Optimized strategies to synthesize β-cyclodextrin–oxime conjugates as a new generation of organophosphate scavengers

Romain Le Provost,[a,b] Timo Wille,[c] Ludivine Louise,[a] Nicolas Masurier,[a,b] Susanne Müller,[c] Georg Reiter,[c] Pierre-Yves Renard,[a] Olivier Lafont,[b] Franz Worek,[c] François Estour*[a,b]

[a] UMR 6014 & FR 3038 CNRS, rue Tesnière, 76821 Mont-Saint-Aignan Cedex, France.

[b] Université de Rouen, UFR de Médecine-Pharmacie, Laboratoire de Pharmacochimie, 22 boulevard Gambetta, 76183 Rouen Cedex 1, France

[c] Bundeswehr Institute of Pharmacology and Toxicology, Munich, Germany

E-mail: francois.estour@univ-rouen.fr

Contents:

General :

A detailed NMR analysis is explained for compound **(22)** as a specific and representative example. Routine NMR ^{1}H and ^{13}C NMR spectra obtained for monosubstituted β-cyclodextrin derivatives **(18-25)** are given.

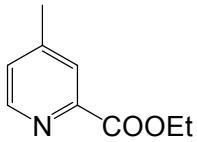
NMR spectra for the detailed analysis of compound **(22)** were recorded on a Bruker Advance DMX 500 instrument. All NMR experiments were performed (^{1}H at 500.13 MHz, ^{13}C at 125.75 MHz) in water-d_2 at 300 K with careful temperature regulation. The assignment of ^{1}H and ^{13}C signals was supported by one- and two-dimensional esperiments.

Routine NMR ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 instruments. All NMR were performed (^{1}H at 300 MHz, ^{13}C at 75 MHz) in dimethylsulfoxide-d_6 at 300 K.

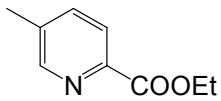
1. Experimental Procedures :

6-Methylpyridine-2-carbaldehyde was purchased from Sigma-Aldrich.

Ethyl 4-methylpicolinate 1a and ethyl 5-methypicolinate 2a: A solution of methylpicolinonitrile (1.28 g, 10.8 mmol) in HCl 3.3N in ethanol (19 mL) was refluxed overnight and concentrated. The crude product was dissolved in saturated $NaHCO_3$ and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give the desired product.



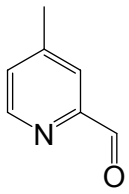
Ethyl 4-methypicolinate (1a): yellow oil, 86% yield; IR (KBr) ν_{max}/cm^{-1} 3455, 2982, 1740, 1715, 1602, 1366, 1301, 1210, 1123, 1098, 1024, 784; ^1H NMR ($CDCl_3$) δ 8.57 (d, 1H, J = 5 Hz, H6), 7.94 (s, 1H, H3), 7.27 (dd, 1H, J = 5, 1 Hz, H5), 4.41 (q, 2H, J= 7 Hz, CH_2CH_3), 2.41 (s, 3H, CH_3), 1.40 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 165.3 (C8), 149.5 (C6), 148.8 (C2), 147.9 (C4), 127.5 (C5), 125.9 (C3), 61.7 (CH_2CH_3), 20.9 (CH_3), 14.2 (CH_2CH_3); ESI-MS (m/z): 166 $[M+H]^+$, 188 $[M+Na]^+$; anal. calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48; found: C, 65.36; H, 6.52; N, 8.69.



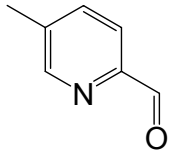
Ethyl 5-methylpicolinate (2a): yellow oil, 79% yield; IR (KBr) ν_{max}/cm^{-1} 3443, 2982, 1715, 1574, 1367, 1309, 1248, 1223, 1121, 1029, 783, 705; ^1H NMR ($CDCl_3$) δ 8.47 (d, 1H, J = 1 Hz, H6), 7.91 (d, 1H, J = 8 Hz, H3), 7.50 (dd, 1H, J = 8, 1 Hz, H4), 4.32 (q, 2H, J = 7 Hz, CH_2CH_3), 2.31 (s, 3H, CH_3), 1.30 (t, 3H, J = 7 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$): δ 165.2 (C8), 150.2 (C6), 145.5 (C2), 137.2 (C5), 137.1 (C4), 124.6 (C3), 61.6 (CH_2CH_3), 18.5 (CH_3), 14.2 (CH_2CH_3); ESI-MS (m/z): 166 $[M+H]^+$, 188 $[M+Na]^+$; anal. calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48; found: C, 65.11; H, 6.89; N, 8.64.

4-Methylpicolinaldehyde 1b and 5-methylpicolinaldehyde 2b: Ethyl methylpicolinate **(1a, 2a)** (1.5 g, 9.08 mmol) was dissolved in anhydrous dichloromethane (56 mL) and the solution

was cooled to -60°C. DIBAL-H (1 M in dichloromethane, 18.2 mL) was added dropwise and five minutes after the end of addition, the reaction mixture was treated with the addition of methanol (9 mL) and then with 10% aqueous solution of NaOH (40 mL). The organic layer was collected and the aqueous phase is extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the desired product.

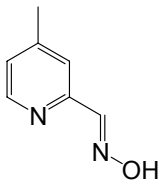


4-Methylpicolinaldehyde (1b): yellow oil, 80% yield; ^{1}H NMR ($CDCl_3$) δ 10.04 (s, 1H, H8), 8.61 (d, 1H, *J* = 5Hz, H6), 7.75 (s, 1H, H3), 7.32 (dd, 1H, *J* = 5, 1 Hz, H5), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 193.6 (C8), 152.6 (C2), 149.9 (C6), 148.5 (C5), 128.7 (C4), 122.4 (C5), 20.9 (CH_3); ESI-MS (m/z): 122 $[M+H]^+$.

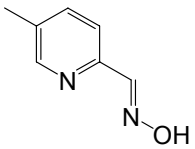


5-Methylpicolinaldehyde (2b): white solid, 78% yield; white solid, mp 165-167°C, ^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1H, H8), 8.55 (d, 1H, *J* = 1Hz, H6), 7.79 (d, 1H, *J* = 8 Hz, H3), 7.50 (dd, 1H, *J* = 8, 1 Hz, H4), 2.38 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 193.2 (C8), 150.7 (C6), 150.7 (C2), 138.7 (C5), 137.4 (C4), 121.4 (C3), 18.8 (CH_3); ESI-MS (m/z): 122 $[M+H]^+$.

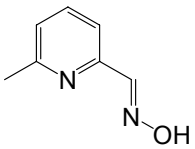
4-Methylpicolinaldehyde oxime 1c, 5-methylpicolinaldehyde oxime 2c and 6-methyl-picolinaldehyde oxime 3c: To a solution of methylpicolinaldehyde (0.74 g, 6.1 mmol) in ethanol (15 mL) was added hydroxylamine hydrochloride (0.63 g, 9.15 mmol) and sodium acetate (1.24 g, 9.15 mmol). The mixture was stirred at room temperature overnight and concentrated. The crude product was dissolved in ethyl acetate and washed with brine. The organic layer was then dried over Na_2SO_4 and concentrated to give the desired product.



4-Methyl-picolinaldehyde oxime (1c): white solid, 80% yield; IR (KBr) ν_{max}/cm^{-1} 3179, 2994, 2731, 1605, 1557, 1321, 976, 816, 782, 671; ^1H NMR ($CDCl_3$) δ 8.36 (d, 1H, *J* = 5 Hz, H6), 8.08 (s, 1H, H8), 7.70 (s, 1H, H3), 7.21 (dd, 1H, *J* = 5, 1 Hz, H5), 2.40 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 153.2 (C2), 150.3 (C4), 149.6 (C8), 149.3 (C6), 126.2 (C5), 122.4 (C3), 21.0 (CH_3); ESI-MS (m/z): 137 $[M+H]^+$; anal. calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58; found: C, 61.82; H, 5.64; N, 20.52.



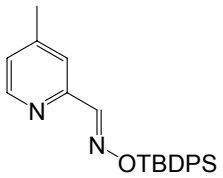
5-Methylpicolinaldehyde oxime (2c): white solid, 158-159 °C, 88% yield; IR (KBr) ν_{max}/cm^{-1} 3170, 2983, 2867, 2720, 1522, 1484, 1318, 1215, 989, 793, 655; ^1H NMR ($CDCl_3$) δ 9.34 (s, 1H, H9), 8.45 (s, 1H, H6), 8.29 (s, 1H, H8), 7.70 (d, 1H, *J* = 8 Hz, H3), 7.51 (dd, 1H, *J* = 8, 2 Hz, H4), 2.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 150.7 (C6), 150.0 (C8), 149.1 (C2), 137.4 (C4), 134.2 (C5), 120.6 (C3), 18.5 (CH_3); ESI-MS (m/z): 137 $[M+H]^+$; anal. calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58; found: C, 61.72; H, 5.96; N, 20.50.



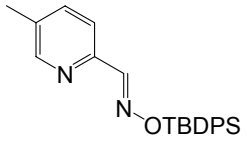
6-Methylpicolinaldehyde oxime (3c): white solid, 170-171°C, 91% yield; IR (KBr) ν_{max}/cm^{-1} 2749, 1593, 1576, 1518, 1460, 1401, 1325, 1251, 1161, 1004, 976, 786, 733, 654; ^1H NMR ($CDCl_3$) δ 8.08 (s, 1H, H8), 7.63 (m, 2H, H3 and H4), 7.20 (dd, 1H, *J* = 7, 2 Hz, H5), 2.51 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 159.3 (C6), 152.9 (C2), 149.6 (C8), 138.7 (C4), 124.8 (C5), 118.8 (C3), 23.7 (CH_3); ESI-MS (m/z): 136($M^{+\bullet}$), 106 (-NOH), 93 (-CH); anal. calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58; found: C, 61.76; H, 5.89; N, 20.64.

