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An Efficient Protocol for Accessing β-Amino Dicarbonyl Compounds through aza-Michael Reaction

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General remarks

All common laboratory chemicals were purchased from commercial sources and used without further purification. Melting points were determined using a Thomas Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 310 spectrometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 300 spectrometer and TMS as an internal standard. Coupling constants (*J*) are given in hertz. The FAB mass spectra were obtained on a Hewlett-Packard 5989A Mass Spectrometer (70 eV). Elemental analyses (C, N and H) were performed by the Service Central Analyses (CURI, Université Sidi Mohamed Ben Abdellah, Fès, Morocco) and the results lay within the acceptable range (±0.4%). CCD Saphire 3 Xcalibur diffractometer (Oxford Diffraction) with graphite monochromatized MoKα radiation was used to record the X-ray analysis.

General procedure

To a solution of ethyl malonate (15 g, 93 mmol) in 40 mL of ethanol, were added the respective aldehyde (100 mmol), 1.5 mL of piperidine and 1 mL of glacial acetic acid. Then the mixture was stirred at refluxing temperature of ethanol for 12 h, until thin-layer chromatography indicated the complete consume of the starting material. After removing solvent, the crude product was washed with a saturated solution of sodium bisulfite (20 mL). The product was extracted by diethyl ether (2 x 20 mL), dried with sodium sulphate and evaporated to give the respective pure oil.

Diethyl 2-benzylidenemalonate (**4a**): Yellow oil, 71% of yield, Rf 0.7 (ether/*n*-hexane, 1/1). IR (KBr): ν_{max}/cm^{-1} 2875-2982 (CH), 1722 (C=O), 1629 and1497 (C=C), 1294-1254 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, 3H, H_2C-C$\underline{H}_3$, ^{3}J 7.1 Hz), 1.31 (t, 3 H, CH_2-C$\underline{H}_3$, ^{3}J 7.1 Hz), 4.28 (q, H, C$\underline{H}_2$-CH_3, ^{3}J 7.2 Hz), 4.32 (q, 2H, C$\underline{H}_2$-CH_3, ^{3}J 7.2 Hz), 7.45–7.32 (m, 5H, Ph), 7.72 (s, 1H, C=C$\underline{H}$-Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 61.6/61.6 (2C, 2$\underline{C}H_2$-CH_3), 14.1/13.8 (2C, 2CH_2-$\underline{C}H_3$), 126.1 (C_{quat}, =C-), 128.7 (2C_{tert}, ortho), 129.4 (C_{tert}, *para*), 130.5 (2C_{tert}, *meta*), 132.8 (C_{quat}, Ph), 142.0 (Ph-$\underline{C}$H), 166.6 and 166.2 (2C=O). MS (IE): Calc. for $[M]^+$ $C_{14}H_{16}O_4$: 248, $[M+H]^+$ (*m/z*) = 249 (100%).

Diethyl 2-(4-chlorobenzylidene)malonate (**4b**)**:** Yellow oil, 77% yield, Rf 0.73 (ether/hexane, 1/1). IR (KBr): ν_{max}/cm^{-1} 2906-2982 (CH), 1724 (CO) 1591/1631 (C=C), 1254/1308 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31-1.25 (2 t, 6H, $2H_2C$-C$\underline{H}_3$, ^{3}J 7.11 Hz), 4.31-4.4 (2 q, 4H, 2C$\underline{H}_2$-CH_3, ^{3}J 7.12 Hz), 7.45-7.30 (m, 4H, Ph), 7.7 (s, 1H, C=C$\underline{H}$-ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.7 and 13.8 (2$\underline{C}H_3$-CH_2), 61.4 and 61.7 (2$\underline{C}H_2$-CH_3), 125.4 (C=$\underline{C}$-$(CO_2Et)_2$), 129.0 (2C_{ortho}), 130.3 (2C_{meta}), 130.4 (C_{quat}, *para*/Cl), 132.9 (C_{quat}, $\underline{C}$-Cl-Ph), 140.0 (ClPh-$\underline{C}$H=), 166.3 and 163.8 (2C=O). MS (IE): Calc. for $[M]^+$ $C_{14}H_{15}ClO_4$: 282.07; $[M+H]^{+\cdot}$ = 283 (100%).

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Diethyl 2-(3-methoxybenzylidene)malonate (**4c**)**:** Yellow oil, 70% yield, Rf 0.53 (ether/hexane, 2/1). IR (KBr): ν_{max}/cm^{-1} 2906-2982 (CH), 1754 (C=O), 1254/1308 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31-1.25 (2 t, 6H, $2H_2C$-C$\underline{H}_3$, ^3J 7.11 Hz), 4.31-4.4 (m, 4H, 2C$\underline{H}_2$-CH_3), 4.01 (s, 3H, CH_3O), 7.30 -7.45 (m, 4H, Ph), 7.4 (s, 1H, C=C$\underline{H}$-Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.7 and 14.0 (2CH_3-$\underline{C}H_2$), 61.4 and 60.1 (2$\underline{C}H_2$-CH_3), 125.4 (C=$\underline{C}$-$(CO_2Et)_2$), 125.4 (C=$\underline{C}$-$(CO_2Et)_2$), 129.0 (2C_{ortho}), 130.3 (2C_{meta}), 130.4 (C_{quat}, *para*/CH_3O), 132.9 (C_{quat}, $\underline{Ph}$-OMe), 140.0 (Ph-$\underline{C}$H=), 166.3 and 163.8 (2C=O). Elemental analysis for $C_{15}H_{18}O_5$ Calc. (Found): C 64.74 (65.03) H 6.52 (6.32)%.

General procedure for the synthesis of ***6-15***

To a solution of the intermediate **4a-d** (8.1 mmol) in water (25 mL) was added the respective secondary amine (6 mmol) at the presence or absence of acetic acid (0.1 mL) and the mixture was stirred at room temperature until the complete consume of the starting materials. After removing solvent, the crude products were dissolved in diethyl ether (2 × 40 mL) and washed with water until the pH became neutral. The organic solvent was dried with sodium sulphate and then evaporated to give the respective pure compound.

*Diethyl 2-(phenyl(piperidin-1-yl)methyl)malonate (**6**)*: White powder, mp 67-68 °C. Rf = 0.72 (ether/hexane, 1/1). IR (KBr): ν_{max}/cm^{-1} 2848-2974 (C-H, Ph), 2754/2800 (C-H, aliph), 1750/1740 (C=O), 1514/1450 (C=C), 1313/1257 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00 (t, 3H, H_2C-C$\underline{H}_3$, ^3J 7.1 Hz); 1.26 (m, 2H, -C$^{3'}\underline{H}_2$-, piper), 1.35 (t, 3H, H_2C-C$\underline{H}_3$, ^3J 7.1 Hz), 1.50 (m, 4H, 2C$^{2'}\underline{H}_2$, piper), 2.20 (s large, 2H, C$^{1'}\underline{H}_2$, piper), 2.59 (s large, 2H, C$^{1'}\underline{H}_2$, piper), 4.02 (dq, $2H_{AB}$, O-C$\underline{H}_2$ –CH_3, $^2J_{A-B}$ 10.7 Hz, ^3J 6.9 Hz), 4.23 (d, 1H, C$^2\underline{H}$-$(CO_2Et)_2$, ^3J 12.1 Hz), 4.33 (dq, 2H, O-C$\underline{H}_2$ –CH_3, J_{A-B} 0.2 Hz, ^3J 7.1 Hz), 4.43 (d, 1H, ph-C$^3\underline{H}$, ^3J 12 Hz), 7.15-7.34 (m, 5H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.30/13.75 (2C, $2OCH_2CH_3$), 24.40 (C, $\underline{C}^{3'}H_2$, piper), 26.50 (2C, 2$\underline{C}^{2'}H_2$, piper), 50.55 (2C, 2$\underline{C}^{1'}H_2$, piper), 54.96 (C_{tert}, $\underline{C}^2H(CO_2Et)_2$), 61.30/ 61.15 (2C, $2O\underline{C}H_2CH_3$), 69.15 (C_{tert}, PhC^{2}H), 127.53 (2C_{ter}t, *meta*, Ph), 127.80 (C_{tert}, *para*, Ph), 128.69 (2C_{tert}, *ortho*, Ph), 133.93 (C_{quat}, Ph), 167.22/168.04 (2C=O). MS (IE): Calc. for $[M]^+$ $C_{19}H_{27}NO_4$: 333.19, $[M+H]^+$ (*m/z*) = 334 (35%), 174 (100%). Elemental analysis for $C_{19}H_{27}NO_4$ Calc. (Found): C 68.46 (67.89), H 8.40 (7.89), N 4.20 (4.22)%.

*Diethyl 2-((4-chlorophenyl)(morpholino)methyl) malonate (**7**)*: White crystals, mp 68-69 °C. Rf = 0.55 (ether/ hexane: 1/1). IR (KBr): ν_{max}/cm^{-1} 2935-2985 (C-H, 4-Cl-Ph), 2826-2887 (C-H), 1747 (C=O), 1712 (C=O), 1590-1489 (C=C), 1306-1258 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (t, 3H, $OCH_2C\underline{H}_3$, ^3J 7.1 Hz), 2.30 (s, 2H, C$^{1'}\underline{H}_2$), 2.53 (s, 2H, C$^{1'}\underline{H}_2$), 3.93 (s, 4H, C$^{2'}\underline{H}_2$OC$^{2'}\underline{H}_2$), 3.90-4.07 (m, 2H, $OC\underline{H}_2CH_3$), 4.20 (d, 1H, C$^2\underline{H}$ $(CO_2Et)_2$, ^3J 10.3 Hz), 4.25-4.39 (m, 3H, $OC\underline{H}_2CH_3$ + PhC$^3\underline{H}$), 7.12 (d, 2H, *meta*, ^3J 8.30 Hz), 7.35 (d, 2H, *ortho*, ^3J 8.30 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.8 (C, $OCH_2\underline{C}H_3$, ester), 14.3 (C, $OCH_2\underline{C}H_3$, ester), 49.5 (2C, 2 C$^{1'}H_2$N, morph), 54.6 (C_{tert}, $\underline{C}^2H(CO_2Et)_2$), 61.5 (C, $\underline{C}H_2OCH_3$, ester), 61.6 (C, $\underline{C}H_2OCH_3$, ester), 67.1 (2C, 2$\underline{C}^{2'}H_2O$, morph), 68.0 (C_{tert}, $\underline{C}^3$H-Ph), 128.4 ($C_{tert,}$ 2C-*meta*, Ph), 130 ($C_{tert,}$ 2C-*ortho*, Ph), 131.8 (C_{quat}, Ph, *para*/Cl), 134.8 (C_{quat}, CCl, Ph), 167.6 (2 C=O). 2D NMR experiments have confirmed the signals observed and the different correlations of homo and heteronuclear. MS (IE): Calc. for $[M]^+$ $C_{18}H_{24}ClNO_5$: 369.13, $[M+H]^+$ (*m/z*) = 370 (15%), $[M-CH(CO_2Et)_2]^+$ (*m/z*) = 210 (100%). Elemental analysis for $C_{18}H_{24}NO_5Cl$ Calc. (Found): C 58.53 (58.60), H 6.50 (6.71), N 3.79 (4.03)%.

*Diethyl 2-((3,5-dimethyl-pyrazol-1-yl)(phenyl)methyl) malonate (**8**)*: White powder, mp 86-88 °C. Rf = 0.69 (ether/hexane: 1/1). IR (KBr): ν_{max}/cm^{-1} 2868-2974 (C-H), 1747/1719 (C=O), 1586/1554 (C=C), 1460/1419 (C=N), 1269/1264 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.98 (t, 3H, $CH_2C\underline{H}_3$, ^3J 7.1 Hz), 1.17 (t, 3H, $CH_2C\underline{H}_3$, ^3J 7.1 Hz), 2.21 (s, 1H, C$^{3'}\underline{H}$, pyrazol), 2.25 (s, 1H, C$^{1'}\underline{H}$, pyrazol), 3.97(q, 2H, $OC\underline{H}_2CH_3$, ^3J 7.1 Hz), 4.16-3.99 (2q, 2H, $OC\underline{H}_2CH_3$, ^3J 7.3 Hz), 4.9 (d, 1H, PhC^{3}HC$^2\underline{H}$, ^3J 11.4 Hz), 5.74 (s, 1H, H$^{2'}$, pyrazol), 7.45-7.25 (m, 5H, Ph), 7.78 (d, 1H, ph-C^{3}H, ^3J 11.2 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.67 (C, $\underline{C}^{3'}H_3$, pyrazol), 13.64/10.06 (2C, $2CH_2\underline{C}H_3$), 13.87 (C, $\underline{C}^{1'}$H3, pyrazol), 57.52 (C_{tert}, Ph-C^{3}H$\underline{C}^2$H), 60.35 (C_{tert}, Ph$\underline{C}^3$HC^{2}H), 61.57 (2C, $2\underline{C}H_2CH_3$), 105 (C_{tert}, $\underline{C}^{2'}$H, pyrazol), 128.50/128.3/127.93 (5C, Ph), 137.30 (C_{quat}, C$^{3'}$, pyrazol), 139.30 (C_{quat}, Ph), 147.3 (C_{quat}, C$^{1'}$, pyrazol), 166.90/166.85 (2C=O). MS (IE): Calc. for $[M]^+$ $C_{19}H_{24}N_2O_4$: 344.17, $[M+H]^+$ (*m/z*) = 345 (11%), 83 (100%). Elemental analysis for $C_{19}H_{24}N_2O_4$ Calc. (Found): C 66.27 (65.71), H 6.97 (5.80), N 8.13 (8.78)%.

