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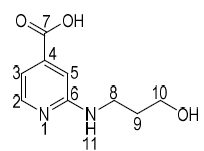
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# General

All solvents and reagents were obtained from commercial suppliers (Sigma Aldrich, VWR or ABCR) and were used without purification. Anhydrous solvents were purchased from Acros Organics. Microwave-assisted syntheses were performed using an Anton Paar Monowave 300 reactor operated in closed vessel mode using G30-vials with 20 mL total capacity; temperature control was performed via integrated IR sensor, stirring speed was 600 rpm. Thin layer chromatography (TLC) was executed on pre-coated silica gel 60 F254 aluminum foil sheets purchased from Merck. Visualization of compounds invisible to the naked eye was accomplished by UV-light (254 nm and 366 nm). Preparative column chromatography at ambient pressure was done on silica gel from Macherey-Nagel (particle size 50–100 μm,140–270 mesh ASTM). Chromatographic purification of products by flash chromatography was performed on silica gel (20–45 µm from Carl Roth) applying pressured air up to 0.8 bar. NMR spectra were recorded on a Bruker Avance III instrument (1H NMR: 400 MHz, 13C NMR: 100.6 MHz). Chemical shifts were referenced to tetramethylsilane (TMS) as internal standard in deuterated solvents and reported in parts per million (ppm). Coupling constants (*J*) are reported in Hz using the abbreviations: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and combinations thereof. Mid-infrared spectra were recorded on an ALPHA FT-IR instrument from Bruker Optics or on a Nicolet IR200 FT-IR from Thermo Electron Corporation, both equipped with a diamond ATR accessory unit, and are indicated in terms of absorption frequency [cm-1]. Melting points were measured in open capillary tubes using a Melting Point M-565 apparatus from Büchi and are uncorrected. High accuracy mass spectra were recorded on a Shimadzu LCMS-IT-TOF using ESI ionization. Purity of final compounds was determined by HPLC with DAD (applying the 100% method at 220 nm and 254 nm). Preparative and analytical HPLC were performed using Shimadzu devices CBM-20A, LC-20A P, SIL-20A, FRC-10A with SPD 20A UV/Vis detector and an ELSD-LT II. In analytical mode a LiChroCART (250×4 mm) and in preparative mode a Hibar RT (250×25 mm) column were used, both containing LiChrospher 100 RP-18 endcapped (5 µm). All compounds are >95% pure by HPLC analysis.

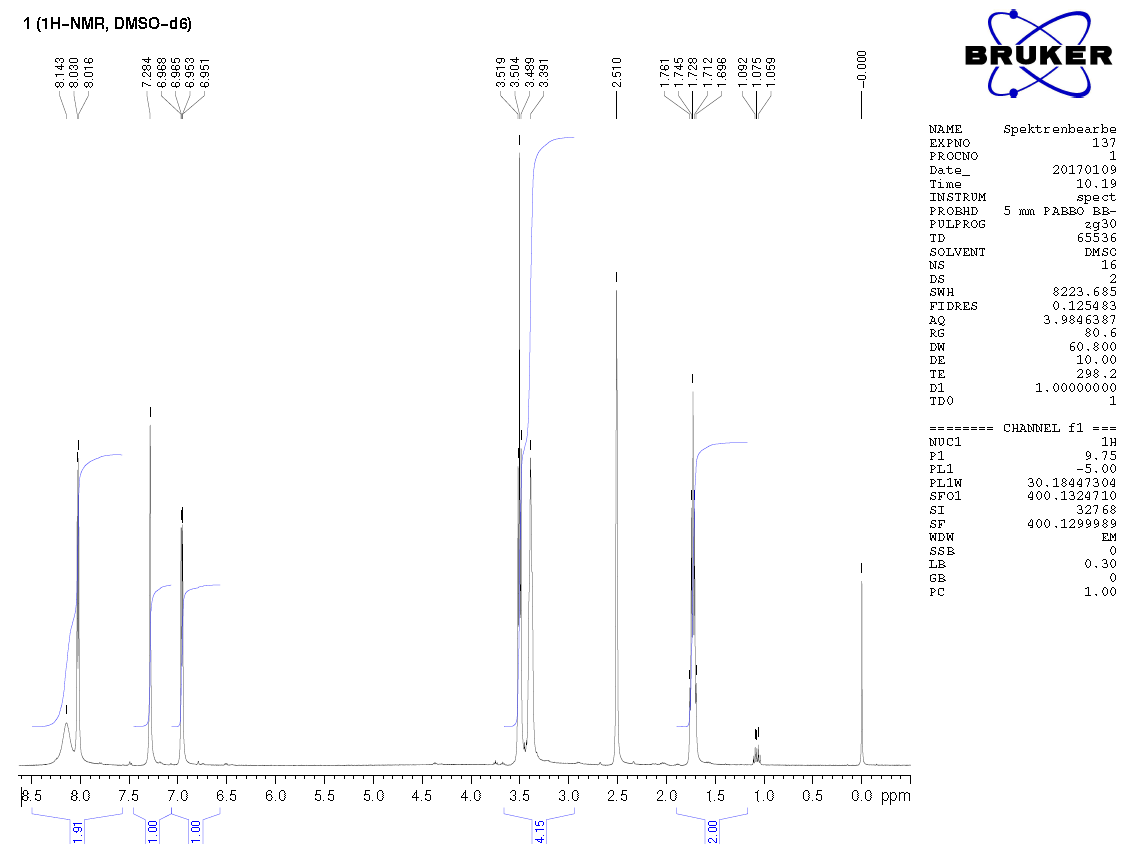
## 2-[(3-Hydroxypropyl)amino]isonicotinic acid (CAS RN 1220019-59-9) (**1**)

A mixture of 2-chloro isonicotinic acid (**11**, 1.0 g, 7.2 mmol) and 3-aminopropan-1-ol (10 mL, 130 mmol) was stirred in a round-bottom flask for 22 h at 120 °C. Subsequently, the reaction mixture was diluted with demineralized water (50 mL) and concentrated hydrochloric acid (25 mL). An acidic pH of 1-2 resulted and heating to reflux was maintained for 16 h. The total volume was reduced to approximately one quarter under reduced pressure and the residual volume was cooled to 5 °C to initiate crystallization. After 12 h, the solid was collected, washed with tetrahydrofuran, dissolved in water and purified by preparative HPLC (C18 column, 250×25 mm, eluents: A: H2O and B: MeOH, isocratic, 30% B) and freeze dried to afford a colorless amorphous powder (366 mg, 26% yield). 1H-NMR (DMSO-*d*6): ** ppm = 1.73 (m, 2H, C(9)H2, 3*J* = 6.4 Hz), 3.39 (s, 2H, C(8)H2), 3.50 (t, 2H, C(10)H2, 3*J* = 6.4 Hz), 6.96 (d, 1H, C(3)H, 3*J* = 5.6 Hz), 7.28 (s, 1H, C(5)H), 8.02 (d, 1H, C(2)H, 3*J* = 5.6 Hz), 8.14 (s, 1H, N(11)H). 13C-NMR (DMSO-*d*6): ** ppm = 31.5 (C9), 38.6 (C8), 58.1 (C10), 109.8 (C5), 111.7 (C3), 140.8 (C4), 142.4 (C2), 156.3 (C6), 165.5 (C7). FTIR (*ṽ*): 3240 (m, *ν*O-H), 3182 (m, *ν*N-H), 1713 (s, *v*C=O) cm−1. HRMS (ESI): calcd for C9H13N2O3 [M + H]+ *m/z*,197.0921; found *m/z*, 197.0914; mp range 194–196 °C.

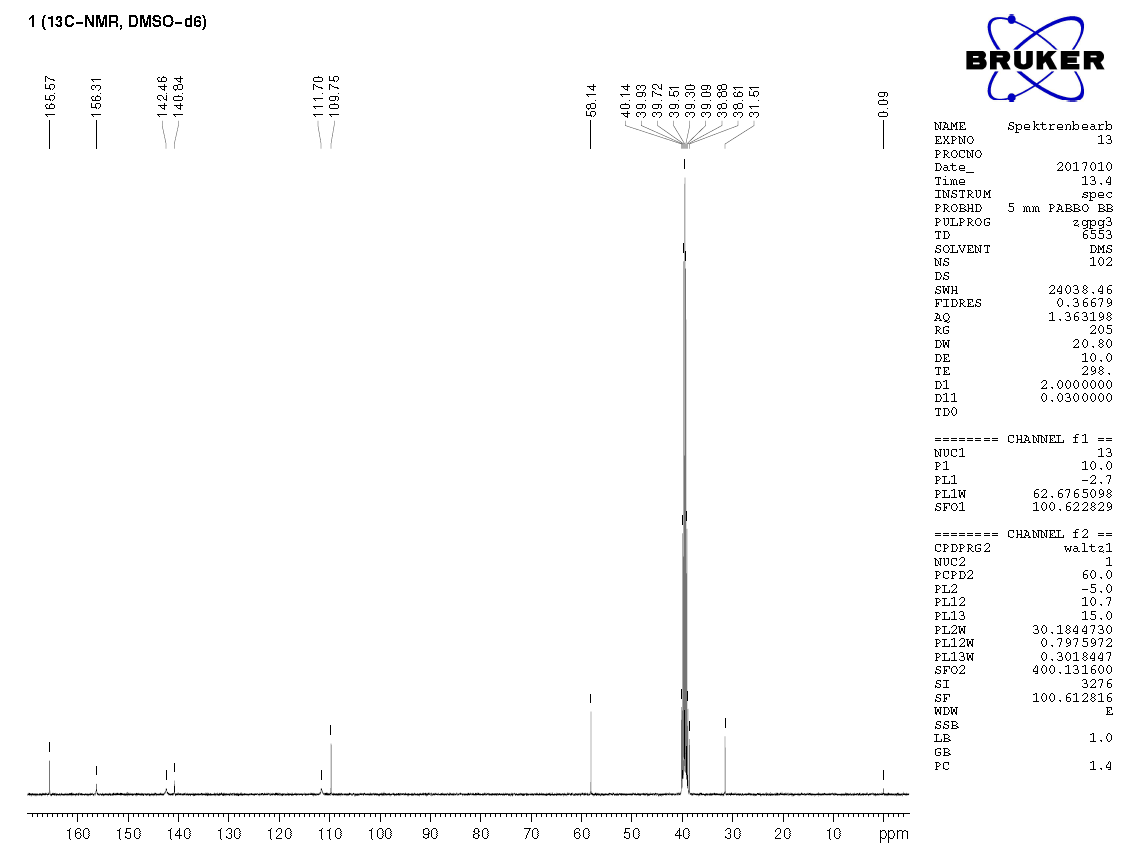


(Numbering for assignment of signals only)