4-Methylpicolinaldehyde O-tert-butyldiphenylsilyl oxime 1d, 5-methylpicolin-aldehyde O-tert-butyldiphenylsilyl oxime 2d and 6-methylpicolinal-dehyde O-tert-butyldiphe-nylsilyl oxime 3d: Pyridine aldoxime **(1c - 3c)** (0.9 g, 6.6 mmol) and imidazole (0.58 g, 8.58 mmol) were dissolved in anhydrous dichloromethane (20 mL). *Tert*-butyldiphenylsilylchloride (2.2 mL, 8.58 mmol) was added dropwise and the mixture was stirred at room temperature overnight. Water was added to the mixture and the organic layer was collected. The organic layer was then washed with saturated NaCl, dried over Na_2SO_4 and concentrated to give a

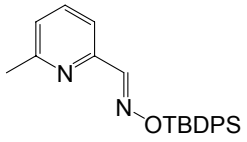
yellow oil which was purified by flash chromatography with a dichloromethane/cyclohexane (0:100 to 50/50) to give the desired product.



4-Methylpicolinal-dehyde O-tert-butyldiphe-nylsilyl oxime (1d): colorless oil, 82% yield; IR (KBr) ν_{max}/cm^{-1} 2932, 2857, 1594, 1471, 1427, 1338, 1108, 959, 935, 850, 823, 760, 702, 651; ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H, H8), 8.47 (d, 1H, *J* =5 Hz, H6), 7.78 (m, 4H, CH-Ph), 7.62 (s, 1H, H3), 7.38 (m, 6H, CH-Ph), 7.05 (dd, 1H, *J* = 5, 1 Hz, H5), 2.30 (s, 3H, CH_3), 1.20 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 155.7 (C8), 151.8 (C2), 149.2 (C6), 147.6 (C4), 135.6 (CH-Ph), 133.4 (C-Ph), 129.8 (CH-Ph), 127.7 (CH-Ph), 125.3 (C5), 121.4 (C3), 27.2 ($C(CH_3)_3$), 21.1 ($C(CH_3)_3$), 19.5 (CH_3); ESI-MS (m/z): 375 $[M+H]^+$, 397 $[M+Na]^+$; anal. calcd for $C_{23}H_{26}N_2OSi$: C, 73.75; H, 7.00; N, 7.48; found: C, 73.68; H, 6.88; N, 7.42.

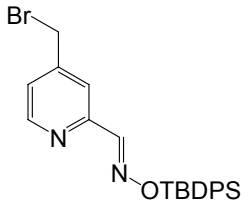


5-Methylpicolin-aldehyde O-tert-butyldiphenylsilyl oxime (2d): colorless oil, 93% yield; IR (KBr) ν_{max}/cm^{-1} 2944, 2859, 1567, 1483, 1427, 1334, 1114, 948, 815, 702, 609; ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H, H8), 8.43 (s, 1H, H6), 7.74 (m, 4H, CH-Ph), 7.68 (d, 1H, *J* = 8 Hz, H3), 7.38 (m, 7H, H4, CH-Ph), 2.33 (s, 3H, CH_3), 1.17 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 155.4 (C6), 149.9 (C8), 149.5 (C2), 137.0 (C4), 135.6 (CH-Ph), 134.1 (C5), 133.5 (C-Ph), 129.8 (CH-Ph), 127.7 (CH-Ph), 120.4 (C3), 27.2 ($C(CH_3)_3$), 19.5 ($C(CH_3)_3$), 18.5 (CH_3); ESI-MS (m/z): 375 $[M+H]^+$, 397 $[M+Na]^+$; anal. calcd for $C_{23}H_{26}N_2OSi$: C, 73.75; H, 7.00; N, 7.48; found: C, 73.46; H, 7.29; N, 6.97.

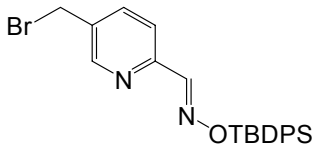


6-Methylpicolinaldehyde O-tert-butyldiphenylsilyl oxime (3d): colorless oil, 94% yield; IR (KBr) ν_{max}/cm^{-1} 2960, 2858, 1587, 1458, 1428, 1115, 990, 956, 855, 736, 699, 613; ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H, H8), 7.78 (m, 4H, CH-Ph), 7.62 (d, 1H, *J*= 8 Hz, H3), 7.47 (t, 1H, *J*= 8

Hz, H4), 7.38 (m, 6H, CH-Ph), 7.08 (d, 1H, *J*= 8 Hz, H5), 2.58 (s, 3H, CH_3), 1.20 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 158.2 (C6), 155.7 (C8), 151.4(C2), 136.6 (C4), 135.6 (CH-Ph), 133.4 (C-Ph), 129.8 (CH-Ph), 127.7 (CH-Ph), 123.7 (C5), 117.8 (C3), 27.2 ($C(CH_3)_3$), 24.4 (CH_3), 19.5 ($C(CH_3)_3$); ESI-MS (m/z): 317 (-*t*Bu); anal. calcd for $C_{23}H_{26}N_2OSi$: C, 73.75; H, 7.00; N, 7.48; found: C, 73.71; H, 6.92; N, 7.42.

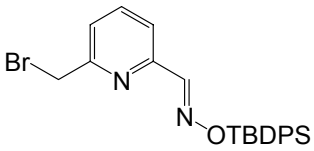


4-Bromomethylpicolinaldehyde,O-tert-butyldiphenylsilyloxime (1): To a solution of 5-methylpyridine **(4d)** (3.9 g, 10.4 mmol) in tetrachloromethane (104 ml) was added freshly recristallized *N*-bromosuccinimide (1.8 g, 10.4 mmol). The reaction was activated by a halogen lamp and followed by ^1H NMR. After 5 hours, the mixture was concentrated under vacuum and purified on silica gel chromatography with a cyclohexane/DCM (100:0 to 30:70) mixture to give the desired product (1.4 g,). Brown oil, 30% yield; IR (KBr) ν_{max}/cm^{-1} 3413, 3057, 2931, 2845, 1592, 1470, 1427, 1114, 950, 849, 700, 700, 600, 523, 503; ^1H NMR ($CDCl_3$) δ 8.58 (d, 1H, *J* = 5 Hz, H6), 8.50 (s, 1H, H8), 7.73 (m, 4H, CH-Ph), 7.38 (m, 7H, H3, CH-Ph), 7.27 (dd, 1H, *J* = 5, 1 Hz, H5), 4.33 (s, 2H, CH_2Br), 1.16 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 155.2 (C8), 152.8 (C2), 150.1 (C6), 146.7 (C4), 135.6 (CH-Ph), 133.3 (C-Ph), 129.9 (CH-Ph), 127.8 (CH-Ph), 124.2 (C5), 120.4 (C3), 30.4 (CH_2Br), 27.2 ($C(CH_3)_3$), 19.5 ($C(CH_3)_3$); ESI-MS (m/z): 453 $[M+H]^+$; anal. calcd for $C_{23}H_{25}BrN_2OSi$: C, 60.92; H, 5.56; N, 6.18; found: C, 60.72; H, 5.55; N, 6.17.



5-Bromomethylpicolinaldehyde,O-tert-butyldiphenylsilyloxime (2): To a solution of 5-methylpyridine **(3d)** (1.46 g, 3.9 mmol) in tetrachloromethane (20 ml) was added freshly recristallized *N*-bromosuccinimide (695 mg, 3.9 mmol). The reaction was activated by a 300W halogen lamp and followed by ^1H NMR. After 1 hour, the mixture was concentrated under vacuum and purified on silica gel chromatography with a cyclohexane/DCM (100:0 to 30:70) mixture to give the desired product (850 mg). Brown solid, 50% yield; mp 85-87°C; IR (KBr) ν_{max}/cm^{-1} 2929, 2855, 1591, 1471, 1427, 1114, 949, 825, 698, 615; ^1H NMR

($CDCl_3$) δ 8.61 (d, *J* = 1 Hz, H6), 8.50 (s, 1H, H8), 7.73 (m, 4H, CH-Ph), 7.64 (d, 1H, *J* = 8, 1 Hz, H3), 7.38 (m, 7H, H4, H11 and H12), 4.45 (s, 2H, CH_2Br), 1.17 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 155.2 (C6), 152.5 (C8), 149.9 (C2), 137.6 (C4), 136.0 (CH-Ph), 134.6 (C5), 133.7 (C-Ph), 130.3 (CH-Ph), 128.2 (CH-Ph), 121.2 (C3), 29.8 (CH_2Br), 27.6 ($C(CH_3)_3$), 19.9 ($C(CH_3)_3$); ESI-MS (m/z): 453 $[M+H]^+$, 928 $[2M+Na]^+$; anal. calcd for $C_{23}H_{25}BrN_2OSi$: C, 60.92; H, 5.56; N, 6.18; found: C, 61.42; H, 5.53; N, 6.27.



