Efficient and Selective Acetylation of Biomolecules with 1-Acetylimidazole Catalyzed by $Er(OTf)_3$.

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Electronic Supplementary Material

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Experimental Section

All chemicals and solvents were purchased from common commercial sources and were used as received without any further purification. All reactions were monitored by TLC on silica Merck 60 F254 pre-coated aluminum plates and were developed by spraying with sulfuric acid in ethanol solution when possible. The tautomeric forms of acetyl cytosine was purified by semipreparative RP-HPLC chromatography [Phenomenex Jupter C18, 250 × 10 mm, 10 µm, UV 272 nm, 4.0 mL/min, (H_2O 100%). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on a Brüker spectrometer at 300 MHz. Chemical shifts are reported in δ units (ppm) with TMS as reference (δ 0.00). All coupling constants (J) are reported in Hertz. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Brüker at 75 MHz. Chemical shifts are reported in δ units (ppm) relative to $CDCl_3$ (δ 77.0).

MW-assisted reactions were performed on a Synthos 3000 instrument from Anton Paar, equipped with a 4×24MG5 Rotor and an IR probe used for external temperature control.

General MW-assisted protocol for acetylation of substrates.

To water solution (3 mL) of substrate (0.8 mmol) into a 3 mL glass vials to 1-acetylimidazole (2.4 mmol) and $Er(OTf)_3$ (10 mol %) was added. The mixture was reacted for 30 min in a Synthos 3000 microwave instrument, fixed on the temperature value of 60 °C (IR Limit). The appearance of protected product was controlled by TLC and, after, completion, water was removed under reduced pressure and the resulting crude was purified by flash chromatography (CH_2Cl_2/MeOH 9.5:0.5).

Methyl 6-*O*-acetyl α-D-glucopyranoside (**1a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz).[45]

Methyl 6-*O*-acetyl α-D-mannopyranoside (**2a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz). [46]

Methyl 6-*O*-acetyl α-D-galattopyranoside (**3a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz). [47]

Methyl 6-*O*-acetyl α-D-glucopyranoside (**4a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz).[2a]

Methyl 6-*O*-acetyl α-D-mannopyranoside (**5a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz).[46]

Methyl 6-*O*-acetyl α-D-galattopyranoside (**6a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz).[48]

Phenyl 6-*O*-acetyl α-D-glucopyranoside (**7a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz).[49]

Phenyl 6-*O*-acetyl α-D-glucopyranoside (**8a**) : ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz).[49]

N-acetyl-5'-*O*-acetyl adenosine (**9a**): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.02 (s, 3H, CH_3COO), 2.18 (s, 3H, CH_3CON), 3.85 (d, 1H, $H_{5'}$, J=13.15), 3.98 (d, 1H, $H_{5'}$, J_{gem}=13.15), 4.37 (s, 1H, $H_{3'}$), 5.69 (s, 1H, $H_{2'}$), 6.01-6.03 (m, 4H, $H_{4'}$, $H_{1'}$ 2OH), 7.84 (s, 1H, H_8), 8.34 (s, 1H, H_2). ^{13}C NMR ($CDCl_3$, 75.5 MHz).

5'-*O*-acetyl thymidine (**10a**): ^{1}H NMR (DMSO, 300 MHz): δ 1.93 (s, 3H, CH_3), 2.09 (s, 1H, $H_{2'}$), 2.13 (s, 3H, CH_3COO), 2.18 (s, 1H, $H_{2'}$), 2.46-2.44 (br, 1H, OH), 4.19 (t, 1H, $H_{3'}$, J= 3.40), 4.27 (t, 1H, $H_{4'}$, J= 3.29), 4.30 (dd, $H_{5'}$, J=11.84, J=3.29), 4.36-4.40 (m, 1H, $H_{5'}$), 3.98 (d, 1H, $H_{5'}$, J_{gem}=13.15), 6.30 (t, 1H, $H_{1'}$, J= 6.47), 7.32 (s, 1H, H_6), 9.78 (s, 1H, NH). ^{13}C NMR (DMSO, 75.5 MHz): 19.8, 21.5, 40.6, 63.9, 69.3, 82.6, 84.8, 109.7, 150.4, 163.8, 170.5.

5'-*O*-acetyl-2'-deoxyguanosine (**11a**): ^{1}H NMR (DMSO, 300 MHz): δ 1.90 (s, 3H, CH_3CON), 2.19 (s, 3H, CH_3COO), 2.30 (m, 1H, $H_{2'}$), 2.52 (m, 1H, $H_{2'}$), 3.58-3.60 (m br, 2H, $H_{3'}$ OH), 4.08 (dd, 1H, $H_{5'}$, J_{gem}= 13.17, J=3.31), 4.33 (dd, 1H, H', J_{gem}=13.17, J=3.31), 4.89 (t, 1H, $H_{4'}$, J=3.31), 5.95 (t, 1H, $H_{1'}$, J= 6.50), 7.96 (s, 1H, H_8). ^{13}C NMR (DMSO, 75.5 MHz): 20.8, 40.2, 61.5, 75.0, 82.6, 84.9, 116.7, 135.1, 150.9, 153.9, 156.7, 169.9, 165.5.

2'-deoxy-3',5'-di-*O*-acetylguanosine (**11b**): ^{1}H NMR (DMSO, 300 MHz): δ 2.03 (s, 3H, CH_3COO), 2.08 (s, 3H, CH_3COO), 2.41 (1H, ddd, ^{2}J = 14.26 Hz, $^{3}J_1$ = 5.47 Hz, $^{3}J_2$ = 2.1 Hz, H-2b') (m, 1H, $H_{2'}$), 2.92 (1H, ddd, ^{2}J = 14.27 Hz, ^{3} J_1 = 8.7 Hz, $^{3}J_2$ = 6.4 Hz, H-2a'), 4.15-4.30 (m, 3H, $H_{5'}$, $H_{3'}$), 5.28 (d, 1H, $H_{4'}$, J=6.83), 6.08-6.15 (m, 1H, $H_{1'}$), 6.52 (2H, s, NH_2), 7.92 (1H, s, H_8), 10.68 (1H, s, NH, ^{13}C NMR (DMSO, 75.5 MHz): 20.4, 20.7, 35.4, 63.6, 74.4, 81.4, 82.9, 116.7, 151.0, 153.7, 156.9, 169.9, 170.1.[45]

N-acetyl-cytidine (**12a**), 5'-O-acetyl-cytidine (**12b**), 6-O-acetyl-cytidine (**12c**): ^{1}H NMR (DMSO, 300 MHz): δ 2.05 (s, 3H, CH_{3A}), 2.08 (s, 6H, CH_{3B} + CH_{3C}), 3.51-3.71 (m, 6H, $H_{5'A}$, $H_{5'C}$, $H_{3'C}$, , $H_{2'C}$), 3.82-4.01 (m, 3H, , $H_{5'A}$, $H_{5'C}$,$H_{4'A}$), 4.11-4.29 (m, 4H, $H_{3'A}$, $H_{4'A}$, $H_{4'C}$, $H_{3'B}$), 5.03-5.07 (m, 3H, H_{5A}, H_{5B}, $H_{5'B}$), 5.19 (t, 1H, $H_{2'B}$, J=

4.81), 5.27 (t, 1H, $H_{2'A}$, J= 5.04), 5.45 (d, $H_{4'B}$, J=5.04), 5.48 (d, 1H, $H_{5'B}$), 5.65 (d, 1H, $H_{1'C}$, J=6.19), 5.76 (m, 2H, H_{6C},H_{5C}), 5.83 (d, 1H, $H_{1'A}$, J=5.96), 5.97 (d, 1H, $H_{1'B}$), 7.60 (d, 1H, H_{6B}, J=7.56), 7.83 (d, 1H, H_{6A}, J=7.56). ^{13}C NMR (DMSO, 75.5 MHz): 60.5, 60.7, 68.1, 69.6, 71.8, 72.4, 73.2, 75.3, 79.1, 80.4, 81.9, 84.7, 86.7, 88.7, 90.0, 94.2, 94.3, 94.4, 141.3, 155.2, 155.4, 155.4, 165.5, 165.5, 169.6, 169.7, 178.3.

4-[2-(Acetyloxy)ethyl]phenyl acetate (**13a**): ^{1}H NMR (DMSO, 300 MHz): δ 1.98 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.88 (t, 2H, CH_2, J= 7.50), 4.20 (t, 2H, CH_2, J= 7.11), 7.05 (d, 2H, H_{ar}, J= 8.49), 7.28 (d, 2H, H_{ar}, J= 8.46), ^{13}C NMR (DMSO, 75.5 MHz): Spectroscopic data compared to those reported in the literature.[50]

3,4-dihydroxyphenethyl acetate (**14a**): ^{1}H NMR (DMSO, 300 MHz): δ 1.97 (s, 3H, CH_3), 2.68 (t, 2H, CH_2, J= 6.87), 4.10 (t, 2H, CH_2, J= 7.11), 6.45-6.48 (m, 1H, H_{ar}), 6.48-6.62 (m, 2H, H_{ar}). ^{13}C NMR (DMSO, 75.5 MHz): 19.9, 33.8, 64.8, 114.5, 116.6, 128.6, 133.9, 143.8, 145.2, 170.4.

4-hydroxy-3-methoxyphenethyl acetate (**15a**): ^{1}H NMR (DMSO, 300 MHz): δ 1.99 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.85 (t, 2H, CH_2, J= 7.50), 3.73 (s, 3H, CH_3), 4.33 (t, 2H, CH_2, J= 7.11), 7.03 (d, 2H, H_{ar}, J= 8.43), 7.25 (d, 2H, H_{ar}, J= 8.43). ^{13}C NMR (DMSO, 75.5 MHz): 20.0, 35.1, 56.2, 64.9, 121.5, 121.1, 133.1, 142.9, 151.1, 170.0.

Acetyl-3,5-Dihydroxybenzyl alcohol (**16a**): ^{1}H NMR (DMSO, 300 MHz): 2.05 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 6.14-6.18 (m, 3H, H_{ar}). ^{13}C NMR (DMSO, 75.5 MHz): 20.6, 35.1, 64.8, 121.5, 128.3, 134.1, 143.2, 169.1, 170.0. ^{13}C NMR (DMSO, 75.5 MHz): 20.6, 65.3, 101.9, 105.6, 105.6, 137.9, 158.3, 170.0.

