, 50.4, 44.0, 38.2, 38.1, 37.2, 36.8, 32.5, 32.1, 27.9, 26.6, 24.8, 21.5, 20.9, 19.4, 13.2; IR (KBr): 2942, 2903, 1731, 1375, 1364, 1248, 1032, 756, 736 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{37}N_2O_2$ $[M+H]^+$ 433.2850, found 433.2843.



*17β-(8'-Methylimidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (**3ba**)*:

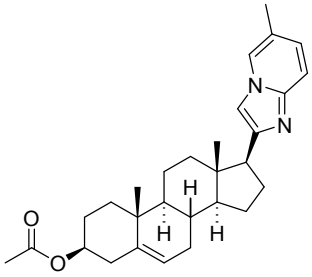
Yield 68 mg (77%, 0.2 mmol); yellow solid; mp 94-95 °C; R_f = 0.63 (petroleum ether – EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 6.5 Hz, 1H, Ar), 7.35 (s, 1H, Ar), 6.89 (d, *J* = 5.9 Hz, 1H, Ar), 6.62 (dd, *J* = 5.9, 6.5 Hz, 1H, Ar), 5.44 – 5.39 (m, 1H, 6-CH), 4.74 – 4.52 (m, 1H, 3α-CH), 2.95 (t, *J* = 9.9 Hz, 1H, 17α-CH), 2.60 (s, 3H, CH_3), 2.43 – 2.25 (m, 2H), 2.21 – 1.96 (m, 3H), 2.05 (s, 3H, 3-$OCOCH_3$), 1.96 – 1.74 (m, 3H), 1.73 – 1.50 (m, 4H), 1.49 – 1.16 (m, 6H), 1.16 – 0.96 (m, 1H), 1.04 (s, 3H, 19-CH_3), 0.56 (s, 3H, 18-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 147.6, 144.9, 139.9, 126.9, 123.1, 122.7, 122.6, 111.7, 109.8, 74.0, 56.3, 50.8, 50.3, 43.9, 38.2, 37.8, 37.1, 36.8, 32.5, 32.0, 27.8, 27.0, 24.8, 21.5, 20.9, 19.4, 17.2, 13.2; IR (KBr): 2945, 2908, 2871, 2361, 1730, 1438, 1364, 1248, 1032, 907, 732 cm^{-1}; HRMS (ESI): m/z calcd for $C_{29}H_{39}N_2O_2$ $[M+H]^+$ 447.3006, found 447.3004.



*17β-(7'-Methylimidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (**3ca**)*:

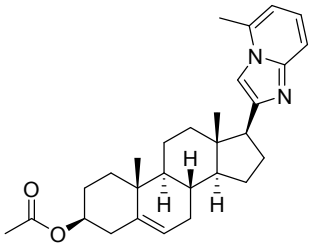
Yield 65 mg (73%, 0.2 mmol); yellow solid; mp 124-126 °C; R_f = 0.18 (petroleum ether – EtOAc, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 6.9 Hz, 1H, Ar), 7.35 (s, 1H, Ar), 7.28 (s, 1H, Ar), 6.56 (d, *J* = 6.9 Hz, 1H, Ar), 5.44 – 5.39 (m, 1H, 6-CH), 4.74 – 4.41 (m, 1H, 3α-CH), 2.86 (t, *J* = 9.8 Hz, 1H, 17α-CH), 2.41 – 2.23 (m, 3H), 2.38 (s, 3H, CH_3), 2.20 –

1.99 (m, 3H), 2.05 (s, 3H, 3-OCOCH$_3$), 2.00 – 1.70 (m, 5H), 1.70 – 1.48 (m, 4H), 1.46 – 1.32 (m, 3H), 1.32 – 1.05 (m, 1H), 1.03 (s, 3H, 19-CH$_3$), 0.55 (s, 3H, 18-CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 170.6, 147.9, 145.2, 139.9, 134.8, 124.5, 122.6, 115.6, 114.4, 108.9, 74.1, 56.4, 50.8, 50.4, 44.0, 38.2, 38.1, 37.2, 36.8, 32.5, 32.1, 27.9, 26.6, 24.7, 21.5, 21.4, 20.9, 19.4, 13.2; IR (KBr): 3422, 2964, 2941, 2905, 1732, 1374, 1366, 1249, 1034, 731 cm^{-1}; HRMS (ESI): m/z calcd for $C_{29}H_{39}N_2O_2$ [M+H]$^+$ 447.3006, found 447.2991.



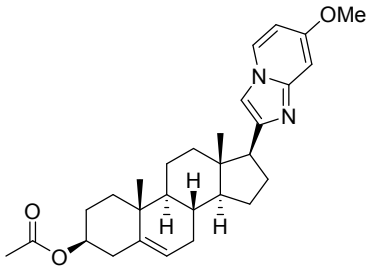
17β-(6'-Methylimidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene ***(3da)***:

Yield 33 mg (38%, 0.2 mmol); yellow solid; mp 91-93 °C; R_f = 0.15 (petroleum ether – EtOAc, 1:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.84 (s, 1H, Ar), 7.47 (d, *J* = 9.1 Hz, 1H, Ar), 7.28 (s, 1H, Ar), 6.95 (d, *J* = 9.1 Hz, 1H, Ar), 5.44 – 5.39 (m, 1H, 6-CH), 4.77 – 4.47 (m, 1H, 3α-CH), 2.85 (t, *J* = 9.8 Hz, 1H, 17α-CH), 2.52 – 2.23 (m, 2H), 2.30 (s, 3H, CH$_3$), 2.23 – 1.98 (m, 3H), 2.05 (s, 3H, 3-OCOCH$_3$), 2.00 – 1.74 (m, 4H), 1.75 – 1.48 (m, 4H), 1.48 – 1.08 (m, 6H), 1.03 (s, 3H, 19-CH$_3$), 0.55 (s, 3H, 18-CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ 170.5, 148.1, 143.9, 139.9, 126.7, 123.0, 122.6, 121.1, 116.5, 109.3, 74.1, 56.4, 50.9, 50.4, 44.0, 38.2, 38.1, 37.1, 36.8, 32.4, 32.0, 27.9, 26.5, 24.7, 21.4, 20.9, 19.4, 18.2, 13.2; IR (KBr): 3423, 2964, 2945, 1732, 1247, 1031, 907, 800, 731, 439 cm^{-1}; HRMS (ESI): m/z calcd for $C_{29}H_{39}N_2O_2$ [M+H]$^+$ 447.3006, found 447.3009.



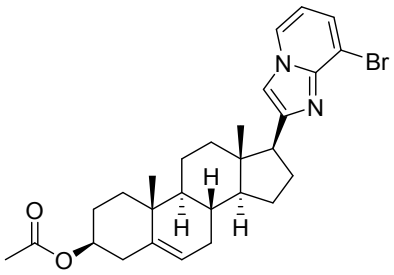
17β-(5'-Methylimidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene ***(3ea)***:

Yield 40 mg (9%, 1.0 mmol); yellow solid; mp 81-83 °C; R_f = 0.22 (petroleum ether – EtOAc, 1:1); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.51 (d, *J* = 9.0 Hz, 1H, Ar), 7.24 (s, 1H, Ar), 7.16 – 7.03 (dd, *J* = 6.8, 9.0 Hz, 1H, Ar), 6.58 (d, *J* = 6.8 Hz, 1H, Ar), 5.45 – 5.41 (m, 1H, 6-CH), 4.72 – 4.57 (m, 1H, 3α-CH), 2.92 (t, *J* = 9.8 Hz, 1H, 17α-CH), 2.72 – 2.43 (m, 3H), 2.58 (s, 3H, CH$_3$), 2.42 – 2.29 (m, 2H), 2.29 – 1.96 (m, 4H), 2.05 (s, 3H, 3-OCOCH$_3$), 1.95 – 1.74 (m, 3H), 1.73 – 1.49 (m, 3H), 1.48 – 1.35 (m, 4H), 1.04 (s, 3H, 19-CH$_3$), 0.60 (s, 3H, 18-CH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$): δ 170.5, 139.7, 122.4, 114.1, 106.7, 73.9, 56.2, 50.2, 44.0, 38.1, 37.8, 37.0, 36.7, 32.3, 31.9, 30.9, 29.6, 27.7, 26.5, 24.6, 21.4, 20.7, 19.3, 18.7, 13.1 (several signals were not observed); IR (KBr): 3423, 2928, 2851, 1732, 1458, 1365, 1249, 1034, 781, 551, 427 cm^{-1}; HRMS (ESI): m/z calcd for $C_{29}H_{39}N_2O_2$ [M+H]$^+$ 447.3006, found 447.3012.



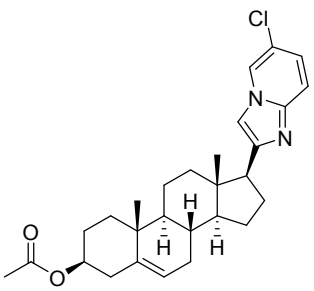
*17β-(7'-Methoxyimidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (**3fa**)*:

Yield 64 mg (70%, 0.2 mmol); brown solid; mp 171-172 °C; R_f = 0.45 (petroleum ether – EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.2 Hz, 1H, Ar), 7.16 (s, 1H, Ar), 6.86 (d, J = 2.4 Hz, 1H, Ar), 6.43-6.41 (m, 1H, Ar), 5.39 (d, J = 5.2 Hz, 1H, 6-CH), 4.65-4.56 (m, 1H, 3α-CH), 3.81 (s, 3H, OCH_3), 2.79 (t, J = 9.6 Hz, 1H, 17α-CH), 2.35-2.30 (m, 2H), 2.07-2.02 (m, 8H), 1.89-1.84 (m, 2H), 1.80-1.74 (m, 1H), 1.65-1.55 (m, 3H), 1.52-1.50 (m, 1H), 1.43-1.31 (m, 3H), 1.26-1.19 (m, 2H), 1.01 (s, 3H, 19-CH_3), 0.54(s, 3H, 18-CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.6, 157.4, 147.9, 146.2, 139.9, 125.6, 122.6, 108.2, 106.6, 94.6, 74.1, 56.3, 55.5, 50.8, 50.3, 43.9, 38.2, 38.1, 37.1, 36.8, 32.4, 32.0, 27.9, 26.4, 24.7, 21.5, 20.9, 19.4, 13.2; Anal. Calcd for $C_{29}H_{38}N_2O_3$: C, 75.29; H, 8.28; N, 6.06%; Found: C, 75.13; H, 8.31; N, 6.11%.



*17β-(8'-Bromo-imidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (**3ga**)*:

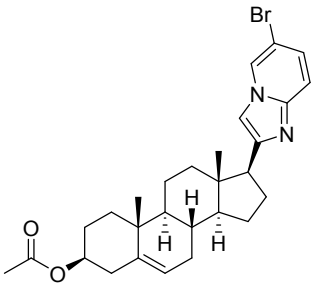
Yield 65 mg (64%, 0.2 mmol); brown gummy mass; R_f = 0.45 (petroleum ether – EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-8.01 (m, 1H, Ar), 7.43 (s, 1H, Ar), 7.35-7.33 (m, 1H, Ar), 6.58 (t, J = 7.2 Hz, 1H, Ar), 5.39 (d, J = 4.8 Hz, 1H, 6-CH), 4.64-4.58 (m, 1H, 3α-CH), 2.95 (t, J = 10.0 Hz, 1H, 17α-CH), 2.35-2.30 (m, 2H), 2.10-2.03 (m, 5H), 1.90-1.86 (m, 3H), 1.74 (s, 2H), 1.63-1.53 (m, 4H), 1.46-1.38 (m, 2H), 1.28-1.24 (m, 4H), 1.01 (s, 3H, 19-CH_3), 0.53 (s, 3H, 18-CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.6, 149.5, 142.7, 139.9, 126.1, 124.6, 122.6, 115.2, 111.7, 111.2, 74.1, 56.3, 50.8, 50.3, 44.1, 38.2, 37.8, 37.1, 36.8, 32.5, 32.0, 27.9, 26.9, 24.8, 21.5, 20.9, 19.5, 13.3; Anal. Calcd for $C_{28}H_{35}BrN_2O_2$: C, 65.75; H, 6.90; N, 5.48%; Found: C, 65.93; H, 6.86; N, 5.40%.



*17β-(6'-Chloro-imidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (**3ha**)*:

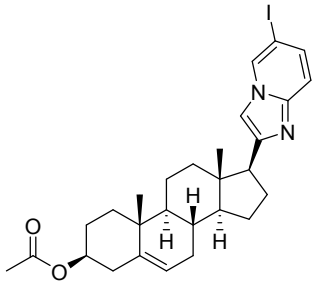
Yield 81 mg (87%, 0.2 mmol); yellow solid; mp 130-132 °C; R_f = 0.15 (petroleum ether – EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, J = 1.9 Hz, 1H, Ar), 7.51 (d, J = 9.5 Hz, 1H, Ar), 7.35 (s, 1H, Ar), 7.07 (dd, J = 1.9, 9.5 Hz, 1H, Ar), 5.46 – 5.36 (m, 1H, 6-CH), 4.71 – 4.56 (m, 1H, 3α-CH), 2.86 (t, J = 9.8 Hz, 1H, 17α-CH), 2.43 – 2.24 (m, 2H), 2.24 – 1.97 (m, 4H), 2.04 (s, 3H, 3-$OCOCH_3$), 1.96 – 1.74 (m, 4H), 1.73 – 1.49 (m, 3H), 1.48 – 1.33 (m, 3H), 1.31 – 1.14 (m, 3H), 1.02 (s, 3H, 19-CH_3), 0.54 (s, 3H, 18-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 149.7, 143.2, 139.9, 125.1, 123.0, 122.5, 119.9, 117.5, 110.1, 74.1, 56.3, 50.8, 50.4, 44.2, 38.2, 38.1, 37.2, 36.8, 32.4, 32.0, 27.9, 26.5, 24.7, 21.5, 20.9, 19.4,

13.2; IR (KBr): 2964, 2941, 2905, 1732, 1703, 1520, 1500, 1374, 1249, 1068, 1037, 801, 793, 731, 706 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{36}ClN_2O_2$ $[M+H]^+$ 467.2460, found 467.2452.



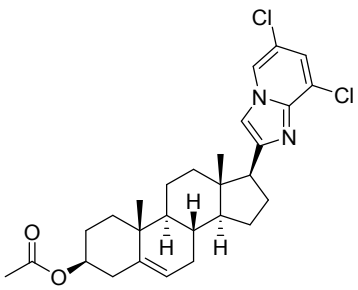
*17β-(6'-Bromo-imidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (**3ia**)*:

Yield 73 mg (72%, 0.2 mmol); yellow solid; R_f = 0.25 (petroleum ether – EtOAc, 3:1); ^1H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, *J* = 1.5 Hz, 1H, Ar), 7.50 (d, *J* = 9.5 Hz, 1H, Ar), 7.35 (s, 1H), 7.20 (dd, *J* = 1.5, 9.5 Hz, 1H, Ar), 5.46 – 5.36 (m, 1H, 6-CH), 4.72 – 4.55 (m, 1H, 3α-CH), 2.87 (t, *J* = 9.8 Hz, 1H, 17α-CH), 2.47 – 2.15 (m, 4H), 2.14 – 1.97 (m, 2H), 2.05 (s, 3H, 3-$OCOCH_3$), 1.97 – 1.73 (m, 5H), 1.72 – 1.49 (m, 5H), 1.11 – 0.85 (m, 3H), 1.04 (s, 3H, 19-CH_3), 0.55 (s, 3H, 18-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 139.7, 127.1, 125.1, 117.6, 109.8, 56.2, 54.8, 50.6, 50.1, 49.9, 44.0, 38.1, 38.0, 37.9, 37.0, 36.7, 32.3, 31.9, 29.7, 27.7, 26.3, 24.6, 24.5, 21.4, 20.7, 19.3, 13.1; IR (KBr): 2942, 2904, 1729, 1701, 1509, 1499, 1373, 1247, 1031, 907, 798, 732 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{36}BrN_2O_2$ $[M+H]^+$ 511.1955, found 511.1950.



*17β-(6'-Iodo-imidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (**3ja**)*:

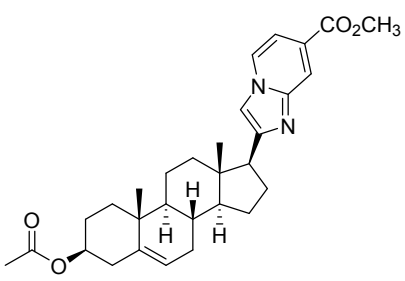
Yield 82 mg (74%, 0.2 mmol); yellow solid; mp 168-170 °C; R_f = 0.20 (petroleum ether – EtOAc, 3:1); ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (s, 1H, Ar), 7.40 (d, *J* = 9.4 Hz, 1H, Ar), 7.30 (d, *J* = 9.4 Hz, 1H, Ar), 7.28 (s, 1H, Ar), 5.46 – 5.36 (m, 1H, 6-CH), 4.71 – 4.55 (m, 1H, 3α-CH), 2.86 (t, *J* = 9.8 Hz, 1H, 17α-CH), 2.43 – 2.26 (m, 2H), 2.23 – 1.99 (m, 3H), 2.05 (s, 3H, 3-$OCOCH_3$), 1.98 – 1.72 (m, 4H), 1.70 – 1.47 (m, 4H), 1.30 – 1.15 (m, 3H), 1.12 – 0.96 (m, 3H), 1.03 (s, 3H, 19-CH_3), 0.54 (s, 3H, 18-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 150.3, 140.6, 139.7, 123.7, 123.0, 122.4, 121.8, 118.7, 111.5, 73.9, 56.2, 50.6, 50.1, 44.0, 38.1, 37.7, 37.0, 36.7, 32.3, 31.9, 27.7, 26.6, 24.6, 21.4, 20.7, 19.3, 13.1; IR (KBr): 2942, 2903, 1727, 1493, 1373, 1365, 1332, 1248, 1030, 917, 797, 754, 733, 671 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{36}IN_2O_2$ $[M+H]^+$ 559.1816, found 559.1818.



*17β-(6',8'-Dichloro-imidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (**3ka**)*:

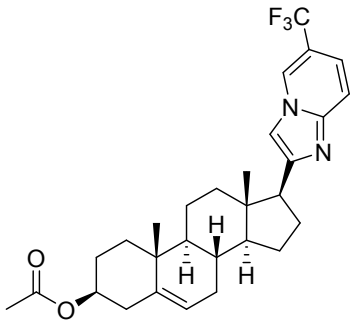
Yield 35 mg (7%, 1.0 mmol); yellow solid; R_f = 0.66 (petroleum ether – EtOAc, 3:1); ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H, Ar), 7.42 (s, 1H, Ar), 7.21 (s, 1H, Ar), 5.47 – 5.38 (m, 1H, 6-CH), 4.75 – 4.59 (m, 1H, 3α-CH), 2.94 (t, *J* = 9.9 Hz, 1H, 17α-CH), 2.42 – 2.21 (m, 2H), 2.20 – 2.00 (m, 2H), 2.06 (s, 3H, 3-$OCOCH_3$), 1.99 – 1.74 (m, 3H), 1.73 – 1.49 (m, 7H), 1.48 – 1.33 (m, 3H), 1.32 – 1.16 (m, 2H), 1.04 (s, 3H, 19-CH_3), 0.55 (s, 3H, 18-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 150.4, 140.6, 139.7, 123.7,

123.0, 122.4, 121.8, 118.7, 111.5, 73.9, 56.2, 50.6, 50.1, 44.0, 38.1, 37.7, 37.0, 36.7, 32.3, 31.9, 27.7, 26.6, 24.6, 21.4, 20.7, 19.3, 13.1; IR (KBr): 3343, 2945, 2904, 1727, 1516, 1374, 1249, 1030, 933, 819, 754 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{35}Cl_2N_2O_2$ $[M+H]^+$ 501.2070, found 501.2059.



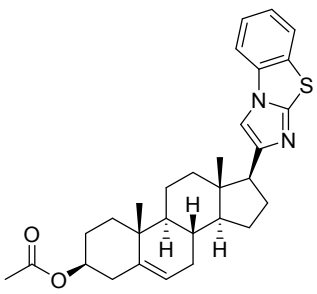
*17β-(Methyl imidazo[1',2'-a]pyridine-6'-carboxylate)-3β-acetoxy-androst-5-ene (**3la**)*:

Yield 142 mg (29%, 1.0 mmol); yellow solid; mp 229-231°C; R_f = 0.16 (petroleum ether – EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (s, 1H, Ar), 8.09 (d, *J* = 7.1 Hz, 1H, Ar), 7.48 (s, 1H, Ar), 7.34 (d, *J* = 7.1 Hz, 1H, Ar), 5.47 – 5.39 (m, 1H, 6-CH), 4.75 – 4.44 (m, 1H, 3α-CH), 3.95 (s, 3H, OCH_3), 2.90 (t, *J* = 9.8 Hz, 1H, 17α-CH), 2.41 – 2.30 (m, 2H), 2.27 – 1.93 (m, 4H), 2.04 (s, 3H, 3-$OCOCH_3$), 1.91 – 1.77 (m, 3H), 1.73 – 1.50 (m, 4H), 1.49 – 1.34 (m, 3H), 1.33 – 1.13 (m, 3H), 1.02 (s, 3H, 19-CH_3), 0.55 (s, 3H, 18-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 166.0, 151.3, 143.7, 139.9, 125.0, 124.6, 122.5, 119.8, 111.3, 111.1, 74.0, 56.3, 52.5, 50.9, 50.3, 44.2, 38.2, 38.0, 37.1, 36.8, 32.4, 32.0, 27.8, 26.4, 24.7, 21.5, 20.8, 19.4, 13.2; IR (KBr): 2964, 2941, 2900, 1722, 1436, 1332, 1240, 1088, 1040, 761, 743 cm^{-1}; HRMS (ESI): m/z calcd for $C_{30}H_{39}N_2O_4$ $[M+H]^+$ 491.2904, found 491.2895.



17β-(6'-Trifluoromethyl-imidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (***3ma***):

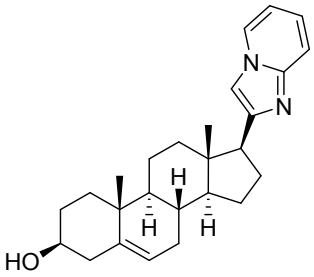
Yield 82 mg (82%, 0.2 mmol); brown gummy mass; R_f = 0.55 (petroleum ether – EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.42 (s, 1H, Ar), 7.63 (d, *J* = 9.6 Hz, 1H, Ar), 7.44 (s, 1H, Ar), 7.24-7.21 (m, 1H, Ar), 5.38 (d, *J* = 4.8 Hz, 1H, 6-CH), 4.64-4.56 (m, 1H, 3α-CH), 2.86 (t, *J* = 10.0 Hz, 1H, 17α-CH), 2.32-2.29 (m, 2H), 2.16-2.01 (m, 6H), 1.95-1.92 (m, 1H), 1.88-1.80 (m, 3H), 1.65-1.49 (m, 4H), 1.40-1.36 (m, 3H), 1.28-1.11 (m, 3H), 1.00 (s, 3H, 19-CH_3), 0.51 (s, 3H, 18-CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 170.6, 150.7, 144.5, 139.8, 124.2 (q, $J_{C\text{-}F}$ = 6.0 Hz), 122.5, 119.6, 117.7, 116.1 (q, $J_{C\text{-}F}$ = 34.0 Hz), 112.6 (q, $J_{C\text{-}F}$ = 288.0 Hz), 110.9, 74.0, 56.3, 50.8, 50.2, 44.2, 38.2, 38.0, 37.1, 36.8, 32.4, 32.0, 27.8, 26.4, 24.7, 21.5, 20.8, 19.4, 13.2; Anal. Calcd for $C_{29}H_{35}F_3N_2O_2$: C, 69.58; H, 7.05; N, 5.60%; Found: C, 69.41; H, 7.09; N, 5.51%.