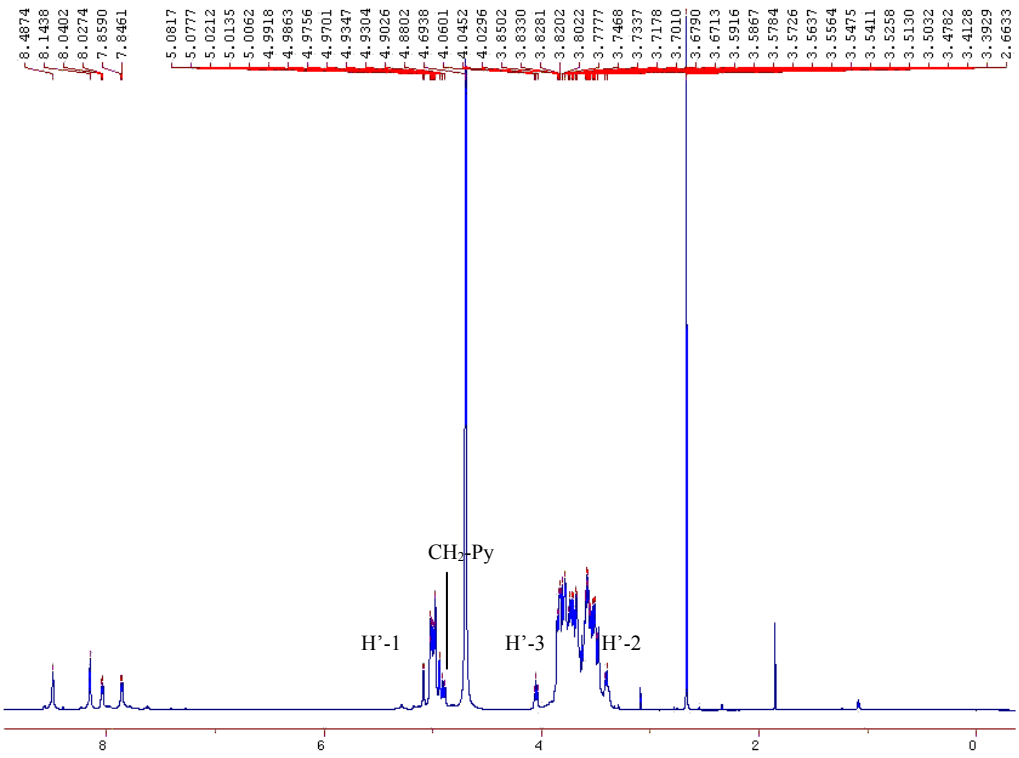
6-Bromomethylpicolinaldehyde,O-tert-butyldiphenylsilyloxime (3): To a solution of 6-methylpyridine **(2d)** (5.5 g, 14.7 mmol) in tetrachloromethane (165 ml) was added freshly recristallized *N*-bromosuccinimide (5.2 g, 29.4 mmol) and AIBN (120 mg, 0.73 mmol). The mixture was stirred under reflux and the reaction was followed by ^1H NMR. After six days of heating, the mixture was concentrated under vacuum and purified on silica gel chromatography with a cyclohexane/dichloromethane (100:0 to 75:25) mixture to give the desired product (2.56 g). White solid, 39% yield; mp 107-109°C; IR (KBr) ν_{max}/cm^{-1} 3049, 2949, 2858, 1571, 1457, 1427, 1115, 979, 936, 859, 820, 739, 700, 635, 521; ^1H NMR ($CDCl_3$) δ 8.52 (s, 1H, H8), 7.74 (m, 4H, CH-Ph), 7.70 (d, 1H, *J* = 8 Hz, H3), 7.59 (t, 1H, *J* = 8 Hz, H4), 7.46-7.36 (m, 7H, H11, CH-Ph), 4.55 (s, 2H, CH_2Br), 1.18 (s, 9H, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 156.7 (C6), 155.1 (C8), 152.1(C2), 137.5 (C4), 135.6 (CH-Ph), 133.3 (C-Ph), 129.9 (CH-Ph), 127.7 (CH-Ph), 123.9 (C5), 120.1 (C3), 33.6 (CH_2Br), 26.7 ($C(CH_3)_3$), 19.1 ($C(CH_3)_3$); ESI-MS (m/z): 395, 397 $[M-tBu]^{+\bullet}$; anal. calcd for $C_{23}H_{25}BrN_2OSi$: C, 60.92; H, 5.56; N, 6.18; found: C, 60.78; H, 5.61; N, 6.11.

2. Detailed NMR analysis of compound (9)

Identification of 2-monosubstituted β-CD regioisomers was carried out using a previously described methodology[1].

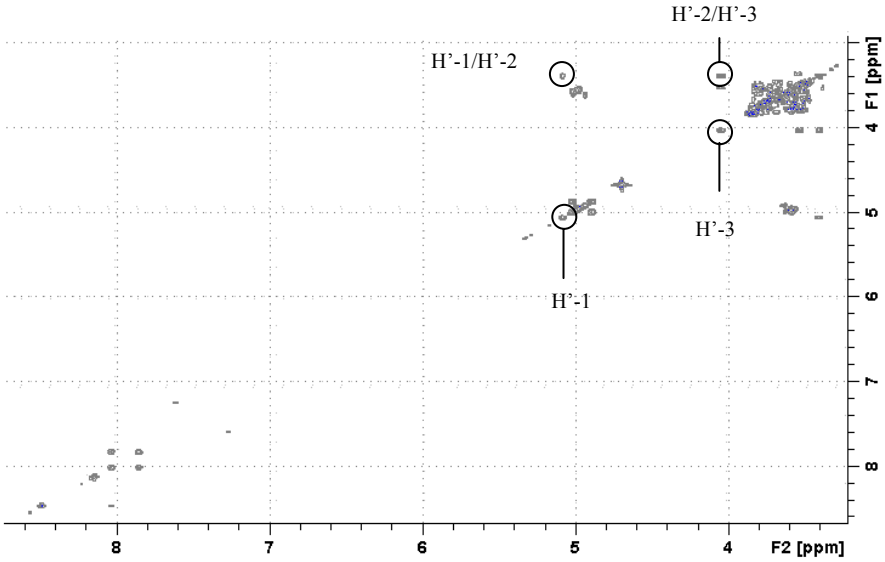
In the case of compound **(9)**, the ^{1}H NMR and COSY correlation revealed four relatively distinct signals at 3.40 ppm (H'-2), 4.04 ppm (H'-3), 4.89 ppm (CH_2-Py) and 5.08 ppm (H'-1).

*2.1 ^{1}H NMR spectrum of **(9)** (D_2O, 500 MHz)*



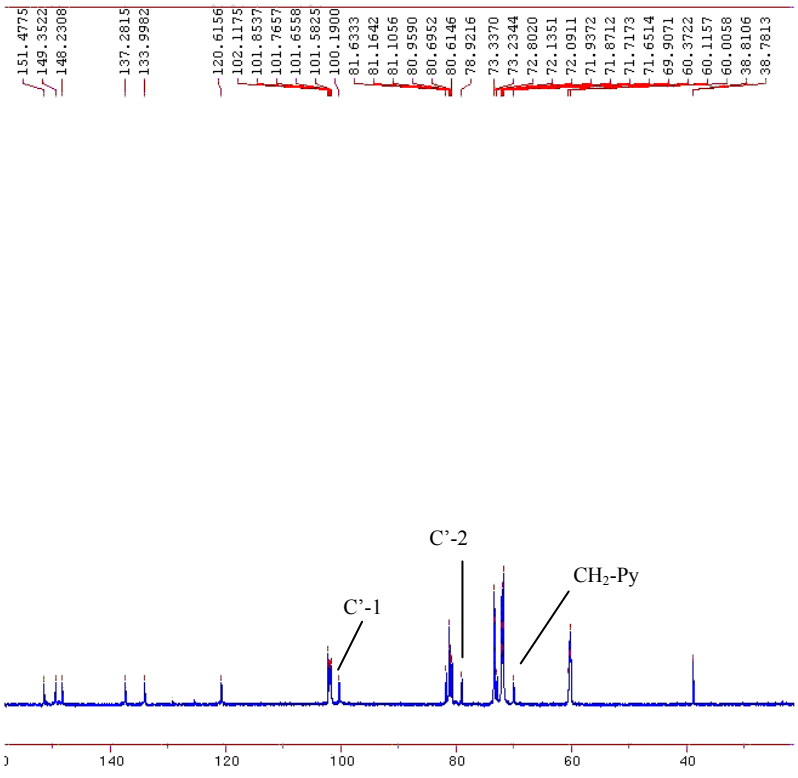
[1] N. Masurier, O. Lafont, R. Le Provost, D. Lesur, P. Masson, F. Djedaïni-Pilard, F. Estour, *Chem. Commun*. **2009**, 589-591.

