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Short Report

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

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Compostos β-amino-dicarbonilados constituem uma classe de ligantes promissores para a química de coordenação. Diante desta perspectiva, um método eficiente e fácil visando à síntese de compostos β-amino-dicarbonilados foi desenvolvido, explorando a reação de adição do tipo azo-Michael em meio aquoso. Com isso, uma série de dez dietil 2-(feniletil)malonatos dissubstituídos foram obtidos de uma maneira regiosseletiva e facilmente purificados, levando à rendimentos satisfatórios. As análises cristalográficas de dois destes compostos forneceram as informações apropriadas sobre a conformação e configuração dos mesmos. Por último, uma proposta complementar do mecanismo reacional para as reações de adição de Michael em meio aquoso foi também descrito.

β-Amino dicarbonyl compounds comprise a class of useful ligands on the coordination chemistry. In view of their importance, an efficient and facile method for the synthesis of β-amino dicarbonyl compounds has been developed, exploring the aza-Michael addition reactions in an aqueous medium. It was possible to achieve good to excellent yields, along with regioselectivity, the substituted diethyl 2-(phenylmethyl)malonates that were easily isolated without any chromatographic purification. The correct configuration of two of these β-amino dicarbonyl compounds were confirmed by X-ray crystallography. A complementary mechanism of this aza-Michael protocol is proposed to explain the results obtained.

Keywords: polydentate ligands, β-amino dicarbonyl compounds, Michael addition, aqueous medium

Introduction

The rational design of new HIV-1 Integrase (HI) inhibitors, a valid target for chemotherapeutic intervention,[1] is primarily based on intermolecular coordination between HI / chemical inhibitor / metals (Mg^{2+} and Mn^{2+}, co-factors of the HI), leading to the formation of bimetallic complexes.[2,3] A number of bimetallic metal complexes, in many cases exploring the well-known polydentate ligands, appear therefore in this context to be the most promising drug candidates to HI inhibitors.[4,5] Another interesting application for such polydentate ligands involves the synergic water activation that occurs by way of the so-called 'remote metallic atoms'. Such organometallic

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compounds are considered in structural terms to block the intramolecular electron transfer on the HI structure.[6] This explanation clearly demonstrates that polydentate ligands are of special interest in the field of bioorganometallic chemistry.[7] In view of our interest in designing novel bimetallic coordinating ligands[8] endowed with potential action to inhibit the HI enzyme, the object of this study is the synthesis of polydentate ligands with the same topology, as drawn in Figure 1.[9]

For preparation of such polydentate ligands, the aza-Michael reactions appear to be the key-step leading the expected β-amino esters adducts.[10] In fact, this kind of reaction has been widely employed to generate structurally diverse β-amino dicarbonyl compounds, where the undoubted importance of the aza-Michael step can be seen from the large number of unconventional methodologies, as well as the broad range of applications.[11] Most of these unconventional methodologies have used Lewis acids, which although leading to satisfactory yields, require to remove the Lewis acids through tediously chromatography.[12] Moreover, the use of an aqueous medium also has been successful achieved.[13] As a drawback, the use of substituted alkenes, such as benzylidene-malonic acid diethyl ester, is rarely reported in the literature. These substrates are expected to be less reactive or conversely more resistant to undergo the Michael condensation, resulting in low conversion of the desired adducts.[14] For a synthetic point of view, this is a considerable limitation on the aza-Michael reaction process and poses a significant challenge.

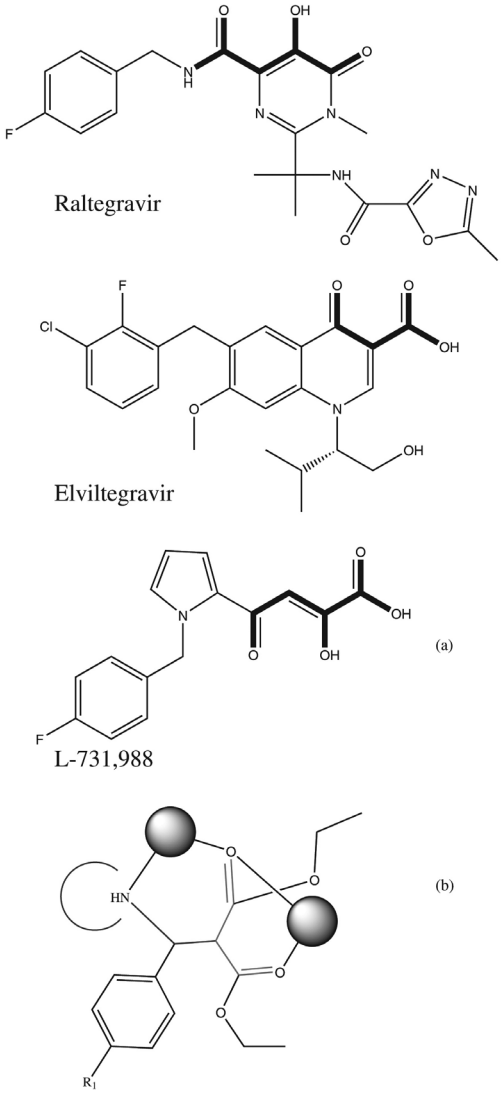


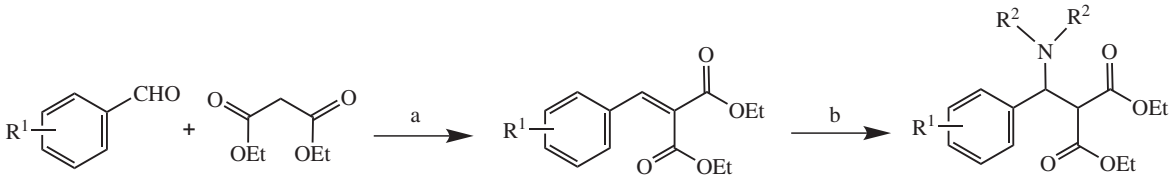
Figure 1. (a) Structures of representative HI inhibitors that act through the sequestration of enzyme's co-factors; [5] (b) Expected coordination mode for the ligands (**6-15**) after metallic complexation.

To this end, we decided to investigate the feasibility of applying the aza-Michael reactions to the more challenging substituted alkene derivatives. Our plan also included the application of this key-step to the synthesis of a novel set of polydentate ligands, in order to highlight the versatility of the procedure as well as to generate some insights regarding the reaction mechanism.

Results and Discussion

Firstly, diethyl 2-benzylidenemalonates (**4a-d**) were prepared from the classical condensation of benzaldehydes with diethyl malonate under ethanol reflux, using piperidine and glacial acetic acid as a catalyst system. This procedure furnished the intermediates, 2-arylidene-malonic acid diethyl esters (**4a-d**), very quickly and in excellent yields (Scheme 1).

To understand the scope and limitations of the aza-Michael reactions, compound **6** was chosen as the model reaction because of its thermostability and also because piperidinyl is considerably less reactive when employing the traditional Michael protocols. Some of these conditions are presented in Table 1. During the investigation of experimental conditions, it was possible to observe that the acid catalyst (HOAc, 0.1 mL) accelerates such reactions. Interestingly, only a short reaction time (3 h) was required to furnish product **6** on very good yields with no detected by-products (Table 1, entries 4 and 5). In contrast, neither the presence of co-solvent (EtOH) nor the heating were crucial, the yields remaining similar to or lower than those expected when using pure water (entries 2 and 3). Boric acid also well works, but it was necessary additional purification by chromatography. Apart from the aqueous medium, the use of dichloromethane as solvent at catalyst-free condition led to low conversion (yield < 20%) of the desired product **6**, in agreement with the previous results by Shou and colleagues.[15]



4a: R^1 = H
4b: R^1 = *p*-Cl
4c: R^1 = m-OCH_3
4d: R^1 = *p*-OCH_3

compounds **6**-**15**

Scheme 1. General synthesis of the polydentate ligands (**6-15**). Reagents and conditions: a) piperidine, HOAc, EtOH, reflux, 12 h; b) secondary amine, water, r.t., catalyst.

Table 1. Investigation of the aza-Michael condensation promoted by aqueous medium for the synthesis of compound **6**

Entry	Catalyst	Co-solvent	Temp (°C)	time (h)	Yield [a] (%)
1	None	None	30	120	80
2	None	None	100	3	30[b]
3	None	EtOH[c]	30	120	61
4	HOAc[d]	None	30	3	78
5	HOAc[d]	None	60	3	75
6	Boric acid (10% mol)[e]	None	30	4	63

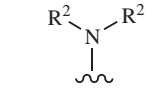
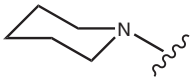
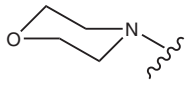
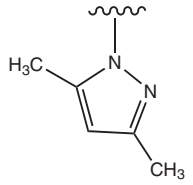
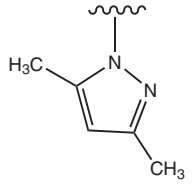
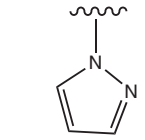
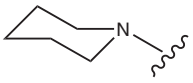
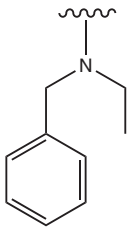
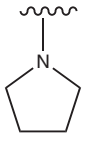
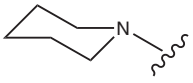
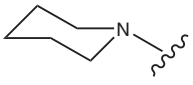
[a] Determined as isolated products after recrystallization; [b] The starting materials were recovered and at the same time, by-products were observed; [c] Using only EtOH, as reported in reference 9; [d] 0.1 mL of HOAc (pH = 4.5); [e]Similar to reported by Chaudhuri.[12]

Having determined the best conditions, it was identified that precursors **4a-d** reacted satisfactorily, albeit slowly, with various secondary amines under catalyst-free conditions to provide the desired adducts **6-15** in good to excellent yields, along with regioselectivity and without needs of column chromatography (Table 2). Moreover, the reactions proceeded normally even when the methoxy group was attached on aromatic ring (**14** and **15**), in contrast with the protocol described by Shou and colleagues.[15] It is worth noting that the yields were found to be essentially the same as those obtained when the reactions were performed under either the presence or absence of the acid catalyst (HOAc). These results suggest that the acid catalyst accelerates the aza-Michael reactions under these substrates.

These products were characterized using spectroscopic and micro-analytical data. Compounds **8** and **9** were crystallized from ethanol solutions and gave single crystals suitable for X-ray analysis. These single crystals displayed centrosymmetric space groups for both compounds, indicative that each crystalline structure was composed of both enantiomers. An ORTEP view of the polydentate ligands **8** and **9** are shown in Figures 2 and 3, while the crystal data for these are reported in Table 3 and the bond lengths and angles of compound **9** are summarized in supplementary material. In the molecular structure of **9**, the nitrogen (N2) and the two oxygen (O1 and O3) of the carbonyl groups are in cisoidal / transoidal conformations, with respective dihedral angles of the 0.04(1), 145.7(2) and 88.3(1) for the planes O1–C3–C6–O2, O1–C3–C1–N1 and O3–C6–C1–N1. We have note that after the *trans* addition around the C1=C2 double bond; the observed angles were quite different from 180° [H1–C1–C2–H2 = 176.9(2), C3–C2–C1–C9 = 56.9(1) and N1–C1–C2–C6 = 60.6(9)]. In fact, these untypical values were confirmed by the angle of atoms in *trans* positions, which was again different of 180°, as the example the [N1–C1–C2–H2 = −60.3(5)]. More unexpected, it was possible to observe that, in contrast with the polydentate ligand **8**, the crystal structure of the ligand **9** was stabilized by one unusual intramolecular type-H bonding within the $C–Cl^{+\delta\cdots-\delta}N=C$, resulting in an interesting 3D network, as depicted in Figure 4.

