

Supplementary Information for

Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles

Christopher D. Smith and Michael F. Greaney*

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK.

michael.greaney@manchester.ac.uk

www.greaney.chemistry.manchester.ac.uk

Contents

Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles	1
Experimental.....	2
Starting Materials	3
Azides	3
Alkynes	4
Synthesis of Final Products	6
General Procedure for the Synthesis of 1,4-Substituted 1,2,3-Triazoles	6
Synthesis of 1,4,5-Substituted 1,2,3-Triazoles	18
NMR Spectra	23
¹ H- and ¹³ C-NMR Spectra of Novel Starting Materials.....	23
¹ H- and ¹³ C-NMR Spectra of 1,5-Substituted Triazoles.....	28
¹ H- and ¹³ C-NMR Spectra of 1,4,5-Substituted Triazoles	49

Experimental

¹H-NMR spectra were recorded on 500, 400 or 300 Bruker spectrometers with residual chloroform or DMSO as the internal reference (CHCl₃, δ_{H} = 7.26 ppm; DMSO, δ_{H} = 2.50 ppm). ¹³C-NMR spectra used the central resonance of CDCl₃ or DMSO as the internal reference (CDCl₃, δ_{C} = 77.0 ppm; DMSO, δ_{C} = 39.5 ppm). ¹⁹F-NMR spectra are measured relative to CFCl₃ δ_{F} = 0.0 (external reference). Assignments were made using a range of NMR experiments (DEPT135, COSY, HMQC and HMBC). All chemical shifts are quoted in parts per million (ppm) down field from tetramethylsilane, measured from the centre of the signal except in the case of multiplets of more than one proton which are quoted as a range. Coupling constants are quoted to the nearest 0.5 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), sextet (sex.), septet (sept.), multiplet (m), apparent (ap.), broad (br.) and combinations thereof.

Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer as a thin film and are reported in cm⁻¹. Letters in parentheses refer to the relative absorbency of the main peak: w, weak, < 40%; m, medium, 41-74%; s, strong >75%; and br, broad.

Melting points were determined using a Büchi M-565 melting point apparatus.

High Resolution Mass Spectrometry (HRMS) were recorded on one of the following: Waters QTOF (ES, HRMS) or Thermo Finnigan MAT95XP (GC/MS, EI, HRMS).

LCMS analysis was performed on an Agilent HP 1100 chromatograph (Atlantis RP column) attached to an HPLC/MSD mass spectrometer (API-ES). Elution was carried out using a reversed-phase gradient of MeOH:*i*-PrOH (9:1) / water, with both solvents containing 0.2% formic acid. The gradient of the 6.0 min run is described in Table 1.

Table 1. LCMS conditions.

Time (min)	MeOH: <i>i</i> -PrOH (9:1) (%)	Total flow rate (mL/min)
0.00	2	0.9
3.50	98	0.9
4.50	98	0.9
4.60	2	0.9

All THF was distilled under N₂ over sodium wire and benzophenone. Toluene and dichloromethane were distilled under N₂ and over calcium hydride. All reagents were used as obtained from commercial sources.

Starting Materials

Azides

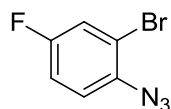
CAUTION: Azides are both shock sensitive and toxic. The use of acids in the presence of the azide ion is advised against due to the possible release of hydrazoic acid gas, a known poison. Furthermore, the use of CH_2Cl_2 in the presence of the azide ion may lead to the formation of diazidomethane ($\text{N}_3\text{CH}_2\text{N}_3$) which is known to self detonate. No incidents occurred during the synthesis or use of azides but for these reasons the reactions were not performed on scales greater than 5 g.

Benzyl azide was synthesised using known procedures.¹

General procedure for the synthesis of aromatic azides from their corresponding anilines.² A solution of the aniline (5 mmol) was dissolved in MeCN (25 mL), azidotrimethylsilane (6 mmol) was added before cooling to 0 °C. *tert*-Butyl nitrite (5.5 mmol) was added portion wise over 15 minutes to the solution. The reaction was allowed to warm to ambient temperature and stirred until complete by HPLC, typically 2 hours. The solvent was removed *in vacuo* and the crude material was purified by passing through a plug of silica and eluted with CH_2Cl_2 .

The following known azides were synthesised using the above procedure 4-azidobenzonitrile,³ 2-azido-1,3-dichlorobenzene,⁴ 1-azido-3-bromobenzene,⁵ 1-azido-4-chlorobenzene,⁴ 1-azido-4-nitrobenzene,⁴ ethyl 4-azidobenzoate,⁶ *N*-(4-azidophenyl)acetamide,⁷ 1-azido-4-iodobenzene,² 5-azido-1,2,3-trimethoxybenzene.⁸

Novel Starting Materials



Azide precursor to 3c

1-Azido-2-bromo-4-fluorobenzene – novel

Orange solid (5 mmol scale, 94%, 1015 mg); R_t = 3.37 min, no mass observed; ν_{max} (thin film) 2122s, 2079m, 1598w, 1590w, 1481s, 1308m, 1267m, 1205s, 1032w, 891w, 864w, 805m, 781m, 636m; δ_{H} (400 MHz; CDCl_3) 7.31 (1H, dd, J = 8.0, 2.5 Hz, Ar-H), 7.16-7.05 (2H, m, Ar-H); δ_{C} (101 MHz; CDCl_3) 159.2 (d, J = 248.9 Hz, CF), 134.9 (d, J = 3.3 Hz, C), 121.0 (d, J = 25.5 Hz, CH), 120.0 (d, J = 8.7 Hz, CH), 115.7 (d, J = 23.0 Hz, CH), 114.0 (d, J = 9.8 Hz, C); δ_{F} (376 MHz; CDCl_3) -115.67; Mp = < 50 °C; Elemental calculated C 33.36, H 1.40, N 19.45, found C 33.56, H 1.61, N 19.33.

¹ D.-R. Hou, T.-C. Kuan, Y.-K. Li, R. Lee, K.-W. Huang, *Tetrahedron*, **2010**, 66, 9415–9420

² K. Barral, A. D. Moorhouse and J. E. Moses, *Org. Lett.* **2007**, 9, 1809.

³ K. D. Grimes, A. Gupte, C. C. Aldrich, *Synthesis* **2010**, 9, 1441–1448

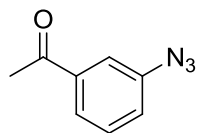
⁴ M. Kitamura, M. Yano, N. Tashiro, S. Miyagawa, M. Sando, T. Okauchi, *Eur. J. Org. Chem.* **2011**, 458–462.

⁵ K. Knepper, S. Vanderheiden, S. Bräse, *Eur. J. Org. Chem.*, **2006**, 1886–1898.

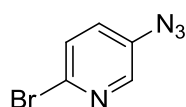
⁶ F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, *Org. Lett.*, **2008**, 10, 2409–2412.

⁷ M. Novak, M. J. Kahley, Jing Lin, S. A. Kennedy, T. G. James, *J. Org. Chem.*, **1995**, 60, 8294–8304.

⁸ F. Kloss, U. Köhn, B. O. Jahn, M. D. Hager, H. Görls, U. S. Schubert, *Chem. Asian J.*, **2011**, 6, 2816–2824

**Azide precursor to 3n****1-(3-azidophenyl)ethanone – only ¹H-NMR reported previously⁹**

Orange oil (5 mmol scale, 94%, 757 mg); R_t = 2.20 min, no mass observed; ν_{\max} (thin film) 2099s, 1683s, 1582m, 1481w, 1435m, 1357m, 1286s, 1247s, 1230w, 884w, 870w, 787m, 683; δ_H (300 MHz; CDCl₃) 7.64 (1H, ddd, J = 8.0, 1.5, 1.0 Hz, Ar-H), 7.54 (1H, t, J = 1.5 Hz, Ar-H), 7.39 (1H, t, J = 8.0 Hz, Ar-H), 7.14 (1H, ddd, J = 8.0, 2.0, 1.0 Hz, Ar-H), 2.53 (3H, s, CH₃); δ_C (75 MHz; CDCl₃) 197.0 (CO), 140.9 (C), 138.6 (C), 130.0 (CH), 124.8 (CH), 123.5 (CH), 118.4 (CH), 26.7 (CH₃); Elemental calculated C 59.62, H 4.38, N 26.07, found C 59.55, H 4.41, N 25.93.

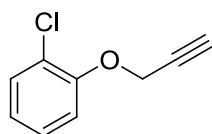
**Azide precursor to 3p****5-Azido-2-bromopyridine – novel**

Brown solid (5 mmol scale, 93%, 925 mg); R_t = 2.30 min, no mass observed; ESI+ 201, 199, 173, 171, 92; ν_{\max} (thin film) 2129m, 2098s, 1453s, 1377w, 1298m, 1232w, 1134w, 1087m, 1015w, 826w; δ_H (400 MHz; CDCl₃) 8.13 (1H, dd, J = 3.0, 0.5 Hz, Ar-H), 7.46 (1H, dd, J = 8.5, 0.5 Hz, Ar-H), 7.23 (1H, dd, J = 8.5, 3.0 Hz, Ar-H); δ_C (101 MHz; CDCl₃) 141.3 (CH), 136.9 (C), 136.9 (C), 128.7 (CH), 128.6 (CH); Mp = < 50 °C; HRMS (+ESI) calculated for C₅H₄N₄Br [M + H]⁺ calculated 198.9614, found 198.9614

Alkynes

4-Phenyl-1-butyne, phenylacetylene, 1-hexyne, ethynyltrimethylsilane, 1,8-nonadiyne and 3-butyne-1-ol were purchased from Aldrich. Mestranol was purchased from TCI-UK,

But-3-ynyl benzoate¹⁰ and 2-(prop-2-ynylthio)benzo[d]thiazole¹¹ were synthesised using known procedures.

**Alkyne precursor to 3g**

⁹ Y. Ohba, S. Kubo, M. Nakai, A. Nagai, M. Yoshimoto, *Bull. Chem. Soc. Jpn.*, **1986**, 59, 2317–2320.

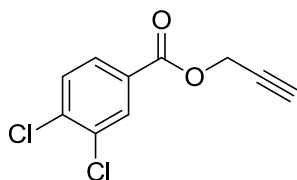
¹⁰ M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, C. Santi, R. Terlizzi, *Eur. J. Org. Chem.*, **2004**, 3447–3458.

¹¹ R. Abele, E. Abele, K. Rubina, O. Dzenitis, P. Arsenyan, I. Shestakova, A. Nesterova, I. Domracheva, J. Popelis, S. Grinberga, E. Lukevics, *Chem. Heterocycl. Compd.*, **2002**, 38, 867–872.

1-Chloro-2-(prop-2-yn-1-yloxy)benzene – ¹H-NMR only¹²

2-Chlorophenol (10 mmol, 1.28 g) was dissolved in THF (40 mL) and cooled to 0 °C. KOH pellets (11 mmol, 620 mmol) were added and after 30 min propargyl bromide (80% in toluene; 12 mmol, 1.34 mL) was added. The reaction allowed to warm to ambient temperature and stirred overnight (~24 hours). The reaction was partitioned between EtOAc (50 mL) and sat. NH₄Cl (aq) (100 mL). The organic phase was washed with water (100 mL), dried with Na₂SO₄, and concentrated *in vacuo*. The crude was passed through a plug of silica gel (eluted with CH₂Cl₂) to yield a clear oil. (74%, 1.23 g).

R_t = 3.45 min, no mass observed; v_{max} (thin film) 3294m, 1588m, 1482s, 1452m, 1295m, 1278m, 1230s, 1061s, 1042w, 1020s, 928w, 747s, 684m; δ_H (300 MHz; CDCl₃) 7.38 (1H, dd, *J* = 8.0, 1.5 Hz, Ar-H), 7.25-7.20 (1H, m, Ar-H), 7.09 (1H, dd, *J* = 8.5, 1.5 Hz, Ar-H), 6.95 (1H, td, *J* = 7.5, 1.5 Hz, Ar-H), 4.79 (2H, d, *J* = 2.5 Hz, CH₂), 2.54 (1H, t, *J* = 2.5 Hz, CCH); δ_C (75 MHz; CDCl₃) 153.1 (C), 130.5 (CH), 127.5 (CH), 123.3 (C), 122.4 (CH), 114.4 (CH), 77.20 (alkyne C-H), 76.11 (alkyne C), 56.79. (CH₂); Elemental calculated C 64.88, H 4.23, found C 65.10, H 4.20.

**Alkyne precursor to 3i****Prop-2-yn-1-yl 3,4-dichlorobenzoate – novel**

3,4-Dichlorobenzoic acid (10 mmol, 1.91 g) was suspended in CH₂Cl₂ (20 mL) and was cooled to 0 °C. An oxalyl chloride solution in CH₂Cl₂ (12 mmol, 6 mL, 2 M in CH₂Cl₂) was added in one portion followed by 3 drops of DMF which led to the formation of bubbles. The reaction was stirred for 3 hours until no further bubbles were observed. The reaction was then concentrated *in vacuo* before the crude was redissolved in CH₂Cl₂ (20 mL) and cooled to 0 °C. A CH₂Cl₂ solution (20 mL) containing propargylic alcohol (20 mmol, 1.12 g), triethylamine (20 mmol, 2.8 mL) and one crystal of 4-dimethylaminopyridine (~3 mg) was added dropwise to the crude reaction. The reaction was allowed to warm to ambient temperature and stirred overnight (~18 hours). The mixture was partitioned between with sat. NH₄Cl (aq) (30 mL) and CH₂Cl₂ (10 mL). The organic phase was washed with sat. brine (20 mL), dried with Na₂SO₄, and concentrated *in vacuo*. The crude was passed through a plug of silica gel (eluted with CH₂Cl₂) to yield a white solid (86%, 3.94 g).

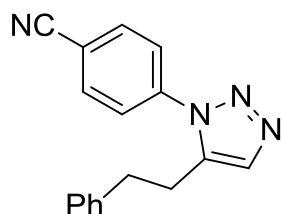
R_t = 3.49 min, no mass observed; v_{max} (thin film) 3300brw, 1727s, 1591w, 1564w, 1468w, 1434w, 1386w, 1369w, 1270s, 1234s, 1145w, 1106s, 1033m, 987w, 840w, 756m, 676w, 641w; δ_H (400 MHz; CDCl₃) 8.14 (1H, d, *J* = 2.0 Hz, Ar-H), 7.89 (1H, dd, *J* = 8.5, 2.0 Hz, Ar-H), 7.53 (1H, d, *J* = 8.5 Hz, Ar-H), 4.92 (2H, d, *J* = 2.5 Hz, CH₂), 2.55 (1H, t, *J* = 2.5 Hz, C≡C-H); δ_C (101 MHz; CDCl₃) 163.9 (C=O), 138.1 (CH), 133.0 (C), 131.67 (C), 130.6 (CH), 129.1 (C), 128.8 (CH), 77.1 (C), 75.5 (CH), 53.0 (CH₂); Elemental calculated C 52.43, H 2.64, found C 52.69, H 3.02.

¹² B. Li, S.-Q. Zang, C. Ji, T. C. W. Maka, *J. Organomet. Chem.*, **2011**, 696, 2820-2828
S5

Synthesis of Final Products

General Procedure for the Synthesis of 1,4-Substituted 1,2,3-Triazoles

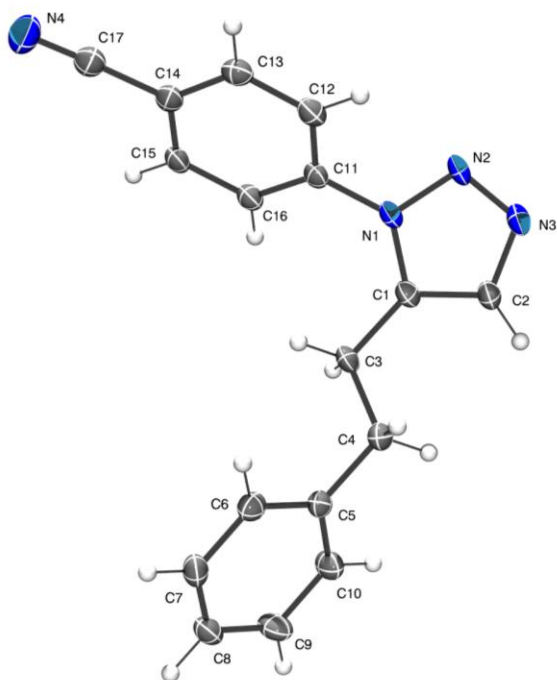
The azide (1 mmol), alkyne (1.2 mmol) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a glass vial or round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours) before quenching with sat. NH₄Cl (aq) (20 mL) – Caution – ethane gas is evolved at this stage. The mixture was partitioned between water (20 mL) and EtOAc (40 mL) and the organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford the pure material.



(3a)

4-(5-Phenethyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel

White solid (1 mmol 75%; 10 mmol 76%); *R*_t = 2.90 min, *M* + *H* = 275.2; *v*_{max} (thin film) 2227m, 1602m, 1508m, 1455m, 1418w, 1252m, 1117w, 1082m, 1073m, 1014w, 979m, 855s, 842s, 833s, 827s, 752m, 722s, 699s, 667m, 577s, 557s; δ_H (300 MHz; CDCl₃) 7.79 (2H, d, *J* = 8.5 Hz, Ar-H), 7.65 (1H, s, Ar-H), 7.44 (2H, d, *J* = 8.5 Hz, Ar-H), 7.28-7.20 (3H, m, Ar-H), 7.03 (2H, dd, *J* = 7.5, 2.0 Hz, Ar-H), 3.03 (2H, m, CH₂), 2.94 (2H, m, CH₂); δ_C (75 MHz; CDCl₃) 139.7 (C), 139.1 (C), 137.3 (C), 133.4 (CH), 133.2 (CH), 128.7 (CH), 128.2 (CH), 126.8 (CH), 125.6 (CH), 117.5 (C), 113.3 (C), 34.8 (CH₂), 25.7 (CH₂); *Mp* = 118 °C; HRMS (+ESI) calculated for C₁₇H₁₅N₄ [*M* + *H*]⁺ calculated 275.1290, found 275.1290; Elemental calculated C 74.43, H 5.14, N 20.42, found C 74.61, H 5.14, N 20.55.



CCDC Reference: 931414

Manchester reference number: s3793ma

Formula: C₁₇ H₁₄ N₄

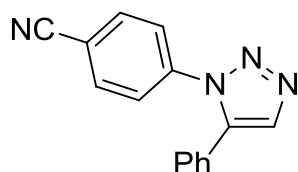
Thermal ellipsoids at 50%

Unit cell parameters: Cell lengths – a = 6.7136(5), b = 10.0540(7), c = 11.3384(8)

Cell angles – α = 90.113(4), β = 106.818(4), γ = 107.293(5)

Triclinic

Space Group – P-1

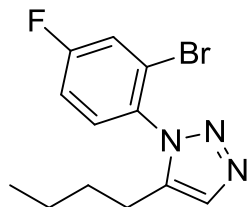


(3b)

4-(5-Phenyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel

Pale yellow solid (72%); R_t = 2.70 min, $M + H$ = 247.2; ν_{\max} (thin film) 2234m, 1605m, 1509m, 1480m, 1416m, 1376m, 1359m, 1232m, 1159s, 1129s, 1118m, 1108m, 1046w, 1001m, 988m, 966m, 842s, 831m, 766s, 696s, 617s, 610s, 566s; δ_H (300 MHz; CDCl₃) 7.86 (1H, s, Ar-H), 7.73 (2H, d, J = 8.5 Hz, Ar-H), 7.52 (2H, s, J = 8.5 Hz, Ar-H), 7.45-7.36 (3H, m, Ar-H), 7.23 (2H, dd, J = 7.5, 1.5 Hz,

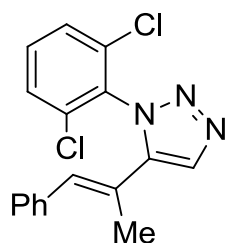
Ar-H); δ_{C} (75 MHz; CDCl_3) 139.9 (C), 137.9 (C), 134.1 (CH), 133.4 (CH), 129.9 (CH), 129.3 (CH), 128.7 (CH), 126.2 (C), 125.3 (CH), 117.7 (C), 113.0 (C); Mp = 116 °C; HRMS (M + H, +ESI) $\text{C}_{15}\text{H}_{11}\text{N}_4$ calculated 247.0978, found 247.0972.



(3c)

1-(2-Bromo-4-fluorophenyl)-5-butyl-1H-1,2,3-triazole – novel

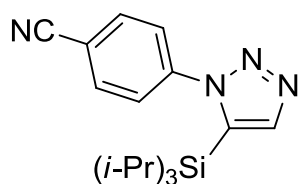
Yellow oil (71%); R_t = 3.22 min, M + H = 298.2 and 300.2 [Br]; ν_{max} (thin film) 1598w, 1502s, 1467w, 1260s, 1236w, 1202m, 1073w, 1017w, 975m, 876m, 861m, 821m, 6776w, 617m, 587w; δ_{H} (400 MHz; CDCl_3) 7.57 (1H, s, Ar-H), 7.48 (1H, dd, J = 8.0, 3.0 Hz, Ar-H), 7.37 (1H, dd, J = 9.0, 5.5 Hz, Ar-H), 7.20 (1H, ddd, J = 9.0, 7.5, 3.0 Hz, Ar-H), 2.45 (2H, br s, CH_2), 1.53 (2H, quin., J = 7.5 Hz, CH_2), 1.29 (2H, sex., J = 7.5 Hz, CH_2), 0.84 (3H, t, J = 7.5 Hz, CH_3); δ_{C} (101 MHz; CDCl_3) 162.9 (d, J = 255.5 Hz, CF), 139.5 (C), 132.0 (d, J = 3.5 Hz, C), 131.6 (CH), 130.4 (d, J = 9.4 Hz, CH), 122.6 (d, J = 10.5 Hz, C), 120.9 (d, J = 25.5 Hz, CH), 115.6 (d, J = 22.6 Hz, CH), 29.9 (CH_2), 22.8 (CH_2), 22.0 (CH_2), 13.5 (CH_3); δ_{F} (376 MHz, CDCl_3) -107.2; HRMS (M + H, +ESI) $\text{C}_{12}\text{H}_{14}\text{N}_3\text{BrF}$ calculated 298.0350, found 298.0344.



(3d)

(E)-1-(2,6-Dichlorophenyl)-5-(1-phenylprop-1-en-2-yl)-1H-1,2,3-triazole – novel

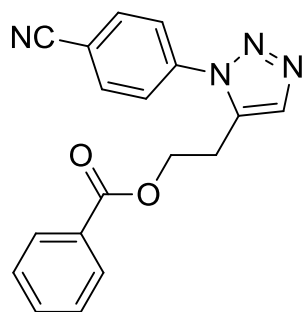
Yellow solid (55%); R_t = 3.48 min, M + H = 330.2 and 332.1 [Cl]; ν_{max} (thin film) 1568w, 1480m, 1438s, 1234m, 1199w, 1143w, 1076w, 1049w, 1014w, 976w, 962w, 929w, 886w, 834w, 792s, 786s, 761s, 734m, 711m, 699s, 556w; δ_{H} (300 MHz; CDCl_3) 7.88 (1H, s, Ar-H), 7.55-7.50 (2H, m, Ar-H), 7.48-7.43 (1H, m, Ar-H), 7.38-7.25 (3H, m, Ar-H), 7.15 (2H, d, J = 7.5 Hz, Ar-H), 6.46 (1H, br s, vinyl-H), 2.14 (3H, d, J = 1.5 Hz, CH_3); δ_{C} (75 MHz; CDCl_3) 141.7 (C), 136.0 (C), 134.4 (C), 133.4 (C), 132.2 (CH), 131.8 (CH), 131.7 (CH), 128.9 (CH), 128.8 (CH), 128.2 (CH), 127.5 (CH), 123.0 (C), 17.4 (CH_3); Mp = 84 °C; HRMS (+ESI) calculated for $\text{C}_{17}\text{H}_{14}\text{N}_3\text{Cl}_2$ [M + H]⁺ calculated 330.0565, found 330.0568.



(3e)

4-(5-(Triisopropylsilyl)-1H-1,2,3-triazol-1-yl)benzonitrile – novel

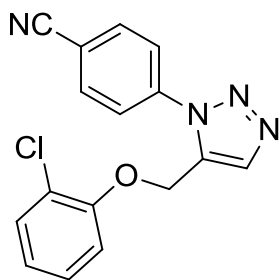
Yellow solid (67%); $R_t = 3.70$ min, $M + H = 327.3$; ν_{\max} (thin film) 2956w, 2943w, 2867w, 2226w, 1606m, 1508m, 1460w, 1384w, 1244w, 1174w, 1054m, 1021w, 1010w, 994w, 974w, 883m, 856s, 831m, 682s, 648m, 583m, 569m; δ_H (300 MHz; $CDCl_3$) 7.88 (1H, s, Ar-H), 7.82 (2H, d, $J = 8.5$ Hz, Ar-H), 7.59 (2H, d, $J = 8.5$ Hz, Ar-H), 1.17-1.06 (3H, m, $SiCHMe_2$), 0.98 (18H, d, $J = 7.0$ Hz, CH_3); δ_C (75 MHz; $CDCl_3$) 143.4 (CH), 142.6 (C), 133.2 (C), 133.0 (CH), 127.3 (CH), 117.5 (C), 114.0 (C), 18.5 (CH_3), 12.0 (CH); $Mp = 122$ °C; HRMS (+ESI) calculated for $C_{18}H_{27}N_4Si$ $[M + H]^+$ calculated 327.2005, found 327.2010.



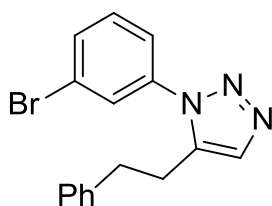
(3f)

2-(1-(4-Cyanophenyl)-1H-1,2,3-triazol-5-yl)ethyl benzoate – novel

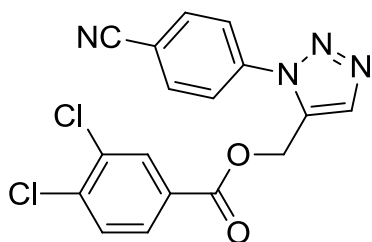
Orange solid (68%); $R_t = 2.82$ min, $M + H = 319.3$; ν_{\max} (thin film) 2228w, 1716s, 1601w, 1508m, 1454w, 1438w, 1391w, 1309m, 1281s, 1236m, 1173w, 1118s, 1086m, 1072m, 1021w, 1011w, 971w, 852m, 835m, 824m, 807w, 709s, 689w, 678w, 635w, 619w, 561w; δ_H (300 MHz; $CDCl_3$) 7.89 (2H, dd, $J = 8.5, 1.5$ Hz, Ar-H), 7.83-7.75 (3H, m, Ar-H), 7.67-7.53 (3H, m, Ar-H), 7.42 (2H, t, $J = 8.0$ Hz, Ar-H), 4.54 (2H, t, $J = 6.5$ Hz, CH_2), 3.23 (2H, t, $J = 6.5$ Hz, CH_2); δ_C (75 MHz; $CDCl_3$) 166.0 (C=O), 139.5 (C), 134.4 (C), 133.7 (CH), 133.6 (CH), 133.4 (CH), 129.5 (CH), 129.2 (C), 128.5 (CH), 125.6 (CH), 117.4 (C), 113.5 (C), 62.1 (CH_2), 23.7 (CH_2); $Mp = 76$ °C; HRMS (+ESI) calculated for $C_{19}H_{14}N_4O_2$ $[M + H]^+$ calculated 319.1195, found 319.1210.

**(3g)****4-((5-((2-Chlorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)benzonitrile – novel**

White solid (59%); $R_t = 3.08$ min, $M + H = 311.2$ and 313.2 [Cl]; ν_{\max} (thin film) 2227m, 1606w, 1581w, 1515m, 1498s, 1464w, 1448w, 1432w, 1391w, 1292w, 1238s, 1180m, 1168w, 1135w, 1113w, 1086m, 1060m, 1039w, 1001s, 966m, 870w, 844s, 767w, 747s, 709w, 699w, 683m, 664m, 559w; δ_H (300 MHz; $CDCl_3$) 7.88-7.73 (5H, m, Ar-H), 7.31 (1H, dd, $J = 8.0, 1.5$ Hz, Ar-H), 7.16 (1H, td, $J = 8.0, 1.5$ Hz, Ar-H), 6.97-6.87 (2H, m, Ar-H), 5.08 (2H, s, CH_2); δ_C (75 MHz; $CDCl_3$) 152.6 (C), 139.2 (C), 136.0 (CH), 133.5 (CH), 132.2 (C), 130.7 (CH), 127.9 (CH), 125.1 (CH), 123.5 (CH), 123.3 (C), 117.5 (C), 114.6 (CH), 113.5 (C), 59.0 (CH_2); Mp = 136 °C; HRMS ($M + H$, +ESI) $C_{16}H_{12}N_4OCl$ calculated 311.0694, found 311.0683.

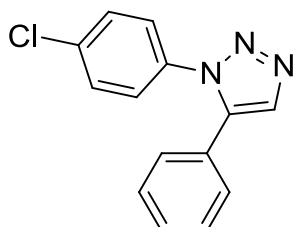
**(3h)****1-(3-Bromophenyl)-5-phenethyl-1H-1,2,3-triazole – novel**

Orange oil (76%); $R_t = 3.40$ min, $M + H = 328.1$ and 330.1 [Br]; ν_{\max} (thin film) 1591m, 1579m, 1485s, 1453w, 1250w, 1070m, 1043w, 999w, 977m, 874w, 824w, 786m, 750s, 712m, 698s, 686s, 643w; δ_H (300 MHz; $CDCl_3$) 7.66-7.59 (2H, m, Ar-H), 7.44 (1H, t, $J = 2.0$ Hz, Ar-H), 7.37 (1H, t, $J = 8.0$ Hz, Ar-H), 7.26-7.20 (4H, m, Ar-H), 7.04 (2H, dd, $J = 7.5, 2.0$ Hz, Ar-H), 2.99 (2H, m, CH_2), 2.91 (2H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 139.3 (C), 137.3 (C), 137.2 (C), 132.7 (CH), 132.6 (CH), 130.6 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 126.7 (CH), 123.9 (CH), 122.9 (C), 34.8 (CH_2), 25.5 (CH_2); HRMS ($M + H$, +ESI) $C_{16}H_{15}N_3Br$ calculated 328.0444, found 328.0455.

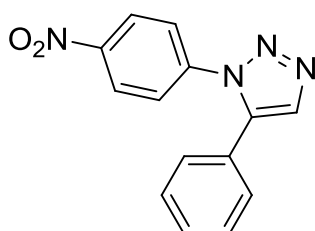


(3i)**(1-(4-Cyanophenyl)-1*H*-1,2,3-triazol-5-yl)methyl 3,4-dichlorobenzoate – novel**

Orange solid (73%); $R_t = 3.38$ min, $M + H = 373.2$ and 375.5 [Cl]; ν_{\max} (thin film) 2237w, 1726s, 1606w, 1588w, 1509m, 1464w, 1442w, 1412w, 1387m, 1311w, 1272s, 1238s, 1170w, 1152w, 1143w, 1115m, 1091s, 1034m, 1013w, 1000w, 991w, 971m, 900w, 884w, 848m, 841m, 833s, 824m, 794w, 772w, 753s, 709w, 692w, 678w, 660w, 565m; δ_H (300 MHz; $CDCl_3$) 7.99 (1H, s, Ar-H), 7.97 (1H, d, $J = 2.0$ Hz, Ar-H), 7.90 (2H, d, $J = 8.5$ Hz, Ar-H), 7.77 (1H, dd, $J = 8.5, 2.0$ Hz, CH), 7.76 (2H, d, $J = 8.5$ Hz, Ar-H), 7.55 (1H, d, $J = 8.5$ Hz, Ar-H), 5.45 (2H, s, CH_2); δ_C (75 MHz; $CDCl_3$) 163.7 (C=O), 139.2 (C), 138.7 (C), 136.2 (CH), 133.8 (CH), 133.4 (C), 132.0, 131.5 (CH), 130.9 (CH), 128.6 (CH), 128.4 (C), 125.2 (CH), 117.3 (C), 114.0 (C), 54.6 (CH_2); Mp = 134 °C; HRMS ($M + H$, +ESI) $C_{17}H_{11}O_2N_4Cl_2$ calculated 373.0254, found 373.0257.

