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An unexpected formation of the novel 7-oxa-2-azabicyclo[2.2.1]hept-5-ene skeleton during the reaction of furfurylamine with maleimides and their bioprospection using zebrafish embryo model

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ELECTRONIC SUPPORTING INFORMATION

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1. General

Infrared (FT-IR) spectra were recorded on Lumex Infraclum FT-02 spectrometer, ν_{max} in cm¹. Bands are characterized according to the functional group. ¹H-NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl₃: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br = broad, m = multiplet), coupling constants (Hz) and integration. ¹³C-NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from solvent resonance as the internal standard (CDCl₃: δ 77.00 ppm). On DEPT-135 spectra, the signals of CH₃ and CH carbons are shown as positive (+) and CH₂ carbons are shown negative (-). Quaternary carbons are not shown. COSY, ¹³C-HMBC and HSQC experiments were recorded using standard Bruker pulse sequences. A Hewlett Packard 5890a Series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector (MSD) with an HP MS ChemStation Data system was used for MS identification at 70 eV using a 60 m capillary column coated with HP-5 [5%-phenylpoly(dimethylsiloxane)]. High-resolution mass spectrometry was performed on a Micromass Q-TOF by electrospray ionisation (ESI). Melting points were measured on a Fisher Johns melting point apparatus and are uncorrect.

Unless otherwise noted, all reactions have been carried out with distilled and dried solvents and under atmosphere pressure. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Aldrich and Merck) in air. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). Column chromatography was performed using silicagel 60 (0,063-0,200 mm) 70-230 mesh.

2. Reagents and catalysts

Benzaldehyde: Was purchased from Merck and used as received.

4-Chlorobenzaldehyde: Was purchased from Aldrich and used as received.

4-Fluorobenzaldehyde: Was purchased from Aldrich and used as received.

4-Methylbenzaldehyde: Was purchased from Aldrich and used as received.

4-Methoxybenzaldehyde: Was purchased from Aldrich and used as received.

3,4-Methylenedioxybenzaldehyde: Was purchased from Merck and used as received.

1-Naphthaldehyde: Was purchased from Merck and used as received.

Hydroxylamine hydrochloride: Was purchased from Merck and used as received.

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Sodium carbonate: Was purchased from Merck and used as received.

Palladium on activated charcoal (10 %): Was purchased from Aldrich and used as received.

Maleic anhydride: Was purchased from Merck and used as received.

Sodium acetate anhydrous: Was purchased from Merck and dried at 100 °C for 3 days.

Acetic anhydride: Was purchased from Merck and used as received.

(S)-(-)-α-Methylbenzylamine: Was purchased from Aldrich and used as received.

(R)-(+) -α-Methylbenzylamine: Was purchased from Aldrich and used as received.

Furfurylamine: Was purchased from Aldrich and used as received.

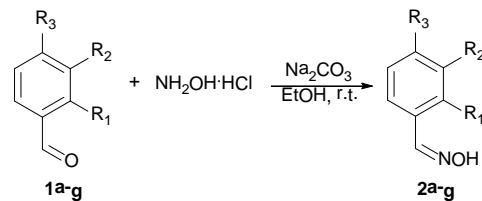
Boric acid: Was purchased from Aldrich and used as received.

Polyethylene glycol 400 (PEG-400): Was purchased from Merck and used as received.

Maleimide: Was purchased from Aldrich and used as received.

N-Phenylmaleimide: Was purchased from Aldrich and used as received.

3. Preparation and characterization of benzaldehyde oximes



A mixture of Na₂CO₃ (17 mmol) and hydroxylamine hydrochloride (17 mmol) was dissolved in 20 mL of deionized water and 4 mL of ethanol at room temperature for 5 min. To the above mixture, small amounts of the corresponding (hetero)aromatic aldehydes **1a-g** (14.13 mmol) were added for a period of 5 min. with constant stirring. The reaction mixture was stir for another 15 min. and at the end of the reaction (confirmed by TLC) the reaction was diluted with water (30 mL) and the precipitated product was filtered off and dried in vacuum. In cases, where product did not precipitate out the reaction, the mixture was extracted with ethyl acetate (3 x 10 mL). The organic extract was dried over anhydrous Na₂SO₄ and the solvent concentrate under reduced pressure to yield the pure product, the substituted oximes **2a-g**.

Benzaldehyde oxime (2a): Extraction with ethyl acetate afforded a white solid (1.71 g, 14.13 mmol, quantitative yield); R_f = 0.77 (2:1 hexane/EtOAc); mp. 34-36 °C; FT-IR (KBr, cm⁻¹): 3455 (OH), 2969 (=CHAr), 1604 (C=N), 1511 (-OH), 1419 (C-N); GC: R_t = 6.02 min.; MS (EI),

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m/z (%): 121 (M⁺, 100), 94 (38), 78 (61), 77 (60), 51 (46). Acquired data are in agreement with the literature.¹

4-Chlorobenzaldehyde oxime (2b): Extraction with ethyl acetate afforded a white solid (1.66 g, 10.67 mmol, quantitative yield); R_f = 0.52 (2:1 hexane/EtOAc); mp. 92-94 °C; FT-IR (KBr, cm⁻¹): 3301 (OH), 1589 (C=N), 1496 (C-N), 971 (C-H), 694 (C-Cl); GC: R_t = 11.08 min.; MS (EI), *m/z* (%): 155 (M⁺, 99), 139 (100), 136 (82), 111 (73), 75 (70). Acquired data are in agreement with the literature.²

4-Fluorobenzaldehyde oxime (2c): Extraction with ethyl acetate afforded a white solid (1.66 g, 10.67 mmol, quantitative yield); R_f = 0.72 (2:1 hexane/EtOAc); mp. 85-87 °C; FT-IR (KBr, cm⁻¹): 3313 (OH), 1584 (C=N), 1502 (C-N), 970 (C-H), 703 (C-F); GC: R_t = 15.34 min.; MS (EI), *m/z* (%): 139 (M⁺, 95), 123 (100), 108 (58), 95 (61), 75 (70). Acquired data are in agreement with the literature.³

4-Methylbenzaldehyde oxime (2d): Extraction with ethyl acetate afforded a white solid (1.66 g, 10.67 mmol, quantitative yield); R_f = 0.52 (2:1 hexane/EtOAc); mp. 54-55 °C; FT-IR (KBr, cm⁻¹): 3333 (OH), 2994 (CH₃), 1572 (C=N), 1497 (C-N), 1028 (C-H); GC: R_t = 10.41 min.; MS (EI), *m/z* (%): 135 (M⁺, 96), 119 (100), 104 (76), 91 (83), 75 (61). Acquired data are in agreement with the literature.⁴

4-Methoxybenzaldehyde oxime (2e): Extraction with ethyl acetate afforded a yellowish solid (1.66 g, 11.01 mmol, quantitative yield); R_f = 0.54 (2:1 hexane/EtOAc); mp. 102-104 °C; FT-IR (KBr, cm⁻¹): 3178 (OH), 3008 (OCH₃), 1604 (C=N), 1249 (C-O-C); GC: R_t = 9.71 min.; MS (EI), *m/z* (%): 151 (M⁺, 53), 119 (99), 91 (100), 77 (34), 63 (20). Acquired data are in agreement with the literature.²

3,4-Methylenedioxybenzaldehyde oxime (2f): Precipitation with water afforded a white solid (1.65 g, 9.99 mmol, quantitative yield); R_f = 0.65 (2:1 hexane/EtOAC); mp. 110-112 °C; FT-IR (KBr, cm⁻¹): 3224 (OH), 2915 (CH₂), 1604 (C=N), 1249 (C-O-C); GC: R_t = 11.83 min.; MS

¹ R. Joseph, T. Ravindranathan and A. Sudalai, *Tetrahedron Lett.*, 1995, **36**, 1903.

² J-T. Li, X-L. Li and T-S. Li, *Ultras. Sonochem.*, 2006, **13**, 200.

³ B. C. Sanders, F. Friscourt, P. A. Ledin, N. E. Mbua, S. A. Arumugam, J. Guo, T. J. Boltje, V. V. Popik and G-J. Boons, *J. Am. Chem. Soc.*, 2011, **133**, 949.

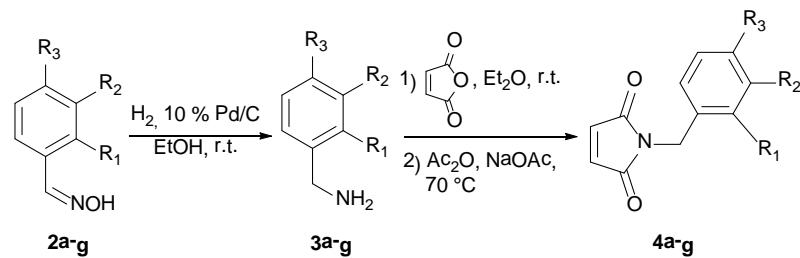
⁴ S. Minakata, S. Okumura, T. Nagamachi and Y. Takeda, *Org. Lett.*, 2011, **13**, 2966.

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(EI), *m/z* (%): 165 (M⁺, 100), 122 (60), 121 (53), 65 (37), 63 (42). Acquired data are in agreement with the literature.⁵

1-Naphthylaldehyde oxime (2g): Precipitation with water afforded a white solid (1.64 g, 9.61 mmol, quantitative yield); R_f = 0.74 (2:1 hexane/EtOAc); mp. 99–100 °C; FT-IR (KBr, cm⁻¹): 3394 (OH), 3070 (=CHAr), 1619 (C=N), 1511 (-OH), 1450 (C-N); GC: R_t = 14.30 min.; MS (EI), *m/z* (%): 171(M⁺, 50), 154 (100), 153 (87), 127 (93), 125 (50). Acquired data are in agreement with the literature.⁵

4. Preparation and characterization of N-benzylmaleimides



A solution of the corresponding benzaldehyde oxime **2a-g** (8.25 mmol) in ethanol (25 mL) was hydrogenated under H₂ atmosphere using 10 % Pd/C (200 mg) until the complete consumption of the oxime was verified by TLC. The suspension was filtered through a small pad of Celite and the filter was washed with EtOH (10 mL); the combined filtrates were concentrated *in vacuo* to furnish the unstable benzylamines **3a-g**, as an oils. Without further purification, the crude amine **3a-g** (8.25 mmol), was dissolved in anhydrous diethyl ether (10 mL), was added dropwise into an ice-cooled solution of maleic anhydride (8.25 mmol) in anhydrous diethyl ether (15 mL). The solid, which precipitated out of the reaction mixture after 1 h, was filtered, washed thoroughly with ethyl ether and mixed with acetic anhydride (1.6 mL) and sodium acetate (4.12 mmol). The reaction mixture was then heated at 70 °C (6 h) until the complete consumption of the starting amine was ascertained by TLC. After cooling the system at room temperature, the solution was alkalinized with aqueous Na₂CO₃ 2 M and the product was extracted with CH₂Cl₂ (3 x 10 mL) the organic extracts were combined, dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and eluted with hexane/EtOAc (1:1) to afford the desired maleimide.

N-Benzylmaleimide (4a): Same procedure as above was followed on a 7.28 mmol scale. Purification by silica gel flash chromatography afforded a white crystalline solid (0.94 g, 5.02

⁵ R. S. Ramón, J. Bosson, S. Díez-González, N. Marion, S. P. Nolan, *J. Org. Chem.*, 2010, 7, 1197.

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mmol, 69 % yield); R_f = 0.6 (1:1 hexane/EtOAc); mp. 71-73 °C; FT-IR (KBr, cm⁻¹): 3101 (=CHAr), 1697 (C=O), 1403 (CH₂), 694 (HC=CH); GC: R_t = 11.29 min.; MS (EI), m/z (%): 187 (M⁺, 100), 130 (41), 106 (59), 105 (53), 78 (23). Acquired data are in agreement with the literature.⁶

N-(4-Chlorobenzyl)maleimide (4b): Same procedure as above was followed on a 6.16 mmol scale. Purification by silica gel flash chromatography afforded a white crystalline solid (1.09 g, 4.93 mmol, 80 % yield); R_f = 0.58 (1:1 hexane/EtOAc); mp. 68-70 °C; FT-IR (KBr, cm⁻¹): 3101 (=CHAr), 1712 (C=O), 1403 (CH₂), 833 (C-Cl), 694 (HC=CH); GC: R_t = 14.29 min.; MS (EI), m/z (%): 221 (M⁺, 95), 186 (41), 140 (100), 137 (64), 89 (42). Acquired data are in agreement with the literature.⁷

N-(4-Fluorobenzyl)maleimide (4c): Same procedure as above was followed on a 7.99 mmol scale. Purification by silica gel flash chromatography afforded a white crystalline solid (1.41 g, 6.87 mmol, 86 % yield); R_f = 0.66 (1:1 hexane/EtOAc); mp. 88-90 °C; FT-IR (KBr, cm⁻¹): 3101 (=CHAr), 1697 (C=O), 1403 (CH₂), 848 (C-F), 694 (HC=CH); GC: R_t = 11.49 min.; MS (EI), m/z (%): 205 (M⁺, 100), 148 (55), 124 (71), 122 (97), 109 (51). Acquired data are in agreement with the literature.⁶

N-(4-Methylbenzyl)maleimide (4d): Same procedure as above was followed on a 8.25 mmol scale. Purification by silica gel flash chromatography afforded a white crystalline solid (1.26 g, 6.27 mmol, 76 % yield); R_f = 0.78 (1:1 hexane/EtOAc); mp. 94-96 °C; FT-IR (KBr, cm⁻¹): 3101 (=CHAr), 2946 (CH₃), 1712 (C=O), 1403 (CH₂), 694 (HC=CH); GC: R_t = 12.76 min.; MS (EI), m/z (%): 201 (M⁺, 100), 120 (59), 118 (47), 92 (24), 91 (25). Acquired data are in agreement with the literature.⁸

N-(4-Methoxybenzyl)maleimide (4e): Same procedure as above was followed on a 6.39 mmol scale. Purification by silica gel flash chromatography afforded a white crystalline solid (0.73 g, 3.39 mmol, 53 % yield); R_f = 0.66 (1:1 hexane/EtOAc); mp. 101-103 °C; FT-IR (KBr, cm⁻¹): 3101 (=CHAr), 2946 (OCH₃), 1712 (C=O), 1403 (CH₂), 1249 (C-O-C), 694 (HC=CH); GC: R_t

⁶ X. Z. Zhao, K. Maddali, M. Metifiot, S. J. Smith, B. Christie Vu, C. Marchand, S. H. Hughes, Y. Pommier and T. R. Burke Jr., *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2986.

⁷ E. Schweizer, A. Hoffmann-Röder, J. A. Olsen, P. Seiler, U. Obst-Sander, B. Wagner, M. Kansy, D. W. Banner and F. Diederich, *Org. Biomol. Chem.*, 2006, **4**, 2364.

⁸ A. L. Schwartz and L. M. Lerner, *J. Org. Chem.*, 1974, **39**, 21.

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= 15.51 min.; MS (EI), *m/z* (%): 217 (M⁺, 100), 174 (62), 136 (51), 134 (45), 77 (43). Acquired data are in agreement with the literature.⁹

N-(3,4-Methylenedioxybenzyl)maleimide (4f): Same procedure as above was followed on a 5.75 mmol scale. Purification by silica gel flash chromatography afforded a white crystalline solid (0.90 g, 3.91 mmol, 68 % yield); R_f = 0.66 (1:1 hexane/EtOAc); mp. 101-103 °C; FT-IR (KBr, cm⁻¹): 3001 (=CHAr), 2915 (CH₂), 1712 (C=O), 1403 (CH₂), 1249 (C-O-C), 694 v(HC=CH); GC: R_t = 17.91 min.; MS (EI), *m/z* (%): 231 (M⁺, 100), 150 (28), 148 (32), 135 (23), 77 (24). Acquired data are in agreement with the literature.¹⁰

N-(Naphthalen-1-ylmethyl)maleimide (4g): Same procedure as above was followed on a 4.18 mmol scale. Purification by silica gel flash chromatography afforded a white crystalline solid (0.82 g, 3.43 mmol, 62 % yield); R_f = 0.73 (1:1 hexane/EtOAc); mp. 73-75 °C; FT-IR (KBr, cm⁻¹): 3070 (=CHAr), 1697 (C=O), 1403 (CH₂), 1373 (C=C_{Ar}), 694 (HC=CH); GC: R_t = 24.22 min.; MS (EI), *m/z* (%): 237 (M⁺, 100), 127 (71), 115 (67), 55 (92), 54 (68). Acquired data are in agreement with the literature.⁶

S-(-)-N-(1-Feniletil)maleimide (4h): Compound **7h** was obtained from commercial available α-(S)-methyl-benzylamine **3h** according to the procedure described in section 4. Purification by silica gel flash chromatography a transparent oil (0.99 g, 5.12 mmol, 62 % yield) was obtained; R_f = 0.66 (1:1 hexane/EtOAc); FT-IR (KBr, cm⁻¹): 3101 (=CHAr), 2977 (CH₃), 1712 (C=O), 1388 (CH₃), 694 (HC=CH); GC: R_t = 11.99 min.; MS (EI), *m/z* (%): 201 (M⁺, 100), 186 (64), 158 (67), 104 (50), 77 (59). Acquired data are in agreement with the literature.¹¹

R-(+)-N-(1-Feniletil)maleimide (4i): Compound **7i** was obtained from commercial available α-(R)-methyl-benzylamine **3i** according to the procedure described in section 4. Purification by silica gel flash chromatography a transparent oil (1.02 g, 4.95 mmol, 60 % yield) was obtained; R_f = 0.65 (1:1 hexane/EtOAc); FT-IR (KBr, cm⁻¹): 3101 (=CHAr), 2977 (CH₃), 1712 (C=O), 1388 (CH₃), 694 (HC=CH); GC: R_t = 12.02 min.; MS (EI), *m/z* (%): 201 (M⁺, 100), 186 (65), 158 (39), 104 (57), 77 (72). Acquired data are in agreement with the literature.¹¹

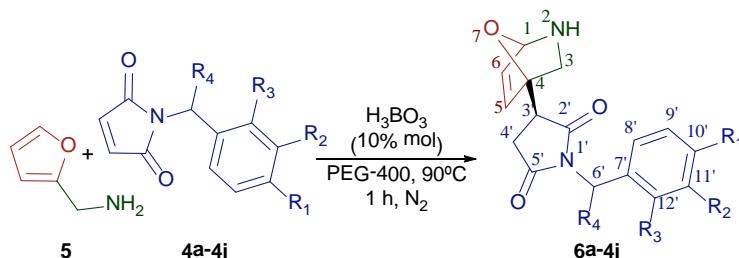
⁹ E. Awuah and A. Capretta, *J. Org. Chem.*, 2011, **76**, 3122.

¹⁰ J. R. Cashman, M. MacDonald, S. Ghirmai, K. J. Okolotowicz, E. Sergienko, B. Brown, X. Garcia, D. Zhai, R. Dahl and J. C. Reed, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6560.

¹¹ A. Chihab-Eddine, A. Daïch, A. Jilale, B. Decroix, *Tetrahedron Lett.* 2001, **42**, 573.

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5. General procedure for the synthesis of the 7-oxa-2-azabicyclo[2.2.1]hept-5-enes 6a-6i



A solution of the corresponding maleimide **4a-4i** (2.13 mmol) in 10 mL of polyethylenglycol 400 (PEG-400) was placed in a 50 mL Schlenk round-bottom flask heated at 90 °C and under positive nitrogen pressure, then boric acid (10 % mol) was added in one portion and after 20 min, furfurylamine (2.55 mmol) were added over a few minutes in small portions. The reaction was monitored by TLC after 60 min and the mixture was poured into 50 mL of NaHCO₃ solution 1 M and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to obtain brown oils. The residue was purified by column chromatography on silica gel and eluted with hexane/EtOAc (2:1) to afford the desired products as colored oils.

4-(N-Benzyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene (6a): Purification by silica gel column chromatography afforded pure **6a** as a red oil (490 mg, 1.72 mmol, 82 % yield). R_f = 0.43 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3317 (NH), 3039 (=CHAr), 1712 (C=O), 1403 (CH₂), 1342 (HC=CH). ¹H NMR δ (400 MHz, CDCl₃): 7.35 (3H, dd, J = 6.2, 1.1 Hz, H_{Ph}-9', 11' y H-1), 7.32 – 7.26 (3H, m, H_{Ph}-8', 10', 12'), 6.30 (1H, dd, J = 3.1, 1.9 Hz, H-6), 6.19 (1H, d, J = 3.1 Hz, H-5), 4.63 (2H, s, H-CH₂Ph), 3.91 (1H, d, J = 14.6 Hz, H_{eq}-3), 3.83 (1H, d, J = 14.6 Hz, H_{ax}-3), 3.72 (1H, dd, J = 8.2, 5.0 Hz, H_{eq}-3'), 2.86 (1H, dd, J = 17.9, 8.3 Hz, H_{eq}-4'), 2.46 (1H, dd, J = 17.9, 5.0 Hz, H_{ax}-4'), 2.11 (2H, br.s., NH) ppm. ¹³C NMR δ (400 MHz, CDCl₃): 177.4, 174.8, 152.2, 142.5 (+), 135.5, 128.9 (2xCH, +), 128.7 (2xCH, +), 128.1 (+), 110.4 (+), 108.1 (+), 55.1 (+), 44.1 (-), 42.5 (-), 36.3 (-) ppm. COSY Correlation [δ_H/δ_H]: 7.32-7.26 [H_{Ph}-9',11'/H_{Ph}-8',10',12'], 7.35/6.30[H-1/H-6], 7.35/6.19 [H-1/H-5], 7.35/4.63 [H_{Ph}-9',11'/H-CH₂Ph], 7.32-7.26 /4.63 [H_{Ph}-8',10',12'/H-CH₂Ph], 6.30/6.19 [H-6/H-5], 6.30/3.91 [H-6/H_{eq}-3], 6.30/3.83 [H-6/H_{ax}-3], 6.19/3.91 [H-5/H_{eq}-3], 6.19/3.83 [H-5/H_{ax}-3], 4.63/2.46 [H-CH₂Ph/H_{ax}-4'], 4.63/2.86 [H-CH₂Ph/H_{eq}-4'], 3.72/2.46 [H_{eq}-3'/H_{ax}-4'], 3.72/2.86 [H_{eq}-3'/H_{eq}-4'], 2.86/2.46 [H_{eq}-4'/H_{ax}-4']. HSQC Correlation [δ_H/δ_C]: 7.35-7.26/128.1-128.9 [H_{Ph}/C_{Ph}], 7.35/142.5 [H-1/C-1], 6.30/110.4 [H-6/C-6], 6.19/108.1 [H-5/C-5], 4.63/42.5 [H-CH₂Ph/C-6'], 3.91/44.1 [H_{eq}-3/C-3], 3.83/44.1 [H_{ax}-3/C-3], 3.72/55.1 [H_{eq}-3'/C-3'], 2.86/36.3

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[H_{eq}-4'/C-4'], 2.46/36.3 [H_{ax}-4'/C-4']. HMBC Correlation [δ_H/δ_C]: 7.35/42.5/128.1/128.9/135.5 [H_{Ph}-9',11'/C-6'/C-10'/C-8',12'/C-7'], 7.35/108.1/110.4/152.2 [H-1/C-5/C-6/C-4], 7.32-7.26 /42.5/128.1-128.9/135.5 [H_{Ph}-8',10',12'/C-6'/C-8',9',10',11',12'/C-7'], 6.30/108.1/142.5 /152.2 [H-6/C-5/C-1/C-4], 6.19/44.1/110.4/142.5/152.2 [H-5/C-3/C-6/C-1/C-4], 4.63/128.1-128.9/ 135.5/174.8/177.4 [H-CH₂Ph/C-8',9',10',11',12'/C-7'/C-5'/C-2'], 3.91/55.1/108.1/110.4/ 142.5/152.2 [H_{eq}-3/C-3'/C-5/C-6/C-1,C-4], 3.83/55.1/108.1/110.4/142.5/152.2 [H_{ax}-3/C-3'/C- 5/C-6/C-1,C-4], 3.72/36.3/44.1/174.8/177.4 [H_{eq}-3'/C-4'/C-3/C-5'/C-2'], 2.86/55.1/174.8/177.4 [H_{eq}-4'/C-3'/C-5'/C-2'], 2.46/55.1/174.8/177.4 [H_{ax}-4'/C-3'/C-5'/C-2']. GC: R_t = 22.87 min.; MS (EI), m/z (%): 283 (M⁺, 1), 267 (1), 96 (100), 91 (25), 81 (36), 53 (12). HRMS (ESI+): m/z: calcd for C₁₆H₁₇N₂O₃ (M+H⁺) 285.1234, found: 285.1237; Calcd for C₁₆H₁₆N₂O₃Na (M+Na⁺) 307.1053, found: 307.1049.

4-(N-(4-Chlorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene (6b): Purification by silica gel column chromatography afforded pure **6b** as a yellow oil (480 mg, 1.52 mmol, 84 % yield). R_f = 0.45 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3317 (NH), 2931 (=CHAr), 1712 (C=O), 1403 (CH₂), 1342 (HC=CH), 740 (C-Cl). ¹H NMR δ (400 MHz, CDCl₃): 7.36 (1H, dd, J = 1.9, 0.8 Hz, H-1), 7.31-7.24 (4H, m, H_{Ar}-8', 9', 11', 12'), 6.30 (1H, dd, J = 3.2, 1.9 Hz, H-6), 6.20 (1H, d, J = 3.2 Hz, H-5), 4.59 (2H, s, H-CH₂Ar), 3.91 (1H, d, J = 14.6 Hz, H_{eq}-3), 3.82 (1H, d, J = 14.6 Hz, H_{ax}-3), 3.72 (1H, dd, J = 8.3, 5.0 Hz, H_{eq}-3'), 2.86 (1H, dd, J = 18.0, 8.3 Hz, H_{eq}-4'), 2.46 (1H, dd, J = 18.0, 5.0 Hz, H_{ax}-4'), 2.10 (1H, br.s., NH) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 177.4, 174.7, 152.2, 142.5 (+), 134.1, 133.9, 130.4 (2xCH, +), 128.9 (2xCH, +), 110.4 (+), 108.1 (+), 55.0 (+), 44.1 (-), 41.8 (-), 36.3 (-) ppm. COSY Correlation [δ_H/δ_H]: 7.36/6.20 [H-1/H-5], 7.36/6.30 [H-1/H-6], 7.31-7.24/4.59 [H_{Ar}-8', 9', 11', 12'/H-CH₂Ar], 6.30/6.20 [H-6/H-5], 6.20/3.82 [H-5/H_{ax}-3], 3.72/2.46 [H_{eq}-3'/H_{ax}-4'], 3.72/2.86 [H_{eq}-3'/H_{eq}-4'], 2.86/2.46 [H_{eq}-4'/ H_{ax}-4']. HSQC Correlation [δ_H/δ_C]: 7.36/142.5 [H-1/C-1], 7.31-7.24 /128.9-130.4 [H_{Ar}/C_{Ar}], 6.30/110.4 [H-6/C-6], 6.20/108.1 [H-5/C-5], 4.59/41.8 [H-CH₂Ar/C-6'], 3.91/44.1 [H_{eq}-3/C-3], 3.82/44.1 [H_{ax}-3/C-3], 3.72/55.0 [H_{eq}-3'/C-3'], 2.86/36.3 [H_{eq}-4'/C-4'], 2.46/36.3 [H_{ax}-4'/C-4']. HMBC Correlation [δ_H/δ_C]: 7.36/108.1/110.4/152.2 [H-1/C-5/C-6/C-4], 7.31-7.24/41.8/128.9-130.4/133.9/134.1 [H_{Ar}-8',9',11',12'/C-8',9',11',12/C-10'/C-7'], 6.30/ 108.1/142.5/152.2 [H-6/C-5/C-1/C-4], 6.20/110.4/142.5/152.2 [H-5/C-6/C-1/C-4], 4.59/128.9-134.1/174.7/177.4 [H-CH₂Ar/C-7',8',9',10',11',12'/C-5'/C-2'], 3.91/55.0/108.1 /152.2 [H_{eq}-3/C-3'/C-5/C-4], 3.82/55.1/108.1/152.2[H_{ax}-3/C-3'/C-5/C-4], 3.72/36.3/44.1/174.7 /177.4 [H_{eq}-3'/C-4'/C-3/C-5'/C-2'], 2.86/55.0/174.7/177.4 [H_{eq}-4'/C-3'/C-5'/C-2'], 2.46/55.0/ 174.7/177.4 [H_{ax}-4'/C-3'/C-5'/C-2']. GC: R_t = 25.28 min.; MS (EI), m/z (%): 317 (M⁺, 1), 301

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(1), 127 (7), 125 (22), 96 (100), 81 (36), 53 (9). HRMS (ESI+): *m/z*: calcd for C₁₆H₁₆ClN₂O₃ (M+H⁺) 319.0844, found: 319.0851; Calcd for C₁₆H₁₅ClN₂O₃Na (M+Na⁺) 341.0663, found: 341.0667.

4-(*N*-(4-Fluorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene (6c):

Purification by silica gel column chromatography afforded pure **6c** as a yellow oil (510 mg, 1.71 mmol, 88 % yield). R_f = 0.56 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3317 (NH), 2931 (=CHAr), 1712 (C=O), 1403 (CH₂), 1342 (HC=CH), 632 (C-F). ¹H NMR δ (400 MHz, CDCl₃): 7.36 (1H, dd, *J* = 1.8, 0.6 Hz, H-1), 7.35-7.31 (2H, m, H_{Ar}-8', 12'), 7.00-6.92 (2H, m, H_{Ar}-9', 11'), 6.30 (1H, dd, *J* = 3.1, 1.9 Hz, H-6), 6.19 (1H, d, *J* = 3.2 Hz, H-5), 4.59 (2H, s, H-CH₂Ar), 3.91 (1H, d, *J* = 14.6 Hz, H_{eq}-3), 3.82 (1H, d, *J* = 14.6 Hz, H_{ax}-3), 3.72 (1H, dd, *J* = 8.2, 5.0 Hz, H_{eq}-3'), 2.85 (1H, dd, *J* = 17.9, 8.2 Hz, H_{eq}-4'), 2.45 (1H, dd, *J* = 17.9, 5.0 Hz, H_{ax}-4'), 2.07 (1H, br.s., NH) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 177.4, 174.8, 162.5, 152.2, 142.5 (+), 131.4, 130.9 (2xCH, +), 115.6 (2xCH, +), 110.4 (+), 108.1 (+), 55.0 (+), 44.1 (-), 41.7 (-), 36.3 (-) ppm. COSY Correlation [δ_H/δ_H]: 7.36/6.19 [H-1/H-5], 7.36/6.30 [H-1/H-6], 7.35-7.31/4.59 [H_{Ar}-8', 12'/H-CH₂Ar], 7.35-7.31/7.00-6.92 [H_{Ar}-8', 12'/H_{Ar}-9', 11'], 6.30/6.19 [H-6/H-5], 6.19/3.91 [H-5/H_{eq}-3], 6.19/3.82 [H-5/H_{ax}-3], 3.72/2.45 [H_{eq}-3'/H_{ax}-4'], 3.72/2.85 [H_{eq}-3'/H_{eq}-4'], 2.85/2.45 [H_{eq}-4'/H_{ax}-4']. HSQC Correlation [δ_H/δ_C]: 7.36/142.5 [H-1/C-1], 7.35-7.31/130.9 [H_{Ar}-8', 12'/C-8', 12'], 7.00-6.92/115.6 [H_{Ar}-9', 11'/C-9', 11'], 6.30/110.4 [H-6/C-6], 6.19/108.1 [H-5/C-5], 4.59/41.7 [H-CH₂Ar/C-6'], 3.91/44.1 [H_{eq}-3/C-3], 3.82/44.1 [H_{ax}-3/C-3], 3.72/55.0 [H_{eq}-3'/C-3'], 2.85/36.3 [H_{eq}-4'/C-4'], 2.45/36.3 [H_{ax}-4'/C-4']. HMBC Correlation [δ_H/δ_C]: 7.36/108.1/110.4/152.2 [H-1/C-5/C-6/C-4], 7.35-7.31/41.7/115.6/131.4/162.5[H_{Ar}-8', 12'/C-6'/C-9', 11'/C-7'/C-10'], 7.00-6.92/130.9/131.4/162.5 [H_{Ar}-9', 11'//C-8', 12'/C-7'/C-10'], 6.30/108.1/142.5/152.2 [H-6/C-5/C-1/C-4], 6.19/110.4/142.5/152.2 [H-5/C-6/C-1/C-4], 4.59/130.9/131.4/174.8/177.4 [H-CH₂Ar/C-8', 12'/C-7'/C-5'/C-2'], 3.91/55.0/108.1/152.2 [H_{eq}-3/C-3'/C-5/C-4], 3.82/55.0/108.1/152.2 [H_{ax}-3/C-3'/C-5/C-4], 3.72/36.3/44.1/174.8/177.4 [H_{eq}-3'/C-4'/C-3/C-5'/C-2'], 2.85/55.0/174.8/177.4 [H_{eq}-4'/C-3'/C-5'/C-2'], 2.45/55.0/174.8/177.4 [H_{ax}-4'/C-3'/C-5'/C-2']. GC: R_t = 23.17 min.; MS (EI), *m/z* (%): 301 (M⁺, 1), 285 (1), 109 (33), 97 (6), 96 (100), 81 (42). HRMS (ESI+): *m/z*: calcd for C₁₆H₁₆FN₂O₃ (M+H⁺) 303.1139, found: 303.1135; Calcd for C₁₆H₁₅FN₂O₃Na (M+Na⁺) 325.0959, found: 325.0953.

4-(*N*-(4-Methylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene (6d):

Purification by silica gel column chromatography afforded pure **6d** as a yellow oil (550 mg, 1.84 mmol, 93 % yield). R_f = 0.42 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3317 (NH), 3023

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(CH₃), 2931 (=CHAr), 1712 (C=O), 1403 (CH₂), 1342 (HC=CH). ¹H NMR δ (400 MHz, CDCl₃): 7.38 (1H, dd, *J* = 1.8, 0.8 Hz, H-1), 7.28-7.26 (2H, m, H_{Ar}-8', 12'), 7.12 (2H, d, *J* = 7.8 Hz, H_{Ar}-9', 11'), 6.32 (1H, dd, *J* = 3.2, 1.9 Hz, H-6), 6.21 (1H, d, *J* = 3.2 Hz, H-5), 4.61 (2H, s, H-CH₂Ar), 3.93 (1H, d, *J* = 14.6 Hz, H_{eq}-3), 3.84 (1H, d, *J* = 14.7 Hz, H_{ax}-3), 3.72 (1H, dd, *J* = 8.3, 5.0 Hz, H_{eq}-3'), 2.87 (1H, dd, *J* = 17.9, 8.3 Hz, H_{eq}-4'), 2.47 (1H, dd, *J* = 17.9, 5.0 Hz, H_{ax}-4'), 2.32 (3H, s, CH₃), 2.10 (1H, br.s., NH) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 177.5, 174.9, 152.2, 142.5 (+), 137.9, 132.5, 129.4 (2xCH, +), 128.9 (2xCH, +), 110.4 (+), 108.1 (+), 55.0 (+), 44.1 (-), 42.2 (-), 36.3 (-), 21.2 (+) ppm. GC: R_t = 23.99 min.; MS (EI), m/z (%): 297 (M⁺, 1), 281 (1), 97 (6), 96 (100), 81 (39), 53 (12). HRMS (ESI+): *m/z*: calcd for C₁₇H₁₉N₂O₃ (M+H⁺) 299.1390, found: 299.1387; Calcd for C₁₇H₁₈N₂O₃Na (M+Na⁺) 321.1210, found: 321.1206.

