Design, synthesis, and evaluation of donepezil-like compounds as AChE and BACE-1 inhibitors

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Experimental

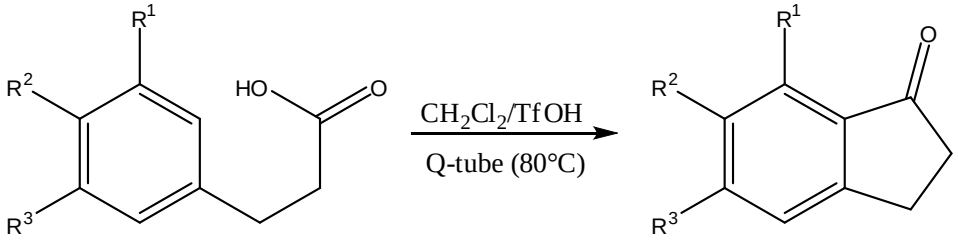
General Information

All chemicals were obtained from Aldrich Chem. Co or Acros Organics and used as received. Q-Tube assisted reactions were performed in a Q-Tube^{TM} safe pressure reactor from Labtech, equipped with a cap/sleeve, a pressure adapter (120 psi), a needle adapter/needle, a borosilicate glass tube, a teflon septum and a catch bottle. US-assisted reactions were performed in a high-power US-bath (19.6 kHz) made by Danacamerini (Torino). Reactions were monitored by a GC–MS Thermo Fisher Scientific workstation, composed by a Focus GC (Thermo TR- 5ms SQC 15m X 0.25mm ID X 0.25 µm, working on split mode, 1.2 mL/min He as carrier gas) and a DSQ II mass detector. Functionalization of unvolatile compound using BSA was performed according to the following procedure: 0.1 mg of compound were solubilized in 50 µl AcOEt and 50 µl of BSA were added under stirring. The mixture was reacted at 65°C for 35 minutes, diluted 1:1000 with AcOEt and injected in the GC/MS apparatus. The $[M+72]^+$ m/z value was detected for each desired product. TLC were performed using silica plates 60-F_{264} on alumina, commercially available from Merk. Liquid flash chromatography was performed on a Supelco VERSA FLASH HTFP station using silica cartridges commercially available from Supelco. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker WM 300 instrument on samples dissolved in $CDCl_3$ (compounds **13, 15, 17-26**) or in d_6-DMSO (compounds **14** and **16**). NOESY spectra were recorded on a Bruker Avance 500 MHz instrument (^{1}H:500.13 MHz), using a standard 5 mm double resonance broadband (BBO) probe. Chemical shifts are given in parts per million (ppm) from tetramethylsilane as the internal standard (0.0 ppm). HRMS measurements were realized on a Thermo Scientific QExactive (Thermo Fisher, Milan, Italy) mass spectrometer working in positive mode at 35,000 resolving power, operating in SIM mode by flow injection (flow rate 15 µL/min for each stock solution). Stock solutions at a concentration of 1 mg/mL were prepared in UHPLC-MS grade MeOH for each analytes separately. Prior to analysis, each solution was diluted 1:1000 (v/v) in a vial to obtain a concentration of 1 mg/L. Detection of the targeted compounds was based on theoretical exact mass. Data were evaluated by Xcalibur 2.2.SP1(Thermo Fisher Scientific, Bremen, Germany). The mass accuracy, directly calculated from Xcalibur, is defined by the formula Δ(ppm) = [(theoretical mass − measured mass)/theoretical mass] × 1.000.000.

eeAChE, hAChE from human erythrocytes, BuChE, acetylthiocholine, butyrylthiocholine, 5',5'-dithiobis-2-nitrobenzoic acid (DTNB), and donepezil, were purchased from Sigma-Aldrich.

The fluorescent peptide substrate containing the Lys-Met/Asn-Leu mutations of the amyloid precursor protein (APP) β-secretase cleavage site was purchased from Sigma-Aldrich. Mouse BACE-1 (recombinant) and BACE-1 Inhibitor I, were from Life Technology; BACE-1 inhibitor IV solution (10 mM in DMSO) was from Calbiochem. Stock solutions of the synthesized compounds were prepared in DMSO at 100 mM final concentration.

General protocol for Q-Tube assisted synthesis of indanones



1: R^1=H; R^2=R^3=OCH_3; **2**: R^1=R^3=H; R^2=OCH_3 **5**: R^1=H; R^2=R^3=OCH_3; **6**: R^1=R^3=H; R^2=OCH_3
3: R^1=OCH_3; R^2=R^3=H; **7**: R^1=OCH_3; R^2=R^3=H; **8**: R^1=R^2=H; R^3=OCH_3
4: R^1=H; R^2=R^3=O-CH_2-O **9**: R^1=H; R^2=R^3=O-CH_2-O

Figure S1

In a 12 mL Q-Tube™ pressure tube, furnished by Q Labtech, trifluoromethan sulfonic acid (3 eq) was gently added to a cooled (0°C) solution of a 3-Phenyl propionic acid (0.5 mmol) in dry dichloromethane (1.0 mL). Temperature was raised to room temperature. A teflon septum was placed on the top of the tube and the appropriate cap with a pressure adapter were used. The mixture was heated in a oil bath at 80°C. The reaction was monitored by TLC and GC/MS until disappearance of the reactant. The mixture was poured into ice and extracted three times with dichloromethane. The organic phase collected were dried on Na_2SO_4, filtered and concentrated under vacuum. The desired pure product was separated from the crude by flash chromatography. See Ref 22 for spectral characterization of products.

General protocol for synthesis of N-benzylpiperidine-4-carboxaldehydes

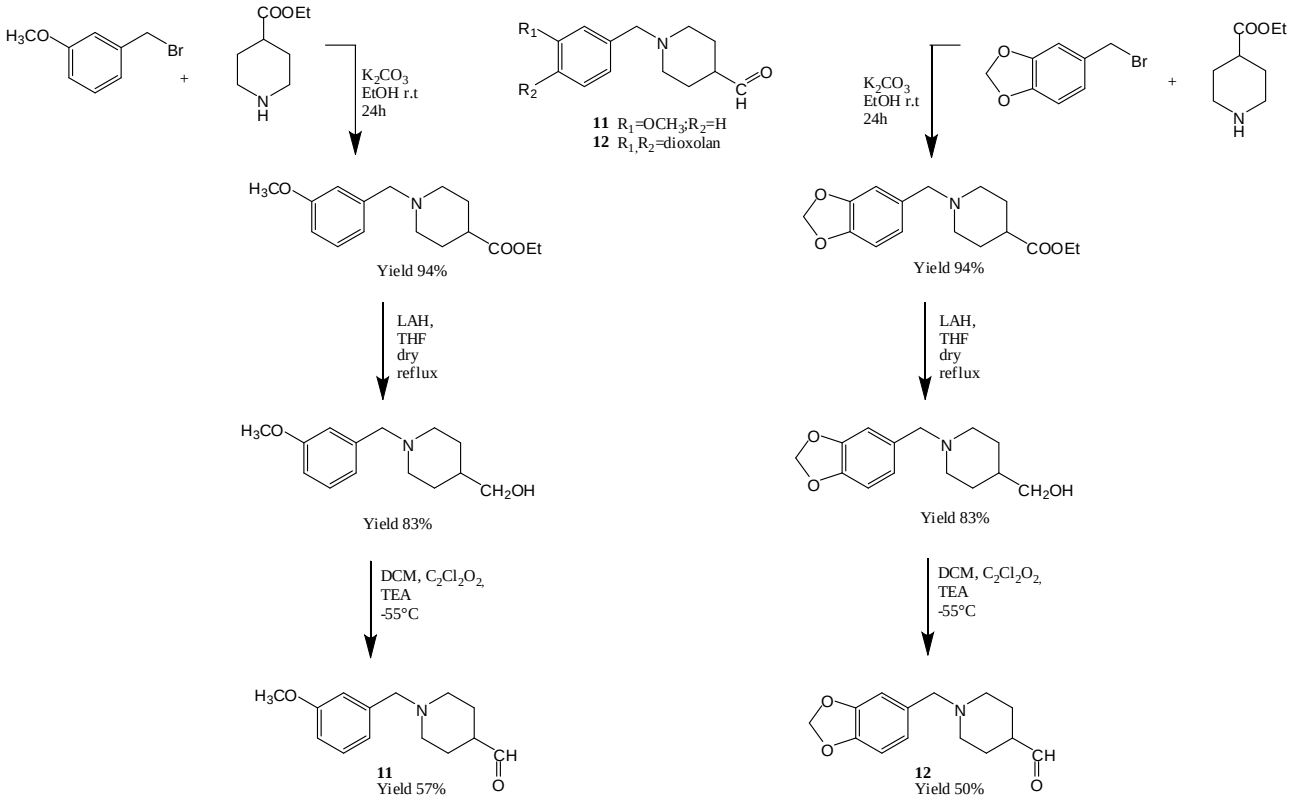


Figure S2

Alkylation

To a solution of ethyl isonipecotate (0.997 g, 6.35 mmol) and K_2CO_3 (2.1 g, 15.3 mmol) in EtOH (32.5 mL), an excess of bromide (7.6 mmol) is added portion wise and under stirring. The mixture is reacted for 24hours at room temperature and monitored by TLC. At the end of reaction the solution is diluted with water and extracted three times with AcOEt. The organic phases were collected, dried with Na_2SO_4, filtered and evaporated under reduced pressure. The product is separated from the crude by flash chromatography (Hexane /AcOEt 8:2 v/v).

Reduction/Oxidation

A solution of N-alkyl-piperidine-4-ethyl carboxylate (1.3 mmol) coming from the previous step in 2.2 ml of dry THF is added under stirring to a suspension of LiAlH4 (0.2087 g, 5.2 mmol) in dry THF (4.3 mL) previously cold down at 0 °C. The mixture is heated until room temperature and stirred for 1 hour, then refluxed for 4 hours. The reaction is monitored by TLC; at the end the mixture is cold down at room temperature and H_2O (5 mL) and a solution of NaOH 2N (1.3 mL) are gently added. The resulting mixture is extracted three times with AcOEt; the organic phases collected are dried on Na_2SO_4, filtered and the solvent is evaporated under reduced pressure. The crude, analyzed by GC/MS after BSA derivatization in order to verify the formation of the desired product, is used in the oxidation step without purification. To a solution of ossalic chloride (2.16 mmol, 0.274 g in 5.38 ml of dry DCM) previously cold down at -48 °C and maintained at this actual temperature for 10 minutes, DMSO (2.52 mmol, 0.196 g) is added drop wise. To the mixture, a solution of the crude in dry dichloromethane (1.08 mmol in 0.6 ml of DCM dry) is added and the

reaction is stirred at -55°C for 15 minutes. After the addition of 0.575 ml of trimethylamine, the mixture is heated until room temperature and stirred for 24 hours. After completion the mixture is diluted with $CHCl_3$ and extracted three times with water. The organic phases were collected, dried with Na_2SO_4, filtered and evaporated under reduced pressure. The product is separated from the crude by flash chromatography (DCM / MeOH 9.5:0.5v/v). See Ref 24 for spectral characterization of products.

*General procedure for synthesis of compounds **17-26***

The synthesis of donepezil precursor **17-26** was realized by US-assisted aldol condensation between indanones **5-9**[1] and the correspondent N-benzylpiperidine-4-carboxyaldehydes **10-12**, itself synthesized according to the procedure reported,[2] when needed.

For a typical synthesis, 0.33 g/mL of resin and methanol (3 mL) were charged in a round bottom flask and stirred at room temperature. 0.5 mmol of 1-indanone and 0.6 mmol of aldheyde were then added. The flask was closed with a silicone cup and equipped with a needle. The mixture was reacted in a high-power US-bath (19.6 kHz) made by Danacamerini with a nominal power 250 W. The temperature was maintained at 40-50 °C. The reaction temperature was controlled by a continuous water steam. The reaction was monitored by TLC until the reactant disappeared. After cooling to room temperature the mixture was filtered, and the resin was washed with dichloromethane, dried and reused for three reaction cycles. Solvent was then evaporated and the dried crude products were crystallized from methanol or purified by flash chromatographic purification where needed. All the compounds were identified by HRMS and characterized by ^{1}H-NMR and ^{13}C-NMR by comparison with the data reported (See Supporting Information).

*General Protocol for demethylation of compounds **17-20***

In a two neck round bottom flask, equipped with magnetic stirrer, 0.26 mmol of donepezil precursor were dissolved in 3 ml of wet DMF and 15 equivalents of iodocyclohexane were added under N_2 atmosphere. The mixture was refluxed at the DMF boiling point and continuously controlled by TLC. A total amount of 45 to 60 equivalents of iodocyclohexane was added at portion of 15 equivalents in a total time ranging from 6 to 10 hours depending on the case. At the end of reaction 10 ml of water was added and the mixture was extracted three times with 10 ml of dichloromethane. The collected organic phases were washed with a hypertonic $NaHSO_4$ solution (30 ml x 3) and a brine solution (30 ml x 3). The organic phases were finally dried on Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The DMF eventually still present was evaporated by azeotropic distillation with toluene. The products **13a/13b**, **14**, **15**, and **16** were separated by chromatographic purification and characterized by HRMS, ^{1}H- NMR and ^{13}C-NMR.

[1] Oliverio, M.; Nardi, M.; Costanzo, P.; Cariati, L.; Cravotto, G.; Giofrè V. S.; Procopio, A. Non-conventional methodologies in the synthesis of 1-indanones, *Molecules*. **2014**, *19*, 5599–5610.

[2] Caruso, A.; Garofalo, A.; Grande, F.; Aiello, F.; Anzini, M.; Ortuso, F.; Alcaro, S.; Panno, A.; Saturnino, C; Sinicropi, M. S. Synthesis and biological evaluation of 1,3-idandione derivatives as acetylcholinesterase inhibitors. *Pharmacologyonline.* **2009**, *1*, 264–277.

Enzymatic and viability assays

Cholinesterase activity was assayed by the Elmann method[3] using acetylthiocholine or butyrylthiocoline as substrate for AChE or BuChE, respectively. The reduction of dithiobisnitrobenzoate by the thiocholine, produced by the enzymatic hydrolysis of thiolated substrates, was followed colorimetrically (412 nm) at room temperature (22-27°C). The reaction mixture (500 µL) contained 330 µM DTNB and the appropriate amount of substrate, in 0.1 M sodium phosphate buffer, pH 7.1. The reaction was started by the addition of 100 mU/ml or 200 mU/ml of AChE or BuChE, respectively, and the initial rate of the reaction was derived from the linear portion of the kinetics.

The reversibility of the inhibition was assessed using a dilution method described previously[4,5]. Briefly, the enzyme was pre-incubated for 20 min with the inhibitors or with DMSO, as a vehicle control; after a 100-fold dilution of the incubation mixture, the residual enzyme activity was measured as reported above.

The concentration of inhibitor required to reduce the enzymatic activity to 50% (IC_{50}) was derived from semi-logarithmic plots in which the residual cholinesterase activity was determined at different concentration of inhibitor, using a thiolated substrate concentration of 500 µM. Linear curve fits were obtained with the least-squares method, and the significance of the correlation was estimated from the squared correlation coefficient r^2, which was always higher than 0.95.

The kinetic parameters of the enzymatic reaction K_m and V_{max}, were derived from the determination of the enzyme activity at 6 different acetylthiocholine or butyrylthiocholine concentration (80 – 500 µM), chosen in order to give the similar weight in the regression. The data were either interpolated in the Michaelis-Menten equation or treated with the Lineweaver-Burk equation giving similar results.

The inhibition constant K_i was derived by measuring the kinetic parameters in the presence of different inhibitor concentration, 0.2 – 30 µM for AChE or 3 – 100 µM for BuChE. The values of K_i were derived from the equation $K_m' = K_m (1 + [I]/K_i)$, in case of competitive inhibition or $V_{max}' = V_{max} / (1 + [I]/K_i)$, in case of non competitive inhibition, or with both in the case of mixed inhibition. In these equations K_m' and V_{max}' represent the values of K_m and V_{max} measured at the [I] concentration of inhibitor. Values of IC_{50} and K_i reported were the mean of at least 4 different determinations.

BACE-1 activity was assayed by a fluorimetric method[6] using the Enspire™ Multimode Plate Reader (Perkin-Elmer) in the kinetic Fluorescence method. The assay was performed in black polystyrene 96-well microtiter plates. The reaction mixtures contained 2.1 ng/µl mouse BACE-1 in 50 mM ammonium acetate buffer, pH 4.5 supplemented with 1 mM triton X-100, and the appropriate amount of the inhibitor. The mixture was incubated for 10 min at room temperature (22-25°C), the reaction started by adding 100 nM final concentration of the fluorescent peptide substrate, and the increase in fluorescence was followed kinetically. The enzymatic cleavage of the

[3] Ellman, G. L.; Courtney, K. D.; Andres, V.; Featherstone, R. M.; A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem. pharmacol*. **1961**, *7*, 88-95.

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[5] Lavecchia, A; Di Giovanni, C.; Pesapane, A.; Montuori, N.; Ragno, P.; Martucci, N. M.; Masullo, M.; De Vendittis, E.; Novellino, E.; Discovery of new inhibitors of Cdc25B dual specificity phosphatases by structure-based virtual screening. *J. Med. Chem*. **2012**, *55*,4142-4158.

[6] Mancini, F.; Naldi, M.; Cavrini, V.; Andrisano, V. Multiwellfluorometric and colorimetric microassays for the evaluation of beta-secretase (BACE-1) inhibitors. *Anal. Bioanal. Chem*. **2007**, *388*, 1175–11831.

peptide led to the appearance of a fluorescence signal using excitation and emission wavelength of 320 and 420 nm, respectively. The rate was derived from the linear portion of the kinetics, usually in the first 30 min of the reaction. The known Inhibitors I (IC_{50}, 240 nM),[7] and IV (IC_{50}, 15 nM)[8] were used as positive controls.

The effect of the synthesized compounds on cell viability was assessed in SH-SY5Y neuroblastomacells. Cells were grown in Roswell Park Memorial Institute medium (RPMI) supplemented with 2 mM L-glutamine, 100 UI/mL penicillin, 100 µg/mL streptomycin and 10% (v/v) fetal bovine serum. Cells were maintained in culture dishes at 37 °C in a saturated humidity atmosphere containing 95% air and 5% CO_2. Cells were seeded at an initial density of 104 cells/cm^2 in culture dishes. At a confluence of 80%, cells were detached by trypsin treatment, suspended in fresh medium without FBS and transferred to multiwell (24 or 96 wells). After 24 h from seeding, cells were incubated in the absence or in the presence of the synthesized compounds, and their viability was evaluated after 48h treatment as mitochondrial activity using the MTT assay.[9] Briefly, after the treatment the medium was removed and cells were incubated with 100 µl MTT (0.5 mg/ml) for 1 h. After that, the solution was removed, the formazan formed solubilized in100 µl of 0.1N HCl in 90 % (v/v) 2-propanol and the absorbance measured at 570 nm using a microplate reader (BioRad). Results were expressed as percentage of cell survival vs. control cells,which have been cultured in the presence of the inhibitor vehicle (0.01 % (v/v) DMSO).

Table S1. IC_{50} of synthesized cumpounds on the BACE-1 activity.[a]

Inhibitor	IC_{50} (µM)	SD	p
Donepezil	0.143	0.025	< 0.0005
13a,b	2.241	0.420	< 0.05
14	1.553	0.022	< 0.05
15	0.608	0.019	< 0.05
16	0.669	0.100	< 0.005
17	0.697	0.248	< 0.05
18	1.335	0.091	< 0.05
19	0.845	0.019	< 0.005
20	0.333	0.104	< 0.0005
21	0.529	0.012	< 0.05
22	0.873	0.283	< 0.05
23	0.996	0.229	< 0.05
24	2.128	0.099	< 0.0005
25	204.18	16.294	< 0.0005
26	14.662	2.649	< 0.005

a Data were derived from semi-logarithmic plots of BACE-1 activity determined at three different inhibitor concentration**.**

[7] May, P. C. Dean, R. A.; Lowe, S. L.; Martenyi, F.; Sheehan, S. M.; Boggs, L. N.; Monk, S. A.; Mathes, B. M.; Mergott, D. J.; Watson, B. M.; Stout, S. L.; Timm, D. E.; Smith Labell, E.; Gonzales, C. R.; Nakano, M.; Jhee, S. S.; Yen, M.; Ereshefsky, L.; Lindstrom, T. D.; Calligaro, D. O.; Cocke, P. J.; Greg Hall, D.; Friedrich, S.; Citron, M.; Audia, J. E. Robust central reduction of amyloid-β in humans with an orally available, non-peptidic β-secretase inhibitor, *J Neurosci*. **2011**, *31*, 16507-16516.

[8] Stachel, S. J.; Coburn, C. A.; Steele, T. G.; Jones, K. G. Loutzenhiser, E. F.; Gregro, A. R.; Rajapakse, H. A.; Lai, M. T.; Crouthamel, M. C.; Xu, M.; Tugusheva, K.; Lineberger, J. E.; Pietrak, B. L.; Espeseth, A. S.; Shi, X. P.; Chen-Dodson, E.; Holloway, M. K.; Munshi, S.; Simon, A. J.; Kuo, L.; Vacca, J. P. Structure-based design of potent and selective cell-permeable inhibitors of human beta-secretase (BACE-1),*J Med Chem.* 47, 6447-6450(2004).

[9] Mossman, T.; Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Methods*. **1983**, *65*,55-63.

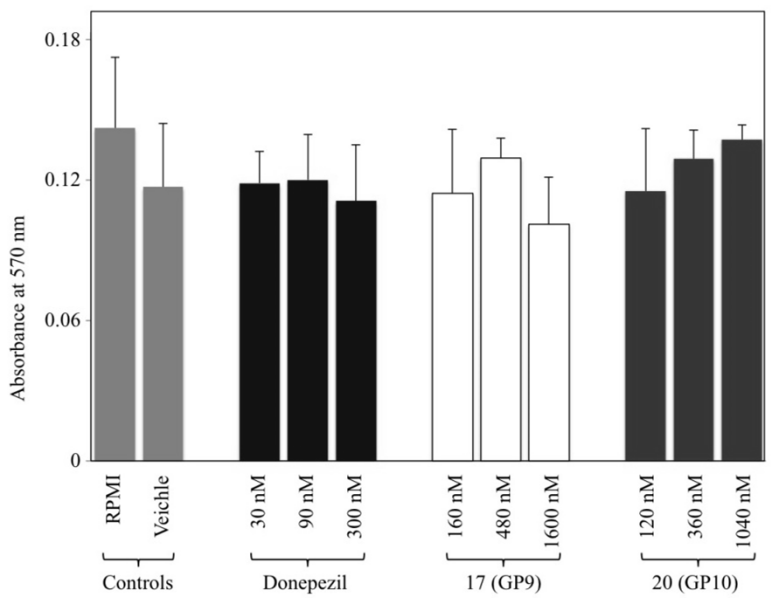


Figure S3. Effect of compounds 17 and 20 on cell viability.

The effect of tested compounds on SH-SY5Y cell viability was evaluated on 3 x 10^4 cells at the indicated final concentration, falling in the 3 – 30 times range of the correspondig IC_{50} exhibited towards hAChE activity. As controls, RPMI medium in the absence or in the presence of 0.1% DMSO, were used.

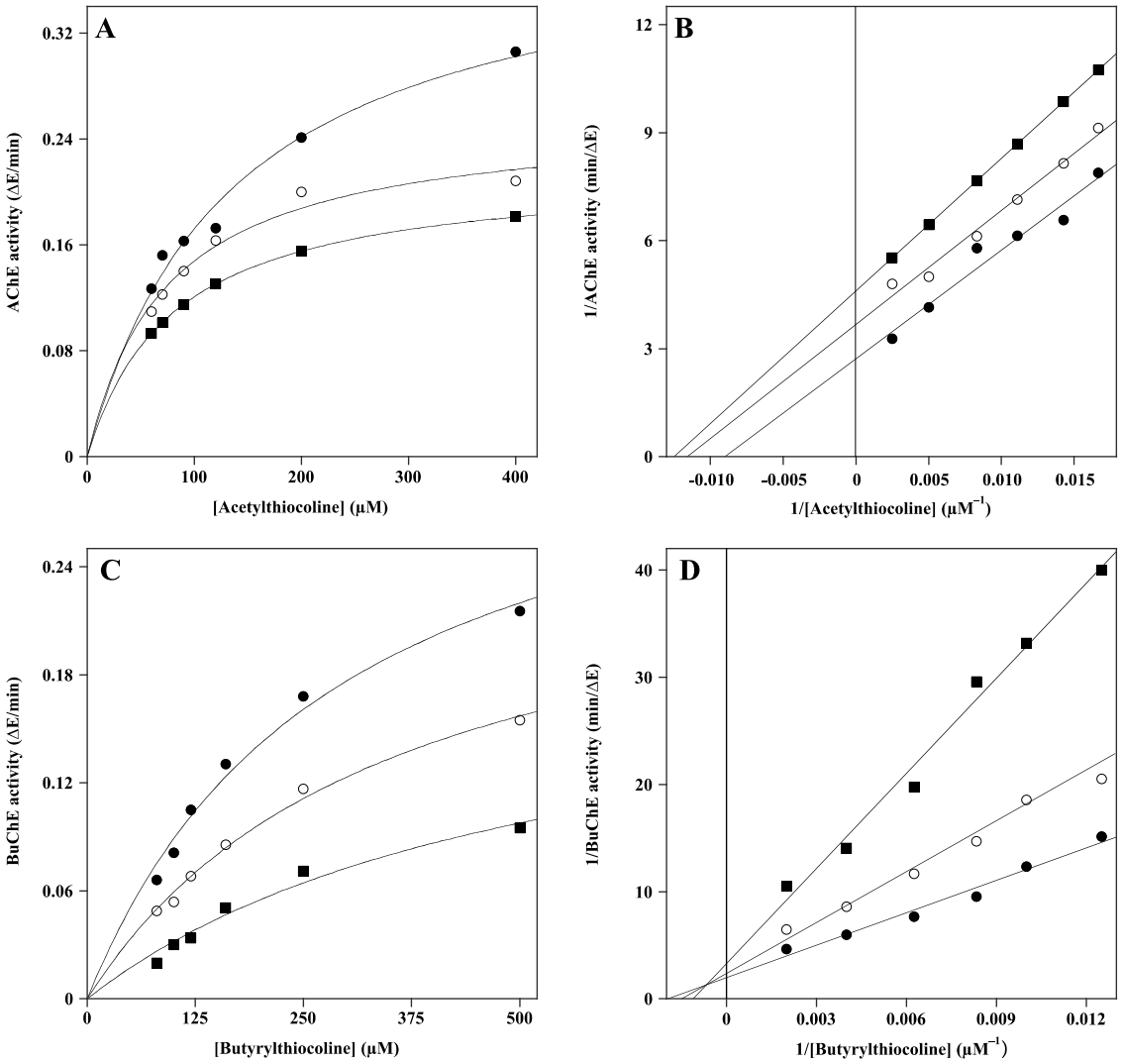


Figure S4. Determination of the inhibition parameters of a representative synthesized compound on AChE and BuChE.

The kinetic parameters Km and Vmax were derived by both interpolation on the Michaelis-Menten equation (Panels A and C) or by Lineweaver-Burk equation. The cholinesterase activity was determined as reported in the Experimental section at different concentration of the specific substrate in the absence (③) or in the presence of 15 (④) and 30 nM (⑤) or 1 (④) and 4 μM (⑤) compound **17** for AChE (Panel A and B) and BuChE (Panel C and D), respectively.

Characterization of compounds

(E)-2-((1-benzylpiperidin-4-yl)methylene)-6-hydroxy-5-methoxy-2,3-dihydro-1H-inden-1-one, (13a), (E)-2-((1-benzylpiperidin-4-yl)methylene)-5-hydroxy-6-methoxy-2,3-dihydro-1H-inden-1-one (13b) ***Isomeric mixture:*** Yellow oil, Yield 45%, R_f= (Chloroform-Methanol 9.5:0.5) 0.13; HRMS: $[M+H]^+$ m/z 364.1906 (theoretical $[M+H]^+$ m/z 364.1907); ^{1}H NMR δ (ppm) (300MHz, $CDCl_3$): 7.48-7.20 (m, 12H), 6.96 (s, 1H), 6.88 (s, 1H), 6.83 (s, 1H), 6.65 (d, *J*=9.5 Hz, 2H), 3.98 (s, 1H), 3.94 (s, 1H), 3.62-3.55 (m, 2H), 2.97 (m, 4H), 2.43-2.27 (m, 8H), 2.20-2.06 (m, 2H), 1.77-1.57 (m, 4H), 1.44-1.08 (m, 4H); ^{13}C NMR (300MHz, $CDCl_3$): 192.4, 152.7, 146.1, 145.1, 142.9, 139.3, 135.6, 129.3, 128.4, 128.1, 127.1, 110.7, 106.5, 63.1, 56.4, 52.5, 37.1, 29.2, 22.7.

(E)-2-((1-benzylpiperidin-4-yl)methylene)-6-hydroxy-2,3-dihydro-1H-inden-1-one (14): Yellow powder, Yield 53%, R_f = (Chloroform-Methanol 9.5:0.5) 0.22; HRMS: $[M+H]^+$ m/z 334.1807 (theoretical $[M+H]^+$ m/z 334.1802), ^{1}H NMR δ (ppm) (300 MHz, d_6-DMSO): 7.50-7.30 (m, 5H), 7.14-7.10 (m, 1H), 7.02 (s, 1H), 6.92-6.94 (m, 1H), 6.51 (d, *J*=9.8 Hz, 1H), 5.45 (s br, 1H), 3.85-3.75 (m, 2H), 3.62 (s, 2H), 3.52-2.98 (m, 4H),2.70-2.40 (m, 1H), 1.80-1.50 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): 192.4, 157.0, 156.9, 156.8, 144.2, 139.1, 137.1, 129.7, 128.5, 128.3, 127.4, 123.3, 108.1, 107.5, 51.7, 40.3, 38.7, 28.4.

(E)-2-((1-benzylpiperidin-4-yl)methylene)-7-hydroxy-2,3-dihydro-1H-inden-1-one (15): Brown oil, Yield 65%, R_f = (Chloroform-Methanol 9.5:0.5) 0.28; HRMS: $[M+H]^+$ m/z 334.1803 (theoretical $[M+H]^+$ m/z 334.1802),^{1}H NMR δ (ppm) (300MHz, $CDCl_3$): 8.02 (s br, 1H), 7.61-7.28 (m, 6H), 7.04-6.88 (m, 1H),6.79 (d, *J*= 8 Hz, 1H),6.71 (d, *J*=9.5 Hz, 1H), 3.82 (s, 2H), 3.64 (s, 2H), 3.46-3.28 (m, 1H), 3.20-3.10 (m, 2H), 3.0-2.80 (m, 2H), 2.55-2.37 (m, 2H), 2.01-1.80 (m, 2H); ^{13}C NMR (300MHz, d_6-DMSO): 179.0, 158.1, 148.9, 139.9, 137.8, 131.1, 130.3, 129.1, 128.8, 128.6, 116.9, 113.7, 113.6, 62.3, 52.1,36.2, 29.8, 29.6.

(E)-2-((1-benzylpiperidin-4-yl)methylene)-5-hydroxy-2,3-dihydro-1H-inden-1-one (16): Yellow powder, Yield 80%, R_f = (Chloroform-Methanol 9.5:0.5) 0.16; HRMS: $[M+H]^+$ m/z 334.1799 (theoretical $[M+H]^+$ m/z 334.1802); ^{1}H NMR δ (ppm) (300 MHz, d_6-DMSO): 7.70-7.38 (m, 7H), 6.95-6.85 (m, 2H), 6.82 (d, *J*=8.3 Hz, 1H), 4.26 (s br, 1H), 3.66 (s, 2H), 3.51 (s, 2H), 3.40-2.52 (m, 5H), 2.10-1.20 (m, 4H); ^{13}C NMR (300 MHz, d_6-DMSO): 205.4, 163.9, 163.8, 156.4, 152.4, 131.3, 129.2, 128.6, 127.7, 125.0, 115. 8, 111.8, 59.0, 51.3, 39.0, 29.1, 28.2.

(E)-2-((1-benzylpiperidin-4-yl)methylene)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (**17**). White powder; Yield: 56%; R_f = (Dichloromethane-Methanol 9:1) 0.44; HRMS: $[M+H]^+$ m/z 378.2061 (theoretical $[M+H]^+$ m/z 378.2064); ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.34-7.21 (m, 6H), 6.92-6.89 (s, 1H), 6.69-6.63 (d, 1H, J=9.8 Hz), 3.97 (s, 3H), 3.93 (s, 3H), 3.61-3.57 (d, 2H, J=1.1 Hz), 3.54 (s, 2H), 2.99-2.90 (m, 2H), 2.40-2.25 (m, 1H), 2.13-2.02 (m, 2H), 1.80-1.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 192.5, 155.3, 149.6, 144.4, 139.6, 135.7, 129.3, 131.8, 129.2, 128.2, 127.0, 107.2, 105.1, 63.3, 56.2, 56.1, 52.9, 37.1, 31.0, 29.5.