In light of this interesting finding, we decided to apply several primary amines (arylamines, benzylamines, 1,4-phenylenediamine and unprotected amino acids) using this same synthetic protocol, but the presence of the desired products was no longer observed in all the cases using either prolonged reaction times or a large excess of amines. In contrast to secondary amines, which enabled functionalized polydentate compounds **6-15** to be obtained in good to excellent yields, the reaction of **4a-d** with the primary amines (arylamines, benzylamine and *para*-phenylenediamine) in water did not furnish the expected polydentate ligands bearing the central RN-H group, either

Table 2. Aqueous medium-promoted aza-Michael condensation

Starting Compound		Products	At HOAc-catalyst [a]		At Catalyst-free [b]	
			time	Yield[c] (%)	time	Yield[c] (%)
4a		**6**	3	78	168	80
4b		**7**	3	80	168	96
4a		**8**	Nd	Nd	168	76
4b		**9**	Nd	Nd	168	73
4b		**10**	5	68	168	71
4b		**11**	3	70	168	67
4b		**12**	Nd	Nd	168	73
4b		**13**	5	70	168	83
4c		**14**	5	63	168	75
4d		**15**	5	78	168	77

[a] See the entry 4 on Table 1; [b] See the entry 1 on Table 1; [c] Isolated yields, when Nd is not determined.

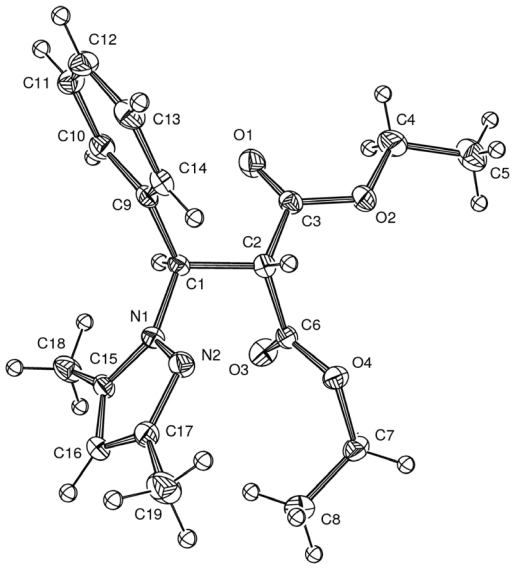


Figure 2. ORTEP drawing of compound **8** in its correct configuration with thermal ellipsoid plot (50% probability). Critical distances [O1—O3 = 3.5(2) Å, O3—N2 = 3.9(3) Å and O1—N2 = 5.0(6) Å].

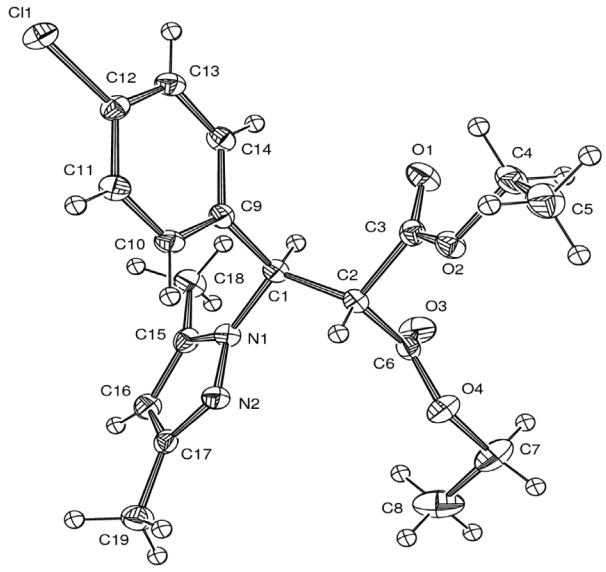


Figure 3. ORTEP view of the compound **9** with the atom numbering scheme. Displacement ellipsoids for non-H atoms are drawn at the 50% probability level. Critical distances [O1—O3 = 3.3(3) Å, O3—N2 = 3.8(2) Å and O1—N2 = 5.0(3) Å].

in the presence of the acid catalyst (HOAc) or with the addition of more than one equivalent of aniline.

Moreover, the mechanism for formation of the aza-Michael adducts should be mentioned. This is different from the Lewis acid-promoted aza-Michael reactions, in that such Lewis acids function by activating the unsaturated double bond, generating a nucleophilic attack by way of chelation of the 1,3-dicarbonyl core. More recently, Ranu and Banerjee[13] have argued that the aqueous medium creates a dual action through the H-bonds, increasing

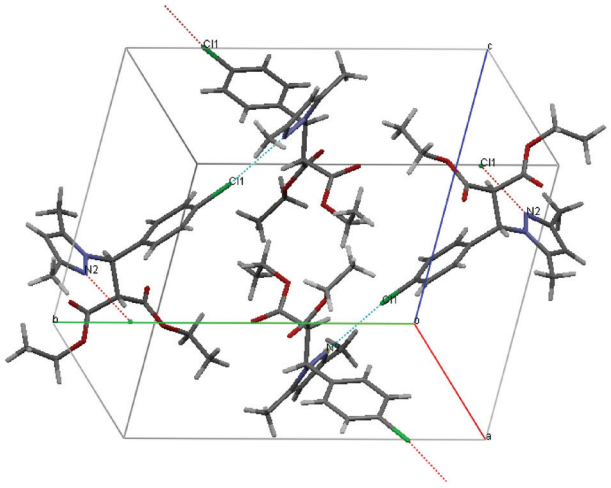
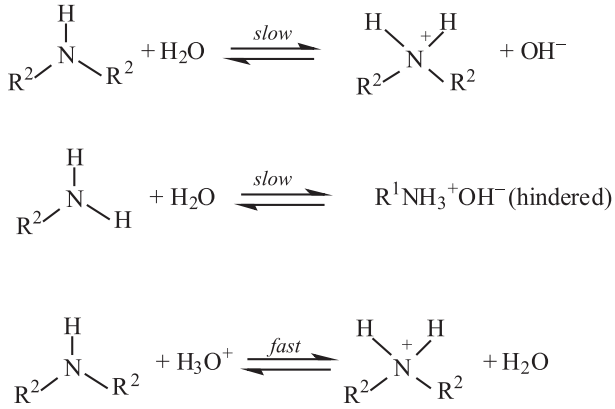


Figure 4. View of the H-bonding interactions of the ligand **9** in the unit cell.

the nucleophilic character of the nitrogen atom of the amine. This proposed mechanism would seem to present a plausible and satisfactory explanation of the formation of enol intermediates. To complement this, we would like to address the issue of why this protocol did not work well with primary amines. Since the chemical behaviour of primary and secondary amines undergoing these aza-Michael reactions is quite different, it is plausible to suggest that secondary amines in an aqueous medium probably give rise to the formation of ammonium species, which easily attacks the electrophilic alkene, thereby furnishing the unstable intermediate of addition with subsequent proton abstraction from protonated water by way of the enolate. On the other hand, using primary amines under aqueous medium probably results in the formation of ammonium salts. This implies that these ammonium salts are catalytically deactivated species or, conversely, less nucleophilic and thus less susceptible to attack from the respective alkenes (Scheme 2). Furthermore, the



Scheme 2. Possible paths of equilibrium of the reactions of amines in aqueous medium.

Table 3. Crystal data and structure refinement for the compounds **8** and **9**

X-ray data	**8**	**9**
Empirical formula	$C_{19}H_{24}N_2O_4$	$C_{19}H_{23}N_2O_4Cl$
Formula weight	344.40	378.13
Temperature	110(2) K	110(2) K
Wavelength	0.71073Å	0.71073 Å
Crystal system, space group	Monoclinic, P21/a	Monoclinic, P21/c
Unit cell dimensions		
A = 8.65020(10) Å	alpha = 90 deg.	alpha = 90 deg.
B = 16.7029(2) Å	beta = 90.220(2) deg.	beta = 92.147(2) deg.
C = 13.5938(2) Å	gamma = 90 deg.	gamma = 90 deg.
Volume	1826.25(9)Å^3	1962.70(6) Å^3
Z	4	4
Calculated density	1.253 g cm^{-3}	1.282 g cm^{-3}
F(000)	736	800
Absorption coefficient	0.218 mm^{-1}	0.220 mm^{-1}
Theta range for data collection	2.65 to 27.00 deg.	2.65 to 27.00 deg.
Limiting indices	−11<=h<=10, −21<=k<=21, −16<=l<=17	−11<=h<=10, −21<=k<=21, −16<=l<=17
Reflections collected / unique	17406 / 4274 [R(int) = 0.0479]	17406 / 4274 [R(int) = 0.0316]
Completeness to theta = 27.00	99.8 %	99.8 %
CCDC number	734198	734197

equilibrium steps occurring in the course of the aza-Michael reactions are probably the slowest, and are, consequently, speeded up when an acid catalyst is used. Additionally, a referee commented that the water effect in reactions with amines is more complex than dual activation. This statement is genuine and we agree with him. For instance, the nature of species generated from mixture of primary / secondary amines and water depends on the nucleophilicity of the employed amine.[16] Likewise, solubilization of reactants and products in water is usually of relevancy to get desirable yields in such aza-Michael reactions.[14]

Conclusions

One important result of this study was a straightforward synthesis of ten novel 2-(aryl-disubstituted amino-1-yl-methyl)-malonic acid diethyl esters (**6-15**), which constitute a functionalized class of polydentate ligands. Despite prolonged reaction times, this aza-Michael protocol led to higher yields in an aqueous medium at room temperature, and consequently, would appear to be a simple and useful synthetic protocol. Considering their high efficiency on the gram-scale synthesis, in addition to the especially high purity of the final products, this protocol appears to be of use for synthesis and pharmacological screening of drug candidates.

Experimental

General methods

*Synthesis of intermediates **4a-d***

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 × 20 mL), dried with sodium sulphate and evaporated to give the respective pure oil.

*General procedure for the synthesis of compounds **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 material. 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.

Supplementary Information

Detailed experimental procedures, full set of ^{1}H and ^{13}C NMR spectra and X-ray data are available free of charge at http://jbcs.sbq.org.br, as a PDF file.

