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Electronic Supplementary Information

Synthesis of fluorinated donepezil by palladium-catalyzed decarboxylative allylation of α-fluoro-β-keto ester with tri-substituted heterocyclic alkene and the self-disproportionation of its enantiomers

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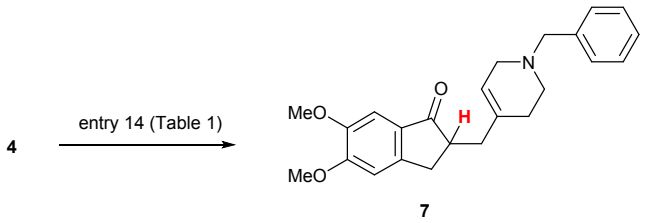


Scheme ES-1. The DcA reaction of **4** to **7**, which is a potential new method for the synthesis of Aricept®

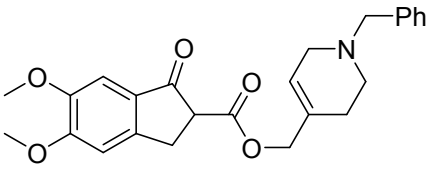
General Information

All reactions were performed in dried glassware under a positive pressure of nitrogen. Solvents were transferred by syringe through a rubber septum. Commercially available chemicals were obtained from Ark Pharm Inc., Aldrich Chemical Co., Nacalai tesque, TCI, Wako and used as received unless otherwise stated. The reactions were monitored by thin-layer chromatography (TLC) performed with 0.25 mm Merck silica-gel (60-F254). The TLC plates were visualized with UV light (254 or 364 nm) and phosphomolybdic acid or *p*-anisaldehyde in ethanol/heat. Column chromatography was performed on a column packed with silica gel 60M spherical neutral size 40-63 μm. ^{1}H (300 MHz), ^{13}C (75.5 MHz) and ^{19}F (282 MHz) NMR spectra for solution in $CDCl_3$ were recorded on Varian Mercury 300. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane (δH = 0.00 ppm) or $CHCl_3$ (δC = 77.0 ppm) or hexafluorobenzene (δF = –162.2 ppm). The following abbreviations were used to show the multiplicities: s: singlet, d: doublet, t: triplet, dd: doublet of doublet, m: multiplet. Optical rotations were measured with a Horiba SEPA-300 operating at 589 nm. High resolution mass spectrometry (HRMS) was carried out on an electrospray ionization mass spectrometer with a micro-TOF analyzer. The wave numbers (ν˜) of recorded IR-signals are quoted in cm^{-1} on a JASCO FT/IR-4100 spectrometer. HPLC analyses were performed on a JASCO U-2080 Plus using 4.6 x 250 mm CHIRALCEL OZ-3 or CHIRALPAK IA column. (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-methanol (**3**)[1] and methyl 2,3-dihydro-5,6-dimethoxy-1-oxo-1*H*-indene-2-carboxylate (**2**)[2] were prepared referring to previously reported procedure.

Preparation of β-ketoallyl ester 4

(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-methanol (**3**) (1.52 g, 7.5 mmol), methyl 2,3-dihydro-5,6-dimethoxy-1-oxo-1*H*-indene-2-carboxylate (**2**) (1.25 g, 5.0 mmol) and *N*,*N*-dimethylamino pyridine (61.1 mg, 0.5 mmol) were dissolved in toluene (10 mL) and the mixture was heated to 120 ˚C. After stirring for 6 h, the solvent was removed under reduced pressure. The residure was purified by flash silica-gel column chromatography (CH_2Cl_2 / Et_2O / diethylamine = 2/ 1 / 0.05) to give the desired product.

(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl 2,3-dihydro-5,6-dimethoxy-1-oxo-1*H*-indene-2-carboxylate (4)



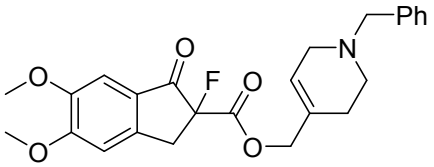
Slightly yellow solid; 1.59 g; 75% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5H), 7.17 (s, 1H), 6.91 (s, 1H), 5.74 (s, 1H), 4.60 (m, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 3.73 (dd, *J* = 3.6, 8.0 Hz, 1H), 3.59 (s, 1H), 3.45 (dd, *J* = 3.6, 17.1 Hz, 1H), 3.27 (dd, *J* = 8.1, 17.1 Hz, 1H), 3.01 (s, 2H), 2.61 (t, *J* = 5.7, 2H), 2.19 (bs, 2H) ppm. **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 197.6, 169.0, 155.8, 149.5, 148.9, 137.9, 131.0, 128.9, 128.0, 127.7, 126.8, 123.8, 107.0, 104.5, 68.1, 62.4, 56.1, 55.8, 53.3, 52.2, 49.1, 29.8, 26.3 ppm. **IR** (KBr):

$\tilde{\nu}$ = 2923, 2819, 2753, 2370, 2343, 1732, 1702, 1591, 1500, 1465, 1450, 1364, 1303, 1268, 1208, 1184, 1152, 1107, 1032, 973, 918, 861, 848, 737, 699 cm^{-1}. **HRMS** (ESI) *m*/*z*: $[M+H]^+$ Calcd. for $C_{25}H_{28}NO_5$ 422.1967; Found 422.1969.

Preparation of α-fluoro-β-ketoallyl ester 5

To a 0 ˚C suspension of NaH (95%, 186 mg, 7.77 mmol) in THF (40 mL) was added a solution of (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl 2,3-dihydro-5,6-dimethoxy-1-oxo-1*H*-indene-2-carboxylate (2.52 g, 5.98 mmol) in THF (10 mL) dropwise and the mixture was stirred for 1 hour, then a solution of *N*-fluorobenzenesulfonimide (2.83 g, 8.97 mmol) in THF (10 mL) was added dropwise to the mixture. After stirring for 2 hours at 0 ˚C, the reaction was quenched by adding water and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2 / Et_2O / diethylamine = 2 / 1 / 0.05) to give the desired product.

(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl 2-fluoro-2,3-dihydro-5,6-dimethoxy-1-oxo-1*H*-indene
-2-carboxylate (5)



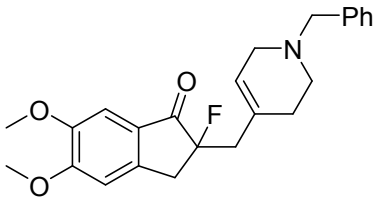
Yellow powder; 1.96 g; 75% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 5H), 7.21 (s, 1H), 6.89 (s, 1H), 5.65 (s, 1H), 4.63 (s, 2H), 4.00 (s, 3H), 3.92 (s, 3H), 3.69 (dd, *J* = 10.8, 17.6 Hz, 1H), 3.56 (s, 2H), 3.34 (dd, *J* = 17.7, 22.4 Hz, 1H), 2.97 (s, 2H), 2.56 (t, *J* = 5.7 Hz, 2H), 2.06 (s, 2H) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −164.1 (dd, *J* = 11.0, 21.7 Hz, 1F) ppm. **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 193.2 (d, *J* = 18.8 Hz), 167.2 (d, *J* = 28.2 Hz), 157.0, 150.1, 146.7 (d, *J* = 3.9 Hz), 137.8, 130.3, 128.9, 128.0, 126.9, 125.8, 124.4, 107.2, 105.2, 94.8 (d, *J* = 201.4 Hz), 68.8, 62.3, 56.3, 56.0, 52.1, 49.0, 37.8 (d, *J* = 24.4 Hz), 26.2 ppm. **IR** (KBr): $\tilde{\nu}$ = 2940, 2802, 2364, 1765, 1713, 1589, 1504, 1456, 1366, 1324, 1274, 1225, 1187, 1103, 1073, 921, 864, 775, 744, 701 cm^{-1}. **HRMS** (ESI) *m*/*z*: $[M+H]^+$ Calcd. for $C_{25}H_{27}FNO_5$ 440.1873; Found 440.1873.

