# Synthesis of 3-tetrazolylmethyl-azepino[4,5-*b*]indol-4-ones in two reaction steps: (Ugi-azide / *N*-acylation / $S_N2$) / free radical cyclization and docking studies to a 5-$Ht_6$ model

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## 1.- Experimental

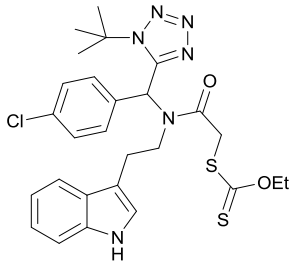
### General Information

$^{1}H$ and $^{13}C$ NMR spectra were acquired on either, Varian Unit (300 MHz) or Bruker Advance (300 MHz) spectrometers in deuterated chloroform ($CDCl_3$) solutions with internal reference (TMS, $\delta$ = 0.0 ppm). Chemical shifts are reported in parts per million ($\delta$/ppm). Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of the signals are reported using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). $^{13}C$ NMR spectra were recorded at 75 MHz on the same spectrometers. IR spectra were acquired on a Bruker Tensor 27 spectrophotometer. High resolution mass spectra were recorded on a Jeol SX-102A instrument. Microwave assisted reactions were performed using a CEM Discover$^{TM}$ Synthesis Unit with a monomodal open vessel system. Reaction progress was monitored by TLC on precoated silica gel Kieselgel 60 F254 plates; the spots were visualized under UV light (254-365 nm). Flash column chromatography was performed using silica gel (230-400 mesh) and different solvent mixtures as mobile phase. Melting points were determined on a Fisher-Johns apparatus and were uncorrected. All starting materials were purchased from commercial sources and were used as soon as received. The solvents were distilled and dried according to standard procedures (THF using Na/Benzophenone; 1,2-dichloroethane and dichloromethane using $CaH_2$).

### Synthesis and characterization of xanthates 6a-i

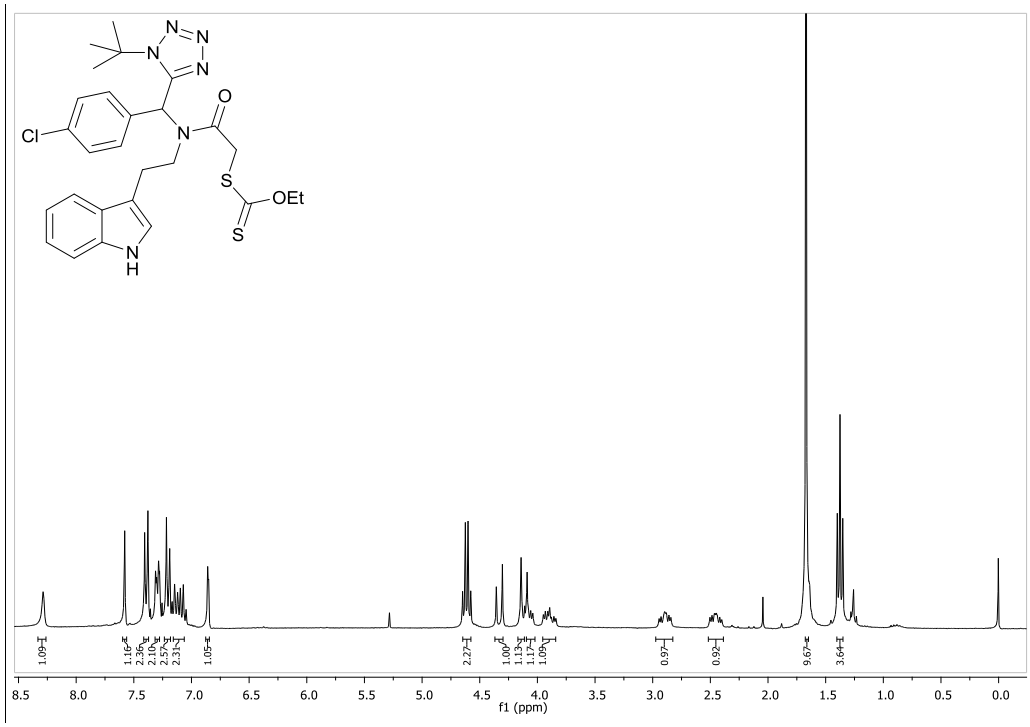
General procedure for the synthesis of xanthates **6a-i**: To a stirred solution of tryptamine (1.0 equiv.) under inert atmosphere ($N_2$) in dry MeOH (0.5 M) at room temperature, trimethylsilyl azide (1.2 equiv.), isocyanide (1.2 equiv.) and aldehyde (1.0 equiv.) were sequentially added. The reaction mixture was stirred for 24 h at room temperature. Then, the solvent was replaced by $CH_2Cl_2$ (0.5 M) and chloroacetyl chloride (1.5 equiv.) and triethylamine (1.5 equiv.) were sequentially added. The reaction mixture was stirred for 2 h at room temperature. Finally, the solvent was replaced by MeOH again (0.5 M) and potassium ethyl xanthogenate salt (3.0 equiv.) was added. The reaction mixture was stirred for 3 h at room temperature and then, the solvent was removed untyl dryness. The crude was dissolved in AcOEt and washed with a concentrated aqueous solution of $NaHCO_3$ and with brine. The organic layer was dried with $Na_2SO_4$ anhydrous and filtered over a celite pad. The solvent was removed untyl dryness. The residue was immediately purified by chromatoflash (Hex-AcOEt = 7/3 V/V) to afford the xanthates **6a-i**.

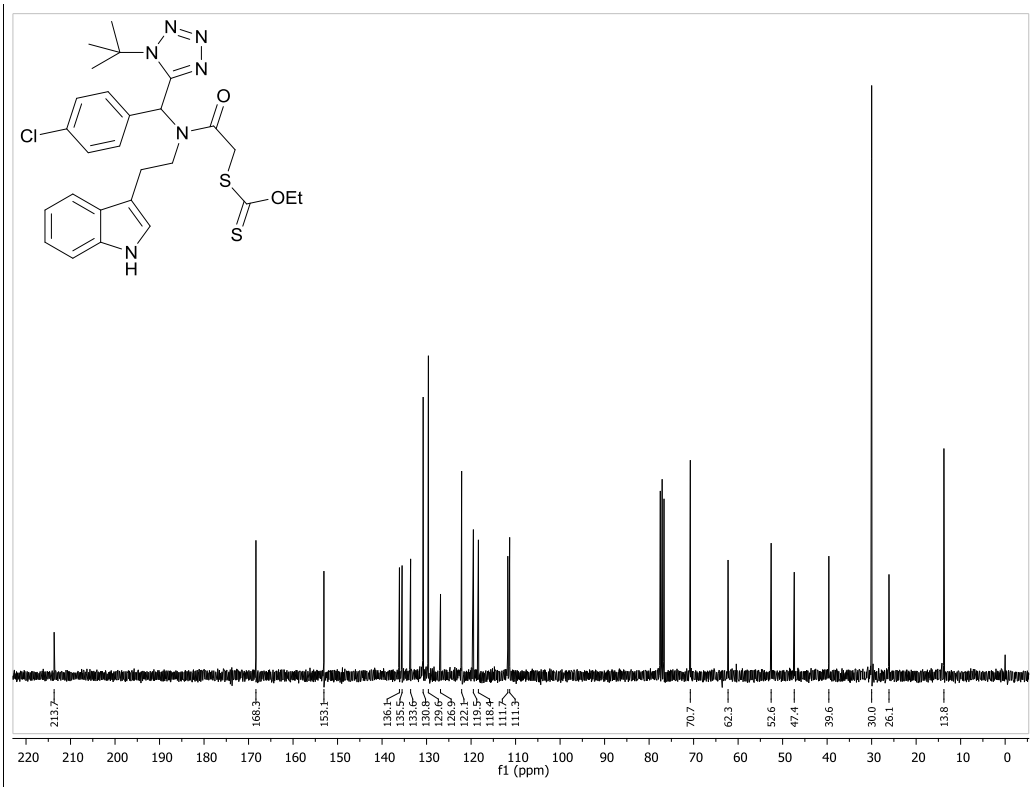
*S*-(*N*-(2-(1*H*-indol-3yl)ethyl)-*N*-((1-*tert*-butyl-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl)carbamoyl)methyl-*O*-ethyl-carbonodithionate (**6a**)



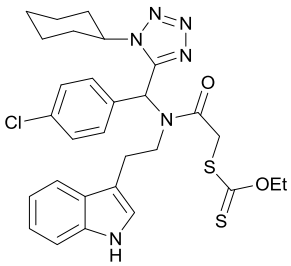

Yield 61 %, physical appearance: pale yellow powder, mp = 150 $^{o}$C, $R_f$ = 0.31 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1050, 1230, 1645 (C=O), 2936 and 3337; $\delta_H$ (300 MHz, $CDCl_3$) 1.37 (3 H, t, *J* 7.1, $CH_3$), 1.66 (9 H, s, 3 $CH_3$), 2.39-2.50 (1 H, m, 1 H of $CH_2$), 2.83-2.94 (1 H, m, 1 H of $CH_2$), 3.82-3.94 (1 H, m, 1 H of $CH_2$), 4.02-4.07 (1 H, m, 1 H of $CH_2$), 4.11 (1 H, d, *J* 15.6, 1 H of $CH_2$), 4.32 (1 H, d, *J* 15.6, 1 H of $CH_2$), 4.61 (2 H, q, *J* 7.1, $CH_2$), 6.85 (1 H, d, *J* 2.1, CH), 7.02-7.17 (2 H, m, ArH), 7.20 (2 H, d, *J* 8.5, ArH), 7.26-7.32 (2 H, m, ArH), 7.39 (2 H, d, *J* 8.5, ArH), 7.57 (1 H, s, ArH) and 8.28 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 13.8, 26.1, 30.0, 39.6, 47.4, 52.6, 62.3, 70.7, 111.3, 111.7, 118.4, 119.5, 122.1, 126.9, 129.6, 130.8, 133.6, 135.5, 136.1, 153.1, 168.3 and 213.7; HRMS (FAB+, M+) calcd. for $C_{27}H_{31}ClN_6S_2O_2$: 571.1717, found: 571.1714.



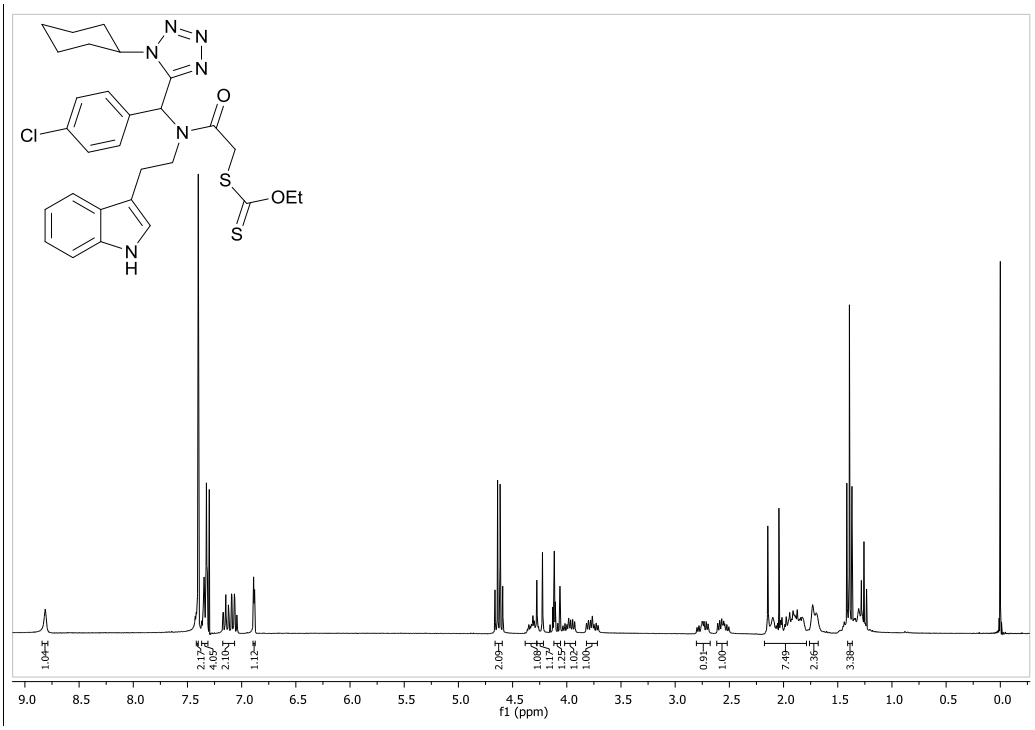


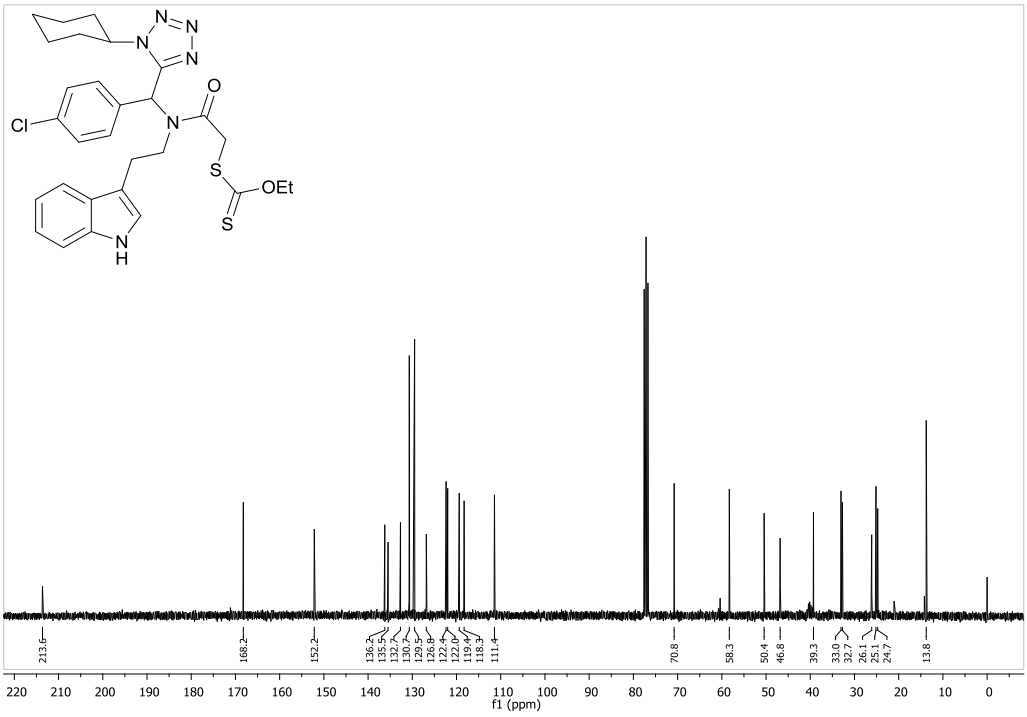

S-(N-(2-(1H-indol-3-yl)ethyl)-N-((4-chlorophenyl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)carbamoyl)methyl O-ethyl carbonodithioate (**6b**)