Acknowledgements

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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)

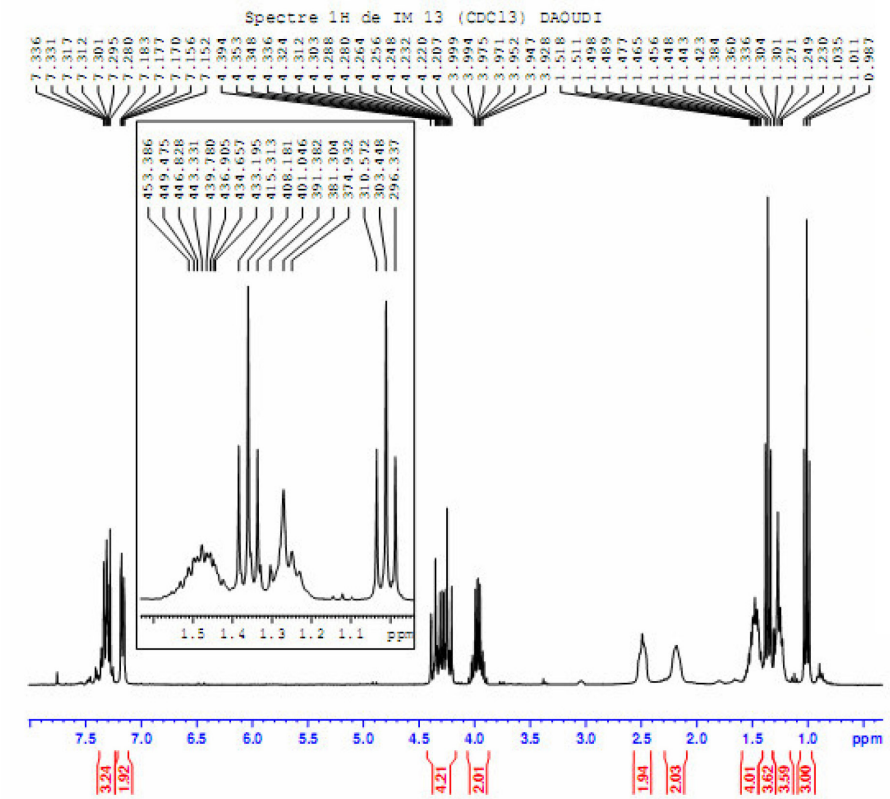

Figure S1. ^{1}H NMR (300 MHz) spectrum of compound **6** in $CDCl_3$.

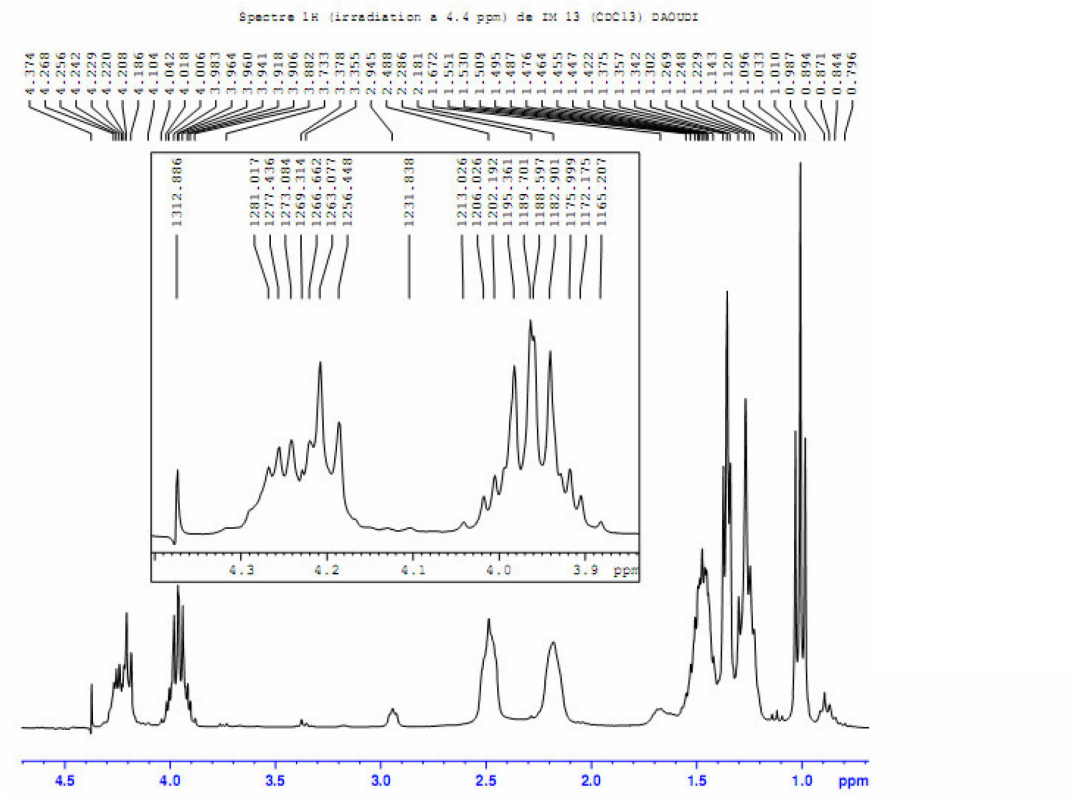

Figure S2. ^{1}H NMR (300 MHz) spectrum of compound **6** in $CDCl_3$ expanded at 4.5-1.0ppm.

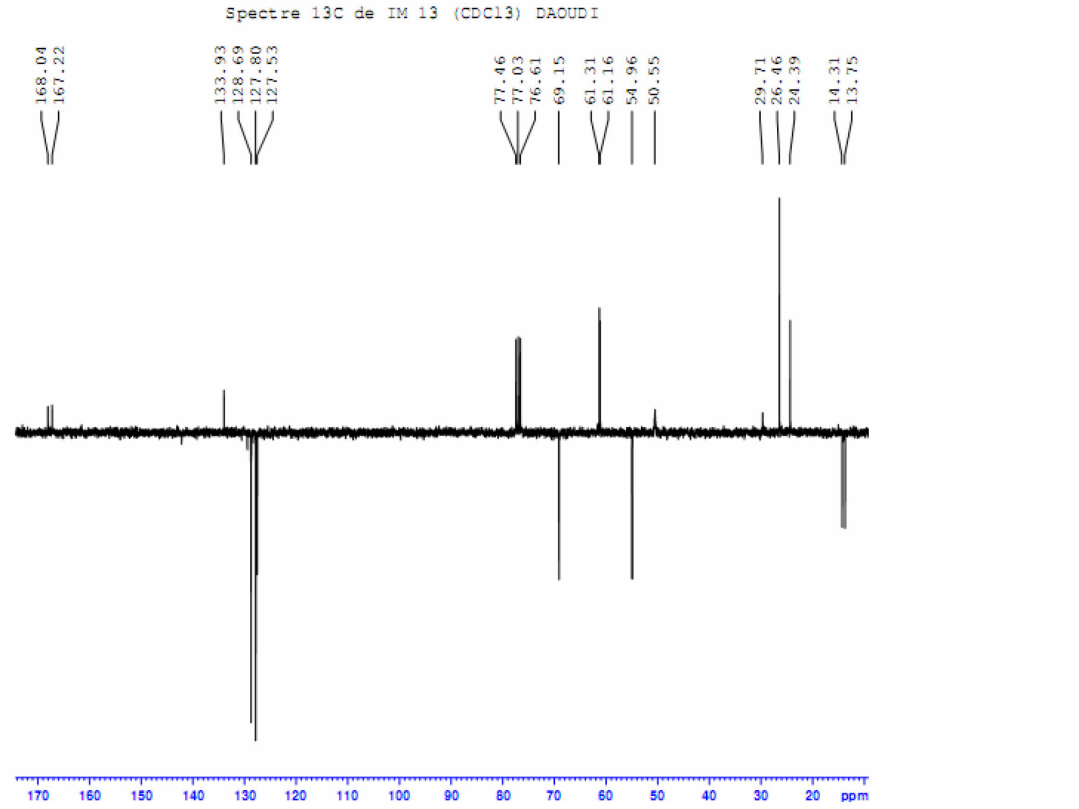

Figure S3. ^{13}C NMR (75 MHz) spectrum of compound **6** in $CDCl_3$.

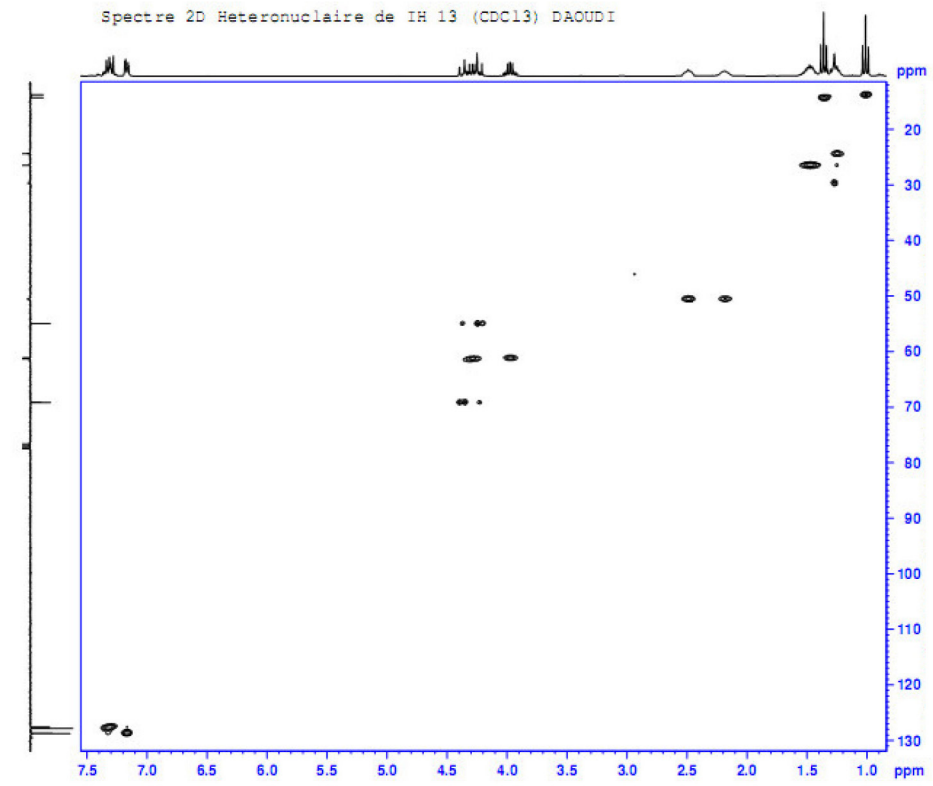

Figure S4. HETCOR of compound **6** in $CDCl_3$.