Glycerol 1,3 diacetate (**17a**): ^{1}H-NMR ($CDCl_3$, 300 MHz), ^{13}C NMR ($CDCl_3$, 75.5 MHz).Spectroscopic data compared to those reported in the literature.[51]

n-butyl acetate (**18a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz).[52]

1, 4-Butanediol, diacetate (**19a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz). Spectroscopic data compared to those of the pure product. GC-MS (EI): 114.0 (11), 73.0 (20), 71.0 (30), 54.0 (45), 43.0 (100).[53]

n-octyl acetate (**20a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz). Spectroscopic data compared to those of the pure product. GC-MS (EI): 112.0 (10), 84.0 (30), 70.0 (36), 56.0 (30), 43.0 (100).[53]

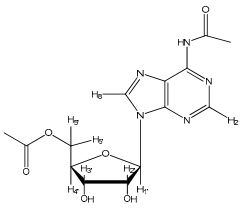
Fmoc-Ser(Ac)-OH **(21a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz). Spectroscopic data compared to those of the pure product.

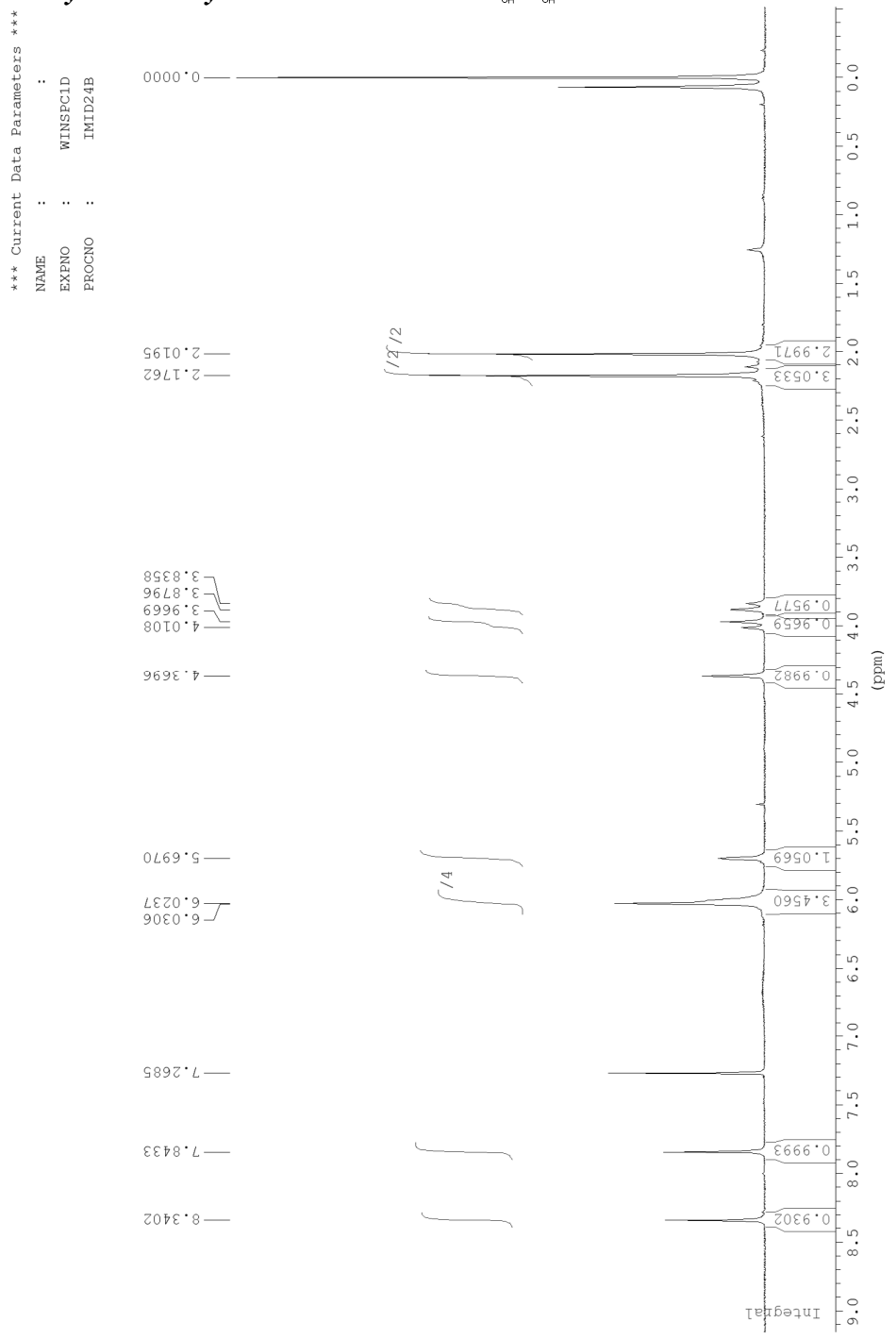
Fmoc-Lys(Ac)-OH (**22a**): ^{1}H NMR ($CDCl_3$, 300 MHz), ^{13}C-NMR ($CDCl_3$, 75.5 MHz). Spectroscopic data compared to those of the pure product.