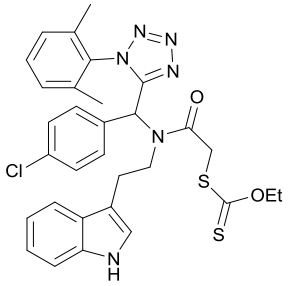

Yield 56 %, physical appearance: pale yellow powder, mp = 153 $^{o}$C, $R_f$ = 0.38 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1049, 1228, 1651(C=O), 2931 and 3324; $\delta_H$ (300 MHz, $CDCl_3$) 1.39 (3 H, t, *J* 7.1, $CH_3$), 1.67-1.75 (2 H, m, $CH_2$), 1.80-2.15 (8 H, m, 4 $CH_2$), 2.49-2.61 (1 H, m, 1 H of $CH_2$), 2.69-2.80 (1 H, m, 1 H of $CH_2$), 3.70-3.82 (1 H, m, 1 H of $CH_2$), 3.92-4.03 (1 H, m, 1 H of $CH_2$), 4.09 (1 H, d, *J* 15.7, 1 H of $CH_2$), 4.25 (1 H, d, *J* 15.7, 1 H of $CH_2$), 4.62 (2 H, q, *J* 7.1, $CH_2$), 6.88 (1 H, d, *J* 2.4, CH), 7.04-7.17 (2 H, m, ArH), 7.31-7.36 (4 H, m, ArH), 7.39-7.41 (2 H, m, ArH), and 8.81 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 13.8, 24.7, 25.1, 26.1, 32.7, 33.0, 39.3, 46.8, 50.4, 58.3, 70.8, 111.4, 118.3, 119.4, 122.0, 122.4, 126.8, 129.5, 130.7, 132.7, 135.5, 136.2, 152.2, 168.2 and 213.6; HRMS (FAB+, M+) calcd. for $C_{29}H_{33}ClN_6O_2S_2$: 597.1873 found 597.1869.



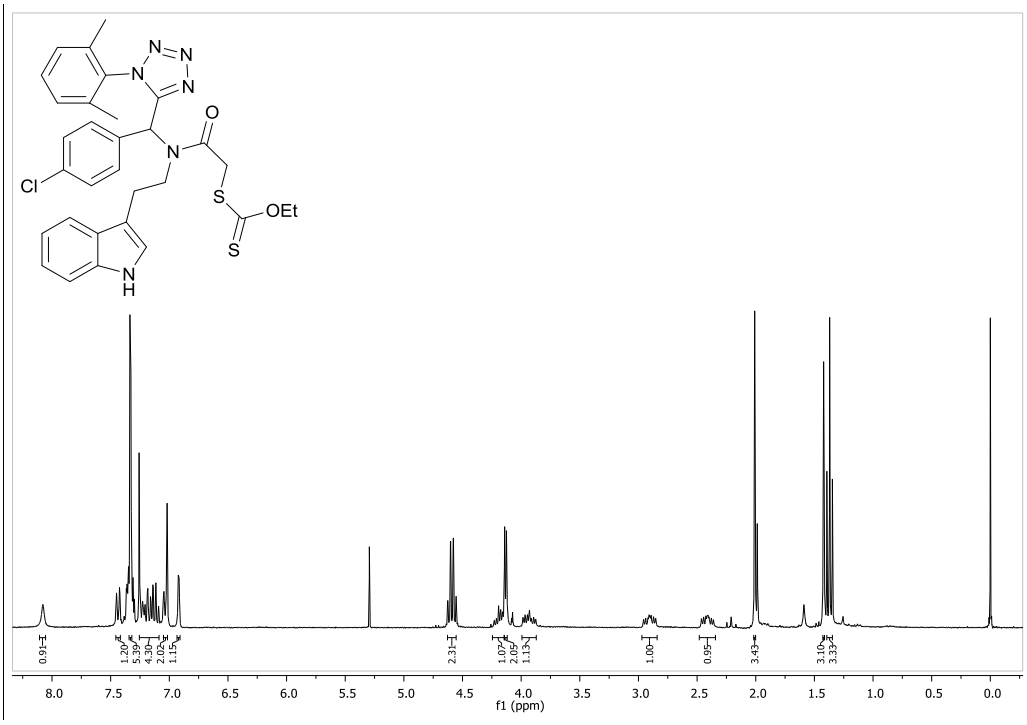



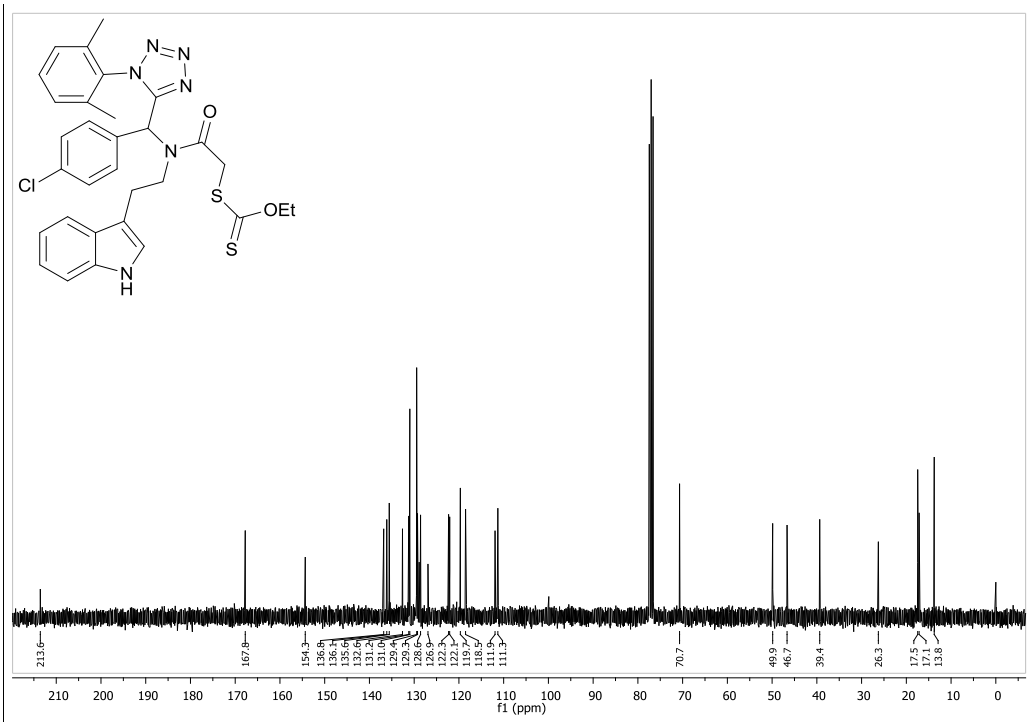
S-(N-(2-(1H-indol-3-yl)ethyl)-N-((4-chlorophenyl)(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)methyl)carbamoyl)methyl O-ethyl carbonodithioate (**6c**)



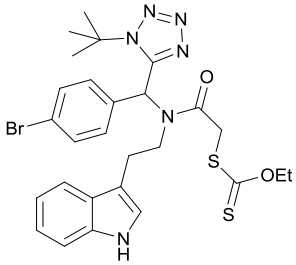

Yield 43 %, physical appearance: pale yellow powder, mp = 182 $^{o}$C, $R_f$ = 0.38 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1049, 1231, 1655(C=O), 2960 and 3366; $\delta_H$ (300 MHz, $CDCl_3$) 1.37 (3 H, t, *J* 7.1, $CH_3$), 1.42 (3 H, s, $CH_3$), 2.01 (3 H, s, $CH_3$), 2.35-2.46 (1 H, m, 1 H of $CH_2$), 2.84-2.96 (1 H, m, 1 H of $CH_2$), 3.87-3.99 (1 H, m, 1 H of $CH_2$), 4.13 (2 H, d, *J* 4.6, $CH_2$), 4.15-4.23 (1 H, m, 1 H of $CH_2$), 4.59 (2 H, q, *J* 7.0, $CH_2$), 6.92 (1 H, d, *J* 2.0, CH), 7.00-7.05 (2 H, m, ArH), 7.08-7.25 (4 H, m, ArH), 7.31-7.35 (5 H, m, ArH), and 8.08 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 13.8, 17.1, 17.5, 26.3, 39.4, 46.7, 49.9, 70.7, 111.3, 111.9, 118.6, 119.7, 122.1, 122.3, 126.9, 128.6, 129.3, 129.4, 131.0, 131.2, 132.6, 135.6, 136.1, 136.8, 154.3, 167.8 and 213.6; HRMS (FAB+, M+) calcd. for $C_{31}H_{31}ClN_6O_2S_2$: 619.1717 found 619.1707.



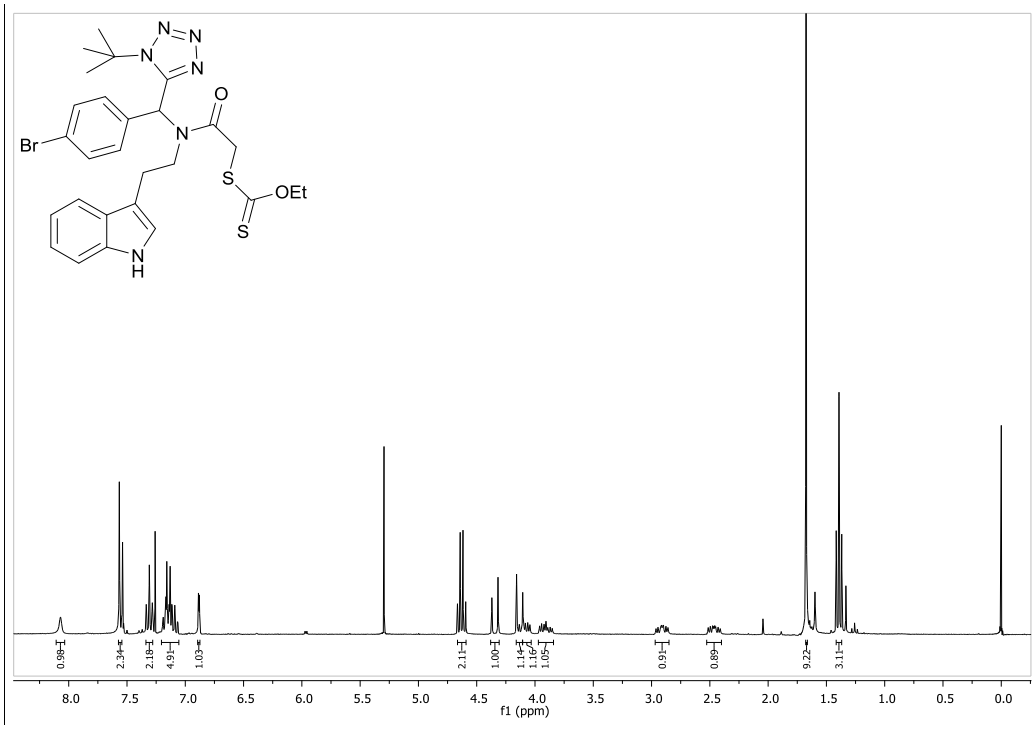


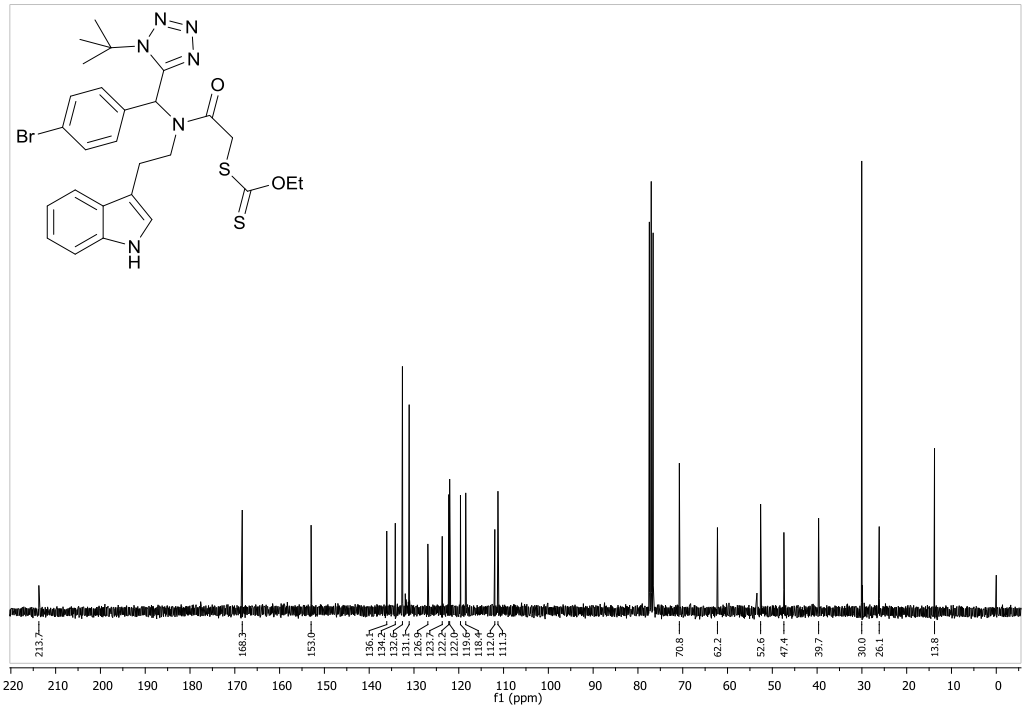

S-(N-(2-(1H-indol-3-yl)ethyl)-N-((1-tert-butyl-1H-tetrazol-5-yl)(4-bromophenyl)methyl)carbamoyl)methyl O-ethyl carbonodithioate (**6d**)



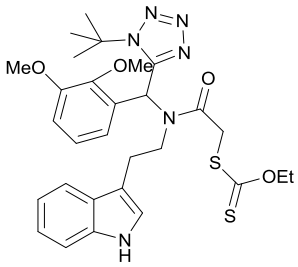

Yield 59 %, physical appearance: pale yellow powder, mp = 92 $^{o}$C, $R_f$ = 0.27 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1050, 1231, 1645 (C=O), 2985 and 3338; $\delta_H$ (300 MHz, $CDCl_3$) 1.39 (3 H, t, *J* 7.1, $CH_3$), 1.67 (9 H, s, 3 $CH_3$), 2.40-2.51 (1 H, m, 1 H of $CH_2$), 2.85-2.96 (1 H, m, 1 H of $CH_2$), 3.84-3.96 (1 H, m, 1 H of $CH_2$), 4.03-4.09 (1 H, m, 1 H of $CH_2$), 4.13 (1 H, d, *J* 15.8, 1 H of $CH_2$), 4.34 (1 H, d, *J* 15.8, 1 H of $CH_2$), 4.63 (2 H, q, *J* 7.1, $CH_2$), 6.88 (1 H, d, *J* 2.3, CH), 7.06-7.19 (5 H, m, ArH), 7.27-7.34 (2 H, m, ArH), 7.53-7.56 (2 H, m, ArH) and 8.07 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 13.8, 26.1, 30.0, 39.7, 47.4, 52.6, 62.2, 70.8, 111.3, 112.0, 118.4, 119.6, 122.0, 122.2, 123.7, 126.9, 131.1, 132.6, 134.2, 136.1, 153.0, 168.3 and 213.7; HRMS (FAB+, M+) calc for $C_{29}H_{36}N_6O_4S_2$: 614.1133 found 614.1133.