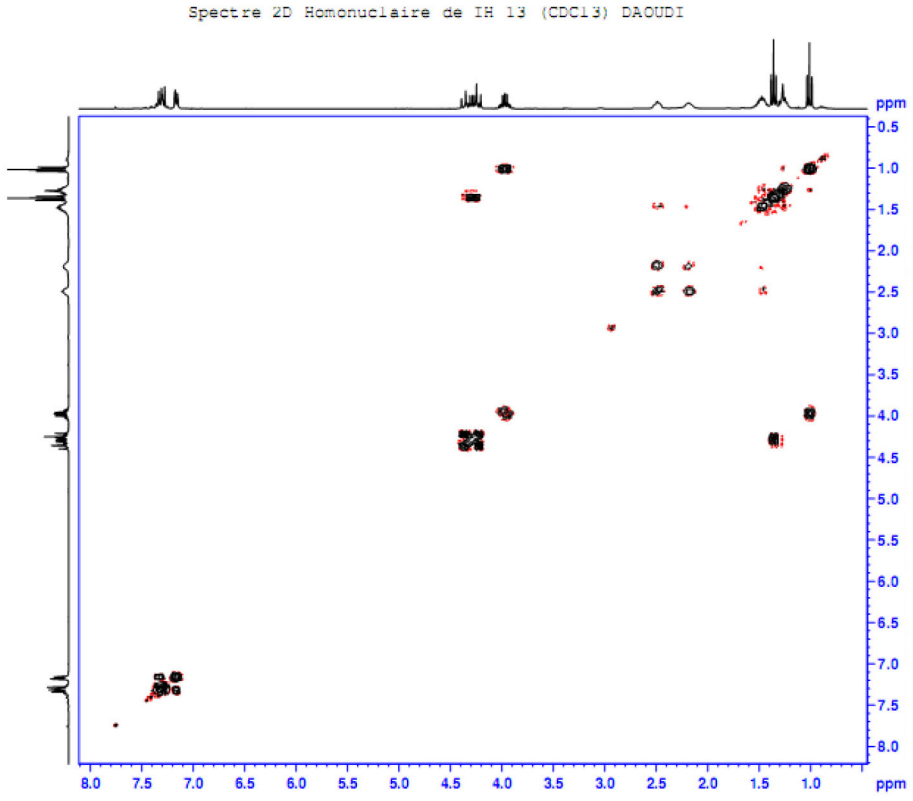

Figure S5. COSY of compound **6** in $CDCl_3$.

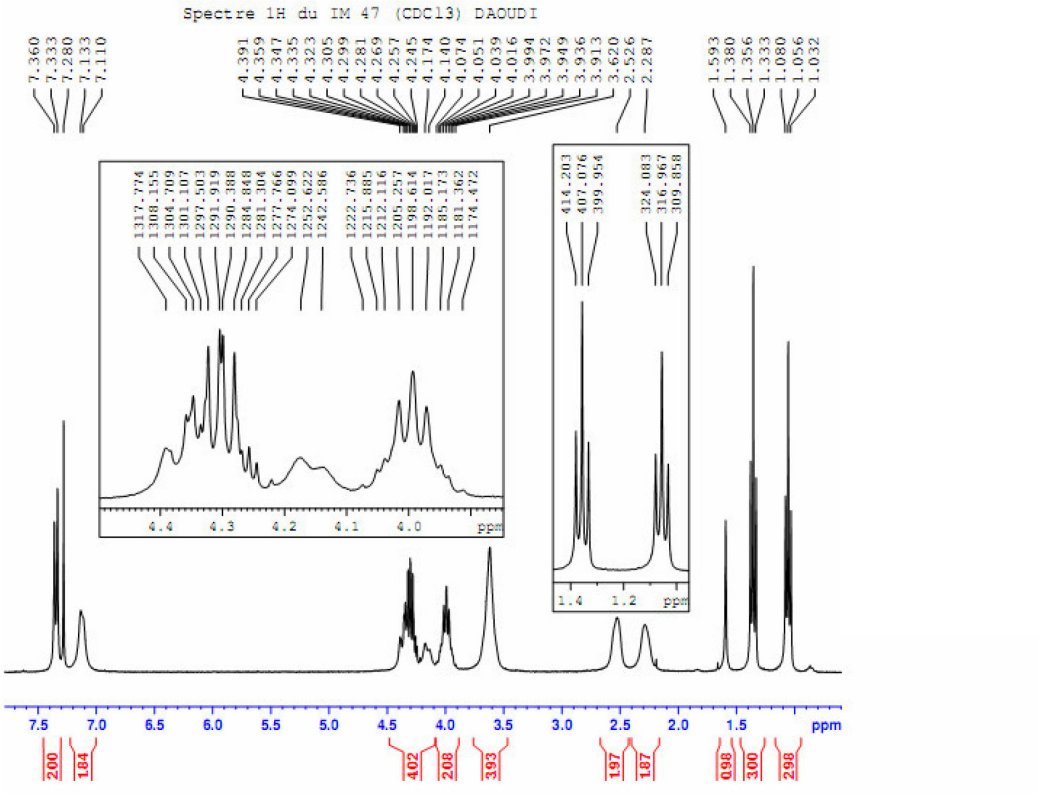

Figure S6. [1]H NMR (300 MHz) spectrum of compound **7** in $CDCl_3$.

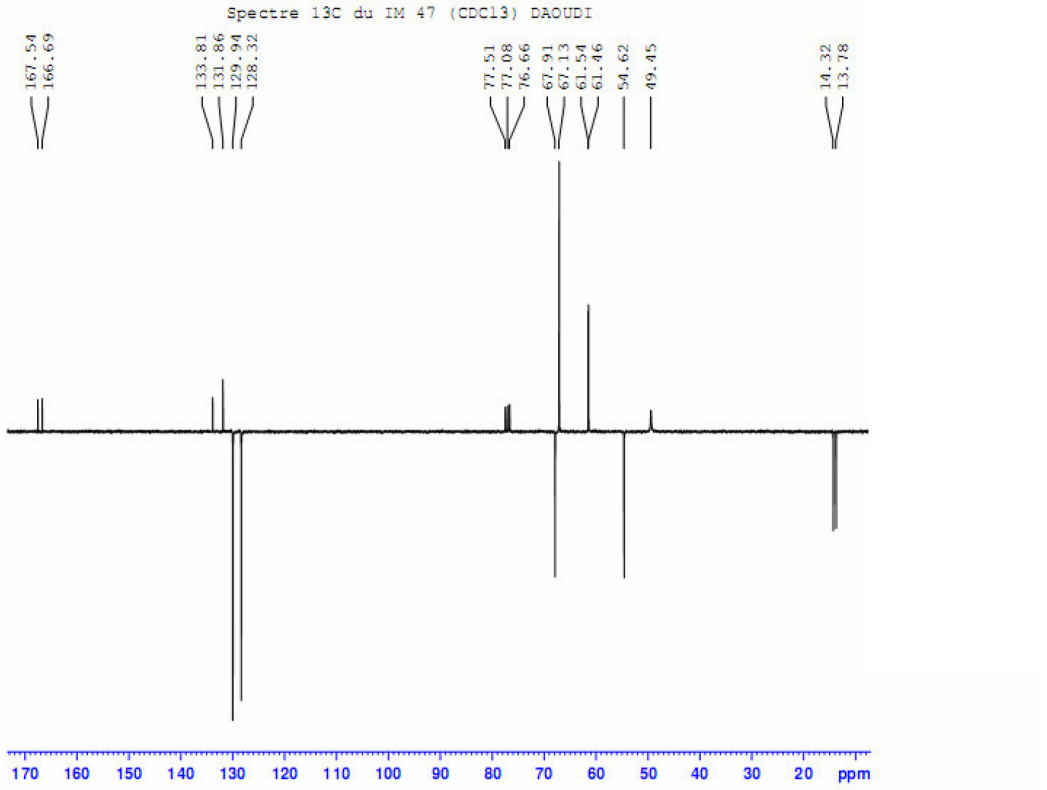

Figure S7. [13]C NMR (75 MHz) spectrum of compound **7** in $CDCl_3$.

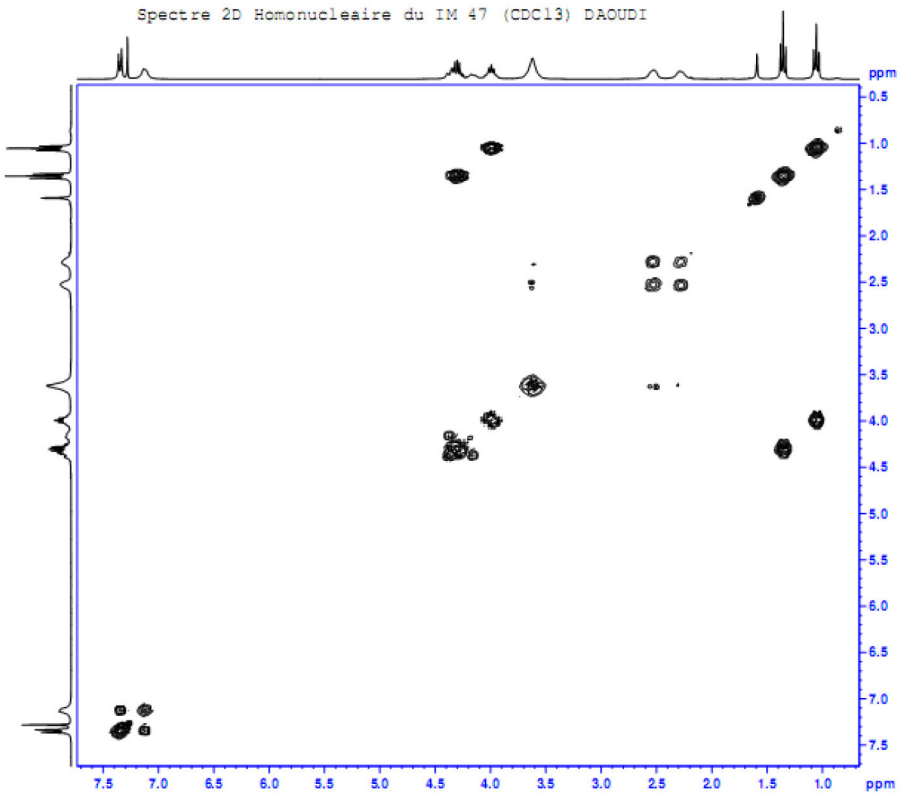

Figure S8. COSY of compound **7** in $CDCl_3$.

