

Supplementary Information

Synthesis of 1-tetrazolylalkan-2-amines and -carbamates

Tom Sundermann, Matthias Lehr*

Institute of Pharmaceutical and Medicinal Chemistry, University of Münster,
Corrensstrasse 48, 48149 Münster, Germany

* Corresponding author. Tel.: +49251 83 33331; fax: +49251 83 32144;

E-mail: lehrm@uni-muenster.de

Supplementary Information content:

1. Synthesis and characterization data of compounds **8a**, **8b**, **9**, **10a**, **10b**, **17b** and **18b**
2. NMR-spectra of new compounds
3. HPLC/UV-traces of the target compounds **18a** and **18b**

1. Synthesis and characterization data of compounds **8a**, **8b**, **9**, **10a**, **10b**, **17b** and **18b**

1-(4-Phenoxyphenoxy)-3-(2H-tetrazol-2-yl)propan-2-ol (8a) and 1-(4-phenoxyphenoxy)-3-(1H-tetrazol-1-yl)propan-2-ol (8b)

[(4-Phenoxyphenoxy)methyl]oxirane^[8] (**7**) (1.00 g, 4.15 mmol) was dissolved in a 0.45 M solution of tetrazole in acetonitrile (10 mL). Then the solvent was evaporated and the residue heated with a heating mantle until a white vapour evolved. After cooling, the mixture was chromatographed on silica gel (1. hexane/ethyl acetate, 7:3 to 5:5; 2. ethyl acetate) to yield **8a** (0.30 g, 23 %) and **8b** (0.54 g, 41 %) as solids.

8a: Mp. 100-101 °C; ¹H NMR (600 MHz, CDCl₃): δ 4.04 – 4.10 (m, 2H), 4.60 (dq, *J* = 7.3 Hz and 4.9 Hz, 1H), 4.92 (dd, *J* = 13.9 Hz and 7.2 Hz, 1H), 4.96 (dd, *J* = 14.0 Hz and 4.4 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.95 (dd, *J* = 8.8 Hz and 1.1 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.06 (tt, *J* = 7.4 Hz and 1.1 Hz, 1H), 7.30 (dd, *J* = 8.7 Hz and 7.4 Hz, 2H), 8.57 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 55.7, 68.7, 69.4, 115.8, 118.0, 120.9, 122.8, 129.8, 151.2, 153.1, 154.3, 158.3. MS (EI, 70 eV) *m/z* (%): 312 (100) M⁺, 127 (98). HRMS (APCI, direct probe) *m/z* [M+H]⁺ calculated: 313.1295, found: 313.1315.

8b: Mp. 118-119 °C; ¹H NMR (600 MHz, CDCl₃): δ 4.00 (dd, *J* = 9.6 Hz and 5.4 Hz, 1H), 4.04 (dd, *J* = 9.6 Hz and 5.2 Hz, 1H), 4.41 – 4.49 (m, 1H), 4.61 (dd, *J* = 14.2 Hz and 7.6 Hz, 1H), 4.80 (dd, *J* = 14.2 Hz and 3.2 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.94 (dd, *J* = 8.8 Hz and 1.1 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.06 (tt, *J* = 7.3 Hz and 1.1 Hz, 1H), 7.30 (dd, *J* = 8.7 Hz and 7.4 Hz, 2H), 8.79 (s, 1H). ¹³C NMR (151 MHz, CDCl₃): δ 51.1, 68.1, 69.3, 115.7, 117.8, 120.7, 122.7, 129.7, 143.8, 151.2, 154.0, 158.1. MS (EI, 70 eV) *m/z* (%): 312 (20) M⁺, 186 (100). HRMS (APCI, direct probe) *m/z* [M+H]⁺ calculated: 313.1295, found: 313.1309.

1-(4-Phenoxyphenoxy)-3-(2H-tetrazol-2-yl)propan-2-ylmethanesulfonate (9)

To a solution of **8a** (250 mg, 0.8 mmol) in dry CH₂Cl₂ (14 mL) was added dropwise in an ice bath a solution of methanesulfonyl chloride (138 mg, 1.2 mmol) in pyridine (4 mL). After extractive work up with dilute HCl and CH₂Cl₂, **9** was afforded as an oil (297 mg, 95 %). ¹H NMR (400 MHz, CDCl₃): δ 2.94 (s, 3H), 4.27 (d, *J* = 4.9 Hz, 2H),

5.11 (dd, $J = 14.5$ Hz and 4.2 Hz, 1H), 5.18 (dd, $J = 14.5$ Hz and 7.1 Hz, 1H), 5.47 (dq, $J = 7.0$ Hz and 4.8 Hz, 1H), 6.91 (d, $J = 9.1$ Hz, 2H), 6.95 (dd, $J = 8.7$ Hz and 1.1 Hz, 2H), 7.00 (d, $J = 9.0$ Hz, 2H), 7.05 – 7.14 (m, 1H), 7.31 (dd, $J = 8.6$ Hz and 7.4 Hz, 2H), 8.60 (s, 1H). ^{13}C NMR (151 MHz, CDCl_3): δ 38.5, 53.3, 67.7, 75.8, 115.9, 118.1, 120.9, 123.0, 129.8, 151.7, 153.5, 153.8, 158.1. MS (EI, 70 eV) m/z (%): 390 (58) M^+ , 77 (100). HRMS (ESI+) m/z [$\text{M}+\text{H}$] $^+$ calculated: 391.1071, found: 391.1067.

(*E*)-2-[3-(4-Phenoxyphenoxy)prop-1-en-1-yl]-2H-tetrazole (10a) and (*Z*)-2-[3-(4-phenoxyphenoxy)prop-1-en-1-yl]-2H-tetrazole (10b)

To a solution of **8a** (250 mg, 0.64 mmol) and 127 μL (0.96 mmol) trimethylsilyl azide in dry THF (16 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (1 mL). The mixture was stirred at room temperature for 24 h. Then the solvent was evaporated and the residue chromatographed on silica gel (hexane/ethyl acetate, 1:1) to yield the *E*-isomer **10a** (0.060 g, 32 %) and the *Z*-isomer **10b** (0.030 g, 16%).

10a: ^1H NMR (600 MHz, CDCl_3): δ 4.78 (dd, $J = 4.7$ Hz and 2.0 Hz, 2H), 6.93 – 6.96 (m, 4H), 6.96 – 7.01 (m, 3H), 7.03 – 7.07 (m, 1H), 7.30 (dd, $J = 8.7$ Hz and 7.4 Hz, 2H), 7.72 (dtd, $J = 14.1$ Hz and 2.0 Hz and 0.6 Hz, 1H), 8.54 (s, 1H). NOE (600 MHz, CDCl_3): δ $^1\text{H}_{\text{irr}}$ / δ $^1\text{H}_{\text{res}}$ 4.78 (OCH₂) / 6.96 – 7.01 (phenoxyprop-1-en-1-yl *ortho*-CH, CH₂CH=CH) and 7.72 (CH₂CH=CH); ^{13}C NMR (101 MHz, CDCl_3): δ 65.4, 116.0, 118.0, 120.9, 121.6, 122.8, 125.4, 129.8, 151.2, 152.9, 154.2, 158.3. HRMS (APCI, direct probe) m/z [$\text{M}+\text{H}$] $^+$ calculated: 295.1190, found: 295.1188.

10b: ^1H NMR (400 MHz, CDCl_3): δ 5.23 (dd, $J = 5.0$ Hz and 2.4 Hz, 2H), 6.08 (dt, $J = 9.9$ Hz and 4.9 Hz, 1H), 6.91 – 7.01 (m, 6H), 7.02 – 7.08 (m, 1H), 7.30 (dd, $J = 8.5$ Hz and 7.5 Hz, 2H), 7.42 (dt, $J = 9.7$ Hz and 2.3 Hz, 1H), 8.61 (s, 1H). NOE (400 MHz, CDCl_3): δ $^1\text{H}_{\text{irr}}$ / δ $^1\text{H}_{\text{res}}$ 5.23 (OCH₂) / 6.08 (CH₂CH=CH) and 6.91 – 7.01 (phenoxyprop-1-en-1-yl *ortho*-CH); ^{13}C NMR (101 MHz, CDCl_3): δ 65.4, 115.9, 117.9, 120.9, 122.2, 122.7, 124.0, 129.8, 151.3, 152.8, 154.3, 158.4; HRMS (APCI, direct probe) m/z [$\text{M}+\text{H}$] $^+$ calculated: 295.1190, found: 295.1183.

1-(4-Phenoxyphenoxy)-3-(1*H*-tetrazol-1-yl)propan-2-amine hydrochloride (17b)

