Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

DEVELOPMENT OF NOVEL TRIAZOLE BASED DENDRIMER SUPPORTED SPIROBORATE CHIRAL CATALYSTS FOR THE REDUCTION OF (E)-O-BENZYL OXIME: AN ENANTIOSELECTIVE SYNTHESIS OF (S)-DAPOXETINE

Anandhan Ramasamy*[a], Mandapati Bhargava Reddy[a] and Sasikumar Murugesan [b]

[a]*Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India. E-mail: ananthanramasamy@gmail.com; Tel: +91 044 22202881.*

[b]*Department of Chemistry, Vel Tech Rangarajan Dr. Sagunthala R&D Institute of Science and Technology, Avadi, Chennai, 600062.*

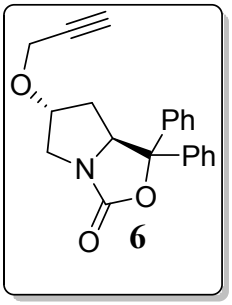
Experimental Procedure:

General Experimental Details:

Infrared spectra for synthesized compounds were recorded on a JASCO FT-IR instrument using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker spectrometers 300, 400, 75 &100 MHz, respectively with TMS as an internal standard. Mass spectra were recorded on Xevo G2S Q-TOF spectrometer. TLC was performed on pre-coated plastic sheets (POLYGRAM@SIL G/U254) and detected under UV light. Column chromatography was carried out with silica gel (ACME, 100-200 mesh). Reagents and solvents were purified as per standard procedures. Optical rotations are measured on RUDOLPH digital polarimeter. Enantiomeric excess was measured by JASCO HPLC using Daicel chiralcel OD-H column.

Synthesis of propargylated cyclic proline 6[1]:

To a suspension of sodium hydride (0.574 g, 11.8 mmol) in dimethylformamide,(2S,3R)-1-ethyl-4-hydroxy-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (2 g, 5.98 mmol) was added at 0°C under nitrogen atmosphere. Next, propargyl bromide (0.6 mL, 7.08 mmol) was added and allowed to stir for 1 hour at rt. The reaction was quenched with saturated NH_4Cl solution and extracted with dichloromethane (3 X 20mL). The organic solvent was removed by rotary evaporator, the crude product was purified by column chromatography (silicagel, hexane/AcOEt: 80/20).



6

Yield: 91% ; white crystalline solid; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.55 (d, *J* = 6 Hz, 2H), 7.53-7.30 (m, 8H), 4.85 (dd, *J* = 6.3 Hz, *J′* = 4.8 Hz, 1H), 4.31 (t, *J*= 3Hz, 1H), 4.08 (d, *J* = 3 Hz, 2H), 4.04 (d,

J=4.8 Hz, 1H), 3.30 (d, *J* =15 Hz, 1H), 2.45 (t, *J* = 3 Hz, 1H), 1.90 (dd, *J* = 9 Hz, *J′* = 6 Hz, 1H), 1.26-1.20 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 160.3, 142.8, 140.0, 128.6, 128.5, 128.4, 127.8, 126.0, 125.3, 85.7, 79.1, 78.1, 74.8, 67.2, 58.08, 56.6, 53.6, 35.9.

General procedure for the synthesis of Cu(I) catalyzed click reaction (procedure A):

$CuSO_4.5H_2O$ (10 mol%) was dissolved in a mixture of THF and water (1:1) followed by addition of sodium ascorbate (20 mmol%), azide compounds (1 equiv.) and acetylene derivatives (1.1 equiv.). Then the reaction mixture was stirred over night at room temperature. The reaction was monitored by TLC periodically. After reaction completion, the solvent was removed by rotary evaporator and the crude was dissolved in water (100 mL) and extracted with ethyl acetate (2 X 10 mL). The combined organic layer was passed through sodium sulphate and solvent was evaporated under vacuum afforded crude compound. Then it was purified by column chromatography (silica gel, $CHCl_3$/MeOH: 95/5) afforded corresponding compound.

General procedure for the decarbonylation reaction (procedure B):

Cyclic proline compounds treat with aqueous KOH (1.5 equiv. per each cyclic proline) in EtOH/ THF (1:1). It was allowed to stir at 70 ^oC until the reaction completed. After reaction completion, the solvent was removed by rotary evaporator and the crude was extracted with ethyl acetate (3 X 10 mL). The combined organic layer was passed through the sodium sulphate and the solvent was removed under vacuum afforded Corresponding amino alcohol.

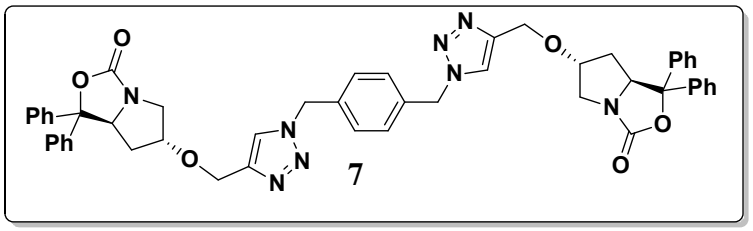
General procedure for Synthesis of immobilized spiroborate esters (procedure C):

An oven-dried, 3-necked 50-mL round bottomed flask is fitted with a reflux condenser on one outer neck, a stoppered 25-mL addition funnel on the middle neck, and a rubber septum on the other outer neck. Magnetic stirrer is added to the flask. An adapter is attached to the top of the reflux condenser and connected to a nitrogen line and gas bubbler. The flask is charged with toluene (5 mL) followed by triisopropyl borate (1 equiv. for each amino alcohol) and ethylene glycol (1 equiv. for each

amino alcohol), each added via syringe. The mixture is stirred and heated with a heating mantle over 20 min to 80°C, at which time the mixture becomes homogeneous. The solution is cooled to 60°C, then a solution of amino alcohol (1 equiv.) in toluene (10 mL) is added via the addition funnel over 3 min, during which time the temperature decreases to 55 °C and white crystalline product is formed. The addition funnel is rinsed with toluene (5 mL). The resulting mixture is cooled to ambient temperature over 30 min. The mixture is transferred to a 100 mL round-bottomed flask and the mixture is concentrated to dryness by rotary evaporation, and then dried.

Synthesis and spectroscopy date of protected proline 7:

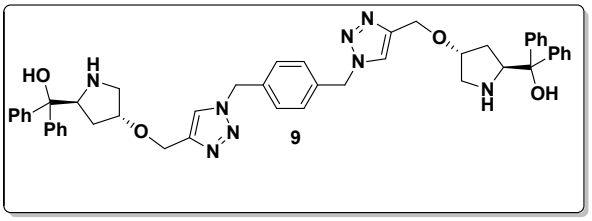
Following the procedure **A**, protected proline **7** was obtained as white amorphous solid.



Yield: 88%; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.44-7.22 (m, 26H), 5.44 (s, 4H), 4.73 (dd, J = 9Hz, J' = 3 Hz, 2H), 4.47 (q, J = 15 Hz, J' = 12 Hz, 4H), 4.09 (d, J = 21Hz, 2H), 3.93 (dd, J = 9 Hz, J' = 3 Hz, 2H), 3.15 (d, J =12 Hz, 2H), 1.88-1.84 (m, 2H), 1.21-1.16 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 160.3, 144.9, 142.8, 139.9, 135.2, 128.7, 128.6, 128.4, 127.8, 126.0, 125.3, 122.6, 85.8, 78.7, 67.3, 62.7, 53.7, 53.6, 35.8; **HRMS:** $(M+H)^+$ calculated for $C_{50}H_{46}N_8O_6$: 855.3619, Found: 855.3647.

Synthesis of amino alcohol 9:

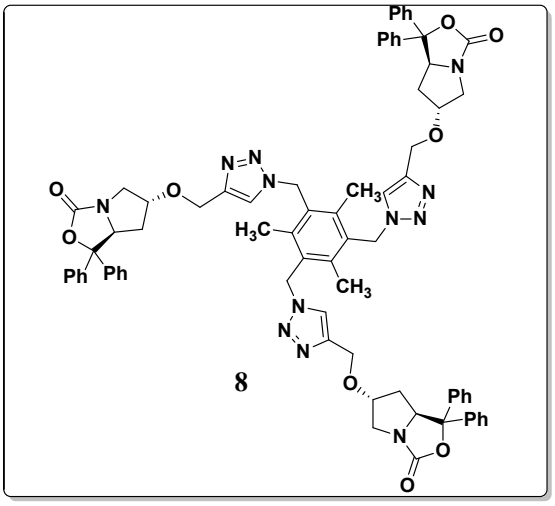
Following the procedure **B**, amino alcohol **9** was obtained as white amorphous solid.



Yield: 85% ; **IR (KBr) ν_{max}** : 3515, 3405, 3031, 2240 cm^{-1}; **^{1}H NMR (300 MHz, $CDCl_3$)**: δ_H 7.48-7.04 (m, 26H), 5.41 (s, 4H), δ4.45 (d, *J* = 6 Hz, 6H), 4.02-3.95 (m, 2H), 3.10-2.97 (m, 4H), 1.76-1.68 (m, 2H), 1.66-1.51 (m, *J* = 6 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$)**: δ_C 147.6, 145.7, 144.9, 135.2, 128.7, 128.2, 128.0, 126.6, 126.4, 125.9, 125.4, 122.4, 79.9, 76.6, 63.3, 62.2, 53.6, 52.3, 32.9; **HRMS:** $(M+H)^+$ calculated for $C_{48}H_{48}N_8O_5$: 803.4033, Found: 803.4016.

Synthesis of protected proline 8:

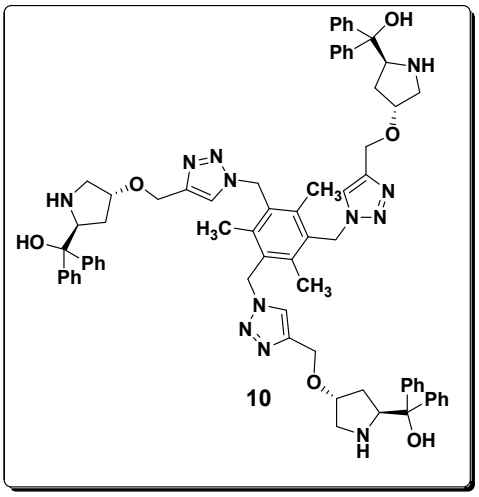
Following the procedure **A**, protected proline **8** was obtained as white amorphous solid.



Yield: 88%; **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.44-7.19 (m, 33H), 5.56 (s, 6H), 4.73 (dd, *J* = 6 Hz, *J'*=12 Hz, 3H), 4.4 (q, *J* = 12 Hz, *J'*= 9 Hz, 6H), 4.37-3.95 (m, 3H), 3.95-3.89 (m, 3H), 3.13 (d, *J* = 12 Hz, 3H), 2.34 (s, 9H), 1.88-1.82 (m, 3H), 1.34-1.06 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 160.3, 144.5, 142.8, 140.0, 139.7, 130.5, 128.6, 128.5, 128.4, 127.8, 126.0, 125.4, 122.1, 85.8, 78.8, 67.3, 62.6, 53.7, 49.0, 35.8, 16.7.

Synthesis of amino alcohol 10:

Following the general procedure **B**, amino alcohol **16** was obtained as white amorphous solid



10

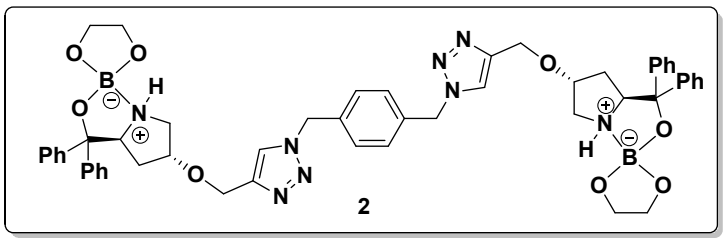
Yield: 82%; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.14-7.15 (m, 33H), 5.61 (s, 6H), δ4.51 (d, J = 6Hz, 9H), 4.05-4.0 (m, 3H), 3.06-3.02 (m, 6H), 2.40 (s, 9H), 1.80-1.70 (m, 3H), 1.75-1.60(m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 145.1, 144.7, 139.7, 130.5, 128.6, 128.3, 128.0, 126.7, 126.5, 125.9, 125.4, 122.0, 79.8, 76.7, 63.3, 62.2, 52.2, 48.9, 32.9, 16.7.

Synthesis of compounds 2 and 3:

Following the general procedure **C**, compound **2** and **3** were obtained as brown solid.