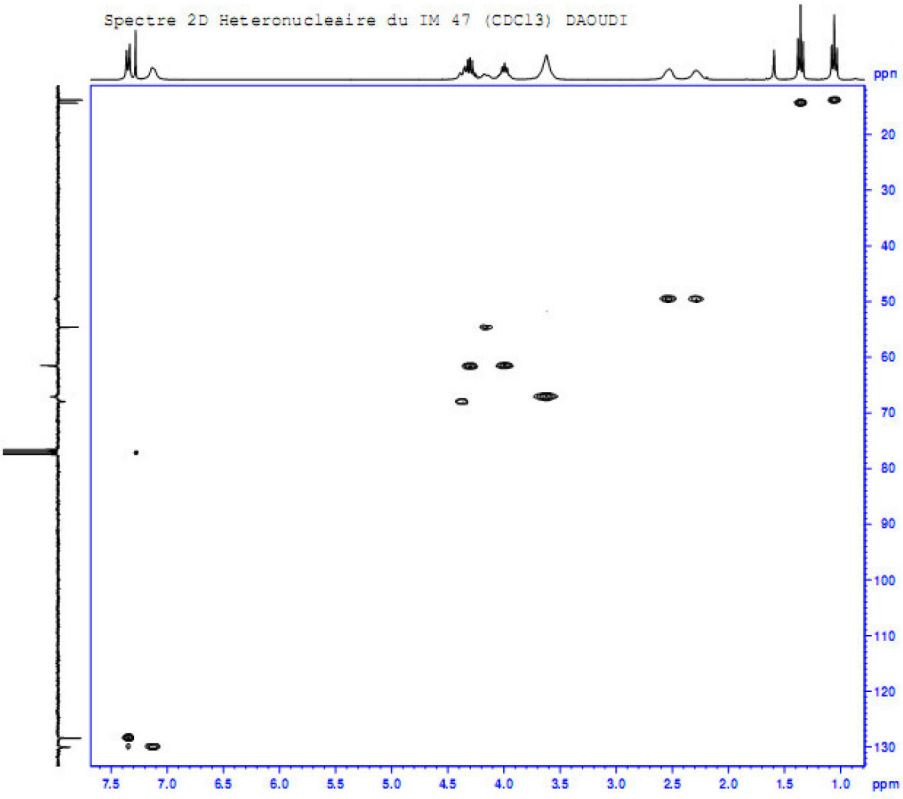

Figure S9. HETCOSY of compound **7** in $CDCl_3$.

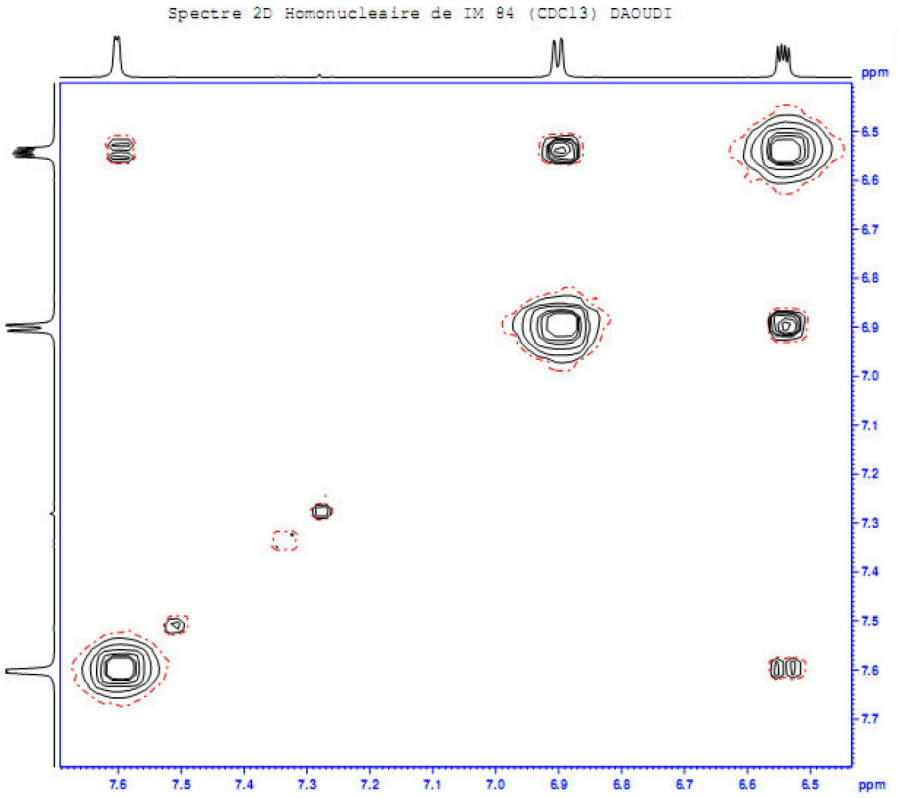

Figure S10. COSY of compound **7** in $CDCl_3$.

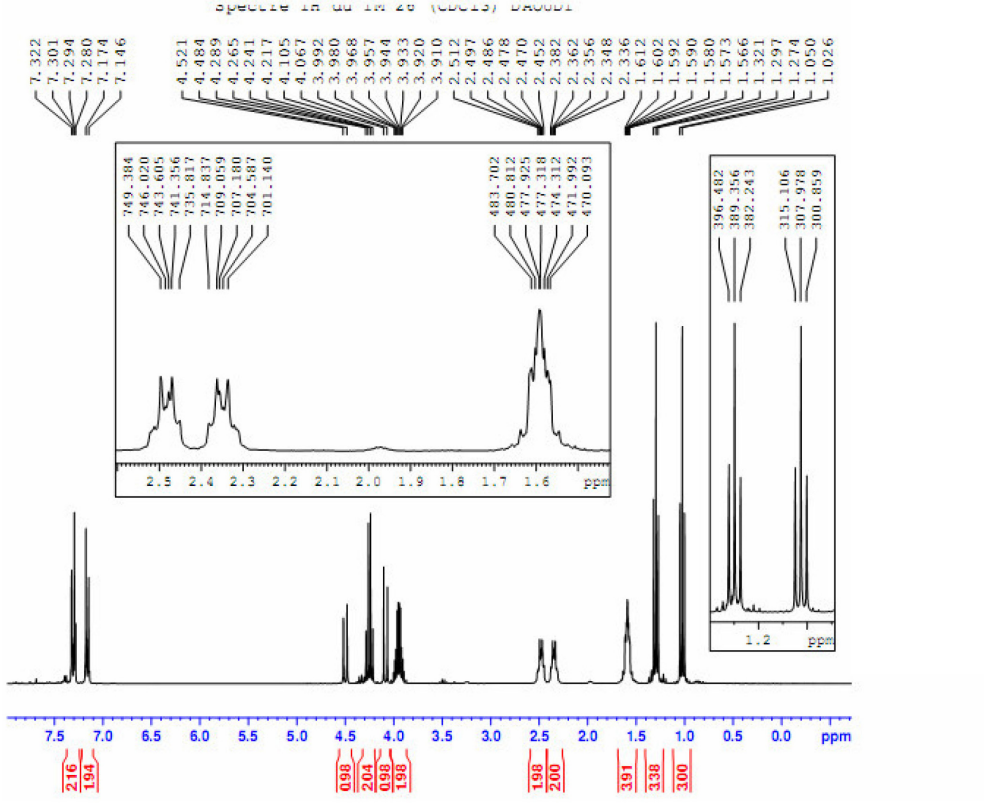

Figure S11. ^1H NMR (300 MHz) spectrum of compound **9** in $CDCl_3$.

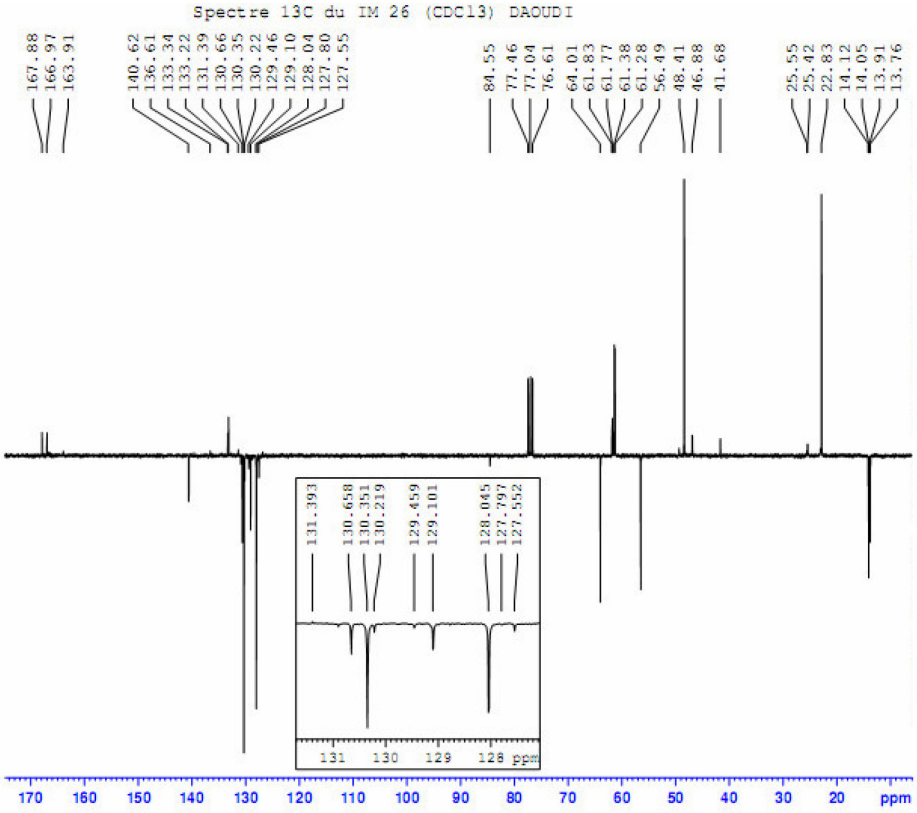

Figure S12. ^{13}C NMR (75.5 MHz) spectrum of compound **9** in $CDCl_3$.

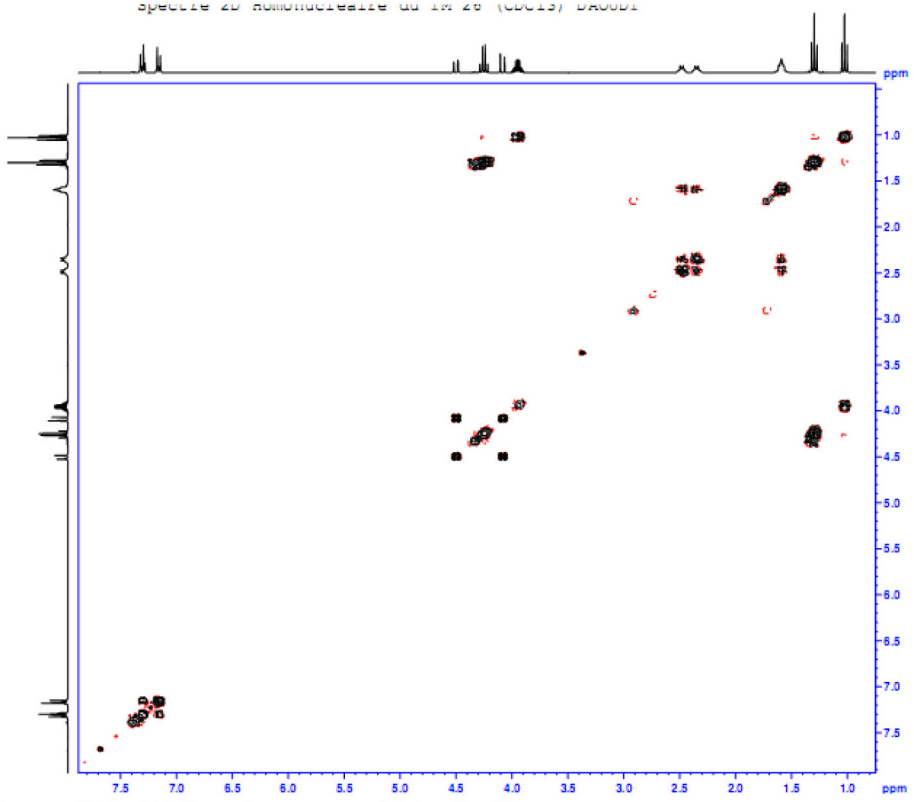

Figure S13. COSY of compound **9** in $CDCl_3$.

