Supporting Information

Positional Isomers of Biphenyl Antimicrobial Peptidomimetic Amphiphiles

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General information

Synthesis

Unless stated otherwise, all solvents and chemicals were laboratory or reagent grade and were purchased from commercial sources. Acetonitrile was dried over 3Å molecular sieves. All solvents used in the Suzuki coupling (**General Procedure B**) were degassed by sparging with N_2 gas and simultaneous ultrasonication for >30 min. All other chemicals were used as received. Water was purified *via* Millipore filtration prior to use. Propargyl bromide and HOBt were purchased with added stabilizers (20% w/w toluene and 10% w/w H_2O, respectively); therefore, the quantities required for reactions were adjusted accordingly and are reflected in the reagent masses reported in the experimental (whereas the reported mmol quantities reflect the true quantity of chemical). All reactions were conducted under normal atmosphere unless noted otherwise. Cold reaction temperatures were obtained by an ice bath (0 ºC) or ice/salt bath (–10 ºC). Heating of reactions was performed with a paraffin oil bath. Small quantities of liquid reagents were measured and added to reactions *via* syringe or autopipette. Unless otherwise noted, all filtrations were conducted as vacuum filtration through a sintered glass funnel (medium porosity). Vacuum filtration was achieved with the aid of a water aspirator. Solvent removal *via* concentration was performed on a rotary evaporator under reduced pressure. All solvent mixtures are expressed in terms of volume ratio (i.e. v/v). Thin layer chromatography (TLC) was performed on aluminium-backed SiO_2 gel plates (F_{254} indicator grade - 0.20 mm thickness). Visualization was achieved with UV light, ninhydrin stain or cerium ammonium molybdate stain. Flash chromatography was performed on SiO_2 gel 60 with positive air pressure. All synthesized compounds were dried under high vacuum (<1 mbar) before determination of chemical yields and spectroscopic characterization.

Characterization and analysis

All final derivatives were subjected to full spectroscopic characterization. ^{1}H NMR spectra were recorded on a Bruker Ascend 400 (400 MHz) or a Bruker Avance Neo 500 (500 MHz) NMR spectrometer. Chemical shifts are reported in ppm and were measured relative to the internal standard. Samples were dissolved in $CDCl_3$ (with TMS as the internal standard – 0.00 ppm), CD_3OD (solvent resonance as internal standard – 3.31 ppm) or DMSO-d_6 (solvent resonance as internal standard – 2.50 ppm). The ^{1}H NMR data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd= doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on a Bruker Avance 400 (101 MHz) or a Bruker Avance Neo 500 (125 MHz) NMR spectrometer with complete ^{1}H decoupling. Chemical shifts are reported in ppm and were measured relative to the internal standard. Samples were dissolved in $CDCl_3$ (solvent resonance as the internal standard – 77.16 ppm), CD_3OD (solvent resonance as the internal standard – 49.20 ppm) or DMSO-d_6 (solvent resonance as internal standard – 39.50 ppm). ^{1}H and ^{13}C NMR assignments were confirmed by analysis of NMR DEPT Q, gCOSY, gHSQC, gHMBC and/or zTOCSY experiments. Carbon resonances that required 2-D NMR analysis for determination (i.e. not observed in 1-D ^{13}C NMR analysis) are marked with the label "*observed by gHMBC*" or "*observed by gHSQC*". Unassigned aromatic hydrogens are

labelled as "ArH", whereas specific/assigned aromatic hydrogens are labelled with the normal nomenclature (i.e. HAr3 = hydrogen atom attached to $C_{Ar}3$). NMR spectra were processed, analysed and prepared with MestReNova (version 9.0) NMR software. Low resolution mass spectra (LRMS) were obtained *via* electrospray ionization (ESI) on a Shimadzu LCMS-2020 mass spectrometer. LRMS data was recorded as the ion mass/charge ratio (*m*/*z*) with the corresponding relative abundance as a percentage. High resolution mass spectrometry (HRMS) was performed on a Waters Quadrupole-Time of Flight (QTOF) Xevo spectrometer *via* ESI and with Leucine-Enkephalin as an internal standard. All mass spectrometry samples were dissolved in high performance liquid chromatography (HPLC) grade MeOH (containing <1% formic acid for ionization). Optical rotations were measured on a Jasco P-2000 polarimeter with a 10 cm path length; rotation values (α) are expressed in units of "deg cm^3 g^{-1} dm^{-1}" with concentration (*c*) expressed in units of "g/100 mL". Solid-state infrared spectroscopy was performed on a Bruker Vertex 70 FTIR Spectrometer. IR peaks are reported as the wavenumber (ν_{max} in cm^{-1}) of the maximum absorption. Analytical HPLC was performed on a Phenomenex Synergi 4u Fusion-Reverse Phase 80Å column (ϕ = 4.6 × 150 mm) with detection at λ = 290 nm and H_2O/CH_3CN (both containing 0.1% TFA) as the mobile phase.

General synthetic procedures (A–E)

General Procedure A: *O*-Alkylation of phenol boronic esters

A reaction vessel was charged with the phenol boronic ester (1.0 eq), K_2CO_3 (2.0 eq), tetrabutylammonium iodide (TBAI – 0.15 eq) and a stir bar. The vessel was purged with N_2 gas to exclude moisture, anhydrous CH_3CN (2.5 mL/mmol) was added and stirring was commenced at rt. Once the boronic ester was fully dissolved, 1-bromo-3-methylbutane (1.5 eq) was added with continued stirring. The reaction mixture was then heated at reflux overnight (18 h) with vigorous magnetic stirring under an N_2 atmosphere. The reaction mixture was then cooled to room temp, diluted with dry CH_3CN (~5 mL/mmol) and the solids were removed by filtration over a pad of Celite. The solids were rinsed with CH_3CN (3 × 25 mL), the filtrate was concentrated and the obtained residue was eluted through a plug of SiO_2 gel with CH_2Cl_2 to afford the desired *O*-alkylated boronic ester product.

General Procedure B: Mono-alkylated biphenol synthesis *via* Suzuki Coupling

A reaction vessel was charged with the aryl iodide (1.0 eq), boronic ester (1.3 eq) and a stir bar. Degassed ethanol (5 mL/mmol aryl iodide) was added and stirring commenced to dissolve the starting materials. Degassed H_2O (5 mL/mmol aryl iodide) was then added, followed by Pd/C (10% w/w – 2.0 mol %) and K_2CO_3 (4.0 eq). The reaction vessel was purged with N_2 gas and the reaction mixture was then heated at 80 °C (oil bath) for 18 h under an atmosphere of N_2 gas. The reaction mixture was cooled to room temp and carefully treated with 1.0 M HCl (10 mL). The aqueous reaction mixture was then extracted with Et_2O (3 × 25 mL) and the combined ethereal extracts were washed with brine (1 × 50 mL), dried

($MgSO_4$), filtered and concentrated. The obtained residue was purified by flash chromatography over SiO_2 gel to furnish the desired mono-alkylated biphenol product.

General Procedure C: *O*-Propargylation of mono-alkylated biphenols

A reaction vessel was charged with the mono-alkylated biphenol (1.0 eq), K_2CO_3 (2.0 eq), tetrabutylammonium iodide (TBAI – 0.15 eq) and a stir bar. Anhydrous CH_3CN (5.0 – 7.0 mL/mmol) was added and stirring was commenced at rt. Once the mono-alkylated biphenol was fully dissolved, propargyl bromide solution (1.5 eq) was added and the reaction mixture was heated at reflux for 18 h with vigorous magnetic stirring. If the reaction was not complete after 18 h (TLC), additional quantities of propargyl bromide solution and K_2CO_3 were added as specified and the reaction was heated at reflux and stirred vigorously for the time specified. The reaction mixture was then cooled to room temp, diluted with CH_3CN (10 mL) and the solids were removed by vacuum filtration over a pad of Celite. The solids were rinsed with CH_3CN (3 × 15 mL), the filtrate was concentrated and the obtained residue was purified by flash chromatography over SiO_2 gel to afford the desired *O*-propargylated biaryl product.

General Procedure D: Copper catalyzed azide-alkyne cycloaddition

To a reaction vessel charged with the azide (1.0 eq), alkyne (2.0 eq), $Cu(OAc)_2{\cdot}H_2O$ (0.2 eq) and sodium ascorbate (0.4 eq) was added *t*-BuOH (20 mL/mmol azide) and H_2O (5 mL/mmol azide). The mixture was initially sonicated for < 1 min followed by vigorous stirring at rt for the specified time. The reaction mixture was diluted with EtOAc (20 mL for reactions that contained ≤ 1.0 mmol azide or 20 mL/mmol azide for larger scale reactions) and washed with an equivalent volume of saturated aqueous NH_4Cl solution (e.g. 20 mL) followed by brine. The organic phase was dried ($MgSO_4$), filtered, concentrated and the residue was subjected to flash chromatography over SiO_2 gel to afford the desired 1,4-disubstituted-1,2,3-triazole product. A plug of SiO_2 gel was most commonly used for chromatographic purification; the crude residue was adhered to a small plug of SiO_2 gel with minimal CH_2Cl_2, the plug was rinsed with CH_2Cl_2 (to remove excess alkyne) and then the target 1,4-disubstituted-1,2,3-triazole product was eluted with EtOAc (or MeOH/CH_2Cl_2 – 10:90).

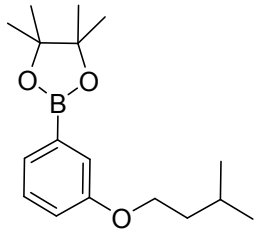
General Procedure E: Side-chain deprotection (*N*-Boc and *N*-Pbf removal)

The *N*-protected substrate (1.0 eq) was dissolved in a CH_2Cl_2 (30 mL/mmol substrate) with magnetic stirring, followed by the addition of H_2O (20.0 eq). Trifluoroacetic acid (30.0 mL/mmol substrate) was then added and the reaction mixture was stirred at rt overnight (> 16 h) followed by removal of the solvent. The residue was dissolved in CH_2Cl_2 (30 mL/mmol substrate), an excess amount of anhydrous HCl (2.0 M in Et_2O, 15 mL/mmol substrate, 30.0 eq) was added and the solvent was then removed. The resulting residue was dissolved in a minimal volume of CH_2Cl_2 (or MeOH) and excess Et_2O (25 mL) was added to precipitate the hydrochloride salt of the amine. The solvent was removed by filtration and the product was triturated with Et_2O (3 × 20 mL). The product was collected by dissolution in MeOH; concentration followed by drying *in vacuo* gave the final di-hydrochloride salt as a

thin, translucent film that was routinely scratched with a spatula into a fine hygroscopic powder or amorphous gum.

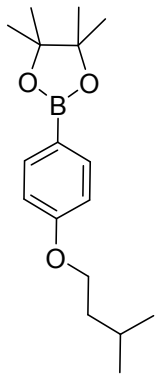
Synthesis and characterization of key aromatic fragments (*m*-11, *p*-11 and 13)

2-(3-(Isopentyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*m*-11)



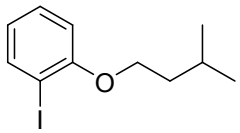
Following **General Procedure A**, 3-hydroxyphenylboronic acid pinacol ester (1.00 g, 4.54 mmol), K_2CO_3 (1.26 g, 9.09 mmol), TBAI (252 mg, 0.68 mmol) and 1-bromo-3-methylbutane (1.03 g, 6.82 mmol) were heated in CH_3CN (11.5 mL) at reflux for 18 h to give the target boronic ester ***m*-11** (1.27 g, 96% yield) as a crystalline white solid. m.p. 30–31 °C; TLC (EtOAc/Hexanes – 5:95): R_F = 0.74; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dt, *J* = 7.2, 1.0 Hz, 1H), 7.32 (br d, *J* = 2.6 Hz, 1H), 7.29 (app. t, *J* = 8.1, 7.2 Hz, 1H), 6.99 (ddd, *J* = 8.2, 2.8, 1.1 Hz, 1H), 4.01 (t, *J* = 6.6 Hz, 3H), 1.91 – 1.77 (m, 1H), 1.67 (q, *J* = 6.7 Hz, 2H), 1.34 (s, 12H), 0.96 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (C_{Ar}-O), 130.2 (C_{Ar}-B – observed by gHMBC), 129.0 (C_{Ar}), 127.1 (C_{Ar}), 119.8 (C_{Ar}), 118.4 (C_{Ar}), 83.9 (2 × $\underline{C}(CH_3)_2$), 66.4 (OCH_2), 38.3 (CH_2), 25.2 (CH), 25.0 (4 × CH_3), 22.8 (2 × CH_3); IR (neat) ν_{max} 2977, 2955, 2935, 2870, 1578, 1490, 1426, 1350, 1313, 1236, 1144, 1024, 965, 906, 855, 793, 702, 671, 540 cm^{-1}; MS (EI) *m/z* 134 (100%), 290 (M^+, 30%), 205 (27%), 220 (25%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{28}BO_3$ 291.2132, found 291.2127 ([M + H]$^+$).

2-(4-(Isopentyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*p*-11)



Following **General Procedure A**, 4-hydroxyphenylboronic acid pinacol ester (2.00 g, 9.08 mmol), K_2CO_3 (2.52 g, 18.18 mmol), TBAI (504 mg, 1.36 mmol) and 1-bromo-3-methylbutane (2.06 g, 13.64 mmol) were heated in CH_3CN (23 mL) at reflux for 18 h to give the target boronic ester ***p*-11** (2.59 g, 98% yield) as a crystalline white solid. m.p. 29–31 °C; TLC (EtOAc/Hexanes – 10:90): R_F = 0.66; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.7 Hz, 2H, ArH), 6.88 (d, *J* = 8.7 Hz, 2H, ArH), 4.00 (t, *J* = 6.7 Hz, 2H, OCH_2), 1.92 – 1.75 (m, 1H, CH), 1.67 (app. q, *J* = 6.7 Hz, 2H, $C\underline{H_2}CH$), 1.33 (s, 12H, 4 × CH_3), 0.95 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (C_{Ar}-O), 136.6 (2 × C_{Ar}), 120.3 (C_{Ar}-B – observed by gHMBC), 114.0 (2 × C_{Ar}), 83.6 (2 × $\underline{C}(CH_3)_2$), 66.3 (OCH_2), 38.1 (CH_2), 25.2 (CH), 25.0 (4 × CH_3), 22.7 (2 × CH_3); IR (neat) ν_{max} 2976, 2951, 2930, 2869, 1604, 1467, 1358, 1320, 1247, 1141, 1091, 1061, 982, 962, 859, 844, 817, 671, 655, 634, 521 cm^{-1}; MS (EI) *m/z* 57 (100%), 134 (49%), 205 (48%), 290 (M^+, 31%), 220 (25%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{28}BO_3$ 291.2132, found 291.2145 ([M + H]$^+$).

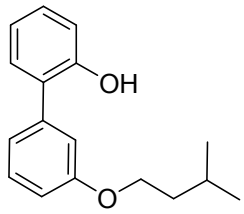
1-Iodo-2-(isopentyloxy)benzene (13)



To a reaction vessel charged with 2-iodophenol (1.00 g, 4.55 mmol), K_2CO_3 (1.26 g, 9.09 mmol), TBAI (252 mg, 0.68 mmol) and a stir bar was added CH_3CN (11.5 mL). Stirring was commenced at rt, 1-bromo-3-methylbutane (1.03 g, 6.82 mmol) was added and the reaction mixture was heated at reflux with vigorous stirring for 18 h. The reaction mixture was cooled to rt, diluted with CH_3CN (50 mL) and filtered over a pad of Celite. The solids were rinsed with CH_3CN (3 × 25 mL) and the filtrate was concentrated. The residue was eluted through a plug of SiO_2 gel with CH_2Cl_2 to furnish the target product as a translucent oil (1.28 g, 97% yield). TLC (EtOAc/Hexanes – 5:95): R_F = 0.75; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.8, 1.6 Hz, 1H, ArH), 7.30 – 7.25 (m, 1H, ArH), 6.80 (dd, *J* = 8.2, 1.3 Hz, 1H, ArH), 6.68 (td, *J* = 7.5, 1.4 Hz, 1H, ArH), 4.03 (t, *J* = 6.5 Hz, 2H, OCH_2), 1.99 – 1.88 (m, 1H, CH), 1.73 (q, *J* = 6.7 Hz, 2H, C$\underline{H_2}$CH), 0.98 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (C_{Ar}-O), 139.6 (C_{Ar}), 129.5 (C_{Ar}), 122.4 (C_{Ar}), 112.2 (C_{Ar}), 86.9 (C_{Ar}-I), 67.7 (OCH_2), 38.0 (CH_2), 25.3 (CH), 22.7 (2 × CH_3); IR (neat) ν_{max} 2954, 2930, 2869, 1581, 1464, 1438, 1385, 1275, 1245, 1121, 1050, 1016, 980, 877, 841, 795, 744, 650 cm^{-1}; MS (EI) *m/z* 220 (100%), 55 (83%), 290 (M^+, 35%); HRMS (ESI +ve TOF) calcd for $C_{11}H_{15}OINa$ 313.0065, found 313.0066 ([M + Na]$^+$).

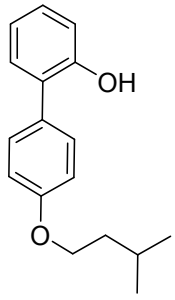
Synthesis and characterization of mono-alkylated biphenols (14a–h)

3'-(Isopentyloxy)-[1,1'-biphenyl]-2-ol (14a)



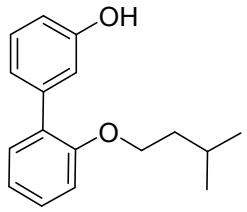
Following **General Procedure B**, 2-iodophenol (100 mg, 0.45 mmol), boronic ester ***m*-11** (171 mg, 0.59 mmol), Pd/C (10 mg, 0.01 mmol) and K_2CO_3 (251 mg, 1.82 mmol) were heated in EtOH (2.5 mL) and H_2O (2.5 mL) at 80 °C for 18 h to give mono-alkylated biphenol **14a** (102 mg, 87% yield) as a crystalline off-white solid after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 5:95). m.p. 42-44 °C; TLC (EtOAc/Hexanes – 5:95): R_F = 0.26, (EtOAc/Hexanes – 10:90): R_F = 0.54; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (t, *J* = 7.7 Hz, 1H, ArH), 7.28 – 7.21 (m, 2H, ArH), 7.03 – 6.90 (m, 5H, ArH), 5.34 (s, 1H, OH), 4.02 (t, *J* = 6.7 Hz, 2H, OCH_2), 1.90 – 1.79 (m, 1H, CH), 1.69 (q, *J* = 6.7 Hz, 2H, C$\underline{H_2}$CH), 0.97 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (C_{Ar}-O), 152.6 (C_{Ar}), 138.5 (C_{Ar}), 130.5 (C_{Ar}), 130.2 (C_{Ar}), 129.3 (C_{Ar}), 128.1 (C_{Ar}), 121.1 (C_{Ar}), 120.9 (C_{Ar}), 115.9 (C_{Ar}), 115.2 (C_{Ar}), 114.3 (C_{Ar}), 66.6 (OCH_2), 38.1 (CH_2), 25.2 (CH), 22.7 (2 × CH_3); IR (neat) ν_{max} 3435, 2955, 2943, 2875, 1591, 1580, 1467, 1423, 1305, 1267, 1207, 1176, 1155, 1010, 991, 867, 794, 753, 740, 702, 513, 438 cm^{-1}; MS (EI) *m/z* 186 (100%), 256 (M^+, 40%), 57 (37%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{20}O_2Na$ 279.1361, found 279.1361 ([M + H]$^+$).

4'-(Isopentyloxy)-[1,1'-biphenyl]-2-ol (14b)



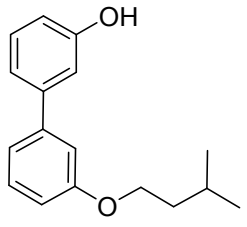
Following **General Procedure B**, 2-iodophenol (100 mg, 0.45 mmol), boronic ester ***p*-11** (171 mg, 0.59 mmol), Pd/C (10 mg, 0.01 mmol) and K_2CO_3 (251 mg, 1.82 mmol) were heated in EtOH (2.5 mL) and H_2O (2.5 mL) at 80 °C for 18 h to give mono-alkylated biphenol **14b** (99 mg, 85% yield) as a viscous, translucent oil after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 5:95). TLC (EtOAc/Hexanes – 5:95): R_F = 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H, ArH), 7.26 – 7.19 (m, 2H, ArH), 7.03 – 6.93 (m, 4H, ArH), 5.21 (s, 1H, OH), 4.03 (t, *J* = 6.6 Hz, 2H, OCH_2), 1.93 – 1.79 (m, 1H, CH), 1.71 (q, *J* = 6.7 Hz, 2H, C<u>H</u>$_2$CH), 0.98 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1 (C_{Ar}-O), 152.7 (C_{Ar}-OH), 130.4 (3 × C_{Ar}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 128.0 (C_{Ar}), 120.9 (C_{Ar}), 115.8 (C_{Ar}), 115.4 (2 × C_{Ar}), 66.6 (OCH_2), 38.1 (CH_2), 25.2 (CH), 22.7 (2 × CH_3); IR (neat) ν_{max} 3534, 3429, 2955, 2929, 2870, 1607, 1516, 1481, 1295, 1273, 1242, 1175, 1152, 1104, 1058, 1001, 980, 827, 752, 606, 568, 471 cm^{-1}; MS (EI) *m/z* 186 (100%), 256 (M^+, 42%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1542 ($[M + H]^+$).

2'-(isopentyloxy)-[1,1'-biphenyl]-3-ol (14c)



Following **General Procedure B**, aryl iodide **13** (145 mg, 0.50 mmol), 3-hydroxyphenylboronic acid pinacol ester (143 mg, 0.65 mmol), Pd/C (11 mg, 0.01 mmol) and K_2CO_3 (276 mg, 2.00 mmol) were heated in EtOH (2.5 mL) and H_2O (2.5 mL) at 80 °C for 18 h to give mono-alkylated biphenol **14c** (117 mg, 91% yield) as a viscous, translucent oil after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 10:90). TLC (EtOAc/Hexanes – 10:90): R_F = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 3H, ArH), 7.13 – 7.08 (m, 1H, ArH), 7.03 – 6.95 (m, 3H, ArH), 6.78 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1H, ArH), 5.00 (br s, 1H, OH), 3.97 (t, *J* = 6.6 Hz, 2H, OCH_2), 1.80 – 1.67 (m, 1H, CH), 1.61 (q, *J* = 6.7 Hz, 2H, CH_2), 0.89 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C_{Ar}-O), 155.2 (C_{Ar}-OH), 140.4 (C_{Ar}), 130.9 (C_{Ar}), 130.6 (C_{Ar}), 129.1 (C_{Ar}), 128.8 (C_{Ar}), 122.4 (C_{Ar}), 120.9 (C_{Ar}), 116.8 (C_{Ar}), 113.8 (C_{Ar}), 112.8 (C_{Ar}), 67.2 (OCH_2), 38.1 (CH_2), 25.2 (CH), 22.7 (2 × CH_3); IR (neat) ν_{max} 3362, 2955, 2930, 2870, 1588, 1470, 1433, 1305, 1273, 1238, 1190, 1161, 1121, 1055, 999, 981, 888, 785, 741, 696, 617, 533 cm^{-1}; MS (EI) *m/z* 186 (100%), 256 (M^+, 38%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{20}O_2Na$ 279.1361, found 279.1369 ($[M + H]^+$).

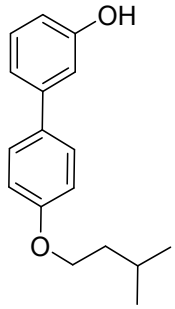
3'-(isopentyloxy)-[1,1'-biphenyl]-3-ol (14d)



Following **General Procedure B**, 3-iodophenol (100 mg, 0.45 mmol), boronic ester ***m*-11** (171 mg, 0.59 mmol), Pd/C (10 mg, 0.01 mmol) and K_2CO_3 (251 mg, 1.82 mmol) were heated in EtOH (2.5 mL) and H_2O (2.5 mL) at 80 °C for 18 h to give mono-alkylated biphenol **14d** (113 mg, 97% yield) as a viscous, translucent oil after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 5:95). TLC (EtOAc/Hexanes – 10:90): R_F = 0.26; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 2H, ArH), 7.18 – 7.08 (m, 3H, ArH), 7.06 – 7.03 (m, 1H, ArH), 6.89 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H, ArH), 6.81 (ddd, *J* = 8.0, 2.5, 0.9 Hz, 1H, ArH), 5.14 (br s, 1H, OH), 4.04 (t, *J* = 6.6 Hz, 2H, OCH_2), 1.91 – 1.79 (m, 1H, CH), 1.70 (q, *J* = 6.7 Hz, 2H. C<u>H</u>$_2$CH), 0.97 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$)

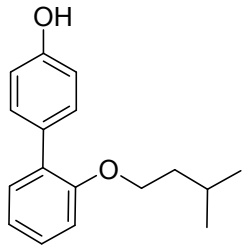
δ 159.6 (C_{Ar}-O), 156.0 (C_{Ar}-OH), 143.1 (C_{Ar}), 142.3 (C_{Ar}), 130.1 (C_{Ar}), 129.8 (C_{Ar}), 119.9 (C_{Ar}), 119.6 (C_{Ar}), 114.4 (C_{Ar}), 114.3 (C_{Ar}), 113.7 (C_{Ar}), 113.6 (C_{Ar}), 66.6 (OCH_2), 38.2 (CH_2) 25.2 (CH), 22.8 (2 × CH_3); IR (neat) ν_{max} 3369, 2955, 2929, 2870, 1596, 1575, 1472, 1421, 1386, 1305, 1281, 1219, 1184, 1162, 1056, 997, 924, 858, 772, 692, 620, 534, 430 cm^{-1}; MS (EI) *m/z* 186 (100%), 256 (M^+, 31%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1536 ($[M + H]^+$).

4'-(isopentyloxy)-[1,1'-biphenyl]-3-ol (14e)



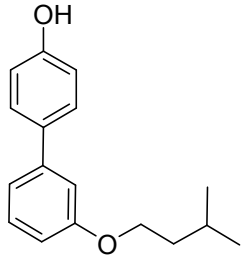
Following **General Procedure B**, 3-iodophenol (100 mg, 0.45 mmol), boronic ester ***p*-11** (171 mg, 0.59 mmol), Pd/C (10 mg, 0.01 mmol) and K_2CO_3 (251 mg, 1.82 mmol) were heated in EtOH (2.5 mL) and H_2O (2.5 mL) at 80 °C for 18 h to give mono-alkylated biphenol **14e** (110 mg, 94% yield) as a white crystalline solid after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 5:95). m.p. 65-67 °C; TLC (EtOAc/Hexanes – 10:90): R_F = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.8 Hz, 2H, ArH), 7.27 (t, *J* = 7.8 Hz, 1H, ArH), 7.12 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H, ArH), 7.01 (dd, *J* = 2.5, 1.6 Hz, 1H, ArH), 6.95 (d, *J* = 8.8 Hz, 2H, ArH), 6.76 (ddd, *J* = 8.0, 2.6, 1.0 Hz, 1H, ArH), 4.98 (br s, 1H, OH), 4.02 (t, *J* = 6.7 Hz, 2H, OCH_2), 1.91 – 1.80 (m, 1H, CH), 1.70 (q, *J* = 6.8 Hz, 2H, C$\underline{H_2}$CH), 0.97 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C_{Ar}-O), 156.0 (C_{Ar}-OH), 142.8 (C_{Ar}), 133.2 (C_{Ar}), 130.0 (C_{Ar}), 128.2 (2 × C_{Ar}), 119.4 (C_{Ar}), 114.9 (2 × C_{Ar}), 113.8 (C_{Ar}), 113.7 (C_{Ar}), 66.7 (OCH_2), 38.2 (CH_2), 25.2 (CH), 22.7 (2 × CH_3); IR (neat) ν_{max} 3310, 2957, 2929, 2867, 1604, 1587, 1523, 1489, 1471, 1390, 1352, 1298, 1280, 1250, 1196, 1188, 1169, 1060, 980, 881, 825, 777, 685, 609, 536, 513, 454 cm^{-1}; MS (EI) *m/z* 186 (100%), 256 (M^+, 32%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1547 ($[M + H]^+$).

2'-(Isopentyloxy)-[1,1'-biphenyl]-4-ol (14f)



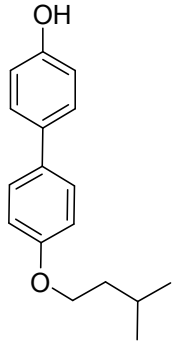
Following **General Procedure B**, aryl iodide **13** (145 mg, 0.50 mmol), 4-hydroxyphenylboronic acid pinacol ester (143 mg, 0.65 mmol), Pd/C (11 mg, 0.01 mmol) and K_2CO_3 (276 mg, 2.00 mmol) were heated in EtOH (2.5 mL) and H_2O (2.5 mL) at 80 °C for 18 h to give mono-alkylated biphenol **14f** as an impure mixture (105 mg – white solid containing ~13% w/w phenol impurity) after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 10:90). The phenol by-product was difficult to separate at this stage, but was readily removed following subsequent *O*-propargylation. TLC (EtOAc/Hexanes – 10:90): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.7 Hz, 2H, ArH), 7.31 – 7.23 (m, 2H, ArH), 7.01 – 6.94 (m, 2H, ArH), 6.85 (d, *J* = 8.8 Hz, 2H, ArH), 5.03 (br s, 1H, OH), 3.97 (t, *J* = 6.6 Hz, 2H, OCH_2), 1.81 – 1.68 (m, 1H, CH), 1.61 (q, *J* = 6.7 Hz, 2H, C$\underline{H_2}$CH), 0.90 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C_{Ar}-O), 154.6 (C_{Ar}-OH), 131.3 (C_{Ar}), 131.0 (2 × C_{Ar}), 130.7 (C_{Ar}), 130.6 (C_{Ar}), 128.2 (C_{Ar}), 120.9 (C_{Ar}), 114.9 (2 × C_{Ar}), 112.7 (C_{Ar}), 67.0 (OCH_2), 38.1 (CH_2), 25.2 (CH), 22.7 (2 × CH_3); IR (neat) ν_{max} 3250, 2952, 2928, 2870, 1596, 1516, 1487, 1472, 1454, 1387, 1367, 1268, 1231, 1177, 1121, 1053, 1015, 977, 828, 687, 563, 501, 457 cm^{-1}; MS (EI) *m/z* 186 (100%), 256 (M^+, 42%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1531 ($[M + H]^+$).

3'-(Isopentyloxy)-[1,1'-biphenyl]-4-ol (14g)



Following **General Procedure B**, 4-iodophenol (100 mg, 0.45 mmol), boronic ester ***m*-11** (171 mg, 0.59 mmol), Pd/C (10 mg, 0.01 mmol) and K_2CO_3 (251 mg, 1.82 mmol) were heated in EtOH (2.5 mL) and H_2O (2.5 mL) at 80 °C for 18 h to give mono-alkylated biphenol **14g** (109 mg, 93% yield) as an off-white solid after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 5:95). m.p. 42-44 °C; TLC (EtOAc/Hexanes – 10:90): R_F = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.6 Hz, 2H, ArH), 7.31 (t, *J* = 7.9 Hz, 1H, ArH), 7.11 (ddd, *J* = 7.6, 1.7, 1.0 Hz, 1H, ArH), 7.07 (dd, *J* = 2.5, 1.7 Hz, 1H, ArH), 6.88 (d, *J* = 8.6 Hz, 2H, ArH), 6.85 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H, ArH), 5.11 (br s, 1H, OH), 4.04 (t, *J* = 6.6 Hz, 2H, OCH_2), 1.90 – 1.80 (m, 1H, CH), 1.70 (q, *J* = 6.7 Hz, 2H, C$\underline{H_2}$CH), 0.97 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (C_{Ar}-O), 155.3 (C_{Ar}-OH), 142.4 (C_{Ar}), 134.0 (C_{Ar}), 129.8 (C_{Ar}), 128.5 (2 × C_{Ar}), 119.2 (C_{Ar}), 115.7 (2 × C_{Ar}), 113.3 (C_{Ar}), 112.8 (C_{Ar}), 66.6 (OCH_2), 38.2 (CH_2), 25.2 (CH), 22.8 (2 × CH_3); IR (neat) ν_{max} 3360, 2953, 2930, 2868, 1593, 1521, 1492, 1455, 1414, 1380, 1298, 1254, 1208, 1162, 1113, 1060, 982, 899, 829, 781, 688, 613, 565, 514, 451 cm^{-1}; MS (EI) *m/z* 186 (100%), 256 (M^+, 36%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1547 ([M + H]$^+$).

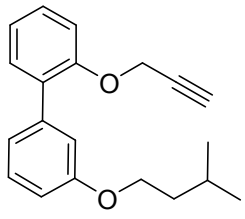
4'-(isopentyloxy)-[1,1'-biphenyl]-4-ol (14h)



Following **General Procedure B**, 4-iodophenol (100 mg, 0.45 mmol), boronic ester ***p*-11** (171 mg, 0.59 mmol), Pd/C (10 mg, 0.01 mmol) and K_2CO_3 (251 mg, 1.82 mmol) were heated in EtOH (2.5 mL) and H_2O (2.5 mL) at 80 °C for 18 h to give mono-alkylated biphenol **14h** (113 mg, 97% yield) as a white, crystalline solid after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 10:90). m.p. 150-152 °C; TLC (EtOAc/Hexanes – 10:90): R_F = 0.29; ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (d, *J* = 8.8 Hz, 2H, ArH), 7.37 (d, *J* = 8.7 Hz, 2H, ArH), 6.90 (d, *J* = 8.8 Hz, 2H, ArH), 6.82 (d, *J* = 8.7 Hz, 2H, ArH), 3.99 (t, *J* = 6.6 Hz, 2H, OCH_2), 1.90 – 1.77 (m, 1H, CH), 1.65 (q, *J* = 6.7 Hz, 2H, C$\underline{H_2}$CH), 0.97 (d, *J* = 6.7 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, CD_3OD) δ 159.4 (C_{Ar}-O), 157.5 (C_{Ar}-OH), 134.9 (C_{Ar}), 133.7 (C_{Ar}), 128.5 (2 × C_{Ar}), 128.4 (2 × C_{Ar}), 116.5 (2 × C_{Ar}), 115.7 (2 × C_{Ar}), 67.4 (OCH_2), 39.2 (CH_2), 26.2 (CH), 23.0 (2 × CH_3); IR (neat) ν_{max} 3394, 2954, 2931, 2869, 2518, 1596, 1499, 1475, 1447, 1386, 1371, 1241, 1172, 1137, 1060, 978, 813, 580, 511 cm^{-1}; MS (EI) *m/z* 186 (100%), 256 (M^+, 41%); HRMS (ESI +ve TOF) calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1549 ([M + H]$^+$).

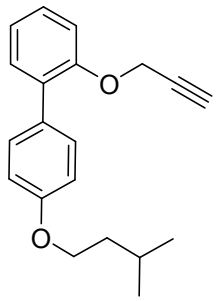
Synthesis and characterization of biaryl alkynes (15a–h)

3'-(Isopentyloxy)-2-(prop-2-yn-1-yloxy)-1,1'-biphenyl (15a)



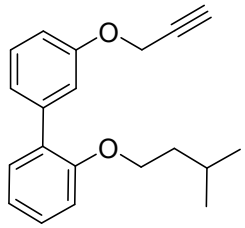
Following **General Procedure C**, mono-alkylated biphenol **14a** (80 mg, 0.31 mmol), propargyl bromide solution (70 mg, 0.47 mmol), TBAI (17 mg, 0.05 mmol) and K_2CO_3 (86 mg, 0.62 mmol) were heated in CH_3CN (2.2 mL) at reflux for 18 h. The reaction was incomplete by TLC analysis, so additional quantities of propargyl bromide solution (47 mg, 0.31 mmol) and K_2CO_3 (22 mg, 0.16 mmol) were added and the reaction was continued for another 72 h (90 h total) to give biaryl alkyne **15a** (89 mg, 97% yield) as a translucent oil after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 2.5:97.5). TLC (EtOAc/Hexanes – 5:95): R_F = 0.40; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 3H, ArH), 7.14 – 7.05 (m, 4H, ArH), 6.87 (ddd, *J* = 8.3, 2.5, 1.1 Hz, 1H, ArH), 4.66 (d, *J* = 2.4 Hz, 2H, $OCH_2C{\equiv}C$), 4.02 (t, *J* = 6.7 Hz, 2H, OCH_2), 2.46 (t, *J* = 2.4 Hz, 1H, C≡C-H), 1.90 – 1.79 (m, 1H, CH), 1.69 (q, *J* = 6.7 Hz, 2H, $C\underline{H_2}CH$), 0.96 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C_{Ar}-O), 154.6 (C_{Ar}-O), 139.6 (C_{Ar}), 131.6 (C_{Ar}), 131.2 (C_{Ar}), 129.0 (C_{Ar}), 128.6 (C_{Ar}), 122.1 (C_{Ar}), 122.0 (C_{Ar}), 115.9 (C_{Ar}), 113.8 (C_{Ar}), 113.6 (C_{Ar}), 79.0 ($\underline{C}{\equiv}C$-H), 75.6 (C≡$\underline{C}$-H), 66.5 (OCH_2), 56.4 (OCH_2), 38.2 (CH_2), 25.2 (CH), 22.8 (2 × CH_3); IR (neat) ν_{max} 3288, 3064, 3030, 2955, 2928, 2870, 2121, 1597, 1584, 1498, 1472, 1422, 1385, 1368, 1277, 1213, 1198, 1164, 1123, 1057, 1020, 981, 924, 879, 784, 750, 696, 633, 542, 473 cm^{-1}; MS (EI) *m/z* 185 (100%), 224 (70%), 294 (M^+, 65%), 128 (45%); HRMS (ESI +ve TOF) calcd for $C_{20}H_{23}O_2$ 295.1698, found 295.1692 ($[M + H]^+$).

4'-(Isopentyloxy)-2-(prop-2-yn-1-yloxy)-1,1'-biphenyl (15b)



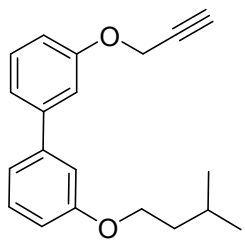
Following **General Procedure C**, mono-alkylated biphenol **14b** (80 mg, 0.31 mmol), propargyl bromide solution (70 mg, 0.47 mmol), TBAI (17 mg, 0.05 mmol) and K_2CO_3 (86 mg, 0.62 mmol) were heated in CH_3CN (2.2 mL) at reflux for 18 h. The reaction was incomplete by TLC analysis, so additional quantities of propargyl bromide solution (47 mg, 0.31 mmol) and K_2CO_3 (22 mg, 0.16 mmol) were added and the reaction was continued for another 72 h (90 h total) to give biaryl alkyne **15b** (85 mg, 92% yield) as a translucent oil after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 2.5:97.5). TLC (EtOAc/Hexanes – 5:95): R_F = 0.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 2H, ArH), 7.30 (m, 2H, ArH), 7.11 (dd, *J* = 8.2, 1.1 Hz, 1H, ArH), 7.06 (td, *J* = 7.4, 1.1 Hz, 1H, ArH), 6.94 (d, *J* = 8.8 Hz, 2H, ArH), 4.65 (d, *J* = 2.4 Hz, 2H, $OCH_2C{\equiv}C$), 4.02 (t, *J* = 6.6 Hz, 2H, OCH_2), 2.46 (t, *J* = 2.4 Hz, 1H, C≡C-H), 1.92 – 1.80 (m, 1H, CH), 1.70 (q, *J* = 6.8 Hz, 2H, $C\underline{H_2}CH$), 0.97 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (C_{Ar}-O), 154.6 (C_{Ar}-O), 131.4 (C_{Ar}), 131.1 (C_{Ar}), 130.7 (2 × C_{Ar}), 130.5 (C_{Ar}), 128.1 (C_{Ar}), 122.1 (C_{Ar}), 114.2 (2 × C_{Ar}), 113.8 (C_{Ar}), 79.0 ($\underline{C}{\equiv}C$-H), 75.5 (C≡$\underline{C}$-H), 66.5 (OCH_2), 56.4 (OCH_2), 38.2 (CH_2), 25.2 (CH), 22.8 (2 × CH_3); IR (neat) ν_{max} 3288, 3064, 3034, 2955, 2928, 2870, 2121, 1608, 1583, 1516, 1484, 1451, 1385, 1367, 1242, 1211, 1177, 1124, 1057, 1024, 980, 924, 830, 750, 671, 638, 565, 537, 484 cm^{-1}; MS (EI) *m/z* 185 (100%), 294 (M^+, 42%); HRMS (ESI +ve TOF) calcd for $C_{20}H_{23}O_2$ 295.1698, found 295.1696 ($[M + H]^+$).

2-(Isopentyloxy)-3'-(prop-2-yn-1-yloxy)-1,1'-biphenyl (15c)



Following **General Procedure C**, mono-alkylated biphenol **14c** (95 mg, 0.37 mmol), propargyl bromide solution (83 mg, 0.56 mmol), TBAI (21 mg, 0.06 mmol) and K_2CO_3 (102 mg, 0.74 mmol) were heated in CH_3CN (2.6 mL) at reflux for 18 h. The reaction was incomplete by TLC analysis, so additional quantities of propargyl bromide solution (55 mg, 0.37 mmol) and K_2CO_3 (26 mg, 0.19 mmol) were added and the reaction was continued for another 66 h (84 h total) to give biaryl alkyne **15c** (98 mg, 90% yield) as a translucent oil after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 2.5:97.5). TLC (EtOAc/Hexanes – 2.5:97.5): R_F = 0.38, (EtOAc/Hexanes – 10:90): R_F = 0.65; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 3H, ArH), 7.20 – 7.15 (m, 2H, ArH), 7.03 – 6.92 (m, 3H, ArH), 4.71 (d, *J* = 2.5 Hz, 2H, $OCH_2C{\equiv}C$), 3.98 (t, *J* = 6.7 Hz, 2H, OCH_2), 2.51 (t, *J* = 2.4 Hz, 1H, C≡C-H), 1.80 – 1.70 (m, 1H, C<u>H</u>CH_2), 1.62 (q, *J* = 6.7 Hz, 2H, CHC<u>H</u>$_2$), 0.90 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4 (C_{Ar}-O), 156.1 (C_{Ar}-O), 140.2 (C_{Ar}), 131.0 (C_{Ar}), 130.6 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 123.2 (C_{Ar}), 120.9 (C_{Ar}), 116.3 (C_{Ar}), 113.6 (C_{Ar}), 112.7 (C_{Ar}), 78.9 (<u>C</u>≡C-H), 75.5 (C≡<u>C</u>-H), 67.0 (OCH_2), 56.0 (OCH_2), 38.1 (CH_2), 25.2 (CH), 22.7 (2 × CH_3); IR (neat) ν_{max} 3288, 3065, 3030, 2955, 2929, 2869, 2123, 1585, 1500, 1471, 1423, 1385, 1368, 1237, 1188, 1121, 1046, 1020, 981, 926, 878, 861, 786, 750, 695, 633, 503, 421 cm^{-1}; MS (EI) *m/z* 223 (100%), 294 (M^+, 54%), 128 (38%); HRMS (ESI +ve TOF) calcd for $C_{20}H_{23}O_2$ 295.1698, found 295.1703 ($[M + H]^+$).

