Supplementary Information for:

Complementary Catalysis and Analysis within Solid-State Additively Manufactured Metal Micro-Flow Reactors

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Device Fabrication

Aluminium 3DP Reactor

Using the same Ultrasonic Additive Manufacturing (UAM) system as that used to manufacture the Copper reactor, an Aluminium reactor of the identical design was also manufactured. This device was manufactured from a combination of Al 5052 and 6061 alloys.

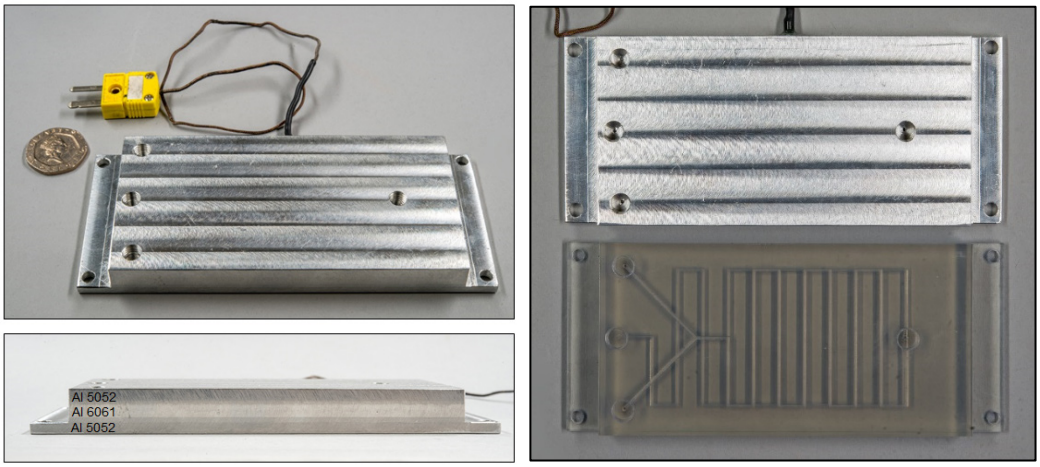

Figure S1. Images of aluminium 3D-printed reactor and its SLA formed prototype

Additional Images of Catalytic Copper Reactor

Additional images of the catalytically active Copper reactor employed in this work are shown in Figure S2.

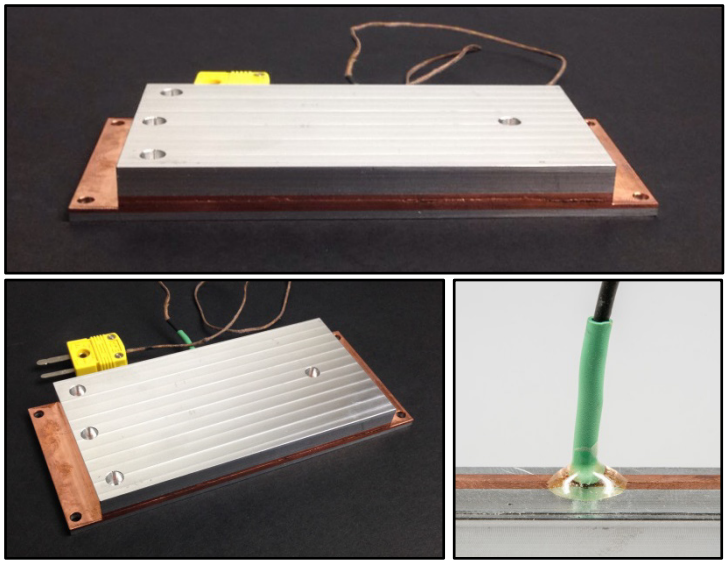

Figure S2. Additional images of copper flow reactor detailing the inserted thermocouple for temperature monitoring

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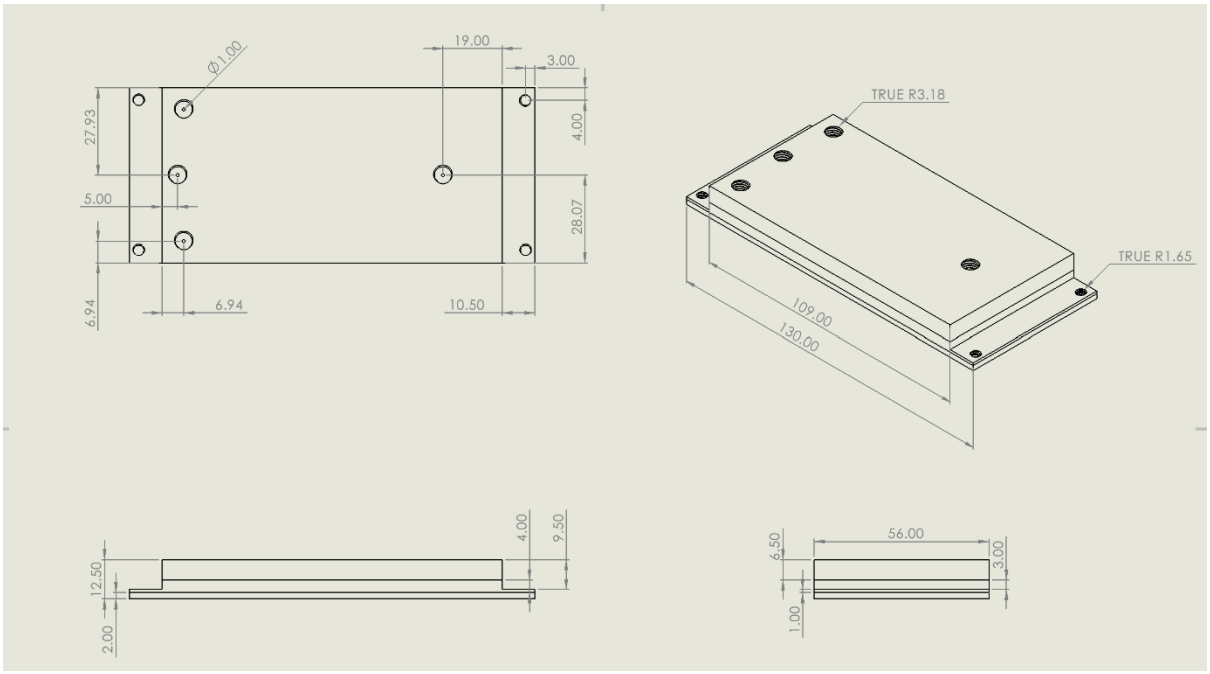