**(3j)****1-(4-Chlorophenyl)-5-phenyl-1*H*-1,2,3-triazole¹³**

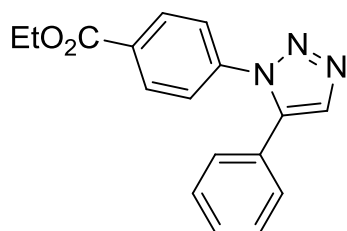
Yellow solid (57%); $R_t = 3.32$ min, $M + H = 256.2$ and 258.2 [Cl]; ν_{\max} (thin film) 1622w, 1512m, 1495s, 1092m, 988w, 832m, 765m, 747w, 697m, 565m; δ_H (400 MHz; $CDCl_3$) 7.86 (1H, s, Ar-H), 7.44-7.35 (5H, m, Ar-H), 7.34-7.29 (2H, m, Ar-H), 7.19 (2H, dd, $J = 8.0, 1.5$ Hz, Ar-H); δ_C (101 MHz; $CDCl_3$) 137.7 (C), 135.2 (C), 135.0 (C), 133.5 (CH), 129.6 (CH), 129.4 (CH), 129.0 (CH), 128.6 (CH), 126.4 (C), 126.3 (CH); Mp = 87 °C; HRMS ($M + H$, +ESI) $C_{14}H_{11}N_3Cl$ calculated 256.0636, found 256.0629.

**(3k)****1-(4-Nitrophenyl)-5-phenyl-1*H*-1,2,3-triazole¹⁴**

¹³ L. K. Rasmussen, B. C. Boren and V. V. Fokin, *Org. Lett.* **2007**, 9, 5337.

¹⁴ S. W. Kwok, J. R. Fotsing, R. J. Fraser, V. O. Rodionov and V. V. Fokin, *Org. Lett.* **2010**, 12, 4217.

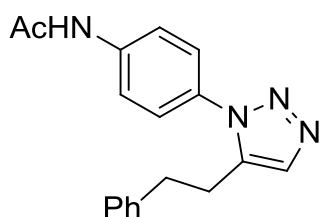
Orange solid (51%); $R_t = 3.06$ min, $M + H = 267.2$; ν_{\max} (thin film) 1594m, 1520m, 1498m, 1453w, 1307s, 1269m, 1237m, 1173w, 1109s, 1076w, 1045w, 989w, 965w, 854s, 762s, 751s, 730m, 697s, 688s, 679m, 565m; δ_H (400 MHz; $CDCl_3$) 8.30 (2H, d, $J = 9.0$ Hz, Ar-H), 7.89 (1H, s, Ar-H), 7.59 (2H, d, $J = 9.0$ Hz, Ar-H), 7.50-7.39 (3H, m, Ar-H), 7.24 (2H, dd, $J = 8.0, 2.0$ Hz, Ar-H); δ_C (101 MHz; $CDCl_3$) 147.5 (C), 141.2 (C), 138.0 (C), 134.2 (CH), 129.9 (CH), 129.3 (CH), 128.7 (CH), 126.0 (C), 125.3 (CH), 124.9 (CH); $Mp = 162$ °C; HRMS ($M + H$, +ESI) $C_{14}H_{11}N_4O_2$ calculated 267.0877, found 267.0876.



(3l)

Ethyl 4-(5-phenyl-1H-1,2,3-triazol-1-yl)benzoate – previous reports by other groups provided no experimental data¹³

Orange solid (73%); $R_t = 3.25$ min, $M + H = 294.3$; ν_{\max} (thin film) 1717s, 1605m, 1511w, 1479w, 1409w, 1367w, 1308w, 1271s, 1233m, 1173m, 1130m, 1111m, 1101m, 1078w, 1019w, 1050w, 989m, 975w, 964w, 860m, 842m, 769s, 701s, 679m, 567m; δ_H (300 MHz; $CDCl_3$) 8.08 (2H, d, $J = 8.5$ Hz, Ar-H), 7.84 (1H, s, Ar-H), 7.42 (2H, s, $J = 8.5$ Hz, Ar-H), 7.39-7.30 (3H, m, Ar-H), 7.20 (2H, dd, $J = 8.0, 1.5$ Hz, CH), 4.37 (2H, q, $J = 7.0$ Hz, CH_2), 1.37 (3H, t, $J = 7.0$ Hz, CH_3); δ_C (75 MHz; $CDCl_3$) 165.3 (C=O), 139.8 (C), 137.7 (C), 133.6 (CH), 130.9 (C), 130.6 (CH), 129.4 (CH), 128.9 (CH), 128.5 (CH), 126.3 (C), 124.6 (CH), 61.3 (CH_2), 14.2 (CH_3); HRMS ($M + H$, +ESI) $C_{17}H_{16}N_3O_2$ calculated 294.1237, found 294.1238.

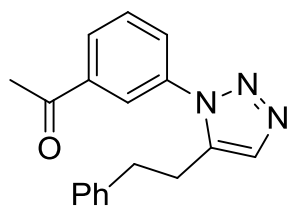


(3m)

N-(4-(5-Phenethyl-1H-1,2,3-triazol-1-yl)phenyl)acetamide – novel

White solid (70%); $R_t = 2.83$ min, $M + H = 307.3$; ν_{\max} (thin film) 1674m, 1604m, 1516s, 1454w, 1409m, 1369m, 1311m, 1253m, 978w, 839m, 750m, 698s, 580w; δ_H (300 MHz; $CDCl_3$) 9.09 (1H, br, NH), 7.72 (2H, d, $J = 8.0$ Hz, Ar-H), 7.58 (1H, s, Ar-H), 7.27-7.15 (3H, m, Ar-H), 7.03 (2H, d, $J = 7.5$ Hz, Ar-H), 3.02-2.81 (4H, m, CH_2CH_2), 2.19 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 169.3 (C=O), 139.8 (C), 139.4 (C), 137.7 (C), 132.3 (CH), 131.1 (C), 128.5 (CH), 128.2 (CH), 126.5 (CH), 125.8 (CH),

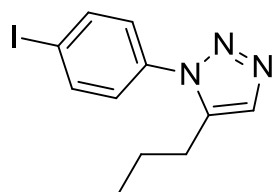
120.3 (CH), 34.4 (CH₂), 25.4 (CH₂), 24.4 (CH₃); Mp 131 °C; HRMS (M + H, +ESI) C₁₈H₁₉N₄O calculated 307.1553, found 307.1557.



(3n)

1-(3-(5-Phenethyl-1H-1,2,3-triazol-1-yl)phenyl)ethanone – novel

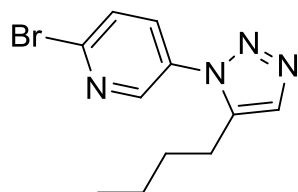
Sticky orange solid (52%); R_t = 3.78 min, M + H = 292.1; ν_{max} (thin film) 2108w, 1687s, 1588m, 1358m, 1255m, 1074w, 978w; δ_H (300 MHz; CDCl₃) 8.07 (1H, dt, *J* = 8.0, 1.5 Hz, Ar-H), 7.92 (1H, t, *J* = 2.0 Hz, Ar-H), 7.65-7.57 (2H, m, Ar-H), 7.49 (1H, ddd, *J* = 8.0, 2.0, 1.0 Hz, Ar-H), 7.25-7.17 (3H, m, Ar-H), 7.03 (2H, dd, *J* = 8.0, 2.0 Hz, Ar-H), 3.02-2.89 (4H, m, CH₂CH₂), 2.53 (3H, s, CH₃); δ_C (75 MHz; CDCl₃) 196.4 (C=O), 139.4 (C), 138.3 (C), 137.4 (C), 136.7 (C), 132.8 (CH), 129.9 (CH), 129.5 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 126.6 (CH), 124.9 (CH), 34.7 (CH₂), 26.7 (CH₃), 25.5 (CH₂); HRMS (M + H, +ESI) C₁₈H₁₈N₃O calculated 292.1444, found 292.1437.



(3o)

5-Butyl-1-(4-iodophenyl)-1H-1,2,3-triazole – novel

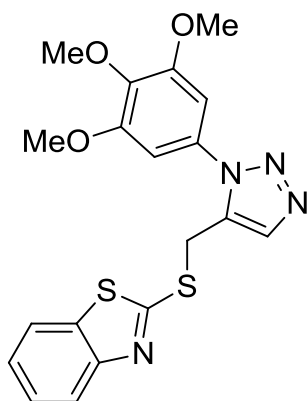
Brown solid (69%); R_t = 3.40 min, M + H = 328.2; ν_{max} (thin film) 5955w, 2869w, 1492s, 1466w, 1395w, 1248w, 1058m, 1006m, 975s, 825s; δ_H (300 MHz; CDCl₃) 7.88 (2H, d, *J* = 8.5 Hz, Ar-H), 7.58 (1H, s, Ar-H), 7.20 (2H, d, *J* = 8.5 Hz, CH), 2.64 (2H, t, *J* = 7.5 Hz, CH₂), 1.57 (2H, quin, *J* = 7.9 Hz, CH₂), 1.33 (2H, sex., *J* = 7.5 Hz, CH₂), 0.88 (3H, t, *J* = 7.5 Hz, CH₃); δ_C (75 MHz; CDCl₃) 138.7 (CH), 138.1 (C), 137.9 (C), 136.2 (C), 132.6 (CH), 126.8 (CH), 117.2 (CH), 94.9 (CI), 30.3 (CH₂), 23.4 (CH₂), 22.2 (CH₂), 13.6 (CH₃); Mp = < 50 °C; HRMS (+ESI) calculated for C₁₂H₁₅N₃I [M + H]⁺ calculated 328.0305, found 328.0297



(3p)

2-Bromo-5-(5-butyl-1*H*-1,2,3-triazol-1-yl)pyridine – novel

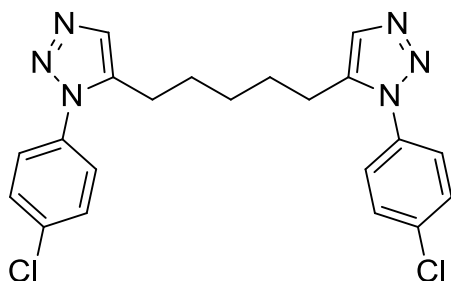
Orange solid (71%); $R_t = 2.85$ min, $M + H = 281.1$ and 283.1 [Br]; ν_{\max} (thin film) 2957w, 2871w, 1541w, 1472s, 1373w, 1256w, 1126w, 1092m, 1072w, 1005w, 974m, 833m, 731w; δ_H (300 MHz; $CDCl_3$) 8.52 (1H, dd, $J = 2.0, 1.0$ Hz, Ar-H), 7.77-7.66 (2H, m, Ar-H), 7.62 (1H, s, Ar-H), 2.67 (2H, t, $J = 7.5$ Hz, CH_2), 1.61 (2H, quin., $J = 7.5$ Hz, CH_2), 1.35 (2H, sex., $J = 7.5$ Hz, CH_2), 0.88 (3H, t, $J = 7.5$ Hz, CH_3); δ_C (75 MHz; $CDCl_3$) 145.7 (CH), 142.6 (C), 138.5 (C), 134.8 (CH), 132.9 (CH), 132.7 (C), 128.9 (CH), 30.3 (CH_2), 23.4 (CH_2), 22.2 (CH_2), 13.6 (CH_3); Mp = 58 °C; HRMS ($M + H$, +ESI) $C_{11}H_{14}N_4Br$ calculated 281.0396, found 281.0395.



(3q)

2-(((1-(3,4,5-trimethoxyphenyl)-1*H*-1,2,3-triazol-5-yl)methyl)thio)benzo[*d*]thiazole - novel

Brown solid (69%); $R_t = 3.21$ min, $M + H = 414.9$; ν_{\max} (thin film) 2938w, 1601m, 1508m, 1463m, 1427m, 1344w, 1232m, 1128s, 1084w, 1000m, 832w, 759w, 728w; δ_H (300 MHz; $CDCl_3$) 7.89 (1H, s, Ar-H), 7.87 (1H, d, $J = 8.0$ Hz, Ar-H), 7.77 (1H, d, $J = 8.0$ Hz, Ar-H), 7.46 (1H, td, $J = 8.0, 1.0$ Hz, Ar-H), 7.35 (1H, td, $J = 8.0, 1.0$ Hz, Ar-H), 6.81 (2H, s, Ar-H), 4.68 (2H, s, CH_2), 3.89 (9H, s, 3 x OCH_3); δ_C (75 MHz; $CDCl_3$) 163.4 (C), 153.8 (C), 152.7 (C), 139.1 (C), 135.4 (C), 134.6 (CH), 133.6 (C), 131.2 (C), 126.4 (CH), 124.9 (CH), 121.7 (CH), 121.2 (CH), 103.1 (CH), 61.0 (OCH_3), 56.4 (OCH_3), 25.0 (CH_2); Mp = 102 °C; HRMS ($M + Na$, +ESI) $C_{19}H_{18}N_4O_3NaS_2$ calculated 437.0713, found 437.0723.

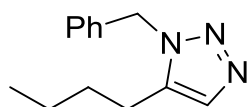


(3r)

1,5-Bis(1-(4-chlorophenyl)-1*H*-1,2,3-triazol-5-yl)pentane – novel

1-Azido-4-chlorobenzene (2.4 mmol, 367 mg), nona-1,8-diyne (1.0 mmol, 120 mg) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (16 mL) was added to dissolve the starting materials before ZnEt₂ (3.0 mmol, 3.0 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours) before quenching with sat. NH₄Cl (aq) (20 mL) and the mixture was partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a brown oil (71%).

R_t = 3.39 min, M + H = 426.9 and 428.4 [Cl]; v_{max} (thin film) 1497s, 1406w, 1252w, 1093m, 1012w, 976m, 833m, 560w; δ_H (300 MHz; CDCl₃) 7.55 (2H, s, Ar-H), 7.52 (4H, dt, *J* = 8.5, 2.0 Hz, Ar-H), 7.36 (4H, dt, *J* = 8.5, 2.0 Hz, Ar-H), 2.61 (4H, t, *J* = 7.5 Hz, CH₂), 1.56 (4H, quin., *J* = 7.5 Hz, CH₂), 1.31 (2H, quin., *J* = 7.5 Hz, CH₂); δ_C (75 MHz; CDCl₃) 137.6 (C), 135.7 (C), 134.8 (C), 132.5 (CH), 129.8 (CH), 126.4 (CH), 28.5 (CH₂), 27.8 (CH₂), 23.5 (CH₂); HRMS (M + Na, +ESI) C₂₁H₂₀N₆Cl₂Na calculated 449.1019, found 449.1020.



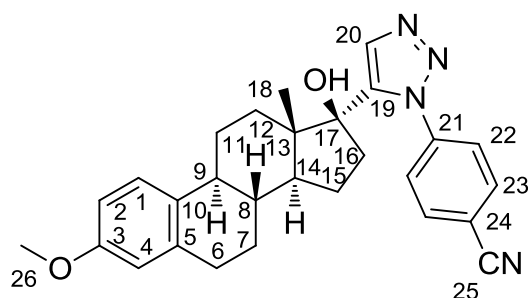
(3s)

1-Benzyl-5-butyl-1*H*-1,2,3-triazole¹⁵

Benzyl azide (1 mmol, 133 mg), hexyne (1.2 mmol, 100 mg) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature for approximately 72 hours before quenching with sat. NH₄Cl (aq) (20 mL) and the mixture was partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a clear oil (65%).

R_t = 3.06 min, M + H = 216.2; v_{max} (thin film) 2957w, 2931w, 1497w, 1456m, 1427w, 1260w, 1235m, 1126w, 1094w, 1073w, 1029w, 983m, 823m, 724s, 710s, 695s, 577m; δ_H (300 MHz; CDCl₃) 7.47 (1H, s, Ar-H), 7.37-7.27 (3H, m, Ar-H), 7.13 (2H, dd, *J* = 7.5, 2.0 Hz, Ar-H), 5.49 (2H, s, PhCH₂), 2.47 (2H, t, *J* = 7.5 Hz, CH₂), 1.49 (2H, quin., *J* = 7.5 Hz, CH₂), 1.29 (2H, sex., *J* = 7.5 Hz, CH₂), 0.85 (3H, t, *J* = 7.5 Hz, CH₃); δ_C (75 MHz; CDCl₃) 137.4 (C), 135.0 (C), 132.5 (CH), 128.9 (CH), 128.2 (CH), 127.0 (CH), 51.6 (PhCH₂), 29.9 (CH₂), 22.8 (CH₂), 22.1 (CH₂), 13.6 (CH₃); HRMS (M + Na, +ESI) C₁₃H₁₇N₃Na calculated 238.1315, found 238.1310.

¹⁵ Y.-H. Lo, T.-H. Wang, C.-Y. Lee, and Y.-H. Feng, *Organometallics* **2012**, *31*, 6887.

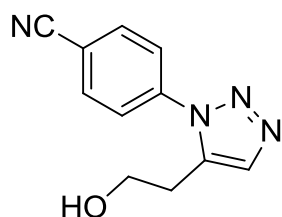


(3t)

4-(5-((8*R*,9*S*,13*S*,14*S*,17*S*)-17-hydroxy-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)-1*H*-1,2,3-triazol-1-yl)benzonitrile – novel

4-Azidobenzonitrile (1.2 mmol, 173 mg), mestranol (1 mmol, 310 mg) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (16 mL) was added to dissolve the starting materials before ZnEt₂ (2.5 mmol, 2.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature for approximately 72 hours before quenching with sat. NH₄Cl (aq) (20 mL). The mixture was partitioned between water (20 mL) and EtOAc (40 mL) and the organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a white solid (49%).

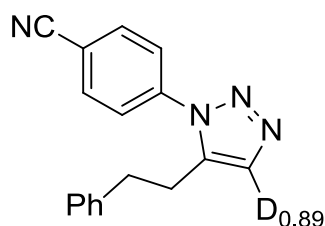
R_t = 3.67 min, M + H = 455.2; ν_{max} (thin film) 3461brs, 2924w, 2872w, 2240w, 1606m, 1503m, 1470w, 1447w, 1386w, 1313w, 1290w, 1251m, 1236s, 1200w, 1164w, 1143w, 1088w, 1059m, 1049m, 1036m, 1013w, 997w, 952w, 922w, 905w, 869w, 850s, 827s, 791w, 711w, 579s; δ_H (500 MHz; DMSO-*d*₆) 8.00 (2H, d, *J* = 8.5 Hz, Ar-H, 22 or 23), 7.77 (2H, d, *J* = 8.5 Hz, Ar-H, 22 or 23), 7.75 (1H, s, Triazole-H, 20), 7.05 (1H, d, *J* = 8.5 Hz, Ar-H, 1), 6.63 (1H, dd, *J* = 8.5, 3.0 Hz, Ar-H, 2), 6.58 (1H, d, *J* = 3.0 Hz, Ar-H, 4), 5.61 (1H, s, OH), 3.66 (3H, s, OCH₃-26), 2.76 (2H, dd, *J* = 4.1, 3.6 Hz, CH₂-6), 2.32 (1H, ddd, *J* = 14.5, 10.0, 5.0 Hz, CH-16), 2.16-2.02 (2H, m, CH-11, CH-16), 1.95-1.80 (3H, m, CH-15, CH-19, CH-7), 1.44 (1H, qd, *J* = 12.0, 5.5 Hz, CH-15), 1.40-1.12 (5H, m, CH-14, CH-12, CH-11, CH-8, CH-7), 0.76 (3H, s, CH₃-18), 0.64 (1H, td, *J* = 13.5, 4.2 Hz, CH-12); δ_C (75 MHz; DMSO) 157.1 (C-3), 144.7 (C), 142.8 (C), 137.4 (C), 133.5 (CH-20), 132.2 (CH-23), 131.9 (C), 129.3 (CH-), 126.0 (CH-1), 118.2 (C), 113.5 (CH-4), 111.9 (C), 111.4 (CH-2), 81.9 (C-17), 54.9 (OCH₃-25), 48.1 (C-13), 47.8 (CH-14), 42.8 (CH-9), 39.0 (CH-8), 40.2 (CH₂-16), 33.8 (CH₂-12), 29.2 (CH₂-6), 27.0 (CH₂-7), 25.9 (CH₂-11), 22.8 (CH₂-15), 13.9 (CH₃-18); [α]_D²⁷ = +140 (c = 0.25 in MeCN); Mp = 278 °C decomposition; HRMS (M + H, +ESI) C₂₈H₃₁N₄O₂ calculated 455.2442, found 455.2452.



(3u)**4-(5-(2-Hydroxyethyl)-1H-1,2,3-triazol-1-yl)benzonitrile – novel**

4-Azidobenzonitrile (1 mmol, 144 mg), but-3-yn-1-ol (1.2 mmol, 84 mg) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (2.5 mmol, 2.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature for approximately 72 hours before quenching with sat. NH₄Cl (aq) (20 mL) and the mixture was partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a white solid (71%).

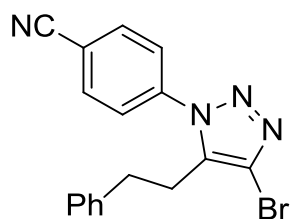
R_t = 1.72 min, M + H = 215.2; v_{max} (thin film) 3257w br, 2231m, 1607m, 1509s, 1413w, 1258m, 1236w, 1126w, 1089m, 1059s, 1015w, 983s, 854m, 837s, 823m, 704m, 561s; δ_H (400 MHz; CDCl₃) 7.85 (2H, dt, *J* = 8.5, 2.0 Hz, Ar-H), 7.72 (2H, dt, *J* = 8.5, 2.0 Hz, Ar-H), 7.67 (1H, s, Ar-H), 3.93 (2H, t, *J* = 6.0 Hz, CH₂), 2.96 (2H, t, *J* = 6.0 Hz, CH₂), 2.65 (1H, br s, OH); δ_C (101 MHz; CDCl₃) 139.6 (C), 135.8 (C), 133.5 (CH), 133.3 (CH), 126.0 (CH), 117.6 (C), 113.4 (C), 60.8 (CH₂), 26.9 (CH₂); Mp = 121 °C; HRMS (M + H, +ESI) C₁₁H₁₁N₄O calculated 215.0927, found 215.0942.

Synthesis of 1,4,5-Substituted 1,2,3-Triazoles**(3v)****4-(4-[²H]-5-phenethyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel**

4-azidobenzonitrile (1 mmol, 144 mg), 4-phenyl-1-butyne (1.2 mmol, 156 mg) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours). D₂O (1 mL) and D₃CCO₂D (1 mL) were added and the mixture was stirred vigorously for 30 minutes. The reaction was partitioned with sat. NH₄Cl (aq) (20 mL), water (20 mL) and EtOAc (40 mL) and the organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, 4:6 EtOAc/hexane) to afford a pale yellow solid (71%).

R_t = 2.91 min, M + H = 276.3; v_{max} (thin film) 2238w, 1603w, 1509m, 1455w, 1409w, 1257w, 1073m, 990m, 854w, 837s, 755m, 724m, 717s, 709s, 698m, 569s, 557s; δ_H (300 MHz; CDCl₃) 7.79 (2H, d, *J* = 8.5 Hz, Ar-H), 7.65 (0.11H, s, Ar-H), 7.44 (2H, d, *J* = 8.5 Hz, Ar-H), 7.28-7.20 (3H, m, Ar-H), 7.03 (2H, dd, *J* = 7.5, 2.0 Hz, Ar-H), 3.03 (2H, m, CH₂), 2.94 (2H, m, CH₂); δ_C (75 MHz; CDCl₃) 139.7 (C), 139.1 (C), 137.3 (C), 133.4 (CH), 133.2 (CH), 128.7 (CH), 128.2 (CH), 126.8 (CH), 125.6 (CH), 117.5 (C), 113.3 (C), 34.8 (CH₂), 25.7 (CH₂); Mp = 118 °C; HRMS (M + H, +ESI) C₁₇H₁₄DN₄ calculated 276.1354, found 276.1352.

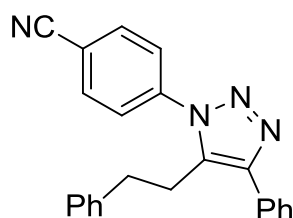
89% deuterium incorporation by ¹H-NMR and LCMS.

**(3w)****4-(4-Bromo-5-phenethyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel**

4-azidobenzonitrile (1 mmol, 144 mg), 4-phenyl-1-butyne (1.2 mmol, 156 mg) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was

stirred at ambient temperature overnight (approximately 18 hours). Bromine (2 mmol, 120 μ L) was added and the mixture was stirred vigorously for 30 minutes. The reaction was partitioned with sat. NH_4Cl (aq) (20 mL), water (20 mL) and EtOAc (40 mL) and the organic layer was washed with water (20 mL), dried with Na_2SO_4 , filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, 4:6 EtOAc/hexane) to afford a pale brown solid (76%).

$R_t = 3.20$ min, $M + H = 353.2$ and 355.2 [Br]; v_{max} (thin film) 2226m, 1602m, 1536w, 1507m, 1451m, 1405w, 1303w, 1269m, 1242m, 1160w, 1116w, 1100w, 1062m, 997m, 970m, 854s, 826m, 759s, 738m, 721m, 702s, 681w, 583s, 559s; δ_{H} (300 MHz; CDCl_3) 7.72 (2H, d, $J = 8.6$ Hz, Ar-H), 7.21-7.09 (5H, m, Ar-H), 6.86 (2H, dd, $J = 6.4, 3.2$ Hz, Ar-H), 3.04 (2H, t, $J = 7.0$ Hz, CH_2), 2.88 (2H, t, $J = 7.0$ Hz, CH_2); δ_{C} (75 MHz; CDCl_3) 139.2 (C), 138.7 (C), 135.3 (C), 133.4 (CH), 128.8 (CH), 128.4 (CH), 126.9 (CH), 125.9 (CH), 121.6 (C), 117.4 (C), 113.9 (C), 33.6 (CH_2), 25.1 (CH_2); Mp = 128 $^{\circ}\text{C}$; HRMS ($M + H$, +ESI) $\text{C}_{17}\text{H}_{14}\text{N}_4\text{Br}$ calculated 353.0396, found 353.0395.

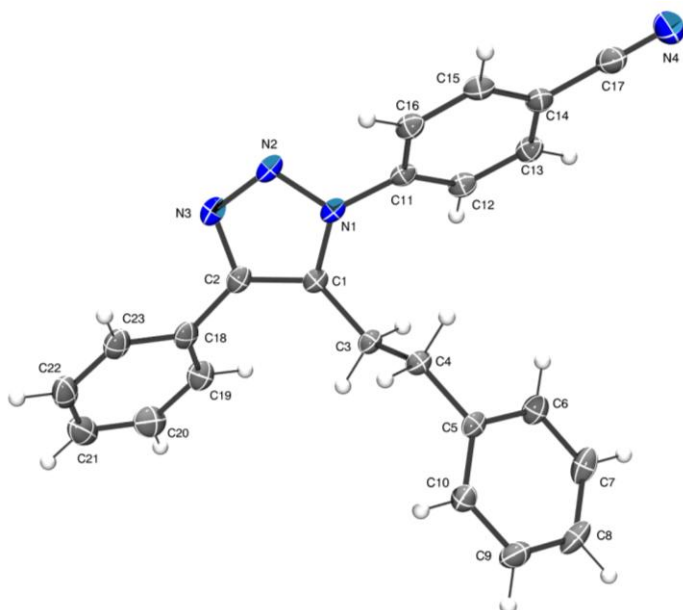


(3x)

4-(5-Phenethyl-4-phenyl-1H-1,2,3-triazol-1-yl)benzonitrile - novel

4-azidobenzonitrile (1 mmol, 144 mg), 4-phenyl-1-butyne (1.2 mmol, 156 mg) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N_2 and kept under a N_2 balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt_2 (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours). A THF solution (10 mL) containing $\text{Pd}(\text{PPh}_3)_4$ (0.02 mmol, 24 mg) and iodobenzene (2 mmol, 408 mg) was added to the reaction and the mixture was stirred at ambient temperature overnight (approximately 18 hours). The reaction was quenched with sat. NH_4Cl (aq) (20 mL) and partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na_2SO_4 , filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a white solid (68%).

$R_t = 3.43$ min, $M + H = 351.3$; v_{max} (thin film) 2229m, 1606m, 1511m, 1495m, 1448w, 1408w, 1369m, 1283m, 1265m, 1116w, 1091m, 1072m, 1002w, 980m, 917w, 848s, 829m, 777m, 755m, 738m, 723m, 696s, 679m, 571m, 559m; δ_{H} (300 MHz; CDCl_3) 7.77 (4H, d, $J = 8.0$ Hz, Ar-H), 7.51 (2H, t, $J = 7.5$ Hz, Ar-H), 7.44 (1H, t, $J = 7.0$ Hz, Ar-H), 7.31 (2H, d, $J = 8.5$ Hz, Ar-H), 7.15 (2H, dd, $J = 5.0, 2.0$ Hz, Ar-H), 7.13 (1H, m, Ar-H), 6.77 (2H, dd, $J = 6.5, 3.0$ Hz, Ar-H), 3.24 (2H, t, $J = 7.5$ Hz, CH_2), 2.72 (2H, t, $J = 7.5$ Hz, CH_2); δ_{C} (75 MHz; CDCl_3) 145.4 (C), 139.7 (C), 138.9 (C), 133.3 (CH), 133.1 (C), 130.9 (C), 128.9 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.3 (CH), 126.7 (CH), 126.3 (CH), 117.6 (C), 113.4 (C), 34.0 (CH_2), 25.3 (CH_2); Mp = 165 $^{\circ}\text{C}$; HRMS ($M + H$, +ESI) $\text{C}_{23}\text{H}_{19}\text{N}_4$ calculated 351.1604, found 351.1609.



CCDC Reference: 931415

Manchester reference number: s3790ma

Formula: C₂₃ H₁₈ N₄

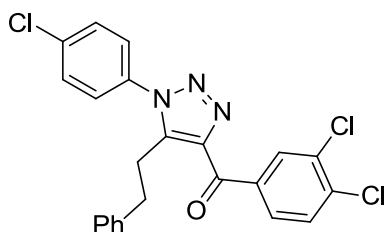
Thermal ellipsoids at 50%

Unit cell parameters: Cell lengths – $a = 10.5311(2)$, $b = 11.4207(3)$, $c = 15.0422(4)$

Cell angles – $\alpha = 90.00$, $\beta = 95.3710(10)$, $\gamma = 90.00$

Monoclinic

Space Group - P2(1)/c



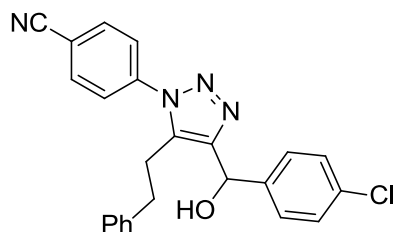
(3y)

(1-(4-Chlorophenyl)-5-phenethyl-1H-1,2,3-triazol-4-yl)(3,4-dichlorophenyl)methanone – novel

1-Azido-4-chlorobenzene (1 mmol, 154 mg), 4-phenyl-1-butyne (1.2 mmol, 156 mg) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours). A THF solution

(10 mL) containing Ni(acac)₂ (0.05 mmol, 13 mg) and 3,4-dichlorobenzoyl chloride (2 mmol, 420 mg) was added to the reaction and the mixture was stirred at ambient temperature overnight (approximately 18 hours). The reaction was quenched with sat. NH₄Cl (aq) (20 mL) and partitioned between water (20 mL) and EtOAc (40 mL). The organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a pale orange solid (66%).

R_t = 4.26 min, M + H = 456.1 and 458.1 [Cl]; v_{max} (thin film) 1647m, 1583w, 1497s, 1453w, 1242m, 1169w, 1093w, 958m, 938m, 832m, 776m, 700m; δ_H (300 MHz; CDCl₃) 8.55 (1H, d, *J* = 2.0 Hz, Ar-H), 8.32 (1H, dd, *J* = 8.5, 2.0 Hz, Ar-H), 7.62 (1H, d, *J* = 8.5 Hz, Ar-H), 7.46 (2H, d, *J* = 8.5 Hz, Ar-H), 7.20-7.15 (3H, m, Ar-H), 7.03 (2H, d, *J* = 8.5 Hz, Ar-H), 6.92 (2H, dd, *J* = 6.5, 3.0 Hz, Ar-H), 3.32 (2H, t, *J* = 7.5 Hz, CH₂), 2.94 (2H, t, *J* = 7.5 Hz, CH₂); δ_C (75 MHz; CDCl₃) 184.5 (C=O), 143.9 (C), 142.8 (C), 139.3 (C), 137.6 (C), 136.7 (C), 136.5 (C), 133.5 (C), 132.9 (C), 132.6 (CH), 130.4 (CH), 129.8 (CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 127.1 (CH), 126.6 (CH), 34.2 (CH₂), 26.1 (CH₂); Mp = 136 °C; HRMS (M + H, +ESI) C₂₃H₁₇N₃OCl₃ calculated 456.0432, found 456.0443.