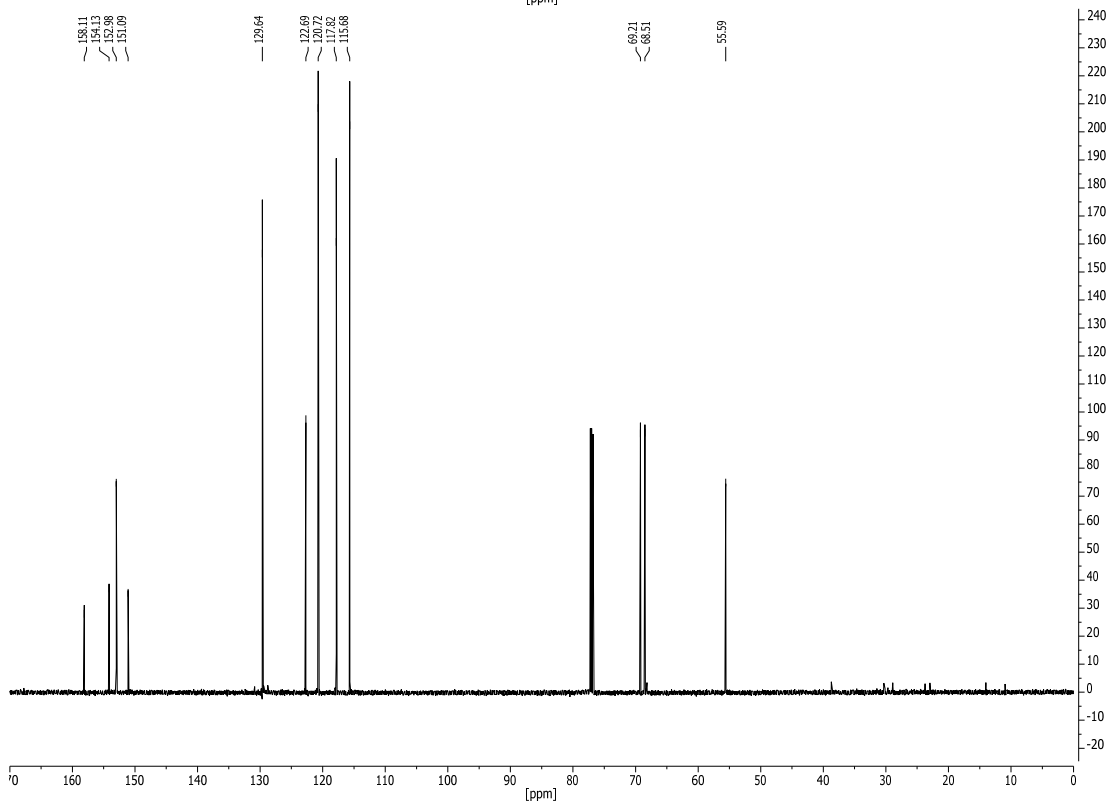
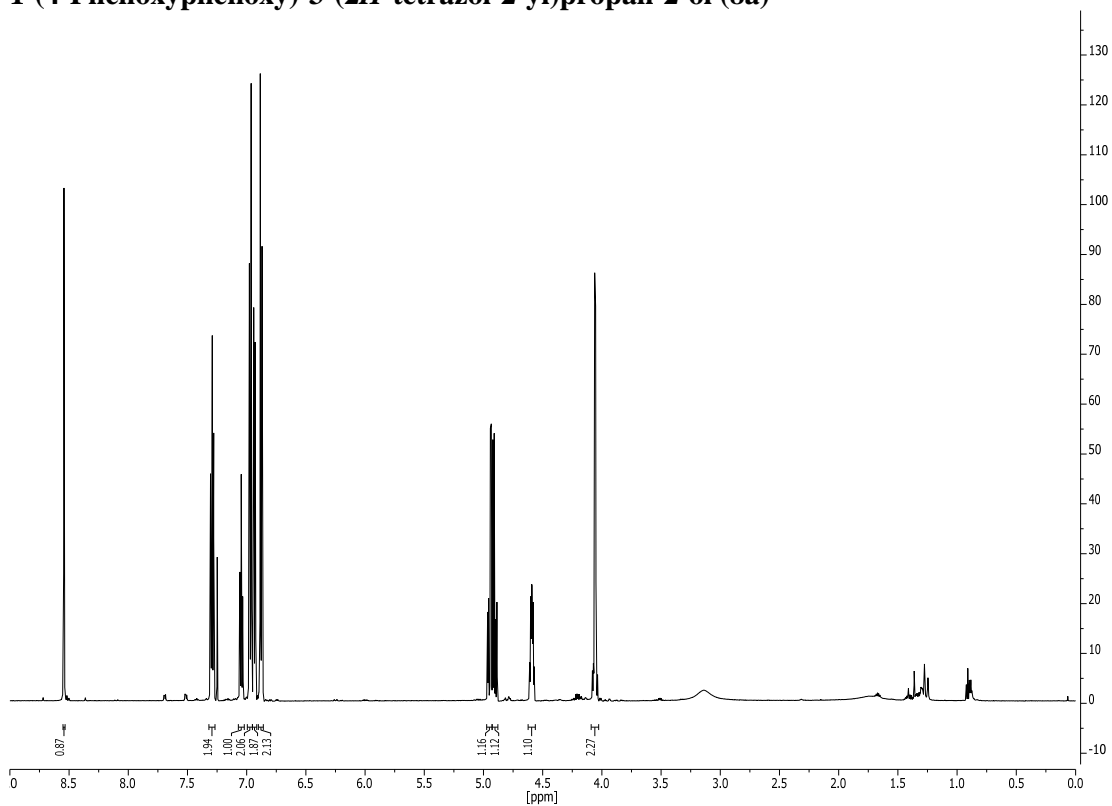
Compound **17b** was synthesized from **16b** (0.200 g, 0.487 mmol) in the same way as **17a**. The product was yielded as a white solid (0.160 g, 95 %). Mp: 122-123 °C; ¹H NMR (600 MHz, DMSO-D₆): δ 4.10 – 4.18 (m, 2H), 4.28 (dd, *J* = 10.1 Hz and 4.0 Hz, 1H), 4.98 (d, *J* = 5.8 Hz, 2H), 6.93 (dd, *J* = 8.7 Hz and 1.0 Hz, 2H), 6.99 – 7.03 (m, 4H), 7.08 (tt, *J* = 7.3 Hz and 1.1 Hz, 1H), 7.35 (dd, *J* = 8.7 Hz and 7.4 Hz, 1H), 8.88 (s broad, 3H), 9.55 (s, 1H). ¹³C NMR (101 MHz, DMSO-D₆): δ 46.9, 49.6, 66.4, 116.6, 117.9, 121.0, 123.2, 130.4, 145.4, 150.7, 154.3, 158.2. HRMS (APCI, direct probe) *m/z* [*M+H*]⁺ calculated: 312.1455, found: 312.1467.

Phenyl *N*-[1-(4-phenoxyphenoxy)-3-(1*H*-tetrazol-1-yl)propan-2-yl]carbamate (18b)

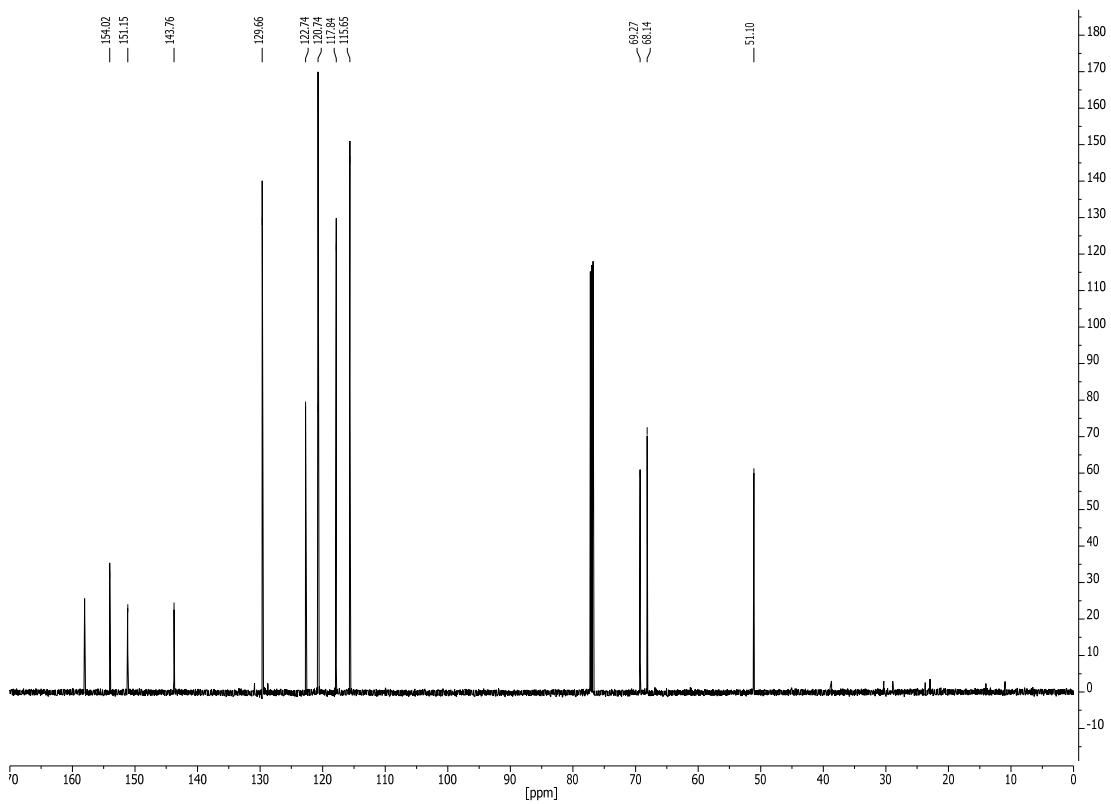
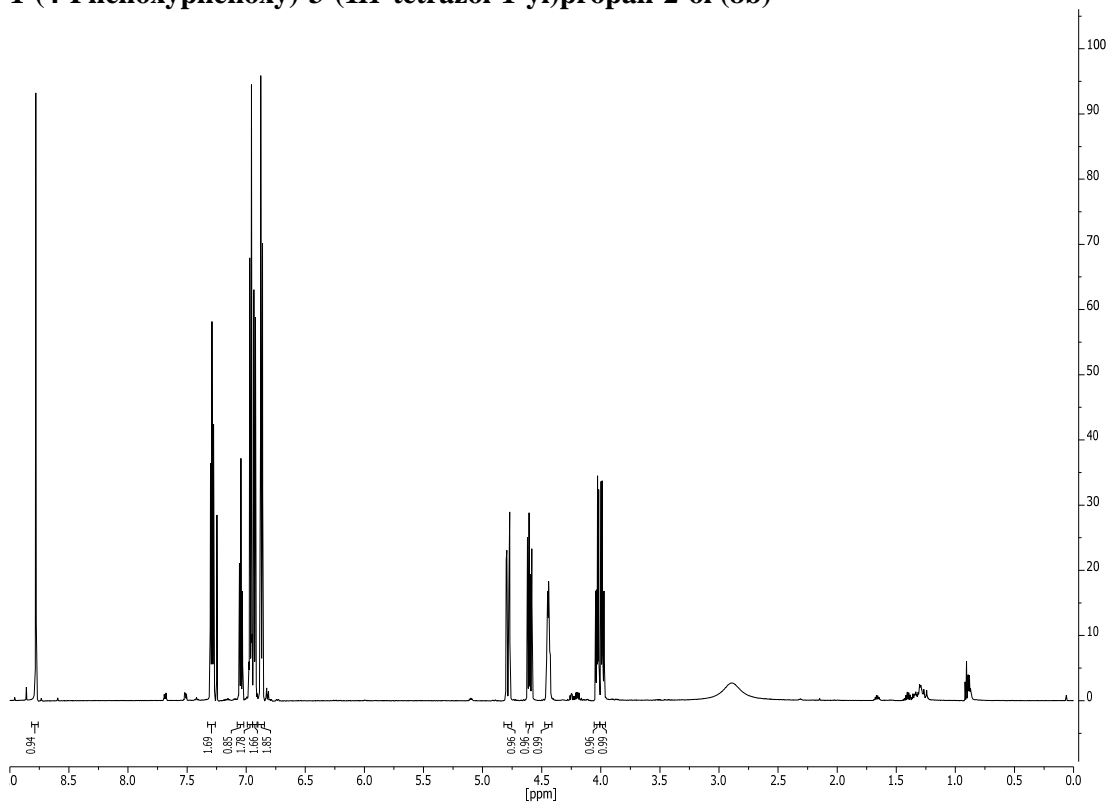
Compound **18b** was synthesized from **17b** (0.090 g, 0.26 mmol) in the same way as **18a**. Yield: 0.108 g, 97 %. ¹H NMR (400 MHz, CDCl₃): δ 4.02 (dd, *J* = 9.8 Hz and 5.3 Hz, 1H), 4.12 (dd, *J* = 9.8 Hz and 3.6 Hz, 1H), 4.47 – 4.59 (m, 1H), 4.80 – 4.92 (m, 2H), 5.81 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.96 (dd, *J* = 8.7 Hz and 1.1 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 7.04 – 7.12 (m, 3H), 7.17 – 7.24 (m, 1H), 7.32 (dd, *J* = 8.6 Hz and 7.4 Hz, 2H), 7.36 (dd, *J* = 8.4 Hz and 7.3 Hz, 2H), 8.70 (s, 1H). ¹³C NMR (101 MHz, CDCl₃): δ 48.3, 50.4, 66.7, 115.6, 118.0, 120.8, 121.4, 122.9, 125.9, 129.5, 129.7, 143.5, 150.5, 151.5, 153.5, 154.3, 157.9. HRMS (ESI+) *m/z* [*M+H*]⁺ calculated: 432.1666, found: 432.1671.

