SUPPORTING INFORMATION

High Throughput Mechanochemistry: Application to Parallel Synthesis of Benzoxazines.

Katia Martina,[1] Laura Rotolo,[1] Andrea Porcheddu,[2] Francesco Delogu,[3] Stephen R. Bysouth,[4] Giancarlo Cravotto,[1,*] Evelina Colacino[1,5]*

[1]Dipartimento di Scienza e Tecnologia del Farmaco, University of Turin, via P. Giuria 9, Turin, 10125, Italy

[2] Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, SS 554 bivio per Sestu, 09028 Monserrato (Ca), Italy

[3] Dipartimento di Ingegneria Meccanica, Chimica, e dei Materiali, Università degli Studi di Cagliari, via Marengo 2, 09123 Cagliari, Italy

[4] Automaxion SARL, L'Auvrairie, 50250 Varenguebec, France

[5] Université de Montpellier, Institut des Biomolécules Max Mousseron (IBMM) UMR5247 CNRS-UM-ENSCM, Université de Montpellier, cc1703, Place Eugène Bataillon, 34095 Montpellier Cedex 05, France

*e-mail : giancarlo.cravotto@unito.it

*e-mail: evelina.colacino@umontpellier.fr

General Remarks and Experimental Procedures

All chemicals were purchased from Sigma-Aldrich (solvents from Carlo Erba SpA) and used without further purification. Reactions were monitored by TLC on Merck 60 F254 (0.25 mm) plates, which were visualized by UV inspection and/or by heating after a spraying with 5% H_2SO_4 in ethanol or phosphomolybdic acid. Merck silica gel was used for column chromatography (CC). NMR spectra were recorded on a NMR Jeol ECZ-R (600 MHz and 150 MHz for ^1H and ^{13}C, respectively) at 25 °C. Chemical shifts (δ) of ^1H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) relative to residual solvent signals ($CHCl_3$ in $CDCl_3$: $\delta = 7.26$ ppm for ^1H and $CDCl_3$: $\delta = 77.04$ ppm for ^{13}C NMR), *J* values are given in Hz. The ball-milling experiments were performed in Automaxion single position P6 mill at 550 rpm, using 8- or 12-multiposition jars hosting 20 mL (with 60 glass balls 3 mm ∅ in each vial) and 2 mL glass vials (with 60 stainless steel beads 1 mm ∅ in each vial) respectively. For the preparation of compound **1** and **2**, the ball-milling experiments were performed in a MM400 vibrational ball mill (Retsch GmbH, Haan, Germany) using 5 mL stainless steel jar (2 stainless steel balls, 5 mm Ø) or a PM100 planetary mill (Retsch GmbH, Haan, Germany) using a 45 mL zirconia jar (11 zirconia balls, 12 mm Ø). GC–MS analyses were performed in a GC Agilent 6890 (Agilent Technologies, USA) that was fitted with a mass detector Agilent Network 5973, using a 40 m long capillary column, i.d. of 0.25 mm and film thickness 0.25 μm (MEGA-MS). GC conditions were: injection split 1:20, injector temperature 250 °C, detector temperature 280 °C. Gas carrier: helium (1.2 mL/min), temperature program: from 50 °C (3 min) to 300 °C at 10 °C/min. Compounds **1-7**, **11** and **13** display the same spectral characteristics of previously reported structures in the literature (see Table 1 for references). Each compound was prepared twice: the reaction scale was 0.531 mmol for 2 mL glass vials and 3.186 mmol for 20 mL glass vials.

General procedure for the mechanochemical synthesis of compounds 1-14 (Scheme 1 and Table 1). The alcohol (1.0 equiv), the amine (1.0 equiv) and paraformaldehyde (4.0 equiv) were added to a 2 mL glass vials containing 60 stainless steel balls (Ø 1 mm). The vial was placed in a 12 position-jar and the reactants were milled at 550 rpm for 4 hours, till complete conversion of starting materials (TLC: *c*-Hex/AcOEt 98:2 v/v). The crude was recovered by $CHCl_3$ (15 mL) and washed with aqueous KOH 3M (15 mL). The organic layer was washed three times with water, dried over anhydrous $MgSO_4$ and concentrated. The crude compounds **1-14** were purified by column chromatography (linear gradient of EtOAc in cyclohexane: 0-1%). A 8 position-jar was used to perform the reaction in a 20 mL glass vials, (with 60 glass balls 3 mm ∅ in each vial). Only for the preparation of compound **3**, HO-PEG-2000-OH (450 mg/mmol of substrate) was used as additive.[1]

General procedure for the synthesis of compounds 6 and 7 under conventional conditions (Scheme 1 and Table 1). To a solution of the aniline (11 mmol) in chloroform, paraformaldehyde (0.66 g, 22 mol) was added and stirred for 15 min at 0 °C. Subsequently, 55 mmol of phenol or 2-allyl phenol were added to the reaction mixture and stirred overnight at 60 °C. After completion of the reaction, it was extracted with ethyl acetate and washed with 2 N NaOH, water, brine and the organic layer concentrated to yield pale yellow liquid**.** The crude compounds were purified by column chromatography (linear gradient of EtOAc in cyclohexane: 0-1%).

Synthesis of compounds 14 under conventional conditions (Scheme 1 and Table 1). To a solution of the *p*-methoxy aniline (11 mmol) in toluene, paraformaldehyde (0.66 g, 22 mol) was added and stirred for 15 min at 0 °C. Subsequently, 55 mmol of 2-allyl phenol were added and the 50 mL two-necked flask connected to a Dean-Stark apparatus. The reaction mixture was brought to reflux and left under stirring for 5 hrs. After completion of the reaction, it was extracted with ethyl acetate and washed with 2 N NaOH, water, brine and the organic layer concentrated to yield pale yellow liquid. The crude compounds were purified by column chromatography (linear gradient of EtOAc in cyclohexane: 0-1%).

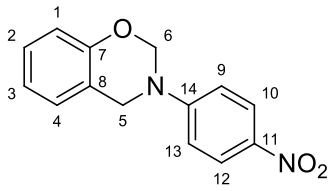
a)

b)

c)

Figure S1. 4-slot milling for a) 4-position jars with 200 mL glass vials; b) 8-position jars with 20 mL glass vials; 4-position jars with polyethylene (HDPE) vials c) (Pictures were kindly provided by Automaxion, www.automaxionltd.com).

3,4-Dihydro-3-(4-nitrophenyl)-1,3-*2H*-benzoxazine, 1 (Scheme 1 and Table 1). CAS [117483-13-3][2]



Yellow powder (61 mg, 45%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 4.74 (s, 2 H), 5.41 (s, 2 H), 6.86 (d, J = 8 *Hz*, 1 H), 6.93 - 6.96 (t, J = 8 *Hz*, 1 H), 7.06 (m, 3 H), 7.13 (t, J = 8 *Hz*, 1 H), 8.16 (d, J =9.31 *Hz*, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$)[2] δ (ppm): 49.51 (C-5), 78.59 (C-6), 115.08 (C-9, C-13), 117.31 (C-1), 120.13 (C-8), 121.61 (C-3), 125.85 (C-10, C-12), 126.77 (C-4), 128.36 (C-2), 140.43 (C-11), 152.92 (C-14), 154.03 (C-7); **GC-MS** (EI), *m/z* calcd for $C_{14}H_{12}N_2O_3$ 256.08 found 256, 150, 134, 120, 106, 78, 51, 39; R_t = 32.615 min

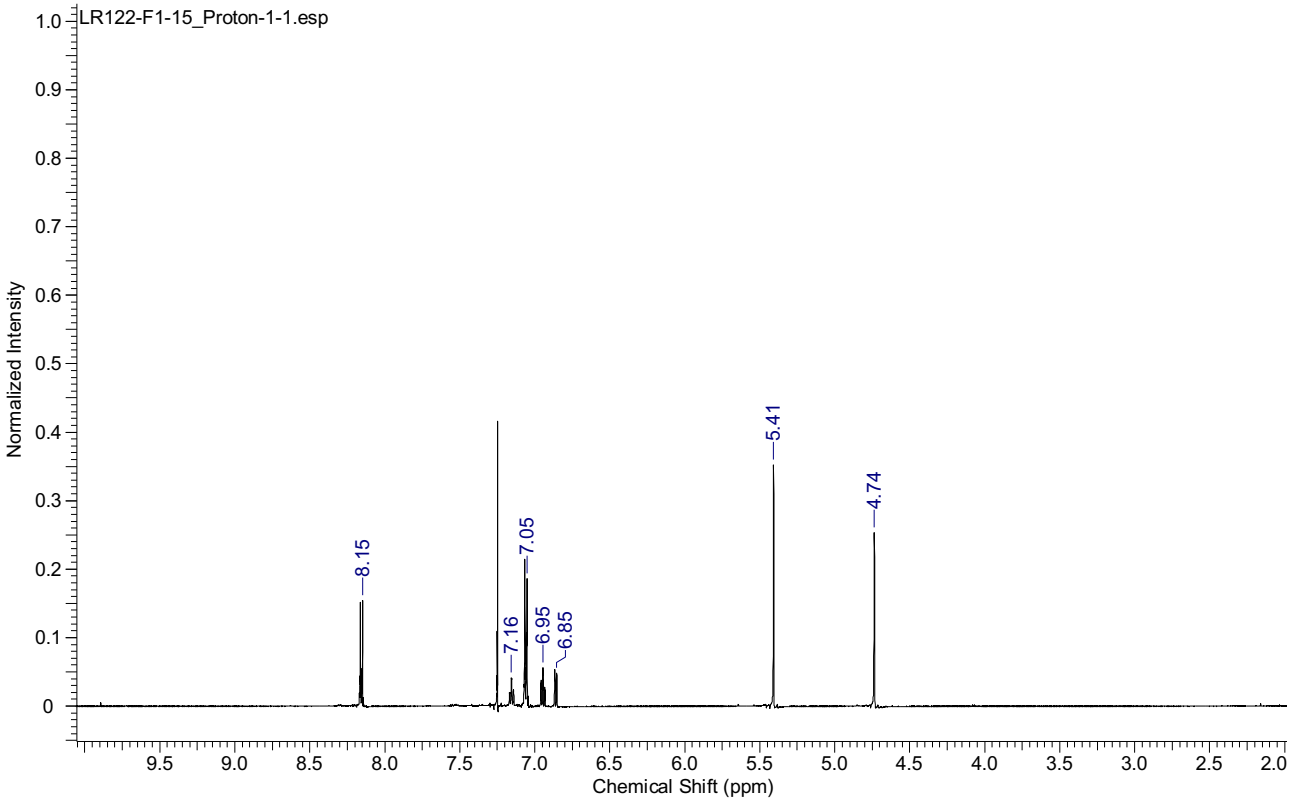


Figure S2. [1]H NMR of 3,4-Dihydro-3-(4-nitrophenyl)-1,3-*2H*-benzoxazine **1**

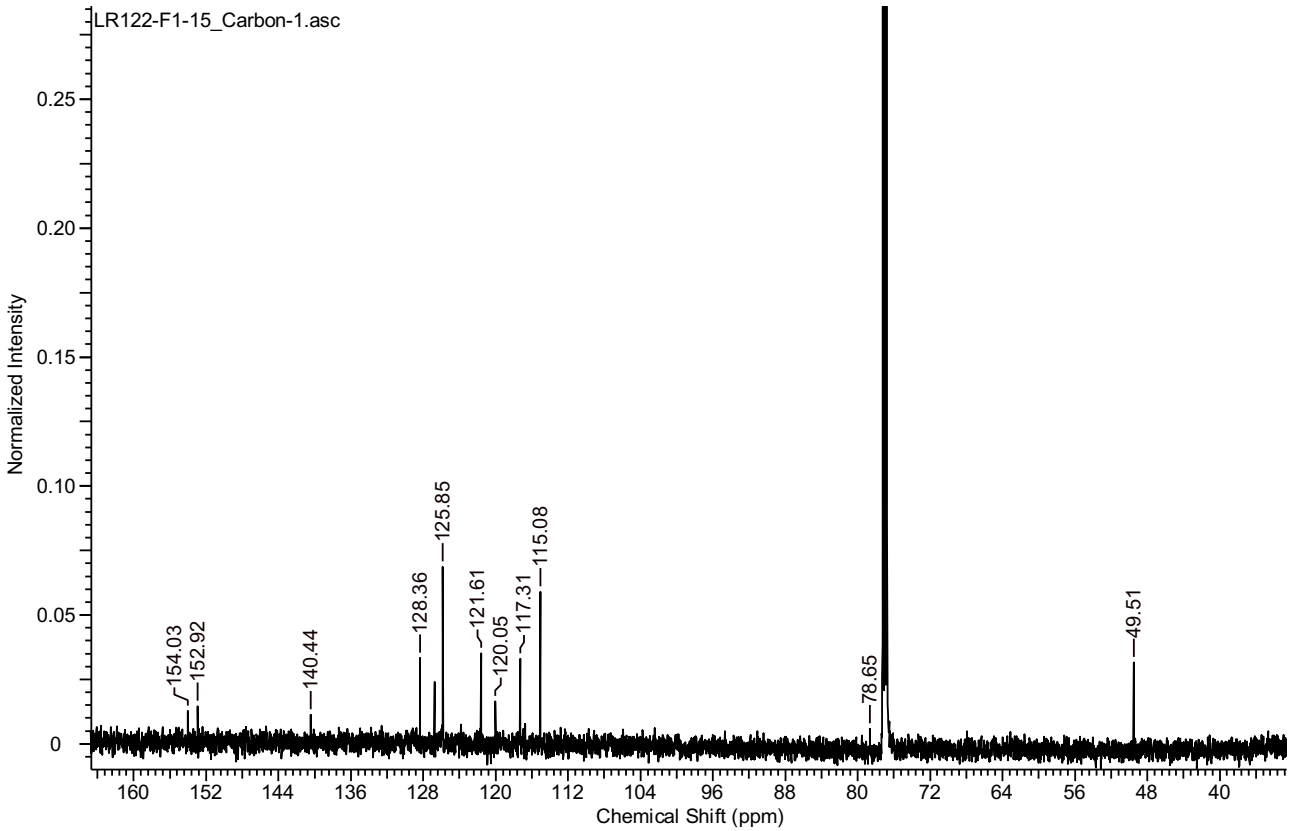


Figure S3. ^{13}C NMR of 3,4-Dihydro-3-(4-nitrophenyl)-1,3-*2H*-benzoxazine, **1**

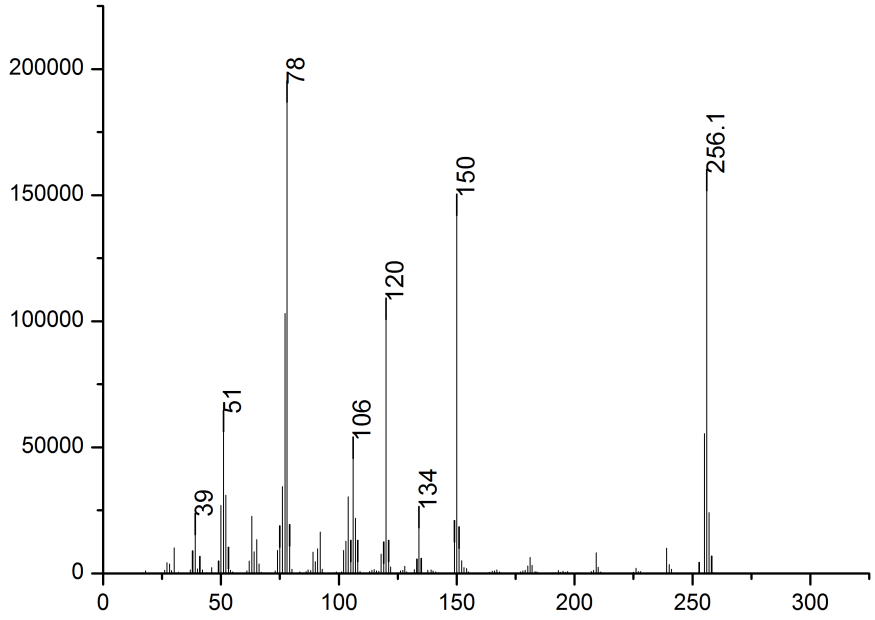
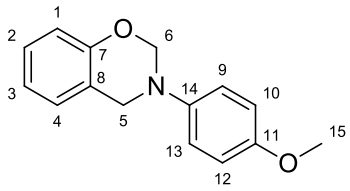


Figure S4. MS (EI) of 3,4-Dihydro-3-(4-nitrophenyl)-1,3-*2H*-benzoxazine, **1**

3,4-Dihydro-3-(4-methoxyphenyl)-1,3-*2H*-benzoxazine, 2 (Scheme 1 and Table 1) CAS [51892-02-5][2, 3]



White powder (83 mg, 65%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 3.73 (s, 3 H, H-15), 4.54 (s, 2 H, CH_2-5) 5.28 (s, 2 H, CH_2-6) 6.80 (m, 3 H, CH-10, CH-12, CH-1), 6.88 (t, J = 8 *Hz*, 1 H, CH-3), 6.99 (d, J = 8 *Hz*, 1 H, CH), 7.07 (d, J = 9 Hz, 2 H), 7.11 (t, J = 8 Hz, 1 H); **^{13}C NMR** (150 MHz, $CDCl_3$)[2] δ (ppm): 51.20 (C-15), 55.57 (C-5), 80.81 (C-6), 114.57 (C-9, C-13), 116.92 (C-1), 120.82 (C-12, C-10), 120.84 (C-3), 120.98 (C-8), 126.81 (C-2), 127.91 (C-4), 142.42 (C-14), 154.43 (C-11) 155.05 (C-7); **GC-MS** (EI), *m/z* calcd for $C_{15}H_{15}NO_2$ 241,11 found 241, 135, 120, 92, 78, 65, 51, 39. R_t = 29.182 min