4-(*N*-(4-Methoxylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene (6e):
Purification by silica gel column chromatography afforded pure **6e** as a yellow oil (520 mg, 1.67 mmol, 91 % yield). R_f = 0.49 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3317 (NH), 2931 (=CHAr), 2838 (OCH₃), 1697 (C=O), 1403 (CH₂), 1342 (HC=CH), 1249 (C-O-C). ¹H NMR δ (400 MHz, CDCl₃): 7.36 (1H, dd, *J* = 1.8, 0.7 Hz, H-1), 7.33-7.27 (2H, m, H_{Ar}-8', 12'), 6.83-6.79 (2H, m, H_{Ar}-9', 11'), 6.30 (1H, dd, *J* = 3.1, 1.9 Hz, H-6), 6.19 (1H, d, *J* = 3.2 Hz, H-5), 4.57 (2H, s, H-CH₂Ar), 3.91 (1H, d, *J* = 14.6 Hz, H_{eq}-3), 3.82 (1H, d, *J* = 14.6 Hz, H_{ax}-3), 3.76 (3H, s, OCH₃), 3.70 (1H, dd, *J* = 8.3, 5.0 Hz, H_{eq}-3'), 2.84 (1H, dd, *J* = 17.9, 8.3 Hz, H_{eq}-4'), 2.44 (1H, dd, *J* = 17.9, 5.0 Hz, H_{ax}-4'), 2.09 (1H, br.s., NH) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 177.5, 174.9, 159.4, 152.3, 142.5 (+), 130.4 (2xCH, +), 127.8, 114.0 (2xCH, +), 110.3 (+), 108.1 (+), 55.3 (+), 55.1 (+), 44.1 (-), 41.9 (-), 36.3 (-) ppm. COSY Correlation [δ_H/δ_H]: 7.36/6.19 [H-1/H-5], 7.36/6.30 [H-1/H-6], 7.33-7.27/4.57[H_{Ar}-8',12'/H-CH₂Ar], 7.33-7.27/6.83-6.79 [H_{Ar}-8',12'/H_{Ar}-9',11'], 6.30/6.19 [H-6/H-5], 6.19/3.91 [H-5/H_{eq}-3], 6.19/3.82 [H-5/H_{ax}-3], 3.70/2.44 [H_{eq}-3'/H_{ax}-4'], 3.70/2.84 [H_{eq}-3'/H_{eq}-4'], 2.84/2.44 [H_{eq}-4'/H_{ax}-4']. HSQC Correlation [δ_H/δ_C]: 7.36/142.5 [H-1/C-1], 7.33-7.27/130.4 [H_{Ar}-8', 12'/C-8',12'], 6.83-6.79/114.0 [H_{Ar}-9',11'/C-9'-11'], 6.30/110.3 [H-6/C-6], 6.19/108.1 [H-5/C-5], 4.57/41.9 [H-CH₂Ar/C-6'], 3.91/44.1 [H_{eq}-3/C-3], 3.82/44.1 [H_{ax}-3/C-3], 3.76/55.3 [H-OCH₃/C-OCH₃], 3.70/55.1 [H_{eq}-3'/C-3], 2.84/36.3 [H_{eq}-4'/C-4'], 2.44/36.3 [H_{ax}-4'/C-4']. HMBC Correlation [δ_H/δ_C]: 7.36/108.1/110.3/152.3 [H-1/C-5/C-6/C-4], 7.33-7.27/41.9/114.0/159.4 [H_{Ar}-8',12'/H-CH₂Ar/C-9',11'/C-10'], 6.83-6.79 /127.8/130.4/159.4 [H_{Ar}-9',11'/C-7'/C-8',12'/C-10'], 6.30/108.1/142.5/152.3 [H-6/C-5/C-1/C-4], 6.19/110.3/142.5/152.3 [H-5/C-6/C-1/C-4], 4.57/127.8/130.4/174.9/177.5 [H-CH₂Ar/C-7/C-8',12'/C-5'/C-2'], 3.91/55.1/108.1/152.3 [H_{eq}-3/C-3'/C-5/C-4], 3.82/55.1/108.1/152.3 [H_{ax}-3/C-3'/C-5/C-4], 3.79/159.4 [H-OCH₃/C-10'].

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3.70/36.3/44.1/174.9/177.5 [H_{eq}-3'/C-4'/C-3/C-5'/C-2'], 2.84/55.1/174.9/177.5 [H_{eq}-4'/C-3'/C-5'/C-2'], 2.44/55.1/174.9/177.5 [H_{ax}-4'/C-3'/C-5'/C-2']. GC: R_t = 25.98 min.; MS (EI), m/z (%): 314 (M⁺, 1), 297 (1), 162 (6), 121 (49), 96 (100), 81 (38), 53 (8). HRMS (ESI+): m/z: calcd for C₁₇H₁₉N₂O₄ (M+H⁺) 315.1339, found: 315.1344; Calcd for C₁₇H₁₈N₂O₄Na (M+Na⁺) 337.1159, found: 337.1155.

4-(N-(3,4-Methylenedioxylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene (6f): Purification by silica gel column chromatography afforded pure **6f** as a yellow oil (460 mg, 1.40 mmol, 89 % yield). R_f = 0.43 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3317 (NH), 2900 (CH₂), 1697 (C=O), 1403 (CH₂), 1326 (HC=CH), 1249 (C-O-C). ¹H NMR δ (400 MHz, CDCl₃): 7.36 (1H, dd, J = 1.9, 0.8 Hz, H-1), 6.86-6.82 (2H, m, H_{Ar}-8', 12'), 6.70 (1H, dd, J = 7.7, 0.6 Hz, H_{Ar}-11'), 6.30 (1H, dd, J = 3.2, 1.9 Hz, H-6), 6.19 (1H, dd, J = 3.2, 0.6 Hz, H-5), 5.91 (2H, s, -OCH₂O-), 4.52 (2H, s, H-CH₂Ar), 3.91 (1H, d, J = 14.6 Hz, H_{eq}-3), 3.82 (1H, d, J = 14.6 Hz, H_{ax}-3), 3.70 (1H, dd, J = 8.3, 5.0 Hz, H_{eq}-3'), 2.84 (1H, dd, J = 17.9, 8.3 Hz, H_{eq}-4'), 2.44 (1H, dd, J = 17.9, 5.0 Hz, H_{ax}-4'), 2.22 (1H, br.s., NH) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 177.3, 174.7, 152.1, 147.7, 147.3, 142.4 (+), 129.2, 122.5 (+), 110.3 (+), 109.4 (+), 108.2 (+), 108.0 (+), 101.1 (-), 55.0 (+), 44.1 (-), 42.2 (-), 36.2 (-) ppm. COSY Correlation [δ_H/δ_H]: 7.36/6.19 [H-1/H-5], 7.36/6.30 [H-1/H-6], 6.86-6.82/4.59 [H_{Ar}-8',12'/H-CH₂Ar], 6.86-6.82/6.70 [H_{Ar}-8',12'/H_{Ar}-11'], 6.30/6.19 [H-6/H-5], 6.19/3.91 [H-5/H_{eq}-3], 6.19/3.82 [H-5/H_{ax}-3], 3.70/2.44 [H_{eq}-3'/H_{ax}-4'], 3.70/2.84 [H_{eq}-3'/H_{eq}-4'], 2.84/2.44 [H_{eq}-4'/H_{eq}-4']. HSQC Correlation [δ_H/δ_C]: 7.36/142.4[H-1/C-1], 6.86-6.82/109.4/122.59 [H_{Ar}-8',12'/C-8',12'], 6.70/108.2 [H-11'/C-11'], 6.30/110.3 [H-6/C-6], 6.19/108.0 [H-5/C-5], 5.91/101.1 [H-OCH₂O/C-OCH₂O], 4.52/42.2 [H-CH₂Ar/C-6'], 3.91/44.1 [H_{eq}-3/C-3], 3.82/44.1 [H_{ax}-3/C-3], 3.70/55.0 [H_{eq}-3'/C-3'], 2.84/36.2 [H_{eq}-4'/C-4'], 2.44/36.2 [H_{ax}-4'/C-4']. HMBC Correlation [δ_H/δ_C]: 7.36/108.0/110.3/152.1 [H-1/C-5/C-6/C-4], 6.86-6.82/42.2/108.0/109.4/147.37/147.75 [H_{Ar}-8',12'/C-6'/C-12'/C-8'/C-10'/C-9'], 6.70/109.4/129.2/147.3/147.75 [H-11'/C-12'/C-7'/C-10'/C-9'], 6.30/108.0/142.4/152.1 [H-6/C-5/C-1/C-4], 6.19/110.3/142.4/152.1 [H-5/C-6/C-1/C-4], 5.91/147.3/147.7 [H-OCH₂O/C-10'/C-9], 4.52/109.4/122.5/129.2/174.7/177.3 [H-CH₂Ar/C-12'/C-8'/C-7'/C-5'/C-2'], 3.91/55.0/108.0/152.1 [H_{eq}-3/C-3'/C-5/C-4], 3.82/55.0/108.0/152.1 [H_{ax}-3/C-3'/C-5/C-4], 3.70/36.2/44.1/174.7/177.3 [H_{eq}-3'/C-4'/C-3/C-5'/C-2'], 2.84/55.0/174.7/177.3 [H_{eq}-4'/C-3'/C-5'/C-2'], 2.44/55.0/174.7/177.3 [H_{ax}-4'/C-3'/C-5'/C-2']. GC: R_t = 27.55 min.; MS (EI), m/z (%): 328 (M⁺, 1), 311 (1), 135 (45), 96 (100), 81 (39), 77 (9), 53 (9). HRMS (ESI+): m/z: calcd for C₁₇H₁₇N₂O₅ (M+H⁺) 329.1132, found: 329.1135; Calcd for C₁₇H₁₆N₂O₅Na (M+Na⁺) 351.0951, found: 351.0945.

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4-(N-(1-Naphthyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene (6g):

Purification by silica gel column chromatography afforded pure **6g** as a yellow oil (530 mg, 1.60 mmol, 95 % yield). R_f = 0.56 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3317 (NH), 3054 (=CArH), 1712 (C=O), 1511 (CAr=CAr), 1403 (CH₂), 1342 (HC=CH). ¹H NMR δ (400 MHz, CDCl₃): 8.27 (1H, d, J = 8.4 Hz, H-14'), 7.85 (1H, d, J = 8.1 Hz, H-11'), 7.80 (1H, d, J = 8.3 Hz, H-10'), 7.56 (2H, ddd, J = 7.1, 4.9, 1.4 Hz, H-8' y 13'), 7.49 (1H, ddd, J = 8.0, 6.9, 1.1 Hz, H-12'), 7.41 (1H, dd, J = 8.1, 7.2 Hz, H-9'), 7.36 (1H, dd, J = 1.9, 0.8 Hz, H-1), 6.29 (1H, dd, J = 3.1, 1.9 Hz, H-6), 6.18 (1H, d, J = 3.2 Hz, H-5), 5.12 (2H, d, J = 3.9 Hz, H-CH₂), 3.91 (1H, d, J = 14.6 Hz, H_{eq}-3), 3.82 (1H, d, J = 14.6 Hz, H_{ax}-3), 3.71 (1H, dd, J = 8.3, 5.0 Hz, H_{eq}-3'), 2.87 (1H, dd, J = 17.9, 8.3 Hz, H_{eq}-4'), 2.49 (1H, dd, J = 17.9, 5.0 Hz, H_{ax}-4'), 2.09 (1H, br.s., NH) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 177.7, 175.0, 152.2, 142.5 (+), 133.8, 131.3, 130.5, 128.9 (+), 128.8 (+), 127.8 (+), 126.6 (+), 125.9 (+), 125.3 (+), 123.5 (+), 110.3 (+), 108.1 (+), 55.0 (+), 44.1 (-), 40.3 (-), 36.3 (-) ppm. COSY Correlation [δ_H/δ_H]: 8.27/7.56 [H-14'/H-13'], 7.85/7.49 [H-11'/H-12'], 7.80/7.41 [H-10'/H-9'], 7.56/5.12 [H-8'/H-CH₂], 7.56/7.41 [H-8'/H-9'], 7.56/7.49 [H-13'/H-12'], 7.36/6.18 [H-1/H-5], 7.36/6.29 [H-1/H-6], 6.29/6.18 [H-6/H-5], 3.91/3.82 [H_{eq}-3/H_{ax}-3], 3.71/2.49 [H_{eq}-3'/H_{ax}-4'], 3.71/2.87 [H_{eq}-3'/H_{eq}-4'], 2.87/2.49 [H_{eq}-4'/H_{ax}-4']. HSQC Correlation [δ_H/δ_C]: 8.27/123.5 [H-14'/C-14'], 7.85/128.8 [H-11'/C-11'], 7.80/128.9 [H-10'/C-10'], 7.56/126.6 [H-13'/C-13'], 7.56/127.8 [H-8'/C-8'], 7.49/125.9 [H-12'/C-12'], 7.41/125.3 [H-9'/C-9'], 7.36/142.5 [H-1/C-1], 6.29/110.3 [H-6/C-6], 6.18/108.1 [H-5/C-5], 5.12/40.3 [H-CH₂/C-6'], 3.91/44.1 [H_{eq}-3/C-3], 3.82/44.1 [H_{ax}-3/C-3], 3.71/55.0 [H_{eq}-3'/C-3'], 2.87/36.3 [H_{eq}-4'/C-4'], 2.49/36.3 [H_{ax}-4'/C-4']. HMBC Correlation [δ_H/δ_C]: 8.27/125.9/130.5/133.8 [H-14'/C-12'/C-7'/C-14^a], 7.85/126.6/131.3/133.8 [H-11'/C-13'/C-10^a/C-14^a], 7.80/127.8/131.3/133.8[H-10'/C-8'/C-10^a/C-14^a], 7.56/131.3 [H-8'/C-10^a], 7.56/128.8/128.9/131.3 [H-13'/C-11'/C-10'/C-10^a], 7.49/123.5/133.8 [H-12'/C-11'/C-14'/C-14^a], 7.41/130.5/133.8 [H-9'/C-7'/C-14^a], 6.29/108.1/142.5/152.2 [H-6/C-5/C-1/C-4], 6.18/110.3/142.5/152.2 [H-5/C-6/C-1/C-4], 5.12/127.8/130.5/175.0/177.7 [H-CH₂Ar/C-8'/C-7'/C-5'/C-2'], 3.91/55.0/108.1/152.2 [H_{eq}-3/C-3'/C-5/C-4], 3.82/55.0/108.1/152.2 [H_{ax}-3/C-3'/C-5/C-4], 3.71/36.3/44.1/175.0/177.7 [H_{eq}-3'/C-4'/C-3/C-5'/C-2'], 2.87/55.0/175.0/177.7 [H_{eq}-4'/C-3'/C-5'/C-2'], 2.49/55.0/175.0/177.7 [H_{ax}-4'/C-3'/C-5'/C-2']. GC: R_t = 31.01 min.; MS (EI), m/z (%): 334 (M⁺, 1), 317 (1), 141 (37), 115 (11), 96 (100), 81 (37), 53 (10). HRMS (ESI+): m/z: calcd for C₂₀H₁₉N₂O₃ (M+H⁺) 335.1390, found: 335.1385; Calcd for C₂₀H₁₈N₂O₃Na (M+Na⁺) 357.1210, found: 357.1214.

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4-(S-(-)-N-(1-Phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene

(6h): Purification by silica gel column chromatography afforded pure **6h** as a yellow oil (510 mg, 1.71 mmol, 86 % yield). R_f = 0.56 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3317 (NH), 2977 (CH₃), 1697 (C=O), 1388 (HC=CH), 1187 (CH₃). ¹H NMR δ (400 MHz, CDCl₃): 7.42 (2H, d, J = 7.9 Hz, H_{Ar}-8', 12'), 7.36 (1H, d, J = 1.0 Hz, H-1), 7.33-7.23 (3H, m, H_{Ar}-9', 10', 11'), 6.30 (1H, dd, J = 3.1, 1.5 Hz, H-6), 6.19 (1H, d, J = 2.6 Hz, H-5), 5.43-5.35 (1H, m, H-6'), 3.90 (1H, dd, J = 14.8, 3.3 Hz, H_{eq}-3), 3.80 (1H, d, J = 14.5 Hz, H_{ax}-3), 3.64 (1H, ddd, J = 16.3, 8.3, 5.3 Hz, H_{eq}-3'), 2.80 (1H, dt, J = 17.7, 7.6 Hz, H_{eq}-4'), 2.47-2.37 (1H, m, H_{ax}-4'), 2.02 (1H, br.s., NH), 1.81-1.78 (3H, m, H-CH₃) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 177.5, 174.9, 152.3, 142.5 (+), 139.5, 128.5 (2xCH, +), 127.9 (+), 127.6 (2xCH, +), 110.4 (+), 108.1 (+), 54.8 (+), 50.4(+), 44.2 (-), 36.3 (-), 16.6 (+) ppm. GC: R_t = 23.39 min.; MS (EI), m/z (%): 298 (M⁺, 1), 281 (1), 106 (25), 96 (100), 81 (46), 77 (9), 53 (12). HRMS (ESI+): m/z: calcd for C₁₇H₁₉N₂O₃ (M+H⁺) 299.1390, found: 299.1394; Calcd for C₁₇H₁₈N₂O₃Na (M+Na⁺) 321.1210, found: 321.1205.

4-(R-(-)-N-(1-Phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene

(6i): Purification by silica gel column chromatography afforded pure **6i** as a yellow oil (480 mg, 1.63 mmol, 82 % yield). R_f = 0.50 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3317 (NH), 2977 (CH₃), 1697 (C=O), 1388 (HC=CH), 1187 (CH₃). ¹H NMR δ (400 MHz, CDCl₃): 7.43-7.40 (2H, m, H_{Ar}-8', 12'), 7.36 (1H, td, J = 2.2, 0.8 Hz, H-1), 7.33-7.23 (3H, m, H_{Ar}-9', 10' and 11'), 6.30 (1H, dt, J = 3.4, 1.7 Hz, H-6), 6.19 (1H, d, J = 2.7 Hz, H-5), 5.39 (1H, qd, J = 7.4, 3.0 Hz, H-6'), 3.89 (1H, dd, J = 14.6, 3.2 Hz, H_{eq}-3), 3.80 (1H, dd, J = 14.6, 1.7 Hz, H_{ax}-3), 3.63 (1H, ddd, J = 17.7, 8.3, 5.3 Hz, H_{eq}-3'), 2.80 (1H, ddd, J = 17.8, 8.2, 7.4 Hz, H_{eq}-4'), 2.42 (1H, ddd, J = 17.9, 8.3, 5.2 Hz, H_{ax}-4'), 2.11 (1H, br.s., NH), 1.79 (3H, dd, J = 7.3, 2.7 Hz, H-CH₃) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 177.5, 174.8, 152.1, 142.4 (+), 139.3, 128.4 (2xCH,+), 127.9 (+), 127.5 (2xCH, +), 110.3 (+), 108.0 (+), 54.7 (+), 50.4 (+), 44.1 (-), 36.2 (-), 16.5 (+) ppm. GC: R_t = 23.12 min.; MS (EI), m/z (%): 298 (M⁺, 1), 281 (1), 106 (24), 98 (7), 96 (100), 81 (38), 53 (8). HRMS (ESI+): m/z: calcd for C₁₇H₁₉N₂O₃ (M+H⁺) 299.1390, found: 299.1386; Calcd for C₁₇H₁₈N₂O₃Na (M+Na⁺) 321.1210, found: 321.1215.

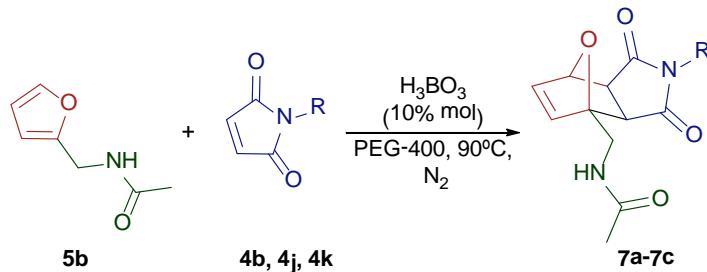
4-(1*H*-Pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene (6j**):** Compound **6j** was obtained from commercial available maleimide **4j** according to the procedure described in section 5. Purification by silica gel column chromatography afforded pure **6j** as a yellow oil (372 mg, 1.91 mmol, 93 % yield). R_f = 0.35 (1:1 hexane/EtOAc); FT-IR (liquid film, cm⁻¹): 3409

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(NH-Maleimide), 3347 (NH-Bicycle), 3000 (CH₂), 1619 (C=O), 1581 (C-N), 1442 (CH₂), 1288 (HC=CH). ¹H NMR δ (400 MHz, CDCl₃): 8.81 (1H, s, 1H, br.s., NH-Maleimide), 7.38 (1H, dd, *J* = 1.9, 0.8 Hz, H-1), 6.32 (1H, dd, *J* = 3.2, 1.9 Hz, H-6), 6.23 (1H, dd, *J* = 3.2, 0.7 Hz, H-5), 3.93 (1H, d, *J* = 14.6 Hz, H_{eq}-3), 3.84 (1H, d, *J* = 14.6 Hz, H_{ax}-3), 3.78 (1H, dd, *J* = 8.3, 5.3 Hz, H_{eq}-3'), 2.88 (1H, dd, *J* = 18.1, 8.3 Hz, H_{eq}-4'), 2.53 (1H, dd, *J* = 18.1, 5.3 Hz, H_{ax}-4'), 2.12 (1H, br.s., NH-Bicycle) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 178.2, 175.5, 152.1, 142.6 (+), 110.4 (+), 108.3 (+), 56.2 (+), 44.1 (-), 37.3 (-) ppm. GC: *R_t* = 6.33 min.; MS (EI), m/z (%): 194 (M⁺, 1), 177 (2), 122 (4), 106 (2), 96 (100), 81 (74), 69 (8), 53 (22). HRMS (ESI+): m/z: calcd for C₉H₁₁N₂O₃ (M+H⁺) 195.0764, found: 195.0768; Calcd for C₉H₁₀N₂O₃Na (M+Na⁺) 217.0584, found: 217.0579.

4-(*N*-Phenyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene (6k): Compound **6k** was obtained from commercial available N-phenylmaleimide **4k** according to the procedure described in section 5. Purification by silica gel column chromatography afforded pure **6k** as a white solid (910 mg, 3.36 mmol, 91 % yield). mp. 90–92 °C. R_f = 0.39 (1:1 hexane/EtOAc); FT-IR (KBr-disk cm⁻¹): 3286 (NH), 2854 (C-H), 1712 (C=O), 1403 (CH₂), 1187 (HC=CH). ¹H NMR δ (400 MHz, CDCl₃): 7.49–7.45 (2H, m, H_{Ar}-7' and 11'), 7.4–7.40 (1H, m, H_{Ar}-9'), 7.39 (1H, dd, *J* = 8.5, 6.2 Hz, H-1), 7.28–7.25 (2H, m, H_{Ar}-8', 10'), 6.34 (1H, dd, *J* = 3.1, 1.9 Hz, H-6), 6.26 (1H, d, *J* = 3.1 Hz, H-5), 3.98 (1H, dd, *J* = 14.6 Hz, H_{eq}-3), 3.91 (1H, dd, *J* = 8.3, 5.2 Hz, H_{eq}-3'), 3.90 (1H, d, *J* = 14.5 Hz, H_{ax}-3), 3.04 (1H, dd, *J* = 18.0, 8.4 Hz, H_{eq}-4'), 2.66 (1H, dd, *J* = 18.0, 5.3 Hz, H_{ax}-4'), 2.41 (1H, br.s., NH) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 176.8, 174.2, 152.1, 142.6 (+), 131.5, 129.3 (2xCH, +), 128.8 (+), 126.4 (2xCH, +), 110.4 (+), 108.3 (+), 55.1 (+), 44.2 (-), 36.4 (-) ppm. GC: *R_t* = 14.28 min.; MS (EI), m/z (%): 270 (M⁺, 1), 252 (1), 192 (32), 96 (100), 81 (25), 77 (48), 53 (17). HRMS (ESI+): m/z: calcd for C₁₅H₁₅N₂O₃ (M+H⁺) 271.1077, found: 271.1074; Calcd for C₁₅H₁₄N₂O₃Na (M+Na⁺) 293.0897, found: 293.0902.

6. General procedure for the synthesis of the *N*-(10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decan-8-ene-3,5-dione-7-ylmethyl)acetamides 7a-7c



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A solution of the corresponding maleimide **4b**, **4j** and **4k** (1.95 mmol) in 10 mL of polyethyleneglycol 400 (PEG-400) was placed in a 50 mL Schlenk round-bottom flask heated at 90 °C and under positive nitrogen pressure, then boric acid (10 % mol) was added in one portion and after 20 min, N-acetyl furfurylamine **5b** (2.34 mmol) were added over a few minutes in small portions; N-acetyl furfurylamine was easily prepared from commercial furfurylamine according to the described procedure.¹² The reaction was monitored by TLC and after 3 hours the mixture was diluted with 50 mL of NaHCO₃ solution 1 M and the precipitated product was filtered off, washed with distillated water and then with ethyl acetate, finally the resulting solid was dried in vacuum to afford the desired products as stable solids.

N-(10-Oxa-1H-4-azatricyclo[5.2.1.0^{2,6}]decan-8-ene-3,5-dione-7-ylmethyl)acetamide (7a):

Compound **7a** was obtained according to the procedure described above after filter, washing and drying the resulting precipitate, obtaining **7a** as a white solid (336 mg, 1.42 mmol, 84 % yield). R_f = 0.42 (1:1 hexane/EtOAc); mp: 148-150 °C; FT-IR (KBr disk, cm⁻¹): 3332 (NH-Maleimide and NH-Amide), 3023 (HC=CH), 1712 (C=O-Maleimide), 1650 (C=O-Amide), 1558 (C-N), 1430 (CH₃), 1187 (C-O-C). ¹H NMR δ (400 MHz, d₆-DMSO): 11.26 (1H, s, NH-Maleimide), 8.00 (1H, t, J = 5.2 Hz, NH-Amide), 6.53 (1H, d, J = 4.8 Hz, H-8), 6.30 (1H, d, J = 5.4 Hz, H-9), 3.95 (1H, dd, J = 14.6, 6.3 Hz, H-1), 3.34 (2H, d, J = 5.2 Hz, H-CH₂), 3.00 (1H, d, J = 6.3 Hz, H-2), 2.88 (1H, d, J = 6.2 Hz, H-6), 1.81 (3H, s, H-CH₃) ppm. ¹³C NMR δ (101 MHz, d₆-DMSO): 177.7, 176.5, 169.6, 137.8 (+), 137.4 (+), 90.5, 80.2 (+), 51.6 (+), 49.5 (+), 37.8 (-), 22.5 (+). HRMS (ESI+): m/z: calcd for C₁₁H₁₃N₂O₄ (M+H⁺) 237.0897, found: 237.0892; Calcd for C₁₁H₁₂N₂O₃Na (M+Na⁺) 259.0689, found: 259.0683.*

N-(4-(Phenyl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decan-8-ene-3,5-dione-7-ylmethyl)acetamide (7b):

Compound **7b** was obtained according to the procedure described above after filter, washing and drying the precipitate, obtaining **7b** as a white solid (474 mg, 1.52 mmol, 78 % yield). R_f = 0.27 (1:1 hexane/EtOAc); mp: 184-186 °C; FT-IR (KBr disk, cm⁻¹): 3378 (NH), 3070 (HC=CH), 1712 (C=O-Maleimide), 1663 (C=O-Amide), 1527 (C-N), 1496 (CH₃), 1203 (C-O). ¹H NMR δ (400 MHz, d₆-DMSO): 8.08 (1H, t, J = 5.9 Hz, NH), 7.53-7.47 (2H, m, H_{Ar}-2' and 6'), 7.45-7.40 (1H, m, H_{Ar}-4'), 7.21 (2H, dt, J = 8.6, 2.0 Hz, H_{Ar}-3' and 5'), 6.61 (1H, dd, J = 5.6, 1.2 Hz, H-8), 6.40 (1H, d, J = 5.7 Hz, H-9), 4.06 (1H, dd, J = 14.8, 6.7 Hz, H-1), 3.38 (2H, d, J = 5.2 Hz, CH₂), 3.23 (1H, d, J = 6.5 Hz, H-6), 3.12 (1H, d, J = 6.5 Hz, H-2), 1.83 (3H, s, H-CH₃) ppm. ¹³C NMR δ (101 MHz, d₆-DMSO): 175.5, 174.2, 169.6, 137.9 (+), 137.5 (+),

¹² S. Naik, G. Bhattacharjya, B. Talukdar,; B. K. Patel, *Eur. J. Org. Chem.*, 2004, 1254.

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132.0, 129.0 (2xCH, +), 128.5 (+), 126.8 (2xCH, +), 90.8, 80.5 (+), 50.5 (+), 48.5 (+), 37.8 (-), 22.4 (+). HRMS (ESI+): *m/z*: calcd for C₁₇H₁₇N₂O₄ (M+H⁺) 313.1183, found: 313.1187; Calcd for C₁₇H₁₆N₂O₄Na (M+Na⁺) 335.1002, found: 335.1005.*

N-(4-(4-Chlorobenzyl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decan-8-ene-3,5-dione-7-ylmethyl)acetamide (7c): Compound **7c** was obtained according to the procedure described above after filter, washing and drying the precipitate, obtaining **7c** as a white solid (637 mg, 1.76 mmol, 92 % yield). R_f = 0.27 (1:1 hexane/EtOAc); mp: 205-207 °C; FT-IR (KBr disk, cm⁻¹): 3317 (NH), 3085 (HC=CH), 1697 (C=O-Maleimide), 1650 (C=O-Amide), 1558 (C-N), 1496 (CH₃), 1295 (C-O), 863 (C-Cl). ¹H NMR δ (400 MHz, CDCl₃): 7.28-7.21 (4H, m, H_{Ar}-2', 3', 5' and 6'), 6.49 (2H, s, H-8 and H-9), 6.22 (1H, t, J = 6.0 Hz, NH), 5.21 (2H, s, H-1), 4.59 (2H, s, H-CH₂Ar), 3.82 (2H, d, J = 6.2 Hz, H-CH₂NH), 2.99 (1H, d, J = 6.3 Hz, H-5), 2.87 (1H, d, J = 6.3 Hz, H-2), 1.99 (3H, s, H-CH₃) ppm. ¹³C NMR δ (101 MHz, CDCl₃): 175.5, 175.0, 170.4, 138.9 (+), 137.2 (+), 133.9, 133.8, 129.6 (2xCH, +), 128.9 (2xCH, +), 90.8, 80.8 (+), 50.3 (+), 48.4 (+), 41.9 (-), 38.6 (-), 23.3 (+) ppm. HRMS (ESI+): *m/z*: calcd for C₁₈H₁₈ClN₂O₃ (M+H⁺) 361.0950, found: 361.0947; Calcd for C₁₈H₁₇ClN₂O₃Na (M+Na⁺) 383.0769, found: 383.0772.*

7. In vitro acetylcholinesterase inhibitory activity essay for compounds 6a-6k and 7a-7c

To assess the inhibitory activity of the compounds toward AChE, we followed the spectrophotometric method described by Ellman¹³ and adapted in our laboratory with some modifications.¹⁴ The colorimetric reaction was performed in a 96 well plates using purified AChE from Electrophorus electricus (type V-S). Inhibition curves were made by preincubating for 30 min 50 μL of a solution of each compound (twelve different concentrations were tested) in phosphate-buffered solution (PBS), at pH 7.5, and 50 μL of a enzymatic solution containing 0.25 U/mL of AChE. After this preincubation period, 100 μL of a substrate solution (0.24 mM of 5,5'-dithiobis-2-nitrobenzoic acid (DTNB), 0.04 M of Na₂HPO₄ and 0.24 mM of acetylthiocholine iodide in distilled water) were added, allowing 5 min more of incubation, where the DTNB produces the yellow anion 5-thio-2-nitrobenzoic acid along with the enzymatic degradation of acetylthiocholine. Changes in absorbance were detected using a multiwell spectrophotometer (VERSAmaxTM, Molecular Devices) at 412 nm. Compounds inhibiting the AChE ativity would reduce the color generation and it intensity; thus, IC values were calculated

* Not detected trough GC-MS due to the retro-Diels-Alder reaction in the vaporization chamber. Only the N-acetyl furfurylamine and the respective maleimide were registered using this technique.

¹³ G. L. Ellman, K. D. Courtney, V. Jr. Andres and R. M. Feather-Stone, *Biochem. Pharmacol.*, 1961, **7**, 88.

¹⁴ V. V. Kouznetsov, L. Y. Vargas Méndez, A. Muñoz Acevedo, *Lett. Drug Des. Discov.*, 2010, **7**, 710.

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as the concentration of compound that produces 50 % of AChE activity inhibition. Data are expressed as the standard error of the mean (SEM) of at least three different experiments in duplicate (Table SI1).

Compound	IC ₅₀ (mM) ^a
6a	0.233 ± 0.003
6b	0.200 ± 0.004
6c	0.267 ± 0.008
6d	0.315 ± 0.014
6e	0.293 ± 0.004
6f	0.235 ± 0.011
6g	0.279 ± 0.015
6h	0.249 ± 0.012
6i	0.262 ± 0.012
6j	0.302 ± 0.008
6k	0.419 ± 0.026
7a	0.236 ± 0.006
7b	0.287 ± 0.009
7c	0.212 ± 0.008
Physostigmine	0.173 ± 0.009 ^b

^a IC₅₀ values are the mean ± SEM of at least three different experiments in duplicate. ^b IC₅₀ values are expressed in μM.