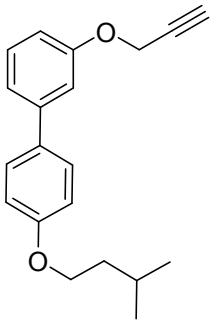
3-(Isopentyloxy)-3'-(prop-2-yn-1-yloxy)-1,1'-biphenyl (15d)



Following **General Procedure C**, mono-alkylated biphenol **14d** (95 mg, 0.37 mmol), propargyl bromide solution (83 mg, 0.56 mmol), TBAI (21 mg, 0.06 mmol) and K_2CO_3 (102 mg, 0.74 mmol) were heated in CH_3CN (1.9 mL) at reflux for 18 h. The reaction was incomplete by TLC analysis, so additional quantities of propargyl bromide solution (440 mg, 2.96 mmol) and K_2CO_3 (51 mg, 0.37 mmol) were added and the reaction was continued for another 102 h (120 h total) to give biaryl alkyne **15d** (95 mg, 87% yield) as a translucent, yellow oil after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 5:95). TLC (EtOAc/Hexanes – 5:95): R_F = 0.51; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.9 Hz, 1H, ArH), 7.32 (t, *J* = 8.0 Hz, 1H, ArH), 7.22 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H, ArH), 7.20 (dd, *J* = 2.6, 1.6 Hz, 1H, ArH), 7.15 (ddd, *J* = 7.6, 1.7, 0.9 Hz, 1H, ArH), 7.11 (dd, *J* = 2.5, 1.6 Hz, 1H, ArH), 6.96 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H, ArH), 6.89 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H, ArH), 4.74 (d, *J* = 2.4 Hz, 2H, $OCH_2C{\equiv}C$), 4.04 (t, *J* = 6.7 Hz, 2H, OCH_2), 2.53 (t, *J* = 2.4 Hz, 1H, C≡C-H), 1.90 – 1.81 (m, 1H, C<u>H</u>CH_2), 1.70 (q, *J* = 6.8 Hz, 2H, CH_2), 0.97 (d, *J* = 6.7 Hz, 6H, 2 × CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6 (C_{Ar}-O), 158.0 (C_{Ar}-O), 142.9 (C_{Ar}), 142.4 (C_{Ar}), 129.9 (2 × C_{Ar}), 120.7 (C_{Ar}), 119.6 (C_{Ar}), 114.1 (C_{Ar}), 113.8 (C_{Ar}), 113.6 (2 × C_{Ar}), 78.7 (<u>C</u>≡C-H), 75.8 (C≡<u>C</u>-H), 66.6 (OCH_2), 56.0 (OCH_2), 38.2 (CH_2), 25.2 (CH), 22.8 (2 × CH_3); IR (neat) ν_{max} 3290, 3064, 3033, 2955, 2928, 2870, 2123, 1597, 1573, 1472, 1418, 1385, 1368, 1295, 1217, 1184, 1170, 1056, 1033, 984, 931, 850, 771, 693, 635, 465 cm^{-1}; MS (EI) *m/z* 223

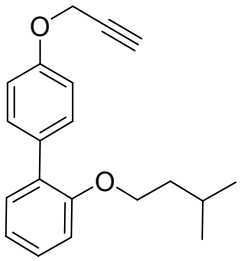
(100%), 294 (M^+, 71%); HRMS (ESI +ve TOF) calcd for $C_{20}H_{23}O_2$ 295.1698, found 295.1705 ($[M + H]^+$).

4'-(Isopentyloxy)-3-(prop-2-yn-1-yloxy)-1,1'-biphenyl (15e)



Following **General Procedure C**, mono-alkylated biphenol **14e** (95 mg, 0.37 mmol), propargyl bromide solution (83 mg, 0.56 mmol), TBAI (21 mg, 0.06 mmol) and K_2CO_3 (102 mg, 0.74 mmol) were heated in CH_3CN (2.6 mL) at reflux for 18 h. The reaction was incomplete by TLC analysis, so additional quantities of propargyl bromide solution (55 mg, 0.37 mmol) and K_2CO_3 (26 mg, 0.19 mmol) were added and the reaction was continued for another 30 h (48 h total) to give biaryl alkyne **15e** (102 mg, 94% yield) as a light beige solid after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 5:95). m.p. 39-40 °C; TLC (EtOAc/Hexanes – 10:90): $R_F = 0.52$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.8 Hz, 2H, ArH), 7.33 (t, J = 7.9 Hz, 1H, ArH), 7.22 – 7.13 (m, 2H, ArH), 6.96 (d, J = 8.8 Hz, 2H, ArH), 6.91 (ddd, J = 8.2, 2.6, 1.0 Hz, 1H, ArH), 4.74 (d, J = 2.4 Hz, 2H, $OCH_2C{\equiv}C$), 4.02 (t, J = 6.7 Hz, 2H, OCH_2), 2.53 (t, J = 2.4 Hz, 1H, C≡C-H), 1.92 – 1.79 (m, 1H, C<u>H</u>CH_2), 1.70 (q, J = 6.7 Hz, 2H, CHC<u>H</u>$_2$), 0.97 (d, J = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C_{Ar}-O), 158.1 (C_{Ar}-O), 142.6 (C_{Ar}), 133.3 (C_{Ar}), 129.8 (C_{Ar}), 128.3 (C_{Ar}), 120.3 (C_{Ar}), 114.9 (C_{Ar}), 113.6 (C_{Ar}), 113.0 (C_{Ar}), 78.8 (<u>C</u>≡C-H), 75.7 (C≡<u>C</u>-H), 66.6 (OCH_2), 56.0 (OCH_2), 38.2 (CH_2), 25.2 (CH), 22.7 (2 × CH_3); IR (neat) ν_{max} 3289, 3065, 3036, 2955, 2928, 2869, 2123, 1607, 1586, 1570, 1517, 1475, 1405, 1385, 1368, 1293, 1244, 1179, 1052, 1028, 981, 926, 875, 829, 776, 693, 640, 537, 453 cm^{-1}; MS (EI) *m/z* 223 (100%), 294 (M^+, 94%), 157 (49%); HRMS (ESI +ve TOF) calcd for $C_{20}H_{23}O_2$ 295.1698, found 295.1702 ($[M + H]^+$).

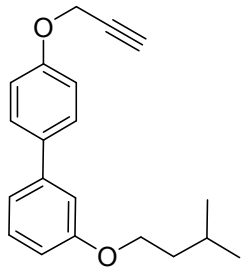
2-(Isopentyloxy)-4'-(prop-2-yn-1-yloxy)-1,1'-biphenyl (15f)



Following **General Procedure C**, impure mono-alkylated biphenol **14f** (83 mg, ~87% pure, 0.28 mmol), propargyl bromide solution (62 mg, 0.42 mmol), TBAI (16 mg, 0.04 mmol) and K_2CO_3 (102 mg, 0.74 mmol) were heated in CH_3CN (2.3 mL) at reflux for 18 h. The reaction was incomplete by TLC analysis, so additional quantities of propargyl bromide solution (125 mg, 0.84 mmol) and K_2CO_3 (58 mg, 0.42 mmol) were added and the reaction was continued for another 110 h (126 h total) to give biaryl alkyne **15f** (80 mg, 69% yield over 2 steps from aryl iodide **13**) as a translucent oil after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 2.5:97.5). TLC (EtOAc/Hexanes – 2.5:97.5): $R_F = 0.42$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.8 Hz, 2H, ArH), 7.30 (dd, J = 7.5, 1.7 Hz, 1H, ArH), 7.28 – 7.24 (m, 1H, ArH), 7.02 – 6.95 (m, 4H, ArH), 4.72 (d, J = 2.4 Hz, 2H, $OCH_2C{\equiv}C$), 3.97 (t, J = 6.6 Hz, 2H, OCH_2), 2.53 (t, J = 2.4 Hz, 1H, C≡C-H), 1.80 – 1.70 (m, 1H, C<u>H</u>CH_2), 1.61 (q, J = 6.7 Hz, 2H, CHC<u>H</u>$_2$), 0.90 (d, J = 6.7 Hz, 6H, 2 × CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6 (C_{Ar}-O), 156.1 (C_{Ar}-O), 132.1 (C_{Ar}), 130.79 (2 × C_{Ar}), 130.76 (C_{Ar}), 130.5 (C_{Ar}), 128.3 (C_{Ar}), 120.9 (C_{Ar}), 114.3 (2 × C_{Ar}), 112.6 (C_{Ar}), 78.9 (<u>C</u>≡C-H), 75.6 (C≡<u>C</u>-H), 67.0 (OCH_2), 56.0

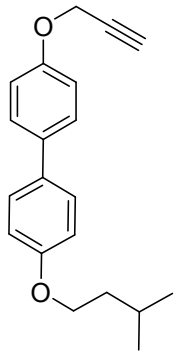
(O<u>C</u>H_2C≡C), 38.1 (CH_2), 25.2 (CH), 22.7 (2 × CH_3); IR (neat) ν_{max} 3288, 3066, 3033, 2955, 2928, 2869, 2122, 1598, 1514, 1486, 1448, 1410, 1385, 1368, 1296, 1216, 1178, 1122, 1055, 1033, 1001, 981, 924, 829, 748, 670, 641, 564, 475 cm^{-1}; MS (EI) *m/z* 185 (100%), 294 (M^+, 87%) 128 (36%), 224 (35%); HRMS (ESI +ve TOF) calcd for $C_{20}H_{23}O_2$ 295.1698, found 295.1691 ($[M + H]^+$).

3-(Isopentyloxy)-4'-(prop-2-yn-1-yloxy)-1,1'-biphenyl (15g)



Following **General Procedure C**, mono-alkylated biphenol **14g** (89 mg, 0.35 mmol), propargyl bromide solution (77 mg, 0.52 mmol), TBAI (19 mg, 0.05 mmol) and K_2CO_3 (97 mg, 0.70 mmol) were heated in CH_3CN (1.7 mL) at reflux for 18 h. The reaction was incomplete by TLC analysis, so additional quantities of propargyl bromide solution (416 mg, 2.80 mmol) and K_2CO_3 (48 mg, 0.35 mmol) were added and the reaction was continued for another 126 h (144 h total) to give biaryl alkyne **15g** (89 mg, 87% yield) as a translucent, yellow oil after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 5:95). m.p. 38-40 °C; TLC (EtOAc/Hexanes – 10:90): R_F = 0.56; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.8 Hz, 2H, ArH), 7.31 (t, *J* = 7.9 Hz, 1H, ArH), 7.12 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H, ArH), 7.08 (dd, *J* = 2.5, 1.7 Hz, 1H, ArH), 7.04 (d, *J* = 8.8 Hz, 2H, ArH), 6.85 (ddd, *J* = 8.1, 2.5, 1.0 Hz, 1H, ArH), 4.72 (d, *J* = 2.4 Hz, 2H, OCH_2C≡C), 4.04 (t, *J* = 6.6 Hz, 2H, OCH_2), 2.53 (t, *J* = 2.4 Hz, 1H, C≡C-H), 1.92 – 1.79 (m, 1H, C<u>H</u>CH_2), 1.70 (q, *J* = 6.7 Hz, 2H, CHC<u>H</u>$_2$), 0.97 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6 (C_{Ar}-O), 157.3 (C_{Ar}-O), 142.3 (C_{Ar}), 134.8 (C_{Ar}), 129.8 (C_{Ar}), 128.3 (2 × C_{Ar}), 119.3 (C_{Ar}), 115.2 (2 × C_{Ar}), 113.3 (C_{Ar}), 112.9 (C_{Ar}), 78.7 (<u>C</u>≡C-H), 75.7 (C≡<u>C</u>-H), 66.5 (OCH_2), 56.0 (O<u>C</u>H_2C≡C), 38.2 (CH_2), 25.2 (CH), 22.8 (2 × CH_3); IR (neat) ν_{max} 3290, 3055, 3037, 2955, 2929, 2868, 2135, 1595, 1516, 1474, 1377, 1304, 1282, 1240, 1211, 1186, 1052, 1019, 980, 899, 833, 776, 690, 658, 610, 536, 452 cm^{-1}; MS (EI) *m/z* 294 (M^+, 100%), 185 (76%), 255 (74%), 157 (40%); HRMS (ESI +ve TOF) calcd for $C_{20}H_{23}O_2$ 295.1698, found 295.1695 ($[M + H]^+$).

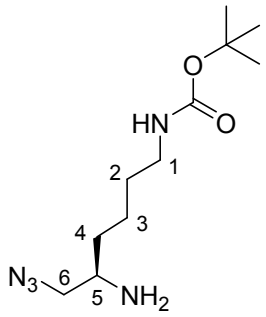
4-(Isopentyloxy)-4'-(prop-2-yn-1-yloxy)-1,1'-biphenyl (15h)



Following **General Procedure C**, mono-alkylated biphenol **14h** (94 mg, 0.37 mmol), propargyl bromide solution (83 mg, 0.56 mmol), TBAI (21 mg, 0.06 mmol) and K_2CO_3 (102 mg, 0.74 mmol) were heated in CH_3CN (2.6 mL) at reflux for 18 h to give biaryl alkyne **15h** (102 mg, 94% yield) as a white, crystalline solid after flash chromatography over SiO_2 gel (EtOAc/Hexanes – 5:95). m.p. 88-90 °C; TLC (EtOAc/Hexanes – 10:90): $R_F = 0.50$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.8 Hz, 2H, ArH), 7.45 (d, J = 8.7 Hz, 2H, ArH), 7.02 (d, J = 8.9 Hz, 2H, ArH), 6.94 (d, J = 8.8 Hz, 2H, ArH), 4.71 (d, J = 2.4 Hz, 2H, $OCH_2C{\equiv}C$), 4.01 (t, J = 6.7 Hz, 2H, OCH_2), 2.53 (t, J = 2.4 Hz, 1H, C≡C-H), 1.91 – 1.80 (m, 1H, C<u>H</u>CH_2), 1.69 (q, J = 6.7 Hz, 2H, CHC<u>H</u>$_2$), 0.97 (d, J = 6.6 Hz, 6H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (C_{Ar}-O), 156.7 (C_{Ar}-O), 134.6 (C_{Ar}), 133.2 (C_{Ar}), 127.88 (2 × C_{Ar}), 127.85 (2 × C_{Ar}), 115.3 (2 × C_{Ar}), 114.9 (2 × C_{Ar}), 78.8 (<u>C</u>≡C-H), 75.7 (C≡<u>C</u>-H), 66.6 (OCH_2), 56.0 (O<u>C</u>H_2C≡C), 38.2 (CH_2), 25.2 (CH), 22.8 (2 × CH_3); IR (neat) ν_{max} 3279, 3043, 2955, 2923, 2869, 2132, 1603, 1568, 1497, 1467, 1377, 1327, 1270, 1238, 1176, 1055, 1028, 1018, 976, 822, 802, 709, 669, 603, 519 cm^{-1}; MS (EI) *m/z* 294 (M^+, 100%), 255 (84%), 157 (41%); HRMS (ESI +ve TOF) calcd for $C_{20}H_{23}O_2$ 295.1698, found 295.1688 ($[M + H]^+$).

Synthesis and characterization of key peptide fragments (17, 19 and 20)

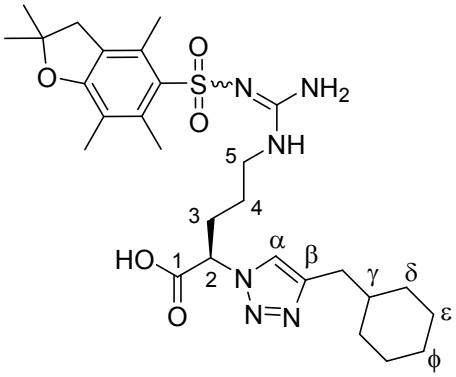
***Tert*-butyl (*R*)-(5-amino-6-azidohexyl)carbamate (17)[1]**



A reaction vessel charged with triphenylphosphine (843 mg, 3.21 mmol), iodine (815 mg, 3.21 mmol), imidazole (239 mg, 3.50 mmol) and CH_2Cl_2 (4.0 mL) was stirred at rt for 10 min followed by the addition a solution of alcohol **16**[1](1.33 g, 2.92 mmol) in CH_2Cl_2 (16.0 mL). The reaction was stirred at rt for 24 h, diluted with CH_2Cl_2 (20 mL) and filtered to remove the white precipitate. The filtrate was concentrated and the residue was subjected to flash chromatography over SiO_2 gel (EtOAc/Hexanes – 30:70) to give the intermediate iodide. The iodide intermediate was dissolved in DMF (15 mL) and NaN_3 (950 mg, 14.60 mmol) was added to the solution followed by vigorous stirring at rt for 18 h. After the azidation reaction was shown to be complete by TLC analysis (EtOAc/P.S. – 20:80), the reaction was heated to 50 °C for 18 h to remove the *N*-Fmoc protecting group.[2] The reaction mixture was cooled to rt, diluted with EtOAc (50 mL) and the solids were removed by vacuum filtration. The solids were rinsed with EtOAc (2 × 20 mL) and the combined EtOAc filtrate was washed with half-saturated aqueous $NaHCO_3$ (50 mL) and then brine (50 mL). The organic layer was placed in a conical flask with H_2O (80 mL) and stirred vigorously while 1.0 M aqueous HCl (3.0 mL, 3.0 mmol) was added to the biphasic mixture. The mixture was stirred for 5 min, the

aqueous phase was separated and the organic phase was extracted with H_2O (2 × 20mL). The combined aqueous phases were washed with Et_2O (2 × 100mL), basified with 15% w/w aqueous NaOH solution (pH ≥ 11) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with H_2O (1 × 150 mL), brine (1 × 100 mL), dried ($MgSO_4$), filtered and concentrated to afford the amine **17** (520 mg, 70% over two steps) as a translucent, colourless oil. The spectroscopic data was found to be in agreement with those previously reported.[1] TLC (MeOH/CH_2Cl_2 – 10:90): R_f = 0.13, (NEt_3/MeOH/CH_2Cl_2 – 2:10:88): R_f = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (br s, 1H, N^1-H), 3.35 (dd, J = 9.3, 4.7 Hz, 1H, $H6_A$ or $H6_B$), 3.18 – 3.04 (m, 3H, $H6_B$ or $H6_A$ and H1), 2.89 (br s, 1H, H5), 1.64 – 1.23 (m, 17H, H2, H3, H4, -$C(CH_3)_3$ and -NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0 (C=O), 78.9 (-$\underline{C}(CH_3)_3$), 58.2 (C6), 50.9 (C5), 40.2 (C1), 34.5 (C4), 30.0 (C2), 28.3 (-$C(\underline{C}H_3)_3$), 23.1 (C3); MS (ESI +ve) *m/z* 258 ($[M + H]^+$, 100%), 280 ($[M + Na]^+$, 10%).

(*R*)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-(2-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentanoic acid (19)

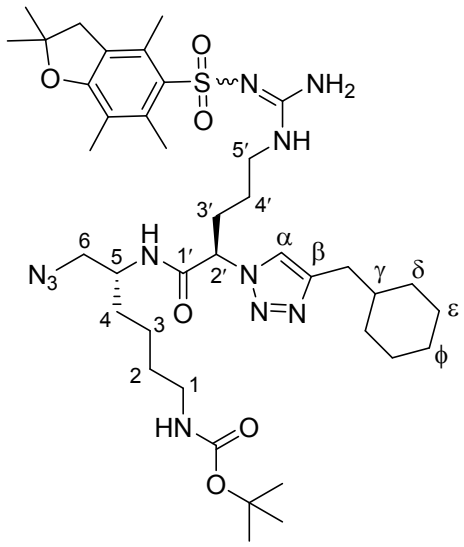


Following **General Procedure D**, azide **18**[3] (1.50 g, 3.32 mmol), 3-cyclohexyl-1-propyne (810 mg, 6.63 mmol), $Cu(OAc)_2{\cdot}H_2O$ (132 mg, 0.66 mmol) and sodium ascorbate (263 mg, 1.33 mmol) were stirred in *t*-BuOH (66 mL) and H_2O (17 mL) for 66 h to give the product triazole **19** (1.36 g, 71%) as a white foam after flash chromatography over SiO_2 gel (EtOAc/P.S. – 50:50 → 100:0). TLC (EtOAc): R_f = 0.59; $[\alpha]_D^{23}$ +1.8 (*c* 0.83, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 7.81 (br s, 1H, Hα), 5.19 (br s, 1H, H2), 3.17 (br s, 2H, H5), 2.99 (s, 2H, Pbf CH_2), 2.56 (br s, 5H, $C\underline{H_2}$Cy and Pbf CH_3), 2.50 (s, 3H, Pbf CH_3), 2.38 – 2.10 (m, 2H, H3), 2.07 (s, 3H, Pbf CH_3), 1.75 – 1.53 (m, 5H, Hγ, Hδ, Hε), 1.45 (s, 6H), 1.38 – 1.13 (m, 6H, H4, Hε, Hφ), 1.03 – 0.89 (m, 2H, Hδ); ^{13}C NMR (101 MHz, MeOD) δ 171.9 (C1)†, 160.0 (Pbf C_{Ar}-O), 158.3 (C=N), 147.9 (Cβ)†, 139.5 (Pbf C_{Ar}), 134.6 (Pbf C_{Ar}), 133.7 (Pbf C_{Ar}), 123.9 (Cα)†, 126.2 (Pbf C_{Ar}), 118.6 (Pbf C_{Ar}), 87.9 ($O\underline{C}(CH_3)_2$), 64.0 (C2)†, 44.2 (Pbf CH_2), 41.3 (C5), 39.6 (Cγ), 34.4 (C4), 34.32 (Cδ or CH_2Cy), 34.30 (CH2Cy or Cδ), 30.8 (C3), 28.9 ($O\underline{C}(CH_3)_2$), 27.7 (Cφ), 27.5 (Cε), 19.8 (Pbf CH_3), 18.6 (Pbf CH_3), 12.7 (Pbf CH_3); IR (neat) ν_{max} 3432, 3331, 3143, 3085, 2970, 2924, 2852, 2100, 1683, 1618, 1547, 1449, 1405, 1367, 1248, 1158, 1104, 1091, 993, 951, 852, 813, 783, 734, 660, 641, 619, 567, 506, 422 cm^{-1};

† These NMR resonances were often not observed in the ^{13}C NMR spectrum of concentrated samples of compound **19**. Furthermore, these resonances could not be observed by 2-D NMR correlation spectroscopy or the use of various NMR solvents ($CDCl_3$, CD_3OD and DMSO-d_6) for pure, concentrated samples. These missing resonances have been previously reported in our laboratory for similar 1,2,3-triazole-acetic acid derivatives, due to proposed intramolecular hydrogen bonding.[1] Interestingly, the missing ^{13}C NMR resonances were easily observed in the ^{13}C NMR spectra of dilute samples of compound **19** (see inset **A** on Figure S40) . The related ^{1}H NMR resonances for the triazole proton (CH) and the adjacent methine (CH) were found to be broadened for concentrated samples of compound **19** and were resolved/sharp for dilute samples of compound **19**.

MS (ESI −ve) m/z 573 ([M − H]$^-$, 100%); HRMS (ESI −ve TOF) calcd for $C_{28}H_{41}N_6O_5S$ 573.2859, found 573.2879 ([M − H]$^-$).

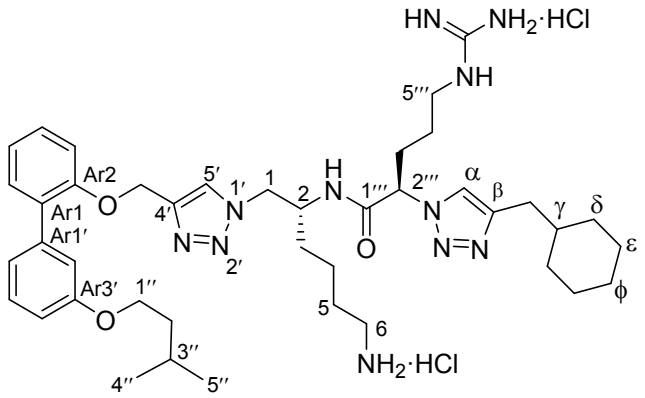
***Tert*-butyl ((*R*)-6-azido-5-((*R*)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-(2-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)pentanamido)hexyl)carbamate (20)**



Carboxylic acid **19** (700 mg, 1.22 mmol), amine **17** (329 mg, 1.28 mmol), EDCI (280 mg, 1.46 mmol) and HOBt (183 mg, 1.22 mmol) were combined in an acetonitrile solution (12 mL) and stirred at rt for 18 h. The solvent was removed and the residue was dissolved in EtOAc (150 mL). The organic solution was washed successively with aqueous HCl (1.0 M – 1 × 75 mL), saturated aqueous $NaHCO_3$ (3 × 75 mL) and brine (1 × 50 mL). The EtOAc solution was dried ($MgSO_4$), filtered, concentrated and the resultant residue was subjected to further purification *via* flash chromatography over SiO_2 gel (EtOAc/hexanes – 60:40 → 80:20) to furnish the target amide **20** (851 mg, 86%) as a white foam or colourless amorphous solid. TLC (EtOAc/hexanes – 80:20): R_f = 0.65; $[\alpha]_D^{23}$ −12.4 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (br s, 1H, N^5-), 7.70 (s, 1H, Hα), 6.38 (br s, 2H, NH_2), 6.15 (br s, 1H, $N^{5'}$-H), 5.67 (br s, 1H, H5), 4.65 (br s, 1H, N^1-), 4.04 – 3.98 (m, 1H, H2′), 3.53 – 3.30 (m, 3H, H6 and H5′$_A$), 3.13 (br s, 1H, H5′$_B$), 3.05 – 2.96 (m, 2H, H1), 2.96 (s, 2H, Pbf CH_2), 2.62 (s, 3H, Pbf CH_3), 2.59 – 2.52 (m, 5H, Pbf CH_3 and C$\underline{H_2}$Cy), 2.28 – 2.13 (m, 2H, H3′), 2.10 (s, 3H, Pbf CH_3), 1.82 – 1.05 (m, 32H, H2, H3, H4, H4′, $C(CH_3)_3$, $OC(CH_3)_2$, Hγ, Hδ, Hε, Hφ), 1.00 – 0.87 (m, 2H, Hδ); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0 (C1′), 159.0 (Pbf C_{Ar}-O), 156.8 (C=N), 156.2 (C=N), 147.1 (Cβ), 138.5 (Pbf C_{Ar}), 132.7 (Pbf C_{Ar}), 132.4 (Pbf C_{Ar}), 124.9 (Pbf C_{Ar}), 121.6 (Cα), 117.8 (Pbf C_{Ar}), 86.6 (O$\underline{C}(CH_3)_2$), 79.2 ($\underline{C}(CH_3)_3$), 62.7 (C2′), 54.4 (C6), 50.0 (C5), 43.4 (Pbf CH_2), 40.4 (C1), 39.1 (C5′), 38.0 (Cγ), 33.6 ($\underline{C}H_2$Cy), 33.2 (Cδ), 31.4 (C4), 30.1 (C3′), 29.7 (C2), 28.7 (Cφ), 28.5 (Cε), 26.5 (OC($\underline{C}H_3)_2$), 26.3 (C($\underline{C}H_3)_3$), 25.7 (C4′), 23.1 (C3), 19.5 (Pbf CH_3), 18.2 (Pbf CH_3), 12.6 (Pbf CH_3); IR (neat) ν_{max} 3431, 3325, 3145, 3077, 2972, 2924, 2852, 2098, 1678, 1618, 1546, 1448, 1391, 1366, 1247, 1165, 1106, 1091, 1045, 993, 895, 852, 806, 783, 734, 661, 641, 620, 567, 507 cm^{-1}; MS (ESI +ve) *m/z* 886 ([M + Na]$^+$, 100%), 814 ([M + H]$^+$, 62%); HRMS (ESI +ve TOF) calcd for $C_{39}H_{64}N_{11}O_6S$ 814.4762, found 814.4769 ([M + H]$^+$).

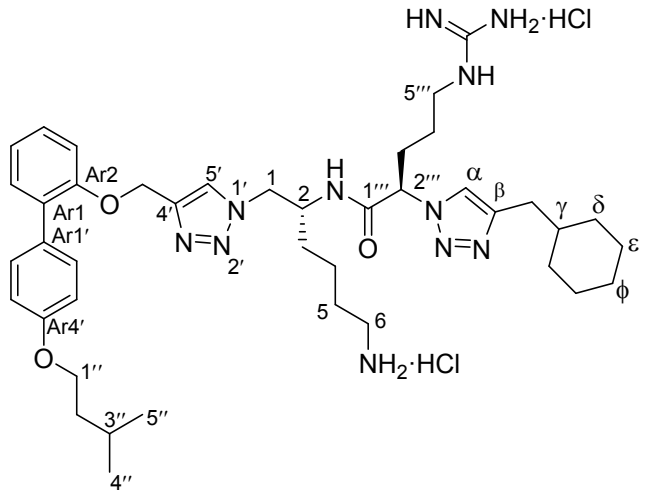
Synthesis of Final Compounds (2–9)

(*R*)-*N*-((*R*)-6-Amino-1-(4-(((3'-(isopentyloxy)-[1,1'-biphenyl]-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)hexan-2-yl)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-guanidinopentanamide dihydrochloride (2)



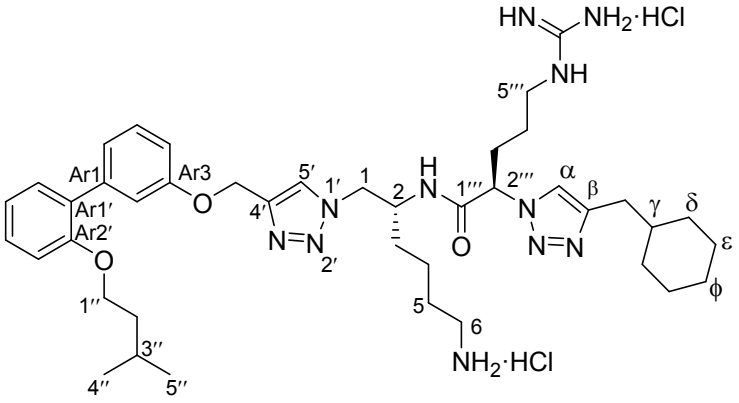
Following **General Procedure D**, azide **20** (50 mg, 0.06 mmol), alkyne **15a** (36 mg, 0.12 mmol), $Cu(OAc)_2 \cdot H_2O$ (2.5 mg, 0.012 mmol) and sodium ascorbate (5 mg, 0.024 mmol) were stirred in *t*-BuOH (1.2 mL) and H_2O (0.3 mL) for 18 h to give the intermediate triazole as a light tan gum after flash chromatography over SiO_2 gel (CH_2Cl_2 → EtOAc). Following **General Procedure E**, the triazole was dissolved in CH_2Cl_2 (1.8 mL) and stirred with H_2O (22 mg, 1.23 mmol) and CF_3CO_2H (1.8 mL) overnight, followed by work-up with ethereal HCl to give the amine salt **2** (31 mg, 61% over two steps) as a light tan powder that rapidly transitioned to a sticky gum. $[\alpha]_D^{23}$ −5.6 (*c* 0.83, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.05 (br s, 1H, H5′), 7.97 (br s, 1H, Hα), 7.37 – 7.30 (m, 2H, ArH), 7.30 – 7.21 (m, 2H, ArH), 7.09 – 6.99 (m, 3H, ArH), 6.84 (dd, *J* = 8.3, 2.4 Hz, 1H, ArH), 5.35 (br s, 1H, H2‴), 5.23 – 5.13 (m, 2H, C$\underline{H_2}$-C4′), 4.61 (d, *J* = 13.1 Hz, 1H, $H1_A$), 4.46 (m, 1H, $H1_B$), 4.32 (br s, 1H, H2), 3.98 (t, *J* = 6.7 Hz, 2H, H1″), 3.08 (br s, 2H, H5‴), 2.89 (br s, 2H, H6), 2.62 (d, *J* = 6.4 Hz, 2H, C$\underline{H_2}$Cy), 2.03 (br s, 1H, $H3'''_A$), 1.93 – 1.78 (m, 2H, $H3'''_B$ and H3″), 1.77 – 1.11 (m, 19H, H3, H4, H5, H2″, H4‴, Hγ, Hδ, Hε, Hφ), 1.04 – 0.89 (m, 2H, Hδ), 0.96 (d, *J* = 6.6 Hz, 6H, H4″ and H5″); ^{13}C NMR (126 MHz, CD_3OD) δ 169.4 (C1‴), 160.4 (C_{Ar}3′), 158.7 (C=N), 156.7 (C_{Ar}2), 146.6 (Cβ), 145.1 (C4′), 141.3 (C_{Ar}), 132.7 (C_{Ar}), 132.2 (C_{Ar}-H), 130.2 (C_{Ar}-H), 130.1 (C_{Ar}-H), 126.8 (C5′), 125.5 (Cα), 123.2 (C_{Ar}-H), 123.1 (C_{Ar}-H), 116.8 (C_{Ar}-H), 115.2 (C_{Ar}-H), 114.5 (C_{Ar}-H), 67.7 (C1″), 65.6 (C2‴), 63.2 (O$\underline{C}H_2$-C4′), 54.8 (C1), 51.5 (C2), 41.6 (C5‴), 40.7 (C6), 39.5 (C2″), 39.3 (Cγ), 34.1 (Cδ), 33.4 ($\underline{C}H_2$Cy), 32.3 (C3), 30.5 (C3‴), 28.3 (C5), 27.5 (Cφ), 27.3 (Cε), 26.4 (C3″), 26.0 (C4‴), 23.9 (C4), 23.25 (C4″ or C5″), 23.22 (C5″ or C4″); IR (neat) ν_{max} 3340, 3264, 3146, 3062, 2924, 2868, 2853, 1910, 1668, 1600, 1550, 1499, 1470, 1448, 1424, 1385, 1367, 1367, 1261, 1196, 1164, 1122, 1045, 1007, 857, 787, 752, 697, 581, 418 cm^{-1}; MS (ESI +ve) *m*/2 379 ($[M + 2H]^{2+}$, 100%), *m/z* 756 ($[M + H]^+$, 42%), 778 ($[M + Na]^+$, 25%); HRMS (ESI +ve TOF) calcd for $C_{41}H_{62}N_{11}O_3$ 756.5037, found 756.5045 ($[M + H]^+$).

(*R*)-*N*-((*R*)-6-Amino-1-(4-(((4'-(isopentyloxy)-[1,1'-biphenyl]-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)hexan-2-yl)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-guanidinopentanamide dihydrochloride (3)



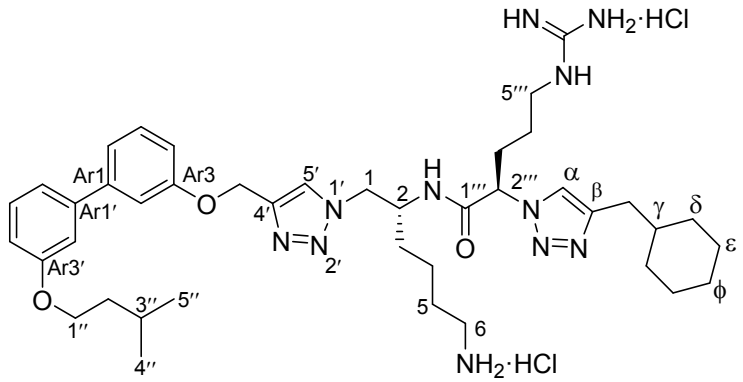
Following **General Procedure D**, azide **20** (50 mg, 0.06 mmol), alkyne **15b** (36 mg, 0.12 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.5 mg, 0.012 mmol) and sodium ascorbate (5 mg, 0.024 mmol) were stirred in *t*-BuOH (1.2 mL) and H_2O (0.3 mL) for 18 h to give the intermediate triazole as a light tan gum after flash chromatography over SiO_2 gel (CH_2Cl_2 → EtOAc). Following **General Procedure E**, the triazole was dissolved in CH_2Cl_2 (1.8 mL) and stirred with H_2O (22 mg, 1.23 mmol) and CF_3CO_2H (1.8 mL) overnight, followed by work-up with ethereal HCl to give the amine salt **3** (39 mg, 77% over two steps) as a light tan powder that rapidly transitioned to a sticky gum. $[\alpha]_D^{23}$ −8.1 (*c* 1.10, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.09 (br s, 1H, H5′), 7.96 (br s, 1H, Hα), 7.44 (d, *J* = 8.2 Hz, 2H, ArH), 7.34 – 7.18 (m, 3H, ArH), 7.04 (t, *J* = 7.3 Hz, 1H, ArH), 6.93 (d, *J* = 8.1 Hz, 2H, ArH), 5.34 (br s, 1H, H2‴), 5.17 (app. q, 2H, C$\underline{H_2}$-C4′), 4.62 (d, *J* = 13.0 Hz, 1H, $H1_A$), 4.52 – 4.43 (m, 1H, $H1_B$), 4.34 (br s, 1H, H2), 4.03 (t, *J* = 6.5 Hz, 2H, H1″), 3.06 (br s, 2H, H5‴), 2.89 (br s, 2H, H6), 2.61 (d, *J* = 6.3 Hz, 2H, C$\underline{H_2}$Cy), 2.01 (br s, 1H, $H3'''_A$), 1.91 – 1.11 (m, 21H, H3, H4, H5, H2″, H3″, $H3'''_B$, H4‴, Hγ, Hδ, Hε, Hφ), 1.02 – 0.89 (m, 2H, Hδ), 0.97 (d, *J* = 6.6 Hz, 6H, H4″ and H5″); ^{13}C NMR (126 MHz, CD_3OD) δ 169.4 (C1‴), 159.8 (C_{Ar}4′), 158.7 (C=N), 156.6 (C_{Ar}2), 146.5 (Cβ), 145.2 (C4′), 132.5 (C_{Ar}), 132.1 (C_{Ar}), 132.0 (C_{Ar}), 131.9 (C_{Ar} × 2), 129.5 (C_{Ar}), 126.8 (C5′), 125.5 (Cα), 123.1 (C_{Ar}), 115.3 (C_{Ar} × 2), 115.2 (C_{Ar}), 67.7 (C1″), 65.6 (C2‴), 63.1 (O$\underline{C}H_2$-C4′), 54.8 (C1), 51.5 (C2), 41.5 (C5‴), 40.7 (C6), 39.4 (C2″), 39.3 (Cγ), 34.1 (Cδ), 33.4 ($\underline{C}H_2$Cy), 32.4 (C3), 30.4 (C3‴), 28.2 (C5), 27.5 (Cφ), 27.3 (Cε), 26.5 (C3″), 26.0 (C4‴), 23.9 (C4), 23.21 (C4″ or C5″), 23.18 (C5″ or C4″); IR (neat) ν_{max} 3342, 3257, 3146, 3063, 2924, 2853, 2104, 1912, 1654, 1550, 1516, 1485, 1465, 1448, 1385, 1367, 1242, 1209, 1176, 1123, 1047, 1009, 999, 831, 853, 751, 565, 436, 579 cm^{-1}; MS (ESI +ve) *m*/2 379 ($[M + 2H]^{2+}$, 100%), *m/z* 756 ($[M + H]^+$, 41%), 778 ($[M + Na]^+$, 9%); HRMS (ESI +ve TOF) calcd for $C_{41}H_{62}N_{11}O_3$ 756.5037, found 756.5041 ($[M + H]^+$).

(*R*)-*N*-((*R*)-6-Amino-1-(4-(((2'-(isopentyloxy)-[1,1'-biphenyl]-3-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)hexan-2-yl)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-guanidinopentanamide dihydrochloride (4)



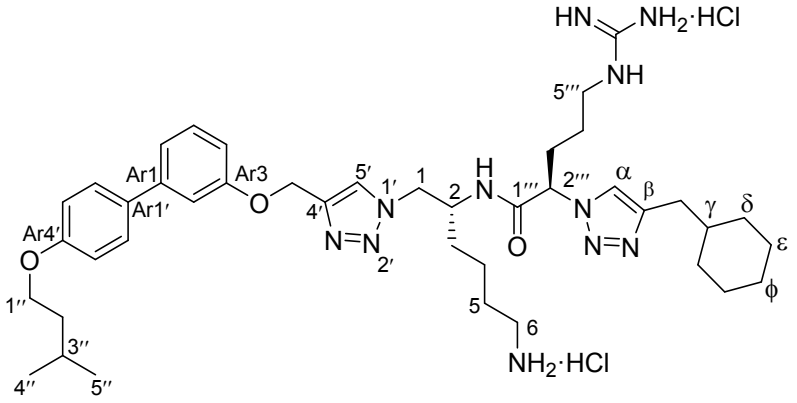
Following **General Procedure D**, azide **20** (50 mg, 0.06 mmol), alkyne **15c** (36 mg, 0.12 mmol), $Cu(OAc)_2 \cdot H_2O$ (2.5 mg, 0.012 mmol) and sodium ascorbate (5 mg, 0.024 mmol) were stirred in *t*-BuOH (1.2 mL) and H_2O (0.3 mL) for 18 h to give the intermediate triazole as a light tan gum after flash chromatography over SiO_2 gel (CH_2Cl_2 → EtOAc/hexanes (70:30) → EtOAc). Following **General Procedure E**, the triazole was dissolved in CH_2Cl_2 (1.8 mL) and stirred with H_2O (22 mg, 1.23 mmol) and CF_3CO_2H (1.8 mL) overnight, followed by work-up with ethereal HCl to give the amine salt **4** (40 mg, 79% over two steps) as a light tan powder that rapidly transitioned to a sticky gum. $[\alpha]_D^{23}$ −4.5 (*c* 1.03, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (s, 1H, H5′), 8.19 (s, 1H, Hα), 7.34 – 7.24 (m, 3H, ArH), 7.19 – 7.10 (m, 2H, ArH), 7.05 (d, *J* = 8.0 Hz, 1H, ArH), 7.02 – 6.93 (m, 2H, ArH), 5.48 (br s, 1H, H2‴), 5.23 (s, 2H, C$\underline{H_2}$-C4′), 4.68 (d, *J* = 13.2 Hz, 1H, $H1_A$), 4.53 (dd, *J* = 13.6, 8.6 Hz, 1H, $H1_B$), 4.36 (br s, 1H, H2), 3.99 (t, *J* = 6.4 Hz, 2H, H1″), 3.21 (br s, 2H, H5‴), 2.92 (br s, 2H, H6), 2.65 (d, *J* = 6.2 Hz, 2H, C$\underline{H_2}$Cy), 2.25 – 2.03 (m, 2H, H3‴), 1.82 – 1.10 (m, 20H, H3, H4, H5, H2″, H3″, H4‴, Hγ, Hδ, Hε, Hφ), 1.05 – 0.90 (m, 2H, Hδ), 0.89 (d, *J* = 6.7 Hz, 6H, H4″ and H5″); ^{13}C NMR (126 MHz, CD_3OD) δ 169.1 (C1‴), 159.5 (C_{Ar}3), 158.7 (C=N), 157.5 (C_{Ar}2′), 146.1 (Cβ), 145.2 (C4′), 142.0 (C_{Ar}), 132.0 (C_{Ar}), 131.8 (C_{Ar}), 130.2 (C_{Ar}), 130.1 (C_{Ar}), 126.8 (C5′), 126.5 (Cα), 124.2 (C_{Ar}), 122.1 (C_{Ar}), 117.5 (C_{Ar}), 114.4 (C_{Ar}), 114.2 (C_{Ar}), 68.2 (C1″), 66.1 (C2‴), 62.6 (O$\underline{C}H_2$-C4′), 54.9 (C1), 51.7 (C2), 41.7 (C5‴), 40.7 (C6), 39.4 (C2″), 39.1 (Cγ), 34.0 (Cδ), 33.0 ($\underline{C}H_2$Cy), 32.2 (C3), 30.4 (C3‴), 28.2 (C5), 27.4 (Cφ), 27.3 (Cε), 26.4 (C3″), 26.2 (C4‴), 23.9 (C4), 23.1 (C4″ and C5″); IR (neat) ν_{max} 3343, 3263, 3177, 3064, 2925, 2868, 2854, 2080, 1900, 1669, 1558, 1469, 1449, 1424, 1190, 1045, 1011, 864, 786, 742, 696, 581, 438 cm^{-1}; MS (ESI +ve) *m*/2 379 ($[M + 2H]^{2+}$, 100%), *m/z* 756 ($[M + H]^+$, 52%), 778 ($[M + Na]^+$, 11%); HRMS (ESI +ve TOF) calcd for $C_{41}H_{62}N_{11}O_3$ 756.5037, found 756.5046 ($[M + H]^+$).

(*R*)-*N*-((*R*)-6-Amino-1-(4-(((3'-(isopentyloxy)-[1,1'-biphenyl]-3-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)hexan-2-yl)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-guanidinopentanamide dihydrochloride (5)



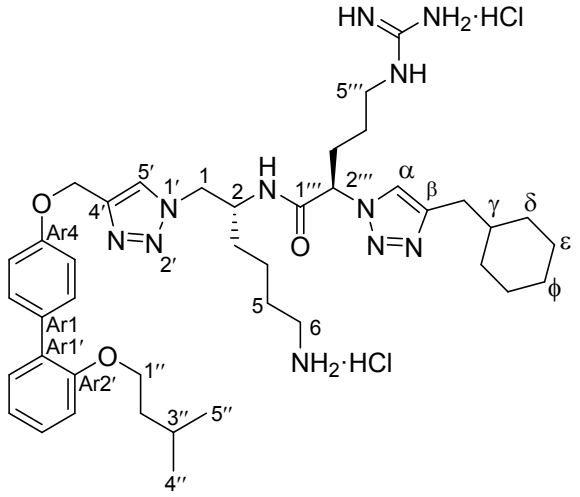
Following **General Procedure D**, azide **20** (50 mg, 0.06 mmol), alkyne **15d** (36 mg, 0.12 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.5 mg, 0.012 mmol) and sodium ascorbate (5 mg, 0.024 mmol) were stirred in *t*-BuOH (1.2 mL) and H_2O (0.3 mL) for 18 h to give the intermediate triazole as a light tan gum after flash chromatography over SiO_2 gel (CH_2Cl_2 → EtOAc/hexanes (70:30) → EtOAc). Following **General Procedure E**, the triazole was dissolved in CH_2Cl_2 (1.8 mL) and stirred with H_2O (22 mg, 1.23 mmol) and CF_3CO_2H (1.8 mL) overnight, followed by work-up with ethereal HCl to give the amine salt **5** (44 mg, 86% over two steps) as a light tan powder that rapidly transitioned to a sticky gum. $[\alpha]_D^{23}$ −5.6 (*c* 1.20, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.25 (s, 1H, H5′), 8.13 (s, 1H, Hα), 7.37 (t, *J* = 7.9 Hz, 1H, ArH), 7.33 (t, *J* = 7.9 Hz, 1H, ArH), 7.26 (s, 1H, ArH), 7.23 (d, *J* = 7.0 Hz, 1H, ArH), 7.17 (d, *J* = 7.5 Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.03 (dd, *J* = 8.1, 2.3 Hz, 1H, ArH), 6.90 (dd, *J* = 8.2, 2.4 Hz, 1H, ArH), 5.47 (br s, 1H, H2‴), 5.28 (s, 2H, C$\underline{H_2}$-C4′), 4.68 (d, *J* = 13.3 Hz, 1H, $H1_A$), 4.53 (dd, *J* = 13.7, 8.9 Hz, 1H, $H1_B$), 4.36 (br s, 1H, H2), 4.06 (t, *J* = 6.5 Hz, 2H, H1″), 3.21 (br t, *J* = 6.5 Hz, 2H, H5‴), 2.92 (br t, *J* = 7.3 Hz, 2H, H6), 2.63 (d, *J* = 6.5 Hz, 2H, C$\underline{H_2}$Cy), 2.17 (br s, 1H, $H3'''_A$), 2.05 (br s, 1H, $H3'''_B$), 1.86 (m, 1H, H3″), 1.79 – 1.08 (m, 19H, H3, H4, H5, H2″, H4‴, Hγ, Hδ, Hε, Hφ), 1.02 – 0.88 (m, 2H, Hδ)**,** 0.98 (d, *J* = 6.6 Hz, 6H, H4″ and H5″); ^{13}C NMR (126 MHz, CD_3OD) δ 169.1 (C1‴), 161.2 (C_{Ar}3′), 160.3 (C_{Ar}3), 158.7 (C=N), 146.0 (Cβ), 145.1 (C4′), 144.2 (C_{Ar}), 143.7 (C_{Ar}), 131.3 (C_{Ar}), 131.1 (C_{Ar}), 126.9 (C5′), 126.4 (Cα), 121.4 (C_{Ar}), 120.6 (C_{Ar}), 115.1 (C_{Ar}), 114.9 (C_{Ar}), 114.7 (C_{Ar}), 114.6 (C_{Ar}), 67.7 (C1″), 66.1 (C2‴), 62.6 (O$\underline{C}H_2$-C4′), 54.9 (C1), 51.7 (C2), 41.6 (C5‴), 40.7 (C6), 39.5 (C2″), 39.1 (Cγ), 34.0 (Cδ), 32.9 ($\underline{C}H_2$Cy), 32.2 (C3), 30.4 (C3‴), 28.2 (C5), 27.4 (Cφ), 27.2 (Cε), 26.4 (C3″), 26.1 (C4‴), 23.9 (C4), 23.2 (C4″ and C5″); IR (neat) ν_{max} 3335, 3259, 3145, 3062, 2924, 2868, 2853, 2089, 1919, 1668, 1597, 1573, 1469, 1449, 1385, 1367, 1217, 1183, 1168, 1046, 1014, 851, 774, 736, 694, 580, 438 cm^{-1}; MS (ESI +ve) *m*/2 379 ($[M + 2H]^{2+}$, 100%), *m/z* 756 ($[M + H]^+$, 39%), 778 ($[M + Na]^+$, 4%); HRMS (ESI +ve TOF) calcd for $C_{41}H_{62}N_{11}O_3$ 756.5037, found 756.5027 ($[M + H]^+$).

(*R*)-*N*-((*R*)-6-Amino-1-(4-(((4'-(isopentyloxy)-[1,1'-biphenyl]-3-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)hexan-2-yl)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-guanidinopentanamide dihydrochloride (6)



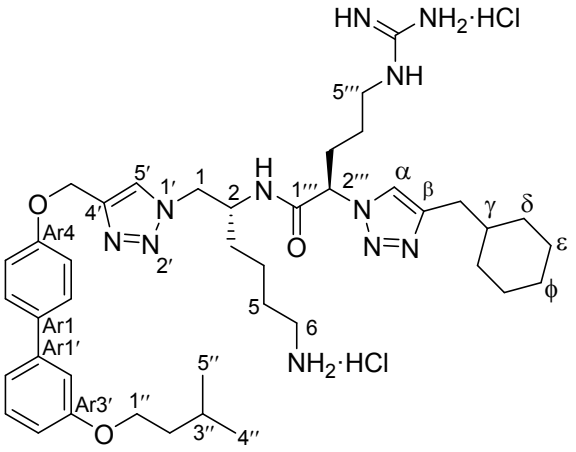
Following **General Procedure D**, azide **20** (50 mg, 0.06 mmol), alkyne **15e** (36 mg, 0.12 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.5 mg, 0.012 mmol) and sodium ascorbate (5 mg, 0.024 mmol) were stirred in *t*-BuOH (1.2 mL) and H_2O (0.3 mL) for 18 h to give the intermediate triazole as a light tan gum after flash chromatography over SiO_2 gel (CH_2Cl_2 → EtOAc). Following **General Procedure E**, the triazole was dissolved in CH_2Cl_2 (1.8 mL) and stirred with H_2O (22 mg, 1.23 mmol) and CF_3CO_2H (1.8 mL) overnight, followed by work-up with ethereal HCl to give the amine salt **6** (42 mg, 82% over two steps) as a light tan powder that rapidly transitioned to a sticky gum. $[\alpha]_D^{23}$ −4.8 (*c* 1.13, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H, H5′), 8.11 (s, 1H, Hα), 7.54 (d, *J* = 8.7 Hz, 2H, ArH), 7.34 (t, *J* = 7.9 Hz, 1H, ArH), 7.25 – 7.16 (m, 2H, ArH), 7.02 – 6.93 (m, 3H, ArH), 5.46 (dd, *J* = 9.4, 5.6 Hz, 1H, H2‴), 5.27 (s, 2H, C$\underline{H_2}$-C4′), 4.68 (dd, *J* = 13.8, 3.7 Hz, 1H, $H1_A$), 4.53 (dd, *J* = 13.8, 9.2 Hz, 1H, $H1_B$), 4.37 (br s, 1H, H2), 4.04 (t, *J* = 6.5 Hz, 2H, H1″), 3.20 (t, *J* = 6.7 Hz, 2H, H5‴), 2.92 (t, *J* = 7.3 Hz, 2H, H6), 2.62 (d, *J* = 6.6 Hz, 2H, C$\underline{H_2}$Cy), 2.22 – 2.10 (m, 1H, $H3'''_A$), 2.10 – 1.98 (m, 1H, $H3'''_B$), 1.91 – 1.80 (m, 1H, H3″), 1.80 – 1.09 (m, 19H, H3, H4, H5, H2″, H4‴, Hγ, Hδ, Hε, Hφ), 0.99 – 0.87 (m, 2H, Hδ), 0.98 (d, *J* = 6.6 Hz, 6H, H4″ and H5″); ^{13}C NMR (101 MHz, CD_3OD) δ 169.2 (C1‴), 160.6 (C_{Ar}4′), 160.3 (C_{Ar}3), 158.7 (C=N), 146.1 (Cβ), 145.1 (C4′), 144.0 (C_{Ar}), 134.4 (C_{Ar}), 131.2 (C_{Ar}), 129.3 (C_{Ar} × 2), 126.8 (C5′), 126.3 (Cα), 120.9 (C_{Ar}), 116.1 (C_{Ar} × 2), 114.4 (C_{Ar}), 114.3 (C_{Ar}), 67.7 (C1″), 66.0 (C2‴, 62.5 (O$\underline{C}H_2$-C4′), 54.9 (C1), 51.7 (C2), 41.6 (C5‴), 40.7 (C6), 39.4 (C2″), 39.1 (Cγ), 34.0 (Cδ), 33.0 ($\underline{C}H_2$Cy), 32.2 (C3), 30.4 (C3‴), 28.2 (C5), 27.4 (Cφ), 27.3 (Cε), 26.5 (C3″), 26.1 (C4‴), 23.9 (C4), 23.2 (C4″ and C5″); IR (neat) ν_{max} 3336, 3262, 3171, 3145, 3064, 2924, 2868, 2853, 2080, 1894, 1668, 1608, 1568, 1517, 1473, 1448, 1385, 1367, 1245, 1179, 1115, 1040, 1005, 873, 830, 782, 733, 694, 579, 536, 450 cm^{-1}; MS (ESI +ve) *m*/2 379 ($[M + 2H]^{2+}$, 100%), *m/z* 756 ($[M + H]^+$, 27%); HRMS (ESI +ve TOF) calcd for $C_{41}H_{62}N_{11}O_3$ 756.5037, found 756.5045 ($[M + H]^+$).

(*R*)-*N*-((*R*)-6-Amino-1-(4-(((2'-(isopentyloxy)-[1,1'-biphenyl]-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)hexan-2-yl)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-guanidinopentanamide dihydrochloride (7)



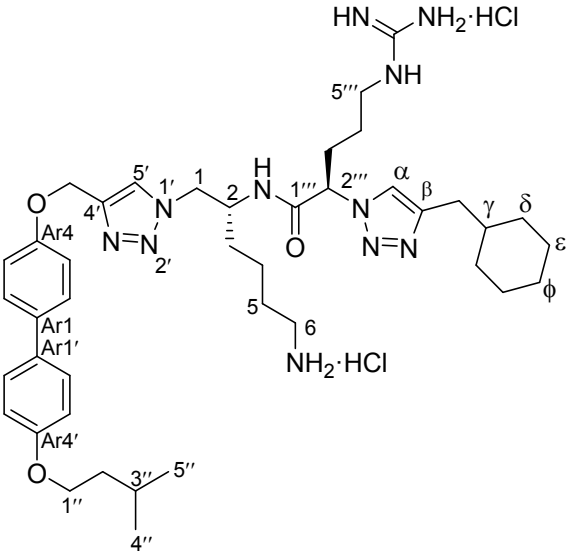
Following **General Procedure D**, azide **20** (50 mg, 0.06 mmol), alkyne **15f** (36 mg, 0.12 mmol), $Cu(OAc)_2 \cdot H_2O$ (2.5 mg, 0.012 mmol) and sodium ascorbate (5 mg, 0.024 mmol) were stirred in *t*-BuOH (1.2 mL) and H_2O (0.3 mL) for 18 h to give the intermediate triazole as a light tan gum after flash chromatography over SiO_2 gel (CH_2Cl_2 → EtOAc/hexanes (70:30) → EtOAc). Following **General Procedure E**, the triazole was dissolved in CH_2Cl_2 (1.8 mL) and stirred with H_2O (22 mg, 1.23 mmol) and CF_3CO_2H (1.8 mL) overnight, followed by work-up with ethereal HCl to give the amine salt **7** (42 mg, 82% over two steps) as a light tan powder that rapidly transitioned to a sticky gum. $[\alpha]_D^{23}$ −6.2 (*c* 1.10, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.26 (s, 1H, H5′), 8.16 (br s, 1H, Hα), 7.47 (d, *J* = 8.6 Hz, 2H, ArH), 7.28 – 7.22 (m, 2H, ArH), 7.08 – 7.00 (m, 3H, ArH), 6.97 (td, *J* = 7.4, 1.1 Hz, 1H, ArH), 5.50 – 5.44 (m, 1H, H2‴), 5.24 (s, 2H, C$\underline{H_2}$-C4′), 4.69 (dd, *J* = 13.9, 3.8 Hz, 1H, $H1_A$), 4.54 (dd, *J* = 13.9, 9.1 Hz, 1H, $H1_B$), 4.41 – 4.32 (m, 1H, H2), 3.98 (t, *J* = 6.5 Hz, 2H, H1″), 3.22 (t, *J* = 6.7 Hz, 2H, H5‴), 2.92 (t, *J* = 7.0 Hz, 2H, H6), 2.62 (d, *J* = 6.7 Hz, 2H, C$\underline{H_2}$Cy), 2.21 – 2.12 (m, 1H, $H3'''_A$), 2.12 – 2.03 (m, 1H, , $H3'''_B$), 1.80 – 1.12 (m, 20H, H3, H4, H5, H2″, H3″, H4‴, Hγ, Hδ, Hε, Hφ), 1.02 – 0.91 (m, 2H, Hδ), 0.89 (d, *J* = 6.6 Hz, 6H, H4″ and H5″); ^{13}C NMR (126 MHz, CD_3OD) δ 169.2 (C1‴), 158.81 (C=N), 158.76 (C_{Ar}2′), 157.5 (C_{Ar}4), 146.2 (Cβ), 145.1 (C4′), 133.5 (C_{Ar}), 132.0 (C_{Ar} × 2), 131.8 (C_{Ar}), 131.6 (C_{Ar}), 129.6 (C_{Ar}), 126.8 (C5′), 126.2 (Cα), 122.1 (C_{Ar}), 115.5 (C_{Ar} × 2), 114.1 (C_{Ar}), 68.1 (C1″), 66.0 (C2‴), 62.5 (O$\underline{C}H_2$-C4′), 54.9 (C1), 51.6 (C2), 41.7 (C5‴), 40.6 (C6), 39.4 (C2″), 39.2 (Cγ), 34.03/34.01 (Cδ), 33.0 ($\underline{C}H_2$Cy), 32.2 (C3), 30.4 (C3‴), 28.2 (C5), 27.5 (Cφ), 27.3 (Cε), 26.4 (C3″), 26.1 (C4‴), 23.9 (C4), 23.1 (C4″ and C5″); IR (neat) ν_{max} 3341, 3267, 3190, 3067, 2925, 2868, 2854, 2086, 1896, 1669, 1629, 1552, 1515, 1487, 1466, 1448, 1385, 1367, 1217, 1179, 1023, 855, 831, 748, 580, 439 cm^{-1}; MS (ESI +ve) *m*/2 379 ($[M + 2H]^{2+}$, 100%), *m/z* 756 ($[M + H]^+$, 55%), 778 ($[M + Na]^+$, 10%); HRMS (ESI +ve TOF) calcd for $C_{41}H_{62}N_{11}O_3$ 756.5037, found 756.5023 ($[M + H]^+$).

(*R*)-*N*-((*R*)-6-Amino-1-(4-(((3'-(isopentyloxy)-[1,1'-biphenyl]-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)hexan-2-yl)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-guanidinopentanamide dihydrochloride (8)



Following **General Procedure D**, azide **20** (50 mg, 0.06 mmol), alkyne **15g** (36 mg, 0.12 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.5 mg, 0.012 mmol) and sodium ascorbate (5 mg, 0.024 mmol) were stirred in *t*-BuOH (1.2 mL) and H_2O (0.3 mL) for 18 h to give the intermediate triazole as a light tan gum after flash chromatography over SiO_2 gel (CH_2Cl_2 → EtOAc). Following **General Procedure E**, the triazole was dissolved in CH_2Cl_2 (1.8 mL) and stirred with H_2O (22 mg, 1.23 mmol) and CF_3CO_2H (1.8 mL) overnight, followed by work-up with ethereal HCl to give the amine salt **8** (40 mg, 79% over two steps) as a light tan powder that rapidly transitioned to a sticky gum. $[\alpha]_D^{23}$ −5.7 (*c* 0.53, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 8.21 (s, 1H, H5′), 7.76 (s, 1H, Hα), 7.55 (d, *J* = 7.6 Hz, 2H, ArH), 7.29 (t, *J* = 7.8 Hz, 1H, ArH), 7.14 – 7.03 (m, 4H, ArH), 6.84 (dd, *J* = 8.2, 2.2 Hz, 1H, ArH), 5.28 (br s, 1H, H2‴), 5.23 (s, 2H, C$\underline{H_2}$-C4′), 4.64 (br s, 1H, $H1_A$), 4.49 (br s, 1H, $H1_B$), 4.36 (br s, 1H, H2), 4.03 (t, *J* = 6.5 Hz, 2H, H1″), 3.15 (br s, 2H, H5‴), 2.87 (br s, 2H, H6), 2.49 (d, *J* = 6.4 Hz, 2H, C$\underline{H_2}$Cy), 2.06 – 1.96 (m, 1H, $H3'''_A$), 1.93 – 1.80 (m, 2H, $H3'''_B$ and H3″), 1.76 – 1.09 (m, 19H, H3, H4, H5, H2″, H4‴, Hγ, Hδ, Hε, Hφ), 0.97 (d, *J* = 6.6 Hz, 6H, H4″ and H5″), 0.95 – 0.85 (m, 2H, Hδ); ^{13}C NMR (126 MHz, CD_3OD) δ 169.9 (C1‴), 161.2 (C_{Ar}3′), 159.5 (C_{Ar}4), 158.7 (C=N), 147.4 (Cβ), 145.4 (C4′), 143.4 (C_{Ar}), 135.6 (C_{Ar}), 131.0 (C_{Ar}), 129.3 (C_{Ar} × 2), 126.7 (C5′), 124.3 (Cα), 120.1 (C_{Ar}), 116.5 (C_{Ar} × 2), 114.1 (C_{Ar}), 113.8 (C_{Ar}), 67.6 (C1″), 64.9 (C2‴), 62.5 (O$\underline{C}H_2$-C4′), 54.9 (C1), 51.3 (C2), 41.7 (C5‴), 40.7 (C6), 39.43 (C2″), 39.37 (Cγ), 34.1 (Cδ), 33.8 ($\underline{C}H_2$Cy), 32.4 (C3), 30.5 (C3‴), 28.2 (C5), 27.5 (Cφ), 27.3 (Cε), 26.4 (C3″), 26.1 (C4‴), 23.8 (C4), 23.1 (C4″ and C5″); IR (neat) ν_{max} 3340, 3259, 3171, 3065, 2924, 2869, 2853, 2104, 1894, 1667, 1608, 1570, 1550, 1516, 1466, 1447, 1385, 1367, 1295, 1204, 1181, 1115, 1048, 1006, 859, 830, 780, 726, 694, 582, 534, 450 cm^{-1}; MS (ESI +ve) *m*/2 379 ($[M + 2H]^{2+}$, 100%), *m/z* 756 ($[M + H]^+$, 44%), 778 ($[M + Na]^+$, 17%); HRMS (ESI +ve TOF) calcd for $C_{41}H_{62}N_{11}O_3$ 756.5037, found 756.5046 ($[M + H]^+$).

(*R*)-*N*-((*R*)-6-Amino-1-(4-(((4'-(isopentyloxy)-[1,1'-biphenyl]-4-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)hexan-2-yl)-2-(4-(cyclohexylmethyl)-1*H*-1,2,3-triazol-1-yl)-5-guanidinopentanamide dihydrochloride (9)



Following **General Procedure D**, azide **20** (50 mg, 0.06 mmol), alkyne **15h** (36 mg, 0.12 mmol), $Cu(OAc)_2 \cdot H_2O$ (2.5 mg, 0.012 mmol) and sodium ascorbate (5 mg, 0.024 mmol) were stirred in *t*-BuOH (1.2 mL) and H_2O (0.3 mL) for 18 h to give the intermediate triazole as a light tan gum after flash chromatography over SiO_2 gel (CH_2Cl_2 → EtOAc). Following **General Procedure E**, the triazole was dissolved in CH_2Cl_2 (1.8 mL) and stirred with H_2O (22 mg, 1.23 mmol) and CF_3CO_2H (1.8 mL) overnight, followed by work-up with ethereal HCl to give the amine salt **9** (28 mg, 55% over two steps) as a light tan powder that rapidly transitioned to a sticky gum. $[\alpha]_D^{23}$ −4.2 (*c* 0.53, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H, H5′), 7.84 (s, 1H, Hα), 7.52 (d, *J* = 8.6 Hz, 2H, ArH), 7.48 (d, *J* = 8.8 Hz, 2H, ArH), 7.08 (d, *J* = 8.7 Hz, 2H, ArH), 6.96 (d, *J* = 8.8 Hz, 2H, ArH), 5.33 (dd, *J* = 9.2, 5.9 Hz, 1H, H2‴), 5.24 (s, 2H, C$\underline{H_2}$-C4′), 4.66 (dd, *J* = 13.9, 3.8 Hz, 1H, $H1_A$), 4.51 (dd, *J* = 13.8, 9.4 Hz, 1H, $H1_B$), 4.37 (s, 1H, H2), 4.03 (t, *J* = 6.6 Hz, 2H, H1″), 3.17 (t, *J* = 6.7 Hz, 2H, H5‴), 2.89 (t, *J* = 7.5 Hz, 2H, H6), 2.52 (d, *J* = 6.8 Hz, 2H, C$\underline{H_2}$Cy), 2.10 – 1.98 (m, 1H, $H3'''_A$), 1.97 – 1.80 (m, 2H, $H3'''_B$ and H3″), 1.77 – 1.09 (m, 19H, H3, H4, H5, H2″, H4‴, Hγ, Hδ, Hε, Hφ), 0.99 (d, *J* = 6.6 Hz, 6H, H4″ and H5″), 0.97 – 0.86 (m, 2H, Hδ); ^{13}C NMR (101 MHz, CD_3OD) δ 169.8 (C1‴), 160.0 (C_{Ar}4′), 158.9 (C_{Ar}4), 158.8 (C=N), 147.3 (Cβ – observed by gHMBC), 145.4 (C4′ – observed by gHMBC), 135.6 (C_{Ar}), 134.4 (C_{Ar}), 128.8 (C_{Ar} × 2), 128.7 (C_{Ar} × 2), 126.7 (C5′), 124.6 (Cα), 116.5 (C_{Ar} × 2), 116.1 (C_{Ar} × 2), 67.7 (C1″), 65.1 (C2‴), 62.6 (O$\underline{C}H_2$-C4′), 54.8 (C1), 51.4 (C2), 41.7 (C5‴), 40.7 (C6), 39.5 (C2″), 39.3 (Cγ), 34.1 (Cδ), 33.6 ($\underline{C}H_2$Cy), 32.4 (C3), 30.5 (C3‴), 28.2 (C5), 27.6 (Cφ), 27.4 (Cε), 26.5 (C3″), 26.1 (C4‴), 23.9 (C4), 23.2 (C4″ and C5″); IR (neat) ν_{max} 3341, 3261, 3155, 3064, 2923, 2952, 2868, 2852, 2096, 1655, 1667, 1607, 1548, 1498, 1465, 1385, 1367, 1313, 1237, 1219, 1173, 1112, 1038, 1007, 997, 846, 735, 579, 520, 414 cm^{-1}; MS (ESI +ve) *m*/2 379 ($[M + 2H]^{2+}$, 100%), *m/z* 756 ($[M + H]^+$, 31%), 778 ($[M + Na]^+$, 17%); HRMS (ESI +ve TOF) calcd for $C_{41}H_{62}N_{11}O_3$ 756.5037, found 756.5039 ($[M + H]^+$).

Experimental procedures for microbiology assays

A. Preliminary antimicrobial growth inhibition assays – MIC determination

Primary microbial growth inhibition assays were performed as described by the Clinical and Laboratory Standards Institute for aerobic[4] and anaerobic[5] bacteria. *S. aureus* (ATCC 29213, NCTC 10442 [MRSA] and Mu50 [VISA]), *E. faecalis* (ATCC 29212 and ATCC 51299) and *E. coli* (NCTC 10418) were tested in Mueller Hinton broth (MHB) and incubation was performed in ambient air at 35 °C for 24 h. *S. pneumoniae* (ATCC 49619) was cultivated in MHB with 2.5% lysed horse blood and incubated with 5% CO_2 at 35 °C for 24 h. MIC studies for *C. difficile* strains ATCC 700057 and NSW132 (RT027) were conducted in pre-reduced (2-4 h) Brucella broth supplemented with haemin and vitamin K and incubation was performed anaerobically at 35 °C in a Don Whitley Scientific anaerobic chamber (A35) for 48 h. Each compound was dissolved in DMSO at 5 mg/mL and then diluted to 512 μg/mL with sterile, distilled water. The compounds were then serially diluted in 100 μL volumes of sterile, distilled water in a 96-well microtitre tray. Each test organism in double strength broth (100 μL) was then added to each well and incubated as described above. Final testing concentrations of the compounds ranged from 1 μg/mL to 128 μg/mL. Vancomycin and a control well (i.e. no antibacterial compound present) were included in the assays. A DMSO control (5% v/v) was also tested to ensure that the solvent did not inhibit bacterial growth. The assay was performed in triplicate for each organism/compound combination and the modal MIC values were recorded. The MIC was determined visually as the lowest concentration that inhibited bacterial growth. Concentrations of ≤5% DMSO were not inhibitory to growth. MIC values for vancomycin were within acceptable QC ranges.[6]

B. Secondary antimicrobial screening, cytotoxicity and hemolysis assays – performed by the Community for Open Antimicrobial Drug Discovery (CO-ADD)

Samples were provided to CO-ADD[7] for antimicrobial screening by whole cell growth inhibition assays (i.e. MIC determination). The inhibition of growth was measured against five bacteria: *E. coli (*ATCC 25922), *K. pneumoniae* (ATCC 700603), *A. baumannii* (ATCC 19606), *P. aeruginosa* (ATCC 27853) and *S. aureus* (ATCC 43300). In addition to the MIC assay, compounds were screened for cytotoxic growth inhibition against a human embryonic kidney cell line (HEK293 – ATCC CRL-1773) by determining their CC_{50} value. Compounds were also screened for hemolytic activity against human red blood cells. Samples were prepared in DMSO to a final testing concentration of 32 μg/mL and serially diluted 1:2 fold for 8 times. Each sample concentration was prepared in 384-well plates; non-binding surface (NBS) plates (Corning 3640) for each bacterial strain and black plates (Corning 3712/3764) for mammalian cell types, all in duplicate (n = 2) and keeping the final DMSO concentration to a maximum of 0.5%. All sample preparation was done using liquid handling robots.

Bacterial growth inhibition assays – MIC determination

All bacteria were cultured in Cation-adjusted MHB at 37 °C overnight. A sample of each culture was then diluted 40-fold in fresh broth and incubated at 37 °C for 1 – 3.5 h. The resultant mid-log phase cultures were diluted (CFU/mL measured by OD_{600}), then added to each well of the compound-containing plates, giving a cell density of 5×10^5 CFU/mL and a total volume

of 50 μL. All plates were covered and incubated at 37 °C for 18 h without shaking. Inhibition of bacterial growth was determined by measuring absorbance at 600 nm (OD_{600}), using a Tecan M1000 Pro monochromator plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (bacteria without inhibitors) on the same plate as references. The MIC was determined as the lowest concentration at which growth was fully inhibited, defined by an inhibition ≥80%. Colistin and vancomycin were used as positive bacterial inhibitor standards for Gram-negative and Gram-positive bacteria, respectively. Each antibiotic standard was provided in four concentrations, with two above and two below its MIC value, and plated into the first eight wells of column 23 of the 384-well NBS plates.

Fungal growth inhibition assays – MIC determination

Fungi strains were cultured for 3 days on Yeast Extract-Peptone Dextrose (YPD) agar at 30 °C. A yeast suspension of 1 × 106 to 5 × 106 CFU/mL (as determined by OD530) was prepared from five colonies. The suspension was subsequently diluted and added to each well of the compound-containing plates giving a final cell density of fungi suspension of 2.5×10^3 CFU/mL and a total volume of 50 μL. All plates were covered and incubated at 35 °C for 36 h without shaking. Growth inhibition of *C. albicans* was determined measuring absorbance at 630 nm (OD630), while the growth inhibition of C. neoformans was determined measuring the difference in absorbance between 600 and 570 nm (OD600-570), after the addition of resazurin (0.001% final concentration) and incubation at 35 °C for 2 h. The absorbance was measured using a Biotek Multiflo Synergy HTX plate reader. In both cases, the percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (fungi without inhibitors) on the same plate. The MIC was determined as the lowest concentration at which the growth was fully inhibited, defined by an inhibition ≥ 80% for C. albicans and an inhibition ≥ 70% for C. neoformans. Due to a higher variance in growth and inhibition, a lower threshold was applied to the data for C. neoformans. In addition, the maximal percentage of growth inhibition is reported as DMax, indicating any compounds with marginal activity.

Cytotoxicity assay – CC_{50} determination

HEK293 cells were counted manually in a Neubauer haemocytometer and then plated in the 384-well plates containing the compounds to give a density of 5000 cells/well in a final volume of 50 μL. Dulbecco's modified eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS) was used as a growth media and the cells were incubated together with the compounds for 20 h at 37 °C in 5% CO_2. Cytotoxicity (cell viability) was measured by fluorescence (ex: 560/10 nm, em: 590/10 nm), after addition of 5 μL of 25 μg/mL resazurin (2.3 μg/mL final concentration) and after incubation for further 3 h at 37 °C in 5% CO_2. The fluorescence intensity was measured using a Tecan M1000 Pro monochromator plate reader, using automatic gain calculation. CC_{50} (concentration at 50% cytotoxicity) values were calculated by curve-fitting the inhibition values vs. log(concentration) using a sigmoidal dose-response function, with variable fitting values for bottom, top and slope. Tamoxifen was utilized as a positive cytotoxicity standard; it was used in eight concentrations in two-fold serial dilutions with 50 μg/mL as the highest concentration tested.

Hemolysis assay (human erythrocytes) – HC_{50} determination

Human whole blood was washed three times with 3 volumes of 0.9% NaCl (saline) and then resuspended in saline to a concentration of 0.5 x 108 cells/mL, as determined by manual cell count in a Neubauer haemocytometer. The washed cells were then added to the 384-well compound-containing plates for a final volume of 50 µL. After a 10 min shake on a plate shaker, the plates were then incubated for 1 h at 37 °C. After incubation, the plates were centrifuged at 1000g for 10 min to pellet cells and debris; 25 µL of the supernatant was then transferred to a polystyrene 384-well assay plate. Hemolysis was determined by measuring the supernatant absorbance at 405 mm (OD405). The absorbance was measured using a Tecan M1000 Pro monochromator plate reader. HC_{50} (concentration at 50% hemolysis) was calculated by curve fitting the inhibition values vs. log(concentration) using a sigmoidal dose-response function with variable fitting values for top, bottom and slope. In addition, the maximal percentage of haemolysis is reported as DMax, indicating any compounds with partial haemolysis. The curve fitting was implemented using Pipeline Pilot's dose-response component, resulting in similar values to curve fitting tools such as GraphPad's Prism and IDBS's XlFit. Any value with > indicates a sample with no activity (low DMax value) or samples with HC_{50} values above the maximum tested concentration (higher DMax value). Melittin was utilized as a positive hemolysis standard; it was used in eight concentrations in two-fold serial dilutions with 50 µg/mL as the highest concentration tested.

C. Hemolysis assay (sheep erythrocytes)

The hemolytic activity of the synthesized compounds was determined by lysis of sheep erythrocytes. Briefly, 500 µL volumes of each compound in phosphate buffer solution (PBS) were mixed with 480 µL PBS and 20 µL washed sheep erythrocytes (100%) in microcentrifuge tubes; this produced a final erythrocyte concentration of 2%. Compounds were tested at both 5 µg/mL and 50 µg/mL. A positive control (980 µL water and 20 µL erythrocytes) and a negative control (980 µL PBS and 20 µL erythrocytes) were also included in the assay. The centrifuge tubes were incubated on a rocker at 37 °C for 2 h and then centrifuged at 12,000 rpm for 5 min; 100 µL volumes of the supernatant fluid were transferred to a 96-well microtitre tray and the optical density of the samples was observed at 540 nm. The value for the negative control was subtracted from the haemolysis values and then the resulting quantities were expressed as a percentage of the positive control (which was defined as 100% hemolysis). The hemolysis assay was repeated in triplicate for all compounds and the mean values and standard deviations were reported.

^{1}H and ^{13}C NMR spectra for all intermediates

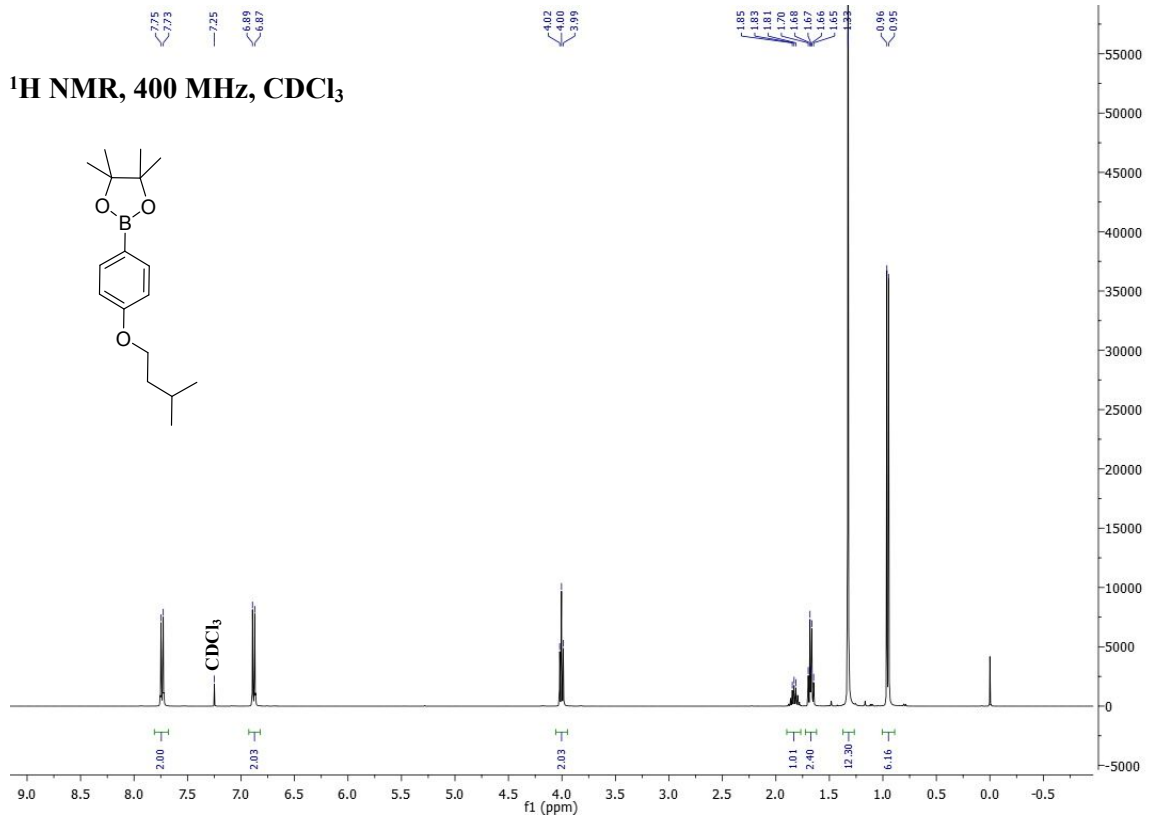


Fig. S1. ^{1}H NMR spectra of compound ***p*-11** (recorded in $CDCl_3$).

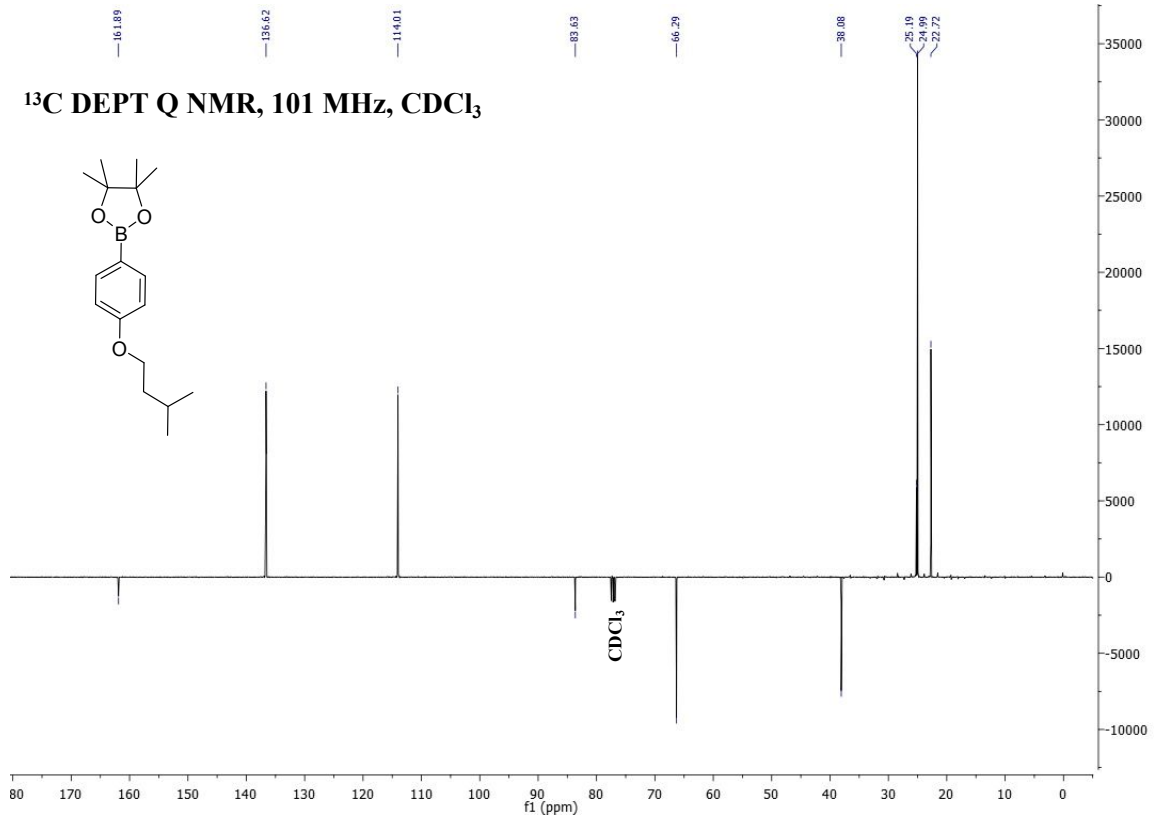


Fig. S2. ^{13}C DEPT Q NMR spectra of compound ***p*-11** (recorded in $CDCl_3$).