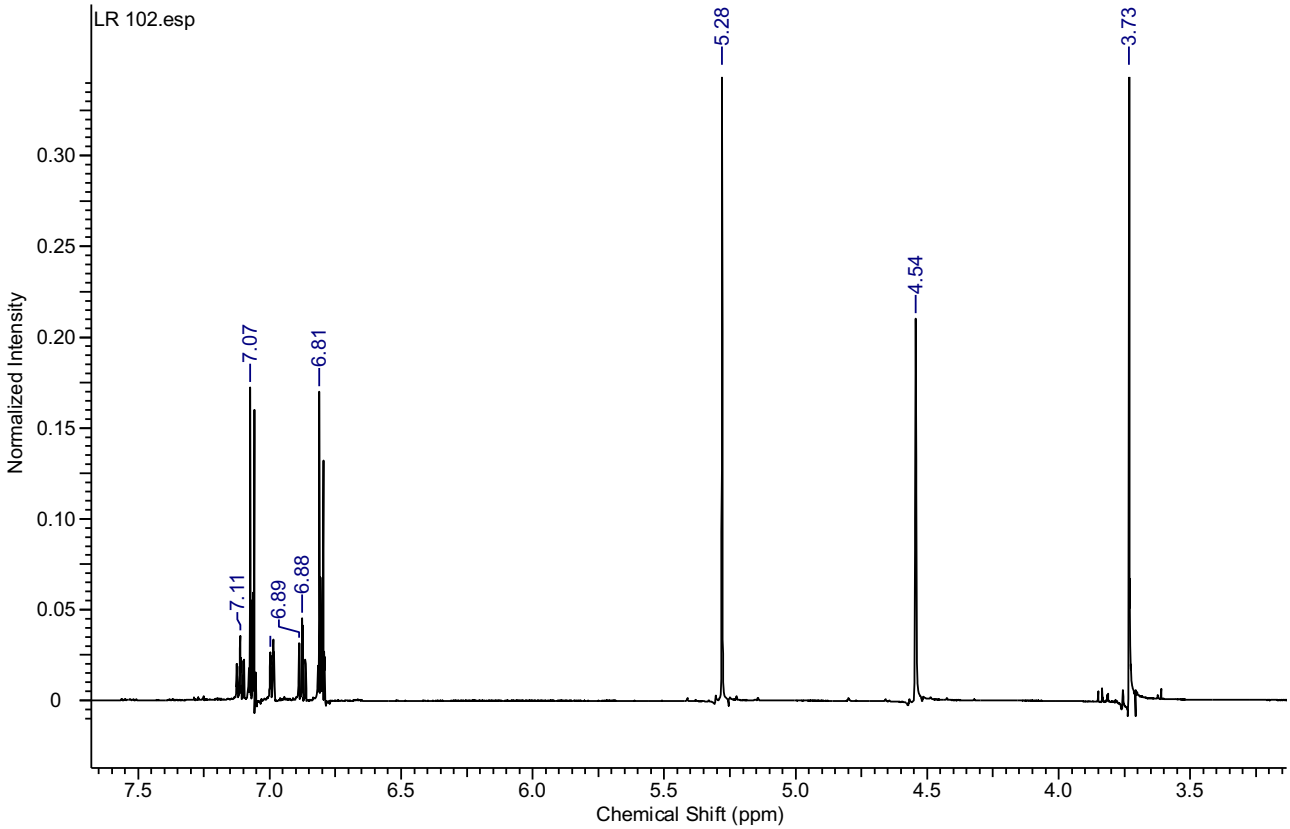


Figure S5. ^{1}H NMR of 3,4-Dihydro-3-(4-methoxyphenyl)-1,3,2H-benzoxazine, **2**

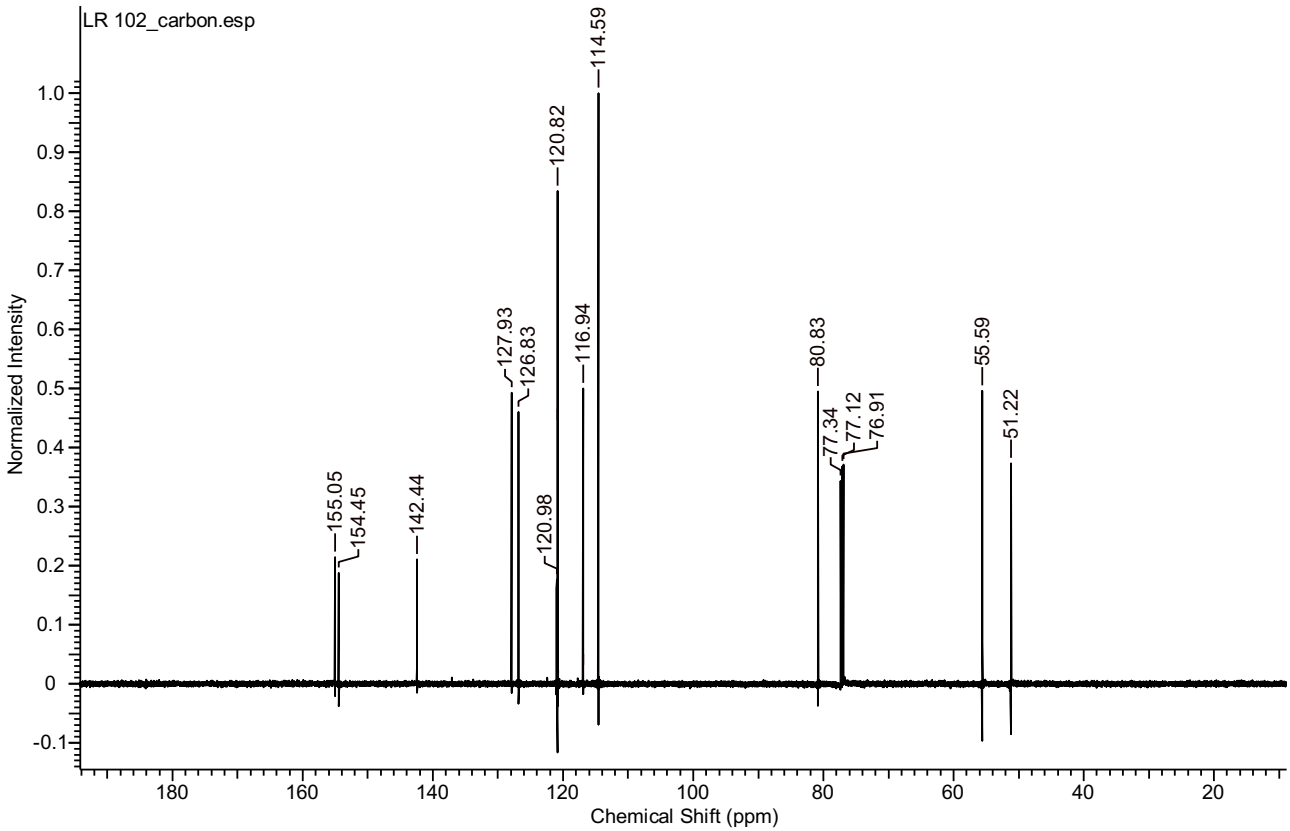


Figure S6. ^{13}C NMR of 3,4-Dihydro-3-(4-methoxyphenyl)-1,3-*2H*-benzoxazine, **2**

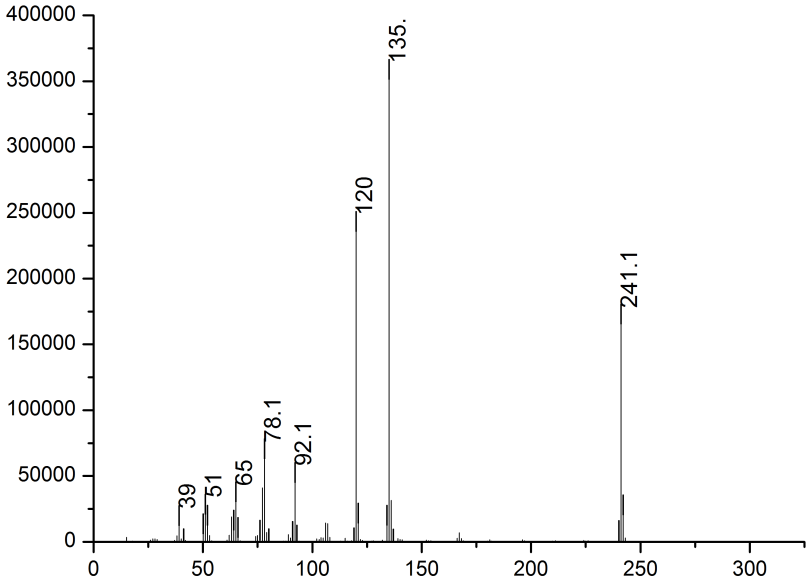
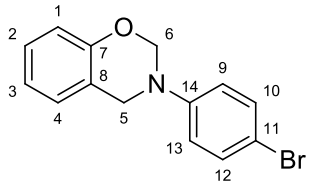


Figure S7. MS (EI) of 3,4-Dihydro-3-(4-methoxyphenyl)-1,3-*2H*-benzoxazine, **2**

3,4-Dihydro-3-(4-bromophenyl)-1,3-*2H*-benzoxazine, 3 (Scheme 1 and Table 1) CAS [100542-25-4][3, 4]



White powder (102 mg, 67%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 4.61 (s, 2 H, PhC$\underline{H_2}$N), 5.33 (s, 2 H, NC$\underline{H_2}$O), 6.82 (dd, J = 8 *Hz*, 1 H), 6.91 (t, J = 8 *Hz*, 1 H), 6.98 - 7.03 (m, 3 H), 7.13 (t, J = 8 *Hz*, 1 H), 7.37 (d, J = 9 *Hz*, 2 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 50.55 (C-5), 79.19 (C-6), 113.99 (C-11), 116.92 (C-1), 119.97 (C-9, C-13), 120.56 (C-8), 120.99 (C-3), 126.71 (C-4) 128,04 (C-2) 132.1 (C-10, C12), 147.47 (C-14), 154.14 (C-7); **GC-MS** (EI), *m/z* calcd for $C_{14}H_{12}BrNO$ 289.01 found 289, 183, 154, 78, 51, 39; R_t = 30.089 min

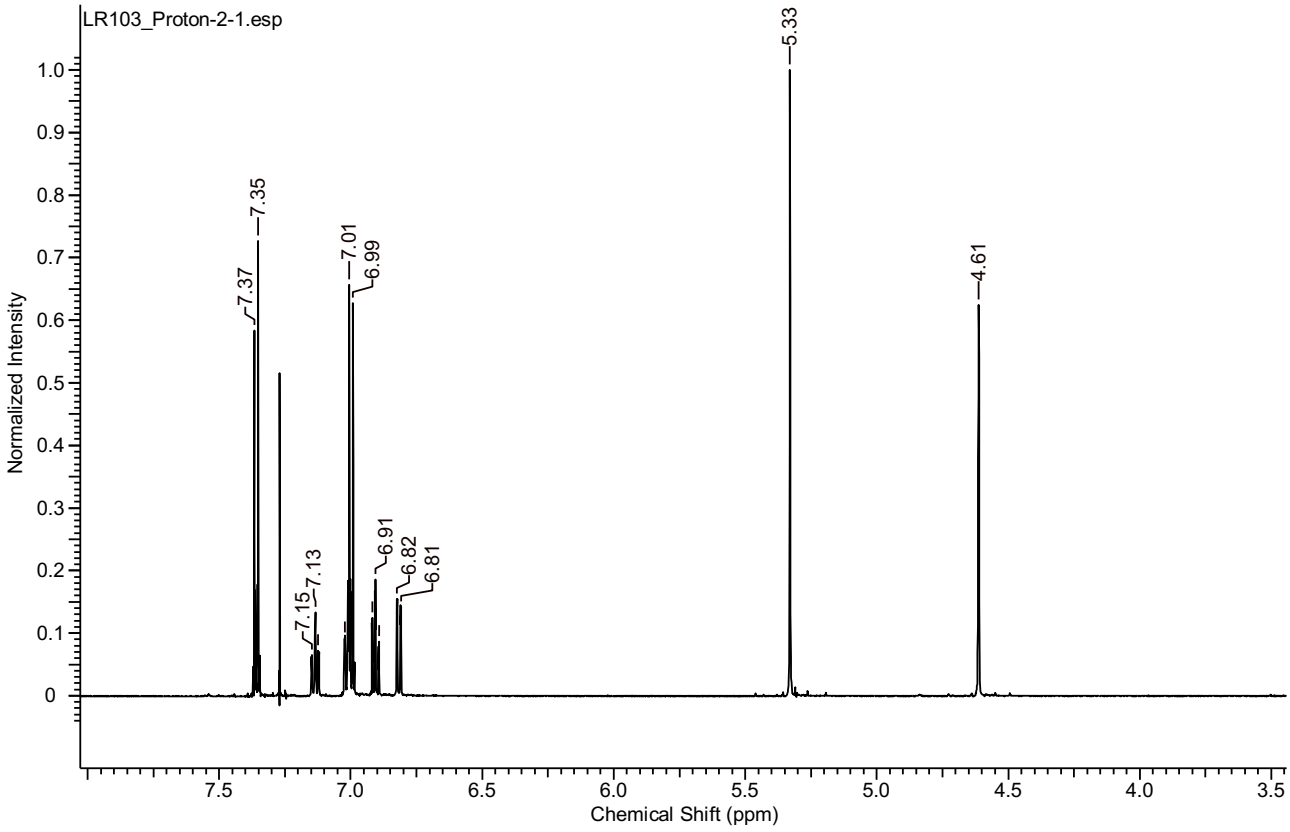


Figure S8. [1] H NMR of 3,4-Dihydro-3-(4-bromophenyl)-1,3-*2H*-benzoxazine, **3**

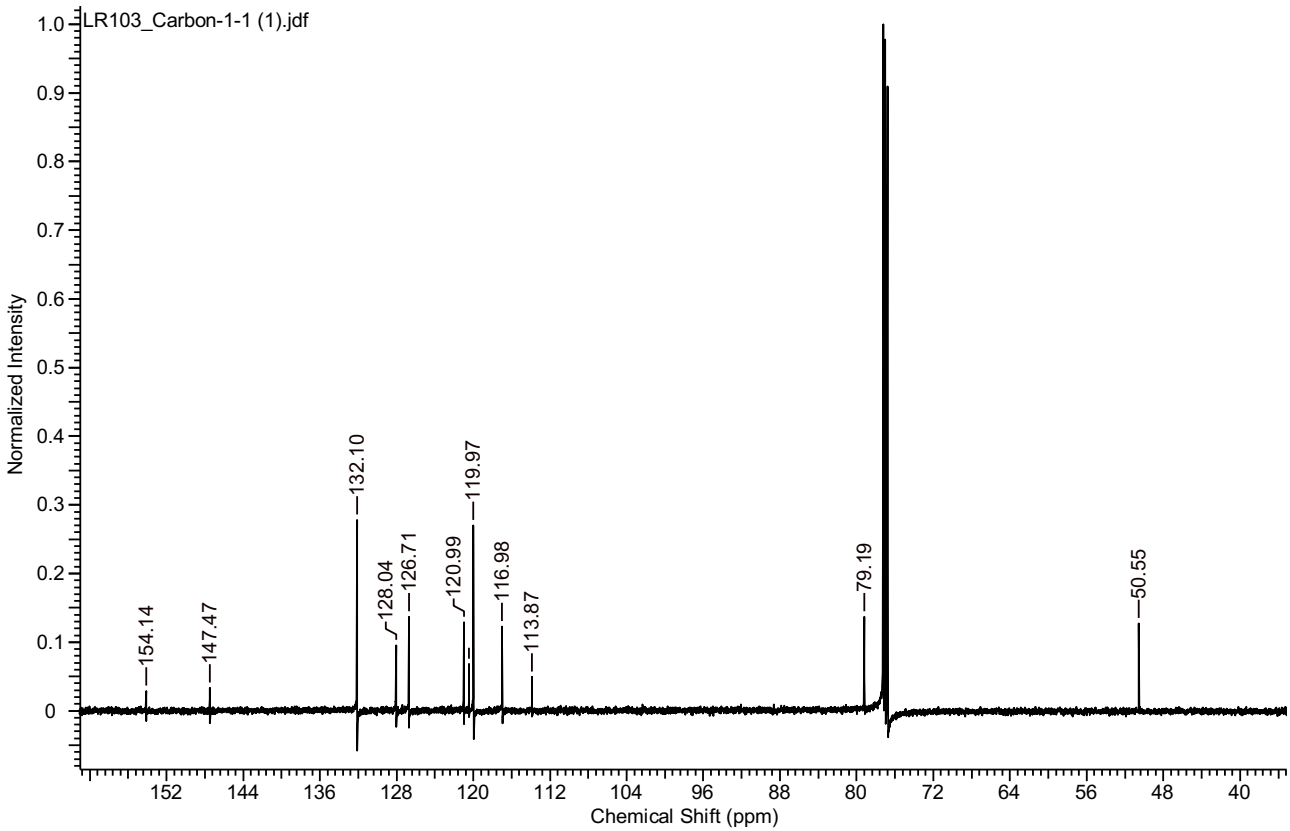


Figure S9. ^{13}C **NMR** of 3,4-Dihydro-3-(4-bromophenyl)-1,3-*2H*-benzoxazine, **3**

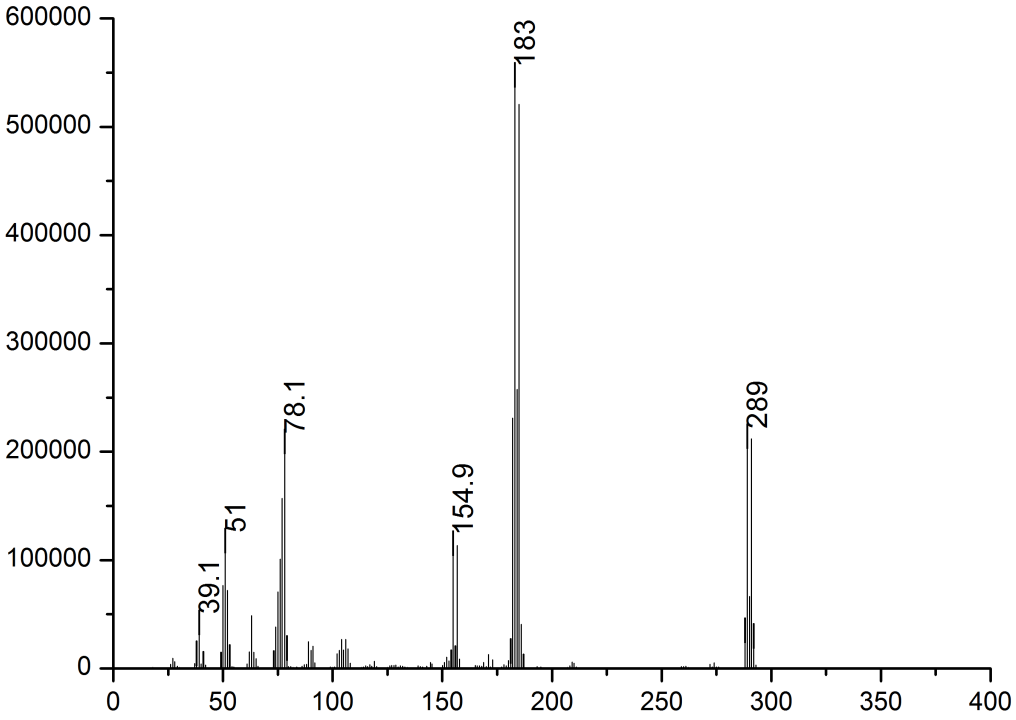
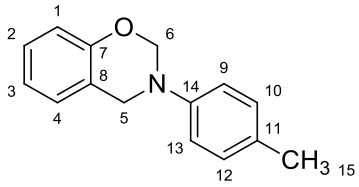


Figure S10. MS (EI) of 3,4-Dihydro-3-(4-bromophenyl)-1,3-*2H*-benzoxazine, **3**

3,4-Dihydro-3-(4-tolyl)-1,3-*2H*-benzoxazine, 4 (Scheme 1 and Table 1) CAS [51891-99-7][2, 3]



Yellow-orange powder (78 mg, 65%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 2.26 (s, 3H), 4.60 (s, 2 H), 5.33 (s, 2H), 6.80 (dd, *J* = 8 *Hz*, 1 *Hz*, 1H), 6.88 (td, *J* = 8 *Hz*, 1 *Hz*, 1H), 6.99 - 7.03 (m, 3H), 7.06 (d, *J* = 9 *Hz*, 2H), 7.11 (td, *J* = 8 *Hz*, 1 *Hz*, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$)[2] δ (ppm): 20.53 (C-15), 50.63 (C-5), 80.02 (C-6), 116.90 (C-1), 118.71 (C-9, C-13), 120.79 (C-3), 126.73 (C-4), 127.84 (C-2), 129.79 (C-10, C-12) 131.28 (C-11), 145.89 (C-14), 154.27 (C-7); **GC-MS** (EI), *m/z* calcd for $C_{15}H_{15}NO$ 225.29 found 225, 119, 91, 78, 65, 51, 39. R_t = 27.8 min