*Diethyl 2-((4-chlorophenyl)(3,5-dimethyl-pyrazol-1-yl)methyl)malonate (**9**)*: White powder, mp 77-79 °C. Rf = 0.68 (ether/hexane: 1/1). IR (KBr): ν_{max}/cm^{-1} 2969 (C-H , Ph), 2674/2806 (C-H), 1747/1720 (C=O), 1592/1464 (C=C), 1329/ 1256 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32-7.29 (m, 2H, aromatic), 7.14-7.18 (m, 2H, Ph), 4.5 (d, 1H, PhC$^3\underline{H}$, ^3J 11.40 Hz), 4.25 (q, 2H, $C\underline{H}_2OCH_3$, ^3J 7.1 Hz), 4.09 (d, 1H, C$^2\underline{H}(CO_2Et)_2$, ^3J 11.40 Hz), 3.95 (m, 2H, $C\underline{H}_2OCH_3$), 2.49 (m, 2H, N-C$^{1'}\underline{H}_2$, pyrazole), 2.35 (m, 2H, NC$^{1'}\underline{H}_2$, pyrazole), 1.59 (m, 4H, 2C$^{1'}H_2C^{2'}\underline{H}_2$, pyrazole), 1.30 (t, 3H, $OCH_2C\underline{H}_3$, ^3J 7.1 Hz), 1.03 (t, 3H, $OCH_2C\underline{H}_3$, ^3J 7.1 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 166.97/167.88

(2C=O), 133.35 (C_{quat}, CCl, Ph), 133.22 (C_{quat}, Ph, *para*/Cl), 130.35 ($C_{tert,}$ 2C *ortho*, Ph), 128.05 ($C_{tert,}$ 2C *meta*, Ph), 64.05 (C_{tert}, C^3HPh), 61.40 (C, O$CH_2$$CH_3$, ester), 61.30 (C, O$CH_2$$CH_3$, ester), 56.50 ($C_{tert}$, C^2H(CO_2Et)$_2$), 48.41/46.88 (2C, 2$C^{1'}H_2$N, pyrazole), 22.84 (2C, 2$C^{1'}H_2C^{2'}H_2$), pyrazole), 13.91/14.12 (2C, 2O$CH_2$$CH_3$). MS (IE): Calc. for $[M]^+$ $C_{18}H_{24}ClNO_4$: 353.14, $[M+H]^+$ (*m/z*)=354 (18%), $[M\text{-}CH(CO_2Et)_2]^+$ (*m/z*)=194 (100%), $[M\text{-pyrol}]^+$ (*m/z*) = 283. Elemental analysis for $C_{18}H_{24}NO_4Cl$ Calc. (Found): C 62.12 (62.10), H 7.08 (7.28), N 3.18 (4.04)%.

*Diethyl 2-((4-chlorophenyl)(pyrazol-1-yl)methyl) malonate (**10**)*: White crystals, mp 87-89 °C. Rf = 0.65 (ether/hexane; 1/1). IR (KBr): ν_{max}/cm^{-1} 2896/2985 (CH), 1748 (C=O), 1514/1595 (C=C), 1292/1308 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.5 (d, 2H, $C^{3'}$H, C^5H, pyrazol, ^3J 14.27 Hz), 7.28-7.44 (m, 4H, Ph, ^3J 8.68 Hz), 6.20 (t, 1H, pyrazol, ^3J 2.08 Hz), 5.85 (d, 1H, PhC^{3}H, ^3J 11.33 Hz), 4.80 (d, 1 H, C^2H(CO_2Et)$_2$, ^3J 11.33 Hz), 4.10 (dq, 2H_{AB}, O$CH_2$$CH_3$, J_{AB} 14.32 Hz, ^3J 7.11 Hz), 4.01 (dq, 2H_{AB}, O$CH_2$$CH_3$, J_{AB} 14.32 Hz, ^3J 7.11 Hz), 2.25 (s, 3H, CH_3, pyrazol), 2.20 (s, 3H, CH_3, pyrazol), 1,13 (t, 3H, O$CH_2$$CH_3$, ^3J 7.11 Hz), 1.04 (t, 3H, O$CH_2$$CH_3$, ^3J 7.11 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 166.36 (C=O), 166.26 (C=O), 147.65 (C_{quat}, pyrazol), 139.3 (C_{quat}, pyrazol), 135.7 (C_{quat}, CCl, Ph), 134.62 (C_{quat}, Ph, *para*/Cl), 129.83 (C_{tert}, 2C *meta*, Ph), 128.7 ($C_{tert,}$ 2C *ortho*, Ph), 129.27 (C_{tert}, $C^{3'}C^{4'}$, pyrazol), 105.45 (C_{tert}, C^4H, pyrazol), 61.75/ 61.70 (C_{sec}, 2CH_2, ester), 59.55 (C_{tert}, C^3HPh), 57.45 (C_{tert}, C^2H(CO_2Et)$_2$), 13.87 (C, O$CH_2$$CH_3$, ester), 13.75 (C, O$CH_2$$CH_3$, ester), 13.66 (C, CH_3, pyrazol), 10.95 (CH_3, pyrazol). MS (IE): Calc. for $[M]^+$ $C_{17}H_{19}N_2O_4Cl$: 350.5, $[M+H]^+$ (*m/z*) = 351 (15%), $[M\text{-}CH(CO_2Et)_2]^+$ (*m/z*)=191 (100%), $[M\text{-pyrol}]^+$ (*m/z*)=283 (21%). Elemental analysis for $C_{18}H_{24}ClNO_4$ Calc. (Found): C 64.55 (64.46), H 6.32 (6.62), N 8.86 (9.06)%.

*Diethyl 2-((4-chlorophenyl)(piperidin-1-yl)methyl) malonate (**11**)*: White powder, mp 63-65 °C. Rf = 0.65 (ether/hexane: 1/1). IR (KBr): ν_{max}/cm^{-1} 2973/2930 (aromatic C-H, Ph), 2797/2848 (aliphatic C-H), 1755 (C=O), 1737 (C=O), 1493/1452 (C=C), 1312/1257 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.05 (t, 3H, O$CH_2$$CH_3$, ^3J 7.10 Hz), 1.26 (m, 2H, 2N(CH_2)$_2$C $^{3'}H_2$, ^3J 5.9 Hz), 1.35 (t, 3H, O$CH_2$$CH_3$, ^3J 7.10 Hz), 1.48 (m, 4 H, NC $^{1'}H_2C^{2'}H_2$), 2.16 (m, 2H, NC$^{1'}H_2$), 2.46 (m, 2H, NC $^{1'}H_2$), 4.16* (d, H, C^2H(CO_2Et)$_2$, ^3J 12.10 Hz), 4.35* (d, H, PhC^{3}H, ^3J 12.20 Hz); 4.02 (dq, 2H_{AB}, O$CH_2$$CH_3$, J_{AB} 11.3 Hz); 4.30 (dq, 2H_{AB}, O$CH_2$$CH_3$, J_{AB} 10.7 Hz); 7.1 (d, 2H, aromatic-*ortho*, ^3J 10.7 Hz), 7.32 (d, 2H, aromatic-*meta*, ^3J 10.9 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.3 and 13.8 (2C, 2CH_3, esters), 24.40 (C, N(CH_2)$_2$$C^{3'}H_2$), 26.4 (2C, 2$C^{2'}H_2CH_2$N), 50.51 (2C, 2$C^{1'}H_2$N), 54.95 ($C_{tert}$, C^2H(CO_2Et), 61.4 and 61.3 (2C, 2$CH_2$$CH_3$, ester), 69.5 ($C_{tert}$, C^3HPh), 129.9 (C_{tert}, 2C meta/Ar), 128.04 (C_{tert}, 2C ortho/Ar), 132.6 ($C_{quat,}$ para/Cl), 133.4 (C_{quat}, ClC), 167.03 (C=O), 167.71 (C=O). MS (IE): Calc. for $[M]^+$ $C_{19}H_{26}ClNO_4$: 367.16, $[M+H]^+$ (*m/z*) = 368 (16%), $[M\text{-}CH(CO_2Et)_2]^+$ (*m/z*) = 208 (100%), $[M\text{-PhCl}]^+$ (*m/z*) = 256. Elemental analysis for $C_{19}H_{26}NO_4Cl$ Calc. (Found): C 62.12 (62.10), H 7.08 (7.28), N 3.18 (3.14)%.

*Diethyl 2-((benzyl(ethyl)amino)(4-chlorophenyl) methyl)malonate **(12)***: White crystals, mp 70-72 °C. Rf = 0.56 (ether/hexane: 1/1). IR (KBr): ν_{max}/cm^{-1} 2808/2985 (CH); 1732 (C=O), 1594/1595 (C=C), 1248/1291 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, 3H, O$CH_2$$CH_3$, ^3J 7.07 Hz); 2.1 (m, 1H, $CHCH_3$, ^3J 12.90 Hz), 1.01 (t, 3H, O$CH_2$$CH_3$, ^3J 7.07 Hz), 2.55 (m, 1H, CHCH_3, ^3J 12.90 Hz), 2.9 (d, 1H, CH-Ph, ^3J 13.80 Hz), 3.9 (d, 1H, CH-Ph, ^3J 13.80 Hz), 4.01 (dq, 2$H_{A\text{-}B}$, O$CH_2$$CH_3$, J_{AB} 14.10 Hz, ^3J 7.07 Hz), 4.24 (d, 1H, C^2H(CO_2Et)$_2$, ^3J 12.30 Hz), 4.30 (dq, 2H_{AB}, O$CH_2$$CH_3$, J_{AB} 14.10 Hz, ^3J 7.07 Hz), 4.62 (d, 1H, ClPhC^{3}H, ^3J 12.30 Hz), 7.23-7.1 (m, 5H, aromatic, ^3J 4.42 Hz), 7.24-7.37 (m, 4H, PhCl, ^3J 8.43 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.41 (C, N$CH_2$$CH_3$), 13.79 (C, O$CH_2$$CH_3$, ester), 14.07 (C, 2O$CH_2$$CH_3$, ester), 54.21 ($C_{sec}$, N$CH_2$$CH_3$), 55.47 ($C_{tert}$, C^2H(CO_2Et)$_2$), 61.75 (C_{tert}, C^3HPhCl), 61.75/61.70 (C_{sec}, 2CH_2, ester), 126.91 ($C_{tert,}$ 2C para, Ph), 167.84 (C-O), 128.15 ($C_{tert,}$ 2C *ortho*, Ph), 128.15 ($C_{tert,}$ 2C *ortho*, Ph-Cl), 128.28 (C_{tert}, 2C *meta*, Ph), 130.81 (C_{tert}, 2C *meta*, Ph-Cl), 133.54 (C_{quat}, Ph, *para*/Cl), 139.41 (C_{quat}, CCl, Ph), 166.93 (C=O). MS (IE): Calc. for $[M]^+$ $C_{23}H_{28}ClNO_4$: 417.5, $[M+H]^+$ (*m/z*)= 418 (12%), $[M\text{-}CH(CO_2Et)_2]^+$ (*m/z*) = 258 (100%), [M- N(CH_2Ph,C_2H_5)]$^+$ (*m/z*) = 283. Elemental analysis for $C_{23}H_{28}ClNO_4$ Calc. (Found): C 66.18 (65.53), H 6.71 (6.66), N 3.35 (3.55)%.