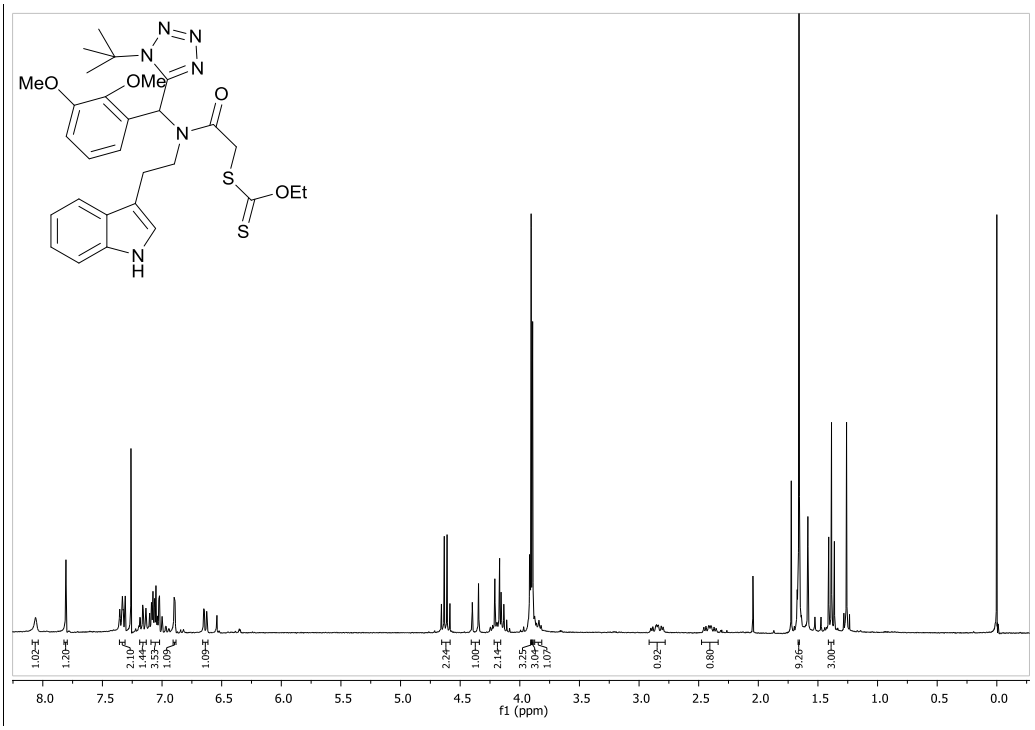



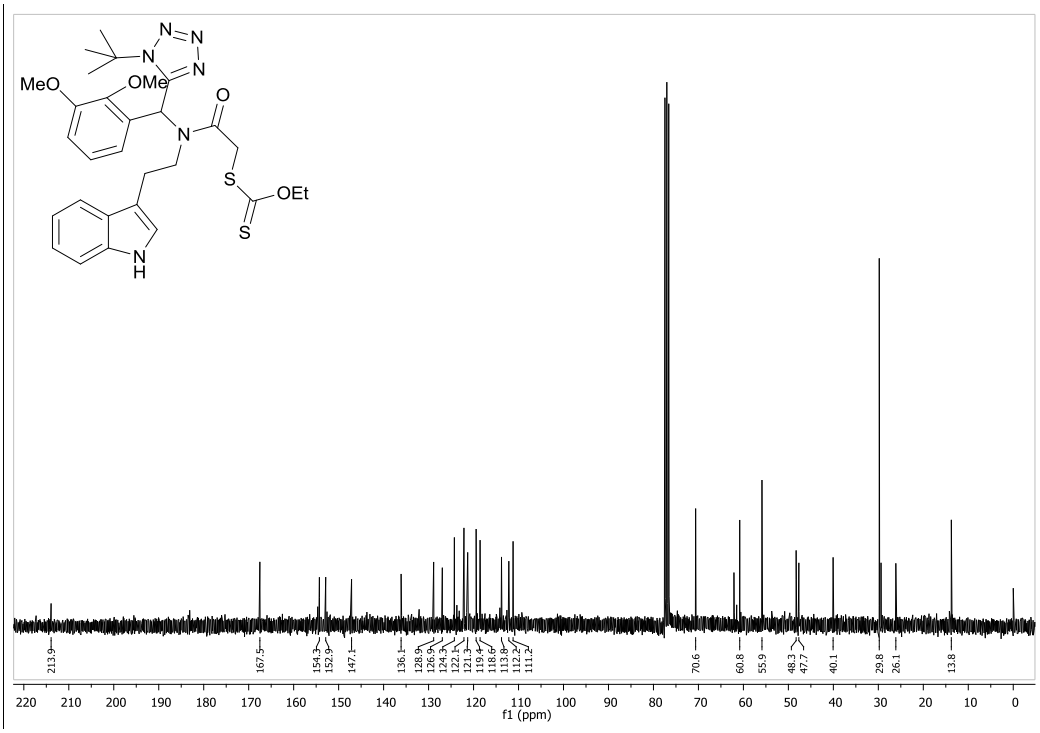
S-(N-(2-(1H-indol-3-yl)ethyl)-N-((1-tert-butyl-1H-tetrazol-5-yl)(2,3-dimethoxyphenyl)methyl)carbamoyl)methyl O-ethyl carbonodithioate (**6e**)



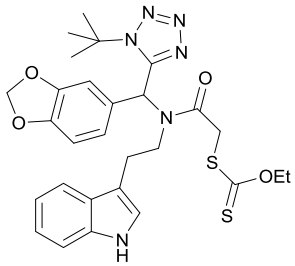

Yield 71 %, physical appearance: pale yellow powder, mp = 86 $^{o}$C, $R_f$ = 0.14 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1047, 1222, 1643 (C=O), 2937 and 3328; $\delta_H$ (300 MHz, $CDCl_3$) 1.39 (3 H, t, *J* 7.1, $CH_3$), 1.66 (9 H, s, 3 $CH_3$), 2.35-2.46 (1 H, m, 1 H of $CH_2$), 2.79-2.91 (1 H, m, 1 H of $CH_2$), 3.81-3.88 (1 H, m, 1 H of $CH_2$), 3.89 (3 H, s, $OCH_3$), 3.91 (3 H, s, $OCH_3$), 4.13-4.22 (2 H, m, $CH_2$), 4.37 (1 H, d, *J* 15.7, 1 H of $CH_2$), 4.62 (2 H, q, *J* 7.1, $CH_2$), 6.64 (1 H, dd, *J* 1.7, 7.5, ArH), 6.89 (1 H, d, *J* 2.4, CH), 7.01-7.09 (3 H, m, ArH), 7.12-7.19 (1 H, m, ArH), 7.30-7.36 (2 H, m, ArH), 7.81 (1 H, s, ArH) and 8.06 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 13.8, 26.1, 29.8, 40.1, 47.7, 48.3, 55.9, 60.8, 70.6, 111.2, 112.2, 113.8, 118.6, 119.4, 121.3, 122.1, 124.3, 126.9, 128.9, 136.1, 147.1, 152.9, 154.3, 167.5 and 213.9; HRMS (FAB+, M+) calc for $C_{29}H_{36}N_6O_4S_2$: 596.2239 found 596.2234.



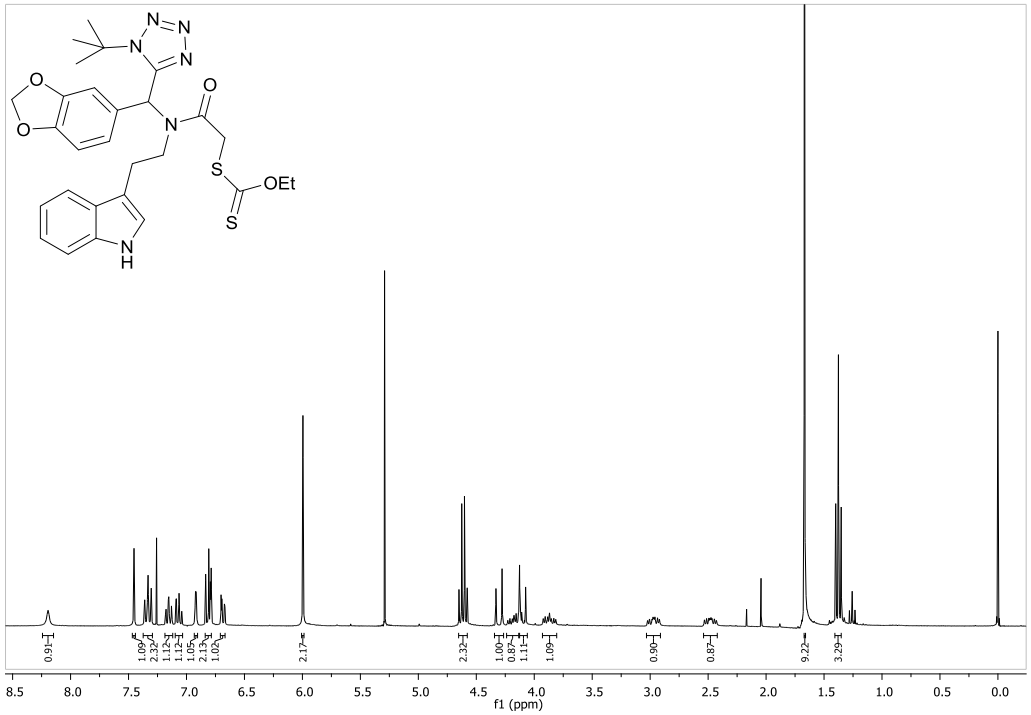


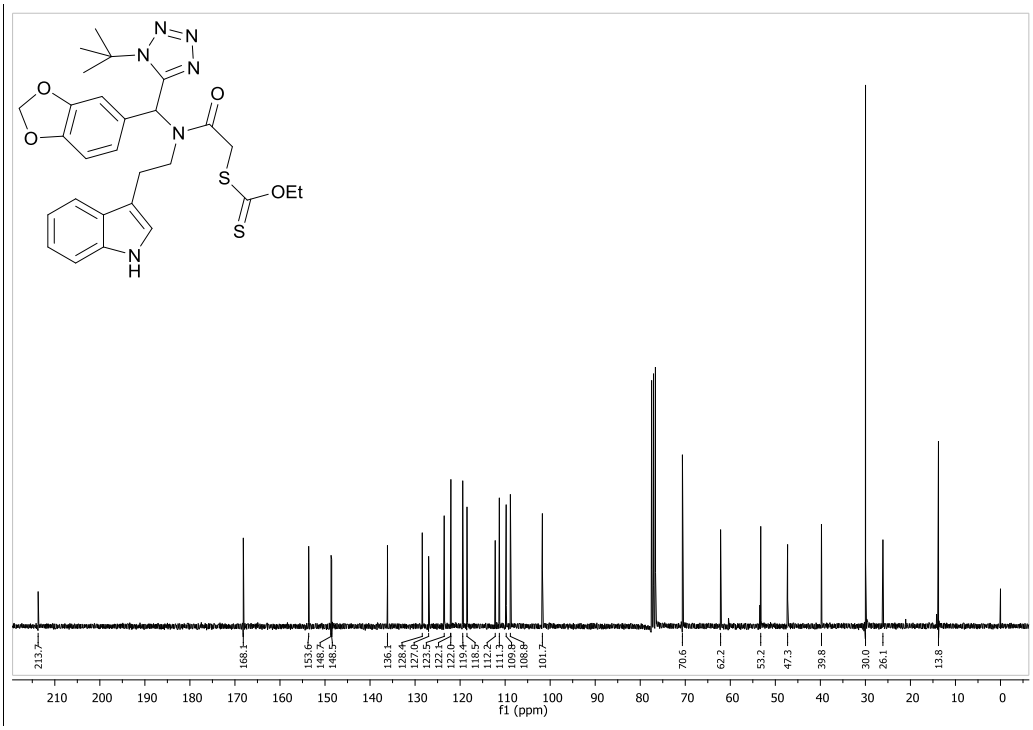

S-(N-(2-(1H-indol-3-yl)ethyl)-N-((1-tert-butyl-1H-tetrazol-5-yl)(benzo[d][1,3]dioxol-6-yl)methyl)carbamoyl)methyl O-ethyl carbonodithioate (**6f**)



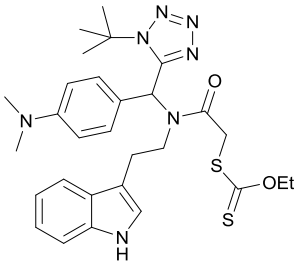

Yield 58 %, physical appearance: pale yellow powder, mp = 100 $^{o}$C, $R_f$ = 0.19 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1049, 1237, 1643 (C=O), 2987 and 3337; $\delta_H$ (300 MHz, $CDCl_3$) 1.38 (3 H, t, *J* 7.1, $CH_3$), 1.67 (9 H, s, 3 $CH_3$), 2.43-2.54 (1 H, m, 1 H of $CH_2$), 2.91-3.03 (1 H, m, 1 H of $CH_2$), 3.81-3.93 (1 H, m, 1 H of $CH_2$), 4.10 (1 H, d, *J* 15.8, 1 H of $CH_2$), 4.14-4.2 (1 H, m, 1 H of $CH_2$), 4.30 (1 H, d, *J* 15.8, 1 H of $CH_2$), 4.61 (2 H, q, *J* 7.1, $CH_2$), 6.00 (2 H, s, $CH_2$), 6.68 (1 H, dd, *J* 1.9, 8.0, ArH), 6.78-6.84 (2 H, m, ArH), 6.92 (1 H, d, *J* 1.9, CH), 7.03-7.09 (1 H, m, ArH), 7.12-7.18 (1 H, m, ArH), 7.29-7.36 (2 H, m, ArH), 7.45 (1 H, s, ArH) and 8.19 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 13.8, 26.1, 30.0, 39.8, 47.3, 53.2, 62.2, 70.6, 101.7, 108.8, 109.8, 111.3, 112.2, 118.5, 119.5, 122.0, 122.1, 123.5, 127.0, 128.4, 136.1, 148.5, 148.7, 153.6 and 213.7; HRMS (FAB+, M+) calc for $C_{28}H_{32}N_6O_4S_2$: 581.2005 found 581.2013.