*2.2 Partial contour plot of COSY experiment of **(9)** (D_2O, 500 MHz)*

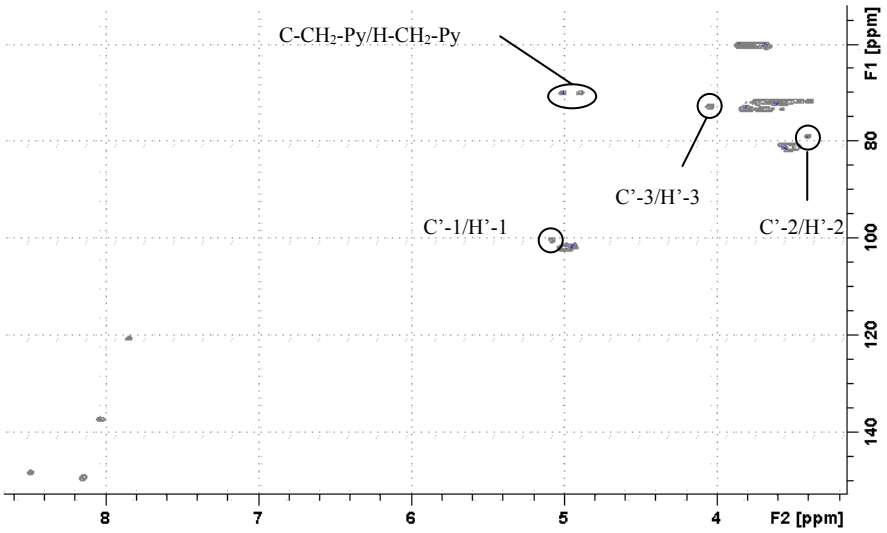


The single HMQC correlation between the carbon signal of C-6 and the corresponding proton signals established that no substitution occurred at O-6. The HMQC allowed to assign carbons at 69.9 ppm (CH_2-Py), 72.8 ppm (C'-3), 78.9 ppm (C'-2) and 100.2 ppm (C'1).

*2.3 ^{13}C NMR spectrum of **(9)** (D_2O, 127.75 MHz)*

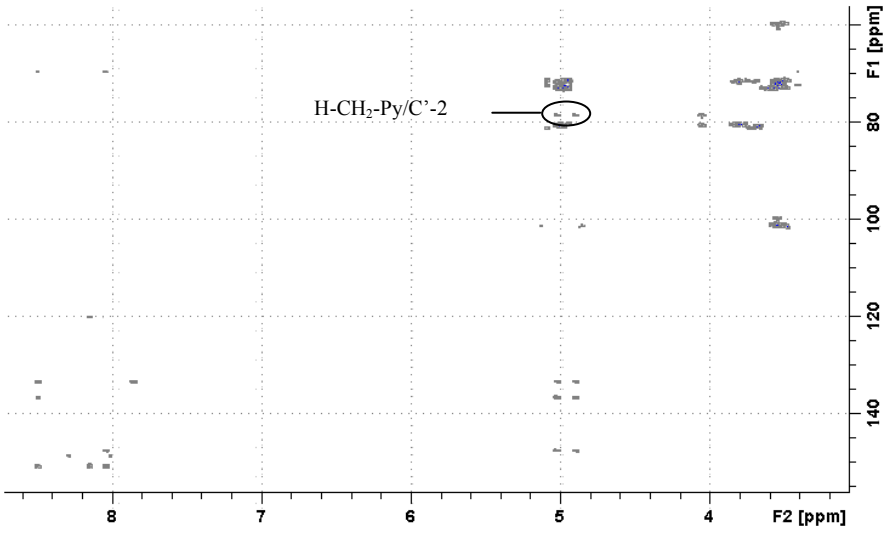


*2.4 Partial contour plot of HMQC experiment of **(9)** (D_2O, 500 MHz)*



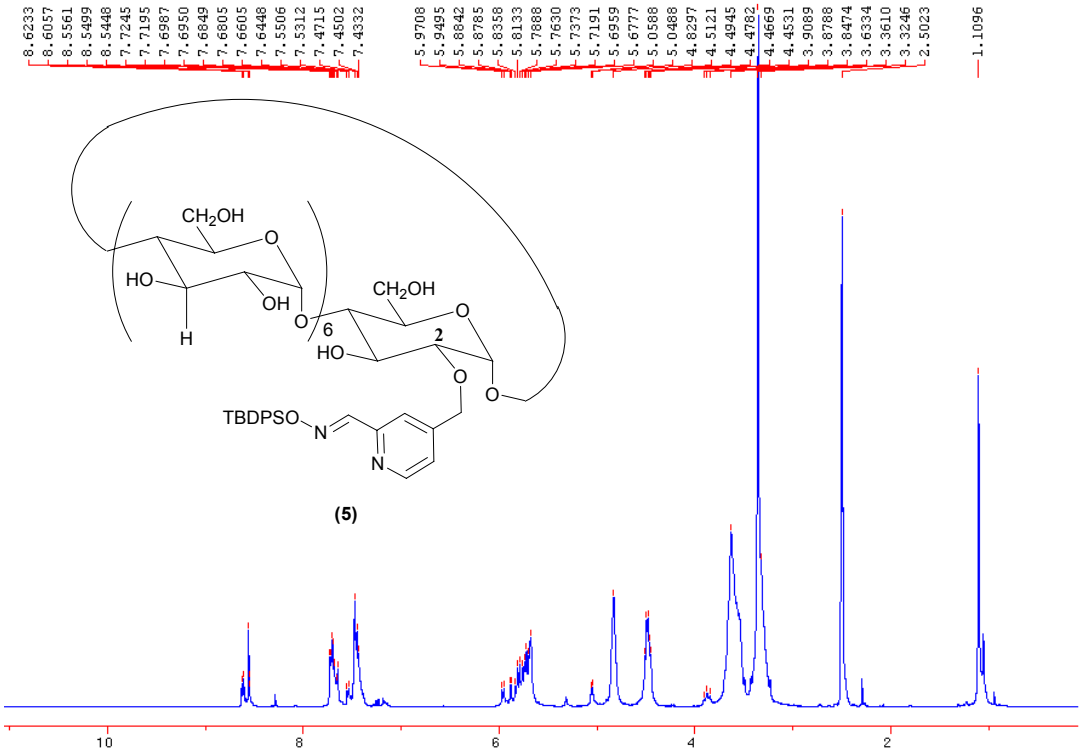
Finally, the presence of an HMBC correlation between the pyridinic protons signal (4.89 and 5.01 ppm) and the carbon C'-2 proved the 2-O substitution in **(9)**.