2. NMR-Spectra of the new compounds

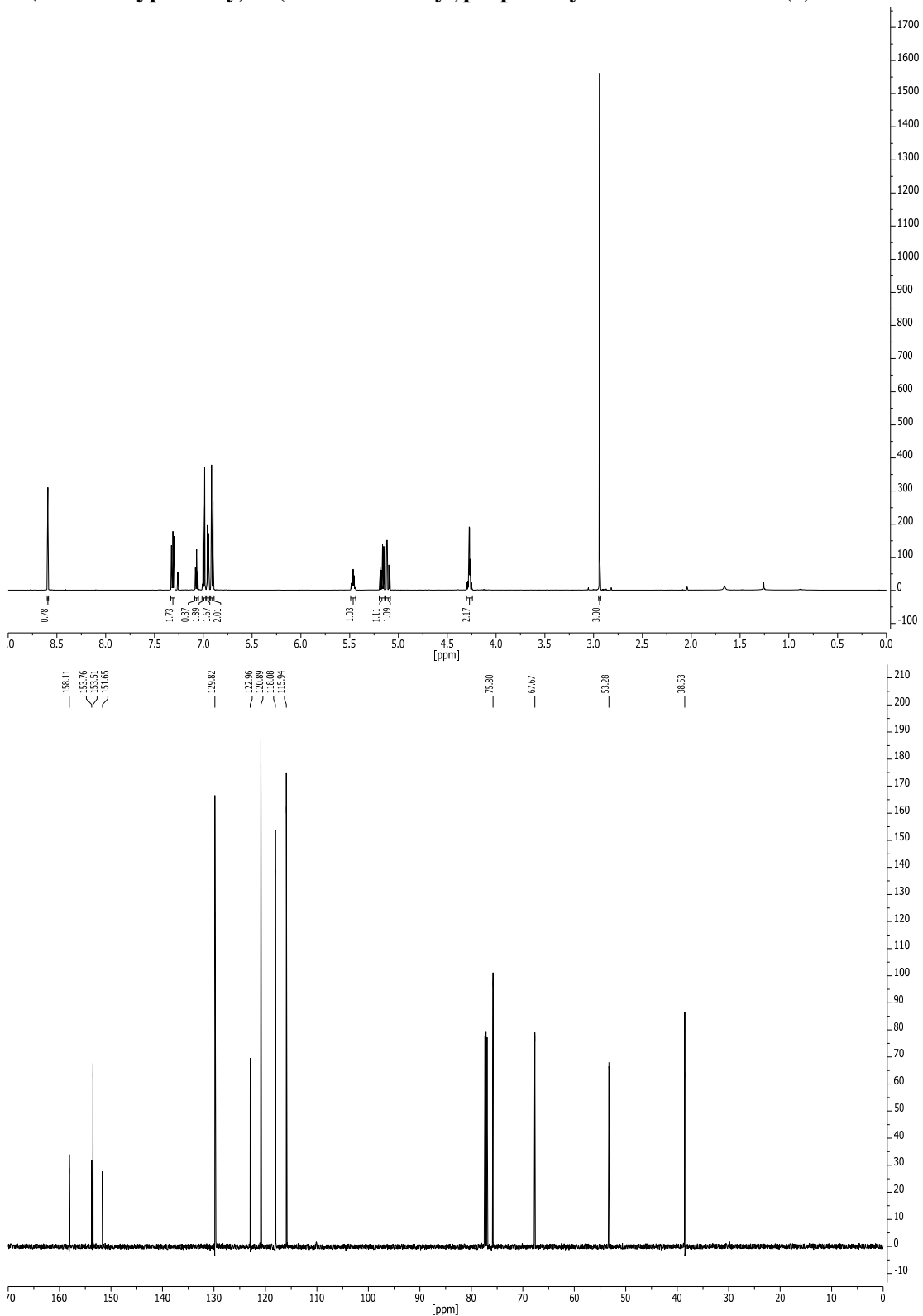
1-(4-Phenoxyphenoxy)-3-(2H-tetrazol-2-yl)propan-2-ol (8a)



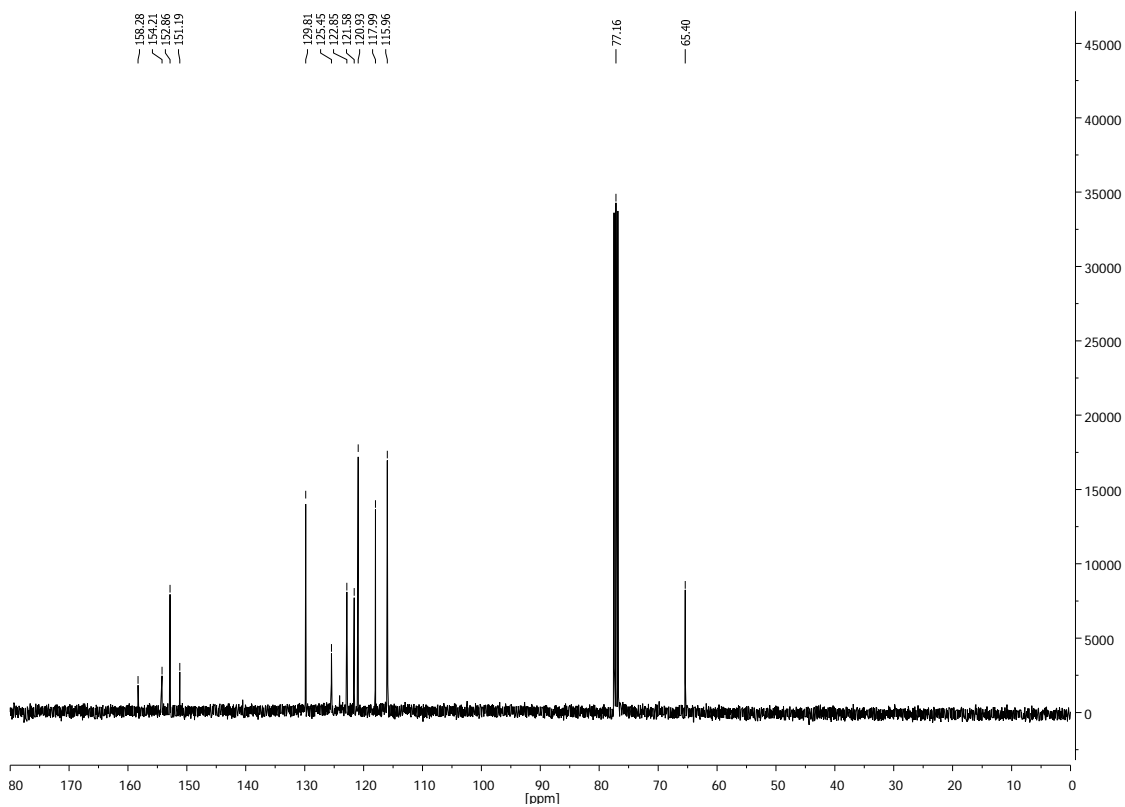
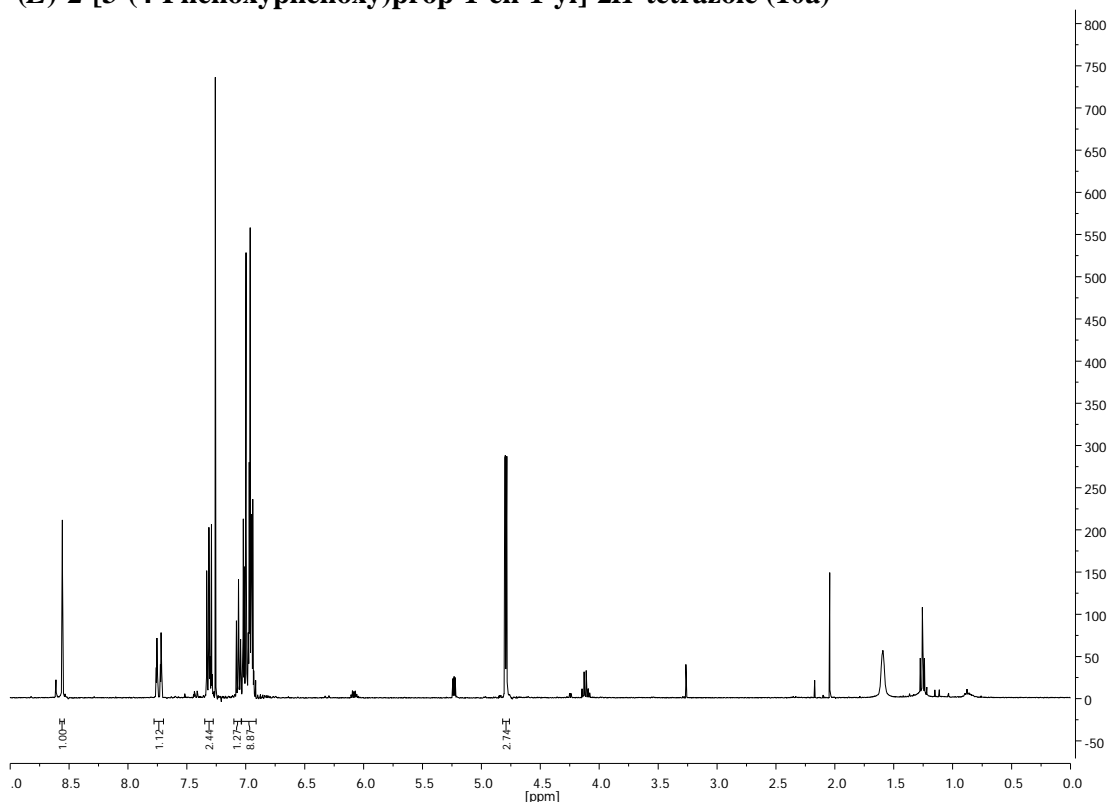
1-(4-Phenoxyphenoxy)-3-(1H-tetrazol-1-yl)propan-2-ol (8b)