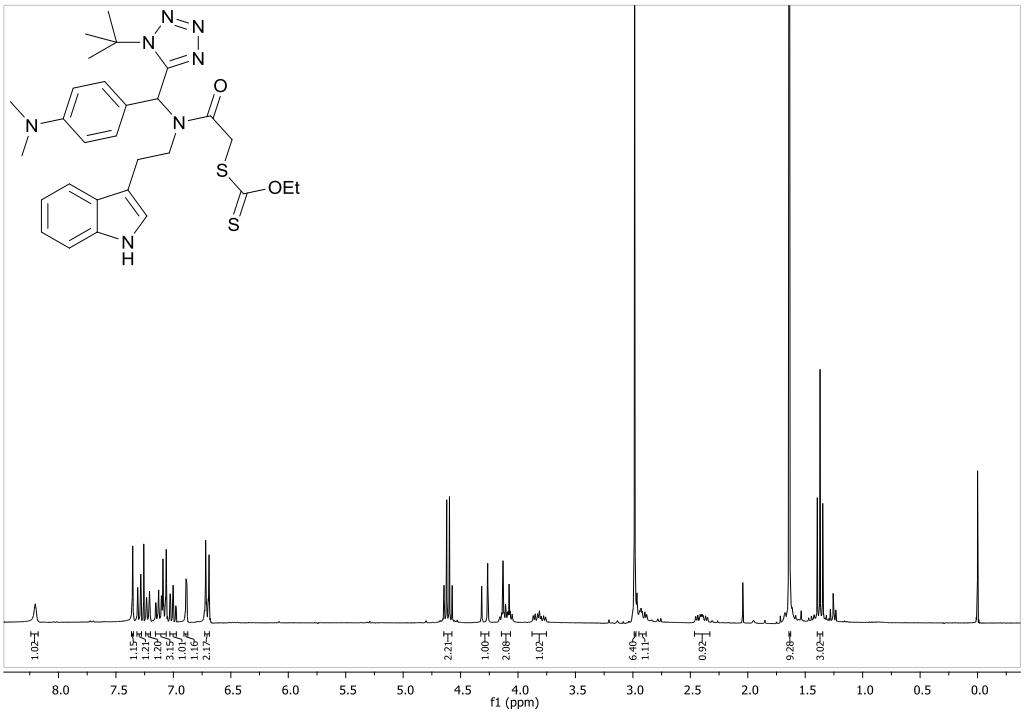



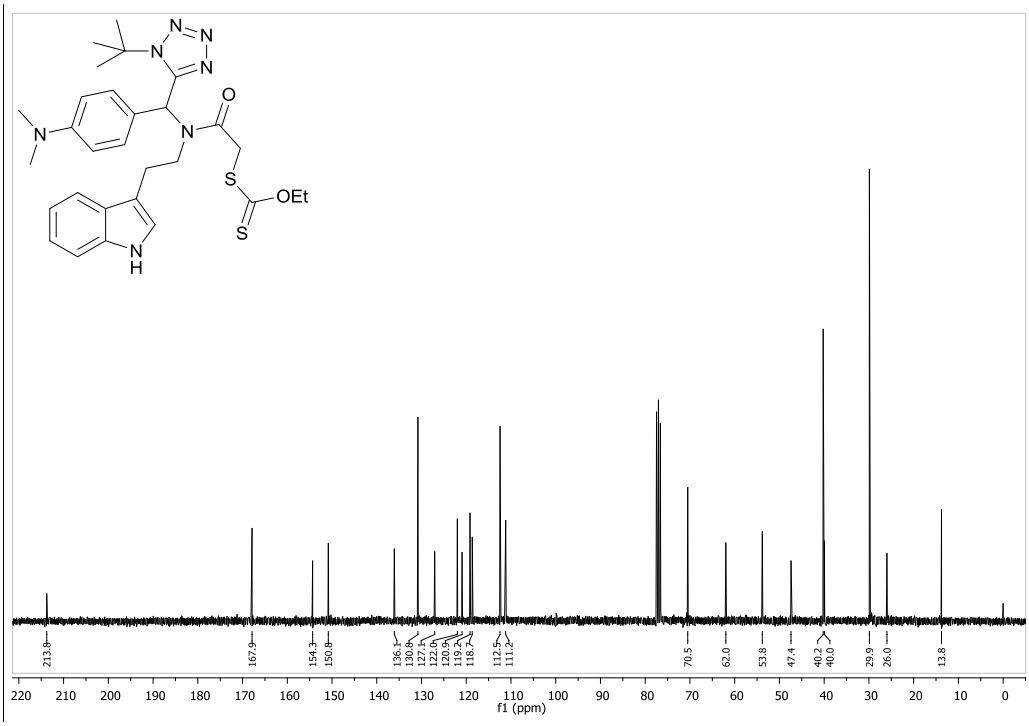
S-(N-(2-(1H-indol-3-yl)ethyl)-N-((1-tert-butyl-1H-tetrazol-5-yl)(4-(dimethylamino)phenyl)methyl)carbamoyl)methyl O-ethyl carbonodithioate (**6g**)



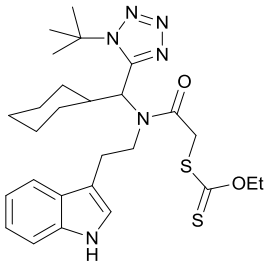
Yield 52 %, physical appearance: pale yellow powder, mp = 148 $^{o}$C, $R_f$ = 0.16 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1051, 1222, 1640 (C=O), 2987 and 3326; $\delta_H$ (300 MHz, $CDCl_3$) 1.37 (3 H, t, *J* 7.0, $CH_3$), 1.64 (9 H, s, 3 $CH_3$), 2.34-2.46 (1 H, m, 1 H of $CH_2$), 2.87-2.95 (1 H, m, 1 H of $CH_2$), 2.98 (6 H, s, 2 $NCH_3$), 3.75-3.87 (1 H, m, 1 H of $CH_2$), 4.04-4.16 (2 H, m, $CH_2$), 4.29 (1 H, d, *J* 15.7, 1 H of $CH_2$), 4.61 (2 H, q, *J* 7.1, $CH_2$), 6.68-6.73 (2 H, m, ArH), 6.88 (1 H, d, *J* 2.3, CH), 7.97-7.03 (1 H, m, ArH), 7.06-7.15 (3 H, m, ArH), 7.22 (1 H, d, *J* 7.6, ArH), 7.28-7.31 (1 H, m, ArH), 7.35 (1 H, s, ArH) and 8.20 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 13.8, 26.0, 29.9, 40.0, 40.2, 47.4, 53.8, 62.0, 70.5, 111.2, 112.5, 118.7, 119.2, 120.9, 122.0, 127.1, 130.8, 136.1, 150.8, 154.3, 167.9 and 213.8; HRMS (FAB+, M+) calcd. for $C_{29}H_{37}N_7O_2S_2$: 579.2450 found 579.2454.



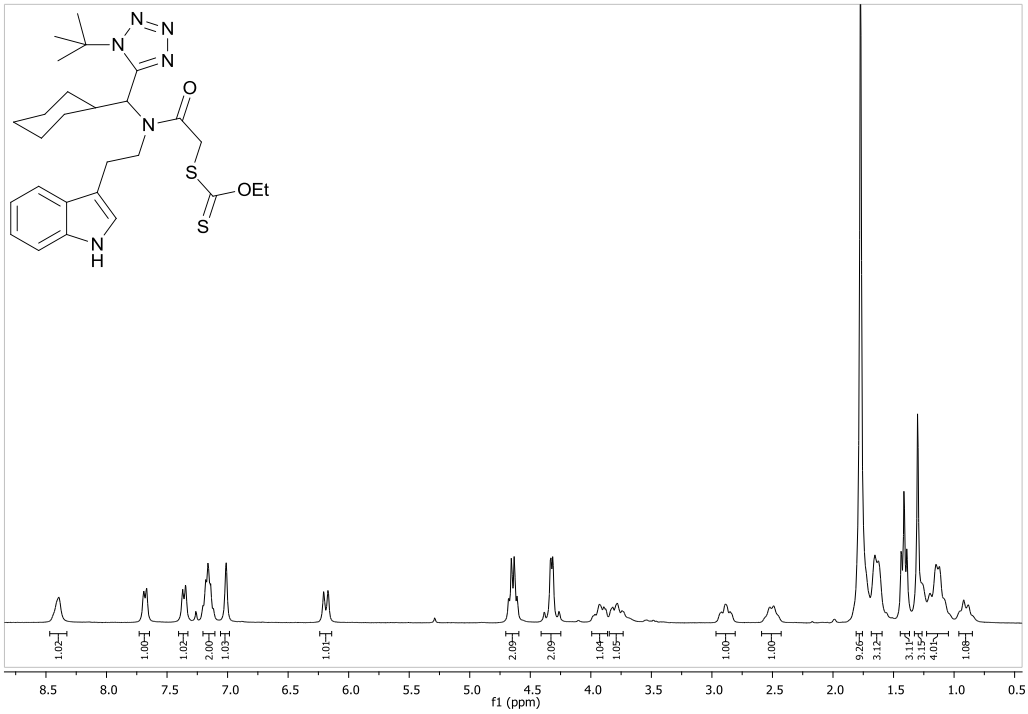


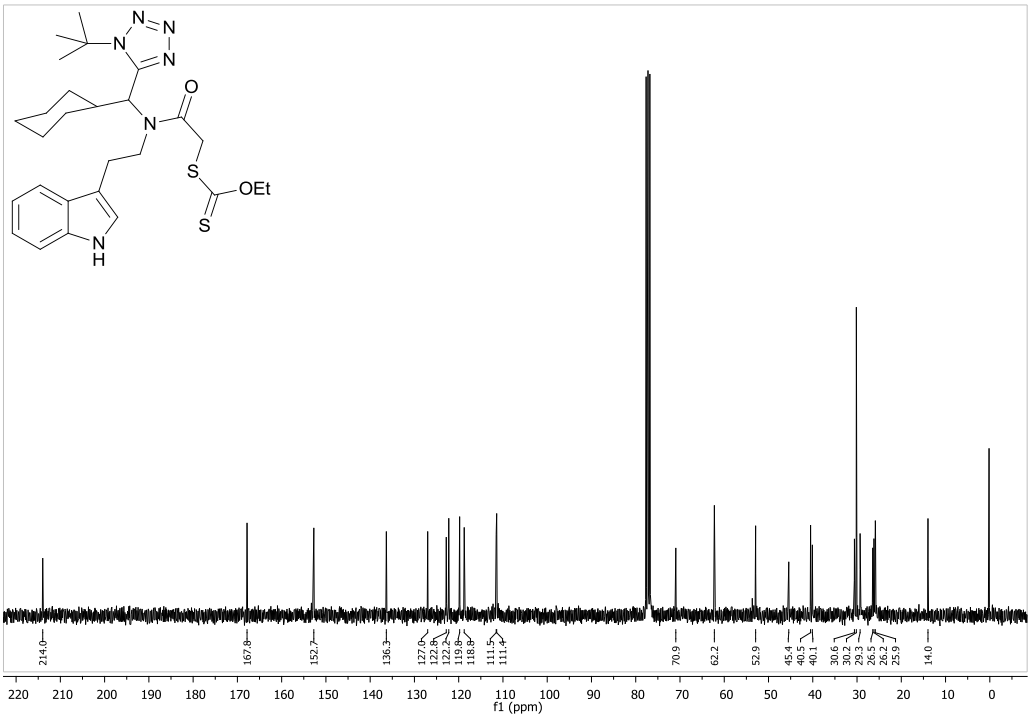

S-(2-((2-(1H-indol-3-yl)ethyl)((1-(tert-butyl)-1H-tetrazol-5-yl)(cyclohexyl)methyl)amino)-2-oxoethyl) O-ethyl carbonodithioate (**6h**)



Yield 63 %, physical appearance: pale yellow powder, mp = 72 $^{o}$C, $R_f$ = 0.33 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1059, 1237, 1634 (C=O), 2965 and 3325; $\delta_H$ (300 MHz, $CDCl_3$) 0.83-0.97 (1 H, m, CH), 1.02-1.23 (4 H, m, 2 $CH_2$), 1.25-1.33 (3 H, m, 1 H of $CH_2$, $CH_2$), 1.41 (3 H, t, *J* 7.1, $CH_3$), 1.58-1.69 (9 H, m, 1 H of $CH_2$, $CH_2$), 1.77 (9 H, s, 3 $CH_3$), 2.43-2.58 (1 H, m, 1H of $CH_2$), 2.82-2.95 (1 H, m, 1 H of $CH_2$), 3.72-3.85 (1 H, m, 1 H of $CH_2$), 3.86-3.99 (1 H, m, 1H of $CH_2$), 4.25-4.39 (2 H, m, $CH_2$), 4.51 (2 H, q, *J* 7.1, $CH_2$), 6.19 (1 H, d, *J* 10.8, CH), 7.01 (1 H, s, ArH), 7.11-7.22 (2 H, m, ArH), 7.36 (1 H, d, *J* 6.8, ArH), 7.68 (1 H, d, *J* 7.1, ArH) and 8.40 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 14.0, 25.9, 26.2, 26.5, 29.3, 30.2, 30.6, 40.1, 40.5, 45.4, 52.9, 62.2, 70.9, 111.4, 111.5, 118.8, 119.8, 122.2, 122.8, 127.0, 136.3, 152.7, 167.8 and 214.0.