*2.5 Partial contour plot of HMBC experiment of **(9)** (D_2O, 500 MHz)*

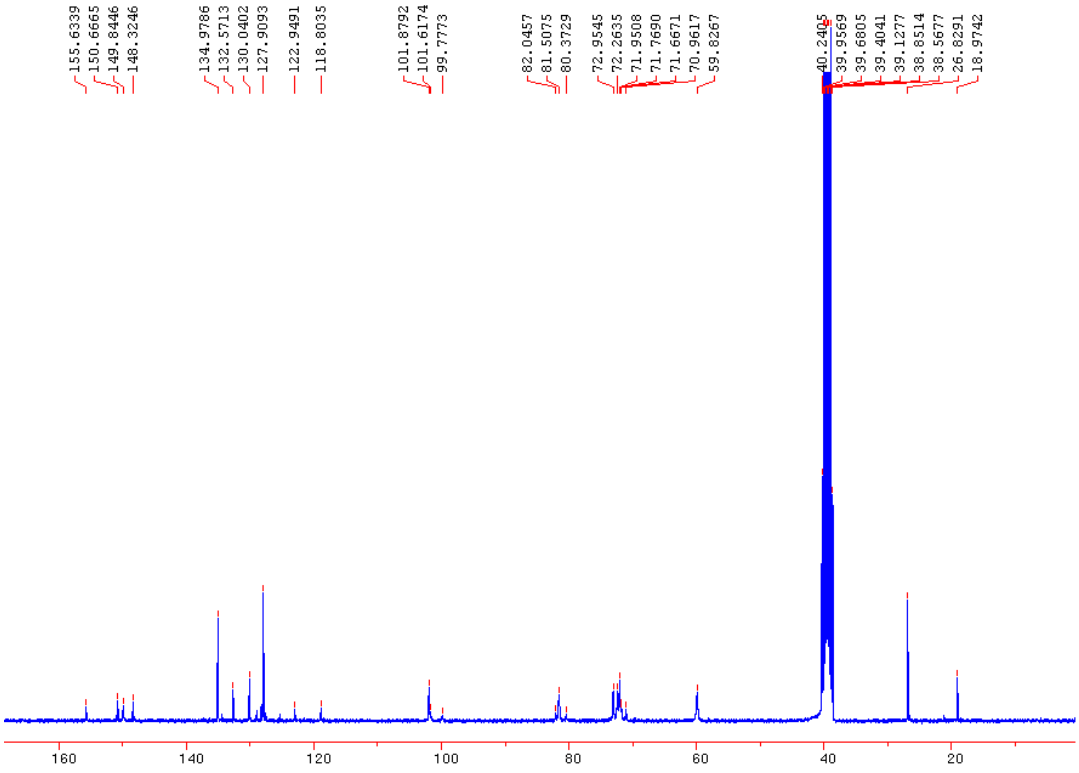


3. Routine NMR analysis

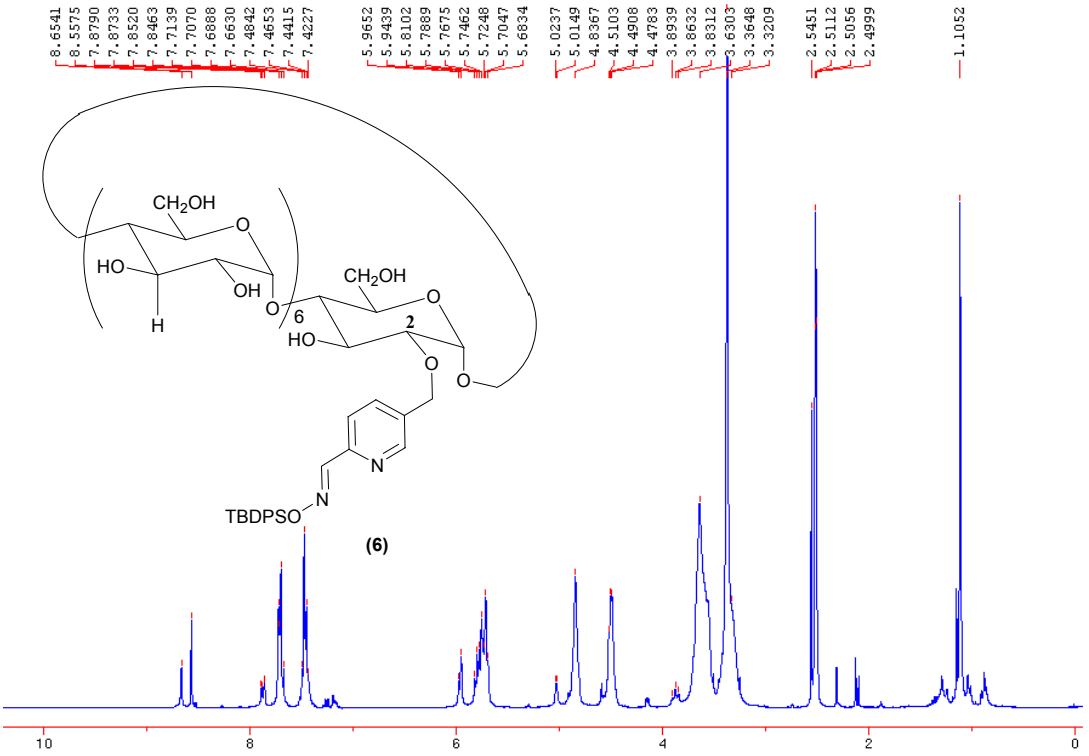
*4.1.1 ^{1}H NMR spectrum of **(5)** (DMSO d_6, 300 MHz)*



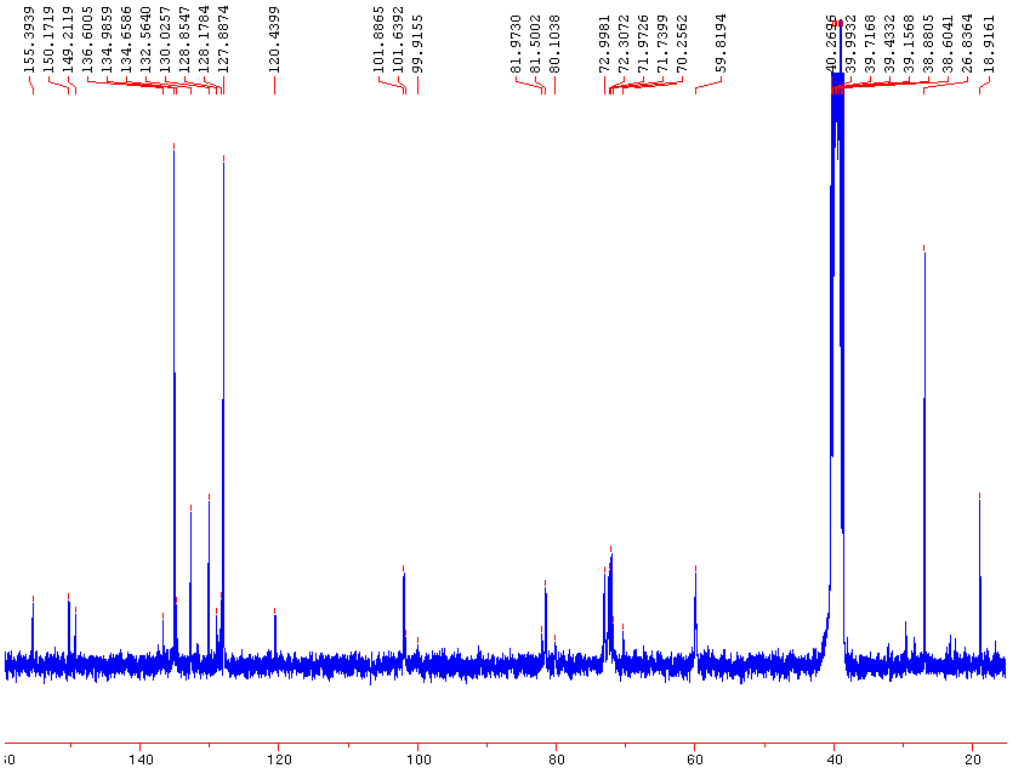
*4.1.2 ^{13}C NMR spectrum of **(5)** (DMSO d_6, 75 MHz)*



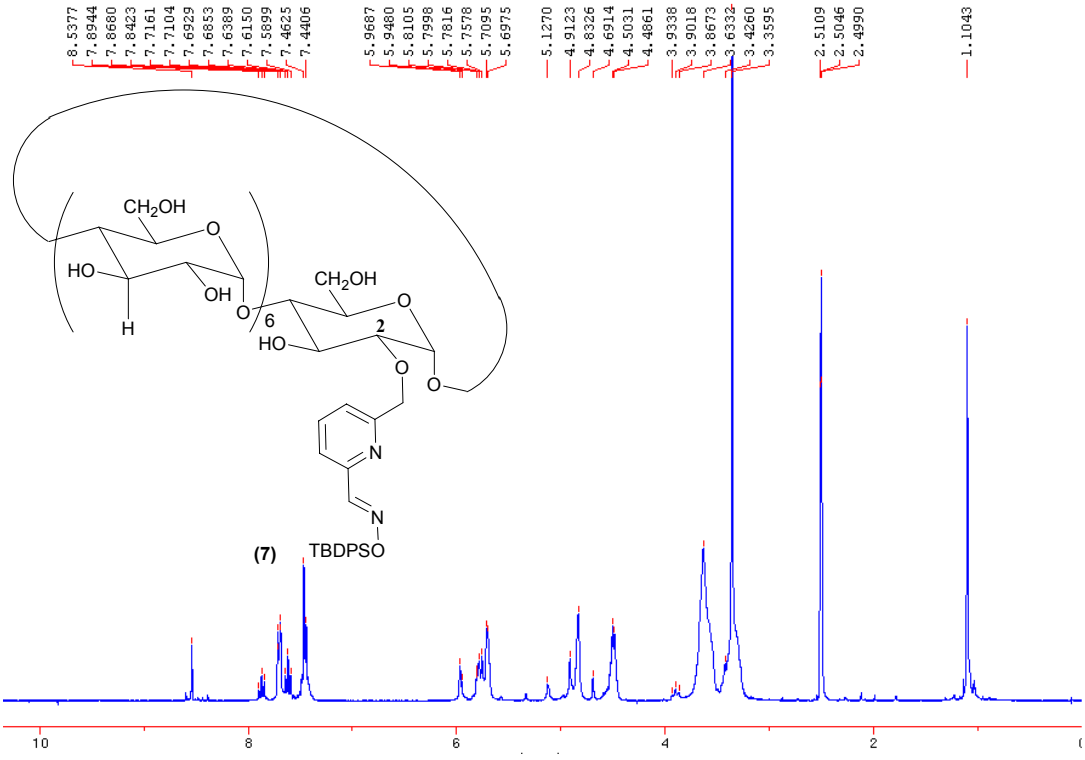
4.2.1 ^{1}H NMR spectrum of **(6)** (DMSO d_6, 300 MHz)



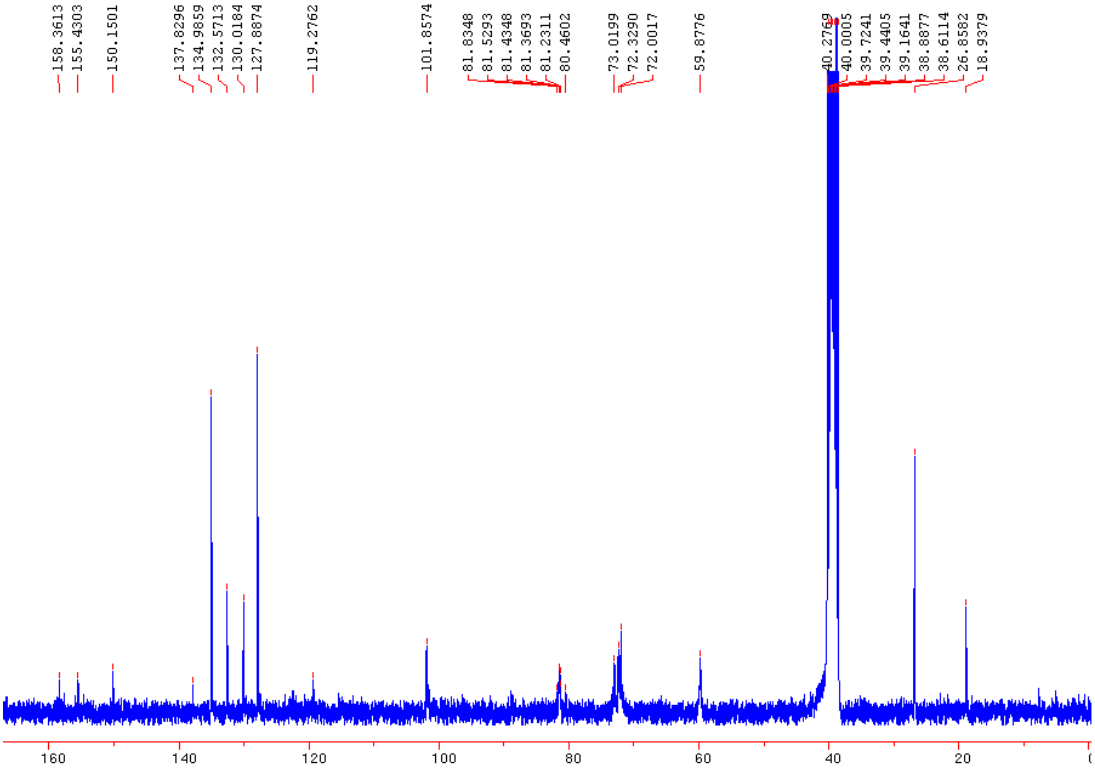
4.2.2 ^{13}C NMR spectrum of **(6)** (DMSO d_6, 75 MHz)