[1]H-NMR Spectra

Sample 9a

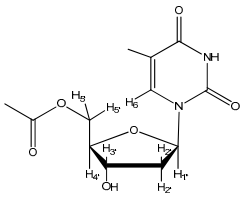
N-acetyl-5'-O-acetyl adenosine

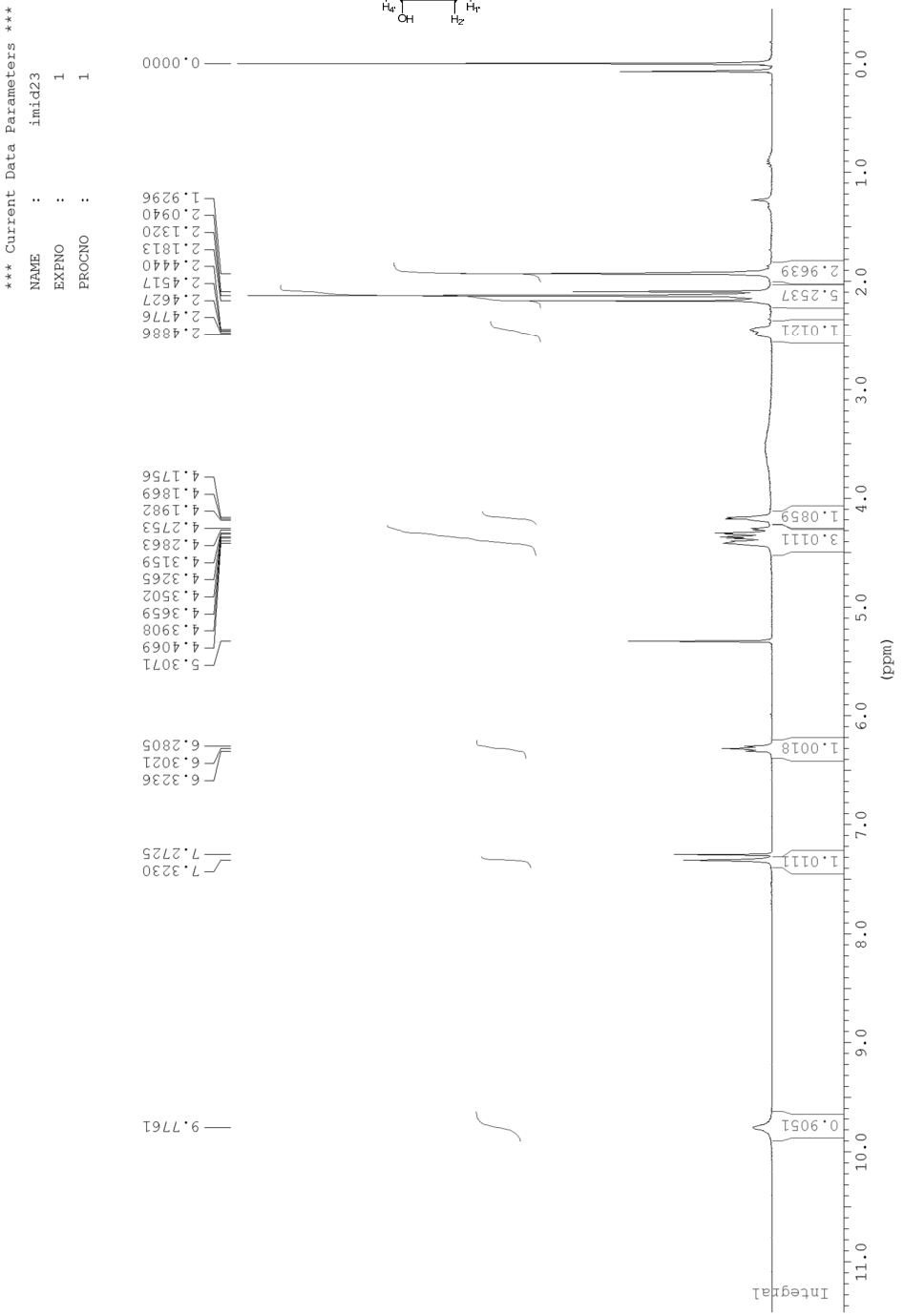




Sample 10a

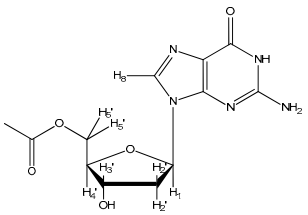
5'-O- acetyl thymidine

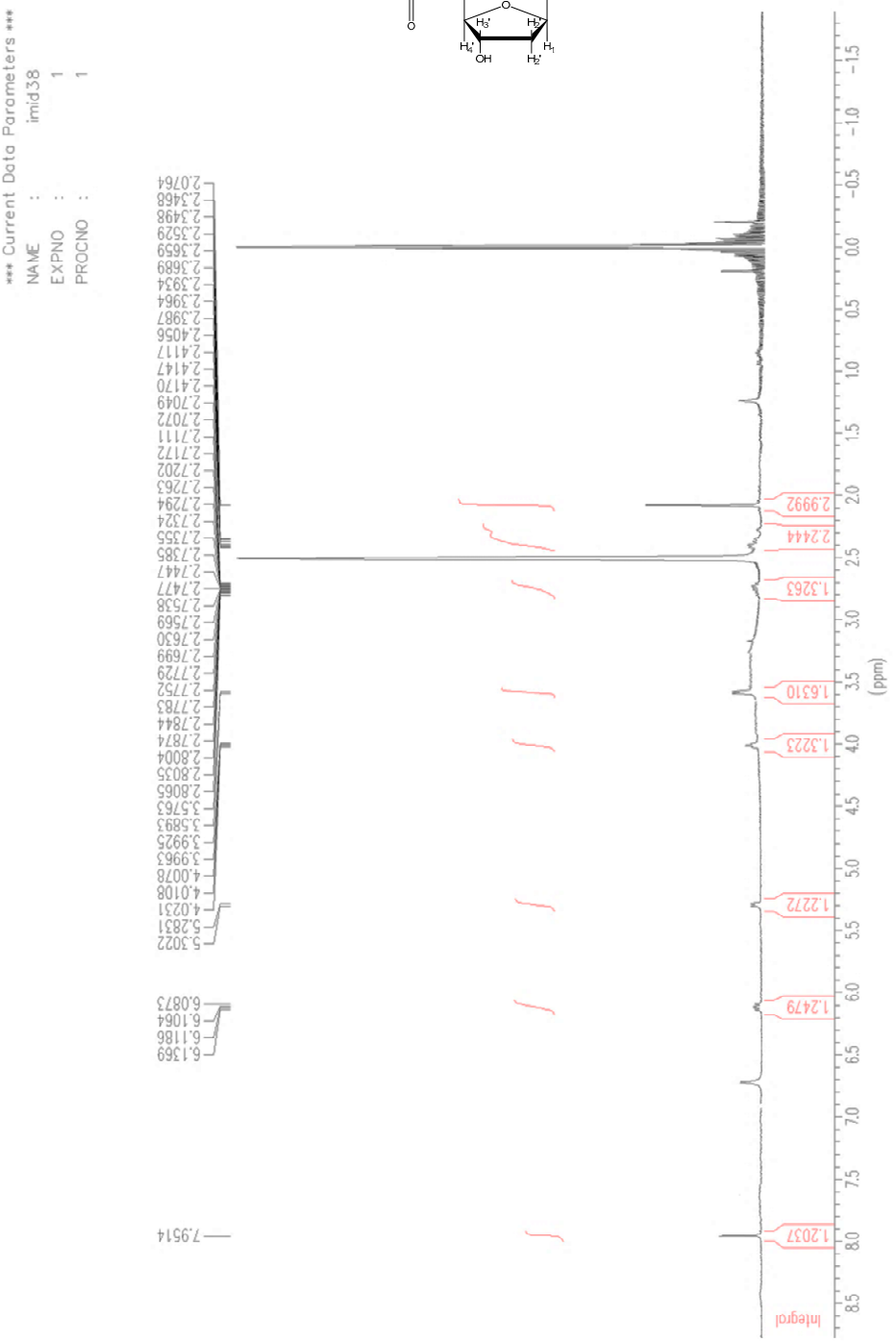




Sample 11a

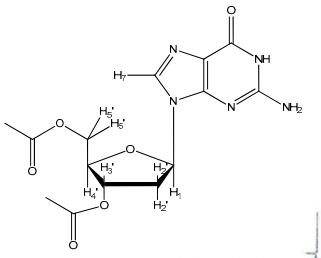
5'-O-acetyl-2'-deoxyguanosine