Yield: 96% and 97% respectively.

Compound 2:

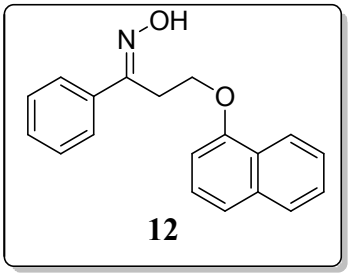


2

IR (KBr) ν_{max} : 3456, 3096, 2445, 1645 cm^{-1}; **^{11}B NMR** (d_6-DMSO) δ: 9.7 (s).

Synthesis of E-oxime (12):

To a mixture of 3-napthoxy propiophenone[2] (3g, 10.8mmol) in ethanol (50 mL) was added dropwise sodium carbonate in (10 mL) water. The mixture was refluxed while maintaining the P^H around 5. After completion of the reaction, the solvent was removed under vacuum the compound was extracted with ethyl acetate and recrystallized in hexane and EA (15:1).

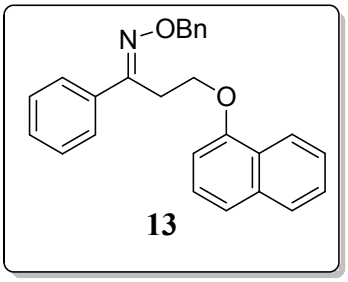


12

Yield: 75%; white crystalline solid; **^{1}HNMR** (300MHz, $CDCl_3$): δ_H 7.80 (d, J = 62.7, 1H), 7.68 (d, J = 4.2, 3H), 7.39-7.19 (m, 7H), 6.72 (d, J = 7.5 Hz,1H), 4.36 (t, J = 6.9 Hz, 2H), 3.40 (t, J = 6.6 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 154.7, 154.1, 136.3, 134.0, 128.4, 128.0, 126.9, 126.0, 125.9, 125.5, 125.2, 124.6, 1218, 119.8, 104.3, 64.4, 26.4.

Synthesis of (E)-O-benzyl oxime ether (13):

To a suspension of NaH (0.3915g, 6.25mmol) in THF, solution of hydroxyl oxime (1.191g, 4.07mmol) was added drop wise and maintaining the temperature at 0°C.After addition the reaction mixture was stirred for 1hour. Then benzyl bromide (0.6975g, 4.07mmol) in THF was added dropwise at 0°C. The resulting mixture was stirred overnight at rt, and then quenched with saturated aqueous NH_4Cl solution and extracted with ether (100 mL). The organic phase were combined and dried over anhydrous Na_2SO_4. The solvent were evaporated under vacuum and the residue was purified by column chromatography (silicagel, hexane/ethyl acetate: (98/2).



13

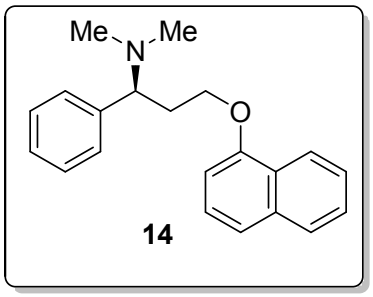
Yield: 72%; white solid, **^{1}H NMR** (300 MHz, $CDCl_3$): δ_H 7.87-7.81 (m, 18Hz, 1H), 7.71-7.66 (m, 4H), 7.38-7.16 (m, 12H), 6.68 (d, *J* = 22.2 Hz, 1H), 5.20 (s, 2H), 4.30 (t, *J* = 6.6 Hz, 2H), 3.35 (t, *J* = 6.9 Hz); **^{13}C NMR** (75 MHz, $CDCl_3$): δ_C 154.8, 153.6, 137.0, 135.1, 133.8, 128.2, 127.5, 127.4, 127.2, 126.8, 126.3, 125.7, 125.2, 125.0, 124.7, 124.0, 121.3, 119.5, 104.1, 75.7, 64.1, 26.8; **HRMS:** $(M+H)^+$ calculated for $C_{26}H_{23}NO_2$: 382.1778, Found: 382.1795.

Synthesis of primary amine: To a 10 mL reaction tube with catalyst under N_2 atmosphere a mixture of 5mL of anhydrous dioxane and 2 mL of BH_3.THF was added in one portion. After the mixture was stirred for 1 hour at room temperature, the clear solution was cooled at 0°C and the benzyl oxime (0.2 g, 0.65 mmol) in 5mL of dioxane was added dropwise during 1h. The resulting mixture was stirred at 0 °C until the conversion was complete in about 48h. The reaction was quenched with 6N HCl and basified with 6N NaOH. The reaction mixture was extracted with ether and combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound (0.120 g) is used for next step without further purification.

Color: Yellow oil

Synthesis of (*S*)-Dapoxetine (14): To a solution of crude amine in 85% formic acid (0.104 g, 2.2 mmol), 37% aqueous formaldehyde (0.040g, 1.33mmol) was added and the mixture was kept at 95 to 100°C for 6 hours. After cooling the solution, acidified with 4N HCl until pH=1 and basified with 4N NaOH. The aqueous phase was extracted with ether and combined organic phase were dried over

Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (Silica gel, CH_2Cl_2/MeOH, 97:3) to afford (*S)*-Dapoxetine.



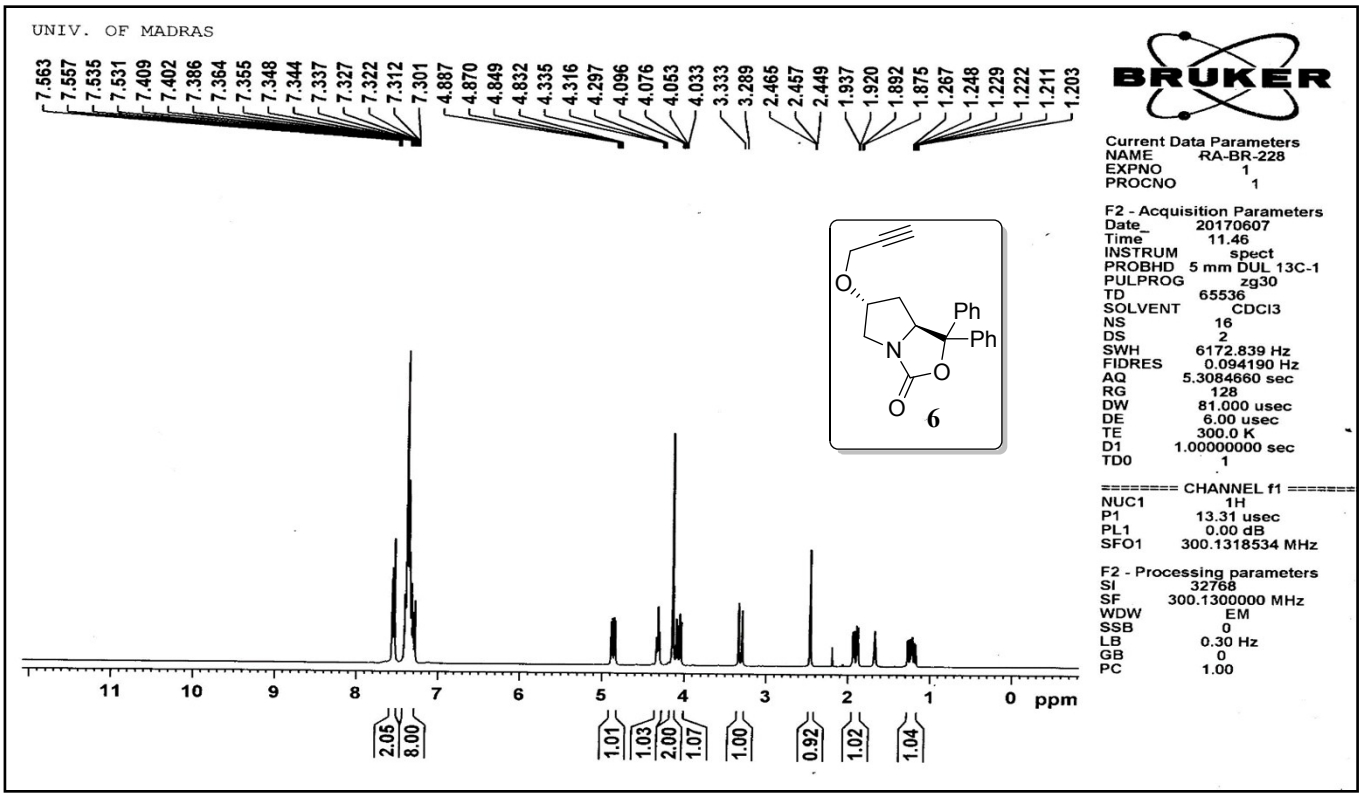
14

Yield: 88%; Yellow oily liquid, **Specific Rotation:** $^{25}[\alpha]_D$= +60.03 (C 0.3, $CHCl_3$), literature value $^{25}[\alpha]_D$= +63.0 (C 0.3, $CHCl_3$); **HPLC Condition[3]:** 94% ee (Daicel OD-H, 2% isopropanol/hexanes, 0.7 mL/min, 210 nm, tr (major) = 7.76 min, tr (minor) = 6.8 min); **^{1}H NMR** (400MHz,$CDCl_3$): δ_H 8.15-8.13 (m, 1H), 7.71-7.43 (m, 1H), 7.29-7.18 (m, 9H), 6.56 (d, *J* = 5.7Hz, 1H), 3.99-3.96 (m, 1H), 3.83-3.78 (m, 1H), 3.58-3.54 (m, 1H), 2.61-2.55 (m, 1H), 2.39-2.20 (m, 1H), 2.19 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 154.5, 134.4, 128.6, 128.3, 127.5, 127.4, 126.5, 126.3, 125.8, 125.0, 122.0, 120.0, 104.5, 67.5, 65.5, 42.7, 32.8; **HRMS:** $(M+H)^+$ calculated for $C_{21}H_{23}NO$: 306.1858, Found: 306.1832.

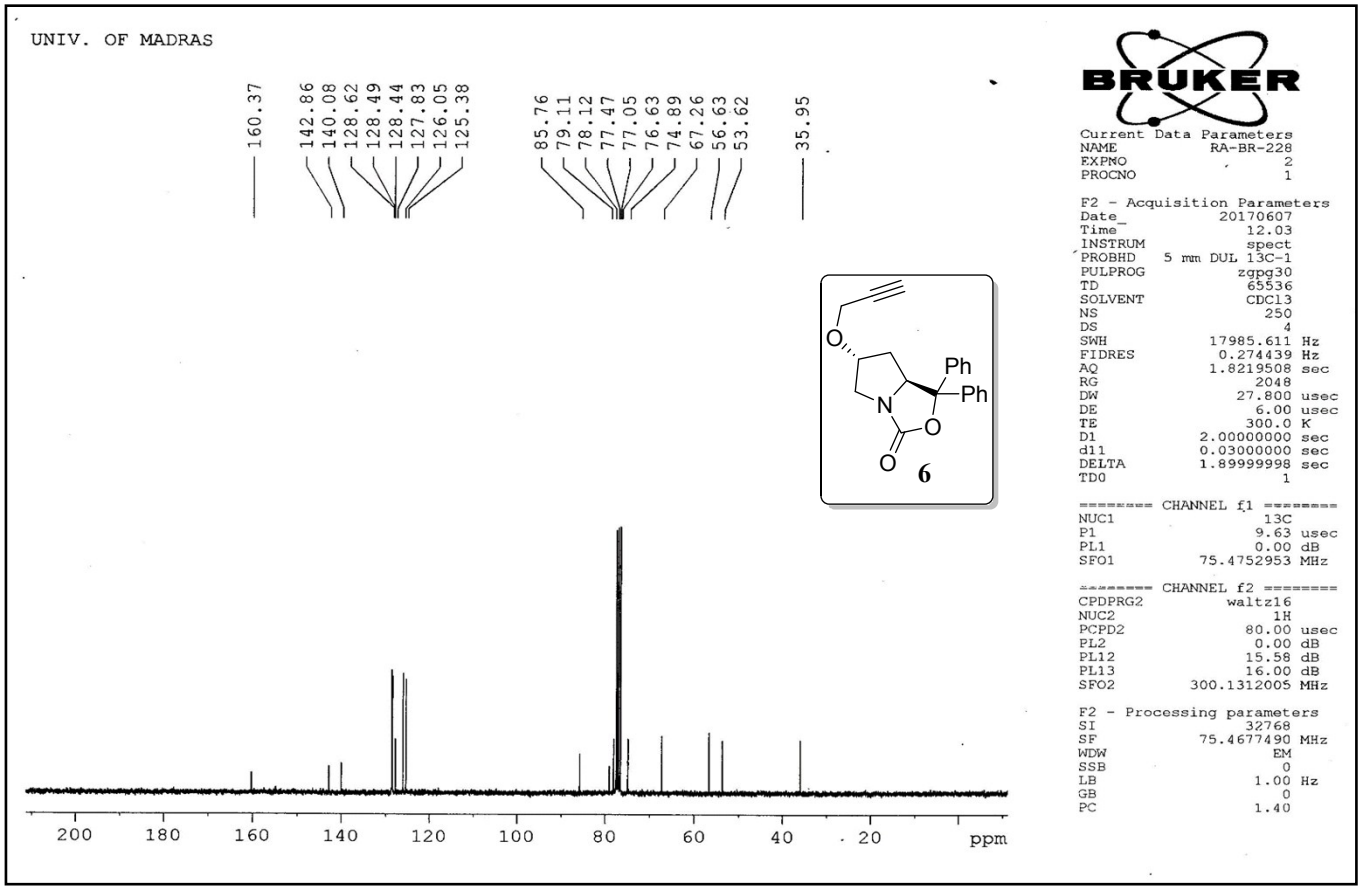
References:

1. I. Mager and K. Zeitler, *Org. Lett.,* 2010, **12**, 1480.
2. D. M. Rajendra, P. C. Sudhir, E. P. Kiran, C. M. Golak and K. G. Mukund, *Org. Process Res. Dev.,* 2012, **16**, 710.
3. K. Soyeong and H. K. Lee *J. Org. Chem.,* 2010, **75**, 237.