*Diethyl 2-((4-chlorophenyl)(pyrrolidin-1-yl)methyl) malonate **(13)***: White crystals, mp 81-83 °C. Rf = 0.67 (ether/hexane: 1/1). IR (KBr): ν_{max}/cm^{-1} 2981/2935 (CH); 1764 (C=O), 1594/1554 (C=C), 1490/1463 (C=N), 1300/1257 (C-O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.04 (t, 3H, O$CH_2$$CH_3$, ^3J 7.1 Hz), 1.16 (t, 3H, O$CH_2$$CH_3$, ^3J 7.1 Hz), 2.20 (s, 3H, CH_3, pyrazol), 2.25 (s, 3H, CH_3, pyrazol), 4.0 (dq, 2H_{AB}, O$CH_2$$CH_3$, J_{AB} 14.3 Hz, ^3J 7.2 Hz); 4.12 (dq, 2H_{AB}, O$CH_2$$CH_3$, J_{AB} 14.3 Hz, ^3J 7.2 Hz), 4.84 (d, 1H, C^2H(CO_2Et)$_2$, ^3J 11,3 Hz), 5.70 (d, 1H, PhC^{3}H, ^3J 11.3 Hz), 5.74 (s, 1H, pyrazol), 7.25-7.44 (m, 4H, Ph, ^3J 8.25 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 10.95 (CH_3, pyrazol), 13.66 (CH_3-pyrazol), 13.75 (O$CH_2$$CH_3$, ester), 13.87 (O$CH_2$$CH_3$, ester), 57.45 ($C_{tert}$, C^2H(CO_2Et)$_2$), 59.55 (C_{tert}, C^3HPh), 61.75/61.70 (C_{sec}, 2CH_2, ester), 105.45

(C_{tert}, CH, pyrazol), 128.7 (C_{tert}, 2C *ortho*, Ph), 129.4 (C_{tert}, 2C *meta*, Ph), 134.25 (C_{quat}, Ph, *para*/Cl), 138.9 (C_{quat}, CCl, Ph), 139.3 (C_{quat}, pyrazol), 147.65 (C_{quat}, pyrazol), 166.60 (C=O), 166.75 (C=O). MS (IE): Calc. for $[M]^+$ $C_{19}H_{23}ClN_2O_4$: 378.13, $[M+H]^+$ (*m/z*) = 379 (17%), $[M-CH(CO_2Et)_2]^+$ (*m/z*) = 219 (100%), $[M-pyrazol)]^+$ (*m/z*) = 283. Elemental analysis for $C_{19}H_{23}N_2O_4Cl$ Calc. (Found): C 60.31 (60.43), H 6.08 (6.05), N 7.40 (7.69)%.

*Diethyl 2-((3-methoxyphenyl)(piperidin-1-yl)methyl) malonate (**14**)*: White crystals, mp 98 °C. Rf = 0.70 (ether/hexane: 2/1). IR (KBr): ν_{max}/cm^{-1} 1760 (C=O), 1320/1277 (C-O). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.30 (t, 3H, $OCH_2C\underline{H}_3$, ^3J 9.0 Hz), 1.58 (t, 3H, $OCH_2\underline{C}H_3$, ^3J 9.0 Hz), 2.45-2.30 (m, 2H, $NC^{1'}\underline{H}_2$), 2.58-2.66 (m, 2H, $NC^{1'}\underline{H}_2$), 4.19 (dq, $2H_{AB}$, $OC\underline{H}_2CH_3$, J_{AB} 10 Hz), 4.07 (s, 3H, CH_3OPh), 4.38 (dq, $2H_{AB}$, $OC\underline{H}_2CH_3$, J_{AB} 10 Hz); 4.73 (d, H, $PhC^3\underline{H}$, ^3J 10 Hz); 7.03 (d, 2H, Ph), 7.25 (d, 2H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.3 and 14.5 (2C, $2\underline{C}H_3$, ester), 22.10 (C, $N(CH_2)_2\underline{C}^{3'}H_2$), 24.8 (2C, $2\underline{C}^{2'}H_2CH_2N$), 50.1 (2C, $2\underline{C}^{1'}H_2N$), 54.1 (C_{tert}, $\underline{C}^2H(CO_2Et)$, 58.3 (C_{tert}, $\underline{C}^3HPh$), 60.5 (CH_3OPh), 61.9 and 62.3 (2C, $2\underline{C}H_2CH_3$, ester), 119.6 (C_{tert}), 130.5 (C_{tert}), 159.3 (C_{quat}, $CH_3O\underline{C}$), 137.2 (C_{quat}), 175.1 (C=O), 176.7 (C=O). MS (IE): Calc. for $[M]^+$ $C_{20}H_{29}NO_5$: 363.56, $[M+H]^+$ (*m/z*) = 364 (10%), $[M-CH(CO_2Et)_2]^+$ (*m/z*) = 204 (100%). Elemental analysis for $C_{20}H_{29}NO_5$ Calc. (Found): C 66.09 (66.12), H 8.04 (8.14), N 3.85 (3.89)%.

*Diethyl 2-((4-methoxyphenyl)(piperidin-1-yl)methyl) malonate (**15**)*: White crystals, mp 101 °C. Rf = 0.71 (ether/hexane: 2/1). IR (KBr): ν_{max}/cm^{-1} 2981/2935 (CH); 1764 (C=O), 1280/1277 (C-O). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, $OCH_2C\underline{H}_3$, ^3J 7.0 Hz), 1.51 (t, 3H, $OCH_2\underline{C}H_3$, ^3J 7.0 Hz), 2.45 (m, 2H, $NC^{1'}\underline{H}_2$), 2.76 (m, 2H, $NC^{1'}\underline{H}_2$), 4.05 (s, 1H, CH_3O), 4.35 (dq, $2H_{AB}$, $OC\underline{H}_2CH_3$, J_{AB} 10 Hz), 4.48 (dq, $2H_{AB}$, $OC\underline{H}_2CH_3$, J_{AB} 11.3 Hz), 4.81 (d, H, $PhC^3\underline{H}$, ^3J 10 Hz); 7.58-7.69 (m, 4H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 15.0 and 14.8 (2C, $2\underline{C}H_3$, ester), 22.10 (C, $N(CH_2)_2\underline{C}^{3'}H_2$), 25.2 (2C, $2\underline{C}^{2'}H_2CH_2N$), 48.61 (2C, $2\underline{C}^{1'}H_2N$), 56.15 (C_{tert}, $\underline{C}^2H(CO_2Et)$, 58.3 (C_{tert}, $\underline{C}^3HPh$), 61.4 and 61.3 (2C, $2\underline{C}H_2CH_3$, ester), 113.10 (C_{tert}), 129.9 (C_{tert}), 132.6 (C_{quat}), 153.1 (C_{quat}, $CH_3O\underline{C}$), 172.71 (C=O), 171.00 (C=O), MS (IE): Calc. for $[M]^+$ $C_{20}H_{29}NO_5$: 363.57, $[M+H]^+$ (*m/z*) = 364 (19%), $[M-CH(CO_2Et)_2]^+$ (*m/z*) = 204 (100%). Elemental analysis for $C_{20}H_{29}NO_5$ Calc. (Found): C 66.09 (65.92), H 8.04 (8.02), N 3.85 (3.68)%.

Table S1. Bond lengths (Å) and angles (deg) for **9**

O(1)-C(3)	1.201(2)	O(4)-C(7)	1.458(2)
O(2)-C(3)	1.331(2)	N(1)-C(15)	1.356(2)
O(2)-C(4)	1.459(2)	N(1)-N(2)	1.366(2)
O(3)-C(6)	1.202(2)	N(1)-C(1)	1.463(2)
O(4)-C(6)	1.335(2)	N(2)-C(17)	1.331(2)
O(1)-C(3)-O(2)	124.78(15)	N(1)-C(1)-C(9)	112.43(13)
O(1)-C(3)-C(2)	124.24(16)	N(1)-C(1)-C(2)	108.00(14)
O(2)-C(3)-C(2)	110.97(14)	N(1)-C(15)-C(16)	105.73(16)
O(2)-C(4)-C(5)	106.59(14)	N(1)-C(15)-C(18)	122.59(15)
O(3)-C(6)-O(4)	124.97(17)	N(2)-C(17)-C(16)	110.85(15)
O(3)-C(6)-C(2)	124.02(17)	N(2)-C(17)-C(19)	119.80(16)
O(4)-C(6)-C(2)	110.99(15)	N(2)-N(1)-C(1)	119.57(13)

Table S2. Torsion angles [deg] for (**9**)

N(1)-C(1)-C(2)-C(3)	178.59(12)	C(1)-C(2)-C(6)-O(3)	39.9(2)
N(1)-C(1)-C(2)-C(6)	60.69(16)	C(1)-N(1)-C(15)-C(16)	−175.55(16)
N(1)-N(2)-C(17)-C(16)	−0.37(18)	C(1)-N(1)-N(2)-C(17)	175.98(14)
N(1)-N(2)-C(17)-C(19)	−179.40(15)	C(1)-N(1)-C(15)-C(18)	5.4(3)
N(1)-C(1)-C(9)-C(14)	−128.96(16)	C(1)-C(2)-C(6)-O(4)	−141.76(14)
N(1)-C(1)-C(9)-C(10)	51.2(2)	C(3)-O(2)-C(4)-C(5)	174.73(15)
N(1)-C(15)-C(16)-C(17)	0.49(19)	C(3)-C(2)-C(6)-O(3)	−79.0(2)
N(2)-N(1)-C(1)-C(2)	41.34(19)	C(3)-C(2)-C(6)-O(4)	99.30(16)
N(2)-N(1)-C(1)-C(9)	−83.05(18)	C(6)-O(4)-C(7)-C(8)	−81.9(2)
N(2)-N(1)-C(15)-C(16)	−0.77(19)	C(7)-O(4)-C(6)-O(3)	−1.1(3)
N(2)-N(1)-C(15)-C(18)	−179.86(16)	C(7)-O(4)-C(6)-C(2)	−179.43(14)

Table S3. Electrostatic-bond parameters for **9** (Å, °)

D-X...A	d(D-X)	d(X...A)	d(D...A)	<(D-X…A)
C12 Cl1 N2	1.74(2)	3.11(4)	4.84(7)	118.5(4)

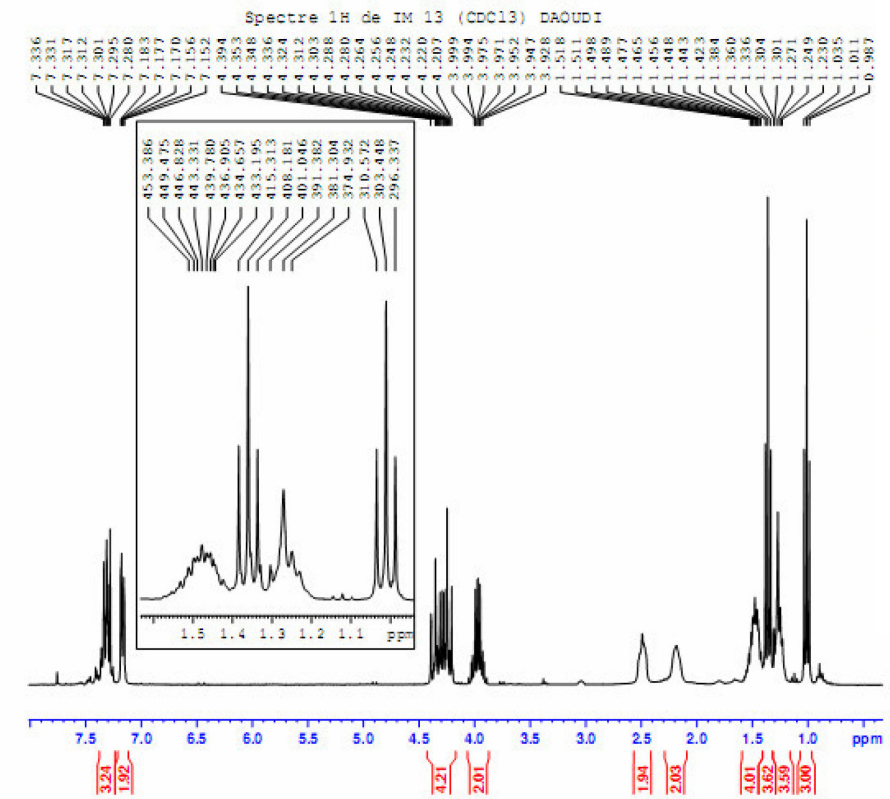

Figure S1. ^{1}H NMR (300 MHz) spectrum of compound **6** in $CDCl_3$.