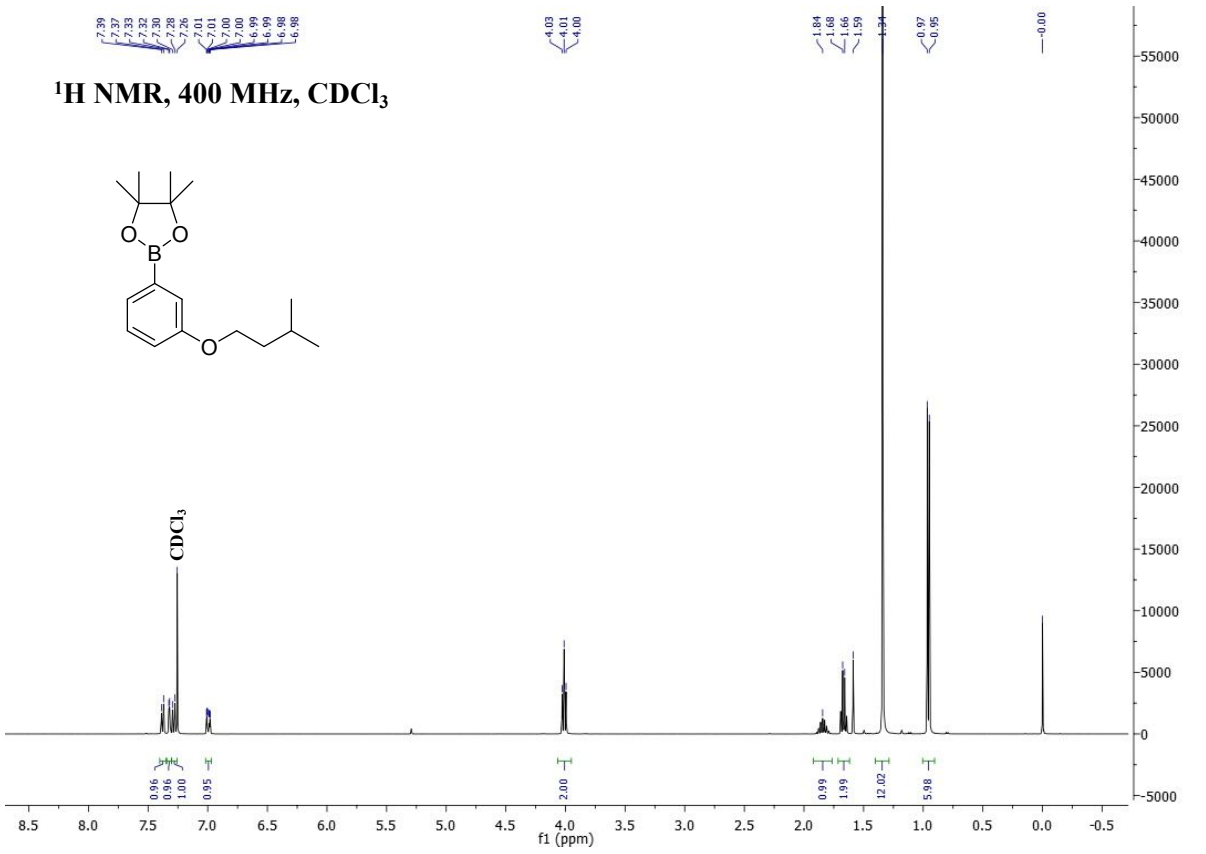


Fig. S3. ^{1}H NMR spectra of compound ***m*-11** (recorded in $CDCl_3$).

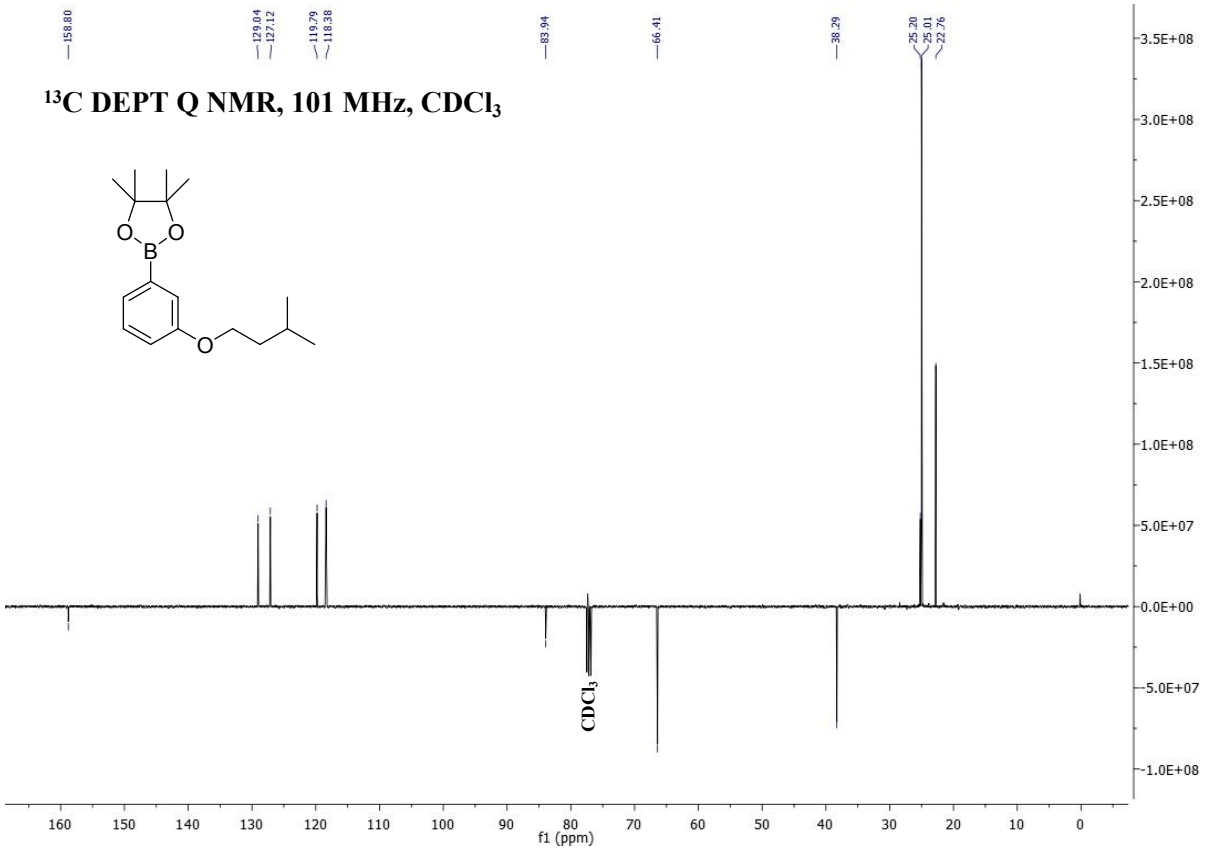


Fig. S4. ^{13}C DEPT Q NMR spectra of compound ***m*-11** (recorded in $CDCl_3$).

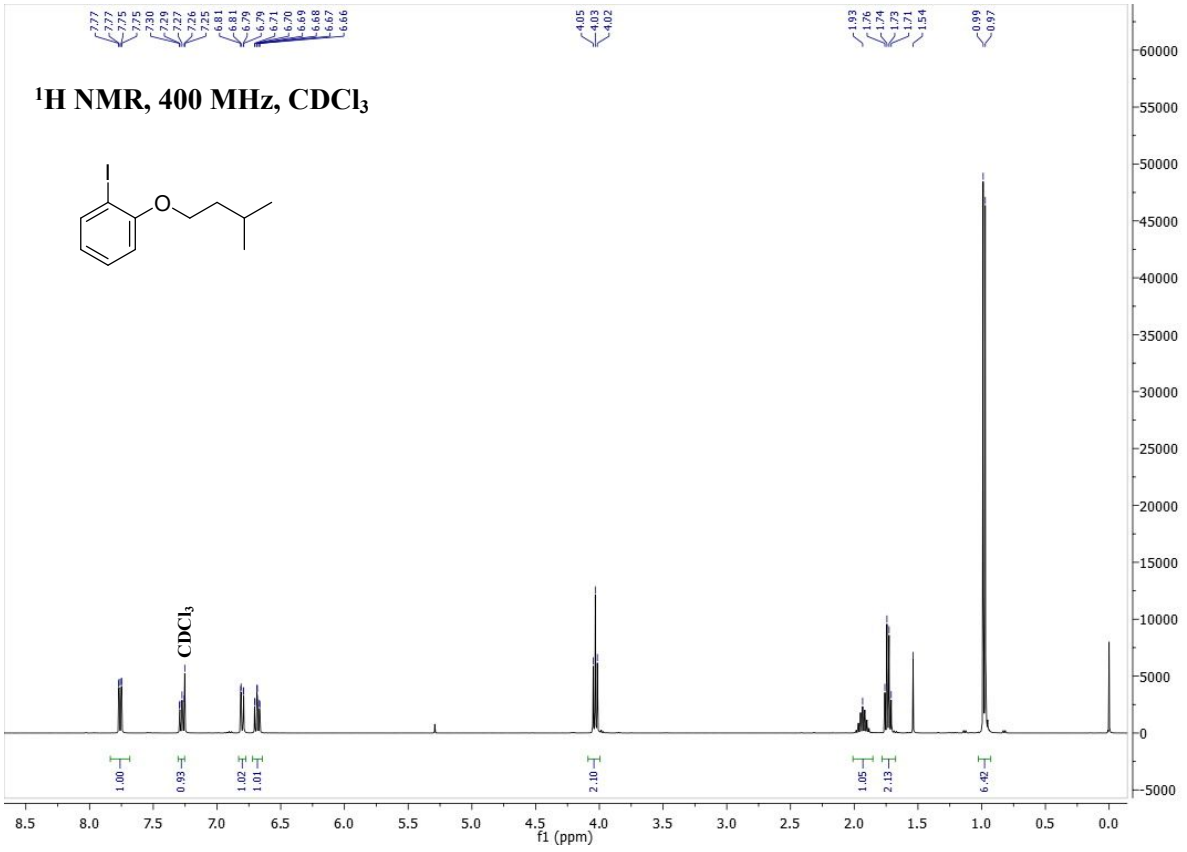


Fig. S5. ^{1}H NMR spectra of compound **13** (recorded in $CDCl_3$).

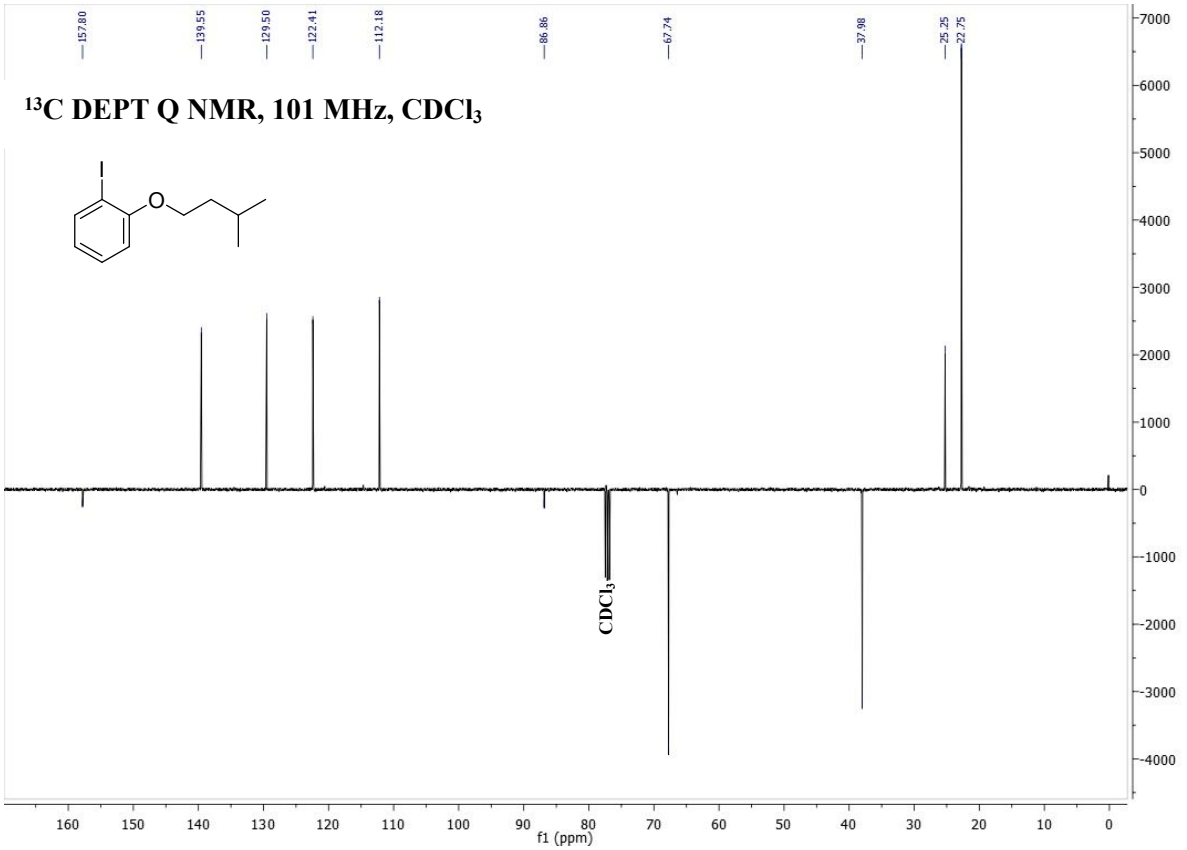


Fig. S6. ^{13}C DEPT Q NMR spectra of compound **13** (recorded in $CDCl_3$).

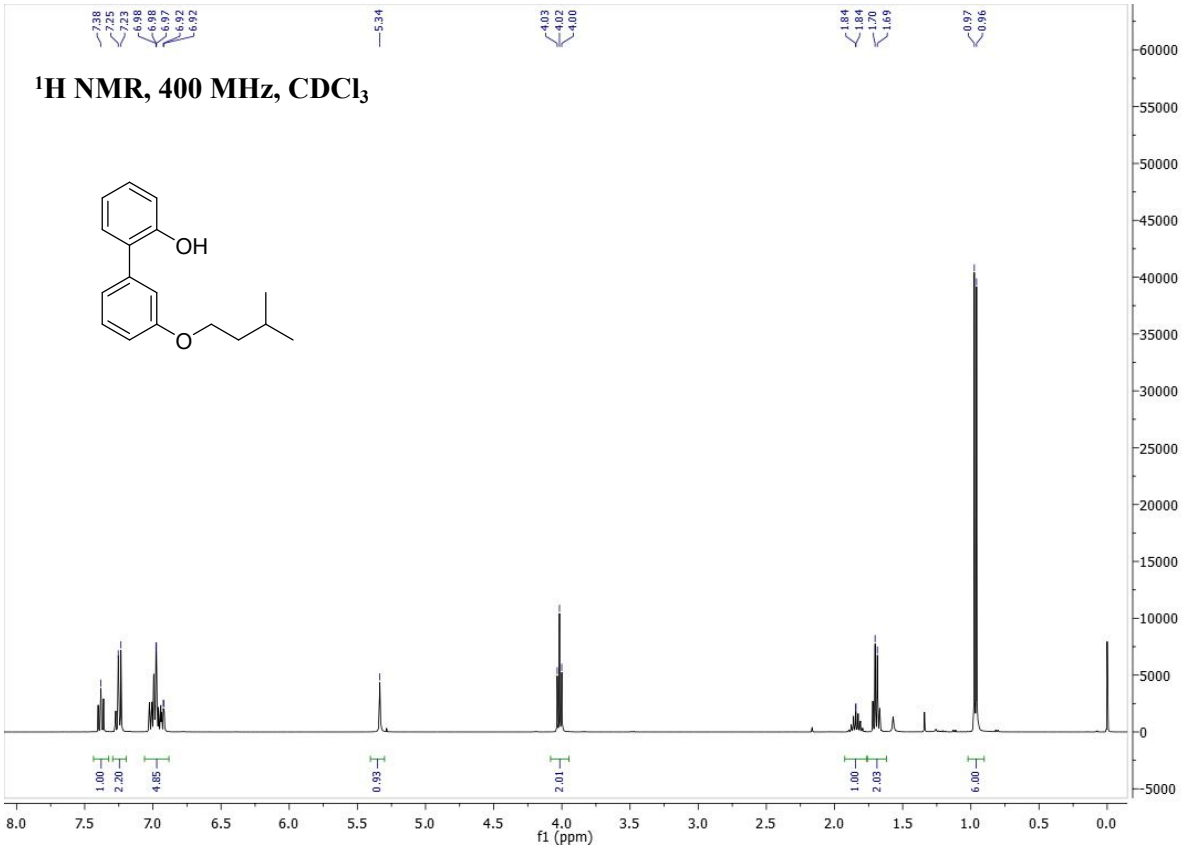


Fig. S7. [1]H NMR spectra of compound **14a** (recorded in $CDCl_3$).

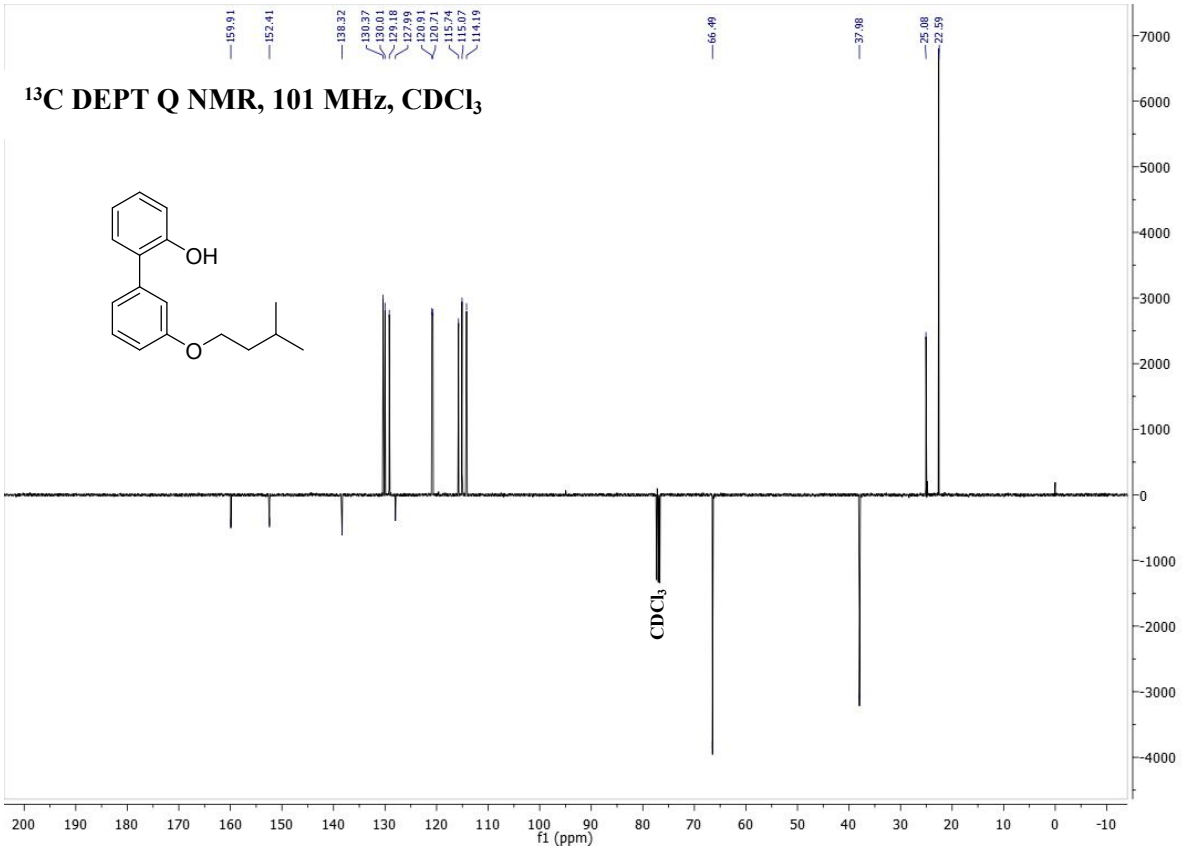


Fig. S8. [13]C DEPT Q NMR spectra of compound **14a** (recorded in $CDCl_3$).

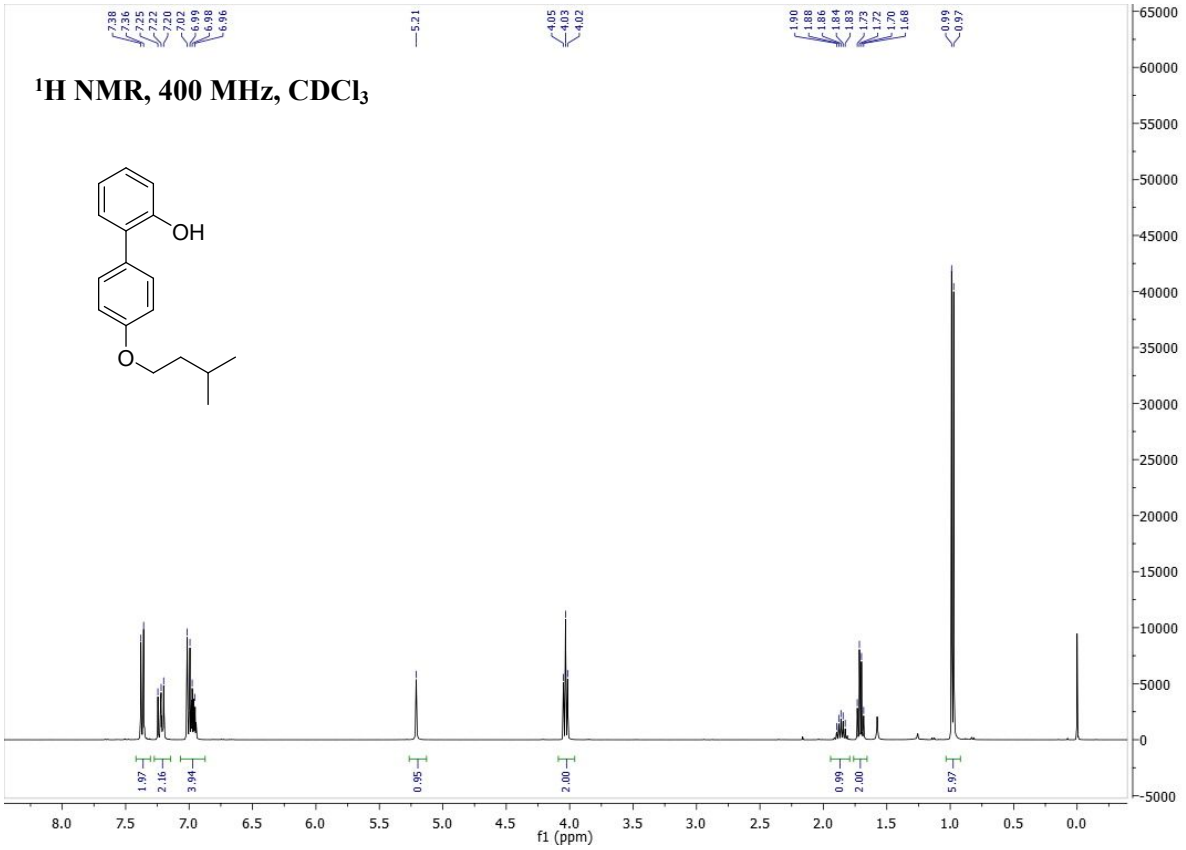


Fig. S9. ^{1}H NMR spectra of compound **14b** (recorded in $CDCl_3$).

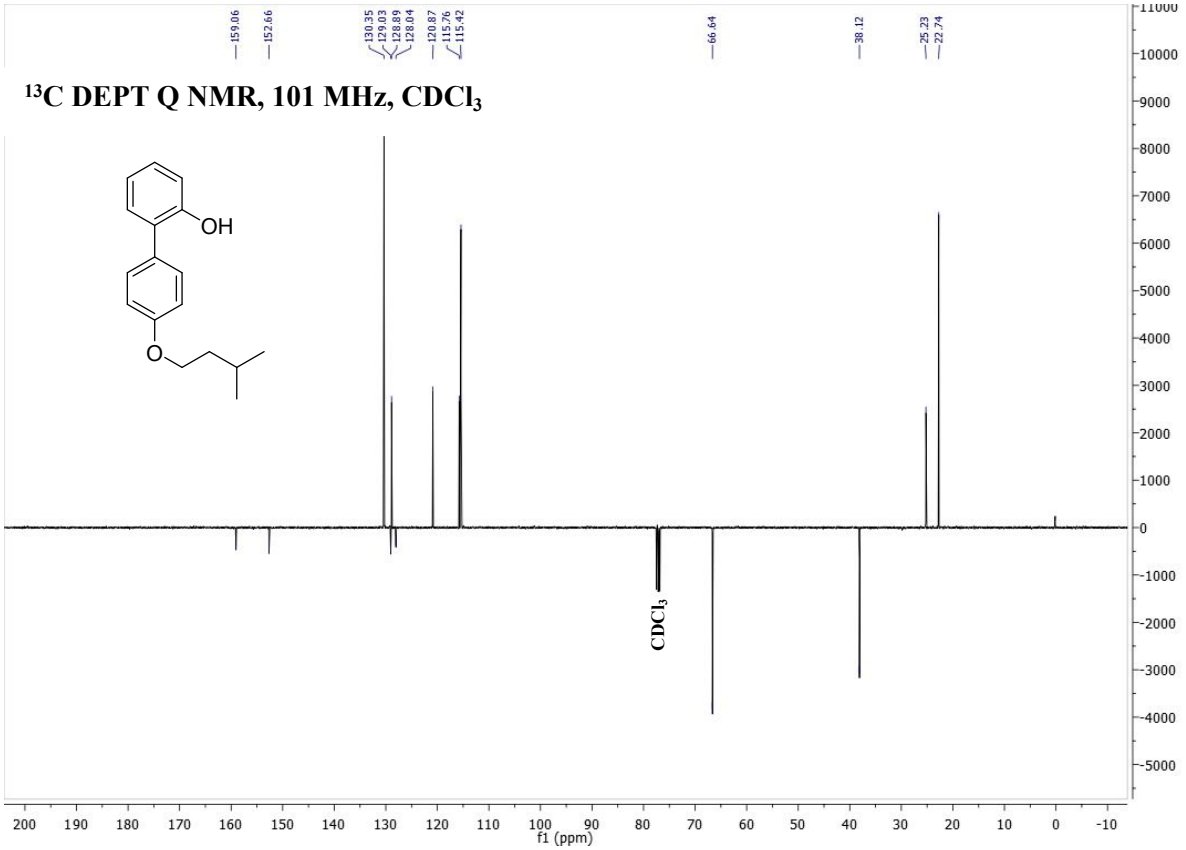


Fig. S10. ^{13}C DEPT Q NMR spectra of compound **14b** (recorded in $CDCl_3$).

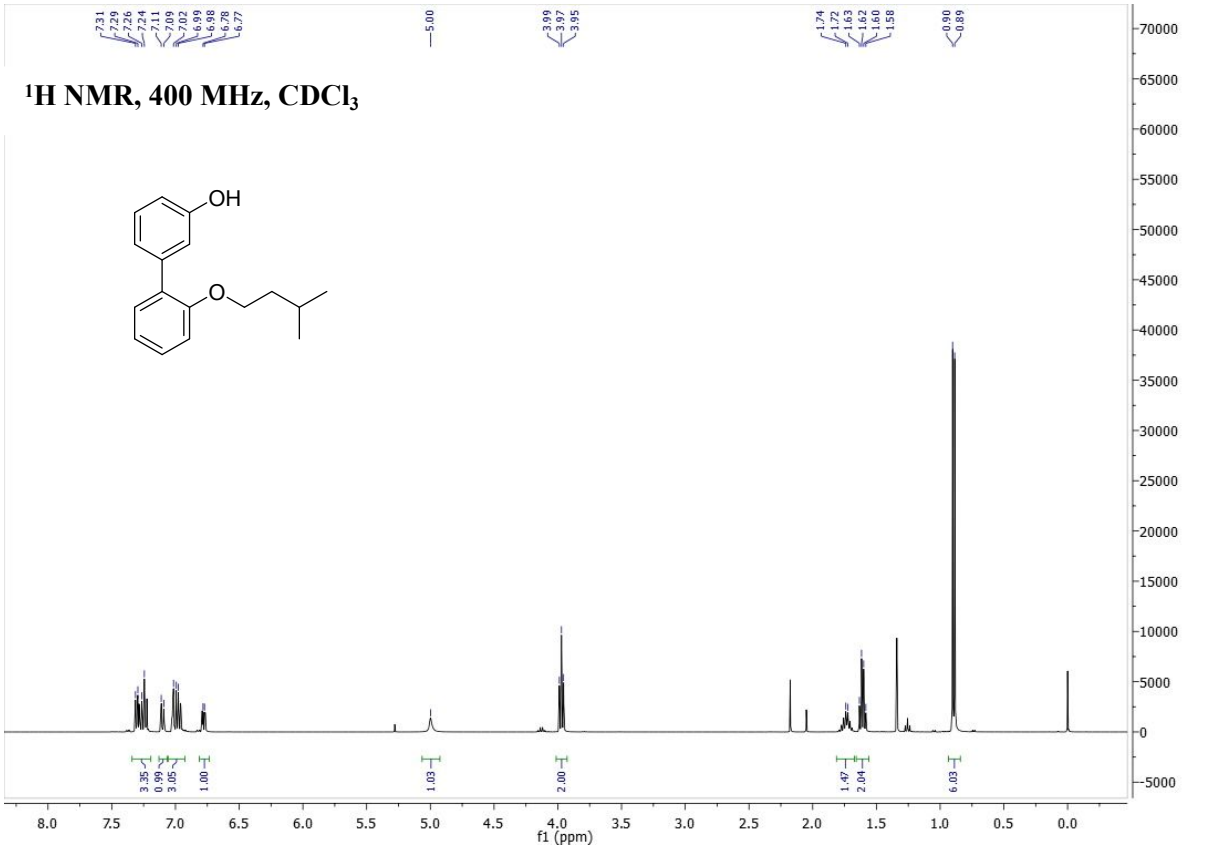


Fig. S11. ^{1}H NMR spectra of compound **14c** (recorded in $CDCl_3$).

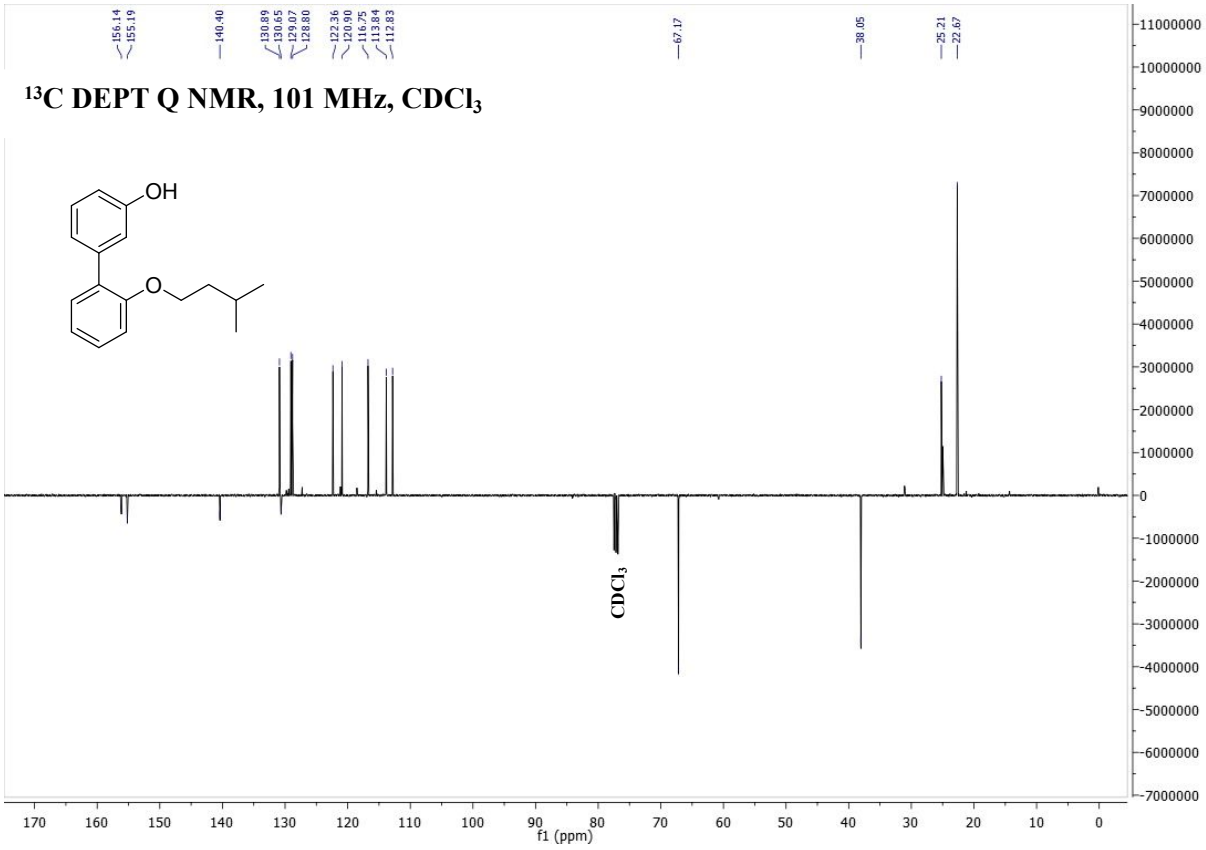


Fig. S12. ^{13}C DEPT Q NMR spectra of compound **14c** (recorded in $CDCl_3$).

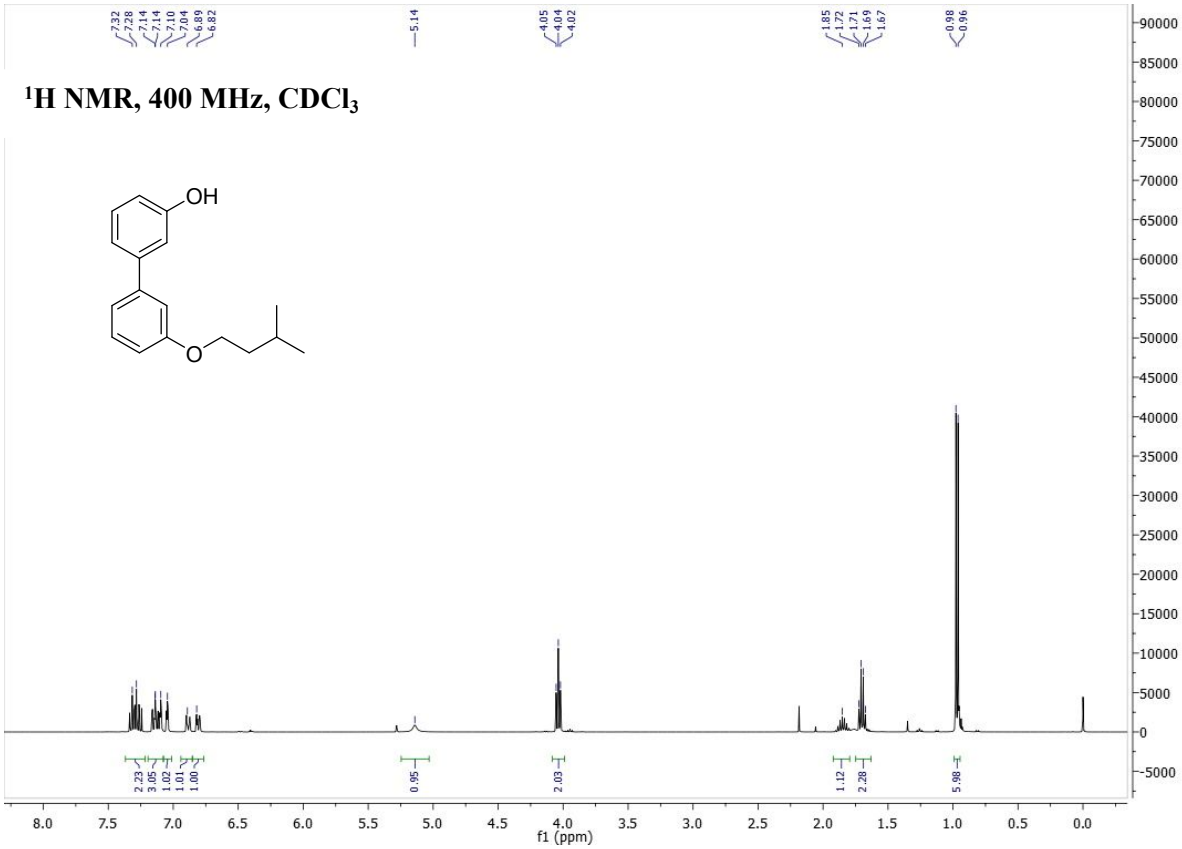


Fig. S13. ^{1}H NMR spectra of compound **14d** (recorded in $CDCl_3$).

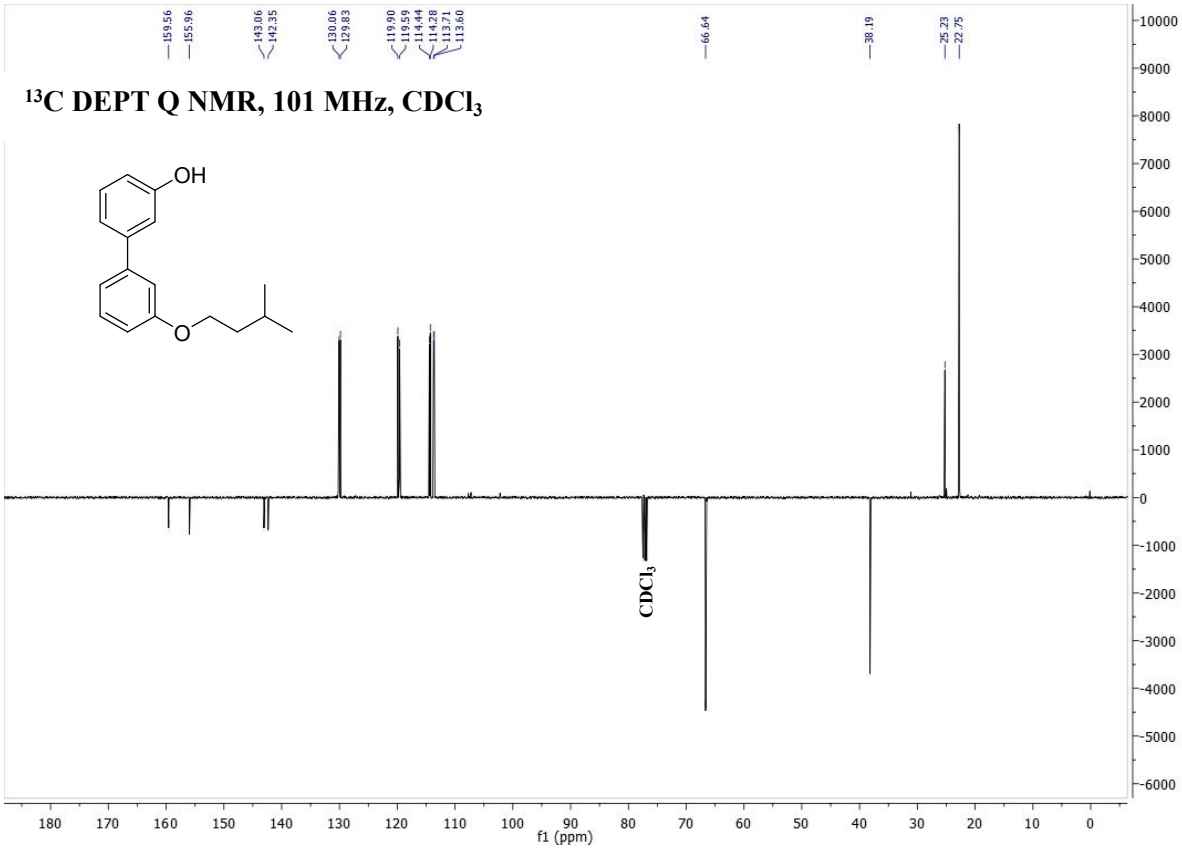


Fig. S14. ^{13}C DEPT Q NMR spectra of compound **14d** (recorded in $CDCl_3$).

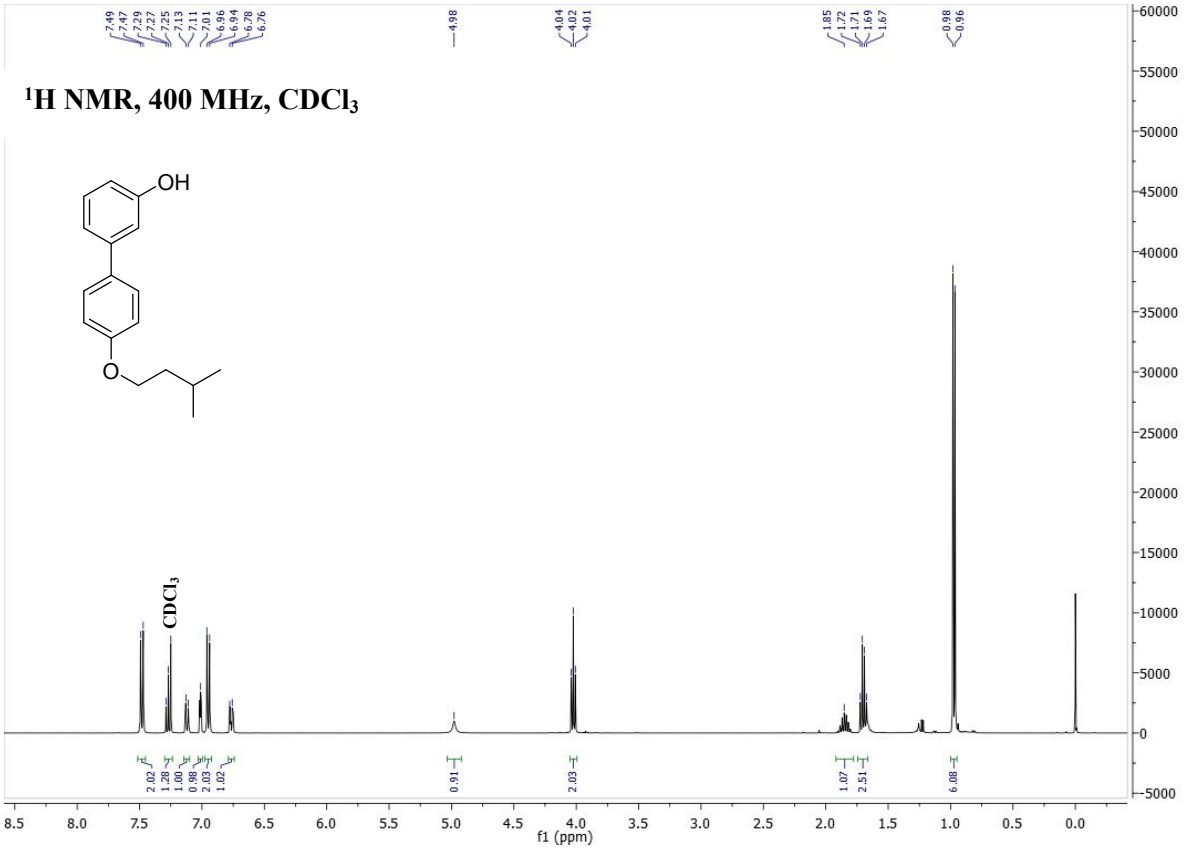


Fig. S15. ^{1}H NMR spectra of compound **14e** (recorded in $CDCl_3$).