(E)-2-((1-benzylpiperidin-4-yl)methylene)-6-methoxy-2,3-dihydro-1H-inden-1-one (**18**). Yellow powder; Yield: 62%; R_f = (Chloroform-Methanol 9:1) 0.83; HRMS: $[M+H]^+$ m/z 348.1958

(theoretical $[M+H]^+$ m/z 348.1958); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39-7.15 (m, 8H), 6.77-6.70 (d, 1H, J=9.8 Hz), 3.85 (s, 3H), 3.63-3.58 (d, 2H, J=1.1 Hz), 3.53 (s, 2H), 2.99-2.87 (m, 2H), 2.43-2.27 (m, 1H), 2.13-2.00 (m, 2H), 1.83-1.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 300MHz): δ 193.5, 159.5, 142.1, 141.4, 140.0, 138.3, 135.9, 129.1, 128.1, 126.9, 123.8, 105.8, 63.4, 55.6, 53.0, 37.3, 30.1, 29.0.

(E)-2-((1-benzylpiperidin-4-yl)methylene)-7-methoxy-2,3-dihydro-1H-inden-1-one (**19**). Yellow oil; Yield: 48%; R_f = (Chloroform-Methanol 9:1) 0.41; HRMS: $[M+H]^+$ m/z 348.1959 (theoretical $[M+H]^+$ m/z 348.1958); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57-7.46 (m, 1H), 7.38-7.22 (m, 5H), 7.02 (d, 1H, *J*=7.5 Hz), 6.81 (d, 1H, *J*= 8.2 Hz), 6.67 (d, 1H, *J*=9.5 Hz), 3.96 (s, 3H), 3.63 (s, 2H), 3.55 (s, 2H), 2.99-2.89 (m, 2H), 2.39-2.22 (m, 1H), 2.15-2.02 (m, 2H), 1.77-1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 300MHz): δ 191.9, 159.2, 152.1, 139.9, 136.5, 135.8, 129.8, 129.1, 129.0 128.7, 127.7, 118.3, 109.6, 63.4, 56.2, 53.0, 37.2, 31.0, 30.0.

(E)-2-((1-benzylpiperidin-4-yl)methylene)-5-methoxy-2,3-dihydro-1H-inden-1-one (**20**)**.** White powder; Yields: 63%; R_f = (Chloroform-Methanol 9:1)0.76; HRMS: $[M+H]^+$ m/z 348.1958 (theoretical $[M+H]^+$ m/z 348.1958); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.82-7.76 (d, 1H, J=9.2 Hz), 7.38-7.21 (m, 6H), 6.95-6.87 (m, 1H), 6.66 (d, 1H, J=9.6 Hz), 3.88 (s, 3H), 3.63 (s, 2H), 3.52 (s, 2H), 2.99-2.87 (m, 2H), 2.40-2.26 (m, 1H), 2.12-2.00 (m, 2H), 1.76-1.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 192.1, 165.1, 152.1, 140.0, 138.3, 135.5, 132.3, 129.1, 128.1, 126.9, 126.1, 115.1, 109.8, 63.4, 55.6, 53.0, 37.2, 31.2, 29.9.

(E)-6-((1-benzylpiperidin-4-yl)methylene)-6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-one (**21**) White powder; Yield: 64%; R_f = (Chloroform-Methanol 9:1) 0.6; HRMS: $[M+H]^+$ m/z 362.1752 (theoretical $[M+H]^+$ m/z 362.1751); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.19 (m, 6H), 6.85 (s, 1H), 6.64 (d, 1H, J= 9.6 Hz), 6.06 (s, 2H), 3.56 (s, 2H), 3.53(s, 2H), 3.00-2.87 (m, 2H), 2.36-2.23 (m, 1H), 2.14-1.97 (m, 2H), 1.76-1.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 191.5, 154.1, 148.6, 146.6, 139.9, 135.8, 129.2, 128.3, 127.1, 105.6, 103.4, 102.1, 63.6, 53.2, 37.4, 31.5, 30.0.

(E)-5-methoxy-2-((1-(3-methoxybenzyl)piperidin-4-yl)methylene)-2,3-dihydro-1H-inden-1-one (**22**). Orange powder; Yield: 40%; R_f = (Chloroform-Methanol 9:1) 0.62; HRMS: $[M+H]^+$ m/z 378.2061 (theoretical $[M+H]^+$ m/z 378.2064); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80 (d, 1H, J=9.2 Hz), 7.28- 7.20 (m, 1H), 6.96-6.88 (m, 4H), 6.84-6.77 (m, 1H), 6.67 (d, 1H, J=9.8 Hz),3.89 (s, 3H), 3,82 (s, 3H), 3.63 (s, 2H), 3.52 (s, 2H), 2.99-2.88 (m, 2H), 2.42-2.26 (m, 1H), 2.14-2.00 (m, 2H), 1.77-1.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 192.6, 165.5, 160.0, 152.5, 140.4, 140.2, 135.9, 132.6, 129.5, 126.5, 121.8, 115.4, 115.0, 112.8, 110.2, 63.7, 56.0, 55.6, 53.4, 37.5, 31.5, 30.2.

(E)-6-methoxy-2-((1-(3-methoxybenzyl)piperidin-4-yl)methylene)-2,3-dihydro-1H-inden-1-one (**23**) Yellow oil; Yield: 40%; R_f = (Chloroform-Methanol 98:2) 0.44;HRMS: $[M+H]^+$ m/z 378.2061 (theoretical $[M+H]^+$ m/z 378.2064); ^{1}H NMR ($CDCl_3$, 300 MHz): δ7.47-6.77 (m, 7H), 6.74 (d, 1H, J=9.8 Hz), 3.85 (s, 3H), 3,82 (s, 3H), 3.61 (s, 2H), 3.52 (s, 2H), 3.00-2.90 (m, 2H), 2.48-1.54 (m, 7H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 192.8, 160.5, 140.8, 29.6, 129.5, 127.3, 124.0, 121.9, 115.3, 113.2, 106.9, 63.5, 61.1, 56.1, 49.1, 37.8, 31.8, 29.6.

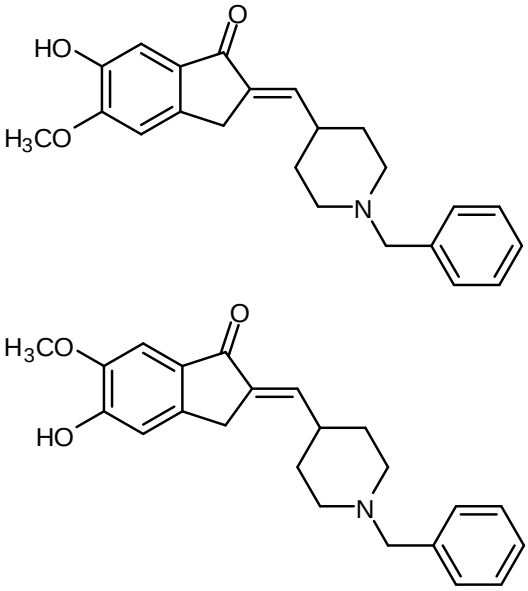
(E)-7-methoxy-2-((1-(3-methoxybenzyl)piperidin-4-yl)methylene)-2,3-dihydro-1H-inden-1-one (**24**) Yellow powder; Yield: 30%; R_f = (Chloroform-Methanol 98:2) 0.4; HRMS: $[M+H]^+$ m/z 378.2060 (theoretical $[M+H]^+$ m/z 378.2064); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51 (t, 1H, J=7.9 Hz), 7.28-7.25 (m, 1H), 7.04-6.99 (m 1H), 6.94-6.89 (m, 2H), 6.84-6.77 (m, 2H), 6.67 (dt, 1H, J=9.6 Hz, 2.0 Hz), 3.88 (s, 3H), 3,81 (s, 3H), 3.63 (s, 2H), 3.51 (s, 2H), 3.00-2.88 (m, 2H), 2.21-2.40 (m,1H), 2.18-2.00 (m, 2H), 1.78-1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 191.2, 161.4, 160.3, 147.2, 145.9, 140.9, 134.9, 130.9, 129.9, 116.2, 112.9, 112.0, 61.4, 56.3, 56.8, 52.0, 34.5, 29.9.

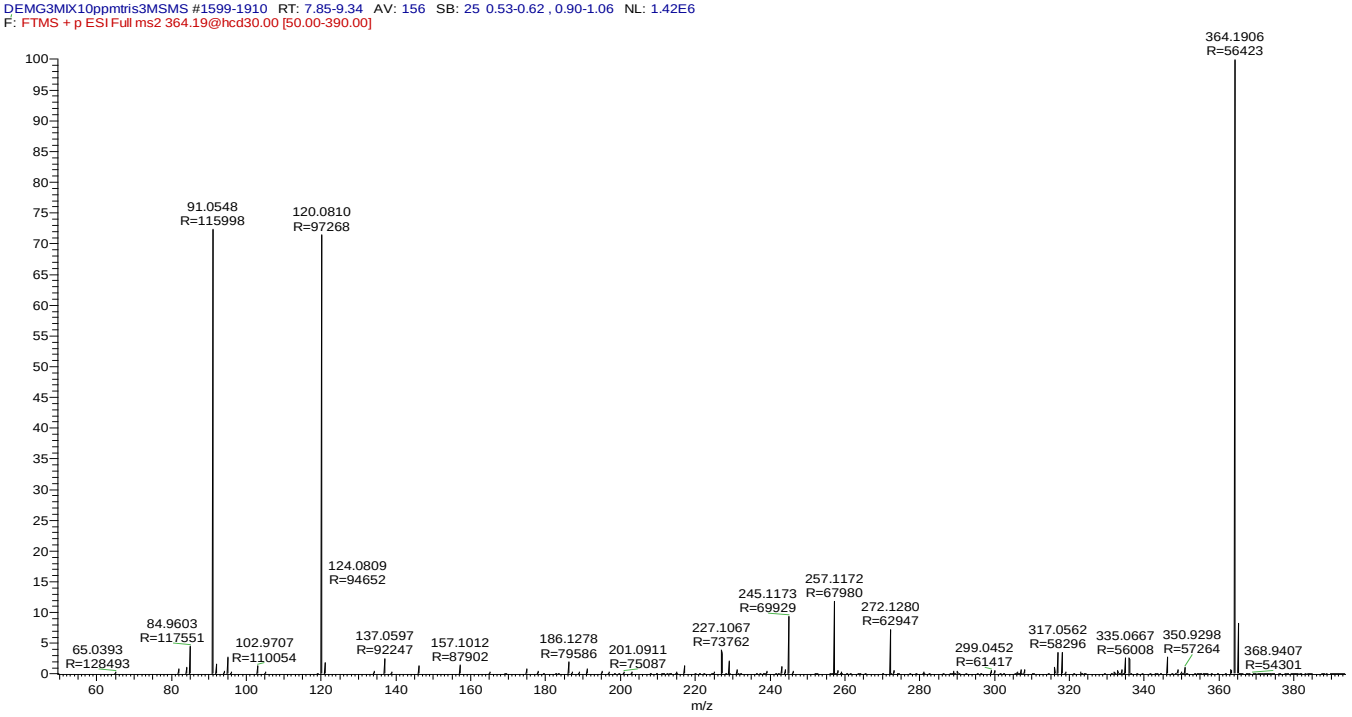
(E)-2-((1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-4-yl)methylene)-6-methoxy-2,3-dihydro-1H-inden-1-one (**25**) White powder; Yield: 30%; R_f = (Chloroform-Methanol 9:1) 0.5; HRMS: $[M+H]^+$ m/z 392.1855 (theoretical $[M+H]^+$ m/z 392.1856); ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.42-7.14 (m, 4H), 6.86 (s, 1H) 6.78-6.70 (m, 2H), 5.95 (s, 2H), 3.83 (s, 3H), 3.61 (s, 2H), 3.44 (s, 2H), 2.97-2.85 (m, 2H), 2.42-2.26 (m, 1H), 2.10-1.57 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 193.9, 159.7, 147.9, 146.8, 142.4, 141.6, 140.3, 136.2, 132.2, 127.2, 124.1, 122.5, 109.8, 108.1, 106.0, 101.1, 63.4, 55.9, 53.1, 37.5, 31.3, 29.3.

(E)-2-((1-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-4-yl)methylene)-7-methoxy-2,3-dihydro-1H-inden-1-one (**26**) Yellow Oil; Yield: 30%; R_f = (Chloroform-Methanol 9:1) 0.46; HRMS: $[M+H]^+$ m/z 392.1855 (theoretical $[M+H]^+$ m/z 378.1856); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55-7.46 (t, 1H, J=7.7 Hz), 7.05-6.98 (d, 1H, J=7.7 Hz), 6.89-6.71 (m, 4H), 6,70-6.62 (dt, 1H, J=9.6 Hz, 1.9 Hz), 5.94 (s, 2H), 3.96 (s, 3H), 3.62 (s, 2H), 3.43 (s, 2H), 2.97-2.85 (m, 2H), 2.39-2.22 (m, 1H), 2.10-1.97 (m, 2H), 1.75-1.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 191.9, 159.0, 152.0, 147.8, 146.8, 140.3, 136.3, 135.5, 132.3, 127.2, 122.4, 118.2, 110.4, 109.8, 109.4, 108.0, 101.1, 63.3, 56.0, 53.1, 37.4, 31.3, 29.9.

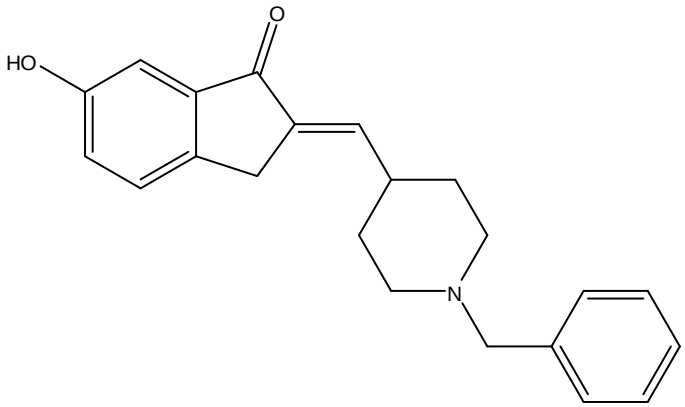
HRMS Spectra

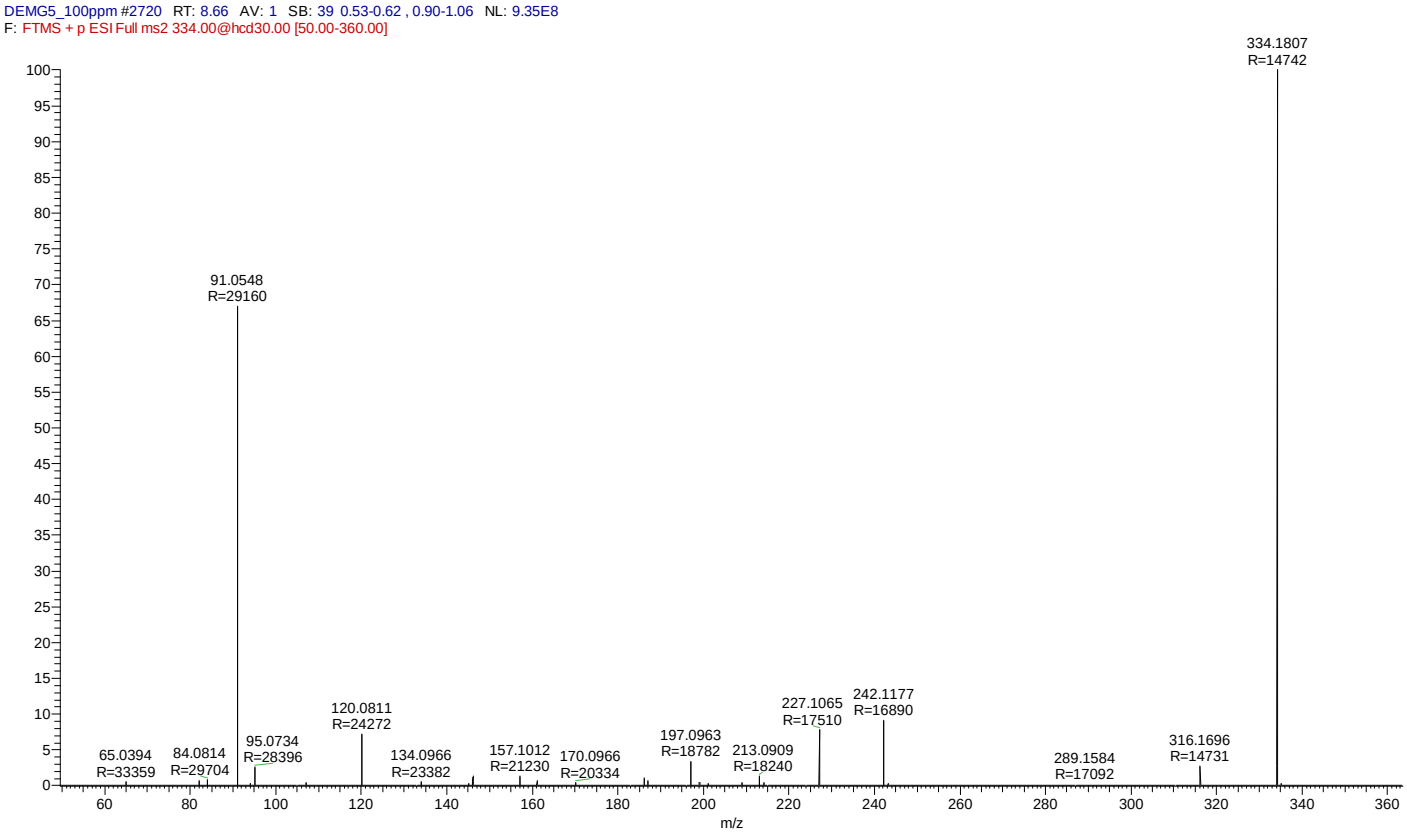
Sample **13a/13b**



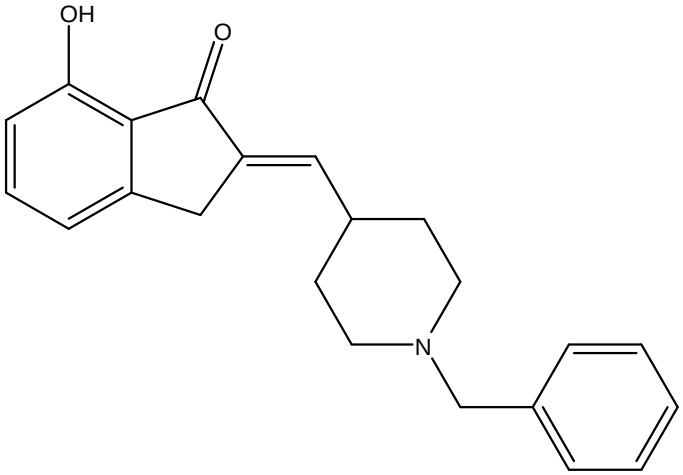


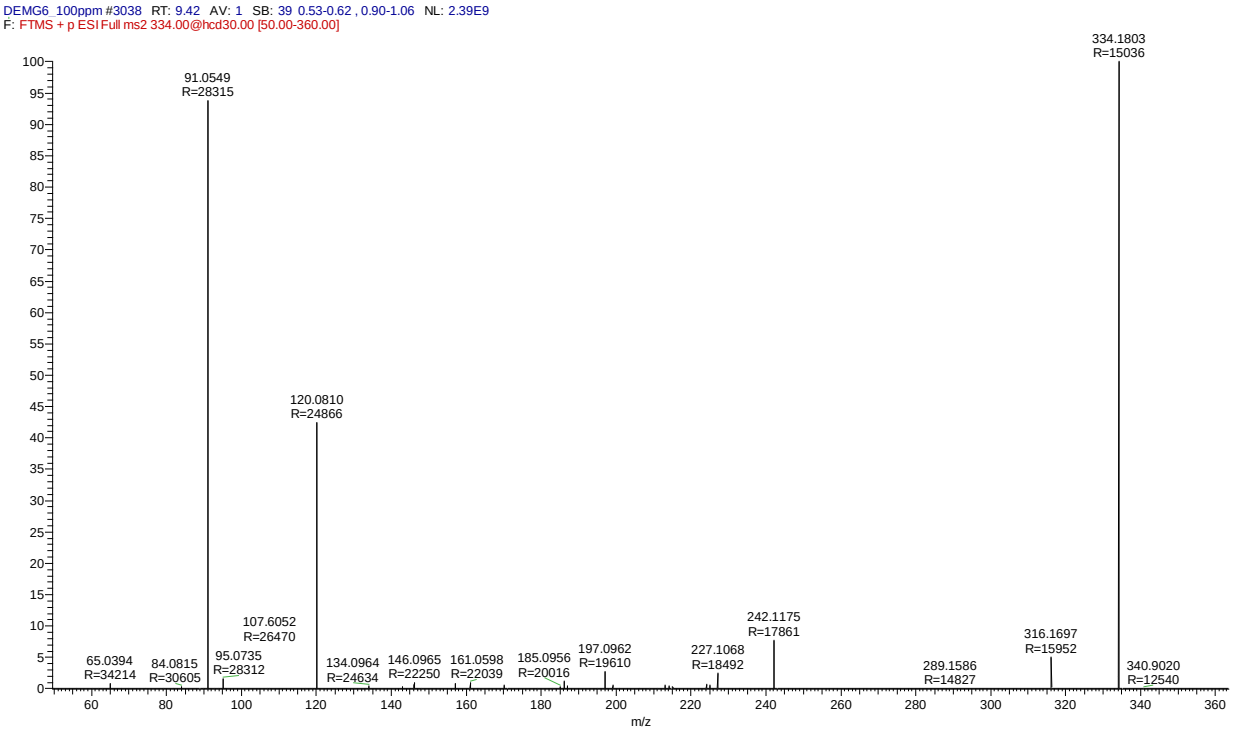
Sample **14**


HO
O
N

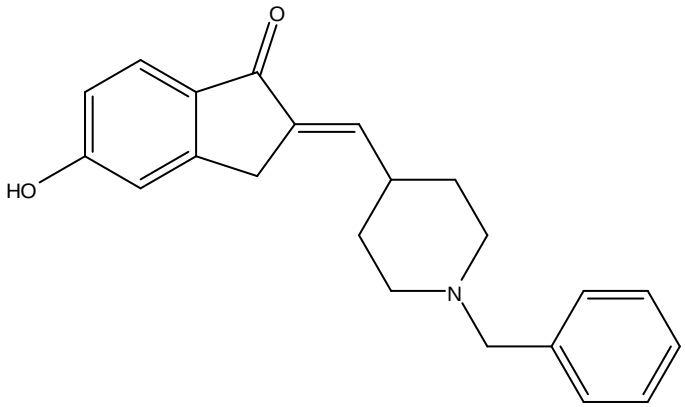

DEMG5_100ppm #2720 RT: 8.66 AV: 1 SB: 39 0.53-0.62 , 0.90-1.06 NL: 9.35E8
F: FTMS + p ESI Full ms2 334.00@hcd30.00 [50.00-360.00]
334.1807 R=14742
91.0548 R=29160
120.0811 R=24272
227.1065 R=17510
242.1177 R=16890
95.0734 R=28396
197.0963 R=18782
316.1696 R=14731
65.0394 R=33359
84.0814 R=29704
134.0966 R=23382
157.1012 R=21230
170.0966 R=20334
213.0909 R=18240
289.1584 R=17092
m/z

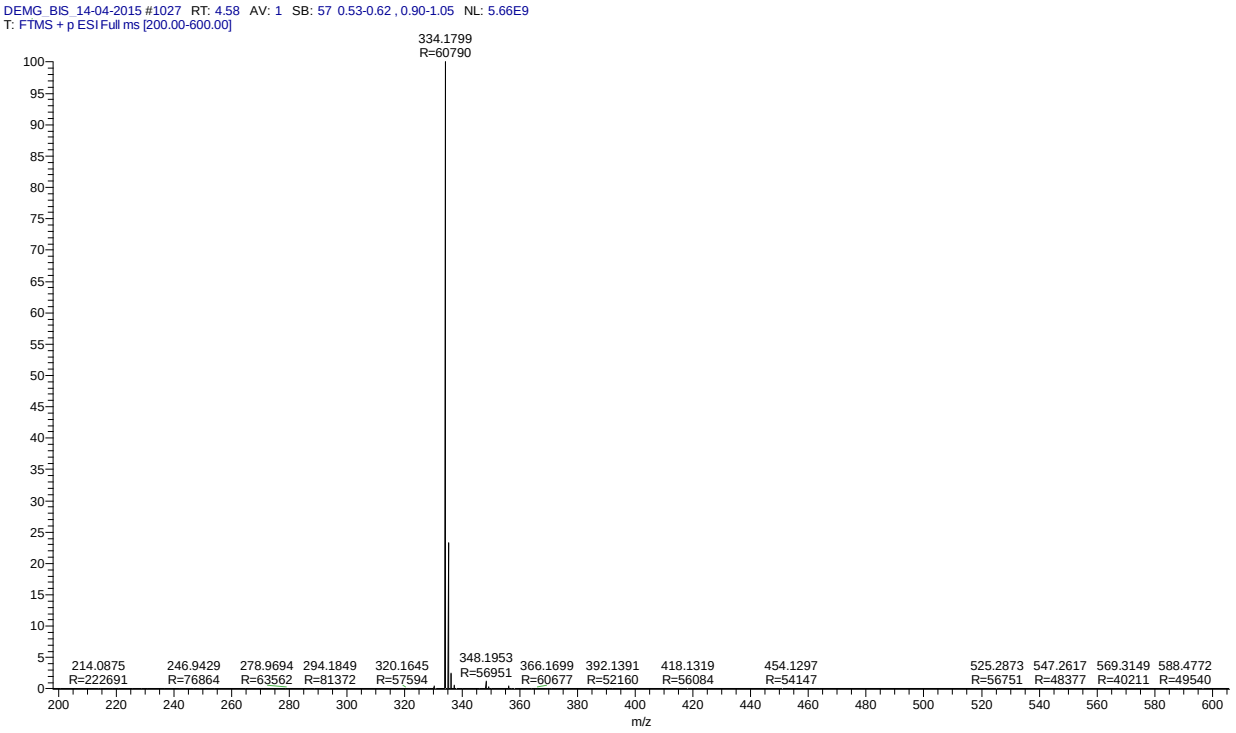
Sample **15**


OH
O
N

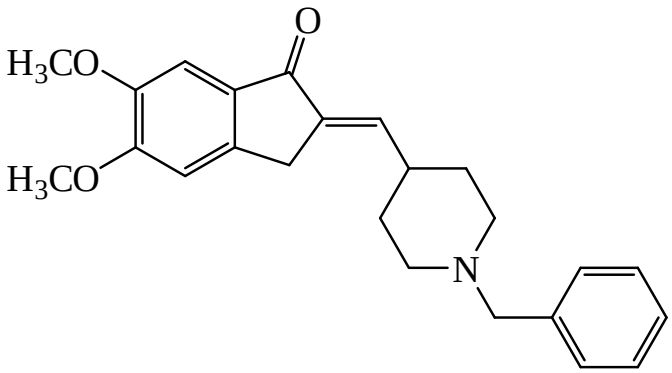

DEMG6_100ppm #3038 RT: 9.42 AV: 1 SB: 39 0.53-0.62 , 0.90-1.06 NL: 2.39E9
F: FTMS + p ESI Full ms2 334.00@hcd30.00 [50.00-360.00]
334.1803
R=15036
91.0549
R=28315
120.0810
R=24866
107.6052
R=26470
242.1175
R=17861
316.1697
R=15952
65.0394
R=34214
84.0815
R=30605
95.0735
R=28312
134.0964
R=24634
146.0965
R=22250
161.0598
R=22039
185.0956
R=20016
197.0962
R=19610
227.1068
R=18492
289.1586
R=14827
340.9020
R=12540
m/z

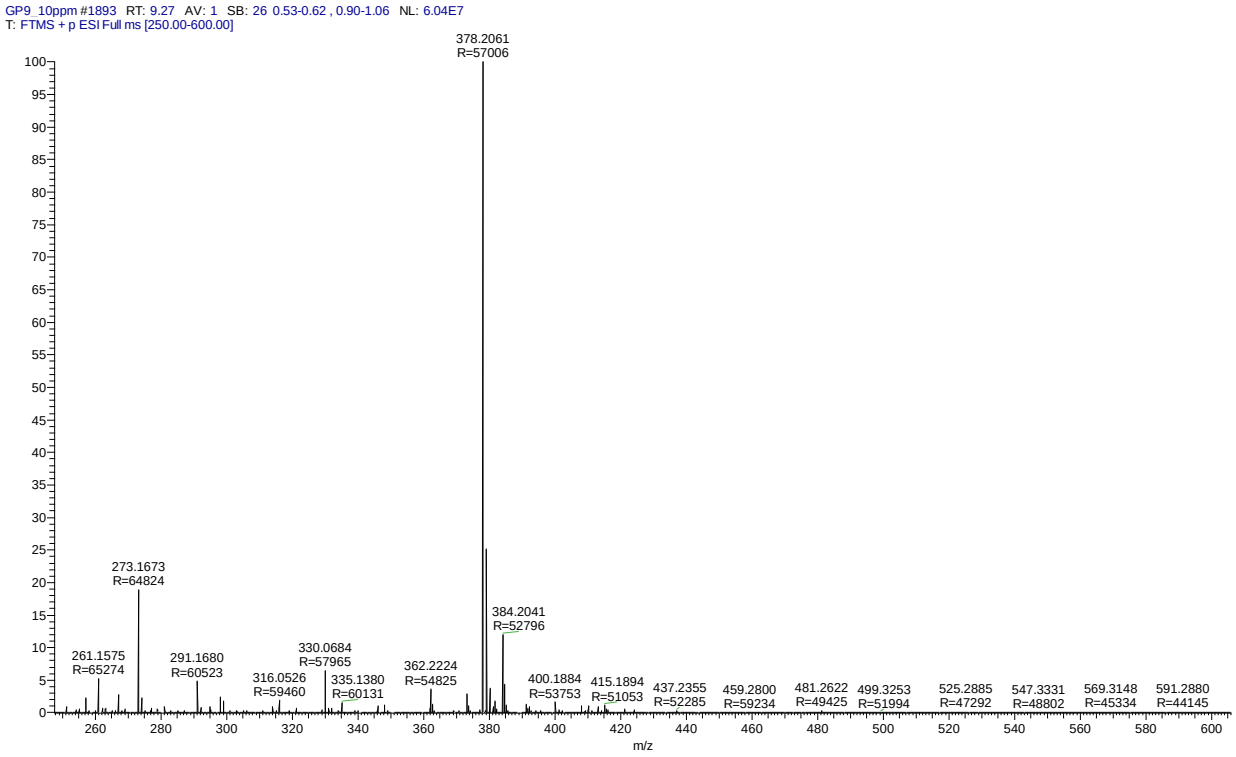
Sample 16


O
HO
N

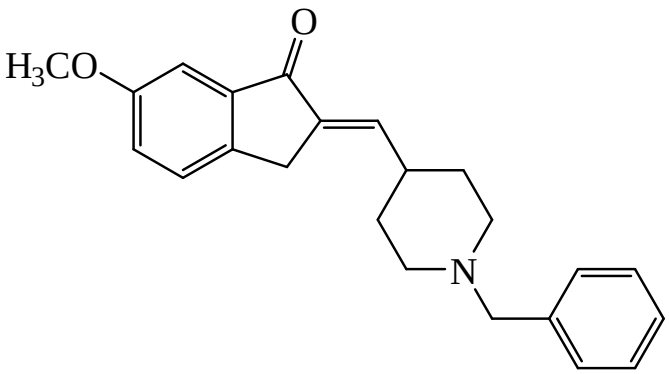

DEMG_BIS_14-04-2015 #1027 RT: 4.58 AV: 1 SB: 57 0.53-0.62 , 0.90-1.05 NL: 5.66E9
T: FTMS + p ESI Full ms [200.00-600.00]
334.1799
R=60790
214.0875
R=222691
246.9429
R=76864
278.9694
R=63562
294.1849
R=81372
320.1645
R=57594
348.1953
R=56951
366.1699
R=60677
392.1391
R=52160
418.1319
R=56084
454.1297
R=54147
525.2873
R=56751
547.2617
R=48377
569.3149
R=40211
588.4772
R=49540
m/z