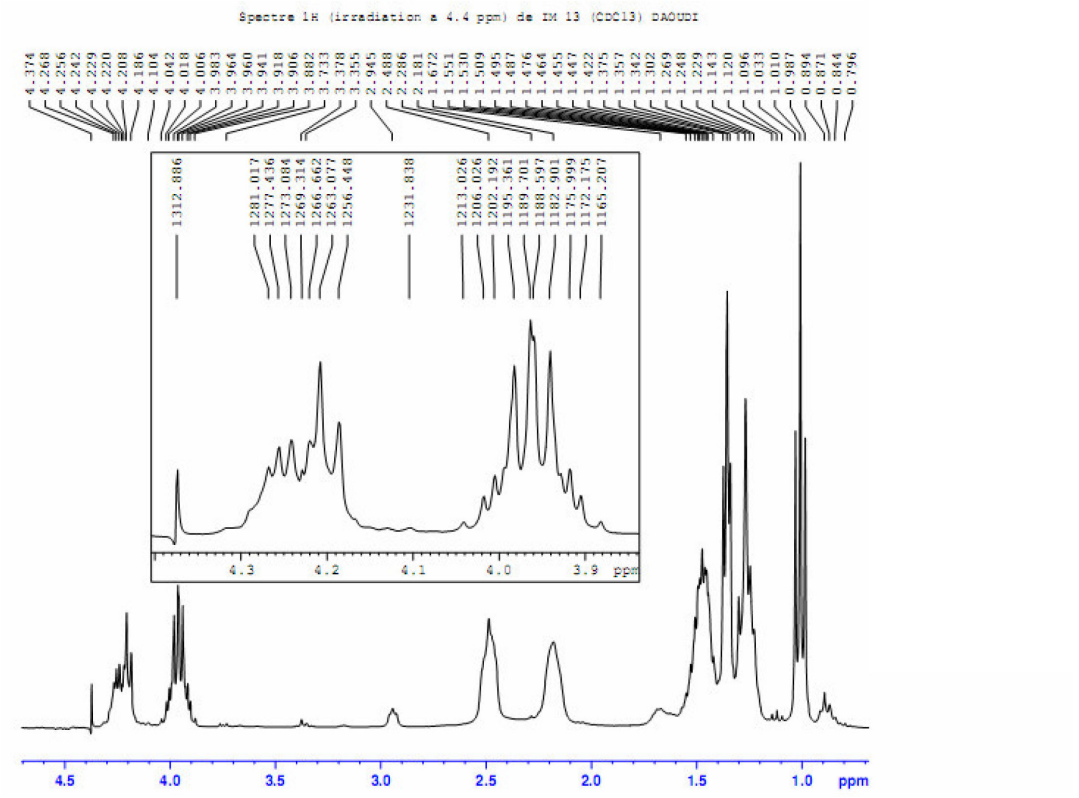

Figure S2. ^{1}H NMR (300 MHz) spectrum of compound **6** in $CDCl_3$ expanded at 4.5-1.0ppm.

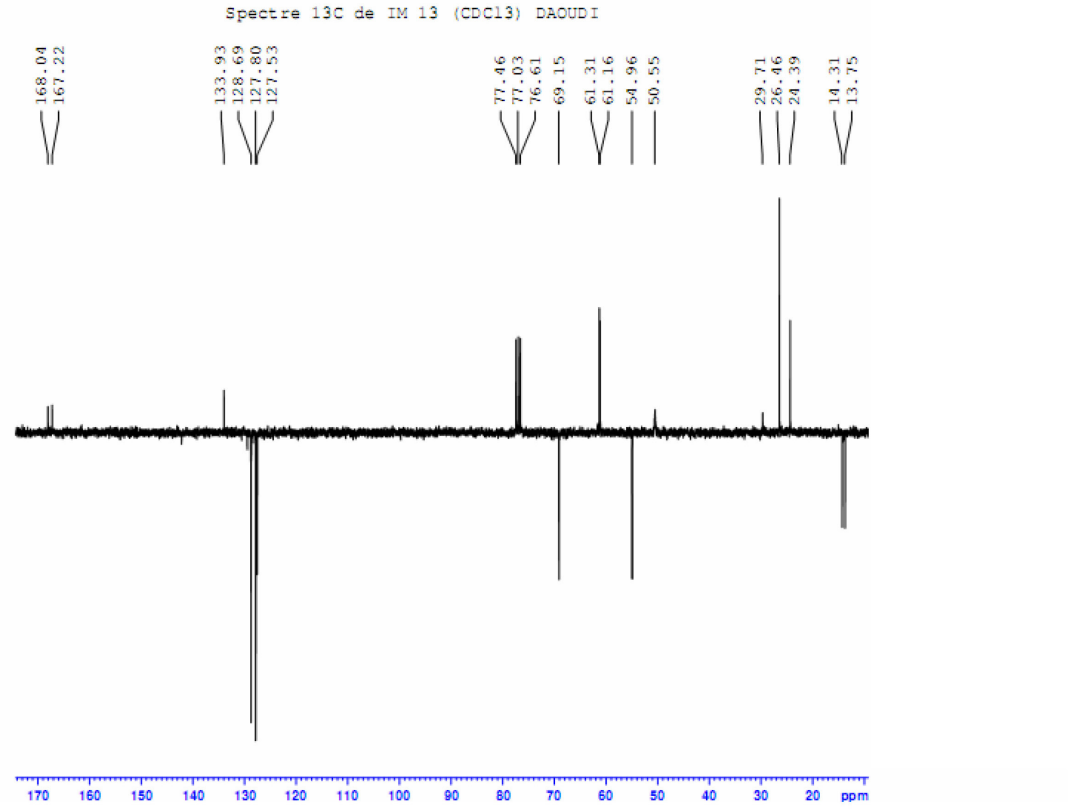

Figure S3. ^{13}C NMR (75 MHz) spectrum of compound **6** in $CDCl_3$.

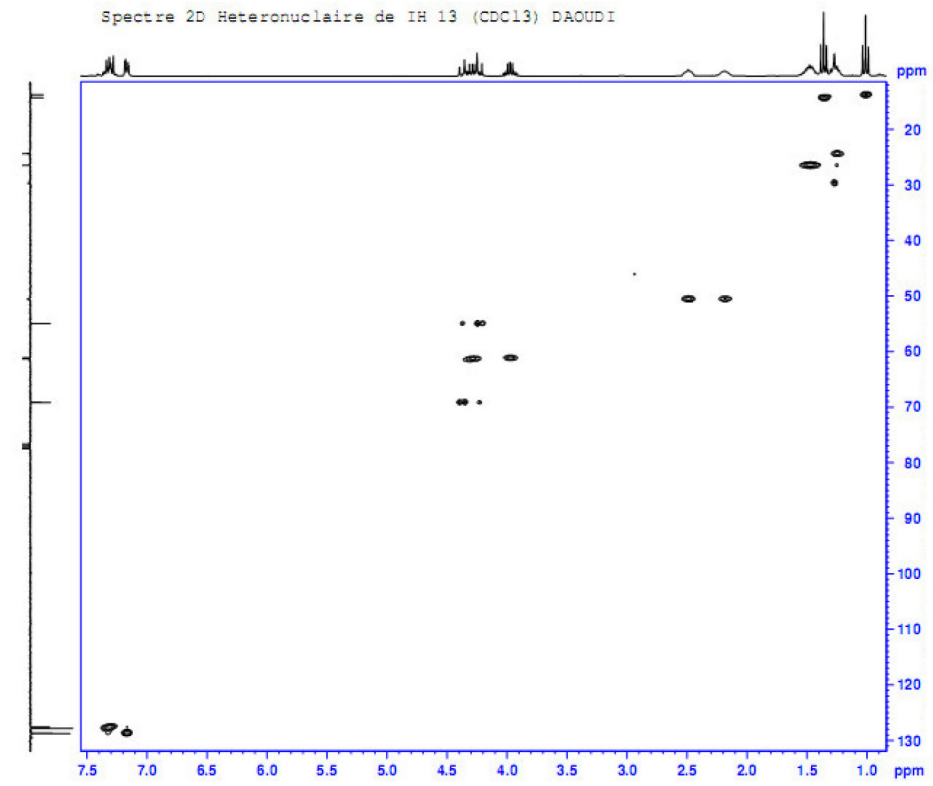

Figure S4. HETCOR of compound **6** in $CDCl_3$.

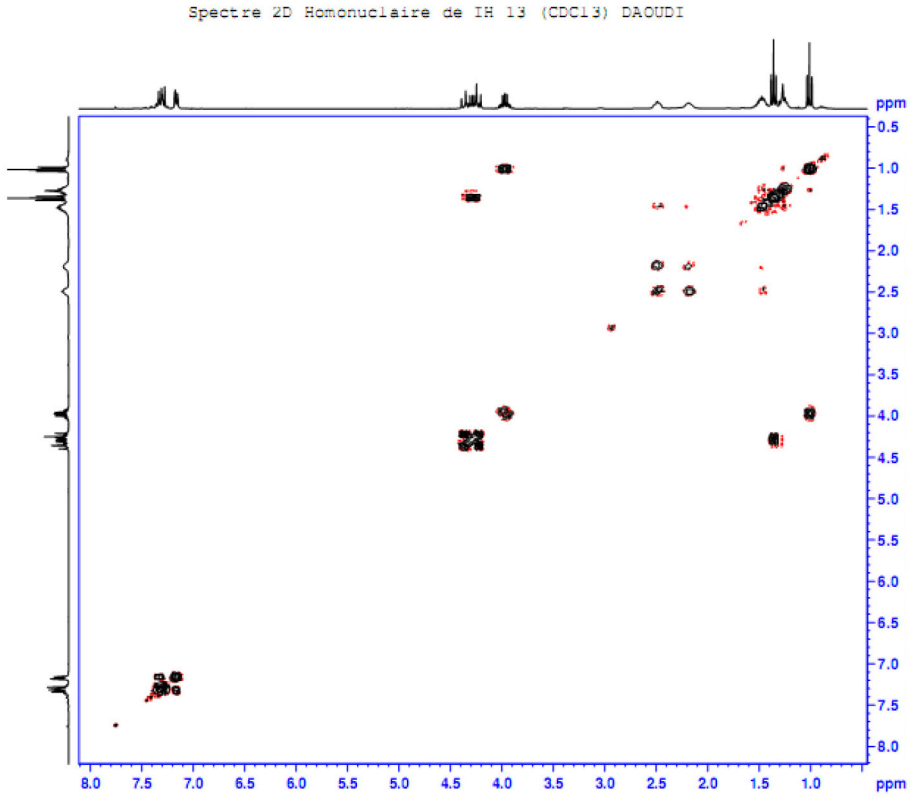

Figure S5. COSY of compound **6** in $CDCl_3$.

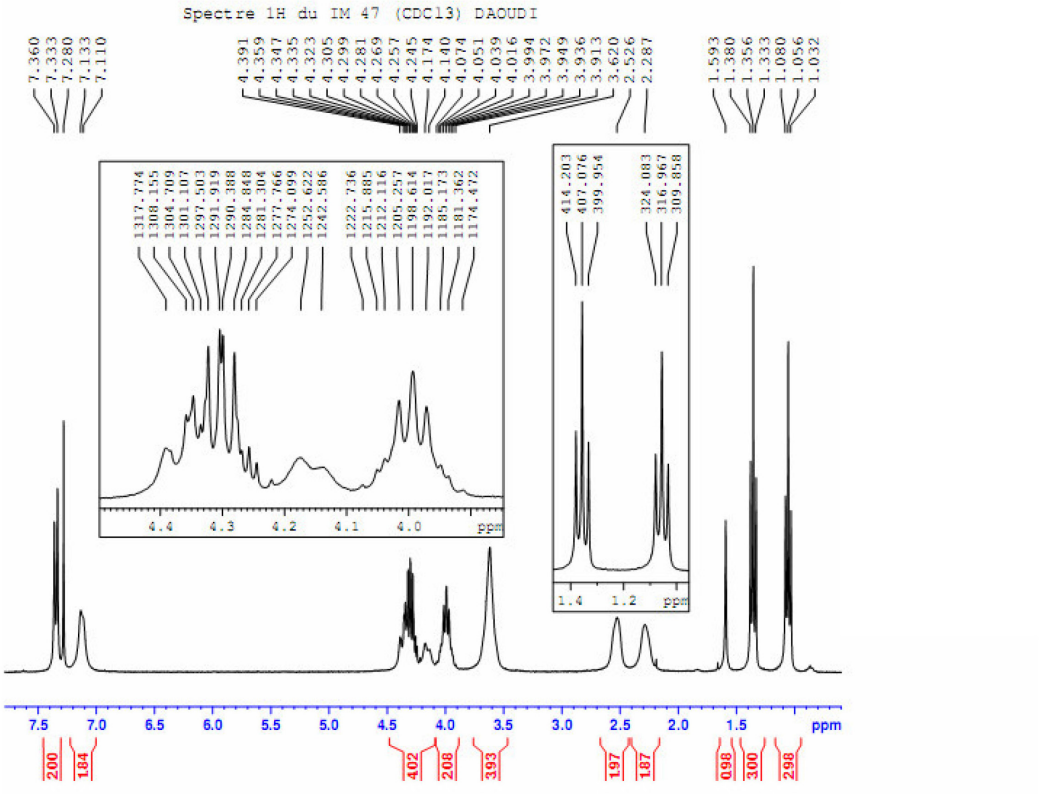

Figure S6. [1]H NMR (300 MHz) spectrum of compound **7** in $CDCl_3$.