4-((4-(4-Chlorophenyl)(hydroxy)methyl)-5-phenethyl-1H-1,2,3-triazol-1-yl)benzonitrile – novel

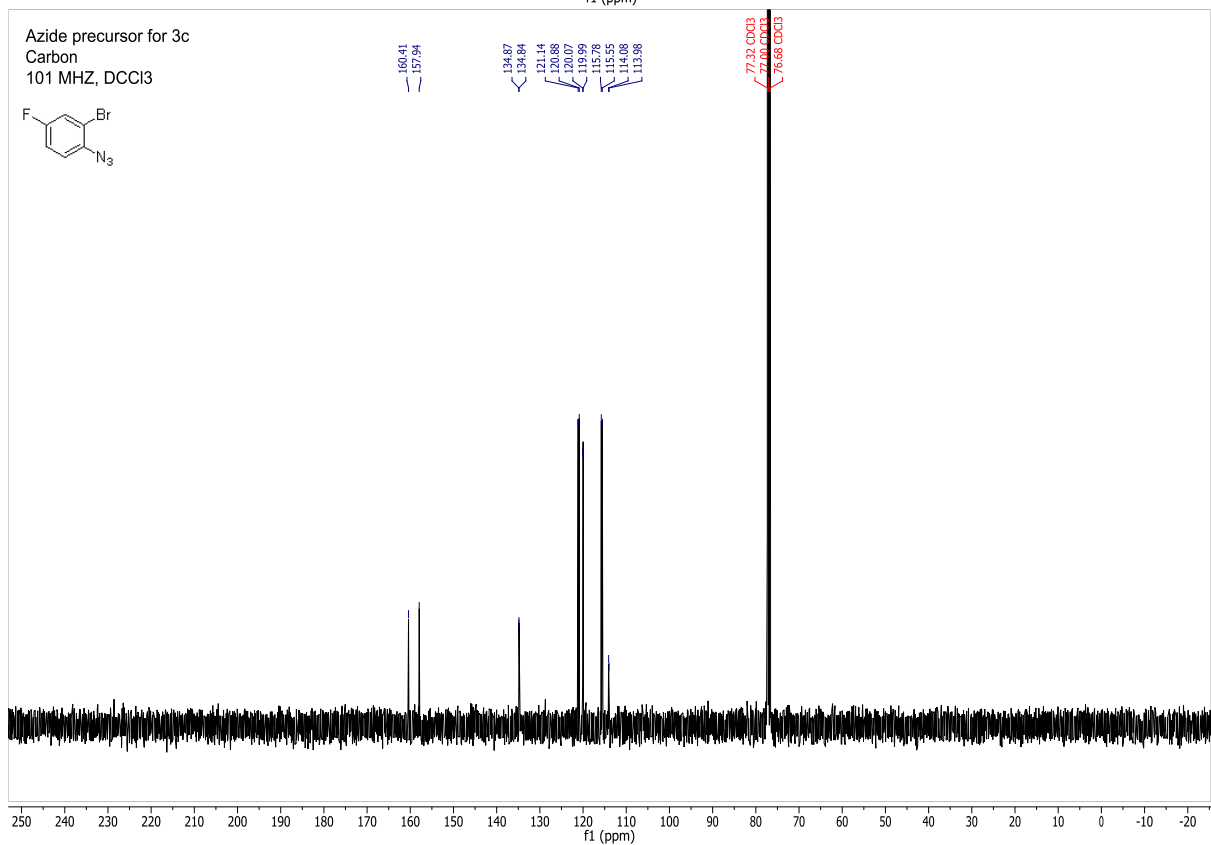
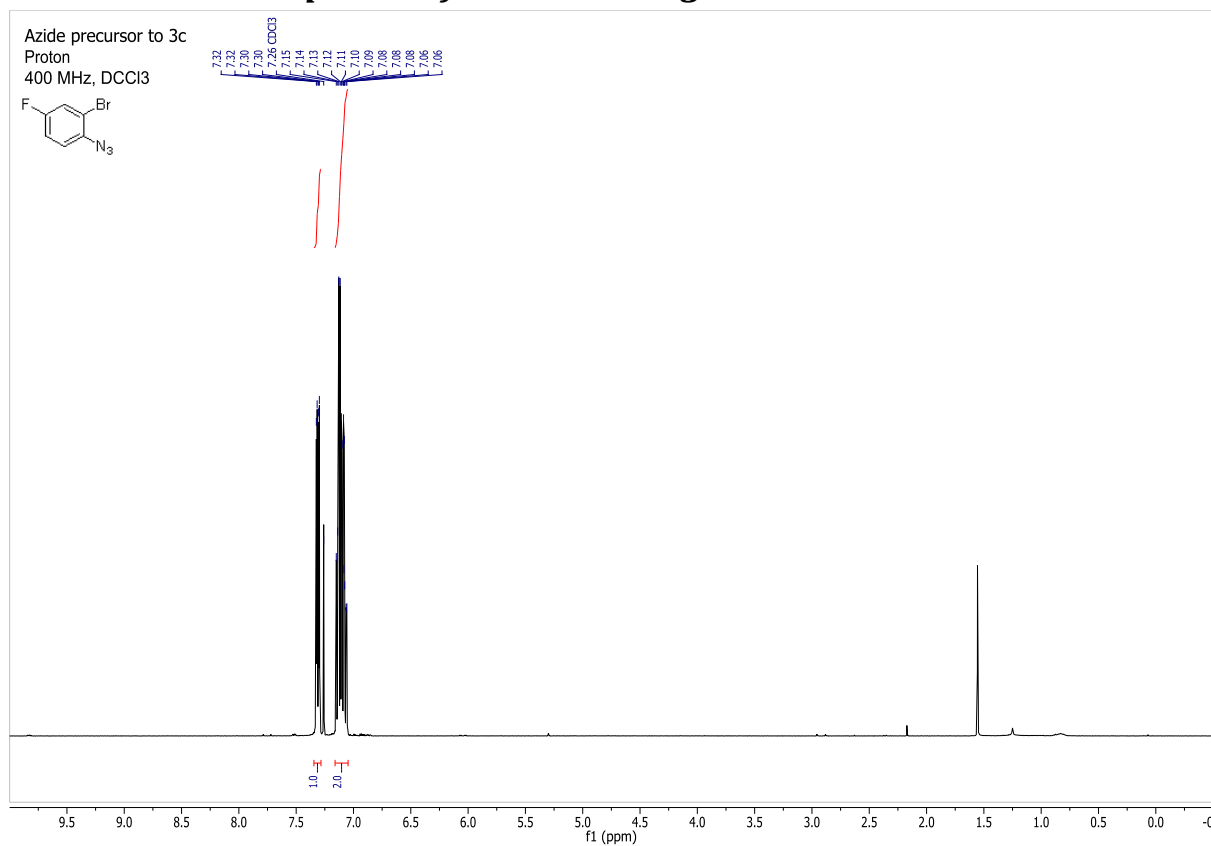
4-Azidobenzonitrile (1 mmol, 144 mg), 4-phenyl-1-butyne (1.2 mmol, 156 mg) and *N*-methylimidazole (0.1 mmol, 8 mg) were added to a round bottomed flask. The vessel was purged with N₂ and kept under a N₂ balloon. Dry THF (8 mL) was added to dissolve the starting materials before ZnEt₂ (1.5 mmol, 1.5 mL, 1 M in hexanes) was added in 2 portions over 5 minutes. The reaction was stirred at ambient temperature overnight (approximately 18 hours). Magnesium turnings (4 mmol, 96 mg) were added to a second round bottomed flask and the vessel was purged with N₂ and kept under a N₂ balloon. Dry THF 10 mL was added and the flask was put in an ambient temperature water bath. 1,2-dichloroethane (2 mmol, 160 μL) was added to the magnesium suspension and the reaction was vigorously stirred for 1 hour. Some white precipitate, in addition to the excess magnesium, was observed and was dissolved with a further 5 mL of dry THF. The decanted solution of MgCl₂ (~2 mmol) was added to a third N₂ purged round bottom flask containing 4-chlorobenzaldehyde (2 mmol, 280 mg). The aryl zinc solution was then added to the MgCl₂/aldehyde solution and the reaction was stirred overnight (approximately 18 hours) at ambient temperature. The reaction was quenched with sat. NH₄Cl (aq) (20 mL) and partitioned between water (20 mL) and EtOAc (40 mL), the organic layer was washed with water (20 mL), dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was dry loaded onto silica gel before purification by column chromatography (silica gel, EtOAc/hexane) to afford a white solid (52%).

R_t = 4.24 min, M + H = 424.1 and 426.1 [Cl]; v_{max} (thin film) 3360br w, 2232m, 1607s, 1511s, 1490s, 1454m, 1409w, 1254m, 1089s, 1013s, 910w, 844s, 795m, 751s, 700s; δ_H (300 MHz; CDCl₃) 7.73 (2H, d, *J* = 8.5 Hz, Ar-H), 7.44 (2H, d, *J* = 8.5 Hz, Ar-H), 7.35 (2H, d, *J* = 8.5 Hz, CH), 7.25 (2H, d, *J* = 8.5 Hz, CH); δ_C (75 MHz; CDCl₃) 139.3 (C), 137.6 (C), 136.7 (C), 136.5 (C), 133.5 (C), 132.9 (C), 132.6 (CH), 130.4 (CH), 129.8 (CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 127.1 (CH), 126.6 (CH), 34.2 (CH₂), 26.1 (CH₂); Mp = 136 °C; HRMS (M + H, +ESI) C₂₃H₁₇N₃OCl₃ calculated 456.0432, found 456.0443.

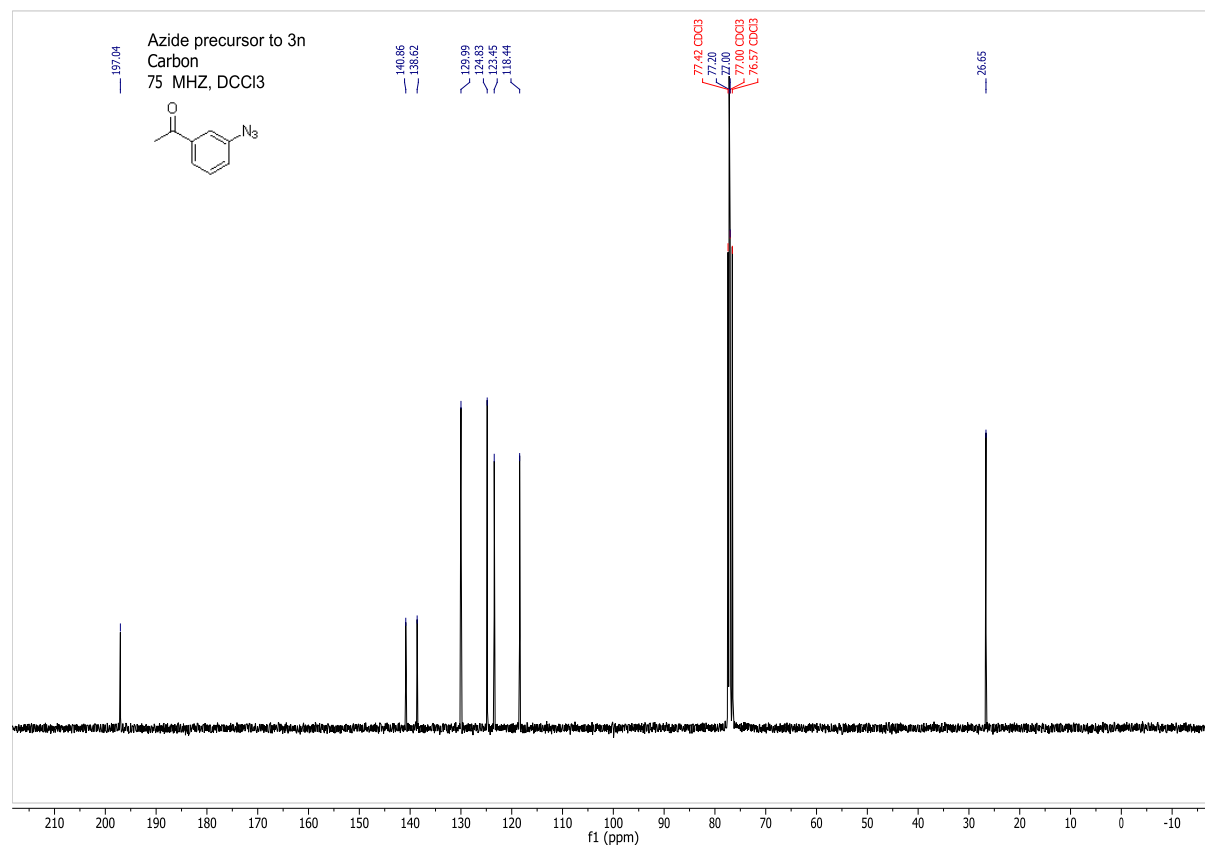
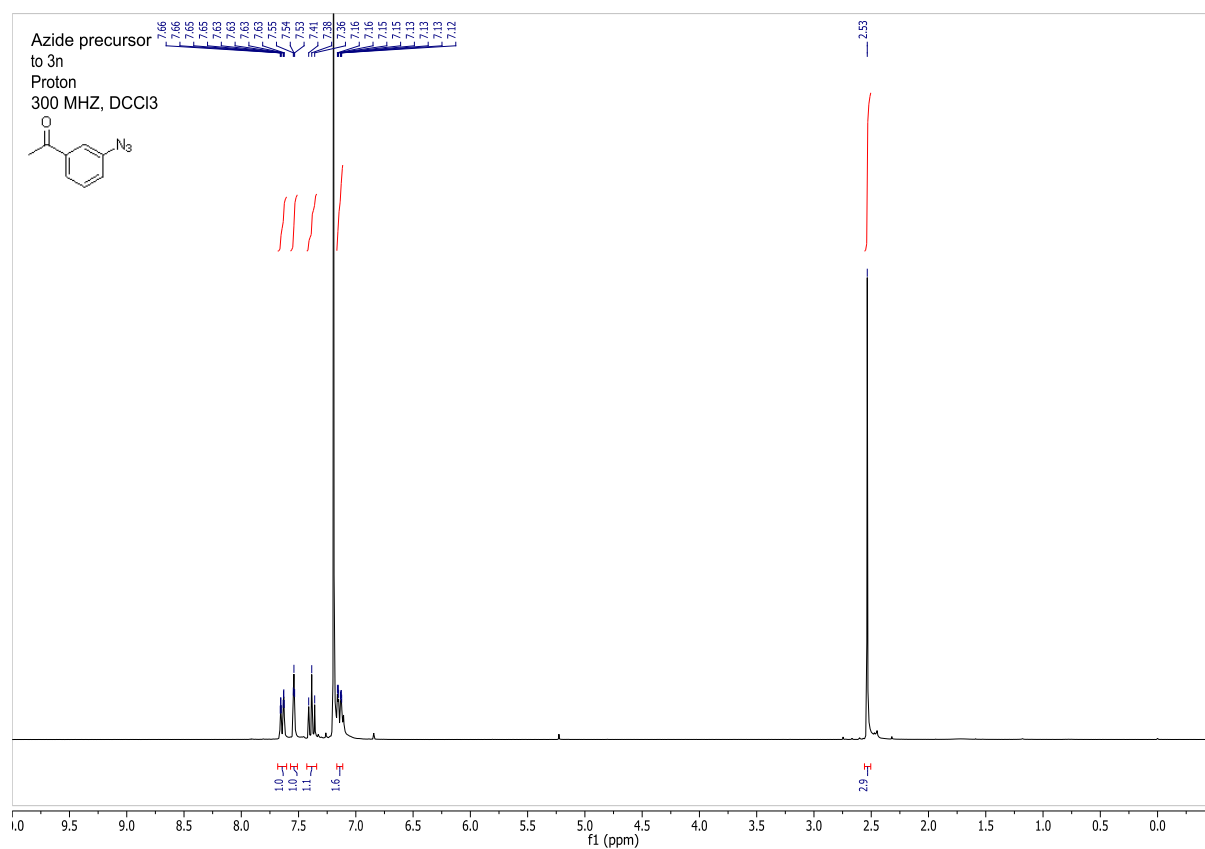
8.5 Hz, Ar-H), 7.19-7.10 (3H, m, Ar-H), 6.70 (2H, dd, $J = 7.5, 2.1$ Hz, Ar-H), 6.06 (1H, s, Ar₂CHOH), 3.7-3.3 (1H, br s, OH), 2.88 (2H, m, CH₂), 2.54 (2H, t, $J = 7.5$ Hz, CH₂); δ_C (75 MHz; CDCl₃) 147.2 (C), 140.0 (C), 139.4 (C), 138.9 (C), 134.3 (C), 133.7 (C), 133.4 (CH), 128.7 (CH), 128.7 (CH), 128.3 (CH), 127.8 (CH), 126.8 (CH), 126.1 (CH), 117.4 (C), 113.5 (C), 68.3 (Ar₂CHOH), 34.7 (CH₂), 24.8 (CH₂); Mp = 152 °C; HRMS (M + H, +ESI) C₂₄H₂₀N₄OCl calculated 415.1320, found 415.1322.

NMR Spectra

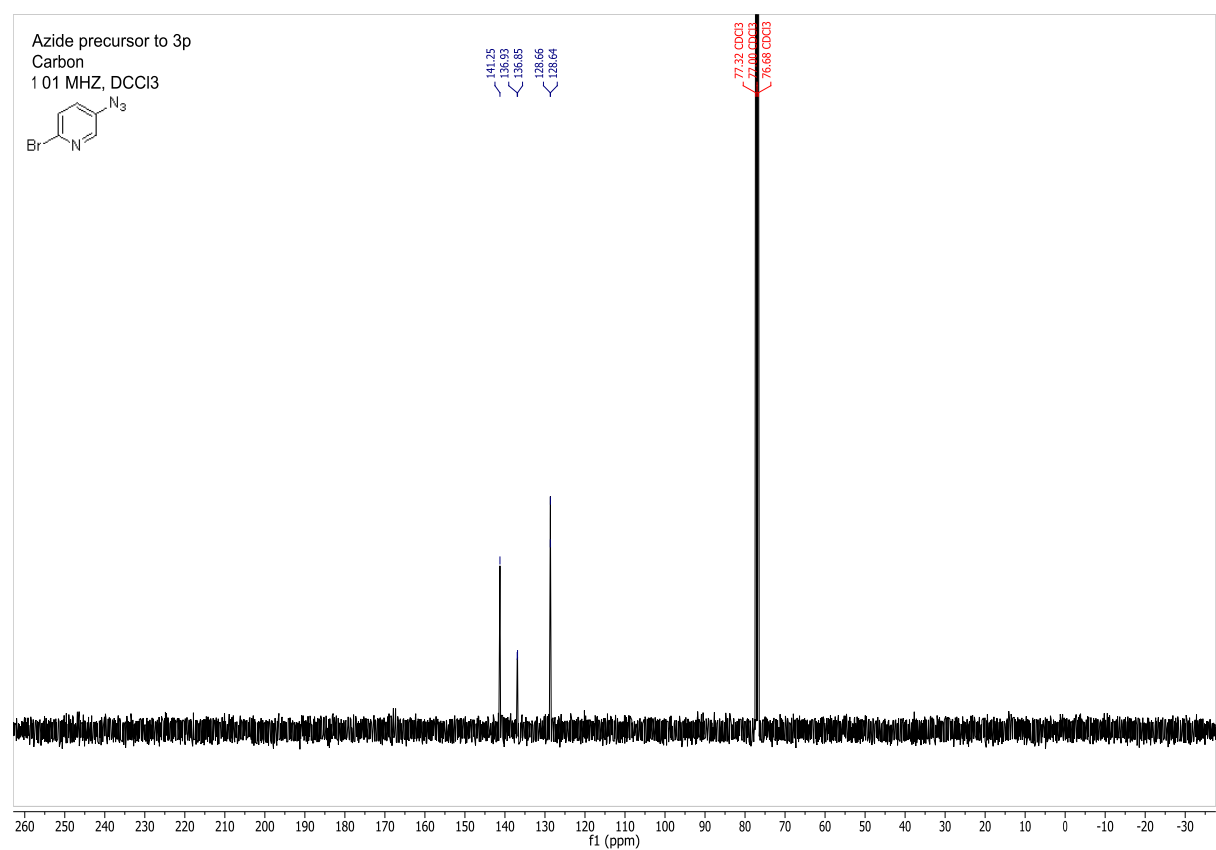
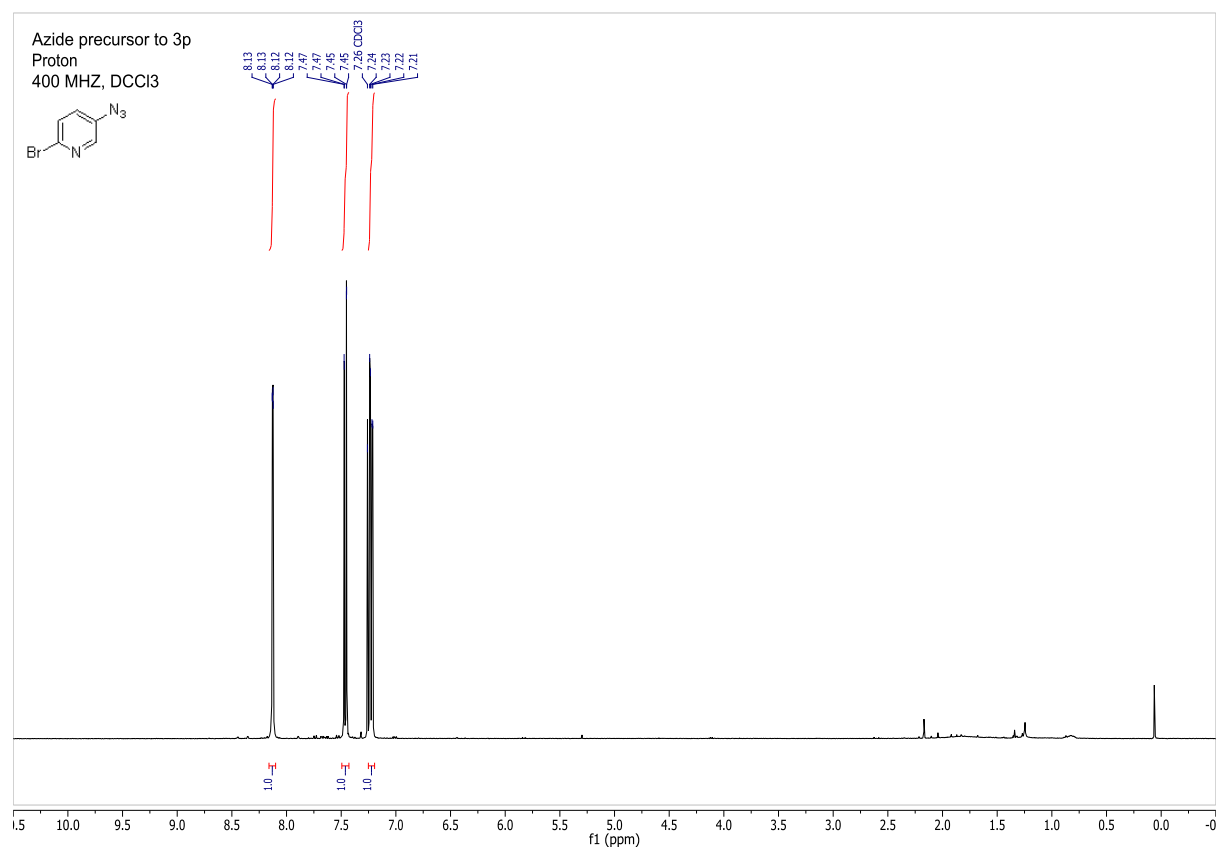
¹H- and ¹³C-NMR Spectra of Novel Starting Materials



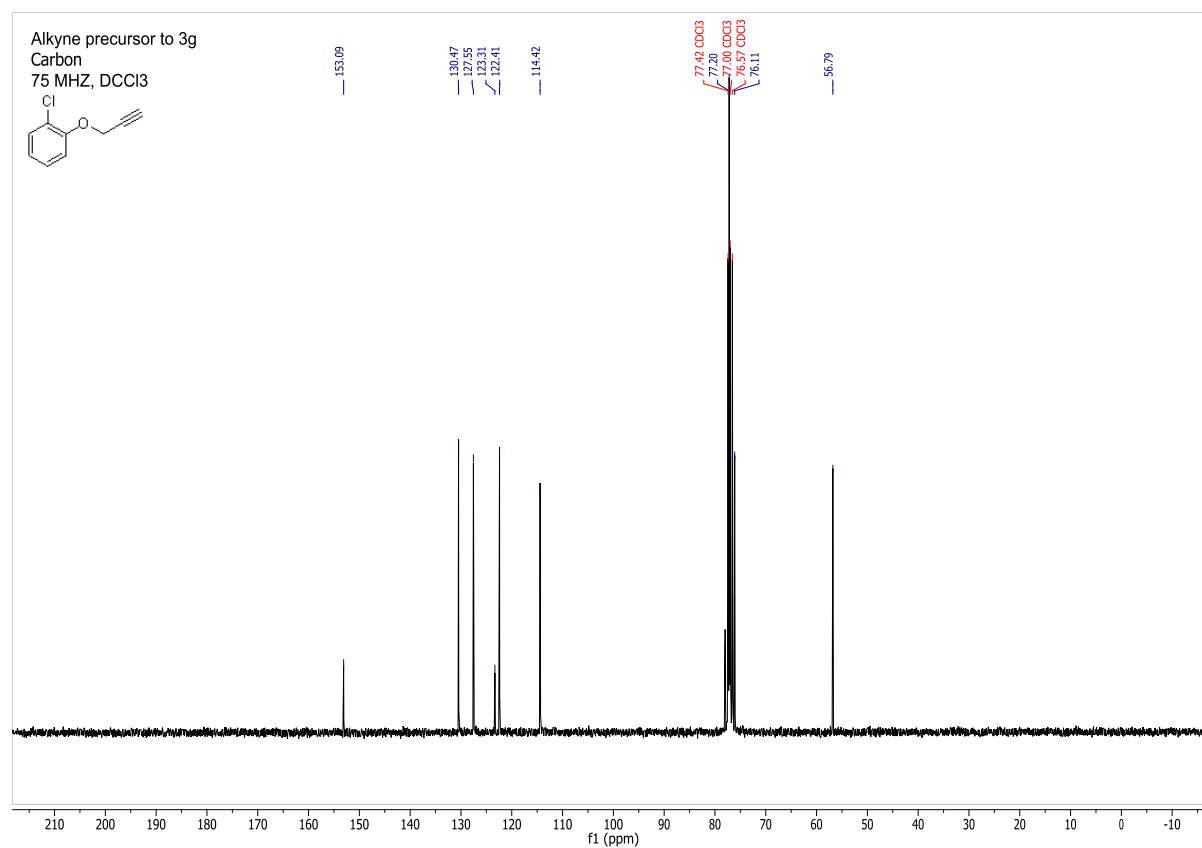
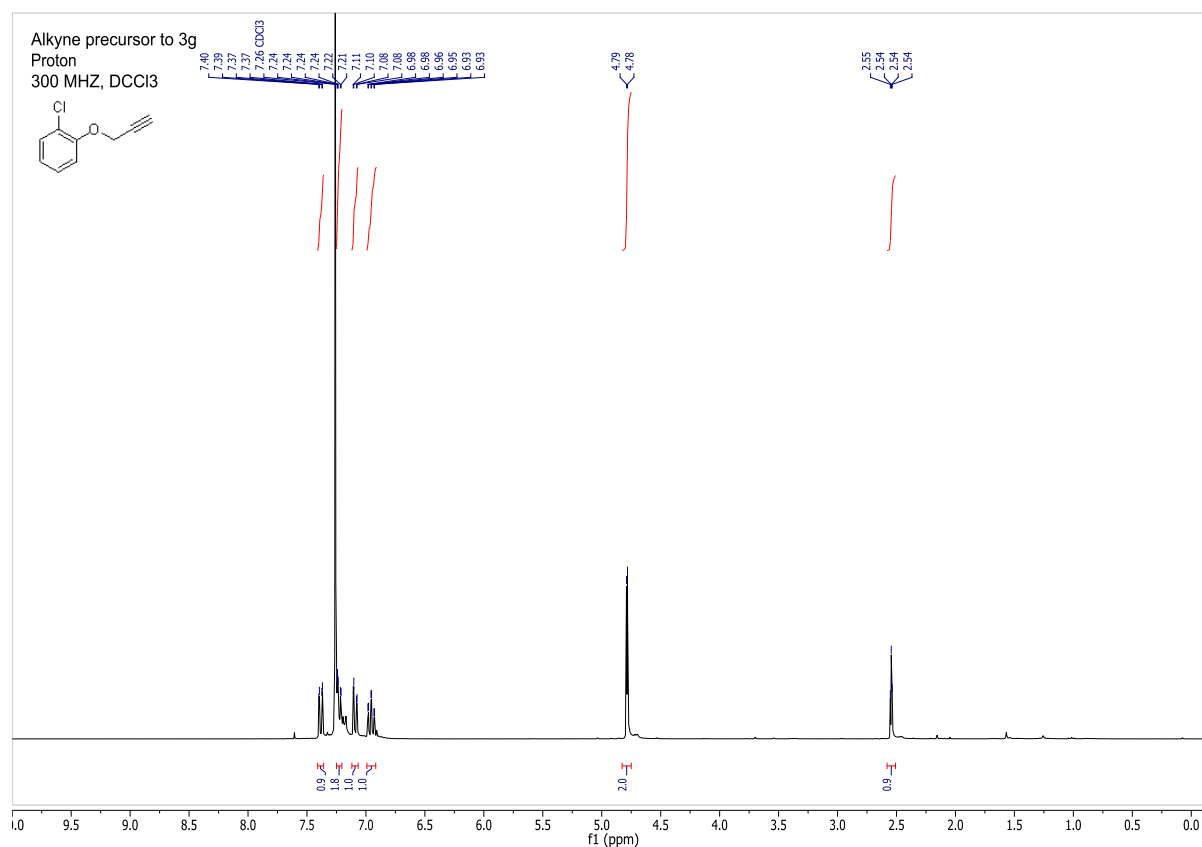
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