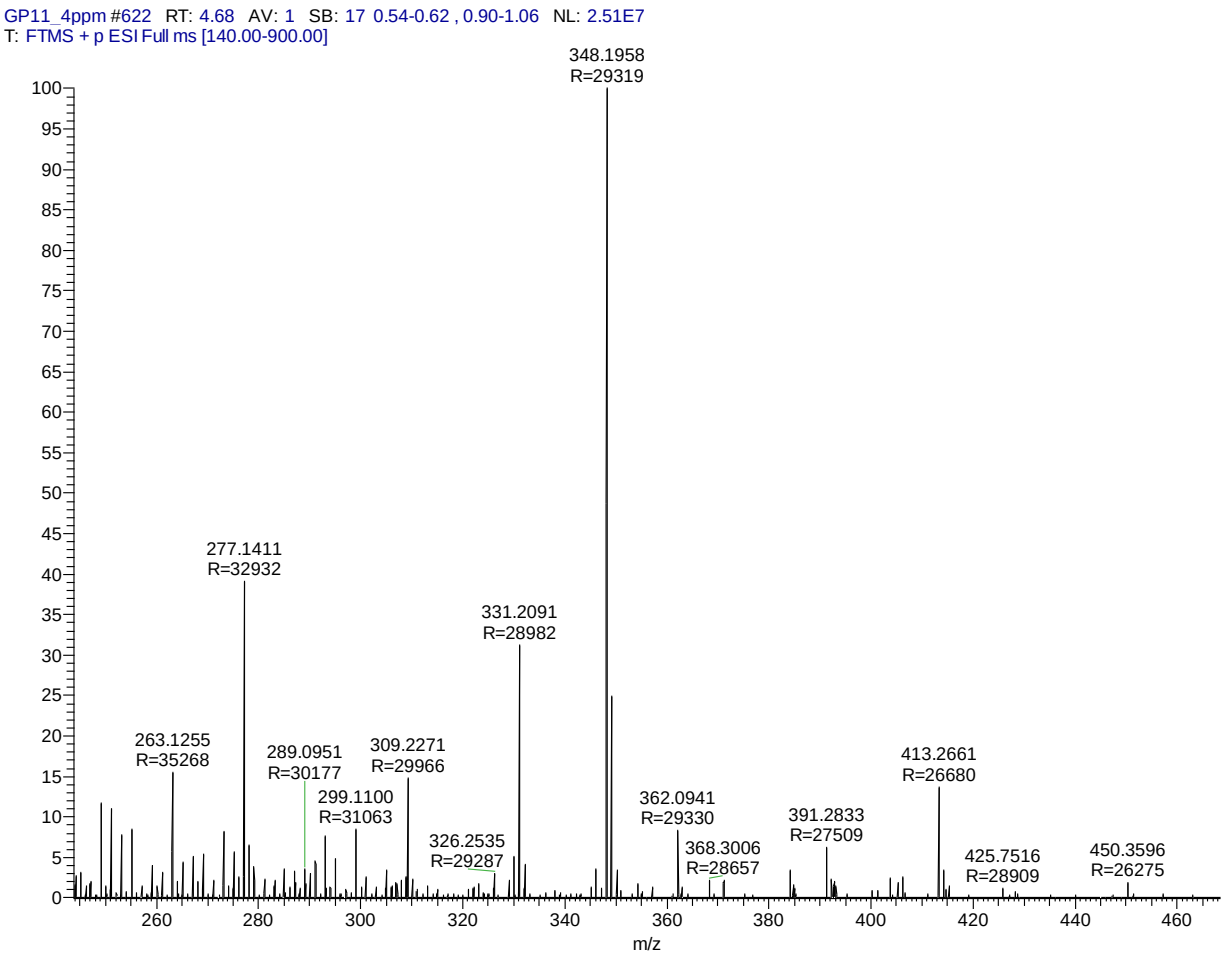
Sample **17**


O
H3CO
H3CO
N

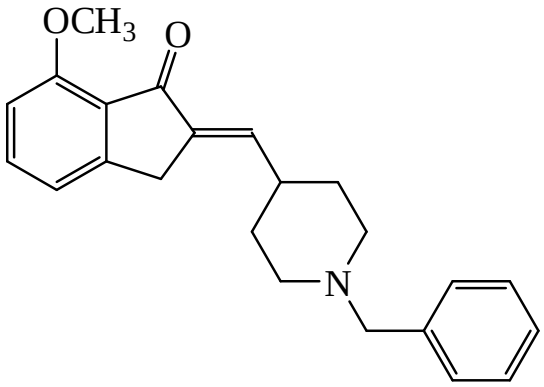

GP9_10ppm #1893 RT: 9.27 AV: 1 SB: 26 0.53-0.62 , 0.90-1.06 NL: 6.04E7
T: FTMS + p ESI Full ms [250.00-600.00]
378.2061
R=57006
273.1673
R=64824
384.2041
R=52796
261.1575
R=65274
291.1680
R=60523
330.0684
R=57965
316.0526
R=59460
335.1380
R=60131
362.2224
R=54825
400.1884
R=53753
415.1894
R=51053
437.2355
R=52285
459.2800
R=59234
481.2622
R=49425
499.3253
R=51994
525.2885
R=47292
547.3331
R=48802
569.3148
R=45334
591.2880
R=44145
m/z

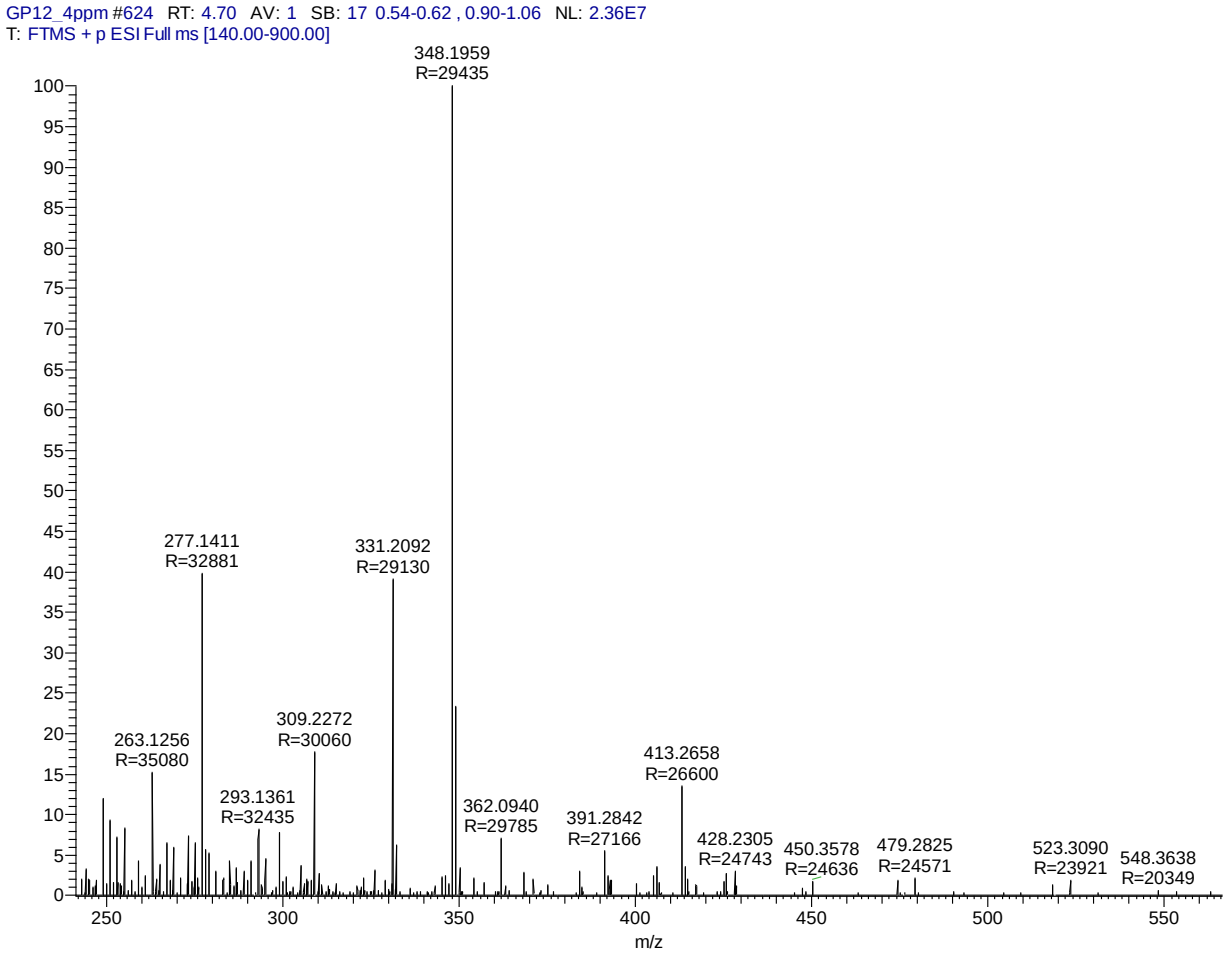
Sample **18**


O
H3CO
N

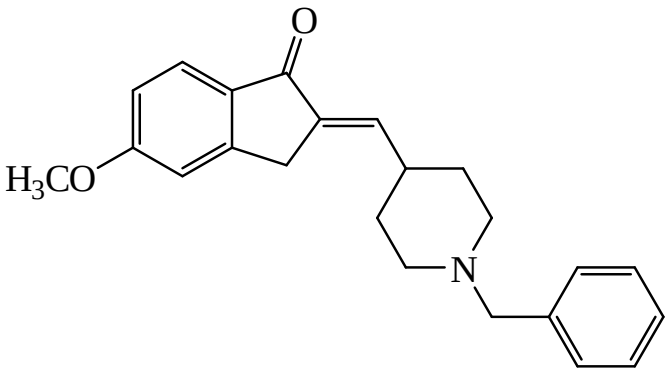

GP11_4ppm #622 RT: 4.68 AV: 1 SB: 17 0.54-0.62 , 0.90-1.06 NL: 2.51E7
T: FTMS + p ESI Full ms [140.00-900.00]
348.1958
R=29319
277.1411
R=32932
331.2091
R=28982
263.1255
R=35268
289.0951
R=30177
309.2271
R=29966
299.1100
R=31063
326.2535
R=29287
362.0941
R=29330
368.3006
R=28657
391.2833
R=27509
413.2661
R=26680
425.7516
R=28909
450.3596
R=26275
m/z

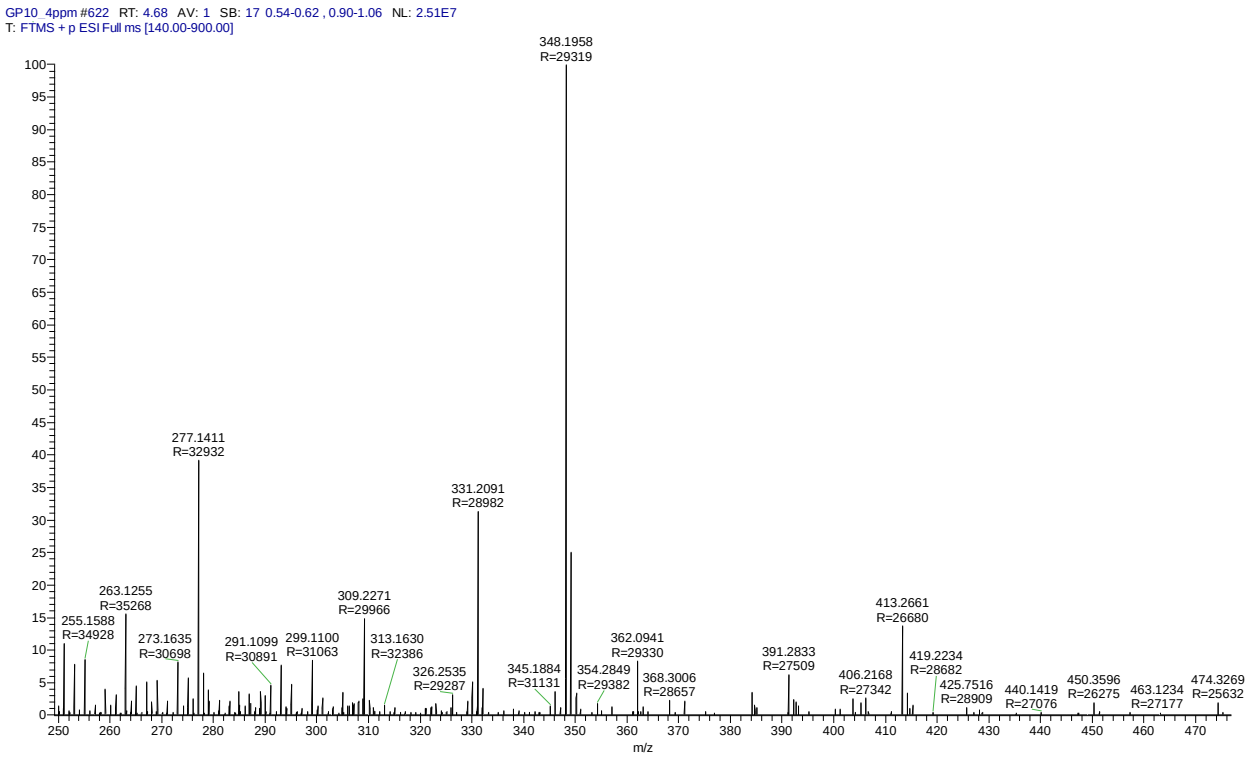
Sample **19**


OCH3
O
N

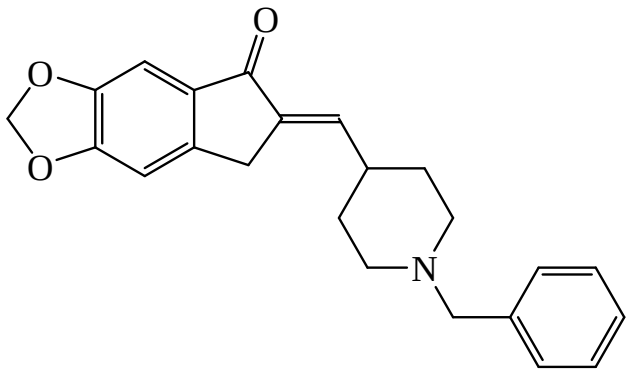

GP12_4ppm #624 RT: 4.70 AV: 1 SB: 17 0.54-0.62 , 0.90-1.06 NL: 2.36E7
T: FTMS + p ESI Full ms [140.00-900.00]
348.1959
R=29435
277.1411
R=32881
331.2092
R=29130
263.1256
R=35080
309.2272
R=30060
293.1361
R=32435
362.0940
R=29785
391.2842
R=27166
413.2658
R=26600
428.2305
R=24743
450.3578
R=24636
479.2825
R=24571
523.3090
R=23921
548.3638
R=20349
m/z

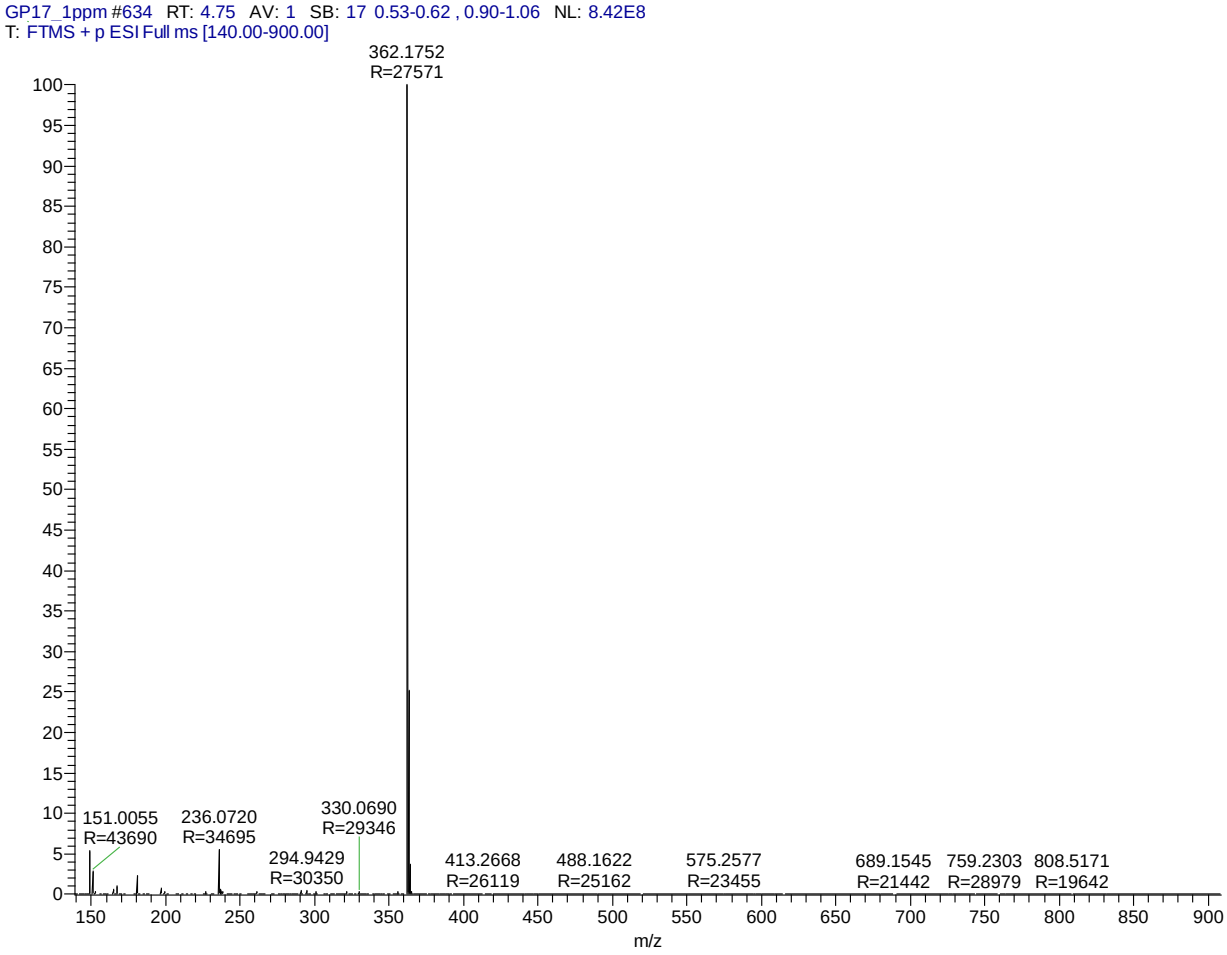
Sample **20**


O
H3CO
N

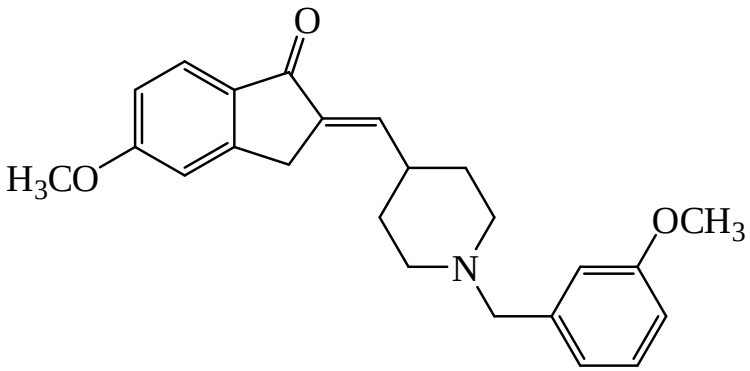

GP10_4ppm #622 RT: 4.68 AV: 1 SB: 17 0.54-0.62 , 0.90-1.06 NL: 2.51E7
T: FTMS + p ESI Full ms [140.00-900.00]
348.1958 R=29319
277.1411 R=32932
331.2091 R=28982
263.1255 R=35268
309.2271 R=29966
255.1588 R=34928
273.1635 R=30698
291.1099 R=30891
299.1100 R=31063
313.1630 R=32386
326.2535 R=29287
345.1884 R=31131
354.2849 R=29382
362.0941 R=29330
368.3006 R=28657
391.2833 R=27509
413.2661 R=26680
406.2168 R=27342
419.2234 R=28682
425.7516 R=28909
440.1419 R=27076
450.3596 R=26275
463.1234 R=27177
474.3269 R=25632
m/z

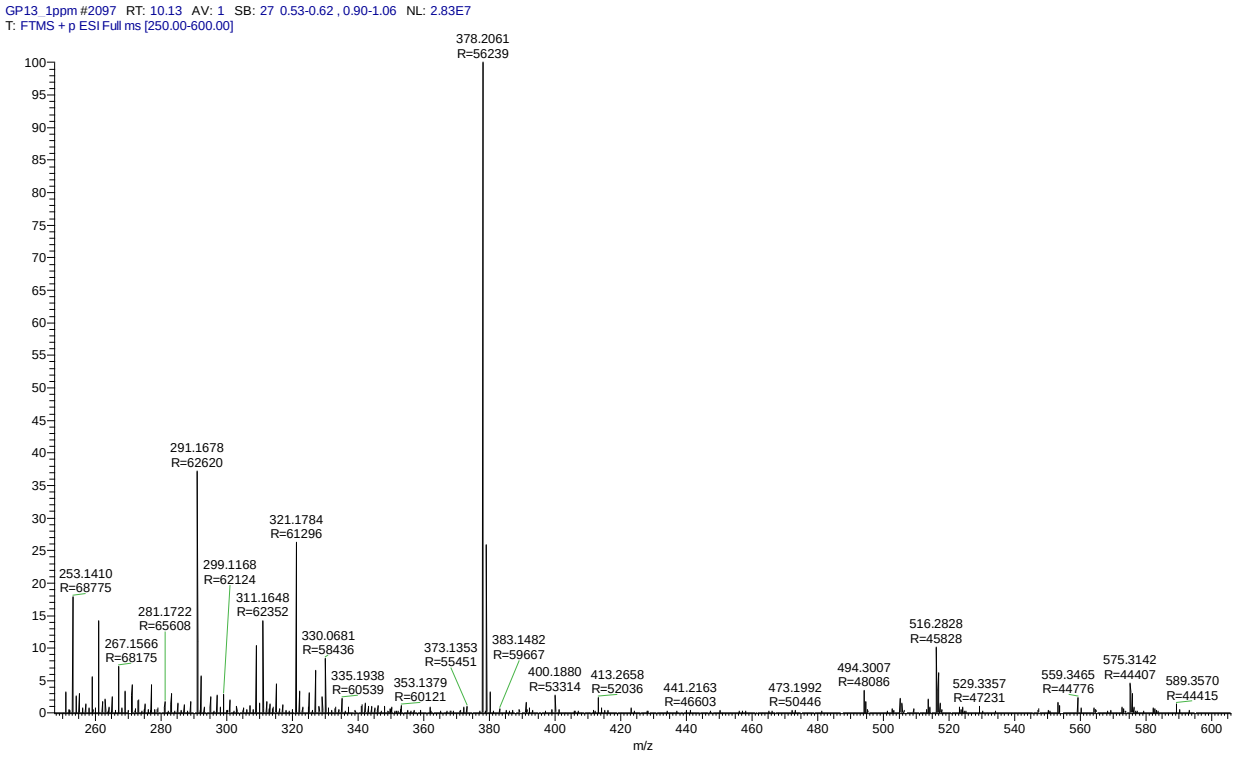
Sample **21**


O
O
O
N

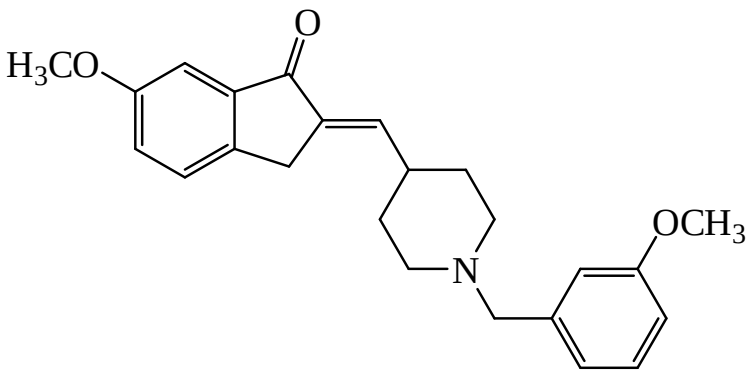

GP17_1ppm #634 RT: 4.75 AV: 1 SB: 17 0.53-0.62 , 0.90-1.06 NL: 8.42E8
T: FTMS + p ESI Full ms [140.00-900.00]
362.1752
R=27571
151.0055
R=43690
236.0720
R=34695
294.9429
R=30350
330.0690
R=29346
413.2668
R=26119
488.1622
R=25162
575.2577
R=23455
689.1545
R=21442
759.2303
R=28979
808.5171
R=19642
m/z

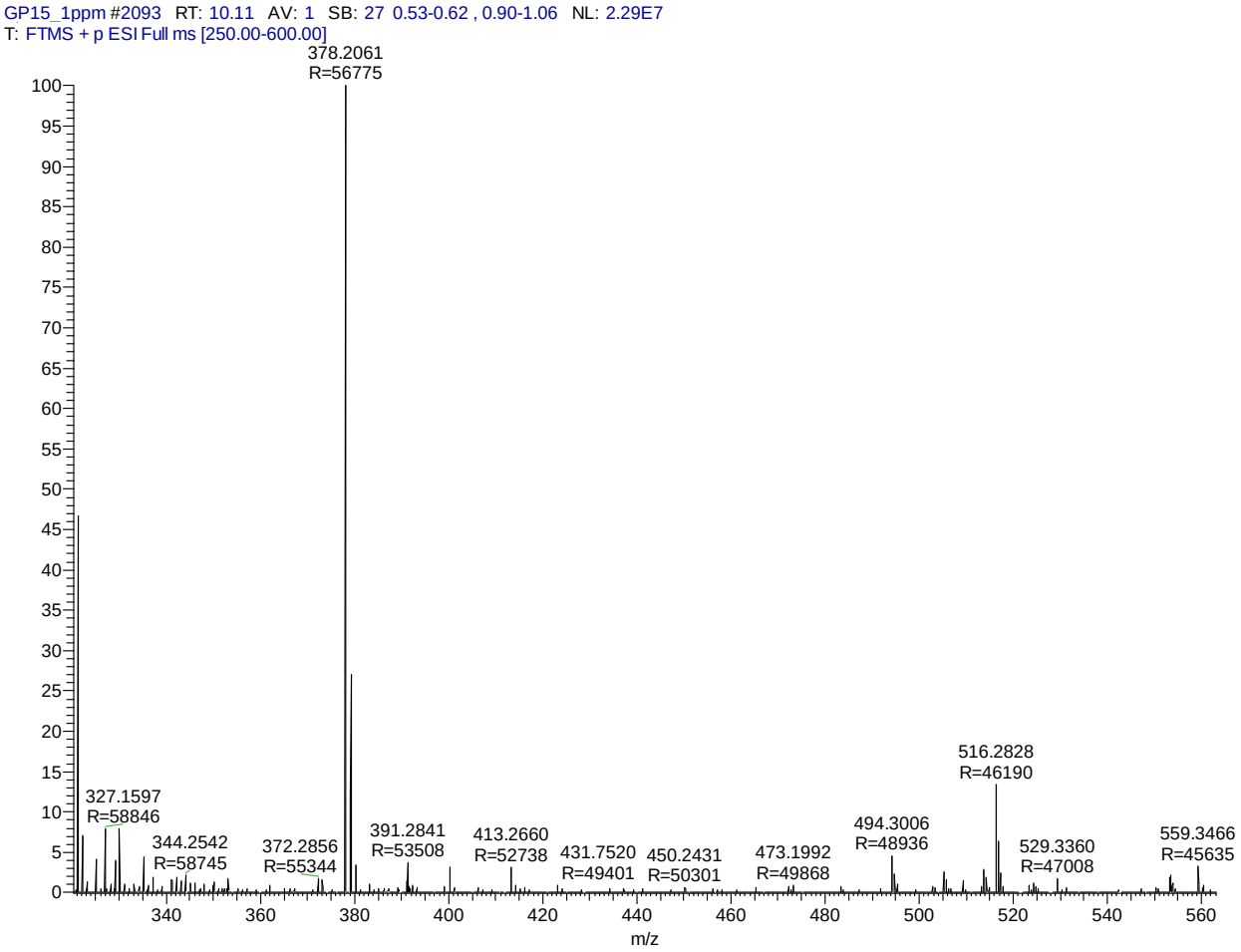
Sample **22**


O
H3CO
OCH3
N

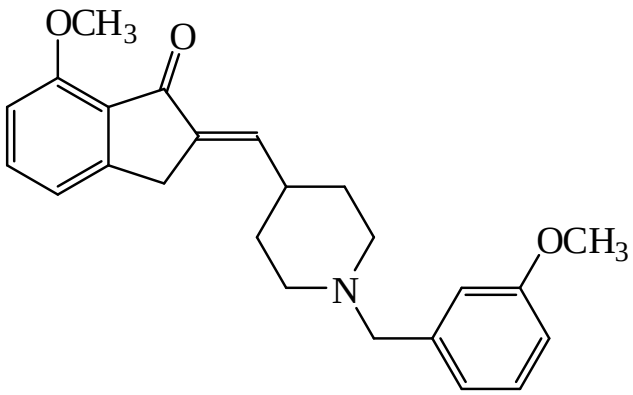

GP13 1ppm #2097 RT: 10.13 AV: 1 SB: 27 0.53-0.62 , 0.90-1.06 NL: 2.83E7
T: FTMS + p ESI Full ms [250.00-600.00]
378.2061 R=56239
291.1678 R=62620
321.1784 R=61296
299.1168 R=62124
253.1410 R=68775
311.1648 R=62352
281.1722 R=65608
330.0681 R=58436
267.1566 R=68175
335.1938 R=60539
373.1353 R=55451
353.1379 R=60121
383.1482 R=59667
400.1880 R=53314
413.2658 R=52036
441.2163 R=46603
473.1992 R=50446
494.3007 R=48086
516.2828 R=45828
529.3357 R=47231
559.3465 R=44776
575.3142 R=44407
589.3570 R=44415
m/z

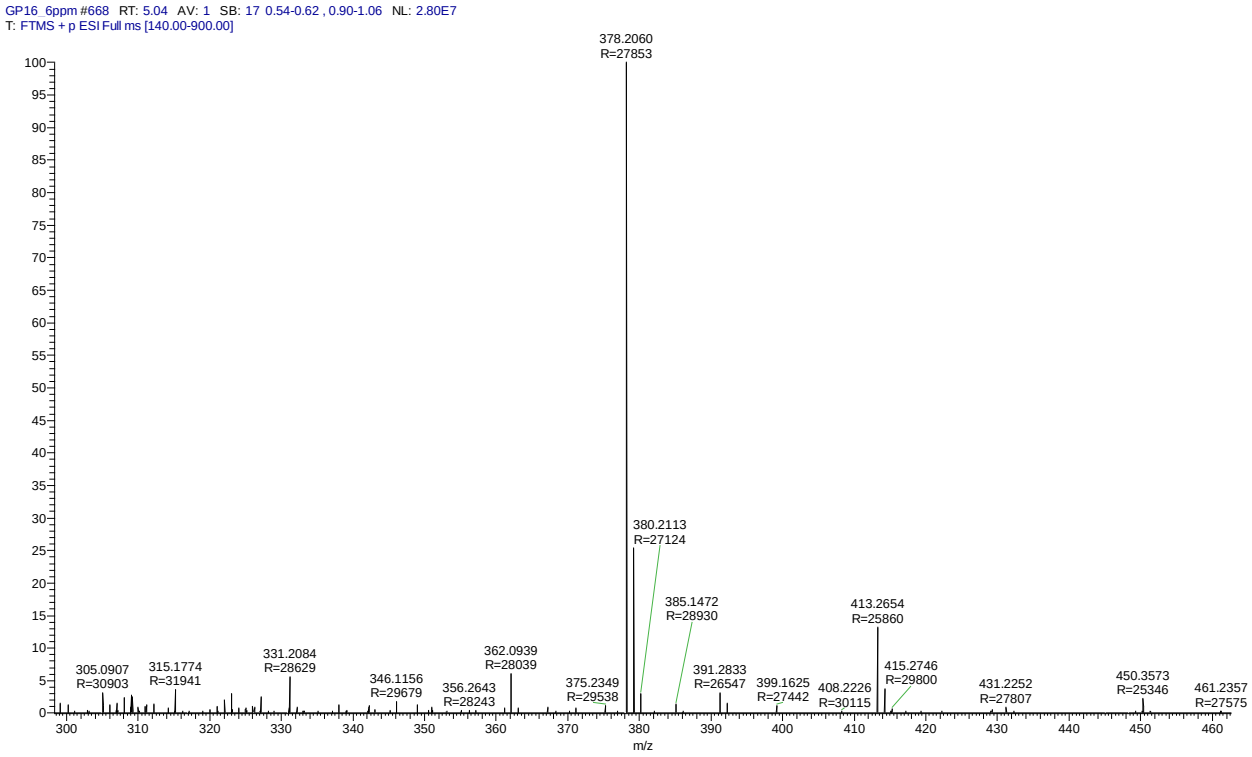
Sample **23**


O
H3CO
OCH3
N

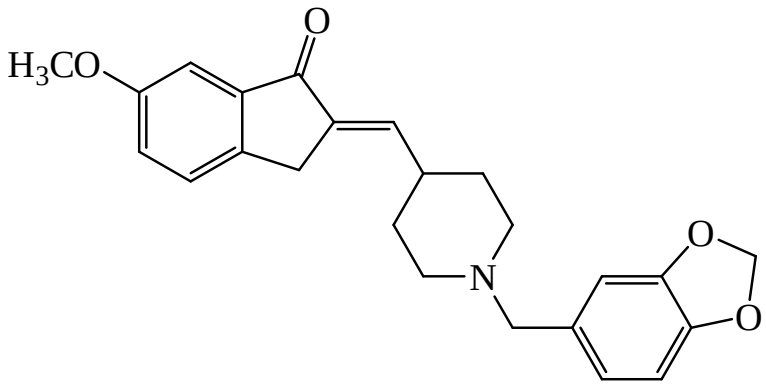

GP15_1ppm #2093 RT: 10.11 AV: 1 SB: 27 0.53-0.62 , 0.90-1.06 NL: 2.29E7
T: FTMS + p ESI Full ms [250.00-600.00]
378.2061
R=56775
327.1597
R=58846
344.2542
R=58745
372.2856
R=55344
391.2841
R=53508
413.2660
R=52738
431.7520
R=49401
450.2431
R=50301
473.1992
R=49868
494.3006
R=48936
516.2828
R=46190
529.3360
R=47008
559.3466
R=45635
m/z