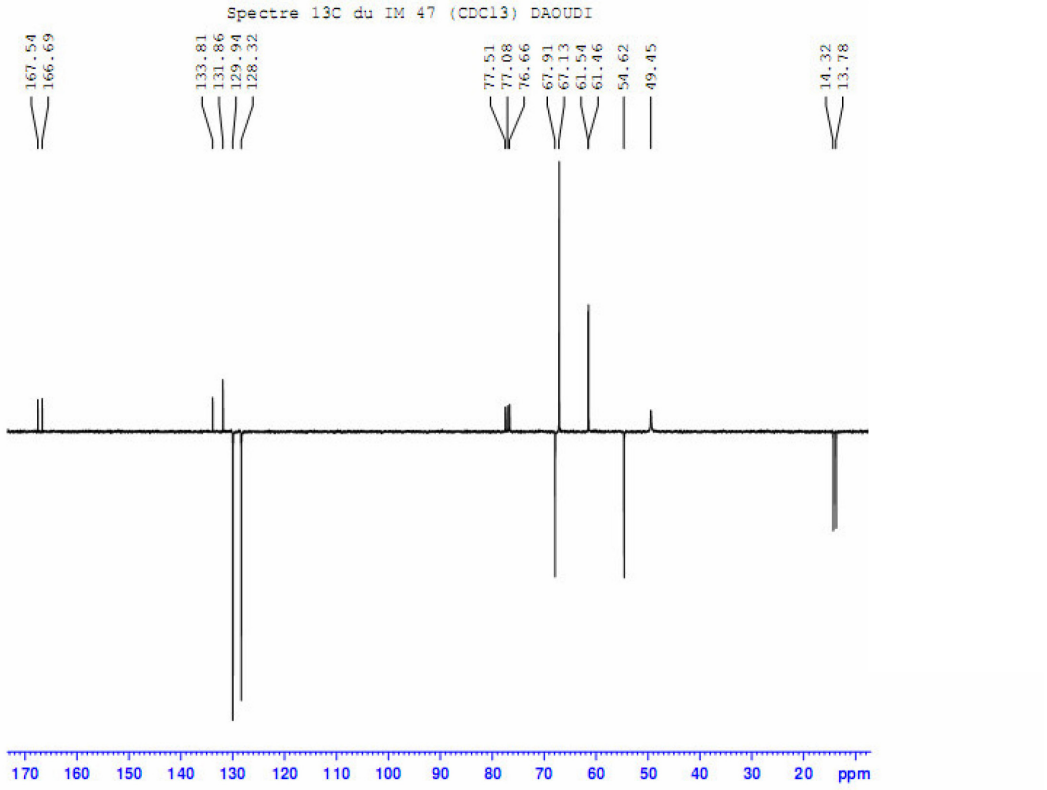

Figure S7. [13]C NMR (75 MHz) spectrum of compound **7** in $CDCl_3$.

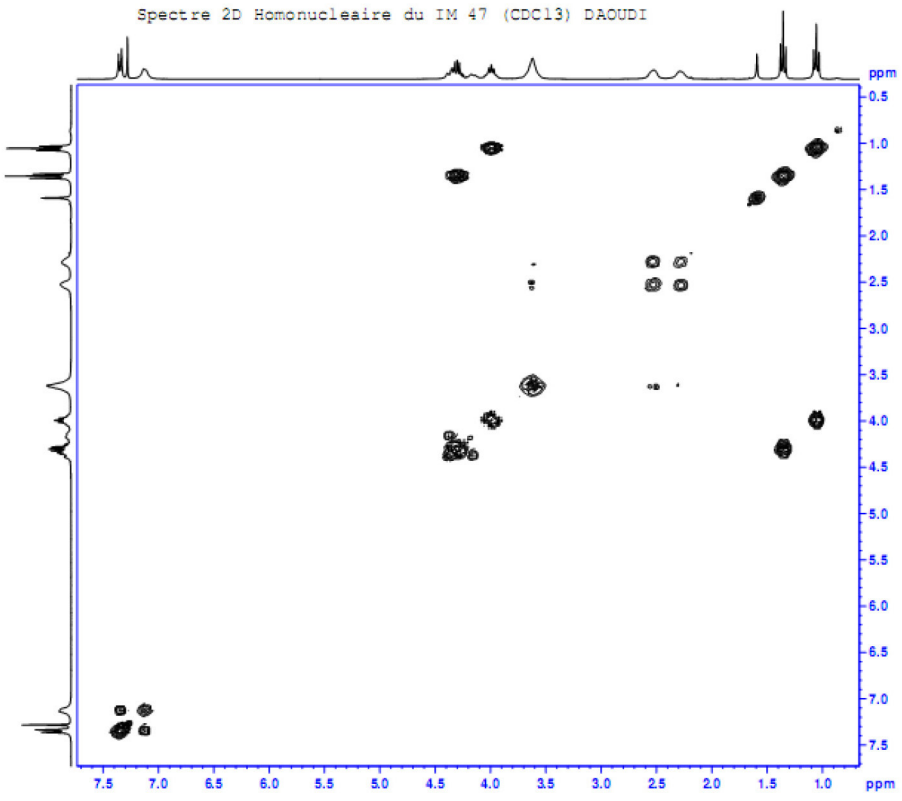

Figure S8. COSY of compound **7** in $CDCl_3$.

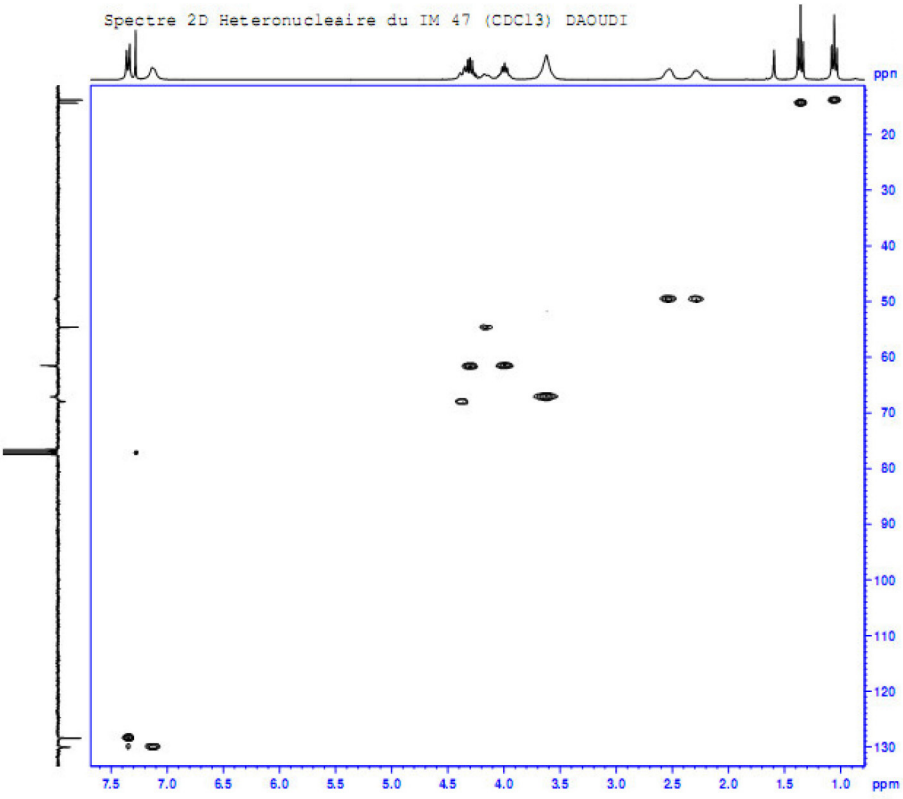

Figure S9. HETCOSY of compound **7** in $CDCl_3$.

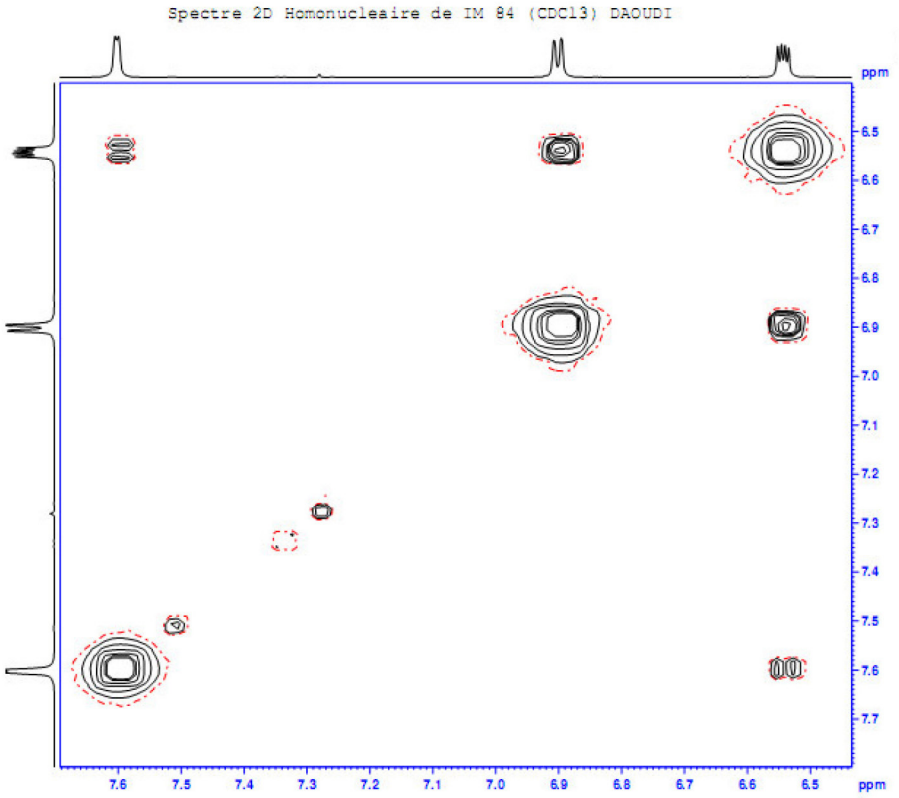

Figure S10. COSY of compound **7** in $CDCl_3$.

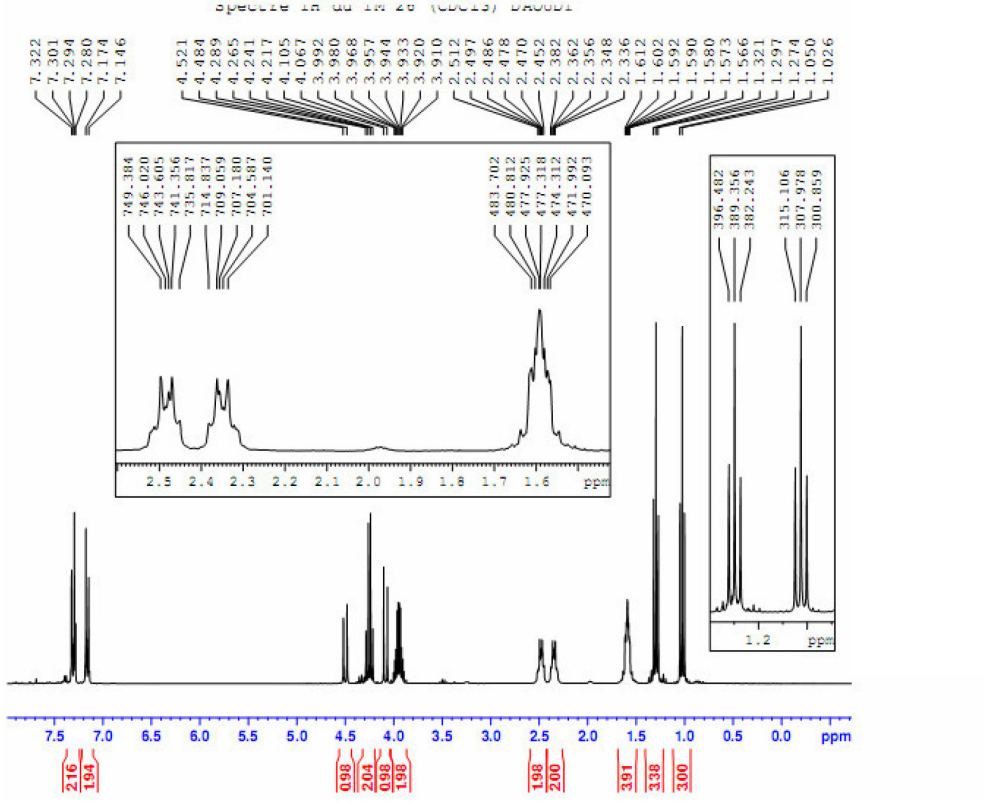

Figure S11. ^1H NMR (300 MHz) spectrum of compound **9** in $CDCl_3$.