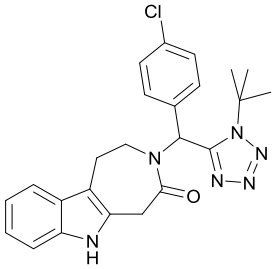



**Synthesis and characterization of 3-tetrazolylmethyl-azepino[4,5-*b*]indol-4-ones 1a-i**

*Method A* (conventional heating conditions): A xanthate (1.0 equiv.) was placed in a round flask equipped with a magnetic stirrer bar under inert atmosphere ($N_2$) and diluted in DCE (0.5 M). The temperature was raised to reflux. Then, the DLP (1.75 equiv.) was added portionwise 0.25 equiv. / 40 min. After 4.6 h at reflux, the starting material was consumed and the crude was immediately purified by chromatoflash (Hex-AcOEt = 3/2 V/V) to afford the final compounds **1a-i**.

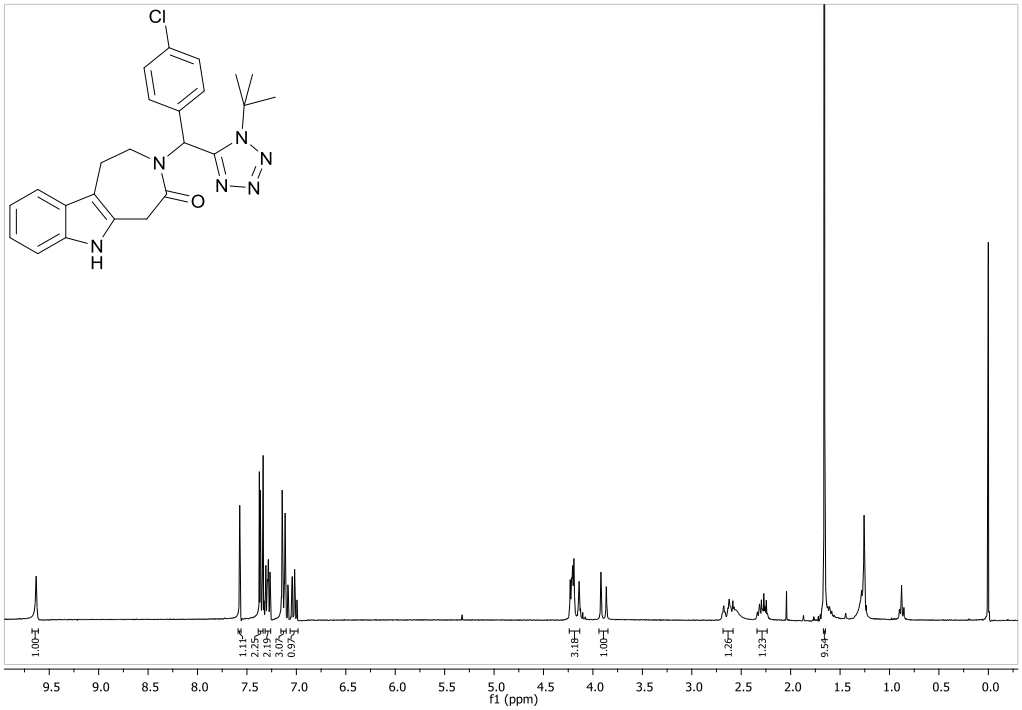
*Method B* (MW heating conditions): A xanthate (1.0 equiv.) was placed in a sealed CEM Discover$^{TM}$ MW reaction tube equipped with a magnetic stirrer bar under inert atmosphere ($N_2$) and diluted in DCE (0.5 M). Then, the DLP (1.75 equiv.) was added portionwise 0.25 equiv. / 10 min. Seven clossed vessel reaction cycles were carried out at at 90 $^{o}$C. After 70 min., the starting material was consumed and the crude was immediately purified by chromatoflash (Hex-AcOEt = 3/2 V/V) to afford the final compounds **1a-i**.

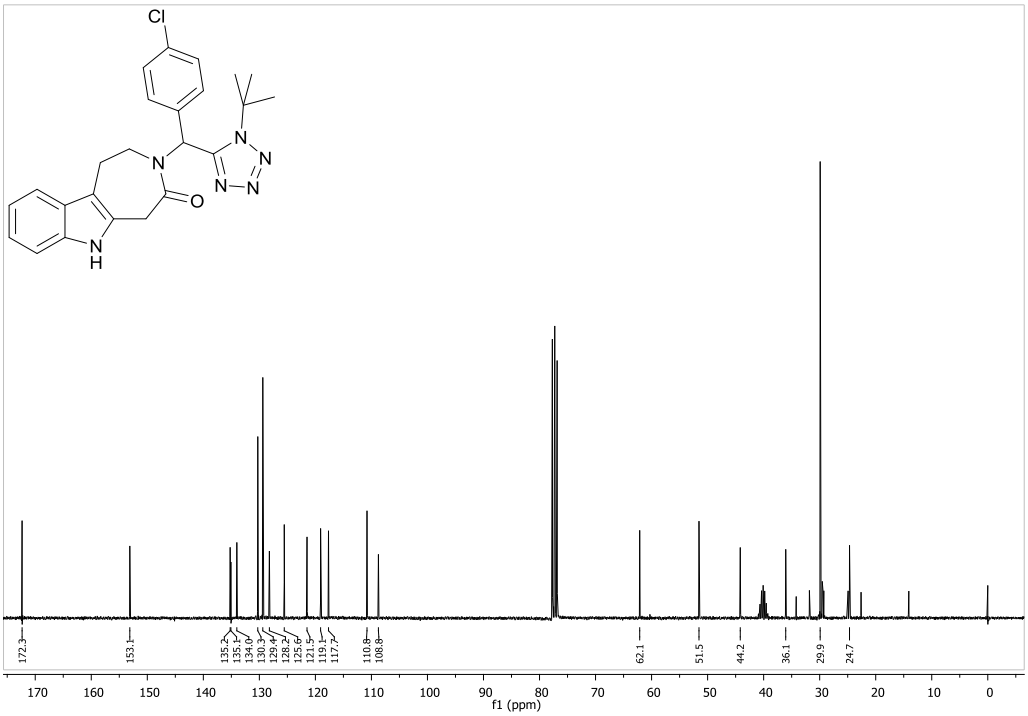
3-((1-tert-butyl-1H-tetrazol-5-yl)(4-chlorophenyl)methyl)-2,3-dihydroazepino[4,5-b]indol-4(1H,5H,6H)-one (**1a**)



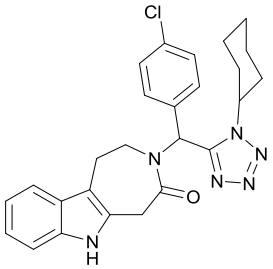

Yield (Δ = 64 %; MW = 57%), physical appearance: white powder, mp = 240 $^{o}$C, $R_f$ = 0.51 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1092, 1638 (C=O), 2920 and 3399; $\delta_H$ (300 MHz, $CDCl_3$) 1.66 (9 H, s, 3 $CH_3$), 2.23-2.34 (1 H, m, 1 H of $CH_2$), 2.52-2.70 (1 H, m, 1 H of $CH_2$), 3.89 (1 H, d, *J* 16.4, 1 H of $CH_2$), 4.12-4.24 (3 H, m, 1 H of $CH_2$ and $CH_2$), 6.98-7.04 (1 H, m, ArH), 7.08-7.16 (3 H, m, ArH), 7.26-7.31 (2 H, m, ArH), 7.33-7.38 (2 H, m, ArH), 7.57 (1 H, s, CH) and 9.63 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 24.7, 29.9, 36.1, 44.2, 51.5, 62.1, 108.8, 110.8, 117.7, 119.1, 121.5, 125.6, 128.2, 129.4, 130.3, 134.0, 135.1, 135.2, 153.1 and 172.3; HRMS (FAB+, M+) calcd. for $C_{24}H_{25}ClN_6O$: 448.1792, found: 448.1783.



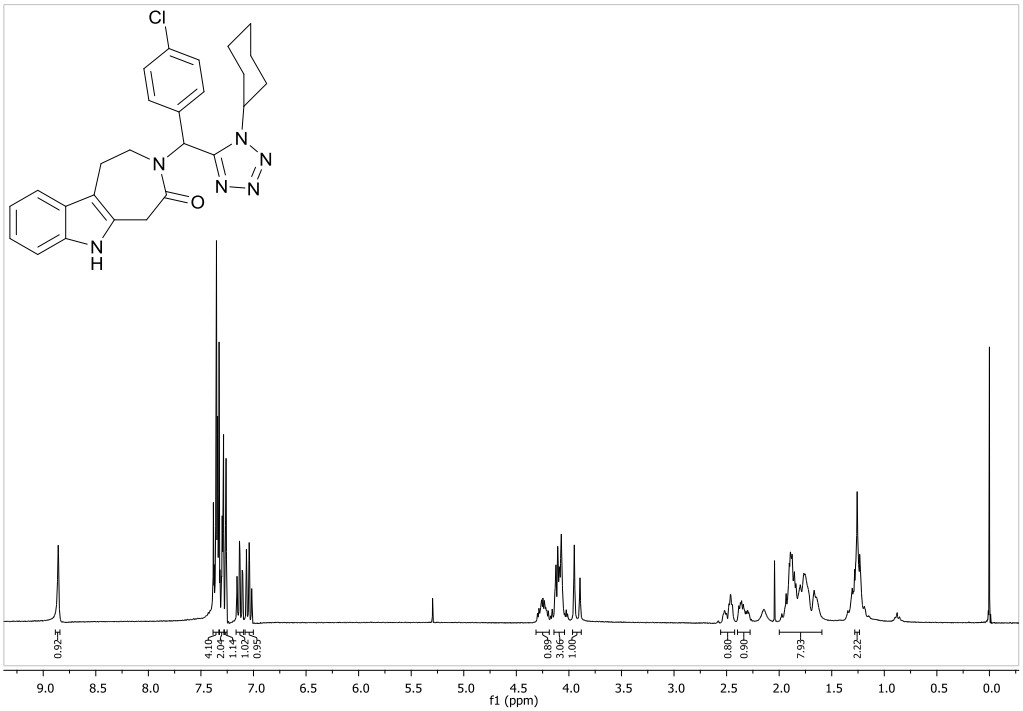



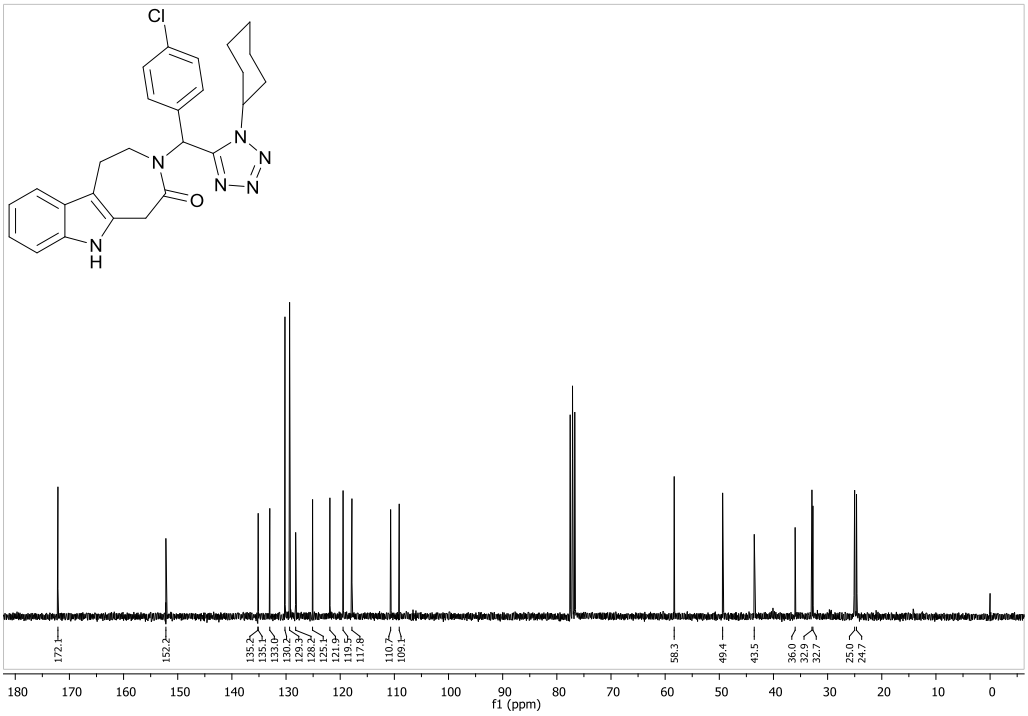
3-((4-chlorophenyl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-2,3-dihydroazepino[4,5-b]indol-4(1H,5H,6H)-one (**1b**)



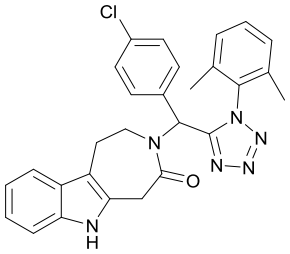

Yield (Δ = 59 %; MW = 53%), physical appearance: white powder, mp = 200 $^{o}$C, $R_f$ = 0.26 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1094, 1639 (C=O), 2942 and 3227; $\delta_H$ (300 MHz, $CDCl_3$) 1.23-1.28 (2 H, m, $CH_2$), 1.61-1.94 (8 H, m, 4 $CH_2$), 2.28-2.39 (1 H, m, 1 H of $CH_2$), 2.44-2.54 (1 H, m, 1 H of $CH_2$), 3.92 (1 H, d, *J* 16.3, 1 H of $CH_2$), 4.05-4.14 (3 H, m, 1 H of $CH_2$ and $CH_2$), 4.19-4.30 (1 H, m, CH), 7.01-7.07 (1 H, m, ArH), 7.10-7.16 (1 H, m, ArH), 7.26 (1 H, s, CH), 7.28-7.31 (2 H, m, ArH), 7.32-7.39 (4 H, m, ArH) and 8.86 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 24.7, 25.0, 32.7, 32.9, 36.0, 43.5, 49.4, 58.3, 109.1, 110.7, 117.8, 119.5, 121.9, 125.1, 128.2, 129.3, 130.2, 133.0, 135.1, 135.2, 152.2, and 172.1; HRMS (FAB+, M+) calcd. for $C_{26}H_{27}ClN_6O$: 474.1938, found: 474.1931.