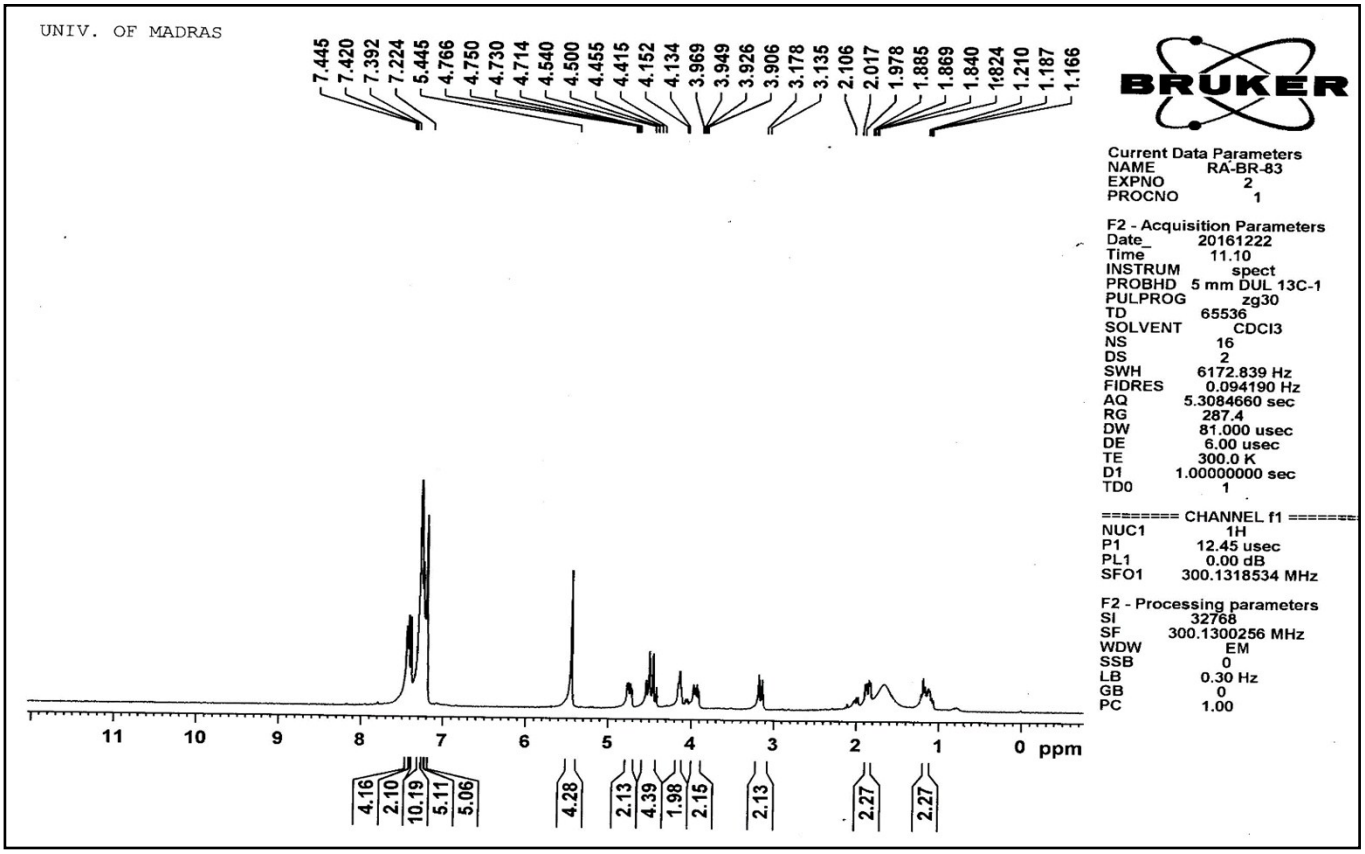
Spectral data:

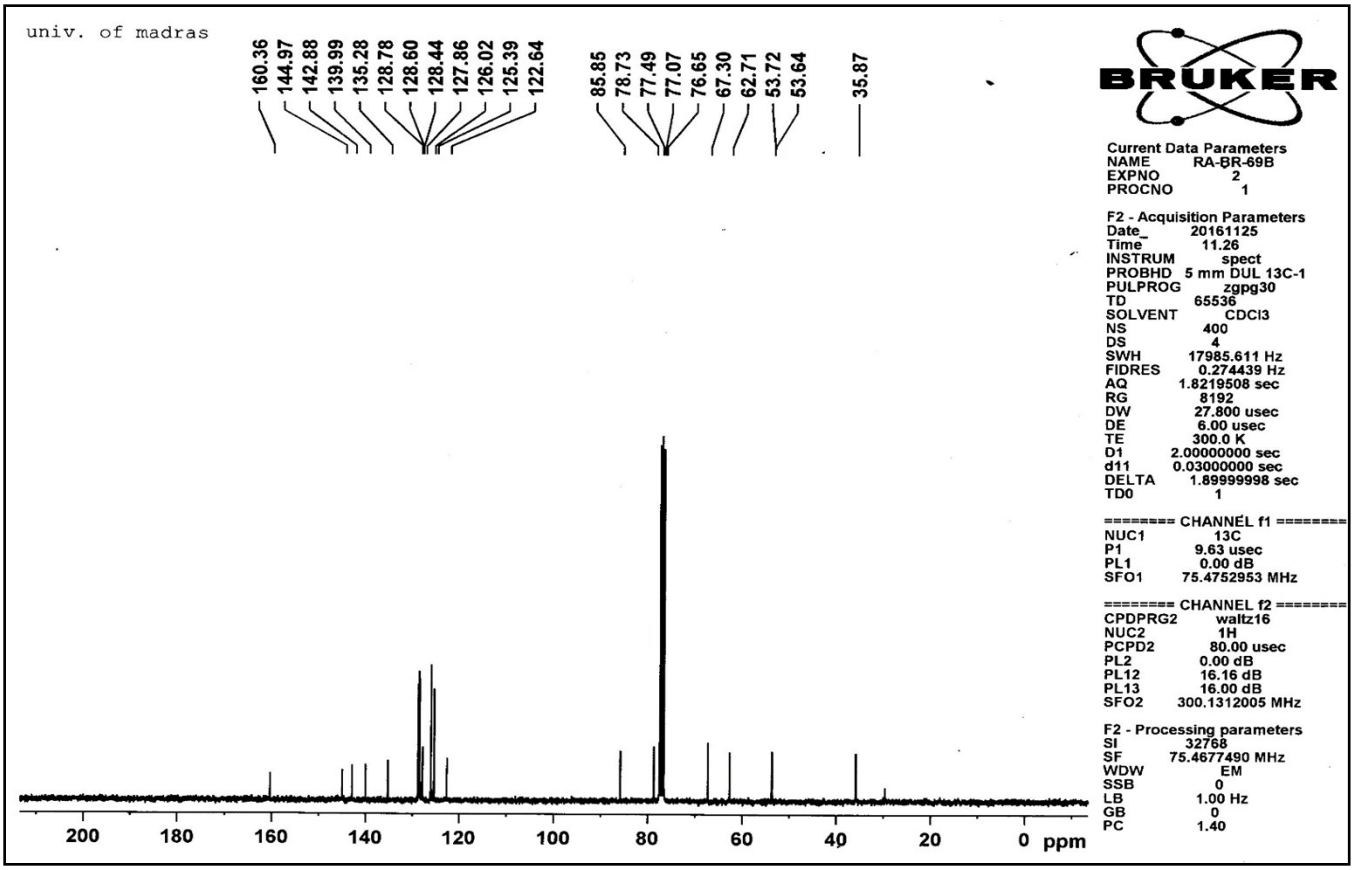


^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **6**



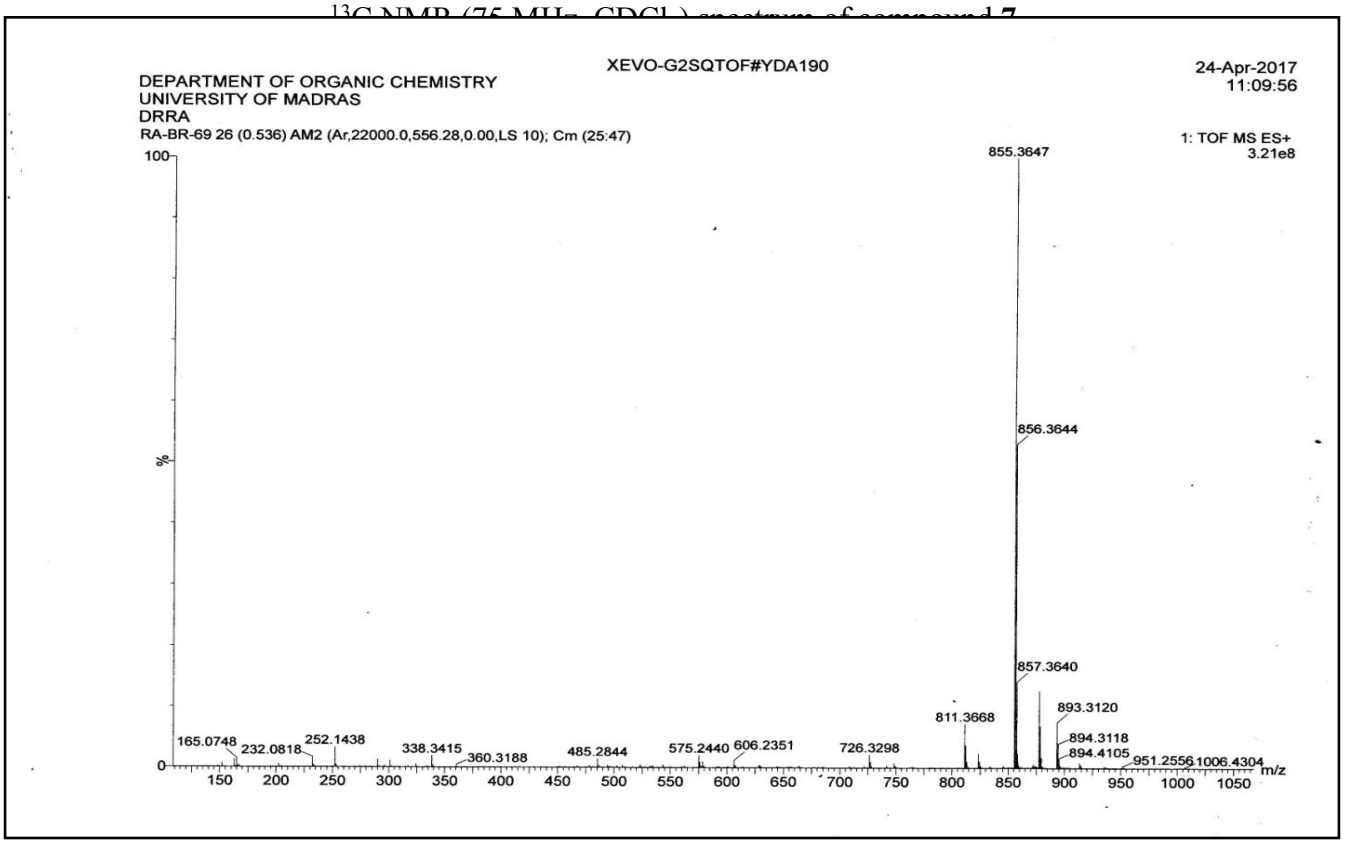
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound **6**