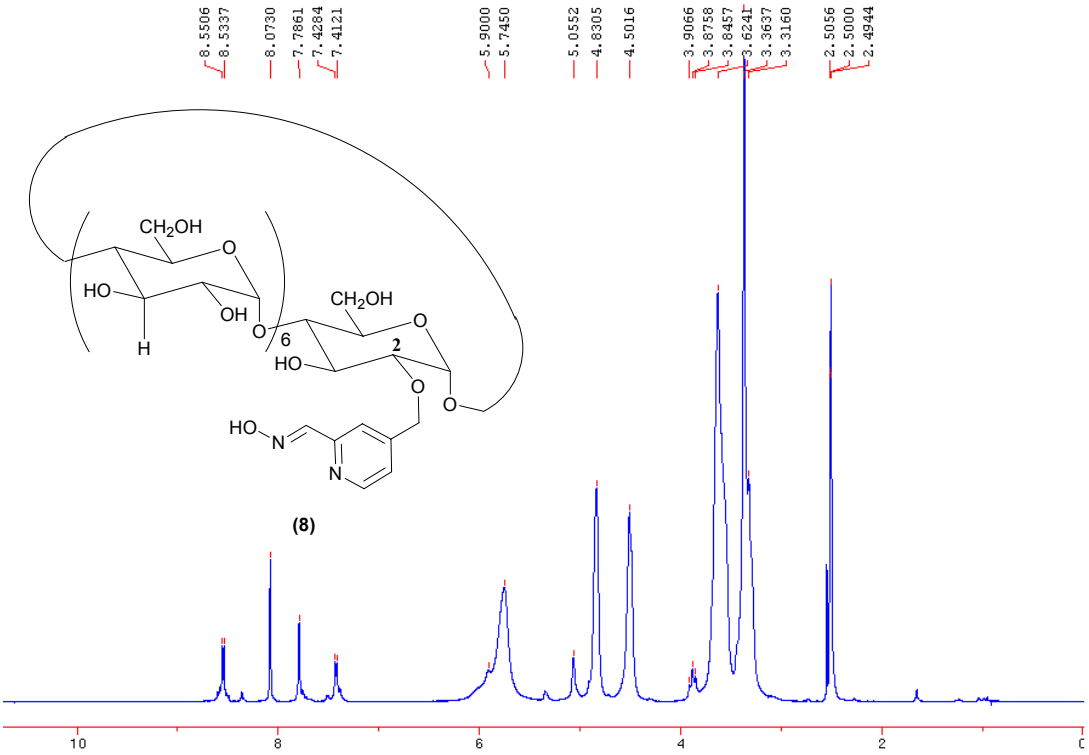
4.3.1 *^{1}H NMR spectrum of **(7)** (DMSO d_6, 300 MHz)*



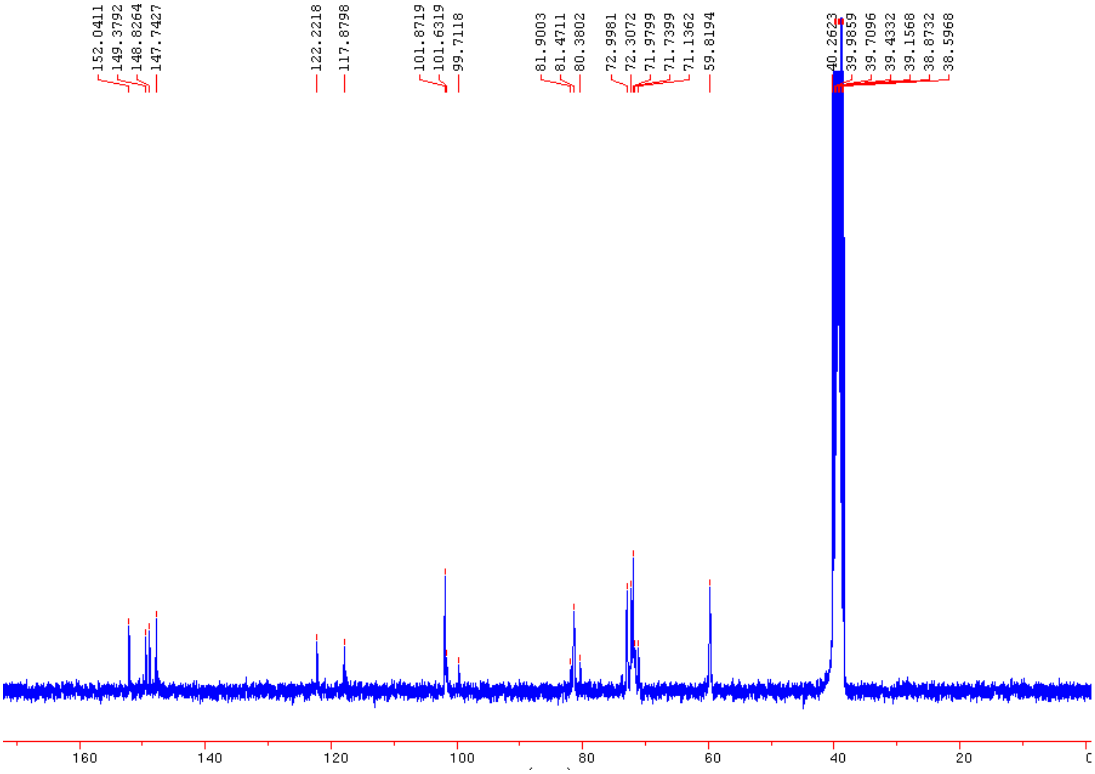
4.3.2 *^{13}C NMR spectrum of **(7)** (DMSO d_6, 75 MHz)*



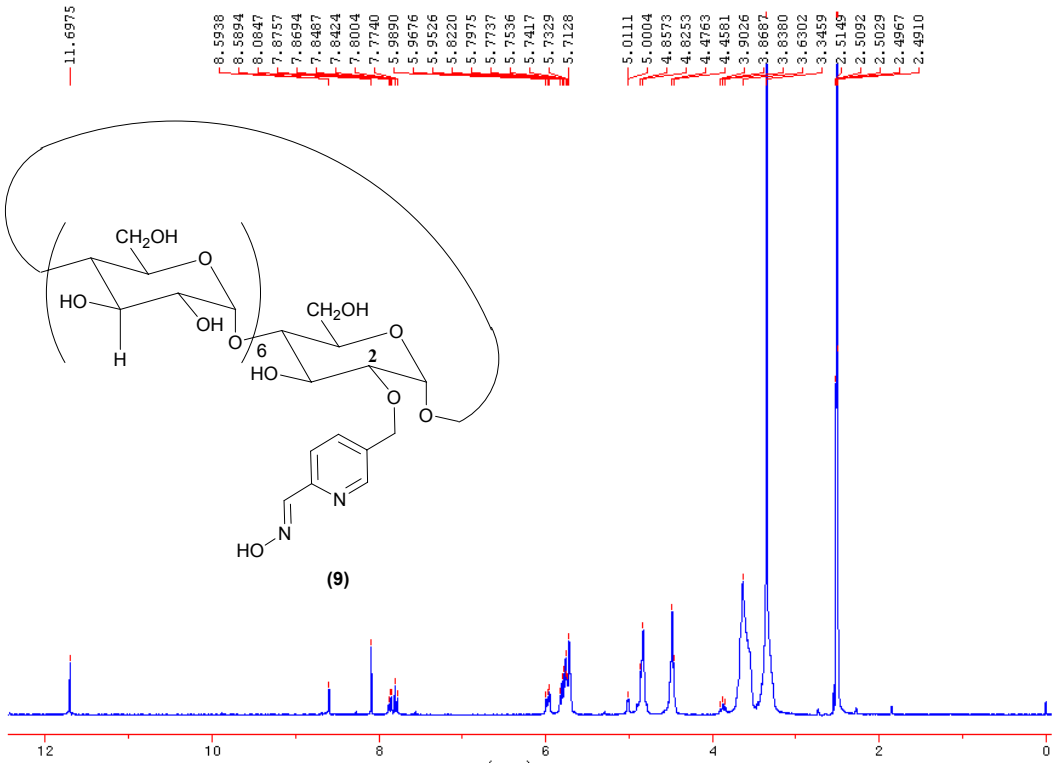
4.4.1 *^{1}H NMR spectrum of **(8)** (DMSO d_6, 300 MHz)*