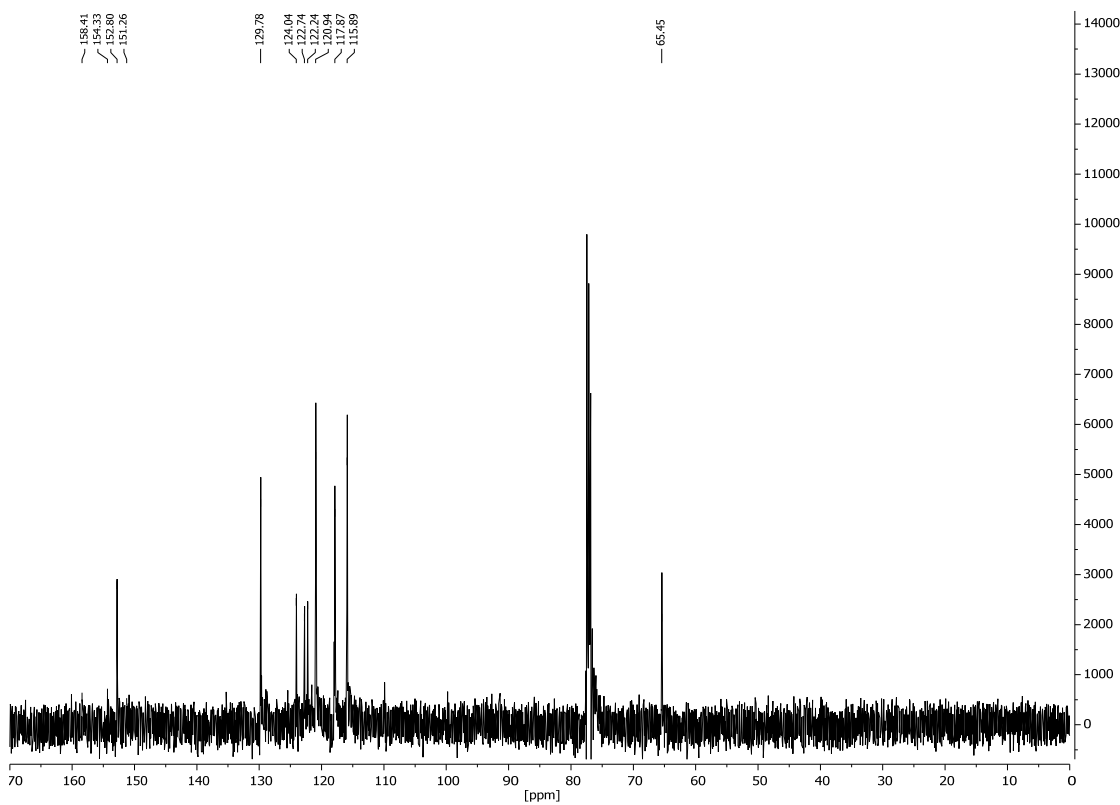
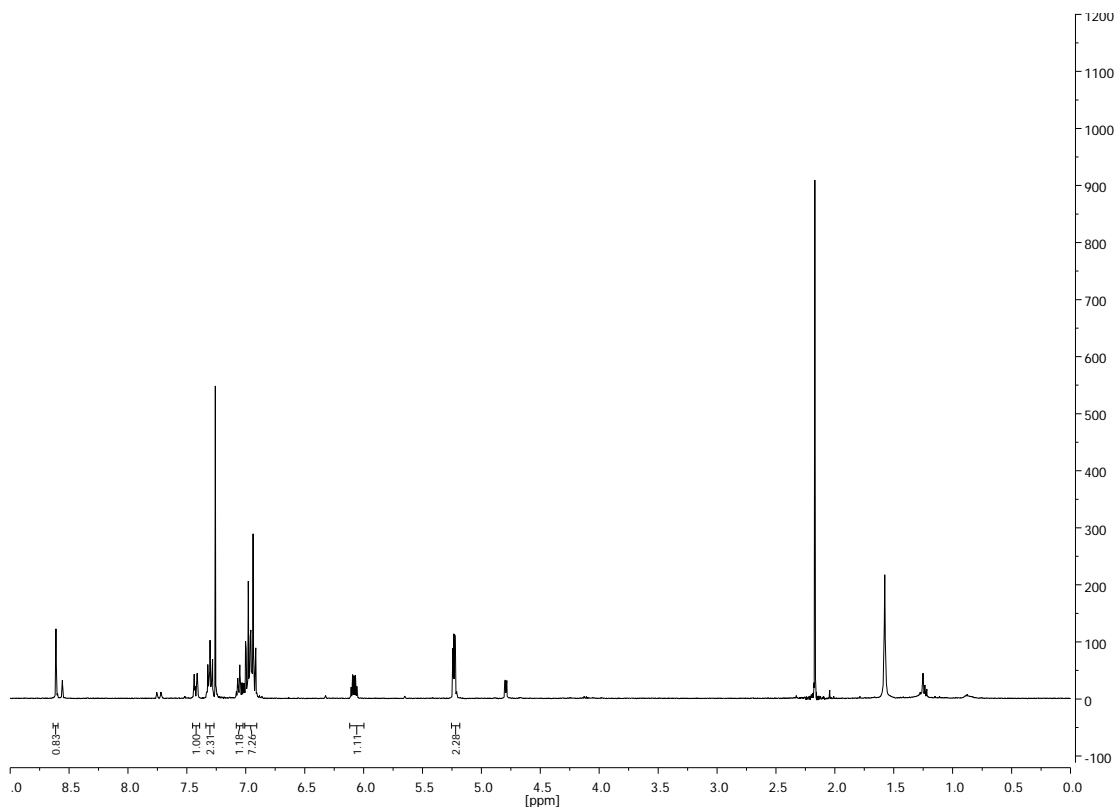
1-(4-Phenoxyphenoxy)-3-(2H-tetrazol-2-yl)propan-2-ylmethanesulfonate (9)



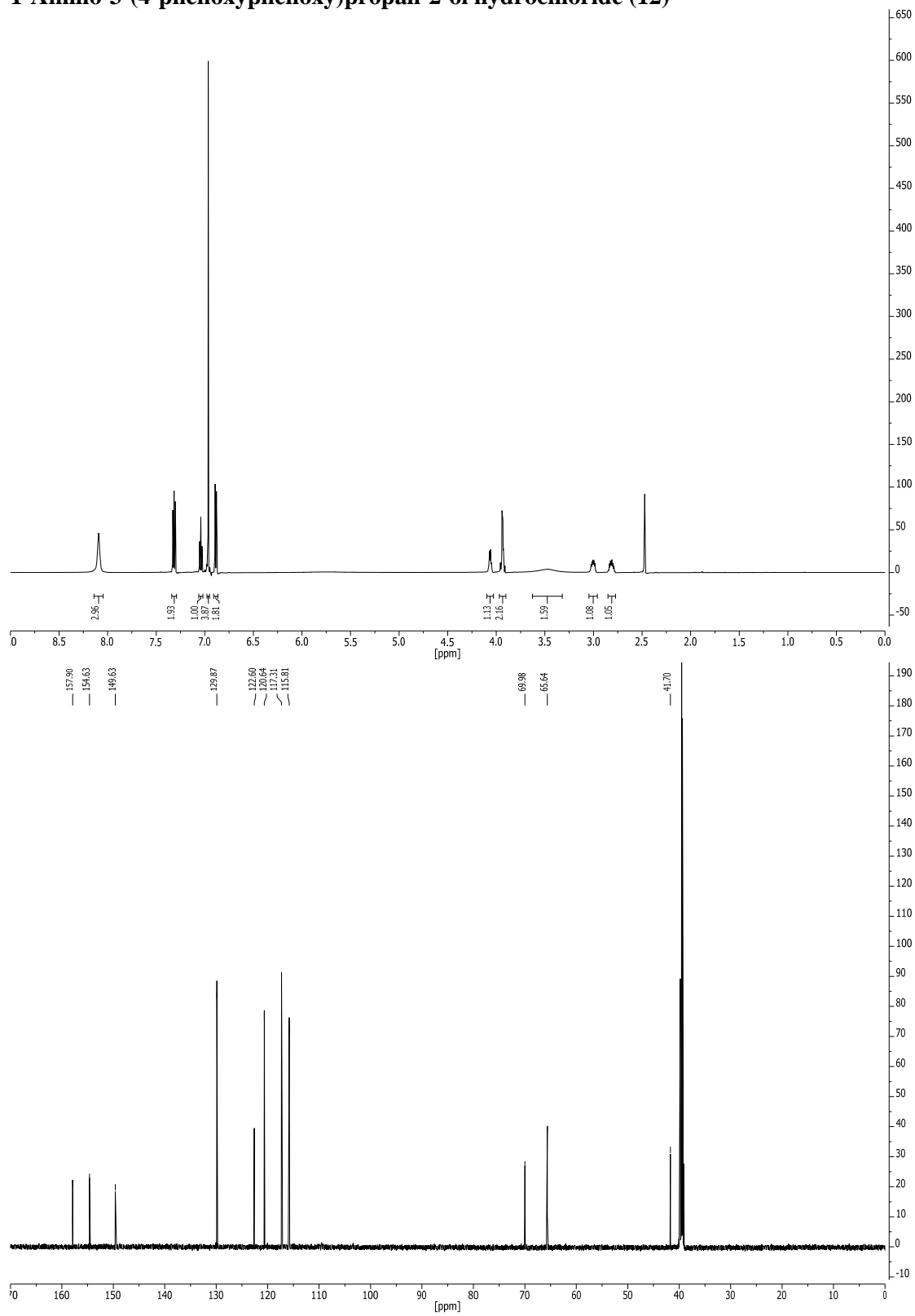
(E)-2-[3-(4-Phenoxyphenoxy)prop-1-en-1-yl]-2H-tetrazole (10a)



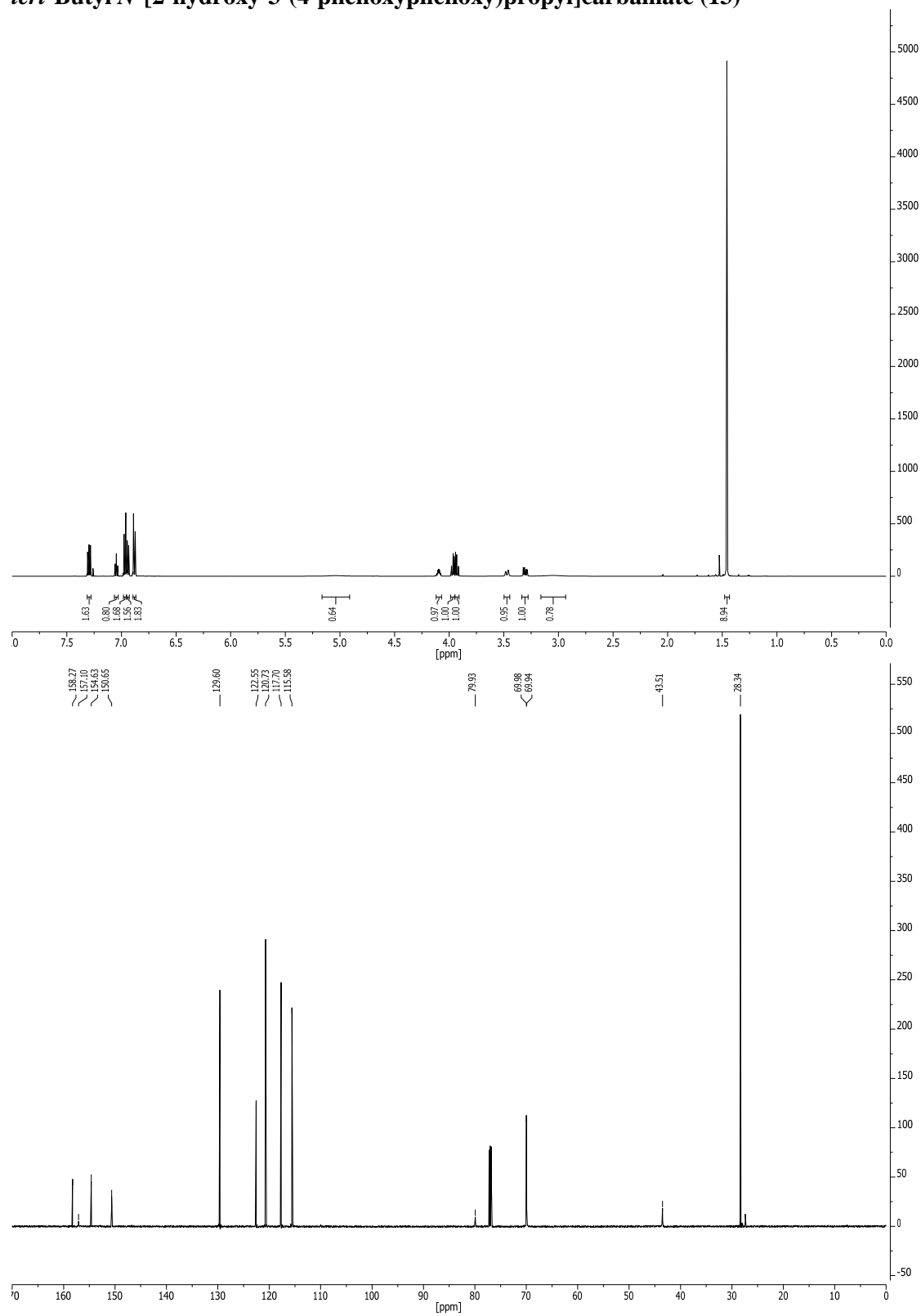
(Z)-2-[3-(4-Phenoxyphenoxy)prop-1-en-1-yl]-2H-tetrazole (10b)