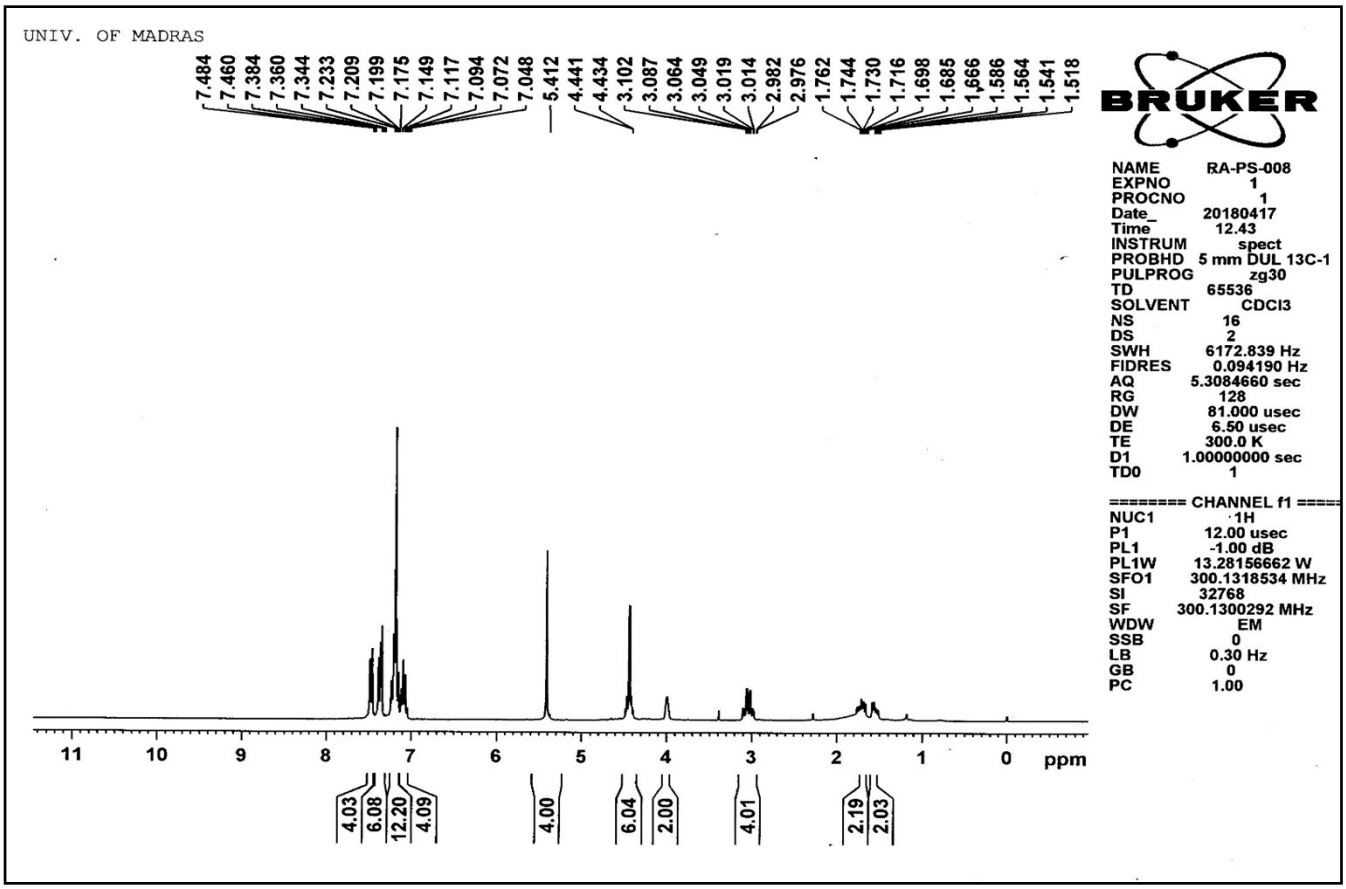




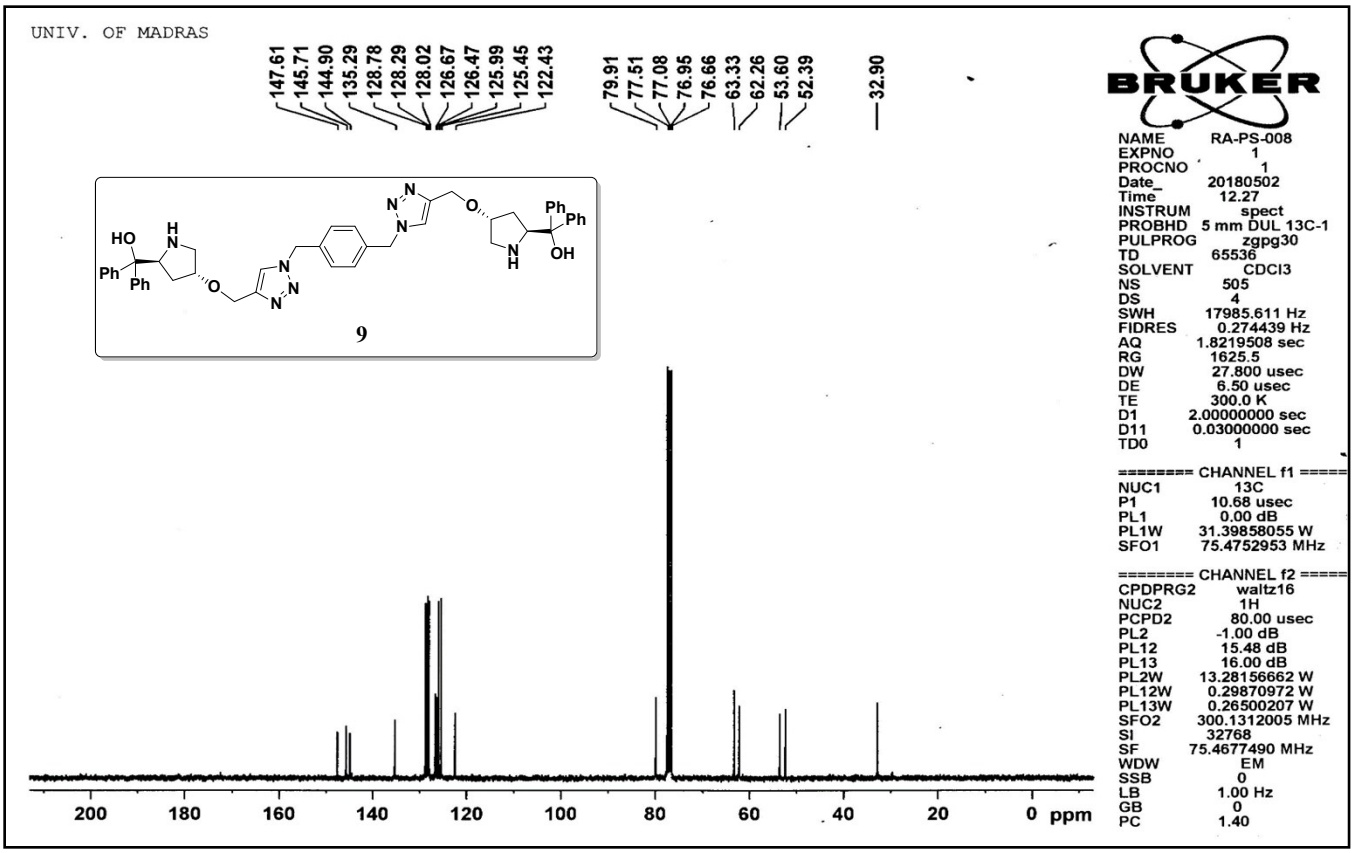
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **7**

