Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Electronic Supporting Information

Novel 1-(1-benzyl-1*H*-indol-3-yl)-*N*,*N*,*N*-trimethylmethanaminium iodides are competitive antagonists of the human α4β2 and α7 nicotinic acetylcholine receptors

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General Experimental

General methods

Calcium influx and radioligand binding experiments.

The concentration–response data for the Ca^{2+} influx and radioligand binding experiments were curve-fitted, and the IC_{50} and Hill coefficient (n_H) values were calculated by nonlinear

least squares analysis using the Prism software (GraphPad Software, San Diego, CA), based on the following equation:

$$\theta = 1 / [1 + ([L] / IC_{50})n_H] \quad (1)$$

where θ is the fractional amount of the radioligand bound in the presence of inhibitor at a concentration [L] compared to the amount of the radioligand bound in the absence of inhibitor (total binding). The observed IC_{50} values from the competition experiments described above were transformed into inhibition constant (K_i) values using the Cheng–Prusoff relationship:

$$K_i = IC_{50} / \{1 + ([[^3H]ligand] / K_d^{ligand})\} \quad (2)$$

where $[[^3H]ligand]$ is the initial concentration of $[^3H]$MLA, $[^3H]$cytisine, or $[^3H]$imipramine, respectively, and K_d^{ligand} is the dissociation constant for $[^3H]$MLA at the hα7 nAChR (1.86 nM)[2], for $[^3H]$cytisine at the hα4β2 nAChR (0.3 nM)[3], and for $[^3H]$imipramine at the hα4β2 (0.83 μM)[4] and hα7 (1 μM)[5] nAChRs, respectively.

Homology Modeling

To construct the extracellular domain of the hα7 and hα4β2 nAChRs, the structure of the acetylcholine binding protein from *Lymnaea stagnalis* (Ls-AChBP) in complex with nicotine at 2.2 Å resolution (PDB 1UW6)[6] was used as a template for homology modeling. The target protein and template were aligned using the Multalin server.[7] The models were built using the MODELLER9v6.[8] In this study, 100 runs were carried out using standard parameters and the outcomes were ranked on the basis of the internal scoring function of the program. The best model was chosen as the target model.

Molecular Docking

In order to obtain information about the most important nAChR-ligand interactions, molecular docking experiments were performed using AutoDock 4.0.[9] For the docking to the orthosteric binding sites, the grid maps were calculated using the autogrid option and centered on the binding sites. The volumes chosen for the grid maps were made up of 60 × 60 × 60 points, with a grid-point spacing of 0.375 Å. The autotors option was used to define the rotating bonds in the ligand. In the Lamarckian genetic algorithm dockings, the number of individuals in a population of 1,500, a maximum number of 2.5×10^6 energy evaluations, a maximum number of 27,000 generations, a mutation rate of 0.02, and a cross-over rate of 0.80, were employed. The ligands **4b**, and **4c** docked to the respective nAChR were built using the lowest docked-energy binding positions using Gaussian03,[10] and the partial charges were corrected using electrostatic potential methodology.[11, 12]

The energy of binding of the best docked compounds was calculated by AutoDock 4.0, AutoDock Vina, and by molecular mechanics (i.e., difference between the energy of the ligand-receptor complex and the sum of energies of the isolated receptor and ligand).

References

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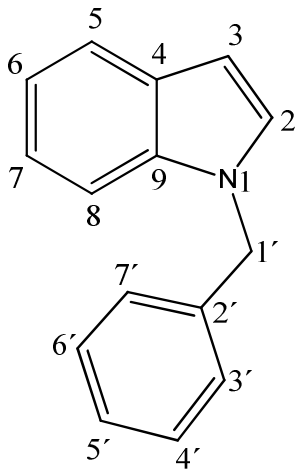
Synthetic Procedures

Microwave reactions were carried out in a CEM Discover reactor. Melting points were determined on a Reichert Galen III hot plate microscope apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker AMX 200, Bruker Avance 400, instruments at 200 or 400 MHz, respectively. ^{13}C NMR were recorded on the same instruments at 50, or 100 MHz. Chemical shifts are reported in δ values (part per million, ppm) relative to an internal standard of tetramethylsilane in $CDCl_3$ or DMSO-d_6 and coupling constants (*J*) are given in Hertz. The elemental analyses were performed in a Fison SA, model EA-1108 apparatus. Precoated silica gel 60 plates (Merck 60 F_{254} 0.2 mm) were used for TLC. TLC spots were visualized by spraying with Dragendorff's reagent, by exposing to iodine vapor or UV light.

General Procedure for microwave reaction: A 50 mL microwave reaction tube was charged with aldehyde (5 mmol, 1 equiv.), indoline (6.0 mmol, 1.2 equiv.), toluene (10 mL), and benzoic acid (1.0 mmol, 0.2 equiv.). The reaction tube was sealed and heated in the microwave reactor at 200 ºC, (200 W, 50–170 psi) for the appropriate time. After cooling with compressed air flow, the crude reaction mixture was diluted with EtOAc (25 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 25 mL). The aqueous layers were extracted with EtOAc (3 x 25 mL) and the combined organic layers dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the product was purified by silica gel column chromatography (hexane:EtOAc).

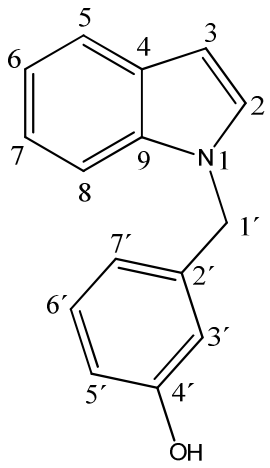
1-Bencyl-1*H*-indole (3a)



Following the general procedure, compound **3a** was obtained from indoline and benzaldehyde (**2a)** as colorless liquid in 27% yield (column chromatography Hexanes: EtOAc 9:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 – 7.65 (m, 1H), 7.46 – 7.29 (m, 4H), 7.28 – 7.22 (m, 1H), 7.22 – 7.10 (m, 4H), 6.64 (dd, J = 3.2, 0.8 Hz, 1H), 5.35 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.5 (C-9), 128.7 (C-4´), 128.7 (C-6´), 128.2 (C-2), 127.6 (C-5´), 127.6 (C-4), 126.7 (C-7´), 126.7 (C-3´), 121.7 (C-5), 121.0 (C-6), 119.5 (C-7), 109.7 (C-8), 101.6 (C-3), 50.0 (C-1´).

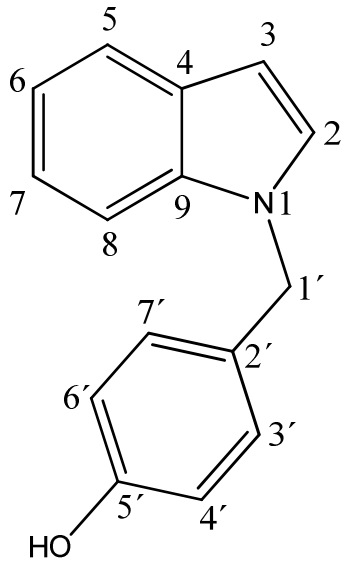
3-((1*H*-Indol-1-yl)methyl)phenol (3b).



Following the general procedure, compound **3b** was obtained from indoline and 3-hydroxybenzaldehyde (**2b)** as colorless liquid in 21% yield (column chromatography Hexanes: EtOAc 7:3).

^{1}H NMR (200 MHz, $(CD_3)_2C=0$): δ 7.67 (d, J = 7.3 Hz, 1H), 7.52 – 7.38 (m, 2H), 7.17 (ddd, J = 18.9, 11.4, 5.6 Hz, 3H), 6.79 (t, J = 7.0 Hz, 2H), 6.68 – 6.55 (m, 2H), 5.43 (s, 2H), 3.16 (d, J = 11.4 Hz, 1H). ^{13}C NMR (50 MHz, $(CD_3)C=0$): δ 158.5 (C-4´), 140.8 (C-2´), 137.1 (C-9), 130.4 (C-6´), 129.7 (C-2), 129.5 (C-4), 128.8 (C-5), 121.4 (C-6), 119.9 (C-7´), 118.7 (C-7), 115.1 (C-3´), 114.3 (C-5´), 110.7 (C-8), 101.9 (C-3), 50.1 (C-1´´).

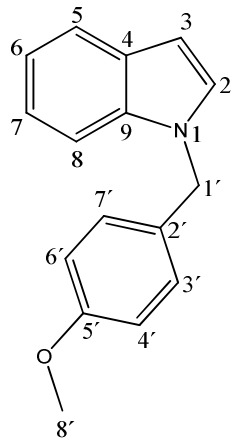
4-((1-*H*-indol-1-yl)methyl)phenol (3c).



Following the general procedure, compound **3c** was obtained from indoline and 4-hydroxybenzaldehyde (**2c**) as colorless solid in 17% yield (column chromatography Hexanes: EtOAc 7:3). Mp. 58,0-60,0 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (d, J = 7.1 Hz, 1H), 7.27 (d, J = 7.7 Hz, 1H), 7.10 (dd, J = 14.7, 5.2 Hz, 3H), 6.94 (d, J = 8.3 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 3.0 Hz, 1H), 5.17 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 155.0 (C-5´), 136.2 (C-9), 129.6 (C-4), 128.7 (C-2´), 128.4 (C-7´), 128.4 (C-3´), 128.2 (C-2), 121.6 (C-5), 121.0 (C-6), 119.5 (C-7), 115.6 (C-6´), 115.6 (C-4´), 109.8 (C-8), 101.5 (C-3), 49.6 (C-1´).

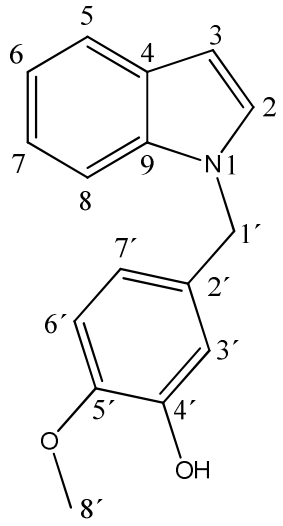
1-(4-Methoxybencyl)-1*H*-indole (3d).



Following the general procedure, compound **3d** was obtained from indoline and 4-methoxybenzaldehyde (**2d**) as colorless liquid in 21% yield (column chromatography Hexanes: EtOAc 8:2).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73 – 7.50 (m, 1H), 7.27 (d, J = 2.6 Hz, 1H), 7.21 – 7.09 (m, 2H), 7.08 – 7.03 (m, 2H), 7.01 (d, J = 2.8 Hz, 1H), 6.92 – 6.69 (m, 2H), 6.52 (dd, J = 3.2, 0.8 Hz, 1H), 5.21 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.1 (C-5´), 136.2 (C-9), 129.5 (C-2), 128.7 (C-4), 128.2 (C-7´), 128.2 (C-3´), 128.1 (C-2´),128.1 (C-5), 121.6 (C-5), 121.0 (C-6), 119.5 (C-7), 114.1 (C-6´), 114.1 (C-4´), 109.7 (C-8), 101.5 (C-3), 55.3 (C-8´), 49.6 (C-1´).

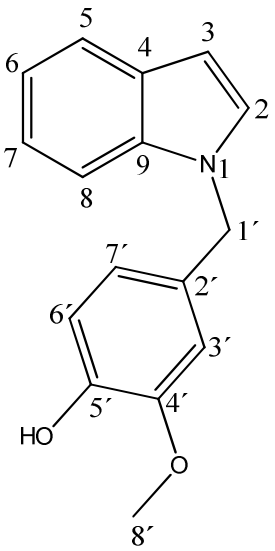
5-((1*H*-Indol-1-yl)methyl)-2-methoxyphenol (3e).



Following the general procedure, compound **3e** was obtained from indoline and 3-hydroxy-4-methoxybenzaldehyde (**2e**) as colorless liquid in 35% yield (column chromatography dichloromethane).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 – 7.56 (m, 1H), 7.32 – 7.22 (m, 1H), 7.21 – 7.11 (m, 1H), 7.12 – 7.04 (m, 2H), 6.76 – 6.66 (m, 2H), 6.62 – 6.53 (m, 1H), 6.50 (dd, J = 3.2, 0.9 Hz, 1H), 5.58 (s, 1H), 5.17 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.8 (C-5´), 137.5 (C-4´), 130.8 (C-9), 128.7 (C-2), 128.2 (C-2´), 121.6 (C-4), 120.9 (C-5), 119.4 (C-6), 118.5 (C-7), 113.3 (C-7´), 110.7 (C-3´), 109.7 (C-6´), 101.5 (C-8), 56.0 (C-1´), 49.7 (C-8´).

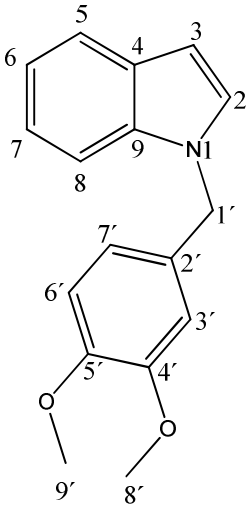
4-((1*H*-Indol-1-yl)methyl)-2-methoxyphenol (3f).



Following the general procedure, compound **3f** was obtained from indoline and 4-methoxybenzaldehyde (**2f**) as colorless liquid in 25% yield (column chromatography dichloromethane).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.71 – 7.57 (m, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.24 – 7.14 (m, 1H), 7.14 – 7.04 (m, 2H), 6.83 (d, J = 8.1 Hz, 1H), 6.69 – 6.62 (m, 1H), 6.63 – 6.46 (m, 2H), 5.20 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 146.8 (C-4´), 145.1 (C-5´), 136.3 (C-9), 129.3 (C-2), 128.7 (C-2´), 128.0 (C-4), 121.6 (C-7´), 120.9 (C-5), 120.1 (C-6), 119.5 (C-7), 114.4 (C-6´), 109.7 (C-3´), 109.5 (C-8), 101.5 (C-3), 55.9 (C-1´), 50.0 (C-8´).

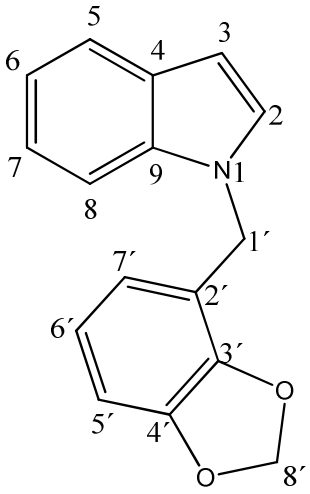
1-(3,4-dimethoxybencyl)-1*H*-indole (3g).



Following the general procedure, compound **3g** was obtained from indoline and 3,4-dimethoxybenzaldehyde (**2g**) as pink solid in 52% yield (column chromatography Hexanes: EtOAc 8:2); m.p: 67.9-69.8 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (m, 1H), 7.34 (m, 1H), 7.22 (d, J = 5.5 Hz, 1H), 7.16 (d, J = 1.8 Hz, 1H), 7.13 – 7.12 (m, 1H), 6.82 – 6.76 (m, 1H), 6.71 – 6.66 (m, 2H), 6.56 (dd, J = 3.2, 0.8 Hz, 1H), 5.26 (s, 2H), 3.85 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.2 (C-4´), 148.5 (C-5´), 136.3 (C-9), 129.9 (C-2´), 128.7 (C-2), 128.1 (C-4), 121.6 (C-7´), 120.9 (C-7), 119.5 (C-5), 119.3 (C-6), 111.2 (C-8), 110.1 (C-6´), 109.7 (C-3´), 101.6 (C-3), 55.9 (C-1´), 49.9 (C-8´), 49.1 (C-9´).

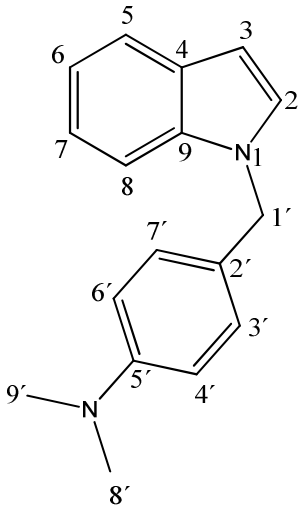
1-(Benzo[*d*][1,3]dioxol-4-ylmethyl)-1*H*-indole (3h).



Following the general procedure, compound **3h** was obtained from indoline and 3,4-dimethoxybenzaldehyde (**2h**) as yellow solid in 41% yield (column chromatography Hexanes: EtOAc 8:2); m.p: 78.8-80.1 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68 (d, J = 7.3 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.28 – 7.19 (m, 1H), 7.18 – 7.08 (m, 2H), 6.76 (d, J = 7.8 Hz, 1H), 6.68 (s, 1H), 6.63 – 6.52 (m, 2H), 5.93 (s, 2H), 5.24 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.1 (C-3´), 147.1 (C-4´), 136.2 (C-9), 131.3 (C-2), 128.7 (C-4), 128.1 (C-2´), 121.7 (C-6´), 121.0 (C-7), 120.2 (C-7´), 119.5 (C-6), 109.6 (C-5), 108.3 (C-8), 107.4 (C-8´), 49.9 (C-1´).