Figure S3. Dimensioned drawings of the copper flow reactor

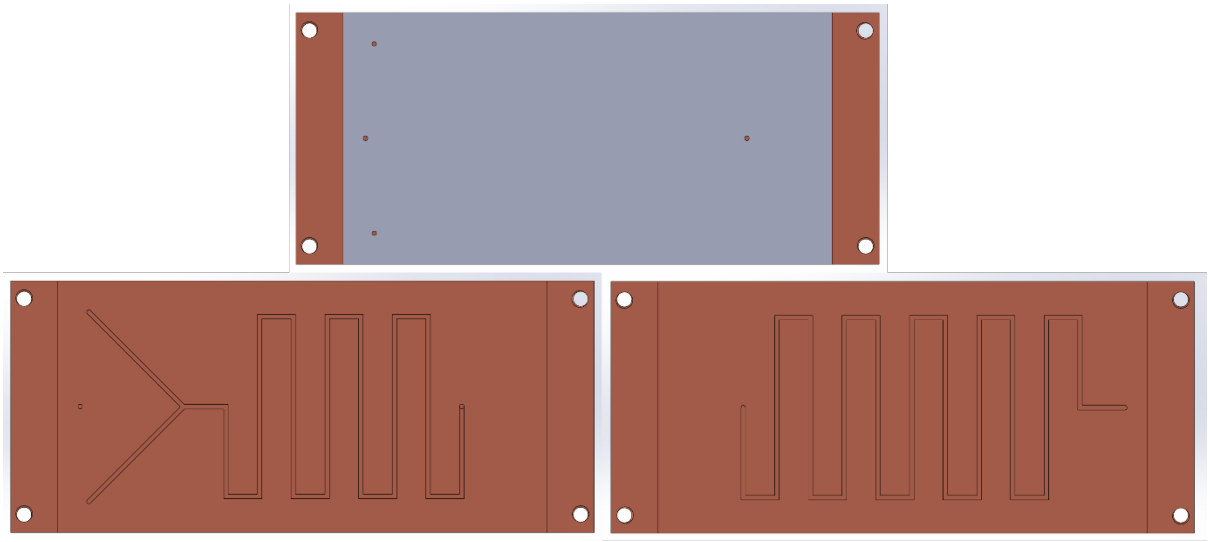


Figure S4. Internal fluidic pathways for the copper flow reactor

Triazole Library Design of Experiments Data

The Huisgen 1,3-dipolar cycloaddition of alkynes and azides to yield 1,2,3-triazoles is considered the premier example of a "Click Reaction". "Click Chemistry" is a term initially introduced by Professor K. B. Sharpless in 2001 to describe high yielding reactions, wide in scope, stereospecific, simple to perform, and can be conducted in easily removable or benign solvents.

Model Reaction

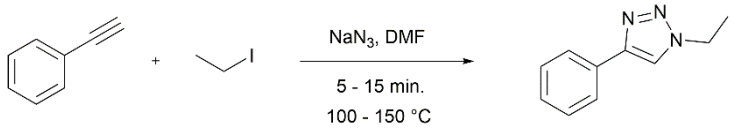


Table S1. Conditions Screened

Variable	Low	Medium	High
Temperature [°C]	100	125	150
Residence Time [min]	5	10	15

Design of experiments was performed using a 3 level, full factorial design with an additional two centre point repeats for a total of 11 experimental runs.

Table S2. DOE Results

Temperature [^{o}C]	Residence time [min]	HPLC Area % Product
100	5	9.69
125	5	22.37
145	5	26.26
100	10	16.25
125	10	33.24
145	10	59.57
100	16.7	30.82
125	16.7	32.03
145	16.7	50.97
125	10	32.7
125	10	46.23

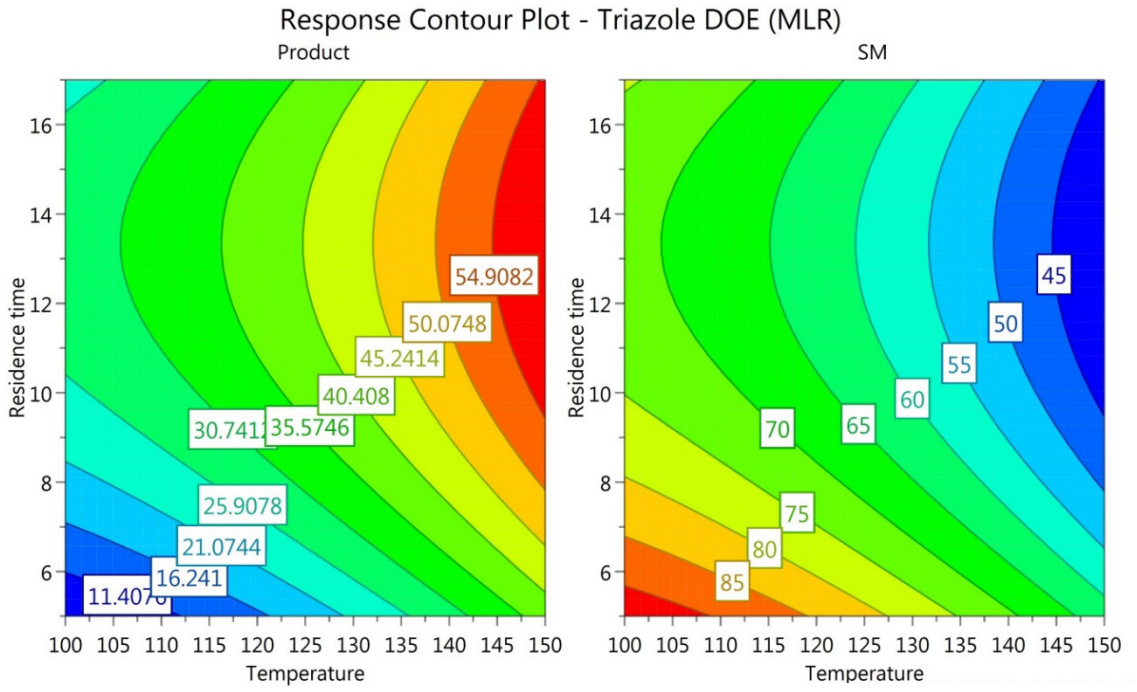


Figure S5. Response Contour Plot (RCP) for the optimisation DOE for a) product and b) starting material

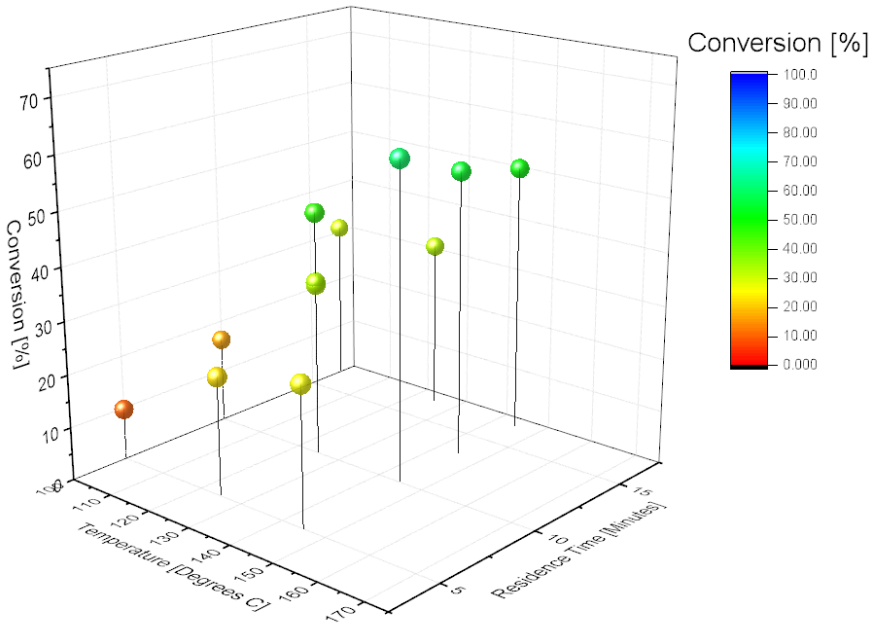


Figure S6. Ball and Stick diagram for individual responses in the DOE

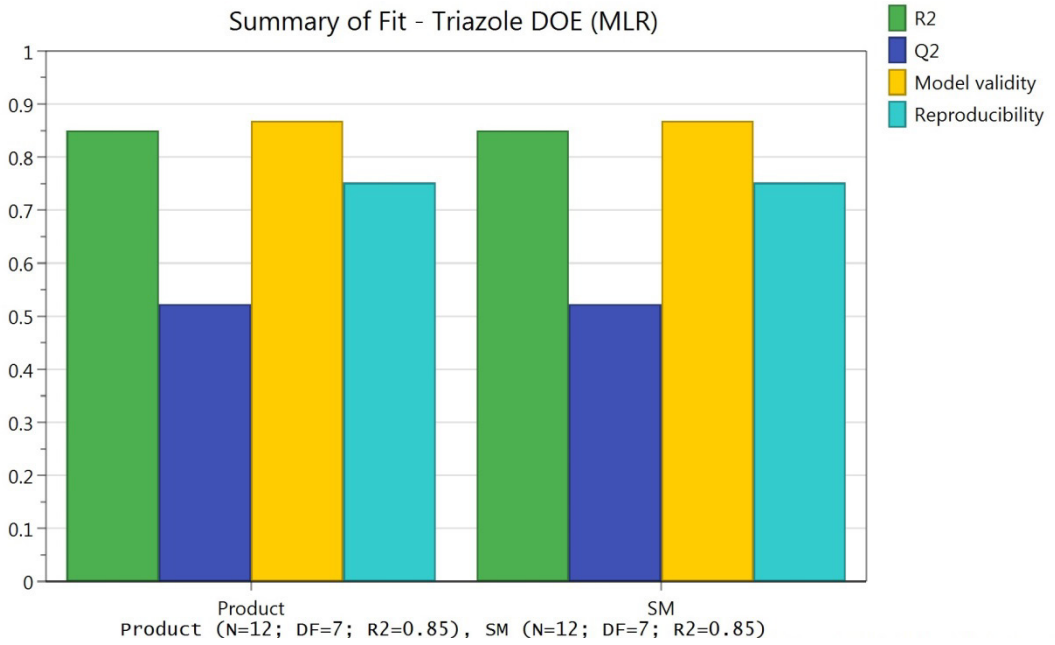


Figure S7. Summary of fit information for DOE model

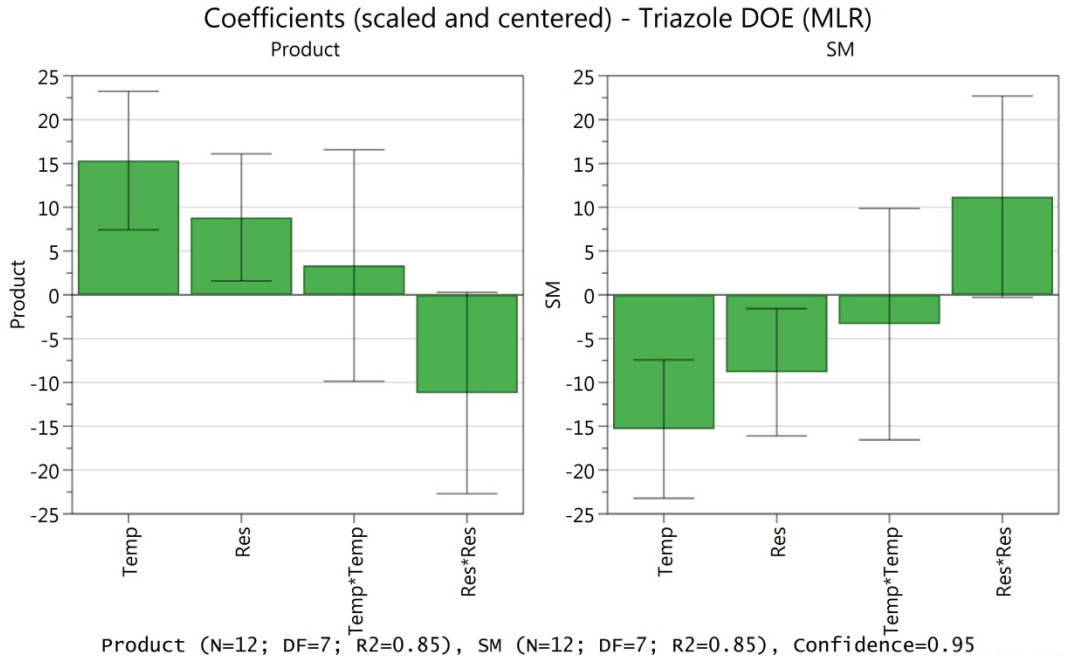


Figure S8. Coefficients for model generated from DOE results

Table S3. Coefficient list for product and starting material plots

Product	Coeff. SC	Std. Err.	P	Conf. int(±)
Constant	38.8323	4.22064	9.29564e-005	10.3276
Temperature	15.5484	3.95008	0.00765766	9.66556
Residence time	8.91594	3.35554	0.0376706	8.21078
Temp*Temp	3.63107	6.33761	0.587498	15.5077
Res*Res	-11.4248	5.45848	0.0812566	13.3565
N = 11	Q2 =	0.361	Cond. no. =	3.677
DF = 6	R2 =	0.823	RSD =	8.049
	R2 adj. =	0.704		
			Confidence =	0.95
SM	**Coeff. SC**	**Std. Err.**	**P**	**Conf. int(±)**
Constant	61.1677	4.22064	6.76579e-006	10.3276
Temperature	-15.5484	3.95007	0.00765764	9.66556
Residence time	-8.91595	3.35554	0.0376706	8.21077
Temp*Temp	-3.63107	6.33761	0.587498	15.5077
Res*Res	11.4248	5.45848	0.081257	13.3565
N = 11	Q2 =	0.361	Cond. no. =	3.677
DF = 6	R2 =	0.823	RSD =	8.049
	R2 adj. =	0.704		
			Confidence =	0.95

All summary terms are of suitable magnitude to suggest that the DOE model generated is good and able to be used with a high degree of reliability. Data suggest that higher temperatures and moderate residence times are favourable for achieving high degrees of product conversion. P values indicate that the model in linear, as the squared terms Temp*Temp and Res*Res are <0.05 and therefore these 2nd order effects are insignificant. Using inbuilt optimisation software in the MODDE Pro software generated the following conditions for maximising product conversion and minimising starting materials;

Table S4. Optimised Conditions based on DOE Model

Temperature [°C]	Residence Time [minutes]	Predicted Product Conversion [%]	Obtained Product Conversion [%]
150	13.3	55.3	53.9

* The close match between predicted and observed values signify the high reliability of the generated model

Hydrogen Peroxide Treatment

In order to fully maximise yields, an additional pre-run was performed in which hydrogen peroxide (36%) was flowed through the reaction chamber. The optimised reaction conditions were then employed to establish if this peroxidation could increase conversions. Whilst all results yielded significant increases in product conversion, a slight drop off was observed after 2.5 minutes, and this was therefore used as the minimum exposure time (Table 6).

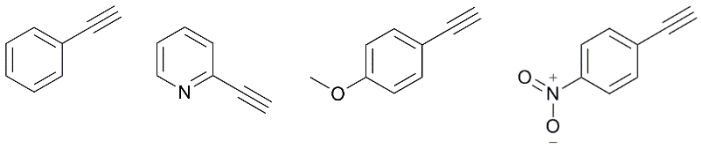
Table S5. Results of Peroxide surface treatment.

Temperature [°C]	Residence Time [minutes]	Hydrogen Peroxide Pre-run Residence Time [minutes]	Product Conversion [%]
150	13.3	0.5	91
150	13.3	1.0	93
150	13.3	2.5	> 95
150	13.3	5.0	> 95
150	13.3	10	> 95
150	13.3	15	> 95

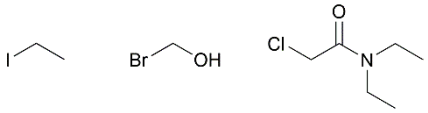
150	13.3	30	> 95

Library Synthesis Procedure

Terminal Acetylenes Used



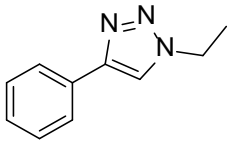
Alkyl Halides Used



Separate solutions of sodium azide (0.25 M, 4:1 DMF:H_2O) iodoethane (0.25 M, DMF) and phenyl acetylene (0.125 M, DMF) were prepared. 3 mL aliquots of each solution were mixed and pumped through the reactor at 75 µL.min^{-1} and 145 °C. The total volume was collected into a *via*l and diluted with 10 mL ethyl acetate. The sample solution was washed with 3 x 10 mL water. The aqueous layers were combined and extracted with 10 mL ethyl acetate, the organic layers were then combined, washed with 3 x 10 mL brine, dried with $MgSO_4$ and filtered before the solvent was removed *in vaccuo.* Samples were purified by column chromatography on silica gel using ethyl acetate prior to analysis *via* NMR, high-resolution mass spectroscopy and HPLC.

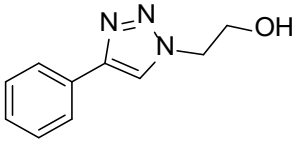
Triazole Library Synthesis Characterisation Data

1-Ethyl-4-phenyl-1*H*-1,2,3-triazole



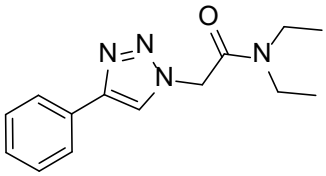
^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.59 (t, 3H, *J* = 7 Hz), 4.45 (q, 2H, *J* = 7 Hz), 7.33-7.35 (m, 1H), 7.40-7.44 (m, 2H), 7.77 (s, 1H), 7.82-7.84 (m, 2H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 15.8, 45.4, 119.0, 125.9, 128.3, 129.0, 130.9, 148.1; HRMS: *m/z* calculated for $C_{10}H_{11}N_3Na$ $[M+Na]^+$ 196.0851; found: 196.0844.

2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1-ol



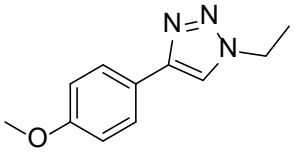
^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.14 (t, 2H, *J* = 5 Hz), 4.54 (t, 2H, *J* = 5 Hz), 7.33 (t, 1H, *J* = 7 Hz), 7.41 (t, 2H, *J* = 7 Hz), 7.76 (d, 2H, *J* = 7 Hz), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 52.9, 61.5, 121.1, 125.8, 128.4, 129.0, 130.5, 147.8; HRMS: *m/z* calculated for $C_{10}H_{11}N_3ONa$ $[M+Na]^+$ 212.0800; found *m/z* 212.0792.

N,N-diethyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetamide



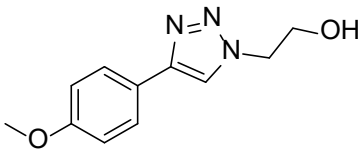
^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.15 (t, 3H, *J* = 7 Hz), 1.26 (t, 3H, *J* = 7 Hz), 3.40-3.47 (m, 4H), 5.24 (s, 2H), 7.30-7.34 (m, 1H), 7.40-7.44 (m, 2H), 7.82-7.86 (m, 2H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 13.0, 14.6, 41.2, 42.2, 51.1, 121.6, 125.9, 128.3, 129.0, 130.7, 148.2, 164.2; HRMS: *m/z* calculated for $C_{14}H_{18}N_4ONa$ $[M+Na]^+$ 281.1378; found *m/z* 281.1369.

1-Ethyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole



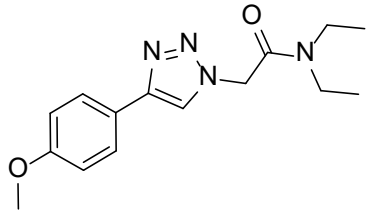
^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.59 (t, 3H, *J* = 7 Hz), 3.84 (s, 3H), 4.44 (q, 2H, *J* = 7 Hz), 6.96 (d, 2H, *J* = 9 Hz), 7.69 (s, 1H), 7.75 (d, 2H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 15.8, 45.5, 55.5, 114.4, 118.3, 127.2, 147.9, 159.7; HRMS: *m/z* calculated for $C_{11}H_{13}N_3ONa$ $[M+Na]^+$ 226.0956; found *m/z* 226.0949.

2-(4-(Methoxyphenol)-1H-1,2,3-triazol-1-yl)ethan-1-ol



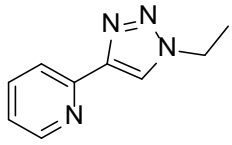
^{1}H NMR ($CDCl_3$ 400 MHz) δ 3.84 (s, 3H), 4.13 (t, 2H, *J* = 5 Hz), 4.45 (t, 2H, *J* = 5 Hz), 6.89 (d, 2H, *J* = 9 Hz), 7.67 (d, 2H, *J* = 9 Hz), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 52.9, 55.5, 61.5, 114.4, 120.3, 123.2, 127.1, 147.6, 159.8; HRMS: *m/z* calculated for $C_{11}H_{13}N_3O_2Na$ $[M+Na]^+$ 242.0905; found *m/z* 242.0897.

N,N-diethyl-2-(4-(-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)acetamide



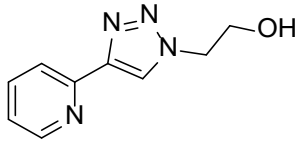
^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.12 (t, 3H, *J* = 7 Hz), 1.23 (t, 3H, *J* = 7 Hz), 3.40 (q, 4H, *J* = 7 Hz), 3.82 (s, 2H), 5.20 (s, 2H), 6.93 (d, 2H, *J* = 9 Hz), 7.75 (d, 2H, *J* = 9 Hz), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 13.0, 14.6, 41.2, 42.2, 51.2, 55.5, 114.4, 120.8, 123.4, 127.3, 148.0, 159.8, 164.2; HRMS: *m/z* calculated for $C_{15}H_{20}N_4O_3Na$ $[M+Na]^+$ 311.1484; found *m/z* 311.1474.

2-(1-Ethyl-1*H*-1,2,3-triazol-4-yl)pyridine



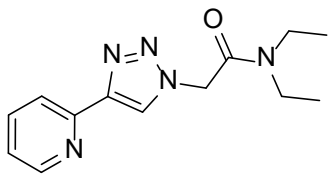
^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.60 (t, 3H, *J* = 7 Hz), 4.48 (q, 2H, *J* = 7 Hz), 7.20-7.24 (m, 1H), 7.75-7.80 (m, 1H), 8.15 (s, 1H) 8.15-8.20 (m, 1H), 8.55-8.59 (m, 1H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 15.6, 45.7, 12.4, 121.5, 123.0, 137.2, 148.6, 149.5, 150.5; HRMS: *m/z* calculated for $C_9H_{10}N_4Na$ $[M+Na]^+$ 197.0803; found *m/z* 197.0797.

2-(4-(Pyridine-2-yl)-1*H*-1,2,3-triazol-1-yl)ethan-1-ol



^{1}H NMR ($CDCl_3$ 400 MHz) δ 4.13 (t, 2H, *J* = 5 Hz), 4.56 (t, 2H, *J* = 5 Hz), 7.21 (t, 1H, *J* = 5 Hz), 7.75 (t, 1H, *J* = 8 Hz), 8.07 (d, 1H, *J* = 8 Hz), 8.30 (s, 1H), 8.46 (d, 1H, *J* = 5 Hz); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 53.2, 61.3, 120.5, 123.1, 123.7, 137.4, 147.8, 149.2, 150.1; HRMS: *m/z* calculated for $C_9H_{10}N_4ONa$ $[M+Na]^+$ 213.0752; found *m/z* 213.0745.

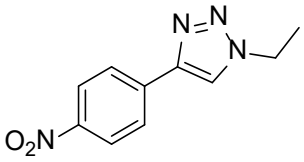
N,N-diethyl-2-(4-(pyridine-2-yl)-1*H*-1,2,3-triazol-1-yl)acetamide



^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.14 (t, 3H, *J* = 7 Hz), 1.26 (t, 3H, *J* = 7 Hz), 3.42 (m, 4H), 5.25 (s, 2H), 7.19-7.23 (m, 1H), 7.74-7.78 (m, 1H), 8.14 (d, 1H, *J* = 8 Hz), 8.35 (s, 1H), 8.57 (d, 1H, *J* = 5 Hz); ^{13}C NMR ($CDCl_3$

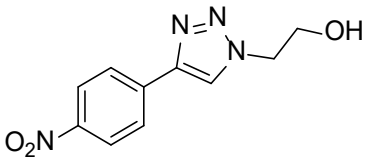
100 MHz) δ 13.0, 14.6, 41.2, 42.1, 51.2, 120.5, 123.0, 124.1, 137.0, 148.8, 149.6, 150.4, 163.9; HRMS: *m/z* calculated for $C_{13}H_{17}N_5ONa$ $[M+Na]^+$ 282.1331; found *m/z* 282.1320.

1-Ethyl-4-(4-nitrophenyl)-1*H*-1,2,3-triazole



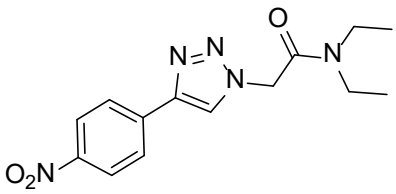
^{1}H NMR ($(CD_3)_2SO$ 400 MHz) δ 1.52 (t, 3H, *J* = 7 Hz), 4.49 (q, 2H, *J* = 7 Hz), 8.14 (d, 2H, *J* = 8 Hz), 8.35 (d, 2H, *J* = 8 Hz), 8.90 (s, 1H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 15.7, 45.8, 120.6, 124.5, 126.3, 137.2, 145.9, 147.5; HRMS: *m/z* calculated for $C_{10}H_{11}N_4O_2$ $[M+H]^+$ 219.0877; found *m/z* 219.0876.

2-(4-(4-Nitrophenyl)-1*H*-1,2,3-triazol-1-yl)ethan-1-ol



^{1}H NMR ($(CD_3)_2SO$ 400 MHz) δ 3.86 (t, 2H, *J* = 6 Hz), 4.50 (t, 2H, *J* = 6 Hz), 5.14 (s, br, 1H), 8.16 (d, 1H, *J* = 9 Hz), 8.34 (d, 1H, *J* = 9 Hz); ^{13}C NMR ($(CD_3)_2SO$ 100 MHz) δ 52.7, 59.7, 124.0, 124.4, 125.9, 137.4, 144.2, 146.5; HRMS: *m/z* calculated for $C_{10}H_{11}N_4O_3$ $[M+H]^+$ 235.0826; found *m/z* 235.0824.

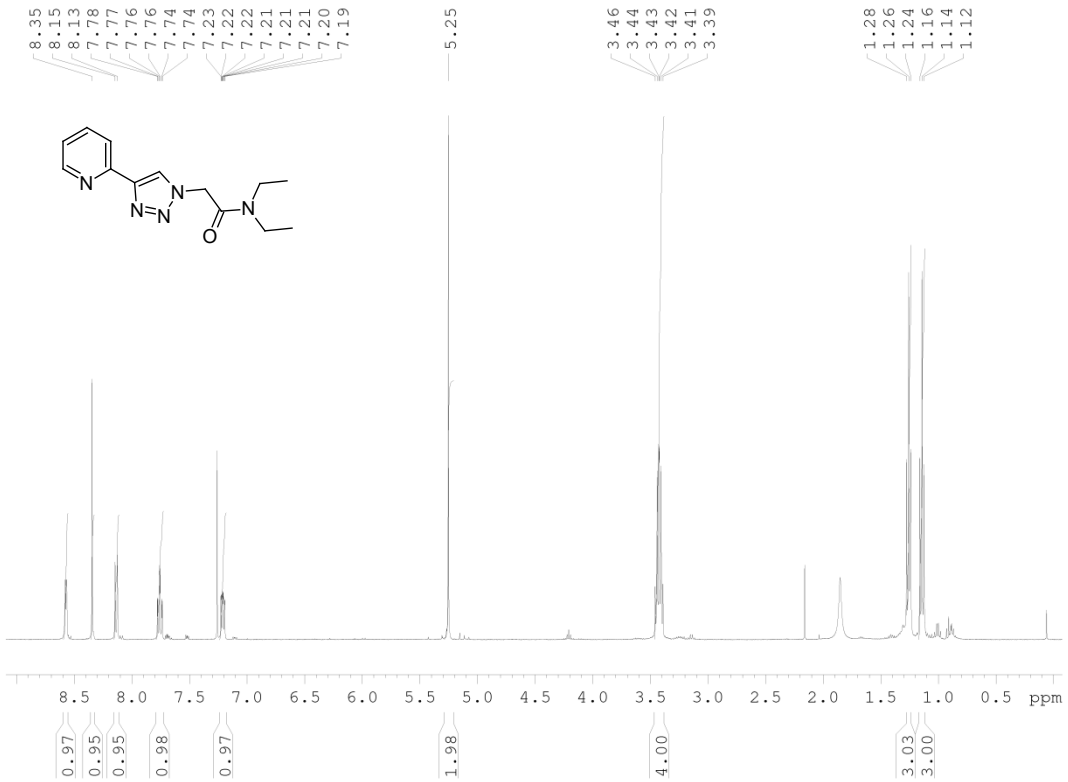
N,N-diethyl-2-(4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl)acetamide



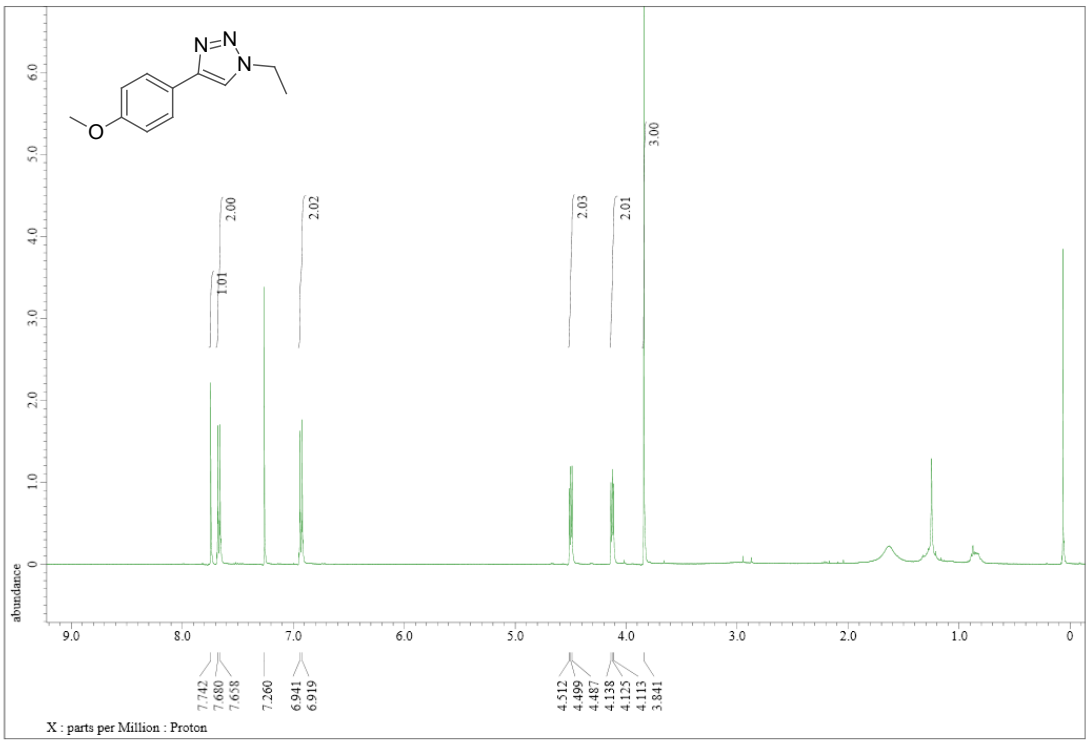
^{1}H NMR ($CDCl_3$ 400 MHz) δ 1.17 (t, 3H, *J* = 7 Hz), 1.31 (t, 3H, *J* = 7 Hz), 3.41-3.50 (m, 4H), 8.02 (d, 2H, *J* = 9 Hz), 8.21 (s, 1H), 8.28 (d, 2H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 12.8, 14.4, 41.2, 42.0, 50.8, 123.1, 124.3, 126.2, 136.9, 145.8, 147.3, 163.6; HRMS: *m/z* calculated for $C_{14}H_{17}N_5O_3Na$ $[M+Na]^+$ 326.1229; found *m/z* 326.1219.

H NMR Spectra for Previously Unreported Compounds

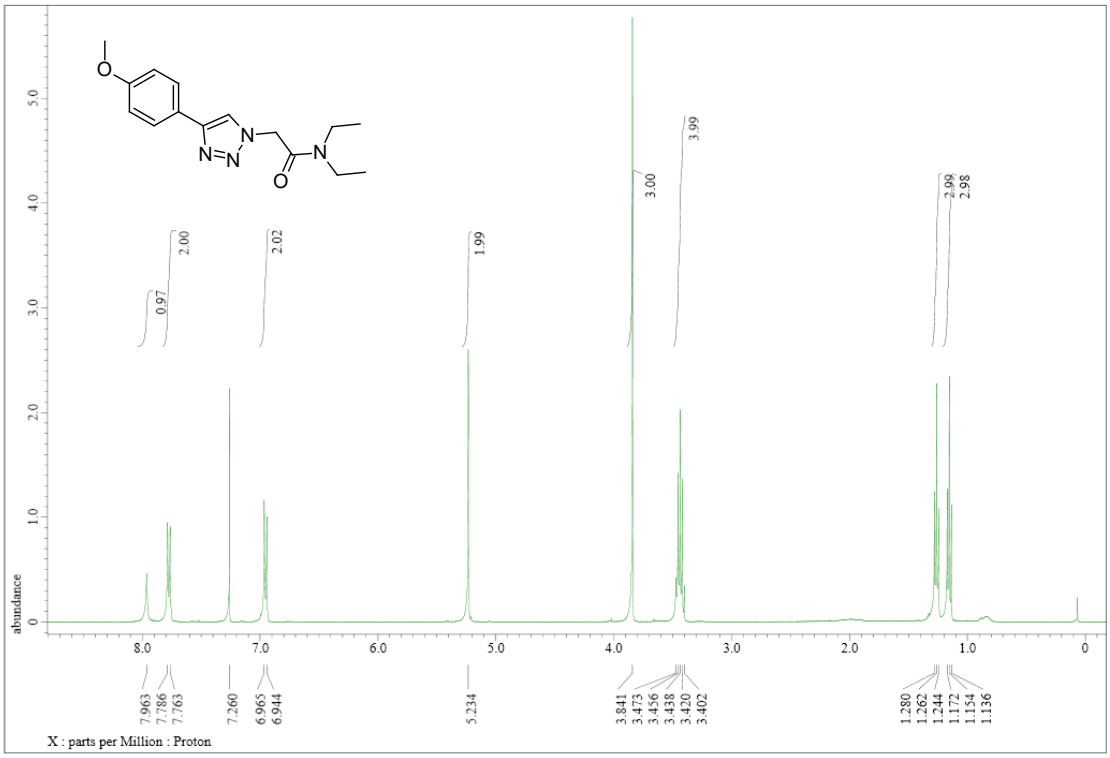
N,N-diethyl-2-(4-(pyridine-2-yl)-1*H*-1,2,3-triazol-1-yl)acetamide



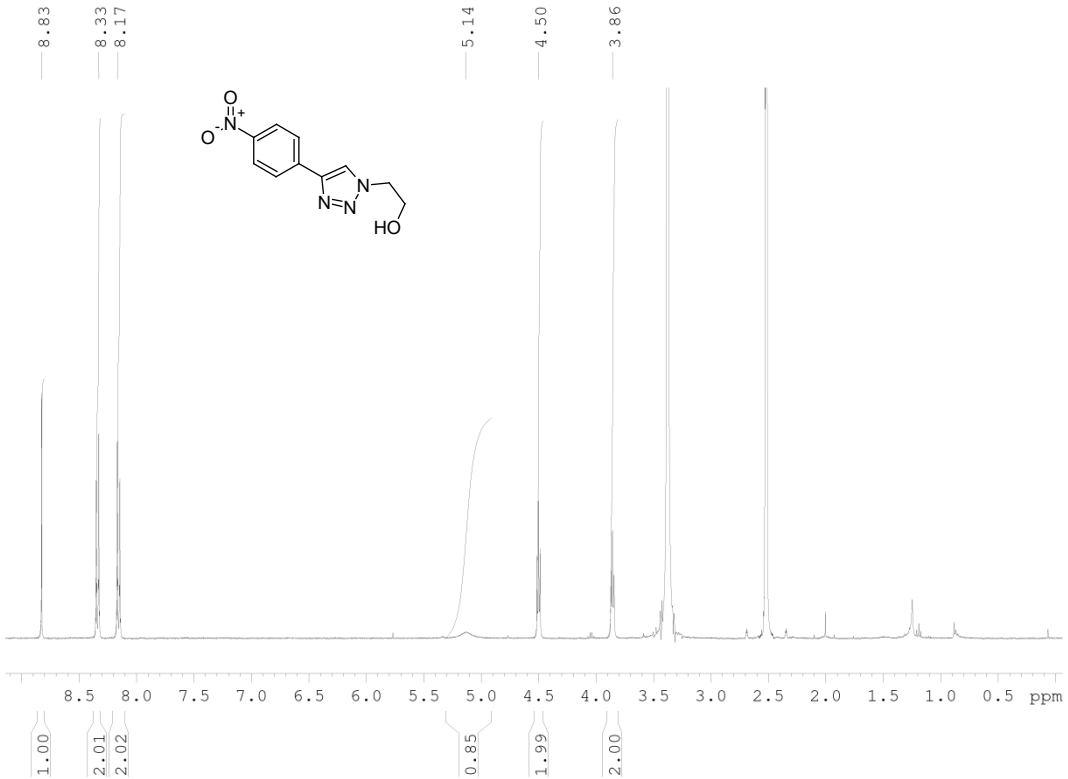
1-Ethyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole



N,N-diethyl-2-(4-(-methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)acetamide



2-(4-(4-nitrophenyl)-1*H*-1,2,3-triazol-1-yl)ethan-1-ol



_N,N_-diethyl-2-(4-(4-nitrophenyl)-1_H_-1,2,3-triazol-1-yl)acetamide