^{13}C NMR (75 MHz, CDCl$_3$) spectrum of compound **7**



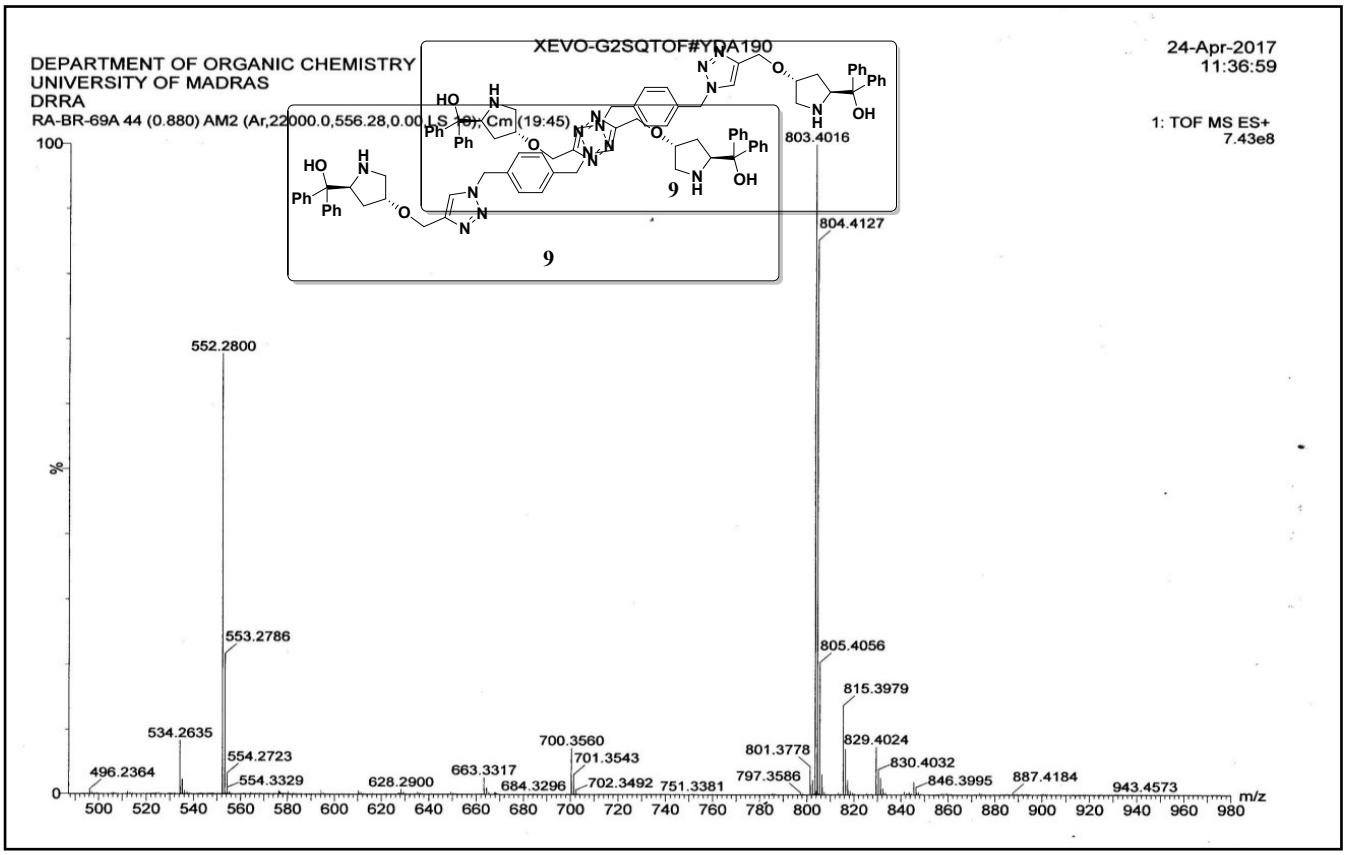


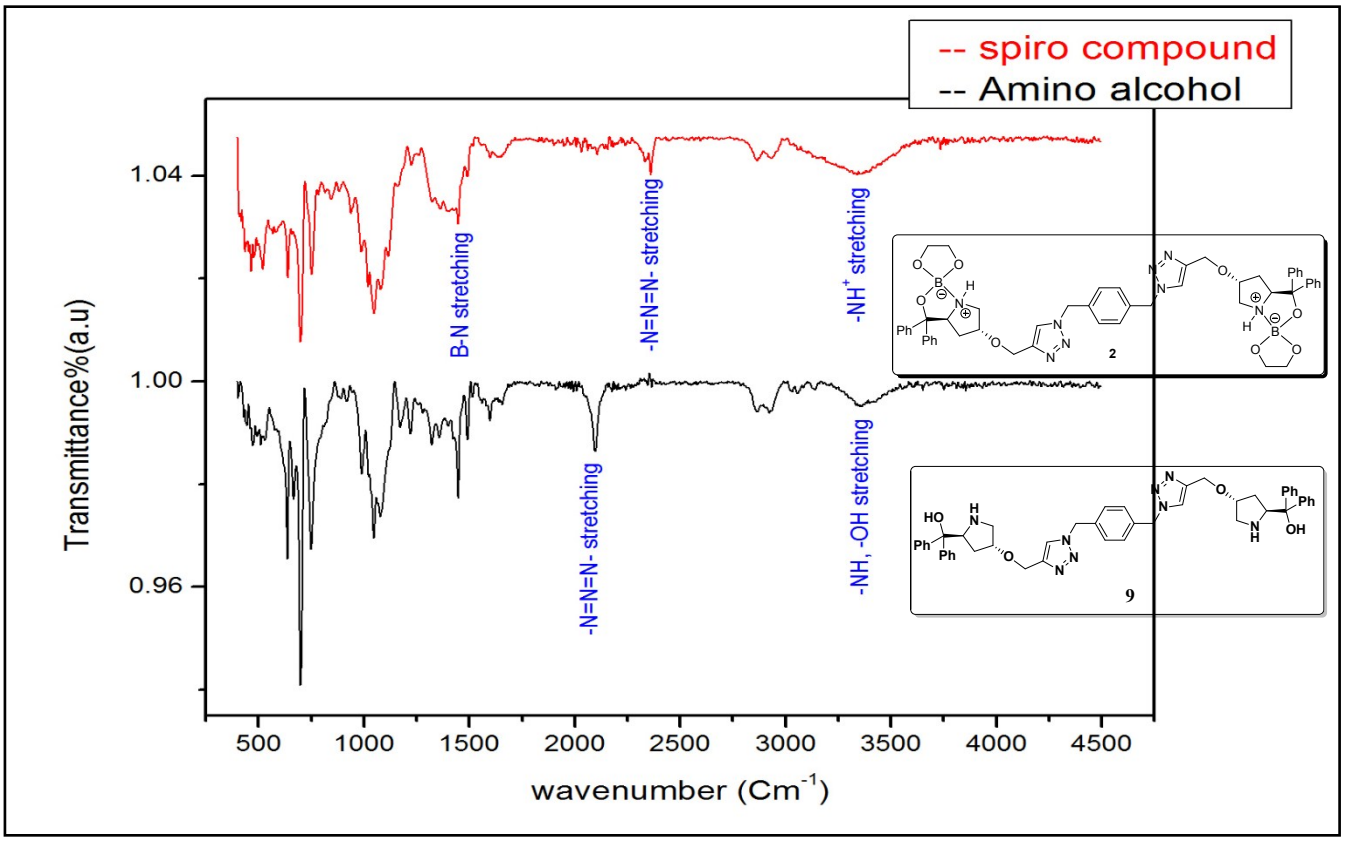
HRMS spectrum of compound **7**



^{1}H NMR (300 MHz, $CDCl_3$) spectrum of amino alcohol **9**

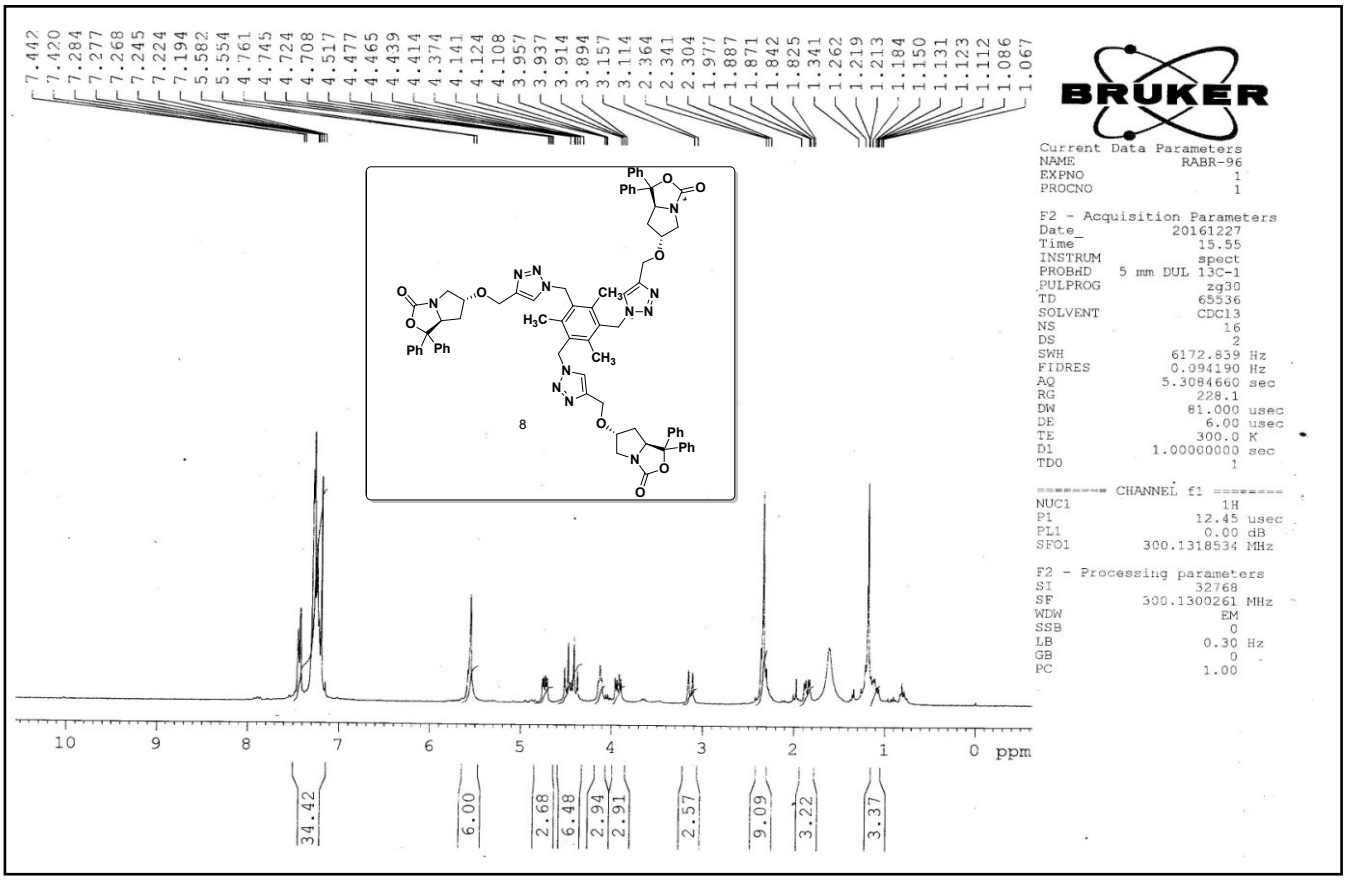
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of amino alcohol **9**