8. Toxicity Assessment in Vivo using zebrafish embryos for compounds **6a-6k** and **7a-7c**

Wild-type adult zebrafish of both sexes were obtained from a pet shop and were separated in two tanks (30 L each), according to their gender, at 26±2 °C under natural light-dark photoperiods. The fish were feed twice daily and the water quality was recorded weekly, in order to acclimate the animals for at least two weeks before experiments begin. For the reproduction of the adult fishes, small breeding tanks were set up in the evening previous to experiment, each containing three males and one female specimen. The tanks were isolated until next morning when the lights switch on and the natural mating occurs, without any perturbation. The embryos were collected, pooled and washed with E3 medium and examined to discarded dead, delayed, malformed and unfertilized embryos, while the adult fish were returned to their corresponding tank. The selected embryos were distributed in 96-well plates as appropriate to the screen, three embryos per well (embryonic plates). Compounds **6a-6k** and **7a-7c** were diluted into the E3 screening medium with 2% V/V of DMSO and aliquots of 200 μL were prepared at concentrations ranging from 200 μM to 5 μM (source plates). The surrounding medium was carefully removed from the embryonic plates using an 8-multichannel pipette and then the appropriate chemical aliquot of each compound (200 μL), from the source plate, were added into the corresponding well of the embryonic plate. Eight controls wells were used peer plate, each containing E3 medium with 2% V/V of DMSO. The embryonic plates were incubated at 28 °C

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and examined at 24, 48, 72 and 96 hours post-fertilization (hpf) by a OPTIKA zoom stereo microscope (trinocular version of model SZM-1) Figure 1. The Ethics and Research Committee of the Heart Institute of Bucaramanga approved the protocol under the Acta Number 050 of May 26 of 2012.

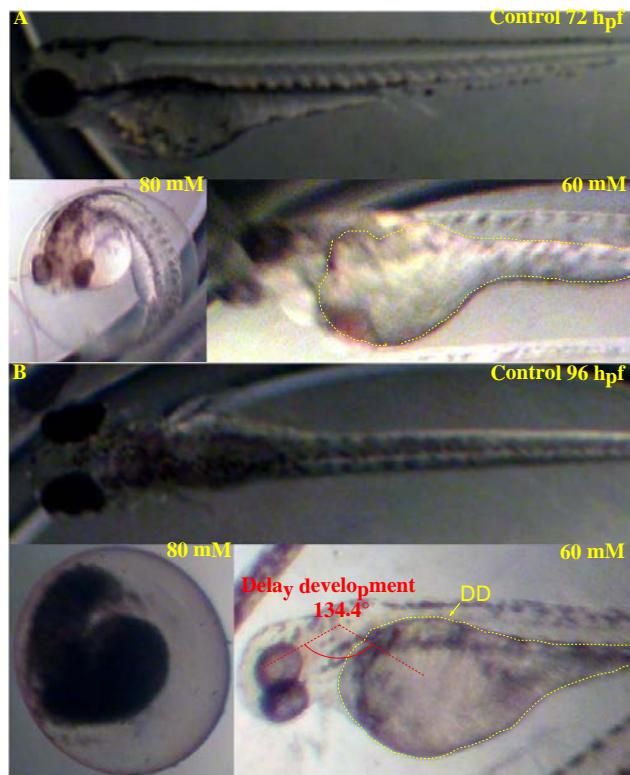
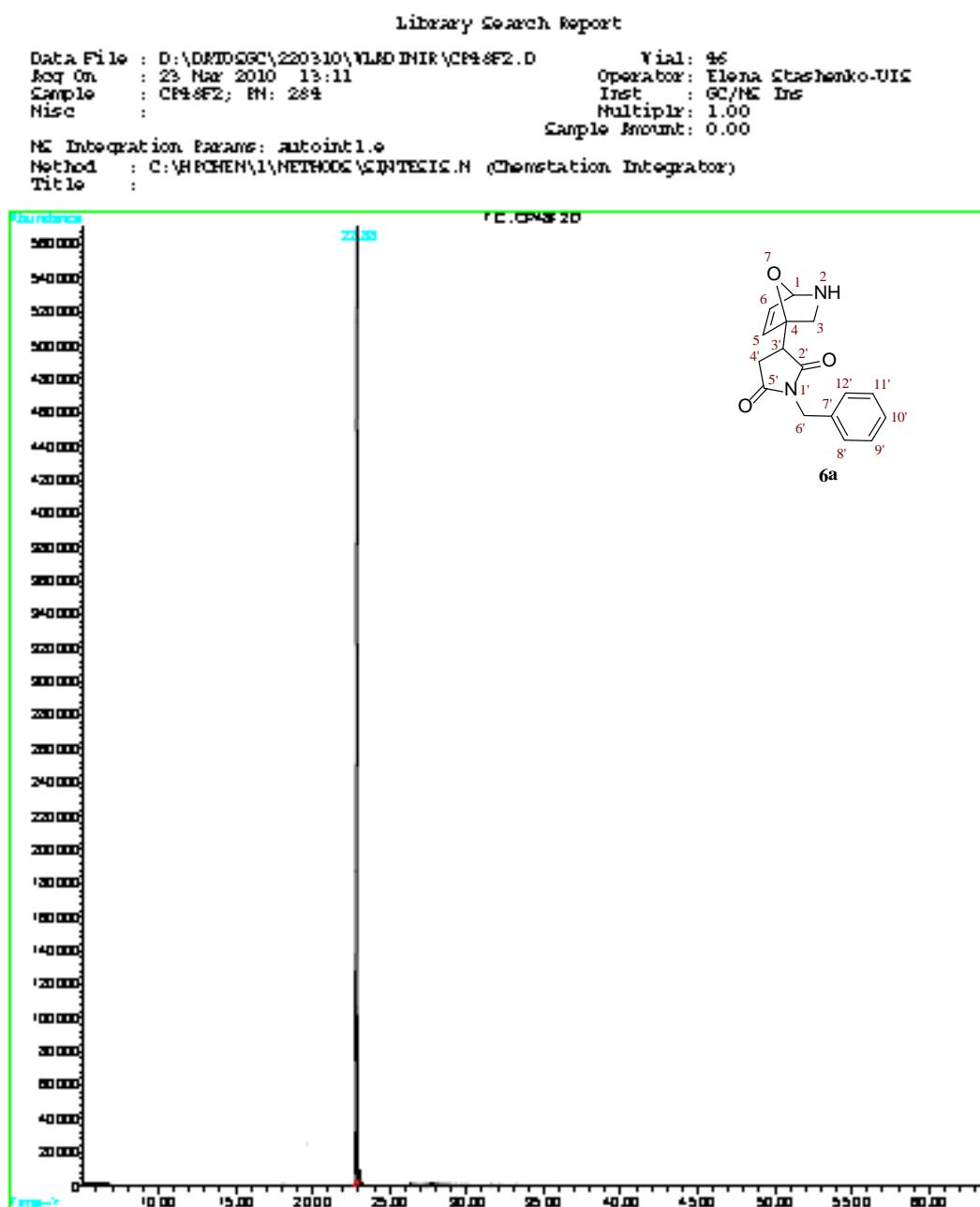


Fig. 1 **A:** Zebrafish embryos treated with compound **6g** at 72 hpf. The embryos treated at 100, 150 and 200 μ M died after chemical exposure at this time. The main visual phenotype, to measure the development delay at this stage, was when the eggs hatch and the alevins could be photographed. At 80 μ M after 72 hpf, the eggs have not hatched at the same rate than the control did and the digestive damage could be observed at 60 μ M. **B:** Zebrafish embryos treated with compound **6g** at 96 hpf. Embryos treated at 80 μ M finally died after 96 hpf. Head–trunk angle (red dotted line) 134.4° (control angle: 148°) at 60 μ M indicating several development delay. The yellow dotted line, indicates that the embryos treated with 60 μ M and below, did not consume their yolk at the same rate to the control fish, putting in evidence the digestive damage (DD) induced by the 7-oxa-2- azabicyclo[2.2.1]hept-5-ene **6g**.

9. Copies of GC, ¹H NMR, ¹³C NMR, DEPT-135, COSY, ¹³C HMBC and HSQC charts of the synthesized 7-Oxa-2-azabicycles

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Figure SI1. Chromatogram of 4-(N-benzyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6a**.



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Figure SI2. ¹H-NMR spectrum of 4-(N-benzyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6a**.

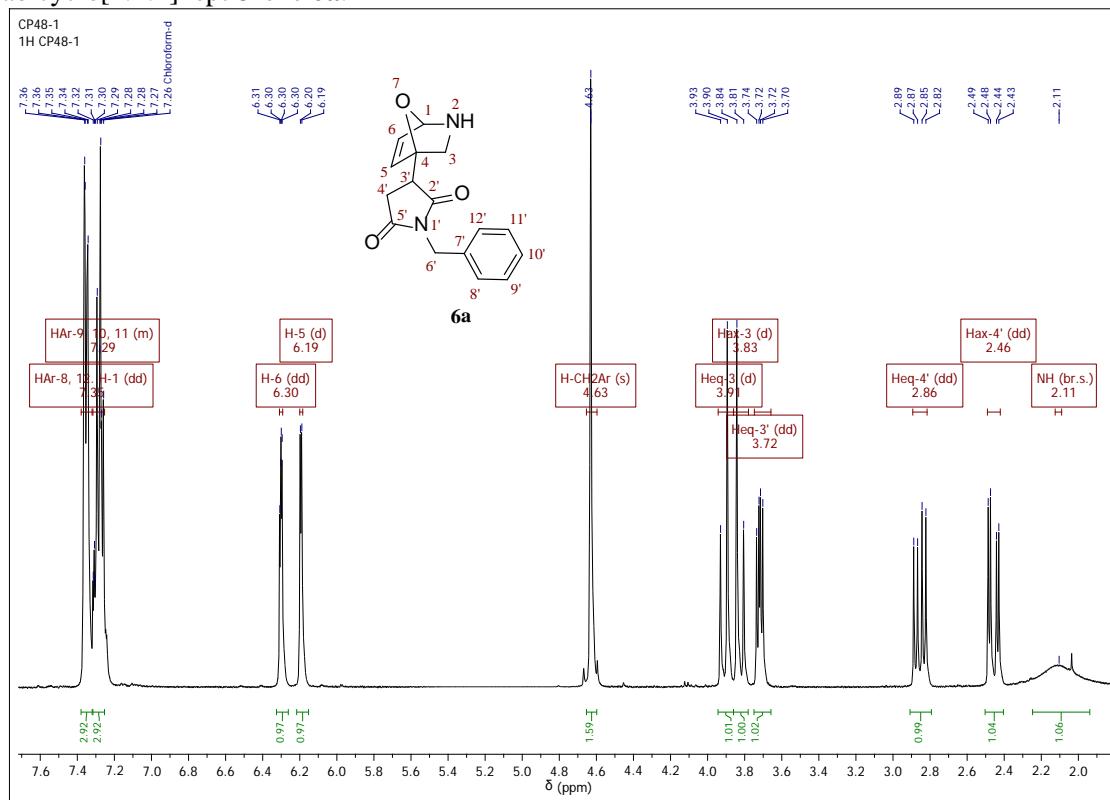
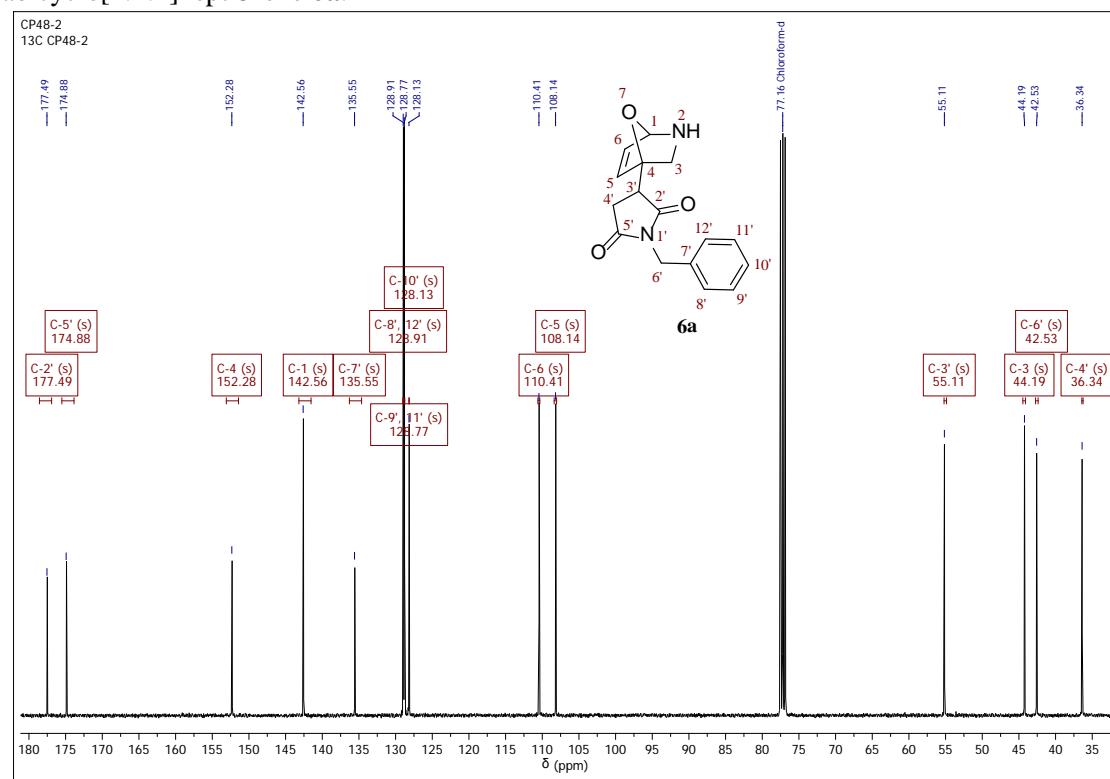


Figure SI3. ¹³C-NMR spectrum of 4-(N-benzyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6a**.



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Figure SI4. DEPT-135 spectrum of 4-(N-benzyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6a**.

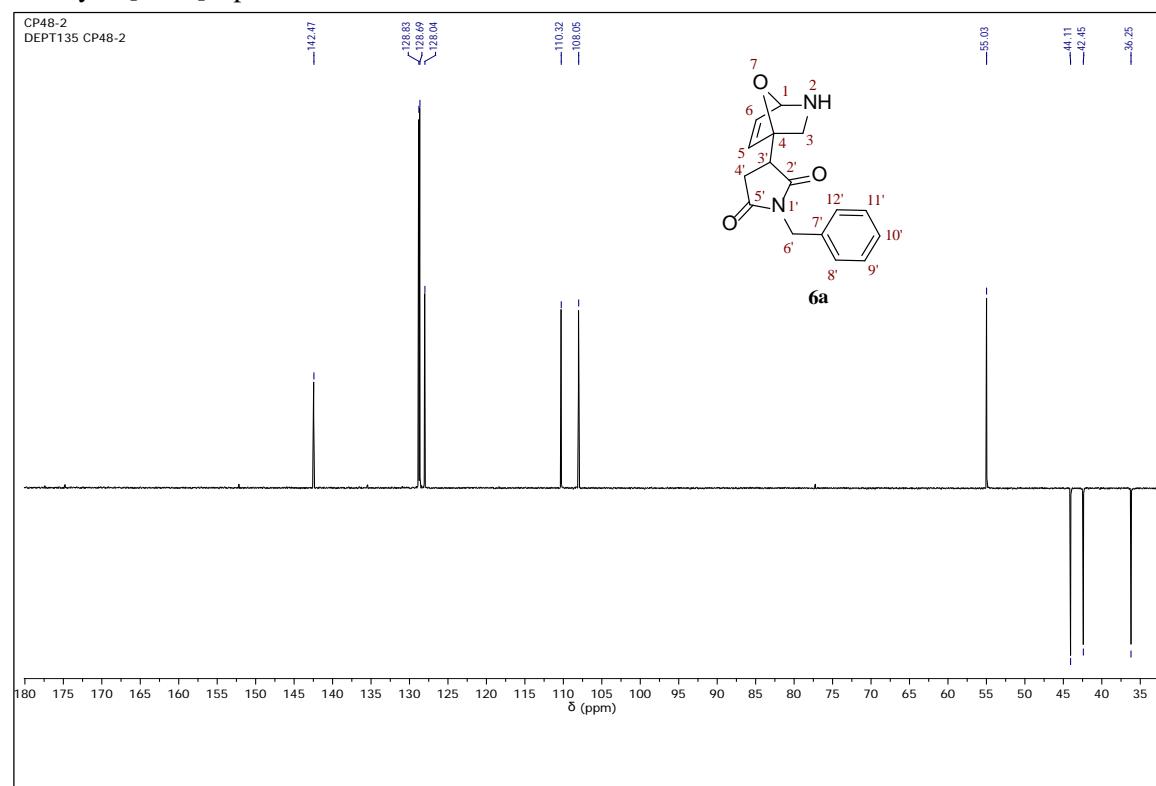
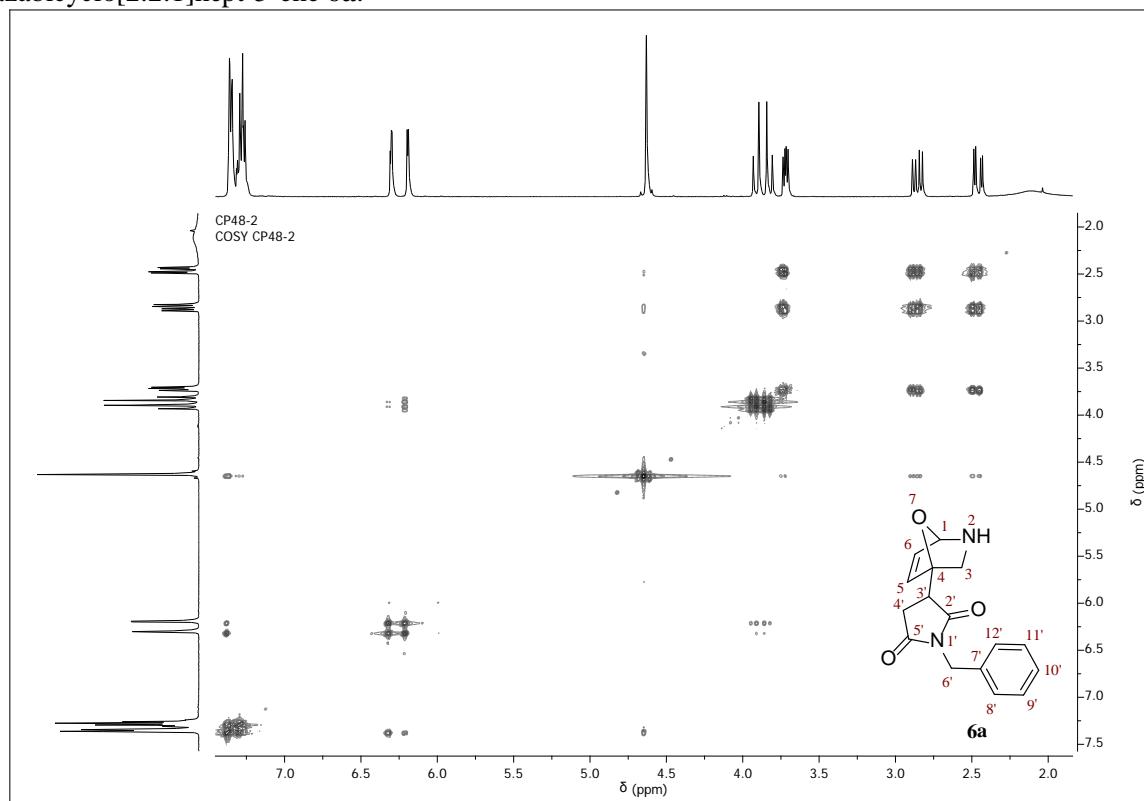


Figure SI5. COSY spectrum of 4-(N-benzyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6a**.



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Figure SI6. HSQC spectrum of 4-(*N*-benzyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6a**.

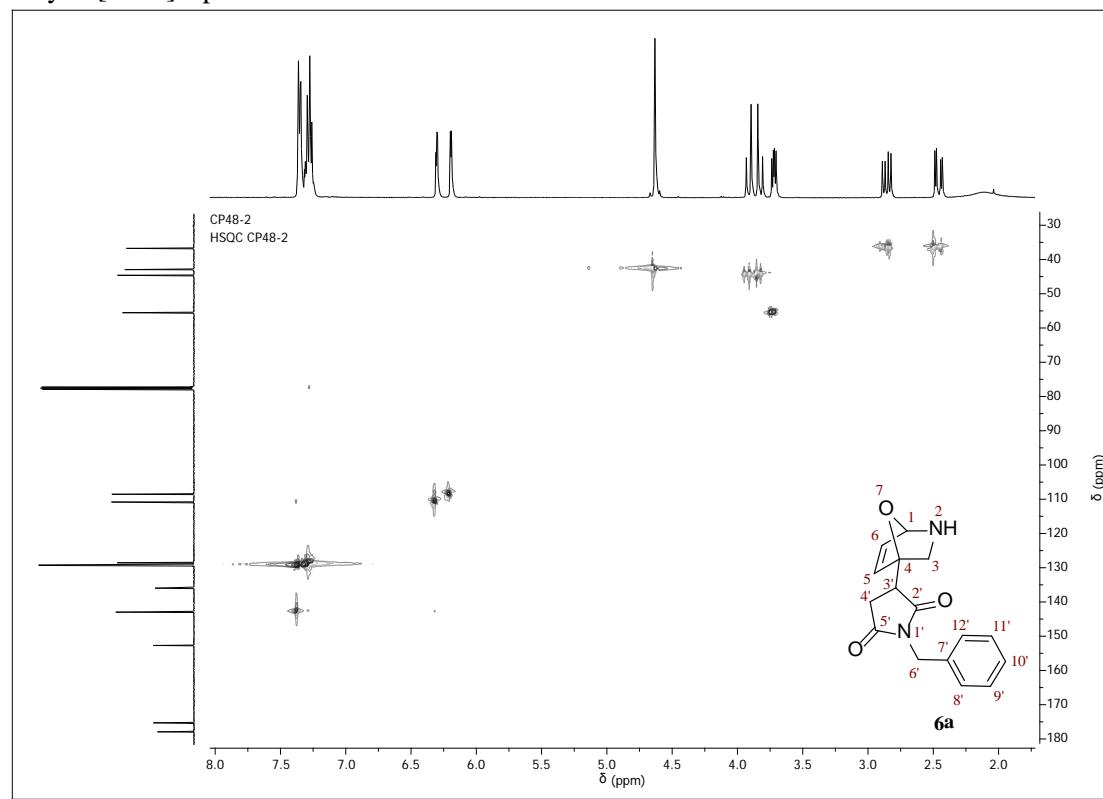
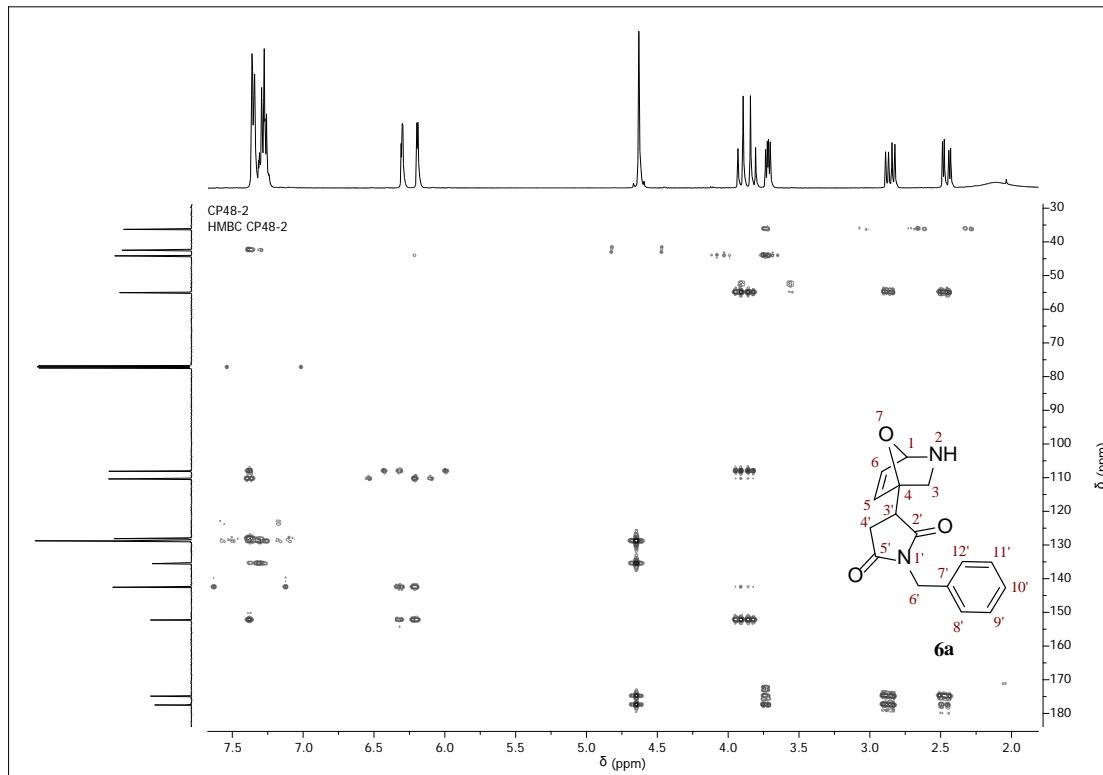
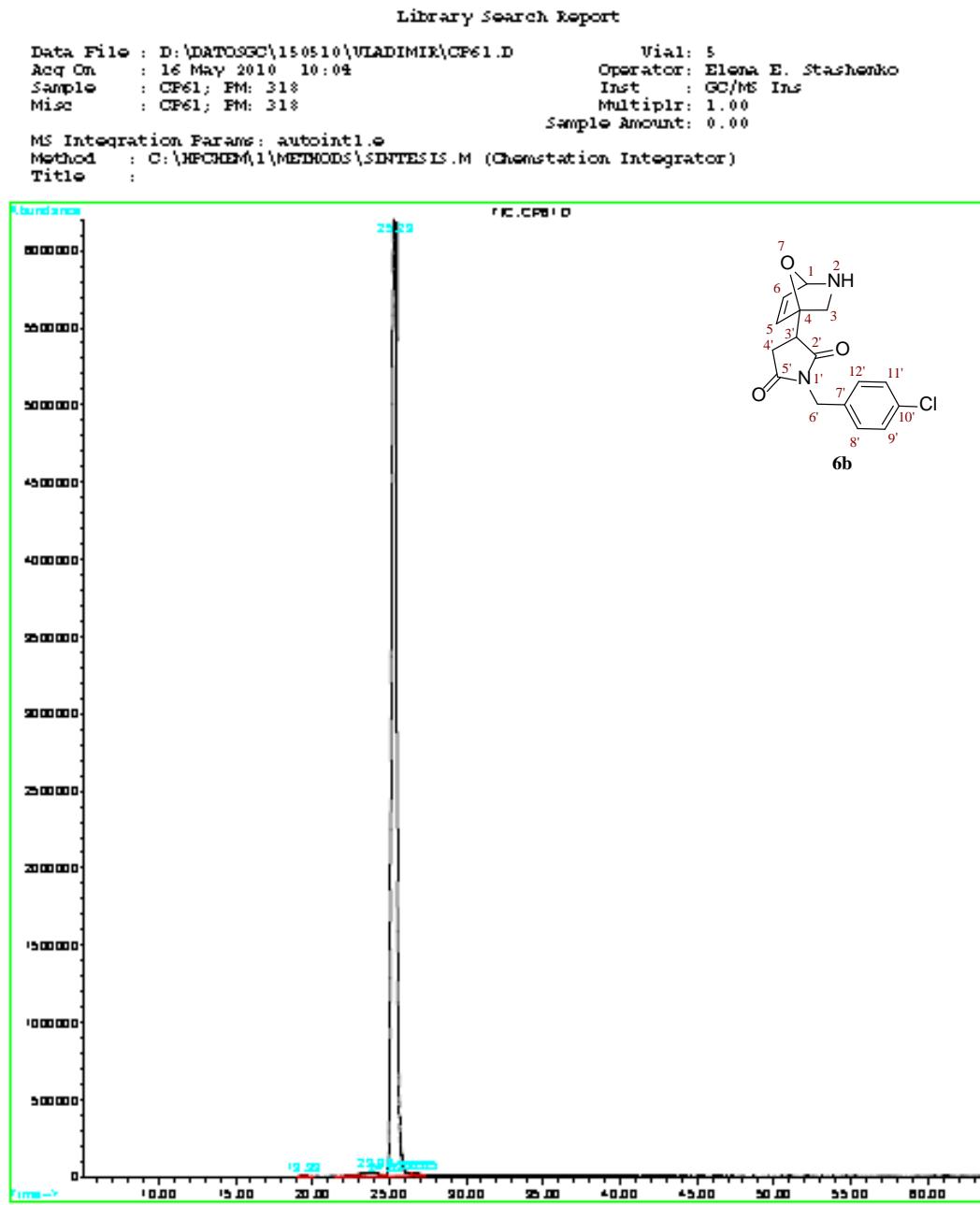


Figure SI7. HMBC spectrum of 4-(*N*-benzyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6a**.



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Figure SI8. Chromatogram of 4-(*N*-(4-chlorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6b**.



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Figure SI9. ¹H-NMR spectrum of 4-(N-(4-chlorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6b**.

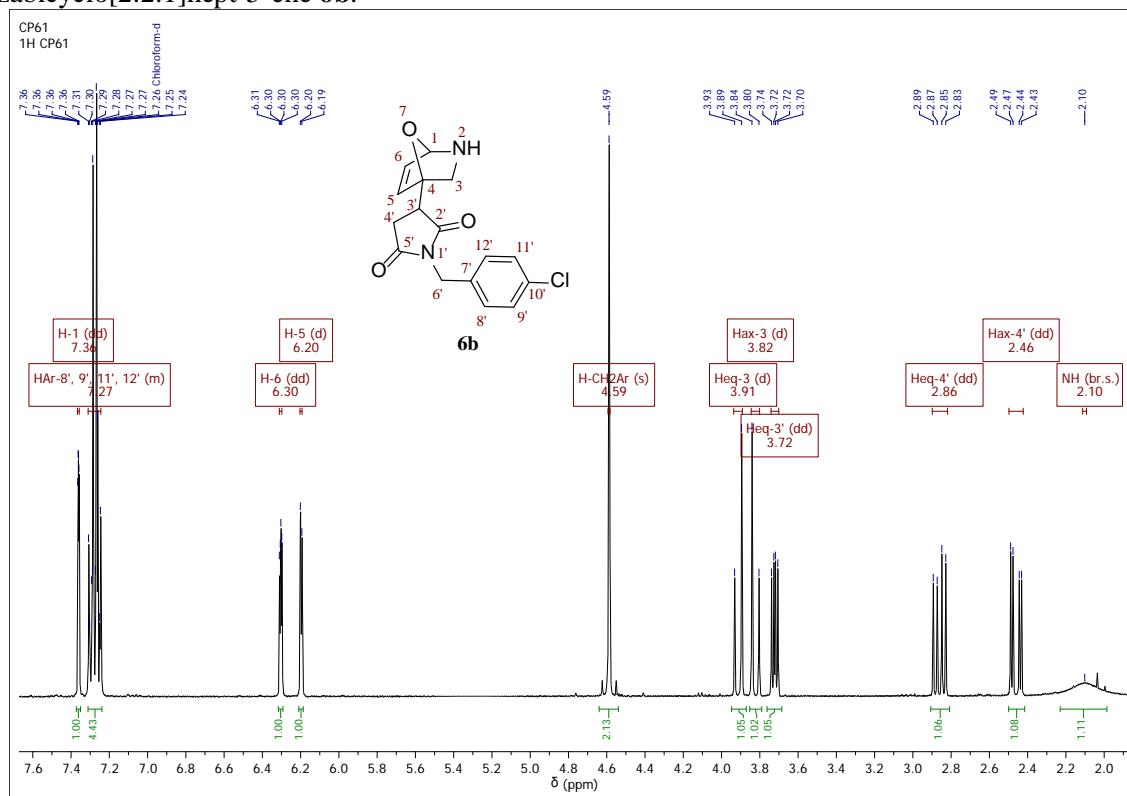
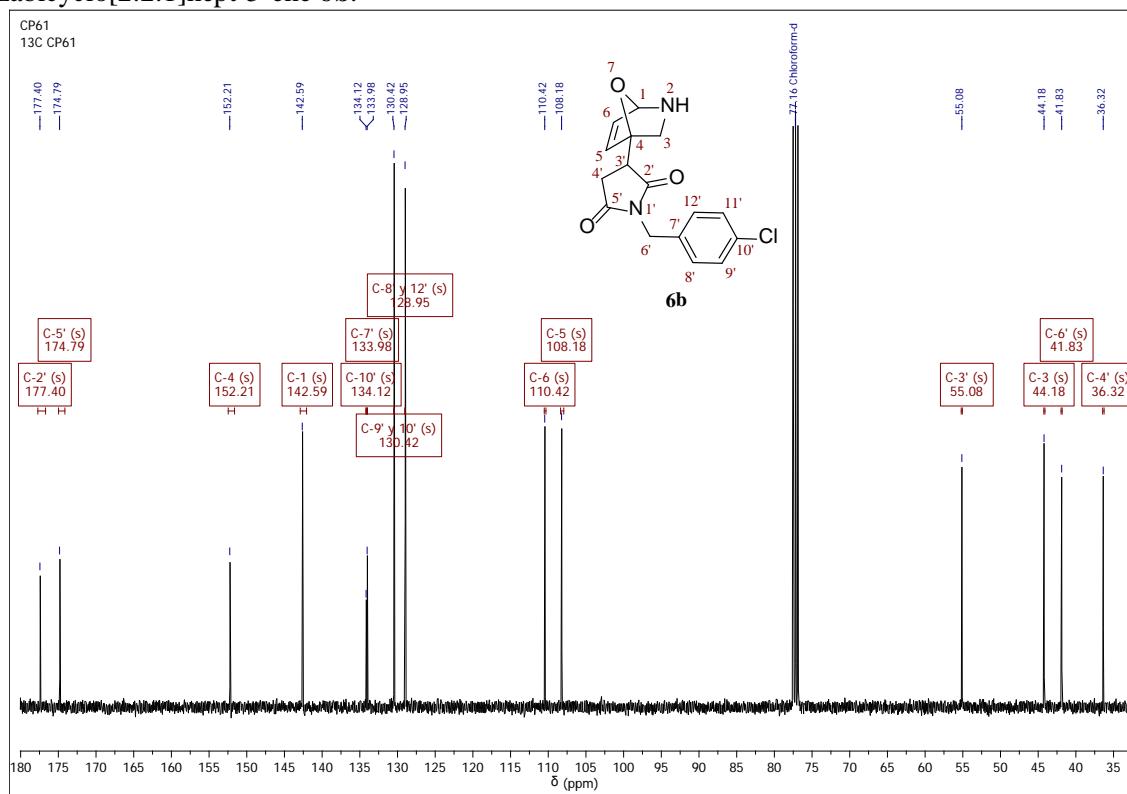


Figure SI10. ¹³C-NMR spectrum of 4-(N-(4-chlorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6b**.



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Figure SI11. DEPT-135 spectrum of 4-(*N*-(4-chlorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6b**.