4-((1*H*-Indol-1-yl)methyl)-*N*,*N*-dimethylaniline (3i).

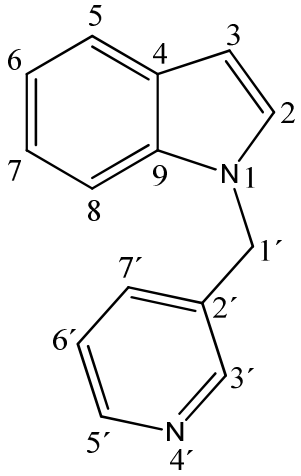


Following the general procedure, compound **3i** was obtained from indoline and 4-dimethylaminebenzaldehyde (**2i**) as colorless solid in 21% yield (column chromatography Hexanes: EtOAc 8:2). M.p: 107,2-108,8 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.61 (ddd, J = 7.3, 1.6, 0.8 Hz, 1H), 7.41 – 7.23 (m, 1H), 7.21 – 7.12 (m, 1H), 7.12 – 7.04 (m, 2H), 7.02 – 6.96 (m, 2H), 6.71 – 6.56 (m, 2H), 6.48 (dd, J = 3.2, 0.9 Hz, 1H), 5.18 (s, 2H), 2.88 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 150.1 (C-5´), 136.3 (C-9), 128.7 (C-2), 128.1 (C-7´), 128.19 (C-3´), 128.11 (C-4), 125.3 (C-2´),

121.4 (C-5), 120.9 (C-6), 119.3 (C-7), 112.7 (C-6´), 112.7 (C-4´), 109.8 (C-8), 101.2 (C-3), 49.7 (C-1´), 40.6 (C-8´), 40.6 (C-9´).

1-(pyridin-3-ylmethyl)-1*H*-indole (3j).



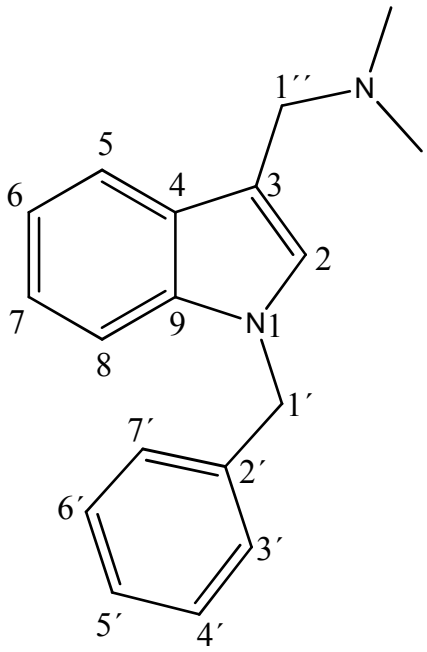
Following the general procedure, compound **3j** was obtained from indoline and 3-pyridinecarboxaldehyde (**2j**) as colorless solid in 59% yield (column chromatography Hexanes: EtOAc 8:2); m.p: 58,6-60,5 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.52 (s, 2H), 7.66 (d, J = 7.3 Hz, 1H), 7.35 – 7.22 (m, 2H), 7.14 (dd, J = 10.3, 3.6 Hz, 4H), 6.57 (d, J = 3.0 Hz, 1H), 5.32 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.2 (C-3´), 148.3 (C-5´), 136.0 (C-9), 134.4 (C-7´), 133.1 (C-2´), 128.8 (C-4), 127.9 (C-2), 123.7 (C-6´), 122.0 (C-5), 121.2 (C-6), 119.8 (C-7), 109.4 (C-8), 102.3 (C-3), 47.6 (C-1´).

General procedure for the Mannich reaction.

To a solution of N^1-bencylindole derivative (**3**, 1 mmol) in acetic acid (3.35 ml) at room temperature was added 40% aqueous dimethylamine (6,85 mmol), formaldehyde (2,76 mmol) and was stirred for 24 h under a nitrogen atmosphere. The reaction was quenched with 10% KOH (p*H* = 10) and extracted with EtoAc (3 × 50 mL), the organic layer was dried over MgSO4 and filtered. The compounds were characterized and used in the next reaction without further purification.

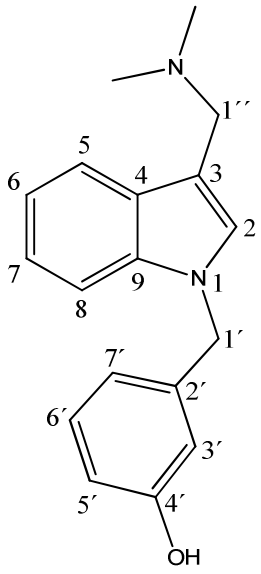
1-(1-benzyl-1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine (3a-1).



Following the general procedure, compound **3a-1** was obtained from **3a** as pink solid. Yield: 92%. M.p: 57,3-59,1 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70 (d, J = 7.5 Hz 1H), 7.25 (s, 4H), 7.10 (d, J = 4.5 Hz, 5H), 5.29 (s, 2H), 3.66 (s, 2H), 2.29 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.5 (C-9), 136.5 (C-2´), 128.7 (C-6´), 128.7 (C-4´), 128.6 (C-4), 127.9 (C-5´), 127.6 (C-2), 126.8 (C-7´), 126.8 (C-3'), 121.7 (C-5), 119.4 (C-6), 119.4 (C-7), 111.9 (C-8), 109.7 (C-3), 54.2 (C-1´´), 49.9 (C-1´), 45.1 (-NCH_3)$_2$.

3-((3-((dimethylamino)methyl)-1*H*-indol-1-yl)methyl)phenol (3b-1).

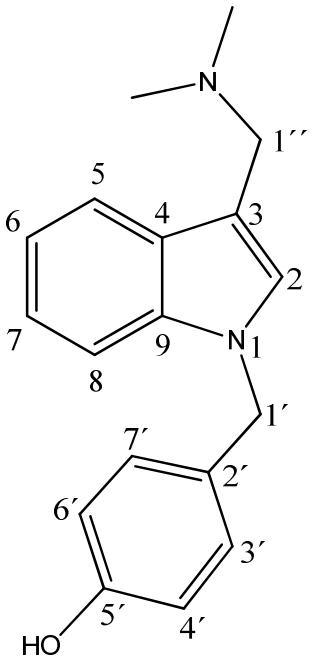


Following the general procedure, compound **3b-1** was obtained from **3b** as colorless liquid. Yield: 80%.

^{1}H NMR (200 MHz, $(CD_3)_2C$=0): δ 7.57 – 7.40 (m, 1H), 7.22 (s, 2H), 7.12 (s, 3H), 6.76 (dd, J = 9.8, 4.2 Hz, 2H), 6.70 – 6.45 (m, 2H), 5.41 (s, 2H), 4.00 (s, 2H), 3.51 (s, 1H), 2.50

(s, 6H). ^{13}C NMR (50 MHz, $(CD_3)C=0$): δ 158.9 (C-4´), 140.5 (C-2´), 130.5 (C-9), 130.2 (C-6´), 129.4 (C-2), 126.5 (C-4), 122.3 (C-5), 120.0 (C-6), 119.5 (C-7´), 118.2 (C-7), 115.3 (C-3´), 114.1 (C-5´), 110.9 (C-8), 107.2 (C-3), 53.8 (C-1´´), 50.1 (C-1´), 43.9 $(-NCH_3)_2$.

4-((3-((dimethylamino)methyl)-1H-indol-1-yl)methyl)phenol (3c-1).

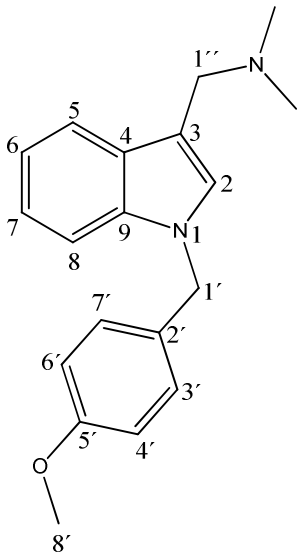


Following the general procedure, compound **3c-1** was obtained from **3c** as white solid. Yield: 97%.m.p: 111,2-112,9 °C.

^{1}H NMR (200 MHz, $(CD_3)_2C=O/CD_3OD$): δ 7.65 – 7.55 (m, 1H), 7.28 (dd, J = 6.7, 1.9 Hz, 1H), 7.23 (s, 1H), 7.16 – 7.02 (m, 2H), 6.91 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 8.6 Hz, 2H), 5.11 (s, 2H), 3.93 (s, 2H), 2.43 (s, 6H). ^{13}C NMR (50 MHz, $(CD_3)_2C=O/CD_3OD$): δ 157.8 (C-5´), 137.0 (C-9), 130.3 (C-4), 129.3 (C-2´), 129.1 (C-7´), 129.1 (C-3´), 128.3 (C-

2), 122.5 (C-5), 120.4 (C-6), 119.5 (C-7), 116.3 (C-6´), 116.3 (C-4´), 110.8 (C-8), 108.0 (C-3), 53.2 (C-1´), 50.3 (C-1´´), 43.8 (-NCH_3)$_2$.

1-(1-(4-methoxybenzyl)-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine (3d-1).

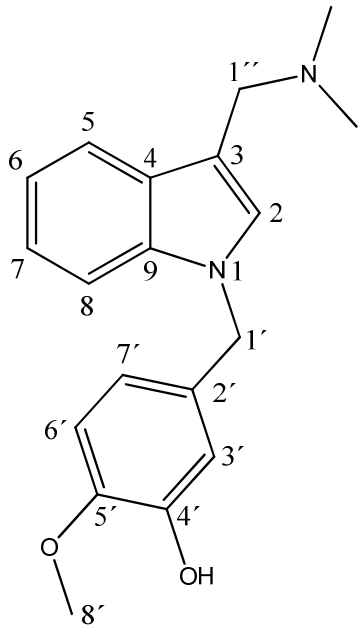


Following the general procedure, compound **3d-1** was obtained from **3d** as colorless liquid. Yield: 98%.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 – 7.66 (m, 1H), 7.31 – 7.23 (m, 1H), 7.23 – 7.15 (m, 1H), 7.14 – 7.10 (m, 1H), 7.09 – 7.06 (m, 1H), 7.05 (d, J = 0.6 Hz, 2H), 6.88 – 6.76 (m, 2H), 5.22 (s, 2H), 3.76 (s, 3H), 3.62 (s, 2H), 2.28 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.0 (C-5´), 136.5 (C-9), 129.5 (C-2), 128.6 (C-4), 128.2 (C-7´), 128.2 (C-3´), 127.5 (C-

2´), 121.6 (C-5), 119.4 (C-6), 119.2 (C-7), 114.1 (C-6´), 114.1 (C-4´), 112.3 (C-8), 109.6 (C-3), 55.3 (C-8´), 54.4 (C-1´), 49.4 (C-1´´), 45.4 $(-NCH_3)_2$.

5-((3-((dimethylamino)methyl)-1*H*-indol-1-yl)methyl)-2-methoxyphenol (3e-1).

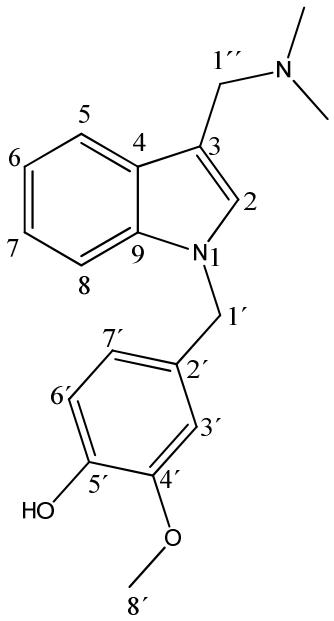


Following the general procedure, compound **3e-1** was obtained from **3e** as colorless liquid. Yield: 94%.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60 (dd, J = 6.3, 2.2 Hz, 1H), 7.29 – 7.19 (m, 1H), 7.17 – 7.07 (m, 2H), 7.02 (s, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.60 (dd, J = 8.2, 2.1 Hz, 1H), 6.46 (s, 1H), 5.13 (s, 2H), 3.81 (s, 3H), 3.50 (s, 2H), 2.21 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ

146.7 (C-5´), 146.6 (C-4´), 136.3 (C-9), 130.4 (C-2), 128.6 (C-2´), 128.2 (C-4), 121.7 (C-5), 119.4 (C-6), 119.0 (C-7), 117.8 (C-7´), 113.4 (C-3´), 111.0 (C-6´), 110.4 (C-8), 109.8 (C-3), 55.9 (C-1´), 53.4 (C-1´´), 49.4 (C-8´), 44.4 ($-NCH_3)_2$.

4-((3-((dimethylamino)methyl)-1H-indol-1-yl)methyl)-2-methoxyphenol (3f-1).

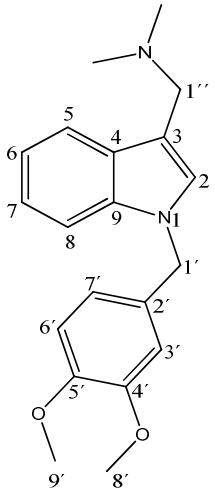


Following the general procedure, compound **3f-1** was obtained from **3f** as colorless liquid. Yield: 97%.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58 (dd, J = 6.5, 2.6 Hz, 1H), 7.31 (s, 2H), 7.16 (dd, J = 7.2, 4.6 Hz, 2H), 6.80 (d, J = 8.5 Hz, 1H), 6.62 (s, 2H), 5.18 (s, 2H), 4.08 (s, 2H), 3.74 (s, 3H), 2.52 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 147.2 (C-4´), 145.7 (C-5´), 136.3 (C-9),

130.3 (C-4), 128.5 (C-2´), 128.3 (C-2), 122.2 (C-7), 120.25 (C-7´), 120.21 (C-6), 118.4 (C-5), 114.7 (C-6´), 110.2 (C-3´), 109.8 (C-8), 105.3 (C-3), 55.8 (C-1´), 51.8 (C-1´´), 50.2 (C-8´), 42.3 (-NCH_3)$_2$.

1-(1-(3,4-dimethoxybenzyl)-1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine (3g-1).

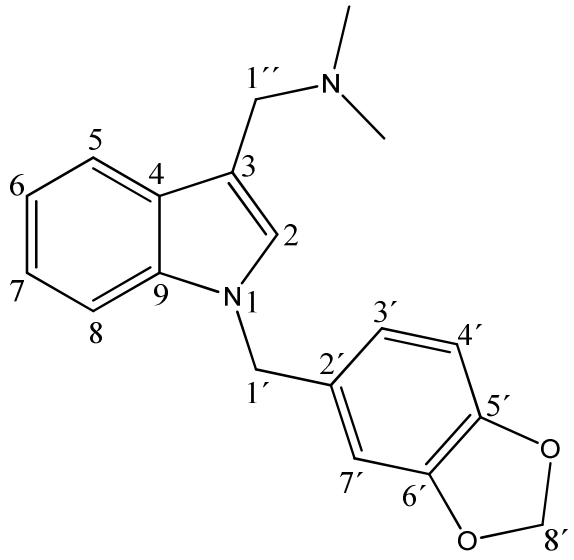


Following the general procedure, compound **3g-1** was obtained from **3g** as colorless liquid. Yield: 92%.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.70 (dd, J = 6.4, 1.9 Hz, 1H), 7.31 (dd, J = 7.1, 2.2 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.13 (d, J = 1.5 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.74 – 6.63 (m, 2H), 5.24 (s, 2H), 3.88 (s, 3H), 3.78 (s, 3H), 3.73 (s, 2H), 2.33 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.2 (C-4´), 148.5 (C-5´), 136.5 (C-9), 129.8 (C-2´), 128.6 (C-4), 128.0 (C-2),

121.7 (C-7´), 119.4 (C-7), 119.37 (C-6), 119.3 (C-5), 111.2 (C-6´), 111.0 (C-3), 110.1 (C-8), 109.7 (C-3´), 55.9 (C-1´), 55.8 (C-1´´), 49.8 (-NCH_3)$_2$, 44.6 (C-8´), 44.6 (C-9´).

1-(1-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-indol-3-yl)-*N*,*N*-dimethylmethanamine (3h-1).