General procedure for the DcA reaction

Pd_2dba_3 (5 mol%) and ligand (12.5 mol%) were dissolved in cyclopentylmethylether (CPME) (1.2 mL) and the mixture was stirred for 2 hours under nitrogen atmosphere. To the solution was added the substrate (0.05 mmol), additive (5.0 equiv.) and CPME (1.3 mL). The resulting mixture was stirred at prescribed temperature. After completion of the reaction, solvent was removed under reduced pressure and the residue

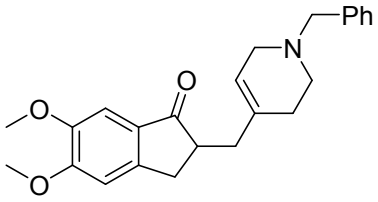
was purified by flash silica-gel column chromatography (CH_2Cl_2 / Et_2O / diethylamine = 3 / 2 / 0.06) to give the desired product.

(±)-2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)-2-fluoro-2,3-dihydro-5,6-dimethoxyinden-1-one (6)



The reaction was performed by Pd_2dba_3 (5 mol%), 1,1-bis(diphenylphosphino)ferrocene (12.5 mol%) and **5** (0.05 mmol) in CPME (2.5 mL) for 5 hours at 40 ˚C. Yellow solid; 16.9 mg; 77% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 5H), 7.19 (s, 1H), 6.83 (s, 1H), 5.49 (s, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.55 (s, 2H), 3.42 (dd, *J* = 11.4, 17.3 Hz, 1H), 3.19 (dd, *J* = 17.4, 22.1 Hz, 1H), 2.97 (s, 2H), 2.77 (t, *J* = 14.1 Hz, 1H), 2.58–2.43 (m, 2H), 2.38–2.04 (m, 4H) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −154.3 (m, 1F) ppm. **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 199.0 (d, *J* = 18.3 Hz), 156.6, 149.8, 145.9 (d, *J* = 4.4 Hz), 138.0, 131.1 (d, *J* = 3.3 Hz), 128.9, 128.0, 126.8, 126.1, 124.4, 107.3, 104.9, 98.0 (d, *J* = 187.5 Hz), 62.3, 56.1, 55.9, 52.5, 49.5, 41.7 (d, *J* = 24.4 Hz), 37.0 (d, *J* = 24.9 Hz), 30.1(d, *J* = 2.3 Hz) ppm. **IR** (KBr): ν̃ = 3006, 2959, 2928, 2911, 2833, 2780, 2319, 1708, 1604, 1589, 1502, 1456, 1423, 1363, 1312, 1283, 1221, 1176, 1121, 1074, 1053, 1025, 996, 961, 905, 867, 839, 779, 744, 703, 663 cm^{-1}. **HRMS** (ESI) *m*/*z*: $[M+H]^+$ Calcd. for $C_{24}H_{27}FNO_3$ 396.1975; Found 396.1975.

(±)-2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)-2,3-dihydro-5,6-dimethoxyinden-1-one (7)



The reaction was performed by 1,1-bis(diphenylphosphino)ferrocene (12.5 mol%) and **4** (0.05 mmol) in CPME (2.5 mL) for 5 hours at 40 ˚C. Yellow solid; 16.7 mg; 76% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 5H), 7.17 (s, 1H), 6.86 (s, 1H), 5.43 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.59 (s, 2H), 3.17 (dd, J = 7.2, 16.8 Hz, 1H), 2.99 (s, 2H), 2.83–2.67 (m, 3H), 2.58 (t, *J* = 5.4 Hz, 2H), 2.15–1.95 (m, 3H) ppm. **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 207.1, 155.4, 149.3, 149.0, 138.1, 134.3, 129.1, 128.1, 126.9, 120.6, 107.3, 104.2, 62.6, 56.1, 56.0, 52.7, 49.7, 45.6, 39.0, 32.2, 29.0 ppm. **IR** (KBr): ν̃ = 2927, 2904, 2804, 2362, 2312, 1683, 1592, 1500, 1456, 1363, 1316, 1266, 1216, 1119, 1046, 968, 864, 744, 701 cm^{-1}. **HRMS** (ESI) *m*/*z*: $[M+H]^+$ Calcd. for $C_{24}H_{28}NO_3$ 378.2069; Found 378.2066.

(–)-2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)-2-fluoro-2,3-dihydro-5,6-dimethoxyinden-1-one (6)

The reaction was performed by Pd_2dba_3 (5 mol%), (*R*, R_p)-Ph-Taniaphos (12.5 mol%) and **5** (0.05 mmol), water (0.0018 wt%) in CPME (25 mL) for 36 hours at room temperature. Yellow solid; 16.8 mg; 85% yield, 46% ee. $[\alpha]_D^{25}$ = –28.2 (*c* = 0.54, $CHCl_3$, 46% ee). **HPLC** (CHIRALCEL OZ-3, 4.6 x 250 mm, EtOH = 100, 0.25 vol% ethanolamine, flow rate 0.5 ml/min, λ = 300 nm), t_R = 13.0 min (minor), 14.4 min (major), 46% ee. Spectral data for (–)-**6** (^{1}H NMR, ^{19}F NMR, ^{13}C NMR, IR, HRMS) corresponded to (±)-**6**.

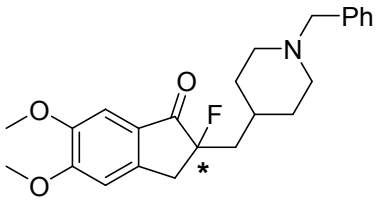
(+)-2-((1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methyl)-2-fluoro-2,3-dihydro-5,6-dimethoxyinden-1-one (6)

The reaction was performed by Pd_2dba_3 (5 mol%), (*S*, S_p)-Ph-Taniaphos (12.5 mol%) and **5** (0.05 mmol), water (0.0018 vol%) in CPME (25 mL) for 40 hours at room temperature. Yellow solid; 14.0 mg; 71% yield, 45% ee. $[\alpha]_D^{25}$ = +23.4 (*c* = 0.47, $CHCl_3$, 45% ee). **HPLC** (CHIRALCEL OZ-3, 4.6 x 250 mm, EtOH = 100, 0.25 vol% ethanolamine, flow rate 0.5 ml/min, λ = 300 nm), t_R = 12.5 min (major), 13.8 min (minor), 45% ee. Spectral data for (+)-**6** (^{1}H NMR, ^{19}F NMR, ^{13}C NMR, IR, HRMS) corresponded to (±)-**6**.

Hydrogenolysis of compound 6

To a solution of (–)-**6** (16.3 mg, 46% ee, 0.041 mmol) in degassed THF (1.4 mL) was added Platinum-Activated Carbon (2%, 40 mg, 0.0041 mmol) and the mixture was hydrogenated by H_2 gas under atmospheric pressure at room temperature. After 1 hour, the reaction mixture was filtered with THF through a pad of celite. Solvent was removed under reduced pressure and the residue was purified by flash silica-gel column chromatography (CH_2Cl_2 / MeOH = 95 / 5) to give the desired product.

(–)-2-((1-benzylpiperidin-4-yl)methyl)-2-fluoro-2,3-dihydro-5,6-dimethoxyinden-1-one (1a)



White solid; 10.4 mg; 64% yield; 50% ee. $[\alpha]_D^{25}$ = –5.94 (*c* = 0.35, $CHCl_3$, 50% ee). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 5H), 7.20 (s, 1H), 6.83 (s, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.47 (s, 2H), 3.32 (s, 1H), 3.26 (d, *J* = 4.8 Hz, 1H), 2.84 (d, *J* = 9.6 Hz, 2H), 2.07–1.91 (m, 3H), 1.75–1.64 (m, 4H), 1.39 (m, 2H) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −155.3 (m, 1F) ppm. **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ = 199.5 (d, *J* = 18.8 Hz), 156.7, 150.0, 145.8 (d, *J* = 4.5 Hz), 138.4, 129.2, 128.1, 126.9, 126.5 (d, *J* = 1.7 Hz), 107.4, 105.2, 98.4 (d, *J* = 185.9 Hz), 63.4, 56.4, 56.2, 53.7, 53.6, 41.2 (d, *J* = 23.8 Hz), 38.8 (d, *J* = 25.4 Hz), 33.3, 31.8 (d, *J* = 3.3 Hz) ppm. **IR** (KBr): ν̃ = 3033, 2948, 2928, 2850, 2804, 2753, 2370, 2320, 1704, 1604,

1590, 1505, 1457, 1369, 1328, 1317, 1293, 1261, 1221, 1122, 1059, 1034, 994, 979, 856, 782, 768, 736, 697 cm^{-1}. **HRMS** (ESI) *m*/*z*: $[M+H]^+$ Calcd. for $C_{24}H_{29}FNO_3$ 398.2131; Found 398.2119. **HPLC** (CHIRALPAK IA, 4.6 x 250 mm, Hexane / *i*PrOH = 70 / 30, flow rate 0.5 ml/min, λ = 271 nm), t_R = 17.7 min (major), 22.7 min (minor), 50% ee.