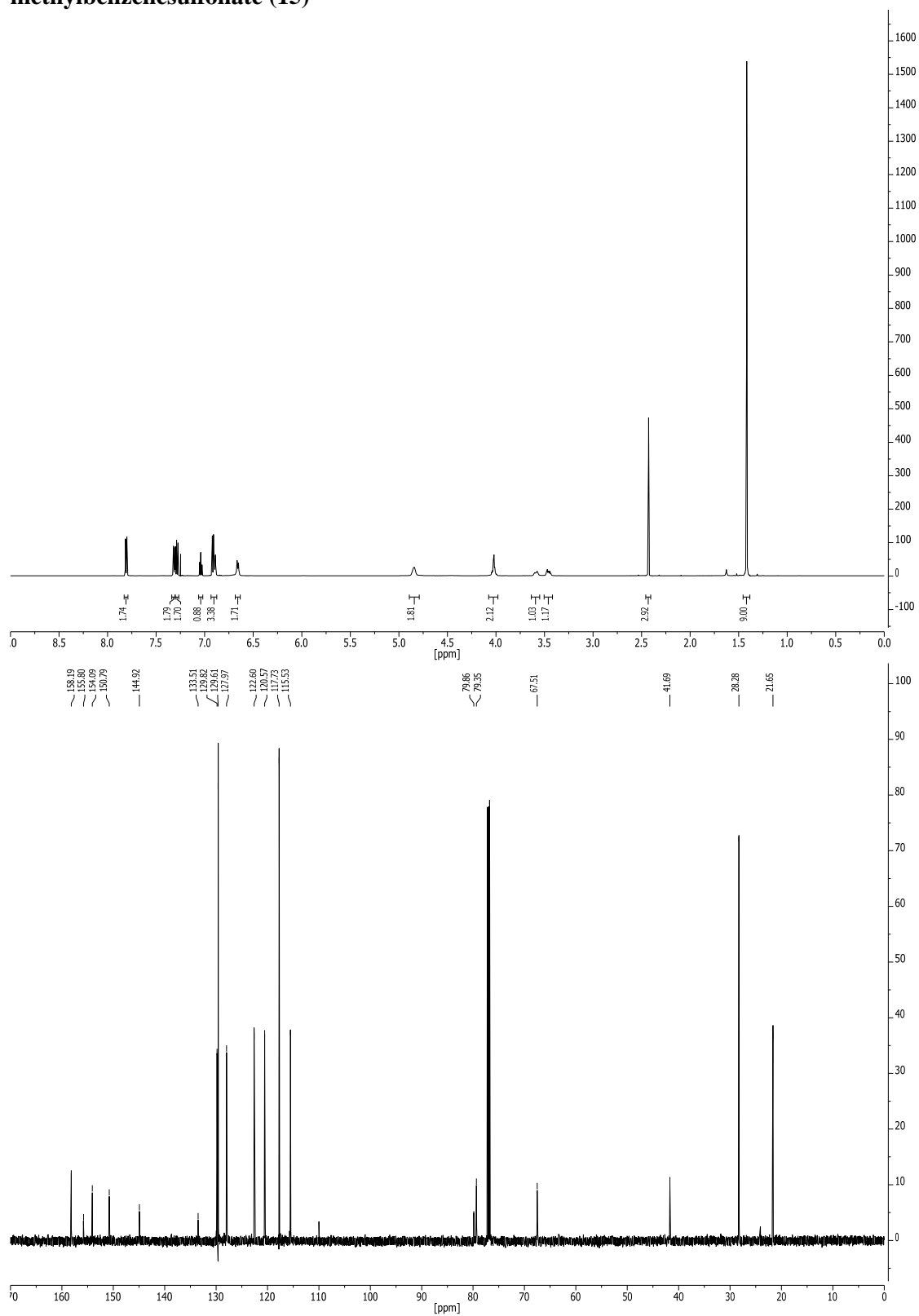
1-Amino-3-(4-phenoxyphenoxy)propan-2-ol hydrochloride (12)



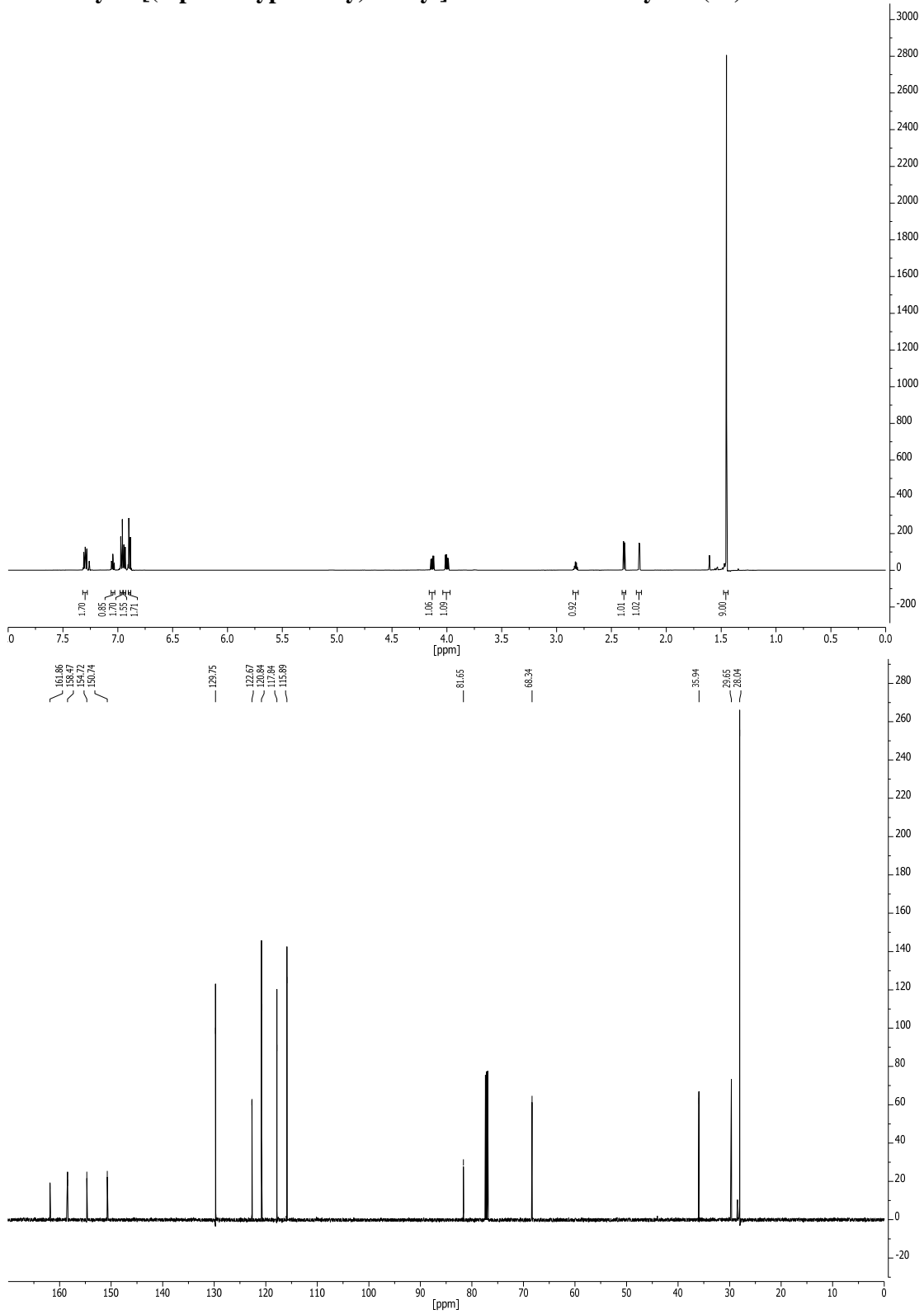
***tert*-Butyl *N*-[2-hydroxy-3-(4-phenoxyphenoxy)propyl]carbamate (13)**