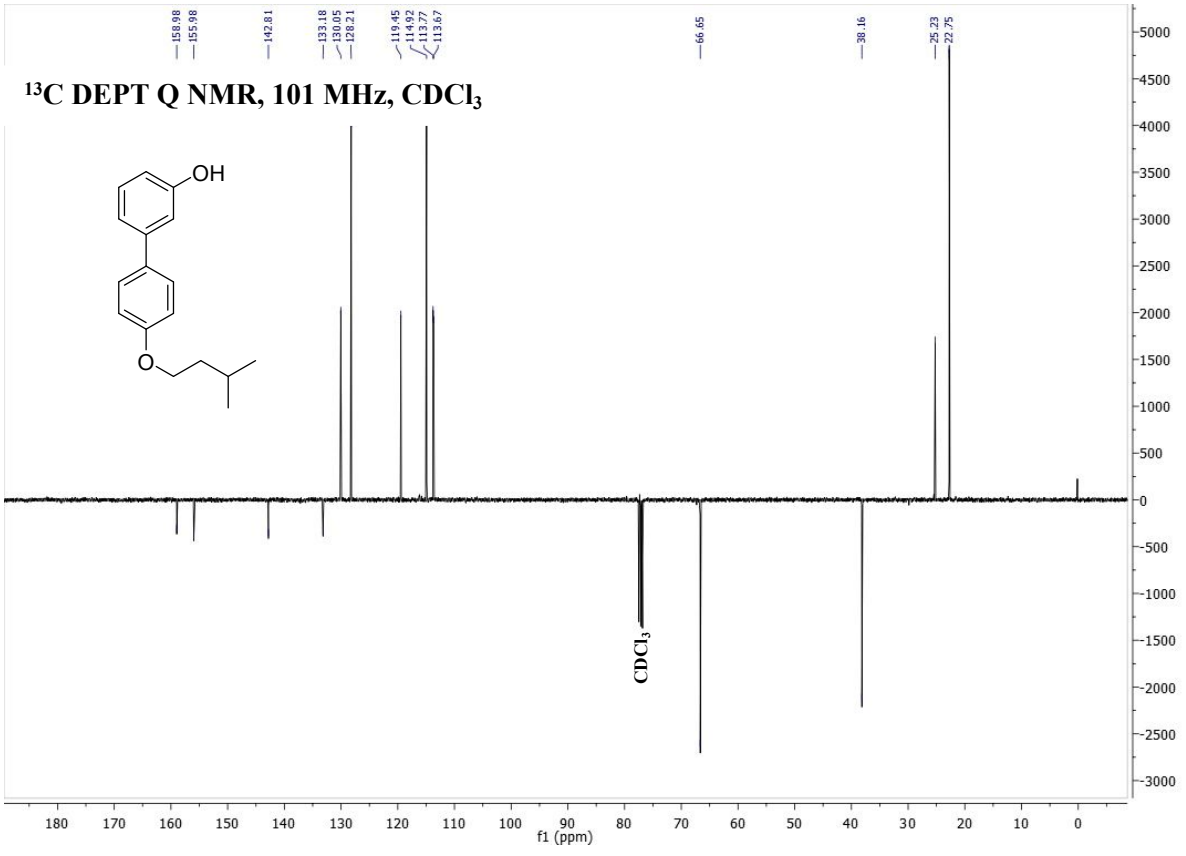


Fig. S16. ^{13}C DEPT Q NMR spectra of compound **14e** (recorded in $CDCl_3$).

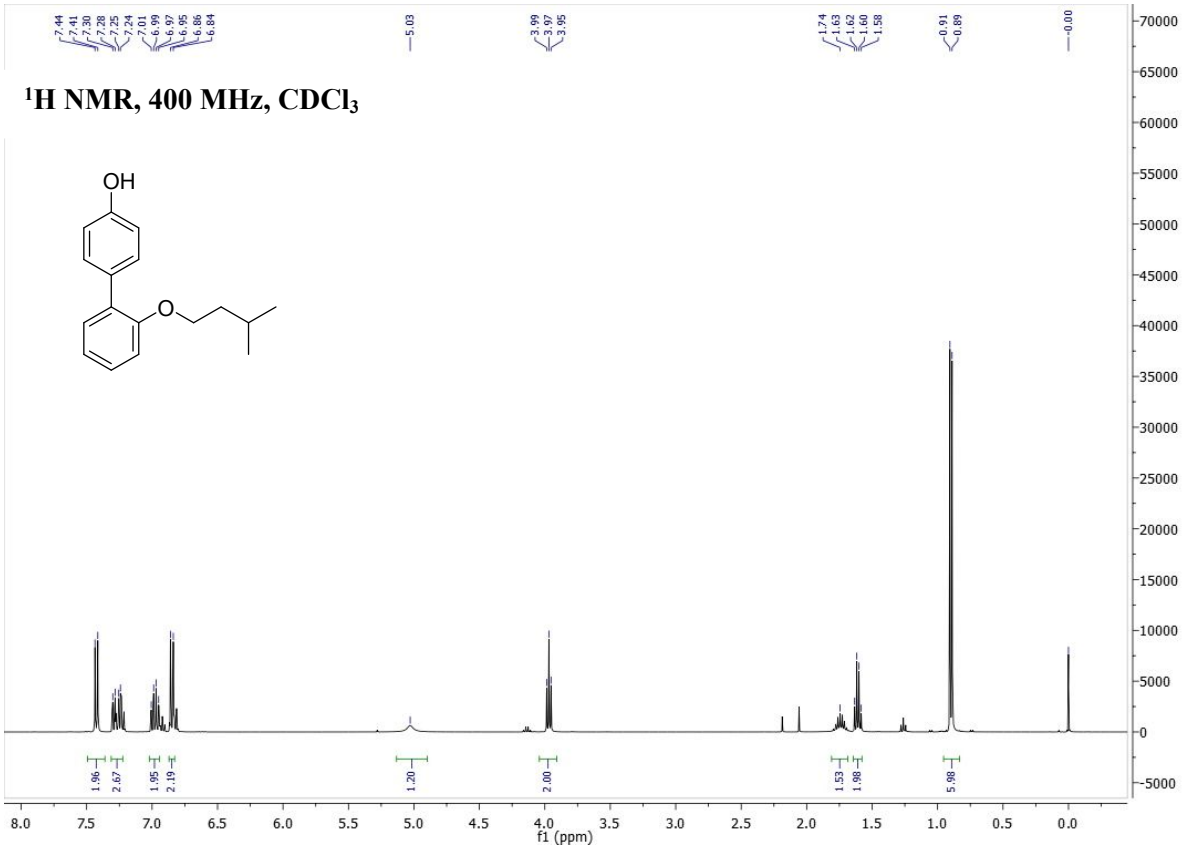


Fig. S17. ^{1}H NMR spectra of compound **14f** (recorded in $CDCl_3$).

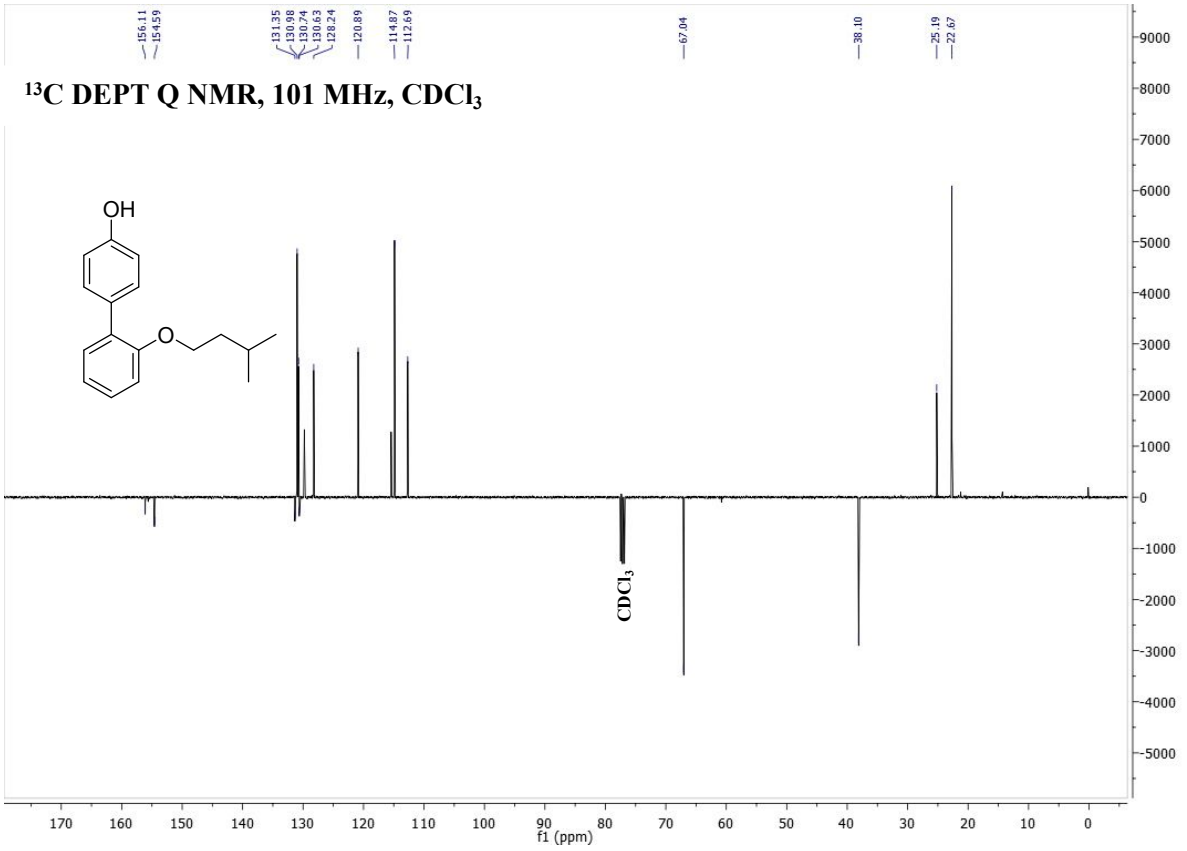


Fig. S18. ^{13}C DEPT Q NMR spectra of compound **14f** (recorded in $CDCl_3$).

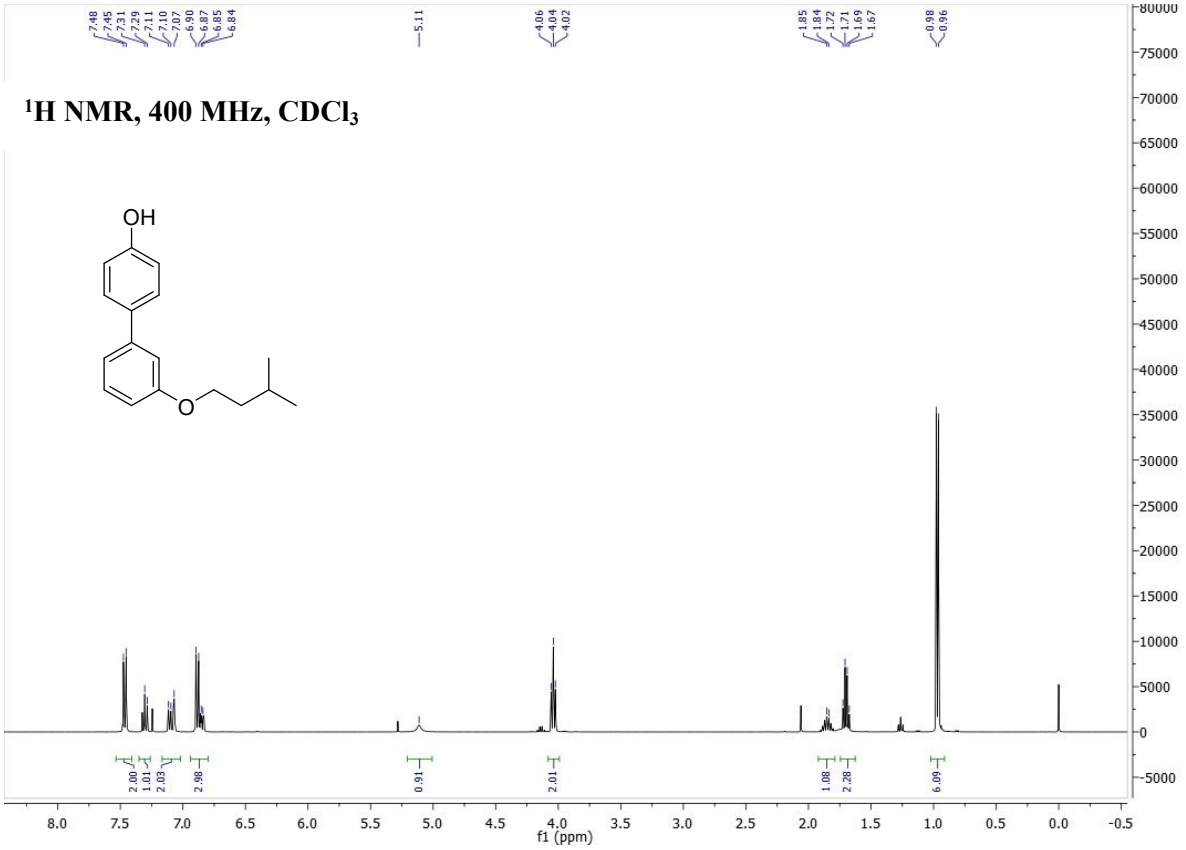


Fig. S19. ^{1}H NMR spectra of compound **14g** (recorded in $CDCl_3$).

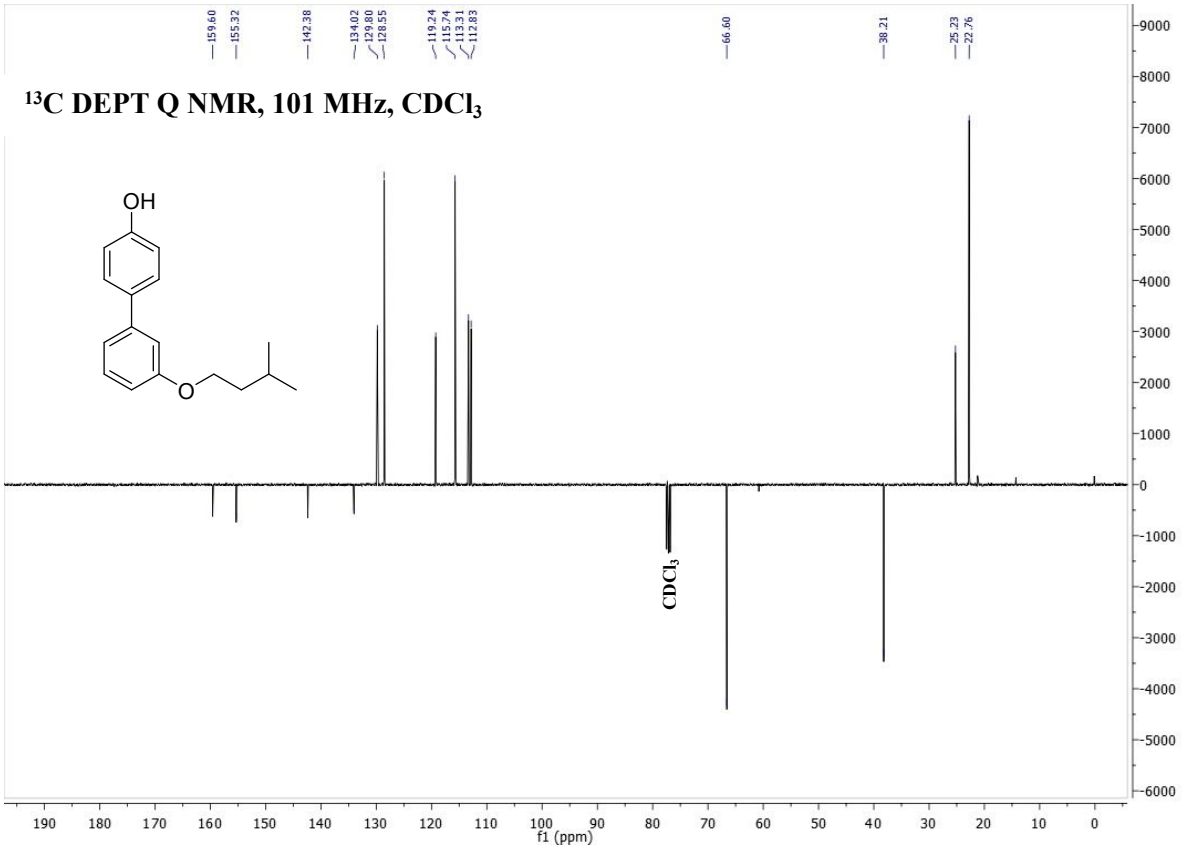


Fig. S20. ^{13}C DEPT Q NMR spectra of compound **14g** (recorded in $CDCl_3$).

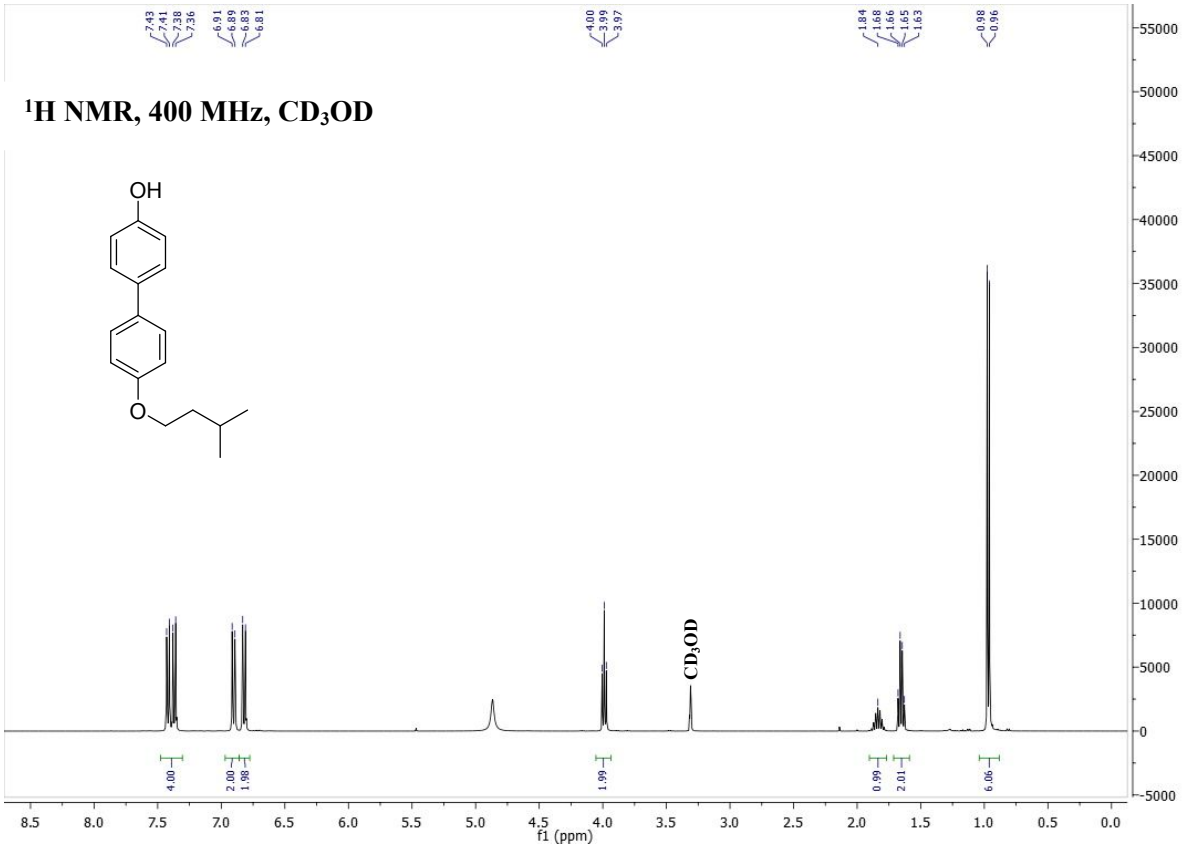


Fig. S21. ^{1}H NMR spectra of compound **14h** (recorded in CD_3OD).

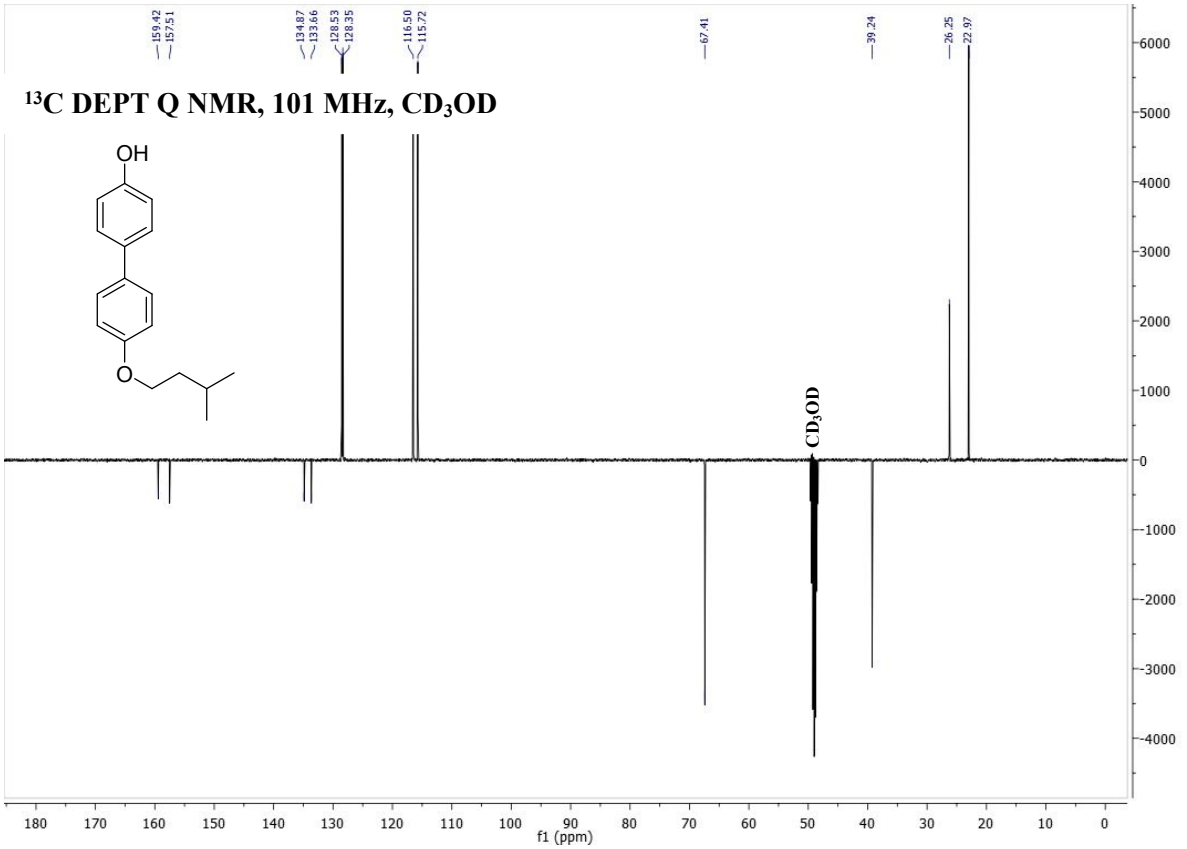


Fig. S22. ^{13}C DEPT Q NMR spectra of compound **14h** (recorded in CD_3OD).

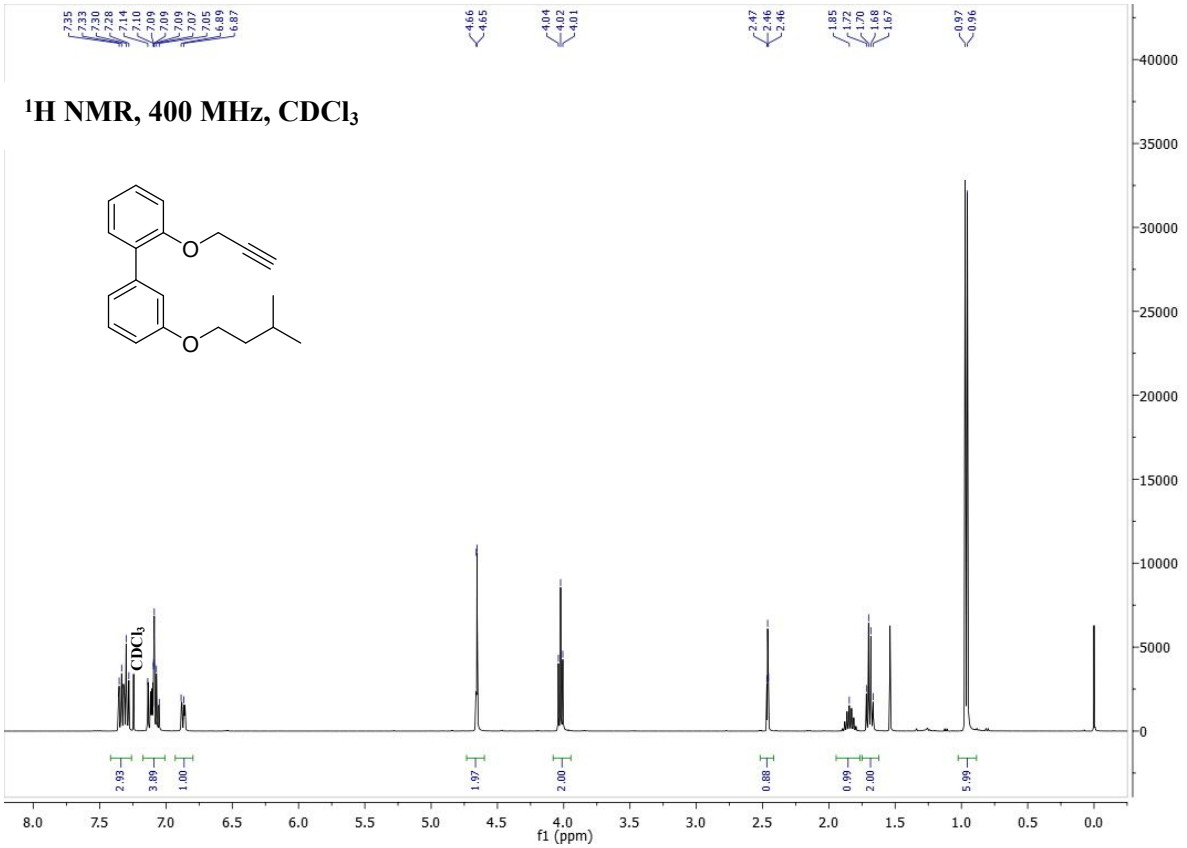


Fig. S23. ^{1}H NMR spectra of compound **15a** (recorded in $CDCl_3$).

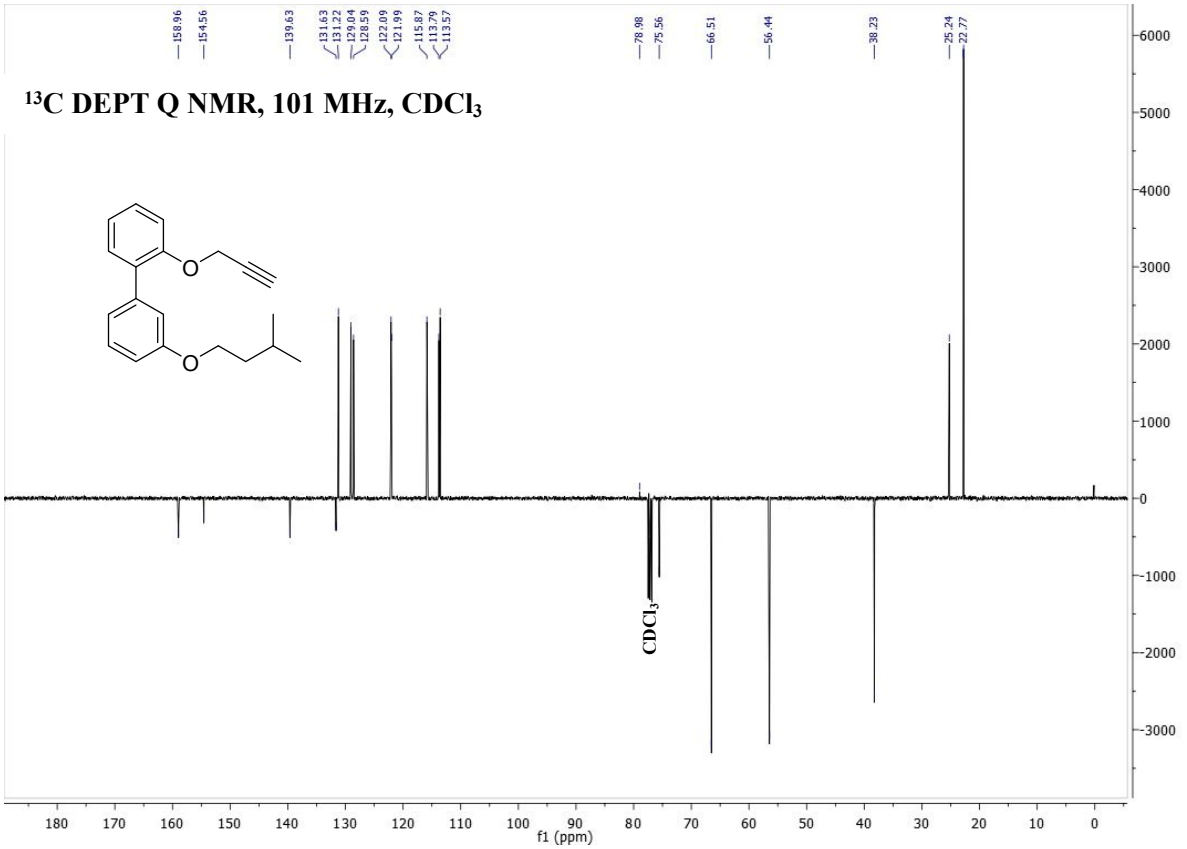


Fig. S24. ^{13}C DEPT Q NMR spectra of compound **15a** (recorded in $CDCl_3$).

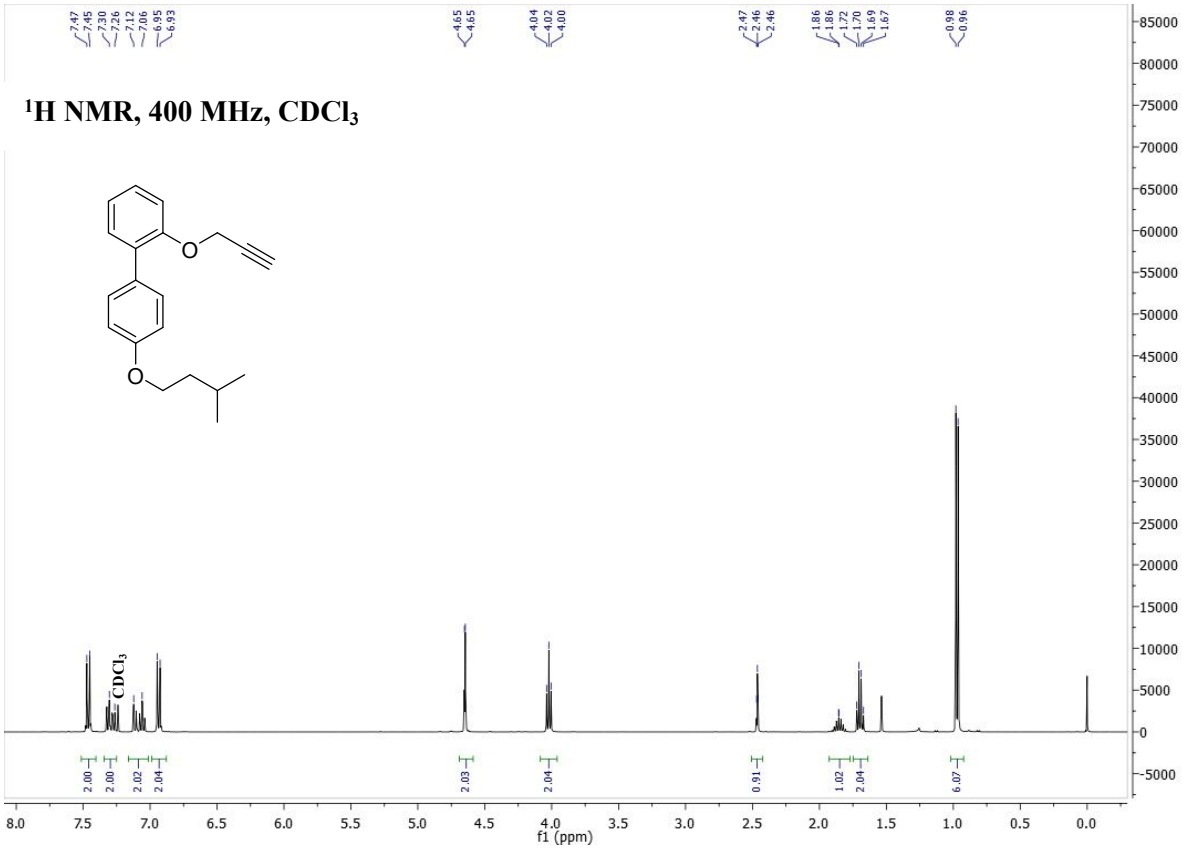


Fig. S25. ^{1}H NMR spectra of compound **15b** (recorded in $CDCl_3$).

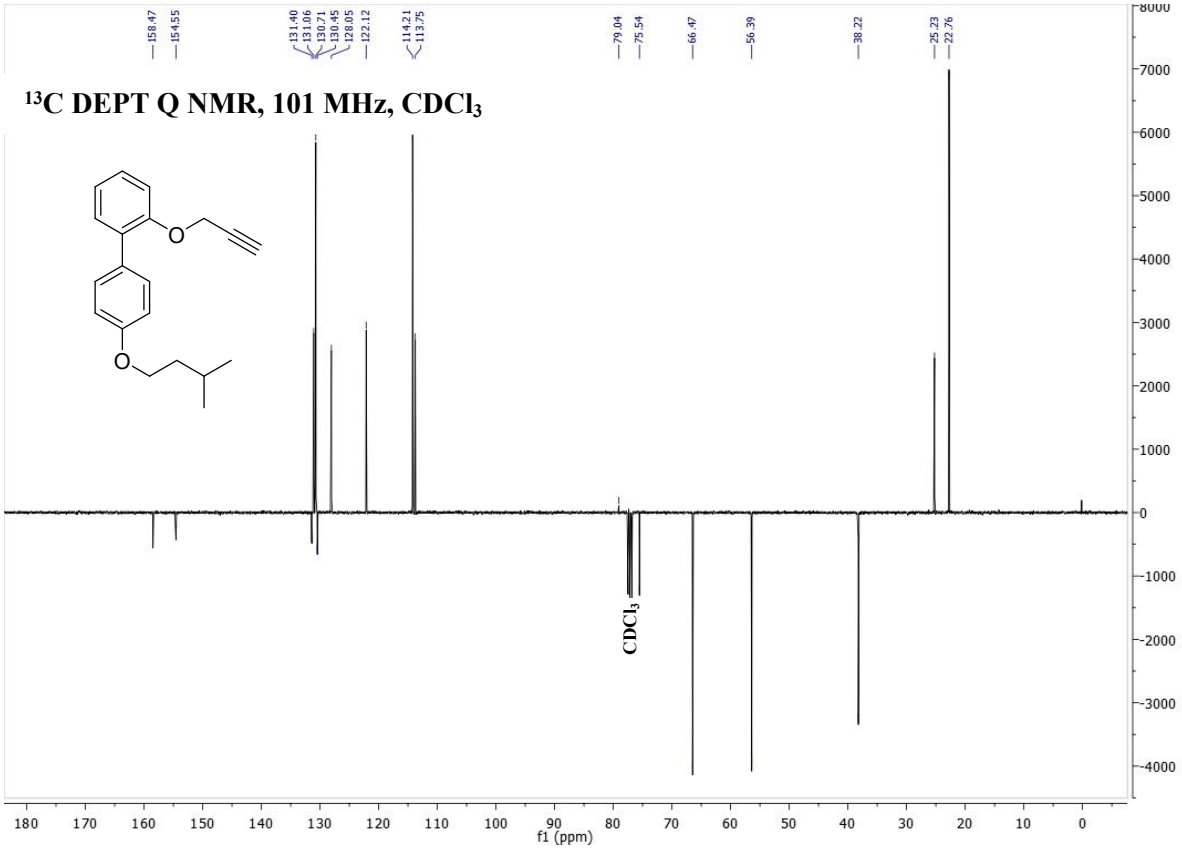


Fig. S26. ^{13}C DEPT Q NMR spectra of compound **15b** (recorded in $CDCl_3$).

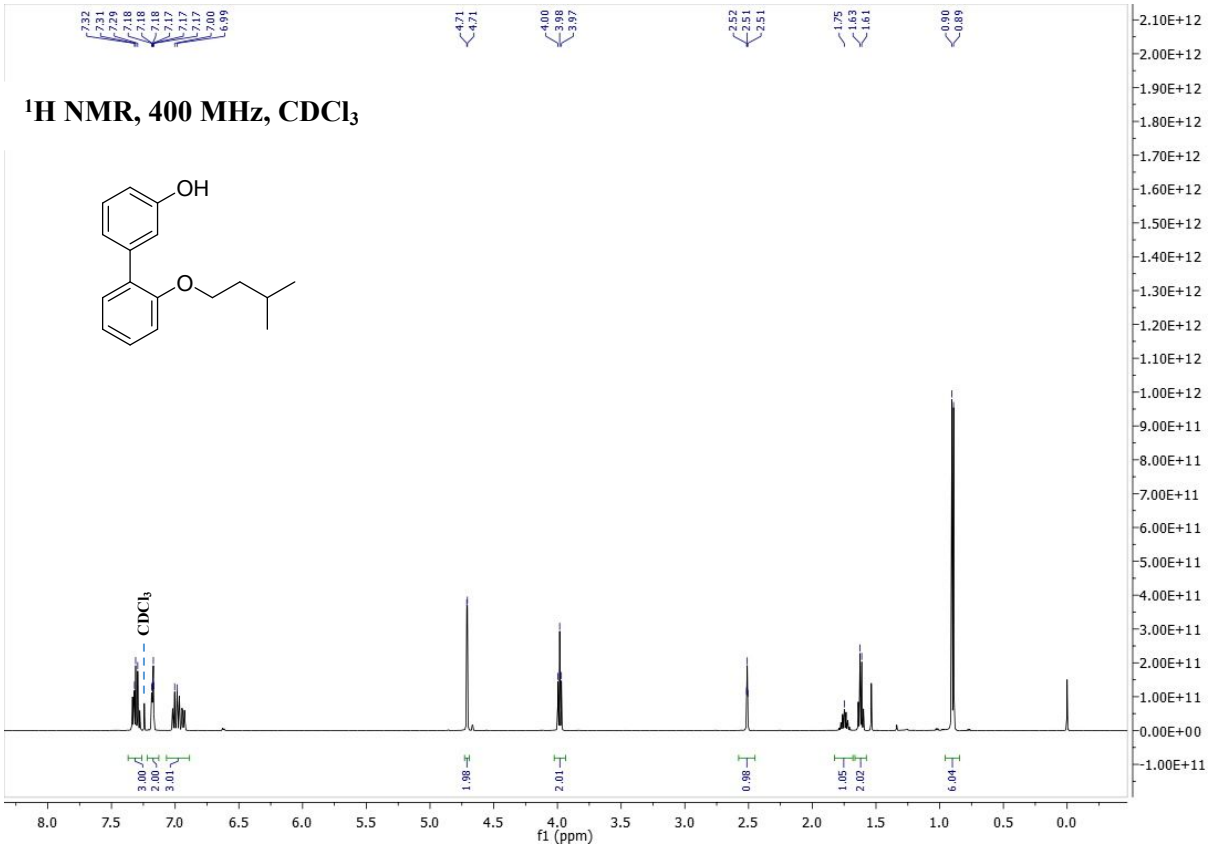


Fig. S27. ^{1}H NMR spectra of compound **15c** (recorded in $CDCl_3$).

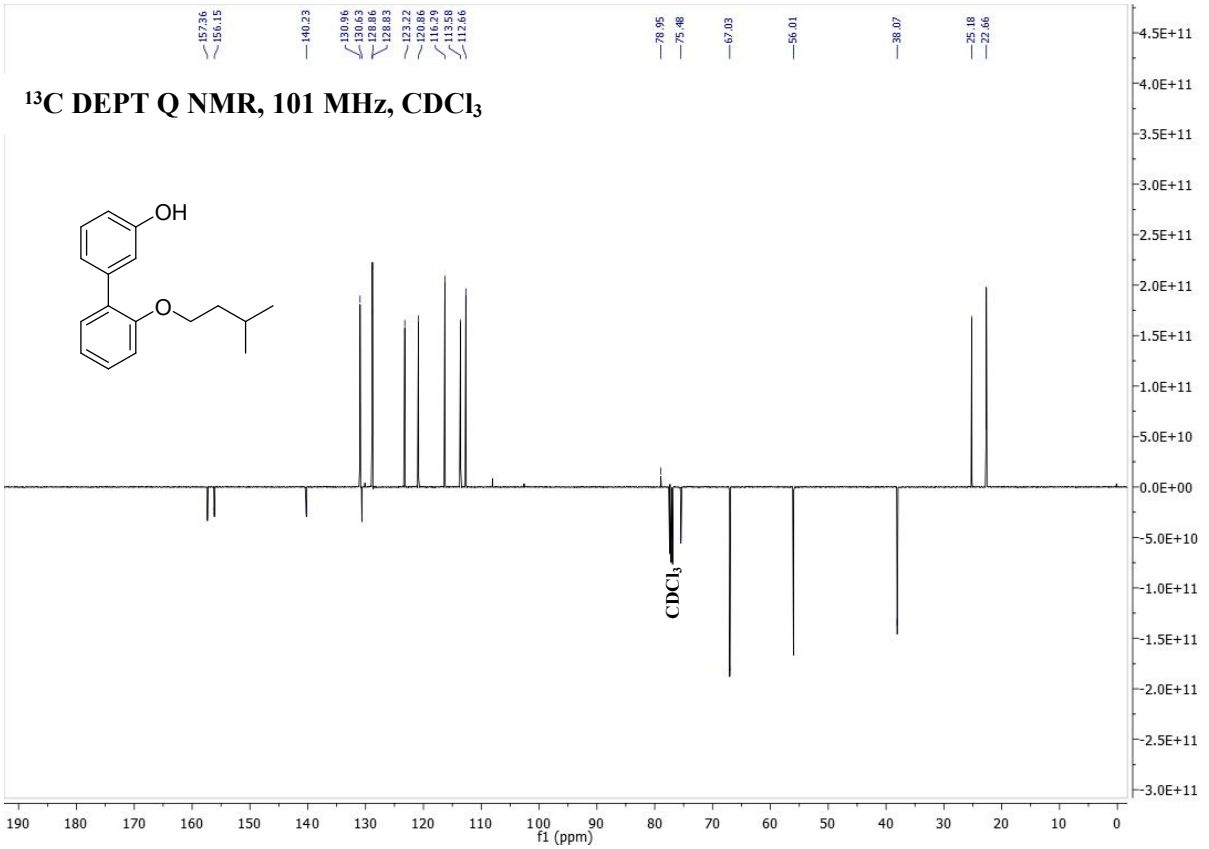


Fig. S28. ^{13}C DEPT Q NMR spectra of compound **15c** (recorded in $CDCl_3$).