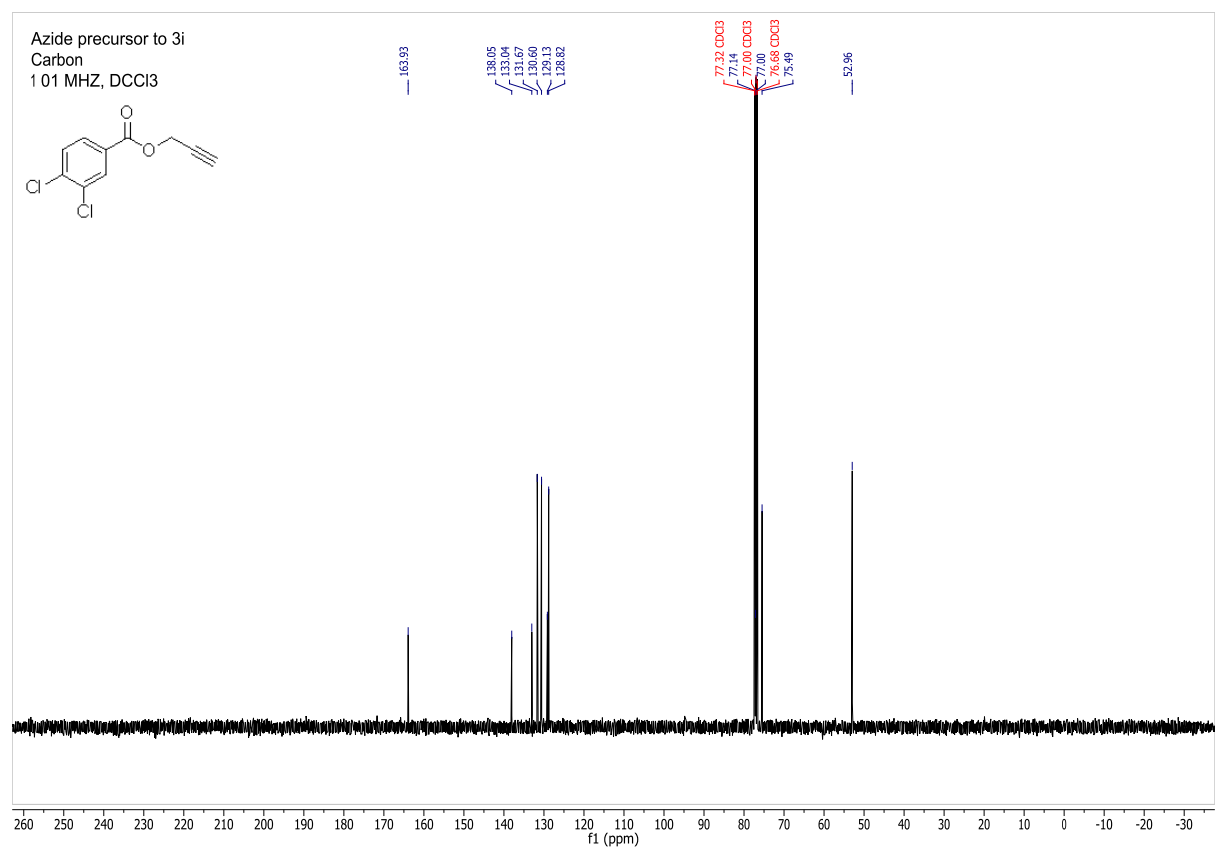
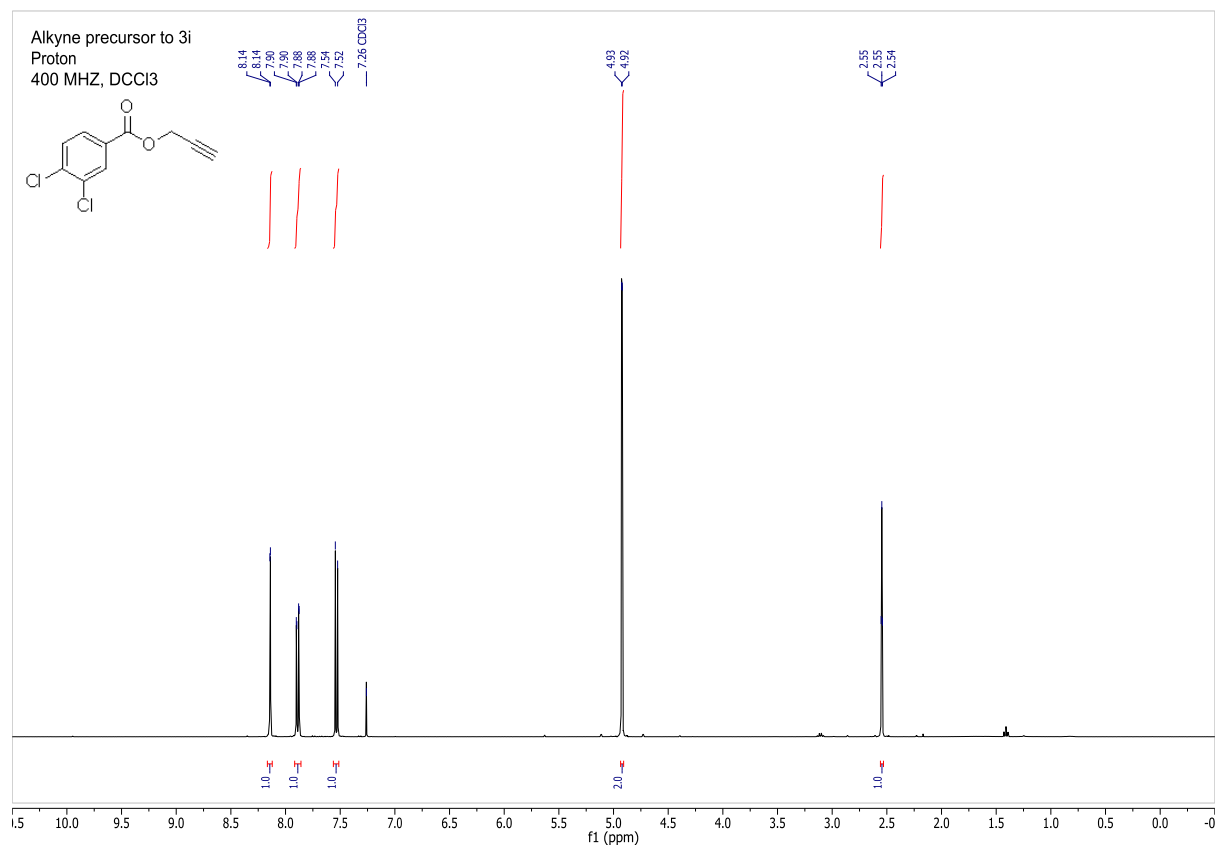
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



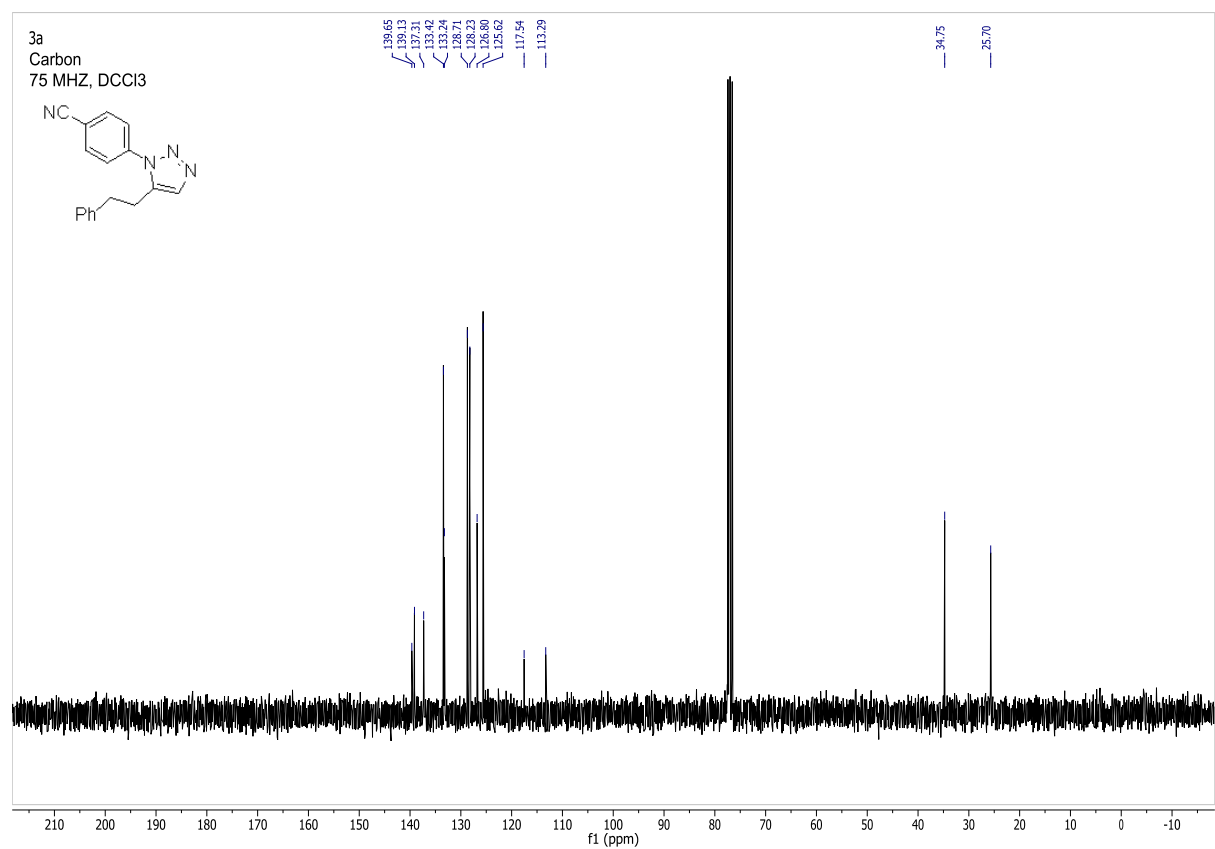
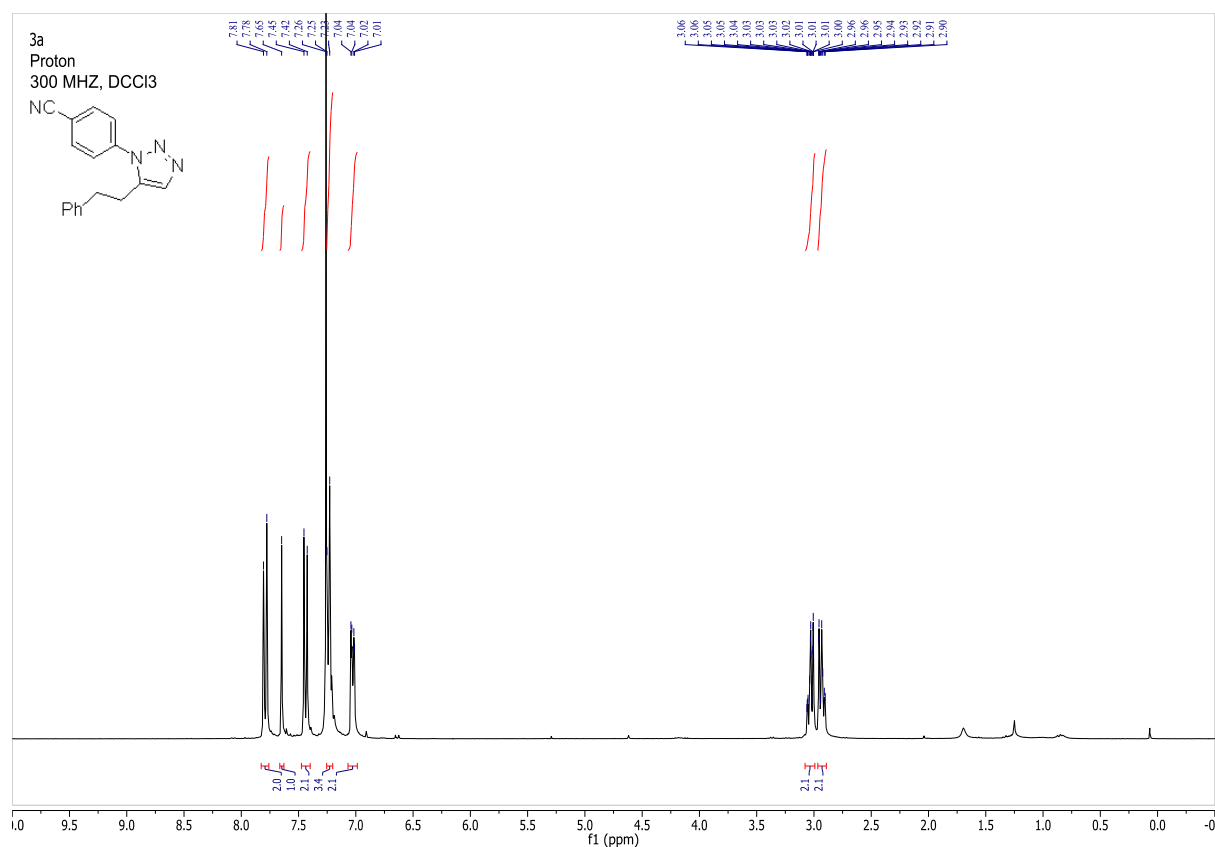
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



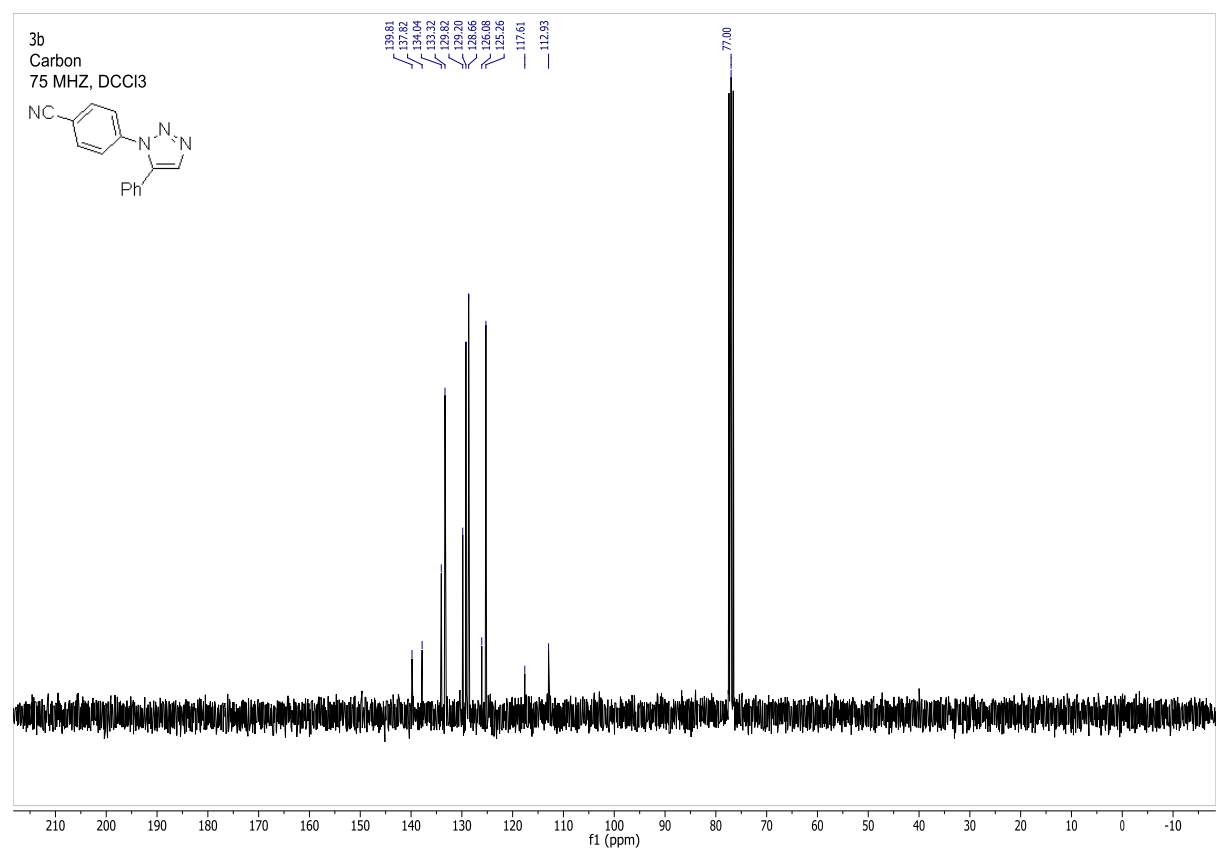
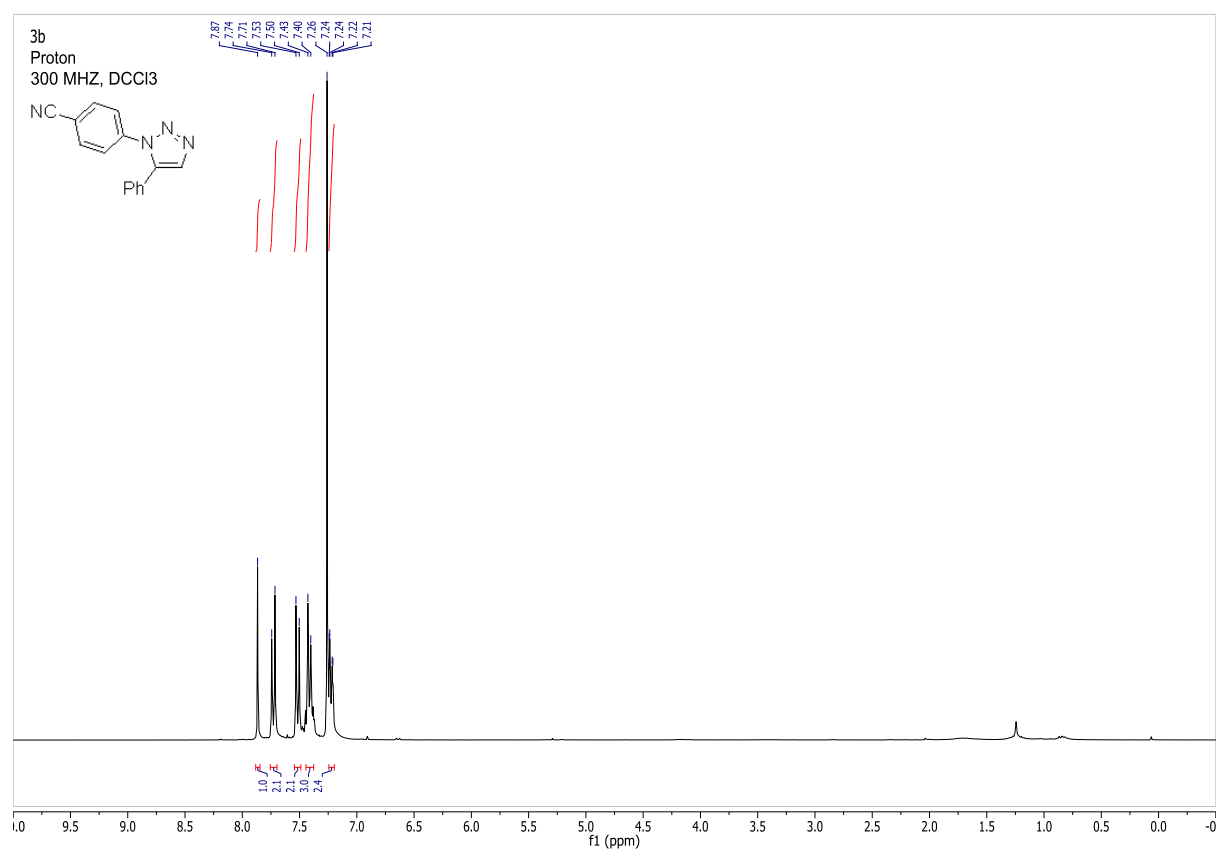
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



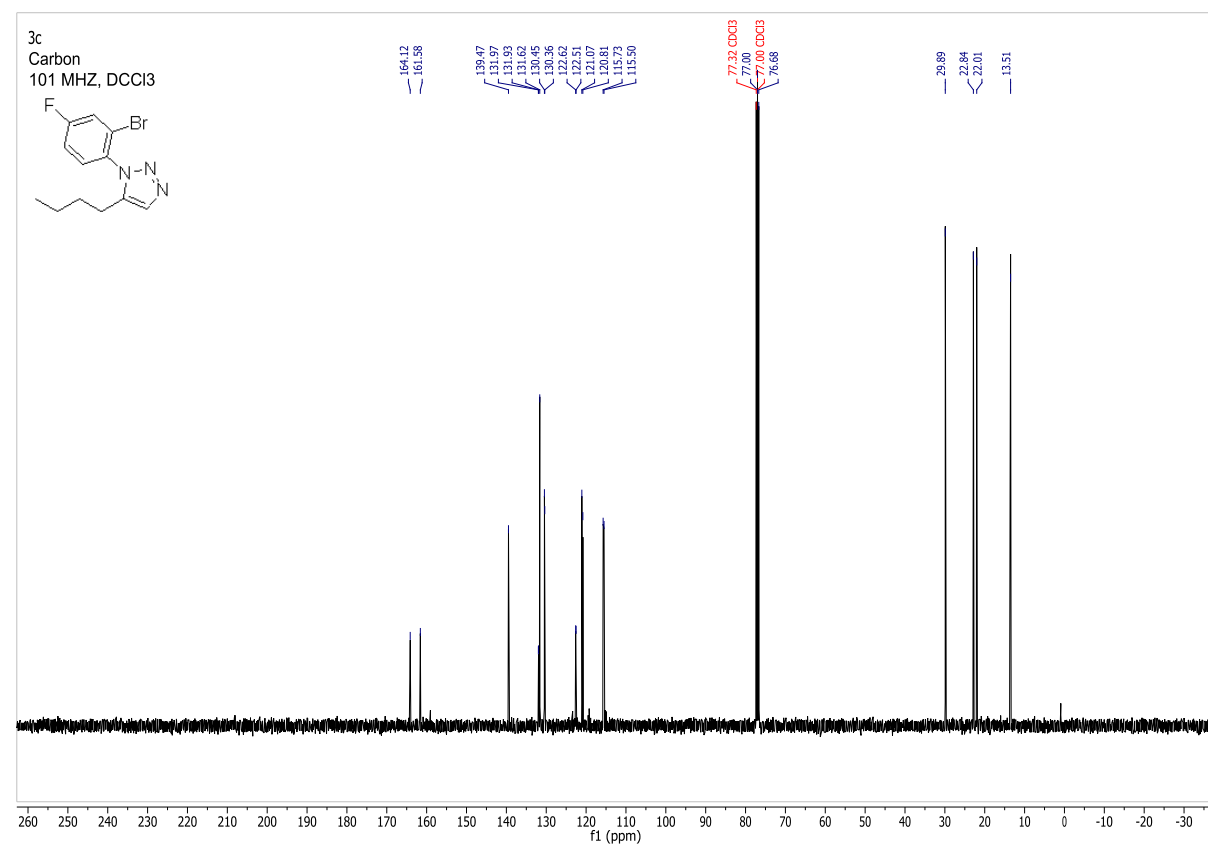
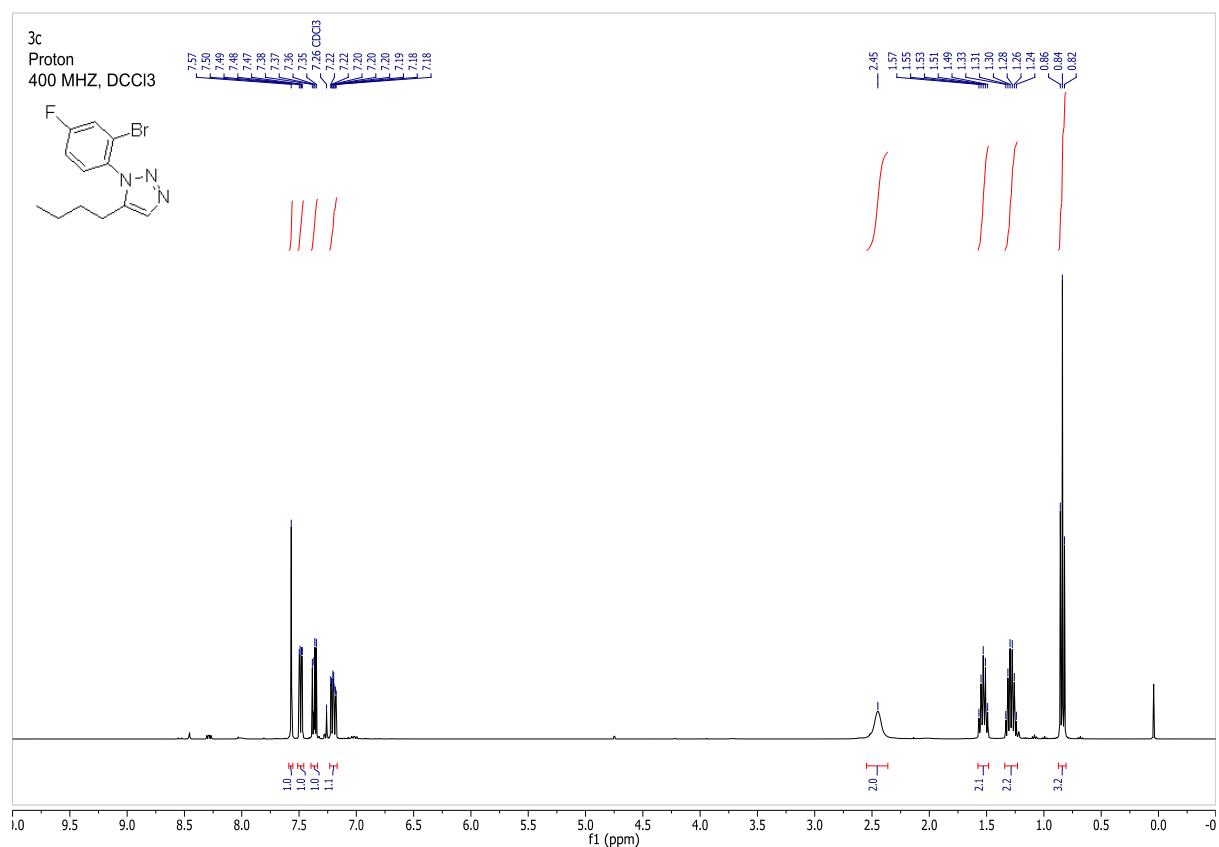
¹H- and ¹³C-NMR Spectra of 1,5-Substituted Triazoles



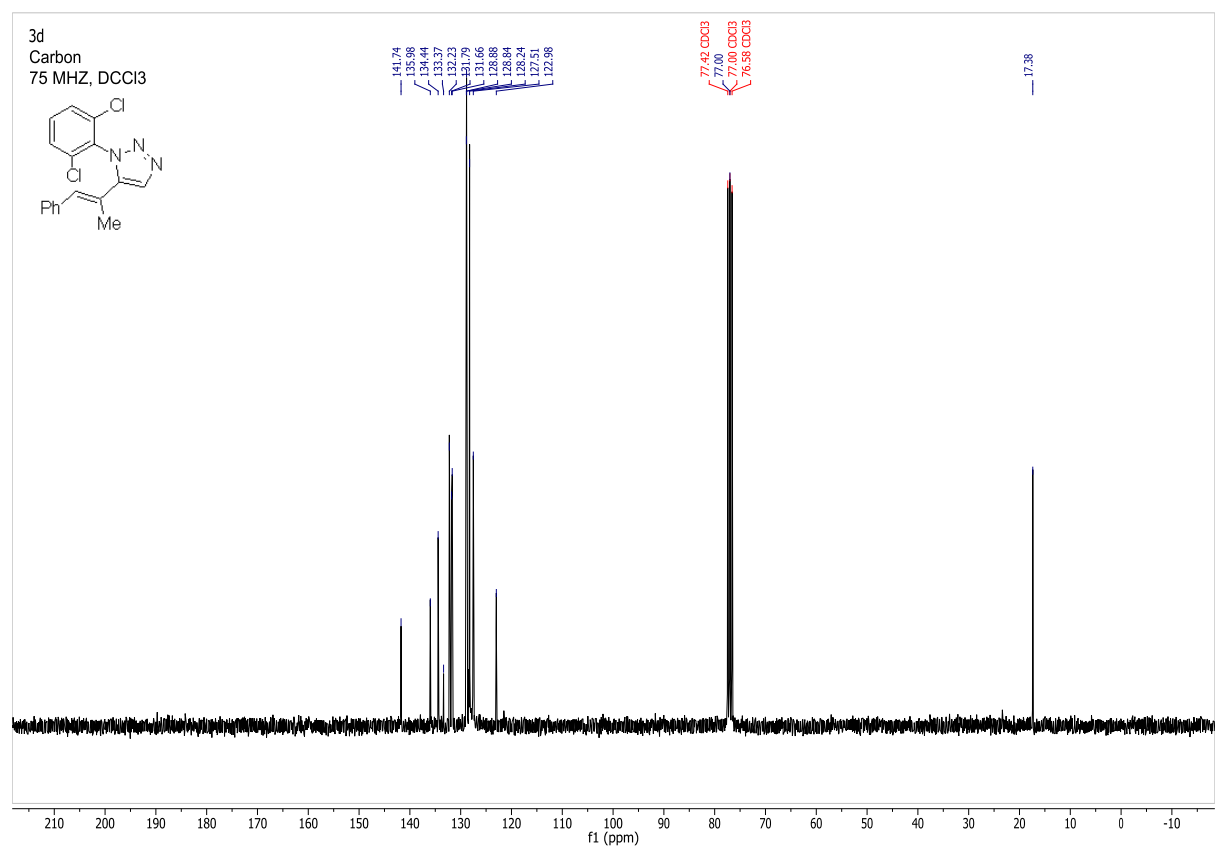
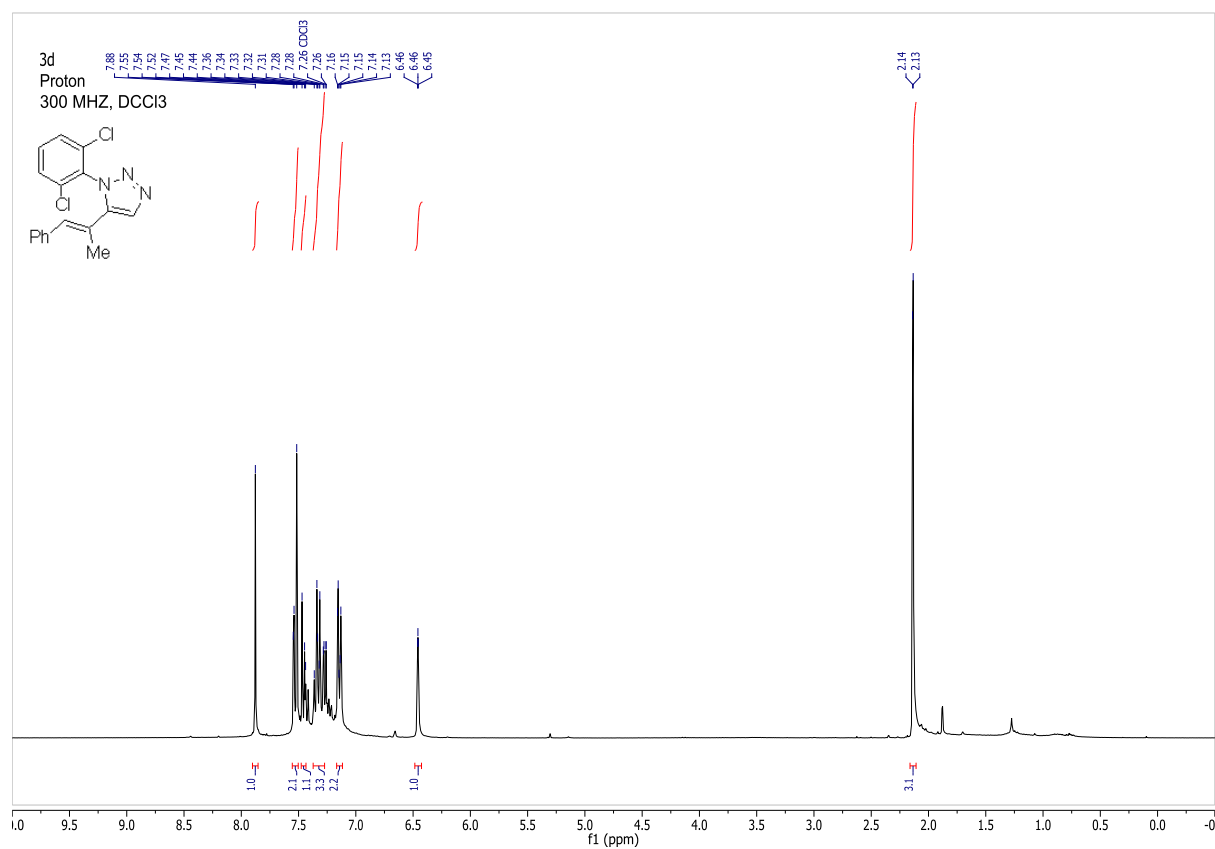
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



