

Supporting Information for:

Synthesis and Nicotinic Receptor Activity of Chemical Space Analogs of N-(3R)-1-azabicyclo[2.2.2]oct-3-yl-4-chlorobenzamide (PNU-282,987) and 1,4-diazabicyclo[3.2.2]nonane-4-carboxylic acid 4-bromophenyl ester (SSR180711)

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Table of Contents

VIRTUAL SCREENING.....	2
NACHR ACTIVITY PROFILES (ELECTROPHYSIOLOGY).....	4
SYNTHESIS.....	8
NMR SPECTRA.....	44
ANALYTICAL HPLC DATA FOR FINAL COMPOUNDS.....	138
REFERENCES.....	140

Virtual Screening

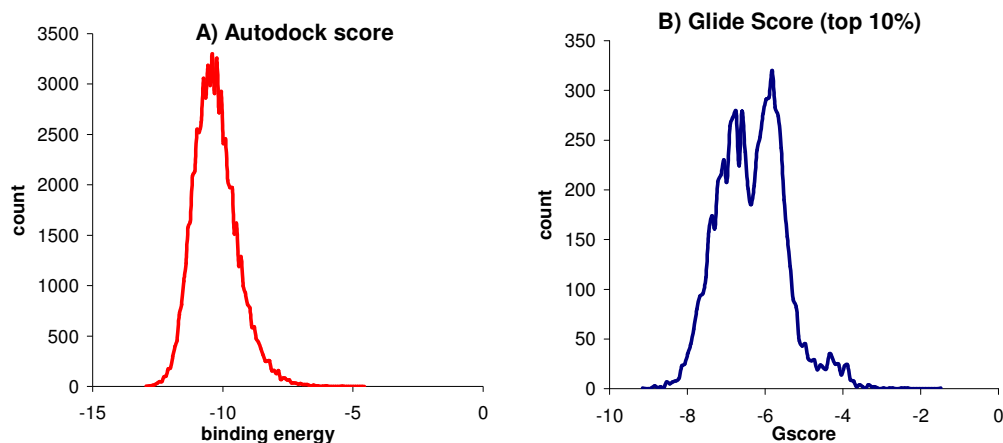


Figure S1. Docking data. **A.** Distribution of docking scores for the best binding stereoisomers of each of the 72,745 SMILES scored by Autodock. **B.** Docking scores for Glide. For Glide the program automatically rejected the weakly docking compounds and only stored data for the top 10% of the SMILES.

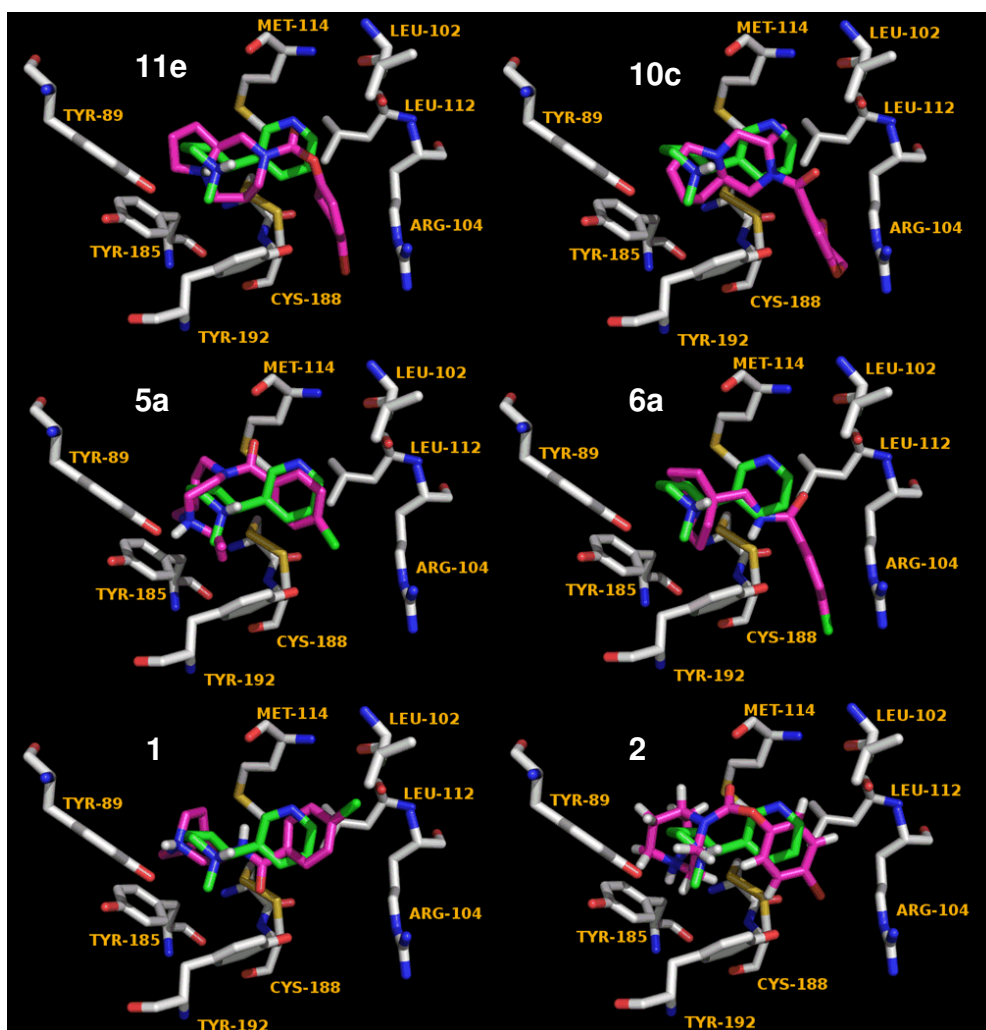


Figure S2. Docking poses of ligands **11e**, **10c**, **5a**, **6a**, and the references **1** and **2** docked in the nicotinic binding site of 1UW6.pdb. Green: reference crystallographic nicotine ligand. Magenta: ligand in its most favourable docked pose as estimated by Autodock (**11e** and **10c**) or Glide (**5a**, **6a**, **1** and **2**).

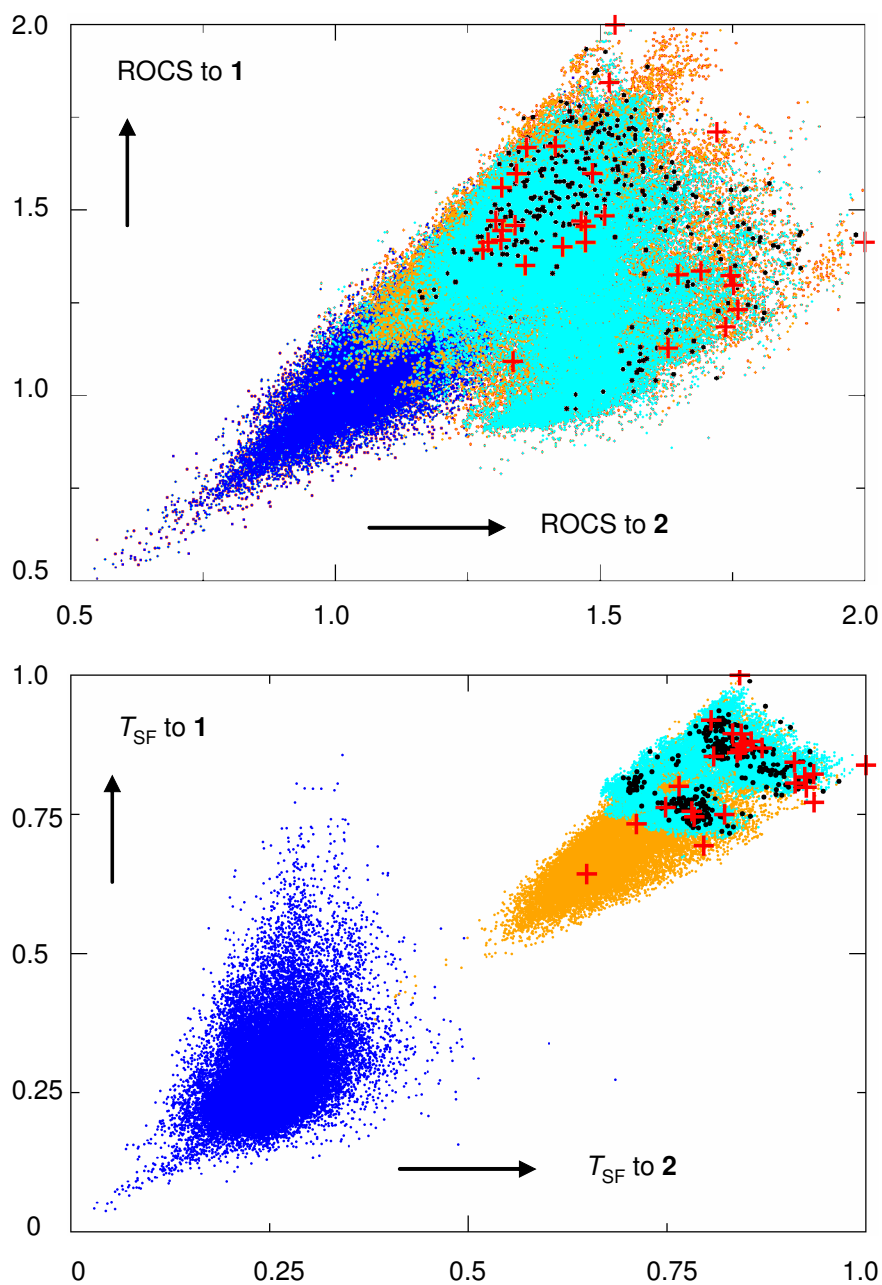


Figure S3. Shape similarity scoring of virtual libraries. For each acylated diamine, the similarity (ROCS Tanimoto Comboscore or T_{SF}) of the bromophenyl carbamate to **2** is plotted in the x-axis and the similarity (ROCS Tanimoto Comboscore or T_{SF}) of the 4-chlorobenzamide to **1** is plotted in the y-axis. orange dots: DiamA, 44,410 cpds; cyan dots: DiamB, 56,294 cpds; black dots: restricted subset of 344 diamines from DiamB; blue dots: ZINC random subset $16 \leq \text{hac} \leq 22$, 39,853 cpds. Red crosses: synthesised compounds **3-28** and the two reference ligands **1** and **2**.

nAChR Activity Profiles (Electrophysiology)

Table S1. Profiling of modulatory effect of compounds on the acetylcholine pulse at nAChRs.^{a)}

no.	$\alpha 7$	$\alpha 3\beta 2$	$\alpha 4\beta 2$	$\alpha 3\beta 4$	$\alpha 4\beta 4$	no.	$\alpha 7$	$\alpha 3\beta 2$	$\alpha 4\beta 2$	$\alpha 3\beta 4$	$\alpha 4\beta 4$
3a	68%	154%	97%	96%	93%	(R)-11e	36%	61%			
3b	94%	146%	96%	96%	90%	(R)-11f	55%	73%			
3c	87%	105%	97%	97%	92%	(R)-11g	40%	66%			
3d	52%	117%	92%	96%	92%	(R)-11k	58%	86%			
4a	84%	97%	110%	94%	87%	12c	79%	83%			
4b	85%	115%	90%	95%	86%	12e	80%	36%			
4c	81%	98%	94%	96%	87%	12f	53%	149%			
4d	90%	108%	92%	97%	91%	12k	84%	256%			
4e	82%	86%	61%	90%	83%	13a	60%	94%			
5a	35%	88%	58%	100%	65%	13c	81%	69%			
5b	40%	121%	87%	95%	85%	13f	68%	104%			
5c	25%	101%	80%	91%	53%	13g	71%	71%			
5d	37%	94%	77%	88%	52%	13k	52%	54%			
6a	32%	486%	85%	86%	64%	14a		91%			
6b	34%	140%	98%	87%	62%	14e		213%			
6c	33%	106%	60%	89%	61%	14f		108%			
6d	29%	96%	91%	103%	75%	14g		87%			
6f	26%	225%				15a	42%	99%			
6g	9%	161%				15b	53%	42%	21%	72%	41%
6h	25%	106%				15e	53%	68%			
6i	35%	117%				16b	71%	99%	87%	87%	21%
6j	32%	117%				17e	27%	90%			
7a	64%	140%	95%	86%	63%	18k	22%	66%			
7b	79%	125%	90%	91%	58%	19b	60%	130%	85%	94%	78%
7d	67%	33%	92%	92%	40%	20b	139%	77%	95%	100%	85%
7e	34%	42%	78%	89%	77%	21b	81%	126%	94%	98%	73%
(R)-8a	21%	186%	53%	85%	85%	22b	94%	118%	68%	94%	83%
(R)-8b	13%	116%	98%	96%	103%	22bR	59%	78%	69%	92%	75%
(S)-8b	88%	127%	89%	96%	81%	23b	56%	94%	93%	94%	49%
(R)-8c	96%	114%	82%	79%	59%	24b	65%	120%	93%	99%	66%
(R)-8d	74%	117%	93%	84%	80%	26a	50%	58%			
(R)-8e	72%	105%	36%	76%	93%	26c	50%	69%			
9a	33%	89%	97%	87%	85%	26e	100%	75%			
9b	20%	115%	63%	95%	88%	26f	35%	79%			
10a	65%	96%	90%	95%	91%	26g	30%	54%			
10b	61%	114%	87%	96%	85%	26k	36%	71%			
10c	75%	117%	77%	93%	88%	27a	61%	37%			
(S)-11a	57%	115%	83%	95%	98%	27c	77%	60%			
(S)-11b	53%	143%	96%	95%	76%	27f	54%	56%			
(S)-11c	56%	96%	94%	96%	82%	27g	66%	54%			
(R)-11c	40%	98%				27k	55%	88%			
(S)-11d	54%	106%	95%	97%	88%	28a	69%	96%	86%	95%	92%
(S)-11e	62%	32%	74%	92%	44%						

^{a)} Modulation of the reference ACh pulse (200 μ M, 5 s) after incubation with the compound (30 s, 10 μ M), measured in oocytes as described in the experimental section.

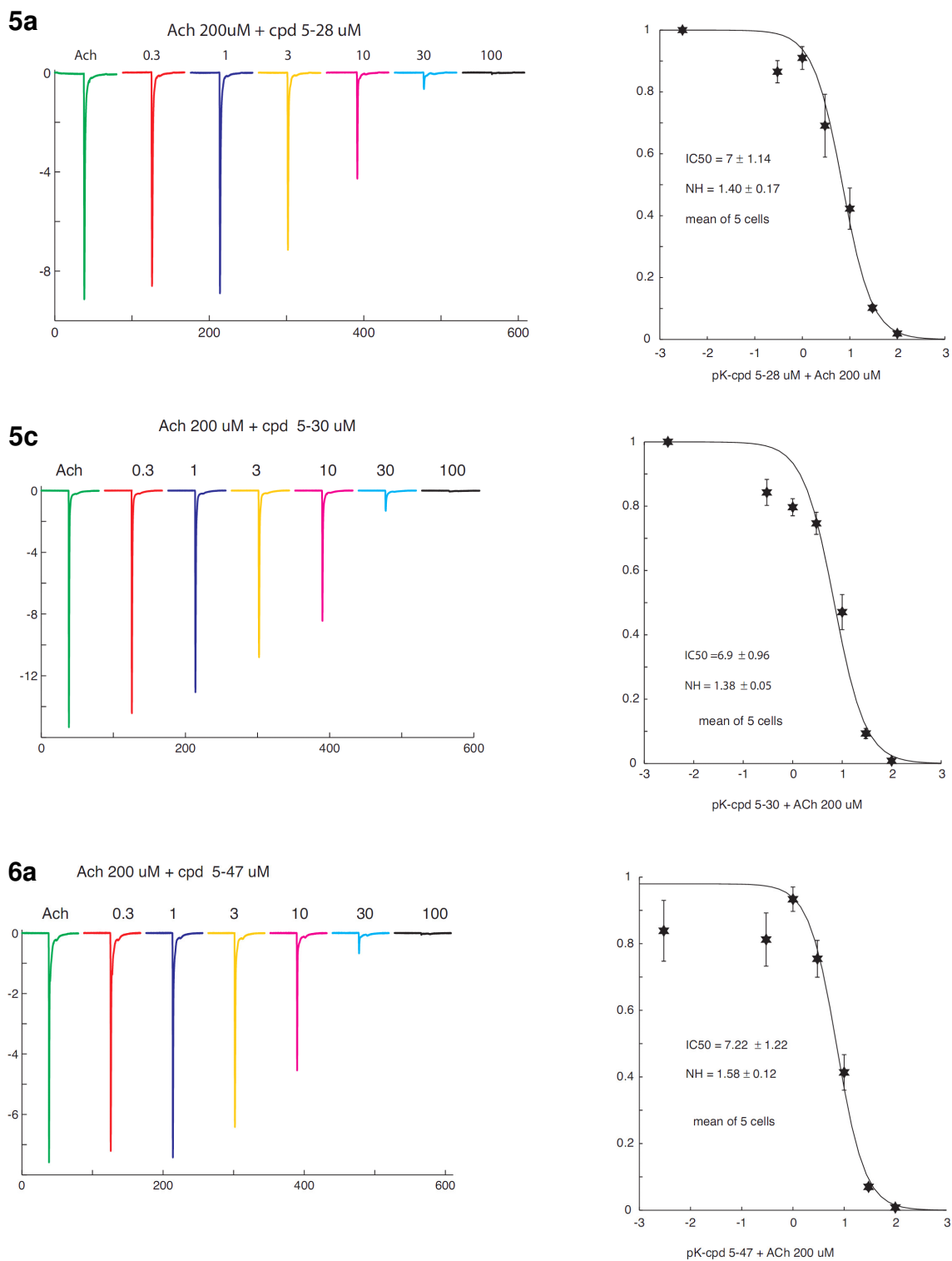


Figure S4. A. Electrophysiology traces for the determination of IC₅₀ at the $\alpha 7$ nAChR for **5a**, **5c**, **6a**.

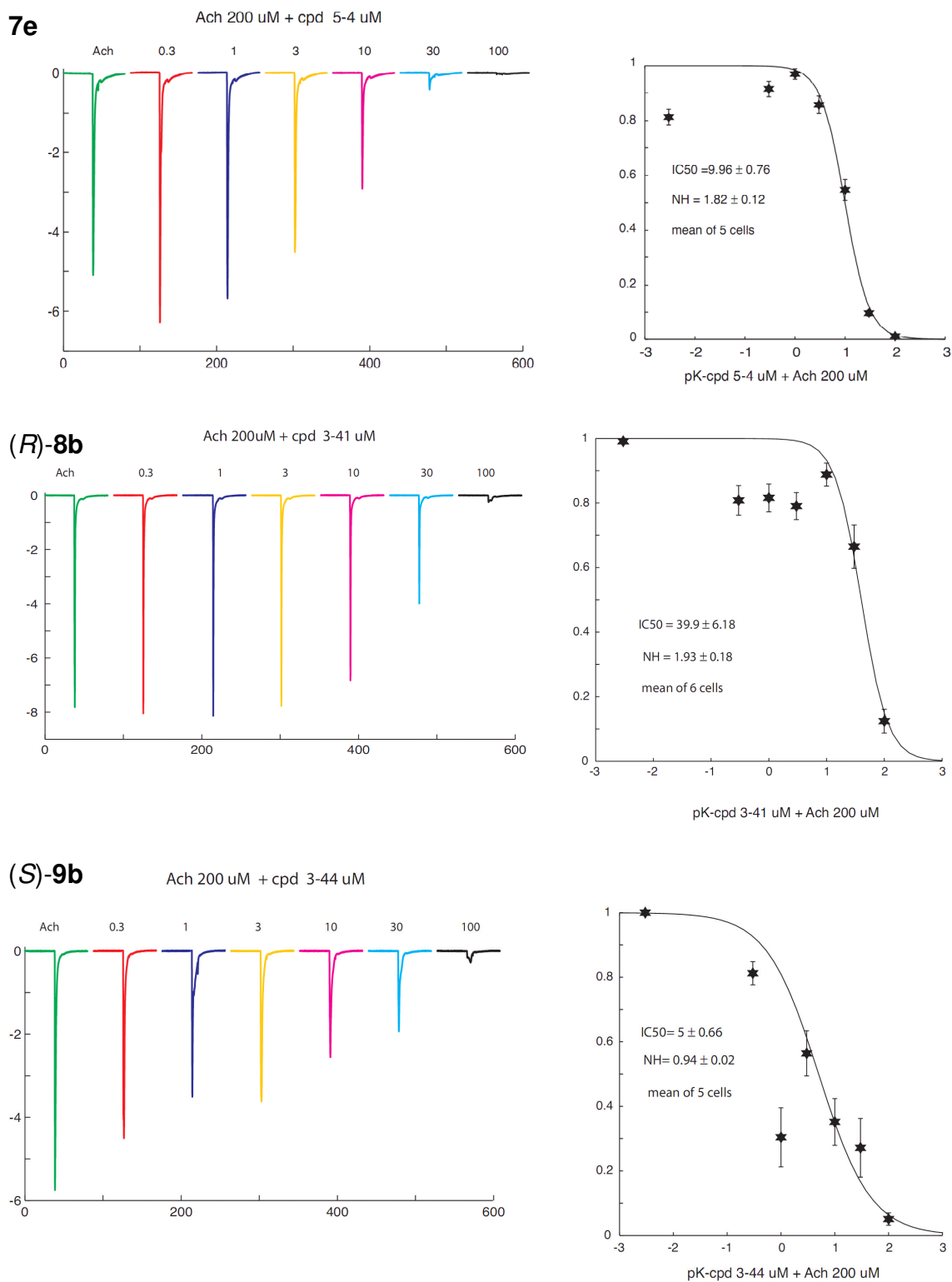


Figure S4. B. Electrophysiology traces for the determination of IC₅₀ at the $\alpha 7$ nAChR for **7e**, **(R)-8b**, **(S)-9b**.

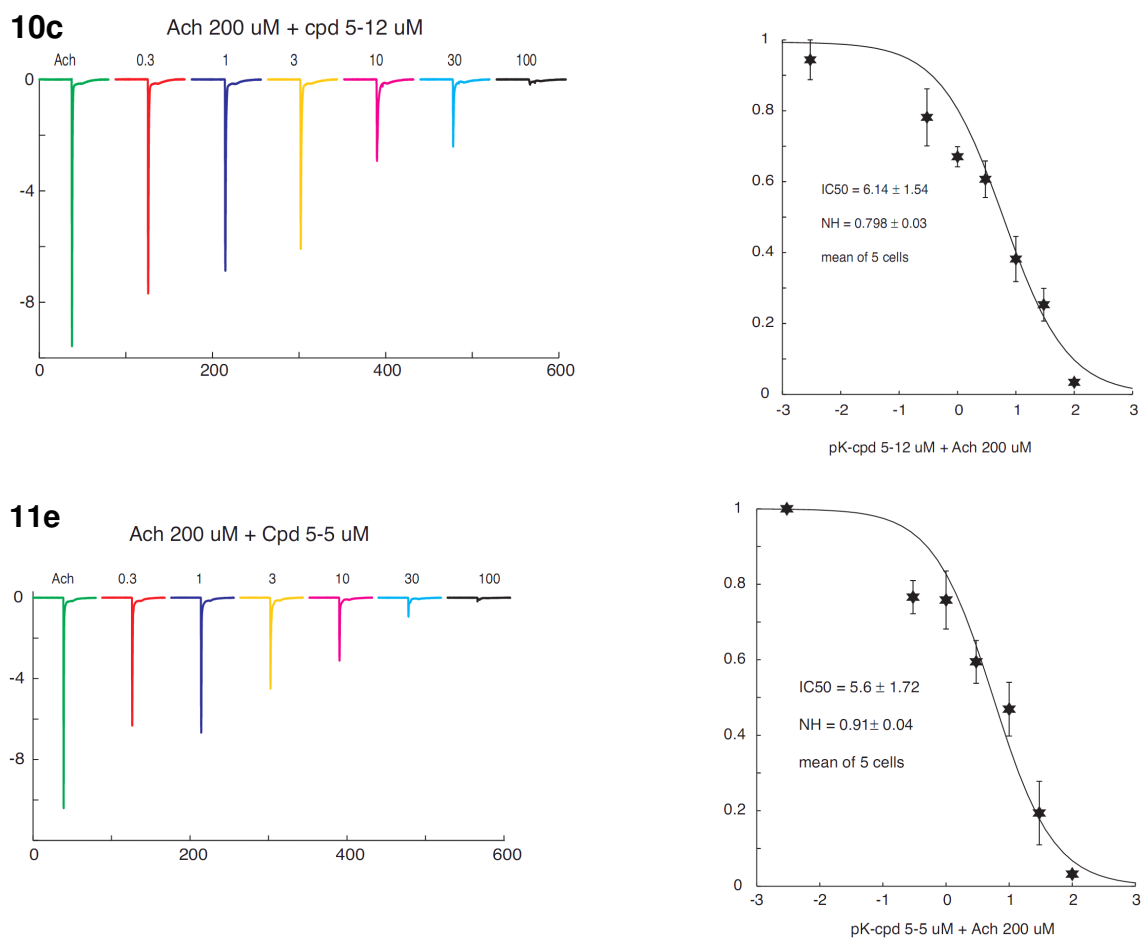


Figure S4. C. Electrophysiology traces for the determination of IC_{50} at the $\alpha 7$ nAChR for **10c**, **11e**.

Synthesis

General. All reagents used were purchased from commercial sources without further purification. All solvents used in reactions were distilled from technical quality. Dry solvents were obtained directly from a drying solvent system. Chromatographic purifications (flash) were performed with Silica Gel 60 from Fluka (0.04-0.063 mm; (230-400) mesh ASTM). Preparative RP-HPLC was performed with a Waters Delta Prep 4000 system with a Waters Prepak Cartridge (500 g) as column and Waters 486 Tunable Absorbance Detector or with a Waters Prep LC Controller system with a Dr. Maisch GmbH Reprospher C18-DE, 100 x 30 mm, particle size 5 μm , 100 \AA pore size column and a Waters 2489 UV/Visible Controller. Analytical RP-HPLC was performed on Waters 600E systems with a Waters Atlantis (4.6 mm \times 100 mm, dC₁₈, 5 μm) column, UV detection with Waters 996 photodiode array detector. Analytical RP-UHPLC was also performed on a Dionex ULTIMATE 3000 RS chromatography system (ULTIMATE 3000 RS Photo diode array detector) using a Dionex Acclaim® RSLC 120 C18, 3.0 x 50 mm, particle size 2.2 μm , 120 \AA pore size, flow rate 1.2 ml min⁻¹ column. Compounds were detected by UV absorption at 214 nm. Eluents for Waters Delta Prep 4000 system and Analytical RP-HPLC were: A: water with 0.1% TFA, C: Acetonitrile/water (90/10) with 0.1% TFA and D: Acetonitrile/water (40/60) with 0.1% TFA and for Waters Prep LC Controller system and Analytical RP-UHPLC were: A: water with 0.1% TFA and D: Acetonitrile/water (90/10) with 0.1% TFA. NMR spectra were acquired on a Bruker 300 MHz or a Bruker 400 MHz instrument. ¹H and ¹³C chemical shifts are quoted relative to solvent signals.¹ Carbons multiplicities have been assigned either by Attached Proton Test (APT), Distorsionless Enhancement Polarization Transfer (DEPT), Heteronuclear Multiple Bond Correlation spectroscopy (HMBC) or Heteronuclear Single Quantum Correlation (HSQC) spectroscopy experiments. Mass spectra were obtained by electron spray ionization (ES-MS) on a Micromass Autospec Q (Waters / Micromass) instrument in the positive mode.

Amide formation : Procedure A : The acid (1 eq), EDC (1.25 eq), HOBt (1.25 eq), *N*-methyl morpholine (2.5 eq, 4.5 eq when the amine was a salt) and the amine (1 eq) were dissolved in this order in CH₂Cl₂ (1 mL per 1 mmol of acid). The reaction was stirred for 14 hours at room temperature under Argon. Once the reaction was completed, it was evaporated under reduced pressure. Only for final compounds the residue was purified using a preparative RP-HPLC and only fractions with a purity >95% were lyophilised (unless otherwise indicated). *Procedure B :* The amine (1 eq) was mixed with the acid (3 eq) and PyBOP (3 eq) in dry DCM (10 mL per 1 mmol of amine) under argon atmosphere. Then diisopropylethylamine (5 eq) was added and the reaction was stirred for 14 hours at room temperature under Argon. Once the reaction was completed, it was

evaporated under reduced pressure and the residue was purified using a preparative RP-HPLC and only fractions with a purity >95% were lyophilised (unless otherwise indicated).

Carbamate formation: Procedure C: The diamine (1 eq) was dissolved in water (5 mL per 1 mmol), followed by the addition to the solution of NaOH in pellets (1 eq). The solution was cooled down to 0 °C. 4-Bromophenyl chloroformate (1.2 eq) was then added dropwise and, after some minutes, a white precipitate started appearing. After 3 hours, the reaction was extracted with CH₂Cl₂ (x3), the organics dried over Na₂SO₄, filtered and evaporated under reduced pressure. Unless otherwise indicated, the residue was purified using a preparative RP-HPLC and only fractions with a purity >95% were lyophilized. *Procedure D:* To a solution of 4-bromophenylchloroformate (1.2 eq) in dry THF (10 mL per 1 mmol) cooled to 0 °C under argon, were added dropwise NEt₃ (2 eq) and the diamine (1 eq) diluted in THF. The reaction mixture was then stirred for 2 hours at room temperature. The reaction was quenched with brine and extracted with EtOAc (x3), the organics layers dried over Na₂SO₄, filtered and evaporated under reduced pressure. Unless otherwise indicated, the residue was purified using a preparative RP-HPLC and only fractions with a purity >95% were lyophilized.

4-chloro-*N*-(2-(dimethylamino)ethyl)benzamide, TFA salt (3a). Using procedure A, this product was obtained from *N*-isopropyl ethylenediamine as a white solid (77 mg, 0.238 mmol, 17% yield). ¹H NMR (MeOD, 300 MHz) δ 7.88-7.81 (m, 2H), 7.50-7.43 (m, 2H), 3.76 (t, *J* = 6 Hz, 2H), 3.38 (t, *J* = 6 Hz, 2H), 2.97 (s, 6H); ¹³C NMR (MeOD, 75 MHz) δ 169.8, 139.2, 133.3, 130.1, 129.7, 58.6, 43.8, 36.3; MS (ESI⁺) *m/z* 227.4 ([M+1, Cl³⁵]⁺), 229.4 ([M+1, Cl³⁷]⁺); HRMS (ESI⁺) calcd. for C₁₁H₁₆Cl³⁵N₂O 227.0951 ([M+1]⁺) found 227.0959; Mp (°C) 150-151.

***N*-(2-(dimethylamino)ethyl)benzo[*d*]thiazole-6-carboxamide, TFA salt (3b).** Using procedure A, this product was obtained from *N*-isopropyl ethylenediamine as a yellow solid (228 mg, 0.658 mmol, 46% yield). ¹H NMR (MeOD, 300 MHz) δ 9.34 (s, 1H), 8.51 (d, *J* = 1 Hz, 1H), 8.03 (d, *J* = 8 Hz, 1H), 7.96 (dd, *J*₁ = 8 Hz, *J*₂ = 2 Hz, 1H), 3.84 (t, *J* = 6 Hz, 2H), 3.46 (t, *J* = 6 Hz, 2H), 3.02 (s, 6H); ¹³C NMR (MeOD, 75 MHz) δ 169.8, 159.8, 156.0, 135.1, 132.1, 126.5, 123.7, 123.1, 58.4, 43.8, 36.4; MS (ESI⁺) *m/z* 250.0 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₂H₁₆N₃OS 250.1014 ([M+1]⁺) found 250.1012; Mp (°C) 111-113.

***N*-(2-(dimethylamino)ethyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide, TFA salt (3c).** Using procedure A, this product was obtained from *N*-isopropyl ethylenediamine as a yellow oil (201 mg, 0.579 mmol, 41% yield). ¹H NMR (CDCl₃, 300 MHz) δ 8.22 (br t, 1H), 7.44-7.29 (m, 2H), 6.81 (dd, *J*₁ = 8 Hz, *J*₂ = 1 Hz, 1H), 4.29-4.18 (m, 4H), 3.80 (q, *J* = 5 Hz, 2H), 3.30 (t, *J* = 5 Hz, 2H), 2.87 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.7, 146.6, 143.0, 126.0, 120.5, 116.8,

116.5, 64.2, 63.8, 57.3, 43.0, 34.9; MS (ESI⁺) m/z 251.4 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₃H₁₉N₂O₃ 251.1395 ([M+1]⁺) found 251.1390.

***N*-(2-(dimethylamino)ethyl)-2,3-dihydrobenzo[*b*][1,4]dioxine-2-carboxamide, TFA salt (3d).**

Using procedure A, this product was obtained from *N*-isopropyl ethylenediamine as a colorless oil (40 mg, 0.115 mmol, 8% yield). ¹H NMR (CDCl₃, 300 MHz) δ 8.03 (br t, J = 6 Hz, 1H), 7.00-6.92 (m, 1H), 6.91-6.80 (m, 3H), 4.70 (dd, J_1 = 6 Hz, J_2 = 3 Hz, 1H), 4.36 (dd, J_1 = 11 Hz, J_2 = 3 Hz, 1H), 4.28 (dd, J_1 = 11 Hz, J_2 = 6 Hz, 1H), 3.82-3.53 (m, 2H), 3.19 (t, J = 6, 2H), 2.77 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.9, 143.1, 141.5, 122.1, 121.9, 117.4, 117.2, 73.0, 64.6, 57.0, 43.3, 34.4; MS (ESI⁺) m/z 251.6 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₃H₁₉N₂O₃ 251.1395 ([M+1]⁺) found 251.1403.

(4-chlorophenyl)(4-isopropylpiperazin-1-yl)methanone (4a). Using procedure A, this product was obtained from 1-(propan-2-yl)piperazine hydrate. The compound slowly hydrolyzes in 0.1% TFA (HPLC conditions). For that reason, after purification by preparative HPLC, the pure fractions were extracted with AcOEt/NaHCO₃ sat. to give **4a** as a foamy yellow oil (71 mg, 0.266 mmol, 25% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.36-7.27 (m, 4H), 3.73 (br s, 2H), 3.40 (br s, 2H), 2.74 (sep, J = 6 Hz, 1H), 2.54 (br s, 4H), 1.01 (d, J = 6 Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.9, 135.6, 133.9, 128.6, 128.5, 54.6, 48.5, 42.1, 18.0; MS (ESI⁺) m/z 267.2 ([M+1, Cl³⁵]⁺), 269.2 ([M+1, Cl³⁷]⁺); HRMS (ESI⁺) calcd. for C₁₄H₂₀Cl³⁵N₂O 267.1264 ([M+1]⁺) found 267.1264.

(benzo[*d*]thiazol-6-yl)(4-isopropylpiperazin-1-yl)methanone (4b). Using procedure A, this product was obtained from 1-(propan-2-yl)piperazine hydrate. The compound slowly hydrolyzes in 0.1% TFA (HPLC conditions). For that reason, after purification by preparative HPLC, the pure fractions were extracted with AcOEt/NaHCO₃ sat. to give **4b** as a yellow oil (80 mg, 0.276 mmol, 26% yield). ¹H NMR (CDCl₃, 300 MHz) δ 9.01 (s, 1H), 8.08 (d, J = 8 Hz, 1H), 7.99 (d, J = 1 Hz, 1H), 7.48 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 1H), 3.74 (br s, 2H), 3.40 (br s, 2H), 2.66 (sep, J = 6 Hz, 1H), 2.52 (br s, 2H), 2.44 (br s, 2H), 0.97 (d, J = 6 Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 169.1, 155.4, 153.6, 133.7, 133.1, 125.0, 123.3, 121.0, 54.3, 48.4, 42.5, 18.1; MS (ESI⁺) m/z 290.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₅H₂₀N₃OS 290.1327 ([M+1]⁺) found 290.1332.

(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(4-isopropylpiperazin-1-yl)methanone (4c). Using procedure A, this product was obtained from 1-(propan-2-yl)piperazine hydrate. The compound slowly hydrolyzes in 0.1% TFA (HPLC conditions). For that reason, after purification by preparative HPLC, the pure fractions were extracted with AcOEt/NaHCO₃ sat. to give **4c** as a yellow oil (130 mg, 0.448 mmol, 43% yield). ¹H NMR (CDCl₃, 300 MHz) δ 6.88-6.74 (m, 3H), 4.17 (s, 4H), 3.53 (br s, 4H), 2.63 (sep, J = 6 Hz, 1H), 2.42 (br s, 4H), 0.95 (d, J = 6 Hz, 6H); ¹³C

NMR (CDCl₃, 75 MHz) δ 169.3, 144.6, 143.0, 128.7, 120.4, 116.8, 116.4, 64.1, 64.0, 54.2, 48.4, 42.5, 18.1; MS (ESI⁺) m/z 291.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₆H₂₃N₂O₃ 291.1708 ([M+1]⁺) found 291.1703.

(2,3-dihydrobenzo[*b*][1,4]dioxin-3-yl)(4-isopropylpiperazin-1-yl)methanone (4d). Using procedure A, this product was obtained from 1-(propan-2-yl)piperazine hydrate. The compound slowly hydrolyzes in 0.1% TFA (HPLC conditions). For that reason, after purification by preparative HPLC, the pure fractions were extracted with AcOEt/NaHCO₃ sat. to give **4d** as a yellow oil was obtained (179 mg, 0.616 mmol, 59% yield). ¹H NMR (CDCl₃, 300 MHz) δ 6.93-6.71 (m, 4H), 4.73 (dd, $J_1 = 8$ Hz, $J_2 = 3$ Hz, 1H), 4.39 (dd, $J_1 = 11$ Hz, $J_2 = 2$ Hz, 1H), 4.22 (dd, $J_1 = 11$ Hz, $J_2 = 8$ Hz, 1H), 3.78-3.41 (m, 4H), 2.66 (sep, $J = 6$ Hz, 1H), 2.58-2.34 (m, 4H), 0.99 (d, $J = 6$ Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 164.3, 143.0, 142.3, 121.7, 121.1, 116.9, 70.2, 64.9, 54.1, 48.6, 47.8, 45.7, 42.0, 18.0; MS (ESI⁺) m/z 291.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₆H₂₃N₂O₃ 291.1708 ([M+1]⁺) found 291.1715.

4-bromophenyl 4-isopropylpiperazine-1-carboxylate (4e). Using procedure C, this product was obtained from 1-(propan-2-yl)piperazine hydrate. The compound slowly hydrolyzes in 0.1% TFA (HPLC conditions). For that reason, purification was done by column chromatography (neutral alumina, hexane/AcOEt 10%) to give **4e** as a white solid (128 mg, 0.391 mmol, 50% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.50-7.41 (m, 2H), 7.05-6.96 (m, 2H), 3.65 (br s, 2H), 3.56 (br s, 2H), 2.74 (sep, $J = 6$ Hz, 1H), 2.55 (t, $J = 5$ Hz, 4H), 1.06 (d, $J = 6$ Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 153.0, 150.4, 132.1, 123.4, 118.1, 54.5, 48.4, 48.2, 44.8, 44.3, 18.3; MS (ESI⁺) m/z 327.2 ([M+1, Br⁷⁹]⁺), 329.2 ([M+1, Br⁸¹]⁺); Mp (°C) 116-117; HRMS (ESI⁺) calcd. for C₁₄H₂₀Br⁷⁹N₂O₂ 327.0703 ([M+1]⁺) found 327.0701.

(benzo[*d*]thiazol-6-yl)(4-isopropyl-1,4-diazocan-1-yl)methanone (5b). Using procedure A, this product was obtained from amine **46**. The final compound slowly hydrolyzes in 0.1% TFA (HPLC conditions) For that reason, purification was done by column chromatography (neutral alumina, CH₂Cl₂/MeOH 0.5%) to give **5b** as a yellow oil (24 mg, 0.076 mmol, 59% yield). ¹H NMR (CDCl₃, 300 MHz) δ 9.03 (s, 1H), 8.13 (d, $J = 8$ Hz, 1H), 7.96 (s, 1H), 7.47 (d, $J = 8$ Hz, 1H), 3.99 (br s, 1H), 3.50 (br s, 2H), 2.97-2.02 (br m, 6H), 1.75 (br s, 4H), 1.18 (br s, 6H); ¹³C NMR (CDCl₃, 75 MHz) δ 170.7 (C), 155.1 (CH), 153.4 (C), 134.9 (C), 133.9 (C), 124.4 (CH), 123.6 (CH), 120.0 (CH), 54.9 (br CH₂), 54.2 (CH₂), 50.3 (br CH₂), 39.9 (br CH₂), 23.4 (CH₂), 20.9 (CH₃); MS (ESI⁺) m/z 318.0 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₇H₂₄N₃OS 318.1635 ([M+1]⁺) found 318.1631.

(2,3-dihydrobenzo[*b*][1,4]dioxin-3-yl)(4-isopropyl-1,4-diazocan-1-yl)methanone (5d). Using procedure A, this product was obtained from amine **46**. The final compound slowly hydrolyzes in

0.1% TFA (HPLC conditions) For that reason, purification was done by column chromatography (neutral alumina, CH₂Cl₂/MeOH 0.5%) to give **5d** as a yellow oil was obtained (15 mg, 0.047 mmol, 37% yield). ¹H NMR (CDCl₃, 300 MHz) diastereomeric mixture (1:2) δ 6.96-6.80 (m, 4H), 4.86 (dd, *J*₁ = 8 Hz, *J*₂ = 2 Hz, 0.3H), 4.81 (dd, *J*₁ = 8 Hz, *J*₂ = 2 Hz, 0.6H), 4.56-4.24 (m, 3H), 3.71-3.55 (m, 0.6H), 3.51-3.33 (m, 1.4H), 2.87-2.48 (m, 6H), 1.85-1.71 (m, 4H), 1.33 (d, *J* = 6 Hz, 2H), 1.24 (d, *J* = 6 Hz, 4H); ¹³C NMR (CDCl₃, 100 MHz) diastereomeric mixture (1:2) and 2 rotamers δ 165.9 (C), 143.3 (C), 142.7 (C), 122.1 (CH), 121.8 (CH), 121.4 (CH), 121.4 (CH), 117.3 (CH), 117.3 (CH), 71.0 (CH), 70.9 (CH), 65.7 (CH₂), 65.5 (CH₂), 56.8 (CH₂), 54.4 (CH₂), 54.2 (CH₂), 48.5 (CH), 47.4 (CH), 43.1 (CH₂), 40.2 (CH₂), 23.4 (CH₂), 21.3 (CH₃), 21.3 (CH₃), 20.3 (CH₃), 20.3 (CH₃); MS (ESI⁺) *m/z* 319.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₈H₂₇N₂O₃ 319.2016 ([M+1]⁺) found 319.2015.

***N*-((hexahydro-1*H*-pyrrolizin-7*a*-yl)methyl)benzo[*d*]thiazole-6-carboxamide (6b).** Using procedure A, this product was obtained from amine **63**. Purification by column chromatography (neutral alumina, CH₂Cl₂/MeOH 2%) gave **6b** as a yellow solid (47 mg, 0.156 mmol, 44% yield). ¹H NMR (CDCl₃, 300 MHz) δ 9.09 (s, 1H), 8.66 (s, 1H), 8.42 (br s, 1H), 8.20-8.07 (m, 2H), 3.72 (d, *J* = 6 Hz, 2H), 3.51-3.34 (m, 2H), 3.51-3.34 (m, 2H), 2.90-2.76 (m, 2H), 2.20-1.75 (m, 8H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.0, 156.5, 155.1, 134.0, 130.9, 125.2, 123.5, 121.9, 78.6, 55.4, 45.6, 35.7, 24.7; MS (ESI⁺) *m/z* 302.0 ([M+1]⁺); Mp (°C) 194-196; HRMS (ESI⁺) calcd. for C₁₆H₂₀N₃O₃ 302.1327 ([M+1]⁺) found 302.1328.

2,3-dihydro-*N*-((hexahydro-1*H*-pyrrolizin-7*a*-yl)methyl)benzo[*b*][1,4]dioxine-6-carboxamide (6c). Using procedure A, this product was obtained from amine **63**. Purification by column chromatography (neutral alumina, CH₂Cl₂/MeOH 2%) gave **6c** as a yellow oil (33 mg, 0.109 mmol, 31% yield). ¹H NMR (CDCl₃, 300 MHz) δ 8.10 (br s, 1H), 7.55-7.42 (m, 2H), 6.86 (d, *J* = 8 Hz, 1H), 4.30-4.18 (m, 4H), 3.63 (d, *J* = 6 Hz, 2H), 3.45-3.32 (m, 2H), 2.87-2.75 (m, 2H), 2.09-1.70 (m, 8H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.0, 146.5, 143.2, 126.9, 120.6, 117.1, 116.9, 78.8, 64.4, 64.0, 55.3, 45.3, 35.6, 24.6; MS (ESI⁺) *m/z* 303.2 ([M+1]⁺); HRMS (ESI⁺) calcd for C₁₇H₂₃N₂O₃ 303.1708 ([M+1]⁺) found 303.1714.

2,3-dihydro-*N*-((hexahydro-1*H*-pyrrolizin-7*a*-yl)methyl)benzo[*b*][1,4]dioxine-2-carboxamide (6d). Using procedure A, this product was obtained from amine **63**. Purification by column chromatography (neutral alumina, CH₂Cl₂/MeOH 2%) gave **6d** as a colorless oil (39 mg, 0.129 mmol, 36% yield). ¹H NMR (CDCl₃, 300 MHz) diastereomeric mixture (1:1) δ 7.62 (br s, 1H), 7.12-7.01 (m, 1H), 6.91-6.76 (m, 3H), 4.71 (t, *J* = 4 Hz, 1H), 4.36 (d, *J* = 4 Hz, 2H), 3.48 (dd, *J*₁ = 13 Hz, *J*₂ = 7 Hz, 1H), 3.19 (dd, *J*₁ = 13 Hz, *J*₂ = 5 Hz, 2H), 2.67-2.44 (m, 3H), 1.89-1.39 (m, 8H);

^{13}C NMR (CDCl_3 , 75 MHz) diastereomeric mixture (1:1) δ 168.0, 143.3, 141.6, 121.9, 121.8, 117.8, 117.2, 75.2, 73.3, 64.8, 55.6, 55.1, 45.8, 36.3, 35.2, 24.9, 24.4; MS (ESI^+) m/z 303.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_3$ 303.1708 ($[\text{M}+1]^+$) found 303.1707.

4-bromo-*N*-((hexahydro-1*H*-pyrrolizin-7*a*-yl)methyl)benzamide, TFA salt (6g). Using procedure A, this product was obtained from amine **63** as a colorless oil (9.2 mg, 0.02 mmol, 10 % yield). ^1H NMR (CDCl_3 , 300 MHz) δ 8.70 (m, 1H), 7.79 (d, $J = 9$ Hz, 2H), 7.58 (d, $J = 9$ Hz, 2H), 3.85 (d, $J = 6$ Hz, 2H), 3.75-3.65 (m, 2H), 3.08-2.98 (m, 2H), 2.30-2.21 (m, 2H), 2.13-1.92 (m, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.4, 132.2, 131.6, 129.3, 127.5, 82.7, 55.9, 45.1, 35.5, 24.6; MS (ESI^+) m/z 323.1 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{20}\text{ON}_2\text{Br}$ 323.0754 ($[\text{M}+1]^+$) found 323.0757.

4-methyl-*N*-((hexahydro-1*H*-pyrrolizin-7*a*-yl)methyl)benzamide, TFA salt (6h). Using procedure A, this compound was obtained from amine **63** as a colorless oil (17 mg, 0.05 mmol, 22 % yield). ^1H NMR (CDCl_3 , 300 MHz) δ 8.55 (bs, 1H), 7.83 (d, $J = 9$ Hz, 2H), 7.23 (d, $J = 9$ Hz, 2H), 3.85 (d, $J = 6$ Hz, 2H), 3.77-3.66 (m, 2H), 3.03-2.93 (m, 2H), 2.38 (s, 3H), 2.30-2.21 (m, 2H), 2.10-2.02 (m, 4H), 1.99-1.89 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.8, 142.8, 130.3, 129.6, 127.7, 82.4, 55.8, 44.8, 35.7, 24.6, 21.7; MS (ESI^+) m/z 259.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}$ 259.1805 ($[\text{M}+1]^+$) found 259.1811.

2-chloro-*N*-((hexahydro-1*H*-pyrrolizin-7*a*-yl)methyl)benzamide, TFA salt (6i). Using procedure A, this product was obtained from amine **63** as a colorless oil (6 mg, 0.015 mmol, 5 % yield). ^1H NMR (CDCl_3 , 300 MHz) δ 8.32 (bs, 1H), 7.51-7.27 (m, 4H), 3.87 (d, $J = 6$ Hz, 2H), 3.77-3.66 (m, 2H), 3.04-2.94 (m, 2H), 2.37-2.28 (m, 2H), 2.21-1.93 (m, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 169.1, 134.8, 131.8, 131.2, 130.6, 129.3, 127.3, 82.3, 55.9, 44.9, 35.6, 24.6; MS (ESI^+) m/z 279.1 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{ClO}$ 279.1259 ($[\text{M}+1]^+$) found 279.1264.

3-chloro-*N*-((hexahydro-1*H*-pyrrolizin-7*a*-yl)methyl)benzamide, TFA salt (6j). Using procedure A, this product was obtained from amine **63** as a colorless oil (37.2 mg, 0.09 mmol, 22% yield). ^1H NMR (MeOD, 300 MHz) δ 7.94 (t, $J = 3$ Hz, 1H), 7.84 (dq, $J_1 = 3$ Hz, $J_2 = 6$ Hz, 1H), 7.63 (dq, $J_1 = 3$ Hz, $J_2 = 6$ Hz, 1H), 7.51 (t, $J = 9$ Hz, 1H), 3.74 (s, 2H), 3.70-3.62 (m, 2H), 3.29-3.21 (m, 2H), 2.27-1.99 (m, 8H); ^{13}C NMR (MeOD, 75 MHz) δ 171.7, 136.1, 135.8, 133.7, 131.6, 129.0, 127.2, 84.4, 56.8, 47.5, 35.9, 25.4; MS (ESI^+) m/z 279.1 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{ClO}$ 279.1259 ($[\text{M}+1]^+$) found 279.1264.

4-chloro-*N*-(2-(piperidin-1-yl)cyclohexyl)benzamide, TFA salt (7a). Using procedure A, this product was obtained from the corresponding amine which was prepared according the ref ¹, as a

white solid (136 mg, 0.325 mmol, 59% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 10.07 (br s, 1H), 8.76 (br d, $J = 10$ Hz, 1H), 7.83 (d, $J = 9$ Hz, 2H), 7.36 (d, $J = 9$ Hz, 2H), 4.44-4.28 (m, 1H), 4.10 (br s, 1H), 3.65-3.46 (m, 2H), 3.24-3.13 (m, 1H), 3.01-2.84 (m, 1H), 2.71-2.53 (m, 1H), 2.28-1.20 (m, 14H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.9, 138.0, 131.7, 128.8, 128.6, 66.6, 52.7, 48.9, 46.4, 33.2, 24.5, 24.4, 23.8, 23.3, 22.7, 22.2; MS (ESI^+) m/z 321.4 ($[\text{M}+1, \text{Cl}^{35}]^+$), 323.4 ($[\text{M}+1, \text{Cl}^{37}]^+$); HRMS (ESI^+) calcd. for $\text{C}_{18}\text{H}_{26}\text{Cl}^{35}\text{N}_2\text{O}$ 321.1733 ($[\text{M}+1]^+$) found 321.1723; Mp ($^\circ\text{C}$) 119-123.

***N*-(2-(piperidin-1-yl)cyclohexyl)benzo[*d*]thiazole-6-carboxamide, TFA salt (7b).** Using procedure A, this product was obtained from the corresponding amine which was prepared according the ref¹ as a yellow solid (148 mg, 0.336 mmol, 61% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 9.82 (br s, 1H), 9.12 (s, 1H), 8.79 (br d, $J = 10$ Hz, 1H), 8.56 (d, $J = 1$ Hz, 1H), 8.12 (d, $J = 8$ Hz, 1H), 8.03 (dd, $J_1 = 8$ Hz, $J_2 = 2$ Hz, 1H), 4.48-4.32 (m, 1H), 3.71-3.46 (m, 2H), 3.27-3.13 (m, 1H), 3.02-2.84 (m, 1H), 2.74-2.56 (m, 1H), 2.23-1.20 (m, 14H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 167.3, 157.0, 154.9, 133.4, 130.7, 125.6, 123.2, 121.7, 66.8, 52.7, 49.1, 46.5, 33.1, 24.4, 24.3, 23.8, 23.3, 22.7, 22.1; MS (ESI^+) m/z 344.4 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_3\text{OS}$ 344.1796 ($[\text{M}+1]^+$) found 344.1794; Mp ($^\circ\text{C}$) 185-186.

2,3-dihydro-*N*-(2-(piperidin-1-yl)cyclohexyl)benzo[*b*][1,4]dioxine-6-carboxamide, TFA salt (7c). Using procedure A, this product was obtained from the corresponding amine which was prepared according the ref¹ as a yellow solid (86 mg, 0.195 mmol, 35% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 10.4 (br s, 1H), 9.54 (br s, 1H), 8.31 (br d, $J = 9$ Hz, 1H), 7.46 (d, $J = 2$ Hz, 1H), 7.38 (dd, $J_1 = 8$ Hz, $J_2 = 2$ Hz, 1H), 6.87 (d, $J = 8$ Hz, 1H), 4.44-4.21 (m, 5H), 3.76-3.64 (m, 1H), 3.60-3.47 (m, 1H), 3.30-3.17 (m, 1H), 3.05-2.89 (m, 1H), 2.75-2.59 (m, 1H), 2.24-1.23 (m, 14H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 167.5, 146.9, 143.3, 126.3, 120.6, 117.0, 116.9, 67.2, 64.5, 64.0, 52.6, 48.8, 46.8, 33.0, 24.3, 23.8, 23.2, 22.7, 22.1; MS (ESI^+) m/z 345.4 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_3$ 345.2178 ($[\text{M}+1]^+$) found 345.2171; Mp ($^\circ\text{C}$) 95-97.

2,3-dihydro-*N*-(2-(piperidin-1-yl)cyclohexyl)benzo[*b*][1,4]dioxine-2-carboxamide, TFA salt (7d). Using procedure A, this product was obtained from the corresponding amine, itself prepared according ref. 40, as a white solid (26 mg, 0.059 mmol, 11% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 10.15 (br s, 1H), 8.36 (br d, $J = 10$ Hz, 1H), 7.06-6.91 (m, 1H), 6.90-6.80 (m, 3H), 4.67 (dd, $J_1 = 8$ Hz, $J_2 = 3$ Hz, 1H), 4.44 (dd, $J_1 = 11$ Hz, $J_2 = 3$ Hz, 1H), 4.38-4.16 (m, 2H), 3.64-3.42 (m, 2H), 3.21-3.11 (m, 1H), 2.95-2.79 (m, 1H), 2.64-2.47 (m, 1H), 2.19-1.19 (m, 14H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.1, 143.0, 141.7, 121.9, 121.8, 117.7, 117.0, 73.3, 66.4, 65.0, 51.8, 48.1, 47.3, 33.3, 24.4, 24.4, 24.2, 23.0, 22.5, 22.2; MS (ESI^+) m/z 345.4 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_3$ 345.2178 ($[\text{M}+1]^+$) found 345.2162; Mp ($^\circ\text{C}$) 206-207.

4-chloro-*N*-(((*R*)-1-(pent-2-ynyl)pyrrolidin-2-yl)methyl)benzamide, TFA salt (8a**).** Using procedure A, this product was obtained from amine **31** as a yellow oil (219 mg, 0.545 mmol, 60% yield). ¹H NMR (CDCl₃, 300 MHz) δ 12.20 (br s, 1H), 8.78 (t, $J = 6$ Hz, 1H), 7.87 (dd, $J_1 = 9$ Hz, $J_2 = 1$ Hz, 2H), 7.39 (dd, $J_1 = 9$ Hz, $J_2 = 2$ Hz, 2H), 4.06-3.63 (m, 6H), 3.35-3.20 (m, 1H), 2.32-1.85 (m, 6H), 1.09 (td, $J_1 = 7$ Hz, $J_2 = 2$ Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.4 (C), 138.2 (C), 131.2 (C), 128.8 (CH), 128.7 (CH), 93.2 (C), 66.6 (C), 65.4 (CH), 53.5 (CH₂), 44.0 (CH₂), 39.7 (CH₂), 27.9 (CH₂), 23.2 (CH₂), 13.0 (CH₃), 12.1 (CH₂); MS (ESI⁺) m/z 305.2 ([M+1, Cl³⁵]⁺), 307.2 ([M+1, Cl³⁷]⁺); HRMS (ESI⁺) calcd. for C₁₇H₂₂Cl³⁵N₂O 305.1420 ([M+1]⁺) found 305.1424.

***N*-(((*S*)-1-(pent-2-ynyl)pyrrolidin-2-yl)methyl)benzo[*d*]thiazole-6-carboxamide, TFA salt ((*S*)-**8b**).** In a similar synthesis to that for (*R*)-**8b**, and starting from L-proline methyl ester hydrochloride (0.400 g, 2.41 mmol), (*S*)-**8b** was obtained after HPLC purification as a colorless oil (0.040 g, 0.094 mmol, 47% yield).

2,3-dihydro-*N*-(((*R*)-1-(pent-2-ynyl)pyrrolidin-2-yl)methyl)benzo[*b*][1,4]dioxine-6-carboxamide (8c**).** Using procedure A, this product was obtained from amine **31** as a yellow oil (98 mg, 0.230 mmol, 28% yield). ¹H NMR (CDCl₃, 300 MHz) δ 12.18 (br s, 1H), 8.54 (t, $J = 6$ Hz, 1H), 7.53 (d, $J = 2$ Hz, 1H), 7.38 (dd, $J_1 = 8$ Hz, $J_2 = 2$ Hz, 1H), 6.83 (d, $J = 8$ Hz, 1H), 4.28-4.17 (m, 4H), 4.02-3.77 (m, 4H), 3.75-3.60 (m, 2H), 3.31-3.18 (m, 1H), 2.29-1.81 (m, 6H), 1.06 (t, $J = 7$ Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.9 (C), 146.9 (C), 143.3 (C), 126.0 (C), 120.6 (CH), 117.1, (CH), 116.9 (CH), 93.0 (C), 66.8 (C), 65.5 (CH), 64.4 (CH₂), 64.0 (CH₂), 53.5 (CH₂), 44.1 (CH₂), 40.0 (CH₂), 28.1 (CH₂), 23.3 (CH₂), 13.0 (CH₃), 12.1 (CH₂); MS (ESI⁺) m/z 329.4 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₉H₂₅N₂O₃ 329.1865 ([M+1]⁺) found 329.1873.

2,3-dihydro-*N*-(((*R*)-1-(pent-2-ynyl)pyrrolidin-2-yl)methyl)benzo[*b*][1,4]dioxine-2-carboxamide (8d**).** Using procedure A, this product was obtained from amine **31** as a colorless oil (106 mg, 0.249 mmol, 28% yield). ¹H NMR (CDCl₃, 300 MHz) diastereomeric mixture (1:1) δ 12.04 (br s, 1H), 8.53 (t, $J = 6$ Hz, 0.5H), 8.24 (t, $J = 6$ Hz, 0.5H), 7.05-6.96 (m, 1H), 6.91-6.77 (m, 3H), 4.79-4.72 (m, 1H), 4.55 (dd, $J_1 = 11$ Hz, $J_2 = 4$ Hz, 0.5H), 4.43-4.30 (m, 1H), 4.27 (dd, $J_1 = 11$ Hz, $J_2 = 3$ Hz, 0.5H), 3.97-3.52 (m, 4H), 3.50-3.31 (m, 1.5H), 3.23-3.06 (m, 1.5H), 2.27-1.66 (m, 6H), 1.12 (td, $J_1 = 7$ Hz, $J_2 = 1$ Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ diastereomeric mixture (1:1) 169.4 (C), 169.3 (C), 143.1 (C), 141.5 (C), 141.3 (C), 122.2 (CH), 122.1 (CH), 122.1 (CH), 118.1 (CH), 117.8 (CH), 117.8 (CH), 117.2 (CH), 117.1 (CH), 93.1 (C), 92.8 (C), 73.2 (CH), 73.1 (CH), 66.8 (C), 66.8 (C), 65.0 (CH), 64.5 (CH₂), 64.1 (CH₂), 53.7 (CH₂), 53.4 (CH₂), 44.0 (CH₂), 43.9 (CH₂), 40.1 (CH₂), 38.8 (CH₂), 28.9 (CH₂), 27.8 (CH₂), 23.5 (CH₂), 23.3 (CH₂), 13.2 (CH₃), 13.1

(CH₃), 12.2 (CH₂); MS (ESI⁺) m/z 329.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₉H₂₅N₂O 329.1865 ([M+1]⁺) found 329.1853.

4-bromophenyl ((R)-1-(pent-2-ynyl)pyrrolidin-2-yl)methylcarbamate, TFA salt (8e). Using procedure C, this product was obtained from amine **31** as a colorless oil (25 mg, 0.054 mmol, 9% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.56 (br t, 1H), 7.44 (d, J = 9 Hz, 2H), 7.02 (d, J = 9 Hz, 2H), 4.12-3.52 (m, 6H), 3.36-3.22 (m, 1H), 2.30-1.86 (m, 6H), 1.15 (t, J = 7 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 155.1 (C), 150.0 (C), 132.2 (CH), 123.3 (CH), 118.3 (CH), 93.3 (C), 66.8 (C), 64.8 (CH), 53.6 (CH₂), 44.0 (CH₂), 41.2 (CH₂), 28.2 (CH₂), 23.2 (CH₂), 13.2 (CH₃), 12.3 (CH₂); MS (ESI⁺) m/z 365.0 ([M+1, Br⁷⁹]⁺), 367.0 ([M+1, Br⁸¹]⁺); HRMS (ESI⁺) calcd. for C₁₇H₂₂N₂O₂Br⁷⁹ 365.0864 ([M+1]⁺) found 365.0870.

4-chloro-N-((S)-1-(2-methylcyclopentyl)pyrrolidin-3-yl)benzamide, TFA salt (9a). Using procedure A, this product was obtained from amine (*S*)-**43** as a yellow oil (75 mg, 0.186 mmol, 42% yield). ¹H NMR (CDCl₃, 300 MHz) diastereomeric mixture (1.5:1) δ 11.58 (br s, 0.6H), 11.40 (br s, 0.4H), 9.00 (br d, J = 8 Hz, 0.6H), 8.86 (br d, J = 7 Hz, 0.4H), 7.88 (d, J = 8 Hz, 1.2H), 7.82 (d, J = 8 Hz, 0.8H), 7.41-7.32 (m, 2H), 5.16-4.95 (m, 1H), 4.02-3.73 (m, 2H), 3.32-2.87 (m, 3H), 2.66-2.49 (m, 1H), 2.45-1.48 (m, 8H), 1.09 (d, J = 7 Hz, 1.2H), 1.03 (d, J = 7 Hz, 1.8H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.6 (C), 166.3 (C), 138.1 (C), 131.4 (C), 128.9 (CH), 128.9 (CH), 128.6 (CH), 71.2 (CH), 71.1 (CH), 60.4 (CH₂), 59.4 (CH₂), 54.4 (CH₂), 53.0 (CH₂), 47.8 (CH), 47.5 (CH), 34.9 (CH), 34.8 (CH), 31.2 (CH₂), 31.1 (CH₂), 30.7 (CH₂), 30.5 (CH₂), 25.5 (CH₂), 25.3 (CH₂), 19.7 (CH₂), 19.5 (CH₂), 13.8 (CH₃), 13.5 (CH₃); MS (ESI⁺) m/z 307.1 ([M+1, Cl³⁵]⁺), 309.1 ([M+1, Cl³⁷]⁺); HRMS (ESI⁺) calcd. for C₁₇H₂₄Cl³⁵N₂O 307.1577 ([M+1]⁺) found 307.1571.

(4-chlorophenyl)((3*S*,9*aR*)-hexahydro-3-methyl-1*H*-pyrido[1,2-*a*]pyrazin-2(6*H*)-yl)methanone, TFA salt (10a). Using procedure A, this product was obtained from amine **48** as a colorless oil (24 mg, 0.061 mmol, 47% yield). ¹H NMR (D₂O, 400 MHz at 353K) δ 8.06 (br s, 2H), 7.92 (br s, 2H), 5.25 (br s, 1H), 4.41 (br s, 2H), 4.30-3.72 (br m, 4H), 3.58 (br s, 2H), 2.64-1.88 (br m, 9H); ¹³C NMR (D₂O, 100 MHz at 353K) δ 172.7 (C), 136.6 (C), 132.9 (C), 129.7 (CH), 128.6 (CH), 57.3 (CH), 54.0 (CH₂), 47.8 (CH₂), 21.6 (CH₂), 21.3 (CH₂), 17.4 (CH₂), 15.3 (CH₃); MS (ESI⁺) m/z 293.2 ([M+1, Cl³⁵]⁺), 295.2 ([M+1, Cl³⁷]⁺); HRMS (ESI⁺) calcd. for C₁₆H₂₂Cl³⁵N₂O 293.1420 ([M+1]⁺) found 293.1407.

(benzo[*d*]thiazol-6-yl)((3*S*,9*aR*)-hexahydro-3-methyl-1*H*-pyrido[1,2-*a*]pyrazin-2(6*H*)-yl)methanone, TFA salt (10b). Using procedure A, this product was obtained from amine **48** as a colorless oil (22 mg, 0.053 mmol, 41% yield). ¹H NMR (D₂O, 400 MHz at 353K) δ 8.67-8.48 (m, 2H), 8.14-7.91 (m, 1H), 5.14 (br s, 1H), 4.51-3.26 (m, 7H), 2.54-1.65 (m, 9H); ¹³C NMR (D₂O, 100

MHz at 353K) δ 160.3 (CH), 134.5 (C), 131.8 (C), 125.3 (CH), 123.6 (CH), 121.6 (CH), 57.3 (CH), 54.0 (CH₂), 47.8 (CH₂), 21.6 (CH₂), 21.3 (CH₂), 17.4 (CH₂), 15.3 (CH₃); MS (ESI⁺) m/z 316.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₇H₂₂N₃OS 316.1483 ([M+1]⁺) found 316.1478.

(4-chlorophenyl)-((S)-hexahydro-1H-pyrrolo[1,2-*a*][1,4]diazepin-2(3H)-yl)methanone, TFA salt ((S)-11a). Using procedure A, this product was obtained from amine **51** as a yellow oil (84 mg, 0.223 mmol, 52% yield). ¹H NMR (D₂O, 400 MHz) mixture of isomers δ 7.53-7.32 (m, 4H), 4.49-4.32 (m, 0.5H), 4.25-4.16 (dd, $J_1 = 15$ Hz, $J_2 = 2$ Hz, 0.2H), 4.15-4.04 (m, 0.6H), 3.99 (dd, $J_1 = 15$ Hz, $J_2 = 3$ Hz, 0.2H), 3.88-3.45 (m, 5.5H), 3.35-3.05 (m, 2H), 2.51-2.40 (m, 0.3H), 2.38-2.27 (m, 0.3H), 2.26-1.75 (m, 5H), 1.64-1.50 (m, 0.3H); ¹³C NMR (D₂O, 75 MHz) mixture of 3 isomers δ 173.0, 172.7, 172.0, 136.1, 135.8, 135.8, 133.1, 132.9, 132.7, 128.9, 128.6, 128.0, 128.0, 66.9, 66.1, 65.3, 57.2, 56.8, 56.6, 53.8, 52.7, 50.9, 50.1, 50.0, 46.8, 46.1, 45.1, 43.3, 28.4, 28.2, 27.9, 26.8, 25.6, 24.4, 23.7, 21.4, 21.2; MS (ESI⁺) m/z 279.0 ([M+1, Cl³⁵]⁺), 281.2 ([M+1, Cl³⁷]⁺); HRMS (ESI⁺) calcd. for C₁₅H₁₉ClN₂NaO 301.1083 ([M+1]⁺) found 301.1091.

(benzo[*d*]thiazol-6-yl)((S)-hexahydro-1H-pyrrolo[1,2-*a*][1,4]diazepin-2(3H)-yl)methanone, TFA salt ((S)-11b). Using procedure A, this product was obtained from amine **51** as a yellow oil (133 mg, 0.334mmol, 47% yield). ¹H NMR (D₂O, 400 MHz) mixture of isomers δ 9.09 (s, 1H), 7.93-7.78 (m, 2H), 7.49-7.18 (m, 1H), 4.40-4.22 (m, 0.5H), 4.15-3.93 (m, 1H), 3.87-3.30 (m, 5.5H), 3.22-2.92 (m, 2H), 2.50-1.25 (m, 6H); ¹³C NMR (D₂O, 75 MHz) mixture of 3 isomers δ 172.8, 172.6, 171.8, 159.3, 159.1, 152.3, 152.1, 133.4, 131.9, 131.7, 131.6, 126.5, 125.4, 124.8, 122.6, 121.6, 120.8, 113.5, 112.3, 66.9, 66.1, 65.2, 57.2, 56.8, 56.6, 53.9, 52.7, 50.9, 50.2, 50.1, 46.8, 46.1, 45.1, 43.3, 28.4, 28.2, 27.9, 26.8, 25.6, 24.4, 23.7, 21.4, 21.2; MS (ESI⁺) m/z 302.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₆H₂₀N₃OS 302.1327 ([M+1]⁺) found 302.1319.

((S)-hexahydro-1H-pyrrolo[1,2-*a*][1,4]diazepin-2(3H)-yl)(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methanone, TFA salt ((S)-11c). Using procedure A, this product was obtained from amine **51** as a yellow oil (86 mg, 0.215mmol, 30% yield). ¹H NMR (D₂O, 400 MHz) δ 7.00-6.88 (m, 3H), 4.48-3.97 (m, 6H), 3.87-3.49 (m, 5H), 3.39-3.05 (m, 2H), 2.54-1.54 (m, 6H); ¹³C NMR (D₂O, 75 MHz) mixture of 3 isomers δ 173.3, 173.0, 172.3, 145.2, 144.9, 143.1, 143.0, 127.7, 127.5, 127.4, 120.9, 120.3, 120.2, 117.5, 116.4, 115.8, 67.1, 66.2, 65.3, 64.6, 64.4, 57.2, 56.8, 56.6, 53.9, 52.7, 50.9, 50.3, 50.2, 46.9, 46.2, 45.1, 43.3, 28.4, 28.2, 28.0, 26.9, 25.7, 24.4, 23.8, 21.5, 21.2; MS (ESI⁺) m/z 303.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₇H₂₃N₂O₃ 303.1708 ([M+1]⁺) found 303.1700.

((S)-hexahydro-1H-pyrrolo[1,2-*a*][1,4]diazepin-2(3H)-yl)(2,3-dihydrobenzo[*b*][1,4]dioxin-2-yl)methanone, TFA salt ((S)-11d). Using procedure A, this product was obtained from amine **51** as a colorless oil (37 mg, 0.109mmol, 15% yield). ¹H NMR (D₂O, 400 MHz) δ 7.10-6.93 (m, 4H),

5.37-5.28 (m, 1H), 4.50-4.26 (m, 3H), 4.22-3.11 (m, 8H), 2.56-1.78 (m, 6H); ^{13}C NMR (D_2O , 75 MHz) mixture of isomers δ 169.0 168.9, 168.3, 142., 142.1, 142.0, 122.4, 122.3, 70.5, 70.1, 70.0, 67.1, 66.7, 65.2, 64.4, 64.2, 57.3, 57.2, 56.2, 54.1, 52.2, 51.2, 48.3, 47.4, 46.1, 45.6, 44.8, 43.0, 28.4, 28.2, 27.6, 27.0, 25.1, 24.6, 23.7, 21.8, 20.9; MS (ESI^+) m/z 303.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_3$ 303.1708 ($[\text{M}+1]^+$) found 303.1697.

((R)-hexahydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methanone, TFA salt ((R)-11c). Using procedure A, this compound was obtained from amine (R)-51 as a colorless oil (33 mg, 0.08 mmol, 37%). ^1H NMR (D_2O , 300 MHz) δ 7.05-6.96 (m, 3H), 4.36 (s, 4H), 4.29-3.53 (m, 7H), 3.42-3.09 (m, 2H), 2.49-1.60 (m, 6H); ^{13}C NMR (D_2O , 75 MHz) mixture of 3 isomers δ 173.6, 173.4, 172.7, 145.3, 145.1, 143.1, 127.7, 127.4, 120.9, 120.3, 118.3, 117.6, 117.5, 116.4, 115.8, 114.5, 67.2, 66.3, 65.4, 64.7, 64.6, 57.2, 56.9, 56.7, 53.9, 52.9, 51.1, 50.3, 47.1, 46.3, 45.2, 43.4, 28.4, 28.1, 26.9, 25.8, 24.5, 23.8, 21.6, 21.3; MS (ESI^+) m/z 303.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}_3$ 303.1703 ($[\text{M}+1]^+$) found 303.1710.

(R)-4-bromophenyl hexahydro-1H-pyrrolo[1,2-a][1,4]diazepine-2(3H)-carboxylate ((R)-11e). Using procedure D, This compound was obtained from amine (R)-51 as a colorless oil (8mg, 0.02 mmol, 9% yield) after purification on silica (DCM, then MeOH). ^1H NMR (CDCl_3 , 300 MHz) δ 7.44 (d, $J=9$ Hz, 2H), 6.98 (d, $J=9$ Hz, 2H), 4.00-3.91 (m, 1H), 3.77-3.48 (m, 2H), 3.22-2.96 (m, 3H), 2.75-2.22 (m, 3H), 2.07-1.66 (m, 6H), 1.55-1.42 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) mixture of 2 isomers δ 154.3, 150.8, 132.6, 132.4, 123.8, 123.8, 118.4, 117.5, 65.7, 65.3, 57.6, 57.5, 54.2, 53.9, 46.4, 46.0, 30.0, 29.7, 28.1, 22.8, 22.7; MS (ESI^+) m/z 339.1 ($[\text{M}+1, \text{Br}^{79}]^+$), 341.1 ($[\text{M}+1, \text{Br}^{81}]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{20}\text{Br}^{79}\text{N}_2\text{O}_2$ 339.0703($[\text{M}+1]^+$) found 339.0697.

((R)-hexahydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)(phenyl)methanone, TFA salt ((R)-11f). Using procedure A, this compound was obtained from amine (R)-51 as a colorless oil (40 mg, 0.08 mmol, 24%). ^1H NMR (D_2O , 300 MHz) δ 7.60-7.44 (m, 5H), 4.48-3.49 (m, 7H), 3.41-3.12 (m, 2H), 2.56-1.56(m, 6H); ^{13}C NMR (D_2O , 75 MHz) mixture of 3 isomers δ 174.5, 174.2, 173.5, 134.6, 134.3, 134.2, 130.8, 130.6, 130.5, 128.9, 126.9, 126.3, 67.2, 66.2, 65.4, 57.3, 56.9, 56.8, 51.1, 50.2, 45.1, 43.4, 28.5, 28.3, 27.9, 26.9, 25.8, 24.5, 23.8, 21.5, 21.3; MS (ESI^+) m/z 245.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}$ 245.1648 ($[\text{M}+1]^+$) found 245.1642.

(4-bromophenyl)((R)-hexahydro-1H-pyrrolo[1,2-a][1,4]diazepin-2(3H)-yl)methanone, TFA salt ((R)-11g). Using procedure A, this compound was obtained from amine (R)-51 as a colorless oil (25 mg, 16%). ^1H NMR (D_2O , 300 MHz) δ 7.70 (d, $J=9$ Hz, 2H), 7.37 (m, 2H), 4.46-3.11 (m, 9H), 2.55-1.57 (m, 6H); ^{13}C NMR (D_2O , 75 MHz) mixture of 3 isomers δ 173.4, 173.1, 172.5, 133.5, 133.3, 133.1, 132.3, 132.0, 128.8, 128.2, 124.6, 124.3, 124.2, 67.1, 66.2, 65.4, 57.3, 56.8,

51.0, 50.2, 50.2, 46.2, 45.2, 28.5, 28.3, 28.0, 26.8, 25.8, 24.5, 23.8, 21.5, 21.3; MS (ESI⁺) m/z 323.1 ([M+1, Br⁷⁹]⁺), 325.1 ([M+1, Br⁸¹]⁺); HRMS (ESI⁺) calcd. for C₁₅H₂₀Br⁷⁹N₂O 323.0754 ([M+1]⁺) found 323.0747.

(4-fluorophenyl)((R)-hexahydro-1H-pyrrolo[1,2-*a*][1,4]diazepin-2(3H)-yl)methanone, TFA salt ((R)-11k). Using procedure A, this compound was obtained from amine (*R*)-**51** as a colorless oil (5mg, 0.013 mmol, 6%). ¹H NMR (D₂O, 300 MHz) δ 7.55-7.47 (m, 2H), 7.29-7.23 (m, 2H), 4.46-3.50 (m, 7H), 3.42-3.12 (m, 2H), 2.53-1.58 (m, 6H); ¹³C NMR (D₂O, 75 MHz) mixture of 3 isomers δ 173.3, 172.7, 164.2 (d, J = 150 Hz, 1C), 129.6 (d, J = 7.5 Hz, 1C), 128.9 (d, J = 15 Hz, 2C), 116.0 (d, J = 22.5 Hz, 2C), 67.1, 66.2, 65.4, 57.3, 52.9, 51.0, 50.3, 47.0, 46.3, 45.2, 43.4, 28.5, 28.2, 28.0, 26.9, 25.8, 24.5, 23.8, 21.6, 21.3; ¹⁹F NMR (D₂O, 376 MHz) mixture of 2 isomers δ -109.5; -110.0; MS (ESI⁺) m/z 263.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₅H₂₀N₂OF 263.1554 ([M+1]⁺) found 263.1558.

2,3-dihydro-*N*-(1-aza-bicyclo[2.2.2]oct-2-ylmethyl)benzo[*b*][1,4]dioxine-6-carboxamide, TFA salt (*rac*-12c). Compound **26c** (69 mg, 0.23 mmol) and Pd/C (30 mg) were diluted in dry MeOH (5 mL) and the solution was stirred for 4 hours under an hydrogen atmosphere. The reaction mixture was then filtered over Celite and washed with MeOH. The filtrate was concentrated under vacuum to afford a yellow oil which was purified by preparative HPLC to give the desired compound as a colorless oil (21mg, 22%). ¹H NMR (CDCl₃, 300 MHz) δ 8.42 (bs, 1H), 7.41 (d, J = 3Hz, 1H), 7.34 (dd, J_1 = 9Hz, J_2 = 3Hz, 1H), 6.83, (d, J = 9Hz, 1H), 4.22 (m, 4H), 4.02 (bs, 1H), 3.94 (dd, J_1 = 10Hz, J_2 = 3Hz, 1H), 3.67 (q, J = 9Hz, 1H), 3.57-3.40 (m, 2H), 3.37-3.15 (m, 3H), 2.24-2.09 (m, 2H), 1.94-1.81 (m, 4H), 1.52-1.45 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.9, 147.1, 143.6, 126.6, 121.0, 117.3, 64.8, 64.3, 59.0, 48.7, 41.4, 40.5, 28.7, 23.6, 22.8, 20.7; MS (ESI⁺) m/z 303.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₇H₂₃N₂O₃ 303.1703 ([M+1]⁺) found 303.1708.

4-bromophenyl-*N*-(1-aza-bicyclo[2.2.2]oct-2-ylmethyl)carbamate, TFA salt (*rac*-12e). This compound was obtained from amine **55** as a white solid (8mg, 5%). ¹H NMR (CDCl₃, 300 MHz) δ 7.43 (d, J = 9Hz, 2H), 7.00 (d, J = 9Hz, 2H), 3.79-3.65 (m, 1H), 3.95-3.47 (m, 3H), 3.37 (t, J = 6Hz, 2H), 3.25-3.17 (m, 1H), 2.60 (bs, 1H), 2.27-2.06 (m, 2H), 1.99-1.84 (m, 4H), 1.42 (q, J = 6Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 155.3, 150.2, 132.4, 123.7, 118.7, 58.1, 48.8, 42.3, 41.4, 28.6, 23.6, 22.8, 20.5; MS (ESI⁺) m/z 339.1 ([M+1, Br⁷⁹]⁺), 341.1 ([M+1, Br⁸¹]⁺); HRMS (ESI⁺) calcd. for C₁₅H₂₀Br⁷⁹N₂O₂ 339.0703([M+1]⁺) found 339.0703.

***N*-(1-aza-bicyclo[2.2.2]oct-2-ylmethyl)benzamide, TFA salt (*rac*-12f).** Compound **26f** (28 mg, 0.12 mmol) and Pd/C (10 mg) were diluted in dry MeOH (5 mL) and the solution was stirred for 3 hours under an hydrogen atmosphere. The reaction mixture was then filtered over Celite and

washed with MeOH. The filtrate was concentrated under vacuum to afford a yellow oil which was purified by preparative HPLC to give the desired compound as a colorless oil (33 mg, 76%). ¹H NMR (CDCl₃, 400 MHz) δ 8.56 (bs, 1H), 7.86 (dd, *J*₁ = 8Hz, *J*₂ = 2Hz, 2H), 7.47 (tt, *J*₁ = 8Hz, *J*₂ = 2Hz, 1H), 7.39 (tt, *J*₁ = 8Hz, *J*₂ = 2Hz, 2H), 3.99 (ddd, *J*₁ = 15Hz, *J*₂ = 7Hz, *J*₃ = 3Hz, 1H), 3.69 (q, *J* = 10Hz, 1H), 3.57-3.46 (m, 2H), 3.40-3.21 (m, 3H), 2.22-2.15 (m, 2H), 1.92-1.84 (m, 4H), 1.49 (q, *J* = 8Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.4, 133.3, 132.0, 128.7, 127.6, 59.0, 48.6, 41.3, 40.4, 28.7, 23.6, 22.8, 20.7.; MS (ESI⁺) *m/z* 245.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₅H₂₁N₂O 245.1648 ([M+1]⁺) found 245.1652.

4-chloro-*N*-((6-methyl-6-aza-bicyclo[2.2.2]octan-2-yl)methyl)benzamide, TFA salt (13a). Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref. ² It was purified and separated from **27a** by preparative HPLC and obtained as a colorless oil (0.98 mg, 2.4 μmol, 3% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.90 (d, *J* = 9 Hz, 2H), 7.41 (bs, 1H), 7.39 (d, *J* = 9 Hz, 2H), 3.81-3.71 (m, 2H), 3.44 (s, 1H), 3.30-3.23 (m, 1H), 2.92-2.85 (m, 1H), 2.83 (d, *J* = 3 Hz, 3H), 2.78-2.70 (m, 1H), 2.15-1.97 (m, 4H), 1.86-1.79 (m, 1H), 1.71-1.61 (m, 1H), 1.28-1.20 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.9, 137.8, 131.6, 128.8, 128.6, 55.5, 54.5, 41.6, 41.5, 34.2, 27.0, 24.3, 22.9, 13.5; MS (ESI⁺) *m/z* 293.14 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₆H₂₂ClN₂O 293.1415 ([M+1]⁺) found 293.1419.

2,3-dihydro-*N*-((6-methyl-6-aza-bicyclo[2.2.2]octan-2-yl)methyl)benzo[*b*][1,4]dioxine-6-carboxamide, TFA salt (13c). Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref. ² It was purified and separated from **27c** by preparative HPLC and obtained as a colorless oil (3 mg, 11% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.46 (d, *J* = 3Hz, 1H), 7.40 (dd, *J*₁ = 9Hz, *J*₂ = 3Hz, 1H), 7.12-7.09 (m, 1H), 6.86 (d, *J* = 9Hz, 1H), 4.29-4.22 (m, 4H), 3.82-3.71 (m, 2H), 3.39 (s, 1H), 3.27-3.20 (m, 2H), 2.82 (d, *J* = 6Hz, 3H), 2.77-2.67 (m, 1H), 2.21-1.94 (m, 4H), 1.85-1.76 (m, 1H), 1.71-1.60 (m, 1H), 1.27-1.20 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.7, 147.0, 143.7, 126.9, 120.9, 117.4, 117.2, 64.8, 64.4, 55.9, 54.9, 41.9, 41.7, 34.7, 27.3, 24.7, 23.4, 14.0; MS (ESI⁺) *m/z* 317.19 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₈H₂₅N₂O₃ 317.1860 ([M+1]⁺) found 317.1866.

***N*-((6-methyl-6-aza-bicyclo[2.2.2]octan-2-yl)methyl)benzamide, TFA salt (13f).** Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref. ² It was purified and separated from **27f** by preparative HPLC and obtained as a colorless oil (2 mg, 5.3 μmol, 6% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.92 (dd, *J*₁ = 6 Hz, *J*₂ = 3 Hz, 2H), 7.51-7.39 (m, 3H), 7.30 (bs, 1H), 3.85-3.72 (m, 2H), 3.44 (s, 1H), 3.31-3.23 (m, 1H), 2.82 (d, *J* = 6 Hz, 3H), 2.77-2.68 (m, 2H), 2.20-1.96 (m, 4H), 1.87-1.78 (m, 1H), 1.72-1.61 (m, 1H), 1.28-1.21 (m,

1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 168.2, 133.5, 131.9, 128.8, 127.5, 55.7, 54.8, 41.9, 41.6, 34.7, 27.3, 24.7, 23.4, 14.0; MS (ESI^+) m/z 259.18 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}$ 259.1805 ($[\text{M}+1]^+$) found 259.1811.

4-bromo-*N*-((6-methyl-6-aza-bicyclo[2.2.2]octan-2-yl)methyl)benzamide, TFA salt (13g). Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref. ². It was purified and separated from **27g** by preparative HPLC and obtained as a colorless oil (0.68 mg, 1.5 μmol , 1.6 % yield). ^1H NMR (CDCl_3 , 300 MHz) δ 7.83 (d, $J=8\text{Hz}$, 2H), 7.54 (d, $J=8\text{Hz}$, 2H), 7.41 (m, 1H), 3.81-3.71 (m, 2H), 3.44 (s, 1H), 3.29-3.23 (m, 1H), 2.94-2.86 (m, 1H), 2.83 (d, $J=8\text{Hz}$, 3H), 2.77-2.70 (m, 1H), 2.11-1.99 (m, 4H), 1.72-1.62 (m, 2H), 1.26-1.21 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.8, 131.8, 131.6, 129.1, 127.7, 55.3, 54.5, 41.6, 41.3, 34.0, 26.9, 24.4, 22.9, 13.5.

4-Fluoro-*N*-((6-methyl-6-aza-bicyclo[2.2.2]octan-2-yl)methyl)benzamide, TFA salt (13k).

Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref. ². It was purified and separated from **27k** by preparative HPLC and obtained as a colorless oil (1 mg, 2.6 μmol , 4% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 7.99 (dd, $J_1=6\text{ Hz}$, $J_2=3\text{ Hz}$, 2H), 7.39 (bs, 1H), 7.08 (t, $J=6\text{ Hz}$, 2H), 3.81-3.70 (m, 2H), 3.47 (s, 1H), 3.27-3.24 (m, 1H), 3.00-2.85 (m, 1H), 2.83 (d, $J=3\text{ Hz}$, 3H), 2.78-2.71 (m, 1H), 2.10-2.00 (m, 4H), 1.86-1.79 (m, 2H), 1.23-1.20 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 178.3, 164.6 (d, $J=187\text{ Hz}$, $1\text{C}_{\text{Ar}}\text{F}$), 129.8 (d, $J=15\text{ Hz}$, $2\text{C}_{\text{Ar}}\text{H}$), 129.6, 115.5 (d, $J=22.5\text{ Hz}$, $2\text{C}_{\text{Ar}}\text{H}$), 55.4, 54.4, 41.7, 41.3, 34.2, 26.9, 24.6, 23.1, 13.6; ^{19}F NMR (CDCl_3 , 376 MHz) δ 75.7 (TFA), -108.3; MS (ESI^+) m/z 277.17 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{16}\text{H}_{22}\text{FN}_2\text{O}$ 277.1711 ($[\text{M}+1]^+$) found 277.1716.

(4-chlorophenyl)(6-methyl-3,6-diaza-bicyclo[3.3.1]nonan-3-yl)methanone, TFA salt (14a).

Using procedure B, this compound was obtained from amine **62** as a colorless oil (8.2 mg, 21 μmol , 13% yield). ^1H NMR (MeOD, 300 MHz) δ 7.53 (d, $J=6\text{ Hz}$, 2H), 7.47 (d, $J=6\text{ Hz}$, 2H), 5.19 (bs, 1H), 3.90-3.52 (m, 3H), 3.49-3.38 (m, 1H), 3.34-3.19 (m, 3H), 3.01 (bs, 3H), 2.28-2.02 (m, 4H), 1.92-1.76 (m, 1H); ^{13}C NMR (MeOD, 75 MHz) δ 172.2, 137.9, 135.0, 130.3, 130.1, 55.9, 53.8, 51.2, 42.5, 40.5, 31.4, 28.4, 25.7; MS (ESI^+) m/z 279.13 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{20}\text{ClN}_2\text{O}$ 279.1259 ($[\text{M}+1]^+$) found 279.1254.

4-bromophenyl 6-methyl-3,6-diaza-bicyclo[3.3.1]nonane-3-carboxylate, TFA salt (14e). This compound was obtained from amine **62** as a colorless oil (6.5 mg, 14.4 μmol , 13% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 7.55 (d, $J=9\text{ Hz}$, 2H), 7.03 (d, $J=9\text{ Hz}$, 2H), 4.77 (d, $J=15\text{ Hz}$, 1H), 4.46-4.28 (m, 1H), 3.64 (s, 1H), 3.58 (dd, $J_1=12\text{ Hz}$, $J_2=6\text{ Hz}$, 1H), 3.51-3.38 (m, 1H), 3.37-3.16 (m, 2H), 2.90 (bs, 3H), 2.57 (d, $J=15\text{ Hz}$, 1H), 2.51-2.33 (m, 1H), 2.22 (s, 1H), 2.02 (d, $J=15\text{ Hz}$, 2H), 1.86

(bs, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 162.7, 150.0 (C_{Ar}), 132.8 (2CH_{Ar}), 123.5 (2CH_{Ar}), 119.3 (C_{Ar}), 53.5, 49.5, 49.4, 42.2, 41.7, 30.0, 27.8, 23.8; MS (ESI^+) m/z 339.07 ($[\text{M}+1, \text{Br}^{79}]^+$), 341.07 ($[\text{M}+1, \text{Br}^{81}]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{20}\text{Br}^{79}\text{N}_2\text{O}_2$ 339.0630 ($[\text{M}+1]^+$) found 339.0686.

(6-methyl-3,6-diaza-bicyclo[3.3.1]nonan-3-yl)(phenyl)methanone, TFA salt (14f). Using procedure B, this compound was obtained from amine **62** as a colorless oil (13 mg, 36 μmol , 22% yield). ^1H NMR (MeOD , 300 MHz) δ 7.52-7.47 (m, 5H), 5.22 (d, $J=15$ Hz, 1H), 3.91-3.77 (m, 1H), 3.75-3.50 (m, 3H), 3.50-3.40 (m, 1H), 3.38-3.24 (m, 3H), 3.03 (bs, 3H), 2.26-2.06 (m, 5H), 1.92-1.76 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 173.4, 136.4, 131.8, 130.1, 128.2, 55.9, 53.9, 51.2, 42.5, 40.5, 31.5, 28.4, 25.7; MS (ESI^+) m/z 245.16 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}$ 245.1648 ($[\text{M}+1]^+$) found 245.1647.

(4-Bromophenyl)(6-methyl-3,6-diaza-bicyclo[3.3.1]nonan-3-yl)methanone, TFA salt (14g). Using procedure B, this compound was obtained from amine **62** as a colorless oil (15.4 mg, 35.3 μmol , 21% yield). ^1H NMR (MeOD , 300 MHz) δ 7.67 (d, $J=9$ Hz, 2H), 7.39 (d, $J=9$ Hz, 2H), 5.19 (bs, 1H), 3.90-3.52 (m, 3H), 3.49-3.38 (m, 1H), 3.34-3.19 (m, 3H), 3.01 (bs, 3H), 2.28-2.02 (m, 4H), 1.92-1.76 (m, 1H); ^{13}C NMR (MeOD , 75 MHz) δ 172.3, 135.4, 133.3, 130.2, 126.0, 55.8, 53.8, 51.2, 42.5, 40.6, 31.4, 28.3, 25.7; MS (ESI^+) m/z 323.07 ($[\text{M}+1, \text{Br}^{79}]^+$), 325.07 ($[\text{M}+1, \text{Br}^{81}]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{20}\text{Br}^{79}\text{N}_2\text{O}$ 323.0754 ($[\text{M}+1]^+$) found 323.0742.