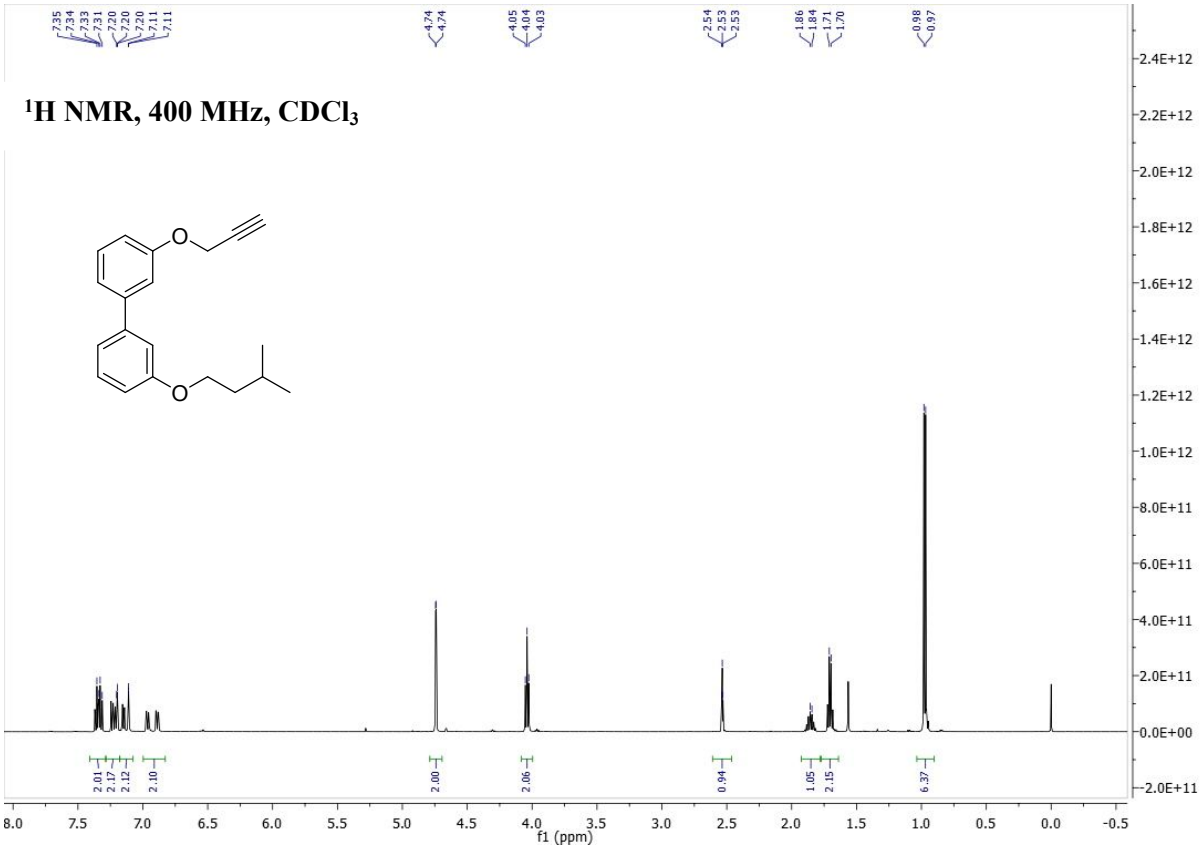


Fig. S29. ^{1}H NMR spectra of compound **15d** (recorded in $CDCl_3$).

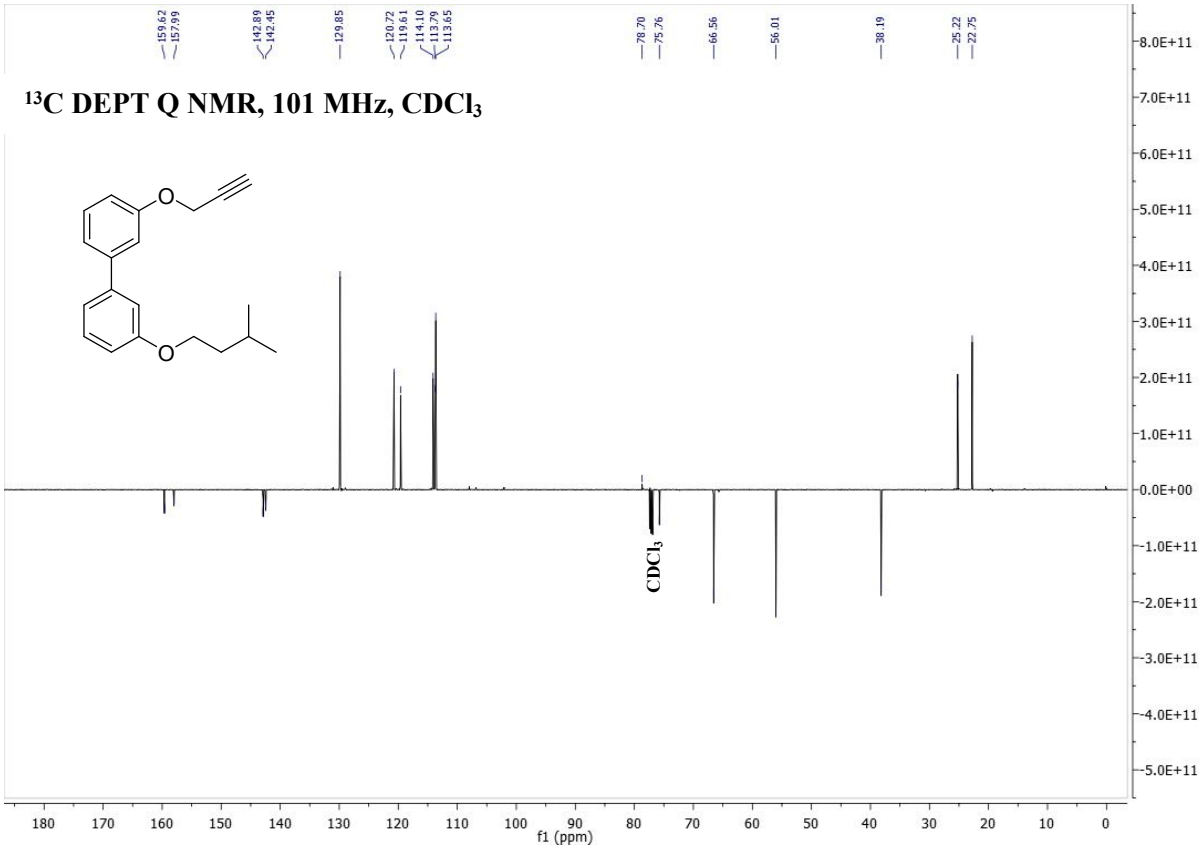


Fig. S30. ^{13}C DEPT Q NMR spectra of compound **15d** (recorded in $CDCl_3$).

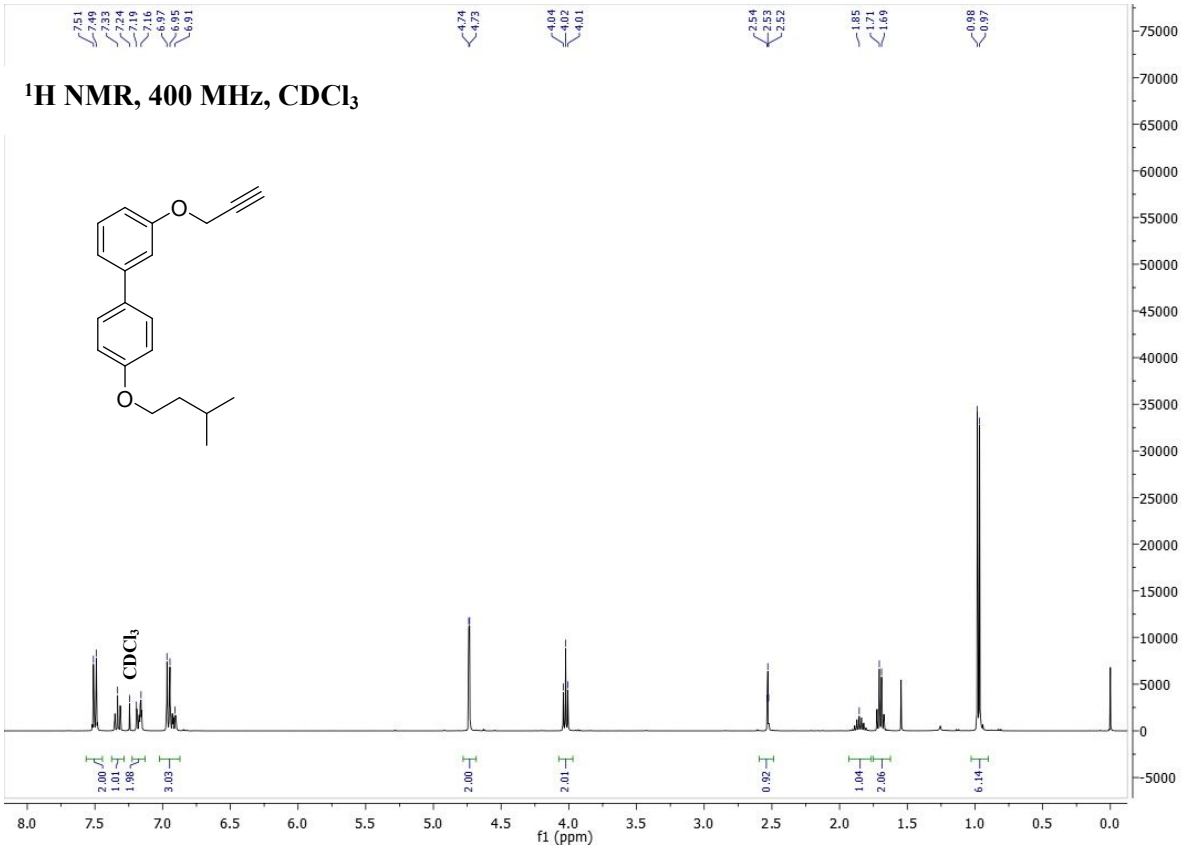


Fig. S31. ^{1}H NMR spectra of compound **15e** (recorded in $CDCl_3$).

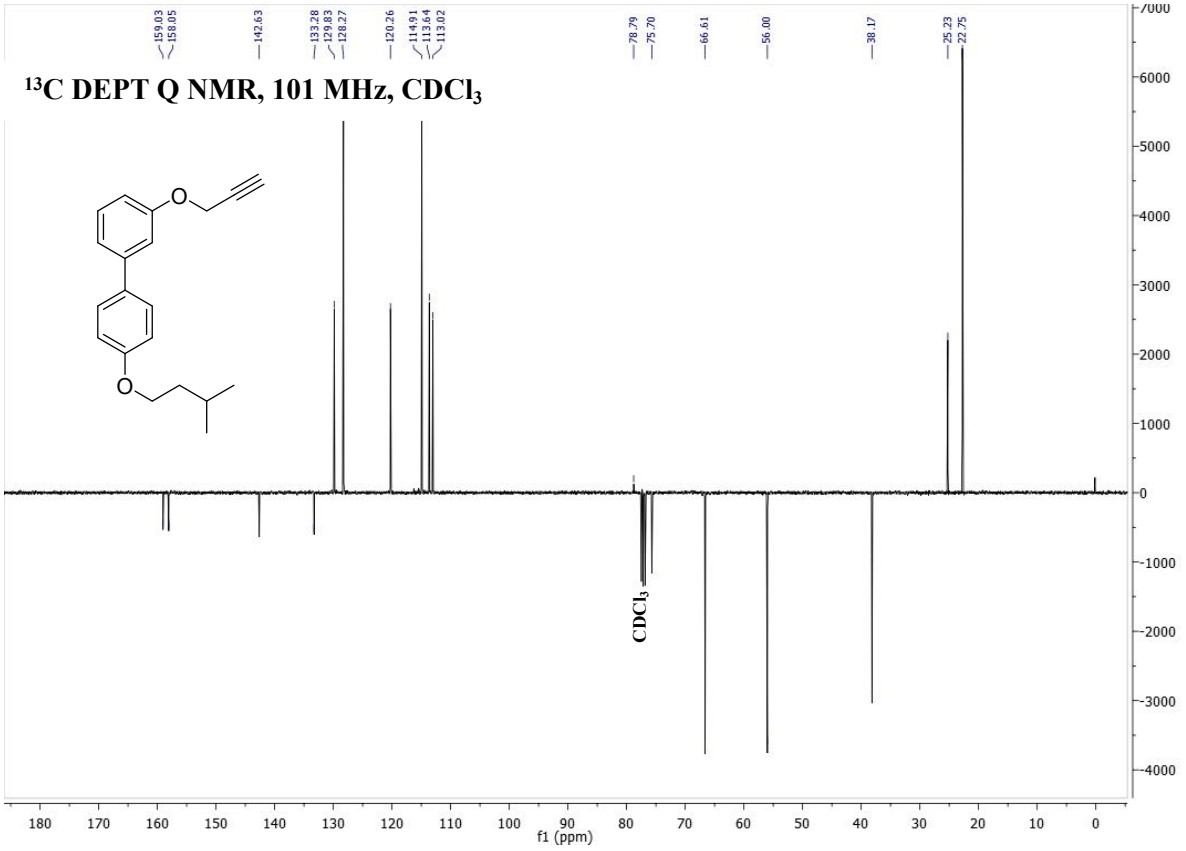


Fig. S32. ^{13}C DEPT Q NMR spectra of compound **15e** (recorded in $CDCl_3$).

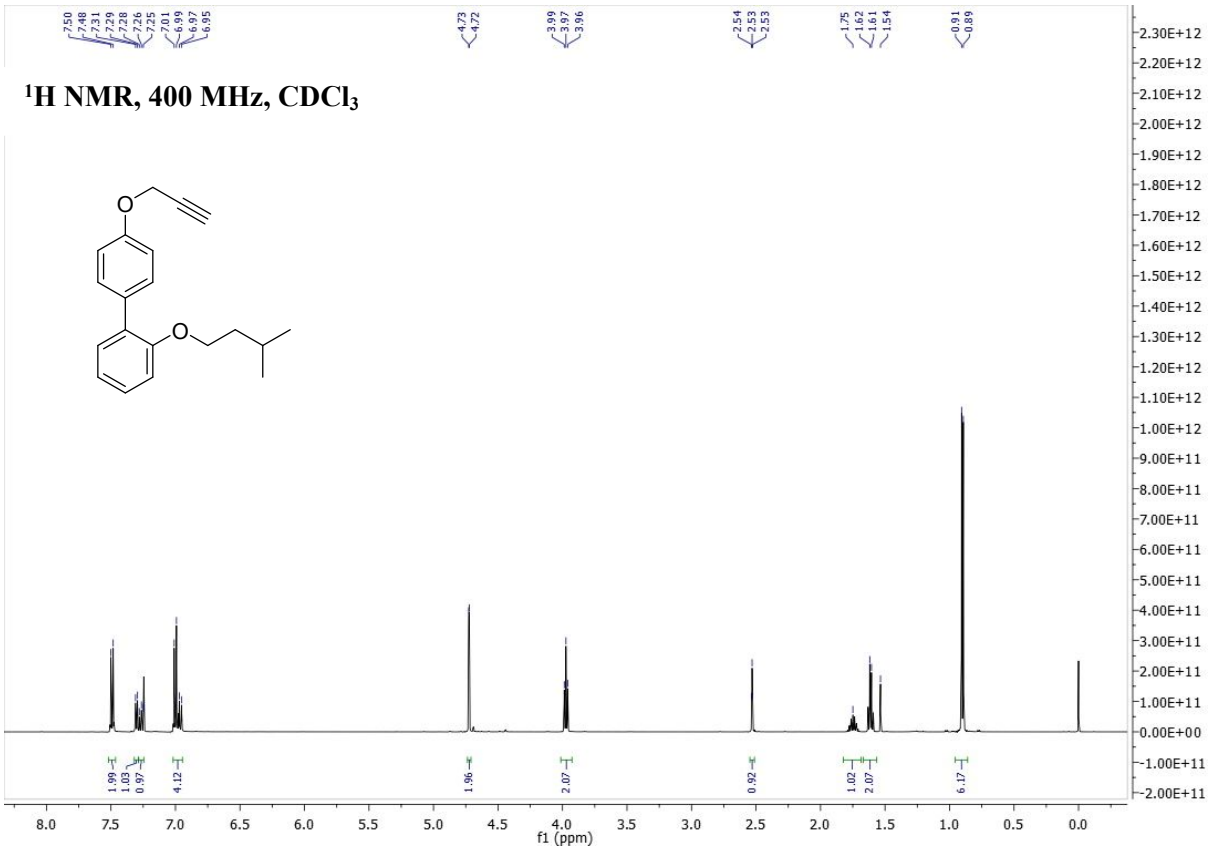


Fig. S33. ^{1}H NMR spectra of compound **15f** (recorded in $CDCl_3$).

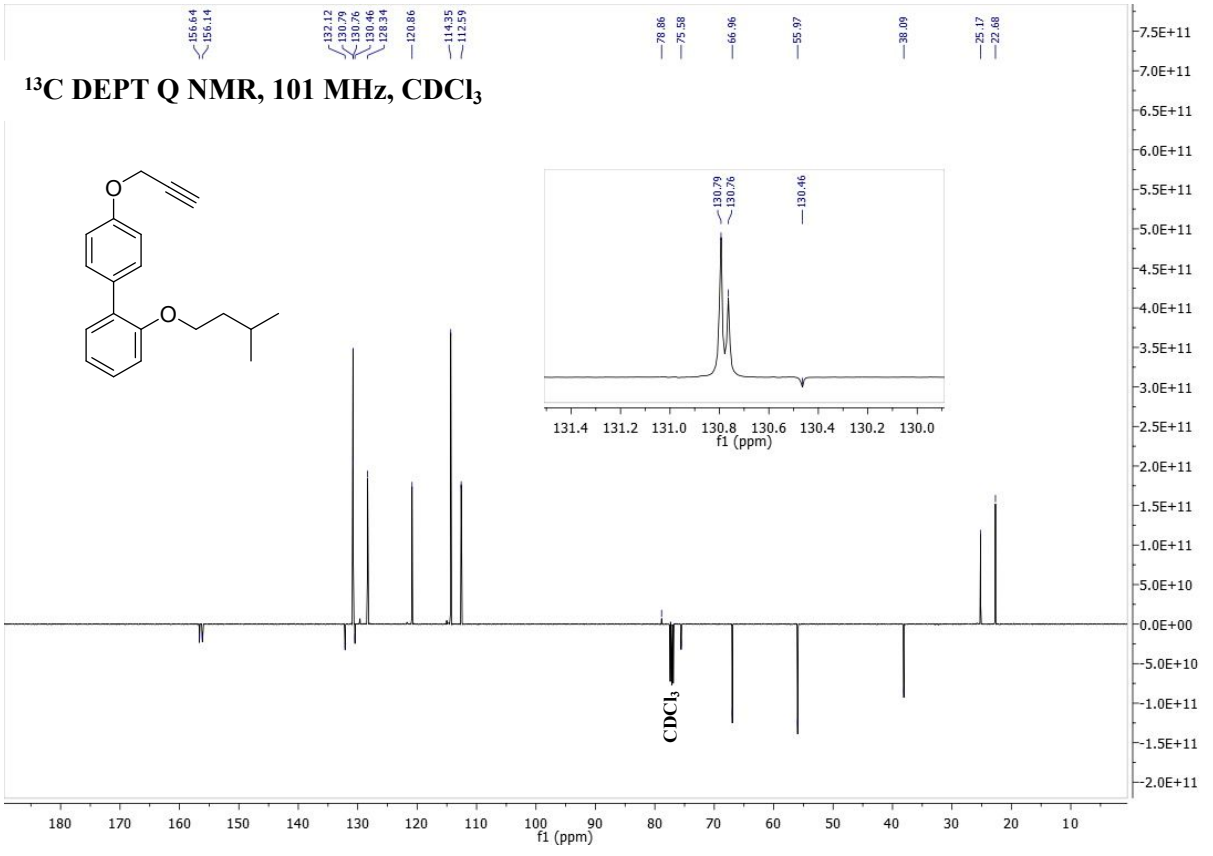


Fig. S34. ^{13}C DEPT Q NMR spectra of compound **15f** (recorded in $CDCl_3$).

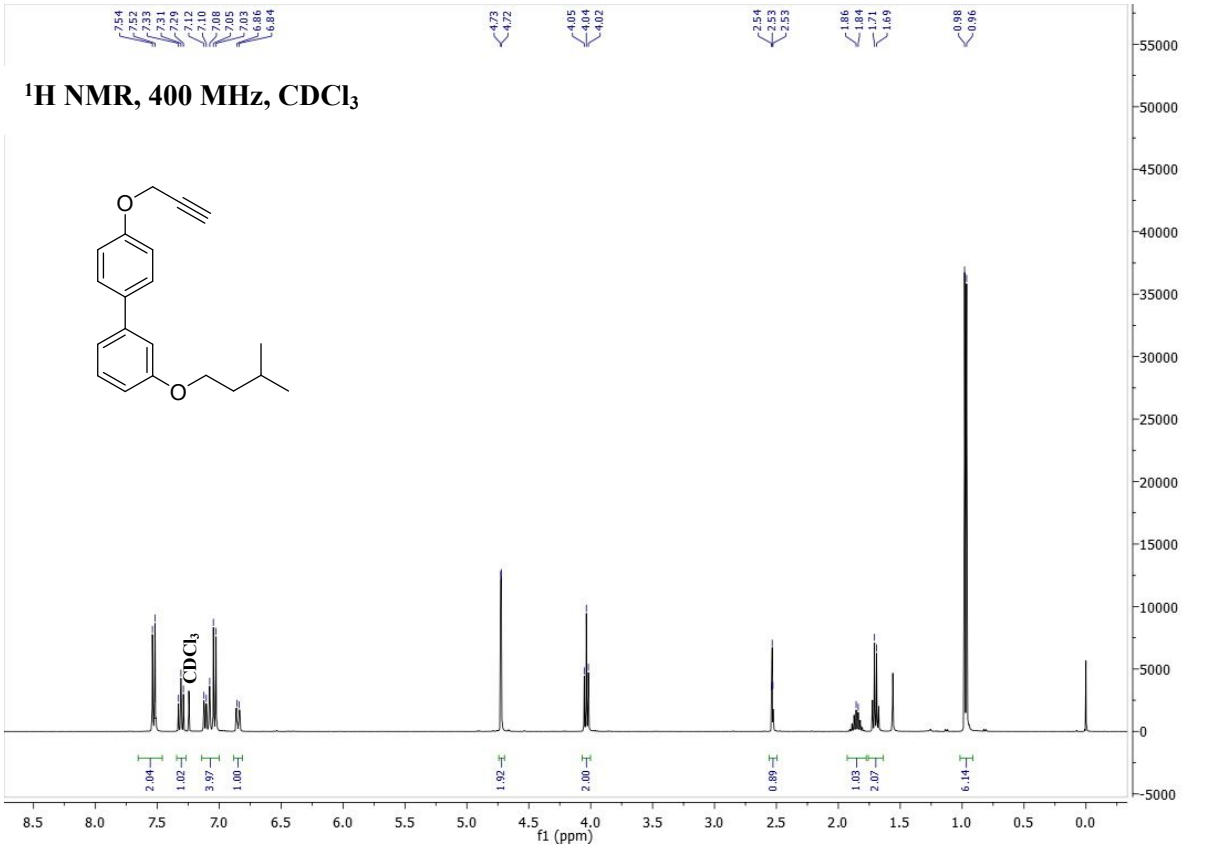


Fig. S35. ^{1}H NMR spectra of compound **15g** (recorded in $CDCl_3$).

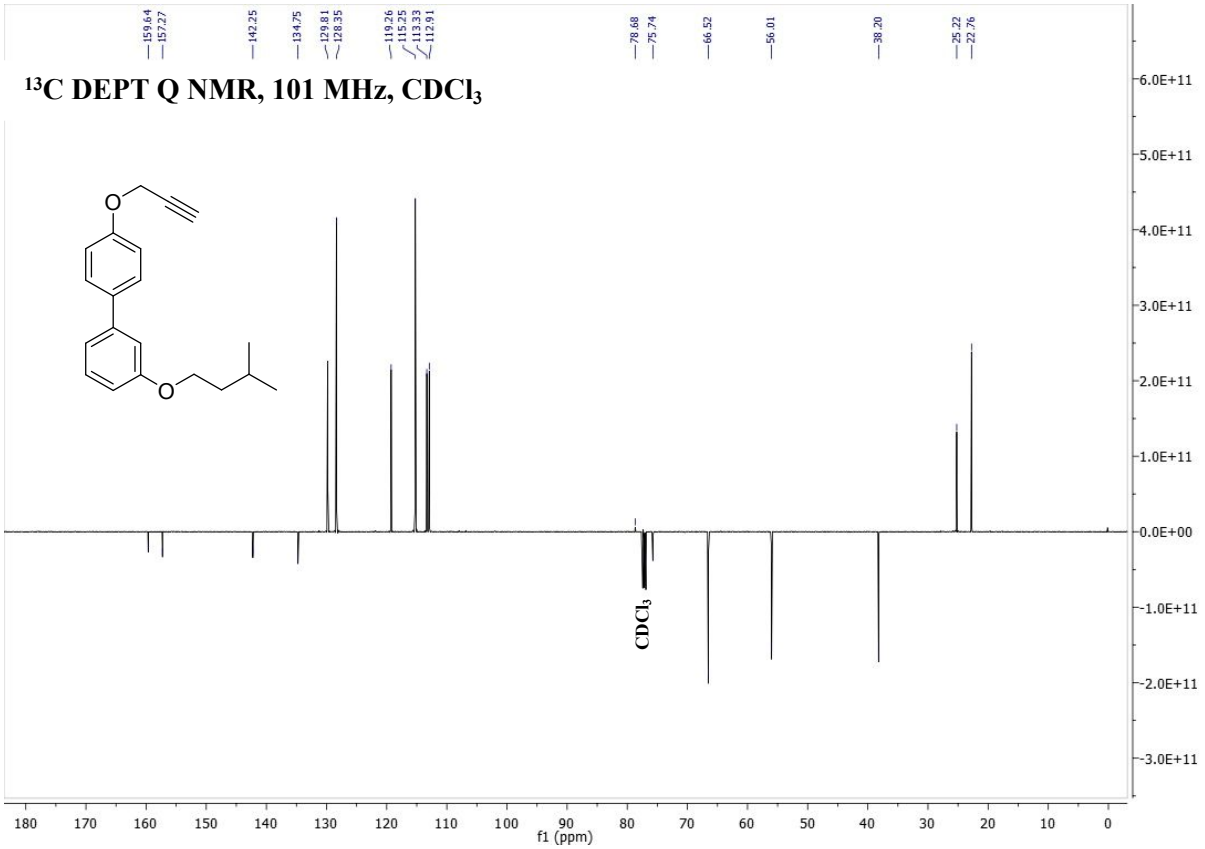


Fig. S36. ^{13}C DEPT Q NMR spectra of compound **15g** (recorded in $CDCl_3$).

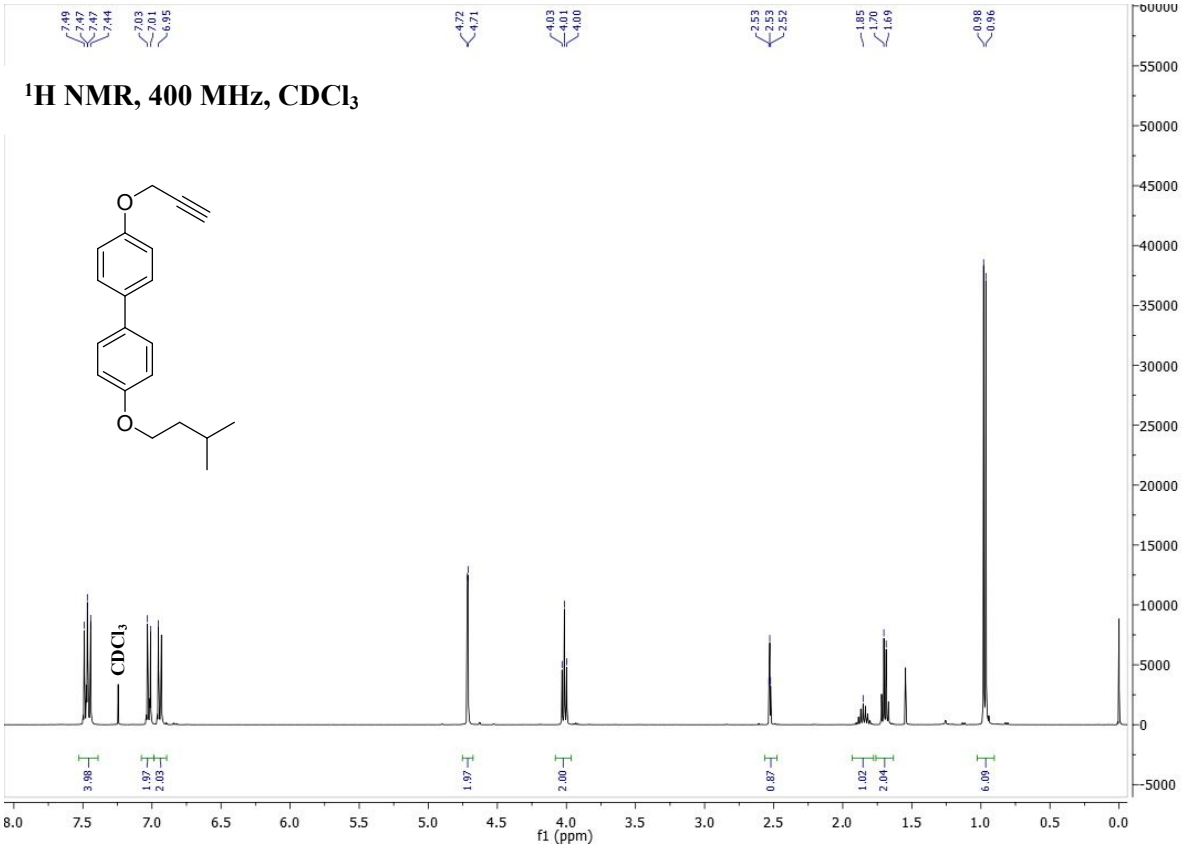


Fig. S37. ^{1}H NMR spectra of compound **15h** (recorded in $CDCl_3$).

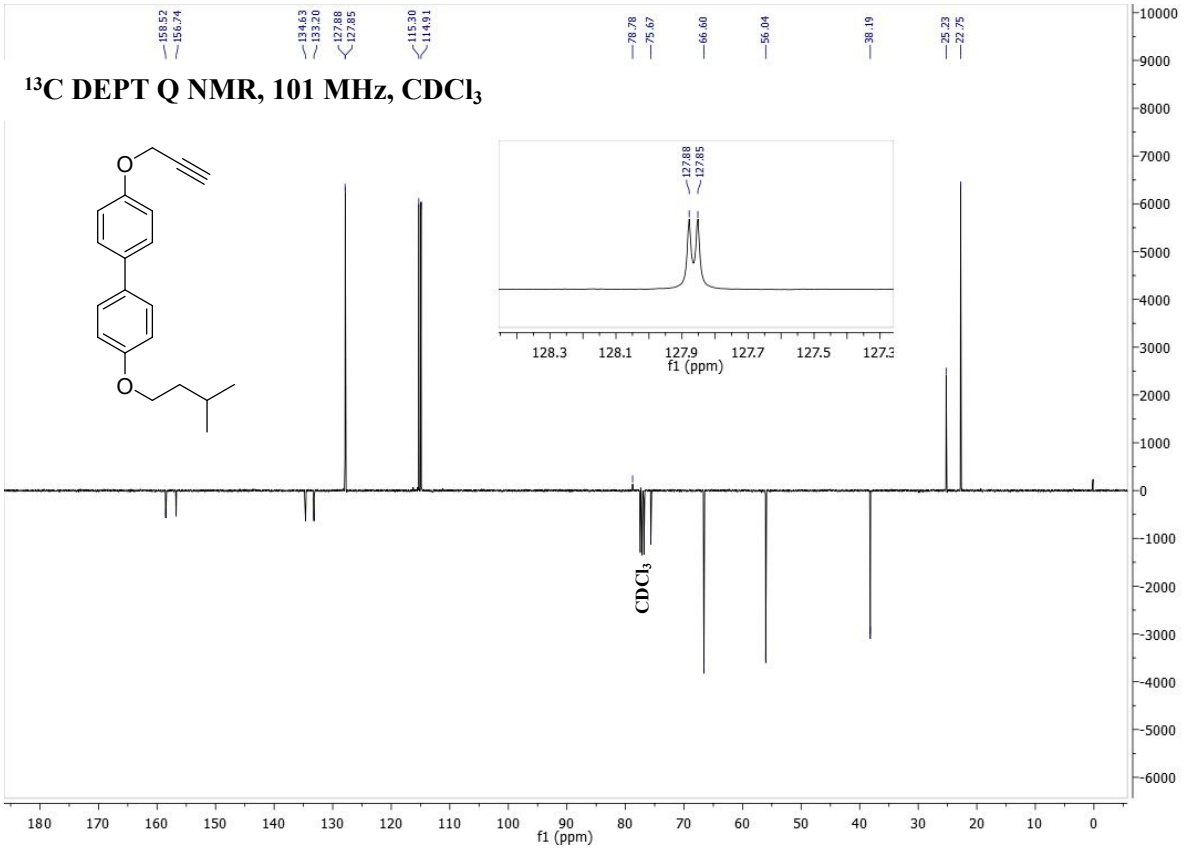


Fig. S38. ^{13}C DEPT Q NMR spectra of compound **15h** (recorded in $CDCl_3$).

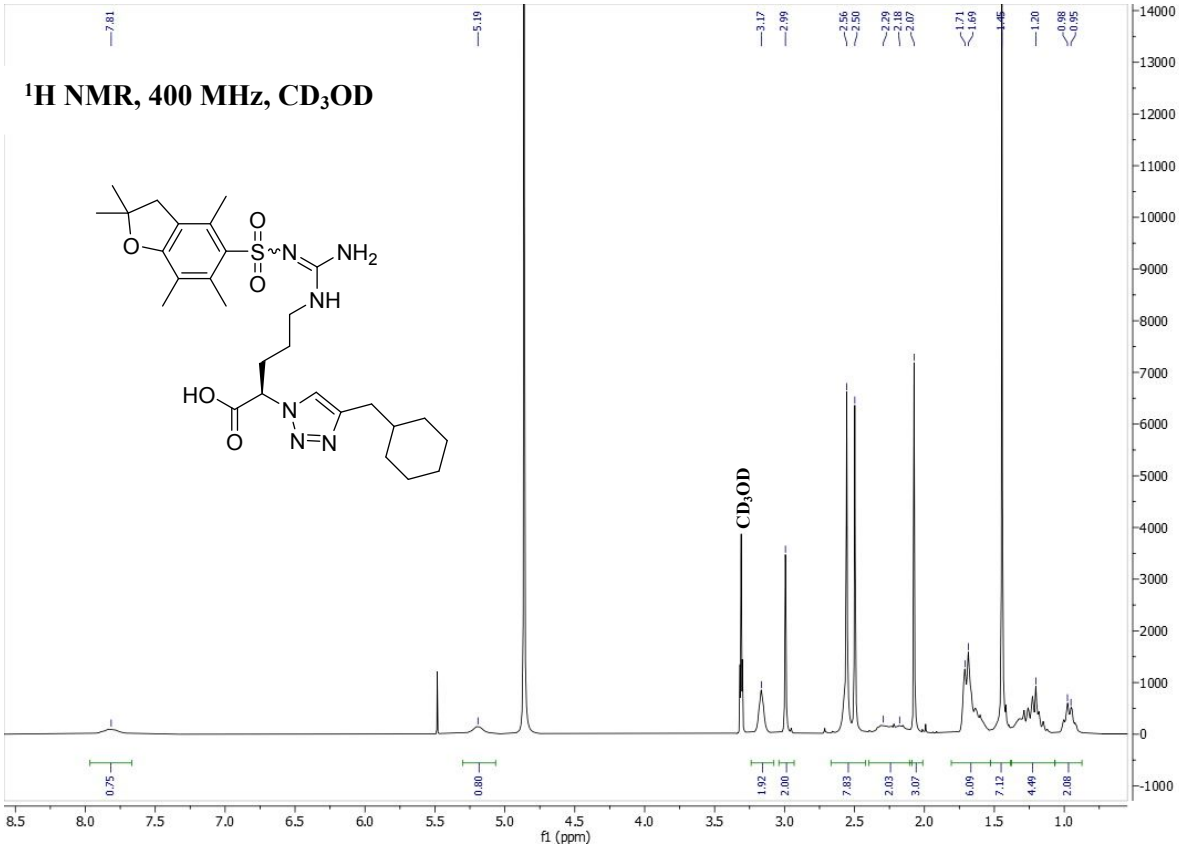


Fig. S39. ^{1}H NMR spectra of compound **19** (recorded in CD_3OD).

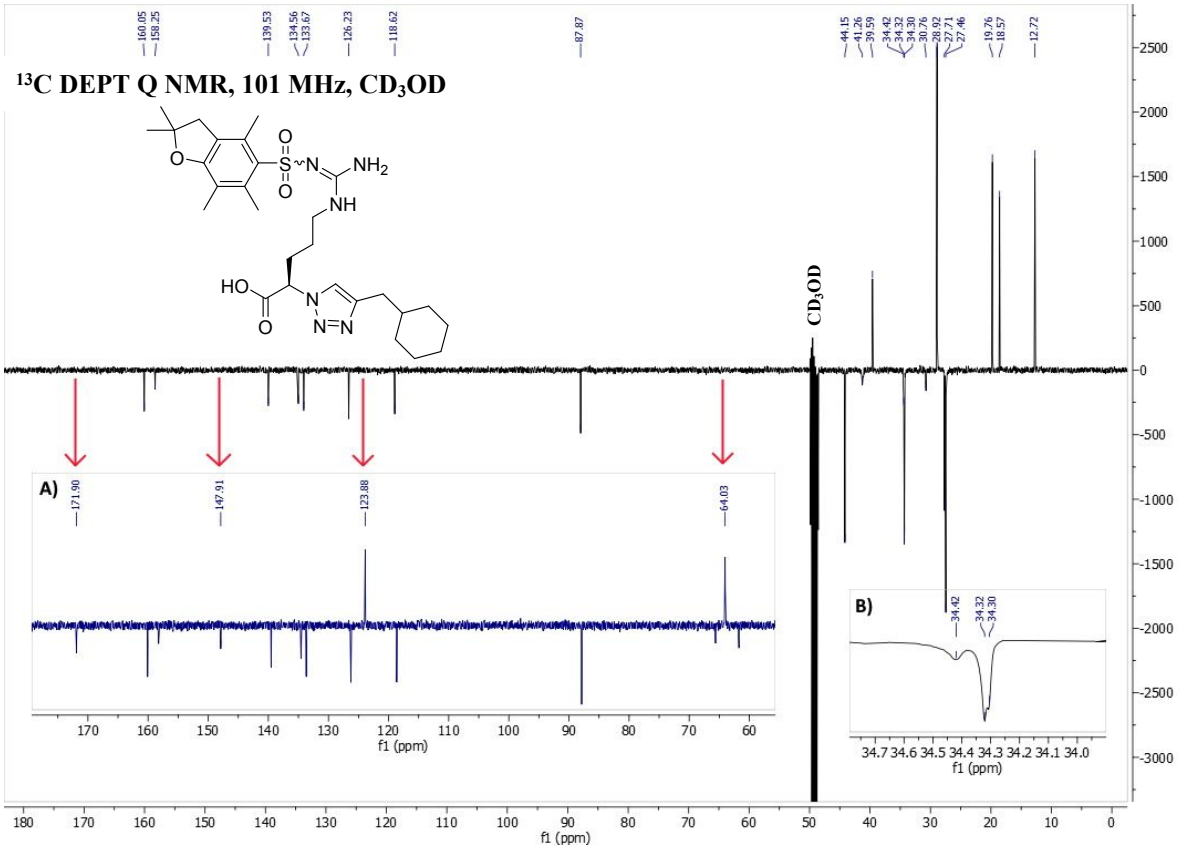


Fig. S40. ^{13}C DEPT Q NMR spectra of compound **19** (recorded in CD_3OD). Non-observable ^{13}C NMR resonances are denoted with red arrows. **Inset (A)**: "Missing" ^{13}C NMR resonances observed in dilute/impure sample of compound **19** (blue spectrum).

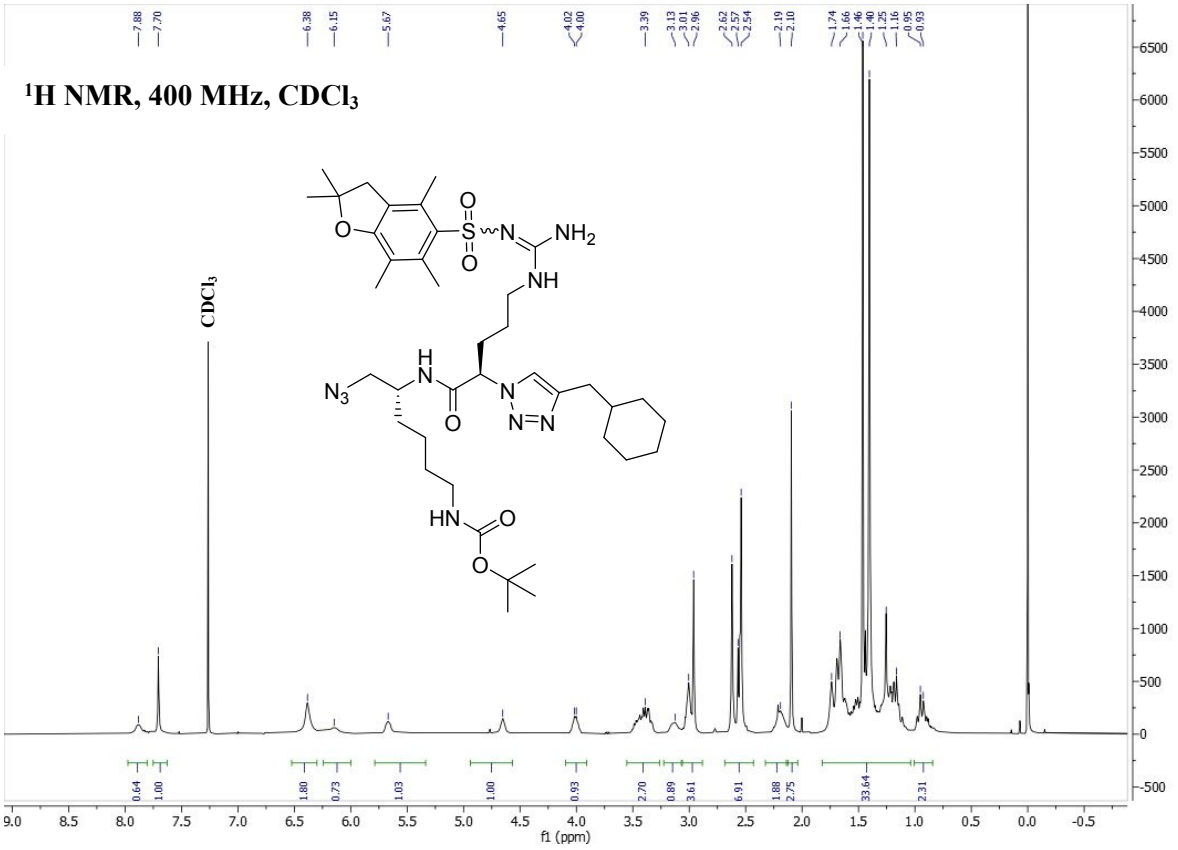


Fig. S41. ^{1}H NMR spectra of compound **20** (recorded in $CDCl_3$).