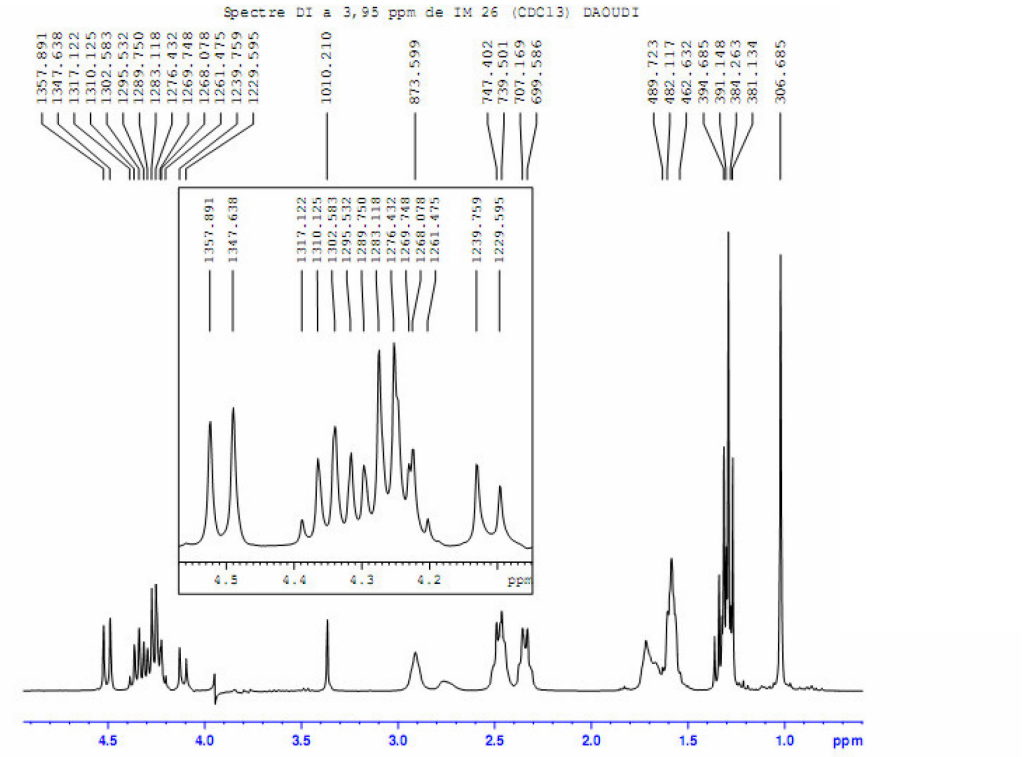

Figure S14. ^{1}H NMR (300 MHz) spectrum of compound **9** in $CDCl_3$ expanded at 4.5-1.0ppm.

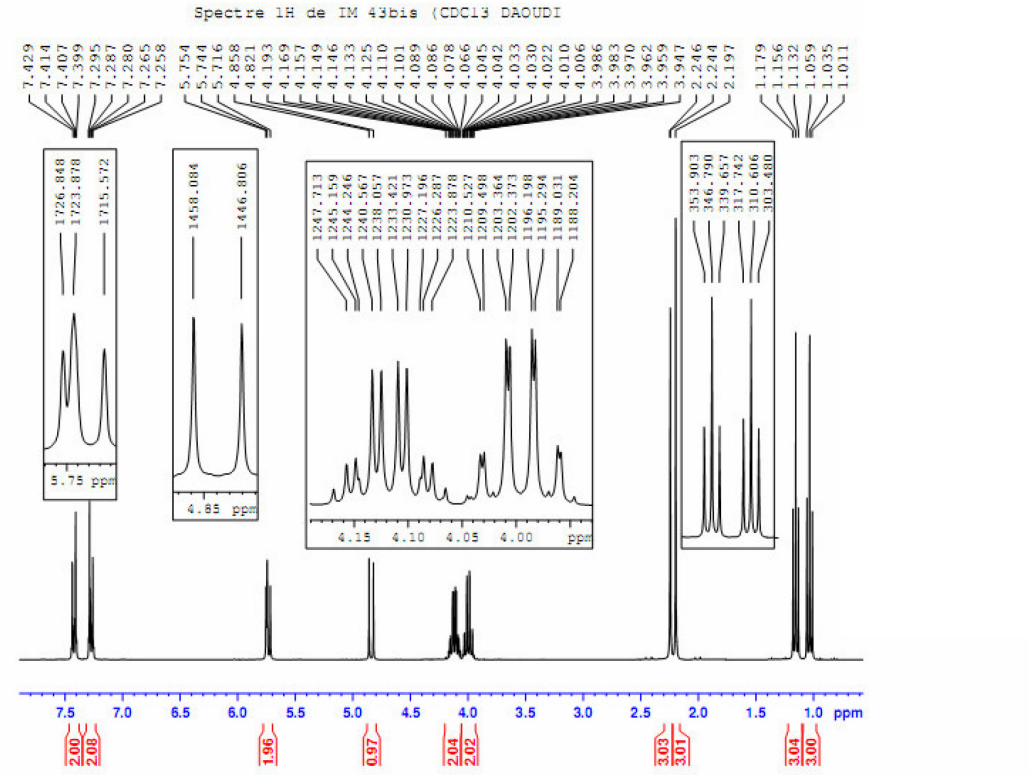

Figure S15. ^{1}H NMR (300 MHz) spectrum of compound **10** in $CDCl_3$.

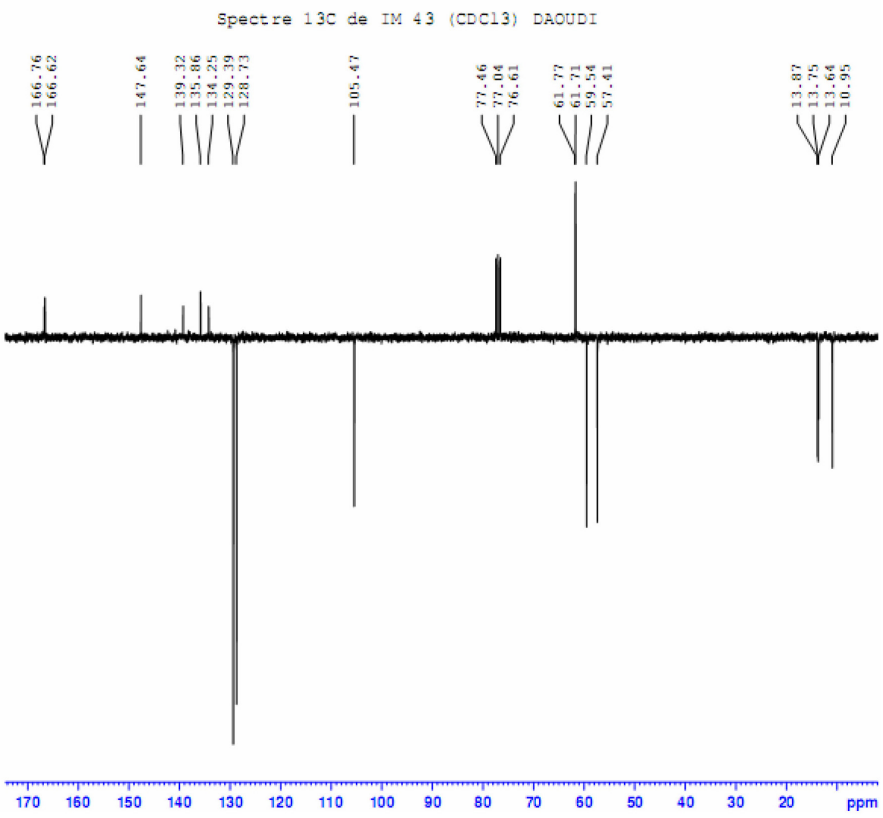

Figure S16. ^{13}C NMR (75.5 MHz) spectrum of compound **10** in $CDCl_3$.

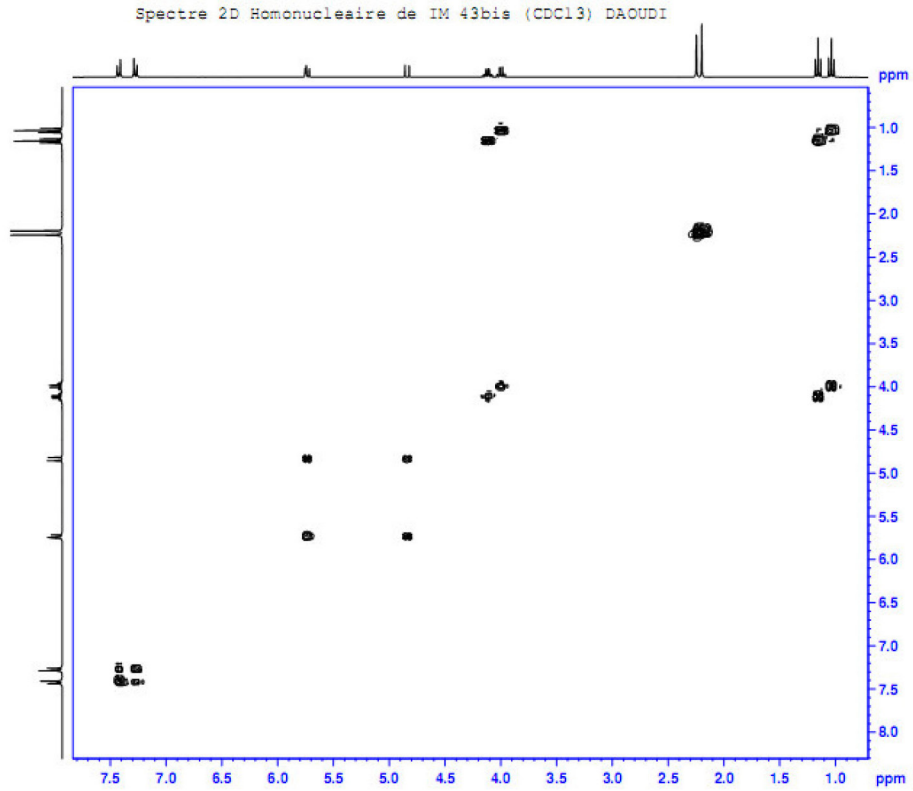

Figure S17. COSY of compound **10** in $CDCl_3$.