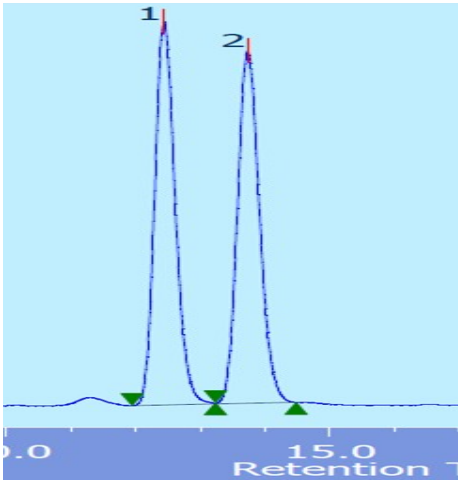
SDE of 1a using a column chromatography with an achiral phase

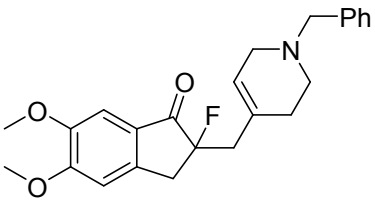
5 g of silica-gel (60N spherical neutral size 40-50μm) was packed in 15 mm diameter of a glass column with hexane / ethyl acetate = 2 / 8 as the eluent under atmospheric pressure at room temperature. A solution of **1a** with 44% ee was loaded on this packed column following which this column was pressurized at the abovementioned pressure and fractions (each 3.0 mL) were collected until no more **1a** was detected by TLC analysis. Each fraction was then subjected to high-performance liquid chromatography (HPLC) analysis to determine enantiomeric excess (ee).

References

1. H. J. M. Gijsen, M. J. A. De Cleyn, C. J. Love, M. Surkyn, S. F. A. V. Brandt, M. G. C. Verdonck, L. Moens, J. Cuypers and J.-P. R. M. A. Bosmans, *Tetrahedron*, 2008, **64**, 2456.
2. X. Wang, H. Zhang, X. Yang, J. Zhao and C. Pan, *Chem. Commun.,* 2013, **49**, 5405.

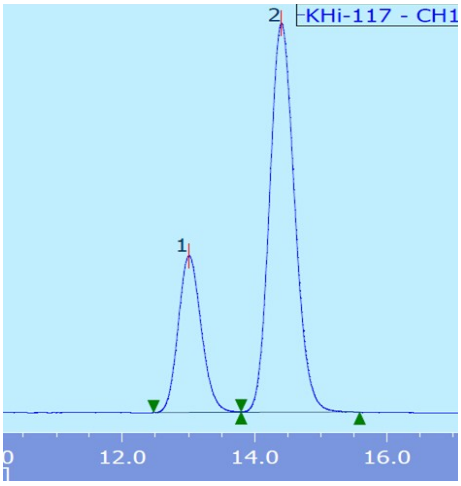
HPLC chromatograms of (±)-6, (–)-6 and (+)-6

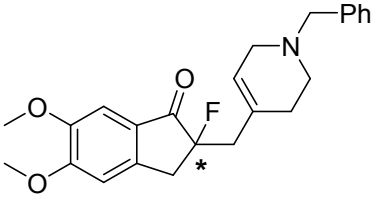




(±)-**6**

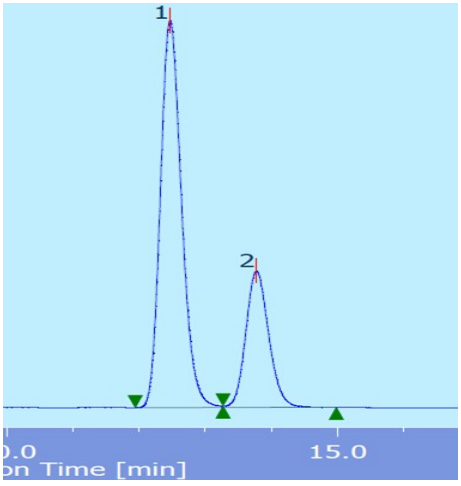
No.	t_R (min)	Area (%)	High (%)
1	12.433	50.255	52.089
2	13.725	49.745	47.911