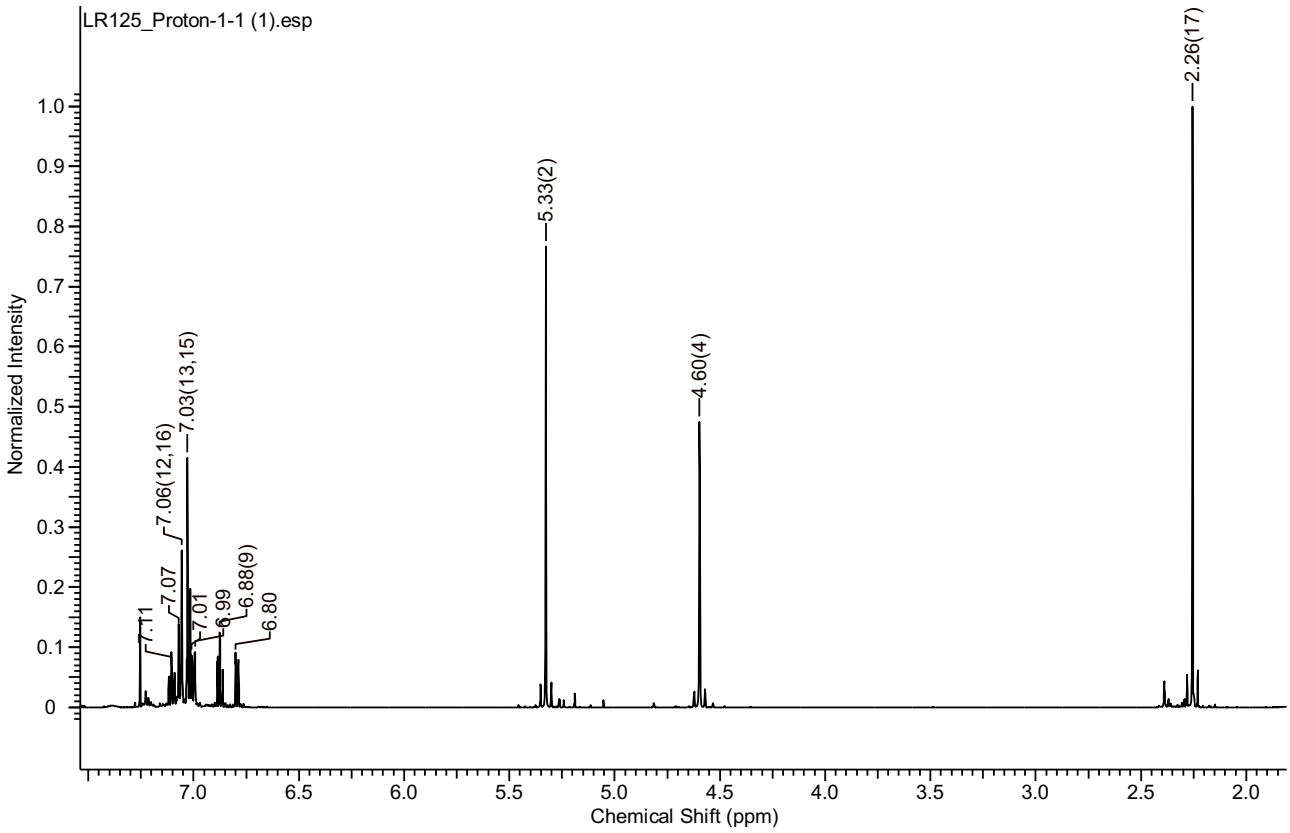


Figure S11. [1]H NMR of 3,4-dihydro-3-(4-tolyl)-1,3-*2H*-benzoxazine, **4**

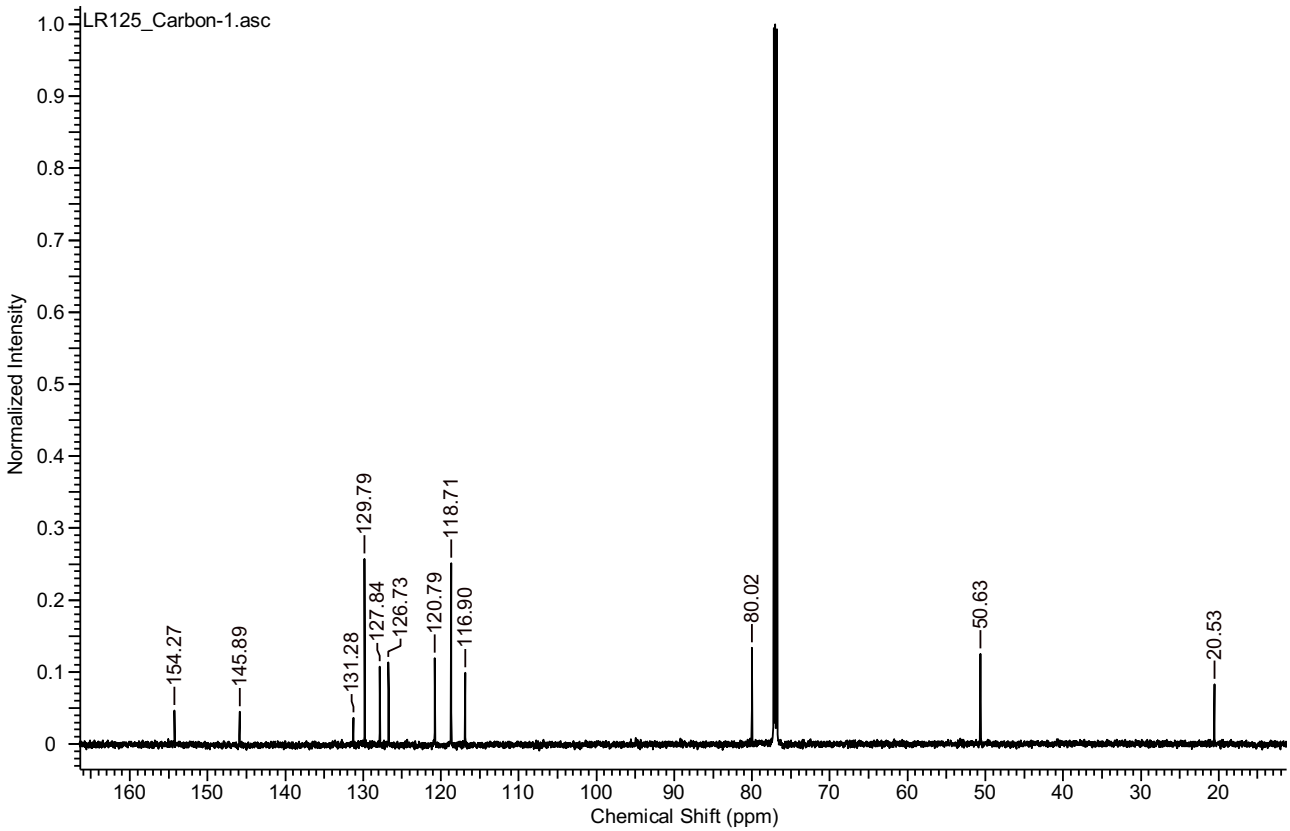


Figure S12. ^{13}C NMR of 3,4-dihydro-3-(4-tolyl)-1,3-*2H*-benzoxazine, **4**

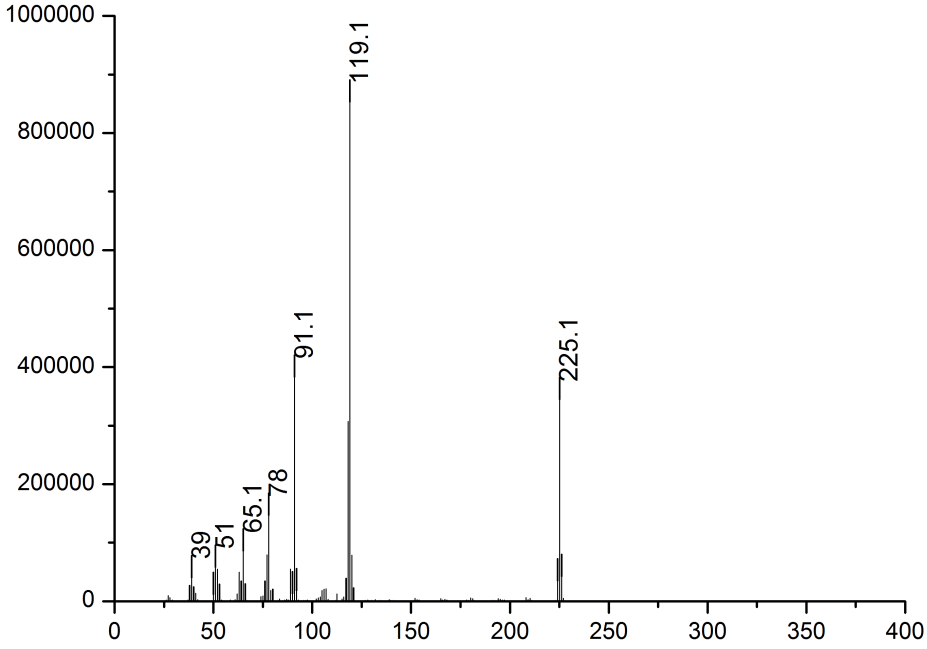
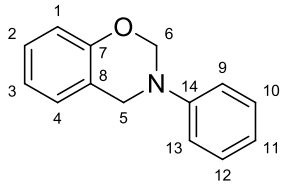


Figure S13. MS (EI) of 3,4-dihydro-3-(4-tolyl)-1,3-*2H*-benzoxazine, **4**

3,4-Dihydro-3-phenyl-1,3-*2H*-benzoxazine, 5 (Scheme 1 and Table 1) CAS [51287-17-3][2, 3]



Yellow oil (81 mg, 73%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 4.64 (s, 2 H), 5.37 (s, 2H), 6.81 (dd, J = 7.4 *Hz*, 1 *Hz*, 1H), 6.89 (td, J = 6.9 *Hz*, 1.3 *Hz*, 1H), 6.94 (tt, J = 7.4 *Hz*, 1.3 *Hz*, 1H), 7.02 (d, J = 7.7 *Hz*, 1H), 7.11-7.13 (m, 3H), 7.26-7.29 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$)[2] δ (ppm): 50.39 (C-5), 79.44 (C-6), 116.93 (C-1), 118.24 (C-9, C-13), 120.78 (C-11), 120.87 (C-8) 121.41 (C-3), 126.71 (C-4), 127.83 (C-2), 129.25 (C-10, C-12) 148.37 (C-14), 154.27 (C-7); **GC-MS** (EI), *m/z* calcd for $C_{14}H_{13}NO$ 211.26 found 211, 105, 77, 51, 39; R_f= 26.778 min

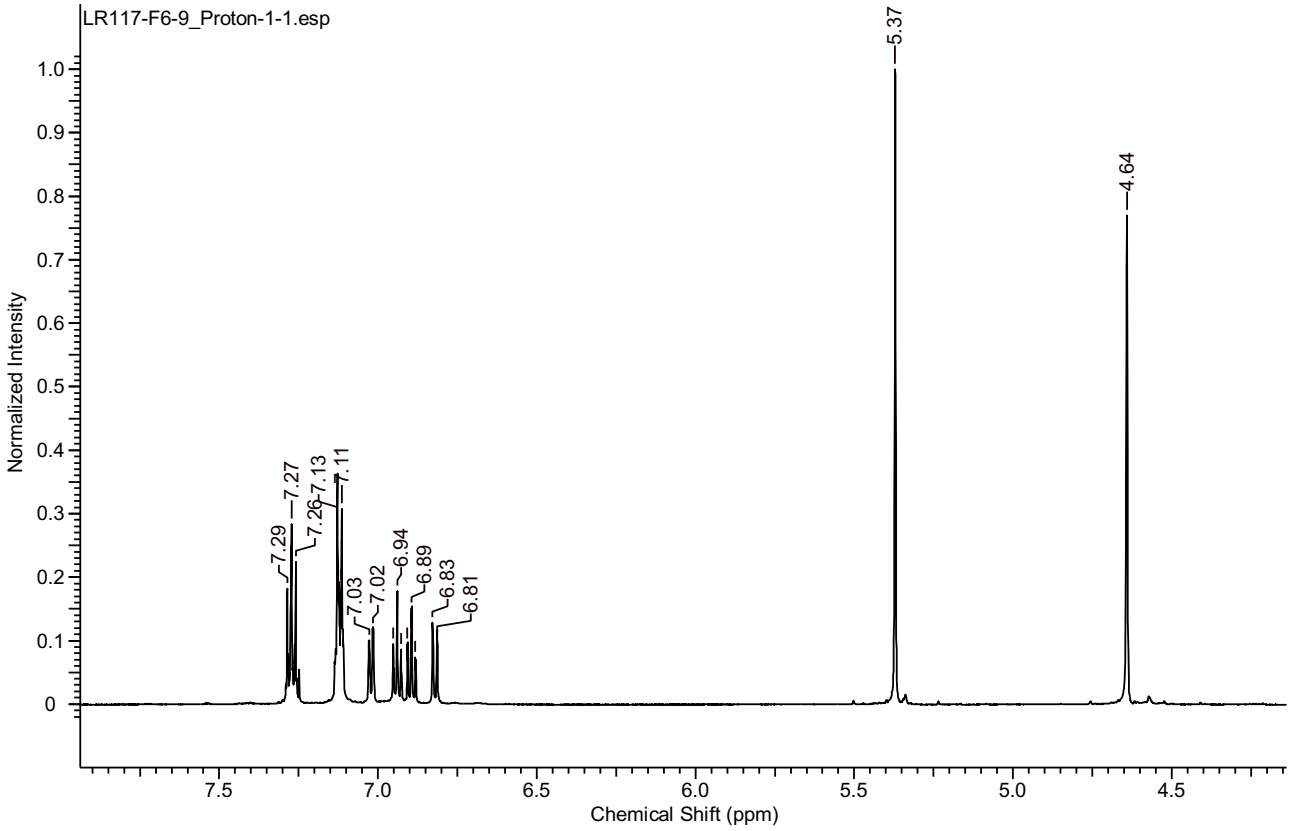


Figure S14. ^{1}H NMR of 3,4-dihydro-3-phenyl-1,3-*2H*-benzoxazine, **5**

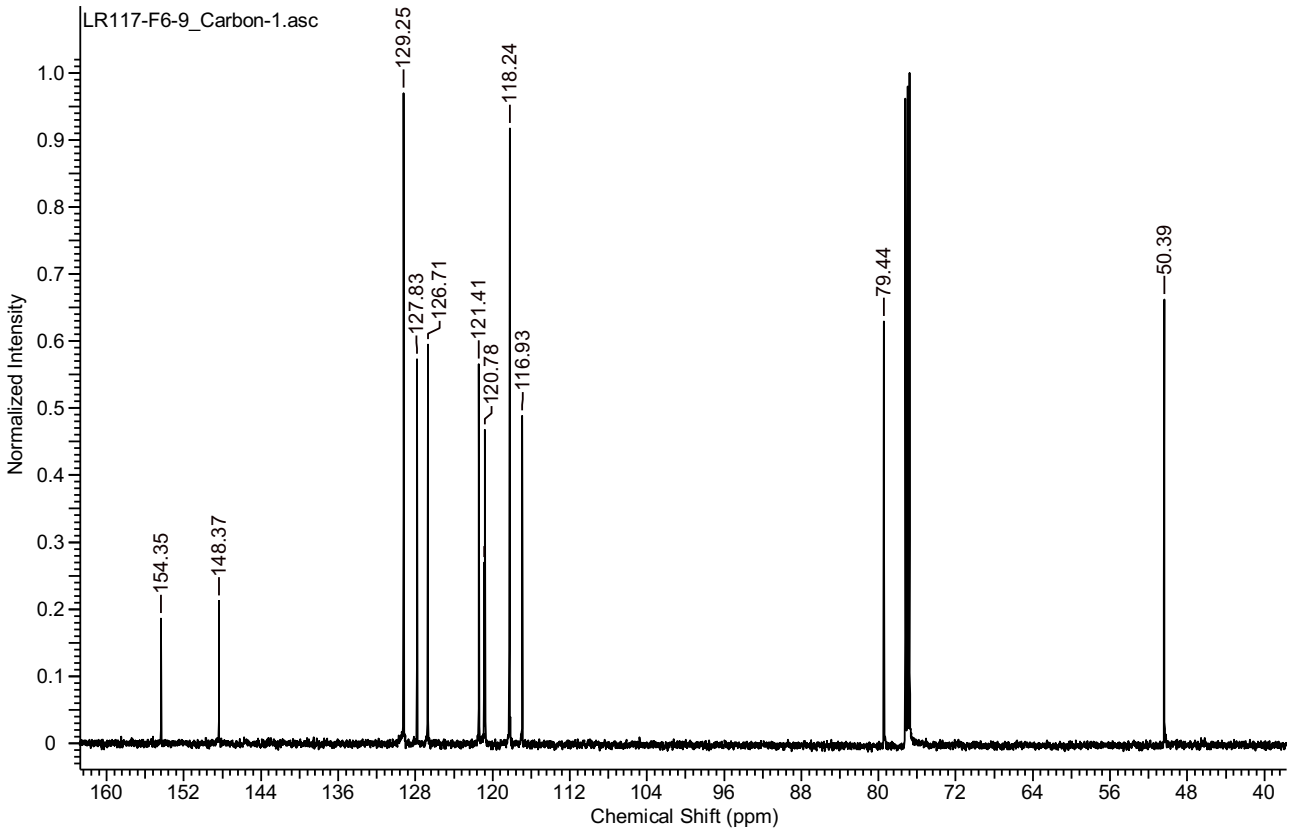


Figure S15. ^{13}C NMR of 3,4-dihydro-3-phenyl-1,3-*2H*-benzoxazine, **5**

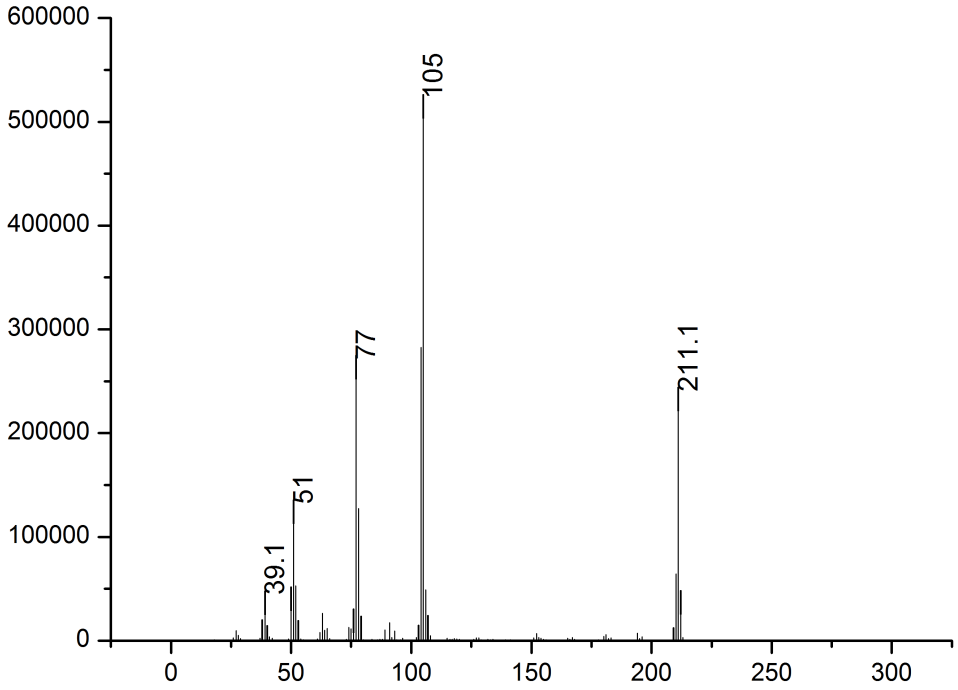
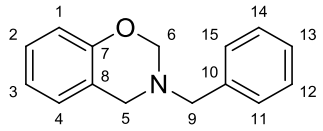


Figure S16. MS (EI) of 3,4-dihydro-3-phenyl-1,3-*2H*-benzoxazine, **5**

3,4-Dihydro-3-benzyl-1,3-*2H*-benzoxazine, 6 (Scheme 1 and Table 1) CAS [128707-70-0][2]



White powder (90 mg, 75%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 3.93 (s, 2H), 3.97 (s, 2H), 4.88 (s, 2H), 6.82 (d, J = 8.3 *Hz*, 1H), 6.87 (td, J = 7.6 *Hz*, J = 14.3 *Hz*, 1H), 6.92 (d, J = 7.6 *Hz*, 1H), 7.14 (t, J = 7.6 *Hz*, 1H), 7.27-7.3 (m, 1H), 7.34-7.37 (m, 4H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 49.70 (C-5), 55.62 (C-9), 82.26 (C-6), 116.53 (C-1), 120.03 (C-8), 120.76 (C-3), 127.5 (C-2), 127.77 (C-4), 127.71 (C-13), 128.56 (C-14, C12), 129.08 (C-11, C15), 138.15 (C-10), 154.19 (C-7). **GC-MS** (EI), *m/z* calcd for $C_{15}H_{15}NO$ 225.29 found 225, 134, 118, 107, 91, 78, 65, 51, 39 R_t = 27.008 min.