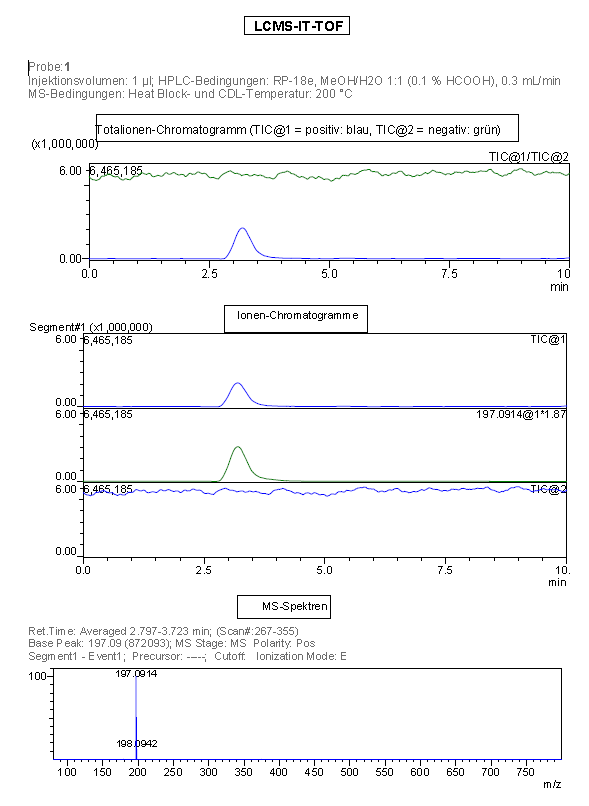
### 1H NMR Spectrum of **1**



### 13C NMR Spectrum of **1**



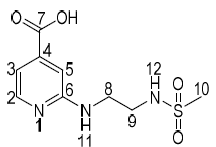
### LCMS Data of **1**



## 2-{[2-(Methanesulfonamido)ethyl]amino}isonicotinic acid (CAS RN 1156429-74-1) (**2**)

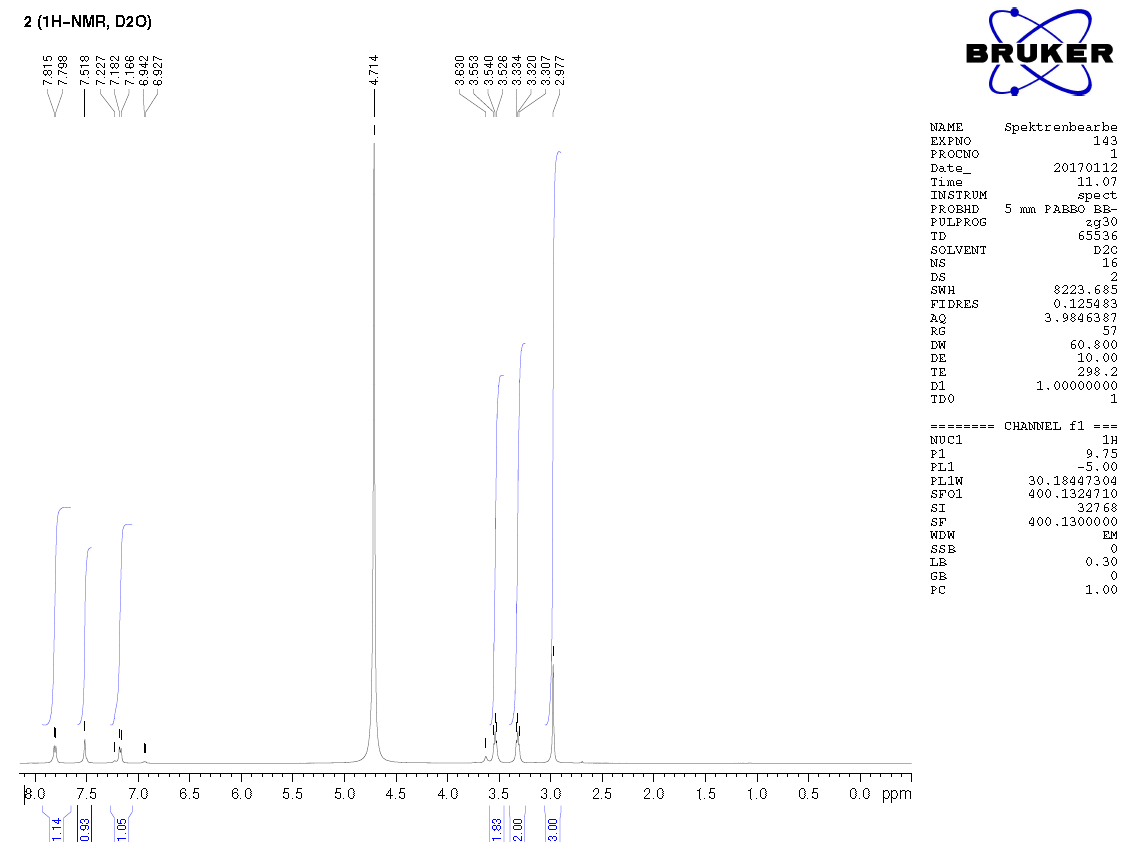
From known starting material **12** (see patent “Preparation of substituted 4-amino[1,2,4]triazolo[4,3-*a*]quinoxalines for treating glycogen synthase kinase 3 (GSK-3) mediated conditions”, Benbow, John W.; Chu-Moyer, Margaret Y.; Kung, Daniel W., United States, US20040192698 A1 2004-09-30)) (CAS Registry Number 766544-99-4)

2-[(2-Aminoethyl)amino]isonicotinic acid hydrochloride (**12**, 400 mg, 1.8 mmol, was suspended in acetonitrile (10 mL). Dilute NaOH solution was added, until a clear solution was obtained. During cooling with ice, methanesulfonyl chloride (420 μL, 5.4 mmol) was added dropwise. Subsequently, the mixture was stirred at room temperature for 20 h. Volatiles were removed under reduced pressure and the residue purified by column chromatography (EtOAc/methanol/ammonia solution 60:40:1 v/v/v). The obtained product-containing fractions were freed from the mobile phase and finally purified by preparative HPLC (C18 column, 250×25 mm, A: water with 0.1% acetic acid and B: methanol, isocratic, 10% B) and freeze dried to afford a colorless amorphous powder (186 mg, 29% yield). A sample for melting range determination was crystallized from EtOH (EtOH/water, 95:5, v/v). 1H-NMR (DMSO-*d*6): ** ppm = 2.89 (s, 3H, C(10)H3), 3.10 (t, 2H, C(9)H2, 3*J* = 6.4 Hz), 3.39 (t, 2H, C(8)H2, 3*J* = 6.4 Hz), 6.88 (d, 1H, C(3)H, 3*J* = 5.6 Hz), 6.97 (m, 2H, C(5)H and N(12)H), 7.09 (d, 1H, C(2)H, 3*J* = 6.0 Hz), 8.10 (s, 1H, N(11)H), 13.25 (s, 1H, C(7)OOH). 13C-NMR (DMSO-*d*6): ** ppm = 39.5 (C10), 40.9 (C9), 41.8 (C8), 108.5 (C5), 110.3 (C3), 138.8 (C2), 148.4 (C4), 159.1 (C6), 166.7 (C7). FTIR (*ṽ*): 3156 (m, *v*N-H), 1677 (s, *v*C=O) cm−1. HRMS (ESI): calcd for C9H14N3O4S [M + H+] *m/z*,260.0700; found *m/z*, 260.0694; mp range 273–275 °C (decomposition).

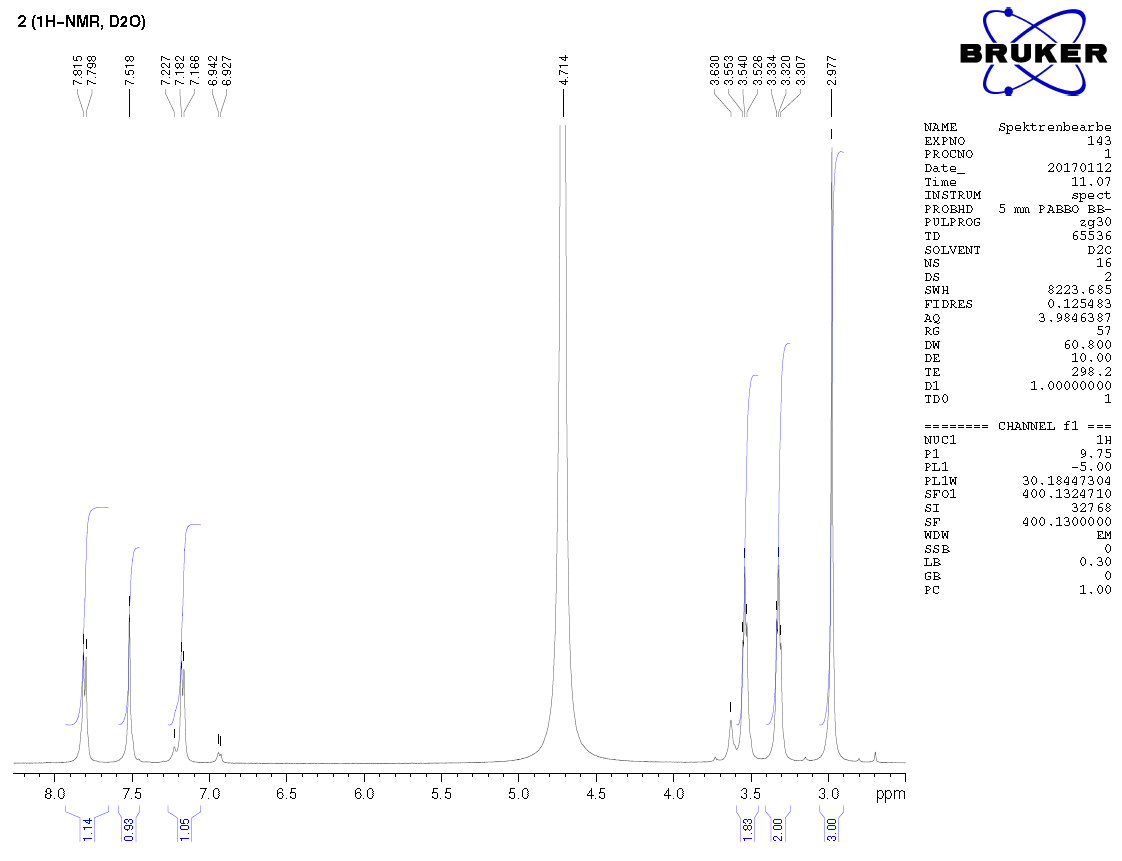


(Numbering for assignment of signals only)