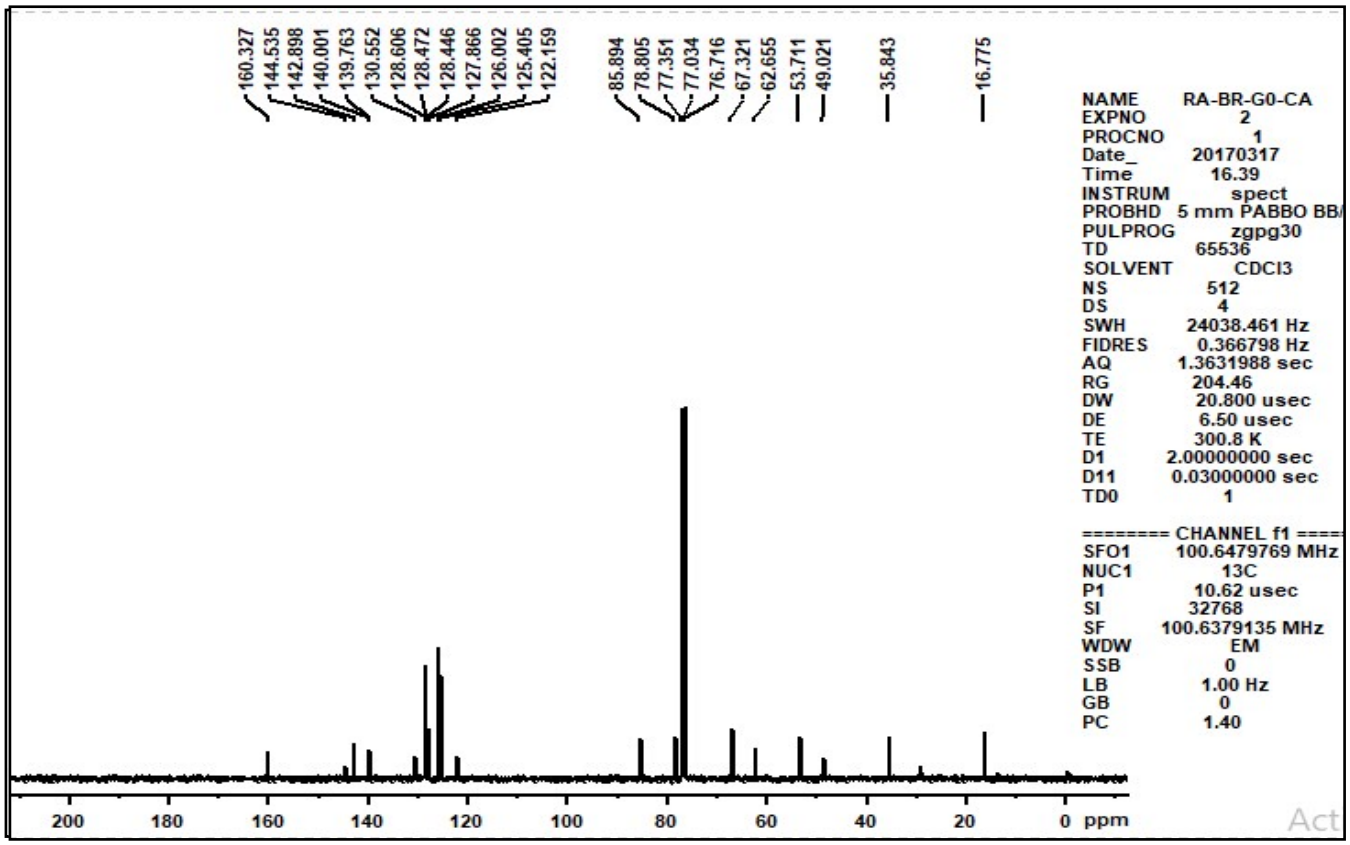




HRMS spectrum of amino alcohol **9**

IR spectrum of compounds **2** and **9**



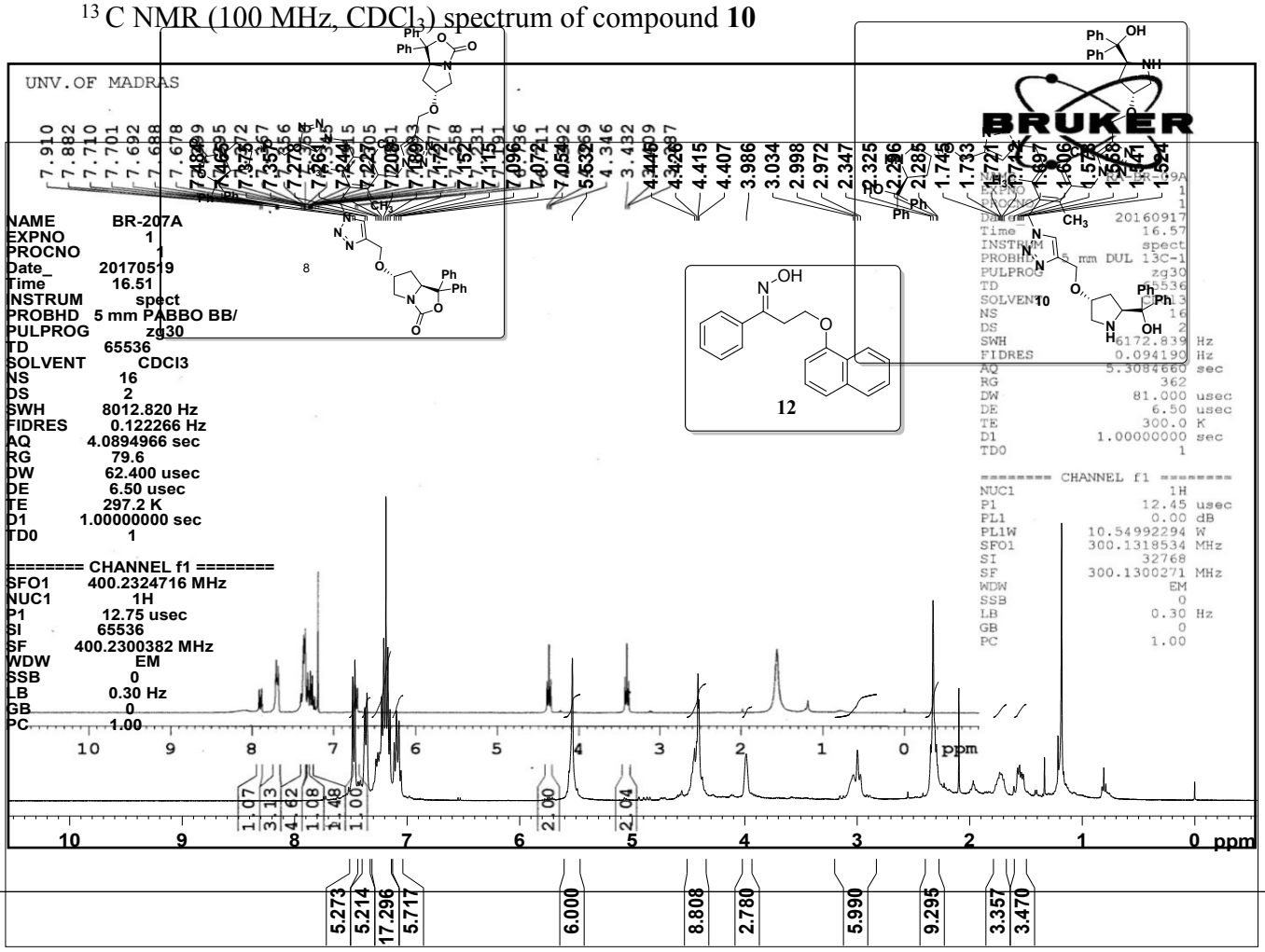


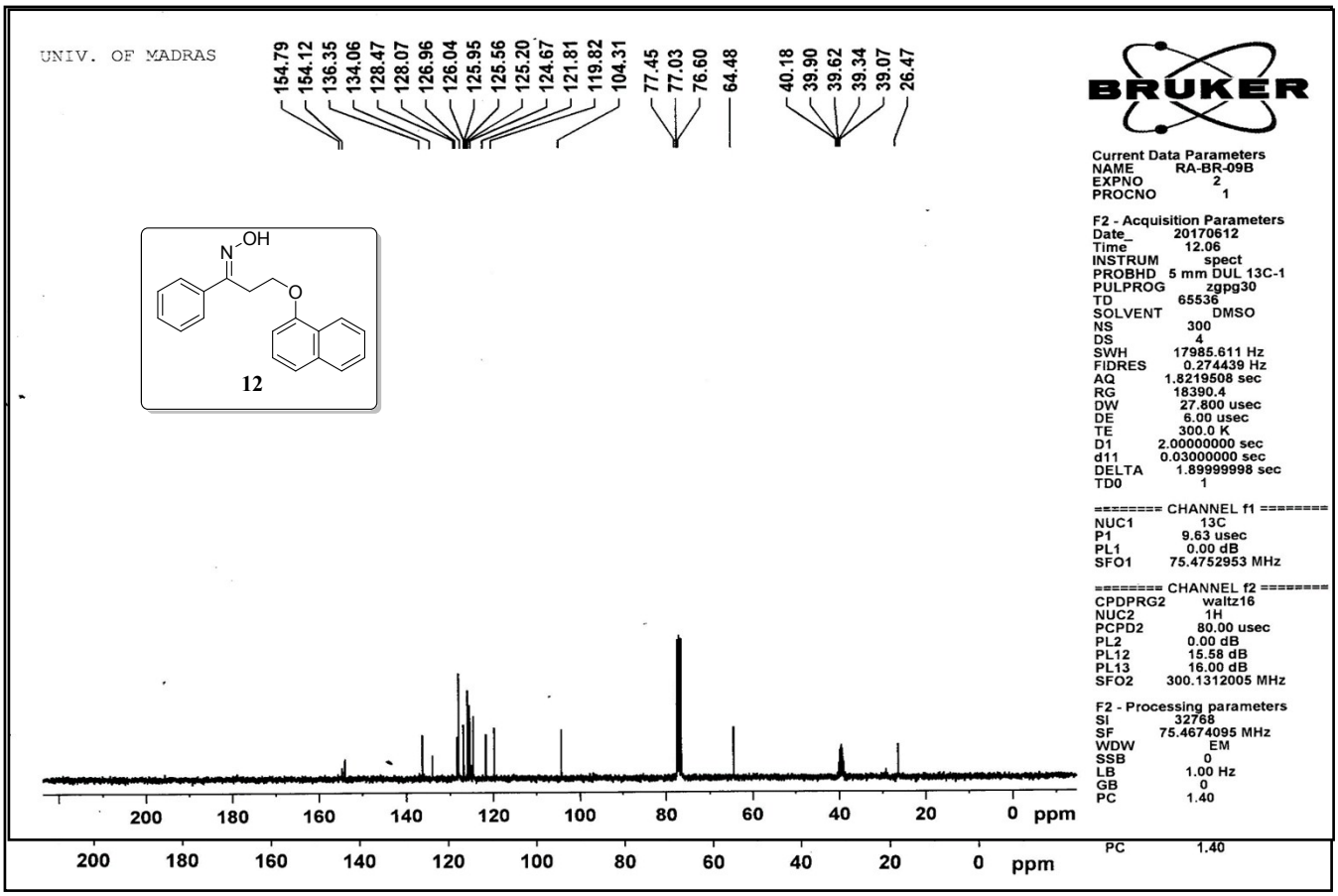
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **8**

^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **8**

^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **10**

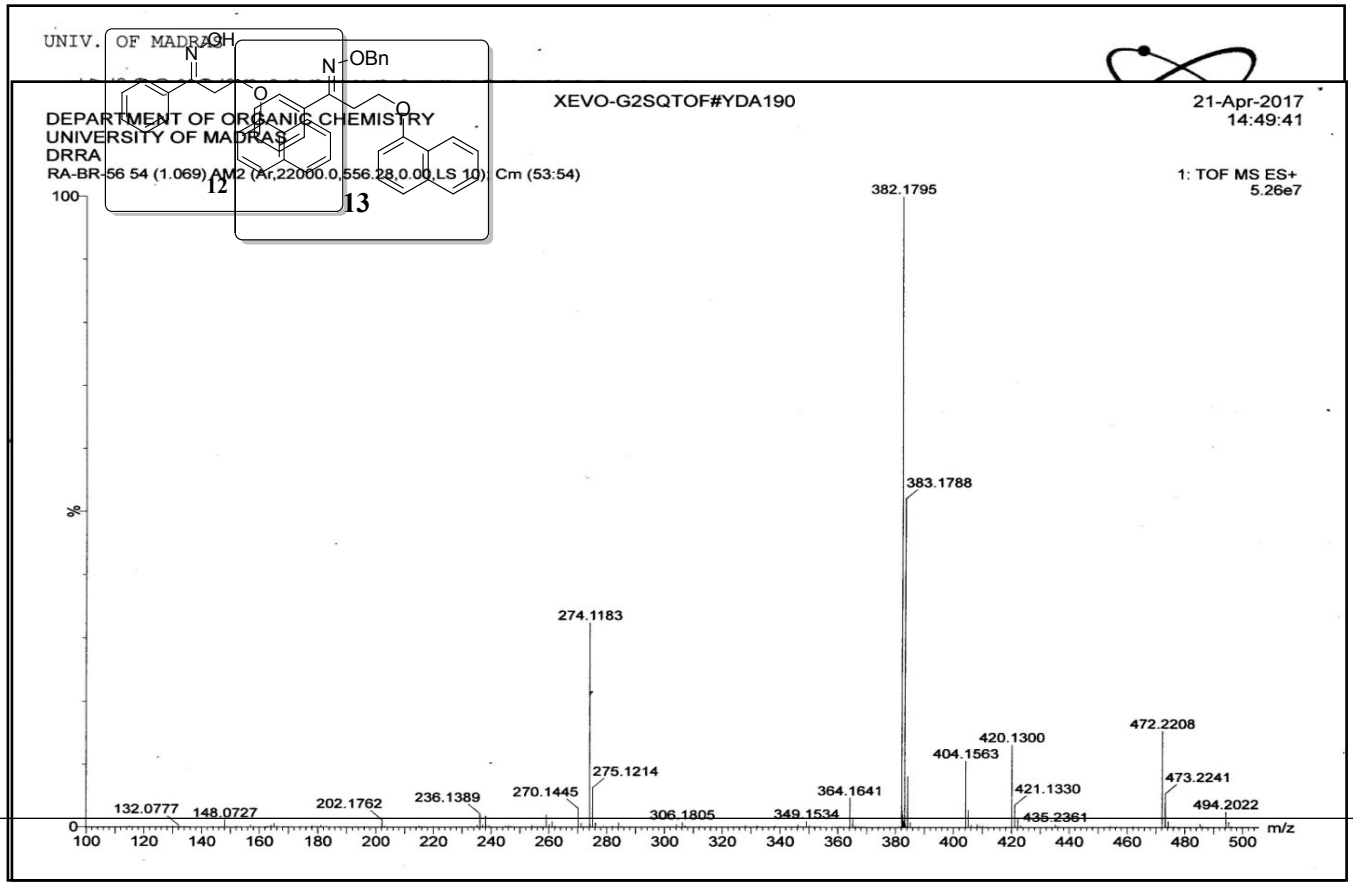
^{13} C NMR (100 MHz, $CDCl_3$) spectrum of compound **10**

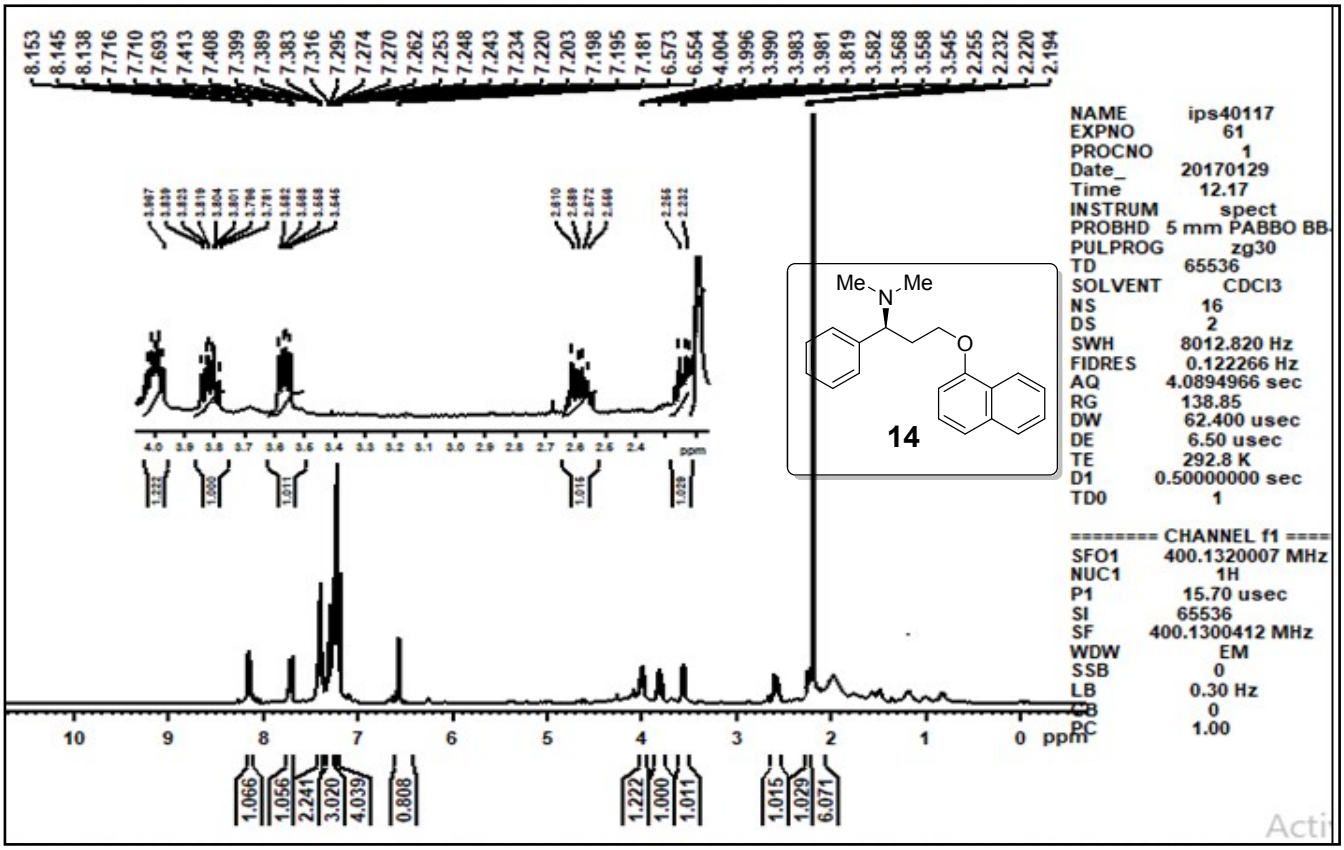




^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12**

^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound **12**
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **13**
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of compound **13**