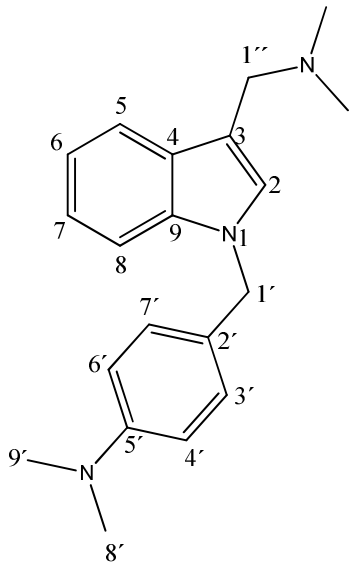


Following the general procedure, compound **3h-1** was obtained from **3h** as colorless liquid. Yield: 95%.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.77 – 7.67 (m, 1H), 7.29 (dd, J = 6.8, 1.8 Hz, 1H), 7.24 – 7.11 (m, 2H), 7.09 (d, J = 2.4 Hz, 1H), 6.71 (dd, J = 14.8, 4.4 Hz, 1H), 5.92 (s, 2H), 5.20 (s, 2H), 3.67 (s, 2H), 2.31 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 148.0 (C-6´), 147.1 (C-5´),

136.4 (C-9), 131.3 (C-2´), 128.6 (C-4), 127.6 (C-2), 121.7 (C-3´), 120.2 (C-7), 119.4 (C-5), 119.4 (C-6), 112.0 (C-3), 109.6 (C-4´), 108.3 (C-7´), 107.5 (C-8), 101.1 (C-8´), 54.2 (C-1´´), 49.8 (C-1´), 45.1 ($-NCH_3)_2$.

4-((3-((dimethylamino)methyl)-1*H*-indol-1-yl)methyl)-*N*,*N*-dimethylaniline (3i-1).

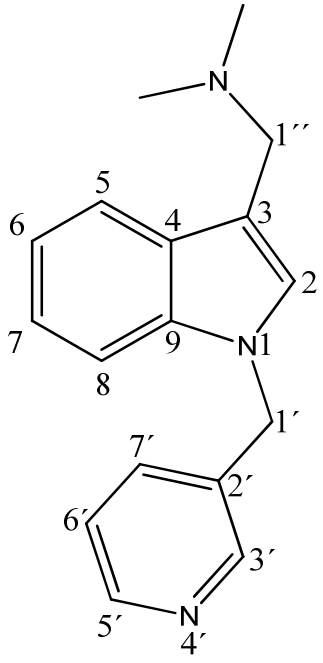


Following the general procedure, compound **3i-1** was obtained from **3i** as white solid. Yield: 98%. M.p: 98-100 °C

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.68 (dd, J = 6.7, 1.7 Hz, 1H), 7.31 (dd, J = 7.0, 1.5 Hz, 1H), 7.14 (ddd, J = 14.5, 7.0, 1.4 Hz, 2H), 7.07 – 7.00 (m, 3H), 6.70 – 6.58 (m, 2H), 5.17 (s, 2H), 3.60 (s, 2H), 2.90 (s, 6H), 2.26 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 150.1 (C-

5´), 136.5 (C-9), 128.6 (C-4), 128.2 (C-7´), 128.2 (C-3´), 127.6 (C-2), 125.0 (C-2´), 121.5 (C-5), 119.3 (C-6), 119.1 (C-7), 112.6 (C-6´), 112.6 (C-4´), 111.9 (C-8), 109.7 (C-3), 54.5 (C-1´´), 49.5 (C-1´), 45.3 $(-NCH_3)_2$, 40.6 (C-8´), 40.6 (C-9´).

_N,N_-dimethyl-1-(1-(pyridin-3-ylmethyl)-1_H_-indol-3-yl)methanamine (3j-1).



Following the general procedure, compound **3j-1** was obtained from **3j** as colorless liquid. Yield: 97%.

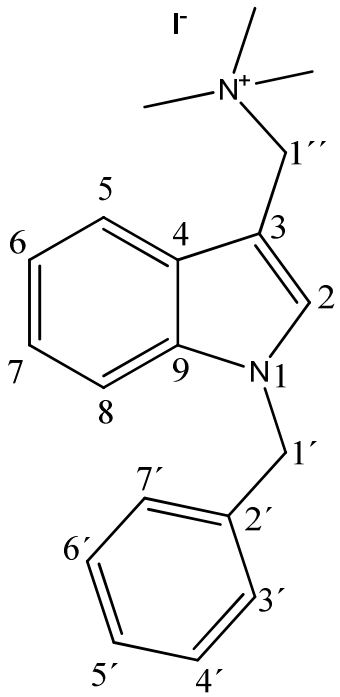
^{1}H NMR (200 MHz, $CDCl_3$): δ 8.49 (d, J = 2.9 Hz, 2H), 7.68 (ddd, J = 6.4, 3.1, 2.4 Hz, 1H), 7.29 (ddd, J = 7.9, 5.1, 1.9 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 2H), 7.10

(dd, J = 5.4, 3.1 Hz, 2H), 5.29 (s, 2H), 3.67 (s, 2H), 2.30 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 149.2 (C-3´), 148.3 (C-5´), 136.3 (C-9), 134.4 (C-7´), 133.0 (C-2´), 128.7 (C-4), 127.7 (C-2), 123.7 (C-6´), 122.1 (C-5), 119.7 (C-6), 119.5 (C-7), 112.2 (C-8), 109.4 (C-3), 53.9 (C-1´´), 47.5 (C-1´), 44.9 $(-NCH_3)_2$.

General procedure for synthesis of *N*,*N*,*N*-trimethylammonium derivarives.

To a solution of gramine (**3**, 0.5 mmol) in acetone (5 mL), iodomethane (8.0 mmol) was added and the reaction mixture was stirred for 16 h. Then, Et_2O (20 mL) was added and the solid collected by filtration to afford the desired trimethylammonium compound. **4a-j.**

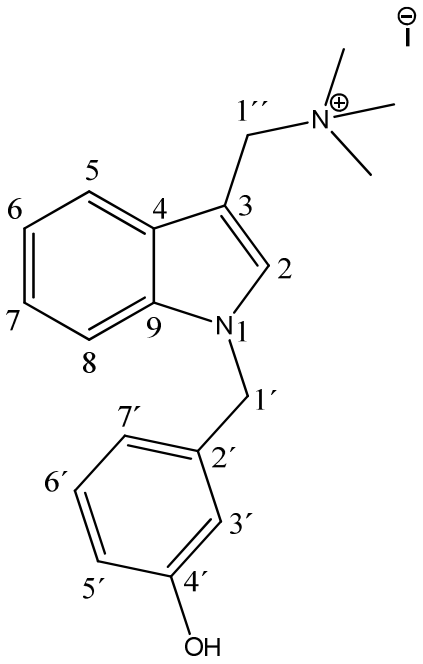
1-(1-benzyl-1H-indol-3-yl)-*N*,*N*,*N*-trimethylmethanaminium iodide (4a).



Following the general procedure, compound **4a** was obtained from **3a-1** as white solid. Yield: 96%. M. p: 167,7-172,1 °C, decomposition.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, J = 3.7 Hz, 2H), 7.54 (d, J= 7.3 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.26 (t, J = 6.6 Hz, 3H), 7.18 (dd, J = 13.1, 6.7 Hz, 2H), 5.53 (s, 2H), 4.75 (s, 2H), 3.08 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 137.9 (C-9), 136.3 (C-2´), 133.9 (C-4), 129.0 (C-6´), 129.0 (C-4´), 128.7 (C-2), 127.9 (C-5´), 127.4 (C-7´), 127.4 (C-3´), 122.5 (C-7), 120.8 (C-6), 119.3 (C-5), 111.3 (C-8), 102.0 (C-3), 60.6 (C-1´´), 51.6 (-$NCH_3)_3$, 49.7 (C-1´). Anal. calculated for: C, 56.17; H, 5.71; N, 6.89, Found: C,56.05; H,5.67; N,6.95

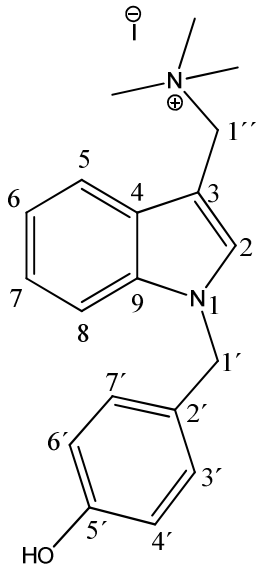
1-(1-(3-hydroxybenzyl)-1*H*-indol-3-yl)-*N*,*N*,*N*-trimethylmethanaminium iodide (4b).



Following the general procedure, compound **4b** was obtained from **3b-1** as white solid. Yield: 98%. M. p: 151,1-156,8 °C, decomposition.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94 – 7.82 (m, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.16 (ddd, J = 21.3, 14.8, 7.2 Hz, 2H), 6.67 (d, J = 8.9 Hz, 1H), 6.53 (s, 2H), 5.44 (s, 1H), 4.75 (s, 2H), 3.13 (d, J= 10.7 Hz, 1H), 3.08 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.9 (C-4´), 139.4 (C-2´), 136.3 (C-9), 134.0 (C-6´), 130.0 (C-2), 128.6 (C-4), 122.4 (C-5), 120.8 (C-6), 119.3 (C-7´), 117.9 (C-7), 114.8 (C-3´), 114.0 (C-5´), 111.3 (C-8), 101.9 (C-3), 60.6 (C-1´), 51.6 $(NCH_3)_3$, 49.6 (C-1´´). Anal. calculated for: C, 54.04; H, 5.49; N, 6.63,. Found: C, 53.99; H, 5.63; N, 6.65.

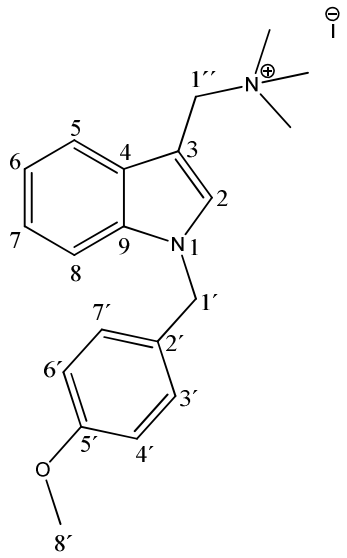
1-(1-(4-hydroxybenzyl)-1H-indol-3-yl)-*N*,*N*,*N*-trimethylmethanaminium iodide (4c).



Following the general procedure, compound **4c** was obtained from **3c-1** as white solid. Yield: 98%. M. p: 153,5-158,4 °C decomposition.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 – 7.71 (m, 2H), 7.56 (d, *J*= 6.5 Hz, 1H), 7.31 – 7.00 (m, 4H), 6.71 (d, *J* = 6.5 Hz, 2H), 5.36 (s, 2H), 4.71 (s, 2H), 3.06 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.2 (C-5´), 136.2 (C-9), 133.6 (C-4), 129.1 (C-7´), 129.1 (C-3´), 128.7 (C-2´), 127.9 (C-2), 122.3 (C-5), 120.7 (C-6), 119.2 (C-7), 115.7 (C-6´), 115.7 (C-4´), 111.3 (C-8), 101.7 (C-3), 60.6 (C-1´), 51.6 (C-1´´), 49.3 (-NCH_3)$_3$. Anal. calculated for: C, 54.04; H, 5.49; N, 6.63,. Found: C, 53.92; H, 5.61; N, 6.67.

1-(1-(4-methoxybenzyl)-1*H*-indol-3-yl)-*N*,*N*,*N*-trimethylmethanaminium iodide (4d).

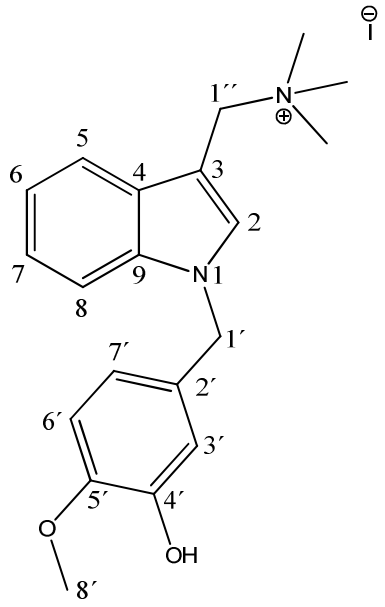


Following the general procedure, compound **4d** was obtained from **3d-1** as white solid. Yield: 98%. M. p: 167,2-171,2 °C, decomposition.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.88 (d, *J* = 9.0 Hz, 2H), 7.57 (d, *J*= 7.7 Hz, 1H), 7.31 – 7.07 (m, 4H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.43 (s, 2H), 4.73 (s, 2H), 3.70 (s, 3H), 3.07 (s, 9H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 159.0 (C-5´), 136.2 (C-9), 133.7 (C-2), 129.7 (C-4), 129.0 (C-7´), 129.0 (C-3´), 128.7 (C-2´), 122.4 (C-5), 120.7 (C-6), 119.3 (C-7), 114.3 (C-6´), 114.3 (C-4´), 111.3 (C-8), 101.8 (C-3), 60.6 (C-1´´), 55.4 (C-8´), 51.6 (-$NCH_3)_3$, 49.2 (C-1´). Anal. calculated for: C, 55.05; H, 5.78; N, 6.42. Found: C, 54.92; H, 5.89; N, 6.44.

1-(1-(3-hydroxy-4-methoxybenzyl)-1*H*-indol-3-yl)-*N*,*N*,*N*-trimethylmethanaminium iodide(4e).

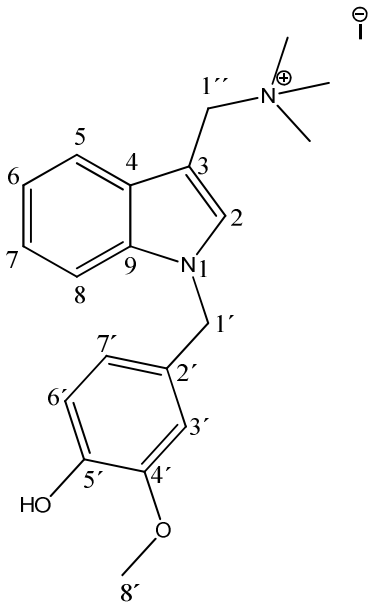


Following the general procedure, compound **4e** was obtained from **4e-1** as white solid. Yield: 89%. M. p: 160,3-164,1 °C, decomposition.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 – 7.77 (m, 2H), 7.54 (d, *J*= 7.8 Hz, 1H), 7.24 – 7.13 (m, 2H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.71 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.63 (d, *J* = 1.8 Hz, 1H), 5.36 (s, 2H), 4.74 (s, 2H), 3.71 (s, 3H), 3.08 (s, 9H). ^{13}C NMR (100 MHz, DMSO-

d_6): δ 147.4 (C-5´), 146.9 (C-4´), 136.3 (C-9), 133.8 (C-4), 130.3 (C-2), 128.6 (C-2´), 122.4 (C-7), 120.7 (C-6), 119.3 (C-7´), 118.5 (C-5), 114.8 (C-3´), 112.5 (C-6´), 111.3 (C-8), 101.7 (C-3), 60.6 (C-1´´), 56.0 (C-8´), 51.6 (-$NCH_3)_3$, 49.4 (C-1´). Anal. calculated for: C, 53.11; H, 5.57; N, 6.19. Found: C,53.00; H,5.63; N,6.25.

1-(1-(4-hydroxy-3-methoxybenzyl)-1*H*-indol-3-yl)-*N*,*N*,*N*-trimethylmethanaminium iodide (4f).

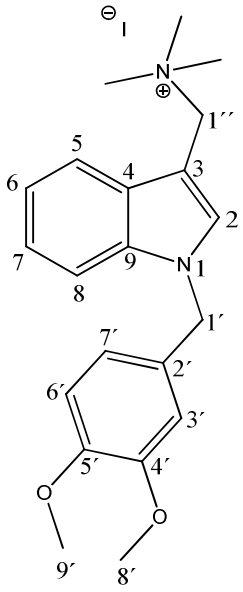


Following the general procedure, compound **4f** was obtained from **4f-1** as white solid. Yield: 85%. M. p: 158,5-162,9 °C, decomposition.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (d, J = 5.5 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.18 (dt, J = 14.7, 7.0 Hz, 2H), 7.00 (s, 1H), 6.69 (q, J = 8.0 Hz, 2H), 5.36 (s, 2H), 4.73 (s, 2H), 3.73 (s, 3H), 3.07 (s, 9H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 147.9 (C-4´), 146.4 (C-5´), 136.2 (C-9), 133.7 (C-4), 128.7 (C-2), 128.5 (C-2´), 122.3 (C-7), 120.7 (C-7´), 120.4 (C-6),

119.2 (C-5), 115.8 (C-6´), 112.3 (C-3´), 111.4 (C-8), 101.7 (C-3), 60.6 (C-1´´), 56.0 (C-8´), 51.5 (-$NCH_3)_3$, 49.6 (C-1´). Anal. calculated for: C, 53.11; H, 5.57; N, 6.19. Found: C,53.05; H,5.60; N,6.23.