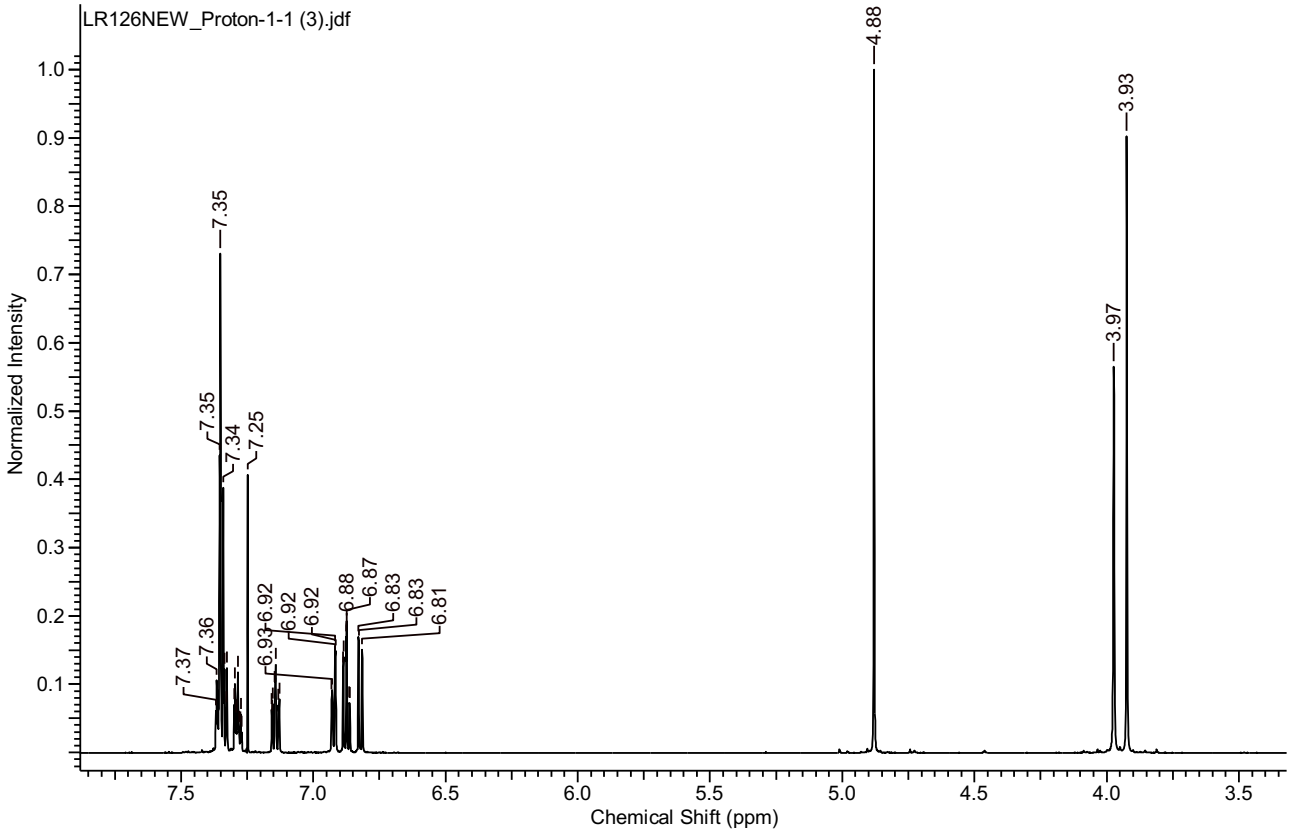


Figure S17. [1]H NMR of 3,4-dihydro-3-benzyl-1,3-*2H*-benzoxazine, **6**

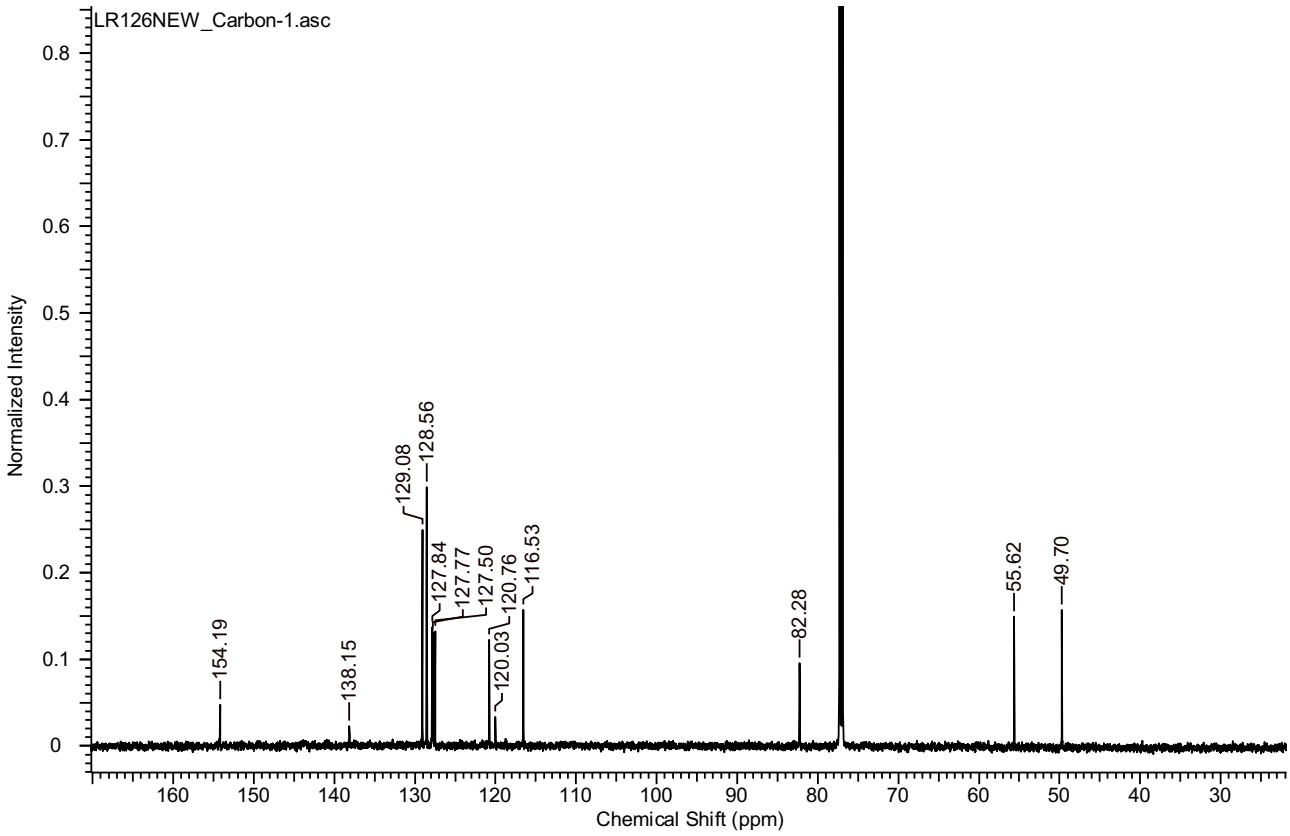


Figure S18. ^{13}C NMR of 3,4-dihydro-3-benzyl-1,3-*2H*-benzoxazine, **6**

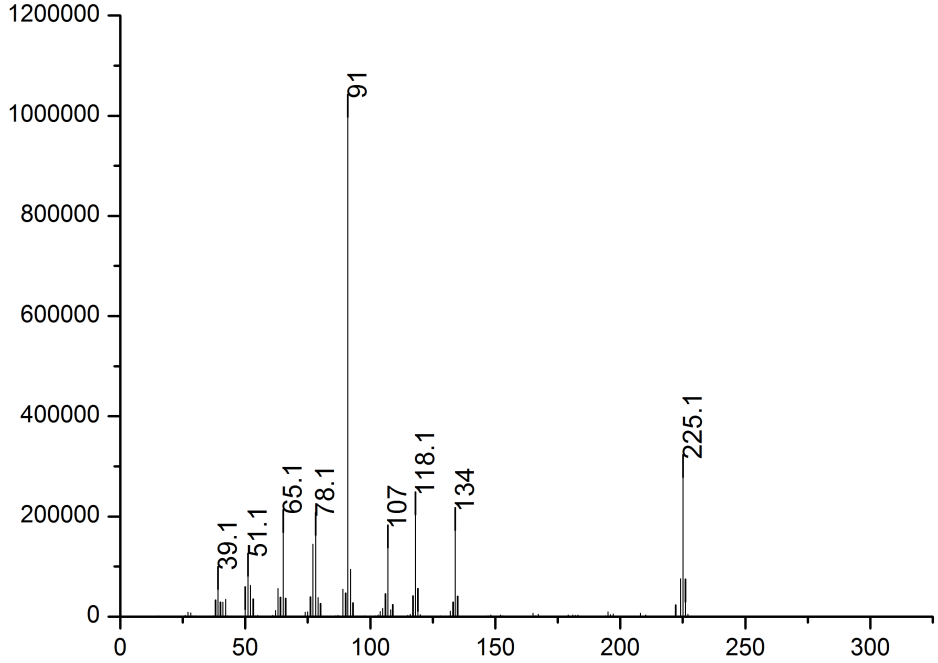
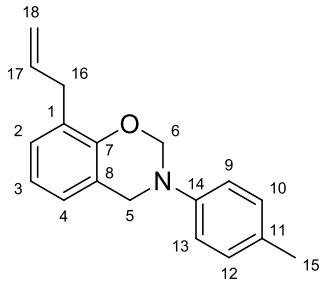


Figure S19. MS (EI) of 3,4-dihydro-3-benzyl-1,3-*2H*-benzoxazine, **6**

3,4-Dihydro-8-allyl-3-(4-tolyl)-1,3-*2H*-benzoxazine, 7 (Scheme 1 and Table 1)



Orange liquid (71 mg, 50%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 2.27 (s, 3H), 3.34 (d, J = 6.5 *Hz*, 2H), 4.59 (s, 2H), 5.02-5.05 (m, 2H), 5.35 (s, 2H), 5.94-6.00 (m, 1H), 6.82 (t, J =7.6 *Hz*, 1H), 6.87 (d, J = 7 *Hz*, 1H), 6.98 (d, J = 7.4 *Hz*, 1H), 7.03 (d, J = 8.4 *Hz*, 2H), 7.07 (d, J = 8.4 *Hz*, 2H).
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 20.5 (C-15), 33.64 (C-16), 50.88 (C-5), 79.80 (C-6), 115.39 (C-18) 118.59 (C-9, C-13), 120.22 (C-3), 120.44 (C-8), 124.72 (C-4), 127.98(C-1) 128.06 (C-2), 129.73 (C-12, C-10), 130.92 (C-11), 136.41 (C-17), 146.16 (C-14), 152.97(C-7); **GC-MS** (EI), *m/z* calcd for $C_{18}H_{19}NO$ 265.15 found 265, 145, 131, 119, 91, 65, 51, 39; R_t = 29.830 min

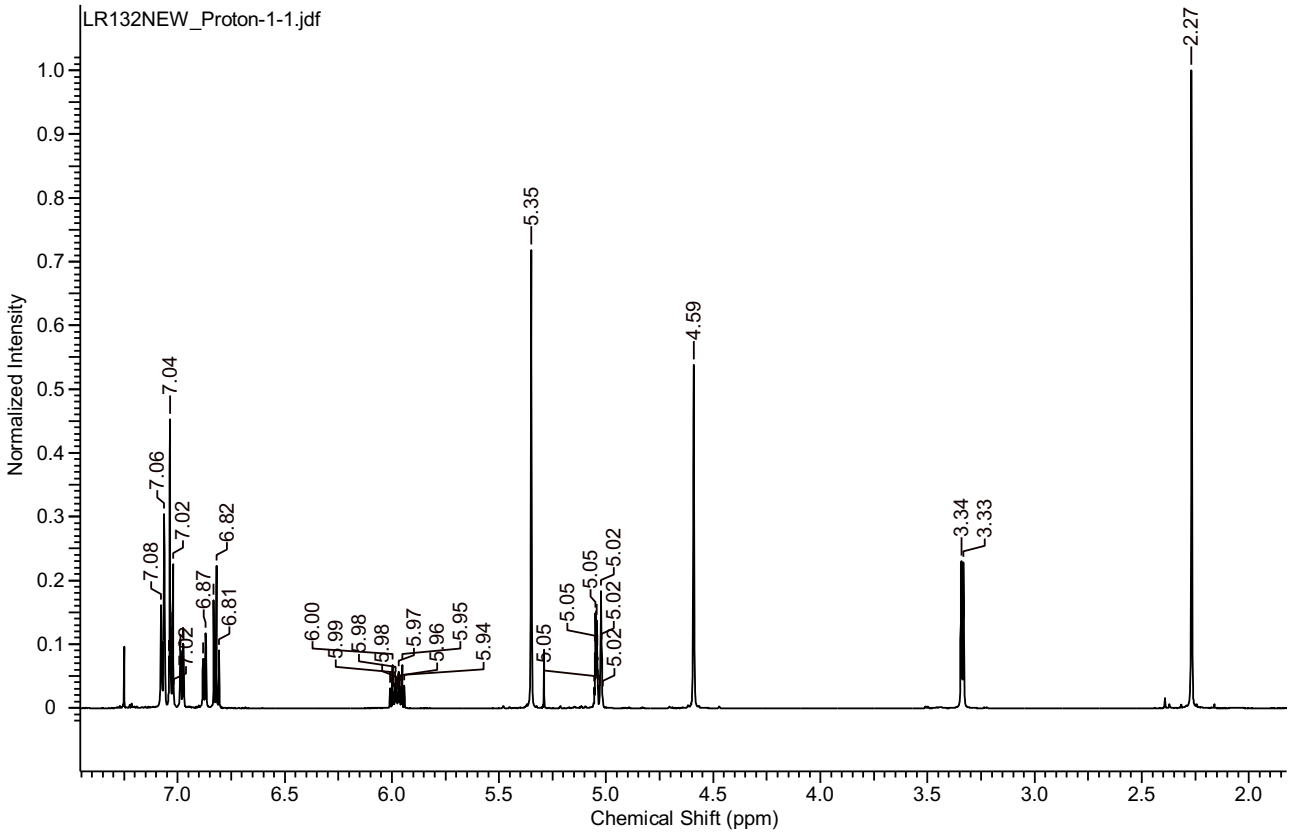


Figure S20. ^{1}H NMR of 3,4-Dihydro-8-allyl-3-(4-tolyl)-1,3-*2H*-benzoxazine, **7**

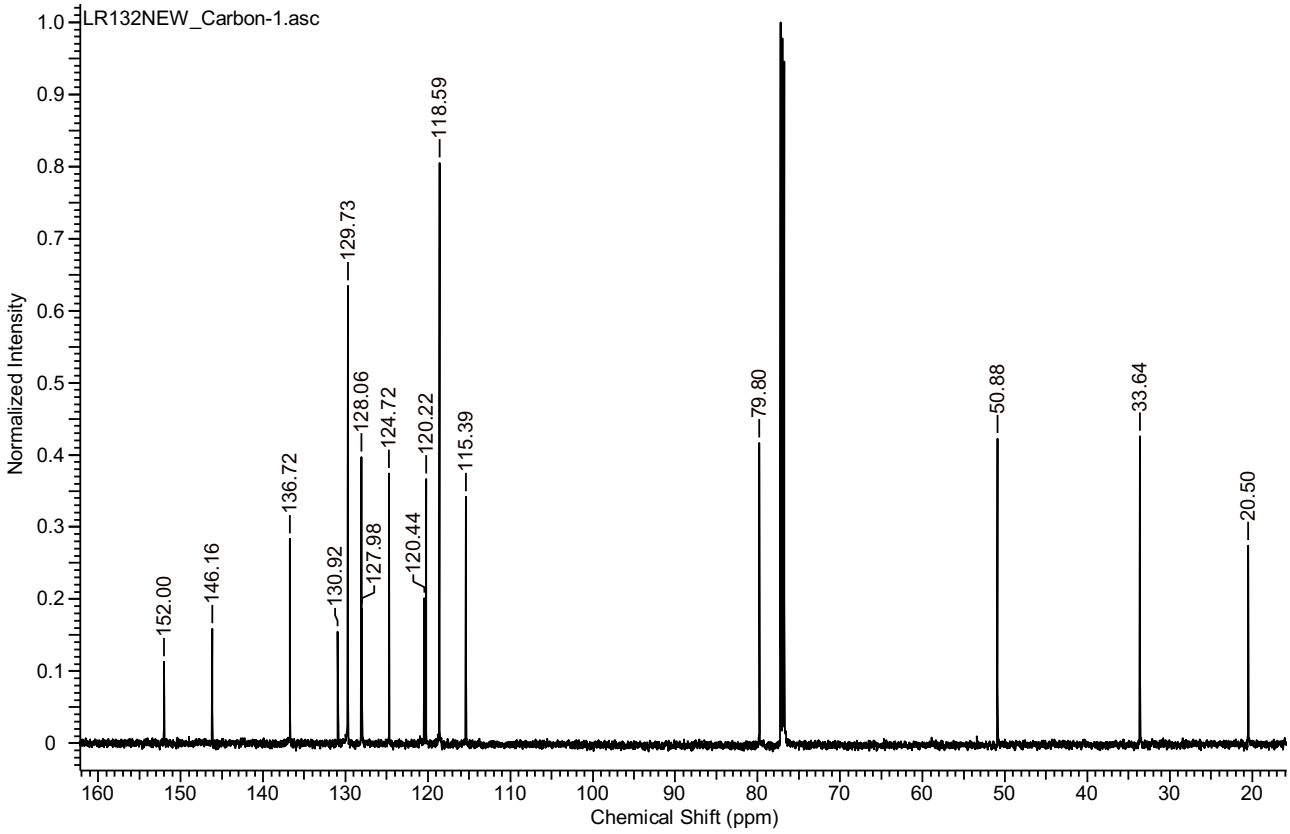


Figure S21. ^{13}C NMR of 3,4-Dihydro-8-allyl-3-(4-tolyl)-1,3-*2H*-benzoxazine, **7**