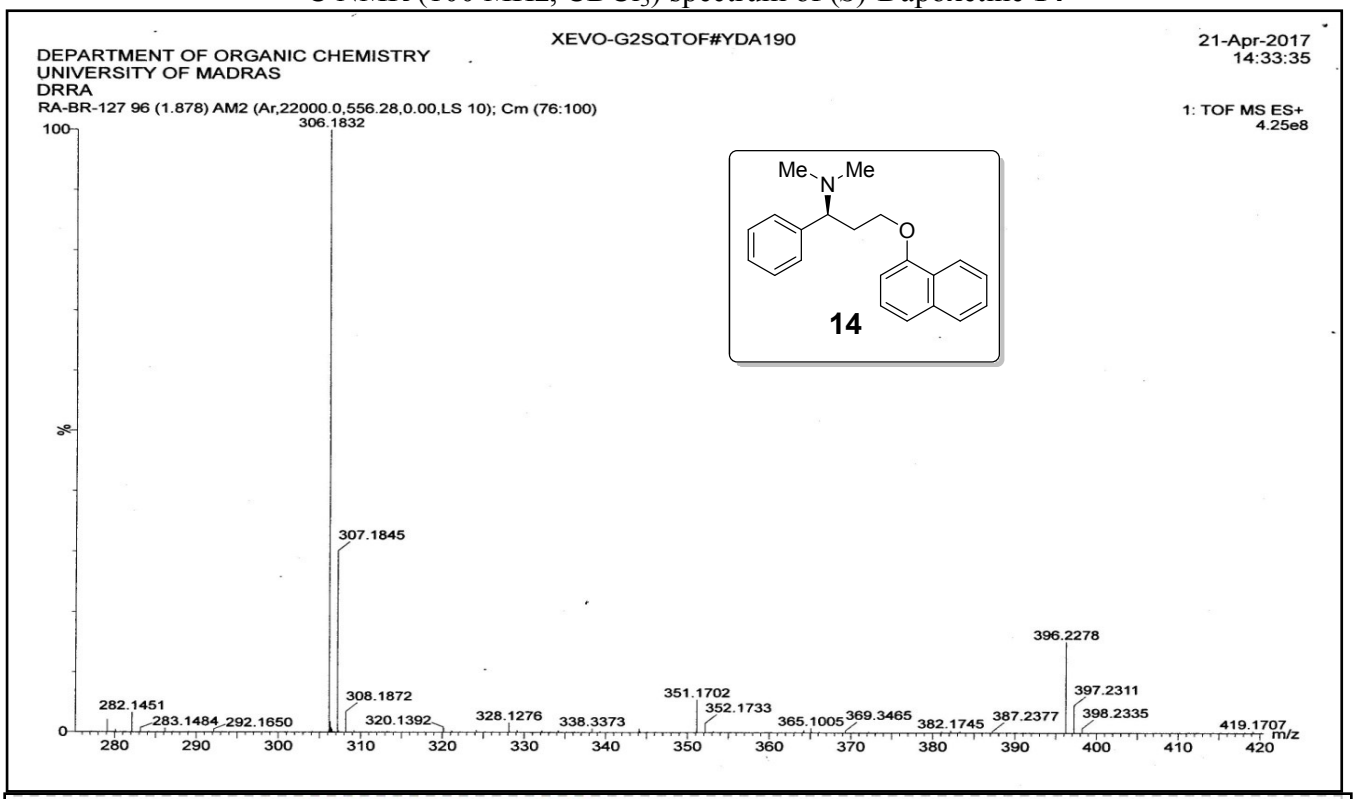


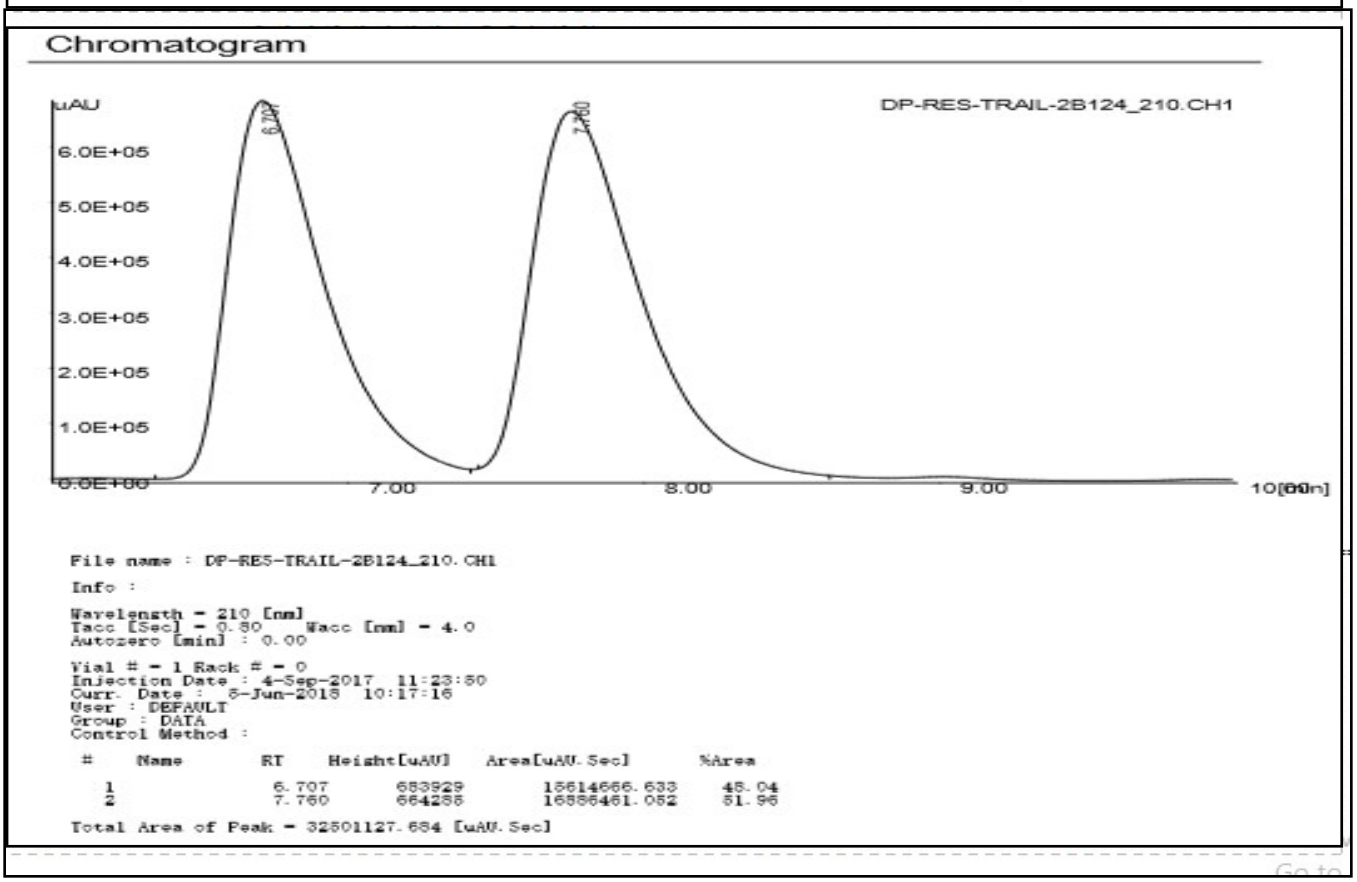


HRMS spectrum of compound **13**

^{1}H NMR (400 MHz, $CDCl_3$) spectrum of (*S*)-Dapoxetine **14**

^{13}C NMR (100 MHz, $CDCl_3$) spectrum of (*S*)-Dapoxetine **14**

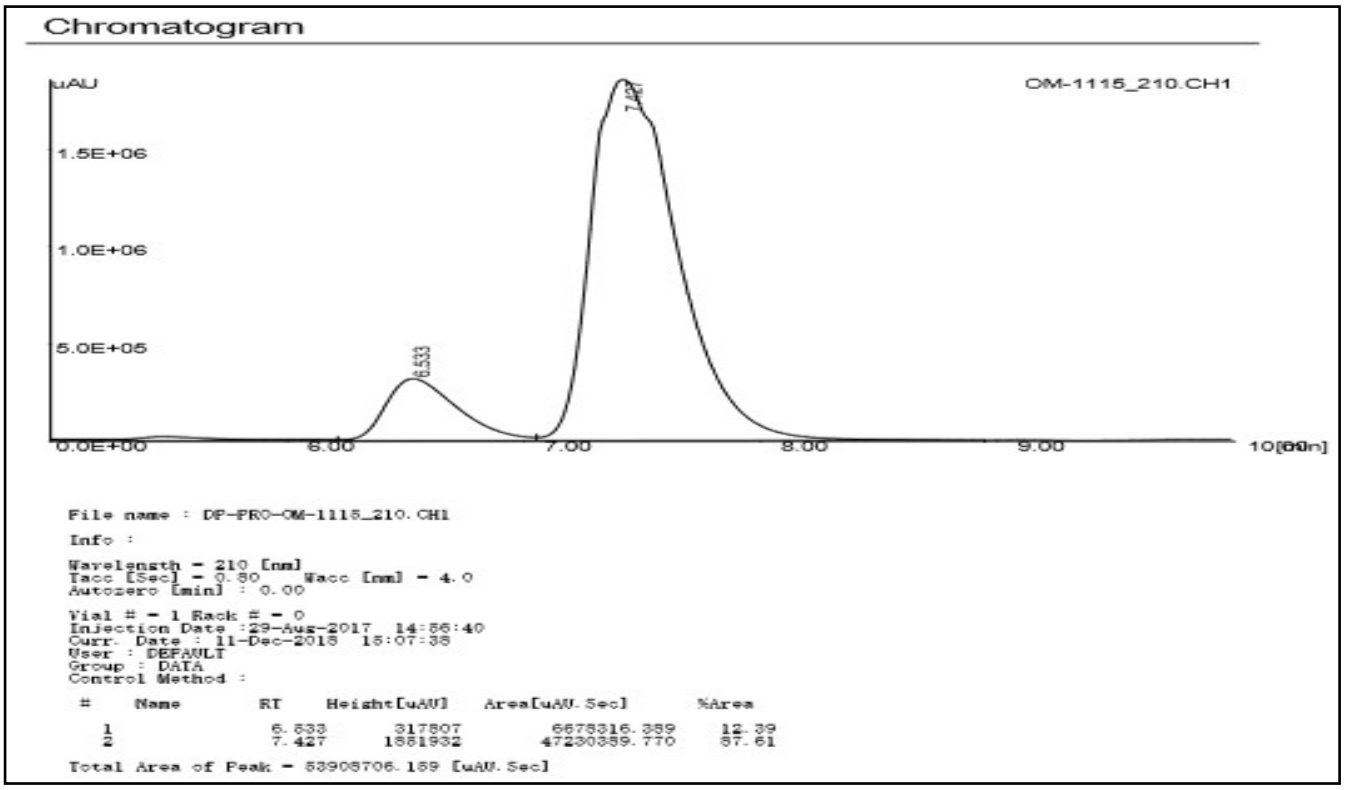




HRMS spectrum of (*S*)-Dapoxitine **14**

HPLC Spectrum of racemic Dapoxetine **14** (Manuscript, Table 1; entry 1; 0% ee)