1-(1-(3,4-dimethoxybenzyl)-1H-indol-3-yl)-N,N,N-trimethylmethanaminium iodide (4g).

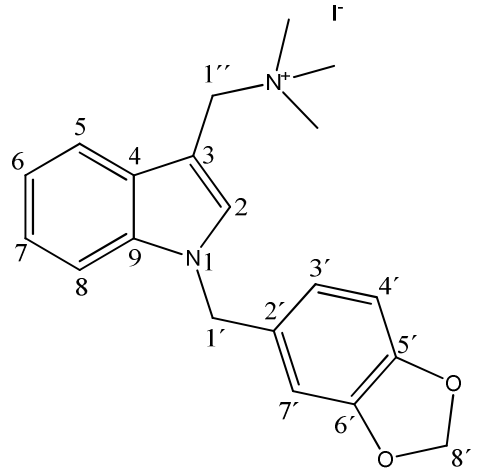


Following the general procedure, compound 4g was obtained from **3g-1** as white solid. Yield: 97%. M. p: 159.2-163.6 °C, decomposition.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.91 (d, J = 7.4 Hz, 1H), 7.81 (s, 1H), 7.30 (dd, J = 13.7, 4.3 Hz, 1H), 7.23 – 7.14 (m, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 5.24 (s, 2H), 5.11 (s, 2H), 3.80 (s, 6H), 3.35 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.2 (C-3), 148.7 (C-5´), 136.4 (C-9), 133.5 (C-2´), 128.2 (C-4), 128.2 (C-2), 122.9 (C-7´), 121.5

(C-7), 119.4 (C-6), 111.4 (C-5), 110.5 (C-3), 110.4 (C-6´), 101.2 (C-8), 110.2 (C-3´), 62.0 (C-1´´), 56.2 (-NCH_3), 56.0 (-$N(CH_3)$, 55.8 (-$N(CH_3)$, 52.5 (C-1´), 50.3 (C-8´), 50.3 (C-9´). Anal. calculated for: C, 54.08; H, 5.84; N, 6.01, Found: C,53.86; H,6.01; N,6,11.

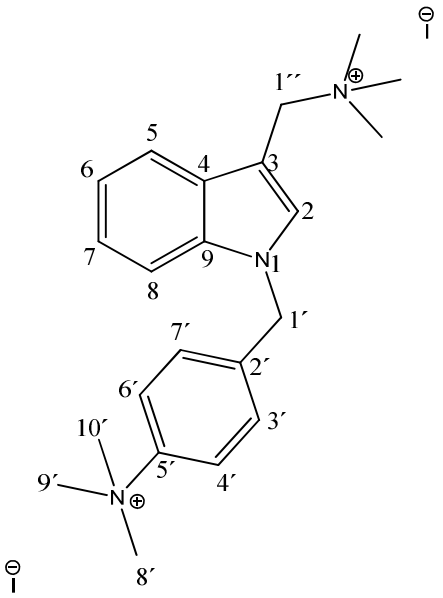
1-(1-(benzo[d][1,3]dioxol-5-ylmethyl)-1H-indol-3-yl)-N,N,N-trimethylmethanaminium iodide (4h).



Following the general procedure, compound **4h** was obtained from **3h-1** as white solid. Yield: 98%. M. p: 173.6-180.2 °C, decomposition.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.53 (d, J = 6.5 Hz, 2H), 7.79 – 7.69 (m, 1H), 7.49 (t, J = 8.4 Hz, 2H), 7.28 – 7.18 (m, 3H), 5.71 (s, 2H), 4.61 (s, 2H), 4.20 (s, 2H), 3.03 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.1 (C-6´), 145.1 (C-5´), 135.9 (C-9), 133.7 (C-2´), 128.2 (C-4), 125.3 (C-2), 123.3 (C-3´), 122.6 (C-7), 121.3 (C-6), 121.3 (C-5), 119.1 (C-3), 119.1 (C-7´), 110.7 (C-4´), 110.7 (C-8), 102.6 (C-8´), 61.2 (C-1´´), 52.0 (-$NCH_3)_3$, 48.6 (C-1´). Anal. calculated for: C, 53.34; H, 5.15; N, 6.22,. Found: C, 53.22; H, 5.21; N, 6.30.

N,N,N-trimethyl-4-((3-((trimethylammonio)methyl)-1H-indol-1-yl)methyl)benzenaminium diiodide (4i).

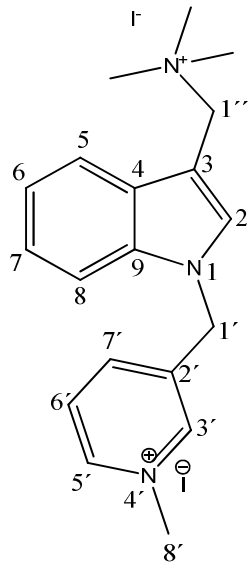


Following the general procedure, compound **4i** was obtained from **3i-1** as white solid. Yield: 96%. M. p: 160,2-163,6 °C, decomposition.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (dd, J = 21.8, 12.7 Hz, 4H), 7.56 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 8.9 Hz, 2H), 7.29 – 7.11 (m, 2H), 5.65 (s, 2H), 4.78 (s, 2H), 3.59 (s, 9H), 3.11 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 146.7 (C-5´), 140.1 (C-9), 136.1 (C-2´), 133.9 (C-4), 128.8 (C-7´), 128.8 (C-3´), 128.7 (C-2), 122.6 (C-5), 121.2 (C-6´), 121.2 (C-4´), 121.0 (C-6), 119.5 (C-7), 111.2 (C-8), 102.3 (C-3), 60.5 (C-1´´), 56.8 (C-8´), 56.8 (C-

9´), 56.8 (C-10´), 51.6 (-NCH_3)$_3$, 48.6 (C-1´). Anal. calculated for: C, 56.90; H, 6.73; N, 9.05. Found: C, 56.85; H, 6.77; N, 9.11.

1-methyl-3-((3-((trimethylammonio)methyl)-1H-indol-1-yl)methyl)pyridin-1-ium iodide (4j).

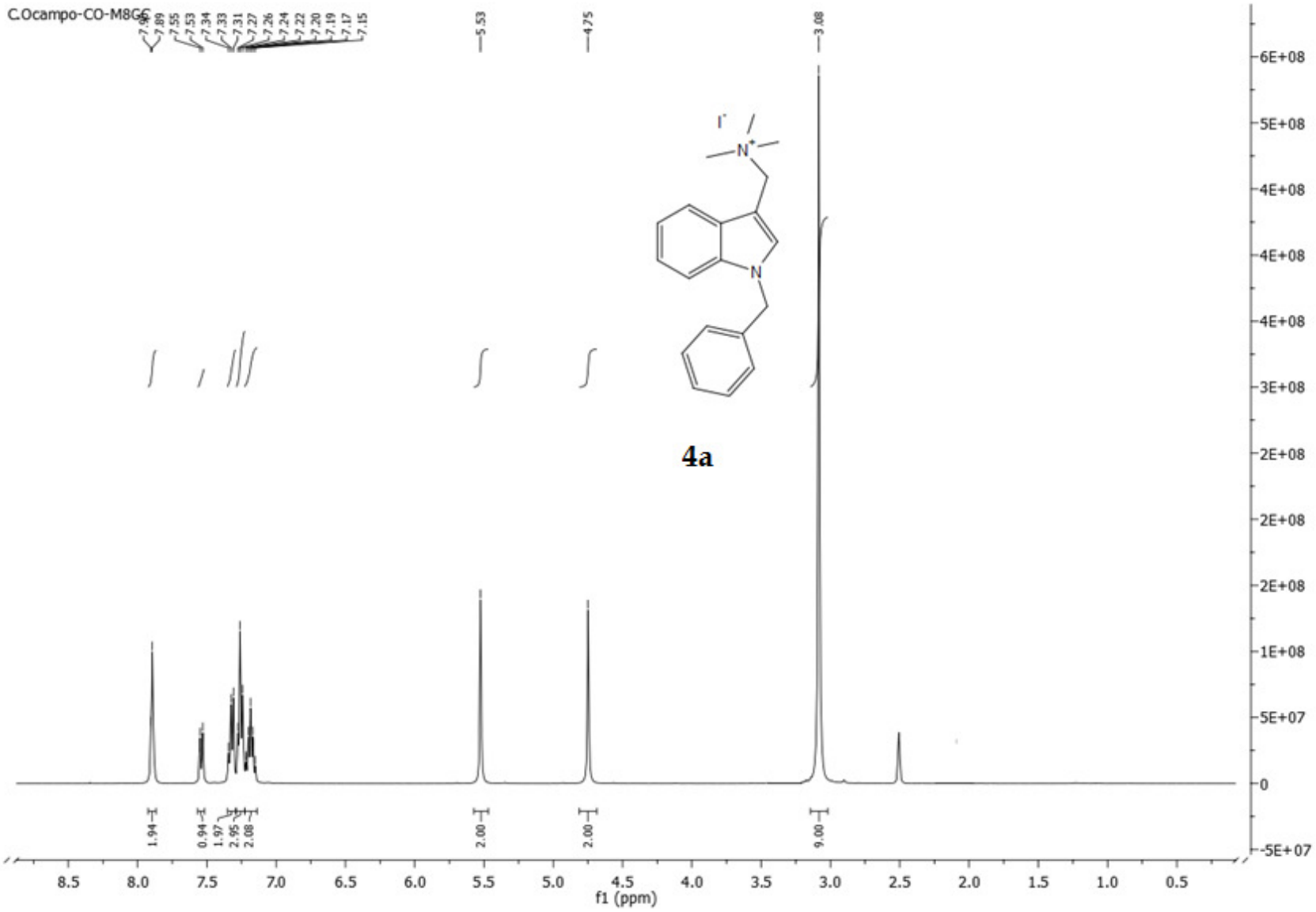


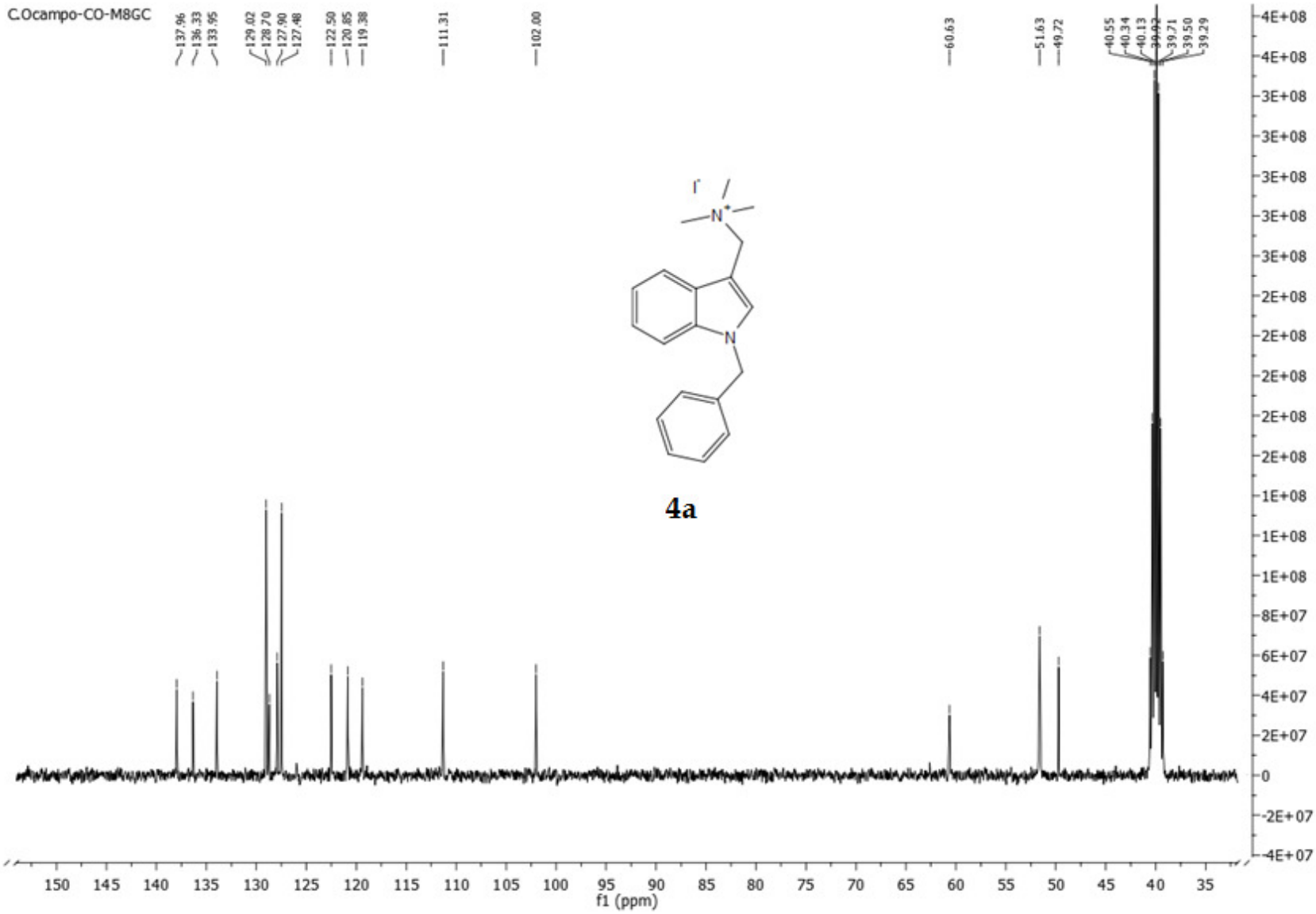
Following the general procedure, compound **4j** was obtained from **3j-1** as white solid. Yield: 97%. M. p: 167,2-173,3 °C, decomposition.

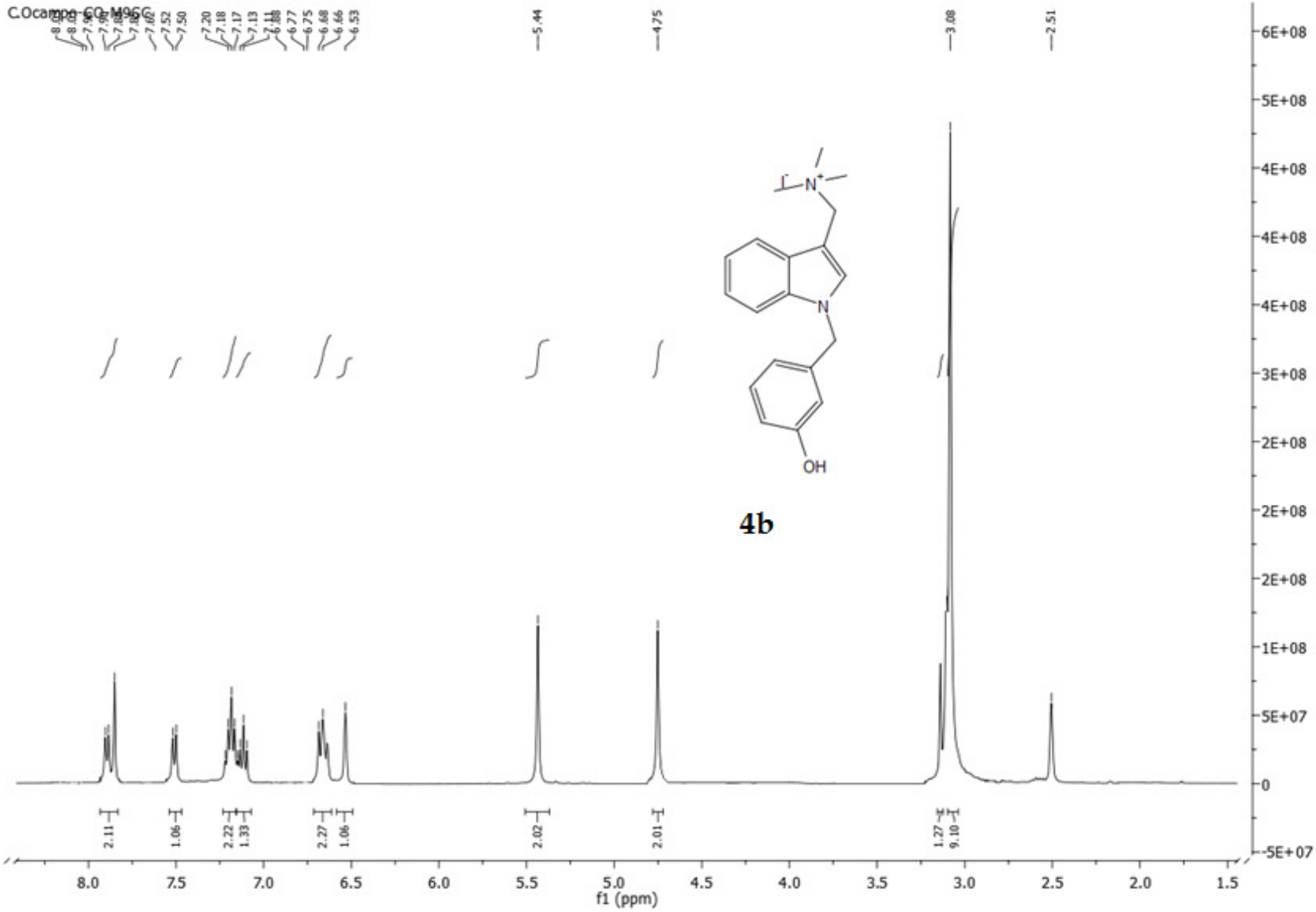
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.95 (d, J = 5.9 Hz, 1H), 8.38 – 8.22 (m, 1H), 8.18 – 8.03 (m, 1H), 8.02 – 7.87 (m, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.33 – 7.09 (m, 2H), 5.79 (s, 2H), 4.79 (s, 2H), 4.37 (s, 3H), 3.11 (d, J = 13.2 Hz, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.7 (C-3´), 144.1 (C-5´), 143.3 (C-9), 137.7 (C-7´), 135.6 (C-2´), 133.5 (C-4), 128.5 (C-2), 127.6 (C-6´), 122.5 (C-5), 120.9 (C-6), 119.2 (C-7) , 110.7 (C-8),