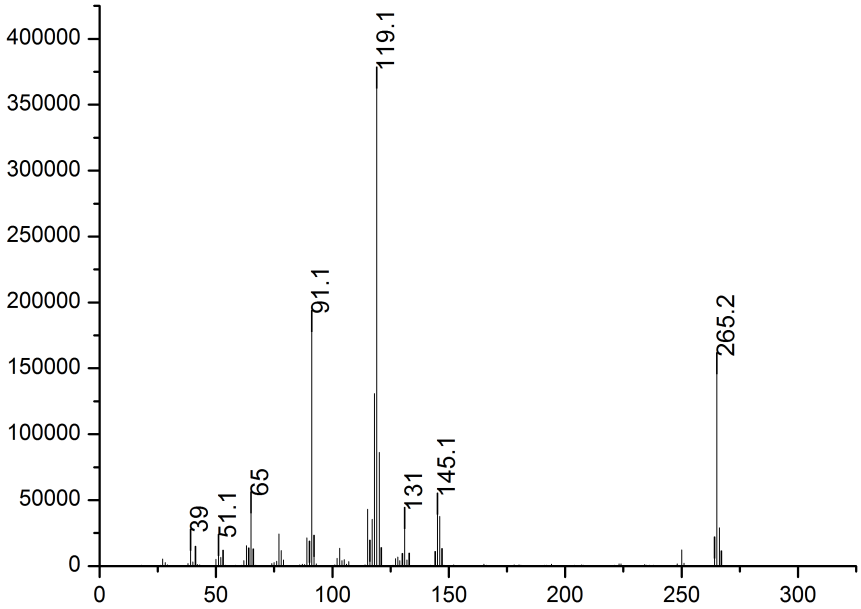
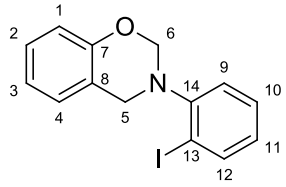


Figure S22. MS (EI**)** of 3,4-Dihydro-8-allyl-3-(4-tolyl)-1,3-*2H*-benzoxazine, **7**

3,4-Dihydro-3-(2-iodophenyl)-1,3-*2H*-benzoxazine, 8 (Scheme 1 and Table 1)



White powder (137 mg, 77%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 4.52 (s, 2 H), 5.24 (s, 2H), 6.80 (td, *J* = 7.5 *Hz*, 1.6 *Hz*, 1H), 6.87 (dd, *J* = 8.0 *Hz*, 1.0 *Hz*, 1H), 6.92 (td, *J* = 7.4 *Hz*, 1.3 *Hz*, 1H), 6.98 (d, *J* = 7.7 *Hz*, 1H), 7.16 (t, *J* = 7.7 *Hz*, 1H), 7.21 (td, *J* = 8 *Hz*, 1.6 *Hz*, 1H), 7.36 (dd, *J* = 8 *Hz*, 1.6 *Hz*, 1H), 7.86 (dd, *J* = 7.7 *Hz*, 1.3 *Hz*, 1H).
^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 51.65 (C-5), 81.05 (C-6), 96.86 (C-13), 116.89 (C-1), 120.63 (C-8), 120.98 (C-3), 123.41 (C-9), 126.23 (C-11), 126.67 (C-4), 128.03 (C-2), 129.27 (C-10), 139.93 (C-12), 150.77 (C-14), 154.09 (C-7). **GC-MS** (EI), *m/z* calcd for $C_{14}H_{12}INO$ 337.00 found 337, 231, 210, 202, 180, 77, 51. R_t = 29.821 min

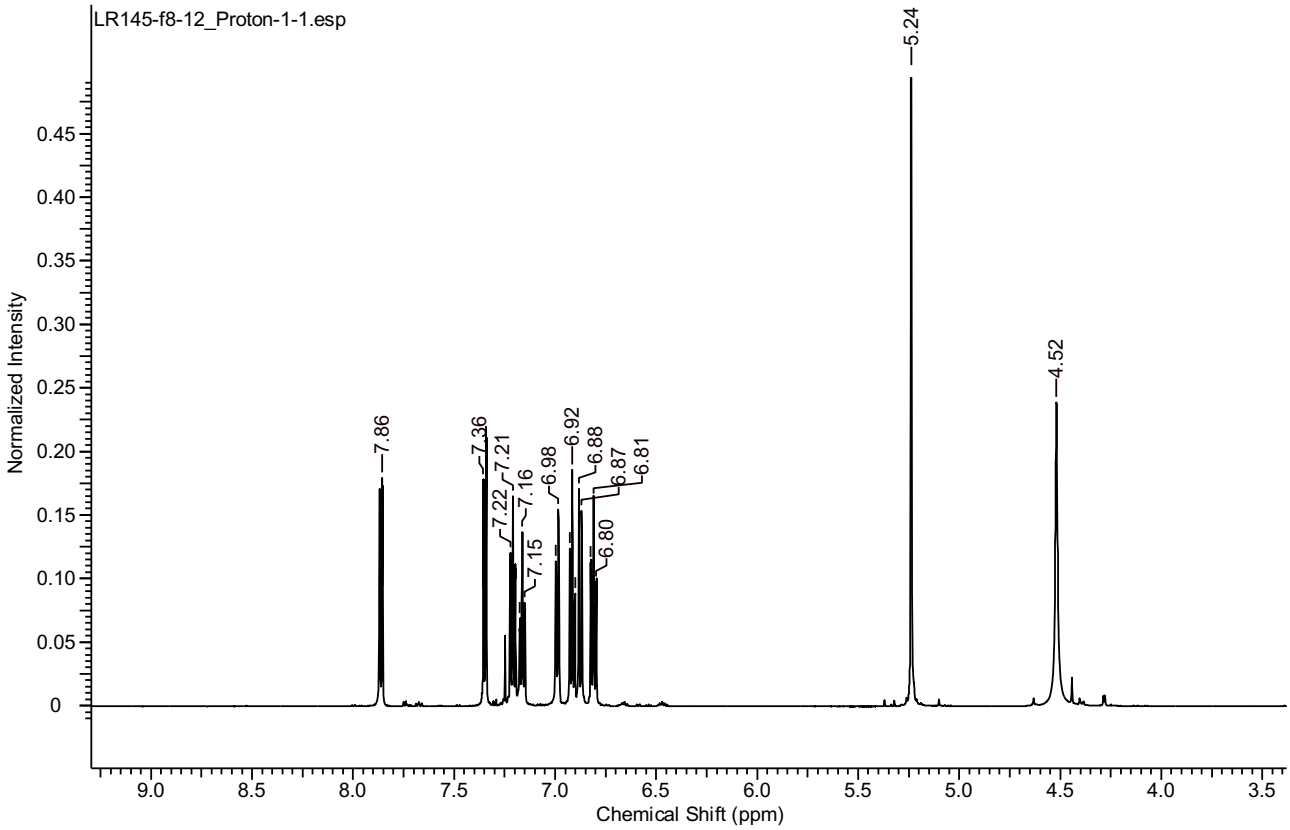


Figure S23. ^{1}H NMR of 3,4-dihydro-3-(2-iodophenyl)-1,3-*2H*-benzoxazine, **8**

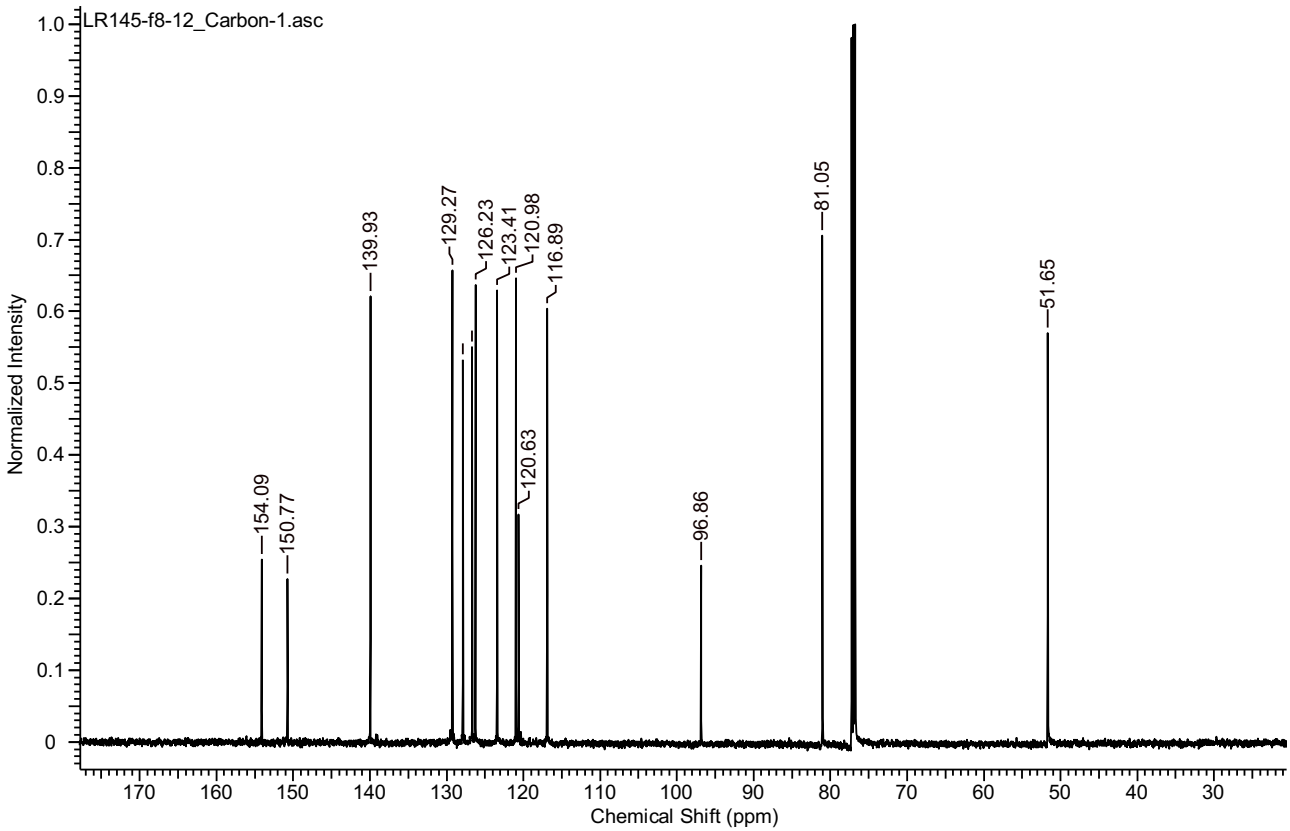


Figure S24. ^{13}C NMR of 3,4-dihydro-3-(2-iodophenyl)-1,3-*2H*-benzoxazine, **8**

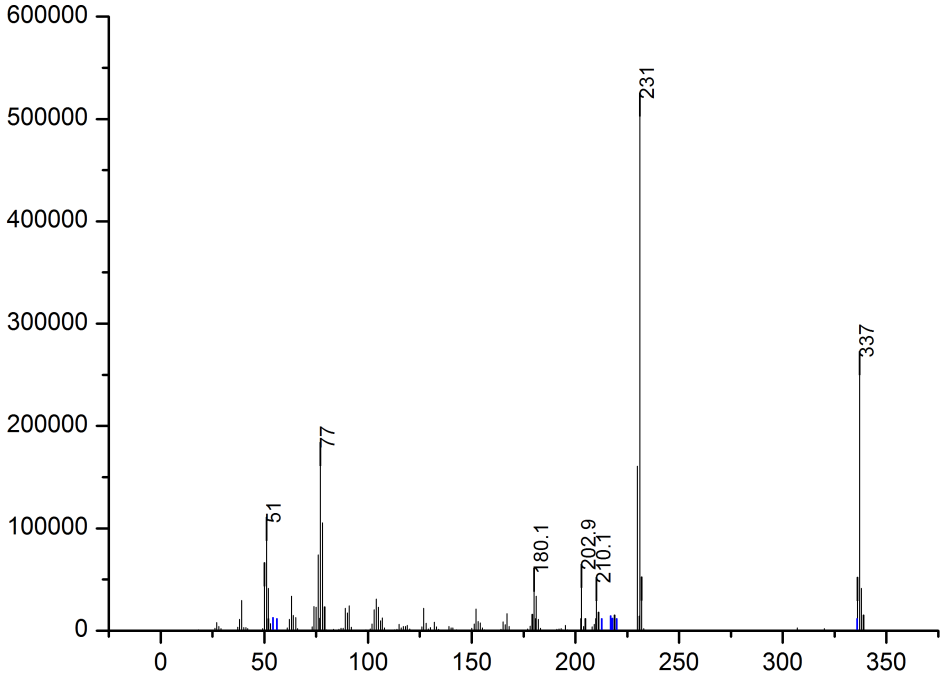
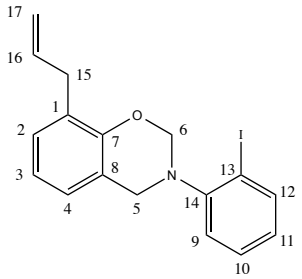


Figure S25. MS (EI) of 3,4-dihydro-3-(2-iodophenyl)-1,3-*2H*-benzoxazine, **8**

3,4-Dihydro-8-allyl-3-(2-iodophenyl)-1,3-*2H*-benzoxazine, 9 (Scheme 1 and Table 1)



White powder (86 mg, 43%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 3.39 (d, J = 6.7 *Hz*, 2H), 4.53 (s, 2H), 5.05-5.09 (m, 2H), 5.27 (s, 2H), 6.00-6.06 (m, 1H), 6.84 (td, J = 7.5 *Hz*, 1.6 *Hz*, 1H), 6.87-6.88 (m, 2H), 7.05 (td, J = 7.4 *Hz*, 1.3 *Hz*, 1H), 6.98 (d, J = 7.7 *Hz*, 1H), 7.21 (t, J = 7.7 *Hz*, 1H), 7.35 (dd, J = 7.8 *Hz*, 1.6 *Hz*, 1H), 7.87 (dd, J = 7.7 *Hz*, 1.3 *Hz*, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 33.66 (C-15), 51.81 (C-5), 81.01 (C-6), 96.86 (C-13), 115.41 (C-17), 120.17 (C-8), 120.45 (C-3), 123.41 (C-9), 124.65 (C-4), 126.14 (C-11), 127.94 (C-1), 128.15 (C-2), 129.21 (C-10), 136.71 (C-16), 139.88 (C-12), 150.86 (C-14), 151.76 (C-7); **GC-MS** (EI), *m/z* calcd for $C_{17}H_{16}INO$ 377.03 found 377, 231, 202, 146, 131, 115, 91, 77, 51, 39. R_t = 31.74 min

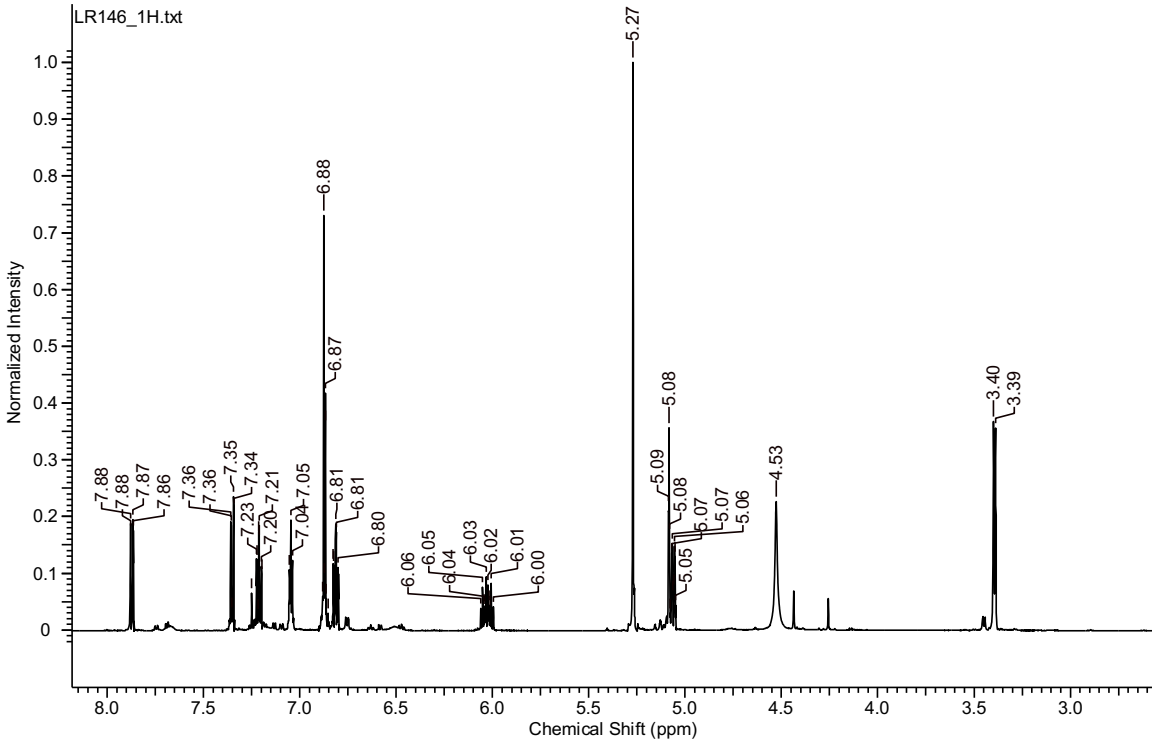


Figure S26. ^{1}H NMR of 3,4-Dihydro-8-allyl-3-(2-iodophenyl)-1,3-*2H*-benzoxazine, **9**

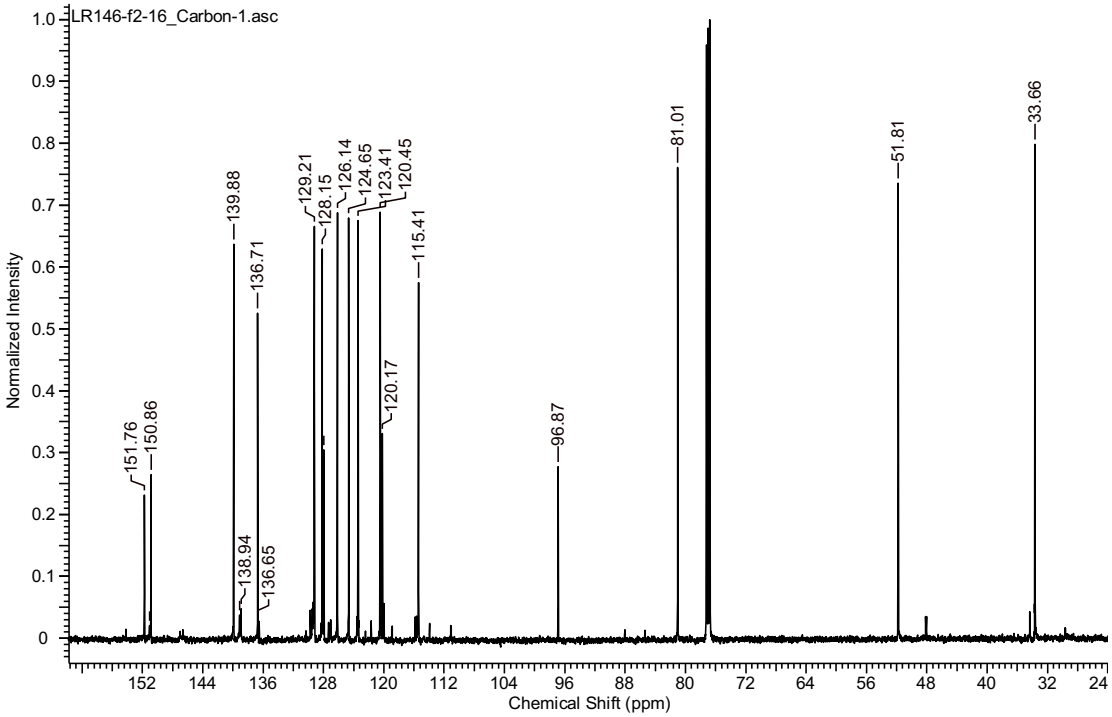


Figure S27. ^{13}C NMR of 3,4-Dihydro-8-allyl-3-(2-iodophenyl)-1,3-*2H*-benzoxazine, **9**