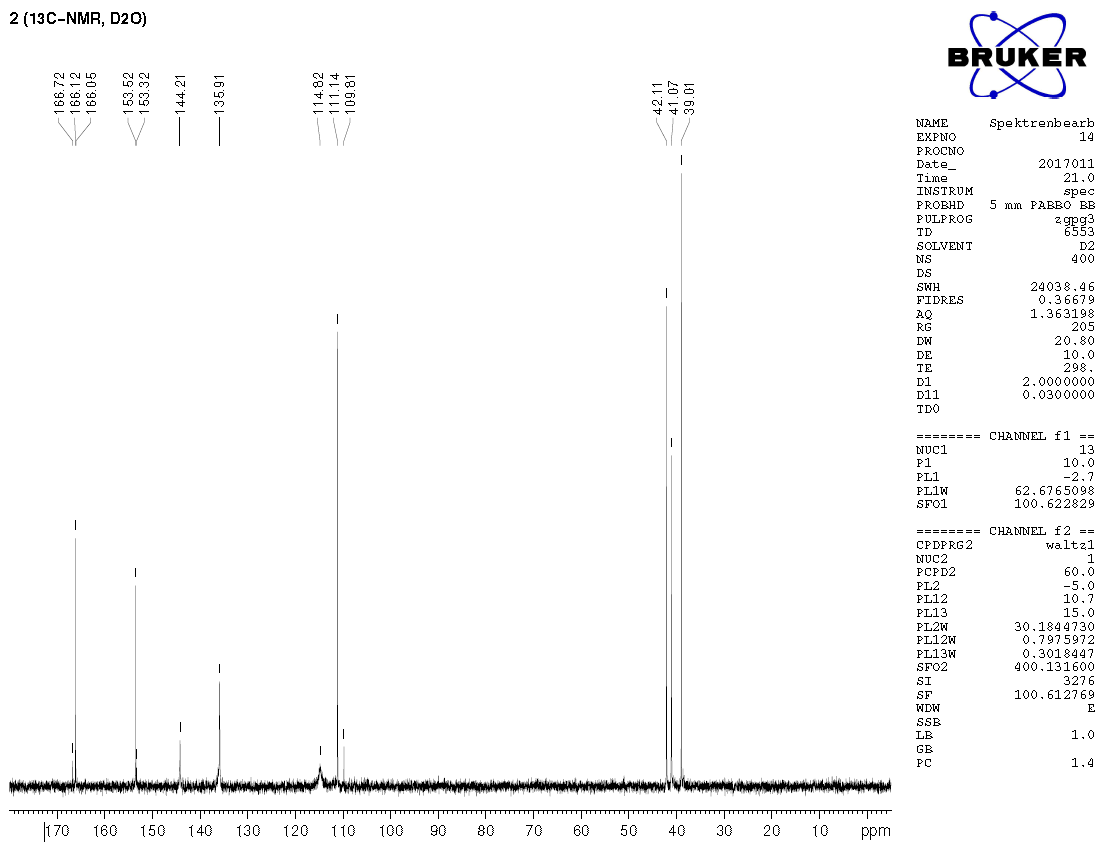
### 1H NMR Spectrum of **2**



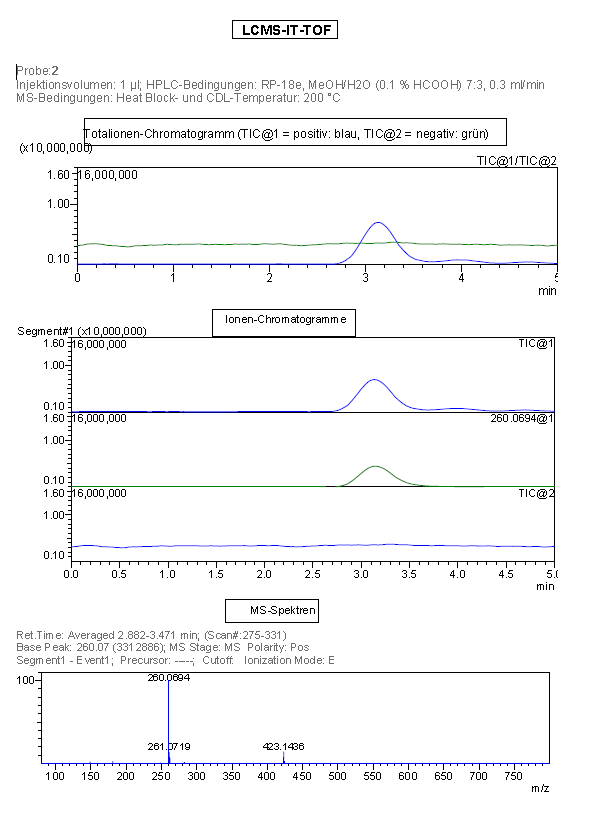
### 1H NMR Spectrum of **2** (zoom)



### 13C NMR Spectrum of **2**

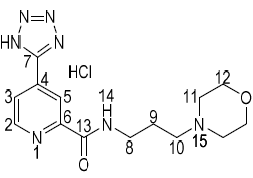


### LCMS Data of **2**



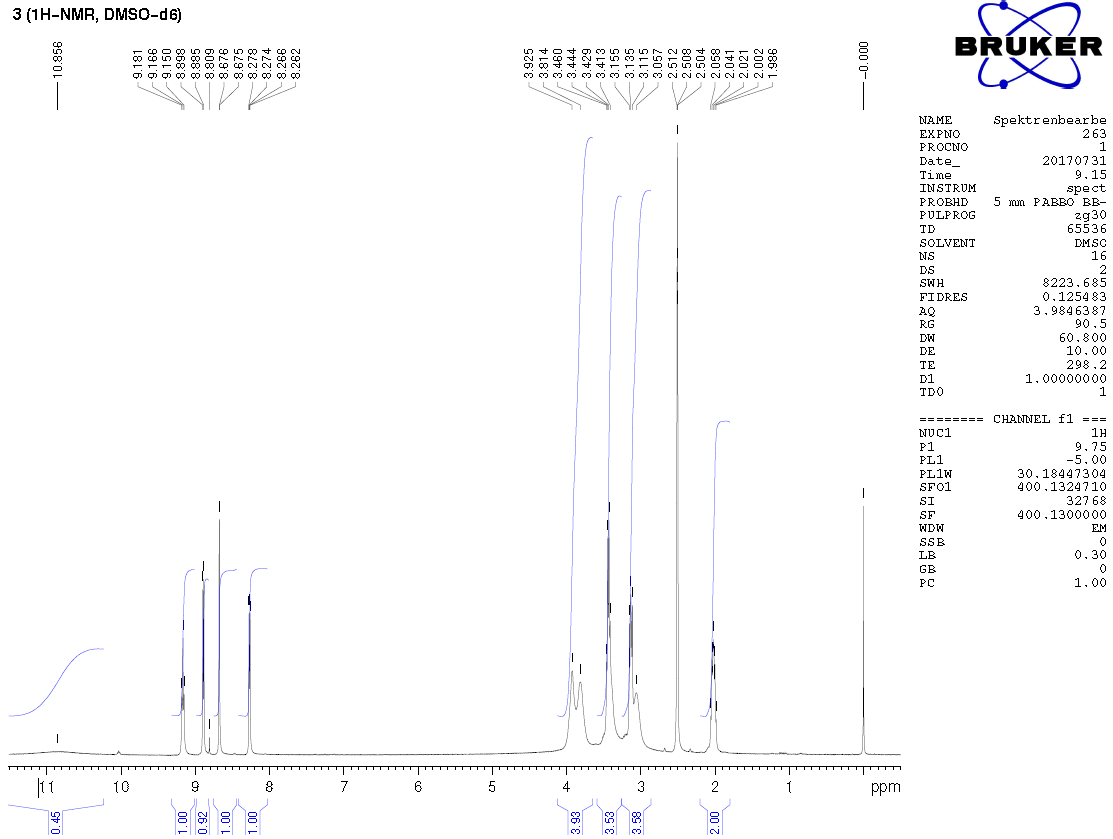
## *N*-(3-Morpholinopropyl)-4-(1*H*-tetrazol-5-yl)picolinamide hydrochloride (**3**)

4-(1*H*-Tetrazol-5-yl)picolinic acid ethyl ester (**13**, 915 mg, 4.1 mmol) and 3-morpholinopropylamine (3.0 mL, 20.5 mmol) in EtOH (15 mL ) were sealed in an Anton Paar G30 tube and heated by means of microwave irradiation to 165 °C for 45 min while stirring in an Anton Paar Monowave 300. After cooling to room temperature the tube was opened and the contents diluted with EtOH to a total volume of 80 mL and acidified by addition of hydrochloric acid (36%). Upon standing at –21 °C, precipitation occurred during 1 h. Solids were collected by filtration and recrystallized from EtOH, twice. The obtained product was washed vigorously with toluene, tetrahydrofuran, and acetone, in this order. After drying, a colorless amorphous product was obtained and dried (233 mg, 18% yield). 1H-NMR (DMSO-*d*6): ** ppm = 2.30 (m, 2H, C(9)H2, 3*J* = 8.0 Hz), 3.06 (s, 2×1H, 2×C(11)H2), 3.14 (m, 2H, C(10)H2, 3*J* = 8.0 Hz), 3.43 (m, 2H and 2×1H, C(8)H2 and 2×C(11)H2), 3.85 (2×s, 2×2H, 2×C(12)H2), 8.27 (d, 1H, C(3)H, 3*J* = 4.8 Hz), 8.67 (s, 1H, C(5)H), 8.88 (d, 1H, C(2)H, 3*J* = 5.2 Hz), 9.16 (t, 1H, N(14)H, 3*J* = 6.4 Hz), 10.98 (s, 1H, N(15)H+). 13C-NMR (DMSO-*d*6): ** ppm = 23.4 (C9), 36.3 (C8), 50.9 (2×C11), 53.9 (C10), 63.2 (2×C12), 118.9, (C5), 123.3 (C3), 133.9 (C4), 149.8 (C2), 151.1 (C6), 155.1 (C7), 163.5 (C13). FTIR (*ṽ*): 3344 (s, *v*N-H), 1644 (s, *v*C=O), 1613 (s, *ν*C=N) cm−1. HRMS (ESI): calcd for C14H20N7O2 [M + H]+ *m/z*,318.1673; found *m/z*, 318.1664; mp range 129–130 °C.

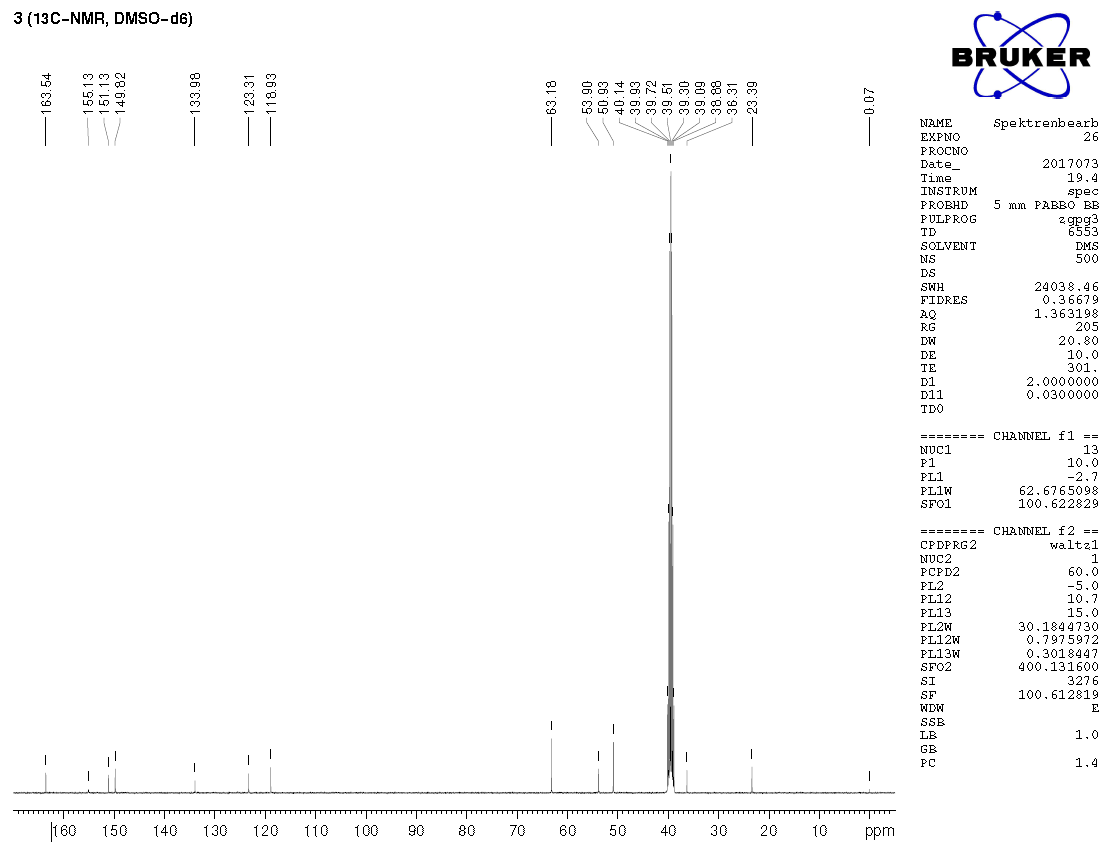


(Numbering for assignment of signals only)