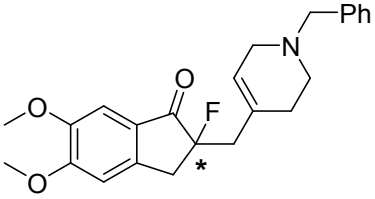




(–)-**6**

No.	t_R (min)	Area (%)	High (%)
1	13.008	27.127	28.734
2	14.400	72.873	71.266

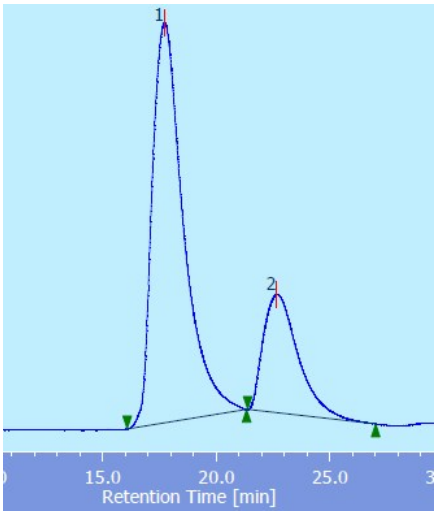


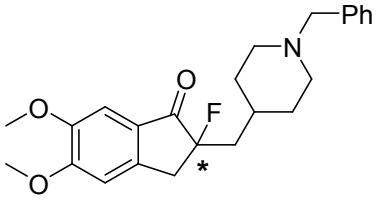


(+)-**6**

No.	t_R (min)	Area (%)	High (%)
1	12.467	72.287	73.913
2	13.767	27.713	26.087

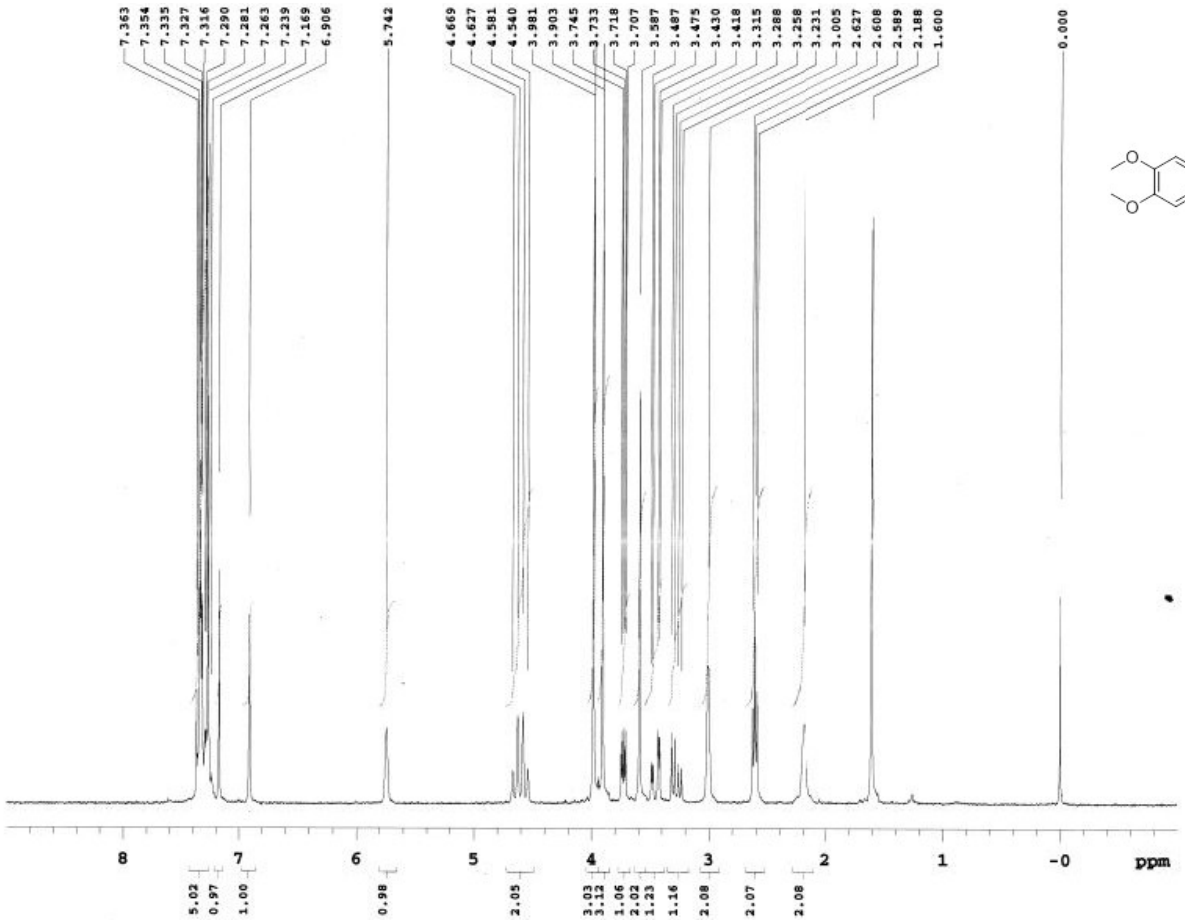
HPLC chromatograms of (–)-1a

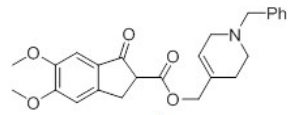




(–)-**1a**

No.	t_R (min)	Area (%)	High (%)
1	17.717	75.181	77.153
2	22.658	24.819	22.847





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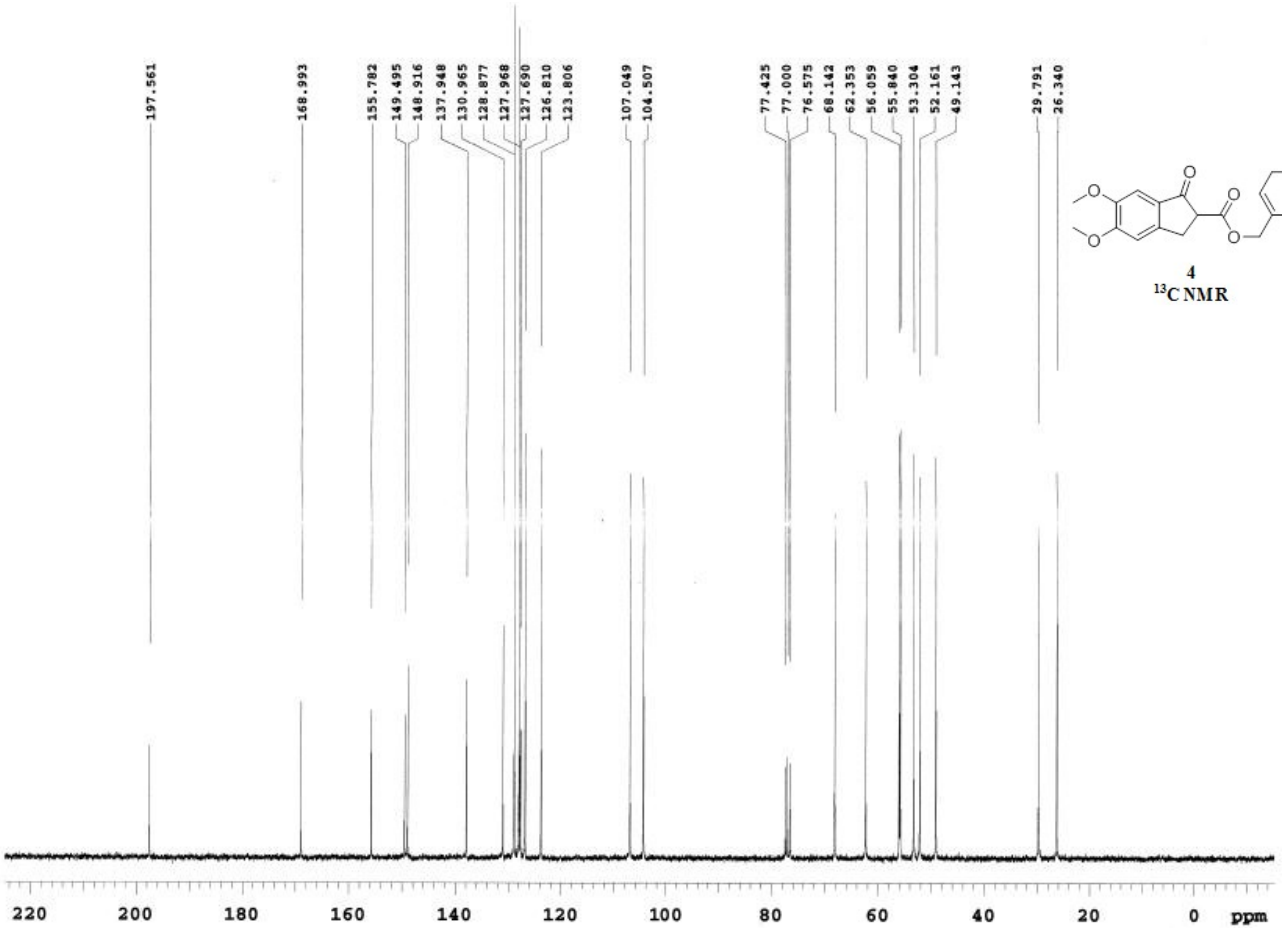
^{1}H NMR



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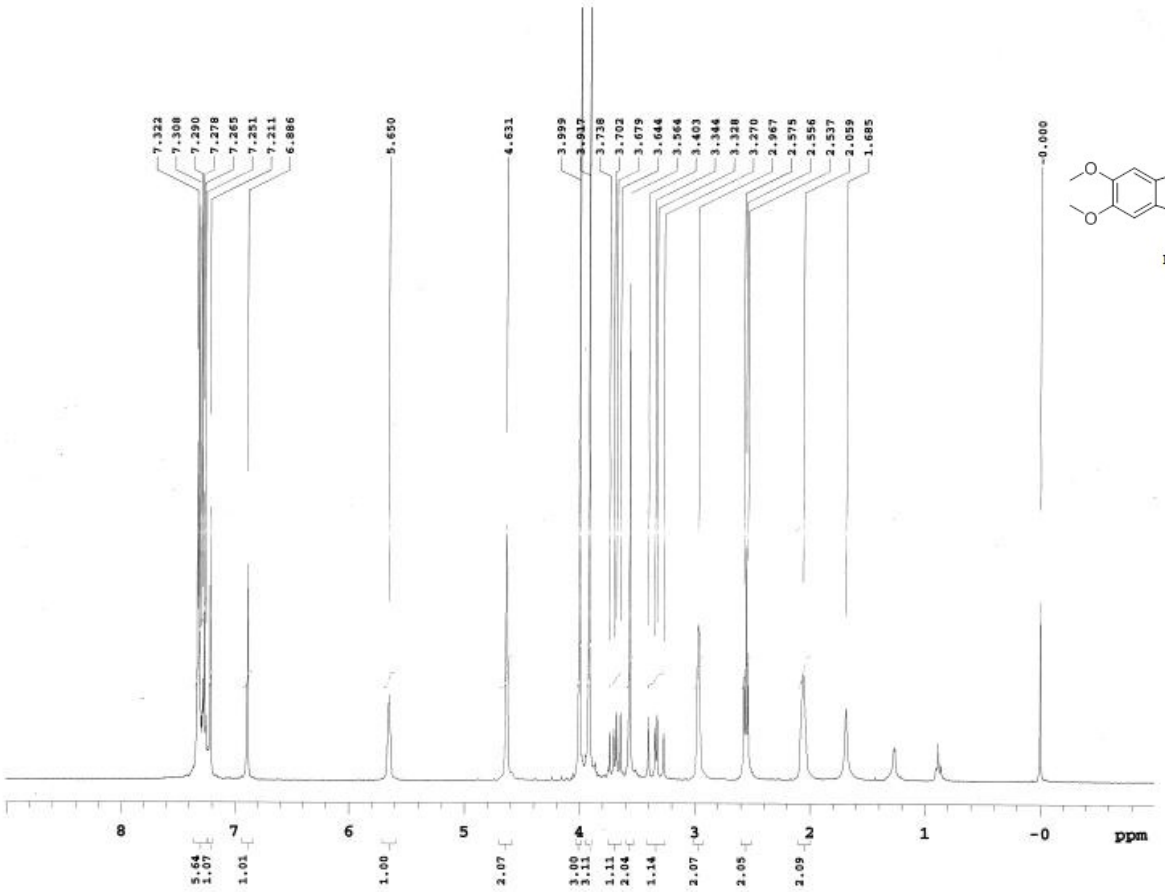
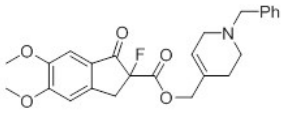
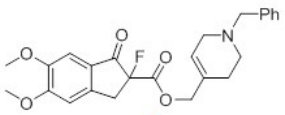
^{13}C NMR