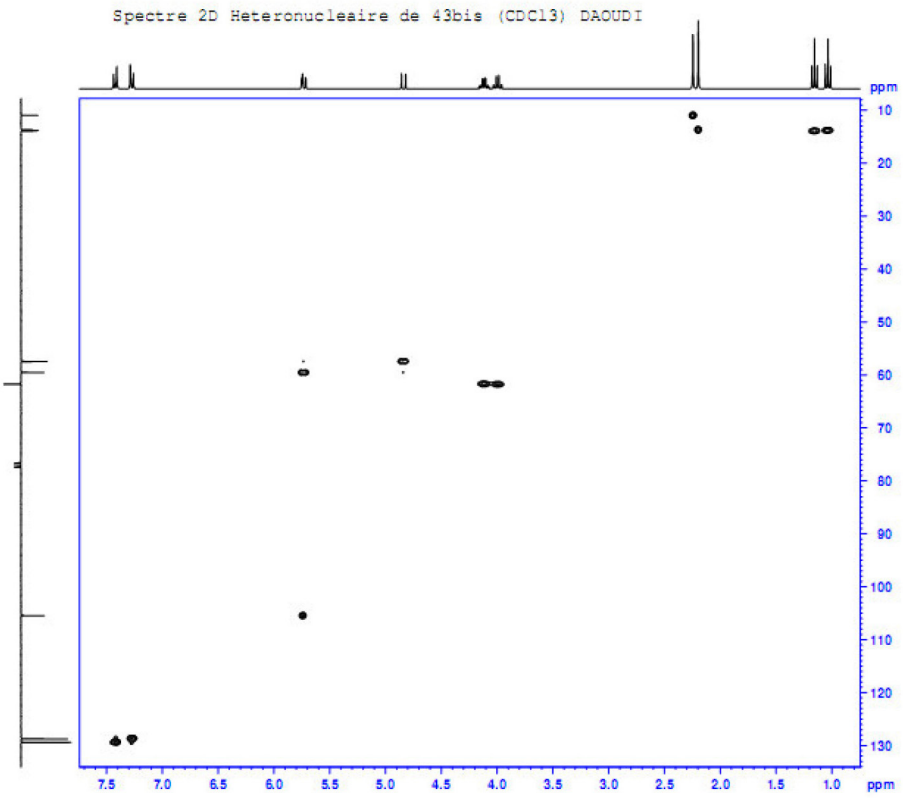

Figure S18. HETCOSY of compound **10** in $CDCl_3$.

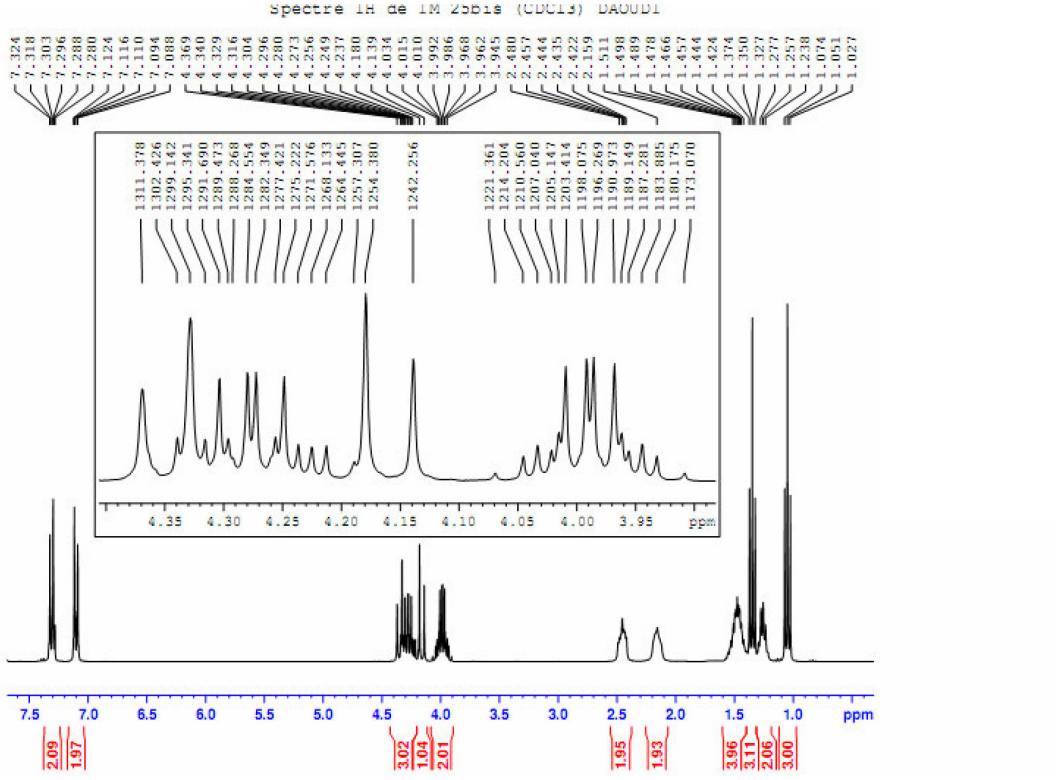

Figure S19. ^1H NMR (300 MHz) spectrum of compound **11** in $CDCl_3$.

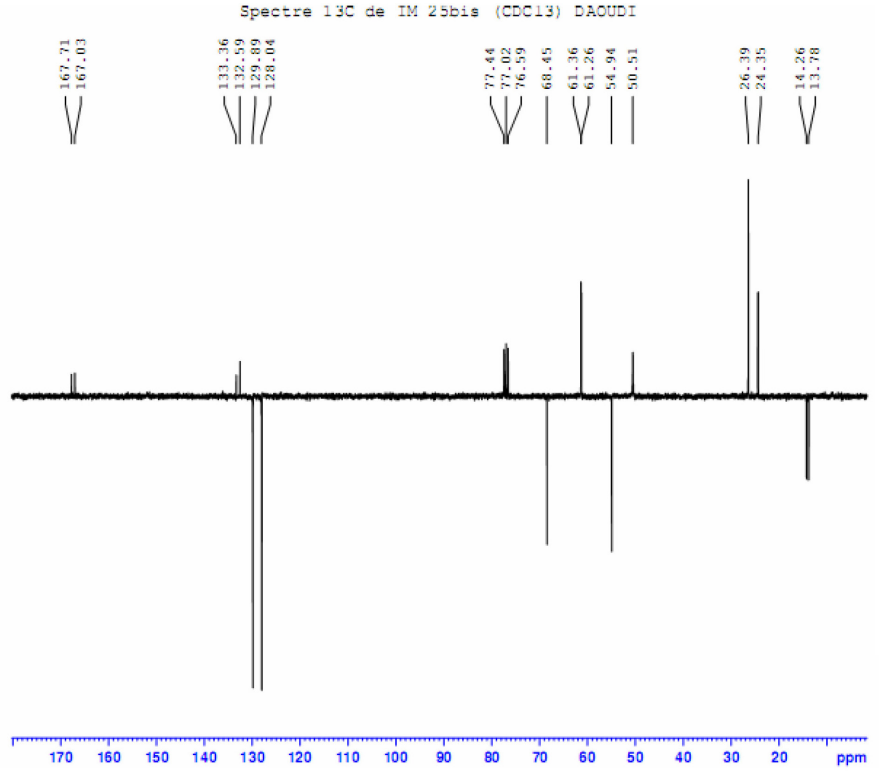

Figure S20. ^{13}C NMR (75.5 MHz) spectrum of compound **11** in $CDCl_3$.

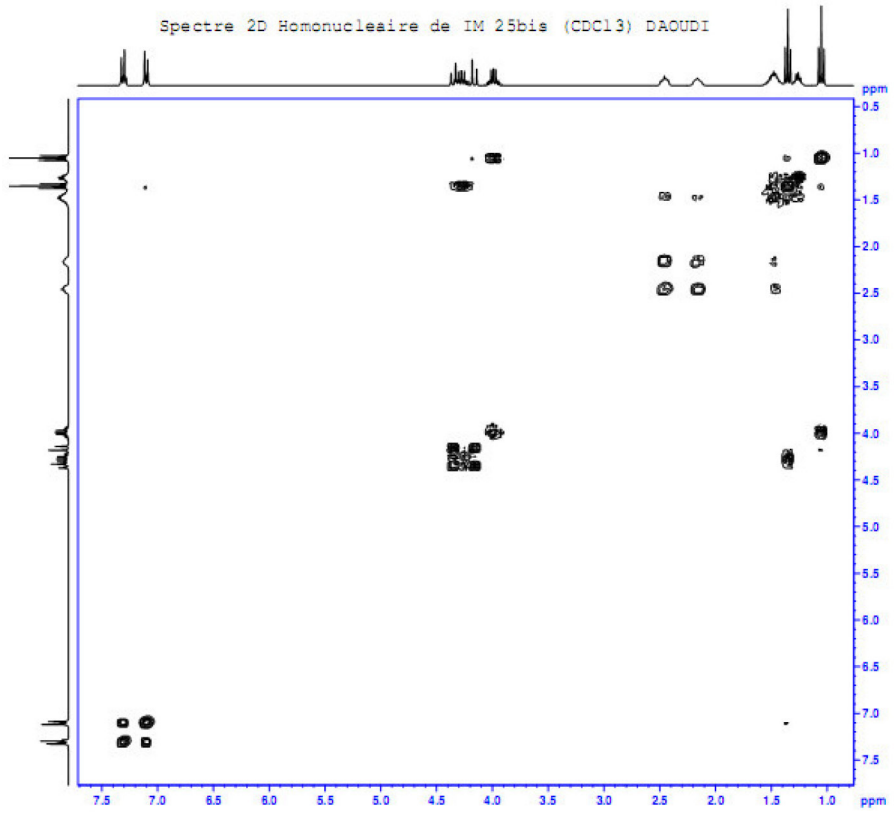

Figure S21. COSY of compound **11** in $CDCl_3$.

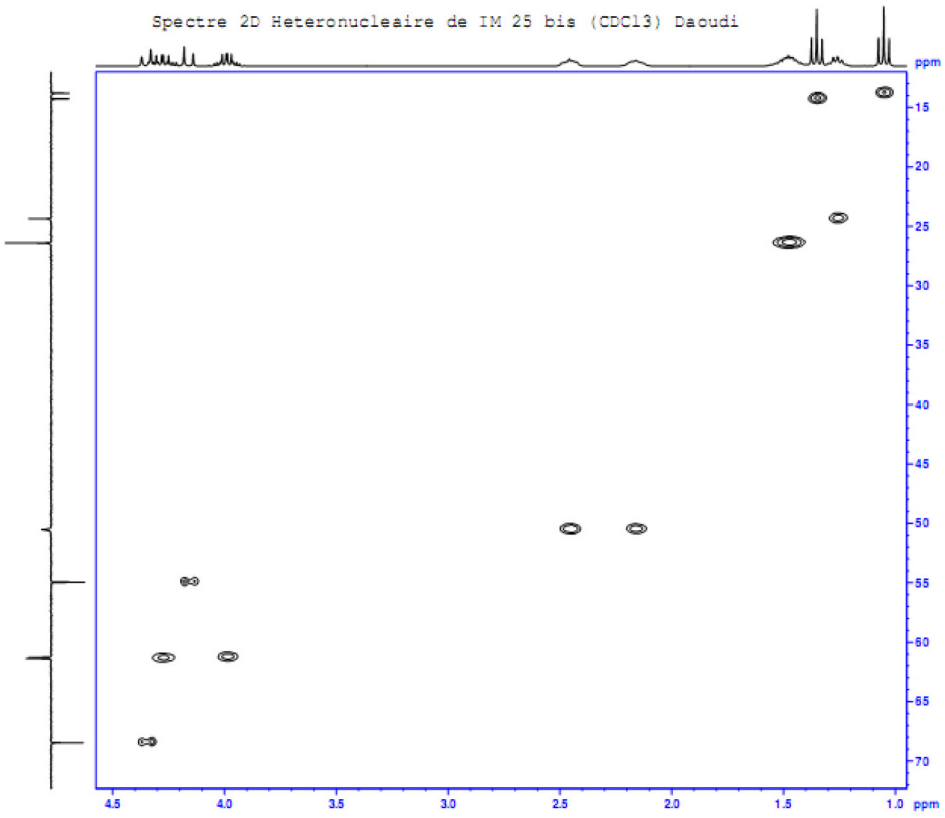

Figure S22. HETCOSY of compound **11** in $CDCl_3$.