4-chloro-N-(((R)-1-ethylpyrrolidin-2-yl)methyl)benzamide (15a). Using procedure A, this product was obtained from (R)-(+)-2-amino methyl-1-ethylpyrrolidine as a yellow oil (95 mg, 0.35 mmol, 55% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 7.70 (d, $J = 9$ Hz, 2H), 7.38 (d, $J = 9$ Hz, 2H), 6.84 (br s, 1H), 3.71-3.63 (qd, $J_1 = 9$ Hz; $J_2 = 3$ Hz, 1H), 3.31-3.24 (m, 1H), 2.87-2.75 (m, 1H), 2.71-2.62 (m, 1H), 2.30-2.14 (m, 2H), 1.94-1.84 (m, 1H), 1.80-1.54 (m, 4H), 1.10 (t, $J = 6$ Hz, 3H), ; ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.8, 137.7, 133.4, 129.0, 128.6, 62.4, 53.8, 48.3, 40.9, 28.4, 23.2, 14.3; MS (ESI^+) m/z 289.1 ($[\text{M}+23]^+$); HRMS (ESI^+) calcd. for $\text{C}_{14}\text{H}_{19}\text{ClN}_2\text{ONa}$ 284.1074 ($[\text{M}+23]^+$) found 289.1078.

N-(((R)-1-ethylpyrrolidin-2-yl)methyl)benzo[d]thiazole-6-carboxamide, TFA salt (15b). Using procedure A, this product was obtained from commercial (R)-(+)-2-amino methyl-1-ethylpyrrolidine as a colorless oil (89 mg, 0.239 mmol, 34% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 11.45 (br s, 1H), 9.20 (br t, $J = 5$ Hz, 1H), 9.06 (s, 1H), 8.55 (s, 1H), 8.13-7.98 (m, 2H), 5.21 (br s, 1H), 3.92 (m, 4H), 3.31-3.13 (m, 1H), 3.06-2.82 (m, 2H), 2.29-2.13 (m, 1H), 2.10-1.80 (m, 3H), 1.24 (t, $J = 7$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 167.6, 156.9, 155.0, 133.9, 130.2, 125.2, 123.3, 121.8, 66.9, 54.0, 51.2, 40.7, 27.6, 23.0, 10.3; MS (ESI^+) m/z 290.1 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{20}\text{N}_3\text{OS}$ 290.1322 ($[\text{M}+1]^+$) found 290.1315.

4-bromophenyl N-((R)-1-ethylpyrrolidin-2-yl)methylcarbamate (15e). This compound was obtained from (R)-(+)-2-amino methyl-1-ethylpyrrolidine as a yellow oil (69 mg, 0.21 mmol, 32% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 7.43 (d, $J = 9$ Hz, 2H), 7.01 (d, $J = 9$ Hz, 2H), 5.56 (br s, 1H), 3.42-3.34 (m, 1H), 3.23-3.20 (m, 1H), 3.19-3.12 (m, 1H), 2.85-2.74 (m, 1H), 2.63-2.51 (m, 1H), 2.27-2.11 (m, 2H), 1.95-1.83 (m, 1H), 1.77-1.59 (m, 4H), 1.10 (t, $J = 6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 154.8, 150.5, 132.5, 123.6, 118.3, 62.5, 53.8, 48.3, 42.6, 28.3, 23.1, 14.2; MS (ESI^+) m/z 327.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{14}\text{H}_{20}\text{BrN}_2\text{O}_2$ 327.0703 ($[\text{M}+1]^+$) found 327.0716.

N-(((R)-1-cyclohexylpyrrolidin-2-yl)methyl)benzo[d]thiazole-6-carboxamide, TFA salt (16b). Using procedure A, this product was obtained from [(2R)-1-cyclohexylpyrrolidinyl]methylamine **64** as a colorless oil (22 mg, 0.050 mmol, 22% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 9.33 (br t, $J = 5$ Hz, 1H), 9.15 (s, 1H), 8.63 (d, $J = 1$ Hz), 8.23-8.06 (m, 2H), 4.15 (m, 1H), 3.96-3.85 (m, 1H), 3.82-3.61 (m, 2H), 3.18-2.99 (m, 2H), 2.23-1.93 (m, 6H), 1.89-1.75 (m, 2H), 1.66-1.55 (m, 1H), 1.47-1.30 (m, 2H), 1.27-0.99 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 168.1 (C), 157.1 (CH), 155.1 (C), 134.1 (C), 130.3 (C), 125.4 (CH), 123.6 (CH), 121.9 (CH), 64.9 (CH), 63.6 (CH), 51.0 (CH_2), 41.9 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 27.0 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 24.0 (CH_2); MS (ESI^+) m/z 344.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_3\text{OS}$ 344.1791 ($[\text{M}+1]^+$) found 344.1793.

4-bromophenyl ((R)-1-isopropylpyrrolidin-2-yl)methylcarbamate, TFA Salt (17e). This compound was obtained from **65** as a colorless oil (4 mg, 0.01 mmol, 3%). ^1H NMR (MeOD, 300 MHz) δ 7.53 (d, $J = 9$ Hz, 2H), 7.10 (d, $J = 9$ Hz, 2H), 3.85-3.75 (m, 3H), 2.30-2.21 (m, 2H), 2.15-1.92 (m, 5H), 1.41 (d, $J = 6$ Hz, 3H), 1.36 (d, $J = 6$ Hz, 3H); MS (ESI^+) m/z 341.1 ($[\text{M}+1, \text{Br}^{79}]^+$), 343.1 ($[\text{M}+1, \text{Br}^{81}]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2\text{Br}$ 341.0859 ($[\text{M}+1]^+$) found 341.0858.

4-fluoro-N-(((R)-1-propylpyrrolidin-2-yl)methyl)benzamide (18k). This compound was obtained from **66** as a yellow solid (8 mg, 0.03 mmol, 10% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 7.78-7.74 (m, 2H), 7.11-7.06 (m, 2H), 6.81 (bs, 1H), 3.68 (ddd, $J_1 = 3$ Hz, $J_2 = 9$ Hz, $J_3 = 12$ Hz, 1H), 3.30 (ddd, $J_1 = 3$ Hz, $J_2 = 5$ Hz, $J_3 = 14$ Hz, 1H), 3.27-3.24 (m, 1H), 2.69-2.60 (m, 2H), 2.23-2.12 (m, 2H), 1.92-1.83 (m, 1H), 1.75-1.44 (m, 5H), 0.90 (t, $J = 6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.8, 164.9 (d, $J = 247.5$ Hz, 1C), 131.3 (d, $J = 7.5$ Hz, 1C), 129.4 (d, $J = 7.5$ Hz, 2C), 115.8 (d, $J = 22.5$ Hz, 2C), 62.5, 56.2, 54.1, 40.7, 28.3, 23.3, 22.3, 12.2; ^{19}F NMR (CDCl_3 , 376 MHz) δ -108.8; MS (ESI^+) m/z 265.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{OF}$ 265.1711 ($[\text{M}+1]^+$) found 265.1705.

((S)-1-(pent-2-ynyl)pyrrolidin-2-yl)methyl benzo[d]thiazole-6-carboxylate, TFA salt (19b).

This product was synthesized following general procedure for amide formation from (S)-**32**. After purification by preparative HPLC and lyophilization of the pure fractions, a colorless oil was obtained (7 mg, 0.016 mmol, 17% yield). ¹H NMR (CDCl₃, 300 MHz) δ 9.15 (s, 1H), 8.63 (s, 1H), 8.23-8.06 (m, 2H), 4.90-4.80 (m, 1H), 4.79-4.70 (m, 1H), 4.30-3.70 (m, 4H), 3.40-3.20 (m, 1H), 2.40-2.00 (m, 7H), 1.27-0.99 (m, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 165.4 (C), 157.9 (CH), 156.3 (C), 134.0 (C), 127.4 (CH), 126.3 (CH), 124.6 (CH), 123.6 (CH), 93.4 (C), 66.9 (C), 62.8 (CH), 62.2 (CH₂), 52.8 (CH₂), 42.5 (CH₂), 26.9 (CH₂), 21.9 (CH₂), 13.2 (CH₃), 12.3 (CH₂); MS (ESI⁺) *m/z* 329.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₈H₂₁N₂O₂S 329.1318 ([M+1]⁺) found 329.1324.

N-((S)-1-ethylpyrrolidin-3-yl)benzo[d]thiazole-6-carboxamide, TFA salt (20b) The Boc protected amine (S)-**39b** was deprotected with TFA/CH₂Cl₂ for 10 minutes. The solvent was removed under vacuum and the residue was dissolved in CH₂Cl₂ and washed with NaOH 1M, dried (Na₂SO₄), filtered and concentrated. This amine (0.114 g, 0.461 mmol) and distilled acetaldehyde (26 μL, 0.461 mmol) were dissolved in dry MeOH (1.5 mL), activated molecular sieves (3Å) were added, and the solution was stirred for 5 minutes under N₂. NaBH₃CN (0.020 g, 0.318 mmol) was added to the solution and the mixture stirred for 30 minutes. The reaction was filtered, the solvent evaporated under reduced pressure and the residue extracted with AcOEt/NaHCO₃ sat. After purification by preparative HPLC and lyophilization of the pure fractions, **20b** was obtained as a yellow oil (18 mg, 0.048 mmol, 10% yield). ¹H NMR (CDCl₃, 300 MHz) δ 9.11 (s, 1H), 8.95 (br d, *J* = 8 Hz, 1H), 8.60 (d, *J* = 1 Hz, 1H), 8.17-8.06 (m, 2H), 5.20-5.08 (m, 1H), 3.99-3.77 (m, 2H), 3.39 (br s, 1H), 3.31-3.05 (m, 3H), 2.99-2.84 (m, 1H), 2.69-2.54 (m, 1H), 2.41-2.27 (m, 1H), 1.42 (t, *J* = 7 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 166.5 (C), 156.9 (CH), 155.1 (C), 133.9 (C), 130.4 (C), 125.6 (CH), 123.3 (CH), 121.8 (CH), 59.1 (CH₂), 52.6 (CH₂), 50.6 (CH₂), 47.8 (CH), 30.7 (CH₂), 10.9 (CH₃); MS (ESI⁺) *m/z* 275.4 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₄H₁₈N₃OS 276.1165 ([M+1]⁺) found 276.1169.

N-((S)-1-(pent-2-ynyl)pyrrolidin-3-yl)benzo[d]thiazole-6-carboxamide (21b). The Boc protected amine (S)-**39b** was deprotected with TFA/CH₂Cl₂ for 10 minutes. The solvent was removed under vacuum and the residue was dissolved in CH₂Cl₂ and washed with NaOH 1M, dried (Na₂SO₄), filtered and concentrated. This amine (0.114 g, 0.461 mmol) and K₂CO₃ (0.113 g, 0.817 mmol) were dissolved in DMF (1.2 mL), cooled down to 0° C, treated with 1-bromo-2-pentyne (47 μL, 0.461 mmol), and warmed up to room temperature. The reaction was stirred for 7 hours. After this time, the solvent was evaporated under reduced pressure and extracted with AcOEt/NaHCO₃ sat. The combined organic phases were dried (Na₂SO₄), filtered and evaporated to give **21b** as a yellow solid (109 mg, 0.348 mmol, 75% yield). ¹H NMR (CDCl₃, 300 MHz) δ 9.10 (s, 1H), 8.46 (d, *J* = 2

Hz, 1H), 8.15 (d, $J = 9$ Hz, 1H), 7.86 (dd, $J_1 = 9$ Hz, $J_2 = 2$ Hz, 1H), 6.62 (br d, $J = 8$ Hz, 1H), 4.77-4.64 (m, 1H), 3.42-3.35 (m, 2H), 3.04-2.93 (m, 1H), 2.84-2.71 (m, 2H), 2.51-2.34 (m, 2H), 2.26-2.14 (m, 2H), 1.87-1.72 (m, 1H), 1.13 (t, $J = 7$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.0 (C), 156.3 (CH), 154.8 (C), 133.9 (C), 131.9 (C), 124.6 (CH), 123.3 (CH), 121.5 (CH), 86.6 (C), 74.1 (C), 59.2 (CH_2), 50.9 (CH_2), 49.6 (CH), 43.1 (CH_2), 32.7 (CH_2), 13.9 (CH_3), 12.2 (CH_2); MS (ESI^+) m/z 314.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{17}\text{H}_{20}\text{N}_3\text{OS}$ 314.1322 ($[\text{M}+1]^+$) found 314.1323; Mp ($^\circ\text{C}$) 127-128.

***N*-((*S*)-1-benzylpyrrolidin-3-yl)benzo[*d*]thiazole-6-carboxamide, TFA salt (22b).** Using procedure A, this product was obtained from the commercial 3*S*-*N*-benzyl-3-aminopyrrolidine as a yellow oil (65 mg, 0.150 mmol, 41% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 12.88 (br s, 1H), 9.11 (s, 1H), 8.90 (br d, $J = 8$ Hz, 1H), 8.55 (d, $J = 1$ Hz, 1H), 8.14-8.00 (m, 2H), 7.42 (m, 5H), 5.96 (br s, 1H), 5.18-5.02 (m, 1H), 4.36 (d, $J = 13$ Hz, 1H), 4.13 (d, $J = 13$ Hz, 1H), 3.89-3.75 (m, 1H), 3.57 (d, $J = 12$ Hz, 1H), 3.28-3.14 (m, 1H), 3.02 (q, $J = 10$ Hz, 1H), 2.68-2.52 (m, 1H), 2.38-2.22 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.4, 157.0, 154.9, 133.8, 130.4, 130.3, 130.2, 129.5, 128.9, 125.6, 123.2, 121.8, 58.7, 58.6, 52.6, 47.5, 30.6; MS (ESI^+) m/z 338.1 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_3\text{OS}$ 338.1322 ($[\text{M}+1]^+$) found 338.1311.

***N*-((*S*)-1-cyclohexylpyrrolidin-3-yl)benzo[*d*]thiazole-6-carboxamide, TFA salt (23b).** The Boc protected amine (*S*)-**39b** was deprotected with TFA/ CH_2Cl_2 for 10 minutes. The solvent was removed under vacuum and the residue was dissolved in CH_2Cl_2 , washed with aq. NaOH 1M, dried (Na_2SO_4), filtered and concentrated. This amine (0.114 g, 0.461 mmol) and cyclohexanone (48 μL , 0.461 mmol) were dissolved in dry MeOH (1.5 mL), activated molecular sieves (3 \AA) were added, and the solution was stirred for 5 minutes under N_2 . NaBH_3CN (0.020 g, 0.318 mmol) was added to the solution and the mixture stirred for 1 day. The reaction was filtered, the solvent evaporated under reduced pressure and the residue extracted with AcOEt/ NaHCO_3 sat. Purification by preparative HPLC and lyophilization of the pure fractions gave **23b** as a yellow oil (98 mg, 0.230 mmol, 50% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 11.88 (br s, 1H), 9.09 (s, 1H), 8.95 (br d, $J = 8$ Hz, 1H), 8.53 (s, 1H), 8.11-7.94 (m, 2H), 7.46 (br s, 1H), 5.10-4.92 (m, 1H), 3.97-3.57 (m, 2H), 3.27-3.11 (m, 1H), 3.04-2.75 (m, 2H), 2.61-2.45 (m, 1H), 2.31-2.14 (m, 1H), 2.10-1.95 (m, 2H), 1.90-1.73 (m, 2H), 1.68-1.35 (m, 3H), 1.30-1.01 (m, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.5 (C), 157.0 (CH), 154.8 (C), 133.7 (C), 130.4 (C), 125.5 (CH), 123.0 (CH), 121.7 (CH), 64.9 (CH), 56.8 (CH_2), 50.4 (CH_2), 47.5 (CH), 30.4 (CH_2), 28.5 (CH_2), 24.4 (CH_2), 24.3 (CH_2); MS (ESI^+) m/z 330.2 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{18}\text{H}_{24}\text{N}_3\text{OS}$ 330.1635 ($[\text{M}+1]^+$) found 330.1635.

***N*-(1-(2-methylcyclopentyl)piperidin-4-yl)benzo[*d*]thiazole-6-carboxamide, TFA salt (24b).**

The Boc protected amine **44b** was deprotected with TFA/CH₂Cl₂ for 10 minutes. The solvent was removed under vacuum and the residue was dissolved in CH₂Cl₂ and washed with NaOH 1M, dried (Na₂SO₄), filtered and concentrated. This amine (0.078 g, 0.299 mmol) and 2-methylcyclopentanone (32 μL, 0.299 mmol) were dissolved in dry MeOH (1 mL), activated molecular sieves (3Å) were added, and the solution was stirred for 5 minutes under N₂. NaBH₃CN (0.013 g, 0.209 mmol) was added to the solution and the mixture stirred for 1 day. The reaction was filtered, the solvent evaporated under reduced pressure and the residue extracted with AcOEt/NaHCO₃ sat. After purification by preparative HPLC and lyophilization of the pure fractions, **24b** was obtained as a white solid (41 mg, 0.093 mmol, 27% yield). ¹H NMR (CDCl₃, 300 MHz) diastereomeric mixture (1:3.5) δ 11.78 (br s, 0.2H), 10.91 (br s, 0.7H), 9.09 (s, 1H), 8.54-8.48 (m, 1H), 8.11 (d, *J* = 8 Hz, 1H), 7.97 (dd, *J*₁ = 8 Hz, *J*₂ = 2 Hz, 1H), 7.67 (br d, *J* = 8 Hz, 0.7H), 7.51 (br d, *J* = 8 Hz, 0.2H), 4.41-4.21 (m, 1H), 3.82-3.53 (m, 2H), 3.47-3.20 (br s, 1H), 3.16-3.01 (m, 1H), 2.99-2.72 (m, 2H), 2.58-1.51 (m, 11H), 1.09 (d, *J* = 7 Hz, 0.7H), 1.05 (d, *J* = 7 Hz, 2.3H); ¹³C NMR (CDCl₃, 100 MHz) diastereomeric mixture (1:3.5) δ 166.7 (C), 156.7 (CH), 155.1 (C), 133.9 (C), 131.2 (C), 125.2 (CH), 123.4 (CH), 121.8 (CH), 74.6 (CH), 71.8 (CH), 53.4 (CH₂), 52.4 (CH₂), 51.0 (CH₂), 50.2 (CH₂), 45.1 (CH), 44.8 (CH), 35.3 (CH₂), 34.0 (CH₂), 33.7 (CH₂), 31.1 (CH₂), 29.3 (CH₂), 28.8 (CH₂), 28.4 (CH₂), 28.3 (CH₂), 24.0 (CH₂), 23.8 (CH₂), 19.2 (CH₂), 13.2 (CH₂); MS (ESI⁺) *m/z* 344.2 ([M+1]⁺); Mp (°C) 196-198; HRMS (ESI⁺) calcd. for C₁₉H₂₆N₃OS 344.1791 ([M+1]⁺) found 344.1780.

(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(4-isopropyl-1,4-diazepan-1-yl)methanone (25c). The Boc protected amine **45** was deprotected with TFA/CH₂Cl₂ for 10 minutes. The solvent was removed under vacuum and the obtained TFA salt was then used for the coupling step without further purification. The final compound slowly hydrolyzes in 0.1% TFA (HPLC conditions) For that reason, purification was done by column chromatography (neutral alumina, hexane/AcOEt 10%) to give **25c** as a yellow oil (128 mg, 0.391 mmol, 50% yield). ¹H NMR (CDCl₃, 300 MHz) mixture of 2 rotamers δ 6.94-6.80 (m, 3H), 4.24 (s, 4H), 3.77-3.65 (m, 2H), 3.54-3.40 (m, 2H), 2.99-2.52 (m, 5H), 1.95-1.66 (m, 2H), 1.07-0.92 (m, 6H); ¹³C NMR (CDCl₃, 75 MHz) mixture of 2 rotamers δ 170.8 (C), 144.3 (C), 143.1 (C), 130.1 (C), 120.1 (CH), 119.9 (CH), 116.9 (CH), 116.1 (CH), 116.0 (CH), 64.2 (CH₂), 64.1 (CH₂), 55.2 (CH), 52.4 (br CH₂), 51.2 (br CH₂), 51.1 (br CH₂), 50.4 (br CH₂), 49.8 (br CH₂), 48.5 (br CH₂), 47.3 (br CH₂), 45.1 (br CH₂), 29.7 (br CH₂), 27.5 (br CH₂), 18.2 (CH₃); MS (ESI⁺) *m/z* 305.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₇H₂₅N₂O₃ 305.1860 ([M+1]⁺) found 305.1857.

***N*-((1-aza-bicyclo[2.2.2]oct-2-en-2-yl)methyl)-4-chlorobenzamide (26a).** Using procedure A, this

compound was obtained from amine **54** as yellowish solid after filtration on neutral alumina (DCM) and crystallisation in Hexanes (30 mg, 0.11 mmol, 22% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.72 (d, *J*= 6 Hz, 2H), 7.38 (d, *J*= 9 Hz, 2H), 6.73 (bs, 1H), 6.38 (d, *J*= 6 Hz, 1H), 4.05 (d, *J*= 9 Hz, 2H), 3.00- 2.92 (m, 2H), 2.62-2.49 (m, 3H), 1.62-1.56 (m, 2H), 1.48-1.48 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.2, 148.3, 137.8, 133.2, 129.5, 129.0, 128.6, 49.4, 41.9, 28.7, 27.1; MS (ESI⁺) *m/z* 277.1 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₅H₁₈ClN₂O 277.1102 ([M+1]⁺) found 277.1095.

***N*-((1-azabicyclo[2.2.2]oct-2-en-2-yl)methyl)2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide (26c).**

Using procedure A, this compound was obtained from amine **54** as yellowish solid after filtration on neutral alumina (DCM) and crystallisation in Hexanes (17 mg, 0.06 mmol, 11% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.34 (d, *J*= 3Hz, 1H), 7.28 (dd, *J*₁= 9Hz, *J*₂= 3Hz, 1H), 6.86 (d, *J*= 9 Hz, 1H), 6.67 (bs, 1H), 6.37 (d, *J*= 6 Hz, 1H), 4.26 (m, 4H), 4.02 (d, *J*= 6 Hz, 2H), 3.02-2.94 (m, 2H), 2.65-2.52 (m, 3H), 1.68-1.55 (m, 2H), 1.50-1.38 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.6, 146.7, 143.6, 132.5, 129.4, 128.1, 120.6, 117.4, 116.8, 64.8, 64.4, 49.5, 41.6, 28.3, 27.1; MS (ESI⁺) *m/z* 301.2 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₇H₂₁N₂O₃ 301.1547 ([M+1]⁺) found 301.1537.

4-bromophenyl (1-aza-bicyclo[2.2.2]oct-2-en-2-yl)methylcarbamate, TFA salt (26e). Using procedure A, this compound was obtained from amine **54** as a colorless oil (11 mg, 0.024 mmol, 5%). ¹H NMR (CDCl₃, 300 MHz) δ 7.43 (d, *J*= 9Hz, 2H), 6.98 (d, *J*= 9Hz, 2H), 6.68 (d, *J*= 6 Hz, 1H), 4.11 (d, *J*= 6 Hz, 1H), 3.58-3.49 (m, 2H), 3.13-3.00 (m, 3H), 2.70 (bs, 1H), 2.02-1.89 (m, 2H), 1.85-1.71 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 154.8, 150.2, 140.1, 132.5, 132.2, 123.5, 118.6, 50.3, 40.5, 26.6, 24.2; MS (ESI⁺) *m/z* 337.1 ([M+1, Br⁷⁹]⁺), 339.1([M+1, Br⁸¹]⁺); HRMS (ESI⁺) calcd. for C₁₅H₂₀Br⁷⁹N₂O₂ 337.0546 ([M+1]⁺) found 337.0553.

***N*-((1-aza-bicyclo[2.2.2]oct-2-en-2-yl)methyl)-benzamide (26f).** Using procedure A, this compound was obtained from amine **54** as a colorless solid after filtration on neutral alumina (DCM) and crystallisation in Hexanes (7 mg, 0.03 mmol, 6% yield). ¹H NMR (CDCl₃, 300 MHz) δ 7.78 (d, *J*= 9Hz, 2H), 7.48-7.38 (m, 3H), 6.66 (bs, 1H), 6.37 (d, *J*= 9 Hz, 1H), 4.05 (dd, *J*₁= 6Hz, *J*₂= 3Hz, 2H), 3.00-2.91 (m, 2H), 2.62-2.50 (m, 3H), 1.62-1.55 (m, 2H), 1.47-1.38 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.3 148.8, 134.9, 131.6, 129.4, 128.8, 127.1, 49.4, 42.0, 28.9, 27.1; MS (ESI⁺) *m/z* 243.1 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₅H₁₉N₂O 243.1492 ([M+1]⁺) found 243.1497.

***N*-1-aza-bicyclo[2.2.2]oct-2-en-2-yl)methyl)-4-bromobenzamide (26g).** Using procedure A, this compound was obtained from amine **54** as a colorless solid after filtration on neutral alumina (DCM) and crystallisation in Hexanes (77 mg, 0.24 mmol, 48% yield). ¹H NMR (MeOD, 300 MHz)

δ 7.76 (d, J = 9 Hz, 2H), 7.64 (d, J = 9 Hz, 2H), 6.35 (d, J = 6 Hz, 1H), 4.60 (bs, 1H), 3.99 (d, J = 3Hz, 2H), 3.03-2.94 (m, 2H), 2.66-2.56 (m, 3H), 1.74-1.65 (m, 2H), 1.52-1.43 (m, 2H); ^{13}C NMR (MeOD, 75 MHz) δ 169.2, 149.5, 134.0, 133.0, 130.3, 129.5, 127.3, 49.9, 42.4, 29.3, 28.2; MS (ESI⁺) m/z 321.2 ([M+1, Br⁷⁹]⁺), 323.2 ([M+1, Br⁸¹]⁺); HRMS (ESI⁺) calcd. for C₁₅H₁₈Br⁷⁹N₂O 321.0597 ([M+1]⁺) found 321.0597.

2-methyl-2-azabicyclo[2.2.2]oct-6-yl-*exo*-methyl(4-chlorobenzamide), TFA salt (27a). Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref. ². It was purified and separated from **13a** by preparative HPLC and obtained as a colorless oil (1.52 mg, 3.7 μmol , 4% yield). ^1H NMR (CDCl₃, 300 MHz) δ 8.45 (bs, 1H), 7.83 (d, J = 8Hz, 2H), 7.40 (d, J = 8Hz, 2H), 3.88 (dt, J_1 = 16Hz, J_2 = 4Hz, 1H), 3.73-3.67 (m, 1H), 3.32 (s, 1H), 3.19 (dq, J_1 = 20Hz, J_2 = 8Hz, 1H), 2.84 (d, J = 6 Hz, 3H), 2.69-2.50 (m, 2H), 2.19-1.99 (m, 3H), 1.75 (m, 3H), 1.31-1.24 (m, 1H); ^{13}C NMR (CDCl₃, 75 MHz) δ 166.6, 137.7, 131.7, 128.7, 128.6, 56.4, 53.8, 42.1, 41.7, 34.8, 27.2, 23.9, 22.5, 19.1; MS (ESI⁺) m/z 293.14 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₆H₂₂ClN₂O 293.1415 ([M+1]⁺) found 293.1419.

2-methyl-2-azabicyclo[2.2.2]oct-6-yl-*exo*-methyl-(benzo[1,4]dioxine-6-carboxamide), TFA salt (27c). Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref. ². It was purified and separated from **13c** by preparative HPLC and obtained as a colorless oil (3 mg, 6.9 μmol , 11% yield). ^1H NMR (CDCl₃, 300 MHz) δ 8.20 (bs, 1H), 7.45 (d, J = 3 Hz, 1H), 7.38 (d, J = 6 Hz, 1H), 6.88 (d, J = 6 Hz, 1H), 4.28-4.23 (m, 4H), 3.88-3.81 (m, 1H), 3.74-3.69 (m, 1H), 3.30 (s, 1H), 3.26-3.18 (m, 1H), 2.84 (d, J = 3 Hz, 3H), 2.70-2.55 (m, 2H), 2.15-1.98 (m, 4H), 1.75-1.69 (m, 3H), 1.30-1.23 (m, 1H); ^{13}C NMR (CDCl₃, 75 MHz) δ 167.6, 146.9, 143.6, 127.0, 120.9, 117.5, 117.2, 64.8, 64.4, 56.8, 54.1, 42.5, 42.1, 35.1, 27.5, 24.4, 22.7, 19.6; MS (ESI⁺) m/z 317.19 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₈H₂₅N₂O₃ 317.1860 ([M+1]⁺) found 317.1868.

2-methyl-2-azabicyclo[2.2.2]oct-6-yl-*exo*-methyl benzamide, TFA salt (27f). Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref. ². It was purified and separated from **13f** by preparative HPLC and obtained as a colorless oil (5 mg, 13.4 μmol , 14% yield). ^1H NMR (CDCl₃, 300 MHz) δ 8.34 (bs, 1H), 7.89 (dd, J_1 = 9 Hz, J_2 = 1 Hz, 2H), 7.50-7.39 (m, 3H), 3.95-3.86 (m, 1H), 3.73-3.67 (m, 1H), 3.33 (s, 1H), 3.28-3.18 (m, 1H), 2.83 (d, J = 3 Hz, 3H), 2.68-2.50 (m, 2H), 2.15-2.00 (m, 3H), 1.75-1.60 (m, 3H), 1.30-1.25 (m, 1H); ^{13}C NMR (CDCl₃, 75 MHz) δ 168.2, 133.5, 132.0, 128.8, 127.5, 56.8, 54.2, 42.4, 42.0, 35.2, 27.4, 24.3, 22.7, 19.6; MS (ESI⁺) m/z 259.18 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₆H₂₃N₂O 259.1805 ([M+1]⁺) found 259.1807.

2-methyl-2-azabicyclo[2.2.2]oct-6-yl-*exo*-methyl(4-bromobenzamide), TFA salt (27g). Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref.². It was purified and separated from **13g** by preparative HPLC and obtained as a colorless oil (1.43 mg, 3.16 μ mol, 3% yield). ¹H NMR (CDCl₃, 300 MHz) δ 8.46 (bs, 1H), 7.77 (d, J = 8Hz, 2H), 7.56 (d, J = 8Hz, 2H), 3.89 (dt, J_1 = 16Hz, J_2 = 4Hz, 1H), 3.73-3.68 (m, 1H), 3.31 (s, 1H), 3.22 (dq, J_1 = 16Hz, J_2 = 8Hz, 2H), 2.84 (d, J = 8Hz, 3H), 2.70-2.64 (m, 1H), 2.63-2.55 (m, 1H), 2.16-1.99 (m, 3H), 1.75 (m, 3H), 1.31-1.23 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.7, 131.9, 131.7, 128.9, 127.5, 56.3, 53.6, 42.1, 41.8, 34.6, 27.2, 24.0, 22.3, 19.5.

2-methyl-2-azabicyclo[2.2.2]oct-6-yl-*exo*-methyl(4-fluorobenzamide), TFA salt (27k). Using procedure B, this compound was obtained from the corresponding free amine obtained according to ref.². It was purified and separated from **13k** by preparative HPLC and obtained as a colorless oil (2 mg, 5 μ mol, 8% yield). ¹H NMR (CDCl₃, 300 MHz) δ 8.38 (bs, 1H), 7.91 (dd, J_1 = 6 Hz, J_2 = 3 Hz, 2H), 7.09 (t, J = 9 Hz, 2H), 3.90-3.84 (m, 1H), 3.74-3.70 (m, 1H), 3.32 (s, 1H), 3.27-3.19 (m, 1H), 2.85 (d, J = 6 Hz, 3H), 2.70-2.55 (m, 3H), 2.11 (m, 2H), 1.77-1.72 (m, 3H), 1.31-1.24 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 167.0, 164.9 (d, J = 250 Hz, C_{Ar}F), 129.7 (d, J = 7.5 Hz, 2C_{Ar}H), 129.6, 115.6 (d, J = 15 Hz, 2C_{Ar}H), 56.4, 53.8, 42.2, 41.7, 34.9, 27.1, 24.2, 22.30, 19.11; ¹⁹F NMR (CDCl₃, 376 MHz) δ -108.3; MS (ESI⁺) m/z 277.17 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₁₆H₂₂FN₂O 277.1711 ([M+1]⁺) found 277.1716.

(4-chlorophenyl)(5-isopropyl-2,5-diaza-bicyclo[2.2.1]heptan-2-yl)methanone (28a). This product was obtained from 2-(propan-2-yl)-2,5-diazabicyclo[2.2.1]heptane as an oil (10 mg, 0.035 mmol, 37% yield). For better characterization, the free amine was prepared by treatment with NEt₃ in CH₂Cl₂ and filtration through aluminum oxide. ¹H NMR (CDCl₃, 300 MHz) mixture of 2 rotamers δ 7.52-7.35 (m, 4H), 4.80 (br s, 0.4H), 4.19 (br s, 0.6H), 3.87-3.70 (m, 1.6H), 3.55-3.45 (m, 1H), 3.35-3.28 (m, 0.4H), 3.22-3.13 (m, 1H), 2.82-2.68 (m, 1H), 2.60-2.48 (m, 1H), 2.04-1.73 (m, 2H), 1.15-0.97 (m, 6H); ¹³C NMR (CDCl₃, 75 MHz) mixture of 2 rotamers δ 128.8, 60.5, 59.4, 58.3, 57.7, 57.0, 52.0, 51.3, 47.8, 45.9, 37.7, 35.9, 22.6, 21.9; MS (ESI⁺) m/z 279.2 ([M+1, Cl³⁵]⁺), 281.2 ([M+1, Cl³⁷]⁺); HRMS (ESI⁺) calcd. for C₁₅H₂₀Cl³⁵N₂O 279.1264 ([M+1]⁺) found 279.1258.

(R)-methyl 1-(pent-2-ynyl)pyrrolidine-2-carboxylate (29) Procedure adapted from ref³. A mixture of D-proline methyl ester hydrochloride (8.2 g, 49.5 mmol), 1-bromo-2-pentyne (7.60 mL, 74.2 mmol), NaHCO₃ (16 g, 198 mmol) and LiI (0.464 g, 3.46 mmol) in acetonitrile (140 mL) was heated up to 60 °C for 46 hours. After cooling to room temperature, the mixture was extracted with Et₂O/brine and the combined organic phases were dried (Na₂SO₄), filtered and evaporated. The desired aminoester **29** was obtained (6.2 g, 65% yield) as brown oil and used without further

purification. ^1H NMR (CDCl_3 , 300 MHz) δ 3.71 (s, 3H), 3.51 (t, $J = 2$ Hz, 2H), 3.40 (dd, $J_1 = 9$ Hz, $J_2 = 9$ Hz, 1H), 3.04 (m, 1H), 2.65 (q, $J = 9$ Hz, 1H), 2.22-1.70 (m, 6H), 1.11 (t, $J = 7$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 174.1 (C), 86.7 (C), 73.4 (C), 62.6 (CH_3), 52.1 (CH_2), 51.6 (CH), 41.5 (CH_2), 29.5 (CH_2), 23.1 (CH_2), 13.9 (CH_3), 12.1 (CH_2); MS (ESI $^+$) m/z 196.2 ($[\text{M}+1]^+$).

(*R*)-1-(pent-2-ynyl)pyrrolidine-2-carboxamide (30). The aminoester **29** (0.272 g, 1.39 mmol) was dissolved in a mixture of THF/ NH_3 aq. 25% (1:9). The reaction tube was flushed with N_2 and heated up to 60 $^\circ\text{C}$ for 14 hours. After cooling to room temperature, the solvents were evaporated. The residue was purified by flash chromatography (neutral alumina, AcOEt-AcOEt/MeOH 10%) to give **30** as a white solid (0.135 g, 54% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 3.46 (dt, $J_1 = 17$ Hz, $J_2 = 2$ Hz, 1H), 3.37 (dt, $J_1 = 17$ Hz, $J_2 = 2$ Hz, 1H), 3.29 (dd, $J_1 = 5$ Hz, $J_2 = 5$ Hz, 1H), 3.11-3.02 (m, 1H), 2.73-2.62 (m, 1H), 2.25-2.11 (m, 3H), 1.99-1.87 (m, 1H), 1.84-1.73 (m, 2H), 1.12 (t, $J = 7$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 178.1 (C), 86.4 (C), 74.0 (C), 64.8 (CH), 52.9 (CH_2), 42.6 (CH_2), 31.0 (CH_2), 24.3 (CH_2), 13.9 (CH_3), 12.2 (CH_2); MS (ESI $^+$) m/z 181.1 ($[\text{M}+1]^+$), 136.1 ($[\text{C}_9\text{H}_{14}\text{N}]$).

(*R*)-1-(pent-2-ynyl)pyrrolidin-2-yl)methanamine (31). Procedure adapted from ref.⁴. A suspension of LiAlH_4 (0.044 g, 1.15 mmol) in 5 mL of Et_2O was prepared and purged under Ar. After cooling down to 0 $^\circ\text{C}$, a suspension of the amide **30** (0.160 g, 0.88 mmol) in 5 mL of Et_2O was added. The reaction was warmed up to reflux. After 2 hours, the reaction was quenched by adding 44 μL of water, followed with 44 μL of NaOH 15% and 132 μL of water (in this order). The mixture was filtered over Celite and the cake washed with hot Et_2O . The collected organic solution was concentrated to dryness and the residue was purified by column chromatography (neutral alumina, CH_2Cl_2 - CH_2Cl_2 /MeOH 5%) to give **31** as a yellow solid (0.047 g, 32% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 3.46 (dq, $J_1 = 16$ Hz, $J_2 = 2$ Hz, 1H), 3.30 (dq, $J_1 = 16$ Hz, $J_2 = 2$ Hz, 1H), 3.06-2.94 (m, 1H), 2.77-2.47 (m, 4H), 2.24-2.11 (m, 2H), 1.94-1.80 (m, 1H), 1.78-1.52 (m, 3H), 1.27 (br s, 2H), 1.12 (t, $J = 7$ Hz, 1.5H), 1.11 (tq, $J_1 = 7$ Hz, $J_2 = 1$ Hz, 1.5H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 85.7 (C), 74.4 (C), 62.9 (CH), 53.2 (CH_2), 44.0 (CH_2), 41.4 (CH_2), 28.1 (CH_2), 22.5 (CH_2), 13.9 (CH_3), 12.1 (CH_2); MS (ESI $^+$) m/z 167.6 ($[\text{M}+1]^+$).

(*S*)-1-(pent-2-ynyl)pyrrolidin-2-yl)methanol (32). Compound **32** was obtained as a side-product during the work-up of (*S*)-**31** when quenched only with water. **32** was isolated by column chromatography (neutral alumina, CH_2Cl_2 - CH_2Cl_2 /MeOH 5%) as a white solid (0.016 g, 0.096 mmol, 6%). ^1H NMR (CDCl_3 , 300 MHz) isomeric mixture (1:1) δ 7.15 (br s, 0.5H), 5.71 (br s, 0.5H), 3.64 (d, $J = 4$ Hz, 0.3H), 3.60 (d, $J = 4$ Hz, 0.3H), 3.51-3.36 (m, 2.4H), 3.35-3.23 (m, 0.7H), 3.08-2.98 (m, 1H), 2.88-2.76 (m, 1H), 2.71-2.58 (m, 1H), 2.24-2.10 (m, 2.4H), 1.99-1.65 (m, 4H),

1.12 (t, $J = 7.5$ Hz, 1.5H), 1.11 (t, $J = 7.3$ Hz, 1.5H); ^{13}C NMR (CDCl_3 , 75 MHz) isomeric mixture (1:1) δ 86.5 (C), 86.4 (C), 74.3 (C), 74.1 (C), 64.9 (CH), 62.0 (CH_2), 53.4 (CH_2), 53.0 (CH_2), 42.7 (CH_2), 41.4 (CH_2), 31.1 (CH_2), 27.8 (CH_2), 24.4 (CH_2), 23.3 (CH_2), 14.0 (CH_3), 12.3 (CH_2); MS (ESI^+) m/z 167.4 (M^+), 168.4 ($[\text{M}+1]^+$).

(R)-methyl 1-cyclohexylpyrrolidine-2-carboxylate (33). D-proline methylester hydrochloride (0.346 g, 2.09 mmol), triethylamine (233 μL , 1.67 mmol) and cyclohexanone (217 μL , 2.09 mmol) were dissolved in dry MeOH (7 mL), activated molecular sieves (3 \AA) were added, and the solution was stirred for 5 minutes under N_2 . A solution of 1.25 M HCl in MeOH (400 μL , 0.50 mmol) and NaBH_3CN (0.110 g, 1.75 mmol) were added to the solution and the mixture stirred for 1.5 hours. The reaction was filtered, the solvent evaporated under reduced pressure and the residue extracted with AcOEt/ NaHCO_3 sat. to give **33** as a colorless oil (0.485 g, quantitative yield), which was used without further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 3.70 (s, 3H), 3.47 (dd, $J_1 = 9$ Hz, $J_2 = 4$ Hz, 1H), 3.18-3.09 (m, 1H), 2.67-2.56 (m, 1H), 2.43-2.31 (m, 1H), 2.14-2.00 (m, 1H), 1.97-1.67 (m, 7H), 1.64-1.53 (m, 1H), 1.31-1.04 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 175.8 (C), 62.3 (CH), 61.1 (CH), 51.5 (CH), 50.1 (CH_2), 31.5 (CH_2), 30.5 (CH_2), 29.9 (CH_2), 25.8 (CH_2), 25.1 (CH_2), 23.3 (CH_2); MS (ESI^+) m/z 211.3 ($[\text{M}+1]^+$).

(R)-methyl 1-isopropylpyrrolidine-2-carboxylate (34). To a solution of D-proline methyl ester hydrochloride (1g, 6 mmol) in MeOH (60 mL), were added sequentially NaHCO_3 (2g, 24 mmol), Acetone (0.680 mL, 9 mmol) and $\text{NaBH}(\text{OAc})_3$ (2.54 g, 12 mmol). The reaction mixture was then stirred for 48 hours at room temperature. The mixture was extracted with Et_2O , the organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The desired compound was directly used in the next step, without further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 3.69 (s, 3H), 3.43-3.38 (m, 1H), 3.13-3.06 (m, 1H), 2.81-2.73 (m, 1H), 2.61-2.53 (q, $J = 6$ Hz, 1H), 2.11-2.02 (m, 1H), 1.95-1.73 (m, 3H), 1.05 (d, $J = 6$ Hz, 6H); MS (ESI^+) m/z 172.1 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_9\text{H}_{18}\text{N}_2\text{O}$ 172.1332 ($[\text{M}+1]^+$) found 172.1333.

(R)-methyl 1-propylpyrrolidine-2-carboxylate (35). To a solution of D-proline methyl ester hydrochloride (1g, 6 mmol) in acetonitrile (16 mL), were added sequentially NaHCO_3 (2g, 24 mmol) and 1-bromopropane (0.820 mL, 9 mmol). The reaction mixture was then stirred for 48 hours at 60 $^\circ\text{C}$. After cooling to room temperature, the mixture was extracted with Et_2O , the organic layers were washed with brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. The desired compound (806 mg, 78%) was directly used in the next step, without further purification. ^1H NMR (CDCl_3 , 300 MHz) δ 3.69 (s, 3H), 3.20-3.08 (m, 2H), 2.62-2.53 (m, 1H), 2.36-2.25 (m, 2H), 2.13-2.03 (m, 1H), 1.96-1.75 (m, 3H), 1.55-1.42 (m, 2H), 0.87 (t, $J = 6$ Hz, 3H); ^{13}C NMR (CDCl_3 ,

75 MHz) δ 175.2, 66.5, 57.5, 53.8, 52.0, 29.6, 23.4, 22.1, 12.2. MS (ESI⁺) m/z 170.1 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₉H₁₆N₂O 170.1176 ([M+1]⁺) found 170.1178.

(R)-1-cyclohexylpyrrolidine-2-carboxamide (36). The aminoester **33** (0.441 g, 2.08 mmol) was dissolved in a mixture of THF/NH₃ aq. 25% (1:9). The reaction tube was flushed with N₂ and heated up to 60 °C for 14 hours. After cooling to room temperature, the solvents were evaporated to give **36** as a white solid (0.241 g, 59% yield), which was used without further purification. ¹H NMR (CDCl₃, 300 MHz) δ 3.30-3.14 (m, 1H), 3.10-2.99 (m, 1H), 2.58-2.40 (m, 1H), 2.38-2.20 (m, 1H), 2.09-1.48 (m, 9H), 1.26-0.94 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 179.9 (br C), 63.8 (CH), 61.8 (CH), 50.5 (CH₂), 32.0 (CH₂), 30.9 (CH₂), 30.1 (CH₂), 25.8 (CH₂), 25.3 (CH₂), 25.2 (CH₂), 24.4 (CH₂); MS (ESI⁺) m/z 197.2 ([M+1]⁺).

(R)-1-isopropylpyrrolidine-2-carboxamide (37). The aminoester **34** (6 mmol) was dissolved in a mixture of THF/NH₃ aq. 25% (1:9). The reaction tube was flushed with N₂ and heated up to 60 °C for 24 hours. After cooling to room temperature, the solvents were evaporated. The residue was purified by flash chromatography (neutral alumina, DCM-DCM/MeOH 1%) to give **37** as a white solid (0.186 g, 20% yield over two steps). ¹H NMR (CDCl₃, 300 MHz) δ 5.28 (bs, 1H), 3.22 (dd, $J_1 = 3$ Hz, $J_2 = 9$ Hz, 1H), 3.09-3.03 (m, 1H), 2.76 (sept, $J = 6$ Hz, 1H), 2.53-2.44 (m, 1H), 2.13-1.99 (m, 1H), 1.97-1.88 (m, 1H), 1.80-1.63 (m, 2H), 1.05 (d, $J = 6$ Hz, 3H), 1.03 (d, $J = 6$ Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 180.2, 64.2, 52.9, 50.4, 31.4, 24.8, 21.8, 19.6; MS (ESI⁺) m/z 157.1 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₈H₁₇N₂O 157.1335 ([M+1]⁺) found 157.1339.

(R)-1-propylpyrrolidine-2-carboxamide (38). The aminoester **35** (4.7 mmol) was dissolved in a mixture of THF/NH₃ aq. 25% (1:9) (40 mL). The reaction tube was flushed with N₂ and heated up to 60 °C for 14 hours. After cooling to room temperature, the solvents were evaporated. The residue was purified by flash chromatography (neutral alumina, DCM-DCM/MeOH 1%) to give **38** as a white solid (0.372 g, 51% yield). ¹H NMR (CDCl₃, 300 MHz) δ 5.24 (bs, 1H), 3.21-3.15 (m, 1H), 3.00 (dd, $J_1 = 3$ Hz, $J_2 = 9$ Hz, 1H), 2.64-2.55 (m, 1H), 2.46-2.33 (m, 1H), 2.32-2.12 (m, 2H), 1.95-1.85 (m, 1H), 1.83-1.72 (m, 2H), 1.55-1.26 (m, 5H), 0.93 (t, $J = 6$ Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 179.0, 68.0, 58.1, 54.0, 30.7, 24.4, 22.4, 11.9; MS (ESI⁺) m/z 157.1 ([M+1]⁺); HRMS (ESI⁺) calcd. for C₈H₁₇N₂O 157.1335 ([M+1]⁺) found 157.1339.

(S)-tert-butyl 3-(benzo[d]thiazole-6-carboxamido)pyrrolidine-1-carboxylate ((S)-39b). This product was synthesized following general procedure for amide formation from (S)-(-)-1-Boc-3-aminopyrrolidine. After purification by column chromatography (neutral alumina, AcOEt), **39b** was obtained as a white solid in 83% yield (3.11 g, 8.95 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 9.03 (s, 1H), 8.39 (br s, 1H), 8.02 (d, $J = 8$ Hz, 1H), 7.84 (br d, $J = 8$ Hz, 1H), 7.20 (br s, 0.5H), 7.07 (br s,

0.5H), 4.70-4.53 (m, 1H), 3.77-3.18 (m, 4H), 2.27-2.09 (m, 1H), 2.05-1.85 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 166.8 (C), 156.5 (CH), 154.9 (C), 154.4 (C), 133.8 (C), 131.4 (C), 124.8 (CH), 123.2 (CH), 121.6 (CH), 79.5 (C), 51.6 (br CH_2), 50.7 (br CH_2), 50.1 (br CH), 49.5 (br CH), 44.1 (br CH_2), 43.7 (br CH_2), 31.9 (br CH_2), 30.8 (br CH_2), 28.3 (CH_3); MS (ESI^+) m/z 348.1 ($[\text{M}+1]^+$).

(R)-1-(2-methylcyclopentyl)pyrrolidin-3-ol (40) Procedure adapted from ref. ⁵. 2-methylcyclopentanone (3.7 mL, 34.8 mmol) and (R)-3-pyrrolidinol (0.940 g, 10.8 mmol) were dissolved in 15 mL of MeOH with AcOH (per 100 mL of MeOH add 6 μL AcOH). Molecular sieves 3 Å were added. When cooling down to 0 °C the reaction turned pink. After 5 minutes a solution of NaBH_3CN (1.10 g, 17.5 mmol) in MeOH (5 mL) was added to the reaction. The solution was stirred 14 hours, warming slowly up to room temperature. The reaction was filtered, quenched adding NaOH 1M followed by extraction with CH_2Cl_2 . The organics were dried over Na_2SO_4 , filtered, concentrated to dryness, and the residue was purified by column chromatography (neutral alumina, AcOEt-AcOEt/MeOH 1%) to give **40** as a colorless oil (0.974 g, 54% yield). ^1H NMR (CDCl_3 , 300 MHz) diastereomeric mixture (1:1) δ 4.38-4.29 (m, 1H), 4.09 (br s, 1H), 3.04-2.90 (m, 1H), 2.85-2.74 (m, 1H), 2.73-2.54 (m, 1H), 2.52-2.35 (m, 2H), 2.26-2.04 (m, 2H), 1.86-1.49 (m, 6H), 1.47-1.32 (m, 1H), 0.89 (d, $J = 7$ Hz, 1.5H), 0.88 (d, $J = 7$ Hz, 1.5H); ^{13}C NMR (CDCl_3 , 75 MHz) diastereomeric mixture (1:1) δ 71.1 (CH), 71.0 (CH), 70.2 (CH), 70.1 (CH), 52.3 (CH_2), 52.2 (CH_2), 36.0 (CH), 35.9 (CH), 34.7 (CH_2), 34.6 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 20.4 (CH_2), 20.3 (CH_2), 14.1 (CH_3), 14.0 (CH_3); MS (ESI^+) m/z 170.6 ($[\text{M}+1]^+$).

(R)-1-(2-methylcyclopentyl)pyrrolidin-3-yl methanesulfonate (41). Aminoalcohol **40** (0.940 g, 5.75 mmol) and NEt_3 (1.6 mL, 11.51 mmol) were dissolved in dry THF (10 mL) under N_2 . The solution was cooled down to -10 °C (ice/ NaCl) followed by the addition dropwise of methane sulfonyl chloride (534 μL , 6.90 mmol) to the solution. The reaction was stirred for 14 hours, slowly warming up to room temperature. The organics were evaporated and the residue was filtered through a silica gel (CH_2Cl_2 - CH_2Cl_2 /AcOEt 20%) to eliminate the NEt_3 hydrochloride, to give **41** was obtained as a yellow oil (1.24 g, 90% yield). ^1H NMR (CDCl_3 , 300 MHz) diastereomeric mixture (1:1) δ 5.24-5.12 (m, 1H), 3.04-2.87 (m, 4H), 2.83-2.65 (m, 2H), 2.56-2.21 (m, 3H), 2.14-1.95 (m, 2H), 1.81-1.32 (m, 6H), 0.84 (d, $J = 7$ Hz, 1.5H), 0.83 (d, $J = 7$ Hz, 1.5H); ^{13}C NMR (CDCl_3 , 75 MHz) diastereomeric mixture (1:1) δ 80.4 (CH), 80.3 (CH), 69.9 (CH), 69.8 (CH), 60.1 (CH_2), 59.7 (CH_2), 52.1 (CH_2), 52.0 (CH_2), 38.4 (CH), 38.3 (CH), 36.0 (CH), 35.9 (CH), 32.1 (CH_2), 32.0 (CH_2), 31.3 (CH_2), 31.3 (CH_2), 27.9 (CH_2), 27.8 (CH_2), 20.3 (CH_2), 14.0 (CH_3), 13.8 (CH_3).

2-((S)-1-(2-methylcyclopentyl)pyrrolidin-3-yl)isoindoline-1,3-dione (42). Compound **41** (1.24 g, 5.01 mmol) and phthalimide potassium salt (0.929 g, 5.01 mmol) were dissolved in dry DMF, purged under N₂ and heat up to 90 °C for 38 hours. After cooling to room temperature, the reaction was extracted with CH₂Cl₂/brine and the combined organic fractions were dried (Na₂SO₄), filtered and evaporated to dryness to give **42** as a light yellow solid (1.43 g, 96% yield), which was used without further purification for the next step. A sample was purified by column chromatography (silica gel, AcOEt) for analysis. ¹H NMR (CDCl₃, 300 MHz) diastereomeric mixture (1:1) δ 7.88-7.66 (m, 2H), 7.76-7.64 (m, 2H), 4.99-4.83 (m, 1H), 3.26-2.90 (m, 2H), 2.80-2.36 (m, 3H), 2.30-1.97 (m, 3H), 1.86-1.47 (m, 5H), 1.46-1.30 (m, 1H), 0.85 (t, *J* = 6 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) diastereomeric mixture (1:1) δ 167.8 (C), 167.8 (C), 133.6 (CH), 133.6 (CH), 131.7 (C), 122.8 (CH), 69.8 (CH), 56.1 (CH₂), 55.7 (CH₂), 53.1 (CH₂), 52.8 (CH₂), 48.2 (CH), 48.0 (CH), 35.9 (CH), 35.7 (CH), 31.2 (CH₂), 31.2 (CH₂), 28.3 (CH₂), 27.8 (CH₂), 27.6 (CH₂), 20.3 (CH₂), 20.2 (CH₂), 13.8 (CH₃); MS (ESI⁺) *m/z* 299.2 ([M+1]⁺).

(S)-1-(2-methylcyclopentyl)pyrrolidin-3-amine (43). Compound **42** (0.850 g, 2.85 mmol) and hydrazine monohydrate (425 μL, 8.76 mmol) were dissolved in dry Et₂O (10 mL). The reaction was purged under N₂ and heated up to reflux for 3 hours. The white precipitate was filtered, washed with Et₂O and the organic solvent evaporated to dryness to give **43** as a yellow oil (0.449 g, 94% yield). ¹H NMR (CDCl₃, 300 MHz) diastereomeric mixture (1:1) δ 3.50-3.39 (m, 1H), 2.89-1.96 (m, 7H), 1.80-1.28 (m, 7H), 0.86-0.77 (m, 3H); ¹³C NMR (CDCl₃, 75 MHz) diastereomeric mixture (1:1) δ 70.2 (CH), 63.6 (CH₂), 63.3 (CH₂), 52.8 (CH₂), 50.7 (CH), 50.6 (CH), 35.9 (CH), 34.7 (CH₂), 31.2 (CH₂), 27.8 (CH₂), 20.3 (CH₂), 13.9 (CH₃); MS (ESI⁺) *m/z* 169.2 ([M+1]⁺).

tert-butyl 4-(benzo[*d*]thiazole-6-carboxamido)piperidine-1-carboxylate (44b). This product was obtained following procedure A for amide formation from 4-amino-1-Boc-piperidine. After purification by column chromatography (neutral alumina, AcOEt), **44b** was obtained as a white solid in 89% yield (0.403 g, 1.11 mmol). ¹H NMR (CDCl₃, 300 MHz) δ 9.10 (s, 1H), 8.47-8.43 (m, 1H), 8.17-8.11 (m, 1H), 7.85 (dd, *J*₁ = 8 Hz, *J*₂ = 2 Hz, 1H), 6.31-6.10 (m, 1H), 4.23-3.98 (m, 3H), 2.90 (br t, *J* = 12 Hz, 2H), 2.11-1.97 (m, 2H), 1.46 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 166.1 (C), 156.3 (CH), 154.8 (C), 154.5 (C), 133.8 (C), 131.8 (C), 124.7 (CH), 123.2 (CH), 121.5 (CH), 79.6 (C), 47.4 (CH), 42.6 (br CH₂), 31.9 (br CH₂), 28.3 (CH₃); MS (ESI⁺) *m/z* 361.4 ([M+1]⁺).

tert-butyl 4-isopropyl-1,4-diazepane-1-carboxylate (45). 1-Boc-hexahydro-1,4-diazepine (0.500 g, 2.50 mmol) and acetone (366 μL, 5 mmol) were dissolved in dry MeOH, activated molecular sieves (3Å) were added, and the solution was stirred for 5 minutes under N₂. A solution of 1.25 M HCl in MeOH (400 μL, 0.50 mmol) and NaBH₃CN (0.110 g, 1.75 mmol) were added to the solution

and the mixture stirred for 20 hours. The reaction mixture became turbid. The reaction was filtered, the solvent evaporated under reduced pressure and the residue extracted with AcOEt/NaHCO₃ sat. to give **45** as a colorless oil (0.561 g, 93% yield), which was used without further purification. ¹H NMR (CDCl₃, 300 MHz) mixture of 2 rotamers δ 3.46-3.30 (m, 4H), 2.83 (sep, $J = 6$ Hz, 1H), 2.62-2.46 (m, 4H), 1.78-1.62 (m, 2H), 1.39 (s, 4.5H), 1.39 (s, 4.5H), 0.94 (d, $J = 6$ Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz) mixture of 2 rotamers δ 155.5 (C), 155.4 (C), 78.9 (C), 55.3 (CH), 55.1 (CH), 52.0 (CH₂), 51.5 (CH₂), 50.4 (CH₂), 48.1 (CH₂), 47.7 (CH₂), 45.8 (CH₂), 44.9 (CH₂), 28.6 (CH₂), 28.5 (CH₂), 28.4 (CH₃), 18.3 (CH₃), 18.3 (CH₃); MS (ESI⁺) m/z 243.2 ([M+1]⁺).

1-isopropyl-1,4-diazocane (46). Following ref.⁶, *N*-isopropylethylenediamine (2.5 mL, 19.57 mmol), 1,4-dibromobutane (2.32 mL, 19.57 mmol) and Na₂CO₃ (3.1 g, 29.35 mmol) were mixed in *o*-xylene (100 mL). The reaction was purged under N₂ and heated up to 130 °C for 18 hours. When the reaction was finished, xylene was distilled off and the residue was extracted with AcOEt/HCl 1M. The aqueous phase was then basified with NaOH in pellets to pH = 9 and extracted with AcOEt. This organic phase was dried (Na₂SO₄), filtered and the solvent evaporated under reduced pressure to give **46** as a yellow oil (1.28 g, 42% yield), which was used without further purification for the next step. ¹H NMR (CDCl₃, 400 MHz) δ 2.78 (sep, $J = 6$ Hz, 1H), 2.74-2.67 (m, 2H), 2.62-2.56 (m, 2H), 2.52-2.46 (m, 4H), 1.79-1.70 (br m, 5H), 1.06 (d, $J = 6$ Hz, 6H).

(3*S*,9*aR*)-hexahydro-3-methyl-6*H*-pyrido[1,2-*a*]pyrazine-1,4-dione (47). Procedure adapted from patent WO 2005/058327. To a solution of (*R*)-(+)-*N*-Boc-2-piperidinecarboxylic acid (2.0 g, 8.72 mmol) in CH₂Cl₂ (30 mL) was added EDC hydrochloride (2.01 g, 10.4 mmol), HOBt (1.22 g, 8.98 mmol), NEt₃ (2.43 mL, 21.8 mmol) and L-alanine ethyl ester hydrochloride (1.34 g, 8.72 mmol). The reaction was stirred for 15 hours. Once the reaction was finished it was extracted with HCl 0.5M and brine. The aqueous phase was then basified to pH = 8 with Na₂CO₃ and extracted with CH₂Cl₂. All the organic phases from the acid and basic extractions were combined, dried (Na₂SO₄) and filtered. The organic solvent was evaporated under reduced pressure. TFA (8 mL) was added to the solid residue, the mixture was stirred for 1 hour and afterwards, the excess of TFA was evaporated under reduced pressure. The residue was then dissolved in MeOH (75 mL) and NEt₃ (8 mL) was added to the solution. This mixture was heated up to reflux for 4 hours under N₂. The organic solvents were evaporated to dryness and a white solid was obtained. This solid was purified by recrystallization (48% hexane, 48% ether, 4% ethanol) to give **47** (0.624 g, 34% yield, ~87% purity by NMR, rest is Et₃NHCl). ¹H NMR (CDCl₃, 300 MHz) δ 4.66 (dm, $J = 13$ Hz, 1H), 4.08 (q, $J = 7$ Hz, 1H), 3.88-3.78 (m, 1H), 2.49 (td, $J_1 = 13$ Hz, $J_2 = 3$ Hz, 1H), 2.35-2.24 (m, 1H), 2.03-1.93 (m, 1H), 1.76-1.65 (m, 1H), 1.65-1.35 (m, 6H).

(3*S*,9*aR*)-octahydro-3-methyl-1*H*-pyrido[1,2-*a*]pyrazine (48).⁷ Procedure adapted from patent WO 2005/058327. In a 2-necked round-bottom flask with reflux was prepared a suspension of LiAlH₄ (0.311 g, 8.19 mmol) in dry THF (10 mL) under Ar. That suspension was cooled down to 0 °C followed by the addition dropwise of the diketopiperazine **47** (0.498 g of 87% purity, 0.447 g real weight, 2.45 mmol) dissolved in 10 mL of dry THF. When the H₂ release stopped, the mixture was heat up to reflux for 14 hours. The reaction was quenched by adding dropwise a saturated solution of Rochelle's salt in water. This mixture was stirred for 3 hours, filtered over Celite and the cake washed with THF. The organic solvent was then evaporated under reduced pressure. The residue was extracted with CH₂Cl₂/brine, the organic fractions dried (Na₂SO₄), filtered and evaporated under reduced pressure. The oily residue was distilled under reduced pressure (2 mbar, 100 °C) to yield **48** as colorless oil (0.084g, 22% yield). ¹H NMR (CDCl₃, 300 MHz) δ 3.00-2.87 (m, 1H), 2.86-2.66 (m, 3H), 2.55 (ddd, *J*₁ = 12 Hz, *J*₂ = 10 Hz, *J*₃ = 0.7 Hz, 1H), 2.06-1.94 (m, 1H), 1.81-1.45 (m, 7H), 1.36-1.08 (m, 2H), 1.00 (dd, *J*₁ = 6 Hz, *J*₂ = 0.7 Hz, 3H).

(*S*)-ethyl 1-(2-cyanoethyl)pyrrolidine-2-carboxylate (49). Following the procedure in ref. ⁸, L-proline ethyl ester hydrochloride (7.8 g, 43 mmol) and acrylonitrile (13 mL, 197.8 mmol) were dissolved in 15 mL of water. When the mixture was heated up to 50 °C, a solution of KOH (2.41 g, 43 mmol) in 35 mL of water was added. The reaction was stirred at 50 °C for 1.5 hours and then 1 more hour at 70 °C. After cooling down to room temperature, the mixture was extracted with Et₂O, the organic fractions dried (Na₂SO₄), filtered and evaporated under reduced pressure to obtain **49** as a colorless oil (4.92 g, 58% yield). ¹H NMR (CDCl₃, 300 MHz) δ 4.16 (q, *J* = 7 Hz, 2H), 3.31-3.24 (m, 1H), 3.20-3.11 (m, 1H), 3.05 (td, *J*₁ = 15 Hz, *J*₂ = 12 Hz, 1H), 2.84-2.74 (m, 1H), 2.52 (t, *J* = 7 Hz, 3H), 2.19-2.02 (m, 1H), 2.00-1.76 (m, 3H), 1.26 (t, *J* = 7 Hz, 3H)

(*S*)-octahydropyrrolo[1,2-*a*][1,4]diazepin-1-one (50). The aminoester **49** (4.92 g, 25.1 mmol) was dissolved in MeOH (150 mL). To this solution was added ~ 5 g of Nickel Raney (50% in water), trying to remove as much water as possible by decantation. The reaction was placed under H₂ at 48 bar and was heated at 80 °C for 6 hours (until the reaction stops consuming H₂). The mixture was filtered over Celite and the cake was washed with MeOH. The organic fraction was evaporated, and the obtained solid was recrystallized with acetone to obtain the pure product **50** as a white solid (2.21 g, 57% yield). ¹H NMR (CDCl₃, 300 MHz) δ 6.40 (br s, 1H), 3.39-3.03 (m, 5H), 2.67-2.51 (m, 1H), 2.50-2.30 (m, 2H), 1.94-1.62 (m, 5H).

(*S*)-octahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazepine (51). In a 2-necked round-bottom flask with reflux was prepared a suspension of LiAlH₄ (0.765 g, 20.16 mmol) in dry THF (20 mL) under Ar. That suspension was cooled down to 0 °C followed by the addition dropwise of a solution of the

lactame **50** (1.55 g, 10.08 mmol) in dry THF (20 mL). When the H₂ release stopped, the mixture was heat up to reflux for 14 hours. The reaction was quenched by adding dropwise a saturated solution of Rochelle's salt in water (11.4 g of salt in 6 mL of water). This mixture was vigorously stirred for 30 minutes, filtered over Celite and the cake washed with THF. The organic solvent was then evaporated under reduced pressure and the residue was distilled under reduced pressure (15 mbar, 110 °C). The amine **51** was obtained as a colorless oil (0.516g, 36% yield). ¹H NMR (CDCl₃, 300 MHz) δ 3.07-2.86 (m, 5H), 2.59-2.28 (m, 4H), 2.16 (br s, 1H), 1.97-1.58 (m, 5H), 1.45-1.29 (m, 1H).

3-Hydroxy-2-methylene-1-azabicyclo[2.2.2]octane (52) and **2-Chloromethyl-1-azabicyclo[2.2.2]oct-2-ene (53)**. These compounds were prepared according the literature.⁹

2-Aminomethyl-1-azabicyclo[2.2.2]octane (55). Compound **54** (50 mg, 0.36 mmol) and Pd/C (50 mg) were diluted in dry MeOH (5 mL) and the solution was stirred for 2 hours under an hydrogen atmosphere. The reaction mixture was then filtered over Celite and washed with MeOH. The filtrate was concentrated under vacuum to afford a yellow oil in a quantitative yield. The desired compound was used in the next step without purification. ¹H NMR (MeOD, 300 MHz) 6.16-5.77 (m, 2H), 5.63-5.48 (m, 3H), 5.43-5.25 (m, 2H), 4.70-4.06 (m, 7H), 3.89-3.58 (m, 2H); ¹³C NMR (MeOD, 75 MHz) δ 58.6, 50.2, 42.9, 42.1, 30.3, 25.6, 24.9, 22.; MS (ESI⁺) m/z 141.14 [M+1]⁺.

(±)-(5-exo,6-exo)-5,6-Dihydroxybicyclo[2.2.1]-hept-2-yl acetate (mixture of 2-endo and 2-exo) (56). To a solution of commercial 5-norbornen-2-yl-acetate (endo/exo mixture) (1.5 mL, 10.2 mmol) and *N*-methyl morpholine *N*-oxide (3 g, 22.1 mmol) in acetone (50 mL) and water (5 mL) was added a commercial solution of osmium tetroxide (1.2 mL, 2.5 % by weight solution in *t*-butanol), which caused it to turn brown almost immediately. The solution was stirred at 40 °C for 18 h under argon atmosphere. Then, Na₂S₂O₃ was added to the solution to quench osmium tetroxide and the solution was filtered and the acetone was removed under reduced pressure. The remaining aqueous solution was extracted with EtOAc (4 x 5 mL) and the resulting organic extract was dried (MgSO₄), filtered and the solvent was removed. The crude residue was purified by column chromatography on silica with 1:1 Hexane/ EtOAc, affording a yellowish oil of a mixture of diol in a 72: 28 endo/exo ratio (as determined by ¹H NMR) (2 g, quant.). ¹H NMR (CDCl₃, 300 MHz) *major isomer* δ 4.94-4.87 (m, 1H), 4.23 (d, *J*= 6Hz, 1H), 3.82(d, *J*= 6Hz, 1H), 3.71-3.63 (m, 1H), 2.90 (bs, 2H), 2.41 (d, *J*= 3Hz, 1H), 2.10-2.14 (m, 1H), 2.09-2.03 (m, 1H), 2.01(s, 3H), 1.85-1.81 (m, 1H), 1.23 (d, *J*= 12Hz, 1H), 0.86 (dt, *J*₁= 15Hz, *J*₂=3Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) *mixture of isomers* δ 170.9, 74.1, 73.4, 73.3, 72.8, 70.4, 68.5, 66.8, 55.4, 48.9, 47.2, 43.4, 42.1, 34.8, 32.6, 30.8, 29.0, 21.2, 21.9; MS (ESI⁺) m/z 187.10 ([M+1]⁺); HRMS (ESI⁺) calcd. for

$C_9H_{15}O_4$ 187.0965 ($[M+1]^+$) found 187.0967.

3-benzyl-3-aza-bicyclo[3.2.1]oct-6-yl acetate (57). (\pm)-5,6-Dihydroxybicyclo[2.2.1]-hept-2-yl acetate **56** (1.8 g, 9.7 mmol) was vigorously stirred in H_2O (30 mL) and 1,2-dichloroethane (DCE) (17.5 mL) under argon atmosphere in a cool water bath (0 °C) and treated with sodium periodate ($NaIO_4$) (2.68 g, 12.6 mmol). The reaction mixture was stirred for 18h (followed by TLC) and the layers were separated, and the aqueous layer was extracted with DCE (2 x 9 mL). The organic layer was washed with H_2O (4 x 20 mL) and then dried over $MgSO_4$ and filtered through a cotton plug in a 100 mL round bottom flask. To this was added distilled benzylamine (1.11 mL, 10.2 mmol), and the mixture was stirred for 10 min and then transferred in a syringe. The mixture was added dropwise to a stirred slurry of $NaBH(OAc)_3$ (6.6 g, 31.0 mmol) in DCE (22 mL). After it was stirred for 18h, the reaction was quenched with saturated aqueous Na_2CO_3 solution (10 mL), carefully at first, and the mixture was stirred for 1h (pH 9). The layer were separated, and the aqueous layer was extracted with DCM (3 x 5 mL). The organic layer was washed with brine (10 mL), dried on $MgSO_4$, filtered and evaporated to give **57** as a yellow oil. After purification on column chromatography (30: 70 EtOAc/ Hexane), the desired compound is obtained as a colorless oil (1.57 g, 62 %). 1H NMR ($CDCl_3$, 300 MHz) *major isomer* δ 7.37-7.36 (m, 2H), 7.34-7.15 (m, 3H), 4.974.92 (m, 1H), 3.58 (d, $J=15$ Hz, 1H), 3.34 (d, $J=15$ Hz, 1H), 2.84-2.70 (m, 2H), 2.262.19 (m, 2H), 2.17-2.03 (m, 2H), 2.00 (s, 3H), 2.03-1.93 (m, 1H), 1.78 (dt, $J_1=12$ Hz, $J_2=3$ Hz, 1H), 1.611.53 (m, 1H), 1.39 (dd, $J_1=9$ Hz, $J_2=3$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) *mixture of 2 isomers* δ 171.7, 171.1, 139.8, 139.2, 128.9, 128.8, 128.4, 128.2, 127.0, 126.9, 79.2, 76.7, 62.6, 62.6, 60.6, 58.6, 57.5, 53.8, 37.7, 35.8, 35.7, 35.2, 34.8, 34.2, 21.6, 21.4; MS (ESI^+) m/z 260.16 ($[M+1]^+$); HRMS (ESI^+) calcd. for $C_{16}H_{22}O_2N$ 260.1645 ($[M+1]^+$) found 260.1648.

3-benzyl-3-aza-bicyclo[3.2.1]octan-6-one (58). To a solution of 3-benzyl-3-aza-bicyclo[3.2.1]oct-6-yl acetate **57** (1.57g, 6 mmol) in MeOH (16 ml) and water (16 mL) was added a commercial solution of KOH (24 mL, 1N in MeOH). The solution was stirred at room temperature for 18 hours and the solvent was remove under vacuo. The aqueous layer was extracted with DCM (4 x 10 mL). The organic layers were dried over $MgSO_4$, filtered and evaporated to give 3-benzyl-3-aza-bicyclo[3.2.1]octan-6-ol as a colorless oil (677 mg, 52%). The desired compound was used in the next step without further purification. 1H NMR ($CDCl_3$, 300 MHz) *major isomer* δ 7.30-7.18 (m, 5H), 4.25-4.19 (m, 1H), 3.45 (d, $J=3$ Hz, 2H), 2.97-2.92 (m, 1H), 2.74-2.67 (m, 1H), 2.18-2.10 (m, 4H), 2.07-2.01 (m, 1H), 1.53-1.45 (m, 1H), 1.43-1.38 (m, 2H).MS (ESI^+) m/z 218.2 ($[M+1]^+$); HRMS (ESI^+) calcd. for $C_{14}H_{20}ON$ 218.1539 ($[M+1]^+$) found 218.1534. To a stirring solution of oxalyl chloride (540 μ L, 6.2 mmol) in dry DCM (31 mL), cooled to - 78 °C, was added dropwise DMSO (880 μ L, 12.4 mmol). After 10 min, a solution of 3-benzyl-3-aza-bicyclo[3.2.1]octan-6-ol

(677 mg, 3.1 mmol) in DCM (7 mL) was added dropwise. After an additional 15 min, NEt_3 (1.73 mL, 12.4 mmol) was added and the mixture was allowed to stir at $-78\text{ }^\circ\text{C}$ for 15 min and then warmed to room temperature and stirred for 15 min. The reaction mixture was then placed on a silica gel pad and the compound was eluted with 50 % EtOAc in Hexane to give the compound **56** as a colorless oil (595 mg, 89 %). ^1H NMR (CDCl_3 , 300 MHz) δ 7.27-7.17 (m, 5H), 3.47 (d, $J=12\text{Hz}$, 1H), 3.41 (d, $J=12\text{Hz}$, 1H), 3.12-3.04 (m, 1H), 2.82-2.76 (m, 1H), 2.54-2.47 (m, 1H), 2.38 (dd, $J_1=12\text{Hz}$, $J_2=3\text{Hz}$, 1H), 2.32-2.06 (m, 4H), 2.00-1.92 (m, 1H), 1.72-1.67 (m, 1H). ^{13}C NMR (CDCl_3 , 75MHz) δ 219.8, 138.4, 128.8, 128.5, 127.2, 62.3, 58.4, 57.9, 46.1, 43.6, 36.0, 33.0; MS (ESI^+) m/z 216.14 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{14}\text{H}_{18}\text{ON}$ 216.1383 ($[\text{M}+1]^+$) found 216.1385.

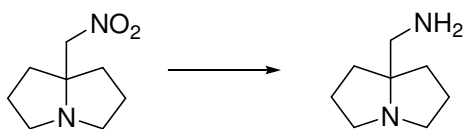
3-benzyl-3-aza-bicyclo[3.2.1]octan-6-one oxime (59). A solution of ketone **58** (1.76 g, 7.56 mmol), hydroxylamine hydrochloride (1.68g, 24.2 mmol) and NaOAc (6.2 g, 75.6 mmol) in MeOH (30 mL) was heated gently at reflux for 3 h. After cooling to room temperature, the reaction mixture was filtered, concentrated under reduced pressure and purified on silica gel with 20% EtOAc/Hexane and then 50% EtOAc/Hexane to afford the desired compound as a colorless oil (1.12g, 65%). ^1H NMR (CDCl_3 , 300 MHz) *major diastereoisomer* δ 9.76 (bs, 1H), 7.25-7.18 (m, 5H), 3.57 (d, $J=12\text{Hz}$, 1H), 3.40 (d, $J=12\text{Hz}$, 1H), 3.02-2.97 (m, 1H), 2.75-2.65 (m, 3H), 2.43-2.18 (m, 4H), 1.78-1.73 (m, 1H), 1.54-1.49 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) mixtures of isomers *cis/trans* δ 168.1, 167.4, 138.6, 138.5, 128.7, 128.3, 126.9, 62.2, 62.1, 59.6, 58.2, 57.8, 56.7, 39.9, 37.1, 36.8, 34.9, 33.4, 33.1, 32.5.; MS (ESI^+) m/z 231.15 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{14}\text{H}_{19}\text{ON}_2$ 231.1492($[\text{M}+1]^+$) found 231.1493.

3-benzyl-3-aza-bicyclo[3.3.1]nonane amide (60). Compound **59** (750 mg, 3.30mmol) was diluted in H_2SO_4 conc. (10 mL) and heated at $100\text{ }^\circ\text{C}$ for 4 h. The reaction mixture was then cooled to room temperature and poured into ice. Na_2CO_3 was then added to neutralized the mixture and the aqueous layer was extracted with EtOAc (x 4). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give a yellow oil (350 mg, 46%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.277.20 (m, 5H), 3.54 (s, 2H), 3.50-3.45 (m, 1H), 2.81-2.70 (m, 2H), 2.52 (dd, $J_1=18\text{Hz}$, $J_2=6\text{Hz}$, 1H), 2.34 (dd, $J_1=9\text{Hz}$, $J_2=3\text{Hz}$, 1H), 2.17-2.09 (m, 2H), 1.96-1.88 (m, 1H), 1.71-1.62 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 174.7, 138.4, 128.6, 128.4, 128.3, 128.2, 126.9, 61.9, 58.8, 58.4, 47.2, 37.3, 29.7, 27.8; MS (ESI^+) m/z 231.15 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_{14}\text{H}_{19}\text{ON}_2$ 231.1497 ($[\text{M}+1]^+$) found 231.1494.

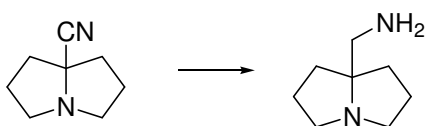
2-methyl-2-aza-3'-benzyl-3'-aza-bicyclo[3.3.1]nonan-3-one (61). To a solution of lactam **60** (565 mg, 2.45 mmol) in dry THF (20 mL) at $0\text{ }^\circ\text{C}$, was added sodium hydride (60% in mineral oil) (294

mg, 7.36 mmol) and the reaction mixture was stirred for 30 min at 0 °C. Then, methyl iodide (460 μ L, 7.36 mmol) was added dropwise and the reaction mixture was stirred for 18 h at room temperature. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl and the compound was extracted with EtOAc (x3). The organic layers were then washed with brine, dried over Na_2SO_4 , filtrated and concentrated under vacuum. After flash chromatography (1% MeOH/DCM), the desired compound was obtained as a colorless oil (491 mg, 82%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.31-7.17 (m, 5H), 3.57 (d, $J=15\text{Hz}$, 1H), 3.43 (d, $J=15\text{Hz}$, 1H), 3.35-2.30 (m, 1H), 2.90-2.75 (m, 4H), 2.54 (dd, $J_1=18\text{Hz}$, $J_2=6\text{ Hz}$, 1H), 2.36 (d, $J=18\text{Hz}$, 1H), 2.28 (dd, $J_1=9\text{Hz}$, $J_2=3\text{Hz}$, 1H), 2.17-2.08 (m, 1H), 1.99-1.91 (m, 2H), 1.69 (dq, $J_1=12\text{Hz}$, $J_2=3\text{Hz}$, 1H), 1.61-1.56 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 171.8, 138.4, 128.3, 128.2, 126.9, 61.9, 59.4, 54.5, 53.7, 37.9, 33.6, 30.5, 28.6 ; MS (ESI^+) m/z 267.14 ($[\text{M}+23]^+$); HRMS (ESI^+) calcd. for $\text{C}_{15}\text{H}_{20}\text{ON}_2\text{Na}$ 267.1468 ($[\text{M}+23]^+$) found 267.1474.

2-methyl-2-aza-3'-aza-bicyclo[3.3.1]nonane (62). A solution of borane in THF (3.6 mL, c=1M in THF) was added dropwise to a solution of compound **61** (291 mg, 1.19 mmol) in dry THF (12 mL) and the reaction mixture was stirred at reflux for 12h. After the mixture was cooled to room temperature, MeOH (5 mL) was added dropwise and the mixture was stirred for 1h and then the solvents were evaporated to dryness. After a flash chromatography (1% MeOH/DCM), 2-methyl-2-aza-3'-benzyl-3'-aza-bicyclo[3.3.1]nonane was obtained as a colorless oil (184 mg, 67%). ^1H NMR (CDCl_3 , 300 MHz) δ 7.33-7.22 (m, 5H), 4.09-3.92 (m, 1H), 3.56 (dd, $J_1=33\text{Hz}$, $J_2=12\text{Hz}$, 1H), 3.27-3.17 (m, 2H), 3.03-2.90 (m, 2H), 2.89-2.80 (m, 1H), 2.73 (s, 1H), 2.49 (s, 3H), 2.38-2.31 (m, 1H), 2.24-2.15 (m, 1H), 2.07 (dd, $J_1=12\text{Hz}$, $J_2=3\text{Hz}$, 1H), 1.97-1.90 (m, 1H), 1.65-1.55 (m, 1H), 1.40 (dq, $J_1=12\text{Hz}$, $J_2=3\text{Hz}$, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) 2 rotamers δ 138.3 (C), 132.3 (C), 129.2 (CH), 120.0 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.4 (CH), 63.6 (CH_2), 63.4 (CH_2), 60.6 (CH), 59.9 (CH), 59.8 (CH_2), 58.2 (CH_2), 57.7 (CH_2), 56.9 (CH_2), 56.0 (CH_2), 53.8 (CH_2), 52.1 (CH_3), 49.8 (CH_3), 29.5 (CH_2), 27.9 (CH_2), 27.6 (CH_2), 26.6 (CH), 26.3 (CH_2), 26.2 (CH_2); MS (ESI^+) m/z 231.19 ($[\text{M}+1]^+$). To a solution of 2-methyl-2-aza-3'-benzyl-3'-aza-bicyclo[3.3.1]nonane (111 mg, 0.48 mmol) in MeOH (5 mL) was added $\text{Pd}(\text{OH})_2$ (46 mg) and the mixture was heated at reflux under H_2 atmosphere (balloon) for 6h. Then, the solution was filtrated over Celite® and washed with MeOH. HCl in MeOH (1 mL, c= 1.75 M) was then added to the solution and the solvent was evaporated to dryness to give the compound **62** as HCl salt (quant.). ^1H NMR (MeOD, 300 MHz) δ 3.65-3.55 (m, 2H), 3.37-3.34 (m, 1H), 3.20-3.10 (m, 4H), 2.78 (s, 3H), 2.23-2.12 (m, 3H), 2.00-1.93 (m, 2H); ^{13}C NMR (MeOD, 75 MHz) δ 55.2, 51.0, 50.1, 44.6, 42.7, 29.5, 28.5, 24.8; MS (ESI^+) m/z s141.14 ($[\text{M}+1]^+$); HRMS (ESI^+) calcd. for $\text{C}_8\text{H}_{17}\text{N}_2$ 141.1386 ($[\text{M}+23]^+$) found 141.1382.



5-aminomethyl-1-azabicyclo[3.3.0]octane (63). Procedure adapted from ref. ¹⁰ To a solution of **67** (1.7 g, 9.99 mmol) and NaOH (0.352 g, 8.80 mmol) in EtOH (8 mL), ~0.600 g of Nickel Raney (50% in water) were added, trying to remove as much water as possible by decantation. The mixture was placed under H₂ (1 atm) at room temperature and stirred for 15 hours. After filtration over Celite, the filtrate was evaporated under reduced pressure. This residue (containing the diamine and NaOH) was used without further purification due to instability of the molecule and the difficulties to purify it. The ¹H NMR matches with the one described in the literature.

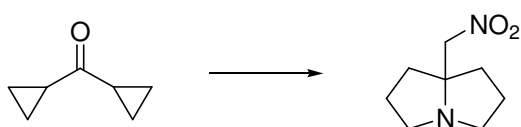


5-aminomethyl-1-azabicyclo[3.3.0]octane (63). To a suspension of LiAlH₄ (665 mg, 17.5 mmol) in dry Et₂O (17 mL) at reflux, was added dropwise a solution of compound **68** (794 mg, 5.83 mmol) in Et₂O (8 mL). The reaction mixture was stirred for 3 hours at reflux. Then a saturated aqueous solution of Rochelle's salt was added dropwise to quench the reaction, and the mixture was filtered over celite and washed with Et₂O. The organics were evaporated to give the desired compound as a colorless oil (340 mg, 42%). This compound was used without further purification due to instability of the molecule and the difficulties to purify it. The ¹H NMR matches with the one described in the literature.¹⁰

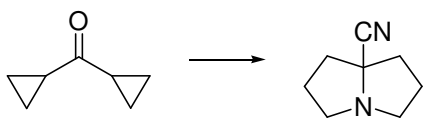
((R)-1-cyclohexylpyrrolidin-2-yl)methanamine (64). A suspension of LiAlH₄ (0.466 g, 12.3 mmol) in 10 mL of Et₂O was prepared and purged under Ar. After cooling down to 0 °C, a suspension of the amide **36** (0.241 g, 1.23 mmol) in 5 mL of Et₂O was added. The reaction was warmed up to room temperature and, after 1.5h, it was quenched by adding water dropwise (quench at 0 °C). The mixture was filtered over Celite and the cake washed with Et₂O. The collected organic solution was concentrated to dryness and the residue was purified by column chromatography (neutral alumina, CH₂Cl₂-CH₂Cl₂/MeOH 4%) to give **64** as a colorless oil (0.042 g, 19% yield). ¹H NMR (CDCl₃, 300 MHz) δ 2.97-2.88 (m, 1H), 2.85-2.75 (m, 1H), 2.69-2.49 (m 3H), 2.48-2.36 (m, 1H), 1.91-1.53 (m, 9H), 1.44 (br s, 2H), 1.32-1.01 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 61.4 (CH), 59.9 (CH), 48.9 (CH₂), 46.0 (CH₂), 32.8 (CH₂), 28.6 (CH₂), 27.7 (CH₂), 26.2 (CH₂), 25.9 (CH₂), 25.6 (CH₂), 23.8 (CH₂); MS (ESI⁺) *m/z* 183.4 ([M+1]⁺).

(R)-(1-isopropylpyrrolidin-2-yl)methanamine (65). To a suspension of LiAlH_4 (60 mg, 1.56 mmol) in dry Et_2O (5 mL) under Argon at 0°C , was added dropwise a suspension of amide **37** (1.2 mmol) in Et_2O (5 mL). The reaction mixture was then heated up to reflux for 12 h. The reaction was quenched at 0°C by dropwise addition of a saturated aqueous solution of Rochelle's salt. The mixture was then filtered over celite and washed with Et_2O . Evaporation of the solvent gave compound **65** (53 mg, 31%), which was used in the next step without further purification.

(R)-(1-propylpyrrolidin-2-yl)methanamine (66). To a suspension of LiAlH_4 (119 mg, 3.13 mmol) in dry Et_2O (10 mL) under Argon at 0°C , was added dropwise a suspension of amide **38** (372 mg, 2.4 mmol) in Et_2O (10 mL). The reaction mixture was then heated up to reflux for 2 h. The reaction was quenched at 0°C by dropwise addition of a saturated aqueous solution of Rochelle's salt. The mixture was then filtered over celite and washed with Et_2O . Evaporation of the solvent gave compound **66** (44 mg, 13%), which was used in the next step without further purification. ^1H NMR (CDCl_3 , 300 MHz) 3.50 (m, 1H), 3.15-2.97 (m, 4H), 2.50-2.48 (m, 2H), 2.06-1.69 (m, 6H), 0.93 (t, $J = 6\text{Hz}$, 3H).



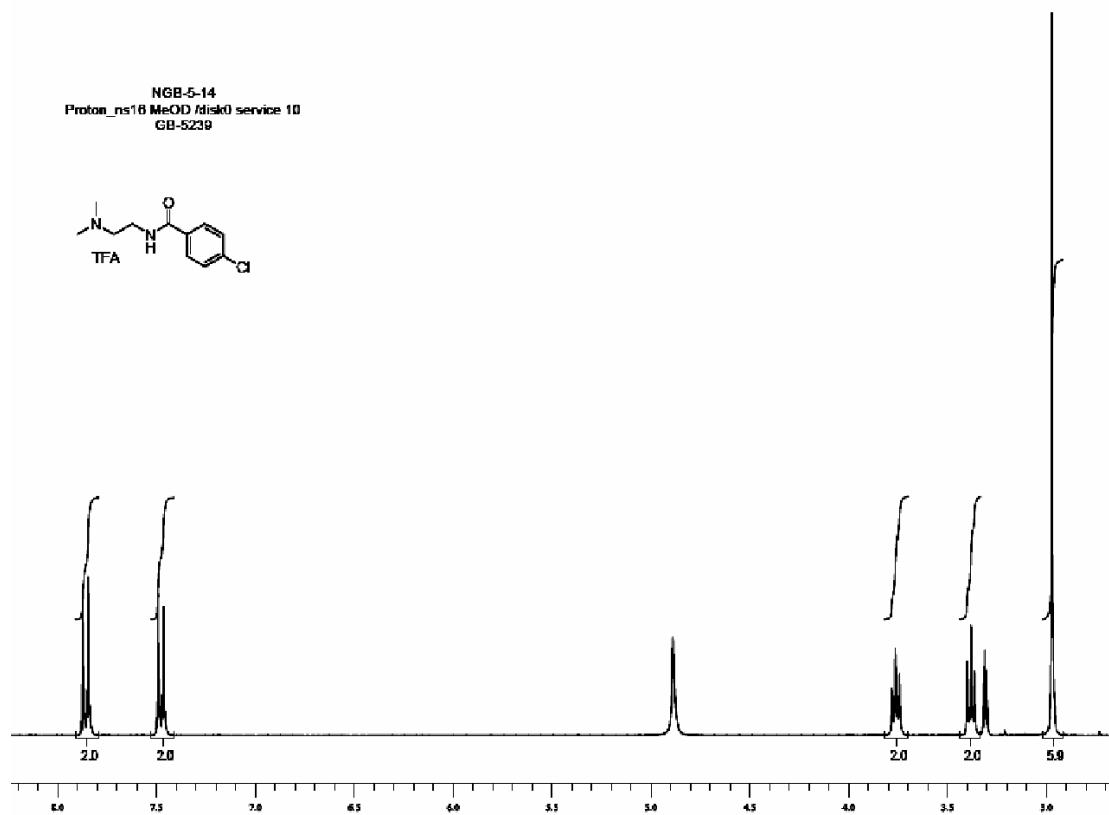
5-nitromethyl-1-azabicyclo[3.3.0]octane (67). Procedure adapted from ref. ¹⁰. Neat dicyclopropyl ketone (3 mL, 26.6 mmol) was cooled down to 0°C followed by bubbling HCl gas through the ketone for 30 min. The HCl flow was stopped, the reaction was allowed to warm up to room temperature and it was stirred for 3 hours. The procedure was repeated again once more and, once finished, pure 1,7-dichloro-heptan-4-one was obtained in quantitative yield (4.87 g). This ketone (3.05 g, 16.6 mmol) was mixed together with nitromethane (3.4 mL, 62.7 mmol) and the solution cooled down to 0°C . Then, NH_3 gas was bubbled through the solution for 30 minutes. The NH_3 flow was stopped, the reaction warm up to room temperature for 2 hours. A white precipitate appeared. The described procedure was repeated 2 times more and finally the reaction stirred for 14 more hours at room temperature. The mixture was extracted with $\text{CH}_2\text{Cl}_2/\text{NaOH}$ 0.1M and the organic phases dried (Na_2SO_4), filtered and the solvent evaporated to dryness. The crude was purified by column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 3%) to yield **67** as a colorless solid (1.7 g, 60% yield). ^1H NMR (CDCl_3 , 300 MHz) δ 4.25 (s, 2H), 3.09-2.99 (m, 2H), 2.65-2.54 (m, 2H), 2.19-2.07 (m, 2H), 1.95-1.57 (m, 6H).