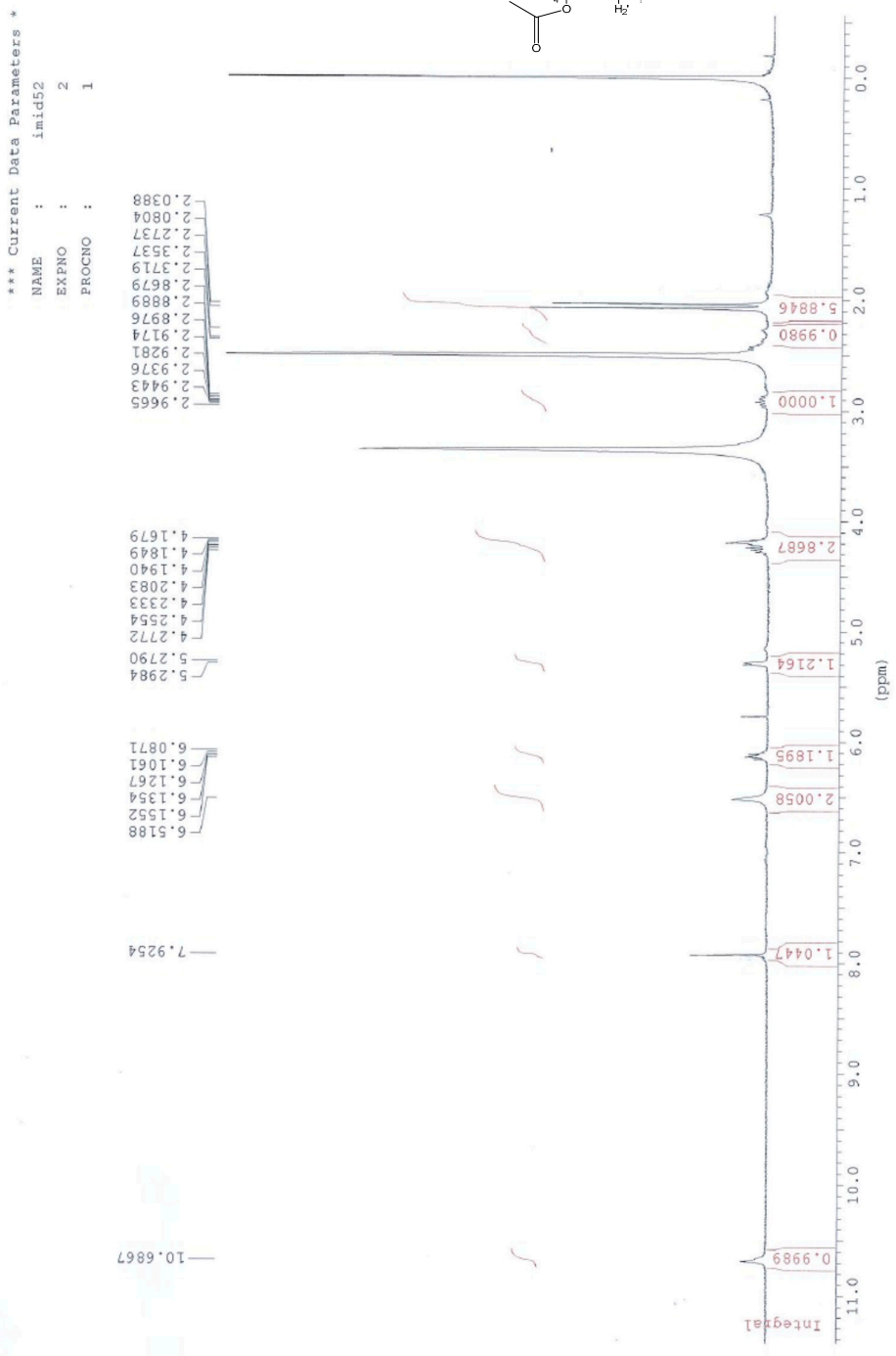


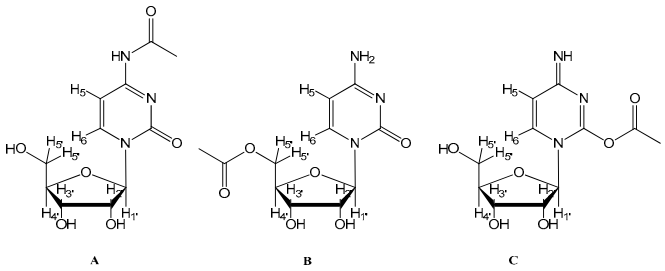


Sample 11b

2'-deoxy-3',5'-di-*O*-acetylguanosine







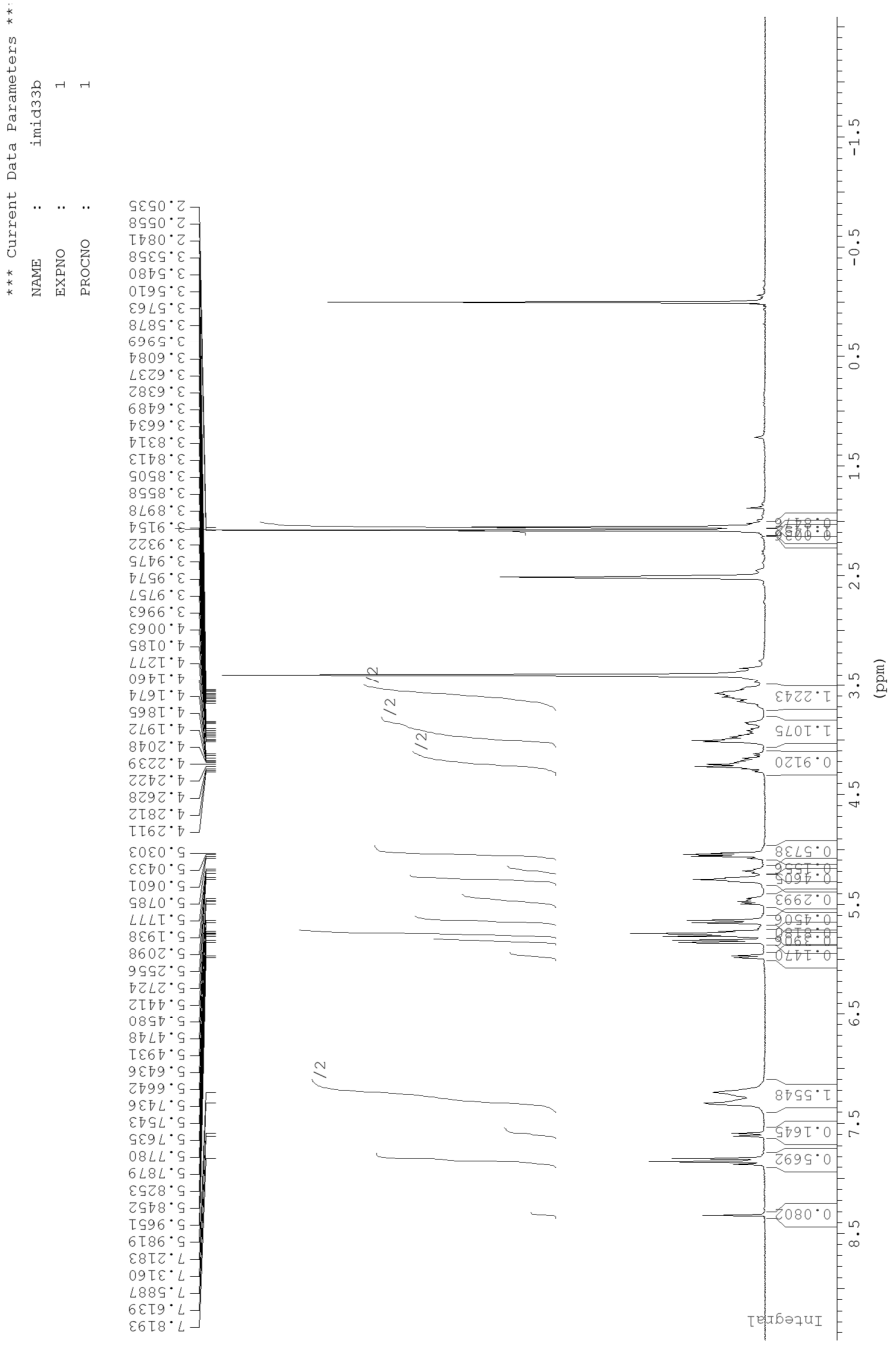
Sample 12°, 12b, 12c

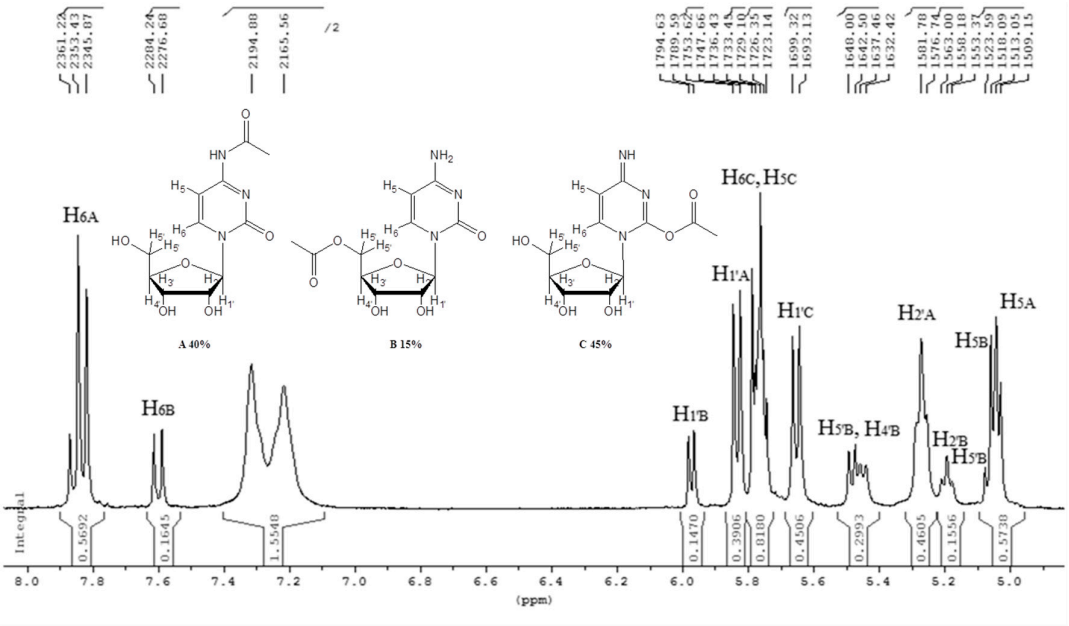
N-acetyl-cytidine (12a),

5'-O-acetyl-cytidine (12b),

6-O-acetyl-cytidine (12c):