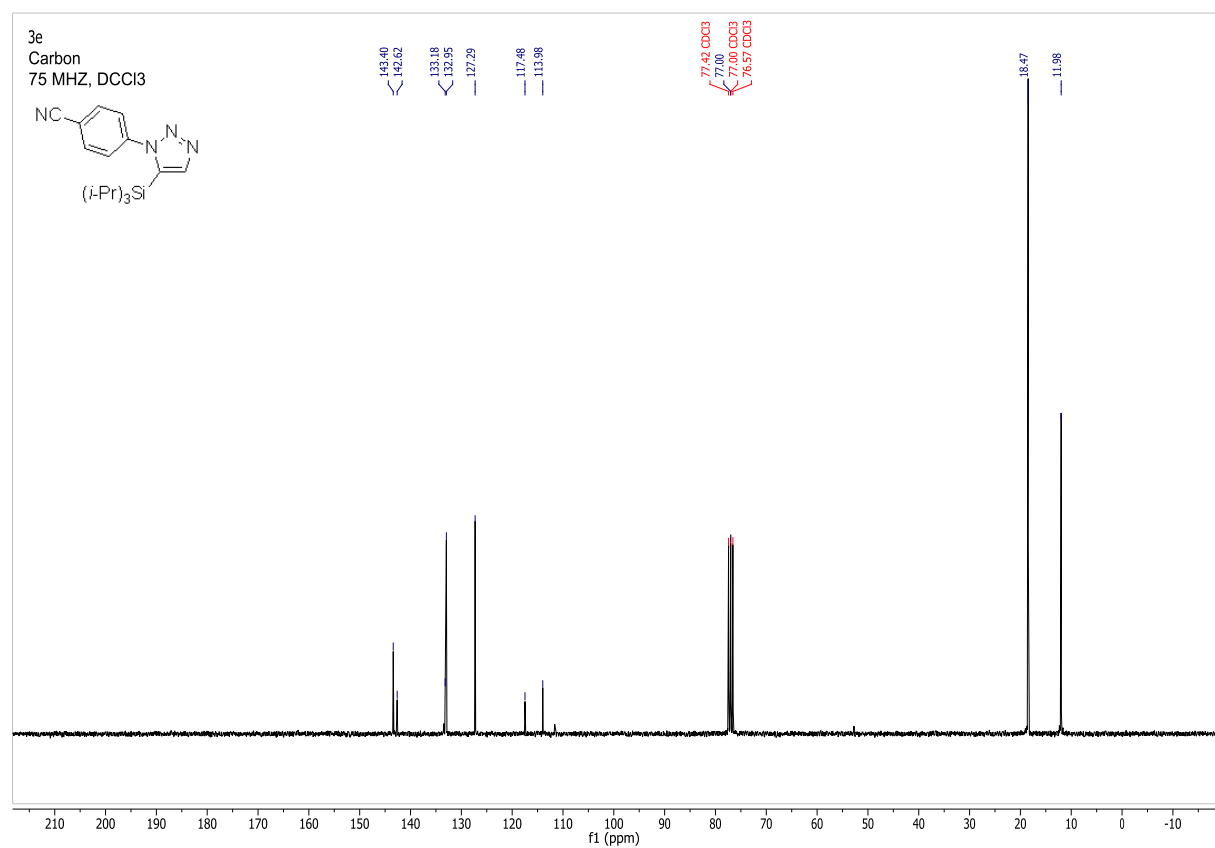
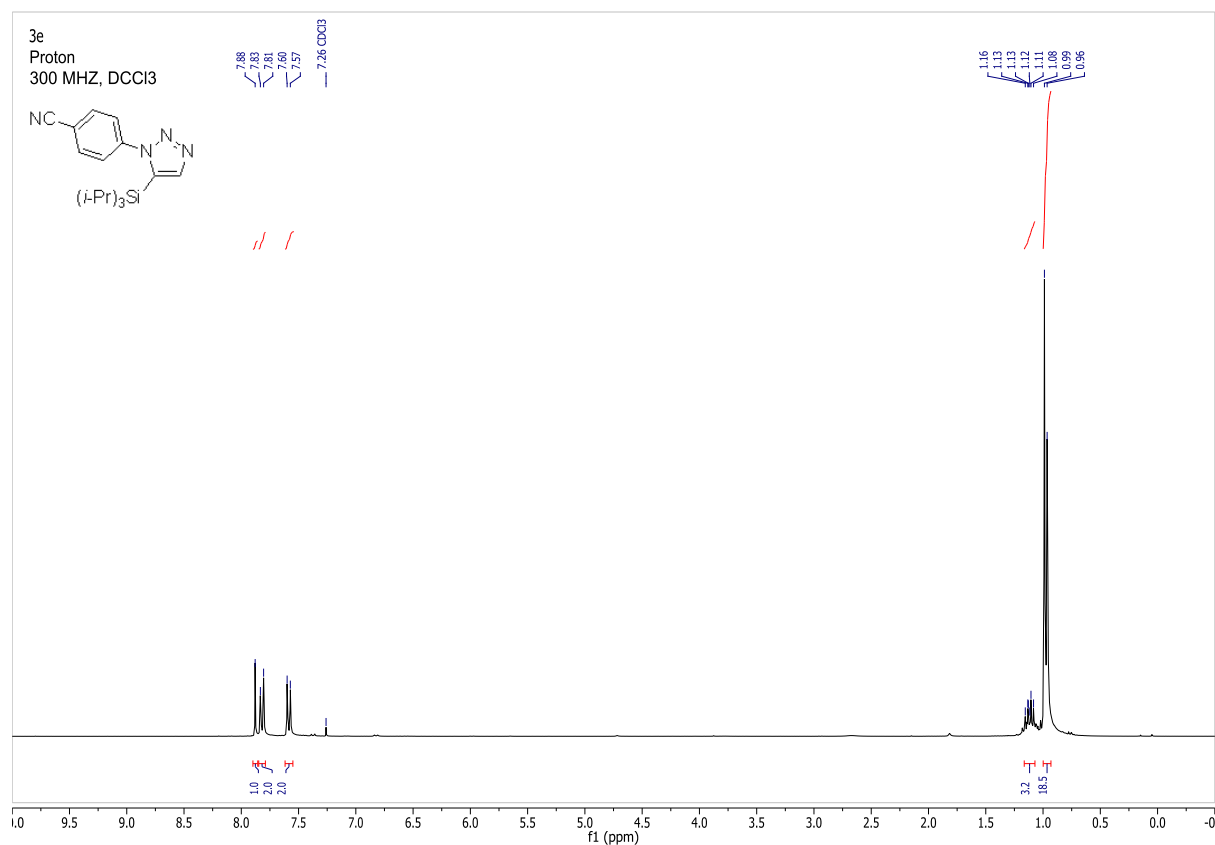
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



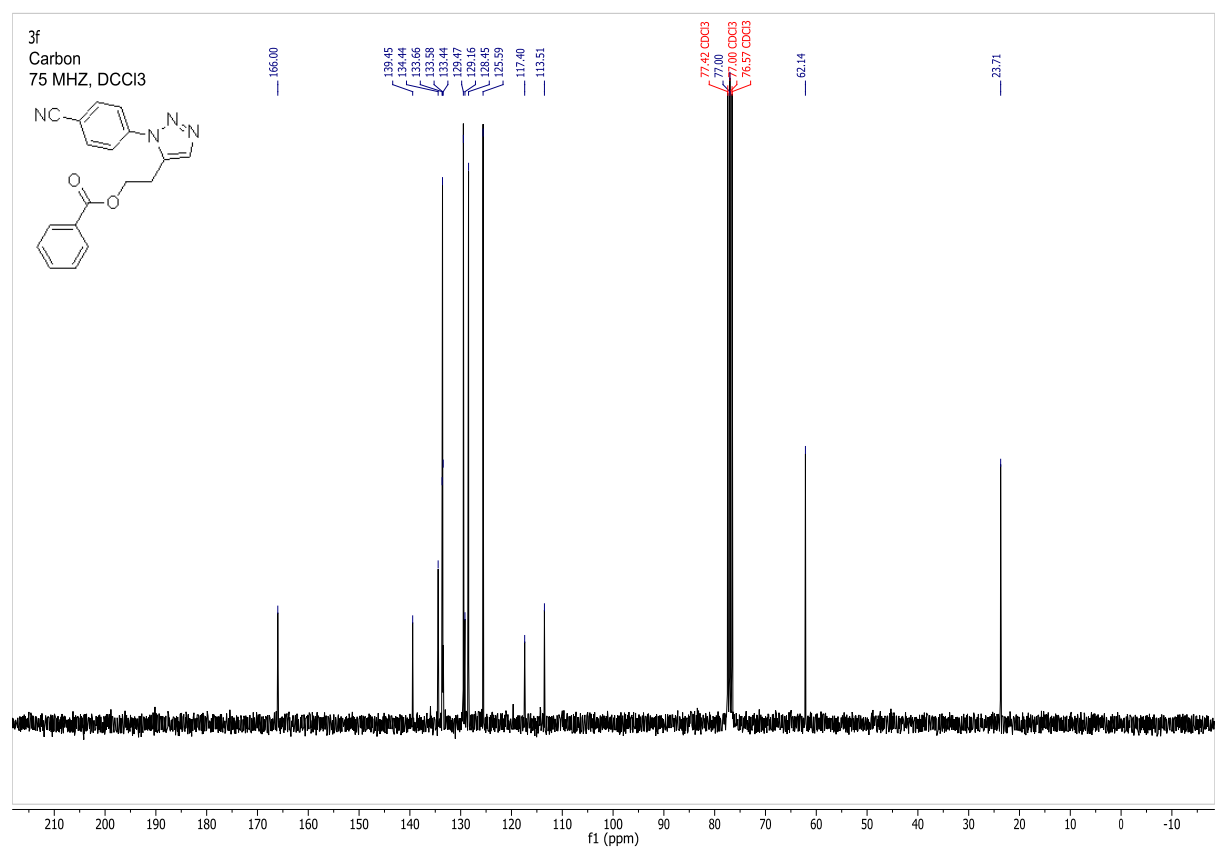
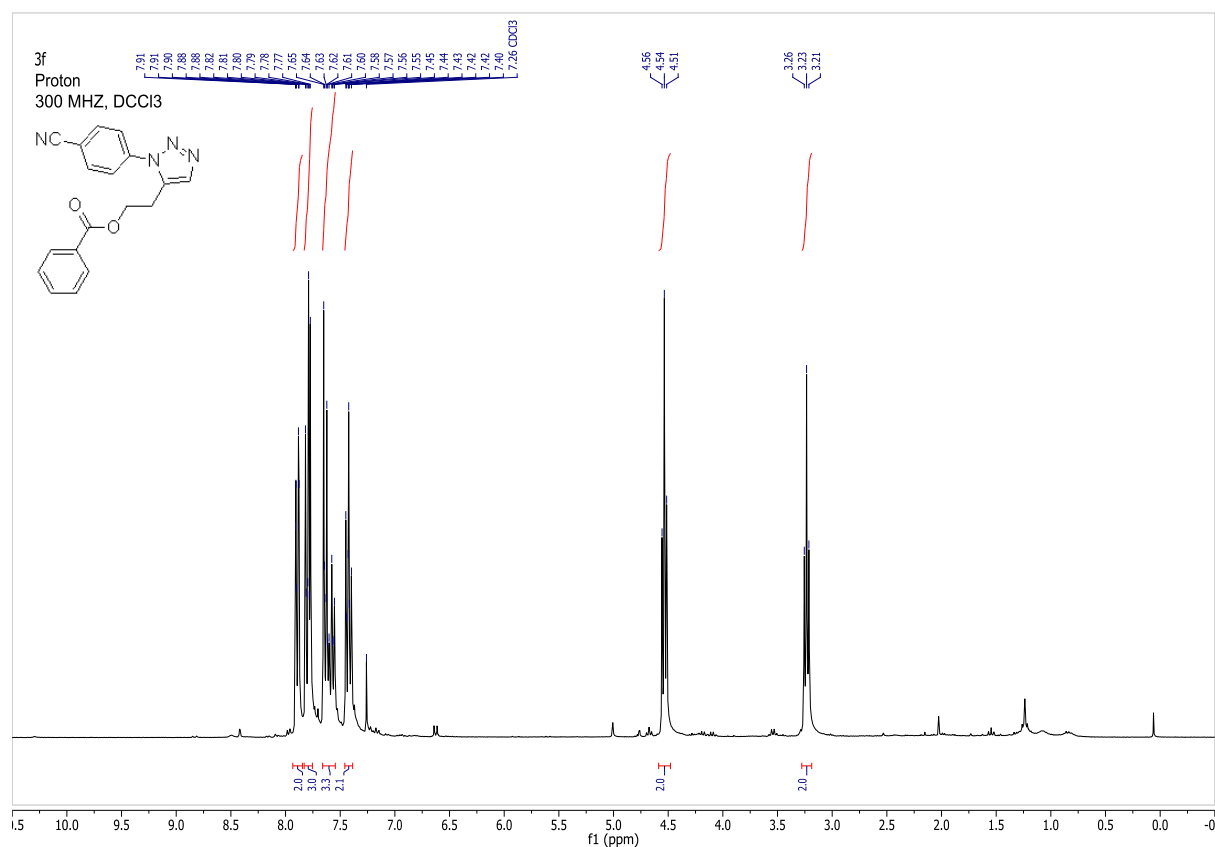
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



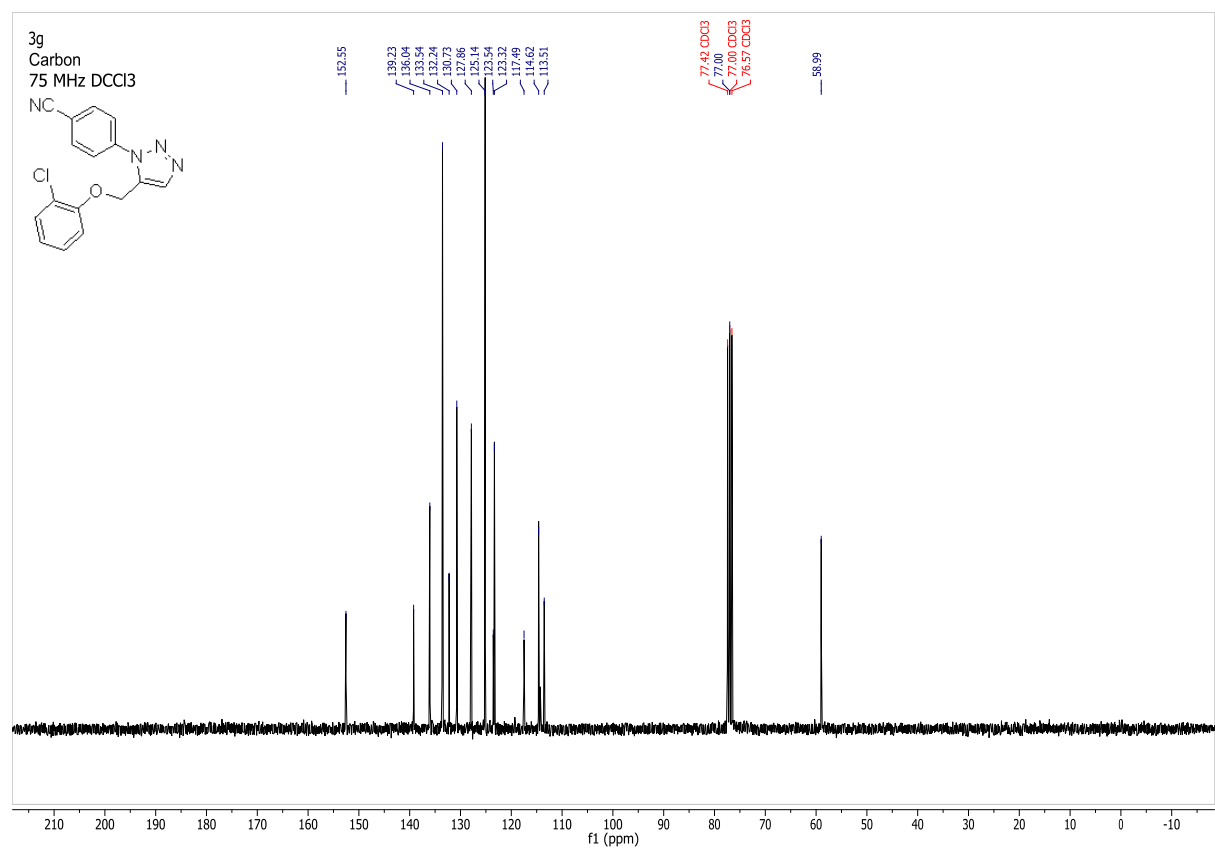
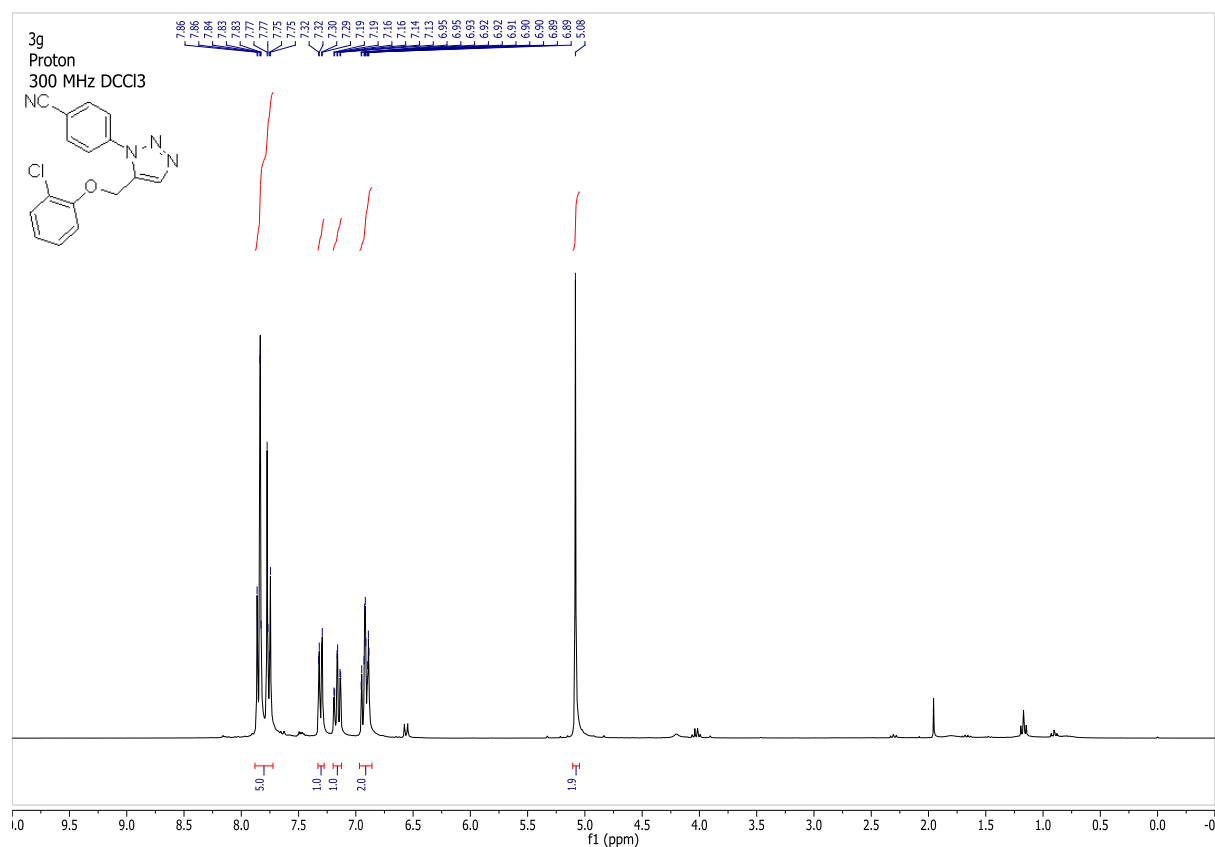
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



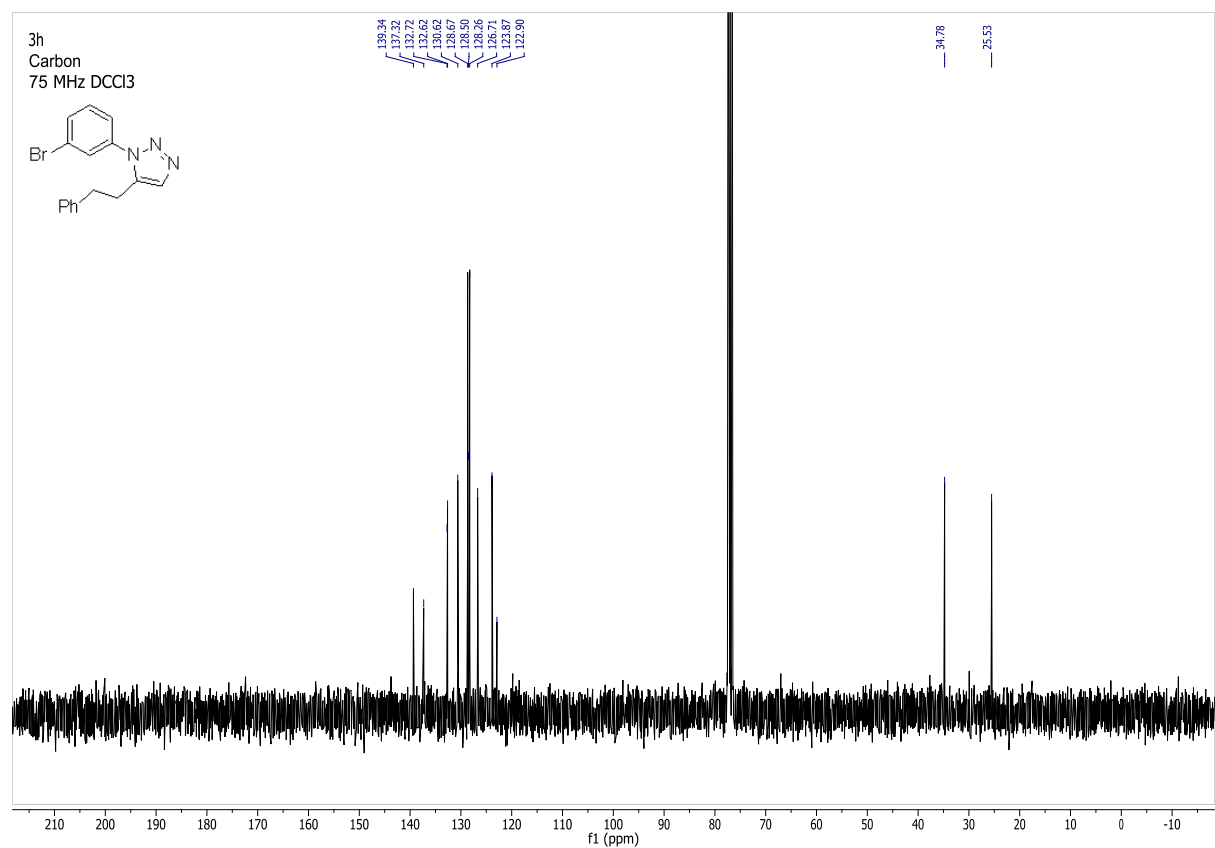
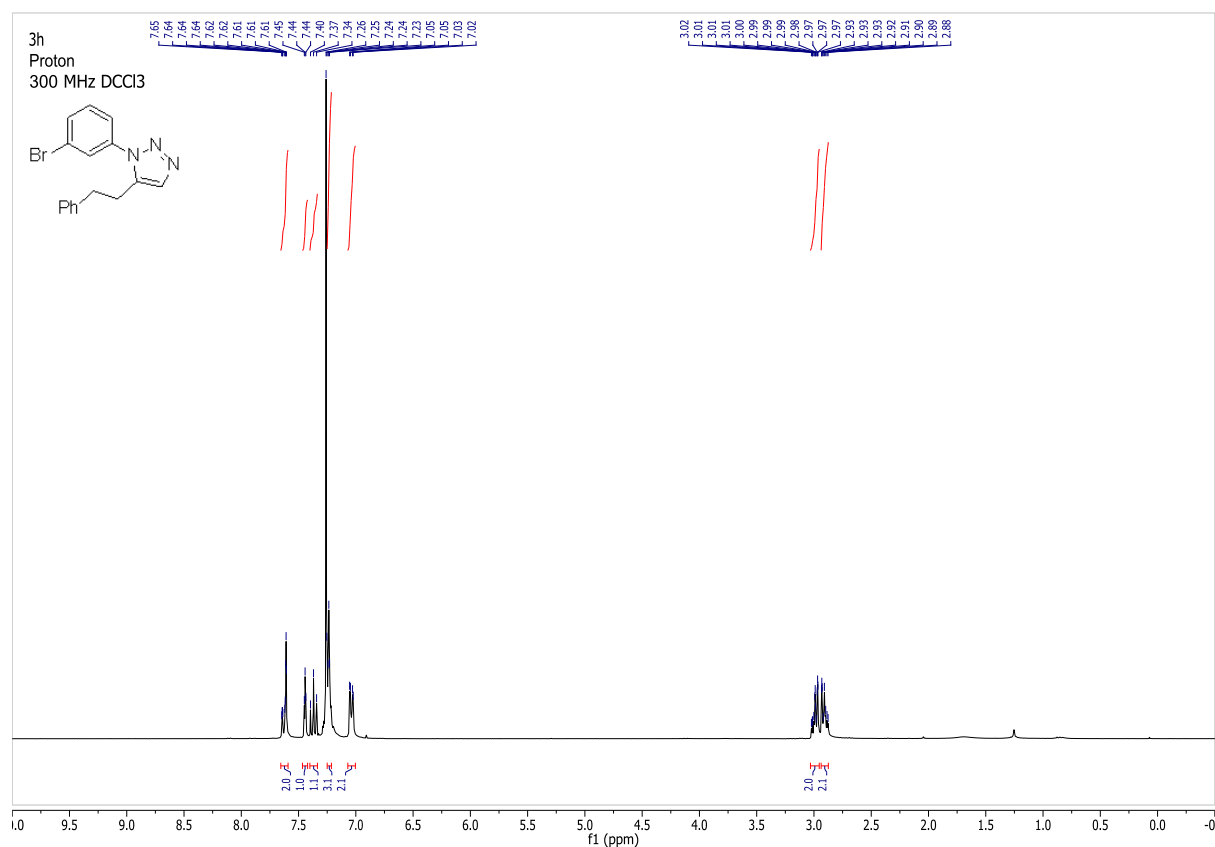
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



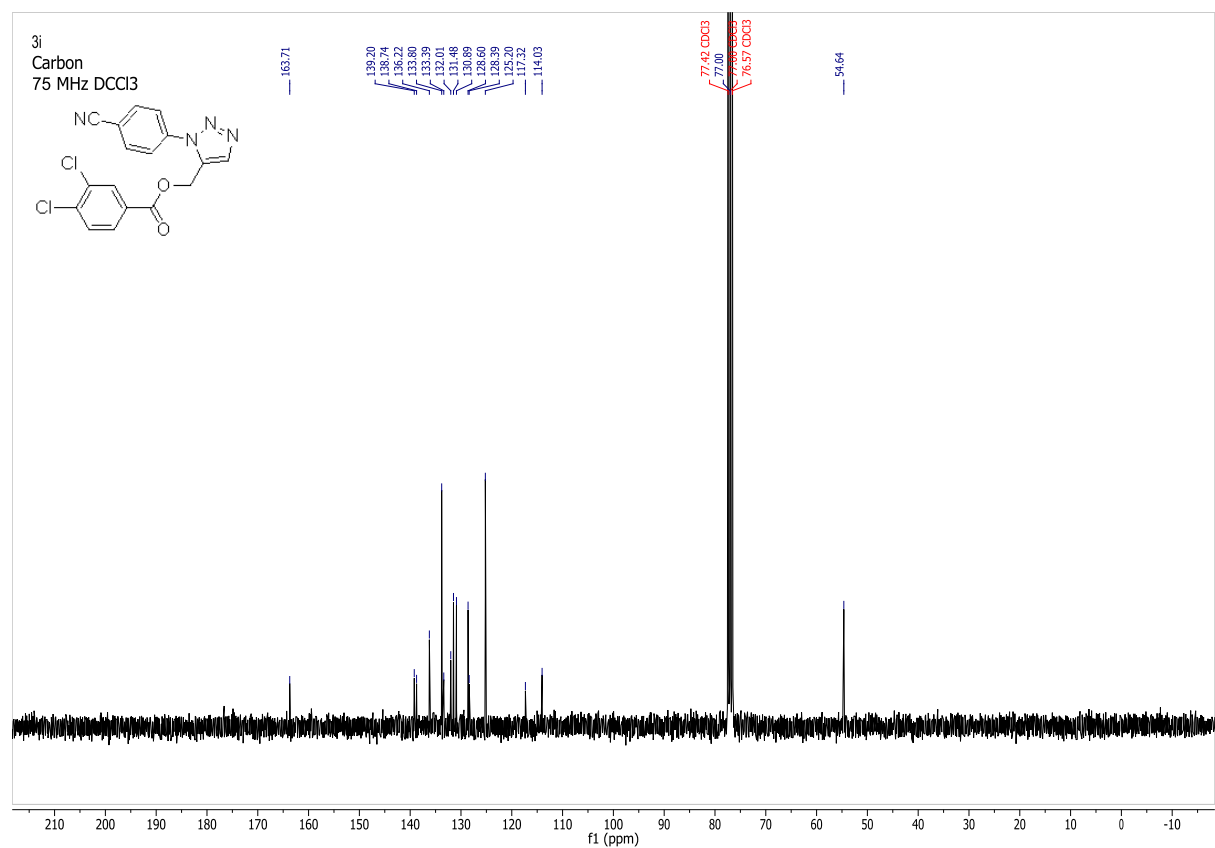
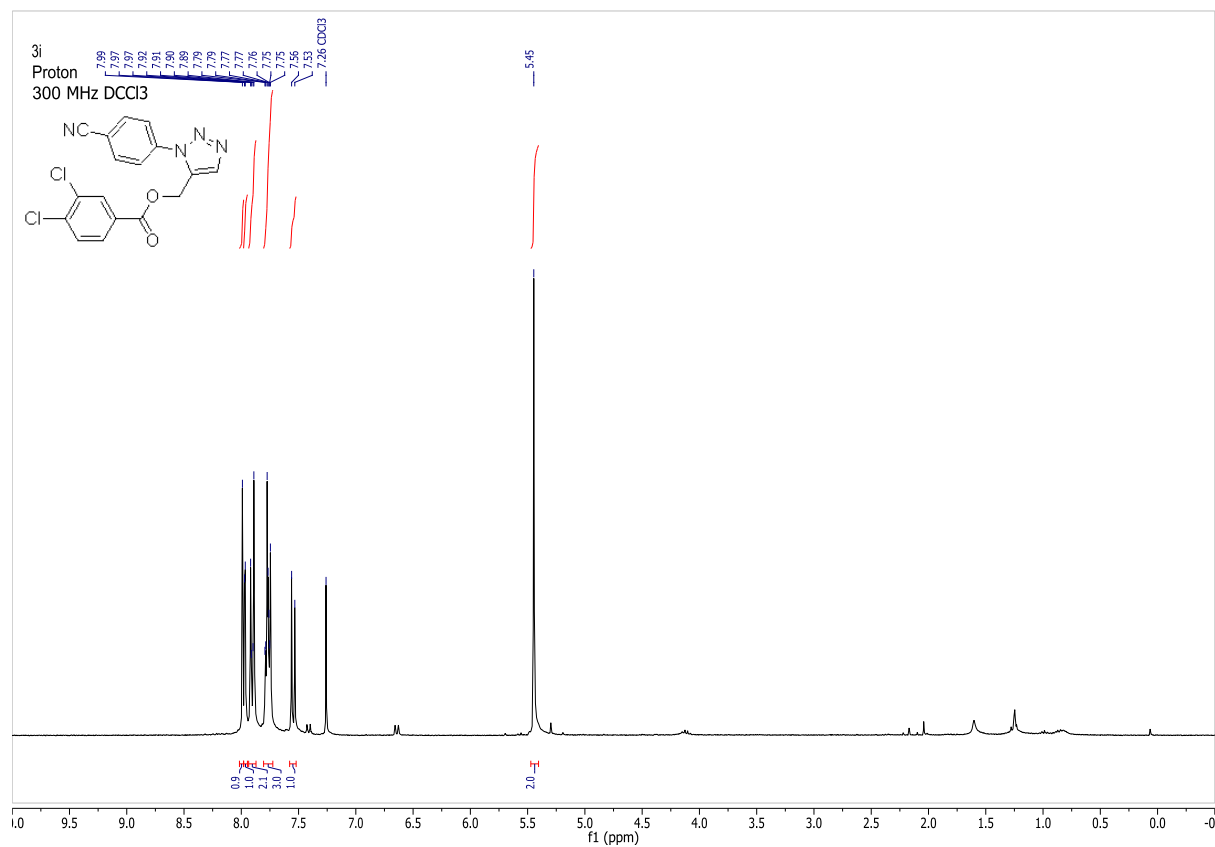
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