5
^{1}H NMR



5
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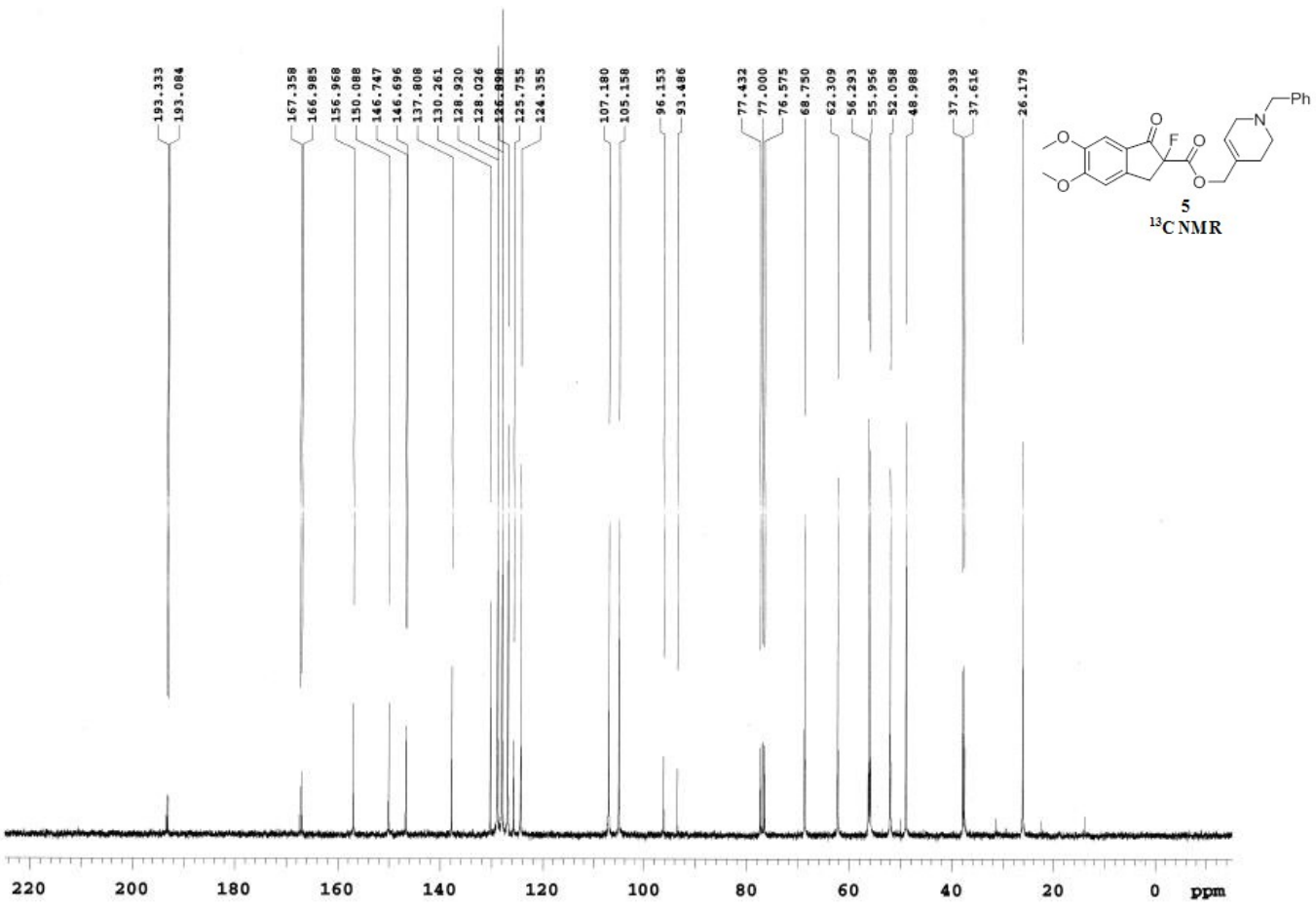

5
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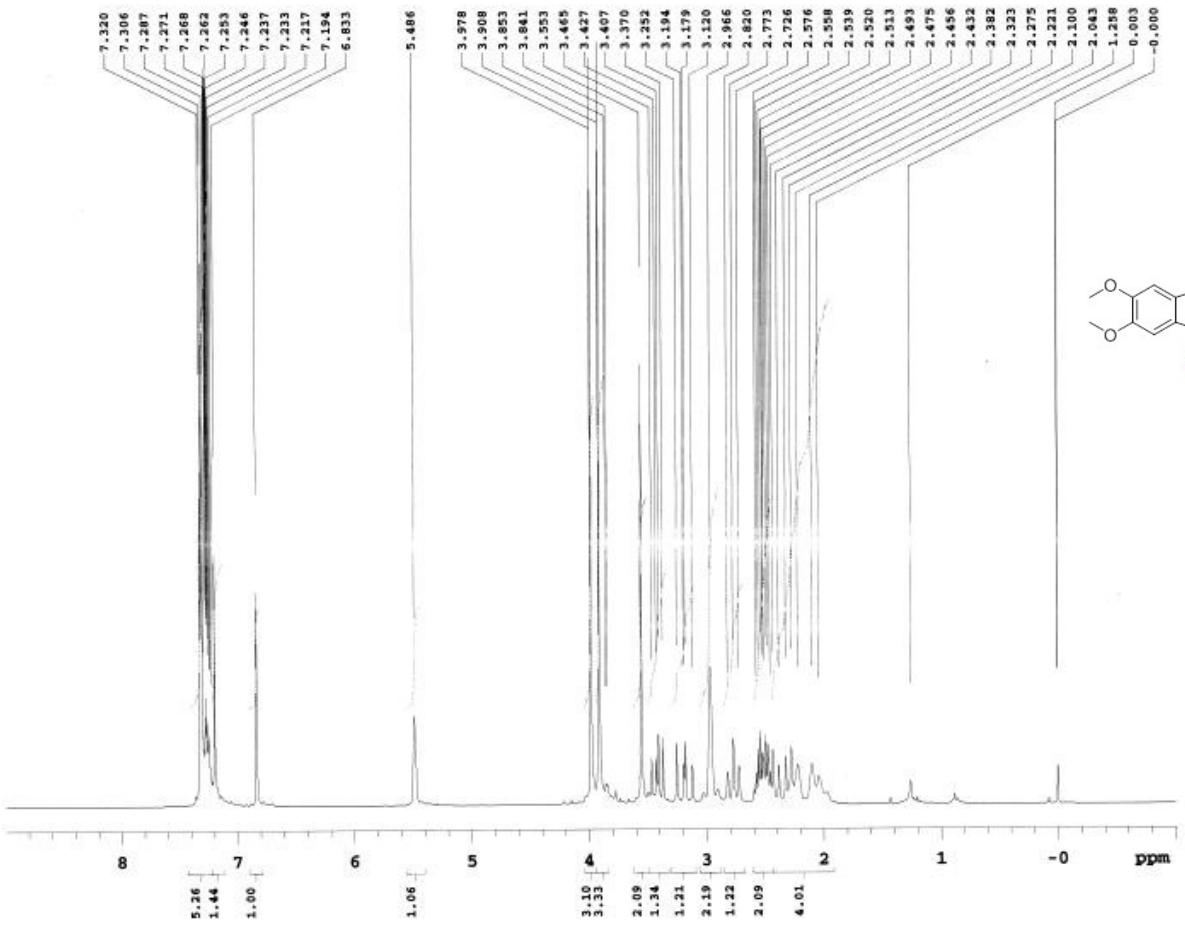