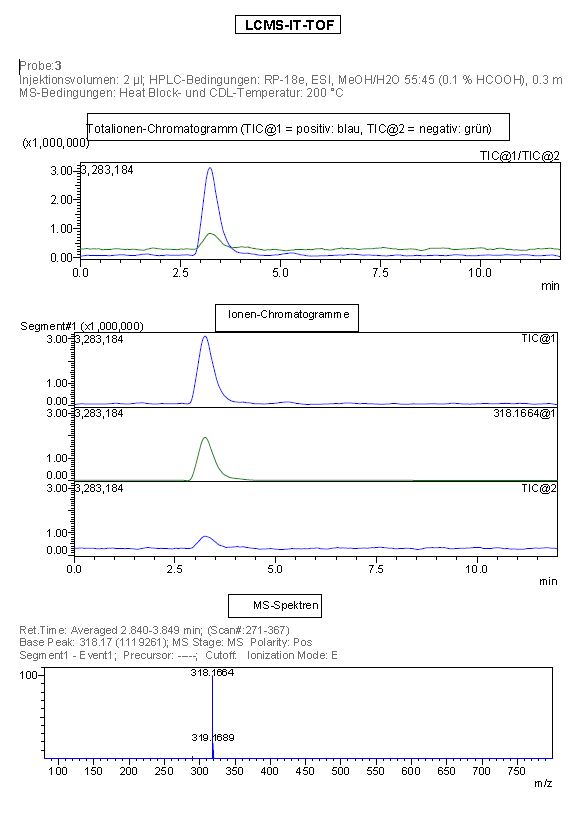
### 1H NMR Spectrum of **3**



### 13C NMR Spectrum of **3**



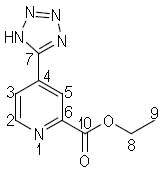
### LCMS Data of **3**



## *N*-Hydroxy-4-(1*H*-tetrazol-5-yl)picolinamide (**4**)

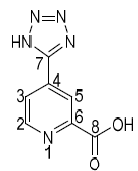
In two steps from intermediates **13** and **14**

### 4-(1*H*-Tetrazol-5-yl)picolinic acid ethyl ester (**14**)

4-Cyanopicolinic acid ethyl ester (**13**, 3.0 g, 17 mmol) was dissolved in toluene (50 mL). NaN3 (1.4 g, 22 mmol) and triethyl amine hydrochloride (3.0 g., 22 mmol) were added and the resulting mixture was stirred at 110 °C. After 16 h, the mixture was concentrated under reduced pressure and treated with aqueous sodium hydroxide solution until a pH of 12 was reached. The aqueous phase was washed three times with EtOAc and subsequently acidified with hydrochloric acid (36 %) resulting in precipitation of 4-(1*H*-tetrazol-5-yl)picolinic acid ethyl ester (**14**). The collected precipitate was washed with 2-propanol and dried to afford a colorless amorphous powder (3.261 g, 88% yield). 1H-NMR (DMSO-*d*6): ** ppm = 1.38 (t, 3H, C(9)H3, 3*J* = 7.2 Hz), 4.42 (q, 2H, C(8)H2, 3*J* = 7.2 Hz), 8.24 (d, 1H, C(3)H, 3*J* = 4.8 Hz), 8.64 (s, 1H, C(5)H), 8.96 (d, 1H, C(2)H, 3*J* = 5.2 Hz). 13C-NMR (DMSO-*d*6): ** ppm = 14.8 (C9), 61.6 (C8), 121.6 (C5), 124.0 (C3), 133.5 (C4), 148.9 (C6), 151.1 (C2), 155.0 (C7), 164.1 (C10). FTIR (*ṽ*): 1724 (s, *v*C=O), 1610 (s, *ν*C=N) cm−1. HRMS (ESI): calcd for C9H10N5O2 [M + H]+ *m/z*,220.0829; found *m/z*, 220.0818; mp range 251–252 °C (decomposition).

(Numbering for assignment of signals only)

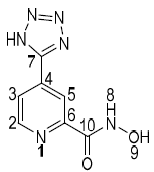
### 4-(1*H*-Tetrazol-5-yl)picolinic acid (**15**)

4-(1*H*-Tetrazol-5-yl)picolinic acid ethyl ester (**14**) (500 mg, 2.3 mmol) was suspended in MeOH (10 mL). An aqueous sodium hydroxide (365 mg, 9.2 mmol in 10 mL) solution was added and the resulting mixture was heated to reflux for 3 h. Upon acidification with hydrochloric acid (36 %), 4-(1*H*-tetrazol-5-yl)picolinic acid (**15**) precipitated, was collected by filtration and washed with aqueous MeOH (MeOH/water, 50:50, v/v) and dried to afford colorless crystals (411 mg, 94% yield). 1H-NMR (DMSO-*d*6): ** ppm = 8.23 (d, 1H, C(3)H, 3*J* = 4.8 Hz), 8.65 (s, 1H, C(5)H), 8.96 (d, 1H, C(2)H, 3*J* = 4.8 Hz). 13C-NMR (DMSO-*d*6): ** ppm = 121.6 (C5), 123.7 (C3), 133.5 (C4), 149.7 (C6), 150.9 (C2), 155.0 (C7), 165.6 (C8). FTIR (*ṽ*): 3352 (m, *v*O-H), 1722 (m, *v*C=O), 1630 (s, *ν*C=N) cm−1. HRMS (ESI): calcd for C7H6N5O2 [M + H]+ *m/z*,192.0516; found *m/z*, 192.0518; mp range 255–257 °C (decomposition).

(Numbering for assignment of signals only)

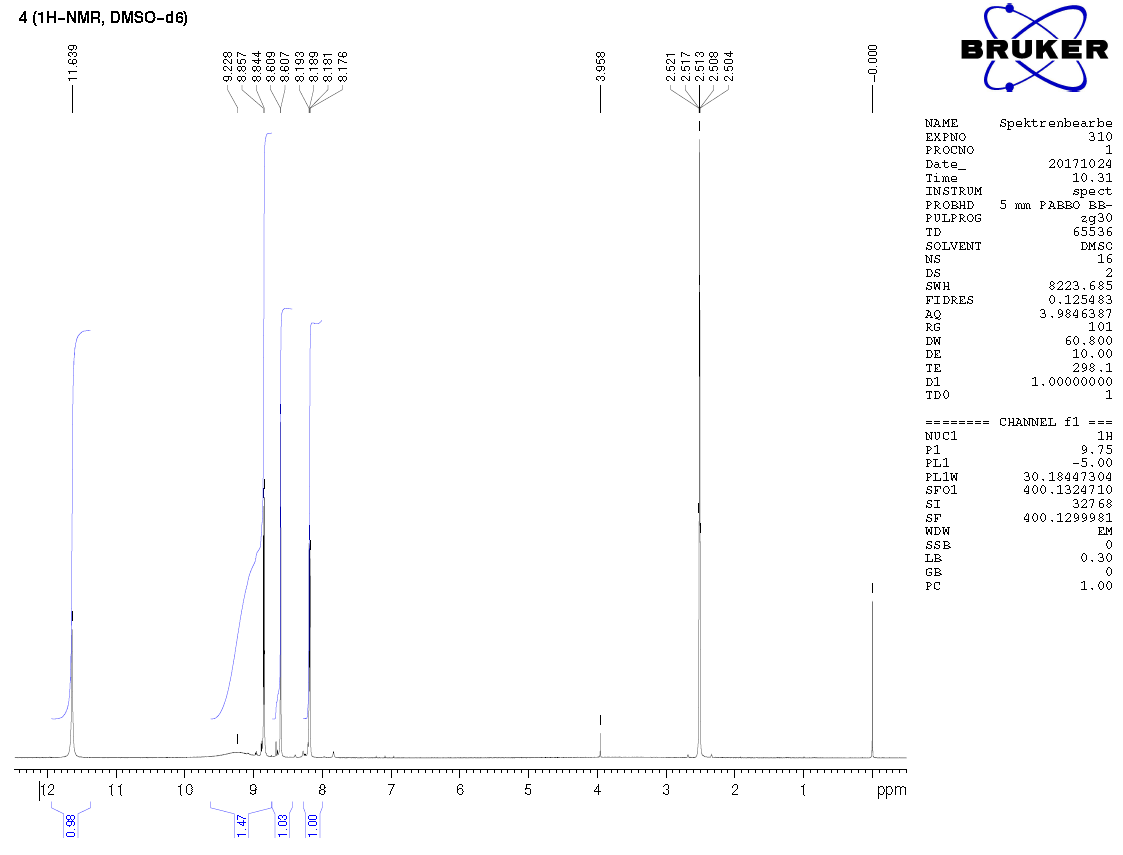
## *N*-Hydroxy-4-(1*H*-tetrazol-5-yl)picolinamide (**4**)

4-(1*H*-Tetrazol-5-yl)picolinic acid (**15**, 200 mg, 1.0 mmol) was dissolved in DMF (10 mL ) and stirred in an ice bath. After addition of oxalyl chloride (120 μL, 1.4 mmol) stirring was continued for 30 min. Subsequently, excess oxalyl chloride was removed *in vacuo* and DIPEA (525 μL, 3 mmol) was added, followed by addition of hydroxylamine hydrochloride (100 mg, 1.4 mmol). The reaction proceeded at room temperature during 18 h. The resulting solution was diluted with EtOH (10 mL) and water (10 mL). The mixture was acidified with hydrochloric acid (36 %) resulting in precipitation of 4-(1*H*-tetrazol-5-yl)picolinic acid (**15**). The precipitate was collected and dissolved in a solution of ammonia in MeOH, adsorbed on diatomaceous earth and purified by column chromatography (eluent EtOAc/MeOH/acetic acid, 50:50:1, v/v/v). Product containing fractions were combined and evaporated. The obtained residue was crystallized from water and dried to afford colorless crystals (45 mg, 21% yield). 1H-NMR (DMSO-*d*6): ** ppm = 8,18 (d, 1H, C(3)H, 3*J* = 5.2 Hz), 8.60 (s, 1H, C(5)H), 8.85 (d, 1H, C(2)H, 3*J* = 5.2 Hz), 9.23 (s, 1H, N(8)H), 11.64 (s, 1H, O(9)H). 13C-NMR (DMSO-*d*6): ** ppm = 118.8 (C5), 123.0 (C3), 133.8 (C4), 149.9 (C2), 151.3 (C6), 154.8 (C7), 160.6 (C10). FTIR (*ṽ*): 3335 (m, *v*N-H), 1643 (s, *v*C=O), 1610 (s, *ν*C=N) cm−1. HRMS (ESI): calcd for C7H7N6O2 [M + H]+ *m/z*,207.0625; found *m/z*, 207.0617; mp range 241–242 °C (decomposition).

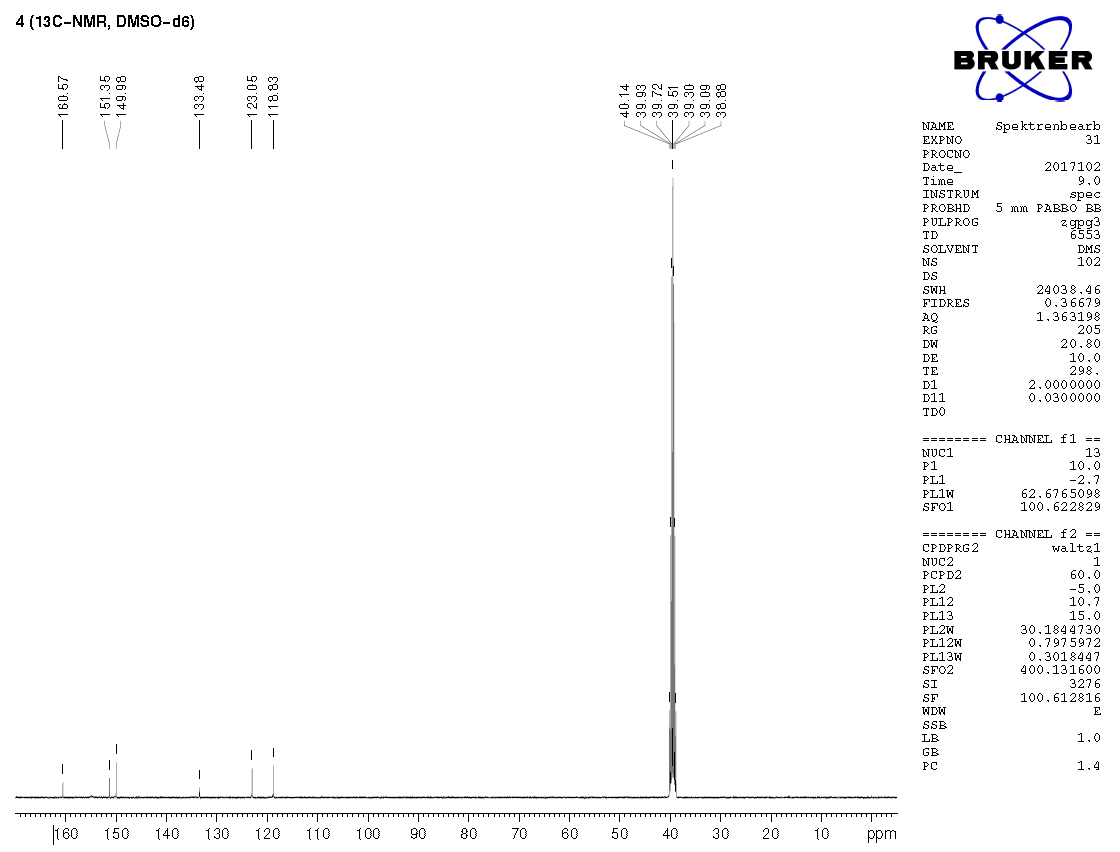


(Numbering for assignment of signals only)

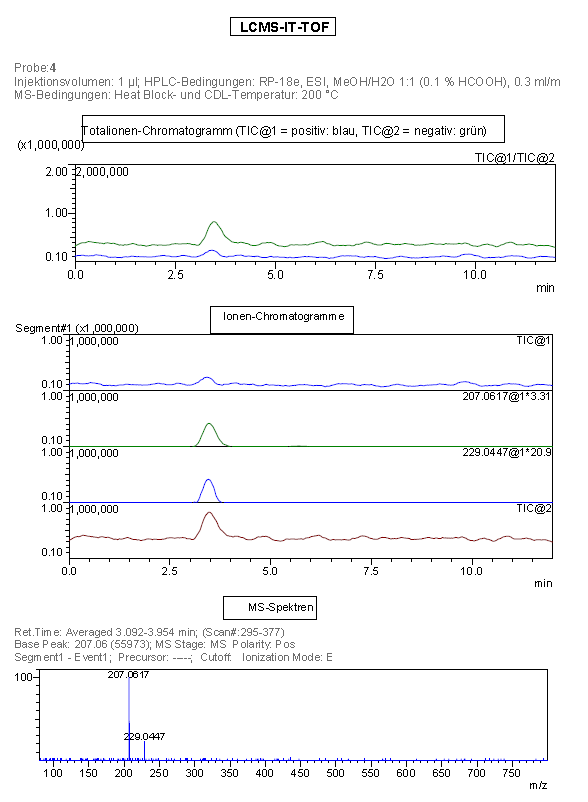
### 1H NMR Spectrum of **4**



### 13C NMR Spectrum of **4**



### LCMS Data of **4**



### 2-Chloroisonicotinic acid (**11**).

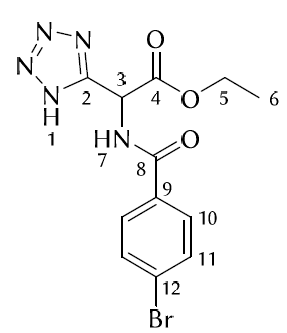
Commercially available 2-chloroisonicotinonitrile (2.8 g, 20 mmol) were dissolved in ethanol (20 mL.) Aqueous NaOH (2.4 g, 60 mmol. dissolved in 10 mL water) were added to the solution. The reaction mixture was refluxed for 3 h. Completion of the reaction was observed when the odor of ammonia ceased. All volatiles were removed under reduced pressure yielding a white solid which was washed with ethyl acetate. The residue was dissolved in water and precipitated with HCl. The solid was filtered off and recrystallized from water to yield a colorless solid (2.0 g, 64%). 1H-NMR (DMSO-*d*6): *δ* ppm = 7.83 (d, 2H, *J* = 4.8 Hz), 8.61 (s, 1H, *J* = 4.8 Hz), 14.01 (s, 1H); 13C-NMR (DMSO-*d*6): *δ* = 122.2, 123.5, 141.8, 151.1, 164.8; FTIR (*ṽ*): 1707 (s), 1367 (s) cm−1. mp range: 235–236 °C (234–235 °C Büchi et al.(Büchi, J.; Labhart, P.; Ragaz, L., Zur Kenntnis lokalanästhetisch wirksamer Pyridin‐4‐carbonsäure‐Derivate. Helvetica Chimica Acta 1947, 30, 507-519)

## (*R*,*S*)-*N*-[2-Hydrazino-2-oxo-1-(1*H*-tetrazol-5-yl)ethyl]-4-bromo benzamid **5**

In two steps from intermediates **16** and **17**.

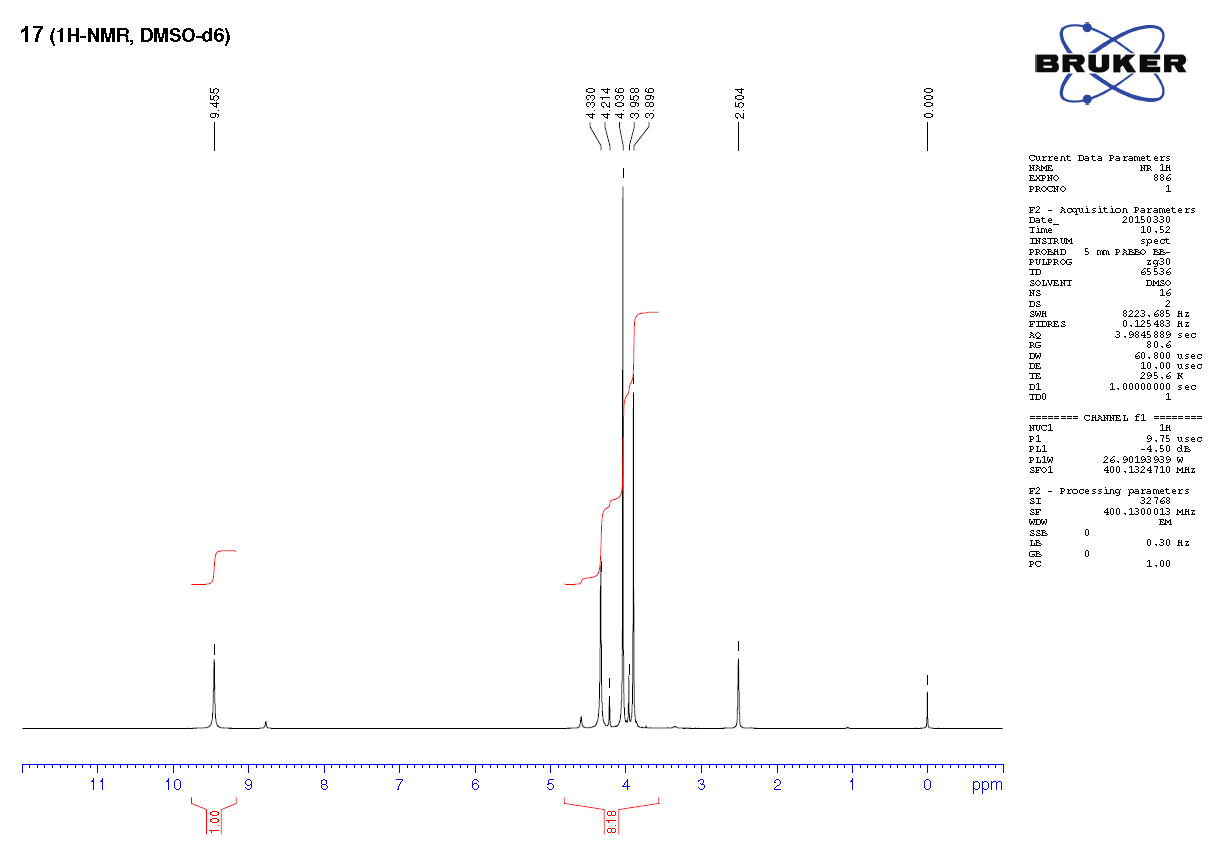
### (2*R*,*S*)-4-Bromobenzamido-2-(1*H*-tetrazol-5-yl)acetic acid ethyl ester (**17**)

(2*R*,*S*)-Amino-2-(1*H*-tetrazol-5-yl) acetic acid ethyl ester hydrochloride (**16**[[1]](#footnote-1), 1.00 g, 4.8 mmol), pyridine (1.14 g, 14.5 mmol), and 4-bromobenzoyl chloride (1.38 g, 5.76 mmol) were suspended in acetonitrile (50 mL) and stirred in a round-bottom flask. The resulting solution was allowed to stir at room temperature for 1 h. After thin layer chromatography showed completion of the reaction, volatiles were removed by means of a rotary evaporator. The liquid residue was dissolved in a mixture of water and EtOAc (100 mL) and brine (100 mL) and extracted three times with brine (100 mL, each) by means of a separation funnel. The combined organic phases were dried over anhydrous MgSO4. After the spent drying agent was removed by filtration, the solvent was evaporated *in vacuo* to yield a colorless solid that was washed multiple times with hot cyclohexane. Drying under reduced pressure at elevated temperature (60 °C) for 24 h afforded a colorless solid (940 mg, 55%). The product was recrystallized from water, and dried for 24 h at reduced pressure and elevated temperature (50–60 °C) for determination of the melting range.

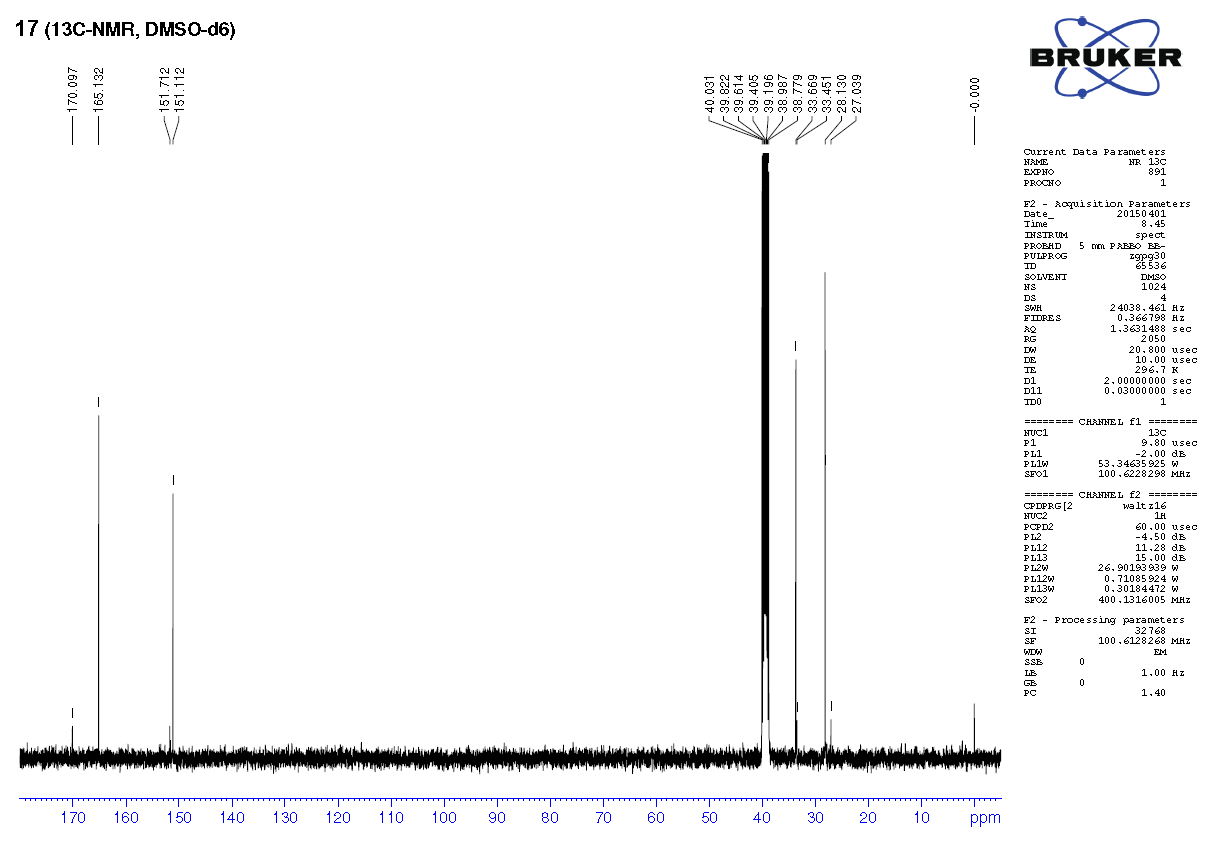
1H-NMR (DMSO-*d*6): ** ppm = 1.19–1.22 (t, 3H, C(6)H3, 3*J* = 7.2 Hz), 4.20–4.26 (q, 2H, C(5)H2, 3*J* = 7.2 Hz), 6.11 (d, 1H, C(3)H, 3*J* = 7.2 Hz), 7.73 (d, 2H, 2 × C(11)H), 7.87 (d, 2H, 2 × C(10)H), 9.73 (d, 1H, N(7)H, 3*J* = 7.2 Hz). 13C-NMR (DMSO-*d*6): ** ppm = 13.9 (C6), 48.2 (C3), 61.9 (C5), 125.9 (C12), 129.8 (2 × C10), 131.5 (2 × C11), 131.9 (C9), 165.7 (C8), 167.1 (C4). FTIR (ν̃): 1635 (s, vC(8)=O), 1745 (s, vC(4)=O) cm−1. HRMS (ESI): calcd for C12H11N5O3Br [M − H]− *m/z*,352.0051; found *m/z*, 352.0034; mp range 180–181 °C.

(Numbering for assignment of signals only)

### 1H NMR Spectrum of **17**

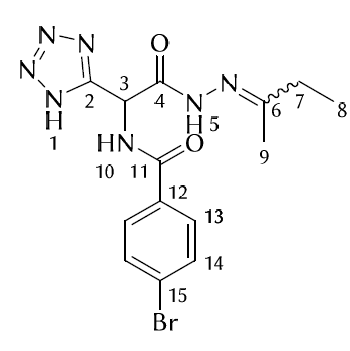


### 13C NMR Spectrum of **17**



### 4-Bromo-*N*-{(1*R*,*S*)-2-[(2*E*/*Z*)-2-(1-methylpropylidene)hydrazino]-2-oxo-1-(1*H*-tetrazol-5-yl)ethyl]benzamide (**18**, NR172)

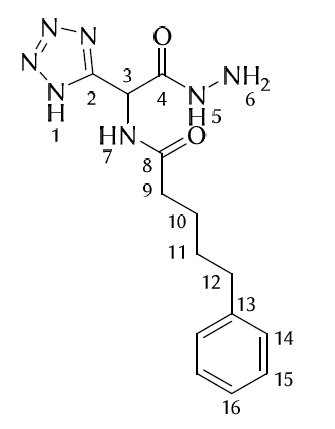
(2*R*,*S*)-4-Bromobenzamido-2-(1*H*-tetrazol-5-yl)acetic acid ethyl ester **17** (772 mg, 2.0 mmol) was dissolved in EtOH (50 mL) denatured with butanone (1%) in a round-bottom flask, combined with an aqueous solution of hydrazine hydrate (3.76 mL (3.87 g) 80% H2N-NH2·H2O, 60.4 mmol), and stirred for 4 h under reflux. Subsequently, the mixture was stirred for 16 h at room temperature. After completion of the reaction solvents were removed *in vacuo*. Residual hydrazine and water were removed by multiple azeotropic drying with EtOH. The resulting solid was filtered over a G4 glass filter funnel, washed with EtOH and dried for 18 h at 8 mbar and 60 °C to yield to yield a colorless solid (250 mg, 36%) that was crystallized from 2-propanol/diethyl ether for melting point analysis.

1H-NMR (DMSO-*d*6): ** ppm = 0.69–0.73/1.03–1.06 (t, 3H, C(8)H3, 3*J* = 7.2 Hz), 1.80/1.88 (s, 3H, C(9)H3), 2.04–2.08/2.27–2.28 (m, 2H, C(7)H2), 6.27/6.66 (d, 1H, C(3)H, 3*J* = 7.2 Hz), 7.69–7.73 (m, 2H, 2 × C(13)H), 7.88–7.92 (m, 2H, 2 × C(14)H), 9.34/9.49 (d, 1H, N(10)H, 3*J* = 7.6 Hz), 10.66/10.73/10.80 (s, 1H, N(5)H). 13C-NMR (DMSO-*d*6): ** ppm = 9.9/10.7 (C8), 16.2/16.3 (C9), 31.1/31.5 (C7), 46.1/48.1 (C3), 129.9 (2 × C14), 131.4 (2 × C13), 133.4 (C12), 155.1/161.4 (C6), 162.4/165.5 (C4), 165.8/167.5 (C11). FTIR (ν̃): 1636 (s, vC(11)=O), 1691 (s, vC(4)=O) cm−1. HRMS (ESI): calcd for C14H15N7O2Br [M − H]− *m/z*,392.0476; found *m/z*, 392.0491; mp range 211–214 °C.

(Numbering for assignment of signals only)

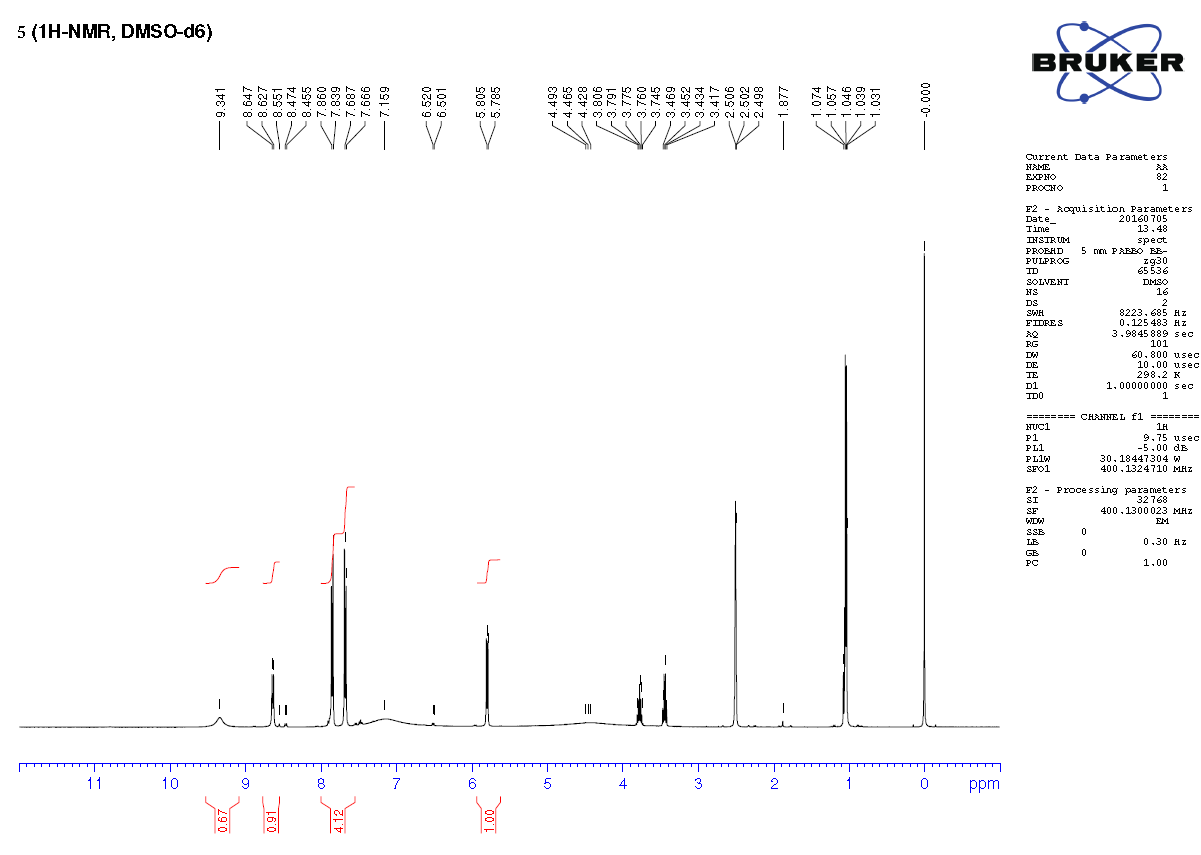
## (*R*,*S*)-*N*-[2-Hydrazino-2-oxo-1-(1*H*-tetrazol-5-yl)ethyl]-4-bromo benzamid (**5**)

(*R*,*S*)-4-Bromo-*N*-{2-[2(*E*/*Z*)-(butan-2-ylidene)hydrazinyl]-2-oxo-1-(1*H*-tetrazol-5-yl)ethyl}benzamid (**18**, 230 mg, 5.70 mmol) was dissolved in boiling EtOH (50 mL) and treated with an aqueous ammonia solution (25% NH3 in water, 15 mL) under reflux. The mixture was kept under reflux for 5 h and subsequently concentrated *in vacuo*. Residual ammonia, water and butanone were removed by multiple azeotropic drying with EtOH. The resulting solid was filtered over a G4 glass filter funnel, washed with EtOH, and dried for 18 h at 8 mbar and 60 °C to yield a colorless solid (190 mg, 97%). Crystallization from 2-propanol yielded a colorless solid (70 mg, 38%).

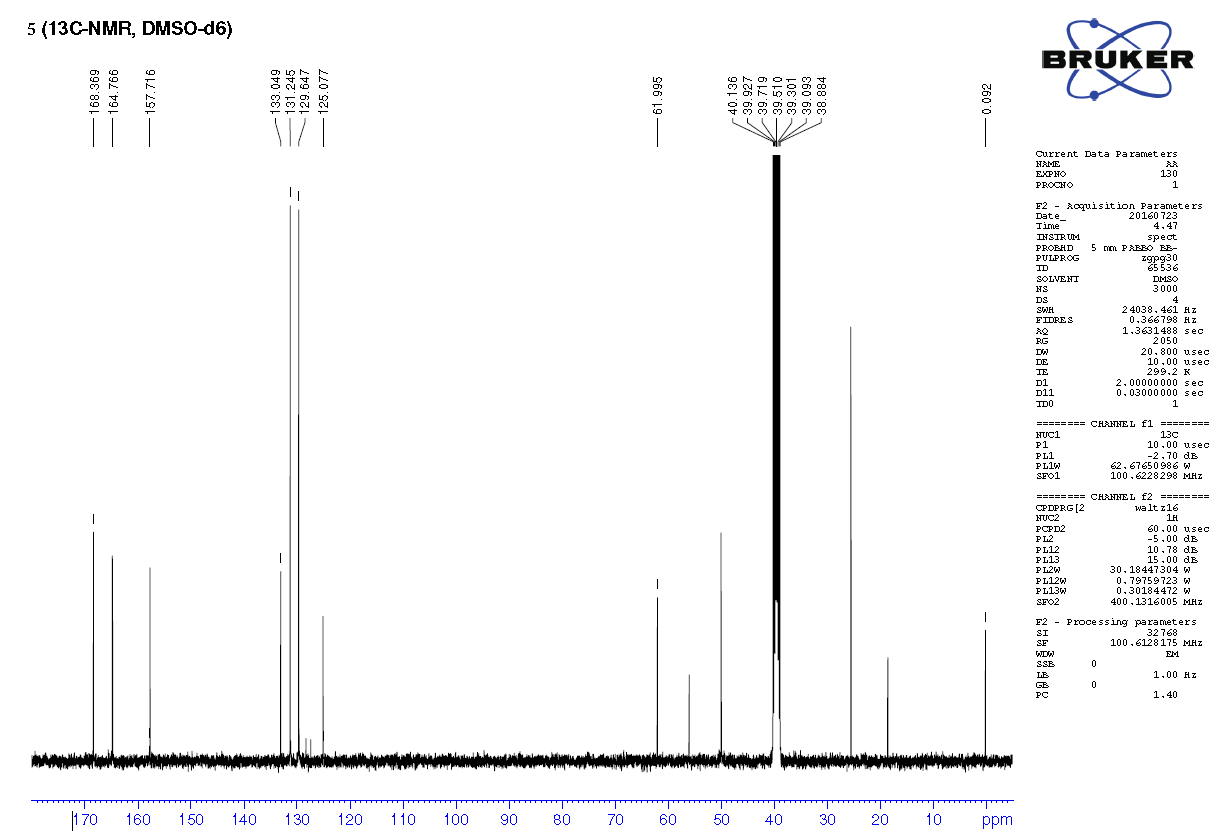
1H-NMR DMSO-*d*6): ** ppm = 5.80 (d, 1H, C(3)H, 3*J* = 8.0 Hz), 7.67–7.69 (m, 2H, 2 × C(11)H), 7.84–7.86 (m, 2H, 2 × C(10)H), 8.65 (d, 1H, N(7)H, 3*J* = 8.0 Hz), 9.34 (s, 1H, N(5)H). 13C-NMR (DMSO-*d*6): ** ppm = 62.0 (C3), 125.1 (C12), 129.7 (2 × C11), 131.3 (2 × C10), 133.1 (C7), 157.7 (C2), 164.8 (C8), 168.4 (C4). FTIR (ν̃) = 1639 (m, vC=O) cm−1. HRMS (ESI): calcd for C10H10N7O2Br [M − H]− *m/z*, 338.0007; found *m/z*, 338.0004; mp range 168–170 °C.