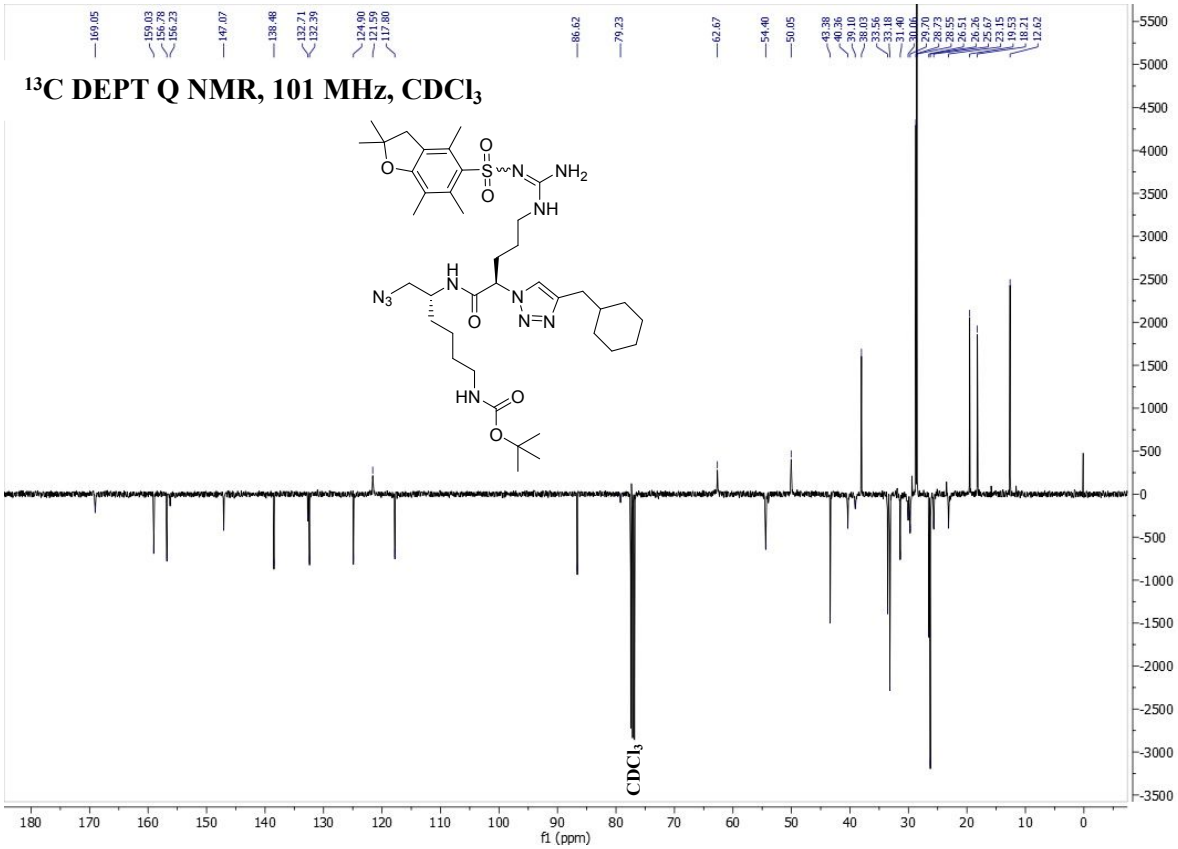


Fig. S42. ^{13}C DEPT Q NMR spectra of compound **20** (recorded in $CDCl_3$).

^{1}H and ^{13}C NMR spectra for all final compounds (2–9)

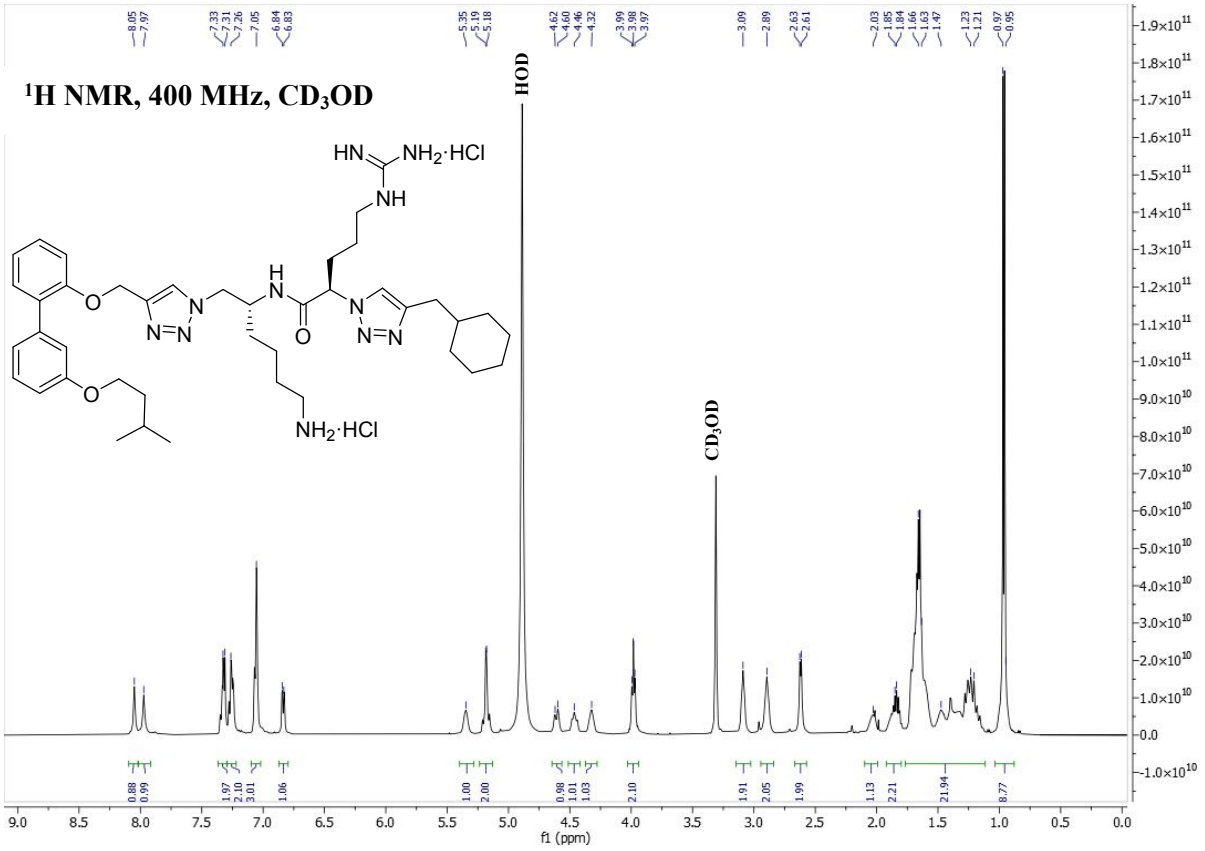


Fig. S43. ^{1}H NMR spectra of compound **2** (recorded in CD_3OD).

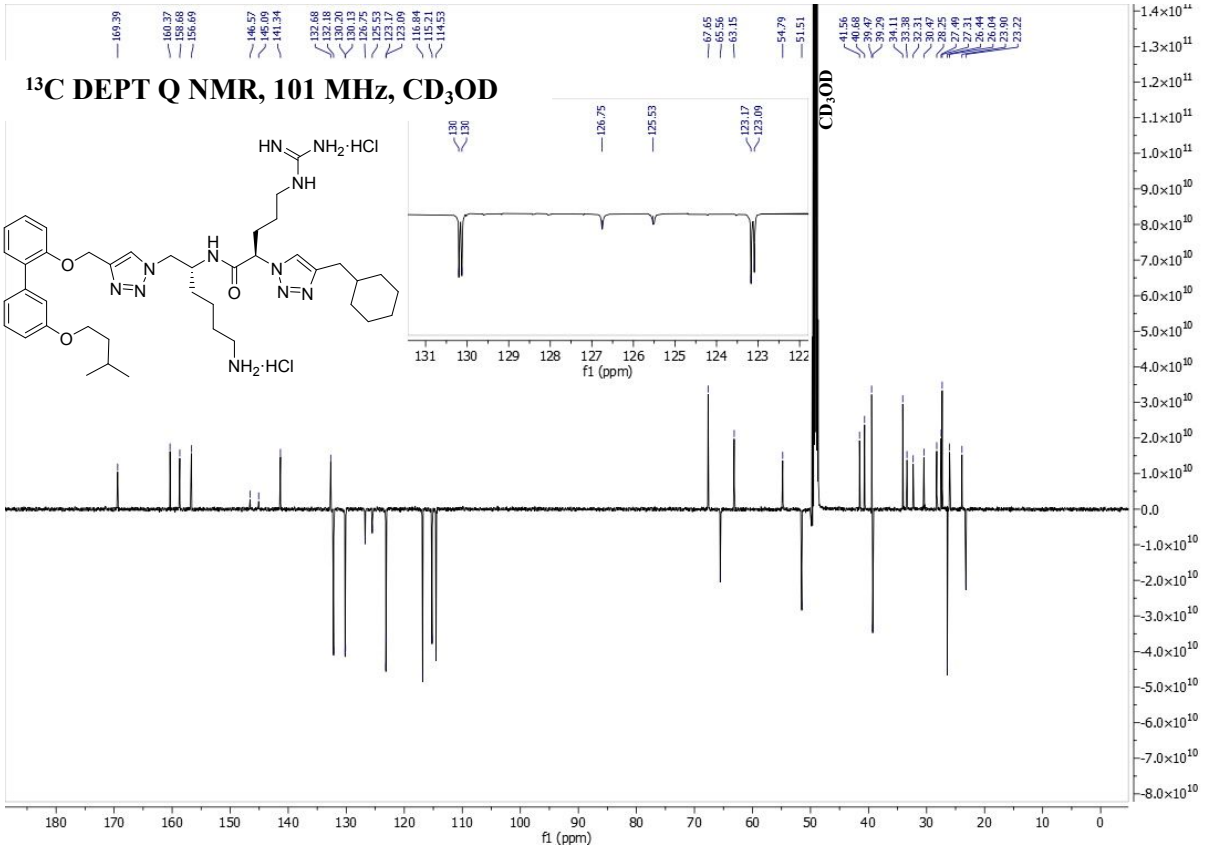


Fig. S44. ^{13}C DEPT Q NMR spectra of compound **2** (recorded in CD_3OD).

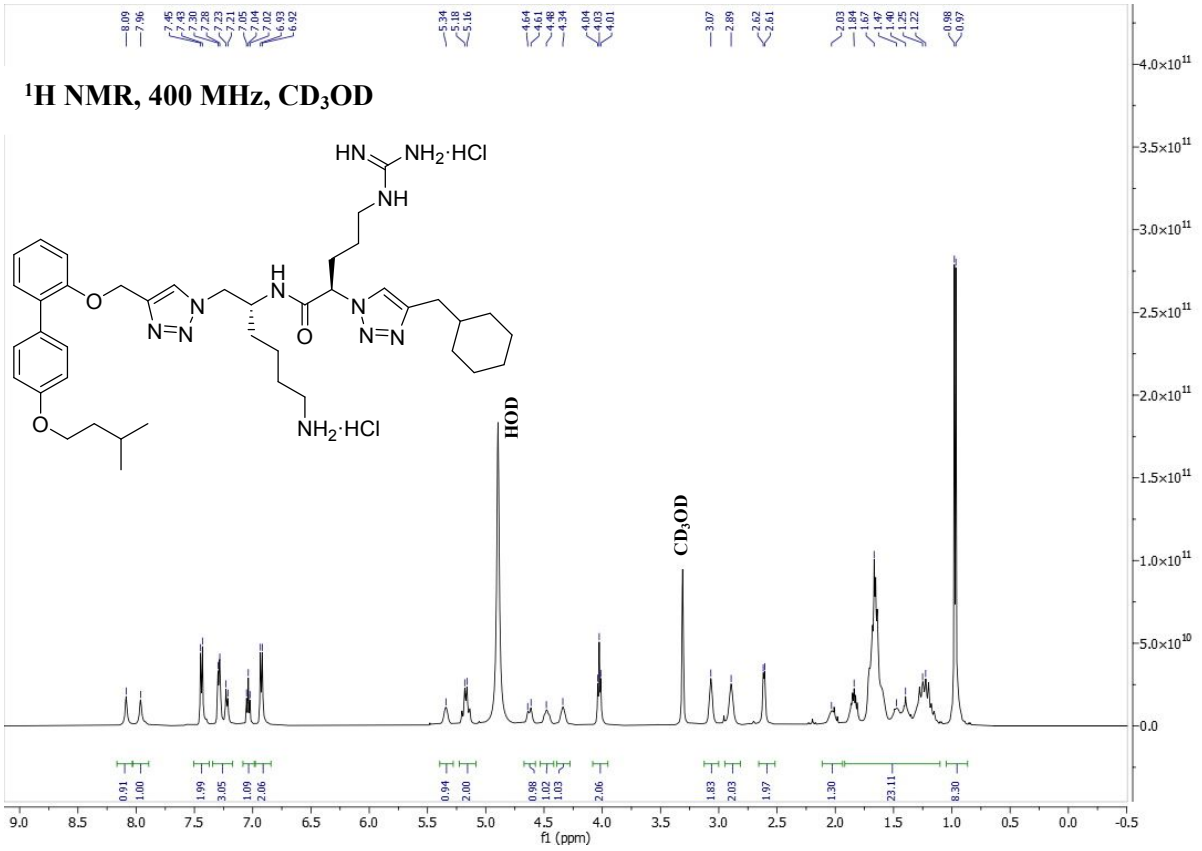


Fig. S45. ^{1}H NMR spectra of compound **3** (recorded in CD_3OD).

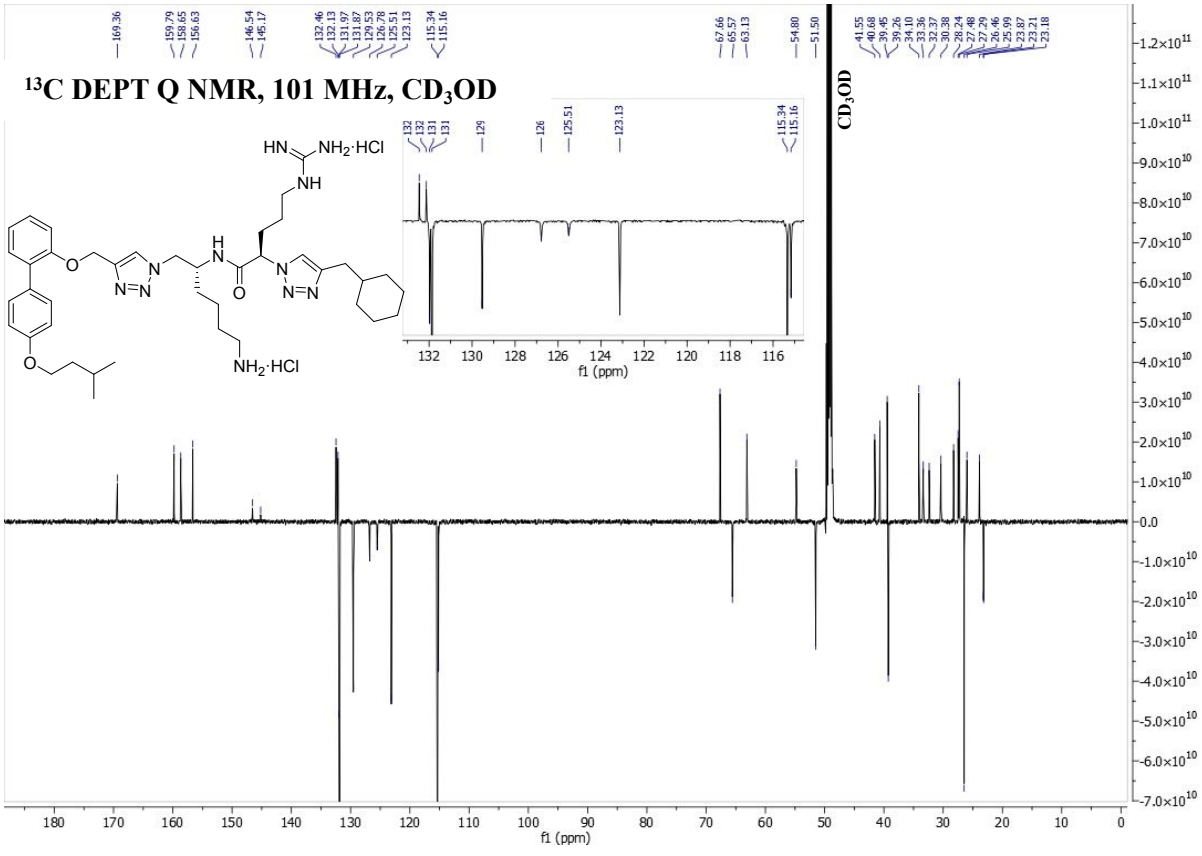


Fig. S46. ^{13}C DEPT Q NMR spectra of compound **3** (recorded in CD_3OD).

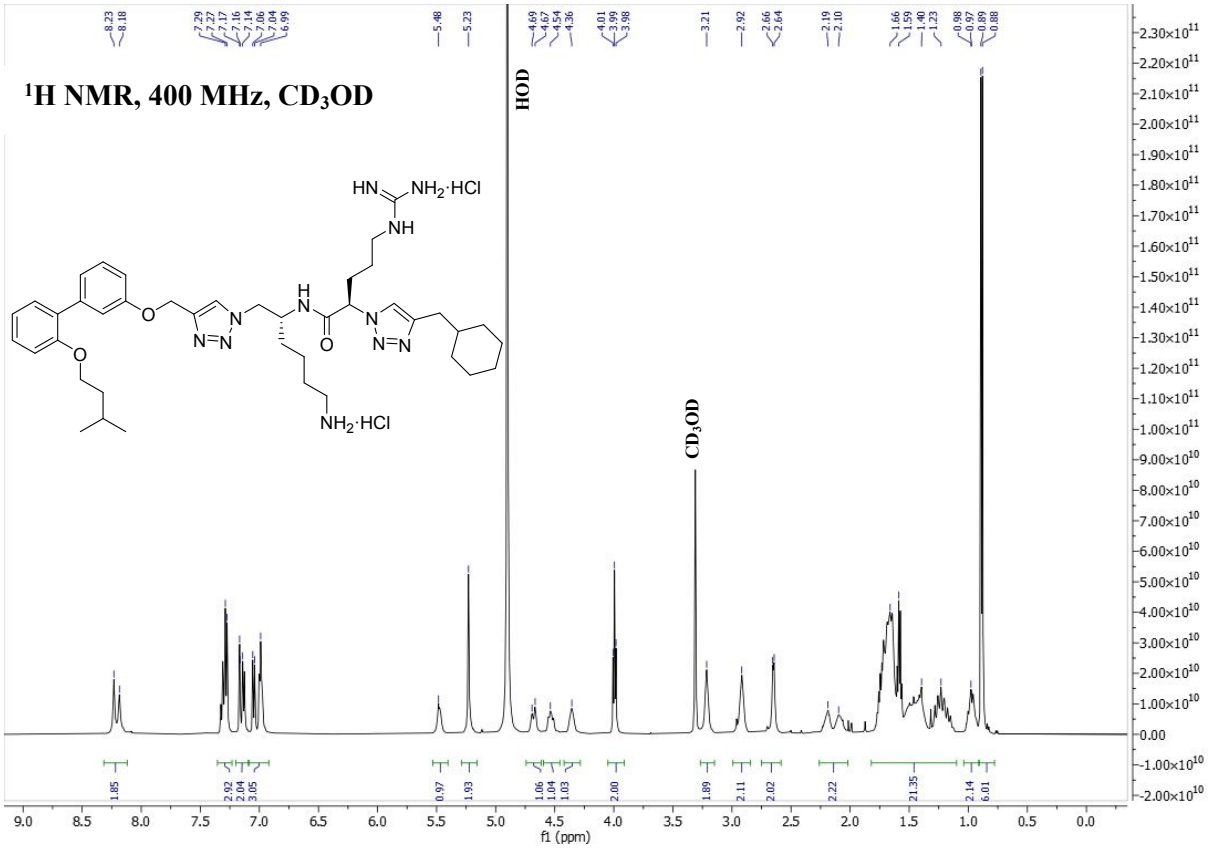


Fig. S47. ^{1}H NMR spectra of compound **4** (recorded in CD_3OD).

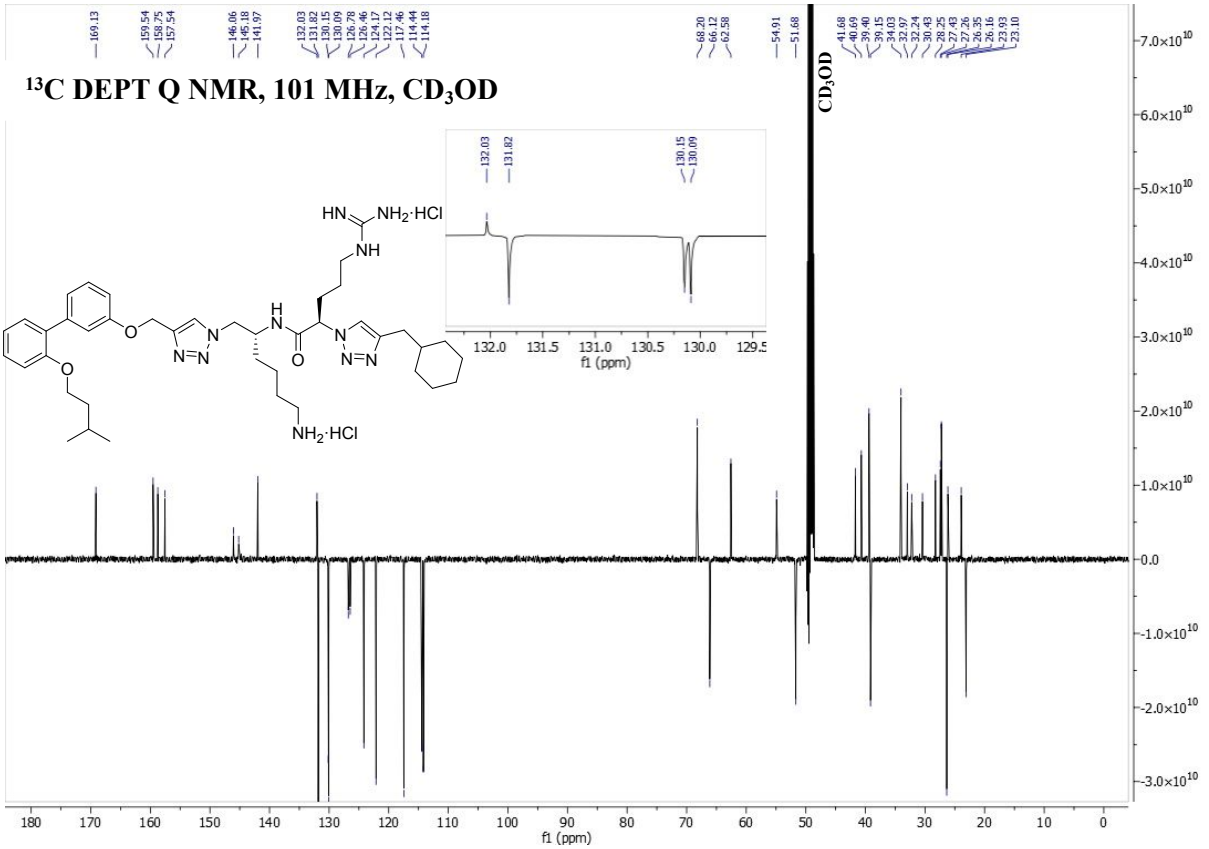


Fig. S48. ^{13}C DEPT Q NMR spectra of compound **4** (recorded in CD_3OD).

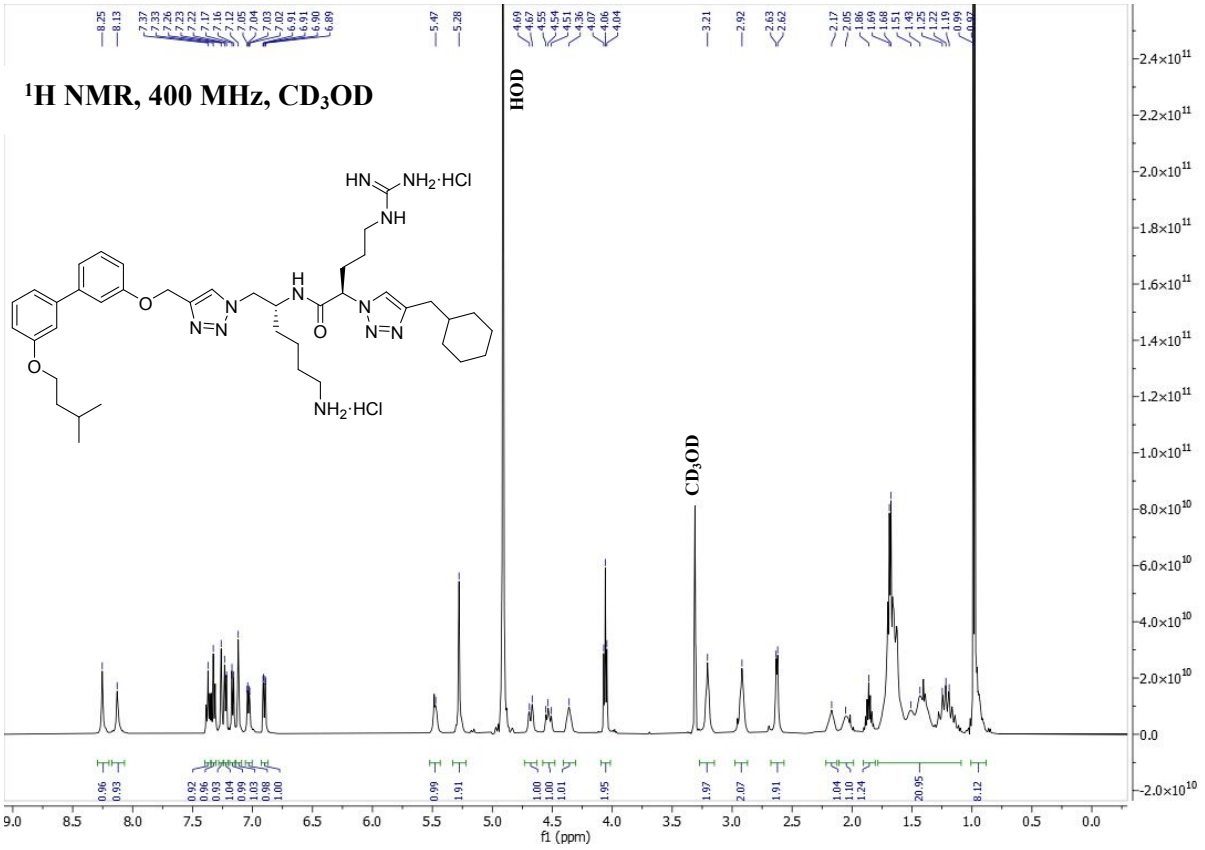


Fig. S49. ^{1}H NMR spectra of compound **5** (recorded in CD_3OD).

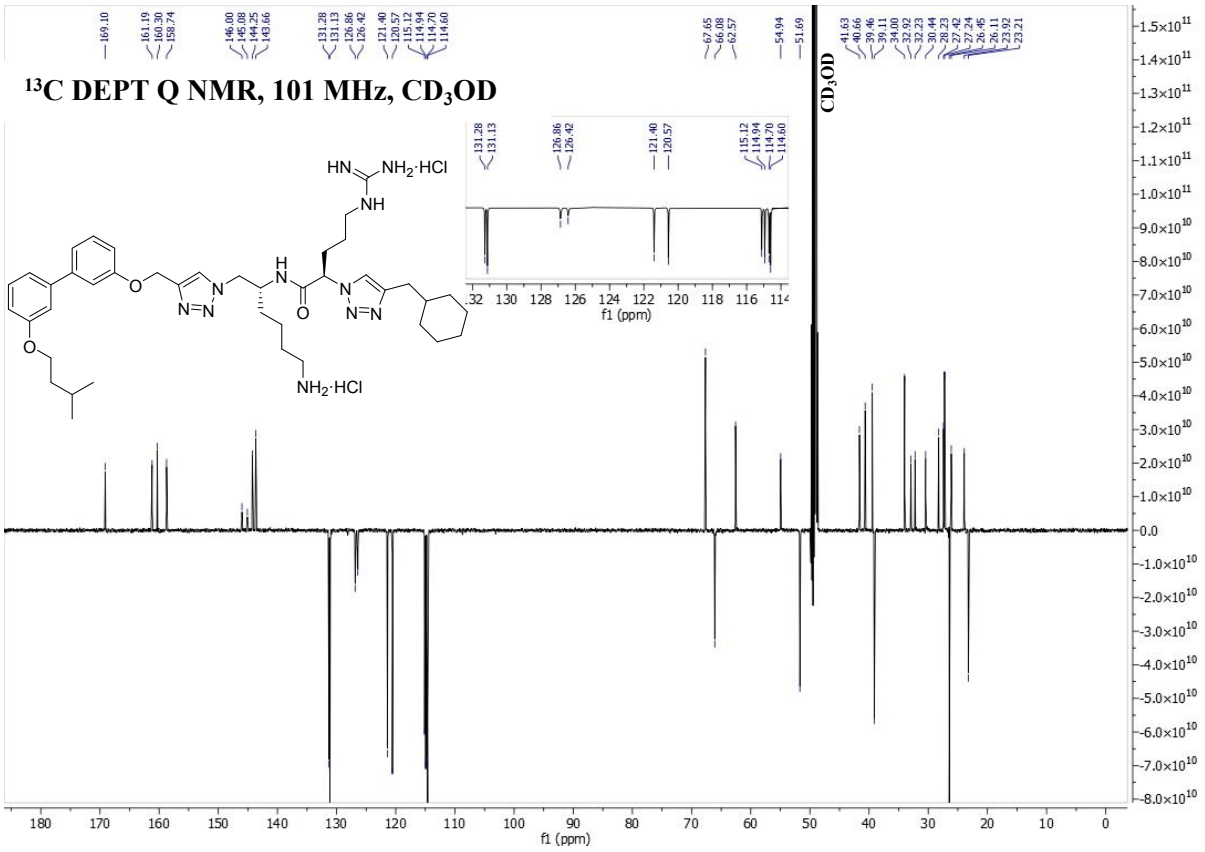


Fig. S50. ^{13}C DEPT Q NMR spectra of compound **5** (recorded in CD_3OD).

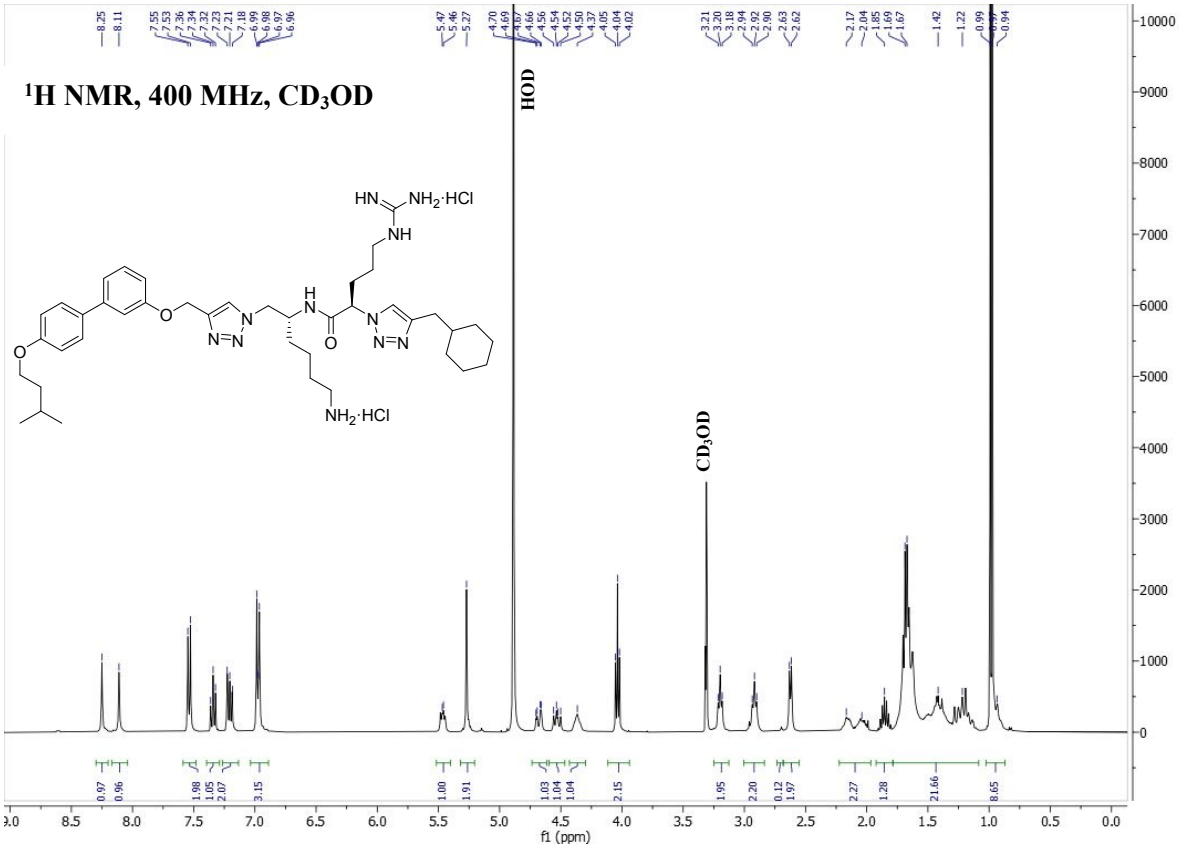


Fig. S51. ^{1}H NMR spectra of compound **6** (recorded in CD_3OD).

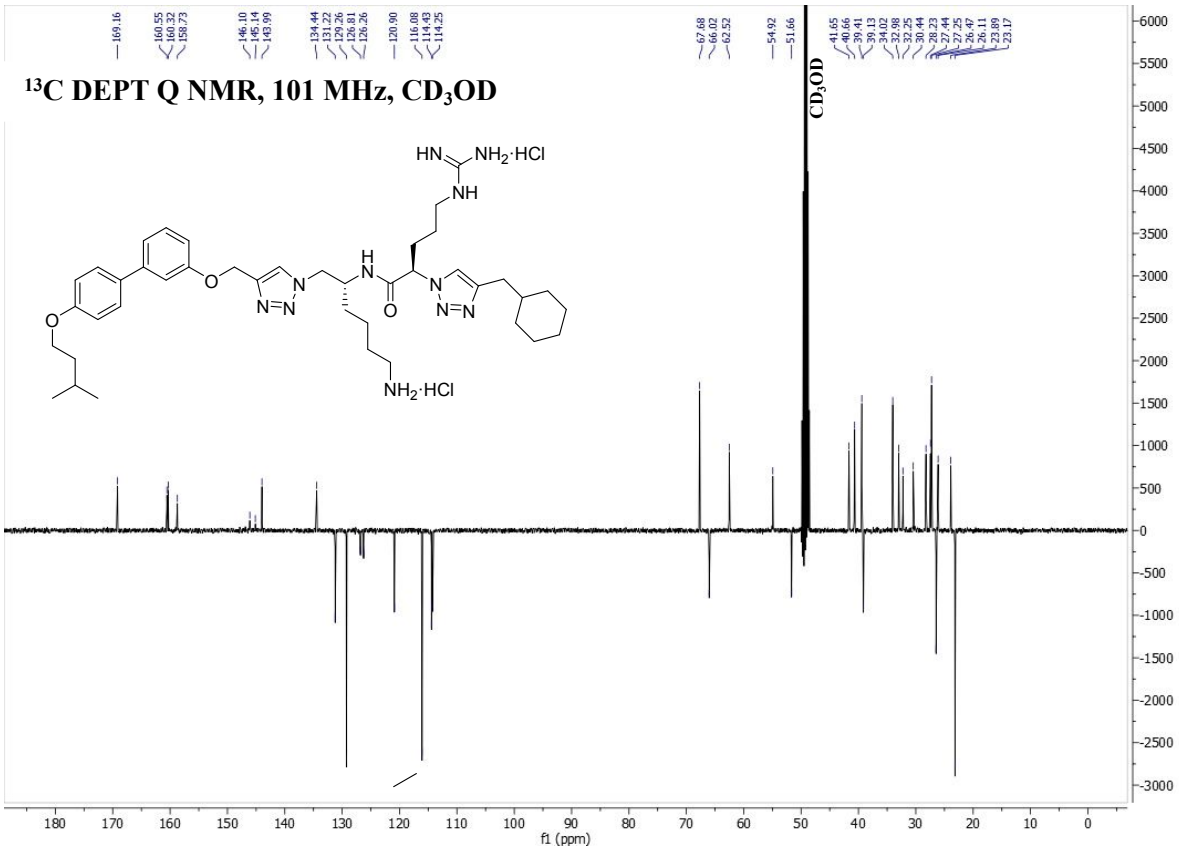


Fig. S52. ^{13}C DEPT Q NMR spectra of compound **6** (recorded in CD_3OD).

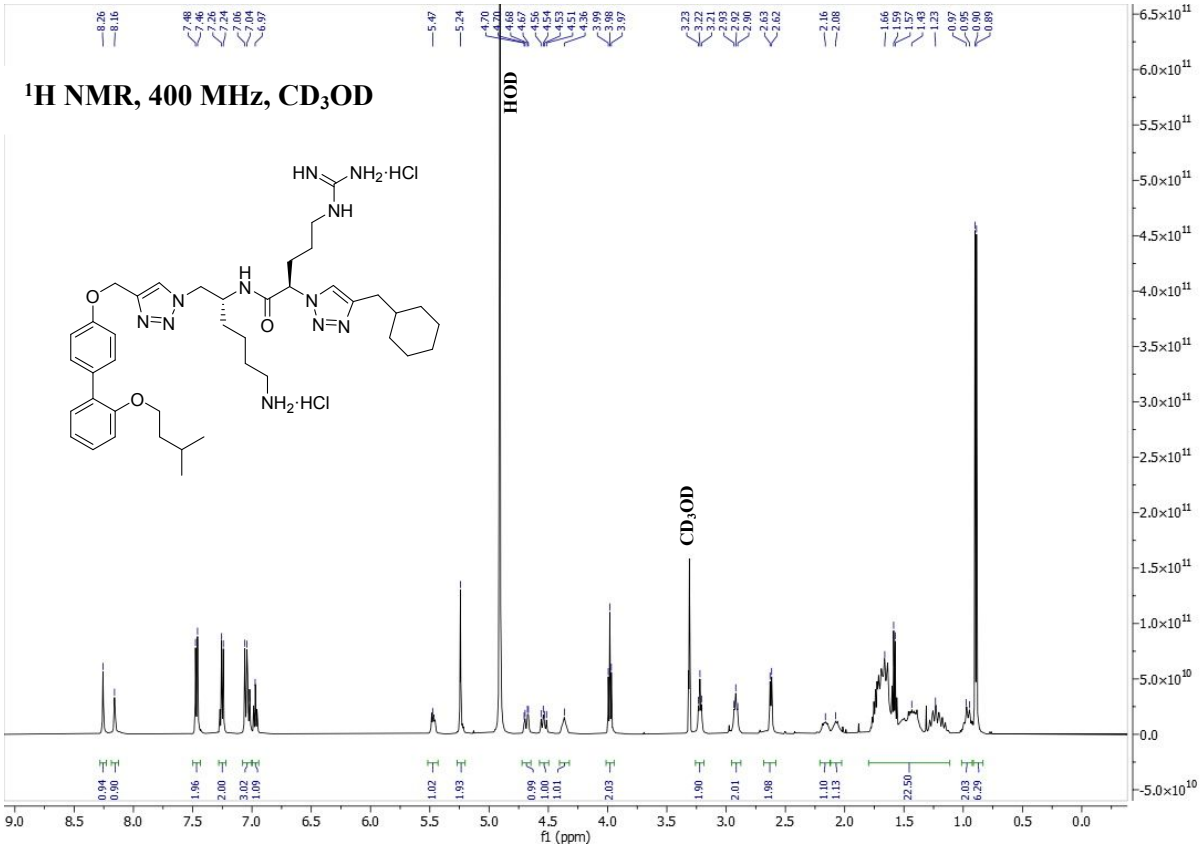


Fig. S53. ^{1}H NMR spectra of compound **7** (recorded in CD_3OD).