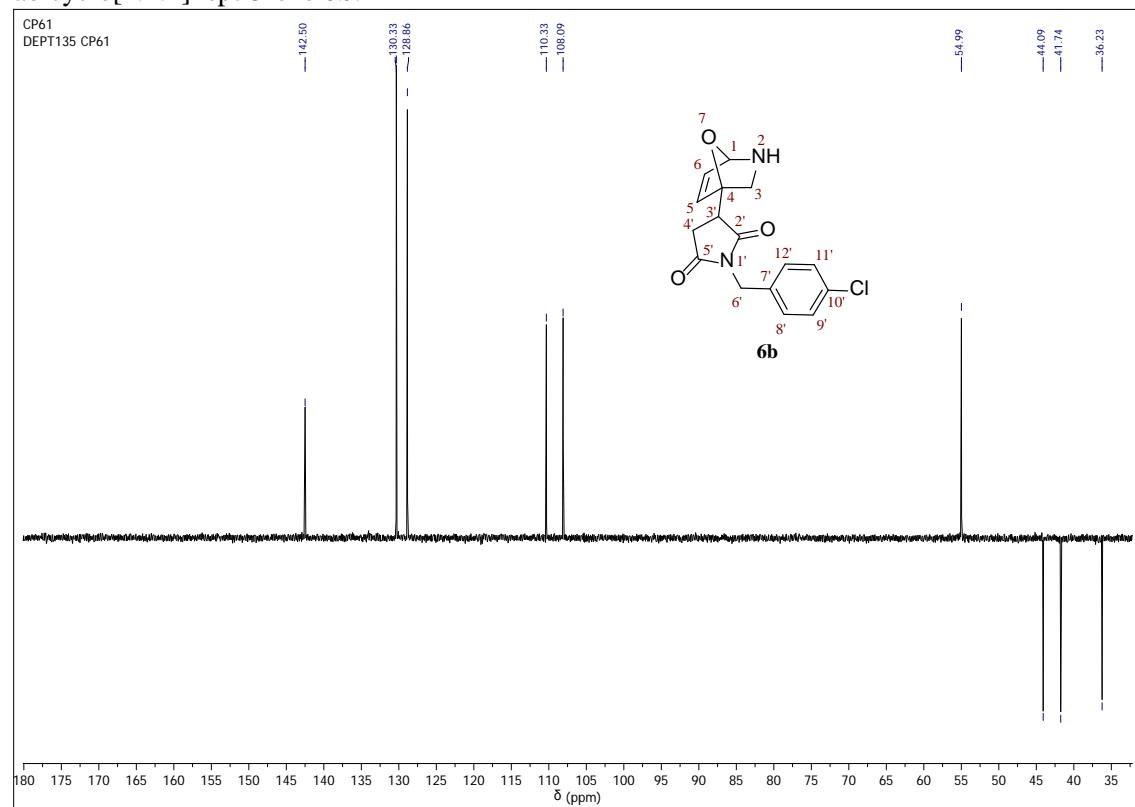
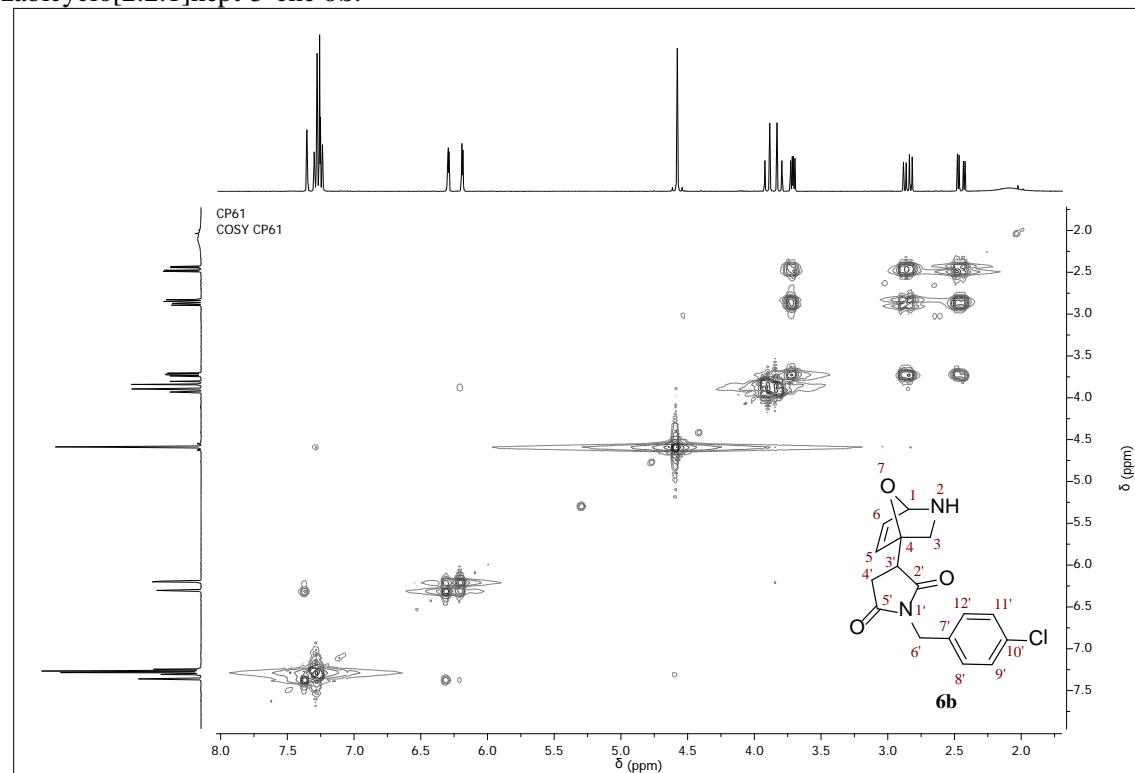


Figure SI12. COSY spectrum of 4-(*N*-(4-chlorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6b**.



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Figure SI13. HSQC spectrum of 4-(*N*-(4-chlorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6b**.

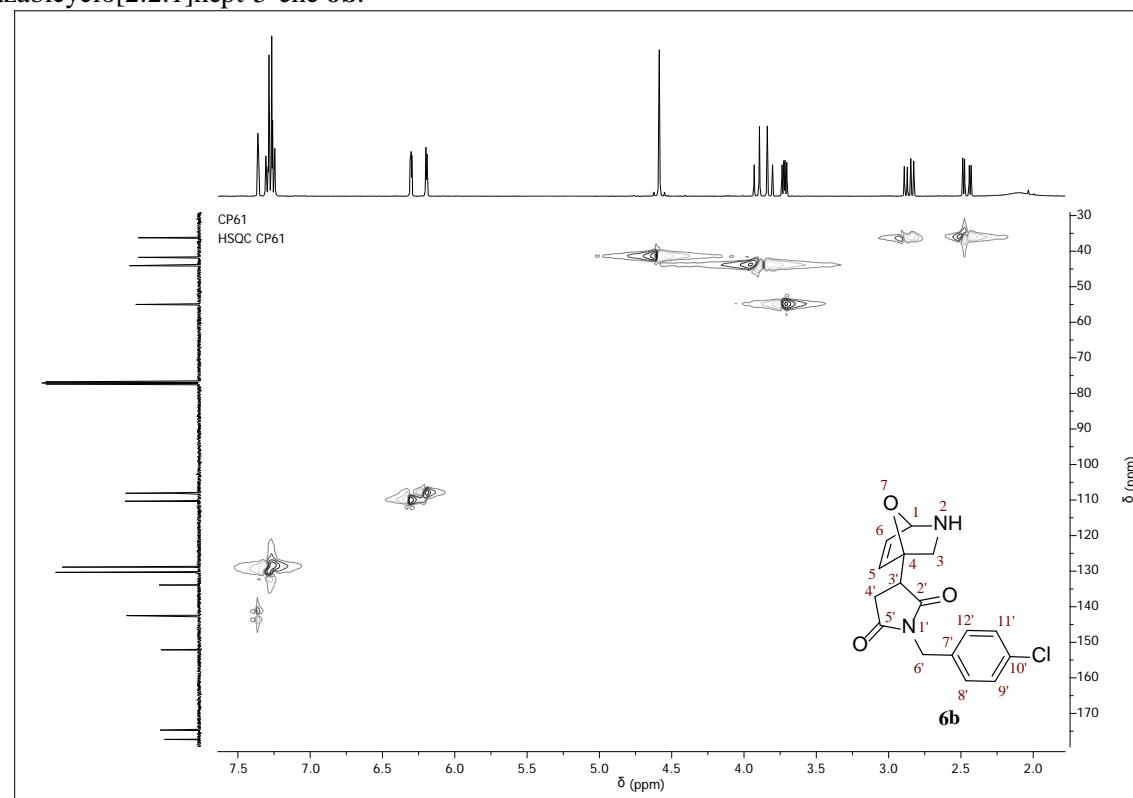
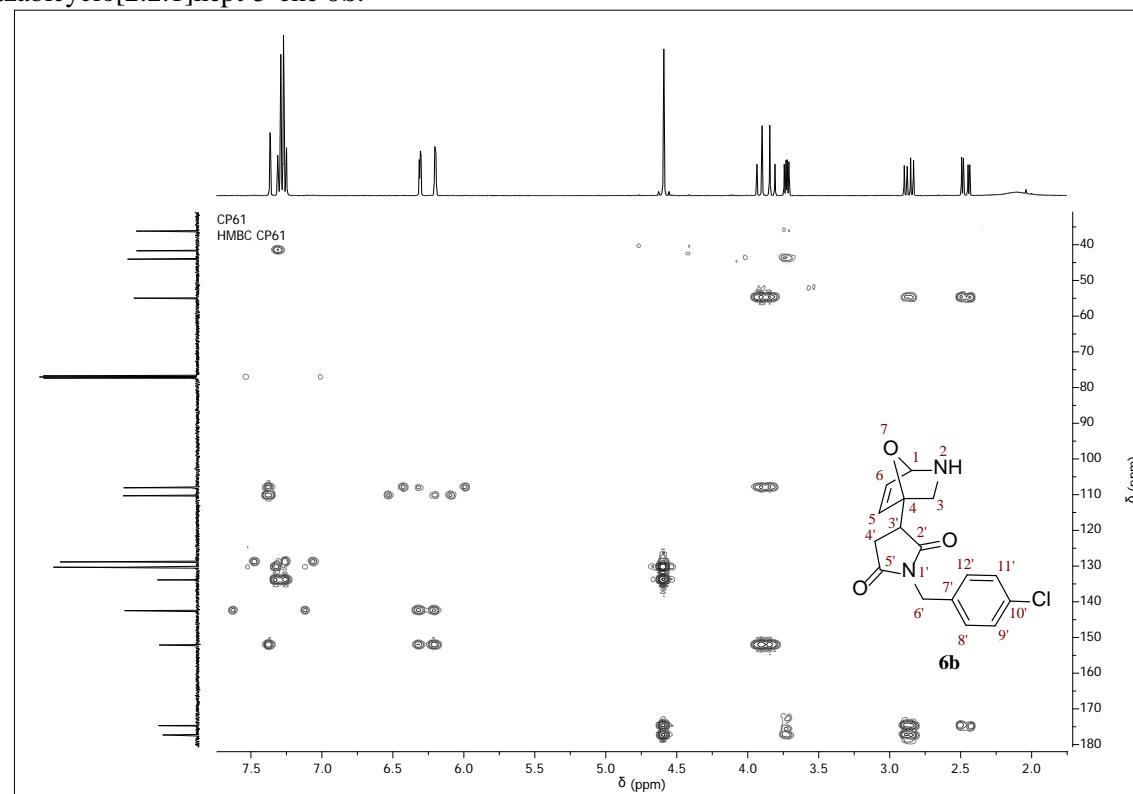
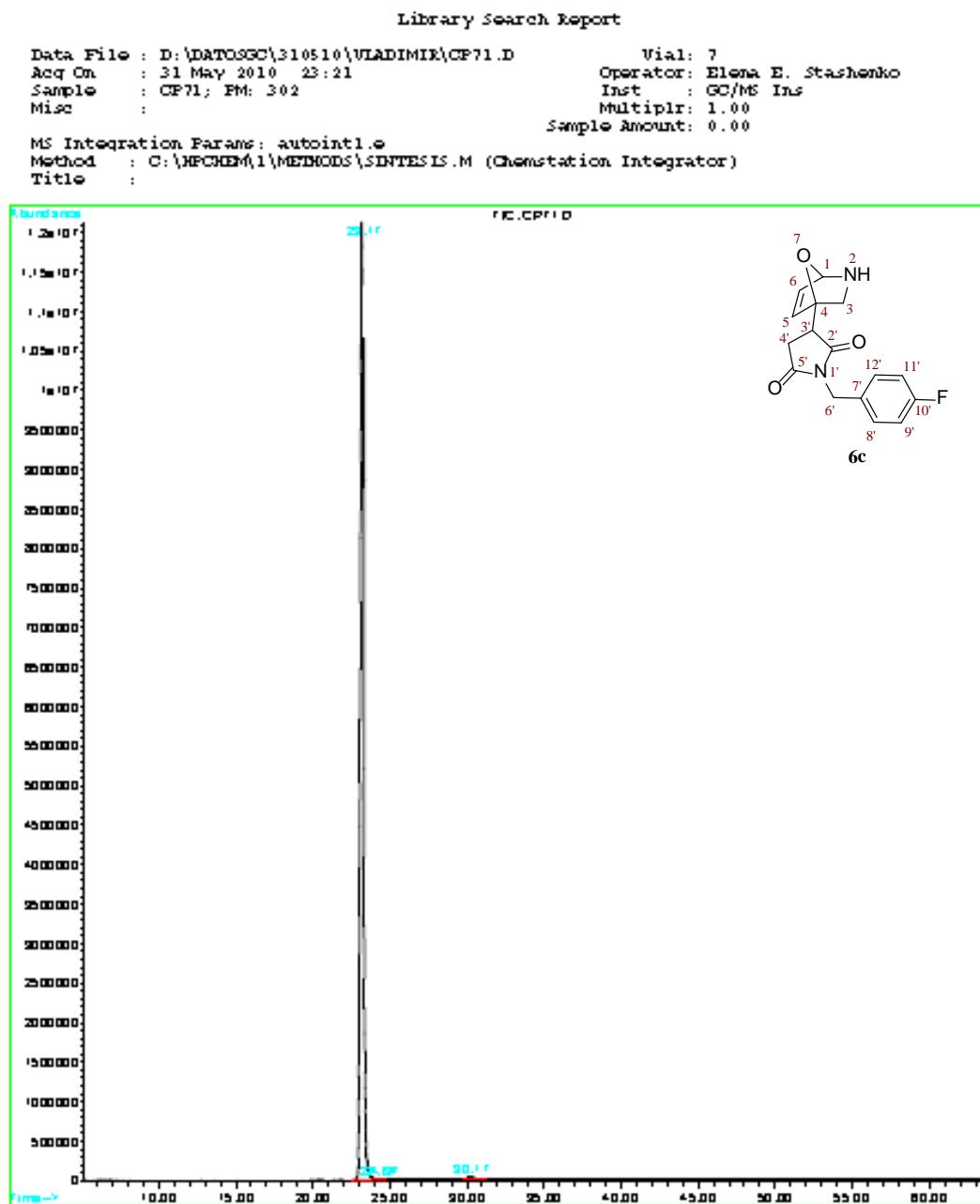


Figure SI14. HMBC spectrum of 4-(*N*-(4-chlorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6b**.



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Figure SI15. Chromatogram of 4-(*N*-(4-fluorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6c**.



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Figure SI16. ¹H-NMR spectrum of 4-(N-(4-fluorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6c**.

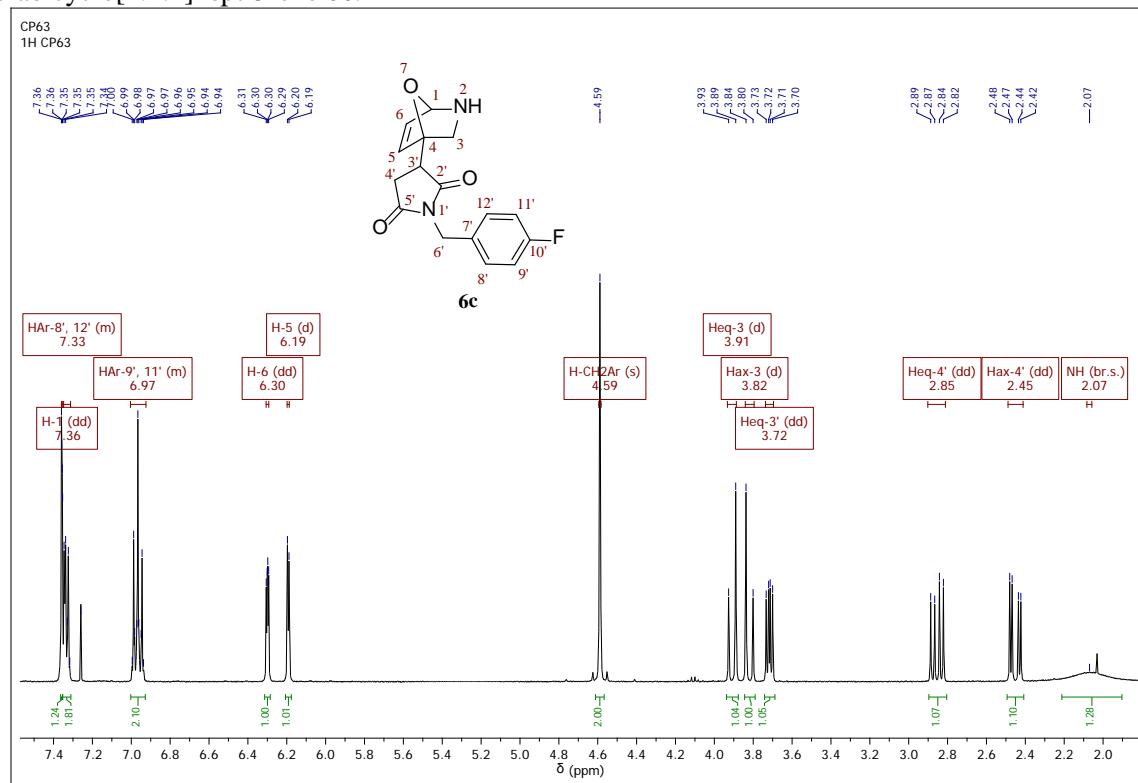
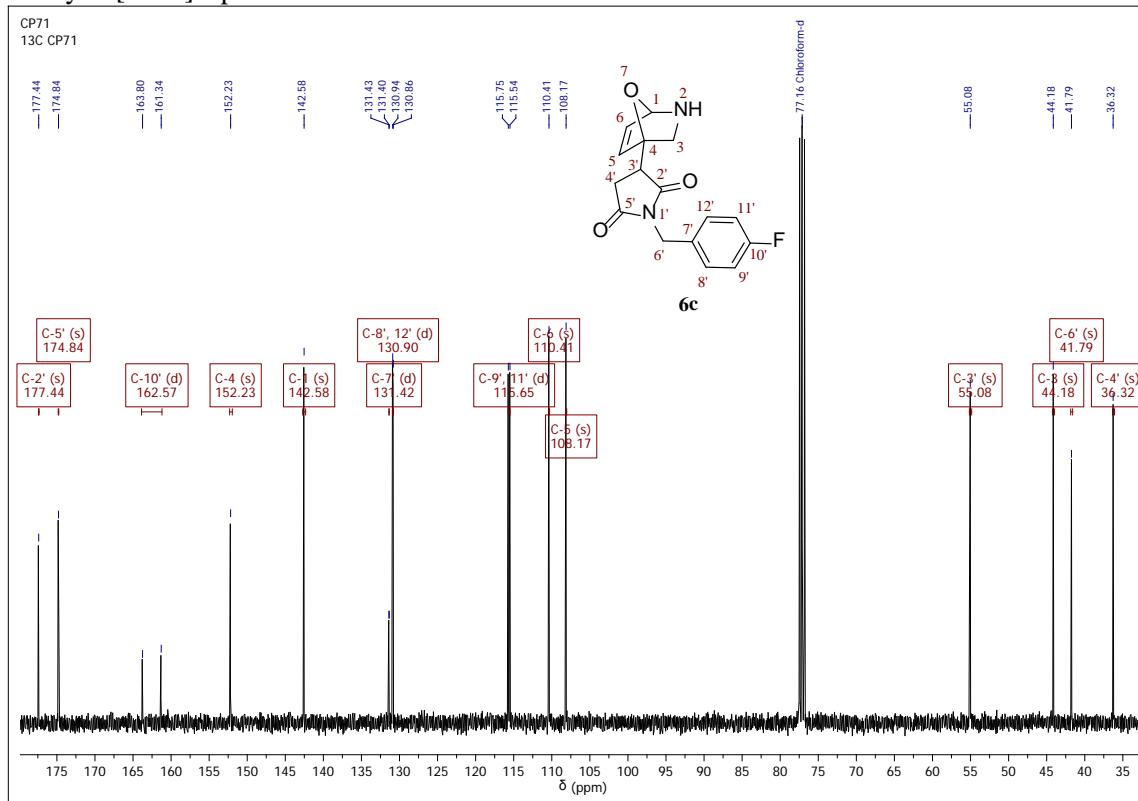


Figure SI17. ¹³C-NMR spectrum of 4-(N-(4-fluorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6c**.



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Figure SI18. DEPT-135 spectrum of 4-(*N*-(4-fluorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6c**.

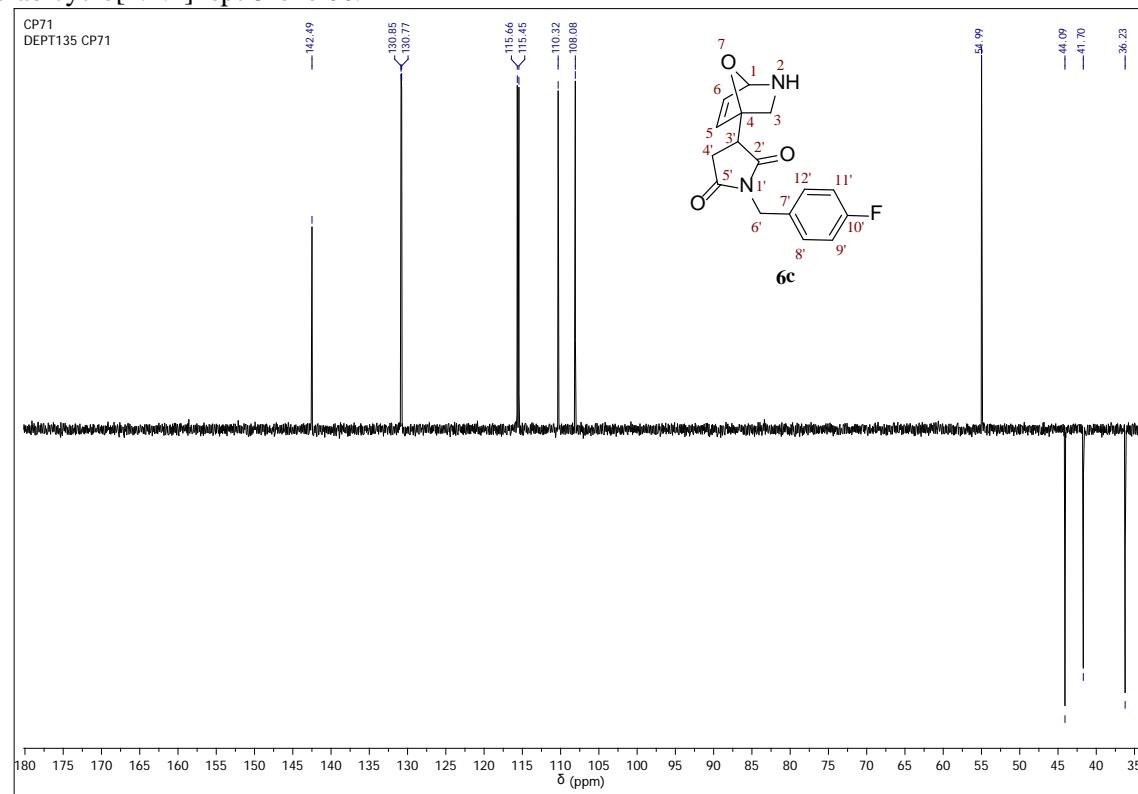
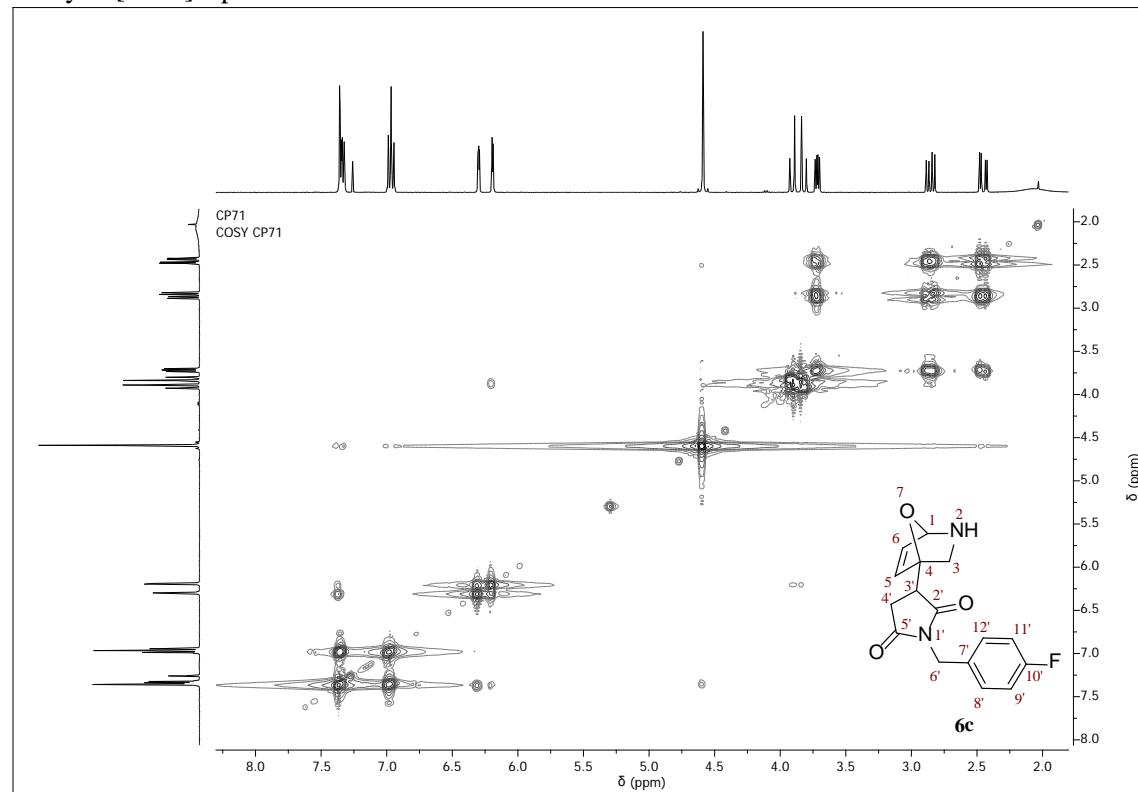


Figure SI19. COSY spectrum of 4-(*N*-(4-fluorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6c**.



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Figure SI20. HSQC spectrum of 4-(*N*-(4-fluorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6c**.

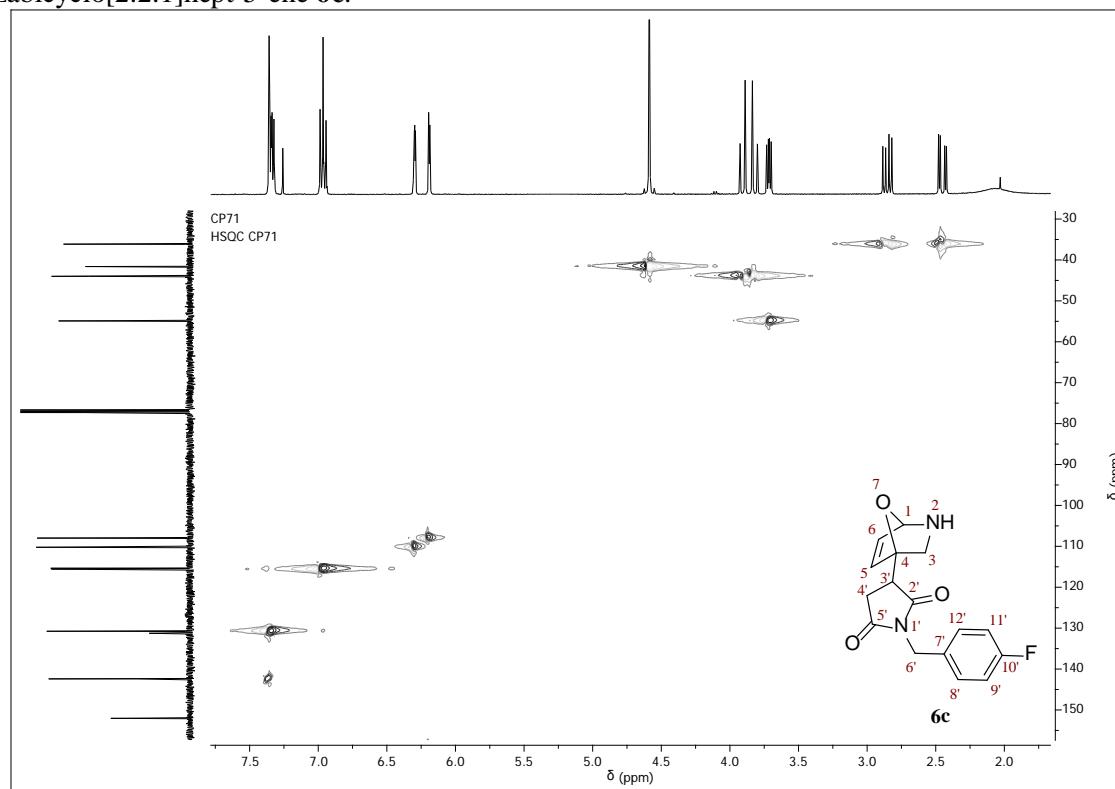
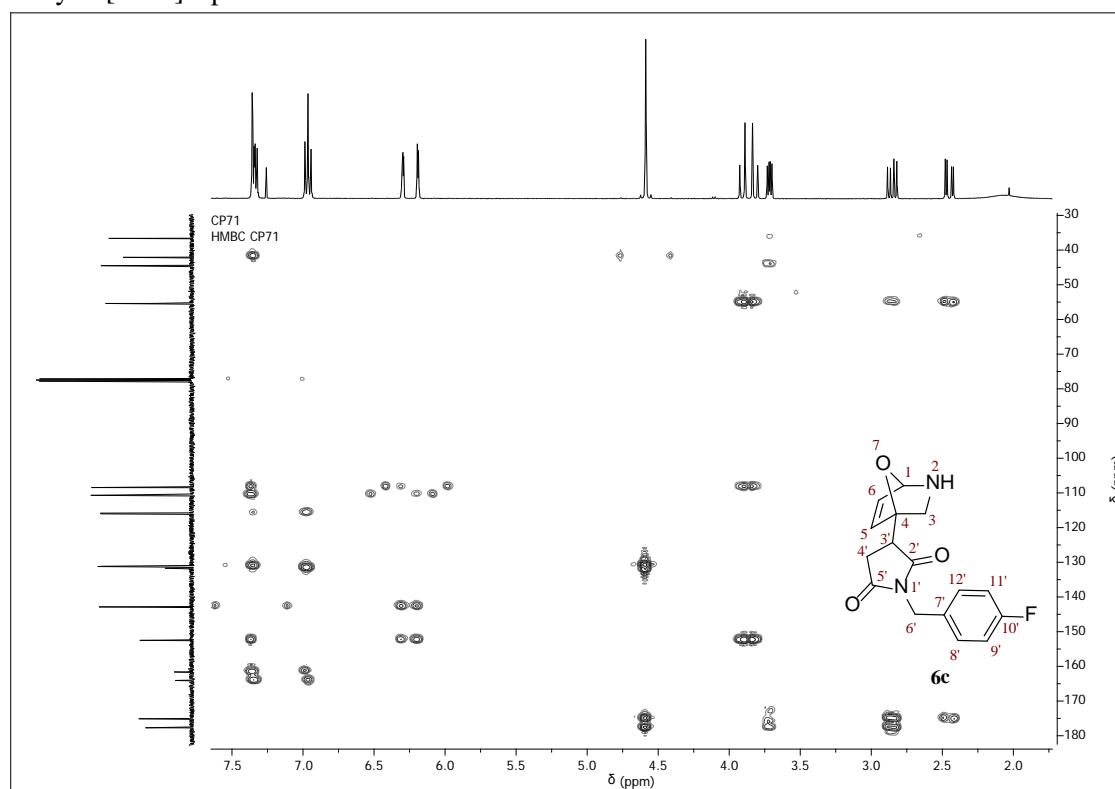
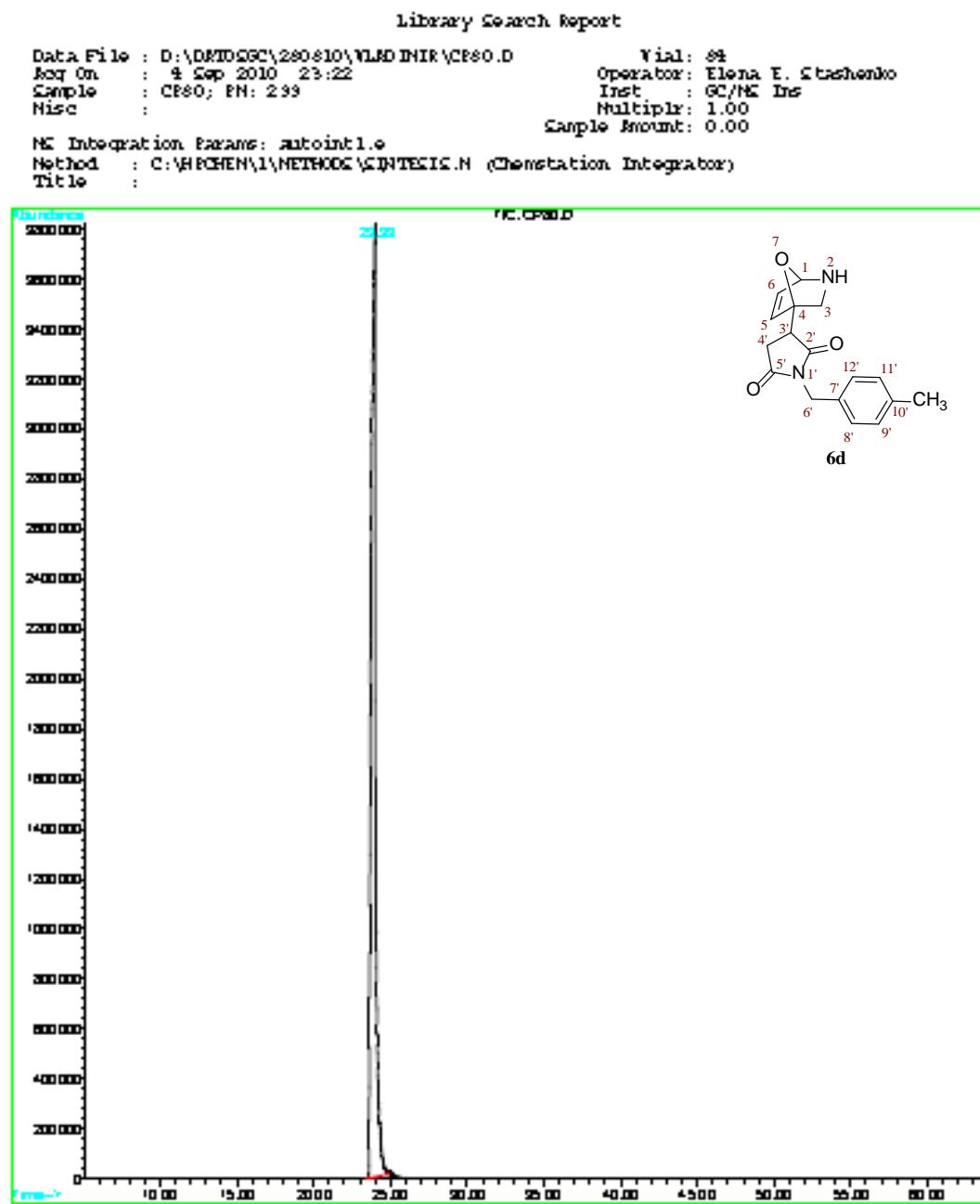


Figure SI21. HMBC spectrum of 4-(*N*-(4-fluorobenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6c**.