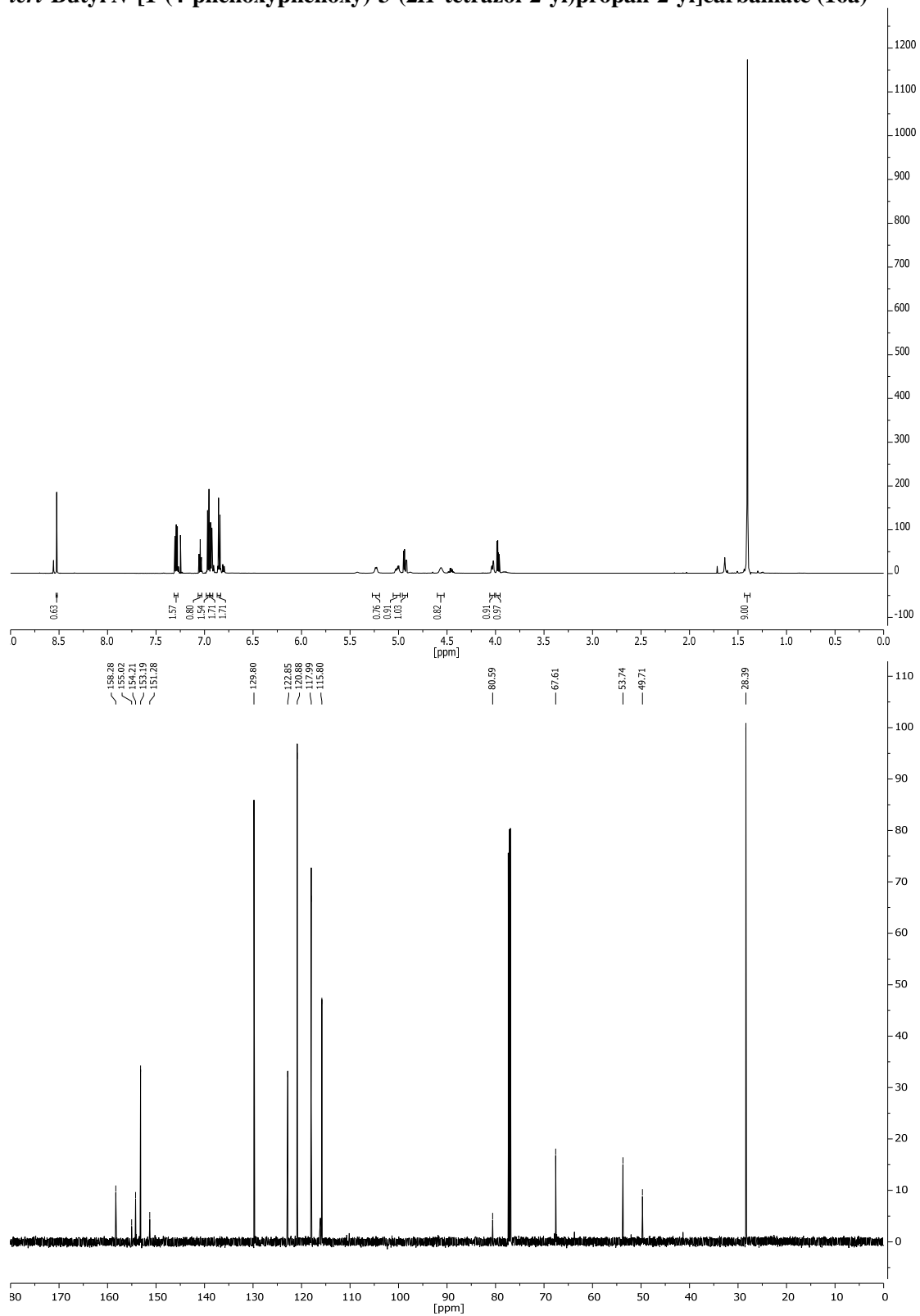
1-[(*tert*-Butoxycarbonyl)amino]-3-(4-phenoxyphenoxy)propan-2-yl 4-methylbenzenesulfonate (15)



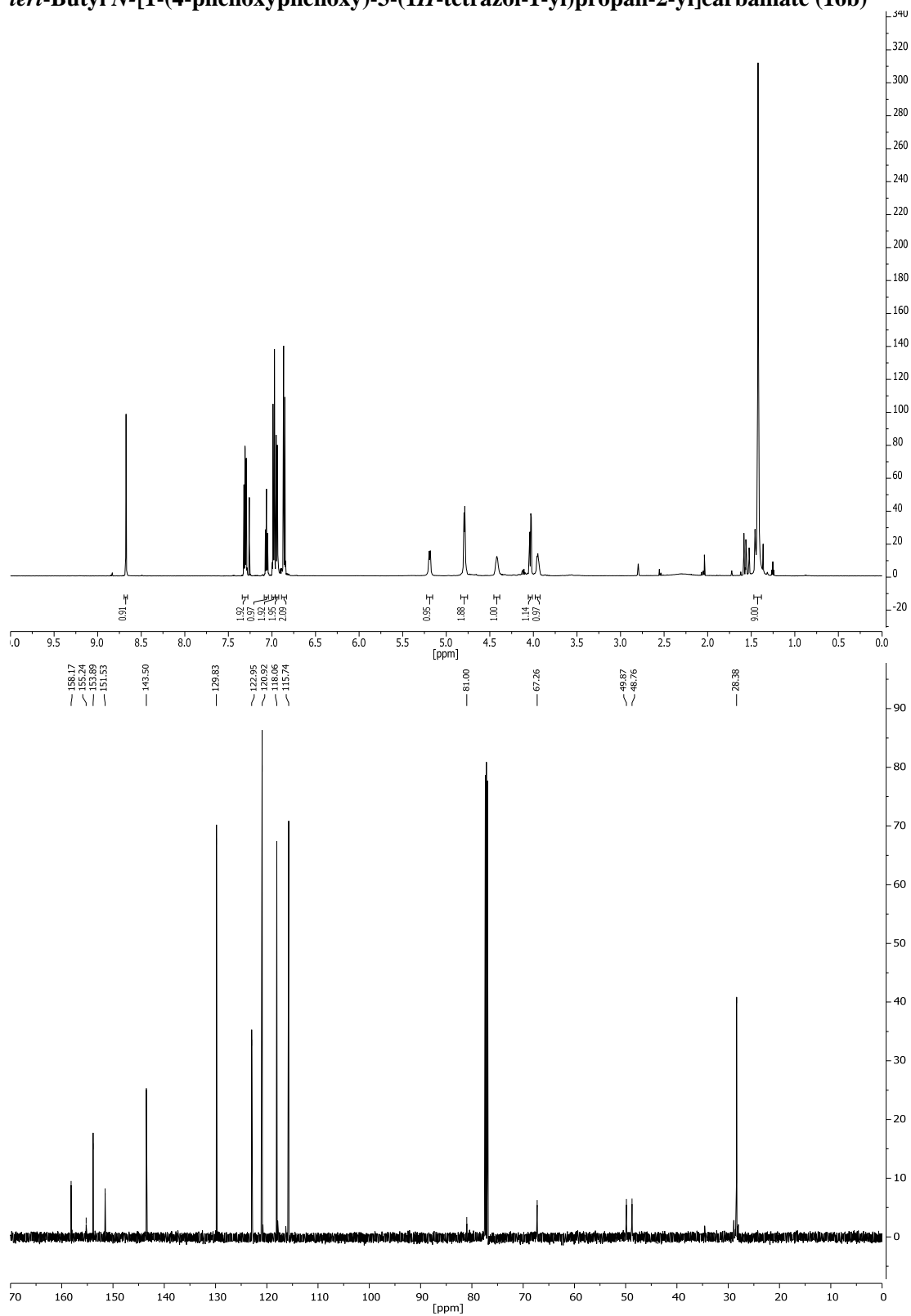
***tert*-Butyl 2-[(4-phenoxyphenoxy)methyl]aziridine-1-carboxylate (15)**



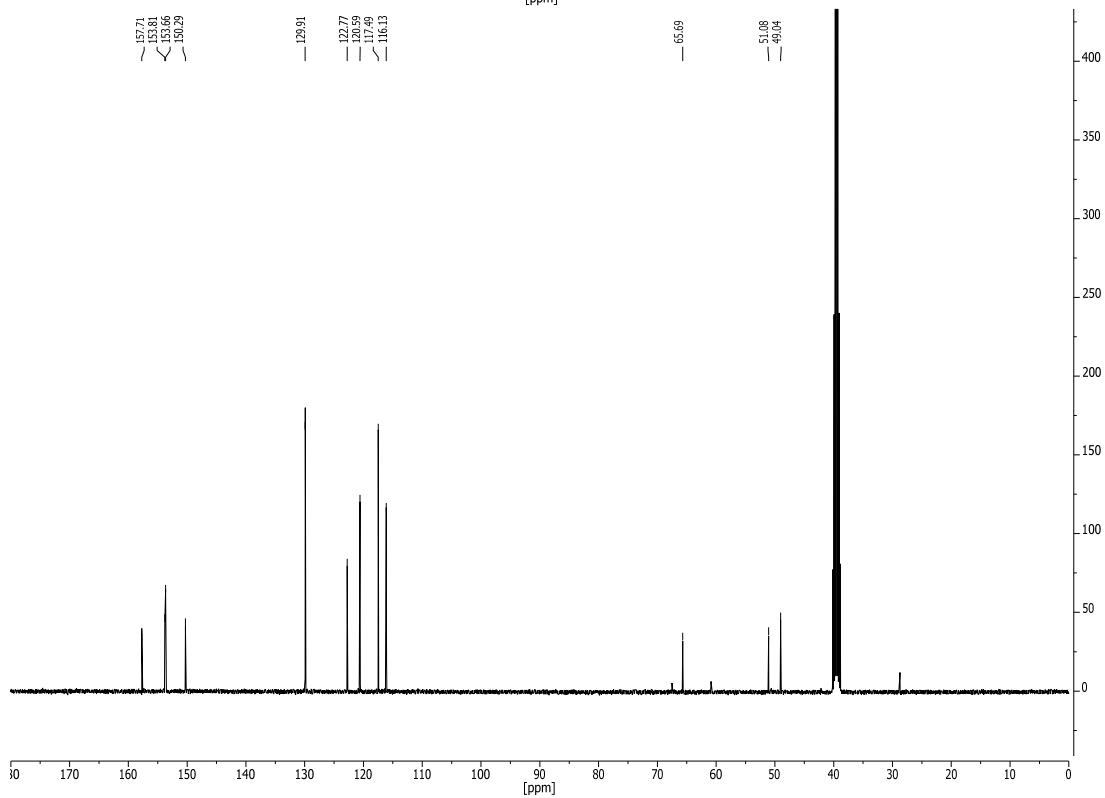
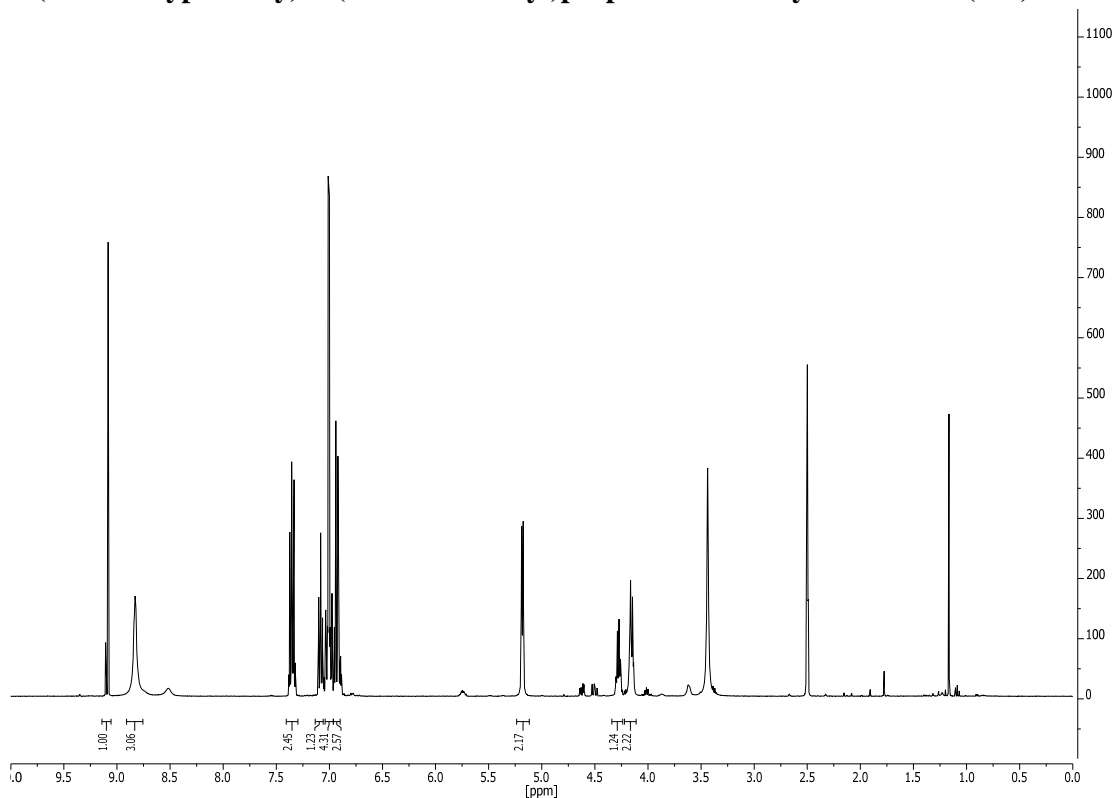
***tert*-Butyl *N*-[1-(4-phenoxyphenoxy)-3-(2*H*-tetrazol-2-yl)propan-2-yl]carbamate (16a)**



