SUPPORTING INFORMATION

Synthesis of 1'-tetrazolylmethyl-spiro[pyrrolidine-3,3'-oxindoles] via two coupled one pot processes Ugi-azide / Pictet-Spengler and oxidative spiro-rearrangement

Nancy V. Alvarez-Rodríguez,[1] Alejandro Islas-Jácome,[2] Angel Rentería-Gómez,[1] Luis E. Cárdenas-Galindo,[3] Unnamatla M. V. Basavanag[1] and Rocío Gámez-Montaño[1,*]

1 Departamento de Química, Universidad de Guanajuato, Noria Alta S/N, Col. Noria Alta, C.P. 36050, Guanajuato, Gto., México.

2 Departamento de Química, Universidad Autónoma Metropolitana-Iztapalapa, San Rafael Atlixco 186, Col. Vicentina, C.P. 09340, Iztapalapa, Ciudad de México.

3 Departamento Química Área Ambiental, Universidad Tecnológica de Salamanca, Av. Universidad Tecnológica No. 200, Col. Ciudad Bajío, C.P. 36750, Salamanca, Gto., México.

* rociogm@ugto.mx (R. G.-M.)

CONTENTS

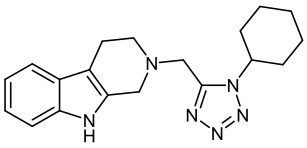
General information, software, instrumentation and chemicals

^{1}H and ^{13}C NMR spectra were acquired on Bruker Advance III spectrometers (400 or 500 MHz). The solvents for NMR samples were $CDCl_3$ or d^6-DMSO. Chemical shifts are reported in parts per million (δ/ppm). Coupling constants are reported in Hertz (*J*/Hz). Internal reference for NMR spectra is TMS at 0.00 ppm. Multiplicities of the signals were reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). NMR spectra were analyzed using the MestreNova software (Ver. 10.0.1-14719). IR spectra were acquired on a Perkin Elmer 100 spectrometer using the ATR method. Absorbance peaks are reported in reciprocal centimeters (υ/cm^{-1}). FT-IR spectra were analyzed using the Report Builder software (Rev. 2.01). HRMS spectra were acquired on a Bruker Daltonics MaXis-Impact (ESI^+)–QqTOF MS spectrometer. HRMS samples were ionized by ESI^+ mode and recorded via the TOF method. HRMS spectra were analyzed using the Bruker data analysis software (Ver. 4.1). Reaction progress was monitored by TLC on precoated silica gel Kieselgel 60 F254 plates and the spots were visualized under UV light (254 or 365 nm). Mixtures in different proportions (v/v) of hexanes (Hex) with ethyl acetate (AcOEt) were used to run TLC, silica-gel column chromatography, and to measure Retention Factors (R_f). Melting points were determined on a Electrothermal apparatus and were uncorrected. All starting materials and solvents were purchased from Sigma-Aldrich-Merck and were used without further purification, distillation, nor dehydration. Chemical structures were drawn using the ChemBioDraw software (Ver. 13.0.2.3020). The purity for all synthesized products (up to 99%) was assessed by NMR.

Synthesis and characterization of the 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carbolines **4a-f**

General procedure 1 (GP1): In a round-bottomed flask (10 ml) equipped with a magnetic stirring bar, to a solution [0.5 M] of tryptamine (1.0 equiv.) in a mixture 1/1 (v/v) of anhydrous MeOH and PhMe under nitrogen atmosphere at room temperature, paraformaldehyde (2.2 equiv. of HCHO), the corresponding isocyanide (1.0 equiv.), and azidotrimethylsilane (1.0 equiv.) were added sequentially. The resulting mixture was stirred at 90 °C for 4 to 7 hours. Then, the solvent was removed to dryness and the crude was purified by silica-gel column chromatography to afford the products **4a-f**.

2-((1-cyclohexyl-1*H*-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**4a**)



According to the GP1, tryptamine (327.0 mg, 2.000 mmol), paraformaldehyde (132.1 mg, 4.400 mmol of HCHO), cyclohexyl isocyanide (253.7 μL, 2.000 mmol), and azidotrimethylsilane (276.9 μL, 2.000 mmol) were reacted together during 7 hours in a mixture of MeOH (2.0 mL) with PhMe (2.0 mL) to afford the product **4a** (579.0 mg, 85%) as a pale-yellow solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 4/1 to 3/2 (v/v) as eluent; R_f = 0.17 (Hex–AcOEt, 1/1, v/v); mp = 214–216 °C; FT-IR (ATR) υ_{max}/cm^{-1} 1265 (N_3), 1443 (CN), 3206 (NH); ^{1}H and ^{13}C NMR: All attempts to acquire NMR spectra were unsuccessful due to unexpected insolubility problems; HRMS (ESI$^+$): *m/z* calcd for $C_{19}H_{24}N_6^+$ $[M+H]^+$ 337.2135, found 337.2141.

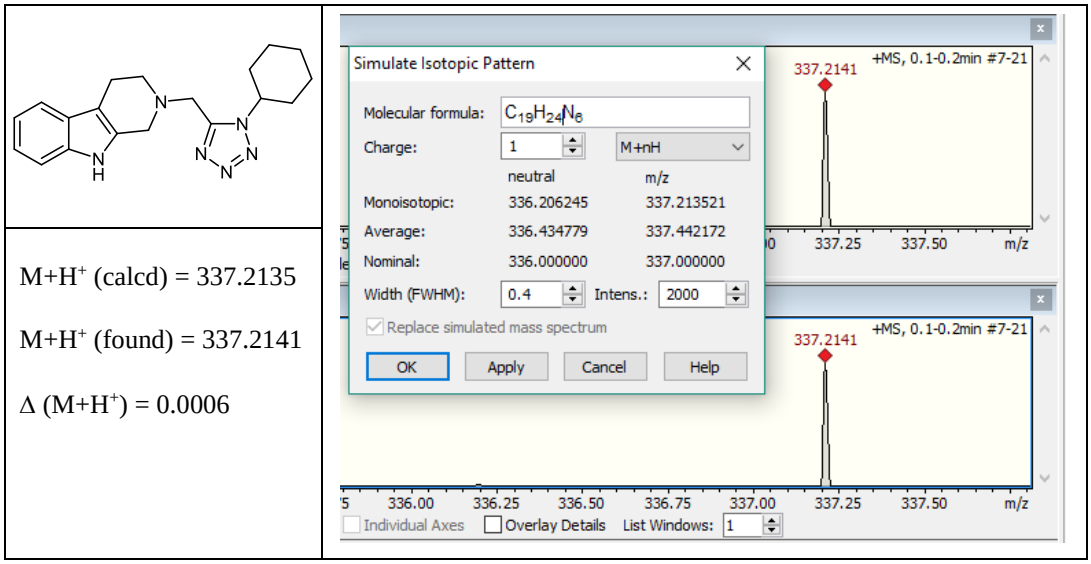
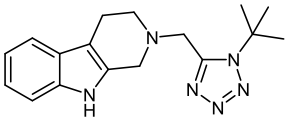


Figure S1. HRMS spectrum of the product **4a**

2-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**4b**)



According to the GP1, tryptamine (327.0 mg, 2.000 mmol), paraformaldehyde (132.0 mg, 4.4 mmol of HCHO), *tert*-butyl isocyanide (232.5 μL, 2.000 mmol), and azidotrimethylsilane (277.0 μL, 2.000 mmol) were reacted together during 4 hours in a mixture of MeOH (2.0 mL) with PhMe (2.0 mL) to afford the product **4b** (603.0 mg, 97%) as a white solid after purification by silica gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 to 3/2 (v/v) as eluent; R_f = 0.46 (Hex–AcOEt, 1/1, v/v); mp = 235–237 °C, FT-IR (ATR) υ_{max}/cm^{-1} 1270 (N_3), 1451 (CN), 3200 (NH); ^{1}H NMR (500 MHz, d^6-DMSO, TMS): δ 1.69 (s, 9H), 2.66–2.69 (m, 2H), 2.80–2.83 (m, 2H), 3.61 (s, 2H), 4.14 (s, 2H), 6.91–6.95 (m, 1H), 6.98–7.02 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 10.68 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 21.1, 29.2, 50.0, 50.5, 50.9, 62.3, 106.7, 111.4, 117.9, 118.8, 121.0, 127.0, 132.3, 136.3, 152.1; HRMS (ESI$^+$): *m/z* calcd for $C_{17}H_{22}N_6^+$ $[M+H]^+$ 311.1979, found 311.1984.