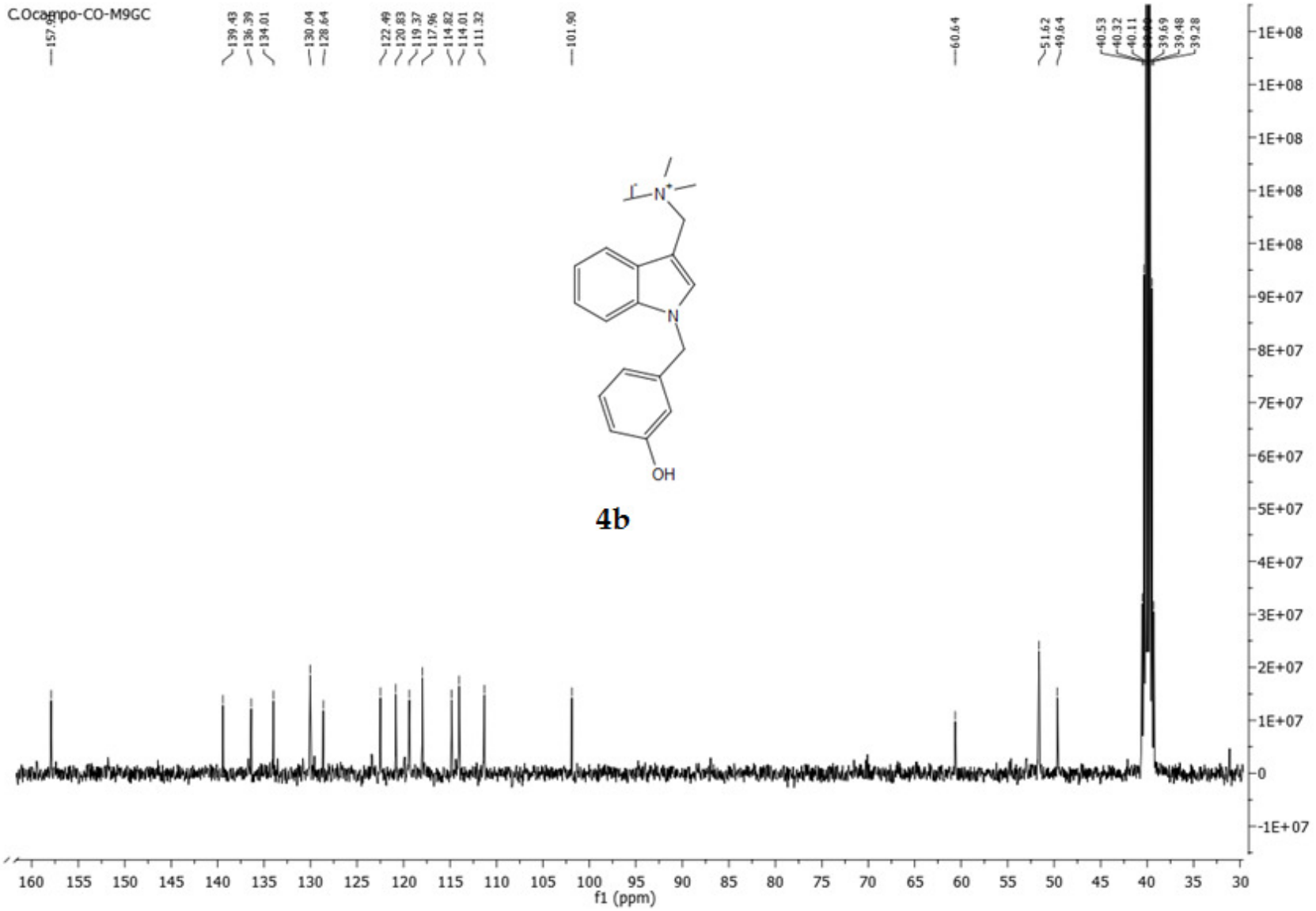
102.5 (C-3), 59.9 (C-1´´), 51.3 (-$NCH_3)_3$, 48.2 (C-1´), 45.9 (C-8´). Anal. calculated for: C, 41.55; H, 4.59; N, 7.65. Found: C, 41.26; H, 4.60; N, 7.72.