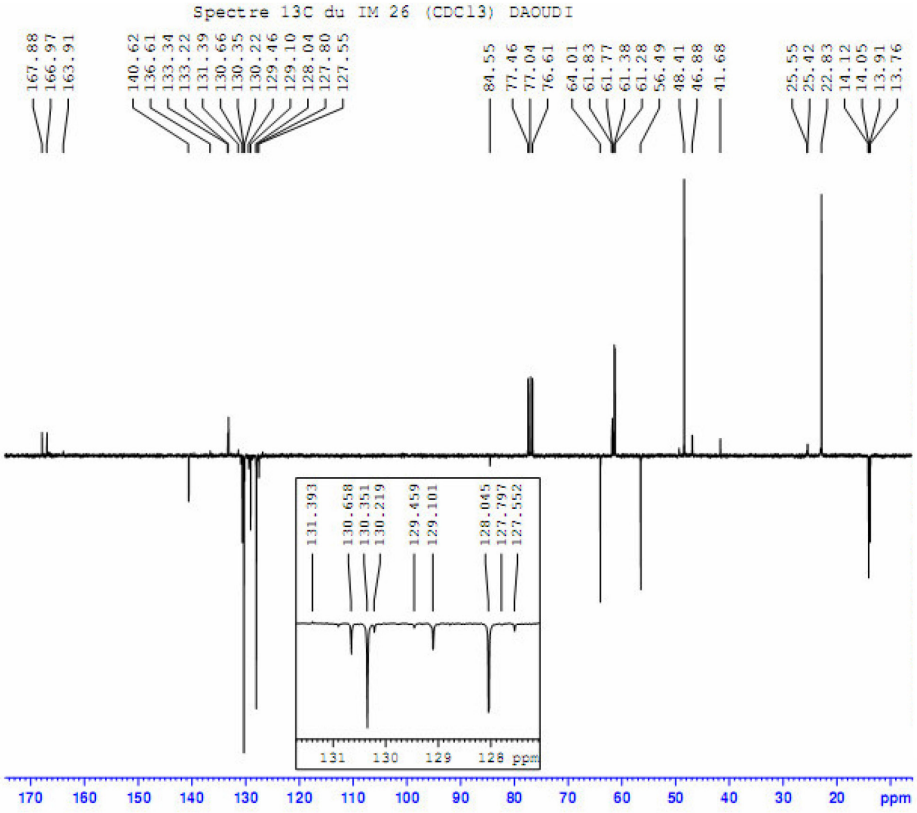

Figure S12. ^{13}C NMR (75.5 MHz) spectrum of compound **9** in $CDCl_3$.

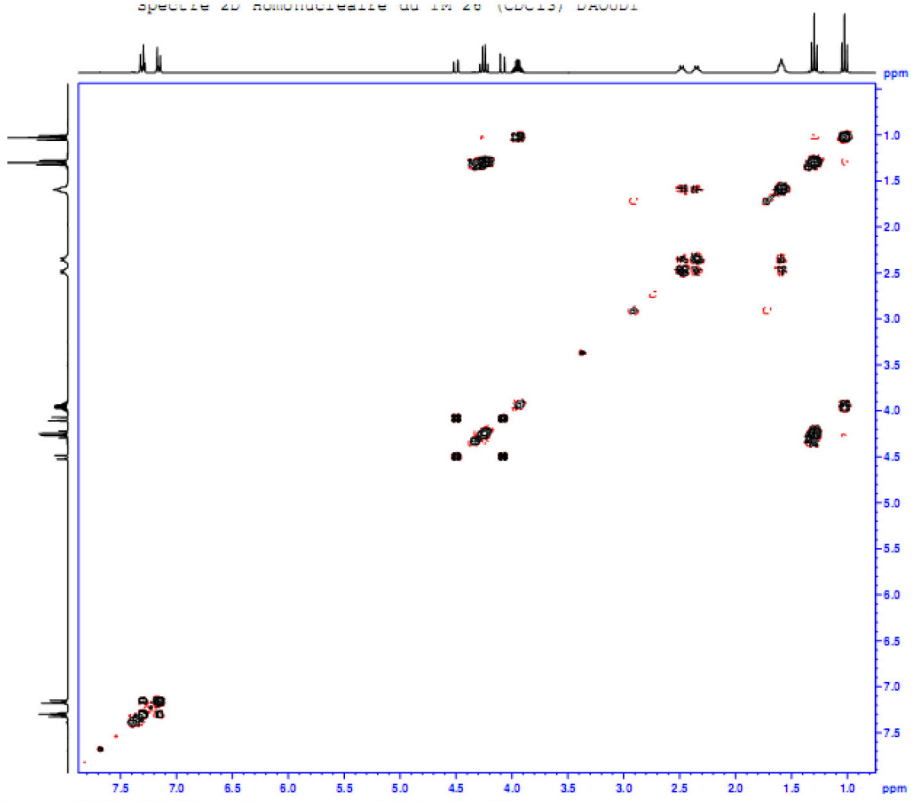

Figure S13. COSY of compound **9** in $CDCl_3$.

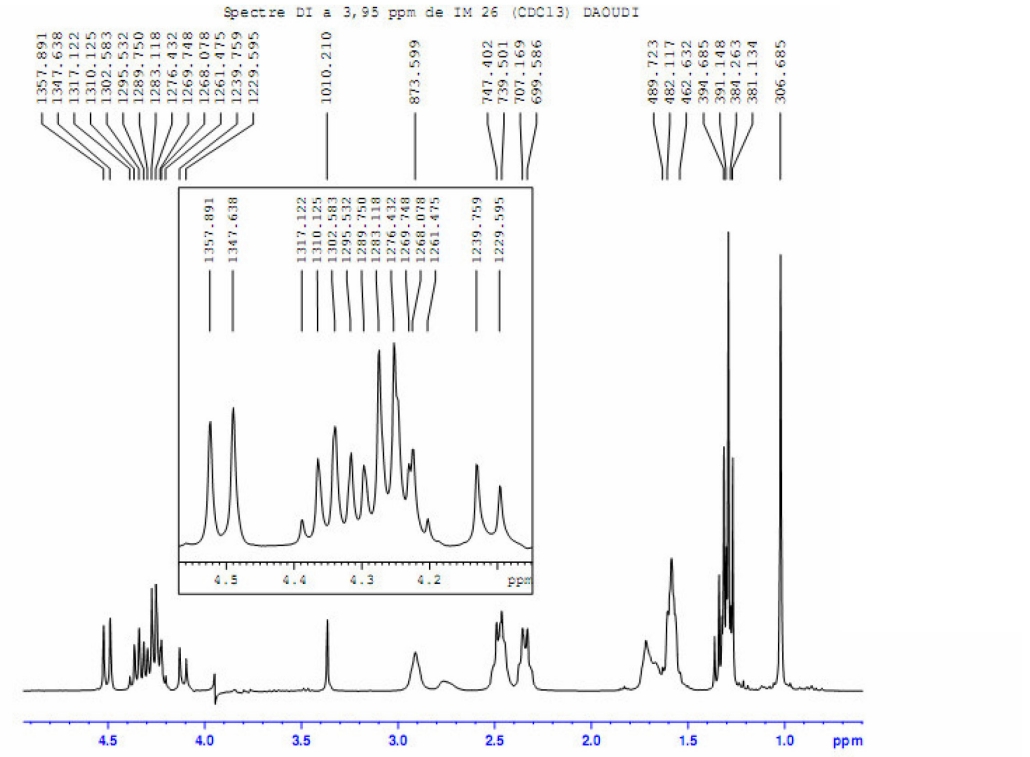

Figure S14. ^{1}H NMR (300 MHz) spectrum of compound **9** in $CDCl_3$ expanded at 4.5-1.0ppm.

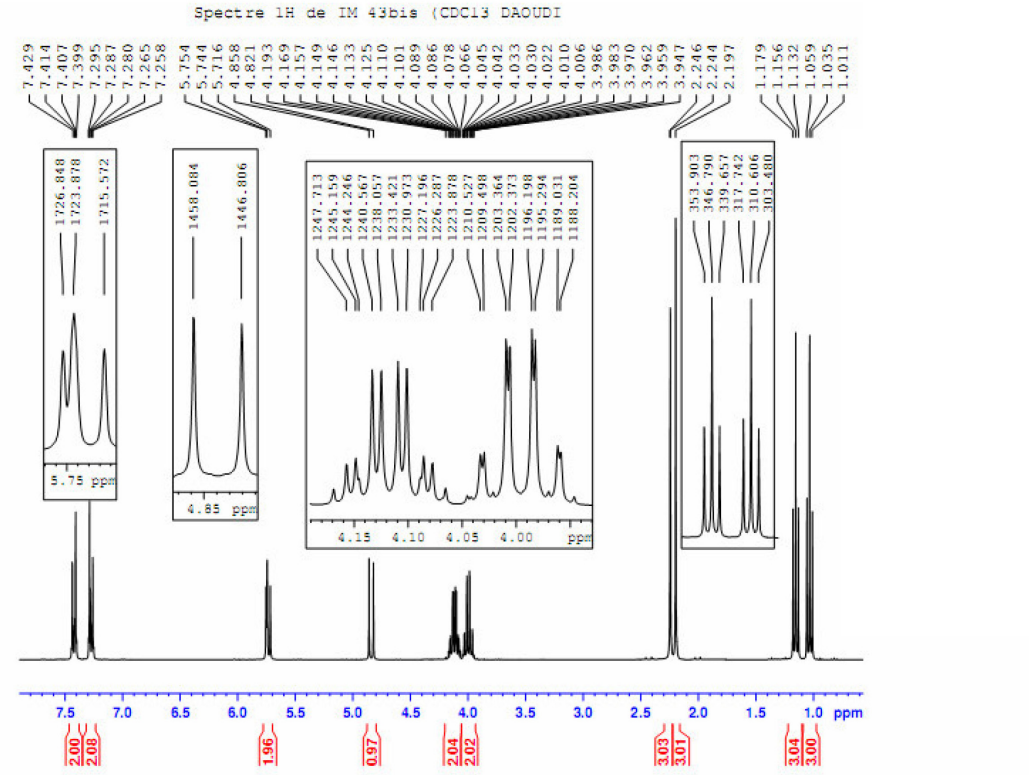

Figure S15. ^{1}H NMR (300 MHz) spectrum of compound **10** in $CDCl_3$.

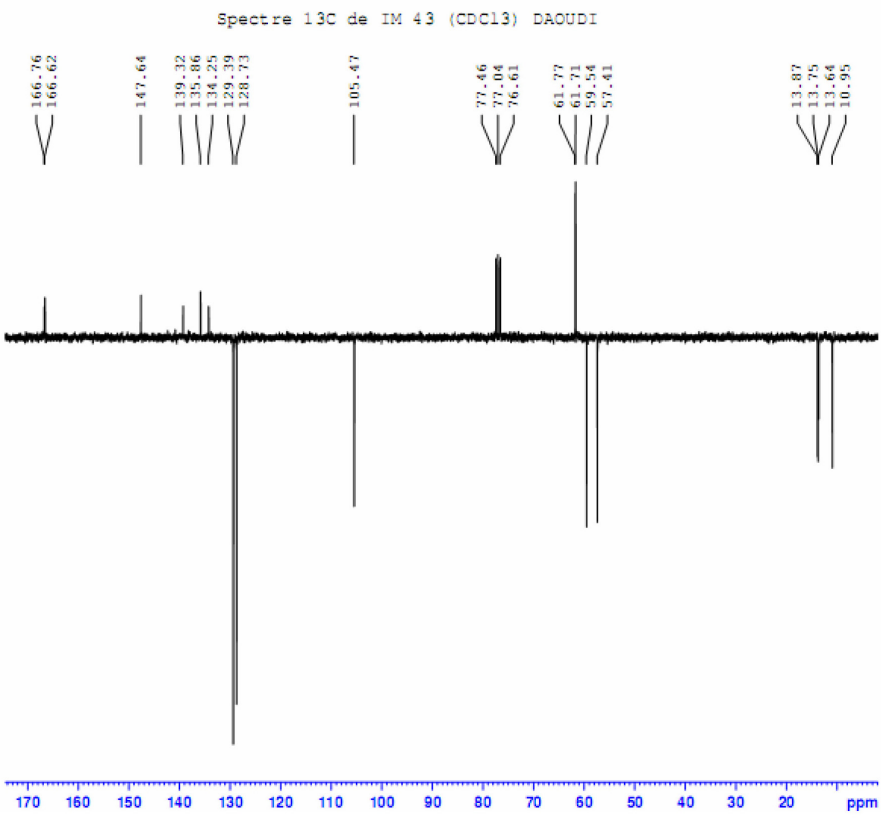

Figure S16. ^{13}C NMR (75.5 MHz) spectrum of compound **10** in $CDCl_3$.