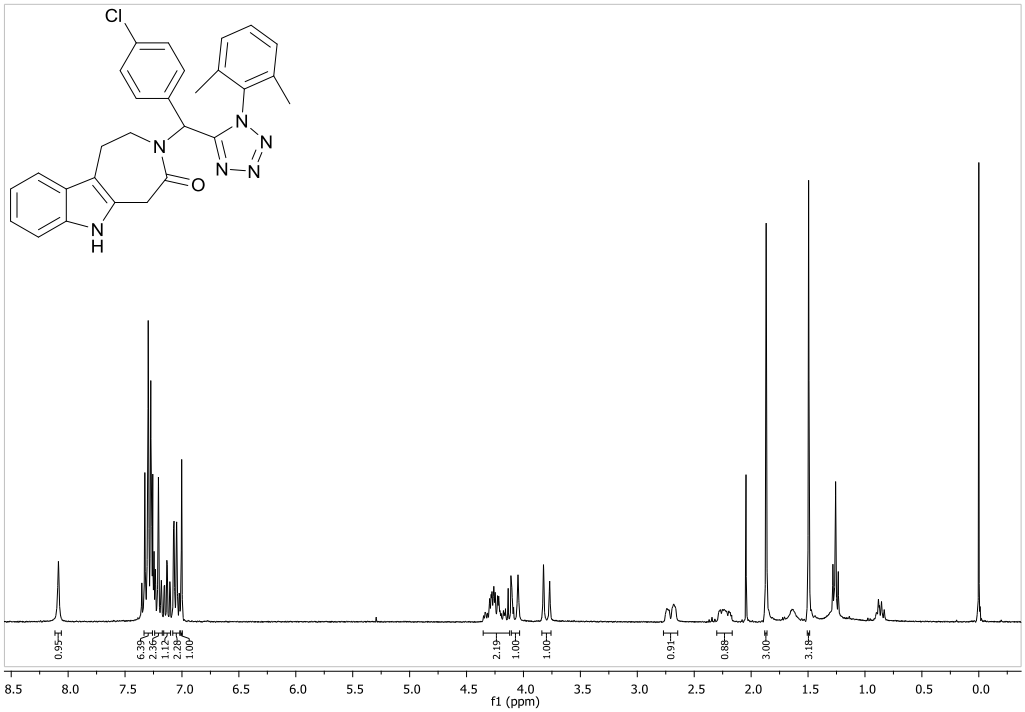


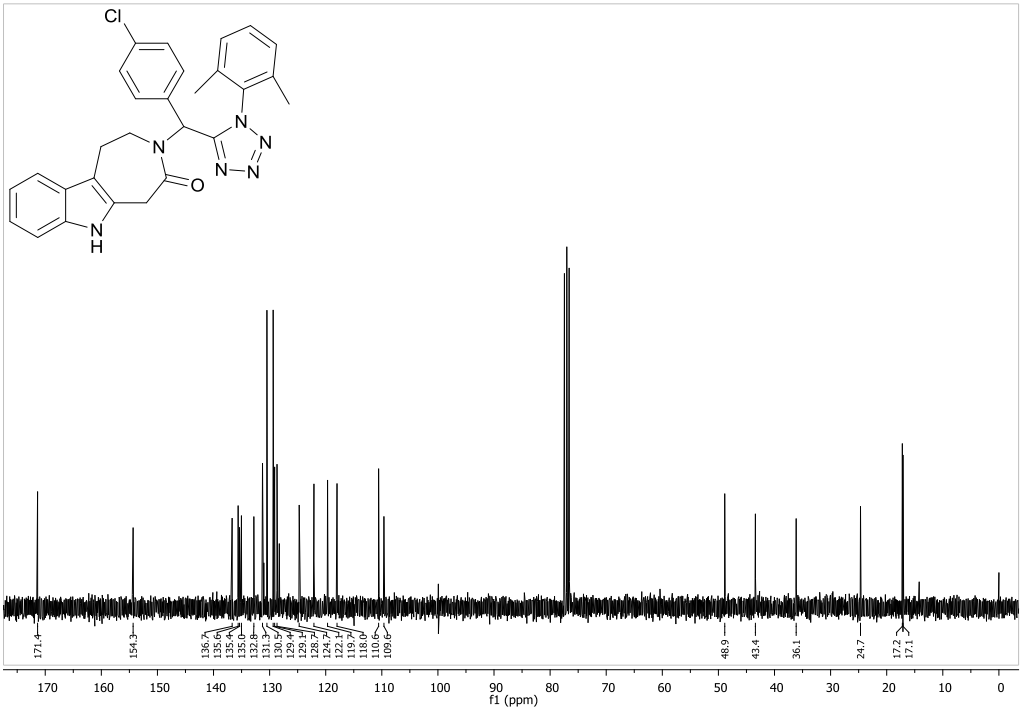

3-((4-chlorophenyl)(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)methyl)-2,3-dihydroazepino[4,5-b]indol-4(1H,5H,6H)-one (**1c**)



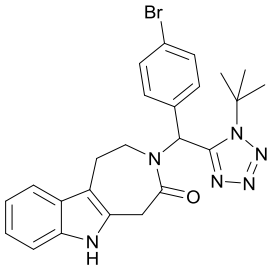

Yield (Δ = 62 %; MW = 50%), physical appearance: white powder, mp = 252 $^{o}$C, $R_f$ = 0.61 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1092, 1647 (C=O), 2923 and 3341; $\delta_H$ (300 MHz, $CDCl_3$) 1.49 (3 H, s, $CH_3$), 1.87 (3 H, s, $CH_3$), 2.17-2.29 (1 H, m, 1 H of $CH_2$), 2.65-2.76 (1 H, m, 1 H of $CH_2$), 3.80 (1 H, d, *J* 16.4, 1 H of $CH_2$), 4.03-4.12 (1 H, m, 1 H of $CH_2$), 4.14-4.31 (2 H, m, $CH_2$), 7.00 (1 H, s, CH), 7.02-7.08 (2 H, m, ArH), 7.10-7.16 (1 H, m, ArH), 7.17-7.24 (2 H, m, ArH), 7.25-7.36 (6 H, m, ArH) and 8.09 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 17.1, 17.2, 24.7, 36.1, 43.4, 48.9, 109.6, 110.6, 118.0, 119.7, 122.1, 124.7, 128.7, 129.1, 129.4, 130.5, 131.3, 132.8, 135.0, 135.4, 135.6, 136.7, 154.3 and 171.4; HRMS (FAB+, M+) calcd. for $C_{28}H_{25}ClN_6O$: 496.1778 found 496.1780.



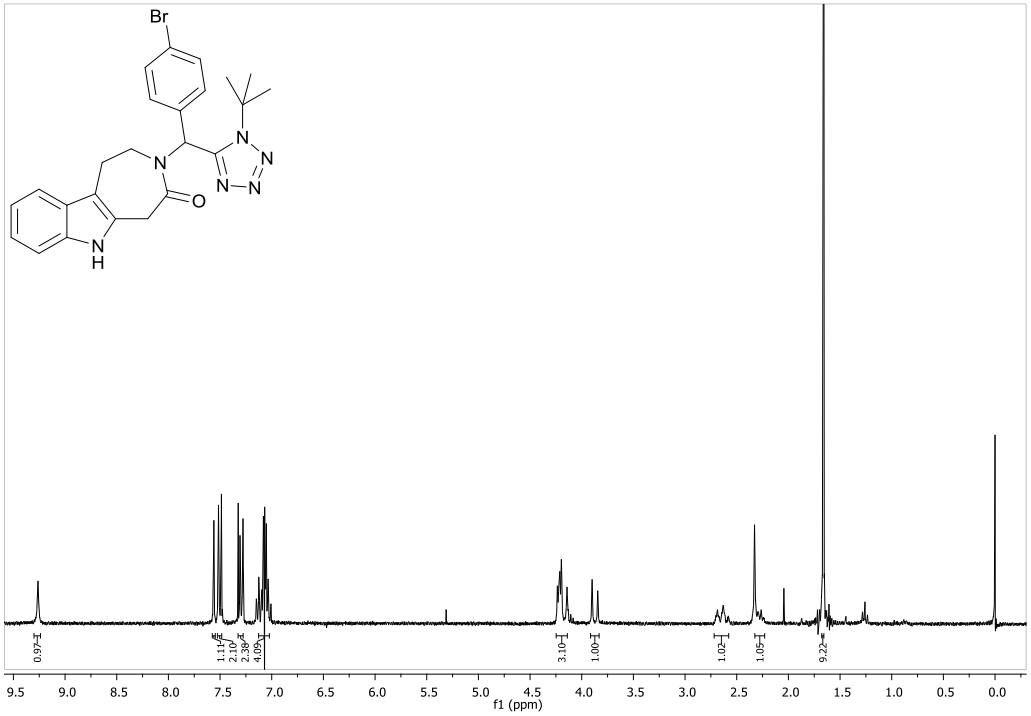



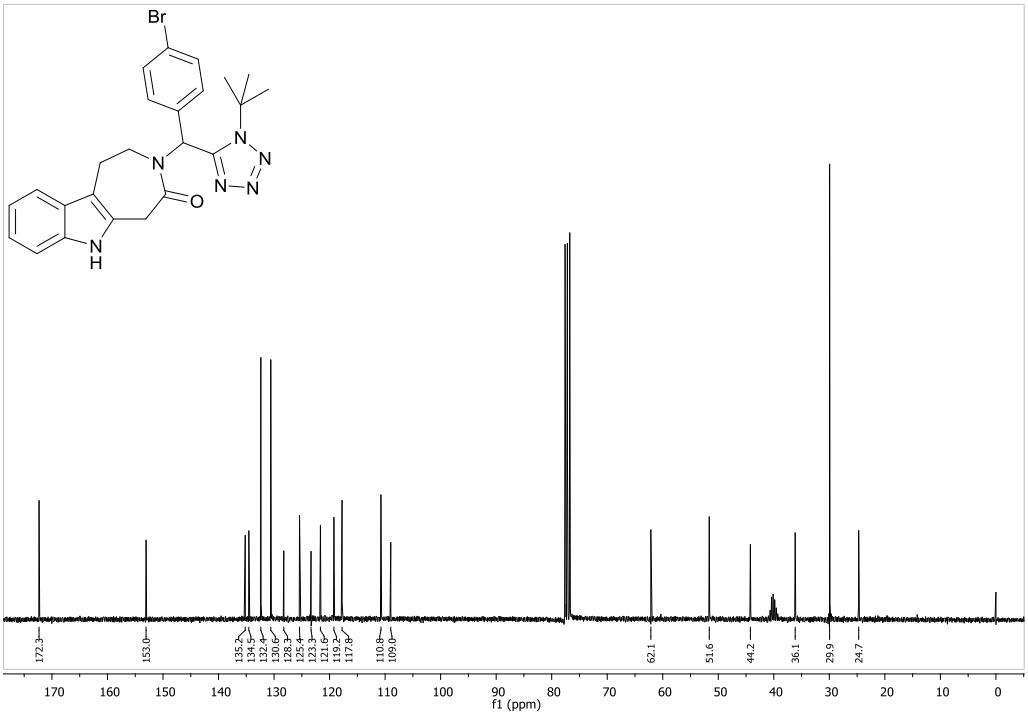
3-((1-tert-butyl-1H-tetrazol-5-yl)(4-bromophenyl)methyl)-2,3-dihydroazepino[4,5-b]indol-4(1H,5H,6H)-one (**1d**)



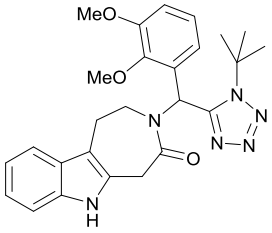

Yield (Δ = 69 %; MW = 67%), physical appearance: white powder, mp = 194 $^{o}$C, $R_f$ = 0.51 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1009, 1638 (C=O), 2928 and 3398; $\delta_H$ (300 MHz, $CDCl_3$) 1.66 (9 H, s, 3 $CH_3$), 2.23-2.34 (1 H, m, 1 H of $CH_2$), 2.57-2.71 (1 H, m, 1 H of $CH_2$), 3.87 (1 H, d, *J* 16.3, 1 H of $CH_2$), 4.12-4.24 (3 H, m, 1 H of $CH_2$ and $CH_2$), 7.00-7.16 (4 H, m, ArH), 7.27-7.33 (2 H, m, ArH), 7.48-7.52 (2 H, m, ArH), 7.56 (1 H, s, CH) and 9.26 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 24.7, 29.9, 36.1, 44.2, 51.5, 62.1, 108.8, 110.8, 117.7, 119.1, 121.5, 125.6, 128.2, 129.4, 130.3, 134.0, 135.1, 135.2, 153.1 and 172.3; HRMS (FAB+, M+) calcd. for $C_{24}H_{25}BrN_6O$: 492.1273 found 492.1281.