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Figure SI22. Chromatogram of 4-(N-(4-methylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6d**.



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Figure SI23. ¹H-NMR spectrum of 4-(N-(4-methylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6d**.

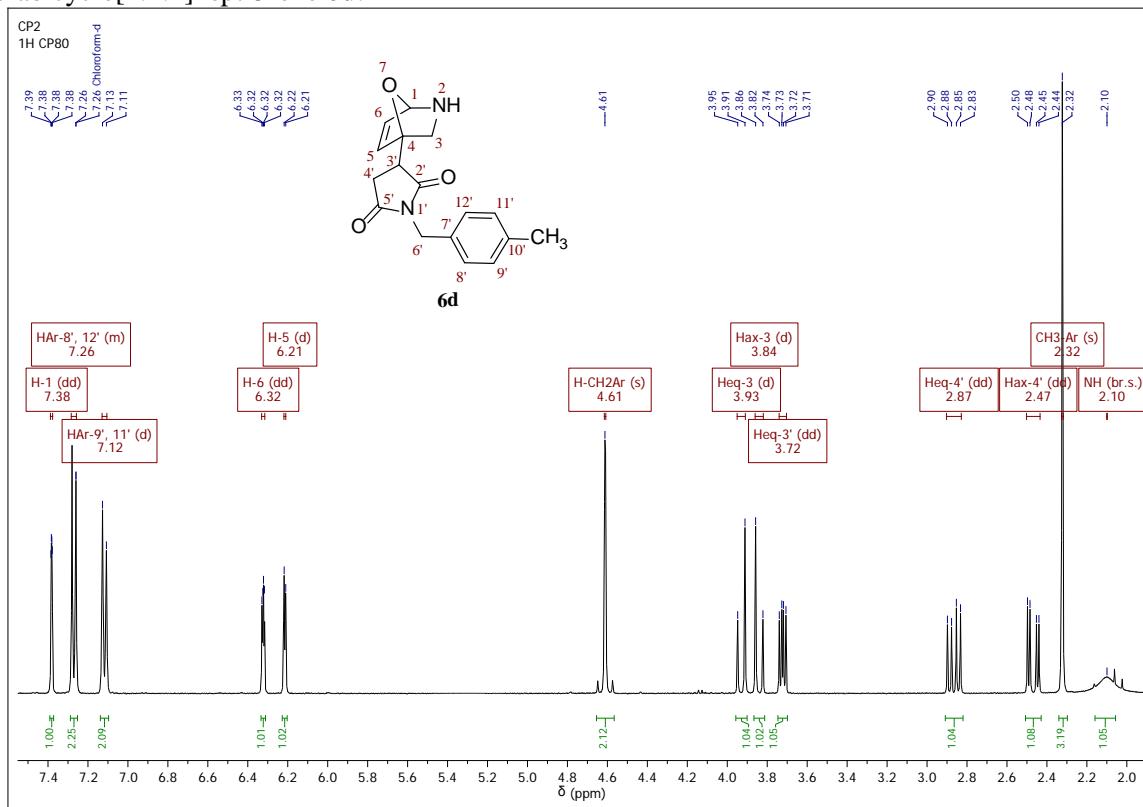
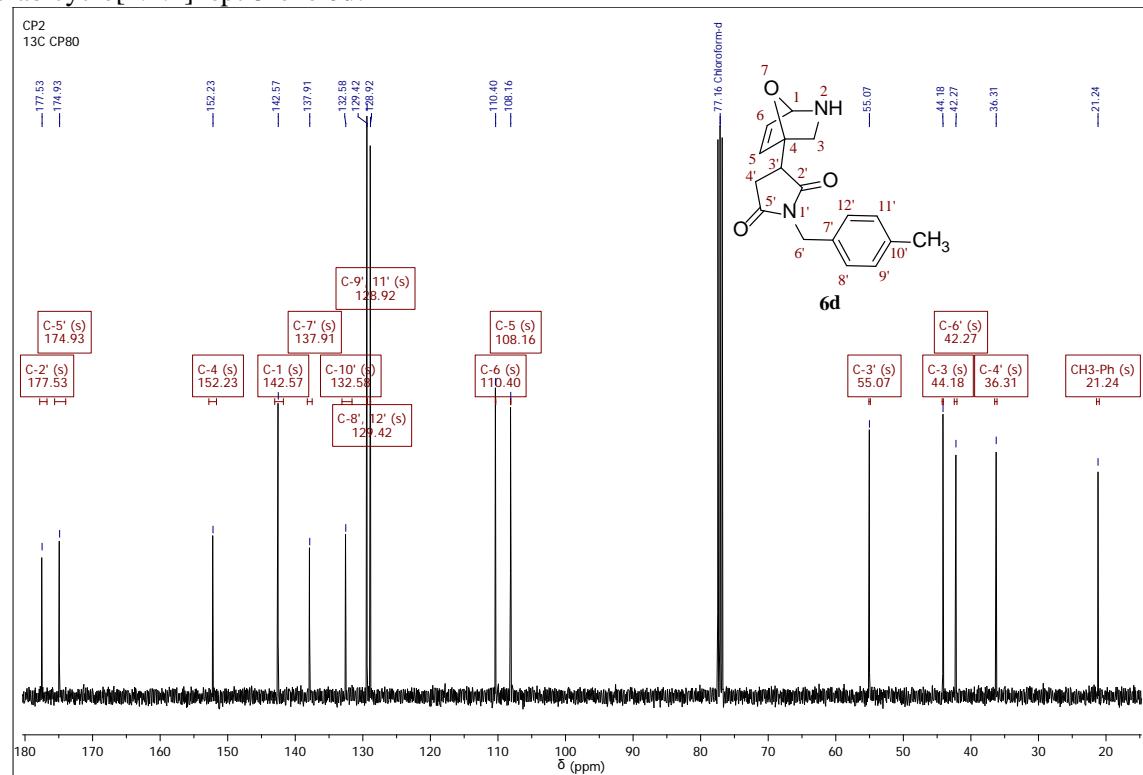
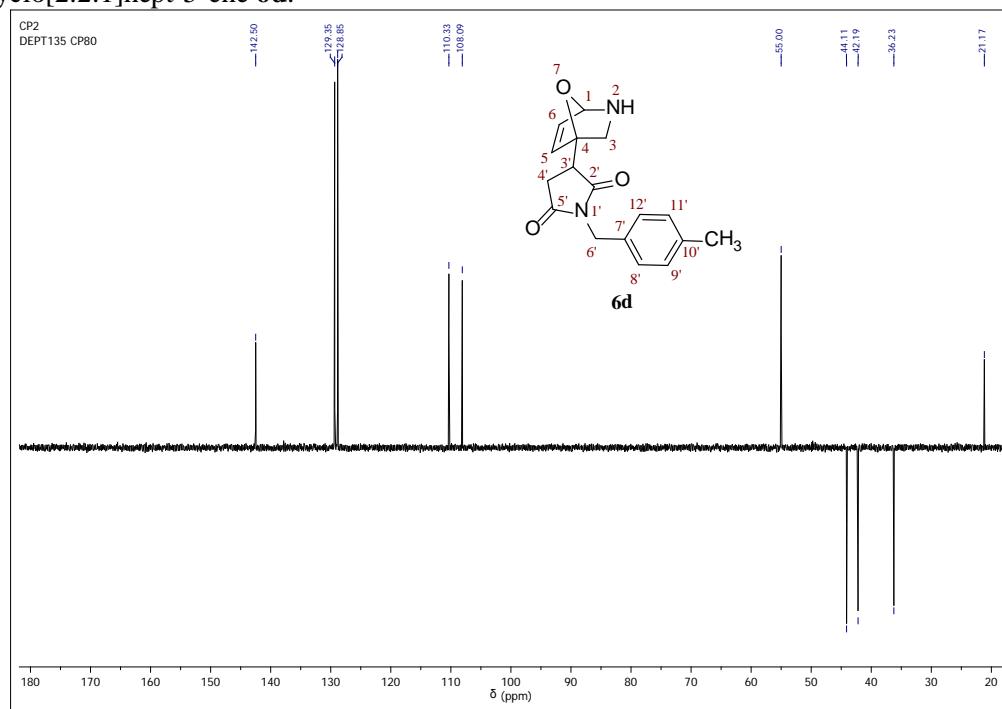


Figure SI24. ¹³C-NMR spectrum of 4-(N-(4-methylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6d**.



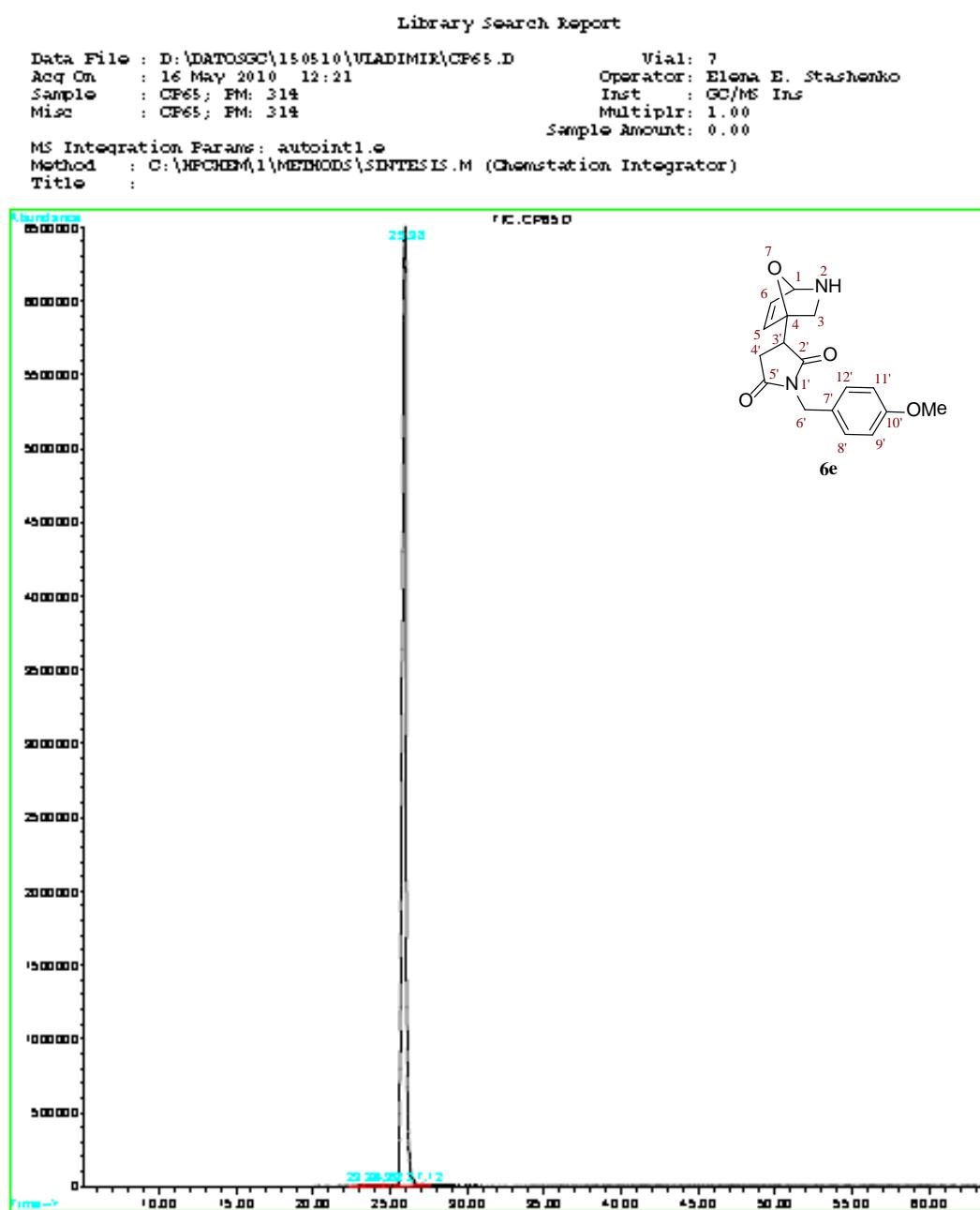
H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI25. DEPT-135 spectrum of 4-(N-(4-methylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6d**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI26. Chromatogram of 4-(N-(4-methoxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6e**.



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Figure SI27. ¹H-NMR spectrum of 4-(N-(4-methoxylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6e**.

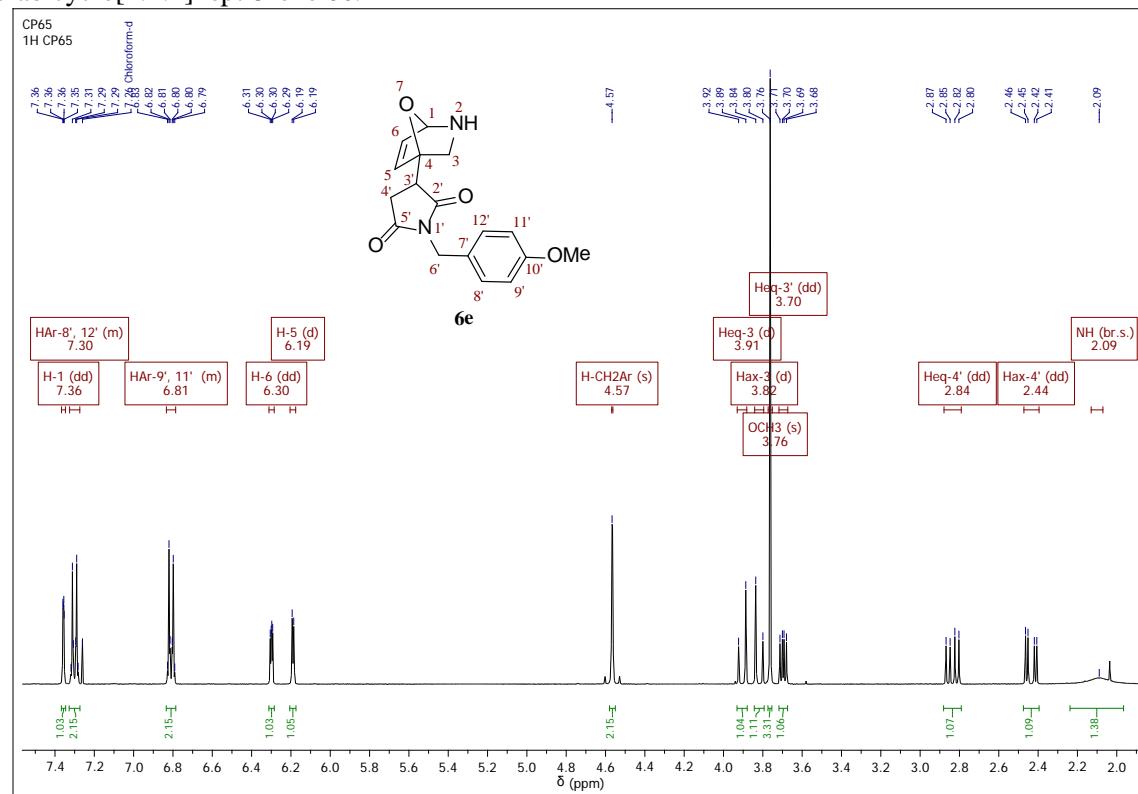
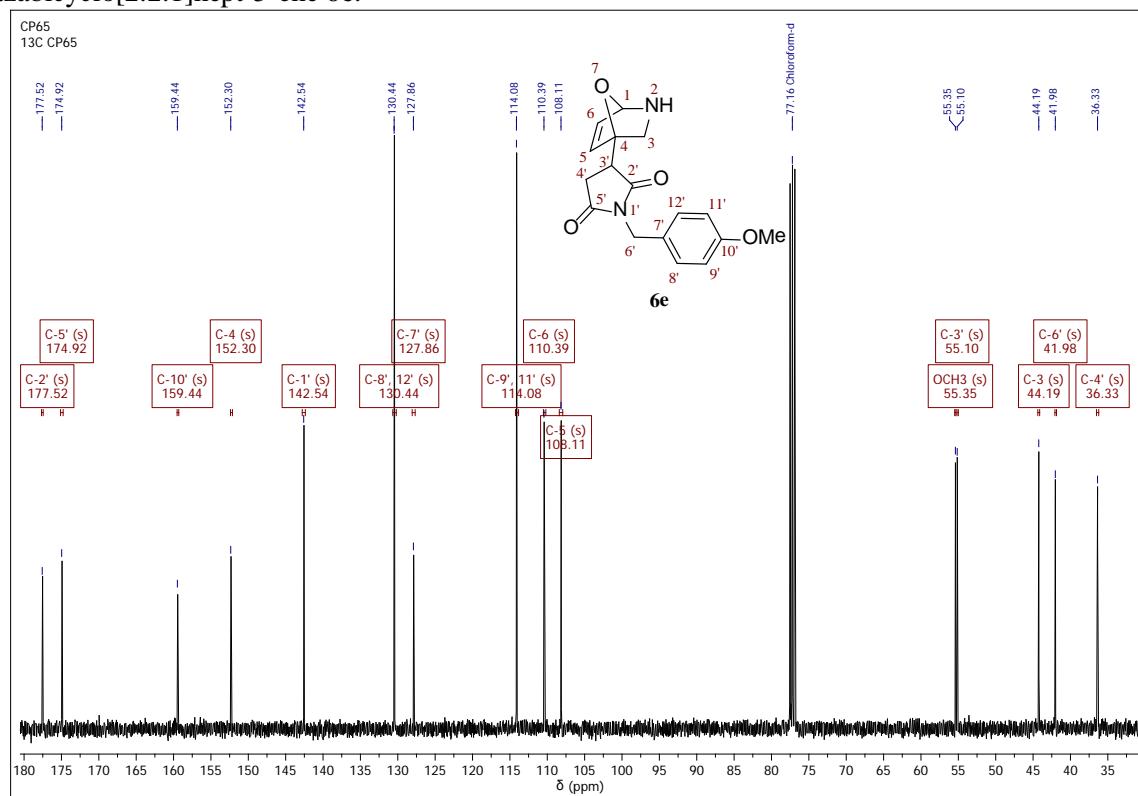


Figure SI28. ¹³C-NMR spectrum of 4-(N-(4-methoxylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6e**.



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Figure SI29. DEPT-135 spectrum of 4-(N-(4-methoxylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6e**.

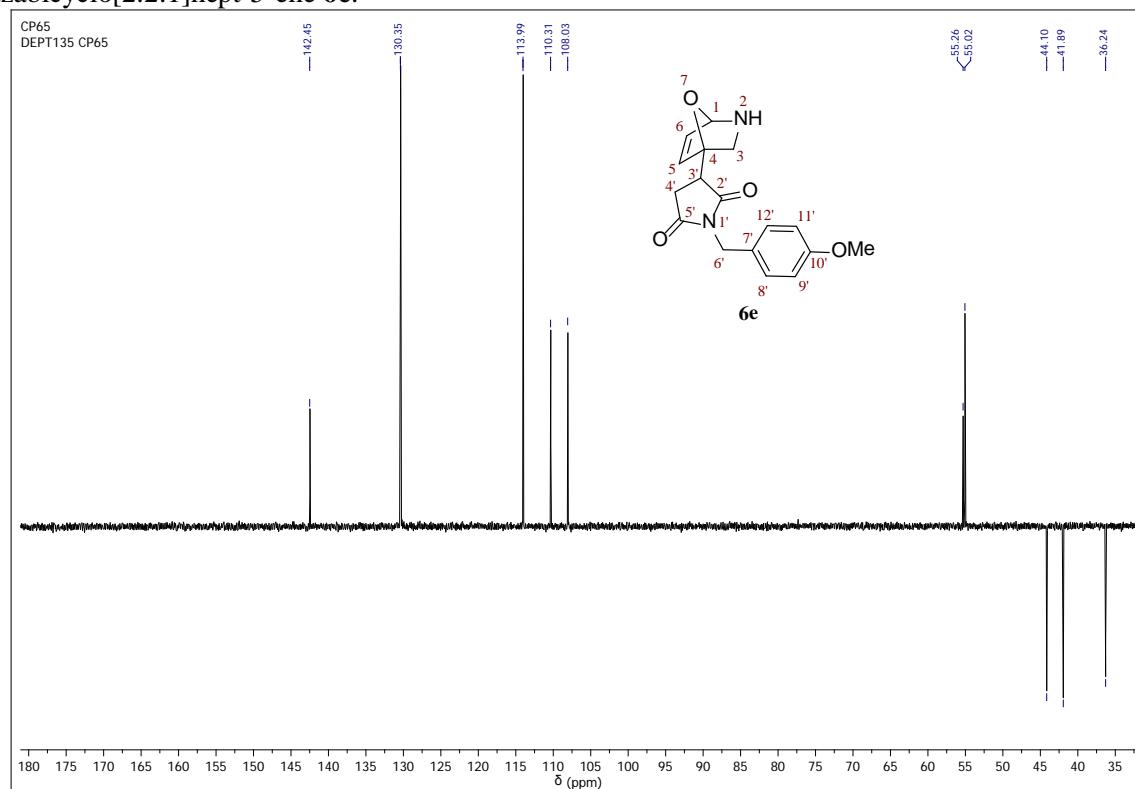
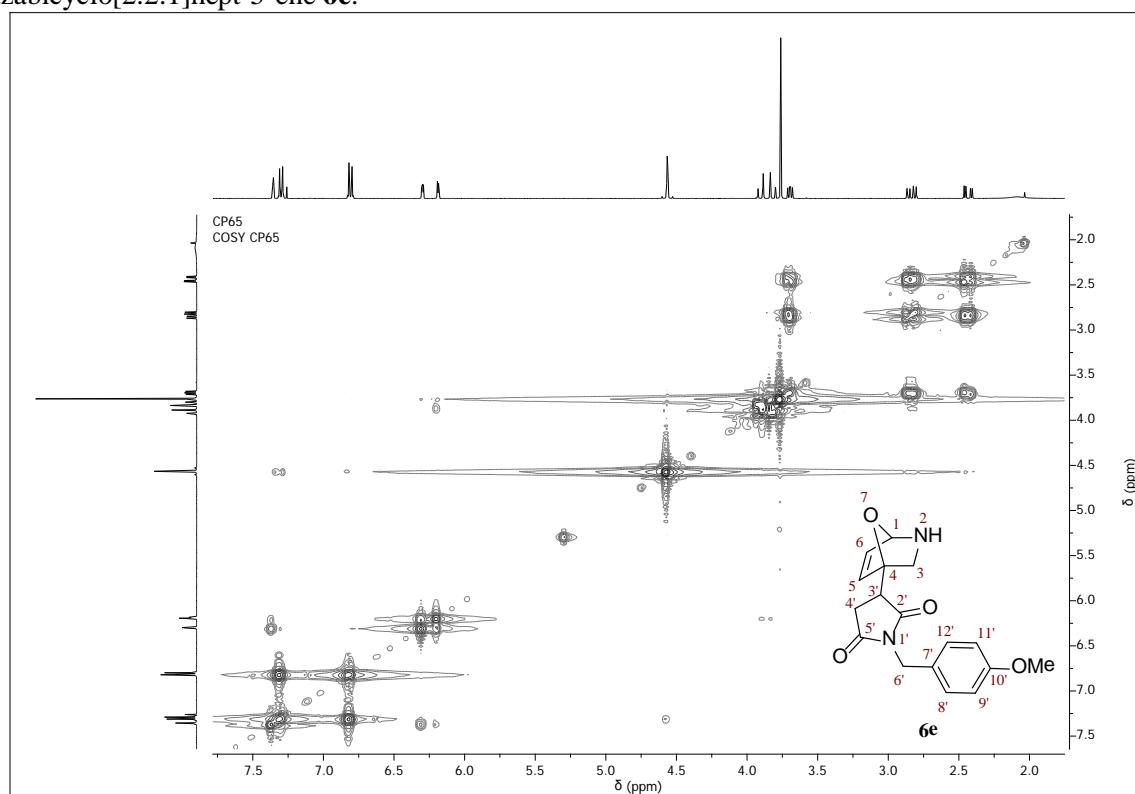


Figure SI30. COSY spectrum of 4-(N-(4-methoxylbenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6e**.



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Figure SI31. HSQC spectrum of 4-(N-(4-methoxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6e**.

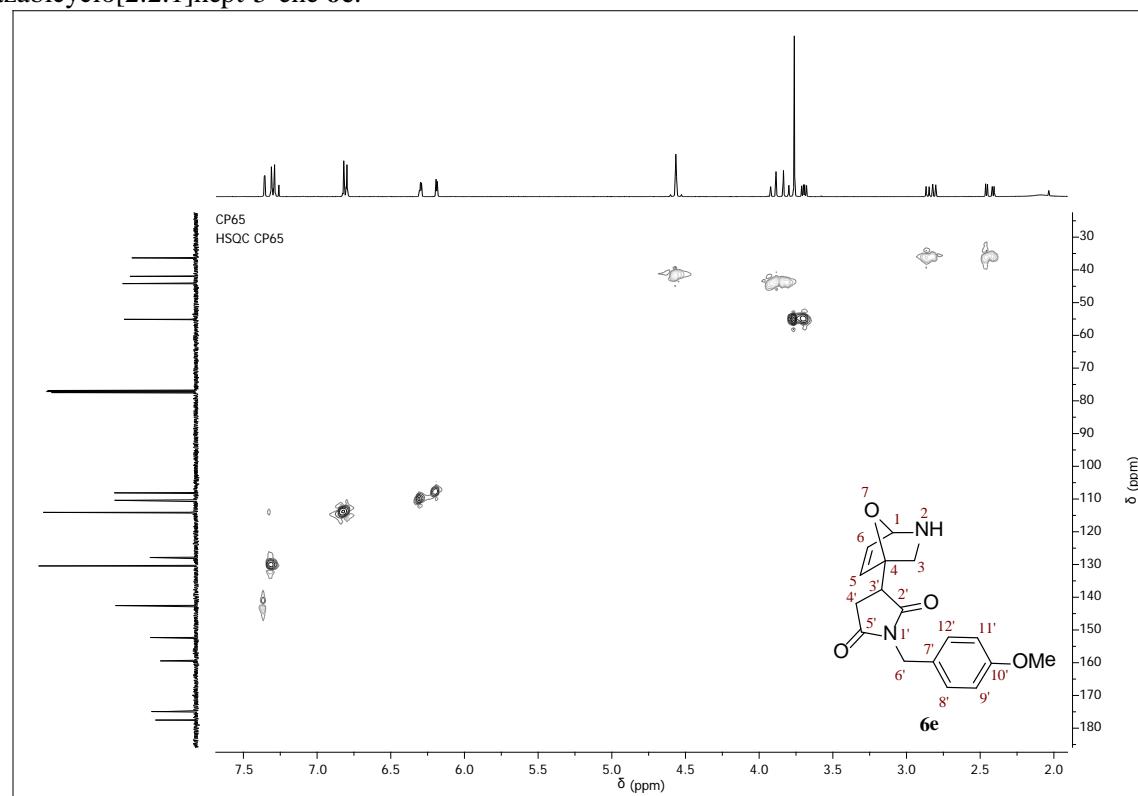
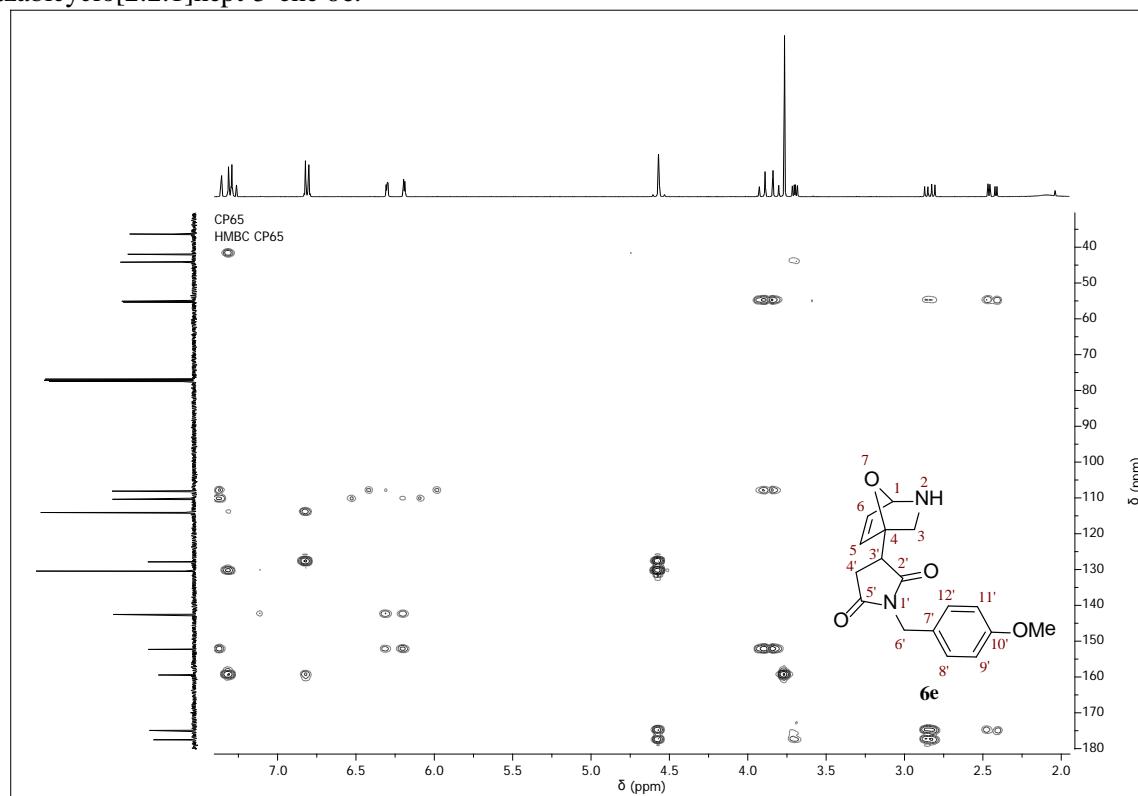
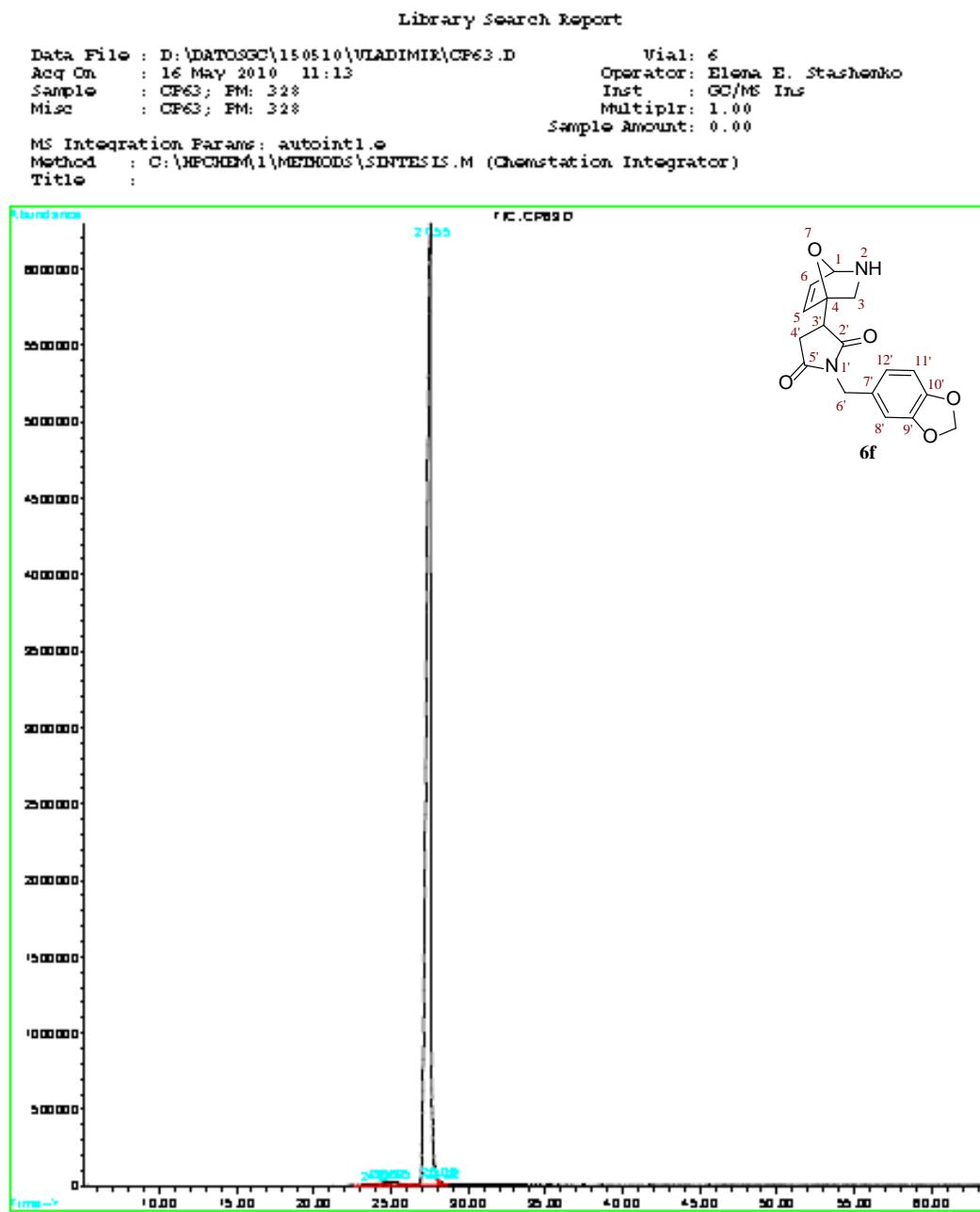


Figure SI32. HMBC spectrum of 4-(N-(4-methoxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6e**.



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Figure SI33. Chromatogram of 4-(N-(3,4-methylenedioxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6f**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI34. ¹H-NMR spectrum of 4-(N-(3,4-methylenedioxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6f**.

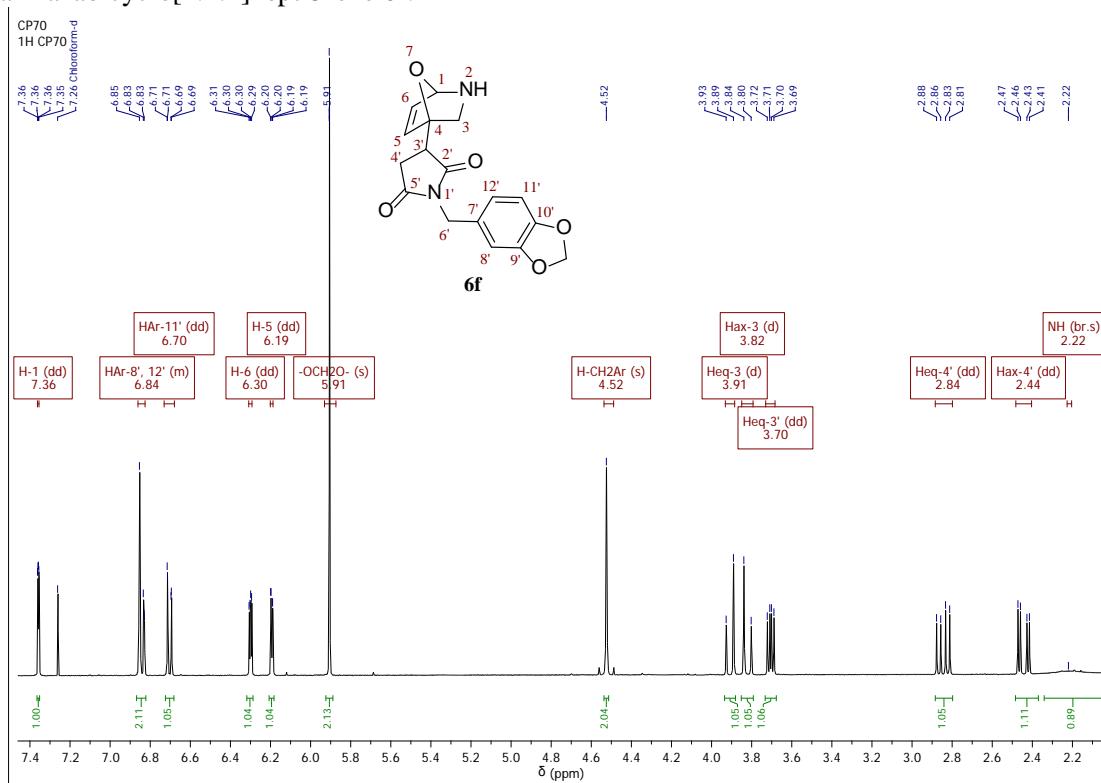
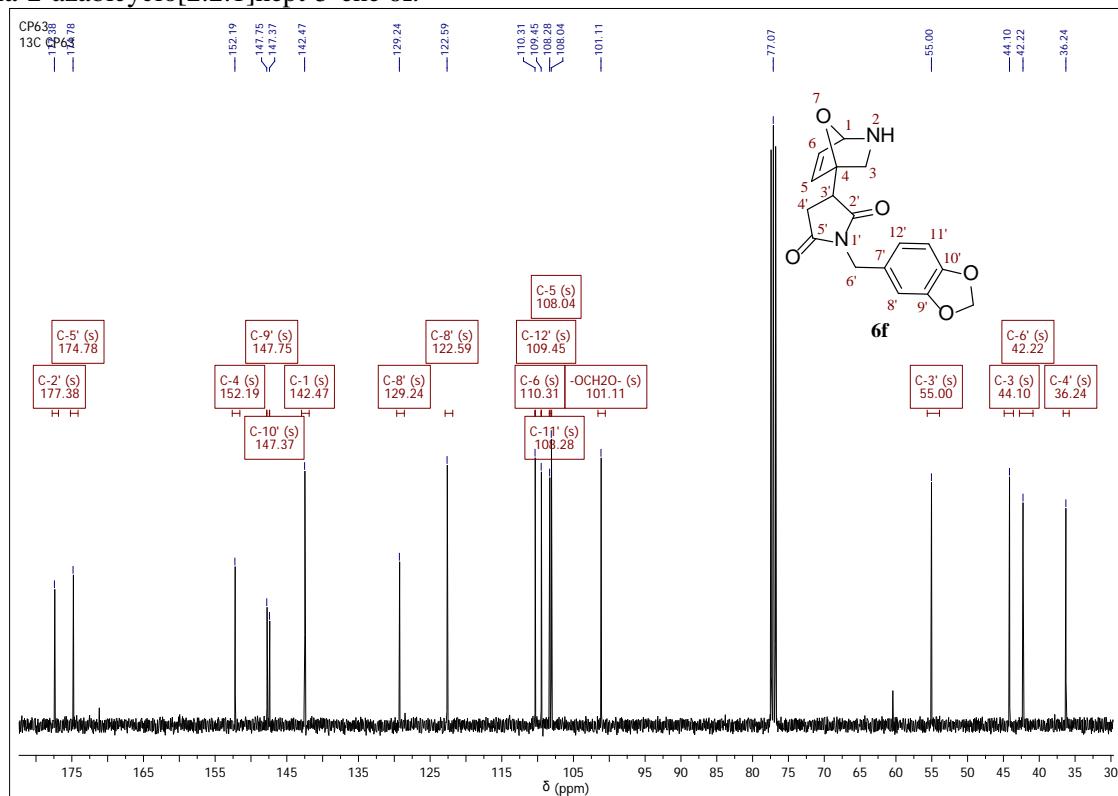


Figure SI35. ¹³C-NMR spectrum of 4-(N-(3,4-methylenedioxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6f**.



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Figure SI36. DEPT-135 spectrum of 4-(*N*-(3,4-methylenedioxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6f**.

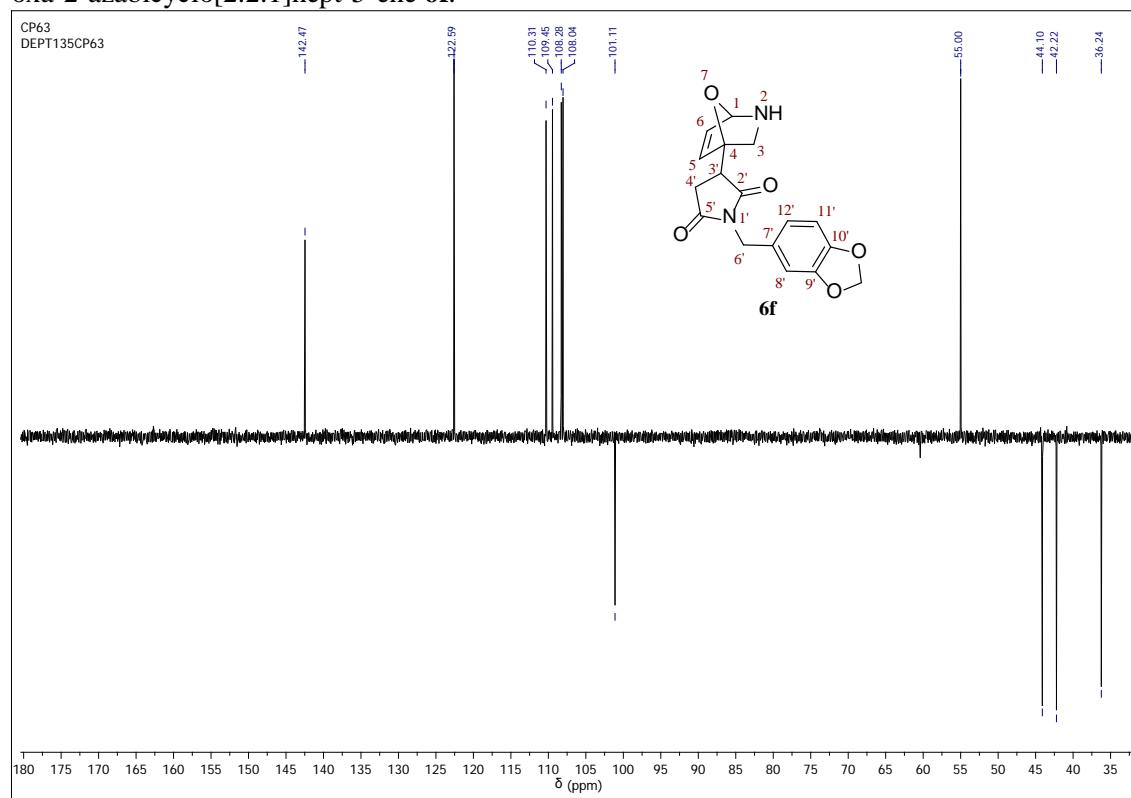
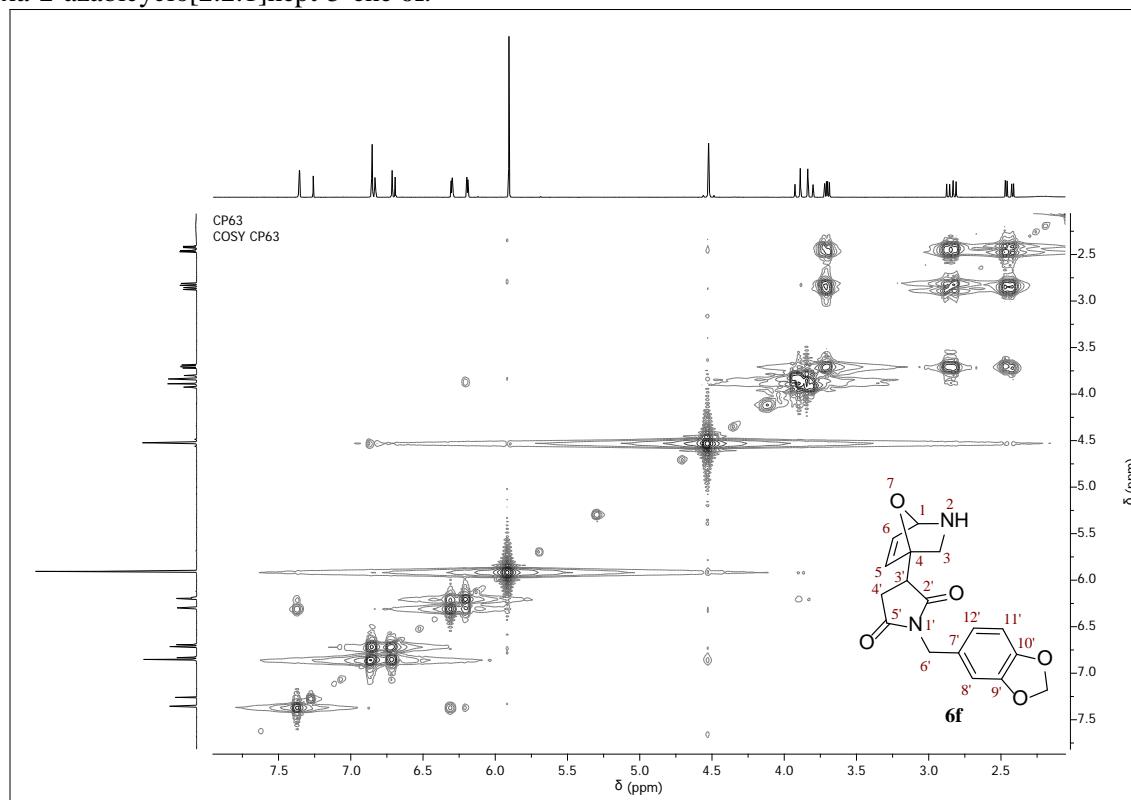


Figure SI37. COSY spectrum of 4-(*N*-(3,4-methylenedioxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6f**.



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Figure SI38. HSQC spectrum of 4-(*N*-(3,4-methylenedioxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6f**.

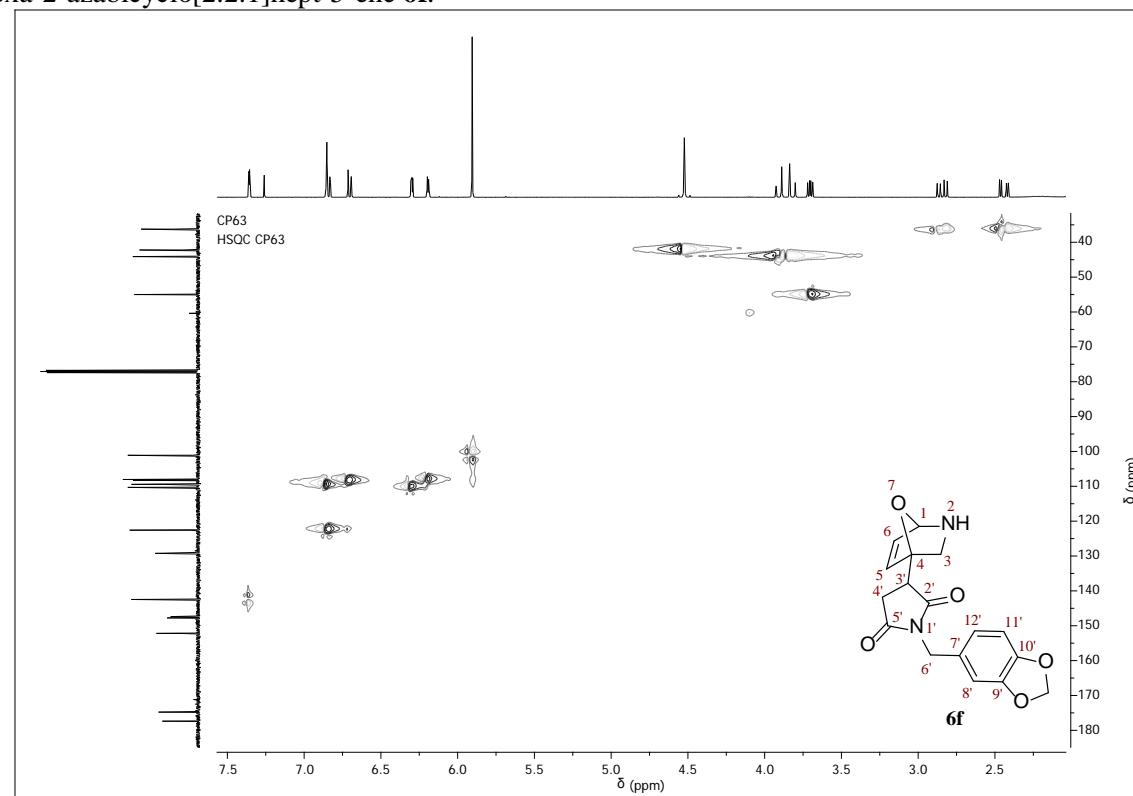
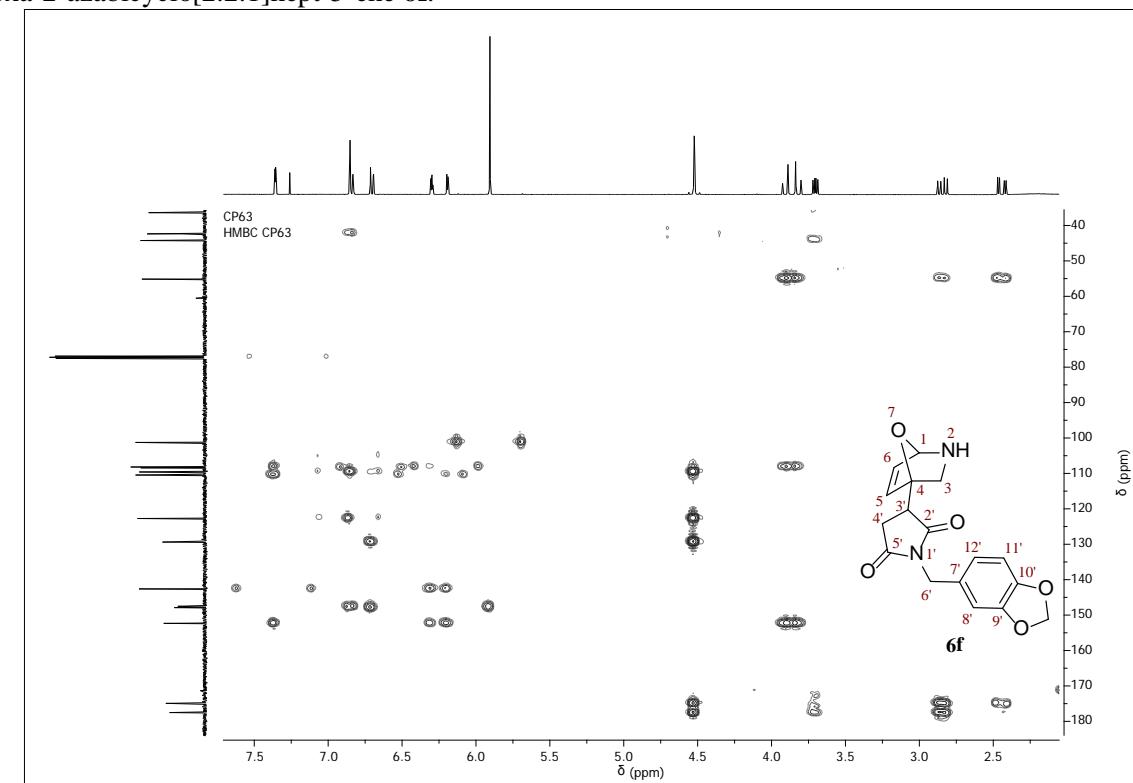
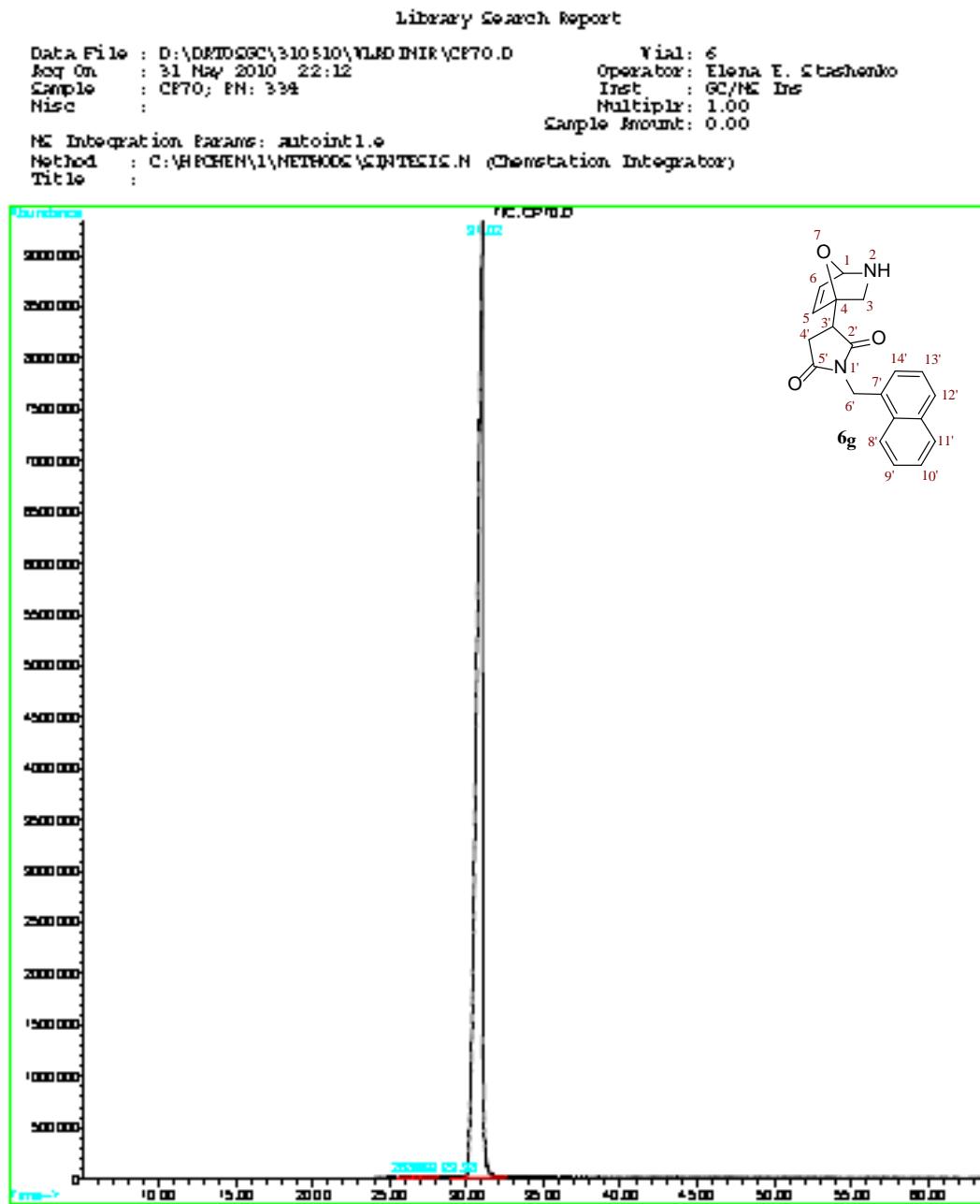


Figure SI39. HMBC spectrum of 4-(*N*-(3,4-methylenedioxybenzyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6f**.



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Figure SI40. Chromatogram of 4-(*N*-(1-naphthyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6g**.



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Figure SI41. ¹H-NMR spectrum of 4-(N-(1-naphthyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6g**.

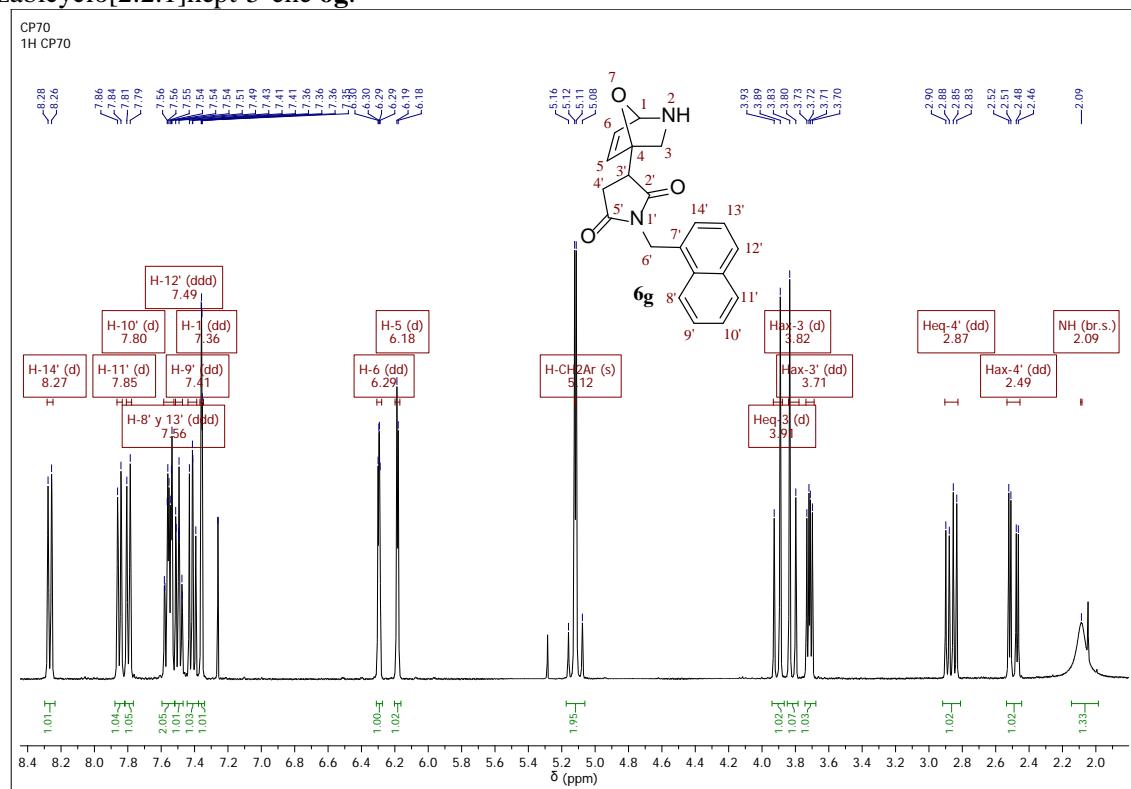
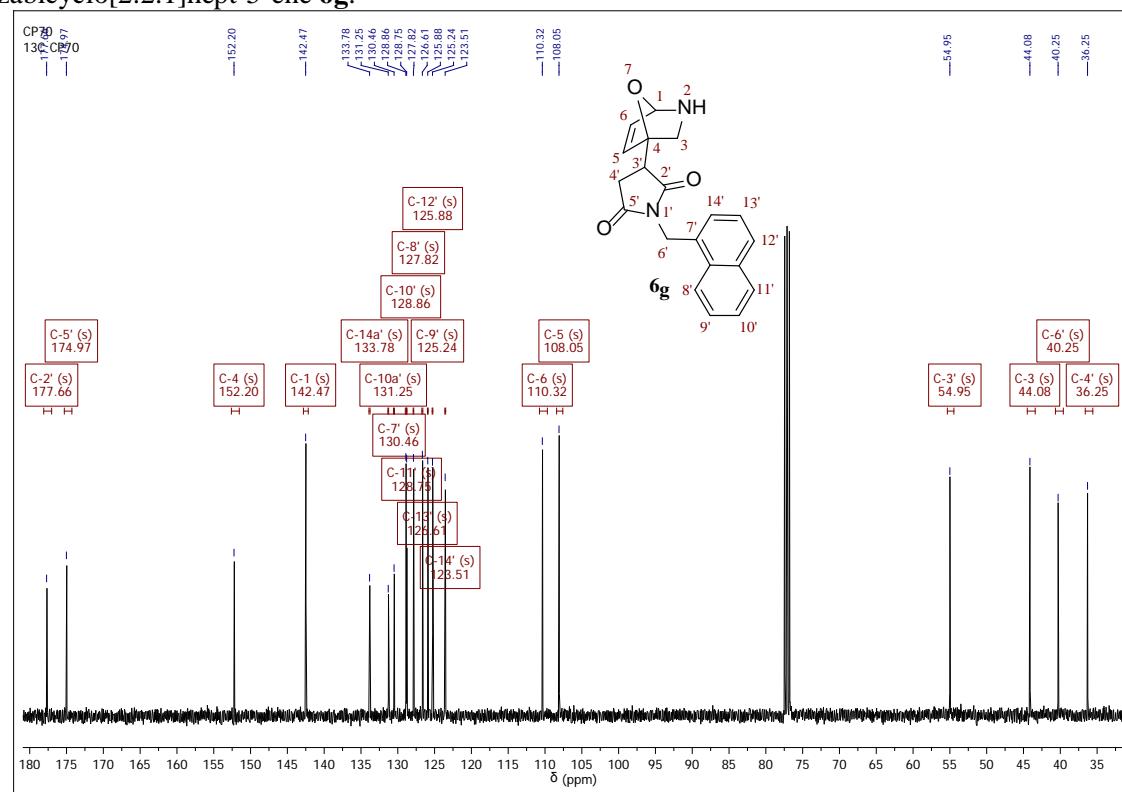


Figure SI42. ¹³C-NMR spectrum of 4-(N-(1-naphthyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6g**.



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Figure SI43. DEPT-135 spectrum of 4-(N-(1-naphthyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6g**.

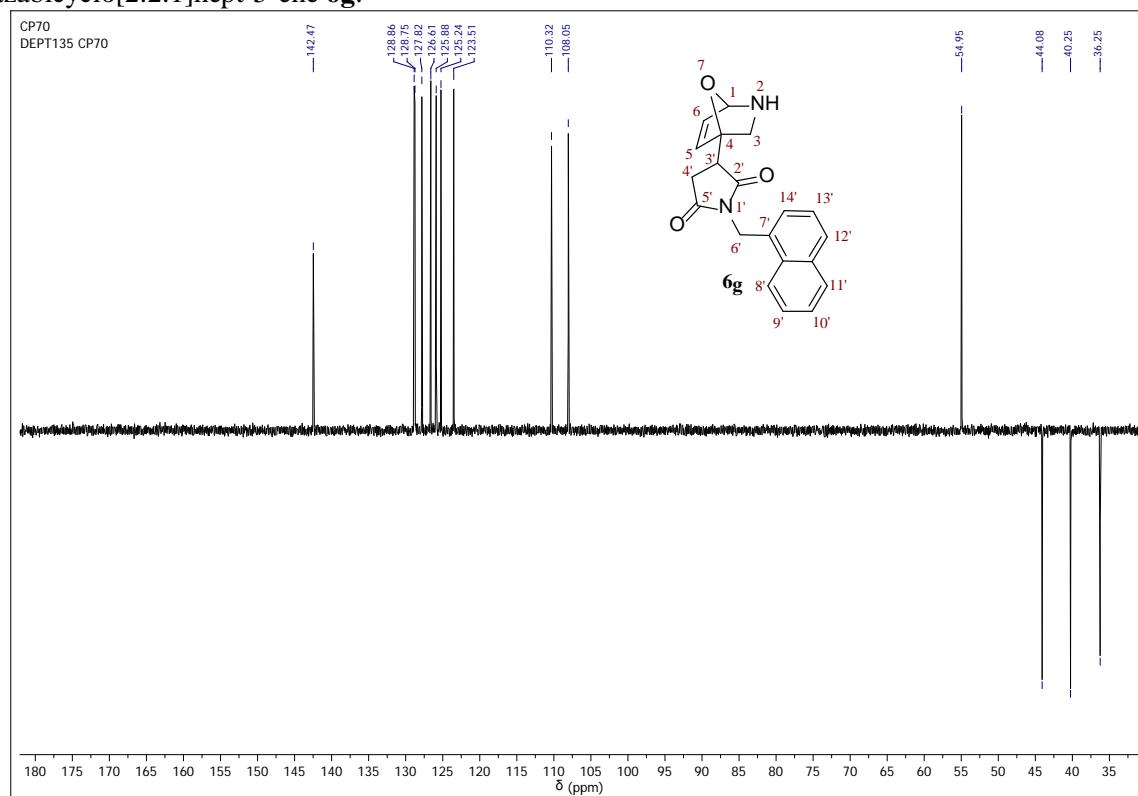
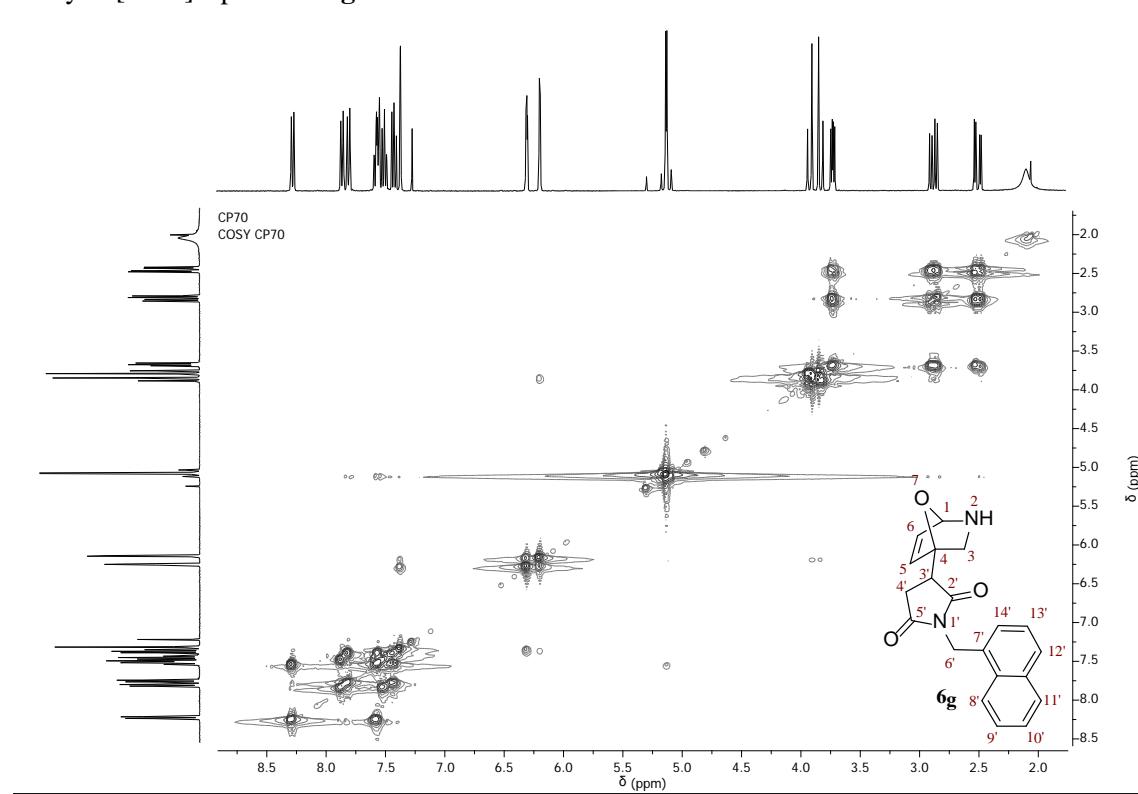


Figure SI44. COSY spectrum of 4-(N-(1-naphthyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6g**.



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Figure SI45. HSQC spectrum of 4-(*N*-(1-naphthyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6g**.