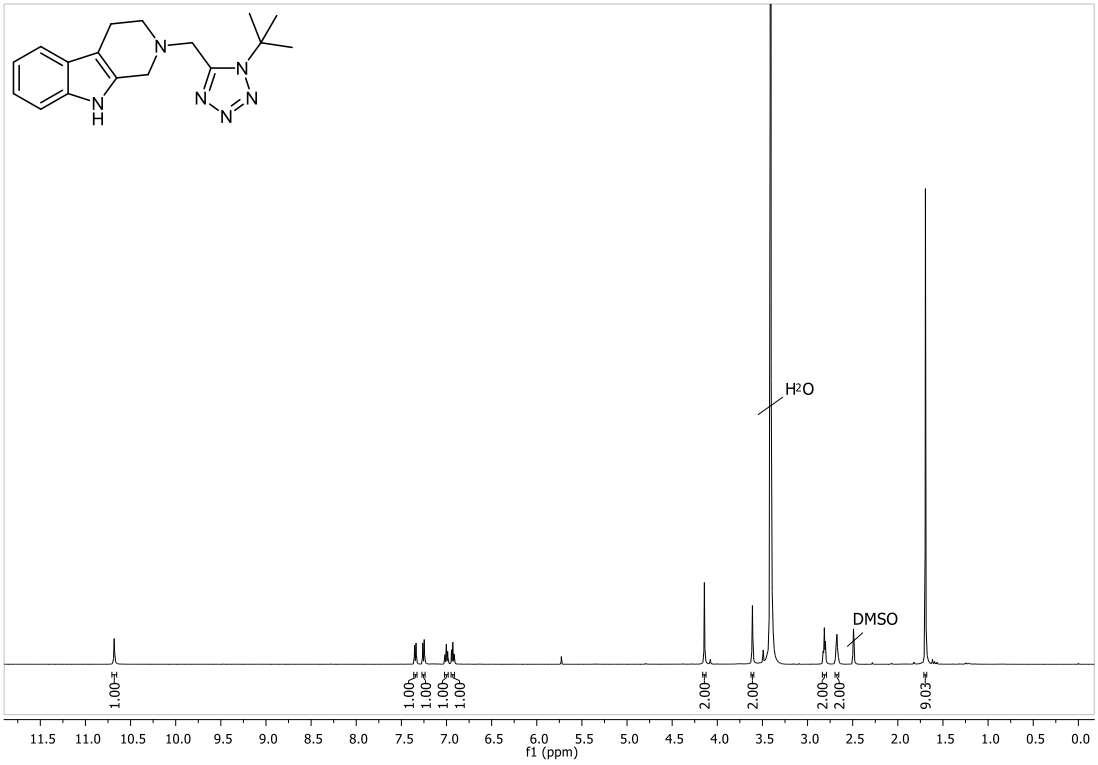


Figure S2. ^{1}H NMR spectrum of the product **4b**

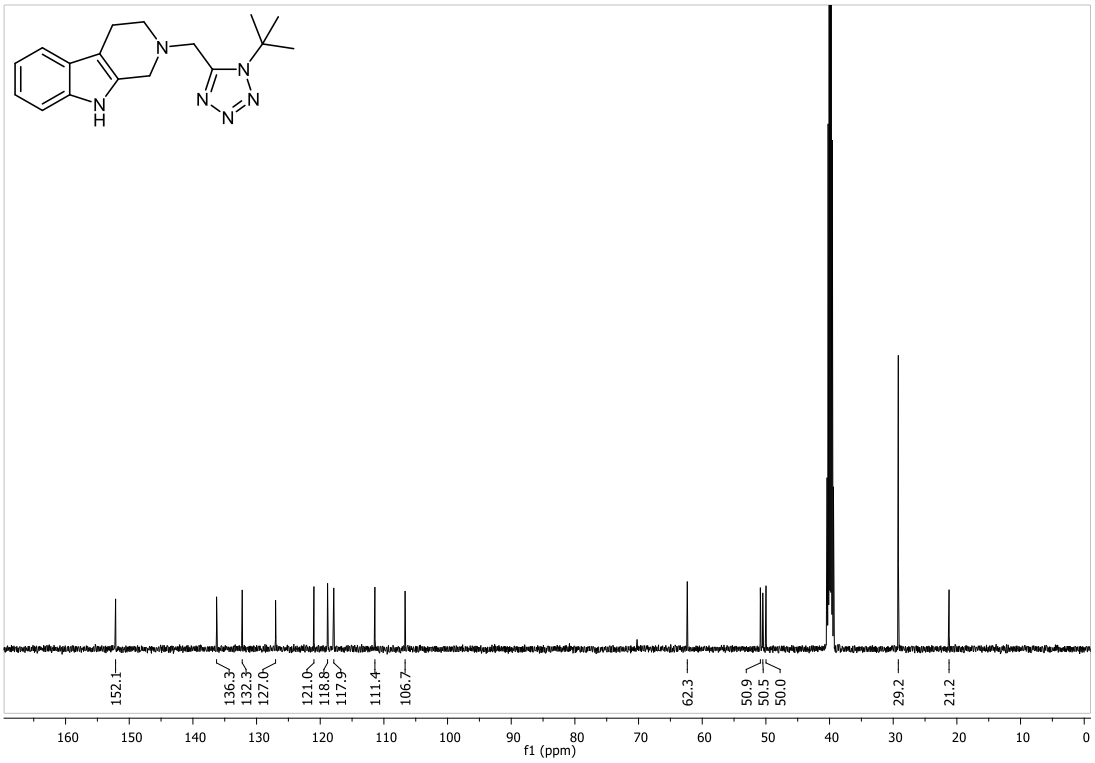
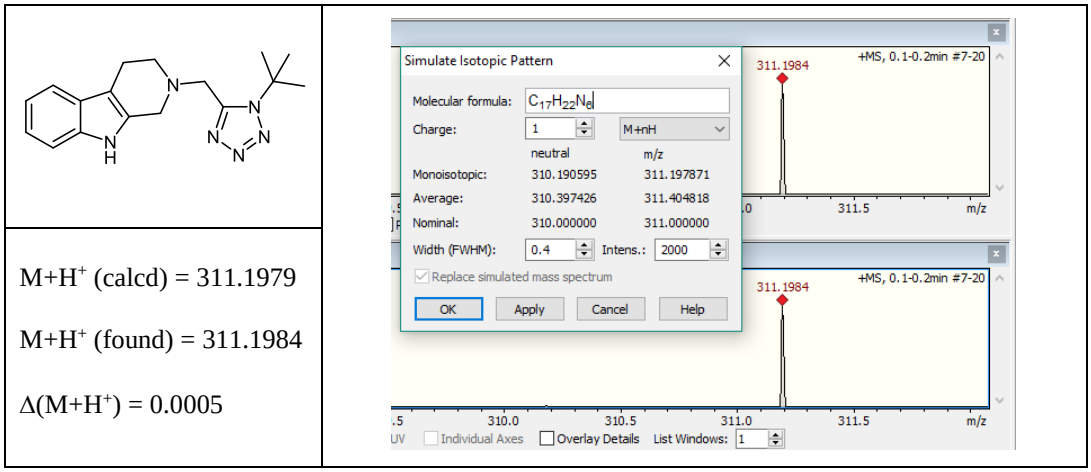


Figure S3. ^{13}C NMR spectrum of the product **4b**



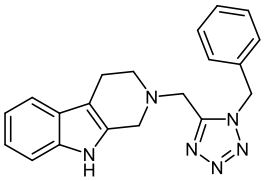
$M+H^+$ (calcd) = 311.1979

$M+H^+$ (found) = 311.1984

$\Delta(M+H^+)$ = 0.0005

Figure S4. HRMS spectrum of the product **4b**

2-((1-benzyl-1*H*-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**4c**)



According to the GP1, tryptamine (164.0 mg, 1.000 mmol), paraformaldehyde (66.0 mg, 2.200 mmol of HCHO), benzyl isocyanide (124.0 μL, 1.000 mmol), and azidotrimethylsilane (138.0 μL, 1.000 mmol) were reacted together during 4.5 hours in a mixture of MeOH (1.0 mL) with PhMe (1.0 mL) to afford the product **4c** (192.0 mg, 56%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 to 3/2 (v/v) as eluent; R_f = 0.40 (Hex–AcOEt, 1/1, v/v); mp = 165–167 °C; FT-IR (ATR) υ_{max}/cm^{-1} 1239 (N_3), 1456 (CN), 3258 (NH); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 2.62–2.71 (m, 2H), 2.82–2.85 (m, 2H), 3.68 (s, 2H), 4.15 (s, 2H), 5.73 (s, 2H), 6.94–6.97 (m, 1H), 7.01–7.04 (m, 1H), 7.27–7.34 (m, 6H), 7.37 (d, *J* = 7.6 Hz, 1H), 10.69 (s, 1H); ^{13}C NMR (126 MHz, d^6-DMSO, TMS): δ 21.1, 49.0, 50.1, 50.7, 50.8, 106.6, 111.4, 117.8, 118.8, 120.9, 127.1, 128.7 (2), 129.1, 132.3, 135.1, 136.3, 153.0; HRMS (ESI$^+$): *m/z* calcd for $C_{20}H_{20}N_6^+$ $[M+H]^+$ 345.1822, found 345.1845.

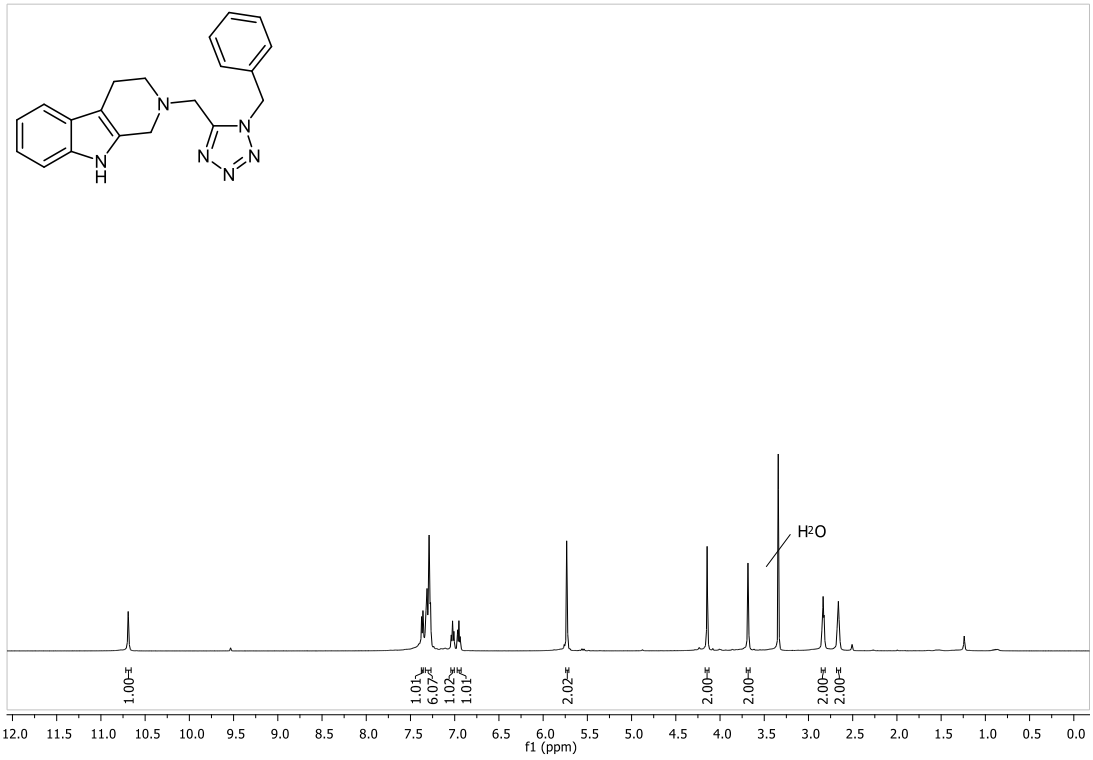


Figure S5. ^{1}H NMR spectrum of the product **4c**

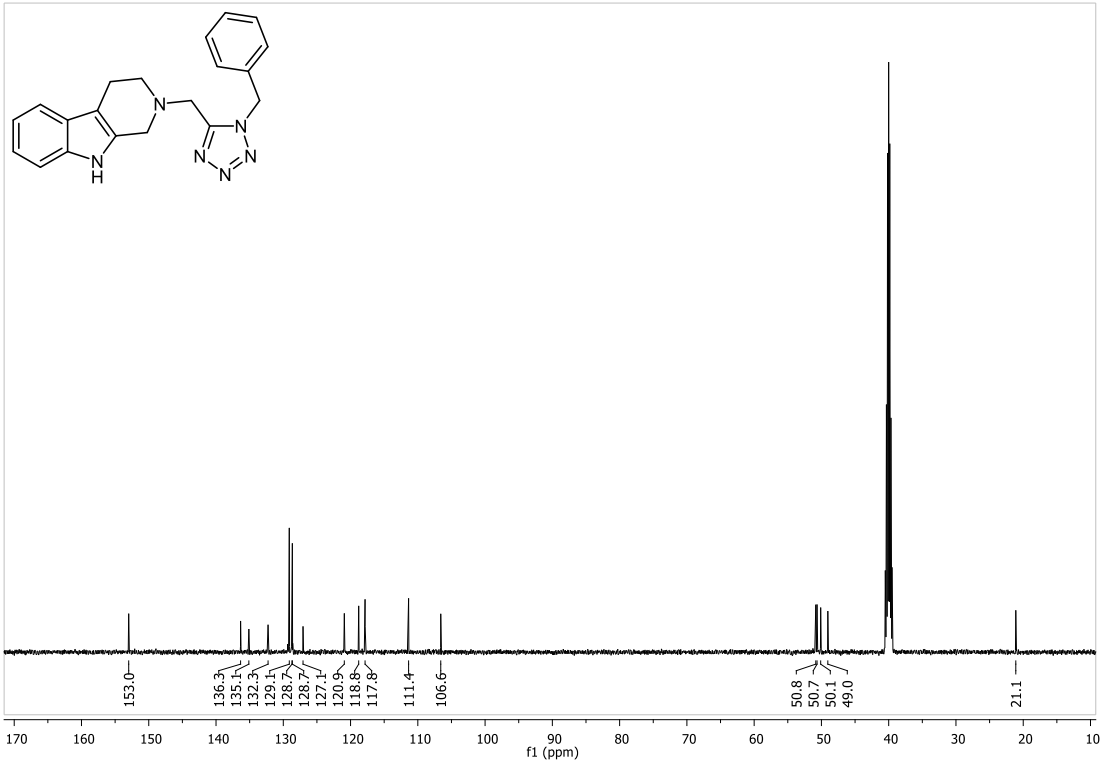


Figure S6. ^{13}C NMR spectrum of the product **4c**

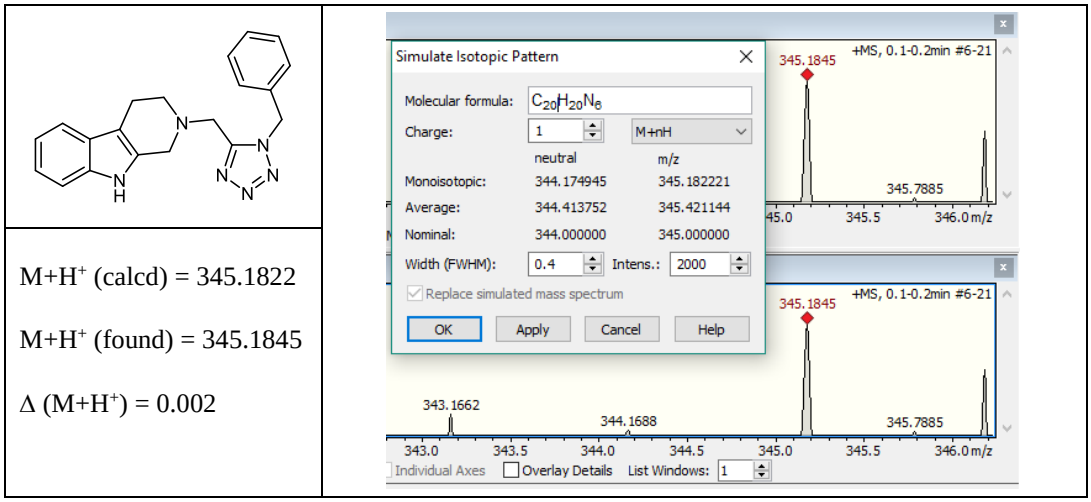
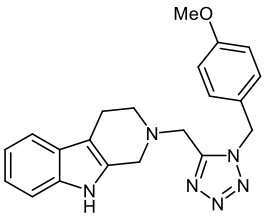


Figure S7. HRMS spectrum of the product **4c**

2-((1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**4d**)



According to the GP1, tryptamine (164.0 mg, 1.000 mmol), paraformaldehyde (66.0 mg, 2.200 mmol of HCHO), 4-methoxybenzyl isocyanide (132.0 μL, 1.000 mmol), and azidotrimethylsilane (138.0 μL, 1.000 mmol) were reacted together during 4.5 hours in a mixture of MeOH (1.0 mL) with PhMe (1.0 mL) to afford the product **4d** (212.0 mg, 57%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 to 3/2 (v/v) as eluent; R_f = 0.36 (Hex–AcOEt, 1/1, v/v); mp = 142–144 °C; FT-IR (ATR) υ_{max}/cm^{-1} 1246 (N_3), 1453 (CN), 3200 (NH); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 2.82–2.87 (m, 2H), 2.89–2.91 (m, 2H), 3.55 (s, 2H), 3.72 (s, 3H), 3.93 (s, 2H), 5.63 (s, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 7.09–7.12 (m, 1H), 7.14–7.16 (m, 1H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.82–7.84 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 21.2, 30.9, 50.0, 50.1, 51.1, 51.3, 55.3, 108.0, 110.9, 114.3, 118.0, 119.6, 121.7, 125.4, 126.9, 129.6 130.5, 136.0, 151.8, 159.9, 207.0; HRMS (ESI$^+$): *m/z* calcd for $C_{21}H_{22}N_6O^+$ $[M+H]^+$ 375.1928, found 375.1927.