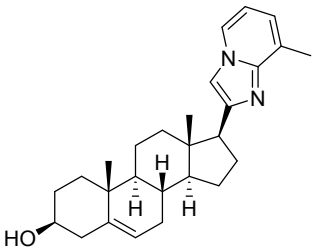
17β-(Benzo[d]imidazo[2',1'-b]thiazole)-3β-acetoxy-androst-5-ene (***3na***):

Yield 87 mg (18%, 1.0 mmol); yellow solid; R_f = 0.50 (petroleum ether – EtOAc, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.8 Hz, 1H, Ar), 7.55 (d, *J* = 7.8 Hz, 1H, Ar), 7.46 (s, 1H, Ar), 7.41 (dd, *J* = 7.8 Hz, 1H, Ar), 7.30 (dd, *J* = 7.8 Hz, 1H, Ar), 5.49 – 5.38 (m, 1H, 6-CH), 4.75 – 4.45 (m, 1H, 3α-CH), 2.81 (t, *J* = 9.9 Hz, 1H, 17α-CH), 2.46 – 2.19 (m, 2H), 2.18 – 1.96 (m, 3H), 2.05 (s, 3H, 3-OCOCH_3), 1.95 – 1.74 (m, 3H), 1.73 – 1.49 (m, 6H), 1.48 – 1.35 (m, 2H), 1.14 – 0.95 (m, 1H), 1.04 (s, 3H, 19-CH_3), 0.94 – 0.72 (m, 2H), 0.59 (s, 3H, 18-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3, 149.8, 139.7, 132.3, 130.1, 126.3, 125.9, 124.2, 122.4, 112.3, 108.2, 73.9, 56.0, 51.0, 50.2, 43.7, 38.1, 38.0, 37.0, 36.7, 32.3, 31.9, 29.6, 27.7, 26.2, 24.5, 21.4, 20.8, 19.3, 13.0; IR (KBr): 2939, 2851, 1729, 1542, 1490, 1465, 1439, 1246, 1028, 748, 425 cm^{-1}; HRMS (ESI): m/z calcd for $C_{30}H_{37}N_2O_2S$ $[M+H]^+$ 489.2570, found 489.2559.

17β-(Imidazo[1',2'-a]pyridine)-3β-hydroxy-androst-5-ene (***3ab***):



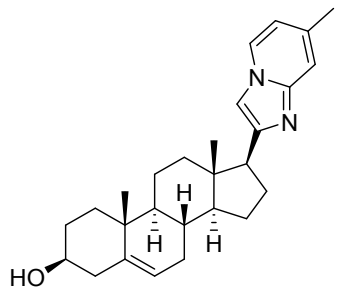
Yield 55 mg (71%, 0.2 mmol); light yellow gummy mass; R_f = 0.45 (petroleum ether – EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.05-8.03 (m, 1H, Ar), 7.55 (d, *J* = 9.2 Hz, 1H, Ar), 7.35 (s, 1H, Ar), 7.11-7.06 (m, 1H, Ar), 6.72-6.68 (m, 1H, Ar), 5.37-5.36 (m, 1H, 6-CH), 3.54-3.52 (m, 1H, 3α-CH), 2.86 (t, *J* = 10.0 Hz, 1H, 17α-CH), 2.33-2.25 (m, 2H), 2.16-2.06 (m, 2H), 1.97-1.93 (m, 1H), 1.88-1.74 (m, 5H), 1.60-1.38 (m, 7H), 1.28-1.22 (m, 2H), 1.00 (s, 3H, 19-CH_3), 0.54 (s, 3H, 18-CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 148.4, 144.8, 141.0, 125.2, 123.7, 121.7, 117.2, 111.7, 109.6, 71.9, 56.4, 50.9, 50.4, 44.1, 42.4, 38.1, 37.4, 36.8, 32.5, 32.1, 31.8, 26.6, 24.8, 20.9, 19.5, 13.2; Anal. Calcd for $C_{26}H_{34}N_2O$: C, 79.96; H, 8.77; N, 7.17%; Found: C, 79.76; H, 8.81; N, 7.11%.



17β-(8'-Methylimidazo[1',2'-a]pyridine)-3β-hydroxy-androst-5-ene (***3bb***):

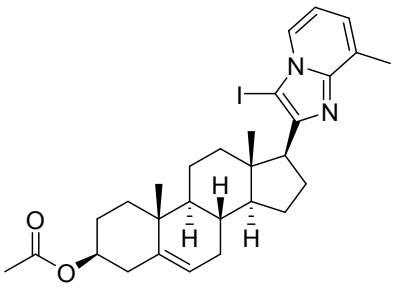
Yield 54 mg (68%, 0.2 mmol); brown gummy mass; R_f = 0.45 (petroleum ether – EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.91 (d, *J* = 6.8 Hz, 1H, Ar), 7.33 (s, 1H, Ar), 6.87 (d, *J* = 6.8 Hz, 1H, Ar), 6.61 (t, *J* = 6.8 Hz, 1H, Ar), 5.37 (d, *J* = 5.2 Hz, 1H, 6-CH), 3.57-3.49 (m, 1H, 3α-CH), 2.93 (t, *J* = 10.0 Hz, 1H, 17α-CH), 2.58 (s, 3H, CH_3), 2.33-2.23 (m, 2H), 2.14-1.98 (m, 4H), 1.88-1.77 (m, 5H), 1.65-1.47 (m, 5H), 1.45-1.35 (m, 3H), 1.00 (s, 3H, 19-CH_3), 0.54 (s, 3H, 18-CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 147.8, 145.1, 141.0, 127.0, 123.1, 122.6, 121.7, 111.7, 109.8, 71.9, 56.4, 50.9, 50.4, 43.9, 42.4, 37.9, 37.4, 36.7, 32.5, 32.1, 31.8,

27.1, 24.8, 21.0, 19.5, 17.3, 13.2; Anal. Calcd for $C_{27}H_{36}N_2O$: C, 80.15; H, 8.97; N, 6.92%; Found: C, 80.27; H, 8.95; N, 6.99%.



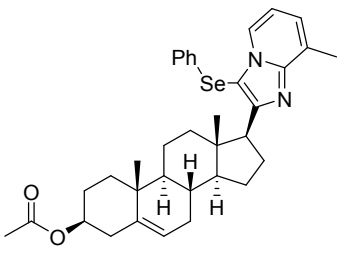
17β-(7'-Methylimidazo[1',2'-a]pyridine)-3β-hydroxy-androst-5-ene (***3cb***):

Yield 55 mg (69%, 0.2 mmol); brown gummy mass; R_f = 0.50 (petroleum ether – EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 6.8 Hz, 1H, Ar), 7.38 (s, 1H, Ar), 7.26 (s, 1H, Ar), 6.55 (d, J = 6.8 Hz, 1H, Ar), 5.35 (s, 1H, 6-CH), 3.56-3.49 (m, 1H, 3α-CH), 2.84 (t, J = 10.4 Hz, 1H, 17α-CH), 2.35 (s, 3H, CH_3), 2.29-2.22 (m, 2H), 2.08-1.98 (m, 5H), 1.86-1.79 (m, 3H), 1.62-1.47 (m, 5H), 1.41-1.37 (m, 2H), 1.26-1.21 (m, 2H), 0.98 (s, 3H, 19-CH_3), 0.52 (s, 3H, 18-CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.9, 145.2, 141.0, 135.0, 124.5, 121.6, 115.6, 114.5, 109.0, 71.8, 56.4, 50.9, 50.4, 44.0, 42.4, 38.2, 37.4, 36.7, 32.4, 32.0, 31.7, 26.7, 24.7, 21.4, 20.9, 19.5, 13.2; Anal. Calcd for $C_{27}H_{36}N_2O$: C, 80.15; H, 8.97; N, 6.92%; Found: C, 79.97; H, 9.00; N, 6.87%.



17β-(3'-Iodo-8'-methylimidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (***4ba***):

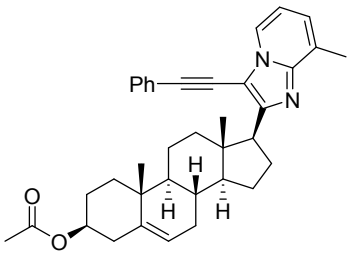
Yield 101 mg (89%, 0.2 mmol); brown gummy mass; R_f= 0.50 (petroleum ether – EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 6.8 Hz, 1H, Ar), 6.93 (d, J = 6.8 Hz, 1H, Ar), 6.73 (t, J = 6.8 Hz, 1H, Ar), 5.40 (d, J = 4.0 Hz, 1H, 6-CH), 4.63-4.58 (m, 1H, 3α-CH), 2.93 (t, J = 9.6 Hz, 1H, 17α-CH), 2.58 (s, 3H, CH_3), 2.34-2.32 (m, 2H), 2.08-1.93 (m, 5H), 1.87-1.84 (m, 3H), 1.65-1.28 (m, 10H), 1.18-1.14 (m, 1H), 1.03-1.01 (m, 4H), 0.72 (s, 3H, 18-CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.6, 150.4, 147.8, 139.8, 127.3, 124.0, 123.1, 122.7, 112.3, 74.1, 56.7, 50.4, 49.8, 46.2, 38.9, 38.2, 37.1, 36.8, 32.3, 32.1, 27.9, 26.9, 25.0, 21.5, 21.0, 19.5, 16.7, 13.5; Anal. Calcd for $C_{29}H_{37}IN_2O_2$: C, 60.84; H, 6.51; N, 4.89%; Found: C, 60.63; H, 6.55; N, 4.95%.



17β-(8'-Methyl-3'-phenylselanyl-imidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (***5ba***):

Yield 86 mg (72%, 0.2 mmol); brown gummy mass; R_f = 0.50 (petroleum ether – EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 6.8 Hz, 1H, Ar), 7.15-7.11 (m, 3H, Ar), 6.99-6.97 (m, 3H, Ar), 6.65 (t, J = 6.8 Hz, 1H, Ar), 5.40 (d, J = 4.8 Hz, 1H, 6-CH), 4.64-4.57 (m, 1H, 3α-CH), 3.21 (t, J = 9.6 Hz, 1H, 17α-CH), 2.69-2.59 (m, 4H), 2.33-2.32 (m, 2H), 2.07-1.98 (m, 5H), 1.86-1.80 (m, 3H), 1.62-1.22 (m, 11H), 1.00 (s, 3H, 19-CH_3), 0.76 (s, 3H, 18-CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.6, 154.3, 147.7, 139.8, 131.7, 129.4, 128.0, 127.2, 126.3, 124.1, 123.1, 122.7, 112.1, 105.5, 74.0, 56.7, 50.3, 49.5, 45.4, 38.2, 38.0,

37.1, 36.8, 32.3, 32.1, 27.8, 27.1, 25.0, 21.5, 20.9, 19.4, 17.0, 13.5; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 194.5; Anal. Calcd for $C_{35}H_{42}N_2O_2Se$: C, 69.87; H, 7.04; N, 4.66%; Found: C, 70.01; H, 7.00; N, 4.77%.



17β-(8'-Methyl-3'-phenylethynyl-imidazo[1',2'-a]pyridine)-3β-acetoxy-androst-5-ene (***6ba***):

Yield 91 mg (84%, 0.2 mmol); brown gummy mass; R_f = 0.50 (petroleum ether – EtOAc, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 6.4 Hz, 1H, Ar), 7.54-7.52 (m, 2H, Ar), 7.40-7.34 (m, 3H, Ar), 6.98 (d, J = 6.8 Hz, 1H, Ar), 6.77 (t, J = 7.2 Hz, 1H, Ar) , 5.40 (d, J = 4.8 Hz, 1H, 6-CH), 4.63-4.58 (m, 1H, 3α-CH), 3.15 (t, J = 10.0 Hz, 1H, 17α-CH), 2.80-2.71 (m, 1H), 2.61 (s, 3H, CH_3), 2.34-2.31 (m, 2H), 2.11-2.03 (m, 6H), 1.88-1.85 (m, 4H), 1.69-1.53 (m, 4H), 1.47-1.30 (m, 4H), 1.20-1.16 (m, 1H) 1.01 (s, 3H, 19-CH_3), 0.70 (s, 3H, 18-CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 170.6, 152.2, 145.0, 139.8, 130.9, 128.6, 128.2, 127.2, 124.1, 123.4, 122.7, 112.3, 107.0, 100.4, 78.8, 74.1, 56.5, 50.8, 50.3, 46.2, 38.3, 38.2, 37.1, 36.8, 32.4, 32.1, 27.8, 25.7, 25.1, 21.5, 20.9, 19.4, 17.1, 13.5 Anal. Calcd for $C_{37}H_{42}N_2O_2$: C, 81.28; H, 7.74; N, 5.12%; Found: C, 81.11; H, 7.76; N, 5.03%.

4. Biology:[1,2]

In vitro ligand screening. Initial screening of the ligands was performed by using HTS (high throughput screening) approach. The 96-well plate was filled by ligand solutions in 50 mM potassium-phosphate buffer (pH 7.4), containing 0.2% CHAPS and 0.3 M NaCl (final ligand concentration was 80 uM). After adding protein solution (final concentration 1 uM) difference spectrum (350-500 nm) was measured (protein+ligand vs. protein+DMSO) using SpectraMax i3 spectrophotofluorometer («Molecular Devices», USA). Compounds for which typical spectral response (type I or II) was detected were picked for further experiments.

Estimation of K_d. Affinity of the ligands was analyzed using spectrophotometric titration in 50 mM potassium-phosphate buffer (pH 7.4), containing 0.2% CHAPS and 0.3 M NaCl with final CYP concentration 1 μM. Ligand solution (stock solutions with concentrations from 10^{-4} to 10^{-2} M) was added to the experimental cuvette and equal volume of the solvent (DMSO) to the control cuvette. For the determination of dissociation constant of enzyme-ligand complex (K_d) equation for the Tight binding was used. Titration data were approximated with the following equation by Levenberg-Marquart algorithm:

$$A = A_{\max} \cdot \frac{[L]_t + [R]_0 + K_d - \sqrt{([L]_t + [R]_0 + K_d)^2 - 4[R]_0[L]_t}}{2[R]_0}$$

where

A – amplitude of the spectral change at [L] ligand concentration;

A_{max} – amplitude of the spectral change at [L] ligand concentration at saturation ligand concentration;

$[L]_t$ – total ligand concentration;

$[R]_0$ – total protein concentration.

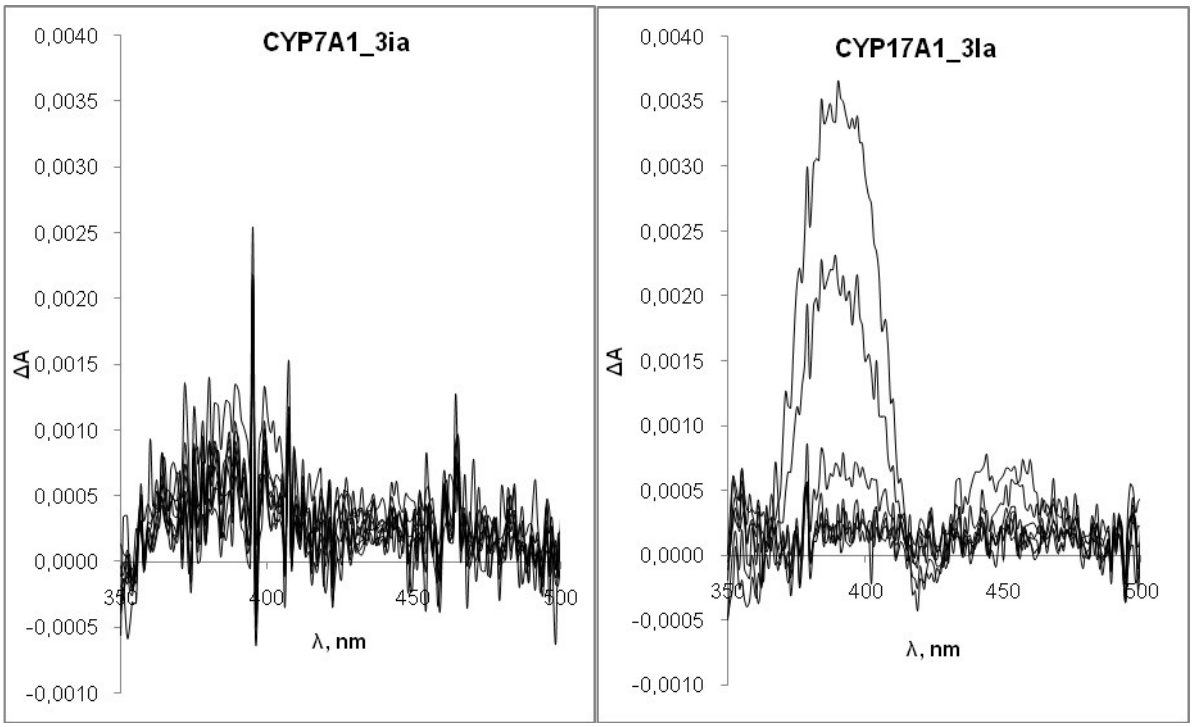


Figure S1. Difference spectra, obtained during spectrophotometric titration of human recombinant CYP7A1 and CYP17A1 by compounds **3ia** and **3la**, respectively.[3]

Cell lines and evaluation of antiproliferative activity. The human prostate cancer cell line 22Rv1, human breast cancer cell line MCF-7, and human ovarian cancer cell line SKOV3 were purchased from the ATCC collection. 22Rv1 cells were cultured in standard RPMI-1640 medium (Gibco) supplemented with 10% fetal calf serum (FCS) (HyClone), RPMI-1640 Vitamins (PanEco) and 0.1 mg/ml sodium pyruvate (Santa Cruz) at 37 °C, 5% CO_2 and 80–85% humidity (NuAir CO_2 incubator). SKOV3 and MCF-7 cells were cultured in standard (4.5 g/L glucose) DMEM medium (Gibco) supplemented with 10% fetal calf serum (FCS) (HyClone), and 0.1 mg/ml sodium pyruvate. The cell growth was evaluated by the modified MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) (Applichem) test [1] as described in [2].

[3] Other compounds were not active enough against Cytochrome P450 enzymes for determination of K_d

22Rv1 cells were seeded at a density of 10^5 cells per well in 24-well plates (Corning) in 900 μL of the medium, MCF-7 and SKOV3 cells - at a density of $4*10^4$ and $5*10^4$ cells per well, respectively.

The synthesized compounds were dissolved in DMSO (Applichem) to 10 mM before experiments and then were diluted in the medium to the required concentrations. The tested compounds with different concentrations in 100 μL of the medium were added 24 h after the seeding, and the cells were grown for 72 h. After incubation with the compounds, the medium was removed, and the MTT reagent dissolved in the medium was added to the final concentration of 0.2 mg/ml to each well and incubated for 3 h. The cell supernatants were removed and the MTT formazan purple crystals were dissolved in 100% DMSO (350 μL per well). Then the plates were gently shaken and the absorbance was measured at 540 nm with a MultiScan reader (ThermoFisher). The viability of the cells was assessed after subtraction of the blank value (the absorbance in the well w/o cells) from all wells. Dose-response curves were analyzed by regression analysis using sigmoidal curves (Log(concentration) vs normalized absorbance). The half maximal inhibitory concentrations (IC_{50}) were determined with GraphPad Prism.

Statistical tests. Statistical analysis was performed using Microsoft Excel and GraphPad Prism. Each biology experiment was repeated three times and results were expressed as mean + S.D. (standard deviation value). Student's t-test was used to evaluate the significance of differences in comparisons. P value of <0.05 was considered statistically significant.

5. References:

1. M. Iselt, W. Holtei and P. Hilgard, *Arzneimittelforschung* 1989, **39**, 747.

2. Y. A. Volkova, Y. S. Antonov, A. V. Komkov, A. M. Scherbakov, A. S. Shashkov, L. G. Menchikov, E. I. Chernoburova and I. V. Zavarzin, *RSC Adv.,* 2016, **6**, 42863.

6. NMR spectra for the synthesized products


8.37
8.07
8.05
7.68
7.60
7.57
7.37
7.28
7.13
7.11
7.08
7.00
6.75
6.72
6.70
5.42
4.63
2.91
2.88
2.85
2.57
2.35
2.20
2.17
2.14
2.12
2.09
2.04
1.98
1.96
1.90
1.87
1.66
1.60
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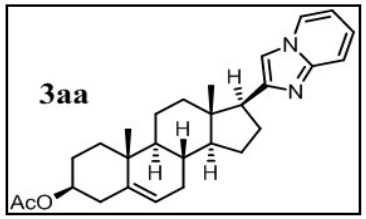
1.19
1.14
1.03
0.94
0.92
0.74
0.56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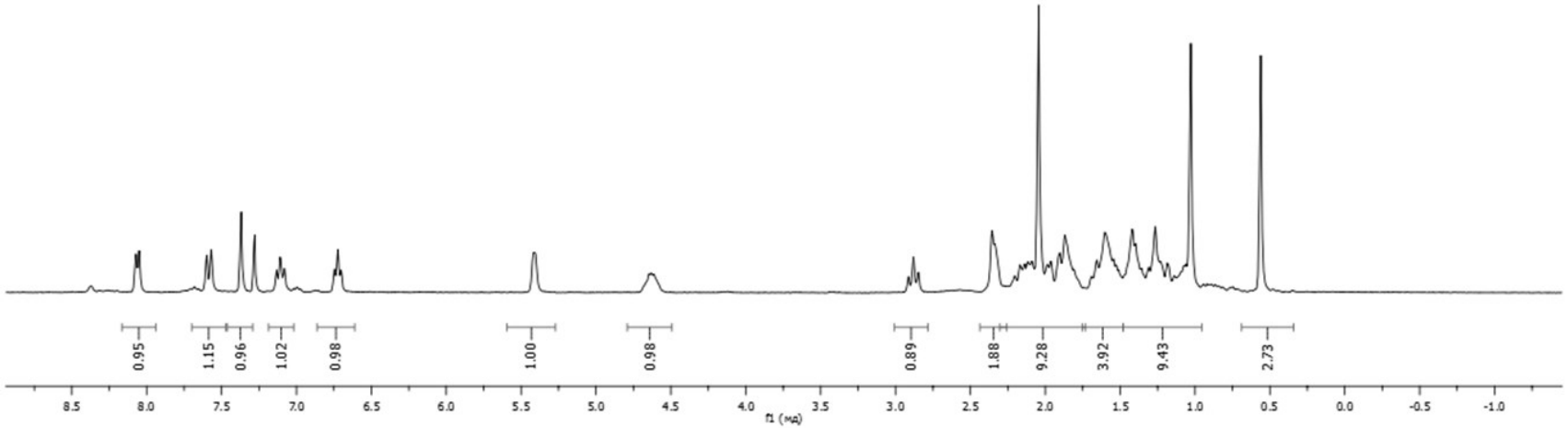
AcO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2.73
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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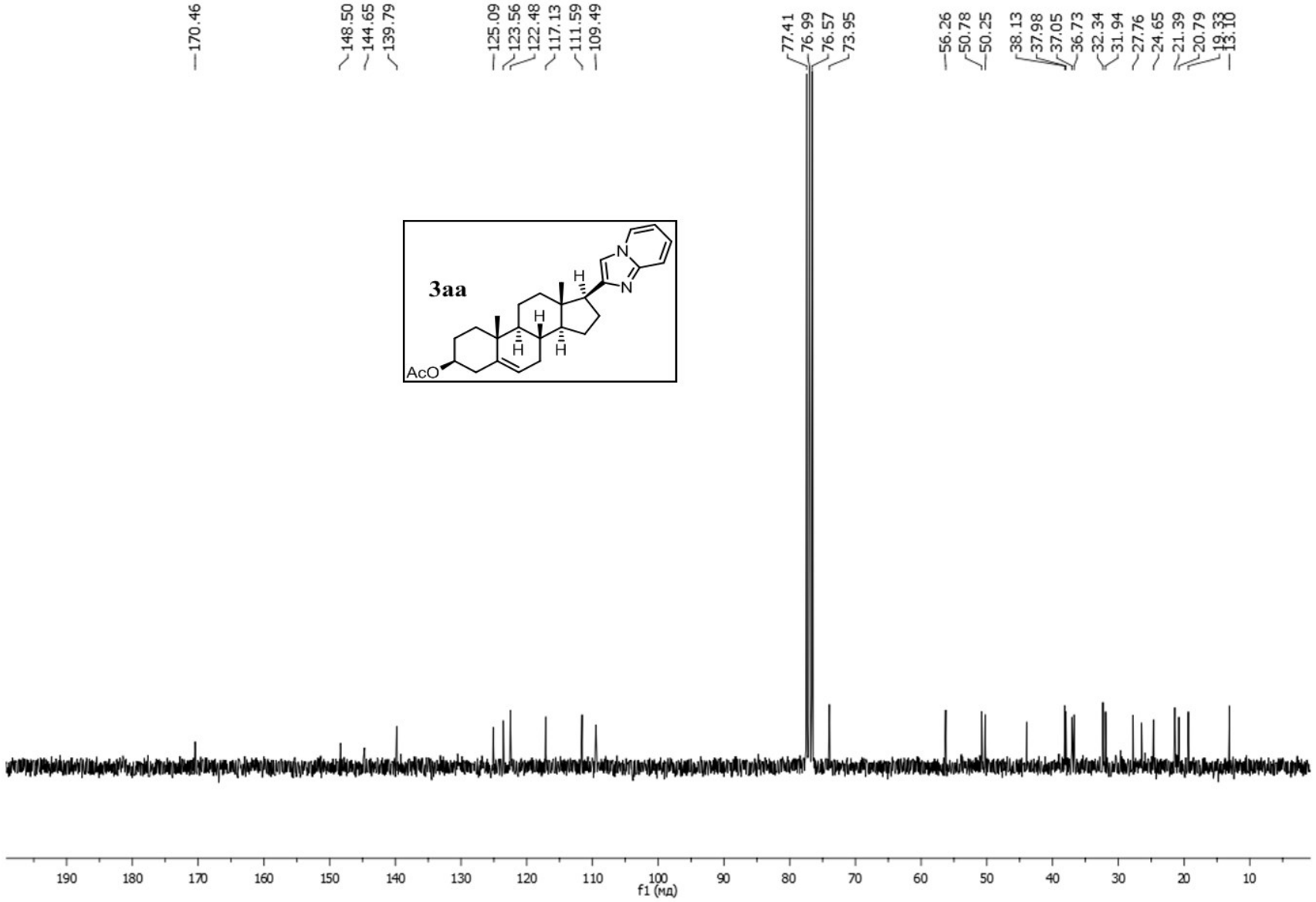
f1 (ppm)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76.57
73.95
56.26
50.78
50.25
38.13
37.98
37.05
36.73
32.34
31.94
27.76
24.65
21.39
20.79
19.33
13.10
3aa
AcO
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (мд)


7.94
7.92
7.35
7.28
6.90
6.88
6.62
5.42
4.63
4.15
4.12
2.98
2.95
2.92
2.60
2.55
2.36
2.05
1.99
1.91
1.87
1.66
1.61
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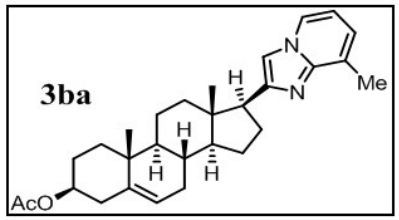
0.50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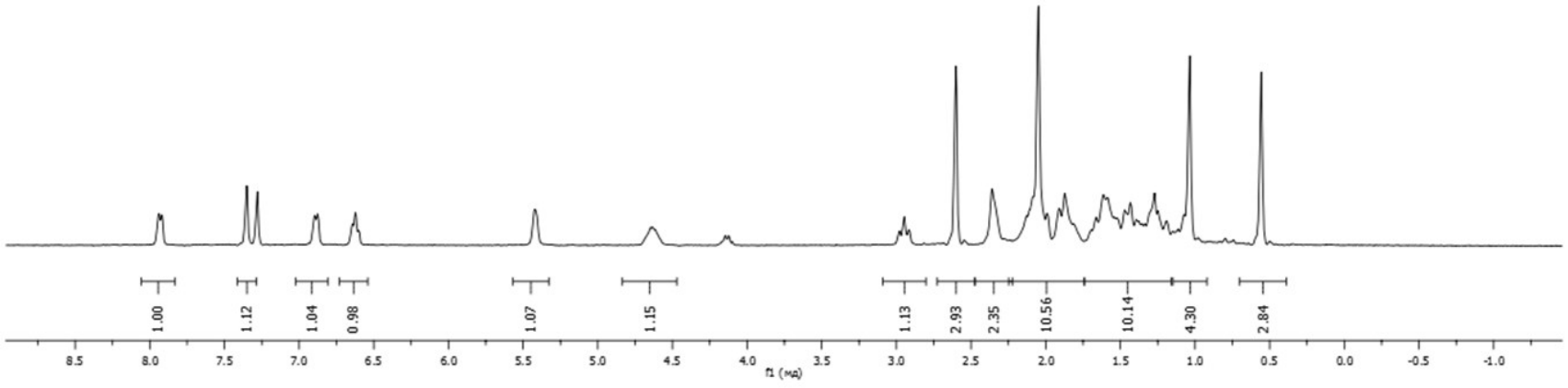
H
H
H
H
AcO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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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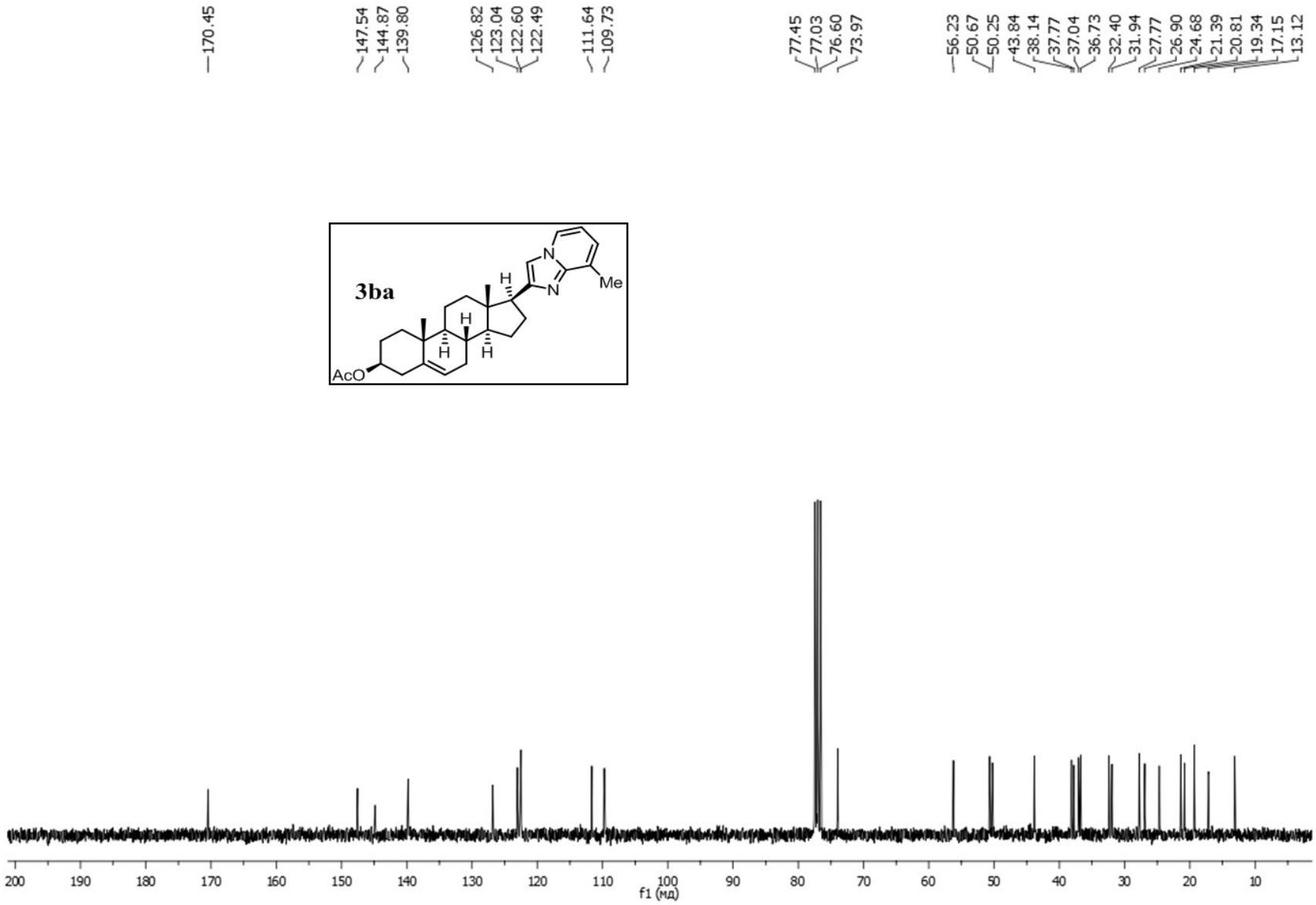
f1 (ppm)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76.60
73.97
56.23
50.67
50.25
43.84
38.14
37.77
37.04
36.73
32.40
31.94
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21.39
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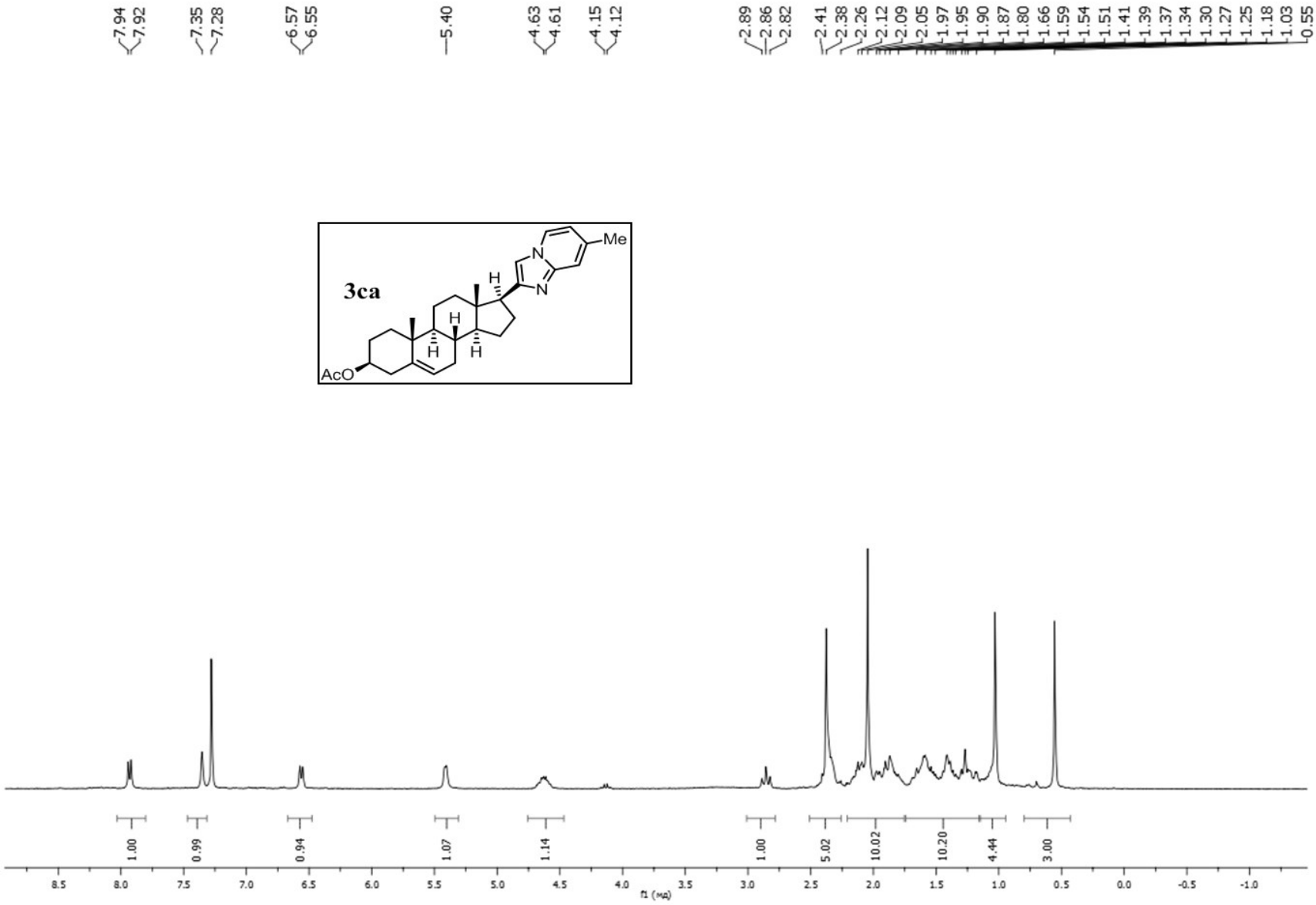
19.34
17.15
13.12
3ba
Me
AcO
f1 (мд)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1.59
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1.41
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1.37
1.34
1.30
1.27
1.25
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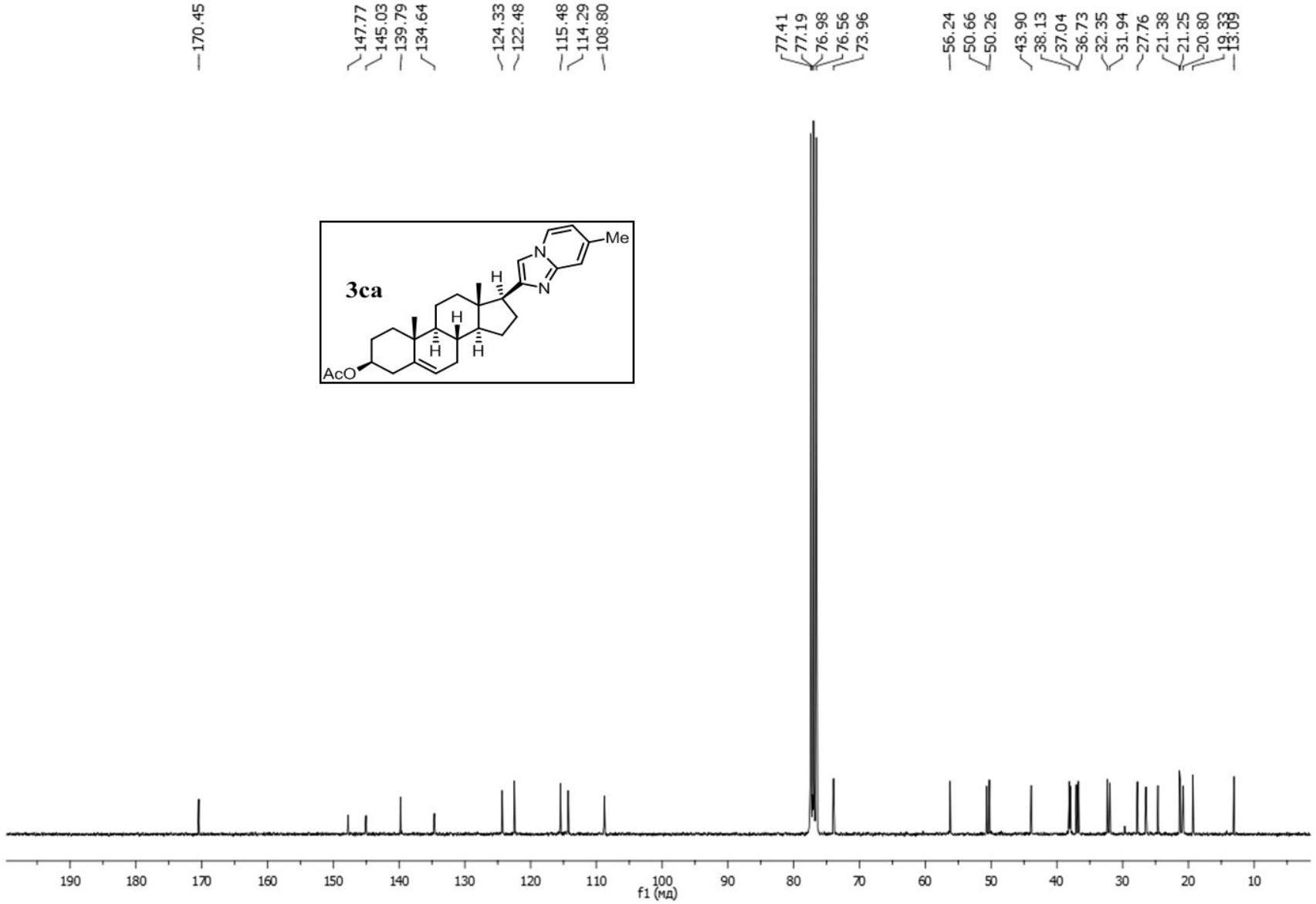
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73.96
56.24
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50.26
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38.13
37.04
36.73
32.35
31.94
27.76
21.38
21.25
20.80
19.33
13.09
3ca
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N
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H
H
H
H
AcO
190
180
170
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150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (мд)


7.80
7.45
7.42
7.24
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6.89
5.37
5.36
4.61
4.59
4.57
2.85
2.81
2.78
2.32
2.30
2.25
2.12
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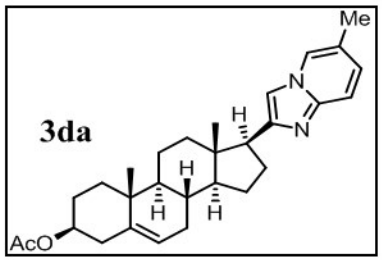
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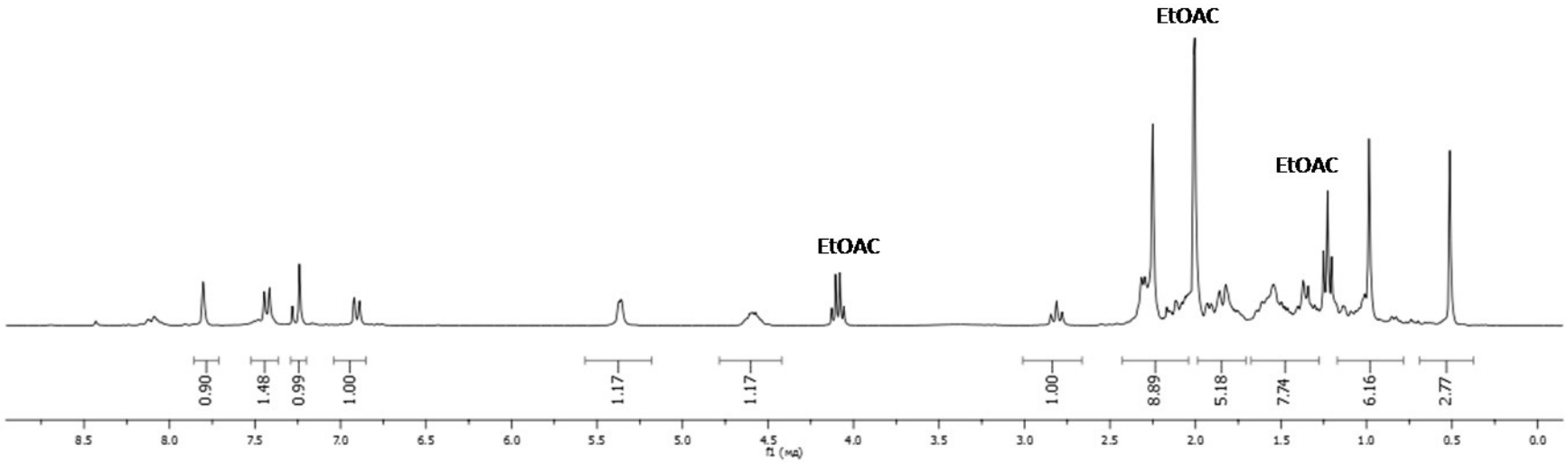
H
H
H
H
AcO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EtOAC
EtOAC
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2.77
8.5
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6.0
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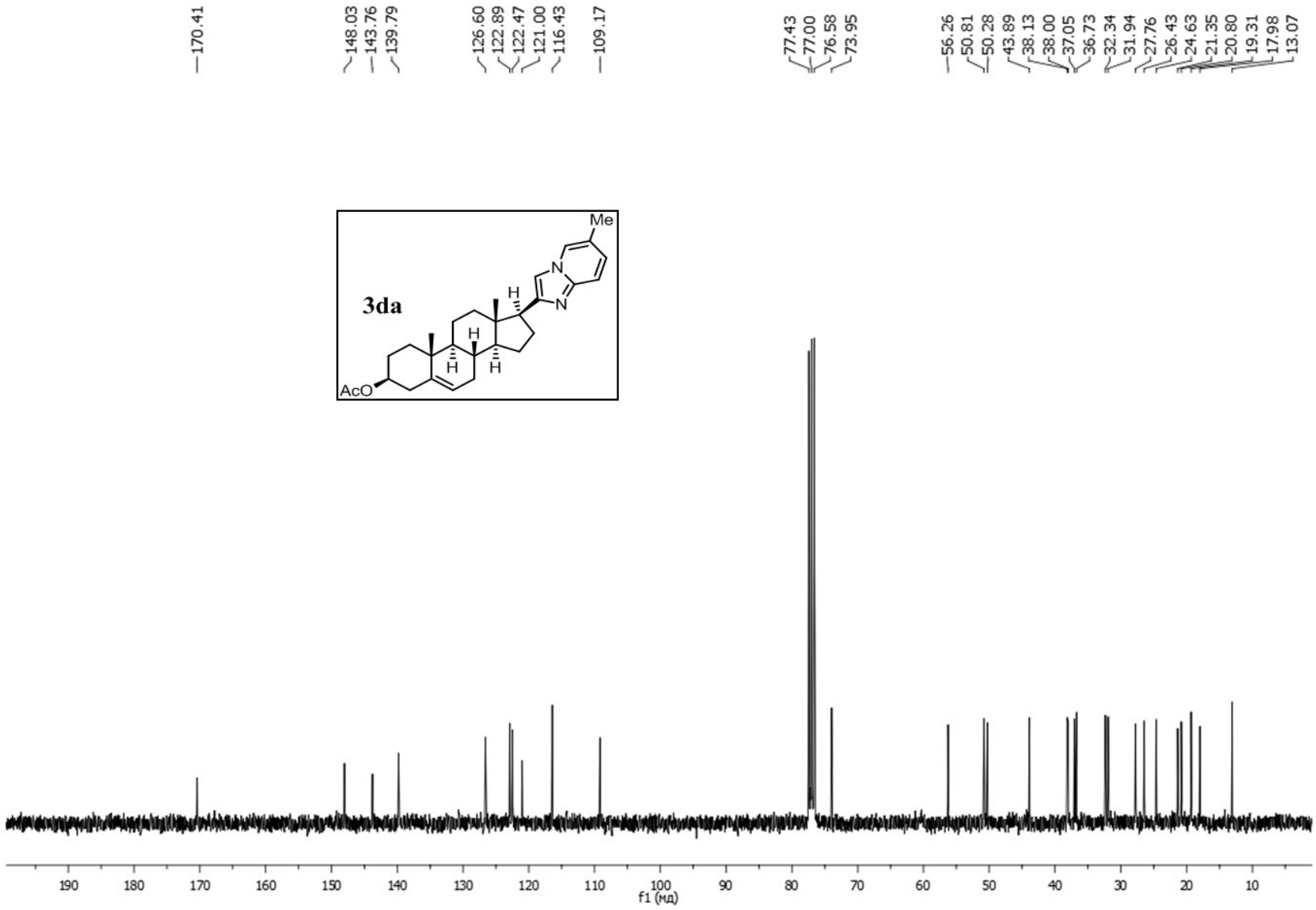
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50.28
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38.00
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36.73
32.34
31.94
27.76
26.43
24.63
21.35
20.80
19.31
17.98
13.07
3da
Me
AcO
H
H
H
H
N
N
190
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110
100
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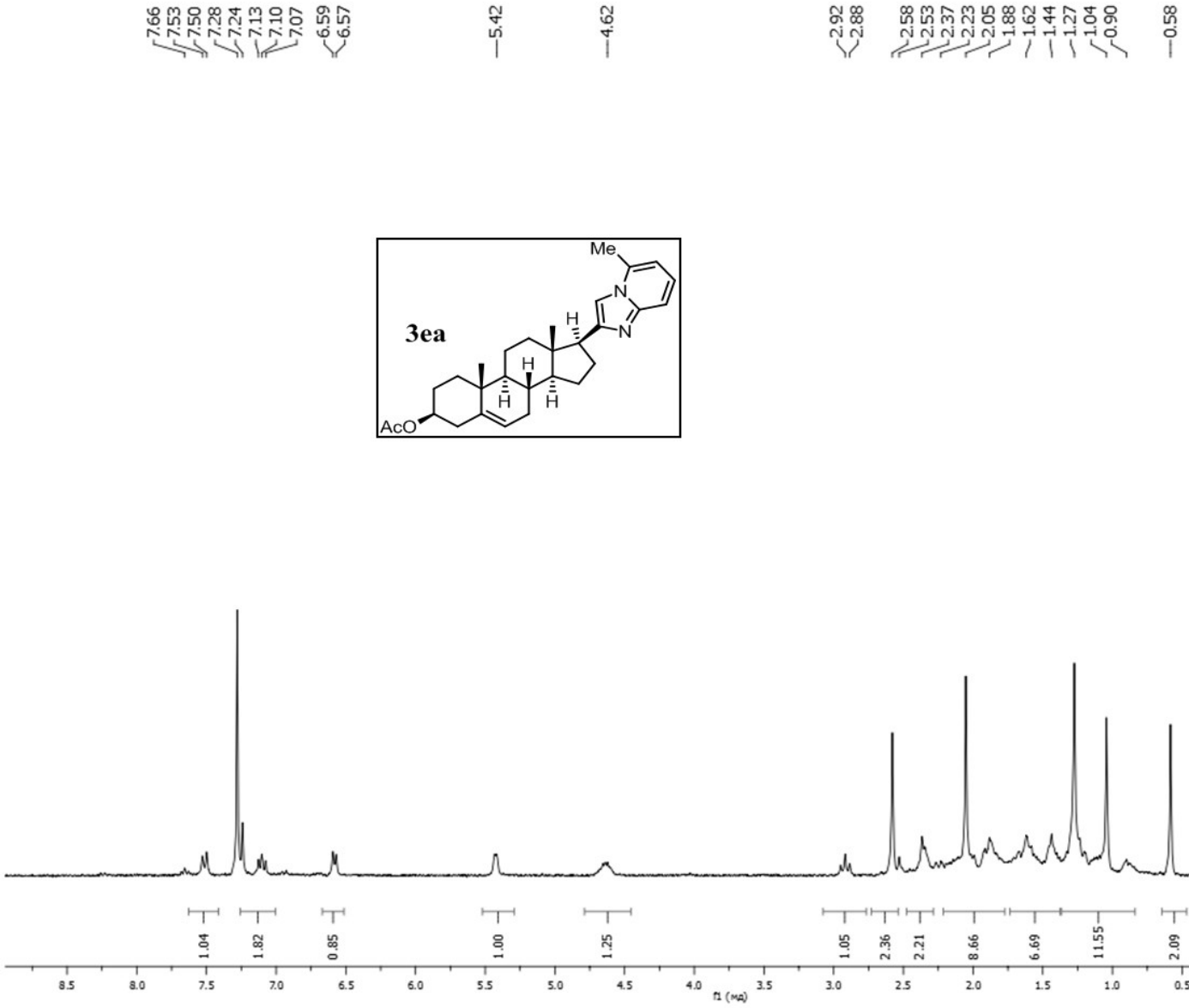
20
10
f1 (мд)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7.07
6.59
6.57
5.42
4.62
2.92
2.88
2.58
2.53
2.37
2.23
2.05
1.88
1.62
1.44
1.27
1.04
0.90
0.58
Me
N
N
H
H
H
H
3ea
AcO
1.04
1.82
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2.36
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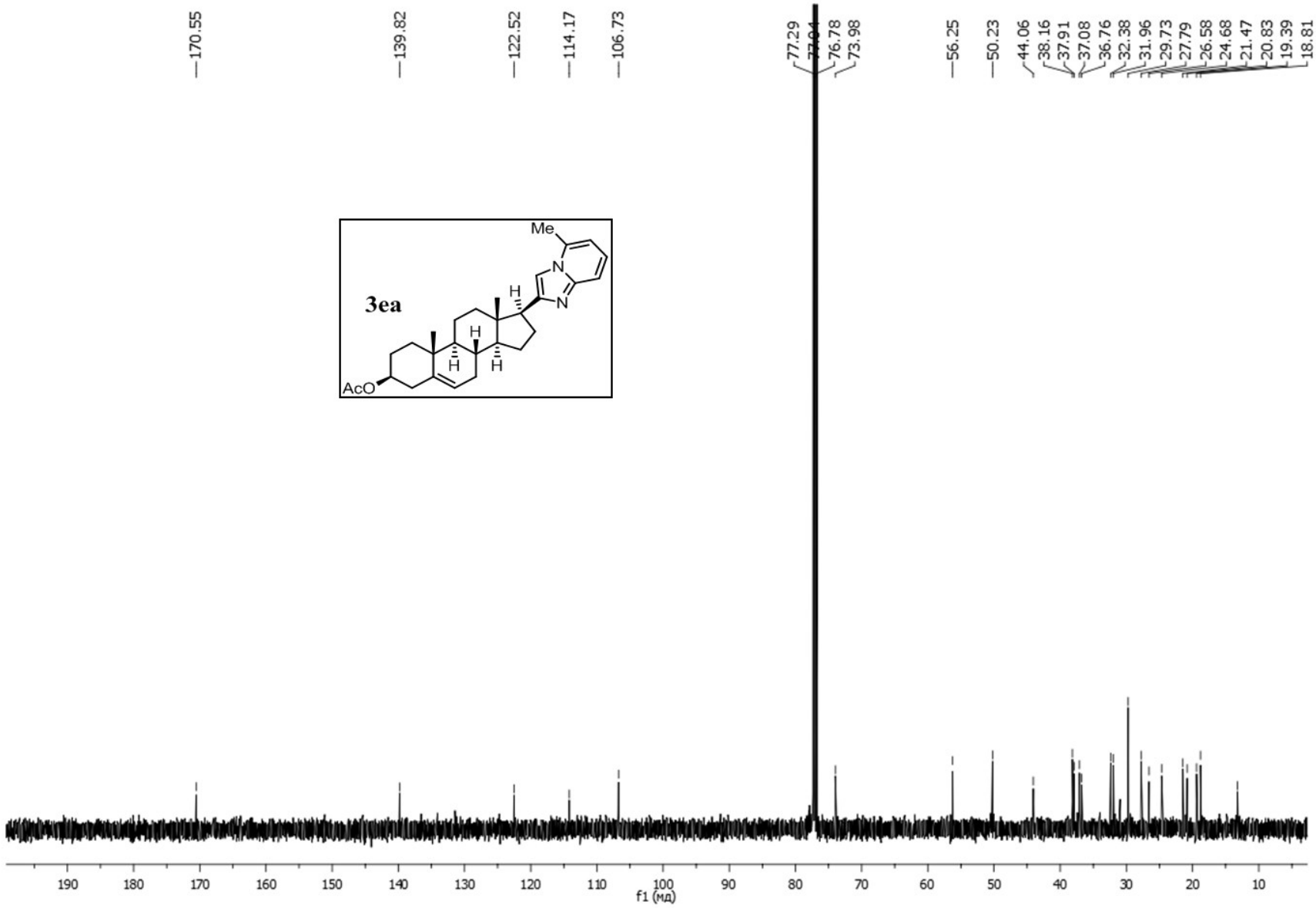
6.69
11.55
2.09
f1 (ppm)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73.98
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50.23
44.06
38.16
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36.76
32.38
31.96
29.73
27.79
26.58
24.68
21.47
20.83
19.39
18.81
3ea
Me
N
N
H
H
H
H
AcO
190
180
170
160
150
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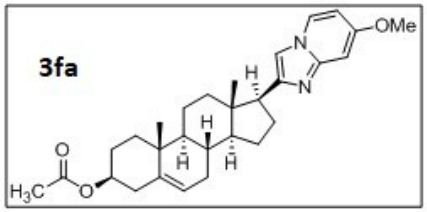
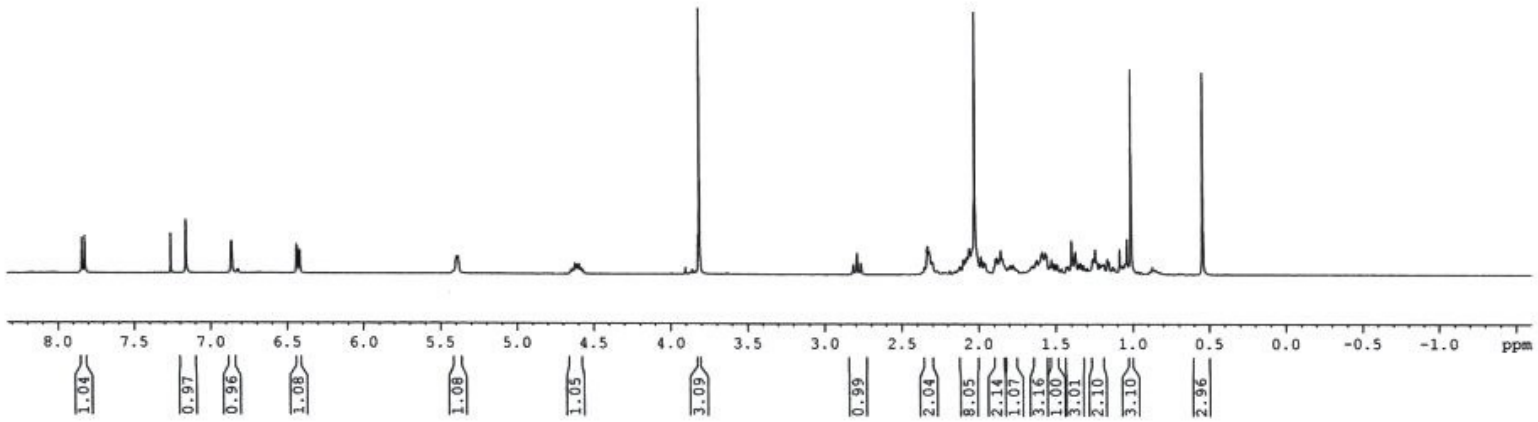
20
10
f1 (мд)

1H of VBSS-148-27





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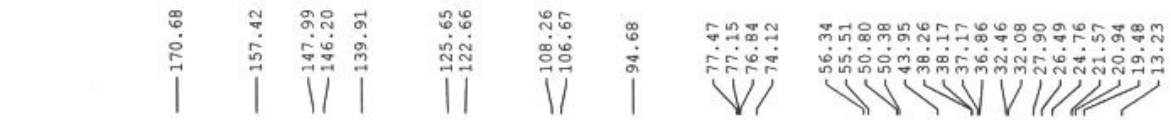

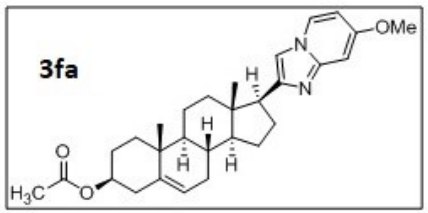

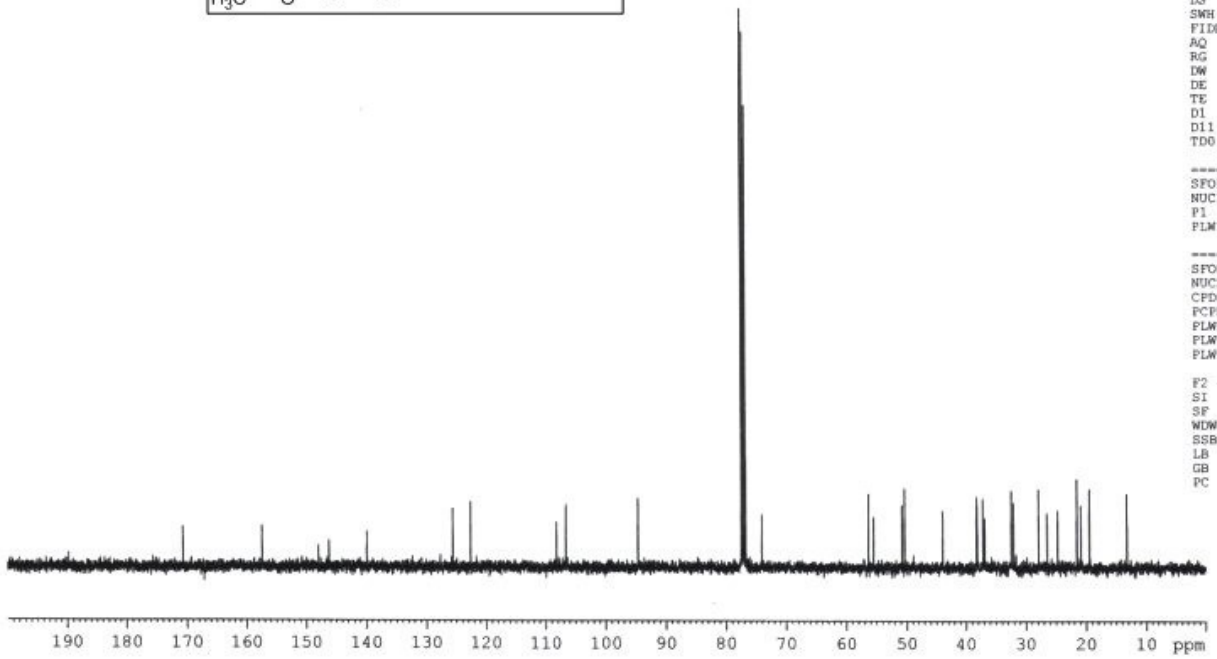


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DE                   6.50 usec
TE                  299.2 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                      1

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P1                    8.90 usec
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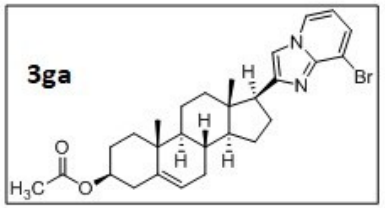
1H of VBSS 148-



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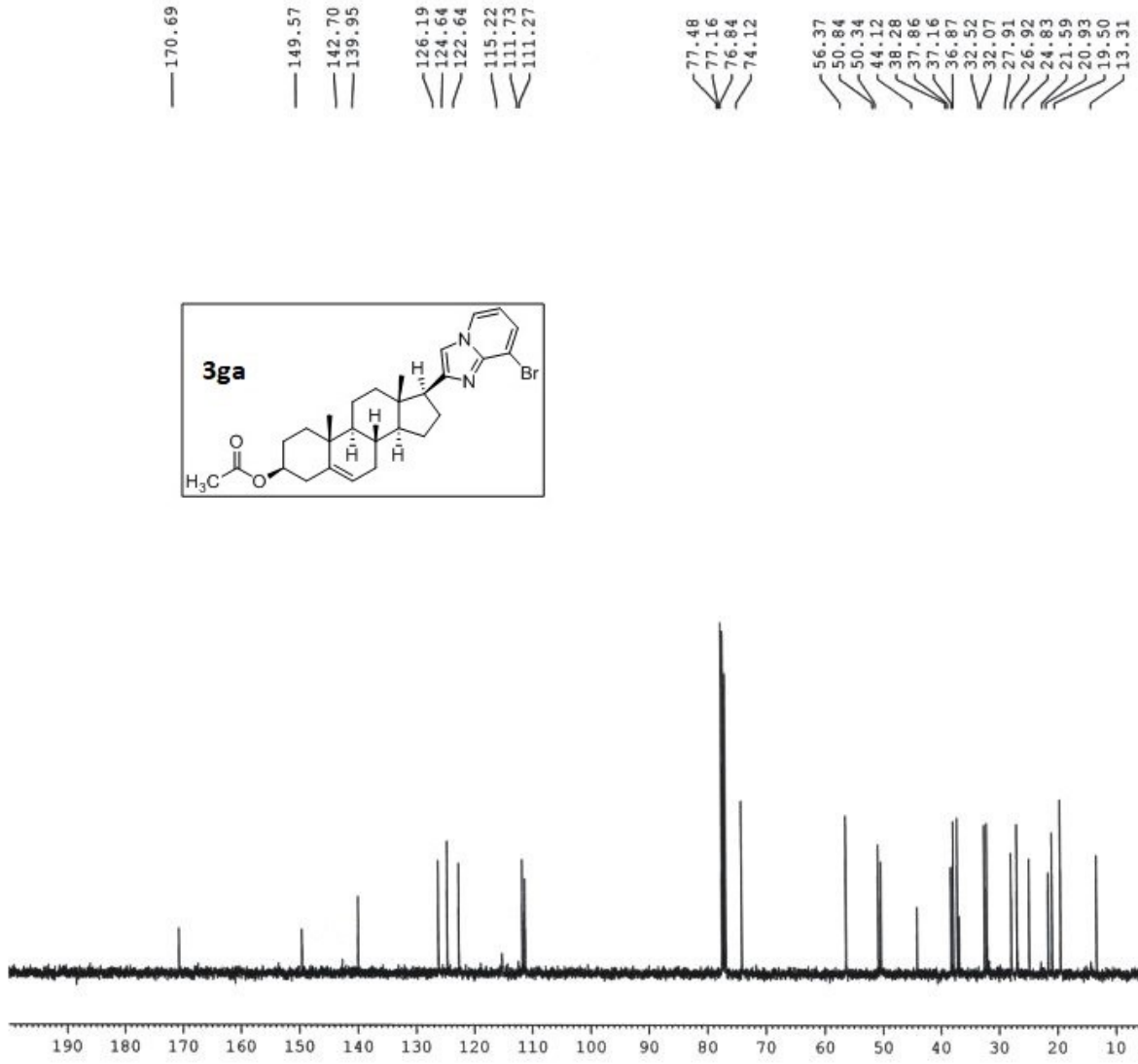

BRUKER

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F2 - Processing parameters
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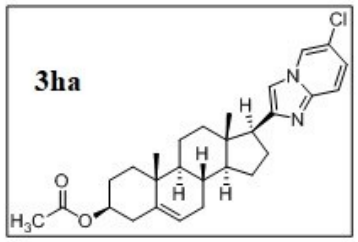
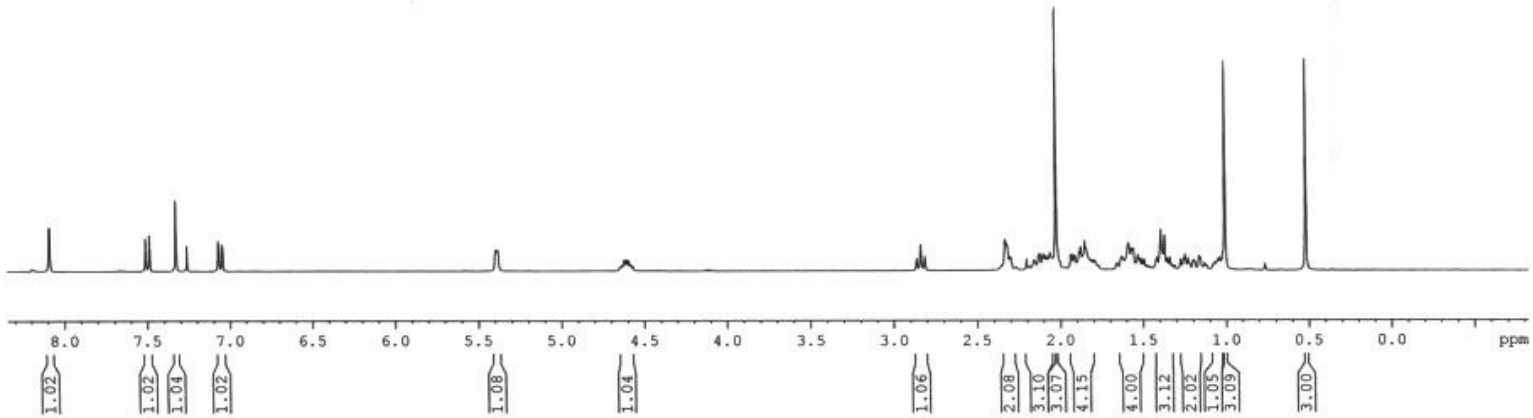
1H of VBSS-148-Cl-7





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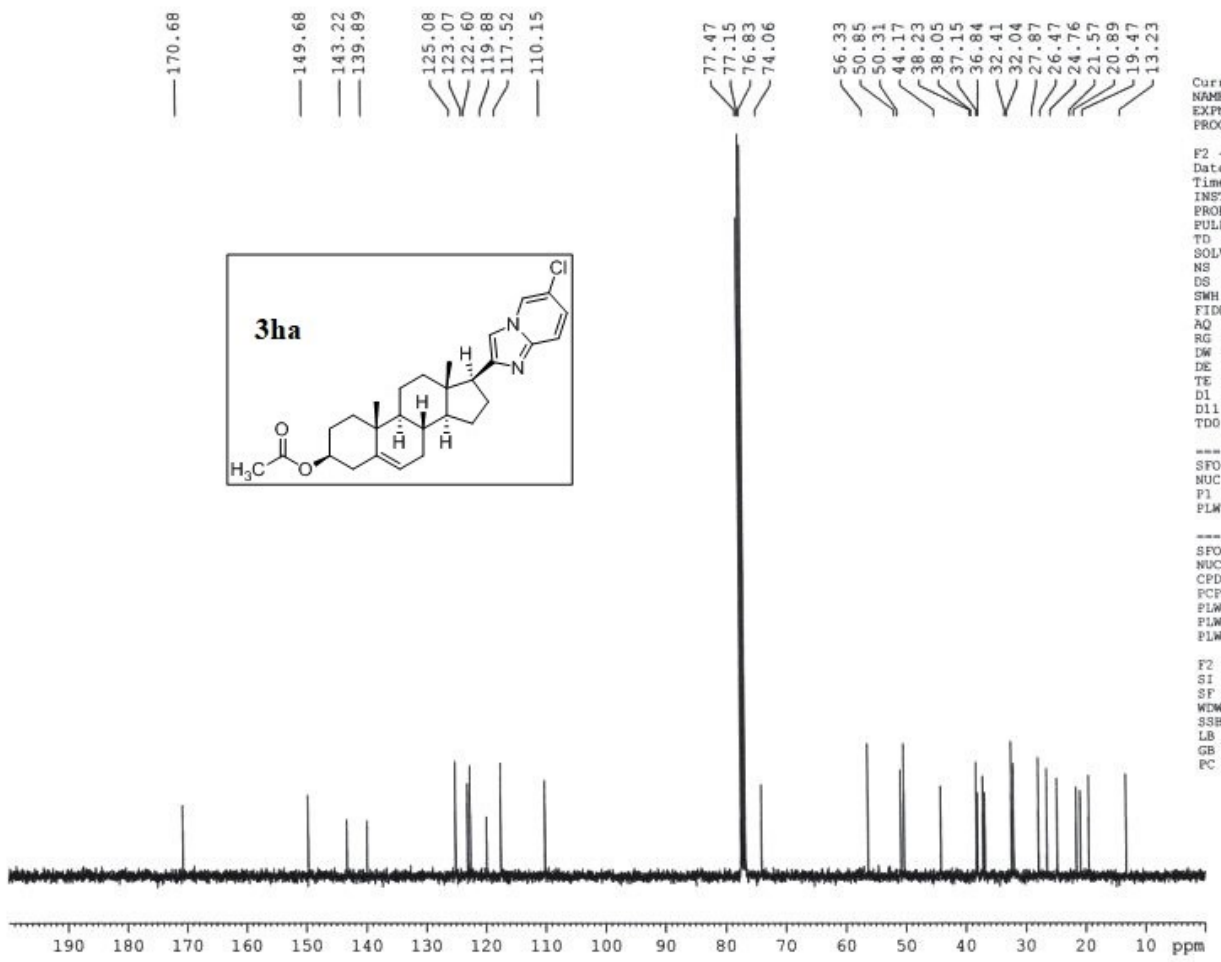

BRUKER

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PROCNO 1

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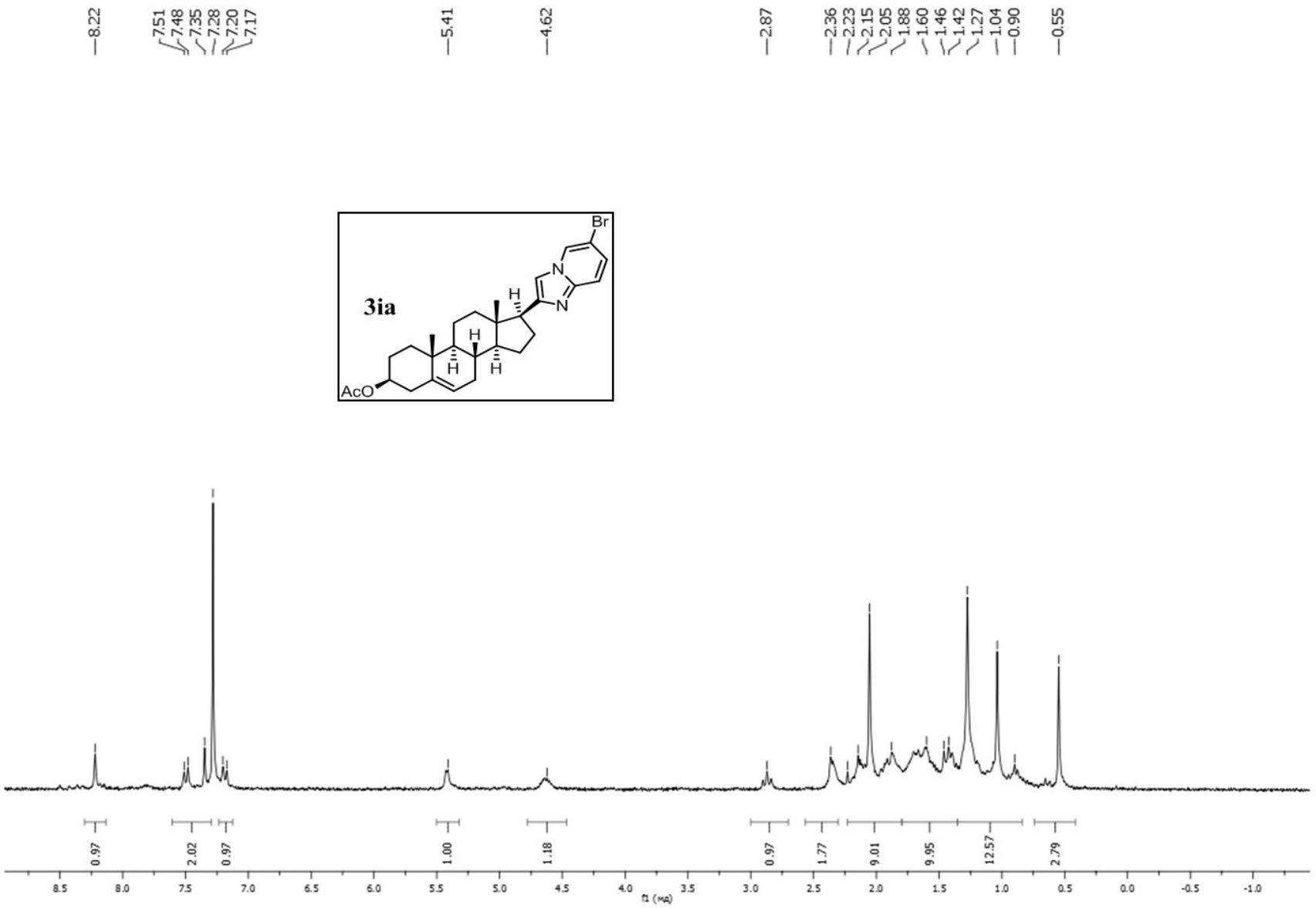
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2.05
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1.60
1.46
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3ia
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AcO
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H
H
N
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0.97
2.02
0.97
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0.97
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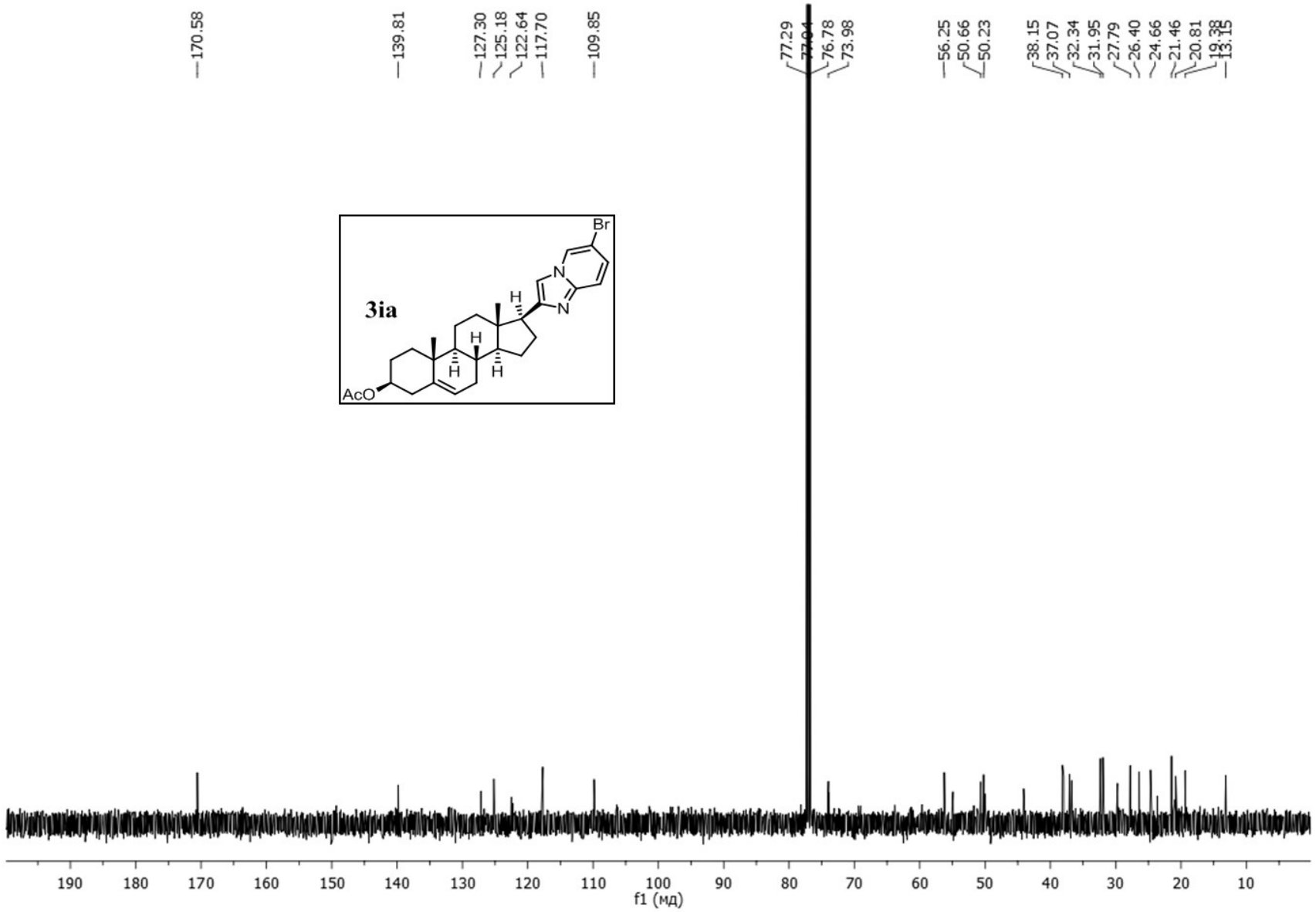
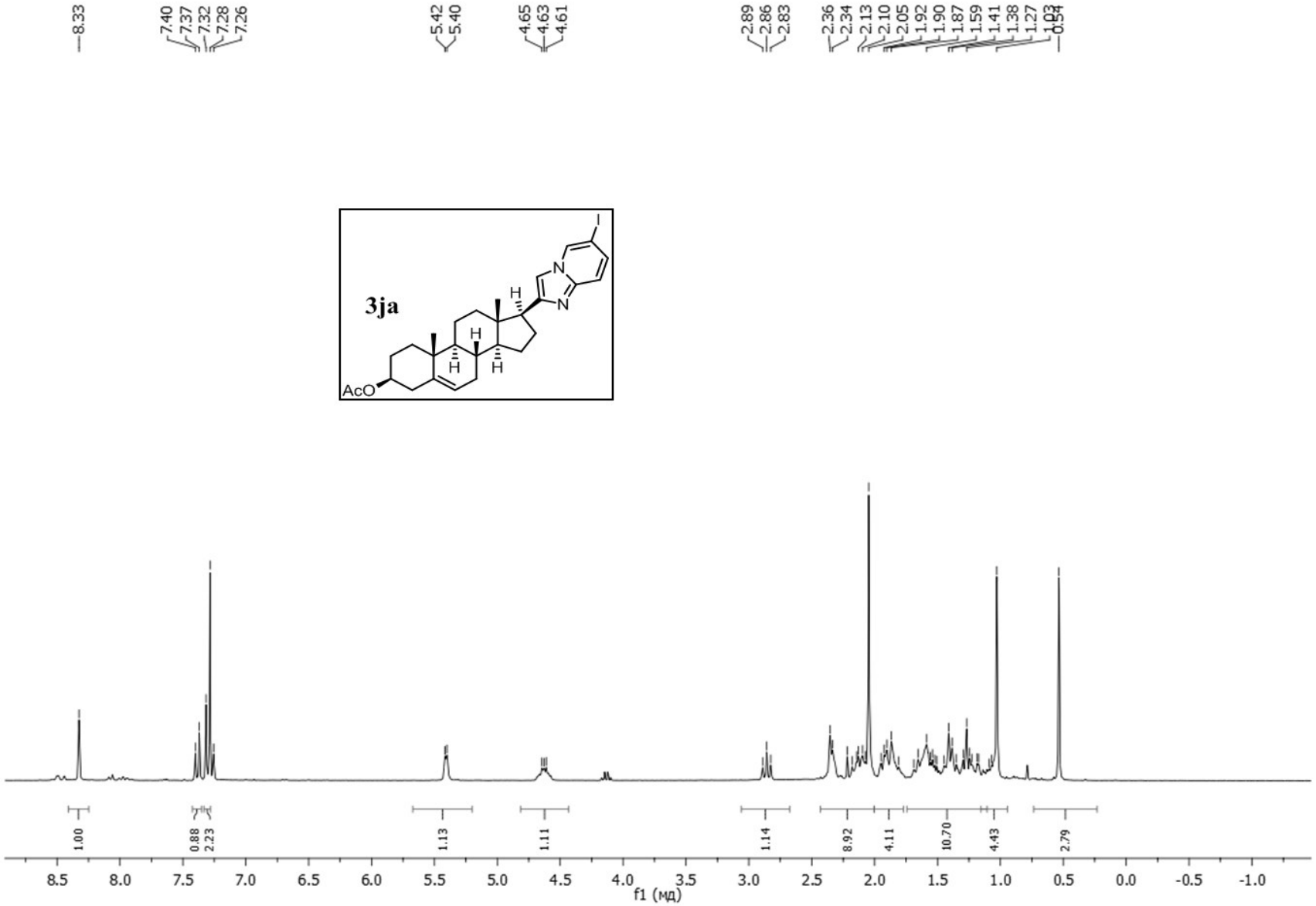
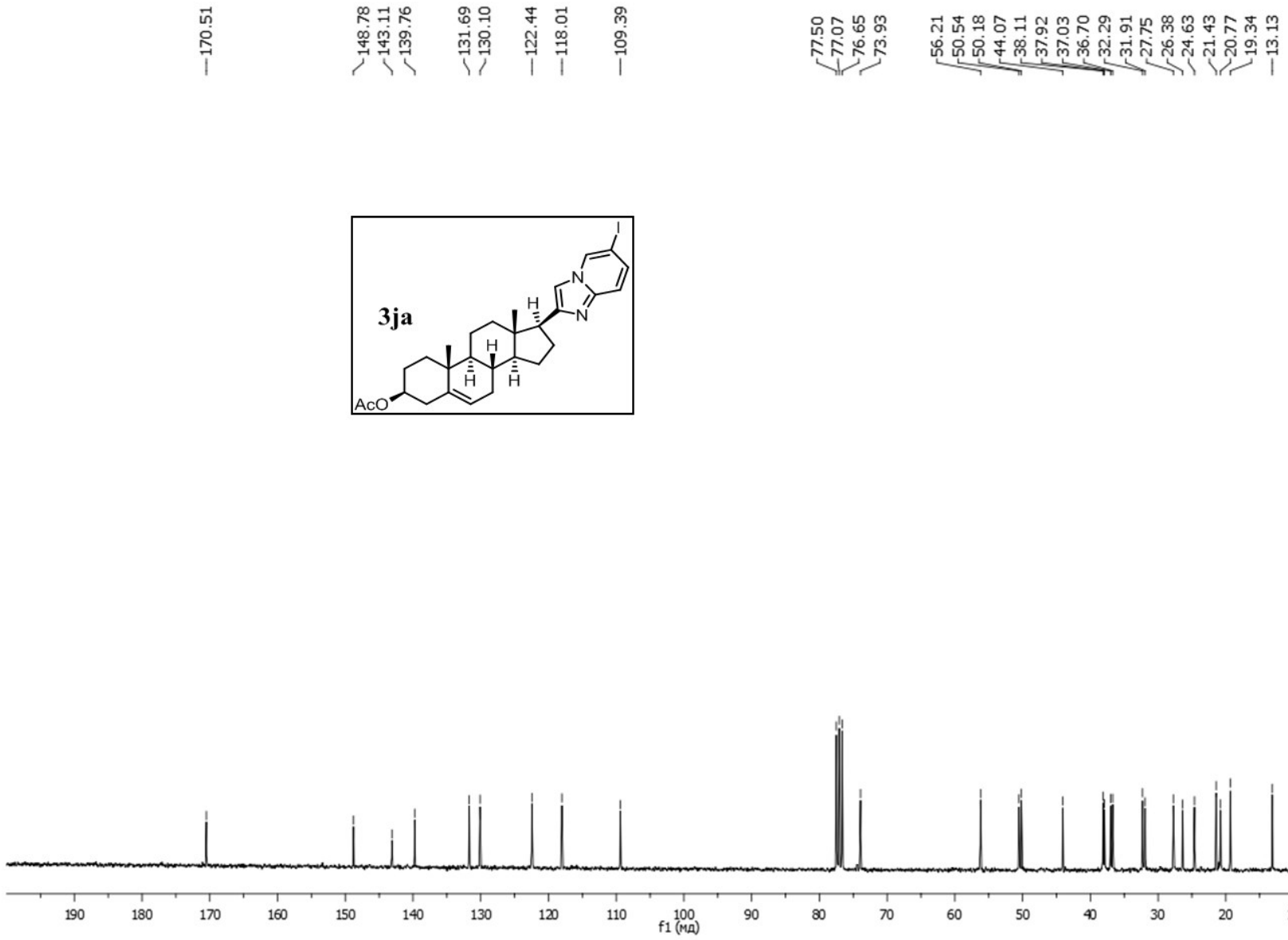
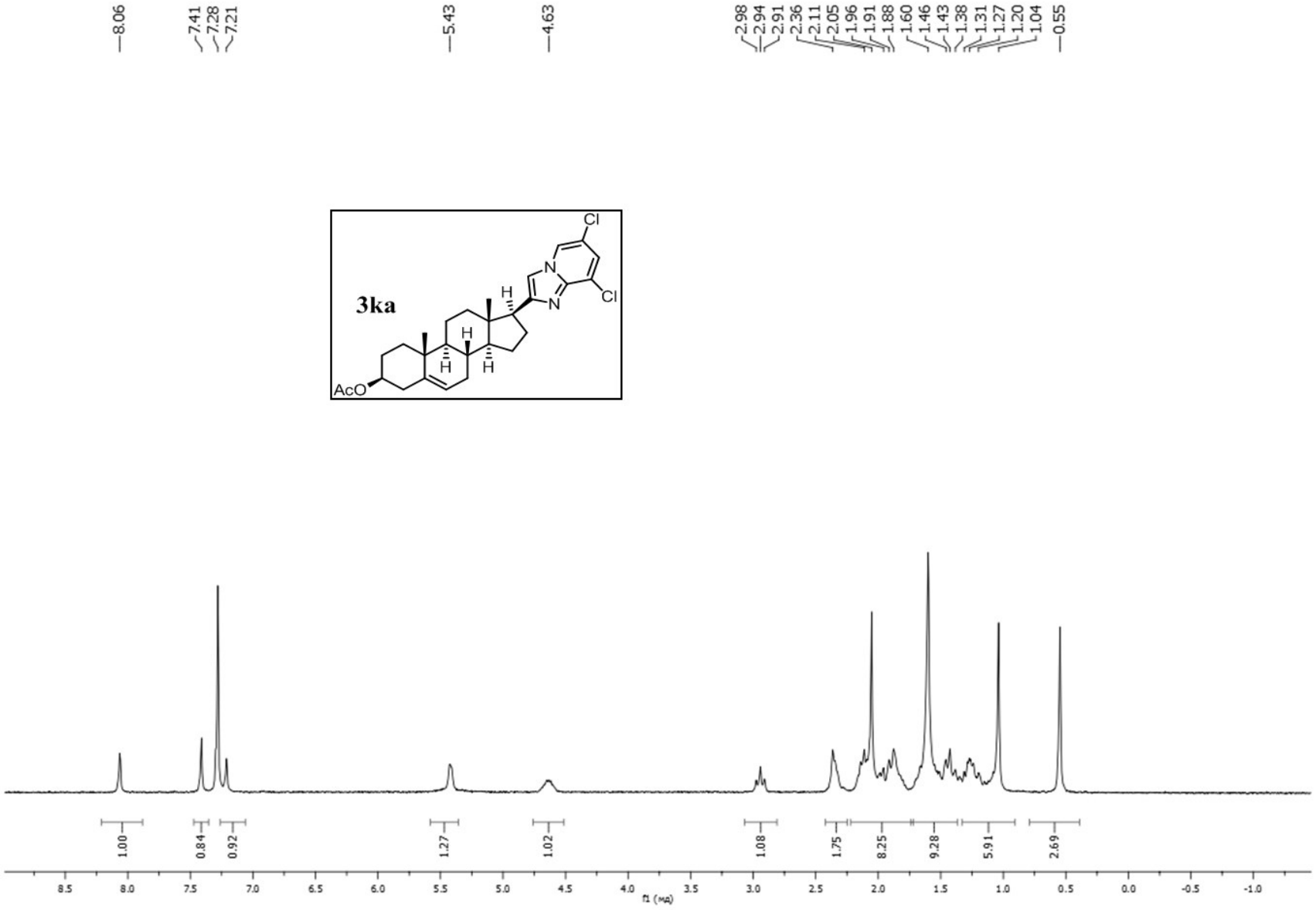
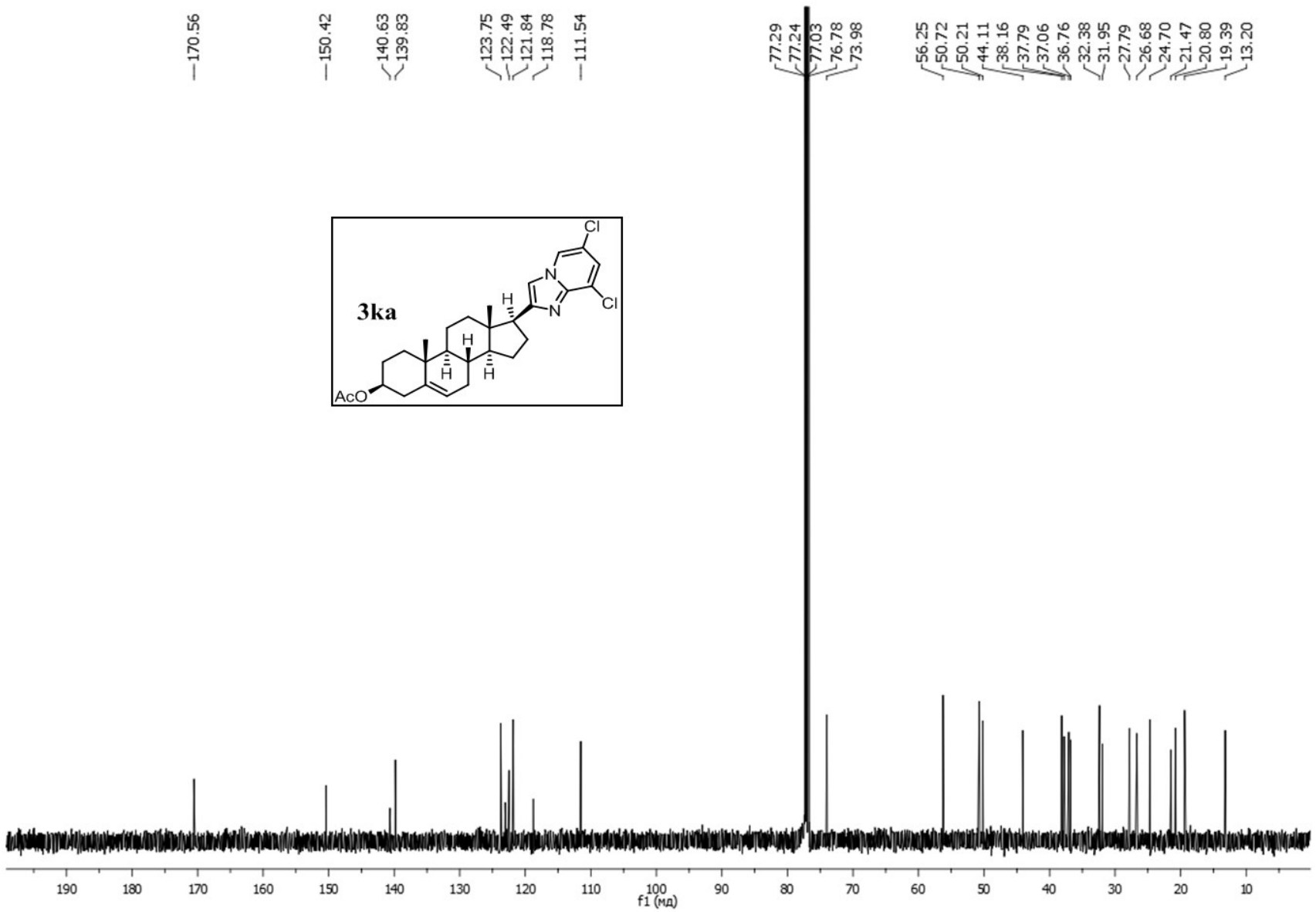
12.57
2.79
f1 (ppm)

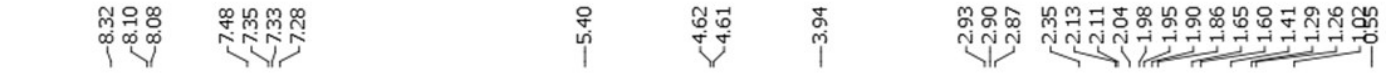

170.58
139.81
127.30
125.18
122.64
117.70
109.85
77.29
76.78
73.98
56.25
50.66
50.23
38.15
37.07
32.34
31.95
27.79
26.40
24.66
21.46
20.81
19.38
13.15
3ia
Br
AcO
H
H
H
H
N
N
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (мд)

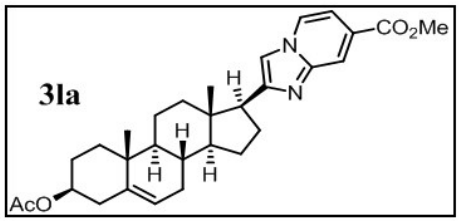

8.33
7.40
7.37
7.32
7.28
7.26
5.42
5.40
4.65
4.63
4.61
2.89
2.86
2.83
2.36
2.34
2.13
2.10
2.05
1.92
1.90
1.87
1.59
1.41
1.38
1.27
0.84
3ja
AcO
I
N
N
H
H
H
H
1.00
0.88
2.23
1.13
1.11
1.14
8.92
4.11
10.70
4.43
2.79
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (мд)

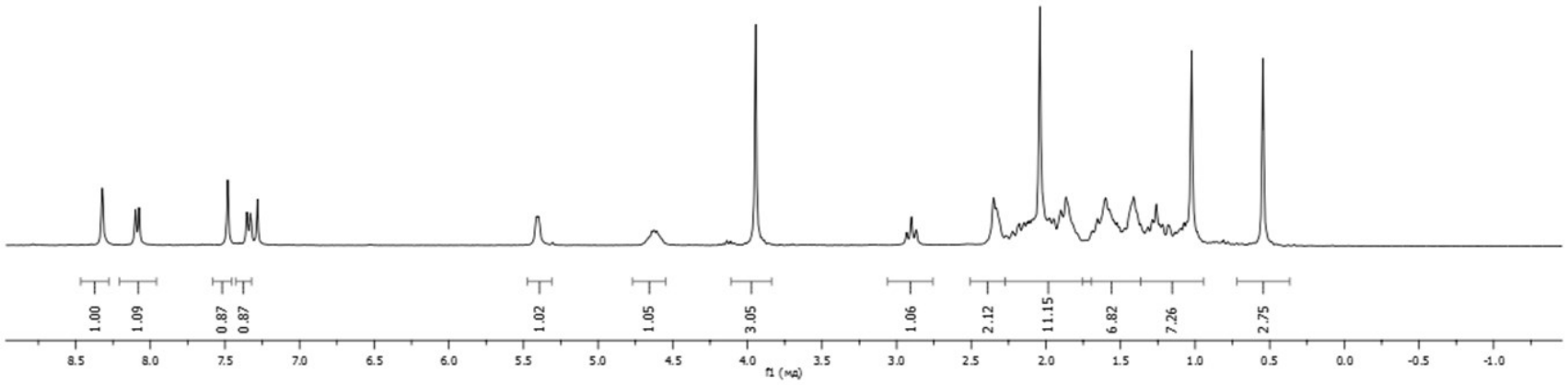

170.51
148.78
143.11
139.76
131.69
130.10
122.44
118.01
109.39
77.50
77.07
76.65
73.93
56.21
50.54
50.18
44.07
38.11
37.92
37.03
36.70
32.29
31.91
27.75
26.38
24.63
21.43
20.77
19.34
13.13
3ja
AcO
I
N
N
H
H
H
H
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (мд)

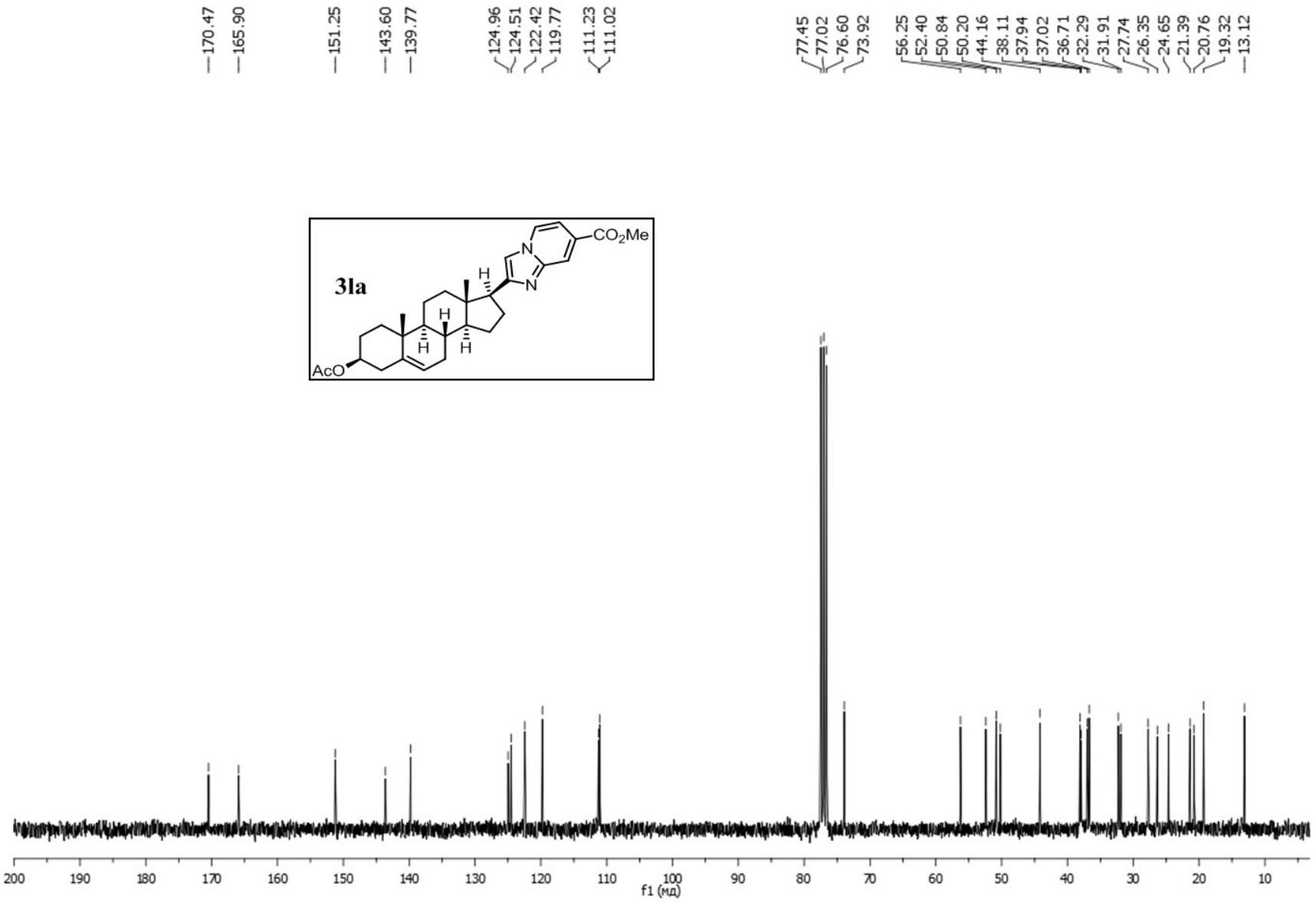

8.06
7.41
7.28
7.21
5.43
4.63
2.98
2.94
2.91
2.36
2.11
2.05
1.96
1.91
1.88
1.60
1.46
1.43
1.38
1.31
1.27
1.20
1.04
0.55
3ka
Cl
Cl
N
N
H
H
H
H
AcO
1.00
0.84
0.92
1.27
1.02
1.08
1.75
8.25
9.28
5.91
2.69
f1 (ppm)


170.56
150.42
140.63
139.83
123.75
122.49
121.84
118.78
111.54
77.29
77.24
77.03
76.78
73.98
56.25
50.72
50.21
44.11
38.16
37.79
37.06
36.76
32.38
31.95
27.79
26.68
24.70
21.47
20.80
19.39
13.20
3ka
Cl
Cl
N
N
H
H
H
H
AcO
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (мд)

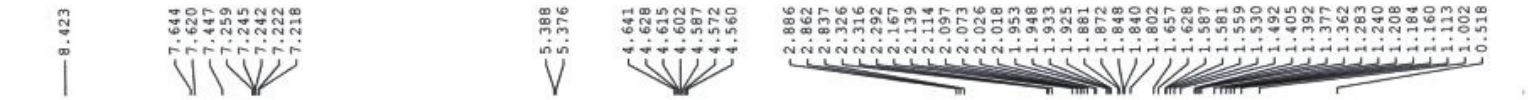

8.32
8.10
8.08
7.48
7.35
7.33
7.28
5.40
4.62
4.61
3.94
2.93
2.90
2.87
2.35
2.13
2.11
2.04
1.98
1.95
1.90
1.86
1.65
1.60
1.41
1.29
1.26
1.02
0.55

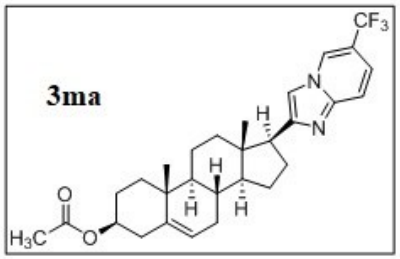

3la
CO2Me
AcO
N
N
H
H
H
H

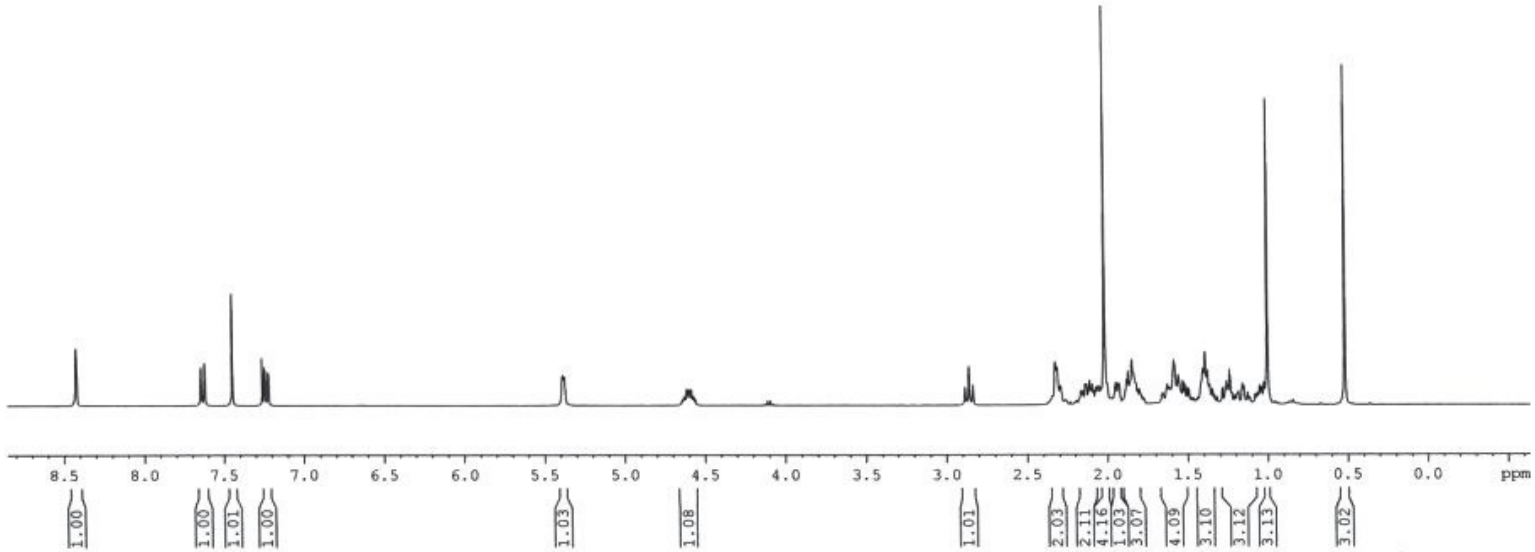

1.00
1.09
0.87
0.87
1.02
1.05
3.05
1.06
2.12
11.15
6.82
7.26
2.75
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


170.47
165.90
151.25
143.60
139.77
124.96
124.51
122.42
119.77
111.23
111.02
77.45
77.02
76.60
73.92
56.25
52.40
50.84
50.20
44.16
38.11
37.94
37.02
36.71
32.29
31.91
27.74
26.35
24.65
21.39
20.76
19.32
13.12
3la
CO2Me
AcO
H
H
H
H
N
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (мд)

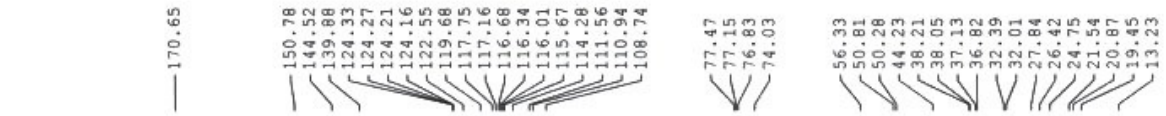
1H of VBSS-148-CF3

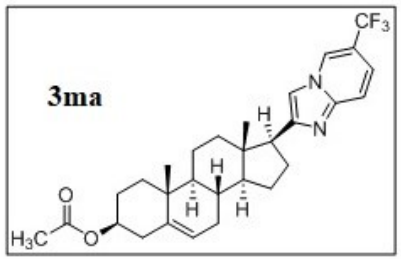


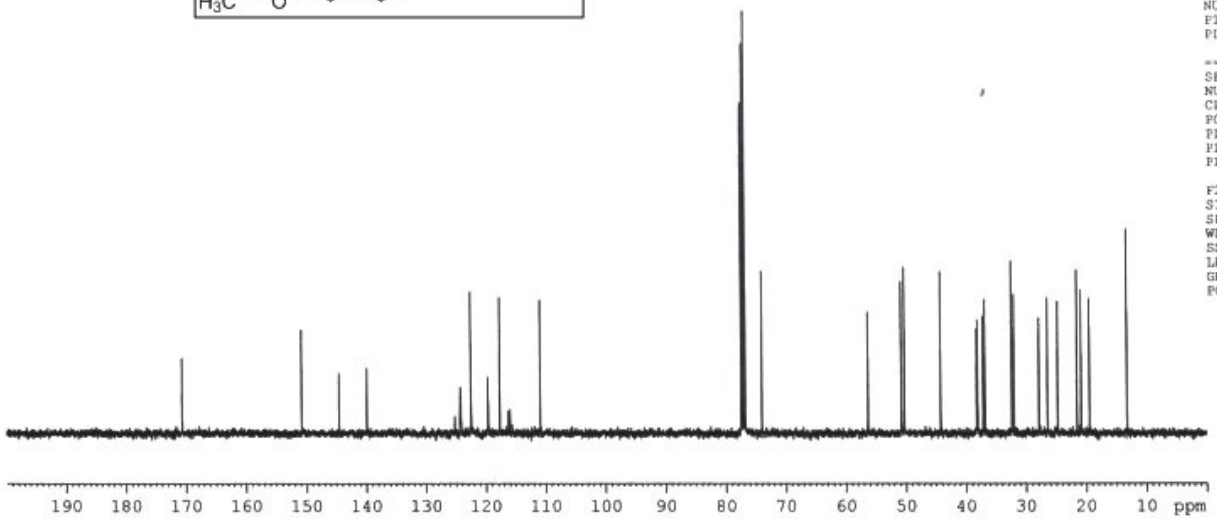




13C of vbSS-148-CF3







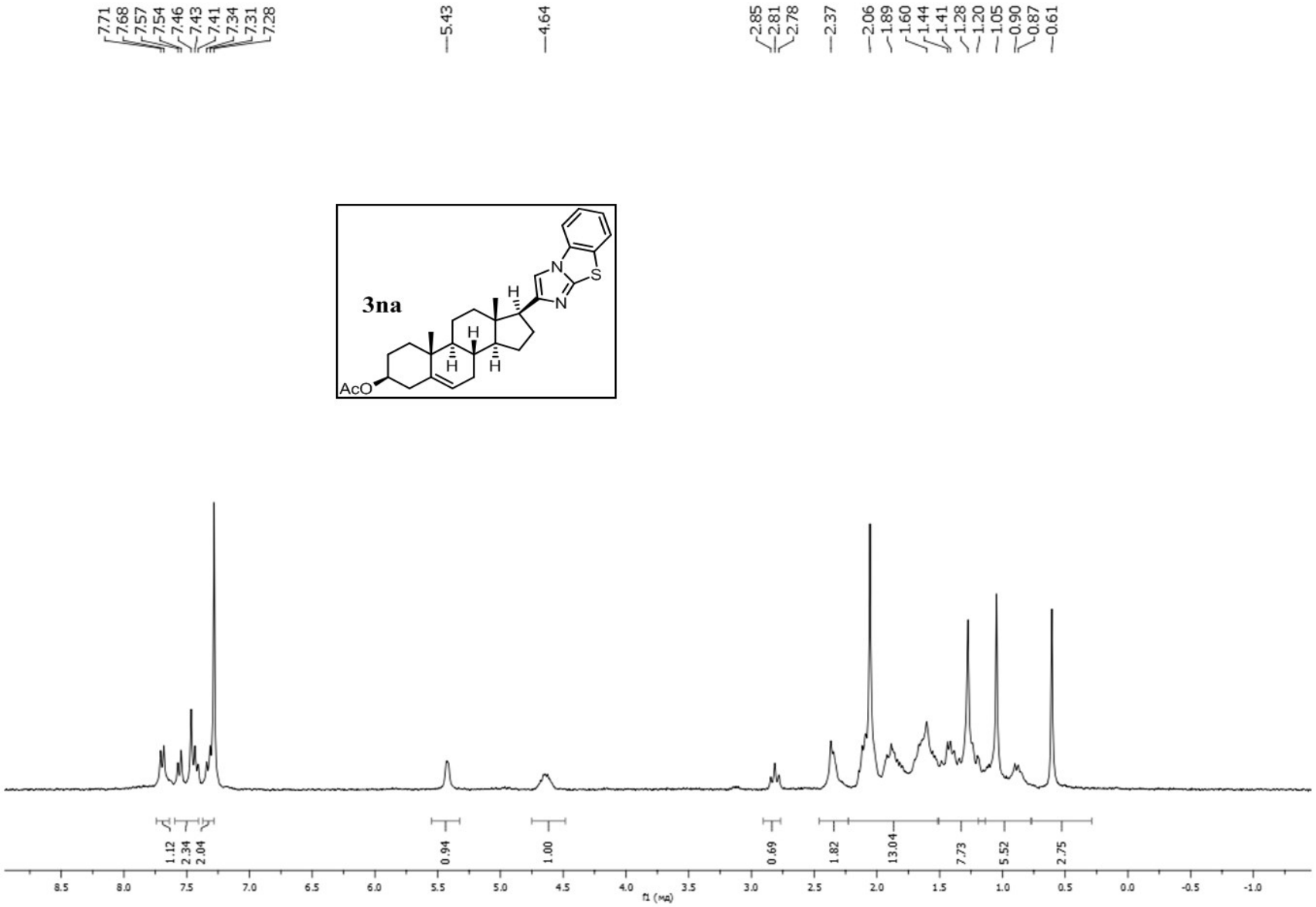
Current Data Parameters
NAME Dr. A HAJRA-2019-13C
EXPNO 81
PROCNO 1

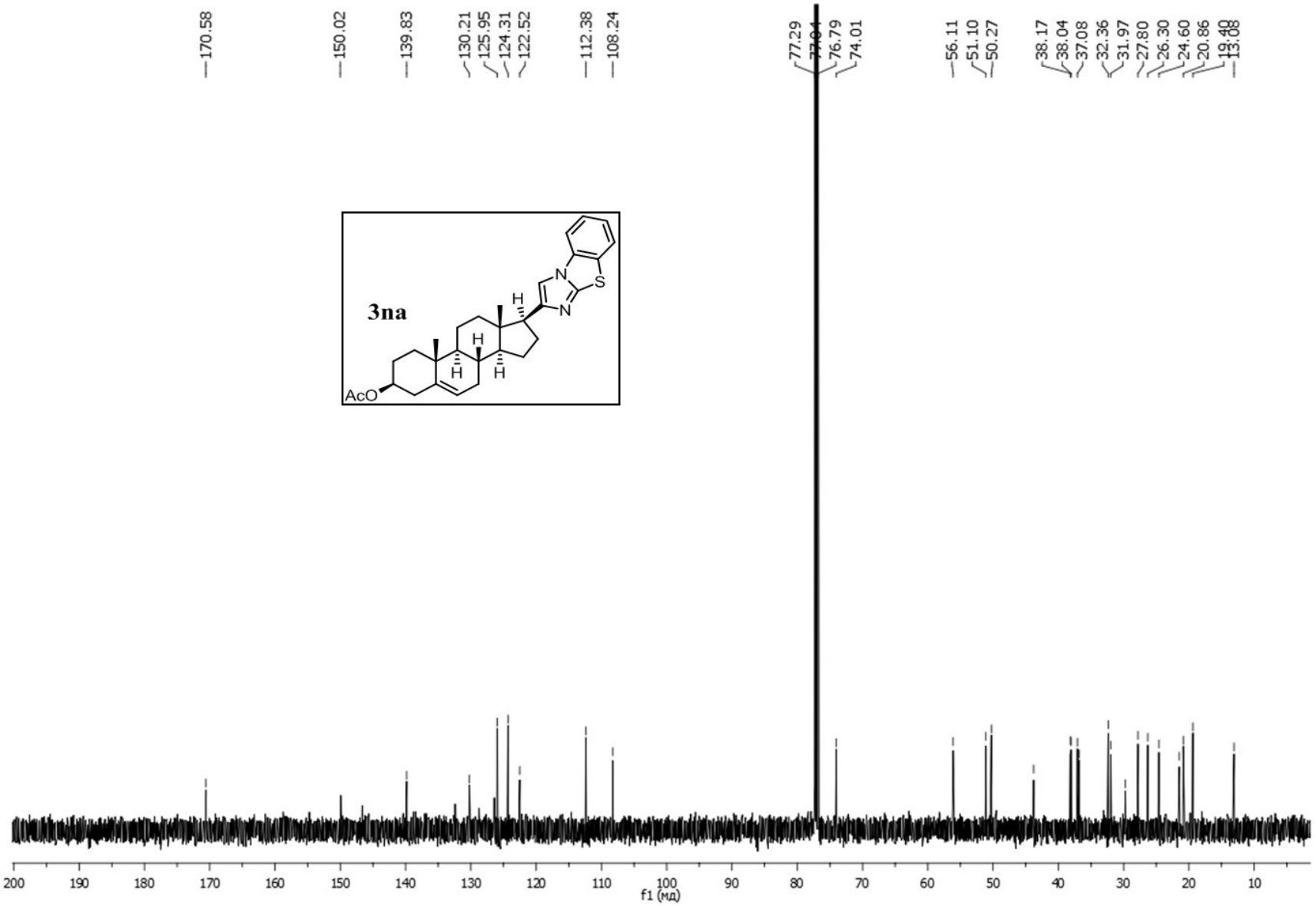
F2 - Acquisition Parameters
Date_ 20190219
Time 19.31
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 240
DS 2
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 0.6815744 sec
RG 47.25
DW 20.800 usec
DE 6.50 usec
TE 296.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

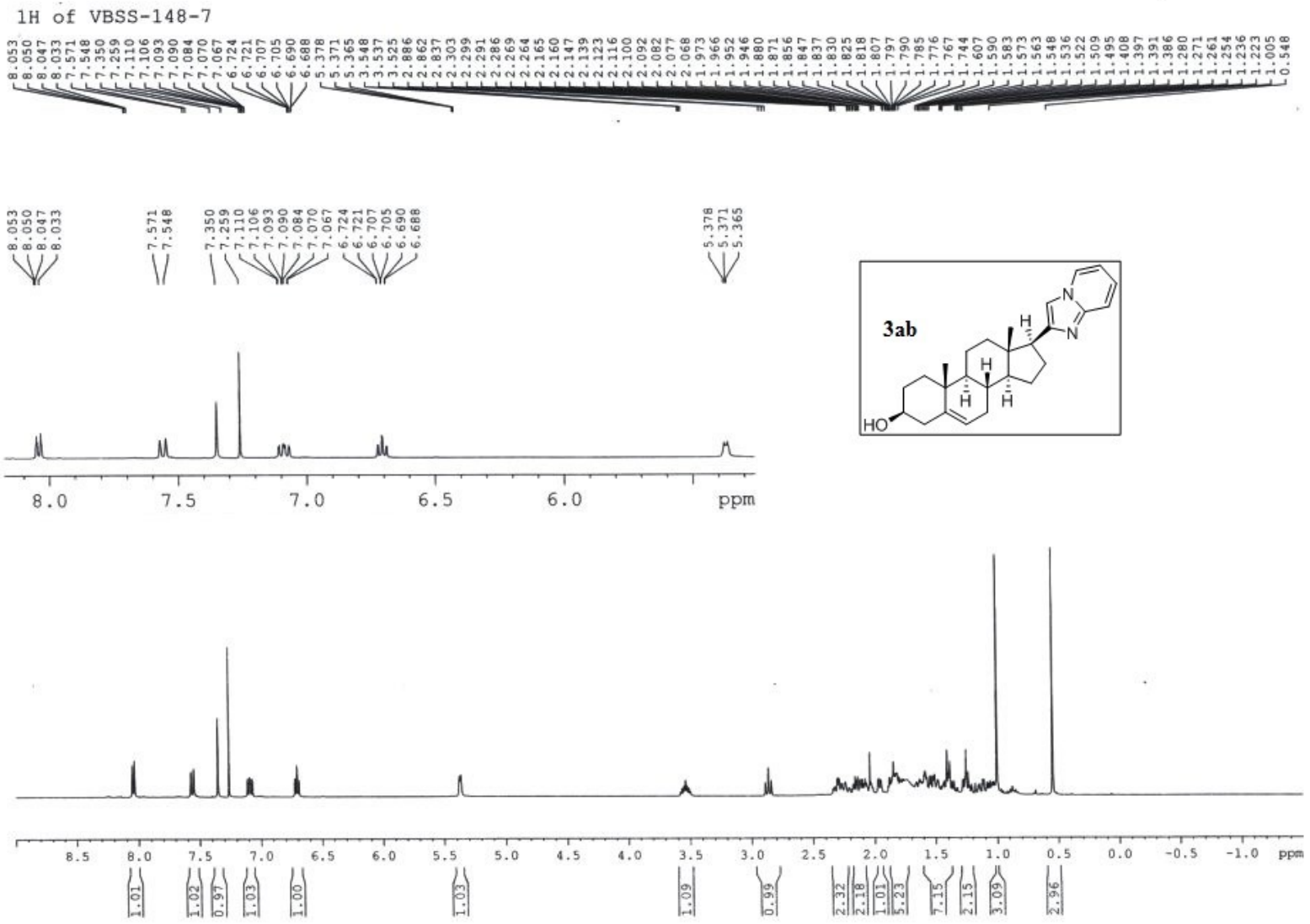
======== CHANNEL f1 ========
SFO1 100.6278588 MHz
NUC1 13C
P1 8.90 usec
PLW1 54.00000000 W

======== CHANNEL f2 ========
SFO2 400.1516006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.32231000 W
PLW13 0.16212000 W

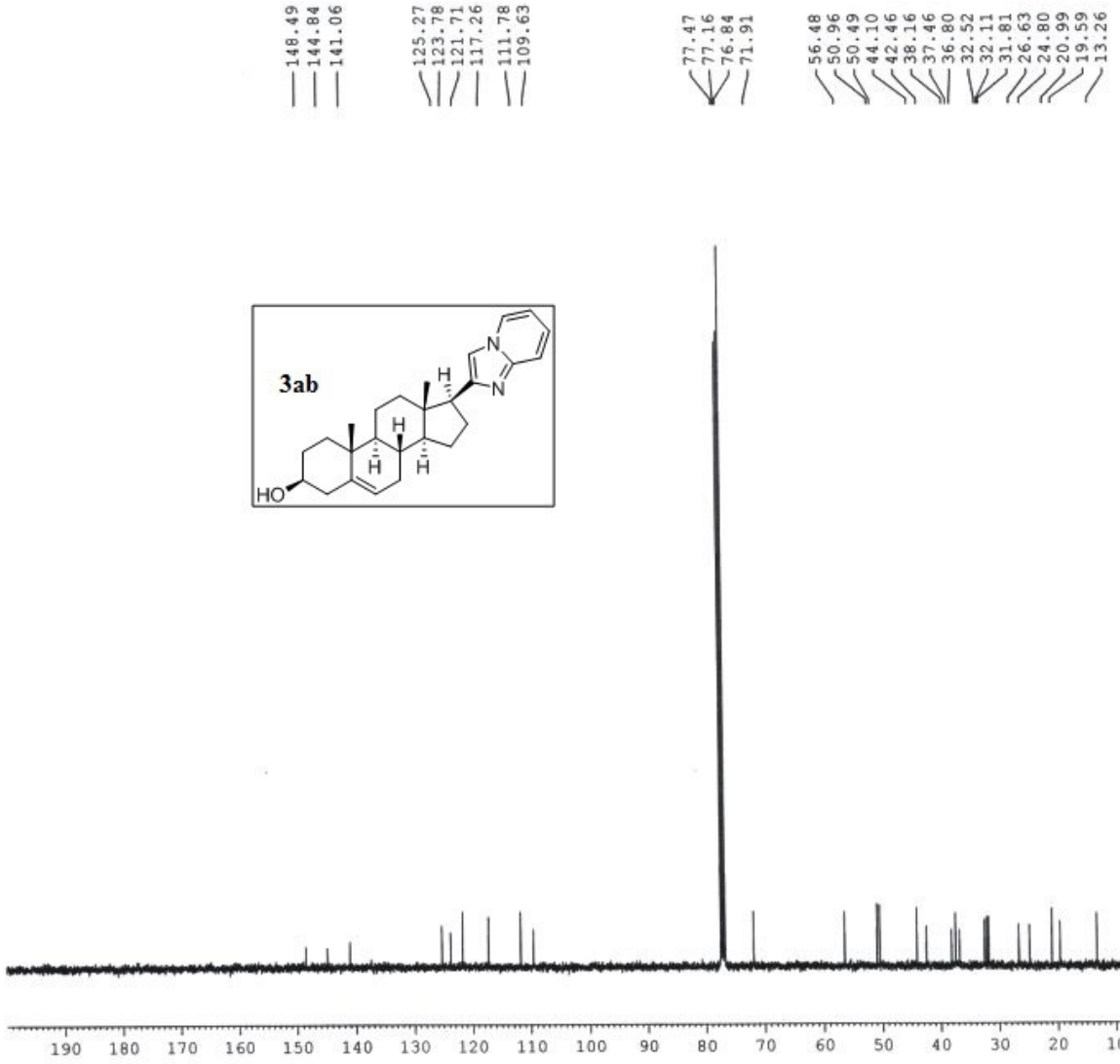
F2 - Processing parameters
SI 16384
SF 100.6177871 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


7.71
7.68
7.57
7.54
7.46
7.43
7.41
7.34
7.31
7.28
5.43
4.64
2.85
2.81
2.78
2.37
2.06
1.89
1.60
1.44
1.41
1.28
1.20
1.05
0.90
0.87
0.61
3na
AcO
N
S
H
1.12
2.34
2.04
0.94
1.00
0.69
1.82
13.04
7.73
5.52
2.75
f1 (ppm)


170.58
150.02
139.83
130.21
125.95
124.31
122.52
112.38
108.24
77.29
77.04
76.79
74.01
56.11
51.10
50.27
38.17
38.04
37.08
32.36
31.97
27.80
26.30
24.60
20.86
19.40
13.08
3na
AcO
f1 (мд)


1H of VBSS-148-7
3ab
HO
ppm

13C of VBSS-148-7



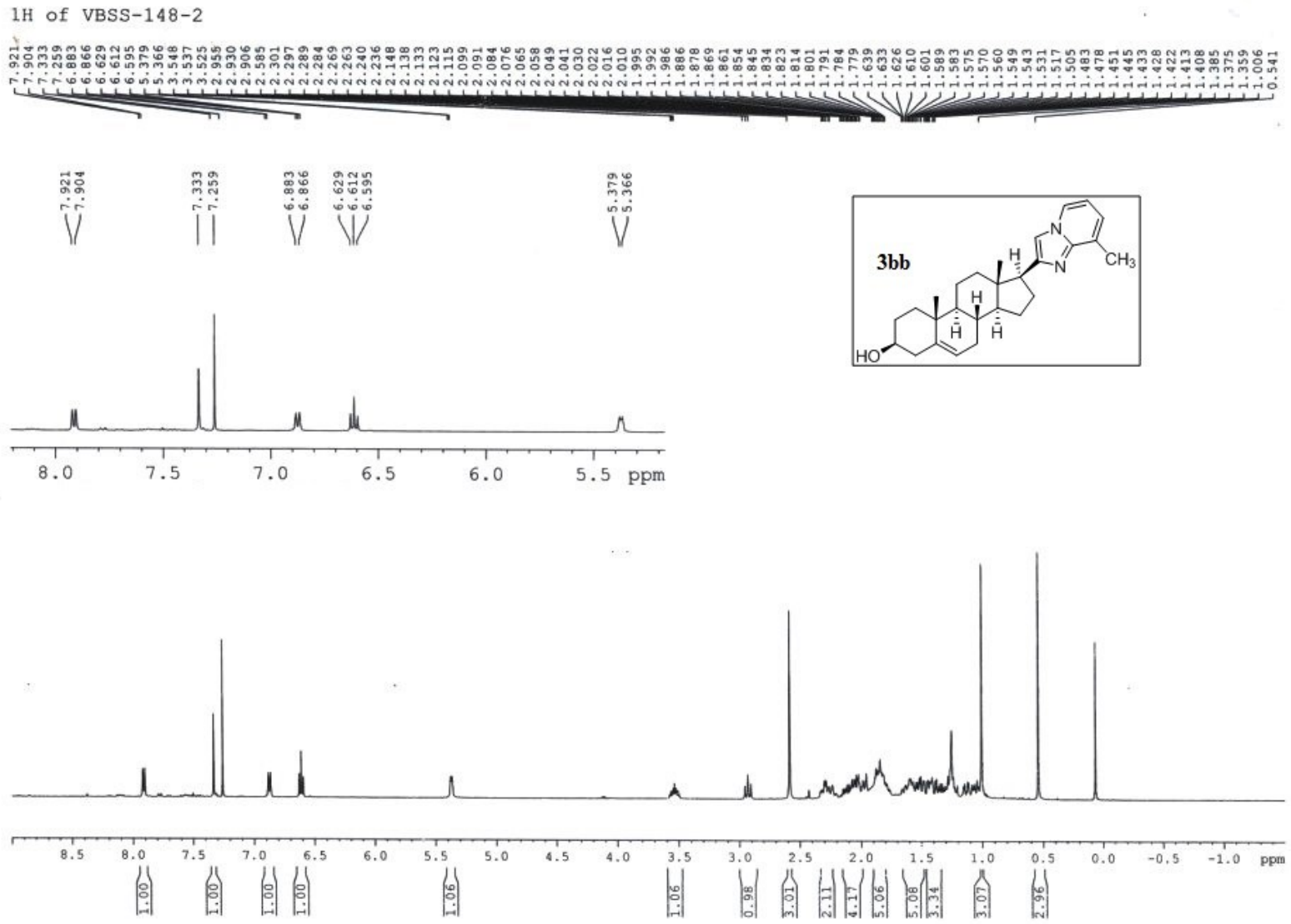
Current Data Parameters
NAME Dr. A HAJRA 2018-2nd
EXPNO 1429
PROCNO 1

F2 - Acquisition Parameters
Date_ 20181009
Time 23.05
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 800
DS 2
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 0.6815744 sec
RG 186.42
DW 20.800 usec
DE 6.50 usec
TE 299.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

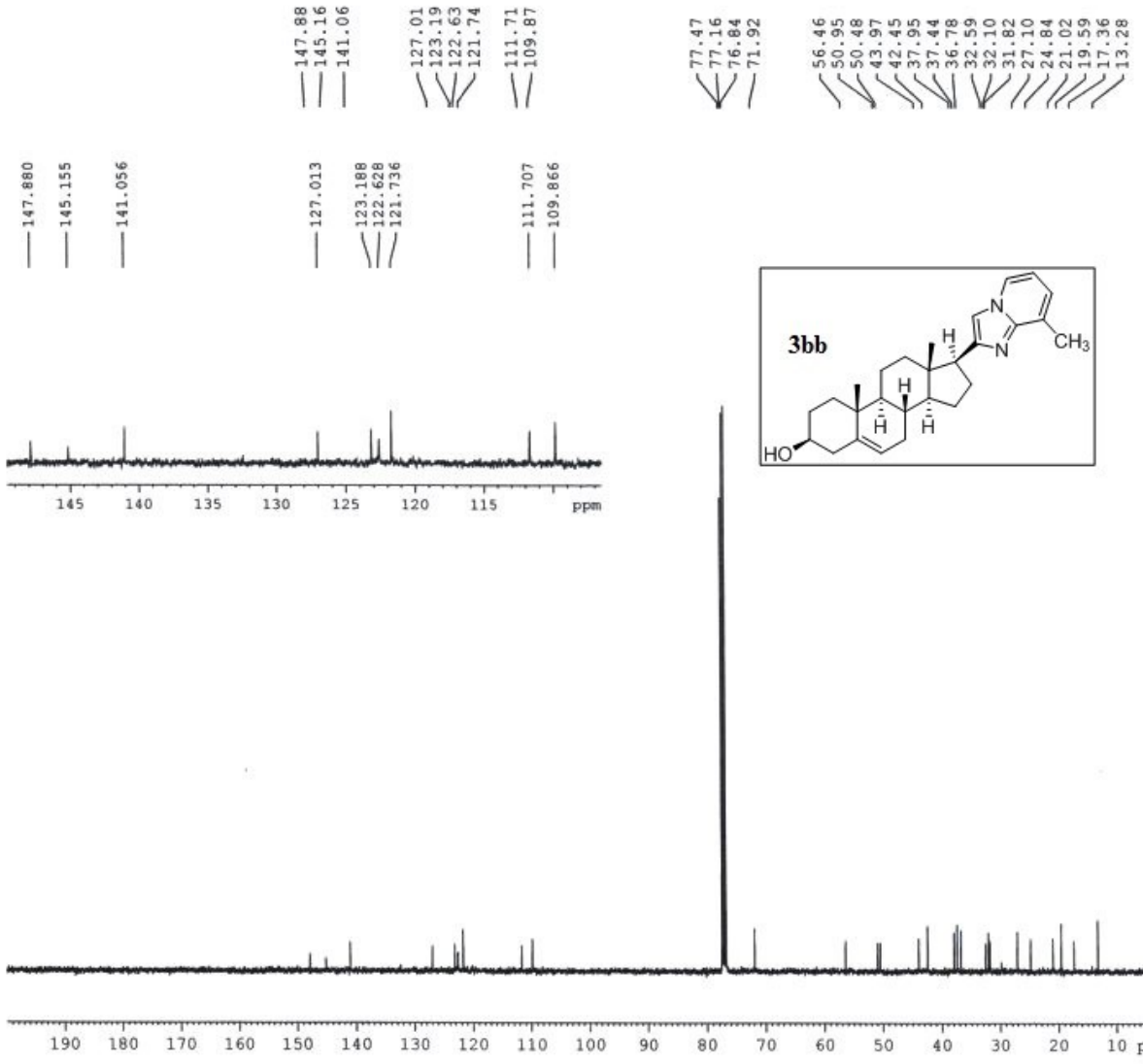
======== CHANNEL f1 ========
SFO1 100.6278588 MHz
NUC1 13C
P1 8.90 usec
PLW1 54.00000000 W

======== CHANNEL f2 ========
SFO2 400.1516006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.32231000 W
PLW13 0.16212000 W

F2 - Processing parameters
SI 16384
SF 100.6177835 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


1H of VBSS-148-2
7.921
7.904
7.333
7.259
6.883
6.866
6.629
6.612
6.595
5.379
5.366
3.548
3.537
3.525
2.955
2.930
2.906
2.585
2.301
2.297
2.289
2.284
2.269
2.263
2.240
2.236
2.148
2.138
2.133
2.123
2.115
2.099
2.091
2.084
2.076
2.065
2.058
2.049
2.041
2.030
2.022
2.016
2.010
1.995
1.992
1.986
1.886
1.878
1.869
1.861
1.854
1.845
1.834
1.823
1.814
1.801
1.791
1.784
1.779
1.639
1.633
1.626
1.610
1.601
1.589
1.583
1.575
1.570
1.560
1.549
1.543
1.531
1.517
1.505
1.483
1.478
1.451
1.445
1.433
1.428
1.422
1.413
1.408
1.385
1.375
1.359
1.006
0.541
3bb
HO
CH3
8.0
7.5
7.0
6.5
6.0
5.5 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
-0.5
-1.0 ppm
1.00
1.00
1.00
1.00
1.06
1.06
0.98
3.01
2.11
4.17
5.06
5.08
3.34
3.07
2.96

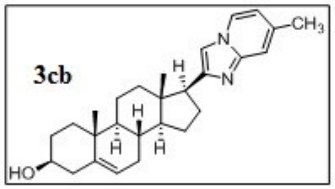
13C of VBSS-148-2

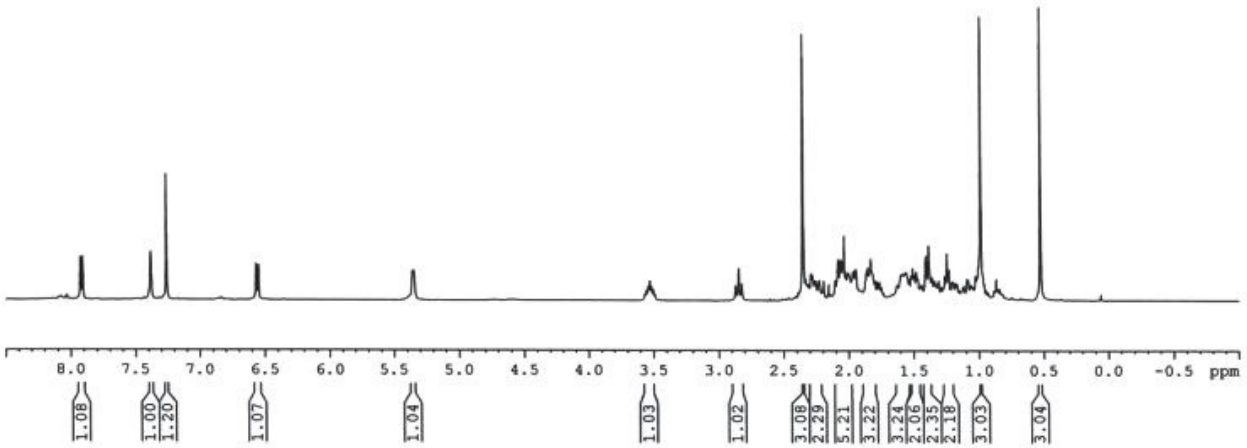



```
Current Data Parameters
NAME      Dr. A HAJRA 2018-2nd
EXPNO              1451
PROCNO                1

F2 - Acquisition Parameters
Date_          20181012
Time_             17.34
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG         zgpg30
TD              32768
SOLVENT           CDCl3
NS                  800
DS                    2
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ             0.6815744 sec
RG                120.16
DW                20.800 usec
DE                 6.50 usec
TE               298.7 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         100.6278588 MHz
NUC1                13C
P1                 8.90 usec
PLW1         54.00000000 W

======== CHANNEL f2 ========
SFO2         400.1516006 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2         12.00000000 W
PLW12         0.32231000 W
PLW13         0.16212000 W

F2 - Processing parameters
SI                 16384
SF           100.6177838 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

1H of VBSS-148-21

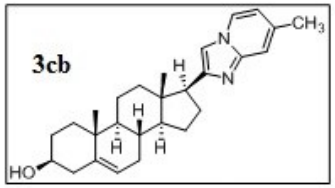
7.923
7.906
7.381
7.260
6.567
6.550
5.359
3.566
3.541
3.525
3.518
3.496
3.490
2.871
2.847
2.821
2.352
2.296
2.280
2.256
2.227
2.082
2.067
2.059
2.036
2.025
2.007
1.987
1.864
1.855
1.829
1.814
1.796
1.623
1.601
1.574
1.551
1.519
1.508
1.482
1.470
1.412
1.398
1.389
1.378
1.267
1.247
1.231
1.214
0.989
0.529

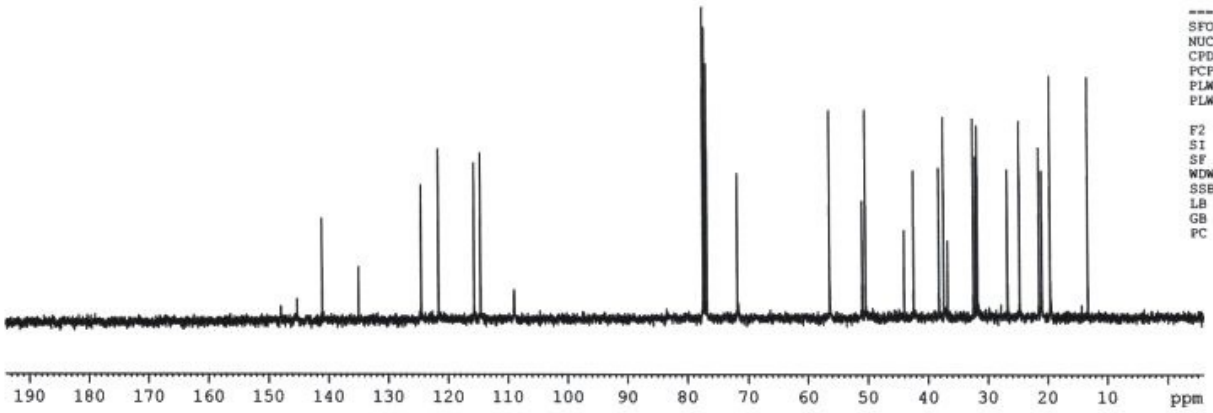




13C of VBSS 148-21

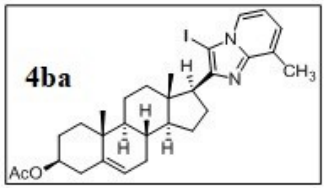
147.98
145.26
141.08
135.00
124.53
121.63
115.66
114.59
109.01
77.47
77.16
76.84
71.83
56.40
50.96
50.42
44.01
42.43
38.22
37.43
36.76
32.49
32.06
31.79
26.78
24.74
21.44
20.96
19.57
13.27

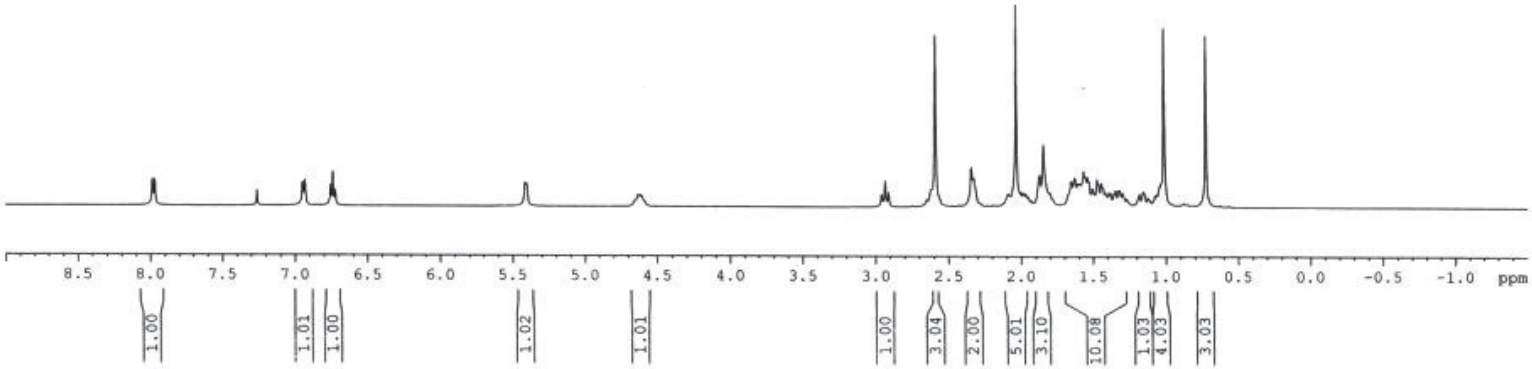




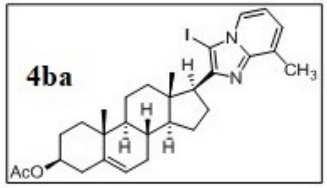

```
Current Data Parameters
NAME      Dr.A.HAJRA 2017
EXPNO               2213
PROCNO                 1

F2 - Acquisition Parameters
Date_           20171226
Time              10.32
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG           zgdc
TD               32768
SOLVENT          CDCl3
NS                 440
DS                   2
SWH          24038.461 Hz
FIDRES        0.733596 Hz
AQ            0.6815744 sec
RG               186.42
DW               20.800 usec
DE                6.50 usec
TE               296.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        100.6278588 MHz
NUC1               13C
P1                8.90 usec
PLW1        54.00000000 W

======== CHANNEL f2 ========
SFO2        400.1516006 MHz
NUC2               1H
CPDPRG[2        waltz16
PCPD2            90.00 usec
PLW2        12.00000000 W
PLW12        0.32231000 W

F2 - Processing parameters
SI                16384
SF          100.6177858 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.00
```

1H of VBSS-148-app-3

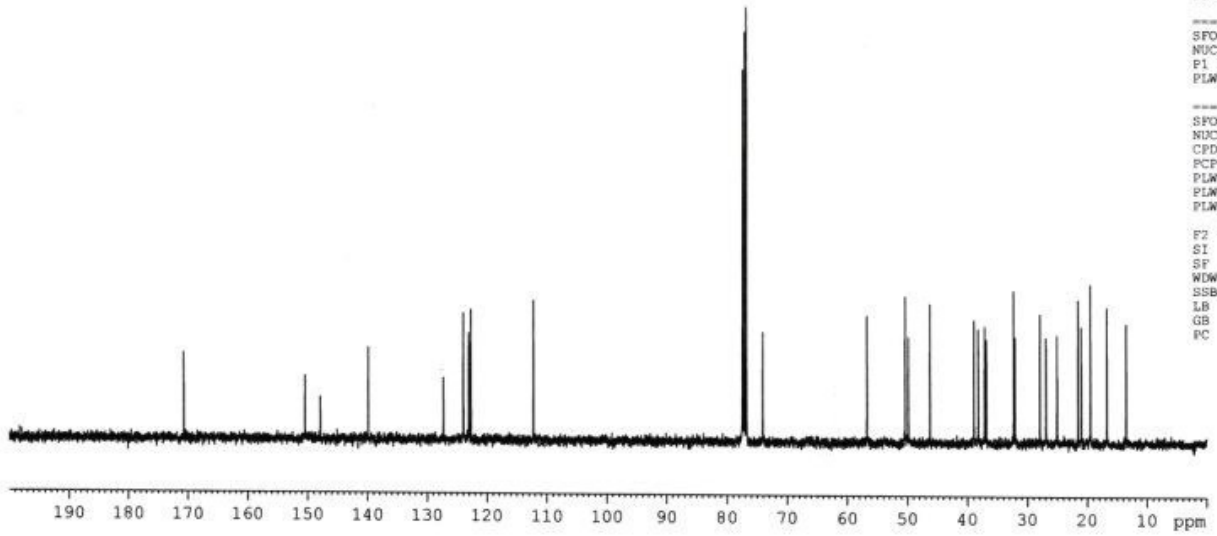




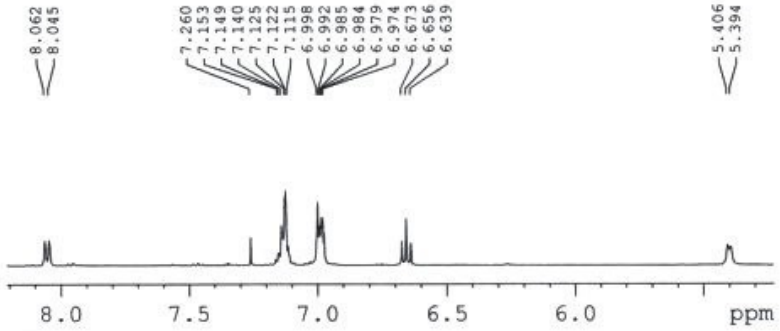
13C of vbSS-148-app-3

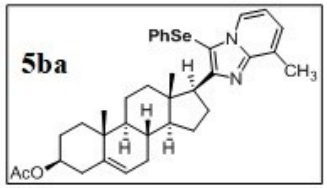


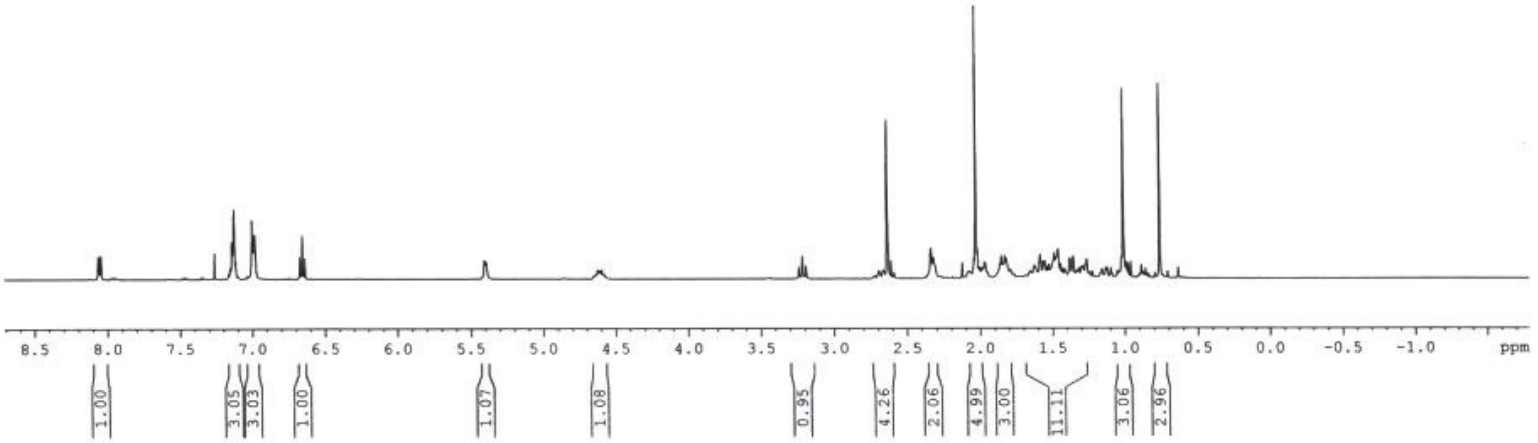

```
Current Data Parameters
NAME      Dr. A HAJRA 2018-2nd
EXPNO              1397
PROCNO                1

F2 - Acquisition Parameters
Date_          20181006
Time               11.44
INSTRUM            spect
PROBHD   5 mm PABBO BB/
PULPROG          zgpg30
TD                32768
SOLVENT           CDCl3
NS                  320
DS                    2
SWH           24038.461 Hz
FIDRES        0.733596 Hz
AQ            0.6815744 sec
RG                186.42
DW               20.800 usec
DE                6.50 usec
TE               299.6 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         100.6278588 MHz
NUC1                 13C
P1                  8.90 usec
PLW1         54.00000000 W

======== CHANNEL f2 ========
SFO2         400.1516006 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2              90.00 usec
PLW2         12.00000000 W
PLW12         0.32231000 W
PLW13         0.16212000 W

F2 - Processing parameters
SI                16384
SF           100.6177843 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



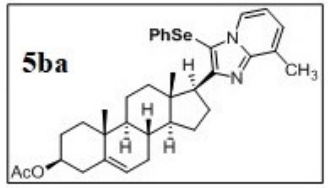
1H of VBSS-148-app-5







13C of vbSS-148-ap



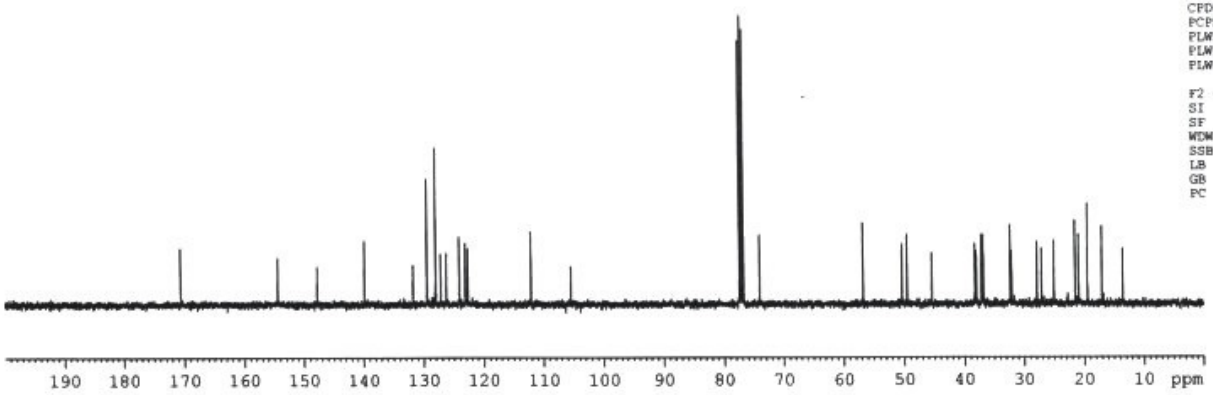
Current Data Parameters
NAME Dr. A HAJRA 2018-2nd
EXPNO 1406
PROCNO 1

F2 - Acquisition Parameters
Date_ 20181007
Time 14.06
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 120
DS 2
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 0.6815744 sec
RG 93.46
DW 20.800 usec
DE 6.50 usec
TE 299.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 100.6270588 MHz
NUC1 13C
P1 8.90 usec
PLW1 54.00000000 W

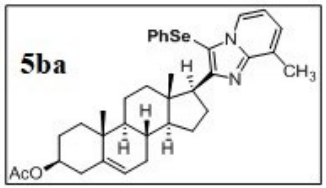
======== CHANNEL f2 ========
SFO2 400.1516006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 12.00000000 W
PLW12 0.32231000 W
PLW13 0.16212000 W

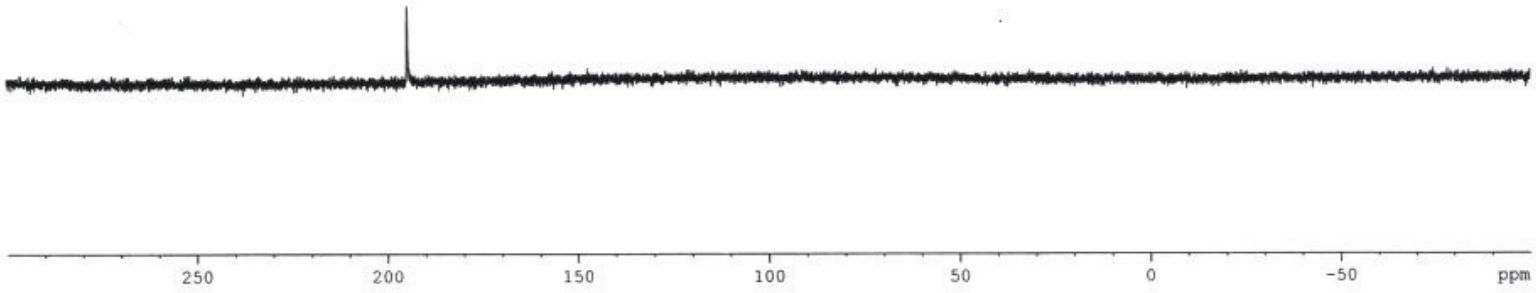
F2 - Processing parameters
SI 16384
SF 100.6177873 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

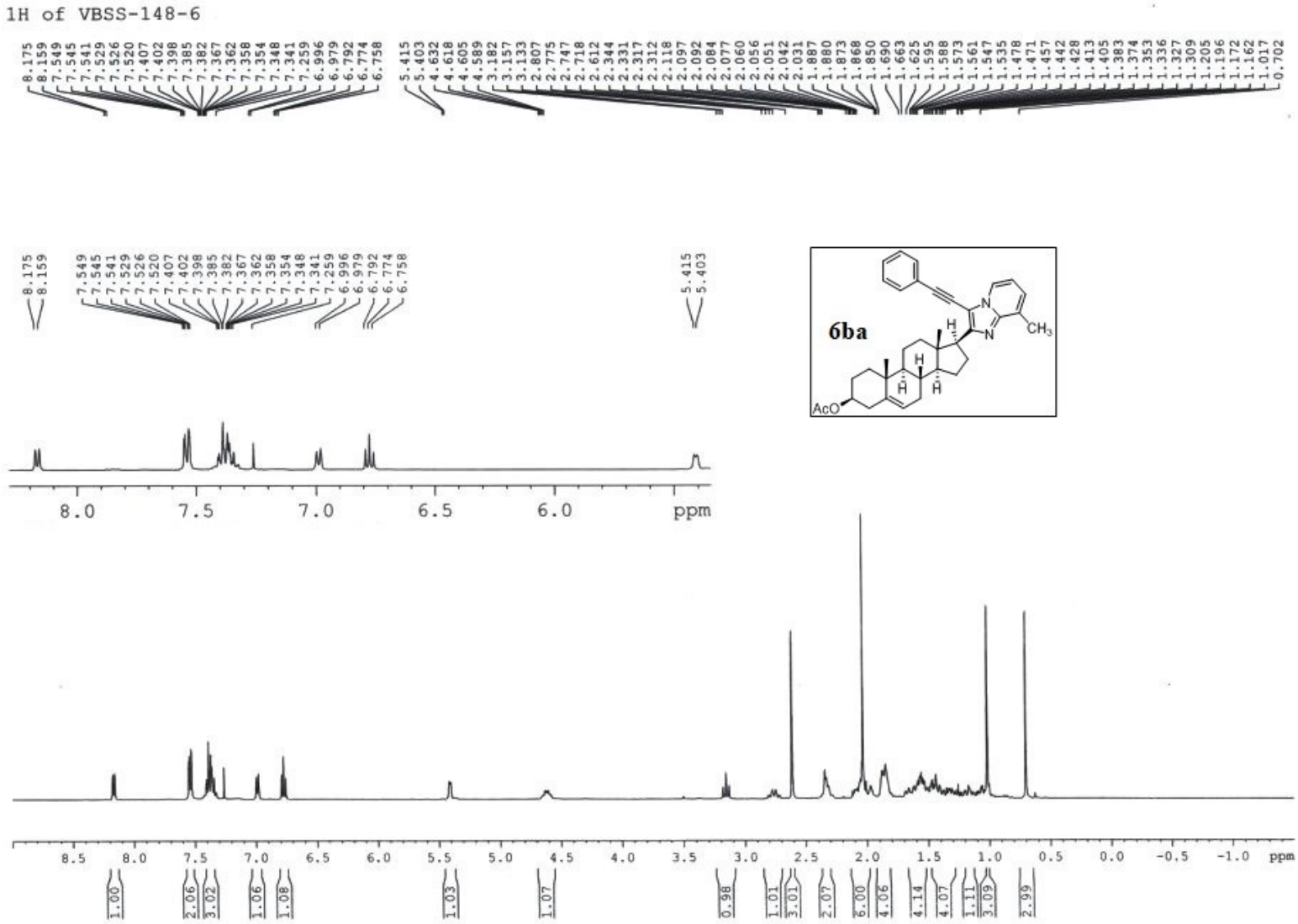


77Se of VBSS-148-app-5

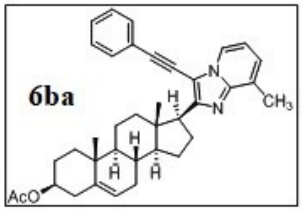
194.55






1H of VBSS-148-6
8.175
8.159
7.549
7.545
7.541
7.529
7.526
7.520
7.407
7.402
7.398
7.385
7.382
7.367
7.362
7.358
7.354
7.348
7.341
7.259
6.996
6.979
6.792
6.774
6.758
5.415
5.403
4.632
4.618
4.605
4.589
3.182
3.157
3.133
2.807
2.775
2.747
2.718
2.612
2.344
2.331
2.317
2.312
2.118
2.097
2.092
2.084
2.077
2.060
2.056
2.051
2.042
2.031
1.887
1.880
1.873
1.868
1.850
1.690
1.663
1.625
1.595
1.588
1.573
1.561
1.547
1.535
1.478
1.471
1.457
1.442
1.428
1.413
1.405
1.383
1.374
1.353
1.336
1.327
1.309
1.205
1.196
1.172
1.162
1.017
0.702
6ba
AcO
CH3
8.0
7.5
7.0
6.5
6.0
ppm
8.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
1.00
2.06
3.02
1.06
1.08
1.03
1.07
0.98
1.01
3.01
2.07
6.00
4.06
4.14
4.07
1.11
3.09
2.99

13C of VBSS-148-6




```
Current Data Parameters
NAME      Dr. A HAJRA 2018-2nd
EXPNO              1453
PROCNO                1

F2 - Acquisition Parameters
Date_          20181012
Time              17.50
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG         zgpg30
TD              32768
SOLVENT          CDCl3
NS                 180
DS                   2
SWH          24038.461 Hz
FIDRES        0.733596 Hz
AQ            0.6815744 sec
RG               120.16
DW               20.800 usec
DE                6.50 usec
TE               298.7 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        100.6278588 MHz
NUC1               13C
P1                8.90 usec
PLW1        54.00000000 W

======== CHANNEL f2 ========
SFO2        400.1516006 MHz
NUC2               1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2        12.00000000 W
PLW12        0.32231000 W
PLW13        0.16212000 W

F2 - Processing parameters
SI                16384
SF          100.6177873 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```