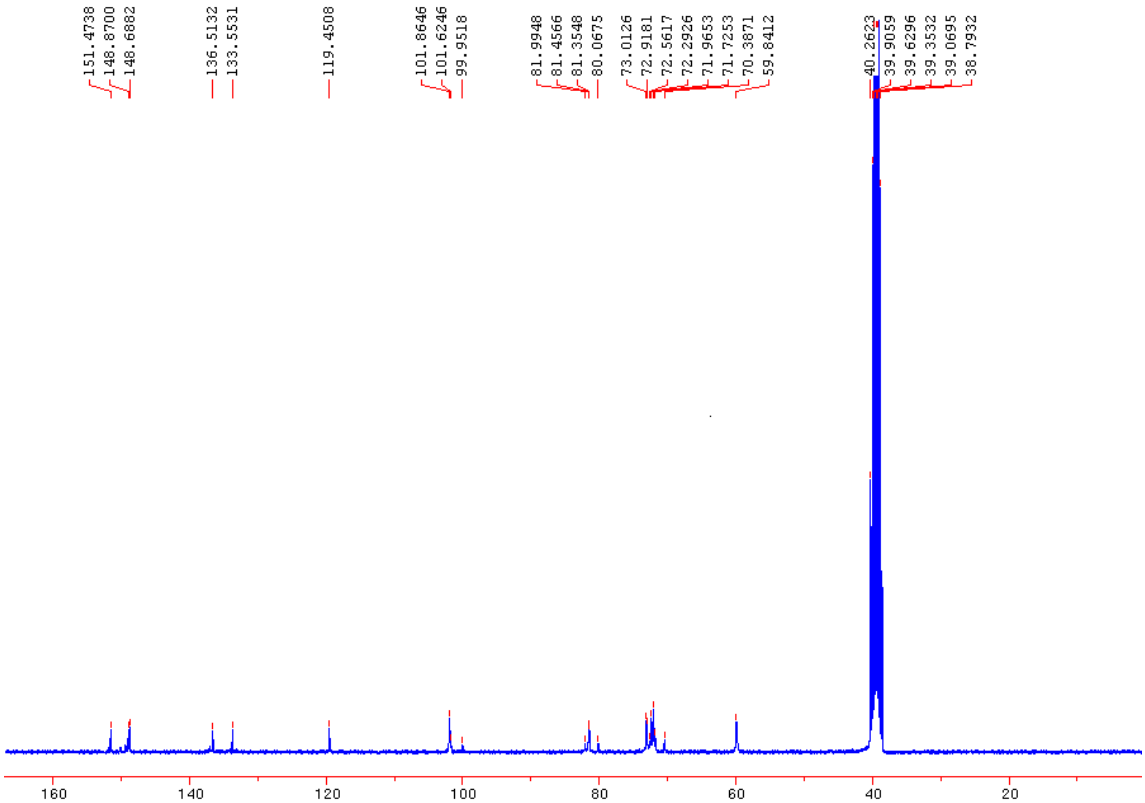
4.4.2 *^{13}C NMR spectrum of **(8)** (DMSO d_6, 75 MHz)*



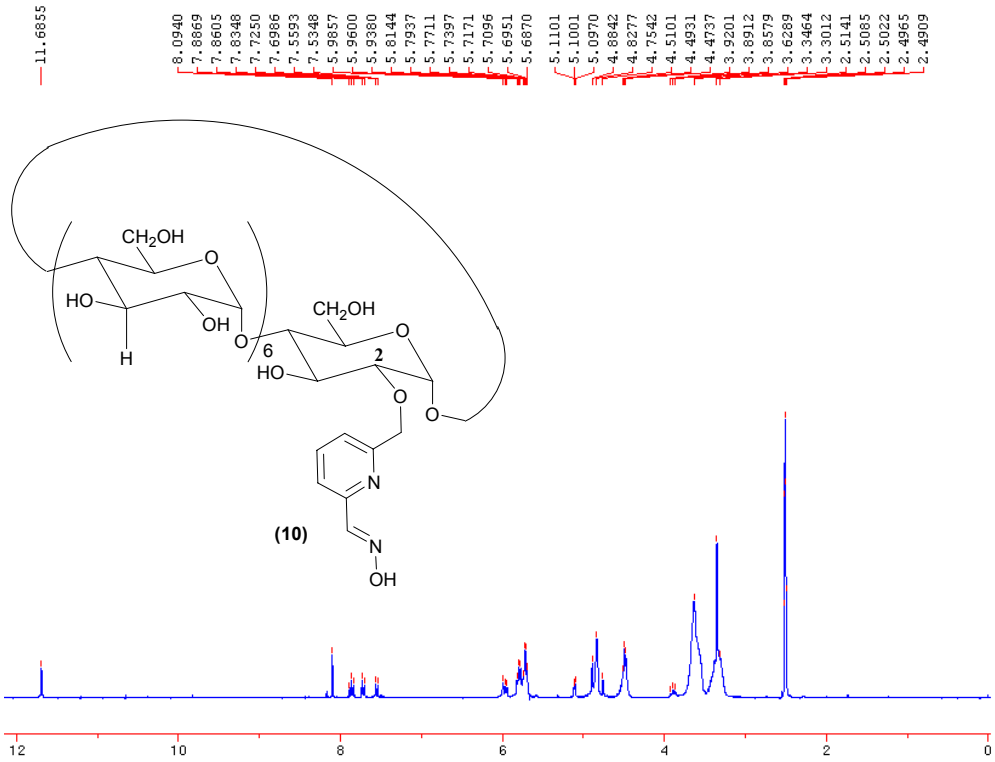
4.5.1 *^{1}H NMR spectrum of **(9)** (DMSO d_6, 300 MHz)*



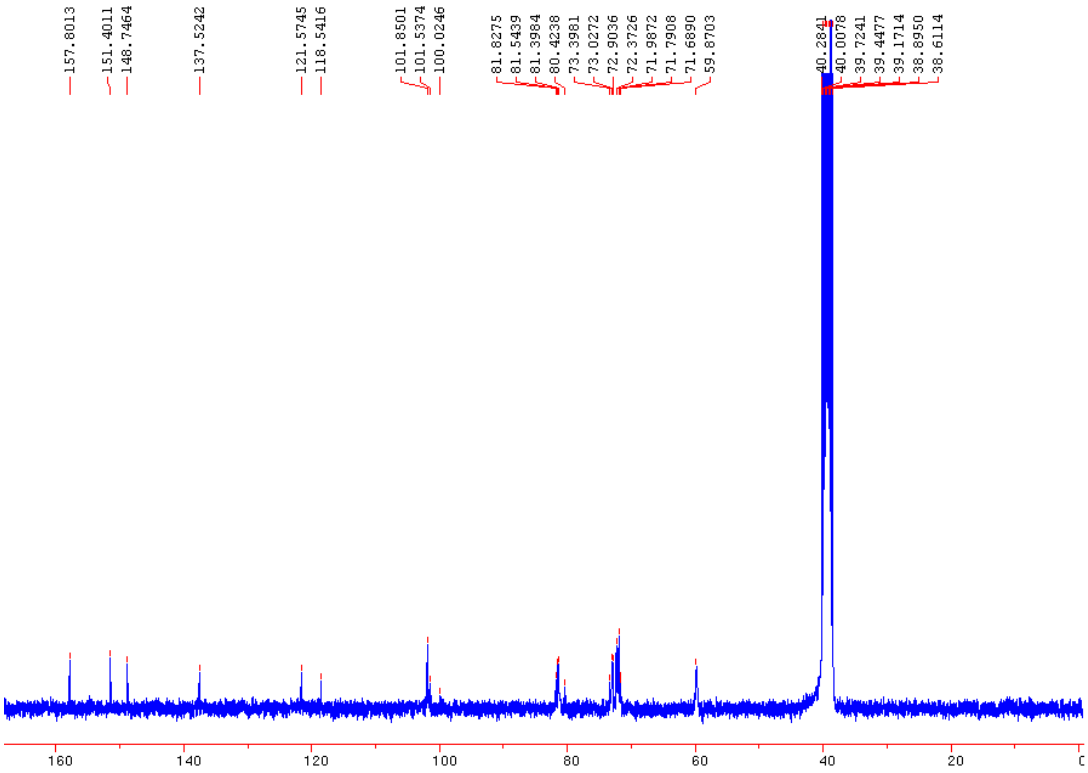
4.5.2 *^{13}C NMR spectrum of **(9)** (DMSO d_6, 75 MHz)*



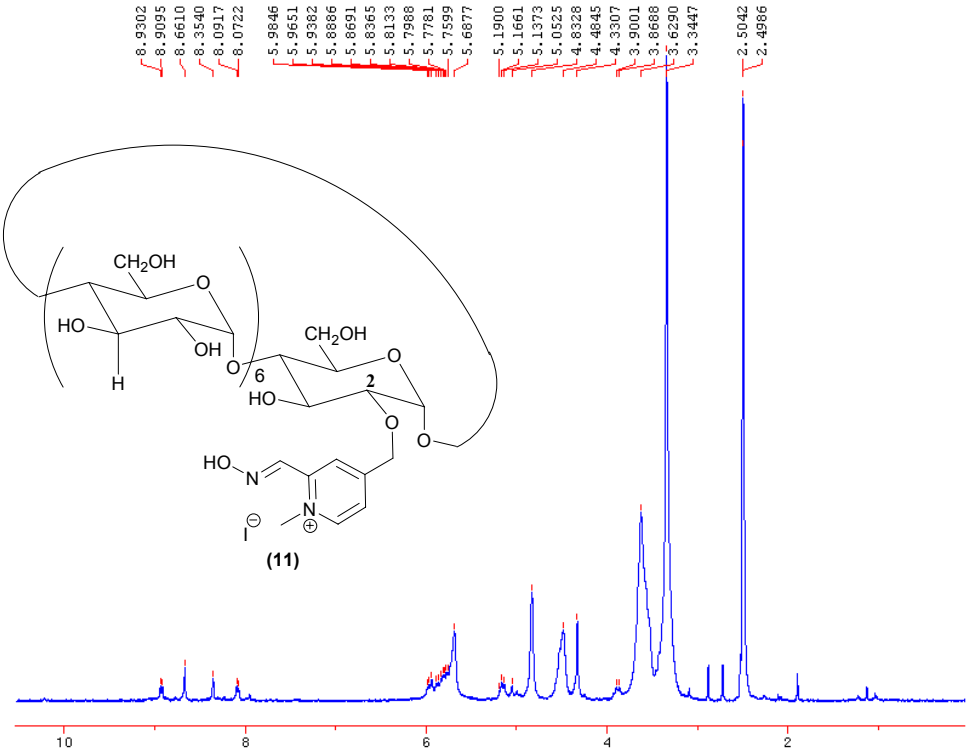
4.6.1 *^{1}H NMR spectrum of **(10)** (DMSO d_6, 300 MHz)*