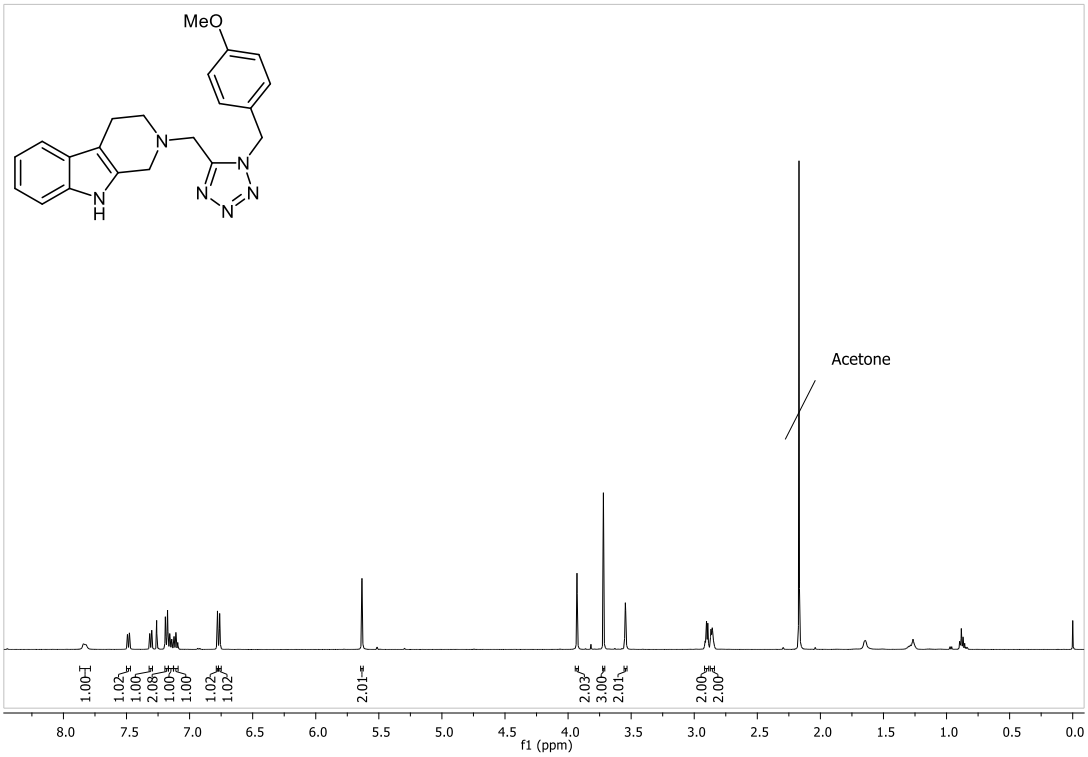


Figure S8. ^{1}H NMR spectrum of the product **4d**

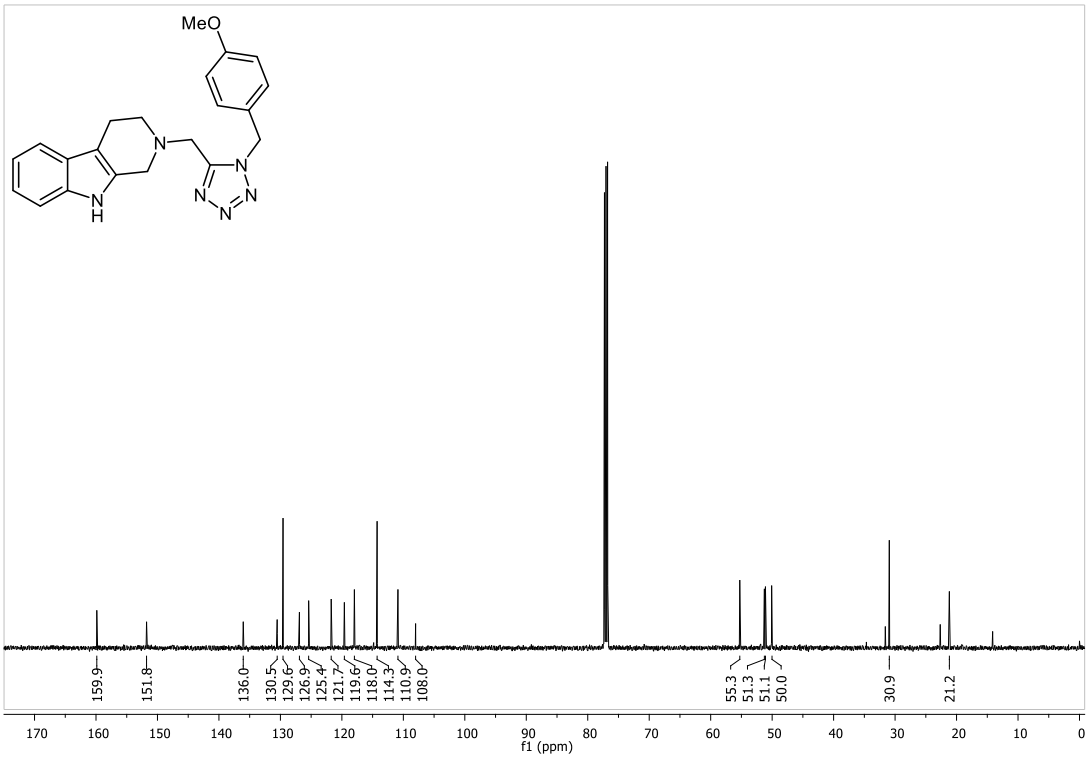


Figure S9. ^{13}C NMR spectrum of the product **4d**

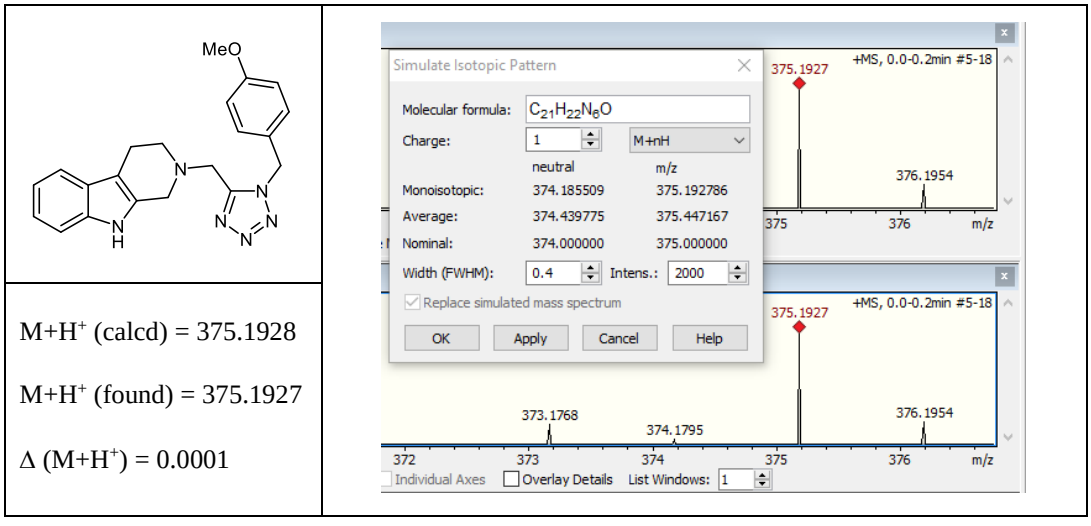
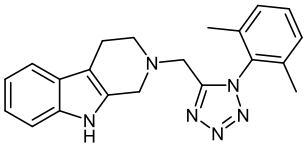


Figure S10. HRMS spectrum of the product **4d**

2-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**4e**)



According to the GP1, tryptamine (164.0 mg, 1.000 mmol), paraformaldehyde (66.0 mg, 2.200 mmol of HCHO), 2,6-dimethylphenyl isocyanide (134.0 μL, 1.000 mmol), and azidotrimethylsilane (138.0 μL, 1.000 mmol) were reacted together during 4.5 hours in a mixture of MeOH (1.0 mL) with PhMe (1.0 mL) to afford the product **4e** (340.0 mg, 95%) as a white crystals after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 (v/v) as eluent and a recrystallization using the same solvent system (CCDC: 1549991); R_f = 0.36 (Hex–AcOEt, 3/2, v/v); mp = 194–196 °C, FT-IR (ATR) υ_{max}/cm^{-1} 1237 (N_3), 1451 (CN), 3200 (NH); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.93 (s, 6H), 2.66–2.68 (m, 2H), 2.81–2.83 (m, 2H), 3.71 (s, 2H), 3.81 (s, 2H), 7.07–7.09 (m, 1H), 7.11–7.14 (m, 1H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (126 MHz, CDCl3, TMS): δ 17.4, 20.8, 48.9, 50.0, 51.3, 107.9, 110.9, 117.9, 119.4, 121.5, 127.0, 128.7, 130.8 (2), 130.9, 132.0, 135.9, 136.0, 153.4; HRMS (ESI$^+$): *m/z* calcd for $C_{21}H_{22}N_6^+$ $[M+H]^+$ 359.1979, found 359.2000.

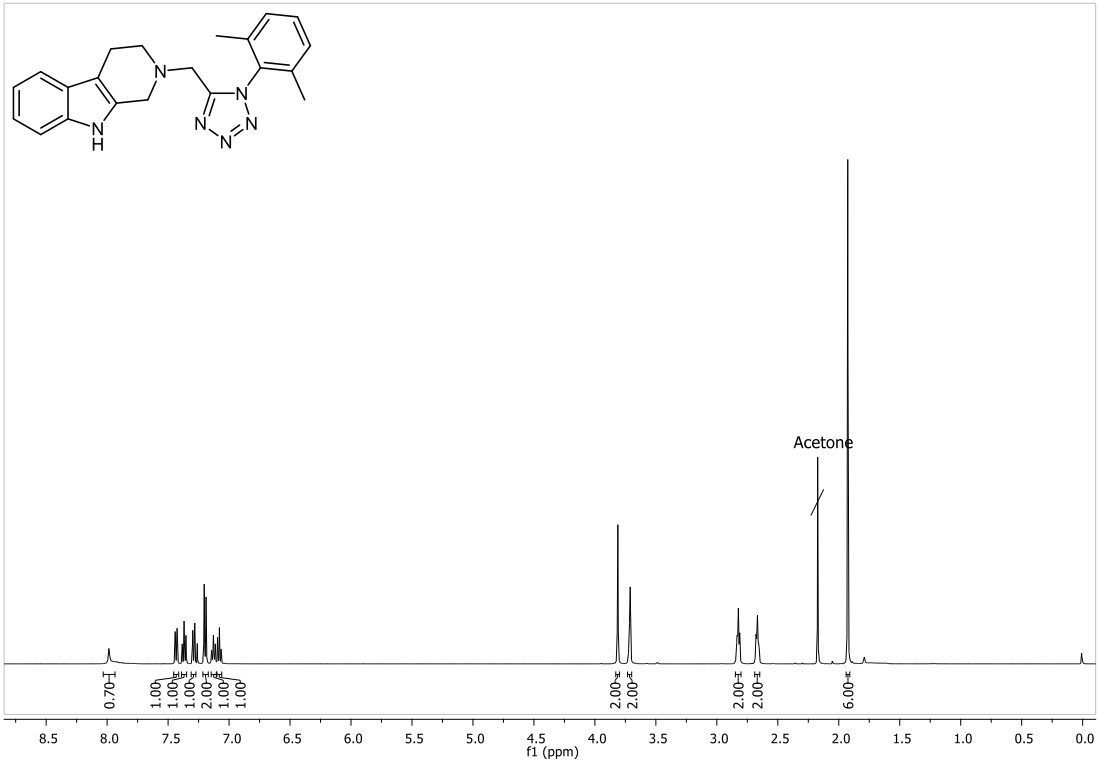


Figure S11. ^{1}H NMR spectrum of the product **4e**

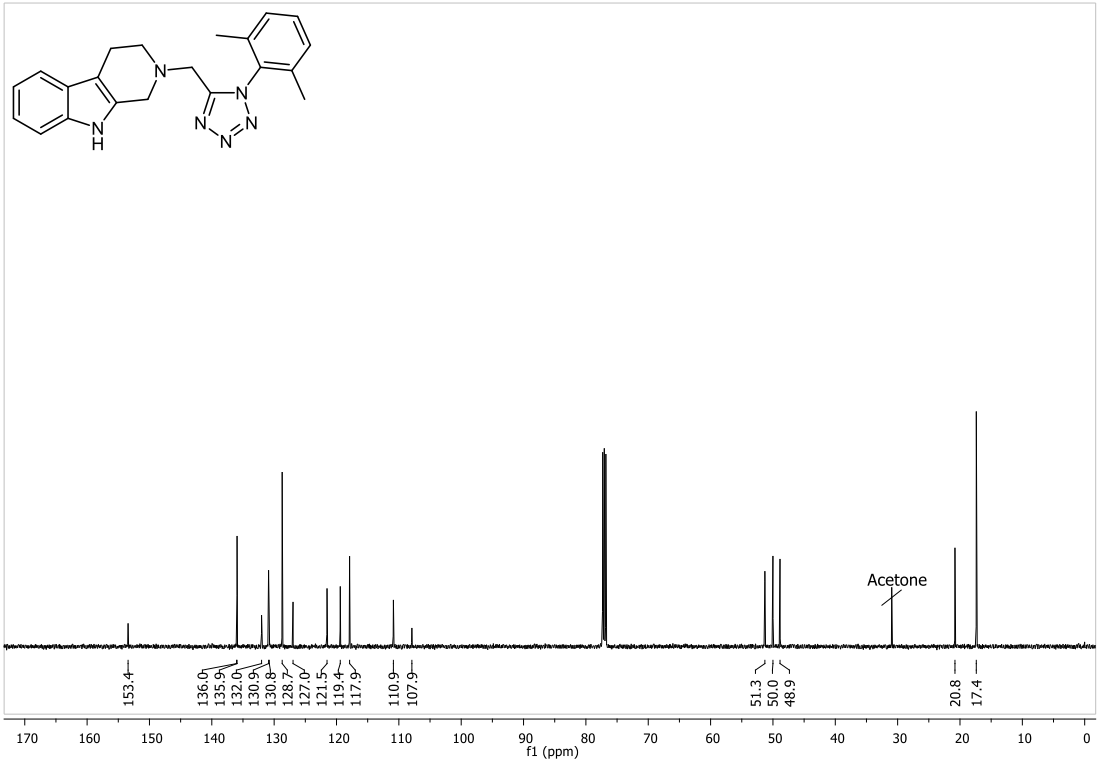


Figure S12. ^{13}C NMR spectrum of the product **4e**

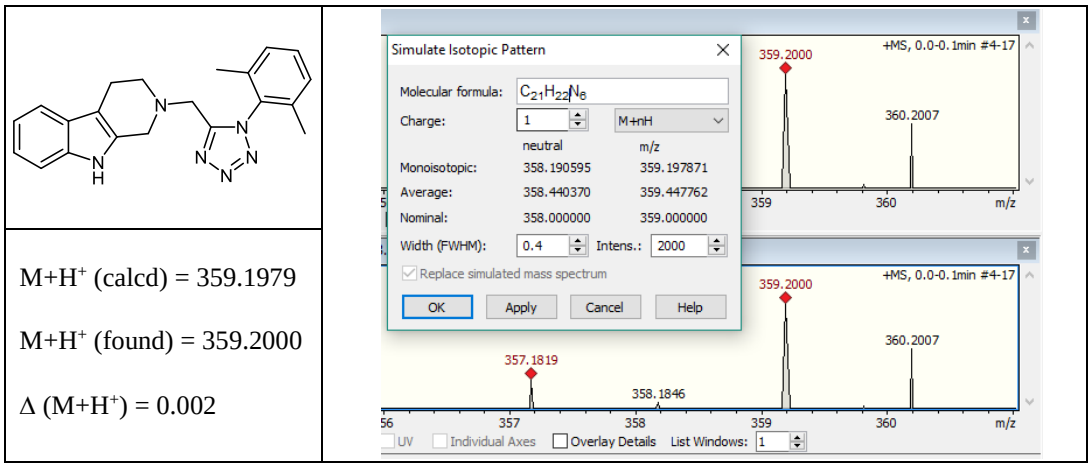


Figure S13. HRMS spectrum of the product **4e**

2-((1-(tosylmethyl)-1*H*-tetrazol-5-yl)methyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**4f**)

According to the GP1, tryptamine (164.0 mg, 1.000 mmol), paraformaldehyde (66.0 mg, 2.200 mmol of HCHO), tosylmethyl isocyanide (199.0 μL, 1.000 mmol), and azidotrimethylsilane (138.0 μL, 1.000 mmol) were reacted together during 6 hours in a mixture of MeOH (1.0 mL) with PhMe (1.0 mL) to afford the product **4f** (350.0 mg, 83%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 1/1 (v/v) as eluent; R_f = 0.56 (Hex–AcOEt, 1/1, v/v); mp = 149–151 °C, FT-IR (ATR) υ_{max}/cm^{-1} 1057 (SO), 1267 (N_3), 1456 (CN), 3229 (NH); ^{1}H and ^{13}C NMR: All attempts to acquire NMR spectra were unsuccessful due to unexpected insolubility problems; HRMS (ESI$^+$): *m/z* calcd for $C_{21}H_{22}N_6O_2S^+$ $[M+H]^+$ 423.1598, found 423.1609.

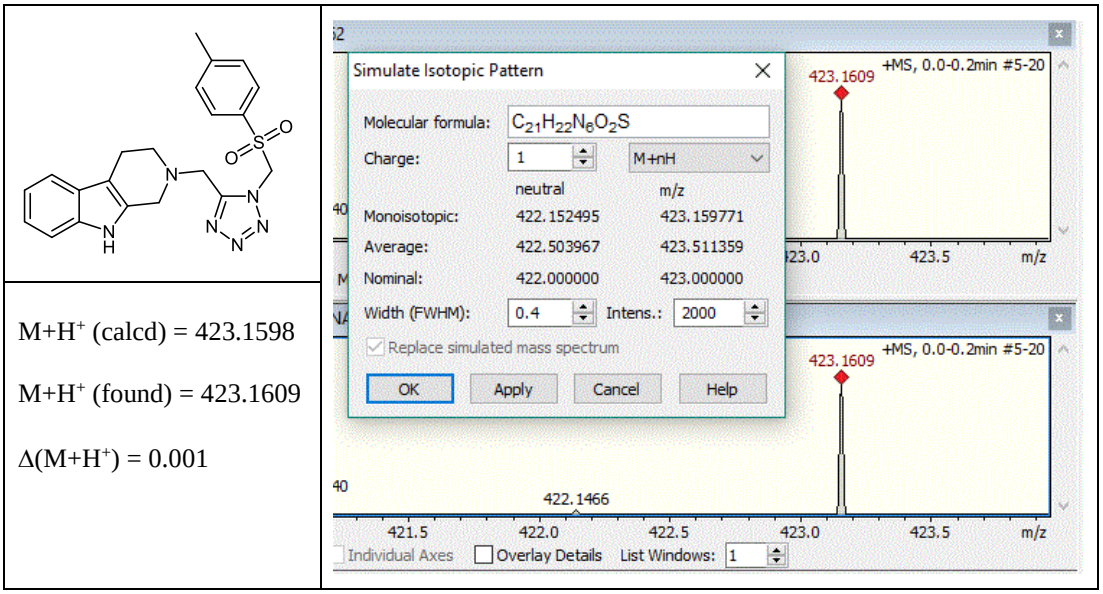
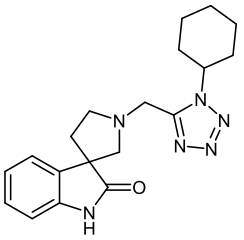


Figure S14. HRMS spectrum of the product **4f**

Synthesis and characterization of the 1'-tetrazolylmethyl-spiro[pyrrolidine-3,3'-oxindoles] **5a-f**

General procedure 2 (GP2): In a round-bottomed flask (10 mL) equipped with a magnetic stirring bar, to a stirred solution [0.5 M] of the corresponding 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carboline **4a-f** (1.0 equiv.) in a mixture 3/2/2 (v/v/v) of tetrahydrofuran (THF) / acetic acid (AcOH) / water (H_2O) under nitrogen atmosphere at -10 °C, *N*-bromo succinimide (NBS) (1.0–1.25 equiv.) was added portion wise. The resulting mixture was stirred at the same temperature for 40–120 minutes. Then, the solvent was removed to dryness and the crude was extracted three times using a concentrated aqueous solution of $NaHCO_3$ (30 mL) and DCM (60 mL). The combined organic layers were dried using anhydrous Na_2SO_4, filtered over a celite pad and concentrated to dryness. The crude was purified by silica-gel column chromatography to afford the products **5a-f**.

1’-((1-cyclohexyl-1*H*-tetrazol-5-yl)methyl)spiro[indoline-3,3’-pyrrolidin]-2-one (**5a**)



According to the GP2, 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carboline **4a** (100.0 mg, 0.291 mmol) and NBS (54.5 mg, 0.303 mmol) were reacted together during 45 min. in a mixture of THF (0.24 mL) with AcOH (0.16 mL) and H_2O (0.16 mL) to afford the product **5a** (96.0 mg, 94%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 1/1 to 2/3 (v/v) as eluent; R_f = 0.26 (Hex–AcOEt, 2/3, v/v); mp = 165–167 °C; FT-IR (ATR) υ_{max}/cm^{-1} 1265 (N_3), 1619 (CN), 1708 (CO), 3081 (NH); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.36–1.43 (m, 1H), 1.49–1.54 (m, 2H), 1.80–1.84 (m, 1H), 1.99–2.08 (m, 6H), 2.10–2.12 (m, 1H), 2.42–2.49 (m, 1H), 2.84 (q, *J* = 8.4 Hz, 1H), 2.94 (dd, *J* = 9.1, 24.0 Hz, 2H), 3.08–3.13 (m, 1H), 4.09 (s, 2H), 4.59–4.66 (m, 1H), 6.93–6.95 (m, 1H), 7.00–7.03 (m, 1H), 7.19–7.23 (m, 1H), 7.27–7.29 (m, 1H), 9.07 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, TMS): δ 24.9, 25.4 (2), 32.9, 33.1, 36.7, 47.5, 53.2, 54.3, 58.1, 64.3, 110.0, 122.7, 122.8, 128.1, 135.8, 140.2, 151.2, 181.9; HRMS (ESI$^+$): *m/z* calcd for $C_{19}H_{25}N_6O^+$ $[M+H]^+$ 353.2084, found 353.2084.

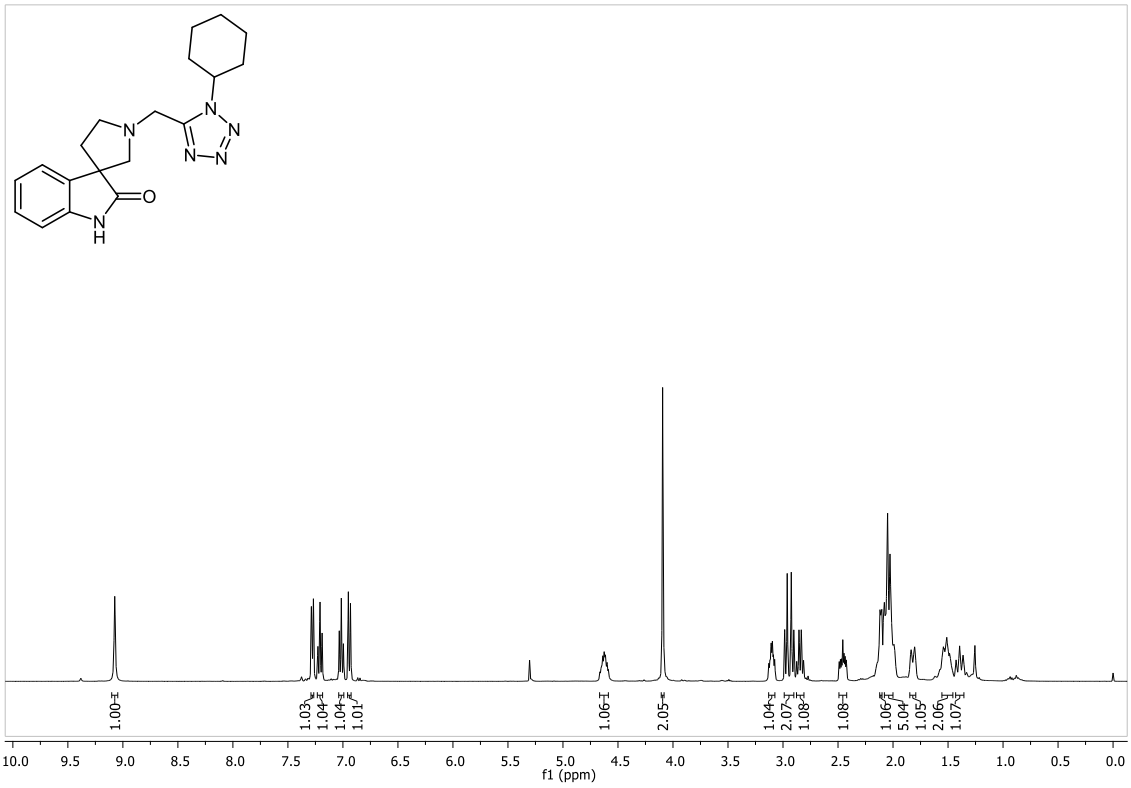


Figure S15. ^{1}H NMR spectrum of the product **5a**

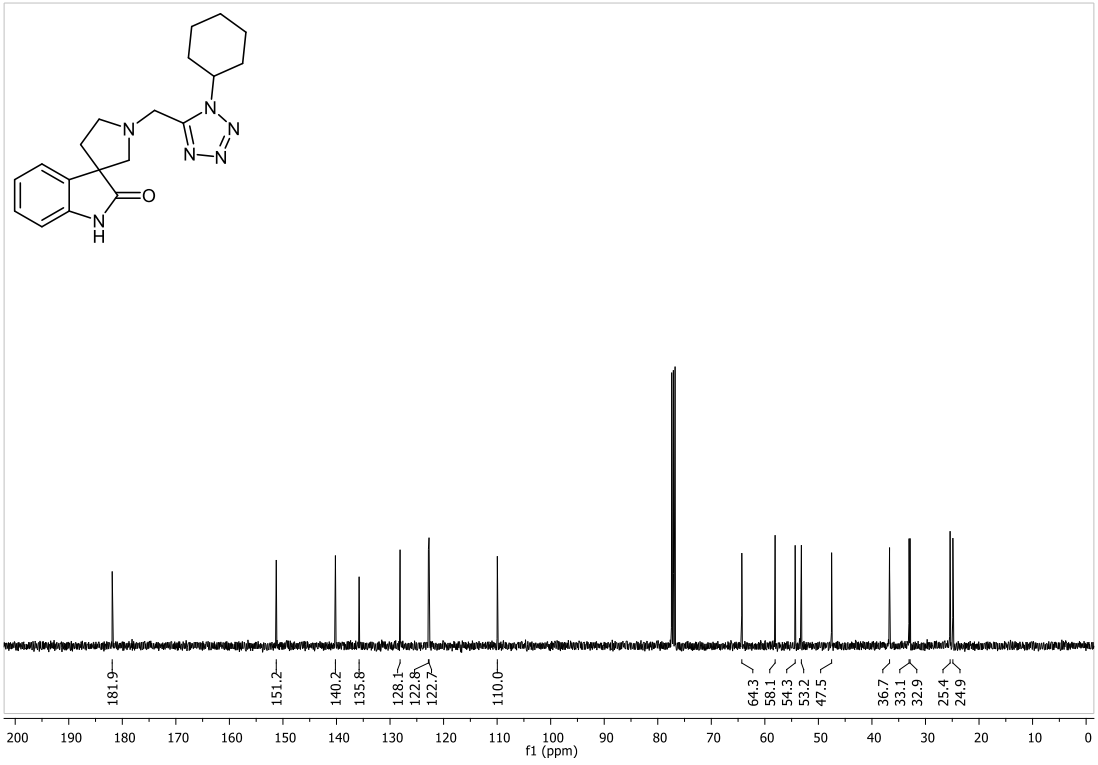
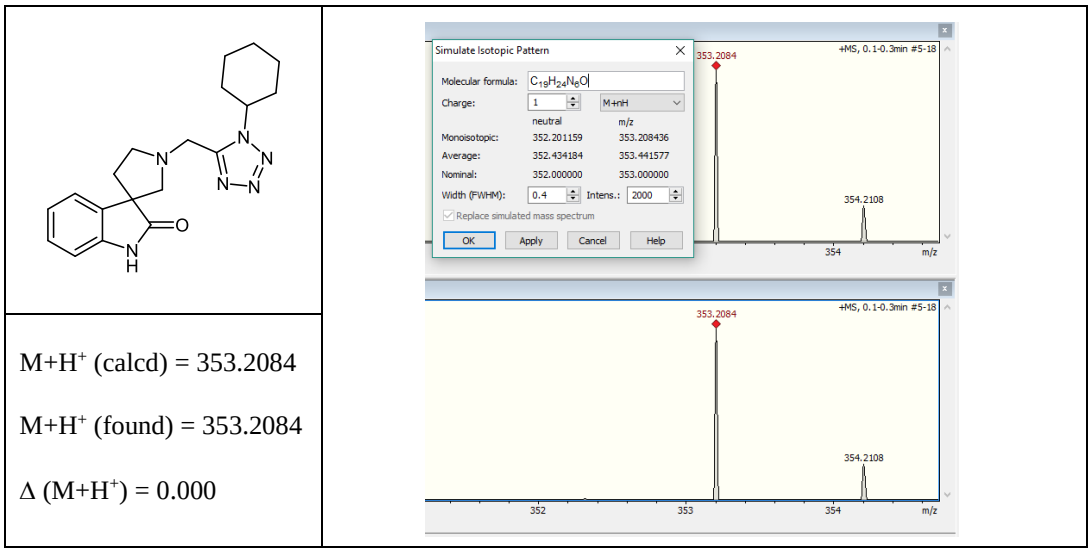


Figure S16. ^{13}C NMR spectrum of the product **5a**



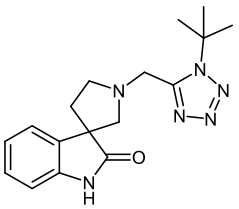
$M+H^+$ (calcd) = 353.2084

$M+H^+$ (found) = 353.2084

Δ ($M+H^+$) = 0.000

Figure S17. HRMS spectrum of the product **5a**

1’-((1-(tert-butyl)-1*H*-tetrazol-5-yl)methyl)spiro[indoline-3,3’-pyrrolidin]-2-one (**5b**)



According to the GP2, 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carboline **4b** (100.0 mg, 0.316 mmol) and NBS (59.0 mg, 0.328 mmol) were reacted together during 45 min. in a mixture of THF (0.27 mL) with AcOH (0.18 mL) and H_2O (0.18 mL) to afford the product **5b** (75.0 mg, 73%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 1/1 (v/v) as eluent; R_f = 0.39 (Hex–AcOEt, 3/7, v/v); mp = 120–122 °C; FT-IR (ATR) υ_{max}/cm^{-1} 1235 (N_3), 1617 (CN), 1704 (CO), 3187 (NH); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 1.84 (s, 9H), 2.05–2.11 (m, 1H), 2.41–2.46 (m, 1H), 2.89 (dd, *J* = 8.1, 16.6 Hz, 1H), 2.96 (d, *J* = 9.4 Hz, 1H), 3.01 (d, *J* = 9.4 Hz, 1H), 3.06–3.10 (m, 1H), 4.14 (s, 2H), 6.87–6.88 (m, 1H), 7.00–7.03 (m, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 8.13 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 29.6, 37.1, 49.2, 53.0, 54.3, 62.0, 64.1, 109.6, 122.9, 123.0, 128.1, 135.6, 140.0, 151.6, 181.7; HRMS (ESI$^+$): *m/z* calcd for $C_{17}H_{22}N_6O^+$ $[M+H]^+$ 327.1928, found 327.1935.

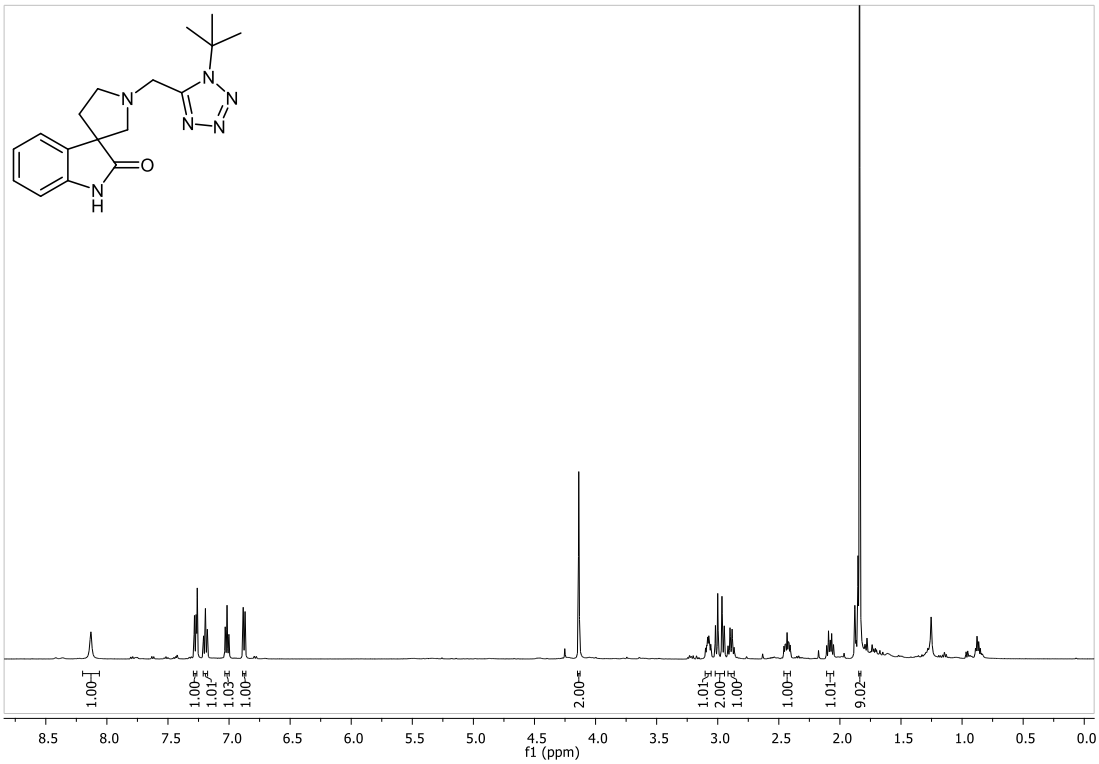


Figure S18. ^{1}H NMR spectrum of the product **5b**

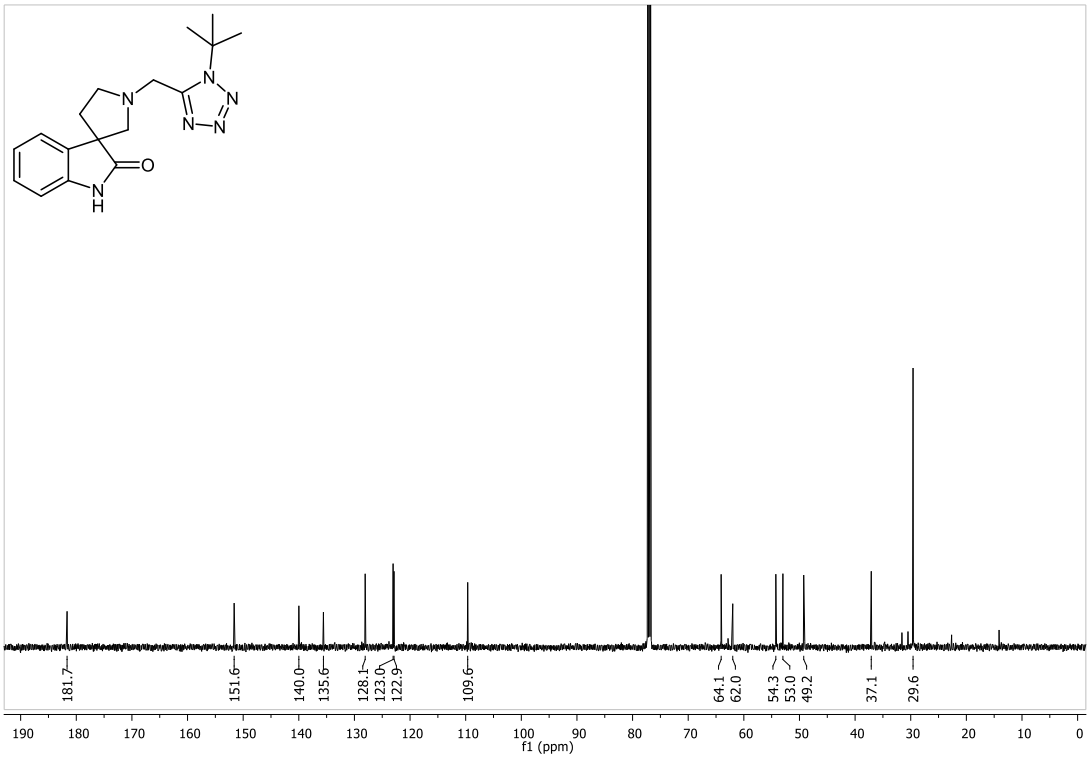
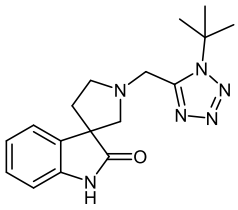


Figure S19. ^{13}C NMR spectrum of the product **5b**



$M+H^+$ (calcd) = 327.1928

$M+H^+$ (found) = 327.1935

Δ ($M+H^+$) = 0.0007

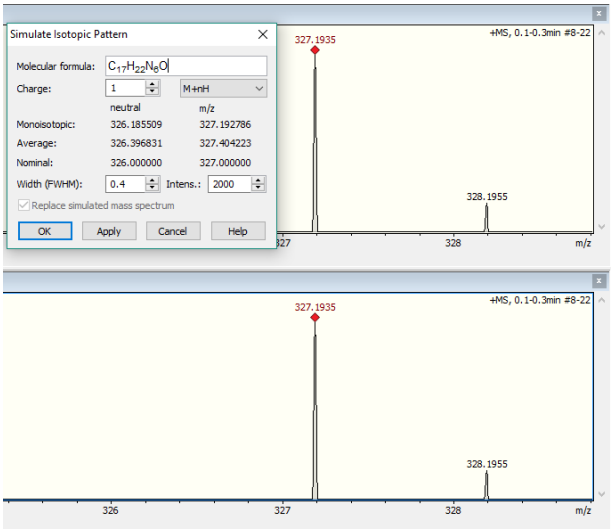


Figure S20. HRMS spectrum of the product **5b**

1’-((1-benzyl-1*H*-tetrazol-5-yl)methyl)spiro[indoline-3,3’-pyrrolidin]-2-one (**5c**)

According to the GP2, 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carboline **4c** (128.0 mg, 0.364 mmol) and NBS (81.2 mg, 0.452 mmol) were reacted together during 120 min. in a mixture of THF (0.30 mL) with AcOH (0.20 mL) and H_2O (0.20 mL) to afford the product **5c** (96.0 mg, 73%) as a white crystals after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 1/1 (v/v) as eluent and a recrystallization using the same solvent system (CCDC: 1549898); R_f = 0.13 (Hex–AcOEt, 1/1, v/v); mp = 202–204 °C, FT–IR (ATR) υ_{max}/cm^{-1} 1243 (N_3), 1614 (CN), 1703 (CO), 3182 (NH); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 2.05–2.10 (m, 1H), 2.42–2.47 (m, 1H), 2.83 (d, *J* = 9.4 Hz, 1H), 2.84–2.89 (m, 1H), 2.94–2.96 (m, 1H), 2.99 (d, *J* = 9.4 Hz, 1H), 3.90 (dd, *J* = 14.0, 18.0 Hz, 2H), 5.83 (s, 2H), 6.88 (d, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.18–7.22 (m, 2H), 7.28–7.30 (m, 2H), 7.35–7.37 (m, 3H), 8.41 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 37.0, 47.5, 51.3, 53.0, 54.4, 64.0, 109.8, 122.9, 123.0, 127.9, 128.2, 128.8, 129.1, 133.6, 135.0, 140.1, 152.2, 182.0; HRMS (ESI$^+$): *m/z* calcd for $C_{20}H_{20}N_6O^+$ [M+H]$^+$ 361.1771, found 361.1772.

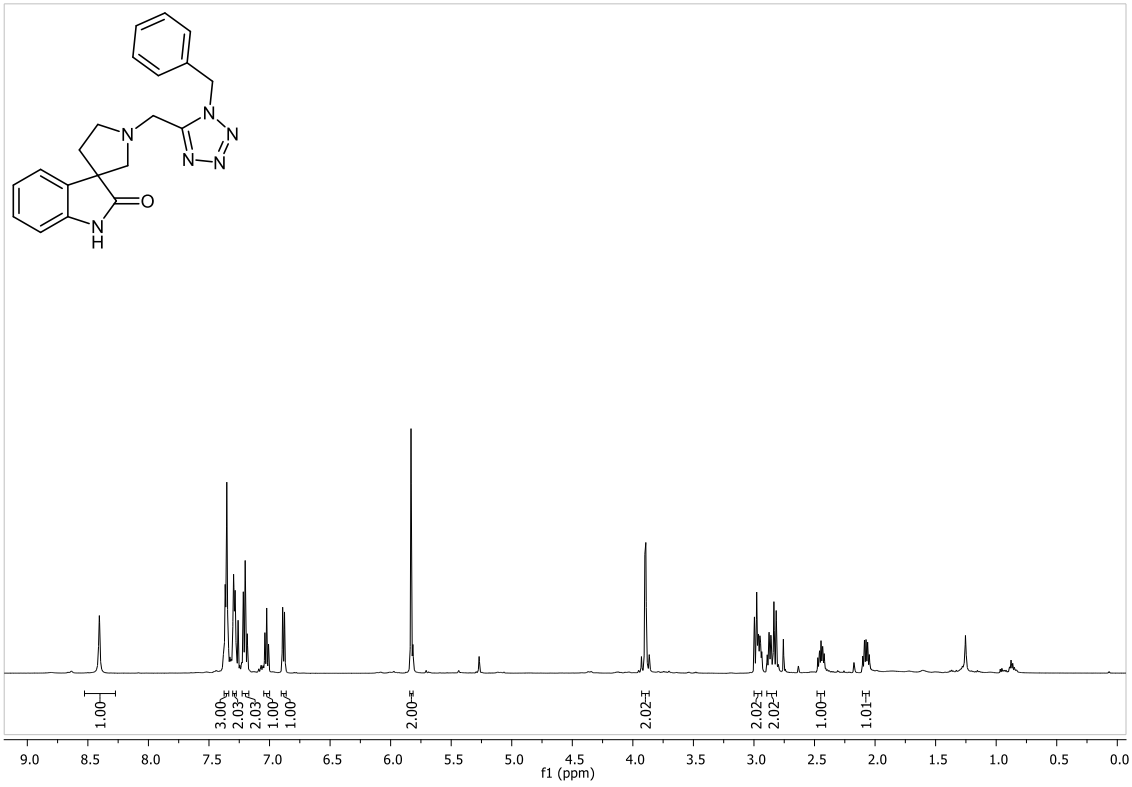


Figure S21. ^{1}H NMR spectrum of the product **5c**

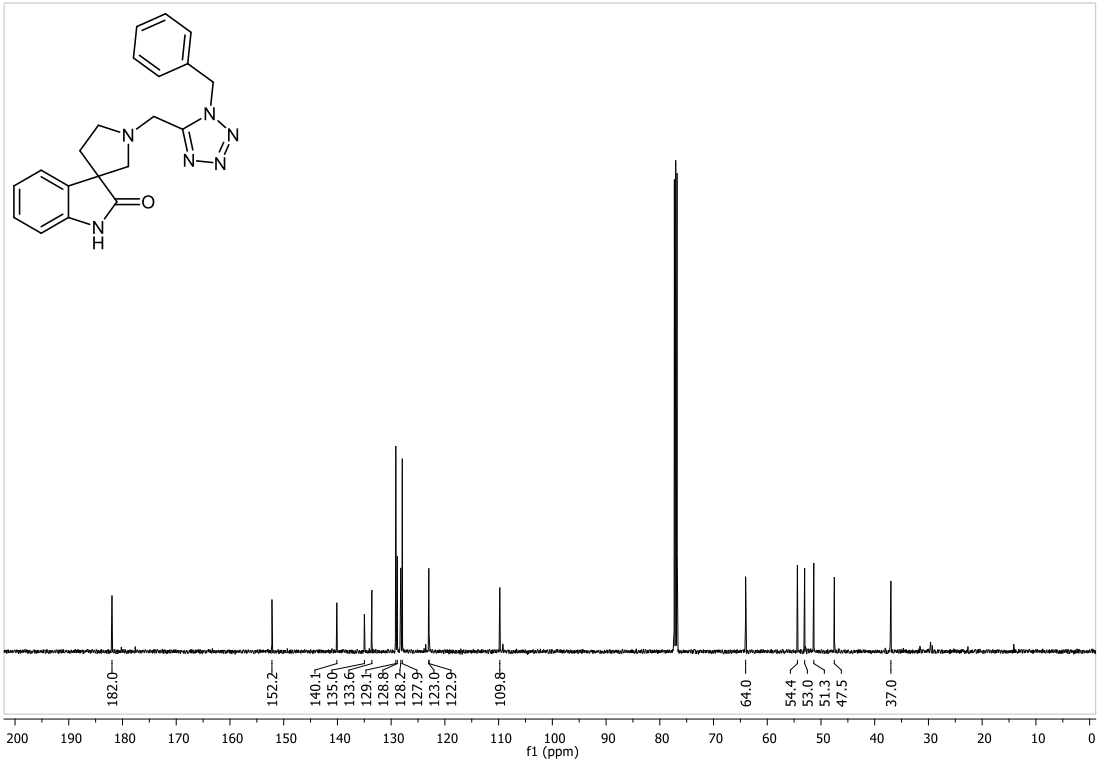
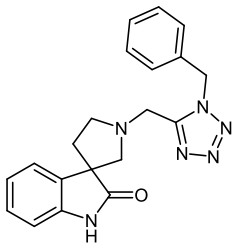


Figure S22. ^{13}C NMR spectrum of the product **5c**



$M+H^+$ (calcd) = 361.1771

$M+H^+$ (found) = 361.1772

Δ ($M+H^+$) = 0.0001

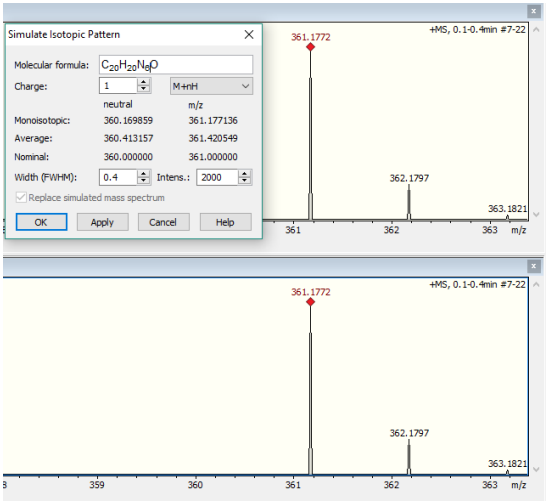
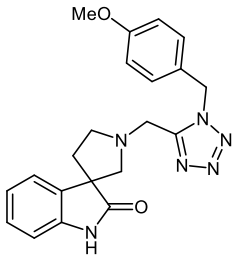


Figure S23. HRMS spectrum of the product **5c**

1'-((1-(4-methoxybenzyl)-1*H*-tetrazol-5-yl)methyl)spiro[indoline-3,3'-pyrrolidin]-2-one (**5d**)



According to the GP2, 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carboline **4d** (100.0 mg, 0.262 mmol) and NBS (48.9 mg, 0.272 mmol) were reacted together during 60 min. in a mixture of THF (0.22 mL) with AcOH (0.14 mL) and H_2O (0.14 mL) to afford the product **5d** (85.0 mg, 83%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 1/1 (v/v) as eluent; R_f = 0.23(Hex–AcOEt, 3/7, v/v); mp = 134–136 °C, FT-IR (ATR) υ_{max}/cm^{-1} 1294 (N_3), 1614 (CN), 1709 (CO), 3185 (NH); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 2.07–2.12 (m, 1H), 2.44–2.49 (m, 1H), 2.84 (d, *J* = 9.4 Hz, 1H), 2.86–2.91 (m, 1H), 2.96–2.98 (m, 1H), 3.00 (d, *J* = 9.4 Hz, 1H), 3.79 (s, 3H), 3.90 (dd, *J* = 14.0, 18.0 Hz, 2H), 5.76 (s, 2H), 6.87–6.90 (m, 3H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.24–7.27 (m, 3H), 8.57 (bs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 37.0, 47.5, 50.9, 53.1, 54.4, 55.3, 64.0, 109.8, 114.5, 123.0, 125.6, 128.2, 129.5, 135.0, 140.2, 152.0, 160.0, 181.9; HRMS (ESI$^+$): *m/z* calcd for $C_{21}H_{22}N_6O_2^+$ $[M+H]^+$ 391.1877, found 391.1879.