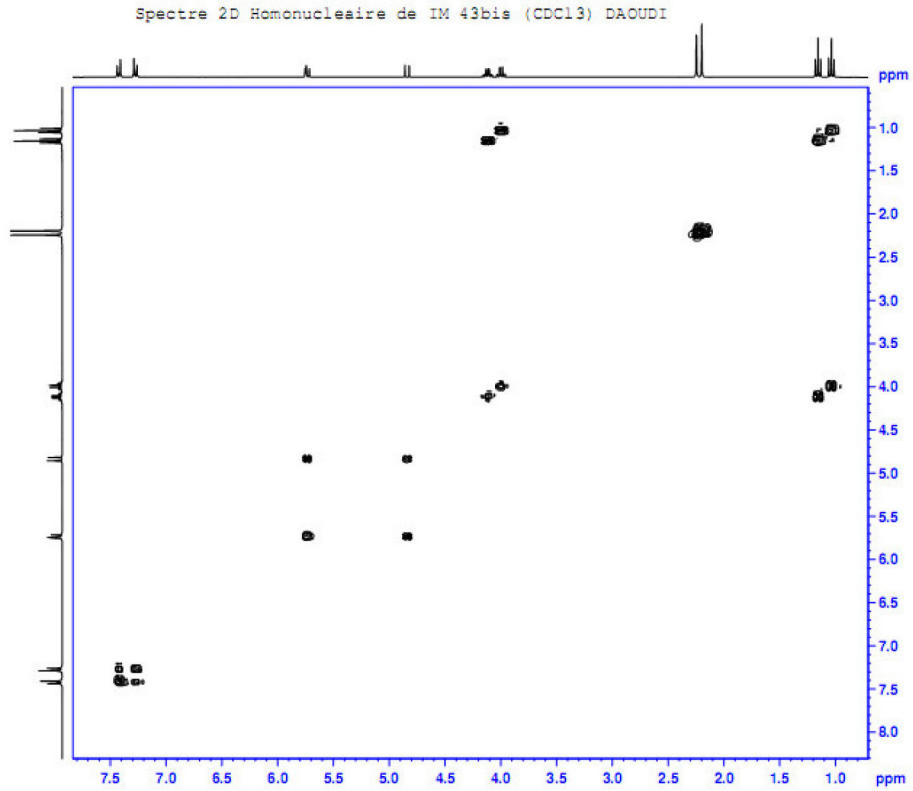

Figure S17. COSY of compound **10** in $CDCl_3$.

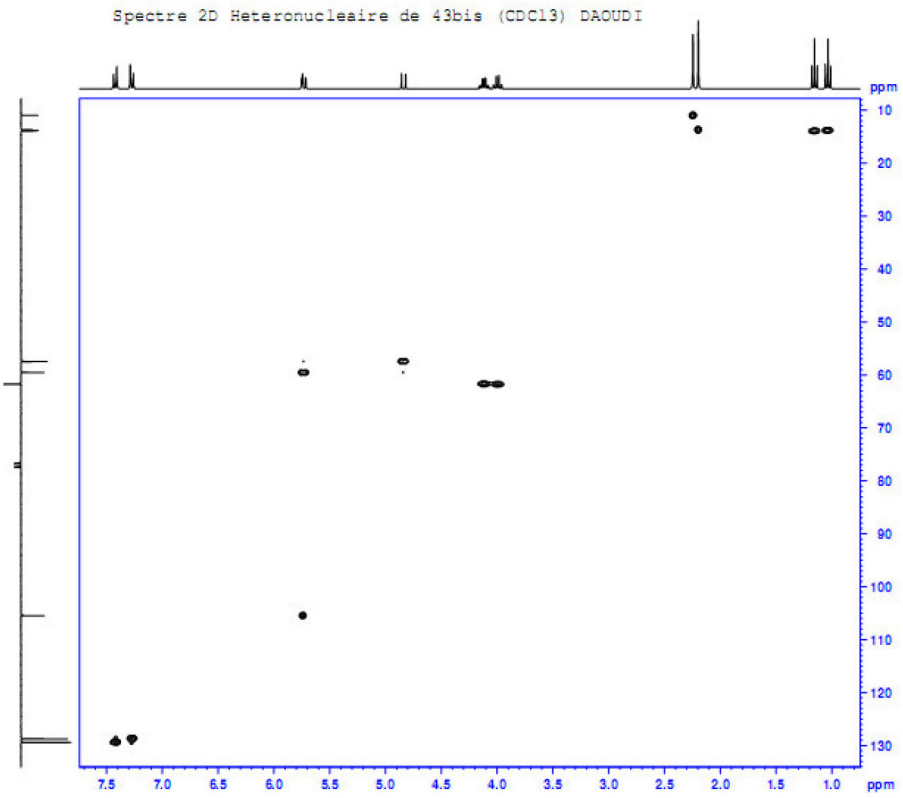

Figure S18. HETCOSY of compound **10** in $CDCl_3$.

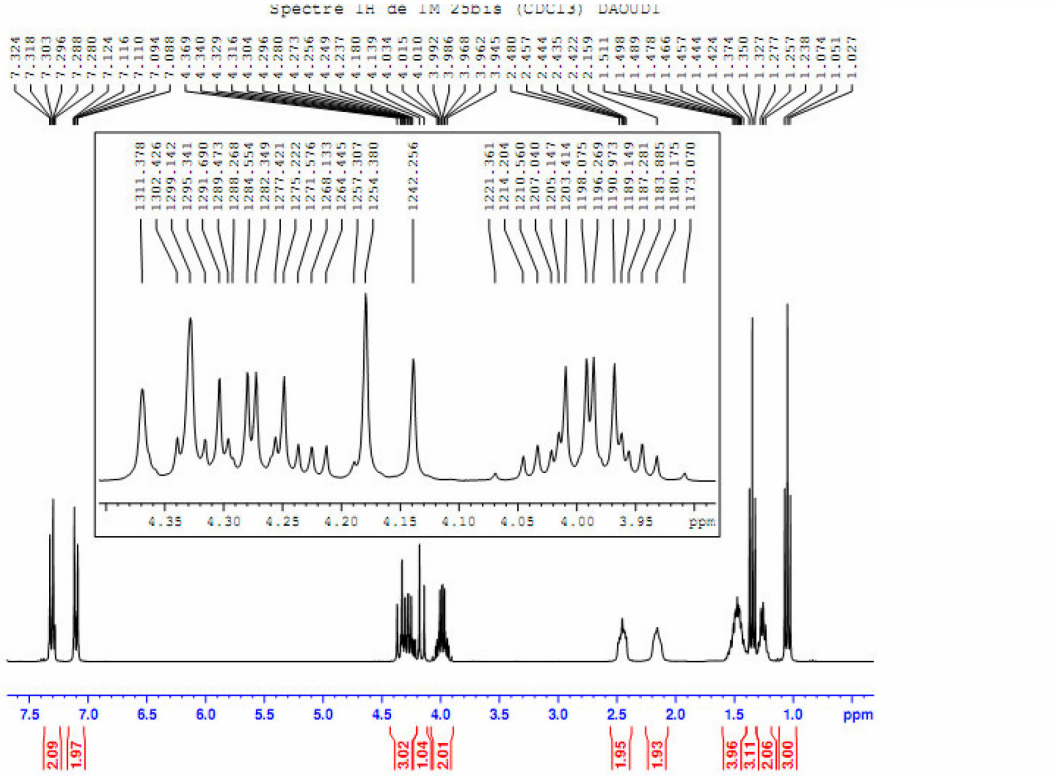

Figure S19. ^1H NMR (300 MHz) spectrum of compound **11** in $CDCl_3$.

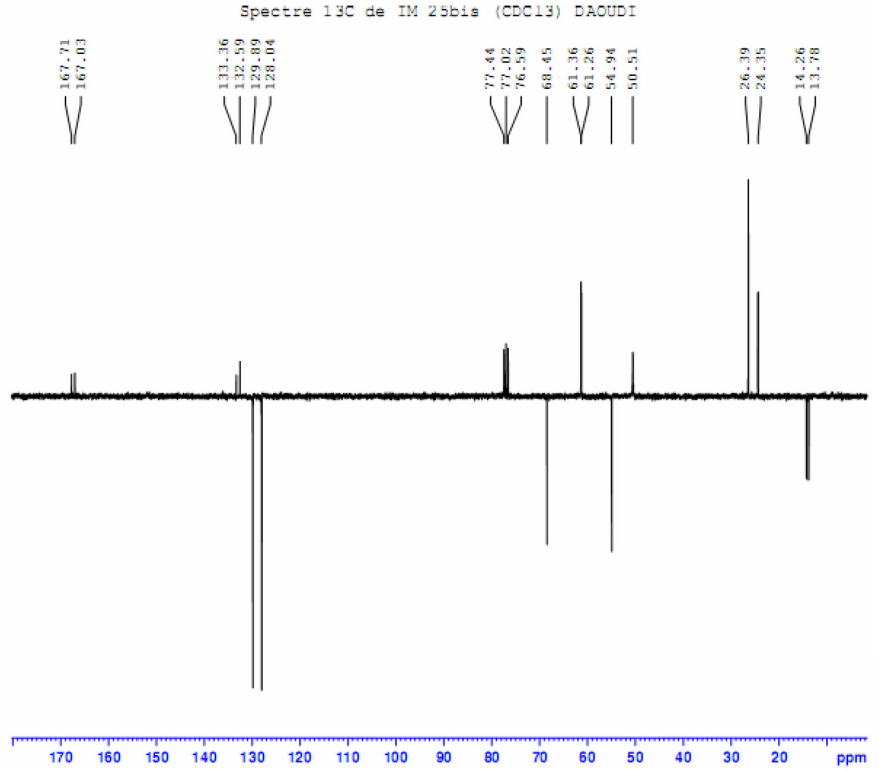

Figure S20. ^{13}C NMR (75.5 MHz) spectrum of compound **11** in $CDCl_3$.

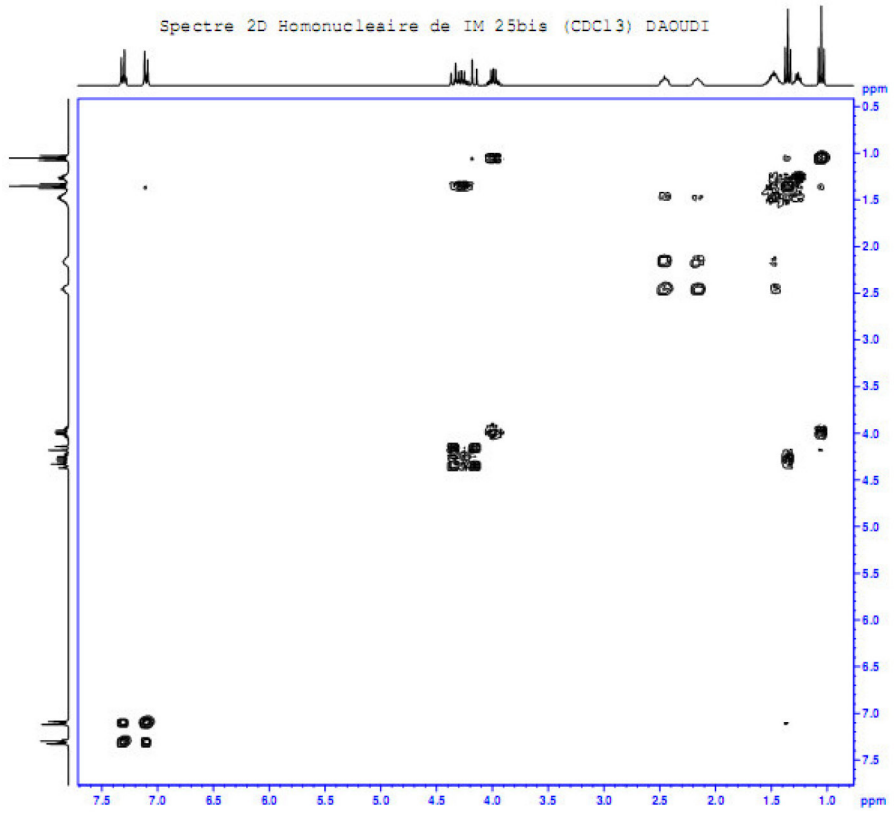

Figure S21. COSY of compound **11** in $CDCl_3$.