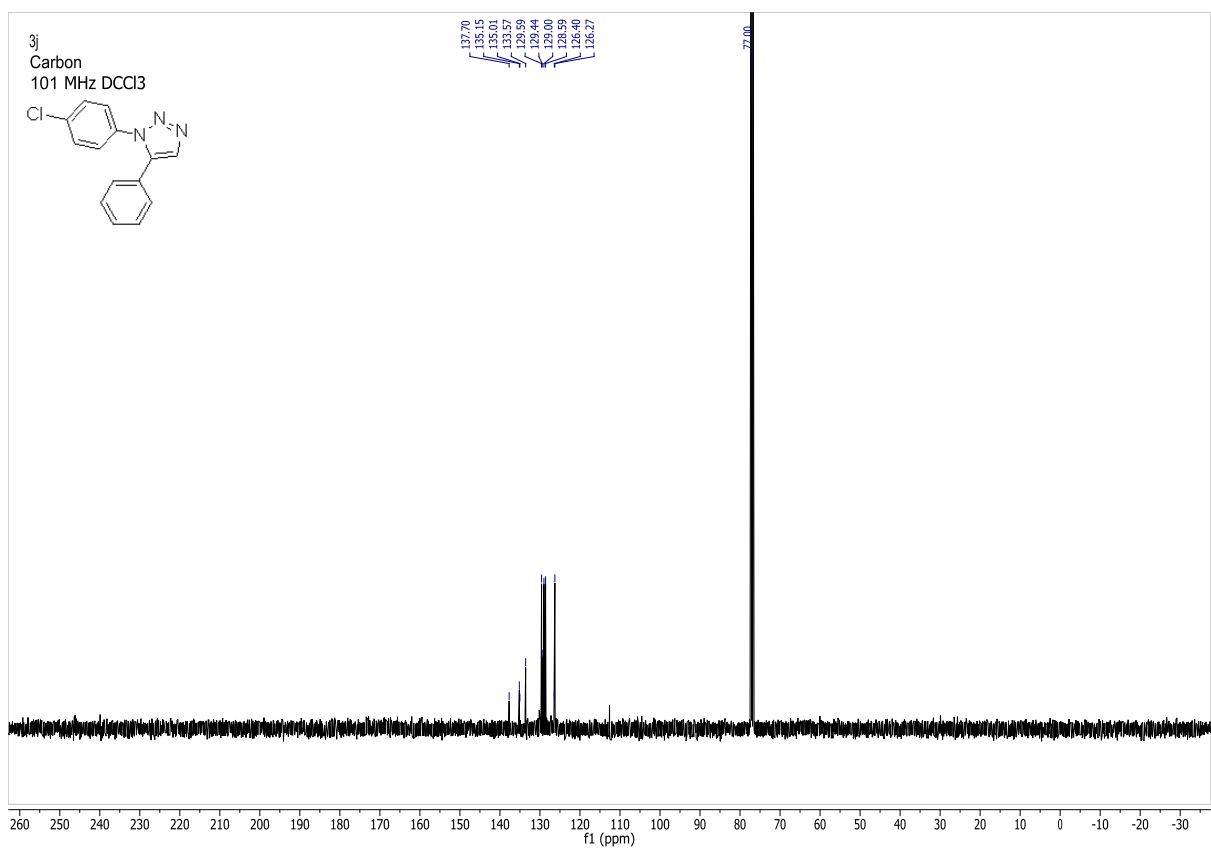
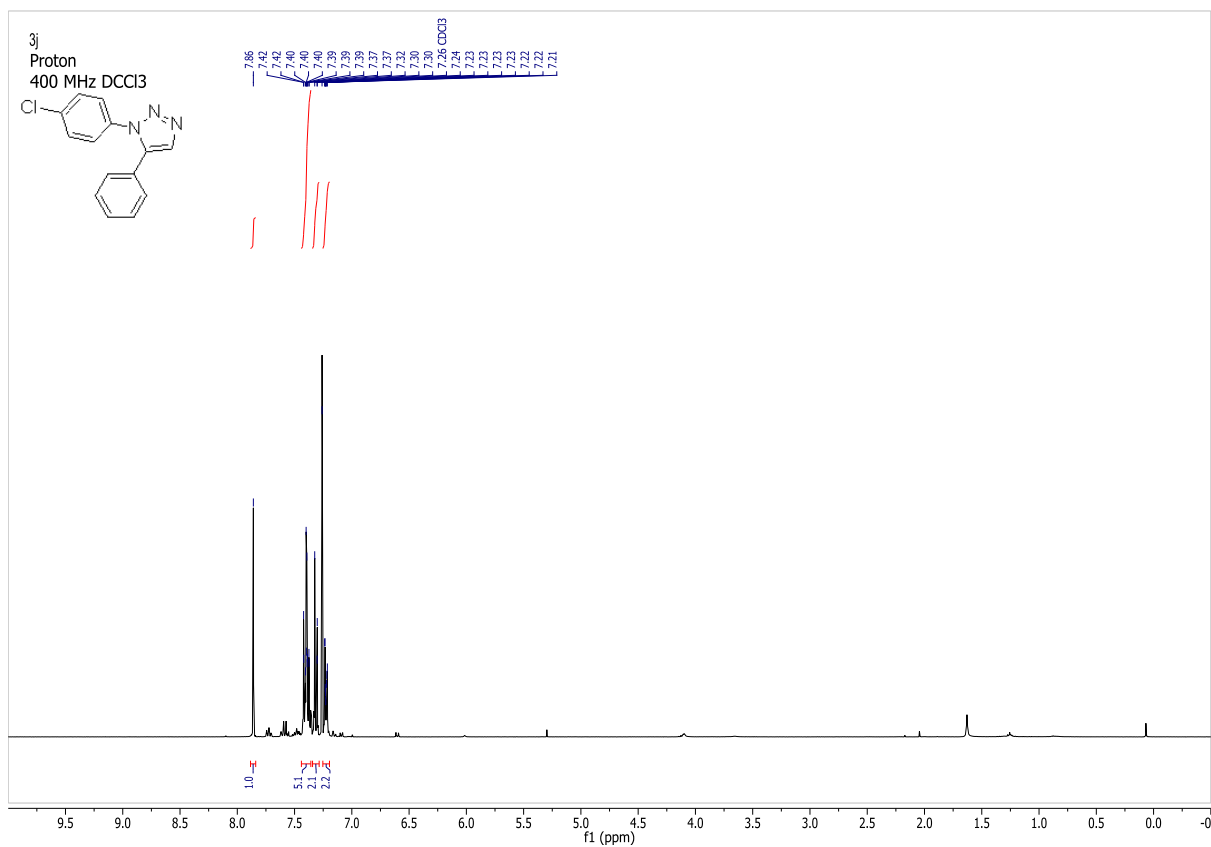
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



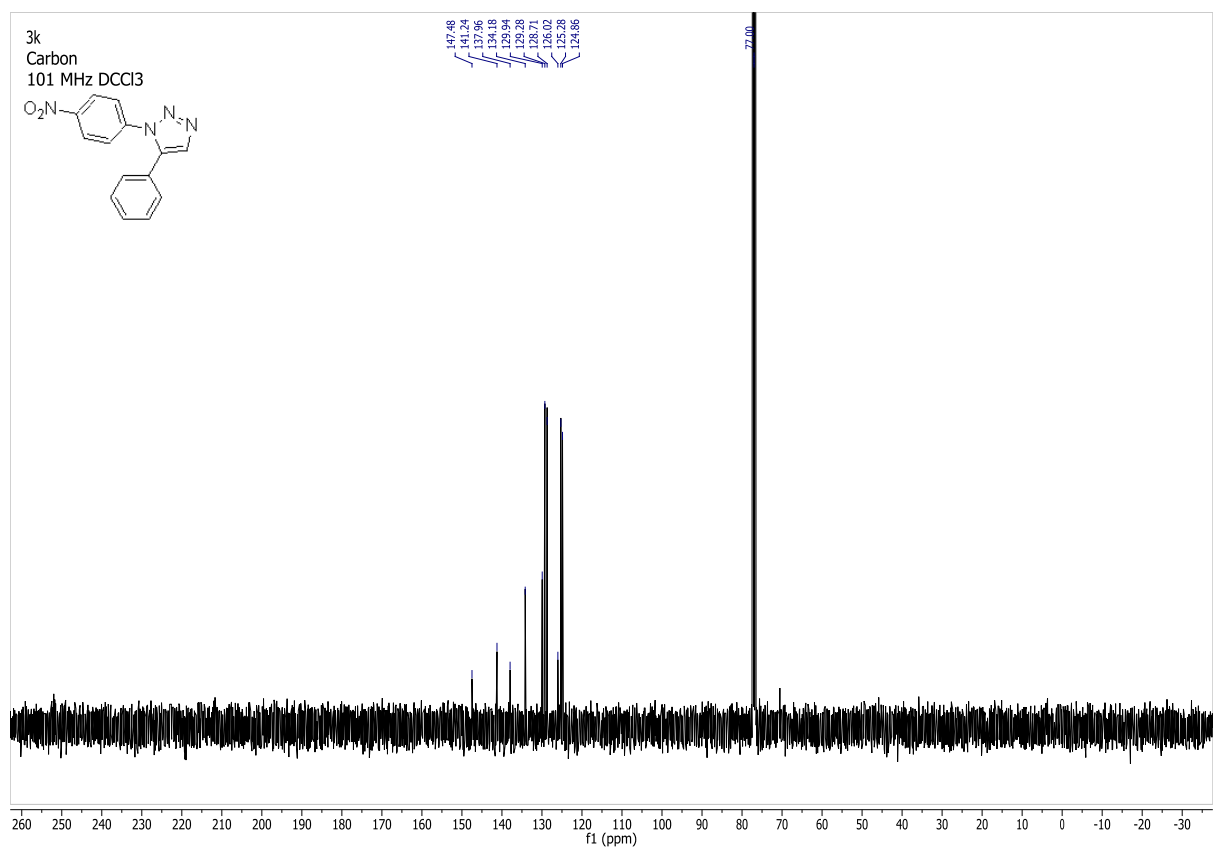
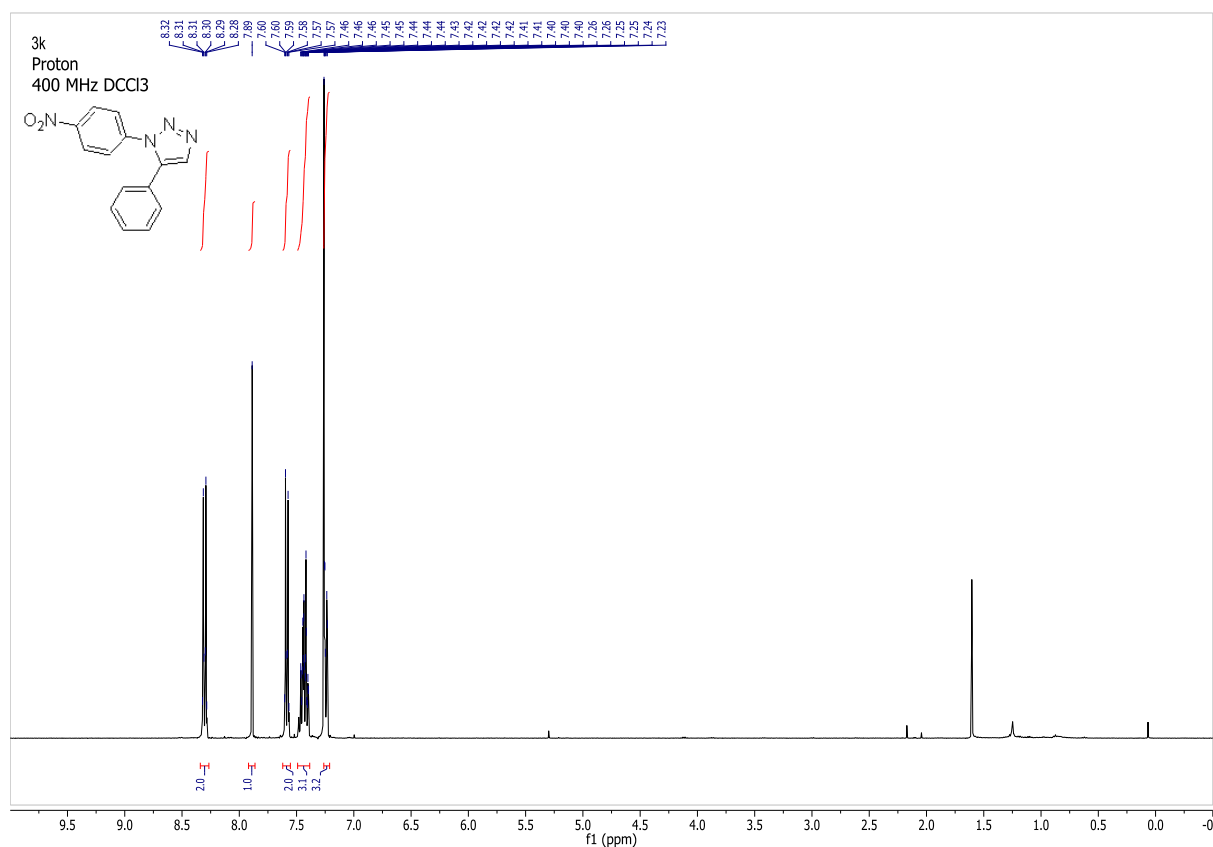
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



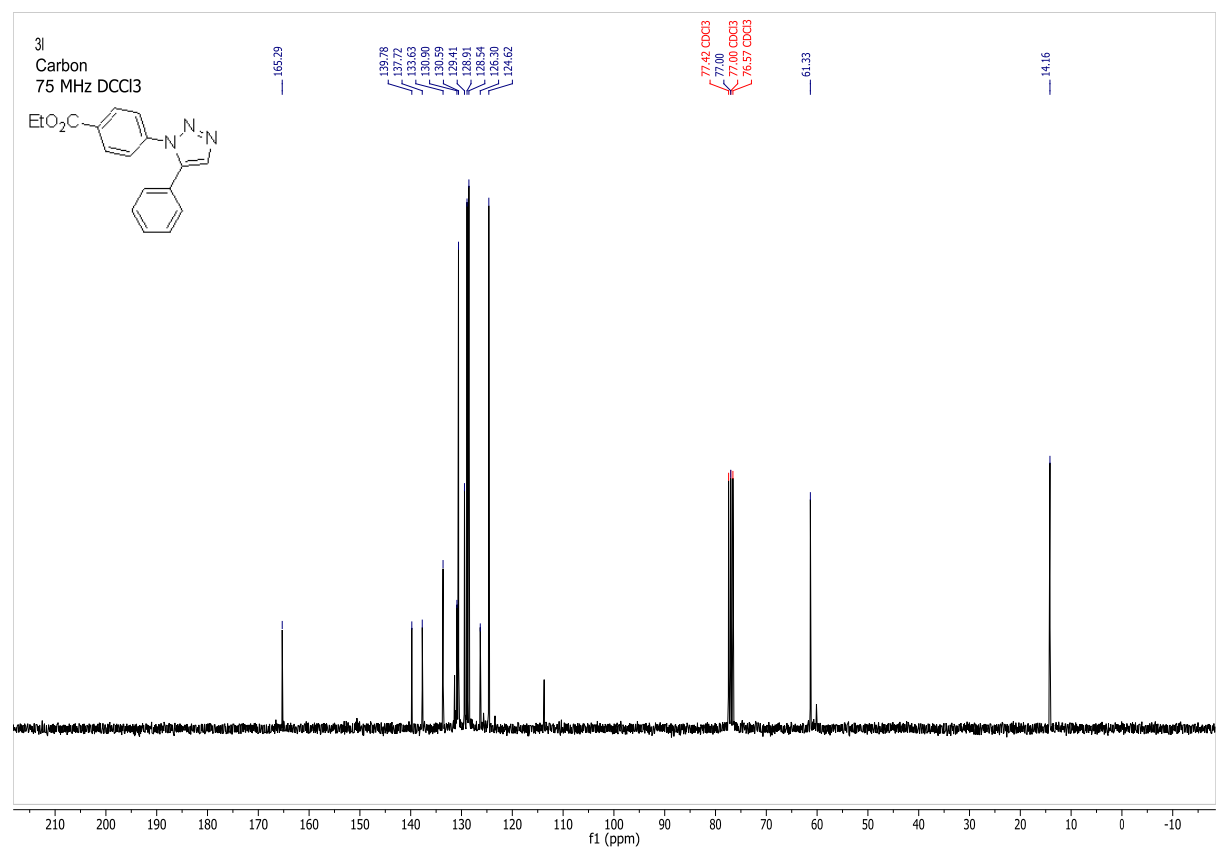
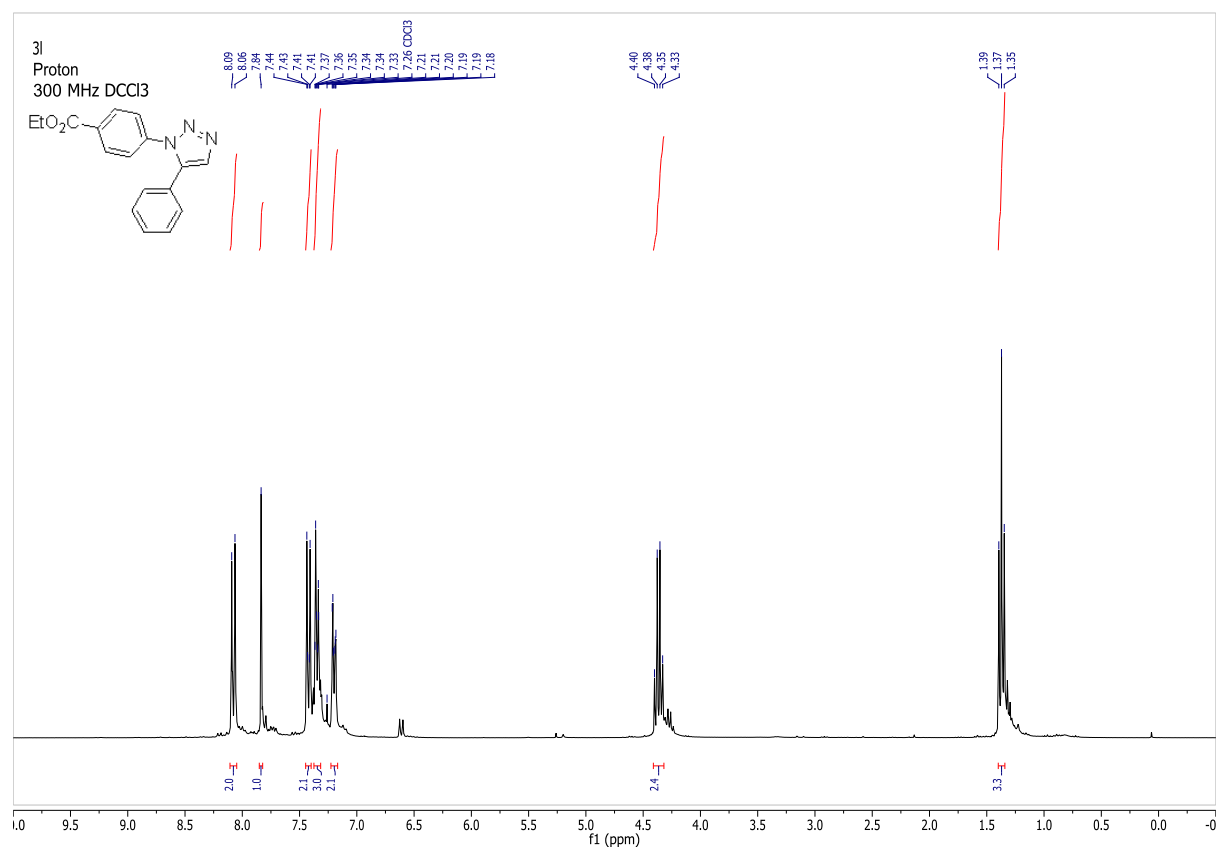
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



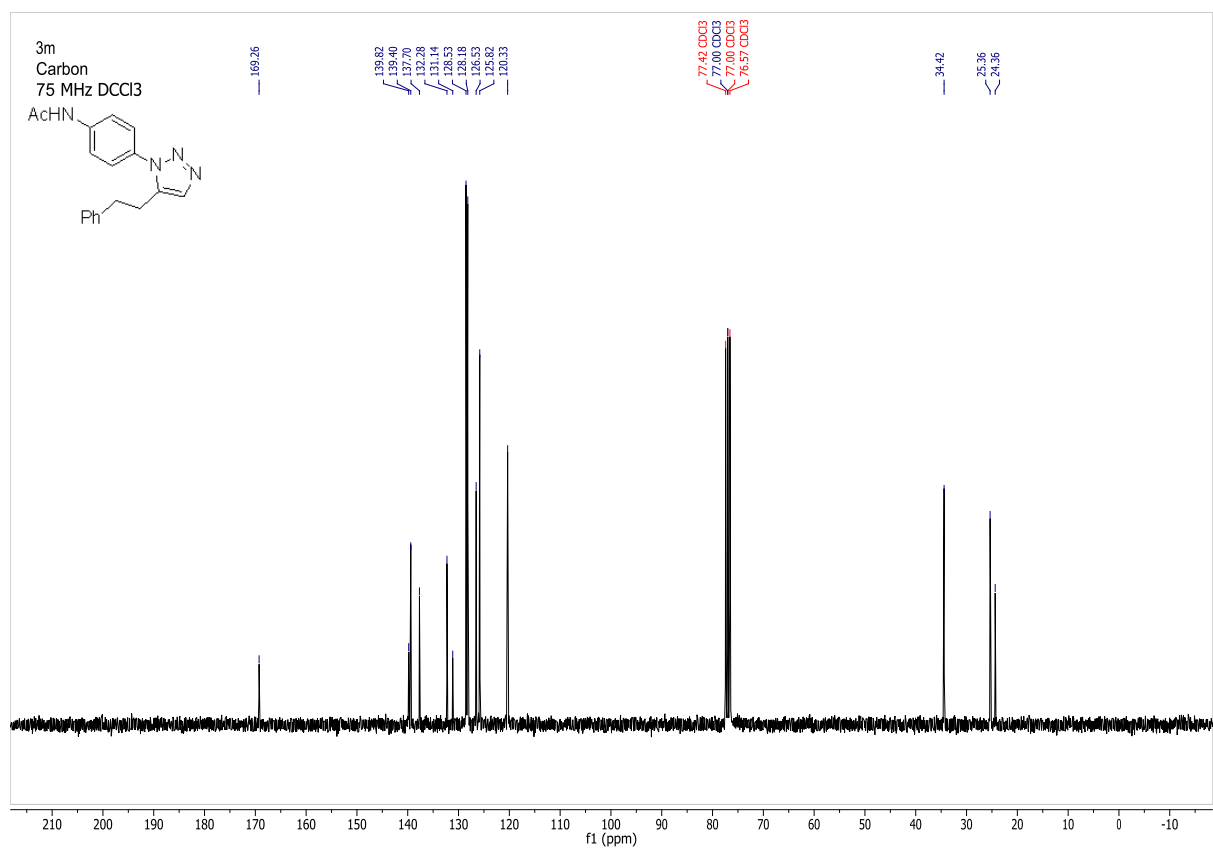
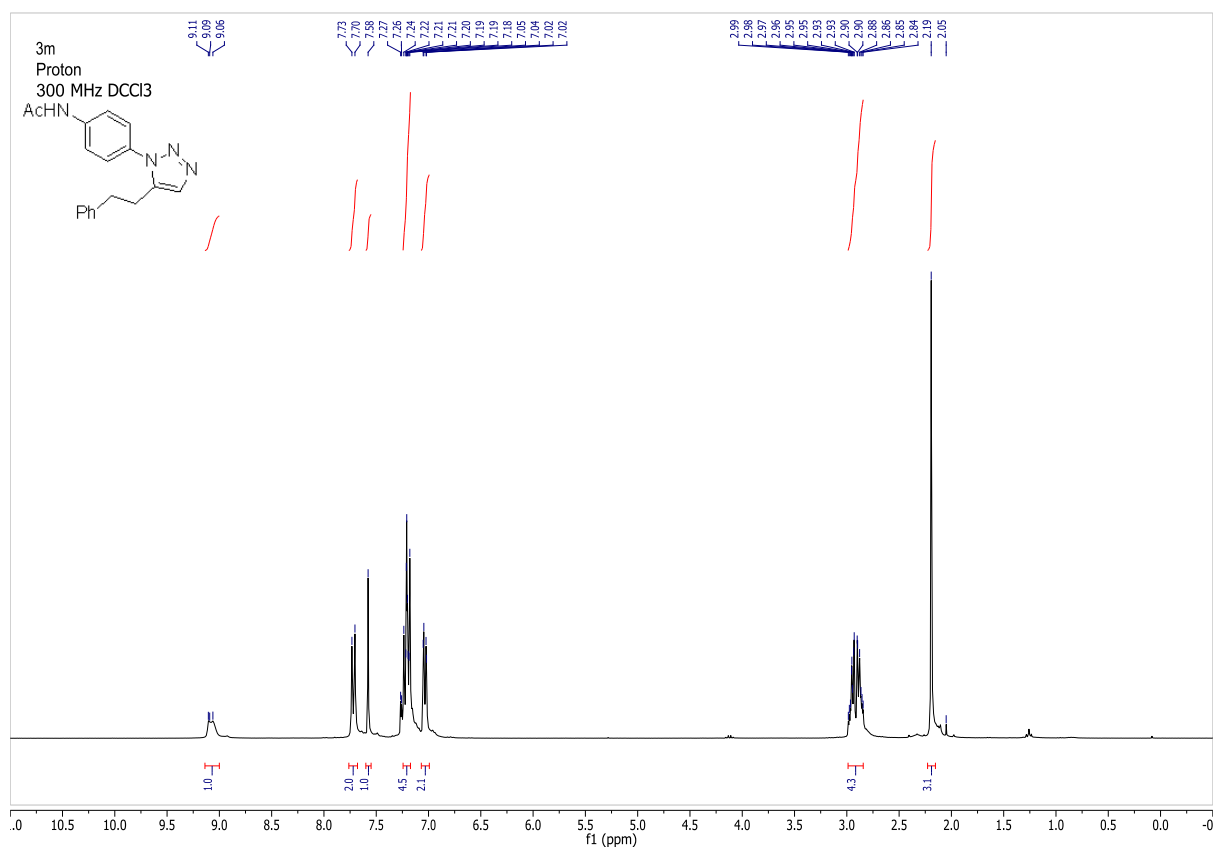
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



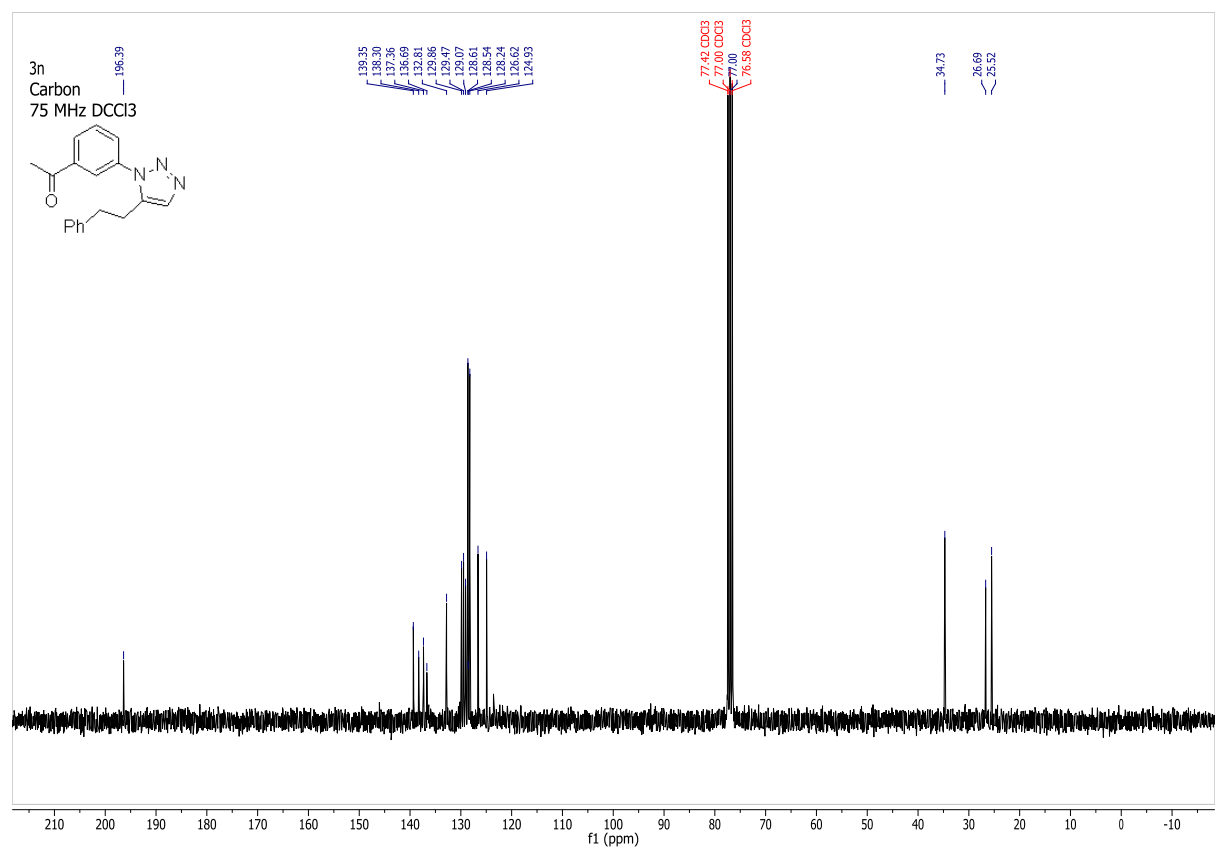
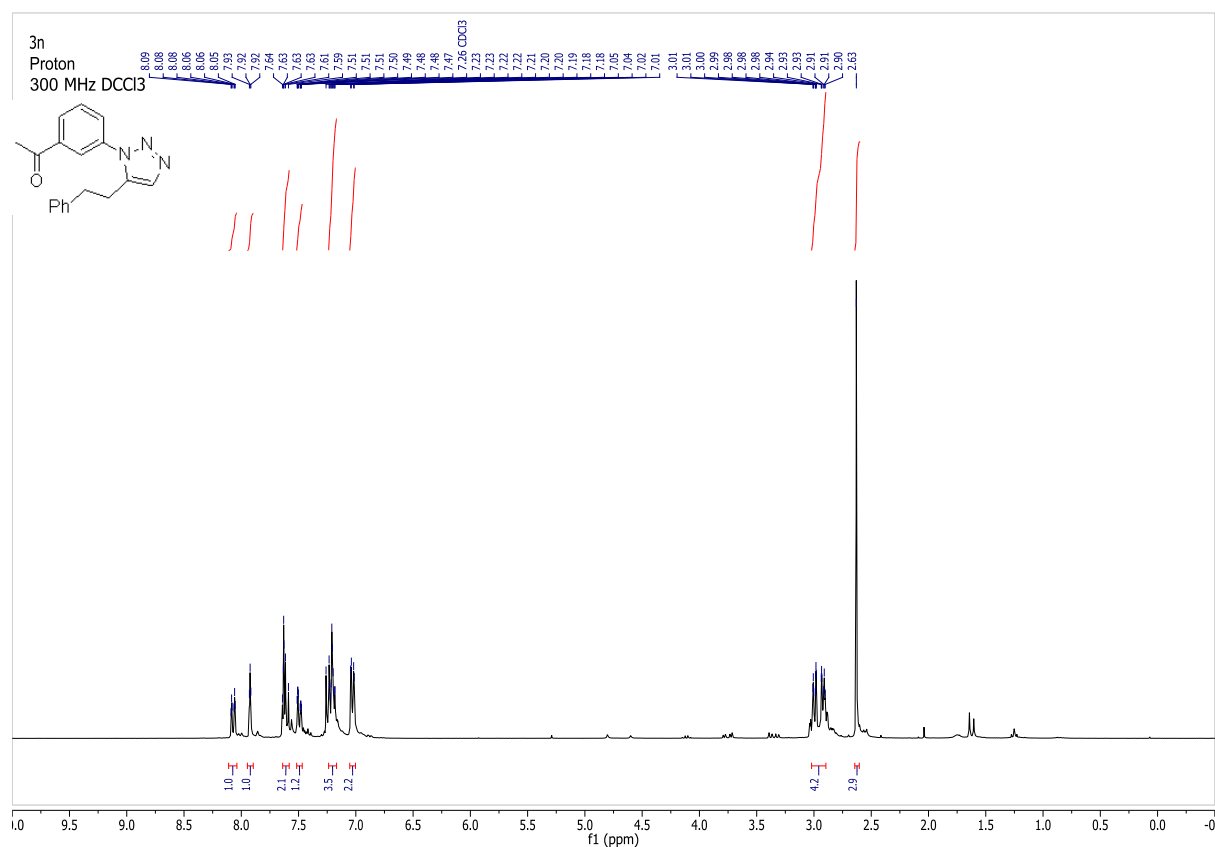
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