**5-Cyano-1-azabicyclo[3.3.0]octane (68).**

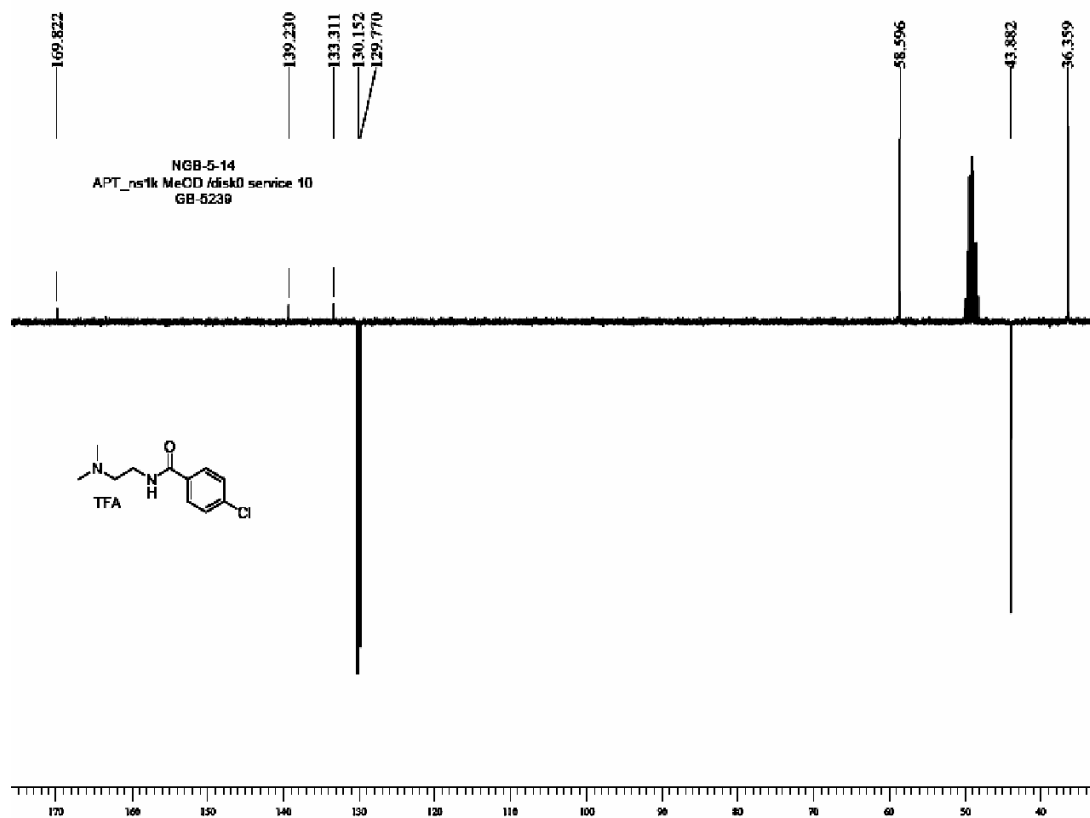
According to the ref. ¹¹. Neat dicyclopropyl ketone (3 mL, 26.6 mmol) was cooled down to 0 °C followed by bubbling HCl gas through the ketone for 30 min. The HCl flow was stopped, the reaction was allowed to warm up to room temperature and it was stirred for 3 hours. The procedure was repeated again once more and, once finished, pure 1,7-dichloro-heptan-4-one was obtained in quantitative yield (4.87 g). This keto-compound (1.85g, 10 mmol) and $(\text{CH}_3)_2\text{C}(\text{NH}_2)\text{CN}$ ¹² (3.6g, 30 mmol) were added to a solution of 7.5 mL NH_3 (25% in H_2O) in 10 mL MeOH at 0 °C. The mixture was stirred for 24h at room temperature and concentrated. The residue was dissolved in 5 N NaOH aqueous solution, and extracted with DCM. The organic layer was dried over Na_2SO_4 and concentrated to afford a colorless oil (794 mg, 58%), which was used in the next step without further purification. The ¹H NMR matches with the one described in the literature.

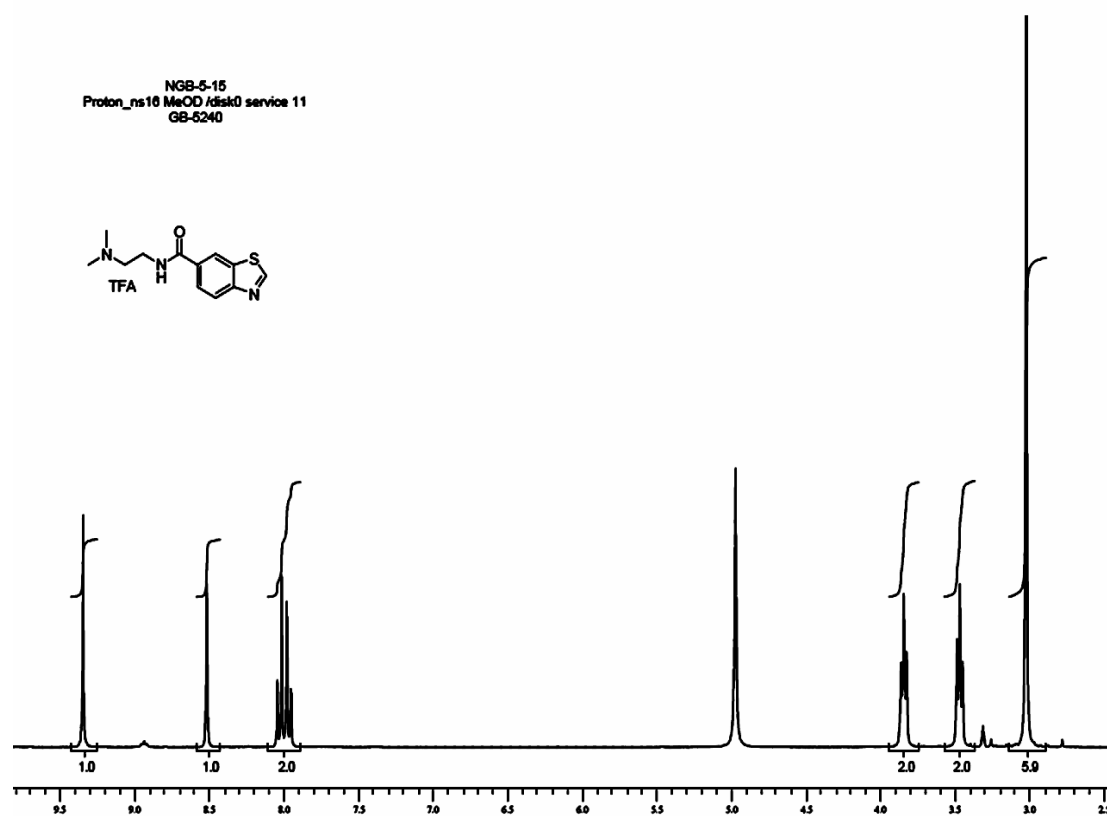
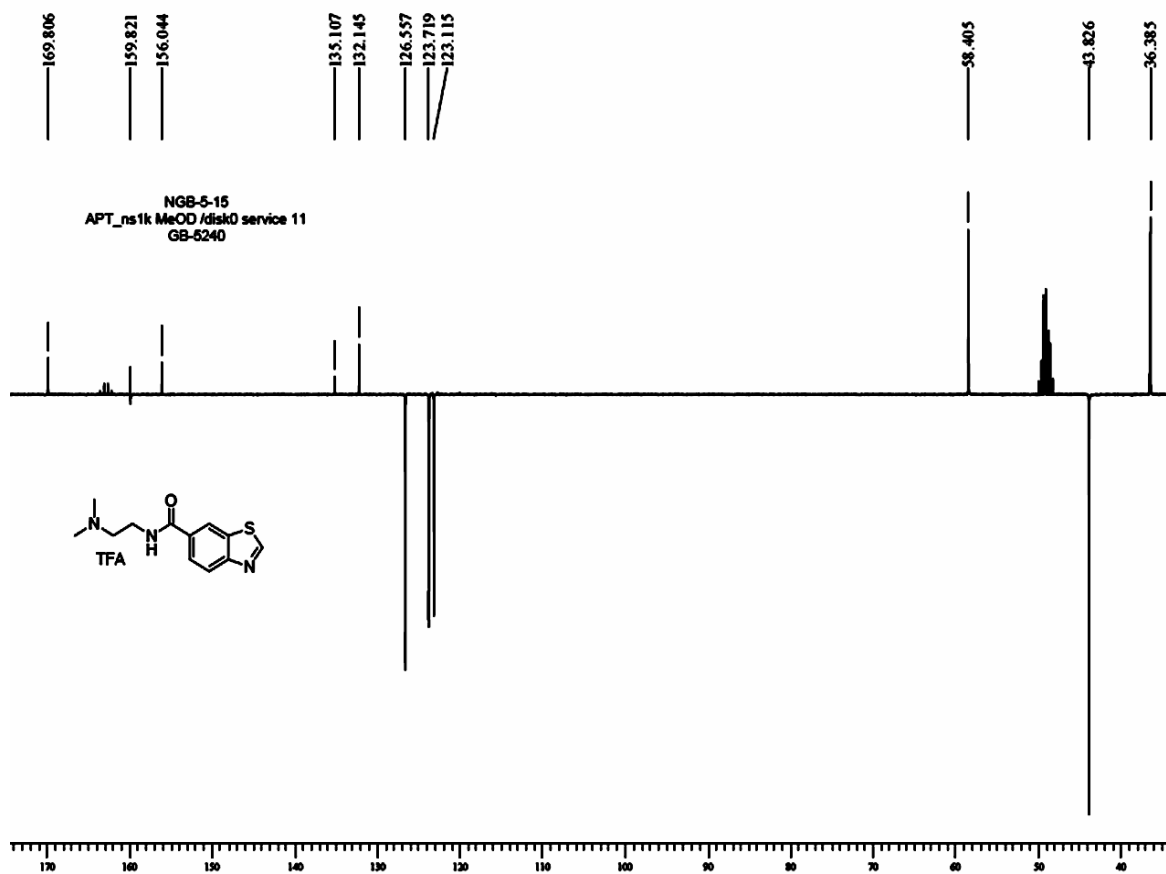
NMR spectra

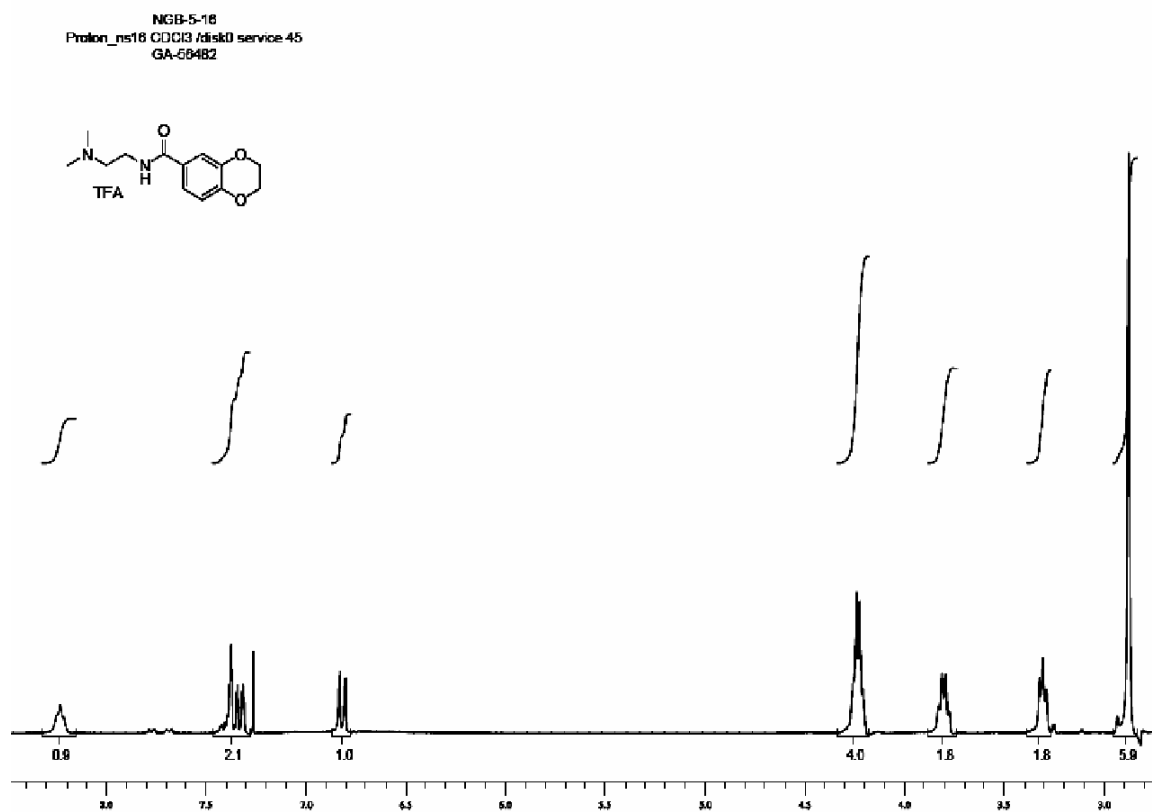
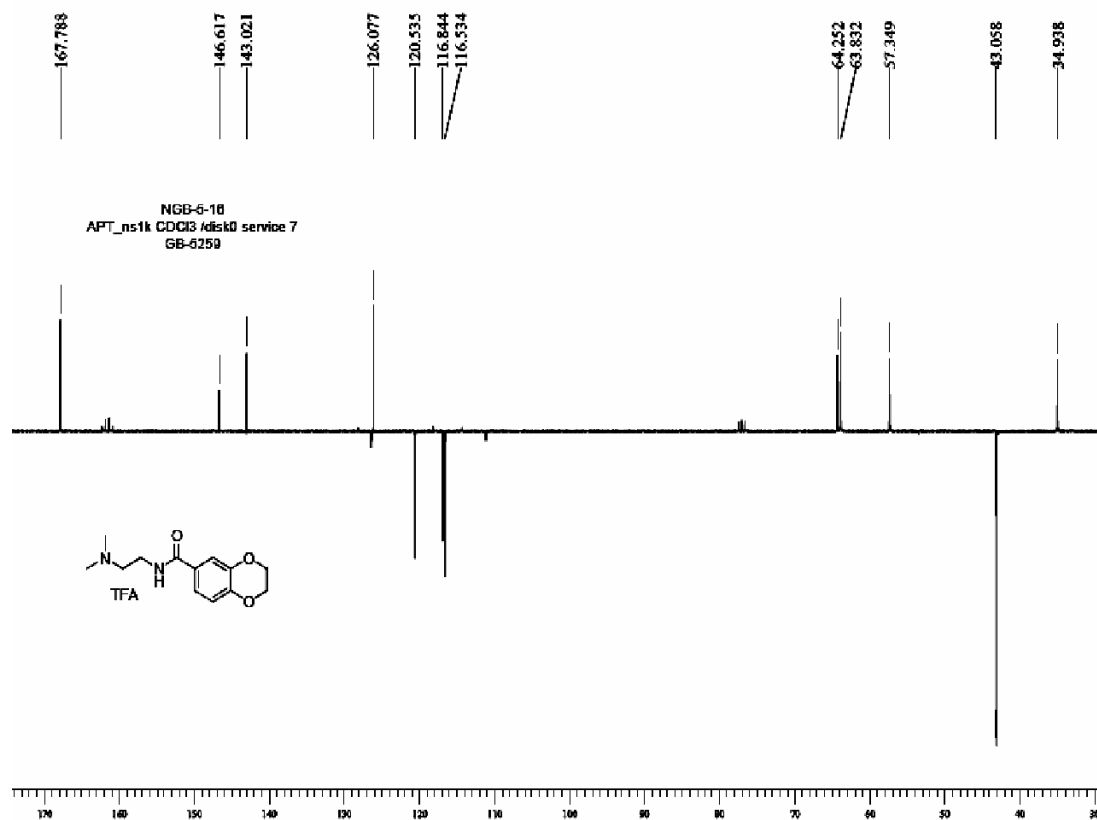
^1H NMR Spectrum of **3a** TFA salt (MeOD, 300 MHz)

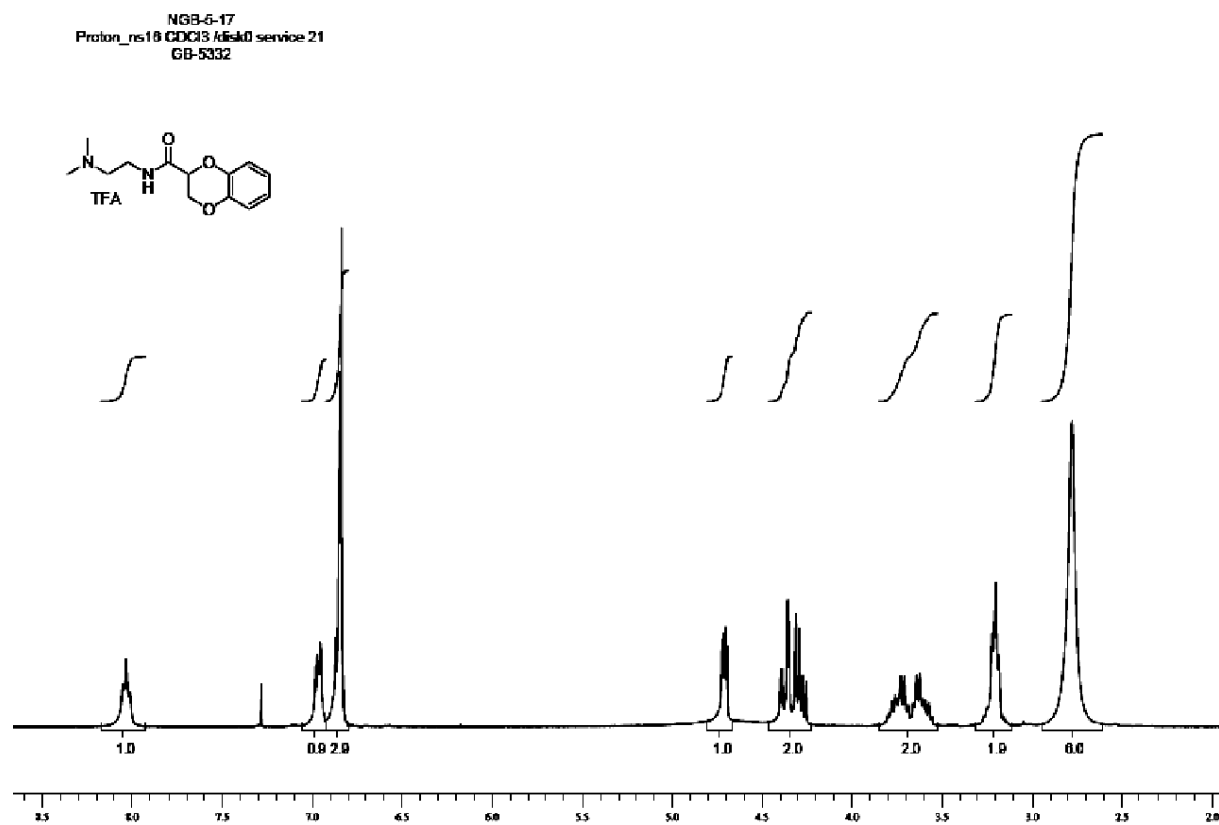
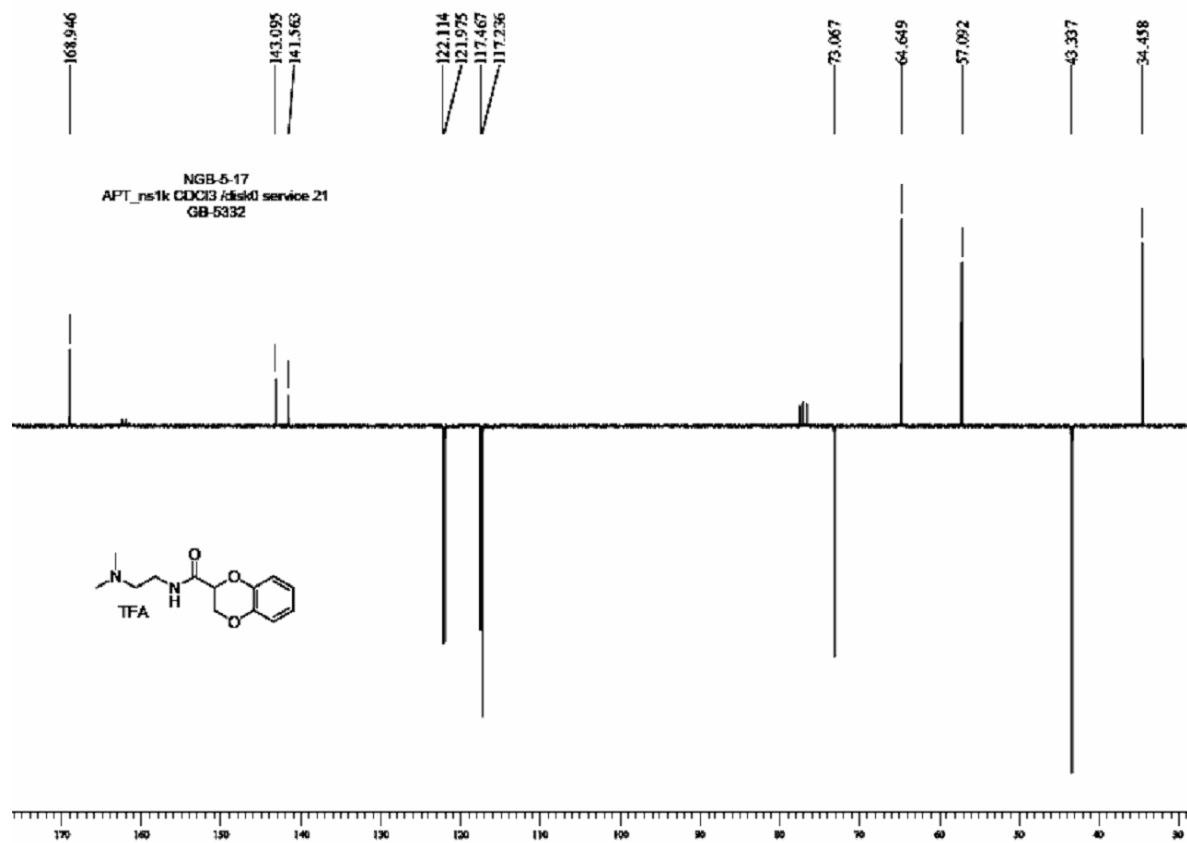


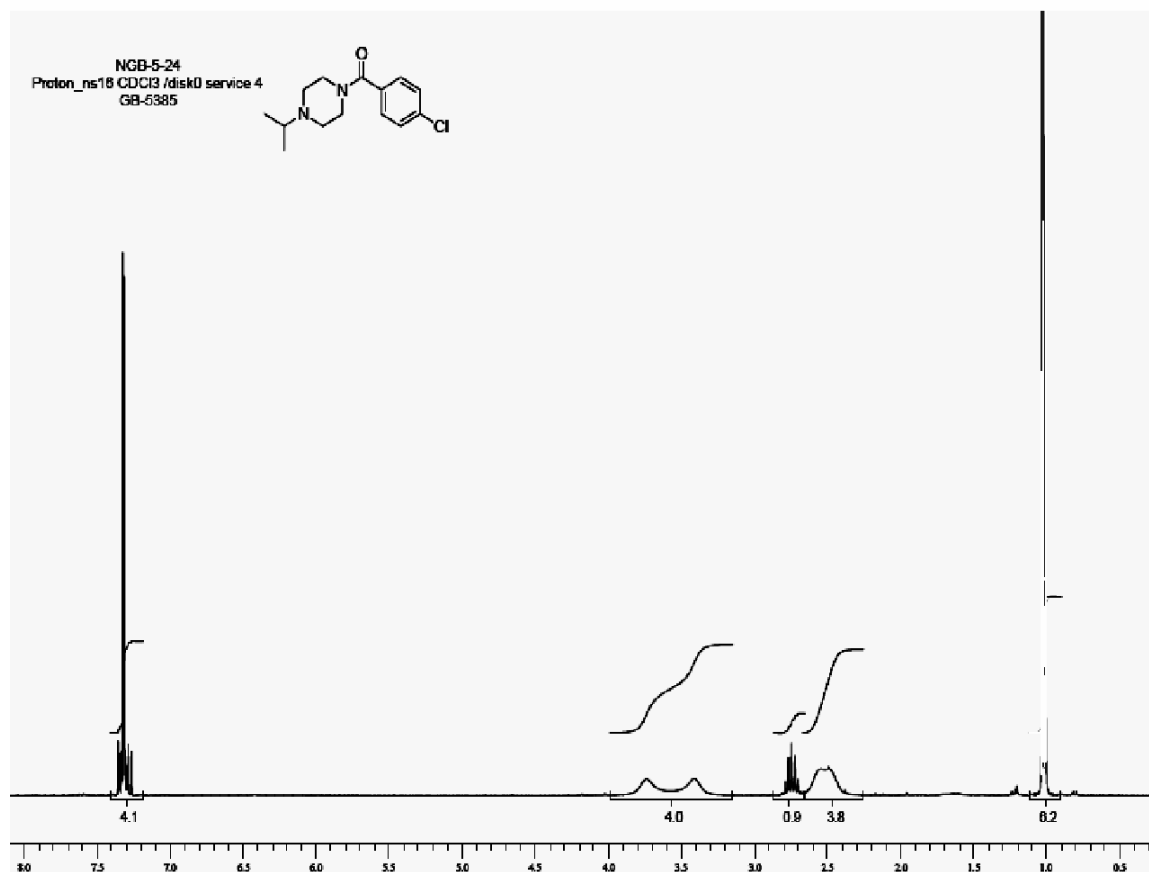
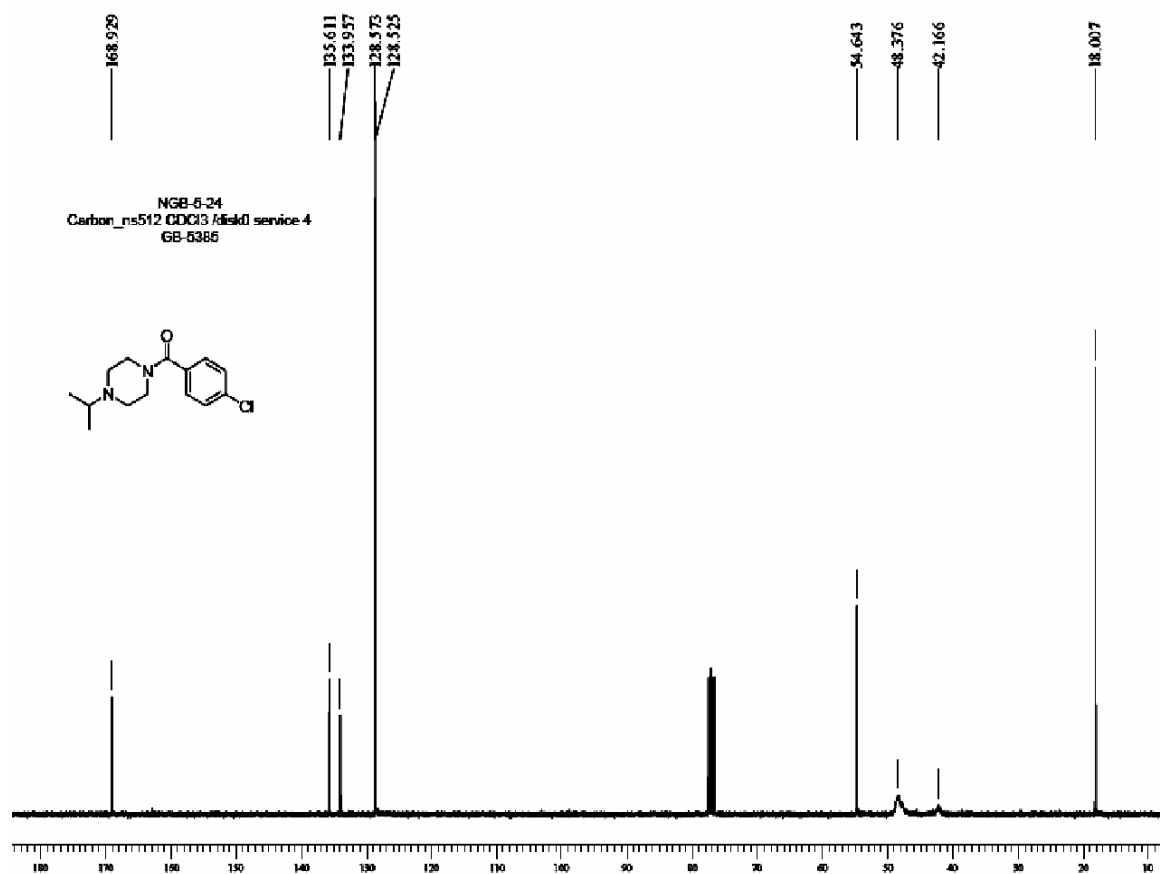
APT- ^{13}C NMR Spectrum of **3a** TFA salt (MeOD, 75 MHz)

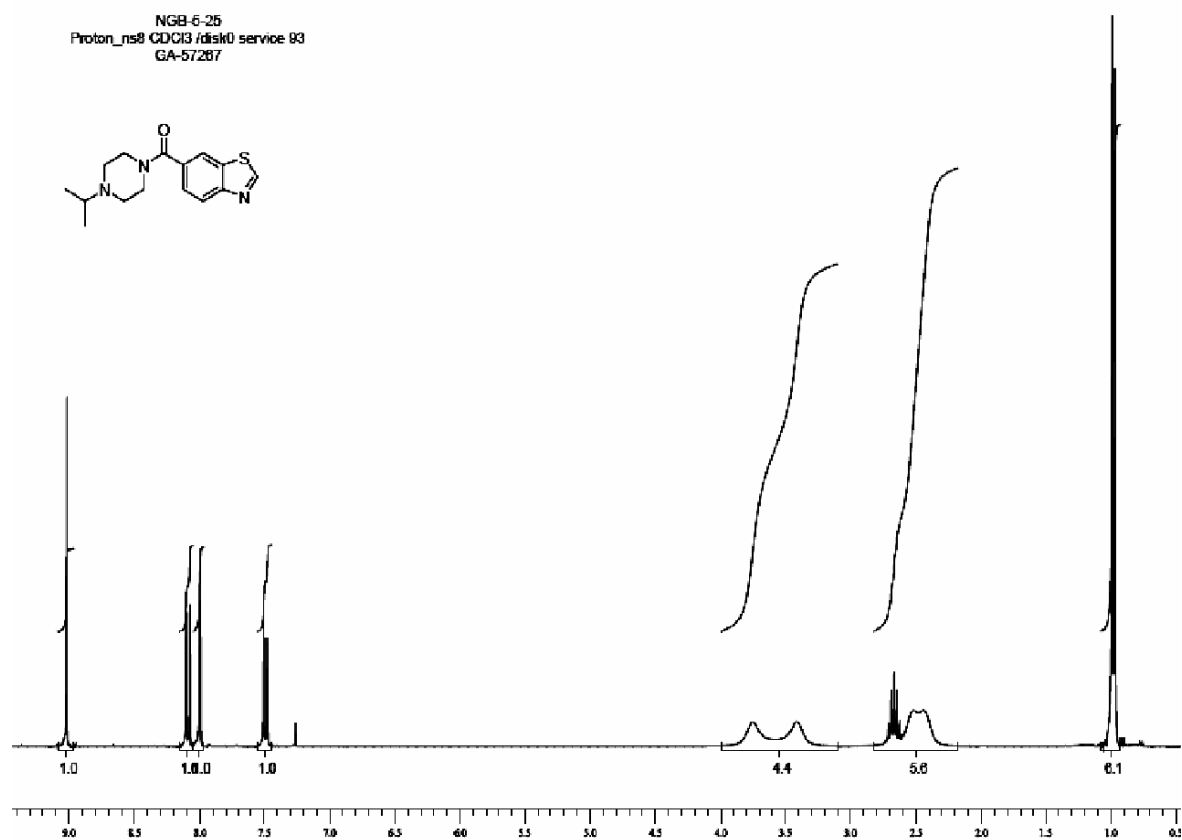
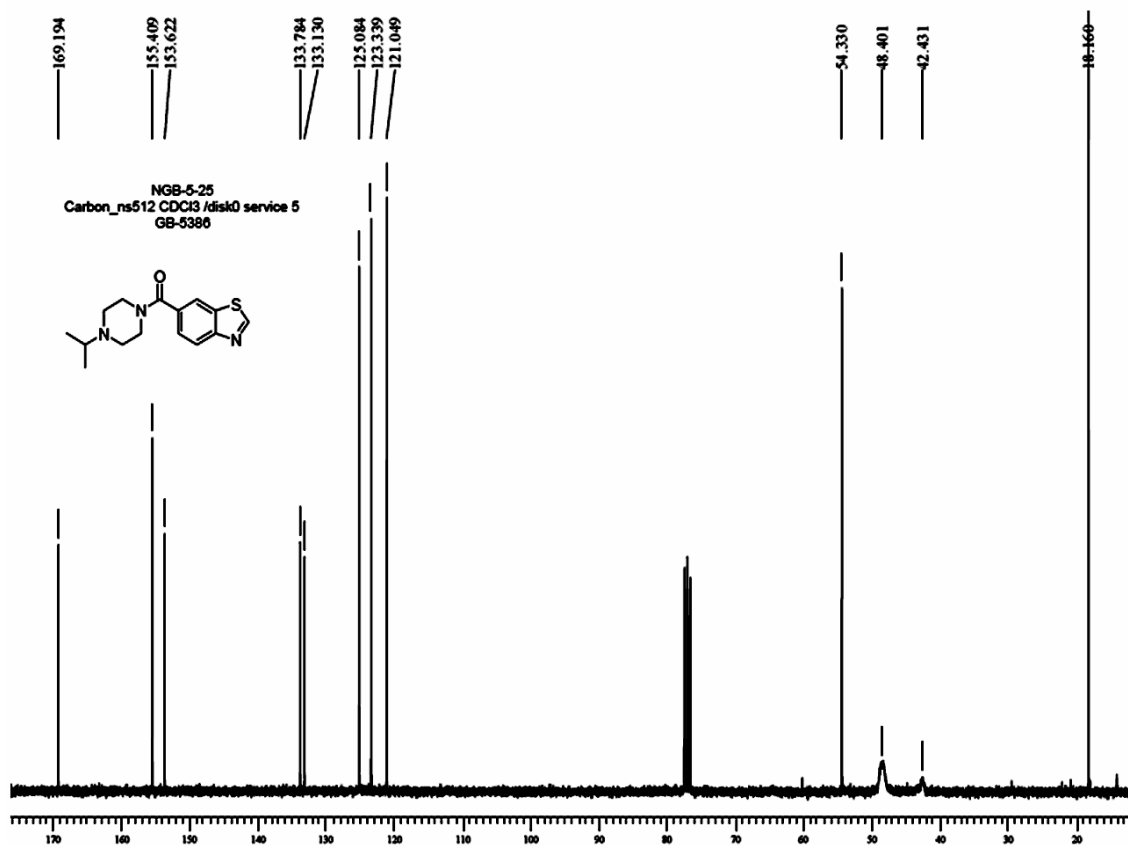


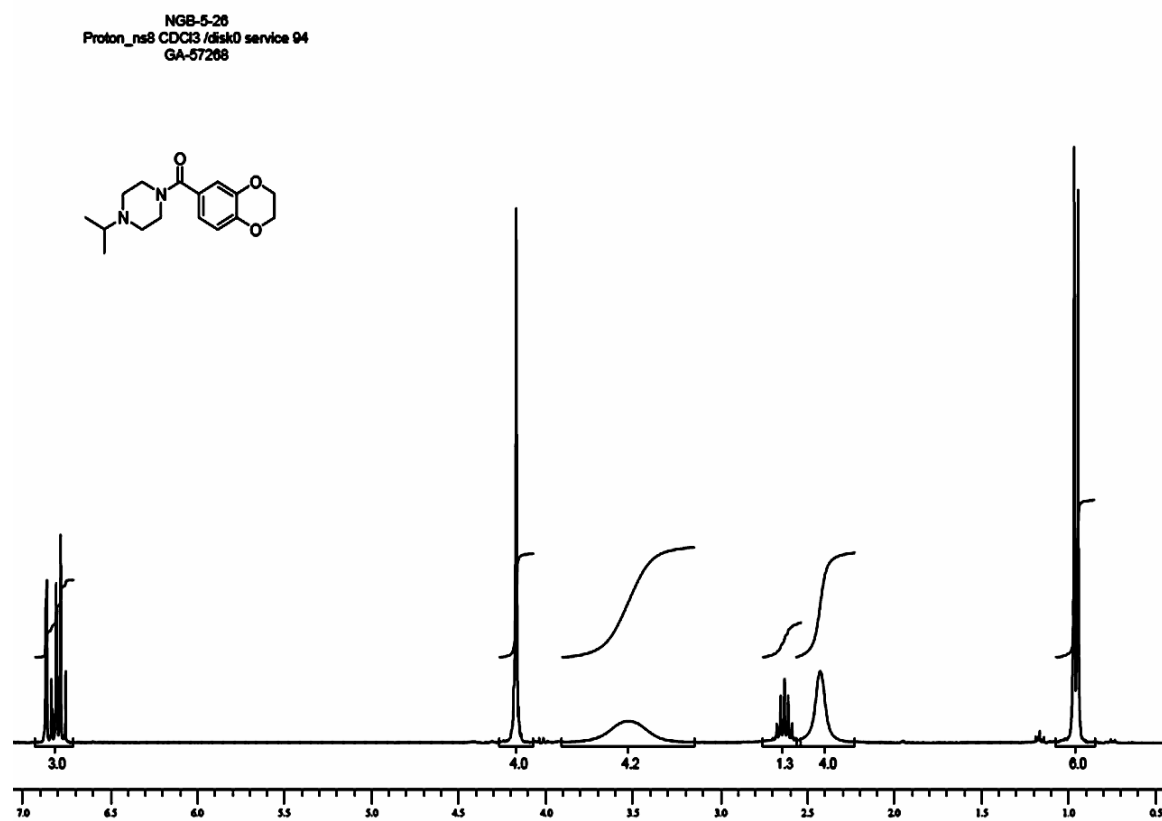
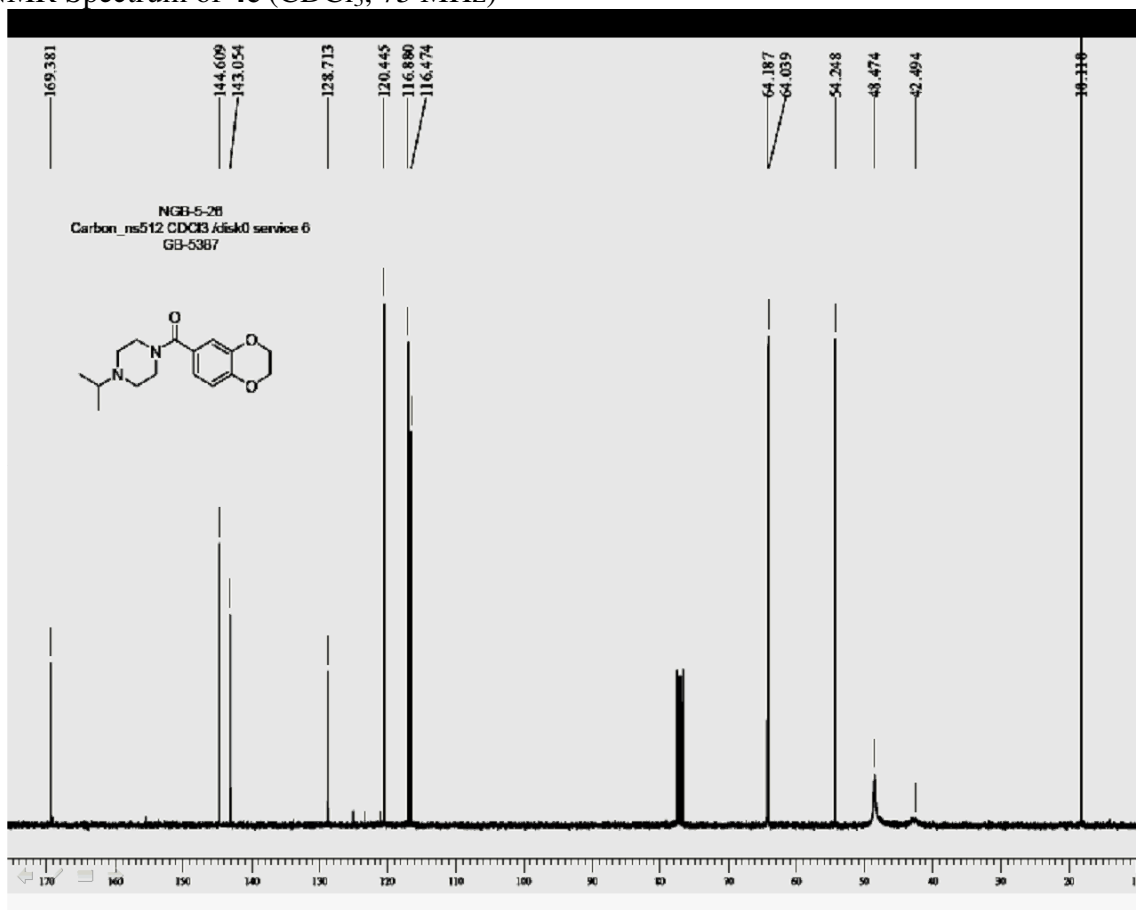
^1H NMR Spectrum of **3b** TFA salt (MeOD, 300 MHz)APT- ^{13}C NMR Spectrum of **3b** TFA salt (MeOD, 75 MHz)

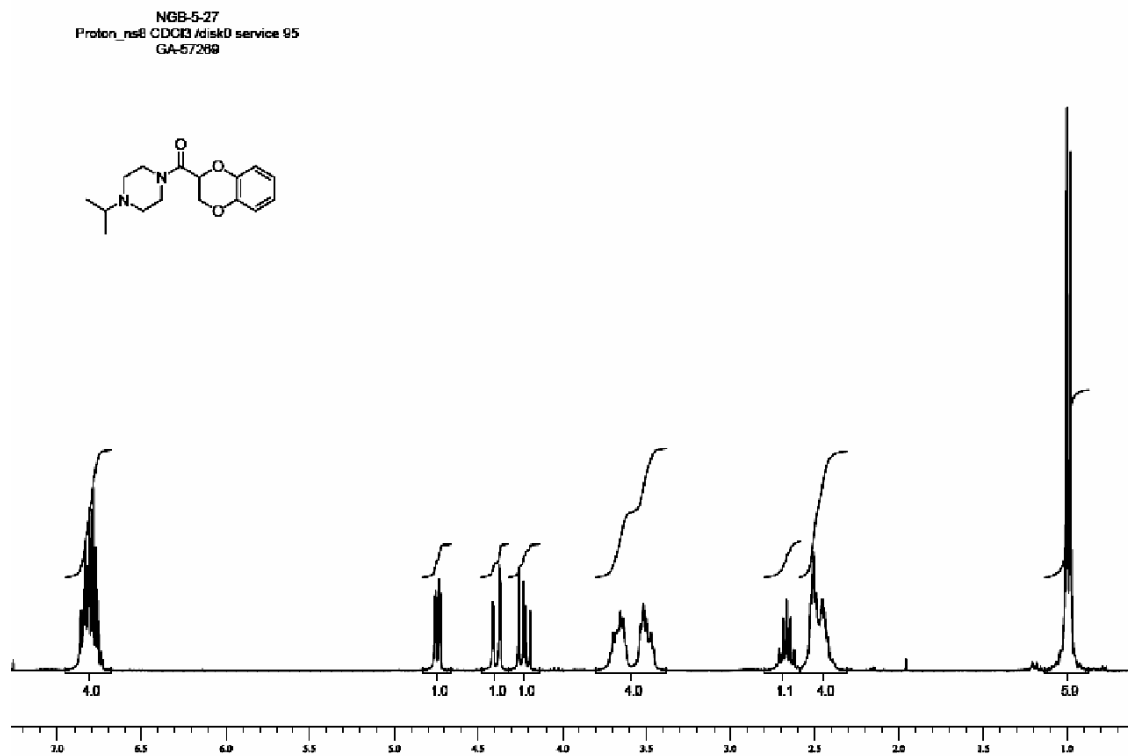
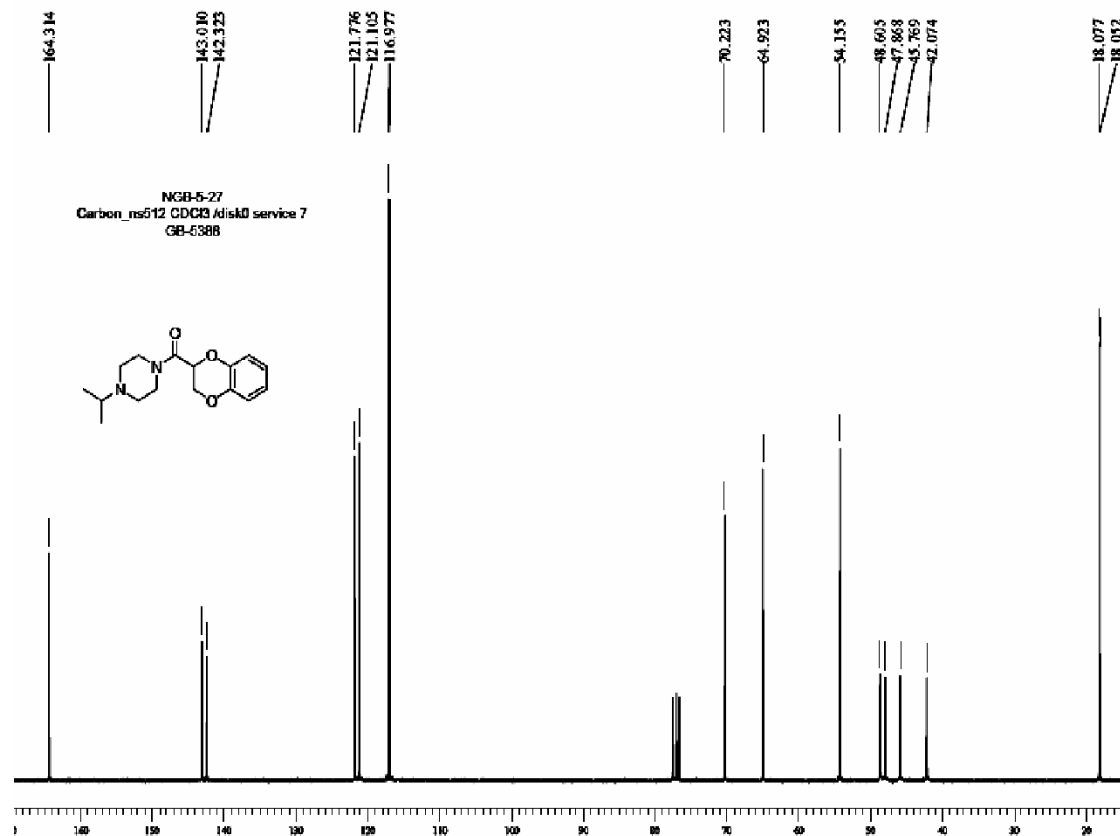
^1H NMR Spectrum of **3c** TFA salt (CDCl_3 , 300 MHz)APT- ^{13}C NMR Spectrum of **3c** TFA salt (CDCl_3 , 75 MHz)

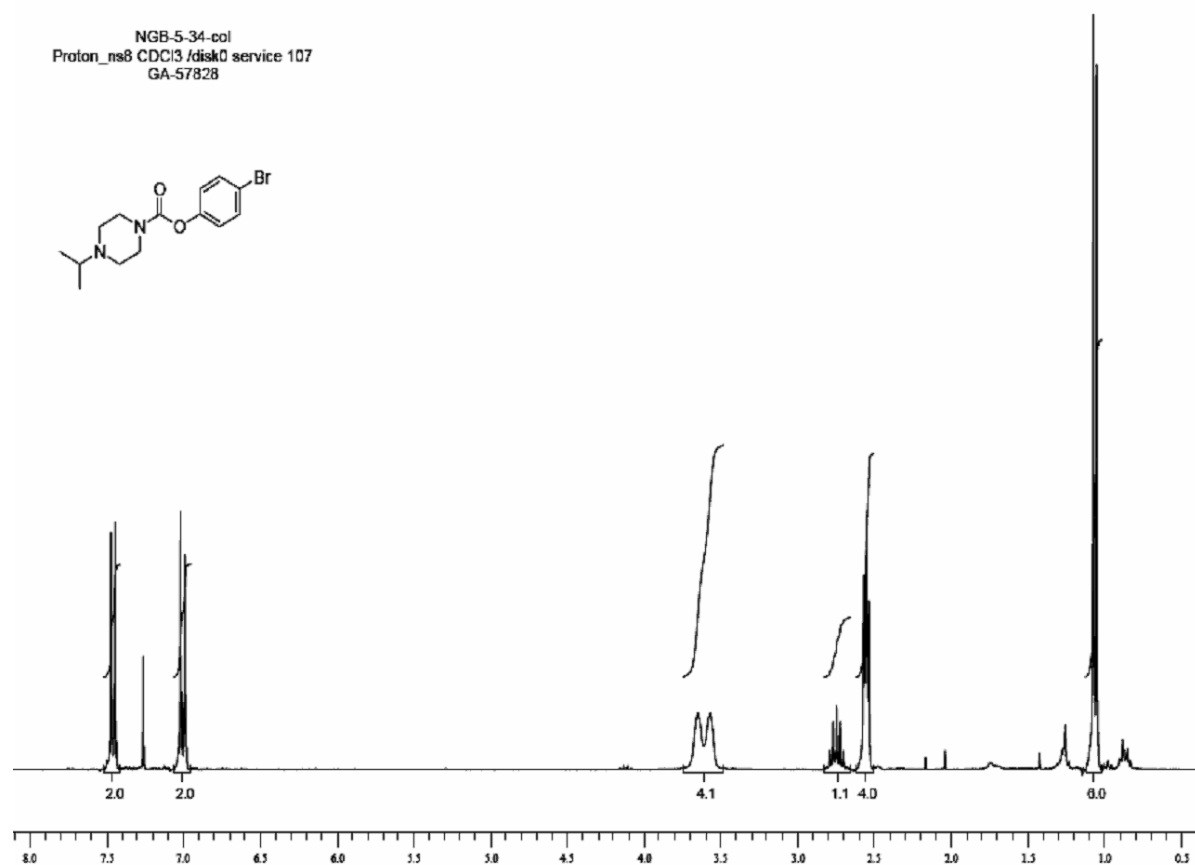
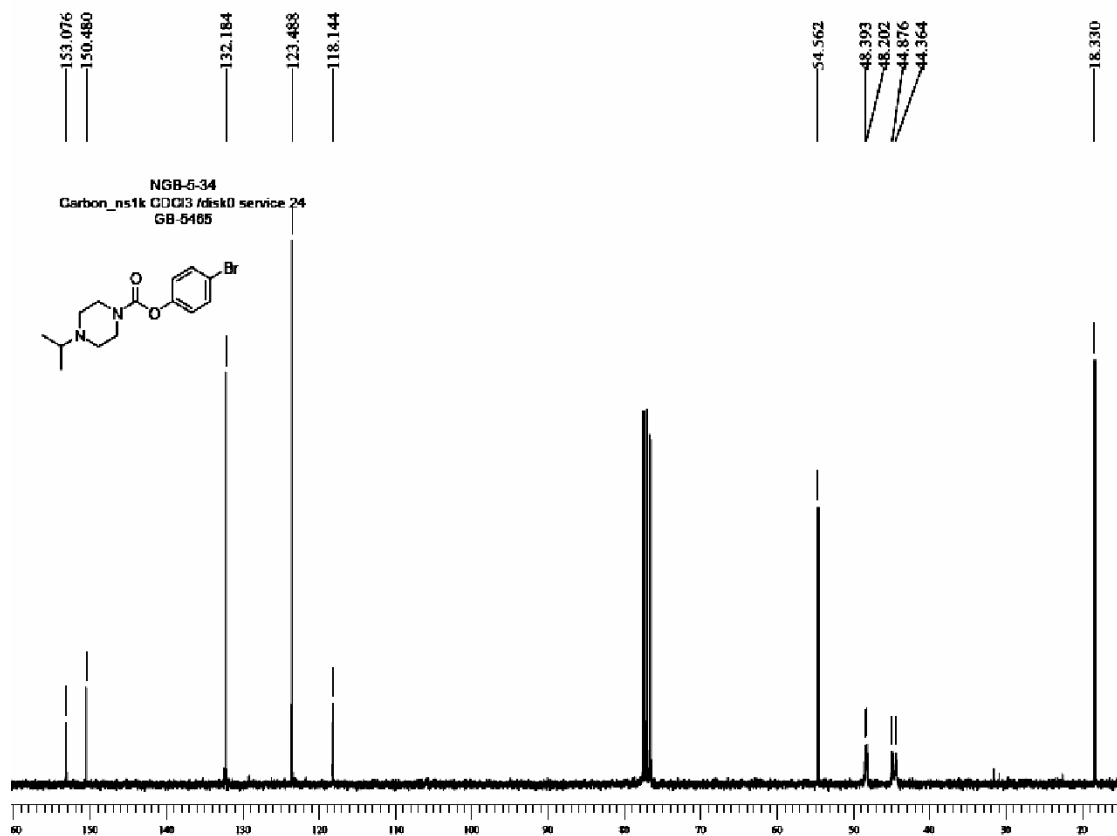
^1H NMR Spectrum of **3d** TFA salt (CDCl_3 , 300 MHz)APT- ^{13}C NMR Spectrum of **3d** TFA salt (CDCl_3 , 75 MHz)

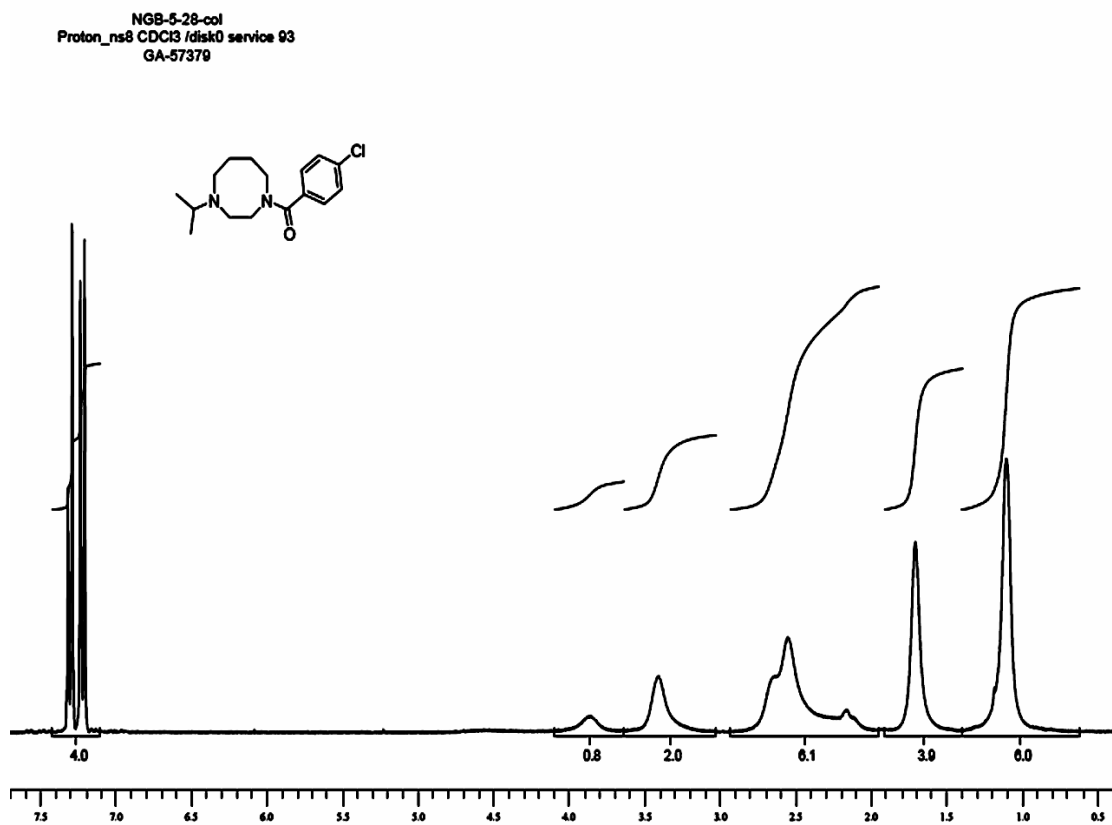
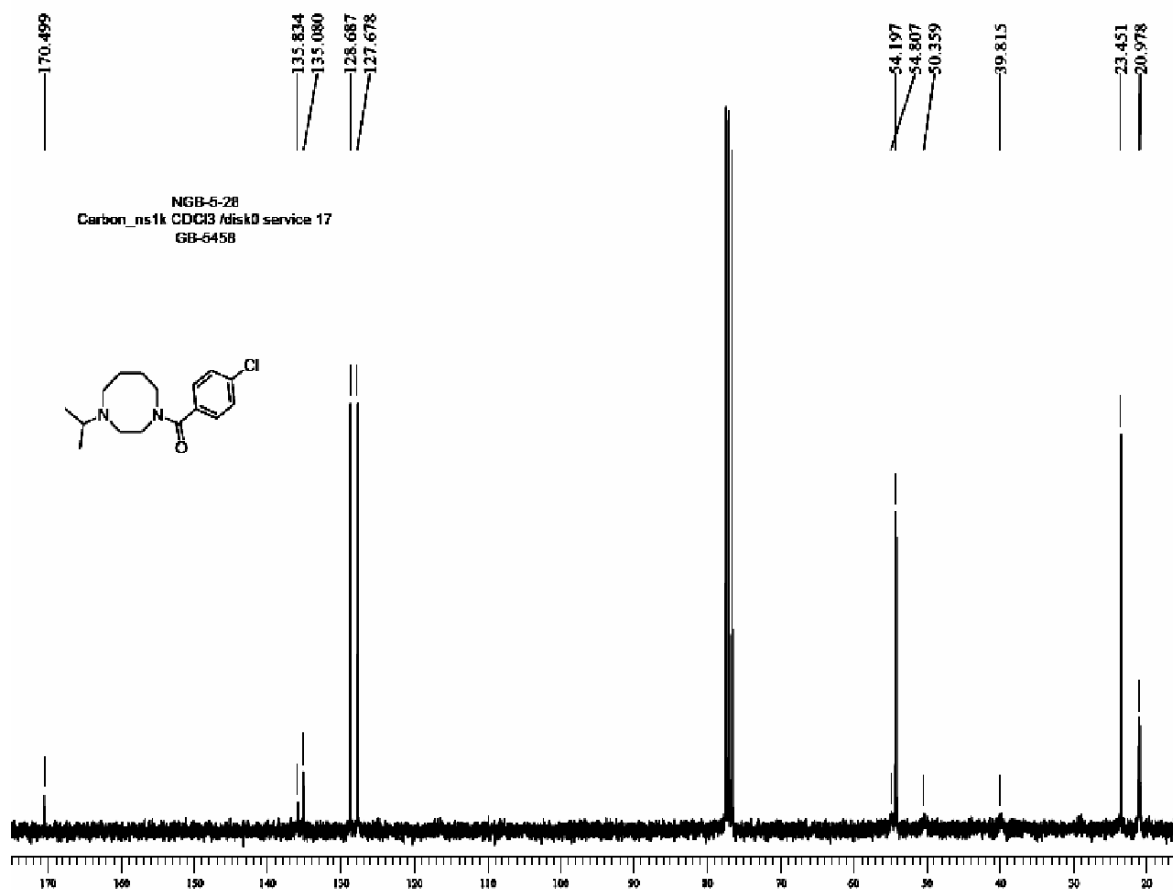
^1H NMR Spectrum of **4a** (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **4a** (CDCl_3 , 75 MHz)

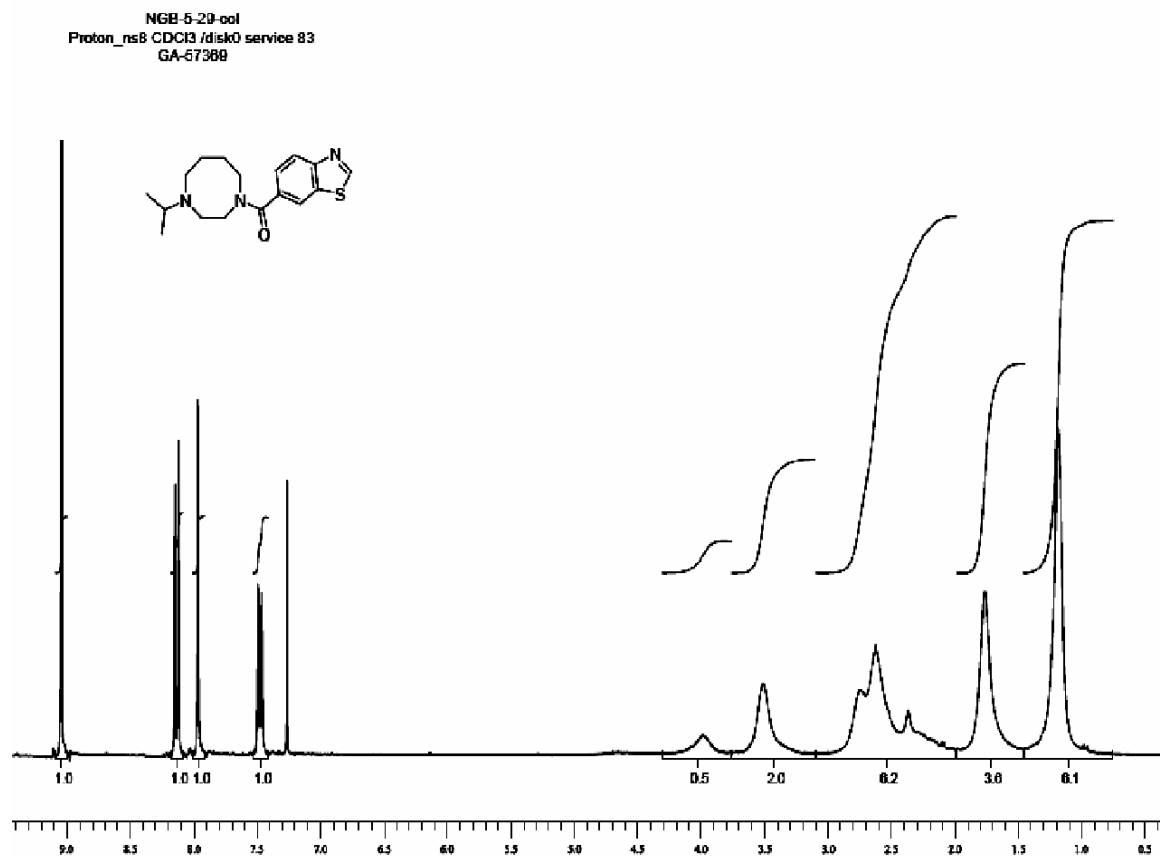
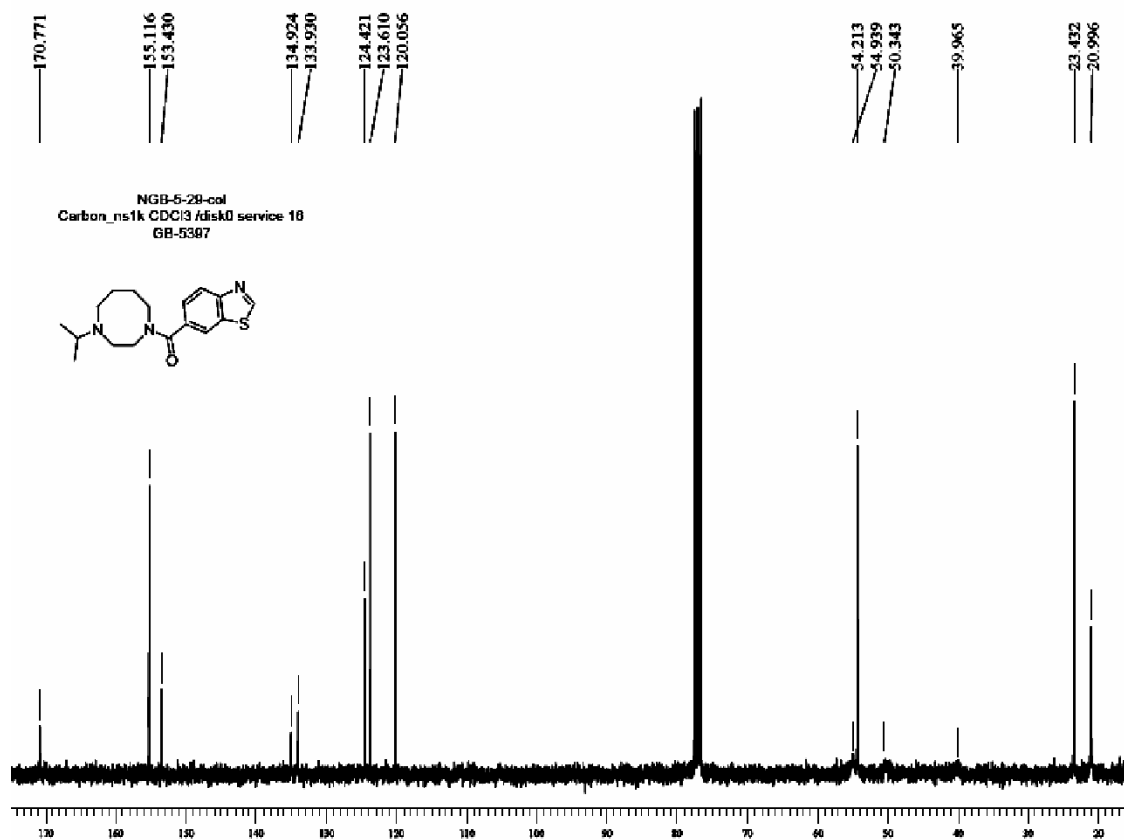
¹H NMR Spectrum of **4b** (CDCl₃, 300 MHz)¹³C NMR Spectrum of **4b** (CDCl₃, 75 MHz)

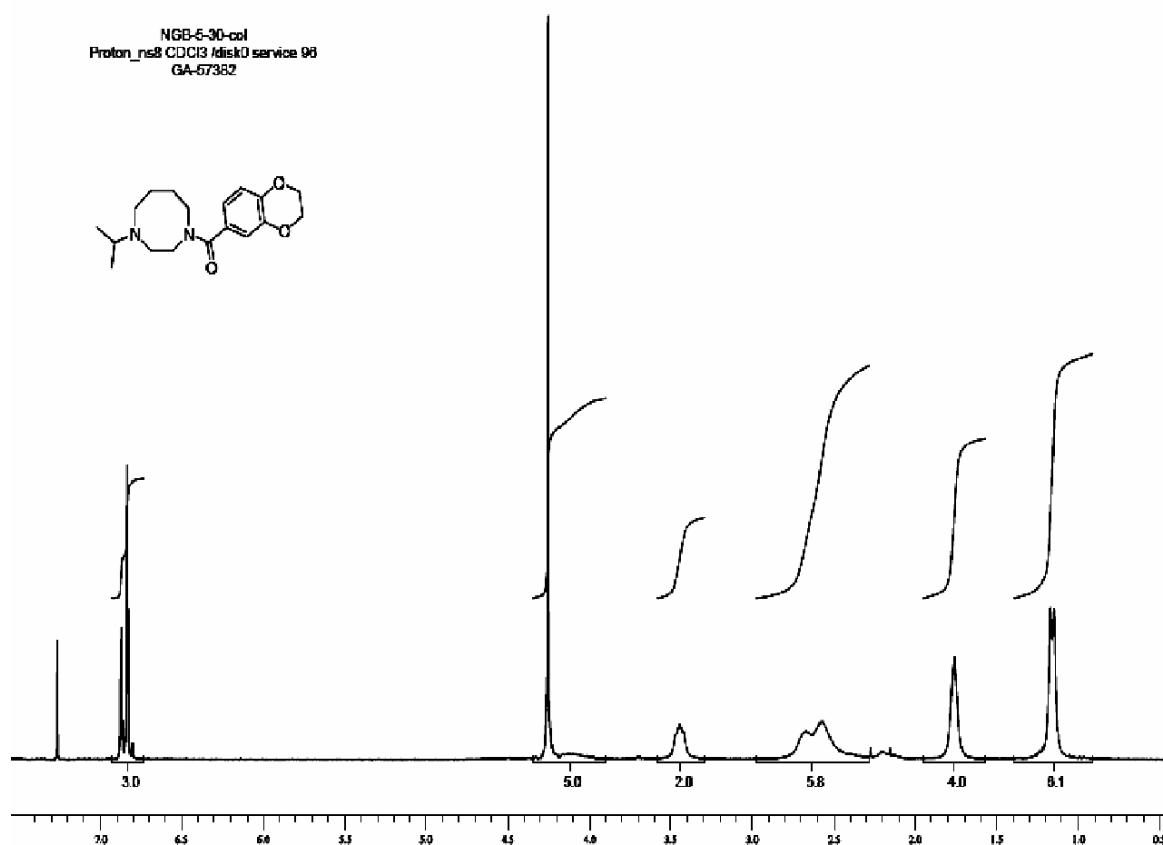
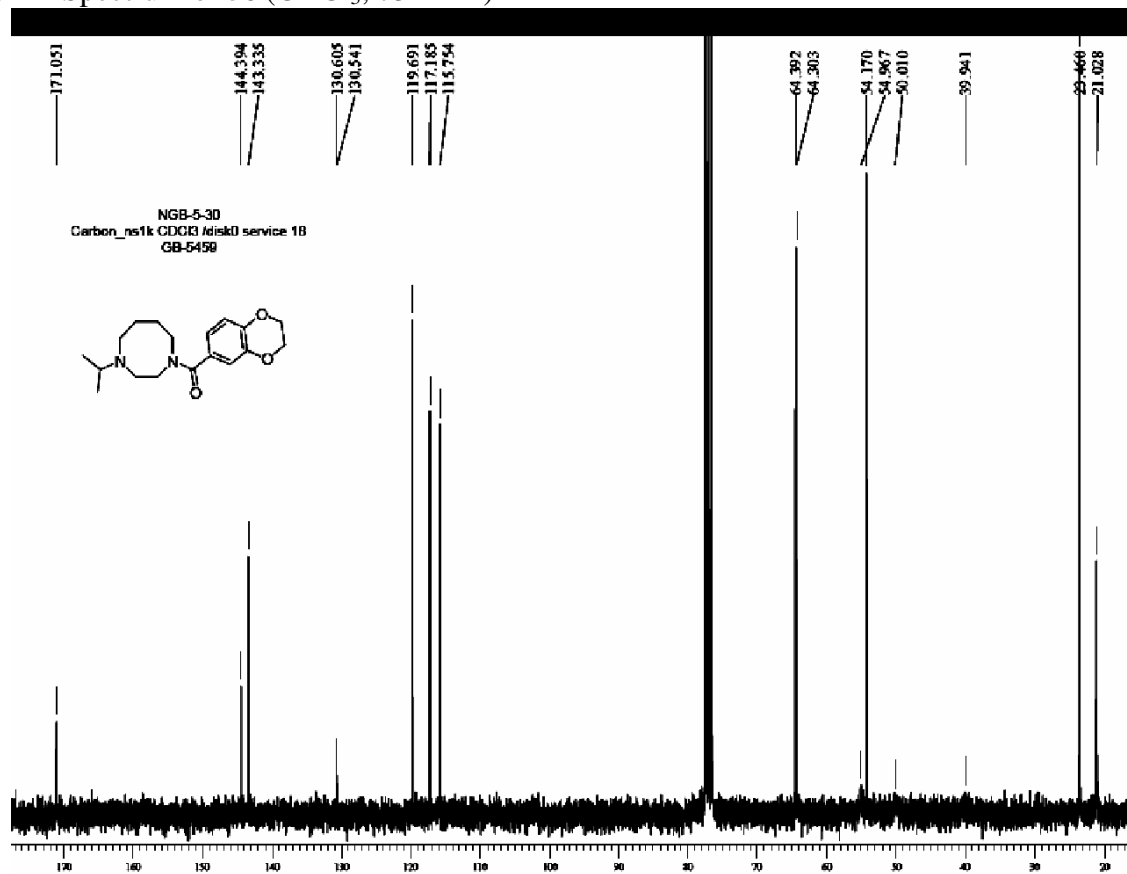
^1H NMR Spectrum of **4c** (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **4c** (CDCl_3 , 75 MHz)

¹H NMR Spectrum of **4d** (CDCl₃, 300 MHz)¹³C NMR Spectrum of **4d** (CDCl₃, 75 MHz)

¹H NMR Spectrum of **4e** (CDCl₃, 300 MHz)¹³C NMR Spectrum of **4e** (CDCl₃, 75 MHz)

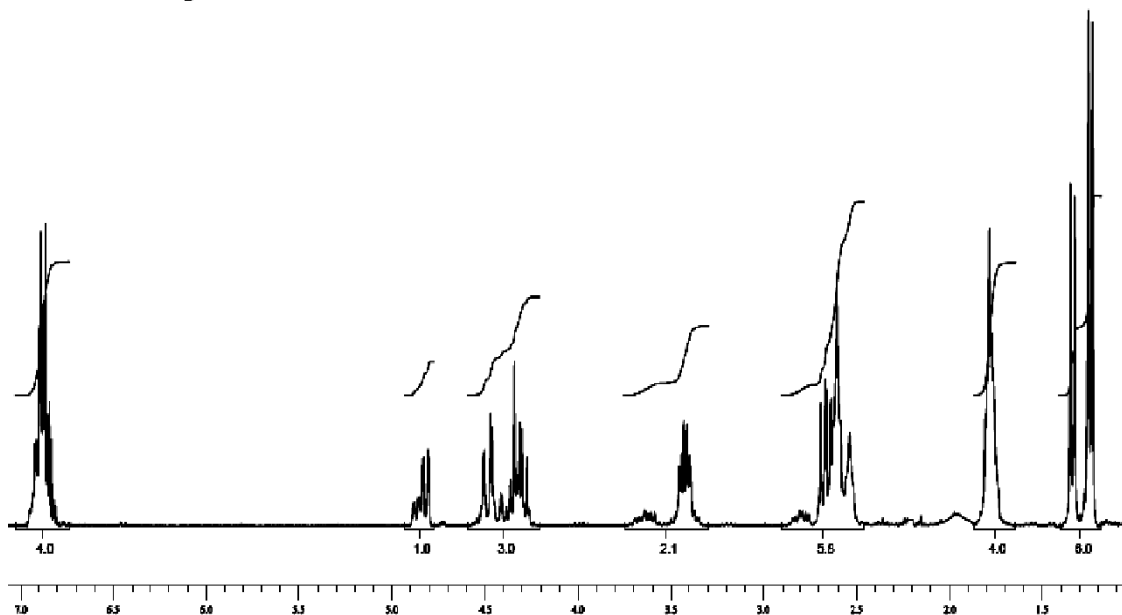
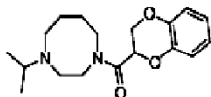
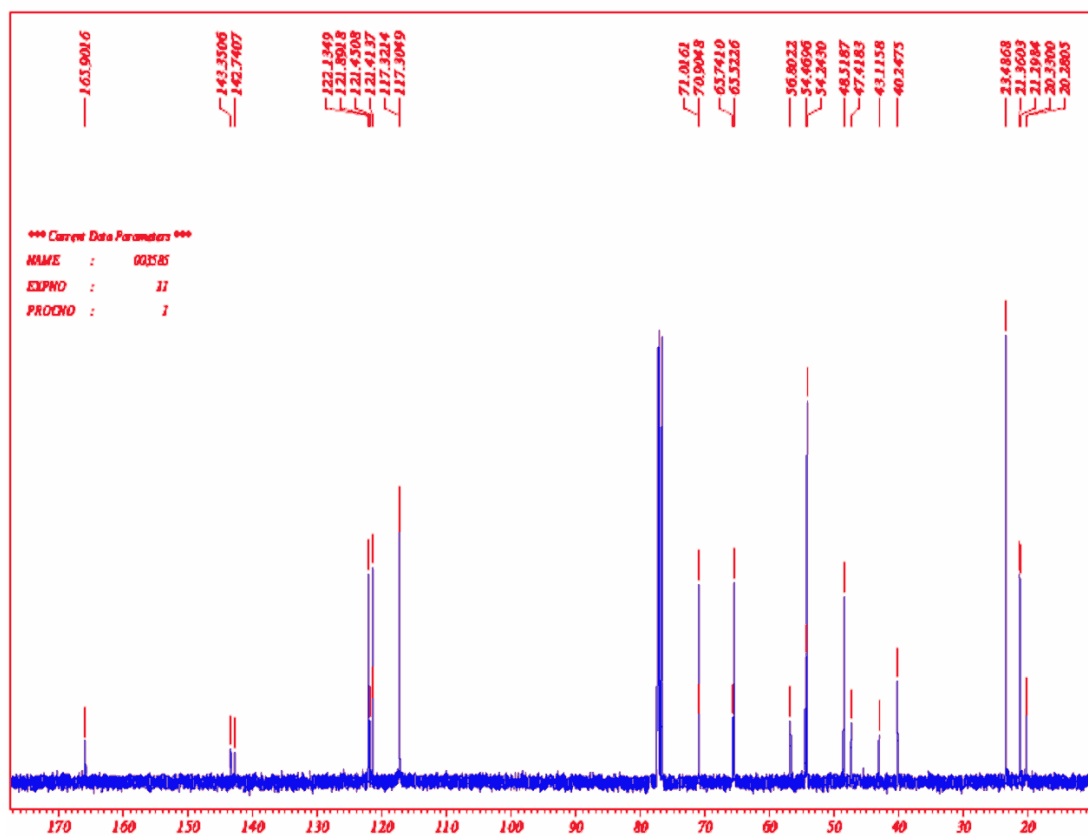
^1H NMR Spectrum of **5a** (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **5a** (CDCl_3 , 75 MHz)

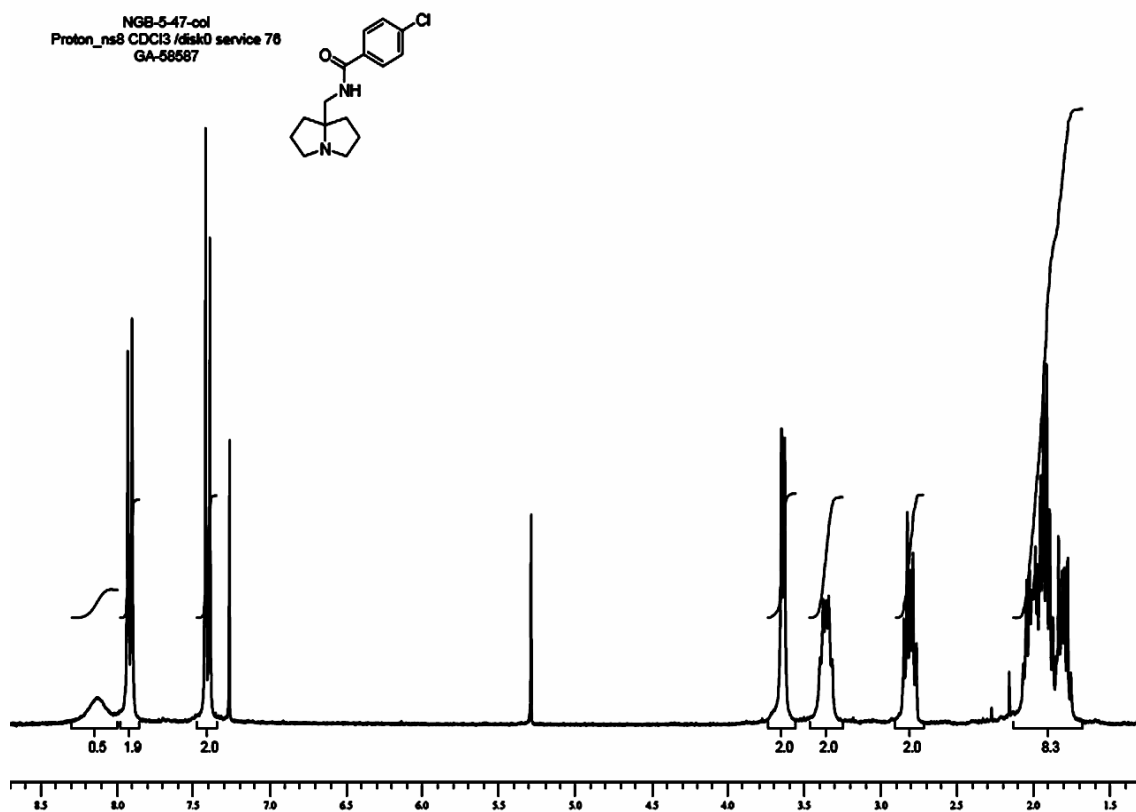
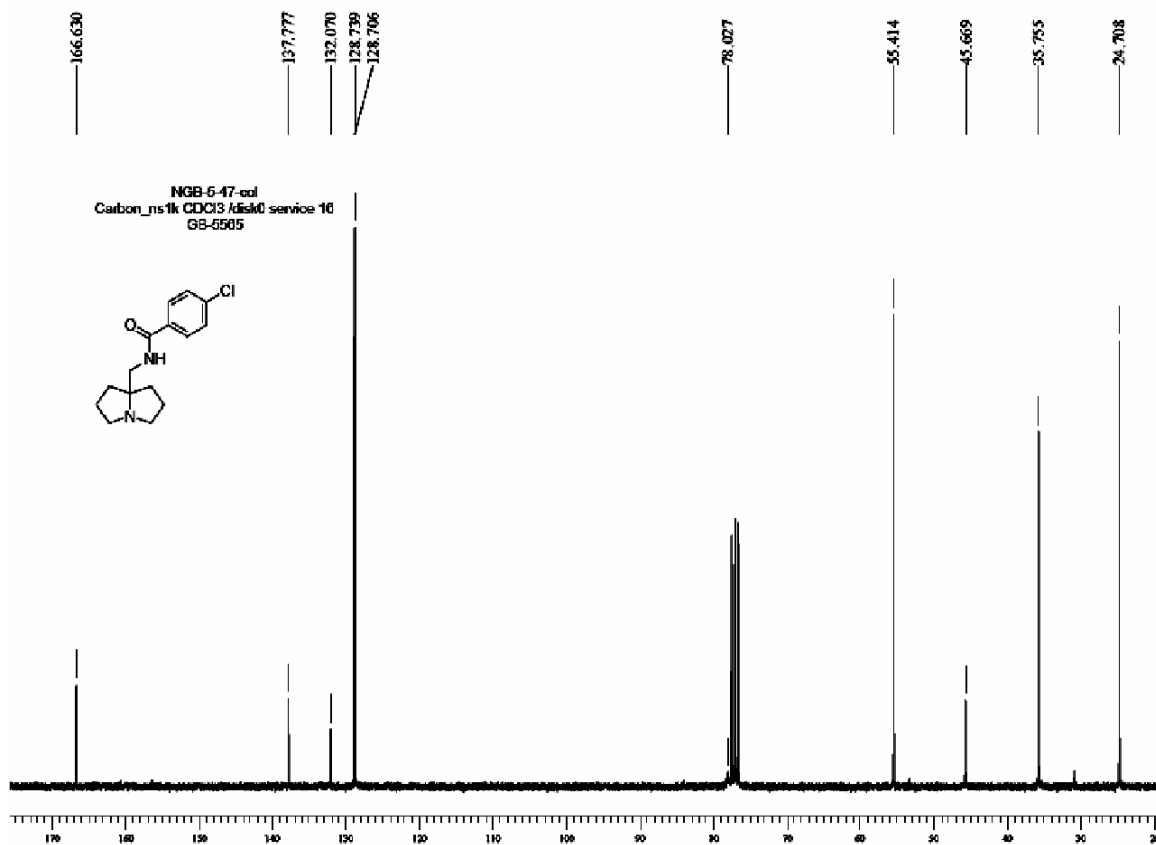
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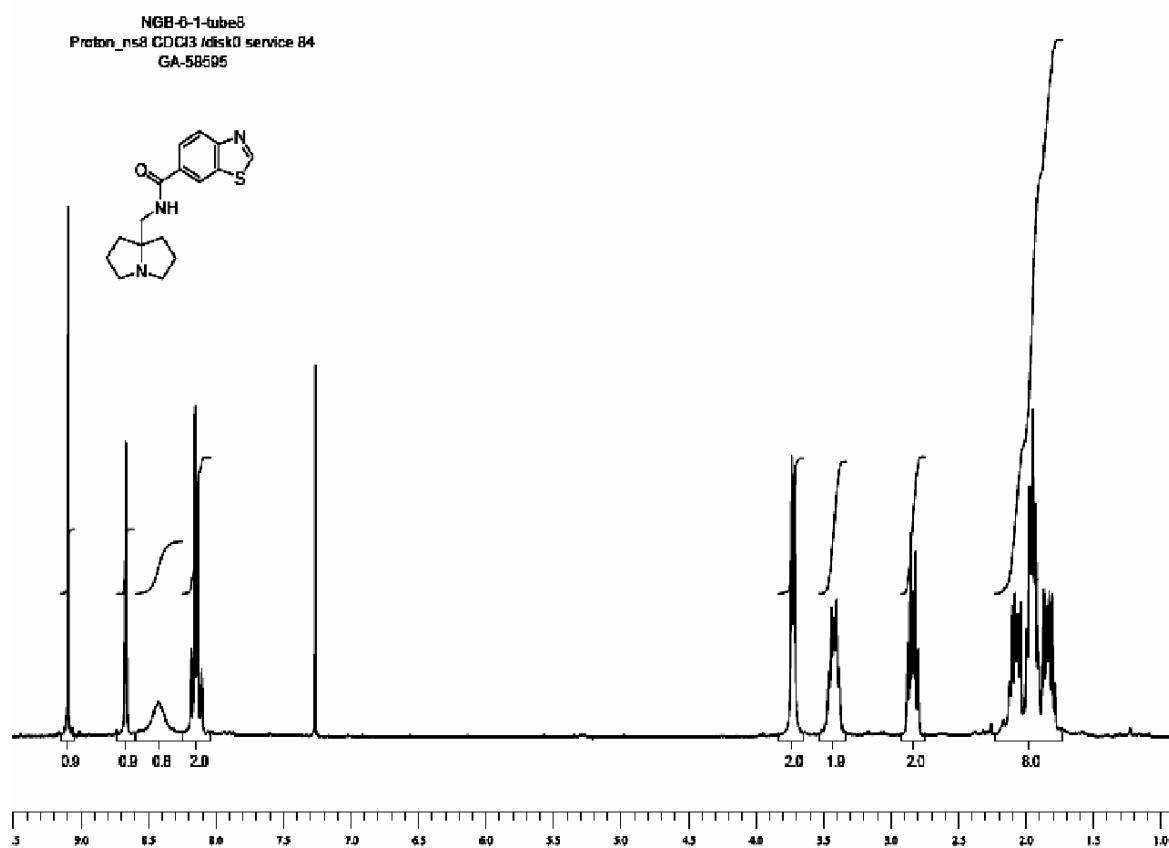
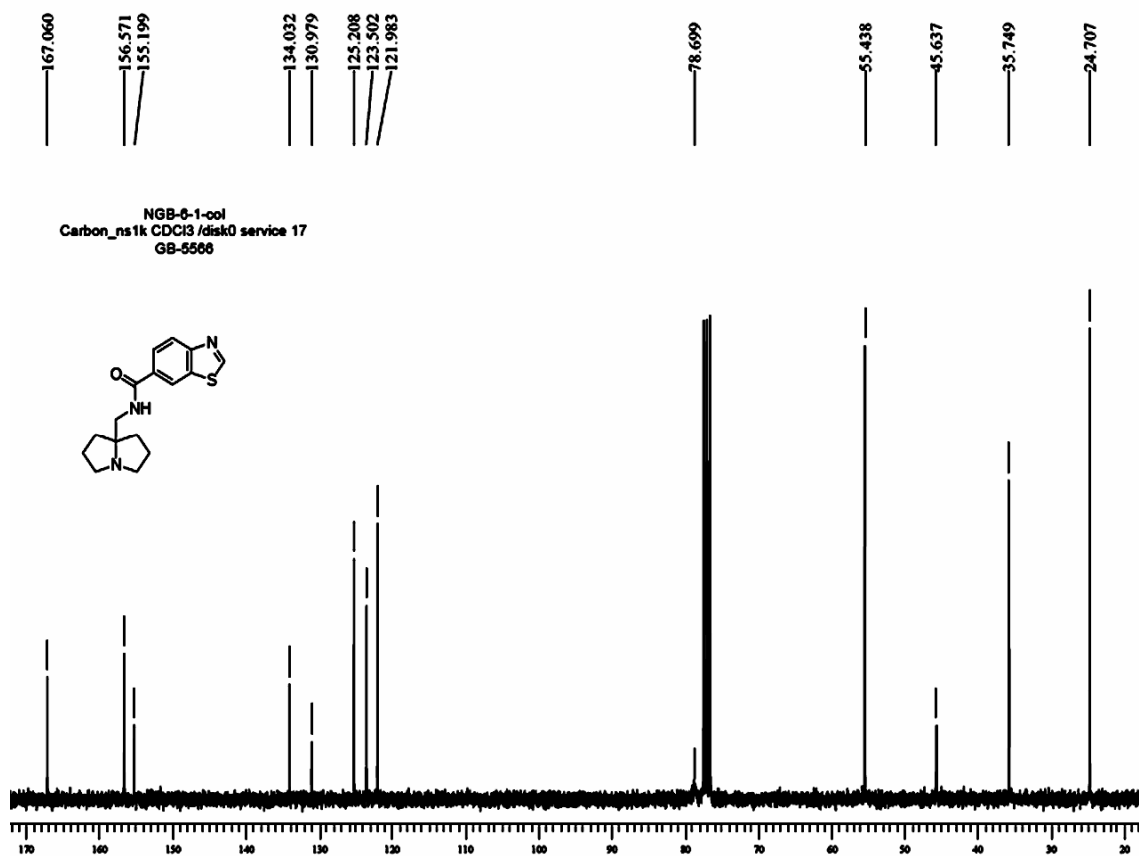
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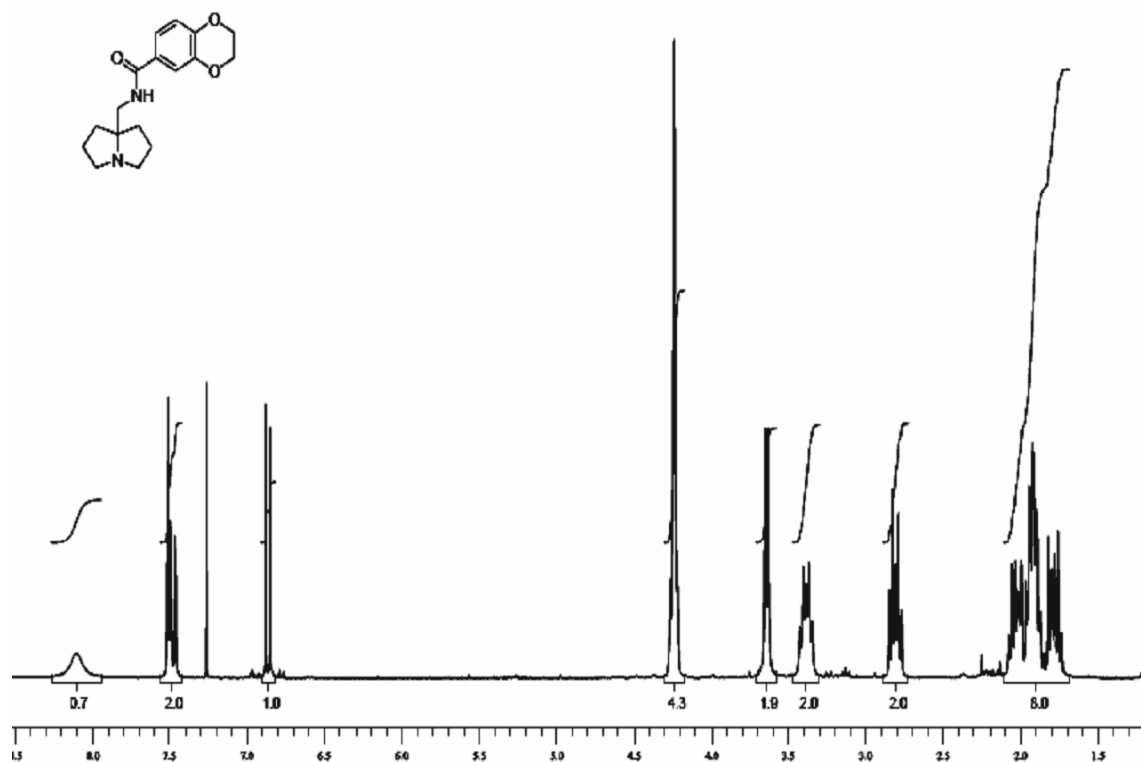
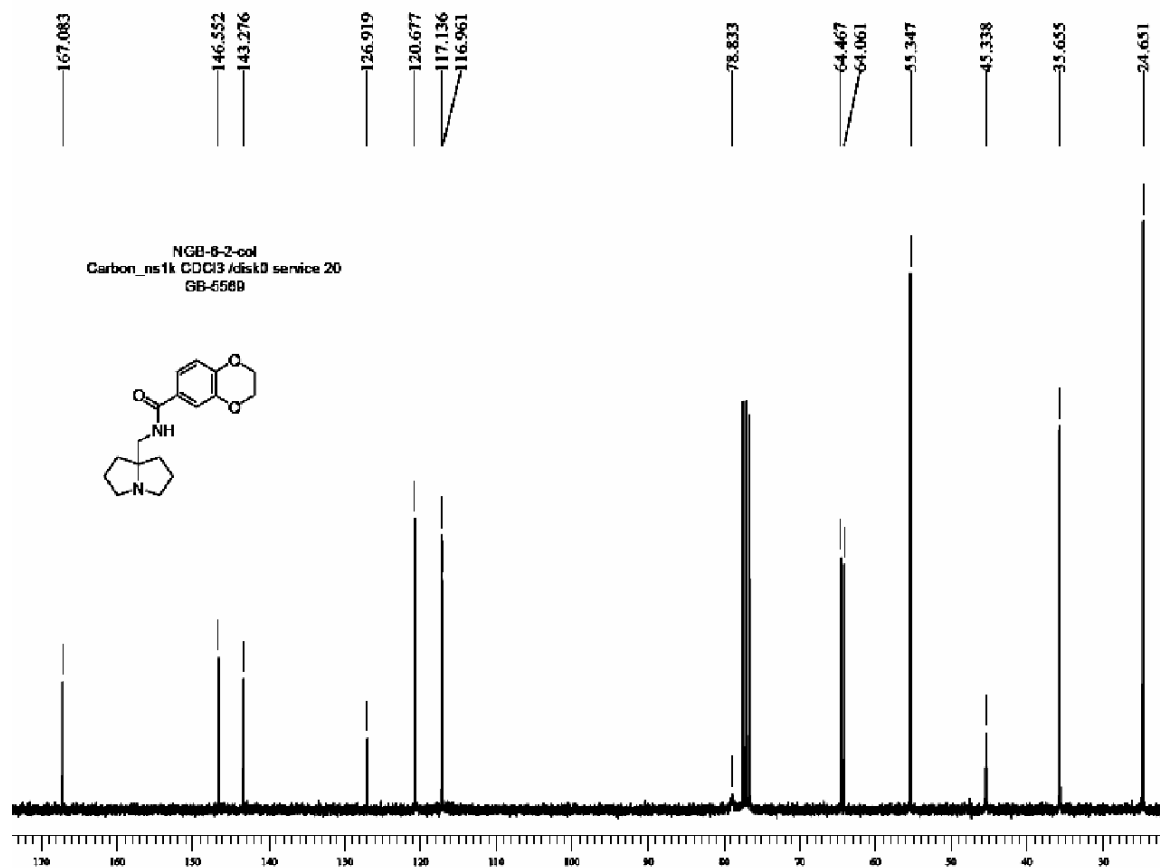
^1H NMR Spectrum of **5d** (CDCl_3 , 300 MHz)