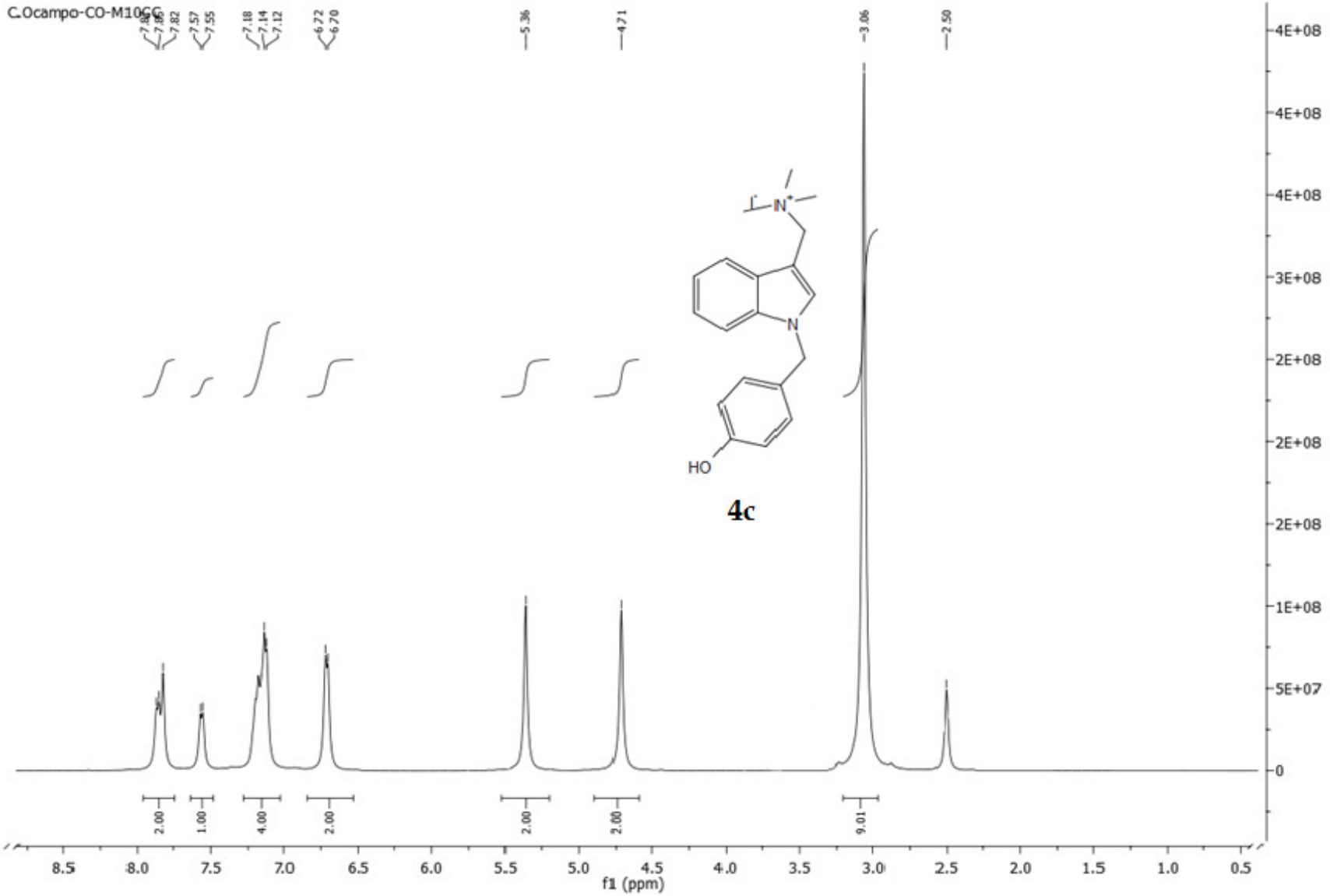
^{1}H and ^{13}C NMR spectrums

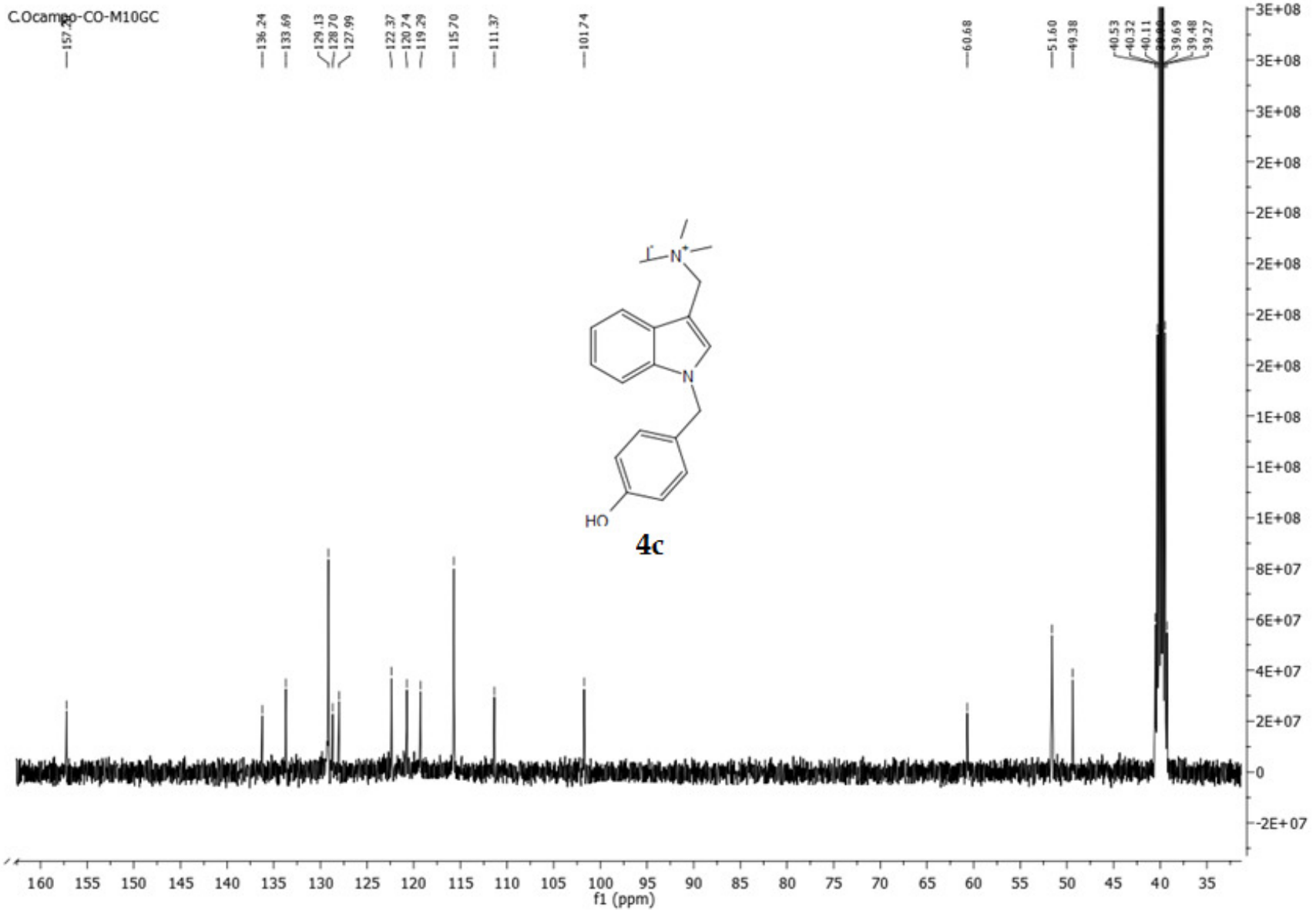


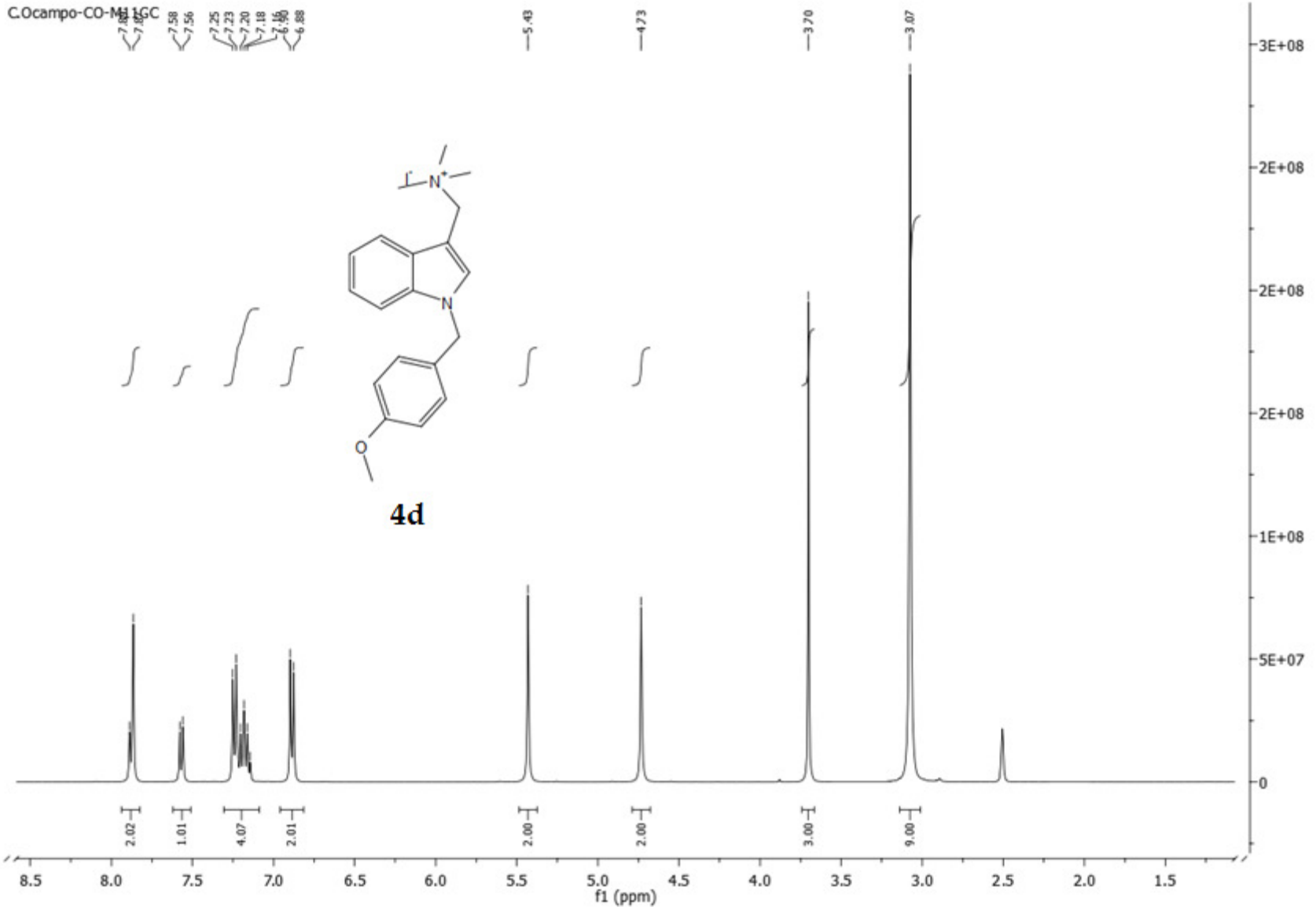


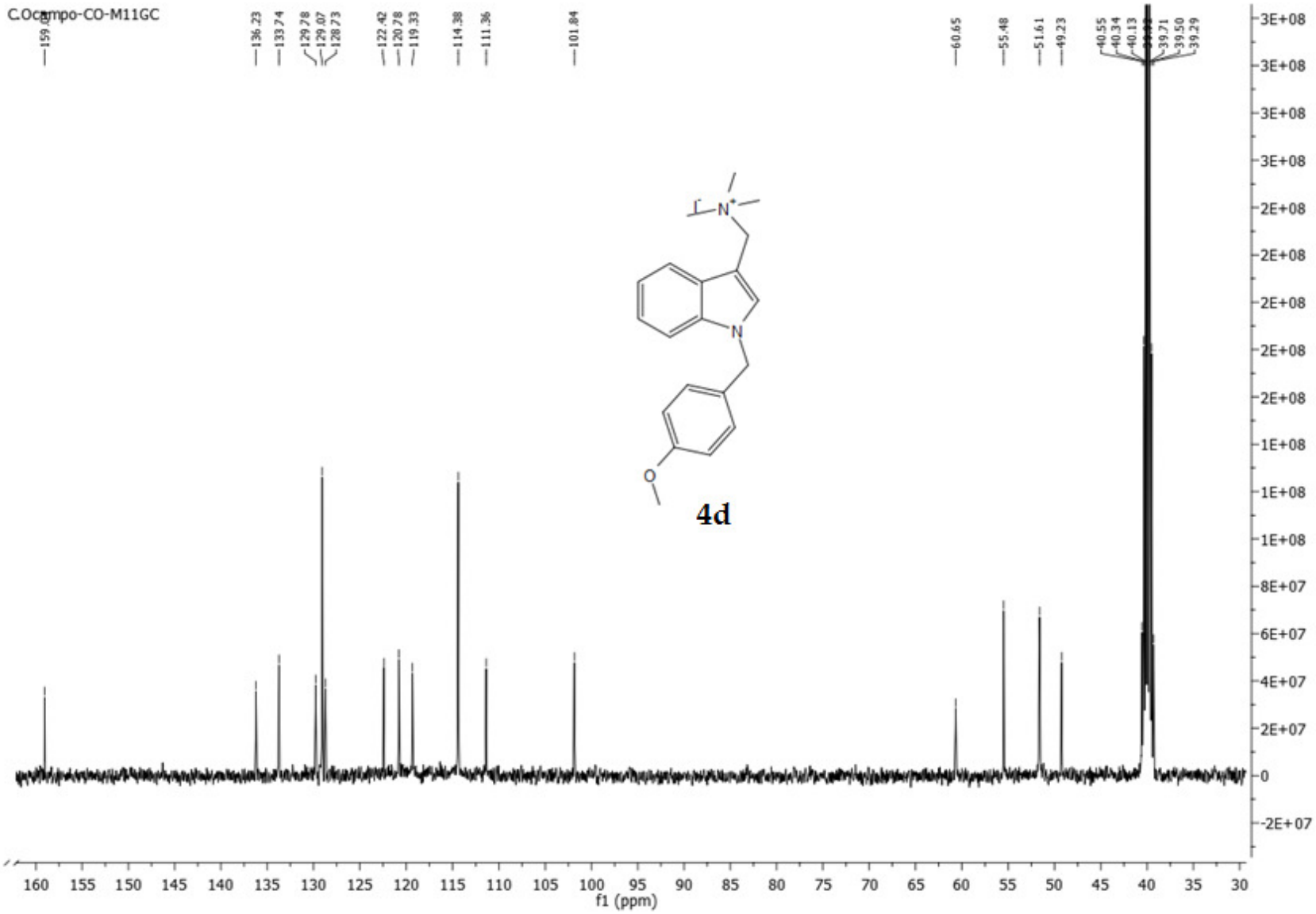


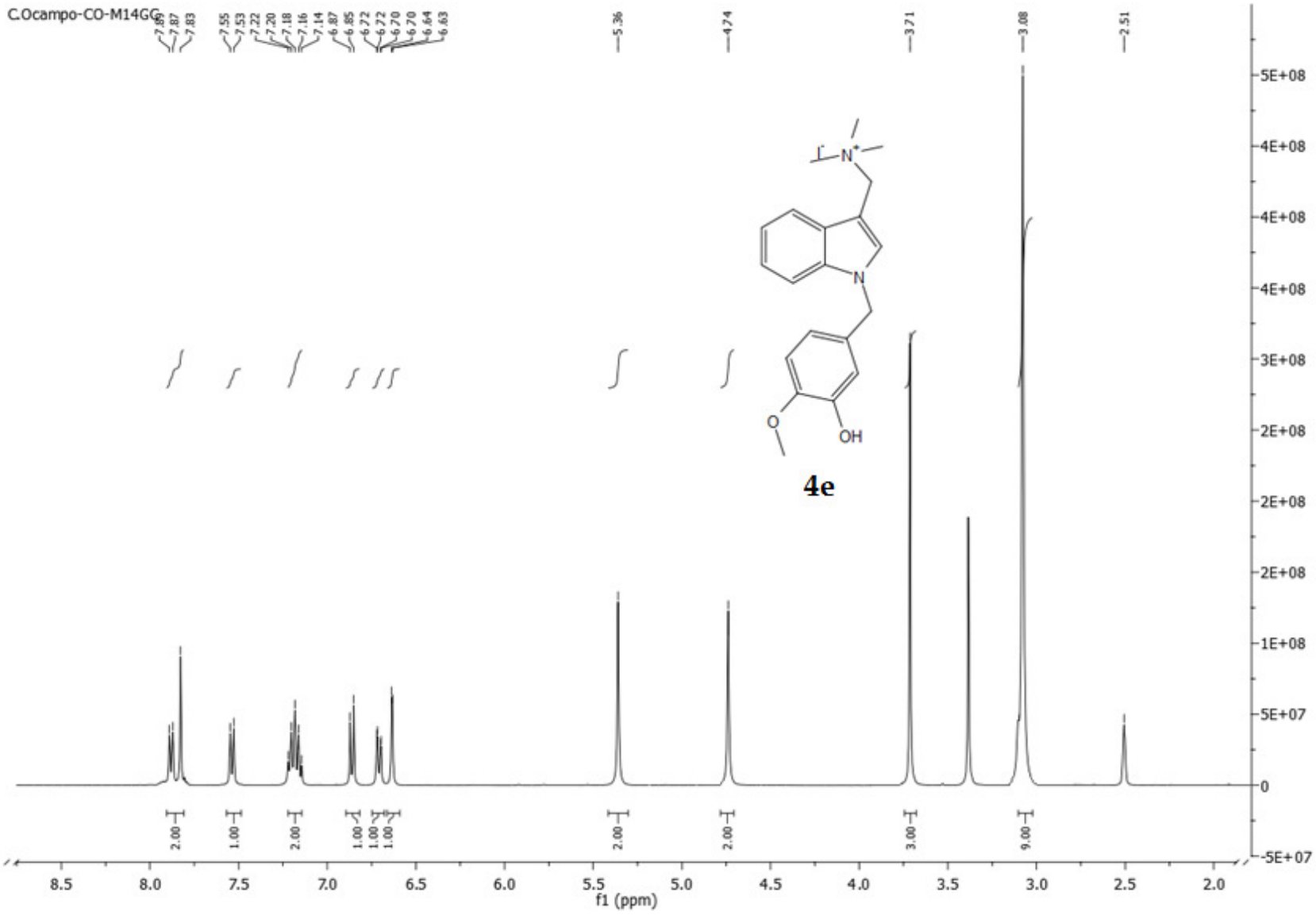