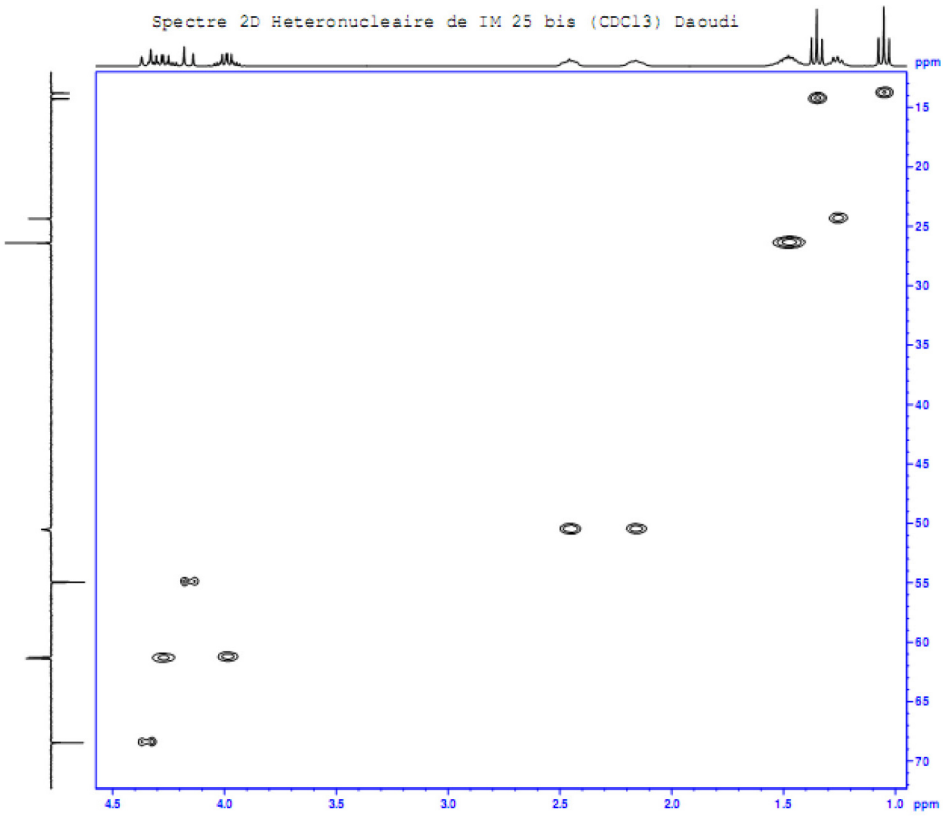

Figure S22. HETCOSY of compound **11** in $CDCl_3$.

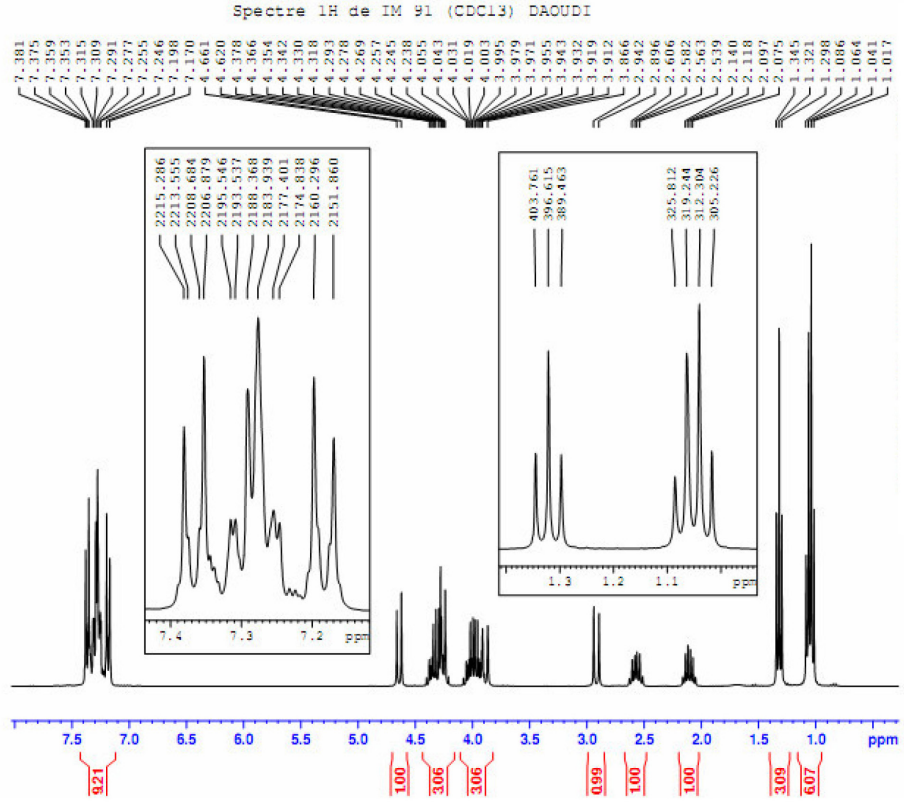

Figure S23. ^1H NMR (300 MHz) spectrum of compound **12** in $CDCl_3$.

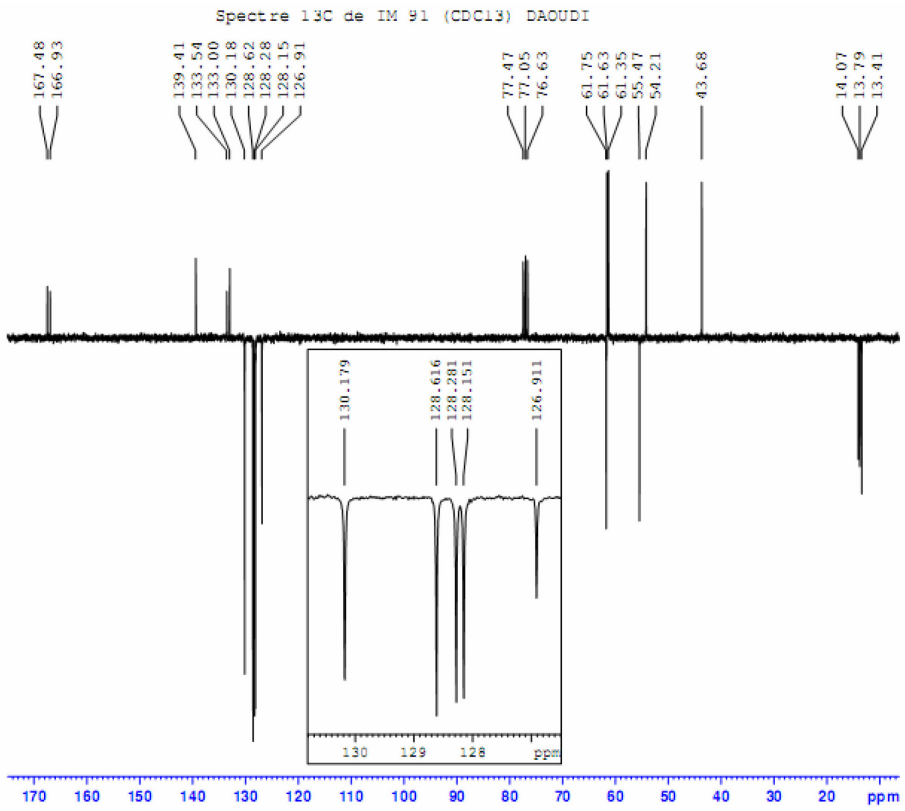

Figure S24. ^{13}C NMR (75.5 MHz) spectrum of compound **12** in $CDCl_3$.

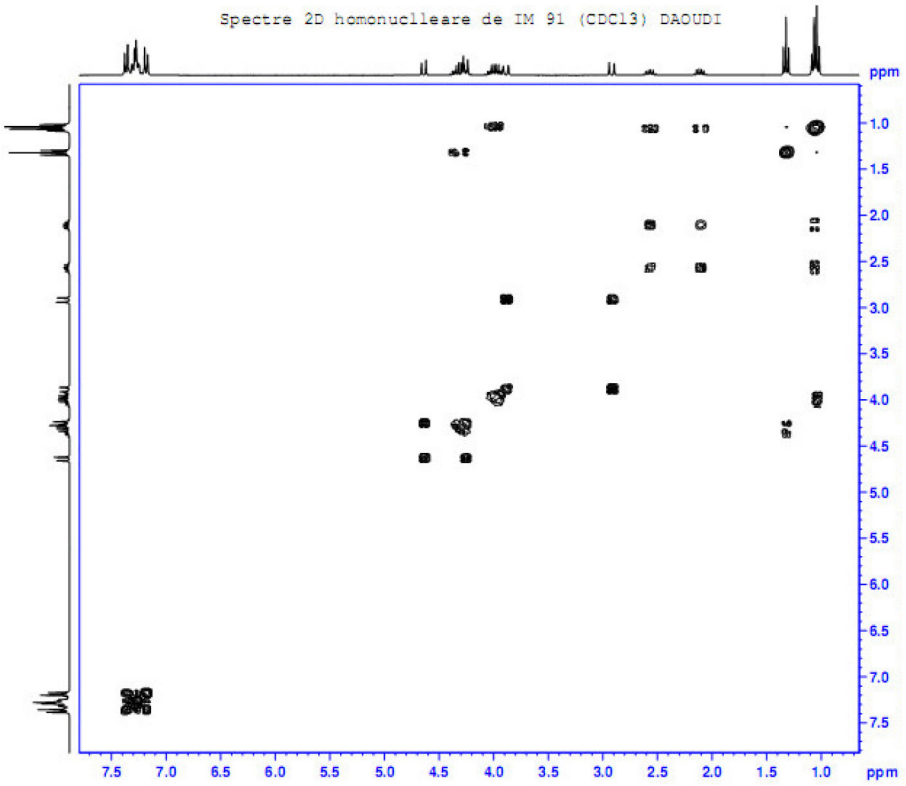

Figure S25. COSY of compound **12** in $CDCl_3$.

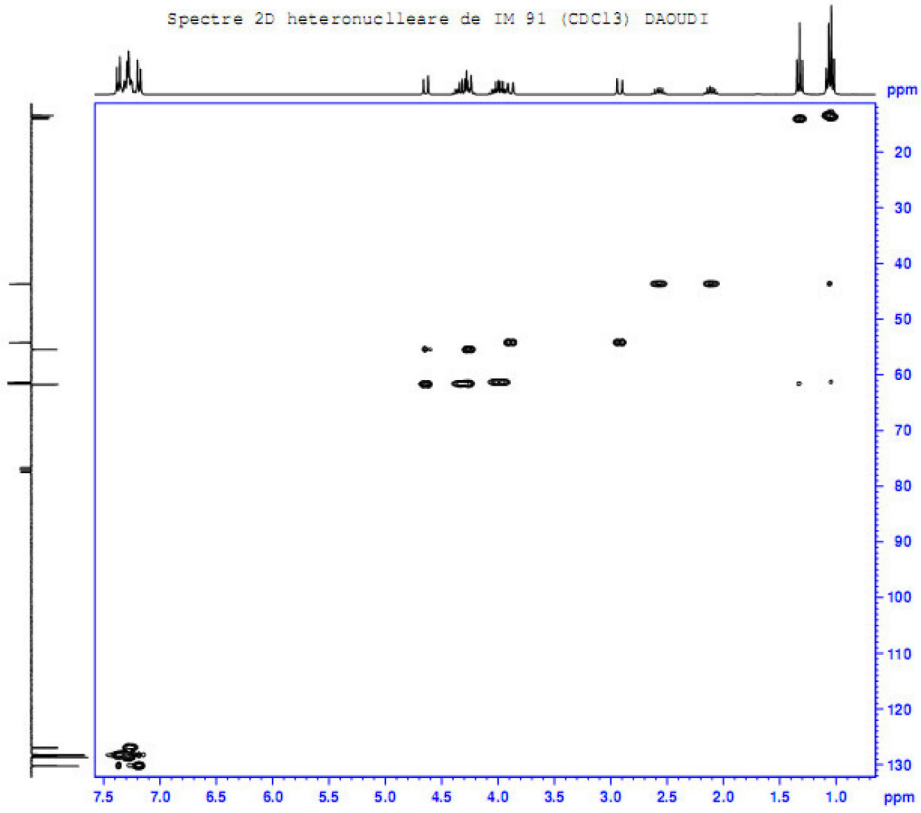

Figure S26. COSY of compound **12** in $CDCl_3$.