(Numbering for assignment of signals only)

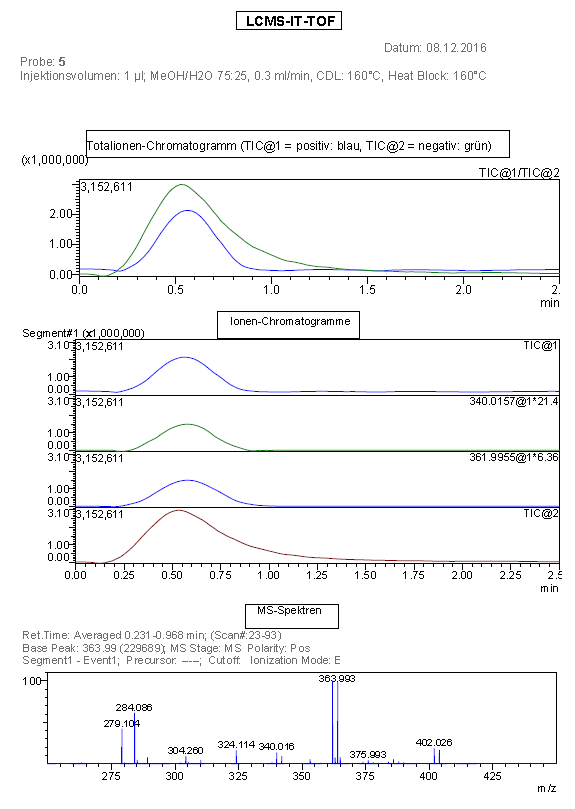
### 1H NMR Spectrum of **5**



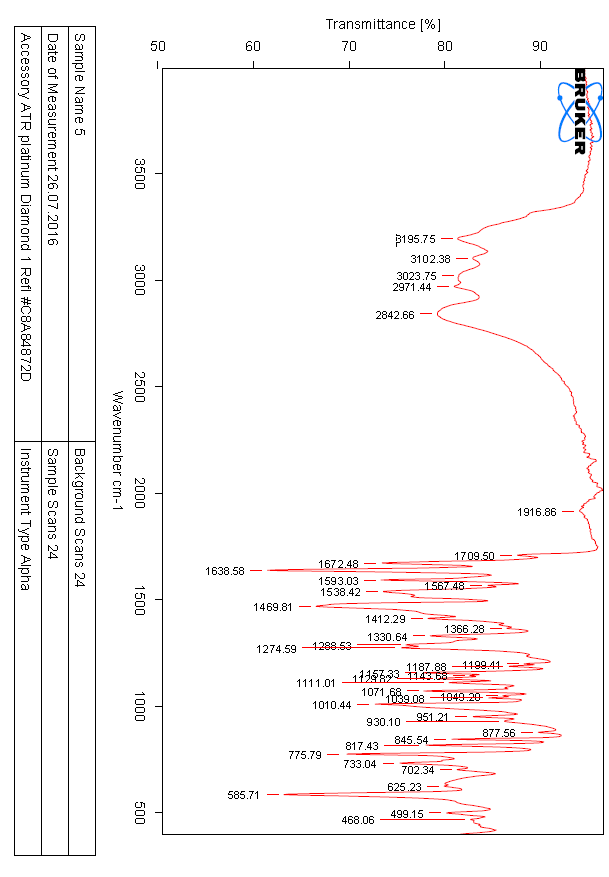
### 13C NMR Spectrum of **5**



### LCMS Data of **5**



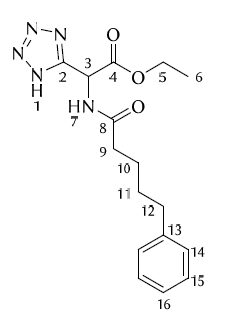
### FTIR spectrum of **5**



### *N*-[(1*R*,*S*)-2-Hydrazinyl-2-oxo-1-(1*H*-tetrazol-5-yl)ethyl]-5-phenylvaleramide (**6**)

From **19** via **20**

(2*R*,*S*)-(5-Phenylvaleramido)-2-(1*H*-tetrazol-5-yl)acetic acid ethyl ester (**19**)

2-Amino-2-(1*H*-tetrazol-5-yl) acetic acid ethyl ester hydrochloride[[2]](#footnote-2) (**16**, 1.00 g, 4.8 mmol), pyridine (1.17 mL, 1,15 g, 14,5 mmol), and 5-phenylpentanoyl chloride (1,89 g, 9,6 mmol) in acetonitrile (100 mL) were stirred in a round-bottom flask. After reaction completion, indicated by TLC analysis, solvents were removed by means of a rotary evaporator. The liquid residue was treated with EtOAc (100 mL) and brine (100 mL) and extracted three times with brine (100 mL, each) by means of a separation funnel. The organic phase was dried over anhydrous MgSO4. After the spent drying agent was removed by filtration, the solvent was evaporated *in vacuo* to yield a pale yellow solid that was washed multiple times with hot cyclohexane. Drying under reduced pressure at elevated temperature (60 °C) for 18 h afforded a pale yellow solid (1.17 g, 73%).

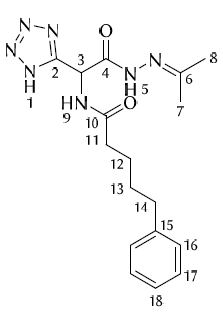
1H-NMR (DMSO-*d*6): ** ppm = 1.15 (t, 3H, C(6)H3, 3*J* = 7.2 Hz), 1.53–1.55 (m, 4H, C(10)H2, C(11)H2), 2.22–2.25 (m, 2H, C(9)H2), 2.55–2.58 (m, 2H, C(12)H2), 4.16 (q, 2H, C(5)H2, 3*J* = 7.2 Hz), 5.91 (d, 1H, C(3)H, 3*J* = 7.6 Hz), 7.14–7.18 (m, 3H, 2 × C(14)H, C(16)H), 7.25–7.28 (m, 2H, 2 × C(15)H), 9.05 (d, 1H, N(7)H), 3*J* = 7.6 Hz). 13C-NMR (DMSO-*d*6): ** ppm = 13.7 (C6), 24.5 C(10), 30.3 (C11), 34.3/34.8 (C9/C12), 47.1 (C3), 61.6 (C5), 125.4 (C16), 128.0 (2 × C14, 2 × C15), 141.9 (C13), 167.1 (C4), 172.5 (C8). FTIR (ν̃): 1525 (w, vC=C), 1657 (w, vC(8)=O), 1737 (w, vC(4)=O) cm−1. HRMS (ESI): calcd for C16H20N5O3 [M − H]− *m/z*,330.1572; found *m/z*, 330.1581; mp range 118–119 °C.

(Numbering for assignment of signals only)

### (*R*,*S*)-*N*-{2-Oxo-2-[2-(propan-2-ylidene)hydrazinyl]-1-(1*H*-tetrazol-5-yl)ethyl}-5-phenylvaleramide (**20**)

Note: This intermediate was prepared because direct synthesis of the target product **6** from **19** with hydrazine was possible but yielded a sticky hygroscopic quality of **6** that was difficult to purify. Therefore, the condensation product with acetone **20** was prepared, purified and treated with aqueous ammonia in order to be able to obtain **6** in very low yield but analytical purity.

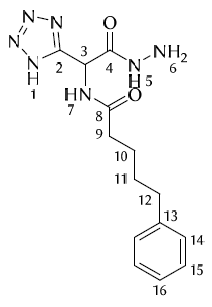
2-(5-Phenylvaleramido)-2-(1*H*-tetrazol-5-yl)acetic acid ethyl ester (**19**, 0.50 g, 1.5 mmol) was dissolved in EtOH (50 mL) in a round-bottom flask, combined with an aqueous solution of hydrazine hydrate (3.76 mL (3.87 g) 80% H2N-NH2·H2O, 60.4 mmol,), and stirred for 4 h at 78 °C under reflux. After addition of acetone (5 mL), stirring under reflux was continued for further 2 h. Subsequently, the mixture was stirred for 16 h at room temperature. After completion of the reaction solvents were removed *in vacuo*. Residual hydrazine and water was removed by multiple azeotropic drying with EtOH. The resulting solid was filtered over a G4 glass filter funnel, washed with EtOH and dried for 18 h at 8 mbar and 60 °C to yield a pale yellow solid (0.23 g, 43%). 1H-NMR (DMSO-*d*6): ** ppm = 1.51–1.54 (m, 4H, C(12)H2, C(13)H2), 1.75–1.95 (m, 6H, C(7)H3, C(8)H3), 2.22–2.28 (m, 2H, C(11)H2), 2.55–2.57 (m, 2H, C(14)H2), 6.08/6.49 (d, 1H, C(3)H, 3*J* = 7.6 Hz/8.0 Hz), 7.14–7.19 (m, 3H, 2 × C(16)H, C(18)H), 7.24–7.28 (m, 2H, 2 × C(17)H), 8.70/8.80 (d, 1H, N(9)H, 3*J* = 8.0 Hz/7.6 Hz), 10.58/10.61 (s, 1H, N(5)H). 13C-NMR (DMSO-*d*6): ** ppm = 17.0/17.7 (C7), 24.6/24.7/24.9 (C3/C12), 30.3/30.5/32.3 (C11/C13/C14), 44.8/47.2 (C3), 125.6 (C18), 128.2 (2 × C16), 128.3 (2 × C17), 142.1 (C15), 151.9 (C6), 158.0 (C2), 167.4 (C10), 172.5 (C4). FTIR: ν̃ = 1520 (w, νC=C), 1650 (m, δN-H), 1687 (w, νC=O) cm−1. HRMS (ESI): calcd for C17H22N7O2 [M − H]− *m/z*,356.1840; found *m/z*, 356.1830; mp range 161–167 °C.