HPLC Spectrum of (*S*)-Dapoxetine **14** (Manuscript, Table 1; entry 4; 52% ee)



File name : DP-PRO-OM-1115_210.CH1

Info :

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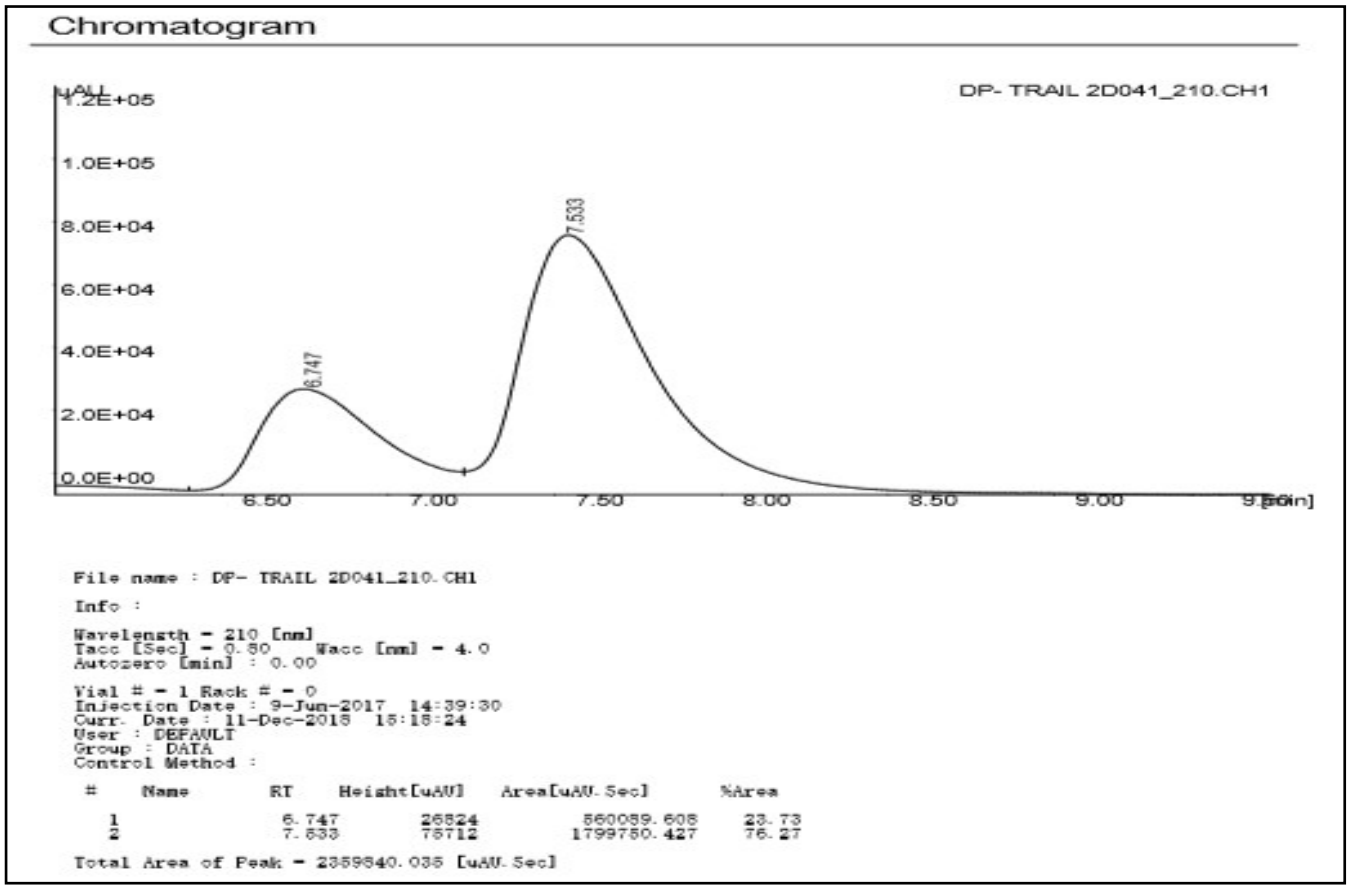
Autozero [min] : 0.00

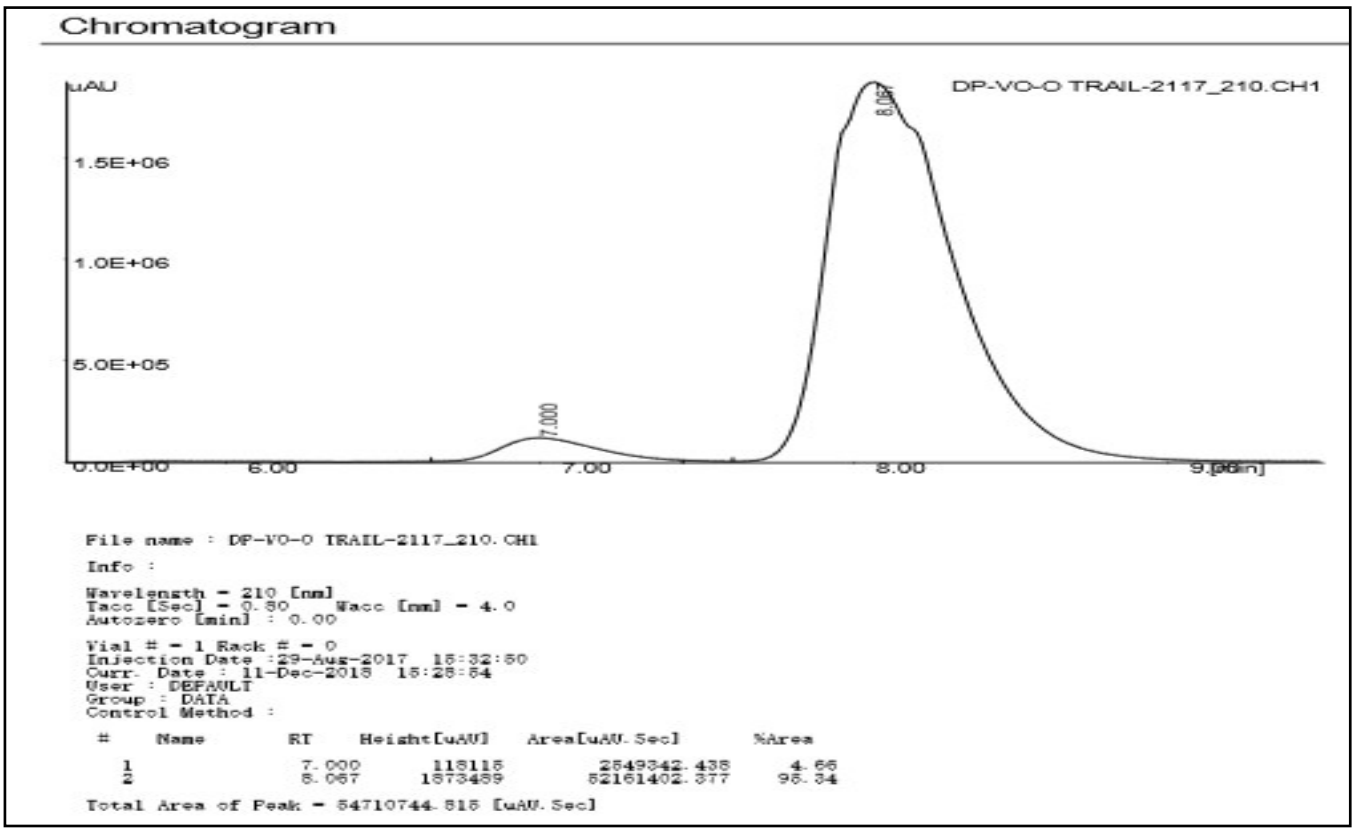
Vial # = 1 Rack # = 0
Injection Date :29-Aug-2017 14:56:40
Curr. Date : 11-Dec-2018 15:07:38
User : DEFAULT
Group : DATA
Control Method :

#	Name	RT	Height[uAU]	Area[uAU.Sec]	%Area
1		6.533	317507	6678316.389	12.39
2		7.427	1861932	47230389.770	87.61

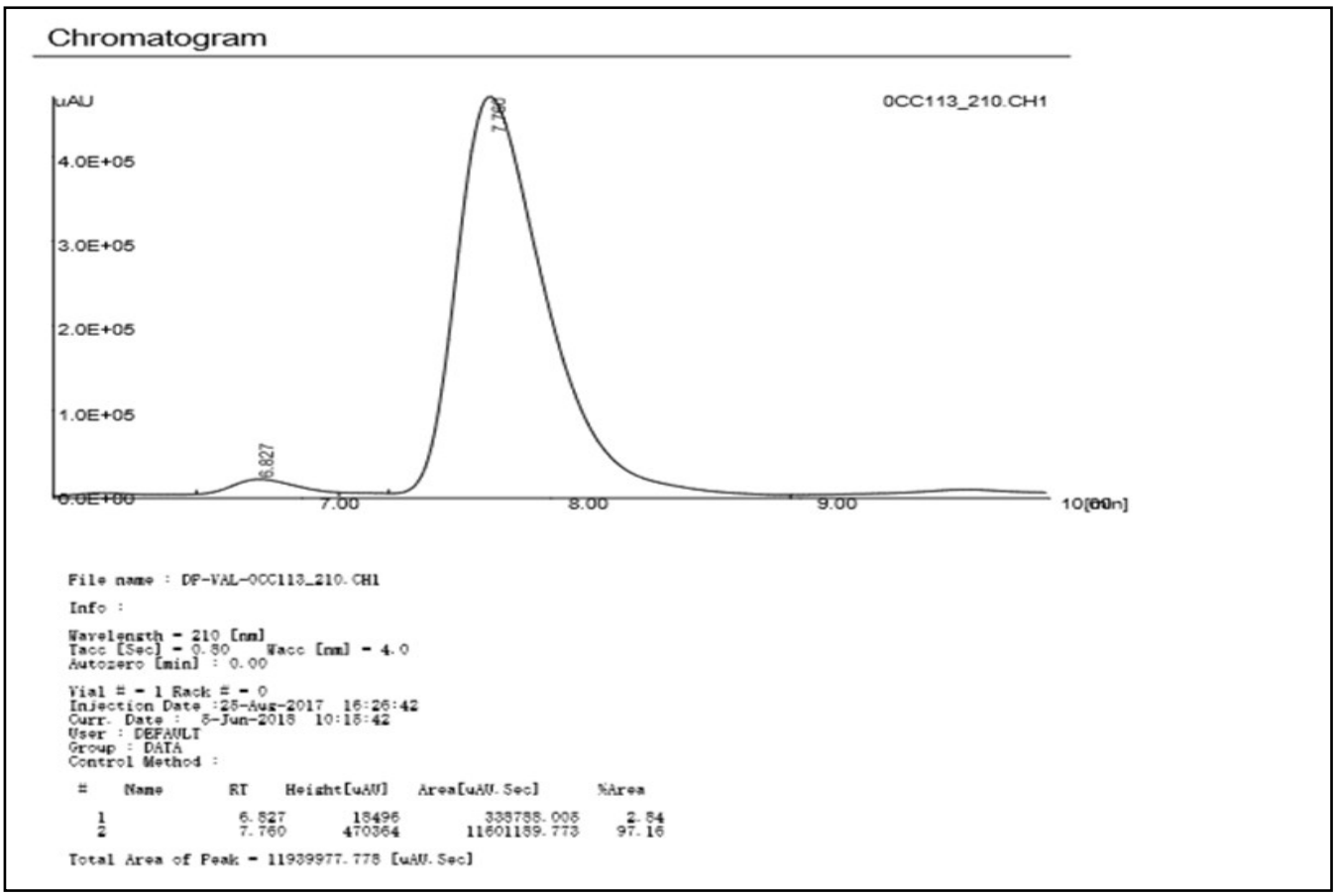
Total Area of Peak = 53908706.159 [uAU.Sec]



HPLC Spectrum of (*S*)-Dapoxetine **14** (Manuscript, Table 1; entry 6; 75% ee)



HPLC Spectrum of (*S*)-Dapoxetine **14** (Manuscript, Table 1; entry 10; 90% ee)



HPLC Spectrum of (*S*)-Dapoxetine **14** (Manuscript, Table 1; entry 12; 94% ee)