1.2 equiv. di 1-acetilimidazolo **A**= 45.6%; **B**= 14,7%; **C**=39.7%

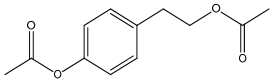


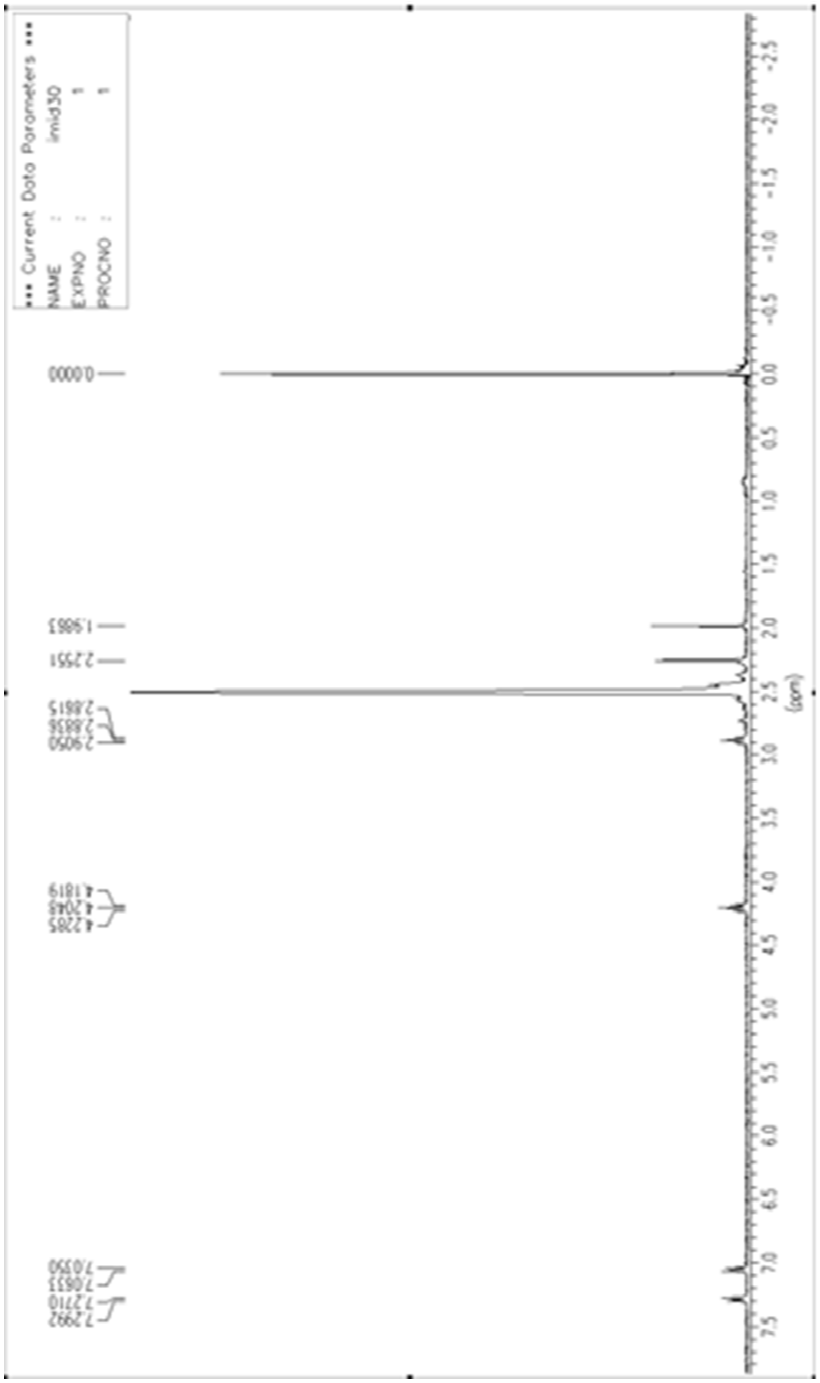


3 equiv. di 1-acetilimidazolo **A**= 40.0%; **B**= 15,0; **C**=40.0%

Sample 13a

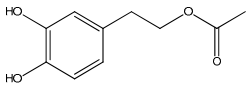
4-[2-(Acetyloxy)ethyl]phenyl acetate

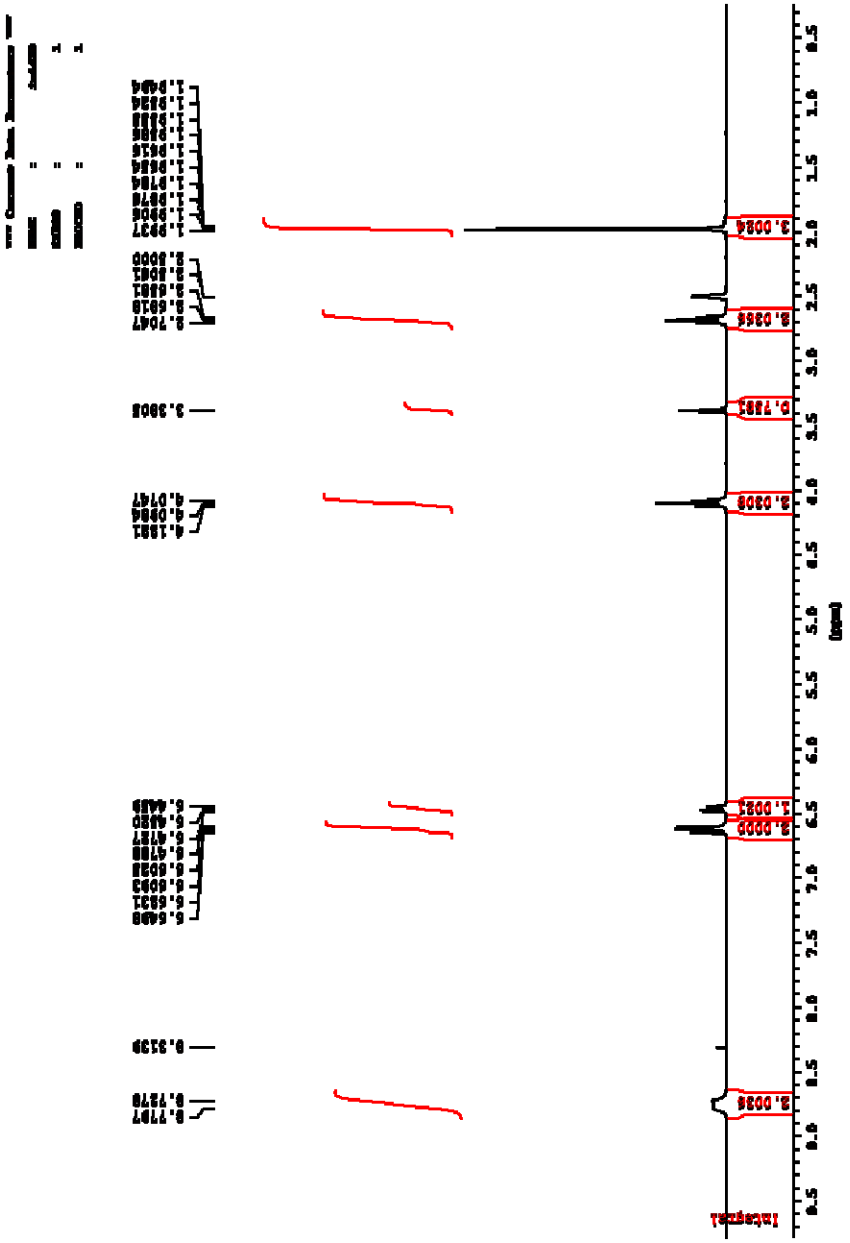




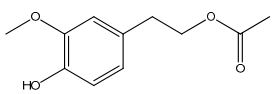
Sample 14a

3,4-dihydroxyphenethyl acetate

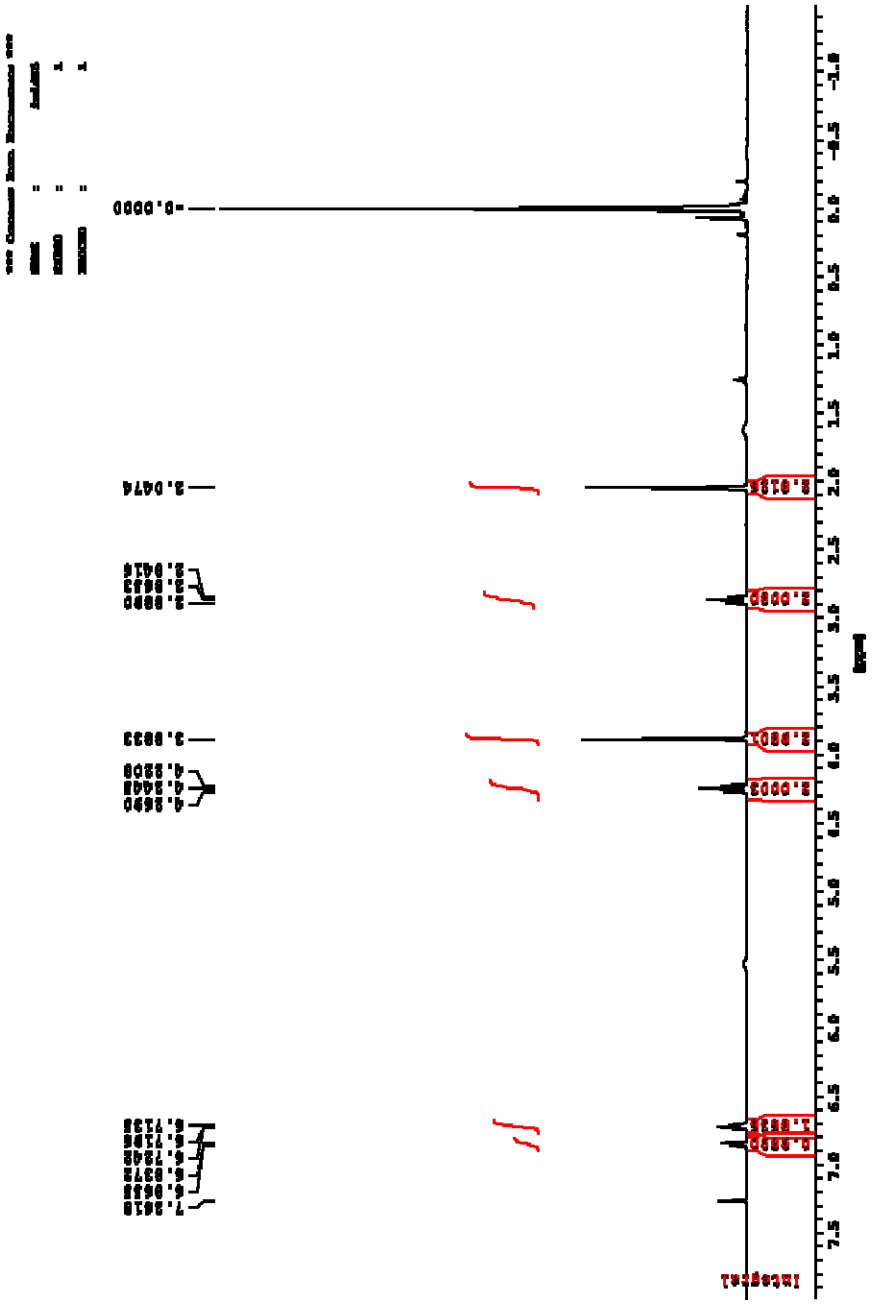




Sample 15a

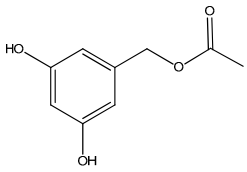


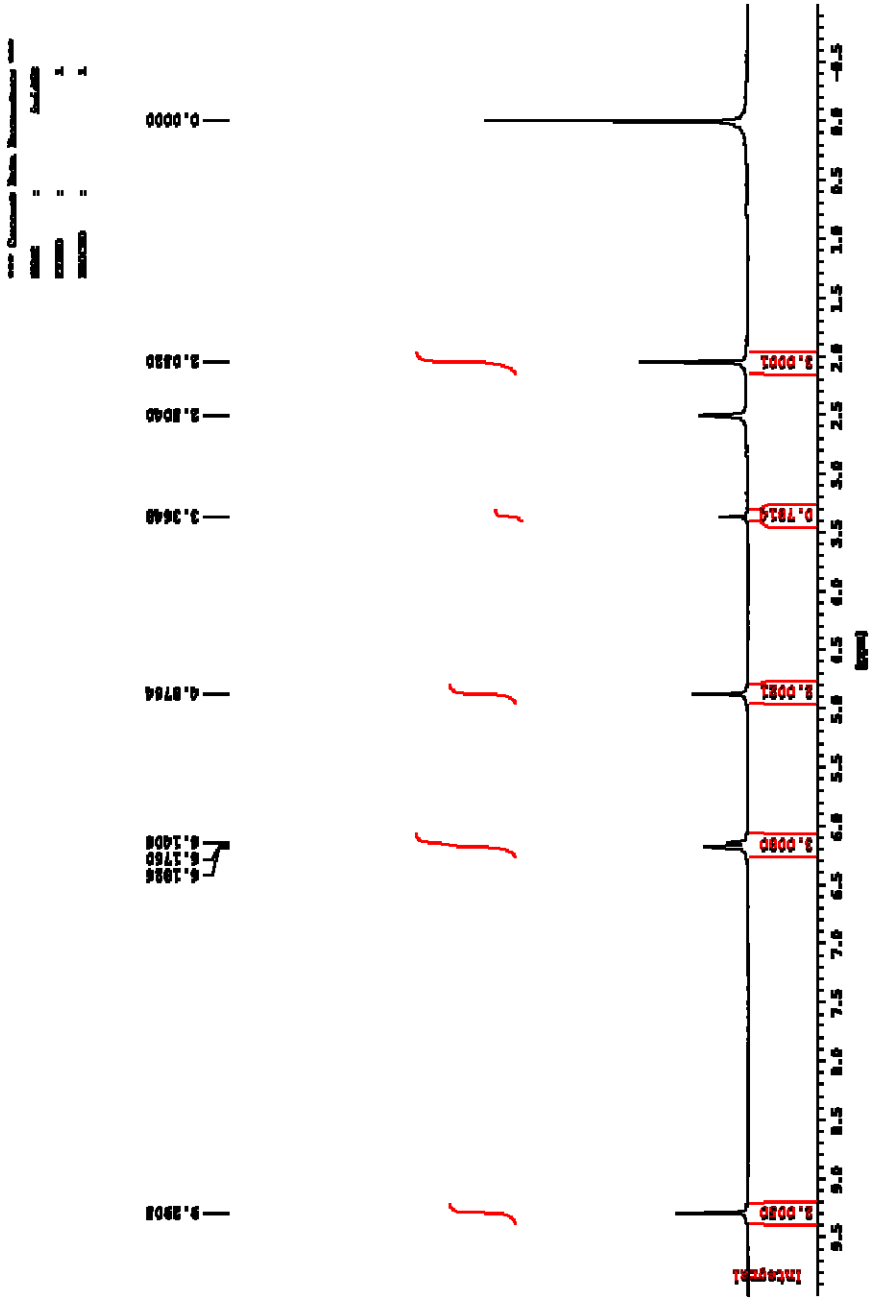
4-hydroxy-3-methoxyphenethyl acetate



Sample 16a

Acetyl-3,5-Dihydroxybenzyl alcohol

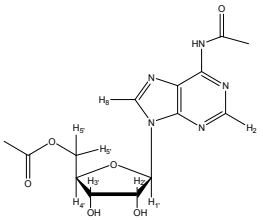


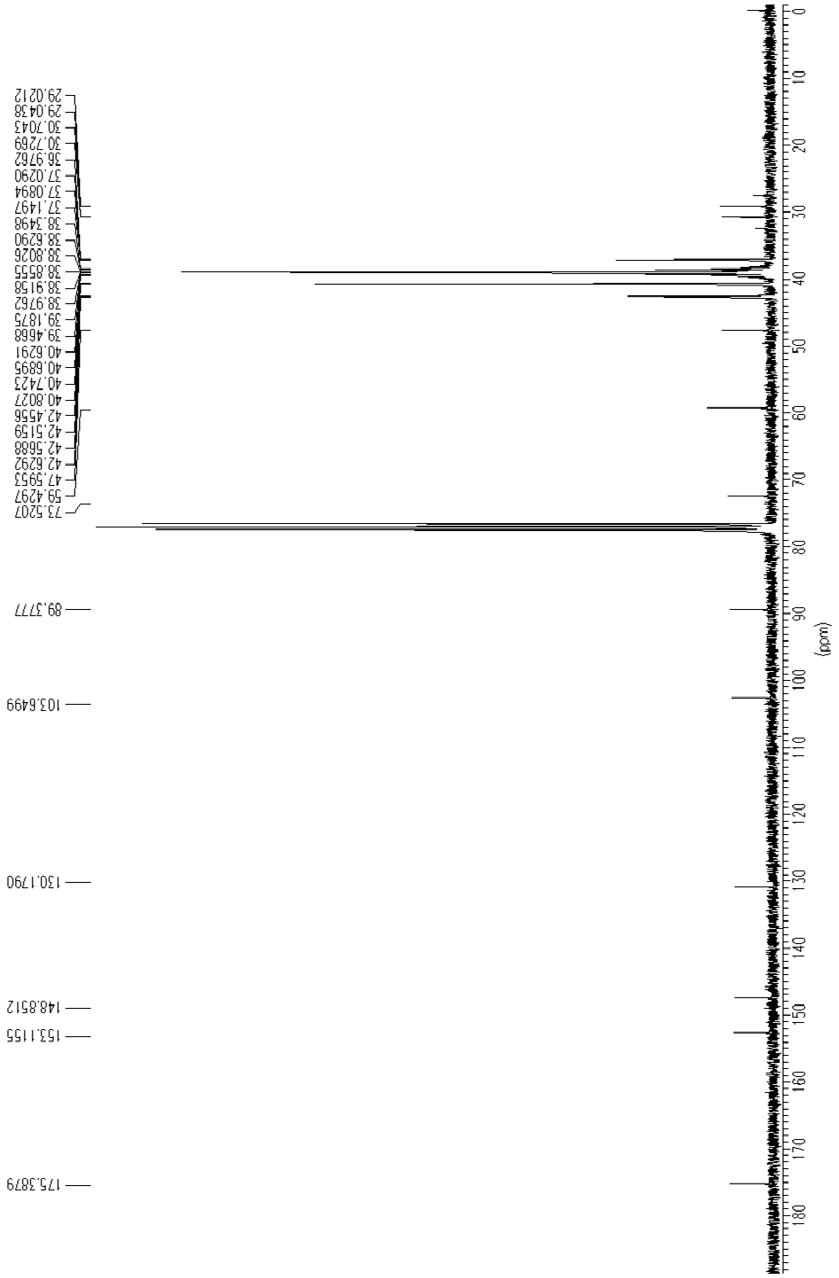


^{13}C-NMR Spectra

Sample 9a

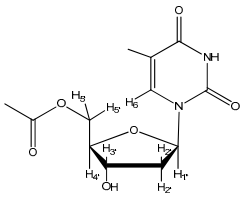
N-acetyl-5'-O-acetyl adenosine





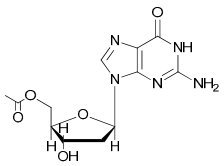
Sample 10a

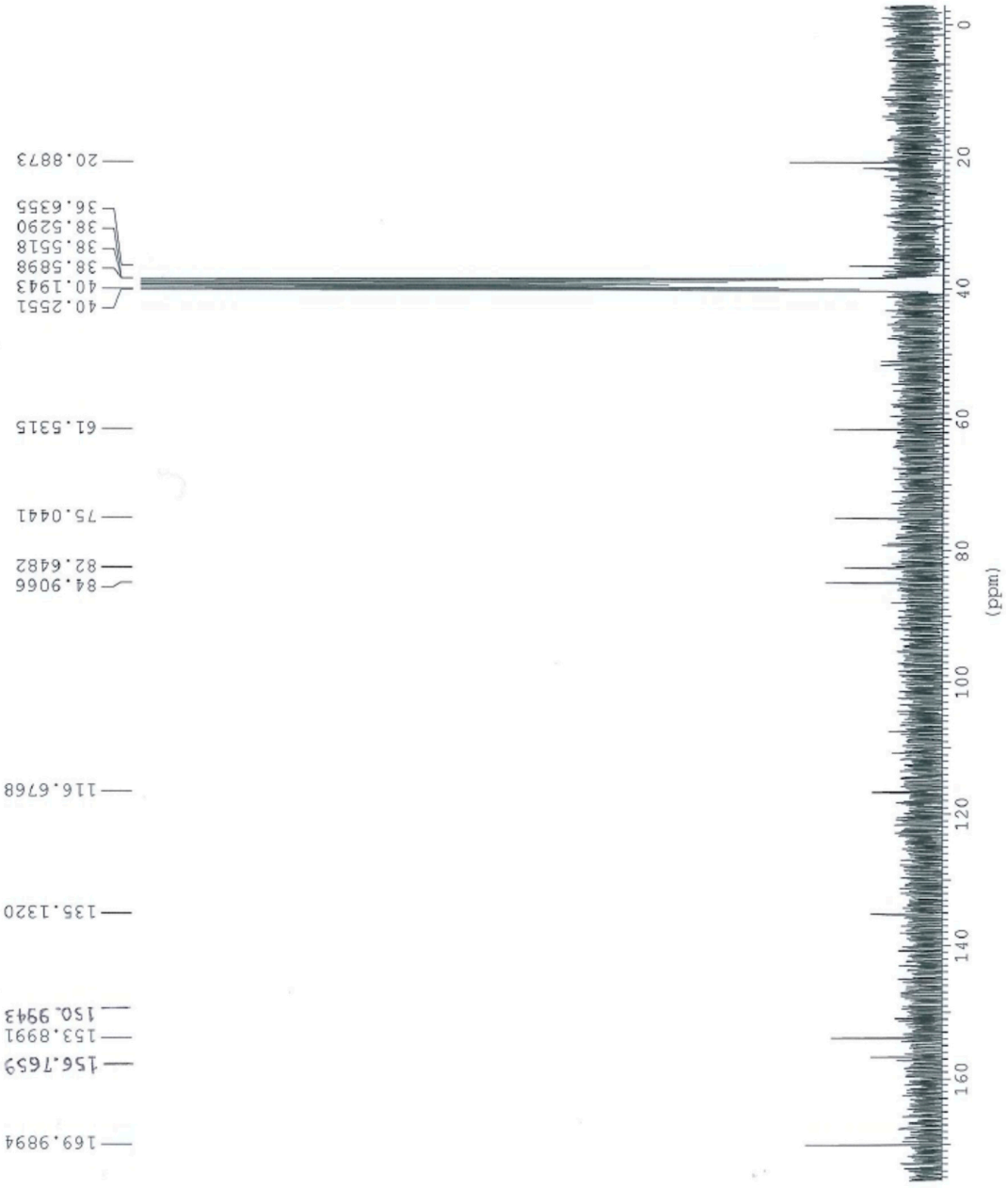
5'-O- acetyl thymidine



Sample 11a

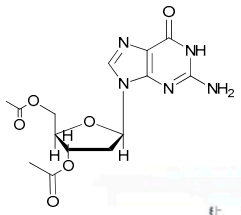
5'-O-acetyl-2'-deoxyguanosine

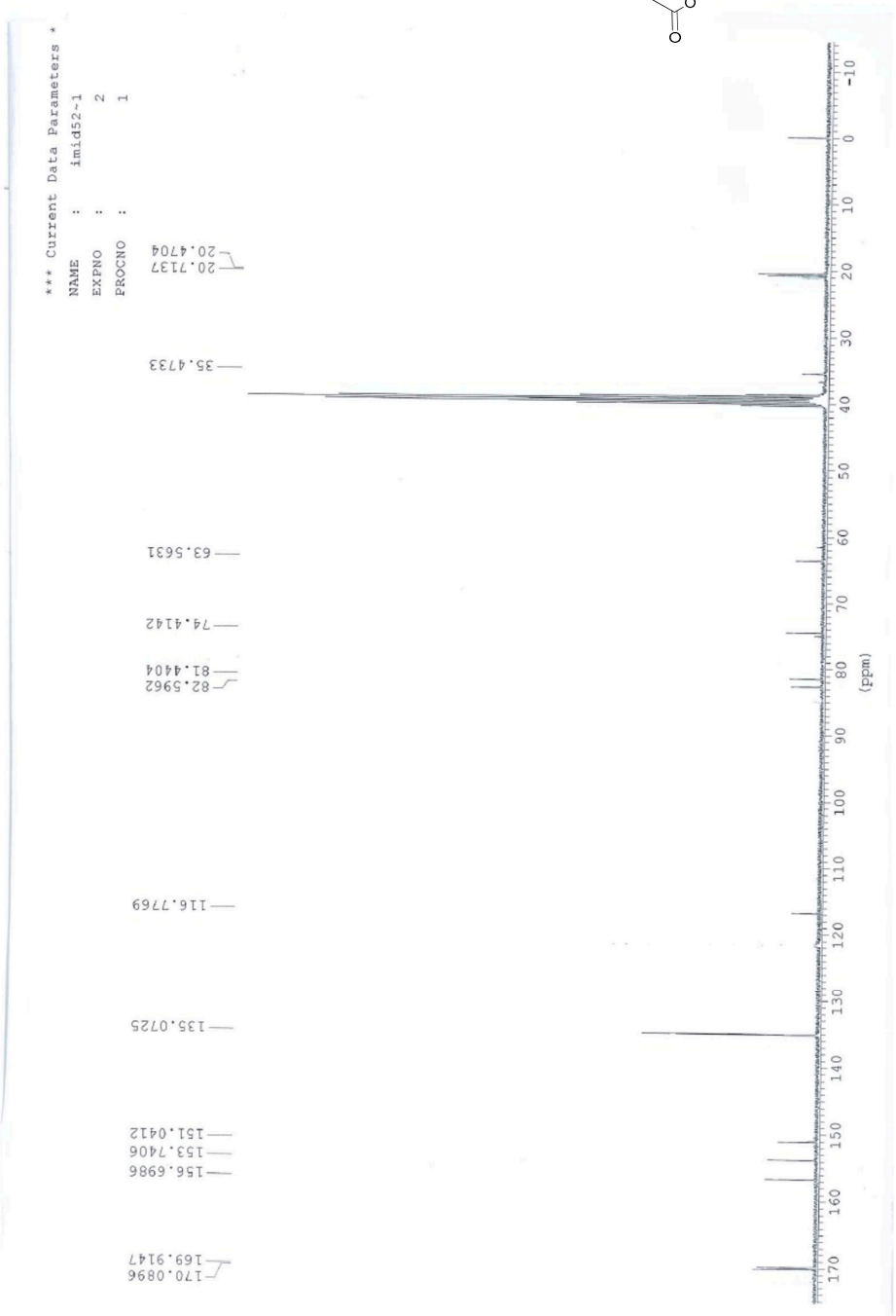




Sample 11b

2'-deoxy-3',5'-di-O-acetylguanosine:



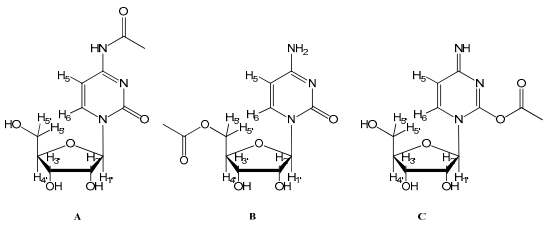


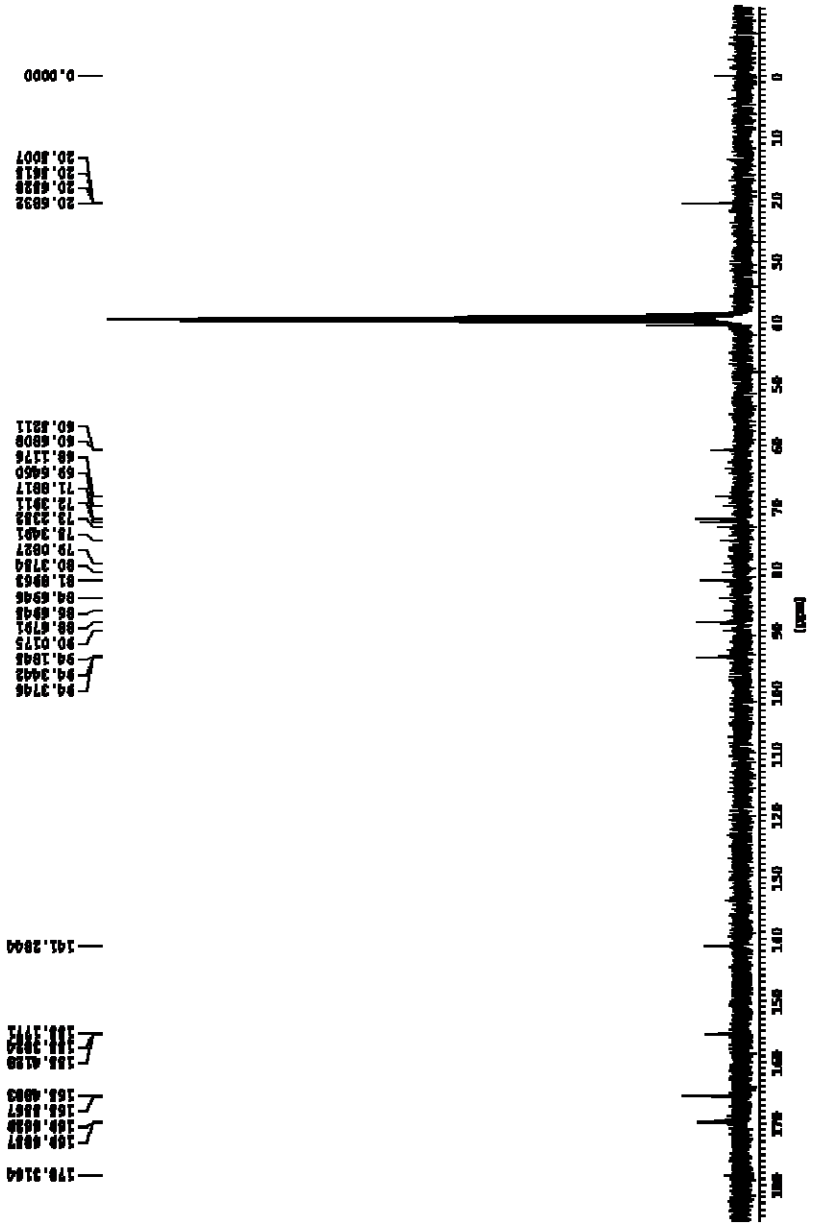
Sample 12a, 12b, 12c

N-acetyl-cytidine (12a),

5'-O-acetyl-cytidine (12b),

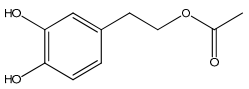
6-O-acetyl-cytidine (12c):

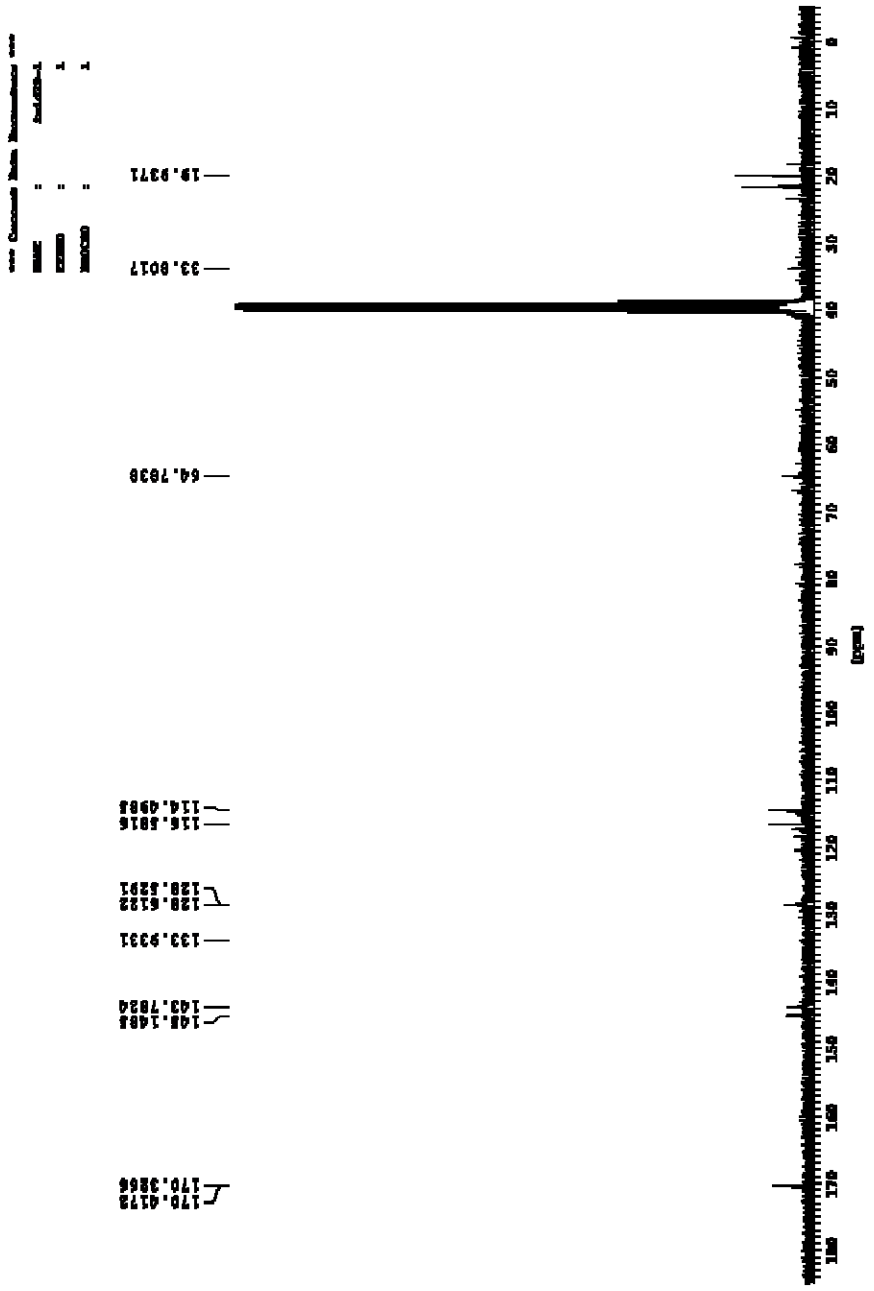




Sample 14a

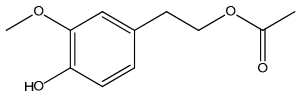
3,4-dihydroxyphenethyl acetate

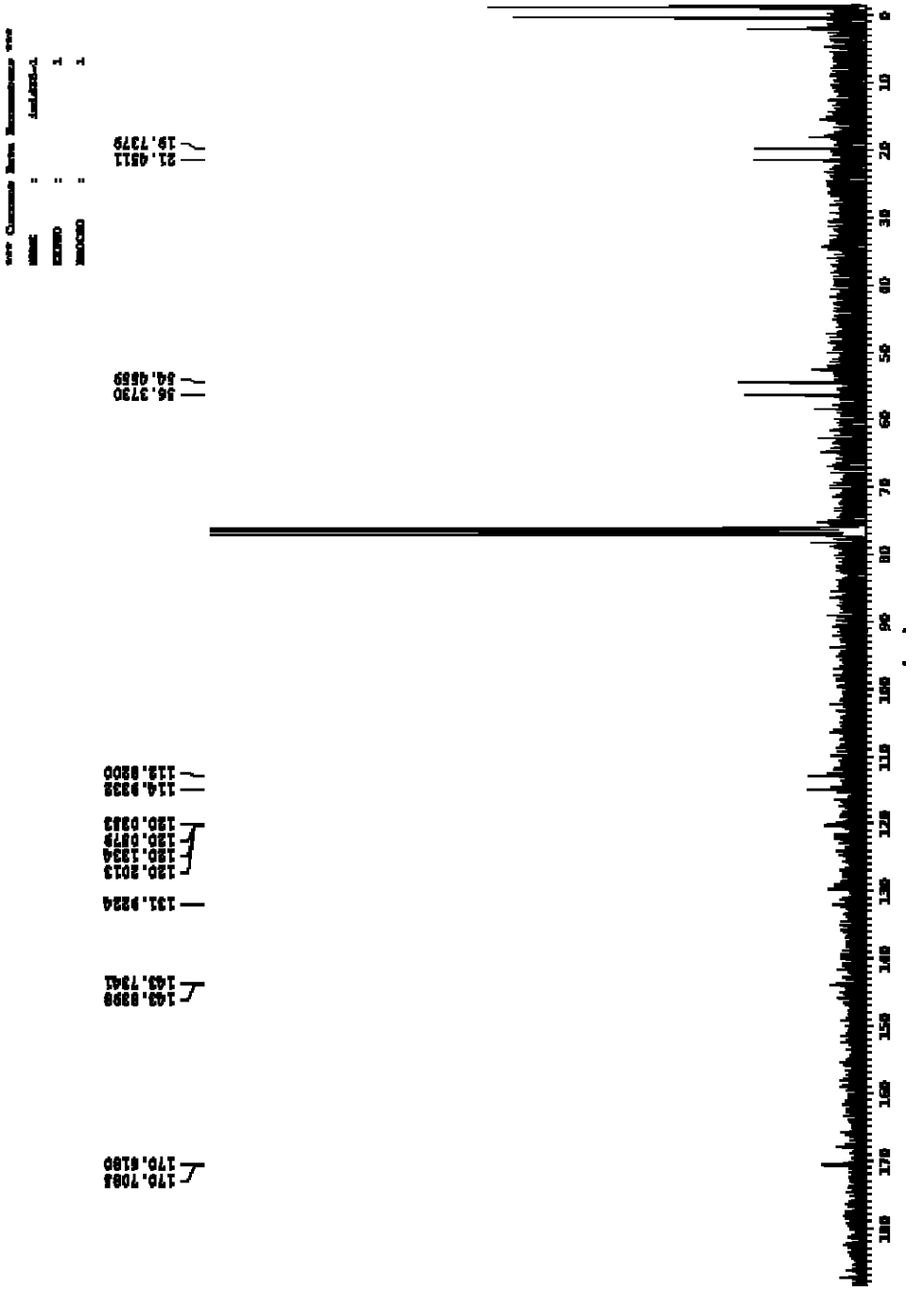




Sample 15a

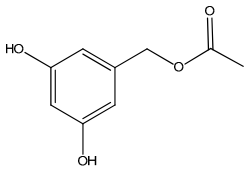
4-hydroxy-3-methoxyphenethyl acetate

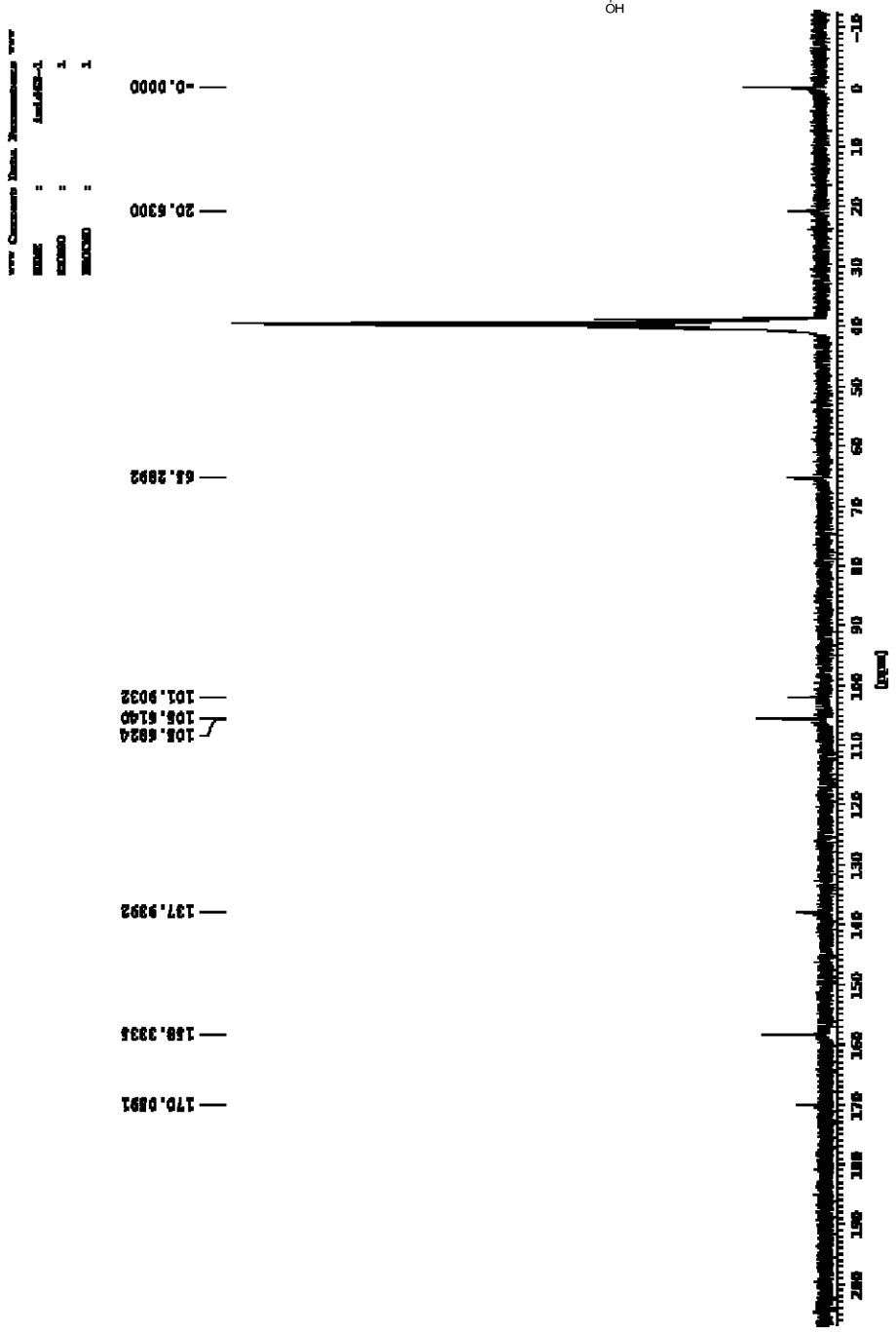




Sample 16a

Acetyl-3,5-Dihydroxybenzyl alcohol

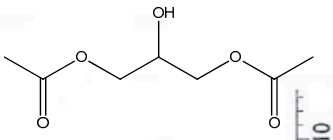


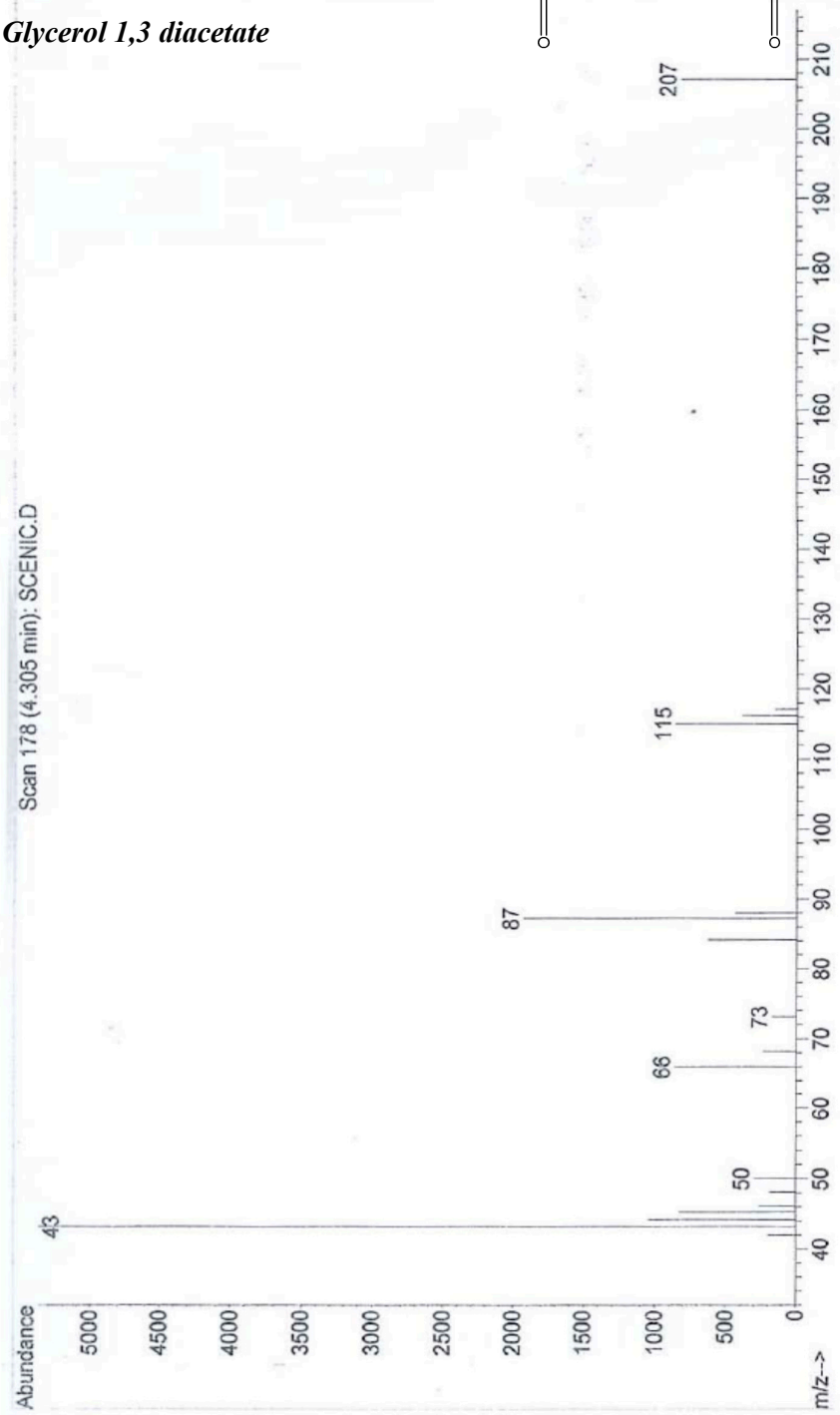


EI/MS Spectra

Sample 17a

Glycerol 1,3 diacetate

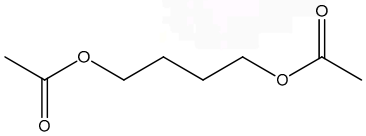




EI/MS Spectra

Sample 19a

Butanediol 1,4 diacetate



EI/MS Spectra

Sample 20a

n-octyl acetate