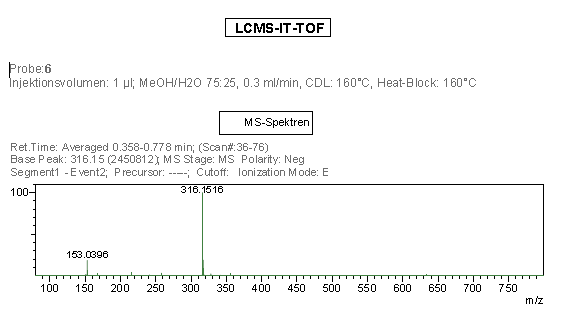
(Numbering for assignment of signals only)

## *N*-[(1*R*,*S*)-2-Hydrazinyl-2-oxo-1-(1*H*-tetrazol-5-yl)ethyl]-5-phenylvaleramide (**6**)

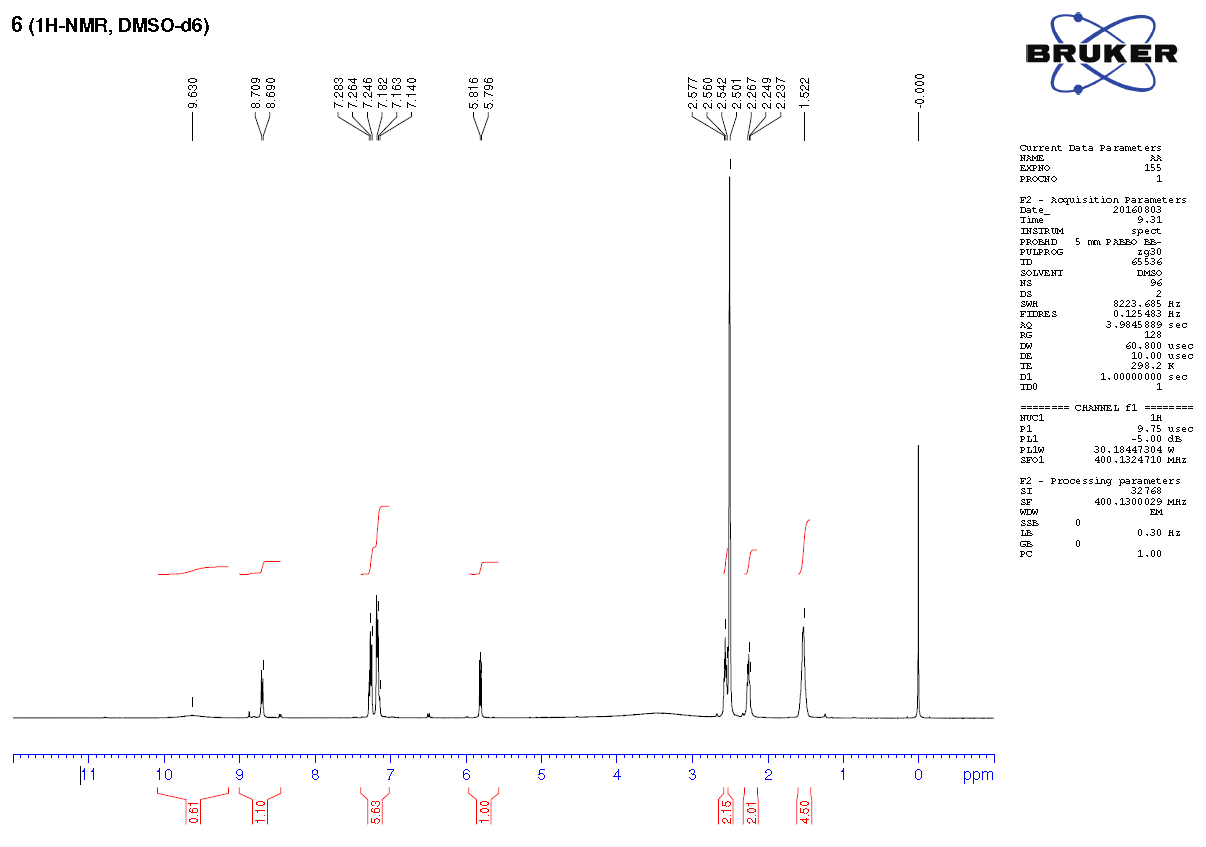
*N*-{2-Oxo-2-[2-(propan-2-yliden)hydrazinyl]-1-(1*H*-tetrazol-5-yl)ethyl}-5-phenylvaleramide (**15**, 300 mg, 0.84 mmol) was dissolved in boiling EtOH (50 mL) and treated with an aqueous ammonia solution (25% NH3 in water, 15 mL) under reflux. The mixture was kept under reflux for 5 h and subsequently concentrated *in vacuo*. Residual ammonia, water and acetone were removed by multiple azeotropic drying with EtOH. The resulting solid was filtered over a G4 glass filter funnel, washed with EtOH and dried for 18 h at 8 mbar and 60 °C to yield a colorless solid (20 mg, 6%).

1H-NMR DMSO-*d*6): ** ppm = 1.52 (s, 4H, C(10)H2, C(11)H2), 2.24–2.27 (m, 2H, C(9)H2), 2.54–2.58 (m, 2H, C(12)H2), 5.81 (d, 1H, C(3)H, 3*J* = 8.0 Hz), 7.14–7.18 (m, 3H, 2 × C(14)H, C(16)H), 7.25–7.28 (m, 2H, 2 × C(15)H), 8.70 (d, 1H, N(7)H, 3*J* = 7.6 Hz), 9.63 (s, 1H, N(5)H). 13C-NMR (DMSO-*d*6): ** ppm = 24.5 (C10), 30.5 (C12), 34.5 (C11), 34.8 (C9), 46.9 (C3), 125.6 (C16), 128.2 (2 × C14), 128.3 (2 × C15), 142.1 (C11), 165.5 (C8), 172.5 (C4). FTIR (ν̃) = 1520 (w, νC=C), 1644 (m, δN-H) cm−1. HRMS (ESI): calcd for C14H19N7O2 [M − H]− *m/z*, 316.1527; found *m/z*, 316.1516; mp range 170–173 °C.

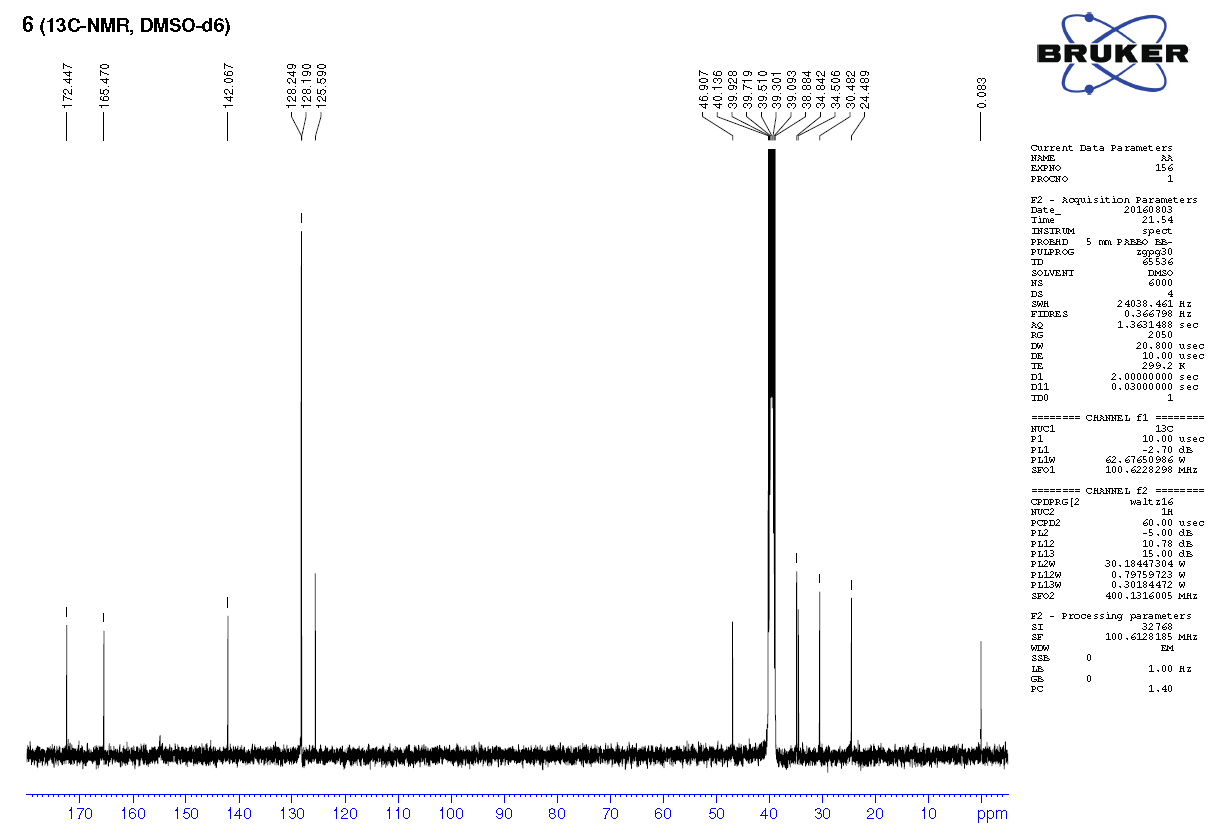
(Numbering for assignment of signals only)



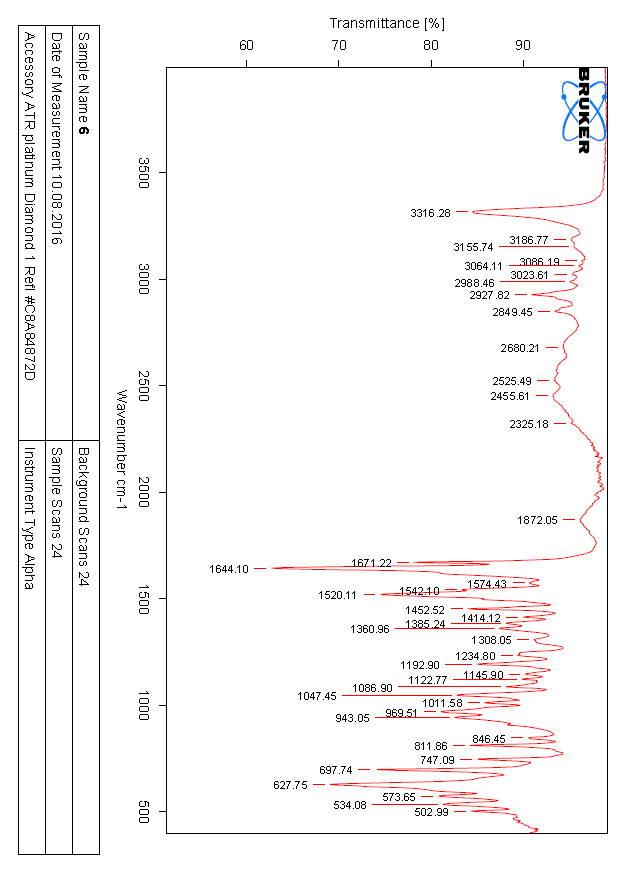
### 1H NMR Spectrum of **6**



### 13C NMR Spectrum of **6**



### FTIR Spectrum of **6**



1. Described in: Potential Neuroprotective Drugs in Cerebral Ischemia: New Saturated and Polyunsaturated Lipids Coupled to Hydrophilic Moieties: Synthesis and Biological Activity, Biraboneye, Alain Cesar; Madonna, Sebastien; Laras, Younes; Krantic, Slavica; Maher, Pamela; Kraus, Jean-Louis, Journal of Medicinal Chemistry (2009), 52(14), 4358-4369) [↑](#footnote-ref-1)
2. Described in: Potential Neuroprotective Drugs in Cerebral Ischemia: New Saturated and Polyunsaturated Lipids Coupled to Hydrophilic Moieties: Synthesis and Biological Activity, Biraboneye, Alain Cesar; Madonna, Sebastien; Laras, Younes; Krantic, Slavica; Maher, Pamela; Kraus, Jean-Louis, Journal of Medicinal Chemistry (2009), 52(14), 4358-4369). [↑](#footnote-ref-2)