

Electronic Supplementary Information

Modular synthesis of triazoles from 2-azidoacrylamides having a nucleophilic amino group

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General Remarks

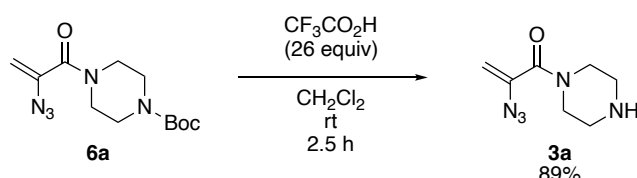
All reactions were performed in a dry glassware under atmosphere of argon otherwise noted. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica-gel plates (Merck Chemicals, Silica Gel 60 F₂₅₄, Cat. No. 1.05715). Column chromatography was conducted using silica-gel (Kanto 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. ¹H NMR spectra were obtained with a Bruker AVANCE 500 spectrometer or a Bruker AVANCE 400 spectrometer at 500 or 400 MHz, respectively. ¹³C NMR spectra were obtained with a Bruker AVANCE 500 spectrometer or a Bruker AVANCE 400 spectrometer at 126 or 101 MHz, respectively. ¹⁹F 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 (CH₃)₄Si (δ 0.00 for ¹H NMR in CDCl₃) or the solvent peak (δ 77.0 for ¹³C NMR in CDCl₃) as an internal reference with coupling constants (*J*) in hertz (Hz). The abbreviations s, d, t, q, sept, m, and br signify singlet, doublet, triplet, quartet, septet, 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. *tert*-Butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**6a**),^{S1} *tert*-butyl 4-(2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**8i**),^{S1} and tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA)^{S2} were prepared according to the reported methods.

CAUTION! Azido-containing compounds are presumed to be potentially explosive. Although we have never experienced such an explosion with azido compounds used in this study, all manipulations should be carefully carried out behind a safety shield in a hood.

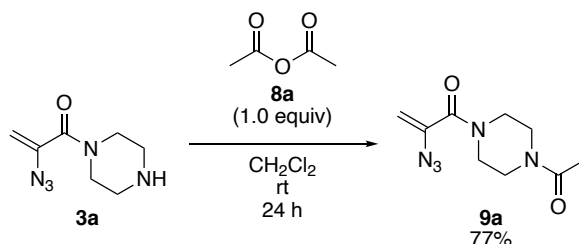
Experimental Procedures

General procedure for the synthesis of amine-type platforms 3



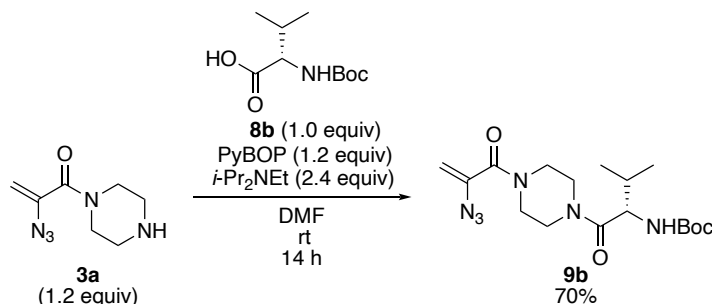
To a solution of *tert*-butyl 4-(2-azidoacryloyl)piperazine-1-carboxylate (**6a**) (281 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was slowly added trifluoroacetic acid (2.0 mL, 26.1 mmol) at 0 °C. After stirring for 2.5 h at room temperature, to the mixture was added aqueous 1 M NaOH (40 mL). The mixture was extracted with CH_2Cl_2 (100 mL \times 3). The combined organic extract was washed with brine (20 mL), and dried with Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure to give 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (161 mg, 0.887 mmol, 89%) as a colorless oil.

Synthesis of 1-(4-acetylpiperazin-1-yl)-2-azidoprop-2-en-1-one (**9a**)



To a solution of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (27.2 mg, 0.150 mmol) in CH_2Cl_2 (0.90 mL) was added acetic anhydride (**8a**) (14.2 μL , 0.150 mmol) at 0 °C. After stirring for 24 h at the same temperature, to the mixture was added aqueous 2 M HCl (50 mL). The mixture was extracted with EtOAc (100 mL \times 2). The combined organic extract was washed with brine (40 mL) and dried with Na_2SO_4 . After filtration, the filtrate was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$) to give 1-(4-acetylpiperazin-1-yl)-2-azidoprop-2-en-1-one (**9a**) (25.7 mg, 0.115 mmol, 77%) as a colorless oil.

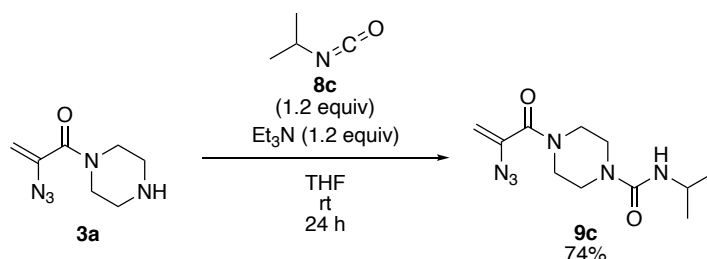
Synthesis of *tert*-butyl (*S*)-(1-(4-(2-azidoacryloyl)piperazin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate (**9b**)



To a solution of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (43.5 mg, 0.240 mmol) and (*tert*-butoxycarbonyl)-*L*-valine (**8b**) (43.5 mg, 0.200 mmol) dissolved in DMF (0.80 mL) were added *i*-Pr₂NEt (82.7 μL , 0.480 mmol) and (benzotriazol-1-yloxy)(trispyrrolidino)phosphonium hexafluorophosphate (PyBOP) (125 mg, 0.240 mmol) at 0 °C. After

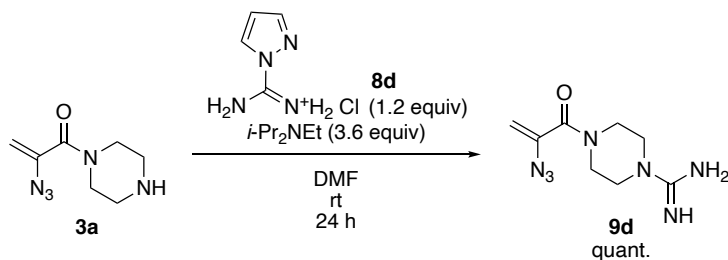
warming to room temperature, the mixture was stirred for 14 h at the same temperature. Then, to the mixture was added saturated aqueous sodium bicarbonate (10 mL). The mixture was extracted with EtOAc (15 mL \times 3). The combined organic extract was washed with brine (10 mL) and dried with Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica-gel 10 g, *n*-hexane/EtOAc = 1/2) to give (*S*)-(1-(4-(2-azidoacryloyl)piperazin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate (**9b**) (52.9 mg, 0.139 mmol, 70%) as a colorless oil.

Synthesis of 4-(2-azidoacryloyl)-*N*-isopropylpiperazine-1-carboxamide (**9c**)



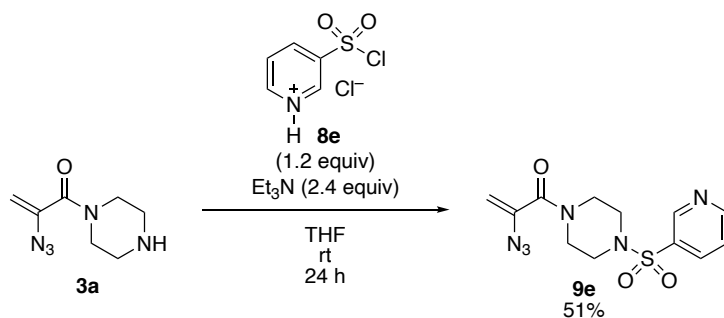
To a solution of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (9.1 mg, 50 μ mol) in THF (0.25 mL) were added 2-isocyanatopropane (**8c**) (5.9 μ L, 60 μ mol) and triethylamine (8.3 μ L, 60 μ mol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH₂Cl₂/MeOH = 15/1) to give 4-(2-azidoacryloyl)-*N*-isopropylpiperazine-1-carboxamide (**9c**) (9.80 mg, 36.8 μ mol, 74%) as a pale yellow oil.

Synthesis of 4-(2-azidoacryloyl)piperazine-1-carboximidamide (**9d**)



To a solution of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (9.1 mg, 50 μ mol) in DMF (0.25 mL) were added 1*H*-pyrazole-1-carboximidamide hydrochloride (**8d**) (8.8 mg, 60 μ mol) and *N,N*-diisopropylethylamine (31.0 μ L, 0.18 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 (CH₂Cl₂/MeOH = 3/1) to give 4-(2-azidoacryloyl)piperazine-1-carboximidamide (**9d**) (11.2 mg, 50.0 μ mol, quant.) as a yellow solid.

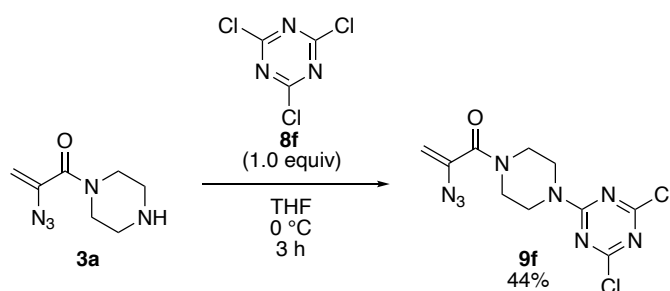
Synthesis of 2-azido-1-(4-(pyridin-3-ylsulfonyl)piperazin-1-yl)prop-2-en-1-one (**9e**)



To a solution of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (9.1 mg, 50 μ mol) in THF (0.25 mL) were added pyridine-3-sulfonyl chloride hydrochloride (**8e**) (12.8 mg, 60.0 μ mol) and triethylamine (16.6 μ mol, 0.120 mmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The

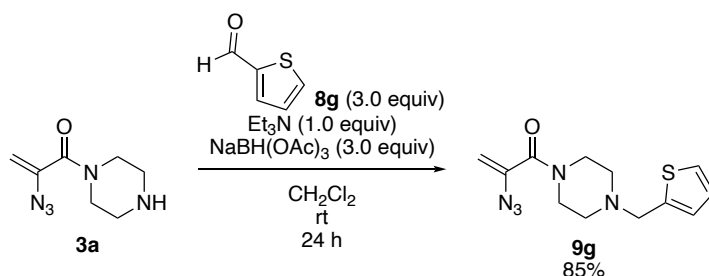
residue was purified by preparative TLC (CH₂Cl₂/MeOH = 15/1) to give 2-azido-1-(4-(pyridin-3-ylsulfonyl)piperazin-1-yl)prop-2-en-1-one (**9e**) (8.30 mg, 25.7 μmol, 51%) as a yellow solid.

Synthesis of 2-azido-1-(4-(4,6-dichloro-1,3,5-triazin-2-yl)piperazin-1-yl)prop-2-en-1-one (**9f**)



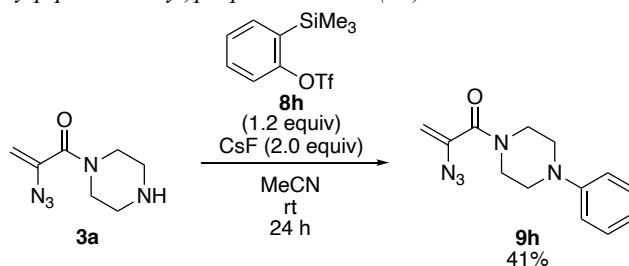
To a solution of 2,4,6-trichloro-1,3,5-triazine (**8f**) (9.2 mg, 50 μmol) in THF (5.0 mL) was slowly added 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (9.1 mg, 50 μmol) dissolved in THF (5.0 mL) at 0 °C. After stirring for 3 h at the same temperature, to the mixture was added water (10 mL). The mixture was extracted EtOAc (20 mL × 2). The combined organic extract was washed with brine (10 mL) and dried with Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (CH₂Cl₂/MeOH = 15/1) to give 2-azido-1-(4-(4,6-dichloro-1,3,5-triazin-2-yl)piperazin-1-yl)prop-2-en-1-one (**9f**) (7.3 mg, 22 μmol, 44%) as a pale yellow oil.

Synthesis of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**9g**)



To a solution of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (9.1 mg, 50 μmol) in CH₂Cl₂ (0.90 mL) were added thiophene-2-carbaldehyde (**8g**) (13.7 μL, 0.150 mmol) and triethylamine (6.9 mg, 50 μmol) at room temperature. After stirring for 10 min at the same temperature, to the mixture was added NaBH(OAc)₃ (31.8 mg, 0.150 mmol). 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 2-azido-1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)prop-2-en-1-one (**9g**) (11.8 mg, 42.5 μmol, 85%) as a pale yellow oil.

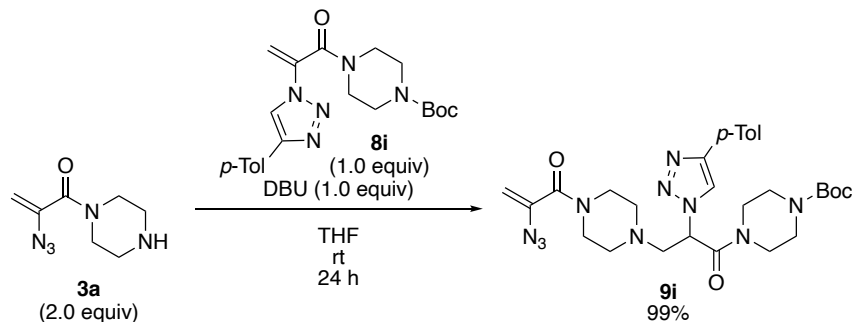
Synthesis of 2-azido-1-(4-phenylpiperazin-1-yl)prop-2-en-1-one (**9h**)



To a solution of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (9.1 mg, 50 μmol) dissolved in MeCN (0.80 mL) was added 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**8h**) (14.6 μL, 60.0 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 water (10 mL). The mixture was extracted with EtOAc (20 mL × 2). The combined organic extract was washed with brine (10 mL) and dried

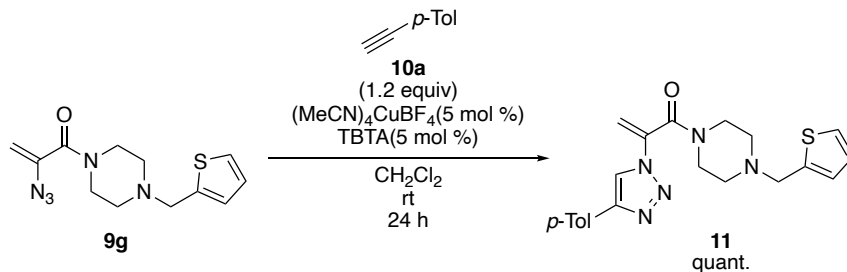
with Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (*n*-hexane/EtOAc = 1/1) to give 2-azido-1-(4-phenylpiperazin-1-yl)prop-2-en-1-one (**9h**) (5.3 mg, 21 μmol, 41%) as a pale yellow oil.

Synthesis of tert-butyl 4-(3-(4-(2-azidoacryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (9i)



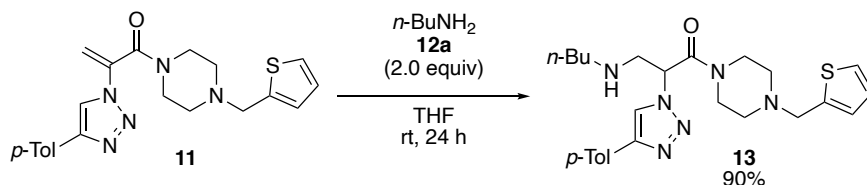
To a solution of *tert*-butyl 4-(2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazine-1-carboxylate (**8i**) (19.9 mg, 50 μmol) in THF (0.20 mL) were added 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (18.1 μL, 0.100 mmol) and DBU (7.5 μL, 50 μmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (CH₂Cl₂/MeOH = 15/1) to give 4-(3-(4-(2-azidoacryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**9i**) (28.8 mg, 49.8 μmol, 99%) as a colorless solid.

Synthesis of 1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)prop-2-en-1-one (11)



To a solution of 2-azido-1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)prop-2-en-1-one (**9g**) (27.7 mg, 0.100 mmol) in CH₂Cl₂ (3.0 mL) were added *p*-ethynyltoluene (**10a**) (15.2 μL, 0.120 mmol), (MeCN)₄CuBF₄ (1.60 mg, 7.5 μmol), and TBTA (2.70 mg, 7.5 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 (40 mL × 2). The combined organic extract was washed with brine (20 mL) and dried with Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (CH₂Cl₂/MeOH = 10/1) to give 1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)prop-2-en-1-one (**11**) (40.9 mg, 0.104 mmol, quant.) as a colorless oil.

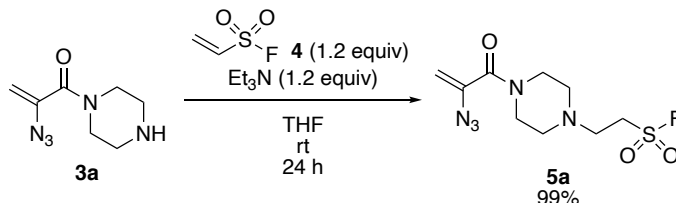
Synthesis of 3-(butylamino)-1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propan-1-one (13)



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-(thiophen-2-ylmethyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)prop-2-en-1-one (**11**) (19.7 mg, 50.0 μmol) in

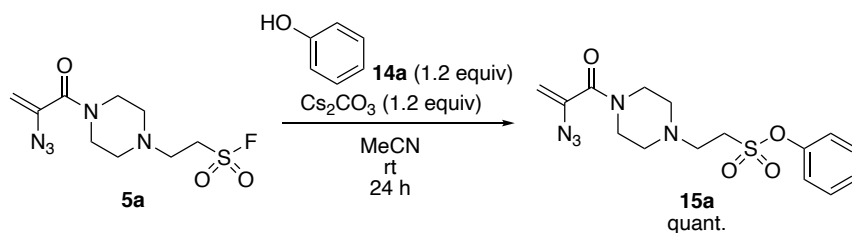
THF (0.20 mL) was added *n*-butylamine (**12a**) (9.9 μ L, 0.10 mmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$) to give 3-(butylamino)-1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propan-1-one (**13**) (21.0 mg, 45.0 μ mol, 90%) as a colorless oil.

Synthesis of 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (5a)



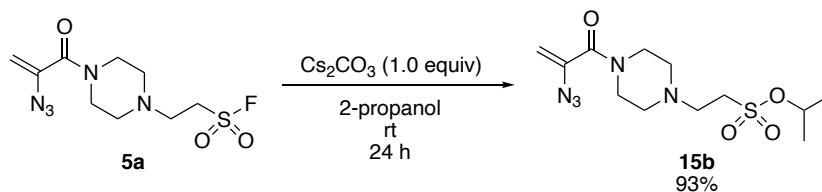
To a solution of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (9.1 mg, 50 μ mol) in THF (0.25 mL) were added ethenesulfonyl fluoride (**4**) (5.0 μ L, 60 μ mol) and triethylamine (8.3 μ L, 60 μ mol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$) to give 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**5a**) (14.4 mg, 49.4 μ mol, 99%) as a colorless solid.

Synthesis of phenyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (15a)



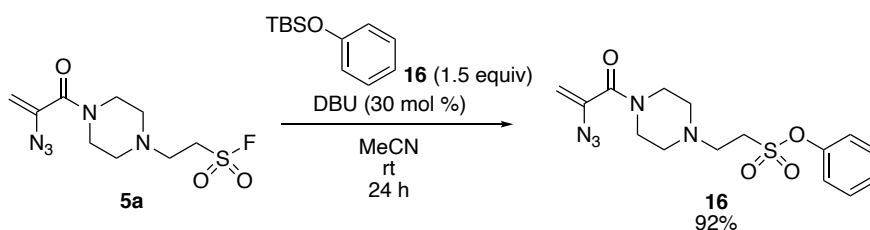
To a solution of 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**5a**) (14.6 mg, 50.0 μ mol) in MeCN (0.50 mL) were added phenol (**14a**) (5.6 mg, 60 μ mol) and cesium carbonate (19.5 mg, 60 μ mol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$) to give phenyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (**15a**) (18.6 mg, 50.0 μ mol, quant.) as a pale yellow oil.