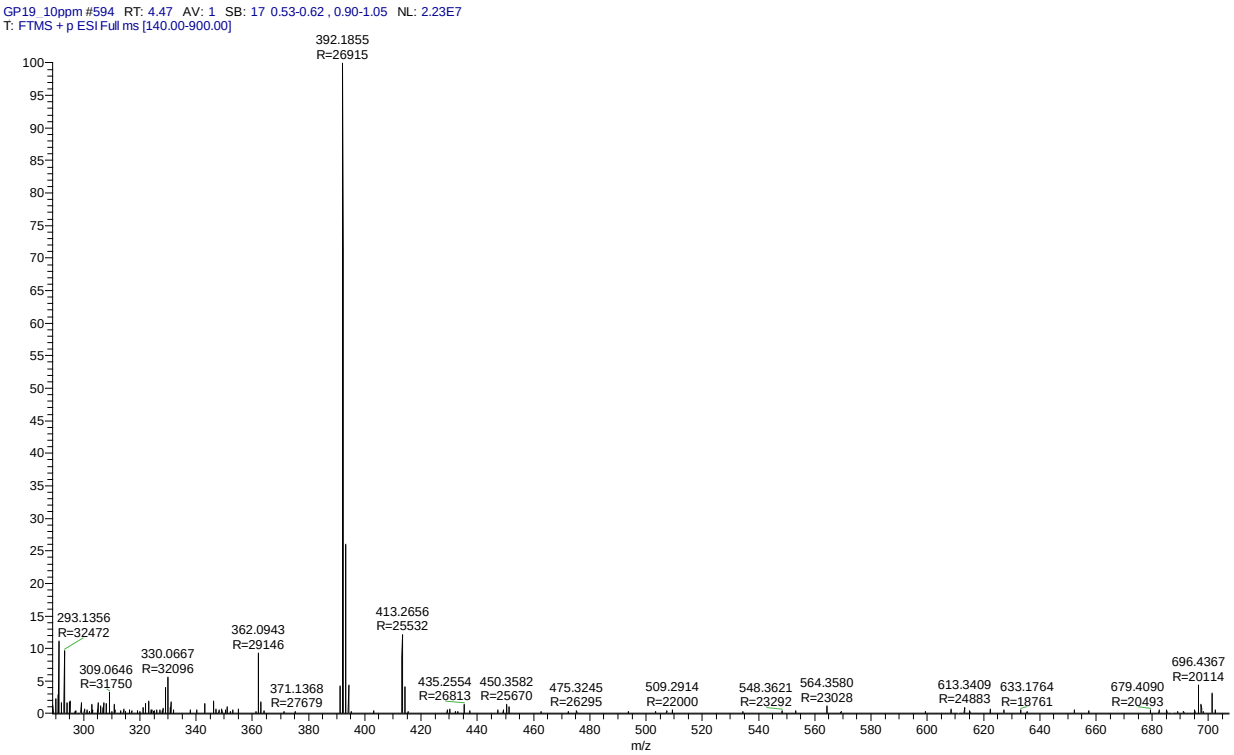
Sample **24**


OCH3
O
N
OCH3

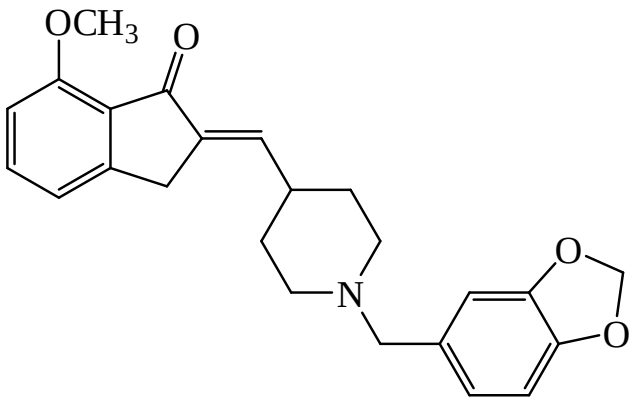

GP16_6ppm #668 RT: 5.04 AV: 1 SB: 17 0.54-0.62 , 0.90-1.06 NL: 2.80E7
T: FTMS + p ESI Full ms [140.00-900.00]
378.2060
R=27853
380.2113
R=27124
385.1472
R=28930
413.2654
R=25860
305.0907
R=30903
315.1774
R=31941
331.2084
R=28629
346.1156
R=29679
356.2643
R=28243
362.0939
R=28039
375.2349
R=29538
391.2833
R=26547
399.1625
R=27442
408.2226
R=30115
415.2746
R=29800
431.2252
R=27807
450.3573
R=25346
461.2357
R=27575
m/z

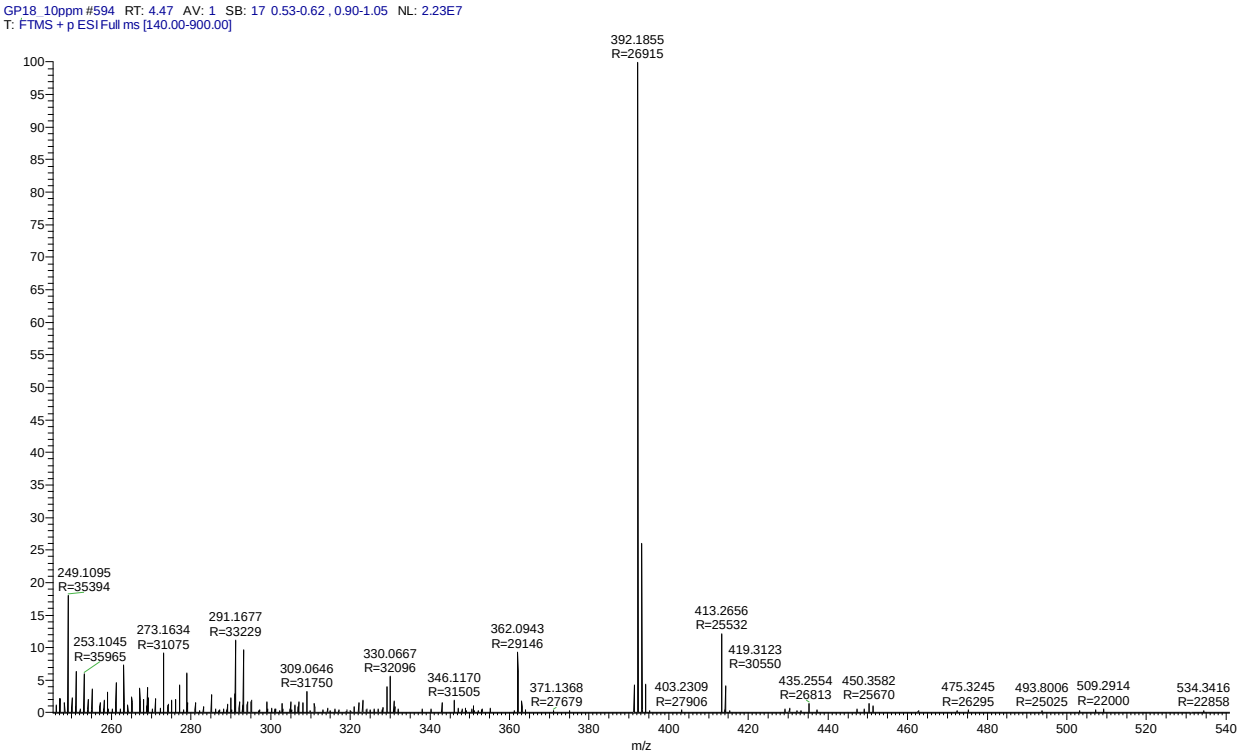
Sample **25**


O
H3CO
N
O
O


GP19_10ppm #594 RT: 4.47 AV: 1 SB: 17 0.53-0.62 , 0.90-1.05 NL: 2.23E7
T: FTMS + p ESI Full ms [140.00-900.00]
392.1855 R=26915
293.1356 R=32472
309.0646 R=31750
330.0667 R=32096
362.0943 R=29146
371.1368 R=27679
413.2656 R=25532
435.2554 R=26813
450.3582 R=25670
475.3245 R=26295
509.2914 R=22000
548.3621 R=23292
564.3580 R=23028
613.3409 R=24883
633.1764 R=18761
679.4090 R=20493
696.4367 R=20114
m/z

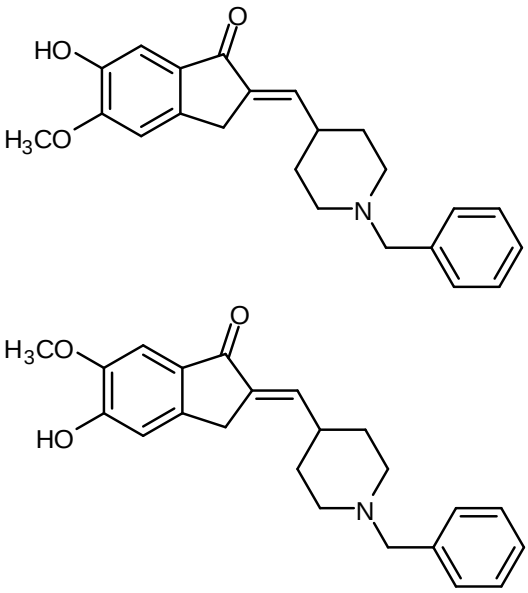
Sample **26**

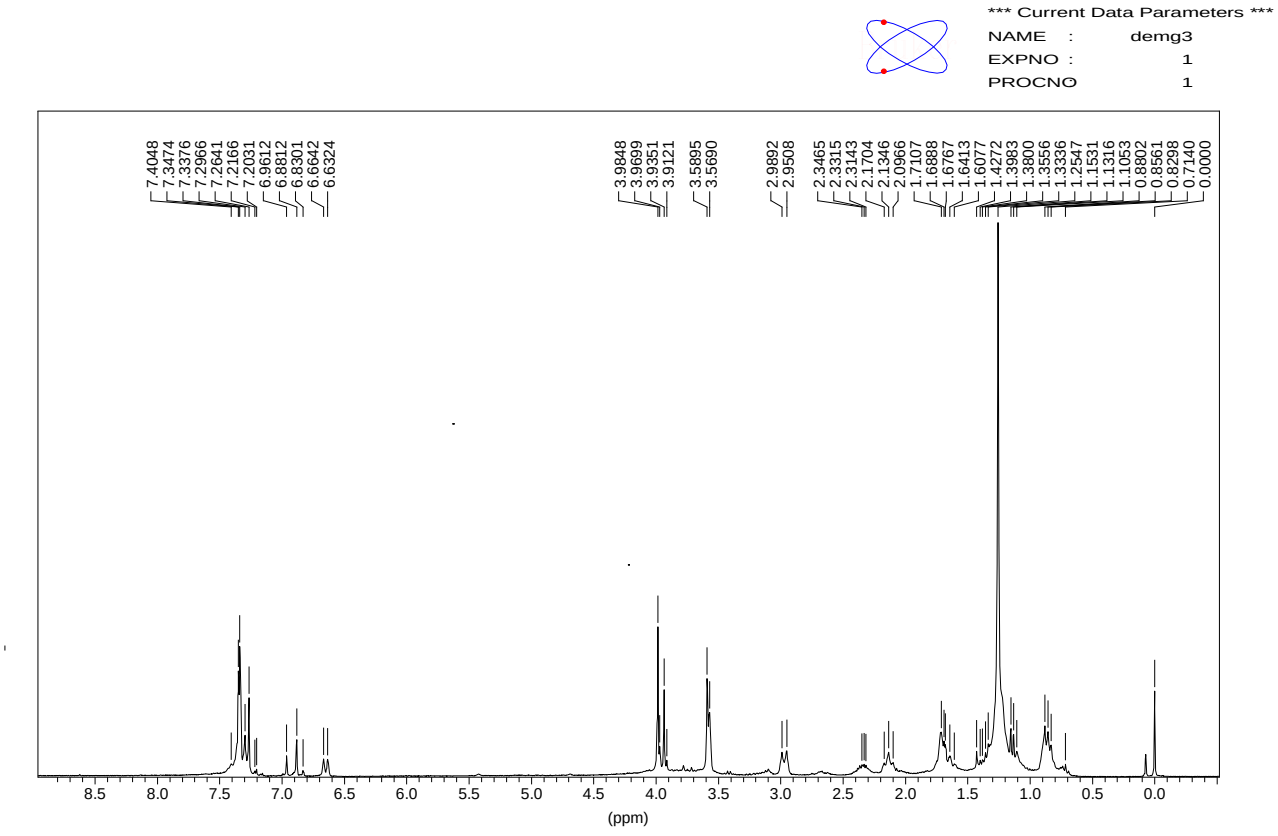

OCH3
O
N
O
O


GP18_10ppm #594 RT: 4.47 AV: 1 SB: 17 0.53-0.62 , 0.90-1.05 NL: 2.23E7
T: FTMS + p ESI Full ms [140.00-900.00]
392.1855 R=26915
249.1095 R=35394
253.1045 R=35965
273.1634 R=31075
291.1677 R=33229
309.0646 R=31750
330.0667 R=32096
346.1170 R=31505
362.0943 R=29146
371.1368 R=27679
403.2309 R=27906
413.2656 R=25532
419.3123 R=30550
435.2554 R=26813
450.3582 R=25670
475.3245 R=26295
493.8006 R=25025
509.2914 R=22000
534.3416 R=22858
m/z

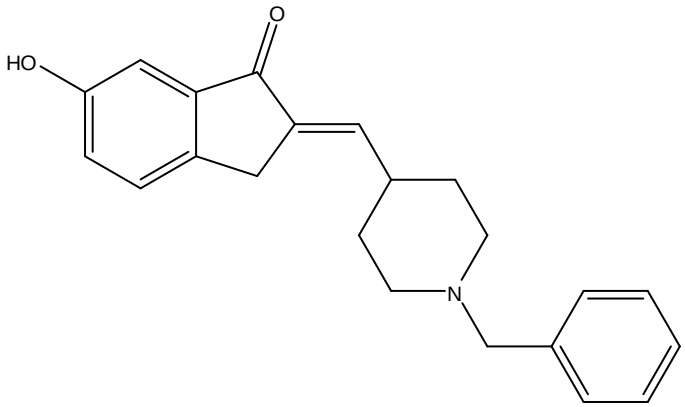
[1]H-NMR Spectra

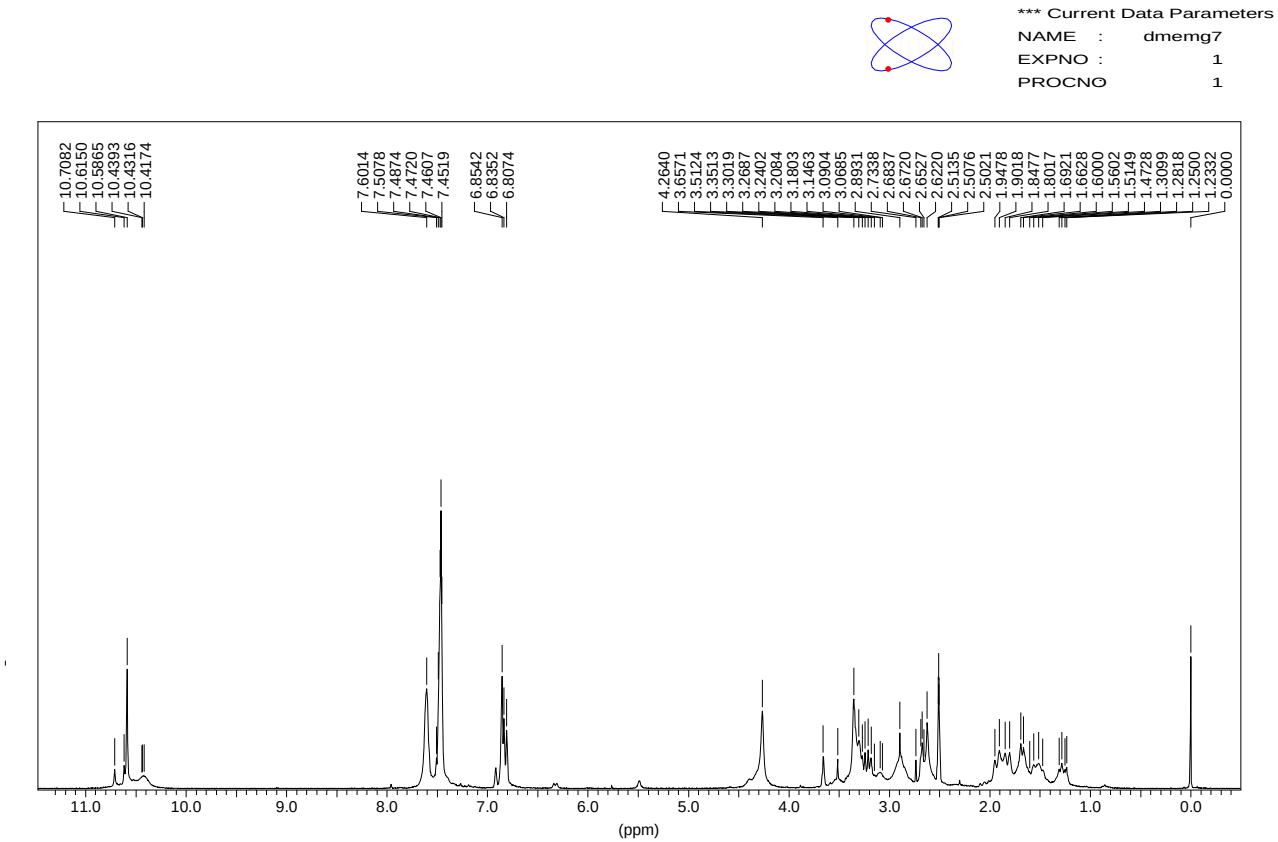
Sample **13a/13b**



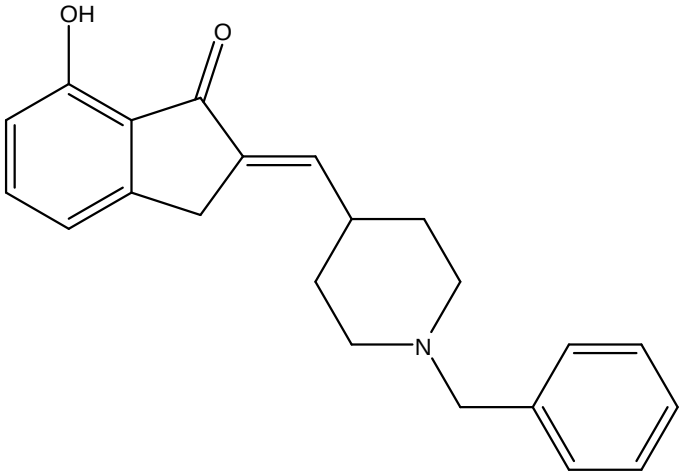


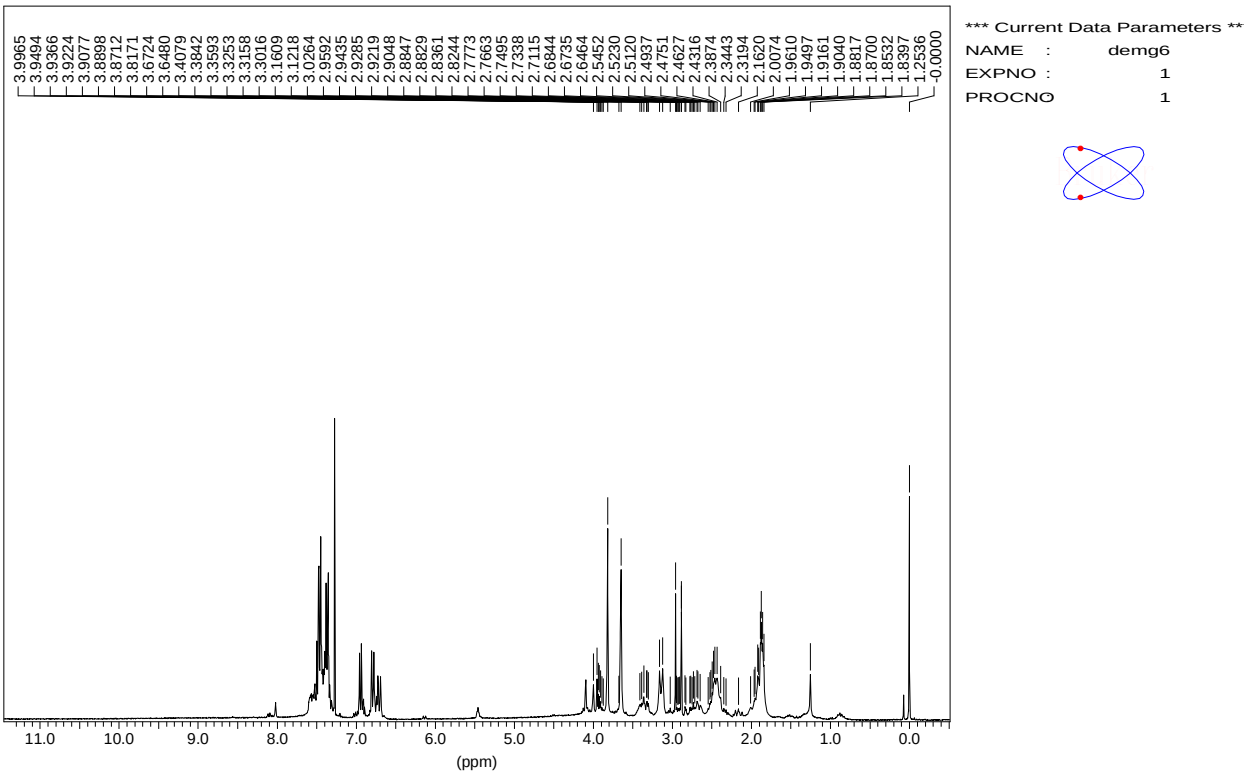
Sample **14**


HO
O
N

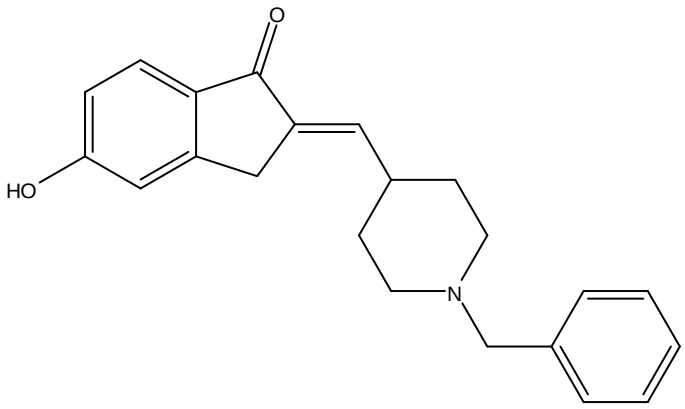

*** Current Data Parameters
NAME : dmemg7
EXPNO : 1
PROCNO 1
10.7082
10.6150
10.5865
10.4393
10.4316
10.4174
7.6014
7.5078
7.4874
7.4720
7.4607
7.4519
6.8542
6.8352
6.8074
4.2640
3.6571
3.5124
3.3513
3.3019
3.2687
3.2402
3.2084
3.1803
3.1463
3.0904
3.0685
2.8931
2.7338
2.6837
2.6720
2.6527
2.6220
2.5135
2.5076
2.5021
1.9478
1.9018
1.8477
1.8017
1.6921
1.6628
1.6000
1.5602
1.5149
1.4728
1.3099
1.2818
1.2500
1.2332
0.0000
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

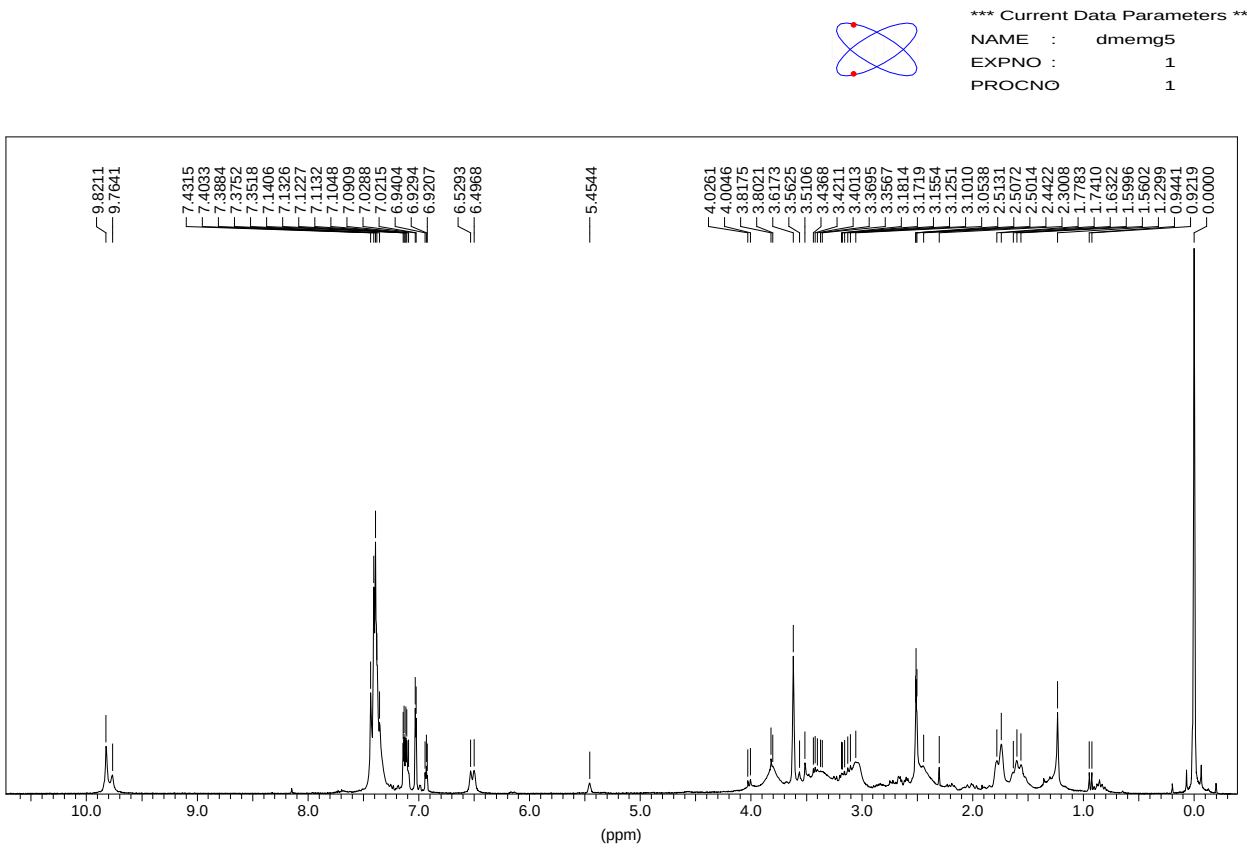
Sample **15**


OH
O
N

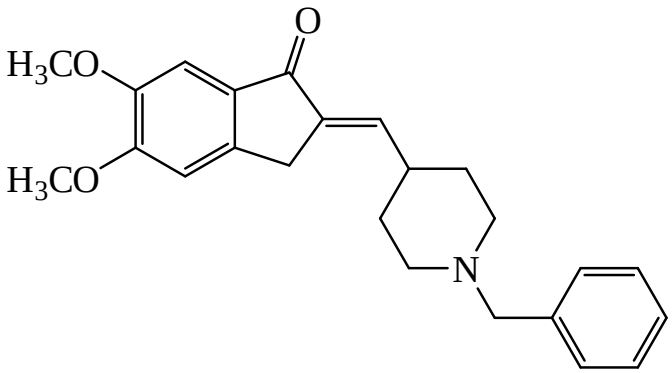

3.9965
3.9494
3.9366
3.9224
3.9077
3.8898
3.8712
3.8171
3.6724
3.6480
3.4079
3.3842
3.3593
3.3253
3.3158
3.3016
3.1609
3.1218
3.0264
2.9592
2.9435
2.9285
2.9219
2.9048
2.8847
2.8829
2.8361
2.8244
2.7773
2.7663
2.7495
2.7338
2.7115
2.6844
2.6735
2.6464
2.5452
2.5230
2.5120
2.4937
2.4751
2.4627
2.4316
2.3874
2.3443
2.3194
2.1620
2.0074
1.9610
1.9497
1.9161
1.9040
1.8817
1.8700
1.8532
1.8397
1.2536
-0.0000
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)
*** Current Data Parameters **
NAME : demg6
EXPNO : 1
PROCNO 1

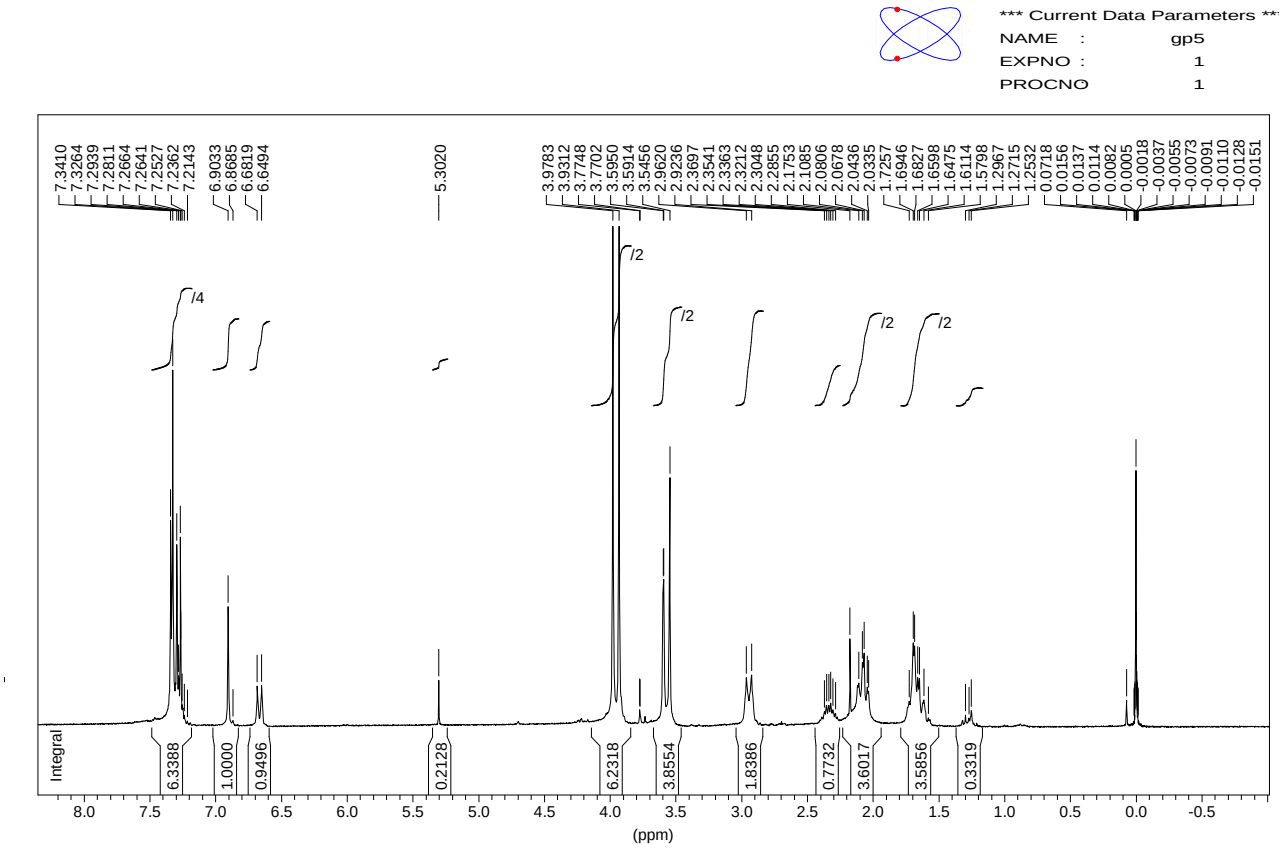
Sample **16**


O
HO
N

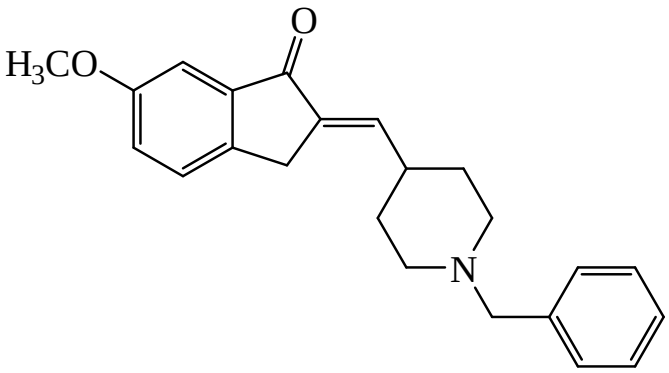

*** Current Data Parameters **
NAME : dmemg5
EXPNO : 1
PROCNO 1
9.8211
9.7641
7.4315
7.4033
7.3884
7.3752
7.3518
7.1406
7.1326
7.1227
7.1132
7.1048
7.0909
7.0288
7.0215
6.9404
6.9294
6.9207
6.5293
6.4968
5.4544
4.0261
4.0046
3.8175
3.8021
3.6173
3.5625
3.5106
3.4368
3.4211
3.4013
3.3695
3.3567
3.1814
3.1719
3.1554
3.1251
3.1010
3.0538
2.5131
2.5072
2.5014
2.4422
2.3008
1.7783
1.7410
1.6322
1.5996
1.5602
1.2299
0.9441
0.9219
0.0000
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