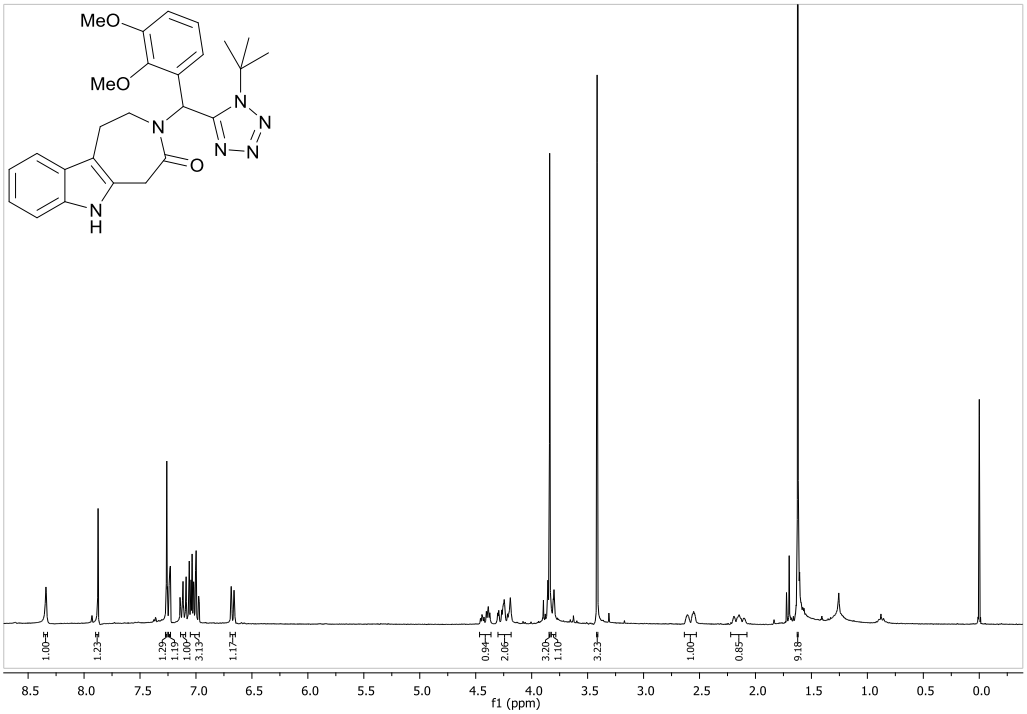


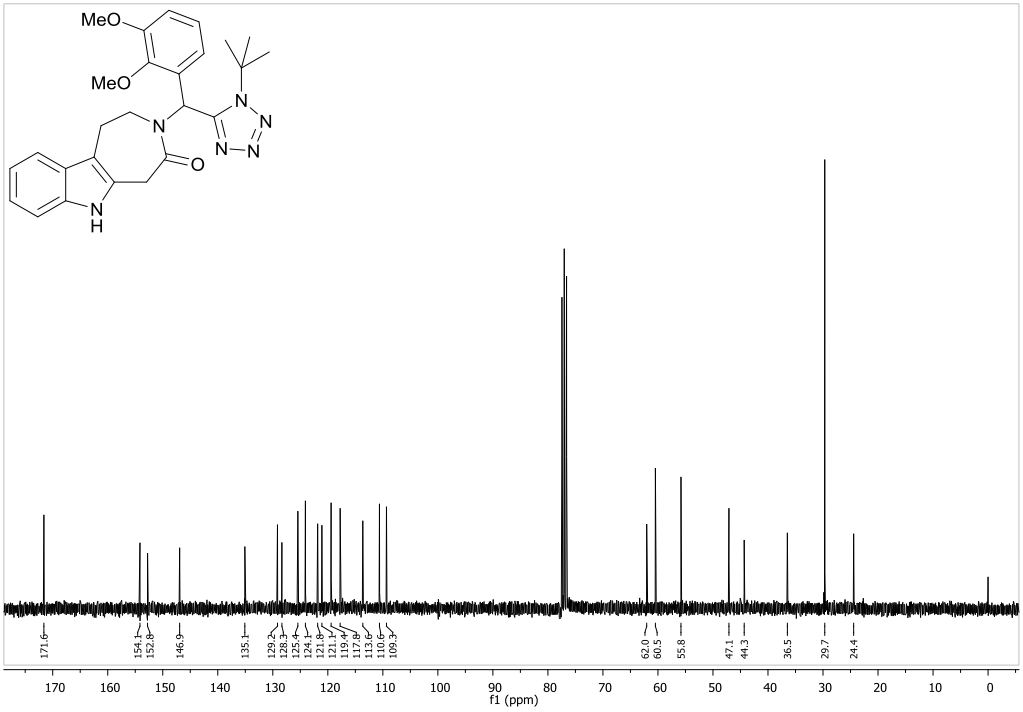

3-((1-tert-butyl-1H-tetrazol-5-yl)(2,3-dimethoxyphenyl)methyl)-2,3-dihydroazepino[4,5-b]indol-4(1H,5H,6H)-one (**1e**)



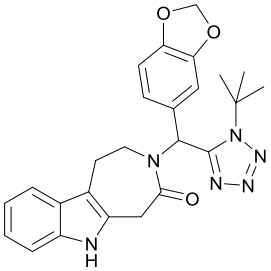

Yield (Δ = 54 %; MW = 51%), physical appearance: white powder, mp = 140 $^{o}$C, $R_f$ = 0.38 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1276, 1636 (C=O), 2983 and 3226; $\delta_H$ (300 MHz, $CDCl_3$) 1.62 (9 H, s, 3 $CH_3$), 2.09-2.20 (1 H, m, 1 H of $CH_2$), 2.53-2.63 (1 H, m, 1 H of $CH_2$), 3.42 (3 H, s, $CH_3$), 3.78-3.81 (1 H, m, 1 H of $CH_2$), 3.84 (3 H, s, $CH_3$), 4.18-4.31 (2 H, m, $CH_2$), 4.37-4.46 (1 H, m, 1 H of $CH_2$), 6.67 (1 H, dd, *J* 1.5, 7.6, ArH), 6.97-7.06 (3 H, m, ArH), 7.08-7.15 (1 H, m, ArH), 7.22-7.24 (1 H, m, ArH), 7.26 (1 H, s, CH), 7.87 (1 H, s, ArH) and 8.34 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 24.4, 29.7, 36.5, 44.3, 47.1, 55.8, 60.5, 62.0, 109.3, 110.6, 113.6, 117.8, 119.4, 121.1, 121.8, 124.1, 125.4, 128.3, 129.2, 135.1, 146.9, 152.8, 154.1 and 171.6; HRMS (FAB+, M+) calcd. for $C_{26}H_{30}N_6O_3$: 474.2505 found 474.2508.



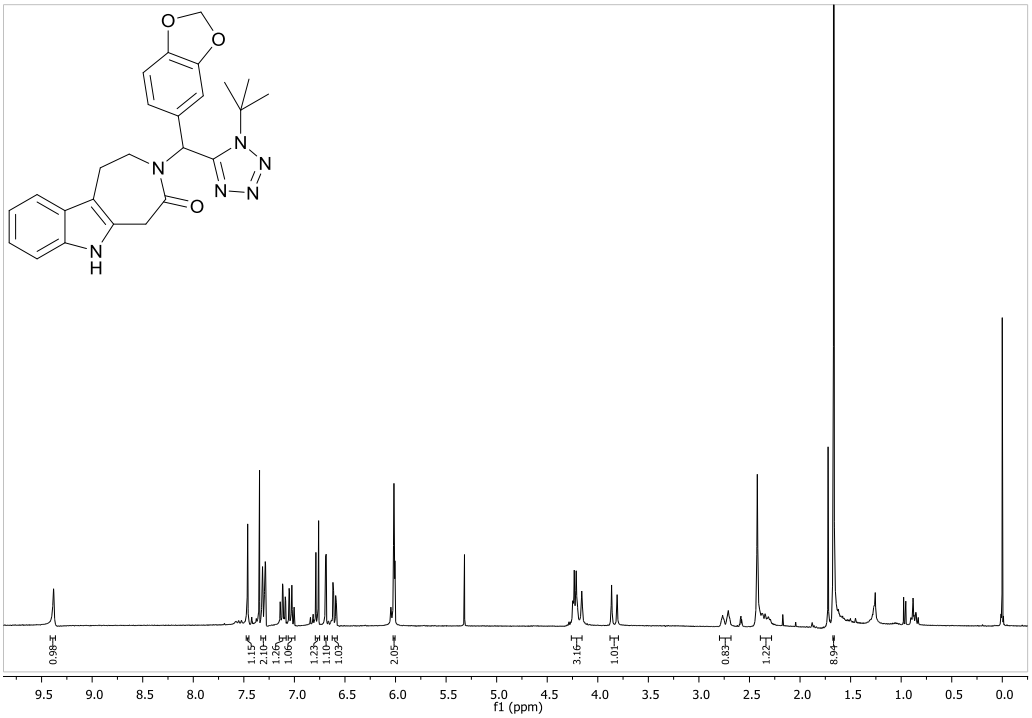



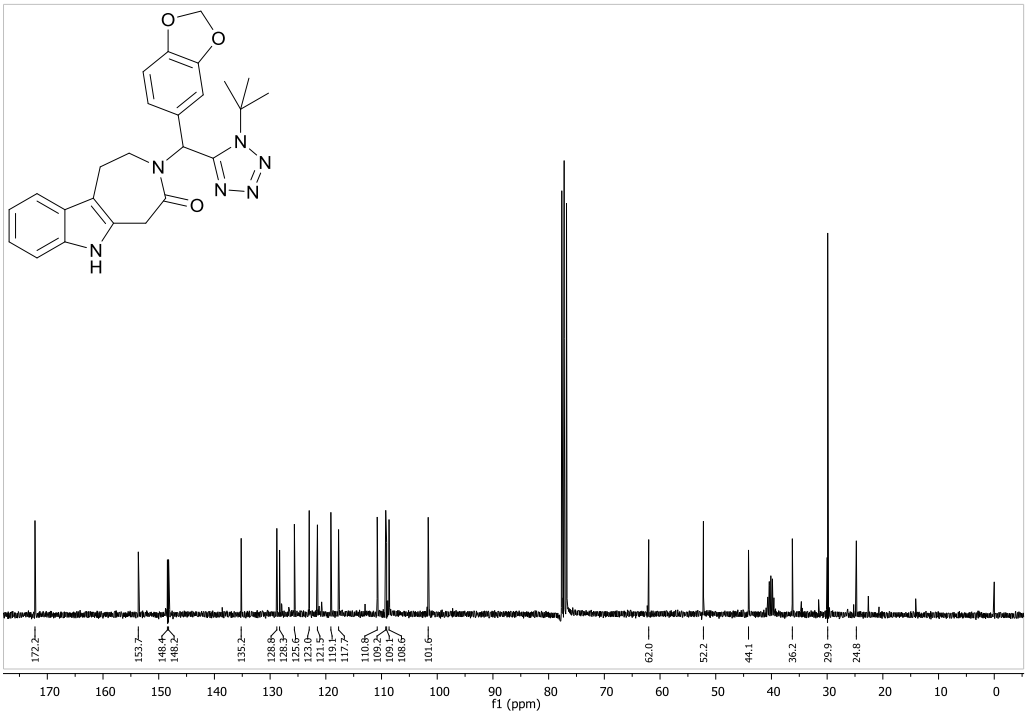
3-((1-tert-butyl-1H-tetrazol-5-yl)(benzo[d][1,3]dioxol-6-yl)methyl)-2,3-dihydroazepino[4,5-b]indol-4(1H,5H,6H)-one (**1f**)



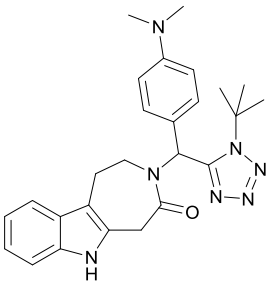
Yield (Δ = 53 %; MW = 45%), physical appearance: white powder, mp = 260 $^{o}$C, $R_f$ = 0.41 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1237, 1646 (C=O), 2987 and 3271; $\delta_H$ (300 MHz, $CDCl_3$) 1.67 (9 H, s, 3 $CH_3$), 2.28-2.39 (1 H, m, 1 H of $CH_2$), 2.69-2.78 (1 H, m, 1 H of $CH_2$), 3.84 (1 H, d, *J* 16.5, 1 H of $CH_2$), 4.15-4.26 (3 H, m, 1 H of $CH_2$ and $CH_2$), 6.00-6.02 (2 H, m, $OCH_2O$), 6.60 (1 H, dd, *J* 1.9, 8.0, ArH), 6.69 (1 H, d, *J* 1.8, ArH), 6.77 (1 H, d, *J* 8.0, ArH), 7.00-7.06 (1 H, m, ArH), 7.08-7.15 (1 H, m, ArH), 7.28-7.33 (2 H, m, ArH), 7.46 (1 H, s, CH) and 9.38 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 24.8, 29.9, 36.2, 44.1, 52.2, 62.0, 101.6, 108.6, 109.1, 109.2, 110.8, 117.7, 119.1, 121.5, 123.0, 125.6, 128.3, 128.8, 135.2, 148.2, 148.4, 153.7 and 172.2; HRMS (FAB+, M+) calcd. for $C_{25}H_{26}N_6O_3$: 458.2066 found 458.2057.