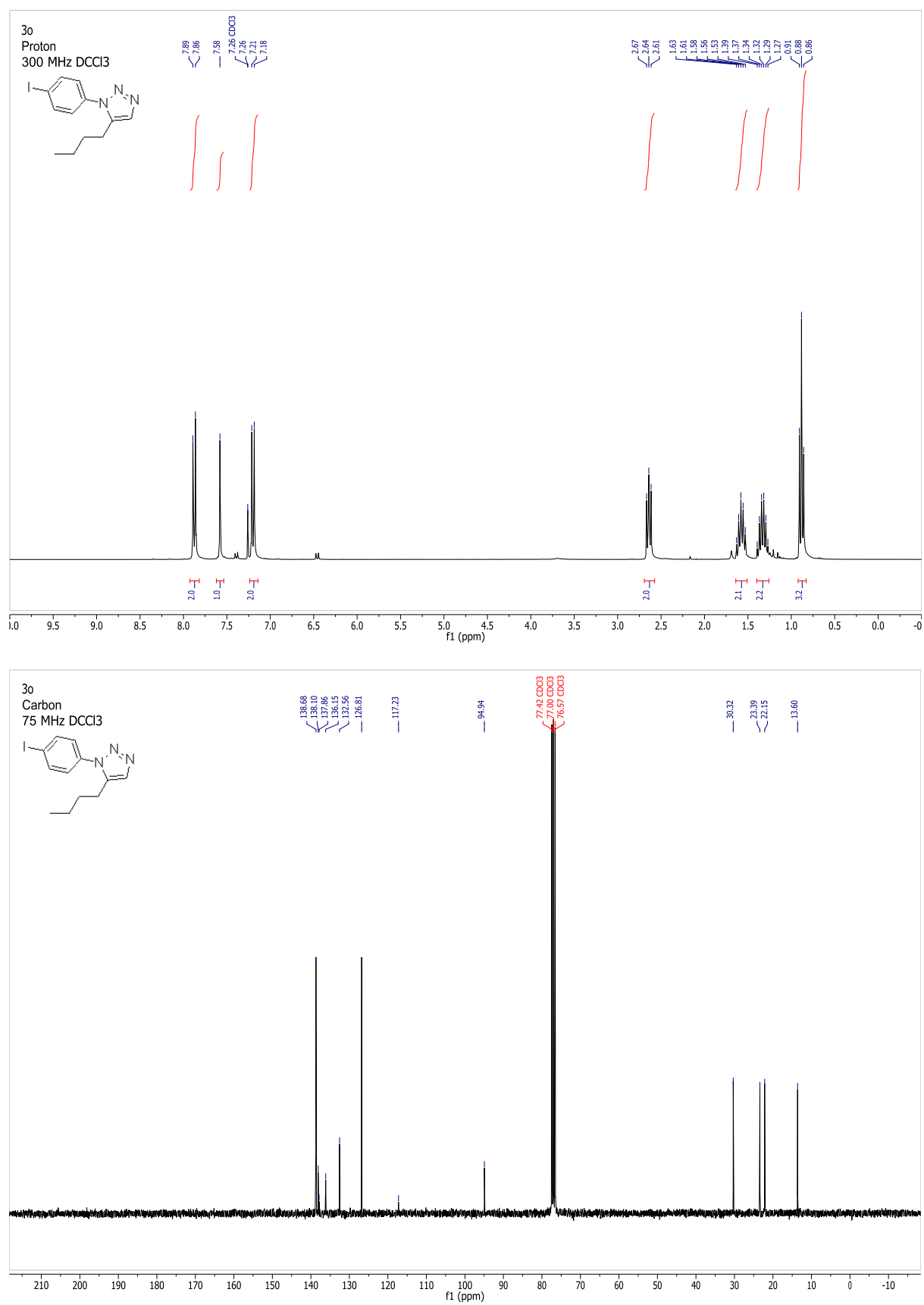
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



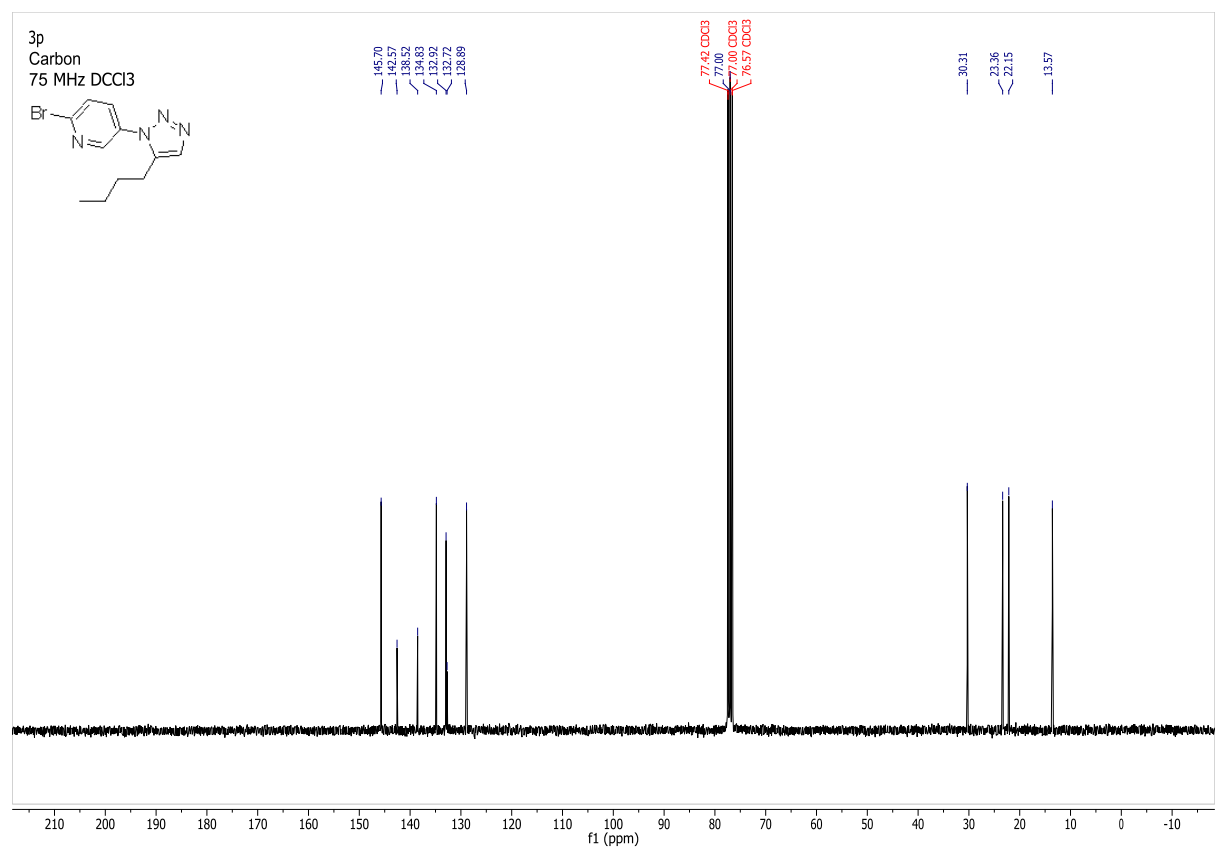
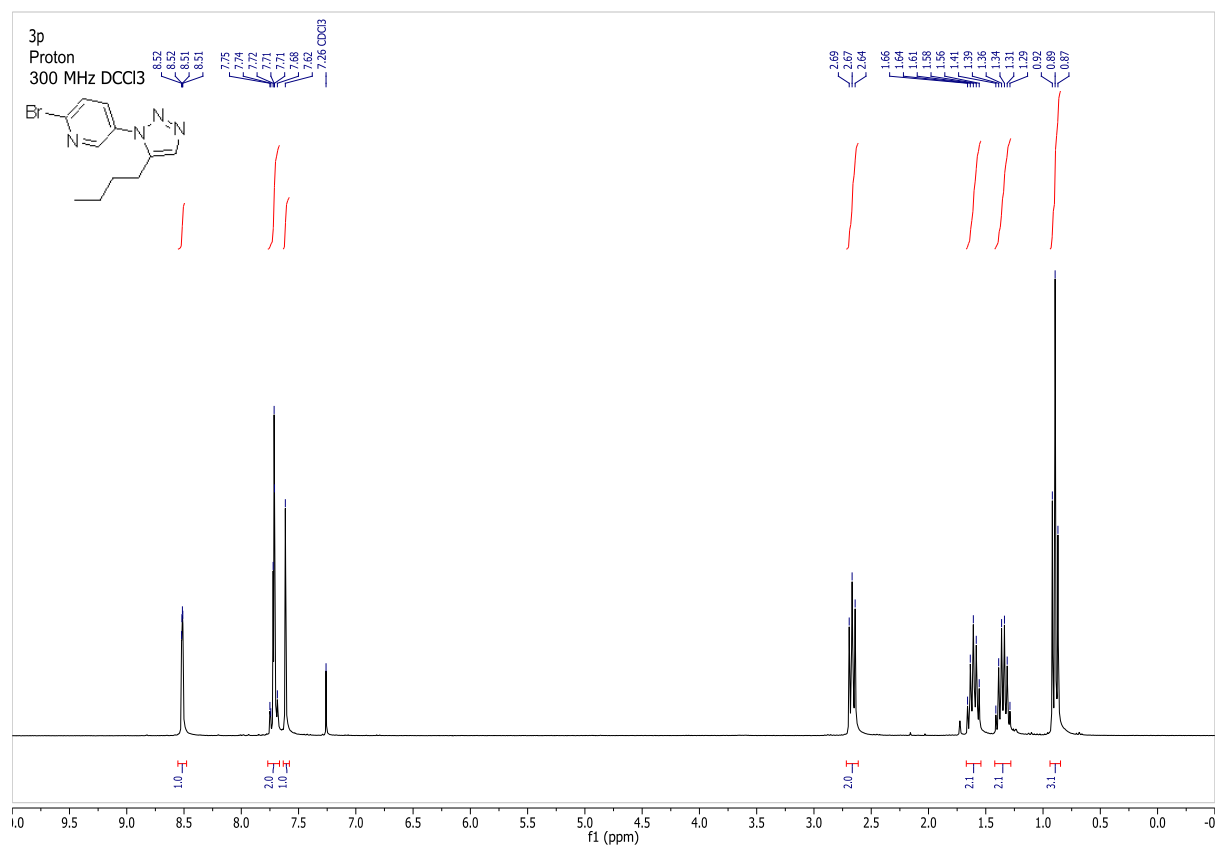
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



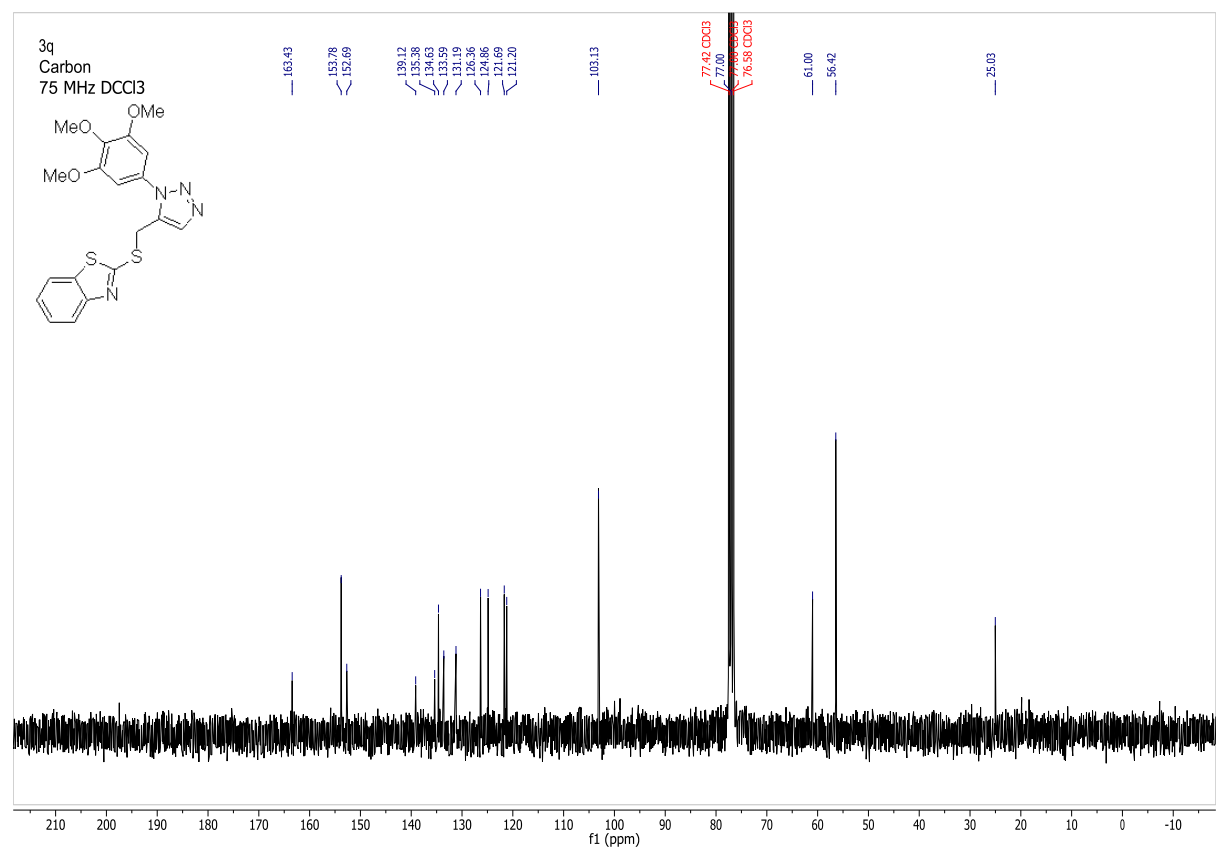
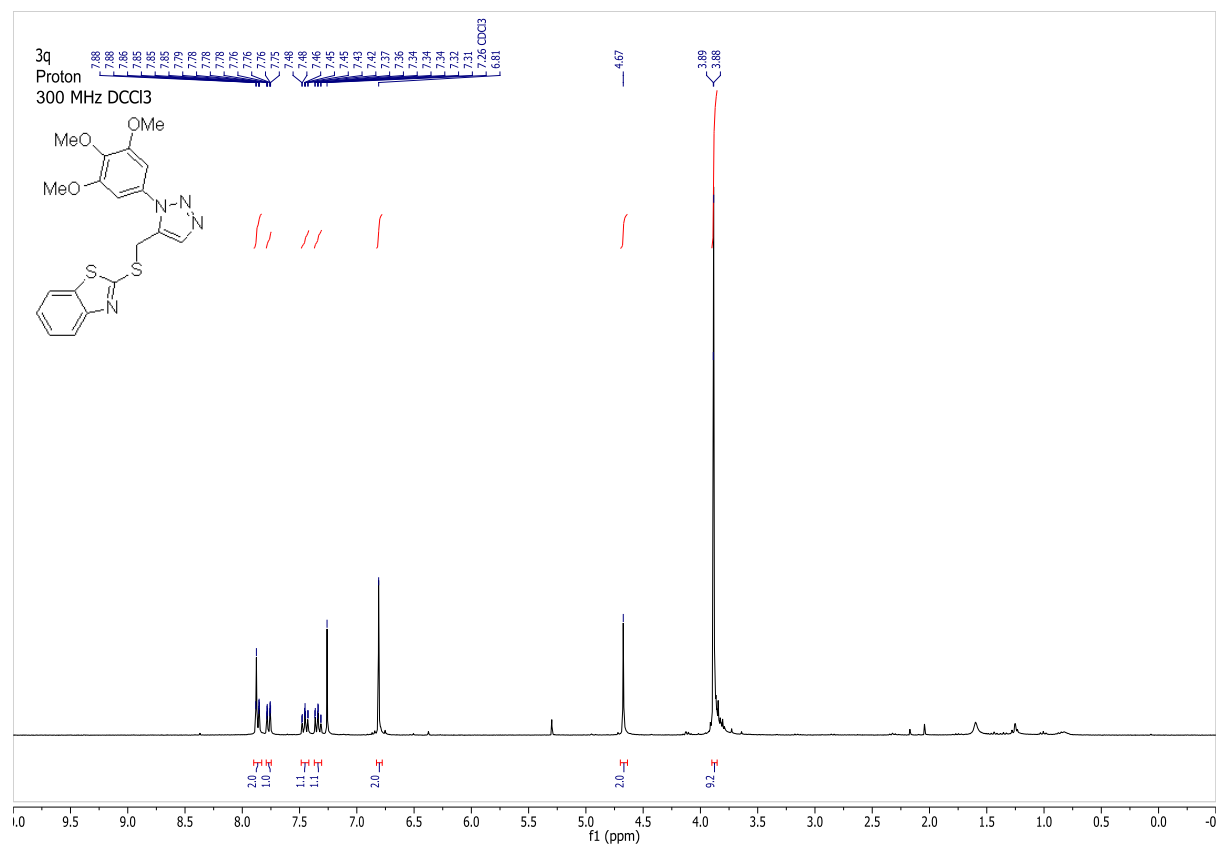
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



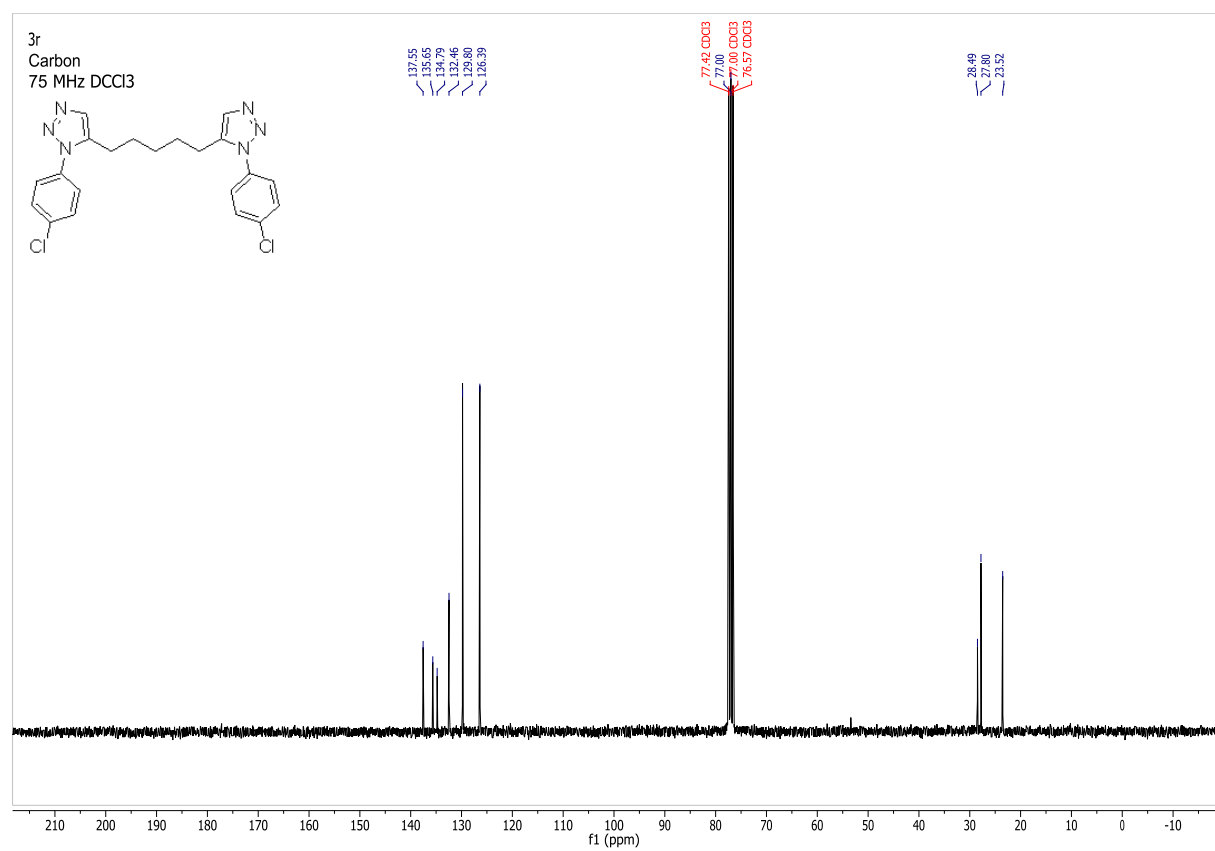
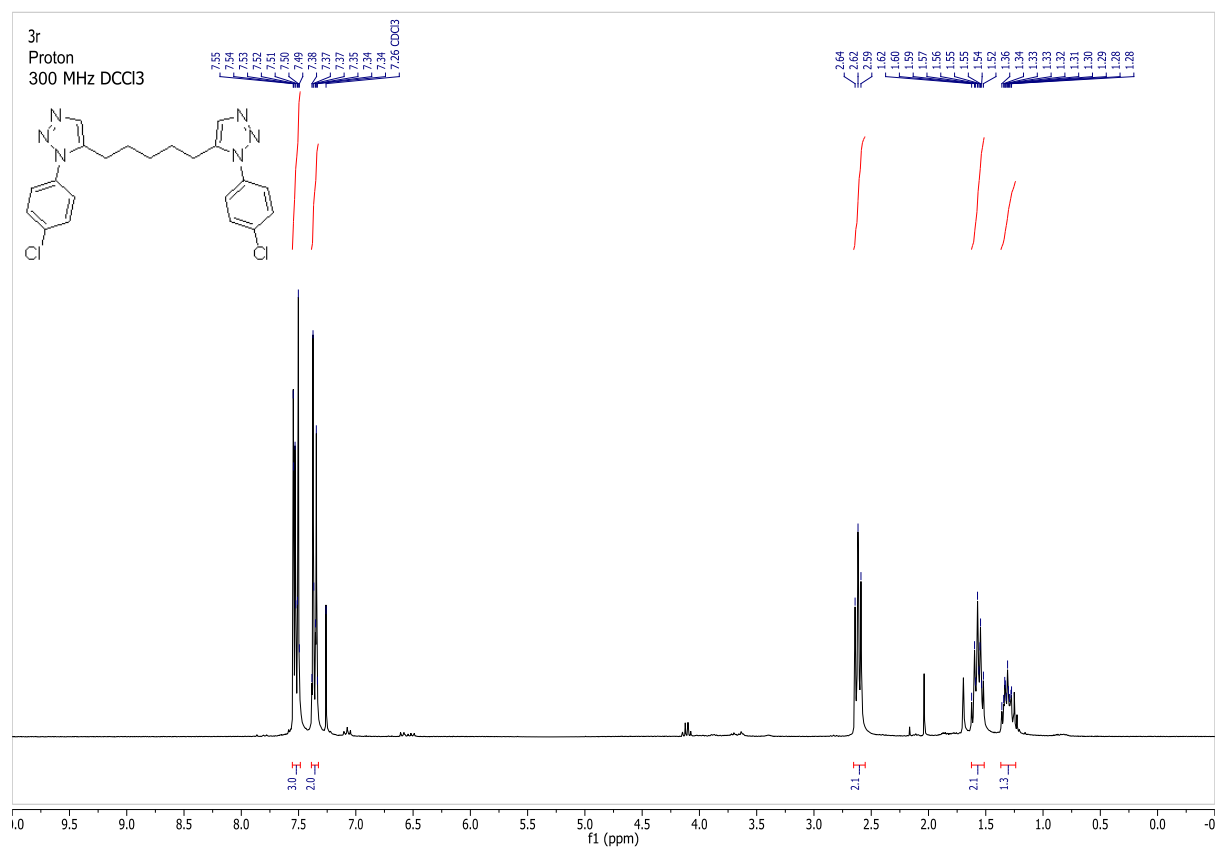
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



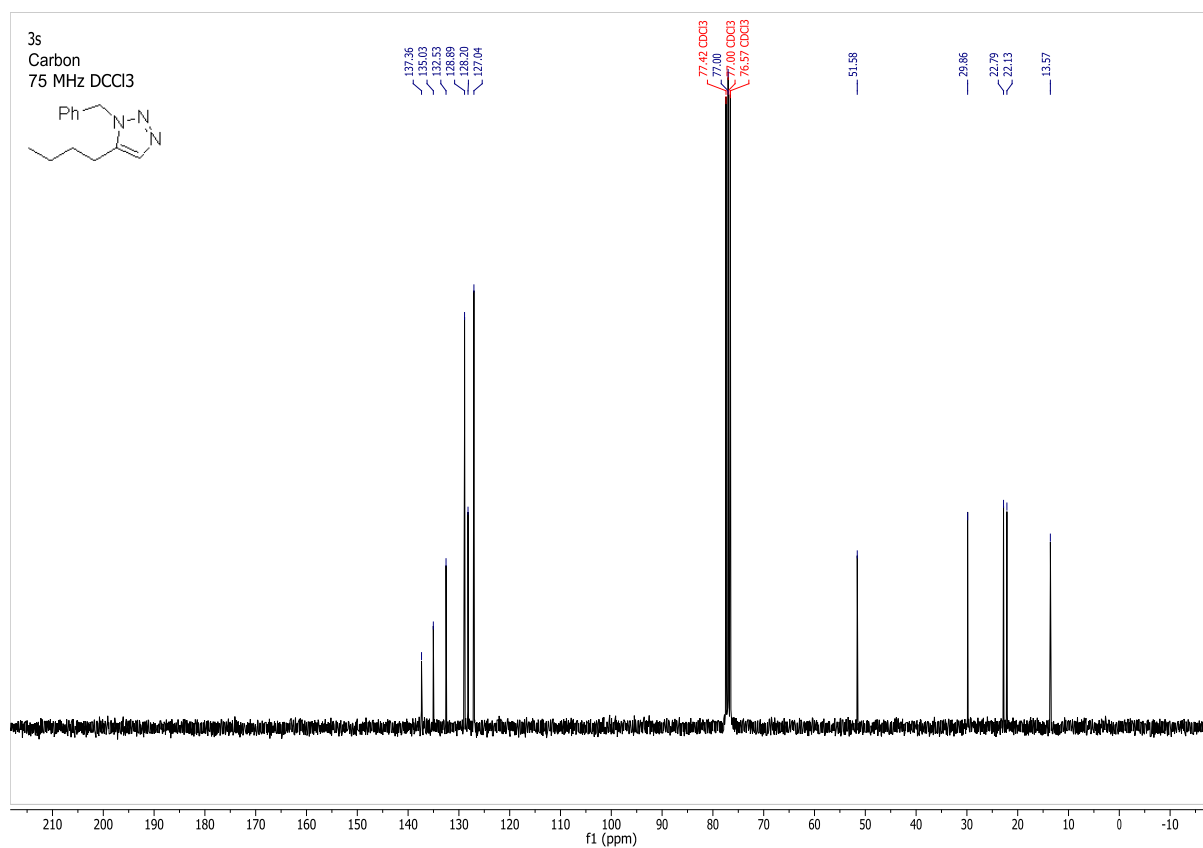
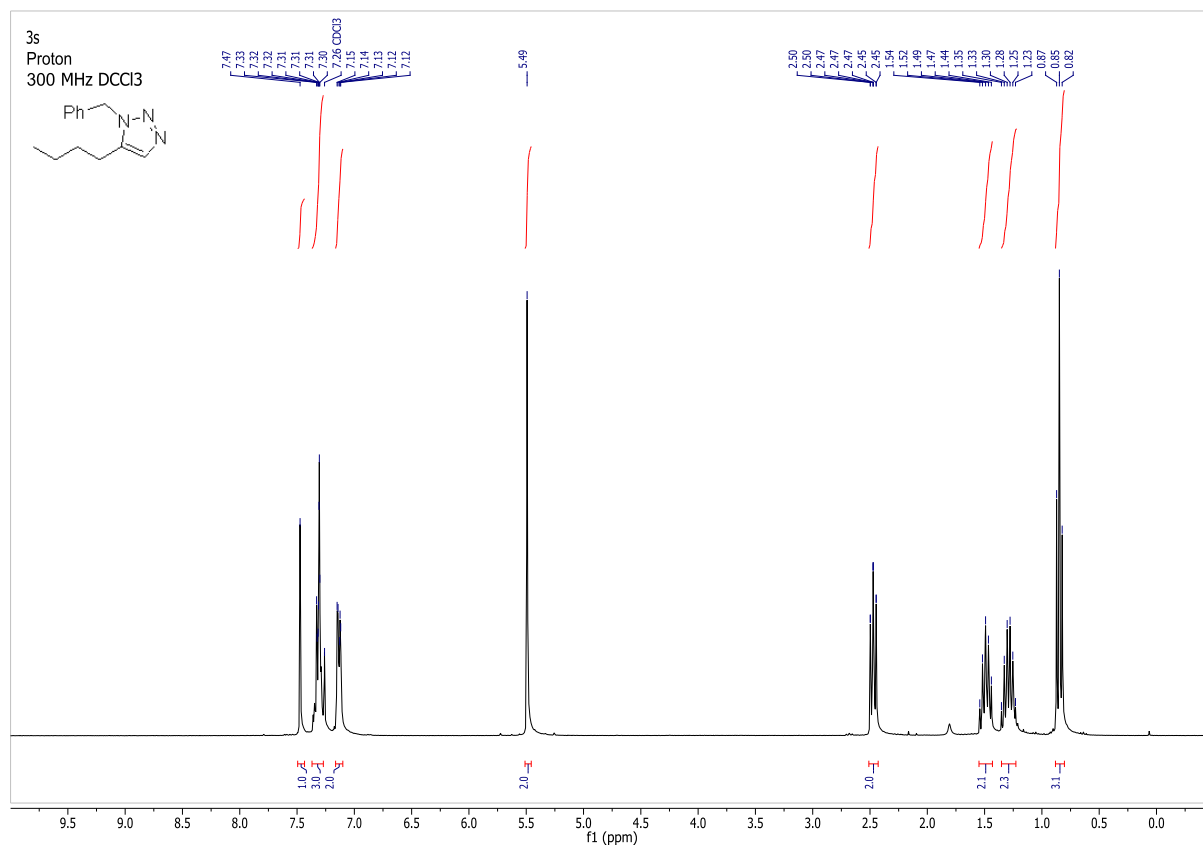
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



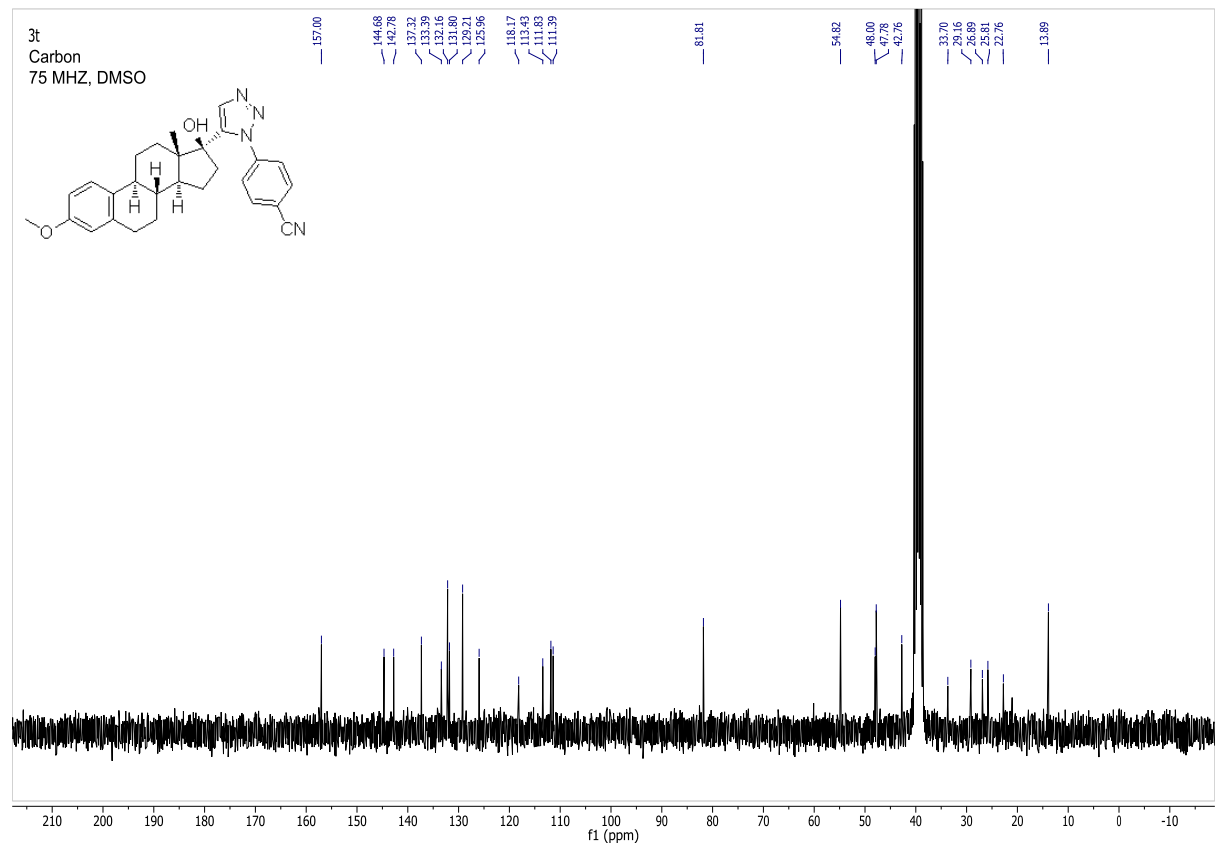
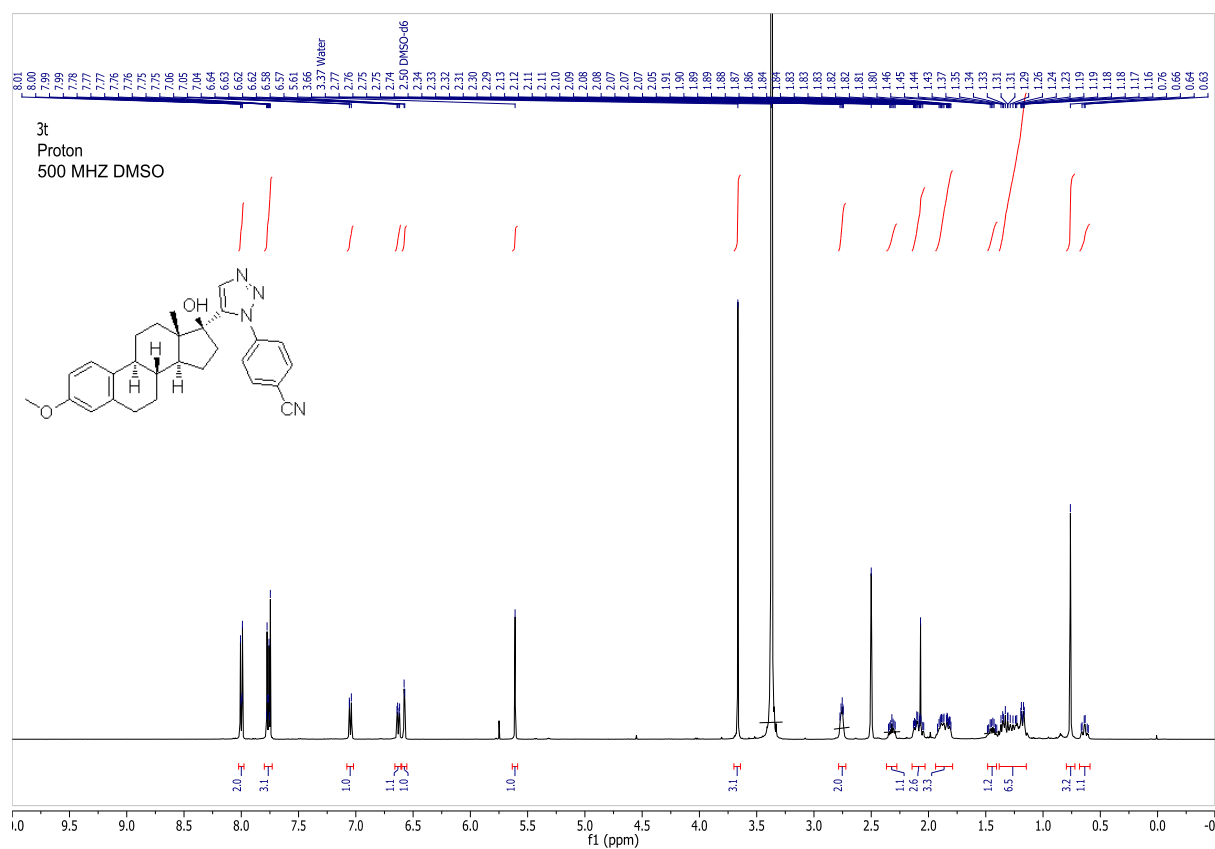
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