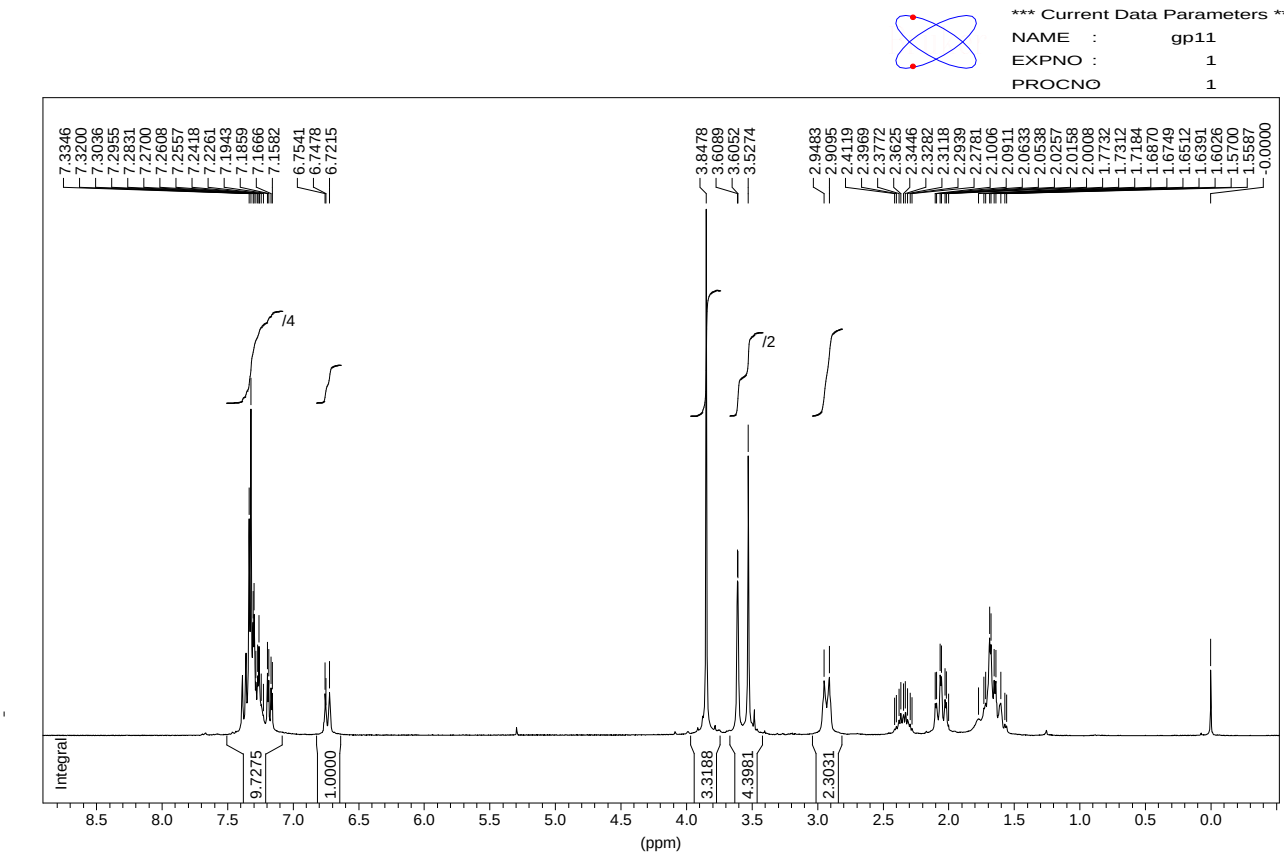
Sample **17**


O
H3CO
H3CO
N

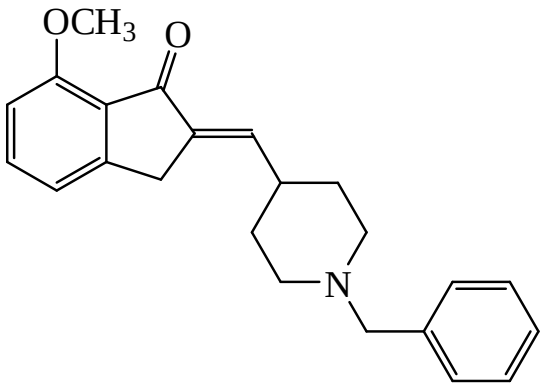

*** Current Data Parameters ***
NAME : gp5
EXPNO : 1
PROCNO 1
7.3410
7.3264
7.2939
7.2811
7.2664
7.2641
7.2527
7.2362
7.2143
6.9033
6.8685
6.6819
6.6494
5.3020
3.9783
3.9312
3.7748
3.7702
3.5950
3.5914
3.5456
2.9620
2.9236
2.3697
2.3541
2.3363
2.3212
2.3048
2.2855
2.1753
2.1085
2.0806
2.0678
2.0436
2.0335
1.7257
1.6946
1.6827
1.6598
1.6475
1.6114
1.5798
1.2967
1.2715
1.2532
0.0718
0.0156
0.0137
0.0114
0.0082
0.0005
-0.0018
-0.0037
-0.0055
-0.0073
-0.0091
-0.0110
-0.0128
-0.0151
Integral
6.3388
1.0000
0.9496
0.2128
6.2318
3.8554
1.8386
0.7732
3.6017
3.5856
0.3319
(ppm)

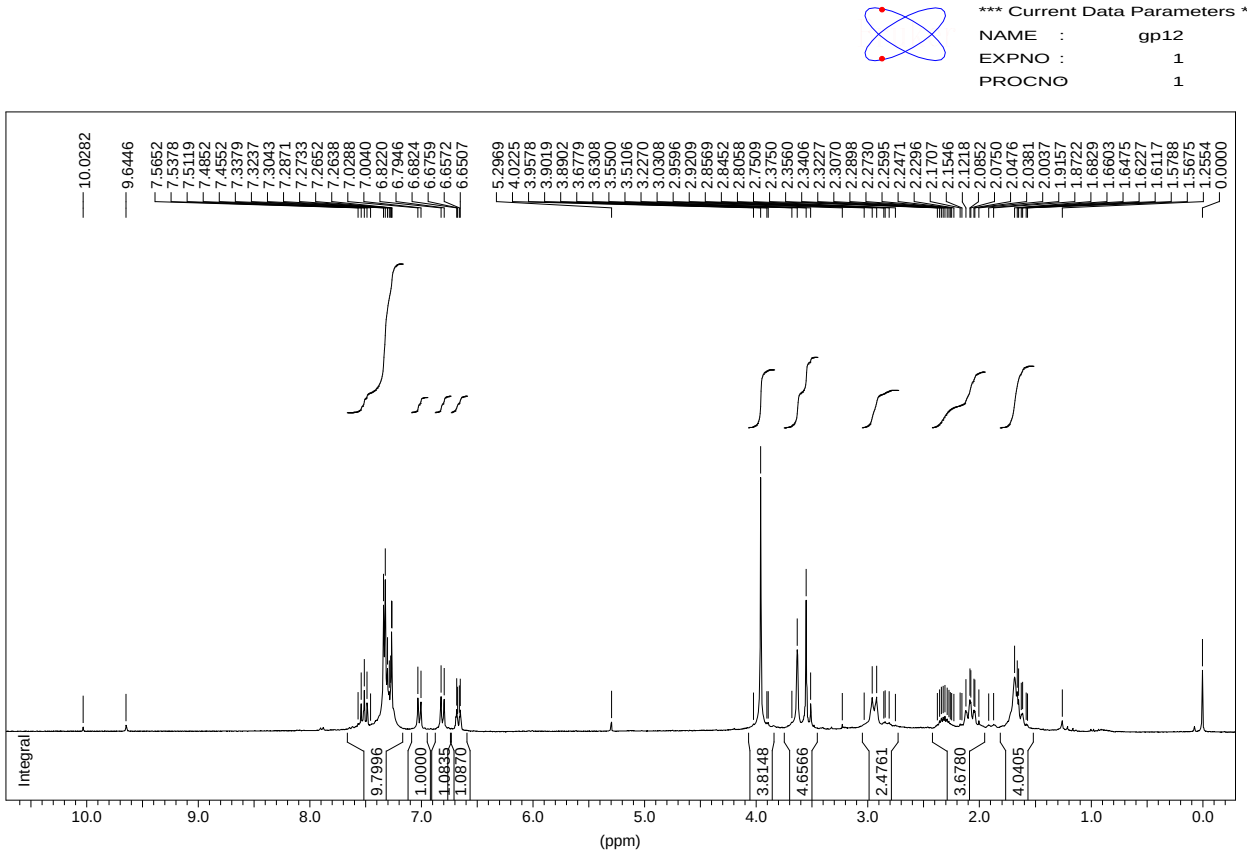
Sample**18**


O
H3CO
N

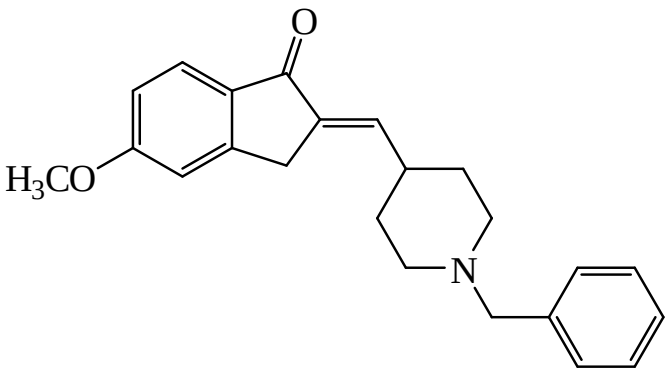

*** Current Data Parameters ***
NAME : gp11
EXPNO : 1
PROCNO 1
7.3346
7.3200
7.3036
7.2955
7.2831
7.2700
7.2608
7.2557
7.2418
7.2261
7.1943
7.1859
7.1666
7.1582
6.7541
6.7478
6.7215
3.8478
3.6089
3.6052
3.5274
2.9483
2.9095
2.4119
2.3969
2.3772
2.3625
2.3446
2.3282
2.3118
2.2939
2.2781
2.1006
2.0911
2.0633
2.0538
2.0257
2.0158
2.0008
1.7732
1.7312
1.7184
1.6870
1.6749
1.6512
1.6391
1.6026
1.5700
1.5587
-0.0000
I4
I2
Integral
9.7275
1.0000
3.3188
4.3981
2.3031
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

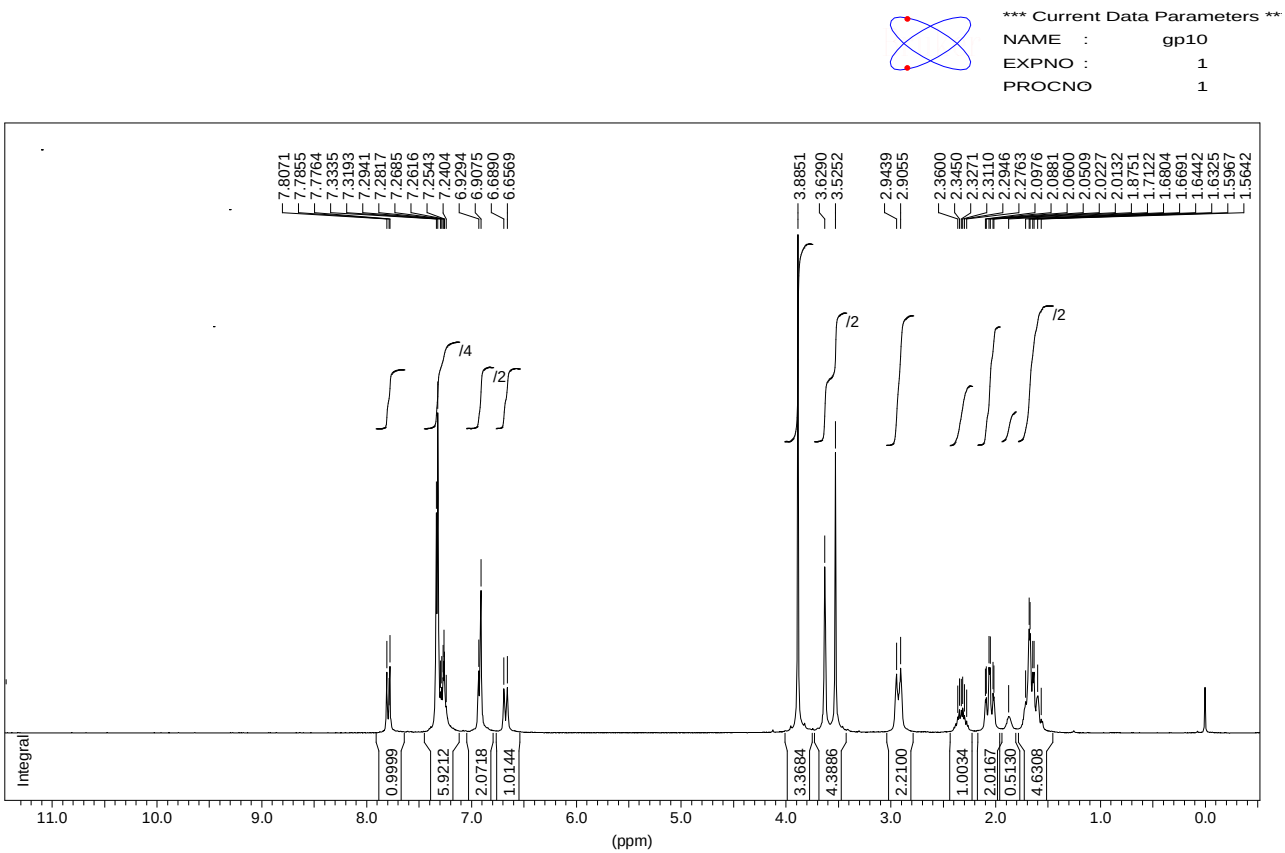
Sample**19**


OCH3
O
N

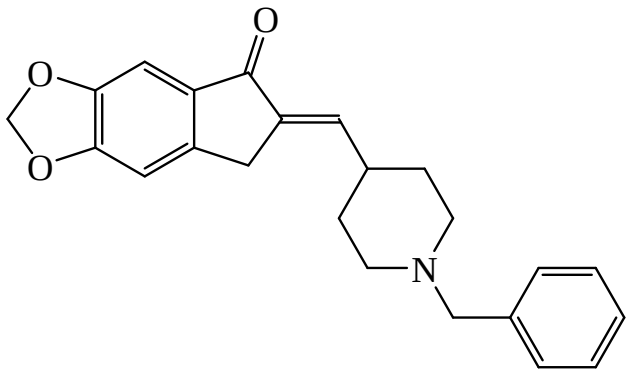

*** Current Data Parameters *
NAME : gp12
EXPNO : 1
PROCNO 1
10.0282
9.6446
7.5652
7.5378
7.5119
7.4852
7.4552
7.3379
7.3237
7.3043
7.2871
7.2733
7.2652
7.2638
7.0288
7.0040
6.8220
6.7946
6.6824
6.6759
6.6572
6.6507
5.2969
4.0225
3.9578
3.9019
3.8902
3.6779
3.6308
3.5500
3.5106
3.2270
3.0308
2.9596
2.9209
2.8569
2.8452
2.8058
2.7509
2.3750
2.3560
2.3406
2.3227
2.3070
2.2898
2.2730
2.2595
2.2471
2.2296
2.1707
2.1546
2.1218
2.0852
2.0750
2.0476
2.0381
2.0037
1.9157
1.8722
1.6829
1.6603
1.6475
1.6227
1.6117
1.5788
1.5675
1.2554
0.0000
Integral
9.7996
1.0000
1.0835
1.0870
3.8148
4.6566
2.4761
3.6780
4.0405
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

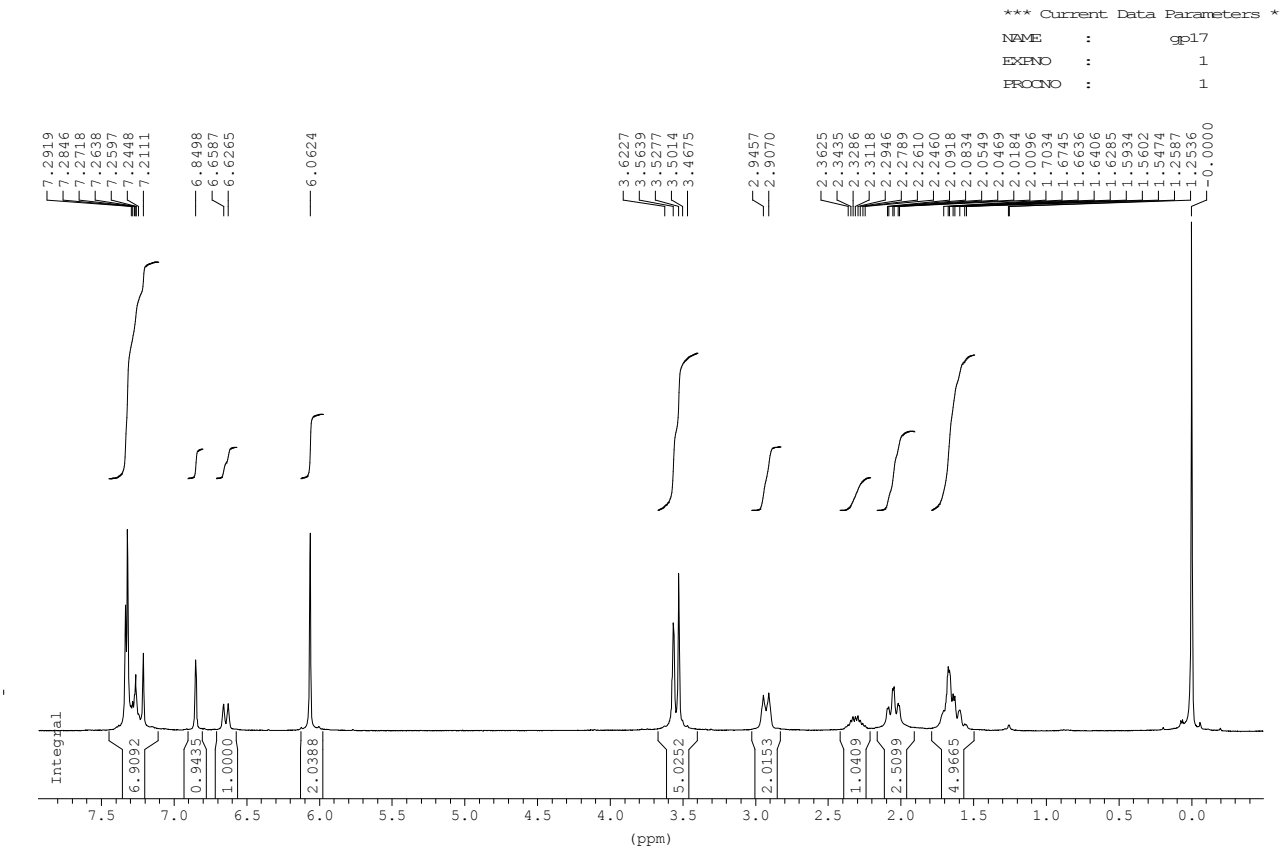
Sample **20**


O
H3CO
N

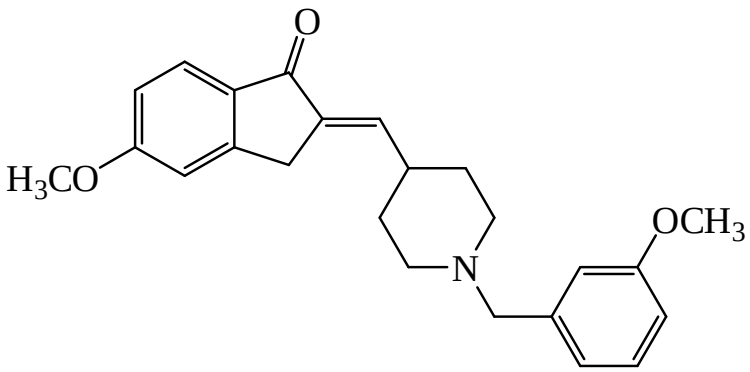

*** Current Data Parameters **
NAME : gp10
EXPNO : 1
PROCNO 1
7.8071
7.7855
7.7764
7.3335
7.3193
7.2941
7.2817
7.2685
7.2616
7.2543
7.2404
6.9294
6.9075
6.6890
6.6569
3.8851
3.6290
3.5252
2.9439
2.9055
2.3600
2.3450
2.3271
2.3110
2.2946
2.2763
2.0976
2.0881
2.0600
2.0509
2.0227
2.0132
1.8751
1.7122
1.6804
1.6691
1.6442
1.6325
1.5967
1.5642
I4
I2
I2
I2
Integral
0.9999
5.9212
2.0718
1.0144
3.3684
4.3886
2.2100
1.0034
2.0167
0.5130
4.6308
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

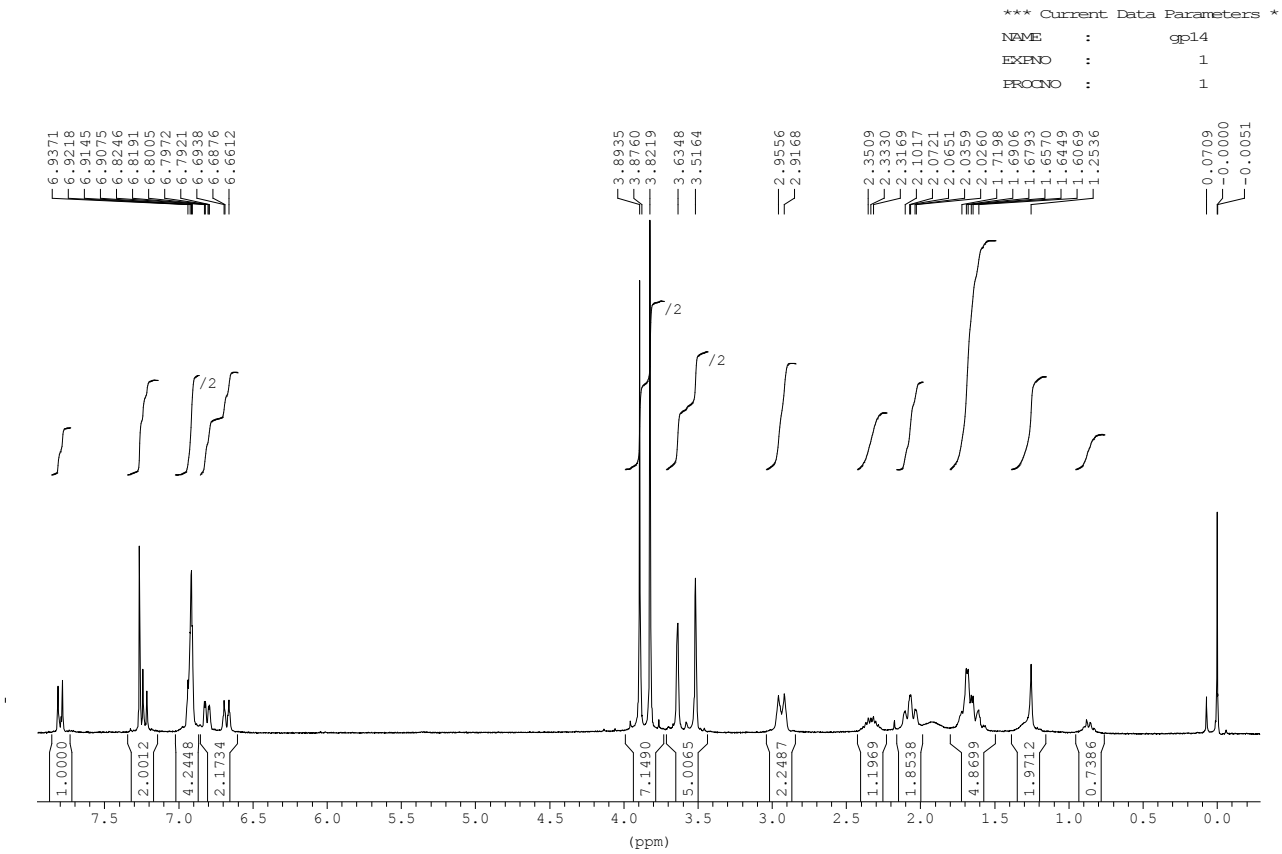
Sample**21**


O
O
O
N

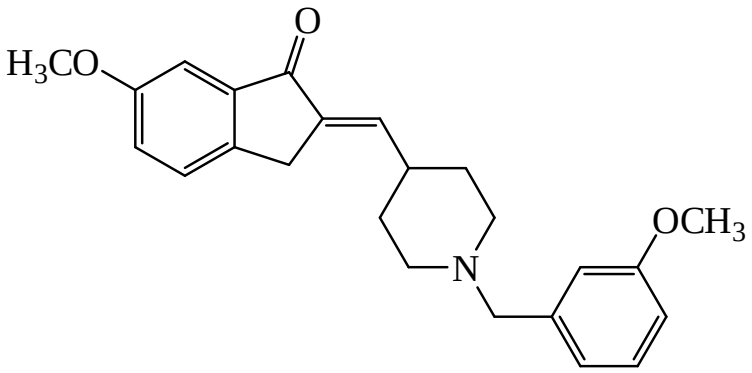

*** Current Data Parameters *
NAME : gp17
EXPNO : 1
PROCNO : 1
7.2919
7.2846
7.2718
7.2638
7.2597
7.2448
7.2111
6.8498
6.6587
6.6265
6.0624
3.6227
3.5639
3.5277
3.5014
3.4675
2.9457
2.9070
2.3625
2.3435
2.3286
2.3118
2.2946
2.2789
2.2610
2.2460
2.0918
2.0834
2.0549
2.0469
2.0184
2.0096
1.7034
1.6745
1.6636
1.6406
1.6285
1.5934
1.5602
1.5474
1.2587
1.2536
0.0000
Integral
6.9092
0.9435
1.0000
2.0388
5.0252
2.0153
1.0409
2.5099
4.9665
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

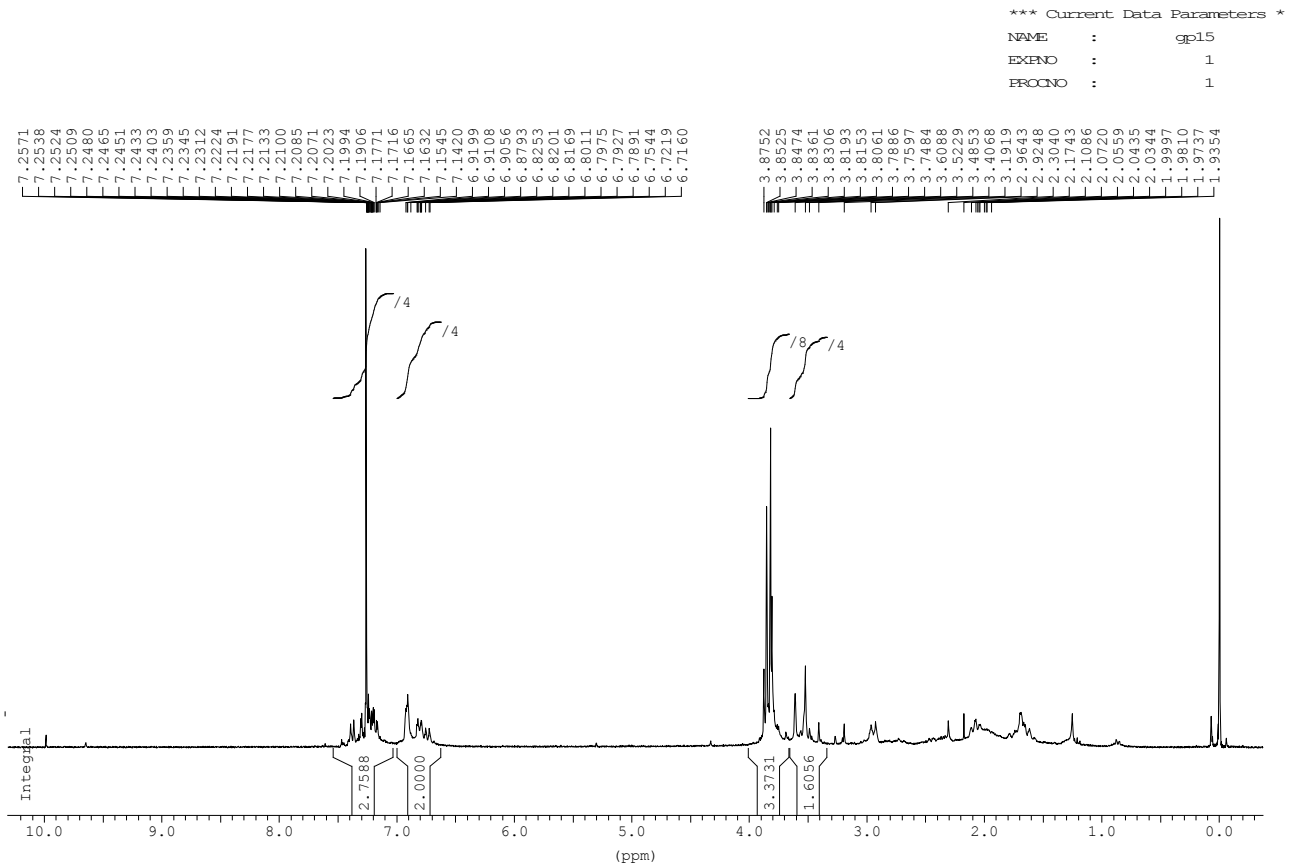
Sample**22**


O
H3CO
OCH3
N

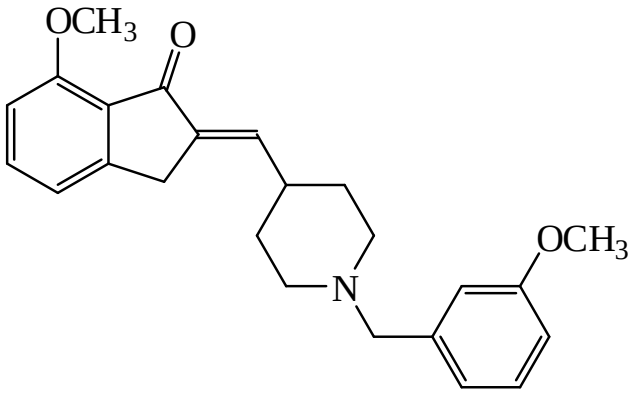

*** Current Data Parameters *
NAME : gp14
EXPNO : 1
PROCNO : 1
6.9371
6.9218
6.9145
6.9075
6.8246
6.8191
6.8005
6.7972
6.7921
6.6938
6.6876
6.6612
3.8935
3.8760
3.8219
3.6348
3.5164
2.9556
2.9168
2.3509
2.3330
2.3169
2.1017
2.0721
2.0651
2.0359
2.0260
1.7198
1.6906
1.6793
1.6570
1.6449
1.6069
1.2536
0.0709
-0.0000
-0.0051
/2
/2
/2
1.0000
2.0012
4.2448
2.1734
7.1490
5.0065
2.2487
1.1969
1.8538
4.8699
1.9712
0.7386
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