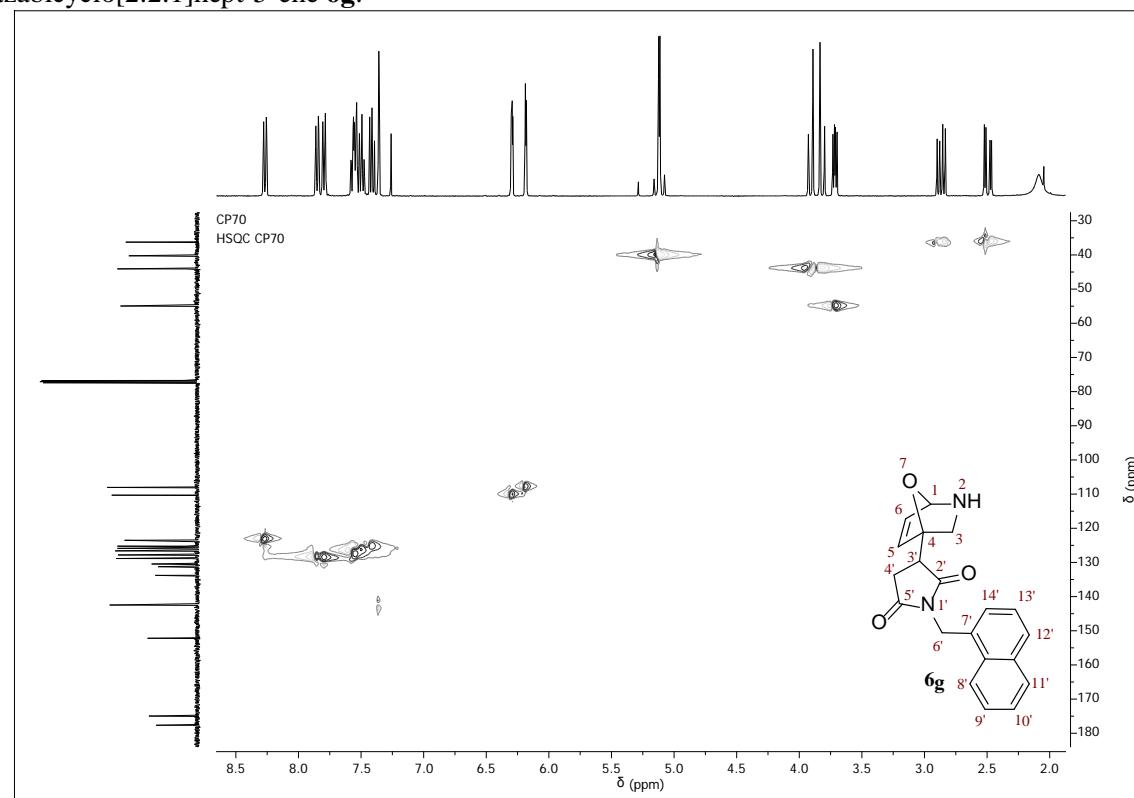
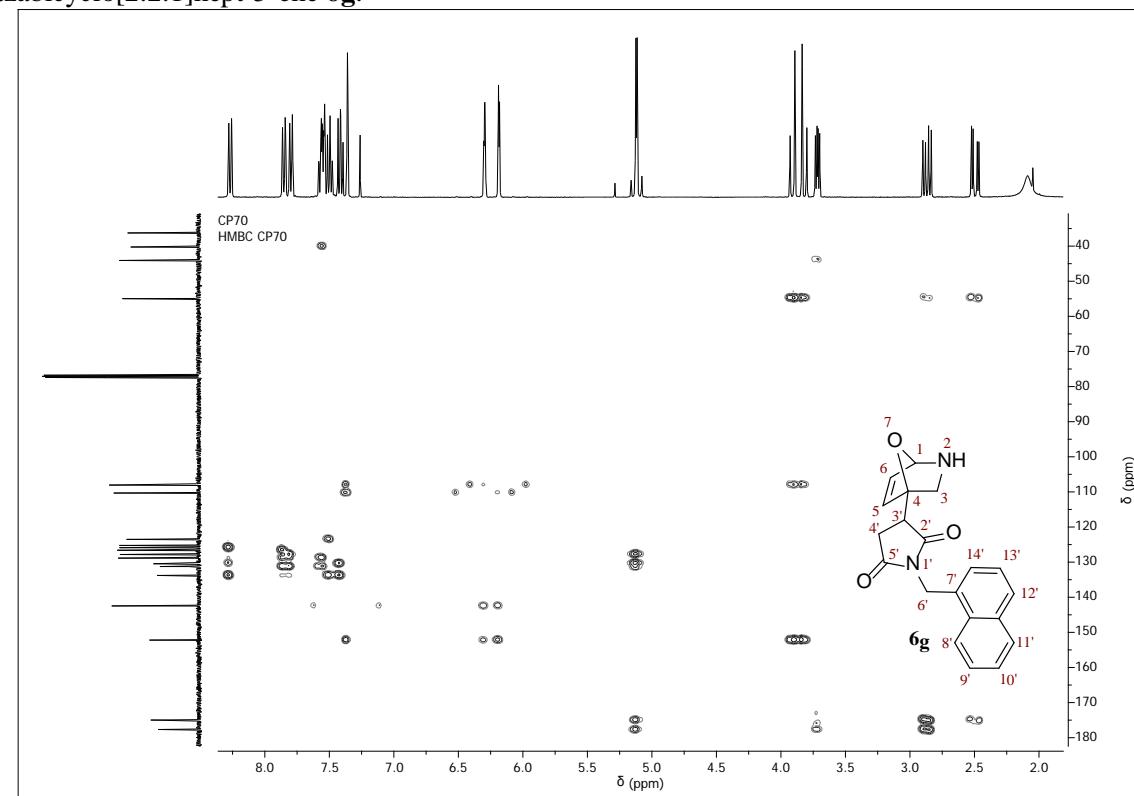
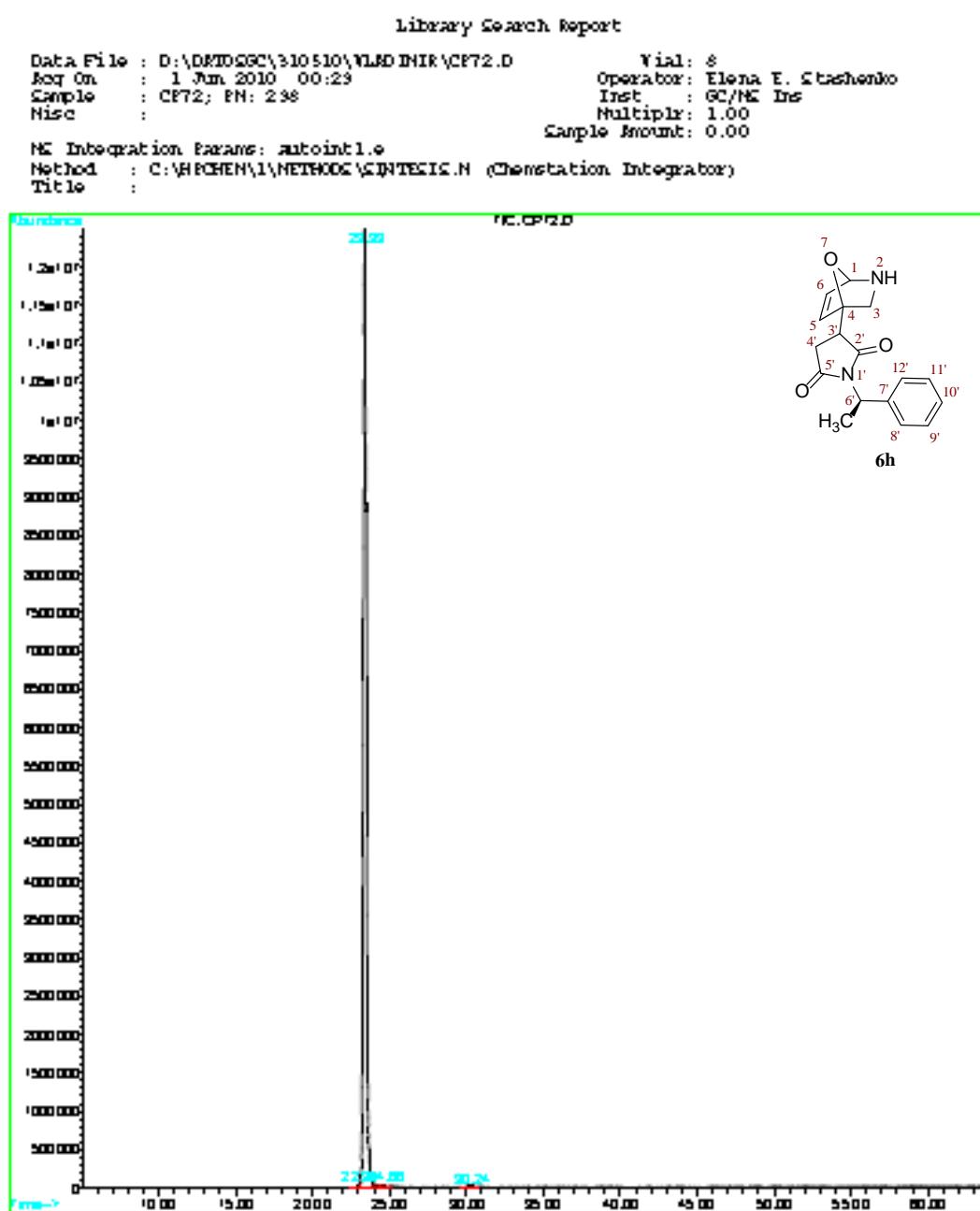


Figure SI46. HMBC spectrum of 4-(*N*-(1-naphthyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6g**.



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Figure SI47. Chromatogram of 4-(S-(-)-N-(1-phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6h**.



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Figure SI48. ¹H-NMR spectrum of 4-(S-(-)-N-(1-phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6h**.

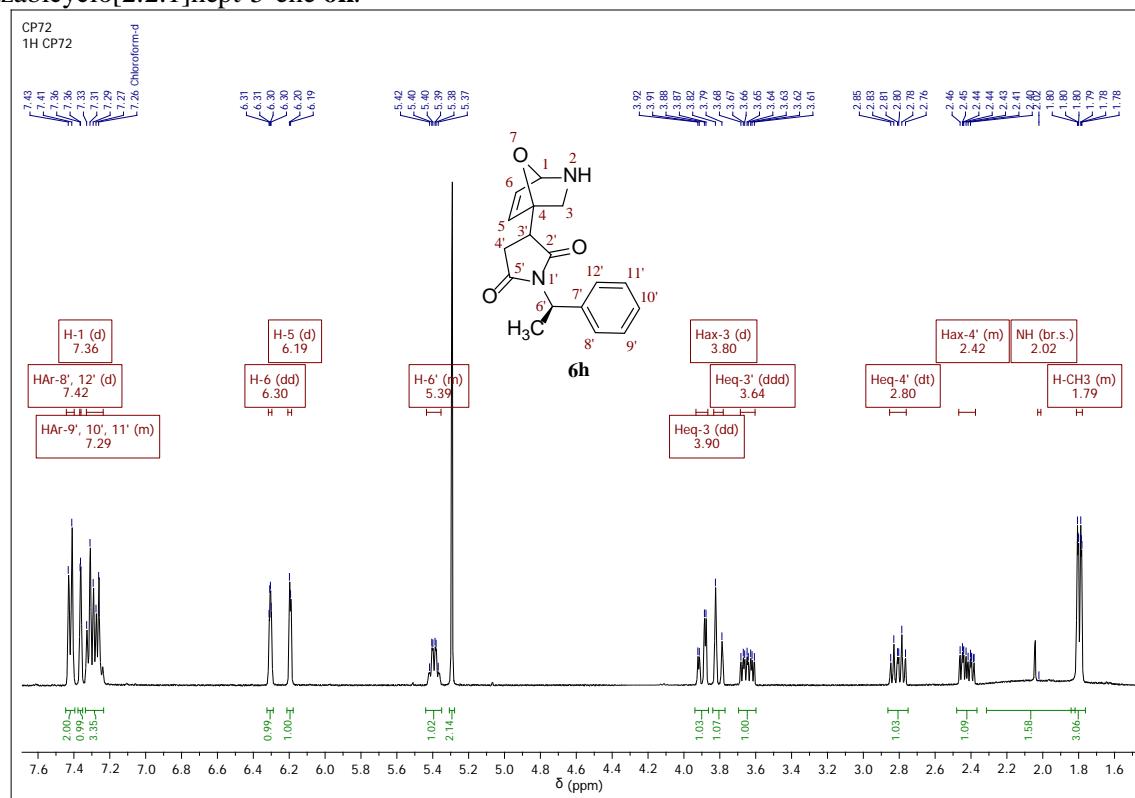
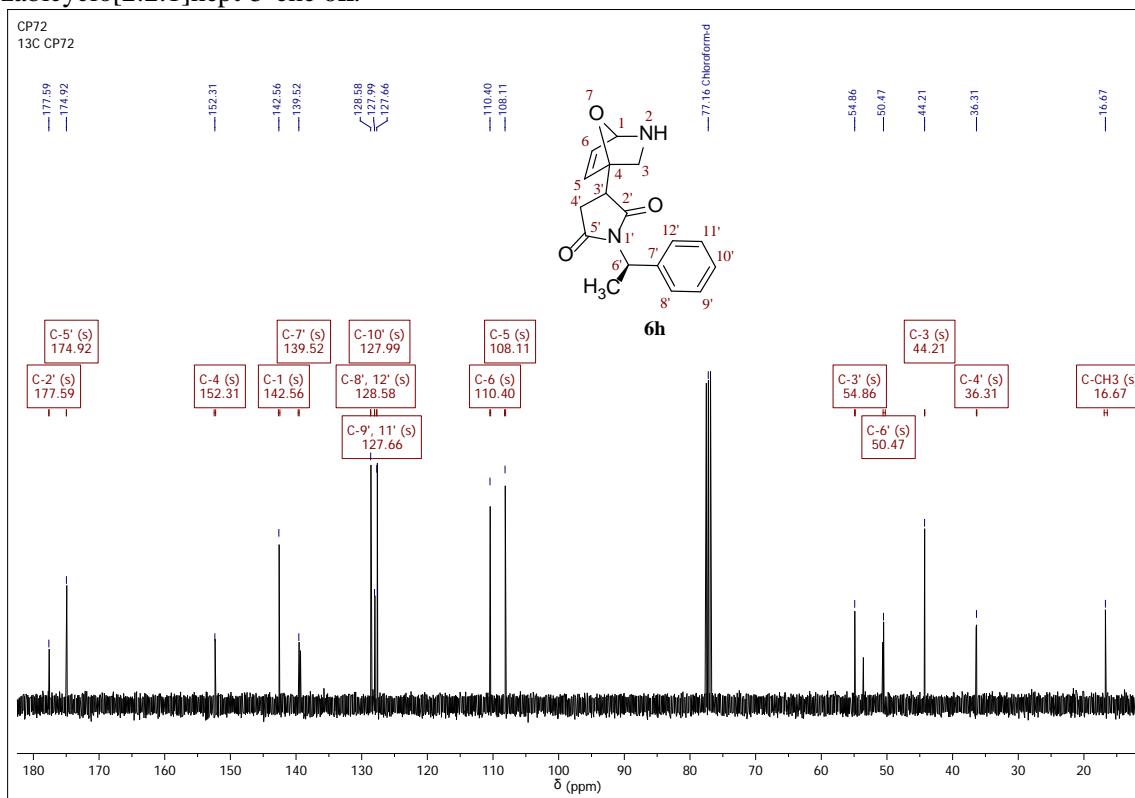
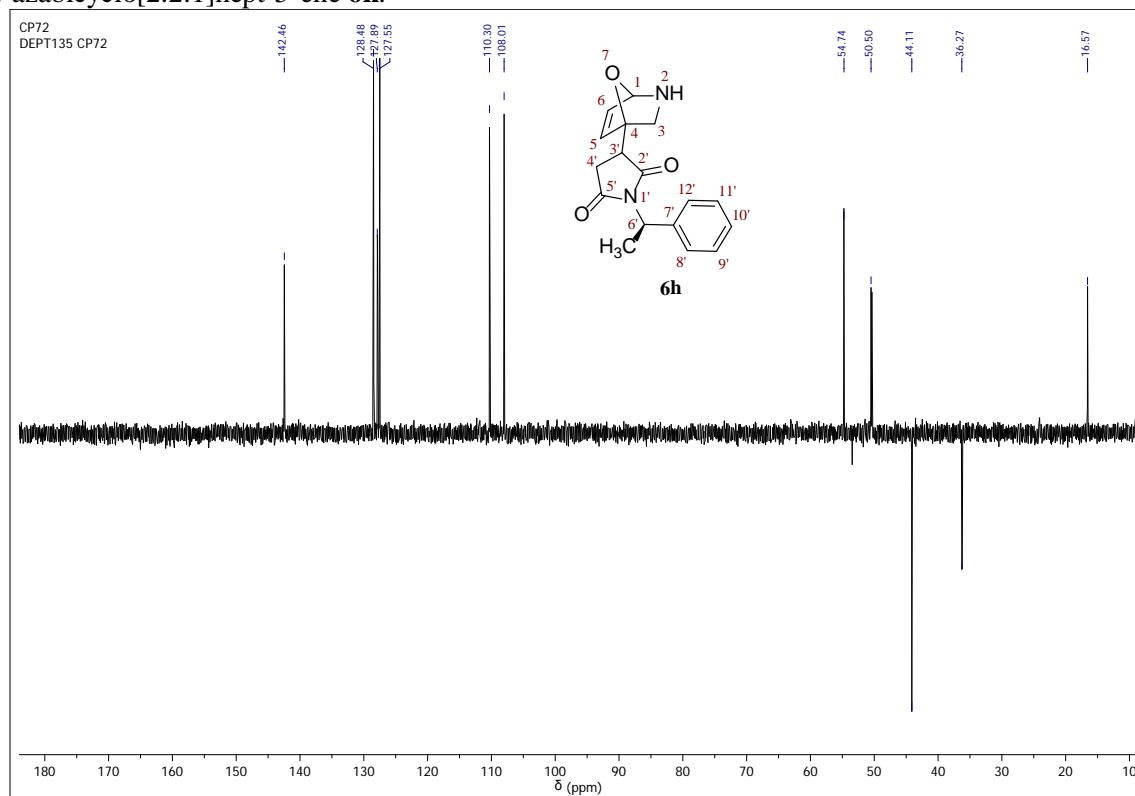


Figure SI49. ¹³C-NMR spectrum of 4-(S-(-)-N-(1-phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6h**.



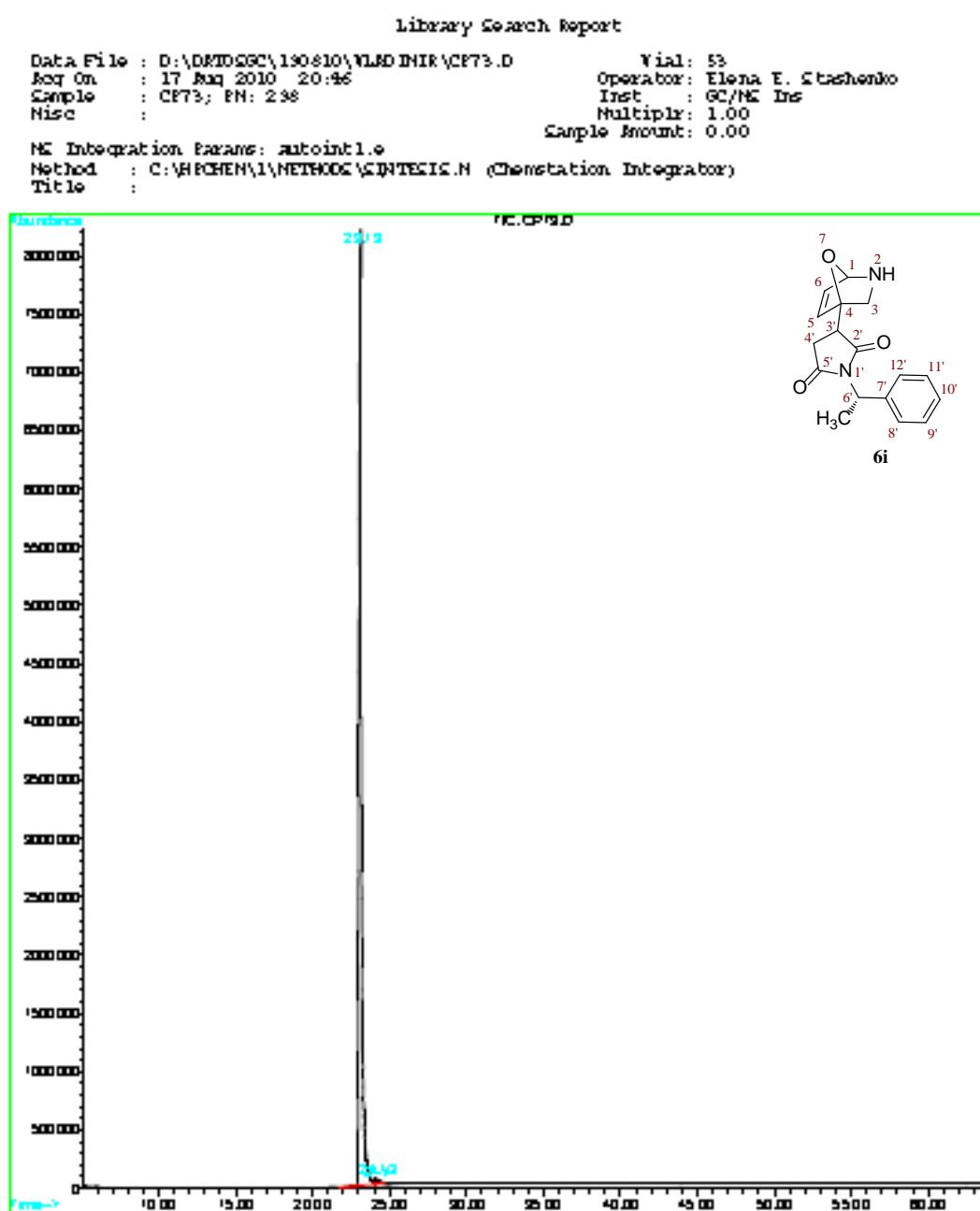
H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI50. DEPT-135 spectrum of 4-(S-(-)-N-(1-phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6h**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI51. Chromatogram of 4-(R-(+)-N-(1-phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6i**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI52. ^1H -NMR spectrum of 4-(R- $(+)$ -N-(1-phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6i**.

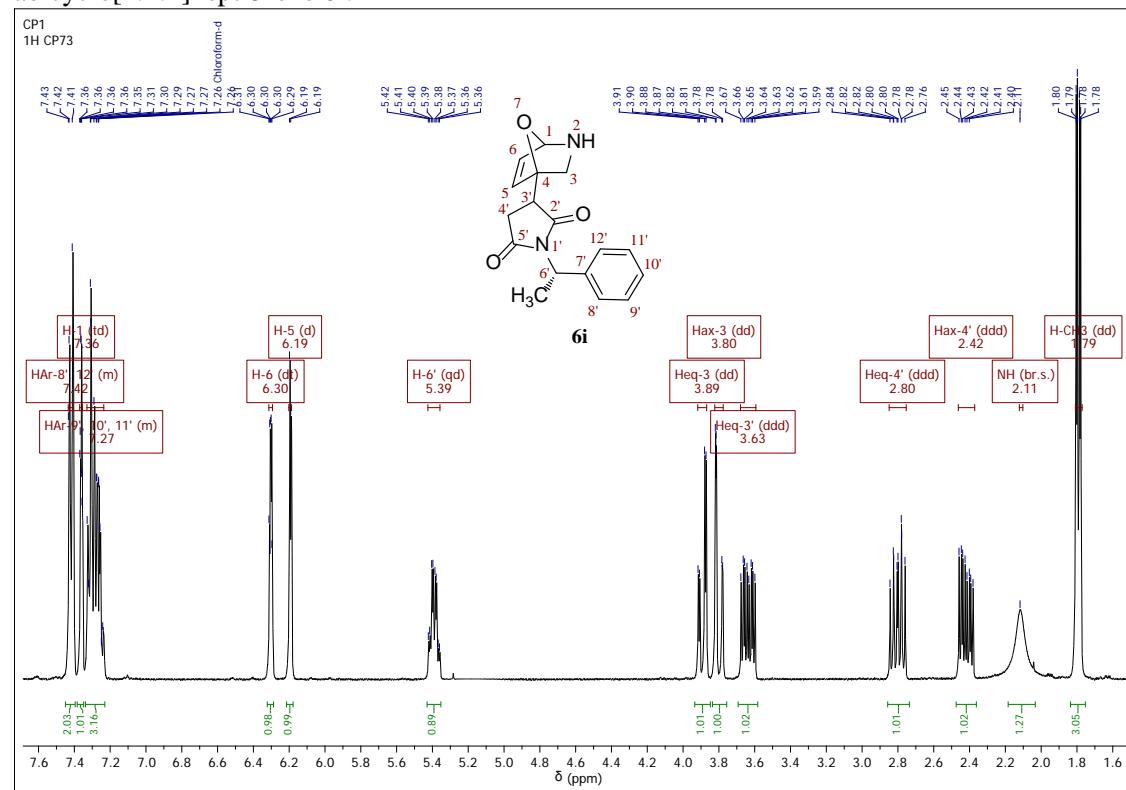
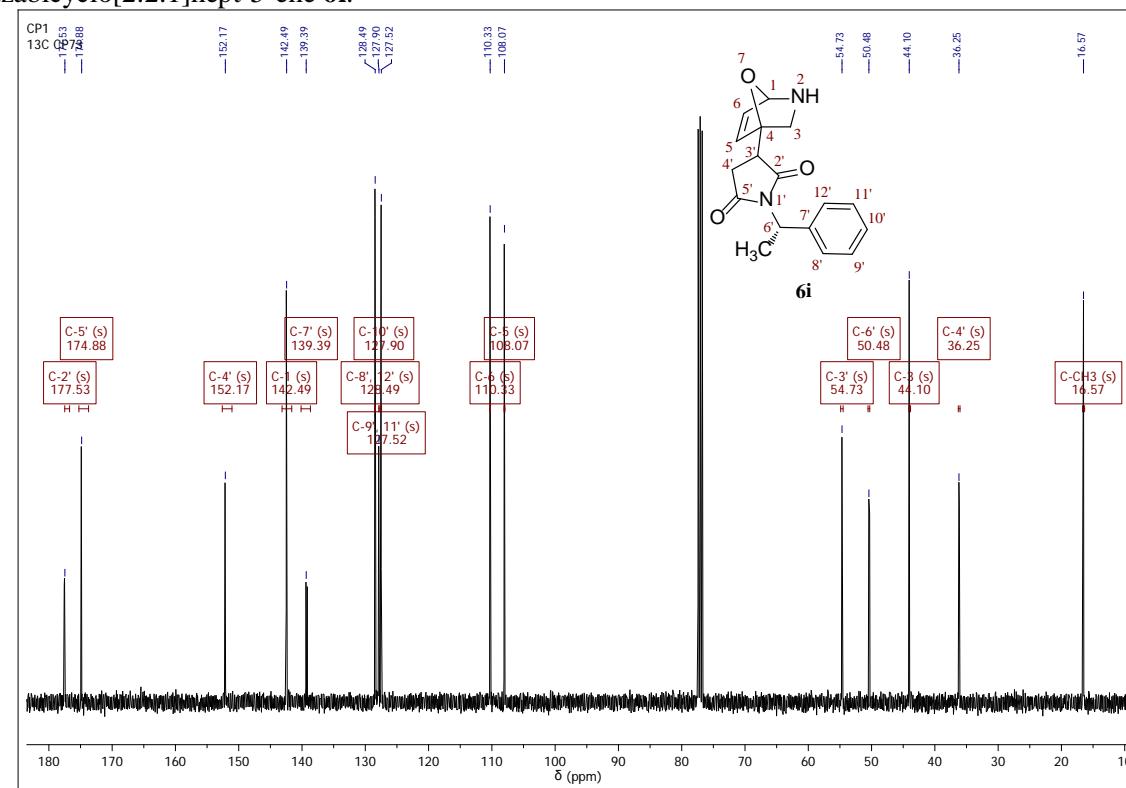


Figure SI53. ^{13}C -NMR spectrum of 4-(R- $(+)$ -N-(1-phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6i**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI54. DEPT-135 spectrum of 4-(R-(+)-N-(1-phenylethyl)-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6i**.

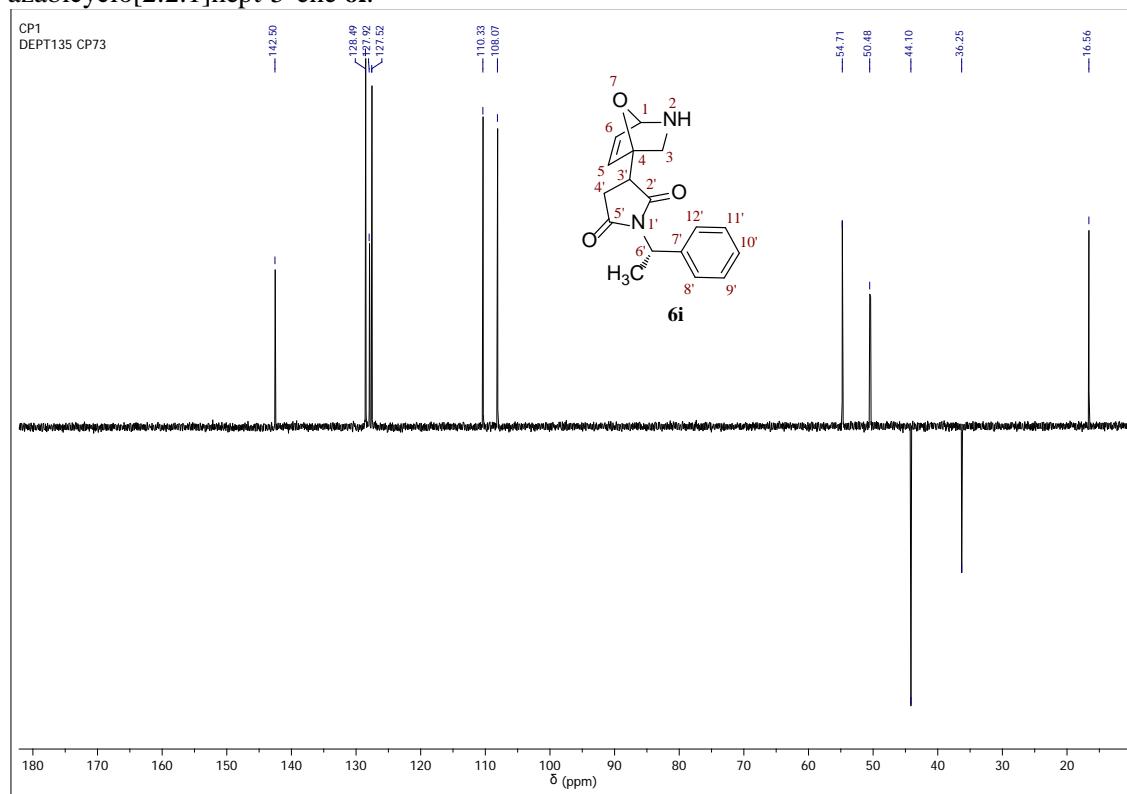
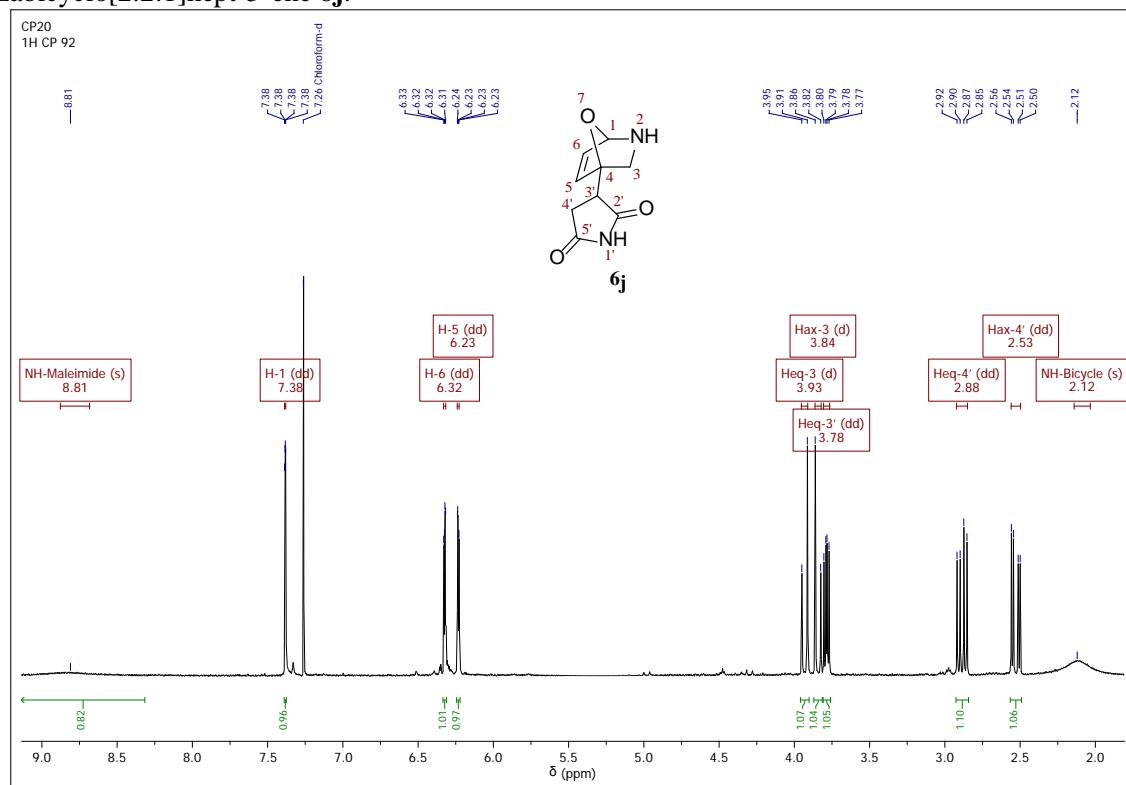


Figure SI55. ¹H-NMR spectrum of 4-(1H-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6j**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI56. ¹³C-NMR spectrum of 4-(1H-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6j**.