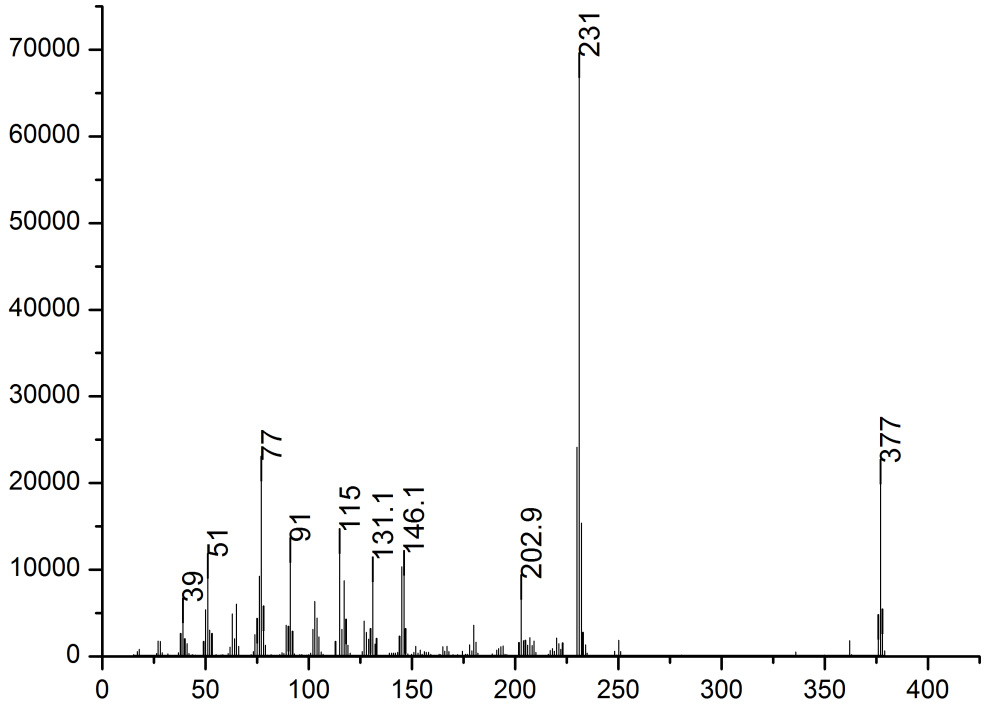
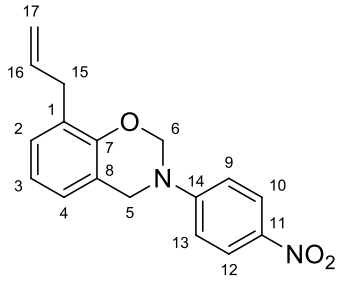


Figure S28. ^{1}H NMR of 3,4-Dihydro-8-allyl-3-(2-iodophenyl)-1,3-*2H*-benzoxazine, **9**

3,4-Dihydro-8-allyl-3-(4-nitrophenyl)-1,3-*2H*-benzoxazine, 10 (Scheme 1 and Table 1)



White powder (36 mg, 23%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 3.33 (d, J = 6.7 *Hz*, 2H), 4.72 (s, 2H), 5.01-5.04 (m, 2H), 5.42 (s, 2H), 5.92-5.96 (m, 1H), 6.88 (t, J = 7 *Hz*, 1H), 6.93 (d, J = 7 *Hz*, 1H), 7.02 (d, J = 7 *Hz*, 1H), 7.04 (d, J = 9.3 *Hz*, 2H), 8.15 (d, J = 9.3 *Hz*, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 33.66 (C-15), 49.58 (C-5), 114.94 (C-13, C-9), 115.85 (C-17), 119.82 (C-8), 121.35 (C-3), 124.85 (C-4), 125.95 (C-12, C-10), 128.73 (C-2), 136.41 (C-16), 140.39 (C-11), 151.9 (C-14), 152.97(C-7). **GC-MS** (EI), *m/z* calcd for $C_{17}H_{16}N_2O_3$ 296.1 found 296, 145, 131, 120, 117, 91, 77, 65, 51, 39. R_t = 34.330 min

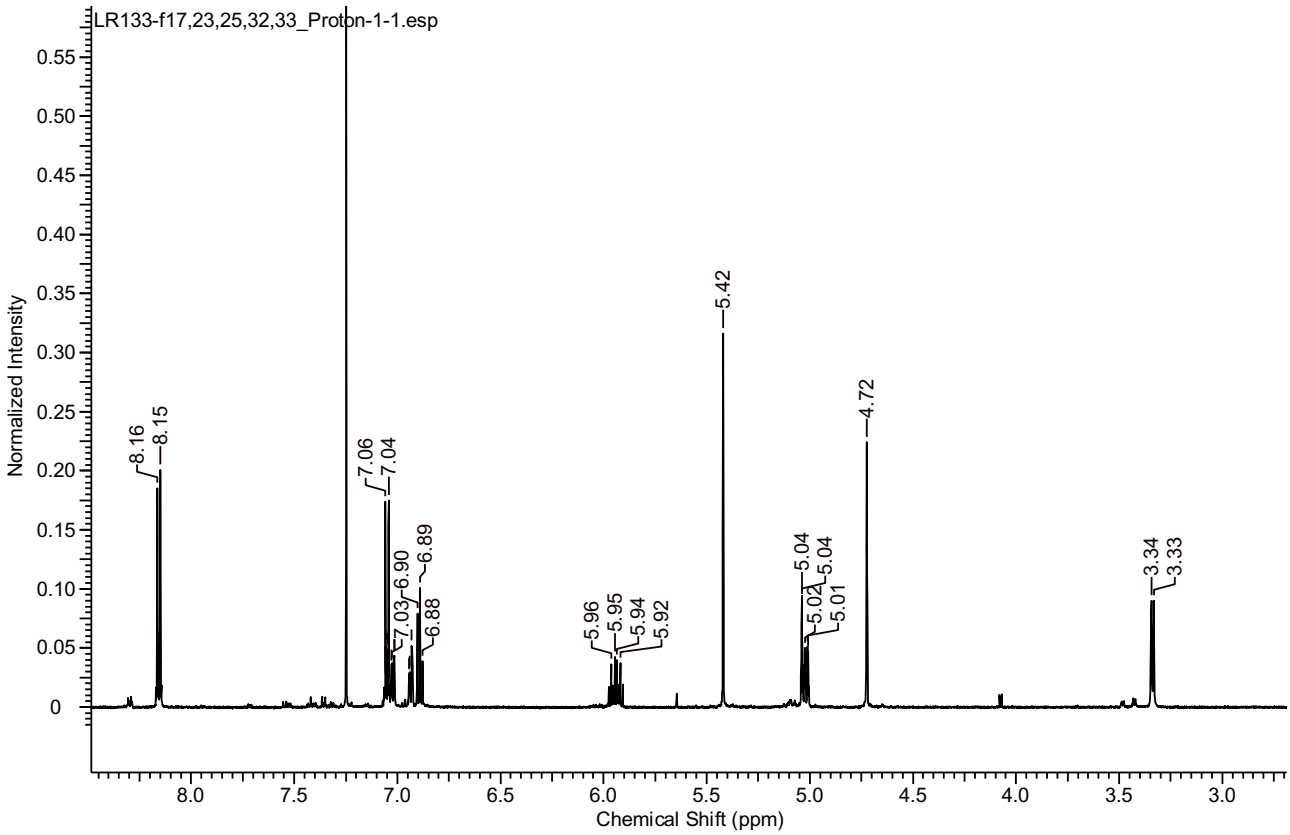


Figure S29. ^{1}H NMR of 3,4-dihydro-8-allyl-3-(4-nitrophenyl)-1,3-*2H*-benzoxazine, **10**

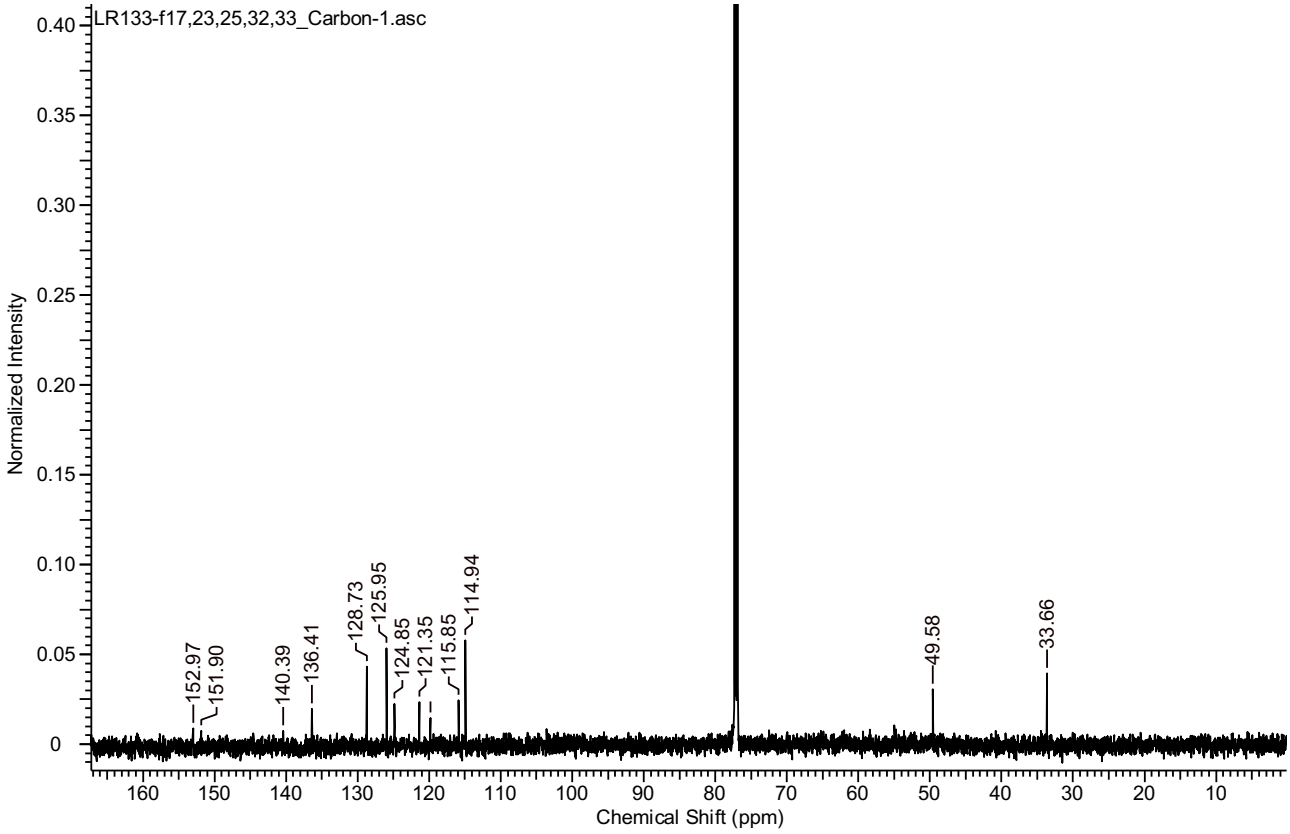


Figure S30. ^{13}C NMR of 3,4-dihydro-8-allyl-3-(4-nitrophenyl)-1,3-*2H*-benzoxazine, **10**

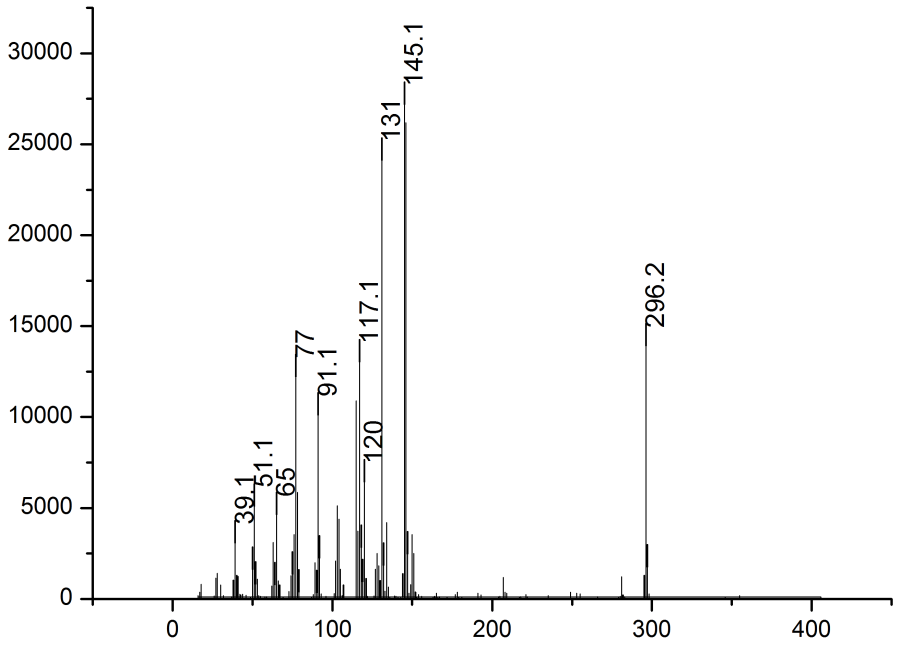
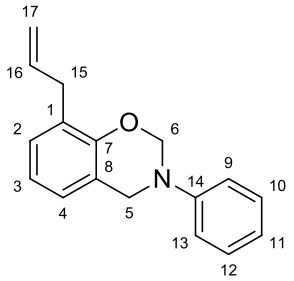


Figure S31. MS (EI) of 3,4-dihydro-8-allyl-3-(4-nitrophenyl)-1,3-*2H*-benzoxazine, **10**

3,4-Dihydro-8-allyl-3-Phenyl-1,3-*2H*-benzoxazine, 11[5] (Scheme 1 and Table 1)



Orange liquid (77 mg, 58%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 3.33 (d, J = 6.5 *Hz*, 2H), 4.62 (s, 2H), 5.00-5.04 (m, 2H), 5.37 (s, 2H), 5.93-5.99 (m, 1H), 6 .82 (t, J = 6.8 *Hz*, 1H), 6.88 (d, J = 6.8 *Hz*, 1H), 6.92 (td, J = 7.4 *Hz*, 1.1 *Hz*, 1H) 6.98 (d, J = 7.0 *Hz*, 1H) 7.10-7.12 (m, 2H) 7.24-7.27 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 33.75 (C-15), 50.74 (C-5), 79.43 (C-6) 115.56 (C-17), 118.34 (C-9, C-13), 120.45 (C-11), 120.51 (C-8), 121.48 (C-3), 124.82 (C-4), 128.19 (C-1), 128.22 (C-2), 129.33 (C-10, C-12), 136.77 (C-16), 148.50 (C-14), 152.12 (C-7). **GC-MS** (EI), *m/z* calcd for $C_{17}H_{17}NO$ 251.13 found 251, 145, 131, 115, 105, 77, 65, 51, 39. R_t = 29.967 min