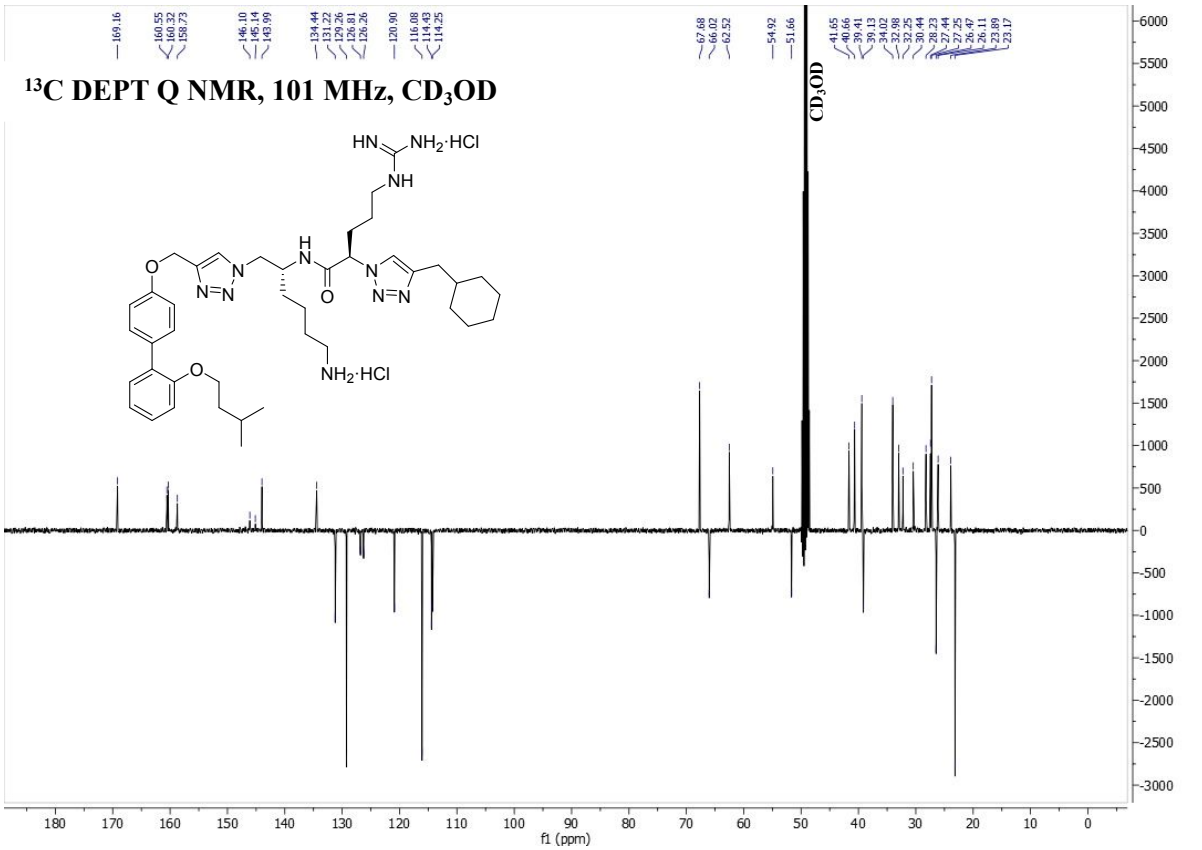


Fig. S54. ^{13}C DEPT Q NMR spectra of compound **7** (recorded in CD_3OD).

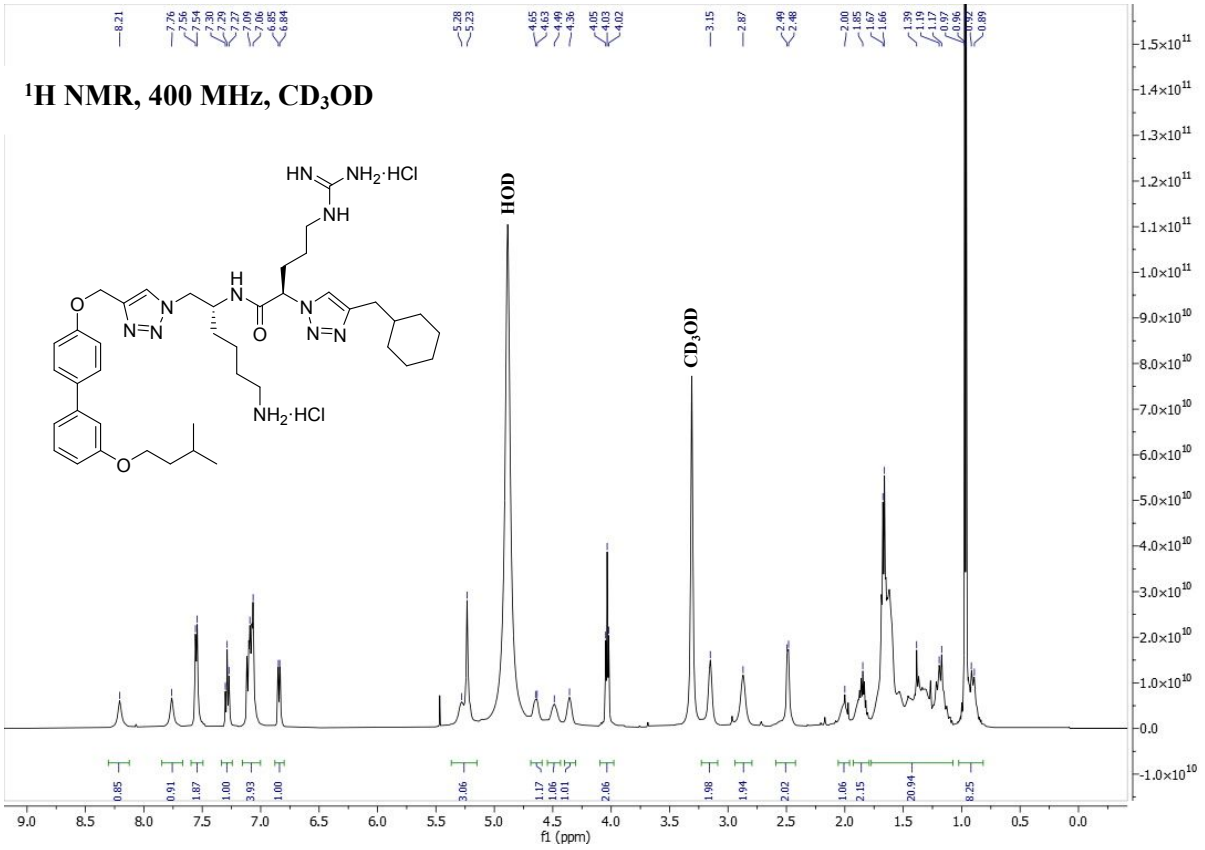


Fig. S55. ^{1}H NMR spectra of compound **8** (recorded in CD_3OD).

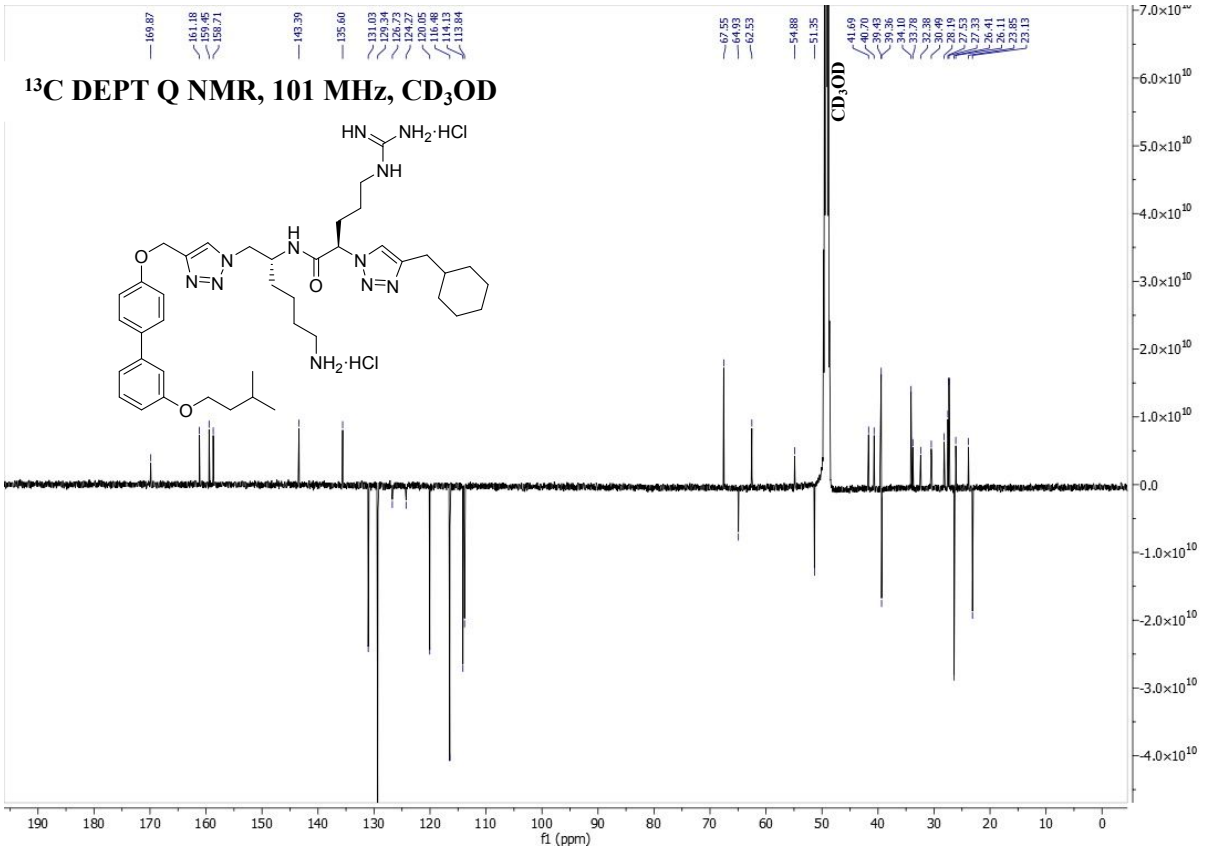


Fig. S56. ^{13}C DEPT Q NMR spectra of compound **8** (recorded in CD_3OD).

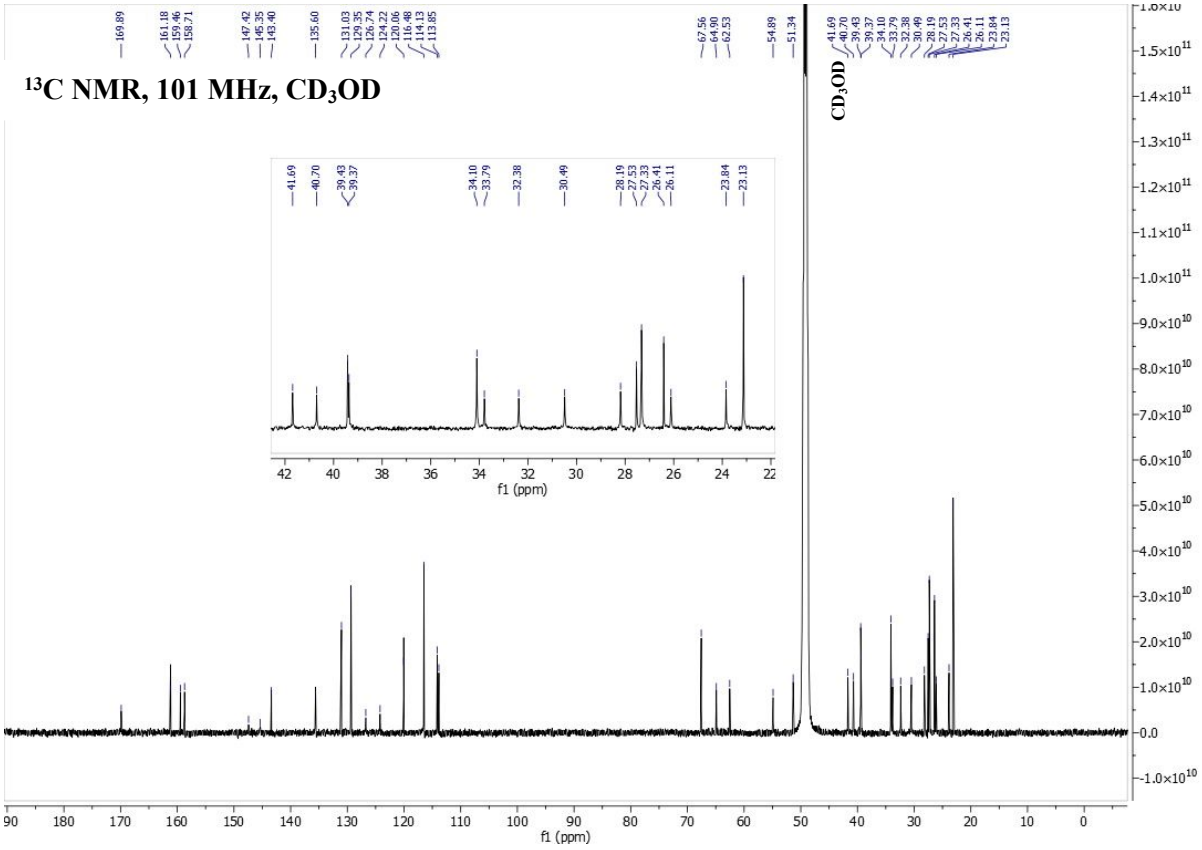


Fig. S57. ^{13}C NMR spectra of compound **8** (recorded in CD_3OD).

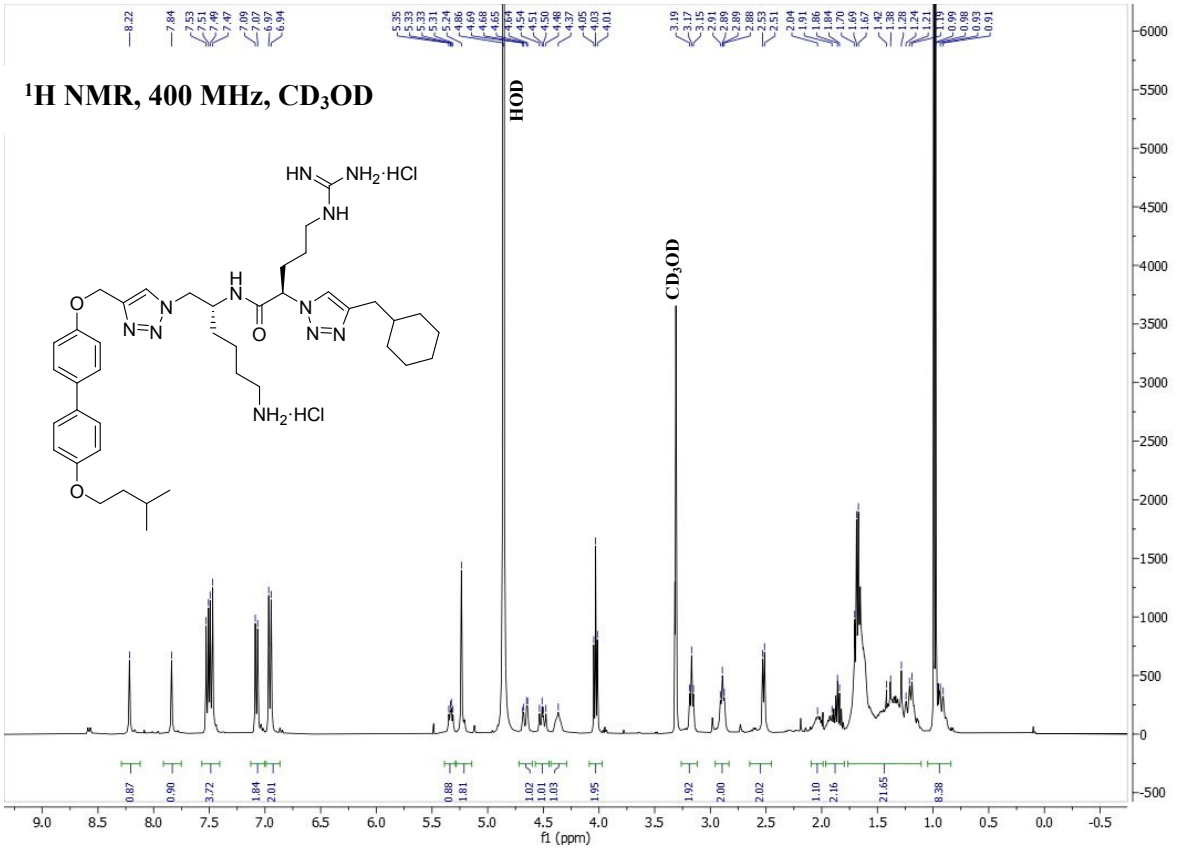


Fig. S58. ^{1}H NMR spectra of compound **9** (recorded in CD_3OD).

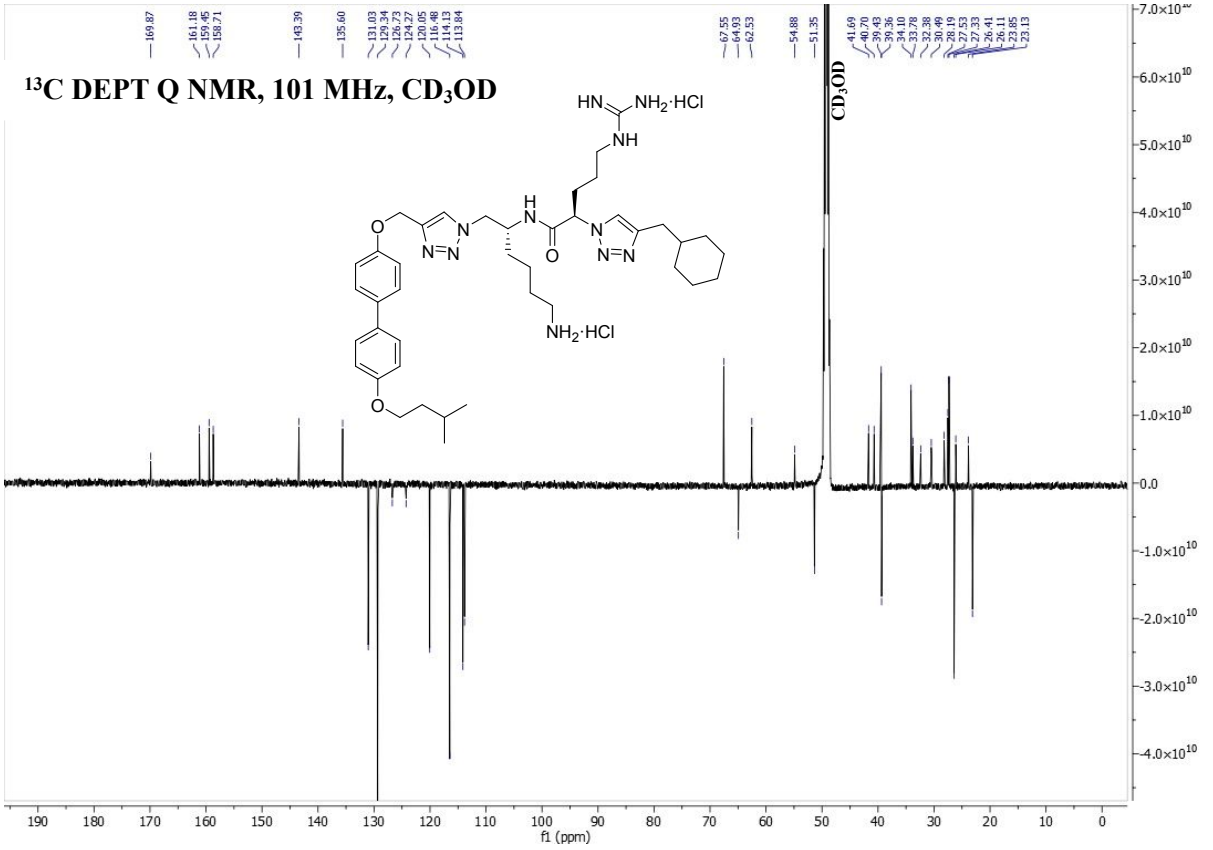


Fig. S59. ^{13}C DEPT Q NMR spectra of compound **9** (recorded in CD_3OD).

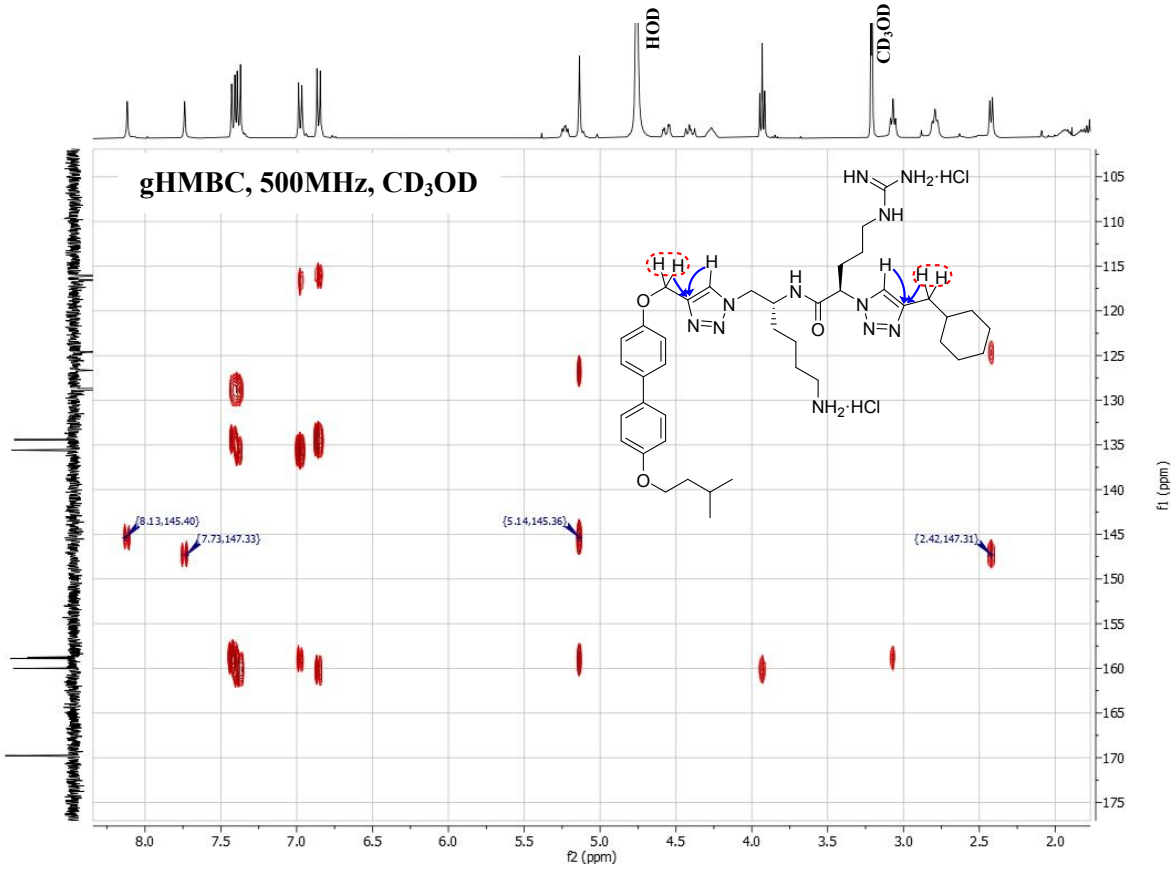
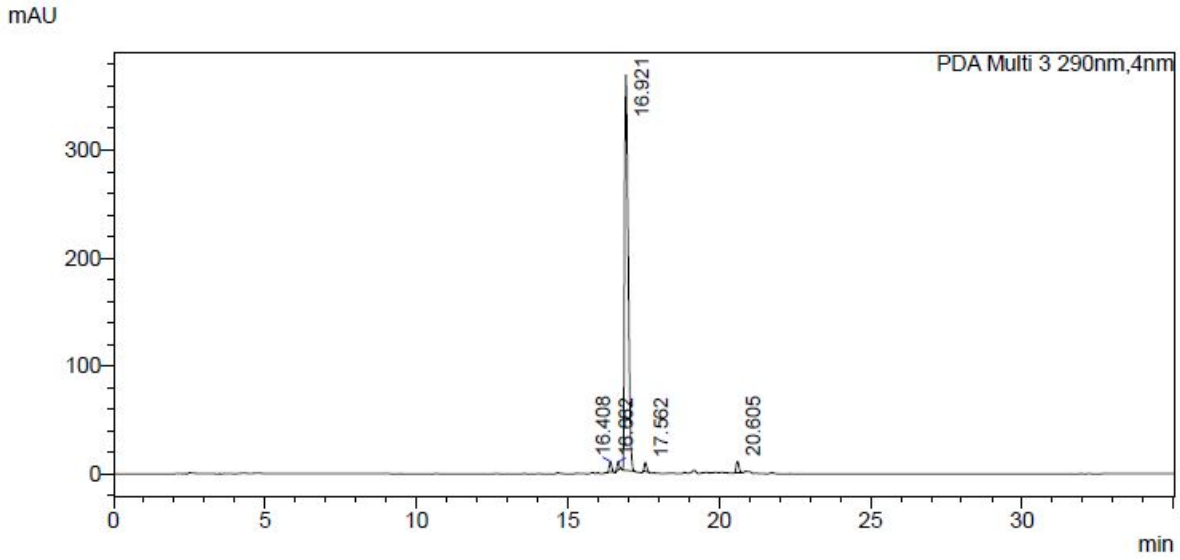


Fig. S60. gHMBC 2-D NMR spectra of compound **9** (recorded in CD_3OD). Correlations to the missing triazole quaternary ^{13}C NMR resonances are highlighted (denoted by chemical shift numbers and depicted by blue arrows).

Analytical reverse phase HPLC – methodology and chromatograms

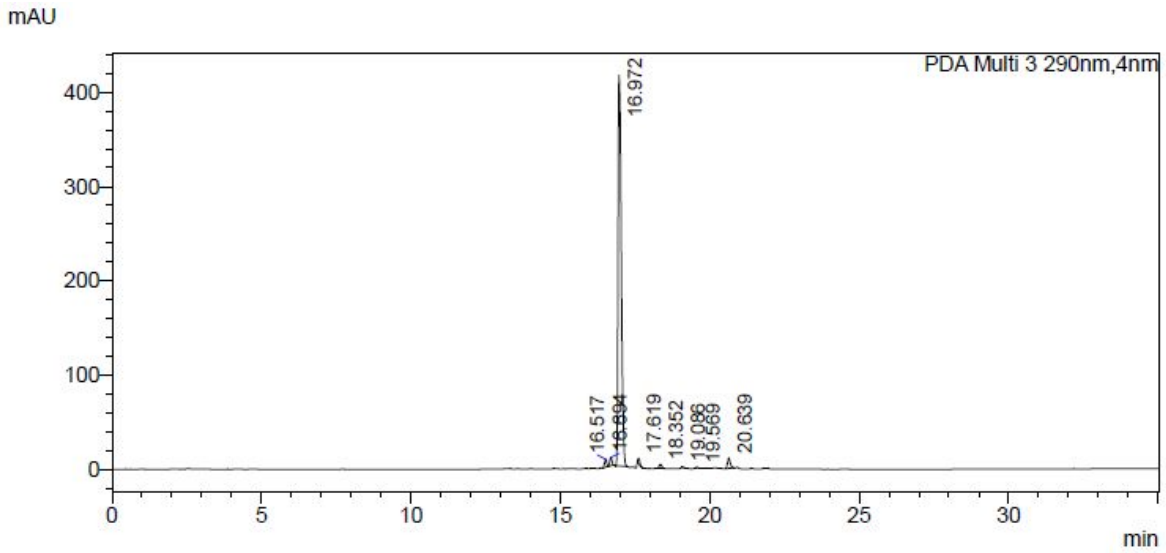
Reverse-phase HPLC analysis was conducted on a Phenomenex Synergi 4u Fusion-Reverse Phase 80Å column (φ = 4.6 × 150 mm) with detection at λ = 290 nm**.** Acetonitrile and H_2O (both with 0.1% v/v TFA) were employed as the non-polar and polar solvents, respectively. A gradient elution from 0:100 → 100:0 (acetonitrile/H_2O) over 30 min was employed and compounds typically eluted between 15 – 20 min. Tested compounds were shown to be >90% pure by HPLC (detected at 290 nm).



PDA Ch3 290nm

Peak#	Ret. Time	Area	Area%
1	16.408	51086	1.624
2	16.662	35733	1.136
3	16.921	2949848	93.789
4	17.562	45727	1.454
5	20.605	62812	1.997
Total		3145207	100.000

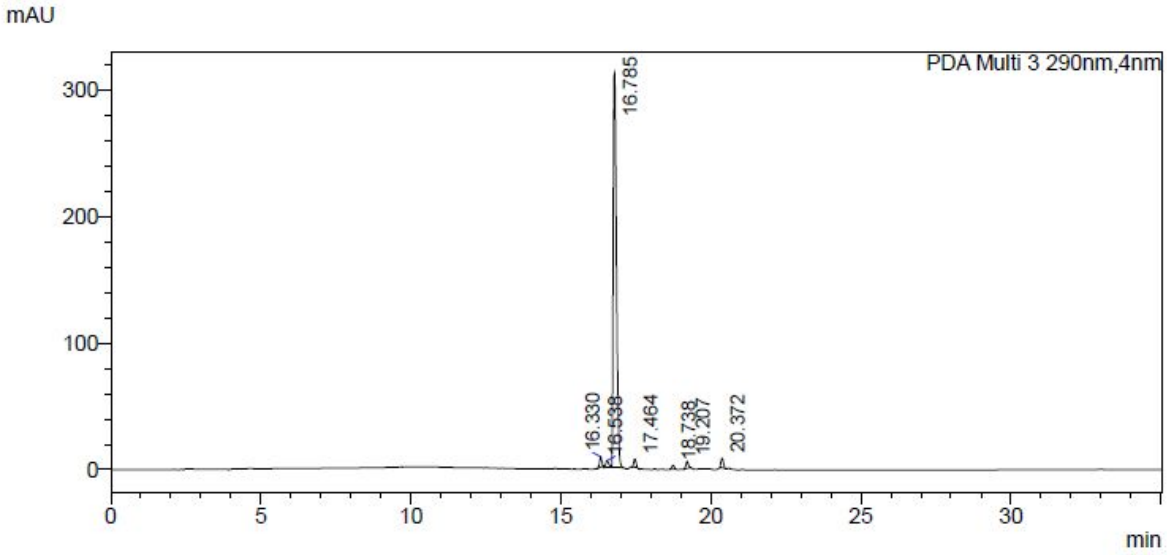
Fig. S61. HPLC chromatogram and peak integration table for compound **2**.



PDA Ch3 290nm

Peak#	Ret. Time	Area	Area%
1	16.517	43866	1.328
2	16.694	42753	1.294
3	16.972	3095578	93.714
4	17.619	24438	0.740
5	18.352	25287	0.766
6	19.086	710	0.021
7	19.569	454	0.014
8	20.639	70117	2.123
Total		3303203	100.000

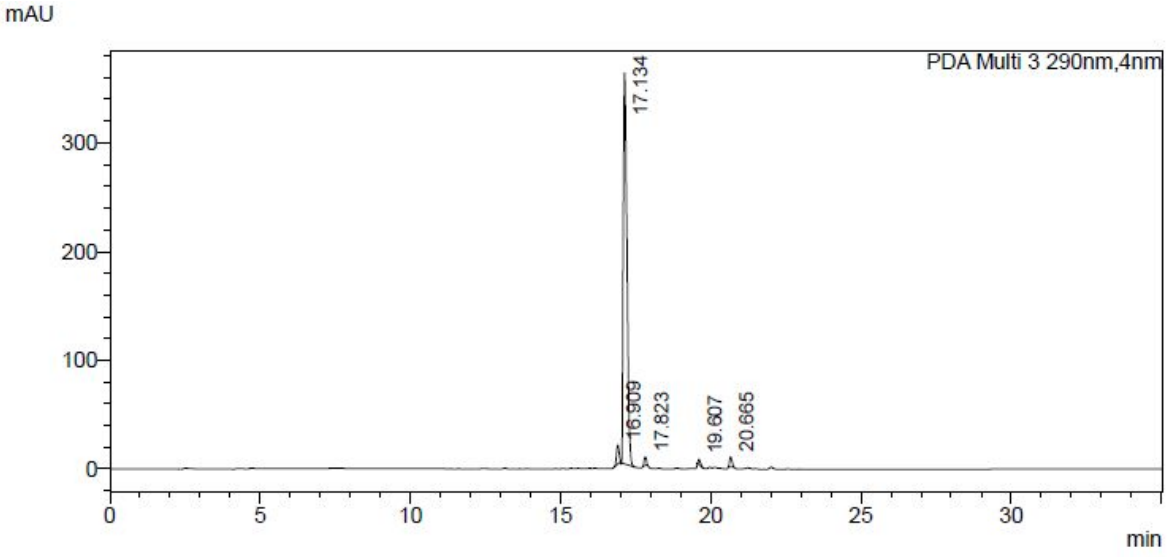
Fig. S62. HPLC chromatogram and peak integration table for compound **3**.



PDA Ch3 290nm

Peak#	Ret. Time	Area	Area%
1	16.330	40579	1.608
2	16.538	35243	1.396
3	16.785	2325769	92.157
4	17.464	33235	1.317
5	18.738	15113	0.599
6	19.207	32513	1.288
7	20.372	41264	1.635
Total		2523717	100.000

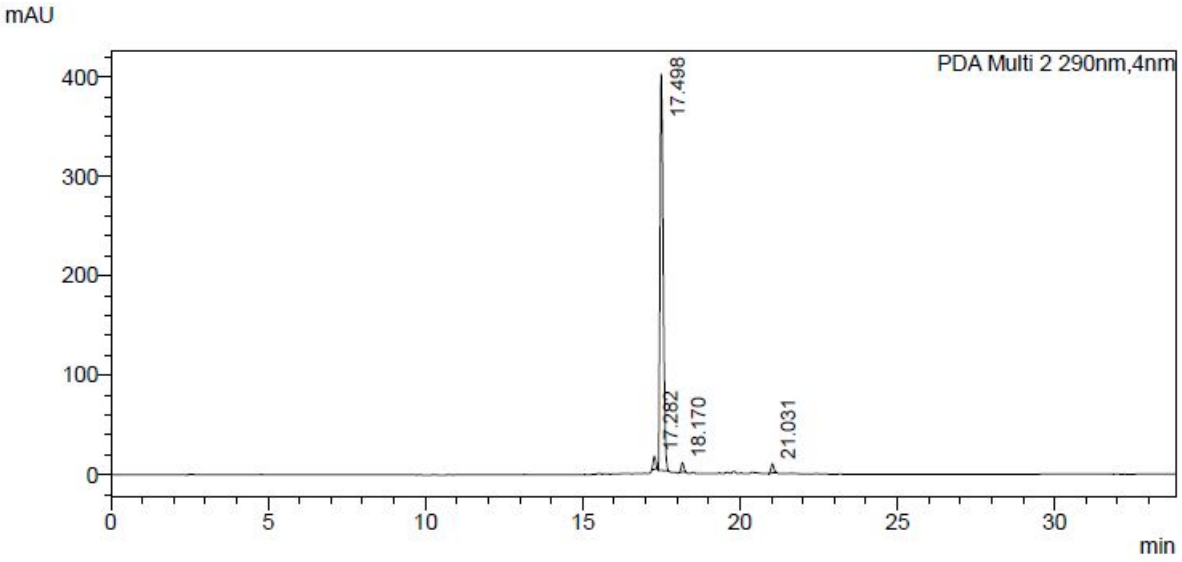
Fig. S63. HPLC chromatogram and peak integration table for compound **4**.



PDA Ch3 290nm

Peak#	Ret. Time	Area	Area%
1	16.909	100941	3.120
2	17.134	3020321	93.358
3	17.823	39086	1.208
4	19.607	22862	0.707
5	20.665	52009	1.608
Total		3235218	100.000

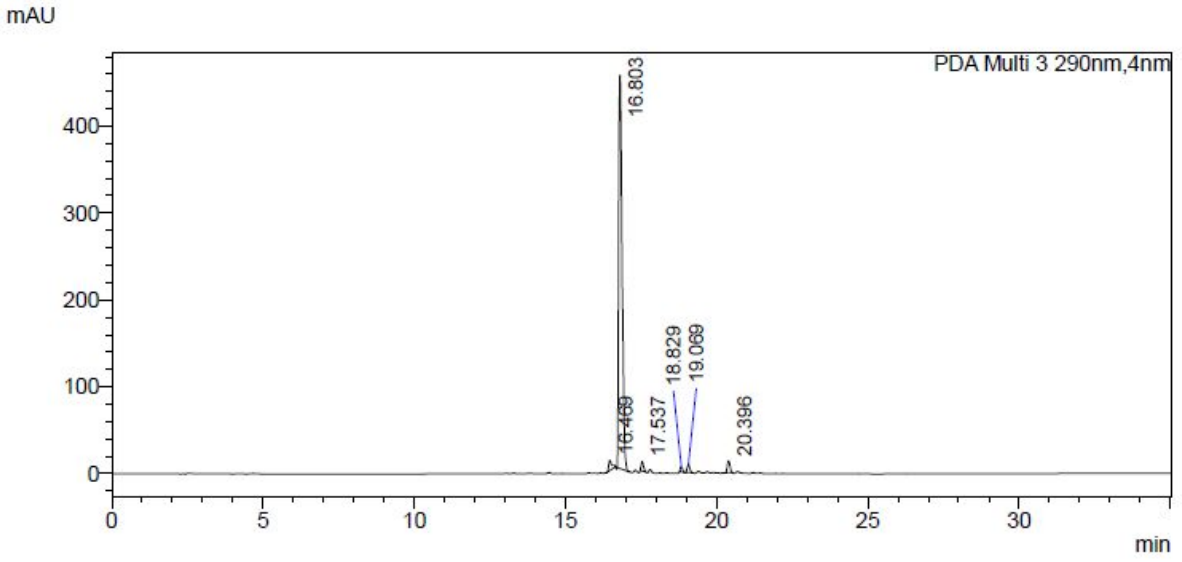
Fig. S64. HPLC chromatogram and peak integration table for compound **5**.



PDA Ch2 290nm

Peak#	Ret. Time	Area	Area%
1	17.282	73551	2.457
2	17.498	2814070	94.000
3	18.170	52082	1.740
4	21.031	53987	1.803
Total		2993690	100.000

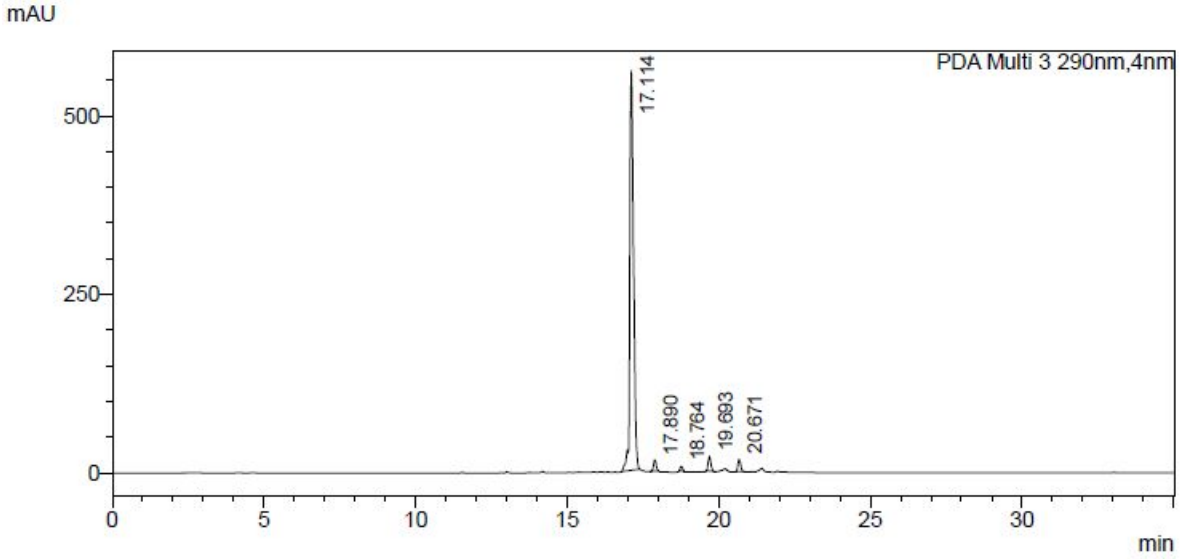
Fig. S65. HPLC chromatogram and peak integration table for compound **6**.



PDA Ch3 290nm

Peak#	Ret. Time	Area	Area%
1	16.469	88898	2.312
2	16.803	3534296	91.899
3	17.537	57259	1.489
4	18.829	27610	0.718
5	19.069	54285	1.412
6	20.396	83516	2.172
Total		3845864	100.000

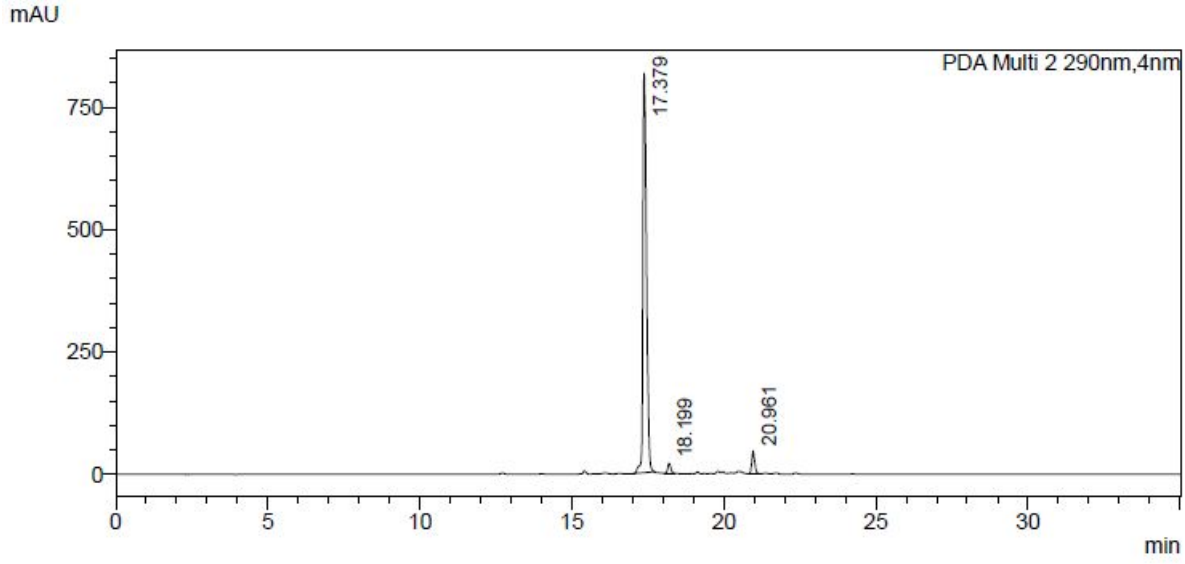
Fig. S66. HPLC chromatogram and peak integration table for compound **7**.



PDA Ch3 290nm

Peak#	Ret. Time	Area	Area%
1	17.114	4775829	92.847
2	17.890	99901	1.942
3	18.764	35362	0.687
4	19.693	123550	2.402
5	20.671	109122	2.121
Total		5143765	100.000

Fig. S67. HPLC chromatogram and peak integration table for compound **8**.



PDA Ch2 290nm

Peak#	Ret. Time	Area	Area%
1	17.379	6804565	93.844
2	18.199	137933	1.902
3	20.961	308440	4.254
Total		7250938	100.000

Fig. S68. HPLC chromatogram and peak integration table for compound **9**.

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