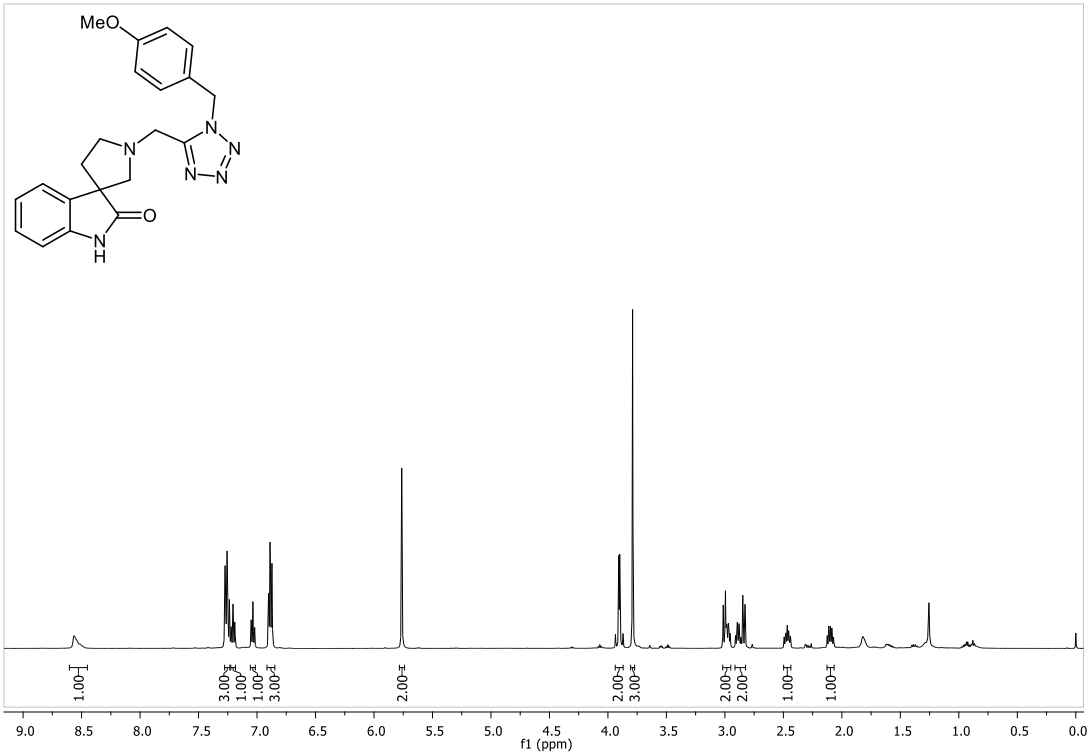


Figure S24. ^{1}H NMR spectrum of the product **5d**

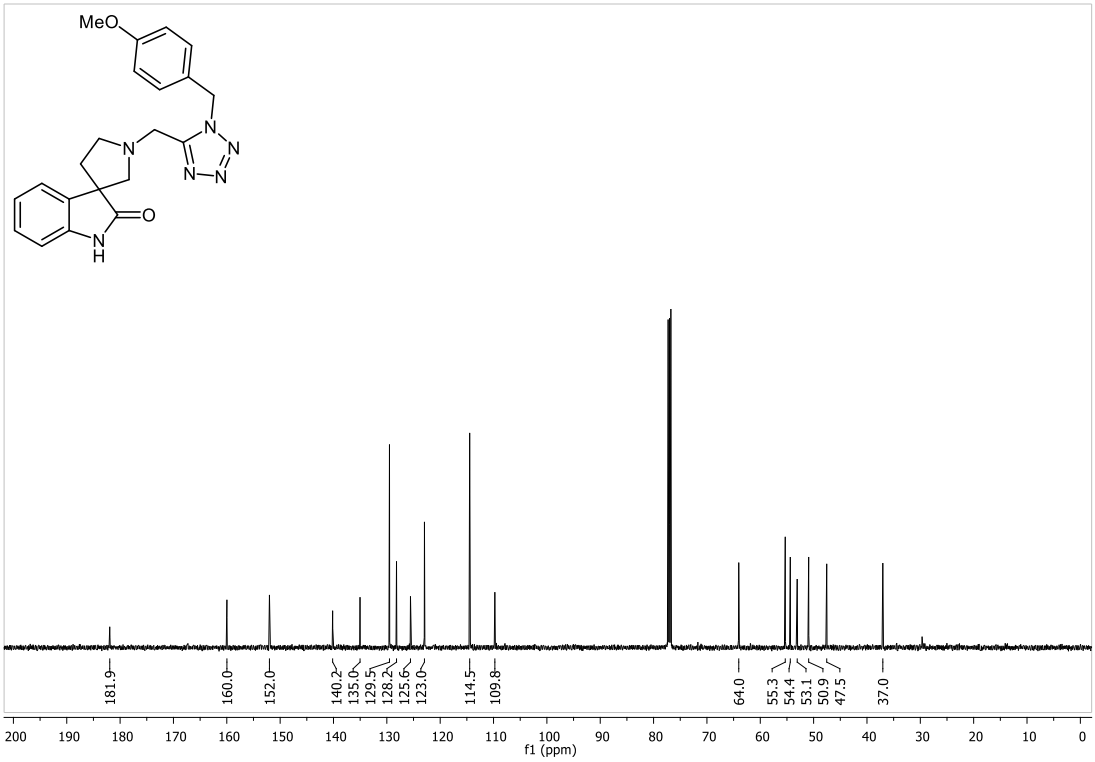


Figure S25. ^{13}C NMR spectrum of the product **5d**

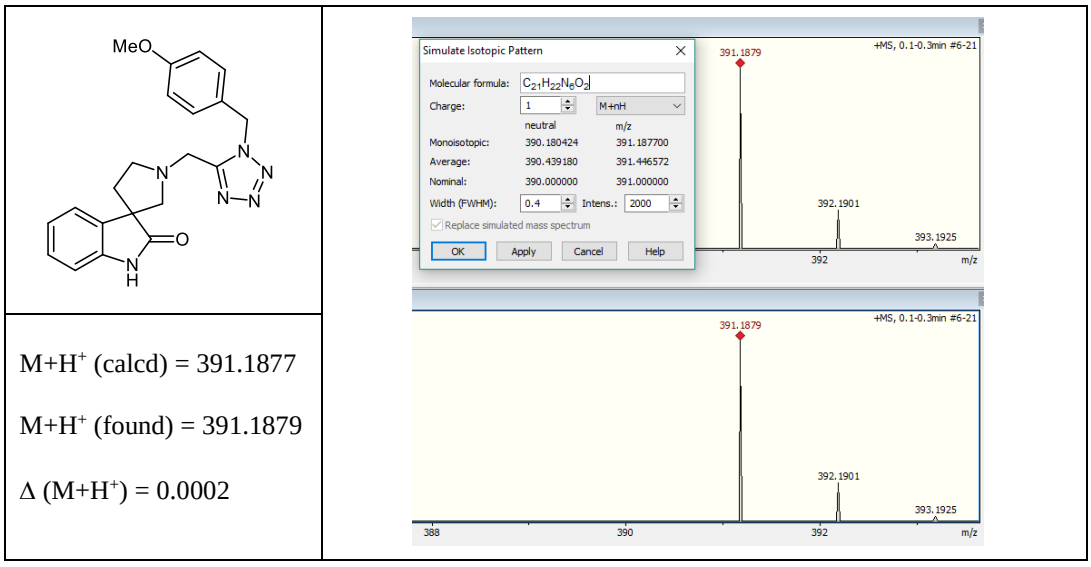
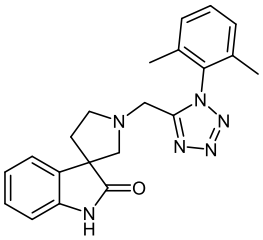


Figure S26. HRMS spectrum of the product **5d**

1’-((1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)methyl)spiro[indoline-3,3’-pyrrolidin]-2-one (**5e**)



According to the GP2, 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carboline **4e** (100.0 mg, 0.273 mmol) and NBS (51.0 mg, 0.284 mmol) were reacted together during 60 min. in a mixture of THF (0.23 mL) with AcOH (0.15 mL) and H_2O (0.15 mL) to afford the product **5e** (88.0 mg, 86%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 7/3 to 3/2 (v/v) as eluent; R_f = 0.21 (Hex–AcOEt, 1/1, v/v); mp = 203–205 °C; FT-IR (ATR) υ_{max}/cm^{-1} 1253 (N_3), 1612 (CN), 1703 (CO), 3196 (NH); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 2.00 (s, 3H), 2.04 (s, 3H), 2.07 (s, 1H), 2.37–2.42 (m, 1H), 2.82 (dd, *J* = 8.7, 17.2 Hz, 1H), 2.92 (d, *J* = 9.3 Hz, 1H), 3.03 (d, *J* = 9.2 Hz, 1H), 3.19–3.23 (m, 1H), 3.83–3.89 (m, 2H), 6.87 (d, *J* = 7.7 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.18–7.22 (m, 2H), 7.28–7.29 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.80 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, TMS): δ 17.5 (2), 37.4, 47.0, 53.0, 54.5, 64.3, 109.4, 122.9, 123.3, 128.0, 128.8, 128.9, 130.9, 135.6, 135.7, 135.9, 139.7, 153.4, 181.5; HRMS (ESI$^+$) *m/z* calcd for $C_{21}H_{22}N_6O^+$ $[M+H]^+$ 375.1928, found 375.1939.

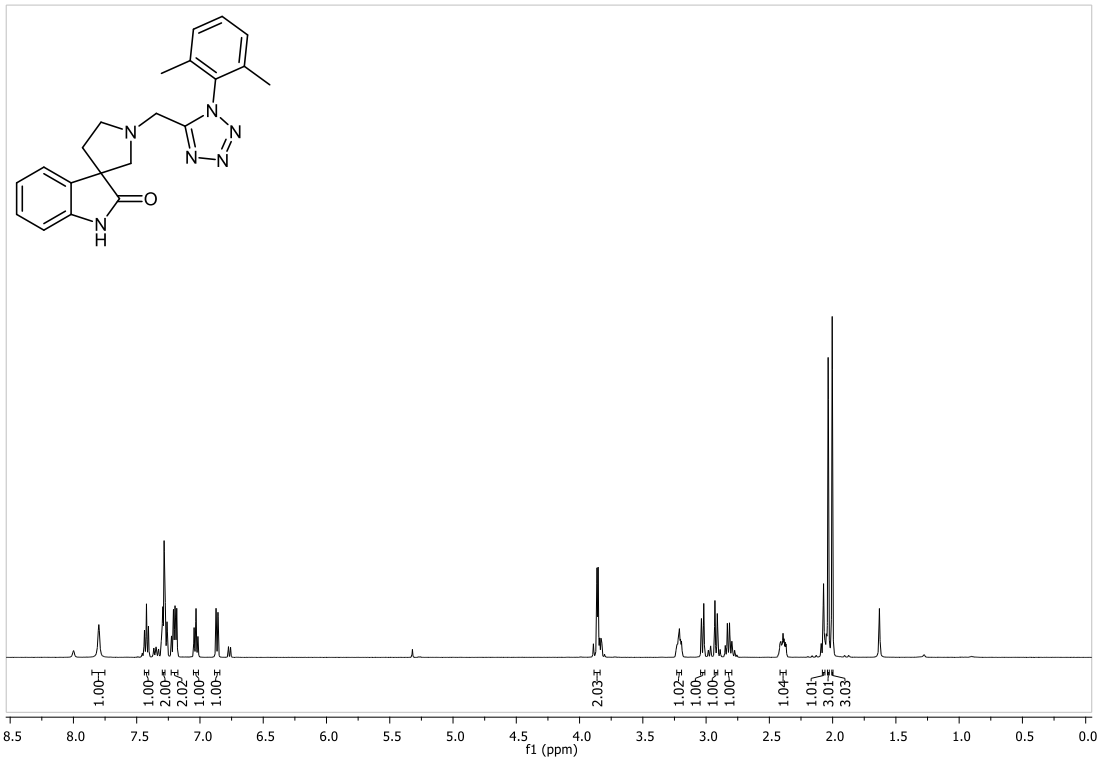


Figure S27. ^{1}H NMR spectrum of the product **5e**

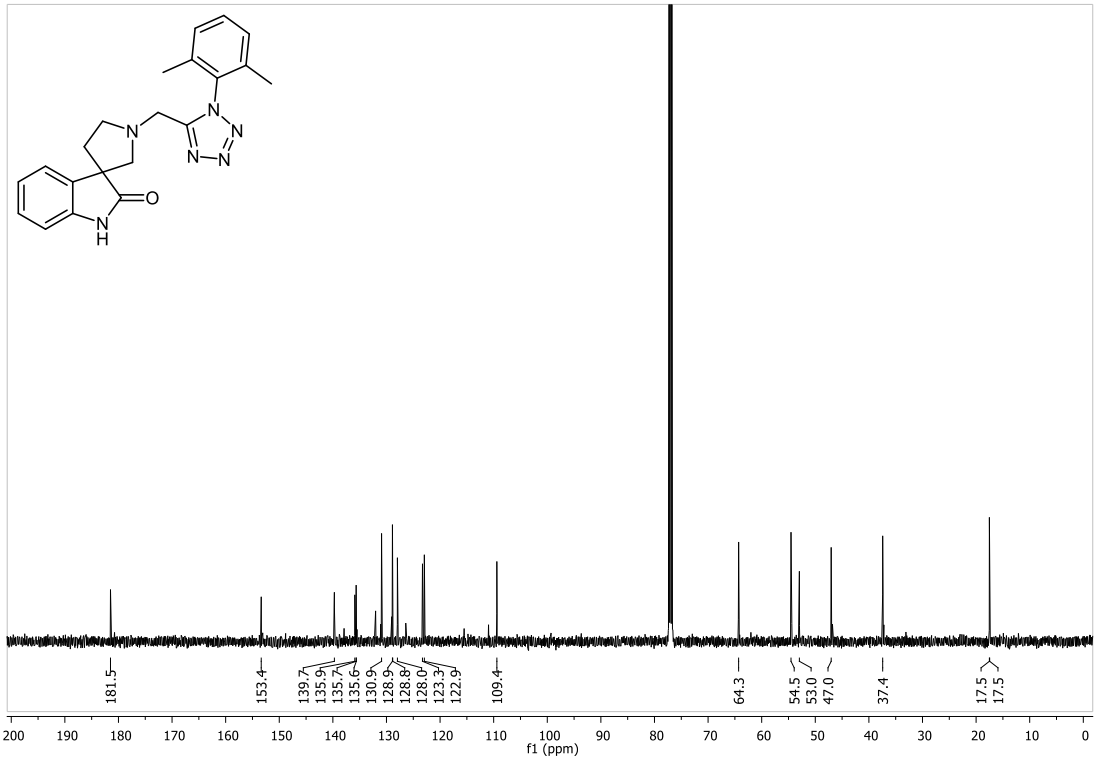


Figure S28. ^{13}C NMR spectrum of the product **5e**

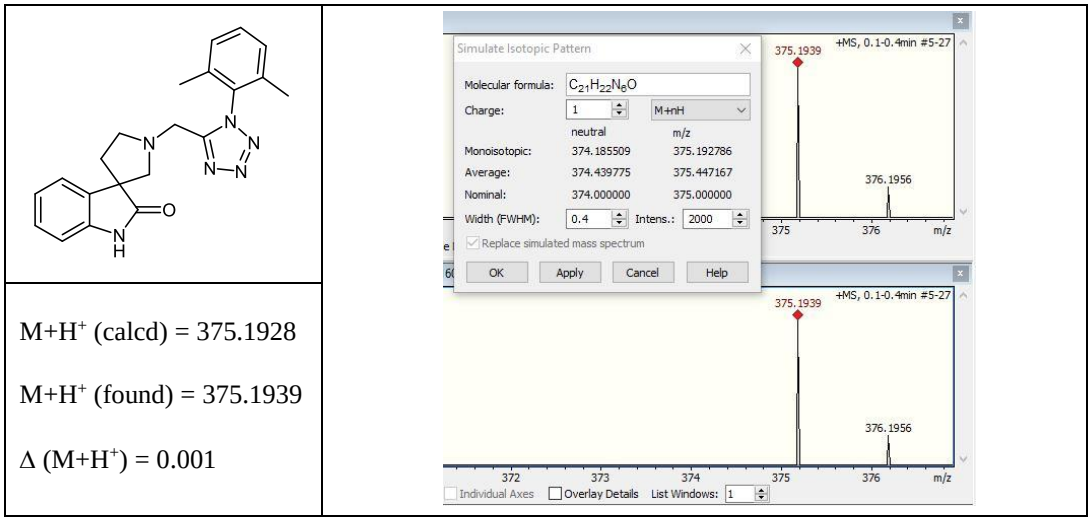
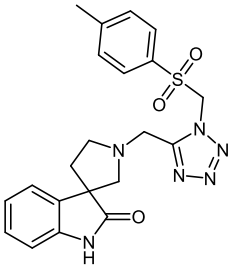


Figure S29. HRMS spectrum of the product **5e**

1’-((1-(tosylmethyl)-1*H*-tetrazol-5-yl)methyl)spiro[indoline-3,3’-pyrrolidin]-2-one (**5f**)



According to the GP2, 2-tetrazolylmethyl-2,3,4,9-tetrahydro-1*H*-β-carboline **4f** (100.0 mg, 0.232 mmol) and NBS (43.4 mg, 0.241 mmol) were reacted together during 40 min. in a mixture of THF (0.20 mL) with AcOH (0.13 mL) and H_2O (0.13 mL) to afford the product **5f** (87.0 mg, 86%) as a white solid after purification by silica-gel column chromatography using a mixture of hexanes with ethyl acetate 1/1 (v/v) as eluent; R_f = 0.36 (Hex–AcOEt, 3/7, v/v); mp = 187–189 °C; FT-IR (ATR) υ_{max}/cm^{-1} 1247 (N_3), 1624 (CN), 1685 (CO), 3199 (NH); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 2.11–2.15 (m, 1H), 2.44 (s, 1H), 2.46–2.50 (m, 3H), 2.80 (d, *J* = 9.6 Hz, 1H), 2.93–2.98 (m, 1H), 3.04 (d, *J* = 9.7 Hz, 1H), 3.07–3.10 (m, 1H), 4.30 (d, *J* = 15.0 Hz, 1H), 4.36 (d, *J* = 15.0 Hz, 1H), 6.29 (s, 2H), 6.92 (d, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.25–7.26 (m, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 8.38 (s, 1H); 13C NMR (126 MHz, $CDCl_3$, TMS): δ 21.8, 36.6, 47.7, 52.9, 54.3, 63.7, 65.5, 109.9, 122.9, 123.0, 128.4, 128.8, 130.4, 132.6, 133.8, 140.3, 146.7, 153.6, 182.2; HRMS (ESI$^+$): *m/z* calcd for $C_{21}H_{22}N_6O_3S^+$ $[M+H]^+$ 439.1547, found 439.1553.

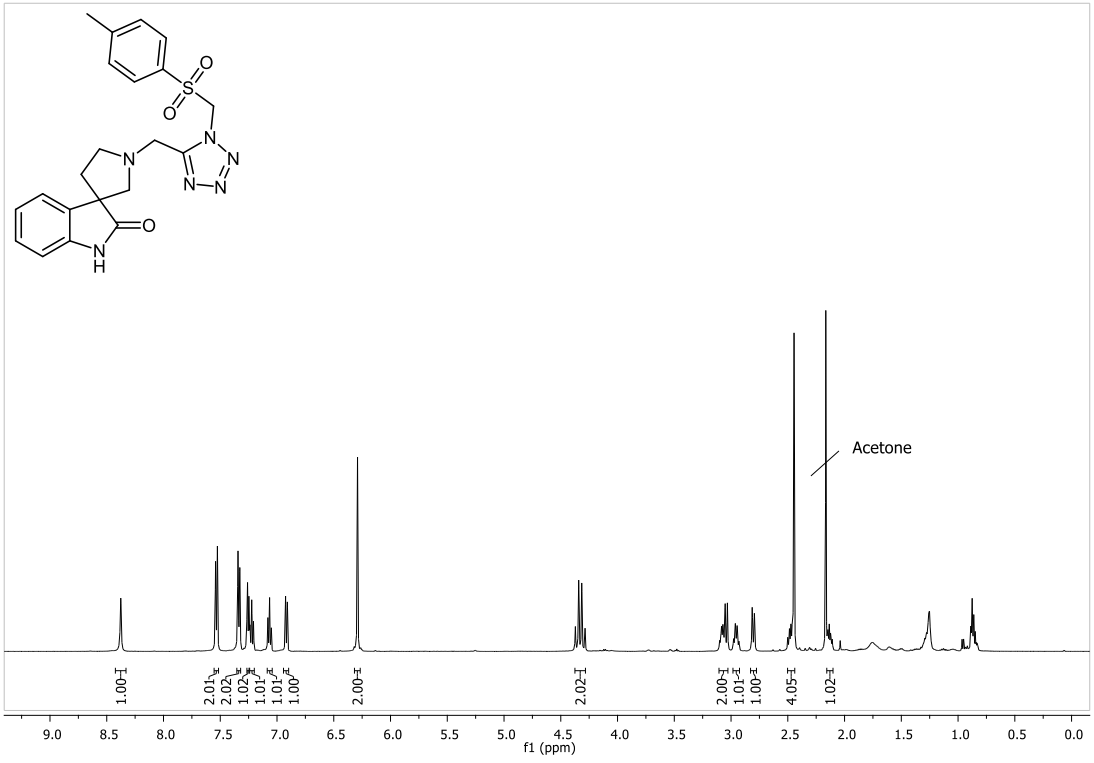


Figure S30. ^{1}H NMR spectrum of the product **5f**

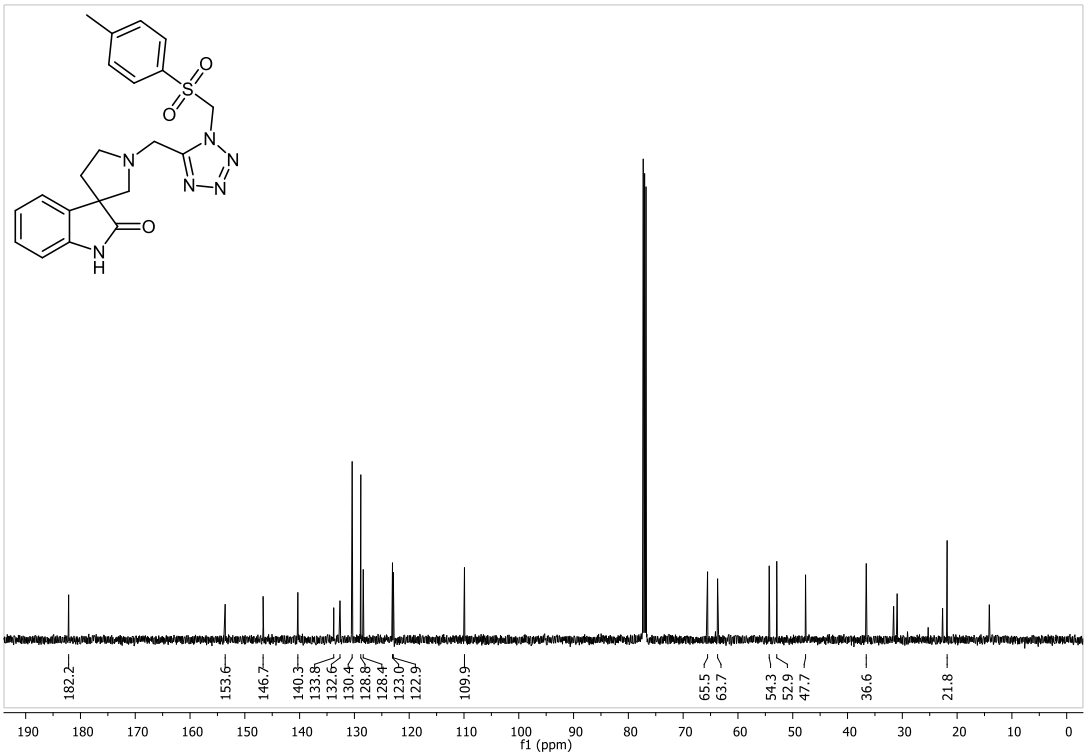


Figure S31. ^{13}C NMR spectrum of the product **5f**

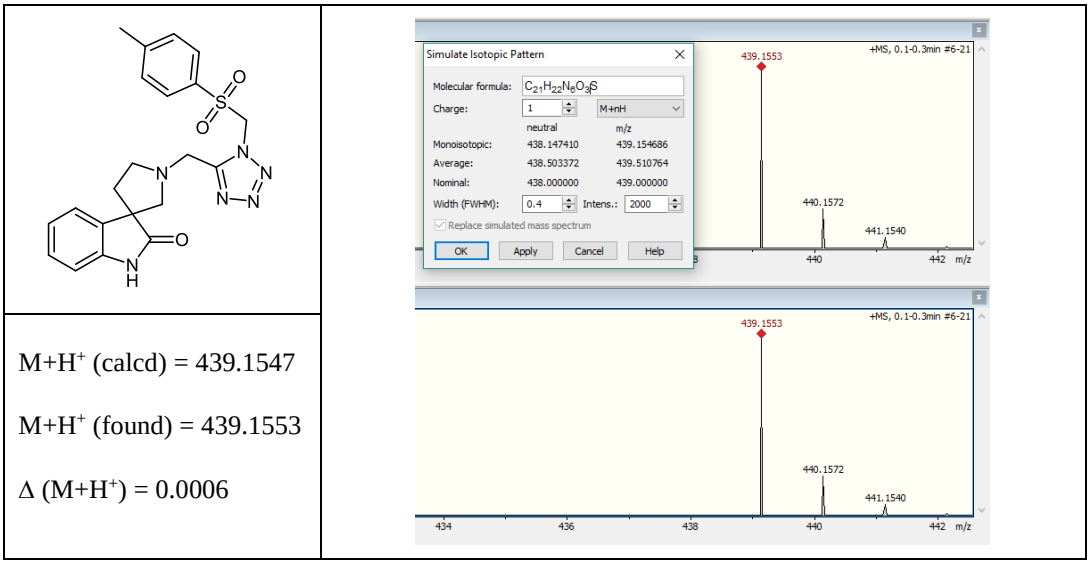


Figure S32. HRMS spectrum of the product **5f**