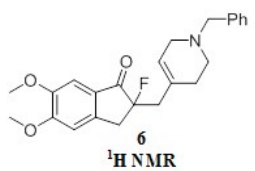

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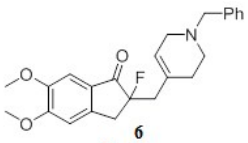
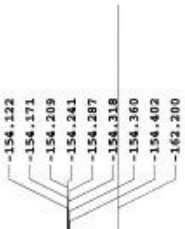
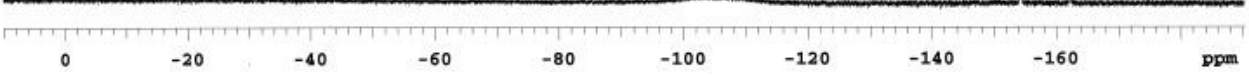
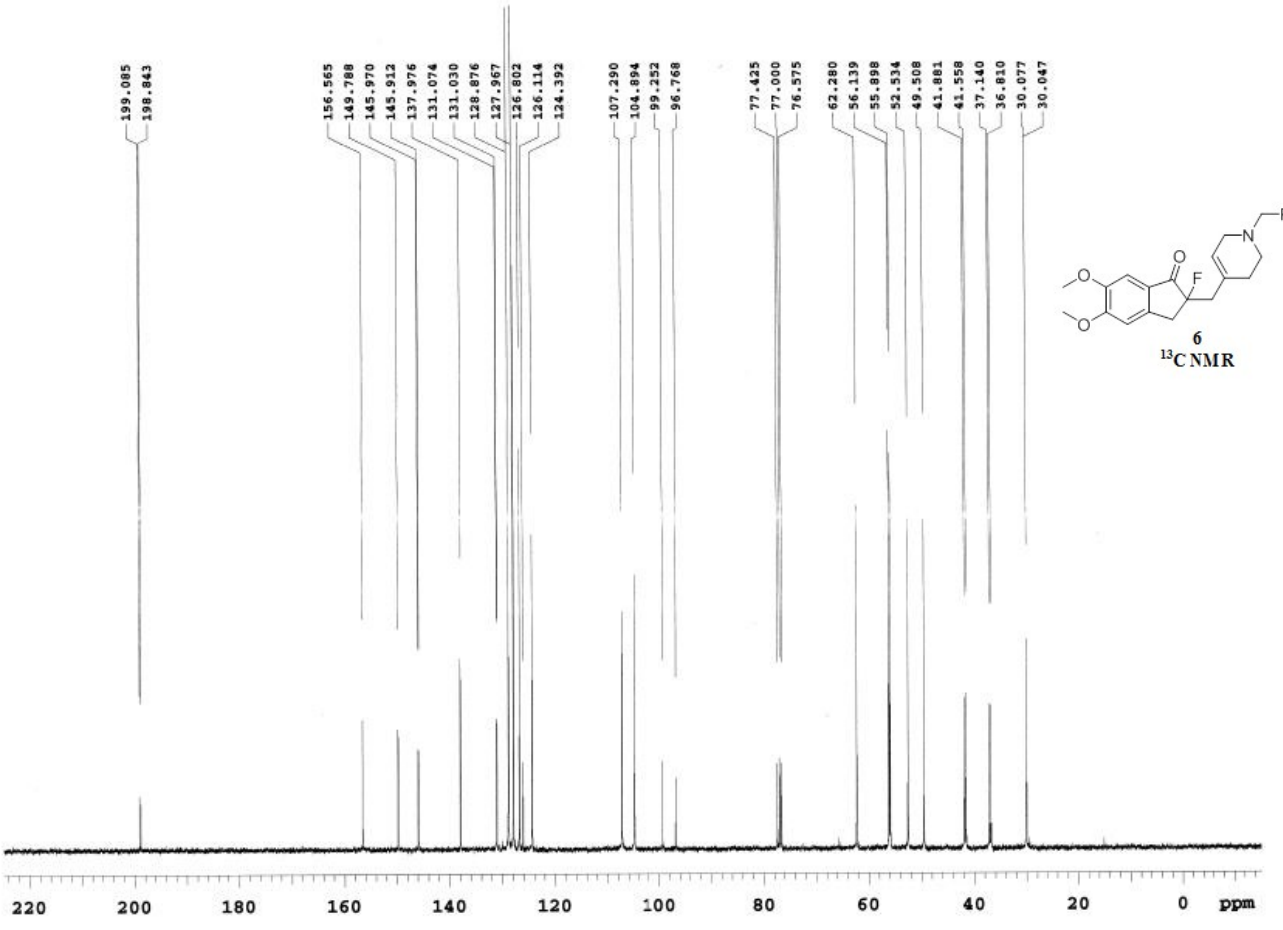