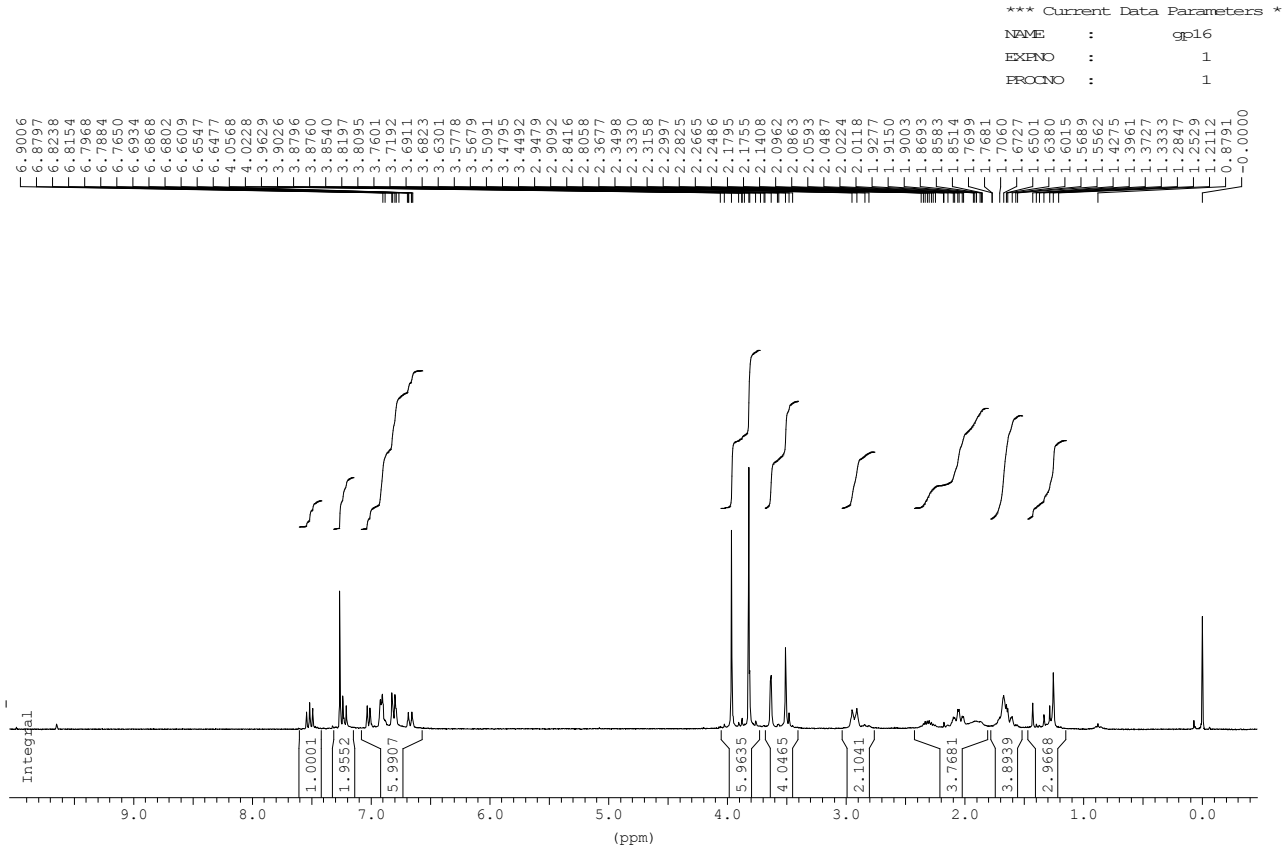
Sample**23**


O
H3CO
OCH3
N

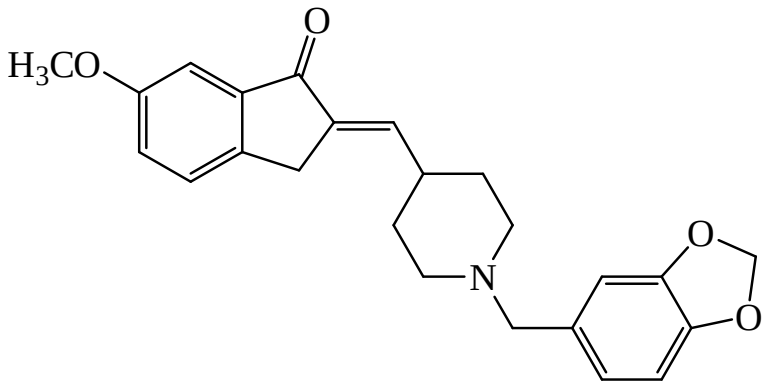

*** Current Data Parameters *
NAME : gp15
EXPNO : 1
PROCNO : 1
7.2571 7.2538 7.2524 7.2509 7.2480 7.2465 7.2451 7.2433 7.2403 7.2359 7.2345 7.2312 7.2224 7.2191 7.2177 7.2133 7.2100 7.2085 7.2071 7.2023 7.1994 7.1906 7.1771 7.1716 7.1665 7.1632 7.1545 7.1420 6.9199 6.9108 6.9056 6.8793 6.8253 6.8201 6.8169 6.8011 6.7975 6.7927 6.7891 6.7544 6.7219 6.7160
3.8752 3.8525 3.8474 3.8361 3.8306 3.8193 3.8153 3.8061 3.7886 3.7597 3.7484 3.6088 3.5229 3.4853 3.4068 3.1919 2.9643 2.9248 2.3040 2.1743 2.1086 2.0720 2.0559 2.0435 2.0344 1.9997 1.9810 1.9737 1.9354
/4
/4
/8
/4
Integral
2.7588
2.0000
3.3731
1.6056
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
(ppm)

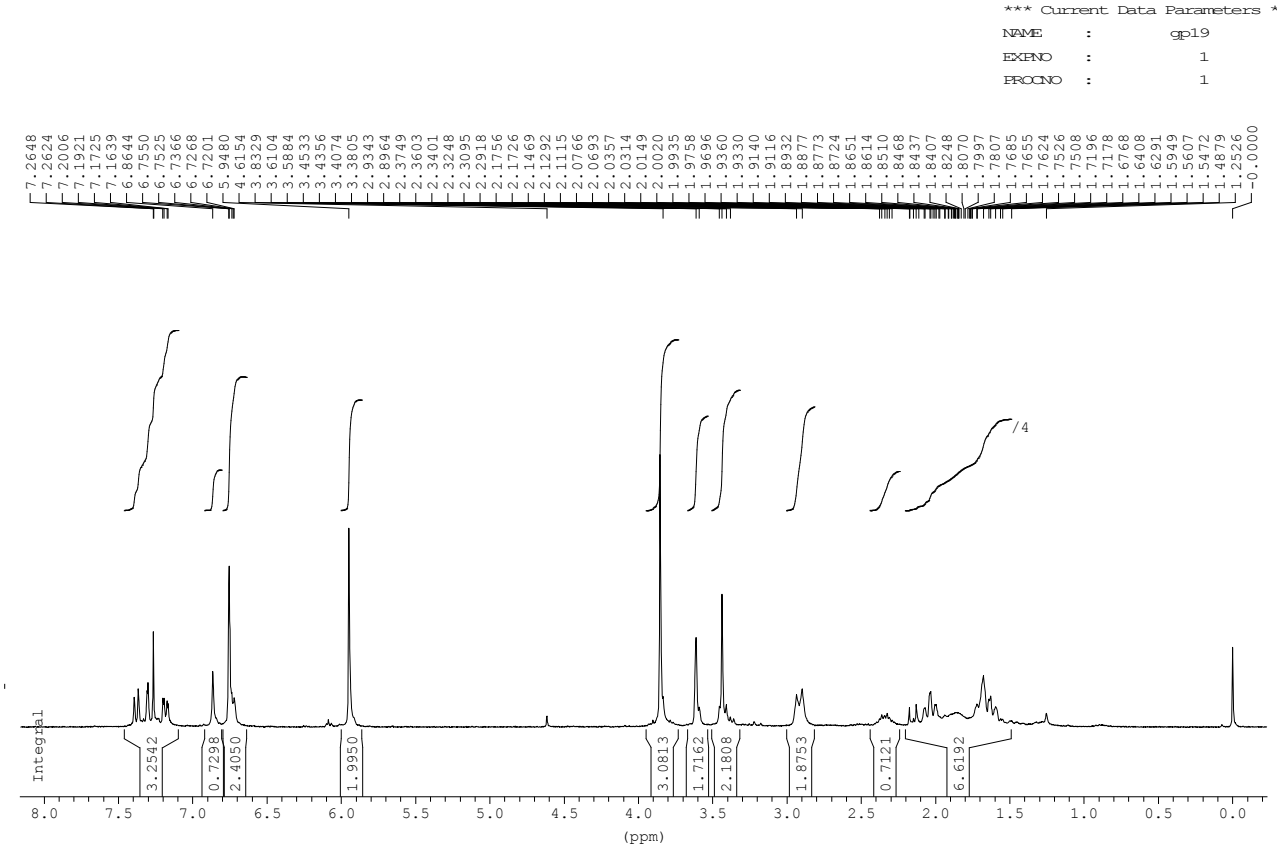
Sample**24**


OCH3
O
N
OCH3

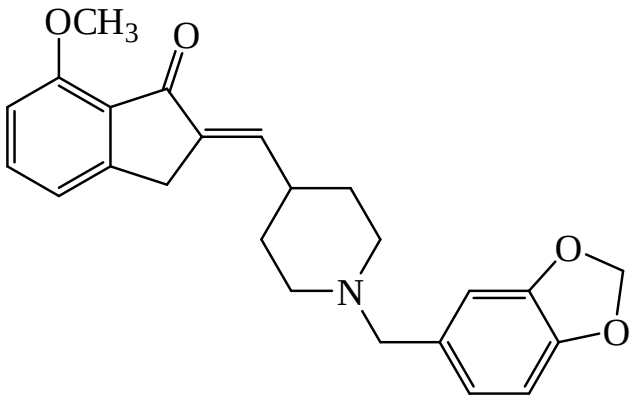

*** Current Data Parameters *
NAME : gp16
EXPNO : 1
PROCNO : 1
Integral
1.0001
1.9552
5.9907
5.9635
4.0465
2.1041
3.7681
3.8939
2.9968
(ppm)

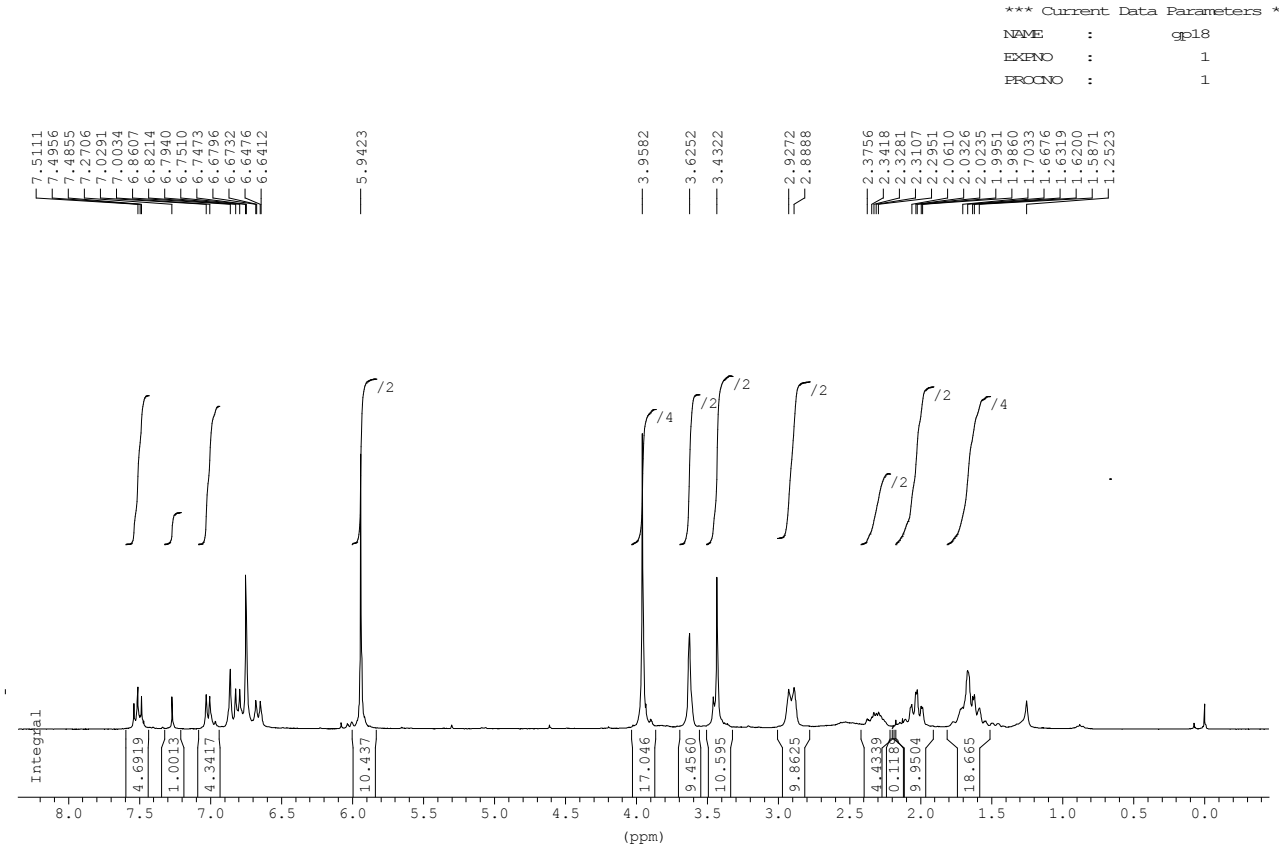
Sample**25**


O
H3CO
O
N
O
O


*** Current Data Parameters *
NAME : gp19
EXPNO : 1
PROCNO : 1
7.2648
7.2624
7.2006
7.1921
7.1725
7.1639
6.8644
6.7550
6.7525
6.7366
6.7268
6.7201
5.9480
4.6154
3.8329
3.6104
3.5884
3.4533
3.4356
3.4074
3.3805
2.9343
2.8964
2.3749
2.3603
2.3401
2.3248
2.3095
2.2918
2.1756
2.1726
2.1469
2.1292
2.1115
2.0766
2.0693
2.0357
2.0314
2.0149
2.0020
1.9935
1.9758
1.9696
1.9360
1.9330
1.9140
1.9116
1.8932
1.8877
1.8773
1.8724
1.8651
1.8614
1.8510
1.8468
1.8437
1.8407
1.8248
1.8070
1.7997
1.7807
1.7685
1.7655
1.7624
1.7526
1.7508
1.7196
1.7178
1.6768
1.6408
1.6291
1.5949
1.5607
1.5472
1.4879
1.2526
-0.0000
/4
Integral
3.2542
0.7298
2.4050
1.9950
3.0813
1.7162
2.1808
1.8753
0.7121
6.6192
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

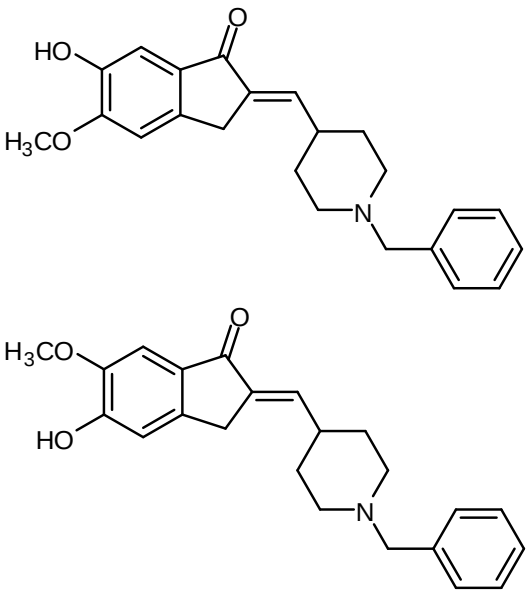
Sample**26**

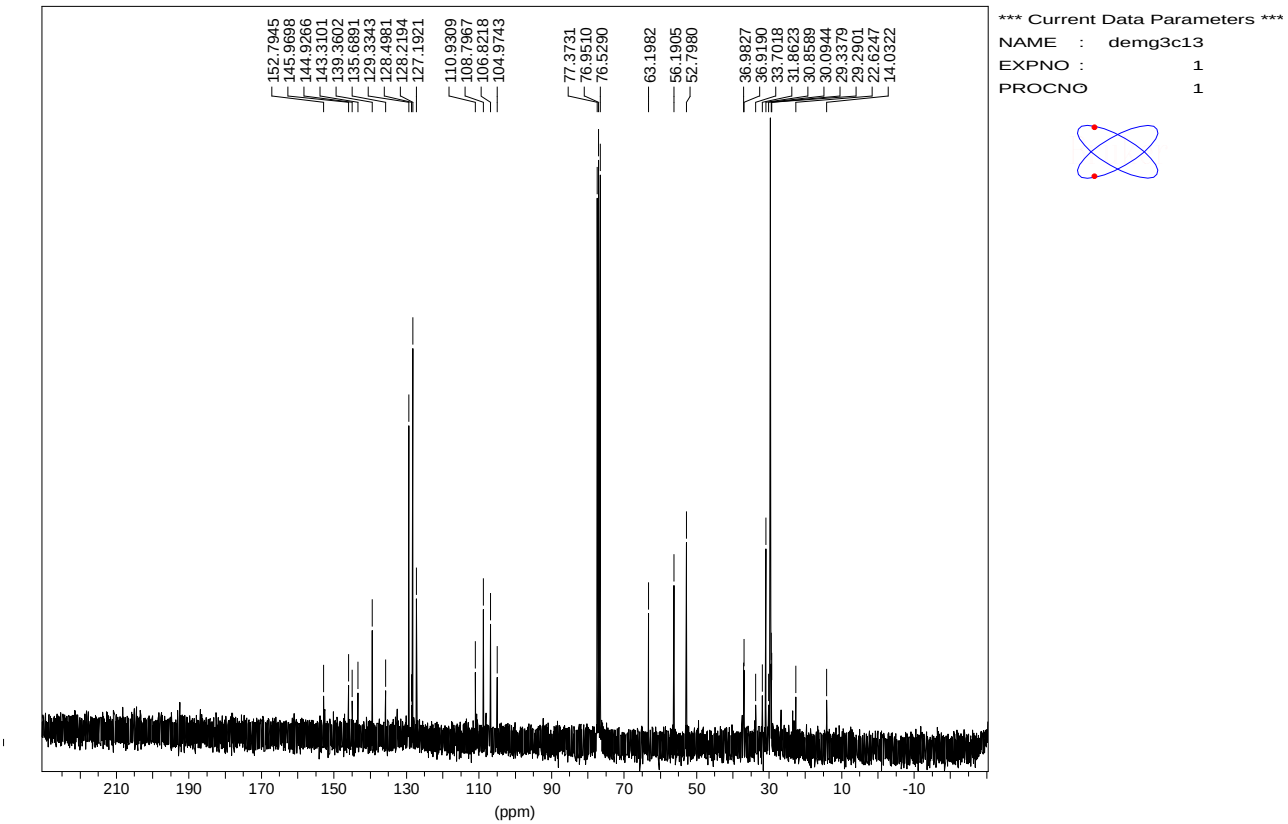

OCH3
O
N
O
O


*** Current Data Parameters *
NAME : gp18
EXPNO : 1
PROCNO : 1
7.5111
7.4956
7.4855
7.2706
7.0291
7.0034
6.8607
6.8214
6.7940
6.7510
6.7473
6.6796
6.6732
6.6476
6.6412
5.9423
3.9582
3.6252
3.4322
2.9272
2.8888
2.3756
2.3418
2.3281
2.3107
2.2951
2.0610
2.0326
2.0235
1.9951
1.9860
1.7033
1.6676
1.6319
1.6200
1.5871
1.2523
Integral
4.6919
1.0013
4.3417
10.437
17.046
9.4560
10.595
9.8625
4.4339
0.118
9.9504
18.665
(ppm)

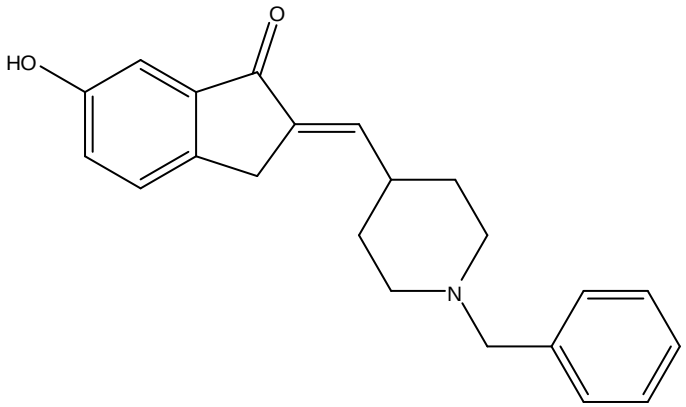
^{13}C-NMR Spectra

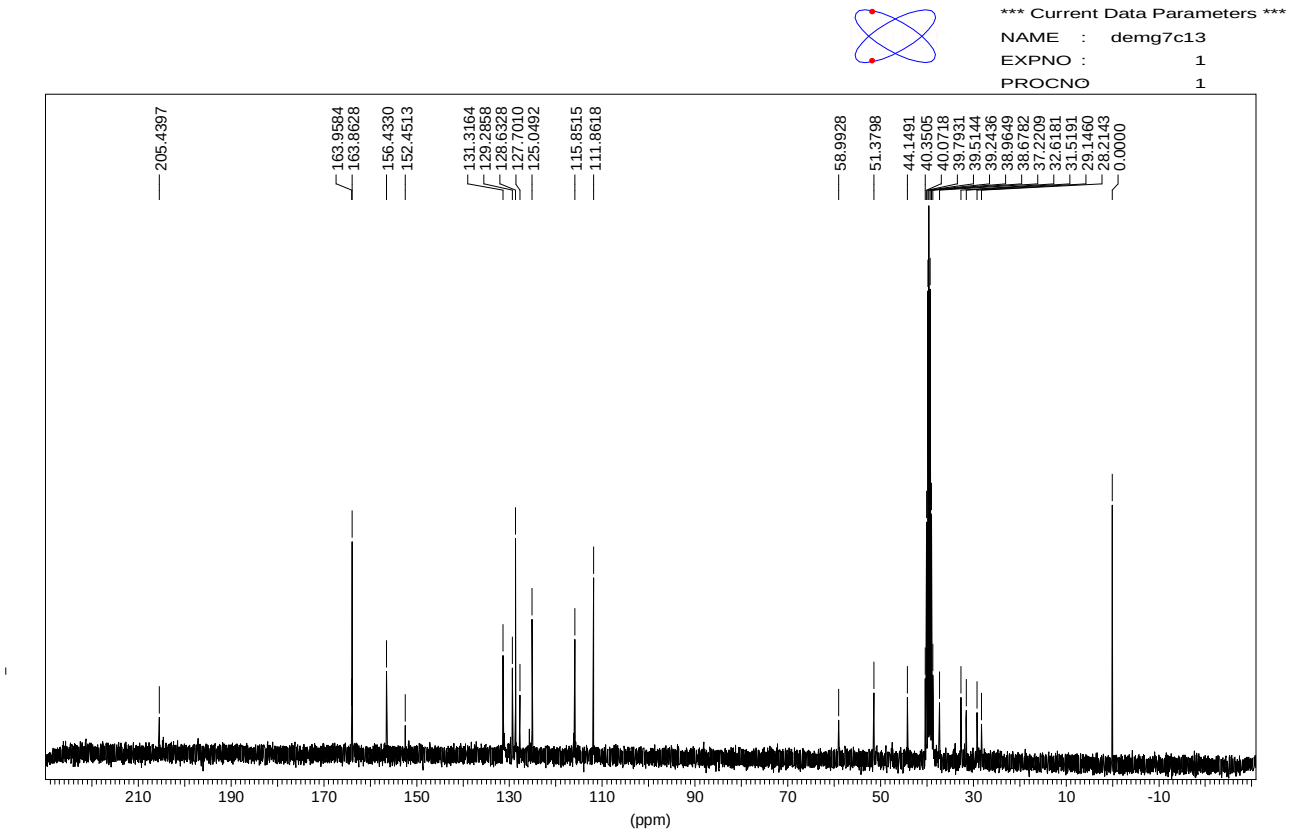
Sample **13a/13b**



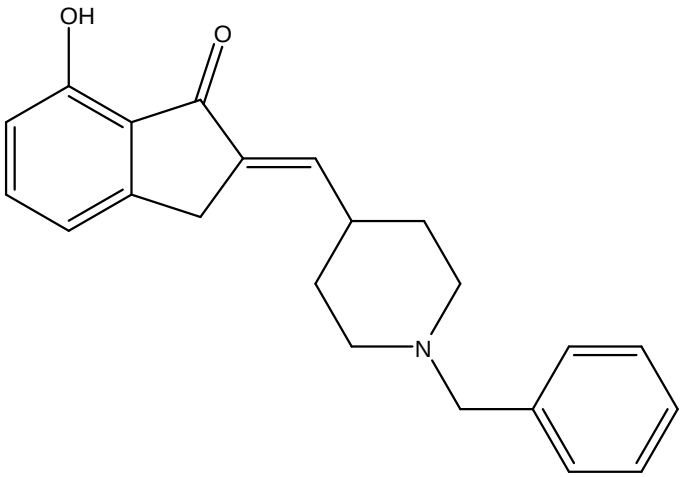


Sample **14**

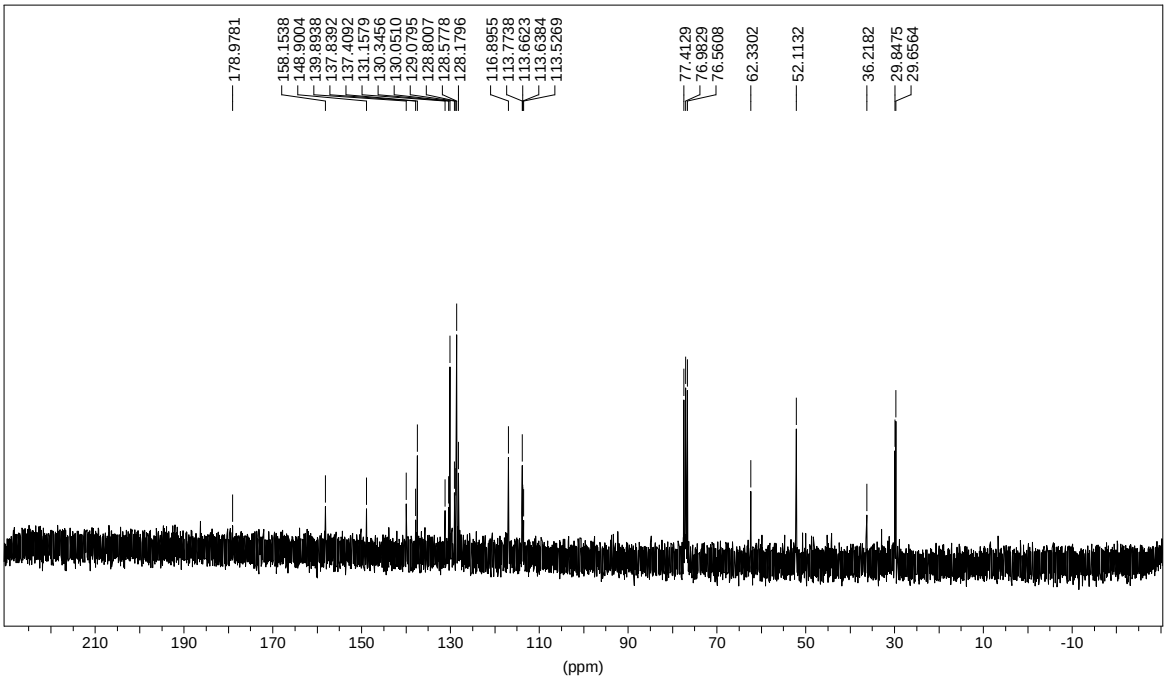

HO
O
N


*** Current Data Parameters ***
NAME : demg7c13
EXPNO : 1
PROCNO 1
205.4397
163.9584
163.8628
156.4330
152.4513
131.3164
129.2858
128.6328
127.7010
125.0492
115.8515
111.8618
58.9928
51.3798
44.1491
40.3505
40.0718
39.7931
39.5144
39.2436
38.9649
38.6782
37.2209
32.6181
31.5191
29.1460
28.2143
0.0000
210
190
170
150
130
110
90
70
50
30
10
-10
(ppm)

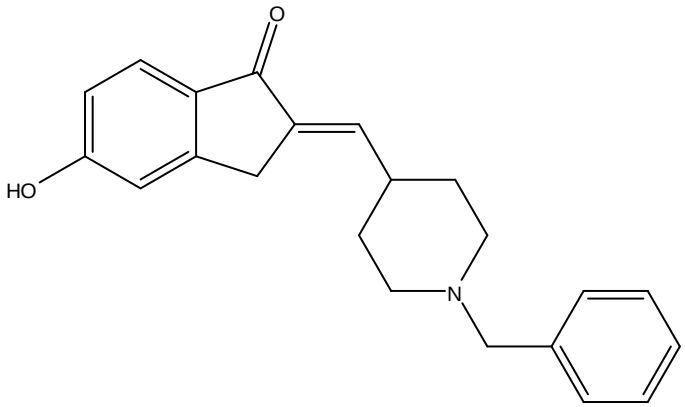
Sample **15**

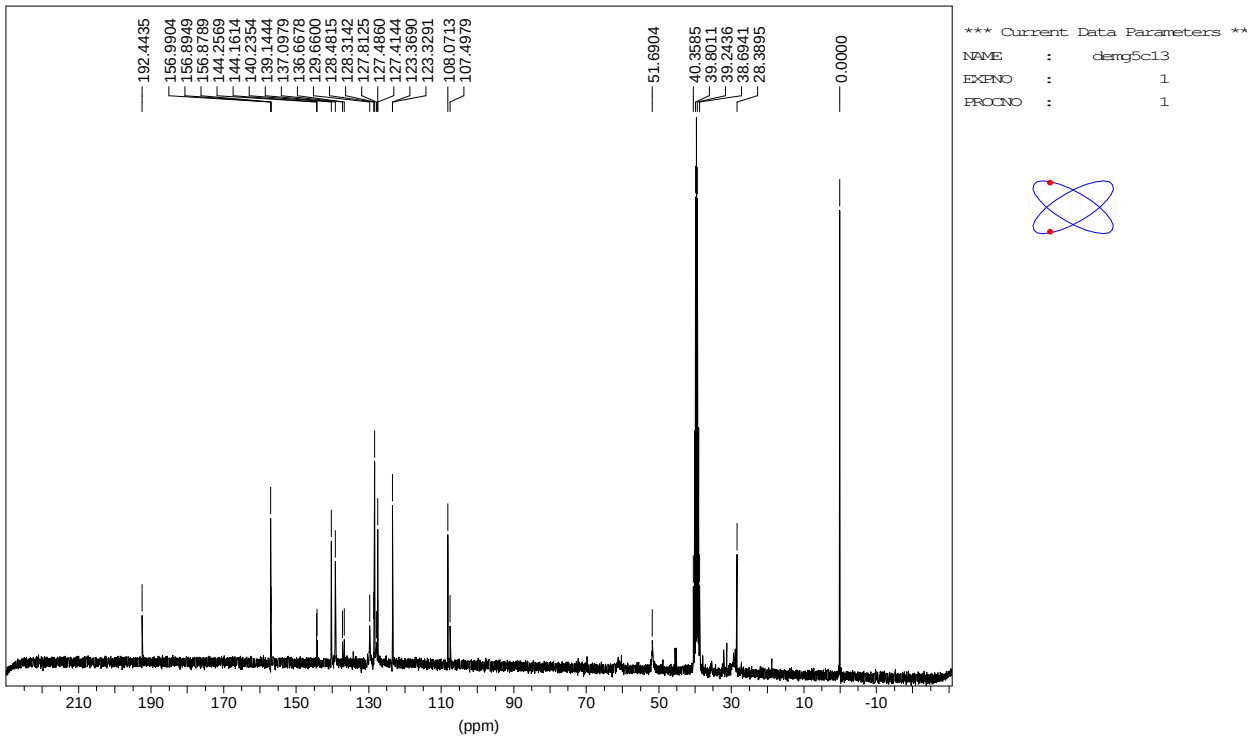


*** Current Data Parameters ***
NAME : dmg6c132
EXPNO : 1
PROCNO 1

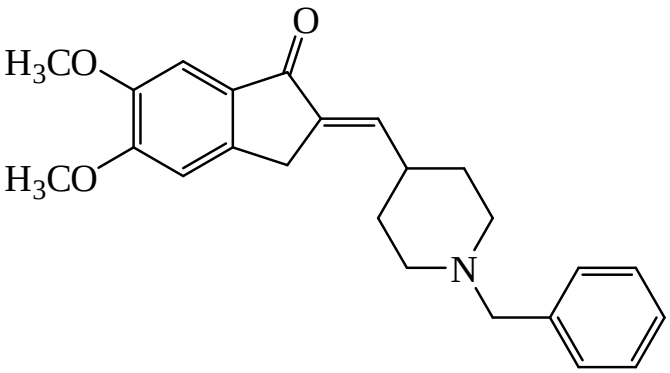


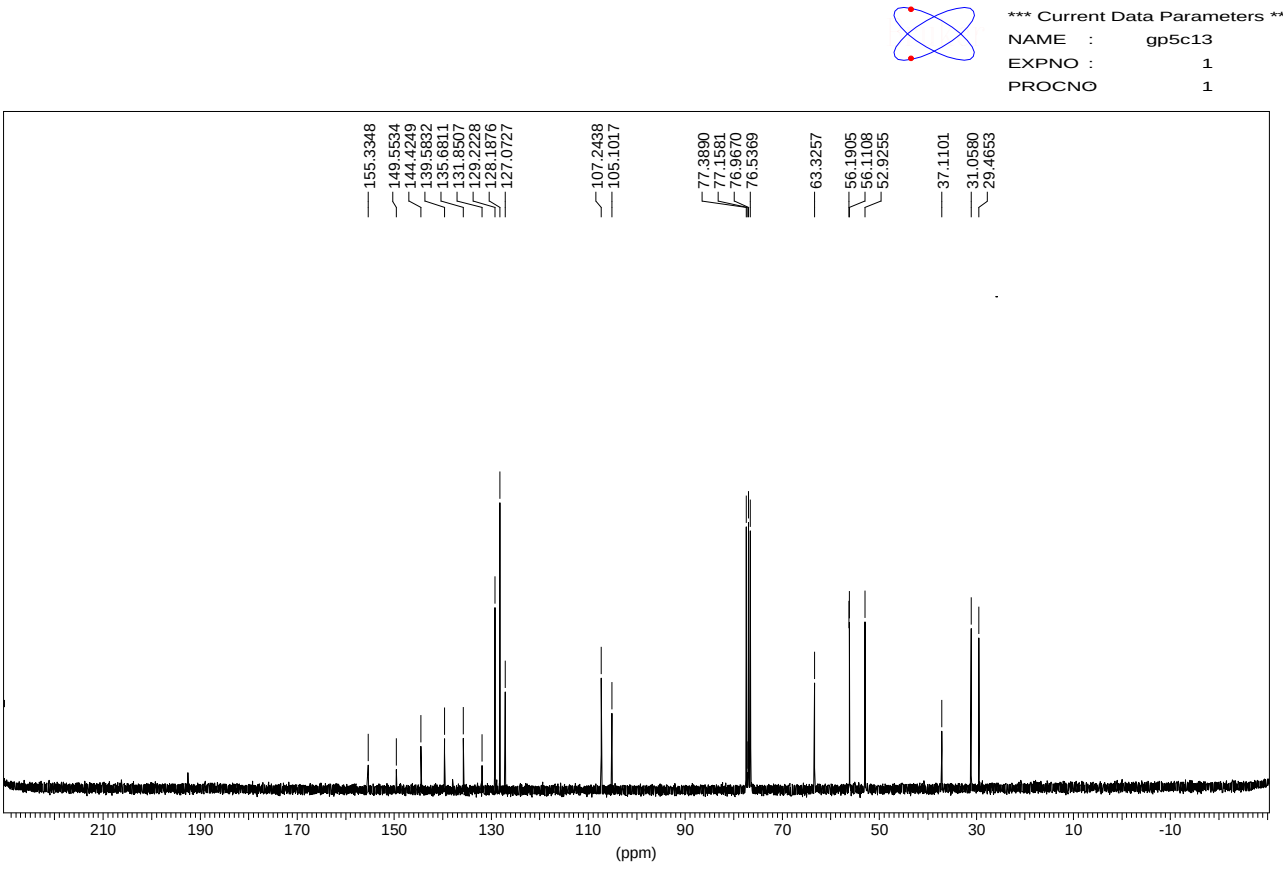
Sample **16**


O
HO
N

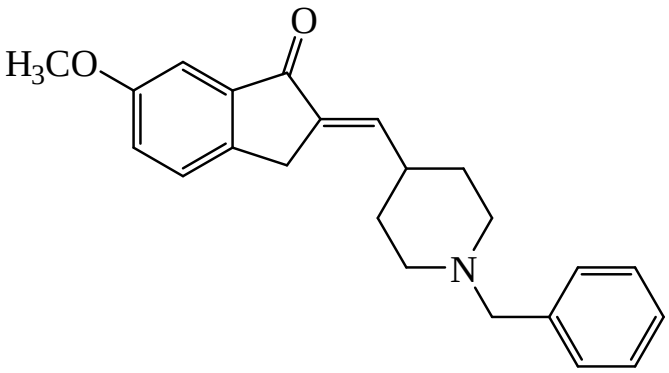

192.4435
156.9904
156.8949
156.8789
144.2569
144.1614
140.2354
139.1444
137.0979
136.6678
129.6600
128.4815
128.3142
127.8125
127.4860
127.4144
123.3690
123.3291
108.0713
107.4979
51.6904
40.3585
39.8011
39.2436
38.6941
28.3895
0.0000
*** Current Data Parameters **
NAME : demg5c13
EXPNO : 1
PROCNO : 1
210
190
170
150
130
110
90
70
50
30
10
-10
(ppm)