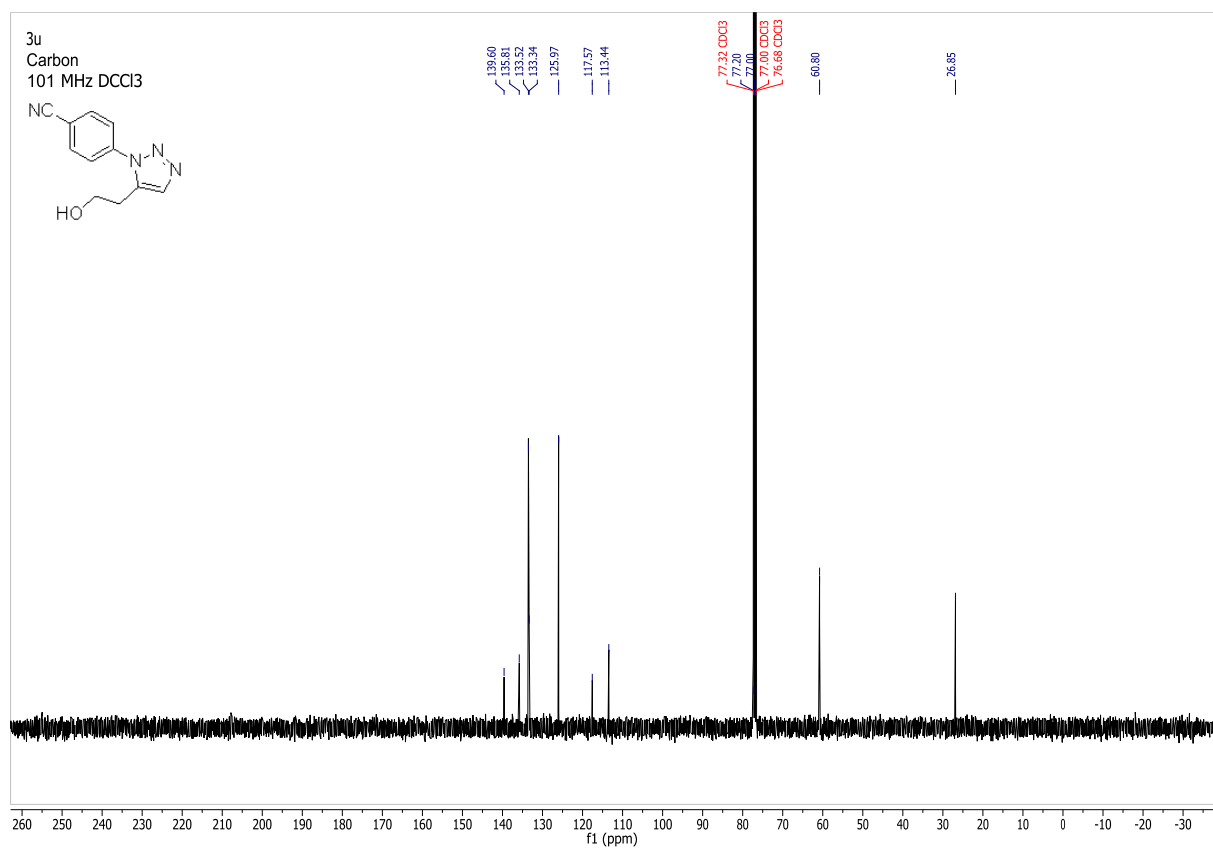
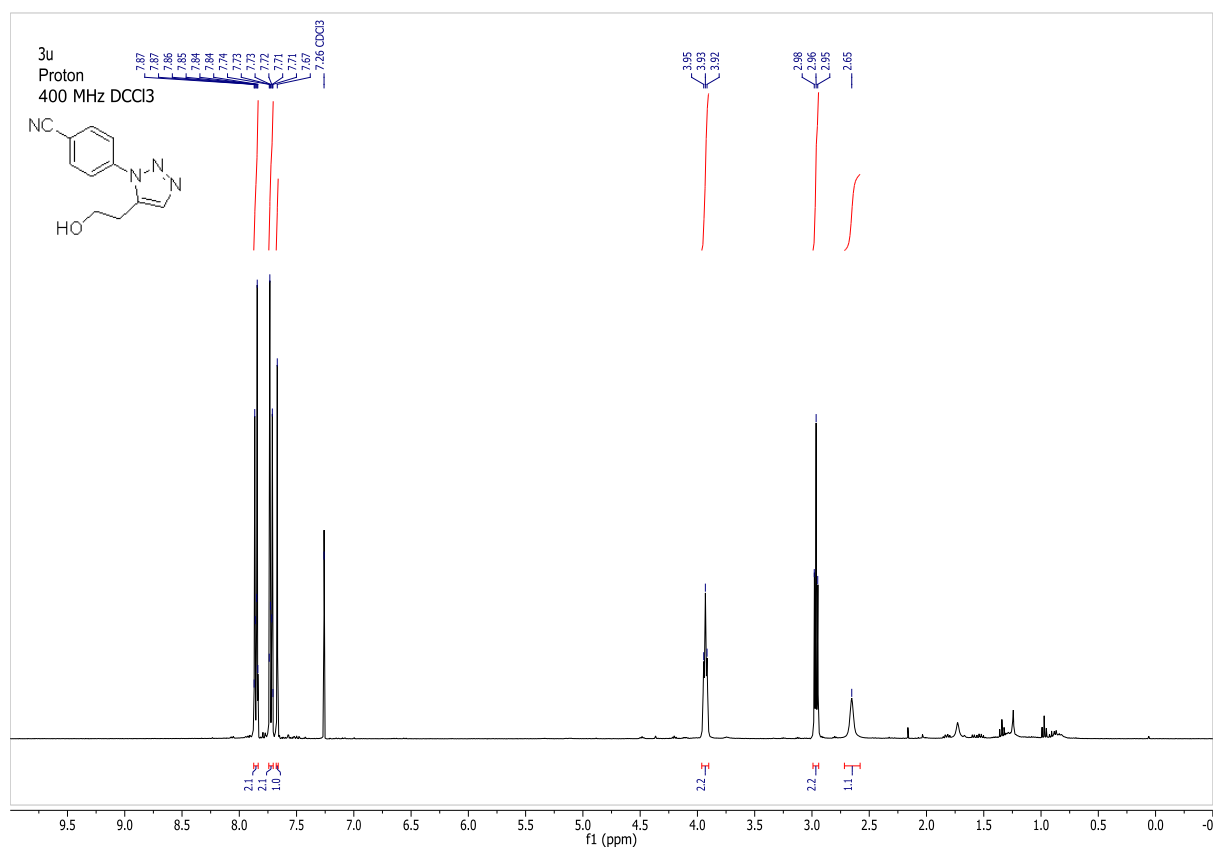
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



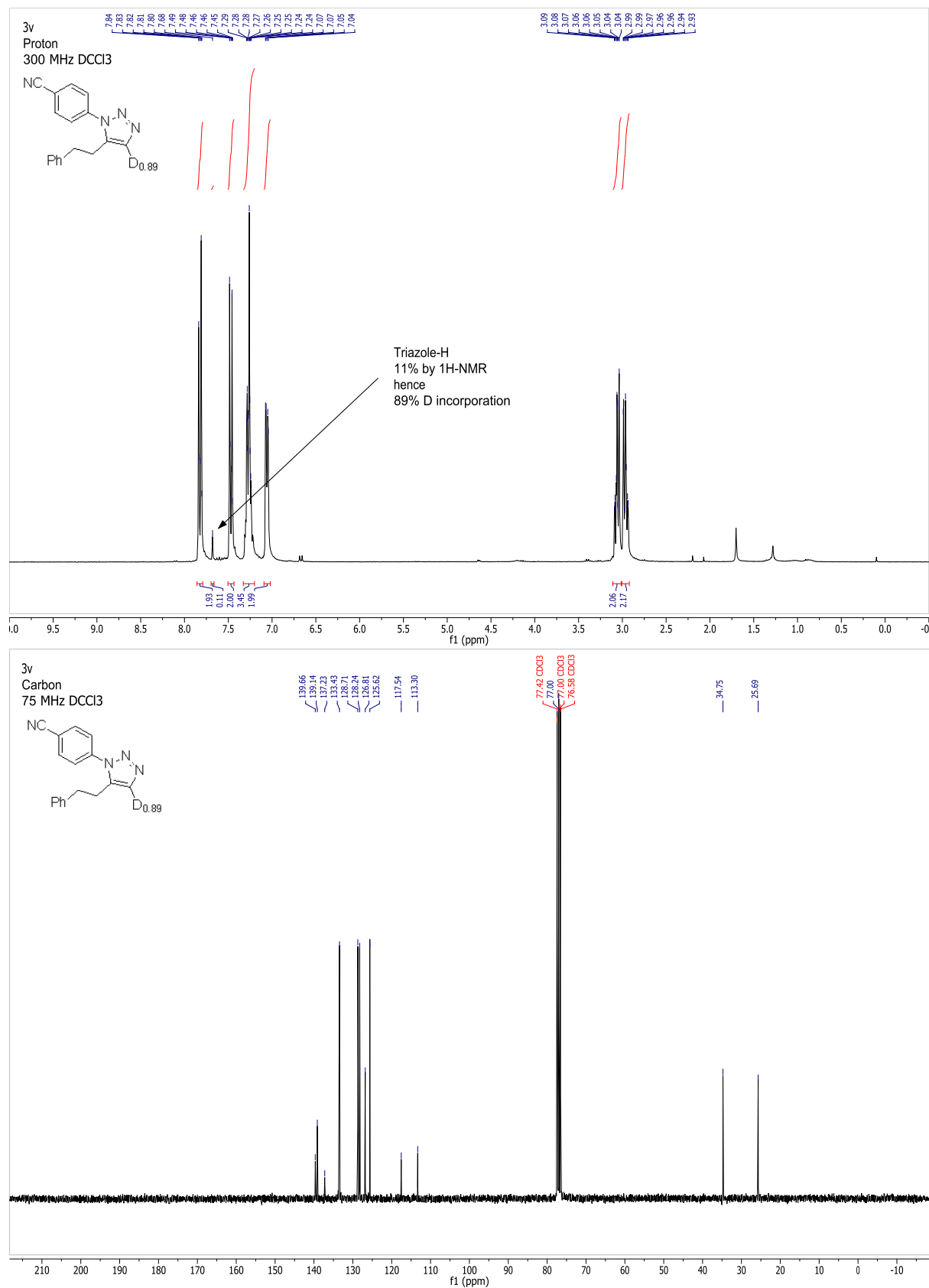
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



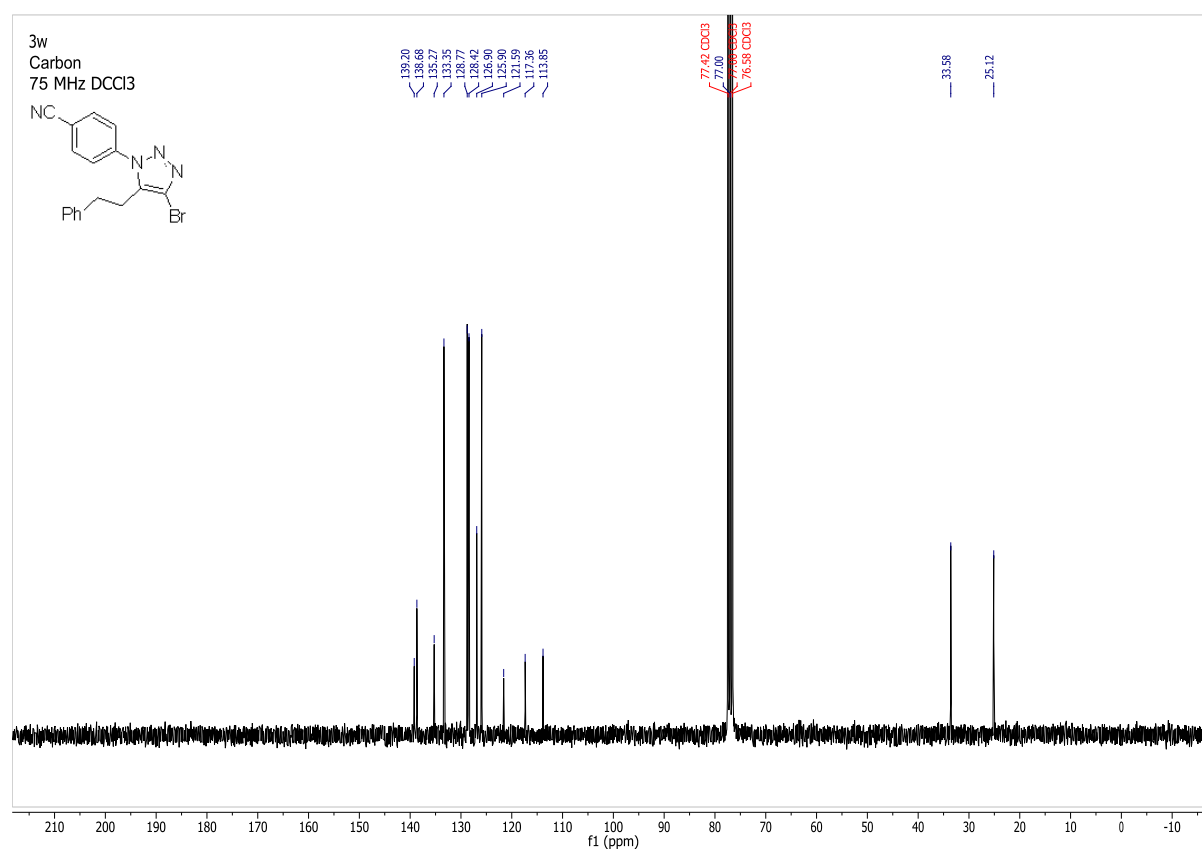
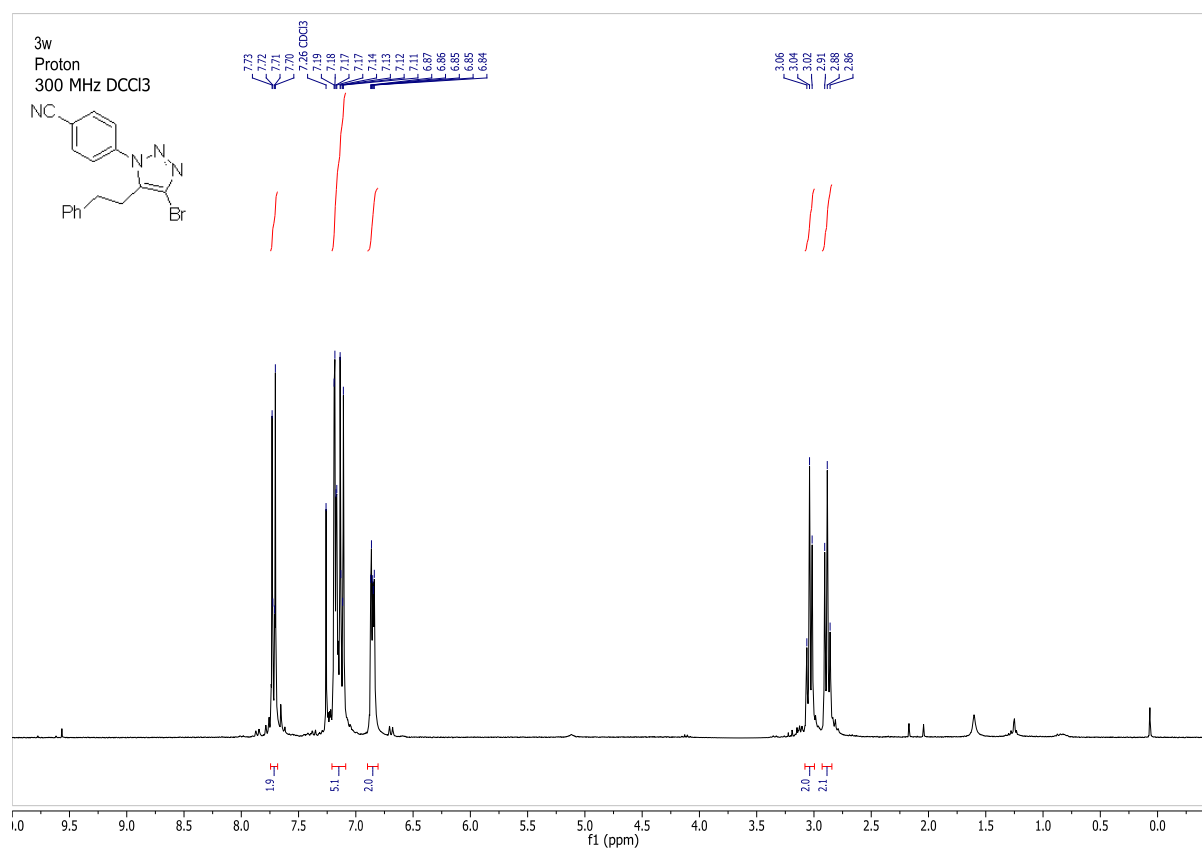
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



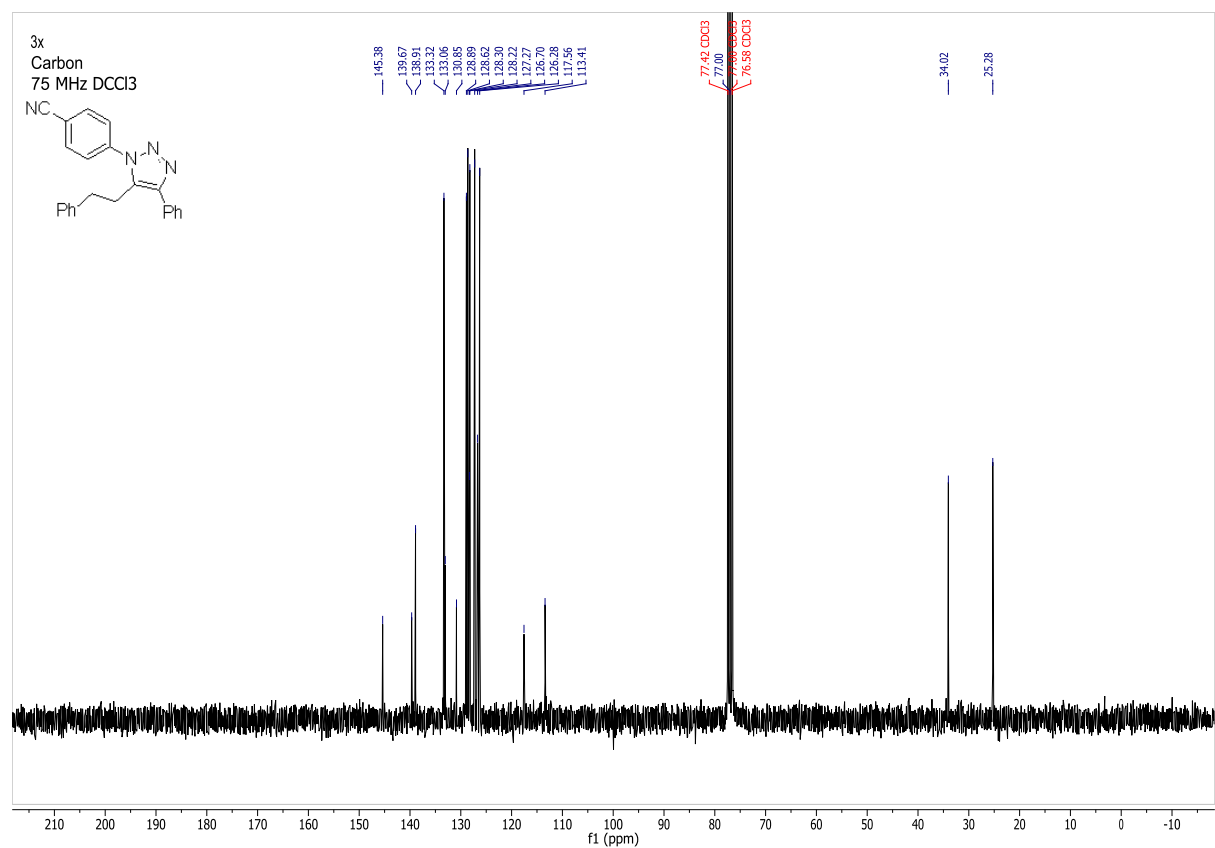
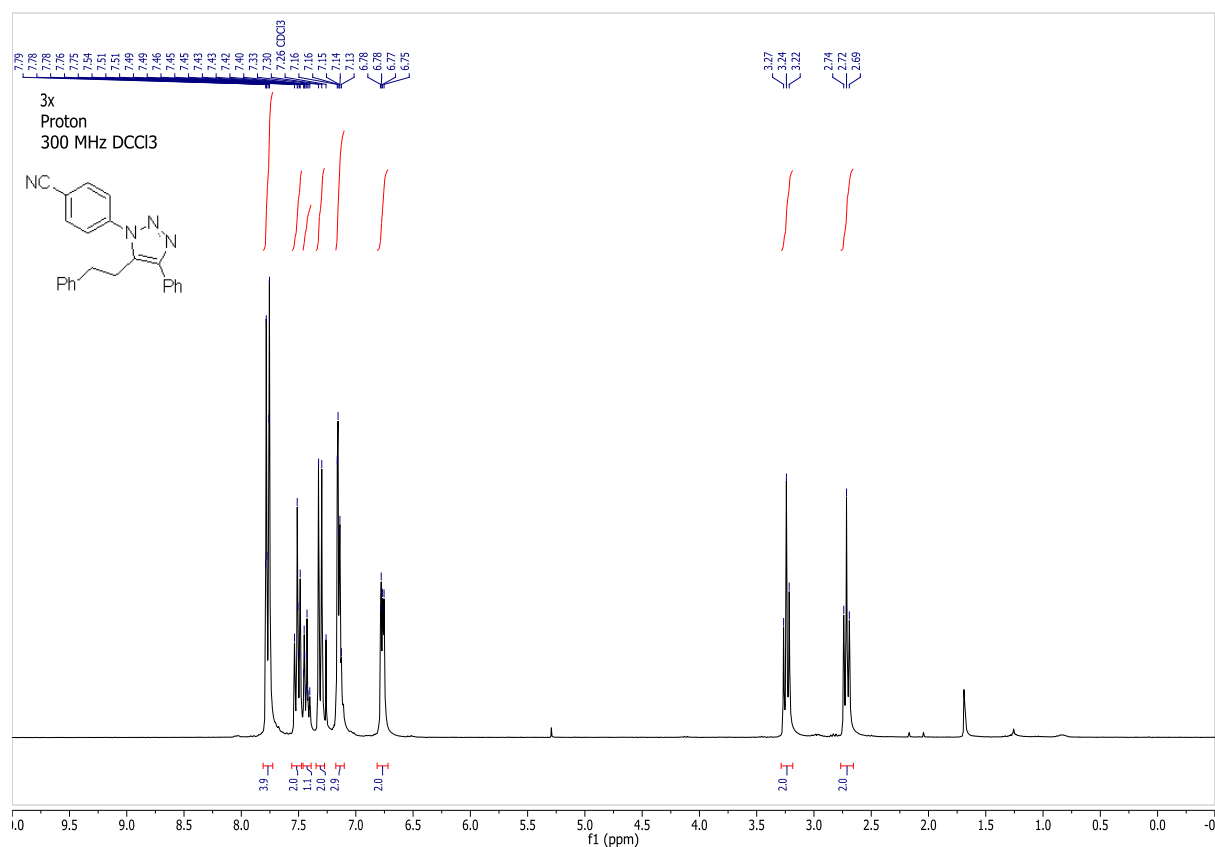
¹H- and ¹³C-NMR Spectra of 1,4,5-Substituted Triazoles



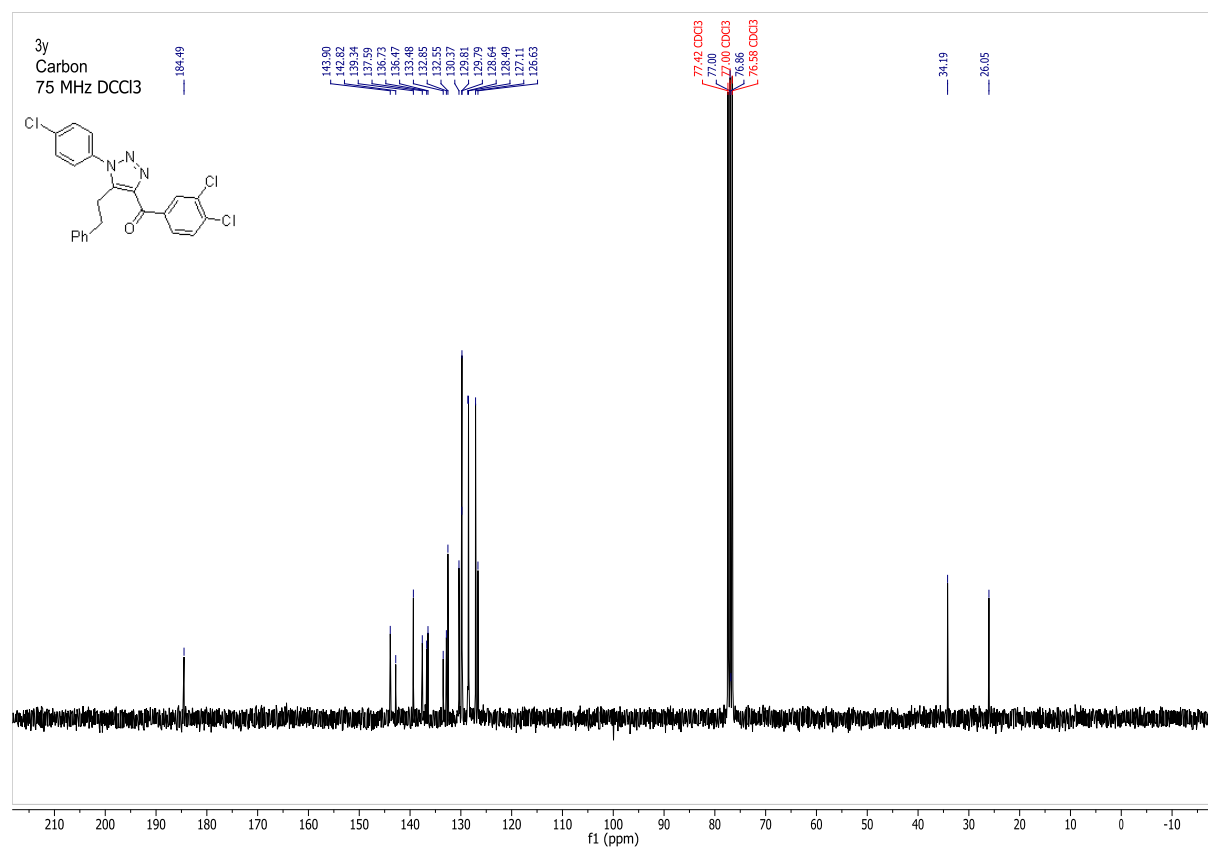
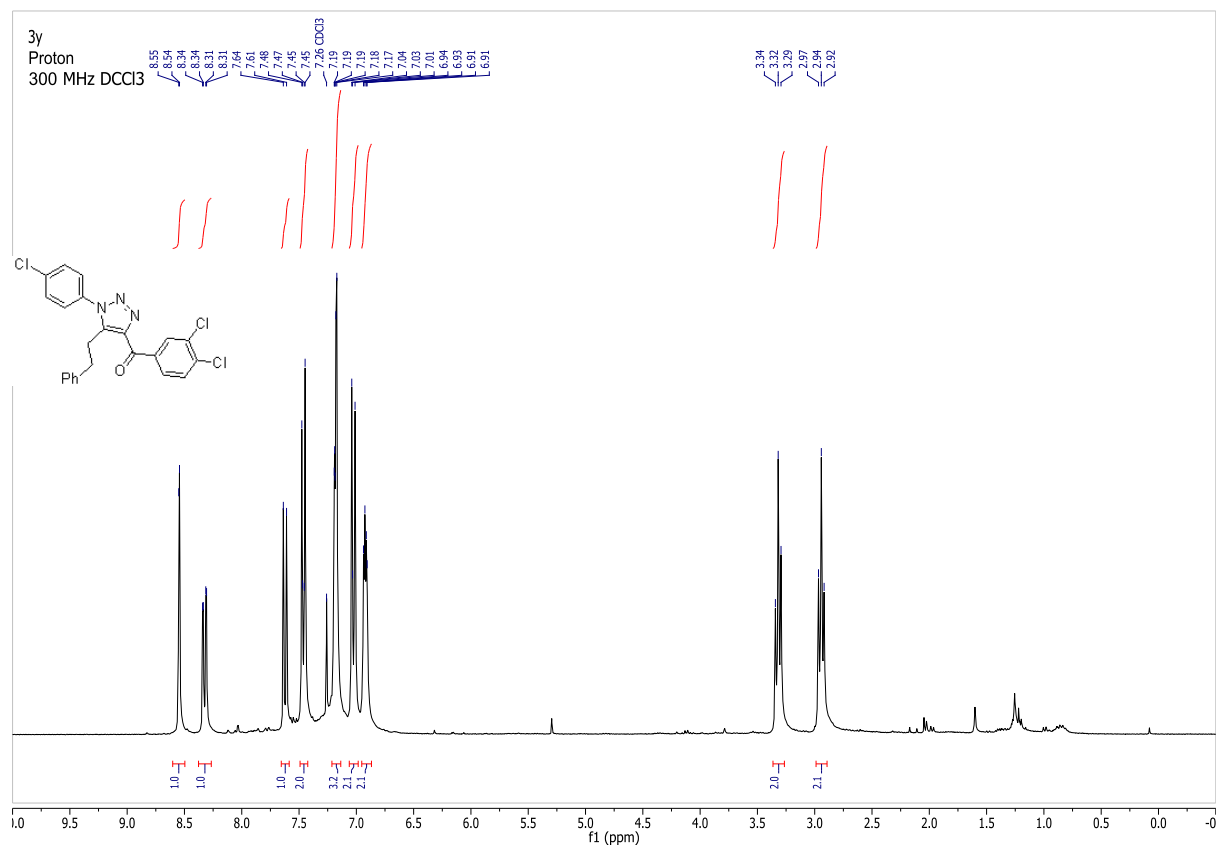
Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI



Zinc Mediated Azide-Alkyne Ligation to 1,5- and 1,4,5-Substituted 1,2,3-Triazoles – SI