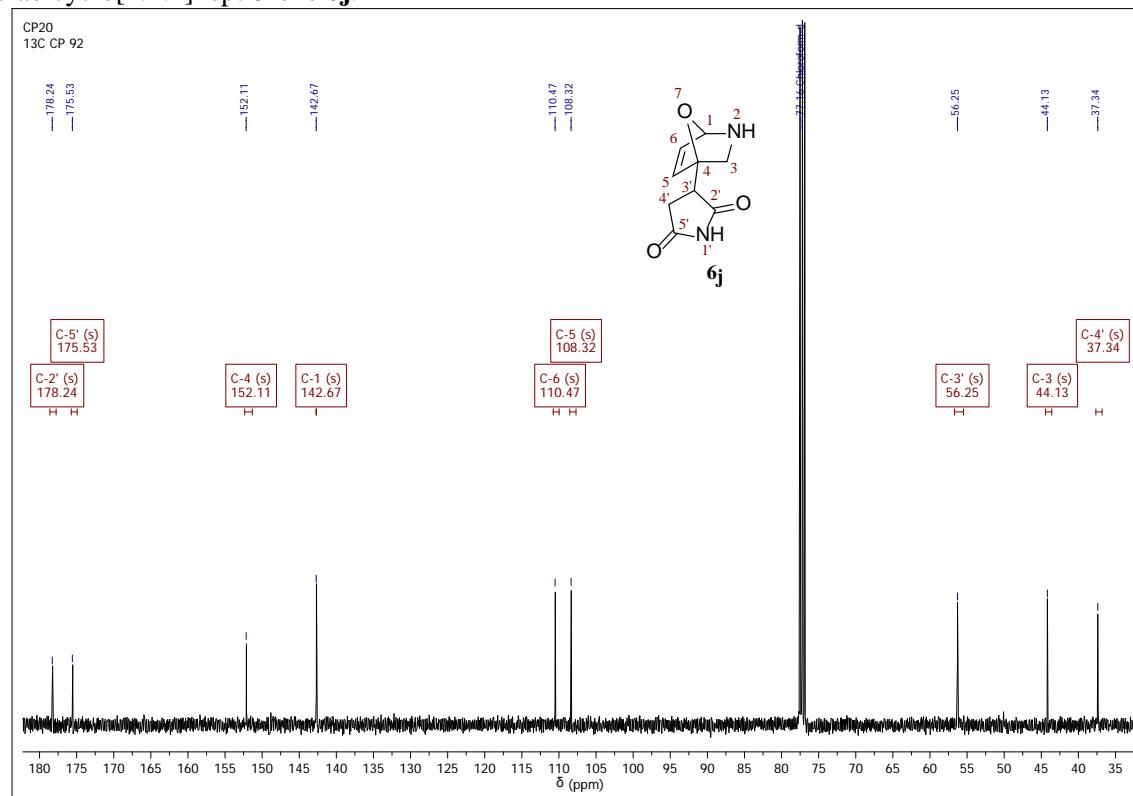
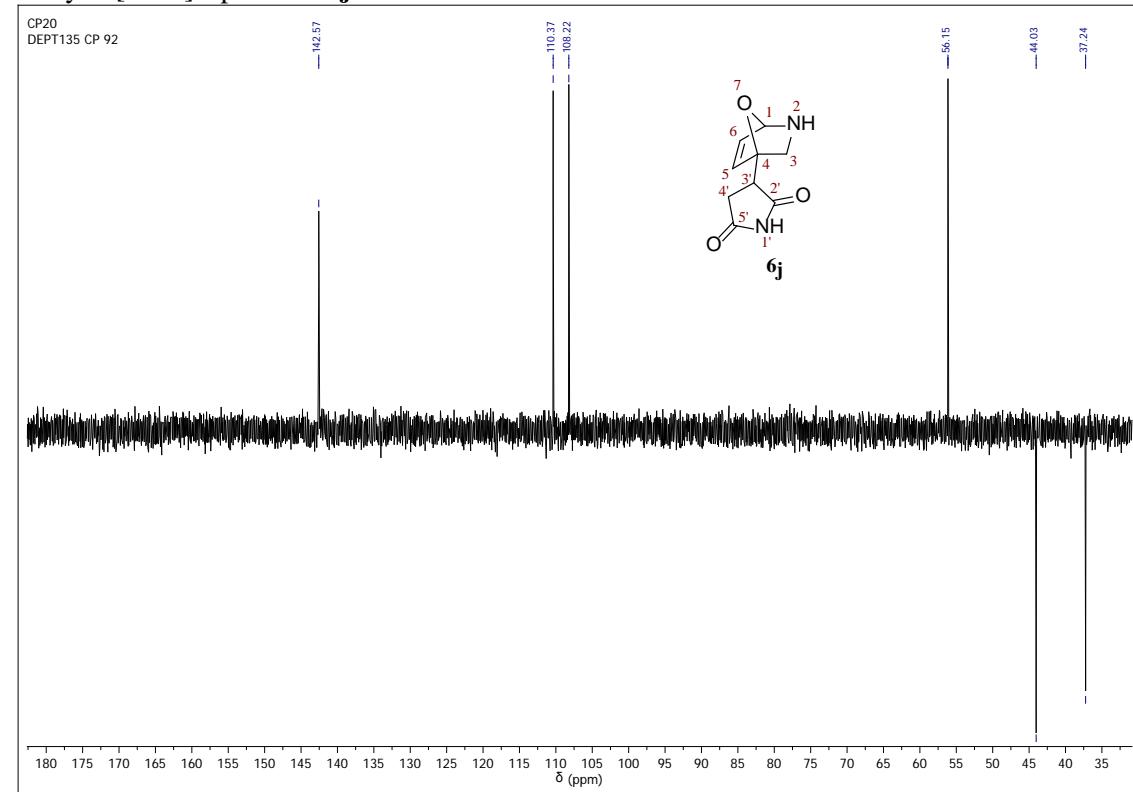
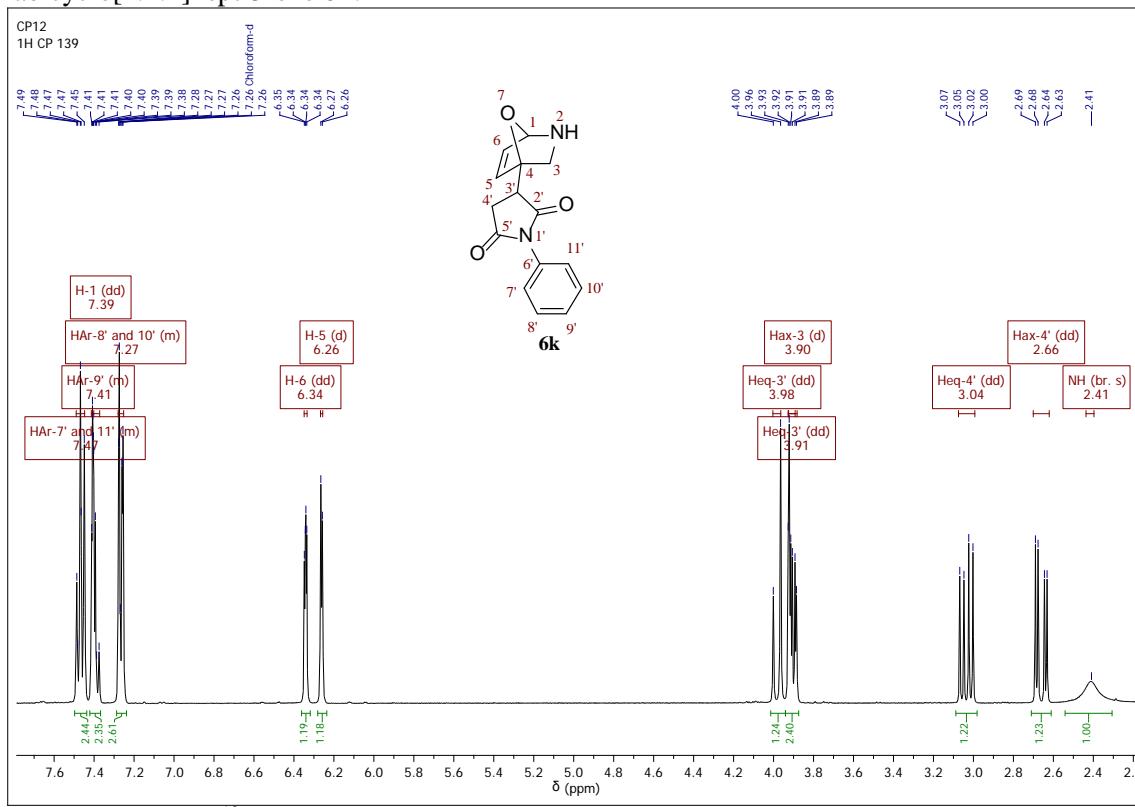


Figure SI57. DEPT-135 spectrum of 4-(1H-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6j**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI58. ¹H-NMR spectrum of 4-(N-phenyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6k**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI60. DEPT-135 spectrum of 4-(N-phenyl-pyrrolidin-3-yl-2,5-dione)-7-oxa-2-azabicyclo[2.2.1]hept-5-ene **6k**.

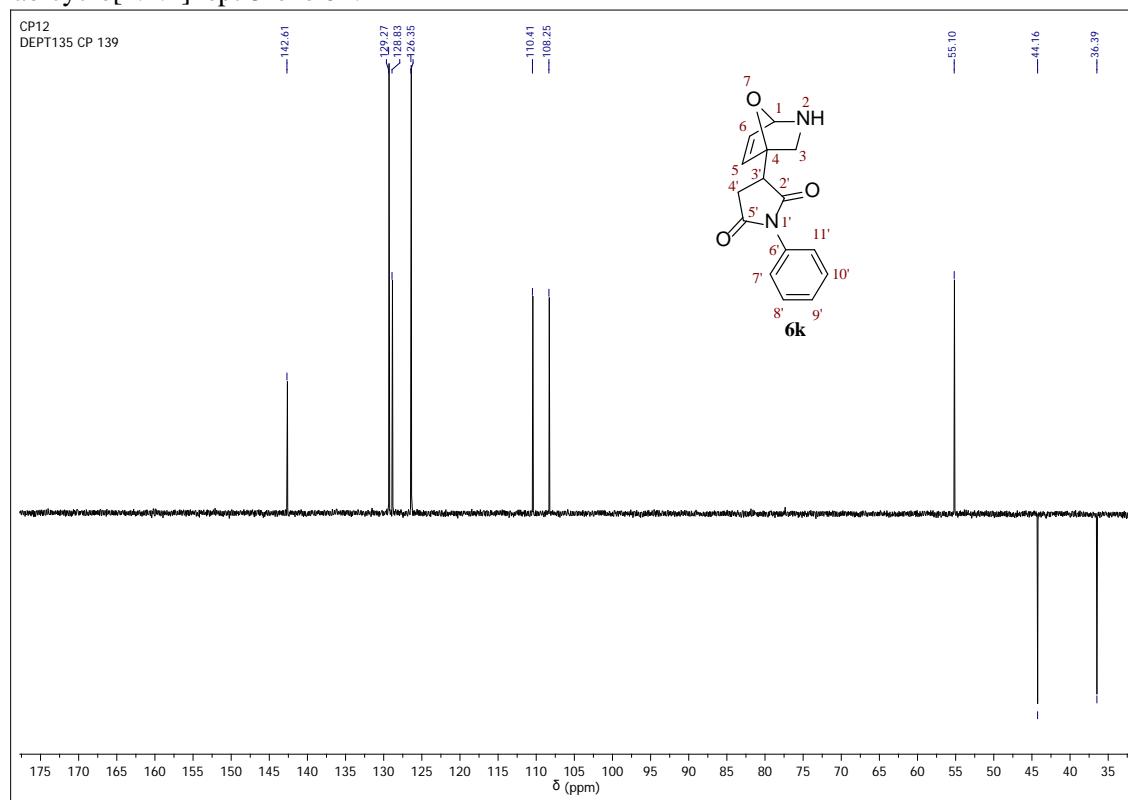
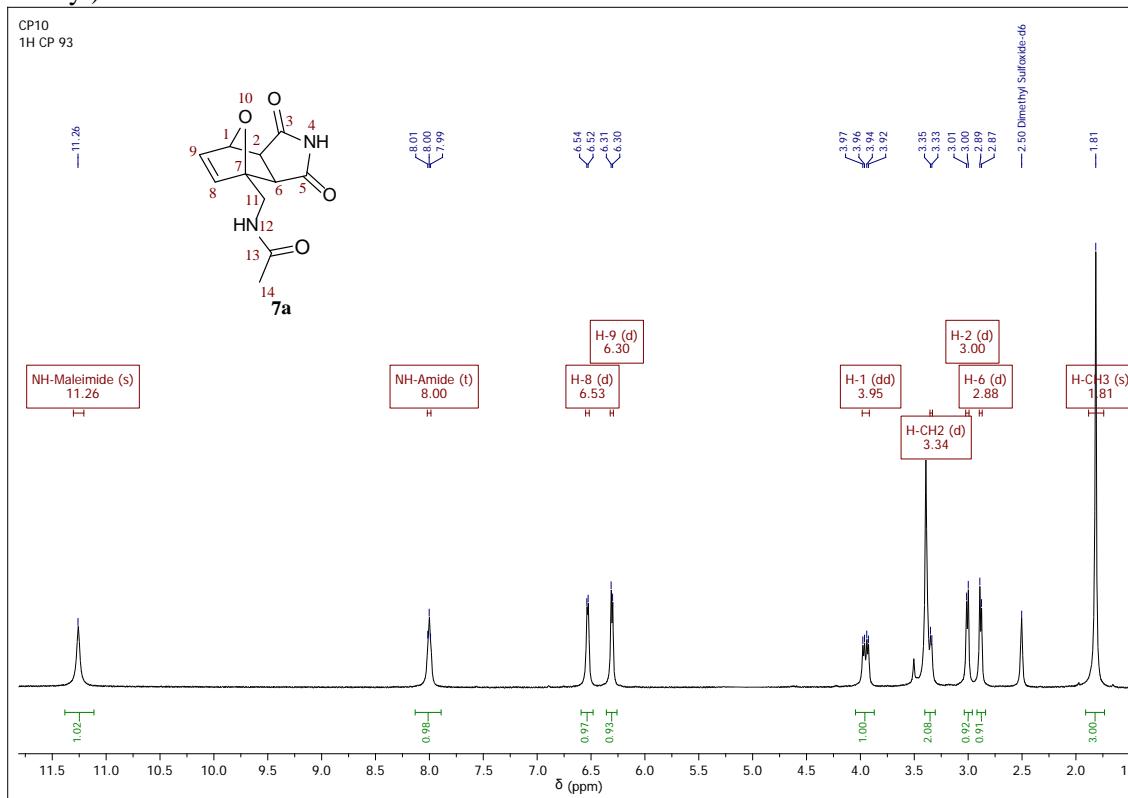


Figure SI61. ¹H-NMR spectrum of *N*-(10-oxa-1H-4-azatricyclo[5.2.1.0^{2,6}]decane-8-ene-3,5-dione-7-ylmethyl)acetamide **7a**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI62. ¹³C-NMR spectrum *N*-(10-oxa-1H-4-azatricyclo[5.2.1.0^{2,6}]decane-8-ene-3,5-dione-7-ylmethyl)acetamide **7a**.

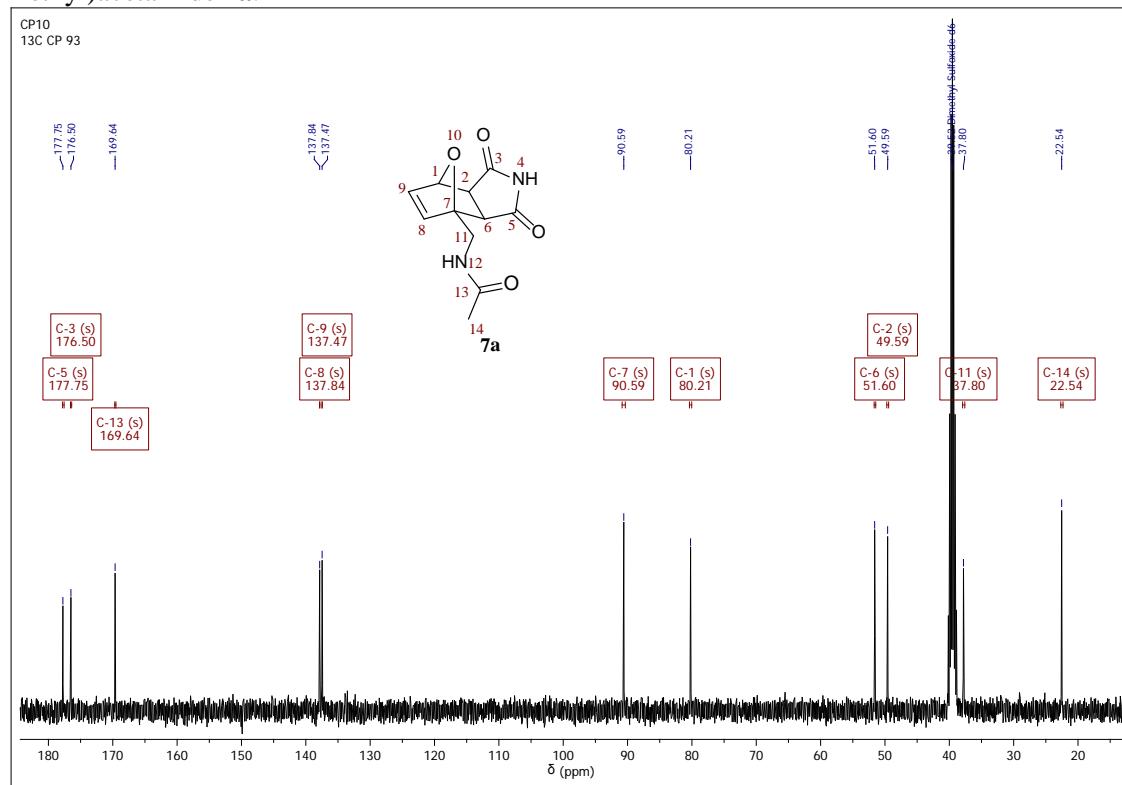
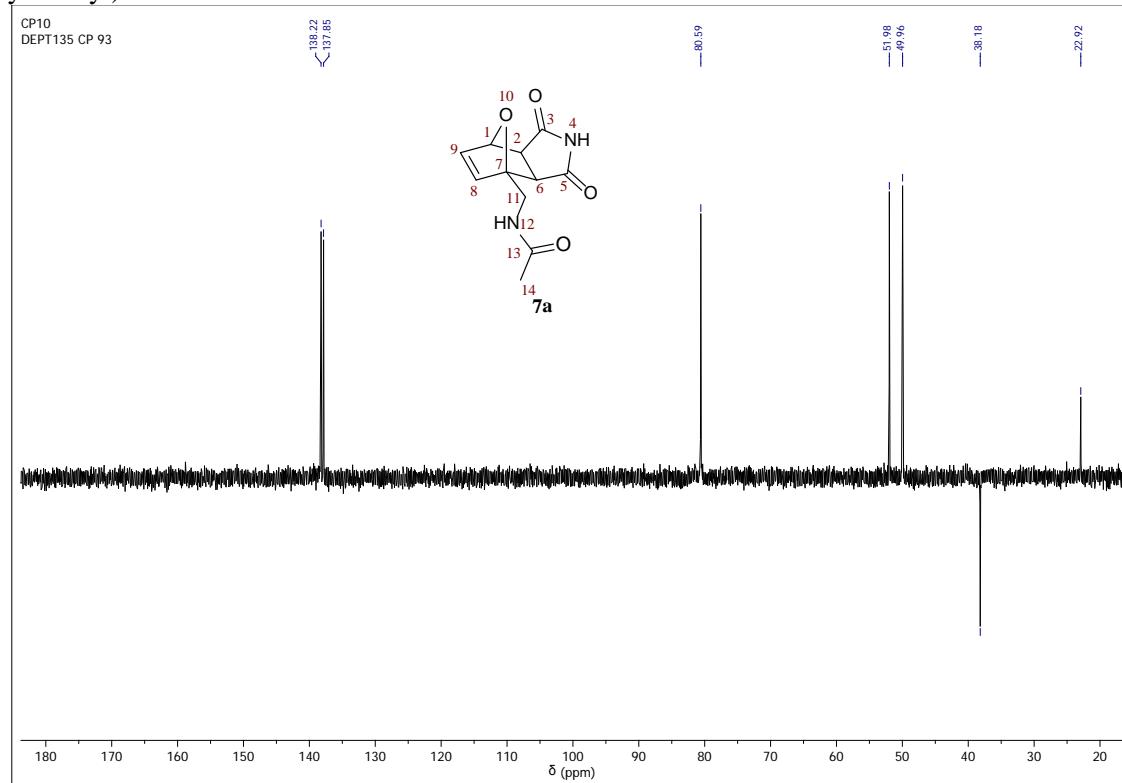


Figure SI63. DEPT-135 spectrum of *N*-(10-oxa-1H-4-azatricyclo[5.2.1.0^{2,6}]decane-8-ene-3,5-dione-7-ylmethyl)acetamide **7a**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI64. ¹H-NMR spectrum of *N*-(10-oxa-4-phenyl-4-azatricyclo[5.2.1.0^{2,6}]decane-8-ene-3,5-dione-7-ylmethyl)acetamide **7b**.

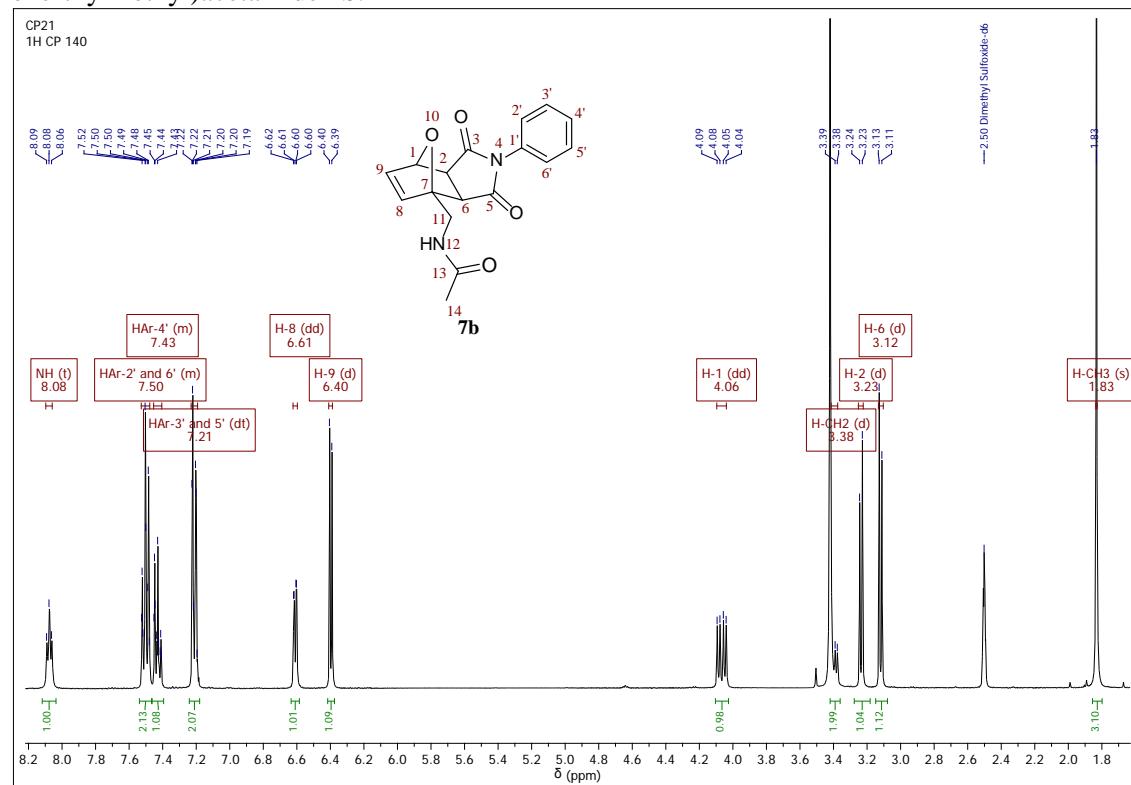
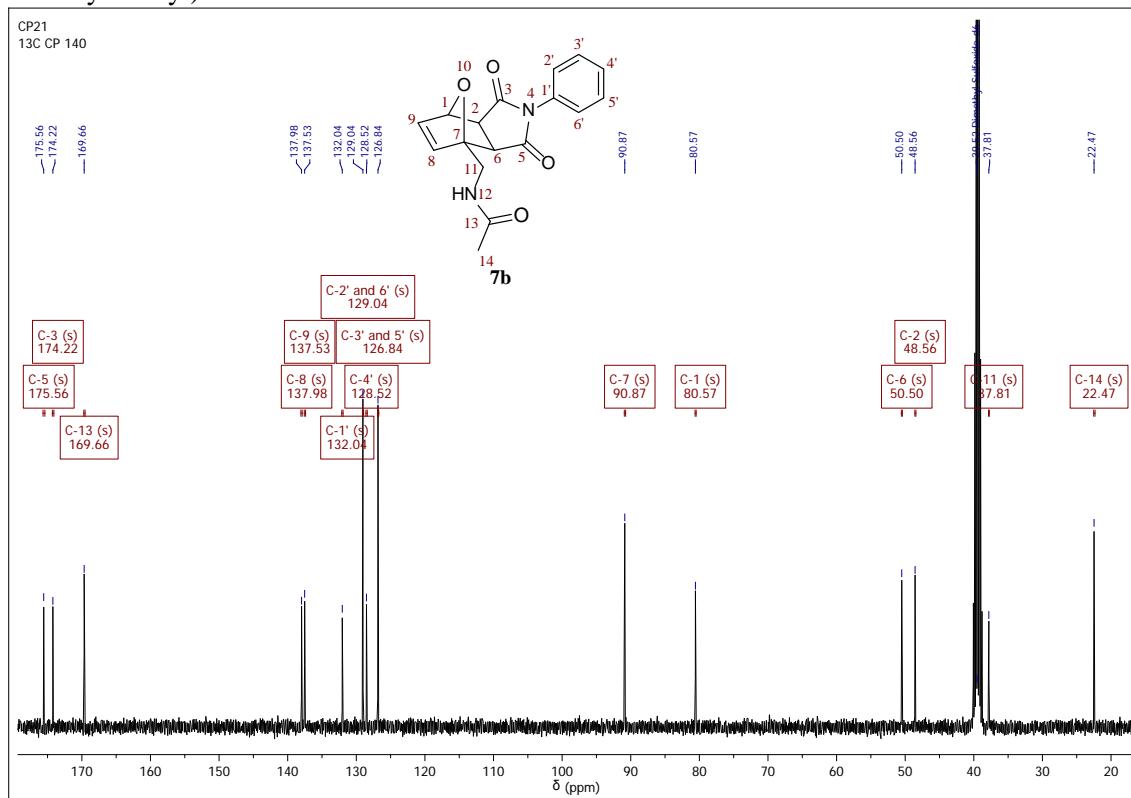


Figure SI65. ¹³C-NMR spectrum of *N*-(10-oxa-4-phenyl-4-azatricyclo[5.2.1.0^{2,6}]decane-8-ene-3,5-dione-7-ylmethyl)acetamide **7b**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI66. DEPT-135 spectrum of *N*-(10-oxa-4-phenyl-4-azatricyclo[5.2.1.0^{2,6}]decane-8-ene-3,5-dione-7-ylmethyl)acetamide **7b**.

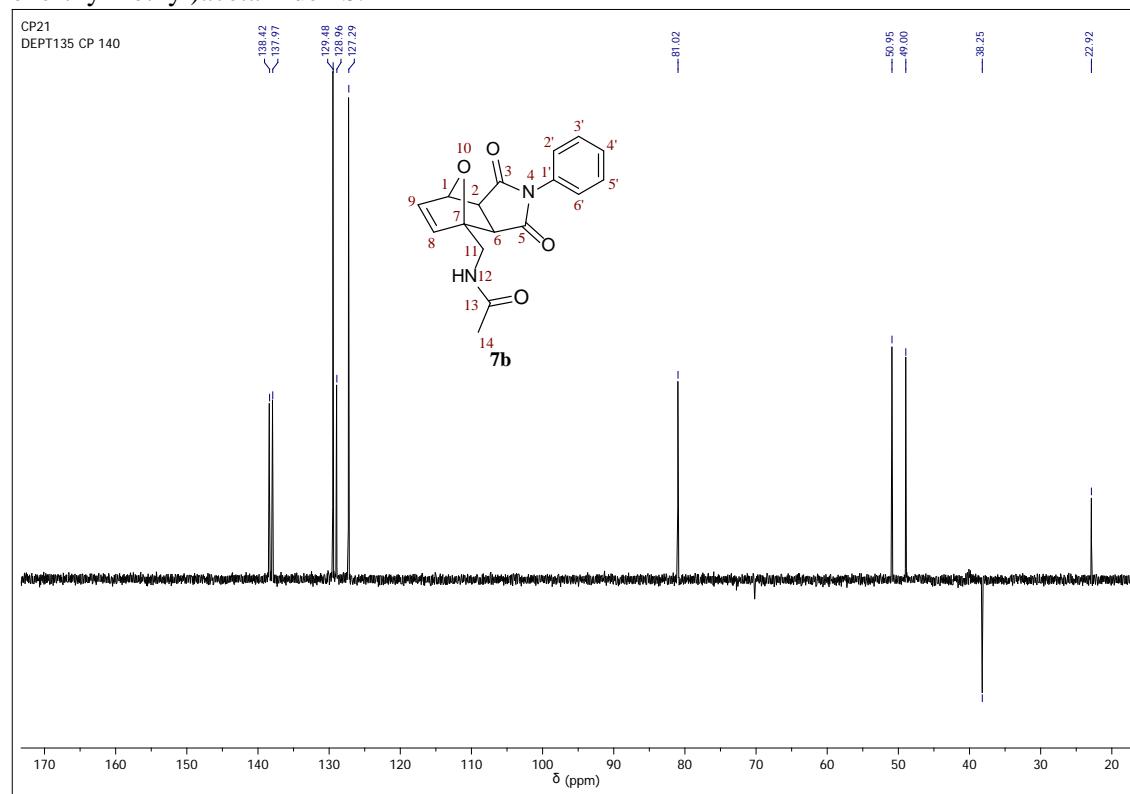
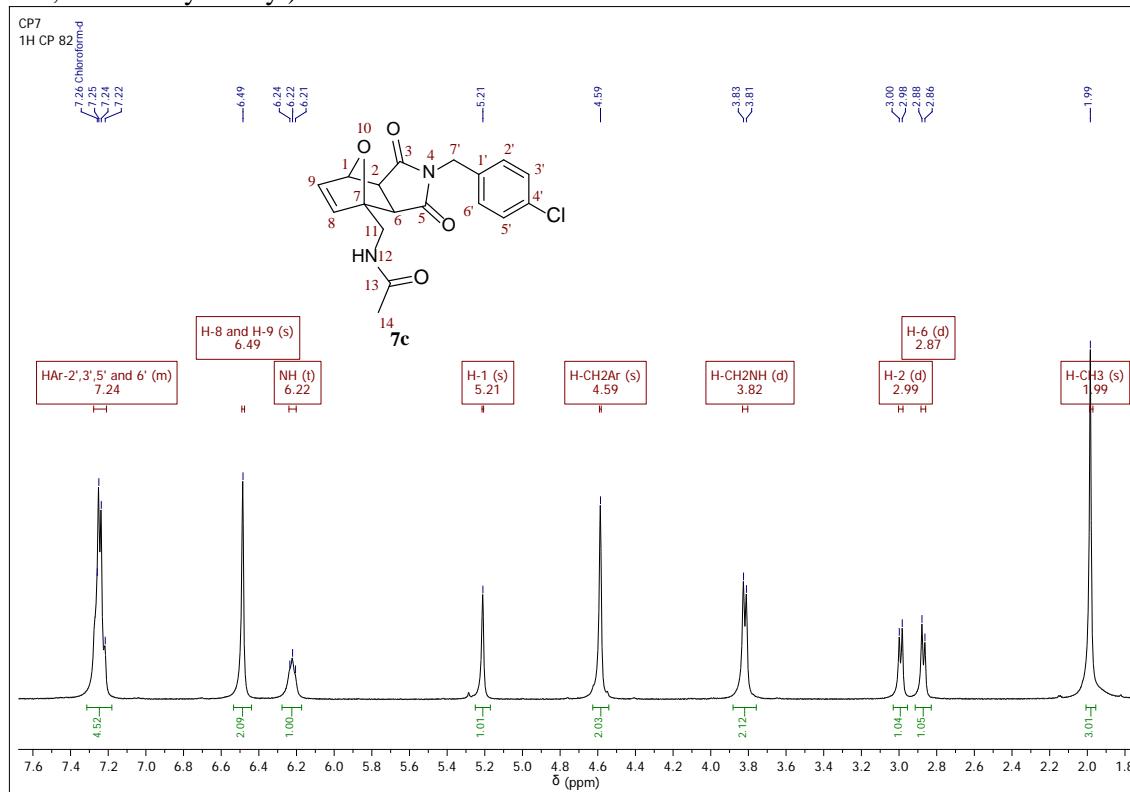


Figure SI67. ¹H-NMR spectrum of *N*-(4-(4-chlorobenzyl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decane-8-ene-3,5-dione-7-ylmethyl)acetamide **7c**.



H₃BO₃-Catalyzed the Unexpected Synthesis of 7-Oxa-2-azabicycles Electr. Supporting Information

Figure SI68. ¹³C-NMR spectrum of *N*-(4-(4-chlorobenzyl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decane-8-ene-3,5-dione-7-ylmethyl)acetamide **7c**.

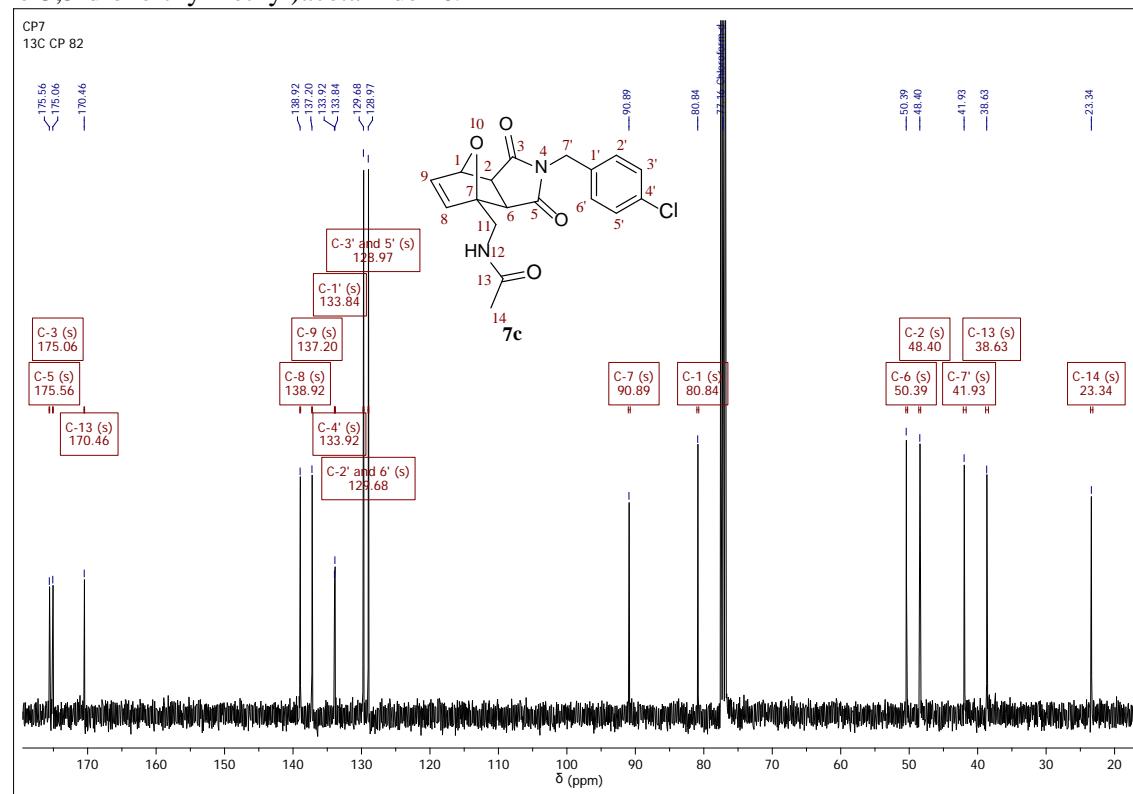


Figure SI69. DEPT-135 spectrum of *N*-(4-(4-chlorobenzyl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]decane-8-ene-3,5-dione-7-ylmethyl)acetamide **7c**.