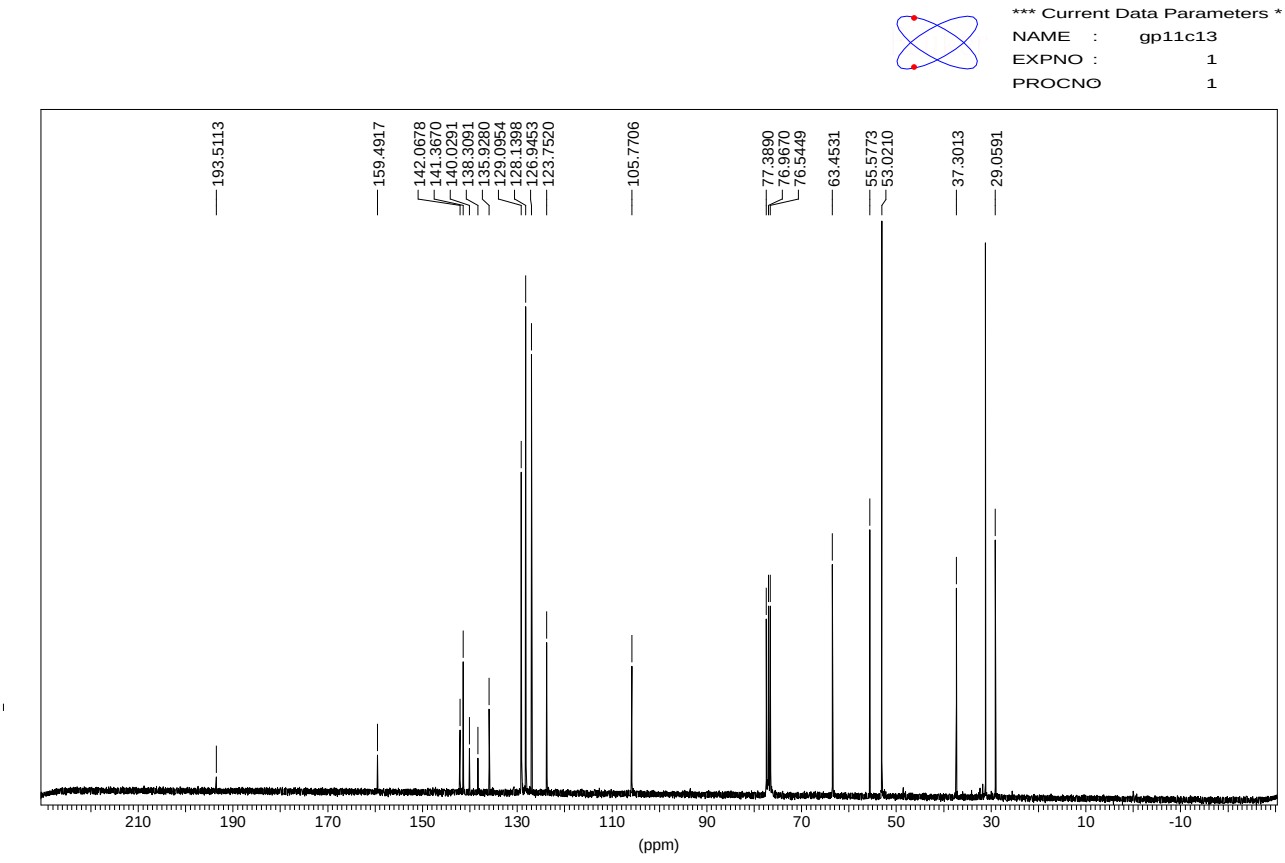
Sample **17**


O
H3CO
H3CO
N

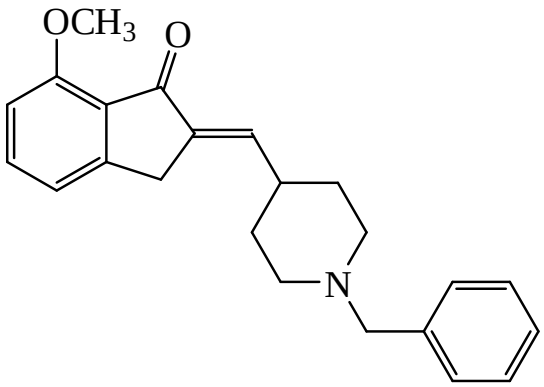

*** Current Data Parameters **
NAME : gp5c13
EXPNO : 1
PROCNO 1
155.3348
149.5534
144.4249
139.5832
135.6811
131.8507
129.2228
128.1876
127.0727
107.2438
105.1017
77.3890
77.1581
76.9670
76.5369
63.3257
56.1905
56.1108
52.9255
37.1101
31.0580
29.4653
210
190
170
150
130
110
90
70
50
30
10
-10
(ppm)

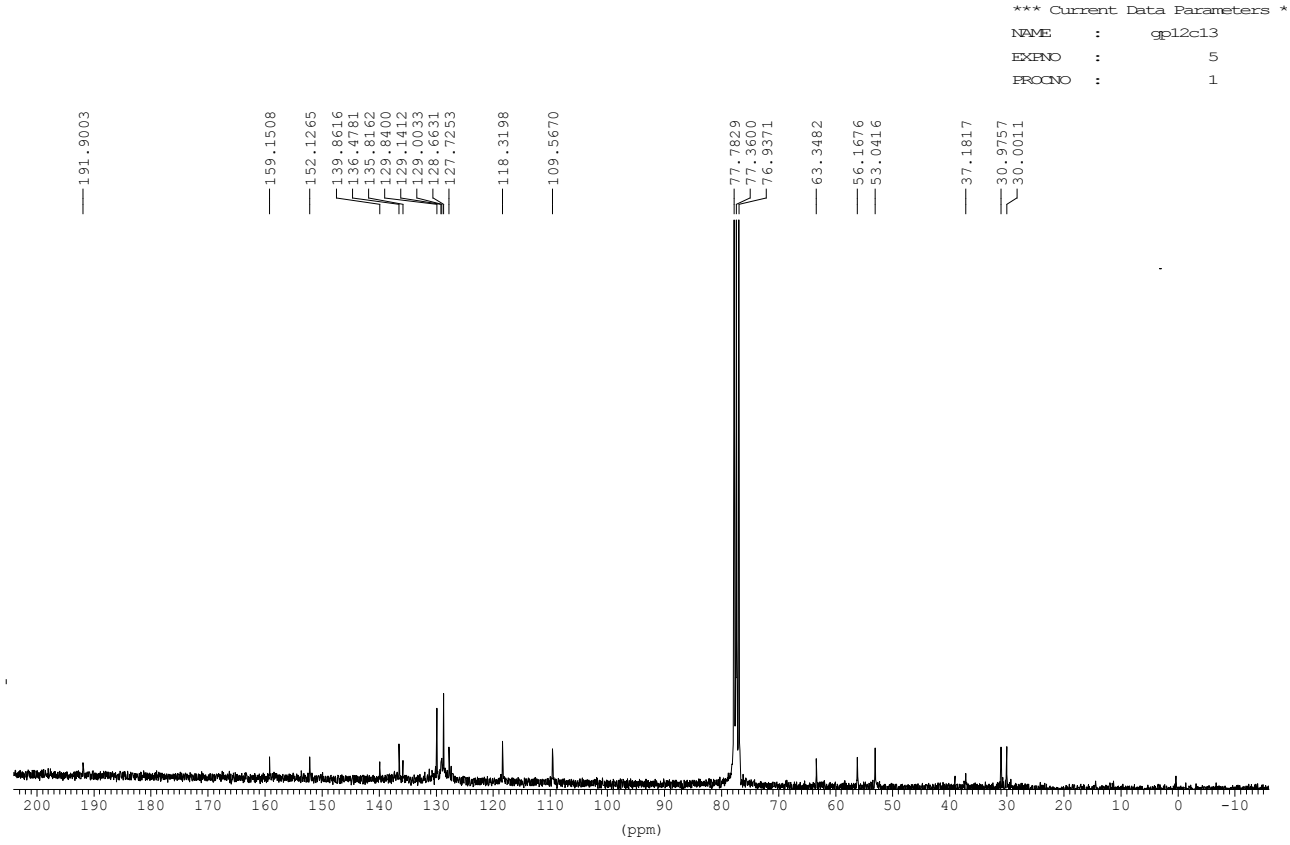
Sample**18**


O
H3CO
N

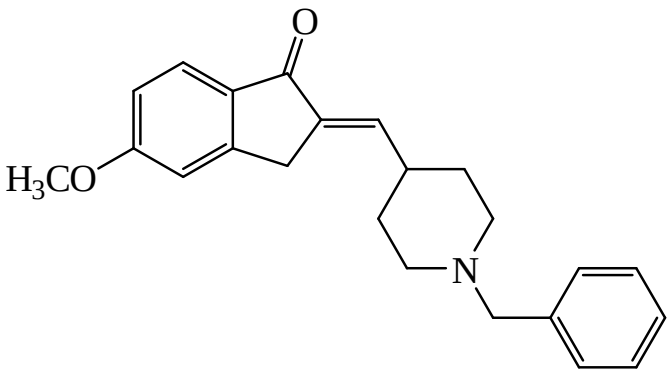

*** Current Data Parameters *
NAME : gp11c13
EXPNO : 1
PROCNO 1
193.5113
159.4917
142.0678
141.3670
140.0291
138.3091
135.9280
129.0954
128.1398
126.9453
123.7520
105.7706
77.3890
76.9670
76.5449
63.4531
55.5773
53.0210
37.3013
29.0591
210
190
170
150
130
110
90
70
50
30
10
-10
(ppm)

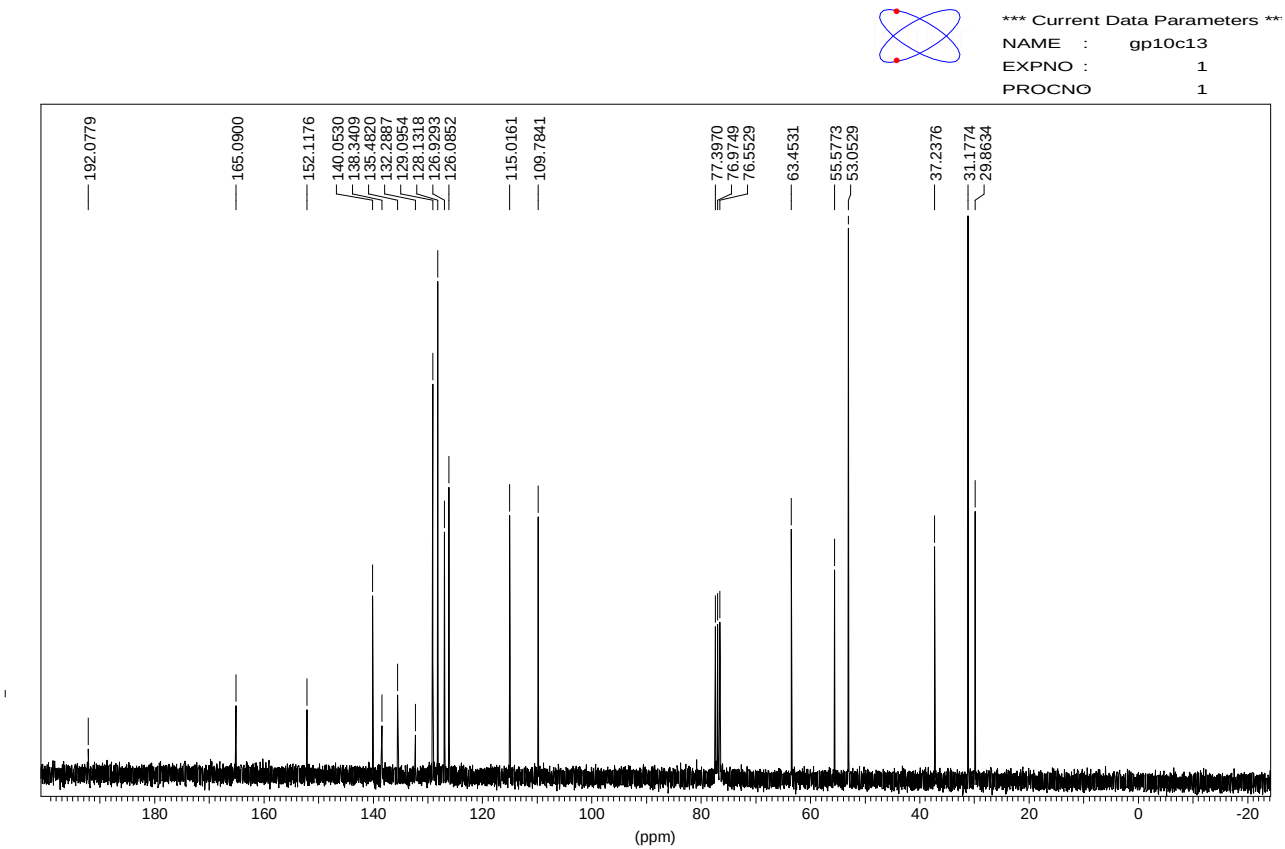
Sample**19**


OCH3
O
N

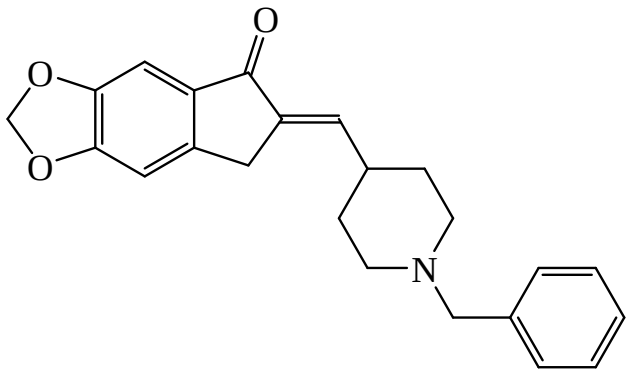

*** Current Data Parameters *
NAME : gp12c13
EXPNO : 5
PROCNO : 1
191.9003
159.1508
152.1265
139.8616
136.4781
135.8162
129.8400
129.1412
129.0033
128.6631
127.7253
118.3198
109.5670
77.7829
77.3600
76.9371
63.3482
56.1676
53.0416
37.1817
30.9757
30.0011
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

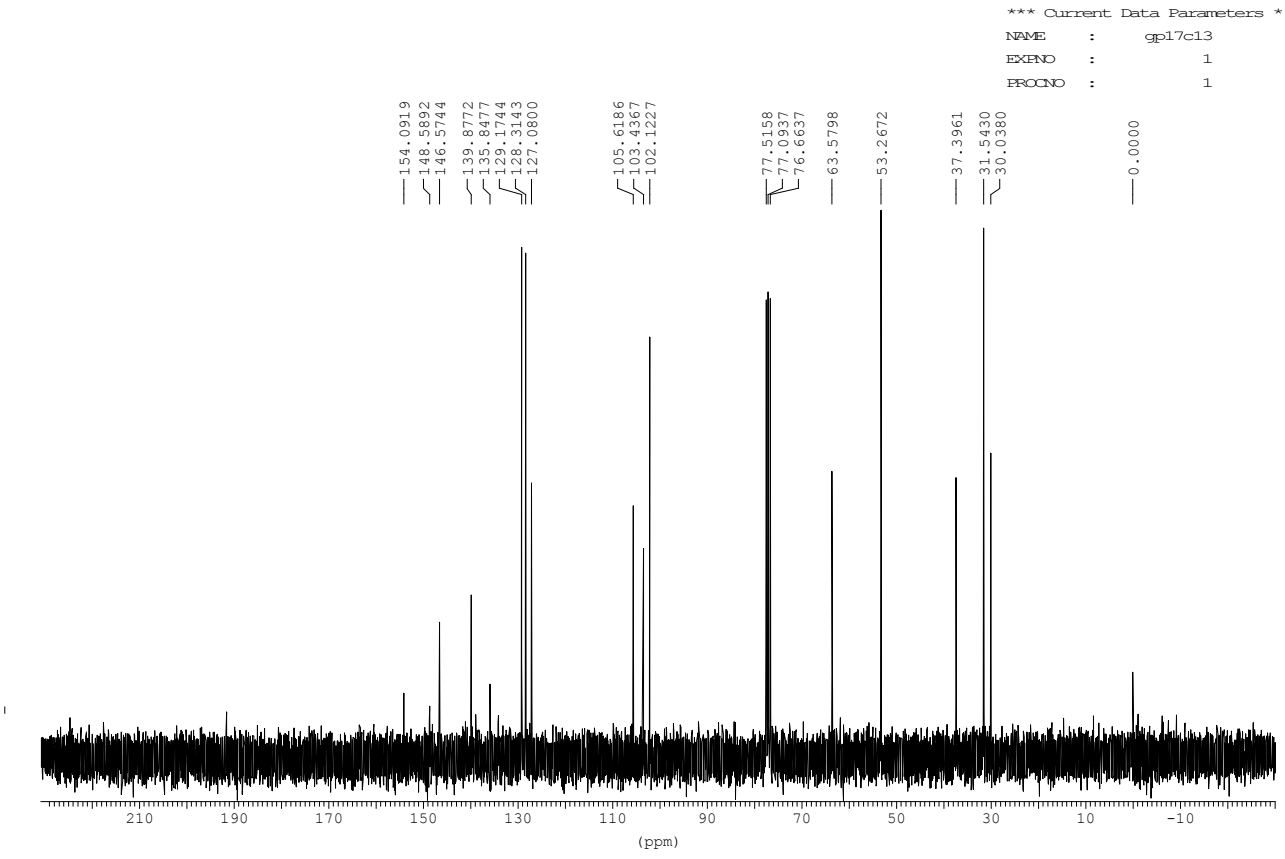
Sample**20**


O
H3CO
N

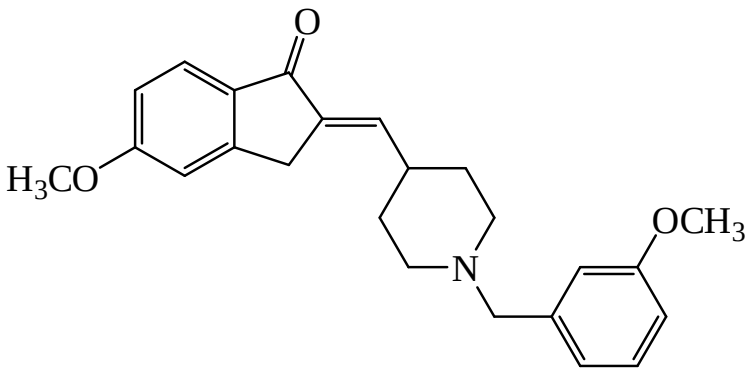

*** Current Data Parameters ***
NAME : gp10c13
EXPNO : 1
PROCNO 1
192.0779
165.0900
152.1176
140.0530
138.3409
135.4820
132.2887
129.0954
128.1318
126.9293
126.0852
115.0161
109.7841
77.3970
76.9749
76.5529
63.4531
55.5773
53.0529
37.2376
31.1774
29.8634
180
160
140
120
100
80
60
40
20
0
-20
(ppm)

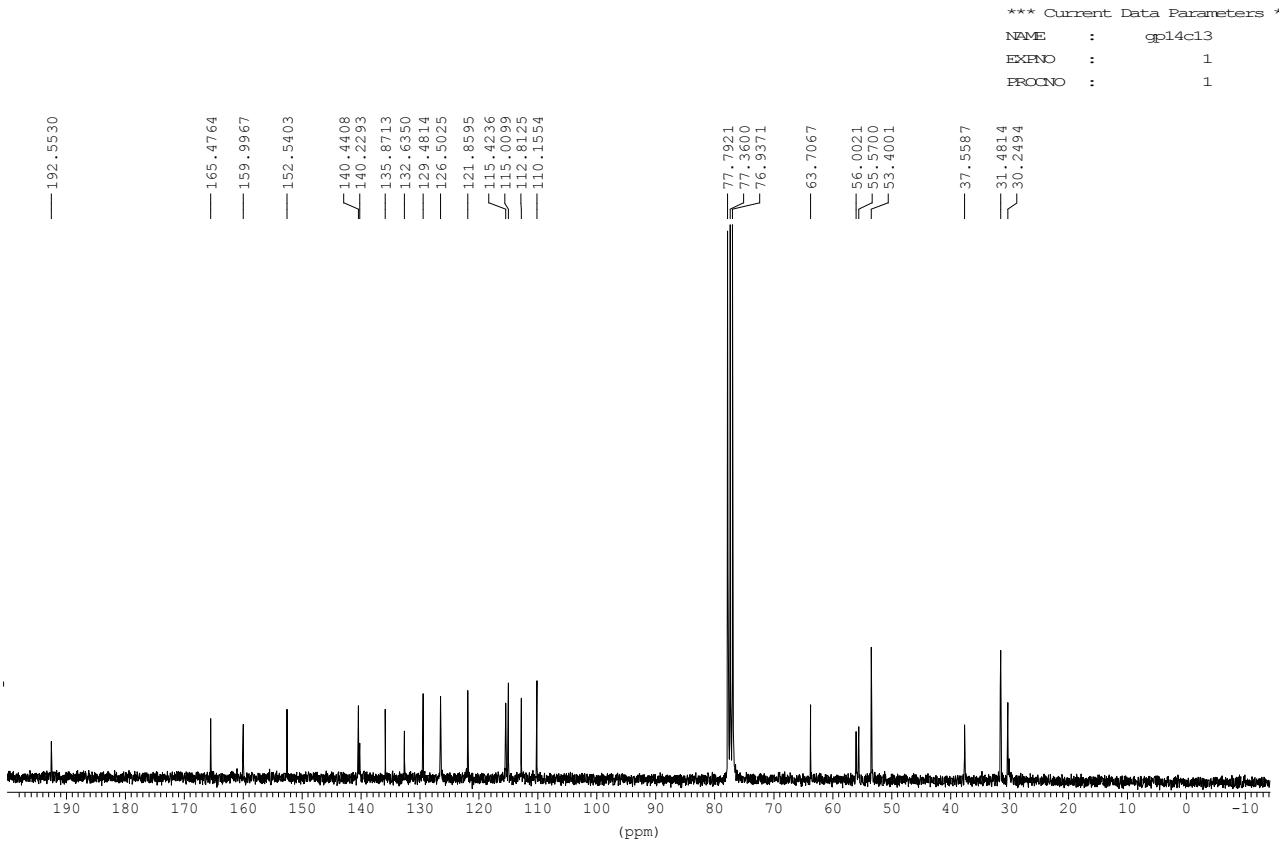
Sample**21**


O
O
O
N

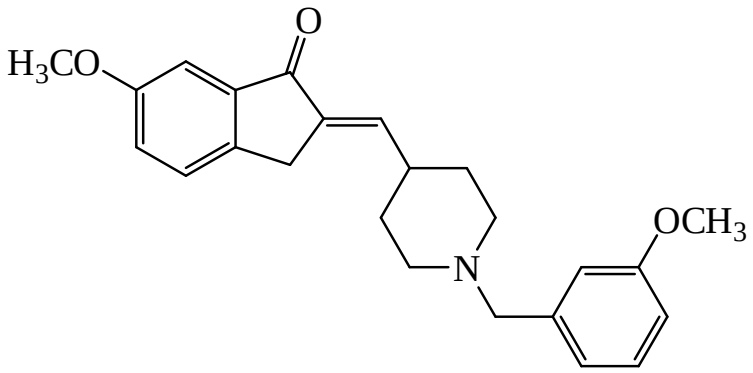

*** Current Data Parameters *
NAME : gp17c13
EXPNO : 1
PROCNO : 1
154.0919
148.5892
146.5744
139.8772
135.8477
129.1744
128.3143
127.0800
105.6186
103.4367
102.1227
77.5158
77.0937
76.6637
63.5798
53.2672
37.3961
31.5430
30.0380
0.0000
210
190
170
150
130
110
90
70
50
30
10
-10
(ppm)

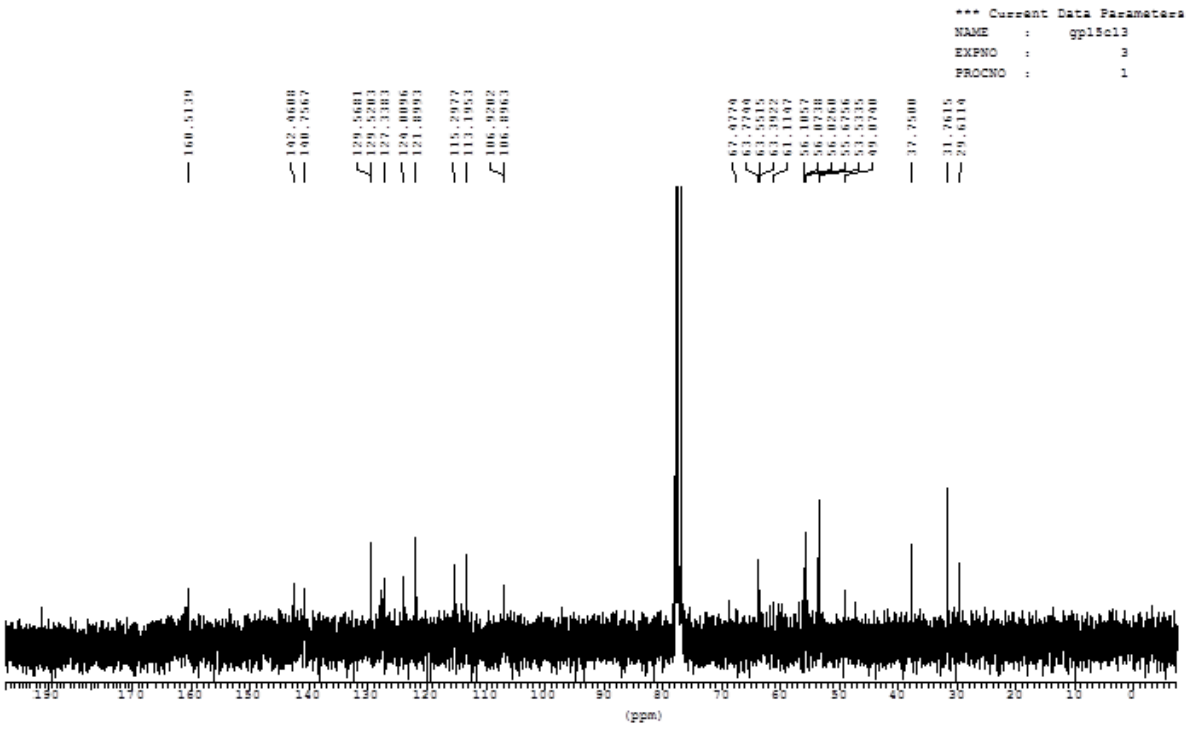
Sample**22**


O
H3CO
OCH3
N

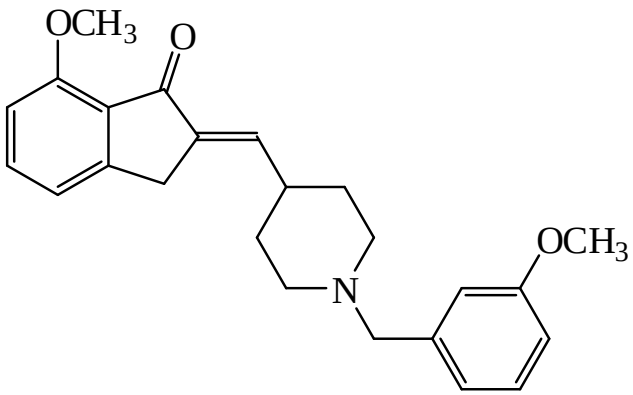

*** Current Data Parameters ***
NAME : gp14c13
EXPNO : 1
PROCNO : 1
192.5530
165.4764
159.9967
152.5403
140.4408
140.2293
135.8713
132.6350
129.4814
126.5025
121.8595
115.4236
115.0099
112.8125
110.1554
77.7921
77.3600
76.9371
63.7067
56.0021
55.5700
53.4001
37.5587
31.4814
30.2494
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

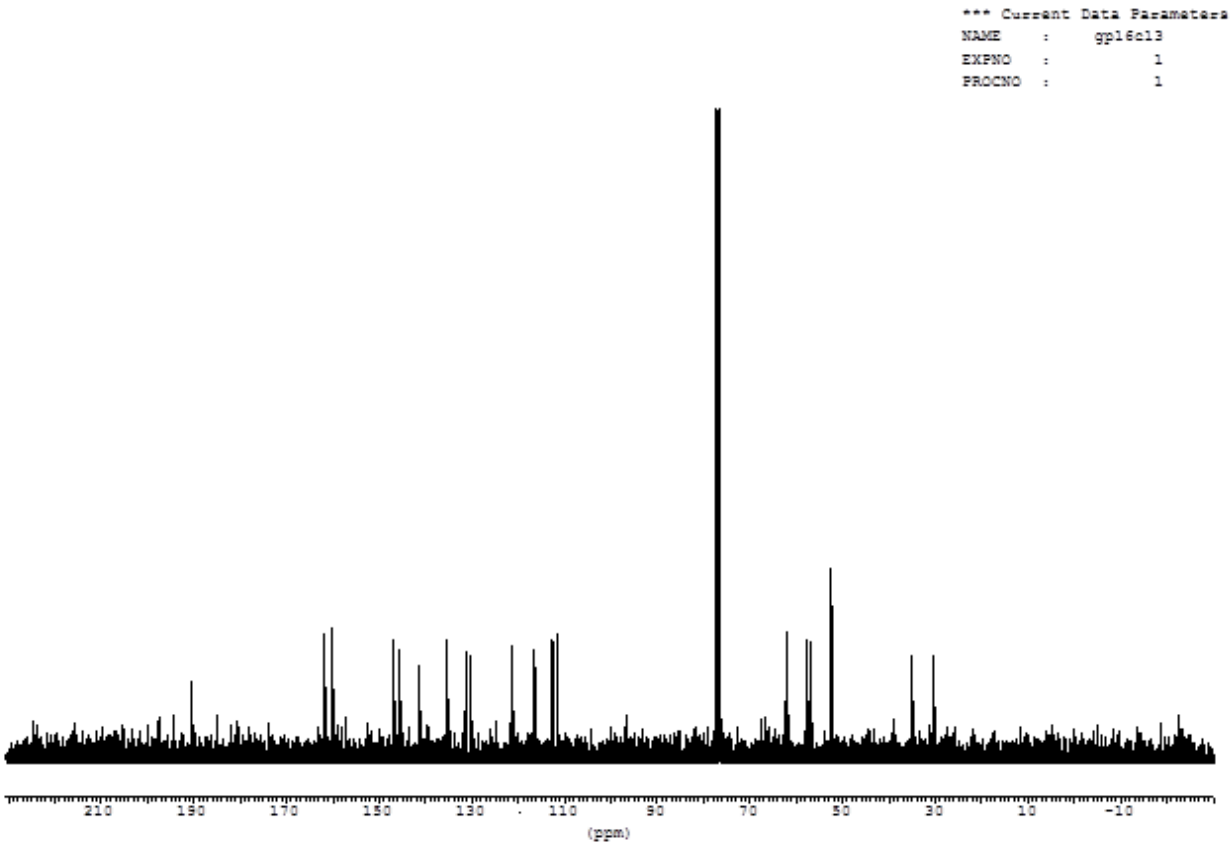
Sample**23**


O
H3CO
OCH3
N

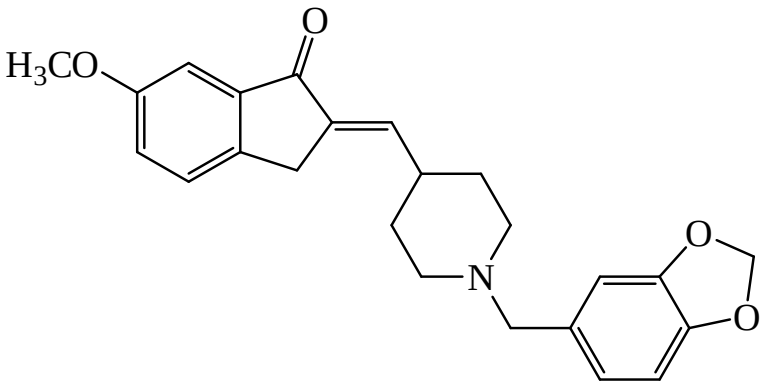

*** Current Data Parameters
NAME : gp15c13
EXPNO : 3
PROCNO : 1
160.5139
152.9688
150.7567
129.5681
129.5203
127.3383
120.8096
121.8993
115.2977
113.1953
106.9282
106.8963
67.9779
63.7794
63.5515
63.3922
61.1147
56.1057
56.0738
56.0260
55.6756
53.5335
49.8740
37.7588
31.7615
29.6114
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