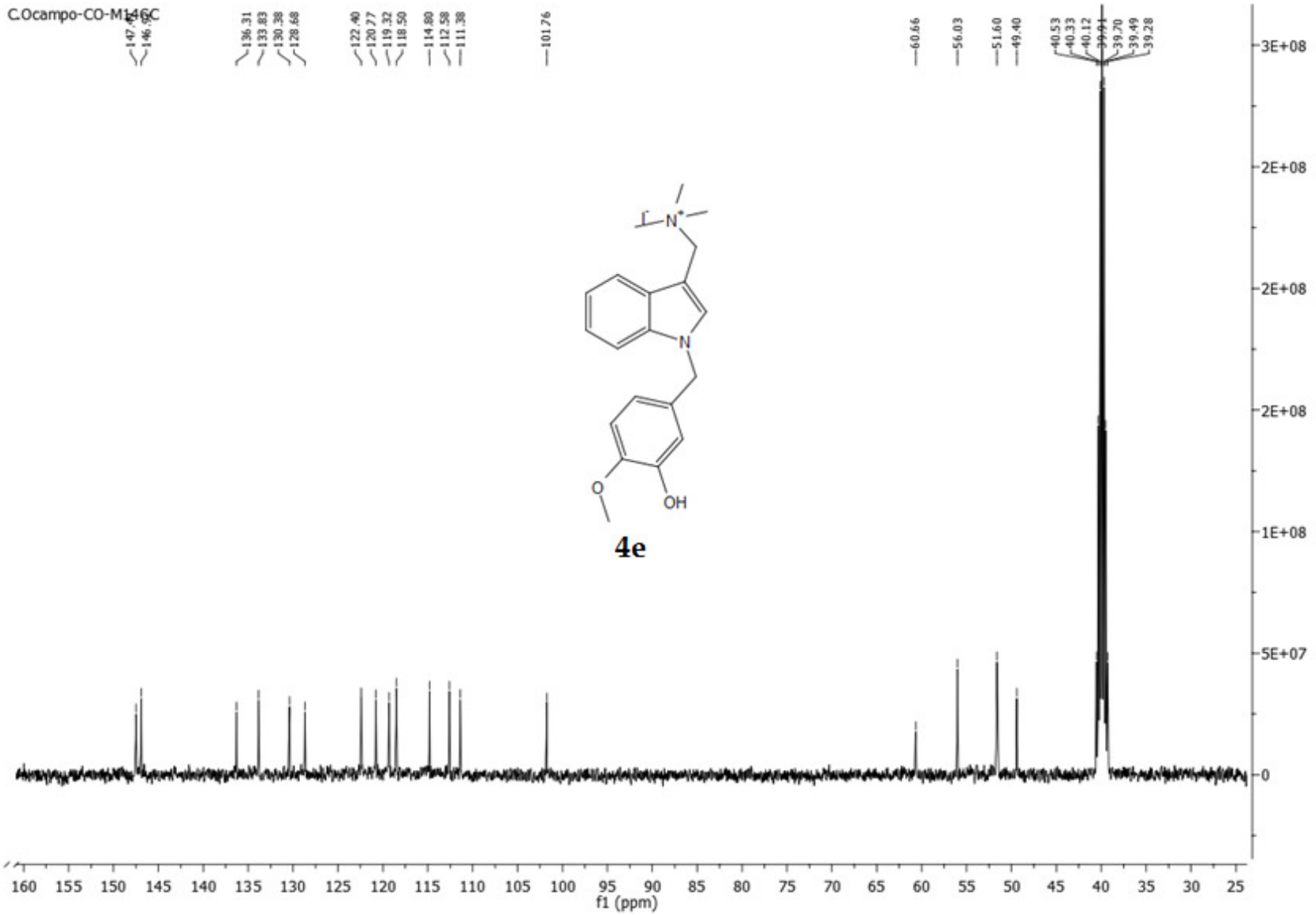




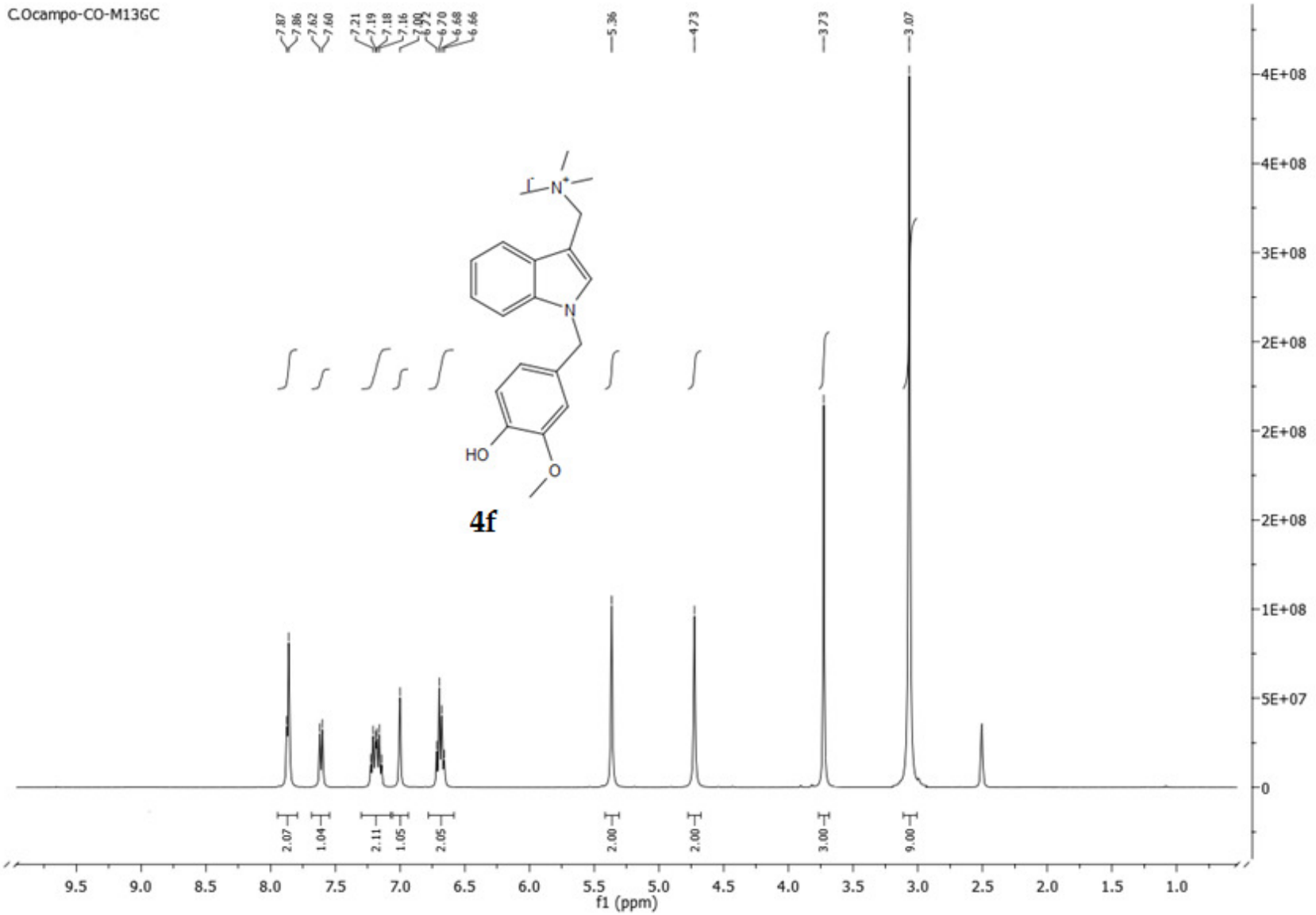


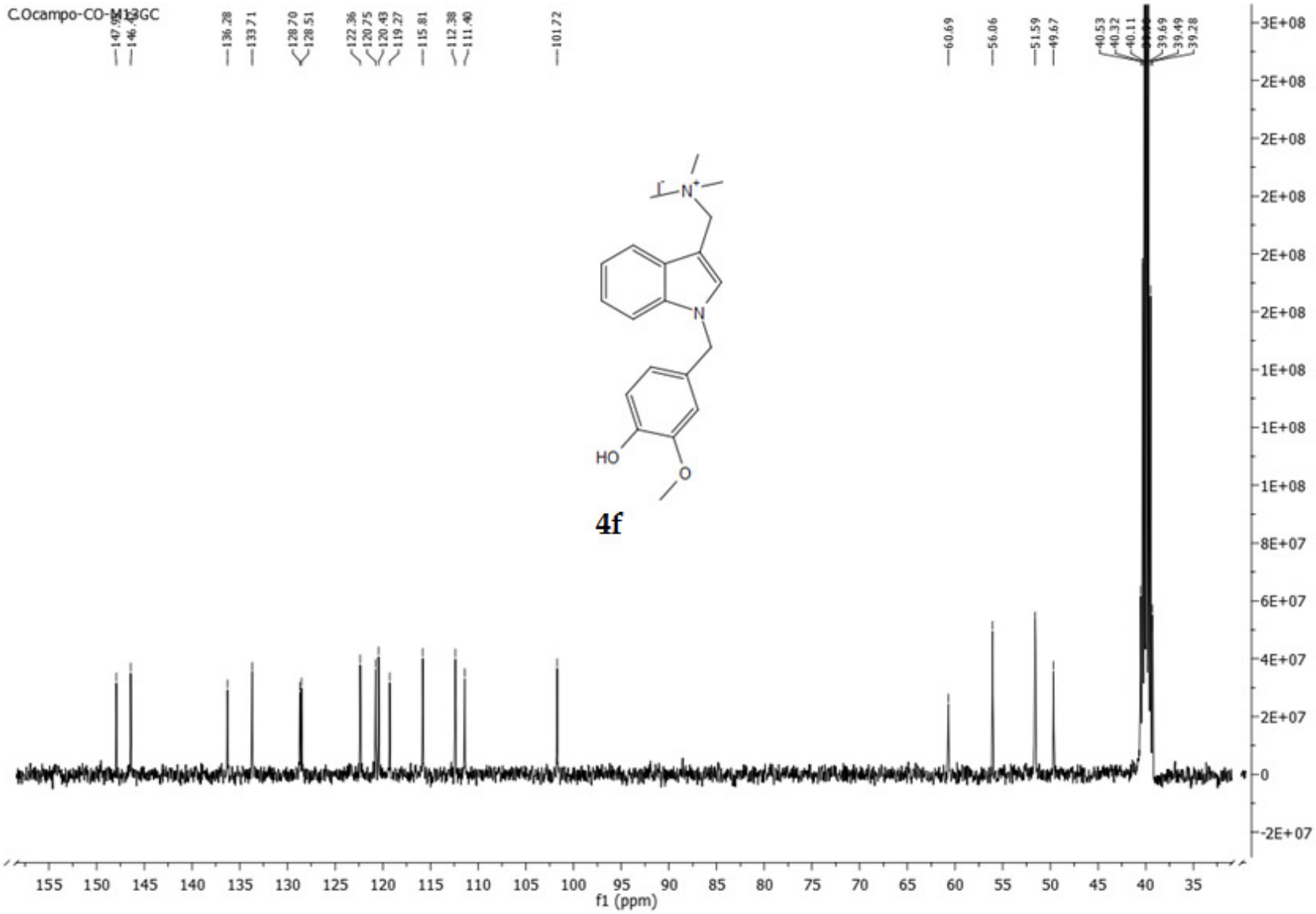


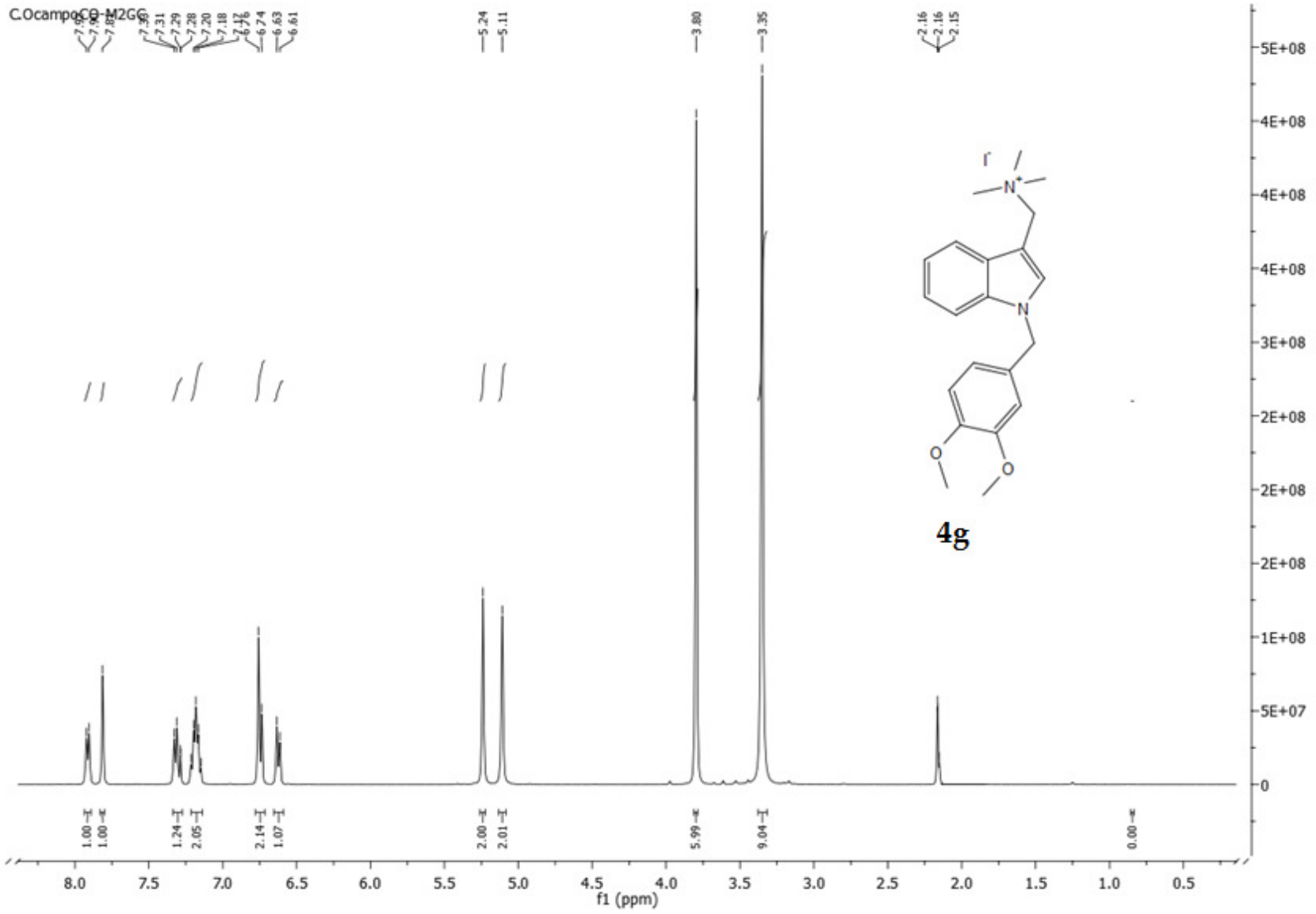




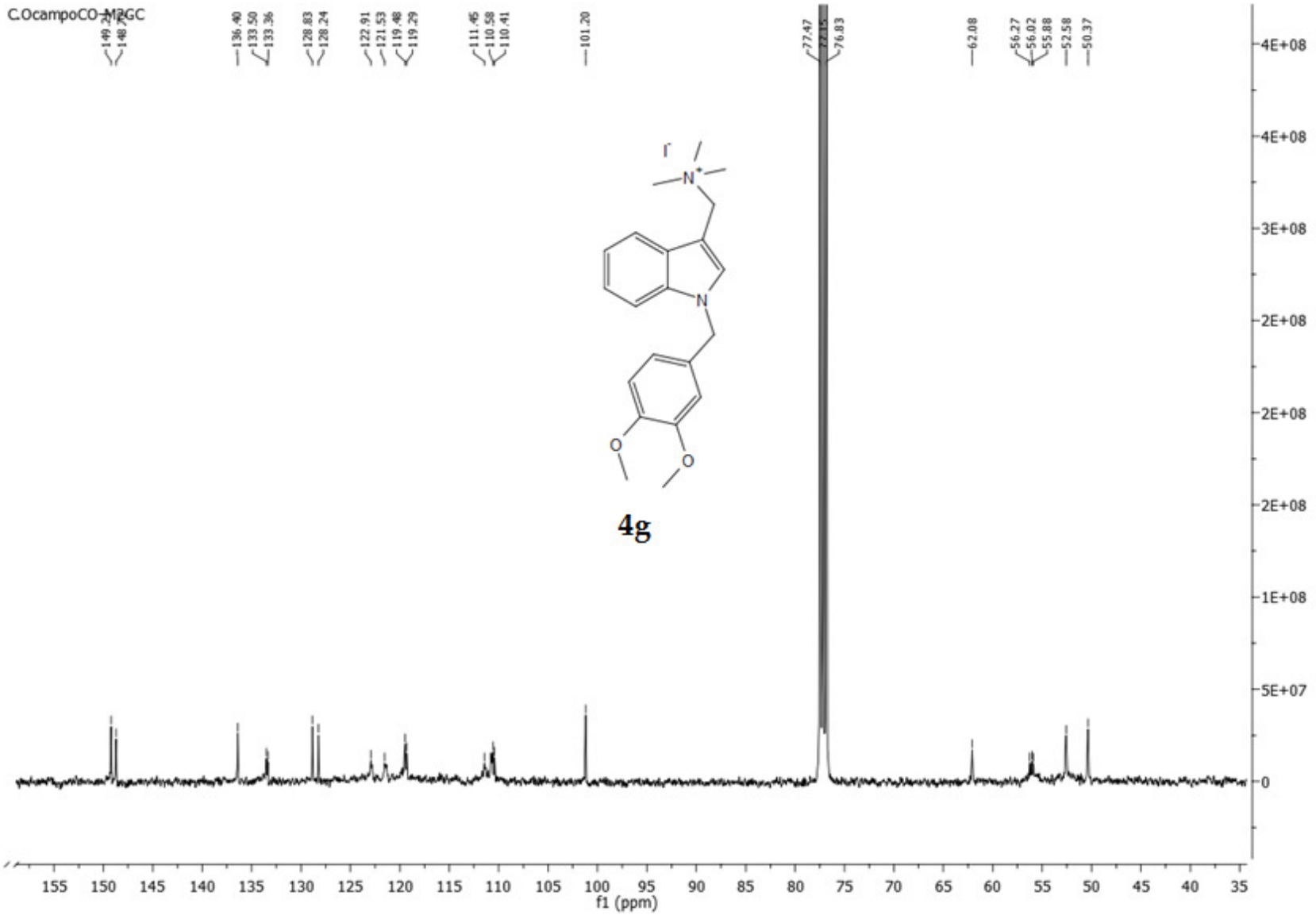
4e

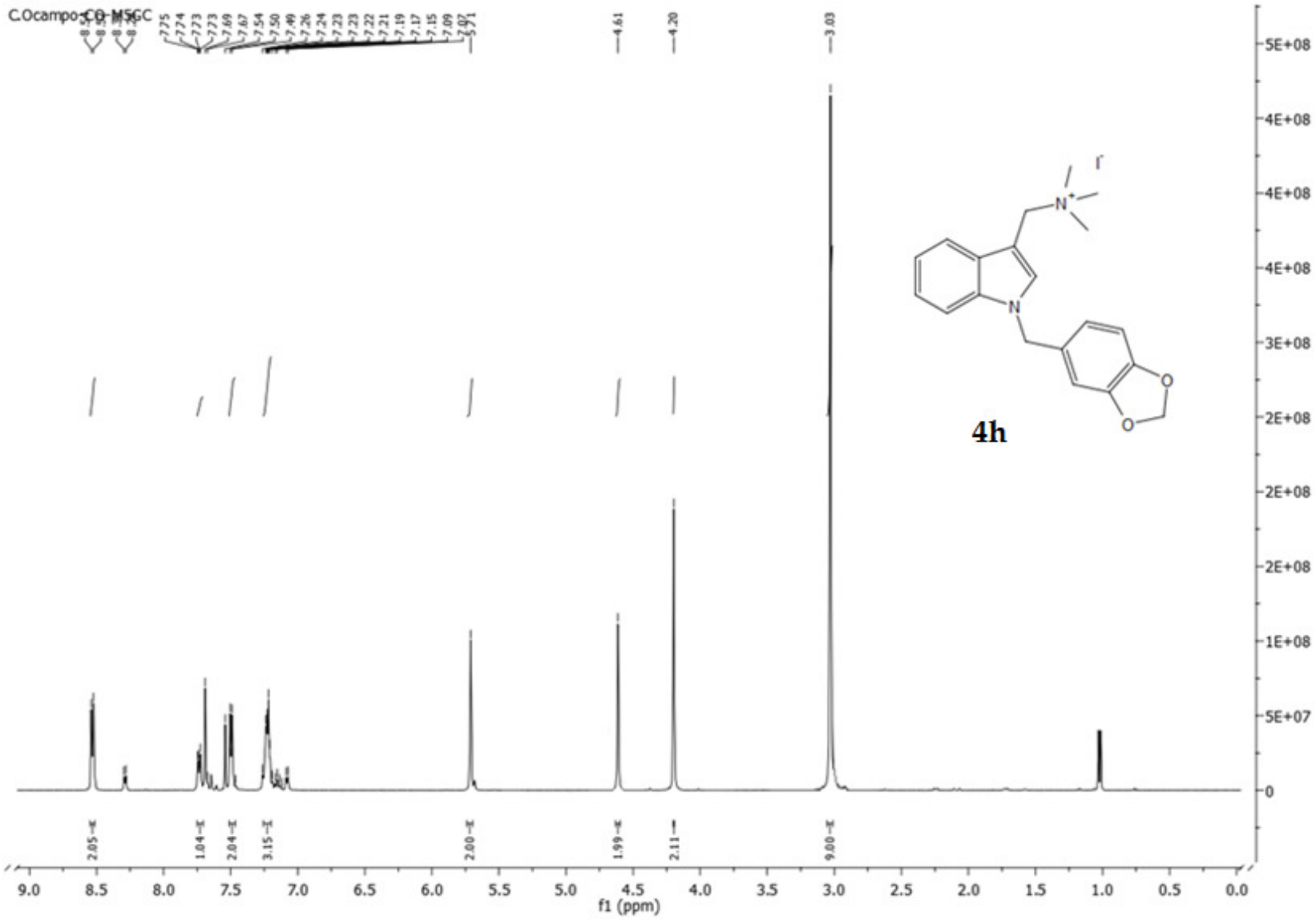