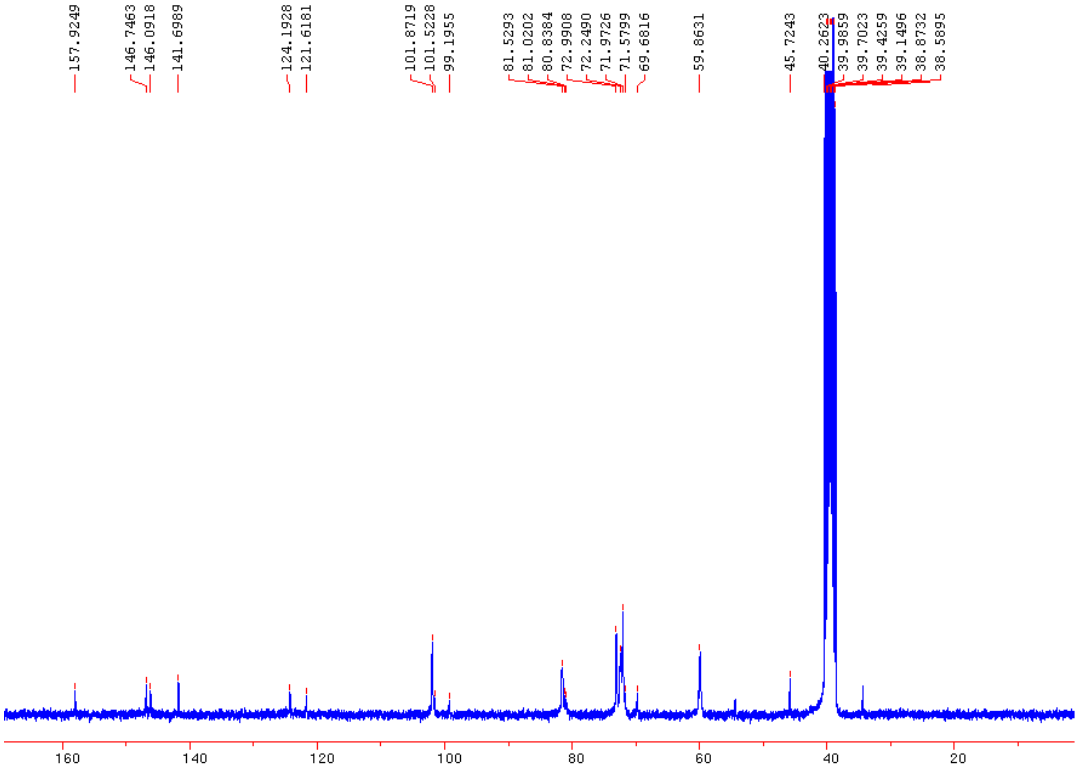
4.6.2 *^{13}C NMR spectrum of **(10)** (DMSO d_6, 75 MHz)*



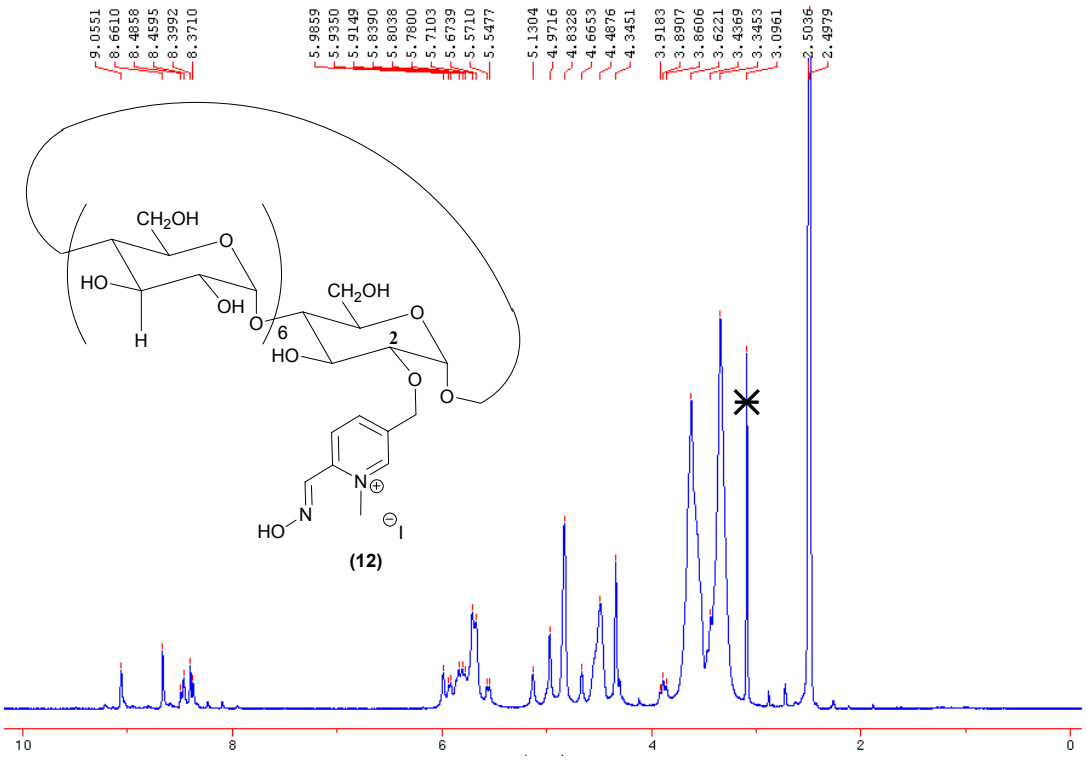
4.7.1 *^{1}H NMR spectrum of **(11)** (DMSO d_6, 300 MHz)*



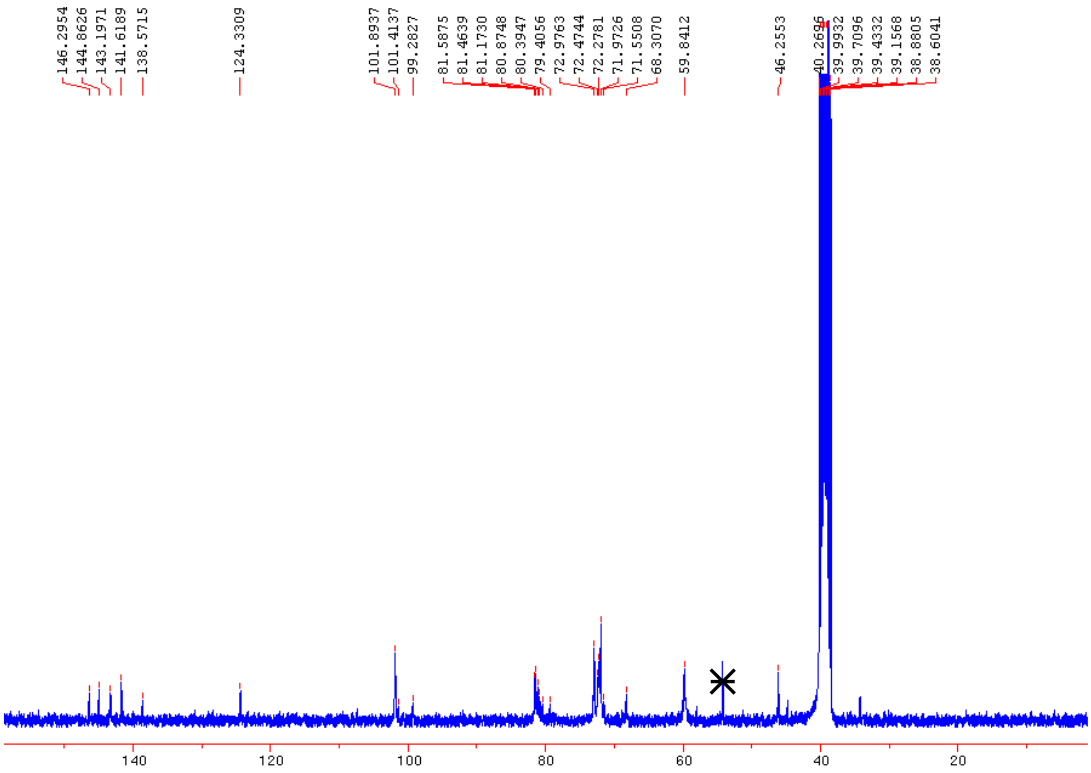
4.7.2 *^{13}C NMR spectrum of **(11)** (DMSO d_6, 75 MHz)*



4.8.1 *^{1}H NMR spectrum of **(12)** (DMSO d_6, 300 MHz)*



4.8.2 *^{13}C NMR spectrum of **(12)** (DMSO d_6, 75 MHz)*



5. Kinetic course of cyclosarin hydrolysis by pyridine-2-aldoxime methiodide