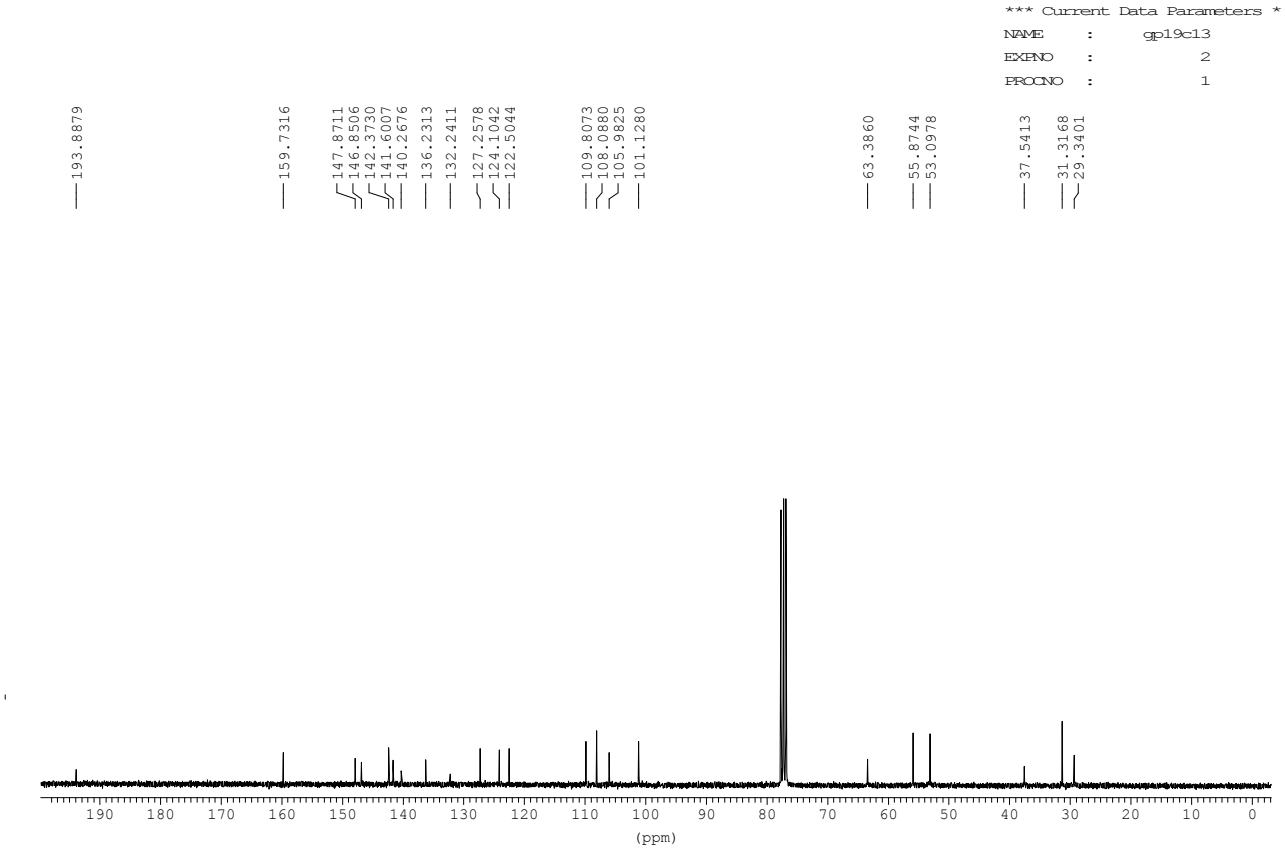
Sample**24**


OCH3
O
N
OCH3

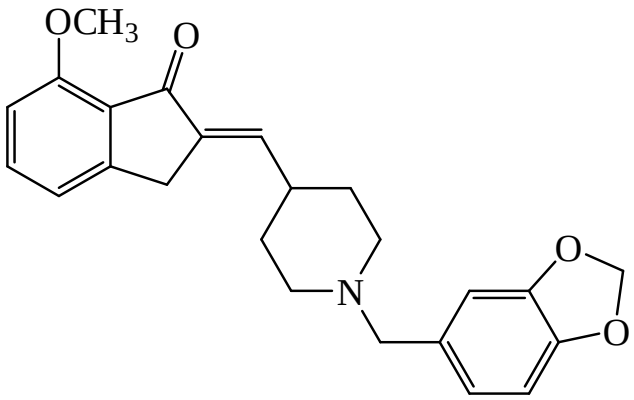

*** Current Data Parameters
NAME : gpl6c13
EXPNO : 1
PROCNO : 1
210
190
170
150
130
110
90
70
50
30
10
-10
(ppm)

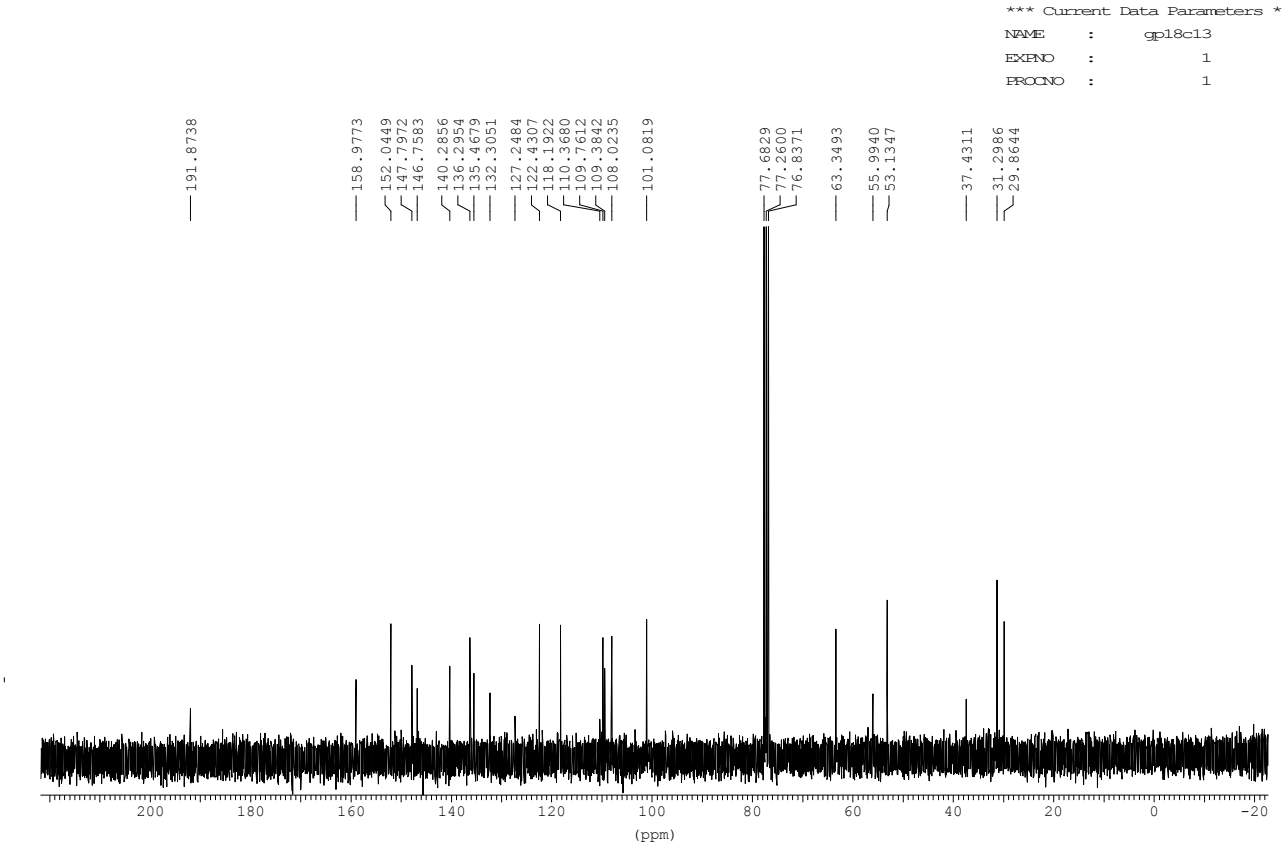
Sample**25**


O
H3CO
N
O
O


*** Current Data Parameters *
NAME : gp19c13
EXPNO : 2
PROCNO : 1
193.8879
159.7316
147.8711
146.8506
142.3730
141.6007
140.2676
136.2313
132.2411
127.2578
124.1042
122.5044
109.8073
108.0880
105.9825
101.1280
63.3860
55.8744
53.0978
37.5413
31.3168
29.3401
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

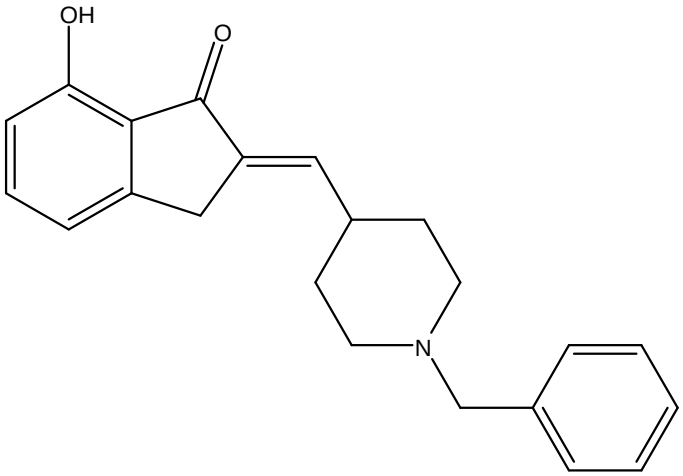
Sample**26**

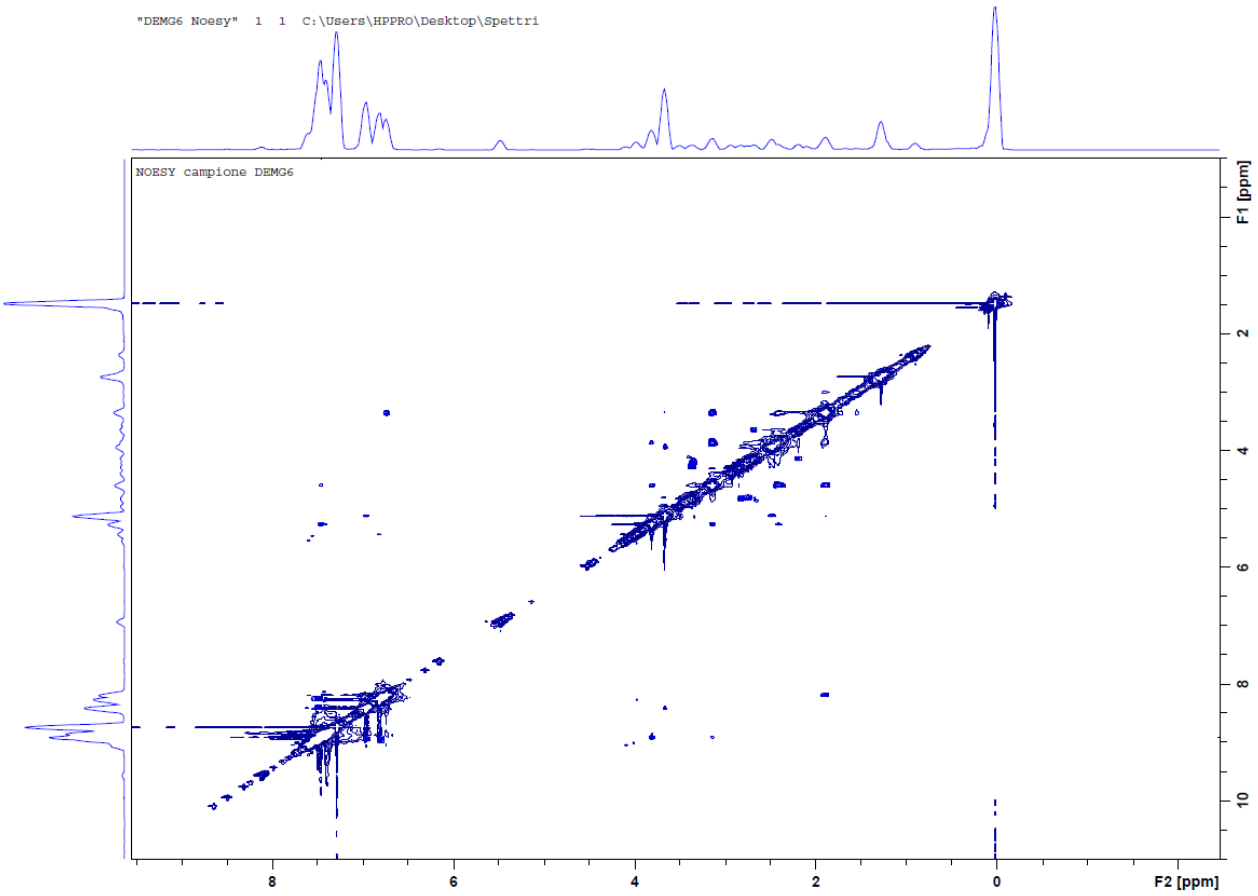

OCH3
O
N
O
O


*** Current Data Parameters *
NAME : gp18c13
EXPNO : 1
PROCNO : 1
191.8738
158.9773
152.0449
147.7972
146.7583
140.2856
136.2954
135.4679
132.3051
127.2484
122.4307
118.1922
110.3680
109.7612
109.3842
108.0235
101.0819
77.6829
77.2600
76.8371
63.3493
55.9940
53.1347
37.4311
31.2986
29.8644
200
180
160
140
120
100
80
60
40
20
0
-20
(ppm)

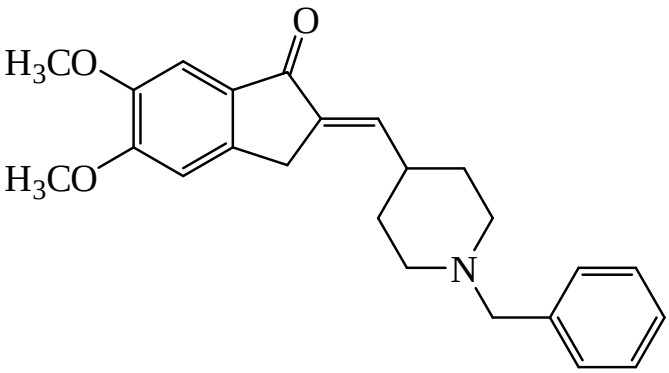
NOESY SPECTRA

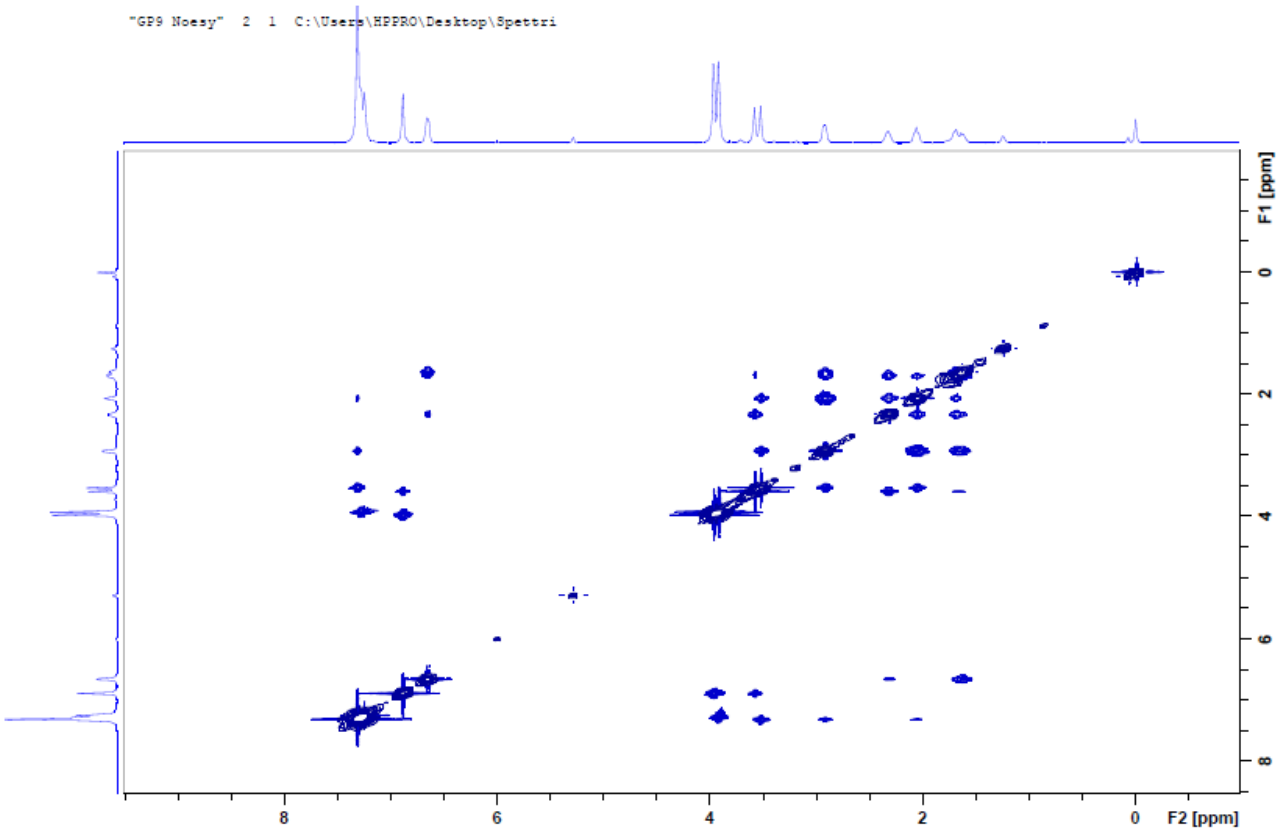
Sample **15**



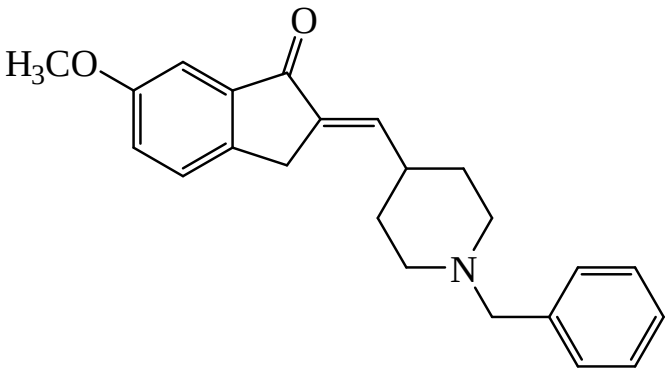


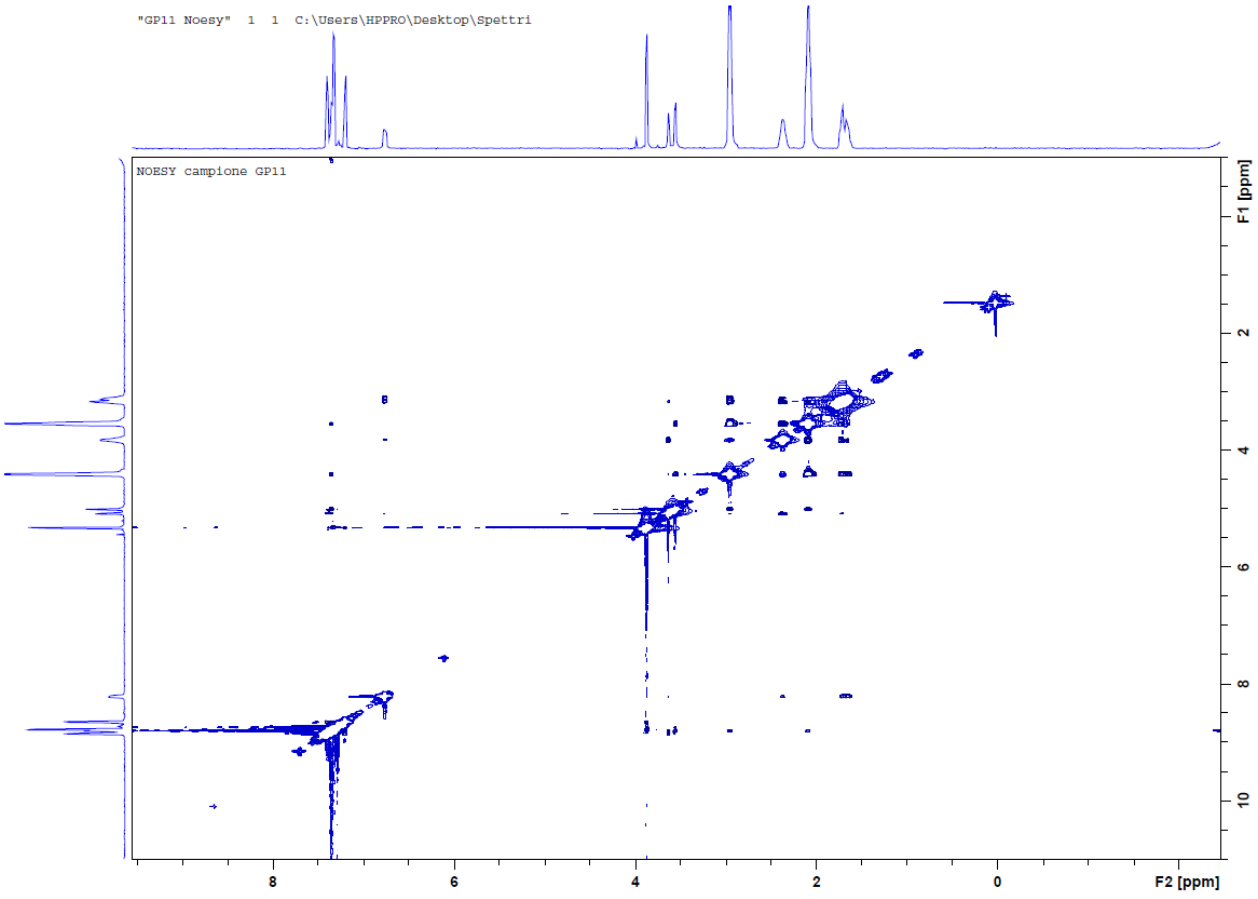
Sample **17**


O
H3CO
H3CO
N

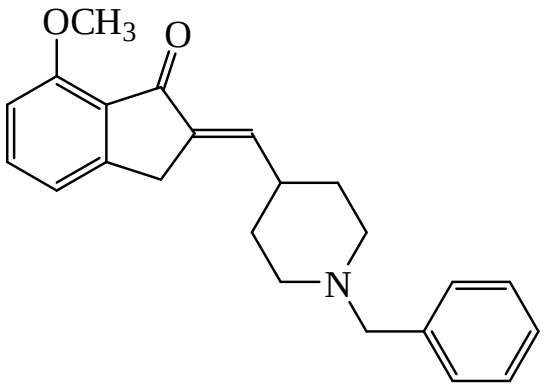

"GP9 Noesy" 2 1 C:\Users\HPPRO\Desktop\Spettri
F1 [ppm]
F2 [ppm]
0
2
4
6
8

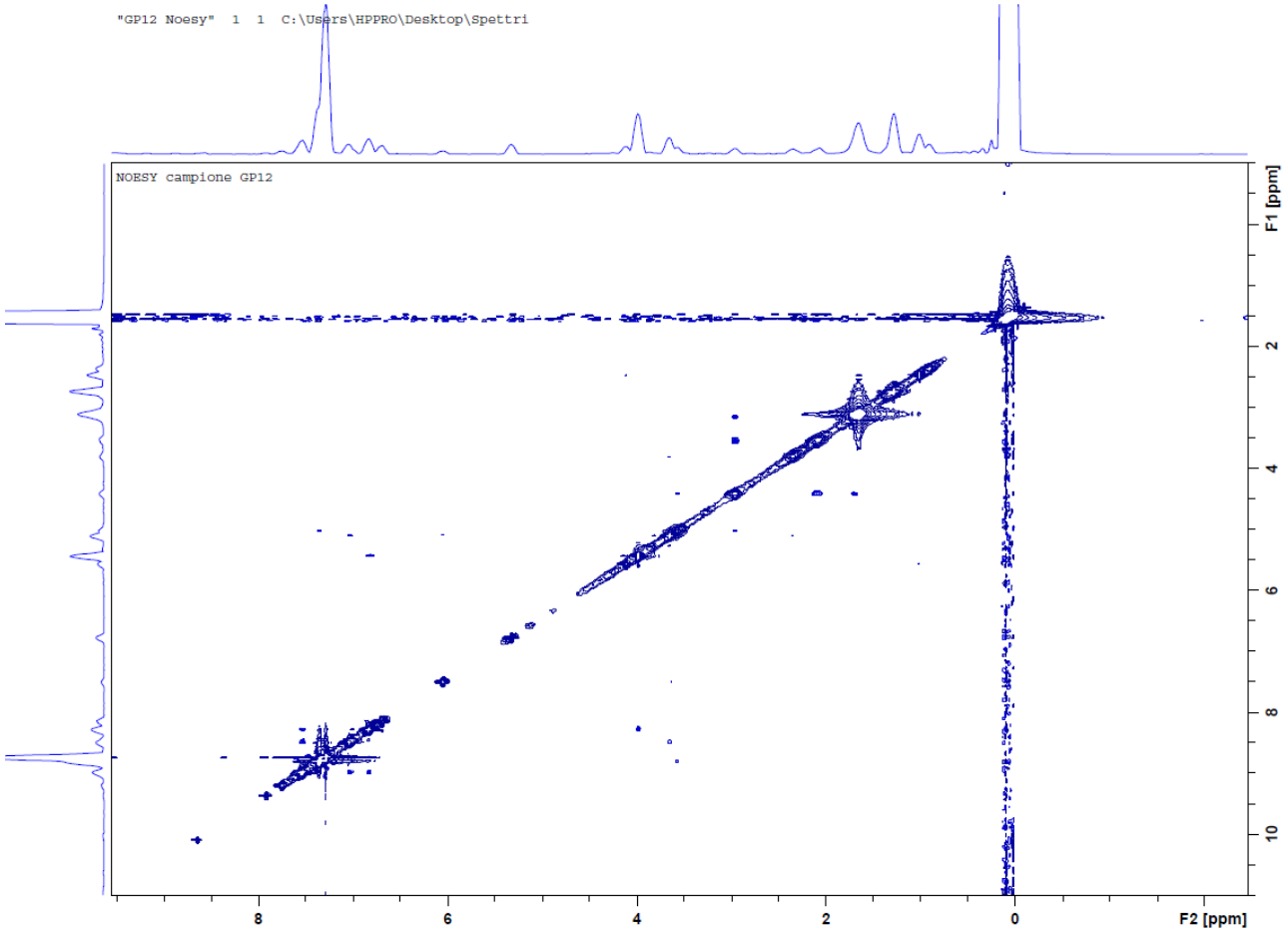
Sample**18**


O
H3CO
N

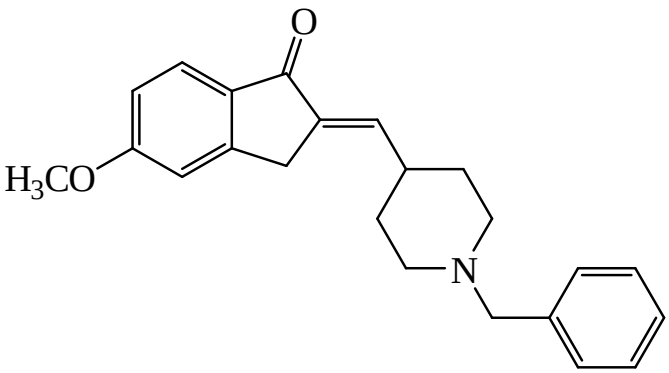

"GP11 Noesy" 1 1 C:\Users\HPPRO\Desktop\Spettri
NOESY campione GP11
F1 [ppm]
F2 [ppm]
2
4
6
8
10
0

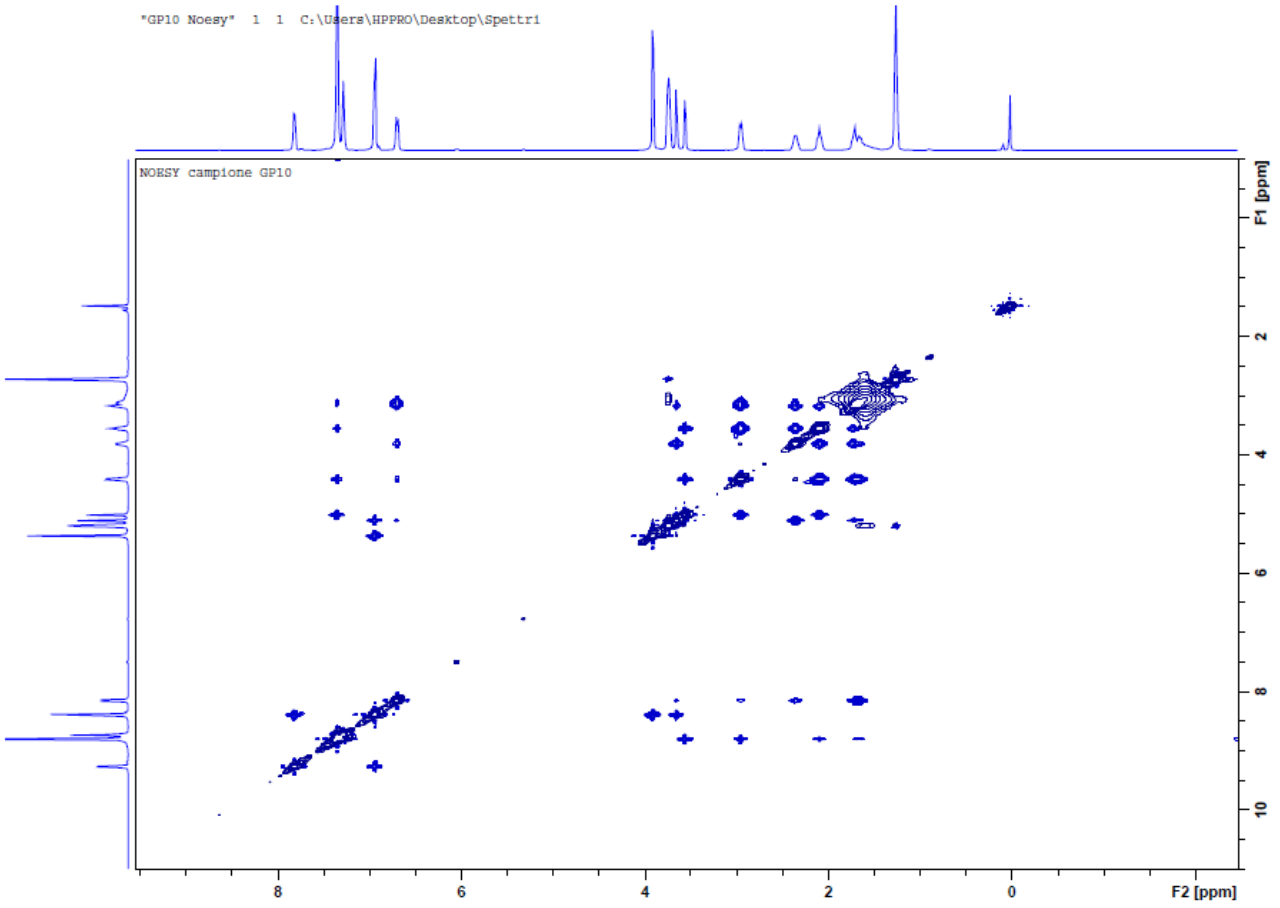
Sample**19**


OCH3
O
N


"GP12 Noesy" 1 1 C:\Users\HPPRO\Desktop\Spettri
NOESY campione GP12
F1 [ppm]
F2 [ppm]
2
4
6
8
10
0

Sample**20**


O
H3CO
N


"GP10 Noesy" 1 1 C:\Users\HPPRO\Desktop\Spettri
NOESY campione GP10
F1 [ppm]
F2 [ppm]
2
4
6
8
10
0