6

^{19}F NMR







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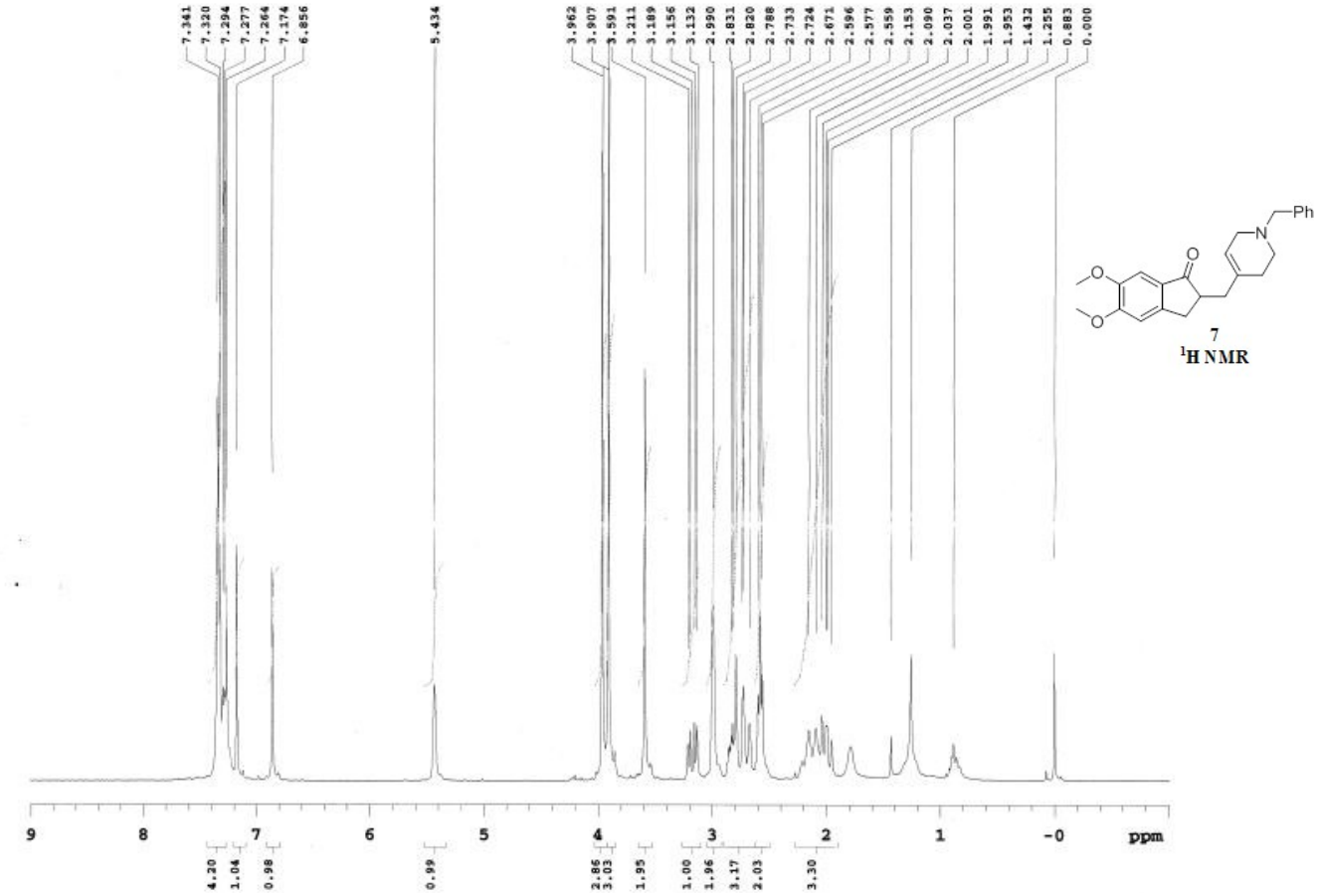
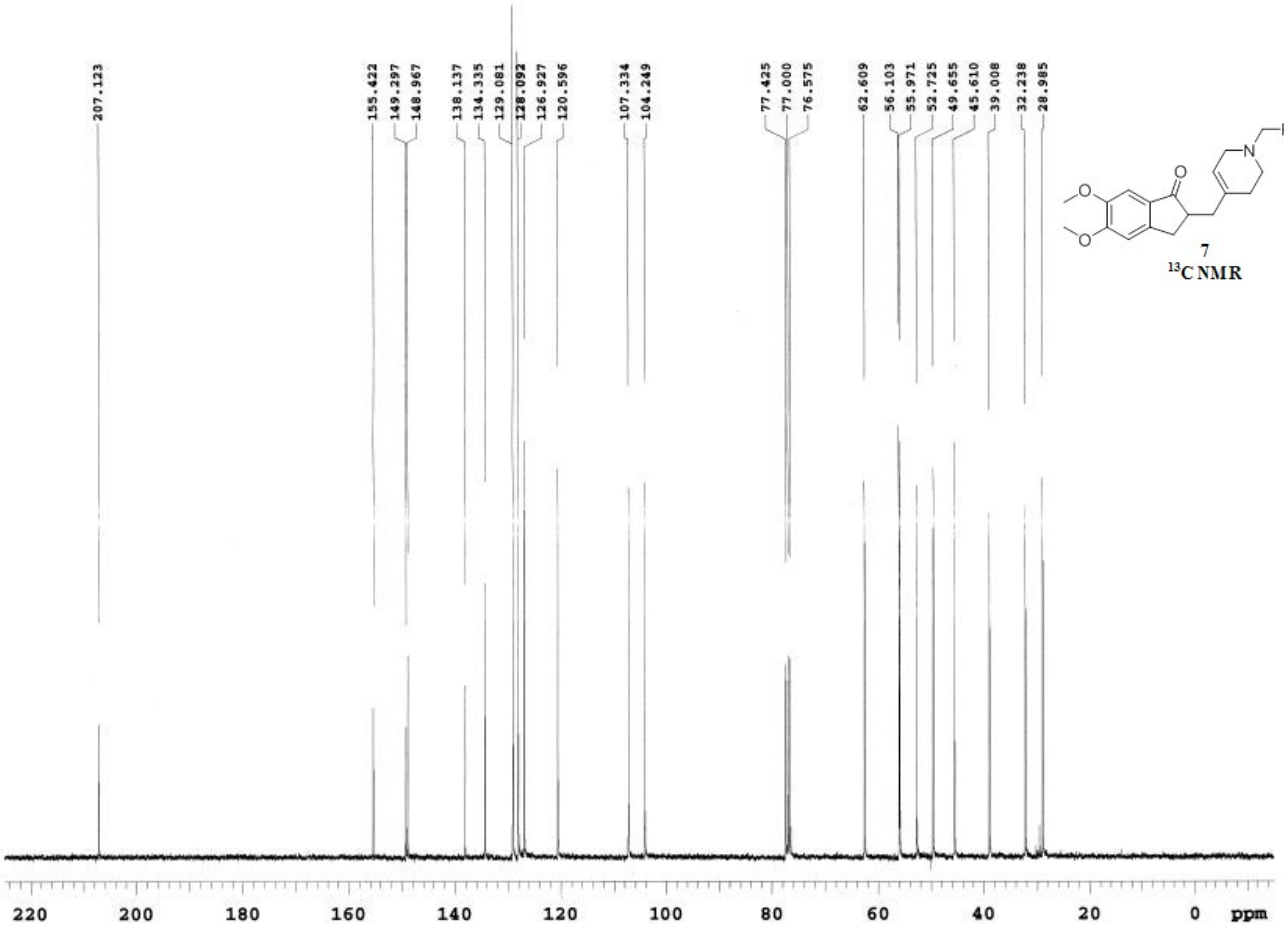