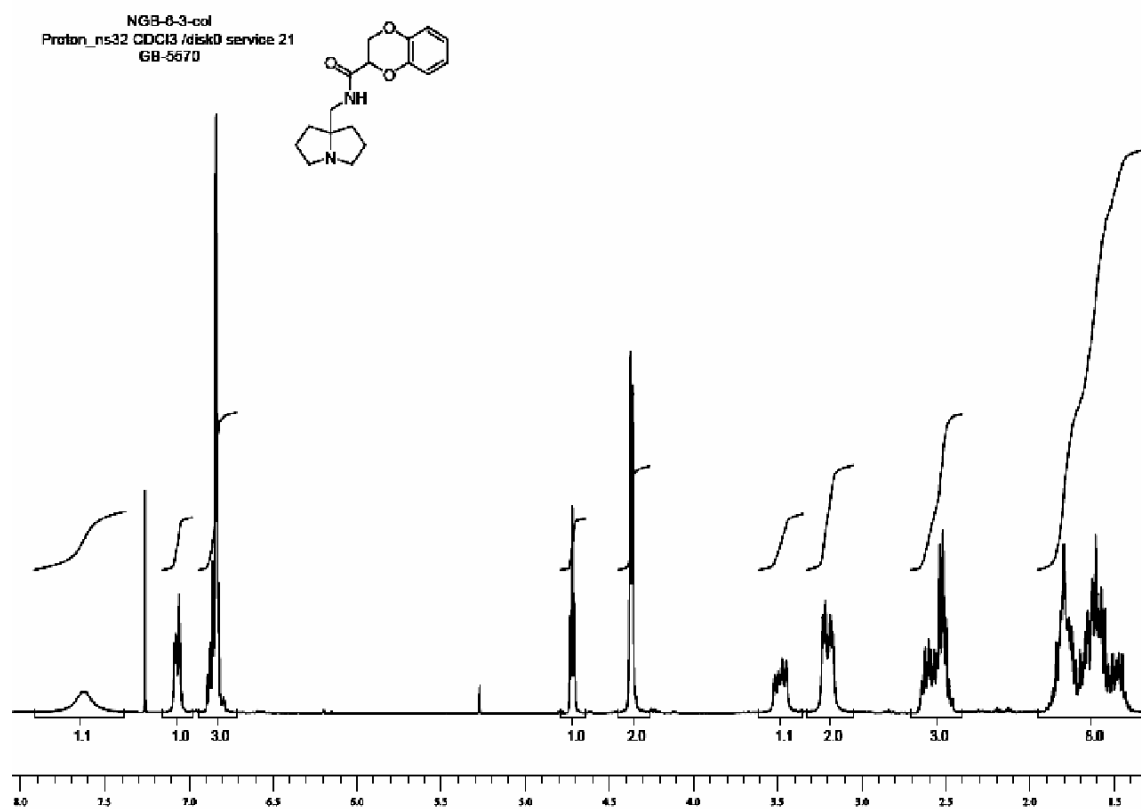
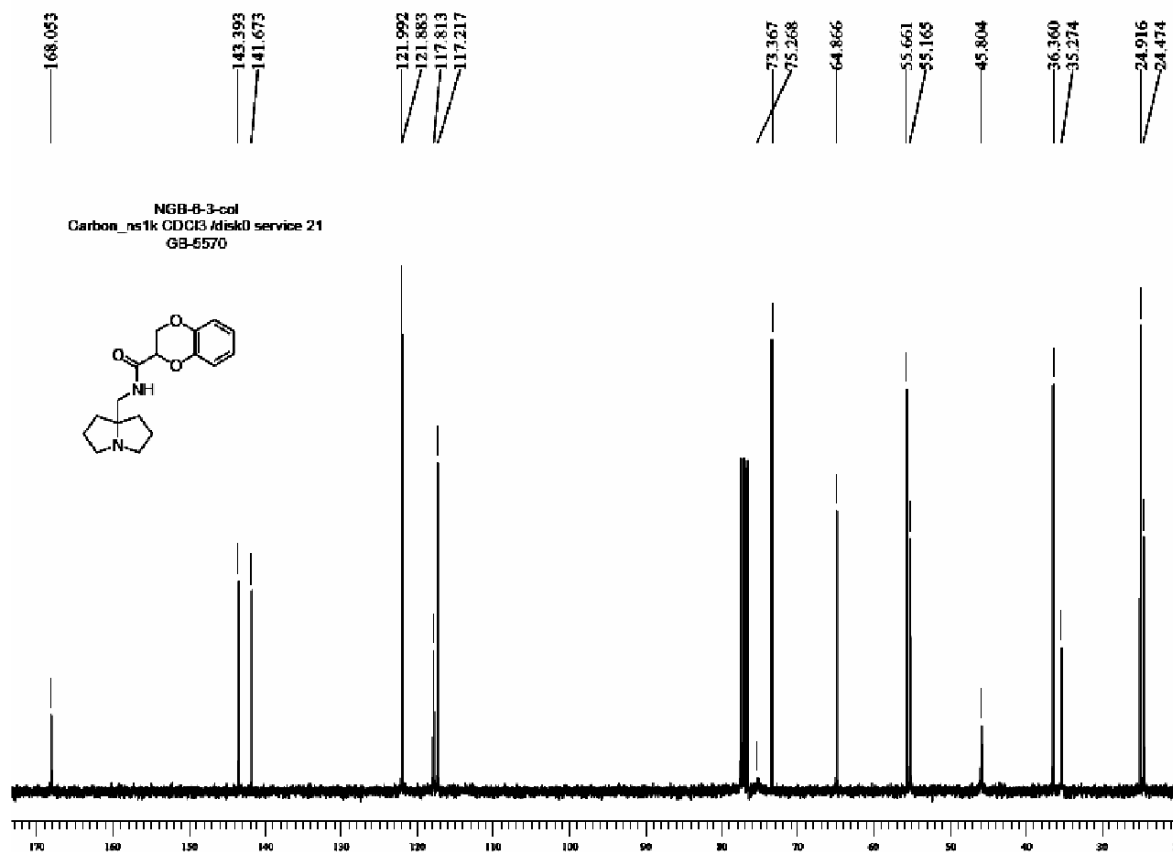
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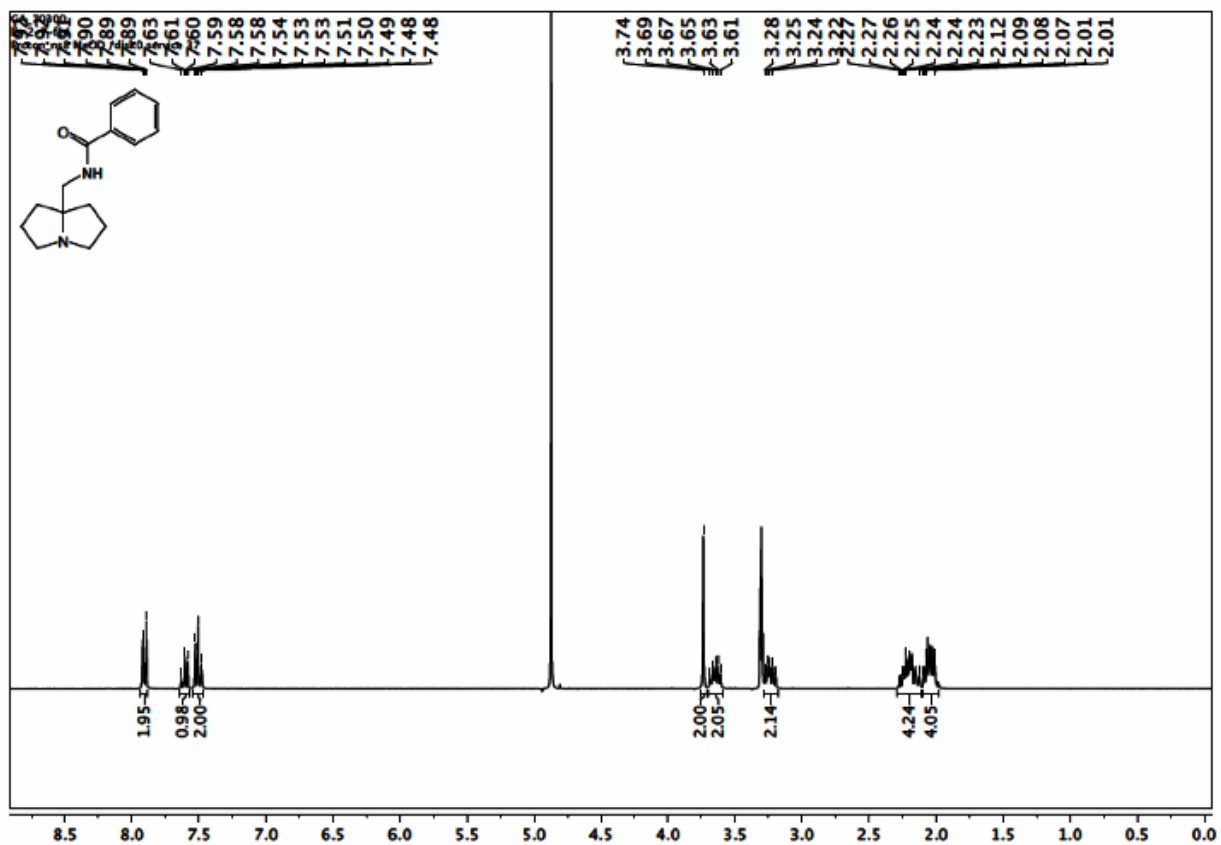
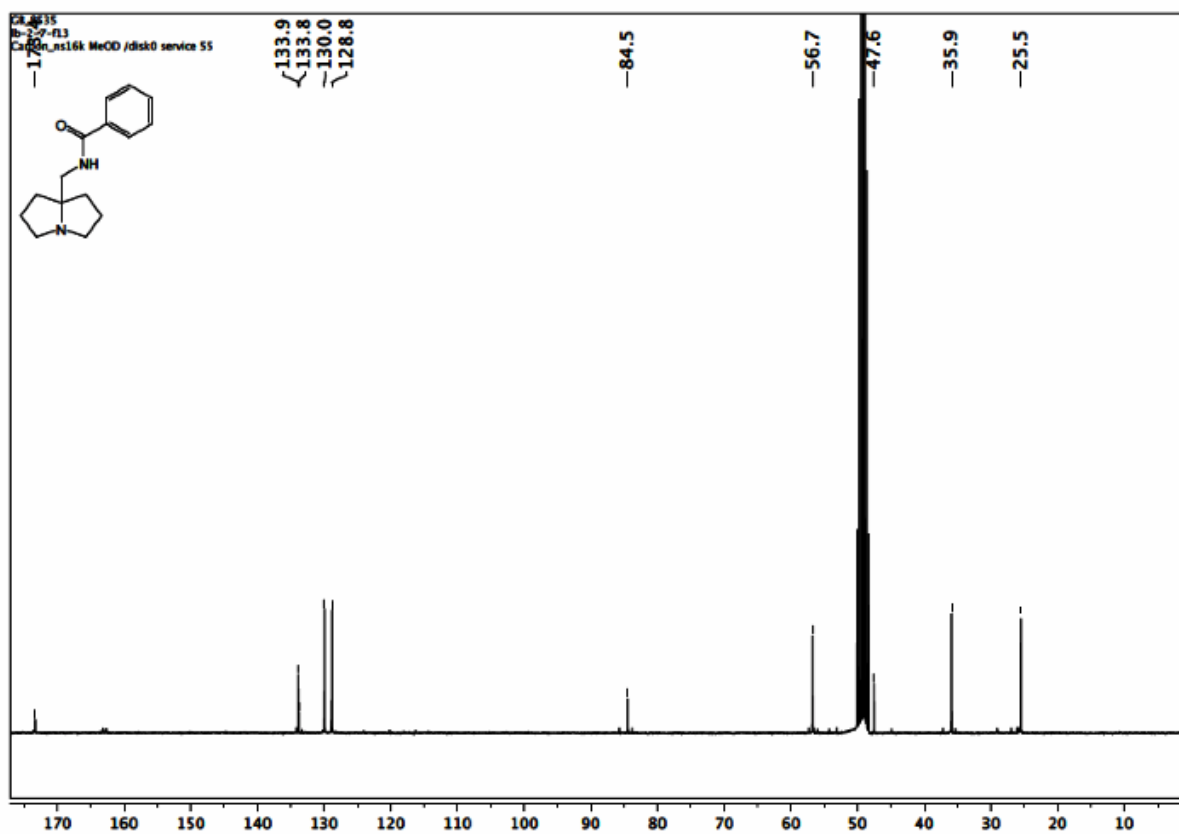
 ^{13}C NMR Spectrum of **5d** (CDCl_3 , 75 MHz)

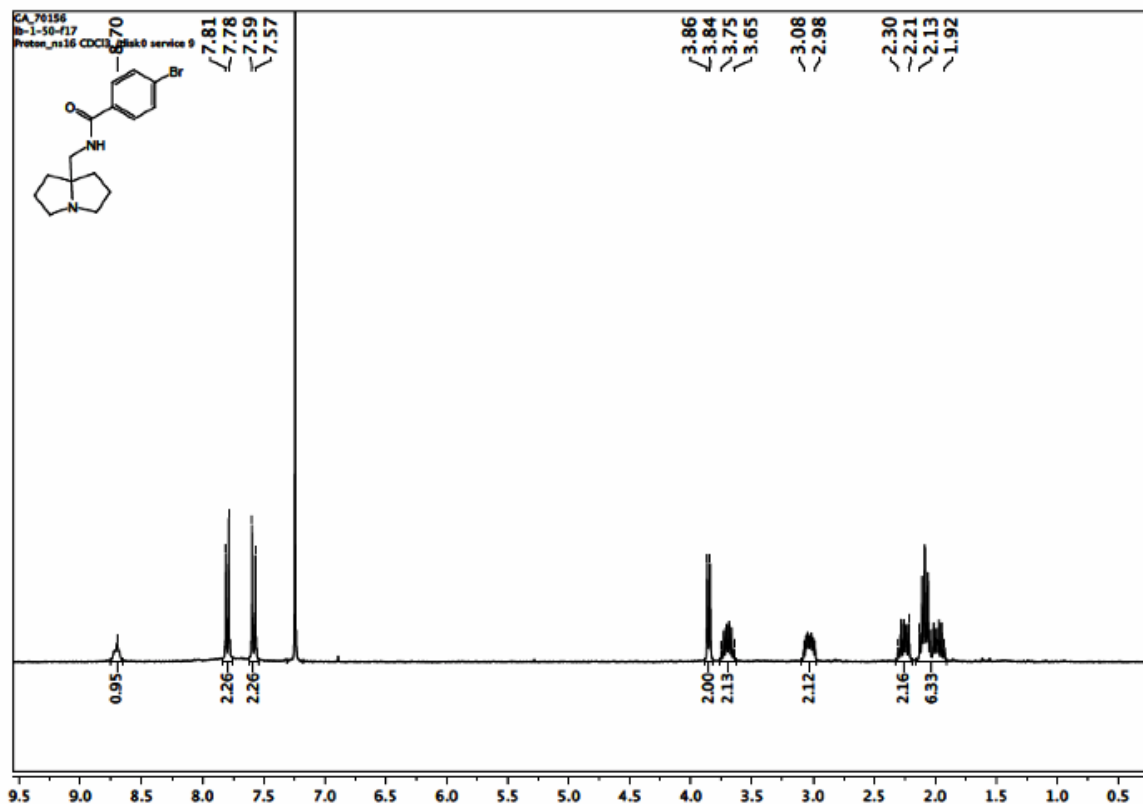
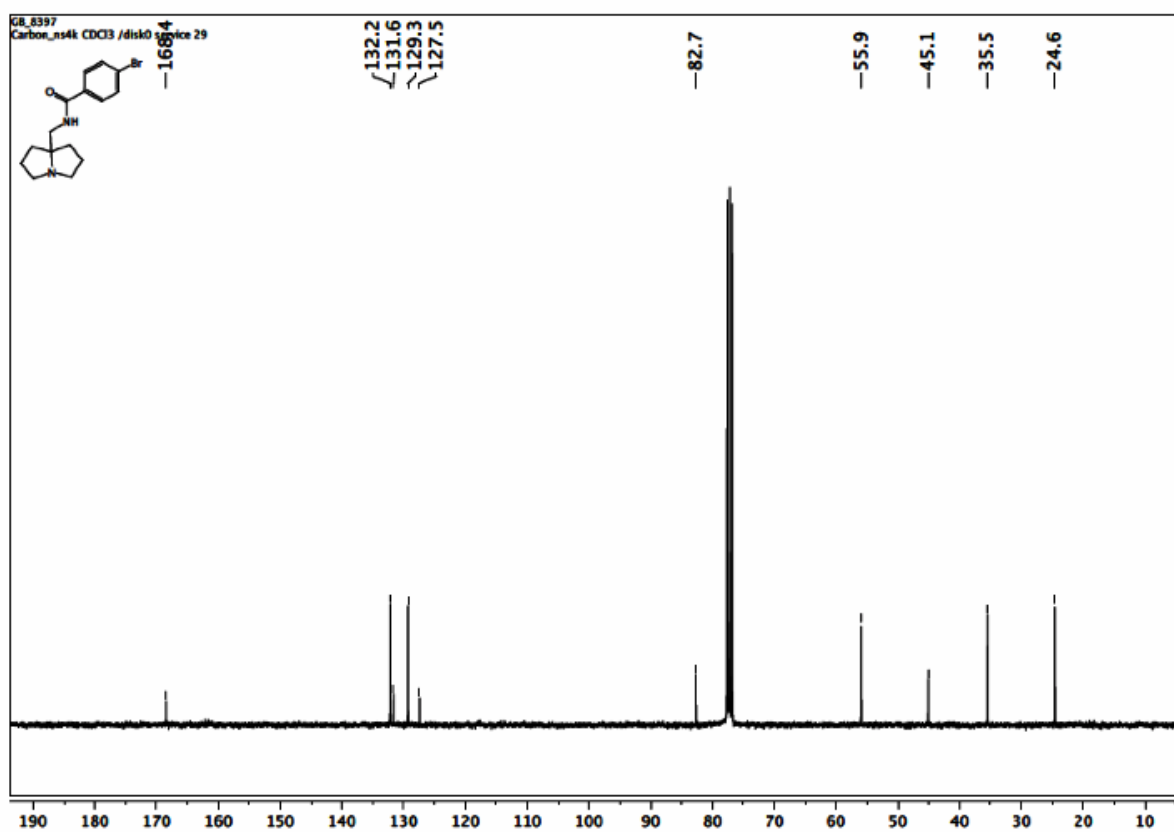
¹H NMR Spectrum of **6a** (CDCl₃, 300 MHz)¹³C NMR Spectrum of **6a** (CDCl₃, 75 MHz)

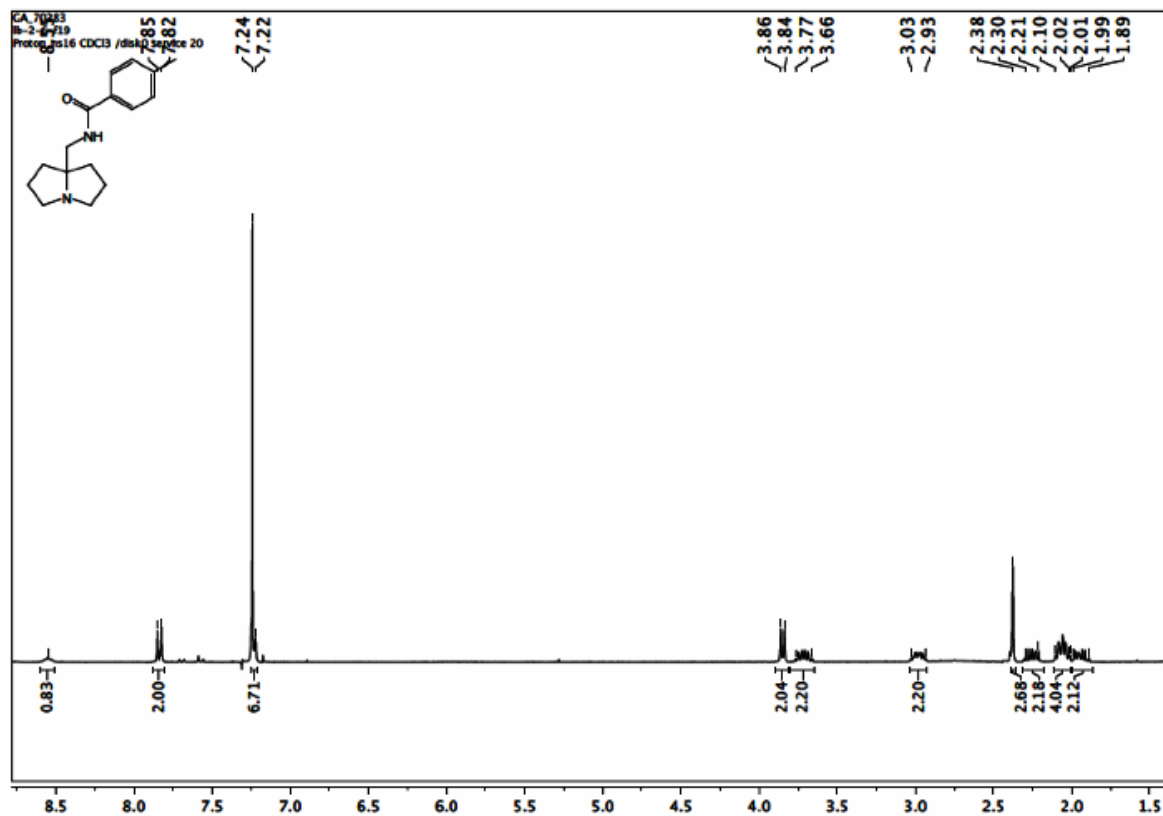
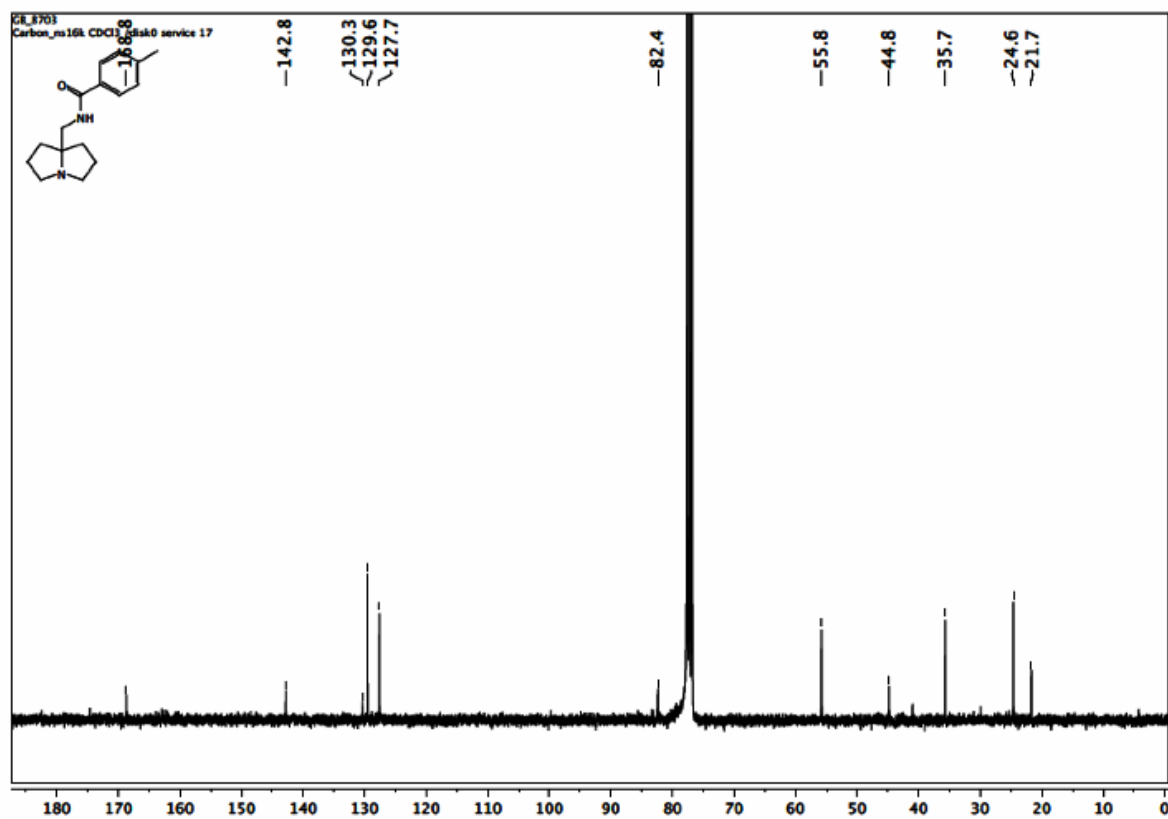
^1H NMR Spectrum of **6b** (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **6b** (CDCl_3 , 75 MHz)

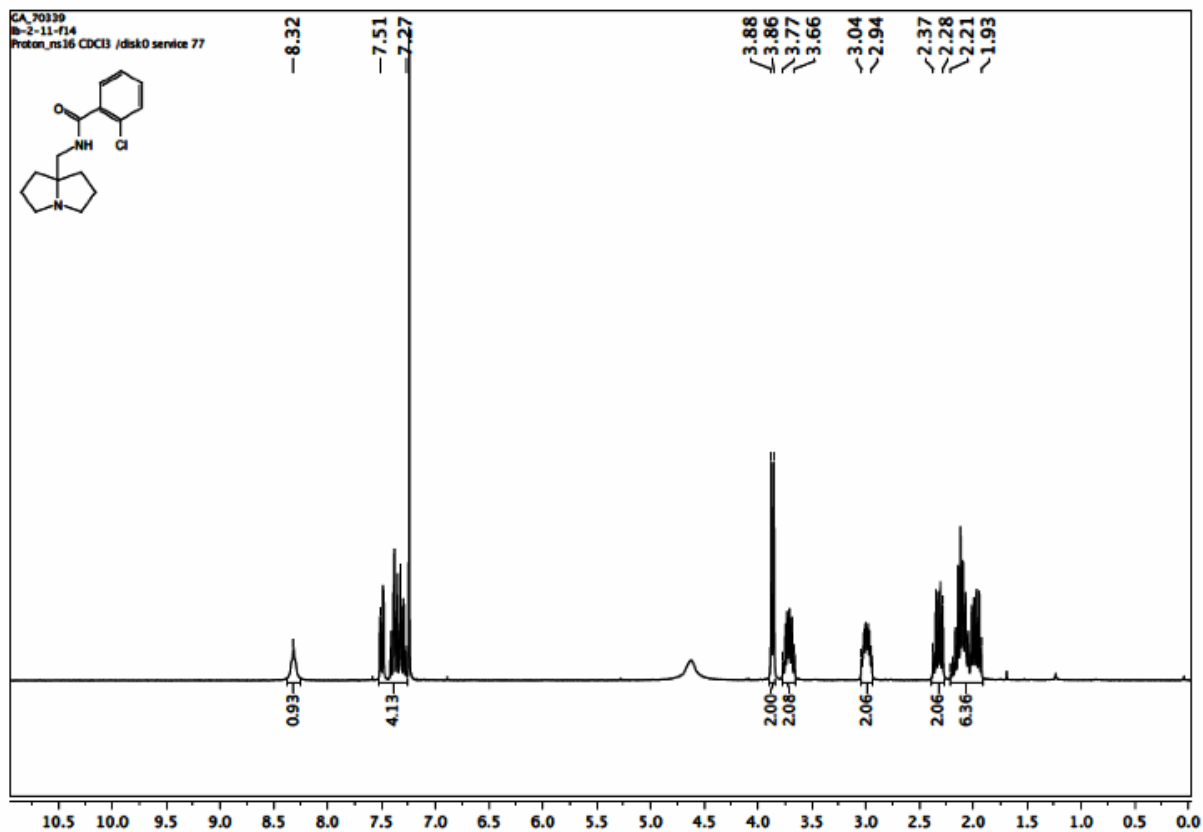
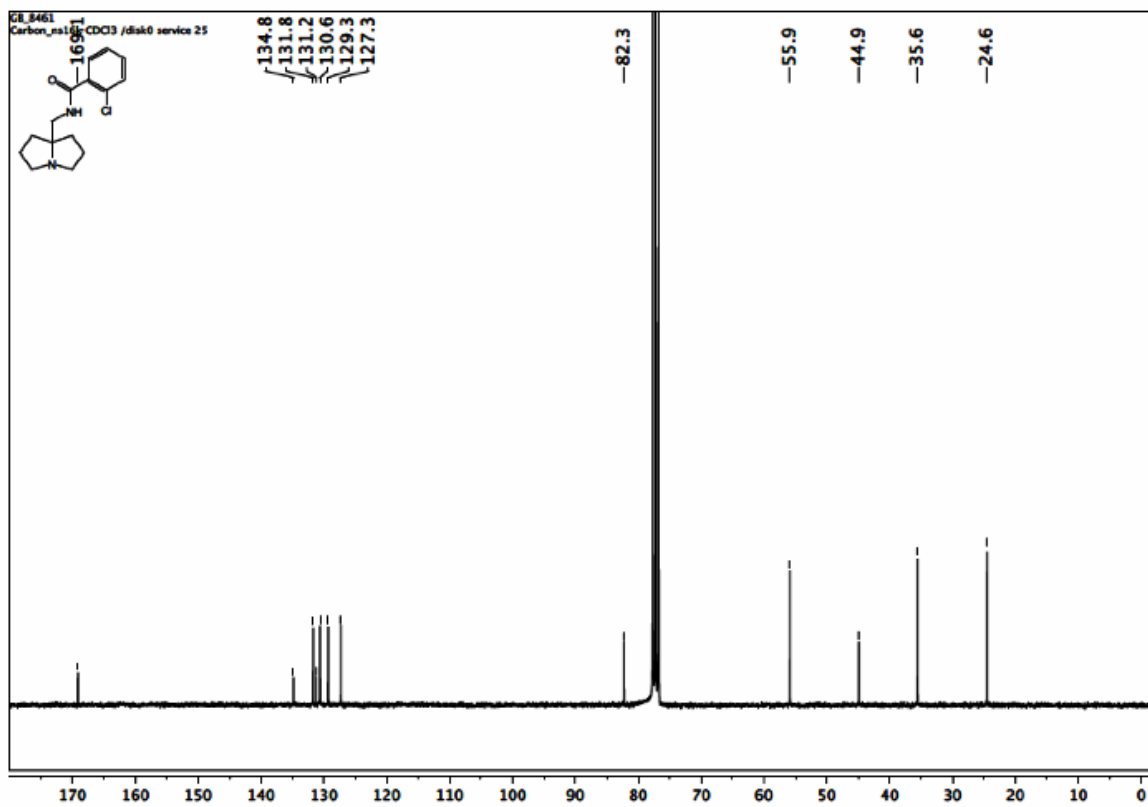
¹H NMR Spectrum of **6c** (CDCl₃, 300 MHz)¹³C NMR Spectrum of **6c** (CDCl₃, 75 MHz)

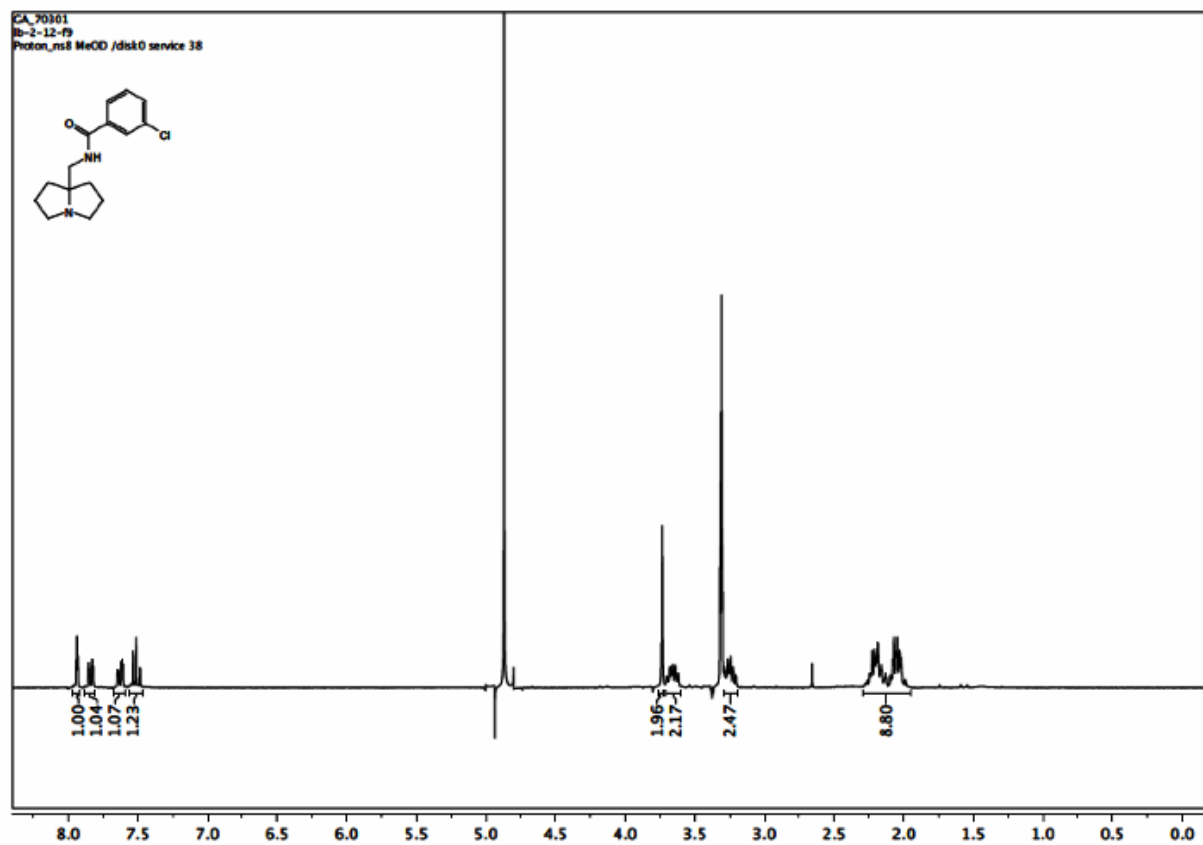
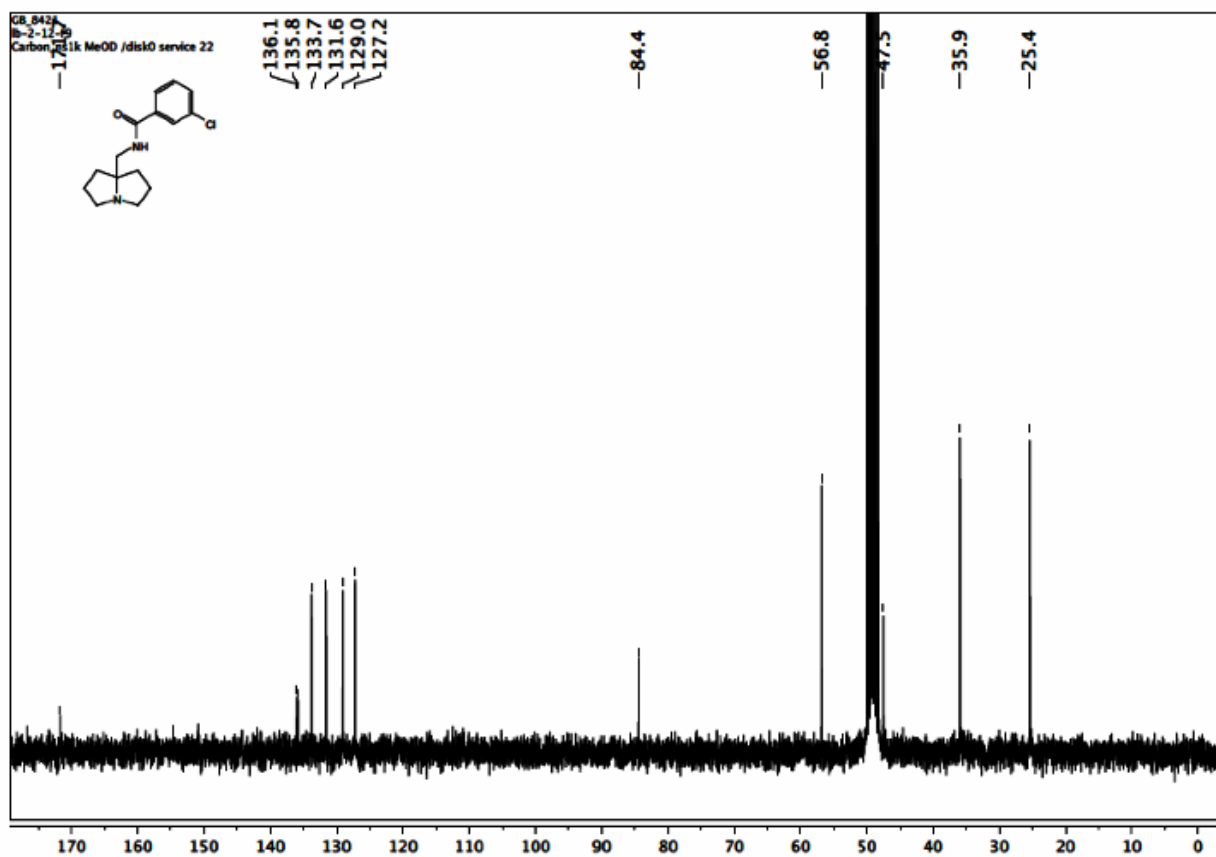
¹H NMR Spectrum of **6d** (CDCl₃, 300 MHz)¹³C NMR Spectrum of **6d** (CDCl₃, 75 MHz)

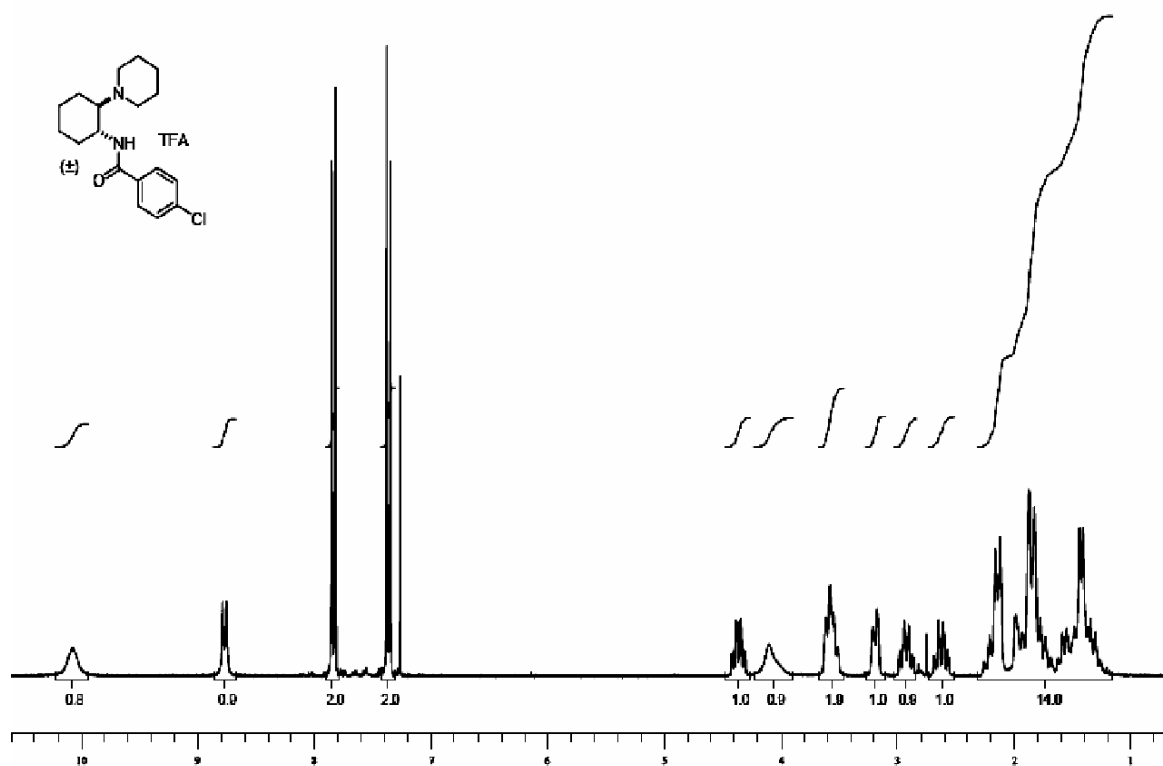
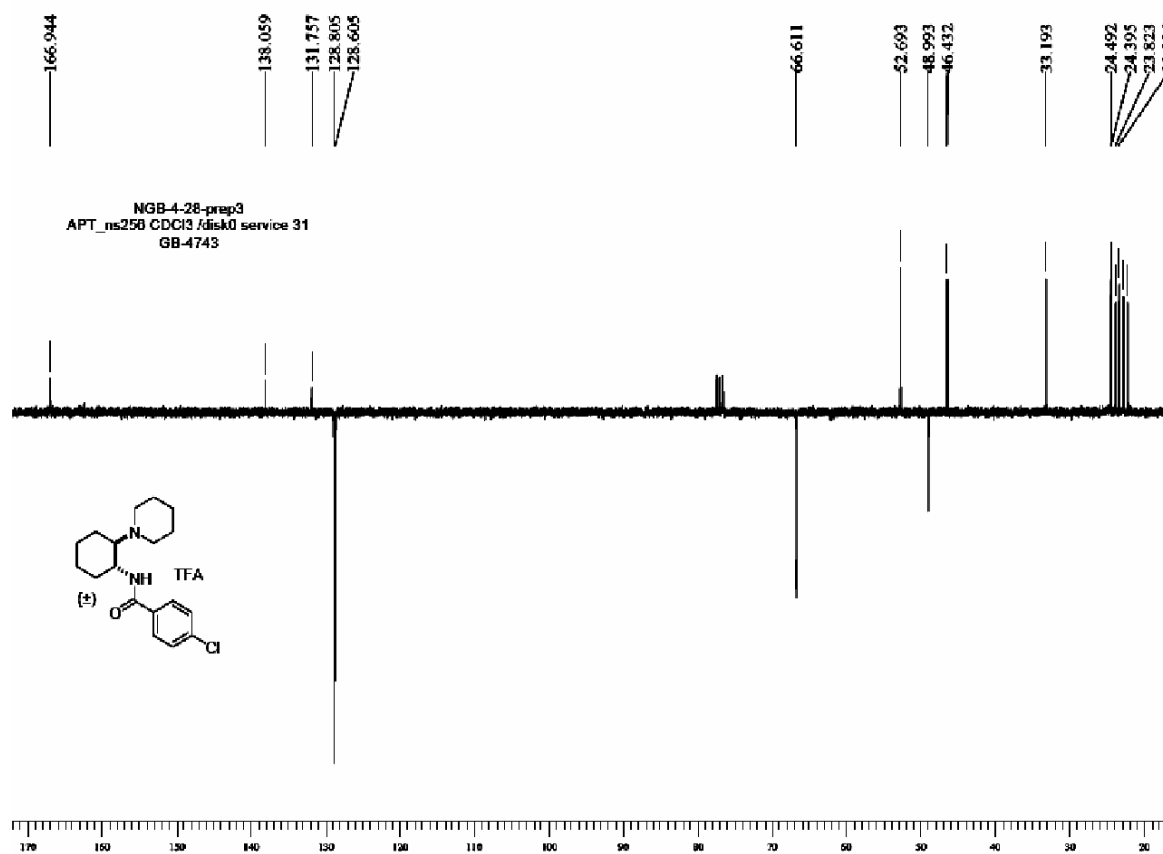
^1H NMR Spectrum of **6f** TFA salt (MeOD, 300 MHz) ^{13}C NMR Spectrum of **6f** TFA salt (MeOD, 75 MHz)

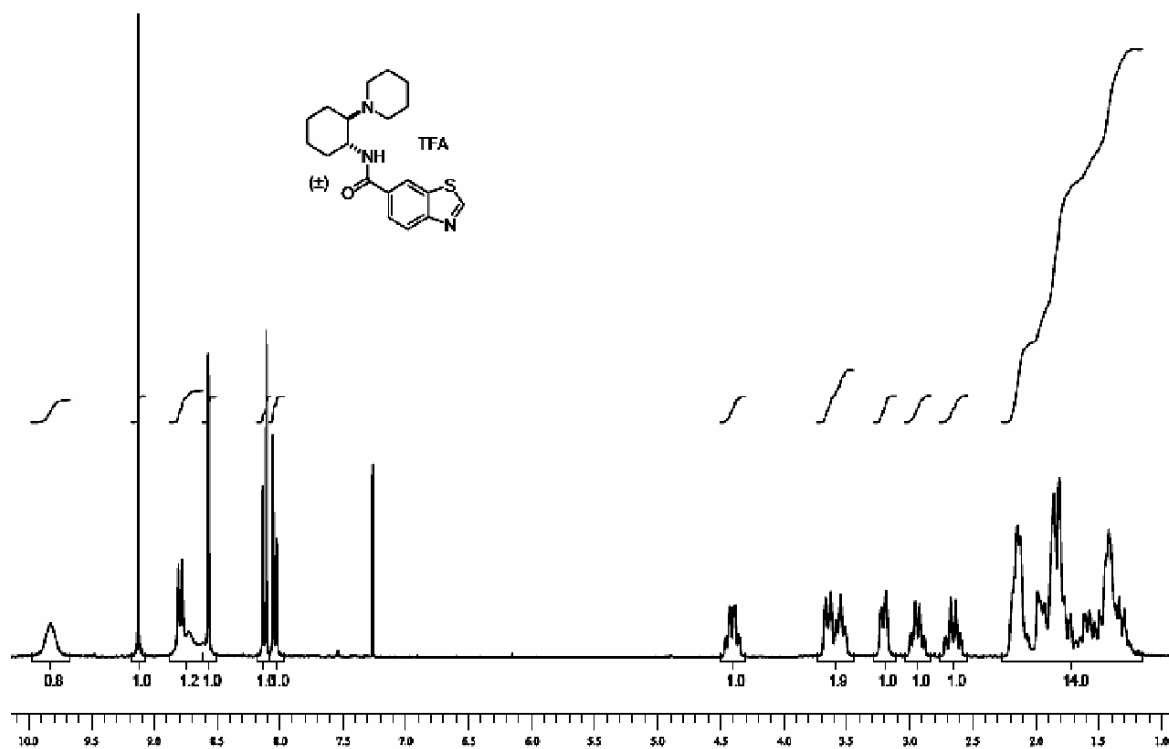
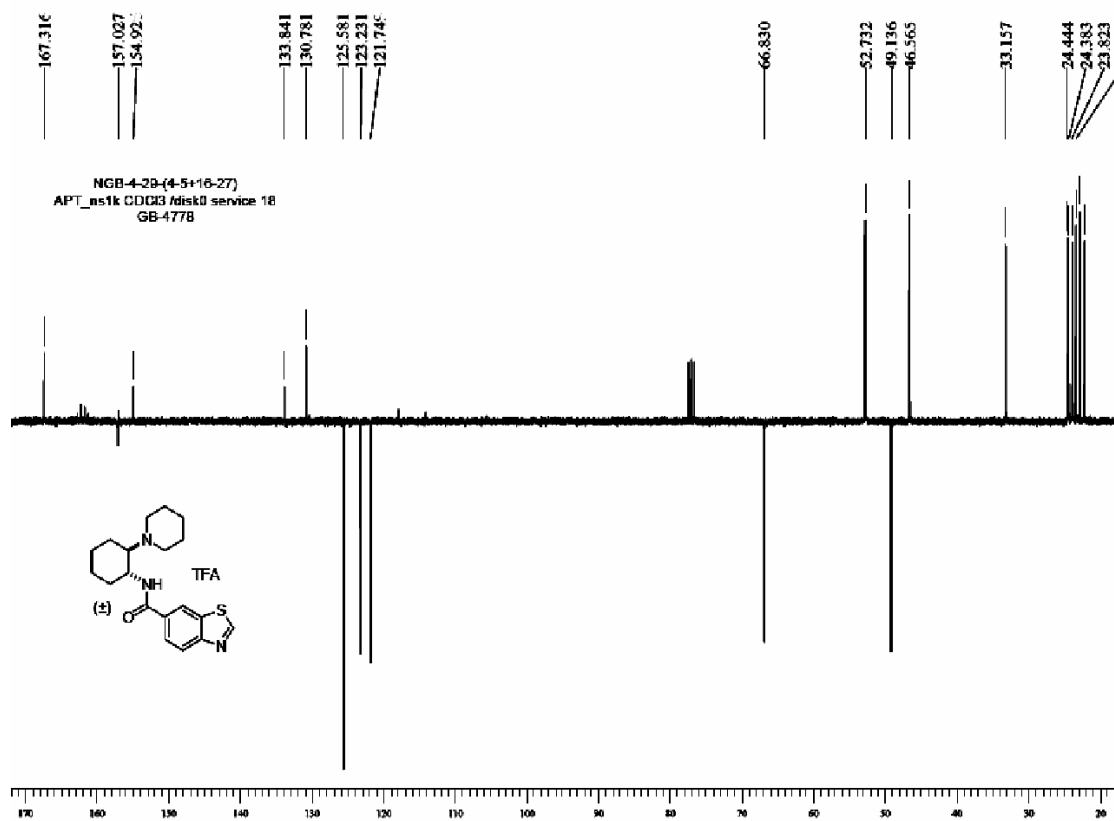
^1H NMR Spectrum of **6g** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **6g** TFA salt (CDCl_3 , 75 MHz)

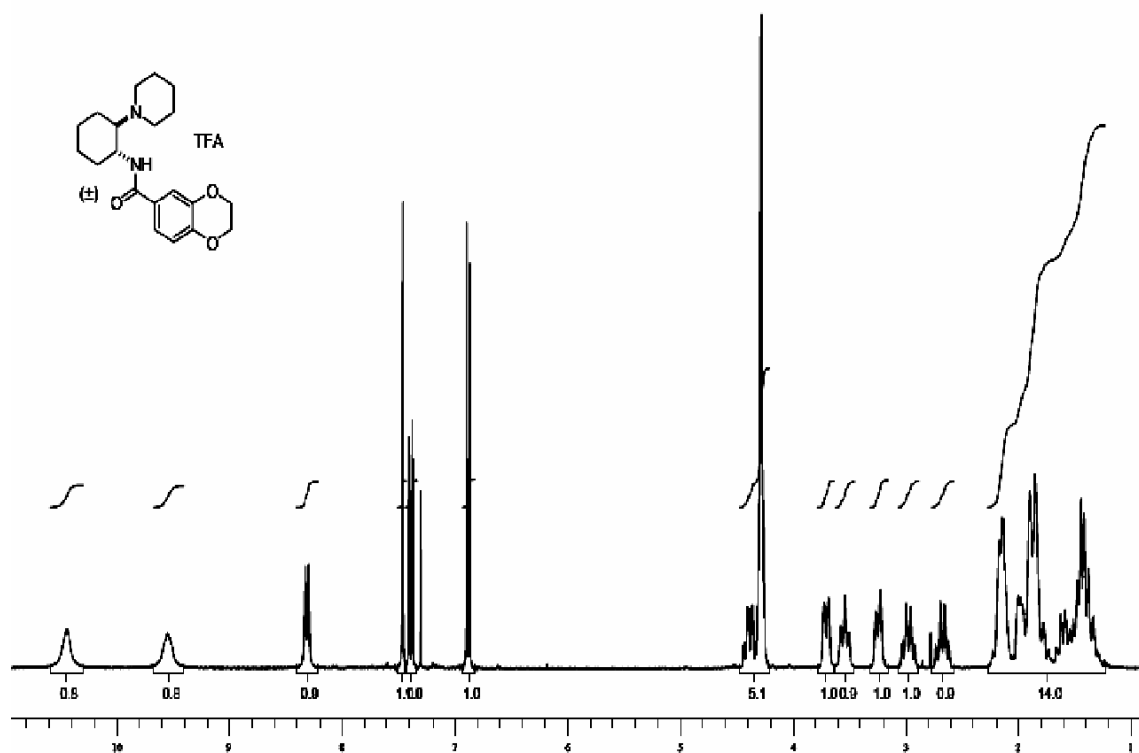
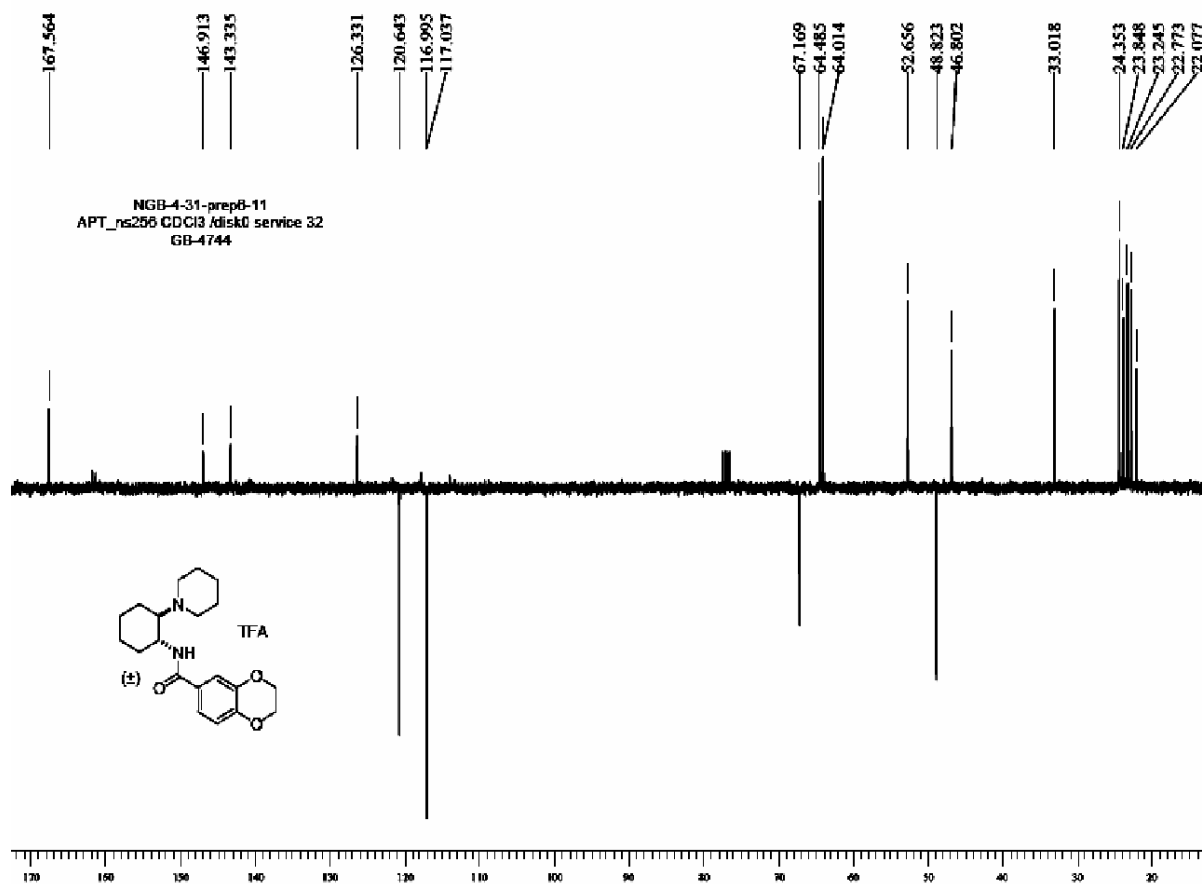
^1H NMR Spectrum of **6h** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **6h** TFA salt (CDCl_3 , 75 MHz)

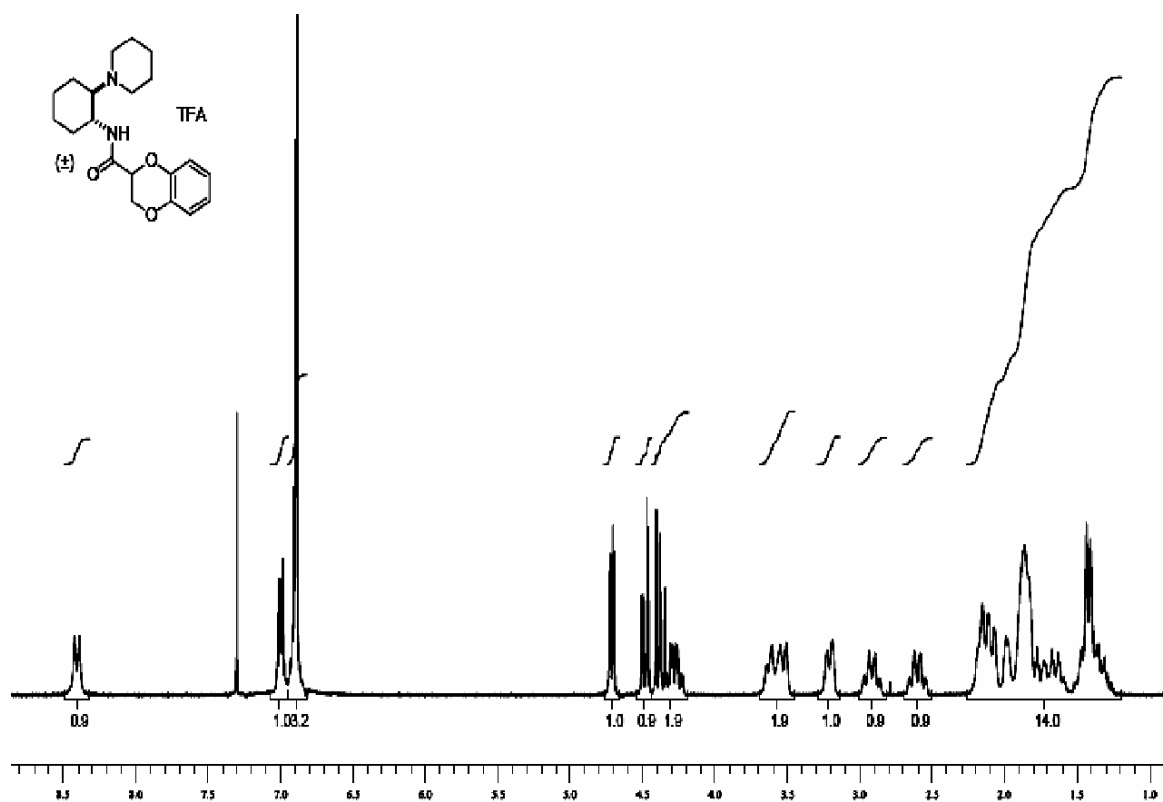
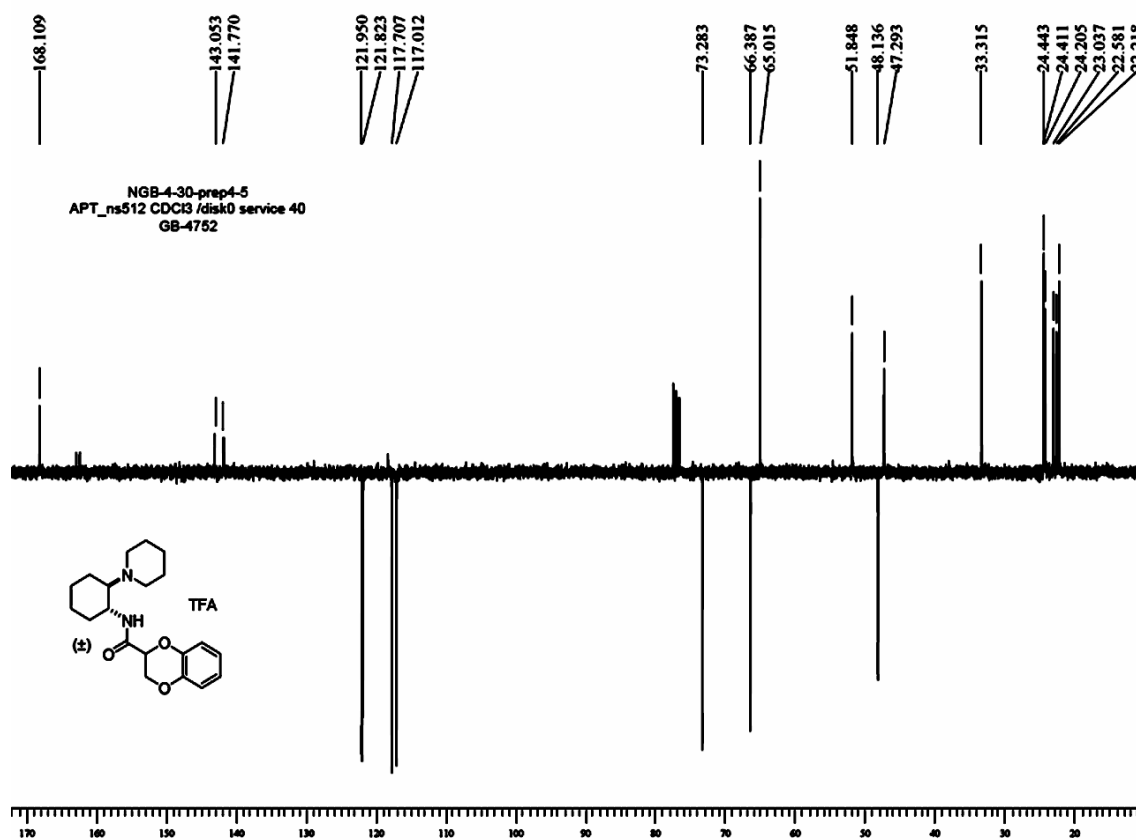
^1H NMR Spectrum of **6i** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **6i** TFA salt (CDCl_3 , 75 MHz)

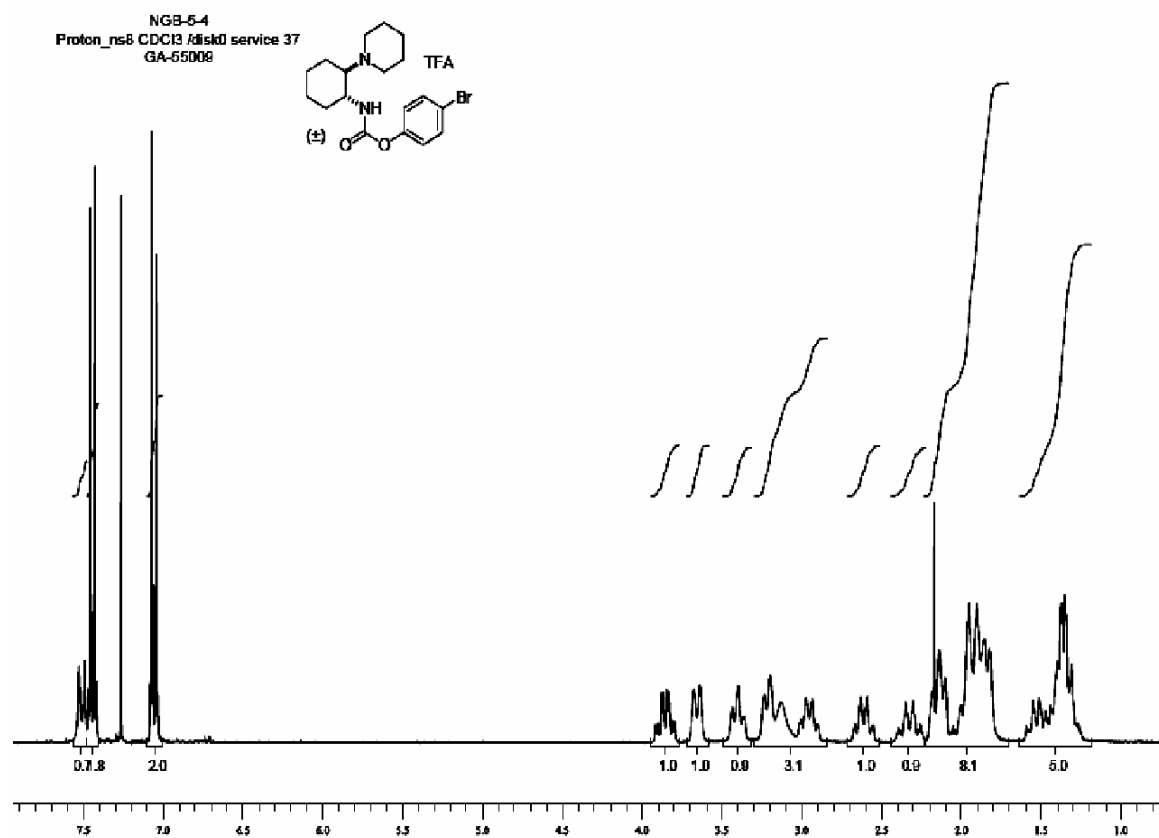
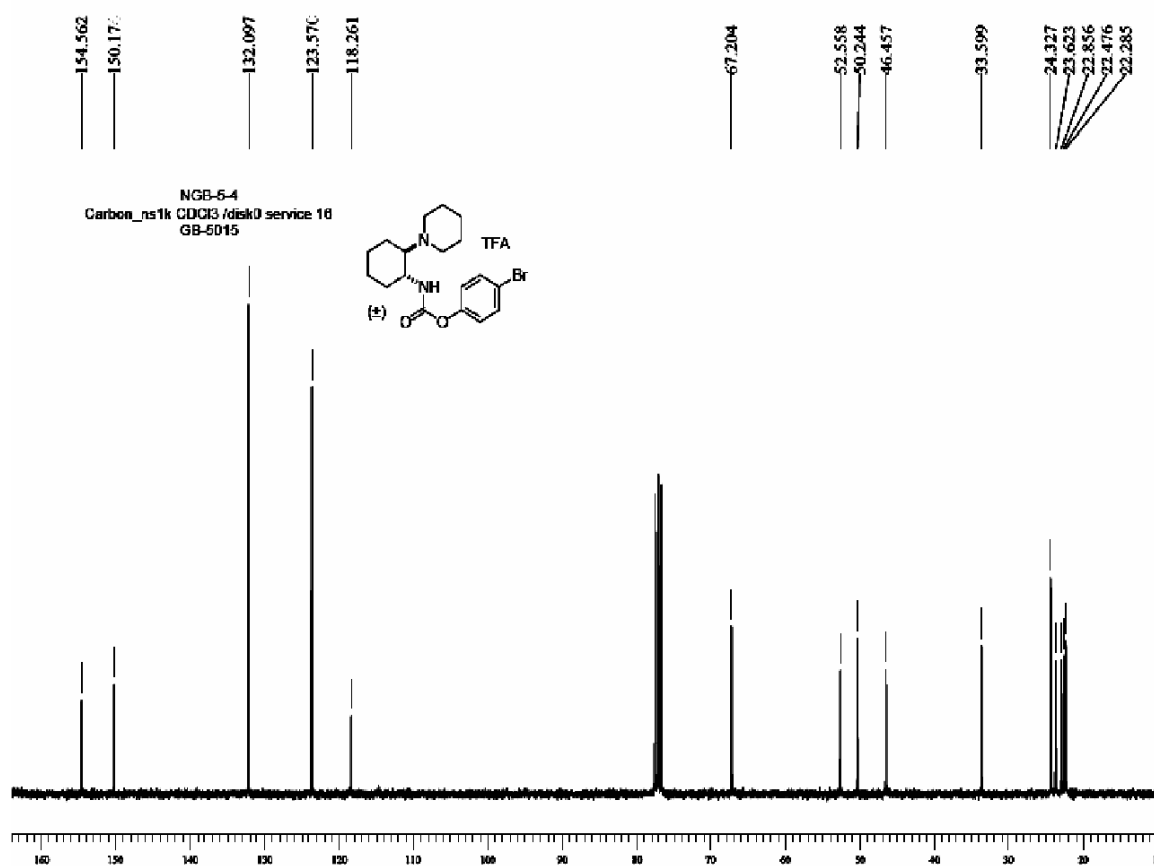
^1H NMR Spectrum of **6j** TFA salt (MeOD, 300 MHz) ^{13}C NMR Spectrum of **6j** TFA salt (MeOD, 75 MHz)

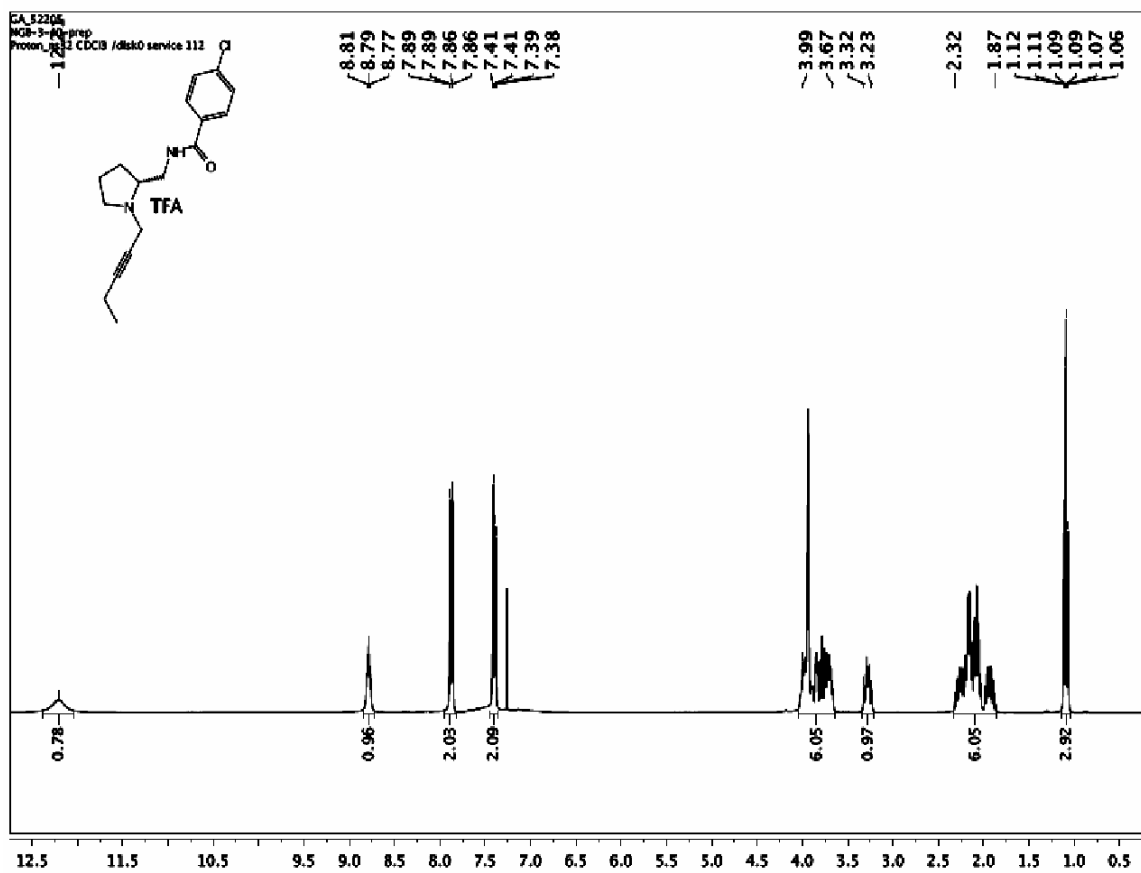
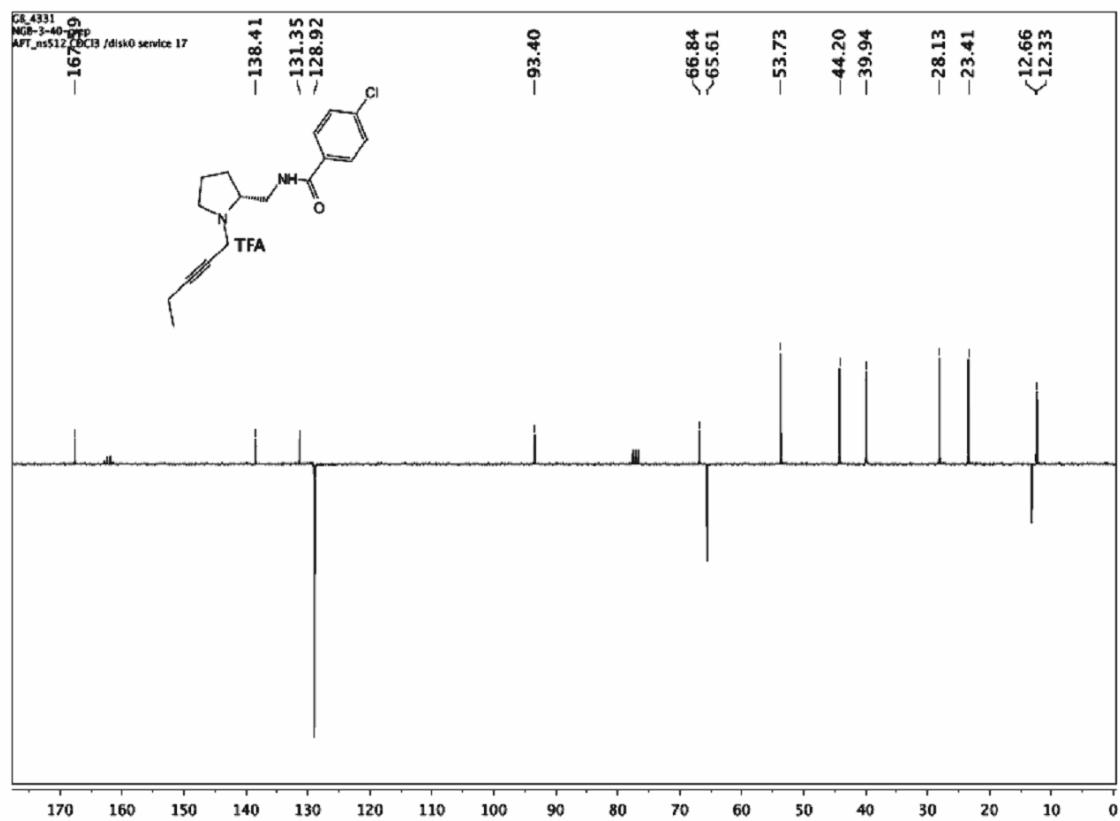
^1H NMR Spectrum of **7a** TFA salt (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **7a** TFA salt (CDCl_3 , 75 MHz)

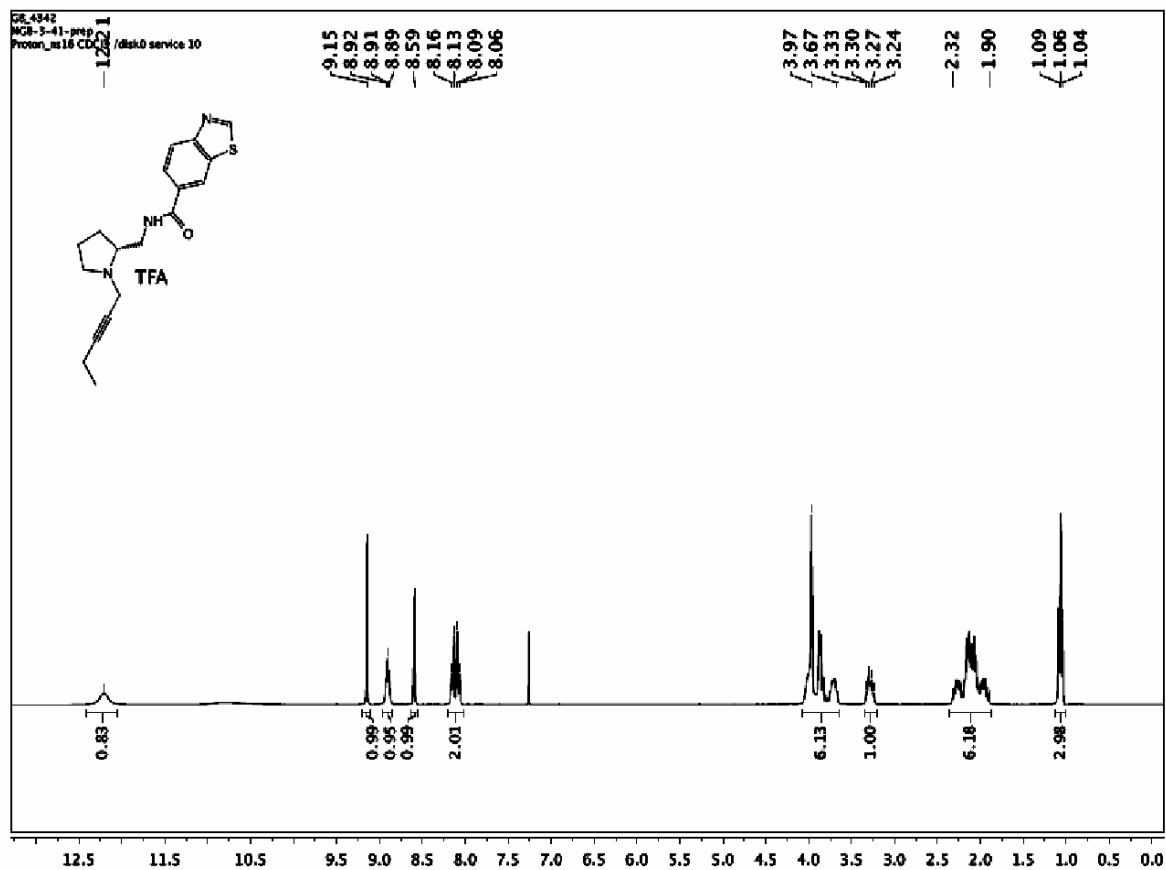
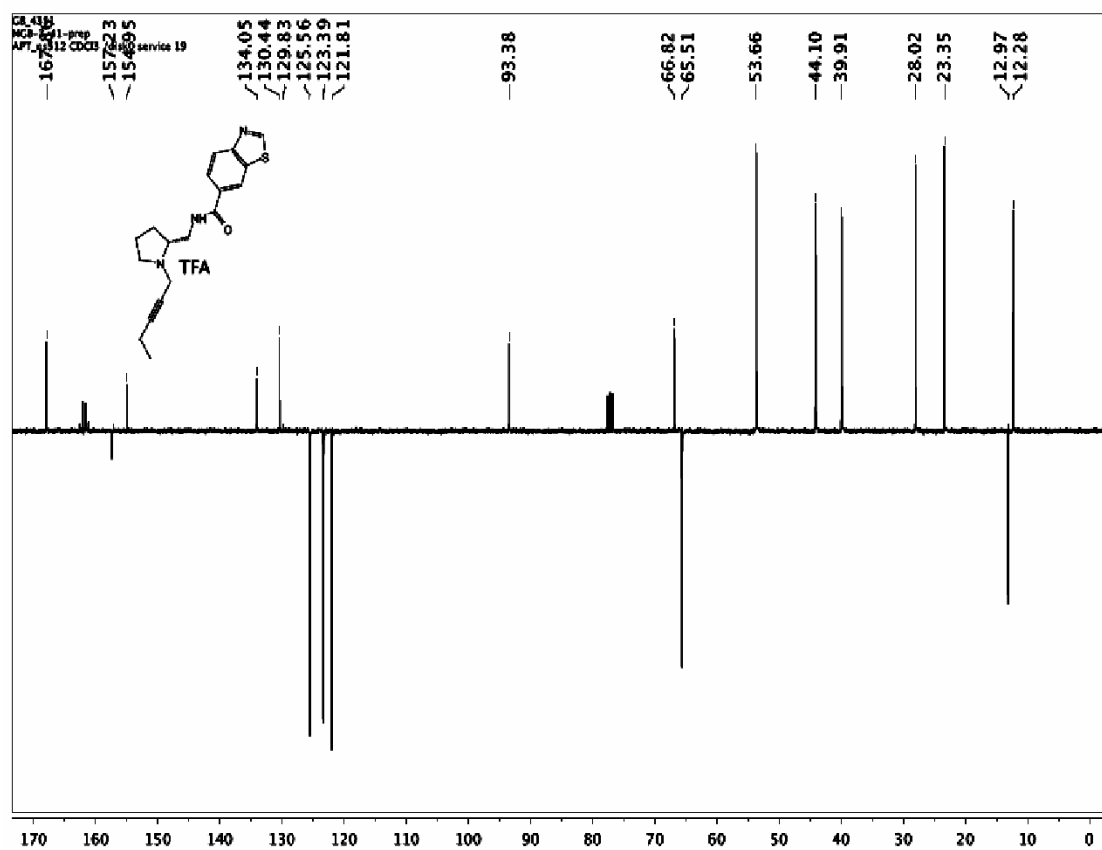
^1H NMR Spectrum of **7b** TFA salt (CDCl_3 , 300 MHz)APT- ^{13}C NMR Spectrum of **7b** TFA salt (CDCl_3 , 75 MHz)

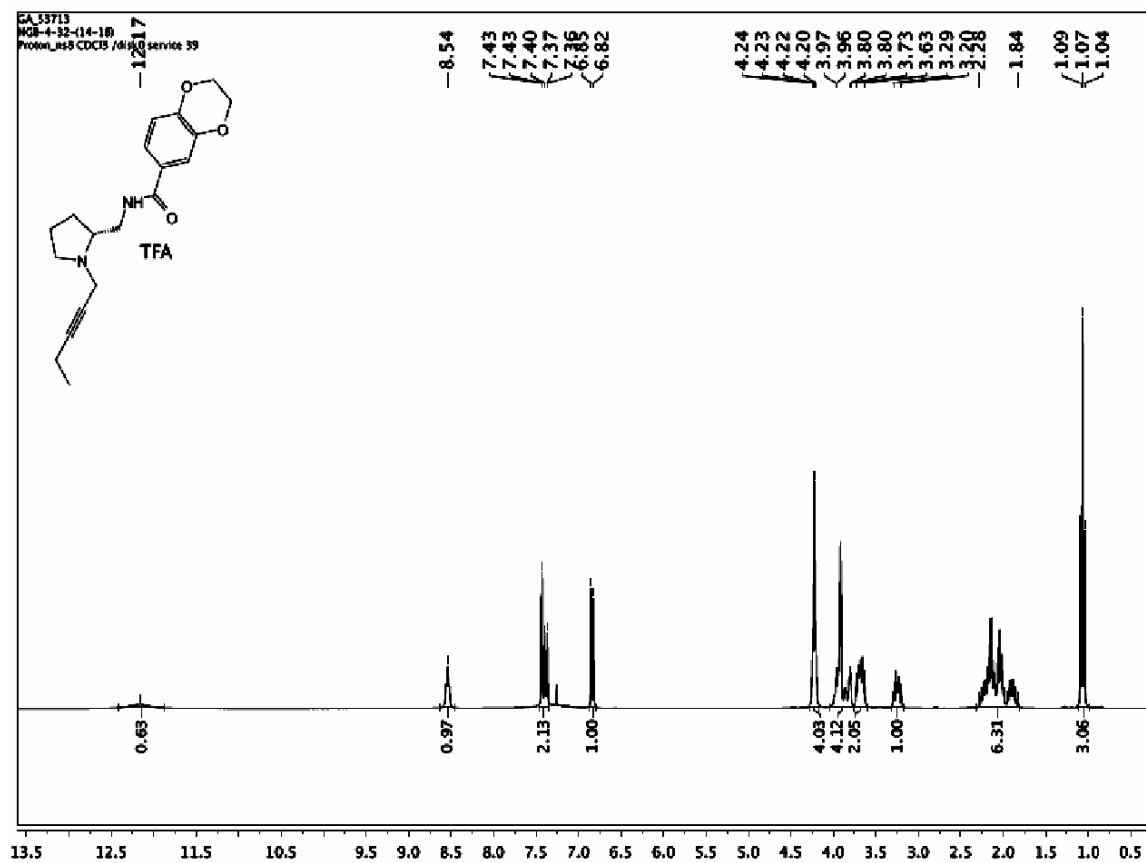
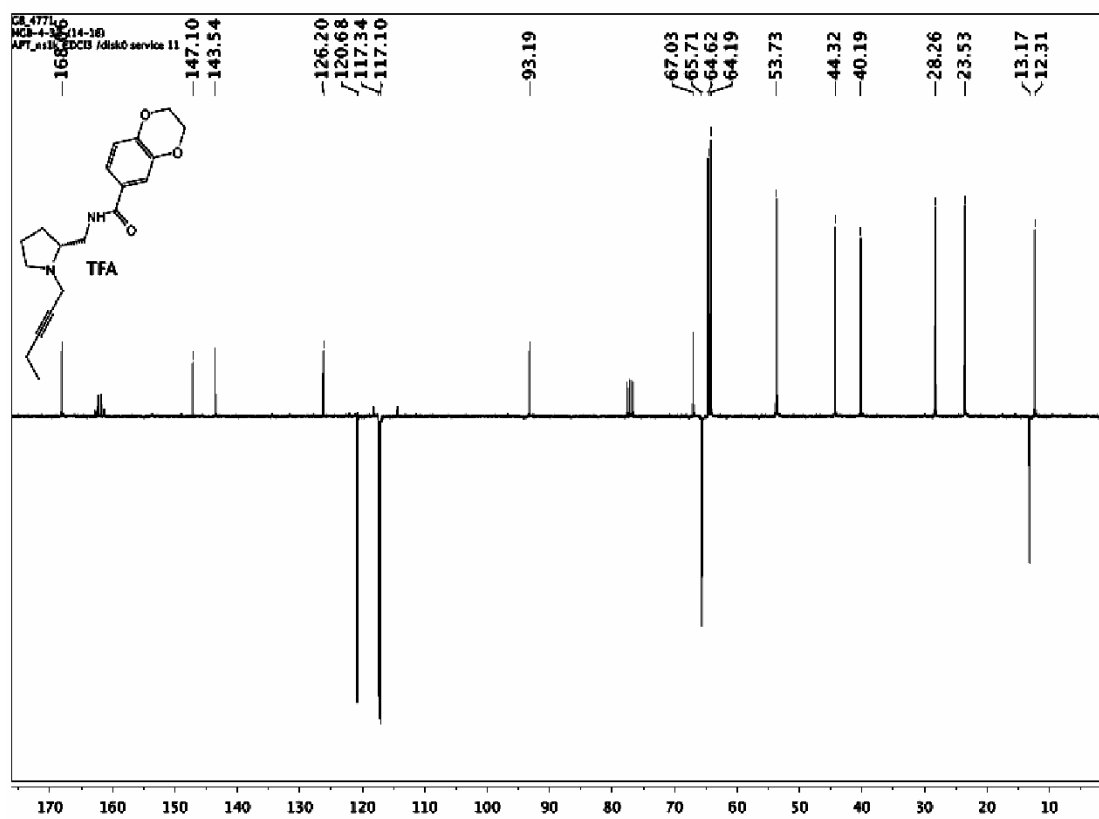
^1H NMR Spectrum of **7c** TFA salt (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **7c** TFA salt (CDCl_3 , 75 MHz)

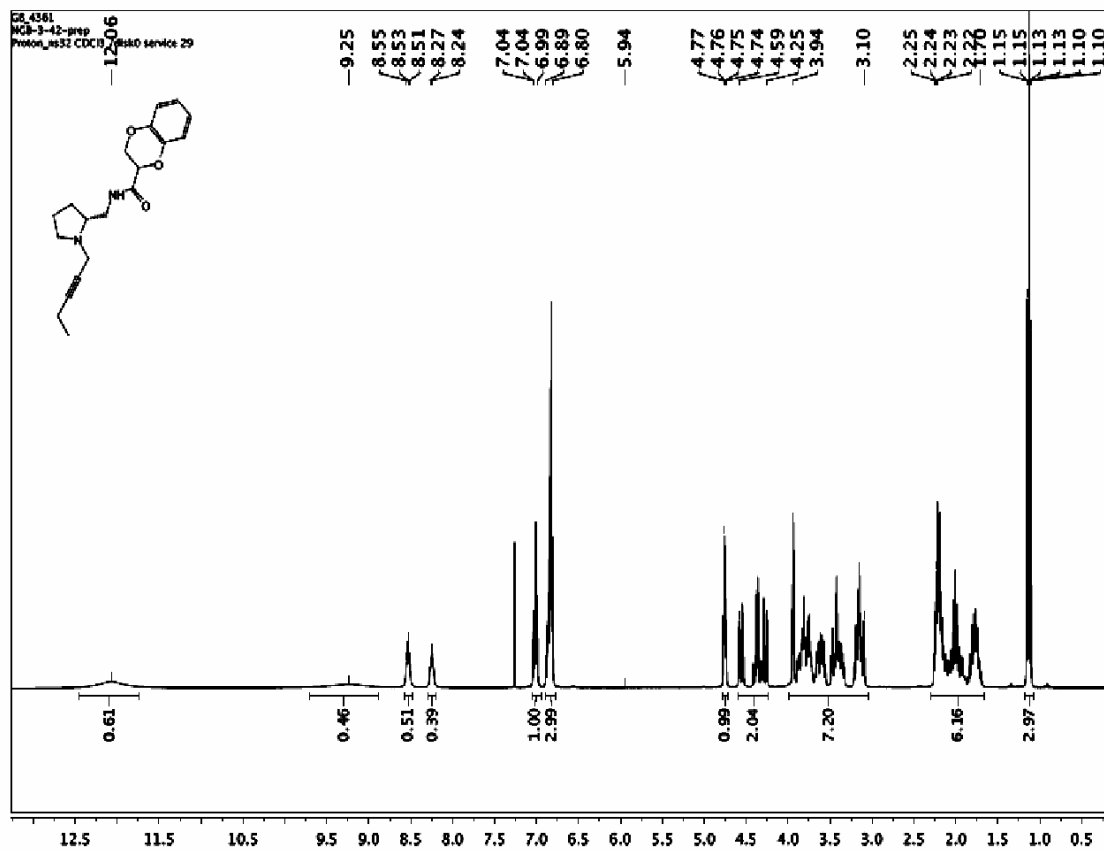
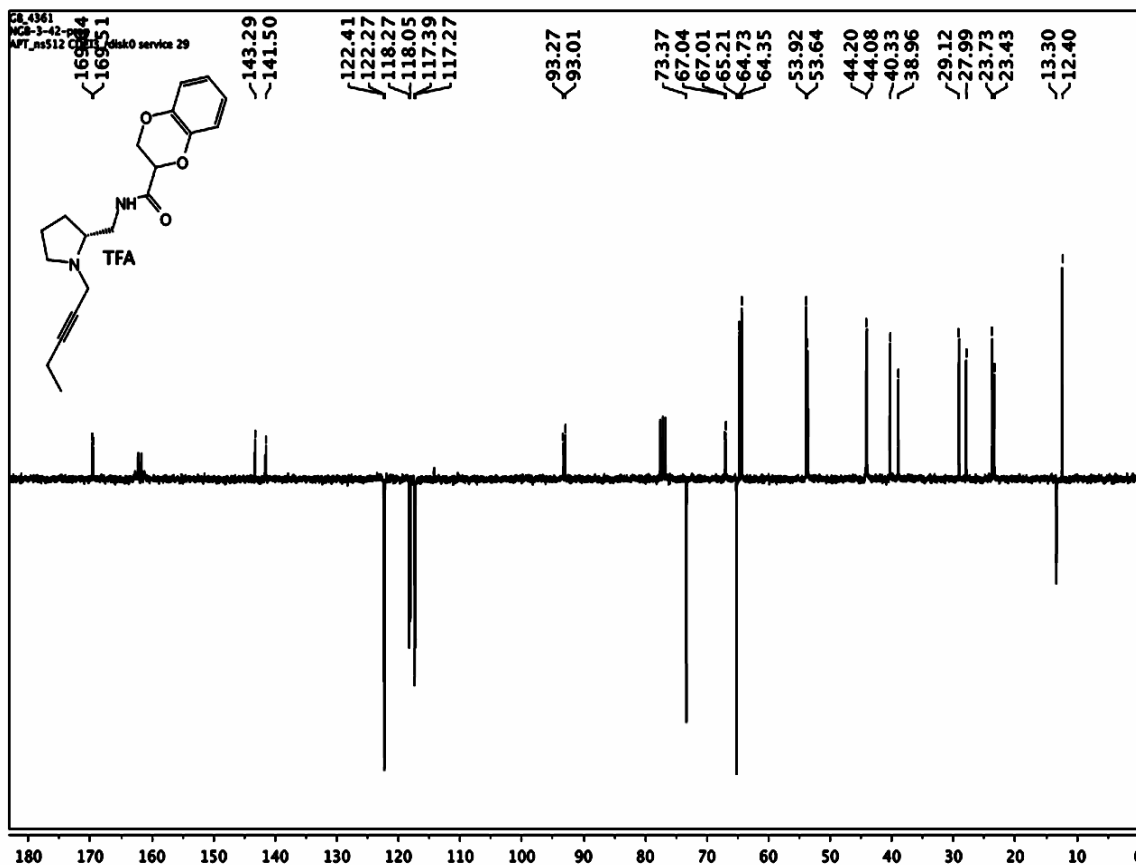
^1H NMR Spectrum of **7d** TFA salt (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **7d** TFA salt (CDCl_3 , 75 MHz)