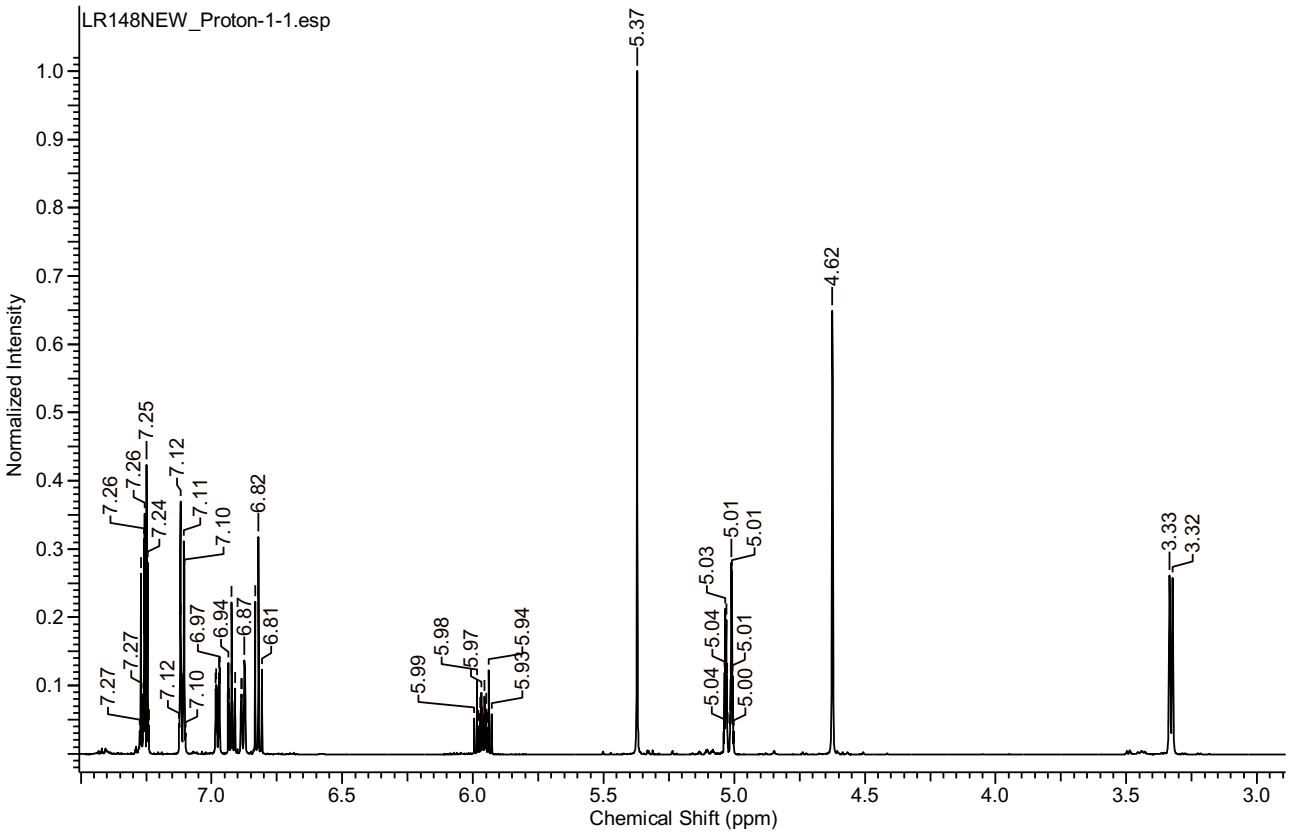


Figure S32. ^{1}H of 3,4-dihydro-8-allyl-3-phenyl-1,3-*2H*-benzoxazine, **11**

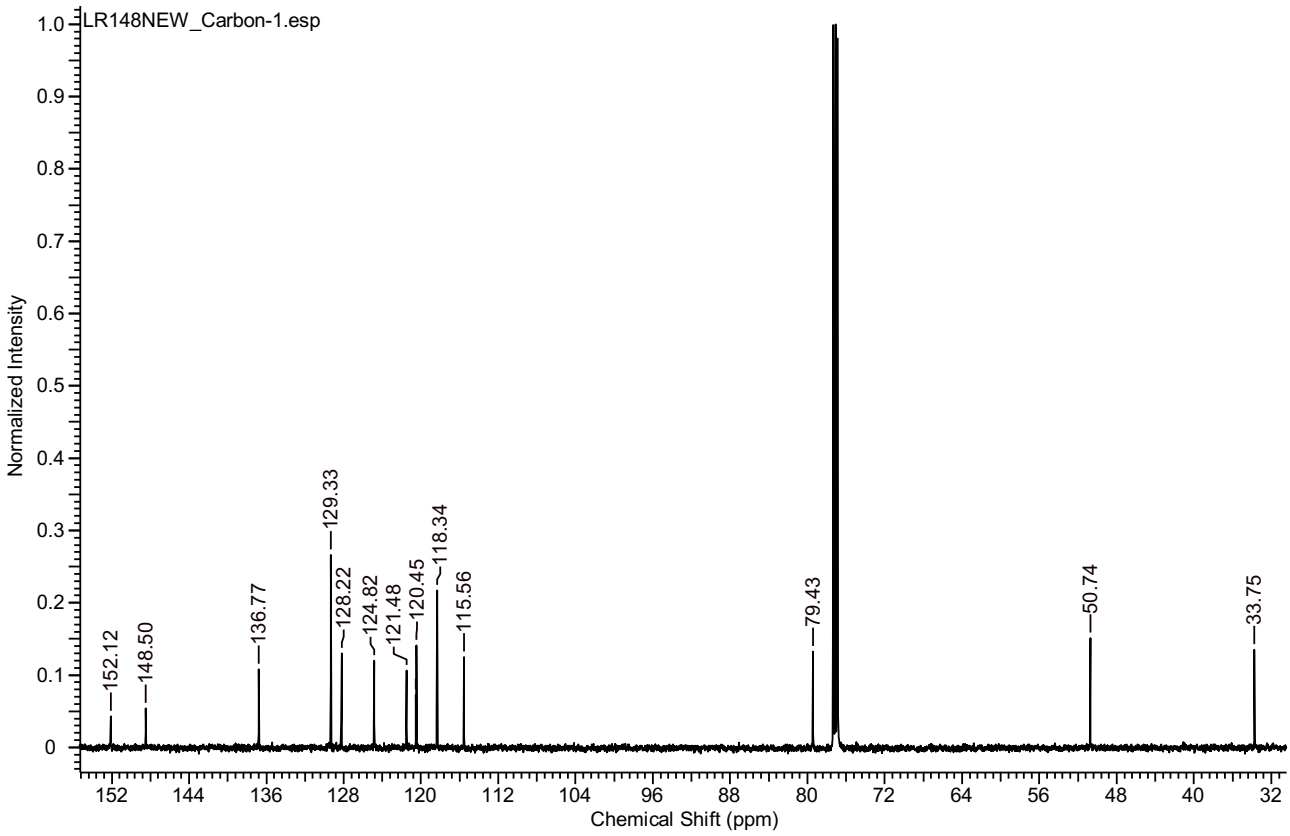


Figure S33. ^{13}C of 3,4-dihydro-8-allyl-3-phenyl-1,3-*2H*-benzoxazine, **11**

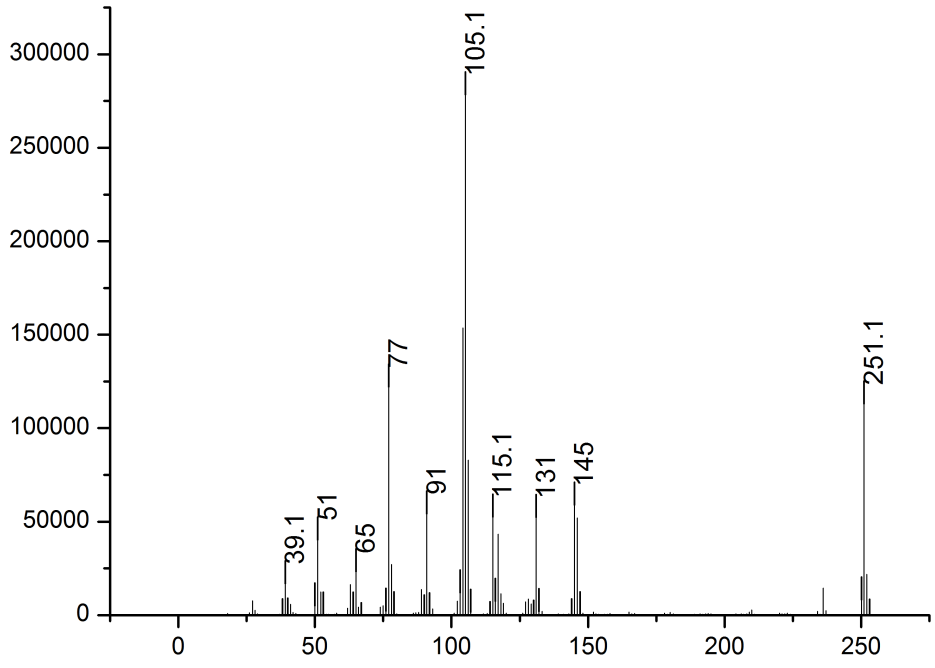
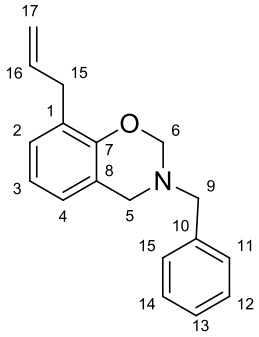


Figure S34. MS (EI) of 3,4-dihydro-8-allyl-3-phenyl-1,3-*2H*-benzoxazine, **11**

3,4-Dihydro-8-allyl-3-benzyl-1,3-2H-benzoxazine, 12 (Scheme 1 and Table 1)



White powder (71 mg, 50%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 3.37 (d, J = 6.5 *Hz*, 2H), 3.92 (s, 2H), 3.99 (s, 2H), 4.9 (s, 2H), 5.06-5.1 (m, 2H), 6.01-6.05 (m, 1H), 6 .81-6.86 (m, 2H), 7.03 (d, J = 7.2 *Hz*, 1H), 7.30 (d, J = 7.2 *Hz*, 1H), 7.34-7.38 (m, 5H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 33.86 (C-15), 49.97 (C-5), 55.63 (C-9), 82.13 (C-6), 115.54 (C-17), 119.45 (C-8), 120.36 (C-3), 125.79 (C-4), 127.51 (C-13), 127.71 (C-1), 128.18 (C-2), 128.60 (C-14, C-12), 129.22 (C-15, C-11), 136.77 (C-16), 138.08 (C-10), 151.77 (C-7). **GC-MS** (EI), *m/z* calcd for $C_{18}H_{19}NO$ 265.1 found 265, 174, 145, 131, 120, 115, 91, 65, 51, 39. R_t = 29.172 min

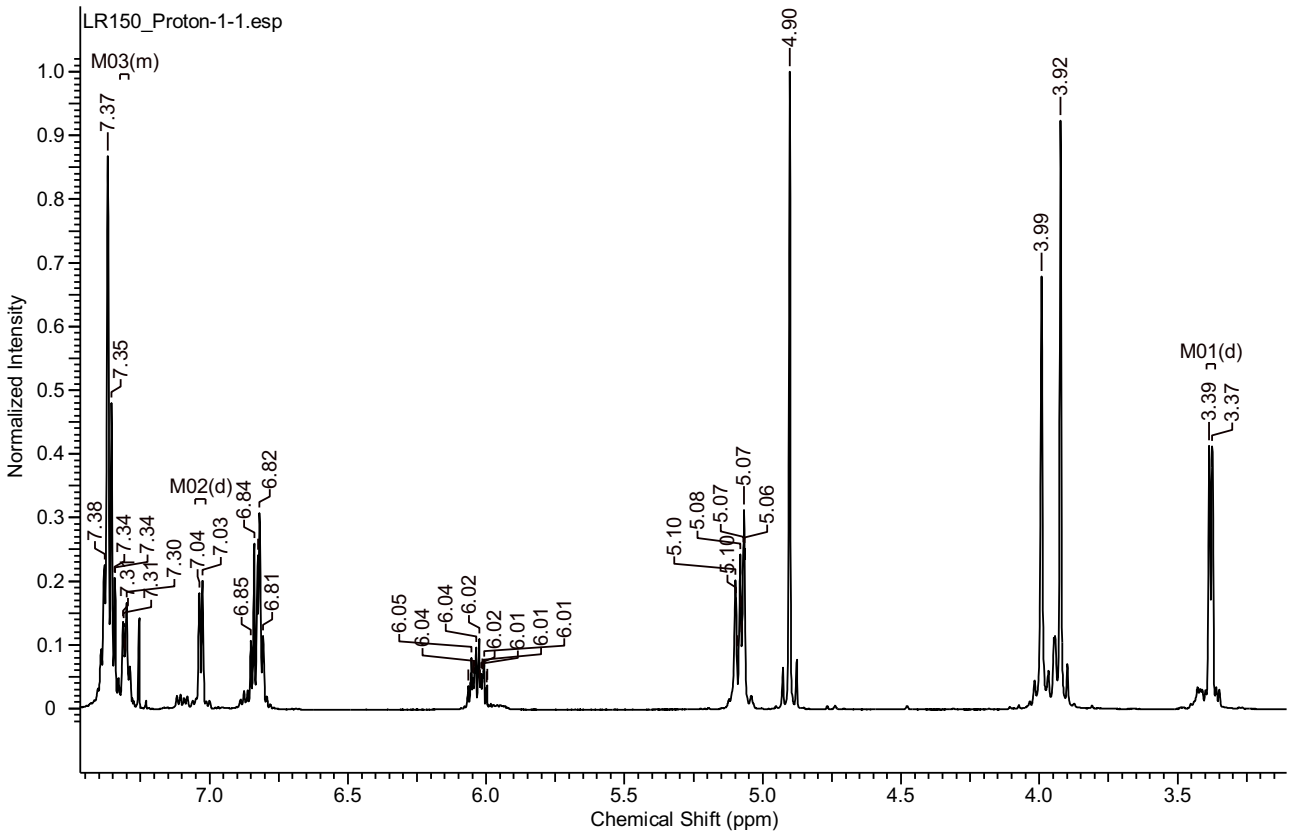


Figure S35. ^{1}H NMR of 3,4-dihydro-8-allyl-3-benzyl-1,3-2H-benzoxazine, **12**

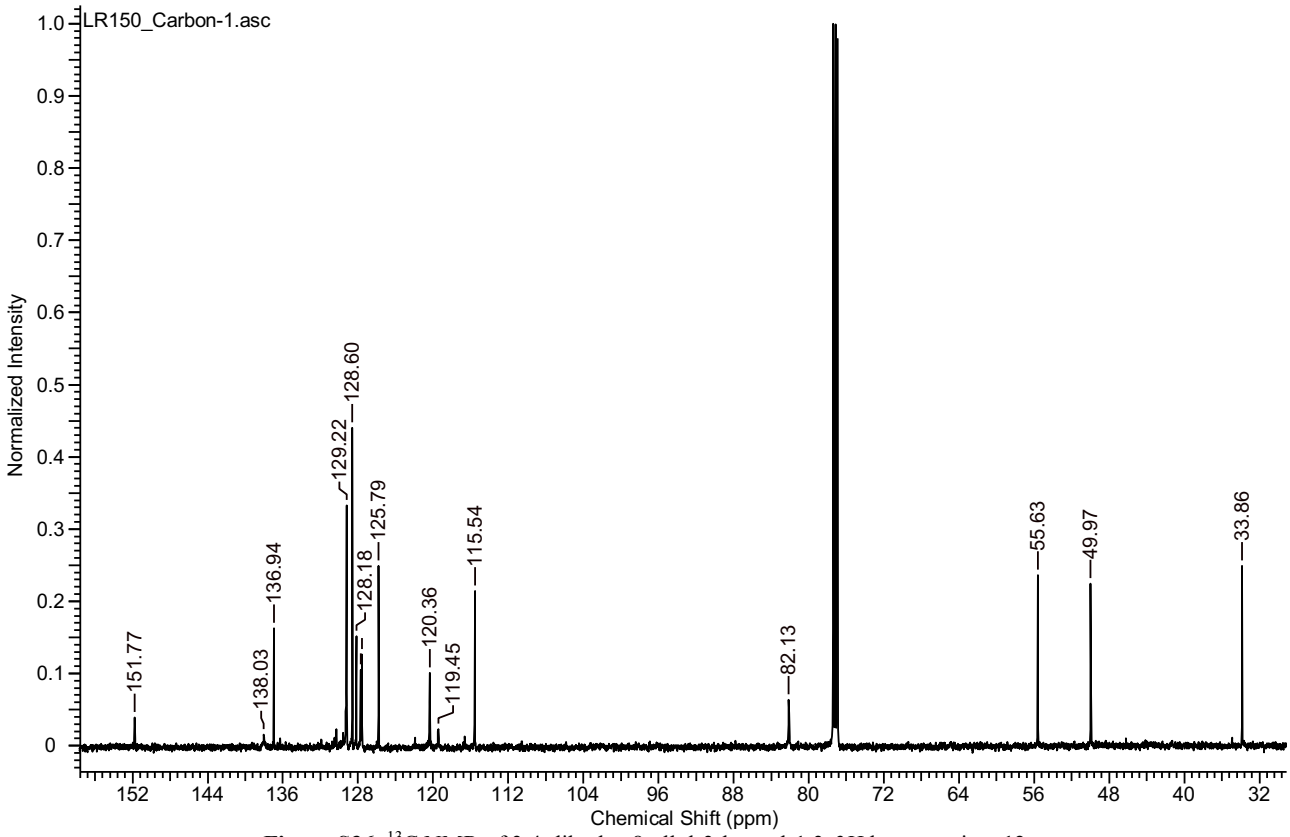


Figure S36. ^{13}C NMR of 3,4-dihydro-8-allyl-3-benzyl-1,3-*2H*-benzoxazine, **12**

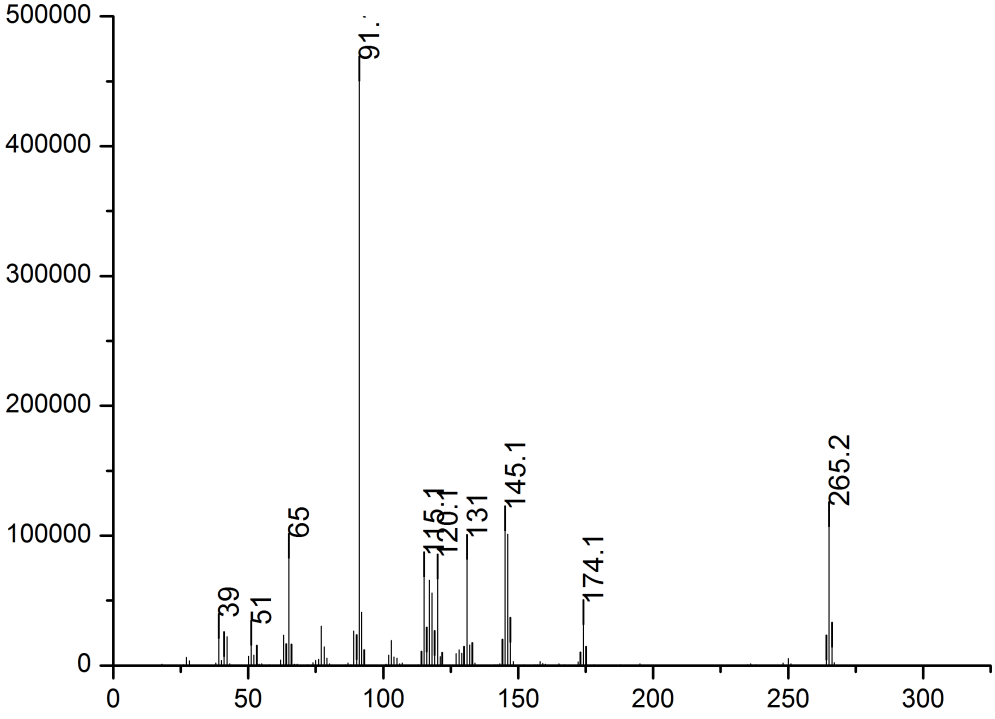
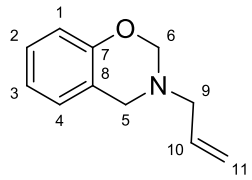


Figure S37. MS (EI) of 3,4-dihydro-8-allyl-3-benzyl-1,3-2H-benzoxazine, **12**

3,4-Dihydro-3-allyl-3-benzyl-1,3,2H-benzoxazine, 13 (Scheme 1 and Table 1)



Pale yellow oil (90 mg, 45%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 3.39 (d, J = 6.5 *Hz*, 2H), 4.00 (s, 2H), 4.87 (s, 2H), 5.19-5.24 (m, 2H), 5.87-5.94 (m, 1H), 6.79 (d, J = 7.9 *Hz*, 2H), 6.87 (t, J = 7.6 *Hz*, 1H), 6.95 (d, J = 7.2 *Hz*, 1H), 7.34-7.12 (t, J = 7.6 *Hz*, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 49.61 (C-5), 54.60 (C-9), 55.63 (C-9), 82.11 (C-6) ,116.50 (C-1), 118.44 (C-11), 120.08 (C-8), 120.69 (C-3), 127.64 (C-4) 127.77 (C-2), 135.08 (C-10), 154.20 (C-7). **GC-MS** (EI), *m/z* calcd for $C_{11}H_{13}NO$ 175.10 found 175, 134, 107, 78, 68, 51, 41, 39. R_t = 20.916 min