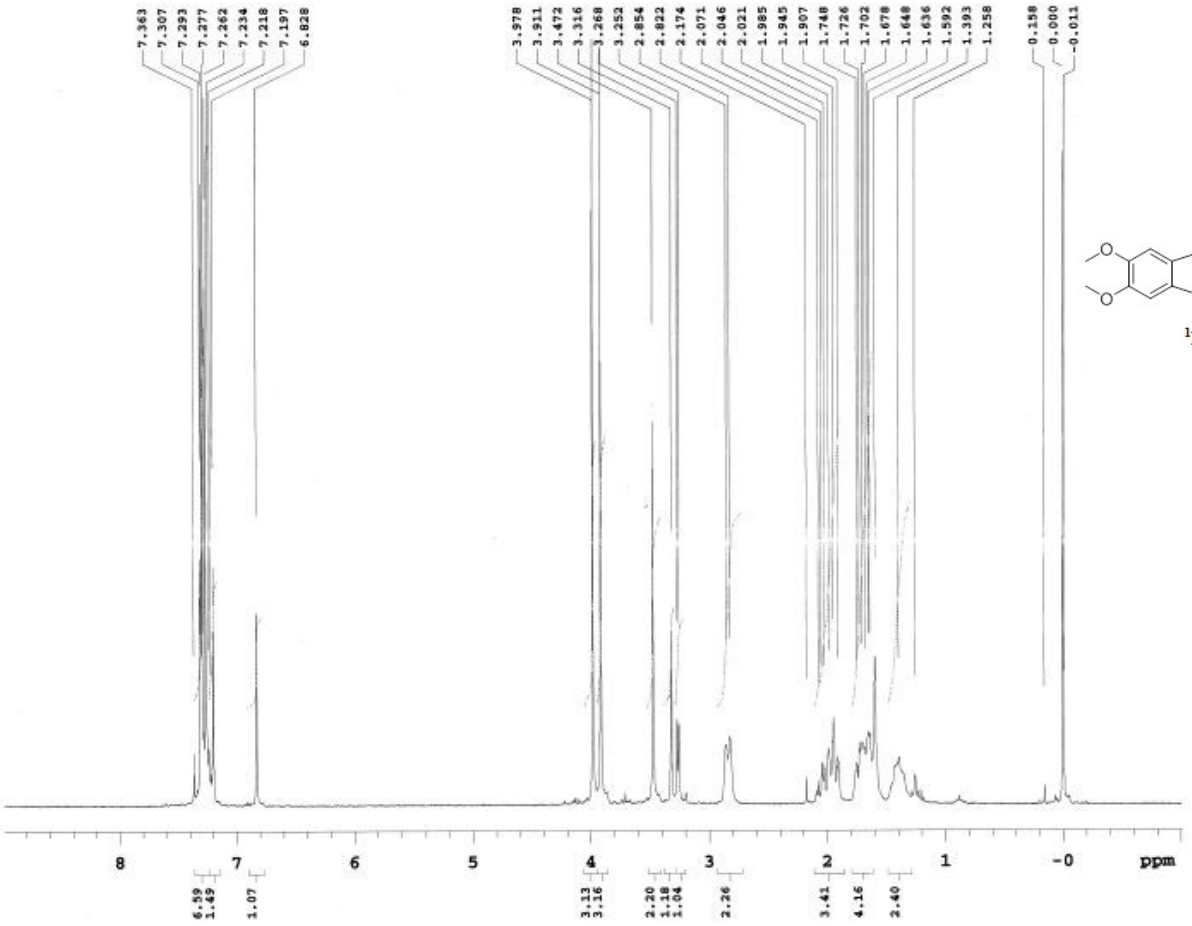
7

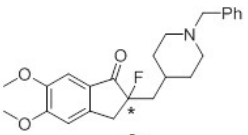
^{1}H NMR



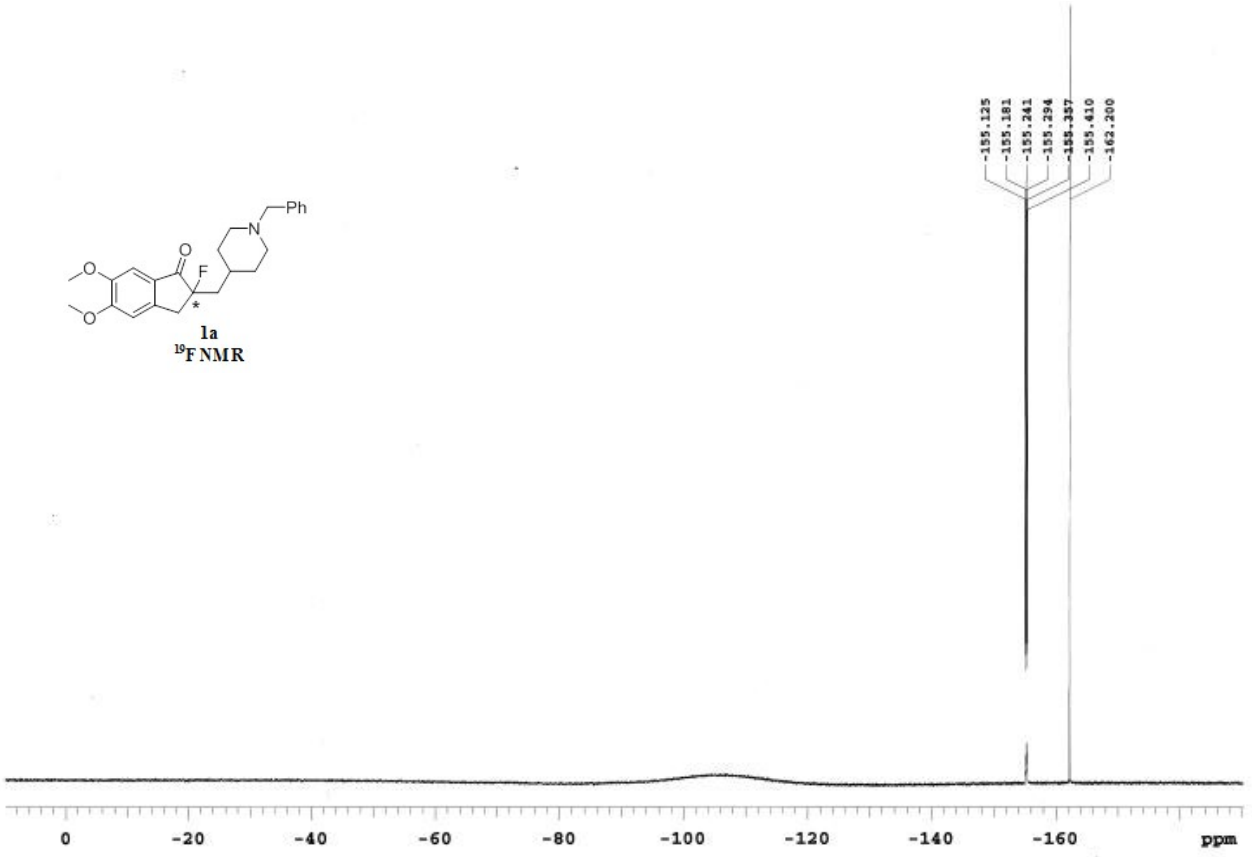
7

^{13}C NMR

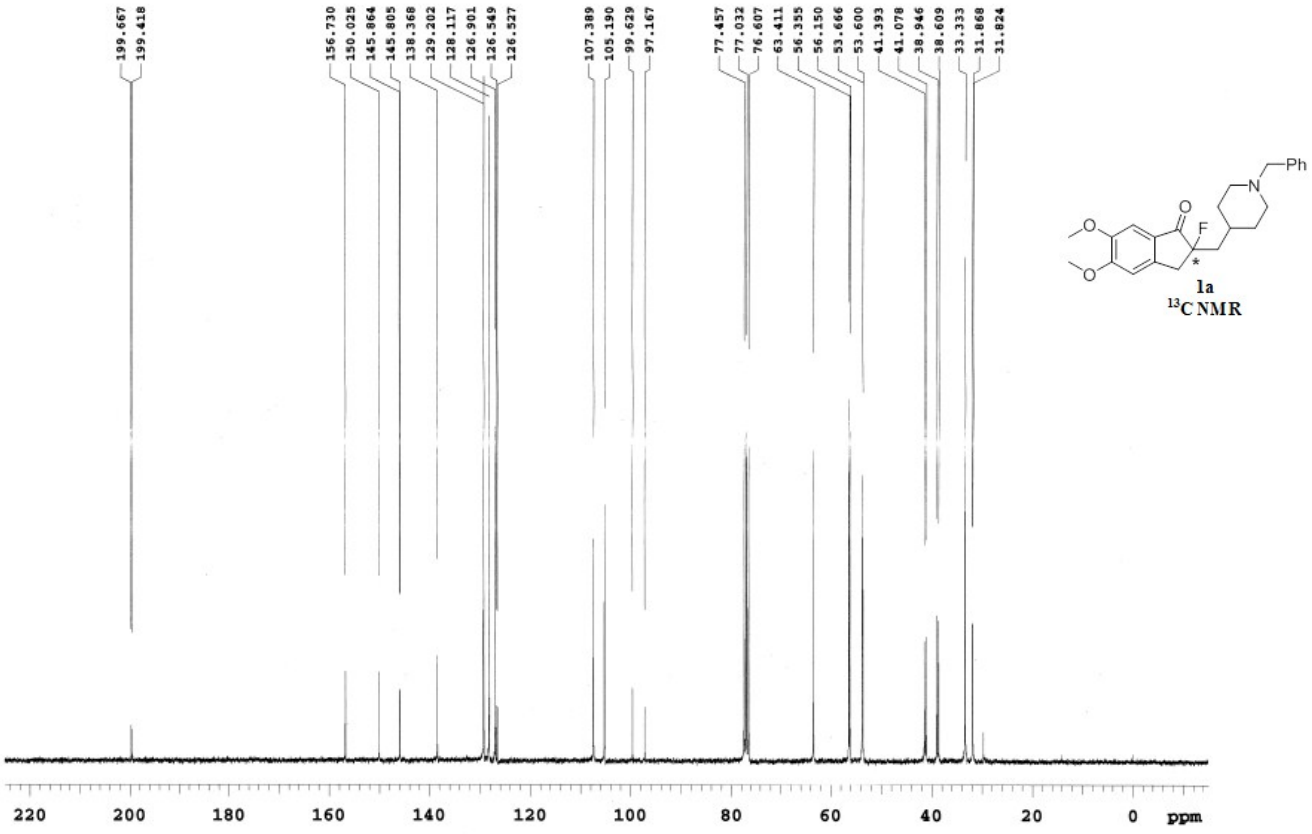




1a
^{1}H NMR



1a
^{19}F NMR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41.078
38.946
38.609
33.333
31.868
31.824
Ph
N
O
F
O
O
*
220
200
180
160
140
120
100
80
60
40
20
0
ppm

1a
^{13}C NMR