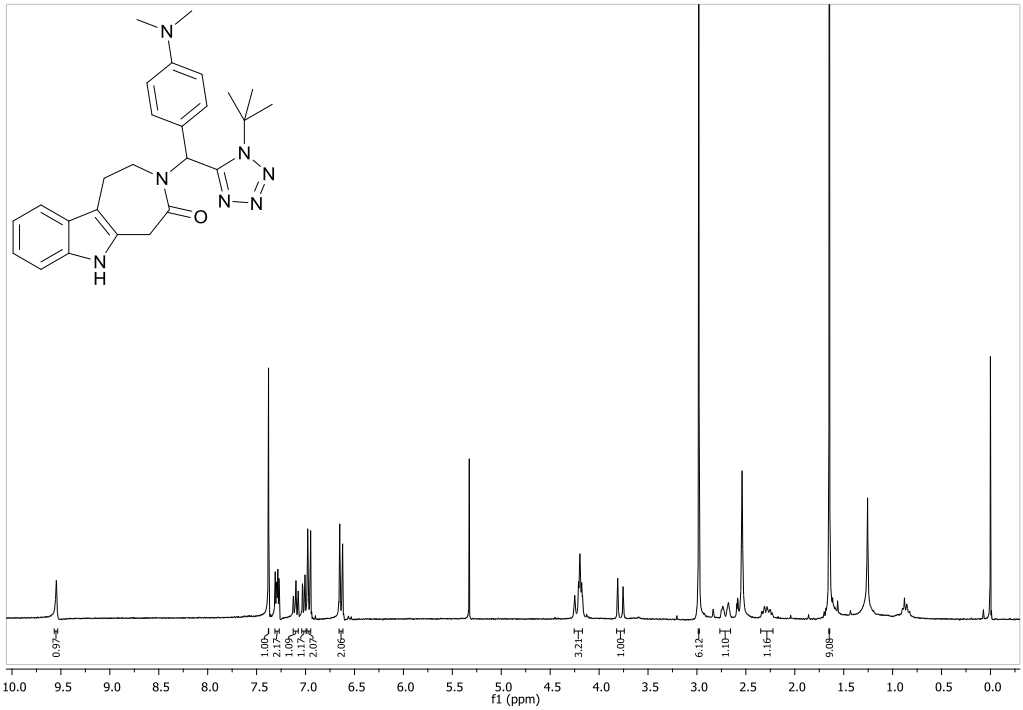


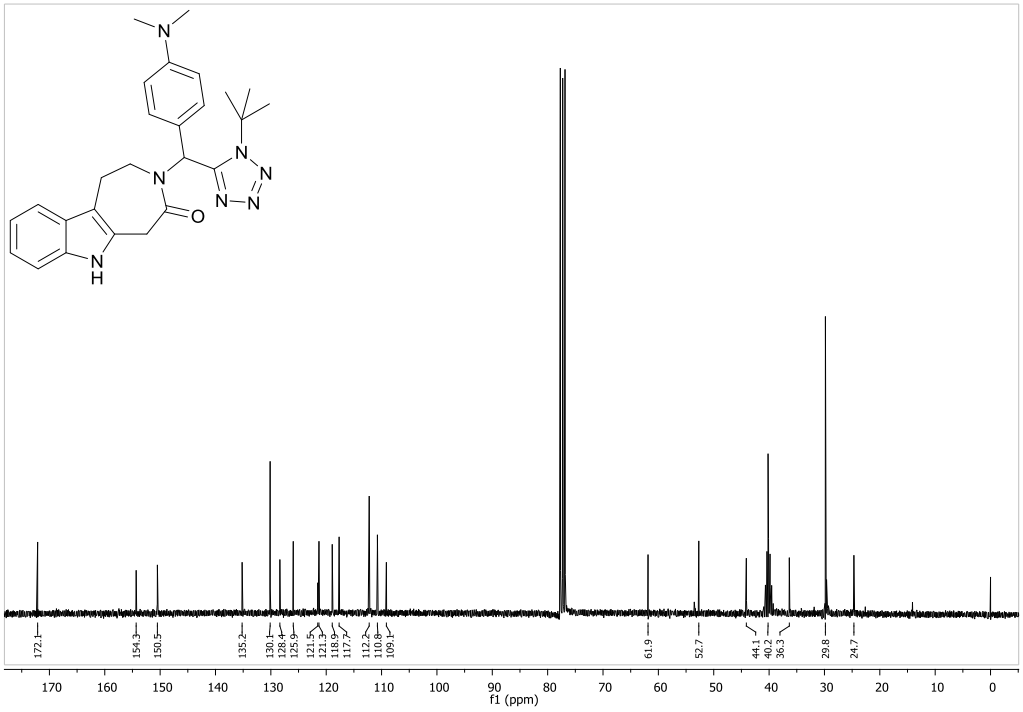

3-((1-tert-butyl-1H-tetrazol-5-yl)(4-(dimethylamino)phenyl)methyl)-2,3-dihydroazepino[4,5-b]indol-4(1H,5H,6H)-one (**1g**)



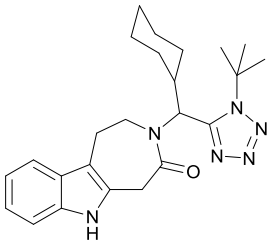
Yield (Δ = 82 %; MW = 76%), physical appearance: white powder, mp = 259 $^{o}$C, $R_f$ = 0.30 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1239, 1629 (C=O), 2986 and 3191; $\delta_H$ (300 MHz, $CDCl_3$) 1.65 (9 H, s, 3 $CH_3$), 2.22-2.35 (1 H, m, 1 H of $CH_2$), 2.66-2.75 (1 H, m, 1 H of $CH_2$), 2.98 (6 H, s, 2 $NCH_3$), 3.78 (1 H, d, *J* 16.4, 1 H of $CH_2$), 4.17-4.26 (3 H, m, 1 H of $CH_2$ and $CH_2$), 6.62-6.66 (2 H, m, ArH), 6.94-6.98 (2 H, m, ArH), 7.00-7.04 (1 H, m, ArH), 7.07-7.13 (1 H, m, ArH), 7.26-7.31 (2 H, m, ArH), 7.38 (1 H, s, CH) and 9.55 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 24.7, 29.8, 36.3, 40.2, 44.1, 52.7, 61.9, 109.1, 110.8, 112.2, 117.7, 118.9, 121.3, 121.5, 125.9, 128.4, 130.1, 135.2, 150.5, 154.3 and 172.1; HRMS (FAB+, M+) calcd. for $C_{26}H_{31}N_7O$: 457.2590 found 457.2584.



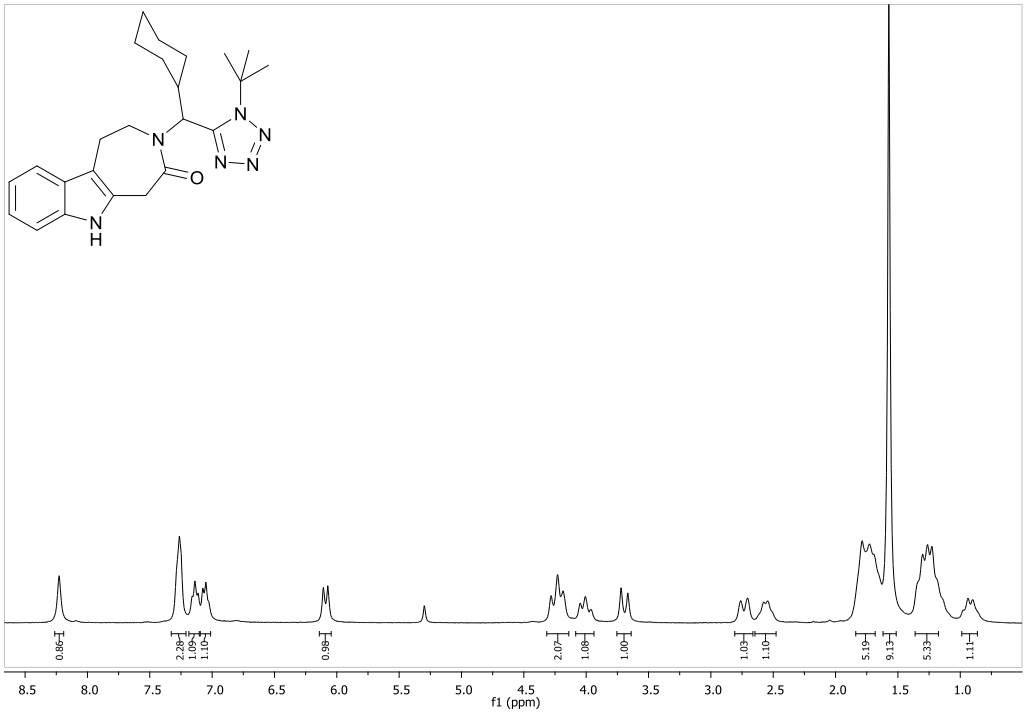



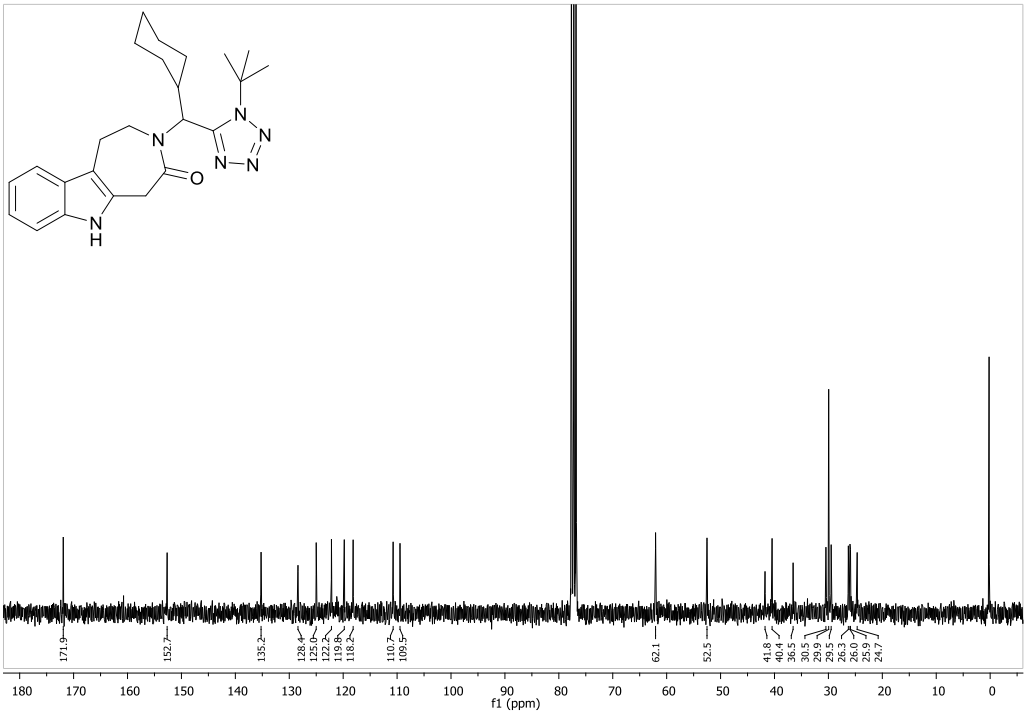
3-((1-tert-butyl-1H-tetrazol-5-yl)(cyclohexyl)methyl)-2,3-dihydroazepino[4,5-b]indol-4(1H,5H,6H)-one (**1h**)



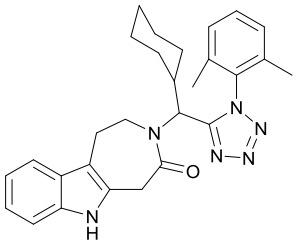
Yield (Δ = 67 %; MW = 62%), physical appearance: white powder, mp = 263 $^{o}$C, $R_f$ = 0.61 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1259, 1646 (C=O), 2922 and 3157; $\delta_H$ (300 MHz, $CDCl_3$) 0.83-0.98 (1 H, m, CH), 1.13-1.39 (5 H, m, 1 H of $CH_2$ and 2 $CH_2$), 1.57 (9 H, s, 3 $CH_3$), 1.63-1.84 (5 H, m, 1 H of $CH_2$ and 2 $CH_2$), 2.49-2.62 (1 H, m, 1 H of $CH_2$), 2.68-2.78 (1 H, m, 1 H of $CH_2$), 3.69 (1 H, d, *J* 16.3, 1 H of $CH_2$), 3.95-4.06 (1 H, m, 1 H of $CH_2$), 4.16-4.29 (2 H, m, $CH_2$), 6.09 (1 H, d, *J* 6.1, CH), 7.01-7.09 (1 H, m, ArH), 7.10-7.17 (1 H, m, ArH), 7.24-7.29 (2 H, m, ArH) and 8.23 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 24.7, 25.9, 26.0, 26.3, 29.5, 29.9, 30.5, 36.5, 36.5, 40.4, 41.8, 52.5, 62.1, 109.5, 110.7, 118.2, 119.8, 122.2, 125.0, 128.4, 135.2, 152.7 and 171.9; HRMS (FAB+, M+) calcd. for $C_{24}H_{32}N_6O$: 420.2638 found 420.2639.






3-(cyclohexyl(1-(2,6-dimethylphenyl)-1H-tetrazol-5-yl)methyl)-2,3,5,6-tetrahydroazepino[4,5-b]indol-4(1H)-one (**1i**)



Yield (Δ = 72 %; MW = 63%), physical appearance: white powder, mp = 190 $^{o}$C, $R_f$ = 0.54 (Hex-AcOEt = 7/3 V/V).

FT-IR (ATR)$\nu_{max}$/cm$^{-1}$ 1290, 1608 (C=O), 2915 and 3201; $\delta_H$ (300 MHz, $CDCl_3$) 0.76-1.03 (2 H, m, $CH_2$), 1.05-1.29 (3 H, m, 1 H of $CH_2$ and $CH_2$), 1.33 (3 H, s, $CH_3$), 1.39-1.47 (1 H, m, CH), 1.62-1.76 (5 H, m, 1 H of $CH_2$ and 2 $CH_2$), 1.94 (3 H, s, $CH_3$), 2.46-2.59 (1 H, m, 1 H of $CH_2$), 2.85-2.95 (1 H, m, 1 H of $CH_2$), 3.72 (1 H, d, *J* 16.1, 1 H of $CH_2$), 4.00 (1 H, d, *J* 16.2, 1 H of $CH_2$), 4.04-4.15 (2 H, m, $CH_2$), 5.47 (1 H, d, *J* 11.3, CH), 6.98-7.05 (2 H, m, ArH), 7.08-7.14 (1 H, m, ArH), 7.18-7.22 (1 H, m, ArH), 7.26-7.33 (1 H, m, ArH) and 9.28 (1 H, bs, NH); $\delta_C$ (75.0 MHz, $CDCl_3$) 16.2, 17.6, 25.0, 25.6, 25.7, 26.0, 29.0, 30.6, 35.6, 39.1, 41.6, 50.5, 108.7, 110.7, 117.7, 119.2, 121.6, 125.6, 128.2, 128.7, 128.8, 131.1, 135.2, 136.5, 154.7 and 171.0; HRMS (FAB+, M+) calcd. for $C_{28}H_{33}N_6O$: 469.2716 found 469.2715.