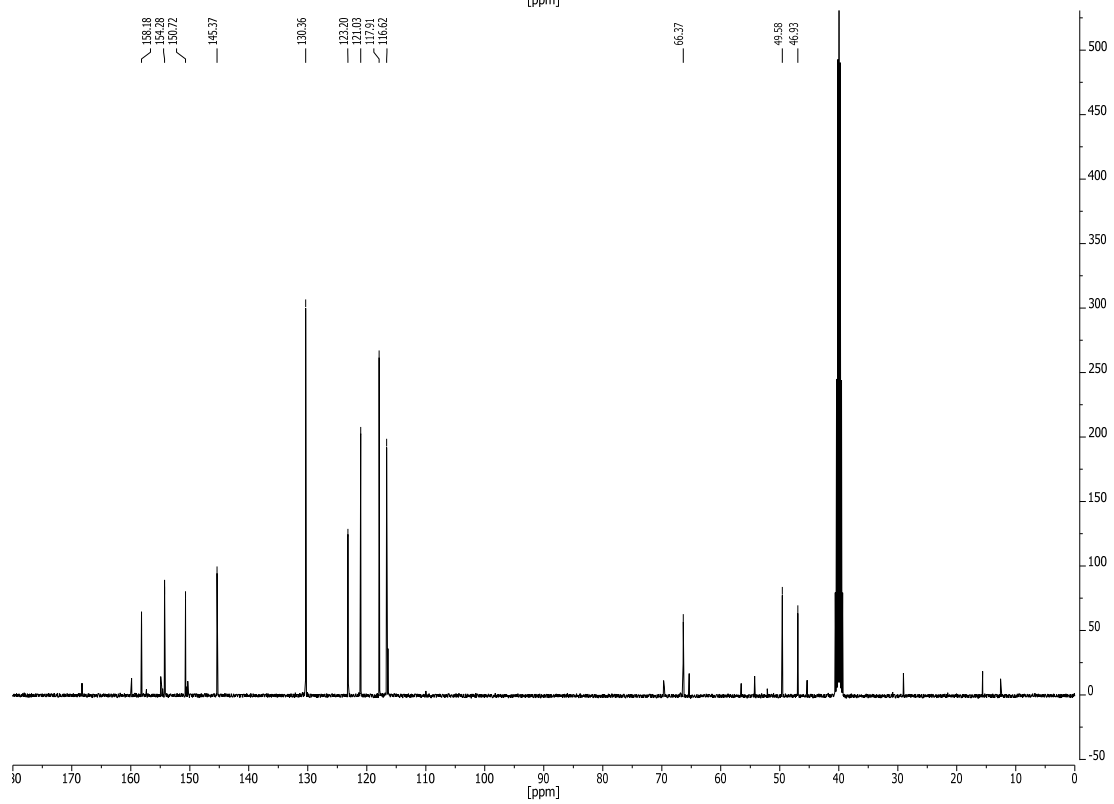
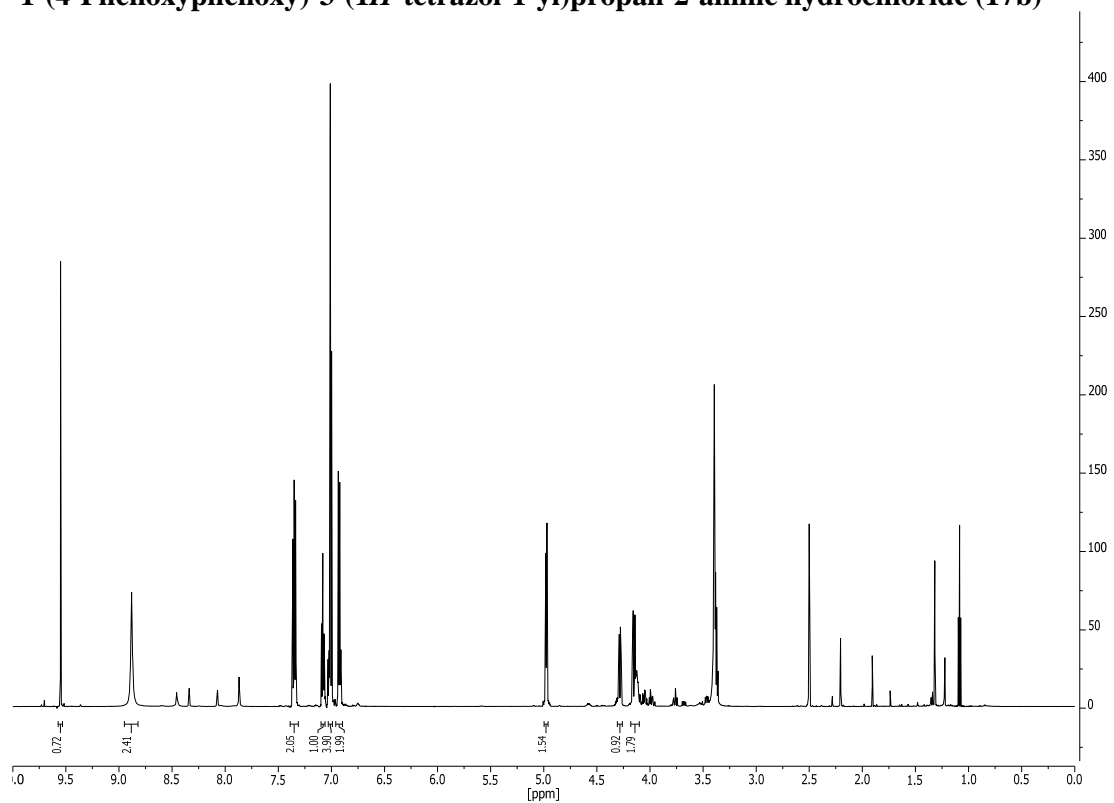
***tert*-Butyl *N*-[1-(4-phenoxyphenoxy)-3-(1*H*-tetrazol-1-yl)propan-2-yl]carbamate (16b)**



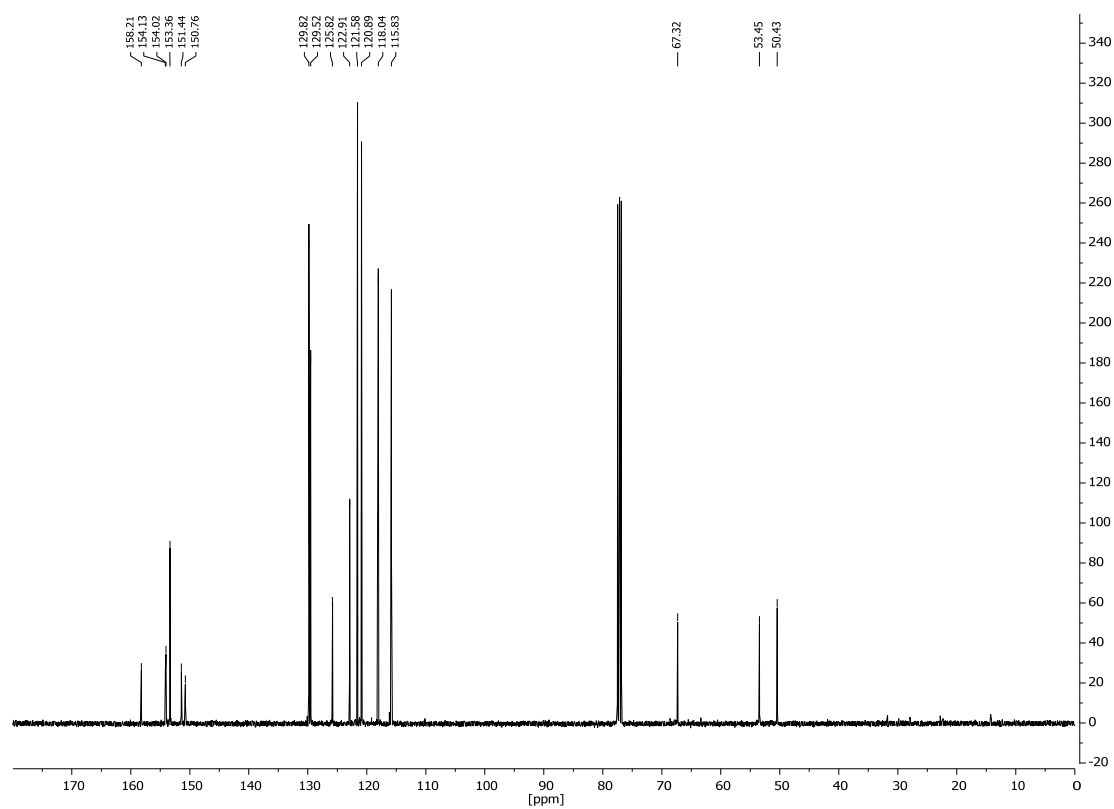
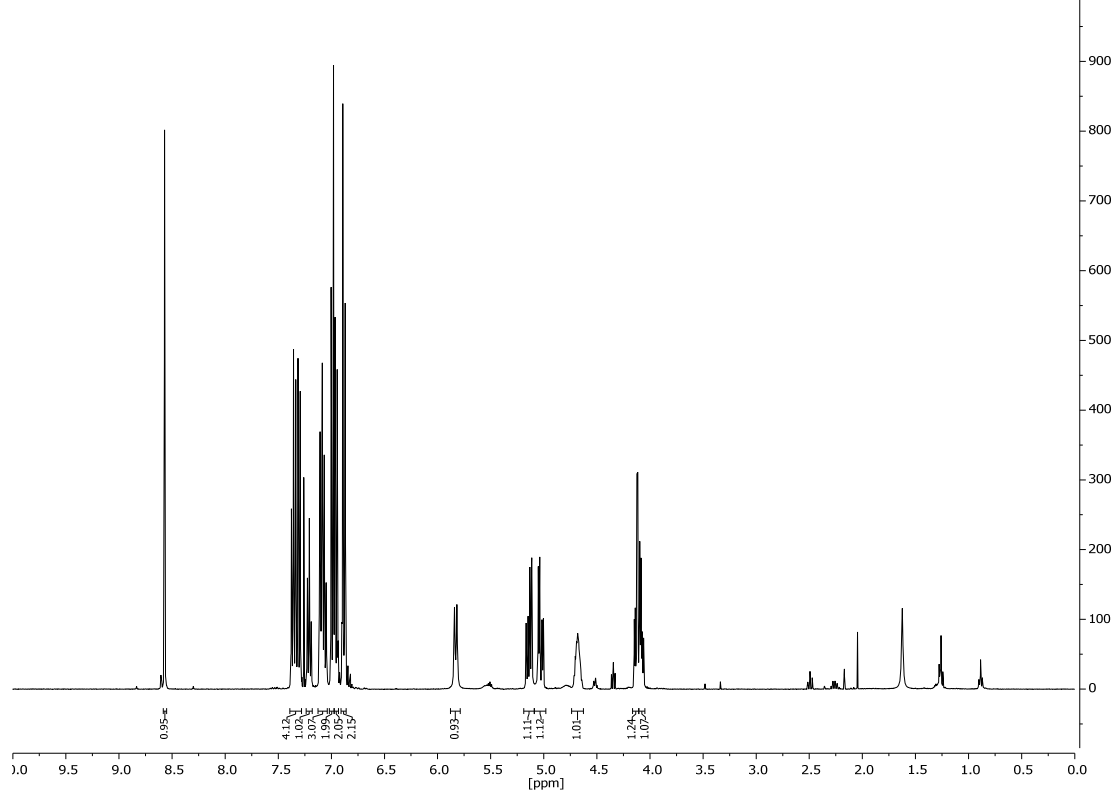
1-(4-Phenoxyphenoxy)-3-(2H-tetrazol-2-yl)propan-2-amine hydrochloride (17a)