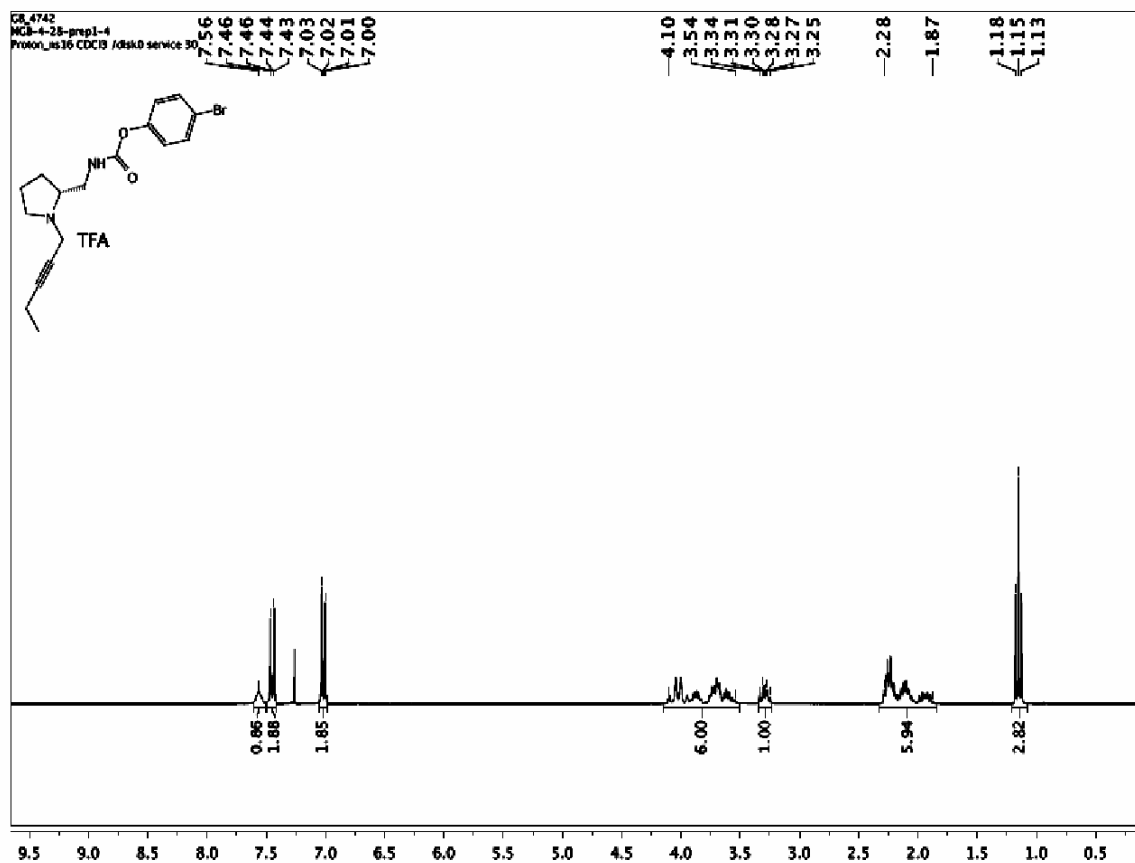
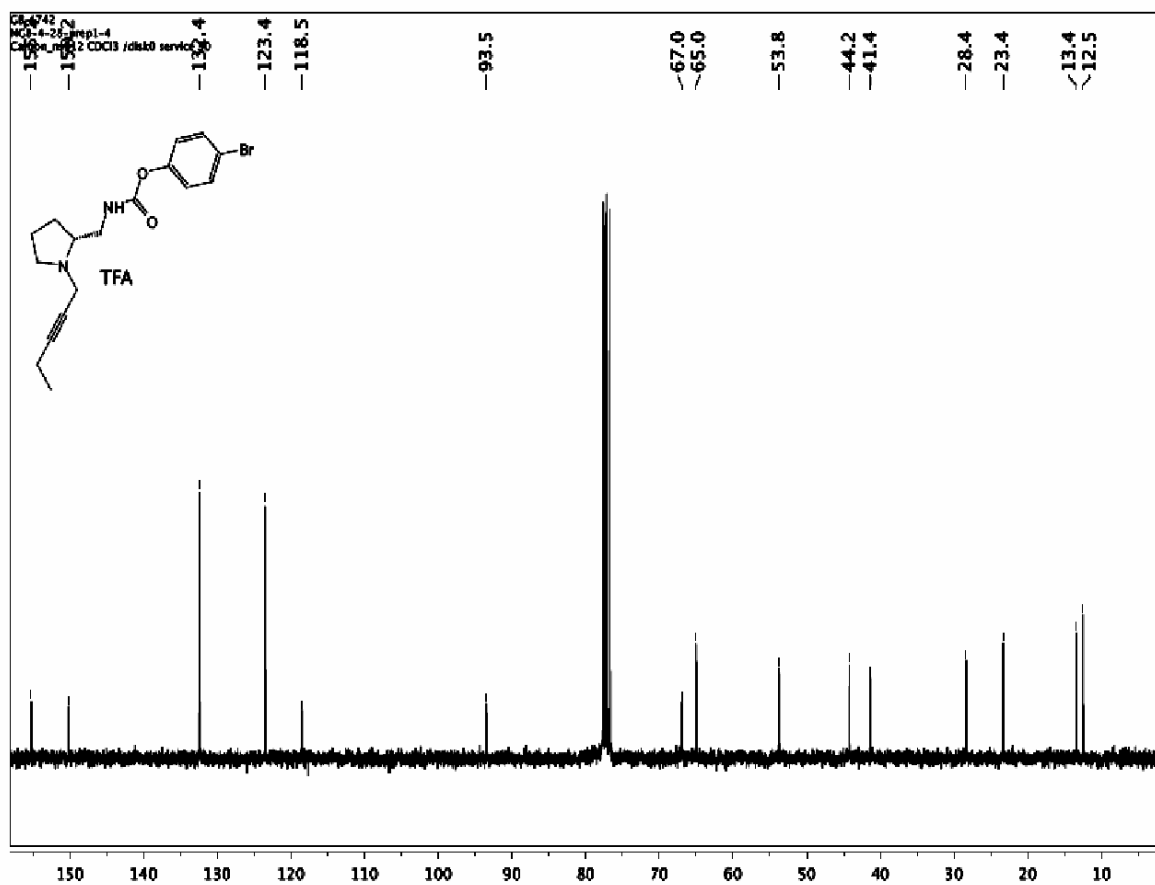
^1H NMR Spectrum of **7e** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **7e** TFA salt (CDCl_3 , 75 MHz)

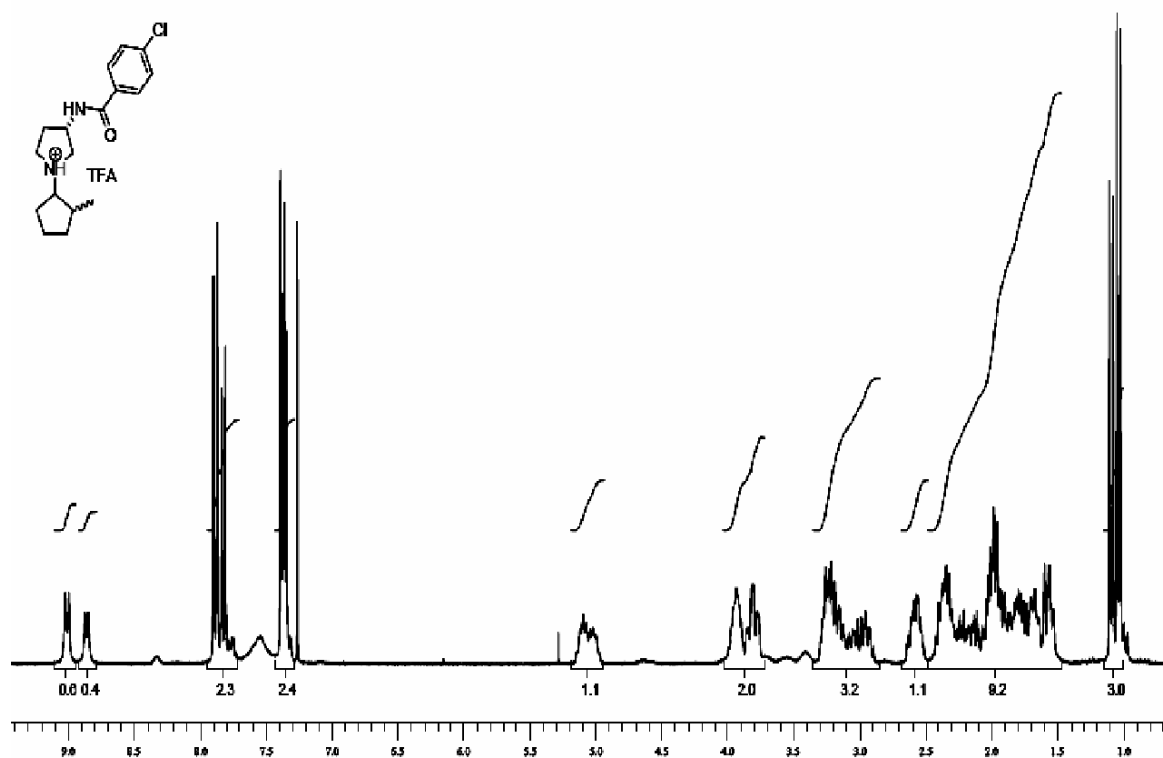
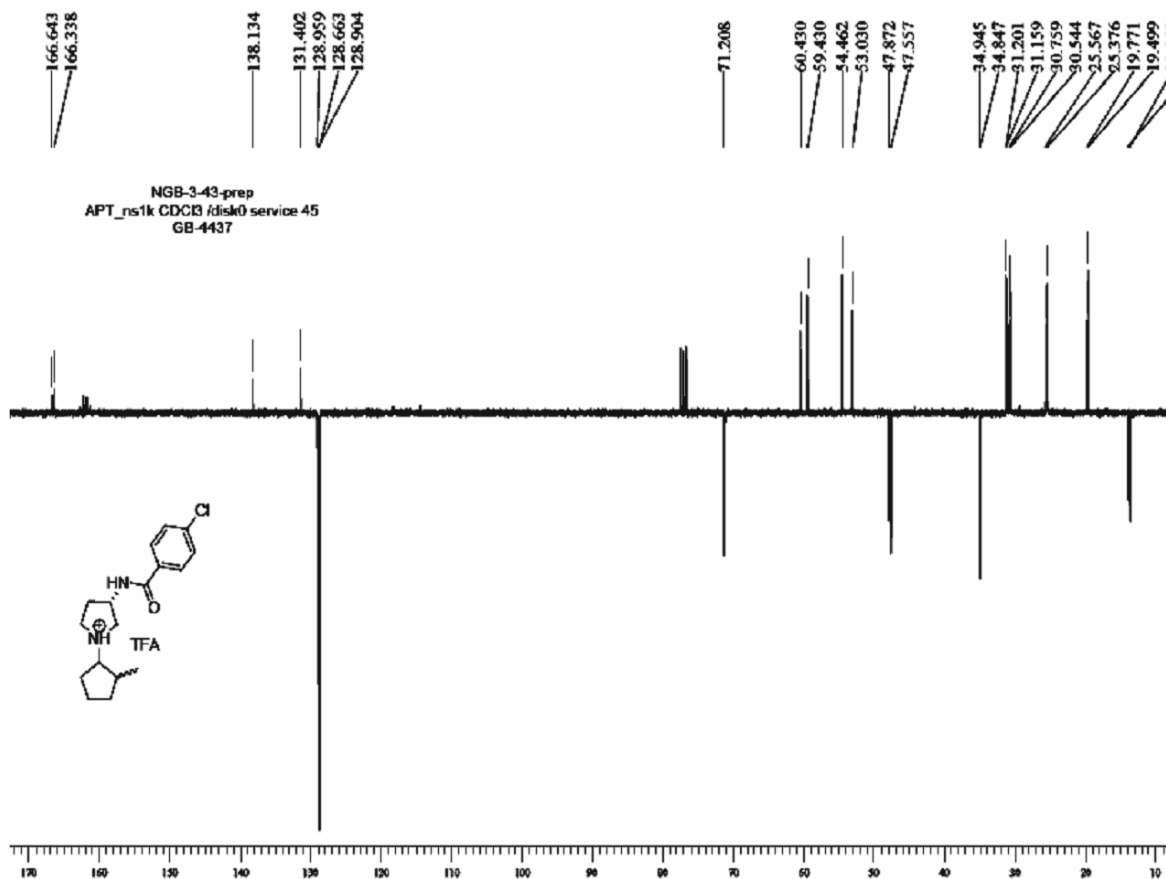
^1H NMR Spectrum of **8a** TFA salt (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **8a** TFA salt (CDCl_3 , 75 MHz)

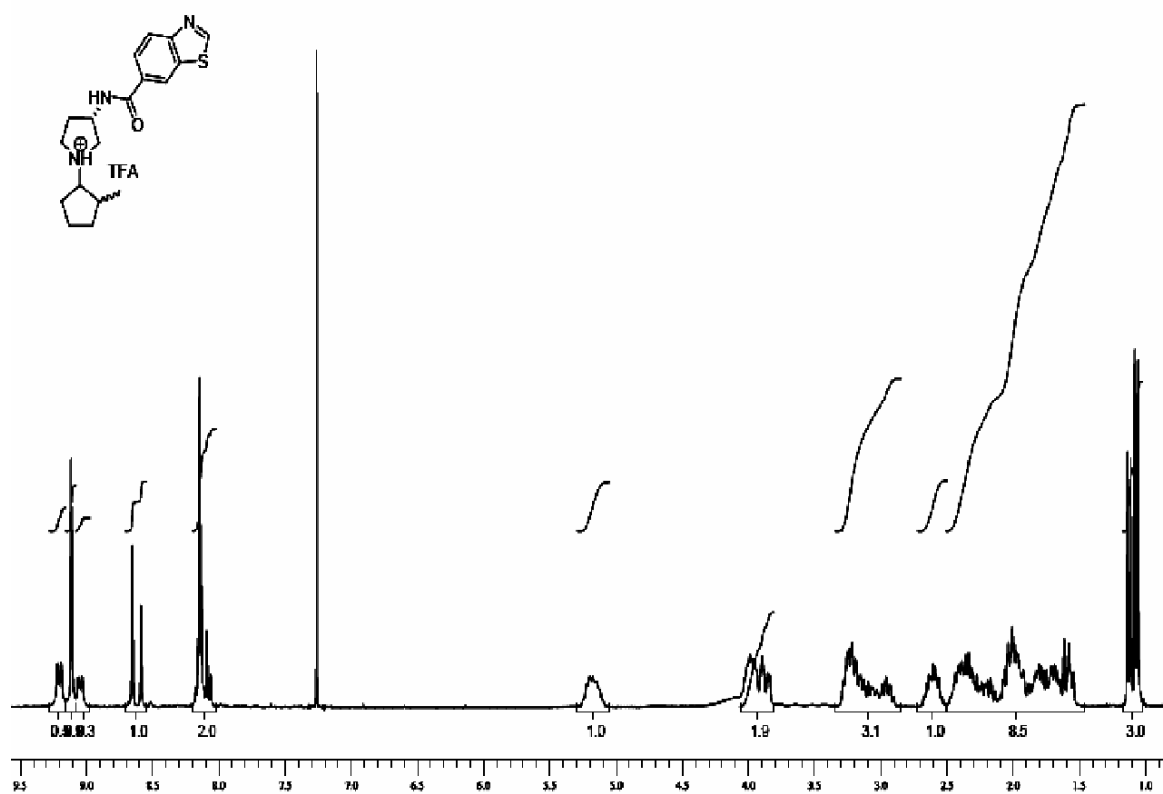
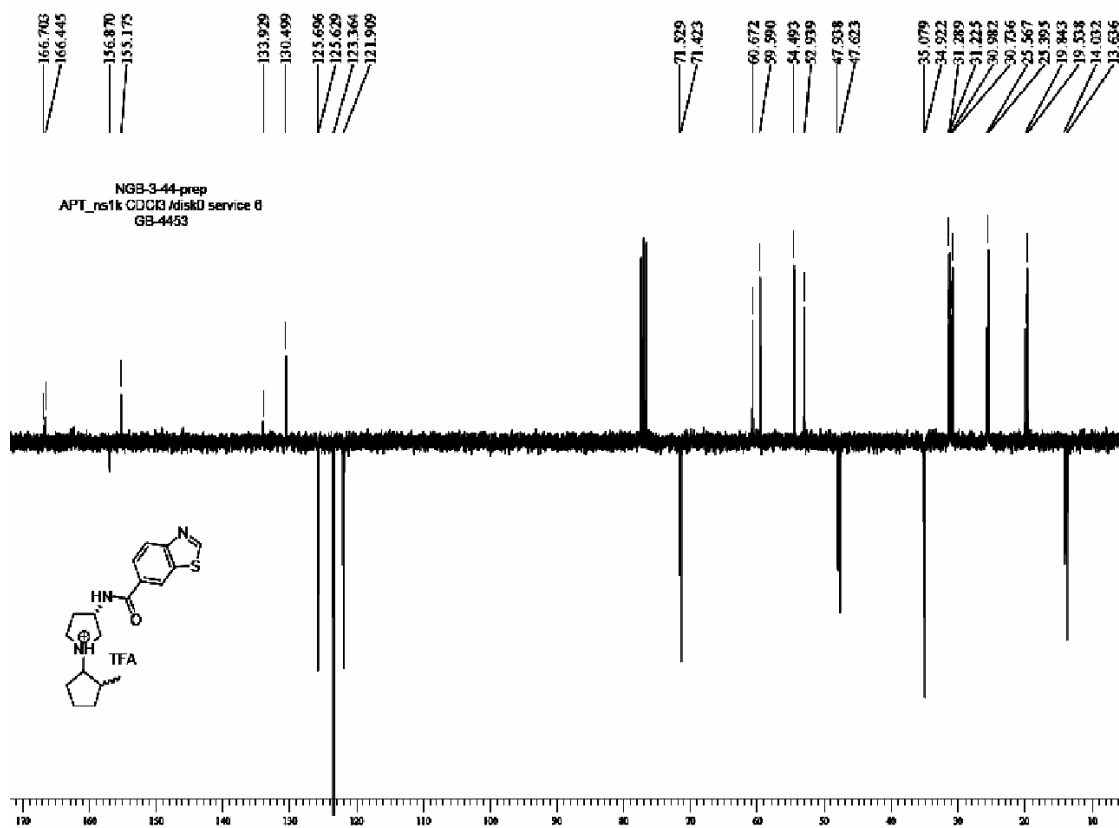
^1H NMR Spectrum of **8b** TFA salt (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **8b** TFA salt (CDCl_3 , 75 MHz)

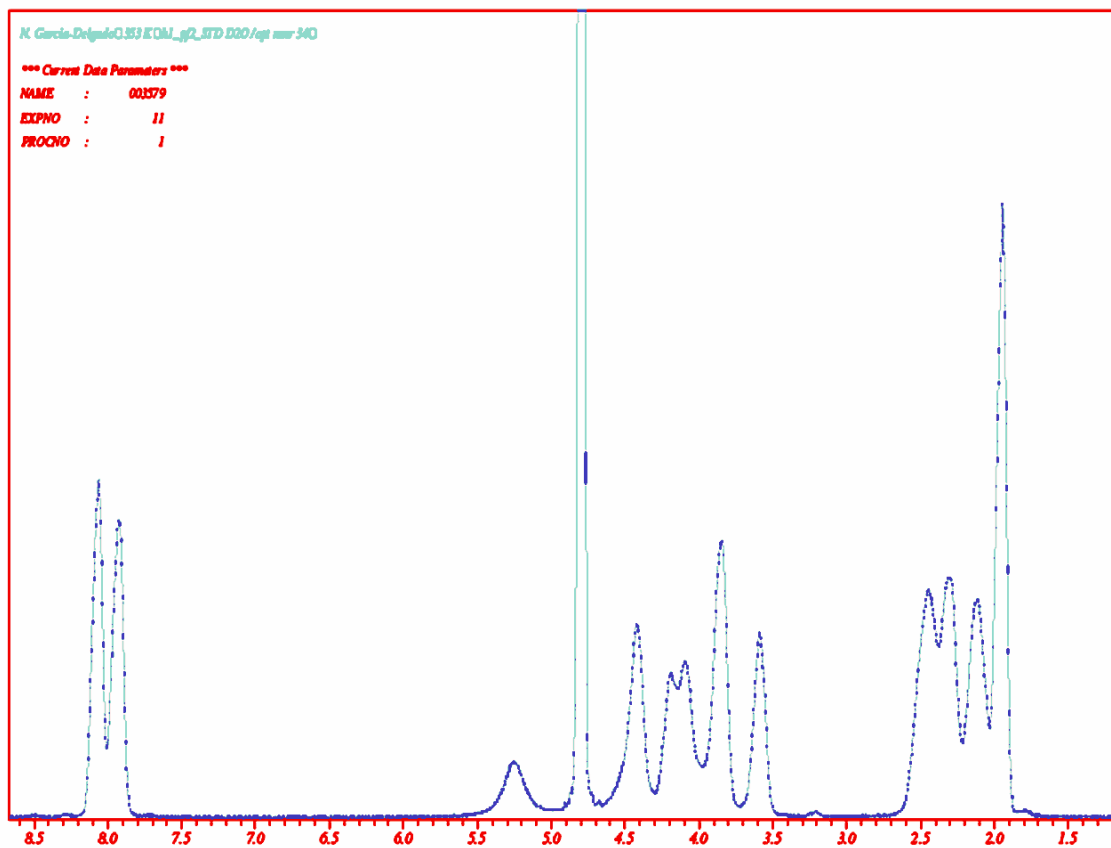
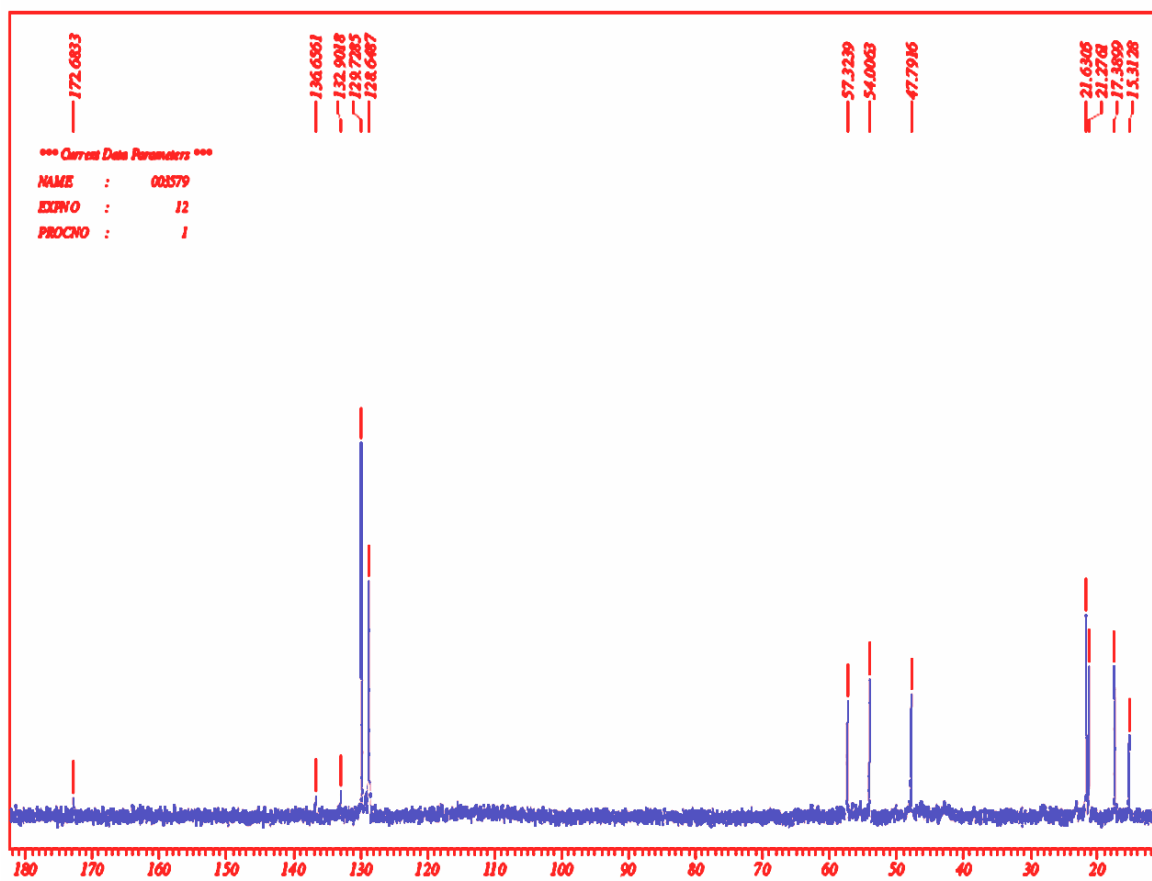
^1H NMR Spectrum of **8c** TFA salt (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **8c** TFA salt (CDCl_3 , 75 MHz)

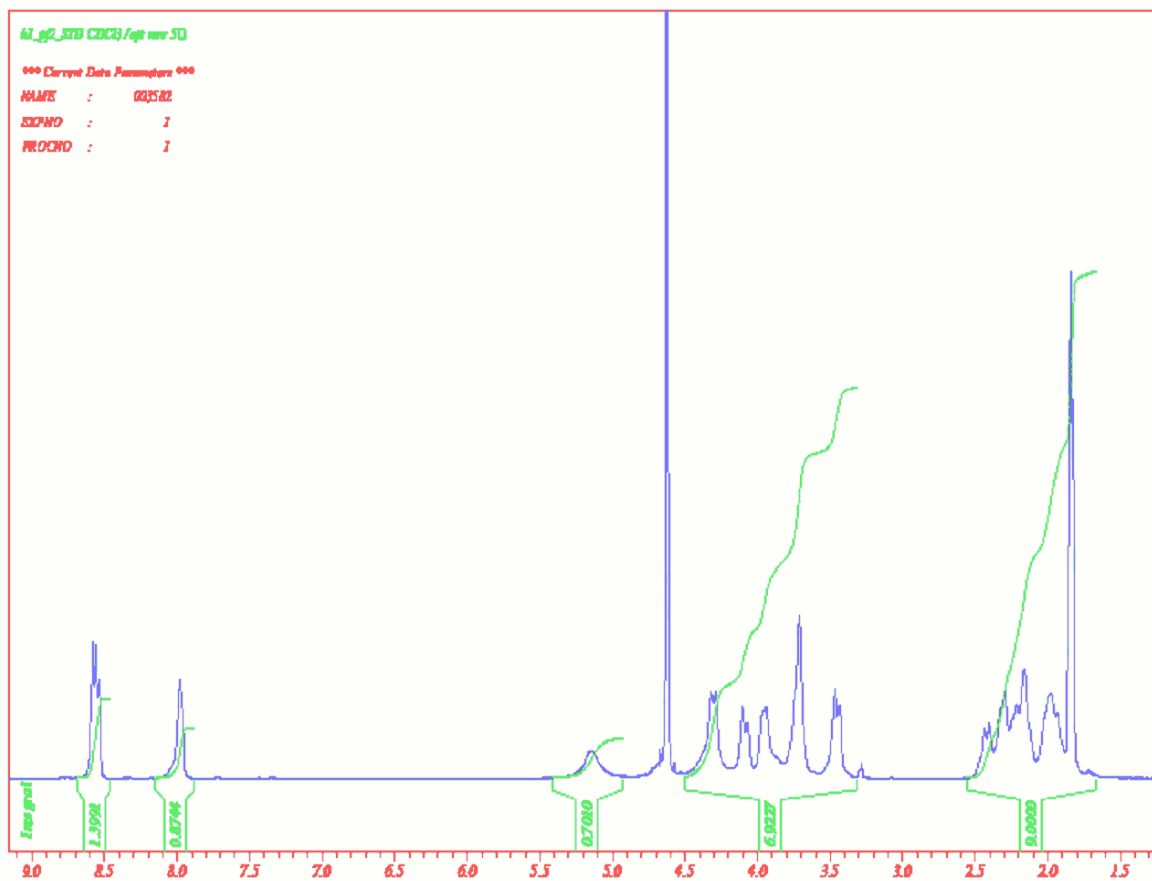
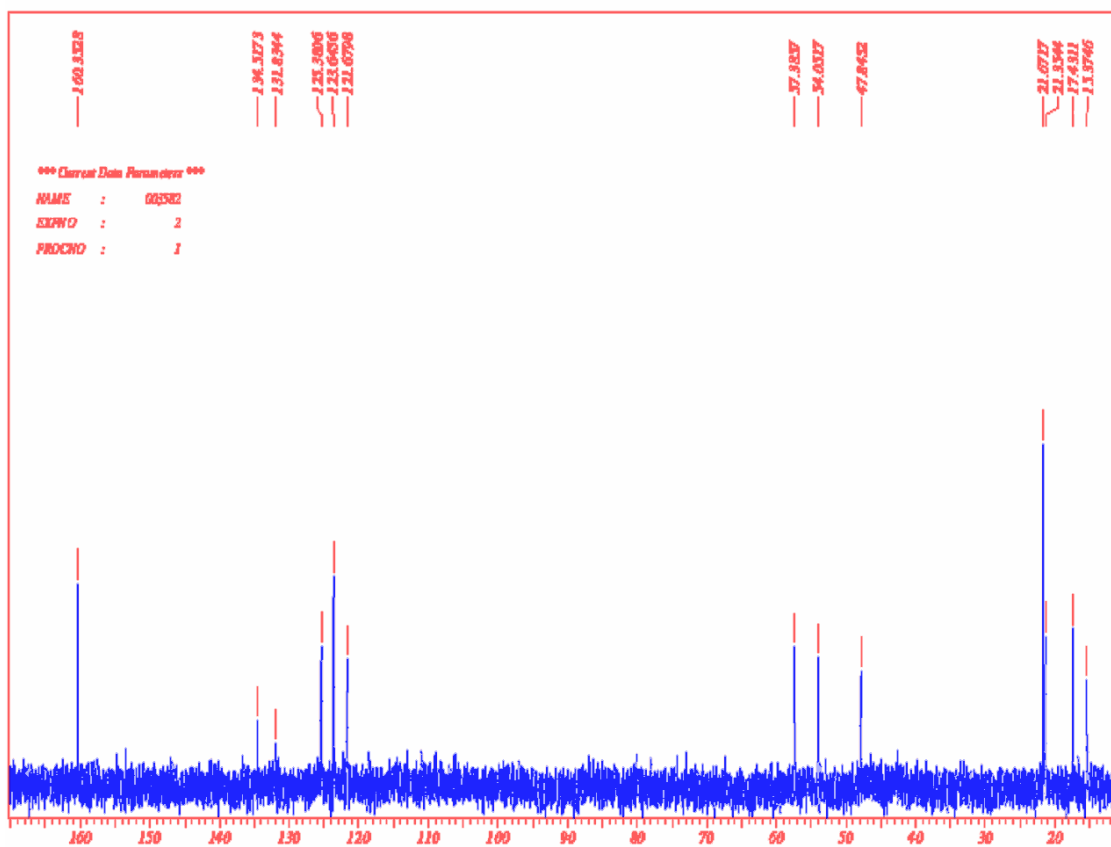
¹H NMR Spectrum of **8d** TFA salt (CDCl₃, 300 MHz)ATP-¹³C NMR Spectrum of **8d** TFA salt (CDCl₃, 75 MHz)

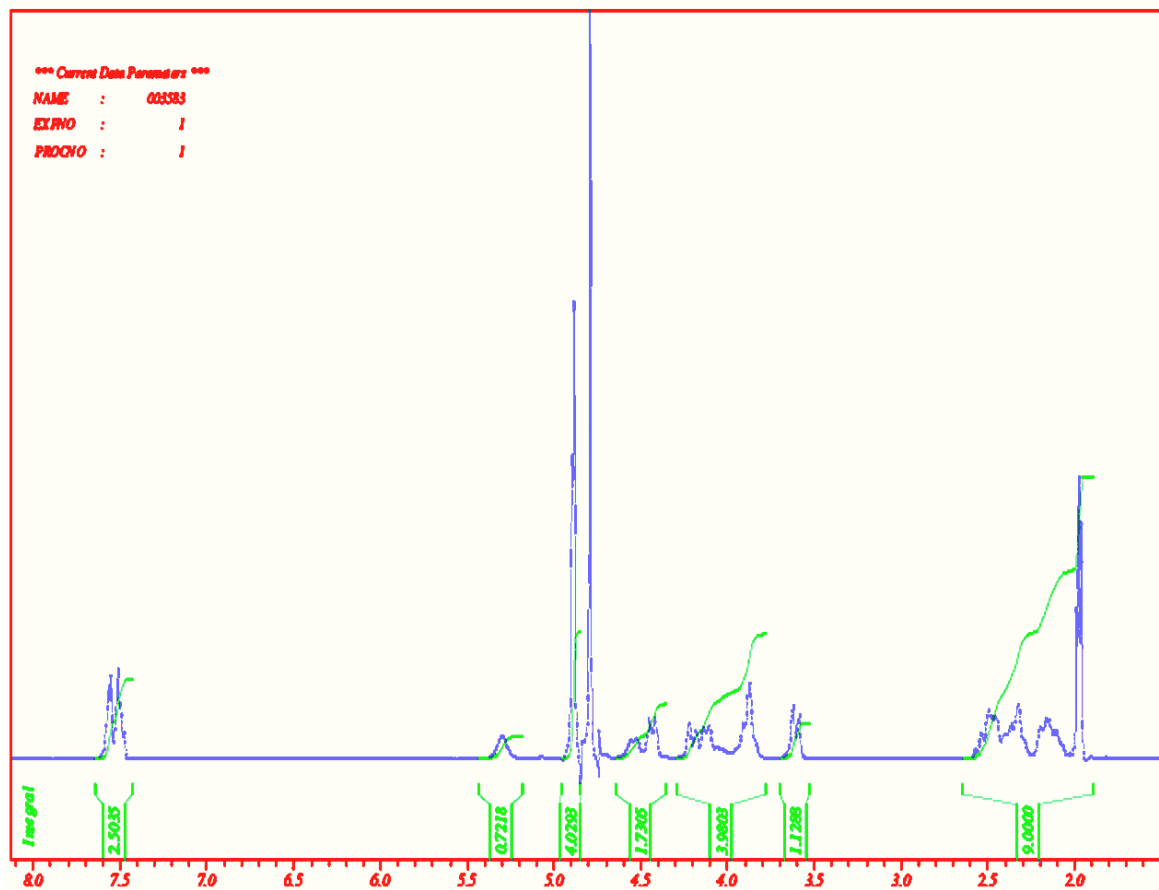
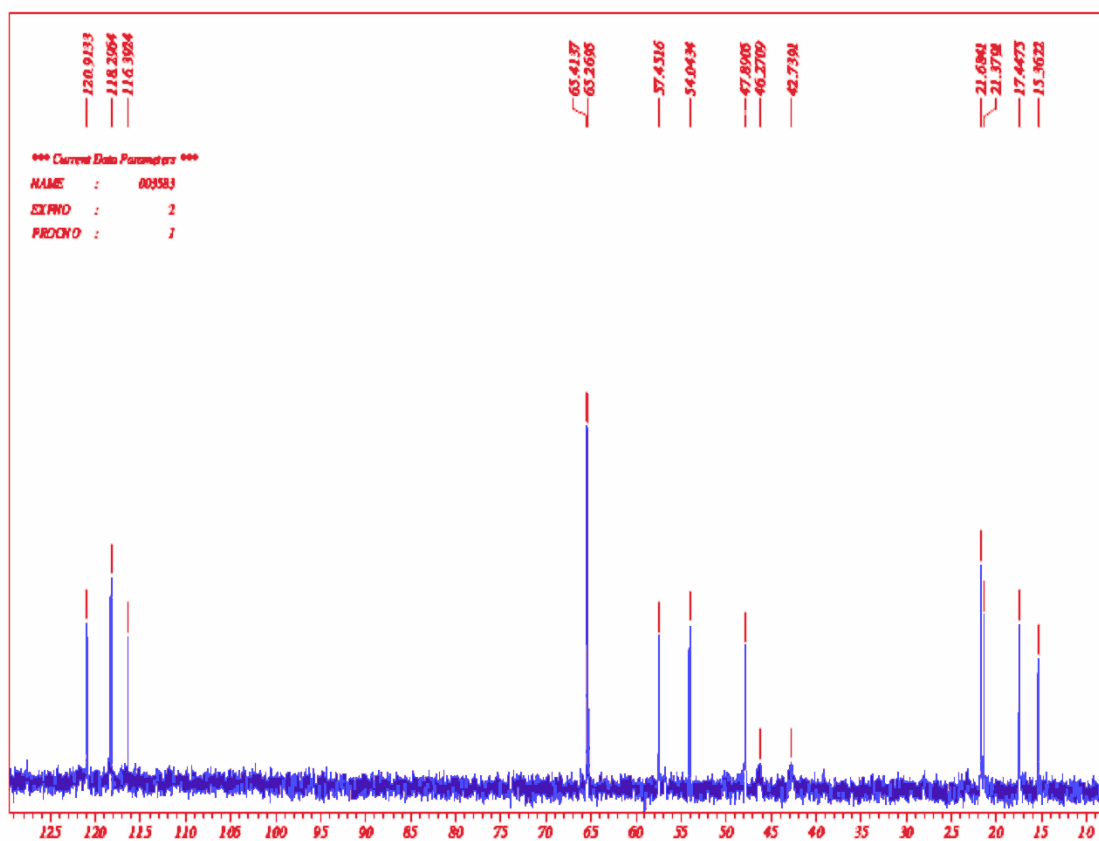
^1H NMR Spectrum of **8e** TFA salt (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **8e** TFA salt (CDCl_3 , 75 MHz)

¹H NMR Spectrum of **9a** TFA salt (CDCl₃, 300 MHz)APT-¹³C NMR Spectrum of **9a** TFA salt (CDCl₃, 75 MHz)

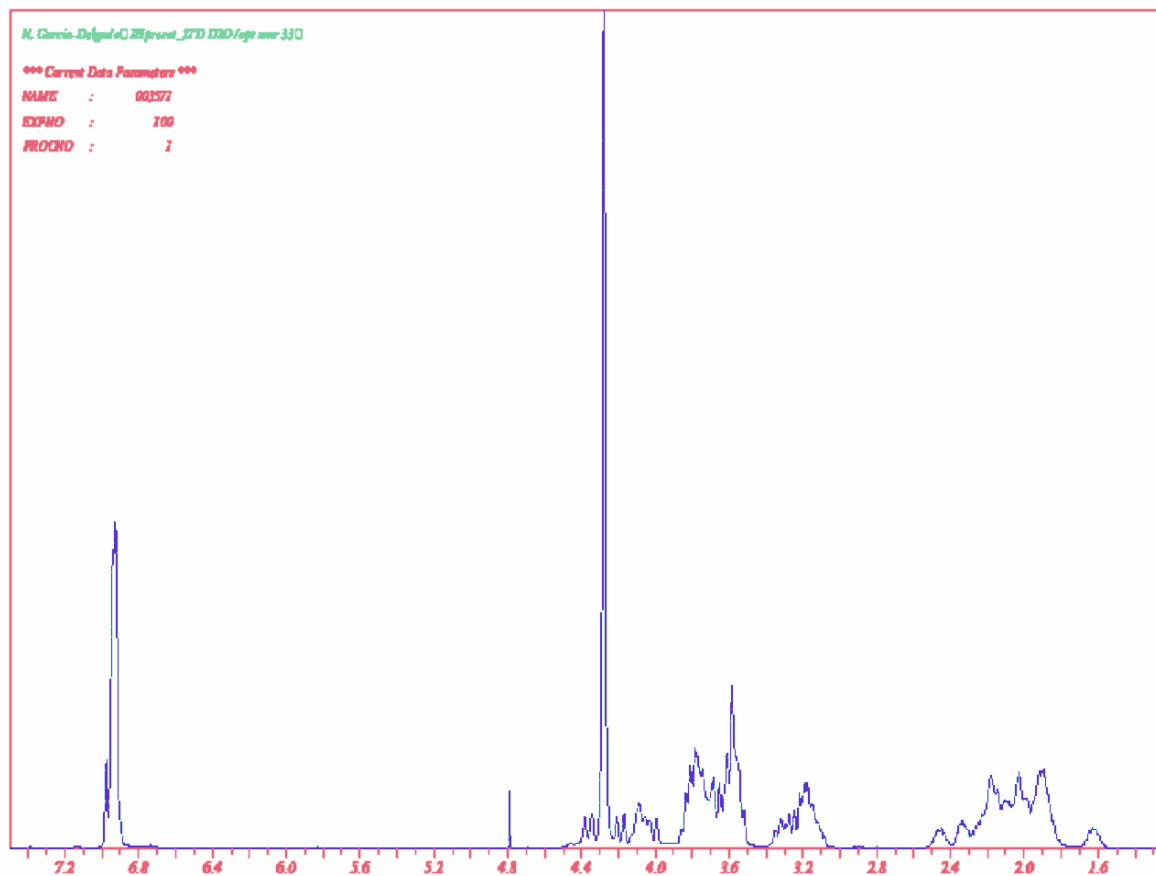
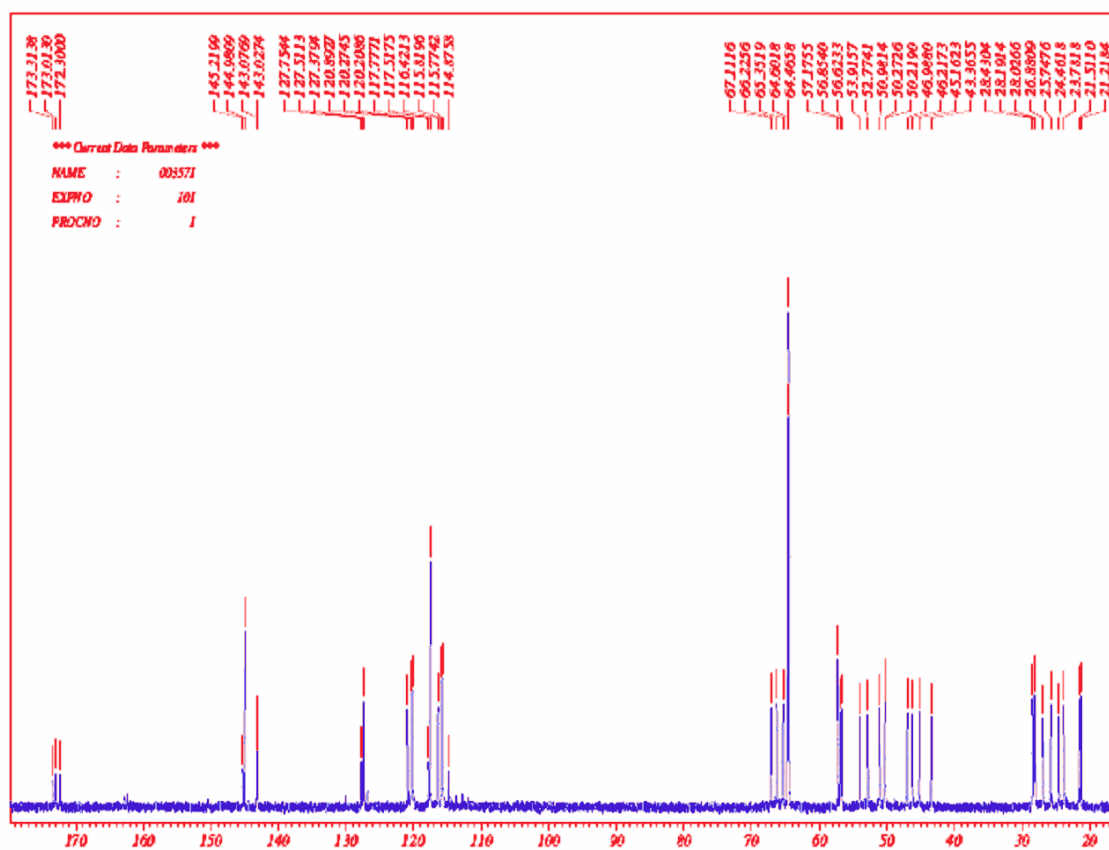
^1H NMR Spectrum of **9b** TFA salt (CDCl_3 , 300 MHz)APT- ^{13}C NMR Spectrum of **9b** TFA salt (CDCl_3 , 75 MHz)

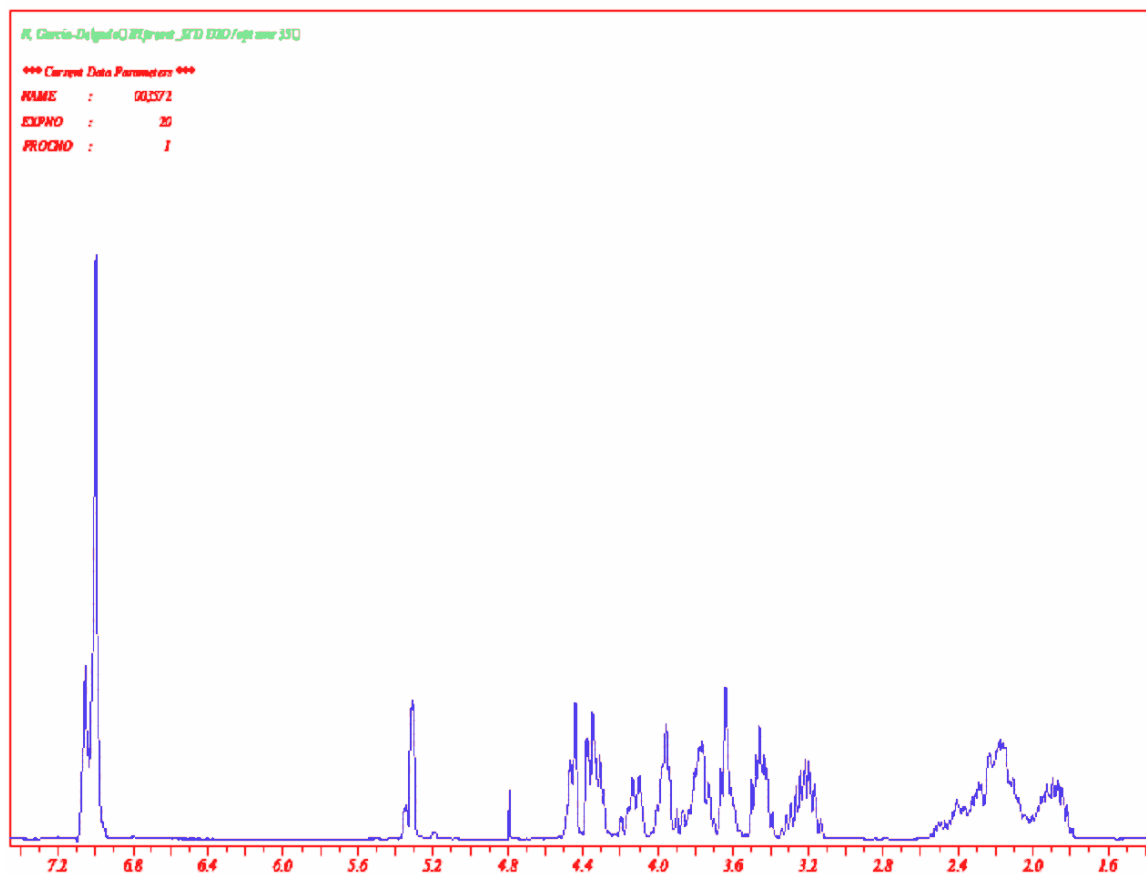
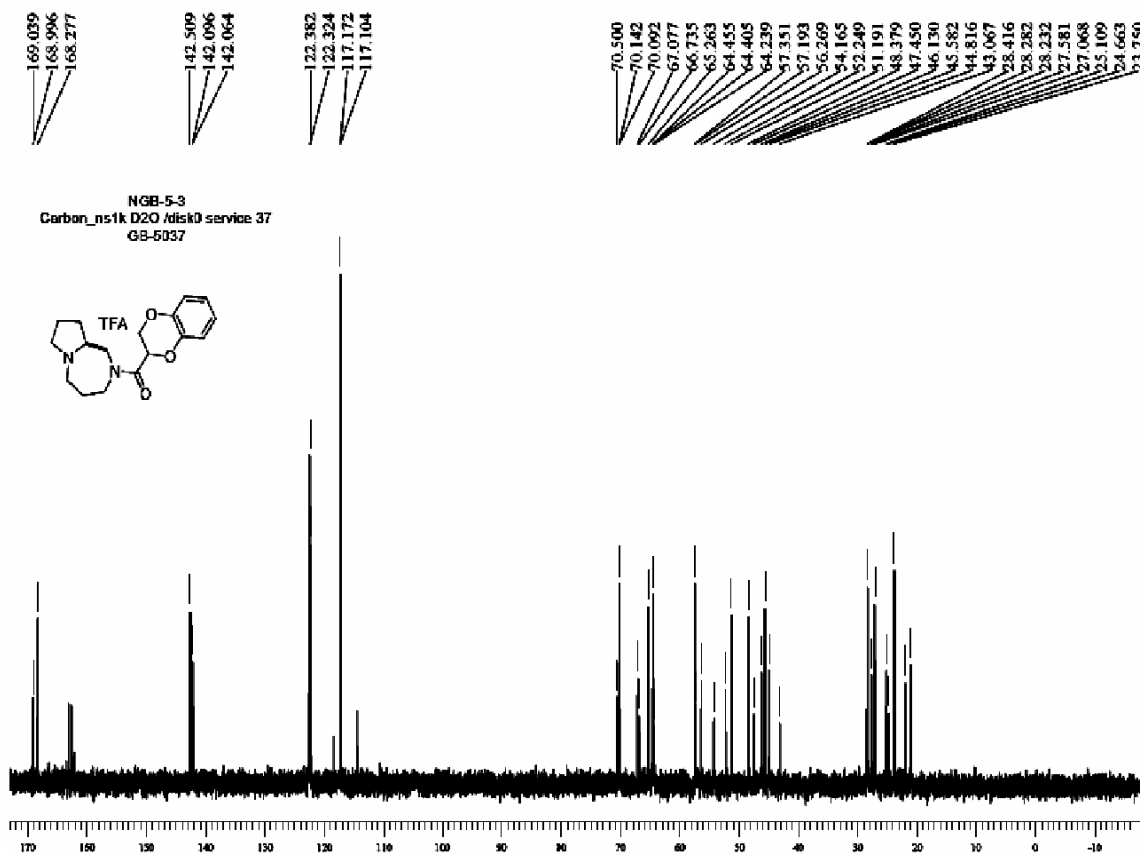
^1H NMR Spectrum of **10a** TFA salt (D_2O , 300 MHz) ^{13}C NMR Spectrum of **10a** TFA salt (D_2O , 75 MHz)

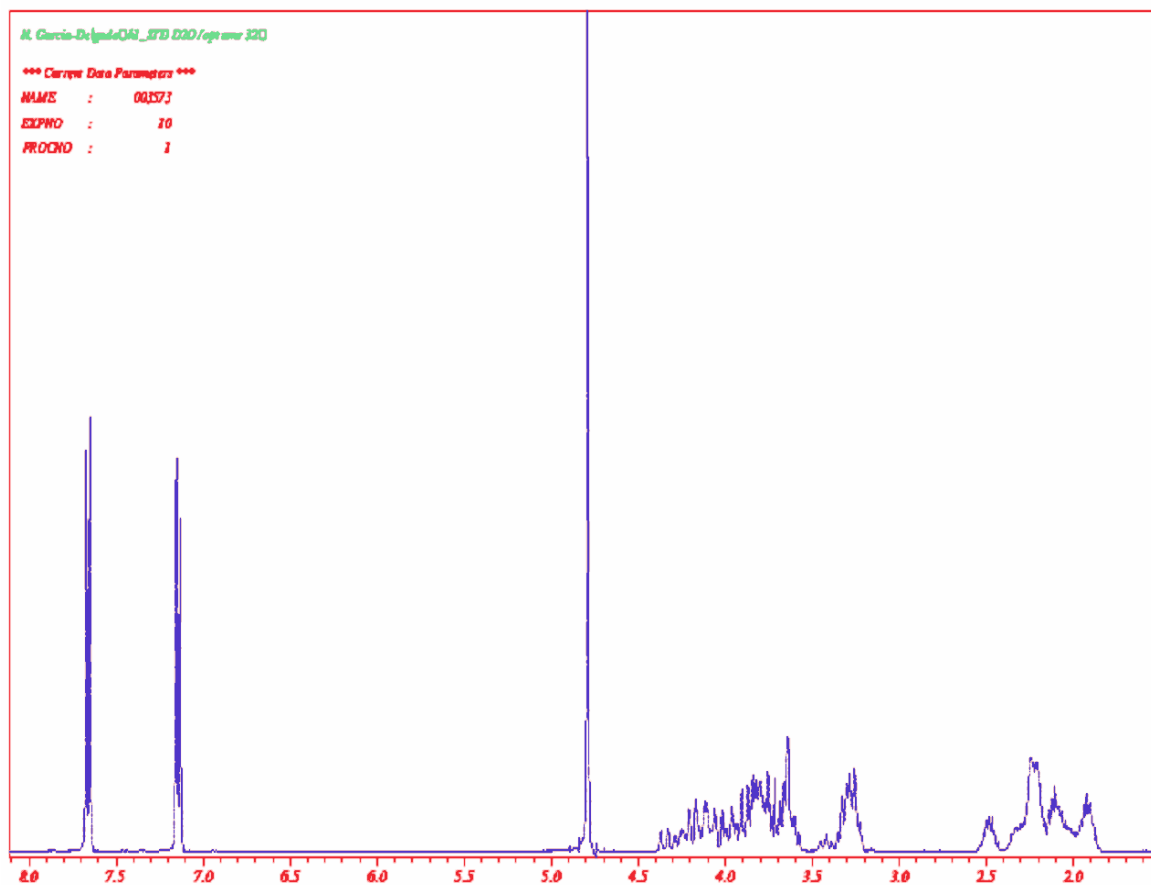
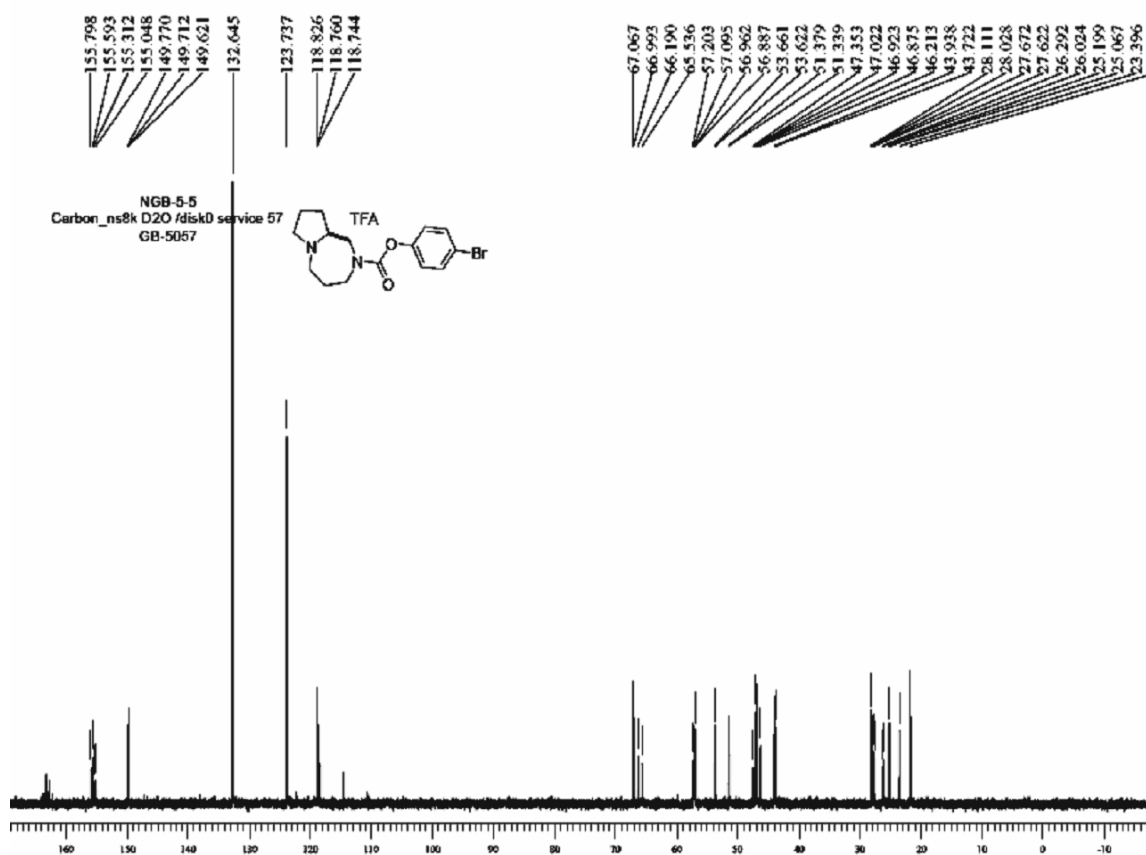
^1H NMR Spectrum of **10b** TFA salt (D_2O , 300 MHz) ^{13}C NMR Spectrum of **10b** TFA salt (D_2O , 75 MHz)

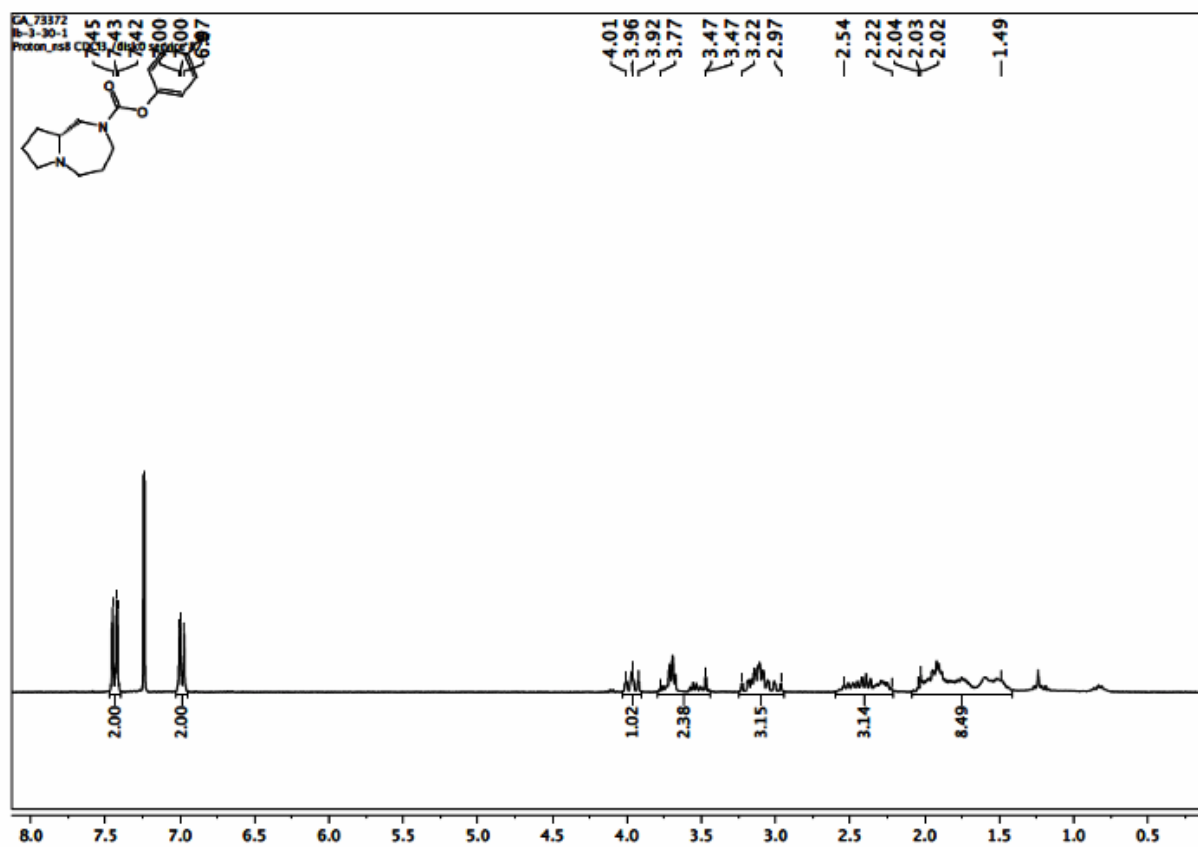
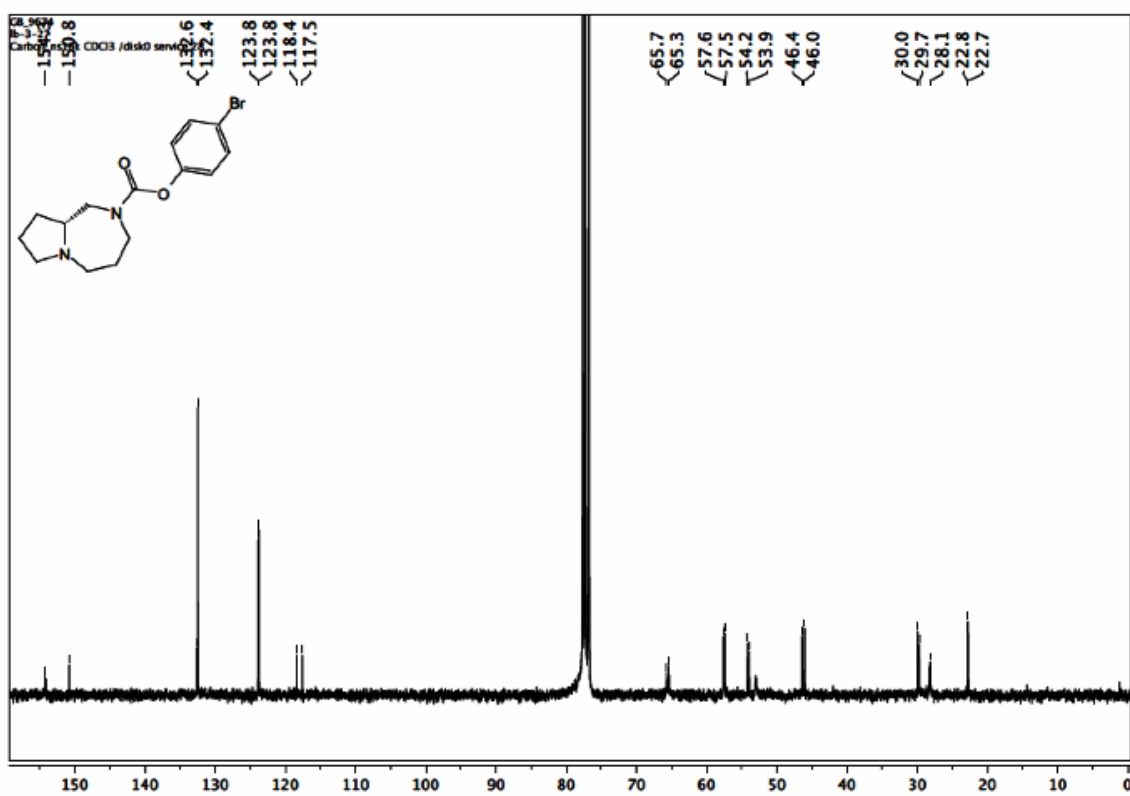
^1H NMR Spectrum of **10c** TFA salt (D_2O , 300 MHz) ^{13}C NMR Spectrum of **10c** TFA salt (D_2O , 75 MHz)

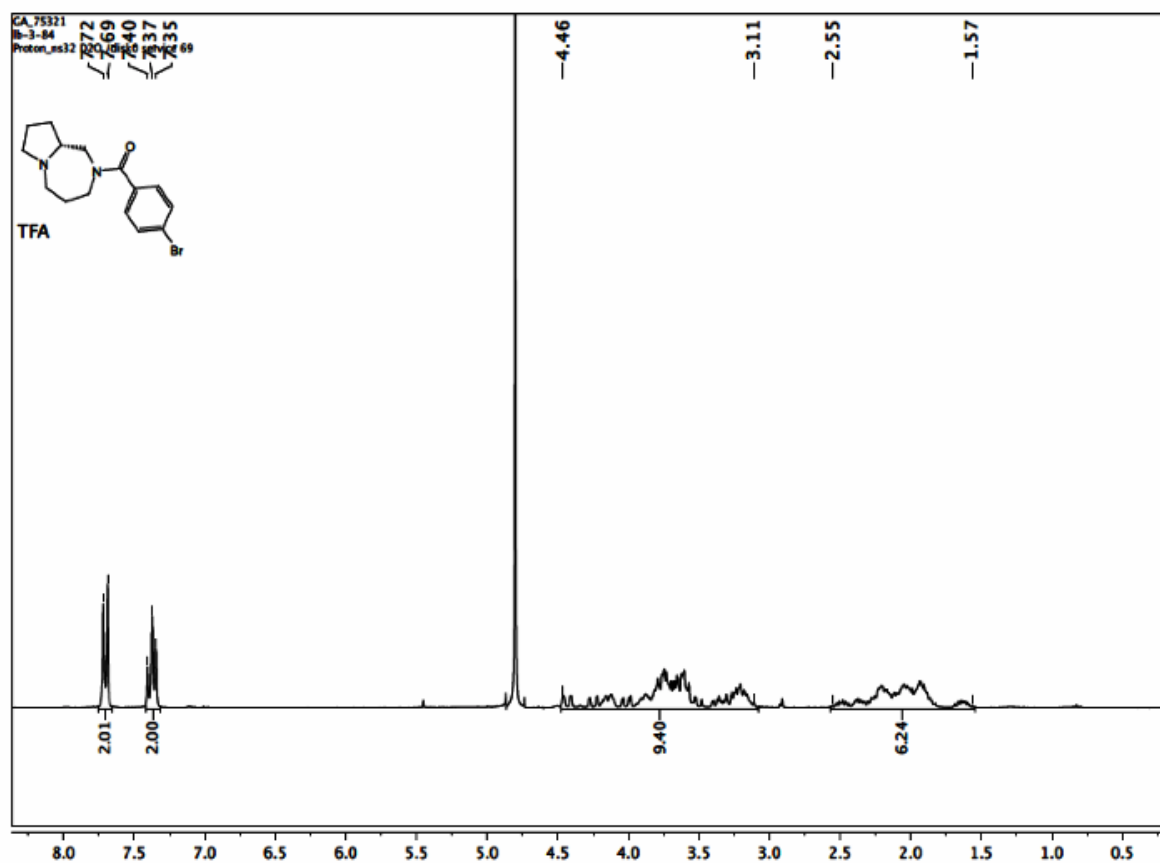
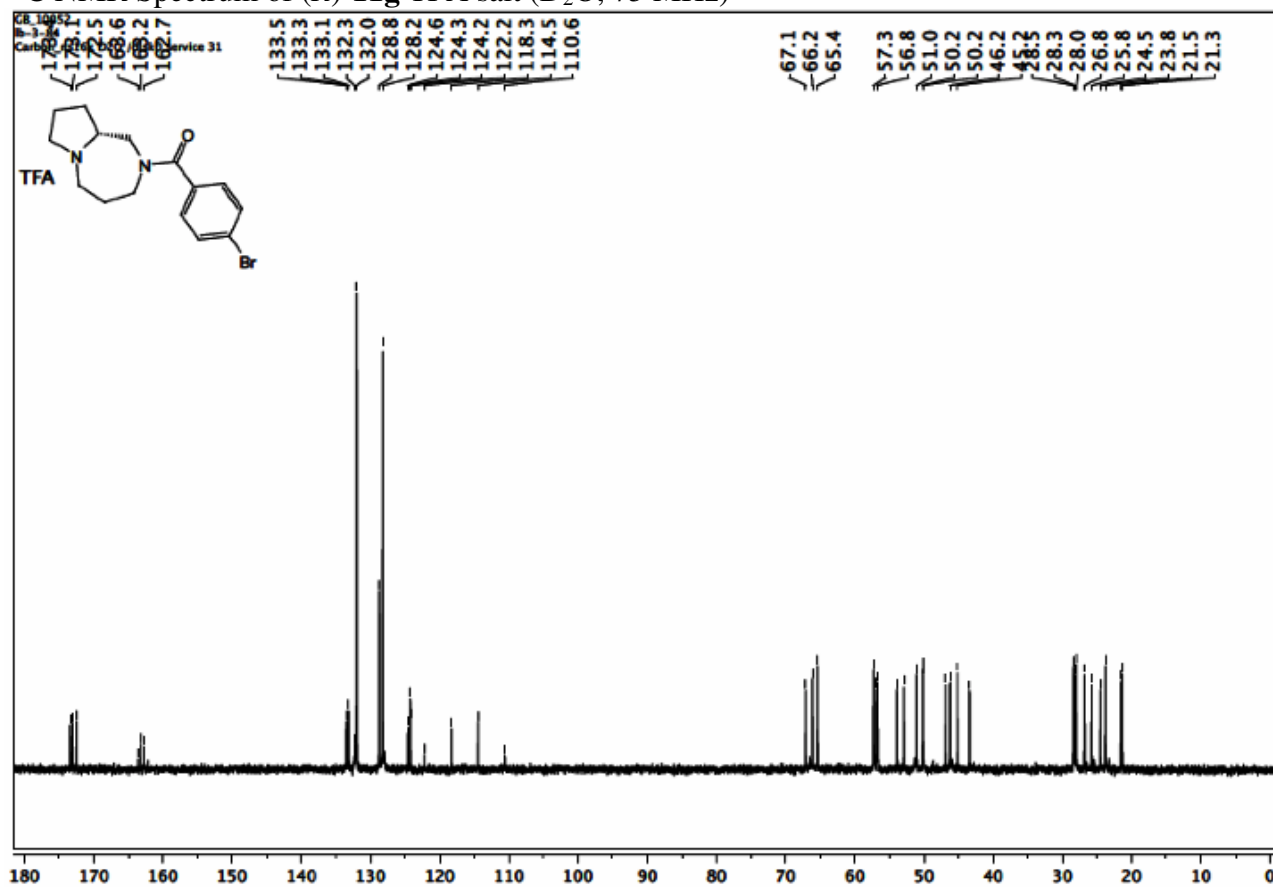
¹H NMR Spectrum of (*S*)-**11a** TFA salt (D₂O, 300 MHz)¹³C NMR Spectrum of (*S*)-**11a** TFA salt (D₂O, 75 MHz)

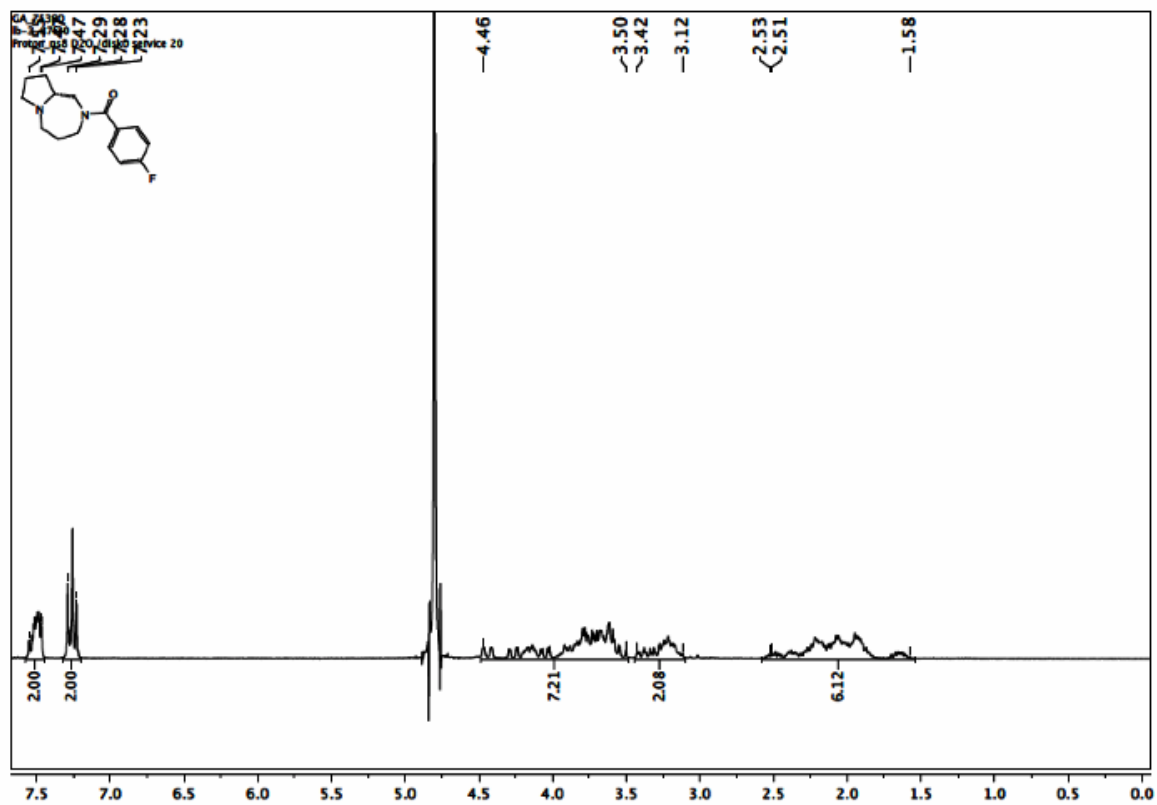
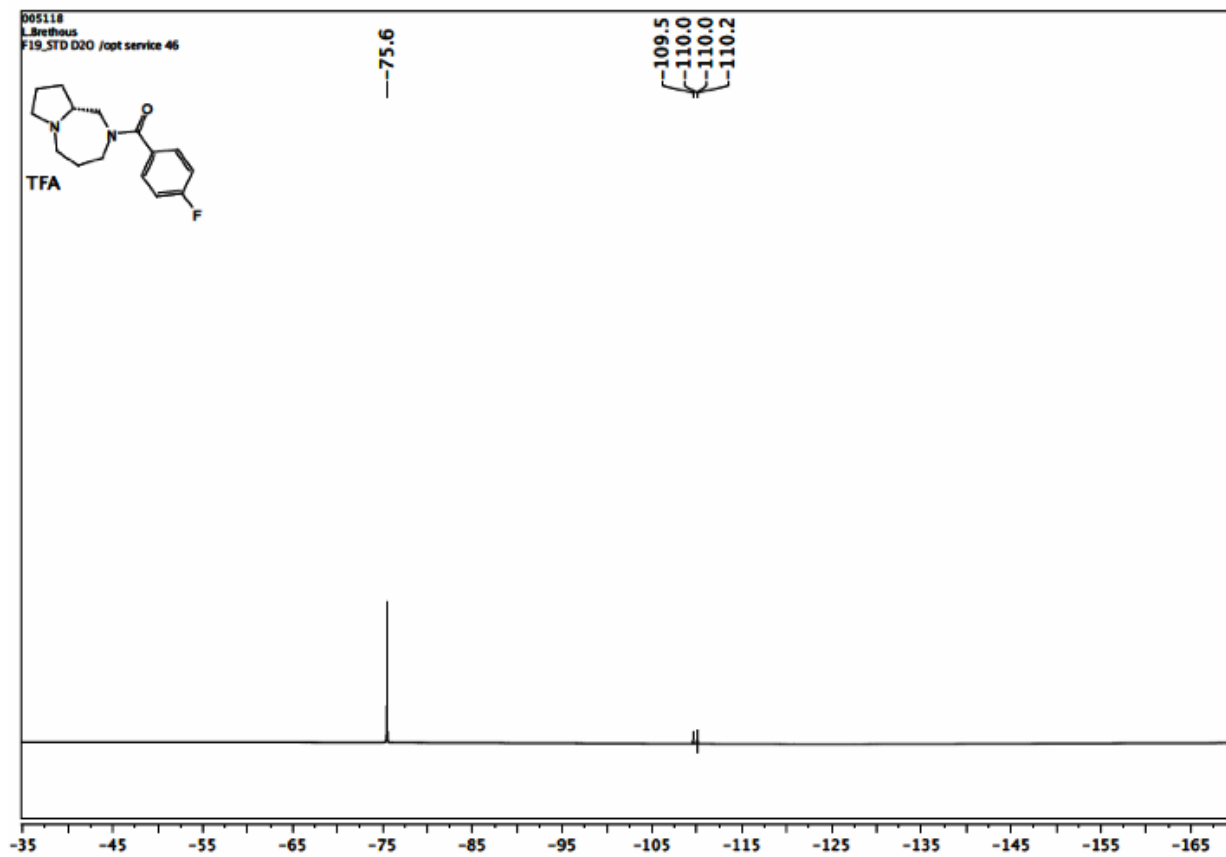
^1H NMR Spectrum of (*S*)-**11c** TFA salt (D_2O , 300 MHz) ^{13}C NMR Spectrum of (*S*)-**11c** TFA salt (D_2O , 75 MHz)

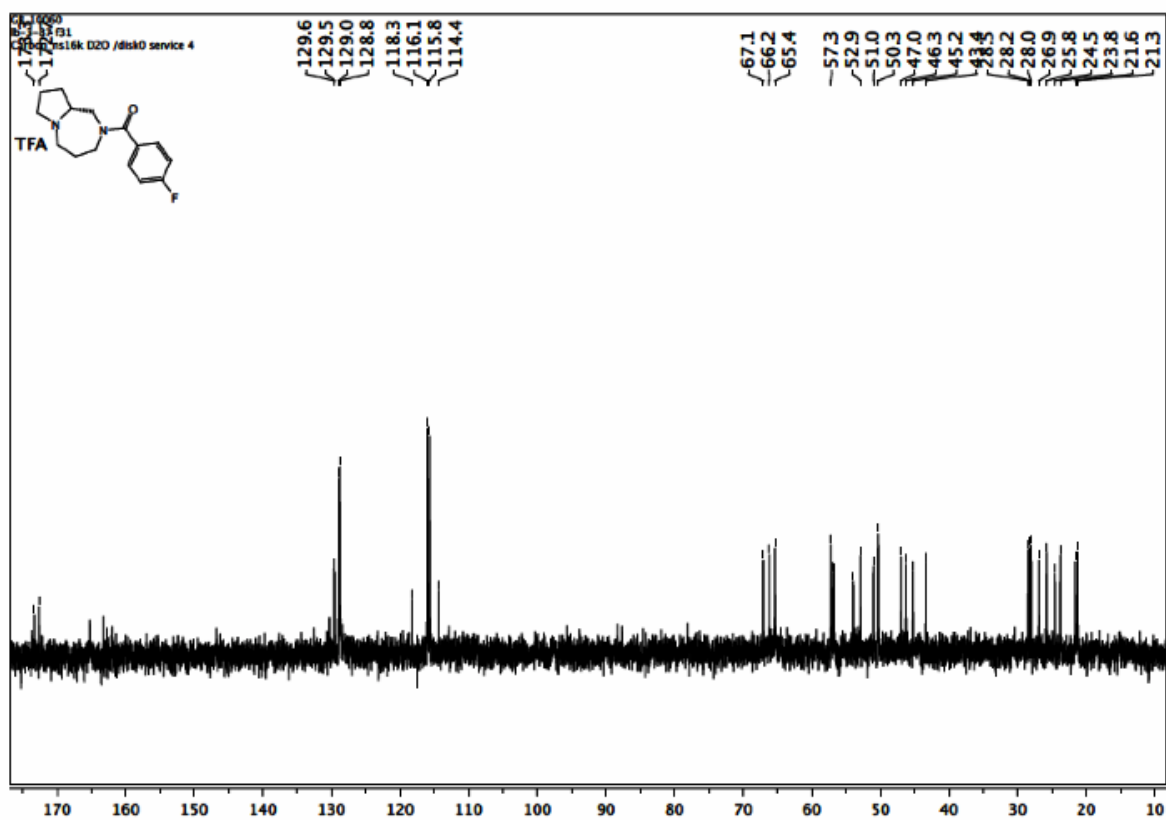
^1H NMR Spectrum of (*S*)-**11d** TFA salt (D_2O , 300 MHz) ^{13}C NMR Spectrum of (*S*)-**11d** TFA salt (D_2O , 75 MHz)

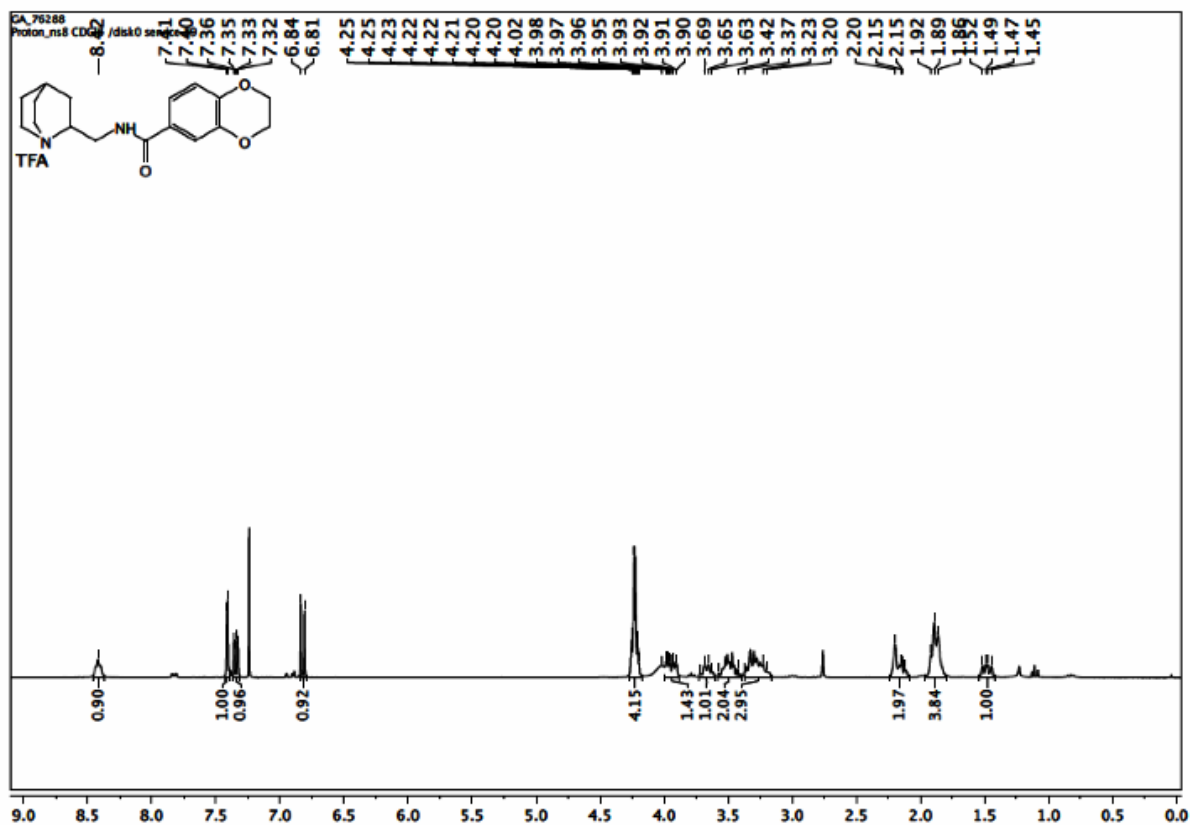
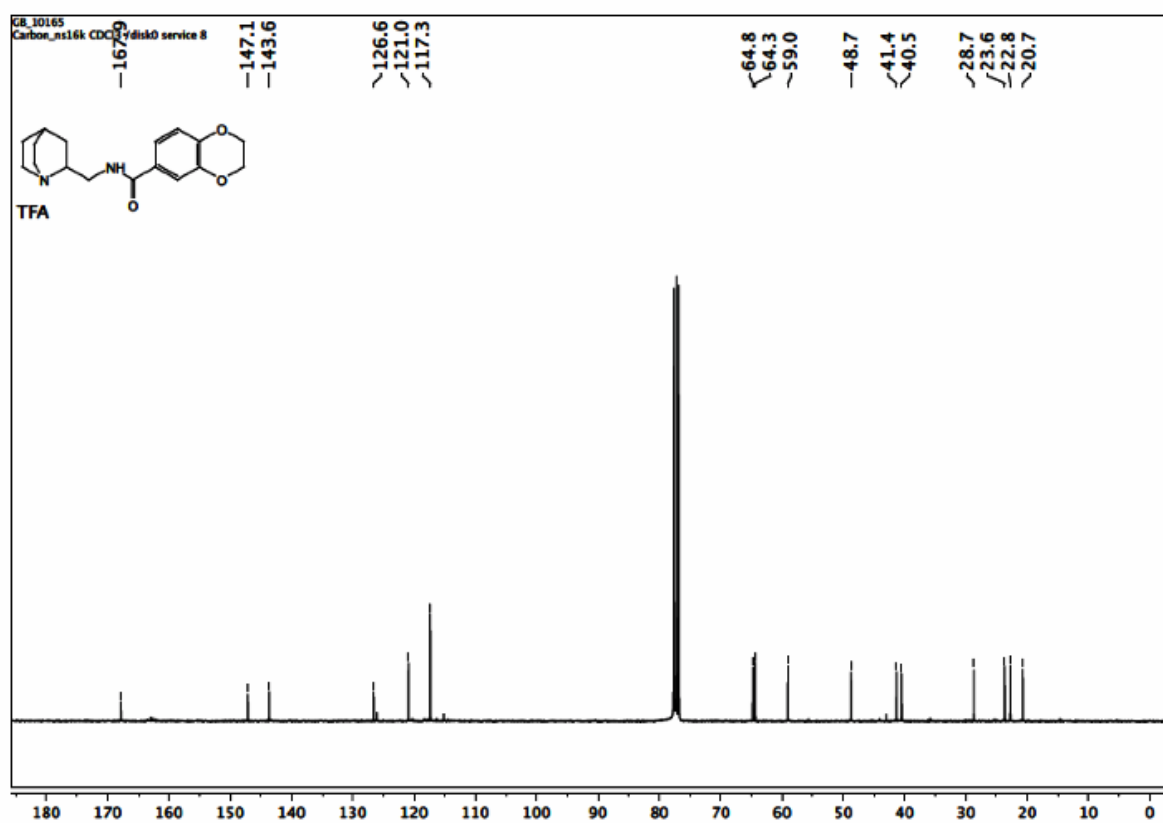
^1H NMR Spectrum of (*S*)-**11e** TFA salt (D_2O , 300 MHz) ^{13}C NMR Spectrum of (*S*)-**11e** TFA salt (D_2O , 75 MHz)

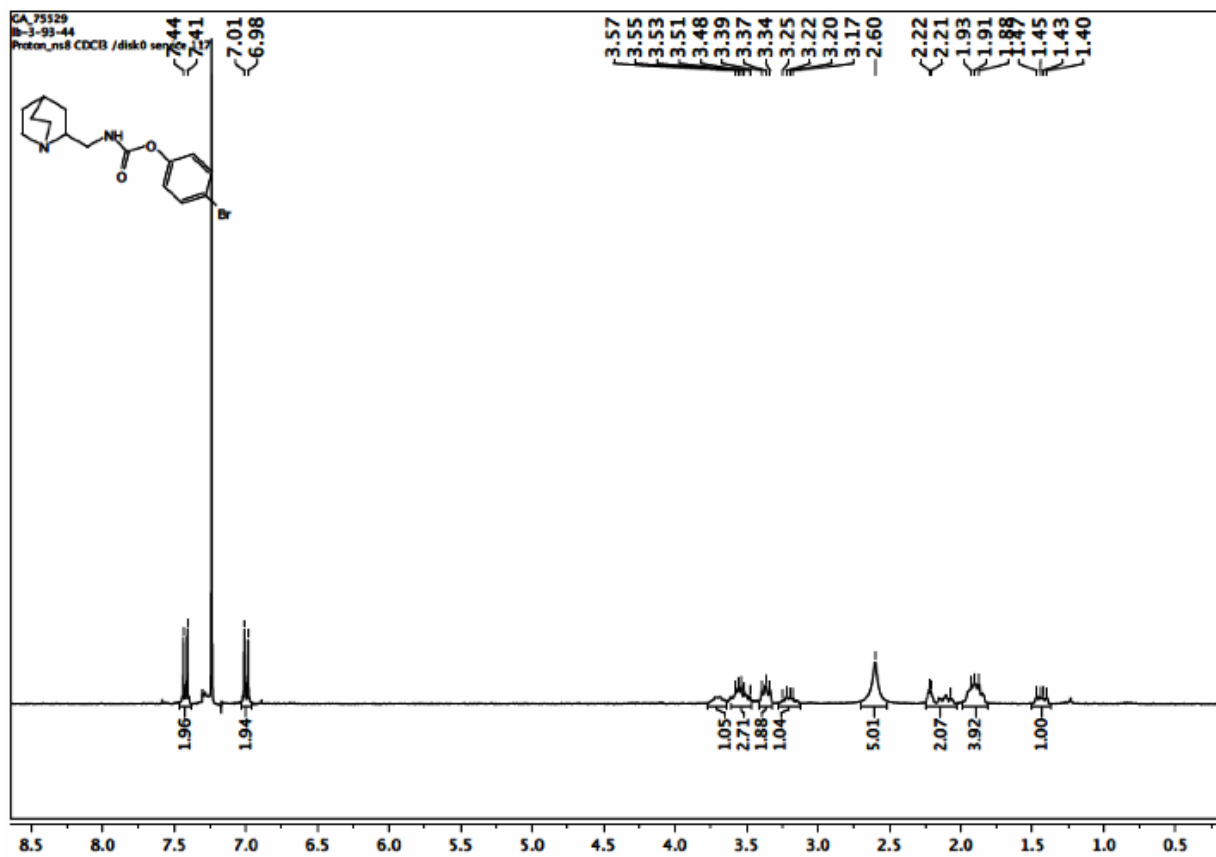
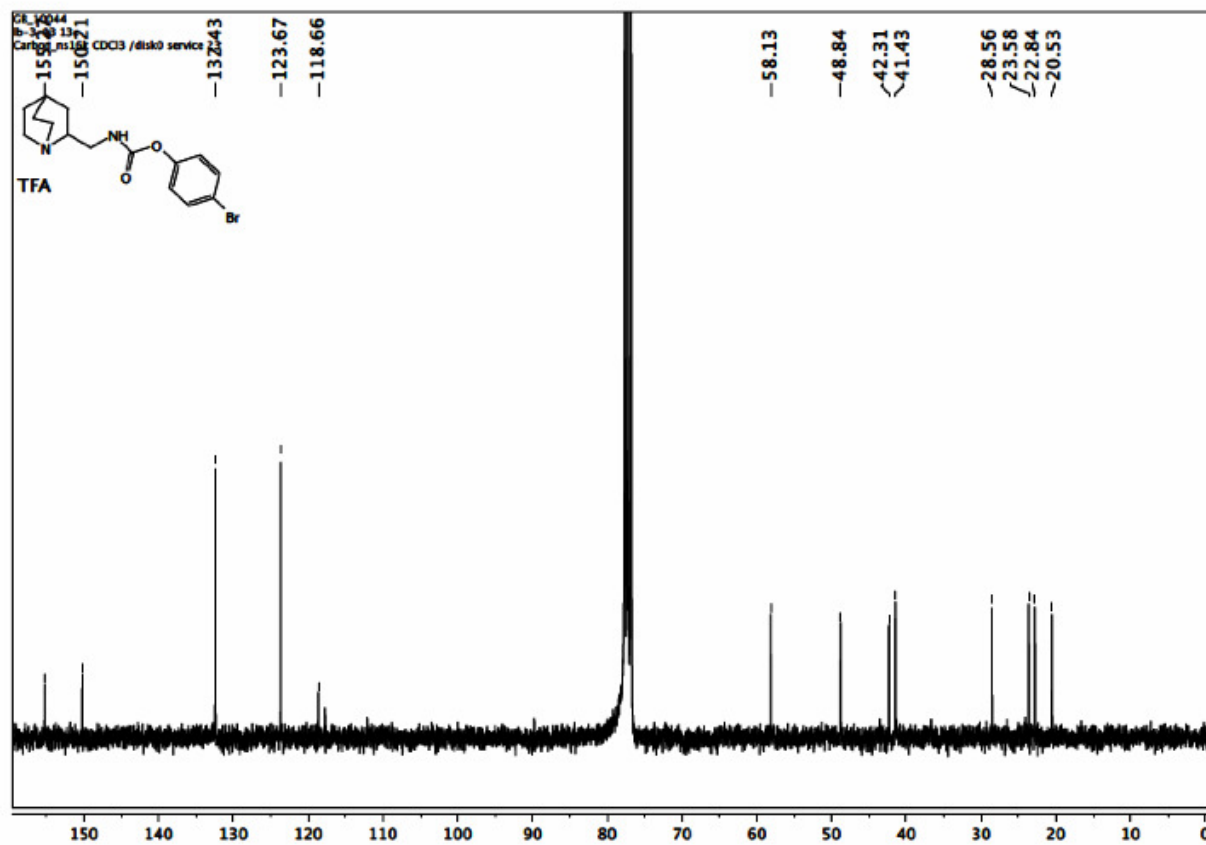
^1H NMR Spectrum of (*R*)-**11e** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of (*R*)-**11e** TFA salt (CDCl_3 , 75 MHz)

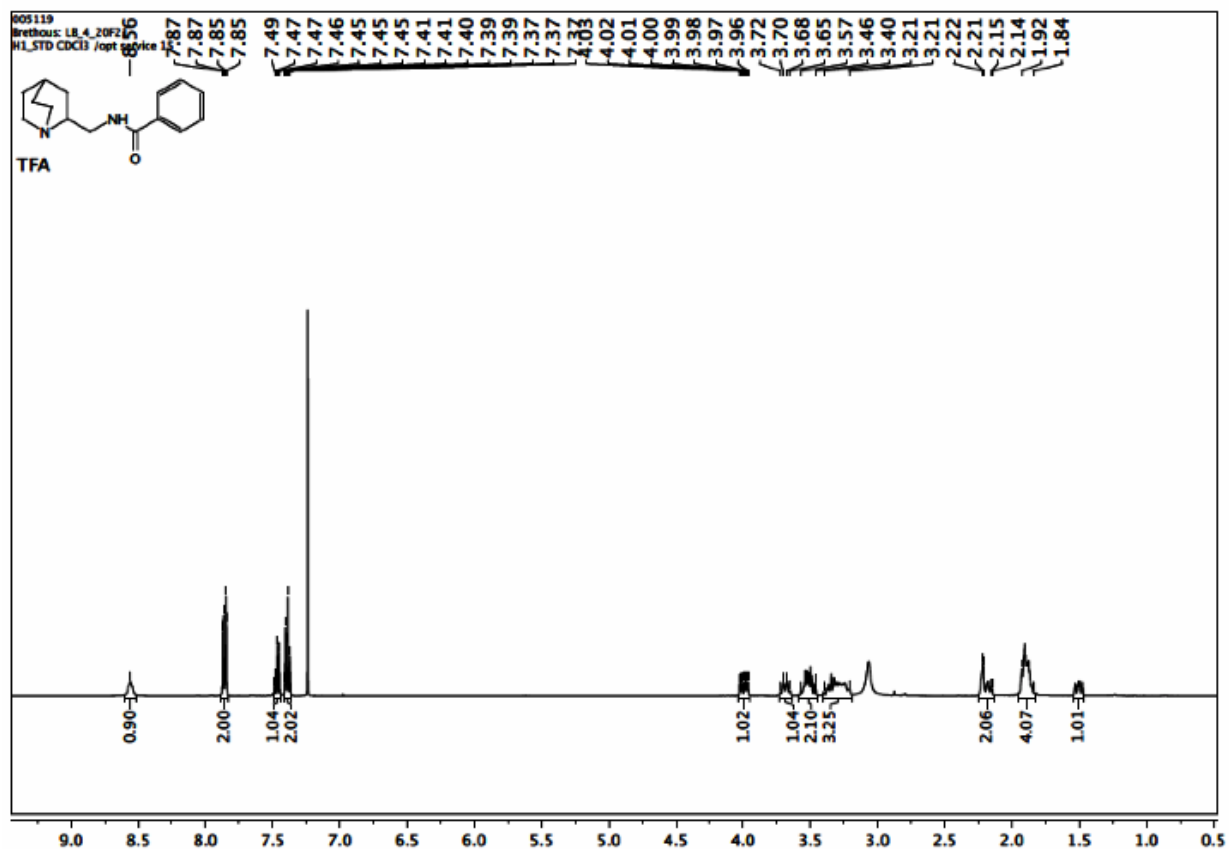
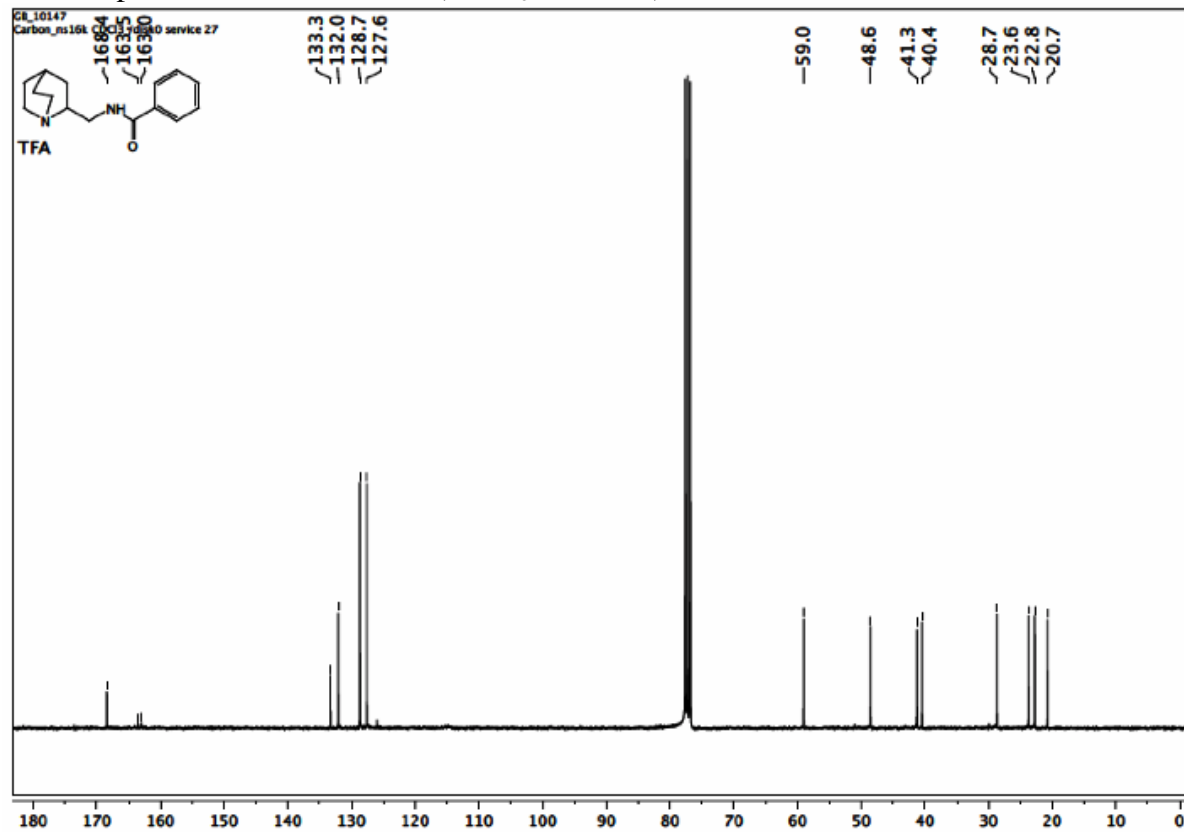
^1H NMR Spectrum of (*R*)-**11g** TFA salt (D_2O , 300 MHz) ^{13}C NMR Spectrum of (*R*)-**11g** TFA salt (D_2O , 75 MHz)

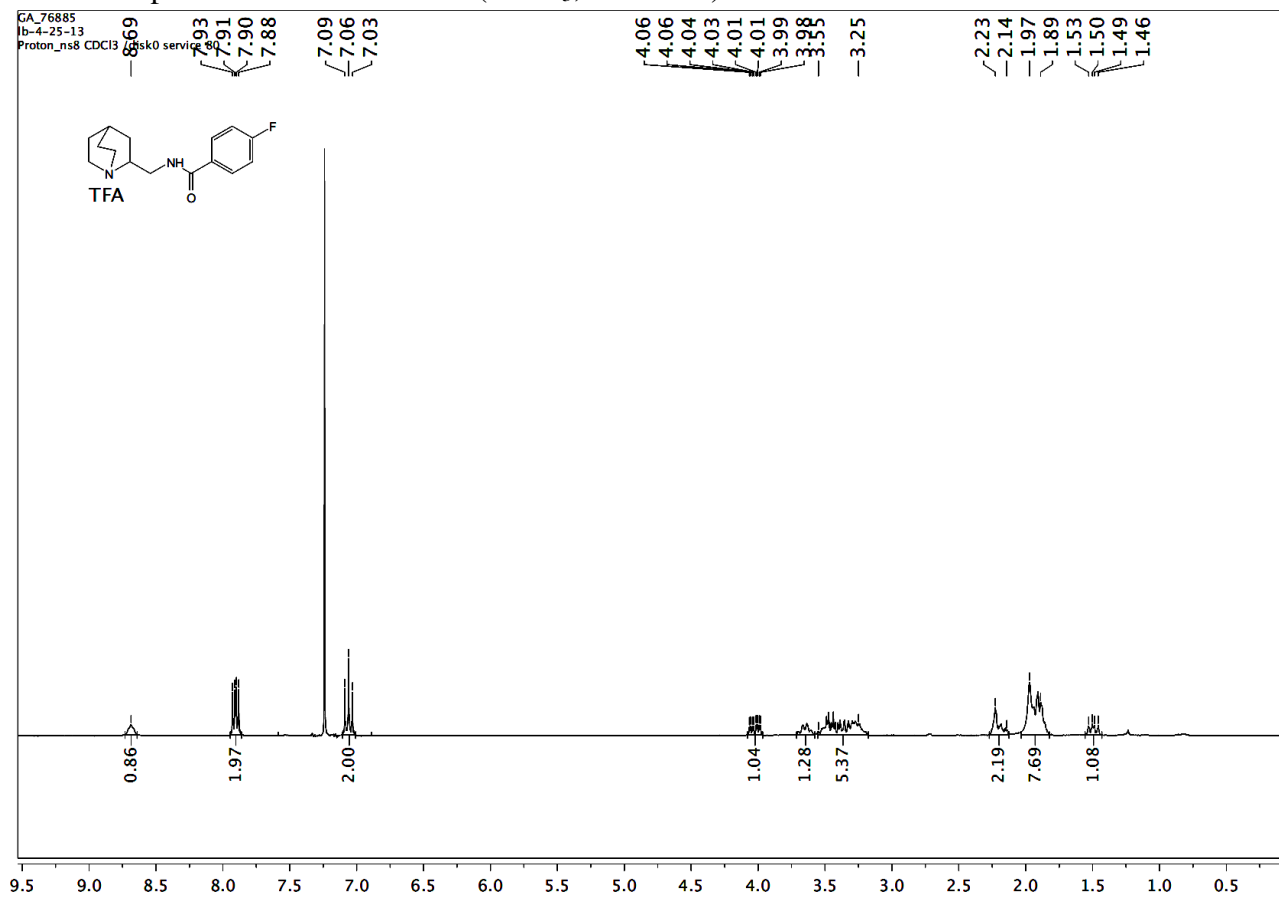
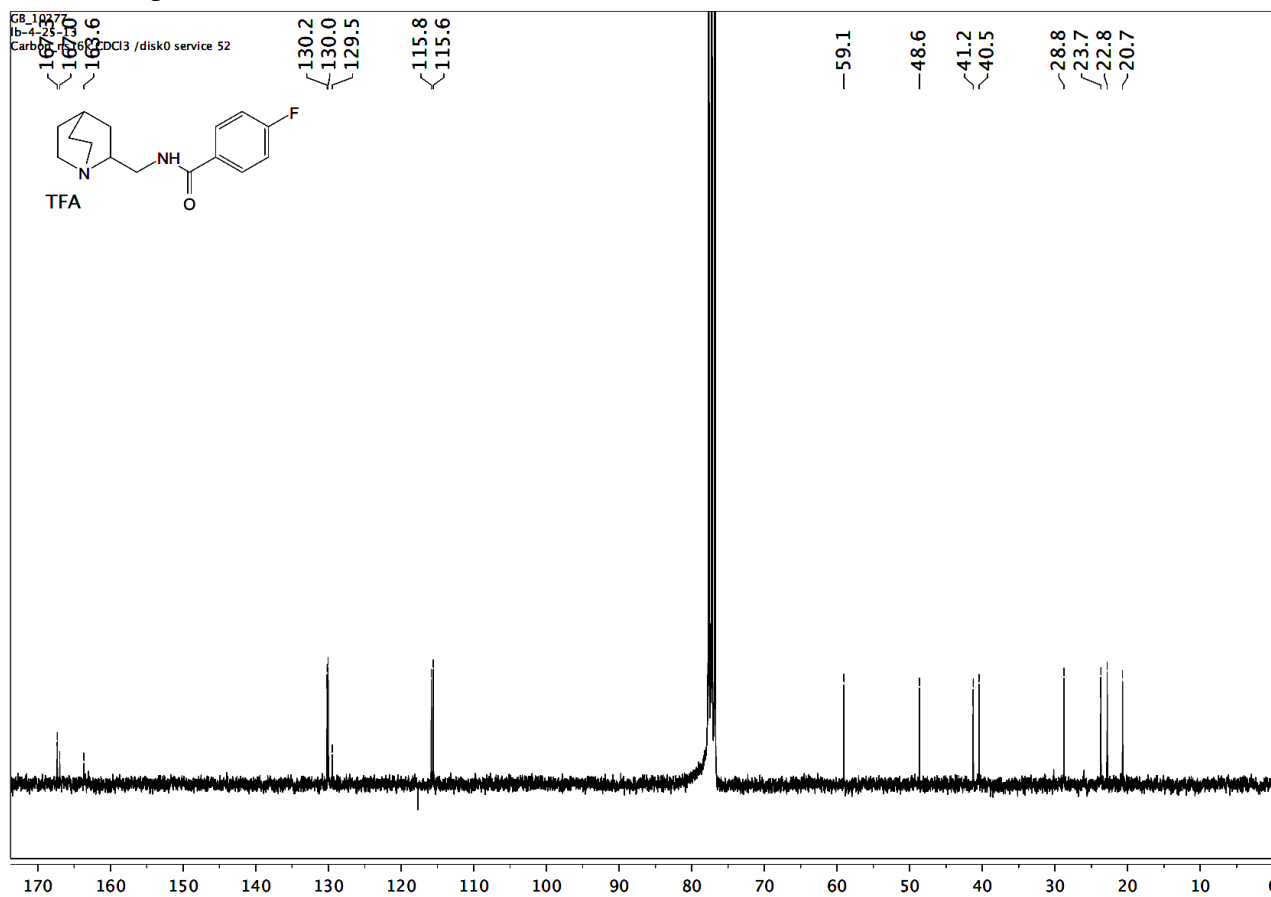
^1H NMR Spectrum of (*R*)-**11k** TFA salt (D_2O , 300 MHz) ^{19}F NMR Spectrum of (*R*)-**11k** TFA salt (D_2O , 376 MHz)

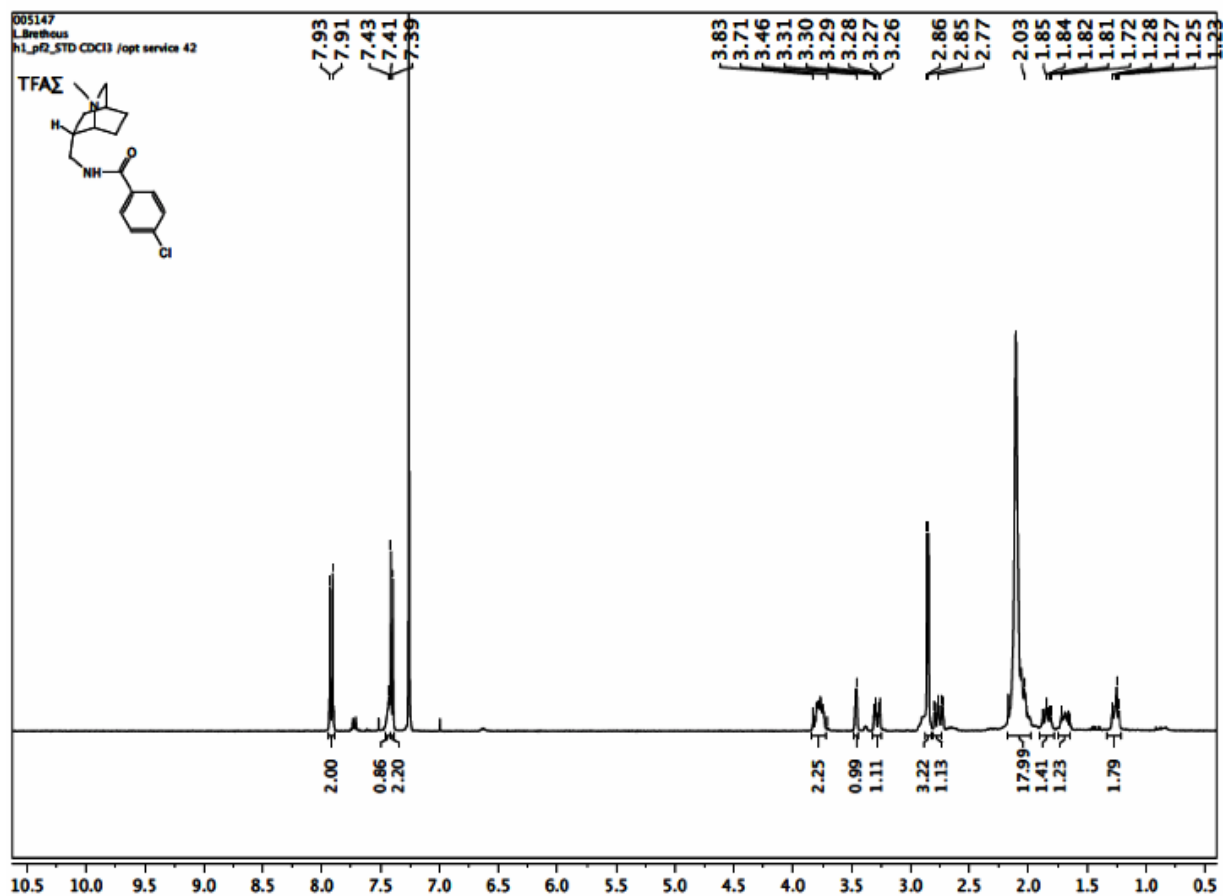
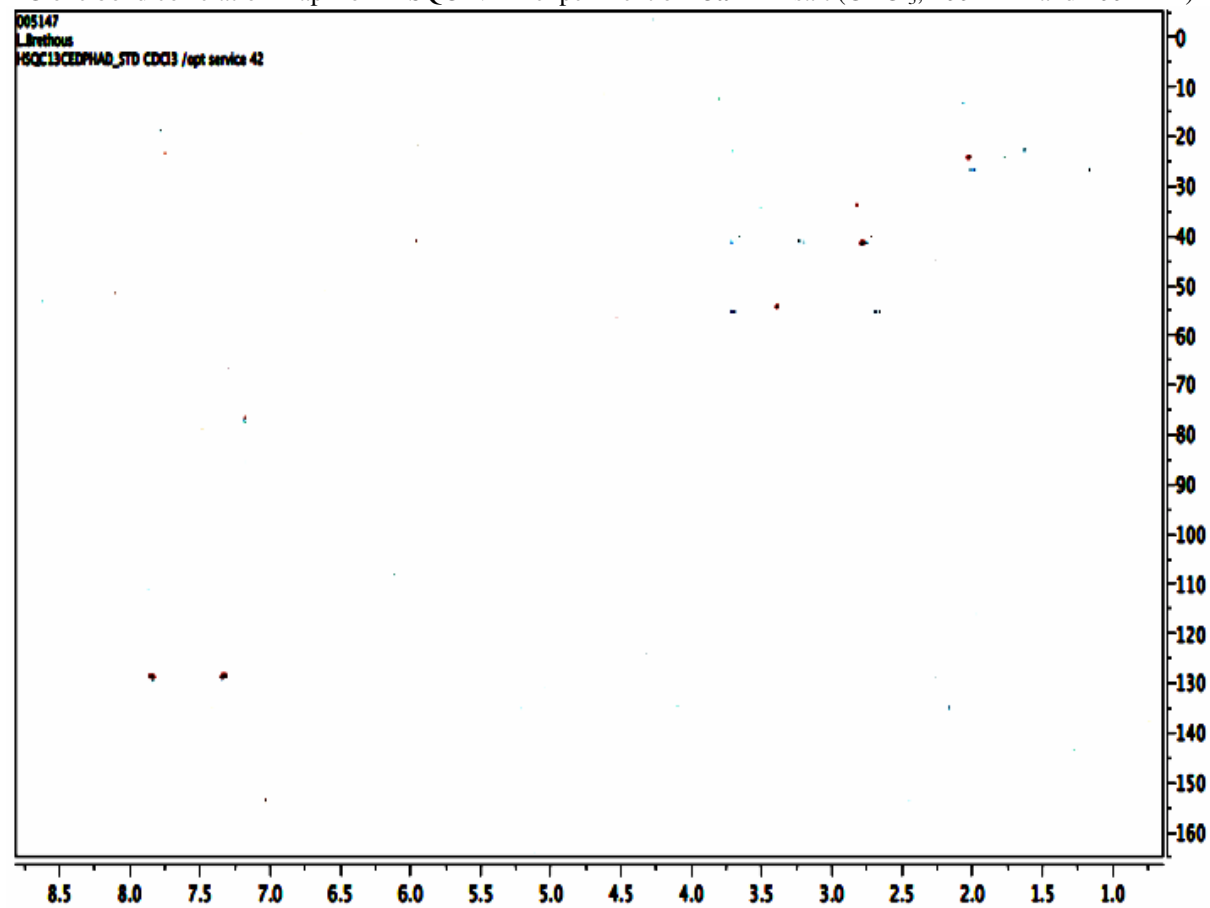
^{13}C NMR Spectrum of (*R*)-**11k** TFA salt (D_2O , 75 MHz)

¹H NMR Spectrum of **12c** TFA salt (CDCl₃, 300 MHz)¹³C NMR Spectrum of **12c** TFA salt (CDCl₃, 75 MHz)

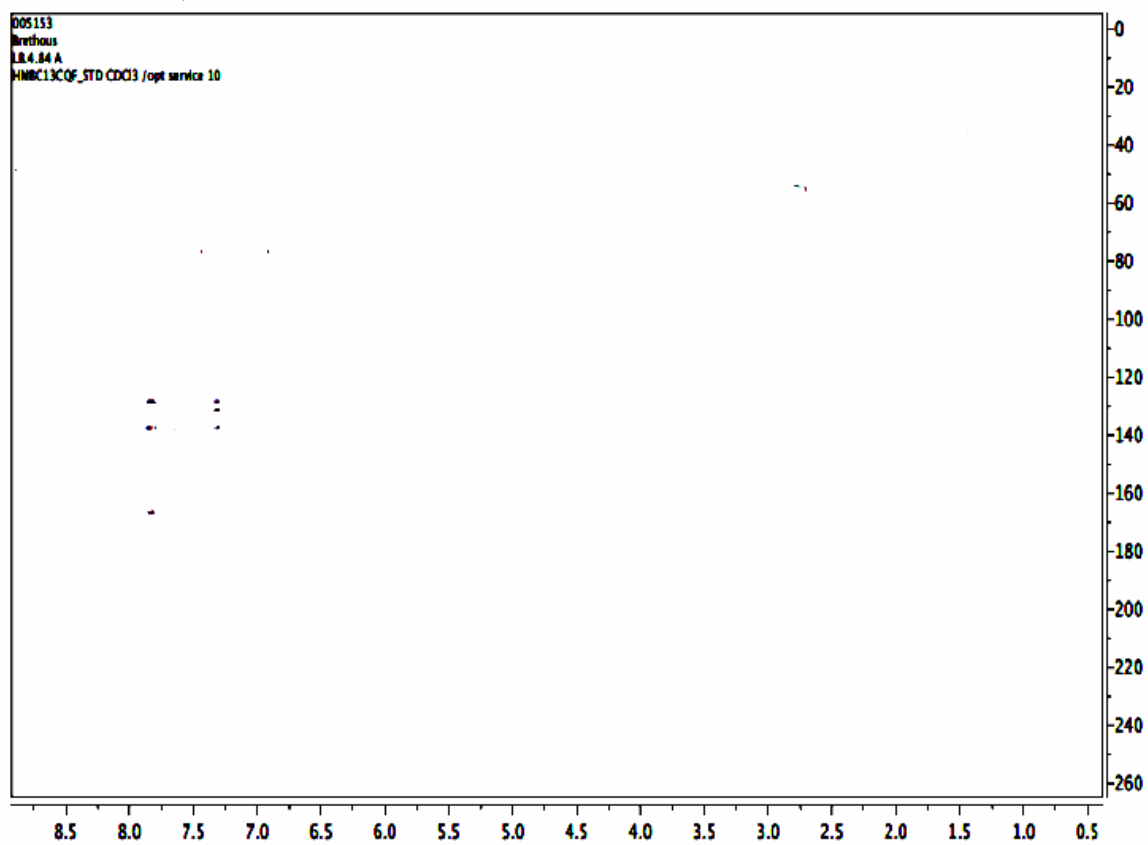
^1H NMR Spectrum of **12e** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **12e** TFA salt (CDCl_3 , 75 MHz)

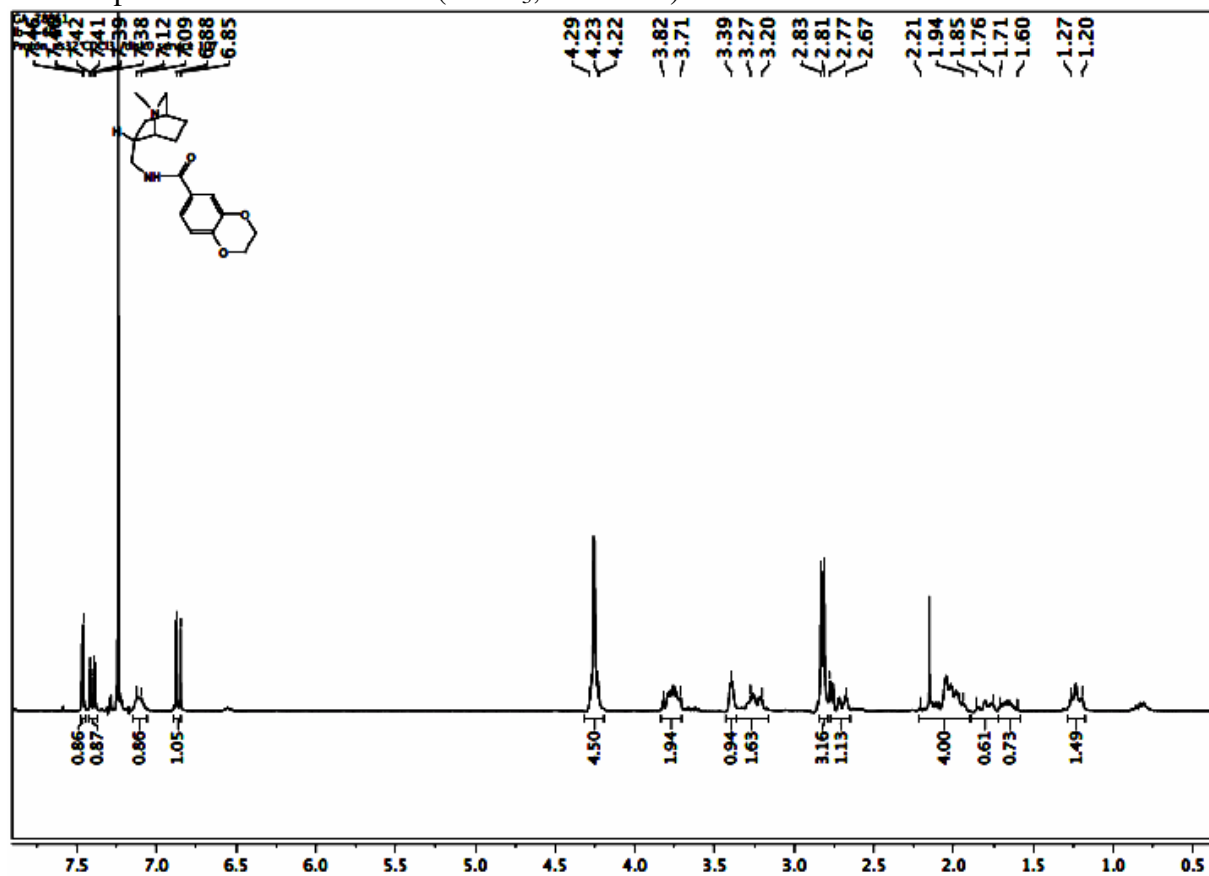
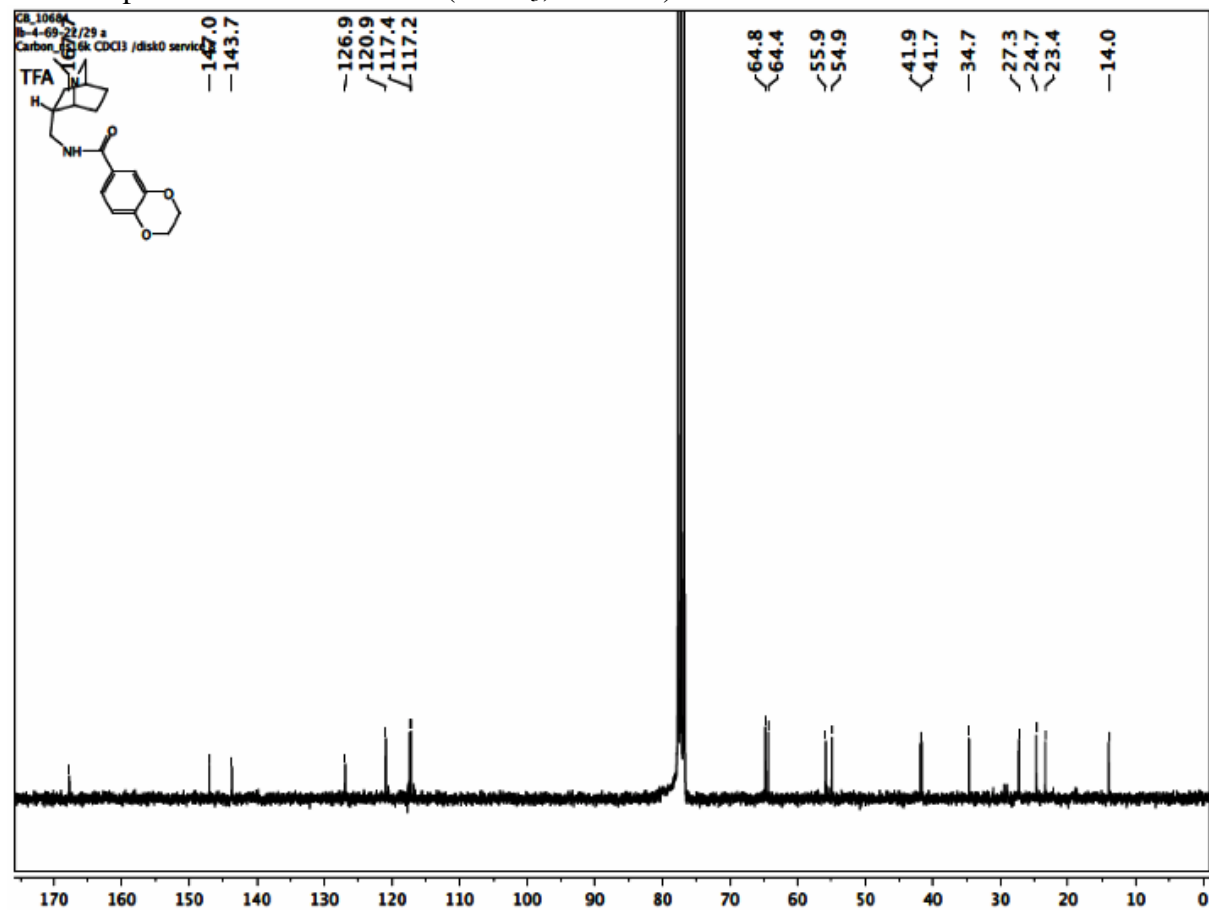
^1H NMR Spectrum of **12f** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **12f** TFA salt (CDCl_3 , 75 MHz)

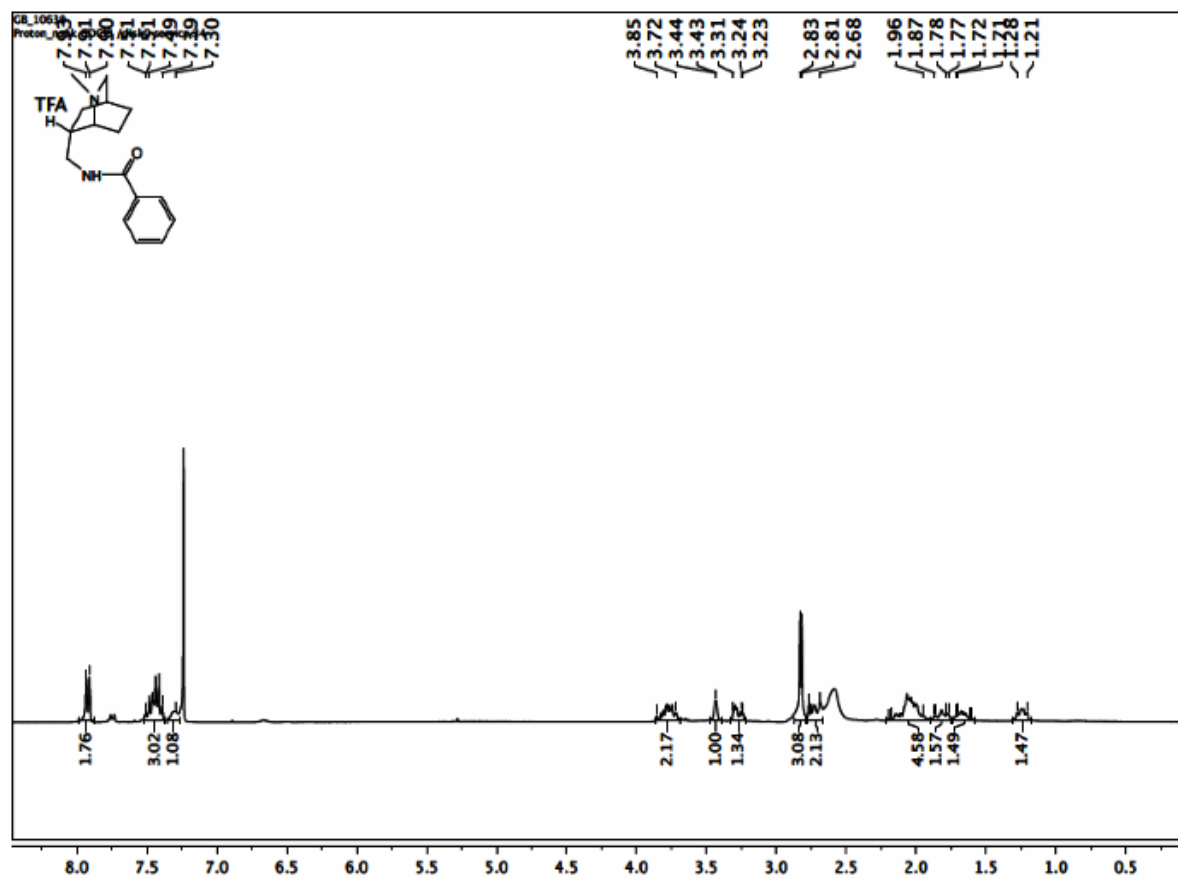
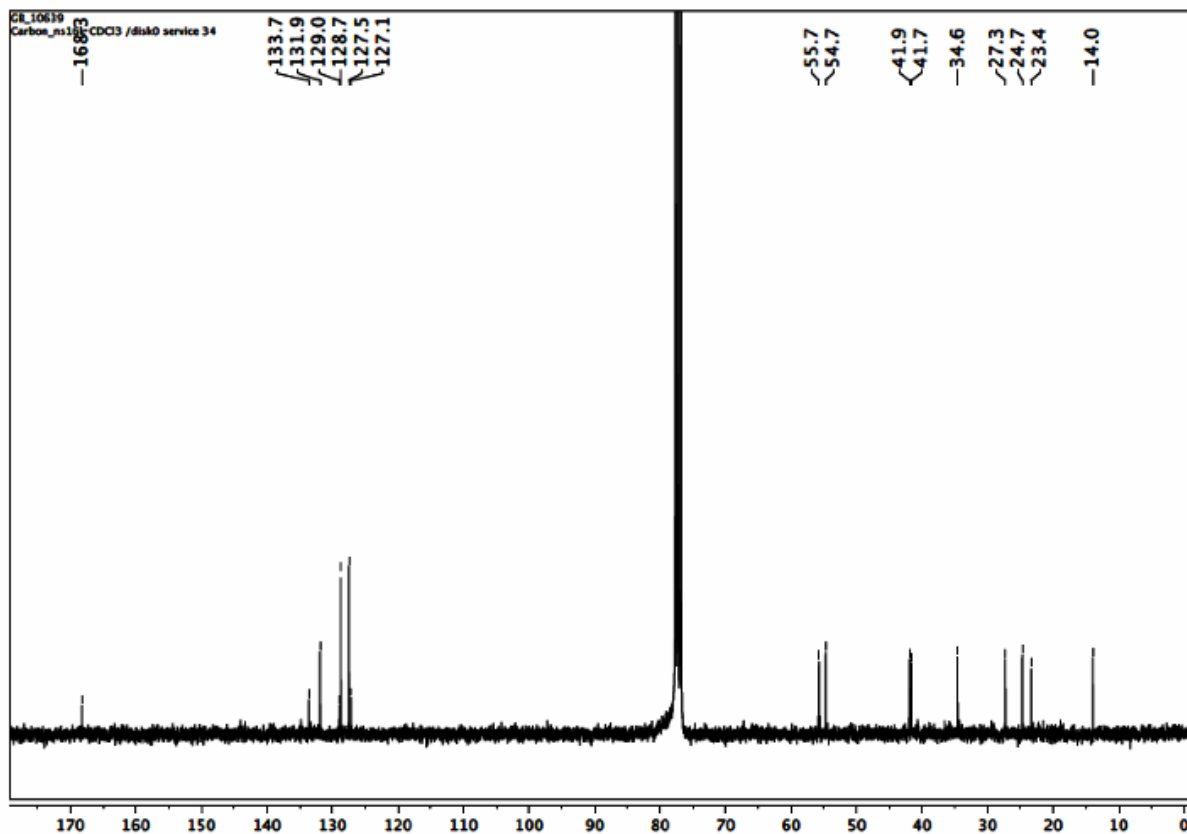
¹H NMR Spectrum of **12k** TFA salt (CDCl₃, 300 MHz)¹³C NMR Spectrum of **12k** TFA salt (CDCl₃, 75 MHz)

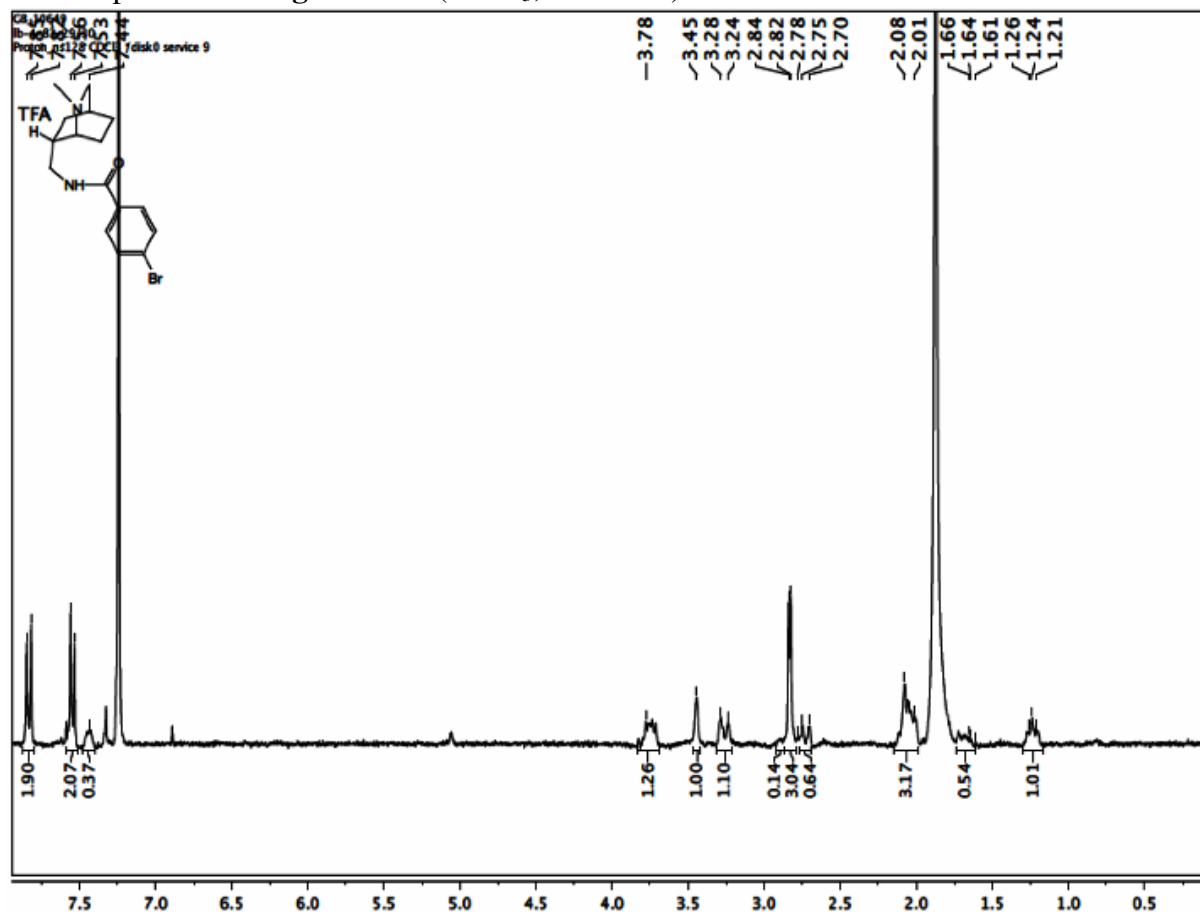
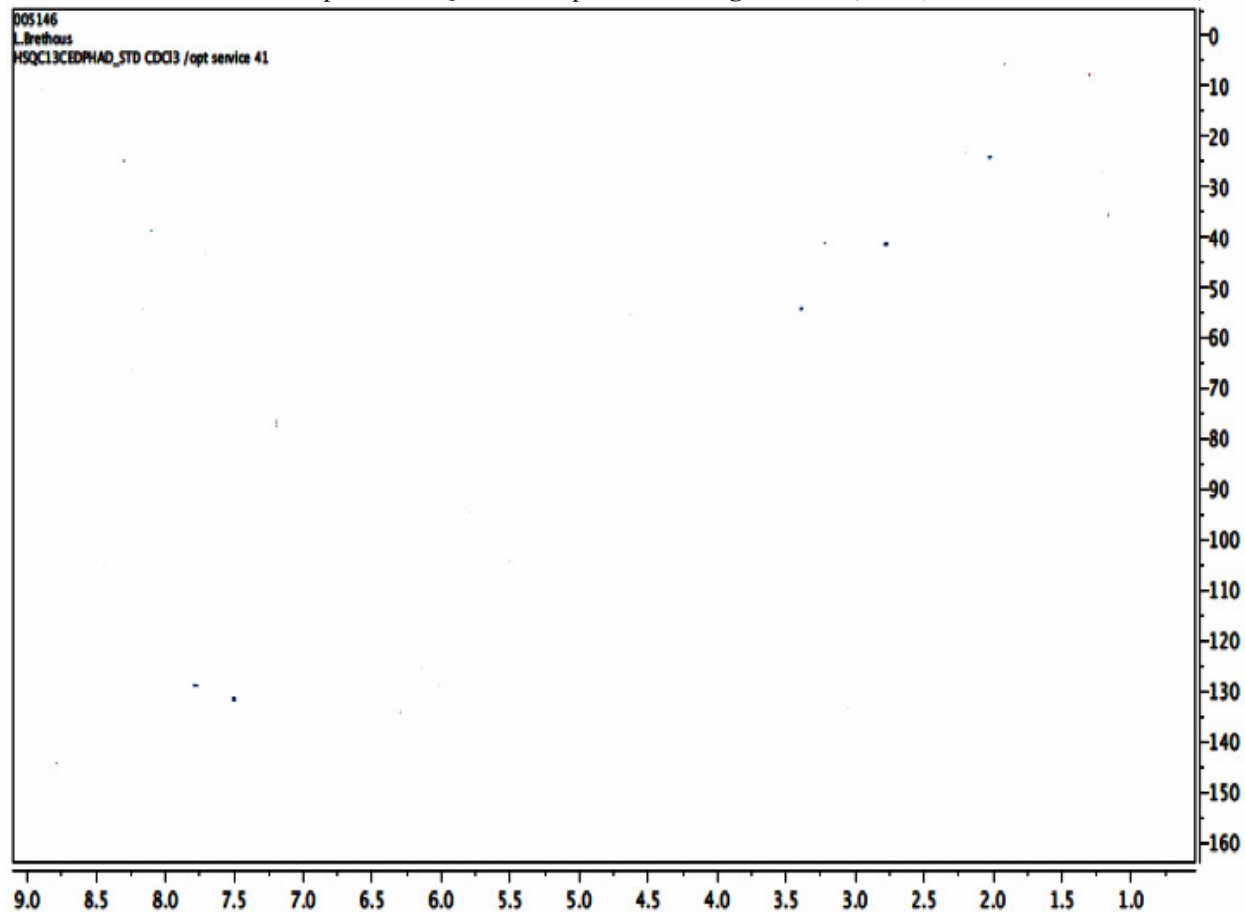
¹H NMR Spectrum of **13a** TFA salt (CDCl₃, 300 MHz)¹H-¹³C one bond correlation map from HSQC NMR experiment of **13a** TFA salt (CDCl₃, 400 MHz and 100 MHz)

^1H - ^{13}C long range correlation map from HMBC NMR experiment of **13a** TFA salt (CDCl_3 , 400 MHz and 100 MHz)

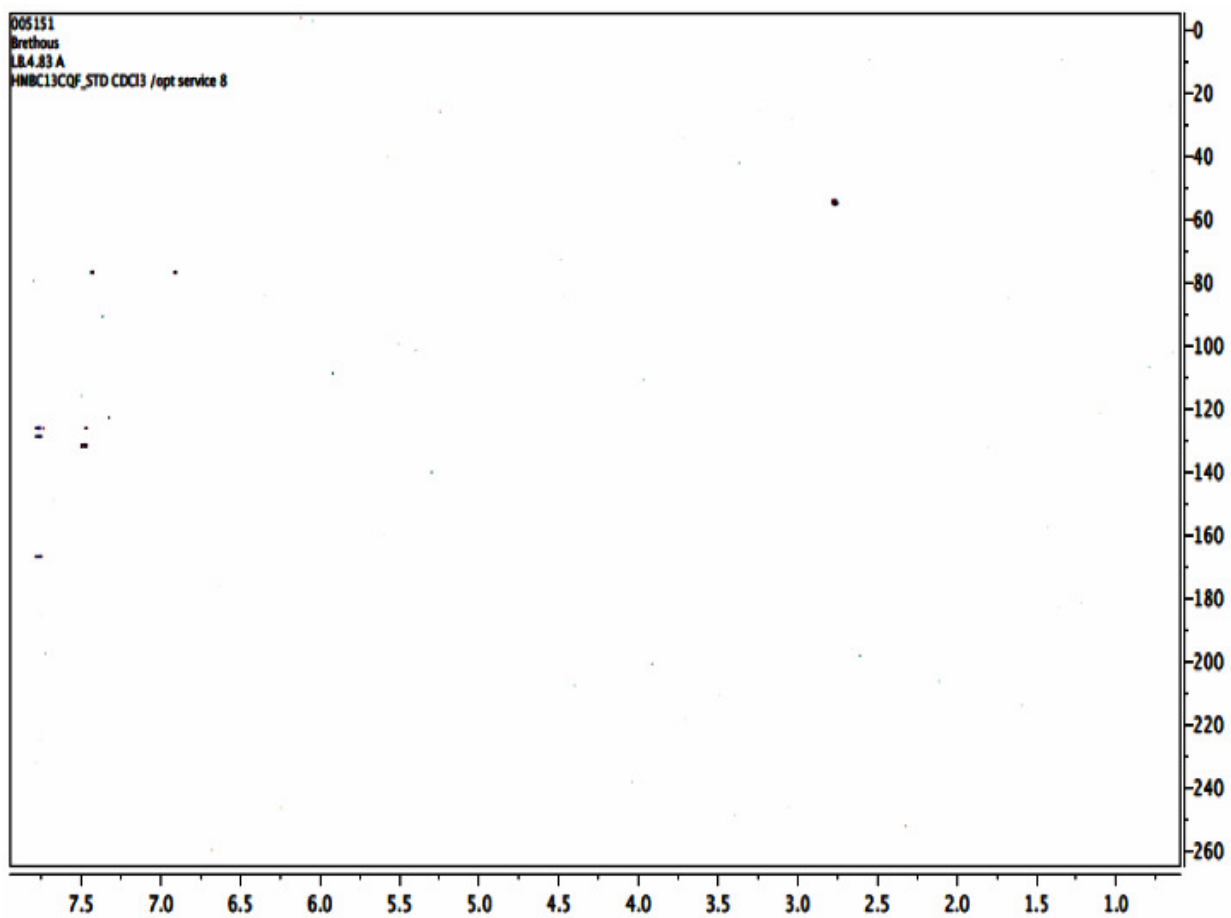


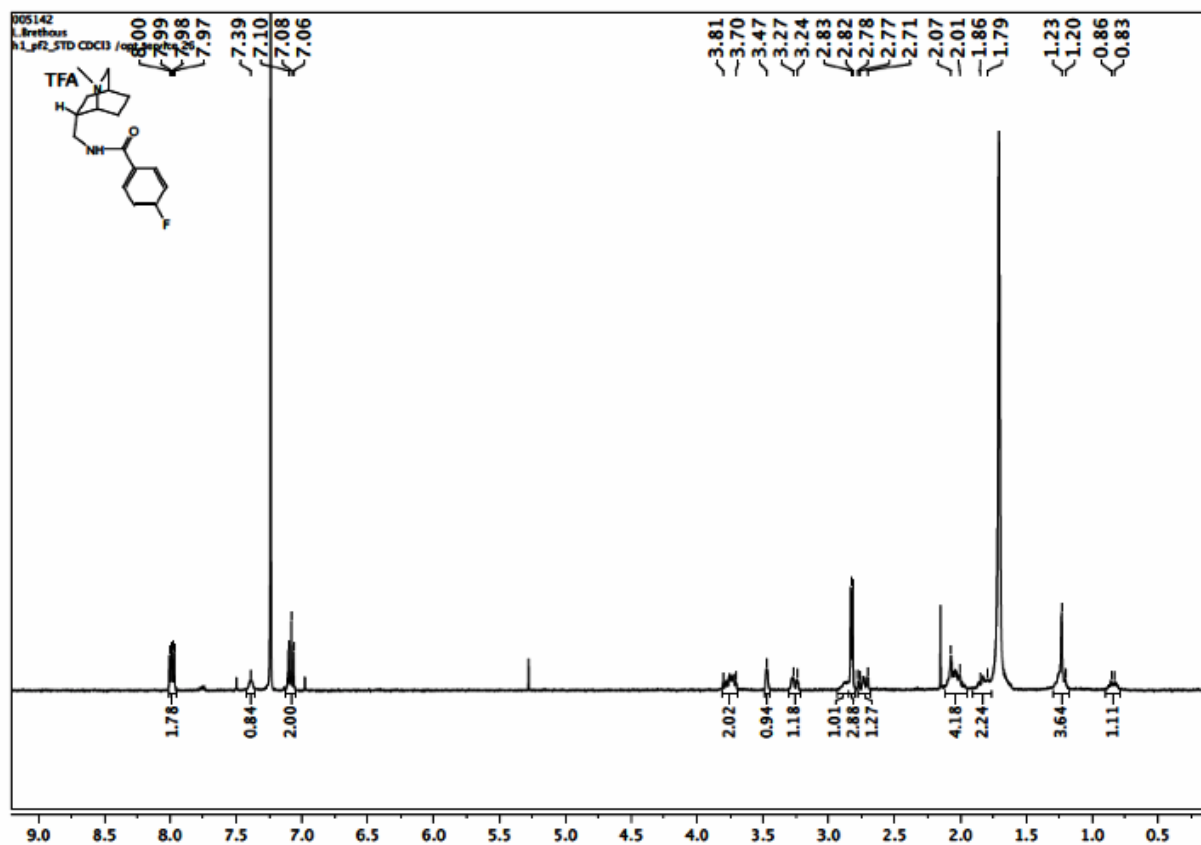
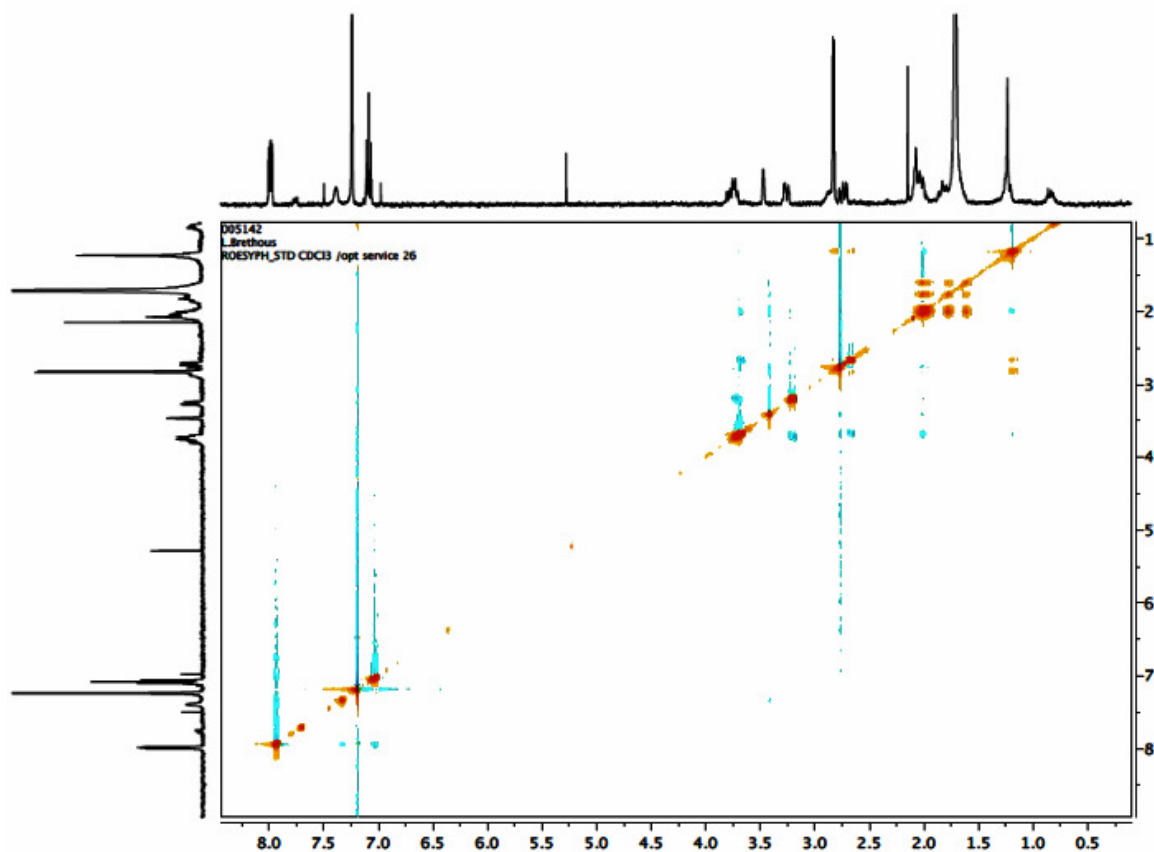
^1H NMR Spectrum of **13c** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **13c** TFA salt (CDCl_3 , 75 MHz)

^1H NMR Spectrum of **13f** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **13f** TFA salt (CDCl_3 , 75 MHz)

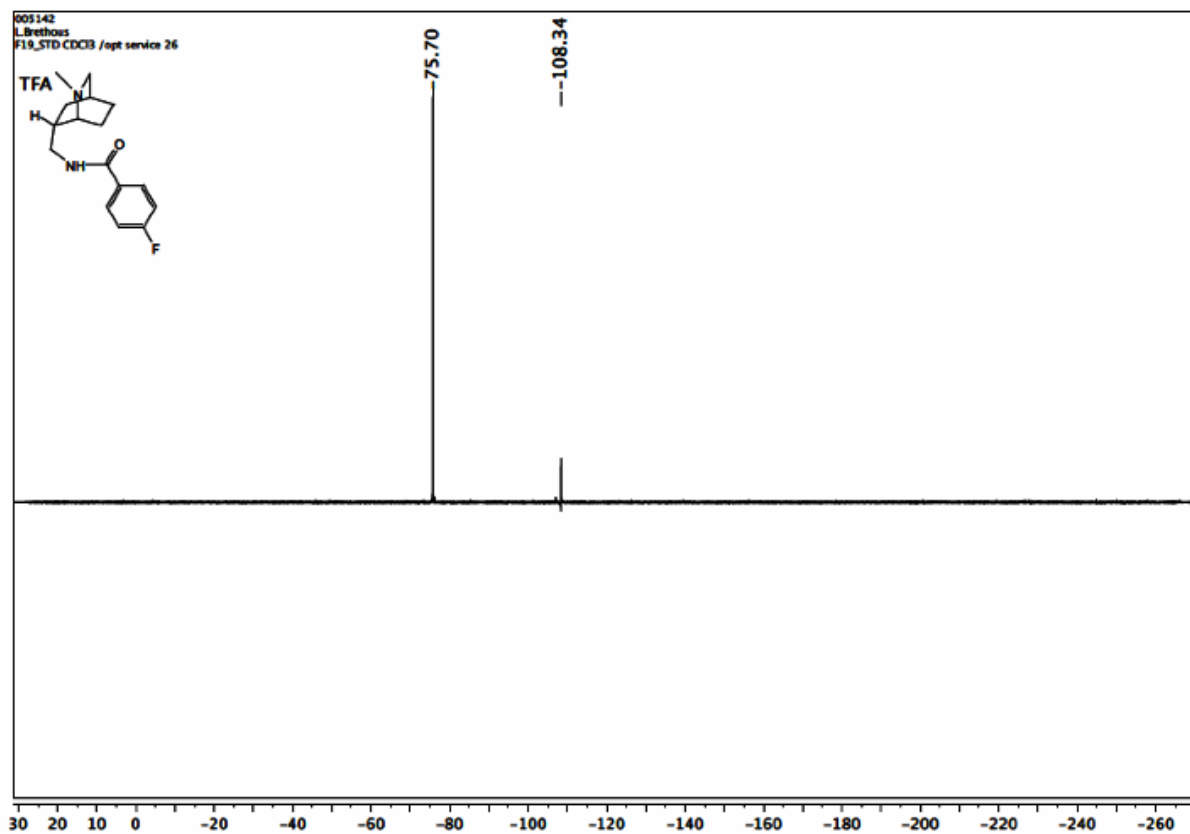
^1H NMR Spectrum of **13g** TFA salt (CDCl_3 , 300 MHz) ^1H - ^{13}C one bond correlation map from HSQC NMR experiment of **13g** TFA salt (CDCl_3 , 400 MHz and 100 MHz)

^1H - ^{13}C long range correlation map from HMBC NMR experiment of **13g** TFA salt (CDCl_3 , 400 MHz and 100 MHz)

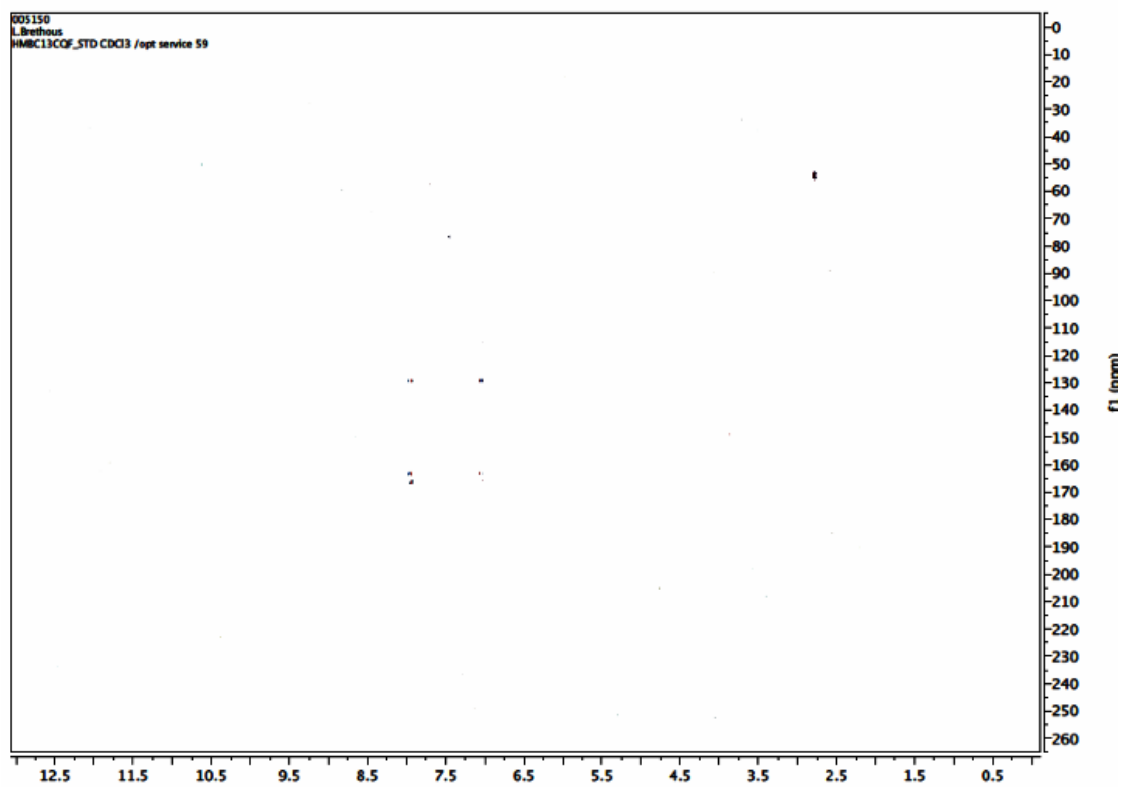


^1H NMR Spectrum of **13k** TFA salt (CDCl_3 , 300 MHz) ^1H -ROESY-NMR Spectrum of **13k** TFA salt (CDCl_3 , 400 MHz)

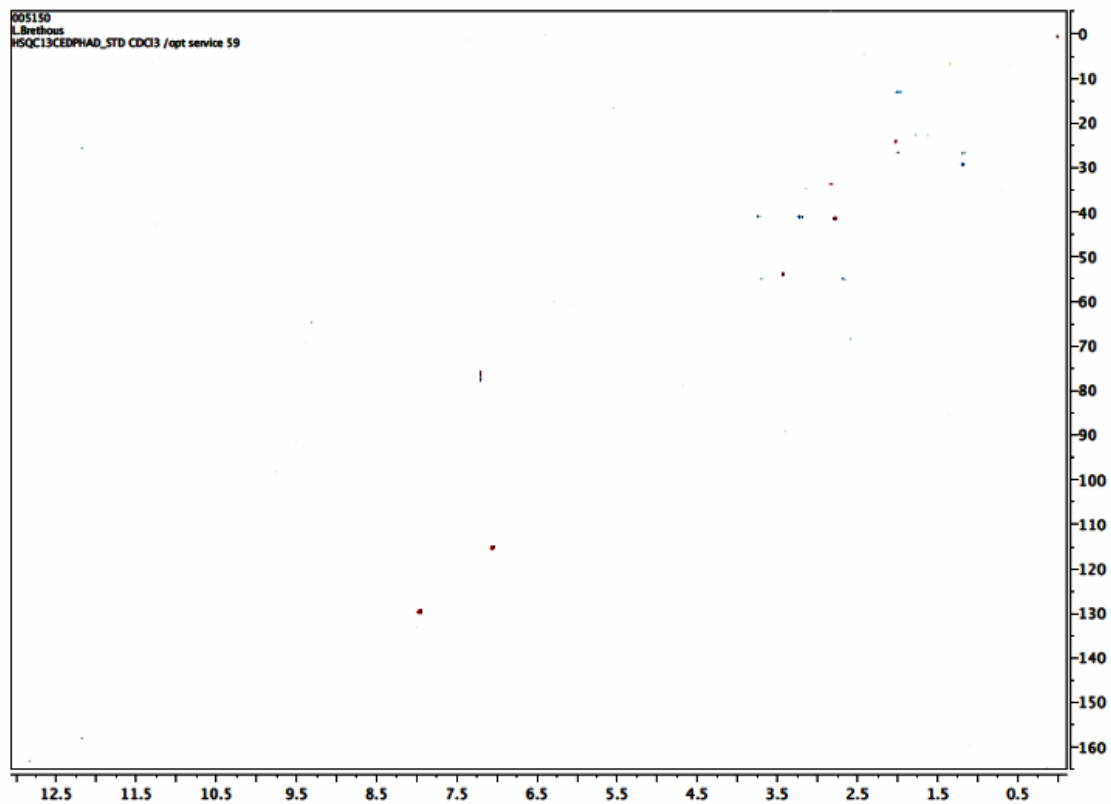
^{19}F NMR Spectrum of **13k** TFA salt (CDCl_3 , 376 MHz)

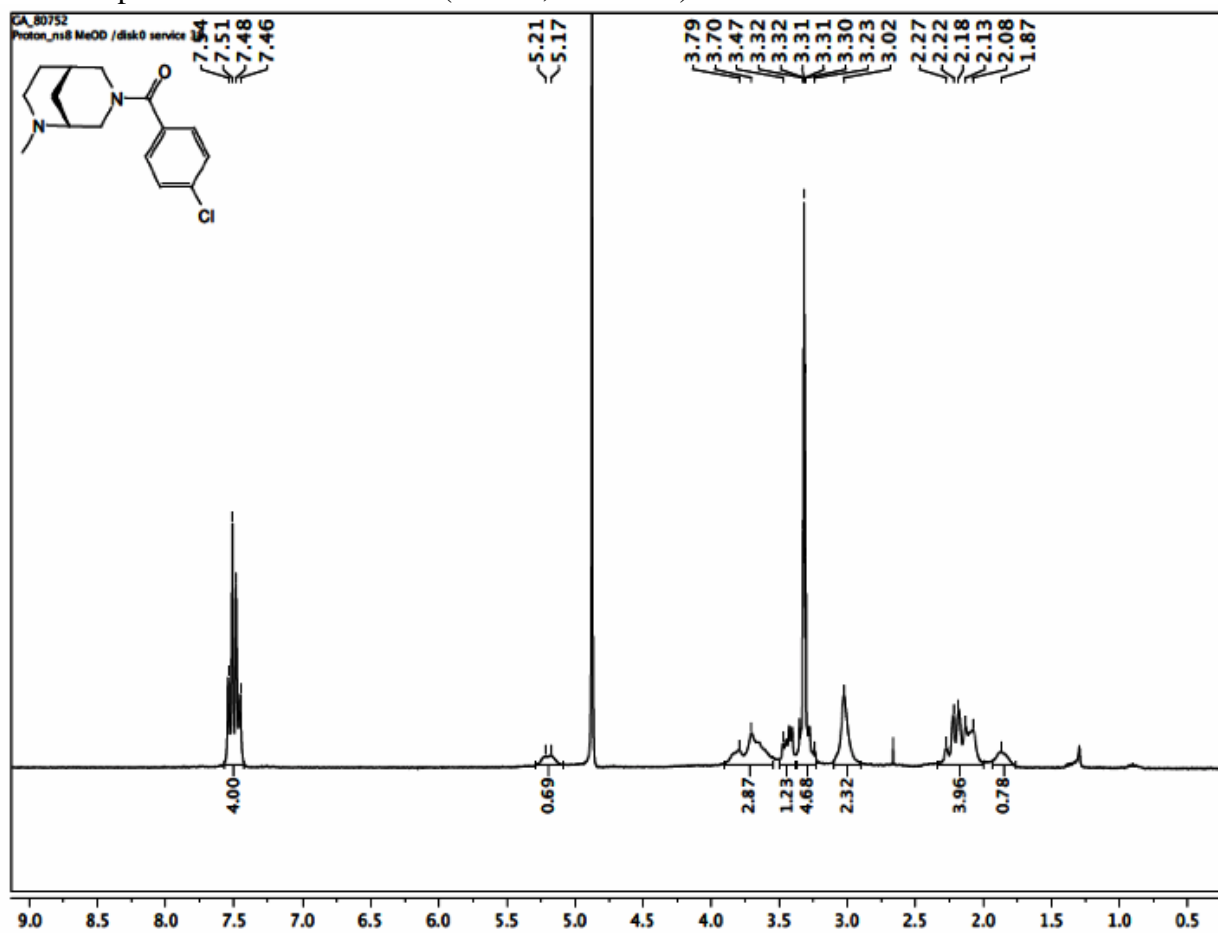
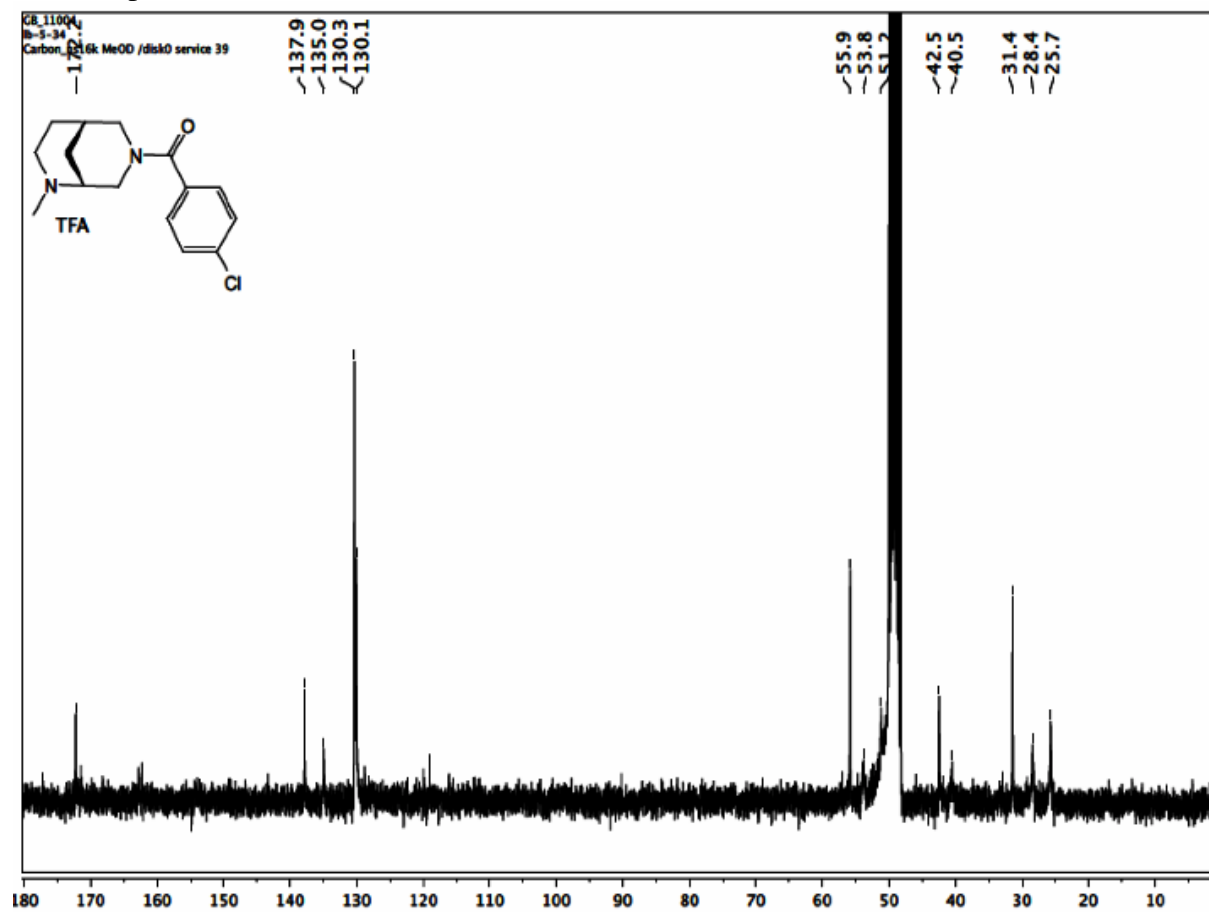


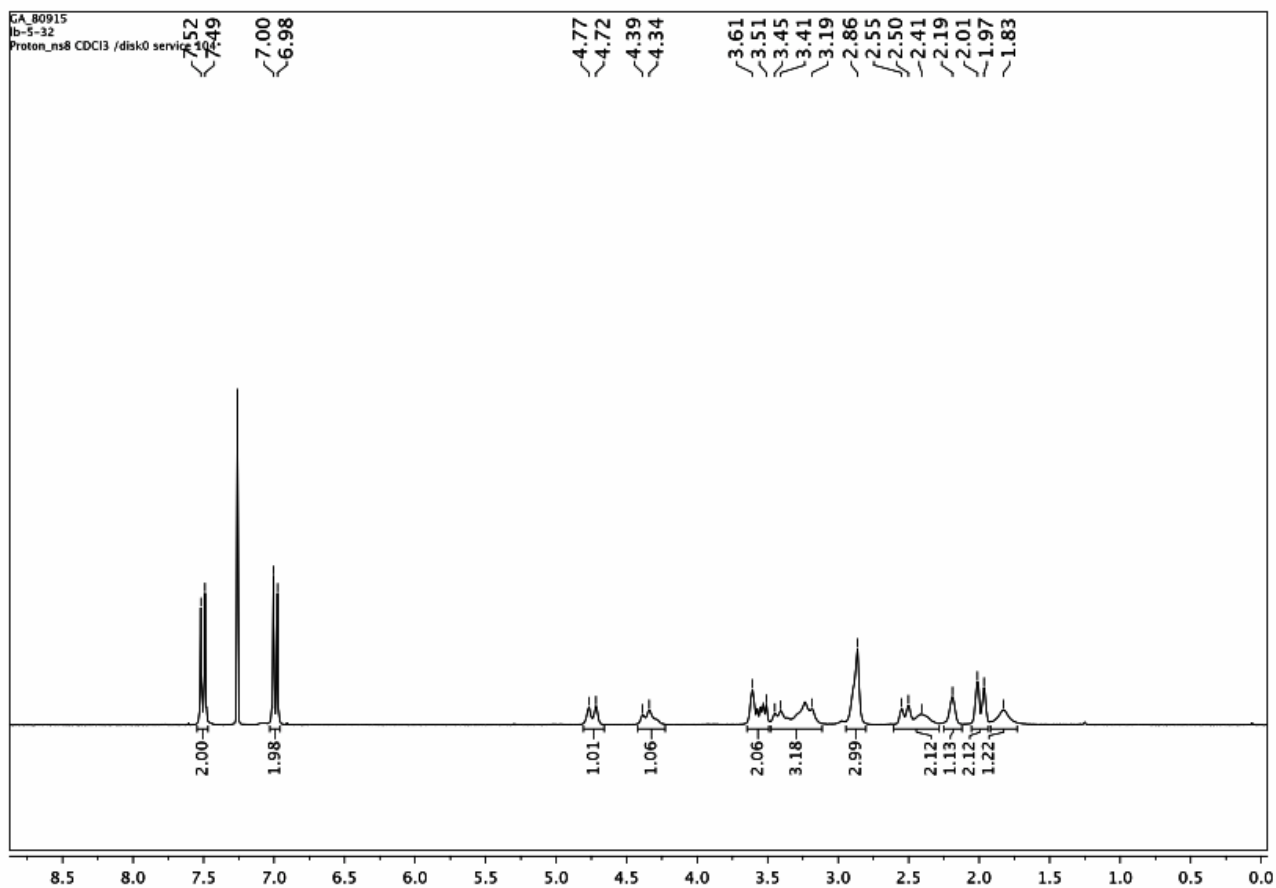
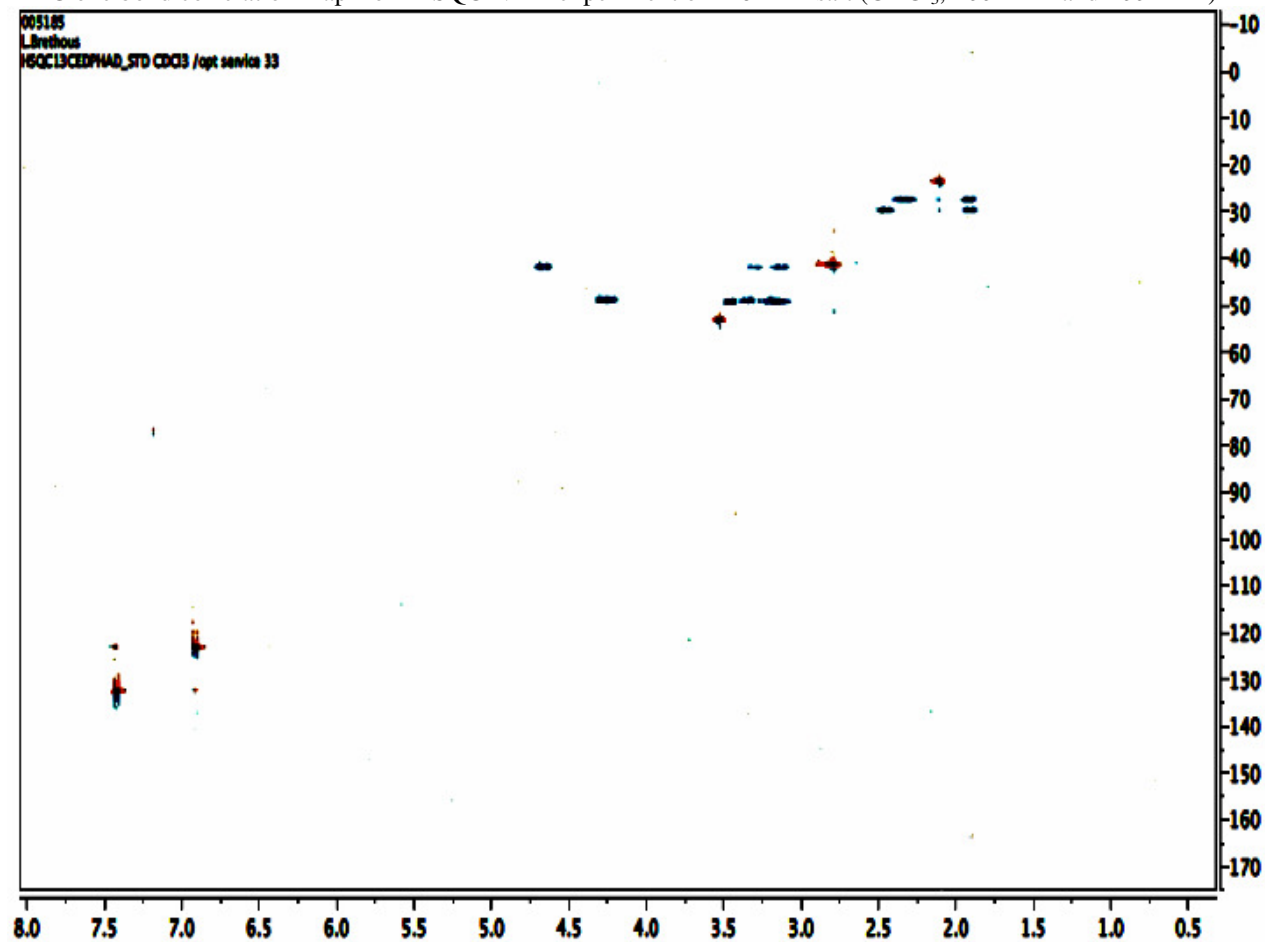
^1H - ^{13}C long range correlation map from HMBC NMR experiment of **13k** TFA salt (CDCl_3 , 400 MHz and 100 MHz)



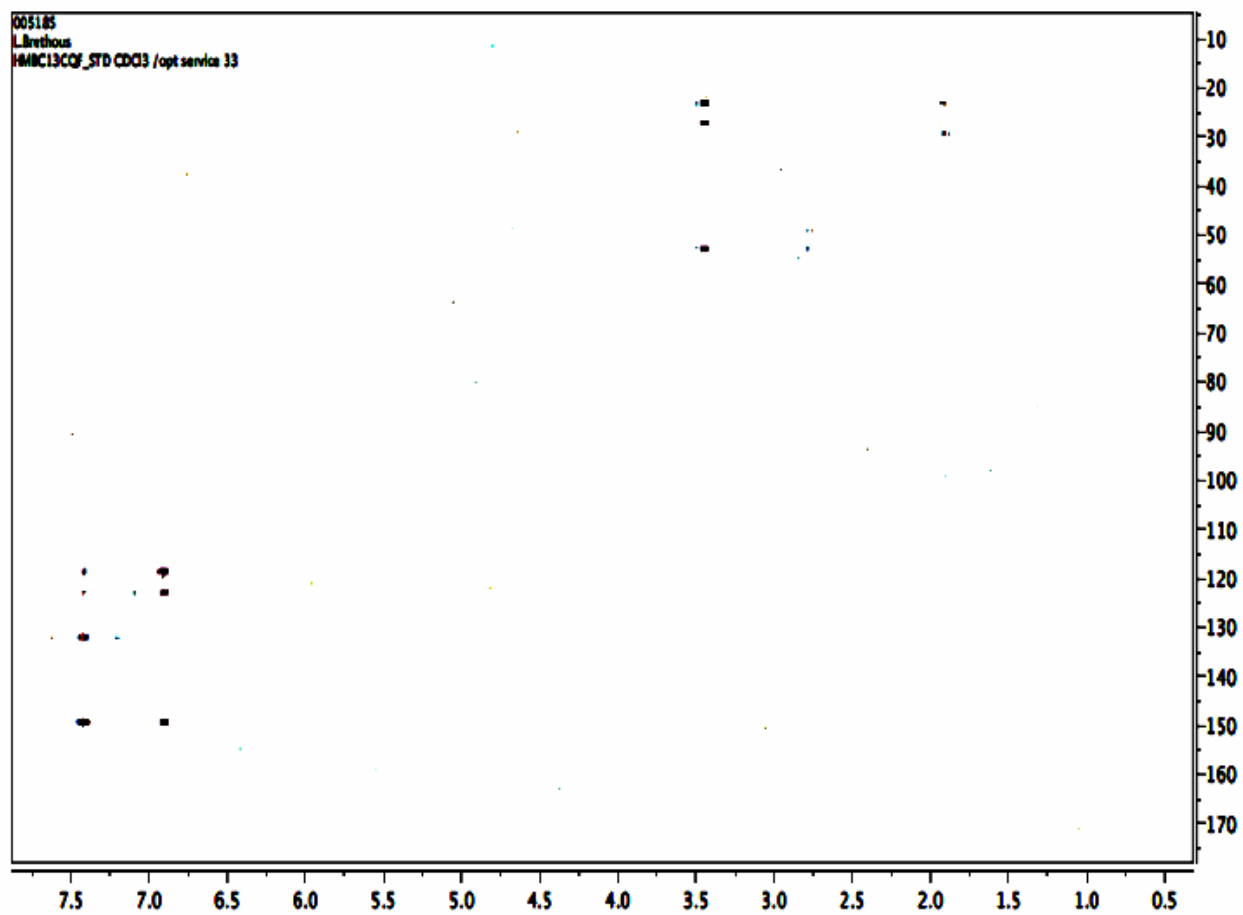
^1H - ^{13}C one bond correlation map from HSQC NMR experiment of **13k** TFA salt (CDCl_3 , 400 MHz and 100 MHz)

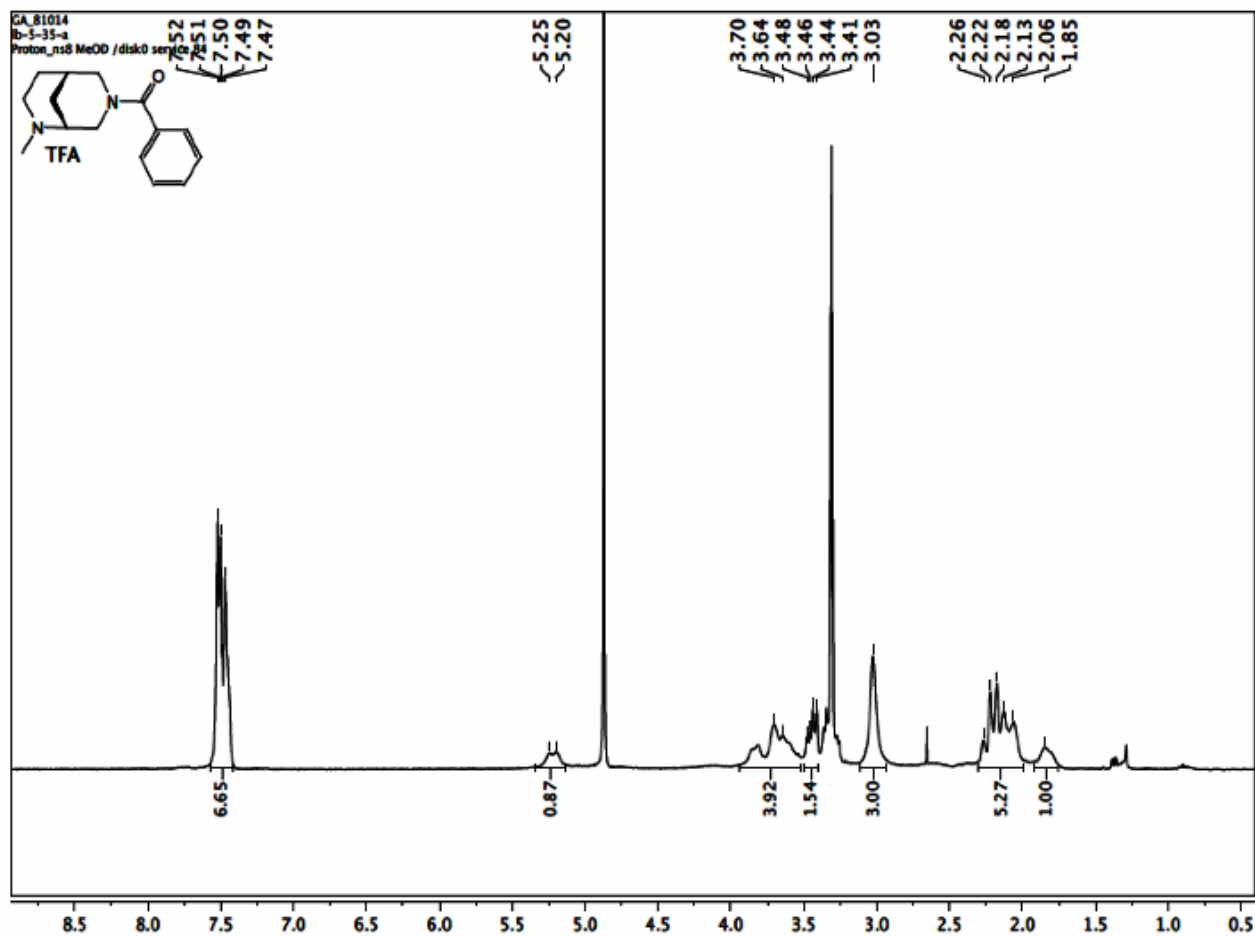
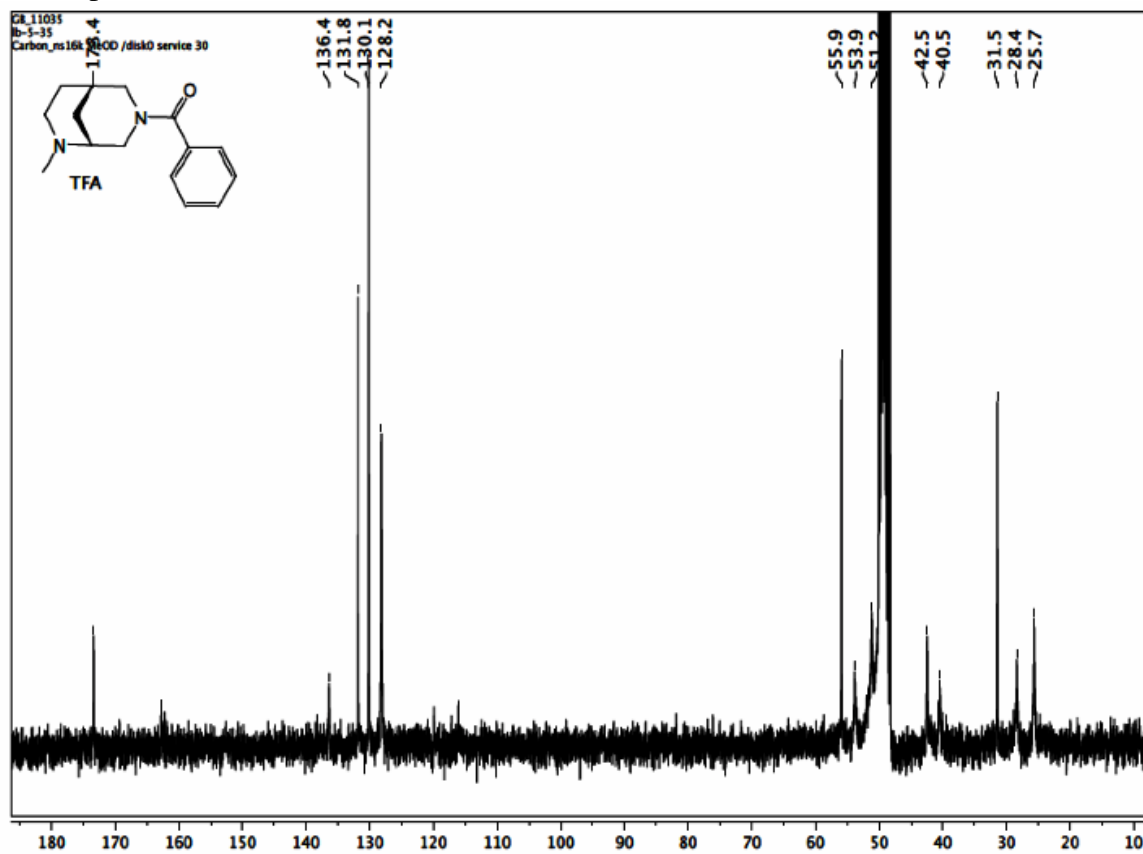


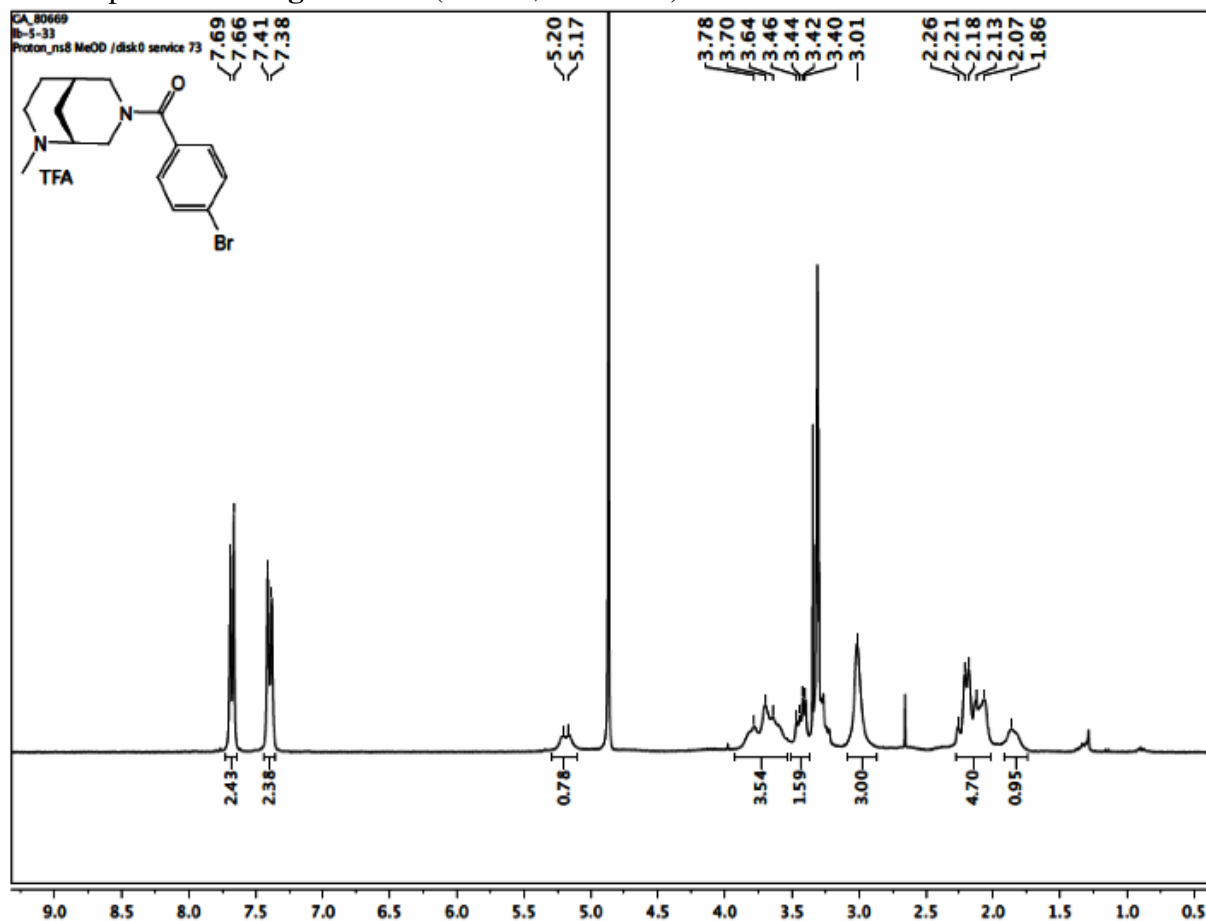
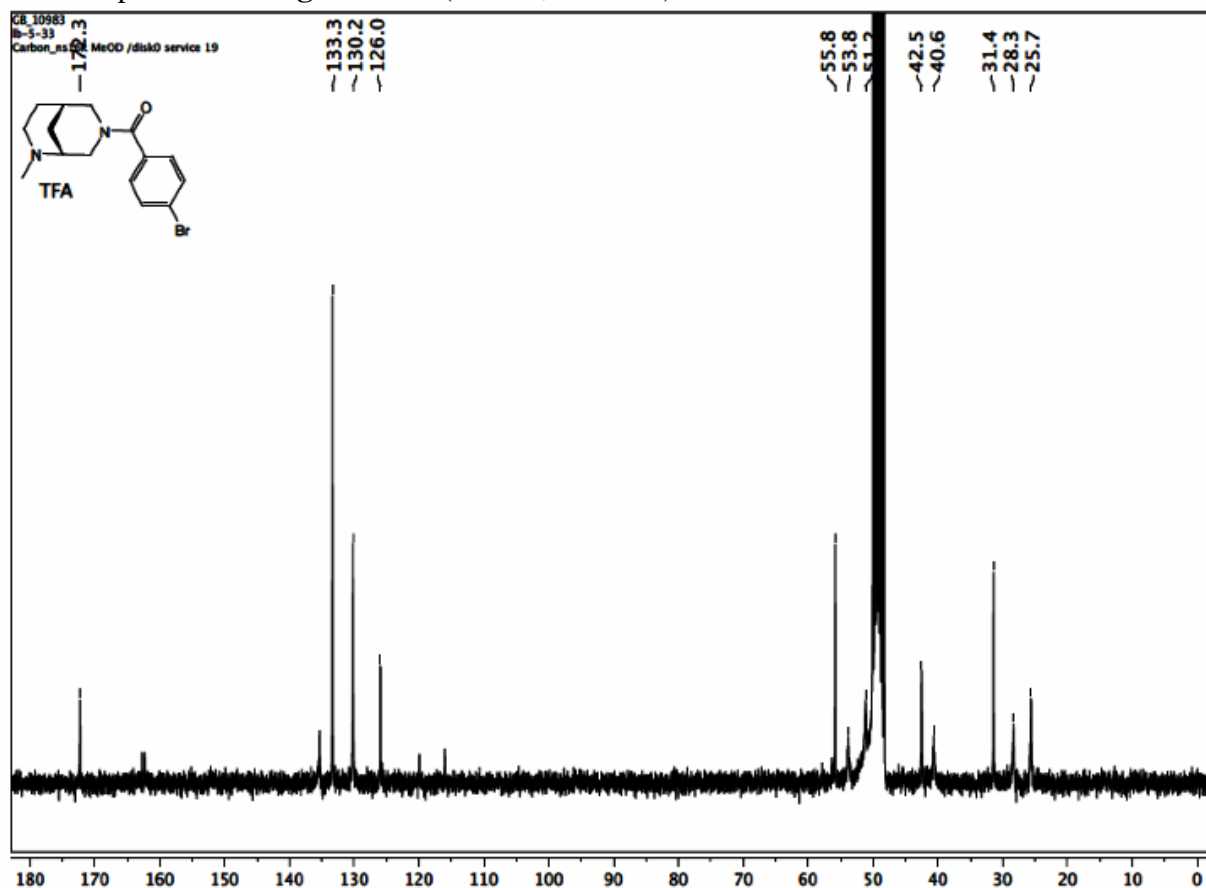
¹H NMR Spectrum of **14a** TFA salt (MeOD, 300 MHz)¹³C NMR Spectrum of **14a** TFA salt (MeOD, 100 MHz)

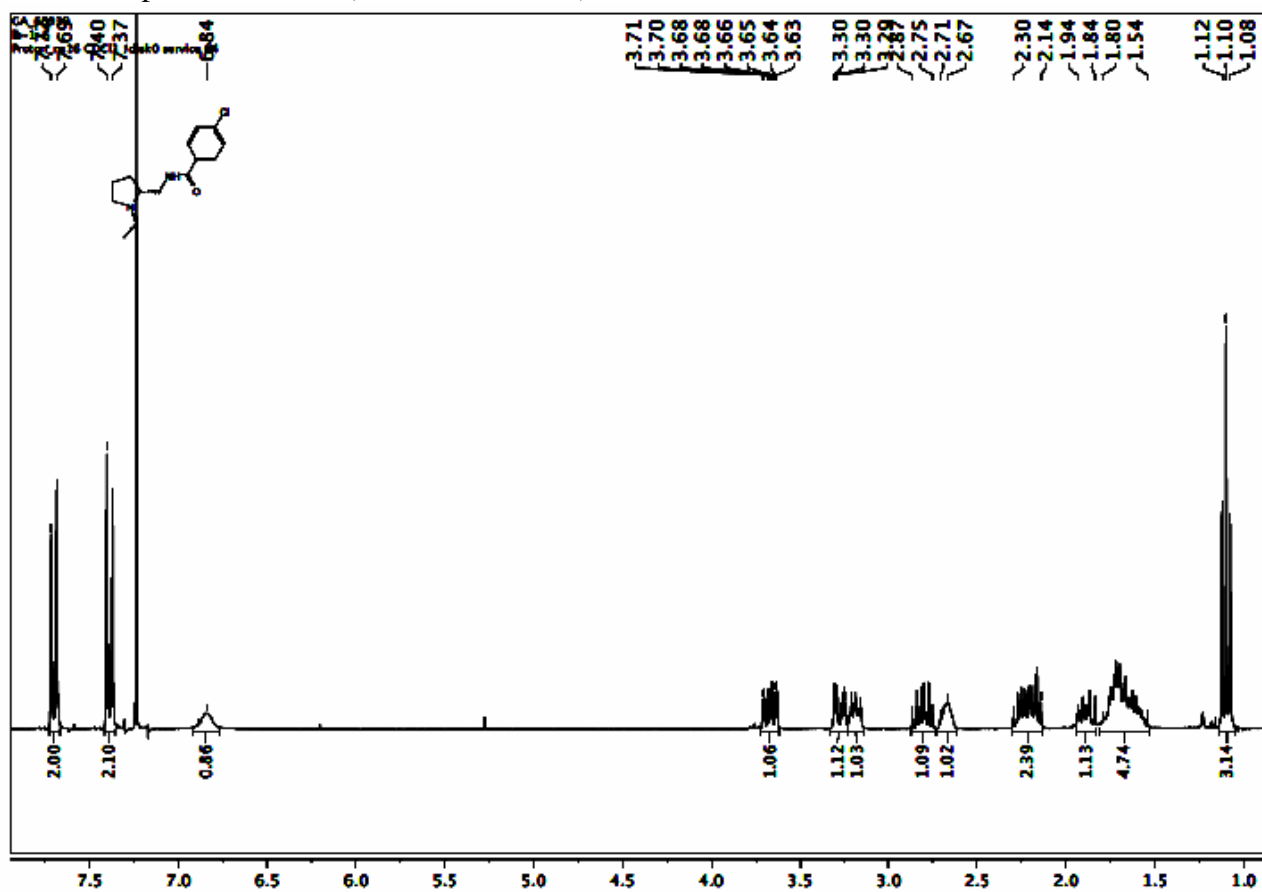
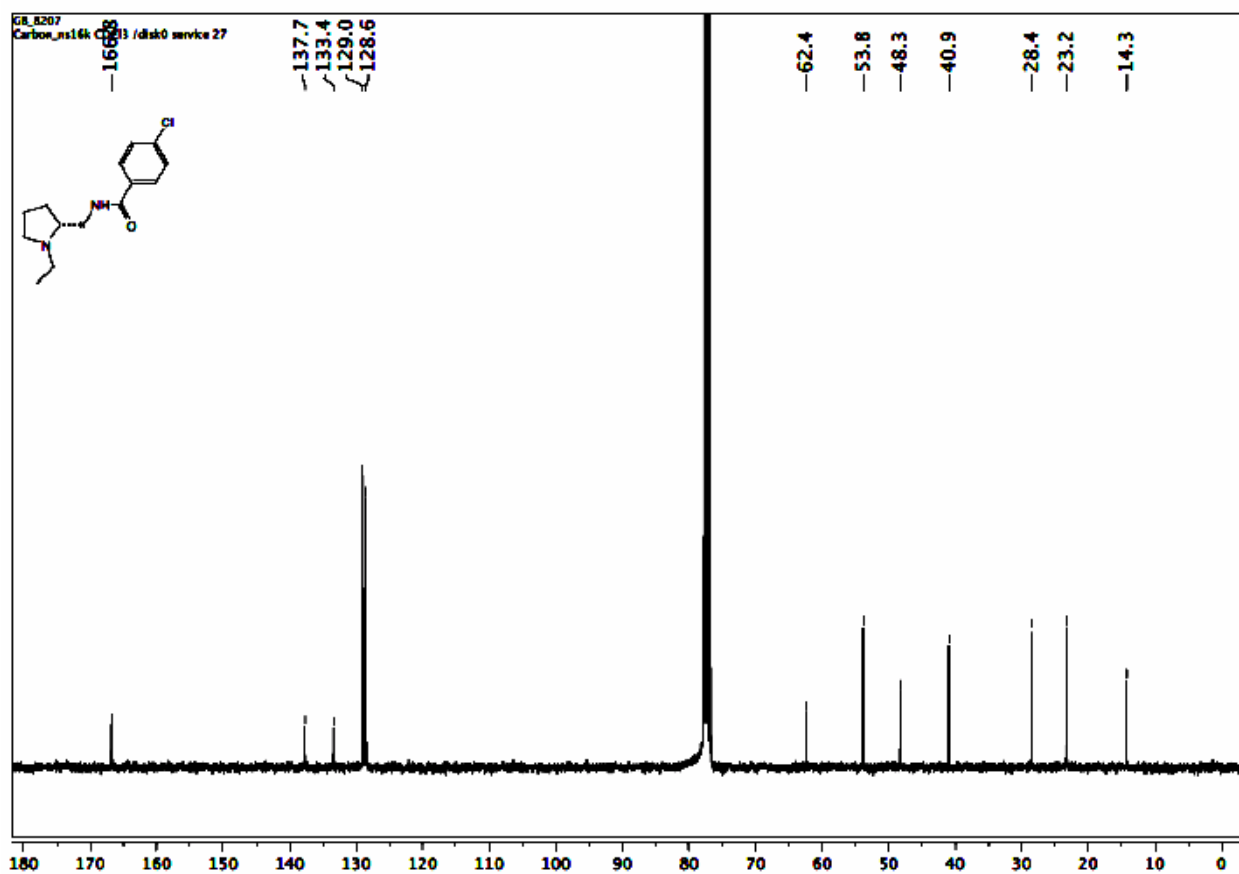
^1H NMR Spectrum of **14e** TFA salt (CDCl_3 , 300 MHz) ^1H - ^{13}C one bond correlation map from HSQC NMR experiment of **14e** TFA salt (CDCl_3 , 400 MHz and 100 MHz)

^1H - ^{13}C long range correlation map from HMBC NMR experiment of **14e** TFA salt (CDCl_3 , 400 MHz and 100 MHz)



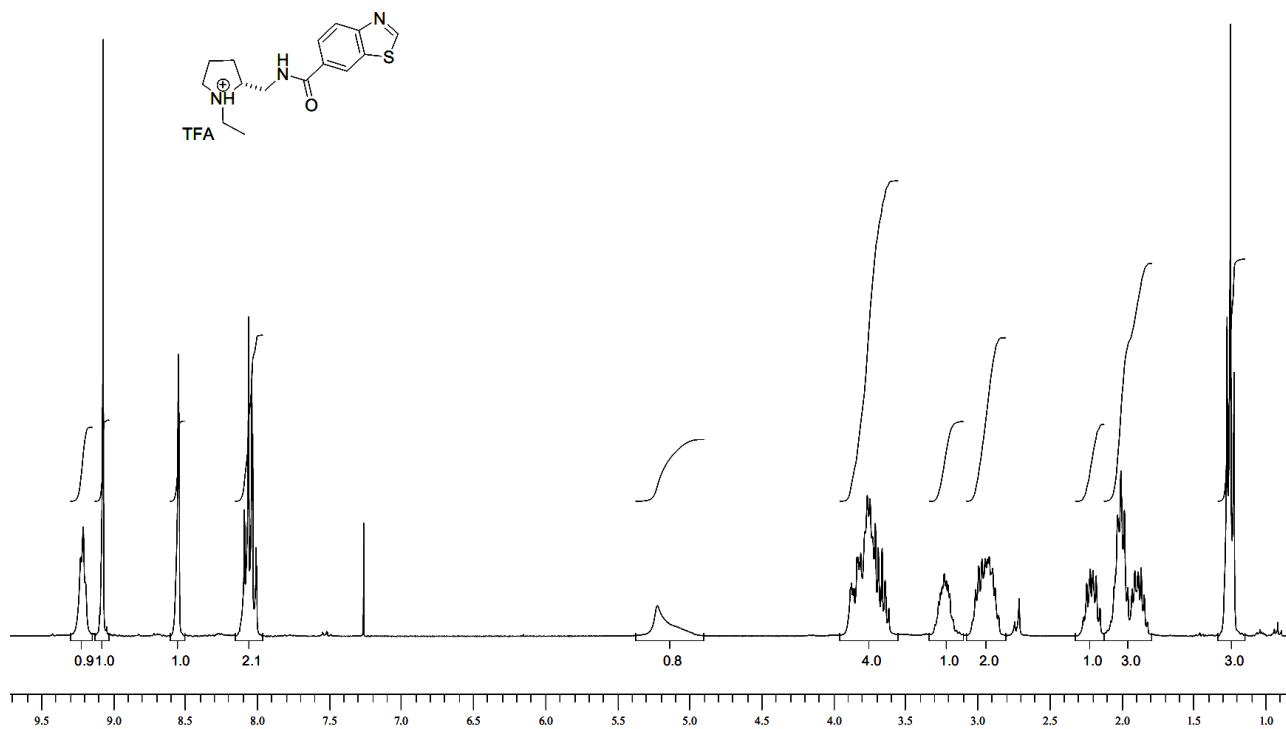
¹H NMR Spectrum of **14f** TFA salt (MeOD, 300 MHz)¹³C NMR Spectrum of **14f** TFA salt (MeOD, 75 MHz)

¹H NMR Spectrum of **14g** TFA salt (MeOD, 300 MHz)¹³C NMR Spectrum of **14g** TFA salt (MeOD, 75 MHz)

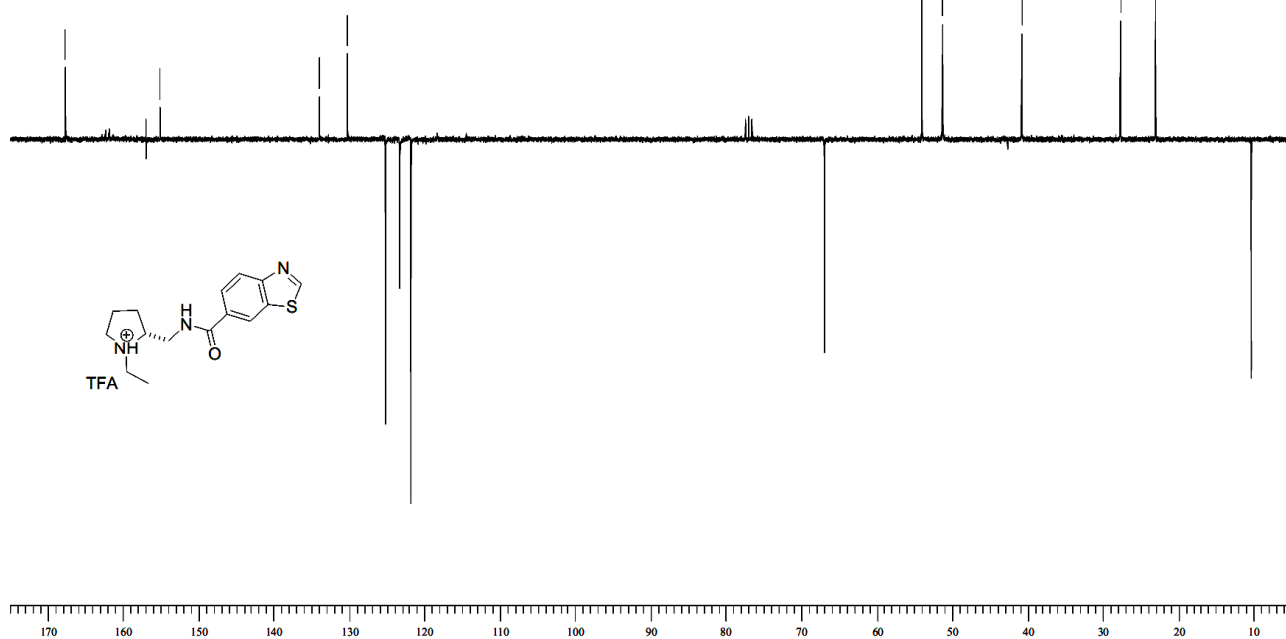
^1H NMR Spectrum of **15a** (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **15a** (CDCl_3 , 75 MHz)

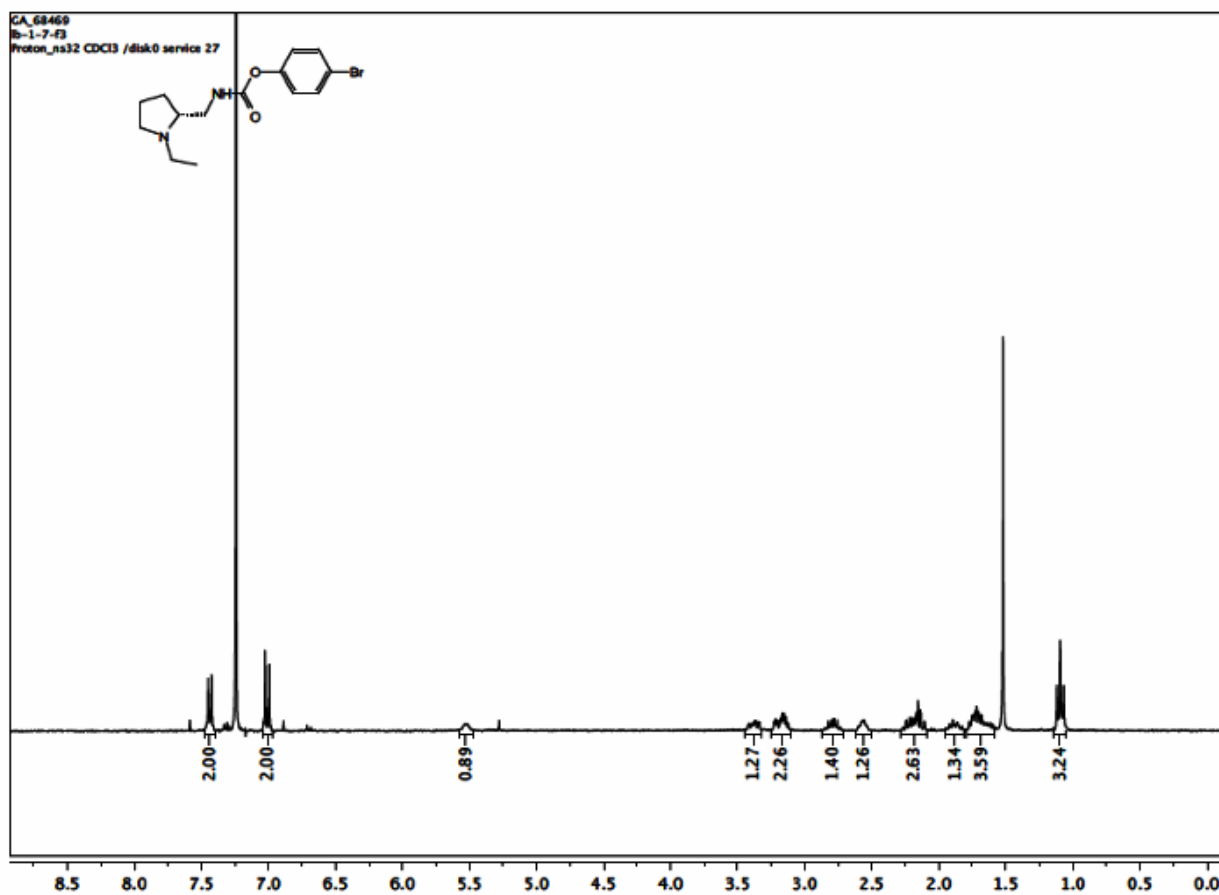
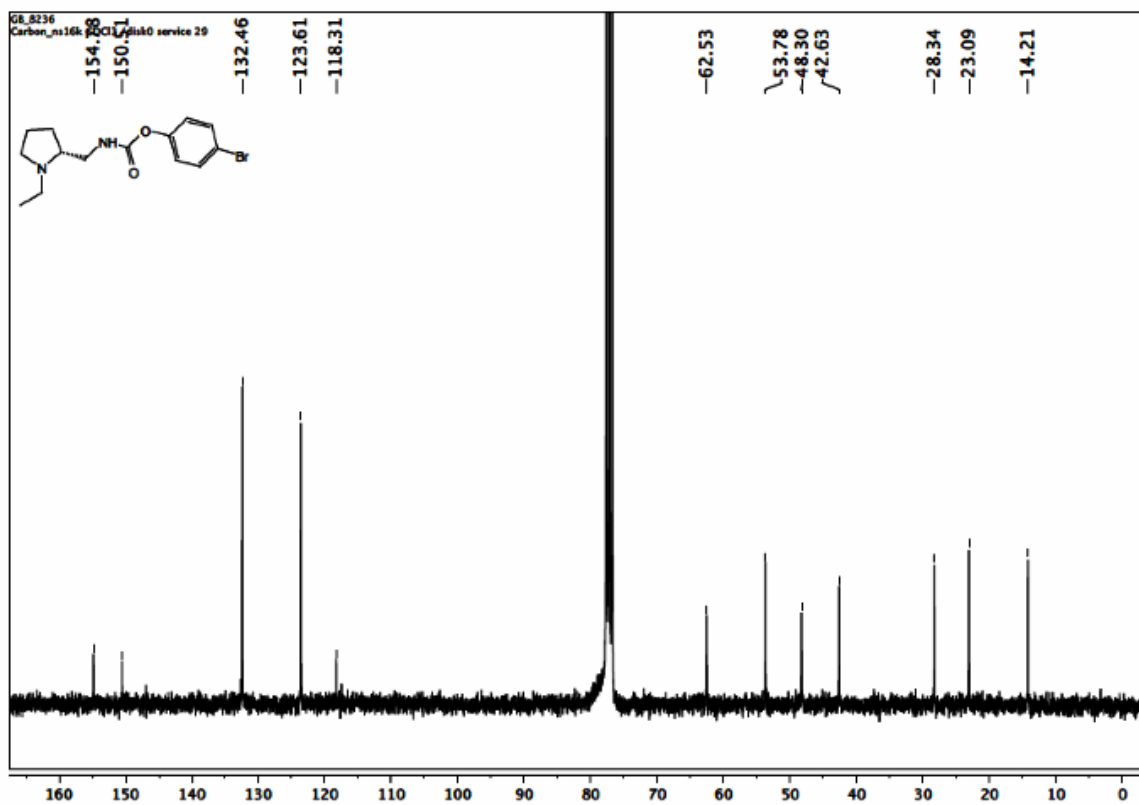
¹H NMR Spectrum of **15b** (CDCl₃, 300 MHz)

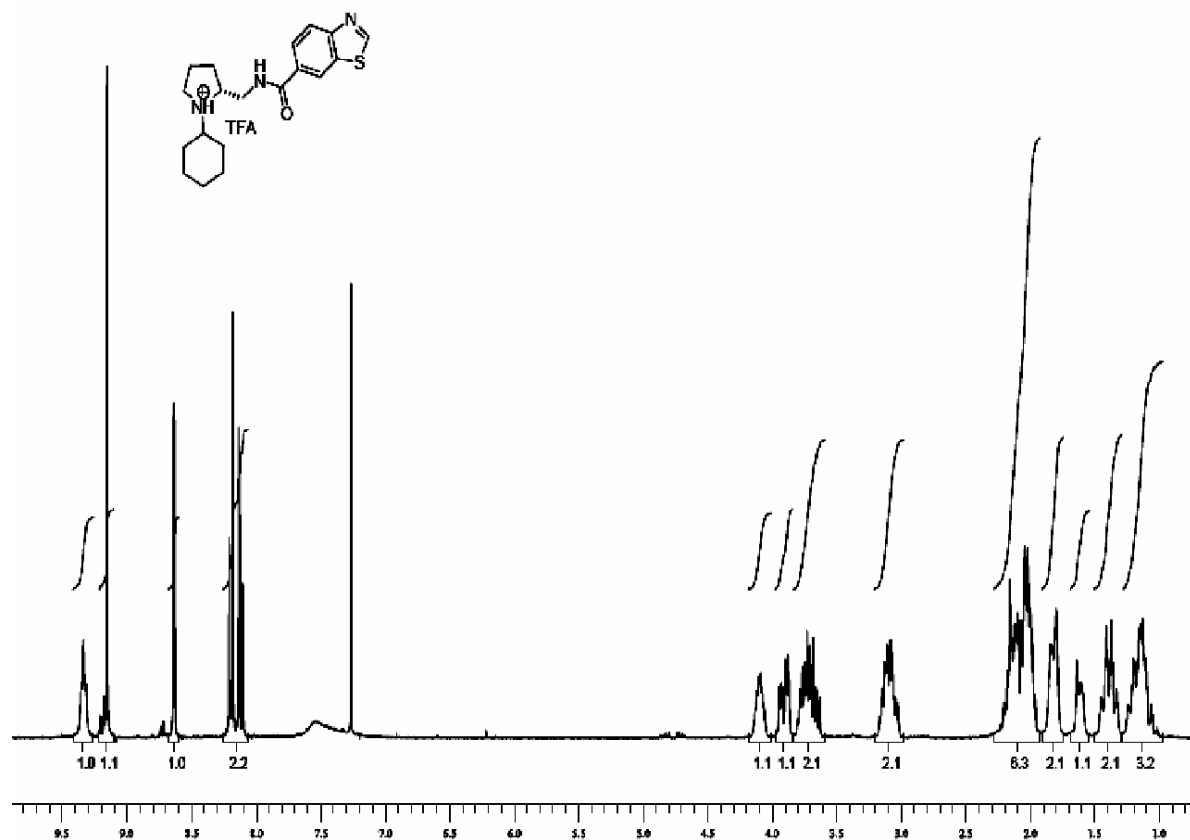
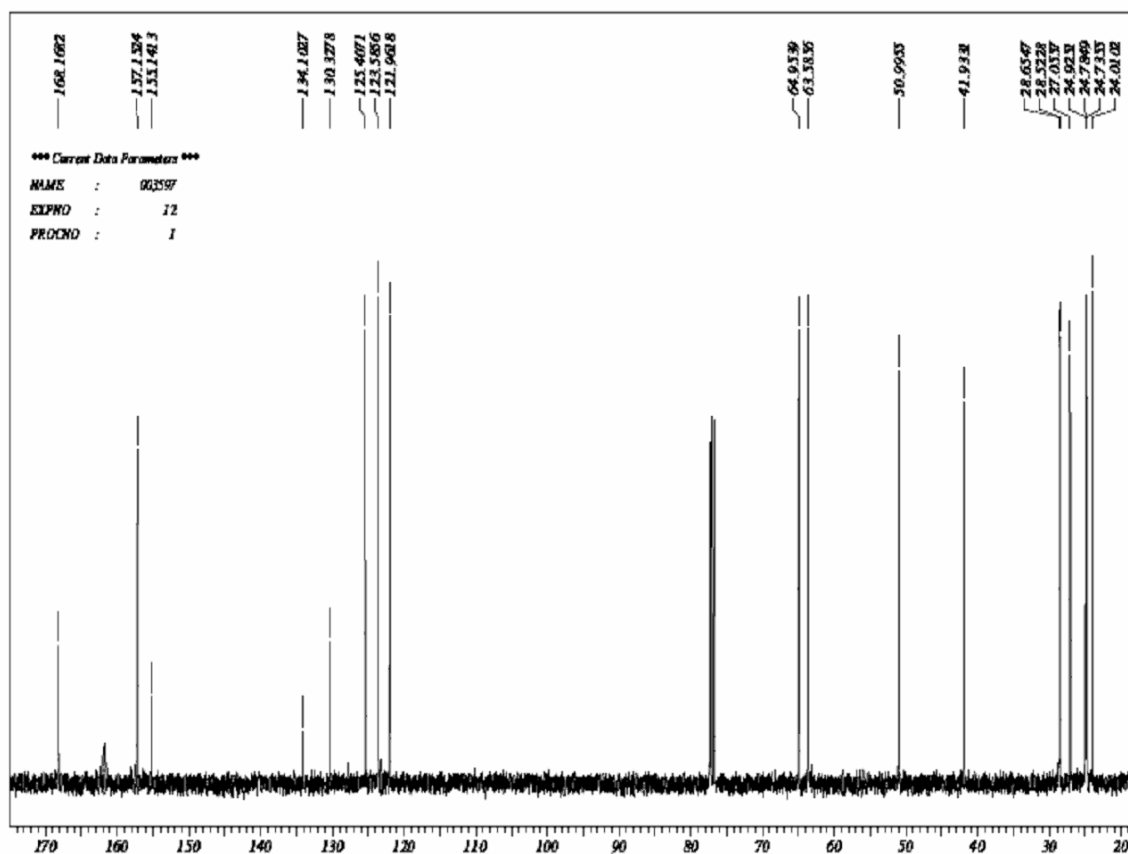
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GB-6682

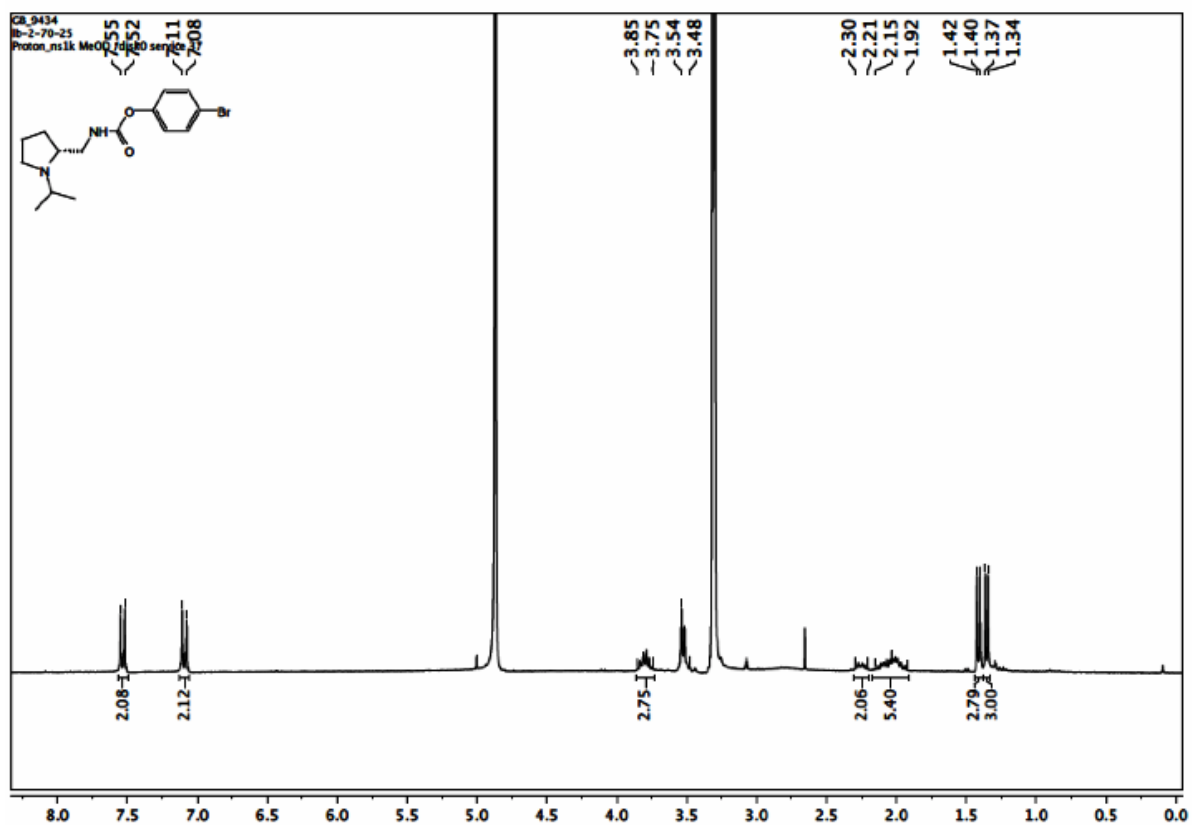
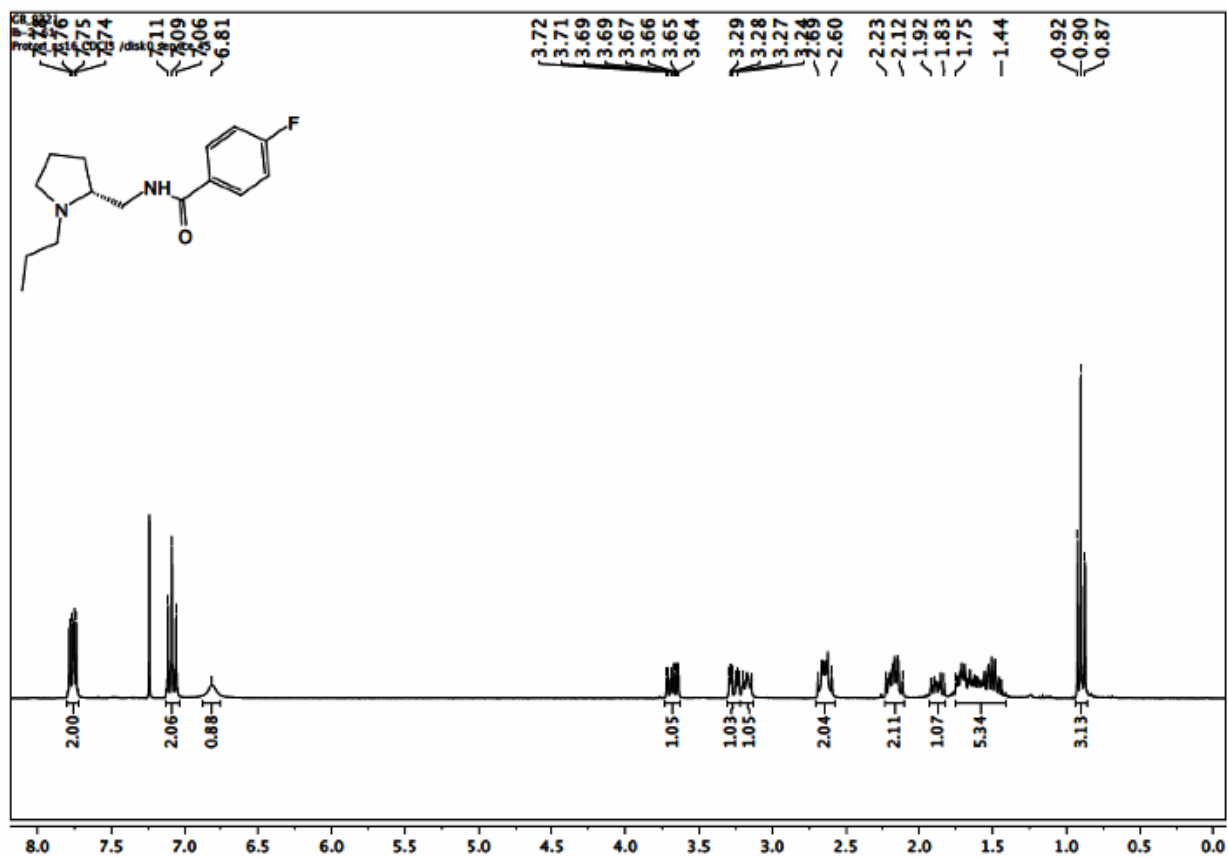
¹³C NMR Spectrum of **15b** (CDCl₃, 75 MHz)

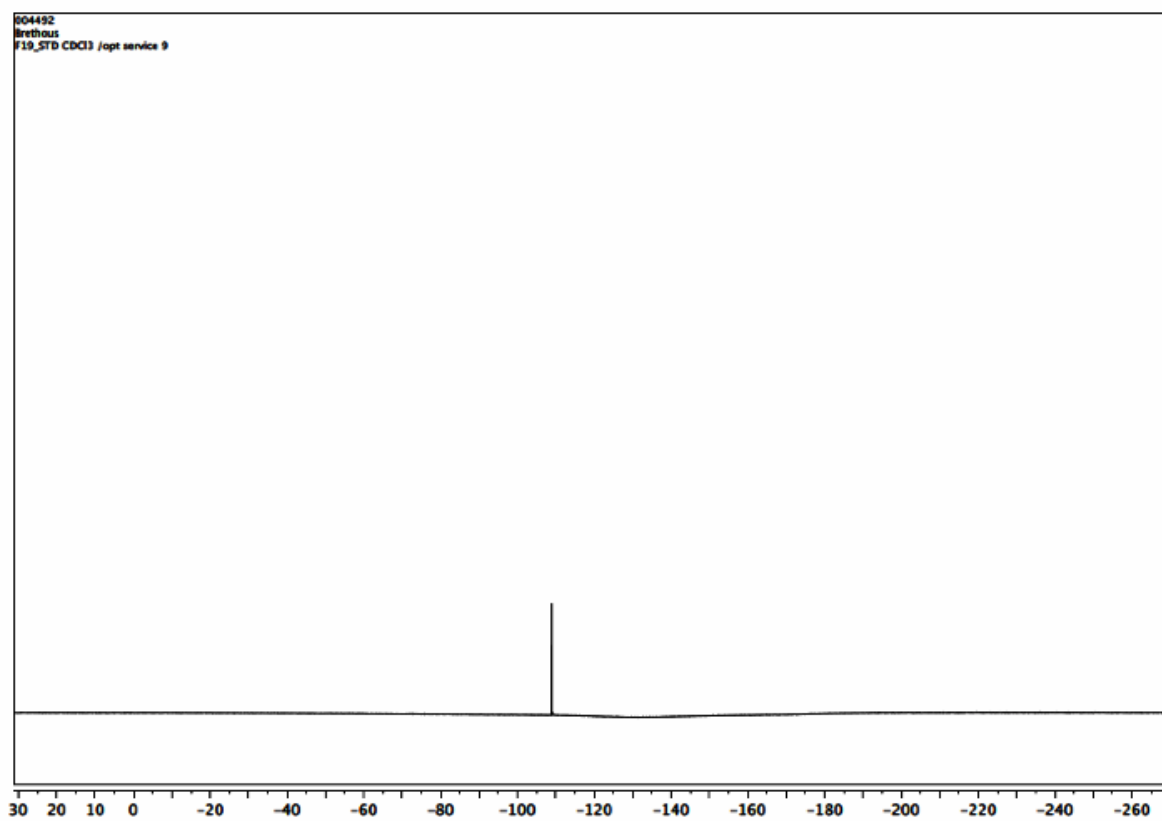
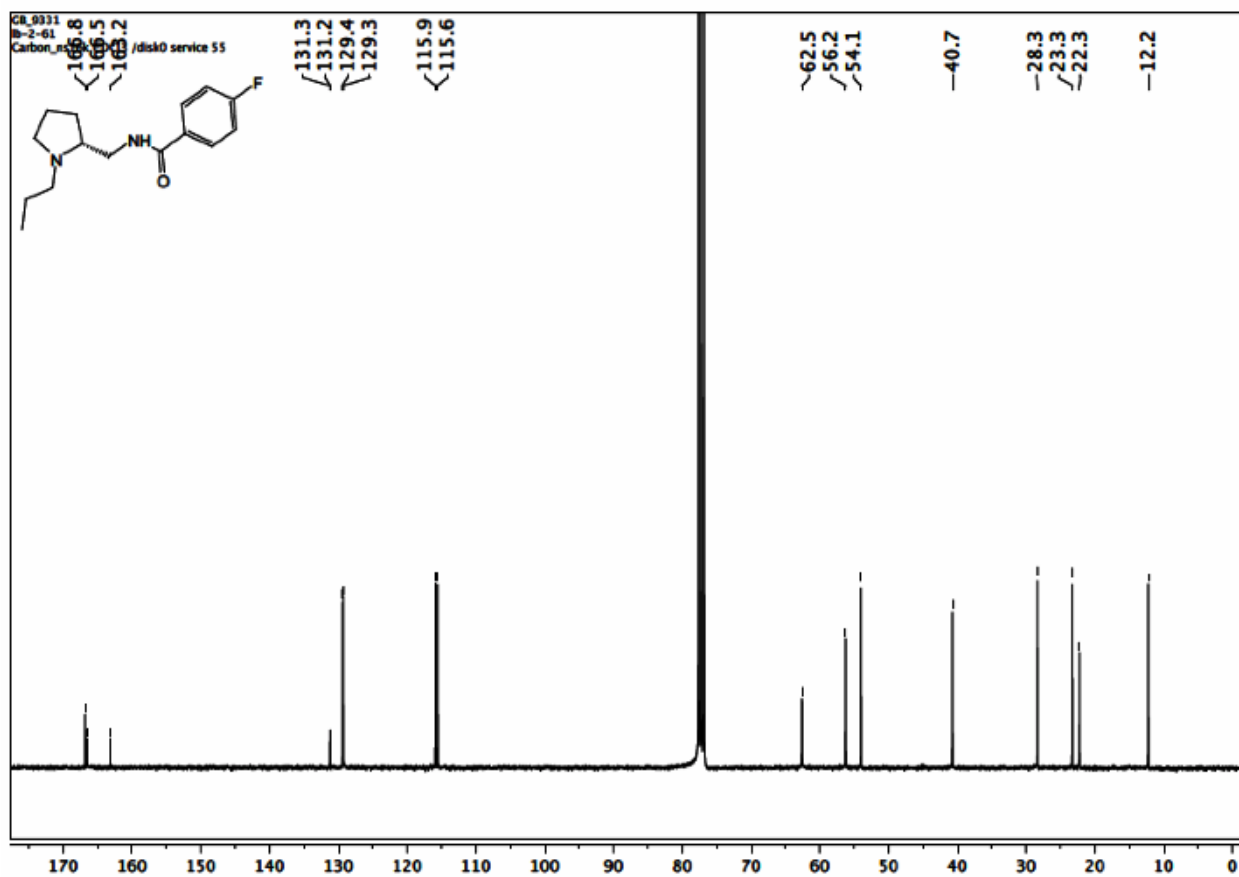
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GB-6682

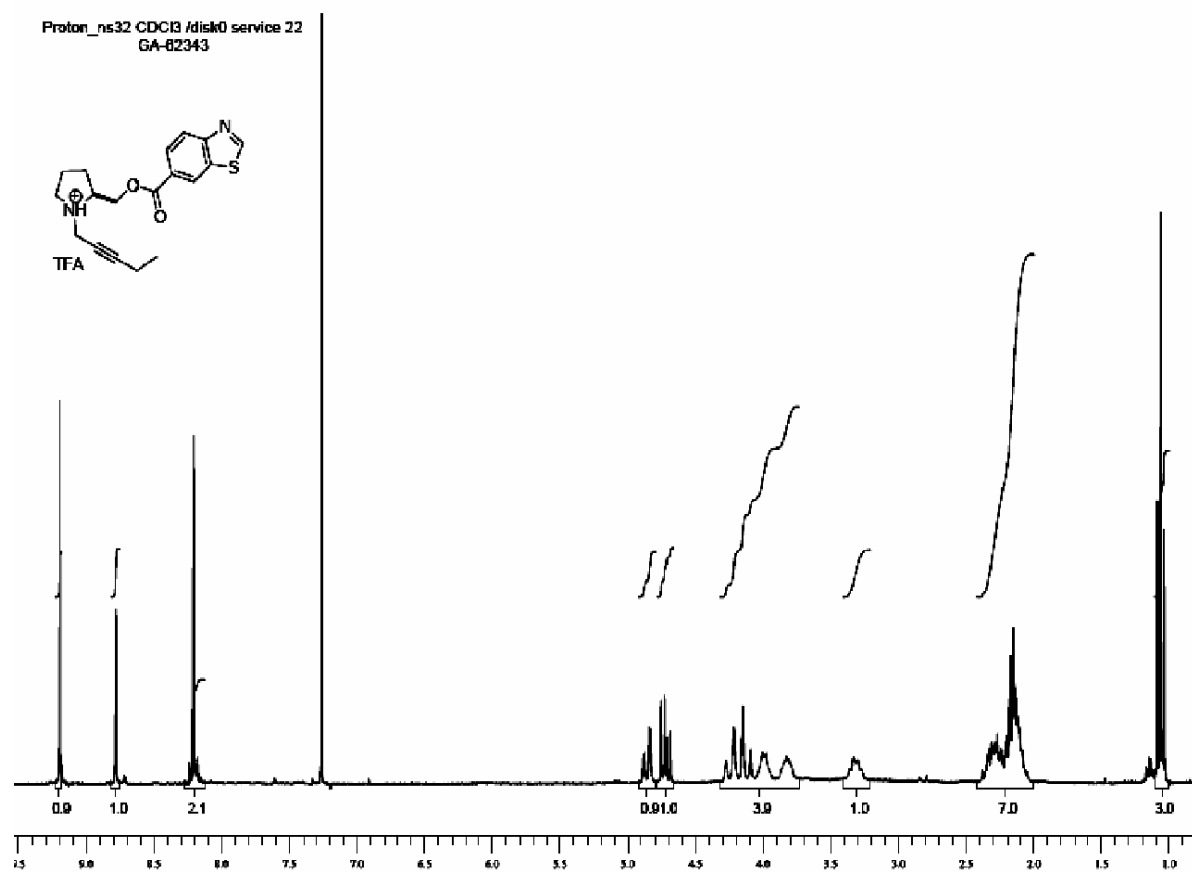
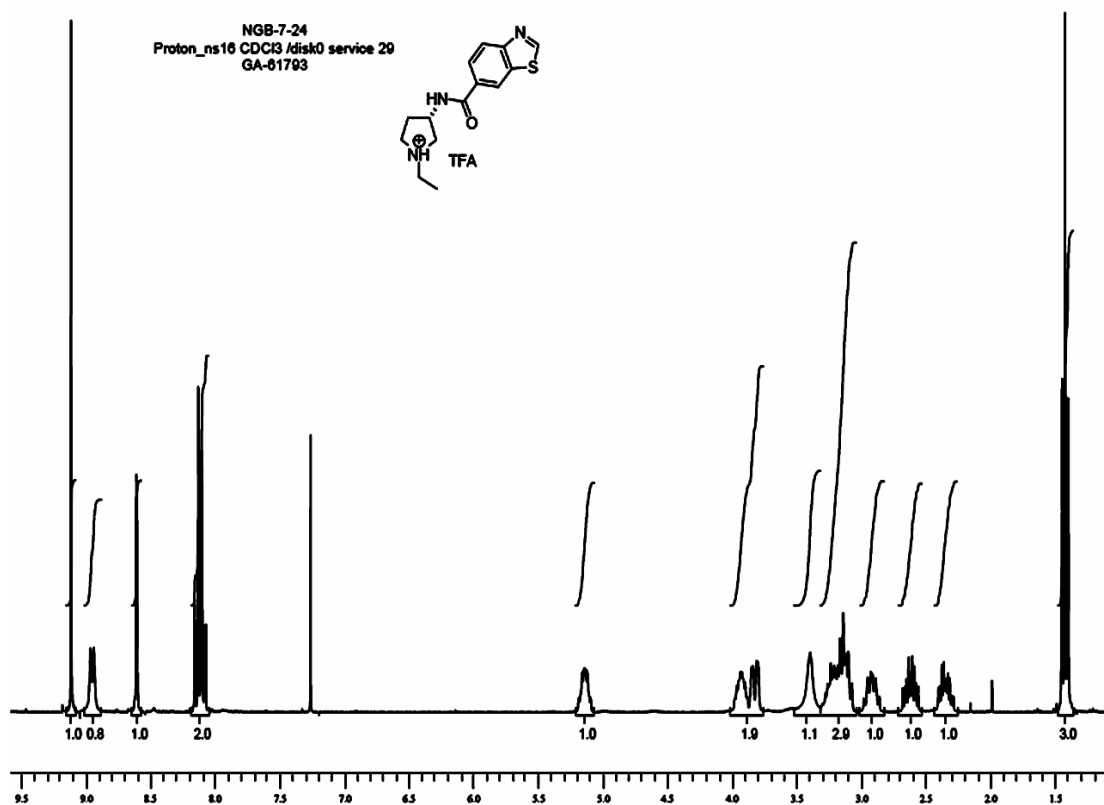


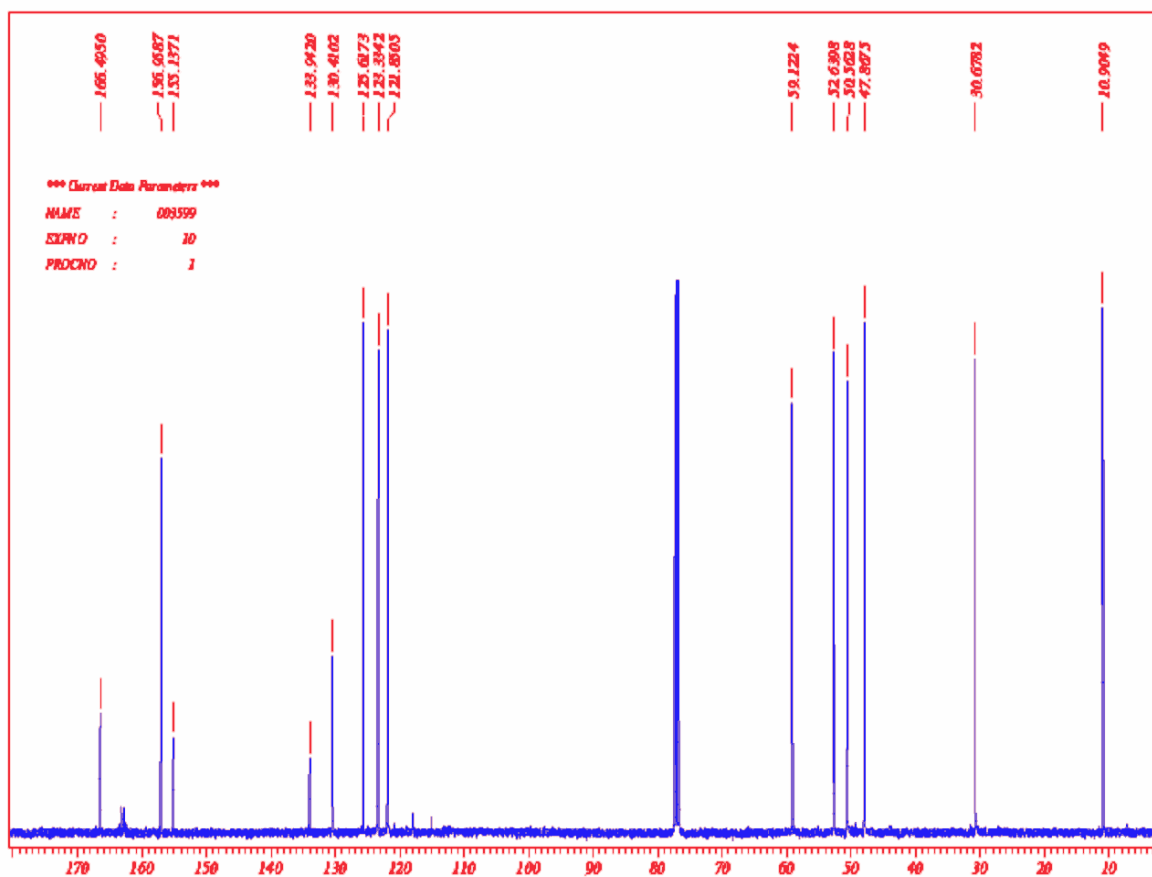
^1H NMR Spectrum of **15e** (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **15e** (CDCl_3 , 75 MHz)

¹H NMR Spectrum of **16b** TFA salt (CDCl₃, 300 MHz)¹³C NMR Spectrum of **16b** TFA salt (CDCl₃, 75 MHz)

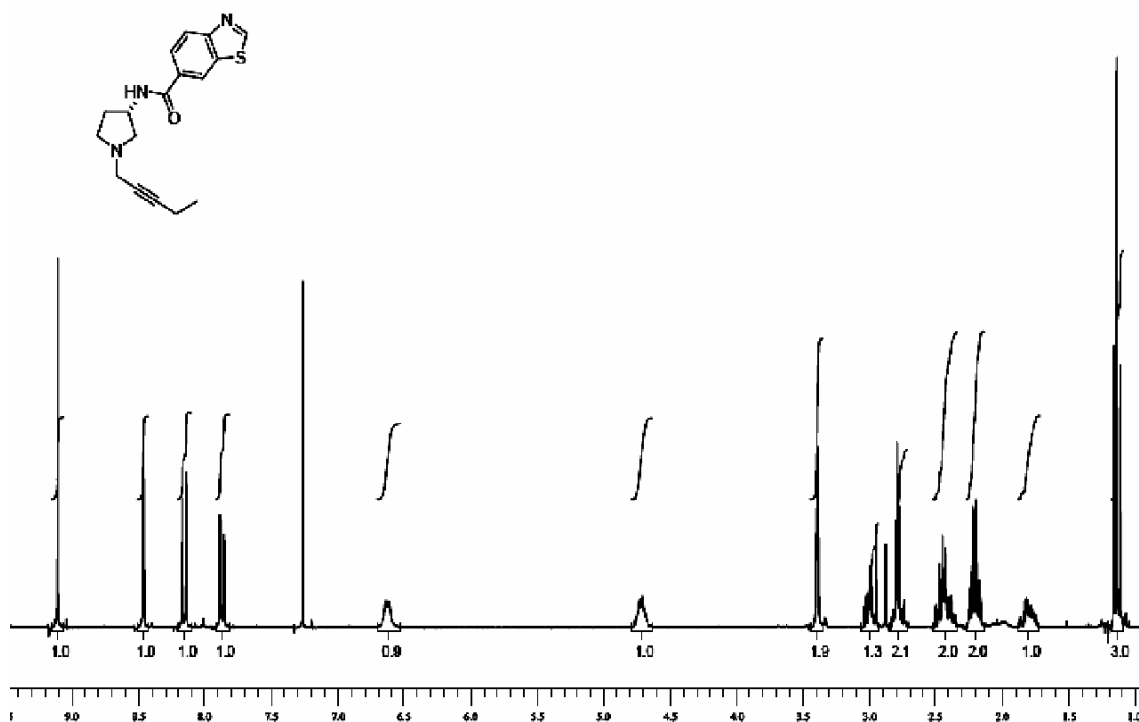
^1H NMR Spectrum of **17e** (MeOD, 300 MHz) ^1H NMR Spectrum of **18k** (CDCl_3 , 300 MHz)

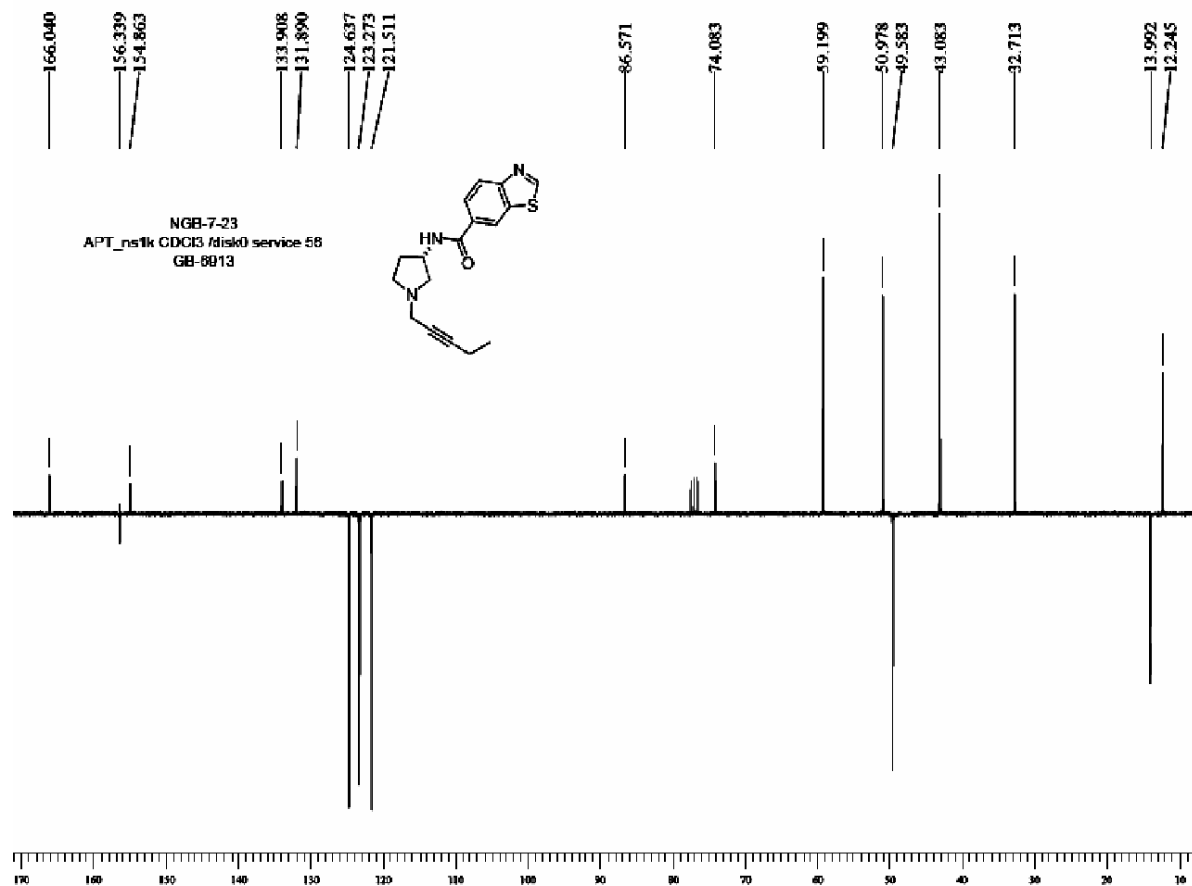
^{19}F NMR Spectrum of **18k** (CDCl_3 , 376 MHz) ^{13}C NMR Spectrum of **18k** (CDCl_3 , 75 MHz)

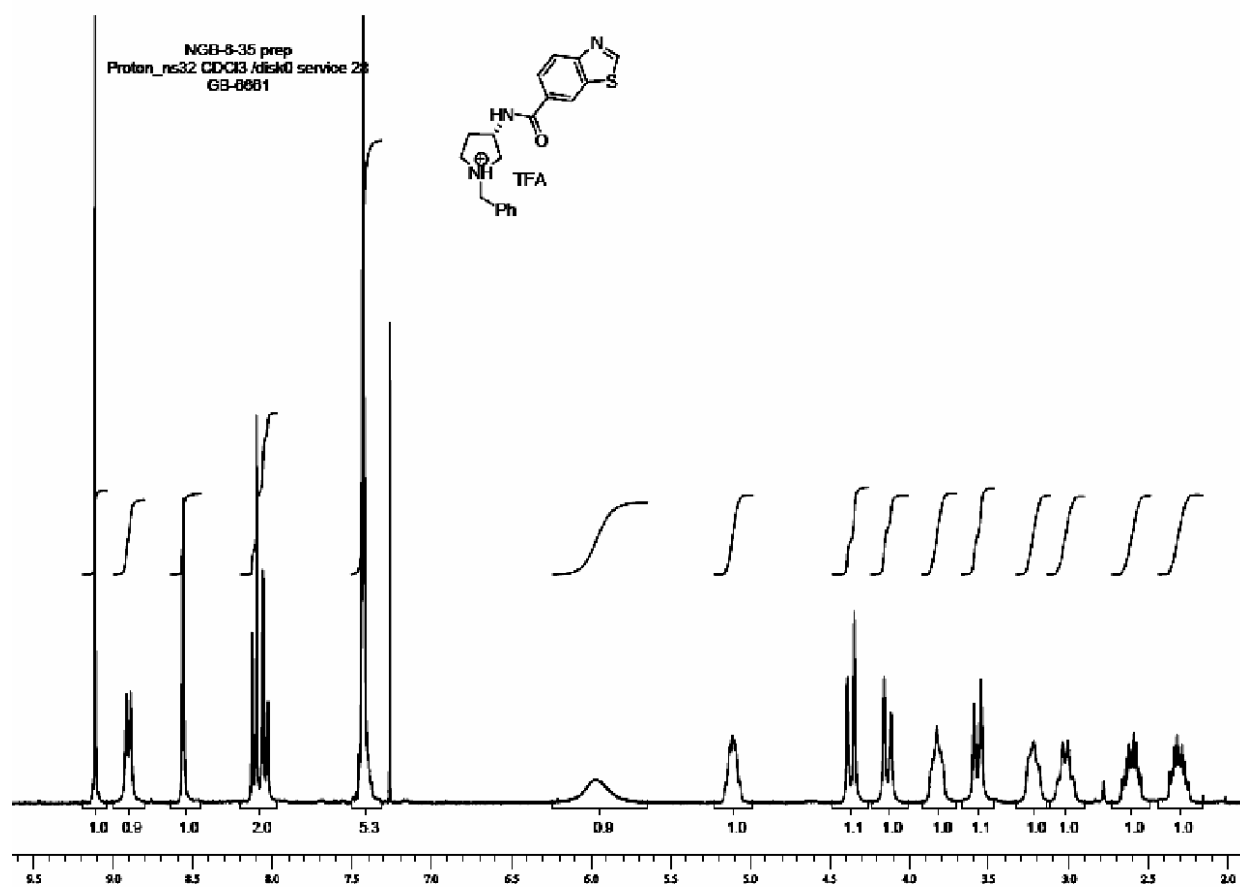
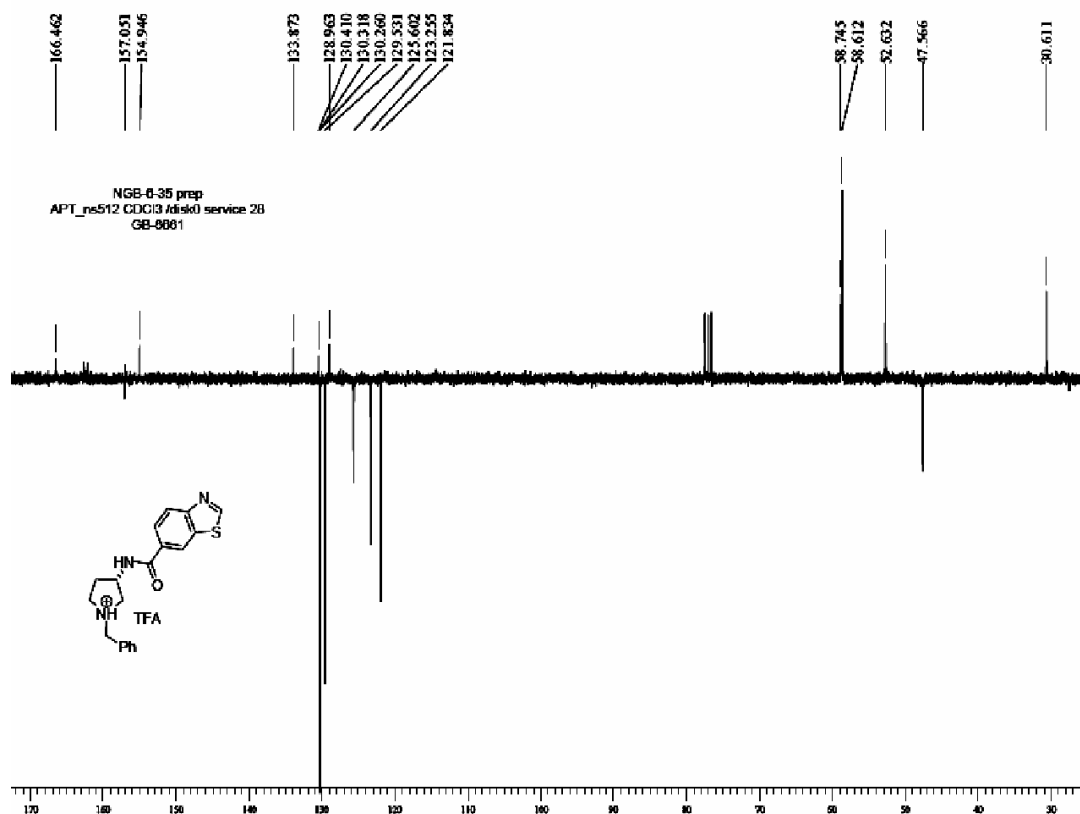
^1H NMR Spectrum of **19b** TFA salt (CDCl_3 , 300 MHz) ^1H NMR Spectrum of **20b** TFA salt (CDCl_3 , 300 MHz)

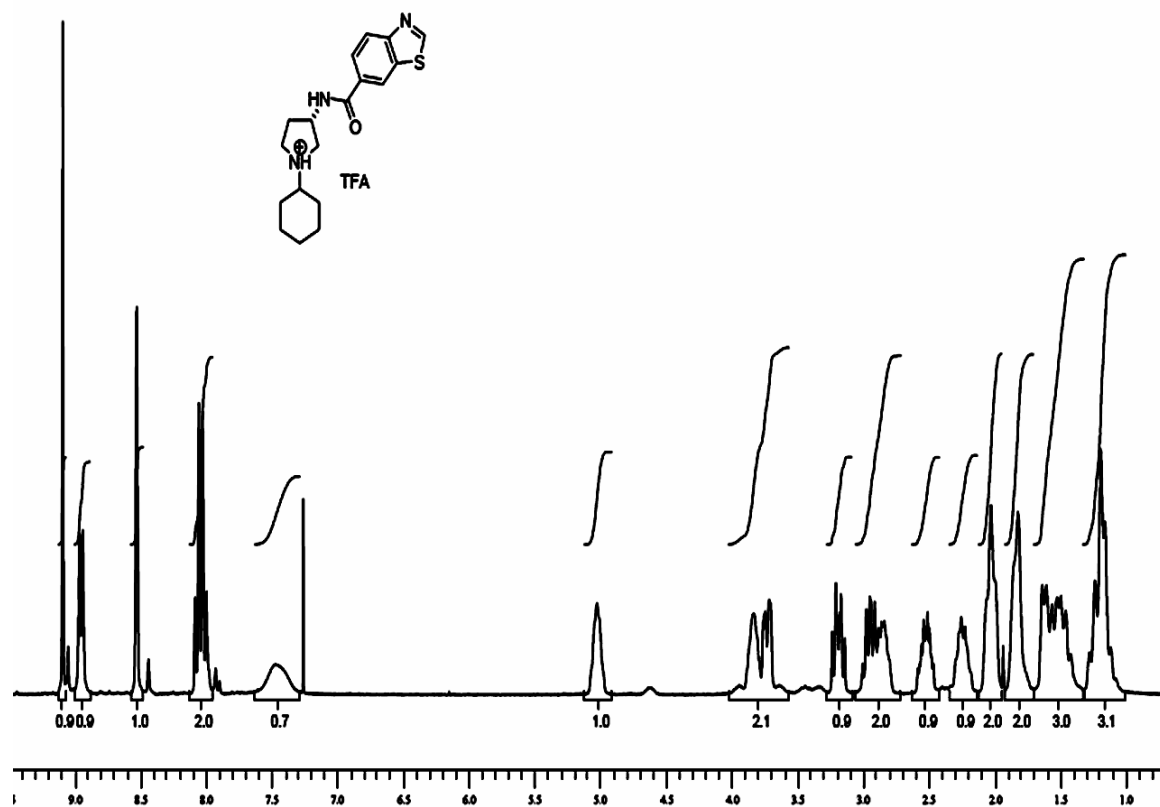
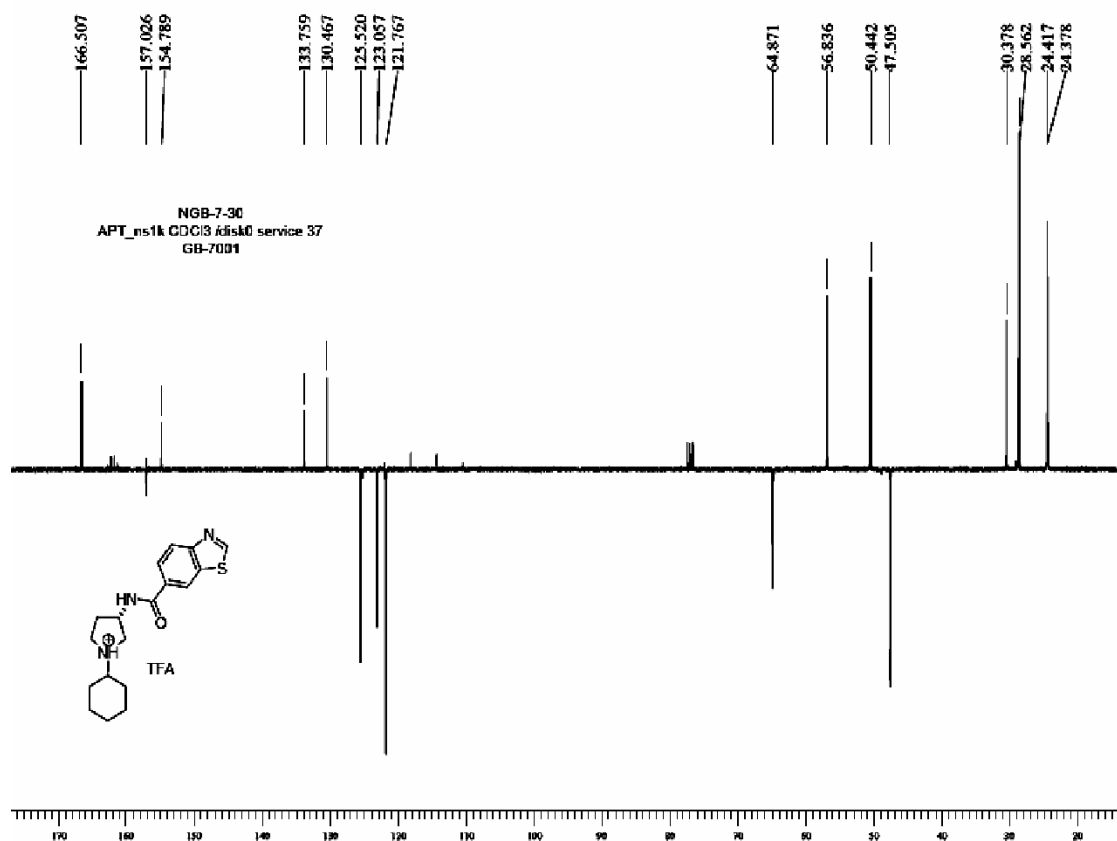
^{13}C NMR Spectrum of **20b** TFA salt (CDCl_3 , 75 MHz) ^1H NMR Spectrum of **21b** TFA salt (CDCl_3 , 300 MHz)

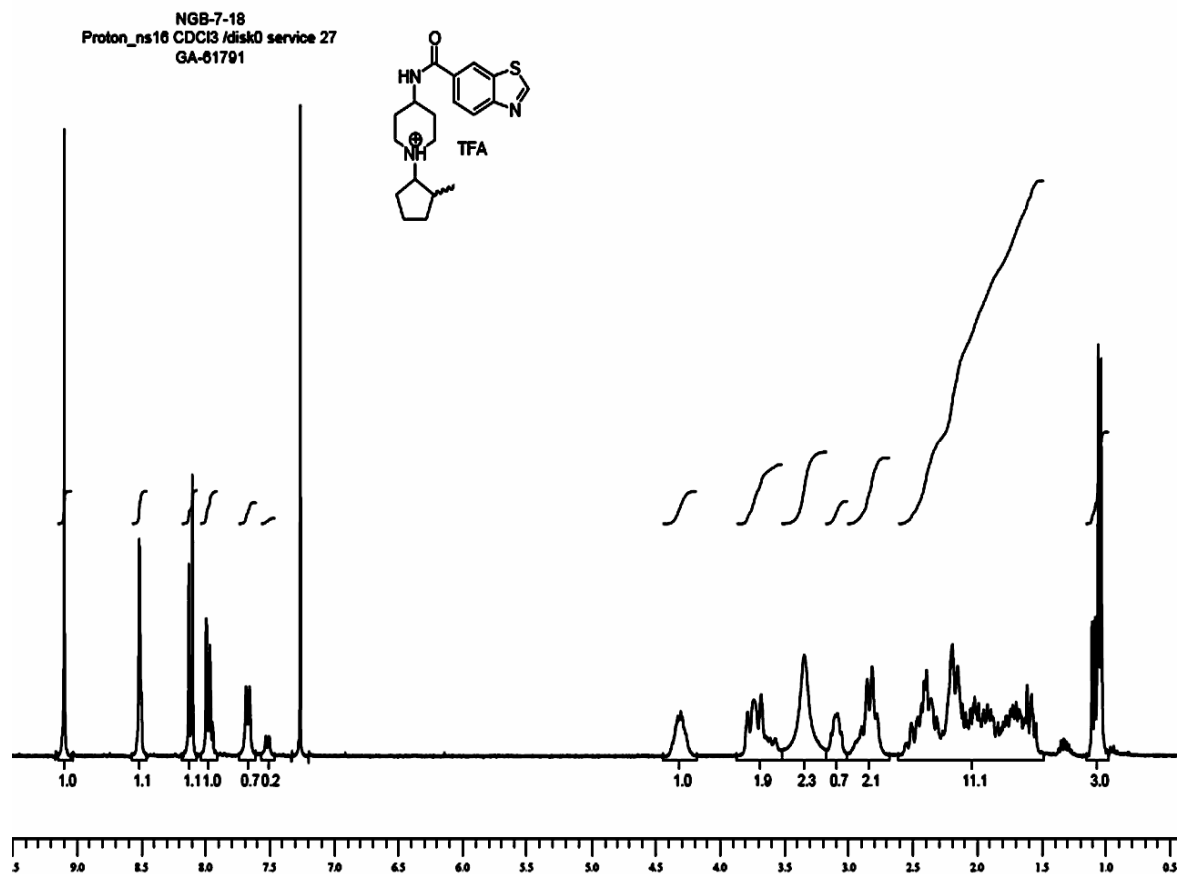
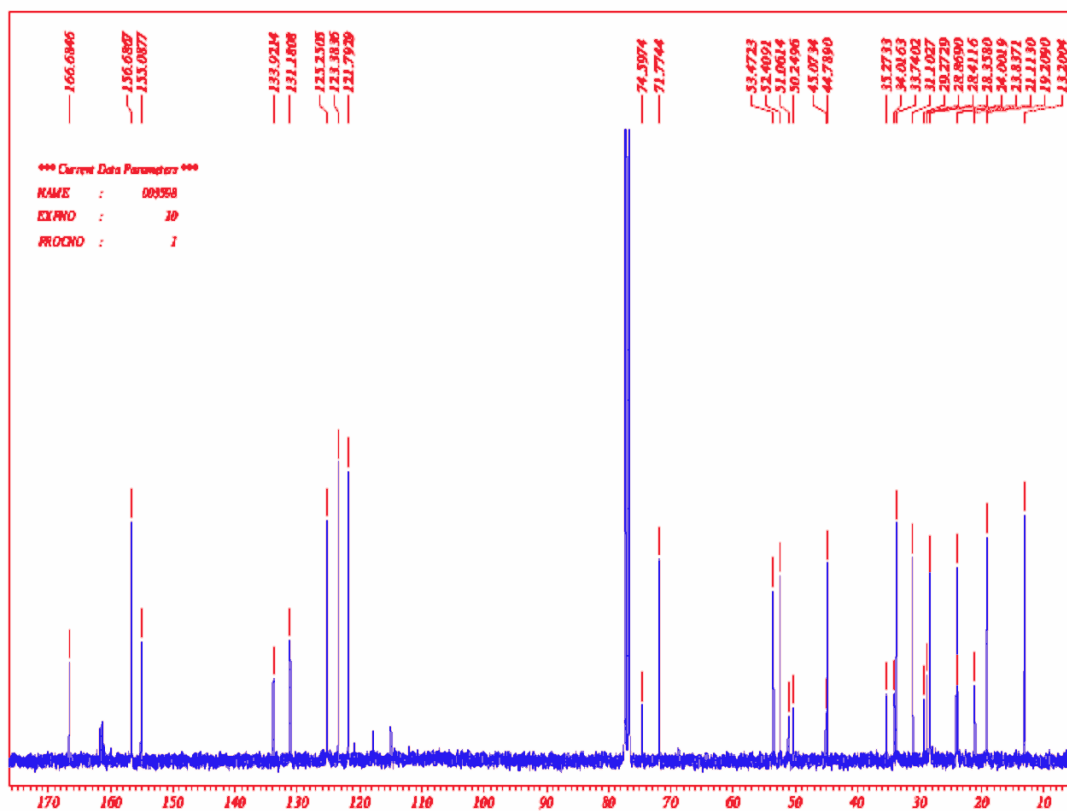
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 GA-01486

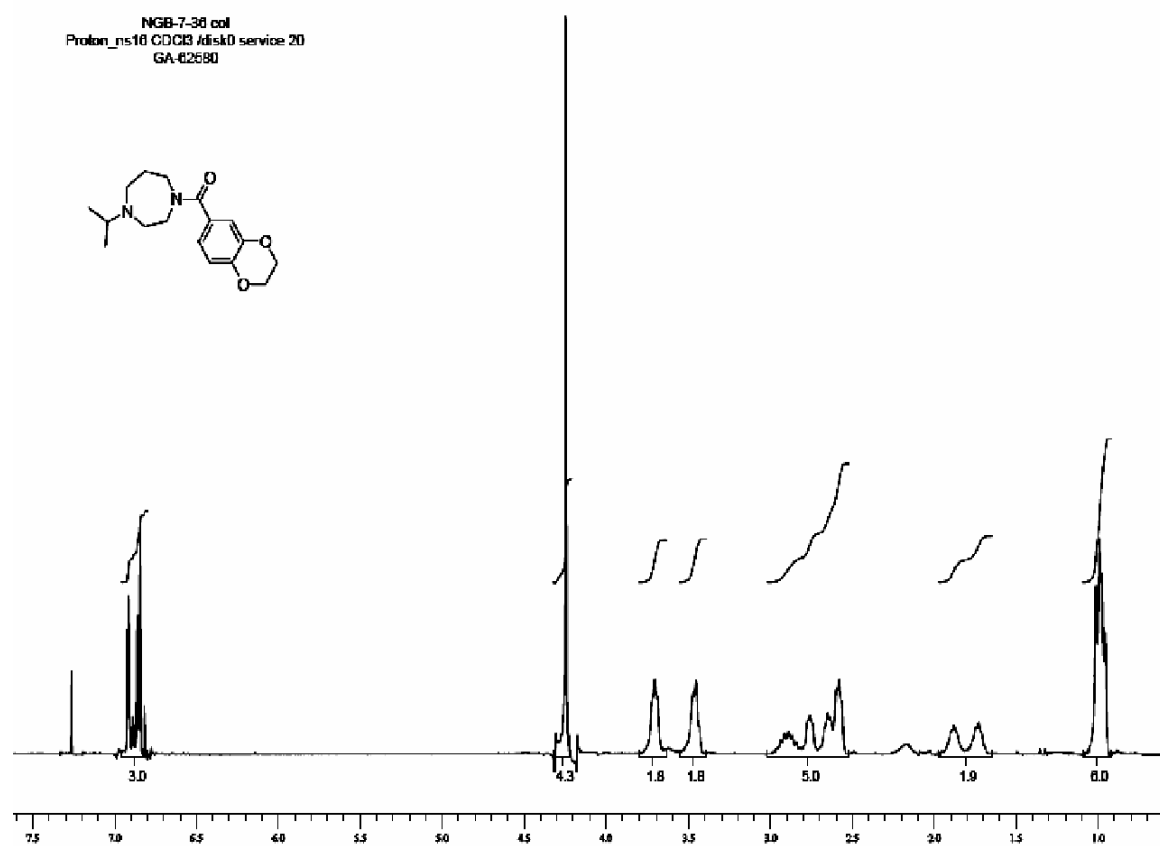
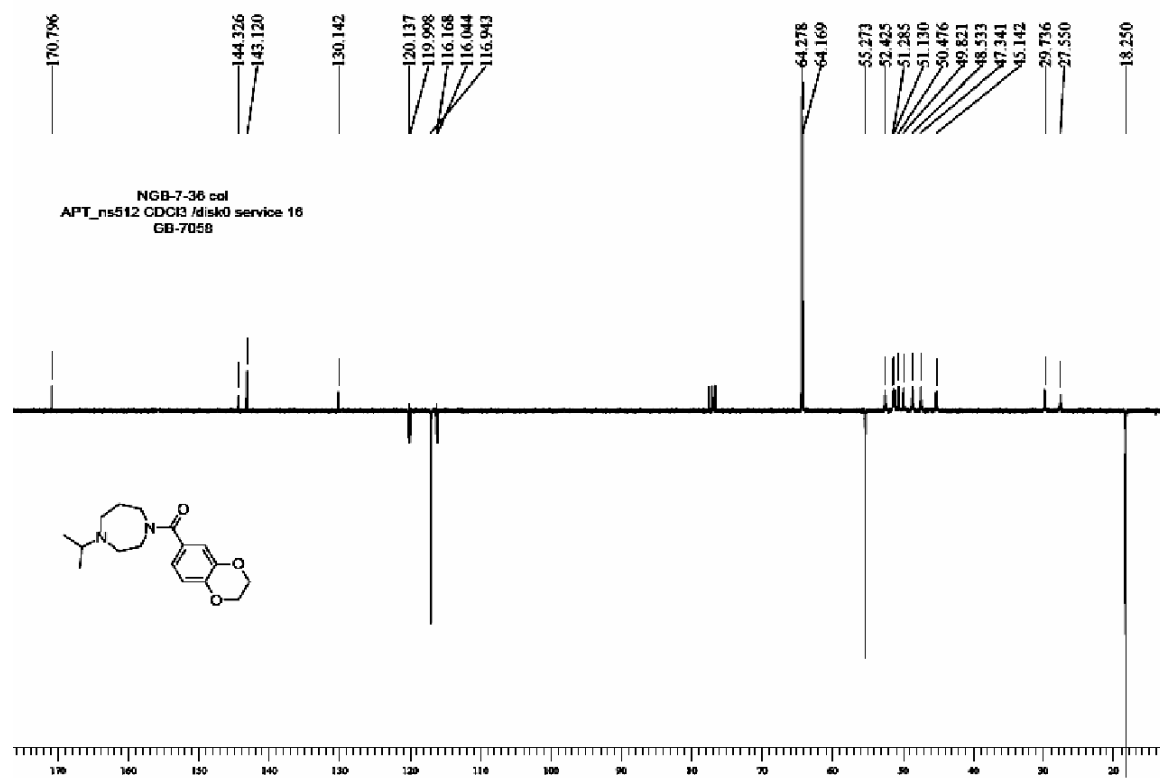


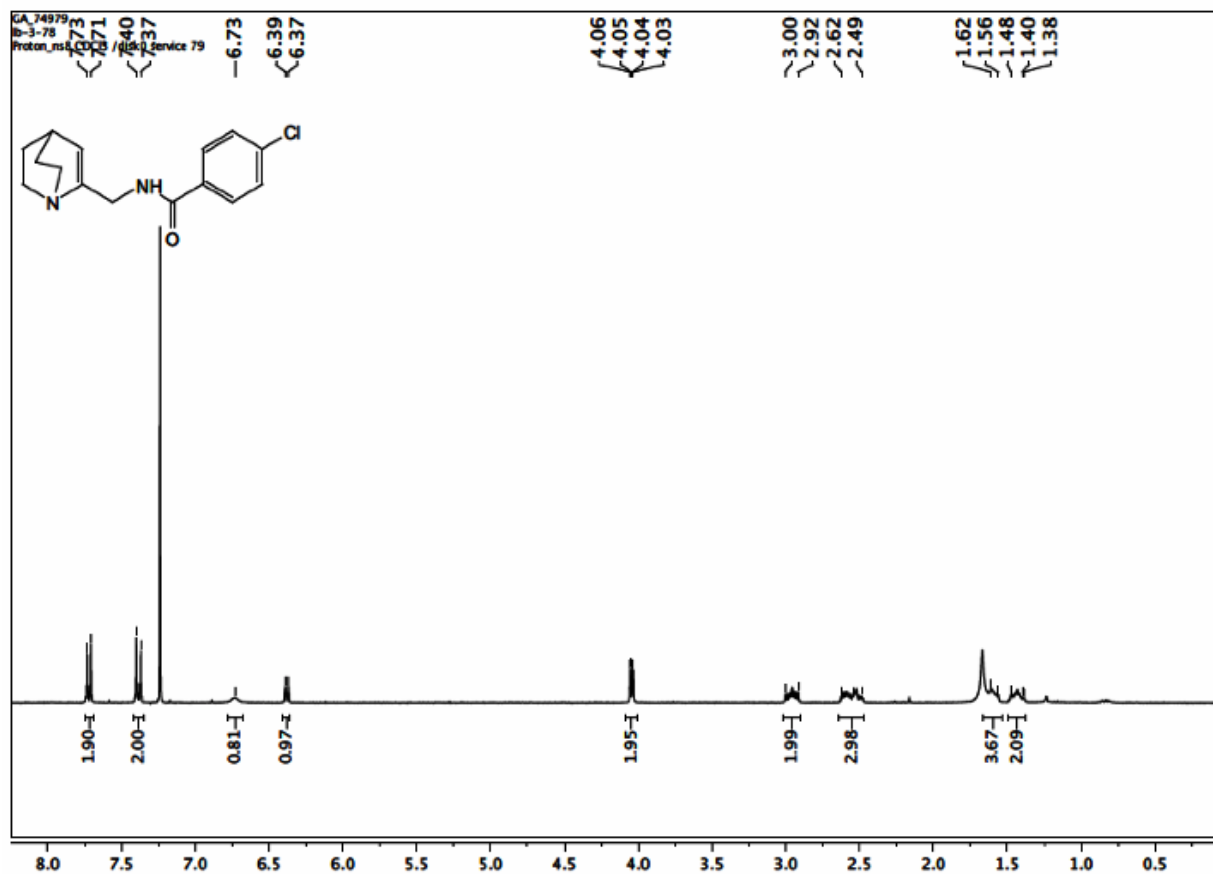
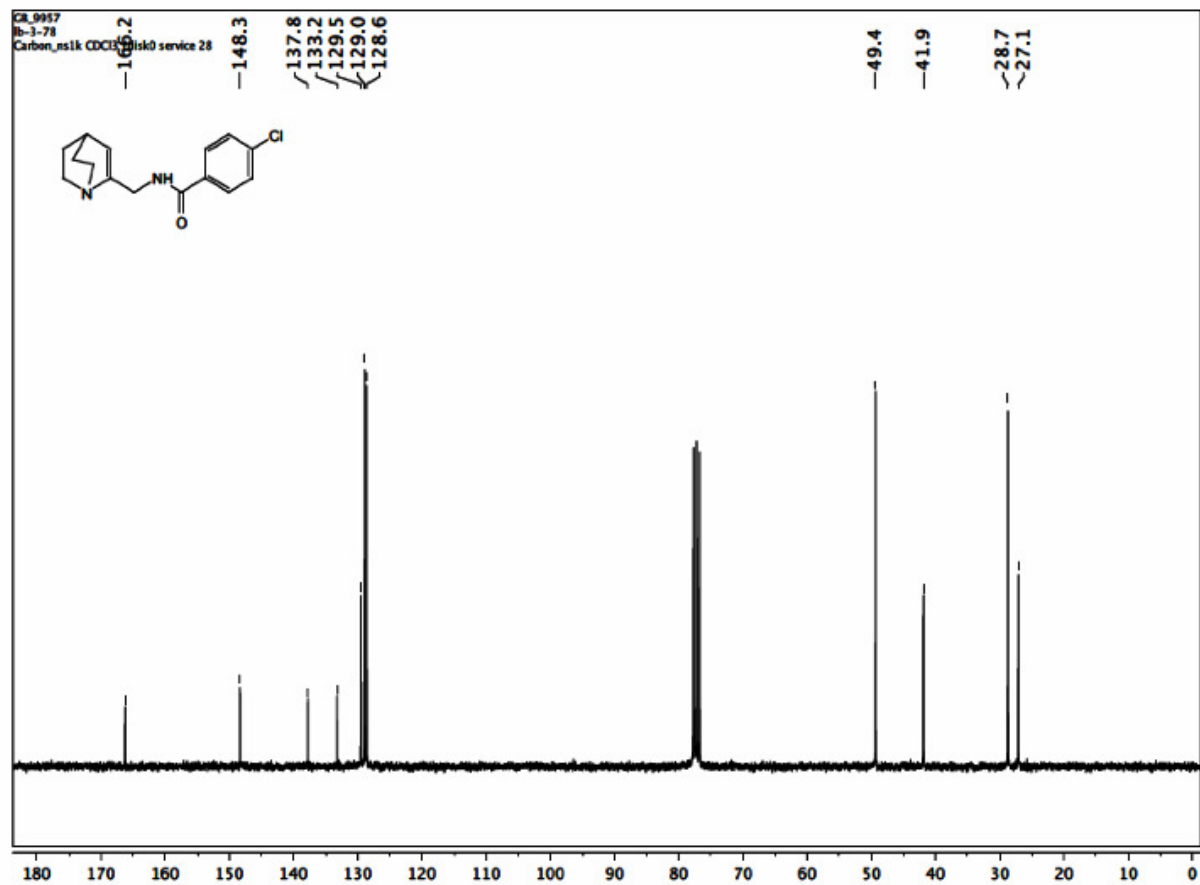
ATP-¹³C NMR Spectrum of **21b** TFA salt (CDCl₃, 75 MHz)

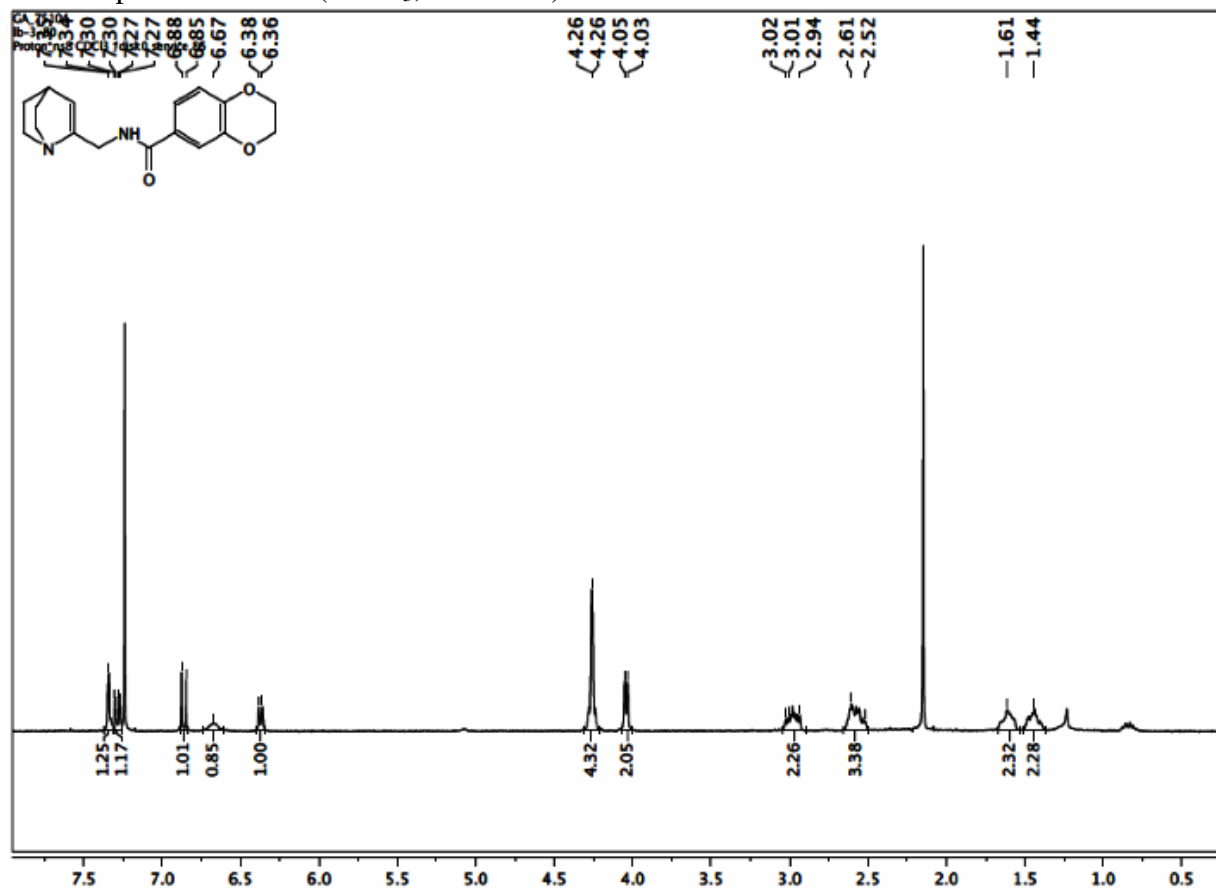
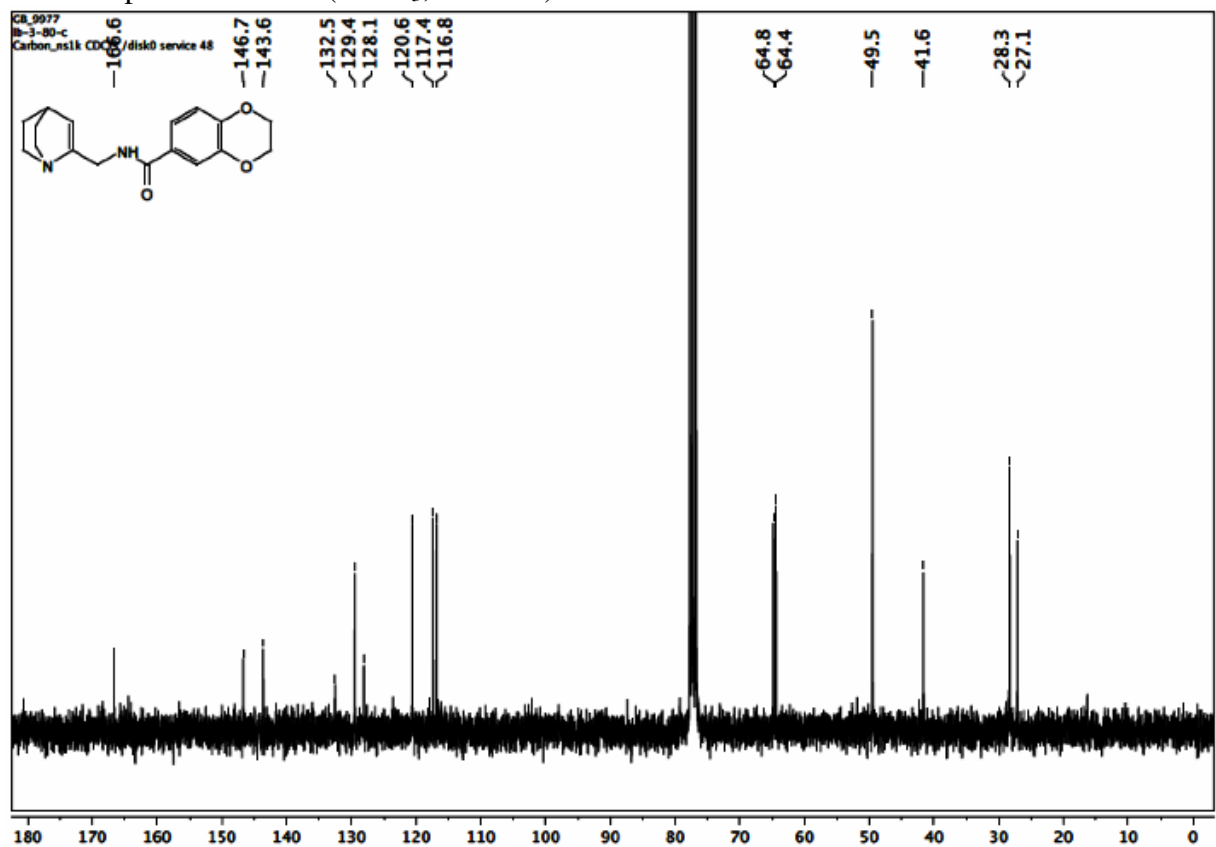
^1H NMR Spectrum of **22b** TFA salt (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **22b** TFA salt (CDCl_3 , 75 MHz)

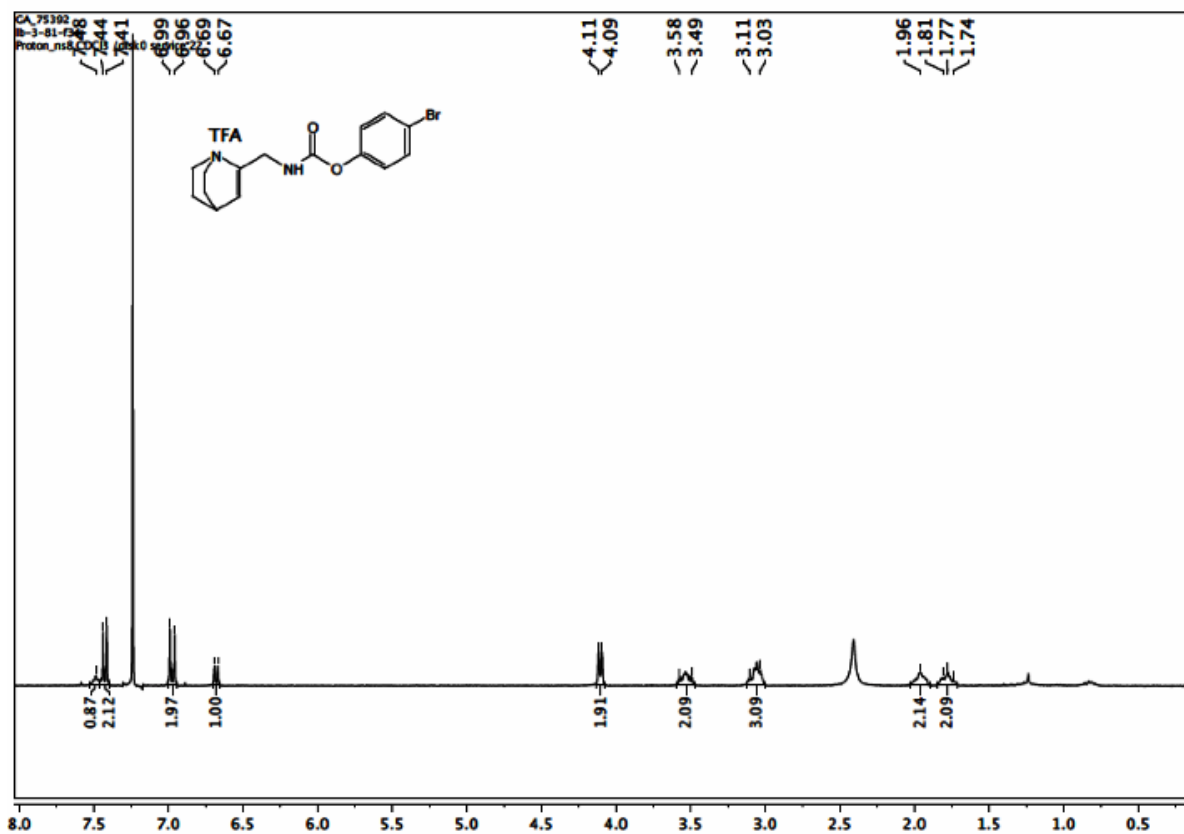
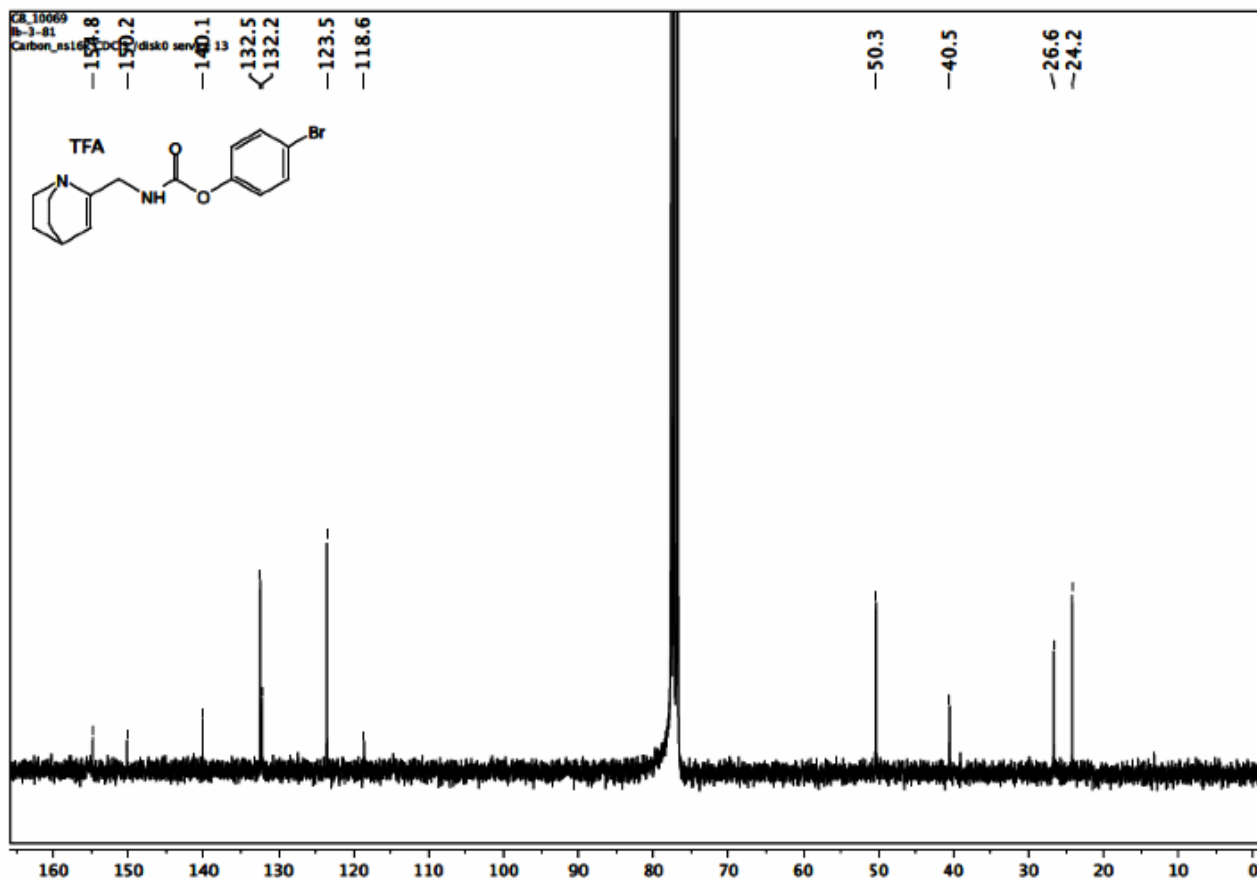
^1H NMR Spectrum of **23b** TFA salt (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **23b** TFA salt (CDCl_3 , 75 MHz)

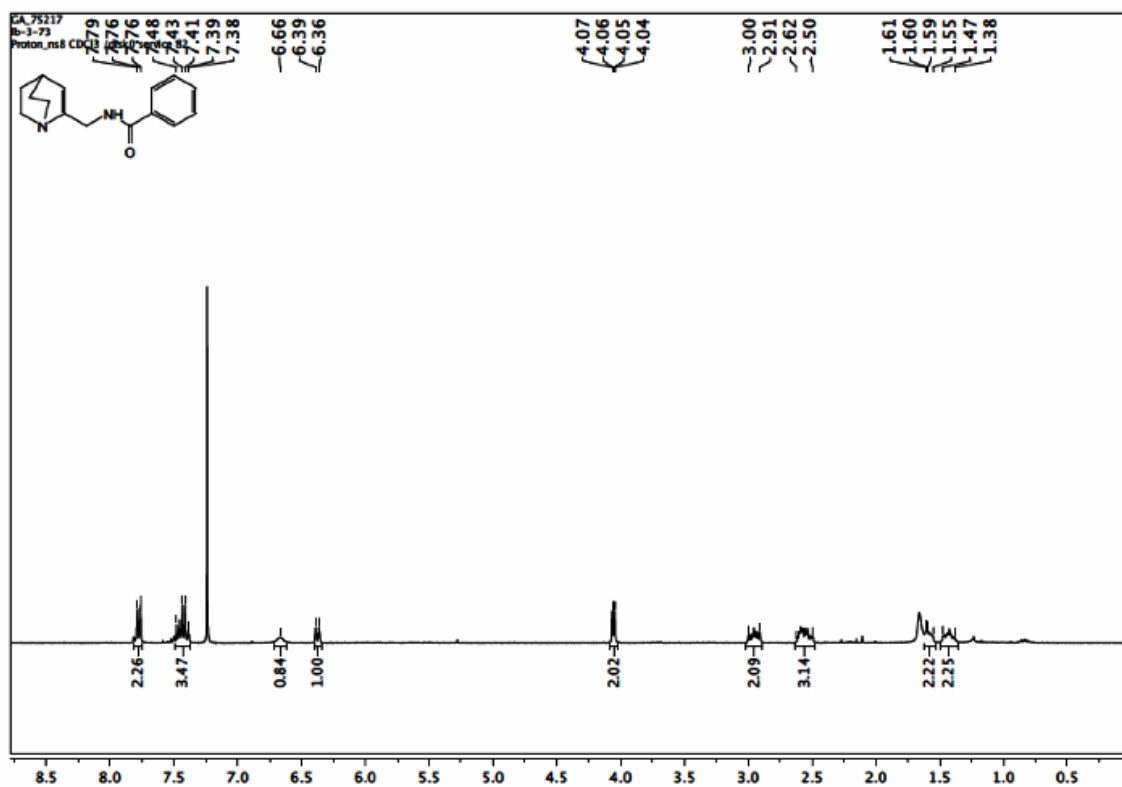
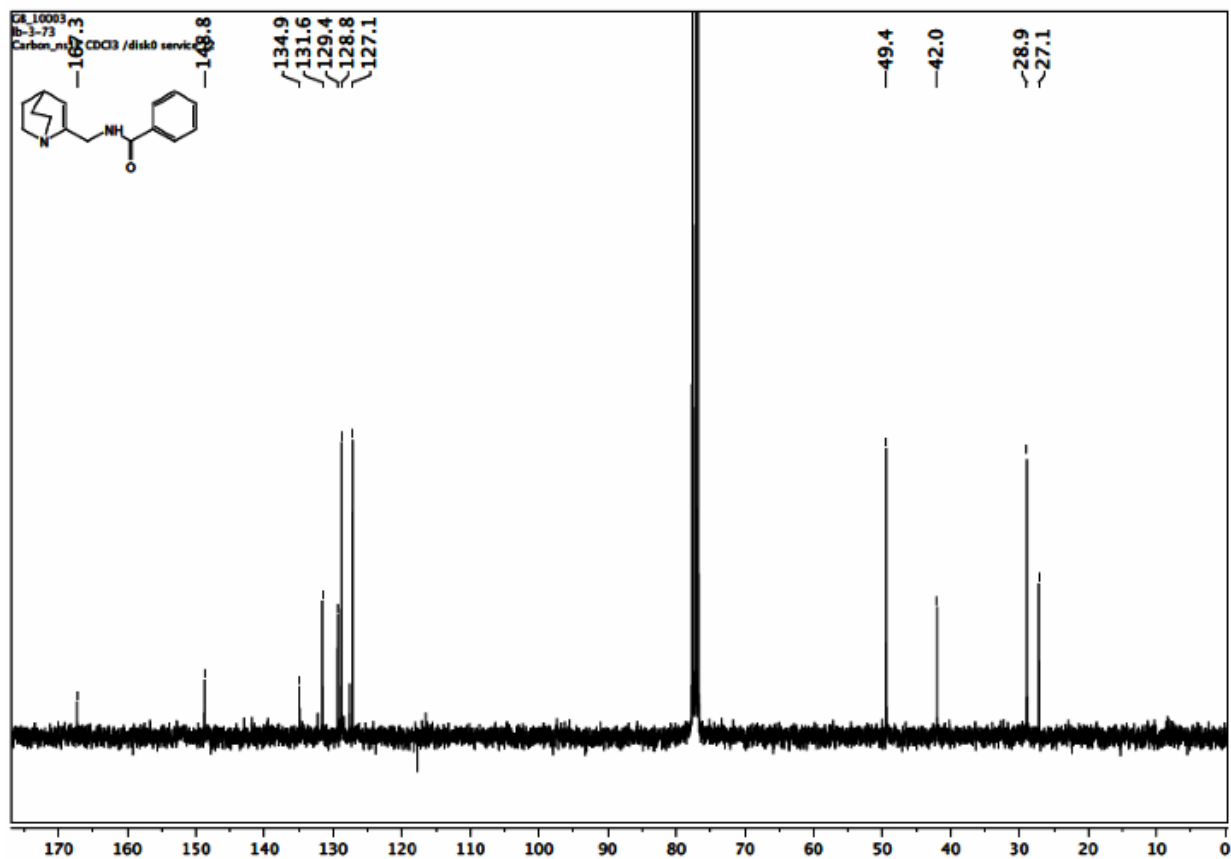
¹H NMR Spectrum of **24b** TFA salt (CDCl₃, 300 MHz)¹³C NMR Spectrum of **24b** TFA salt (CDCl₃, 75 MHz)

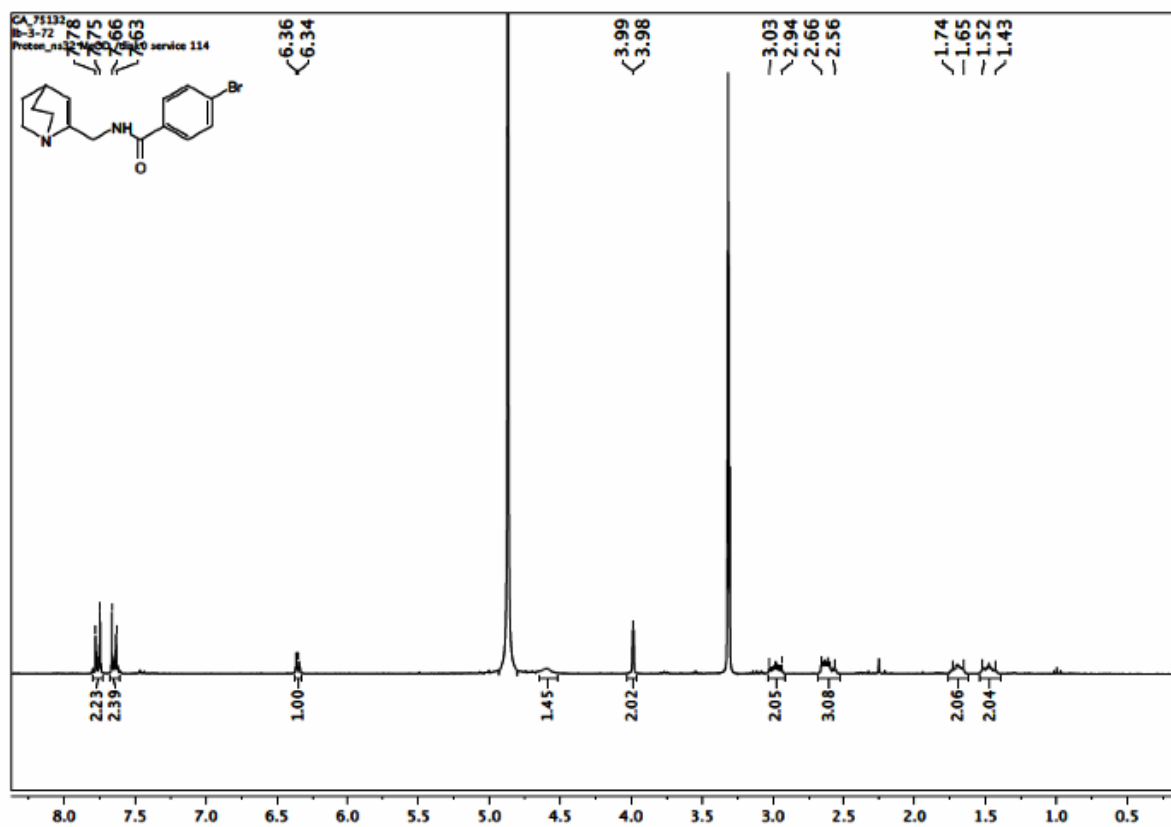
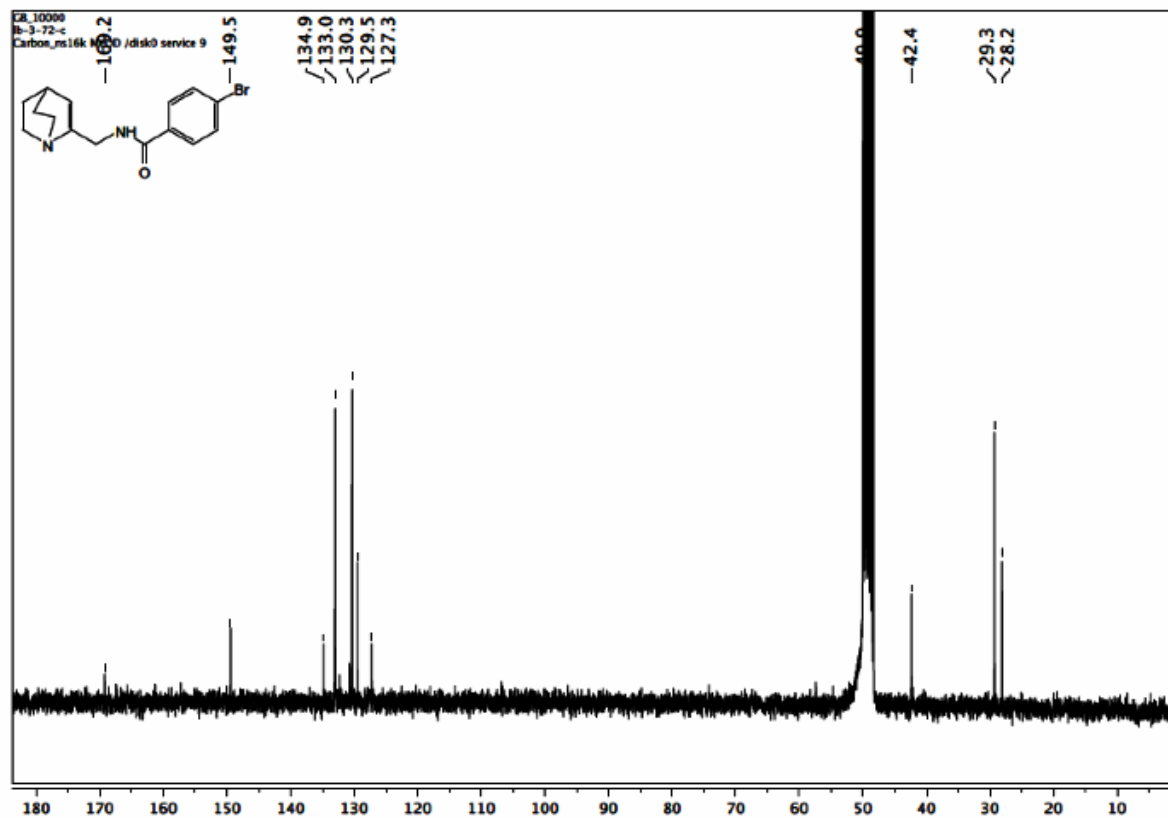
^1H NMR Spectrum of **25c** (CDCl_3 , 300 MHz)ATP- ^{13}C NMR Spectrum of **25c** (CDCl_3 , 75 MHz)

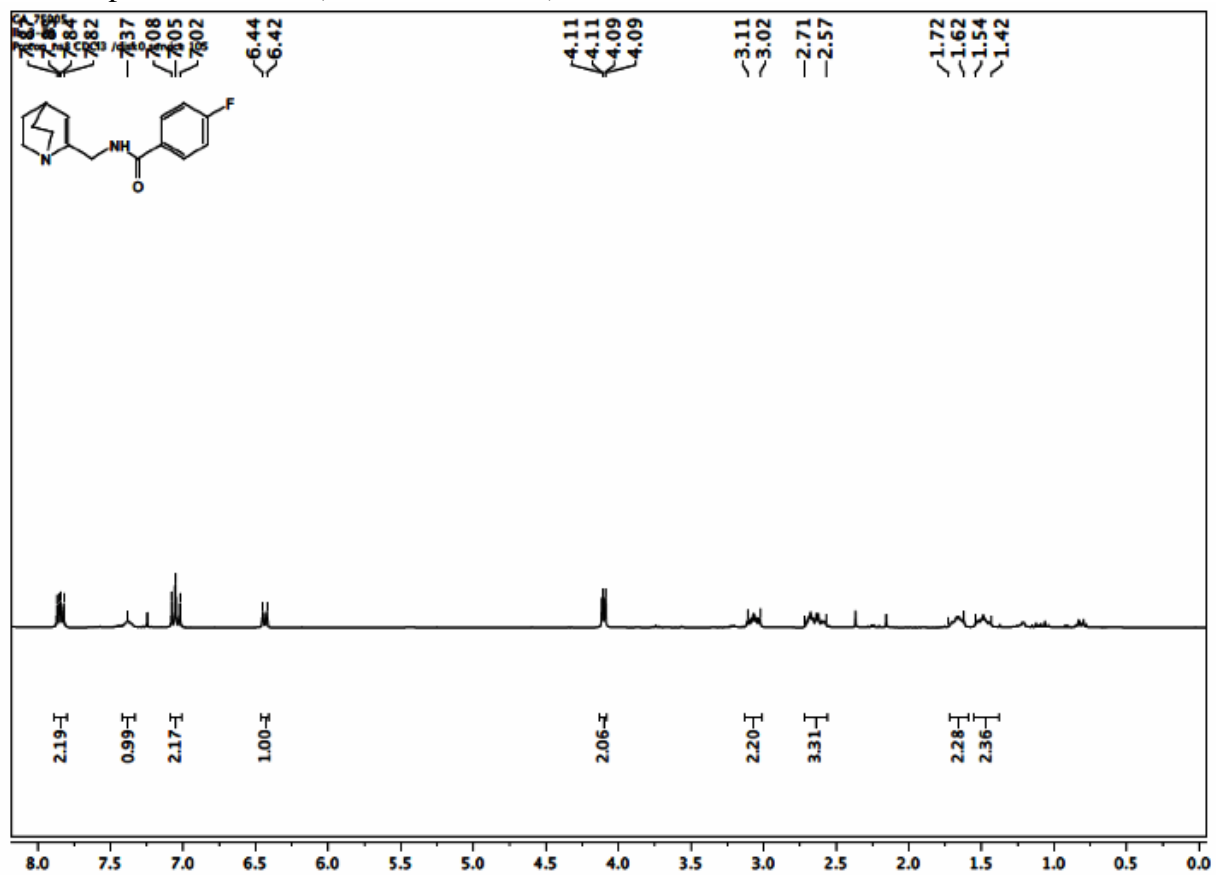
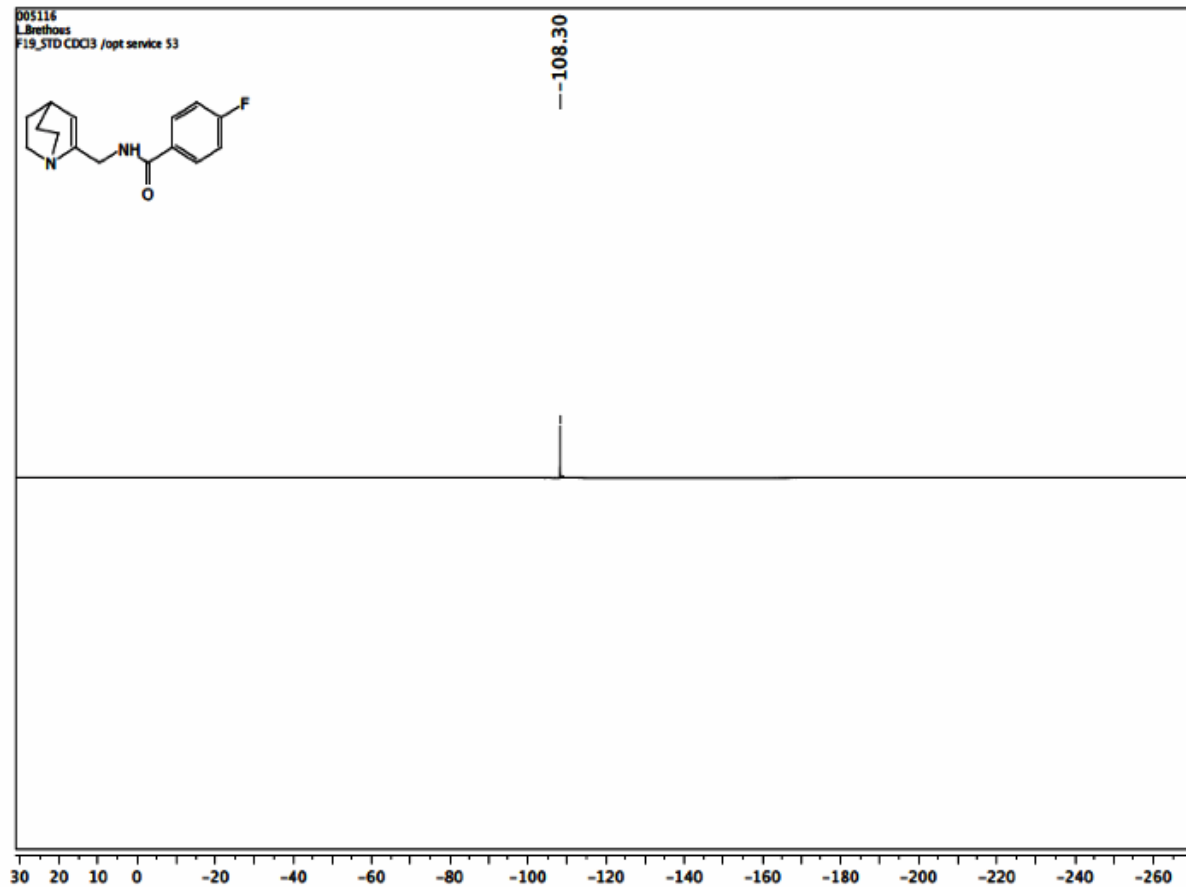
¹H NMR Spectrum of **26a** (CDCl₃, 300 MHz)¹³C NMR Spectrum of **26a** (CDCl₃, 75 MHz)

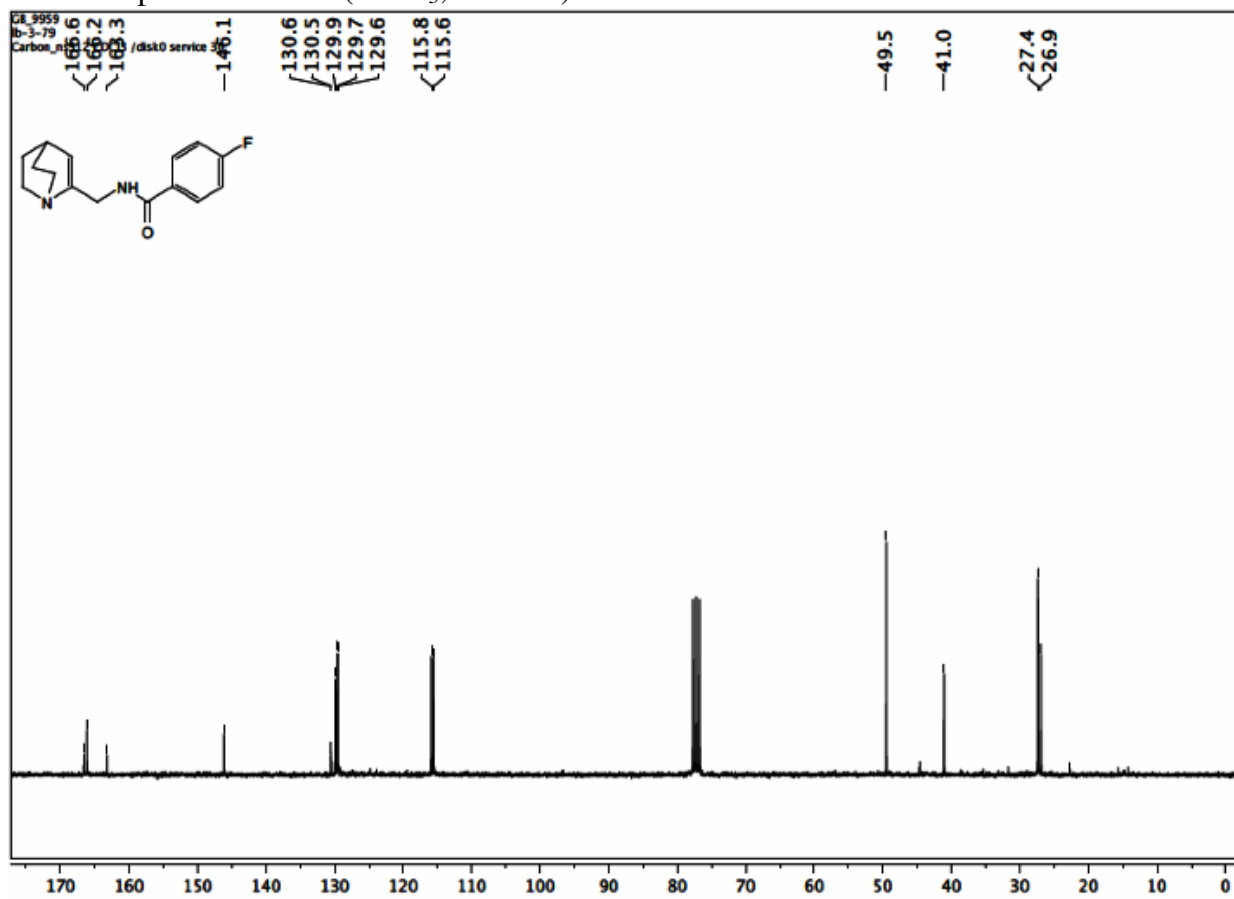
¹H NMR Spectrum of **26c** (CDCl₃, 300 MHz)¹³C NMR Spectrum of **26c** (CDCl₃, 75 MHz)

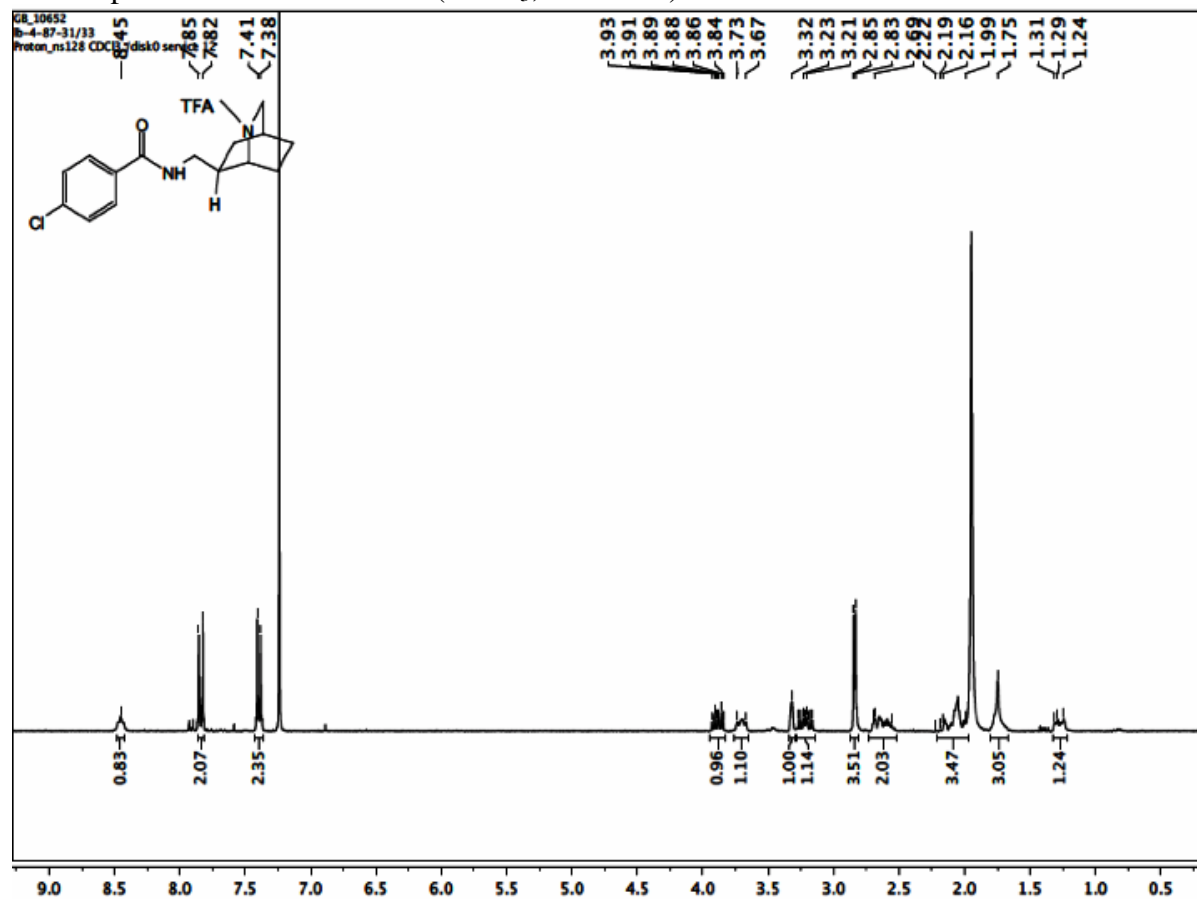
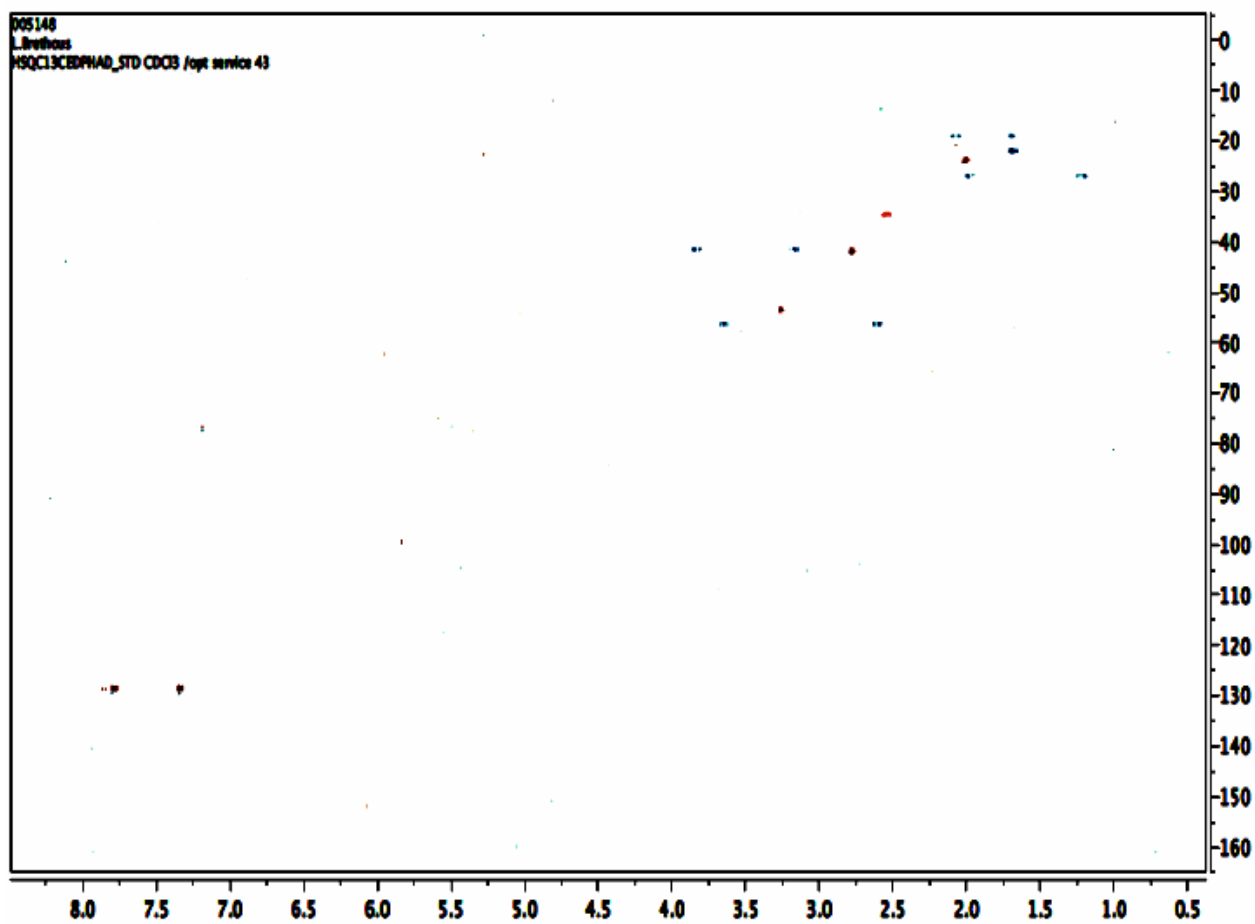
^1H NMR Spectrum of **26e** (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **26e** (CDCl_3 , 75 MHz)

^1H NMR Spectrum of **26f** (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **26f** (CDCl_3 , 75 MHz)

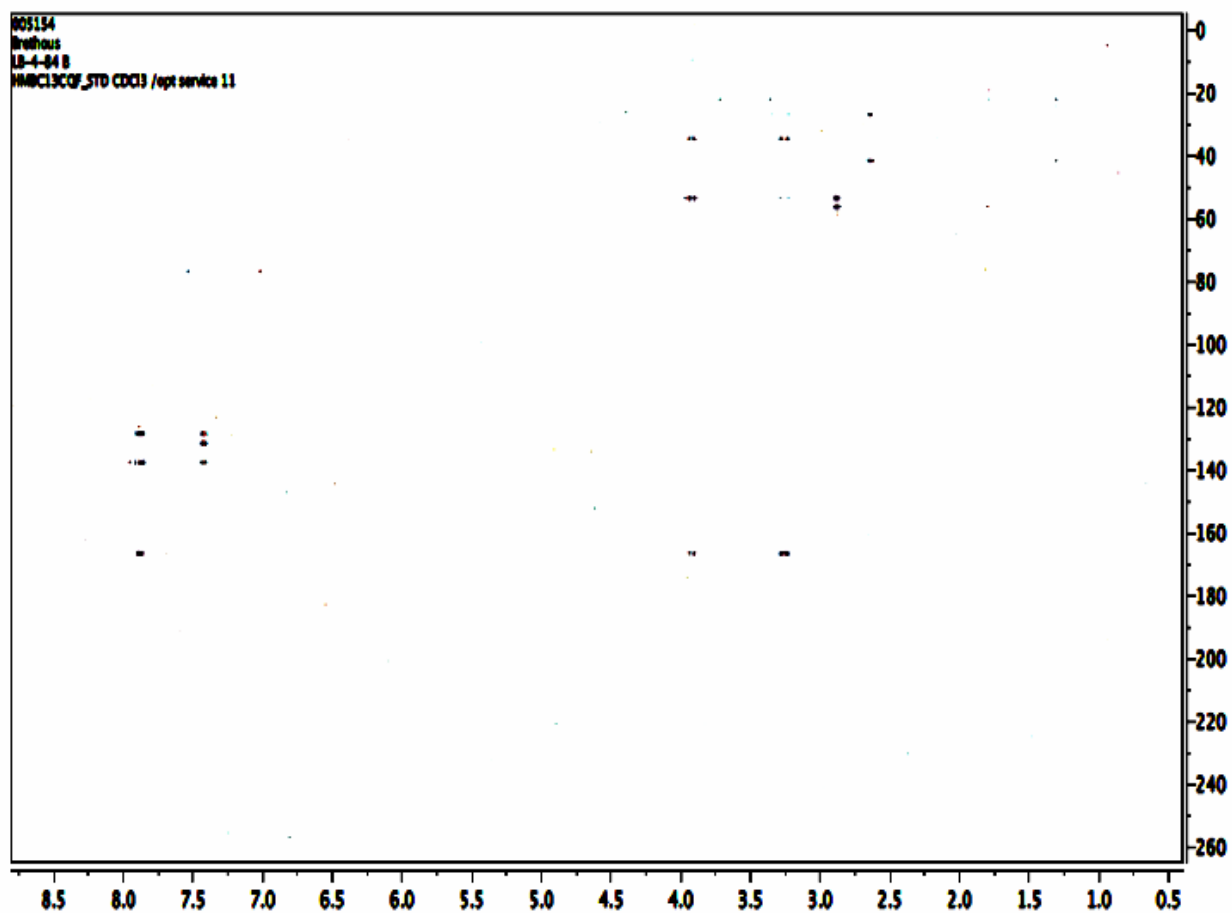
^1H NMR Spectrum of **26g** (MeOD, 300 MHz) ^{13}C NMR Spectrum of **26g** (MeOD, 75 MHz)

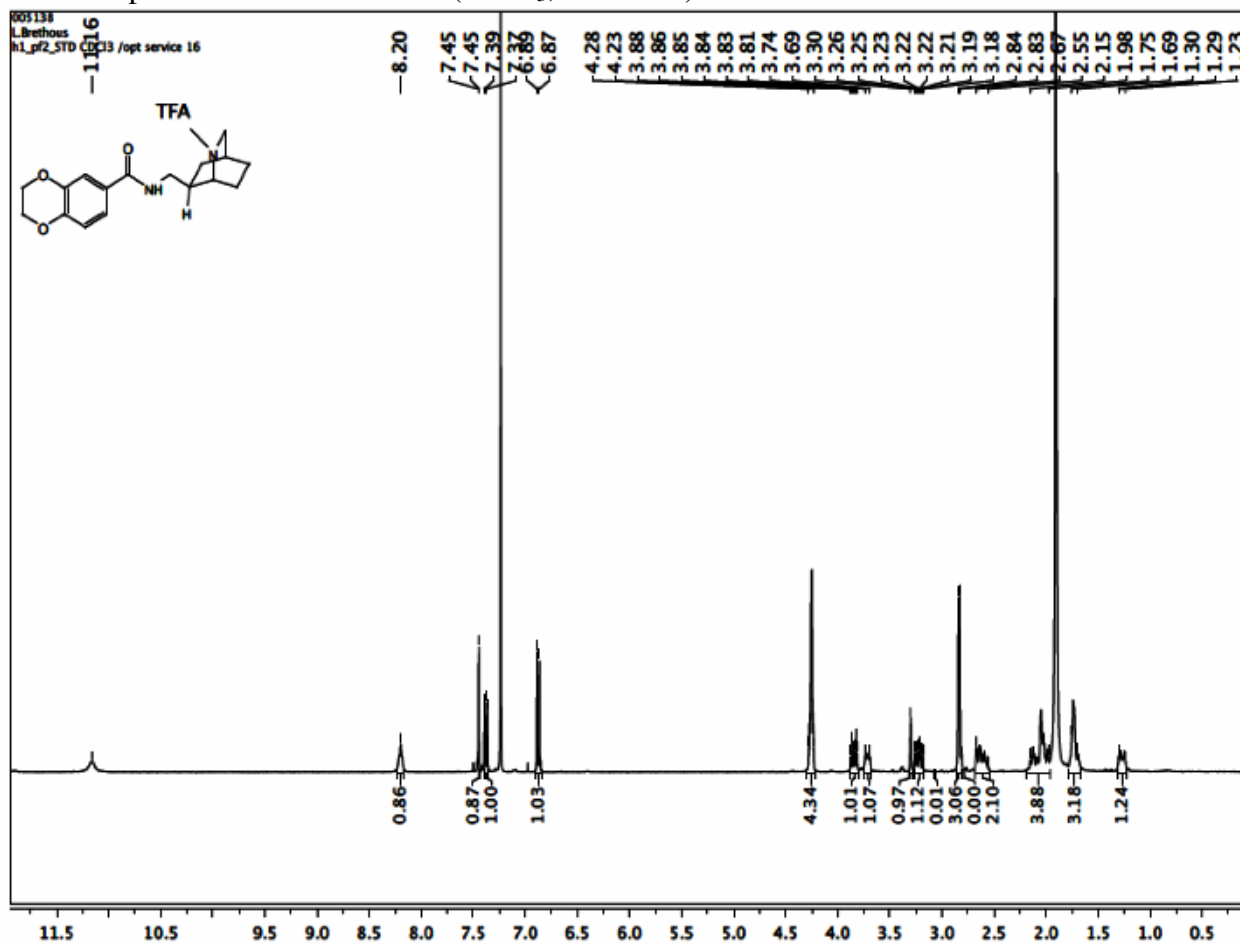
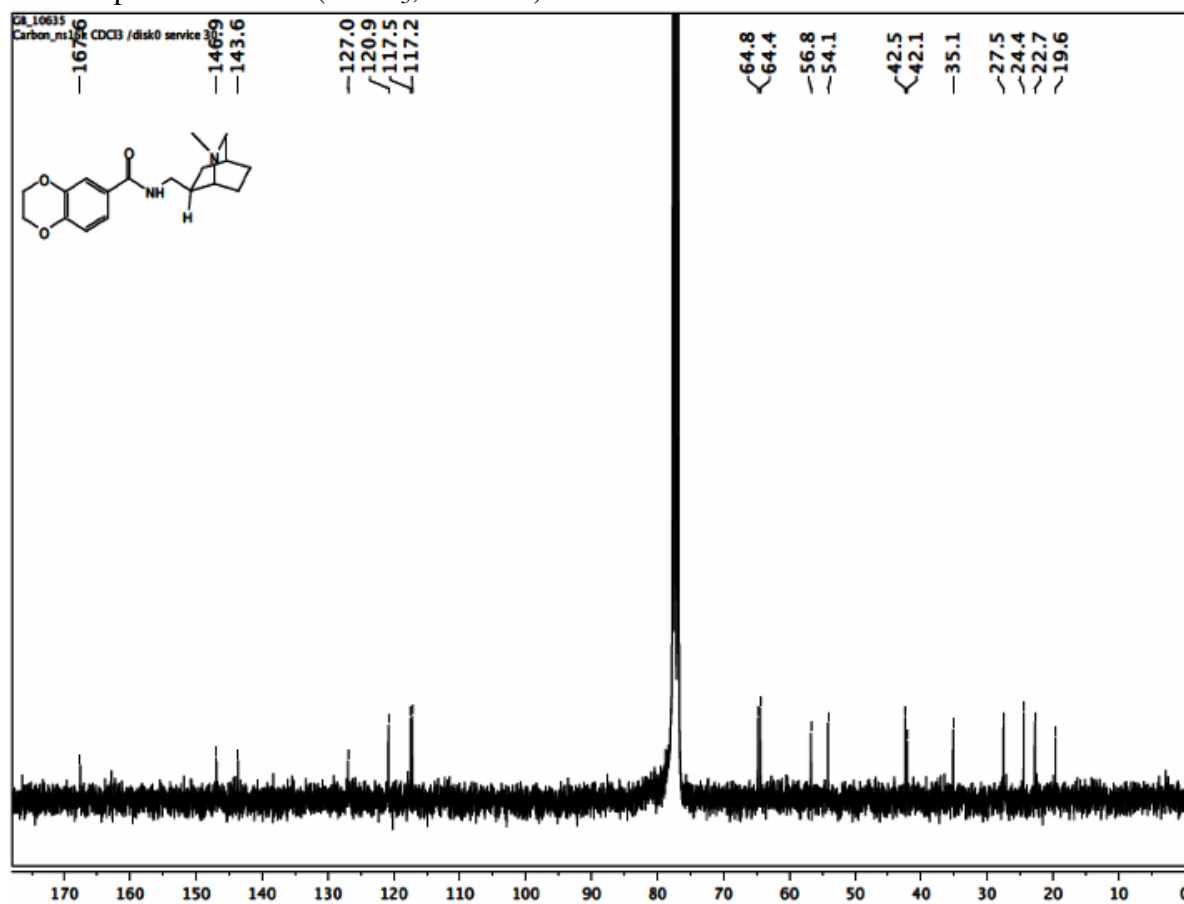
^1H NMR Spectrum of **26k** (CDCl_3 , 300 MHz) ^{19}F NMR Spectrum of **26k** (CDCl_3 , 376 MHz)

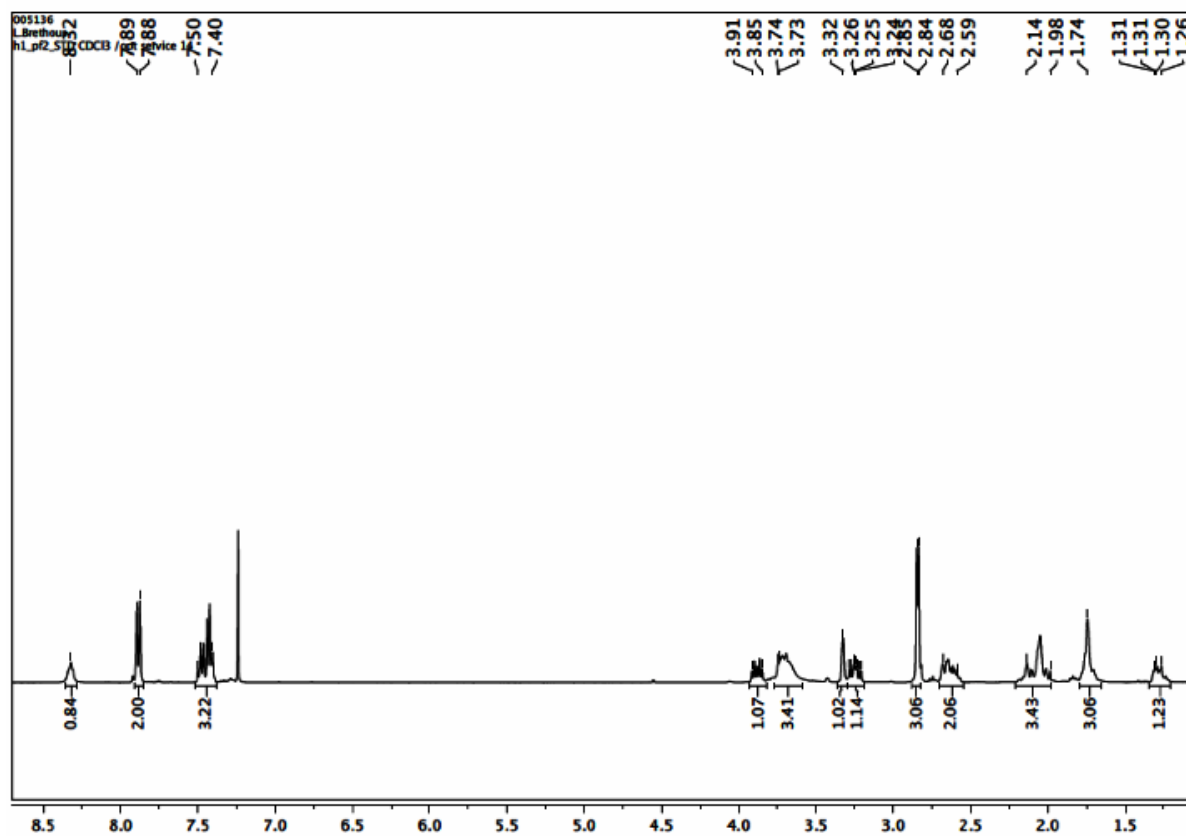
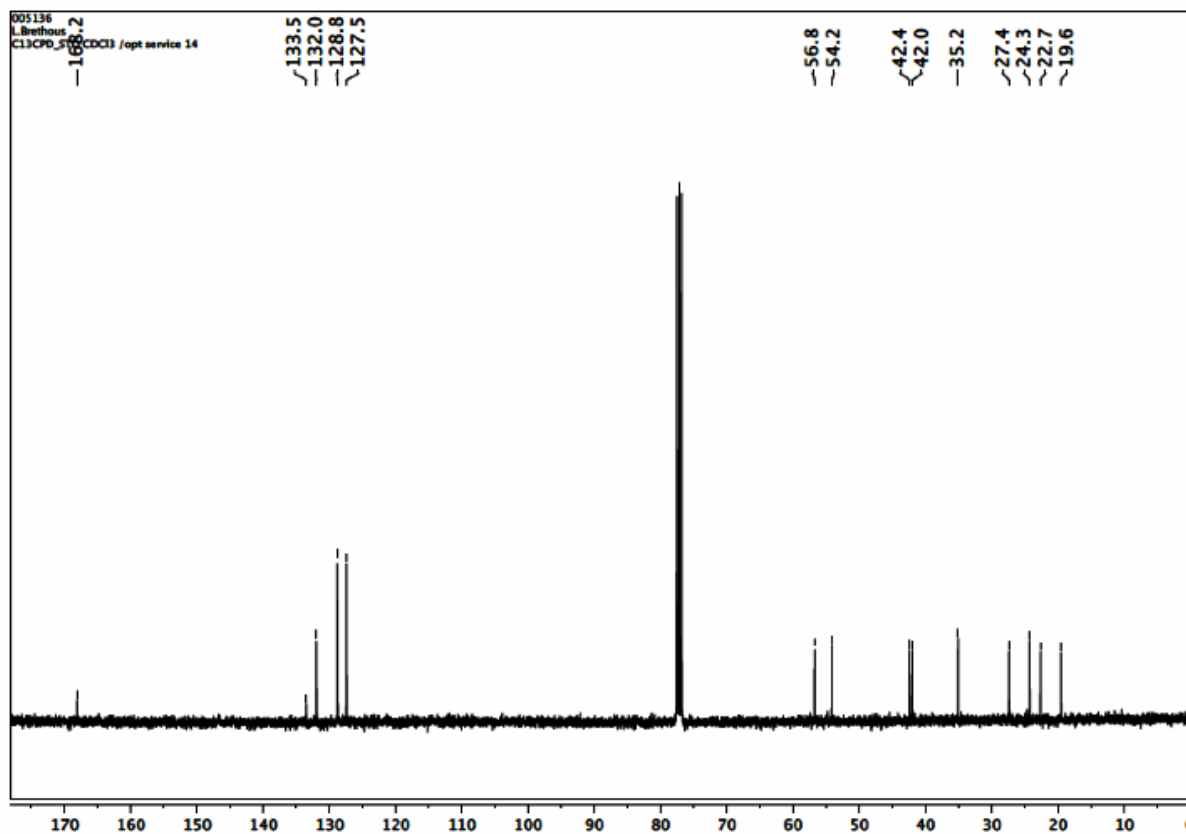
^{13}C NMR Spectrum of **26k** (CDCl_3 , 75 MHz)

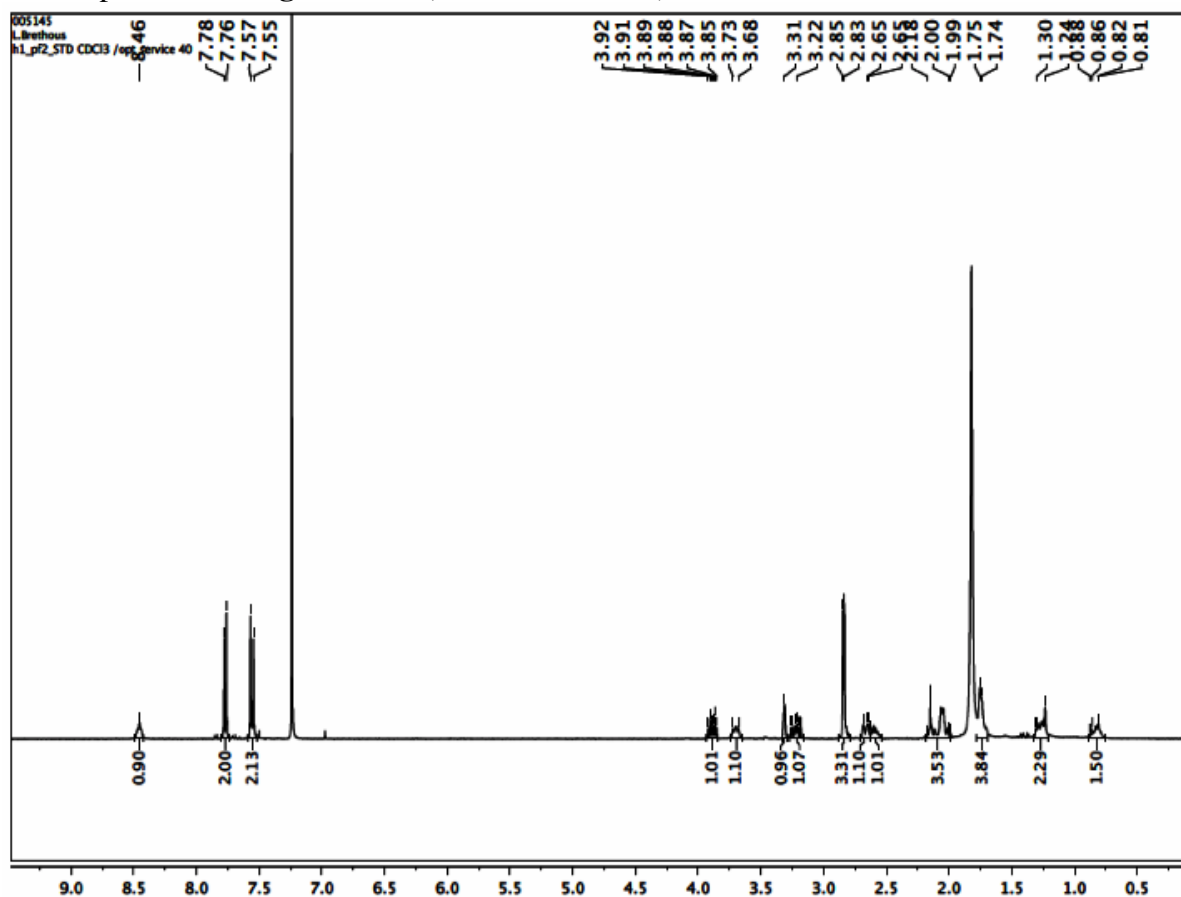
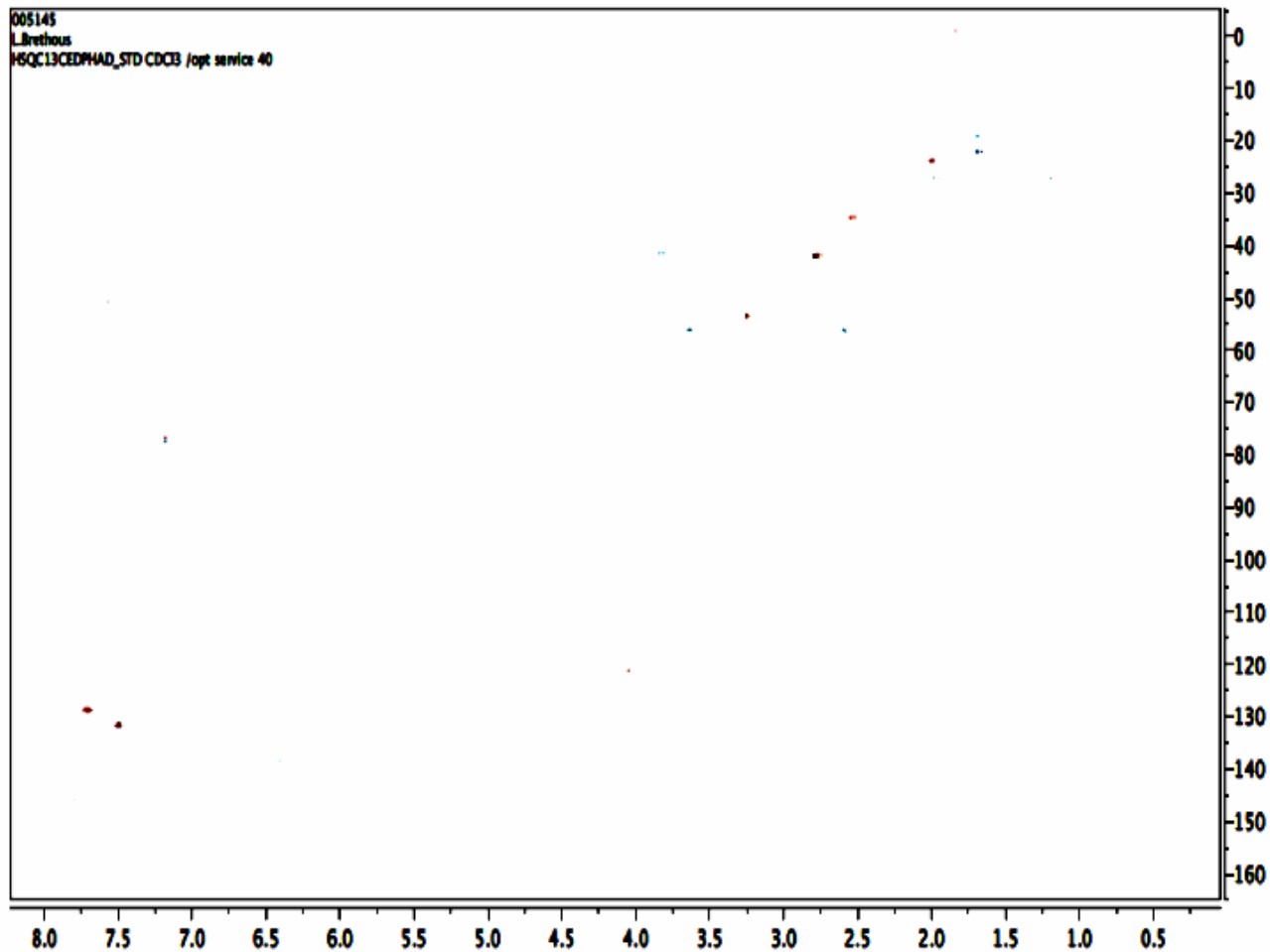
^1H NMR Spectrum of **27a** TFA salt (CDCl_3 , 300 MHz) ^1H - ^{13}C one bond correlation map from HSQC NMR experiment of **27a** TFA salt (CDCl_3 , 400 MHz and 100 MHz)

^1H - ^{13}C large range correlation map from HMBC NMR experiment of **27a** TFA salt (CDCl_3 , 400 MHz and 100 MHz)

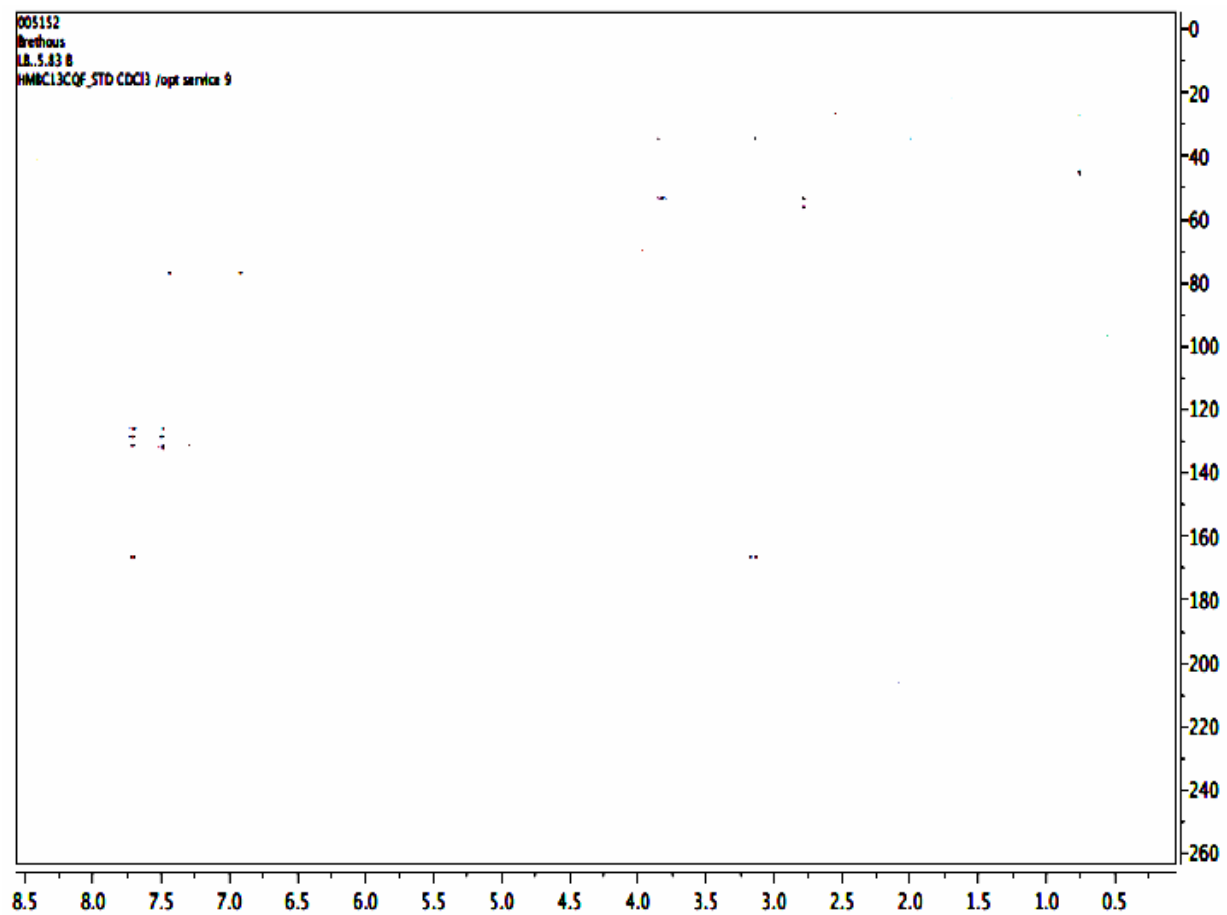


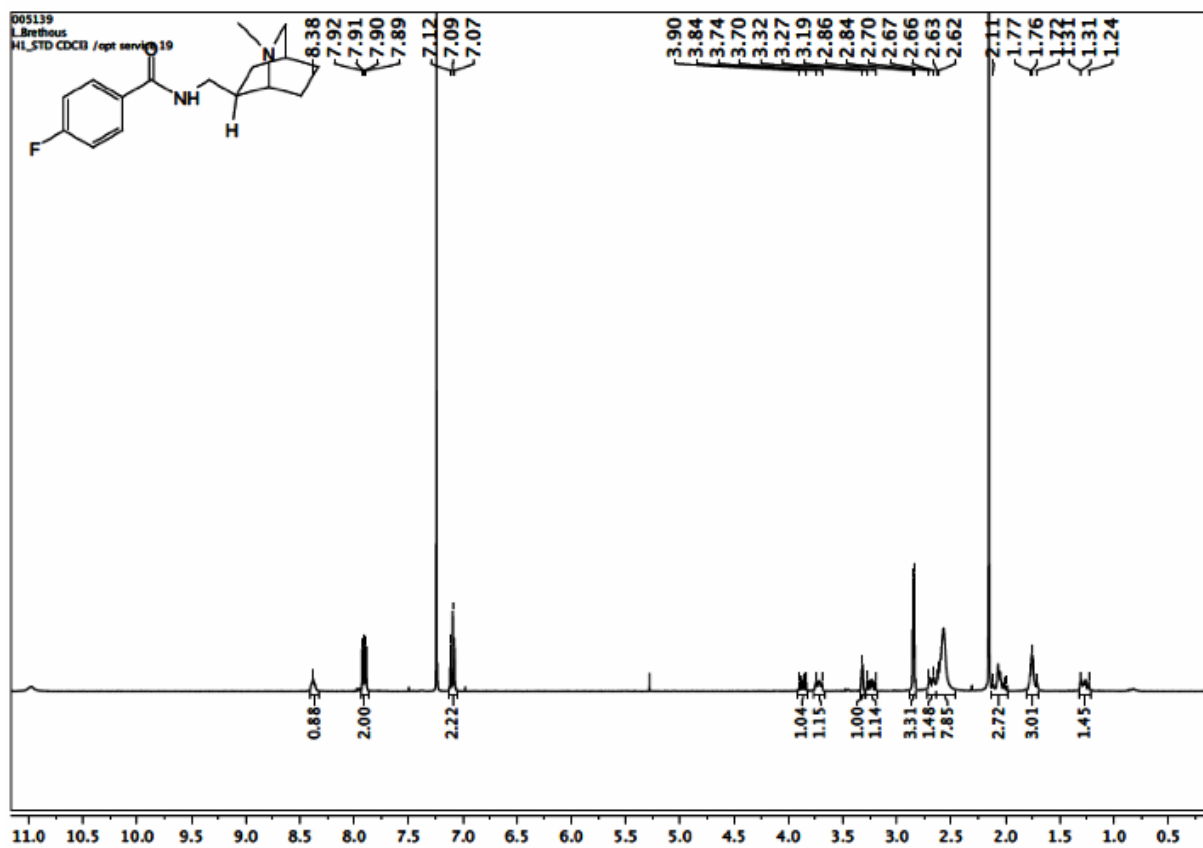
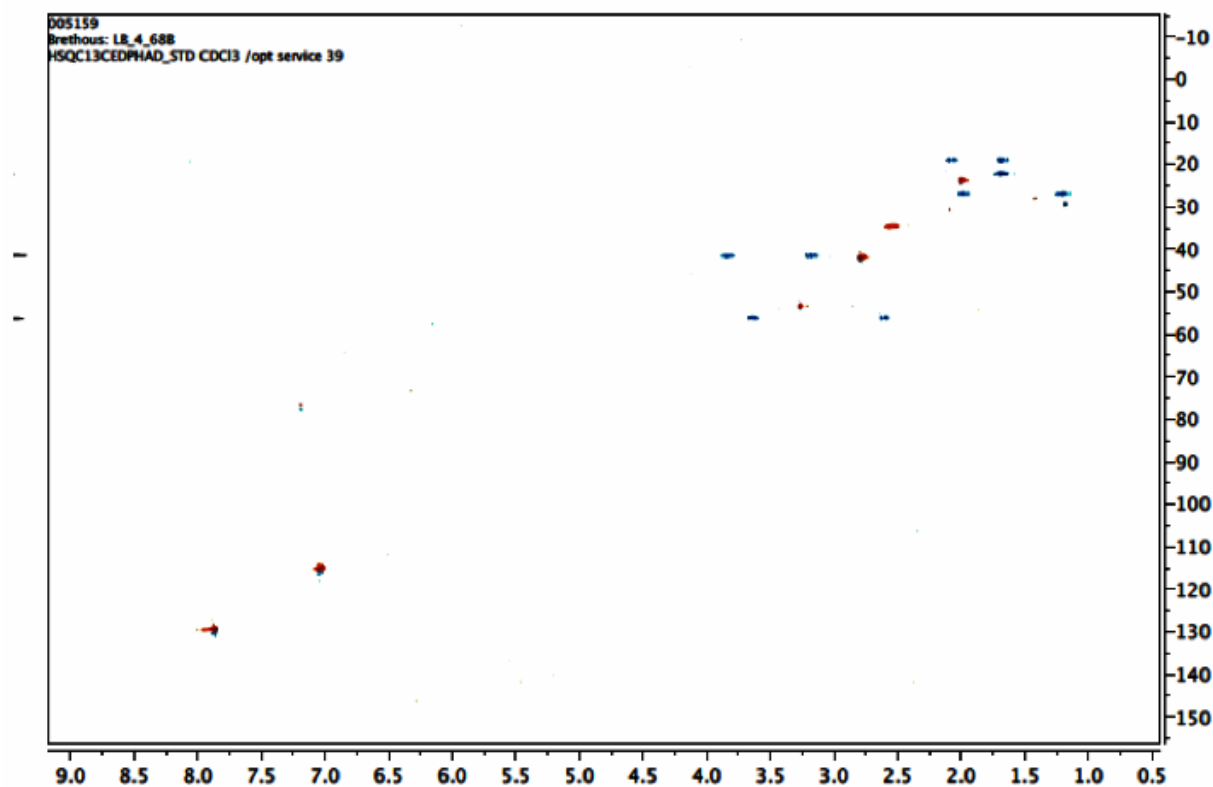
¹H NMR Spectrum of **27c** TFA salt (CDCl₃, 300 MHz)¹³C NMR Spectrum of **27c** (CDCl₃, 75 MHz)

^1H NMR Spectrum of **27f** TFA salt (CDCl_3 , 300 MHz) ^{13}C NMR Spectrum of **27f** TFA salt (CDCl_3 , 75 MHz)

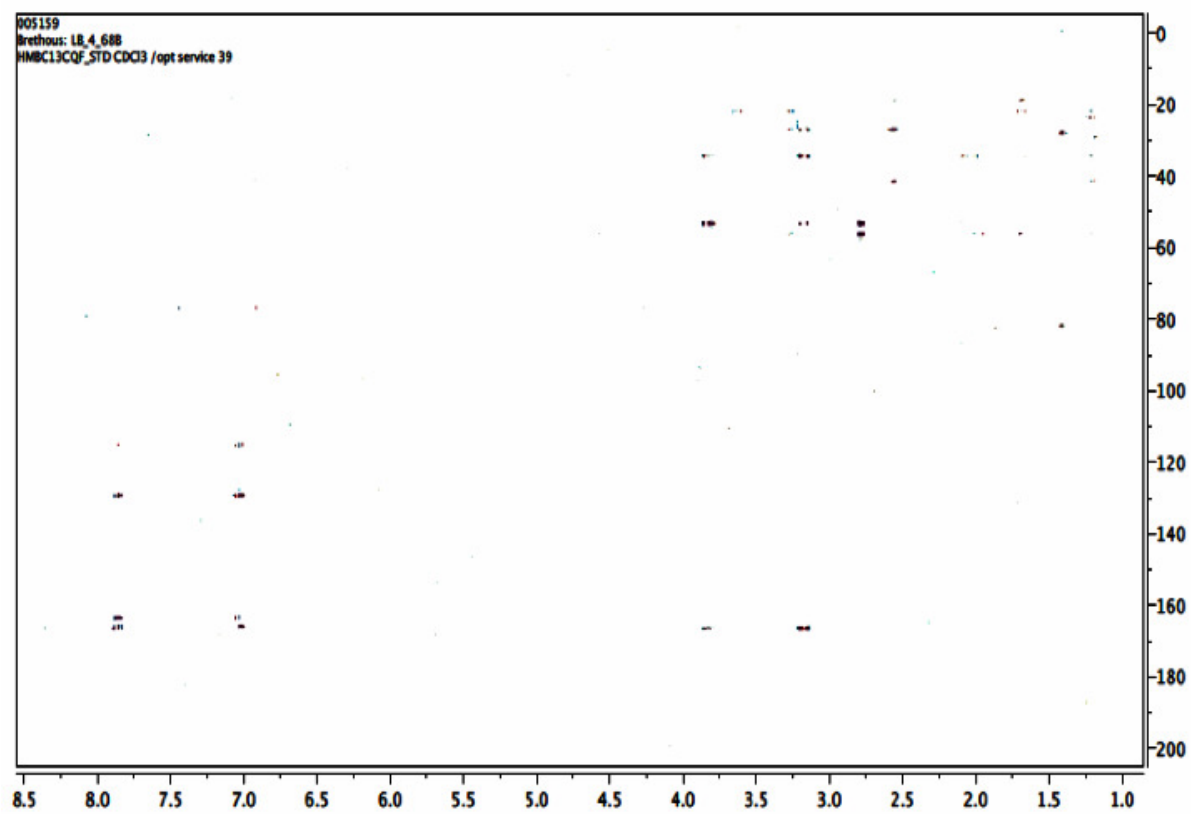
^1H NMR Spectrum of **27g** TFA salt (CDCl_3 , 300 MHz) ^1H - ^{13}C one bond correlation map from HSQC NMR experiment of **27g** TFA salt (CDCl_3 , 400 MHz and 100 MHz)

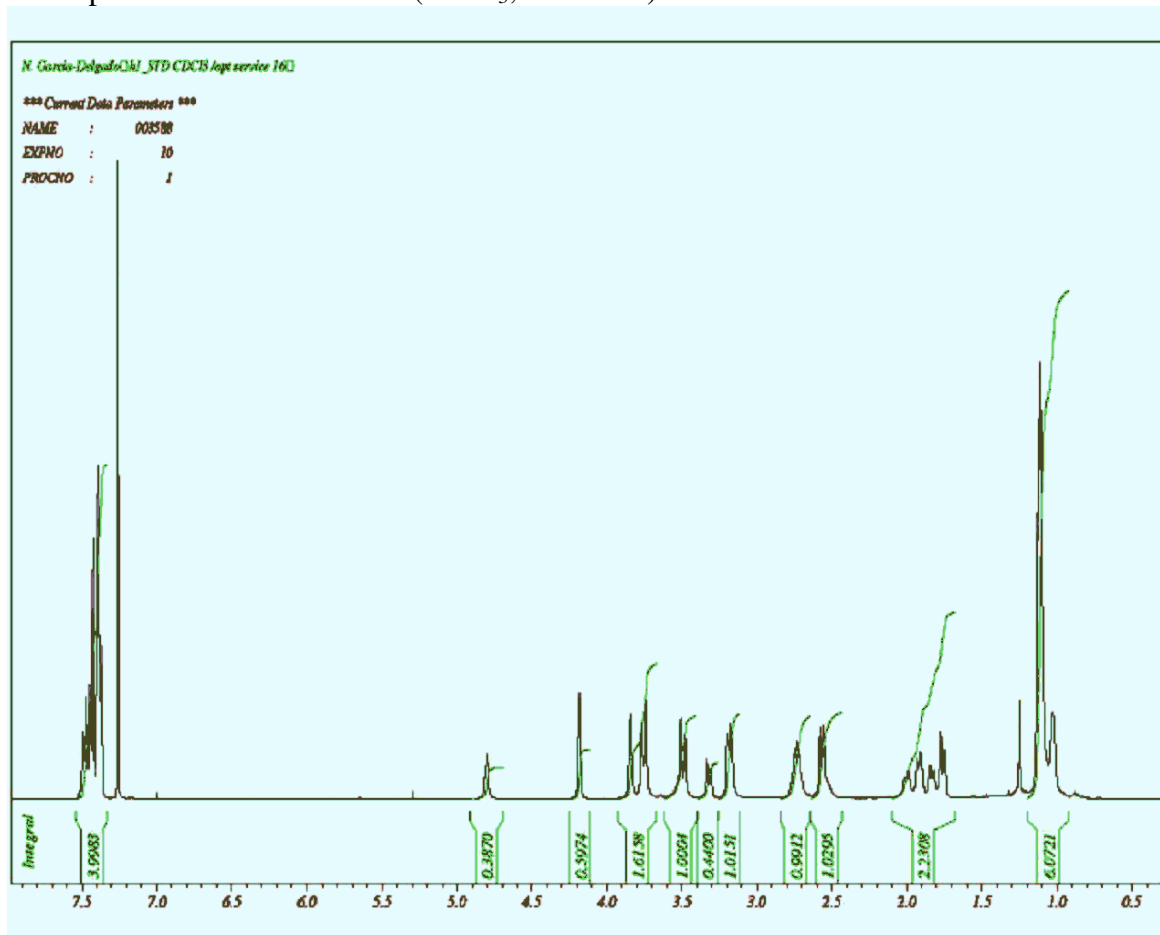
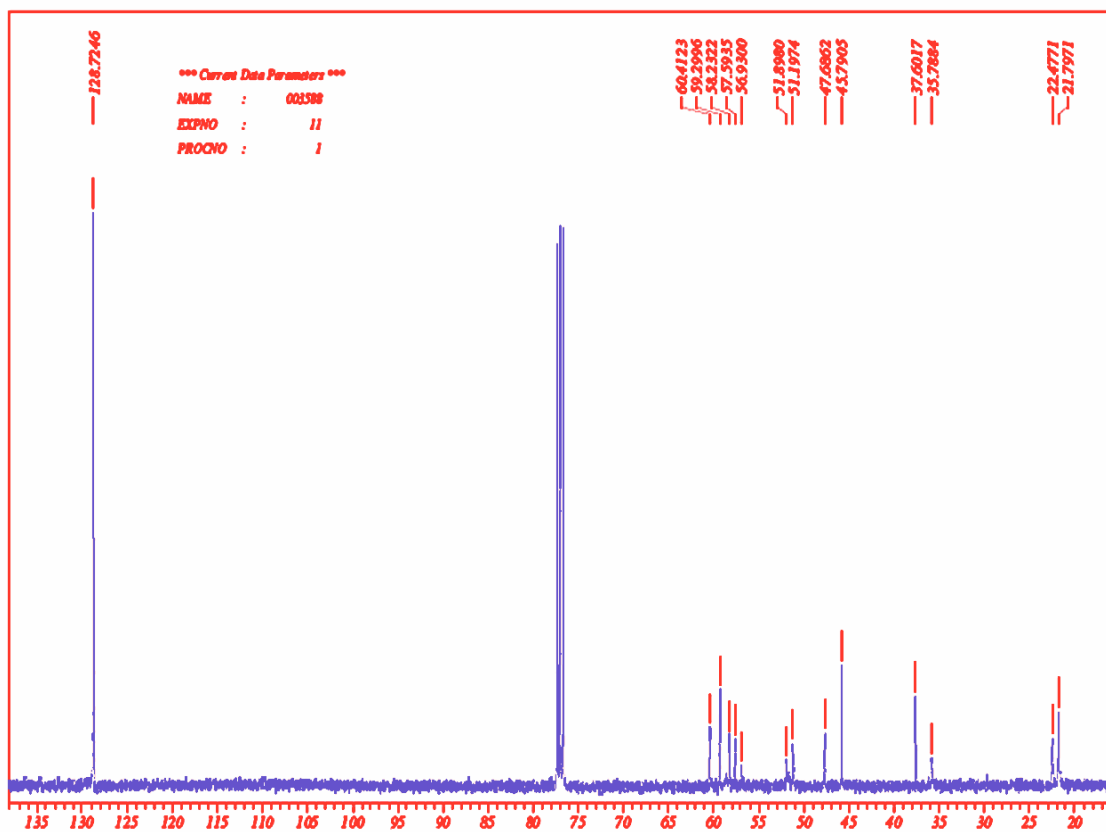
^1H - ^{13}C long range correlation map from HMBC NMR experiment of **27g** TFA salt (CDCl_3 , 400 MHz and 100 MHz)



^1H NMR Spectrum of **27k** TFA salt (CDCl_3 , 300 MHz) ^1H - ^{13}C one bond correlation map from HSQC NMR experiment of **27k** TFA salt (CDCl_3 , 400 MHz and 100 MHz)

^1H - ^{13}C long range correlation map from HMBC NMR experiment of **27k** TFA salt (CDCl_3 , 400 MHz and 100 MHz)



¹H NMR Spectrum of **28a** TFA salt (CDCl₃, 300 MHz)¹³C NMR Spectrum of **28a** TFA salt (CDCl₃, 75 MHz)

Analytical HPLC data for final compounds

Compound	Conditions	RP-HPLC ^a t _R (min)	RP-UHPLC ^b t _R (min)	Purity ^c (%)
3a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.54	99.3
3b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.34	>99
3c	100A to 100D, 5 min, 1.3 mL/min, 310 nm		1.37	>99
3d	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.55	95.0
4a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.57	>99
4b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.34	96.3
4c	100A to 100D, 10 min, 1.4 mL/min , 254 nm	7.59		97.0
4d	100A to 100D, 10 min, 1.4 mL/min , 244 nm	8.41		>99
4e	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.78	96.2
5a	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.80	97.0
5c	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.66	93.0
5d	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.78	86.6
6a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.69	>99
6b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.50	>99
6c	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.57	97.8
6d	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.57	89.5
6f	100A to 50/50 A/D, 15 min, 1.2 mL/min, 240 nm	14.21		>99
6g	100A to 50/50 A/D, 15 min, 1.2 mL/min, 250 nm	18.45		97.1
6h	100A to 50/50 A/D, 15 min, 1.2 mL/min, 250 nm	16.69		89.0
6i	100A to 50/50 A/D, 15 min, 1.2 mL/min, 240 nm	14.31		>99
6j	100A to 100D, 27 min, 1.2 mL/min, 237 nm	21.48		96.4
7a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.85	>99
7b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.67	>99
7c	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.73	97.8
7d	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.77	95.6
7e	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.95	98.5
8a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.73	>99
8b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.59	>99
8c	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.71	98.3
8d	80/20 A/C to 25/75 A/C, 20 min, 1.4 mL/min , 254 nm	10.8		95
8e	70/30 A/C to 30/70 A/C, 20 min, 1.4 mL/min , 254 nm	13.0		98.2
9a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.80	98.4
9b	80/20 A/C to 25/75 A/C, 20 min, 1.4 mL/min , 254 nm	9.1		99
10a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.67	97.5
10b	100A to 30/70 A/D, 20 min, 1.4 mL/min , 220 nm	12.34		>99
10c	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.52	>99
11a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.57	96.8
11b	100A to 100D, 20 min, 1.4 mL/min , 254 nm	10.51		>99
11c	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.42	95.0
11d	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.79	>99
11e	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.89	98.9
(R)-11c	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.34	94.2
(R)-11e	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.77	95.5
(R)-11f	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.33	95.4
(R)-11g	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.55	>99
(R)-11k	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.32	95.1
12c	100A to 100D, 5 min, 1.2 mL/min , 310 nm		1.47	>99
12e	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.69	97.3
12f	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.40	>99
12k	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.49	>99

13a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.64	>99
13c	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.51	>99
13f	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.29	>99
13g	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.60	98.7
13k	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.36	>99
14a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.48	98.2
14e	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.78	>99
14f	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.29	98.5
14g	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.61	>99
15a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.64	>99
15b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.41	>99
15e	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.76	94.4
16b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.72	90.8
17e	n.d			
18k	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.64	95.5
19b	60/40A/D to 100D, 15 min, 1.4 mL/min , 214 nm	7.26		>99
20b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.43	97.4
21b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.61	95.6
22b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.63	98.5
23b	100A to 100D, 5 min, 1.2 mL/min , 310 nm		1.60	98.3
24b	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.81	97.6
25c	100A to 100D, 5 min, 1.2 mL/min , 310 nm		1.42	92.1
26a	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.68	>99
26c	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.38	99.1
26e	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.70	>99
26f	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.43	96.3
26g	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.68	95.9
26k	100A to 100D, 5 min, 1.2 mL/min , 310 nm		1.25	95.4
27a	100A to 100D, 5 min, 1.2 mL/min , 214 nm		1.68	>99
27c	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.55	98.9
27f	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.49	95.0
27g	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.64	97.2
27k	100A to 100D, 5 min, 1.2 mL/min , 254 nm		1.55	97
28a	100A to 100D, 20 min, 1.4 mL/min , 254 nm	12.2		94.5

^{a)} Waters 600E system; Column, Water Atlantis (4.6 mm x 100 mm, dC₁₈, 5µm); UV Detection, Waters 996 photodiode array detector; Eluents, A: water with 0.1%TFA, C: Acetonitrile/water (90/10) with 0.1% TFA and D: Acetonitrile/water (40/60) with 0.1%TFA. ^{b)} Dionex

ULTIMATE 3000 RS chromatography system ; Column, Dionex Acclaim® RSLC 120 C18, 3.0 x 50 mm, particle size 2.2 µm, 120 Å pore size ; UV Detection, ULTIMATE 3000 RS Photo diode array detector ; Eluents, A: water with 0.1% TFA and D: Acetonitrile/water (90/10) with 0.1% TFA.

^{c)} As assessed by pic integration

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