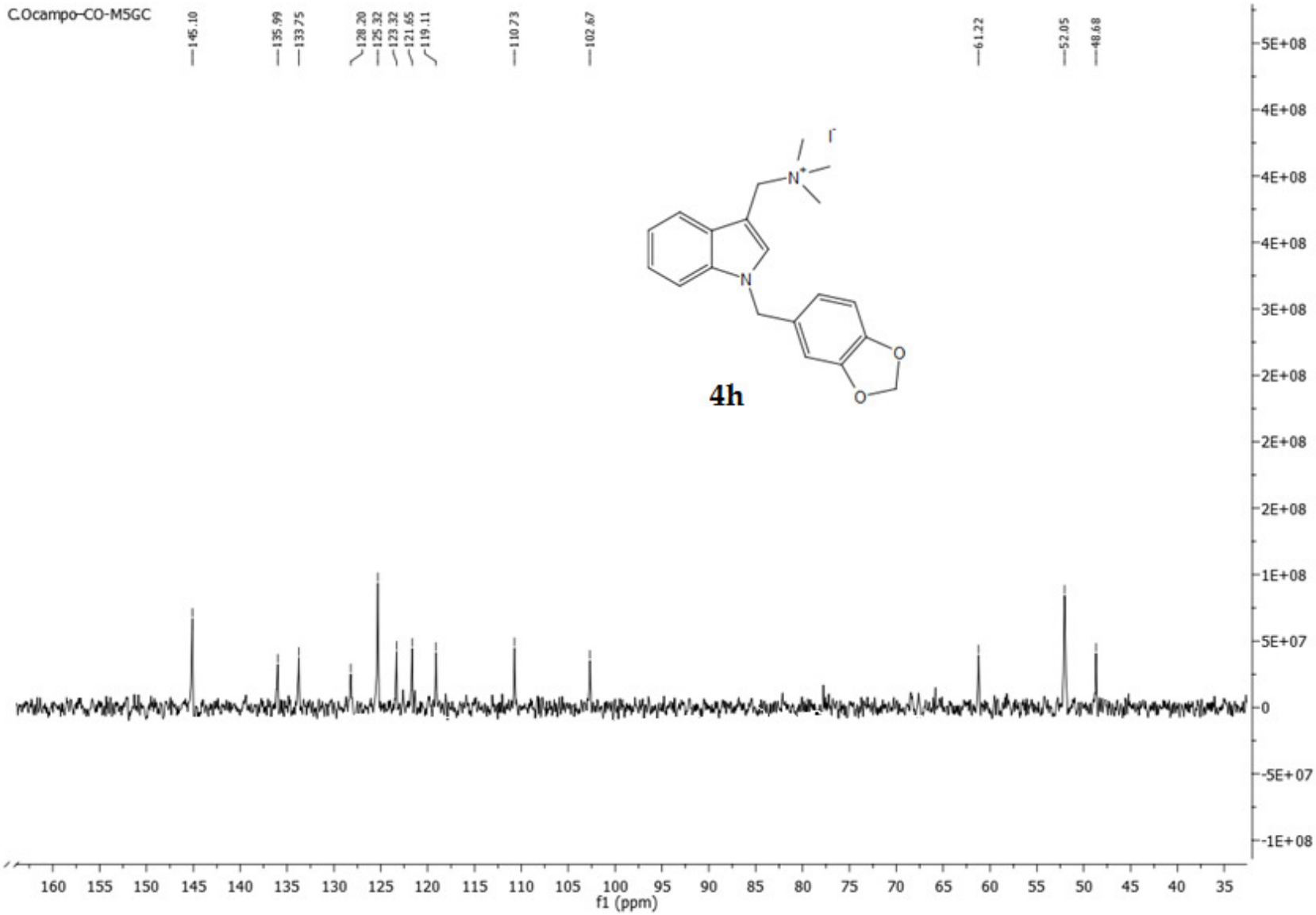


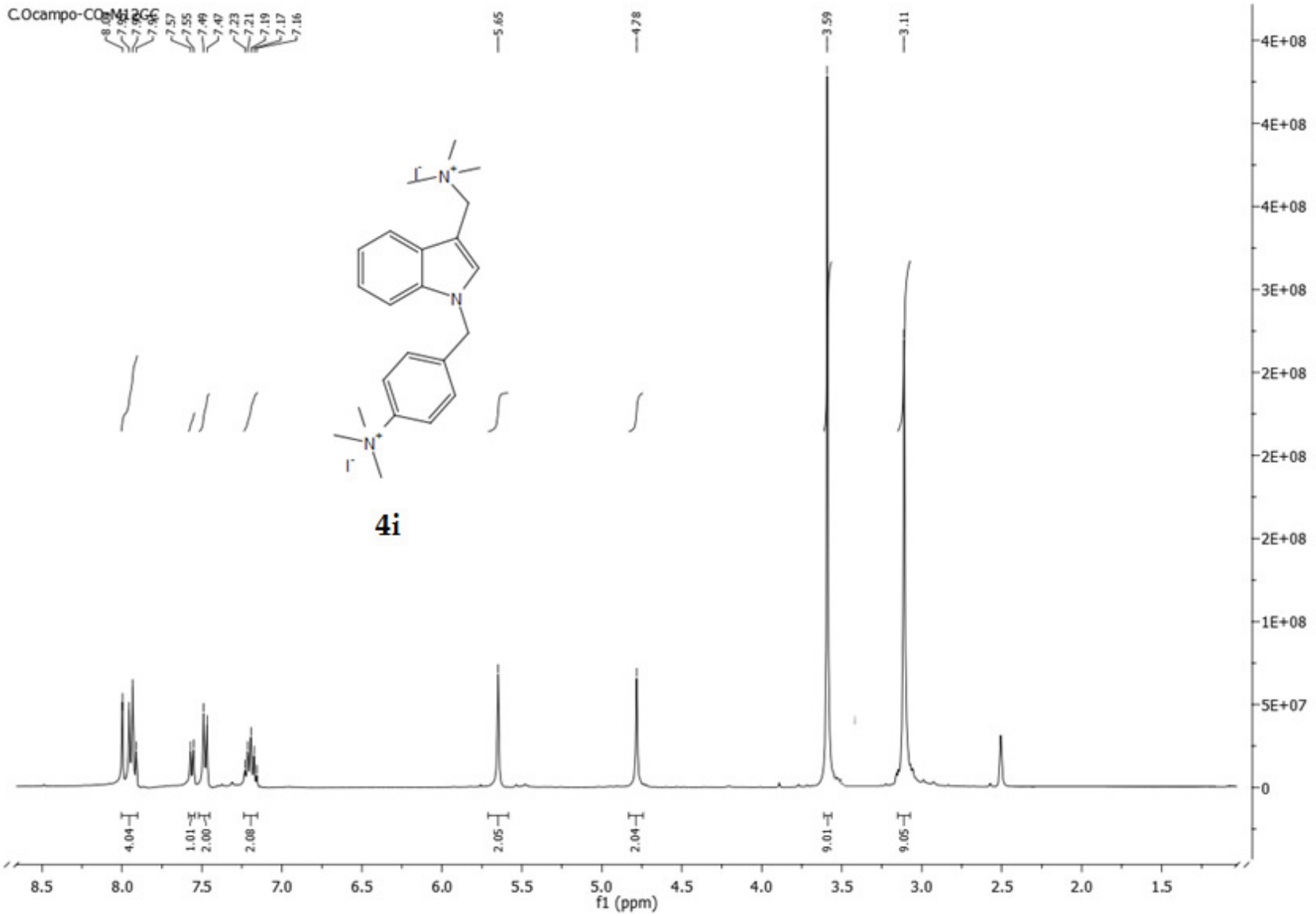


4g

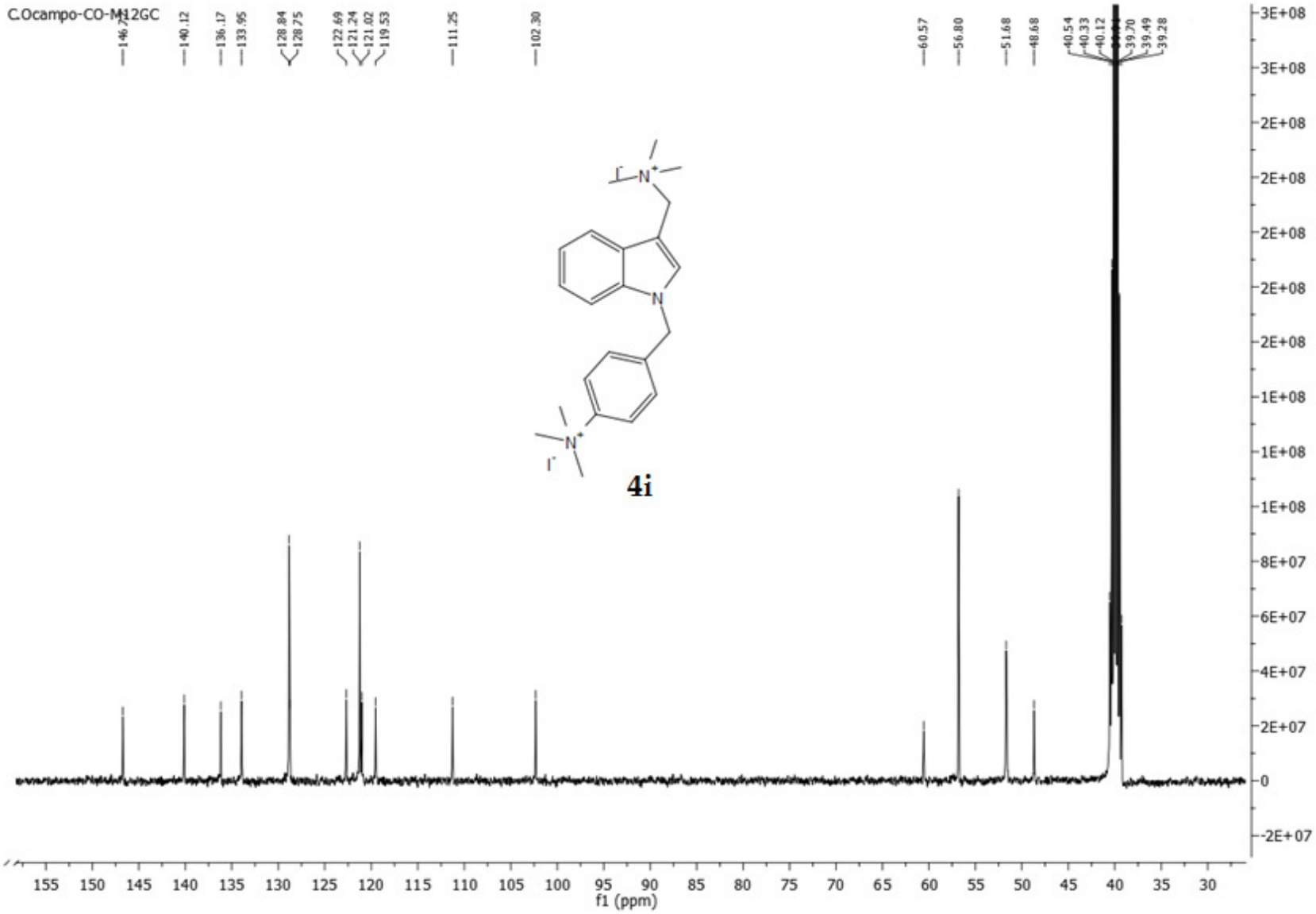


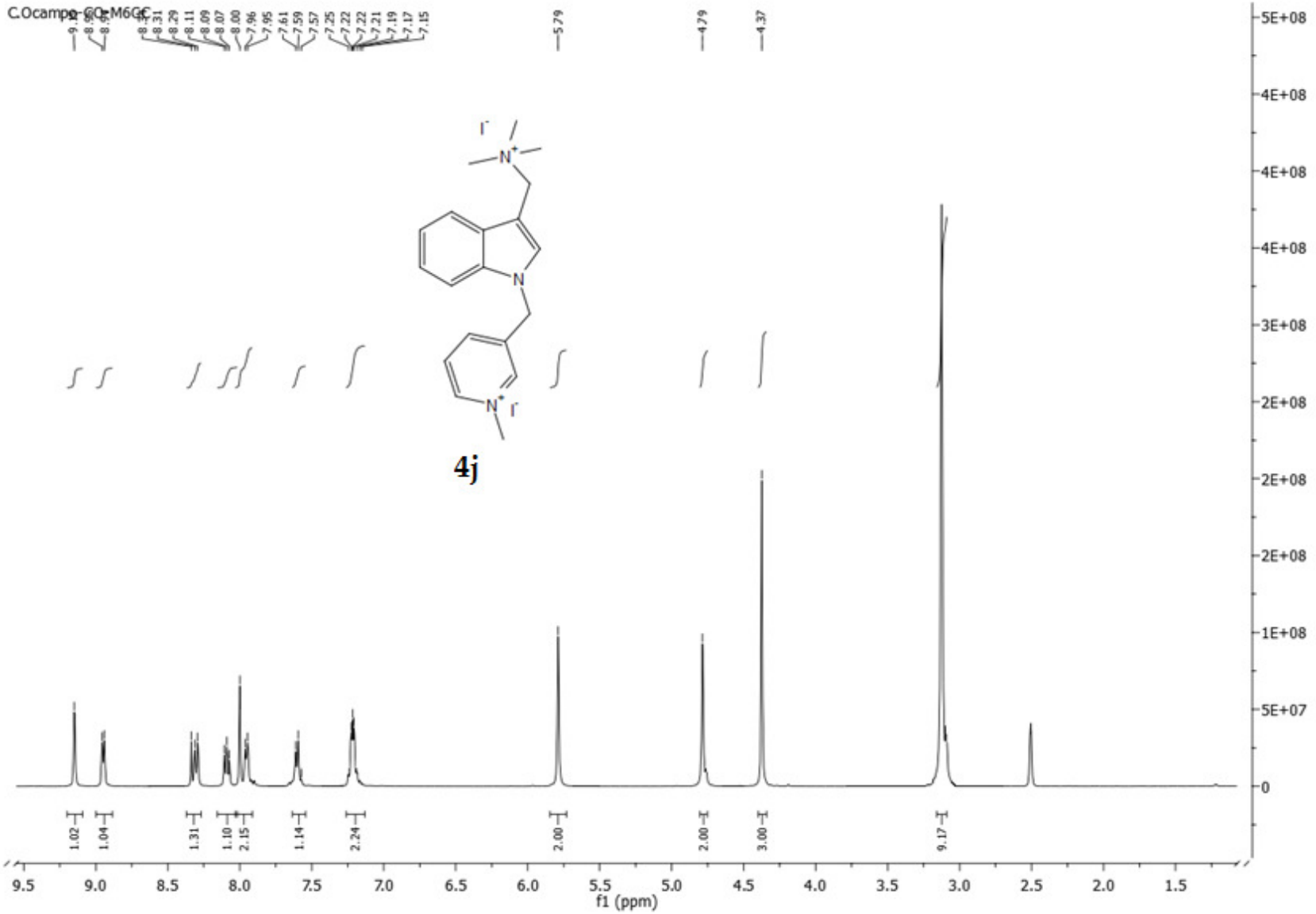


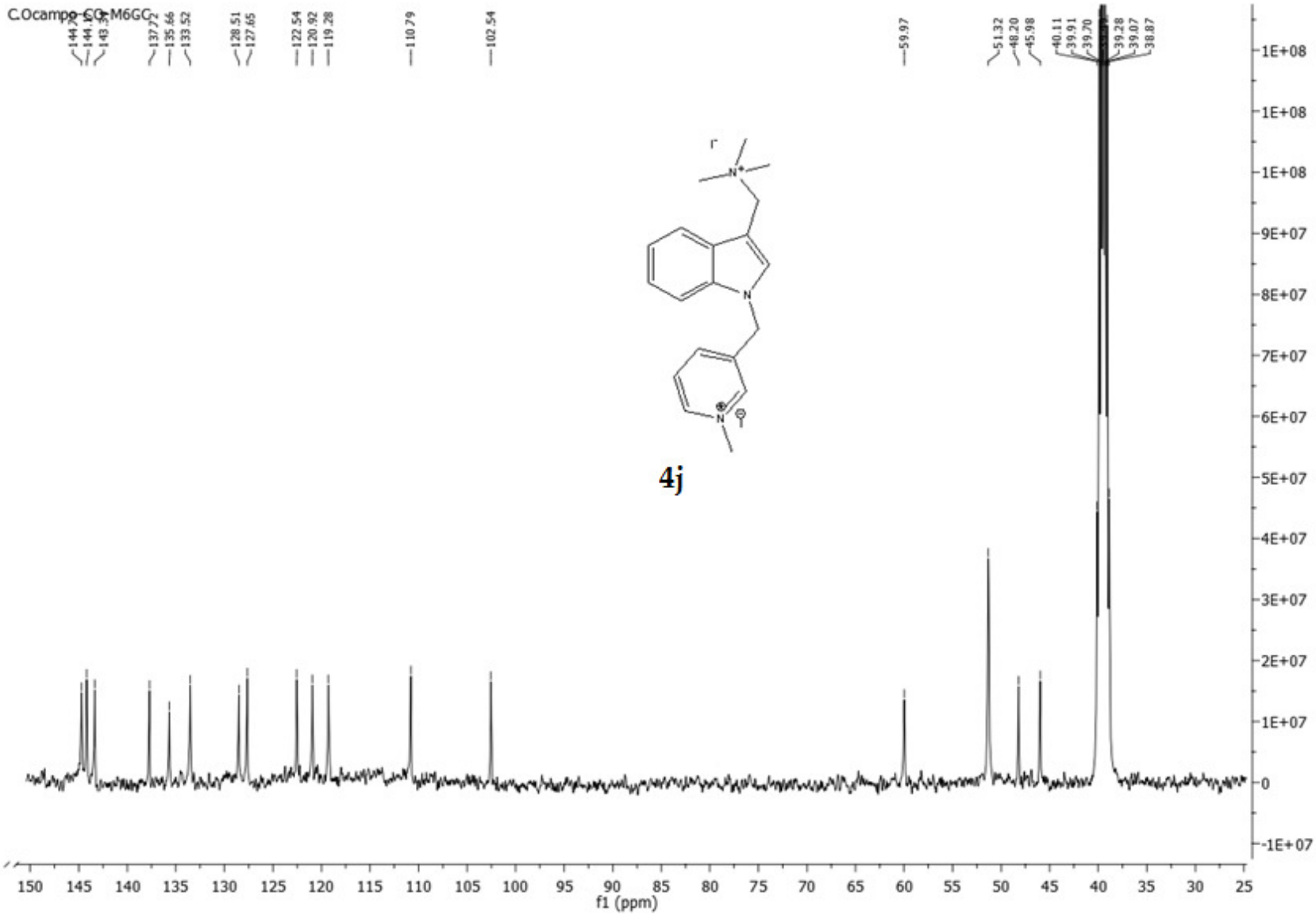




4i







4j