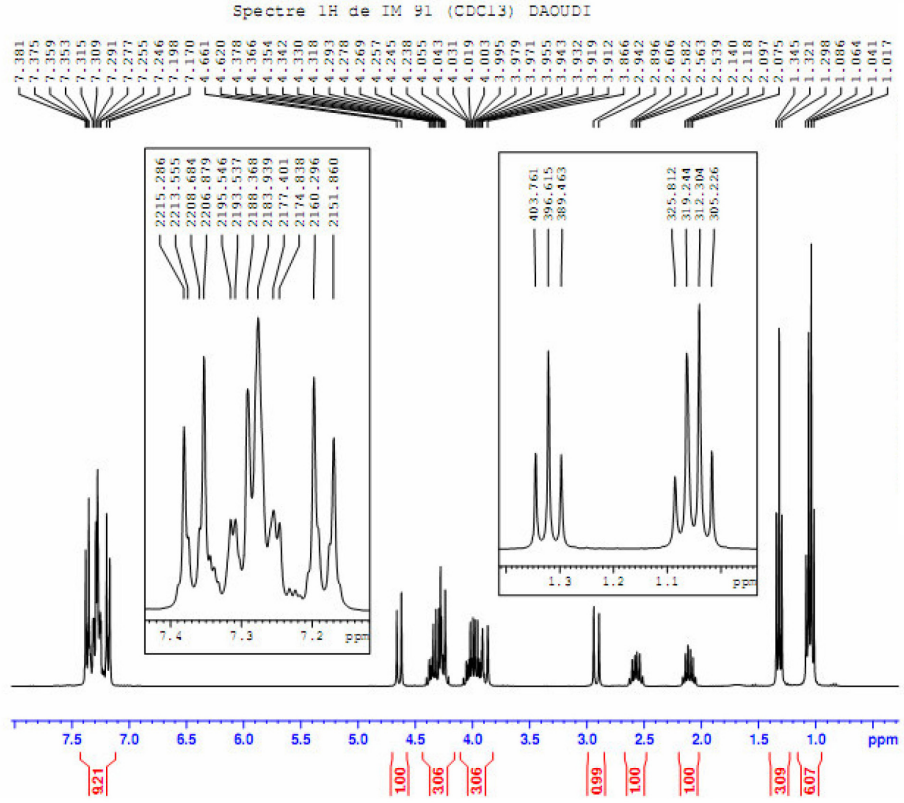

Figure S23. ^1H NMR (300 MHz) spectrum of compound **12** in $CDCl_3$.

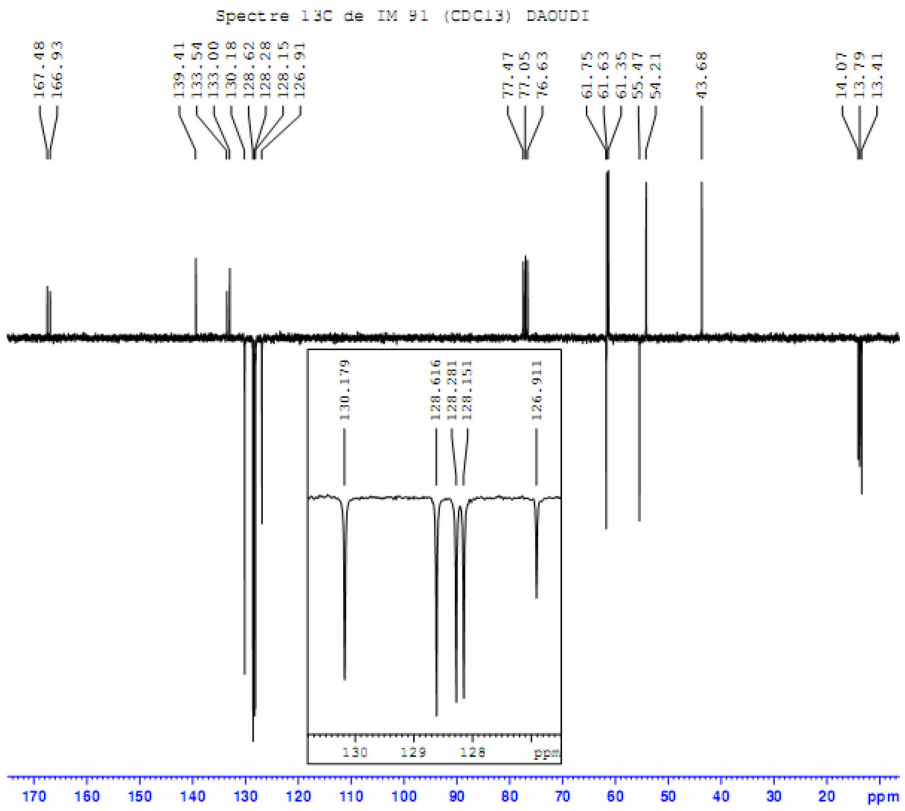

Figure S24. ^{13}C NMR (75.5 MHz) spectrum of compound **12** in $CDCl_3$.

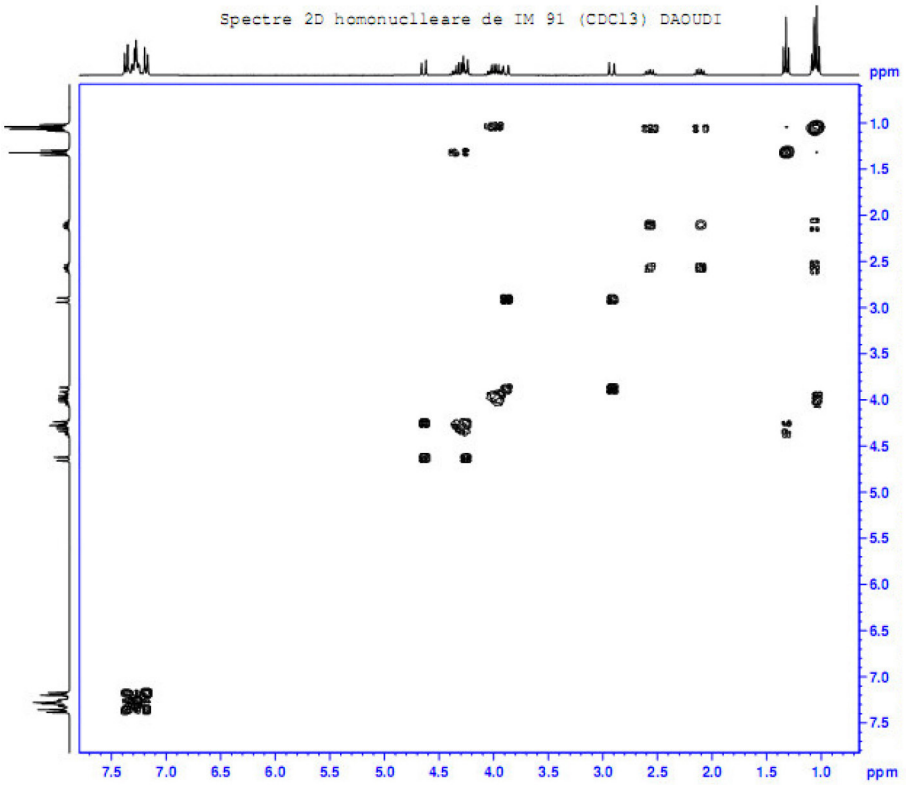

Figure S25. COSY of compound **12** in $CDCl_3$.

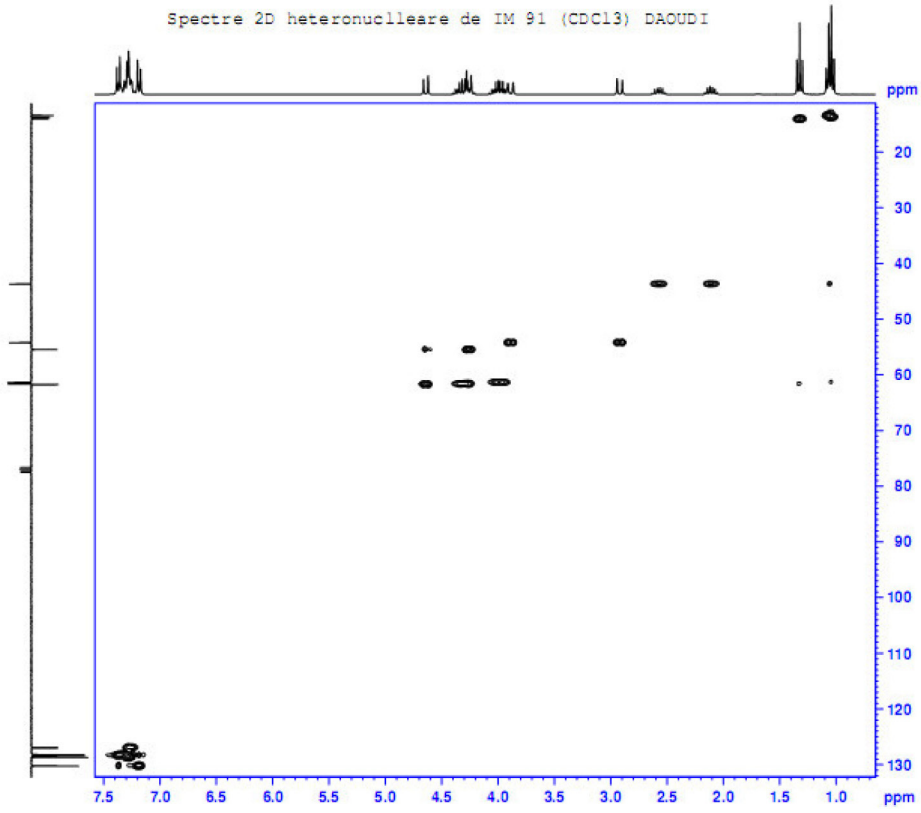

Figure S26. COSY of compound **12** in $CDCl_3$.