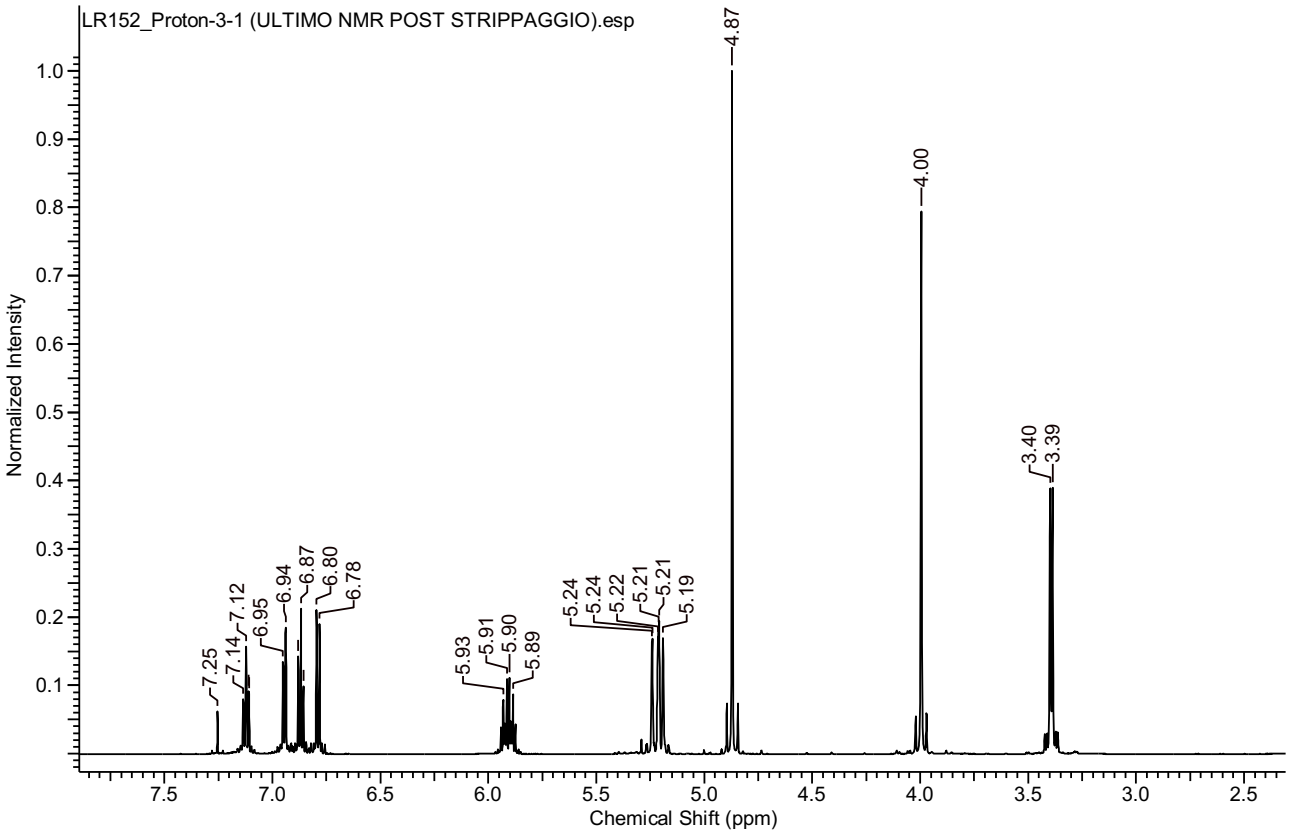


Figure S38. ^{1}H NMR of 3,4-dihydro-3-allyl-3-benzyl-1,3-2H-benzoxazine, **13**

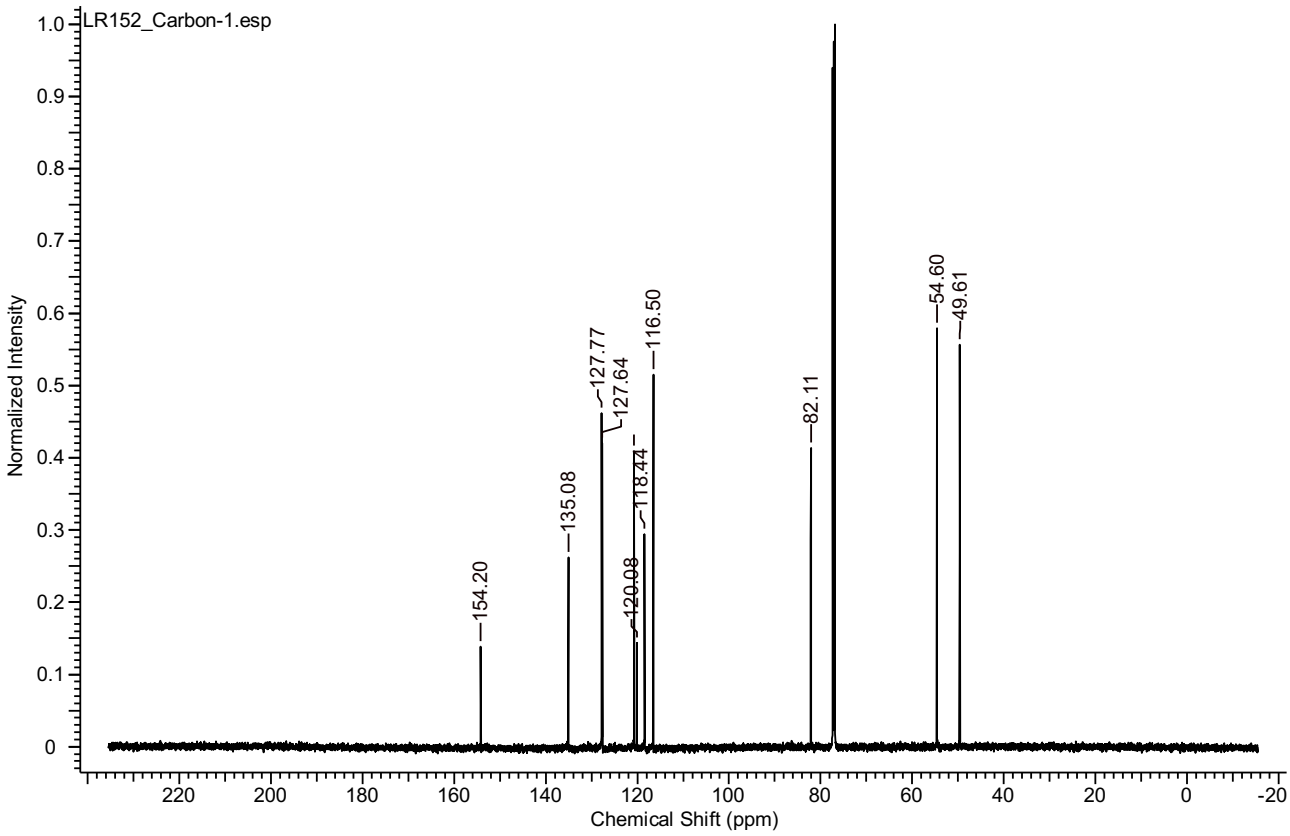


Figure S39. ^{13}C NMR of 3,4-dihydro-3-allyl-3-benzyl-1,3-2H-benzoxazine, **13**

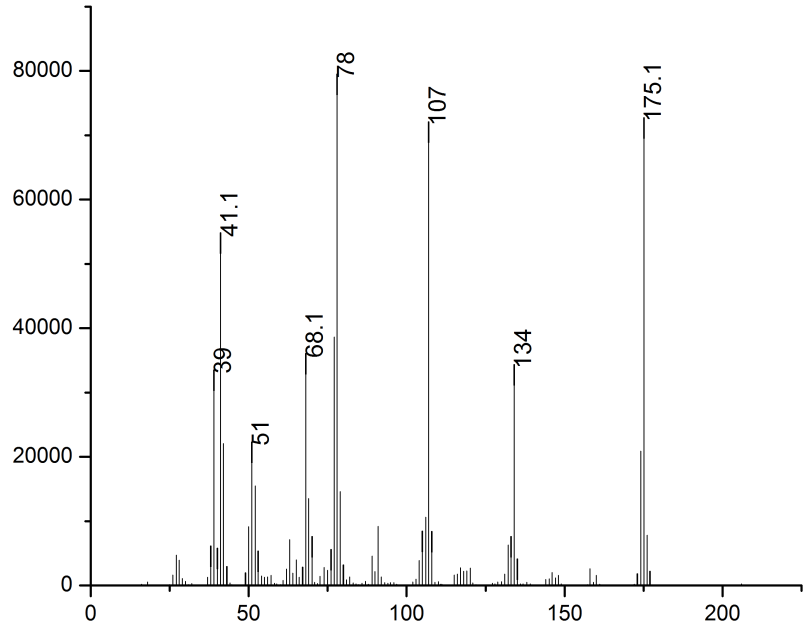
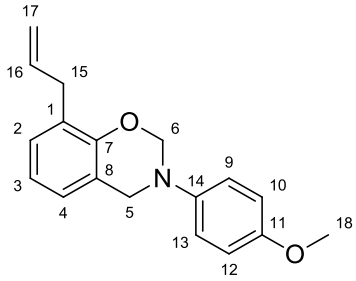


Figure S40. ^{13}C NMR of 3,4-dihydro-3-allyl-3-benzyl-1,3-2*H*-benzoxazine, **13.**

3,4-Dihydro-8-allyl-3-(4-methoxyphenyl)-1,3-*2H*-benzoxazine, 14 (Scheme 1 and Table 1)



Orange Liquid (55 mg, 37%), **^{1}H NMR** (600 MHz, $CDCl_3$) δ (ppm): 3.31 (d, J = 6.5 *Hz*, 2H, CH_2-15), 3.73 (s, 3H, CH3-18), 4.53 (s, 2H, CH_2-5), 4.99-5.03 (m, 2H, CH_2-17), 5.28 (s, 2H, CH_2-6), 5.93-5.98 (m, 1H, CH-16), 6.78-6.81 (m, 3H, CH-3, CH-12, CH-10), 6.85 (d, J = 7 *Hz*, 1H, CH-4), 6.97 (d, J = 7.4 *Hz*, 1H, CH-2), 7.06 (d, J = 8.4 *Hz*, 2H, CH-9, CH-13). **^{13}C NMR** (150 MHz, $CDCl_3$)[1] δ (ppm): 34.22 (C-15), 50.88 (C-18), 56.06 (C-5), 81.15 (C-6), 115.01 (C-9, C-13) 115.99 (C-17), 120.81 (C-3), 120.95 (C-8), 121.31 (C-12, C-10), 125.30 (C-4), 128.52 (C-1), 128.68 (C-2), 137.31 (C-11), 143.00 (C-16), 152.54 (C-14), 155.47(C-7); **GC-MS** (EI), *m/z* calcd for $C_{18}H_{19}NO_2$ 281.35 found 281, 145, 135, 120, 92, 65, 39. R_t = 29.96 min.

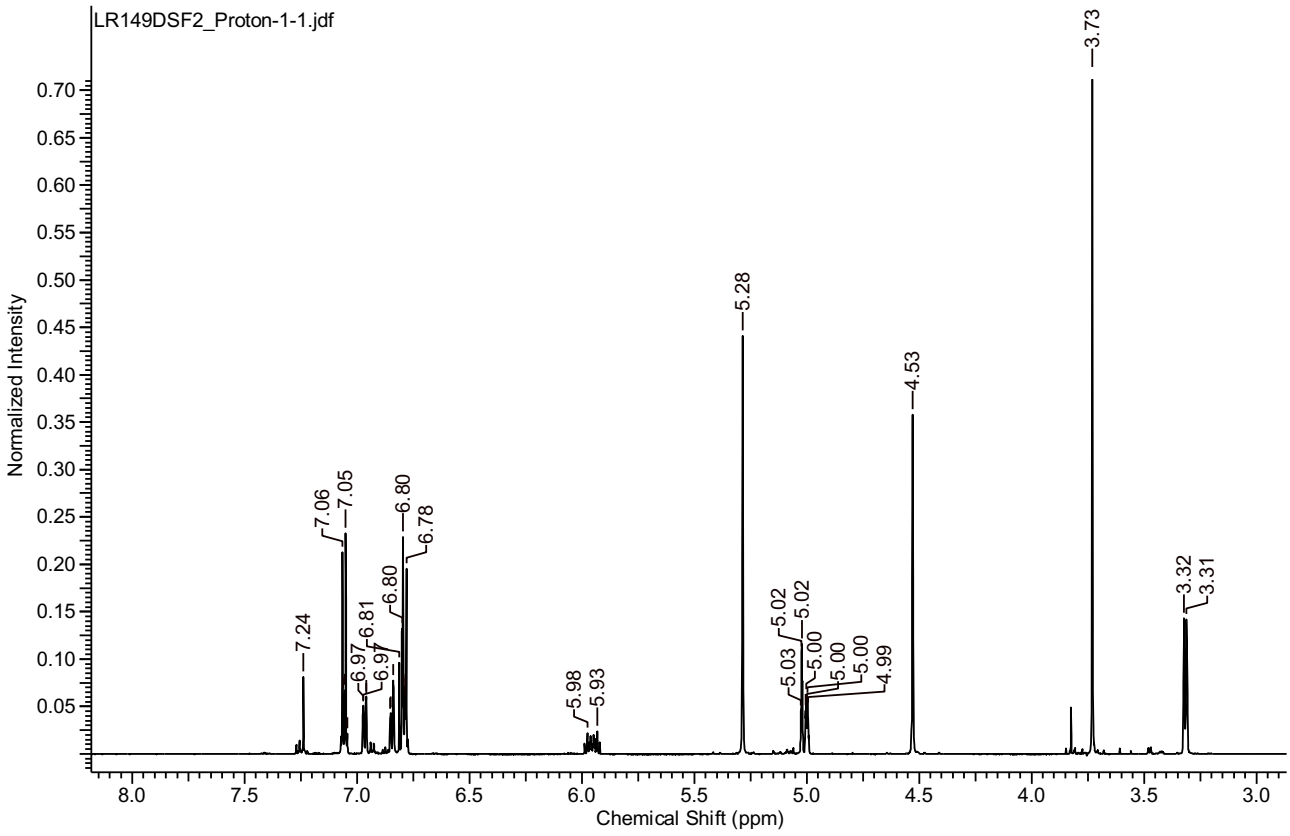


Figure S41. ^{1}H of 3,4-Dihydro-8-allyl-3-(4-methoxyphenyl)-1,3-2H-benzoxazine, **14**

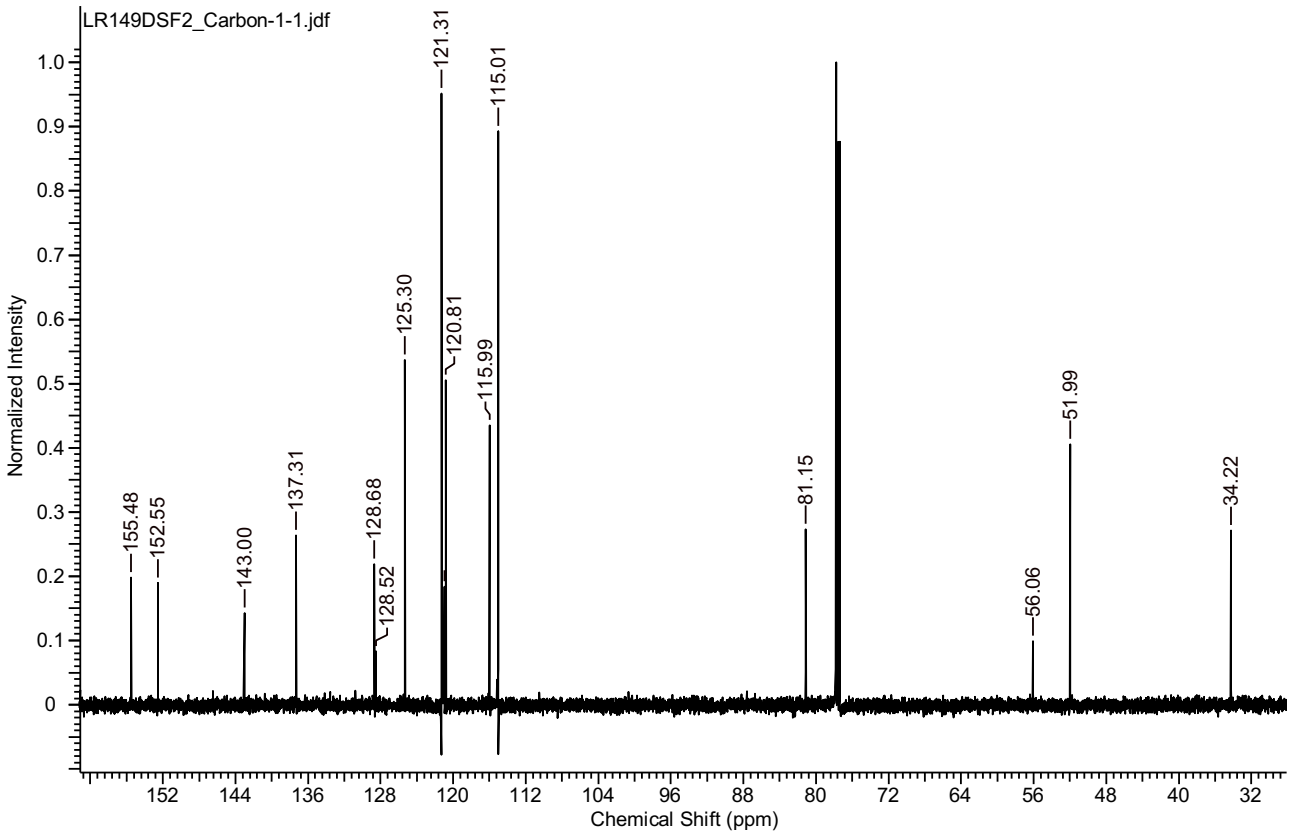


Figure S42. ^{13}C of 3,4-Dihydro-8-allyl-3-(4-methoxyphenyl)-1,3-2H-benzoxazine, **14**

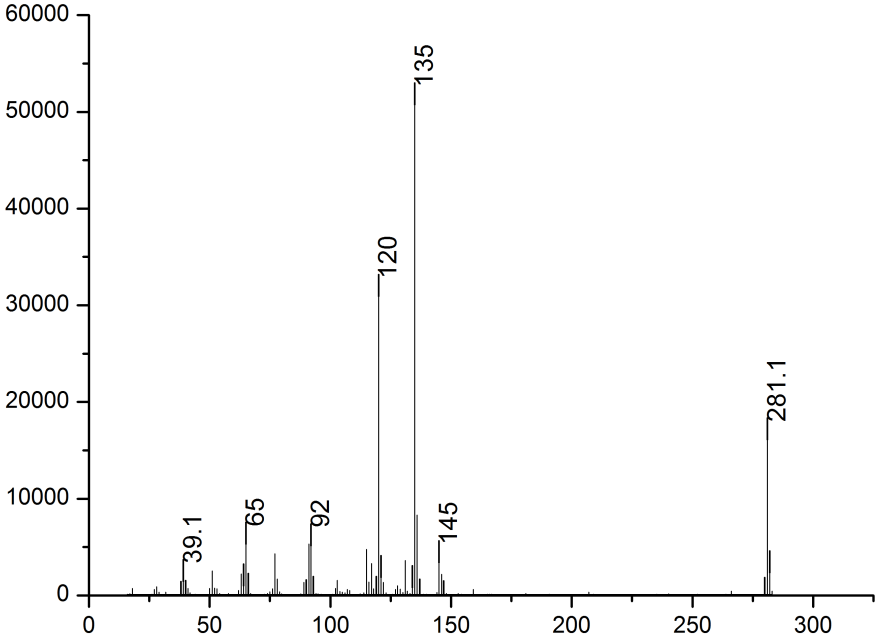


Figure S43. MS (EI) of 3,4-Dihydro-8-allyl-3-(4-methoxyphenyl)-1,3-2H-benzoxazine, **14**

References

1. A. Mascitti, M. Lupacchini, R. Guerra, I. Taydakov, L. Tonucci, N. d'Alessandro, F. Lamaty, J. Martinez and E. Colacino, *Beilstein J. Org. Chem.*, 2017, **13**, 19-25.
2. G. P. Moloney, D. J. Craik and M. N. Iskander, *Magnetic Res. Chem.*, 1990, **28**, 824-829.
3. D. K. Shukla, M. Rani, A. A. Khan, K. Tiwari and R. K. Gupta, *Asian J. Chem.*, 2013, **25**, 5921-5924.
4. J. Liu and G. Yuan, *Tetrahedron Lett.*, 2017, **58** 1470-1473.
5. B. Kiskan and Y. Yagci, *J. Polym. Sci., Part A: Pol. Chem.*, 2014, **52**, 2911–2918.