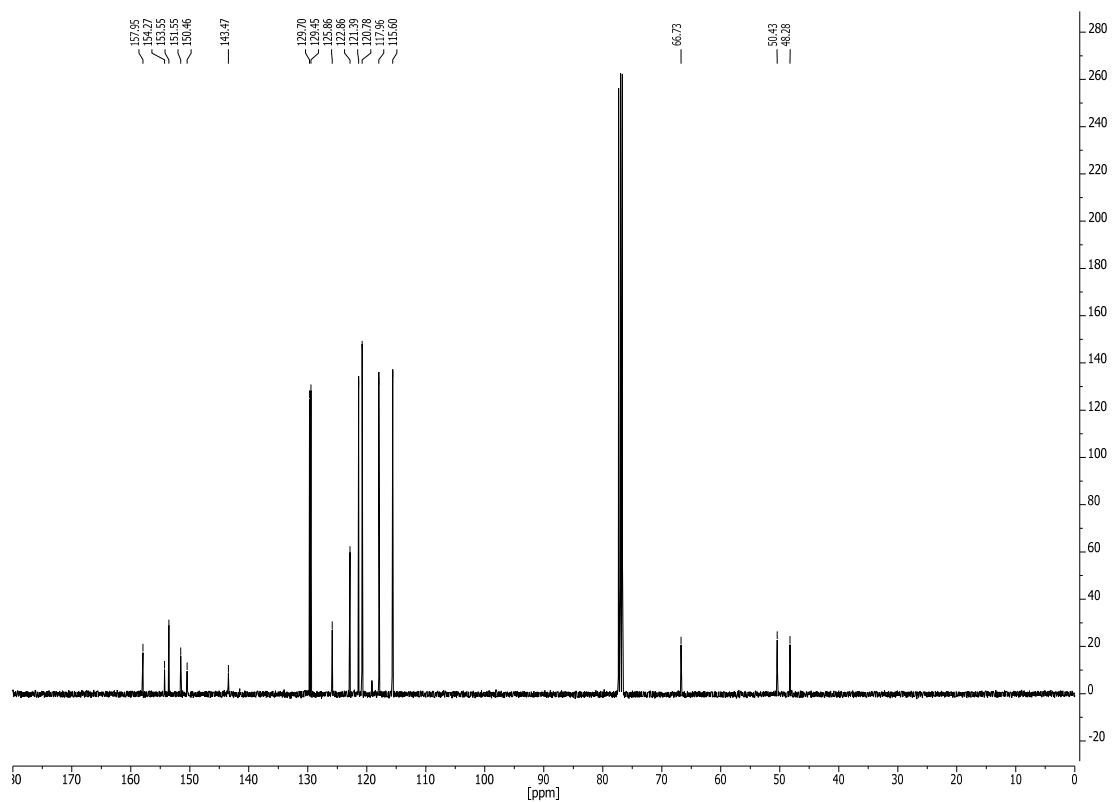
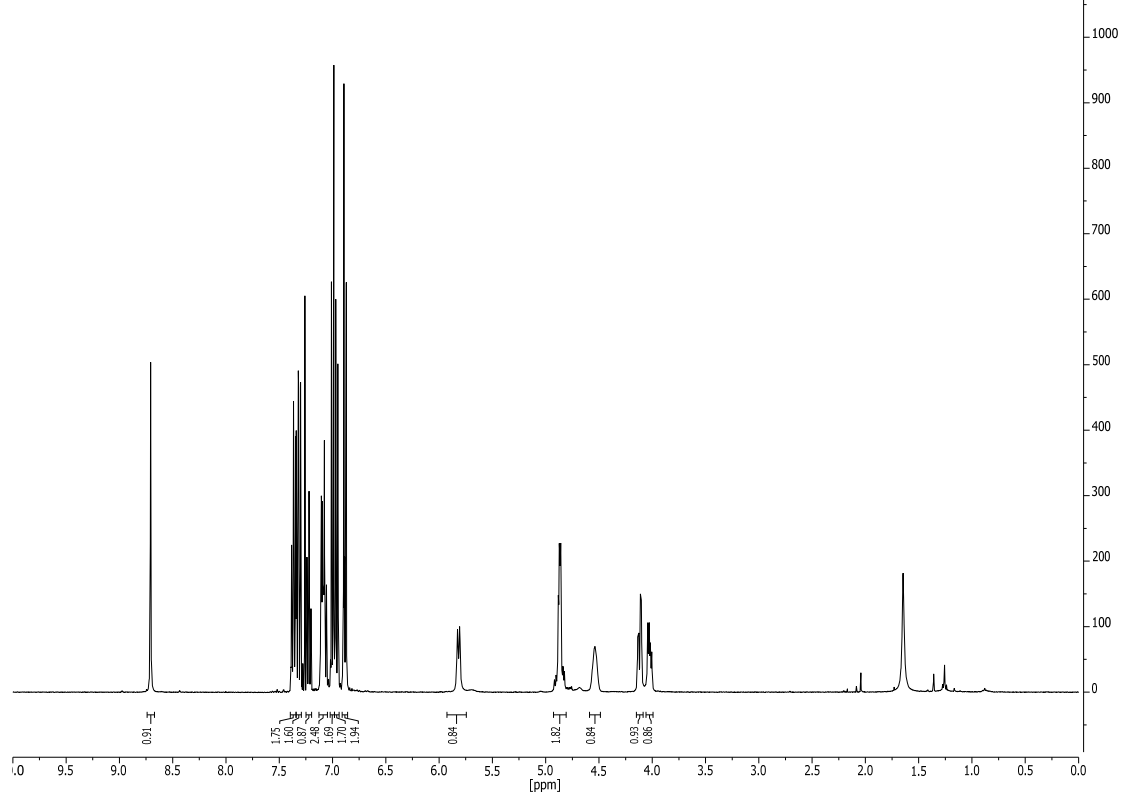
1-(4-Phenoxyphenoxy)-3-(1*H*-tetrazol-1-yl)propan-2-amine hydrochloride (17b)



Phenyl *N*-[1-(4-phenoxyphenoxy)-3-(2*H*-tetrazol-2-yl)propan-2-yl]carbamate (18a)



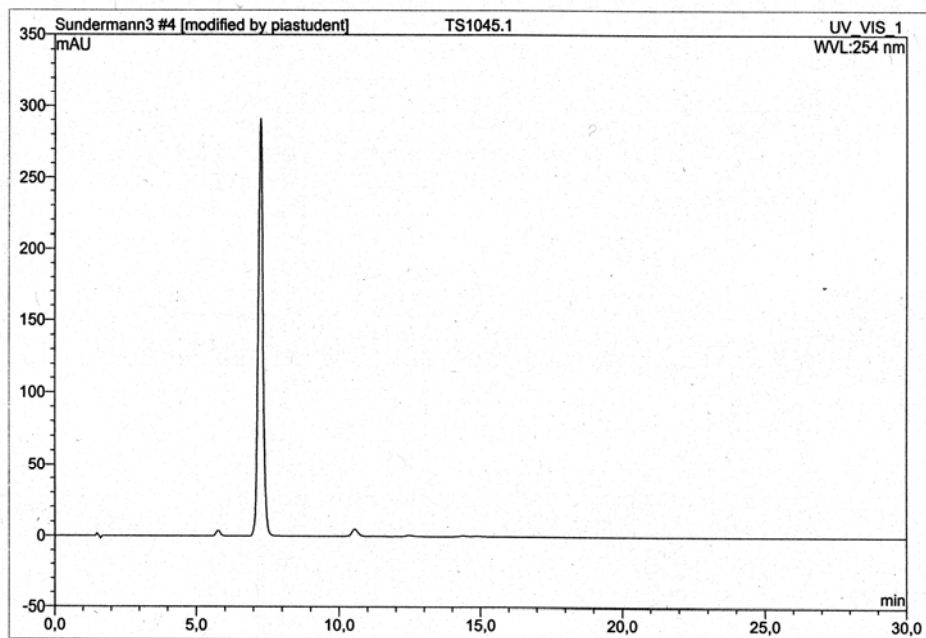
Phenyl N-[1-(4-phenoxyphenoxy)-3-(1*H*-tetrazol-1-yl)propan-2-yl]carbamate (18b)



3. HPLC/UV-traces of the target compounds 18a and 18b

HPLC/UV spectra were recorded on a Dionex Ultimate 3000 apparatus. 20 μ L of the samples dissolved in acetonitrile were injected into the HPLC system. Separation was performed on an Eurospher II 100-5 C18 column (250 x 4.6 mm) from Knauer (Berlin, Germany) protected with a Phenomenex C18 guard column (3 mm inside diameter x 4 mm). The mobile phase consisted of acetonitrile/water/trifluoroacetic acid (70:30:0.1, v/v/v). The flow rate was 1.3 mL/min. The effluents were monitored at 254 nm.

Chromatogram of **18a**:



Chromatogram of **18b**:

