Electronic Supplementary Information

2-Azidoacrylamides as compact platforms for efficient modular synthesis

Hinano Takemura, Sayuri Goto, Takamitsu Hosoya, and Suguru Yoshida*

Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering
Tokyo Medical and Dental University (TMDU)
2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

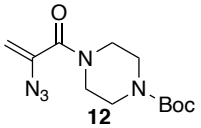
Contents

General Remarks

All reactions were performed in a dry glassware under atmosphere of argon otherwise noted. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica-gel plates (Merck Chemicals, Silica Gel 60 F_{254}, Cat. No. 1.05715). Column chromatography was conducted using silica-gel (Kanto Chemical Co., Inc., Silica Gel 60N, spherical neutral, particle size 40–50 μm, Cat. No. 37563-85 or particle size 63–210 μm, Cat. No. 37565-85). Preparative thin-layer chromatography (PTLC) was performed on silica-gel (Wako Pure Chemical Industries Ltd., Wakogel B5-F, Cat. No. 230-00043). Melting points (Mp) were measured on a YANACO MP-J3 instrument or an OptiMelt MPA100 (Stanford Research Systems), and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AVANCE 500 spectrometer at 500 or 126 MHz, respectively. ^{19}F NMR spectra were obtained with a Bruker AVANCE 400 spectrometer at 376 MHz. Chemical shifts (δ) are given in parts per million (ppm) downfield from $(CH_3)_4Si$ (δ 0.00 for ^{1}H NMR in $CDCl_3$) or the solvent peak (δ 77.0 for ^{13}C NMR in $CDCl_3$) as an internal reference with coupling constants (*J*) in hertz (Hz). The abbreviations s, d, t, q, m, and br signify singlet, doublet, triplet, quartet, multiplet, and broad, respectively. IR spectra were measured by diffuse reflectance method on a Shimadzu IRPrestige-21 spectrometer attached with DRS-8000A with the absorption band given in cm^{-1}. High-performance liquid chromatography (HPLC) was performed on a Shimadzu Prominence HPLC system (CBM-20A lite, LC-20AD × 2, DGU-20A3R, SUS316L, and CTO-20A) equipped with a Shimadzu SPD-20A UV/Vis detector. High-resolution mass spectra (HRMS) were measured on a Bruker micrOTOF mass spectrometer under positive electrospray ionization (ESI^+) conditions.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. 5,6-Didehydro-11,12-dihydrodibenzo[*a*,*e*]cyclooctene (**S12**),[S1] (1α,8α,9α)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (**S13**),[S2] 4,8-ditosyl-4,8-diazacyclononyne (**S14**),[S3] and tris[(1-benzyl-*1H*-1,2,3-triazol-4-yl)methyl]amine (TBTA)[S4] were prepared according to the reported methods.

Structures of Azides, Alkynes, and Amines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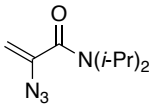
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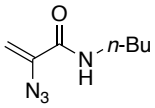
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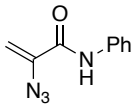
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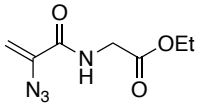
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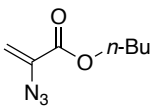
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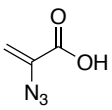
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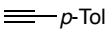
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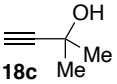
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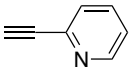
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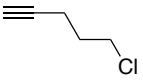
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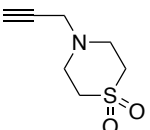
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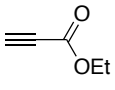
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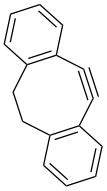
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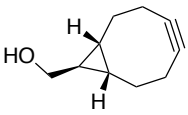
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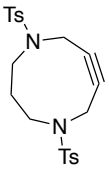
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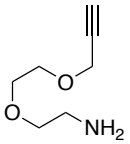
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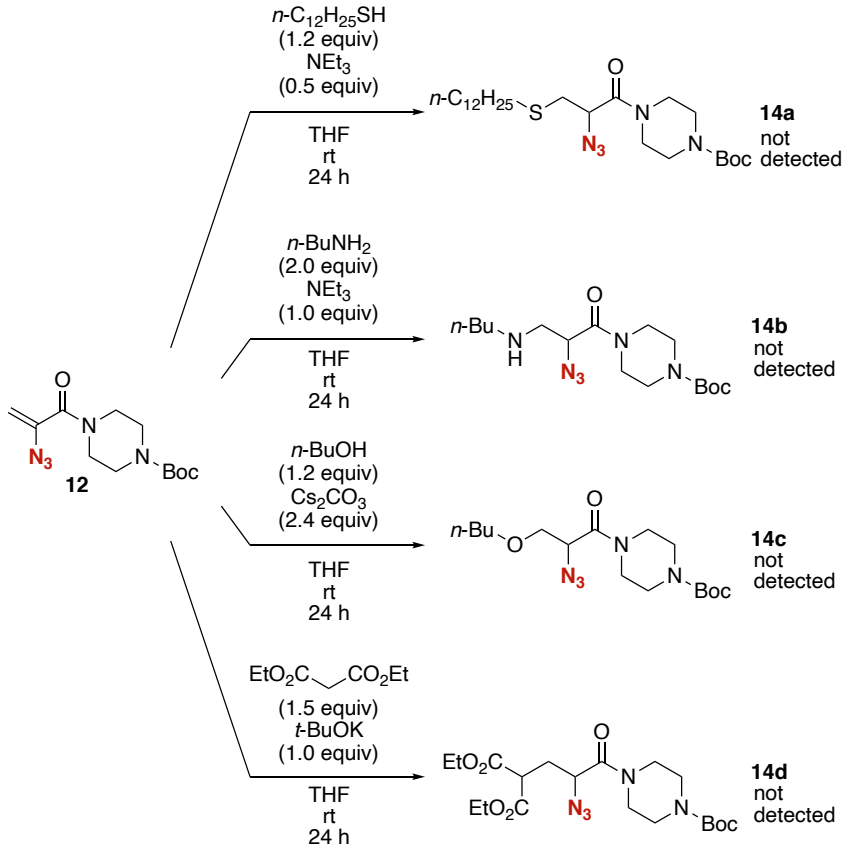
S15

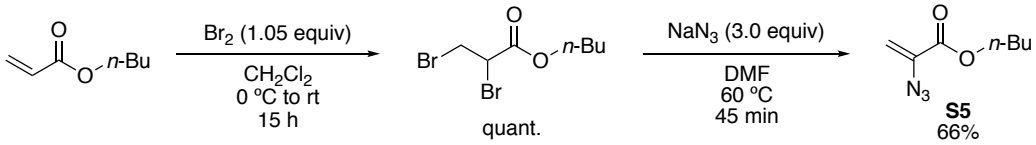

S16

Attempts of Michael Reactions of Acrylamide 12



Experimental Procedures

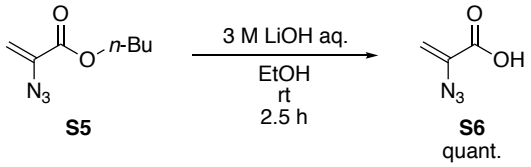
*Synthesis of butyl 2-azidoacrylate (**S5**)*



Under an argon atmosphere, to a solution of butyl acrylate (5.70 mL, 40.0 mmol) dissolved in dichloromethane (17 mL) was slowly added bromine (2.14 mL, 42.0 mmol) dissolved in dichloromethane (2 mL) at 0 ºC over 20 min, and the mixture was stirred for 1 h at the same temperature. After warming to room temperature, the mixture was stirred for 15 h at the same temperature. Then, to the mixture was added saturated aqueous sodium thiosulfate (50 mL), and the mixture was extracted with dichloromethane (125 mL × 2). The combined organic extract was washed with brine (50 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give butyl 2,3-dibromopropanoate (11.5 g, 40.0 mmol, quant.) as a colorless oil.

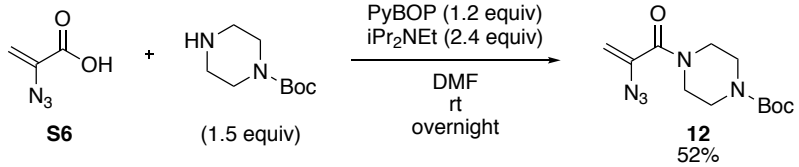
Under an argon atmosphere, to a solution of butyl 2,3-dibromopropanoate (11.5 g, 40.0 mmol) dissolved in DMF (120 mL) was added sodium azide (5.20 g, 80.0 mmol) at 60 ºC. After stirring for 20 min at the same temperature, to the mixture was added sodium azide (2.60 g, 40.0 mmol), and the mixture was stirred for 25 min at the same temperature. Then, after cooling to room temperature, to the mixture was added water (100 mL). The mixture was extracted with diethyl ether (80 mL × 3). The combined organic extract was washed with sodium bicarbonate (50 mL) and brine (50 mL), and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 250 g, *n*-hexane/CH_2Cl_2 = 3/1) to give butyl 2-azidoacrylate (**S5**) (4.45 g, 26.3 mmol, 66%) as a pale yellow oil.

*Synthesis of 2-azidoacrylic acid **(S6)***



Under an argon atmosphere, to a solution of butyl 2-azidoacrylate (4.23 g, 25.0 mmol) dissolved in EtOH (40 mL) was added 3M $LiOH/H_2O$ (33.0 mL, 100 mmol) at 0 ºC. The mixture was stirred for 2.5 h at room temperature. Then, to the mixture was added 2 M HCl solution (100 mL) to be pH 1. The mixture was extracted with EtOAc (120 mL × 3). The combined organic extract was washed with brine (50 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give 2-azidoacrylic acid (**S6**) (2.83 g, 25 mmol, quant.) as a yellow solid.

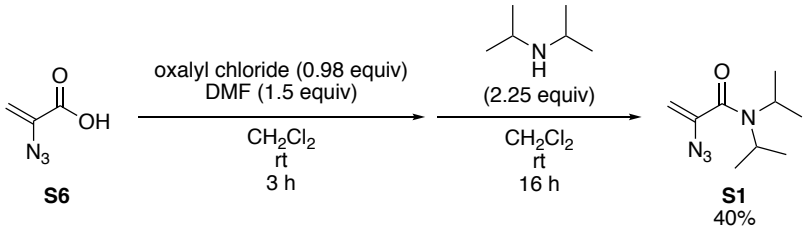
*Synthesis of tert-butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**12**)*



Under an argon atmosphere, to a solution of 2-azidoacrylic acid (33.9 mg, 0.300 mmol) and *tert*-butyl piperazine-1-carboxylate (83.8 mg, 0.450 mmol) dissolved in DMF (1.5 mL) was added *i*-Pr_2NEt (93.1 mg, 0.720 mmol) and (benzotriazol-1-yloxy)(trispyrrolidino)phosphonium hexafluorophosphate (PyBOP) (18.7 mg, 0.360 mmol) at 0 ºC. After warming to room temperature, the mixture was stirred for 14 h at the same temperature. Then, to the mixture was added saturated aqueous sodium bicarbonate (10 mL), and extracted with EtOAc (15 mL × 3). The combined organic extract was washed with brine (10 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 10 g, *n*-hexane/EtOAc = 2/1) to give *tert*-butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**12**) (87.3 mg, 0.310 mmol, 52%) as a colorless solid.

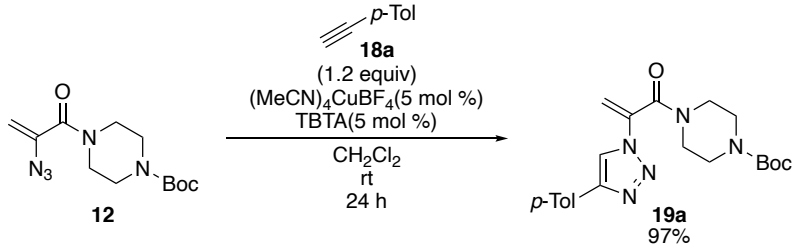
According to the procedure for preparing *tert*-butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**12**), 2-azido-*N*-butylacrylamide (**S2**), 2-azido-*N*-phenylacrylamide (**S3**), ethyl (2-azidoacryloyl)glycinate (**S4**), and 2-azido-*N*-(prop-2-yn-1-yl)acrylamide (**22**) were prepared from *n*-butylamine, aniline, ethyl glycinate, and propargyl amine, respectively.

*Synthesis of 2-azido-N,N-diisopropylacrylamide (**S1**)*



Under an argon atmosphere, to a solution of 2-azidoacrylic acid (0.226 g, 2.00 mmol) and DMF (32.9 mg, 3.00 mmol) dissolved in CH_2Cl_2 (4.0 mL) was added oxalyl chloride (0.249 g, 1.96 mmol) at 0 ºC. After warming to room temperature, the mixture was stirred for 3 h at the same temperature. Then, to the resulting mixture was slowly added a solution of diisopropylamine (0.455 g, 4.50 mmol) dissolved in CH_2Cl_2 (9.0 mL) under an argon atmosphere. After stirring for 16 h at the same temperature, the mixture was extracted with EtOAc (30 mL × 3). The combined organic extract was washed with brine (30 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 6.0 g, *n*-hexane/EtOAc = 7/1) to give 2-azido-*N*,*N*-diisopropylacrylamide (**S1**) (15.8 mg, 80.5 μmol, 40%) as a pale yellow oil.

A typical procedure for the CuAAC reaction of 2-azidoacrylamides

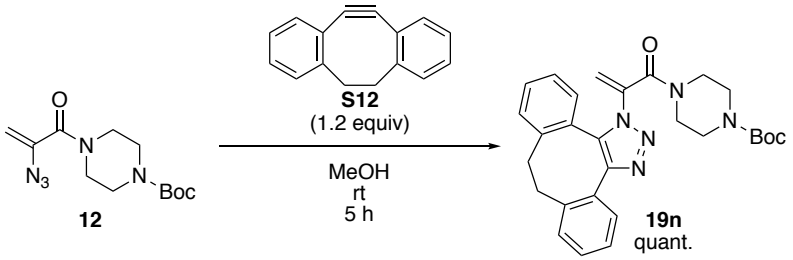


To a solution of *tert*-butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**12**) (14.1 mg, 50.0 μmol) in CH_2Cl_2 (0.40 mL) were added *p*-ethynyltoluene (**18a**) (7.6 μL, 60 μmol), $(MeCN)_4CuBF_4$ (0.80 mg, 25 μmol), and TBTA (1.3 mg, 25 μmol) at room temperature. After stirring for 24 h at the same temperature, to the mixture was added water (20 mL). The mixture was extracted with EtOAc (20 mL × 2). The combined organic extract was washed with brine (10 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 6/1) to give *tert*-butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**) (19.3 mg, 48.6 μmol, 97%) as a colorless solid.

According to the procedure for preparing *tert*-butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**), *N*,*N*-diisopropyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**19b**), *N*-butyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**19c**), *N*-phenyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**19d**), ethyl (2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)glycinate (**19e**), butyl 2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylate (**19f**), and 2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylic acid (**19g**) were prepared from 2-azido-*N*,*N*-diisopropylacrylamide (**S1**), 2-azido-*N*-butylacrylamide (**S2**), 2-azido-*N*-phenylacrylamide (**S3**), ethyl (2-azidoacryloyl)glycinate (**S4**), butyl 2-azidoacrylate (**S5**), and 2-azidoacrylic acid (**S6**), respectively.

Also, according to the procedure for preparing *tert*-butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**), *tert*-butyl 4-(2-(4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19h**), *tert*-butyl 4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19i**), *tert*-butyl 4-(2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19j**), *tert*-butyl 4-(2-(4-(3-chloropropyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19k**), *tert*-butyl 4-(2-(4-((1,1-dioxidothiomorpholino)methyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19l**), and *tert*-butyl 4-(2-(4-(ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19m**) were prepared using 2-ethynylpyridine (**S7**), 2-methylbut-3-yn-2-ol (**18c**), ethynylcyclopropane (**S8**), 5-chloropent-1-yne (**S9**), 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (**19l**), and ethyl propiolate (**S11**) instead of 1-ethynyl-4-methylbenzene (**18a**).

A typical procedure for the SPAAC reaction of 2-azidoacrylamides

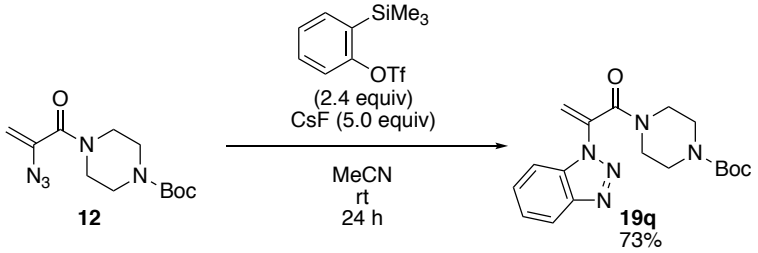


To a solution of *tert*-butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**12**) (14.1 mg, 50.0 μmol) in MeOH (1.0 mL) was added 5,6-didehydro-11,12-dihydrodibenzo[*a*,*e*]cyclooctene (**S12**) (12.3 mg, 60.0 μmol) room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give *tert*-butyl 4-(2-(8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19n**) (24.3 mg, 50.0 μmol, quant.) as a colorless solid.

According to the procedure for preparing *tert*-butyl 4-(2-(8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19n**), *tert*-butyl 4-(2-((5a*S*,6*S*,6a*R*)-6-(hydroxymethyl)-5,5a,6,6a,7,8-hexahydrocyclopropa[5,6]cycloocta[1,2-*d*][1,2,3]triazol-1(4*H*)-yl)acryloyl)piperazine-1-carboxylate (**19o**) was prepared from 2-azidoacrylamide **12** and ((1*R*,8*S*,9*r*)-bicyclo[6.1.0]non-4-yn-9-yl)methanol (**S13**).

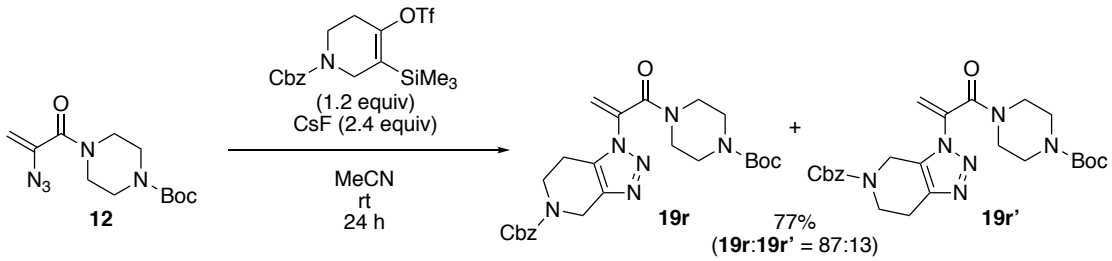
Also, according to the procedure for preparing *tert*-butyl 4-(2-(8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19n**), *tert*-butyl 4-(2-(5,9-bis(tosyl)-5,6,7,8,9,10-hexahydro-[1,2,3]triazolo[4,5-*g*][1,5]diazonin-1(4*H*)-yl)acryloyl)piperazine-1-carboxylate (**19p**) was prepared from *N,N'*-bis(*p*-toluenesulfonyl)-4,8-diazacyclononyne) (**S14**), in which CH_2Cl_2 was used instead of MeOH as a solvent,.

*Synthesis of tert-butyl 4-(2-(1H-benzo[d][1,2,3]triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19q**)*



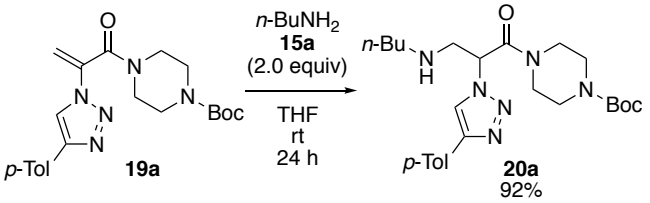
To a solution of *tert*-butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**12**) (14.1 mg, 50.0 μmol) in MeCN (0.50 mL) were added *o*-(trimethylsilyl)phenyl triflate (29.1 μL, 0.120 mmol) and cesium fluoride (38.0 mg, 0.250 mmol) at room temperature. After stirring for 24 h at the same temperature, to the mixture was added saturated aqueous sodium bicarbonate (5 mL). The mixture was extracted with EtOAc (20 mL × 2). The combined organic extract was dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give *tert*-butyl 4-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19q**) (13.0 mg, 36.4 μmol, 73%) as a colorless solid.

*Synthesis of 2-triazolylacrylamides (**19r**/**19r'**)*



To a solution of *tert*-butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**12**) (14.1 mg, 50.0 μmol) in MeCN (0.50 mL) were added Benzyl 4-(triflyloxy)-3-(trimethylsilyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (20.8 μL, 60 μmol) and cesium fluoride (15.2 mg, 0.100 mmol) at room temperature. After stirring for 24 h at the same temperature, to the mixture was added saturated aqueous sodium bicarbonate (5 mL). The mixture was extracted with EtOAc (20 mL × 2). The combined organic extract was dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/5) to give benzyl 1-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-oxoprop-1-en-2-yl)-1,4,6,7-tetrahydro-5*H*-[1,2,3]triazolo[4,5-*c*]pyridine-5-carboxylate (**19r**) (16.8 mg, 33.8 μmol, 67%) as a colorless solid and benzyl 3-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-oxoprop-1-en-2-yl)-3,4,6,7-tetrahydro-5H-[1,2,3]triazolo[4,5-*c*]pyridine-5-carboxylate (**19r'**) (2.6 mg, 5.2 μmol, 10%) as a colorless solid.

A typical procedure for the Michael reaction of 2-triazolylacrylamides with primary amines

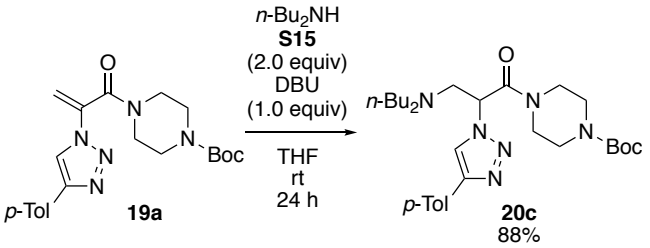


In a 0.3 mL screw-top V-vial® with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of *tert*-butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**) (19.9 mg, 50.0 μmol) in THF (0.20 mL) was added *n*-butylamine (**15a**)(9.9 μL, 0.10 mmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH = 10/1) to give *tert*-butyl 4-(3-(butylamino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20a**) (21.7 mg, 46.1 μmol, 92%) as a colorless solid.

According to the procedure for preparing *tert*-butyl 4-(3-(butylamino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20a**), 4-(3-((2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)amino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20b**) was prepared using 2-(2-(prop-2-yn-1-yloxy)ethoxy)ethan-1-amine (**15b**) instead of *n*-butylamine (**15a**).

Also, according to the procedure for preparing *tert*-butyl 4-(3-(butylamino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20a**), *tert*-butyl 4-(3-(butylamino)-2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20e**), *tert*-butyl 4-(3-(butylamino)-2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20f**), and *tert*-butyl 4-(3-(butylamino)-2-(4-(ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20g**) were prepared from the corresponding 2-triazolylacrylamides.

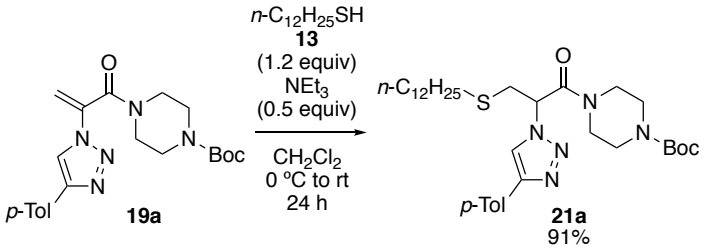
A typical procedure for the Michael reaction of 2-triazolylacrylamides with secondary amines



To a solution of *tert*-butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**) (19.9 mg, 50.0 μmol) in THF (0.20 mL) were added di(*n*-butyl)amine (**S15**) (17.0 μL, 0.100 mmol) and DBU (7.5 μL, 50 μmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give *tert*-butyl 4-(3-(dibutylamino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20c**) (23.2 mg, 44.0 μmol, 88%) as a colorless solid.

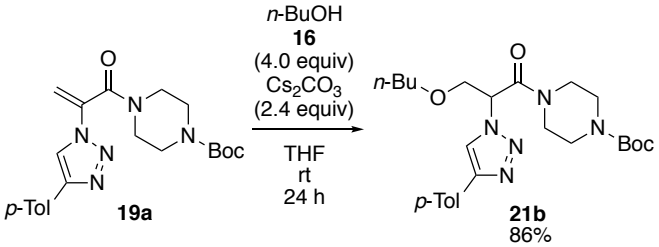
According to the procedure for preparing *tert*-butyl 4-(3-(dibutylamino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20c**), *tert*-butyl 4-(3-(piperidin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20d**) was prepared using piperidine (**S16**) instead of di(*n*-butyl)amine (**S15**).

*Synthesis of tert-butyl 4-(3-(dodecylthio)-2-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**21a**)*



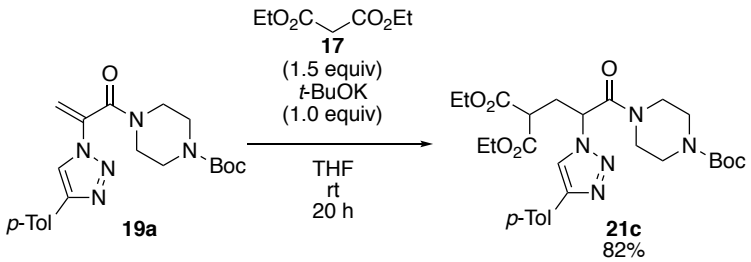
In a 0.3 mL screw-top V-vial® with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of *tert*-butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**) (19.9 mg, 50.0 μmol) in CH_2Cl_2 (0.2 mL) were added triethylamine (2.1 μL, 15 μmol) at 0 °C. After stirring for 3 min at the same temperature, to the mixture was added dodecanethiol (**13**) (8.6 μL, 36 μmol). After warming to room temperature, the mixture was stirred for 24 h. Then, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give t*ert*-butyl 4-(3-(dodecylthio)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**21a**) (16.4 mg, 27.3 μmol, 91%) as a colorless solid.

*Synthesis of tert-butyl 4-(3-butoxy-2-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**21b**)*



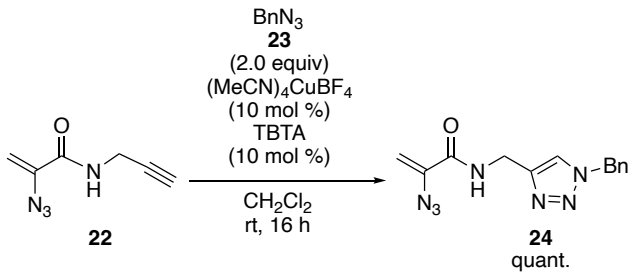
In a 0.3 mL screw-top V-vial® with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of *tert*-butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**) (19.9 mg, 50.0 μmol) in THF (0.2 mL) were added butanol (**16**) (18.3 μL, 0.200 mmol) and cesium carbonate (39.1 mg, 0.120 mmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give *tert*-butyl 4-(3-butoxy-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**21b**) (20.4 mg, 43.3 μmol, 86%) as a colorless oil.

*Synthesis of diethyl 2-(3-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-oxo-2-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)propyl)malonate (**21c**)*



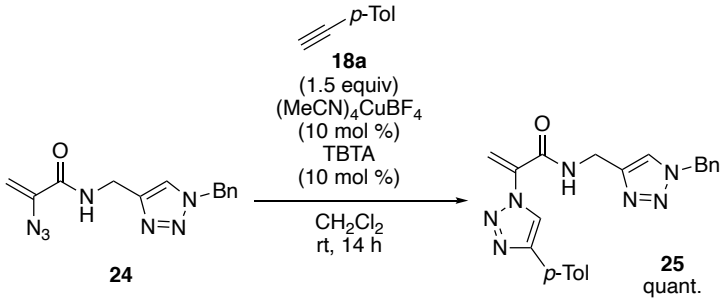
In a 0.3 mL screw-top V-vial® with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a mixture of *tert*-butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**) (19.9 mg, 50.0 μmol) and diethyl malonate (**17**) (11.4 μL, 75.0 μmol) was added sodium *tert*-butoxide (5.6 mg, 50 μmol) dissolved in THF (0.20 mL) at room temperature. After stirring for 20 h at the same temperature, to the mixture was added saturated aqueous ammonium chloride (5 mL). The mixture was extracted with EtOAc (20 mL × 2). The combined organic extract was washed with brine (5 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give diethyl 2-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)malonate (**21c**) (18.1 mg, 41.0 μmol, 82%) as a colorless solid.

*Synthesis of 2-azido-N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)acrylamide (**24**)*



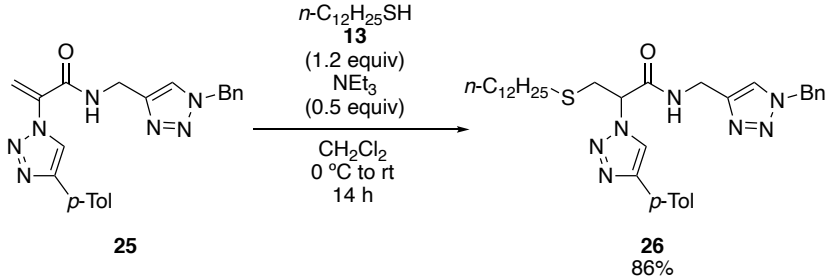
To a solution of benzyl azide (**23**) (266 mg, 2.00 mmol) in CH_2Cl_2 (10.0 mL) were added $(MeCN)_4CuBF_4$ (31.5 mg, 0.100 mmol), TBTA (53.1 mg, 0.100 mmol), and 2-azido-*N*-(prop-2-yn-1-yl)acrylamide (**22**) (149 mg, 1.00 mmol) at room temperature. After stirring for 16 h at the same temperature, the mixture was filtered with celite. Then, the mixture was filtered with a short pad of silica-gel (3 g, CH_2Cl_2/MeCN= 3/1). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 11 g, CH_2Cl_2/MeOH= 20/1) to give 2-azido-*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)acrylamide (**24**) (283 mg, 1.00 mmol, quant.) as a colorless solid.

*Synthesis of N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl) acrylamide (**25**)*



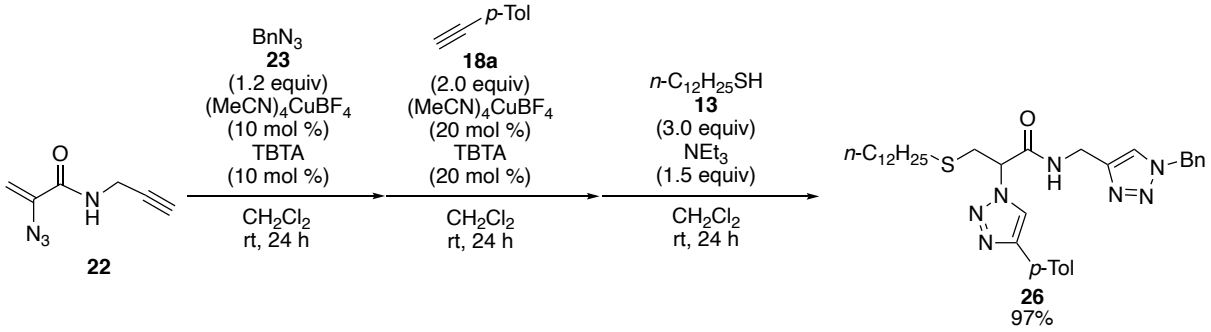
To a solution of 2-azido-*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)acrylamide (**24**) (285 mg, 1.00 mmol) in CH_2Cl_2 (10.0 mL) were added $(MeCN)_4CuBF_4$ (31.5 mg, 0.100 mmol), TBTA (53.1 mg, 0.100 mmol), and *p*-ethynyltoluene (174 mg, 1.50 mmol) at room temperature. After stirring for 16 h at the same temperature, the mixture was filtered with celite. Then, the mixture was filtered by with a short pad of silica-gel (3 g, CH_2Cl_2/MeCN= 3/1). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 12 g, CH_2Cl_2/MeOH= 20/1) to give *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**25**) (399 mg, 1.00 mmol, quant.) as a colorless solid.

*Synthesis of N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-(dodecylthio)-2-(4-(4-tolyl)-1H-1,2,3- triazol- 1-yl)propanamide (**26**)*



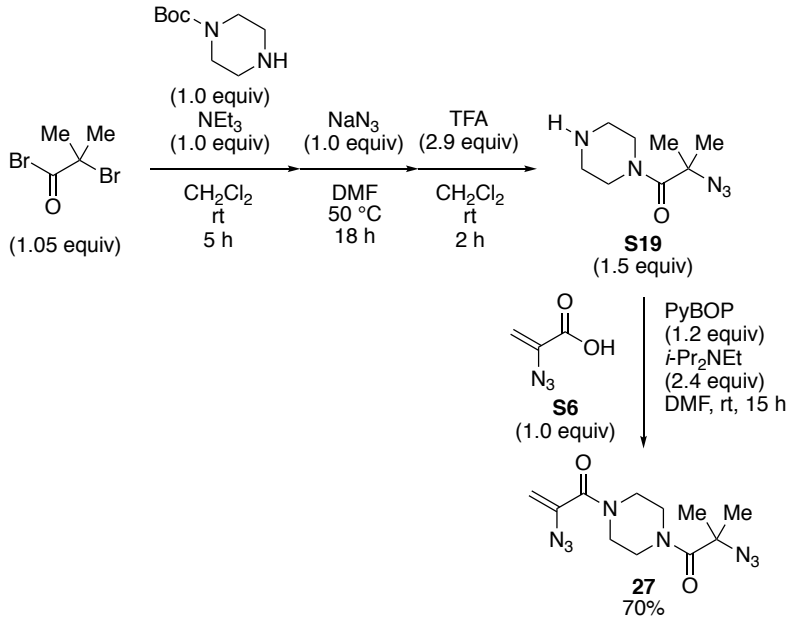
To a solution of *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol- 1-yl)acrylamide (**25**) (20.0 mg, 50.0 μmol) in CH_2Cl_2 (0.1 mL) was added triethylamine (3.5 μL, 25 μmol) at 0 °C. After stirring for 3 min at the same temperature, to the mixture was added 1-dodecanethiol (**13**) (14.2 μL, 60.0 μmol). After warming to room temperature, the mixture was stirred for 14 h at the same temperature. Then, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeCN = 2/1) to give *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-(dodecylthio)-2-(4-(4-tolyl)-1*H*- 1,2,3-triazol-1-yl)propanamide (**26**) (25.8 mg, 42.9 μmol, 86%) as a colorless solid.

*One-pot synthesis of N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-3-(dodecylthio)-2-(4-(4-tolyl)-1H-1,2,3-triazol- 1-yl)propanamide (**26**) from platform **22***



In a 5 mL screw-top V-vial® with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of 2-azido-*N*-(prop-2-yn-1-yl)acrylamide (**22**) (7.5 mg, 50 μmol) in CH_2Cl_2 (1.25 mL) were added benzyl azide (**23**) (7.5 μL, 60 μmol), $(MeCN)_4CuBF_4$ (1.6 mg, 5.0 μmol), and TBTA (2.7 mg, 5.0 μmol) at room temperature. After stirring for 24 h at the same temperature, to the mixture were added *p*-ethynyltoluene (**18a**) (12.6 μL, 0.100 mmol), $(MeCN)_4CuBF_4$ (3.1 mg, 10 μmol), and TBTA (5.3 mg, 10 μmol) at room temperature. After stirring for 24 h at the same temperature, to the mixture was added triethylamine (10.4 μL, 75 μmol) at 0 °C. After stirring for 3 min at the same temperature, to the mixture was added 1-dodecanethiol (**13**) (35.7 μL, 0.150 mmol). After warming to room temperature, the mixture was stirred for 24 h at the same temperature. Then, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-(dodecylthio)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanamide (**26**) (21.0 mg, 48.6 μmol, 97%) as a colorless solid.

*Synthesis of 2-azido-1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)prop-2-en-1-one (**27**)*



To a solution of *N*-Boc-piperazine (0.931 g, 5.00 mmol) and triethylamine (0.693 mL, 5.00 mmol) in CH_2Cl_2 (10 mL) was added a solution of 2-bromo-2-methylpropionyl bromide (0.645 mL, 5.25 mmol) dissolved in CH_2Cl_2 (2 mL) at 0 °C. After stirring for 5 h at room temperature, to the mixture was added saturated aqueous sodium bicarbonate (10 mL). The mixture was extracted with dichloromethane (40 mL × 3). The combined organic extract was washed with brine (10 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give *tert*-butyl 4-(2-bromo-2-methylpropanoyl)piperazine-1-carboxylate (**S17**) (1.55 g, 4.63 mmol, 93%) as a colorless solid.

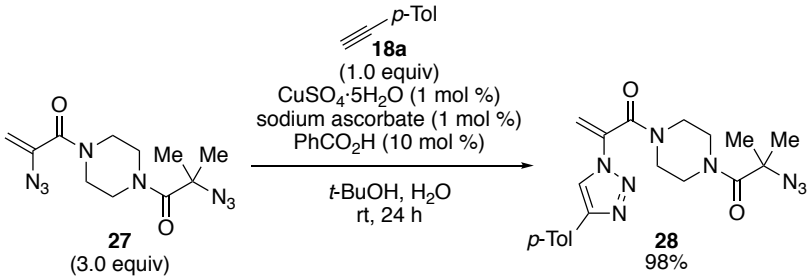
To a solution of *tert*-butyl 4-(2-bromo-2-methylpropanoyl)piperazine-1-carboxylate (**S17**) (1.340 g, 4.00 mmol) in DMF (8.0 mL) was added sodium azide (0.520 g, 8.00 mmol) at room temperature. After stirring for 18 h at the same temperature, to the mixture was added water (10 mL). The mixture was extracted with dichloromethane (30 mL × 3). The combined organic extract was washed with water (30 mL) and then brine (30 mL), and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 43 g, *n*-hexane only to *n*-hexane/EtOAc = 2/1) to give *tert*-butyl 4-(2-azido-2-methylpropanoyl)piperazine-1-carboxylate (**S18**) (0.730 g, 24.6 mmol, 61%) as a colorless solid.

To a solution of *tert*-butyl 4-(2-azido-2-methylpropanoyl)piperazine-1-carboxylate (**S18**) (0.335 g, 1.00 mmol) in

CH_2Cl_2 (10 mL) was slowly added trifluoroacetic acid (2.50 mL, 32.7 mmol) at 0 °C. After stirring for 2 h at room temperature, to the mixture was added saturated aqueous sodium bicarbonate (30 mL). The mixture was extracted with EtOAc (60 mL × 3). The combined organic extract was washed with water (30 mL) and then brine (30 mL), and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give 2-azido-2-methyl-1-(piperazin-1-yl)propan-1-one (**S19**) (0.194 g, 0.985 mmol, 87%) as a colorless oil.

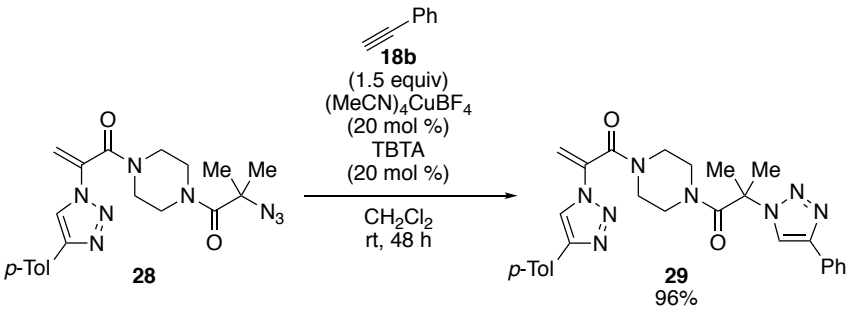
To a solution of 2-azidoacrylic acid (**S6**) (0.113 g, 1.00 mmol) and 2-azido-2-methyl-1-(piperazin-1-yl)propan-1-one (**S19**) (0.296 g, 1.50 mmol) in DMF (4.5 mL) were added *i*-Pr_2NEt (0.414 mL, 2.40 mmol) and PyBOP (0.625 g, 1.20 mmol) at 0 °C. After stirring for 15 h at room temperature, to the mixture was added saturated aqueous sodium bicarbonate (10 mL). The mixture was extracted with EtOAc (30 mL × 3). The combined organic extract was washed with water (30 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 40 g, *n*-hexane only to *n*-hexane/EtOAc = 1/1) to give 2-azido-1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)prop-2-en-1-one (**27**) (0.205 g, 0.703 mmol, 70%) as a colorless oil.

*Synthesis of 1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)-2-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)prop-2-en-1-one (**28**)*



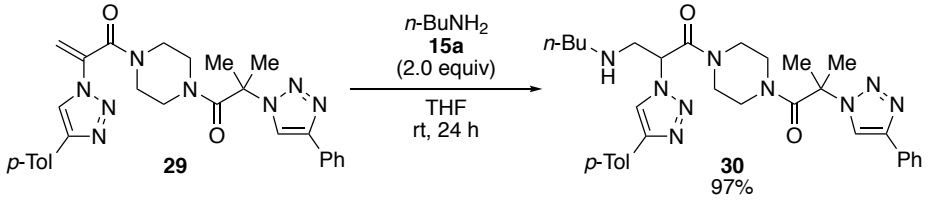
To a solution of 2-azido-1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)prop-2-en-1-one (**27**) (43.8 mg, 0.150 mmol) and *p*-ethynyltoluene (**18a**) (6.3 μL, 50 μmol) in *tert*-butanol (0.13 mL) and water (0.27 mL) were added $CuSO_4·5H_2O$ (0.20 mg, 0.50 μmol), TBTA (0.10 mg, 0.50 μmol), and benzoic acid (0.60 mg, 5.0 μmol) dissolved in *tert*-butanol (0.07 mL) and water (0.13 mL) at room temperature. After stirring for 24 h at the same temperature, to the mixture was added water (5 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic extract was washed with water (5 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/2) to give 1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**28**) (20.0 mg, 49.0 μmol, 98%) as a colorless solid.

*Synthesis of 1-(4-(2-methyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)prop-2-en-1-one (**29**)*



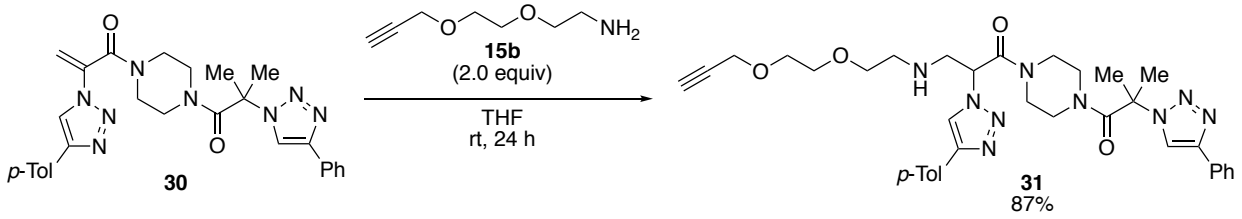
To a solution of 1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**28**) (40.8 mg, 0.100 mmol) and ethynylbenzene (**18b**) (16.5 μL, 0.150 mmol) in CH_2Cl_2 (0.60 mL) were added $(MeCN)_4CuBF_4$ (1.6 mg, 5.0 μmol) and TBTA (2.7 mg, 5.0 μmol) at room temperature. After stirring for 48 h at the same temperature, to the mixture was added water (5 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic extract was washed with water (5 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/5) to give 1-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**29**) (49.1 mg, 96.2 μmol, 96%) as a colorless solid.

*Synthesis of 3-(butylamino)-1-(4-(2-methyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)propan-1-one (**30**)*



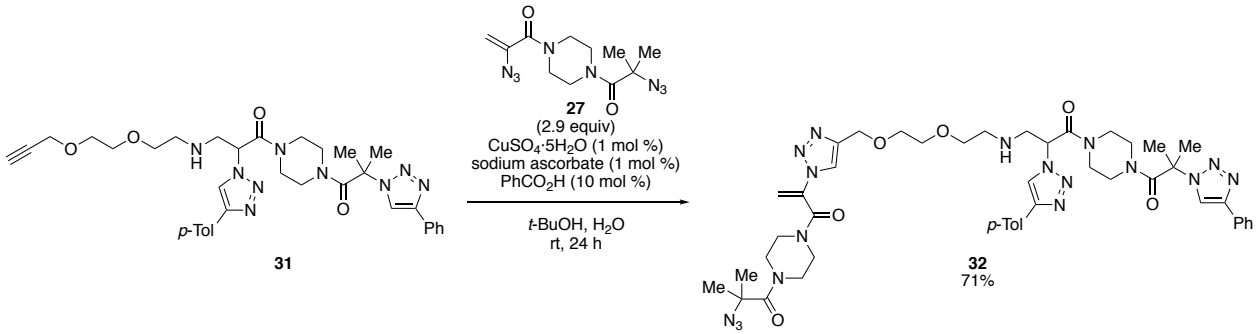
In a 5 mL screw-top V-vial® with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of 1-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**29**) (25.5 mg, 50.0 μmol) in THF (1.0 mL) was added *n*-butylamine (**15a**) (10.0 μL, 0.100 mmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH = 10/1) to give 3-(butylamino)-1-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propan-1-one (**30**) (28.3 mg, 48.5 μmol, 97%) as a colorless solid.

*Synthesis of 2-methyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)-1-(4-(3-((2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)amino)-2-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)propan-1-one (**31**)*



In a 5 mL screw-top V-vial® with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of 1-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**29**) (0.153 g, 0.300 mmol) in THF (5.0 mL) was added (2-(2-(propargyloxy)ethoxy)ethyl)amine (**15b**) (85.1 μL, 0.600 mmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 8 g, CH_2Cl_2/MeOH = 20/1 to 5/1) to give 2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1-(4-(3-((2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)amino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)propan-1-one (**31**) (0.170 g, 0.260 mmol, 87%) as a colorless oil.

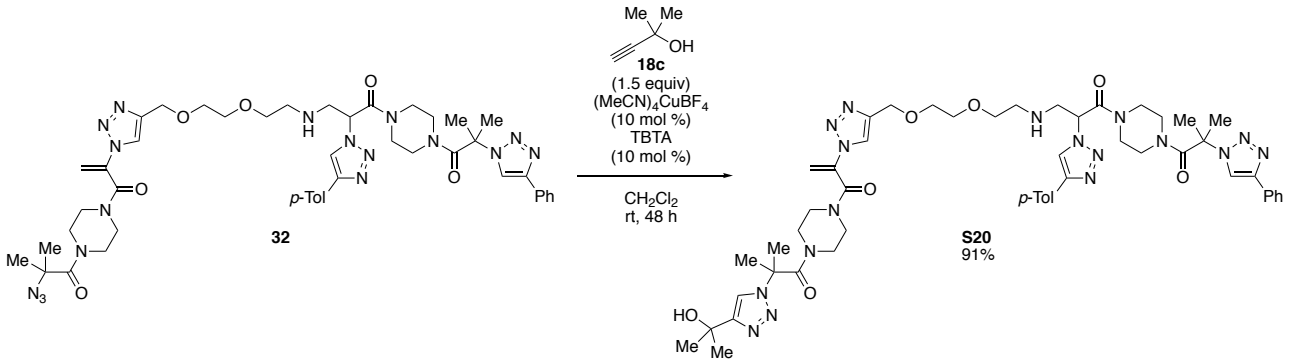
*Synthesis of tris(triazole) (**32**)*



To a solution of 2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1-(4-(3-((2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)amino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)propan-1-one (**31**) (0.170 g, 0.260 mmol) and 2-azido-1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)prop-2-en-1-one (**27**) (0.219 g, 0.750 mmol) in *tert*-butanol (0.17 mL) and water (0.33 mL) were added were added $CuSO_4 \cdot 5H_2O$ (0.70 mg, 2.5 μmol), sodium ascorbate (0.50 mg, 2.5 μmol), and benzoic acid (3.0 mg, 25 μmol) dissolved in *tert*-butanol (0.08 mL) and water (0.17 mL) at room temperature. After stirring for 24 h at the same temperature, to the mixture was added water (5 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic extract was washed with water (5 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 8 g, CH_2Cl_2/MeOH = 20/1 to 5/1) to give 1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**32**) (0.175 g, 0.185

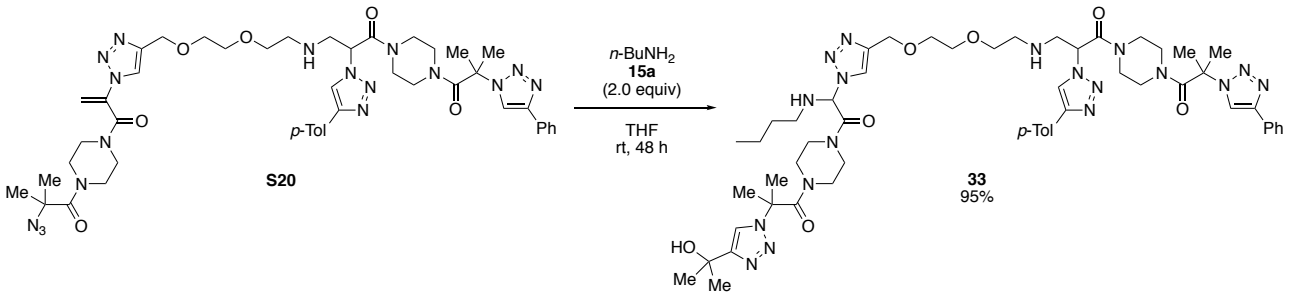
mmol, 71%) as a colorless solid.

*Synthesis of tetrakis(triazole) (**S20**)*



To a solution of 1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**32**) (56.7 mg, 59.9 μmol) in in CH_2Cl_2 (1.5 mL) were added 2-methylbut-3-yn-2-ol (**18c**) (8.8 μL, 90 μmol), $(MeCN)_4CuBF_4$ (1.9 mg, 6.0 μmol) and TBTA (3.2 mg, 6.0 μmol) at room temperature. After stirring for 48 h at the same temperature, to the mixture was added water (5 mL). The mixture was extracted with EtOAc (10 mL × 3). The combined organic extract was washed with water (5 mL) and dried with Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 6 g, CH_2Cl_2/MeOH = 20/1 to 4/1) to give 1-(4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**S20**) (56.0 mg, 54.4 μmol, 91%) as a colorless solid.

*Synthesis of tetrakis(triazole) (**33**)*



In a 0.3 mL screw-top V-vial® with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of 1-(4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**S20**) (41.2 mg, 40.0 μmol) in in THF (0.20 mL) was added *n*-butylamine (8.0 μL, 80 μmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH = 10/1) to give 3-(butylamino)-1-(4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propan-1-one (**33**) (42.0 mg, 38.1 μmol, 95%) as a colorless solid.

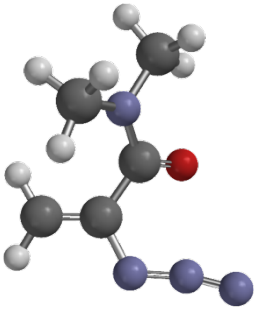
Computational Methods

The optimized structures of acrylamides **4**–**6** and methyl acrylate **7** were computed in Spartan '18 using density functional theory (B3LYP/6-31G(d)).[S5]

2-Azido-*N*,*N*-dimethylacrylamide 4

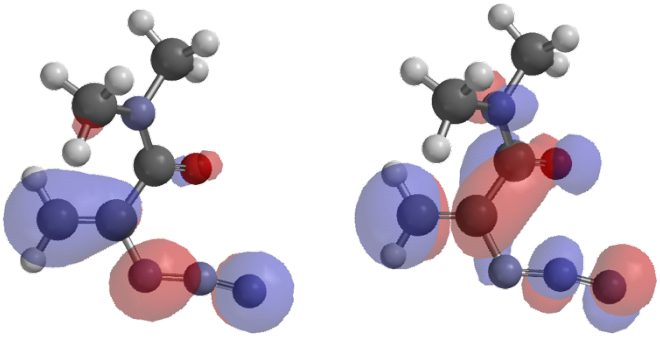
The optimized structure **4** was more stable than the other local minimums **4'**, **4''**, and **4'''**.

Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –489.493707 au)

HOMO (left, –6.35 eV) and LUMO (right, –1.02 eV)

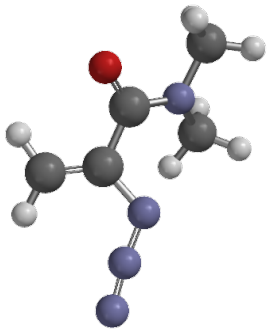


Cartesian Coordinates (Angstroms)

C	-0.799960	-2.032808	0.722045
H	-0.730216	-2.269227	-0.332373
H	-1.313496	-2.733921	1.371233
C	-0.230595	-0.924723	1.221450
C	0.647374	0.004354	0.409886
O	1.730300	0.337345	0.888228
N	0.231592	0.395990	-0.834848
C	1.164049	1.160045	-1.656859
H	2.164754	1.065604	-1.238653
H	0.885656	2.222476	-1.679784
H	1.147998	0.774278	-2.682861
C	-1.137711	0.354172	-1.332516
H	-1.209777	-0.271300	-2.231981
H	-1.461527	1.369282	-1.598035
H	-1.811185	-0.040798	-0.574599
N	-0.335942	-0.688639	2.607224
N	0.294065	0.243002	3.136974
N	0.764622	1.034869	3.805467

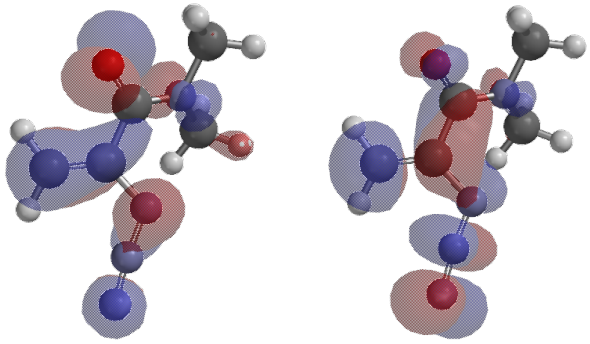
2-Azido-*N*,*N*-dimethylacrylamide 4'

Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –489.491770 au)

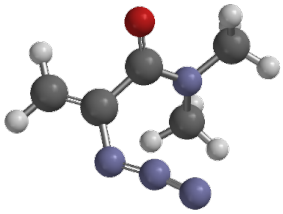
HOMO (left, –6.46 eV) and LUMO (right, –1.36 eV)



```
Cartesian Coordinates (Angstroms)
C       -0.318185     -0.385270      2.530053
H        0.087599      0.505976      2.991749
H       -0.882335     -1.073591      3.152214
C       -0.087739     -0.610559      1.230119
C        0.753916      0.365959      0.433819
O        1.719320      0.895066      0.977998
N        0.428869      0.600550     -0.876658
C        1.335535      1.432027     -1.658544
H        2.328249      1.394912     -1.212310
H        0.999835      2.478405     -1.681179
H        1.371995      1.055019     -2.686769
C       -0.874739      0.367690     -1.484554
H       -0.794421     -0.317581     -2.337509
H       -1.284919      1.321078     -1.844578
H       -1.573182     -0.055927     -0.766451
N       -0.505193     -1.763917      0.501695
N       -1.085295     -2.658877      1.131750
N       -1.619309     -3.550962      1.599156
```

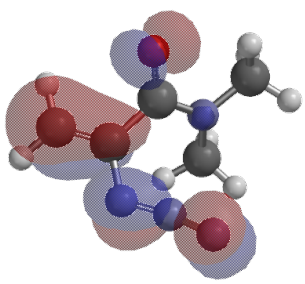
2-Azido-*N*,*N*-dimethylacrylamide 4''

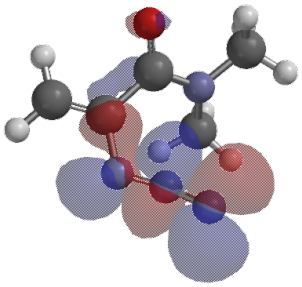
Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –489.491267 au)

HOMO (left, –6.49 eV) and LUMO (right, –1.15 eV)

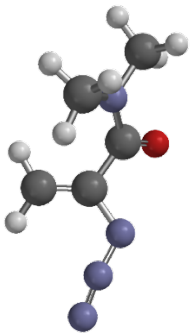




```
Cartesian Coordinates (Angstroms)
C      -0.495200    -0.529932     2.689504
H      -0.091215     0.351706     3.171585
H      -1.121069    -1.202050     3.266397
C      -0.204217    -0.780356     1.408113
C       0.711361     0.153381     0.635101
O       1.786422     0.488121     1.119555
N       0.296551     0.550890    -0.612694
C       1.213100     1.341833    -1.424467
H       2.222210     1.222393    -1.032700
H       0.945759     2.407271    -1.397082
H       1.170322     0.998208    -2.464326
C      -1.087469     0.534080    -1.070149
H      -1.180245    -0.024669    -2.009324
H      -1.432945     1.561595    -1.246858
H      -1.740102     0.083594    -0.322857
N      -0.749447    -1.947273     0.803247
N      -0.276282    -2.356117    -0.266530
N       0.032466    -2.852676    -1.246514
```

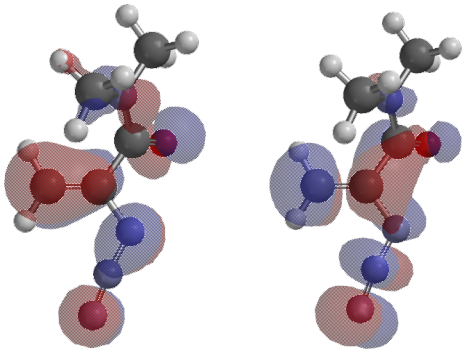
2-Azido-*N*,*N*-dimethylacrylamide 4'''

Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –489.490136 au)

HOMO (left, –6.59 eV) and LUMO (right, –1.24 eV)

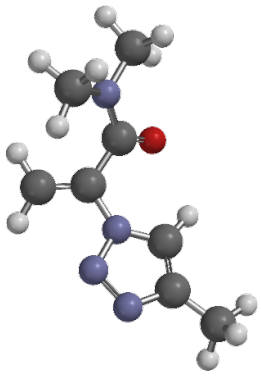


```
Cartesian Coordinates (Angstroms)
C      -0.661898    -1.850532     0.678474
H      -0.507643    -2.144190    -0.352815
H      -1.245268    -2.520980     1.303681
C      -0.113349    -0.721791     1.150746
C       0.853837     0.134764     0.358089
O       1.970781     0.332772     0.820366
N       0.459296     0.590055    -0.874685
C       1.442116     1.311678    -1.674191
H       2.440935     1.046116    -1.330860
H       1.311696     2.398538    -1.575876
H       1.322328     1.040721    -2.729250
C      -0.920272     0.718800    -1.324211
H      -1.055133     0.232128    -2.298762
H      -1.184050     1.779943    -1.434393
H      -1.601470     0.261644    -0.609002
N      -0.216944    -0.240447     2.480430
N      -0.863180    -0.922068     3.287680
N      -1.431782    -1.447153     4.124578
```

***N*,*N*-Dimethyl-(4-methyl-1*H*-1,2,3-triazol-1-yl)acrylamide 5**

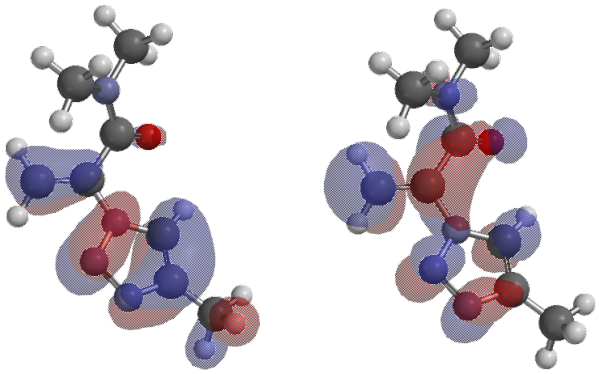
The optimized structure **5** was more stable than the other local minimums **5'**, **5''**, and **5'''**.

Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –606.254447 au)

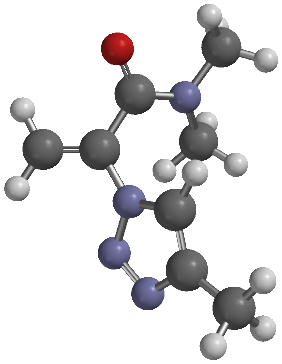
HOMO (left, –6.49 eV) and LUMO (right, –1.15 eV)



```
Cartesian Coordinates (Angstroms)
C      -1.525510    -0.168729     1.831278
H      -1.685781     0.692706     2.469044
H      -1.950341    -1.119065     2.132298
C      -0.817018    -0.053960     0.703705
C      -0.336152     1.268522     0.149579
N       0.420520     2.070874     0.958589
C       0.769630     3.401277     0.471499
H       0.112640     3.659429    -0.357419
H       1.811145     3.429730     0.123978
H       0.653281     4.129230     1.282565
C       1.134235     1.644413     2.156549
H       0.840278     2.256793     3.018540
H       2.215158     1.764684     2.005216
H       0.925946     0.599903     2.379572
O      -0.683185     1.602867    -0.983489
N      -0.561526    -1.187230    -0.112349
N      -0.478330    -2.426026     0.460322
N      -0.256725    -3.278088    -0.493829
C      -0.382628    -1.280682    -1.463350
H      -0.432637    -0.414641    -2.101494
C      -0.190761    -2.622498    -1.697022
C       0.055762    -3.347154    -2.982283
H      -0.679507    -4.146170    -3.126846
H       1.048568    -3.812016    -2.990088
H      -0.007063    -2.664171    -3.834565
```

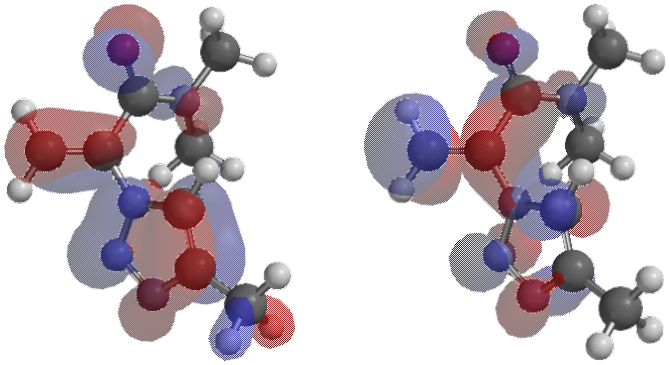
***N*,*N*-Dimethyl-(4-methyl-1*H*-1,2,3-triazol-1-yl)acrylamide 5'**

Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –606.252477 au)

HOMO (left, –6.77 eV) and LUMO (right, –1.19 eV)

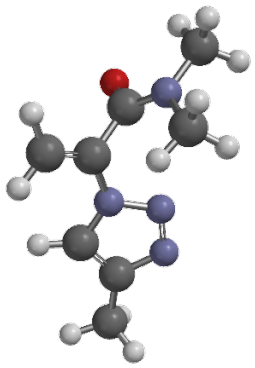


Cartesian Coordinates (Angstroms)

C	-0.047874	-0.016527	2.978365
H	0.797407	-0.192364	3.633281
H	-0.985799	0.314739	3.408631
C	0.091051	-0.193668	1.663020
C	1.392258	-0.699851	1.073834
N	1.899819	-0.020921	-0.004515
C	3.083226	-0.554392	-0.666054
H	3.236258	-1.581870	-0.338622
H	3.974849	0.035273	-0.413454
H	2.944202	-0.523156	-1.753492
C	1.497828	1.321346	-0.409729
H	1.032233	1.312853	-1.403383
H	2.383306	1.968170	-0.447316
H	0.795079	1.753753	0.301718
O	1.930113	-1.691594	1.556650
N	-0.986760	0.056435	0.769848
N	-1.860915	1.080985	0.985016
N	-2.738026	1.049244	0.025958
C	-1.331116	-0.623691	-0.361074
H	-0.779169	-1.483044	-0.709164
C	-2.457722	0.014161	-0.828354
C	-3.299879	-0.276750	-2.030023
H	-3.316918	0.578401	-2.715154
H	-4.336328	-0.482927	-1.741046
H	-2.917124	-1.144605	-2.574940

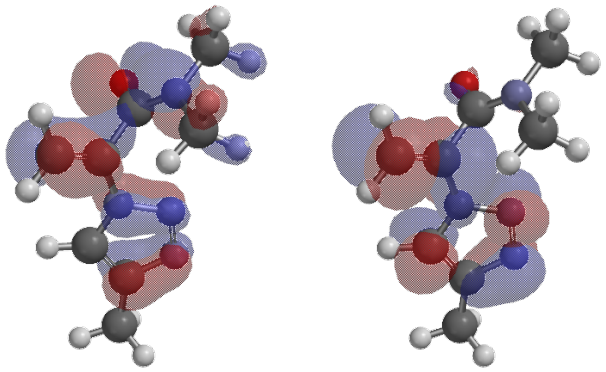
***N*,*N*-Dimethyl-(4-methyl-1*H*-1,2,3-triazol-1-yl)acrylamide 5''**

Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –606.251367 au)

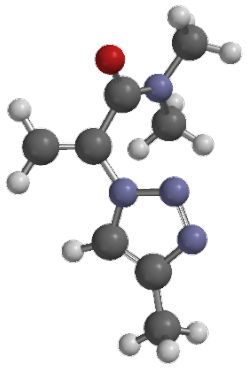
HOMO (left, –6.48 eV) and LUMO (right, –1.04 eV)



```
Cartesian Coordinates (Angstroms)
C      -1.814613     0.101896     1.536918
H      -2.229732     0.965756     2.042778
H      -2.128377    -0.877992     1.882616
C      -0.967400     0.266318     0.518136
C      -0.607527     1.638521    -0.040390
N       0.446750     2.292522     0.527673
C       0.826528     3.590568    -0.014805
H       0.012335     3.959194    -0.637256
H       1.735787     3.505534    -0.624996
H       1.019049     4.292154     0.805139
C       1.413877     1.669003     1.417716
H       1.643122     2.349850     2.246459
H       2.344131     1.436057     0.884010
H       1.011302     0.744080     1.830029
O      -1.312999     2.105216    -0.926818
N      -0.447681    -0.819668    -0.223836
N       0.751440    -0.689111    -0.857747
N       1.019657    -1.825427    -1.425536
C      -0.939544    -2.078988    -0.406555
H      -1.896506    -2.390361    -0.019201
C       0.004024    -2.715476    -1.178268
C       0.022042    -4.107355    -1.724829
H       0.935941    -4.631003    -1.424164
H      -0.004307    -4.099541    -2.820436
H      -0.837300    -4.681748    -1.366637
```

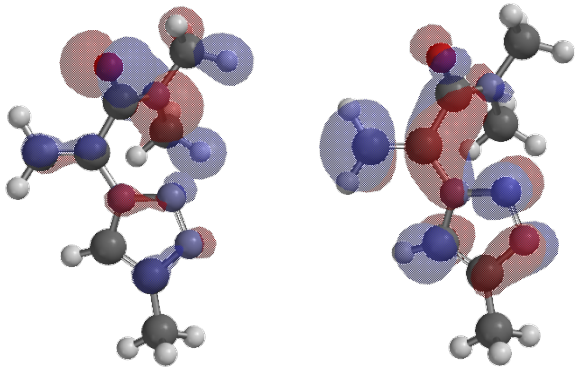
***N*,*N*-Dimethyl-(4-methyl-1*H*-1,2,3-triazol-1-yl)acrylamide 5'''**

Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –606.250956 au)

HOMO (left, –6.52 eV) and LUMO (right, –1.24 eV)

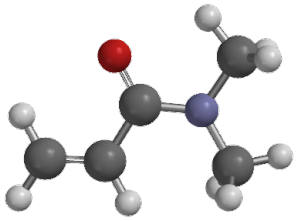


```
Cartesian Coordinates (Angstroms)
C      -0.002930     0.284205     2.659064
H       0.076010     1.171000     3.275856
H      -0.325368    -0.636417     3.133566
C       0.323438     0.355789     1.365914
C       0.875601     1.653198     0.791618
N       0.272821     2.175635    -0.317847
C       0.889398     3.322931    -0.970680
H       1.764174     3.618924    -0.394108
H       0.182090     4.160539    -1.019535
H       1.191684     3.059987    -1.992731
C      -0.903020     1.627885    -0.975196
H      -0.633960     1.051676    -1.869170
H      -1.558915     2.454845    -1.271516
H      -1.467055     0.985748    -0.297320
O       1.804959     2.199613     1.376528
N       0.247703    -0.770707     0.507696
N       1.011923    -0.827403    -0.620003
N       0.780693    -1.969824    -1.193103
C      -0.480246    -1.919298     0.634970
H      -1.172905    -2.084791     1.444785
C      -0.132567    -2.681149    -0.455565
C      -0.597509    -4.040960    -0.869229
H       0.216895    -4.771838    -0.804364
H      -0.946087    -4.032646    -1.907395
H      -1.416828    -4.386943    -0.232233
```

***N*,*N*-dimethylacrylamide 6**

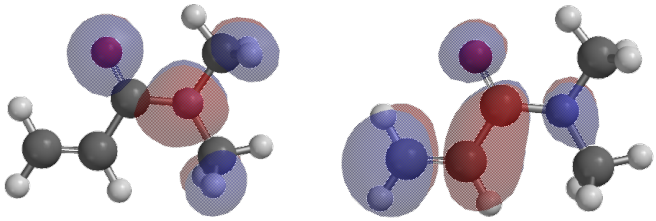
The optimized structure **6** was more stable than the other local minimum **6'**.

Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –325.907209 au)

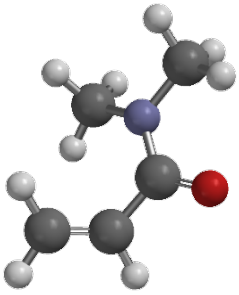
HOMO (left, –6.34 eV) and LUMO (right, –0.83 eV)



```
Cartesian Coordinates (Angstroms)
C       0.272771    -1.451007     2.481185
H       1.059431    -0.903473     2.991847
H      -0.162949    -2.310816     2.981785
C      -0.133184    -1.063400     1.270024
H      -0.915619    -1.612679     0.755962
C       0.503155     0.124338     0.614911
N       0.014895     0.494483    -0.618389
O       1.421881     0.733051     1.162676
C       0.646470     1.607055    -1.315704
H       1.428930     2.008325    -0.673562
H      -0.087043     2.394060    -1.532707
H       1.088942     1.272965    -2.263635
C      -1.065862    -0.196979    -1.313086
H      -0.779031    -1.205594    -1.639059
H      -1.323738     0.379420    -2.204393
H      -1.969048    -0.269750    -0.697853
```

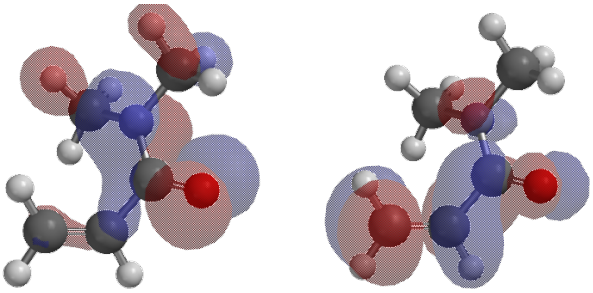
***N*,*N*-dimethylacrylamide 6'**

Optimized structure (C: grey; H: white; O: red; N: red)



(total energy: –325.904192 au)

HOMO (left, –6.39 eV) and LUMO (right, –0.55 eV)

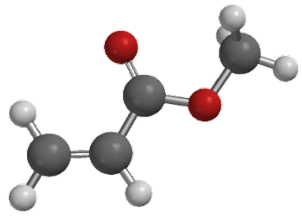


```
Cartesian Coordinates (Angstroms)
C      -1.067725    -1.534642     1.546483
H      -1.855494    -0.866393     1.207734
H      -1.385798    -2.418450     2.093186
C       0.225951    -1.276383     1.338535
H       0.989668    -1.935383     1.745005
C       0.789427    -0.004558     0.775617
N       0.255817     0.524649    -0.376886
O       1.691874     0.550411     1.400103
C       0.732601     1.826574    -0.822345
H       1.287827     2.291779    -0.009288
H      -0.119396     2.457922    -1.103428
H       1.392746     1.728251    -1.695719
C      -0.573936    -0.196178    -1.330038
H      -0.685155    -1.236685    -1.030028
H      -0.106469    -0.167239    -2.323706
H      -1.571937     0.256326    -1.415227
```

Methyl acrylate 7

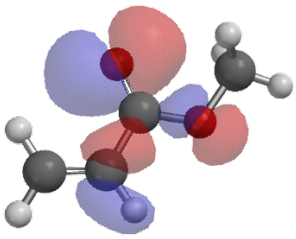
The optimized structure **7** was more stable than the other local minimums **7'**, **7''**, and **7'''**.

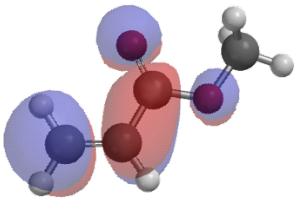
Optimized structure (C: grey; H: white; O: red)



(total energy: –306.467730 au)

HOMO (left, –7.42 eV) and LUMO (right, –1.20 eV)

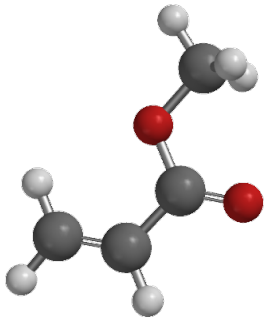




```
Cartesian Coordinates (Angstroms)
C       -0.072224     -1.252814      2.173877
H       -0.059430     -0.349757      2.777694
H       -0.107107     -2.207730      2.689511
C       -0.045322     -1.174246      0.841863
H       -0.056286     -2.054677      0.206201
C        0.004330      0.144280      0.160610
O        0.035062      1.228234      0.707890
O        0.011188     -0.016026     -1.184480
C        0.063003      1.200131     -1.944765
H       -0.799602      1.832278     -1.717297
H        0.049415      0.893104     -2.991057
H        0.976973      1.757224     -1.720046
```

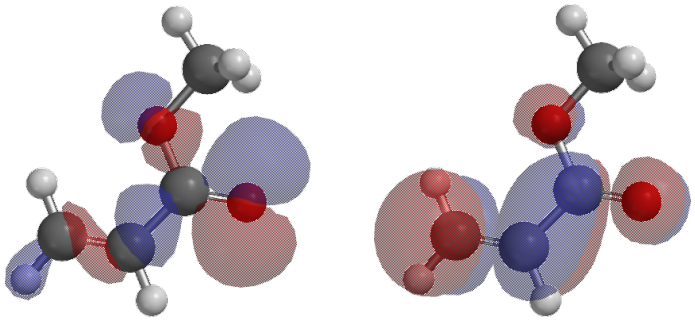
Methyl acrylate 7'

Optimized structure (C: grey; H: white; O: red)



(total energy: –306.466603 au)

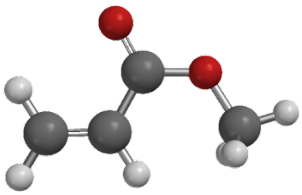
HOMO (left, –7.40 eV) and LUMO (right, –1.23 eV)



```
Cartesian Coordinates (Angstroms)
C       -0.007310    -2.117538     0.672315
H       -0.036259    -2.183514    -0.410610
H       -0.004233    -3.050769     1.228492
C        0.023014    -0.938670     1.298859
H        0.051337    -0.865376     2.382152
C        0.020199     0.380770     0.620627
O        0.042157     1.440577     1.215071
O       -0.009757     0.283644    -0.729254
C       -0.018073     1.535295    -1.430996
H       -0.894871     2.127314    -1.154432
H       -0.048948     1.276877    -2.490052
H        0.882744     2.111391    -1.202173
```

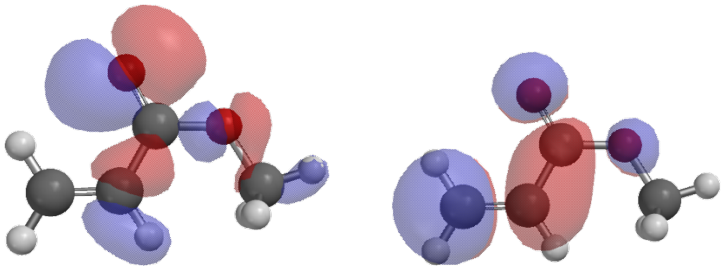
Methyl acrylate 7''

Optimized structure (C: grey; H: white; O: red)



(total energy: –306.453617 au)

HOMO (left, –7.32 eV) and LUMO (right, –1.41 eV)

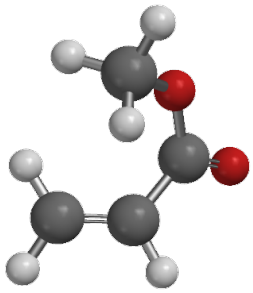


Cartesian Coordinates (Angstroms)

C	0.001229	-0.310964	2.201194
H	-0.007484	0.618232	2.763469
H	0.008300	-1.244074	2.756764
C	0.003052	-0.289863	0.865821
H	0.011678	-1.216091	0.301303
C	-0.006666	1.019547	0.146639
O	-0.014713	2.087336	0.716462
O	-0.006335	1.015266	-1.214390
C	0.001355	-0.197041	-1.968860
H	0.902207	-0.791413	-1.777391
H	-0.001735	0.112763	-3.015318
H	-0.890888	-0.803698	-1.775694

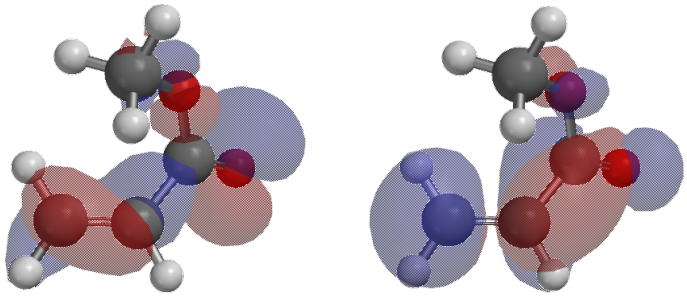
Methyl acrylate 7'''

Optimized structure (C: grey; H: white; O: red)



(total energy: –306.448232 au)

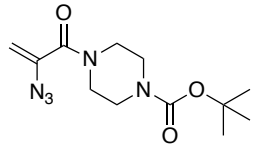
HOMO (left, –7.24 eV) and LUMO (right, –1.16 eV)



```
Cartesian Coordinates (Angstroms)
C       0.515240    -1.201454     1.034993
H       1.223907    -1.283363     0.216047
H       0.433641    -2.065572     1.688541
C      -0.195487    -0.095119     1.268485
H      -0.846182    -0.034491     2.137265
C      -0.047488     1.216098     0.564687
O      -0.036073     2.247072     1.197562
O       0.108563     1.272378    -0.783314
C      -0.225608     0.183331    -1.650595
H       0.658004    -0.426496    -1.867931
H      -0.579848     0.637926    -2.578477
H      -1.008669    -0.450312    -1.227262
```

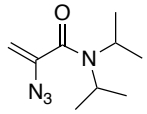
Characterization Data of New Compounds

tert-Butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**12**)



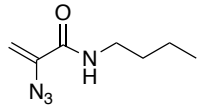
Colorless solid; Mp 111–112 ºC; TLC R_f 0.50 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9H), 3.46–3.47 (m, 4H), 3.54–3.62 (br, 4H), 5.08 (d, 1H, *J* = 2.2 Hz), 5.11 (d, 1H, *J* = 2.2 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 28.3 (3C), 42.0 (br, 2C), 47.0 (br, 2C), 80.5 (1C), 104.1 (1C), 139.6 (1C), 154.4 (1C), 163.5 (1C); IR (KBr, cm^{-1}) 772, 1169, 1238, 1285, 1414, 1612, 1632, 1641, 1692, 2104; HRMS (ESI$^+$) *m/z* 304.1371 ([M + Na]$^+$, $C_{12}H_{19}N_5NaO_3^+$ requires 304.1380).

2-Azido-*N*,*N*-diisopropylacrylamide (**S1**)



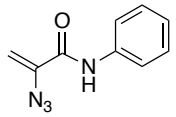
Pale yellow oil; TLC R_f 0.63 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03–1.59 (br, 12H), 3.35–3.62 (br, 1H), 4.02–4.27 (br, 1H), 4.86 (d, 1H, *J* = 1.9 Hz), 4.89 (d, 1H, *J* = 1.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 20.5 (br, 2C+2C, two signals overlapped), 46.1 (br, 1C), 50.9 (br, 1C), 100.6 (1C), 141.7 (1C), 163.9 (1C); IR (KBr, cm^{-1}) 772, 1040, 1260, 1339, 1445, 1636, 2102, 2970; HRMS (ESI$^+$) *m/z* 219.1218 ([M + Na]$^+$, $C_9H_{16}N_4NaO^+$ requires 219.1216).

2-Azido-*N*-butylacrylamide (**S2**)



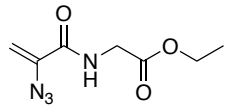
Pale yellow oil; TLC R_f 0.56 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, 3H, *J* = 7.4 Hz), 1.36 (tq, 2H, *J* = 7.4, 7.4 Hz), 1.44–1.58 (m, 2H), 3.31 (dt, 2H, *J* = 6.7, 6.7 Hz), 5.17 (d, 1H, *J* = 1.0 Hz), 6.16 (d, 1H, *J* = 1.0 Hz), 6.29–6.45 (br, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.7 (1C), 20.0 (1C), 31.4 (1C), 39.4 (1C), 106.3 (1C), 138.6 (1C), 160.5 (1C); IR (KBr, cm^{-1}) 883, 1246, 1314, 1533, 1655, 2120, 2959, 3323; HRMS (ESI) *m/z* 191.0904 ([M + Na]$^+$, $C_7H_{12}N_4NaO^+$ requires 191.0903).

2-Azido-*N*-phenylacrylamide (**S3**)



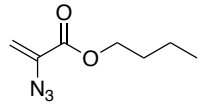
Pale yellow solid; Mp 79–80 ºC; TLC R_f 0.65 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.29 (d, 1H, *J* = 2.3 Hz), 6.30 (d, 1H, *J* = 2.3 Hz), 7.16 (t, 1H, *J* = 7.7 Hz), 7.35 (dd, 2H, *J* = 7.7, 7.7 Hz), 7.58 (d, 2H, *J* = 7.7 Hz), 8.10 (br s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 107.4 (1C), 120.0 (2C), 124.9 (1C), 129.1 (2C), 136.9 (1C), 138.5 (1C), 158.3 (1C); IR (KBr, cm^{-1}) 754, 889, 1288, 1445, 1531, 1597, 1676, 2126, 3310; HRMS (ESI) *m/z* 211.0589 ([M + Na]$^+$, $C_9H_8N_4NaO^+$ requires 211.0590).

Ethyl (2-azidoacryloyl)glycinate (**S4**)



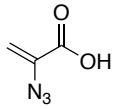
Pale yellow oil; TLC R_f 0.43 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, 3H, *J* = 7.2 Hz), 4.08 (d, 2H, *J* = 5.3 Hz), 4.24 (q, 2H, *J* = 7.2 Hz), 5.22 (d, 1H, *J* = 2.2 Hz), 6.17 (d, 1H, *J* = 2.2 Hz), 6.80–6.94 (br, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.1 (1C), 41.5 (1C), 61.7 (1C), 107.0 (1C), 138.1 (1C), 160.7 (1C), 169.3 (1C); IR (KBr, cm^{-1}) 1022, 1206, 1261, 1300, 1522, 1612, 1674, 1748, 2124; HRMS (ESI$^+$) *m/z* 221.0646 ([M + Na]$^+$, $C_7H_{10}N_4NaO_3^+$ requires 221.0645).

Butyl 2-azidoacrylate (**S5**)



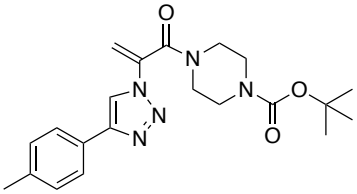
Pale yellow oil; TLC R_f 0.33 (*n*-hexane/CH_2Cl_2 = 3/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, 3H, *J* = 7.4 Hz), 1.42 (tq, 2H, *J* = 7.6 Hz), 1.64–1.73 (m, 2H), 4.25 (t, 2H, *J* = 6.7 Hz), 5.34 (d, 1H, *J* = 1.4 Hz), 5.83 (d, 1H, *J* = 1.3 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.6 (1C), 19.1 (1C), 30.4 (1C), 66.0 (1C), 110.7 (1C), 136.2 (1C), 162.1 (1C); IR (KBr, cm^{-1}) 772, 1148, 1252, 1339, 1616, 1724, 2118, 2961; HRMS (ESI^+) *m/z* 192.0744 ($[M + Na]^+$, $C_7H_{11}N_3NaO_2^+$ requires 192.0743).

2-Azidoacrylic acid (**S6**)



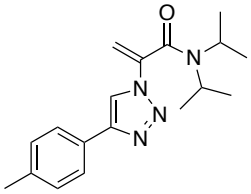
Yellow solid; Mp 67–68 ºC; TLC R_f 0.15 (tailing) (CH_2Cl_2/MeOH = 5/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.49 (s, 1H), 6.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 113.1 (1C), 135.5 (1C), 165.9 (1C); IR (KBr, cm^{-1}) 772, 1148, 1256, 1612, 1713, 1719, 2124, 2916; HRMS (ESI^+) *m/z* 136.0118 ($[M + Na]^+$, $C_3H_3N_3NaO_2^+$ requires 136.0117).

tert-Butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**)



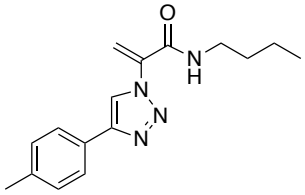
Colorless solid; Mp 159–160 ºC; TLC R_f 0.30 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46 (s, 9H), 2.39 (s, 3H), 3.38–3.58 (br, 6H), 3.66–3.80 (br, 2H), 5.41 (d, 1H, *J* = 2.0 Hz), 6.00 (d, 1H, *J* = 2.0 Hz), 7.25 (d, 2H, *J* = 8.2 Hz), 7.74 (d, 2H, *J* = 8.2 Hz), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 28.3 (3C), 42.1 (br, 2C), 47.0 (br, 2H), 80.6 (1C), 108.4 (1C), 117.4 (1C), 125.8 (2C), 126.8 (1C), 129.6 (2C), 136.7 (1C), 138.6 (1C), 148.3 (1C), 154.4 (1C), 162.9 (1C); IR (KBr, cm^{-1}) 627, 772, 928, 1219, 1422, 1463, 3019, 3429; HRMS (ESI) *m/z* 420.1997 ($[M + Na]^+$, $C_{21}H_{27}N_5NaO_3^+$ requires 420.2006).

N,*N*-Diisopropyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**19b**)



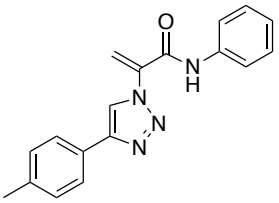
Colorless solid; Mp 131–133 ºC; TLC R_f 0.45 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00–1.24 (br, 6H), 1.38–1.61 (br, 6H), 2.39 (s, 3H), 3.42–3.59 (br, 1H), 4.05–4.20 (br, 1H), 5.28 (d, 1H, *J* = 2.0 Hz), 5.87 (d, 1H, *J* = 2.0 Hz), 7.25 (d, 2H, *J* = 8.2 Hz), 7.74 (d, 2H, *J* = 8.2 Hz), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 20.1 (br, 2C), 20.5 (br, 2C), 21.3 (1C), 46.2 (br, 1C), 51.4 (br, 1C), 105.4 (1C), 117.3 (1C), 125.8 (2C), 127.0 (1C), 129.6 (2C), 138.5 (1C), 138.8 (1C), 148.0 (1C), 163.2 (1C); IR (KBr, cm^{-1}) 773, 822, 1016, 1230, 1331, 1437, 1636, 2972; HRMS (ESI) *m/z* 335.1843 ($[M + Na]^+$, $C_{18}H_{24}N_4NaO^+$ requires 335.1842).

N-Butyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**19c**)



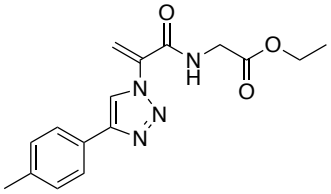
Colorless solid; Mp 111–113 ºC; TLC R_f 0.45 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (t, 3H, *J* = 7.4 Hz), 1.38 (tq, 2H, *J* = 7.4, 7.4 Hz), 1.52–1.61 (m, 2H), 2.40 (s, 3H), 3.41 (dt, 2H, *J* = 5.8, 7.4 Hz), 5.94 (d, 1H, *J* = 1.0 Hz), 6.41 (d, 1H, *J* = 1.0 Hz), 7.26 (d, 2H, *J* = 8.0 Hz), 7.31–7.42 (br, 1H), 7.75 (d, 2H, *J* = 8.0 Hz), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.7 (1C), 20.1 (1C), 21.3 (1C), 31.2 (1C), 40.0 (1C), 117.3 (1C), 120.2 (1C), 125.8 (2C), 126.7 (1C), 129.7 (2C), 137.6 (1C), 138.7 (1C), 147.9 (1C), 160.5 (1C); IR (KBr, cm^{-1}) 507, 810, 934, 1217, 1541, 1618, 2959, 3325; HRMS (ESI) *m/z* 307.1521 ($[M + Na]^+$, $C_{16}H_{20}N_4NaO^+$ requires 307.1529).

N-Phenyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**19d**)



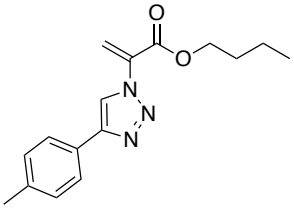
Colorless solid; Mp 157–159 ºC; TLC R_f 0.50 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.41 (s, 3H), 6.05 (s, 1H), 6.56 (s, 1H), 7.18 (t, 1H, *J* = 7.7 Hz), 7.27 (d, 2H, *J* = 8.2 Hz), 7.37 (dd, 2H, *J* = 7.7, 7.7 Hz), 7.63 (d, 2H, *J* = 7.7 Hz), 7.76 (d, 2H, *J* = 8.2 Hz), 8.10 (s, 1H), 9.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 118.4 (1C), 120.3 (1C), 120.6 (2C), 125.3 (1C), 125.8 (2C), 126.5 (1C), 129.1 (2C), 129.7 (2C), 136.9 (1C), 137.7 (1C), 138.9 (1C), 148.2 (1C), 158.1 (1C); IR (KBr, cm^{-1}) 689, 756, 814, 928, 1250, 1533, 1624, 1665, 3314; HRMS (ESI) *m/z* 327.1218 ([M + Na]$^+$, $C_{18}H_{16}N_4NaO^+$ requires 327.1216).

Ethyl (2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)glycinate (**19e**)



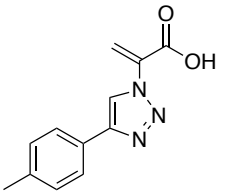
Colorless solid; Mp 95–96 ºC; TLC R_f 0.25 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, 3H, *J* = 7.1 Hz), 2.40 (s, 3H), 4.18 (d, 2H, *J* = 5.4 Hz), 4.24 (q, 2H, *J* = 7.2 Hz), 6.06 (d, 1H, *J* = 1.4 Hz), 6.39 (s, 1H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.71–7.79 (m, 3H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.1 (1C), 21.3 (1C), 41.9 (1C), 61.8 (1C), 117.5 (1C), 120.1 (1C), 125.8 (2C), 126.7 (1C), 129.6 (2C), 136.9 (1C), 138.7 (1C), 148.1 (1C), 161.0 (1C), 169.0 (1C); IR (KBr, cm^{-1}) 671, 772, 1028, 1219, 1528, 1630, 1676, 1744; HRMS (ESI$^+$) *m/z* 315.1454 ([M + H]$^+$ $C_{16}H_{19}N_4O_3^+$ requires 315.1452).

Butyl 2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylate (**19f**)



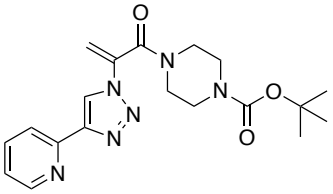
Colorless solid; Mp 61–62 ºC; TLC R_f 0.38 (*n*-hexane/EtOAc = 20/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, 3H, *J* = 7.5 Hz), 1.45 (tq, 2H, *J* = 7.5, 7.5 Hz), 1.70–1.78 (m, 2H), 2.39 (s, 3H), 4.34 (t, 2H, *J* = 6.7 Hz), 6.49 (d, 1H, *J* = 0.7 Hz), 6.57 (d, 1H, *J* = 0.7 Hz), 7.25 (d, 2H, *J* = 8.3 Hz), 7.76 (d, 2H, *J* = 8.3 Hz), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.6 (1C), 19.1 (1C), 21.3 (1C), 30.4 (1C), 66.4 (1C), 120.2 (1C), 121.3 (1C), 125.7 (2C), 127.3 (1C), 129.5 (2C), 133.9 (1C), 138.2 (1C), 147.7 (1C), 161.5 (1C); IR (KBr, cm^{-1}) 772, 930, 1028, 1219, 1420, 1730, 2399, 3019; HRMS (ESI$^+$) *m/z* 308.1372 ([M + Na]$^+$ $C_{16}H_{19}N_3NaO_2^+$ requires 308.1369).

2-(4-(*p*-Tolyl)-1*H*-1,2,3-triazol-1-yl)acrylic acid (**19g**)



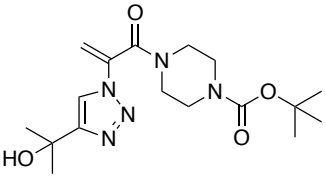
Colorless solid; TLC R_f 0.15 (tailing) (CH_2Cl_2/MeOH = 5/1); ^{1}H NMR (MeOD, 500 MHz) δ 2.39 (s, 3H), 6.47 (s, 1H), 6.59 (s, 1H), 7.29 (d, 2H, *J* = 8.1 Hz), 7.76 (d, 2H, *J* = 8.1 Hz), 8.57 (s, 1H); ^{13}C NMR (MeOD, 126 MHz) δ 19.9 (1C), 121.5 (1C), 121.5 (1C), 125.3 (2C), 127.1 (1C), 129.2 (2C), 138.2 (1C), 147.3 (1C), 162.7 (1C), 174.7 (1C); IR (KBr, cm^{-1}) 515, 806, 1034, 1194, 1433, 1717, 2922, 3161; HRMS (ESI$^+$) *m/z* 230.0920 ([M + H]$^+$, $C_{12}H_{12}N_3O_2^+$ requires 230.0924).

tert-Butyl 4-(2-(4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19h**)



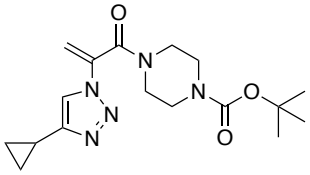
Colorless solid; Mp 183–185 ºC; TLC R_f 0.26 (*n*-hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46 (s, 9H), 3.35–3.58 (br, 6H), 6.76–6.79 (br, 2H), 5.45 (d, 1H, *J* = 2.2 Hz), 6.02 (d, 1H, *J* = 2.2 Hz), 7.24–7.29 (m, 1H), 7.81 (ddd, 1H, *J* = 7.8, 7.8, 1.0 Hz), 8.19 (dd, 1H, *J* = 7.8, 1.0 Hz), 8.45 (s, 1H), 8.57–8.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 28.3 (3C), 42.1 (br, 2C), 46.9 (br, 2C), 80.5 (1C), 108.4 (1C), 120.2 (1C), 120.5 (1C), 123.3 (1C), 136.9 (1C), 137.0 (1C), 148.8 (1C), 149.4 (1C), 149.6 (1C), 154.4 (1C), 162.5 (1C); IR (KBr, cm^{-1}) 772, 928, 1018, 1217, 1422, 1522, 1643, 3019, 3460; HRMS (ESI^+) *m/z* 407.1802 ($[M + Na]^+$ $C_{19}H_{24}N_6NaO_3^+$ requires 407.1802).

tert-Butyl 4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19i**)



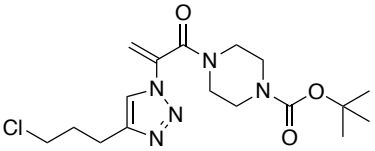
Colorless solid; Mp 45–46 ºC; TLC R_f 0.14 (*n*-hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (s, 9H), 1.65 (s, 6H), 2.42–2.50 (br, 1H), 3.39–3.59 (br, 6H), 3.65–3.77 (br, 2H), 5.36 (d, 1H, *J* = 2.1 Hz), 5.92 (d, 1H, *J* = 2.1 Hz), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 28.3 (3C), 30.4 (2C), 42.1 (br, 2C), 47.1 (br, 2C), 68.6 (1C), 80.6 (1C), 108.1 (1C), 117.9 (1C), 136.8 (1C), 154.4 (1C), 156.1 (1C), 162.9 (1C); IR (KBr, cm^{-1}) 756, 1128, 1170, 1238, 1263, 1366, 1420, 1636, 1684, 2978; HRMS (ESI^+) *m/z* 388.1964 ($[M + Na]^+$ $C_{17}H_{27}N_5NaO_4^+$ requires 388.1955).

tert-Butyl 4-(2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19j**)



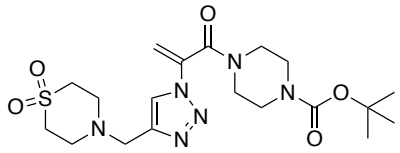
Colorless solid; Mp 114–116 ºC; TLC R_f 0.39 (*n*-hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85–0.91 (m, 2H), 0.95–1.03 (m, 2H), 1.46 (s, 9H), 1.92–1.99 (m, 1H), 3.32–3.53 (br, 6H), 3.64–3.75 (br, 2H), 5.32 (d, 1H, *J* = 2.0 Hz), 5.85 (d, 1H, *J* = 2.0 Hz), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 6.5 (1C), 7.9 (2C), 28.3 (3C), 42.0 (br, 2C), 46.9 (br, 2C), 80.5 (1C), 107.5 (1C), 118.0 (1C), 136.9 (1C), 150.8 (1C), 154.4 (1C), 162.9 (1C); IR (KBr, cm^{-1}) 772, 1020, 1169, 1234, 1420, 1647, 1697, 2978, 3003; HRMS (ESI^+) *m/z* 370.1844 ($[M + Na]^+$ $C_{17}H_{25}N_5NaO_3^+$ requires 370.1850).

tert-Butyl 4-(2-(4-(3-chloropropyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19k**)



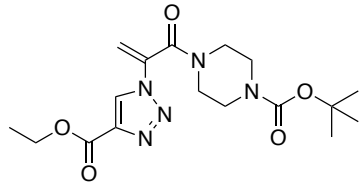
Colorless solid; Mp 96–98 ºC; TLC R_f 0.39 (*n*-hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (s, 9H), 2.19 (tt, 2H, *J* = 7.0, 7.0 Hz), 2.93 (t, 2H, *J* = 7.0 Hz), 3.35–3.56 (br, 6H), 3.60 (t, 2H, *J* = 7.0 Hz), 3.66–3.79 (br, 2H), 5.36 (d, 1H, *J* = 2.0 Hz), 5.91 (d, 1H, *J* = 2.0 Hz), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 22.5 (1C), 28.3 (3C), 31.5 (1C), 42.0 (br, 2C), 44.0 (1C), 47.0 (br, 2C), 80.6 (1C), 107.9 (br, 1C), 119.6 (1C), 136.7 (1C), 147.0 (1C), 154.4 (1C), 162.9 (1C); IR (KBr, cm^{-1}) 465, 496, 621, 671, 772, 1219, 1628, 3420; HRMS (ESI^+) *m/z* 406.1612 ($[M + Na]^+$ $C_{17}H_{26}ClN_5NaO_3^+$ requires 406.1616).

tert-Butyl 4-(2-(4-((1,1-dioxidothiomorpholino)methyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19l**)



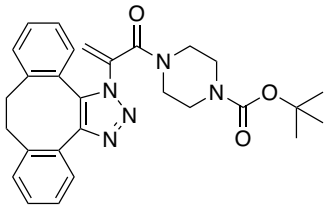
Colorless solid; Mp 153–155 ºC; TLC R_f 0.30 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (s, 9H), 3.07 (s, 8H), 3.39–3.60 (br, 6H), 3.65–3.78 (br, 2H), 3.85 (s, 2H), 5.40 (d, 1H, J = 2.2 Hz), 6.00 (d, 1H, J = 2.2 Hz), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 28.5 (3C), 42.2 (br, 2C), 47.3 (br, 2C), 50.7 (2C), 51.5 (2C), 52.0 (1C), 80.8 (1C), 109.1 (1C), 121.7 (1C), 136.4 (1C), 144.2 (1C), 154.5 (1C), 162.9 (1C); IR (KBr, cm^{-1}) 760, 1125, 1169, 1263, 1420, 1636, 1686, 3462, 3566; HRMS (ESI$^+$) *m/z* 477.1890 ([M + Na]$^+$ $C_{19}H_{30}N_6NaO_5S^+$ requires 477.1891).

tert-Butyl 4-(2-(4-(ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19m**)



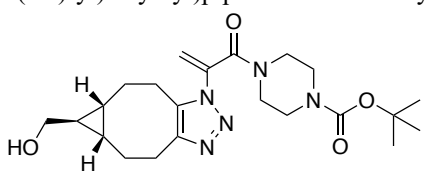
Colorless solid; Mp 150–151 ºC; TLC R_f 0.31 (*n*-hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.42 (t, 3H, J = 8.2 Hz), 1.47 (s, 9H), 3.35–3.78 (br, 8H), 4.43 (d, 2H, J = 8.2 Hz), 5.51 (d, 1H, J = 1.6 Hz), 6.17 (d, 1H, J = 1.6 Hz), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.3 (1C), 28.3 (3C), 42.2 (br, 2C), 47.2 (br, 2C), 61.6 (1C), 80.7 (1C), 110.9 (1C), 126.3 (1C), 135.7 (1C), 140.5 (1C), 154.3 (1C), 160.2 (1C), 162.3 (1C); IR (KBr, cm^{-1}) 772, 1034, 1171, 1219, 1420, 1655, 1694, 1726; HRMS (ESI$^+$) *m/z* 402.1748 ([M + Na]$^+$ $C_{17}H_{25}N_5NaO_5^+$ requires 402.1748).

tert-Butyl 4-(2-(8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19n**)



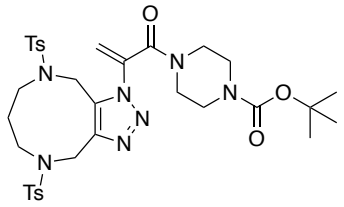
Colorless solid; Mp 212–213 ºC; TLC R_f 0.41 (*n*-hexane/EtOAc = 1/2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46 (s, 9H), 2.93–3.03 (br, 1H), 3.03–3.33 (br, 5H), 3.36–3.61 (br, 6H), 5.58 (s, 1H), 5.89 (d, 1H, J = 1.6 Hz), 7.15–7.27 (m, 5H), 7.29–7.32 (m, 2H), 7.51–7.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 28.3 (3C), 33.7 (1C), 35.6 (1C), 42.0 (br, 2C), 47.0 (br, 2C), 80.5 (1C), 115.8 (br, 1C), 125.7 (1C), 126.2 (2C), 128.5 (1C), 129.3 (1C), 129.8 (1C), 130.1 (1C), 130.2 (1C), 130.6 (1C), 131.3 (1C), 134.1 (1C), 136.1 (1C), 138.2 (1C), 140.8 (1C), 146.5 (1C), 154.4 (1C), 163.2 (1C); IR (KBr, cm^{-1}) 768, 1015, 1169, 1252, 1366, 1420, 1632, 1694; HRMS (ESI$^+$) *m/z* 508.2316 ([M + Na]$^+$ $C_{28}H_{31}N_5NaO_3^+$ requires 508.2319).

tert-Butyl 4-(2-((5a*S*,6*S*,6a*R*)-6-(hydroxymethyl)-5,5a,6,6a,7,8-hexahydrocyclopropa[5,6]cycloocta[1,2-*d*][1,2,3]triazol-1(4*H*)-yl)acryloyl)piperazine-1-carboxylate (**19o**)



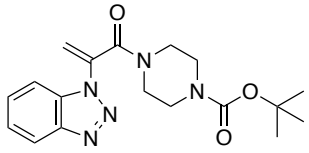
Colorless solid; Mp 50–52 ºC; TLC R_f 0.30 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.72–0.79 (m, 1H), 0.79–0.91 (m, 2H), 1.32–1.42 (m, 2H), 1.47 (s, 9H), 1.70–1.79 (br, 1H), 2.38–2.48 (br, 2H), 2.63–2.71 (m, 1H), 2.84–2.91 (m, 1H), 2.93–3.00 (m, 1H), 3.09–3.17 (m, 1H), 3.29–3.55 (m, 9H), 3.58–3.66 (br, 1H), 5.81 (s, 1H), 5.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 22.1 (1C), 22.3 (1C), 22.9 (1C), 25.6 (1C), 26.9 (1C), 27.4 (1C), 27.9 (1C), 28.3 (3C), 42.2 (br, 2C), 46.5 (br, 2C), 66.3 (1C), 80.5 (1C), 119.0 (1C), 135.0 (1C), 137.3 (1C), 145.5 (1C), 154.4 (1C), 163.8 (1C); IR (KBr, cm^{-1}) 772, 1020, 1169, 1242, 1422, 1632, 1694, 2928; HRMS (ESI$^+$) *m/z* 454.2415 ([M + Na]$^+$ $C_{22}H_{33}N_5NaO_4^+$ requires 454.2425).

tert-Butyl 4-(2-(5,9-bis(tosyl)-5,6,7,8,9,10-hexahydro-[1,2,3]triazolo[4,5-*g*][1,5]diazonin-1(4*H*)-yl)acryloyl)piperazine-1-carboxylate (**19p**)



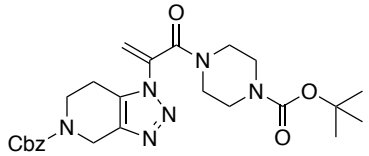
Colorless solid; Mp 108–110 ºC; TLC R_f 0.58 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.44 (s, 9H), 1.94–2.02 (br, 2H), 2.45 (s, 6H), 3.18–3.24 (br, 4H), 3.34–3.49 (br, 4H), 3.52–3.66 (br, 4H), 4.47 (s, 2H), 4.55 (s, 2H), 5.92 (d, 1H, *J* = 1.1 Hz), 6.05 (d, 1H, *J* = 1.1 Hz), 7.30–7.39 (m, 4H), 7.69–7.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.5 (1C), 21.6 (1C), 28.3 (3C), 30.1 (1C), 42.4 (br, 2C+2C, two signals overlapped), 43.6 (1C), 46.8 (1C), 49.1 (1C), 49.4 (1C), 80.4 (1C), 120.4 (br, 1C), 127.5 (2C), 127.6 (2C), 129.9 (2C), 130.1 (2C), 132.5 (1C), 134.0 (1C), 134.1 (1C), 136.3 (br, 1C), 143.0 (1C), 144.0 (1C), 144.3 (1C), 154.4 (1C), 163.4 (1C); IR (KBr, cm^{-1}) 548, 745, 772, 1161, 1252, 1341, 1420, 1695; HRMS (ESI^+) *m/z* 736.2554 ($[M + Na]^+$ $C_{33}H_{43}N_7NaO_7S_2^+$ requires 736.2558).

tert-Butyl 4-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19q**)



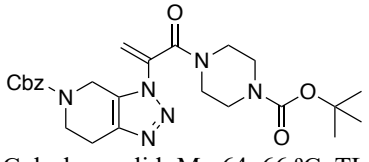
Colorless solid; Mp 146–147 ºC; TLC R_f 0.25 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.44 (s, 9H), 3.13–3.29 (br, 2H), 3.29–3.40 (br, 2H), 3.40–3.53 (br, 2H), 3.66–3.79 (br, 2H), 5.66 (d, 1H, *J* = 1.4 Hz), 6.04 (d, 1H, *J* = 1.4 Hz), 7.45 (ddd, 1H, *J* = 8.4, 7.4, 1.0 Hz), 7.57 (dd, 1H, *J* = 7.4, 7.4 Hz), 7.64 (dd, 1H, *J* = 7.4, 1.0 Hz), 8.12 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 28.3 (3C), 42.1 (br, 2C), 46.6 (br, 2C), 80.5 (1C), 110.5 (1C+1C, two signals overlapped), 120.6 (1C), 124.9 (1C), 128.9 (1C), 131.6 (1C), 137.3 (1C), 146.2 (1C), 154.3 (1C), 163.3 (1C); IR (KBr, cm^{-1}) 772, 1020, 1169, 1234, 1366, 1420, 1647, 1697, 2978; HRMS (ESI^+) *m/z* 380.1688 ($[M + Na]^+$ $C_{18}H_{23}N_5NaO_3^+$ requires 380.1693).

Benzyl 1-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-oxoprop-1-en-2-yl)-1,4,6,7-tetrahydro-5*H*-[1,2,3]triazolo[4,5-*c*]pyridine-5-carboxylate (**19r**)



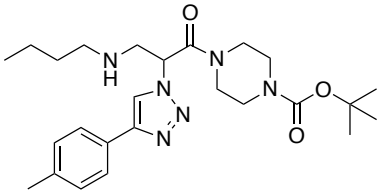
Colorless solid; Mp 84–85 ºC; TLC R_f 0.32 (*n*-hexane/EtOAc = 1/5); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46 (s, 9H), 2.71–2.84 (br, 2H), 3.33–3.54 (br, 6H), 3.70–3.72 (br, 2H), 3.73–3.85 (br, 2H), 4.74 (s, 2H), 5.17 (s, 2H), 5.23 (s, 1H), 5.76 (s, 1H), 7.29–7.40 (br, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.8 (br, 1C), 28.3 (3C), 40.9 (br, 1C), 41.5 (br, 1C), 42.0 (br, 2C), 46.8 (br, 2C), 67.7 (1C), 80.6 (1C), 111.7 (br, 1C), 128.1 (1C), 128.3 (2C), 128.6 (2C), 131.1 (br, 1C), 136.2 (1C), 136.7 (1C), 141.3 (br, 1C), 154.4 (br, 1C), 155.5 (1C), 162.9 (1C); IR (KBr, cm^{-1}) 770, 1167, 1219, 1366, 1423, 1653, 1697, 3447; HRMS (ESI^+) *m/z* 519.2322 ($[M + Na]^+$ $C_{25}H_{32}N_6NaO_5^+$ requires 519.2326).

Benzyl 3-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-oxoprop-1-en-2-yl)-3,4,6,7-tetrahydro-5H-[1,2,3]triazolo[4,5-*c*]pyridine-5-carboxylate (**19r'**)



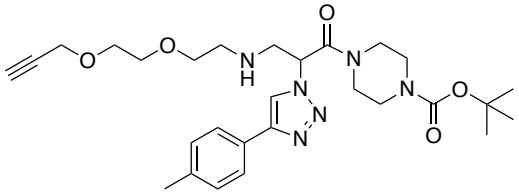
Colorless solid; Mp 64–66 ºC; TLC R_f 0.42 (*n*-hexane/EtOAc = 1/5); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (s, 9H), 2.85–3.95 (br, 2H), 3.30–3.59 (br, 8H), 3.75–3.83 (br, 2H), 4.59–4.71 (br, 2H), 5.15–5.19 (br, 2H), 5.49–5.53 (br, 1H), 5.82 (d, 1H, *J* = 1.9 Hz), 7.32–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 22.7 (br, 1C), 28.3 (3C), 40.5–44.2 (m, 1C+1C+2C), 46.8 (br, 2C), 67.9 (1C), 80.5 (1C), 111.1 (br, 1C), 128.0 (1C), 128.4 (2C), 128.6 (2C), 129.5 (br, 1C), 136.1 (br, 1C), 136.6 (1C), 142.4 (br, 1C), 154.4 (br, 1C), 155.5 (br, 1C), 162.6 (1C); IR (KBr, cm^{-1}) 770, 1018, 1169, 1229, 1420, 1699, 2976, 3480; HRMS (ESI^+) *m/z* 519.2330 ($[M + Na]^+$ $C_{25}H_{32}N_6NaO_5^+$ requires 519.2326).

tert-Butyl 4-(3-(butylamino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20a**)



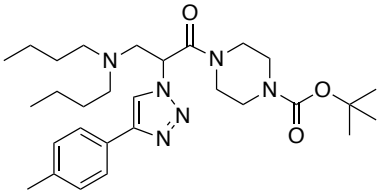
Colorless solid; Mp 104–105 ºC; TLC R_f 0.40 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, 3H, J = 7.3 Hz), 1.30 (tq, 2H, J = 7.3 Hz), 1.41–1.45 (m, 9H), 2.38 (s, 3H), 2.58–2.69 (ddd, 2H, J = 4.3, 7.1, 11.5 Hz), 2.92–3.12 (br, 1H), 3.17 (dd, 1H, J = 12.6, 6.9 Hz), 3.41–3.67 (m, 7H), 3.68–3.75(br, 1H), 5.86 (dd, 2H, J = 6.9, 6.9 Hz), 7.24 (d, 2H, J = 8.0 Hz), 7.72 (d, 2H, J = 8.0 Hz), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.9 (1C), 20.2 (1C), 21.3 (1C), 28.3 (3C), 32.0 (1C), 42.3 (2C), 45.7 (2C), 49.4 (1C), 51.7 (1C), 59.2 (1C), 80.5 (1C), 118.2 (1C), 125.6 (2C), 127.4 (1C), 129.5 (2C), 138.2 (1C), 148.3 (1C), 154.3 (1C), 165.7 (1C); IR (KBr, cm^{-1}) 625, 671, 772, 928, 1219, 1423, 3019, 3067; HRMS (ESI) *m/z* 493.2888 ([M + Na]$^+$, $C_{25}H_{38}N_6NaO_3^+$ requires 493.2898).

tert-Butyl 4-(3-((2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)amino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20b**)



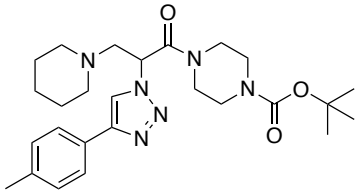
Colorless oil; TLC R_f 0.50 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.44 (s, 9H), 2.38 (s, 3H), 2.43 (s, 1H), 2.77–2.89 (m, 2H), 2.95–3.15 (br, 1H), 3.18–3.30 (br, 2H), 3.39–3.58 (m, 7H), 3.58–3.69 (m, 6H), 3.69–3.80 (br, 1H), 4.17 (d, 2H, J = 2.2 Hz), 5.87 (dd, 1H, J = 6.9, 6.9 Hz), 7.23 (d, 2H, J = 8.0 Hz), 7.72 (d, 2H, J = 8.0 Hz), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 28.3 (3C), 42.3 (br, 2C), 45.8 (br, 2C), 49.0 (1C), 51.6 (1C), 58.4 (1C), 59.3 (1C), 69.0 (1C), 70.1 (1C), 70.5 (1C), 74.6 (1C), 79.6 (1C), 80.5 (1C), 118.2 (1C), 125.6 (2C), 127.5 (1C), 129.5 (2C), 138.2 (1C), 148.2 (1C), 154.3 (1C), 165.8 (br, 1C); IR (KBr, cm^{-1}) 772, 1125, 1167, 1234, 1366, 1418, 1651, 3464; HRMS (ESI$^+$) *m/z* 563.2942 ([M + Na]$^+$ $C_{28}H_{40}N_6NaO_5^+$ requires 563.2952).

tert-Butyl 4-(3-(dibutylamino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20c**)



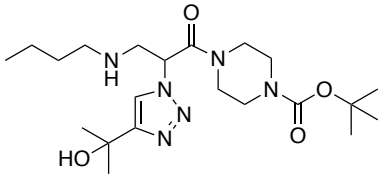
Colorless solid; Mp 113–114 ºC; TLC R_f 0.58 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, 6H, J = 7.3 Hz), 1.17–1.28 (m, 4H), 1.30–1.40 (m, 4H), 1.46 (s, 9H), 2.37 (s, 3H), 2.41–2.52 (m, 4H), 2.95 (dd, 1H, J = 13.4, 6.9 Hz), 3.14–3.39 (br, 3H), 3.40–3.59 (br, 4H), 3.59–3.68 (br, 1H), 3.68–3.78 (br, 1H), 5.80 (dd, 1H, J = 6.9, 6.9 Hz), 7.22 (d, 2H, J = 8.2 Hz), 7.71 (d, 2H, J = 8.2 Hz), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.0 (2C), 20.4 (2C), 21.2 (1C), 28.3 (3C), 29.2 (2C), 42.3 (br, 2C), 46.0 (br, 2C), 54.3 (2C), 57.5 (1C), 57.7 (1C), 80.5 (1C), 118.4 (1C), 125.6 (2C), 127.7 (1C), 129.5 (2C), 138.0 (1C), 148.0 (1C), 154.4 (1C), 166.6 (br, 1C); IR (KBr, cm^{-1}) 772, 1169, 1233, 1366, 1420, 1458, 1647, 1701, 2957; HRMS (ESI$^+$) *m/z* 527.3695 ([M + H]$^+$ $C_{29}H_{47}N_6O_3^+$ requires 527.3704).

tert-Butyl 4-(3-(piperidin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20d**)



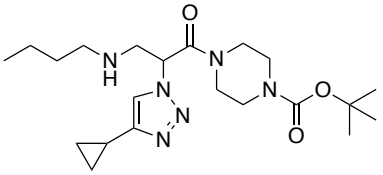
Colorless solid; Mp 93–95 ºC; TLC R_f 0.25 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.36–1.43 (m, 2H), 1.46 (s, 9H), 1.48–1.55 (br, 4H), 2.37 (s, 3H), 2.44–2.51 (br, 4H), 2.88 (dd, 1H, J = 13.1, 7.4 Hz), 3.20 (dd, 1H, J = 13.1, 7.4 Hz), 3.30–3.39 (br, 1H), 3.42–3.51 (br, 1H), 3.51–3.74 (br, 6H), 5.89 (dd, 1H, J = 7.4, 7.4 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.73 (d, 2H, J = 8.0 Hz), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 23.9 (1C), 26.0 (2C), 28.4 (3C), 42.4 (br, 2C), 46.0 (br, 2C), 54.9 (2C), 57.0 (1C), 61.3 (1C), 80.5 (1C), 118.6 (1C), 125.6 (2C), 127.7 (1C), 129.5 (2C), 138.0 (1C), 148.0 (1C), 154.4 (1C), 166.7 (br, 1C); IR (KBr, cm^{-1}) 772, 928, 1045, 1219, 1423, 1522, 1653, 2399, 3019; HRMS (ESI$^+$) *m/z* 505.2891 ([M + Na]$^+$ $C_{26}H_{38}N_6NaO_3^+$ requires 505.2898).

tert-Butyl 4-(3-(butylamino)-2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20e**)



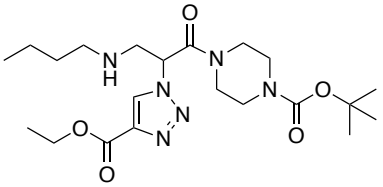
Colorless oil;TLC R_f 0.44 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, 3H, *J* = 7.3 Hz), 1.23–1.35 (m, 2H), 1.37–1.45 (m, 2H), 1.45 (s, 9H), 1.63 (s, 6H), 1.79–2.09 (2H), 2.54–2.69 (m, 2H), 3.11 (dd, 2H, *J* = 12.5, 6.8 Hz), 3.24–3.40 (m, 2H), 3.44–3.62 (br, 5H), 3.62–3.73 (br, 1H), 5.81 (dd, 1H, *J* = 6.8, 6.8 Hz), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.9 (1C), 20.2 (1C), 28.3 (3C), 30.3 (1C), 30.4 (1C), 32.0 (1C), 42.3 (br, 2C), 45.7(br, 2C), 49.4 (1C), 51.7 (1C), 59.1 (1C), 68.4 (1C), 80.5 (1C), 118.3 (1C), 154.3 (1C), 156.0 (1C), 165.8 (1C); IR (KBr, cm^{-1}) 772, 1169, 1234, 1366, 1420, 1458, 1647, 2972, 3304; HRMS (ESI^+) *m/z* 439.3032 ($[M + H]^+$ $C_{21}H_{39}N_6O_4^+$ requires 439.3027).

tert-Butyl 4-(3-(butylamino)-2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20f**)



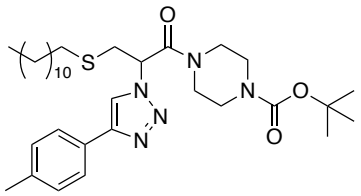
Colorless oil; TLC R_f 0.45 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81–0.87 (m, 2H), 0.89 (t, 3H, *J* = 7.3 Hz), 0.92–0.99 (m, 2H), 1.23–1.35 (m, 2H), 1.36–1.43 (m, 2H), 1.45 (s, 9H), 1.90–1.98 (m, 1H), 2.52–2.67 (m, 2H), 2.94–3.12 (m, 2H), 3.35 (dd, 1H, *J* = 12.4, 7.2 Hz), 3.31–3.61 (br, 7H), 3.63–3.75 (br, 1H), 5.75 (dd, 1H, *J* = 7.2, 7.2 Hz), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 6.8 (1C), 7.81 (1C), 7.83 (1C), 13.9 (1C), 20.2 (1C), 28.3 (3C), 32.0 (1C), 42.3 (br, 2C), 45.6 (br, 2C), 49.4 (1C), 51.6 (1C), 59.1 (1C), 80.5 (1C), 118.5 (1C), 150.7 (1C), 154.3 (1C), 165.8 (1C); IR (KBr, cm^{-1}) 772, 1169, 1234, 1418, 1456, 1647, 1697, 3447; HRMS (ESI^+) *m/z* 421.2914 ($[M + H]^+$ $C_{21}H_{37}N_6O_3^+$ requires 421.2922).

tert-Butyl 4-(3-(butylamino)-2-(4-(ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20g**)



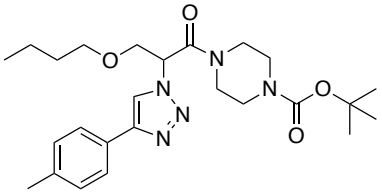
Colorless oil; TLC R_f 0.45 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, 3H, *J* = 7.2 Hz), 1.24–1.34 (m, 2H), 1.37–1.42 (m, 5H), 1.42–1.52 (br, 10H), 2.53–2.66 (m, 2H), 3.12–3.27 (br, 2H), 3.27–3.38 (m, 2H), 3.44–3.72 (m, 6H), 4.37–4.49 (m, 2H), 5.90 (dd, 1H, *J* = 6.7, 6.7 Hz), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.9 (1C), 14.3 (1C), 20.2 (1C), 28.3 (3C), 32.0 (1C), 42.4 (br, 2C), 45.8 (br, 2C), 49.4 (1C), 51.8 (1C), 59.3 (1C), 61.3 (1C), 80.6 (1C), 127.2 (1C), 140.4 (1C), 154.3 (1C), 160.5 (1C), 165.4 (1C); IR (KBr, cm^{-1}) 775, 1026, 1169, 1226, 1416, 1651, 1694, 2930; HRMS (ESI^+) *m/z* 475.2646 ($[M + Na]^+$ $C_{21}H_{36}N_6NaO_5^+$ requires 475.2639).

tert-Butyl 4-(3-(dodecylthio)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**21a**)



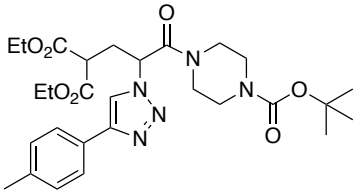
Colorless solid; Mp 99–100 ºC; TLC R_f 0.58 ((*n*-hexane/EtOAc = 1/1)); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, 3H, *J* = 7.1 Hz), 1.20–1.39 (m, 18H), 1.52 (s, 9H), 1.51–1.59 (m, 2H), 2.38 (s, 3H), 2.45–2.57 (m, 2H), 3.02–3.21 (m, 2H), 3.25–3.33 (br, 1H), 3.42 (dd, 1H, *J* = 13.6, 8.6 Hz), 3.45–3.60 (m, 3H), 3.60–3.77 (m, 3H), 5.86 (dd, 1H, *J* = 8.6, 6.1 Hz), 7.23 (d, 2H, *J* = 8.0 Hz), 7.72 (d, 2H, *J* = 8.1 Hz), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.1 (1C), 21.3 (1C), 22.7 (1C), 28.3 (3C), 28.7 (1C), 29.2 (1C), 29.3 (1C), 29.5 (1C), 29.6 (1C), 29.6 (1C), 29.6 (1C), 29.6 (1C), 33.0 (1C), 34.6 (1C), 42.0–44.5 (br, 2C+2C+1C, three signals overlapped), 58.9 (br, 1C), 80.5 (1C), 117.7 (1C), 125.6 (2C), 127.3 (1C), 129.5 (2C), 138.3 (1C), 148.4 (1C), 154.3 (1C), 165.5 (1C); IR (KBr, cm^{-1}) 1169, 1234, 1366, 1416, 1456, 1651, 1697, 2924; HRMS (ESI^+) *m/z* 622.3766 ($[M + Na]^+$ $C_{33}H_{53}N_5NaO_3S^+$ requires 622.3761).

tert-Butyl 4-(3-butoxy-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**21b**)



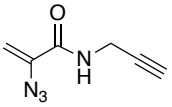
Colorless oil; TLC R_f 0.37 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, 3H, *J* = 7.4 Hz), 1.23–1.35 (m, 2H), 1.45 (s, 9H), 1.47–1.54 (m, 2H), 2.38 (s, 3H), 3.12–3.40 (br, 2H), 3.40–3.53 (m, 4H), 3.53–3.72 (m, 4H), 3.93 (dd, 1H, *J* = 9.8, 7.0 Hz), 4.07 (dd, 1H, *J* = 9.8, 7.0 Hz), 5.90 (dd, 1H, *J* = 7.0, 7.0 Hz), 7.23 (d, 2H, *J* = 8.1 Hz), 7.73 (d, 2H, *J* = 8.1 Hz), 8.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.8 (1C), 19.1 (1C), 21.3 (1C), 28.3 (3C), 31.4 (1C), 42.3 (br, 2C), 45.9 (br, 2C), 58.6 (1C), 70.7 (1C), 71.7 (1C), 80.5 (1C), 118.7 (br, 1C), 125.6 (2C), 127.5 (1C), 129.5 (2C), 138.1 (1C), 148.1 (1C), 154.3 (1C), 165.2 (1C); IR (KBr, cm^{-1}) 471, 505, 548, 1639, 3277, 3302, 3345, 3433; HRMS (ESI^+) *m/z* 494.2746 ($[M + Na]^+$ $C_{25}H_{37}N_5NaO_4^+$ requires 494.2738).

Diethyl 2-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)malonate (**21c**)



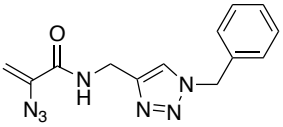
Colorless solid; Mp 137–138 ºC; TLC R_f 0.36 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (t, 3H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.2 Hz), 1.45 (s, 9H), 2.38 (s, 3H), 2.52–2.61 (m, 1H), 2.67–2.77 (m, 1H), 3.05–3.12 (m, 1H), 3.20–3.28 (br, 1H), 3.29–3.37 (m, 1H), 3.45–3.60 (br, 3H), 3.63–3.21 (br, 3H), 4.11–4.19 (m, 2H), 4.19–4.11 (m, 2H), 5.95 (dd, 1H, *J* = 10.1, 5.0 Hz), 7.24 (d, 2H, *J* = 8.1 Hz), 7.73 (d, 2H, *J* = 8.1 Hz), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.0 (2C), 21.3 (1C), 28.3 (3C), 32.1 (1C), 42.4 (br, 2C), 45.7 (br, 2C), 47.7 (1C), 57.3 (1C), 62.1 (1C), 62.1 (1C), 80.5 (1C), 118.2 (1C), 125.7 (2C), 127.4 (1C), 129.6 (2C), 138.3 (1C), 148.7 (1C), 154.3 (1C), 165.8 (1C), 168.3 (1C), 168.4 (1C); IR (KBr, cm^{-1}) 419, 542, 772, 1630, 3238, 3372 3424, 3524; HRMS (ESI^+) *m/z* 580.2751 ($[M + Na]^+$ $C_{28}H_{39}N_5NaO_7^+$ requires 580.2742).

2-Azido-*N*-(prop-2-yn-1-yl)acrylamide (**22**)



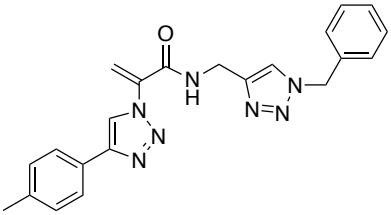
Yellow solid; Mp 56–57 ºC; TLC R_f 0.47 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.27 (t, 1H, *J* = 2.6 Hz), 4.11 (dd, 2H, *J* = 5.4, 2.6 Hz), 5.22 (d, 1H, *J* = 2.2 Hz), 6.19 (d, 1H, *J* = 2.2 Hz), 6.49–6.66 (br, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 29.4 (1C), 72.0 (1C), 78.7 (1C), 107.1 (1C), 138.0 (1C), 160.3 (1C); IR (KBr, cm^{-1}) 1312, 1520, 1611, 1670, 2120, 3298, 3418; HRMS (ESI^+) *m/z* 173.0439 ($[M + Na]^+$ $C_6H_6N_4NaO^+$, requires 173.0434).

2-Azido-*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)acrylamide (**24**)



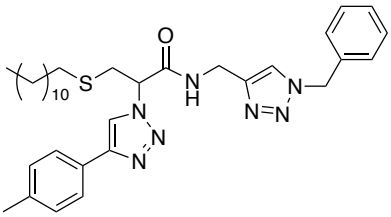
Colorless solid; Mp 85–86 ºC; TLC R_f 0.55 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.54 (d, 2H, *J* = 5.8 Hz), 5.17 (d, 1H, *J* = 2.1 Hz), 5.50 (s, 2H), 6.13 (d, 1H, *J* = 2.1 Hz), 6.95–7.08 (br, 1H), 7.26–7.30 (m, 2H), 7.34–7.41 (m, 3H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 35.1 (1C), 54.2 (1C), 106.7 (1C), 122.1 (1C), 128.1 (2C), 128.8 (1C), 129.1 (2C), 134.4 (1C), 138.4 (1C), 144.3 (1C), 161.0 (1C); IR (KBr, cm^{-1}) 772, 1219, 1263, 1522, 1670, 2120, 3017, 3420; HRMS (ESI^+) *m/z* 306.1072 ($[M + Na]^+$ $C_{13}H_{13}N_7NaO^+$, requires 306.1074).

N-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**25**)



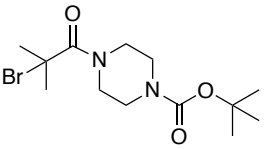
Colorless solid; Mp 170–172 ºC; TLC R_f 0.50 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.39 (s, 3H), 4.64 (d, 2H, *J* = 5.7 Hz), 5.48 (s, 2H), 6.01 (d, 1H, *J* = 1.3 Hz), 6.34 (d, 1H, *J* = 1.3 Hz), 7.20–7.29 (m, 4H), 7.31–7.39 (m, 3H), 7.50 (s, 1H), 7.72 (d, 2H, *J* = 8.1 Hz), 7.82–7.92 (br, 1H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 35.6 (1C), 54.2 (1C), 117.4 (1C), 120.1 (1C), 122.3 (1C), 125.8 (2C), 126.7 (1C), 128.1 (2C), 128.8 (1C), 129.1 (2C), 129.6 (2C), 134.3 (1C), 137.2 (1C), 138.6 (1C), 144.2 (1C), 148.0 (1C), 160.9 (1C); IR (KBr, cm^{-1}) 773, 930, 1028, 1219, 1433, 1528, 1624, 3019; HRMS (ESI$^+$) *m/z* 422.1701 ([M + Na]$^+$ $C_{22}H_{21}N_7NaO^+$, requires 422.1700).

N-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-(dodecylthio)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanamide (**26**)



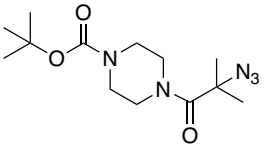
Colorless solid; Mp 162–163 ºC; TLC R_f 0.22 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, 3H, *J* = 7.1 Hz), 1.18–1.30 (m, 18H), 1.41–1.49 (m, 2H), 2.32–2.38 (m, 5H), 3.13–3.20 (m, 1H), 3.31–3.38 (m, 1H), 4.51 (d, 2H, *J* = 7.1 Hz), 5.38 (dd, 1H, *J* = 6.9, 6.9 Hz), 5.43 (s, 2H), 7.19–7.26 (m, 4H), 7.27–7.38 (m, 3H), 7.42 (s, 1H), 7.69 (d, 2H, *J* = 8.1 Hz), 7.73–7.79 (m, 1H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 14.1 (1C), 21.3 (1C), 22.7 (1C), 28.7 (1C), 29.2 (1C), 29.3 (1C), 29.4 (1C), 29.5 (1C), 29.6 (1C), 29.6 (1C), 29.6 (1C), 31.9 (1C), 32.6 (1C), 34.7 (1C), 35.3 (1C), 54.2 (1C), 64.3 (1C), 119.5 (1C), 122.3 (1C), 125.6 (2C), 127.3 (1C), 128.1 (2C), 128.8 (1C), 129.1 (2C), 129.5 (2C), 134.3 (1C), 138.2 (1C), 144.2 (1C), 148.0 (1C), 167.0 (1C); IR (KBr, cm^{-1}) 772, 928, 1047, 1220, 1431, 1530, 1680, 2924, 3019; HRMS (ESI$^+$) *m/z* 624.3454 ([M + Na]$^+$ $C_{34}H_{47}N_7NaOS^+$, requires 624.3455).

tert-Butyl 4-(2-bromo-2-methylpropanoyl)piperazine-1-carboxylate (**S17**)



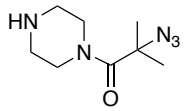
Colorless solid; Mp 130–131 ºC; TLC R_f 0.50 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.47 (s, 9H), 1.97 (s, 6H), 3.43–3.52 (m, 4H), 3.63–3.87 (br, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 28.4 (3C), 32.6 (2C), 42.9 (br, 2C), 43.7 (br, 2C), 56.5 (1C), 80.3 (1C), 154.6 (1C), 169.3 (1C); IR (KBr, cm^{-1}) 762, 1184, 1246, 1362, 1429, 1624, 1686, 2976, 3441; HRMS (ESI$^+$) *m/z* 357.0773 ([M + Na]$^+$ $C_{13}H_{23}BrN_2NaO_3^+$, requires 357.0784).

tert-Butyl 4-(2-azido-2-methylpropanoyl)piperazine-1-carboxylate (**S18**)



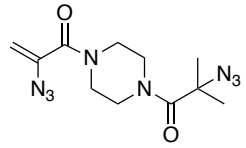
Colorless solid; Mp 105–106 ºC; TLC R_f 0.50 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.47 (s, 9H), 1.53 (s, 6H), 3.38–3.50 (m, 4H), 3.53–3.91 (br, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 25.2 (2C), 28.3 (3C), 43.4 (br, 2C), 44.2 (br, 2C), 64.0 (1C), 80.3 (1C), 154.5 (1C), 170.0 (1C); IR (KBr, cm^{-1}) 772, 1175, 1254, 1364, 1427, 1626, 1684, 2106; HRMS (ESI$^+$) *m/z* 320.1699 ([M + Na]$^+$ $C_{13}H_{23}N_5NaO_3^+$, requires 320.1693).

2-Azido-2-methyl-1-(piperazin-1-yl)propan-1-one (**S19**)



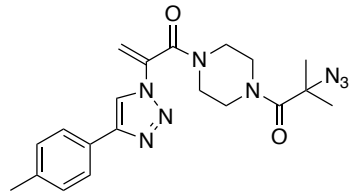
Colorless oil; TLC R_f 0.27 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.52 (s, 6H), 1.65–1.78 (br, 1H), 2.80–2.95 (m, 4H), 3.48–3.98 (br, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 25.2 (2C), 46.4 (br, 2C+2C, two signals overlapped), 64.1 (1C), 169.7 (1C); IR (KBr, cm^{-1}) 772, 1148, 1192, 1250, 1435, 1628, 2104, 3445; HRMS (ESI$^+$) *m/z* 198.1346 ([M + H]$^+$ $C_8H_{16}N_5O^+$, requires 198.1349).

2-Azido-1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)prop-2-en-1-one (**27**)



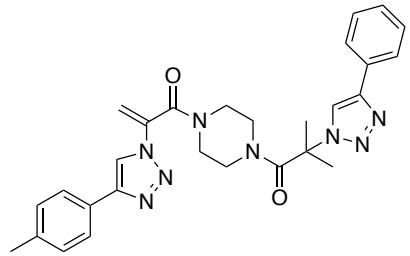
Pale yellow oil; TLC R_f 0.25 (*n*-hexane/EtOAc = 1/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.54 (s, 6H), 3.60–3.71 (br, 4H), 3.71–3.91 (br, 4H), 5.12–5.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 25.2 (2C), 42.4 (br, 2C), 47.2 (br, 2C), 64.0 (1C), 104.4 (1C), 139.5 (1C), 163.5 (1C), 170.1 (1C); IR (KBr, cm^{-1}) 772, 1018, 1219, 1244, 1425, 1638, 2104, 3003; HRMS (ESI$^+$) *m/z* 315.1277 ([M + Na]$^+$ $C_{11}H_{16}N_8NaO_2^+$, requires 315.1288).

1-(4-(2-Azido-2-methylpropanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**28**)



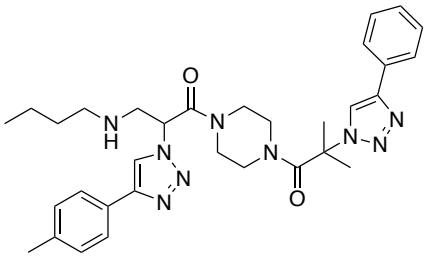
Colorless solid; Mp 65–67 ºC; TLC R_f 0.62 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.53 (s, 6H), 2.39 (s, 3H), 3.50–3.64 (br, 2H), 3.69–3.91 (br, 6H), 5.42 (d, 1H, *J* = 2.2 Hz), 5.96 (d, 1H, *J* = 2.2 Hz), 7.26 (d, 2H, *J* = 7.7 Hz), 7.74 (d, 2H, *J* = 7.7 Hz), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 25.1 (2C), 42.4 (br, 2C), 47.3 (br, 2C), 64.0 (1C), 108.2 (1C), 117.3 (1C), 125.8 (2C), 126.7 (1C), 129.6 (2C), 136.7 (1C), 138.7 (1C), 148.4 (1C), 162.8 (1C), 170.1 (1C); IR (KBr, cm^{-1}) 772, 1015, 1175, 1242, 1431, 1636, 2104, 3447; HRMS (ESI$^+$) *m/z* 431.1914 ([M + Na]$^+$ $C_{20}H_{24}N_8NaO_2^+$, requires 431.1914).

1-(4-(2-Methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**29**)



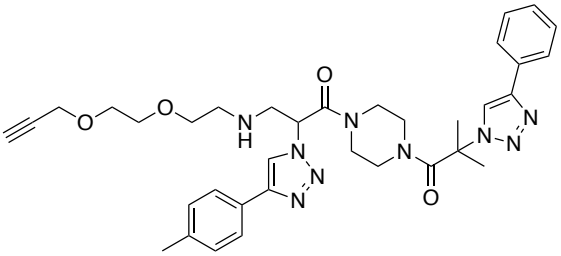
Colorless solid; Mp 122–123 ºC; TLC R_f 0.56 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.95 (s, 6H), 2.38 (s, 3H), 3.15–3.80 (br, 8H), 5.28–5.32 (br, 1H), 5.81–5.90 (br, 1H), 7.24 (d, 2H, *J* = 7.9 Hz), 7.36–7.39 (m, 1H), 7.41–7.47 (m, 2H), 7.70 (d, 2H, *J* = 8.1 Hz), 7.82–7.85 (m, 3H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 27.4 (2C), 41.7 (br, 2C), 46.6 (br, 2C), 65.4 (1C), 108.0 (1C), 117.2 (1C), 117.4 (1C), 125.8 (2C), 125.8 (2C), 126.7 (1C), 128.7 (1C), 129.0 (2C), 129.6 (2C), 129.8 (1C), 136.5 (1C), 138.7 (1C), 148.3 (1C), 148.91 (1C), 162.6 (1C), 168.9 (1C); IR (KBr, cm^{-1}) 696, 768, 1011, 1175, 1233, 1431, 1636, 3447; HRMS (ESI$^+$) *m/z* 533.2392 ([M + Na]$^+$ $C_{28}H_{30}N_8NaO_2^+$, requires 533.2384).

3-(Butylamino)-1-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propan-1-one (**30**)



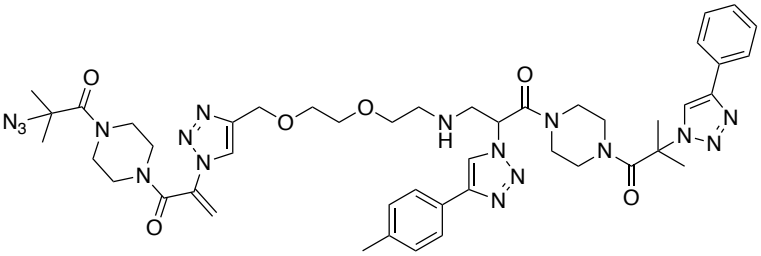
Colorless solid; Mp 98–100 ºC; TLC R_f 0.50 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, 3H, J = 7.3 Hz), 1.20–1.30 (m, 2H), 1.30–1.40 (m, 2H),1.91 (s, 3H), 1.94 (s, 3H), 2.37 (s, 3H), 2.50–2.65 (m, 2H), 3.00–3.75 (m, 11H), 5.63–5.78 (br, 1H), 7.21 (d, 2H, J = 8.1 Hz), 7.36–7.40 (m, 1H), 7.42–7.45 (m, 2H), 7.68 (d, 2H, J = 8.1 Hz), 7.80–7.84 (m, 3H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.9 (1C), 20.2 (2C), 21.3 (1C), 30.0 (1C), 41.9 (br, 2C), 45.3 (br, 2C), 49.4 (1C), 51.5 (1C), 58.9 (1C), 65.4 (1C), 117.4 (1C), 118.1 (1C), 125.6 (2C), 125.8 (2C), 127.3 (1C), 128.7 (1C), 129.0 (2C), 129.5 (2C), 129.8 (1C), 138.2 (2C), 148.2 (1C), 148.9 (1C), 165.7 (1C), 168.9 (1C); IR (KBr, cm^{-1}) 694, 768, 1020, 1231, 1429, 1647, 2928, 3447; HRMS (ESI$^+$) *m/z* 584.3458 ([M + H]$^+$ $C_{32}H_{42}N_9O_2^+$, requires 584.3456).

2-Methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1-(4-(3-((2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)amino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)propan-1-one (**31**)



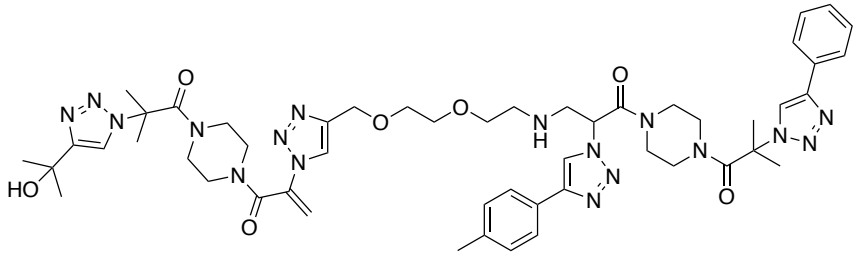
Colorless solid; Mp 67–69 ºC; TLC R_f 0.49 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.92 (s, 3H), 1.95 (s, 3H), 2.37 (s, 3H), 2.42 (t, 1H, J = 2.4 Hz), 2.71–3.64 (br, 19H), 4.14 (d, 2H, J = 1.5 Hz), 5.69–5.82 (br, 1H), 7.21 (d, 2H, J = 8.1 Hz), 7.33–7.39 (m, 1H), 7.44 (dd, 2H, J = 7.8, 7.8 Hz), 7.69 (d, 2H, J = 8.1 Hz), 7.79–7.86 (m, 3H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 27.2 (1C+1C, two signals overlapped) ,41.9 (br, 2C), 45.4 (br, 2C), 48.9 (1C), 51.5 (1C), 58.3 (1C), 59.0 (1C), 65.4 (1C), 69.0 (1C), 70.1 (1C), 70.5 (1C), 74.6 (1C), 79.6 (1C), 117.4 (1C), 118.3 (1C), 125.6 (2C), 125.8 (2C), 127.4 (1C), 128.6 (1C), 129.0 (2C), 129.5 (2C), 129.8 (1C), 138.2 (1C), 148.1 (1C), 148.9 (1C), 165.8 (1C), 168.9 (1C); IR (KBr, cm^{-1}) 772, 1024, 1098, 1219, 1429, 1472, 1647, 3015; HRMS (ESI$^+$) *m/z* 676.3340 ([M + Na]$^+$ $C_{35}H_{43}N_9NaO_4^+$, requires 676.3330).

1-(4-(2-Azido-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**32**)



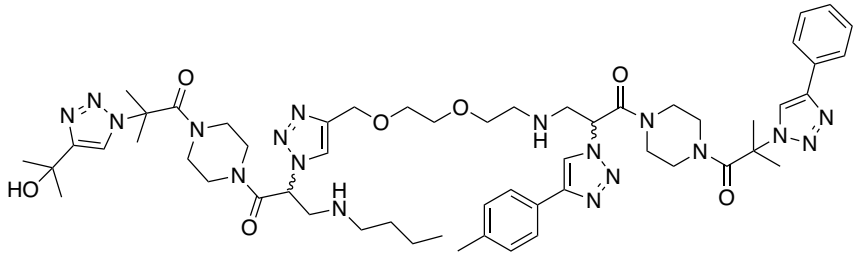
Colorless solid; Mp 105–107 ºC; TLC R_f 0.43 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.52 (s, 6H), 1.92 (s, 3H), 1.94 (s, 3H), 2.36 (s, 3H), 2.71–3.87 (br, 27H), 4.57–4.68 (br, 2H), 5.33 (d, 1H, J = 2.3 Hz), 5.80–5.87 (br, 1H), 5.88 (d, 1H, J = 2.3 Hz), 7.20 (d, 2H, J = 8.0 Hz), 7.33–7.39 (m, 1H), 7.43 (dd, 2H, J = 7.8, 7.8 Hz), 7.67 (d, 2H, J = 8.0 Hz), 7.82–7.89 (m, 3H), 7.91 (s, 1H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 25.2 (2C), 27.2 (1C+1C, two signals overlapped), 41.9 (br, 2C), 42.3 (br, 2C), 45.3 (br, 2C), 47.3 (br, 2C), 49.1 (1C), 51.6 (1C), 59.2 (1C), 64.0 (1C), 64.2 (1C), 65.4 (1C), 69.7 (1C), 70.2 (1C), 70.7 (1C), 108.3 (1C), 117.6 (1C), 118.5 (1C), 121.4 (1C), 125.5 (2C), 125.8 (2C), 127.5 (1C), 128.6 (1C), 129.0 (2C), 129.5 (2C), 129.9 (1C), 136.5(1C), 138.2 (1C), 145.6 (1C), 148.1 (1C), 148.8 (1C), 162.7 (1C), 165.9 (1C), 168.9 (1C), 170.1 (1C); IR (KBr, cm^{-1}) 770, 1018, 1177, 1238, 1427, 1643, 2104, 2918; HRMS (ESI$^+$) *m/z* 968.4726 ([M + Na]$^+$ $C_{46}H_{59}N_{17}NaO_6^+$, requires 968.4726).

1-(4-(2-(4-(2-Hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**S20**)

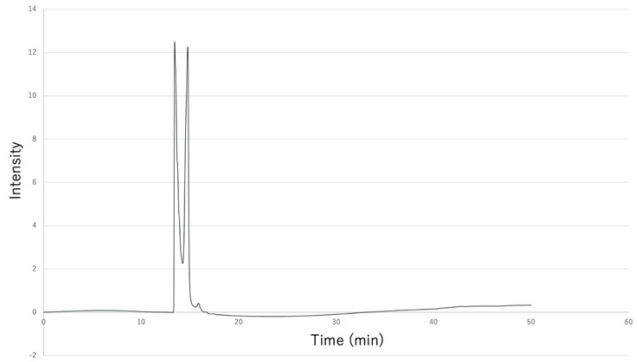


Colorless solid; Mp 120–122 ºC; TLC R_f 0.28 (CH_2Cl_2/MeOH = 10/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57–1.63 (br, 6H), 1.88 (s, 6H), 1.92 (s, 3H), 1.94 (s, 3H), 2.36 (s, 3H), 2.72–3.68 (m, 26H), 4.52–4.65 (br, 2H), 5.19–5.29 (br, 2H), 5.70–5.81 (br, 1H), 5.81–5.91 (br, 1H), 7.20 (d, 2H, J = 7.8 Hz), 7.33–7.39 (m, 1H), 7.43 (dd, 2H, J = 7.3, 7.3 Hz), 7.58 (s, 1H), 7.66 (d, 2H, J = 7.8 Hz), 7.81–7.84 (m, 3H), 7.88 (s, 1H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 21.3 (1C), 27.3 (br, 1C+1C+2C, three signals overlapped), 30.5 (2C), 41.5 (br, 2C), 41.9 (br, 2C), 45.3 (br, 2C), 46.4 (br, 2C), 49.0 (1C), 51.6 (1C), 59.2 (1C), 64.1 (1C), 65.2 (1C), 65.4 (1C), 68.5 (1C), 69.7 (1C), 70.2 (1C), 70.6 (1C), 107.9 (1C), 117.6 (1C), 118.7 (1C), 121.1 (1C), 125.5 (2C), 125.7 (2C), 127.4 (1C), 128.6 (1C), 128.9 (2C), 129.5 (2C), 129.9 (1C), 136.4 (1C), 138.2 (1C), 145.5 (1C), 147.9 (1C), 148.7 (1C), 157.2 (1C), 162.5 (1C), 165.9 (1C), 168.9 (1C), 169.0 (1C); IR (KBr, cm^{-1}) 770, 1009, 1177, 1231, 1429, 1472, 1645, 2924; HRMS (ESI^+) *m/z* 1052.5324 ($[M + Na]^+$ $C_{51}H_{67}N_{17}NaO_7^+$, requires 1052.5302).

3-(Butylamino)-1-(4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propan-1-one (**33**)



Colorless solid; Mp 112–113 ºC; TLC R_f 0.24 (CH_2Cl_2/MeOH = 10/1); ^{1}H and ^{13}C NMR spectra of a mixture of two diastereomers (major:minor = 52:48) were obtained: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, 3H, J = 7.3 Hz), 1.21–1.29 (m, 2H), 1.31–1.38 (m, 2H), 1.59–1.62 (m, 6H), 1.83–1.88 (m, 6H), 1.90–1.97 (m, 6H), 2.36 (s, 3H), 2.49–2.59 (m, 2H), 2.70–3.63 (br, 31H), 4.53–4.62 (br, 2H), 5.65–5.75 (br, 1H), 5.80–5.90 (br, 1H), 7.20 (d, 2H, J = 8.2 Hz), 7.32–7.38 (m, 1H), 7.40–7.47 (m, 2H), 7.55 (s, 1H), 7.65–7.70 (m, 2H), 7.80–7.85 (m, 3H), 7.89 (s, 1H for major isomer), 7.89 (s, 1H for minor isomer), 8.01 (s, 1H for major isomer), 8.02 (s, 1H for minor isomer); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 13.9, 20.2, 21.3, 27.3 (br), 30.5 (br), 32.0, 41.8 (br), 45.2 (br), 45.4, 49.0, 51.4, 59.2, 64.4, 65.1, 65.4, 68.4, 69.7, 70.1, 70.2, 70.37, 70.40, 117.5, 117.7, 118.7, 122.1, 125.5, 125.8, 127.4, 128.6, 129.0, 129.5, 129.9, 138.1, 145.16, 145.26, 147.93, 147.95, 148.8, 157.2, 165.7, 166.0, 168.9, 169.0; HPLC analysis: R*t* = 13.4 min (53%) and 14.8 min (47%) [column: Shiseido CAPCELL PAK MG II (4.6 mm i.d. × 250 mm); mobile phase: MeOH:H_2O = 10:90 (0−5 min), linear gradient from 10:90 to 99:1 (5−30 min), 99:1 (30−40 min); flow rate: 1.00 mL/min; detection: UV at 254 nm]; IR (KBr, cm^{-1}) 764, 1022, 1179, 1233, 1371, 1429, 1645, 1926; HRMS (ESI^+) *m/z* 1125.6191 ($[M + Na]^+$ $C_{55}H_{78}N_{18}NaO_7^+$, requires 1125.6193).
HPLC chart:



References for Supporting Information

S1 G.-J. Boons, J. Guo, X. Ning and M. Wolfert, WO 2009/067663, 2009.

S2 J. Dommerholt, S. Schmidt, R. Temming, L. J. A. Hendriks, F. P. J. T. Rutjes, J. C. M. van Hest, D. J. Lefeber, P. Friedl and F. L. van Delft, *Angew. Chem., Int. Ed.,* 2010, **49**, 9422.

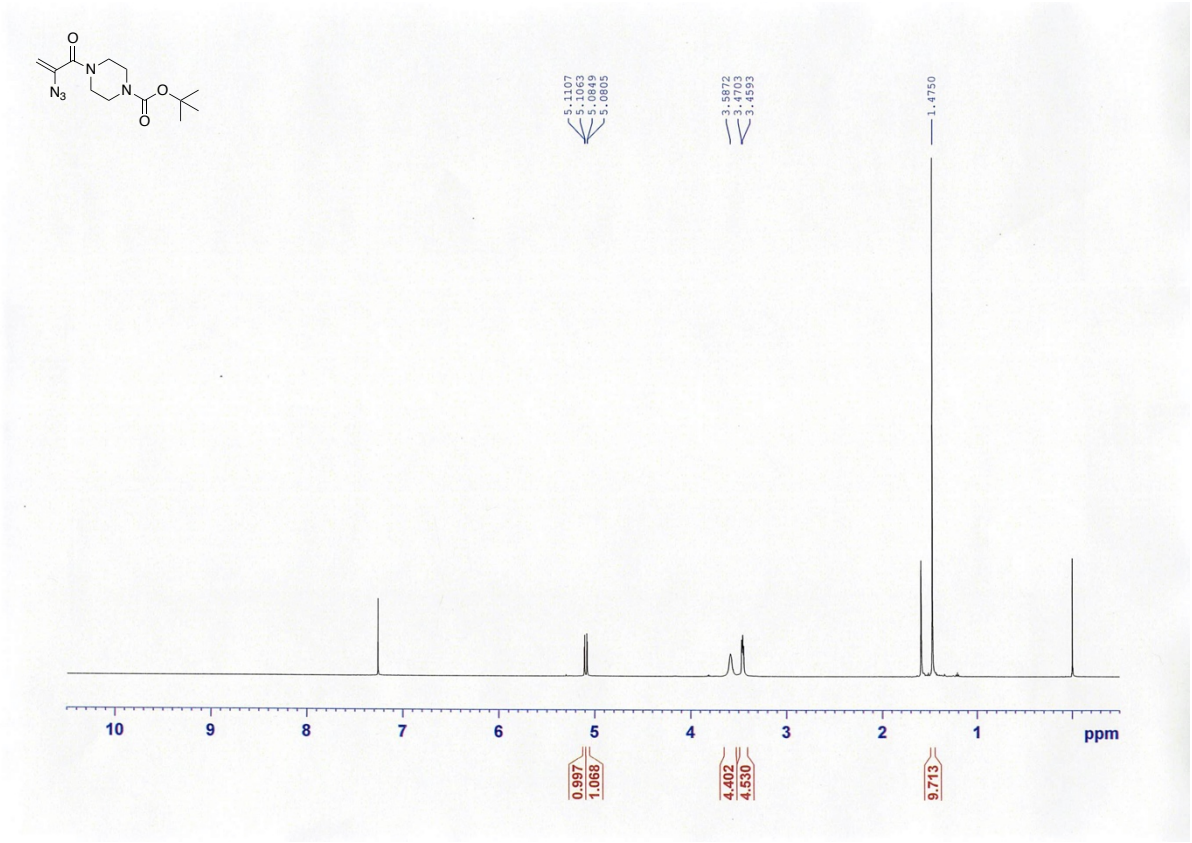
S3 R. Ni, N. Mitsuda, T. Kashiwagi, K. Igawa and K. Tomooka, *Angew. Chem., Int. Ed.,* 2014, **54**, 1190.

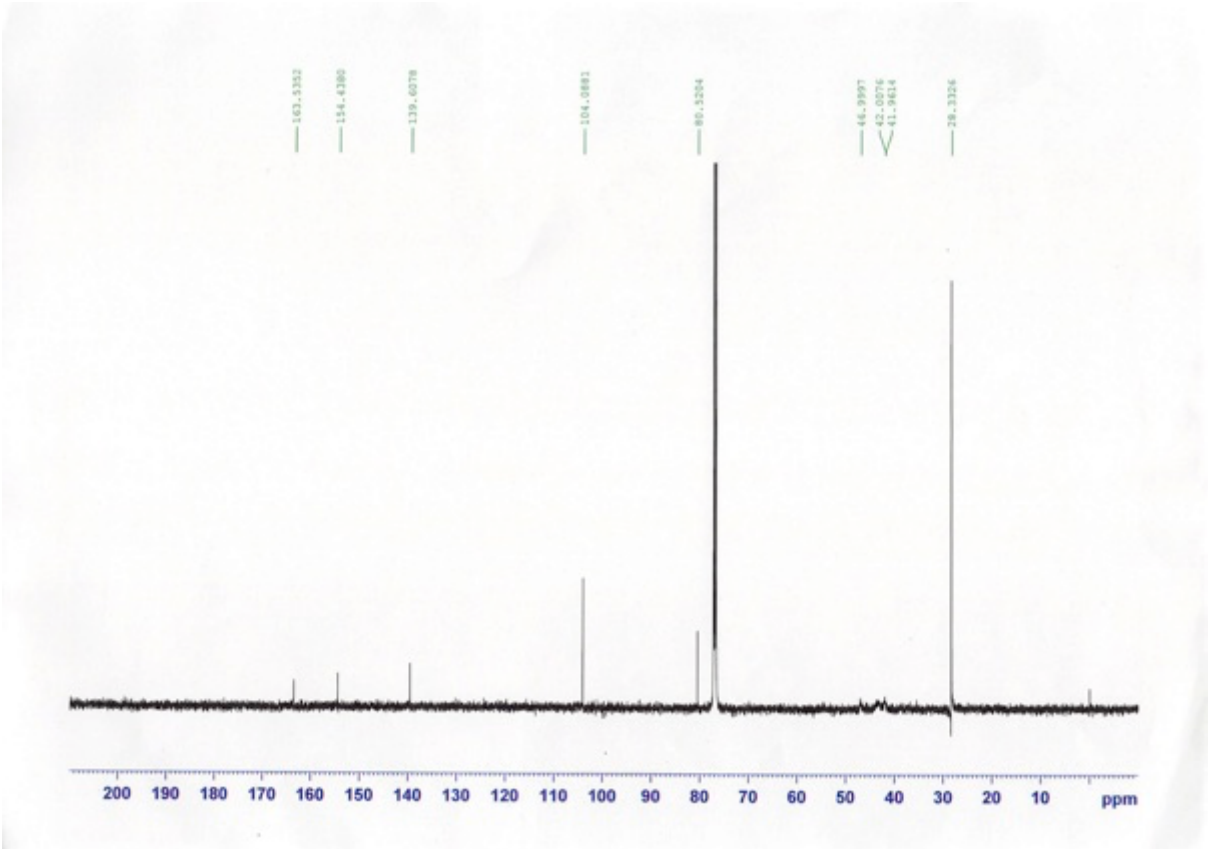
S4 T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Fokin, *Org. Lett.*, 2004, **6**, 2853.

S5 Spartan '18; Wavefunction, Inc: Irvine, CA, 2018.

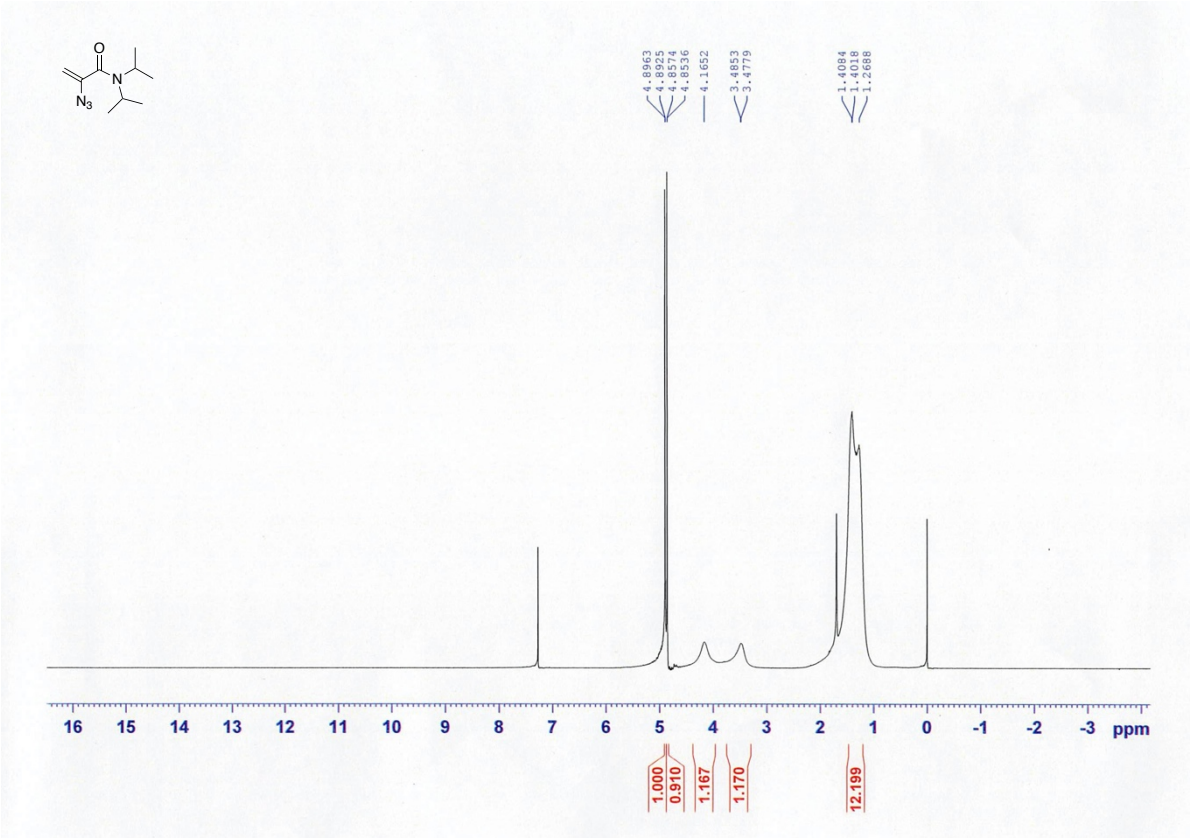
NMR Spectra of New Compounds

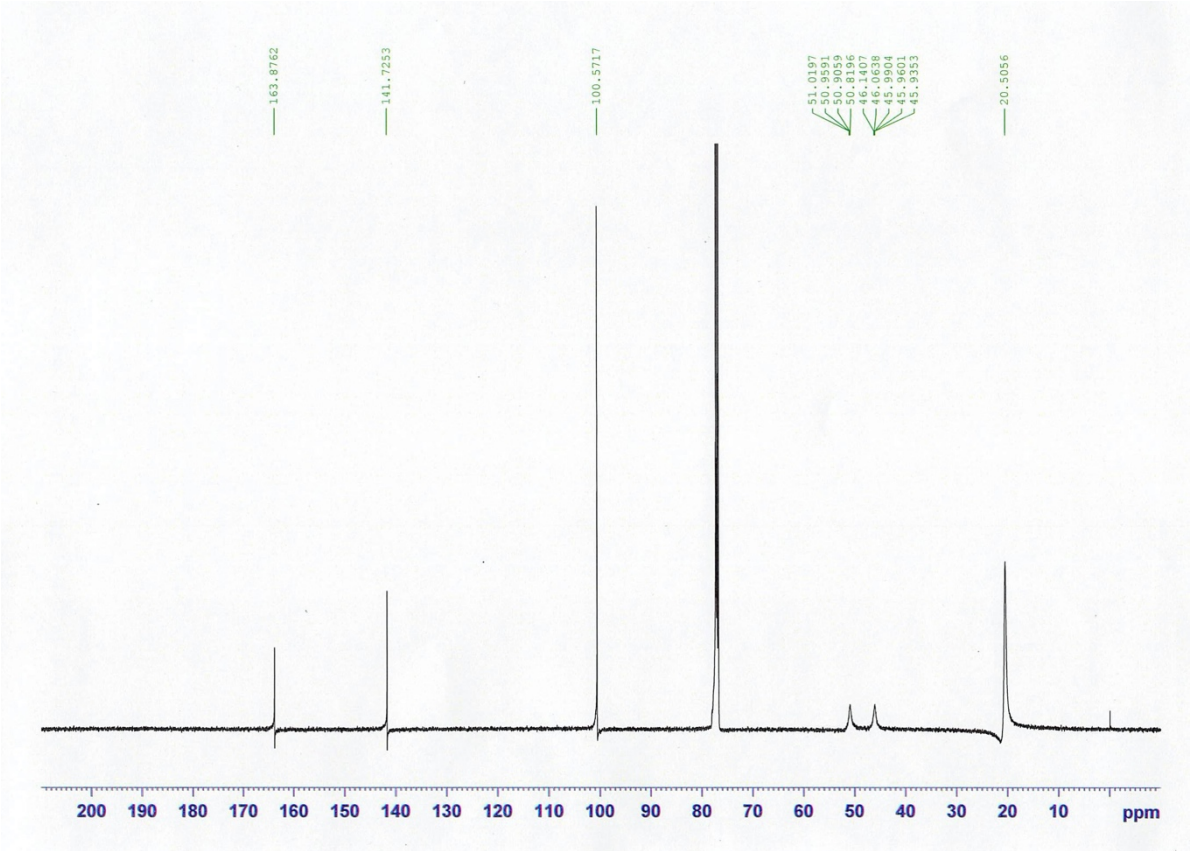
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**12**) ($CDCl_3$)



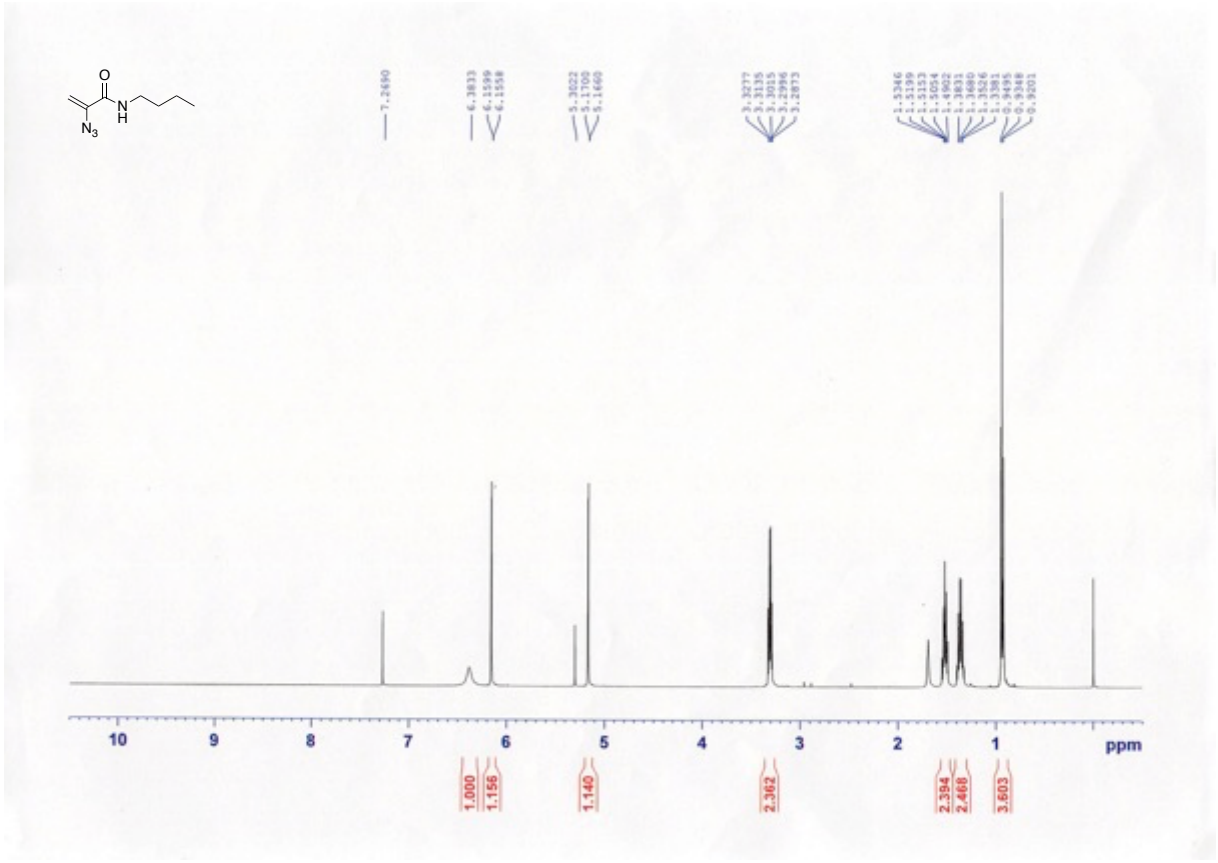


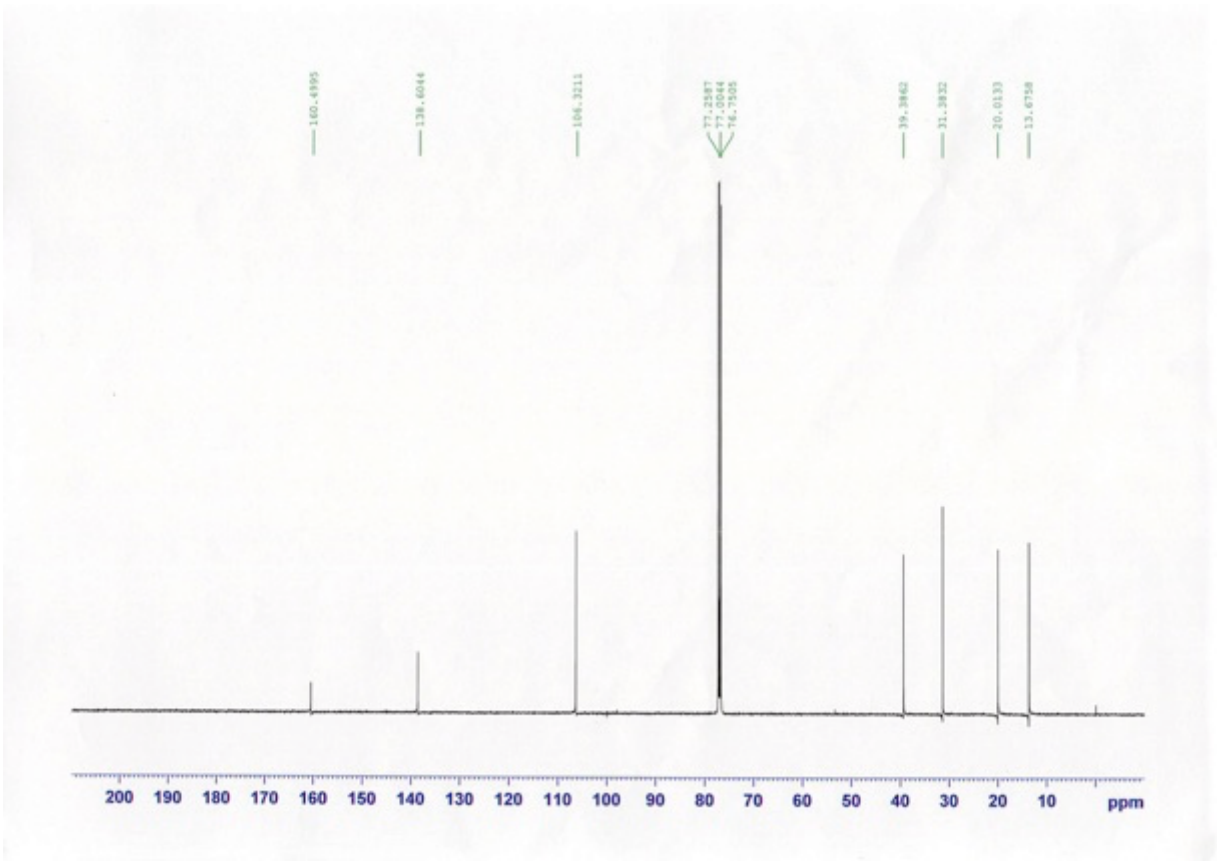
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azido-*N*,*N*-diisopropylacrylamide (**S1**) ($CDCl_3$)



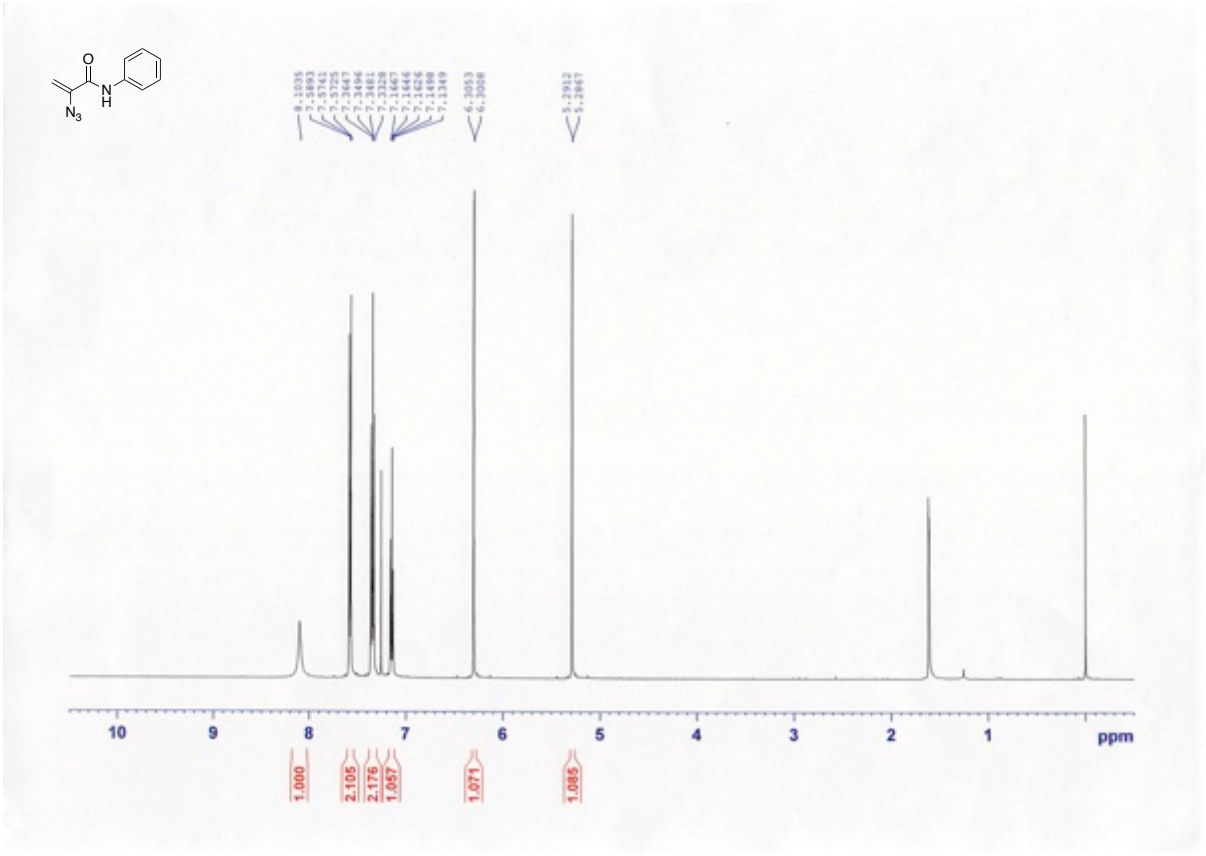


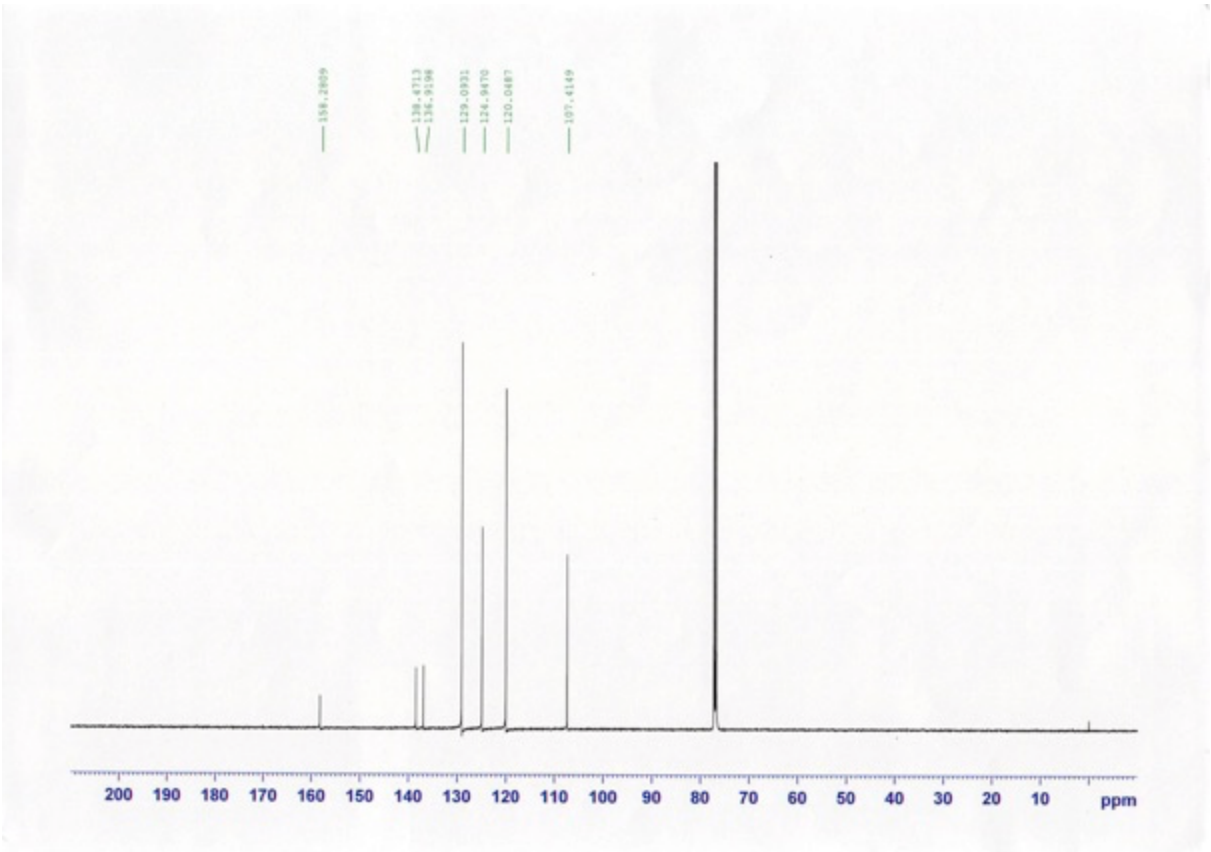
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azido-*N*-butylacrylamide (**S2**) ($CDCl_3$)



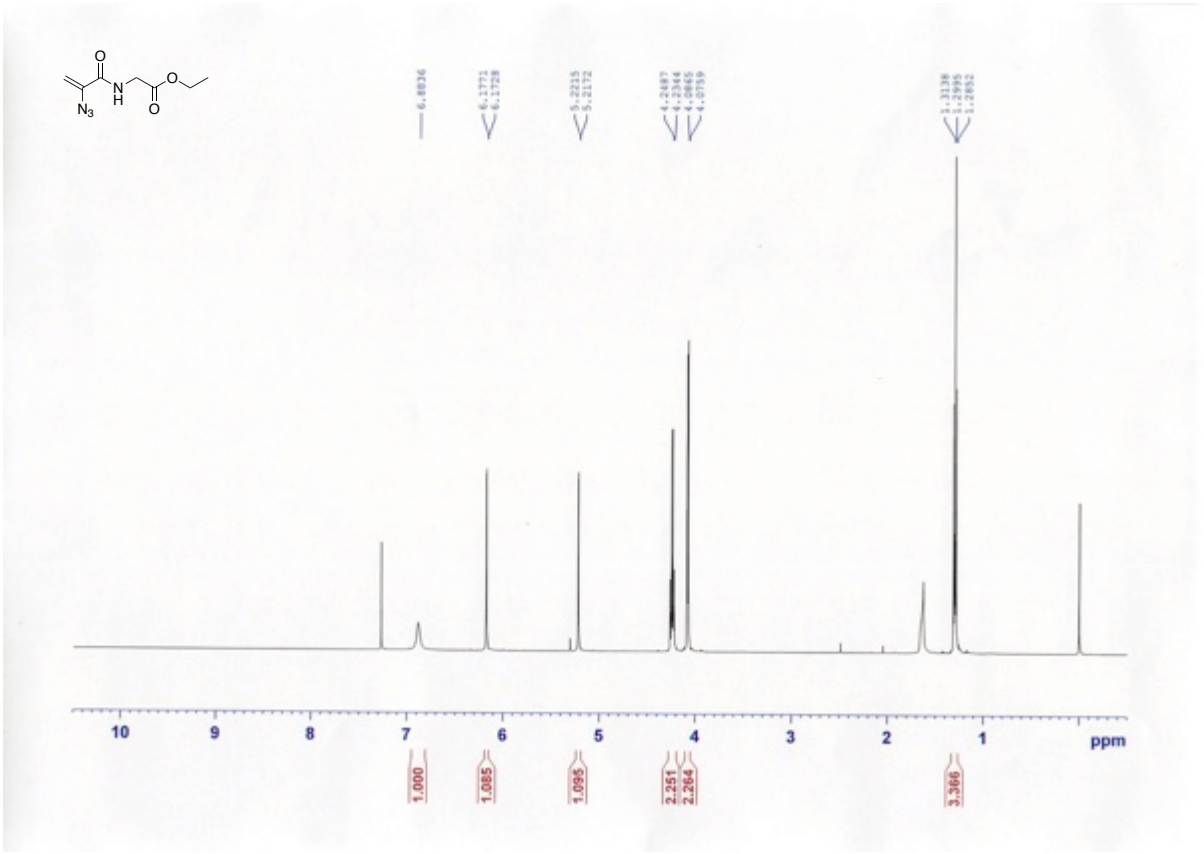


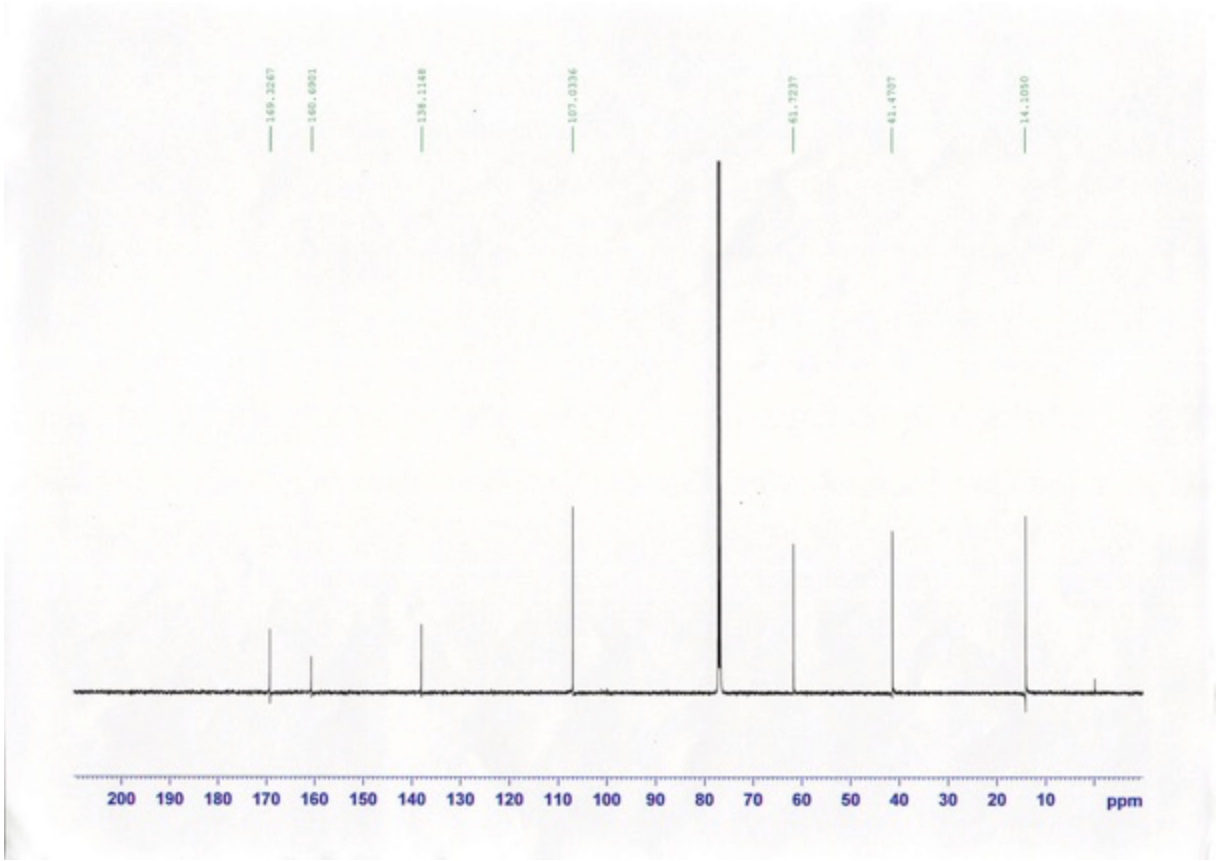
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azido-*N*-phenylacrylamide (**S3**) ($CDCl_3$)



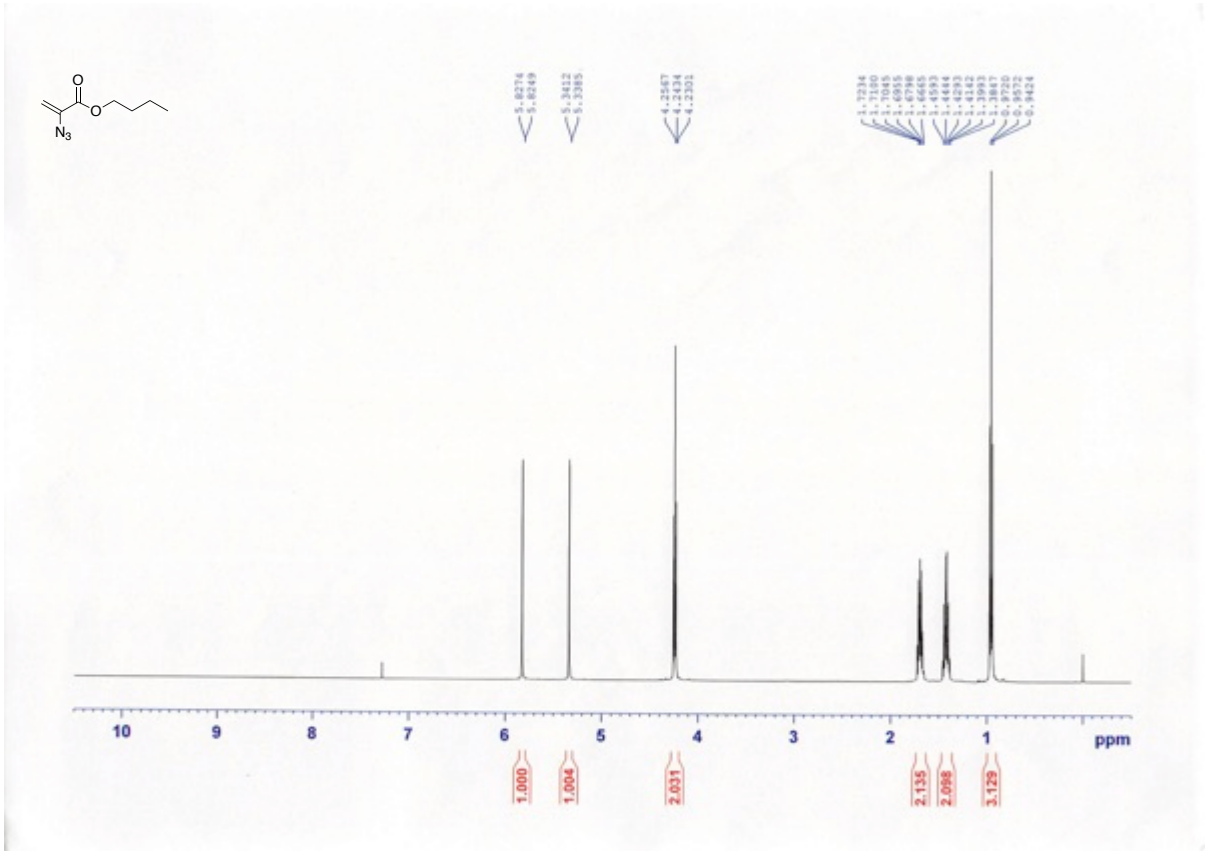


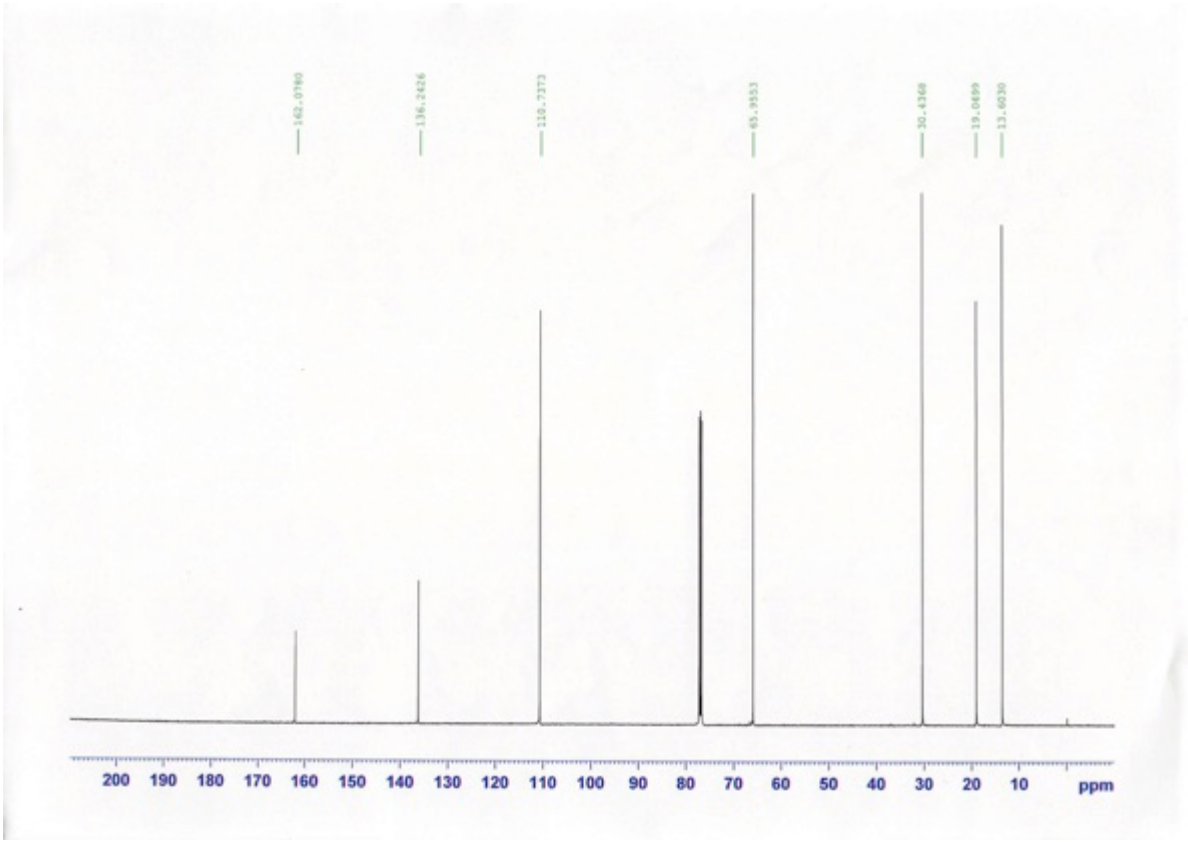
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of ethyl (2-azidoacryloyl)glycinate (**S4**) ($CDCl_3$)



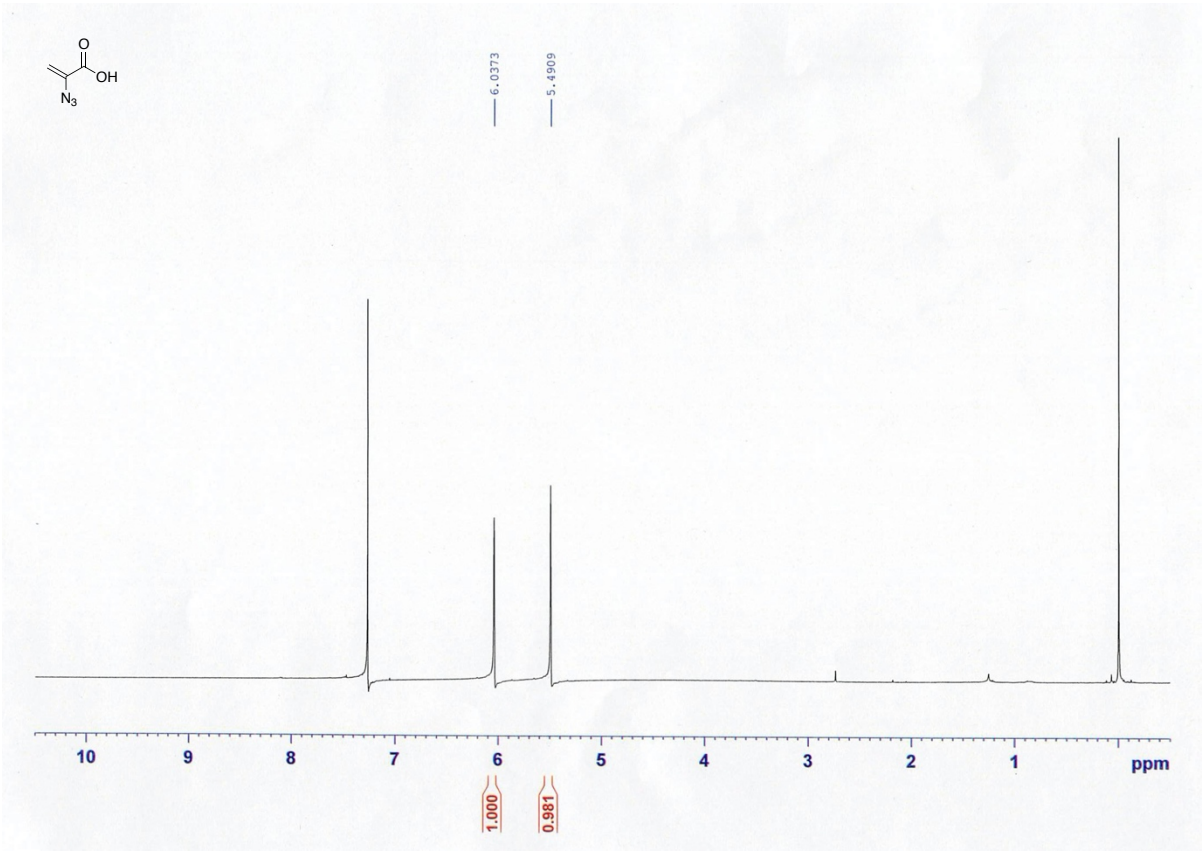


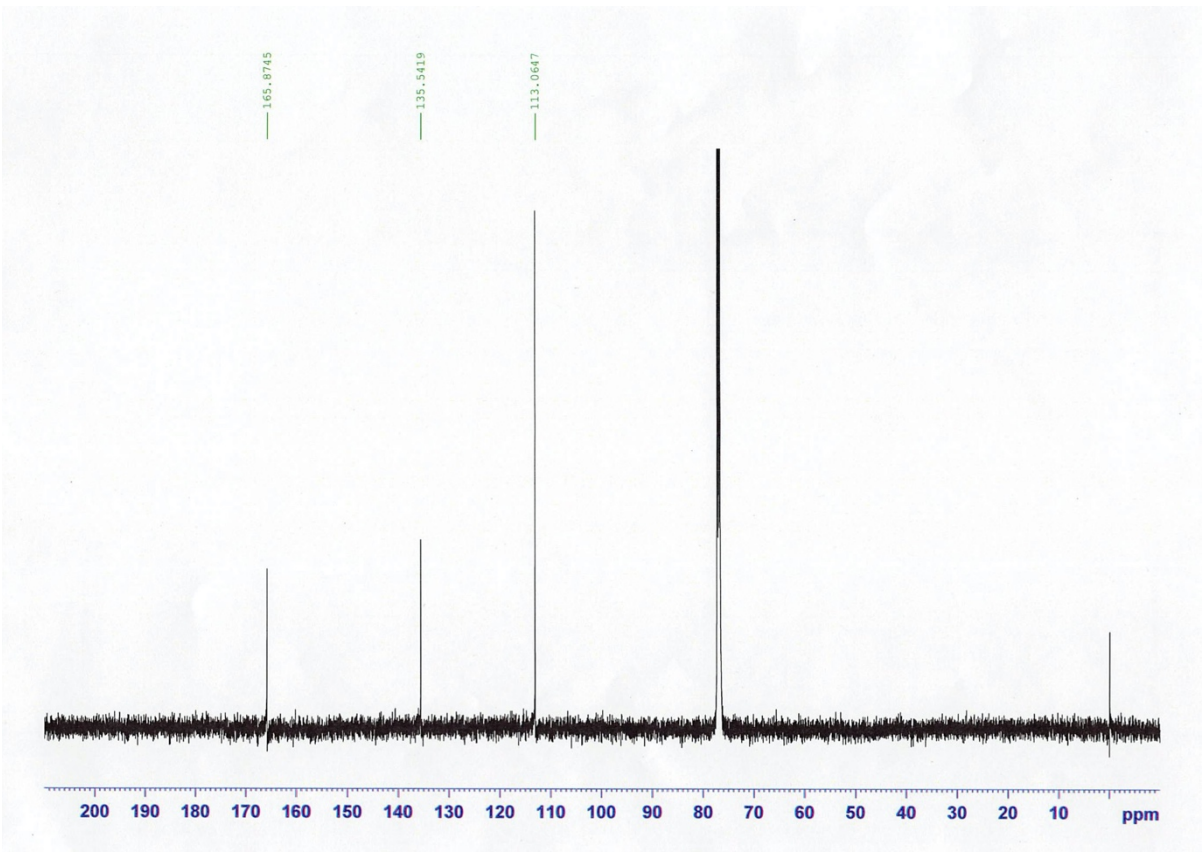
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of butyl 2-azidoacrylate (**S5**) ($CDCl_3$)



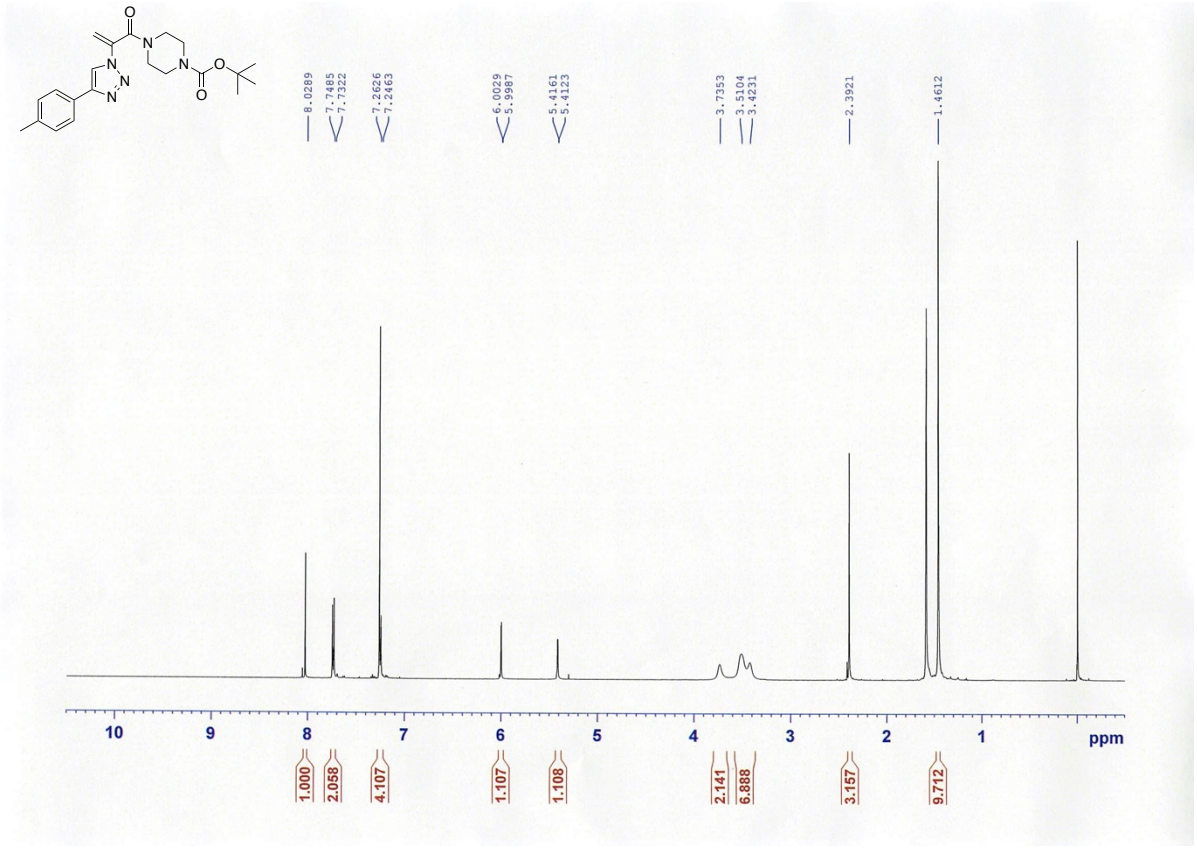


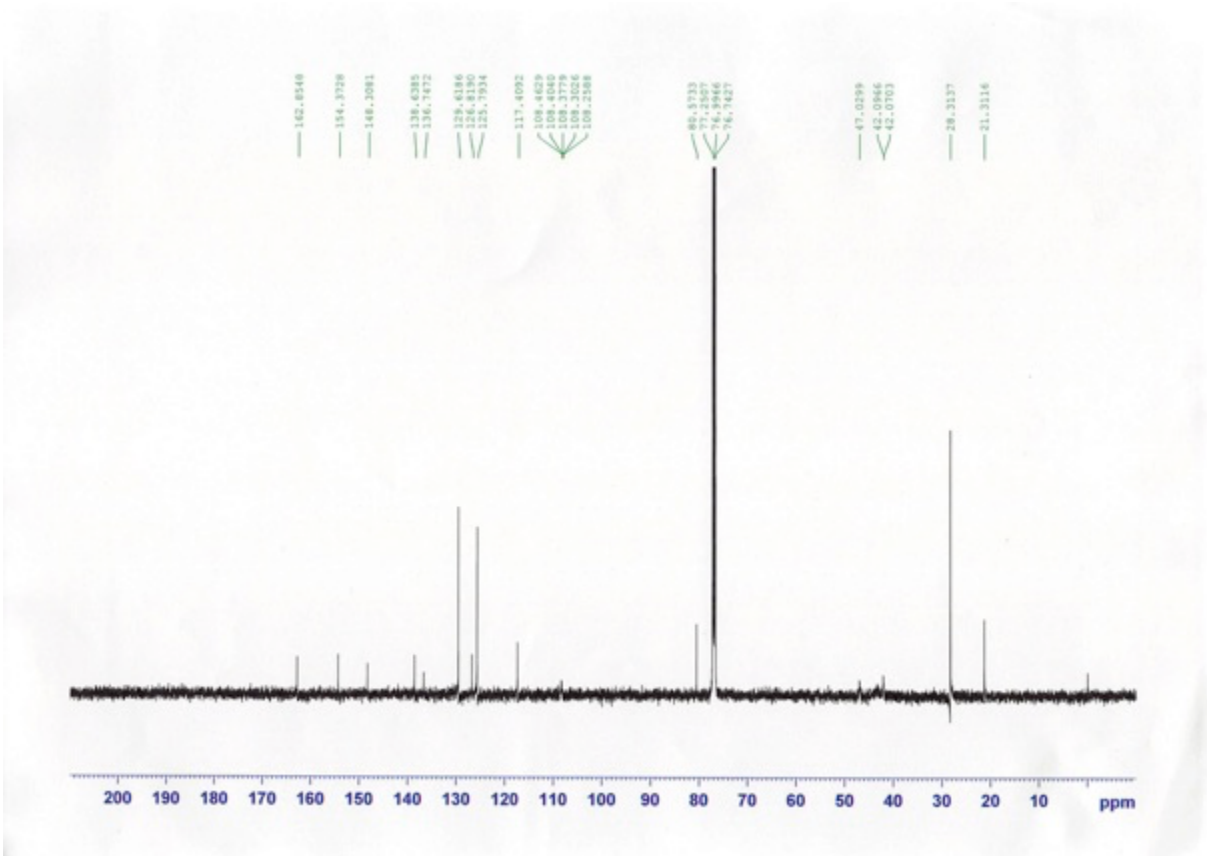
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azidoacrylic acid (**S6**) ($CDCl_3$)



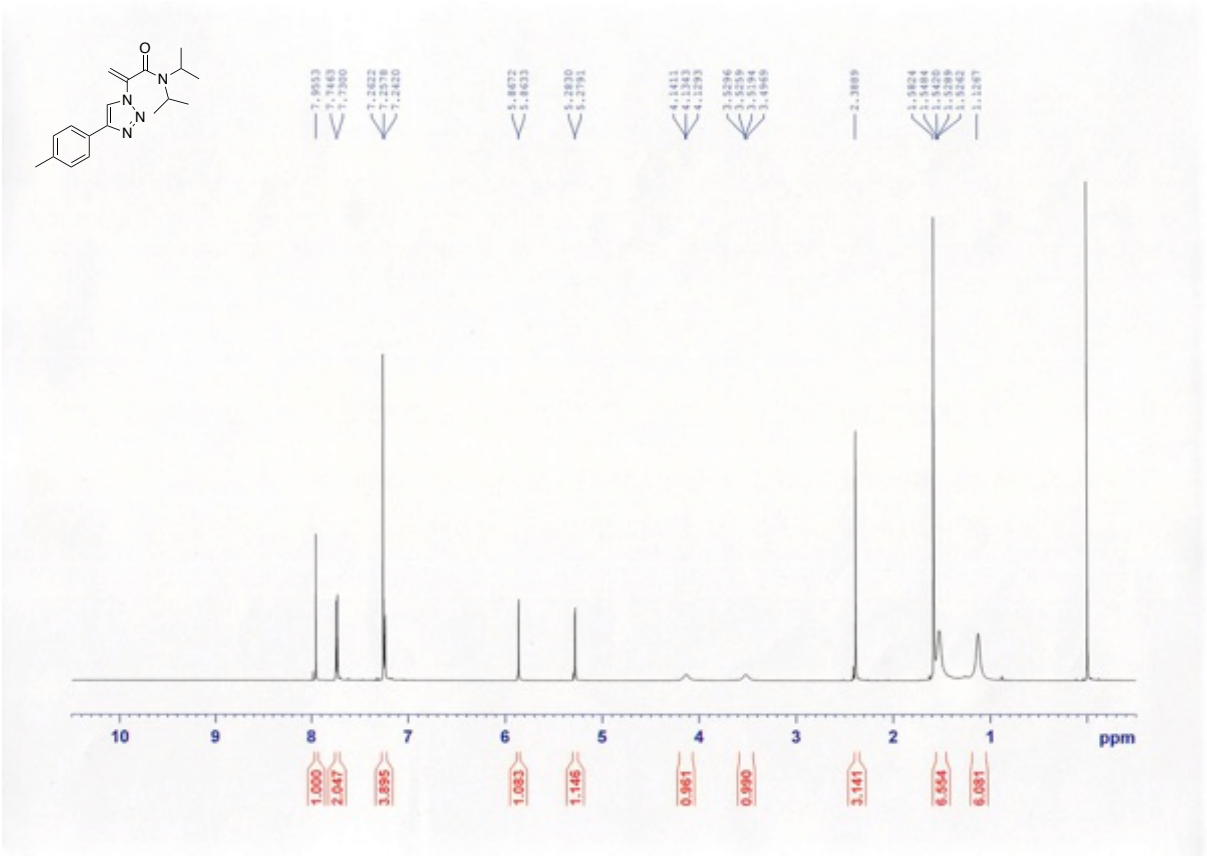


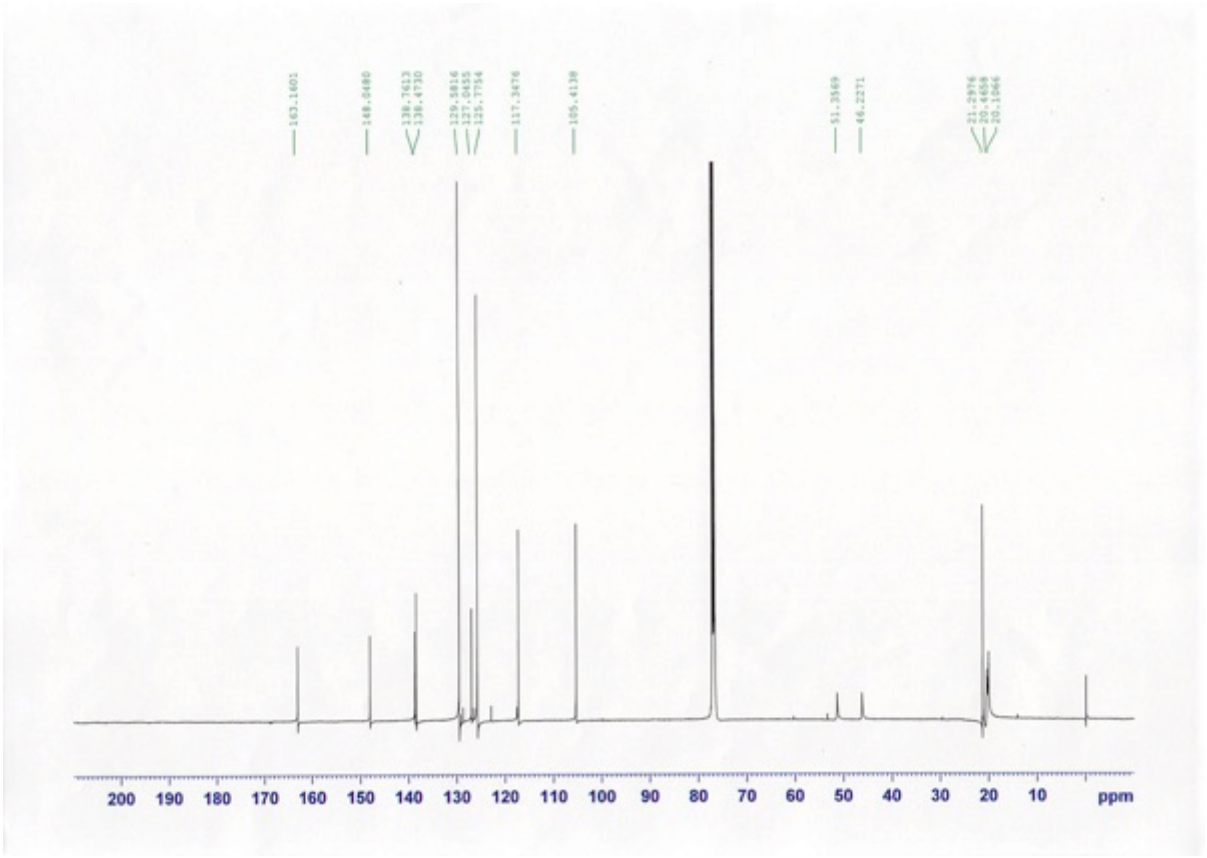
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19a**) ($CDCl_3$)



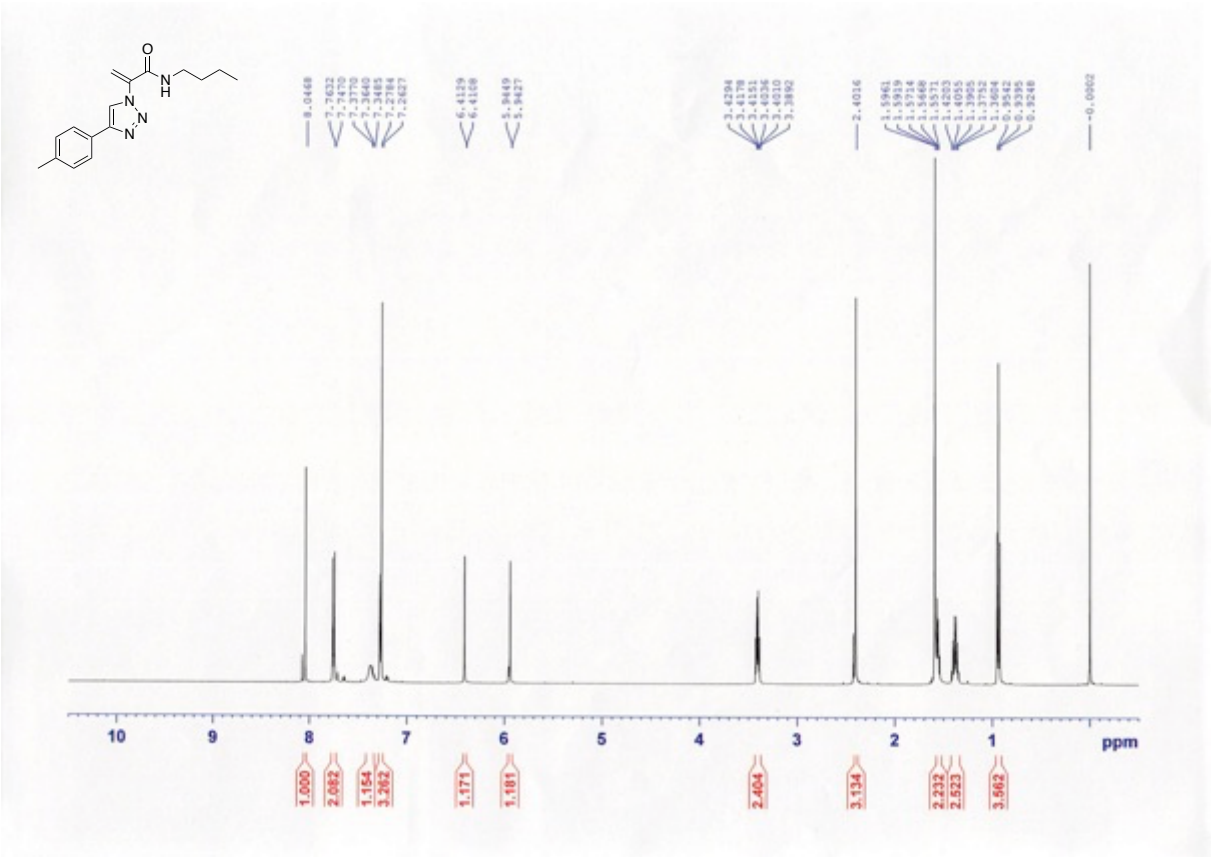


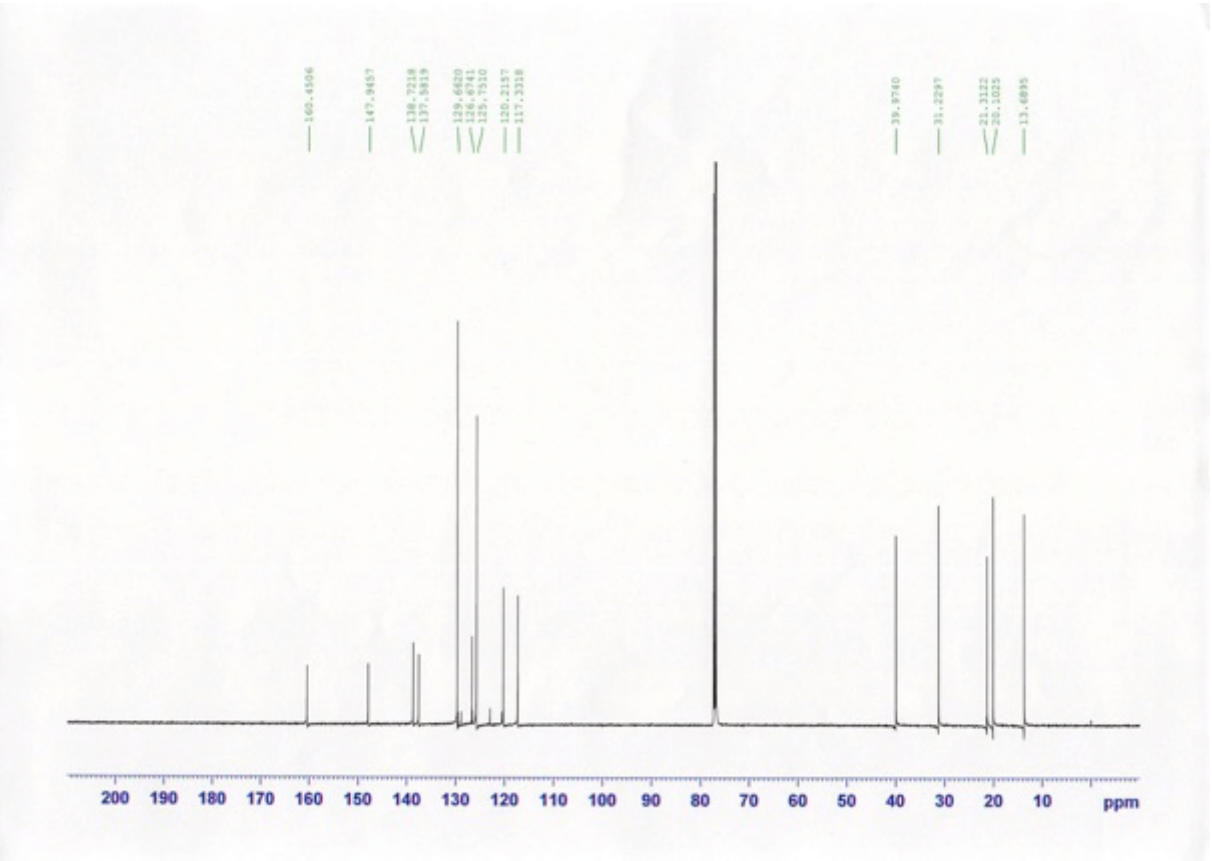
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *N*,*N*-diisopropyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**19b**) ($CDCl_3$)



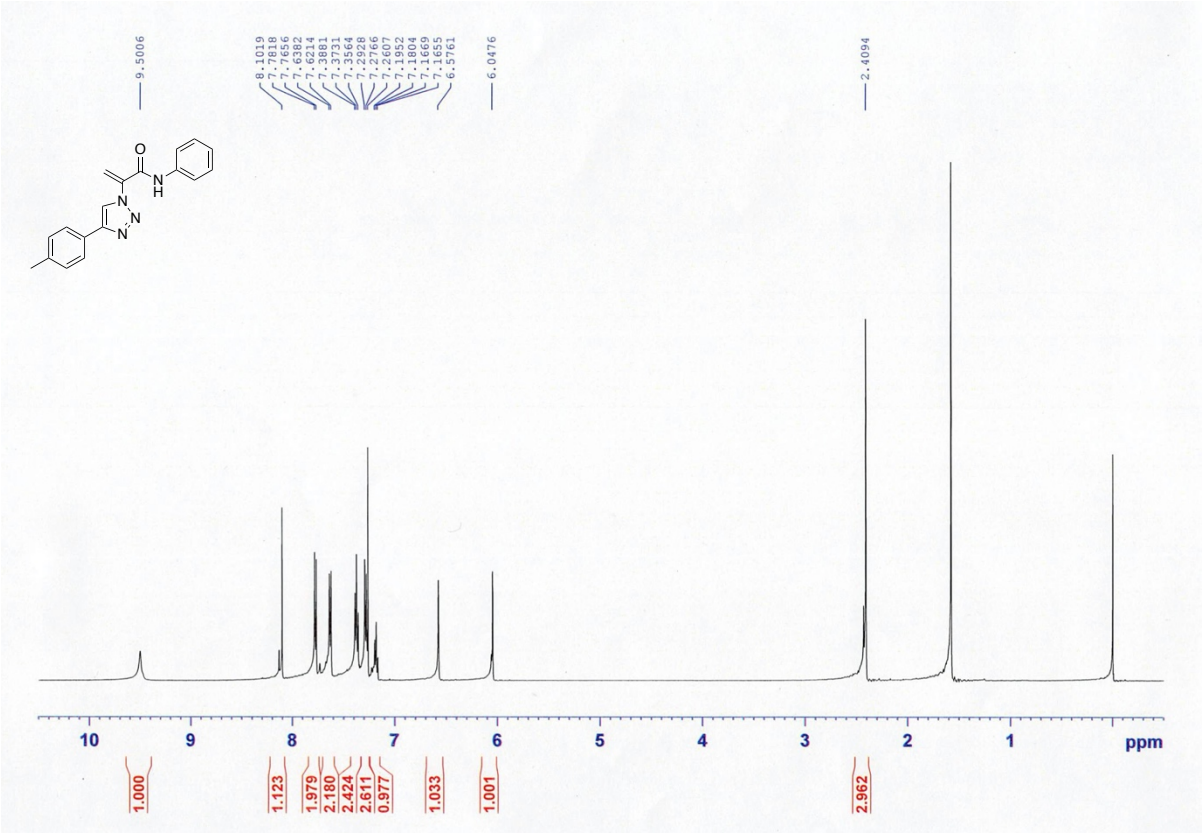


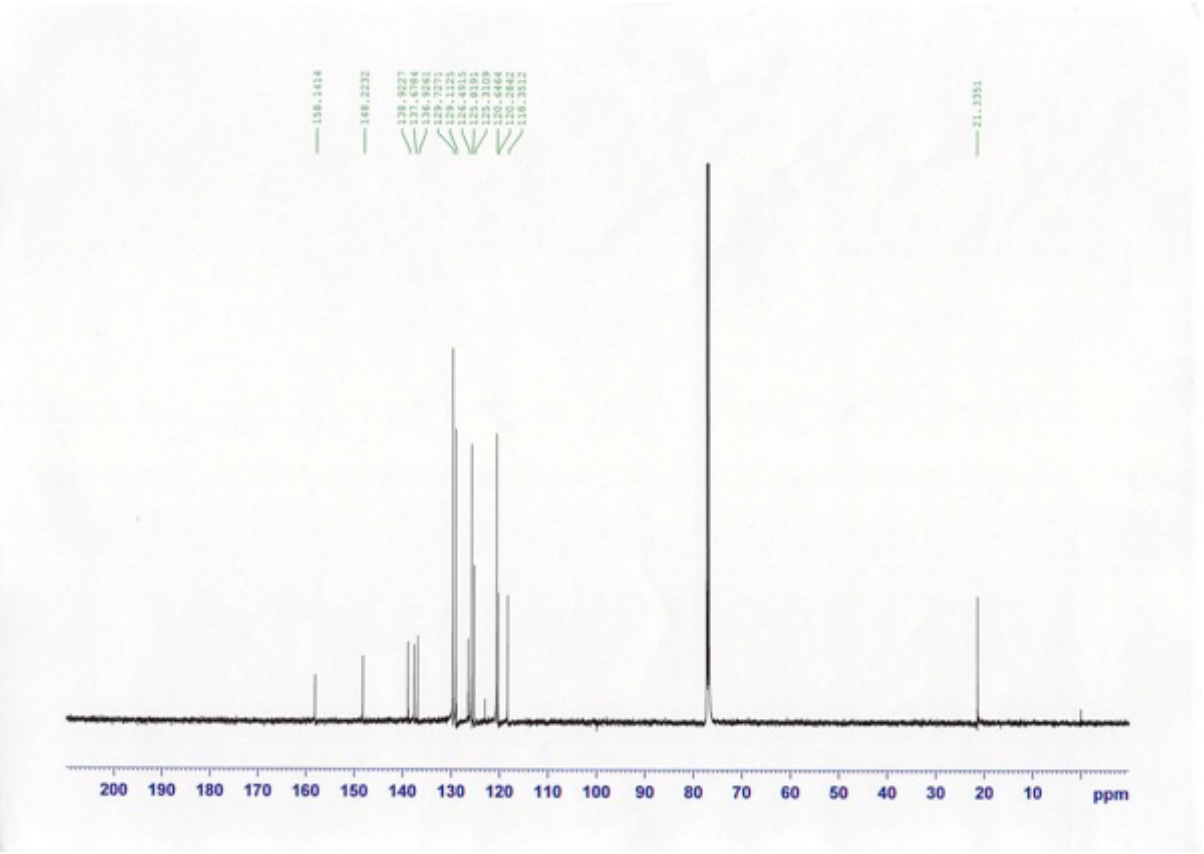
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *N*-butyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**19c**) ($CDCl_3$)



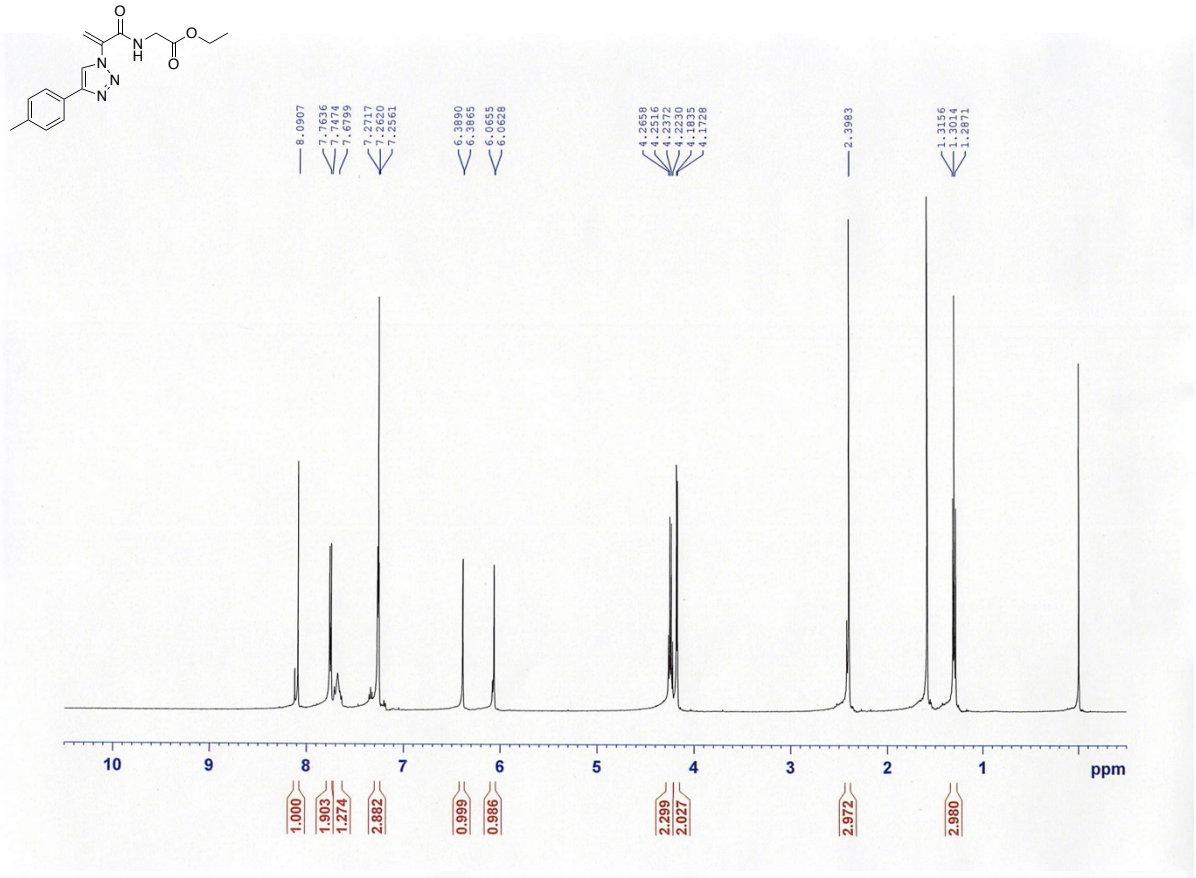


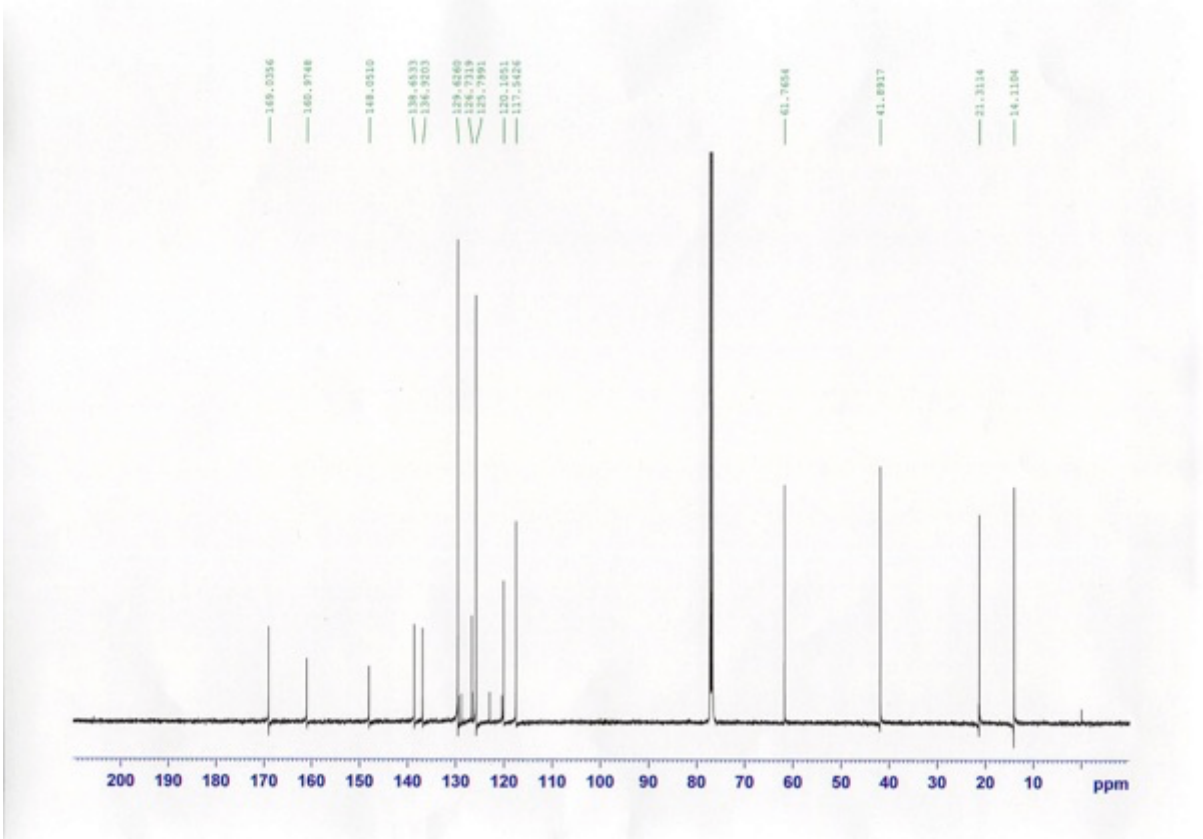
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *N*-phenyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**19d**) ($CDCl_3$)



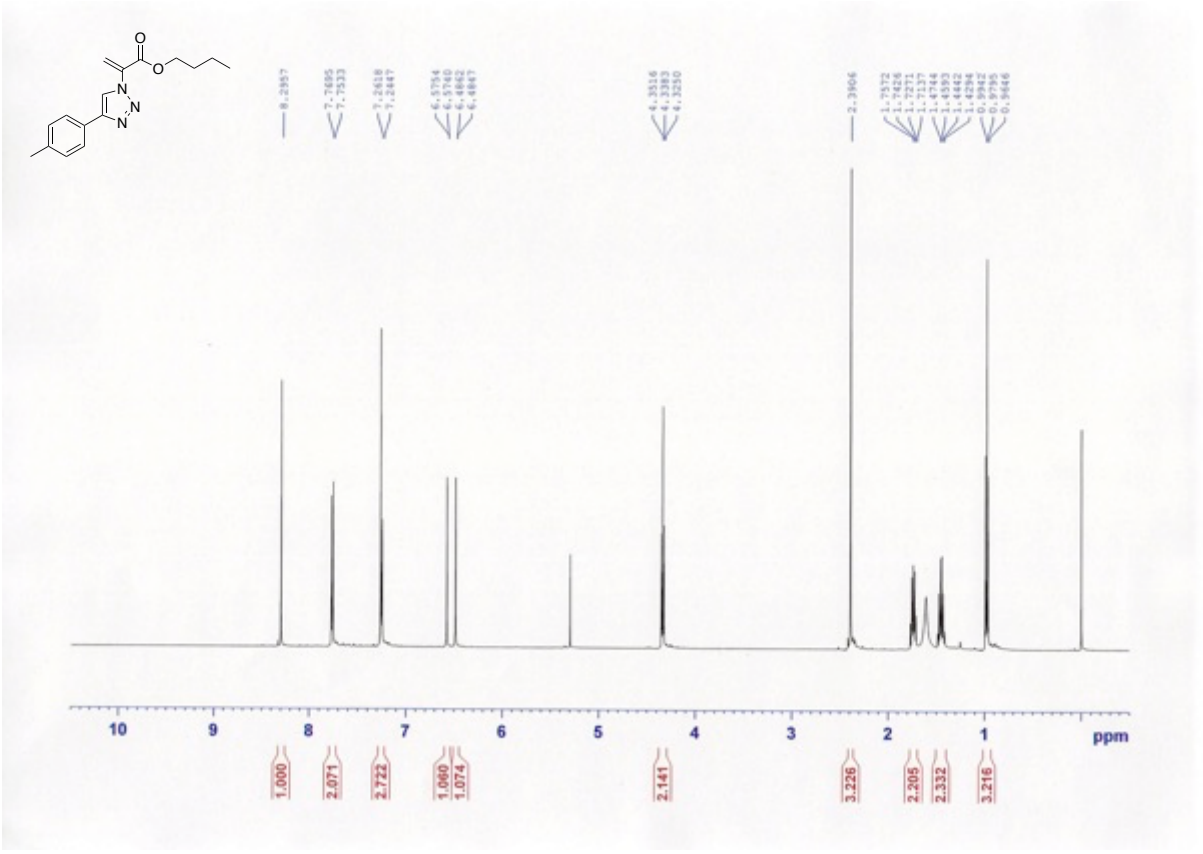


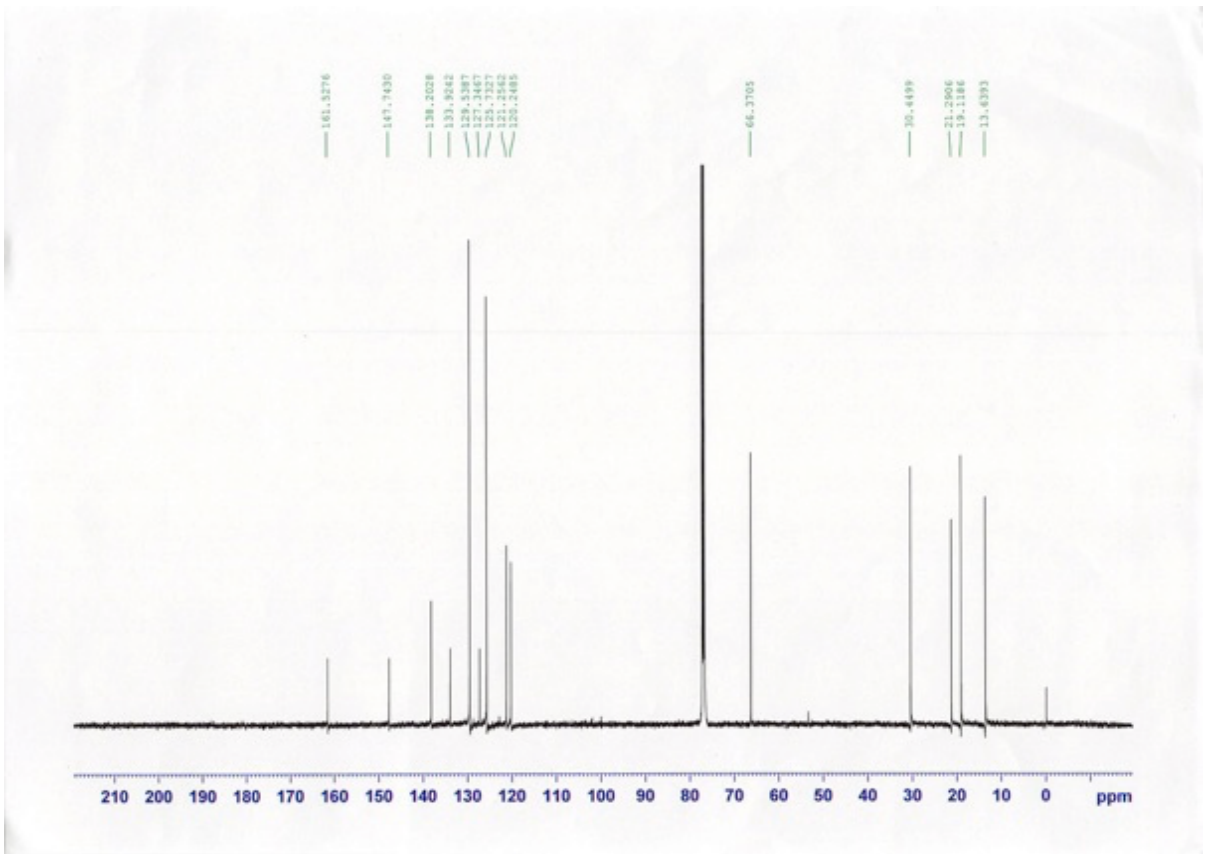
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of ethyl (2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)glycinate (**19e**) ($CDCl_3$)



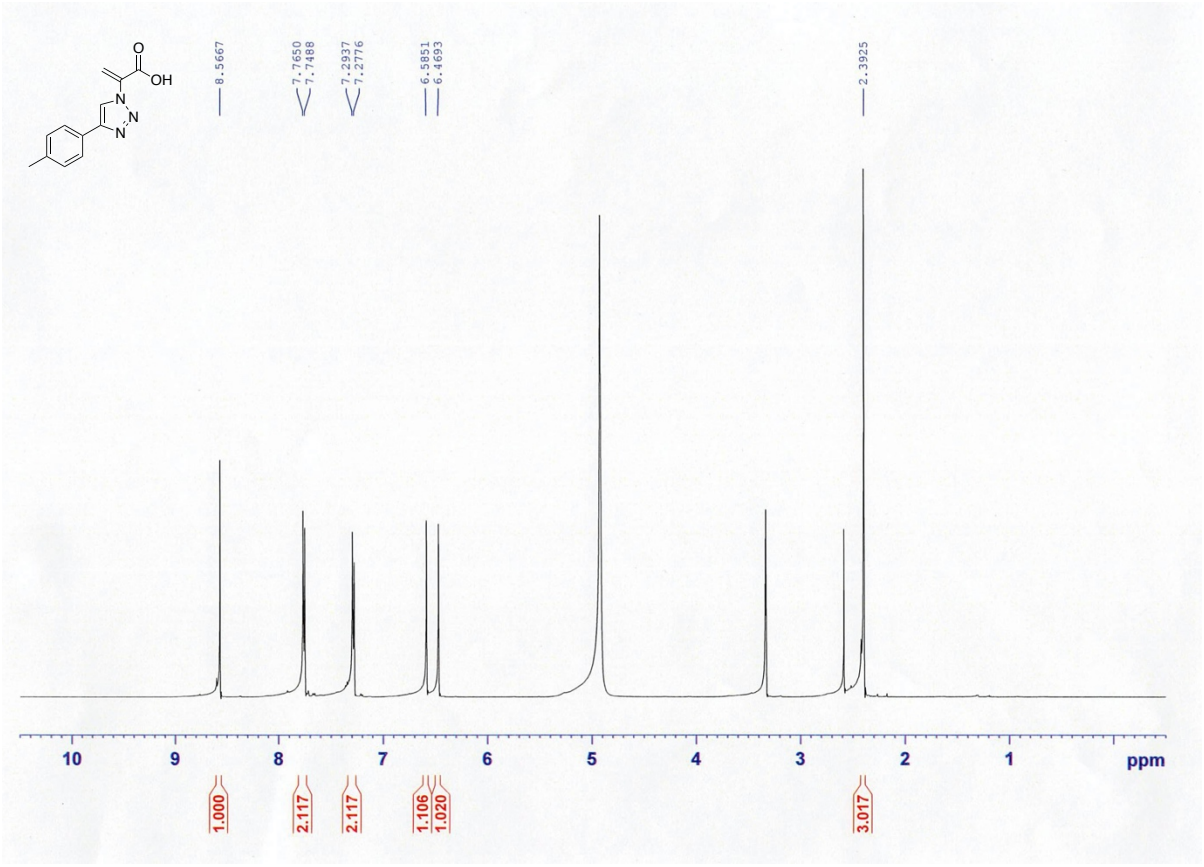


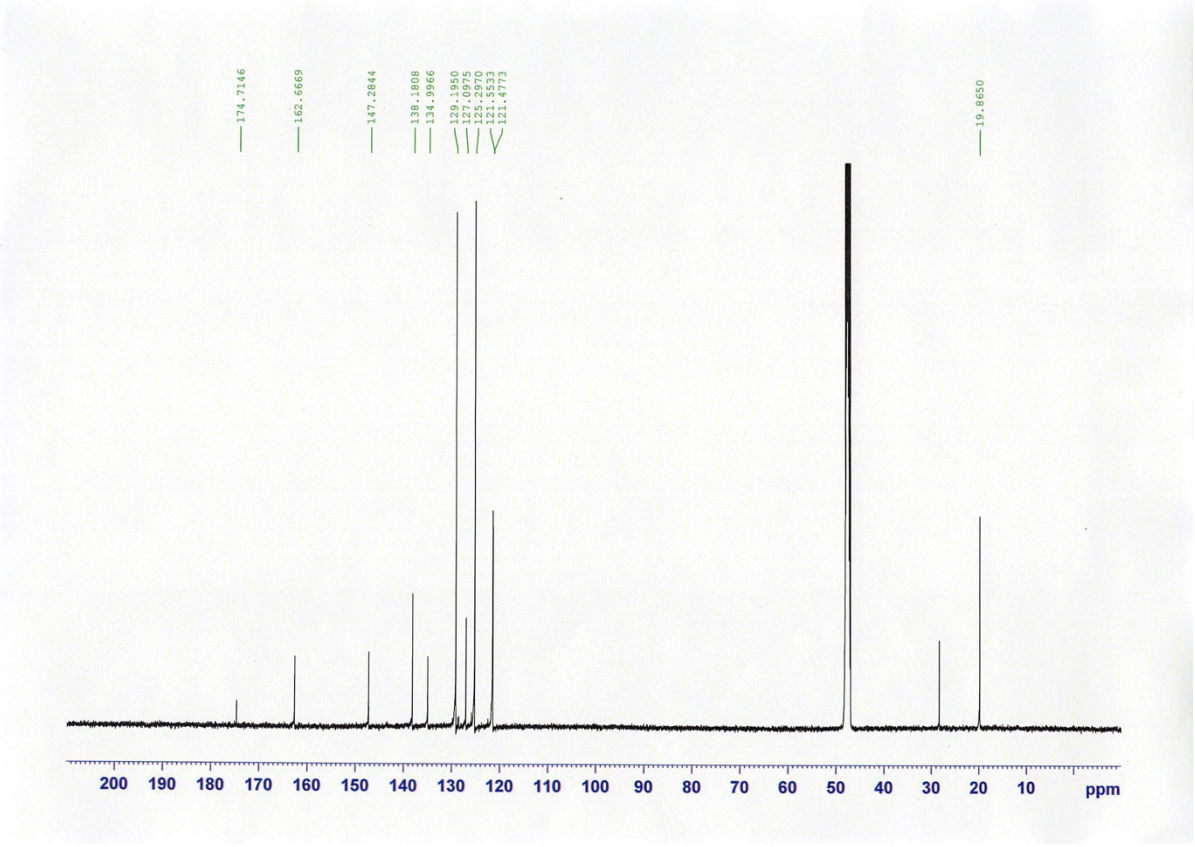
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of butyl 2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylate (**19f**) ($CDCl_3$)



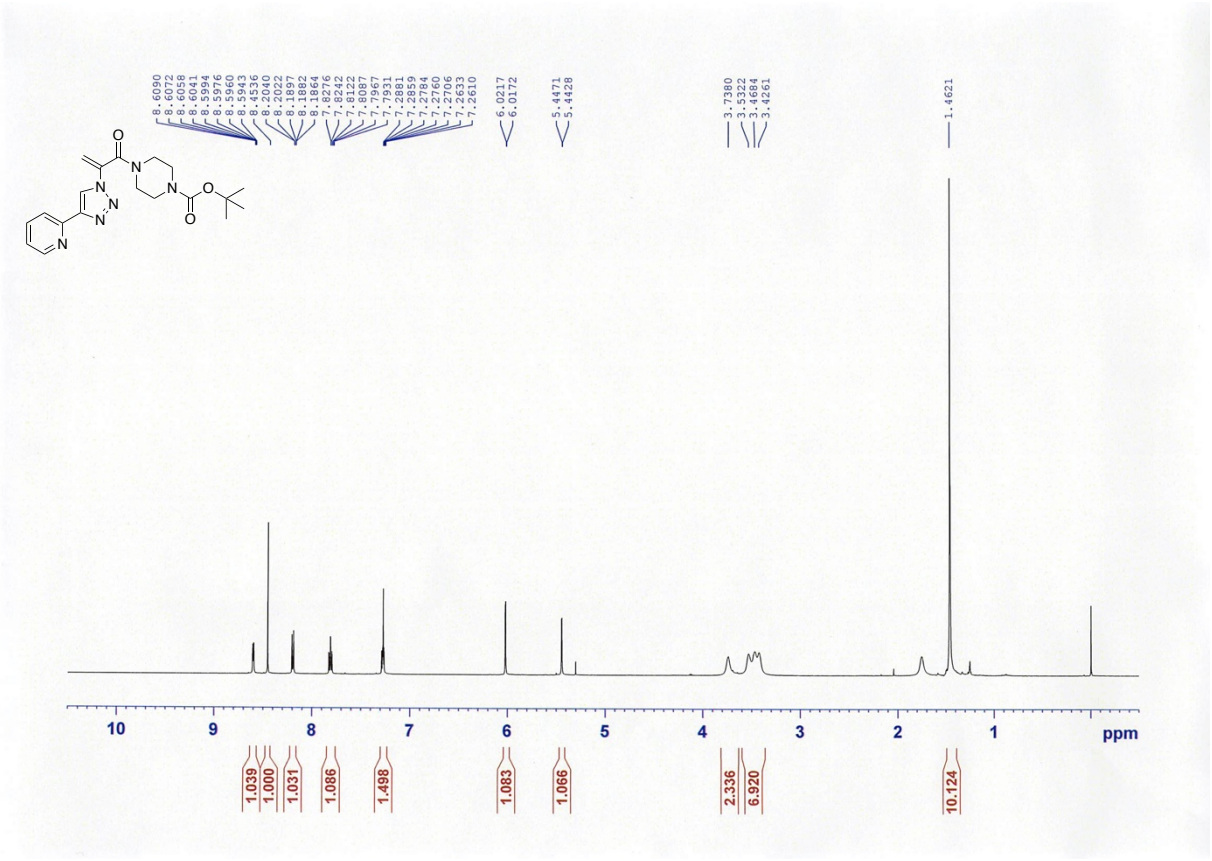


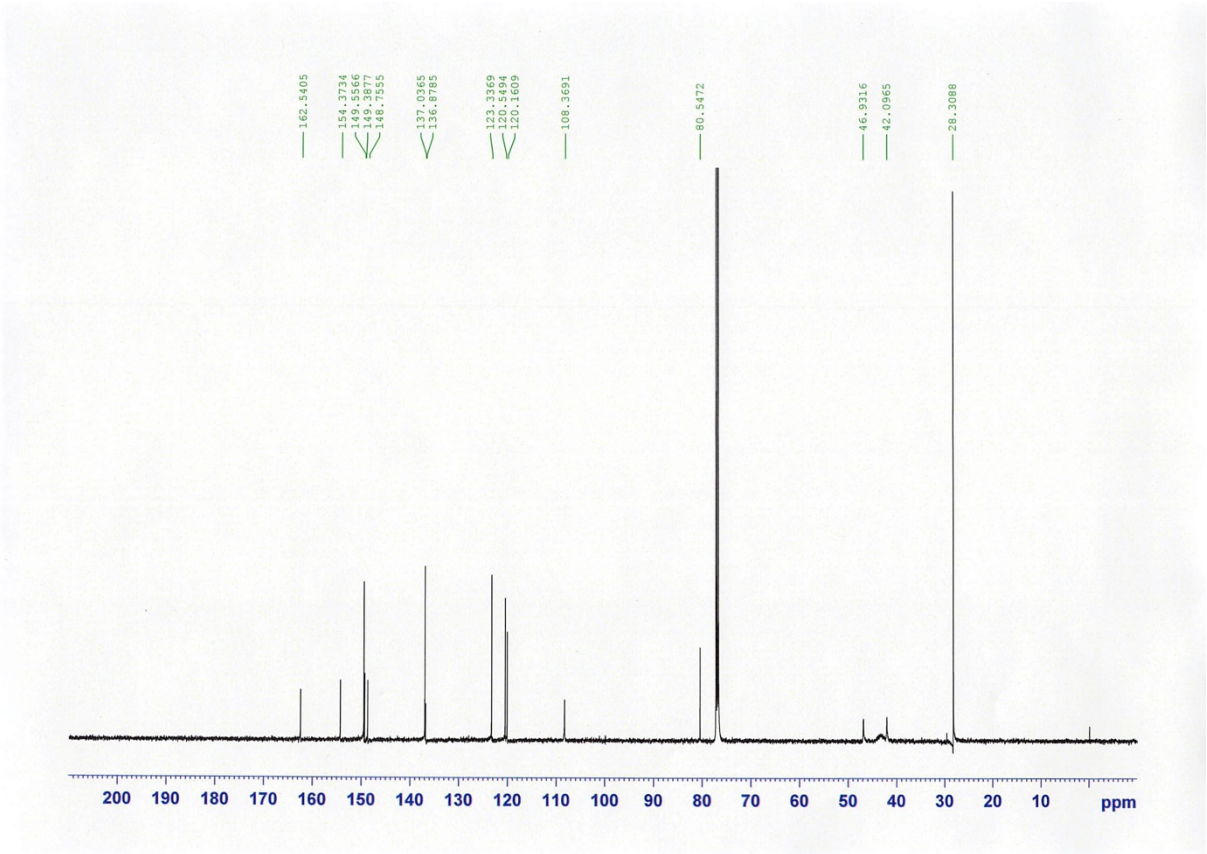
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylic acid (**19g**) ($CDCl_3$)



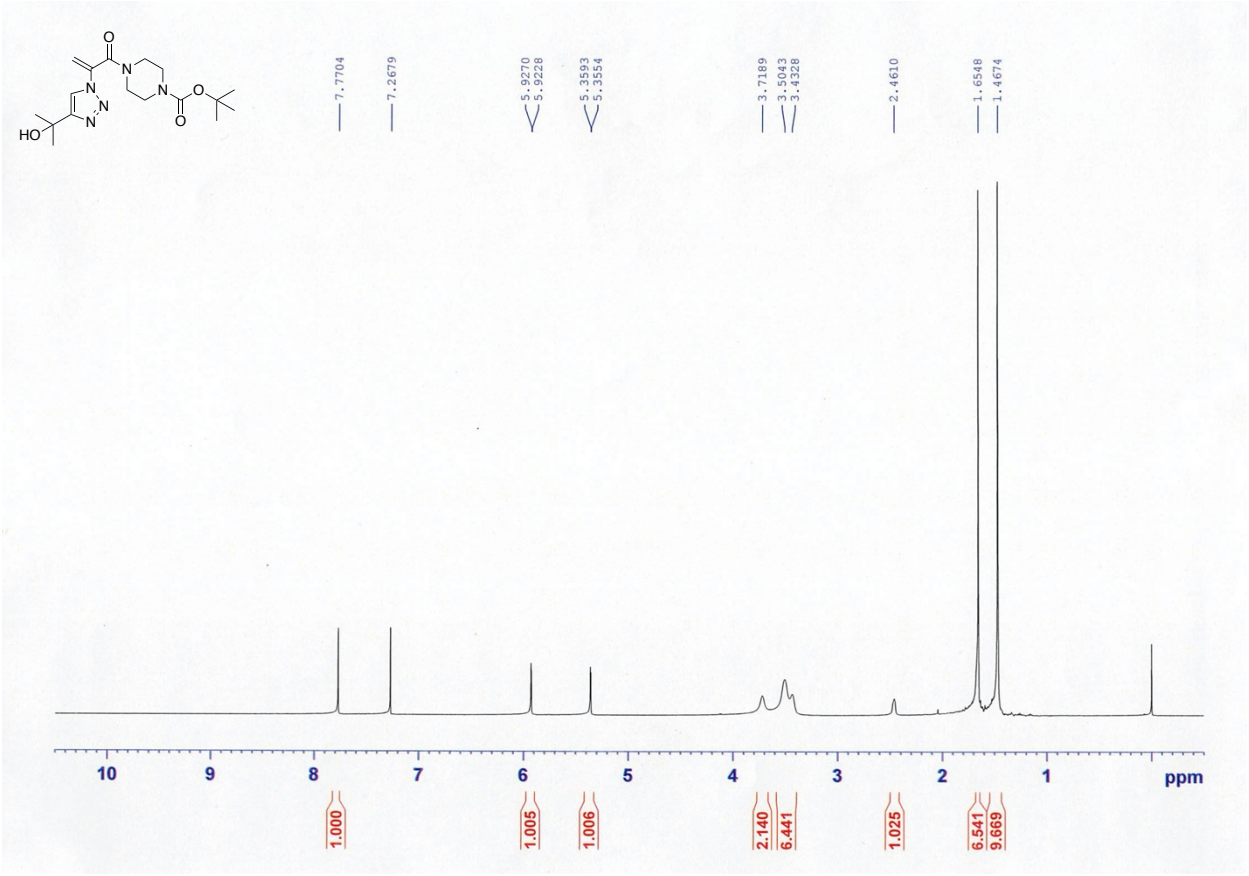


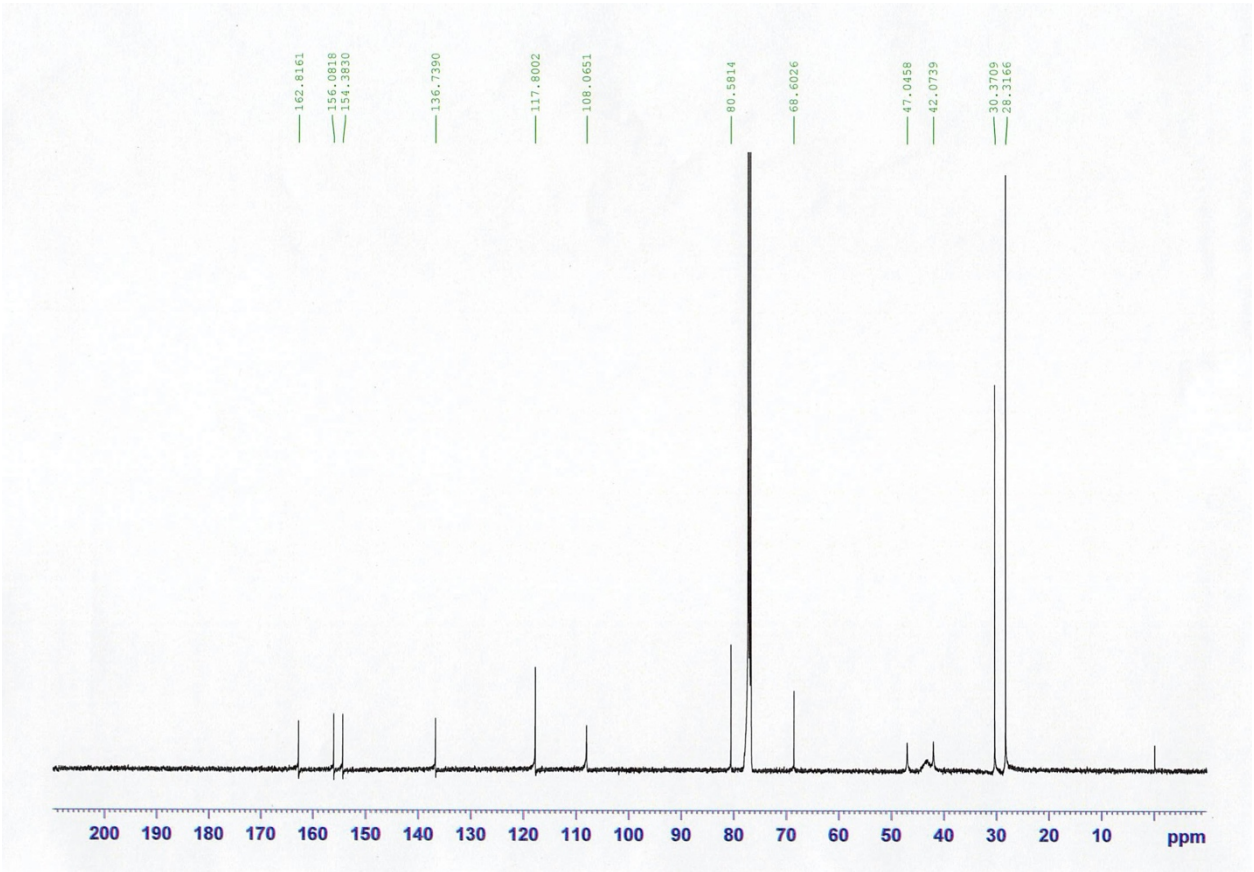
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19h**) ($CDCl_3$)



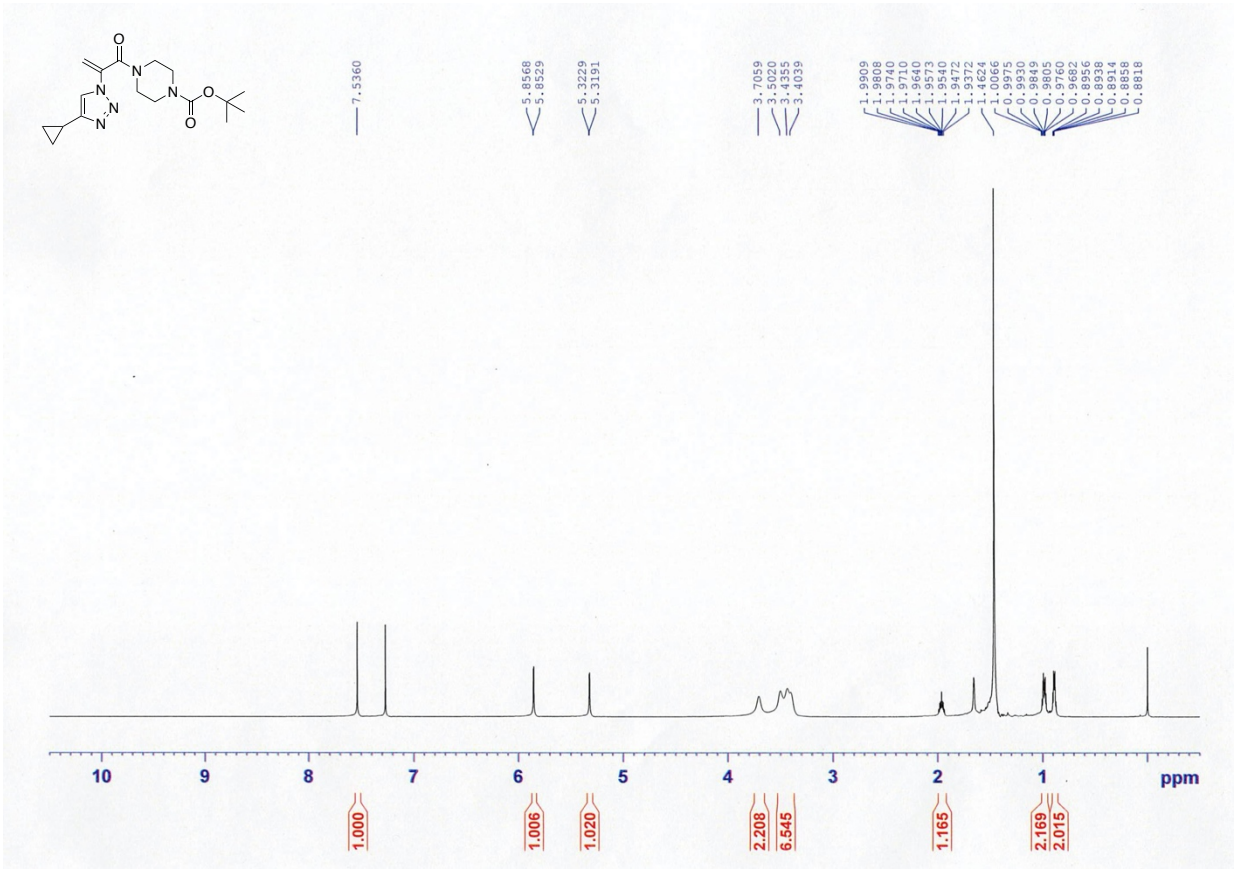


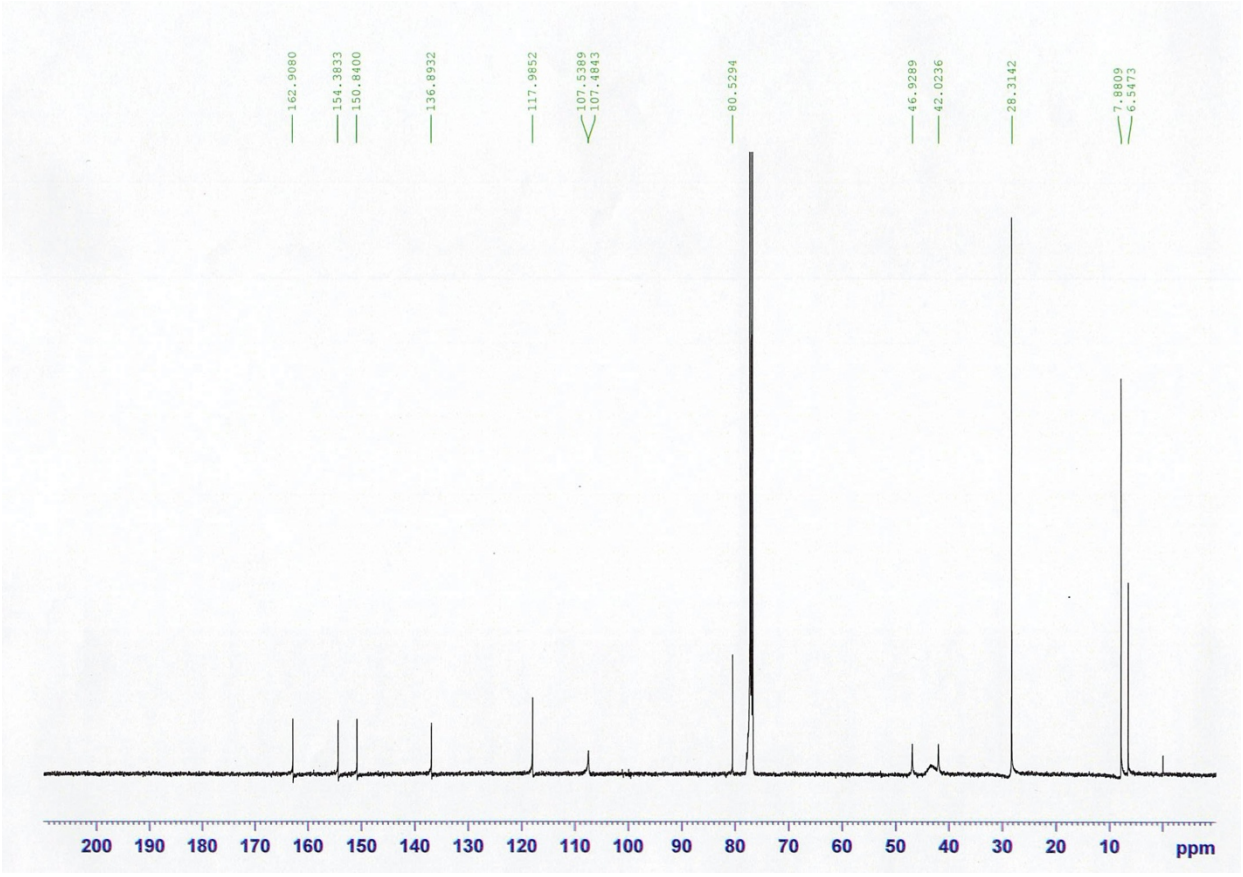
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19i**) ($CDCl_3$)



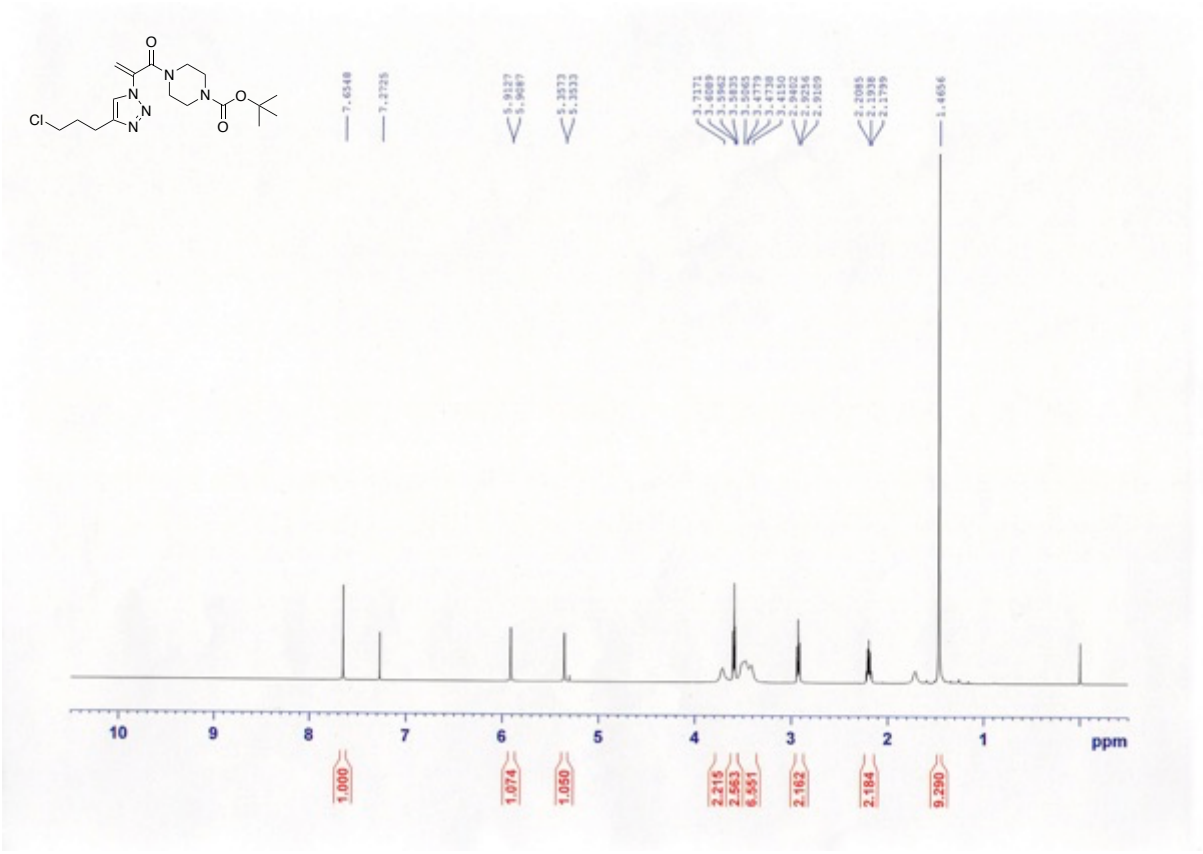


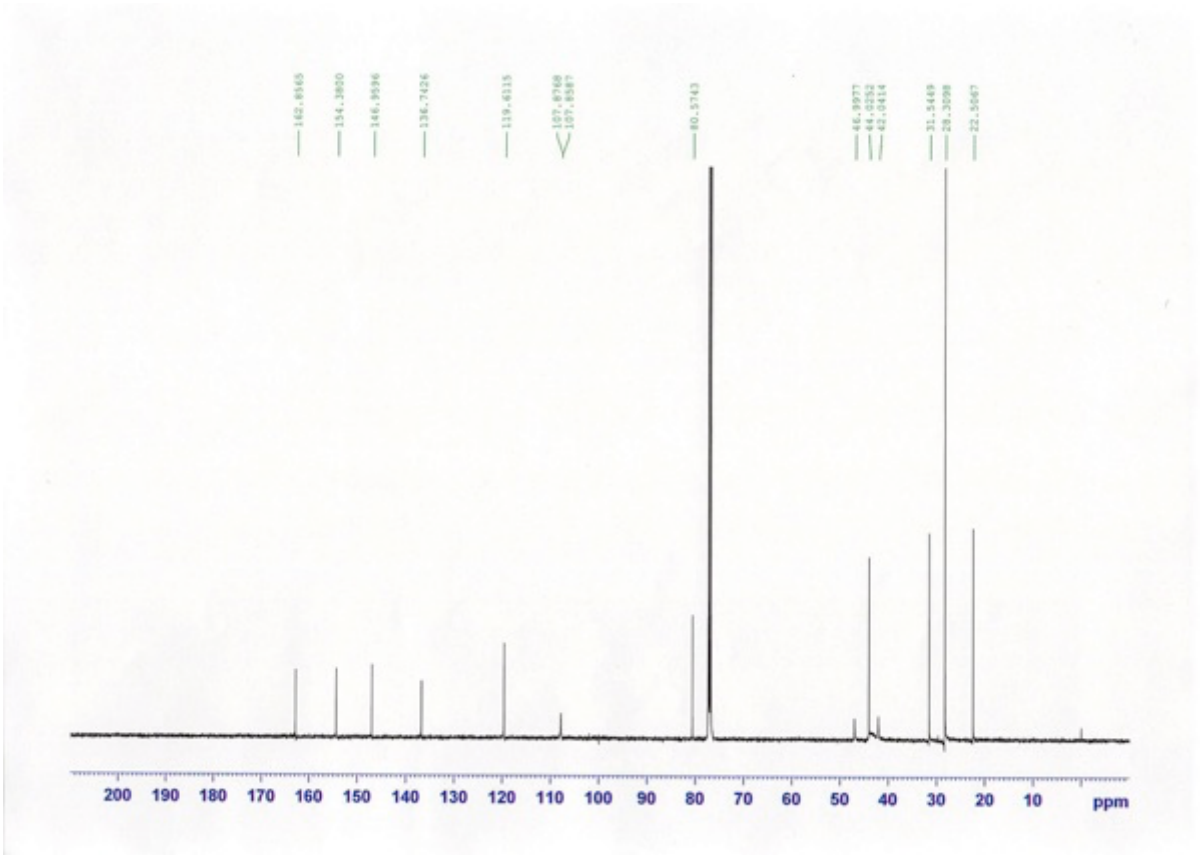
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19j**) ($CDCl_3$)



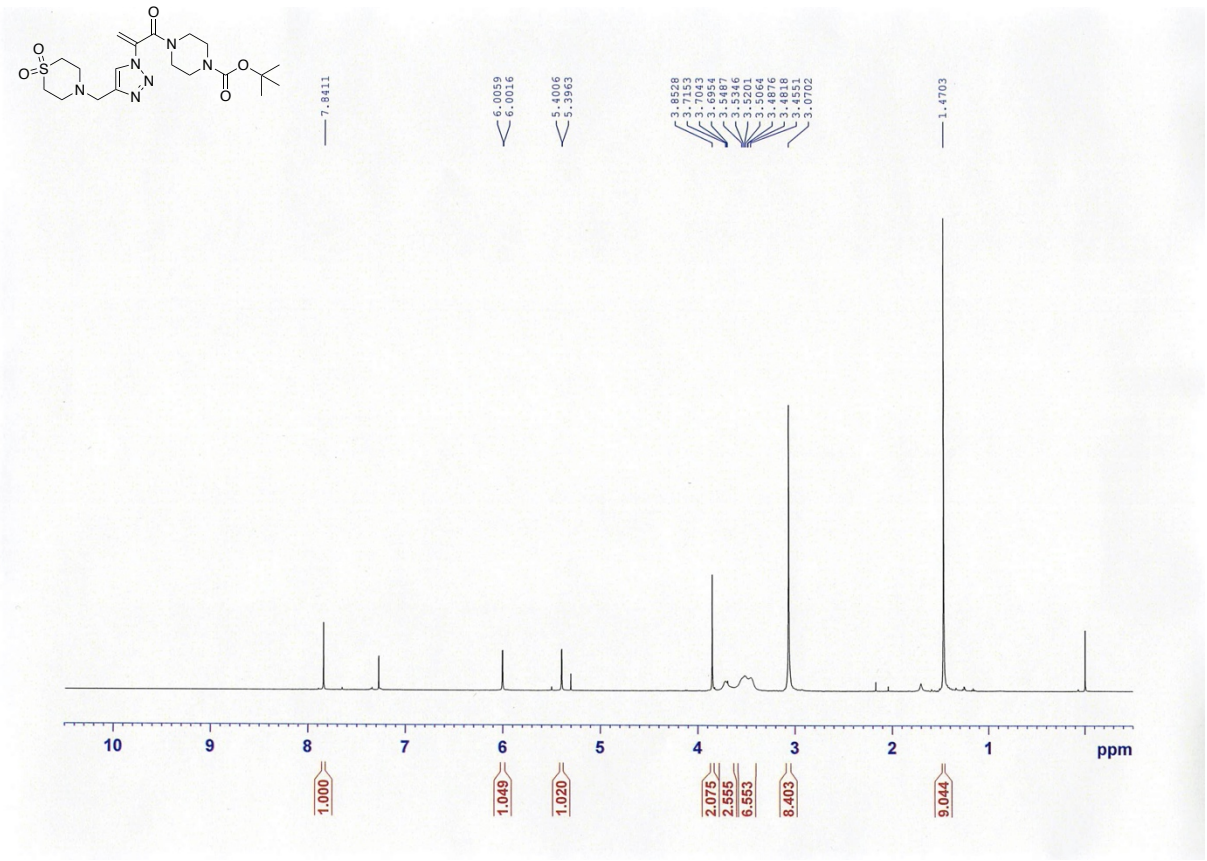


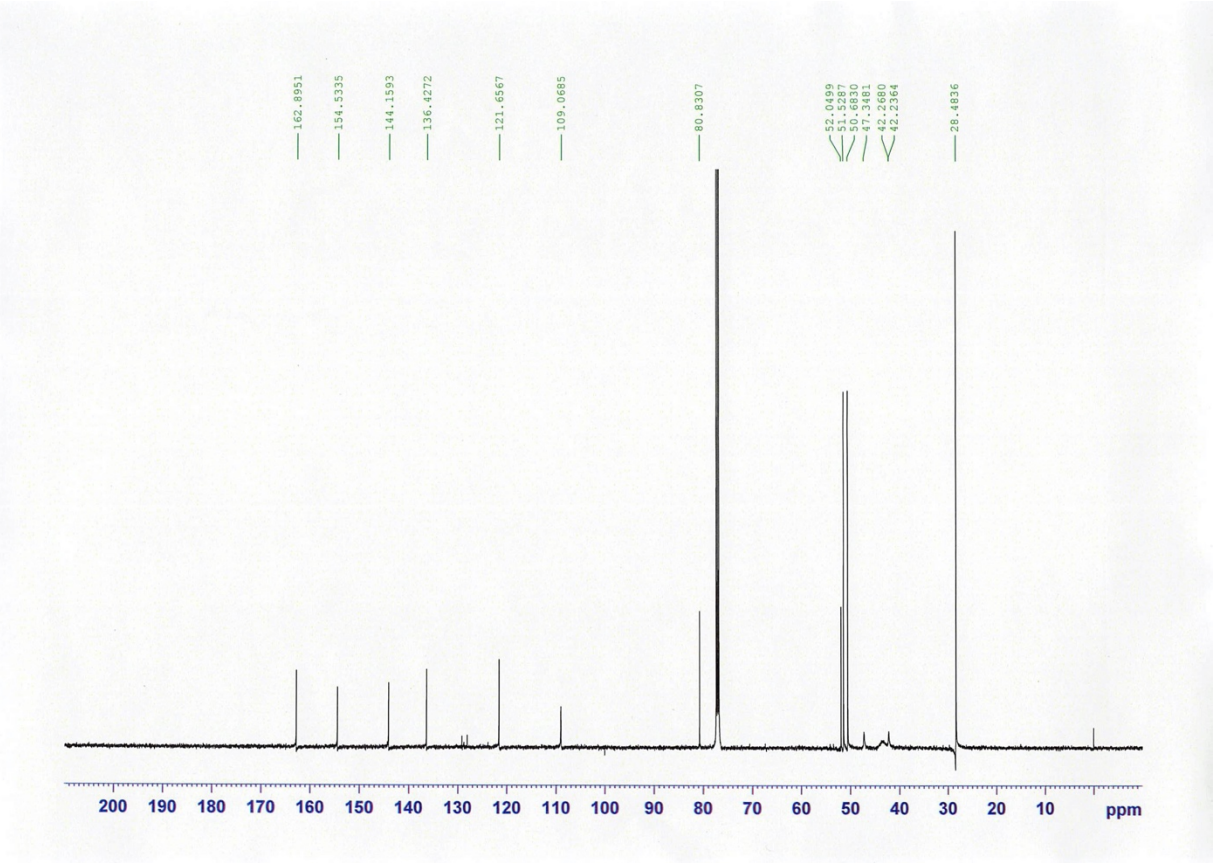
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(4-(3-chloropropyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19k**) ($CDCl_3$)



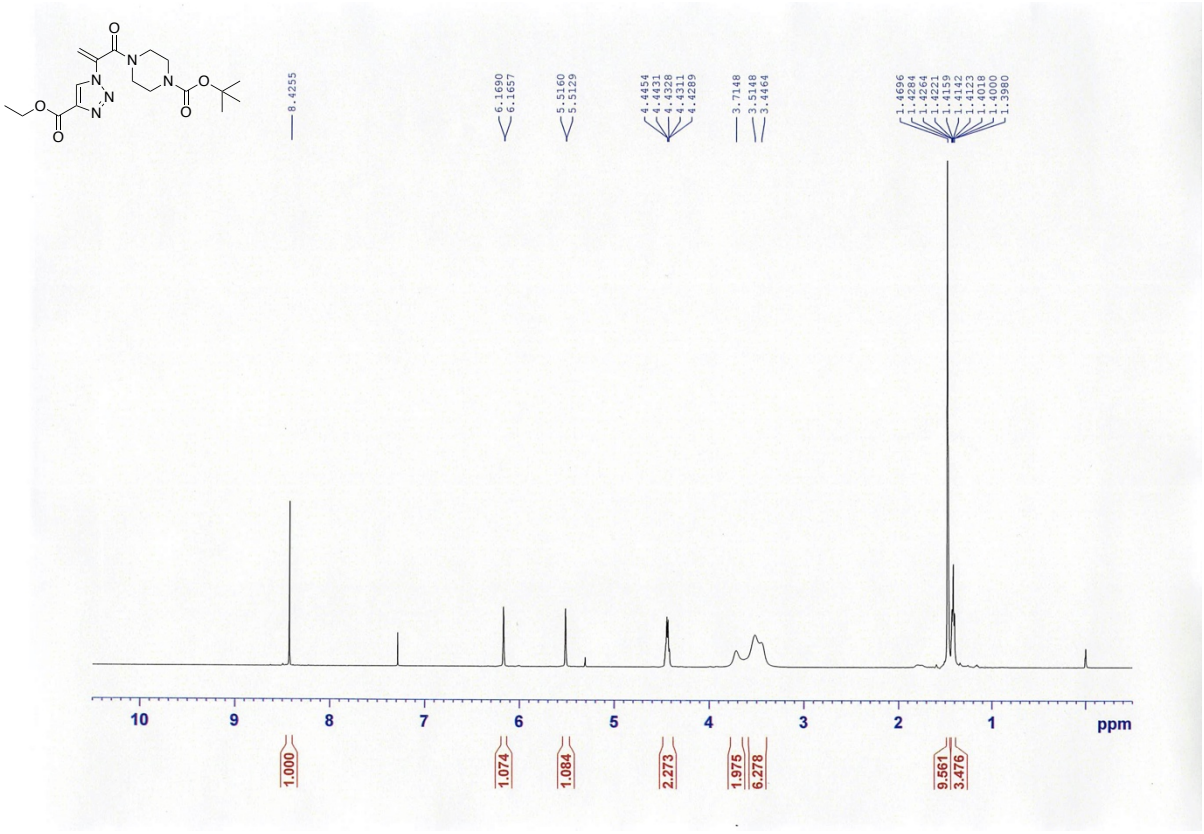


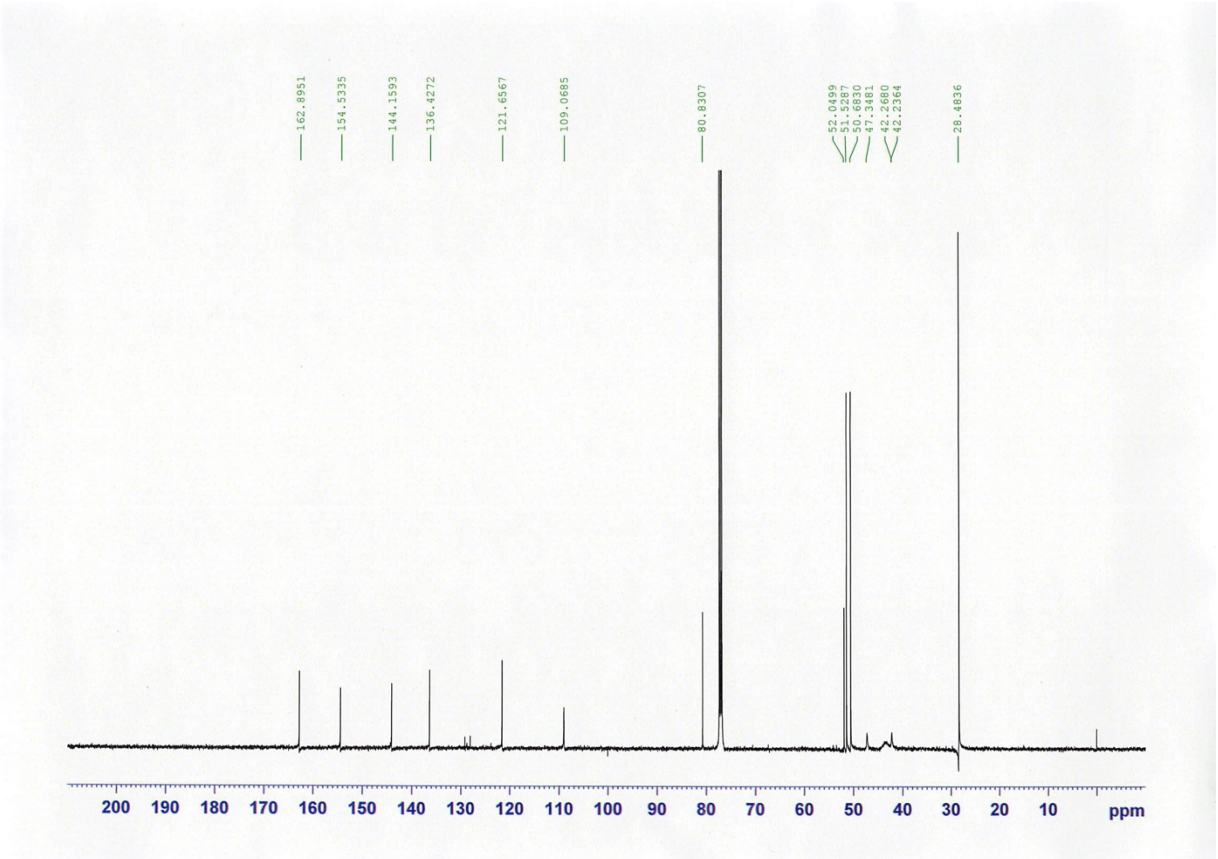
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(4-((1,1-dioxidothiomorpholino)methyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19l**) ($CDCl_3$)



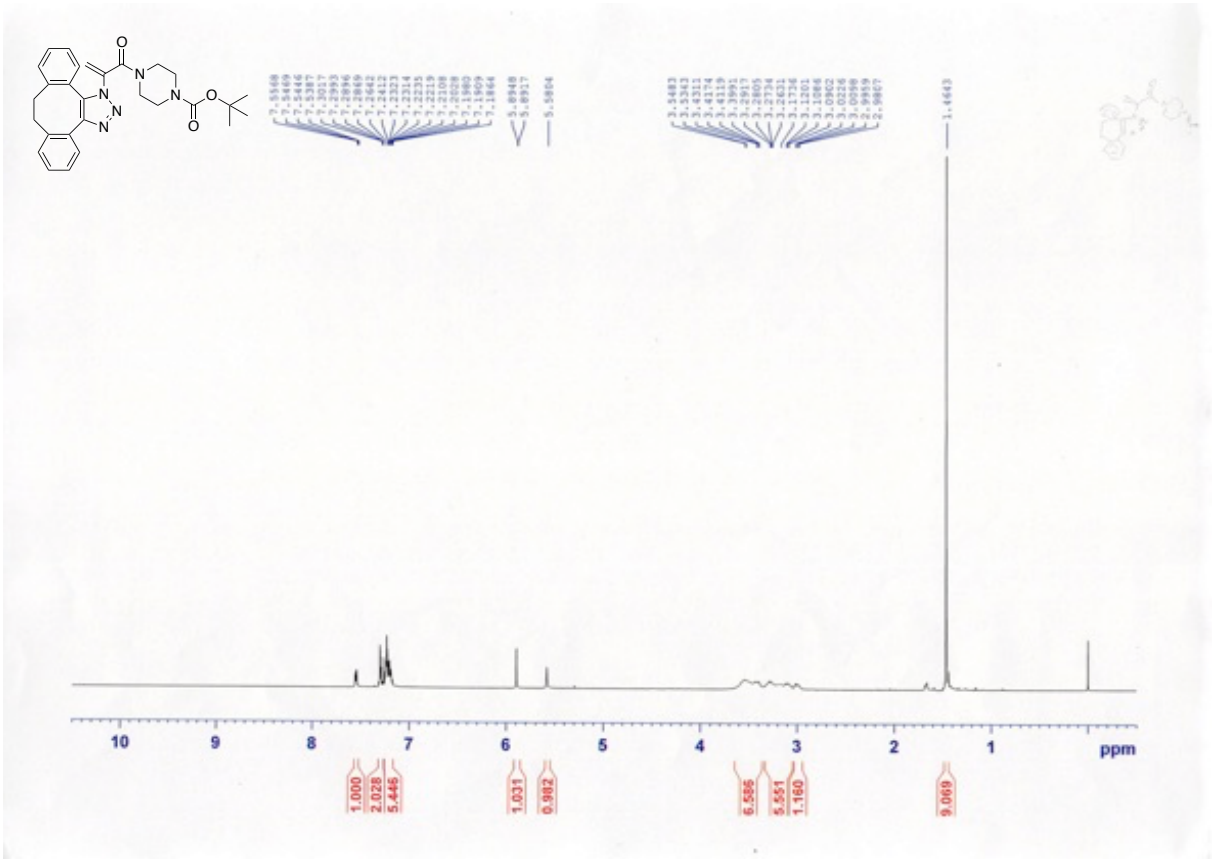


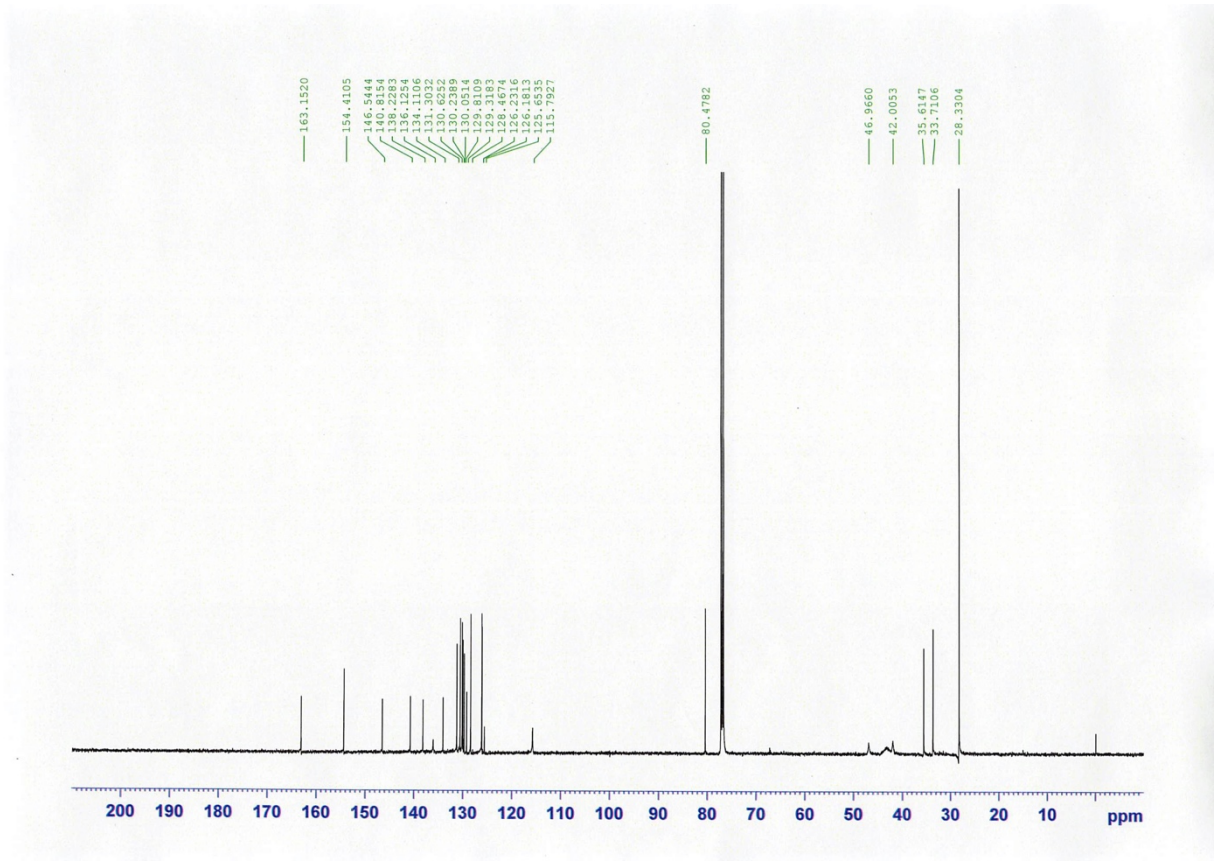
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(4-(ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19m**) ($CDCl_3$)



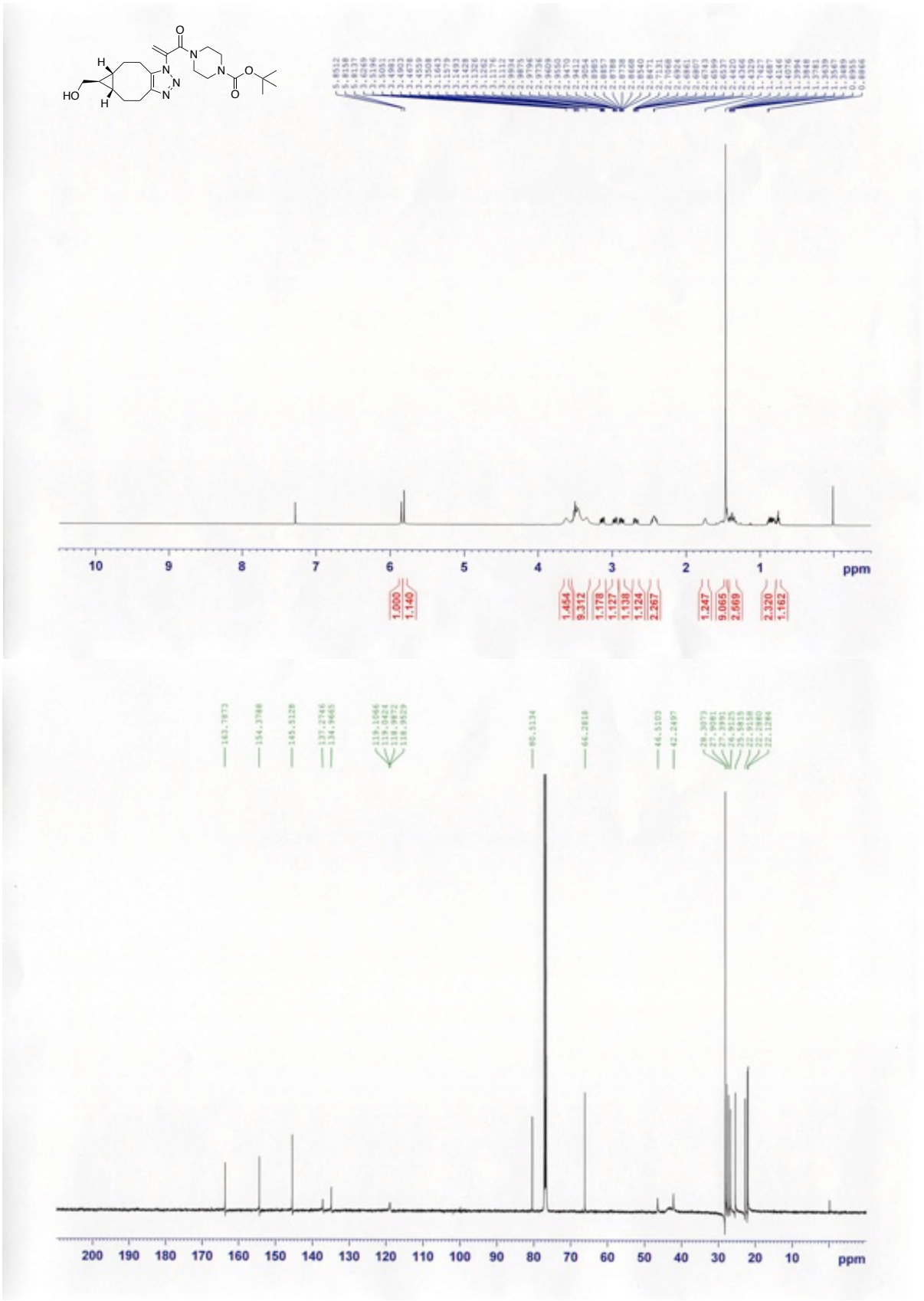


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(8,9-dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*][1,2,3]triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19n**) ($CDCl_3$)

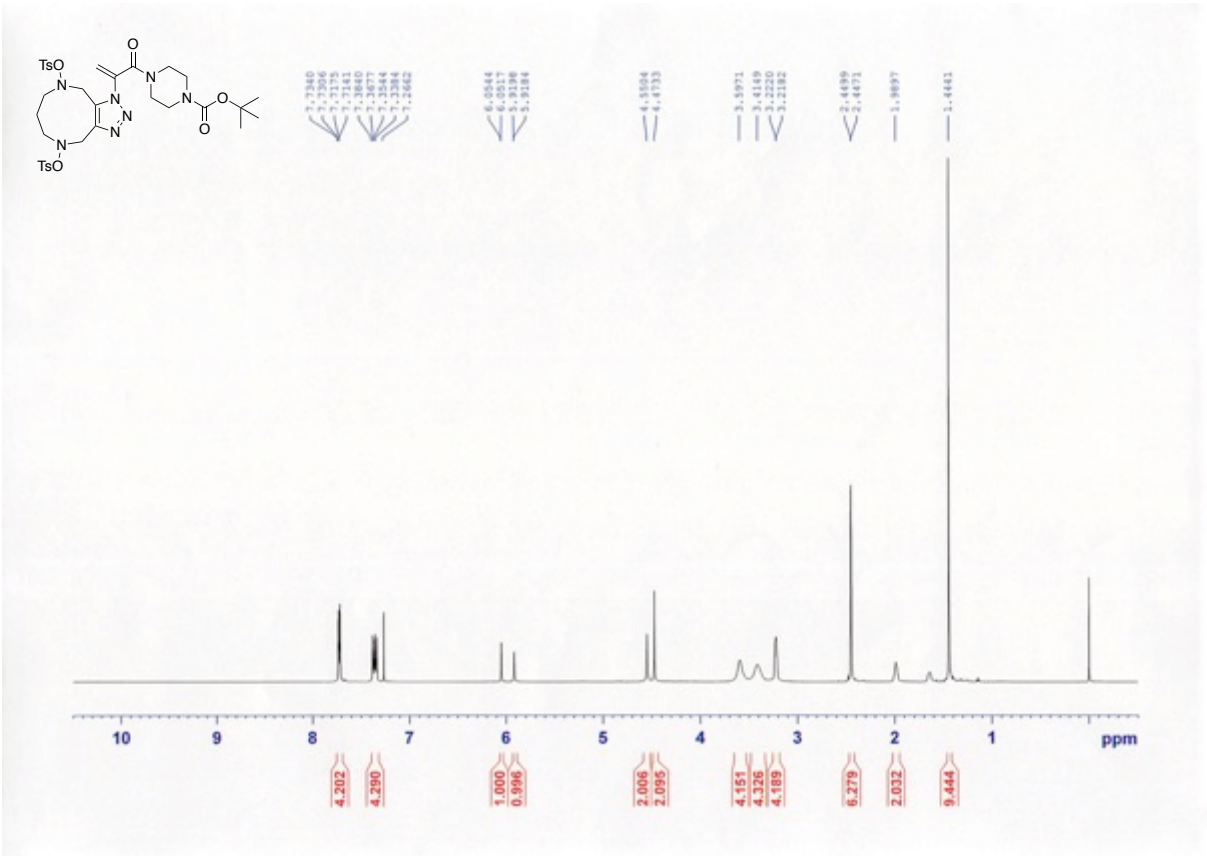


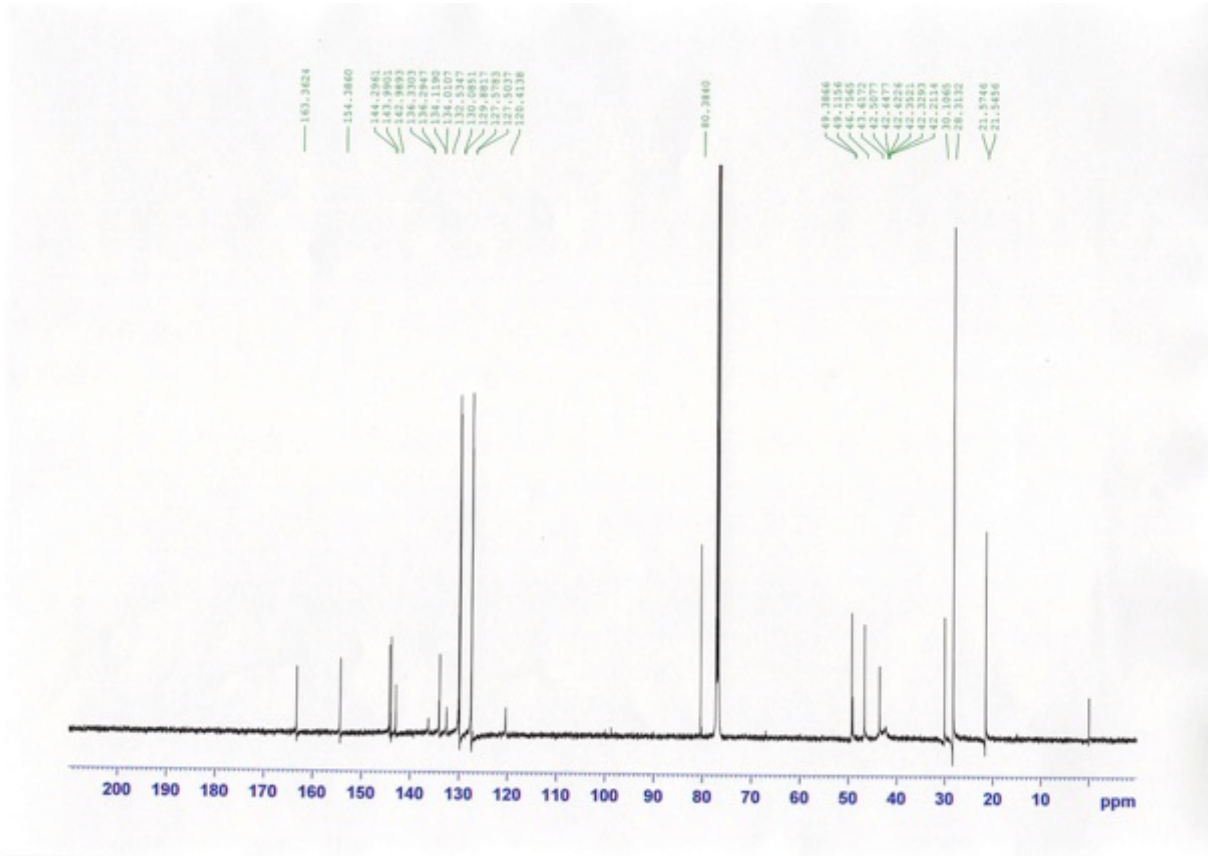


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-((5a*S*,6*S*,6a*R*)-6-(hydroxymethyl)-5,5a,6,6a,7,8-hexahydrocyclopropa[5,6]cycloocta[1,2-*d*][1,2,3]triazol-1(4*H*)-yl)acryloyl)piperazine-1-carboxylate (**19o**) ($CDCl_3$)

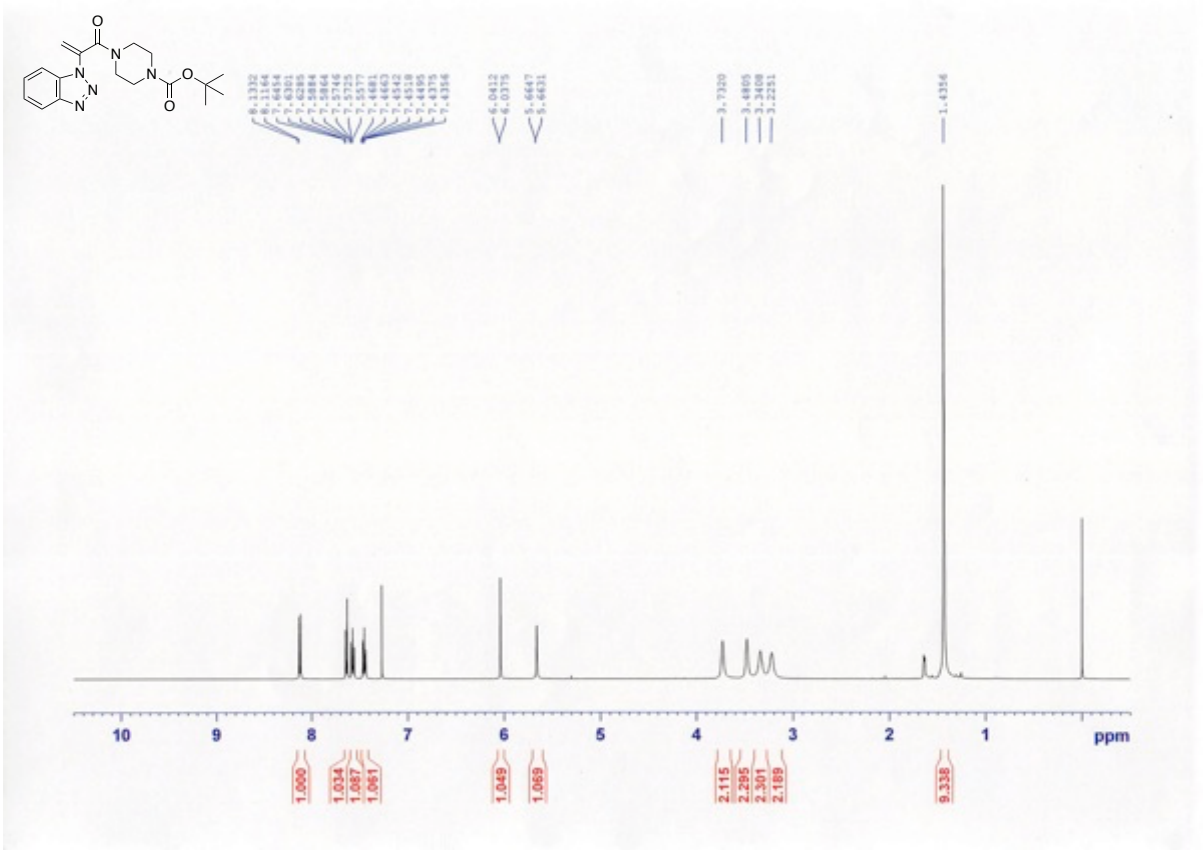


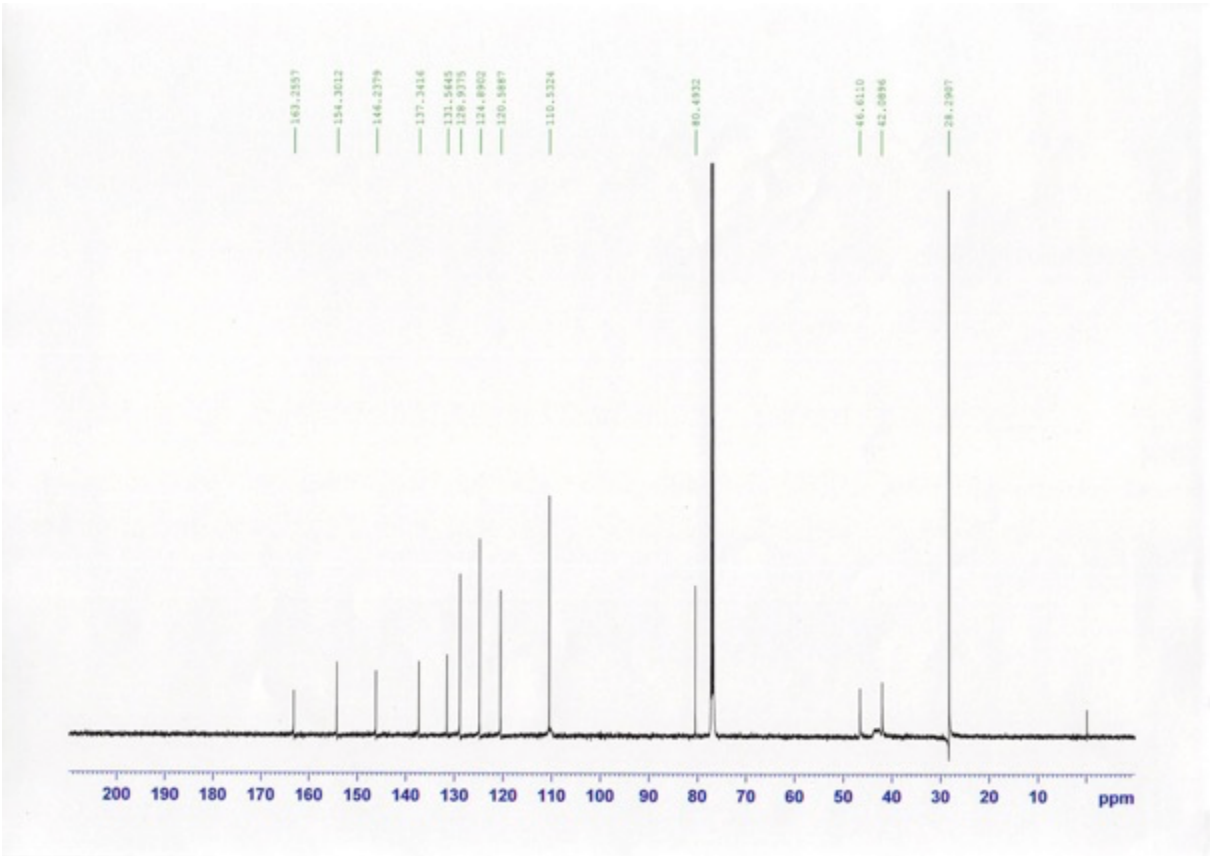
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(5,9-bis(tosyl)-5,6,7,8,9,10-hexahydro-[1,2,3]triazolo[4,5-*g*][1,5]diazonin-1(4*H*)-yl)acryloyl)piperazine-1-carboxylate (**19p**) ($CDCl_3$)



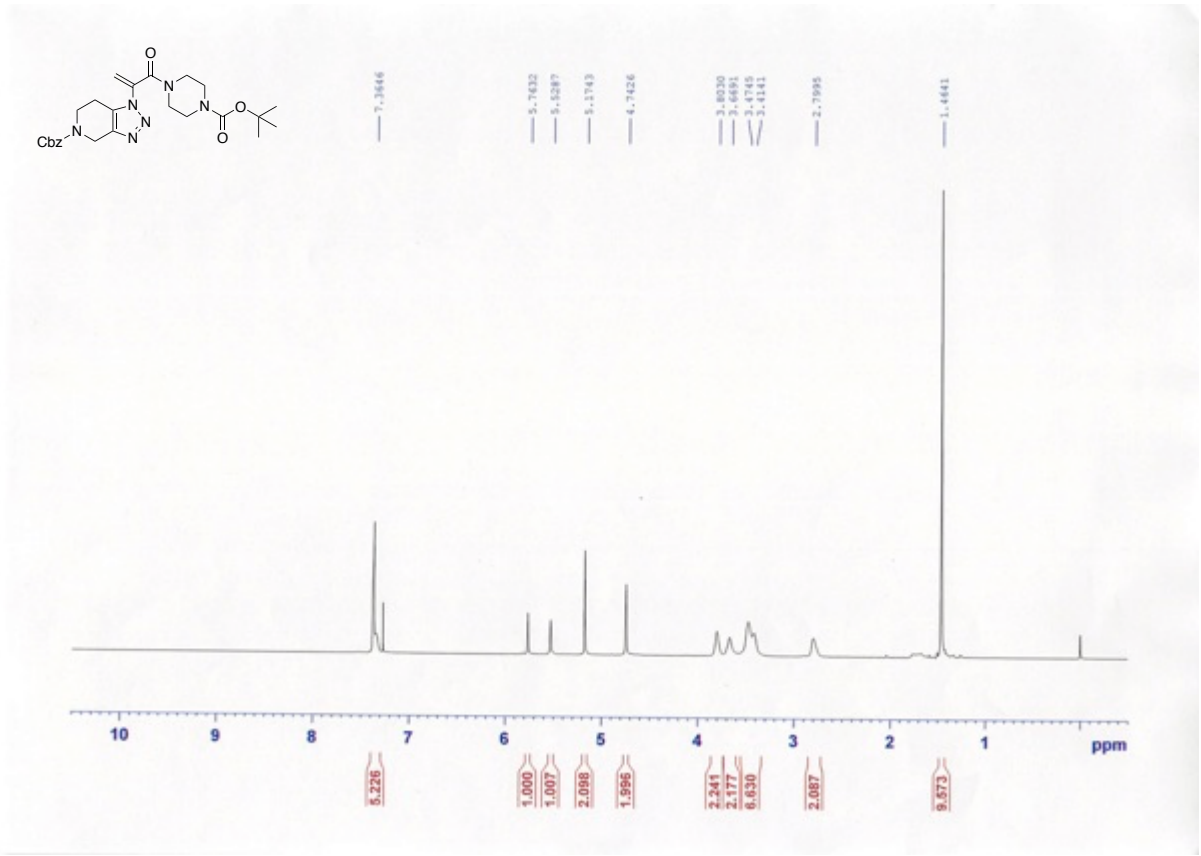


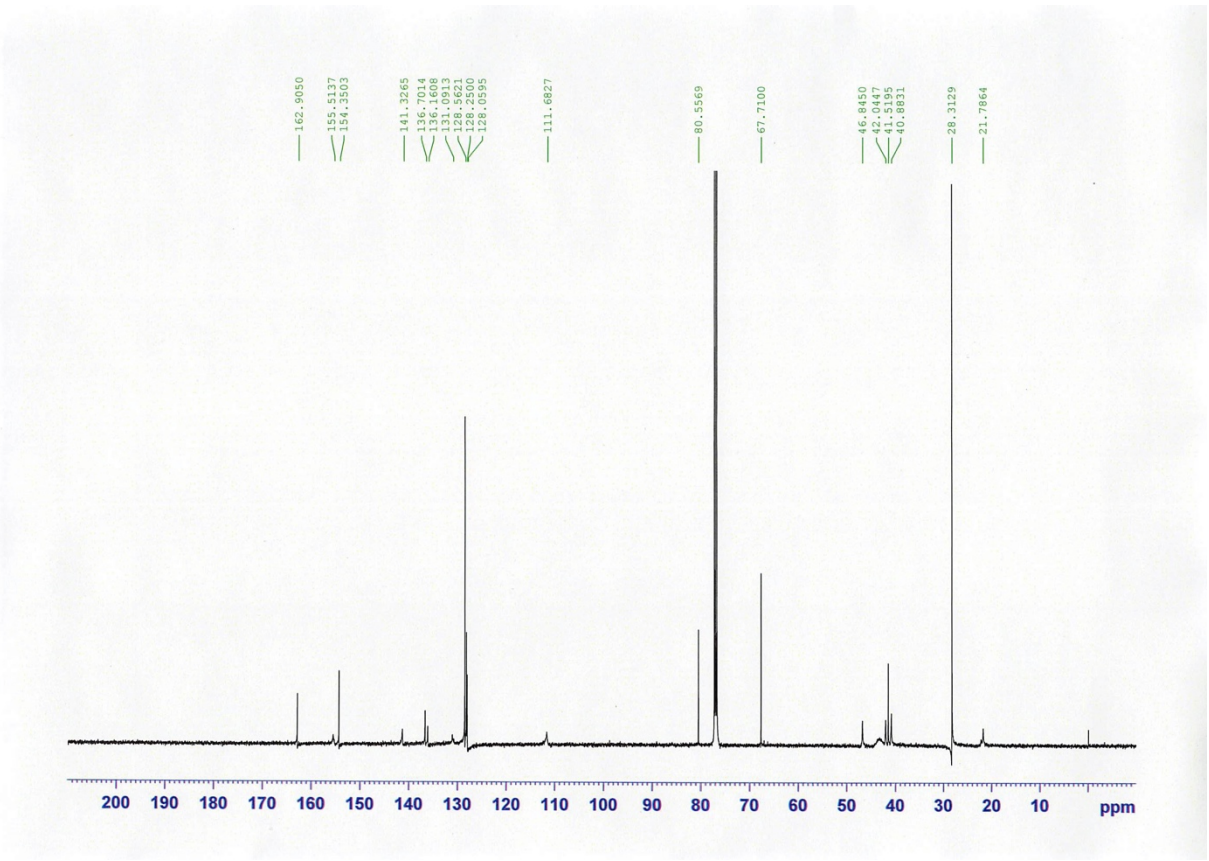
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)acryloyl)piperazine-1-carboxylate (**19q**) ($CDCl_3$)



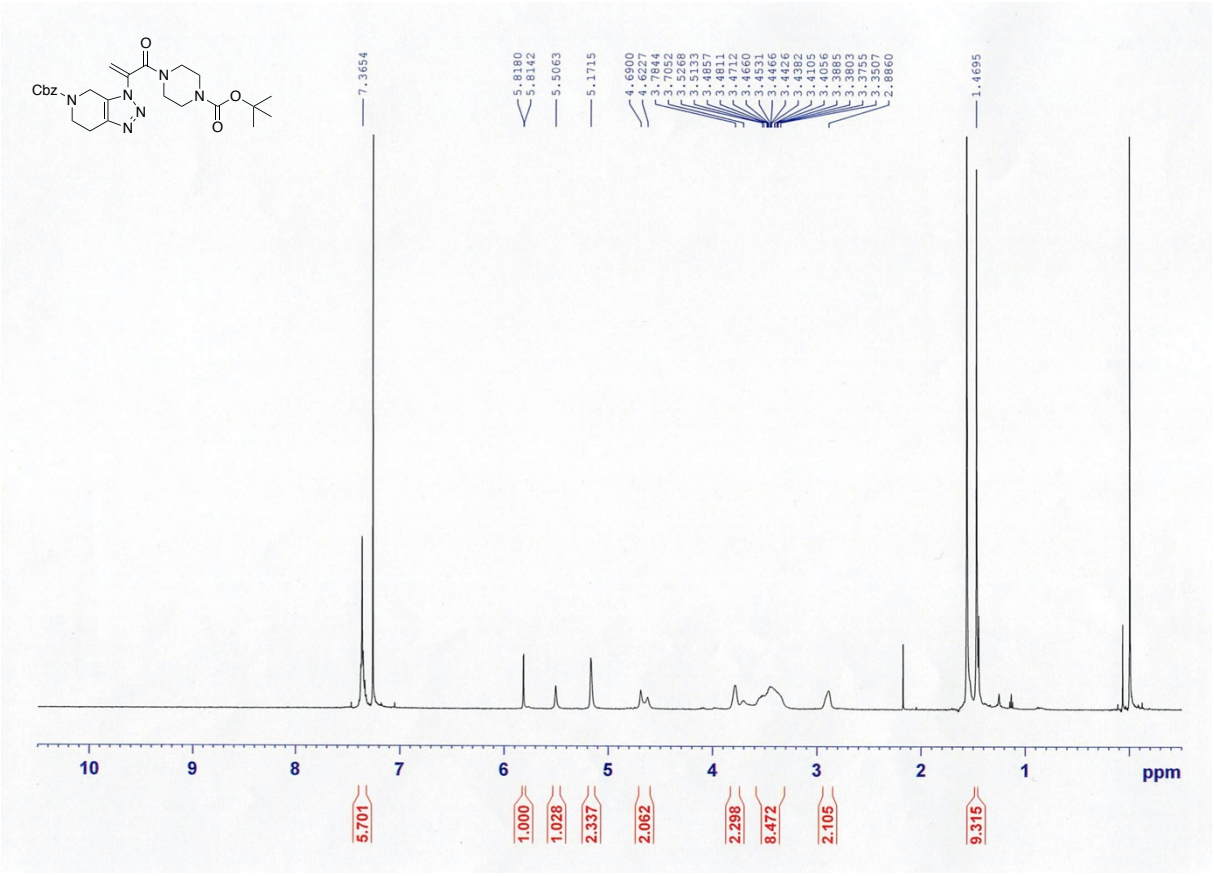


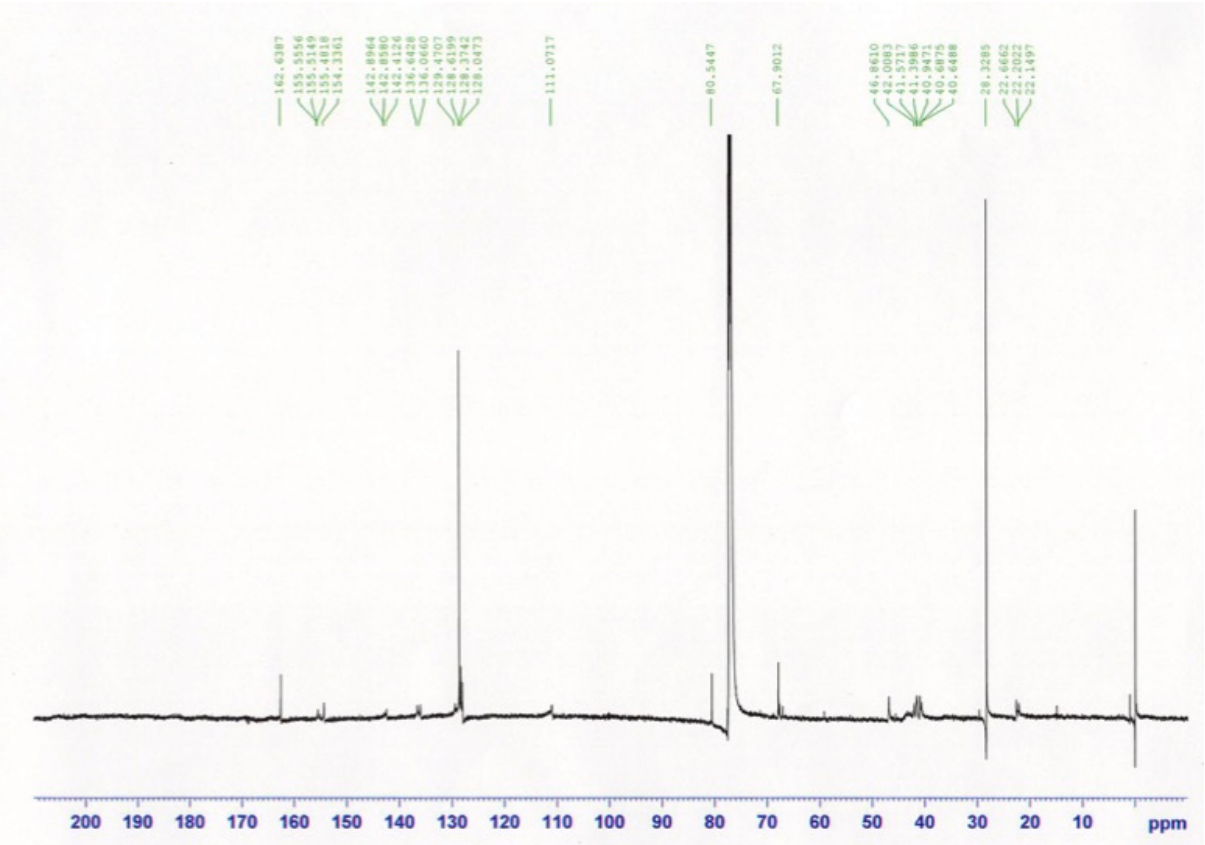
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of benzyl 1-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-oxoprop-1-en-2-yl)-1,4,6,7-tetrahydro-5*H*-[1,2,3]triazolo[4,5-*c*]pyridine-5-carboxylate (**19r**) ($CDCl_3$)



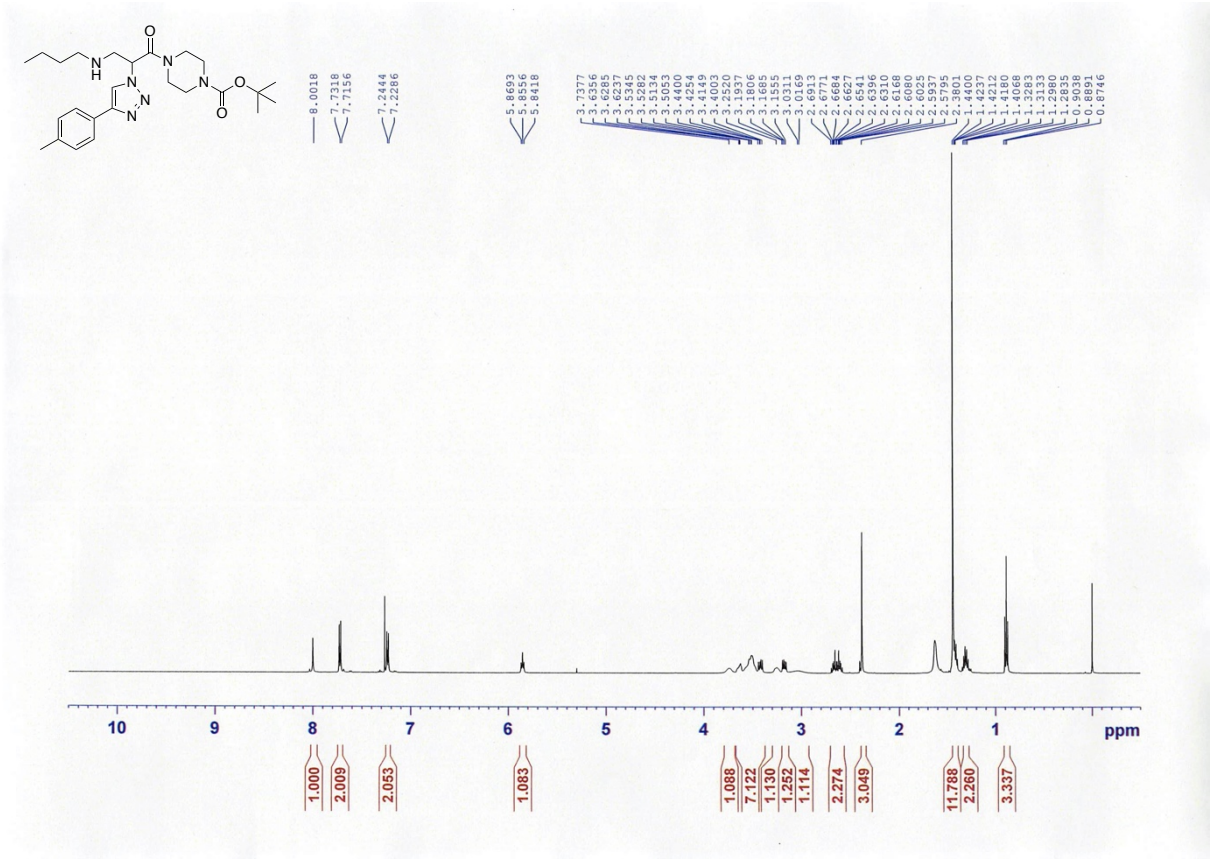


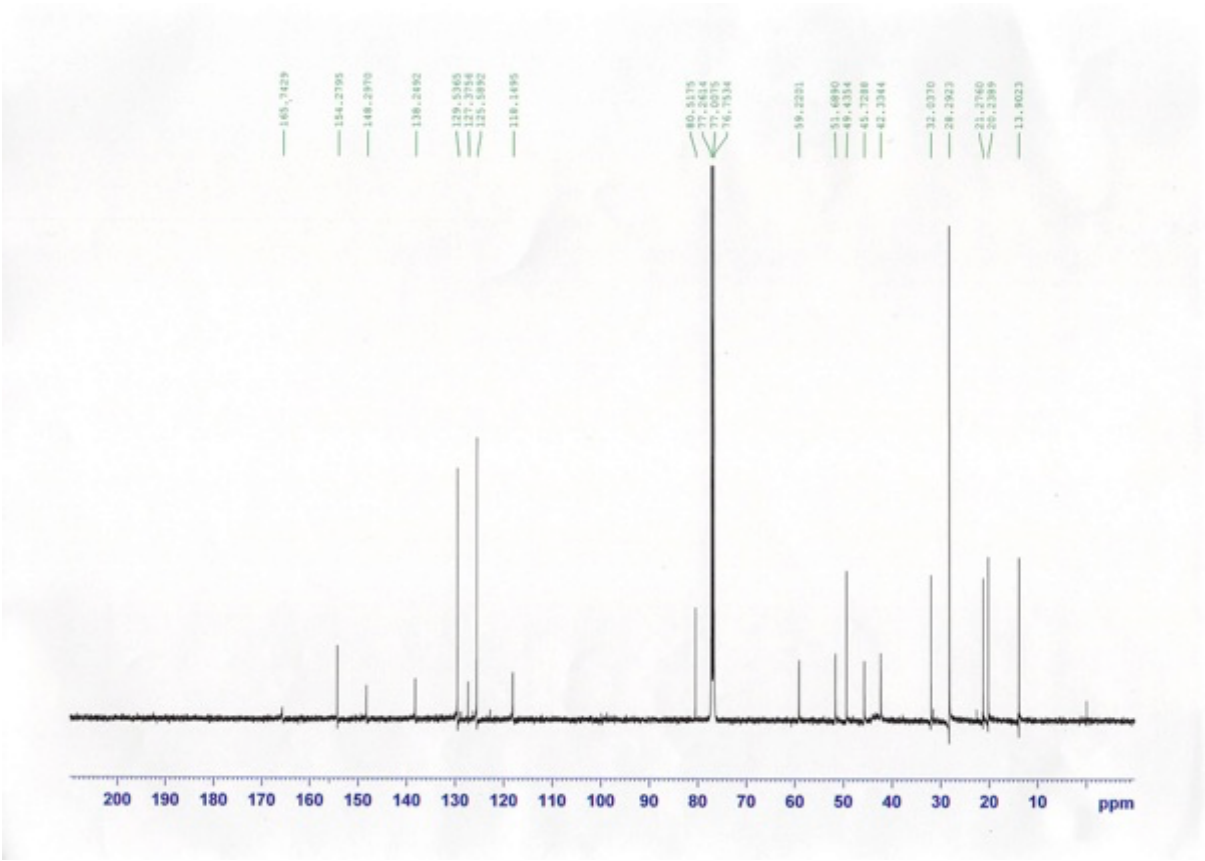
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of Benzyl 3-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-oxoprop-1-en-2-yl)-3,4,6,7-tetrahydro-5H-[1,2,3]triazolo[4,5-*c*]pyridine-5-carboxylate (**19r'**) ($CDCl_3$)



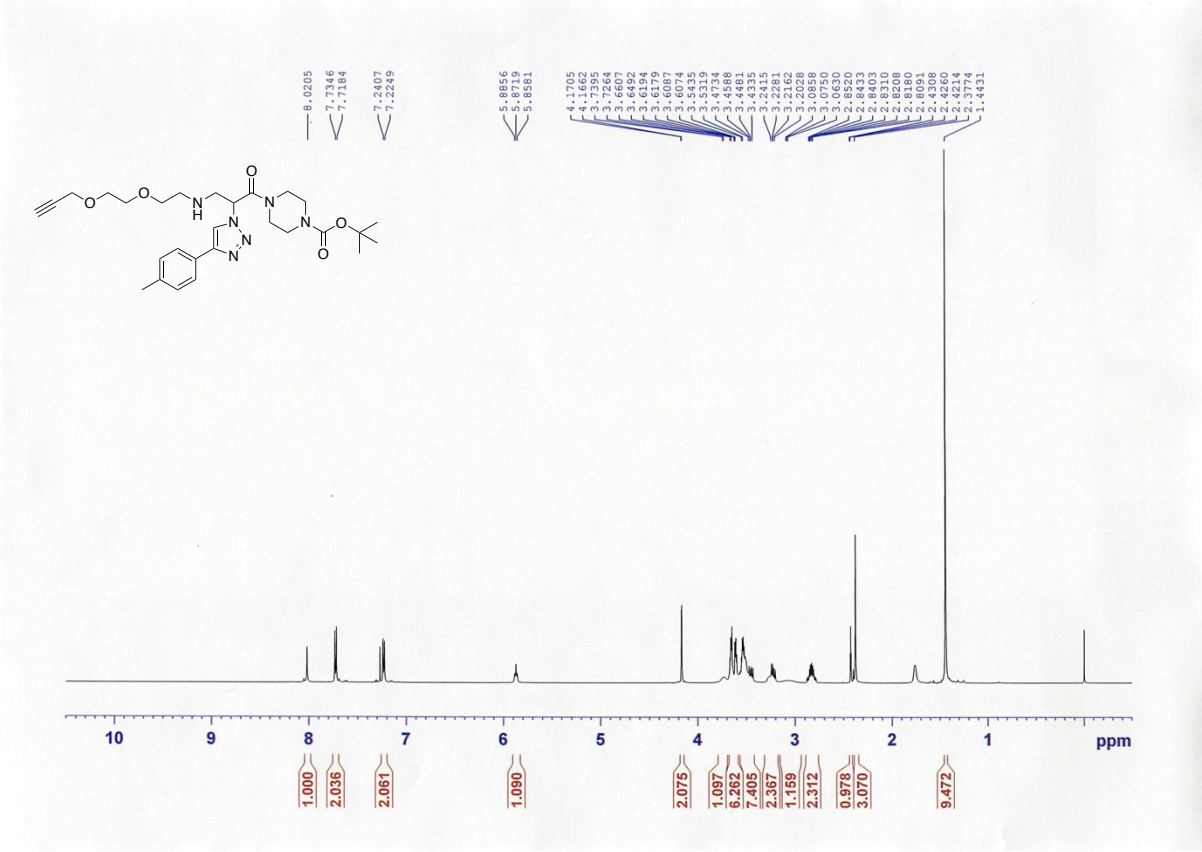


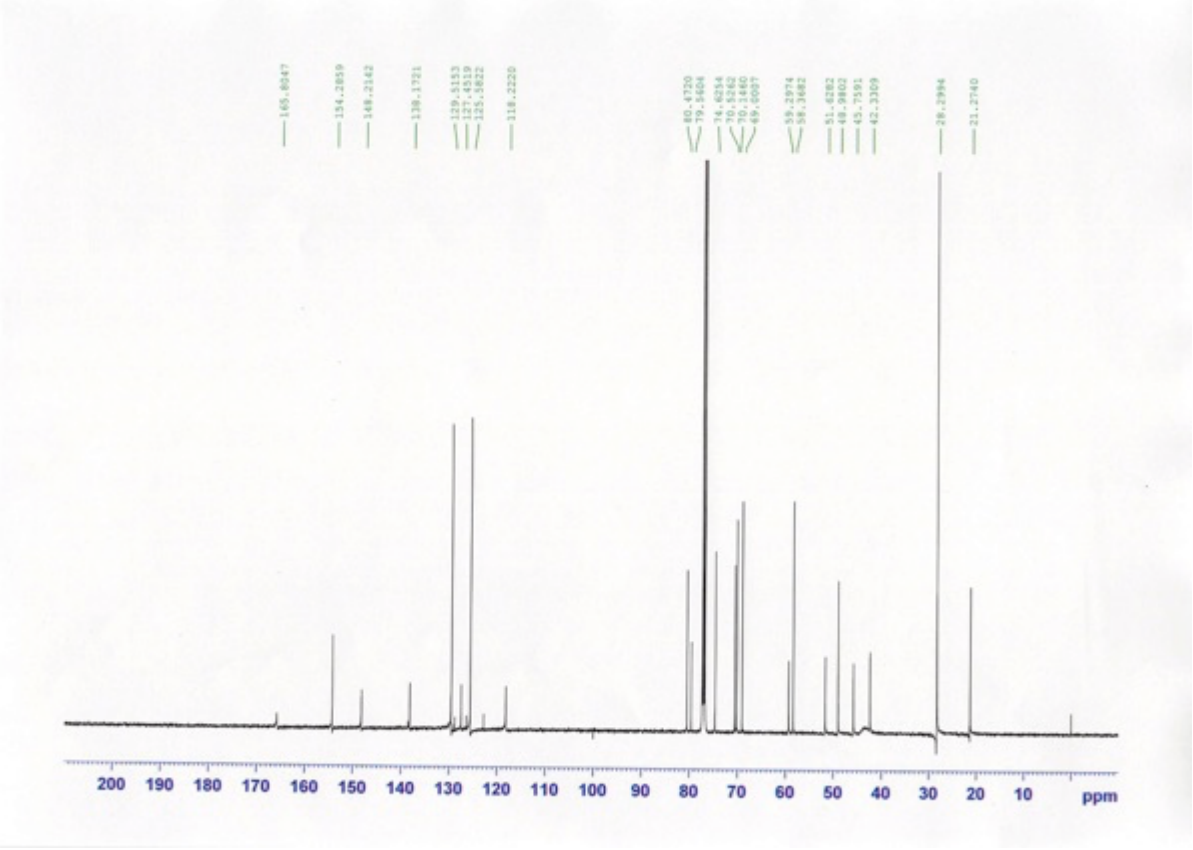
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(3-(butylamino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20a**) ($CDCl_3$)



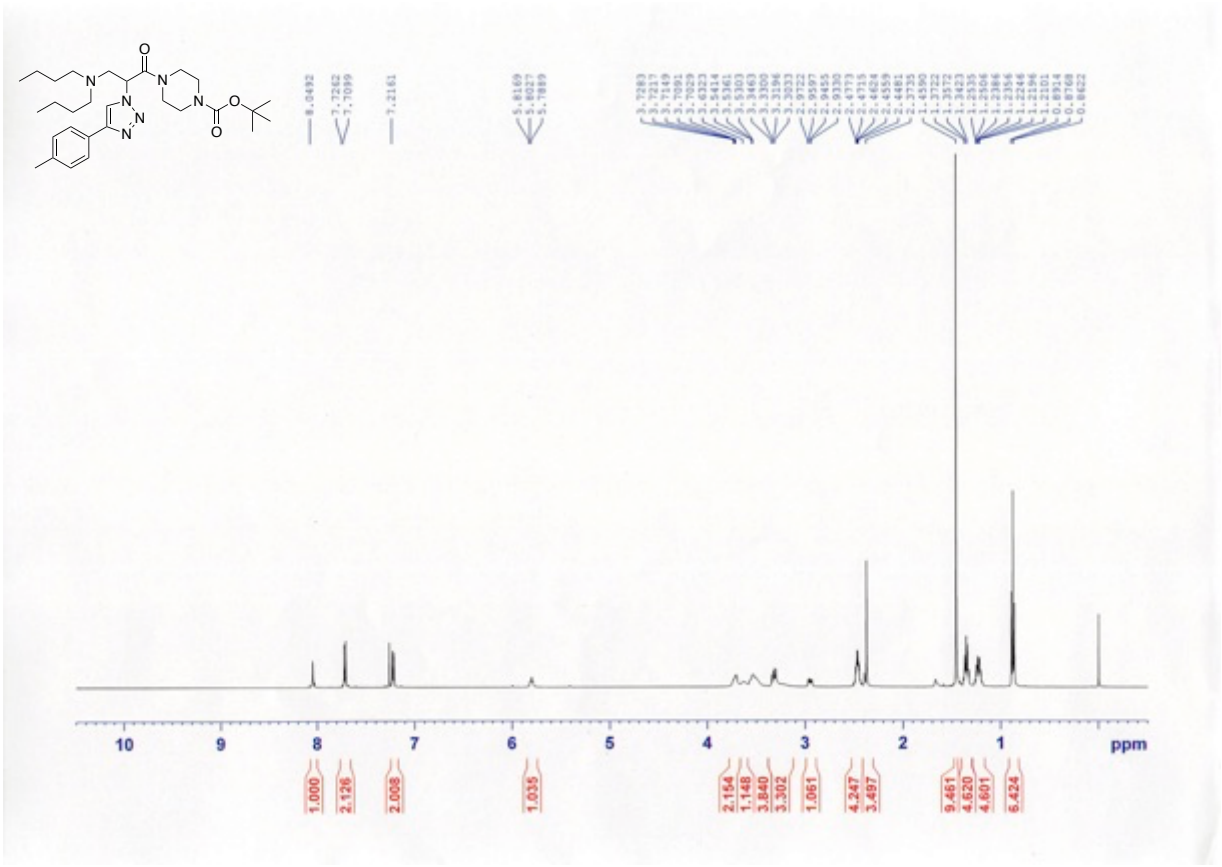


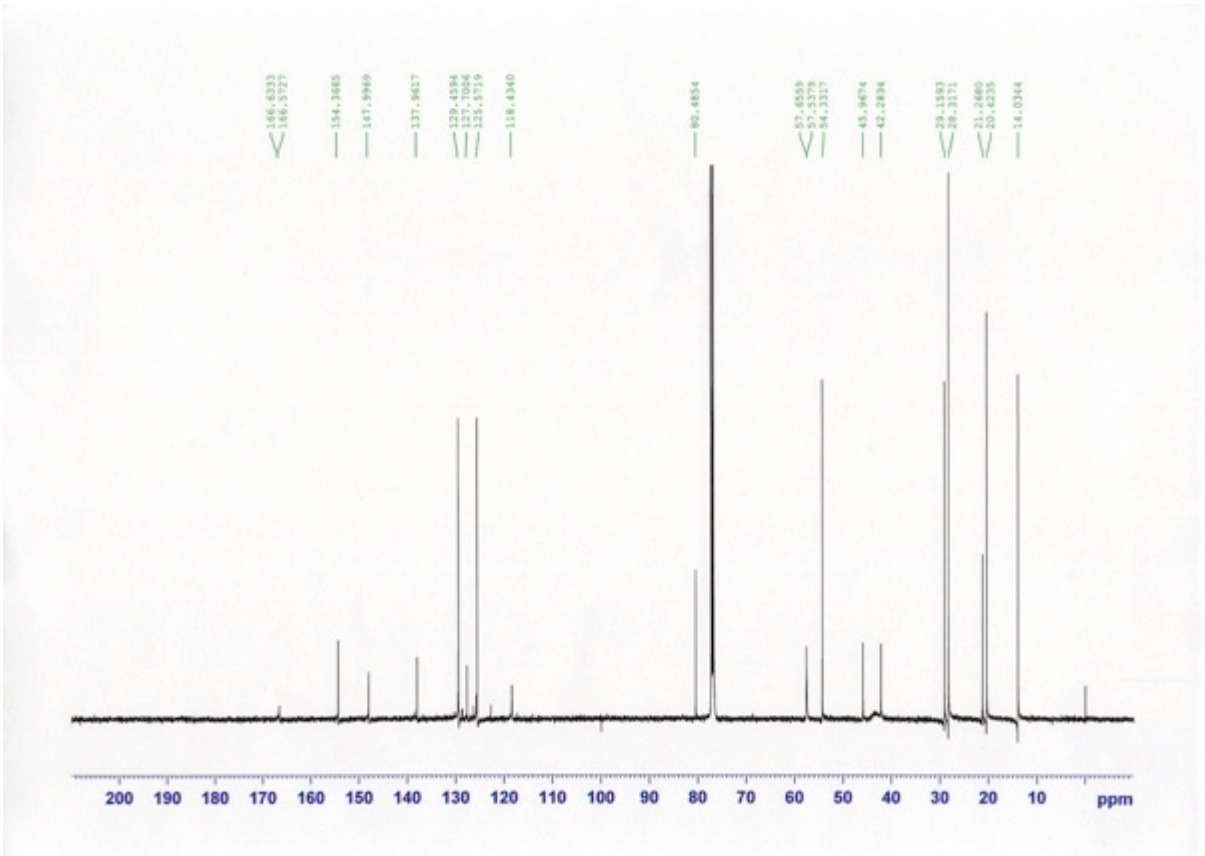
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(3-((2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)amino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20b**) ($CDCl_3$)



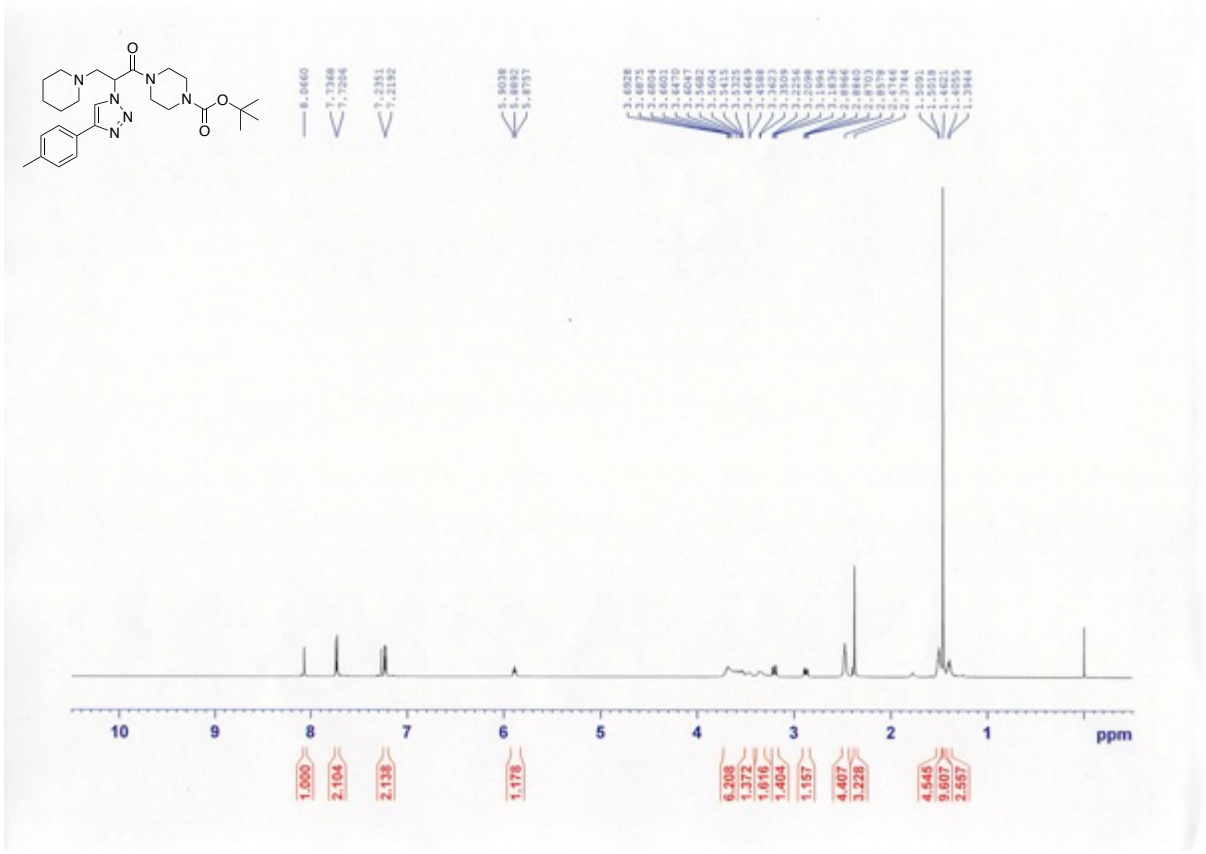


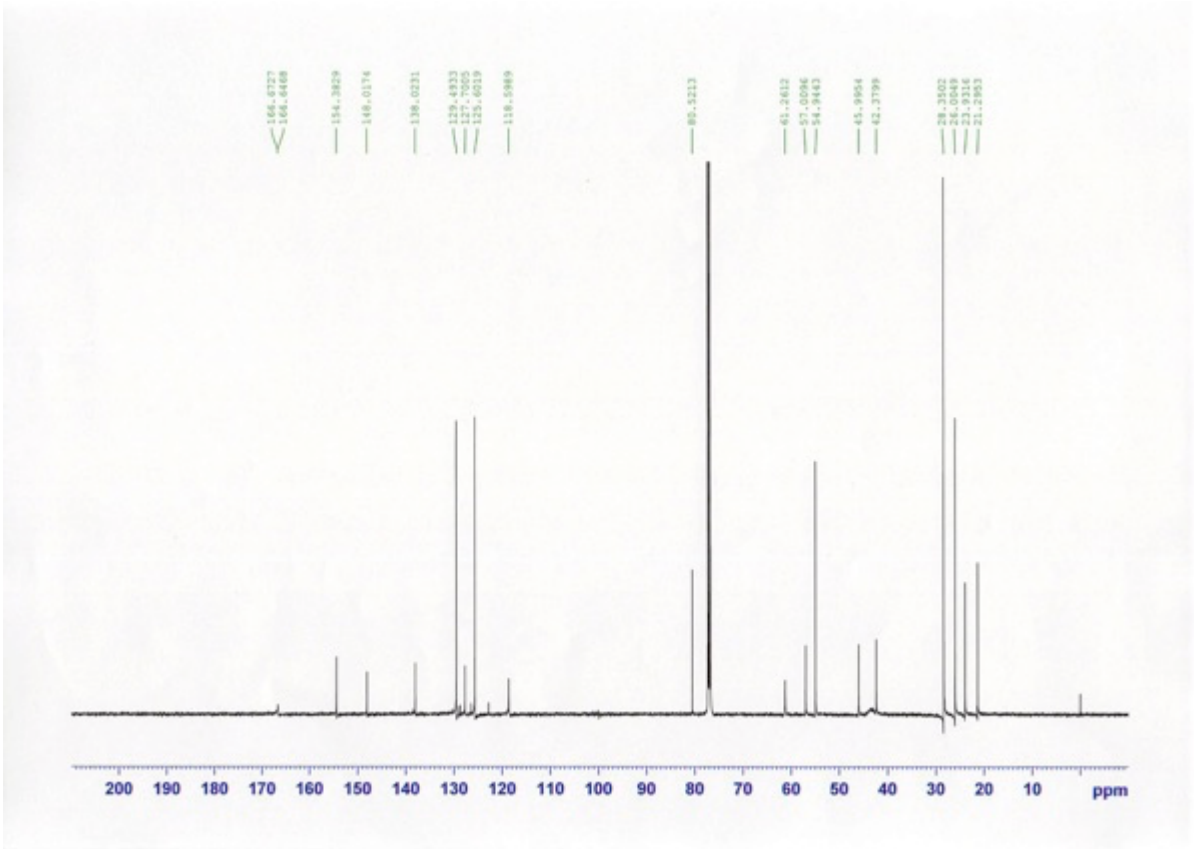
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(3-(dibutylamino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20c**) ($CDCl_3$)



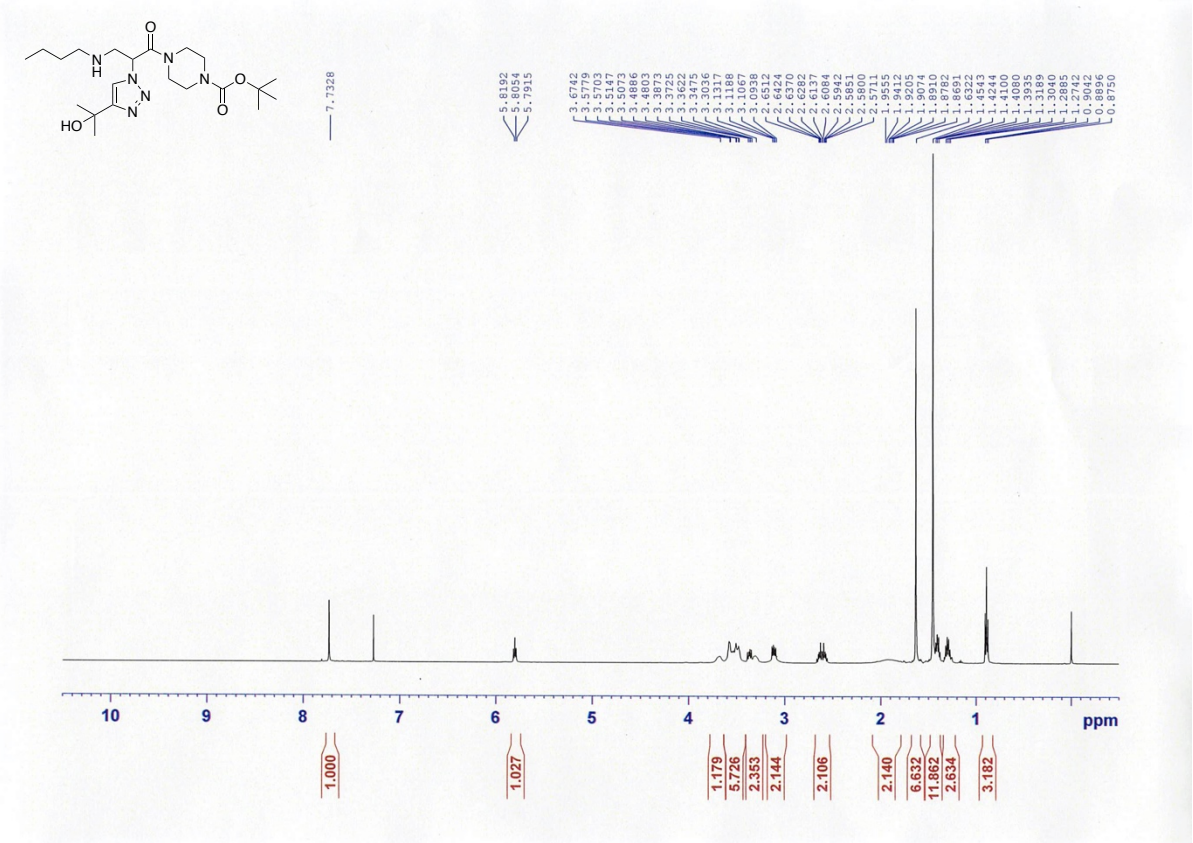


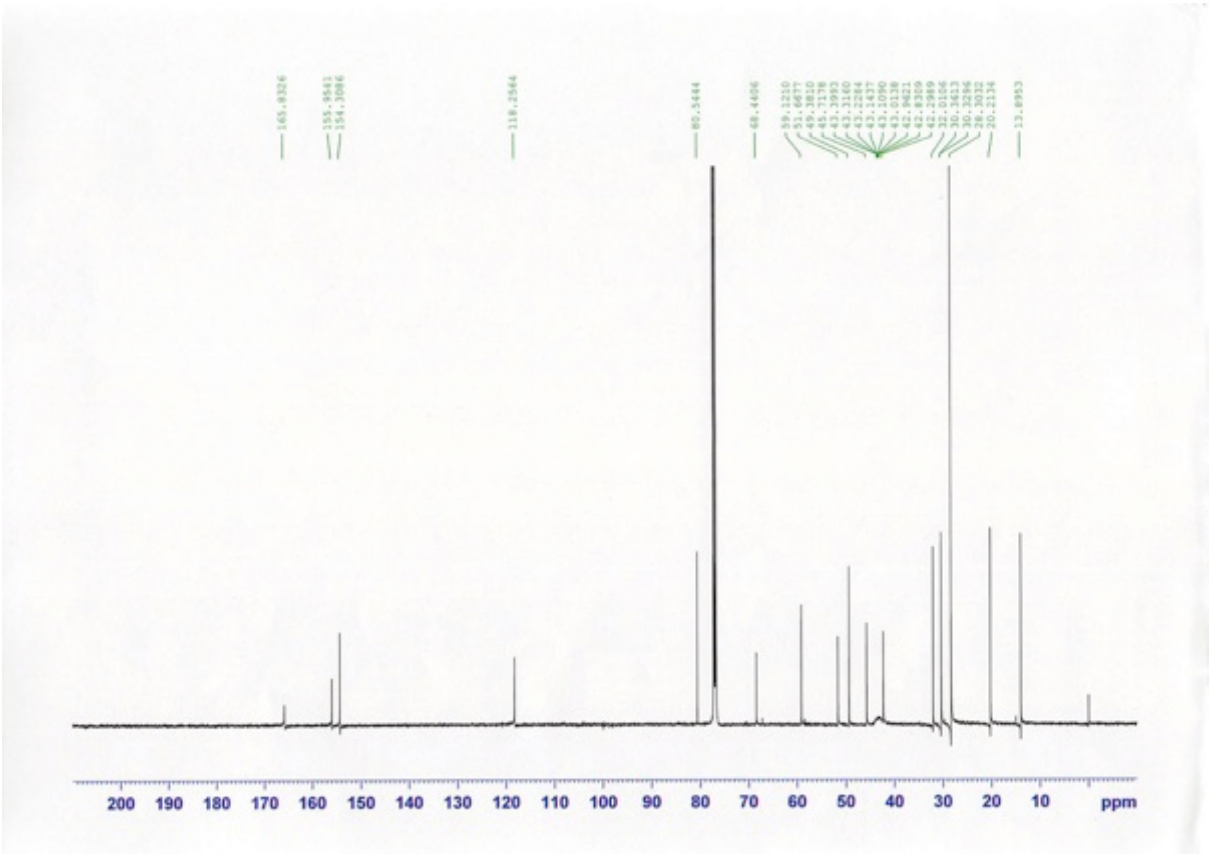
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(3-(piperidin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20d**) ($CDCl_3$)



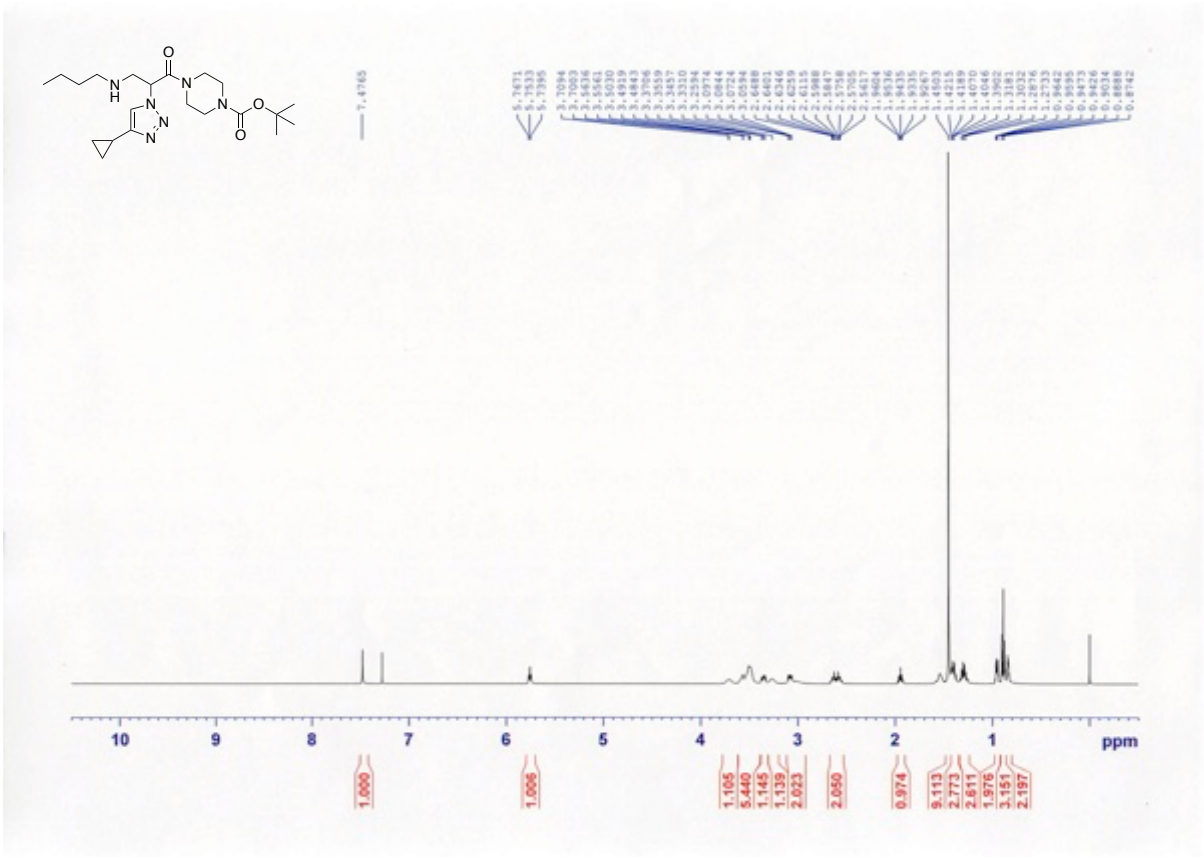


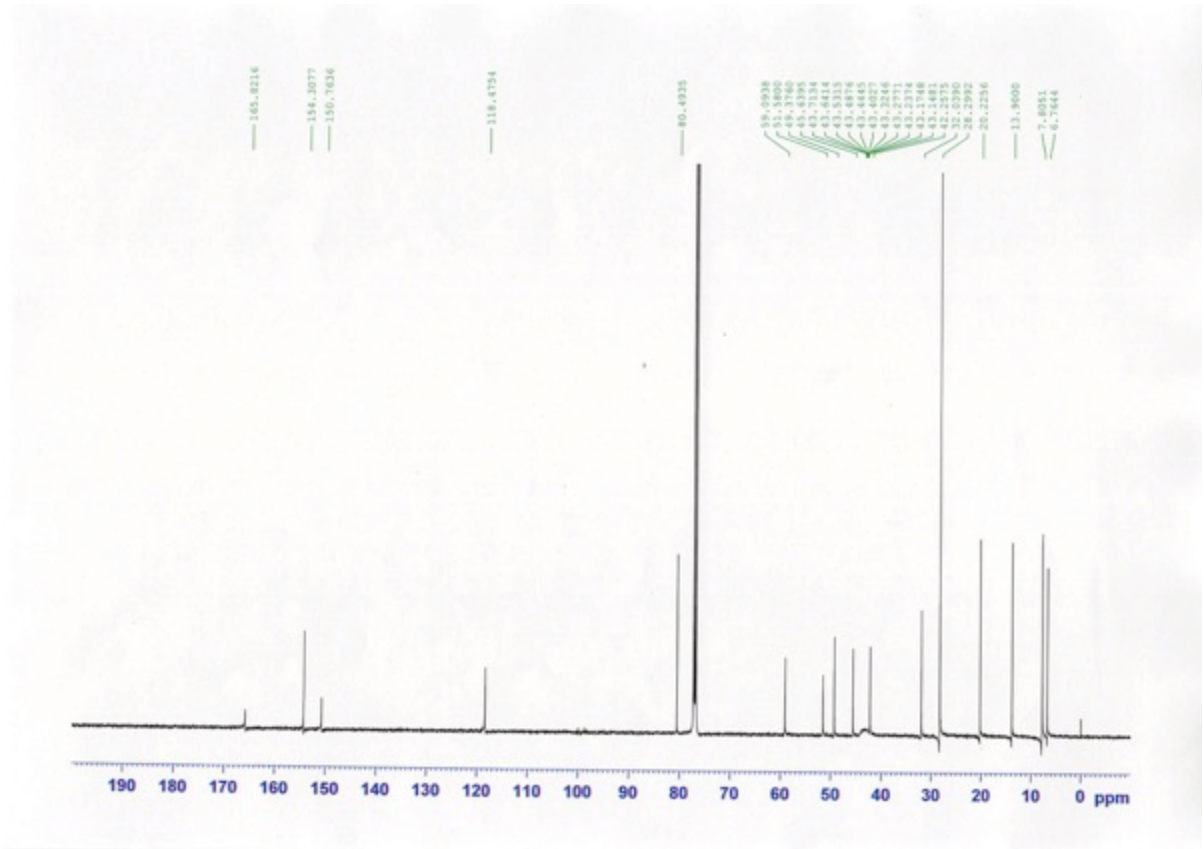
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(3-(butylamino)-2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20e**) ($CDCl_3$)



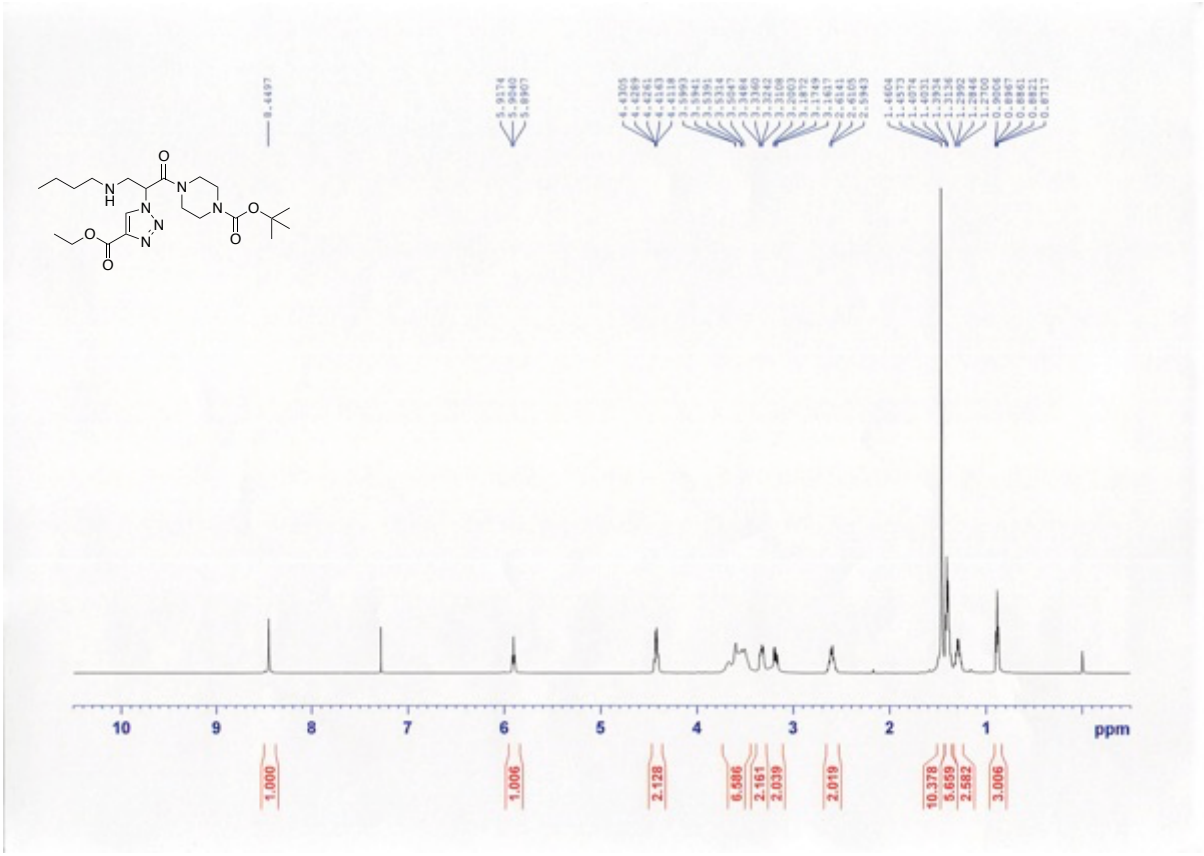


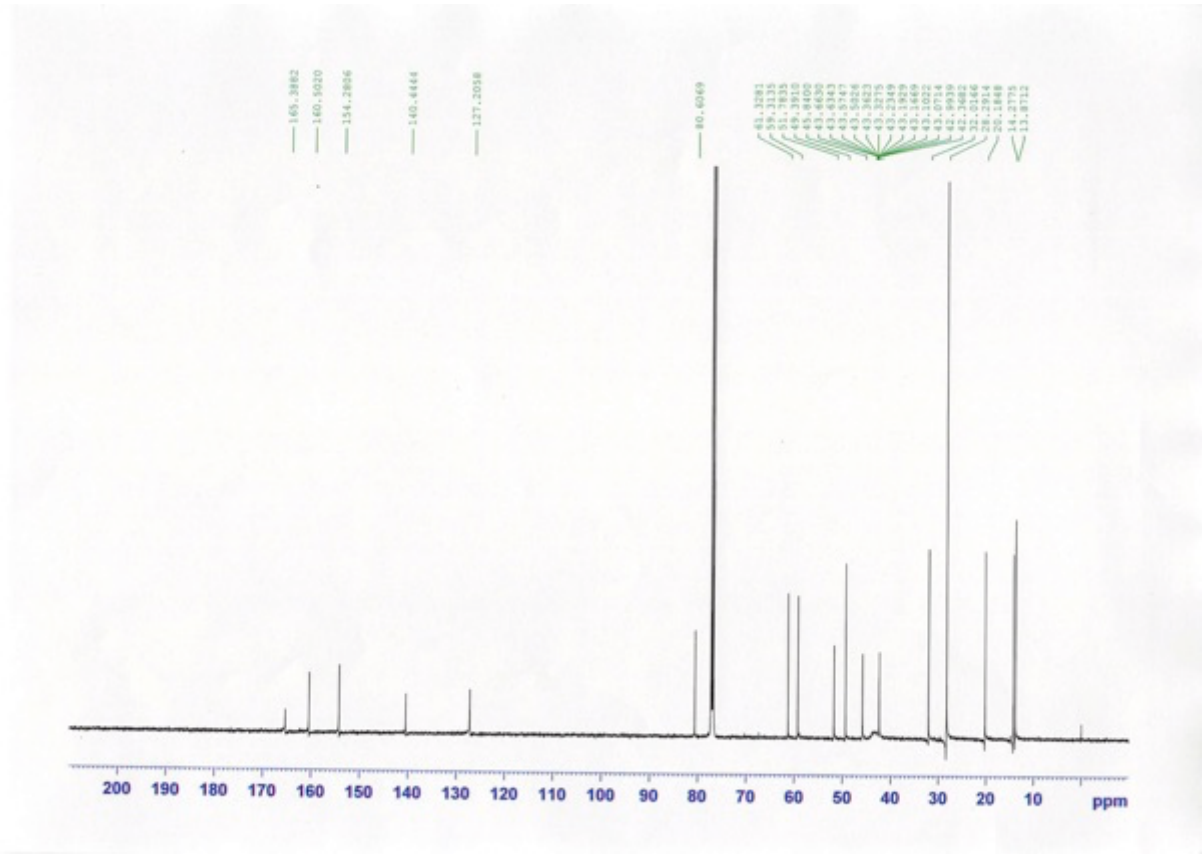
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(3-(butylamino)-2-(4-cyclopropyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20f**) ($CDCl_3$)



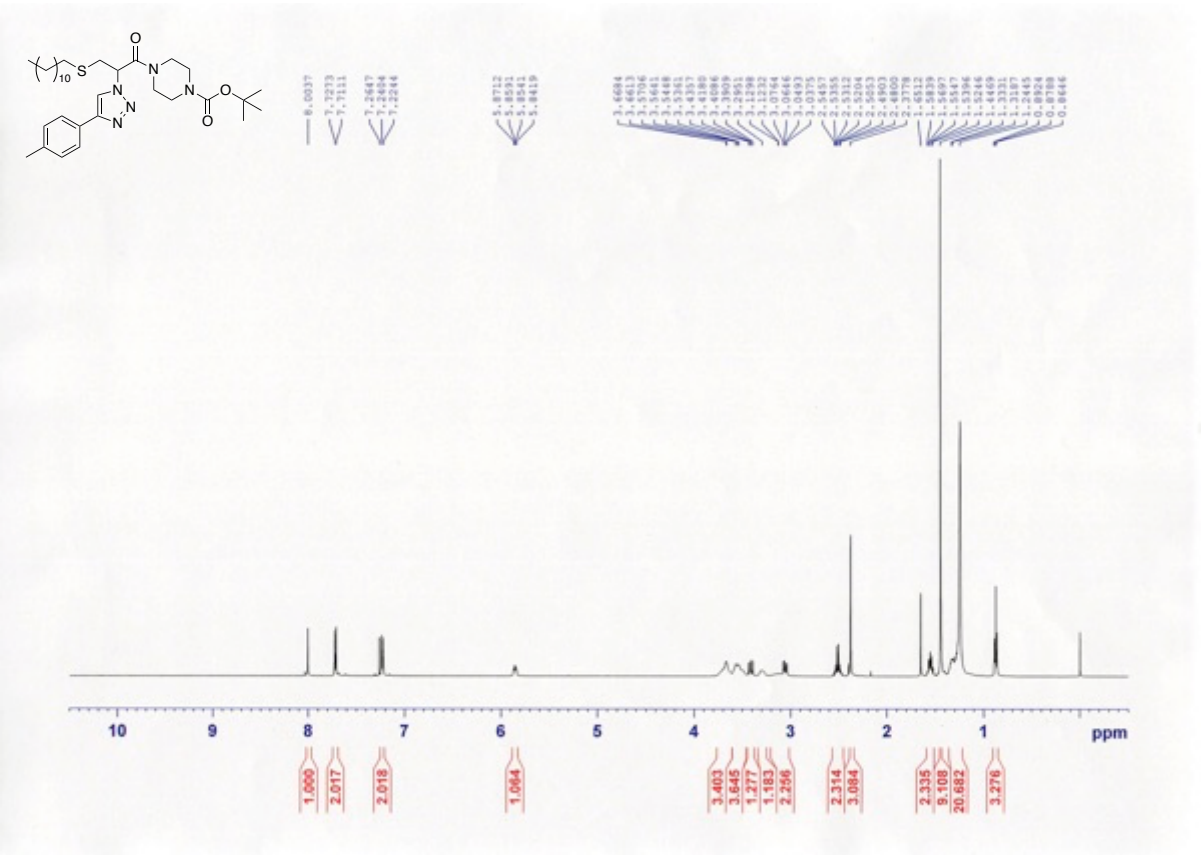


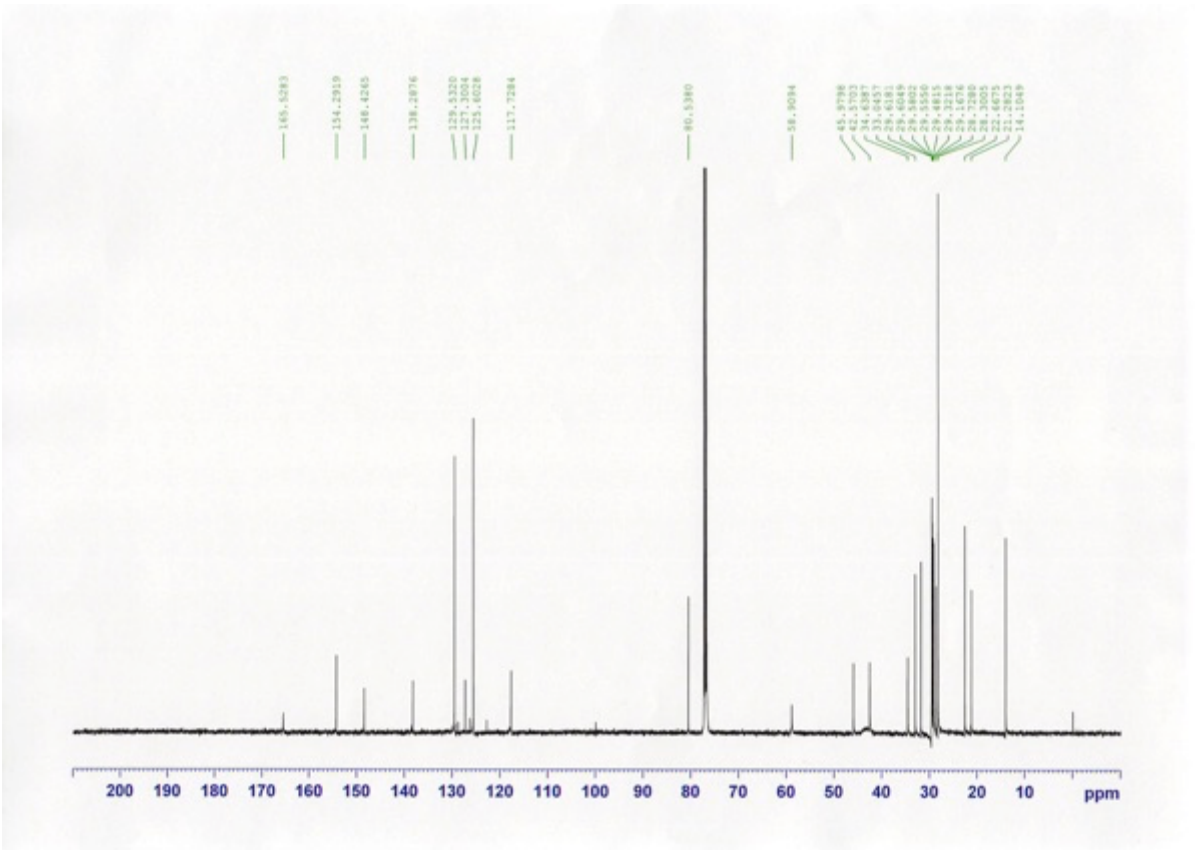
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(3-(butylamino)-2-(4-(ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**20g**) ($CDCl_3$)



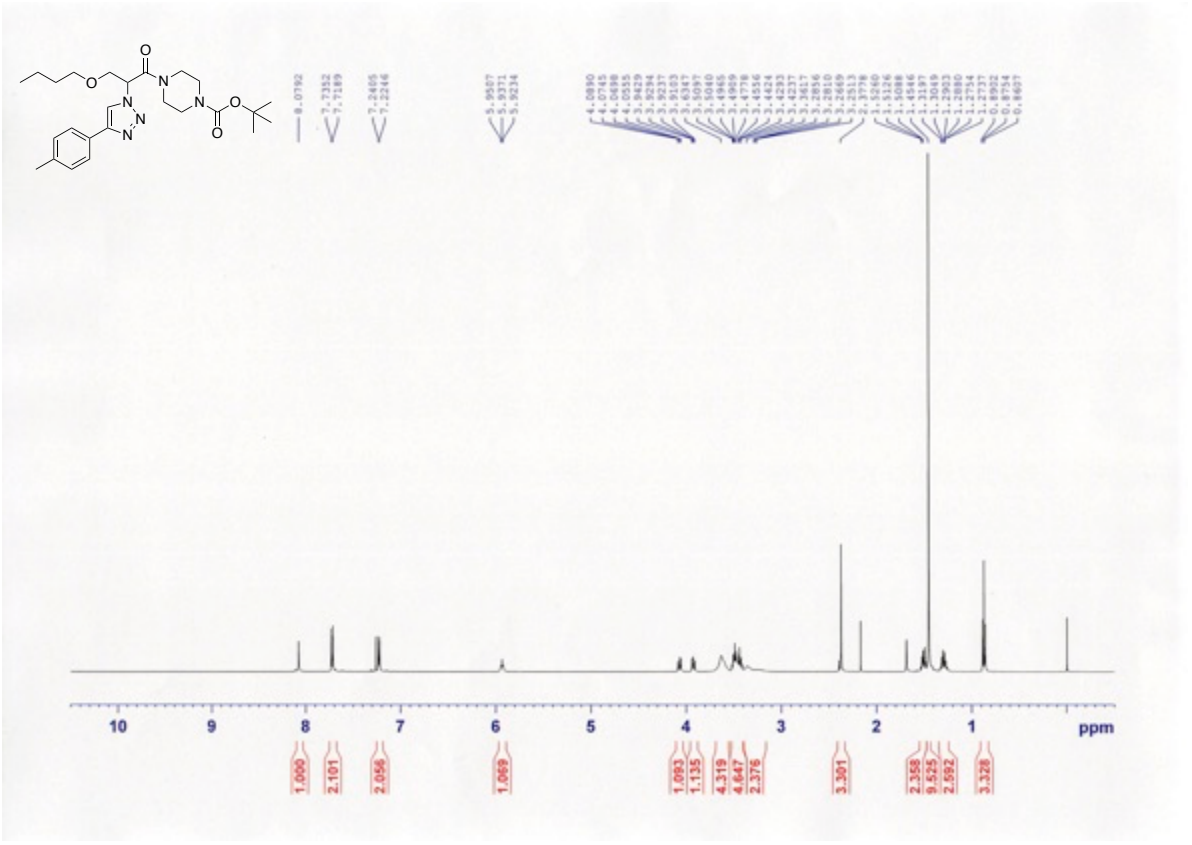


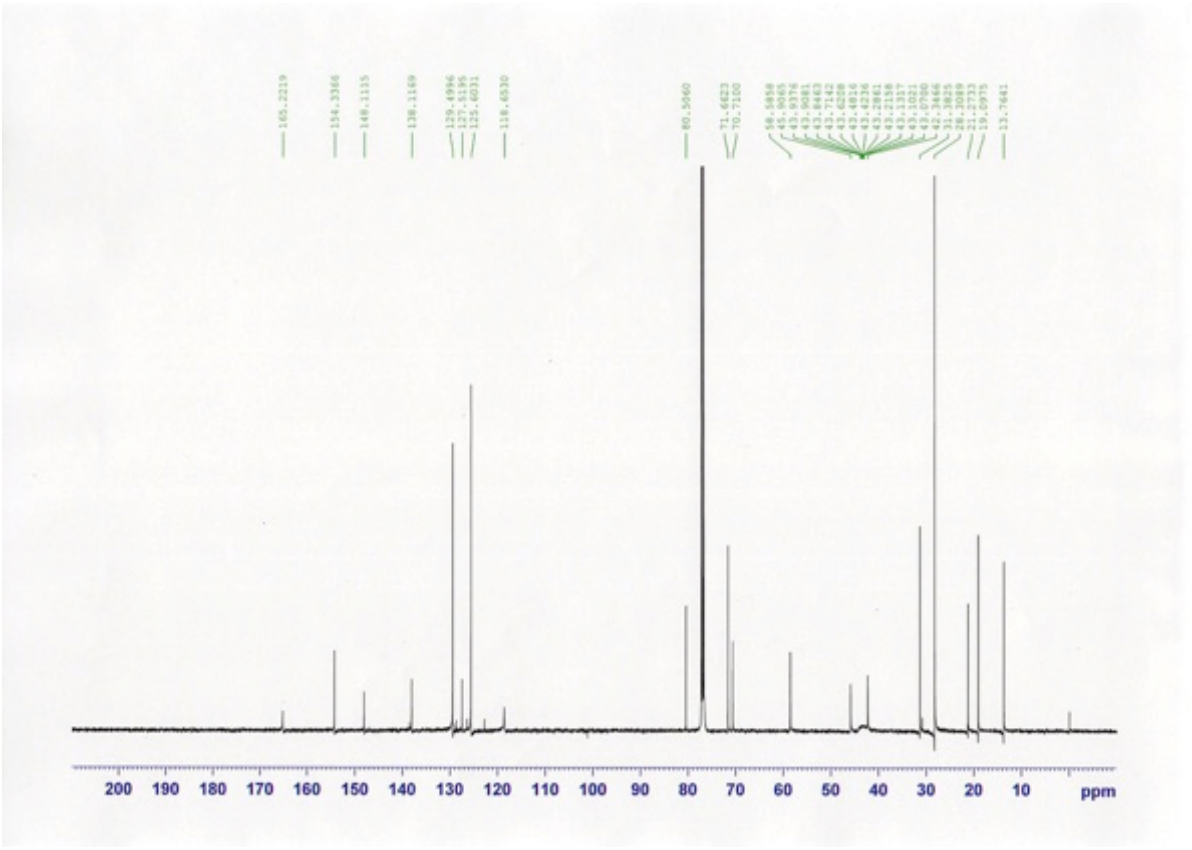
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of t*ert*-butyl 4-(3-(dodecylthio)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**21a**) ($CDCl_3$)



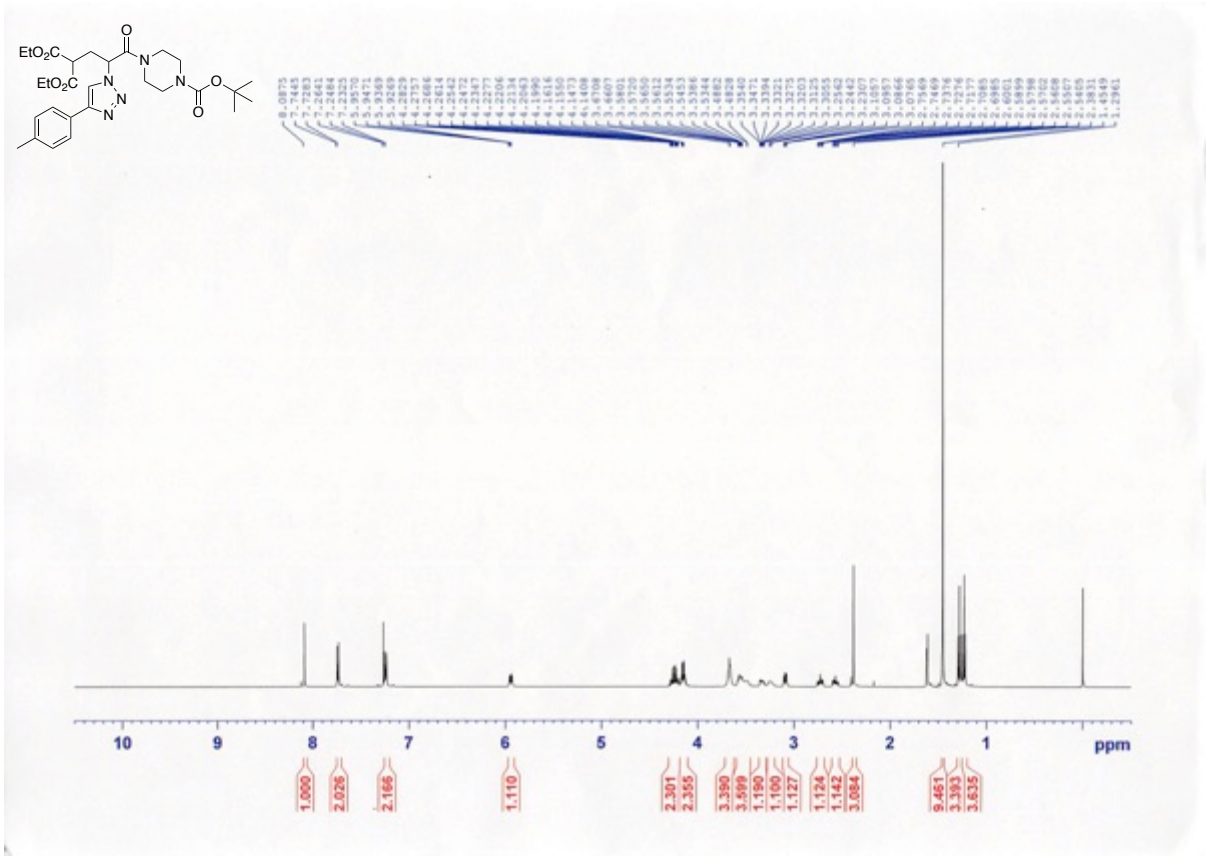


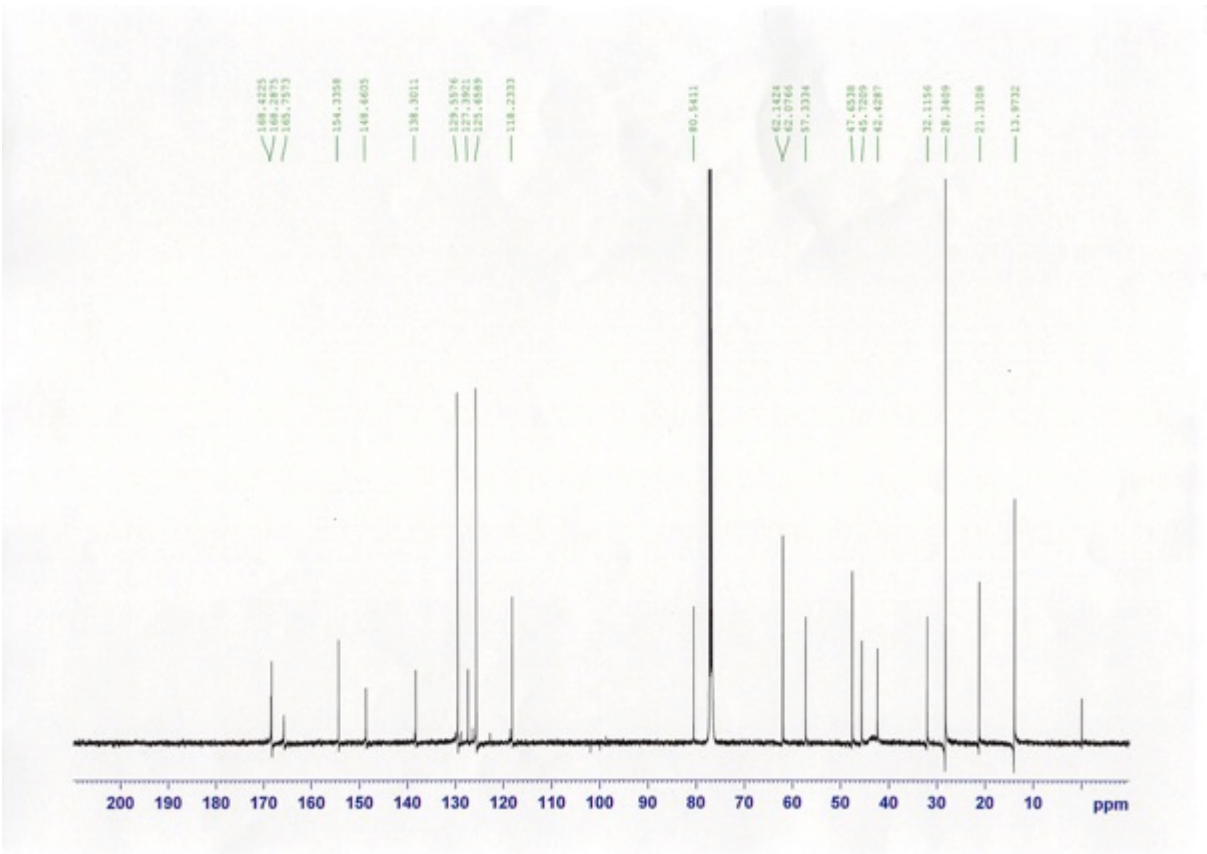
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(3-butoxy-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**21b**) ($CDCl_3$)



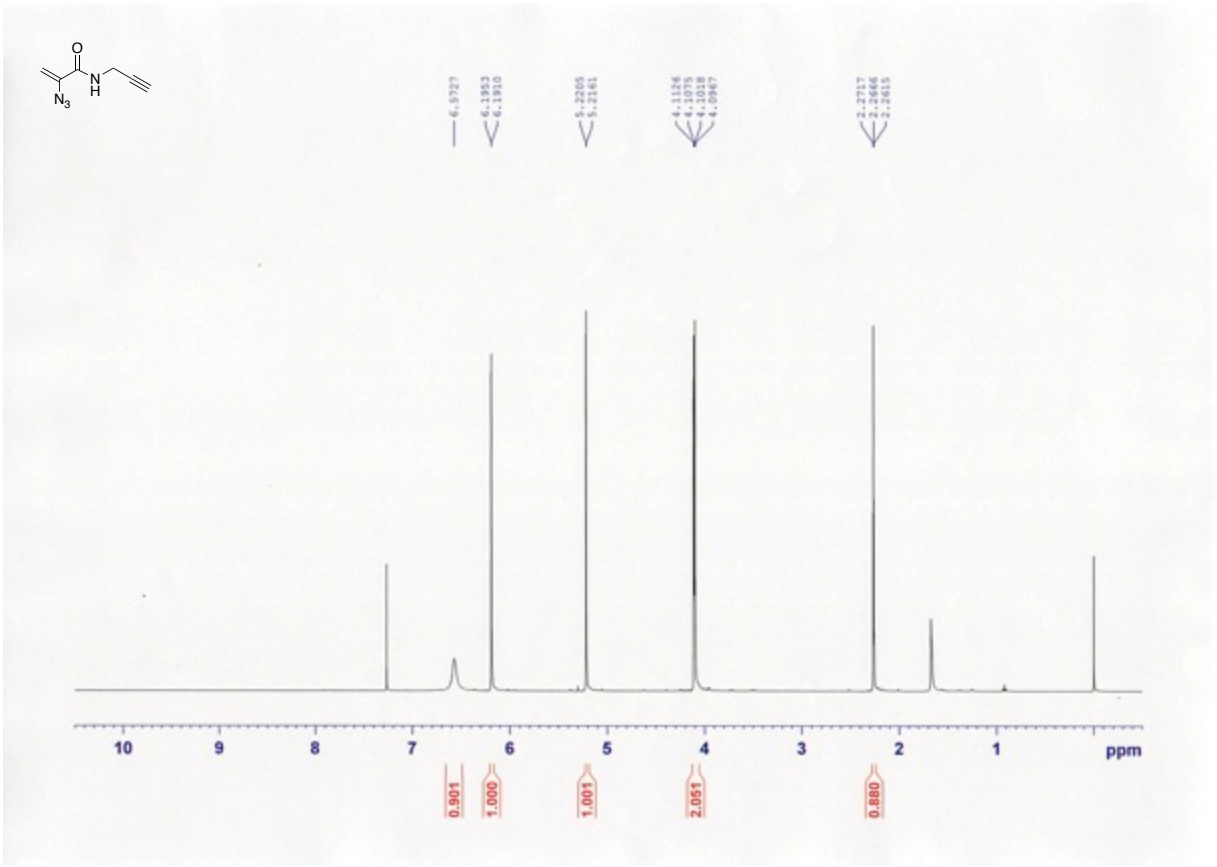


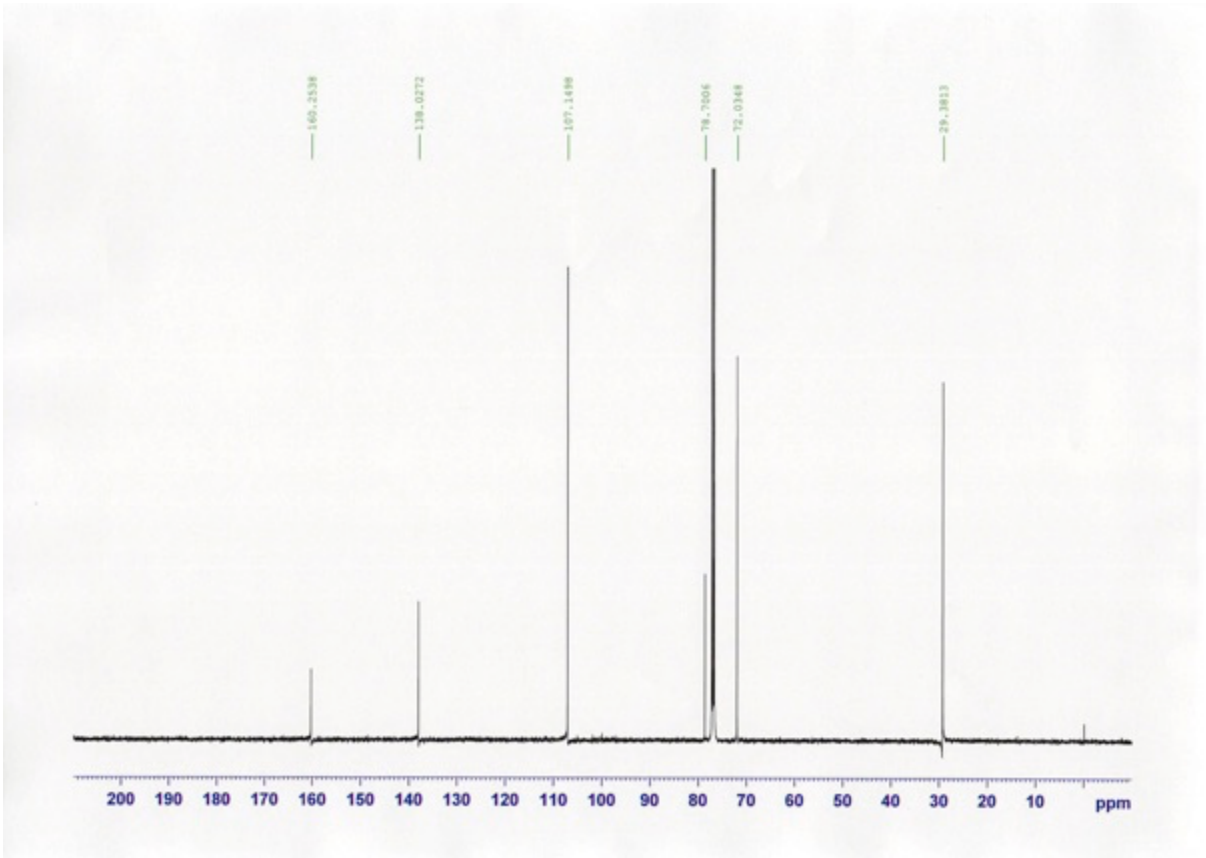
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of diethyl 2-(3-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)malonate (**21c**) ($CDCl_3$)



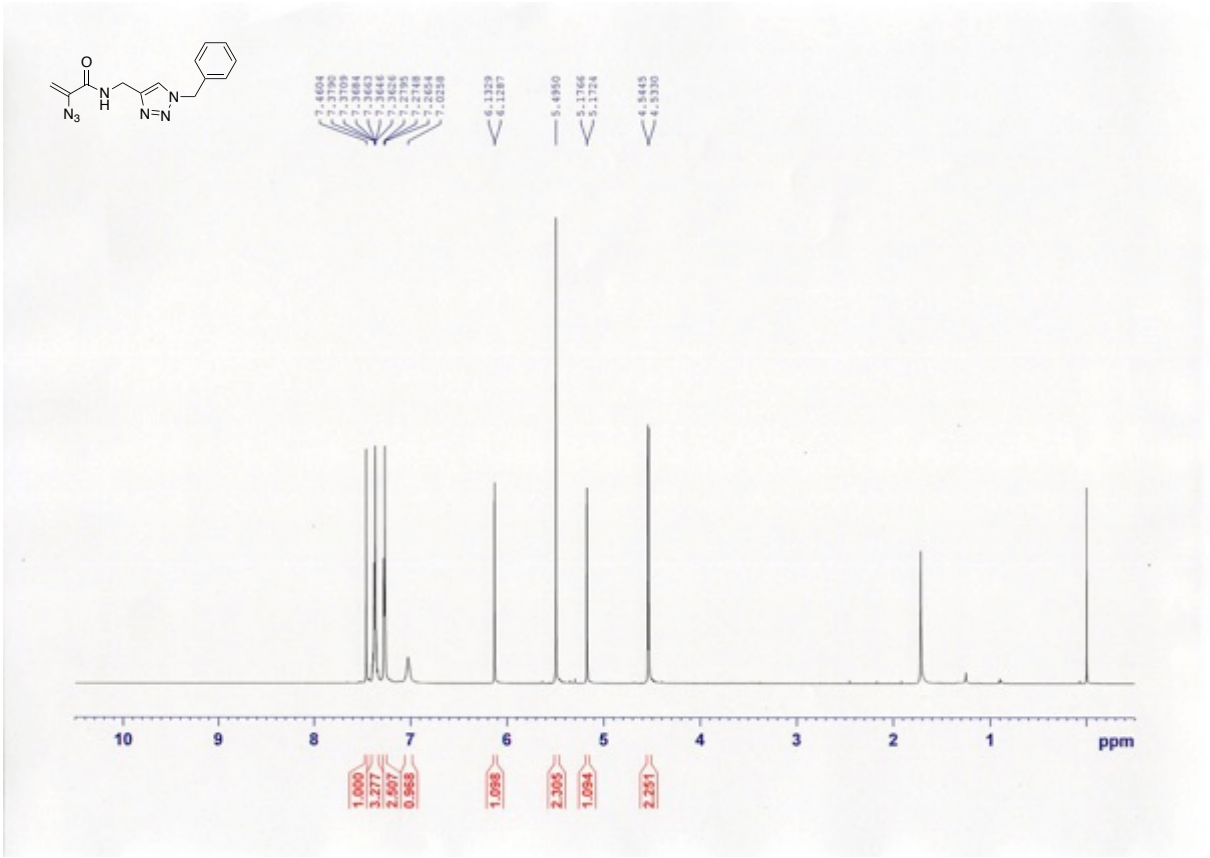


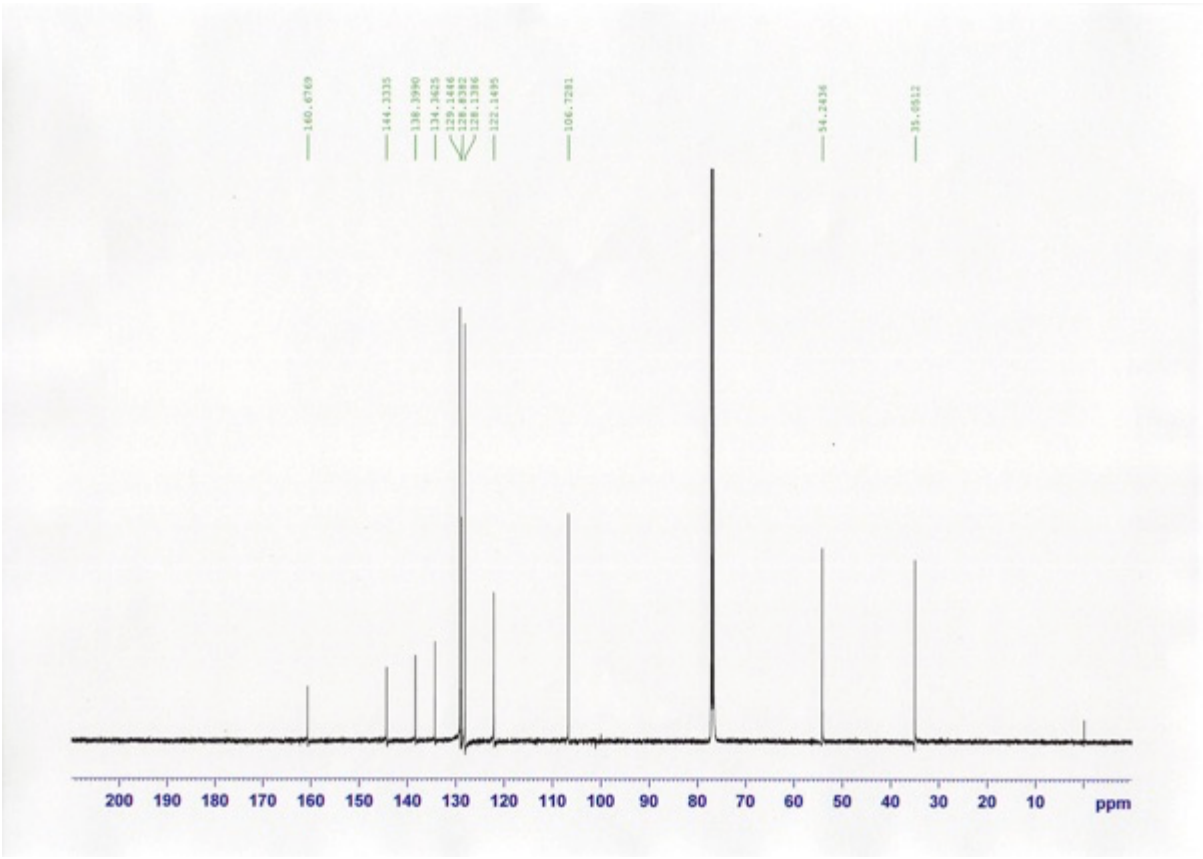
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azido-*N*-(prop-2-yn-1-yl)acrylamide (**22**) ($CDCl_3$)



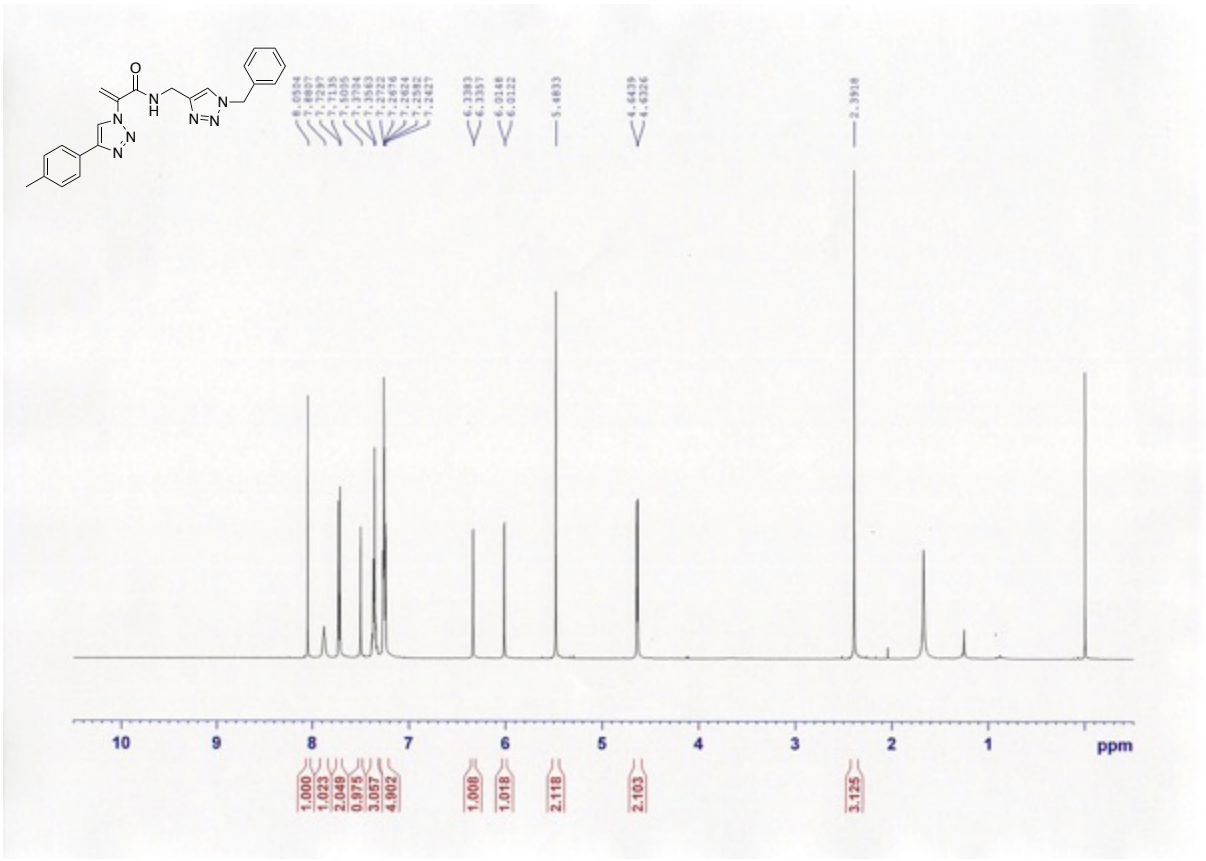


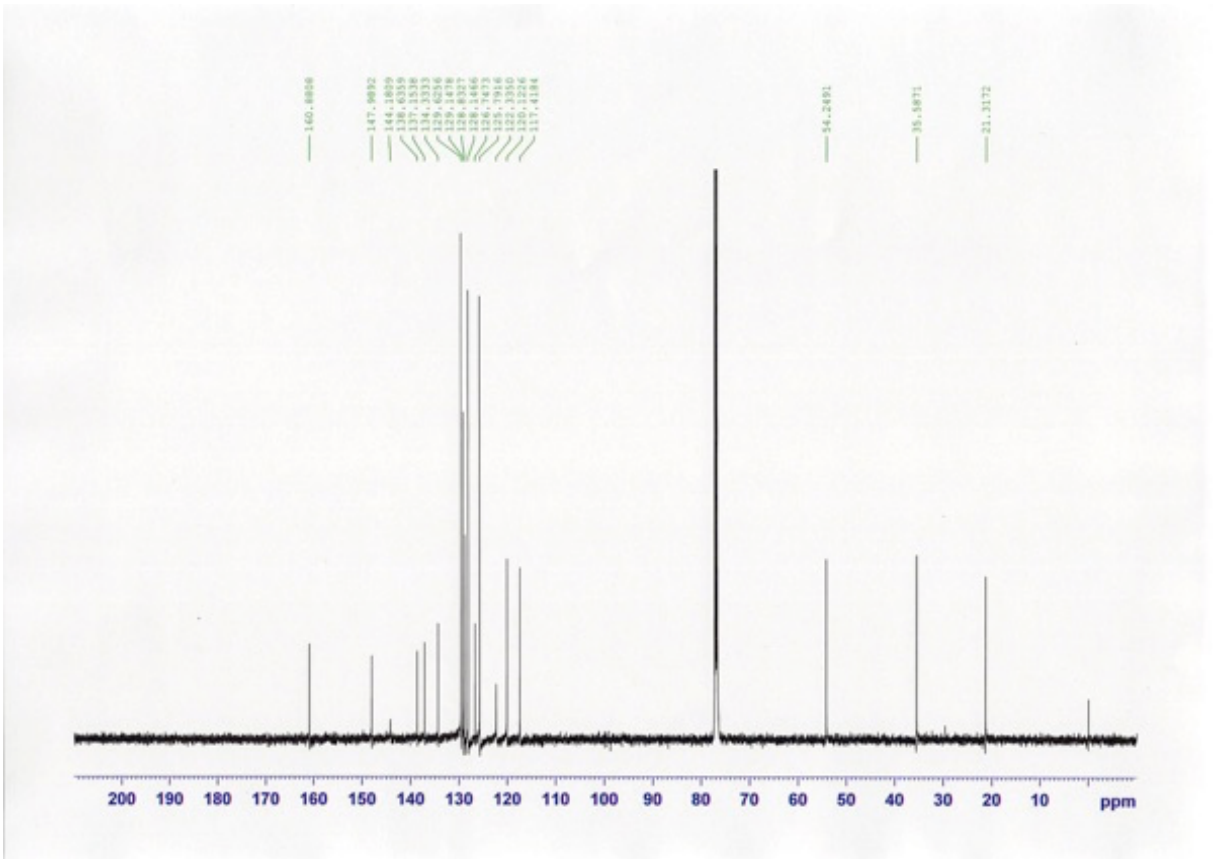
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azido-*N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)acrylamide (**24**) ($CDCl_3$)



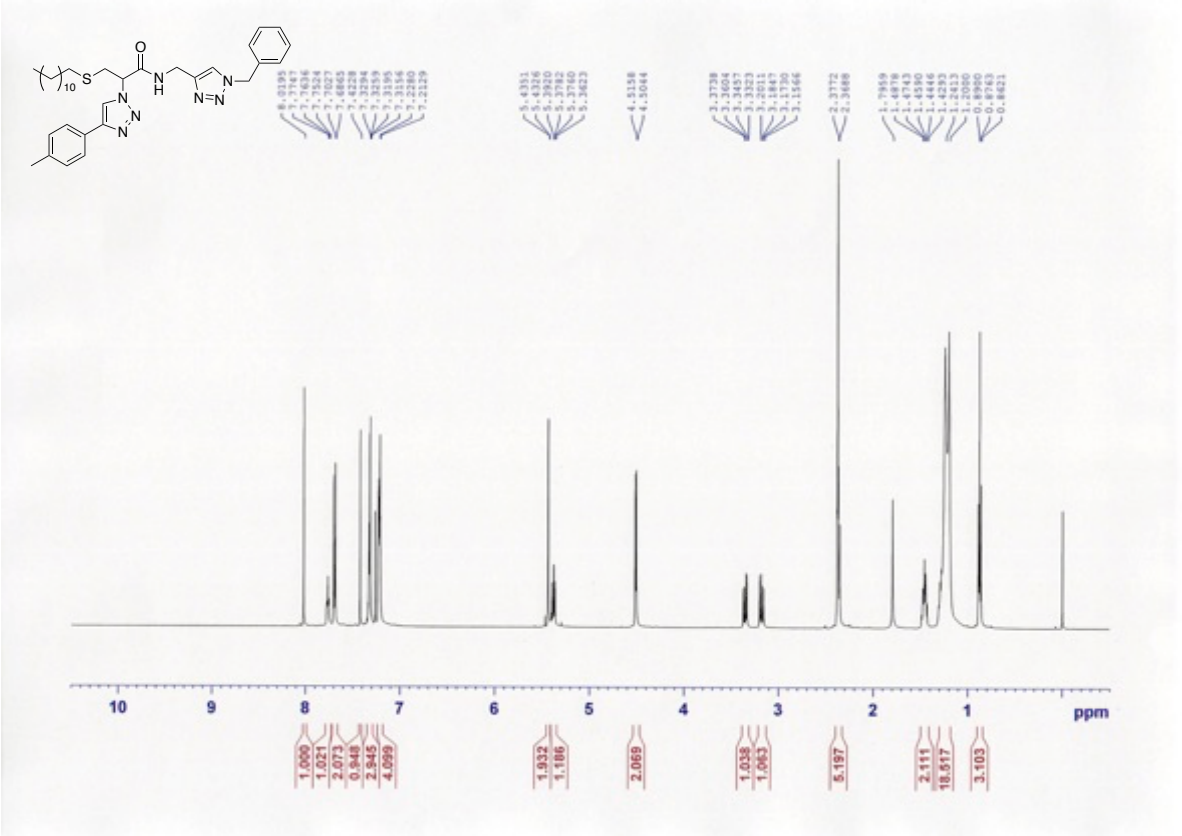


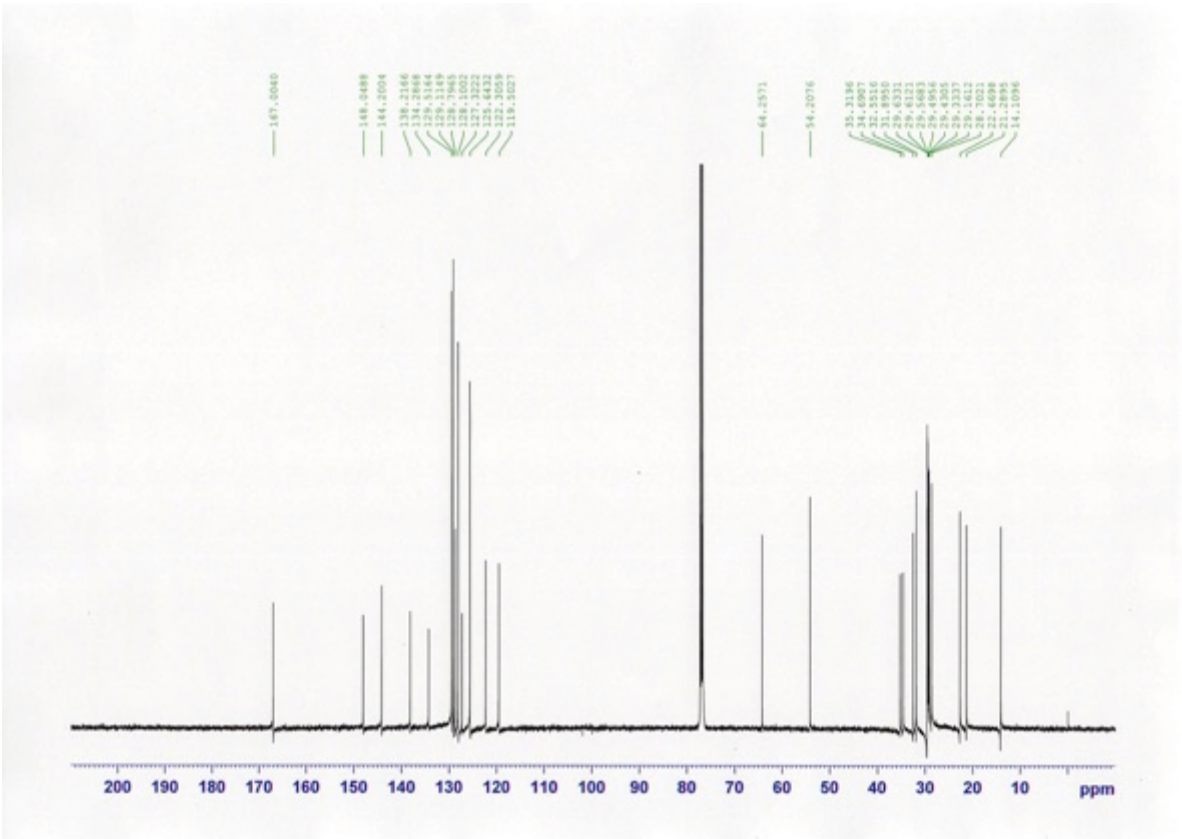
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)acrylamide (**25**) ($CDCl_3$)



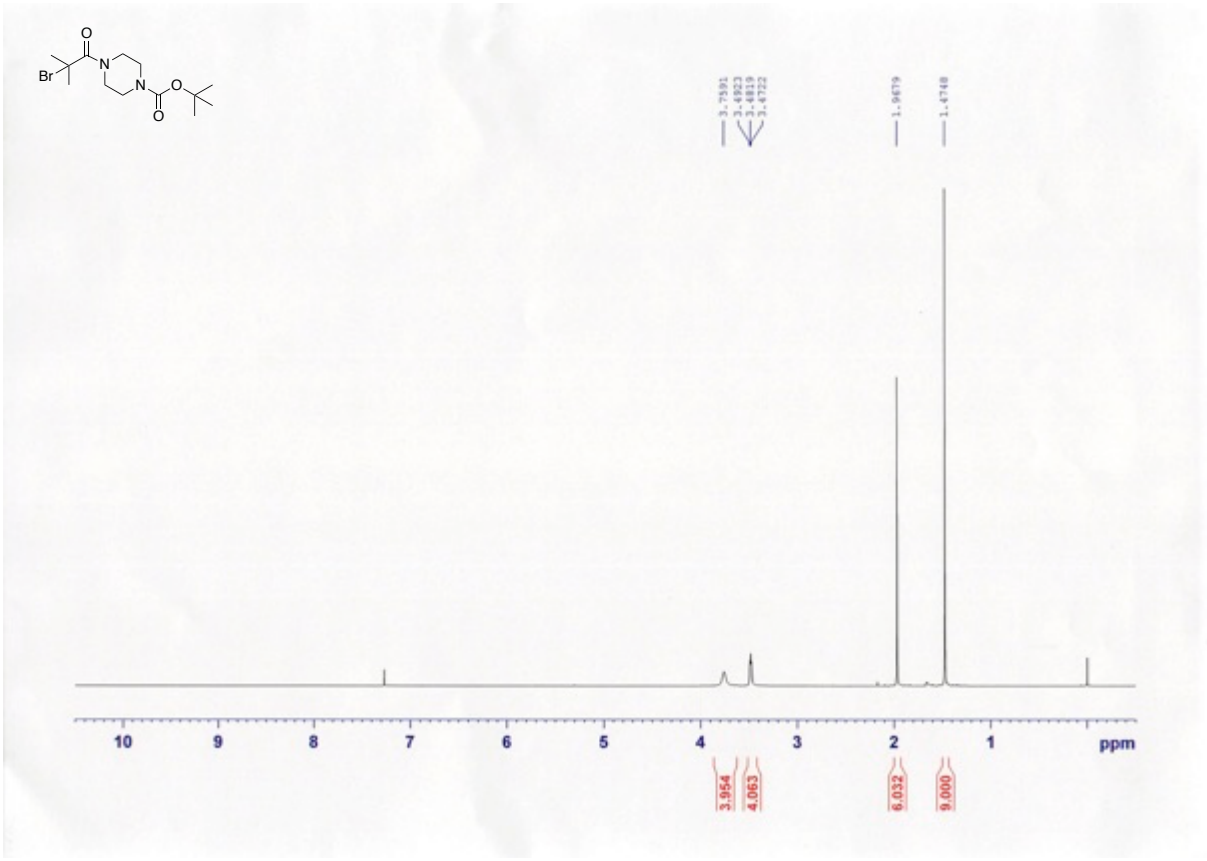


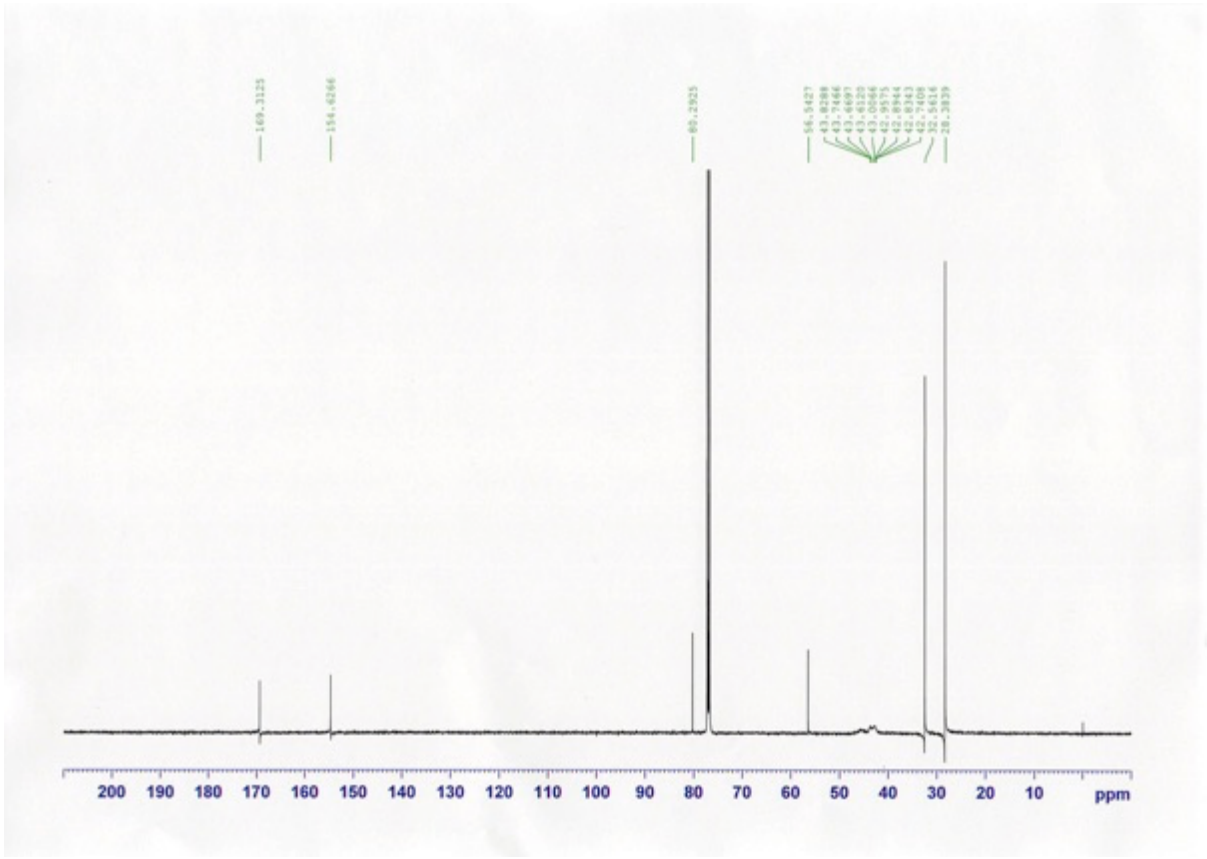
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *N*-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-(dodecylthio)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanamide (**26**) ($CDCl_3$)



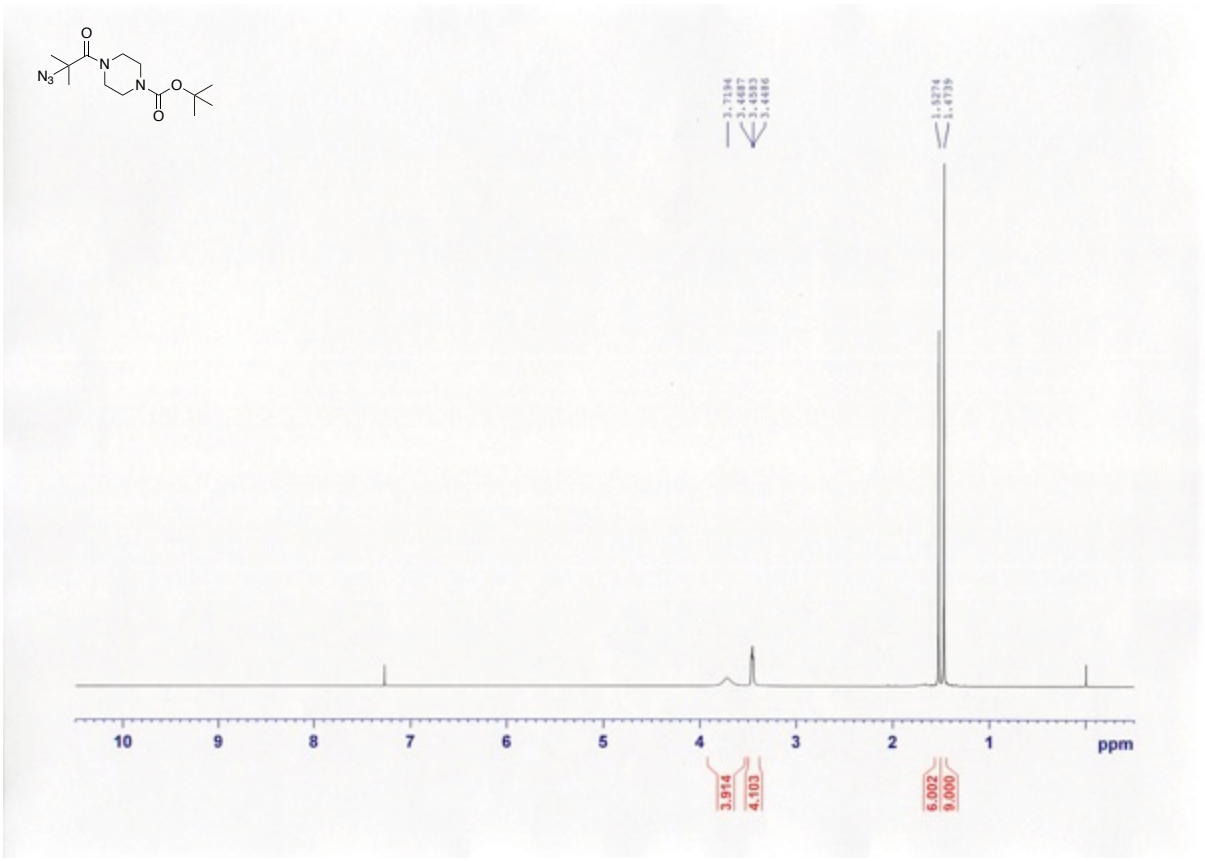


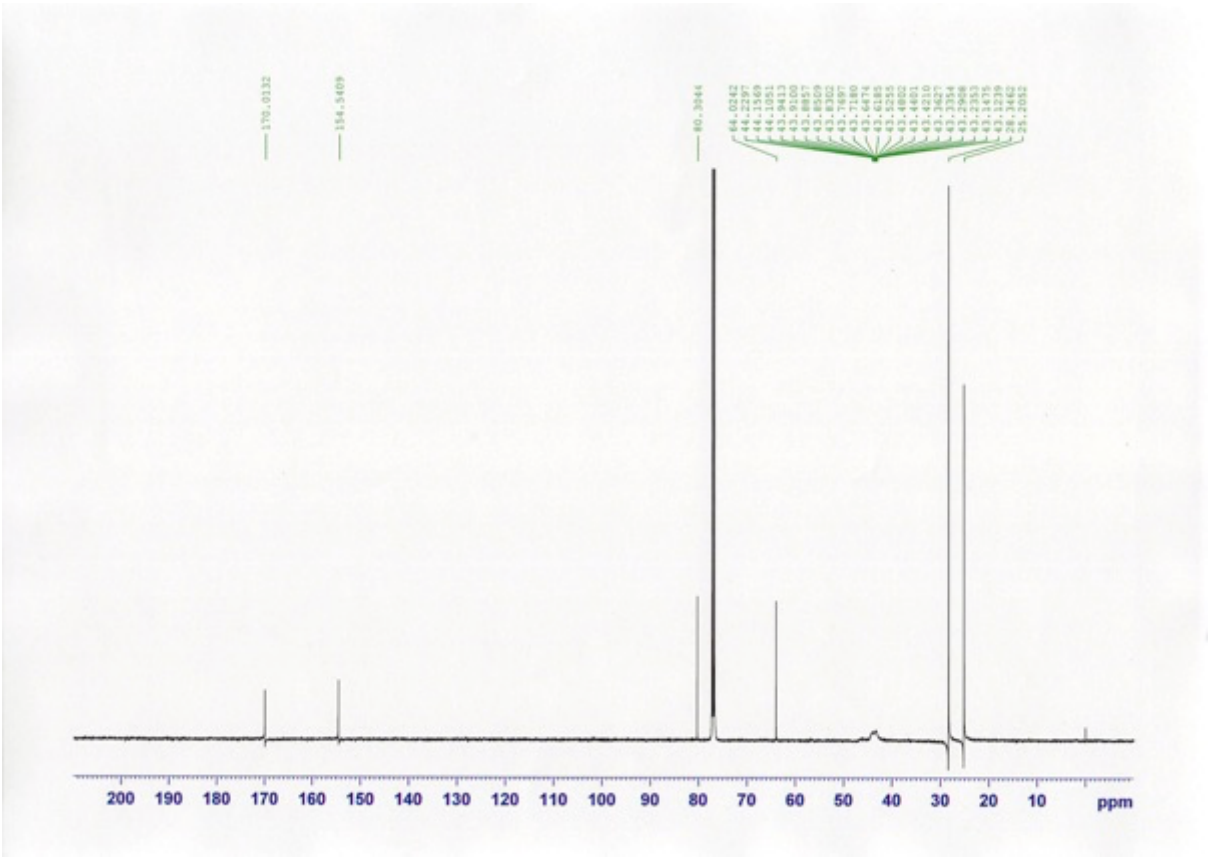
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-bromo-2-methylpropanoyl)piperazine-1-carboxylate (**S17**) ($CDCl_3$)



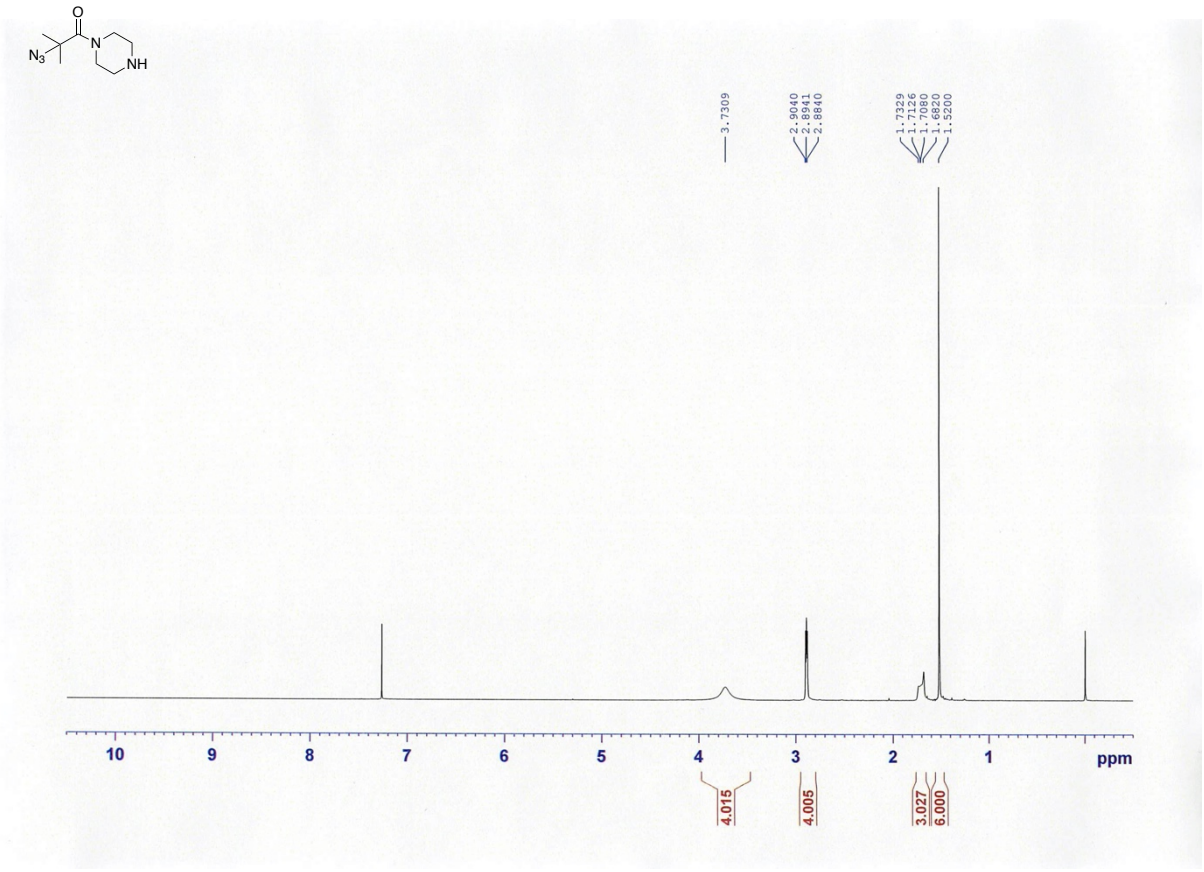


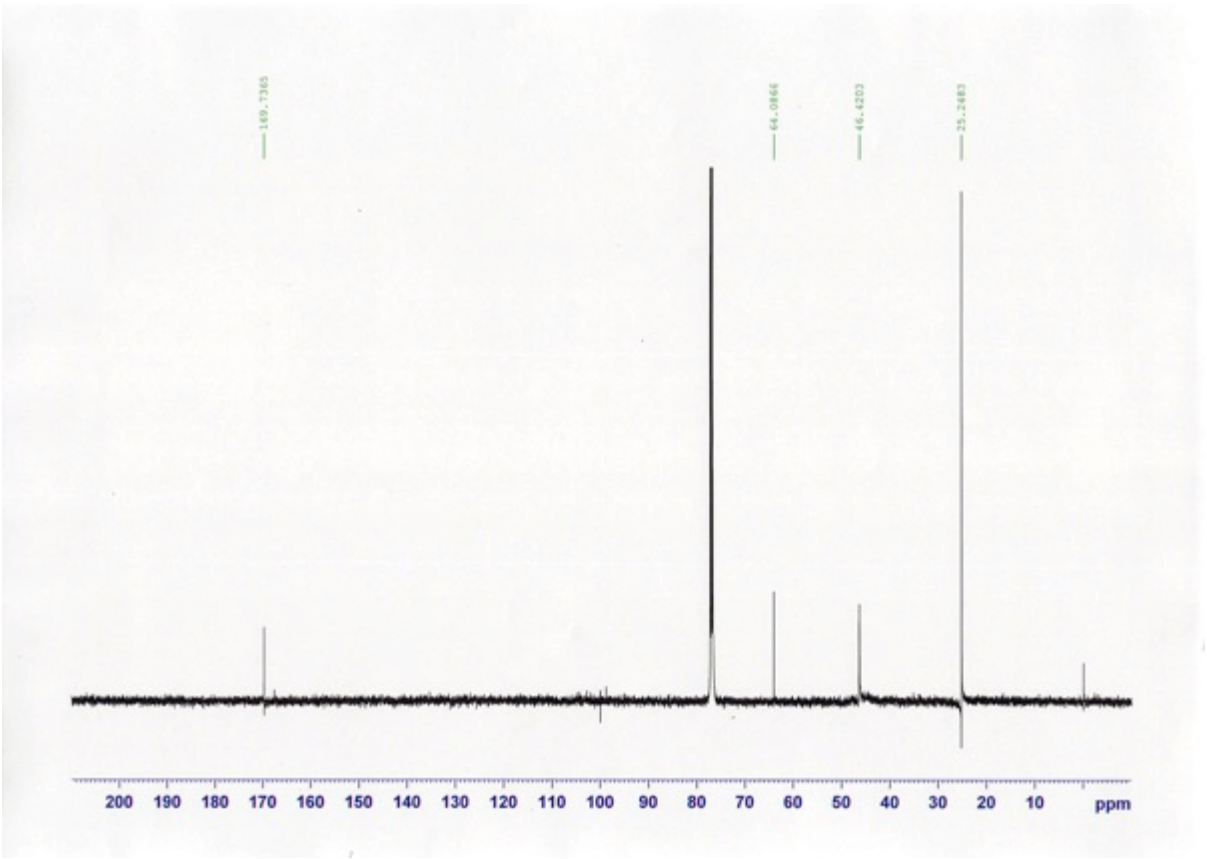
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(2-azido-2-methylpropanoyl)piperazine-1-carboxylate (**S18**) ($CDCl_3$)



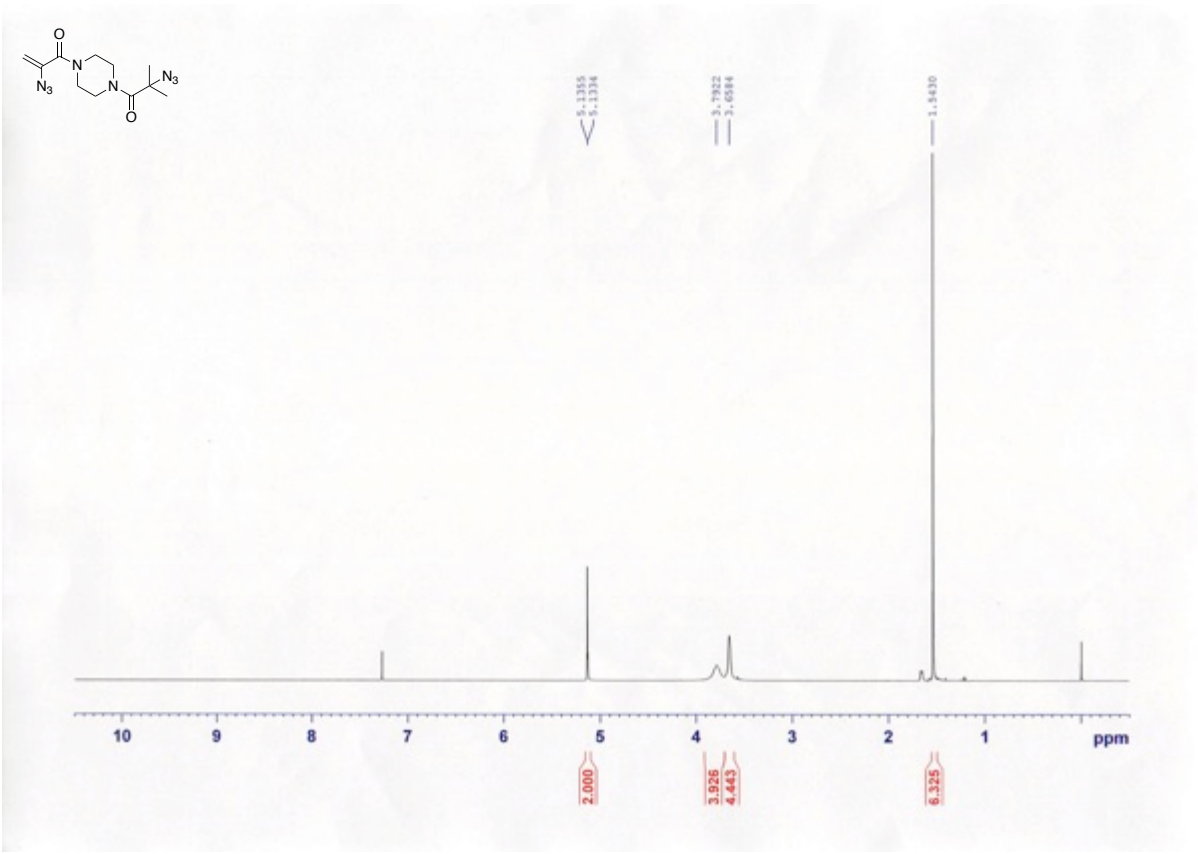


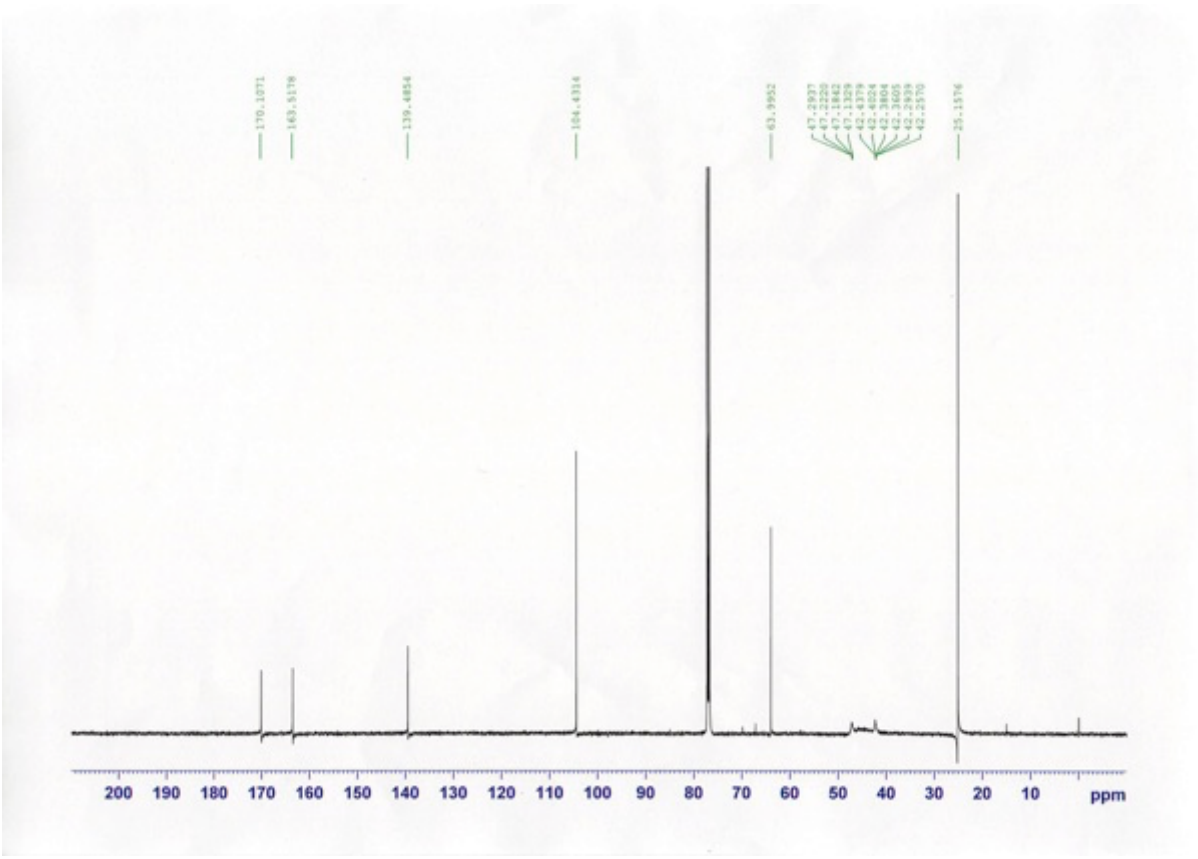
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azido-2-methyl-1-(piperazin-1-yl)propan-1-one (**S19**) ($CDCl_3$)



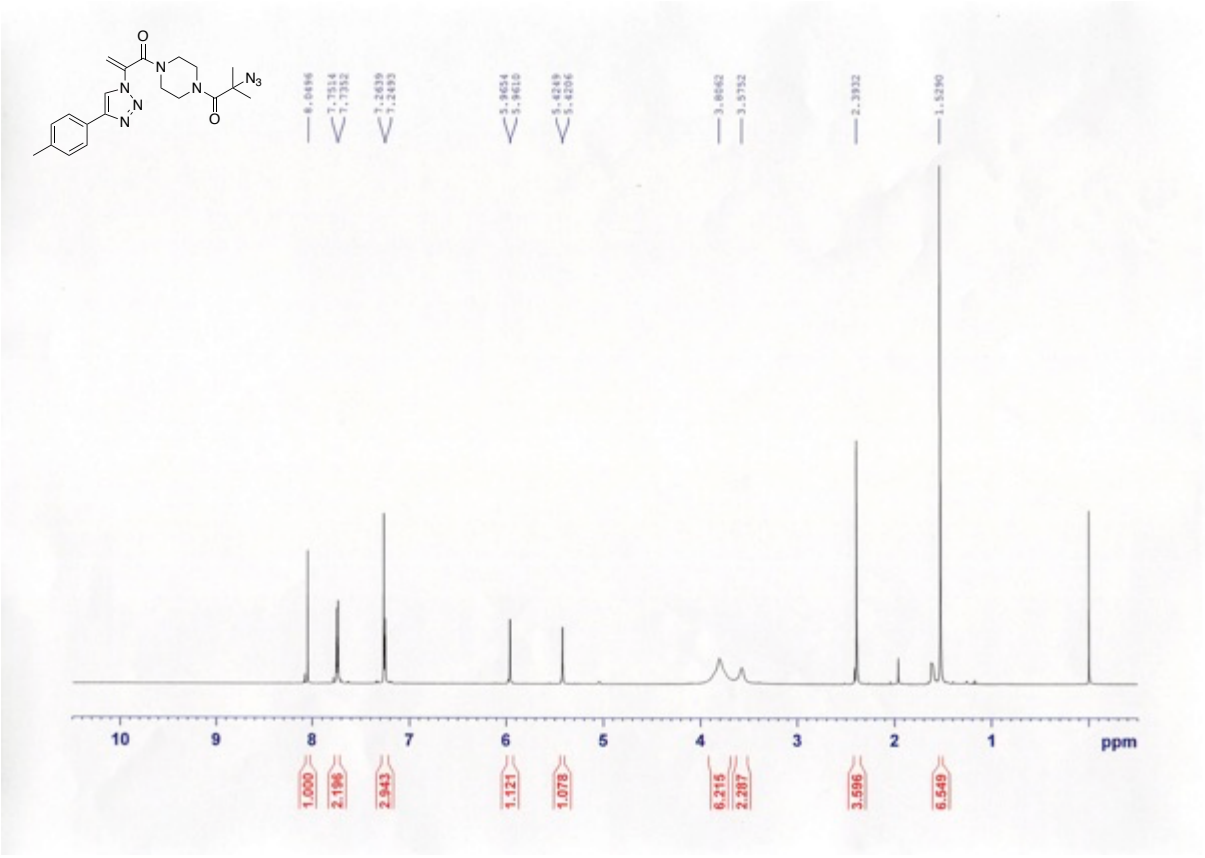


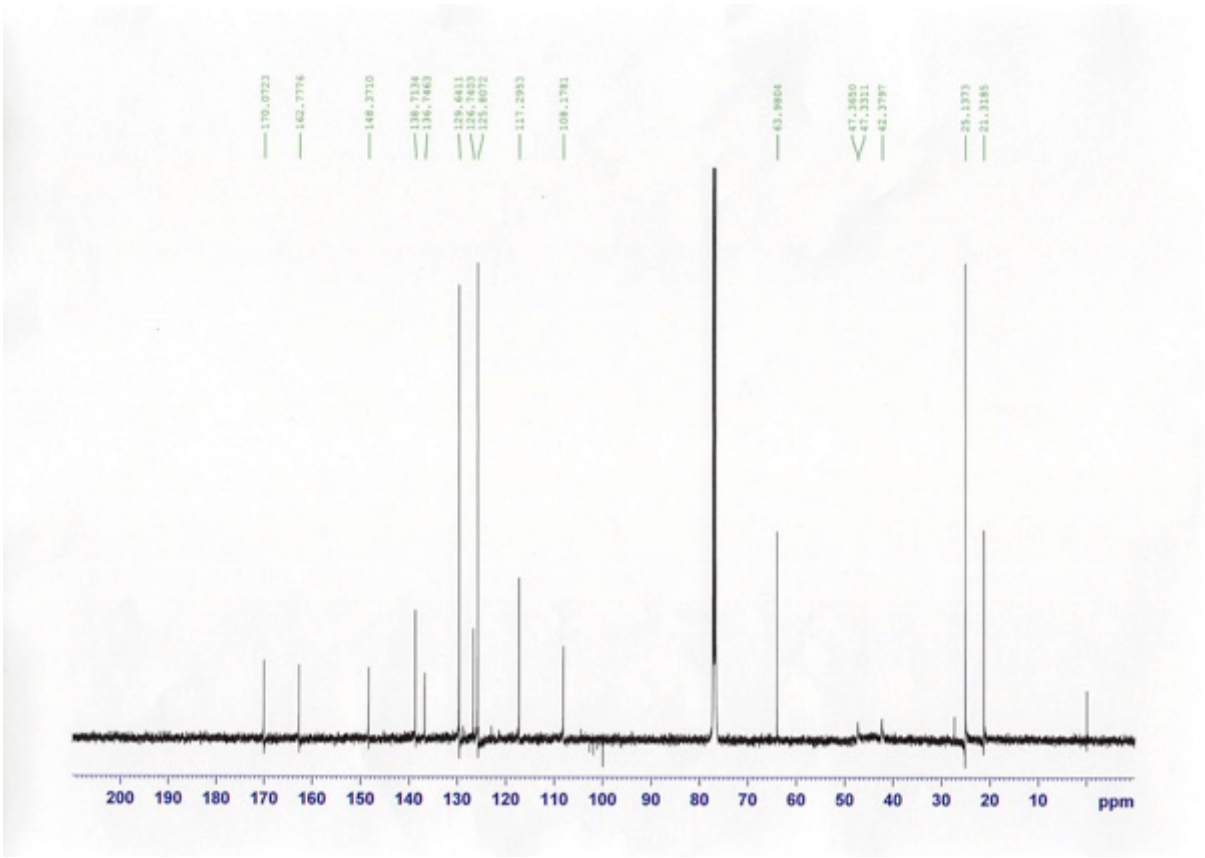
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azido-1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)prop-2-en-1-one (**27**) ($CDCl_3$)



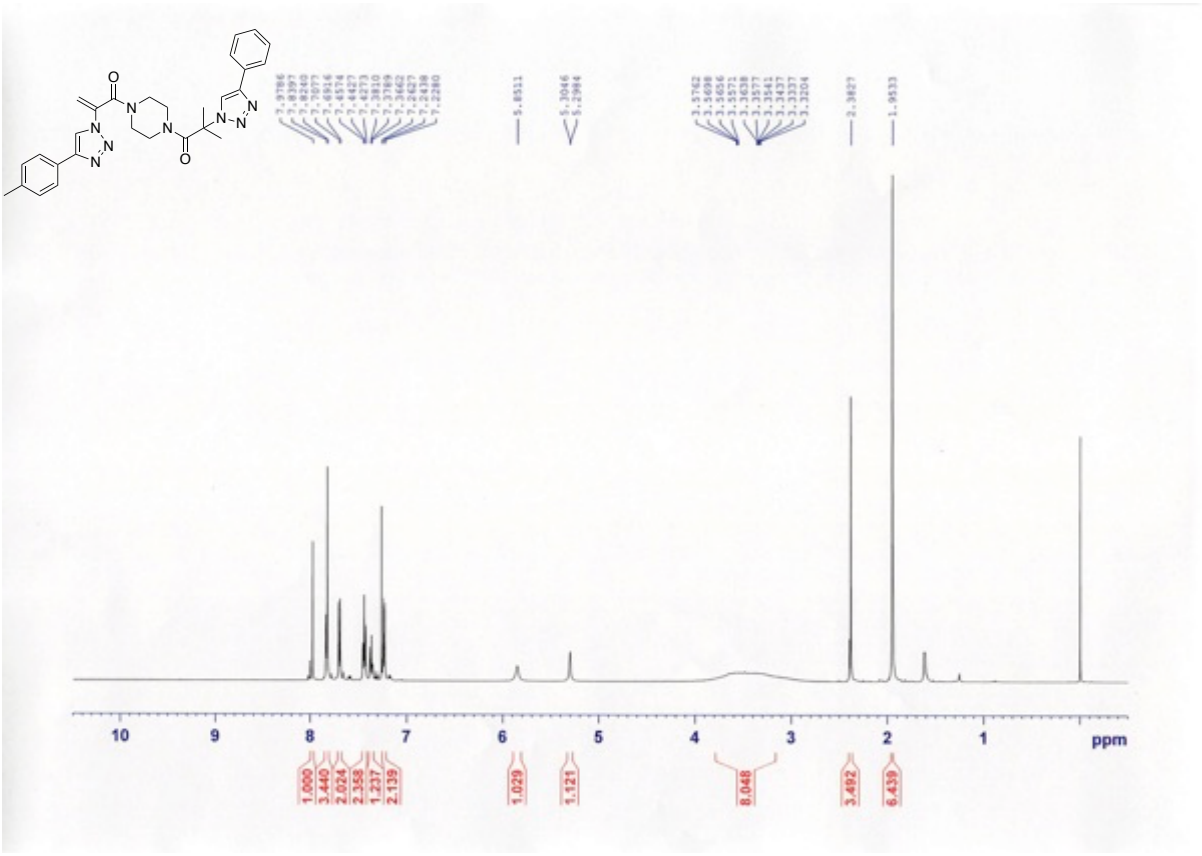


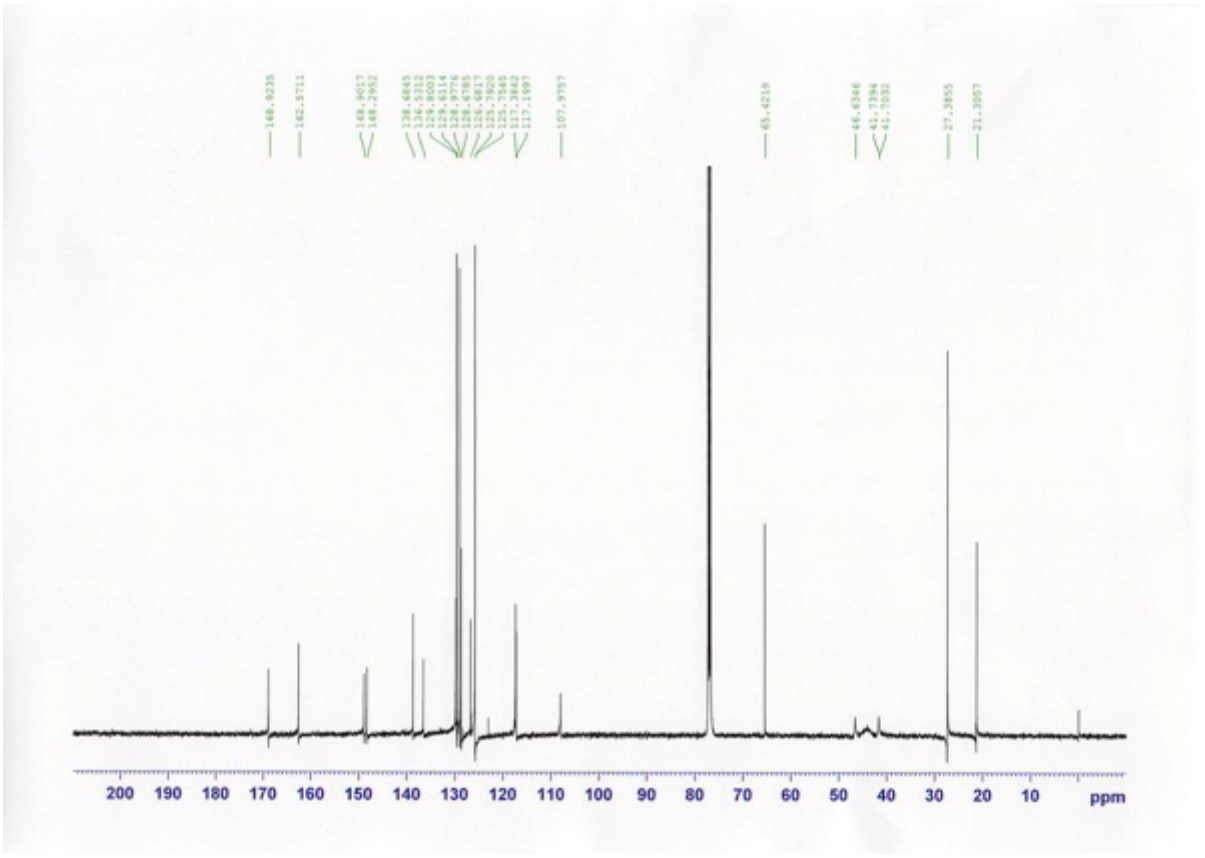
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**28**) ($CDCl_3$)



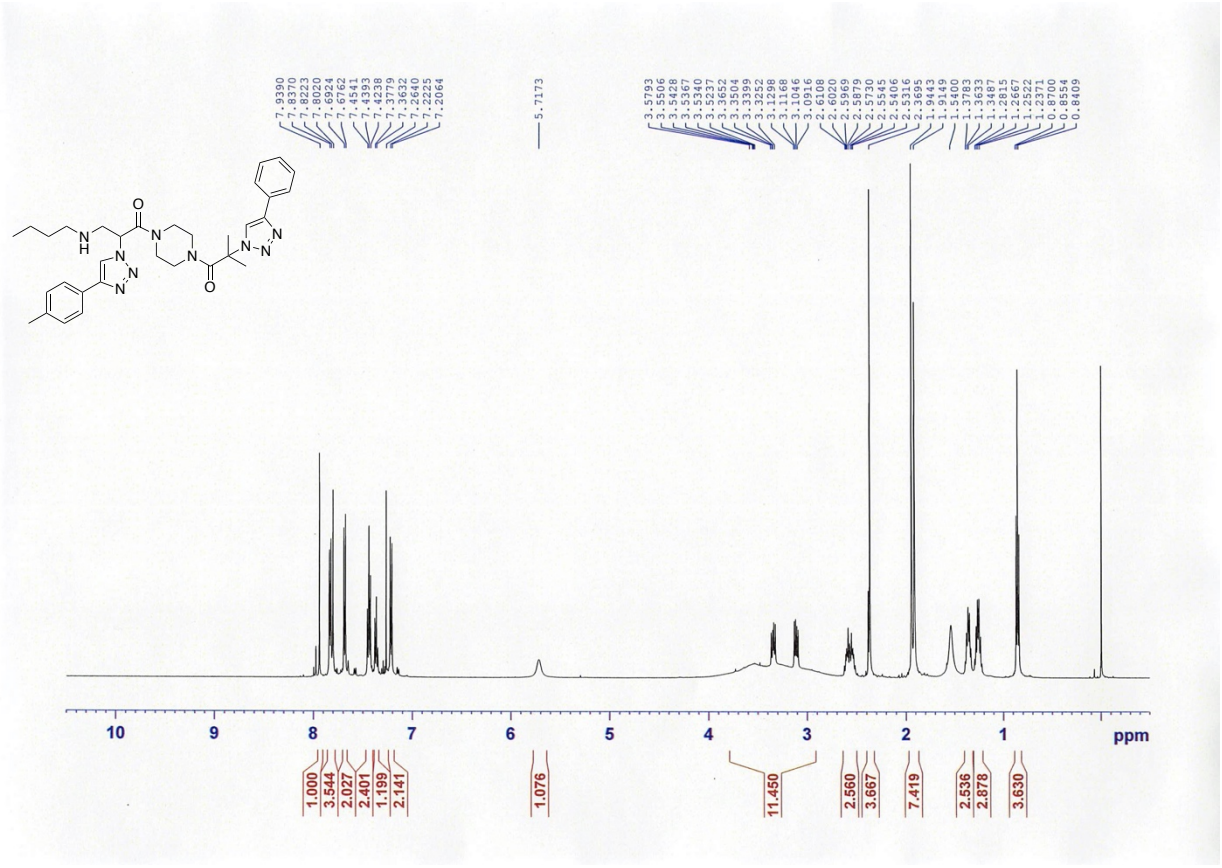


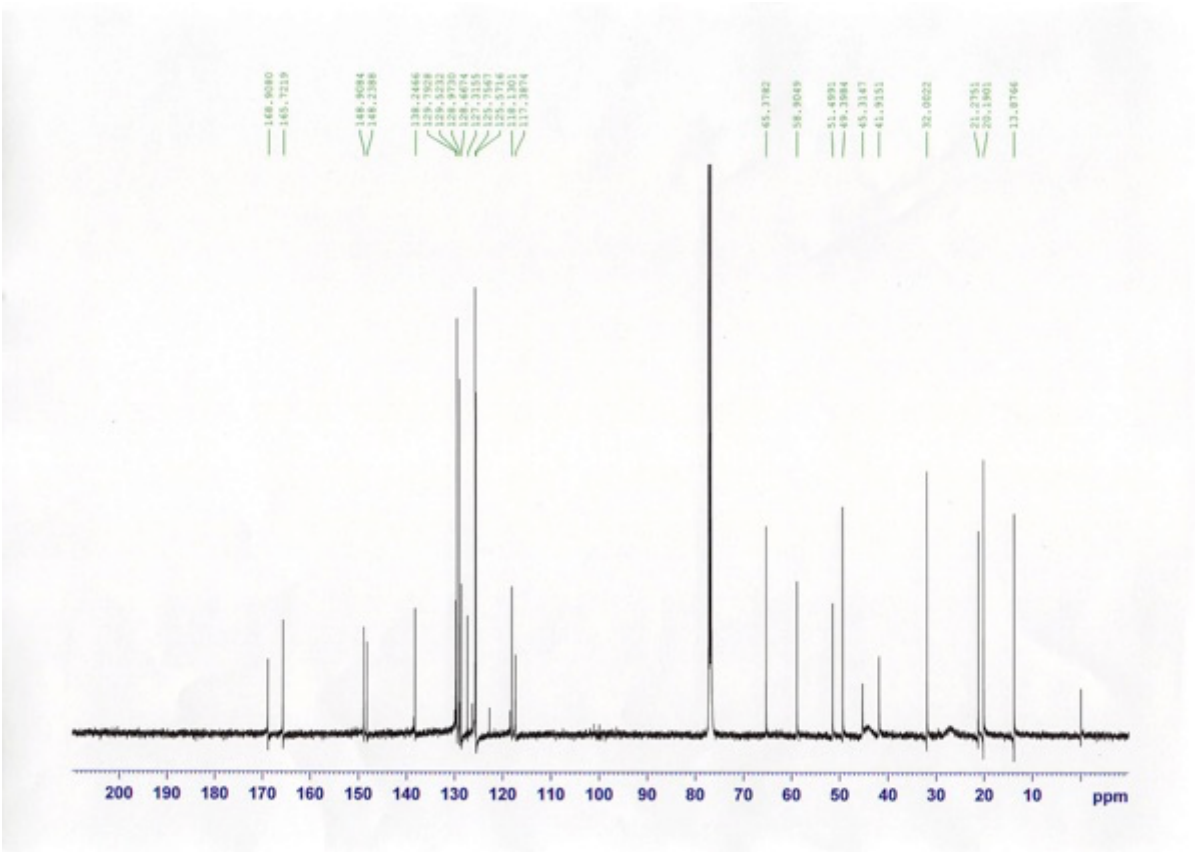
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 1-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**29**) ($CDCl_3$)



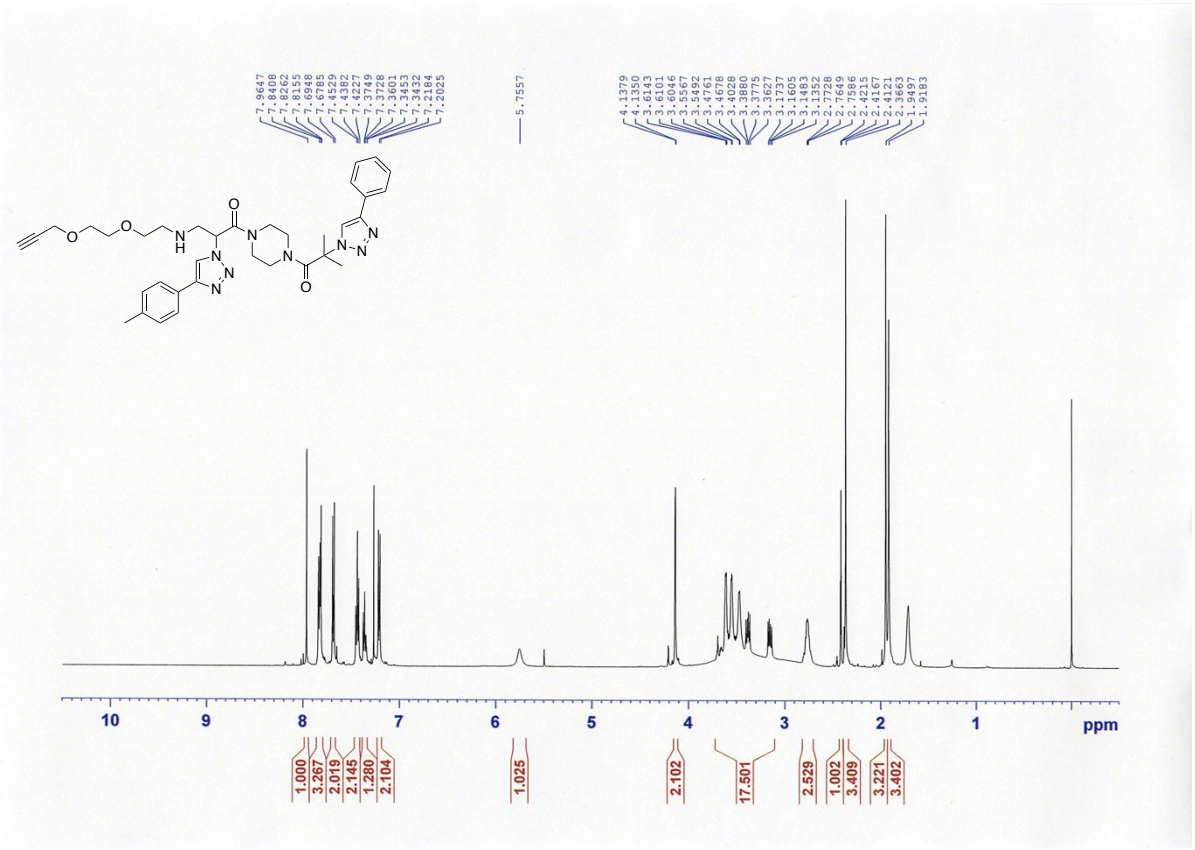


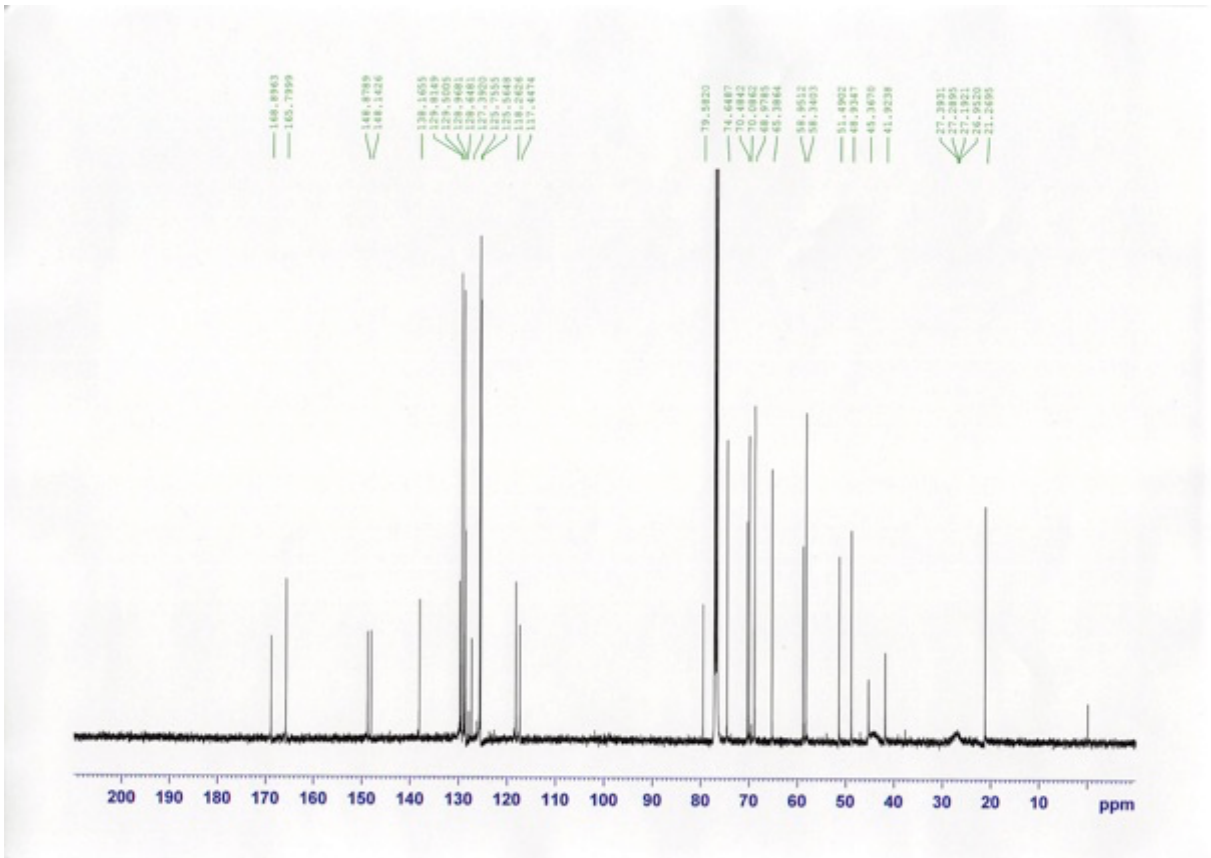
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 3-(butylamino)-1-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propan-1-one (**30**) ($CDCl_3$)



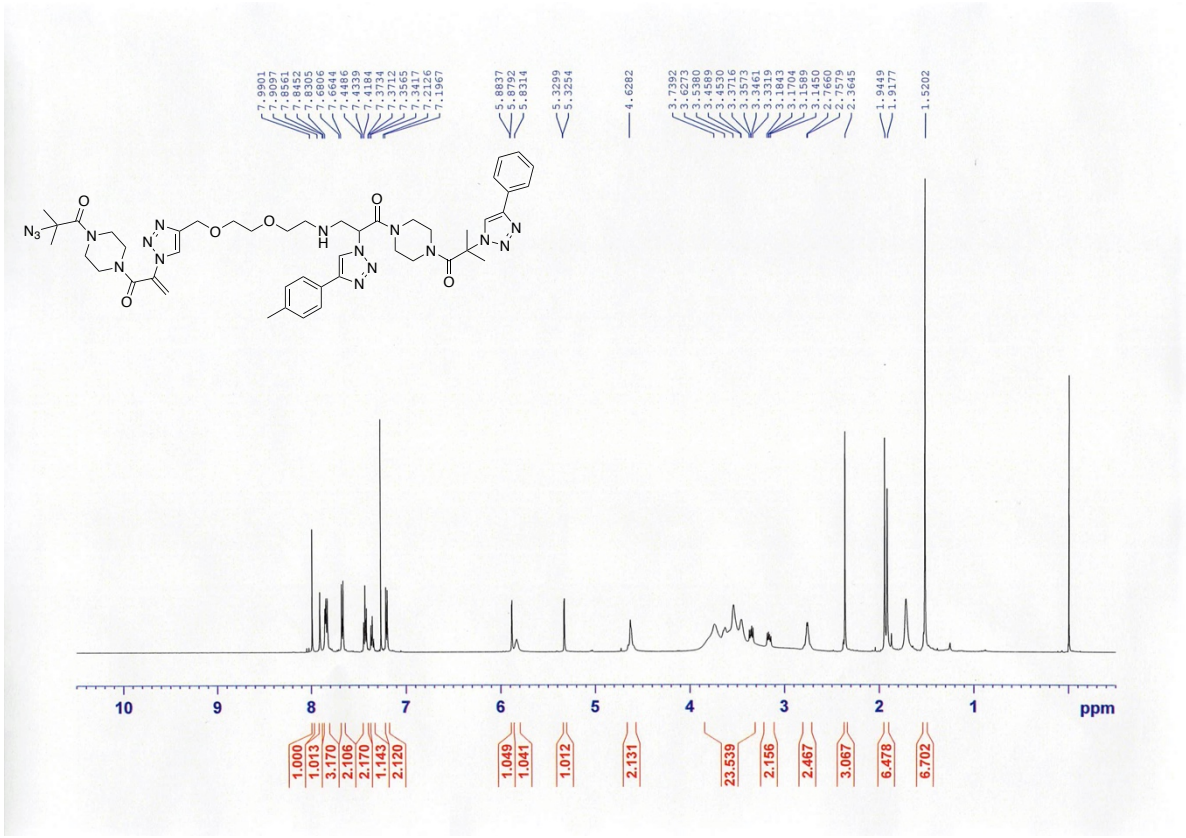


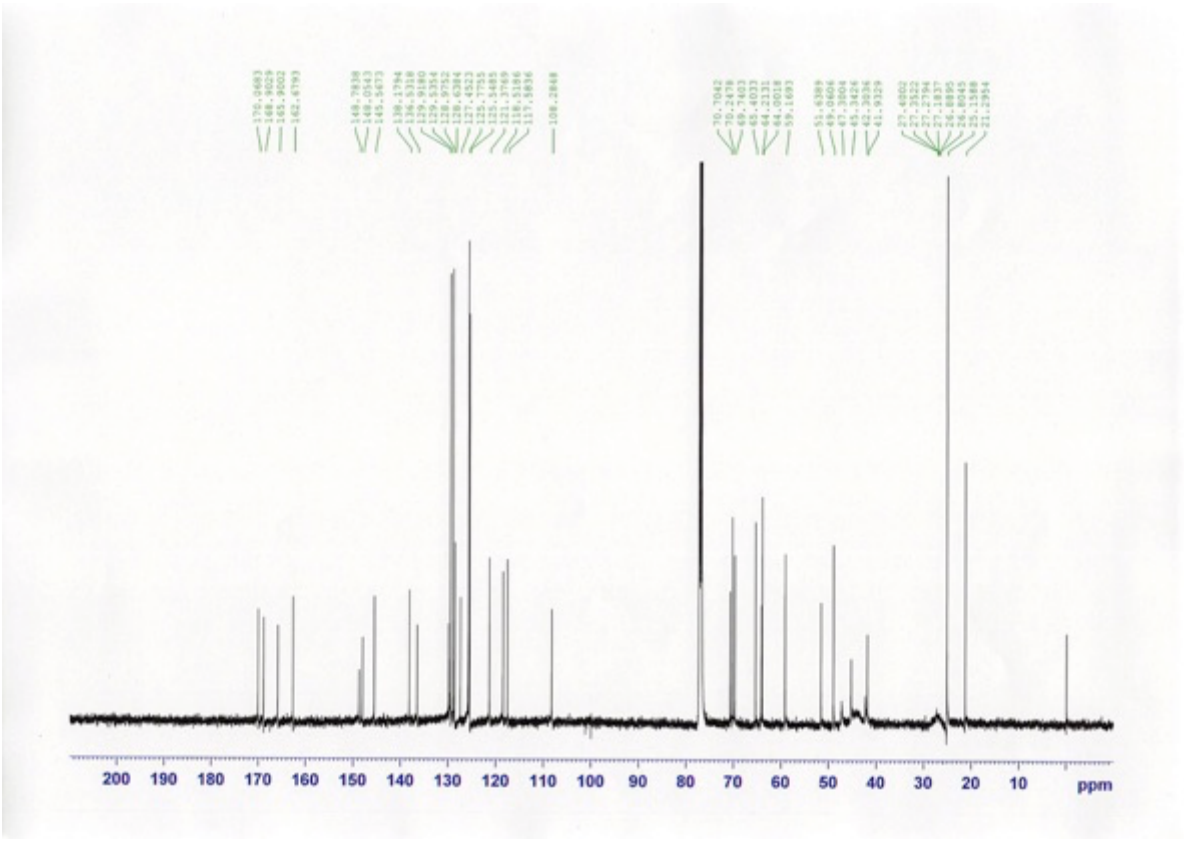
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1-(4-(3-((2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)amino)-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)propan-1-one (**31**) ($CDCl_3$)



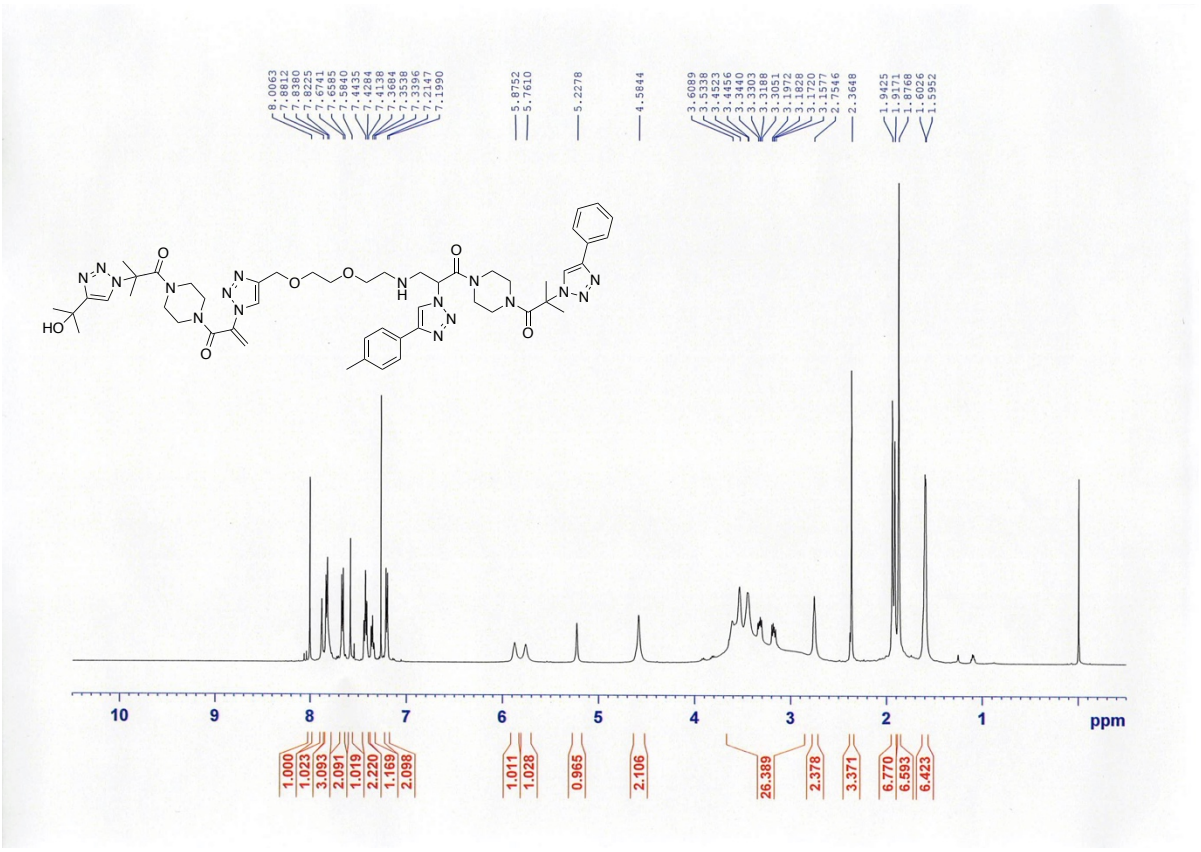


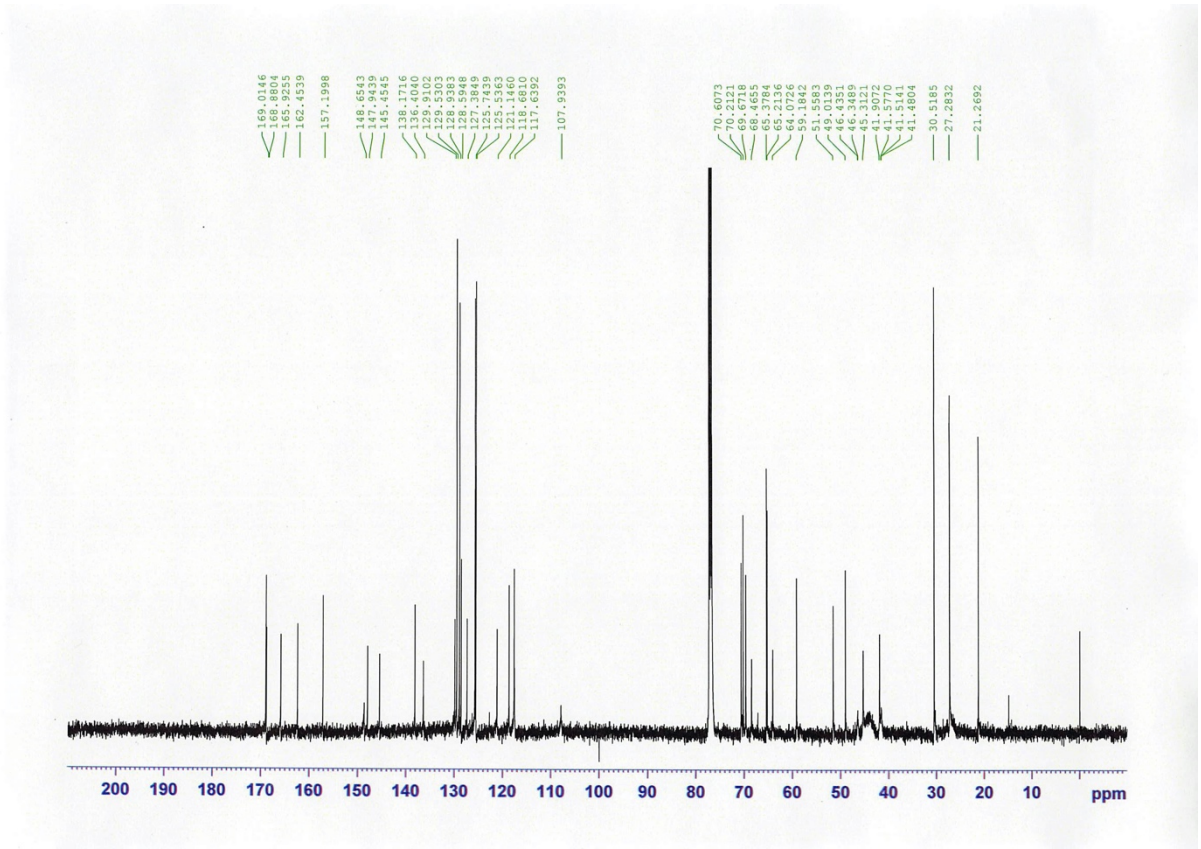
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 1-(4-(2-azido-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**32**) ($CDCl_3$)





^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 1-(4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**S20**) ($CDCl_3$)





^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 3-(butylamino)-1-(4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)-2-methylpropanoyl)piperazin-1-yl)-2-(4-((2-(2-((3-(4-(2-methyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-3-oxo-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)propyl)amino)ethoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)propan-1-one (**33**) ($CDCl_3$)