Synthesis of isopropyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (15b)



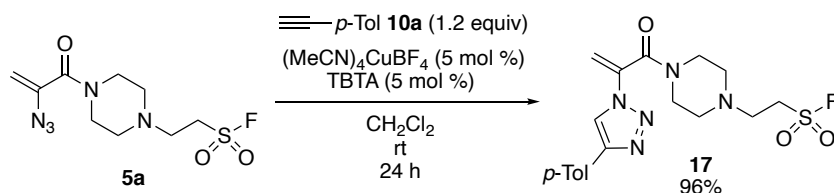
To a solution of 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**5a**) (14.6 mg, 50.0 μ mol) in 2-propanol (**14b**) (0.20 mL) was added cesium carbonate (16.3 mg, 50.0 μ mol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 20/1$) to give isopropyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (**15b**) (15.4 mg, 46.5 μ mol, 93%) as a pale yellow oil.

Synthesis of phenyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (**15a**) from *tert*-butyldimethylsilyl phenyl ether (**16**)



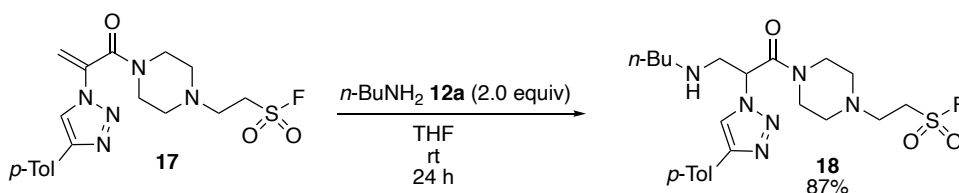
To a solution of 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**5a**) (14.6 mg, 50.0 μ mol) and *tert*-butyldimethylsilyl phenyl ether (**16**) (15.6 mg, 75.0 μ mol) in MeCN (0.25 mL) was added DBU (2.3 mg, 15 μ mol) at room temperature. After stirring for 24 h at the same temperature, to the mixture was added water (10 mL). The mixture was extracted with EtOAc (10 mL \times 3). The combined organic extract was washed with aq. sat. K₂CO₃ (10 mL) and brine (20 mL) and dried with Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (CH₂Cl₂/MeOH = 30/1) to give phenyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (**15a**) (16.8 mg, 46.0 μ mol, 92%) as a pale yellow oil.

Synthesis of 2-(4-(2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**17**)



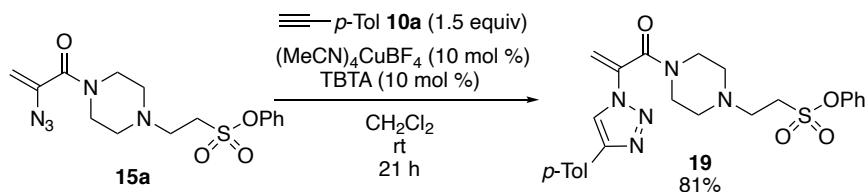
To a solution of 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**5a**) (21.8 mg, 75.0 μ mol) in CH₂Cl₂ (6.0 mL) were added *p*-ethynyltoluene (**10a**) (11.4 μ L, 90 μ mol), (MeCN)₄CuBF₄ (1.2 mg, 3.8 μ mol), and TBTA (2.0 mg, 3.8 μ mol) at room temperature. After stirring for 24 h at the same temperature, to the mixture was added water (10 mL). The mixture was extracted with EtOAc (20 mL \times 2). The combined organic extract was washed with H₂O (10 mL) and dried with Na₂SO₄. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (CH₂Cl₂/MeOH = 15/1) to give 2-(4-(2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**17**) (29.4 mg, 72.2 μ mol, 96%) as a colorless solid.

Synthesis of 2-(4-(3-(butylamino)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**18**)



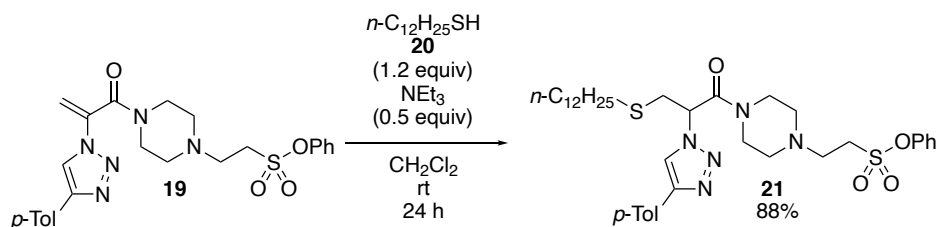
In a 0.3 mL screw-top V-vial[®] with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of 2-(4-(2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**17**) (12.2 mg, 30.0 μ mol) in THF (0.25 mL) was added *n*-butylamine (**12a**) (6.0 μ L, 60 μ mol) 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 (CH₂Cl₂/MeOH = 15/1) to give 2-(4-(3-(butylamino)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**18**) (12.5 mg, 26.0 μ mol, 87%) as a colorless oil.

Synthesis of phenyl 2-(4-(2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonate (**19**)



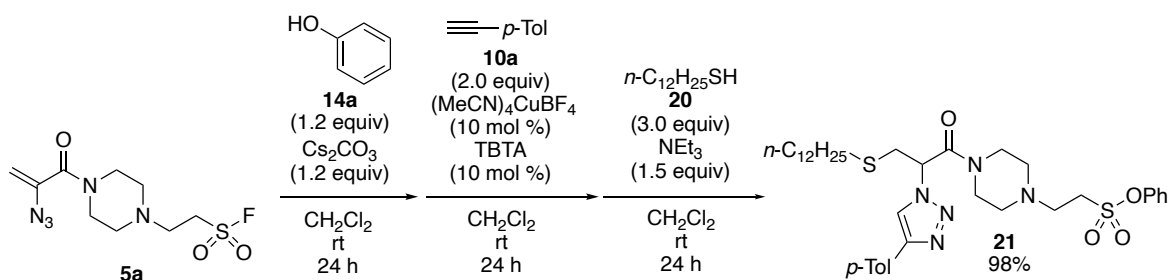
To a solution of phenyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (**15a**) (36.5 mg, 0.100 mmol) in CH_2Cl_2 (6.0 mL) were added *p*-ethynyltoluene (**10a**) (17.0 μL , 0.150 mmol), $(\text{MeCN})_4\text{CuBF}_4$ (3.1 mg, 10 μmol), and TBTA (5.3 mg, 10 μmol) at room temperature. After stirring for 21 h at the same temperature, to the mixture was added water (10 mL). The mixture was extracted with EtOAc (20 mL \times 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$) to give phenyl 2-(4-(2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonate (**19**) (39.2 mg, 81.3 μmol , 81%) as a colorless oil.

Synthesis of phenyl 2-(4-(3-(dodecylthio)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**21**)



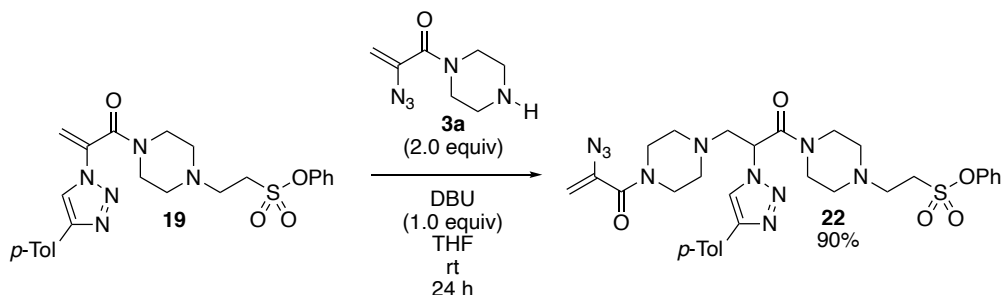
In a 0.3 mL screw-top V-vial[®] with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of phenyl 2-(4-(2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonate (**19**) (24.1 mg, 50.0 μmol) in CH_2Cl_2 (0.20 mL) were added triethylamine (3.5 μL , 25 μmol) and dodecanethiol (**20**) (14.3 μL , 60.0 μmol) at 0 °C. After stirring for 24 h at room temperature, the mixture was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 20/1$) to give phenyl 2-(4-(3-(dodecylthio)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**21**) (29.9 mg, 43.8 μmol , 88%) as a colorless oil.

One-pot synthesis of phenyl 2-(4-(3-(dodecylthio)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**21**)



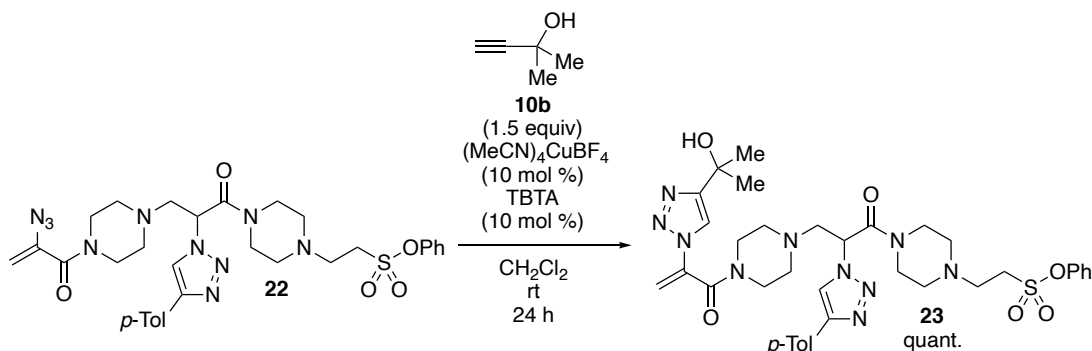
In a 0.3 mL screw-top V-vial[®] with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**5a**) (8.7 mg, 30 μmol) in CH_2Cl_2 (0.30 mL) were added phenol (**14a**) (3.4 mg, 36 μmol) and cesium carbonate (11.7 mg, 36 μmol) at room temperature. After stirring for 24 h at the same temperature, to the mixture were added *p*-ethynyltoluene (**10a**) (7.6 μL , 60 μmol), $(\text{MeCN})_4\text{CuBF}_4$ (0.93 mg, 3.0 μmol), and TBTA (1.6 mg, 3.0 μmol) at room temperature. After stirring for 24 h at the same temperature, to the mixture triethylamine (6.2 μL , 45 μmol) and dodecanethiol (**20**) (21.4 μL , 90.0 μmol) at 0 °C. After stirring for 24 h at room temperature, the mixture was concentrated under reduced pressure. The resulting residue was purified by preparative TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 25/1$) to give phenyl 2-(4-(3-(dodecylthio)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**21**) (20.1 mg, 29.4 μmol , 98%) as a colorless oil.

Synthesis of phenyl 2-(4-(3-(4-(2-azidoacryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**22**)



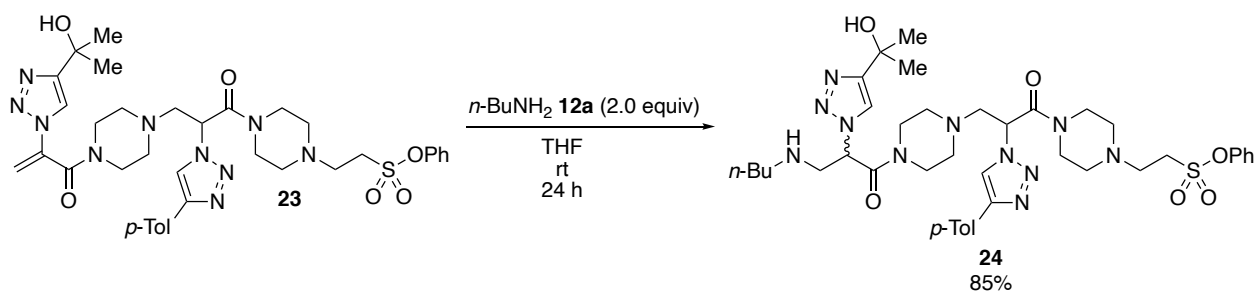
To a solution of phenyl 2-(4-(2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonate (**19**) (96.3 mg, 0.200 mmol) in THF (1.0 mL) were added 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (72.5 mg, 0.400 mmol) and DBU (29.9 μ L, 0.200 mmol) at room temperature. After stirring for 24 h at the same temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$) to give phenyl 2-(4-(3-(4-(2-azidoacryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**22**) (119 mg, 0.179 mmol, 90%) as a colorless oil.

Synthesis of phenyl 2-(4-(3-(4-(2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**23**)



To a solution of phenyl 2-(4-(3-(4-(2-azidoacryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**22**) (112 mg, 0.150 mmol) in CH_2Cl_2 (6.0 mL) were added 2-methylbut-3-yn-2-ol (**10b**) (22.0 μ L, 0.225 mmol), $(\text{MeCN})_4\text{CuBF}_4$ (4.7 mg, 15 μ mol), and TBTA (8.0 mg, 15 μ mol) at room temperature. After stirring for 24 h at the same temperature, to the mixture was add water (10 mL). The mixture was extracted with EtOAc (20 mL \times 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$) to give phenyl 2-(4-(3-(4-(2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**23**) (112 mg, 0.150 mmol, quant.) as a colorless oil.

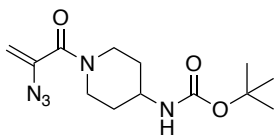
Synthesis of phenyl 2-(4-(3-(4-(2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**24**)



In a 0.3 mL screw-top V-vial[®] with a solid-top cap (Sigma-Aldrich, Cat. No. Z115118), to a solution of phenyl 2-(4-(3-(4-(2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**23**) (11.2 mg, 15.0 μmol) in THF (75 μL) was added *n*-butylamine (**12a**) (3.0 μL , 30 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 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$) to give phenyl 2-(4-(3-(4-(2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**24**) (10.4 mg, 12.7 μmol , 85%) as a colorless solid.

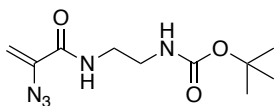
Characterization Data of New Compounds

tert-Butyl (1-(2-azidoacryloyl)piperidin-4-yl)carbamate (**6b**)



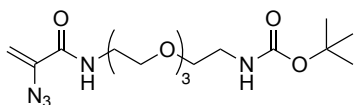
Colorless solid; Mp 105–107 °C; TLC R_f 0.38 (*n*-hexane/EtOAc = 1/1); ^1H NMR (CDCl_3 , 500 MHz) δ 1.30–1.40 (m, 2H), 1.44 (s, 9H), 1.96–2.07 (m, 2H), 2.78–2.98 (br, 1H), 3.09–3.27 (br, 1H), 3.62–3.76 (br, 1H), 3.90–4.10 (br, 1H), 4.33–4.49 (br, 1H), 4.59–4.68 (br, 1H), 5.02 (s, 1H), 5.06 (s, 1H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 28.3 (3C), 31.9 (br, 1C), 33.0 (br, 1C), 41.0 (br, 1C), 46.0 (br, 1C), 47.7 (1C), 79.7 (1C), 103.4 (1C), 139.7 (1C), 155.0 (1C), 163.3 (1C); IR (KBr, cm^{-1}) 772, 1171, 1449, 1522, 1636, 1701, 2106, 2926; HRMS (ESI $^+$) m/z 318.1534 ([M + Na] $^+$ $\text{C}_{13}\text{H}_{21}\text{N}_5\text{NaO}_3^+$ requires 318.1537).

tert-Butyl (2-(2-azidoacrylamido)ethyl)carbamate (**6c**)



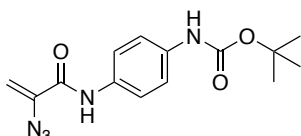
Colorless solid; Mp 77–78 °C; TLC R_f 0.27 (*n*-hexane/EtOAc = 1/1); ^1H NMR (CDCl_3 , 500 MHz) δ 1.45 (s, 9H), 3.24–3.35 (m, 2H), 3.35–3.44 (m, 2H), 4.84–4.97 (br, 1H), 5.18 (d, 1H, J = 1.6 Hz), 6.10–6.12 (br, 1H), 6.90–7.03 (br, 1H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 28.3 (3C), 39.8 (1C), 40.9 (1C), 79.8 (1C), 106.4 (1C), 138.6 (1C), 156.8 (1C), 161.3 (1C); IR (KBr, cm^{-1}) 833, 1171, 1250, 1520, 1694, 2116, 2978, 3329; HRMS (ESI $^+$) m/z 278.1223 ([M + Na] $^+$ $\text{C}_{10}\text{H}_{17}\text{N}_5\text{NaO}_3^+$ requires 278.1224).

tert-Butyl (14-azido-13-oxo-3,6,9-trioxa-12-azapentadec-14-en-1-yl)carbamate (**6d**)



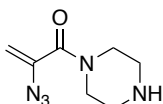
Pale yellow oil; TLC R_f 0.48 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ = 10/1); ^1H NMR (CDCl_3 , 400 MHz) δ 1.46 (s, 9H), 3.30–3.37 (br, 2H), 3.50–3.58 (m, 4H), 3.59–3.71 (m, 10H), 4.98–5.12 (br, 1H), 5.20 (d, 1H, J = 2.0 Hz), 6.09–6.22 (br, 1H), 6.72–6.93 (br, 1H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 28.4 (3C), 39.4 (1C), 40.3 (1C), 69.5 (1C), 70.20 (1C), 70.25 (1C), 70.28 (1C), 70.46 (1C), 70.50 (1C), 79.2 (1C), 106.5 (1C), 138.6 (1C), 156.0 (1C), 160.7 (1C); IR (neat, cm^{-1}) 1122, 1250, 1366, 1529, 1612, 1710, 2118, 2872; HRMS (ESI $^+$) m/z 410.2017 ([M + Na] $^+$ $\text{C}_{16}\text{H}_{29}\text{N}_5\text{NaO}_6^+$ requires 410.2016).

tert-Butyl (4-(2-azidoacrylamido)phenyl)carbamate (**6e**)



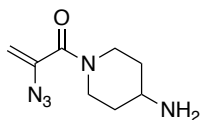
Colorless solid; Mp 144–146 °C; TLC R_f 0.63 (*n*-hexane/EtOAc = 1/1); ^1H NMR (CDCl_3 , 500 MHz) δ 1.51 (s, 9H), 5.27 (d, 1H, J = 2.2 Hz), 6.29 (d, 1H, J = 2.2 Hz), 6.46–6.55 (br, 1H), 7.34 (d, 2H, J = 8.8 Hz), 7.51 (d, 2H, J = 8.8 Hz), 8.01–8.10 (br, 1H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 28.3 (3C), 80.6 (1C), 107.2 (2C), 119.0 (1C), 120.8 (2C), 132.1 (1C), 135.3 (1C), 138.5 (1C), 152.7 (1C), 158.1 (1C); IR (KBr, cm^{-1}) 772, 1161, 1246, 1497, 1541, 1697, 2126, 3362; HRMS (ESI $^+$) m/z 326.1223 ([M + Na] $^+$ $\text{C}_{14}\text{H}_{17}\text{N}_5\text{NaO}_3^+$ requires 326.1224).

2-Azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**)



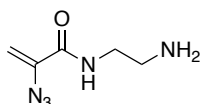
Pale yellow oil; TLC R_f 0.22 (tailing) ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ = 10/1); ^1H NMR (CDCl_3 , 500 MHz) δ 1.57–1.66 (br, 1H), 2.85–2.92 (m, 4H), 3.55–3.67 (br, 4H), 4.94 (d, 1H, J = 2.1 Hz), 5.00 (d, 1H, J = 2.1 Hz); ^{13}C NMR (CDCl_3 , 126 MHz) δ 43.2 (br, 1C), 45.7 (br, 1C), 46.5 (br, 1C), 48.5 (1C), 103.5 (1C), 139.7 (1C), 163.3 (1C); IR (KBr, cm^{-1}) 880, 1032, 1234, 1319, 1437, 1636, 2108, 2916; HRMS (ESI $^+$) m/z 182.1041 ([M + H] $^+$ $\text{C}_7\text{H}_{12}\text{N}_5\text{O}^+$ requires 182.1036).

1-(4-Aminopiperidin-1-yl)-2-azidoprop-2-en-1-one (**3b**)



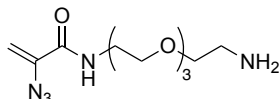
Pale yellow oil; TLC R_f 0.13 (tailing) ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 5/1$); ^1H NMR (CDCl_3 , 500 MHz) δ 1.17–1.28 (m, 2H), 1.36–1.52 (br, 2H), 1.78–1.86 (br, 2H), 2.76–2.92 (br, 1H), 2.92–3.00 (m, 1H), 3.05–3.21 (br, 1H), 3.93–4.09 (br, 1H), 4.30–4.49 (br, 1H), 4.93 (d, 1H, $J = 2.1$ Hz), 4.98 (d, 1H, $J = 2.1$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) δ 35.2 (br, 1C), 35.9 (br, 1C), 40.8 (br, 1C), 45.9 (br, 1C), 48.4 (1C), 103.1 (1C), 139.9 (1C), 163.3 (1C); IR (KBr, cm^{-1}) 772, 1018, 1092, 1261, 1449, 1636, 2104, 2924; HRMS (ESI⁺) m/z 196.1196 ($[\text{M} + \text{H}]^+$ $\text{C}_8\text{H}_{14}\text{N}_5\text{O}^+$ requires 196.1193).

N-(2-Aminoethyl)-2-azidoacrylamide (**3c**)



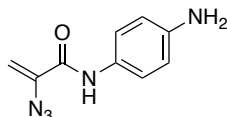
Pale yellow oil; TLC R_f 0.10 (tailing) ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 5/1$); ^1H NMR (CDCl_3 , 500 MHz) δ 1.19–1.30 (br, 2H), 2.85–2.90 (m, 2H), 3.33–3.40 (m, 2H), 5.18 (d, 1H, $J = 2.1$ Hz), 6.16 (d, 1H, $J = 2.1$ Hz), 6.73–6.84 (br, 1H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 41.1 (1C), 42.1 (1C), 106.4 (1C), 138.6 (1C), 160.8 (1C); IR (KBr, cm^{-1}) 772, 1250, 1317, 1527, 1608, 1663, 2928, 3924; HRMS (ESI⁺) m/z 156.0883 ($[\text{M} + \text{H}]^+$ $\text{C}_5\text{H}_{10}\text{N}_5\text{O}^+$ requires 156.0880).

N-(2-(2-(2-(2-Aminoethoxy)ethoxy)ethyl)-2-azidoacrylamide (**3d**)



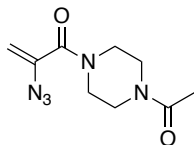
Colorless oil; TLC R_f 0.26 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); ^1H NMR (CDCl_3 , 400 MHz) δ 2.80–2.90 (br, 2H), 3.46–3.51 (m, 4H), 3.54–3.57 (m, 2H), 3.58–3.66 (m, 10H), 5.14 (d, 1H, $J = 2.0$ Hz), 6.07 (d, 1H, $J = 2.0$ Hz), 7.01–7.12 (br, 1H); ^{13}C NMR (CDCl_3 , 101 MHz) δ 39.1 (1C), 41.5 (1C), 69.5 (1C), 70.1 (1C), 70.2 (1C), 70.36 (1C), 70.40 (1C), 73.0 (1C), 106.3 (1C), 138.6 (1C), 160.8 (1C); IR (neat, cm^{-1}) 1124, 1531, 1612, 1673, 2116, 2872; HRMS (ESI⁺) m/z 310.1492 ($[\text{M} + \text{Na}]^+$ $\text{C}_{11}\text{H}_{21}\text{N}_5\text{NaO}_4^+$ requires 310.1491).

N-(4-Aminophenyl)-2-azidoacrylamide (**3e**)



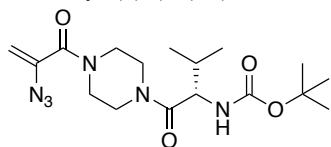
Yellow solid; Mp 75–77 °C; TLC R_f 0.73 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 5/1$); ^1H NMR (CDCl_3 , 500 MHz) δ 3.55–3.72 (br, 2H), 5.25 (d, 1H, $J = 2.2$ Hz), 6.26 (d, 1H, $J = 2.2$ Hz), 6.66 (d, 2H, $J = 8.8$ Hz), 7.35 (d, 2H, $J = 8.8$ Hz), 7.88–7.80 (br, 1H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 106.9 (1C), 115.4 (2C), 121.8 (2C), 128.3 (1C), 138.6 (1C), 143.8 (1C), 158.0 (1C); IR (KBr, cm^{-1}) 772, 829, 1288, 1516, 1608, 1647, 2126, 3335; HRMS (ESI⁺) m/z 226.0699 ($[\text{M} + \text{Na}]^+$ $\text{C}_9\text{H}_9\text{N}_5\text{NaO}^+$ requires 226.0699).

1-(4-Acetylpiperazin-1-yl)-2-azidoprop-2-en-1-one (**9a**)



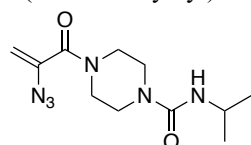
Colorless oil; TLC R_f 0.68 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 1/1$); ^1H NMR (CDCl_3 , 500 MHz) δ 2.14 (s, 3H), 3.48–3.54 (m, 2H), 3.58–3.70 (m, 6H), 5.13 (d, 2H, $J = 1.1$ Hz); ^{13}C NMR (CDCl_3 , 126 MHz) δ 21.4 (1C), 41.2 (br, 1C), 42.2 (br, 1C), 45.9 (br, 1C), 47.0 (br, 1C), 104.4 (1C), 139.5 (1C), 163.6 (1C), 169.1 (1C); IR (KBr, cm^{-1}) 876, 997, 1172, 1242, 1435, 1645, 2106, 2922; HRMS (ESI⁺) m/z 246.0966 ($[\text{M} + \text{Na}]^+$ $\text{C}_9\text{H}_{13}\text{N}_5\text{NaO}_2^+$ requires 246.0961).

tert-Butyl (*S*)-1-(4-(2-azidoacryloyl)piperazin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate (**9b**)



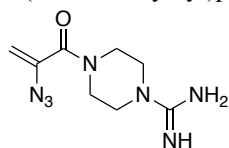
Colorless oil; TLC R_f 0.62 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 1/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 0.91 (d, 3H, $J = 6.8$ Hz), 0.96 (d, 3H, $J = 6.8$ Hz), 1.43 (s, 9H), 1.87–1.99 (m, 1H), 3.44–3.90 (m, 8H), 4.38–4.47 (m, 1H), 5.14 (s, 1H+1H, two signals overlapped), 5.21–5.29 (m, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 17.3 (1C), 19.6 (1C), 28.3 (3C), 31.4 (1C), 42.0 (br, 2C), 45.5 (br, 1C), 47.0 (br, 1C), 54.8 (1C), 79.8 (1C), 104.5 (1C), 139.5 (1C), 155.8 (1C), 163.5 (1C), 171.1 (1C); IR (KBr, cm^{-1}) 772, 1171, 1219, 1437, 1641, 1701, 2106, 2972; HRMS (ESI^+) m/z 403.2061 ($[\text{M} + \text{Na}]^+$ $\text{C}_{17}\text{H}_{28}\text{N}_6\text{NaO}_4^+$ requires 403.2064).

4-(2-Azidoacryloyl)-*N*-isopropylpiperazine-1-carboxamide (**9c**)



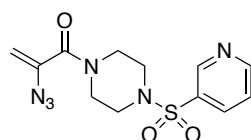
Yellow oil; TLC R_f 0.55 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.16 (d, 6H, $J = 6.5$ Hz), 3.35–3.45 (br, 4H), 3.59–3.69 (br, 4H), 3.92–4.02 (sept, 1H, $J = 6.5$ Hz), 4.20–4.30 (m, 1H), 5.10 (d, 1H, $J = 2.2$ Hz), 5.12 (d, 1H, $J = 2.2$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 23.4 (2C), 41.8 (br, 1C), 42.8 (1C), 43.6 (br, 1C+1C, two signals overlapped), 46.8 (br, 1C), 104.2 (1C), 139.5 (1C), 156.7 (1C), 163.5 (1C); IR (KBr, cm^{-1}) 772, 1001, 1242, 1533, 1628, 2106, 2972, 3348; HRMS (ESI^+) m/z 289.1384 ($[\text{M} + \text{Na}]^+$ $\text{C}_{11}\text{H}_{18}\text{N}_6\text{NaO}_2^+$ requires 289.1383).

4-(2-Azidoacryloyl)piperazine-1-carboximidamide (**9d**)



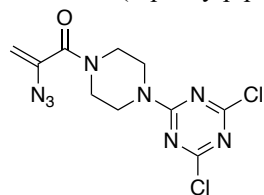
Yellow solid; TLC R_f 0.23 (tailing) ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 3/1$); $^1\text{H NMR}$ (MeOD, 400 MHz) δ 3.56–3.64 (m, 4H), 3.65–3.89 (m, 7H), 5.20 (d, 1H, $J = 2.3$ Hz), 5.25 (d, 1H, $J = 2.3$ Hz); $^{13}\text{C NMR}$ (MeOD, 101 MHz) δ 40.0 (br, 2C), 44.8 (br, 2C), 104.2 (1C), 138.9 (1C), 157.0 (1C), 164.1 (1C); IR (KBr, cm^{-1}) 773, 980, 1244, 1445, 1605, 2108, 2506, 3283; HRMS (ESI^+) m/z 224.1262 ($[\text{M} + \text{H}]^+$ $\text{C}_8\text{H}_{14}\text{N}_7\text{O}^+$ requires 224.1254).

2-Azido-1-(4-(pyridin-3-ylsulfonyl)piperazin-1-yl)prop-2-en-1-one (**9e**)



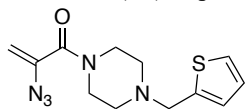
Yellow solid; Mp 85–87 °C; TLC R_f 0.58 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 3.02–3.19 (m, 4H), 3.66–3.81 (br, 4H), 5.11 (d, 2H, $J = 3.5$ Hz), 7.48–7.59 (m, 1H), 7.99–8.10 (m, 1H), 8.82–8.90 (1H), 8.90–9.02 (m, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 45.8 (br, 4C), 104.8 (1C), 123.9 (1C), 132.3 (1C), 135.3 (1C), 139.3 (1C), 148.4 (1C), 153.9 (1C), 163.4 (1C); IR (KBr, cm^{-1}) 583, 754, 945, 1175, 1352, 1647, 2106, 2922; HRMS (ESI^+) m/z 345.0731 ($[\text{M} + \text{Na}]^+$ $\text{C}_{12}\text{H}_{14}\text{N}_6\text{NaO}_3\text{S}^+$ requires 345.0740).

2-Azido-1-(4-phenylpiperazin-1-yl)prop-2-en-1-one (**9f**)



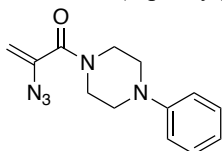
Pale yellow oil; TLC R_f 0.37 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 3.66–3.76 (br, 4H), 3.89–3.98 (m, 4H), 5.18 (d, 1H, $J = 2.2$ Hz), 5.20 (d, 1H, $J = 2.3$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 41.7 (br, 1C), 43.9 (br, 1C+1C, two signals overlapped), 46.4 (br, 1C), 104.8 (2C), 139.4 (1C), 163.6 (1C), 164.3 (1C), 170.7 (1C); HRMS (ESI^+) m/z 351.0241 ($[\text{M} + \text{Na}]^+$ $\text{C}_{10}\text{H}_{10}\text{Cl}_2\text{N}_8\text{NaO}^+$ requires 351.0247).

2-Azido-1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)prop-2-en-1-one (**9g**)



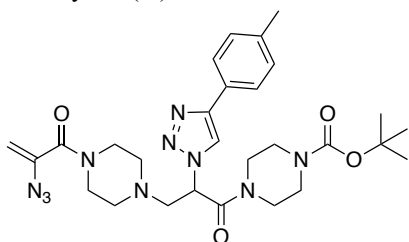
Colorless oil; TLC R_f 0.62 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 2.45–2.56 (br, 4H), 3.58–3.70 (br, 4H), 3.75 (s, 2H), 5.00 (d, 1H, $J = 2.1$ Hz), 5.06 (d, 1H, $J = 2.1$ Hz), 6.90–6.94 (m, 1H), 6.94–6.98 (m, 1H), 7.21–7.29 (m, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 42.0 (br, 1C), 47.2 (br, 1C), 52.3 (br, 1C), 52.9 (br, 1C), 56.9 (1C), 103.6 (1C), 125.4 (1C), 126.3 (1C), 126.5 (1C), 139.6 (1C), 140.7 (1C), 163.2 (1C); IR (KBr, cm^{-1}) 704, 999, 1238, 1437, 1645, 2104, 2808; HRMS (ESI^+) m/z 278.1070 ($[\text{M} + \text{H}]^+$ $\text{C}_{12}\text{H}_{16}\text{N}_5\text{OS}^+$ requires 278.1070).

2-Azido-1-(4-phenylpiperazin-1-yl)prop-2-en-1-one (**9h**)



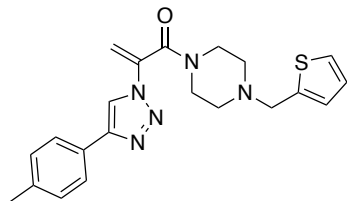
Pale yellow oil; TLC R_f 0.73 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 1/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 3.16–3.23 (m, 4H), 3.75–3.84 (br, 4H), 5.09 (d, 1H, $J = 2.1$ Hz), 5.12 (d, 1H, $J = 2.1$ Hz), 6.90–6.97 (m, 3H), 7.28–7.33 (m, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 42.0 (br, 1C), 47.1 (br, 1C), 49.4 (br, 1C), 49.9 (br, 1C), 104.0 (1C), 116.8 (2C), 120.8 (1C), 129.3 (2C), 139.6 (1C), 150.8 (1C), 163.3 (1C); IR (KBr, cm^{-1}) 760, 1024, 1233, 1441, 1497, 1645, 2104, 2820; HRMS (ESI^+) m/z 280.1169 ($[\text{M} + \text{Na}]^+$ $\text{C}_{13}\text{H}_{15}\text{N}_5\text{NaO}^+$ requires 280.1169).

tert-Butyl 4-(3-(4-(2-azidoacryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**9i**)



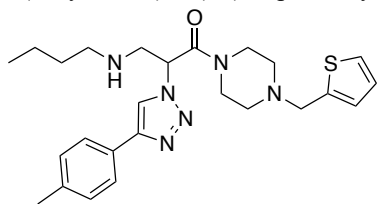
Colorless solid; TLC R_f 0.58 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.45 (s, 9H), 2.38 (s, 3H), 2.47–2.54 (br, 2H), 2.56–2.68 (br, 2H), 2.99–3.11 (m, 2H), 3.19–3.29 (m, 2H), 3.44–3.61 (m, 8H), 3.66–3.73 (m, 1H), 3.73–3.82 (m, 1H), 5.00 (d, 1H, $J = 2.1$ Hz), 5.06 (d, 1H, $J = 2.1$ Hz), 5.86 (dd, 1H, $J = 7.2, 7.2$ Hz), 7.22–7.28 (m, 2H), 7.72 (d, 2H, $J = 8.1$ Hz), 8.08 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 21.3 (1C), 28.3 (3C), 41.9 (br, 1C), 42.5 (2C), 45.8 (2C), 47.1 (br, 1C), 52.9 (br, 1C), 53.4 (br, 1C), 57.1 (1C), 59.5 (1C), 80.6 (1C), 103.9 (1C), 117.8 (1C), 125.6 (2C), 127.3 (1C), 129.6 (2C), 138.4 (1C), 139.5 (1C), 148.4 (1C), 154.3 (1C), 163.2 (1C), 165.5 (br, 1C); IR (KBr, cm^{-1}) 754, 1001, 1169, 1234, 1420, 1458, 1647, 2104; HRMS (ESI^+) m/z 579.3150 ($[\text{M} + \text{H}]^+$ $\text{C}_{28}\text{H}_{39}\text{N}_{10}\text{O}_4^+$ requires 579.3150).

1-(4-(Thiophen-2-ylmethyl)piperazin-1-yl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)prop-2-en-1-one (**11**)



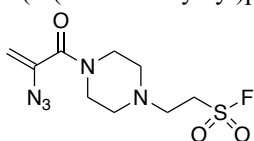
Colorless oil; TLC R_f 0.53 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 2.39 (s, 3H), 2.40–2.48 (br, 2H), 2.52–2.60 (br, 2H), 3.48–3.57 (br, 2H), 3.73 (s, 2H), 3.75–3.83 (br, 2H), 5.38 (d, 1H, $J = 1.0$ Hz), 6.03 (d, 1H, $J = 1.0$ Hz), 6.85–6.90 (m, 1H), 6.90–6.95 (m, 1H), 7.19–7.29 (m, 3H), 7.73 (d, 2H, $J = 7.9$ Hz), 8.01 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 21.3 (1C), 42.2 (br, 1C), 47.3 (br, 1C), 52.1 (br, 1C), 52.7 (br, 1C), 56.8 (1C), 108.3 (1C), 117.7 (1C), 125.4 (1C), 125.8 (2C), 126.3 (1C), 126.5 (1C), 127.0 (1C), 129.6 (2C), 136.7 (1C), 138.5 (1C), 140.7 (1C), 148.2 (1C), 162.6 (1C); IR (KBr, cm^{-1}) 731, 825, 1016, 1238, 1437, 1651, 2918, 3107; HRMS (ESI^+) m/z 394.1696 ($[\text{M} + \text{H}]^+$ $\text{C}_{21}\text{H}_{24}\text{N}_5\text{OS}^+$ requires 394.1696).

3-(Butylamino)-1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propan-1-one (**13**)



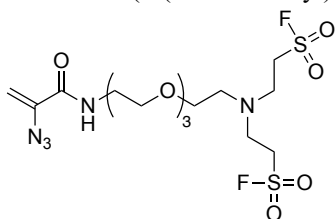
Colorless oil; TLC R_f 0.40 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 0.88 (t, 3H, $J = 7.3$ Hz), 1.24–1.33 (m, 2H), 1.39–1.46 (m, 2H), 1.46–1.58 (br, 1H), 2.10–2.18 (m, 1H), 2.29–2.34 (m, 1H), 2.38 (s, 3H), 2.49–2.57 (m, 2H), 2.57–2.63 (m, 1H), 2.63–2.70 (m, 1H), 3.13–3.20 (m, 1H), 3.35–3.41 (m, 1H), 3.50–3.58 (m, 1H), 3.57–3.62 (m, 1H), 3.62–3.70 (m, 3H), 3.75–3.81 (m, 1H), 5.86 (dd, 1H, $J = 6.9, 6.9$ Hz), 6.83–6.88 (m, 1H), 6.88–6.91 (m, 1H), 7.19–7.21 (m, 1H), 7.21–7.27 (m, 2H), 7.72 (d, 2H, $J = 8.2$ Hz), 8.00 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 13.9 (1C), 20.2 (1C), 21.3 (1C), 32.1 (1C), 42.5 (1C), 45.9 (1C), 49.3 (1C), 51.8 (1C), 52.1 (1C), 52.6 (1C), 56.7 (1C), 59.2 (1C), 118.2 (1C), 125.3 (1C), 125.6 (2C), 126.3 (1C), 126.5 (1C), 127.5 (1C), 129.5 (2C), 138.1 (1C), 140.6 (1C), 148.2 (1C), 165.4 (1C); IR (KBr, cm^{-1}) 731, 997, 1142, 1234, 1454, 1651, 2860, 2924; HRMS (ESI^+) m/z 467.2583 ($[\text{M} + \text{H}]^+$ $\text{C}_{25}\text{H}_{35}\text{N}_6\text{OS}^+$ requires 467.2588).

2-(4-(2-Azidoacryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**5a**)



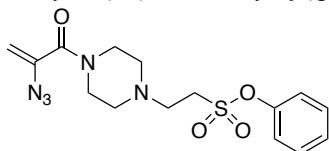
Colorless solid; Mp 82–84 °C; TLC R_f 0.70 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 2.51–2.60 (m, 4H), 2.51–3.04 (m, 2H), 3.58–3.63 (m, 2H), 3.63–3.71 (br, 4H), 5.04 (d, 1H, $J = 2.1$ Hz), 5.09 (d, 1H, $J = 2.1$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 41.8 (br, 1C), 47.0 (br, 1C), 48.9 (d, 1C, $J = 14.5$ Hz), 51.1 (1C), 52.1 (br, 1C), 52.8 (br, 1C), 103.9 (1C), 139.4 (1C), 163.2 (1C); $^{19}\text{F NMR}$ (CDCl_3 , 377 MHz) δ 58.8 (s); IR (KBr, cm^{-1}) 775, 1003, 1200, 1639, 1404, 1643, 2108, 2928; HRMS (ESI^+) m/z 314.0698 ($[\text{M} + \text{Na}]^+$ $\text{C}_9\text{H}_{14}\text{FN}_5\text{NaO}_3\text{S}^+$ requires 314.0694).

17-Azido-3-(2-(fluorosulfonyl)ethyl)-16-oxo-6,9,12-trioxa-3,15-diazaoctadec-17-ene-1-sulfonyl fluoride (**5b**)



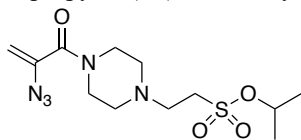
Pale yellow solid; TLC R_f 0.42 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$); $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 2.87 (t, 2H, $J = 4.9$ Hz), 3.22–3.29 (m, 4H), 3.50–3.56 (m, 2H), 3.57–3.70 (m, 16H), 5.20 (d, 1H, $J = 2.0$ Hz), 6.16 (d, 1H, $J = 2.0$ Hz), 6.75–6.85 (br, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 101 MHz) δ 39.4 (1C), 49.2 (2C), 49.5 (d, 2C, $J = 13.1$ Hz), 53.6 (1C), 69.4 (1C), 69.9 (1C), 70.2 (1C), 70.42 (1C), 70.44 (1C), 70.5 (1C), 106.5 (1C), 138.6 (1C), 160.7 (1C); $^{19}\text{F NMR}$ (CDCl_3 , 376 MHz) δ 58.1 (s); IR (neat, cm^{-1}) 1115, 1196, 1408, 1531, 1678, 2121, 2872; HRMS (ESI^+) m/z 530.1146 ($[\text{M} + \text{Na}]^+$ $\text{C}_{15}\text{H}_{27}\text{F}_2\text{N}_5\text{NaO}_8\text{S}_2^+$ requires 530.1167).

Phenyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (**15a**)



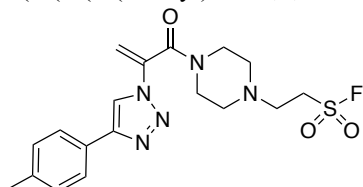
Pale yellow oil; TLC R_f 0.63 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 1/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 2.48–2.57 (m, 4H), 3.02 (t, 2H, $J = 7.3$ Hz), 3.45 (t, 2H, $J = 7.3$ Hz), 3.58–3.69 (br, 4H), 5.04 (d, 1H, $J = 2.0$ Hz), 5.09 (d, 1H, $J = 2.0$ Hz), 7.27–7.30 (m, 2H), 7.31–7.37 (m, 1H), 7.40–7.48 (m, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 41.7 (br, 1C), 47.0 (br, 1C), 48.0 (br, 1C), 51.5 (1C), 52.3 (br, 1C), 53.1 (br, 1C), 104.0 (1C), 122.0 (2C), 127.4 (1C), 130.0 (2C), 139.5 (1C), 149.0 (1C), 163.3 (1C); IR (KBr, cm^{-1}) 775, 866, 1144, 1169, 1240, 1368, 1641, 2106; HRMS (ESI^+) m/z 388.1049 ($[\text{M} + \text{Na}]^+$ $\text{C}_{15}\text{H}_{19}\text{N}_5\text{NaO}_4\text{S}^+$ requires 388.1050).

Isopropyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (**15b**)



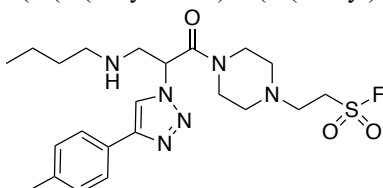
Pale yellow oil; TLC R_f 0.47 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 20/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.43 (d, 6H, $J = 6.3$ Hz), 2.48–2.55 (m, 4H), 2.91 (t, 2H, $J = 7.6$ Hz), 3.26 (t, 2H, $J = 7.6$ Hz), 3.55–3.71 (br, 4H), 4.98 (sext, 1H, $J = 6.3$ Hz), 5.04 (d, 1H, $J = 2.1$ Hz), 5.09 (d, 1H, $J = 2.1$ Hz); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 23.2 (2C+1C, two signals overlapped), 41.9 (br, 1C), 47.0 (br, 1C), 48.9 (1C), 51.7 (1C), 52.3 (br, 1C), 53.0 (br, 1C), 103.9 (1C), 139.5 (1C), 163.2 (1C); HRMS (ESI^+) m/z 354.1206 ($[\text{M} + \text{Na}]^+ \text{C}_{12}\text{H}_{21}\text{N}_5\text{NaO}_4\text{S}^+$ requires 354.1208)

2-(4-(2-(4-(4-Tolyl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**17**)



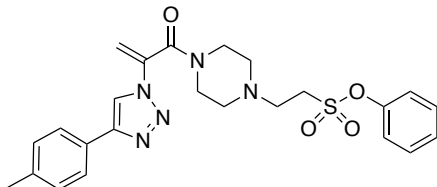
Colorless solid; TLC R_f 0.56 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 2.39 (s, 3H), 2.49–2.65 (m, 4H), 2.98 (t, 2H, $J = 6.9$ Hz), 3.51–3.60 (m, 4H), 3.75–3.84 (br, 2H), 5.39 (d, 1H, $J = 2.1$ Hz), 5.99 (d, 1H, $J = 2.1$ Hz), 7.25 (d, 2H, $J = 8.2$ Hz), 7.74 (d, 2H, $J = 8.2$ Hz), 8.03 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 21.3 (1C), 41.9 (br, 1C), 47.0 (br, 1C), 48.9 (d, 1C, $J = 14.4$ Hz), 51.0 (1C), 52.0 (br, 1C), 52.6 (br, 1C), 108.3 (1C), 117.5 (1C), 125.8 (2C), 126.8 (1C), 129.6 (2C), 136.7 (1C), 138.6 (1C), 148.2 (1C), 162.6 (1C); $^{19}\text{F NMR}$ (CDCl_3 , 377 MHz) δ 59.0 (s); IR (KBr, cm^{-1}) 795, 1184, 1200, 1283, 1406, 1441, 1638, 1653; HRMS (ESI^+) m/z 430.1315 ($[\text{M} + \text{Na}]^+ \text{C}_{18}\text{H}_{22}\text{FN}_5\text{NaO}_3\text{S}^+$ requires 430.1320).

2-(4-(3-(Butylamino)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**18**)



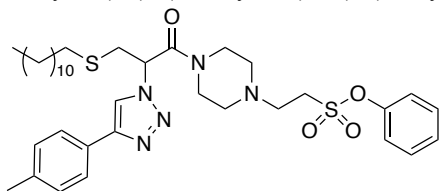
Colorless oil; TLC R_f 0.46 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 0.89 (t, 3H, $J = 7.3$ Hz), 1.27–1.34 (m, 2H), 1.39–1.47 (m, 2H), 1.59–1.69 (br, 1H), 2.11–2.19 (m, 1H), 2.32–2.41 (m, 4H), 2.56–2.70 (m, 4H), 2.88–2.93 (m, 2H), 3.17 (dd, 1H, $J = 12.6, 6.9$ Hz), 3.40 (dd, 1H, $J = 12.6, 6.9$ Hz), 3.48–3.55 (m, 3H), 3.66–3.63 (m, 1H), 3.69–3.75 (m, 1H), 3.81–3.89 (m, 1H), 5.86 (dd, 1H, $J = 6.9, 6.9$ Hz), 7.24 (d, 2H, $J = 7.8$ Hz), 7.72 (d, 2H, $J = 7.8$ Hz), 8.00 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 13.9 (1C), 20.2 (1C), 21.3 (1C), 32.0 (1C), 42.2 (1C), 45.7 (1C), 48.8 (d, 1C, $J = 14.3$ Hz), 49.4 (1C), 51.0 (1C), 51.6 (1C), 52.1 (1C), 52.6 (1C), 59.1 (1C), 118.2 (1C), 125.6 (2C), 127.4 (1C), 129.6 (2C), 138.3 (1C), 148.3 (1C), 165.4 (1C); $^{19}\text{F NMR}$ (CDCl_3 , 377 MHz) δ 58.7 (s); IR (KBr, cm^{-1}) 793, 1042, 1130, 1200, 1408, 1466, 1651, 2928; HRMS (ESI^+) m/z 481.2385 ($[\text{M} + \text{Na}]^+ \text{C}_{22}\text{H}_{34}\text{FN}_6\text{O}_3\text{S}^+$ requires 481.2392).

Phenyl 2-(4-(2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonate (**19**)



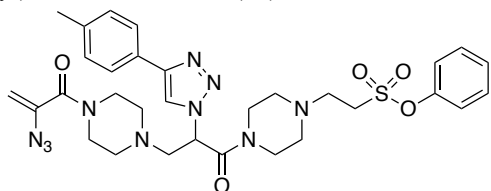
Colorless oil; TLC R_f 0.68 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 2.38 (s, 3H), 2.43–2.62 (m, 4H), 3.00 (t, 2H, $J = 7.4$ Hz), 3.43 (t, 2H, $J = 7.4$ Hz), 3.50–3.60 (br, 2H), 3.70–3.82 (br, 2H), 5.38 (d, 1H, $J = 1.9$ Hz), 6.00 (d, 1H, $J = 1.9$ Hz), 7.21–7.29 (m, 4H), 7.29–7.35 (m, 1H), 7.38–7.43 (m, 2H), 7.75 (d, 2H, $J = 8.1$ Hz), 8.03 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3 , 126 MHz) δ 21.3 (1C), 41.9 (br, 1C), 47.0 (br, 1C), 48.0 (1C), 51.5 (1C), 52.1 (br, 1C), 52.8 (br, 1C), 108.3 (1C), 117.6 (1C), 121.9 (2C), 125.8 (2C), 126.9 (1C), 127.4 (1C), 129.6 (2C), 130.0 (2C), 136.6 (1C), 138.6 (1C), 148.2 (1C), 149.0 (1C), 162.6 (1C); HRMS (ESI^+) m/z 482.1857 ($[\text{M} + \text{H}]^+ \text{C}_{24}\text{H}_{28}\text{N}_5\text{O}_4\text{S}^+$ requires 482.1857).

Phenyl 2-(4-(3-(dodecylthio)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**21**)



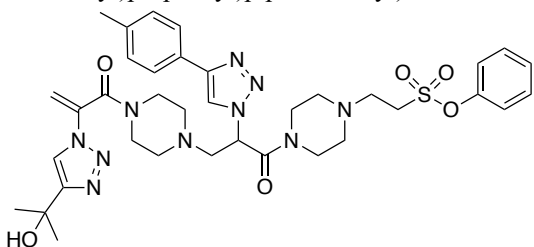
Colorless oil; TLC R_f 0.50 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 20/1$); ^1H NMR (CDCl_3 , 500 MHz) δ 0.88 (t, 3H, $J = 7.3$ Hz), 1.18–1.37 (m, 21H), 1.50–1.60 (m, 2H), 2.18–2.24 (m, 1H), 2.32–2.41 (m, 4H), 2.45–2.53 (m, 2H), 2.53–2.62 (m, 2H), 2.90–2.98 (m, 2H), 3.04–3.10 (m, 1H), 3.36–3.42 (m, 3H), 3.55–3.61 (m, 1H), 3.62–3.77 (m, 2H), 3.77–3.83 (m, 1H), 5.85 (dd, 1H, $J = 6.9, 6.9$ Hz), 7.20–7.27 (m, 2H), 7.29–7.34 (m, 1H), 7.38–7.44 (m, 2H), 7.72 (d, 1H, $J = 8.1$ Hz), 8.00 (s, 1H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 14.1 (1C), 21.3 (1C), 22.7 (1C), 28.8 (1C), 29.2 (1C), 29.4 (1C), 29.5 (1C), 29.6 (1C), 29.6 (1C), 29.7 (1C), 31.9 (1C), 33.0 (1C), 34.7 (1C), 42.5 (1C), 45.9 (1C), 48.0 (1C), 51.4 (1C), 52.3 (1C), 52.8 (1C), 58.9 (1C), 117.8 (1C), 122.0 (2C), 125.6 (2C), 127.4 (1C+1C, two signals overlapped), 129.6 (2C), 130.1 (2C), 138.3 (1C), 148.4 (1C), 149.0 (1C), 165.3 (1C); HRMS (ESI^+) m/z 706.3409 ($[\text{M} + \text{Na}]^+$ $\text{C}_{36}\text{H}_{53}\text{N}_5\text{NaO}_4\text{S}_2^+$ requires 706.3431).

Phenyl 2-(4-(3-(4-(2-azidoacryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**22**)



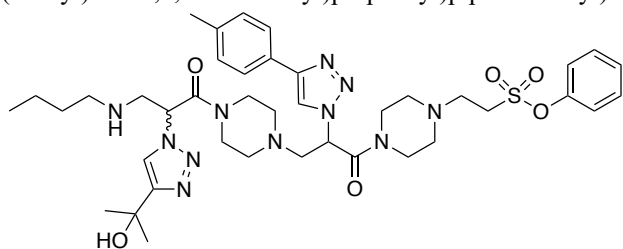
Colorless oil; TLC R_f 0.52 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$); ^1H NMR (CDCl_3 , 500 MHz) δ 2.14–2.20 (m, 1H), 2.32–2.40 (m, 4H), 2.43–2.51 (br, 2H), 2.53–2.65 (m, 4H), 2.89–2.95 (m, 2H), 3.00–3.09 (m, 1H), 3.14–3.21 (m, 1H), 3.36–3.42 (m, 1H), 3.47–3.64 (m, 7H), 3.70–3.79 (m, 1H), 3.79–3.88 (m, 1H), 4.99 (d, 1H, $J = 2.0$ Hz), 5.05 (d, 1H, $J = 2.1$ Hz), 5.87 (t, 1H, $J = 6.7$ Hz), 7.21–7.27 (m, 4H), 7.30–7.35 (m, 1H), 7.38–7.44 (m, 2H), 7.74 (d, 2H, $J = 8.1$ Hz), 7.99 (s, 1H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 21.3 (1C), 42.0 (br, 1C), 42.4 (1C), 45.8 (1C), 47.1 (br, 1C), 48.0 (1C), 51.3 (1C), 52.2 (1C), 52.8 (1C), 53.4 (br, 2C), 56.9 (1C), 59.5 (1C), 103.8 (1C), 118.0 (1C), 121.9 (2C), 125.5 (2C), 127.4 (1C+1C, two signals overlapped), 129.6 (2C), 130.0 (2C), 138.3 (1C), 139.4 (1C), 148.3 (1C), 148.9 (1C), 163.2 (1C), 165.3 (1C); HRMS (ESI^+) m/z 685.2640 ($[\text{M} + \text{Na}]^+$ $\text{C}_{31}\text{H}_{38}\text{N}_{10}\text{NaO}_5\text{S}^+$ requires 685.2640).

Phenyl 2-(4-(3-(4-(2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**23**)



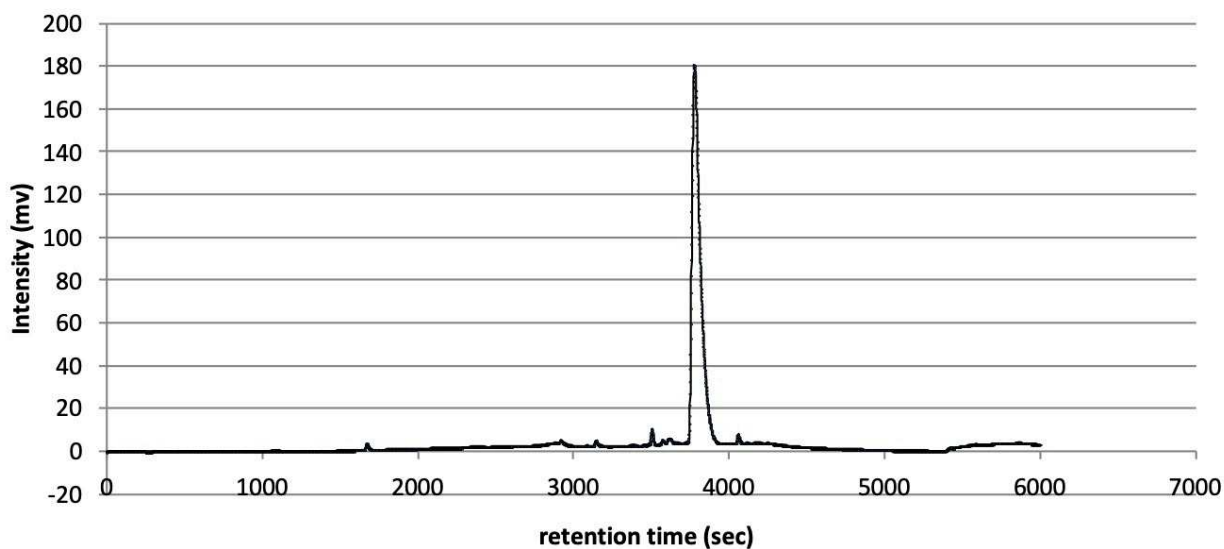
Colorless oil; TLC R_f 0.48 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$); ^1H NMR (CDCl_3 , 500 MHz) δ 1.63 (s, 6H), 2.14–2.21 (m, 1H), 2.31–2.42 (m, 5H), 2.47–2.57 (m, 4H), 2.62–2.70 (br, 1H), 2.99–2.97 (m, 2H), 3.03–3.10 (m, 1H), 3.13–3.22 (m, 2H), 3.35–3.53 (m, 5H), 3.54–3.75 (m, 4H), 3.76–3.83 (m, 1H), 5.28 (d, 1H, $J = 1.7$ Hz), 5.85–5.93 (m, 2H), 7.20–7.27 (m, 4H), 7.29–7.34 (m, 1H), 7.37–7.44 (m, 2H), 7.71 (d, 1H, $J = 8.0$ Hz), 7.76 (s, 1H), 8.00 (s, 1H); ^{13}C NMR (CDCl_3 , 126 MHz) δ 21.3 (1C), 30.4 (2C), 42.0 (1C), 42.4 (1C), 45.8 (1C), 47.2 (1C), 47.9 (1C), 51.3 (1C), 51.3 (1C), 52.2 (1C), 52.4 (1C), 52.8 (1C), 52.9 (1C), 56.8 (1C), 59.4 (1C), 68.4 (1C), 107.8 (1C), 118.1 (1C), 121.9 (2C), 125.6 (2C), 127.4 (1C+1C, two signals overlapped), 129.6 (2C), 130.0 (2C), 136.6 (1C), 138.3 (1C), 148.3 (1C), 148.9 (1C), 156.3 (br, 1C), 162.5 (1C), 165.2 (1C); HRMS (ESI^+) m/z 769.3216 ($[\text{M} + \text{Na}]^+$ $\text{C}_{36}\text{H}_{46}\text{N}_{10}\text{NaO}_6\text{S}^+$ requires 769.3215).

Phenyl 2-(4-(3-(4-(3-(butylamino)-2-(4-(2-hydroxypropan-2-yl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**24**)



Colorless solid; TLC R_f 0.39 (CH₂Cl₂/MeOH = 10/1); ¹H NMR (CDCl₃, 500 MHz) δ 0.87 (t, 3H, J = 7.3 Hz), 1.23–1.31 (m, 2H), 1.34–1.42 (m, 2H), 1.62–1.68 (m, 6H), 2.15–2.64 (m, 15H), 2.91–3.20 (m, 5H), 3.30–3.48 (m, 4H), 3.53–3.56 (br, 2H), 3.57–3.65 (br, 2H), 3.68–3.72 (m, 1H), 5.75–5.85 (m, 2H), 7.21–7.30 (m, 4H), 7.30–7.34 (AA'BB'C, 1H), 7.38–7.42 (AA'BB'C, 2H), 7.70–7.76 (m, 3H), 7.94–8.01 (m, 1H); ¹³C NMR (CDCl₃, 126 MHz) δ 13.9, 20.2, 20.3, 30.2, 30.36, 30.37, 30.5, 31.9, 42.4, 42.5, 45.8, 47.9, 49.3, 51.3, 51.4, 51.6, 52.2, 52.6, 52.8, 52.9, 56.68, 56.73, 58.98, 58.99, 59.3, 59.4, 68.4, 117.85, 117.93, 118.3, 121.9, 125.6, 127.4, 129.6, 130.0, 138.3, 138.4, 148.32, 148.35, 148.9, 155.9, 156.2, 165.11, 165.14, 165.3, 165.4; HPLC analysis: R_t = 31.5 min [column: Shiseido CAPCELL PAK MG II (4.6 mm i.d. \times 250 mm); mobile phase: MeOH:H₂O = 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]; HRMS (ESI⁺) m/z 820.4287 ([M + H]⁺ C₄₀H₅₈N₁₁O₆S⁺ requires 820.4287).

The HPLC chart of **24**

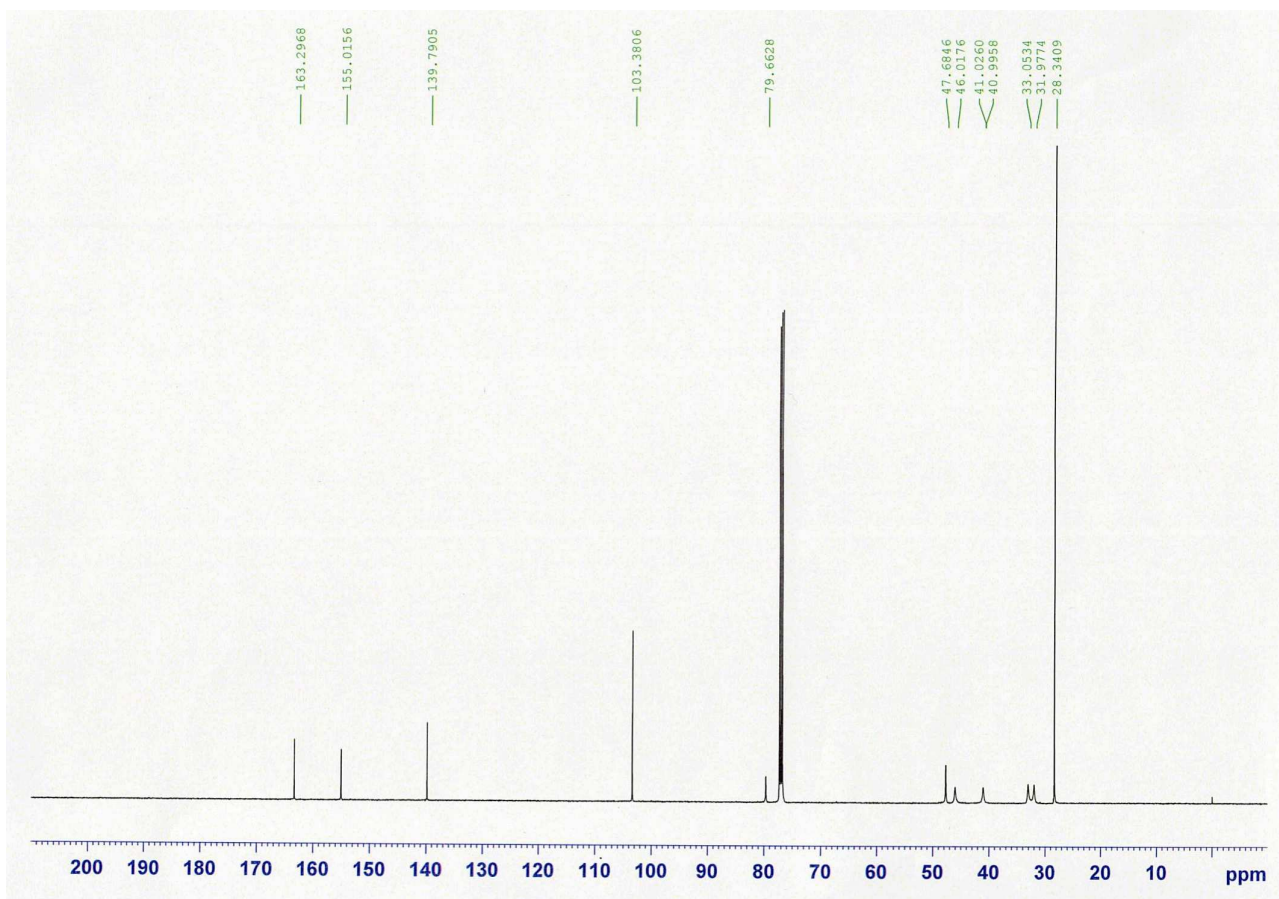
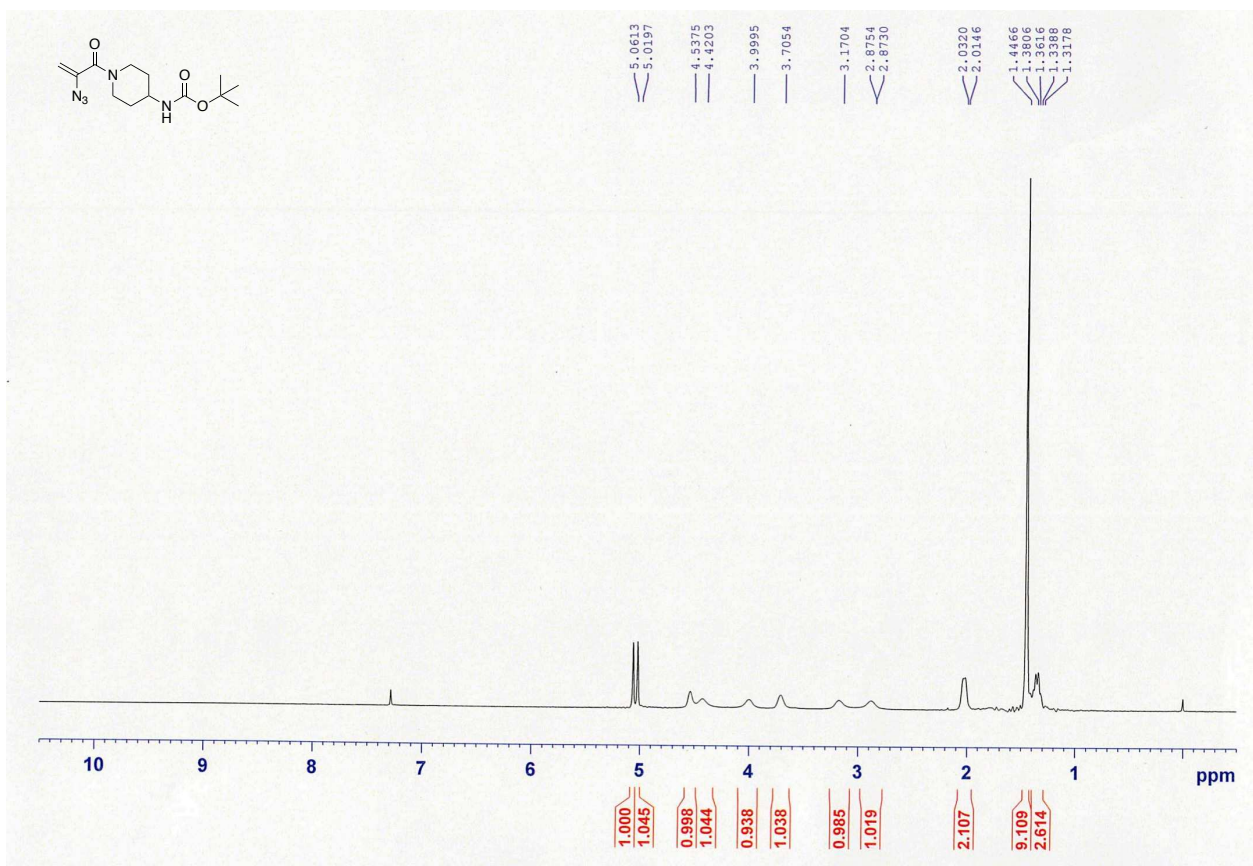


References for Supporting Information

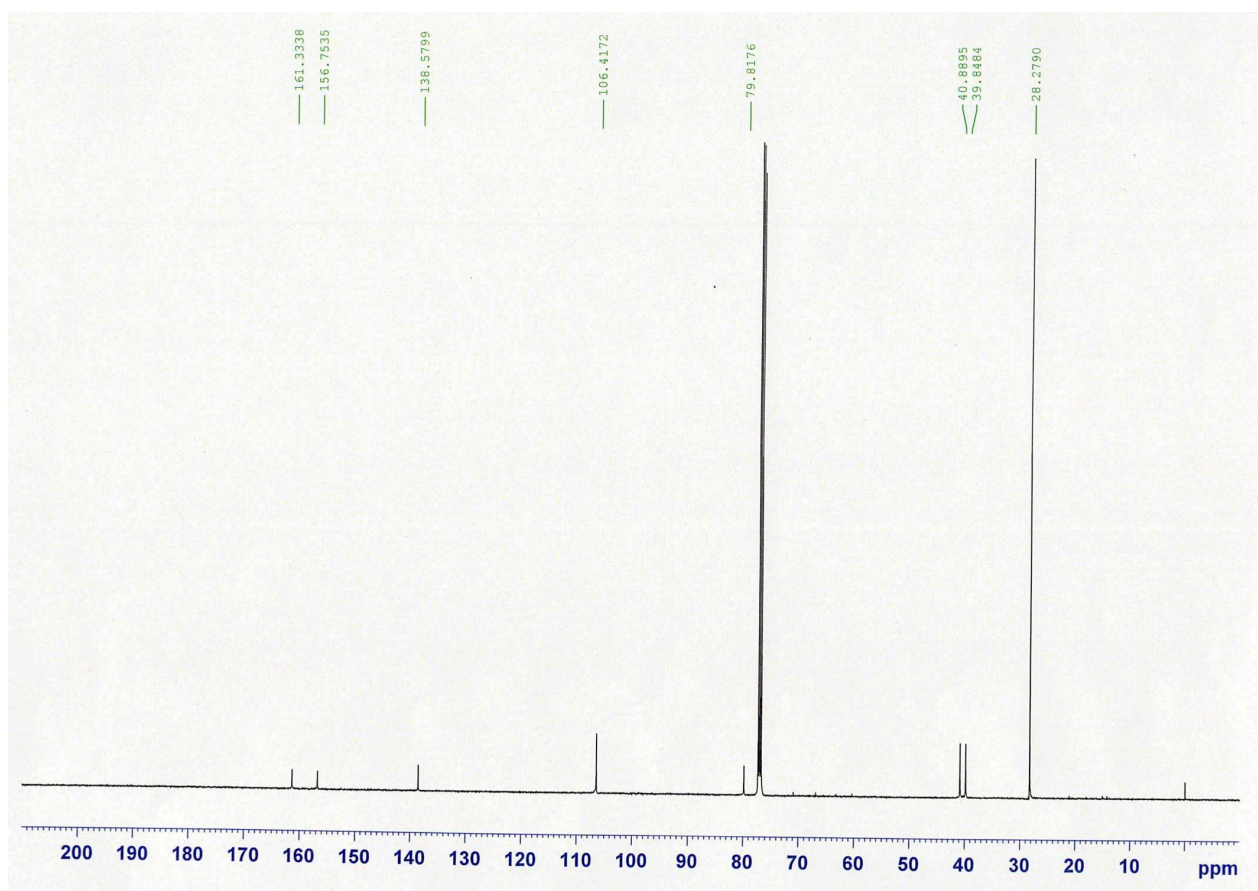
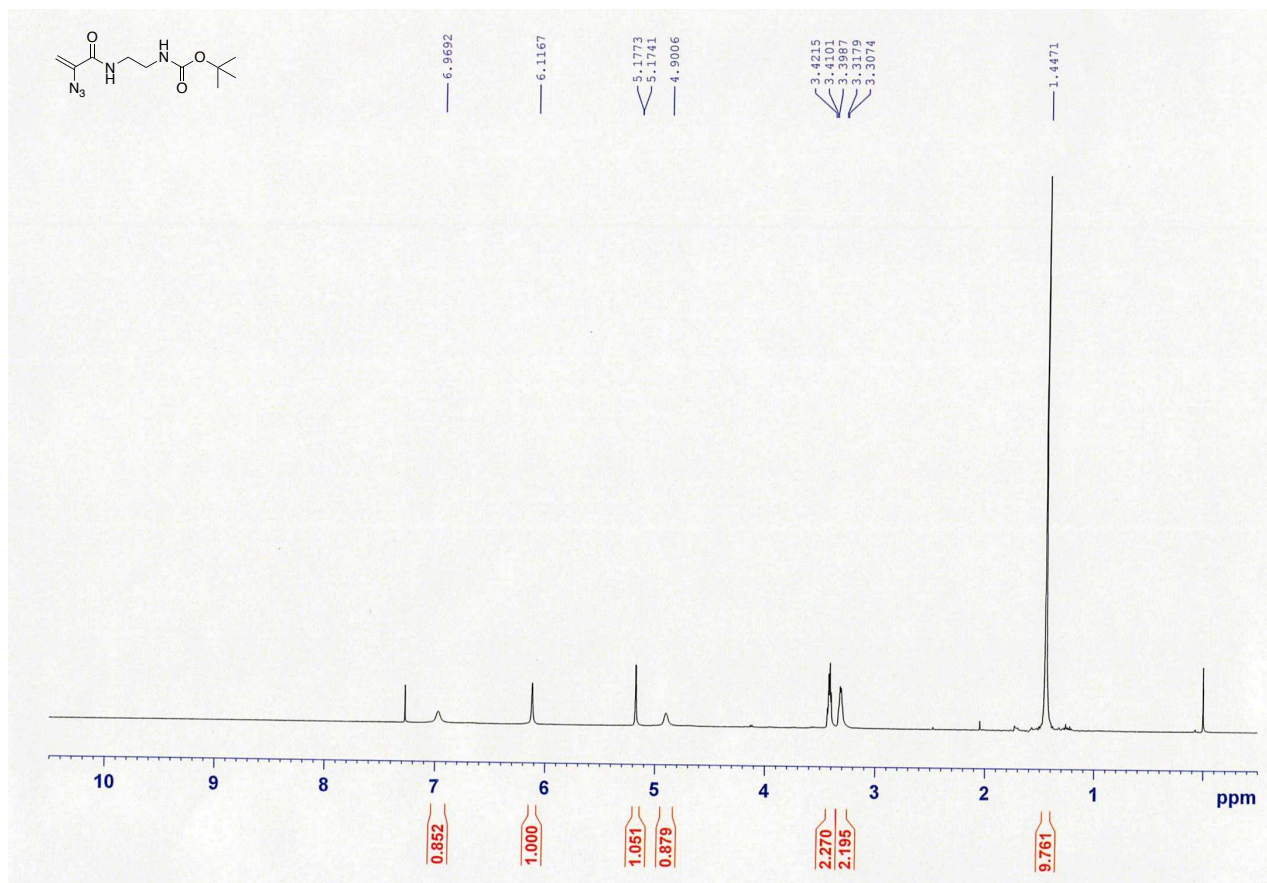
- S1 H. Takemura, S. Goto, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 15541.
- S2 T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Fokin, *Org. Lett.*, 2004, **6**, 2853.

NMR Spectra of New Compounds

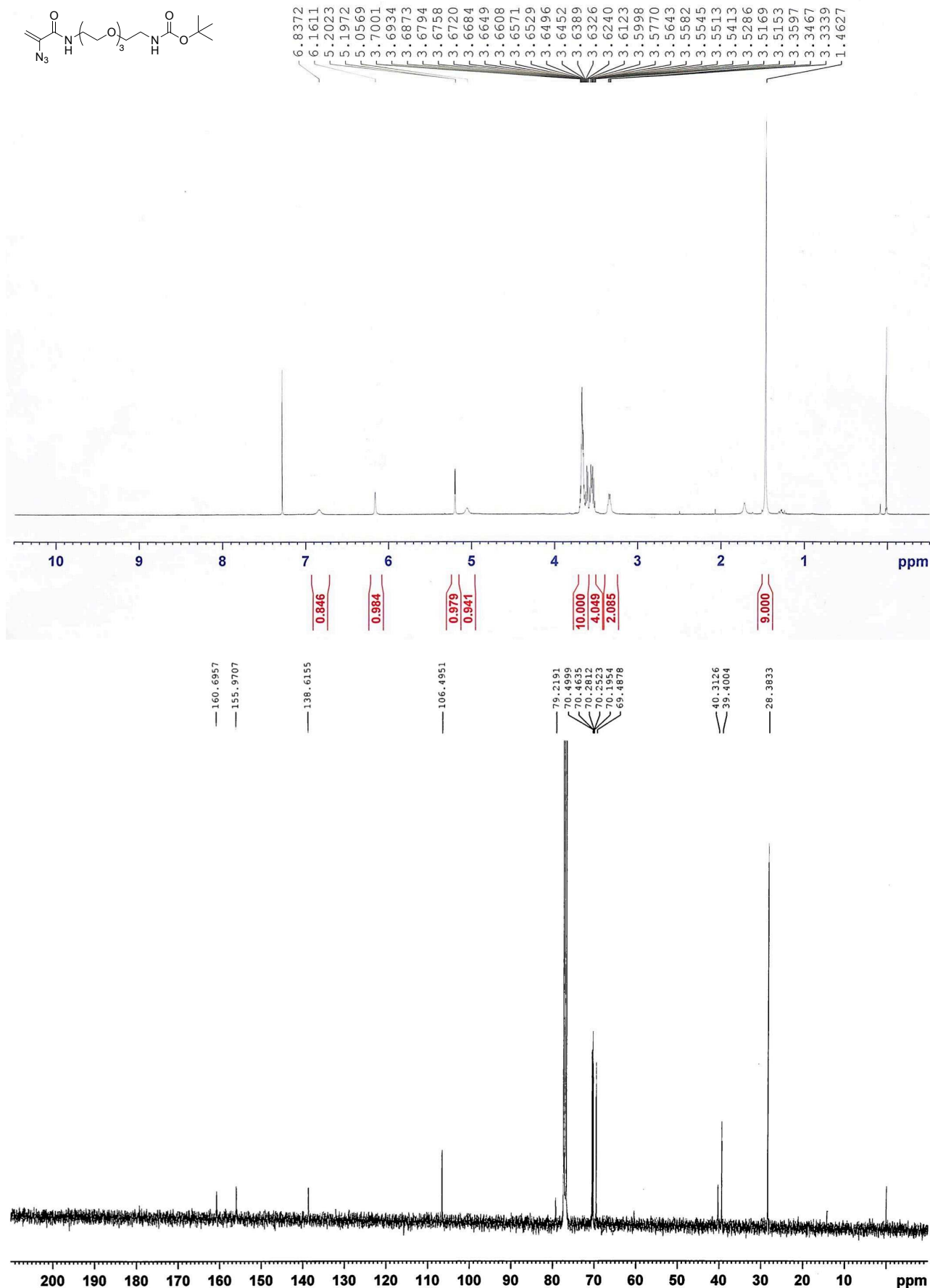
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl (1-(2-azidoacryloyl)piperidin-4-yl)carbamate (**6b**) (CDCl_3)



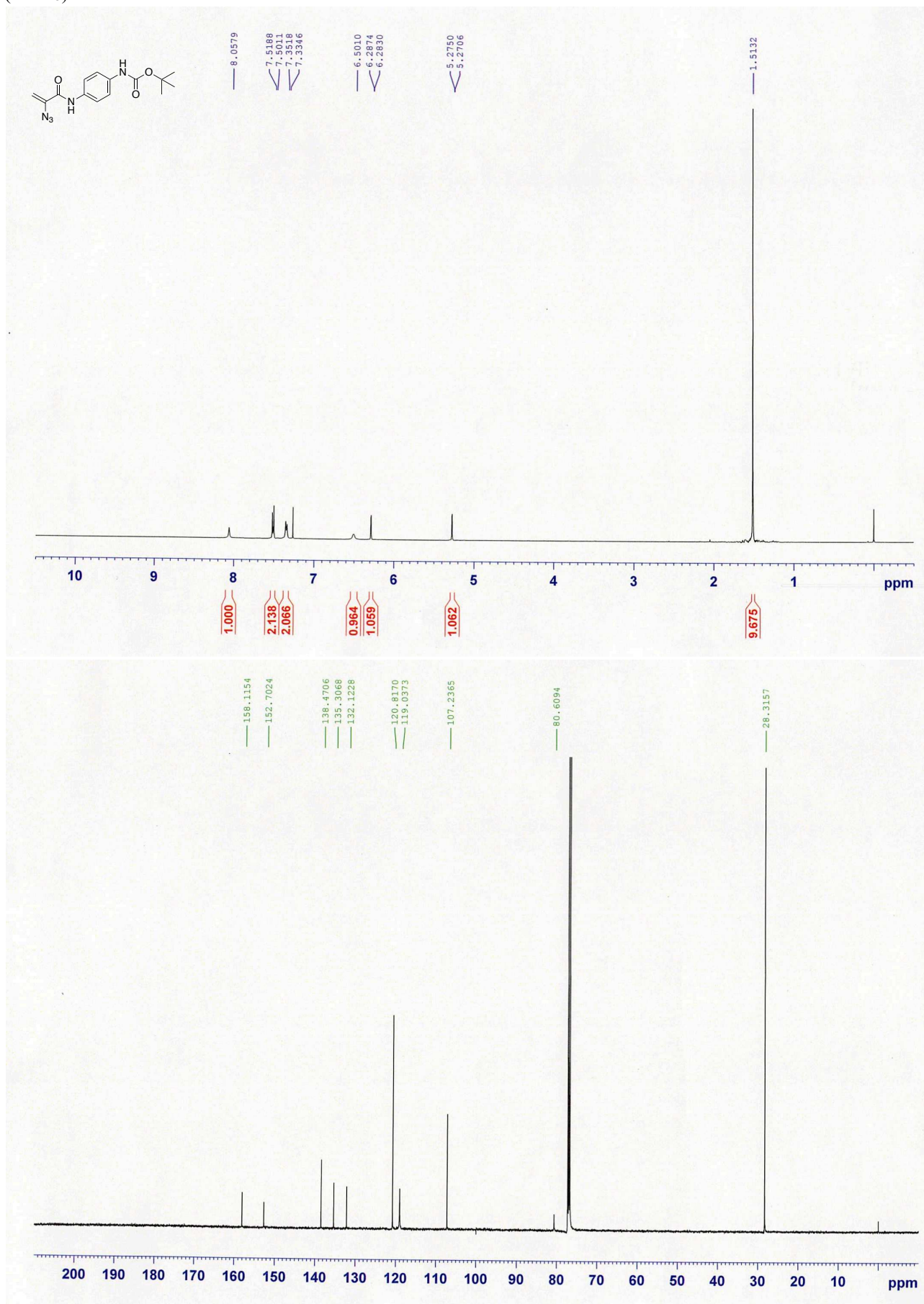
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl (2-(2-azidoacrylamido)ethyl)carbamate (**6c**) (CDCl_3)



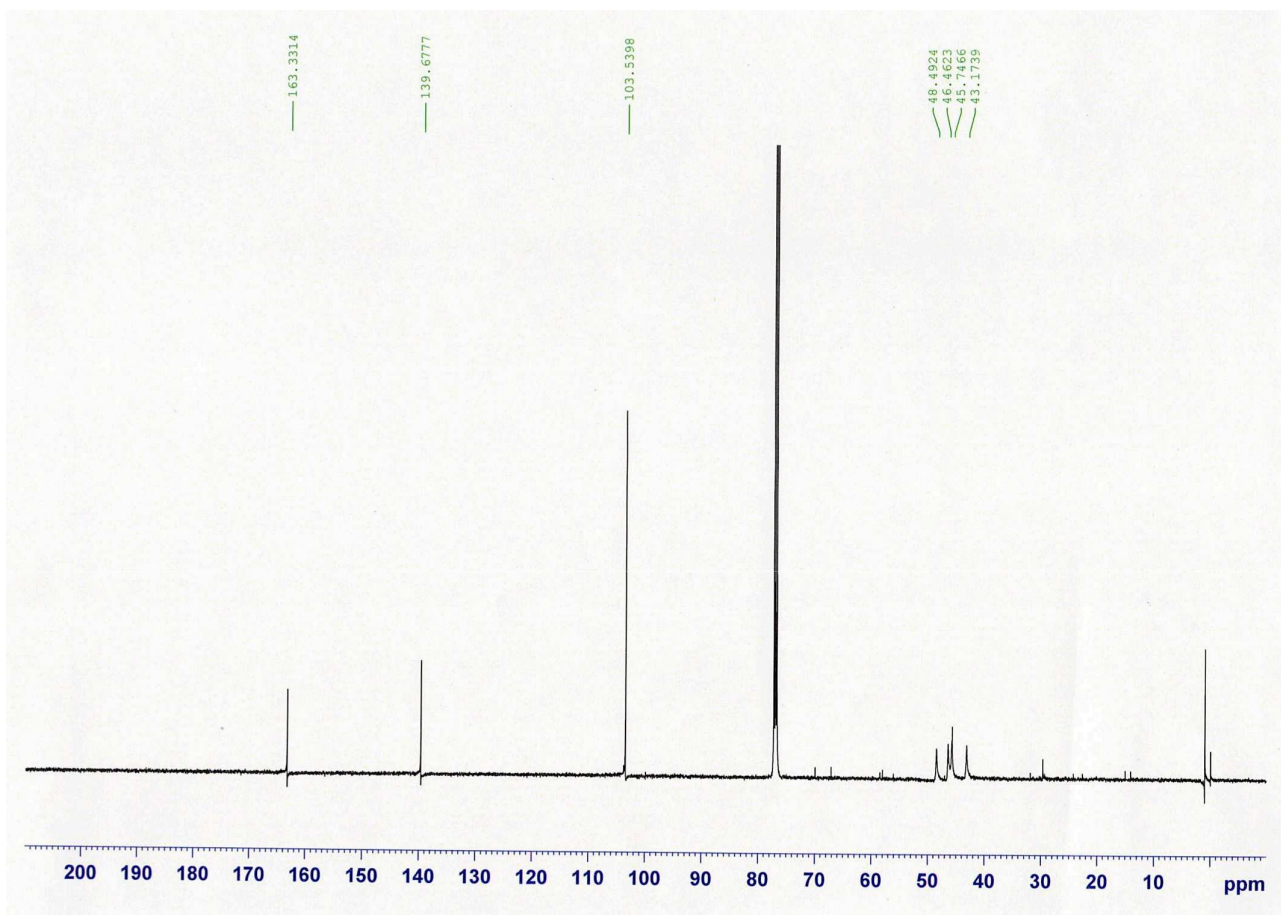
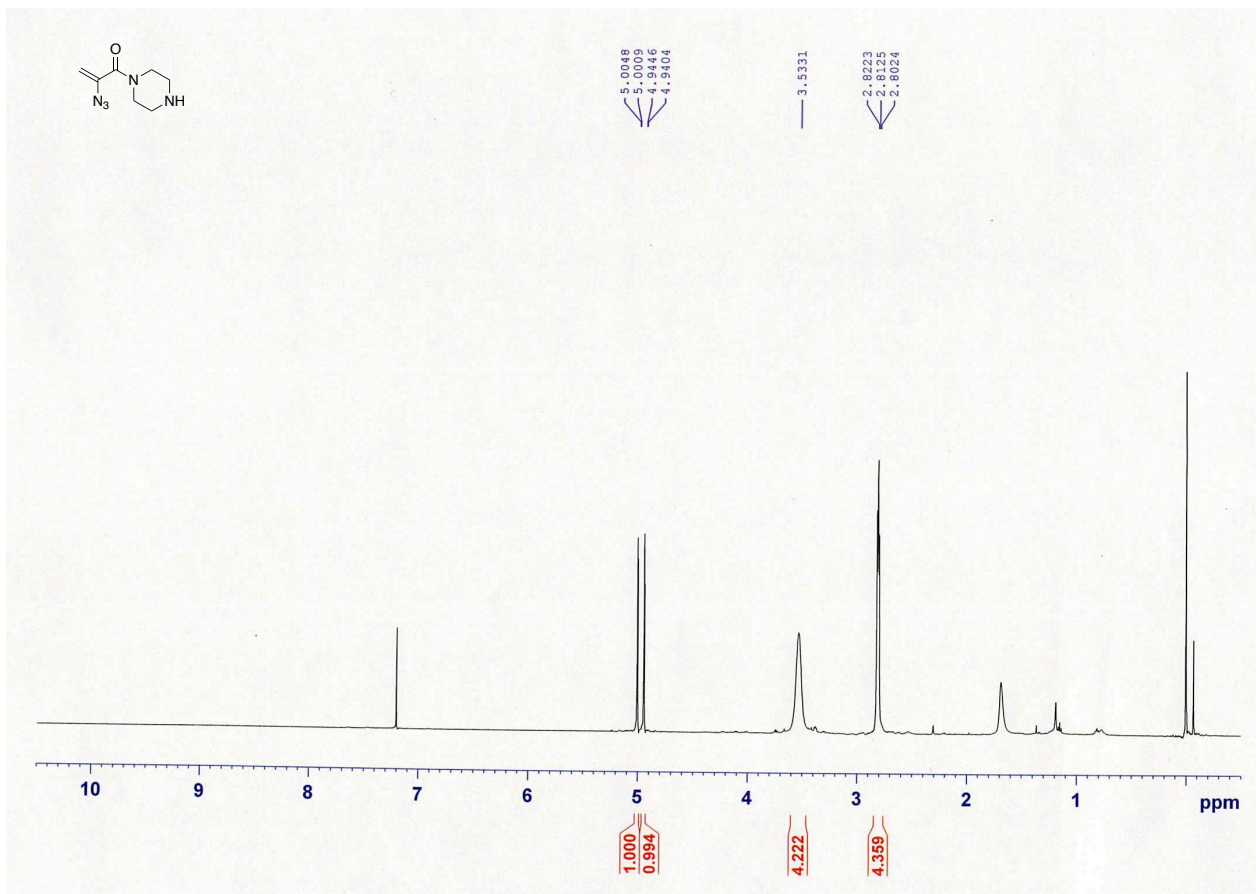
^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra of *tert*-butyl (14-azido-13-oxo-3,6,9-trioxa-12-azapentadec-14-en-1-yl)carbamate (**6d**) (CDCl_3)



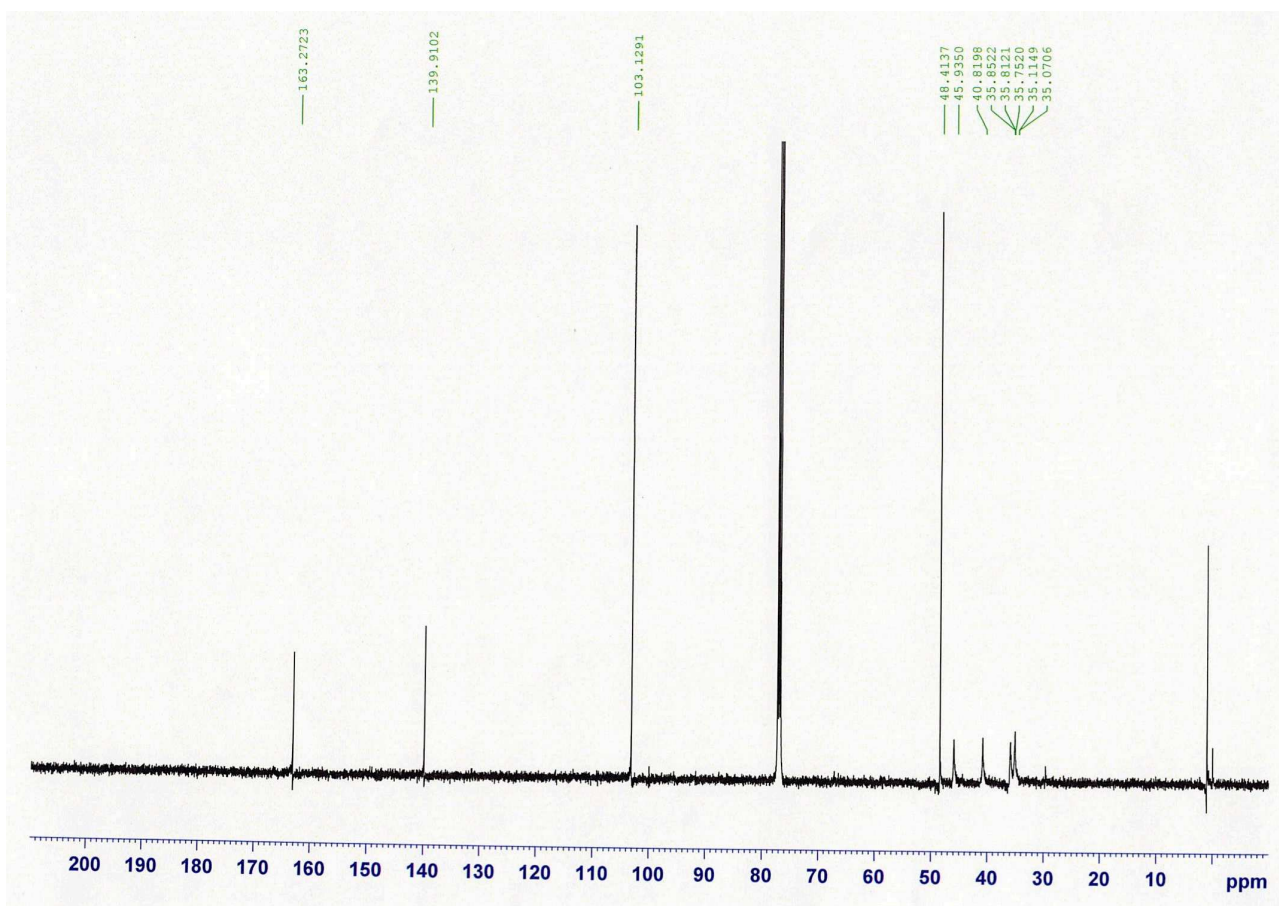
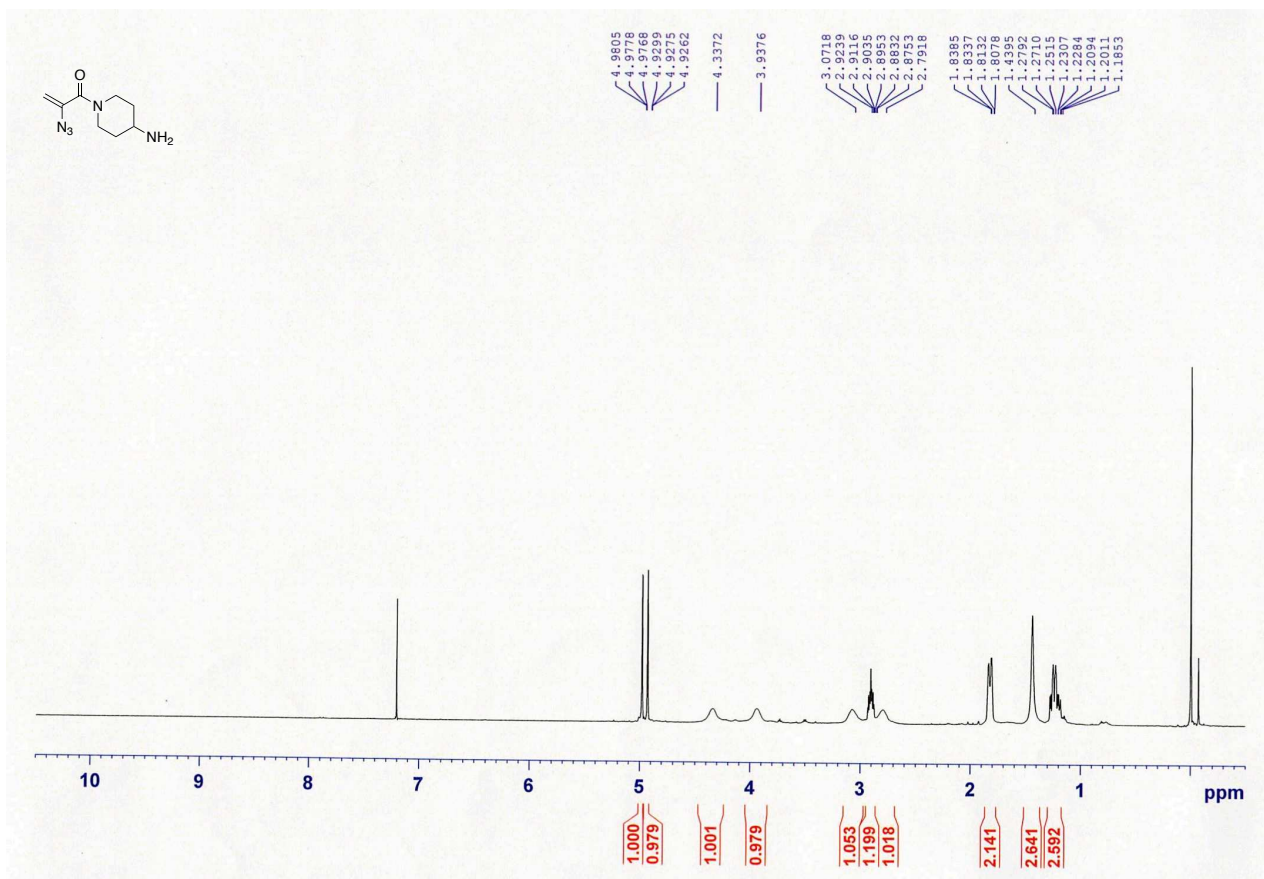
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl (4-(2-azidoacrylamido)phenyl)carbamate (**6e**) (CDCl_3)



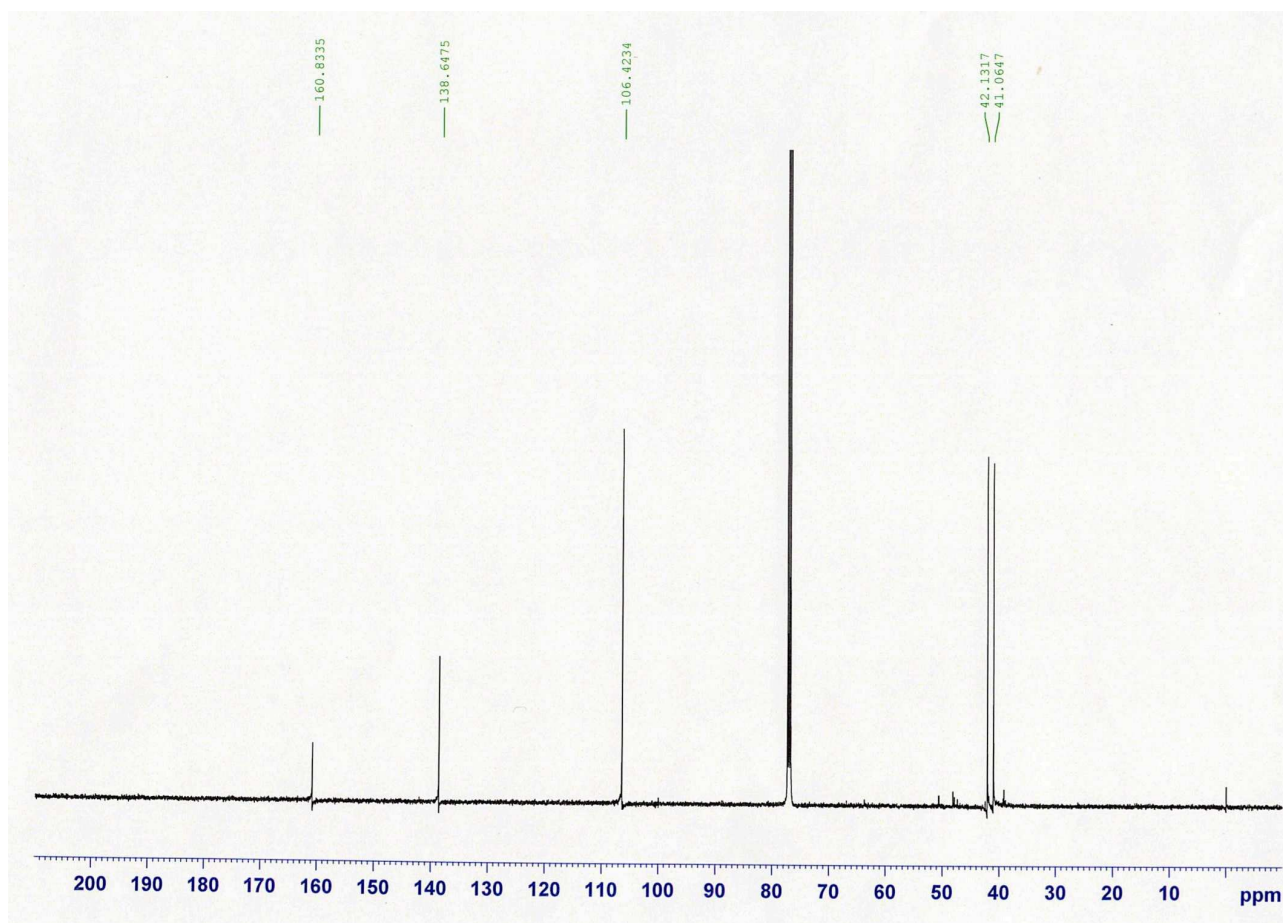
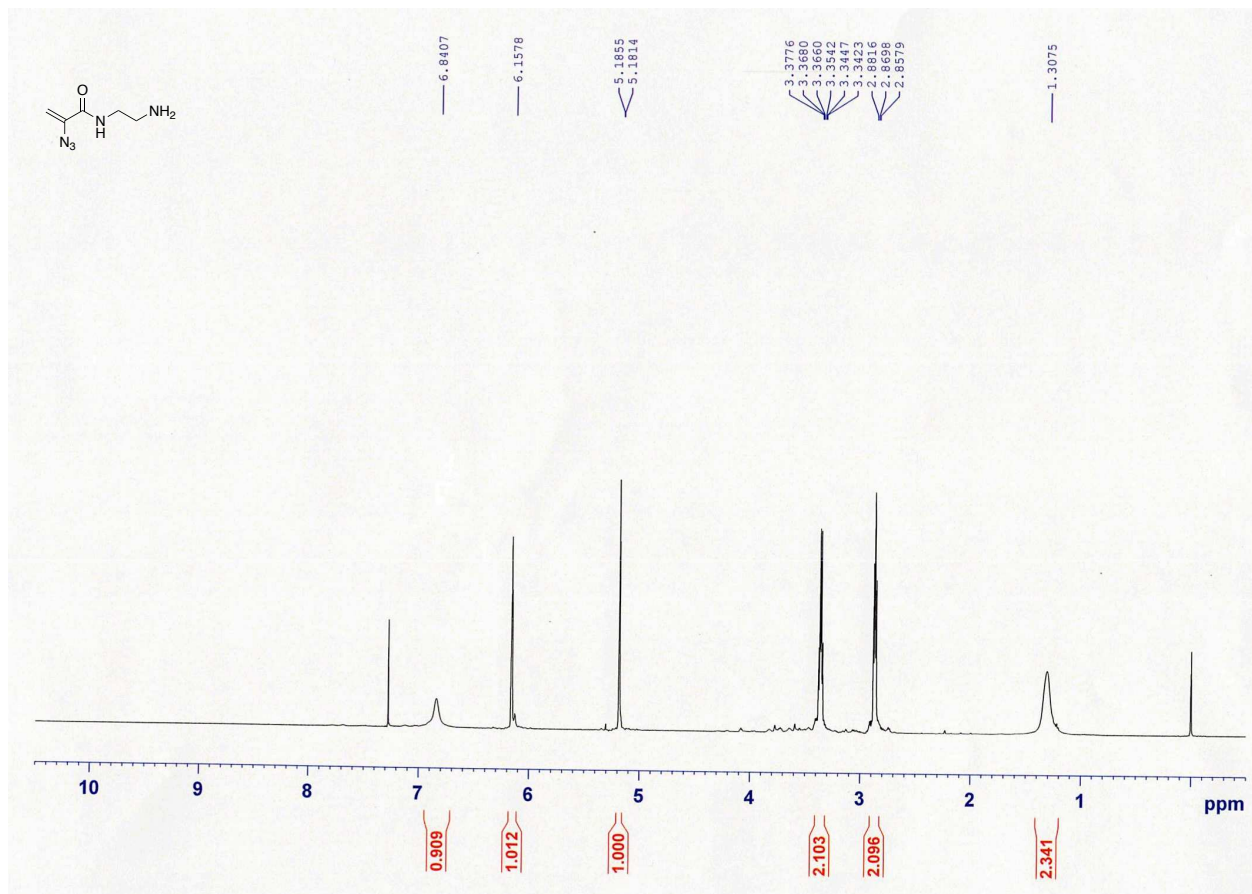
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azido-1-(piperazin-1-yl)prop-2-en-1-one (**3a**) (CDCl_3)



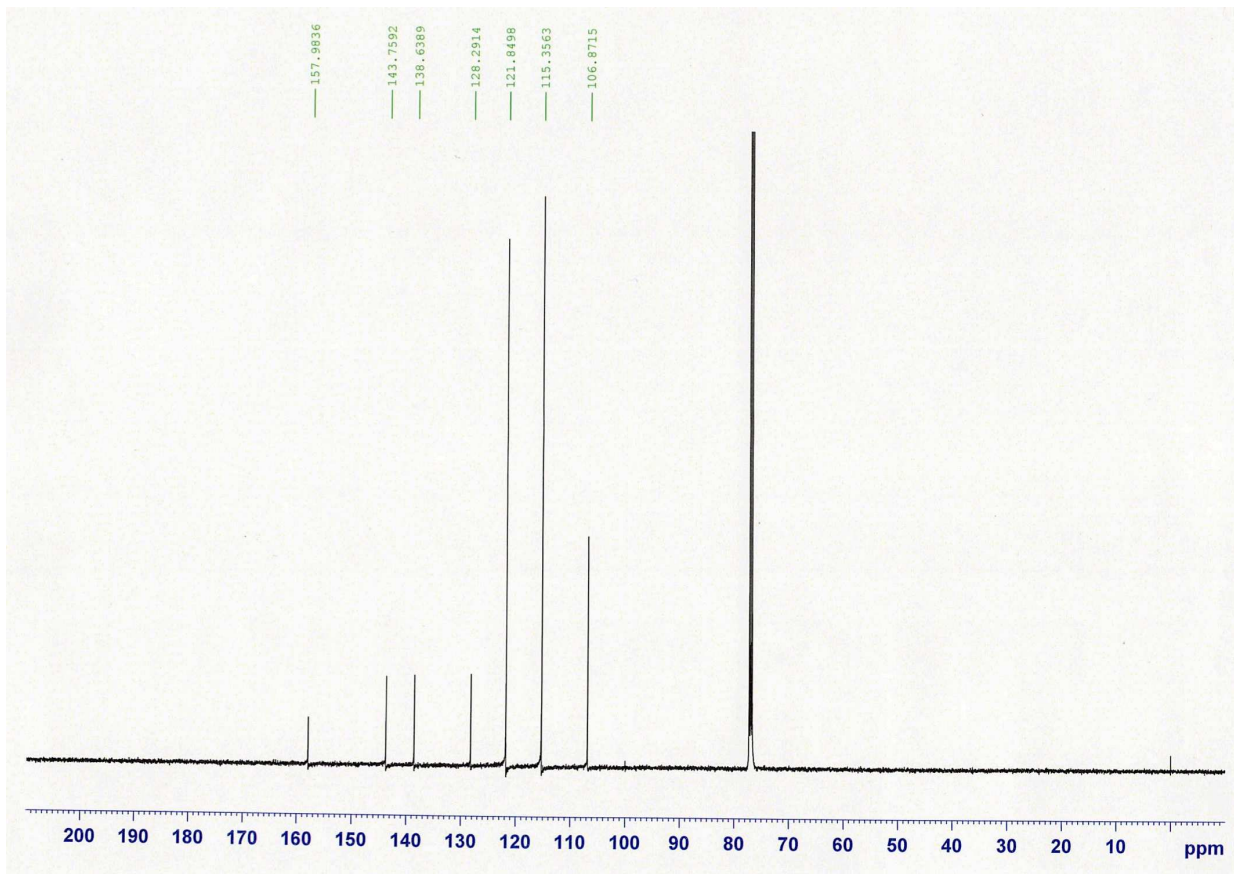
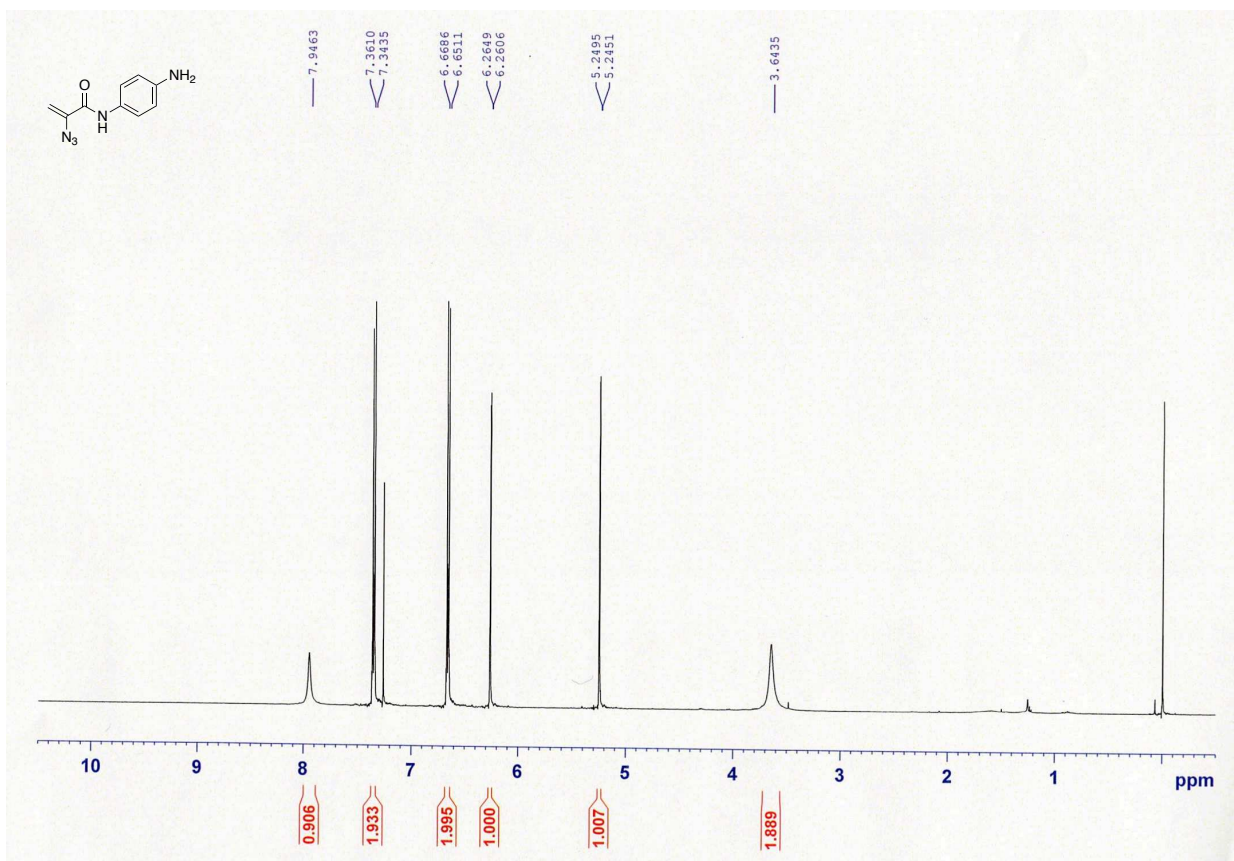
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 1-(4-aminopiperidin-1-yl)-2-azidoprop-2-en-1-one (**3b**) (CDCl₃)



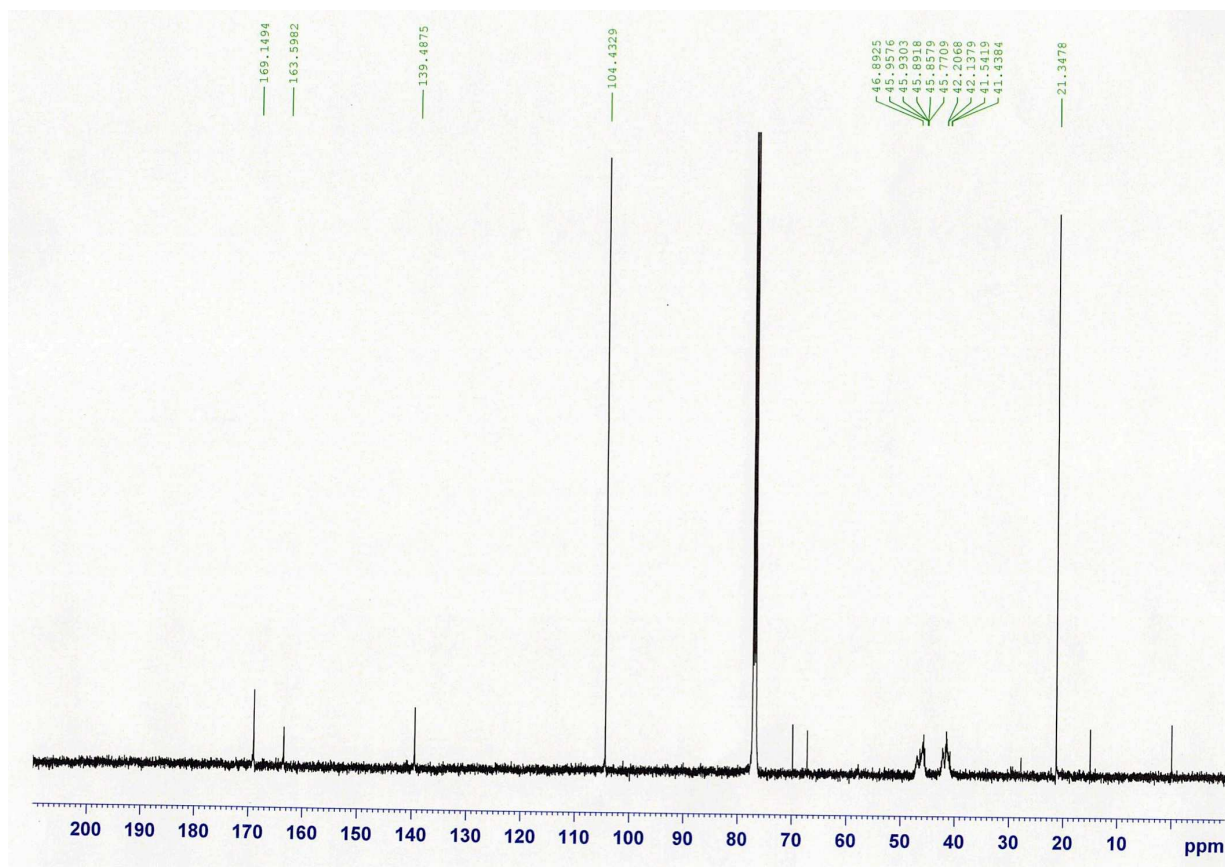
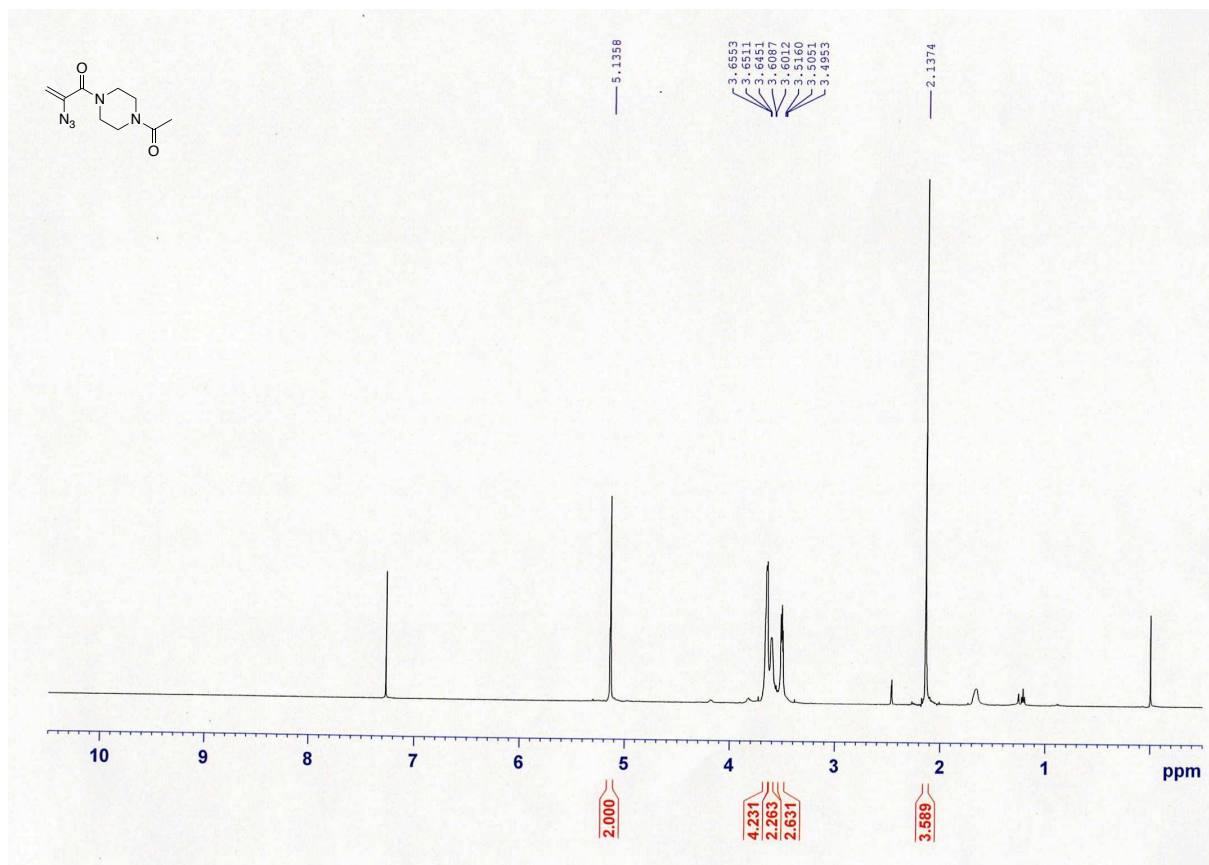
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *N*-(2-aminoethyl)-2-azidoacrylamide (**3c**) (CDCl_3)



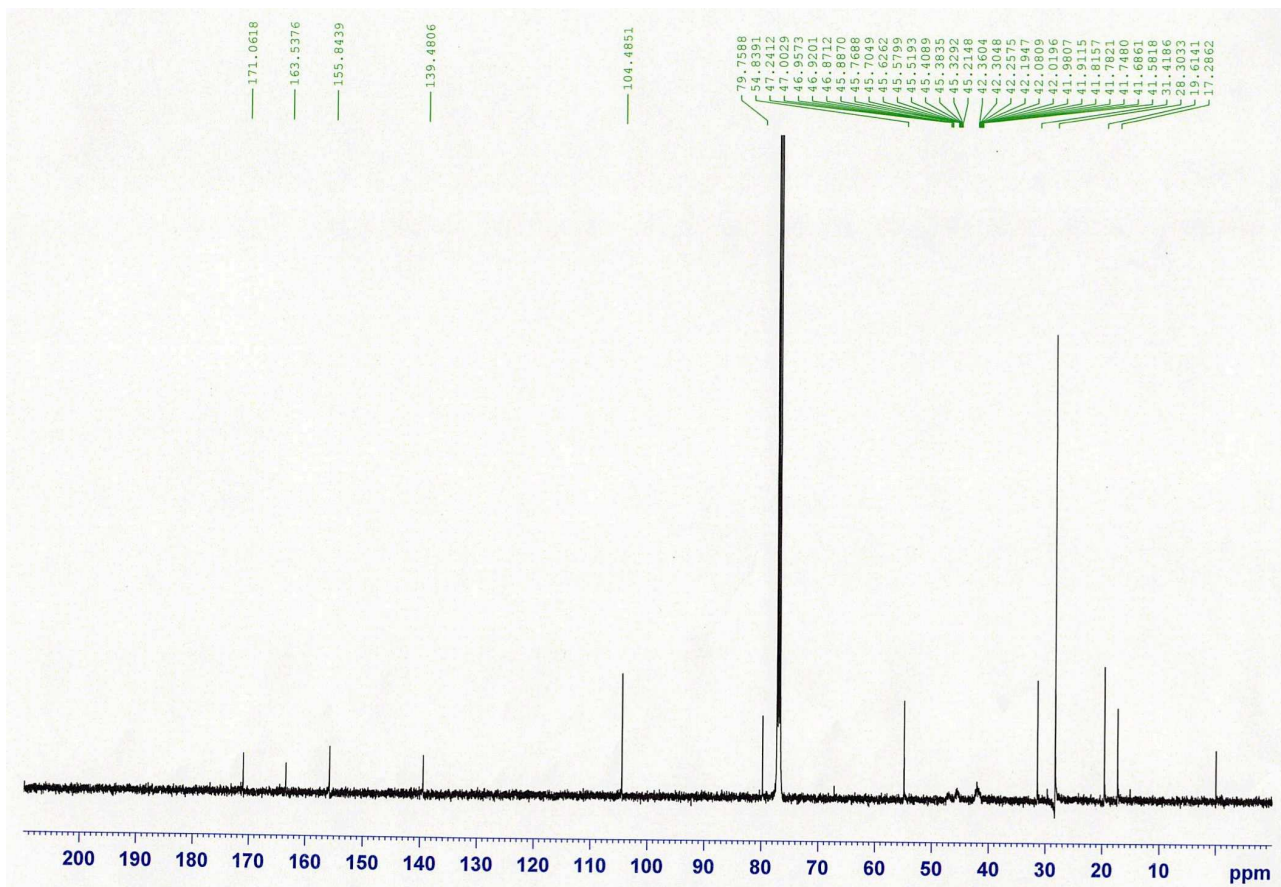
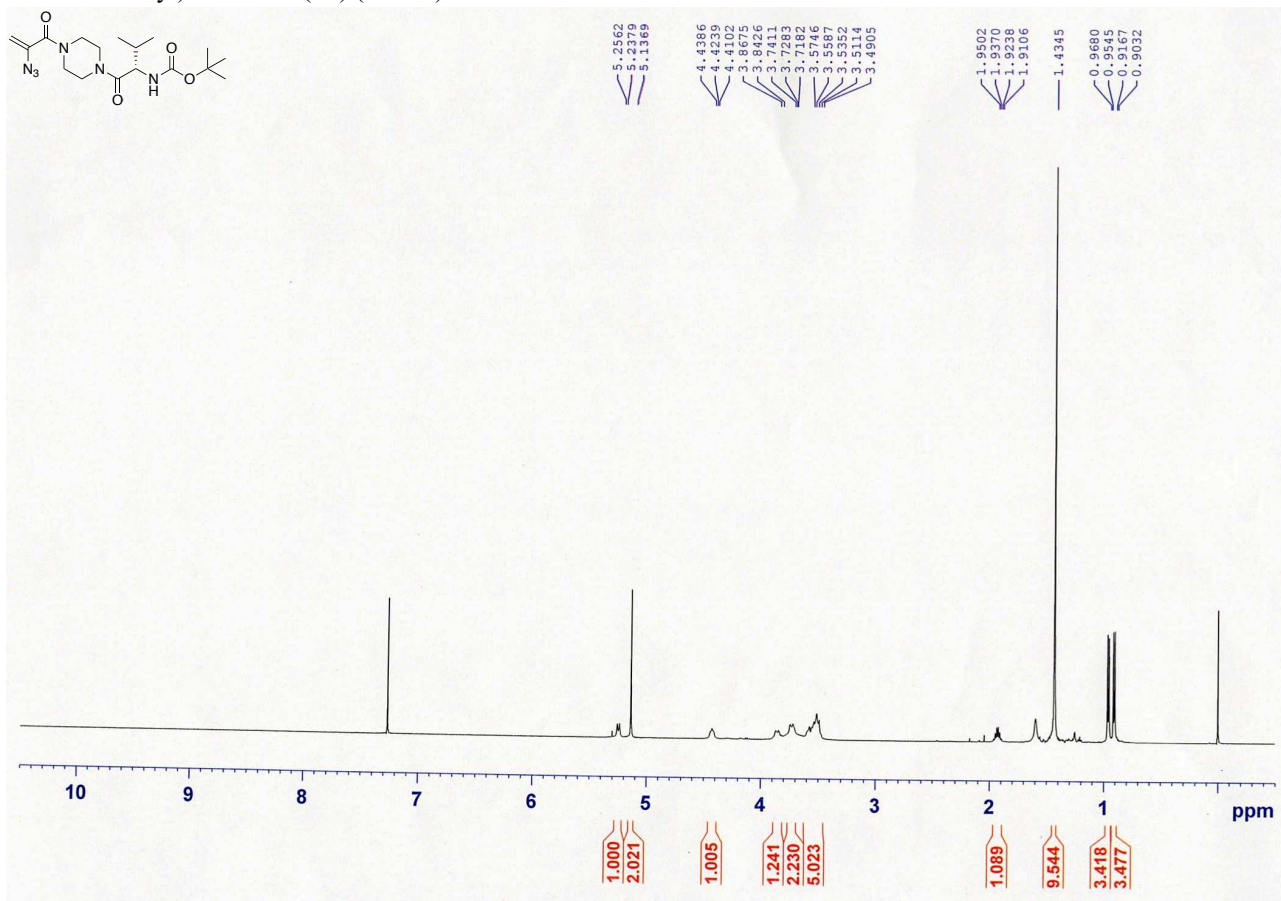
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *N*-(4-aminophenyl)-2-azidoacrylamide (**3e**) (CDCl_3)



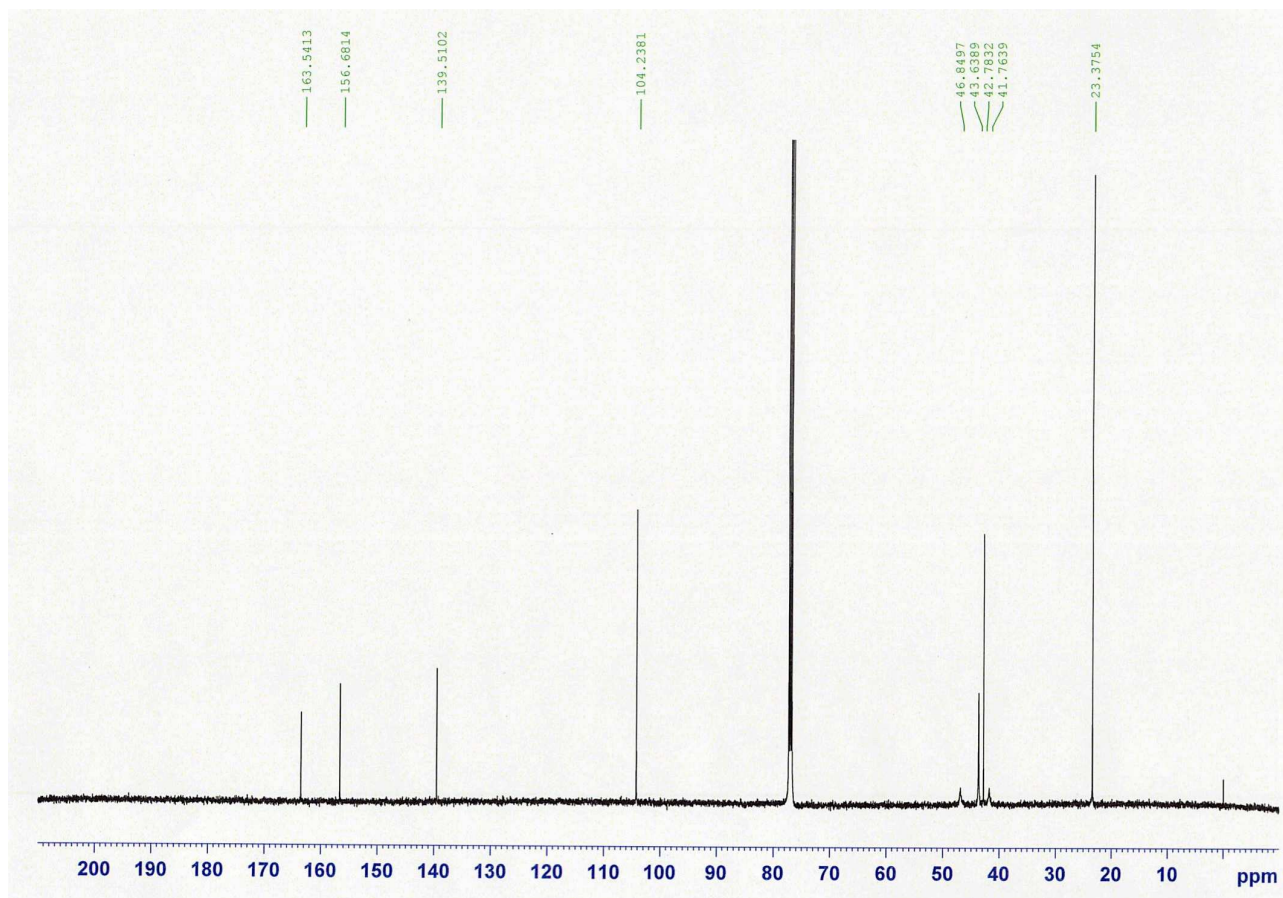
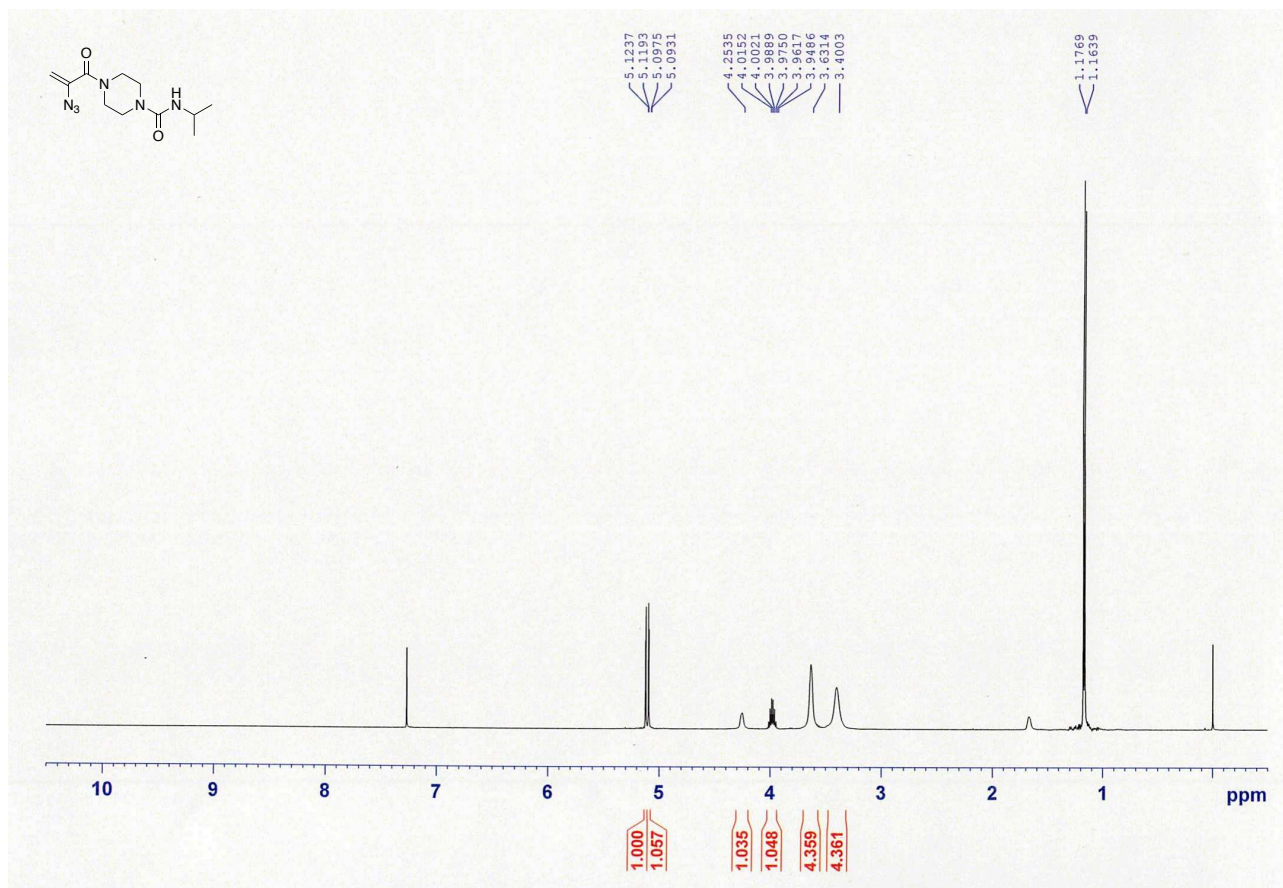
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 1-(4-acetylpiperazin-1-yl)-2-azidoprop-2-en-1-one (**9a**) (CDCl_3)



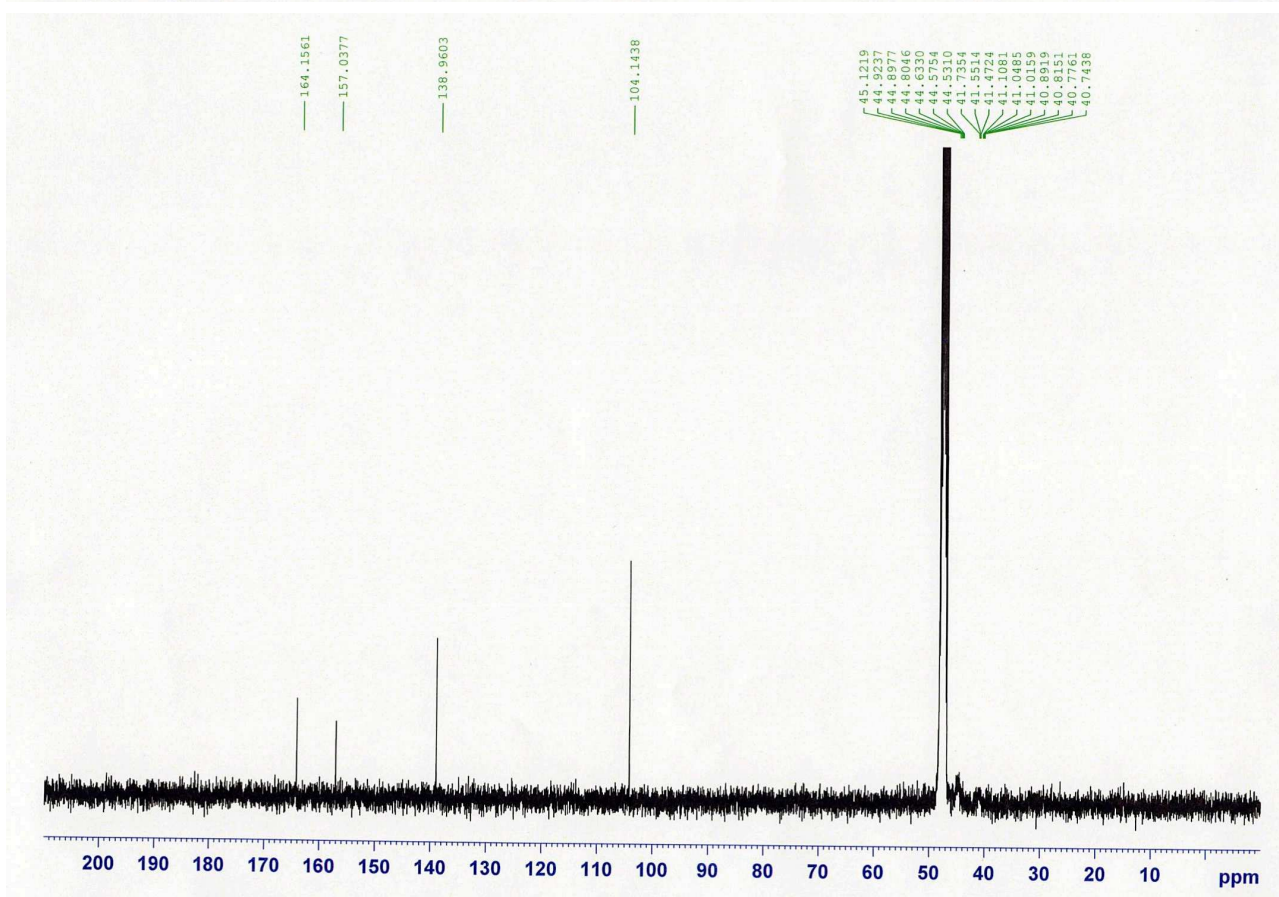
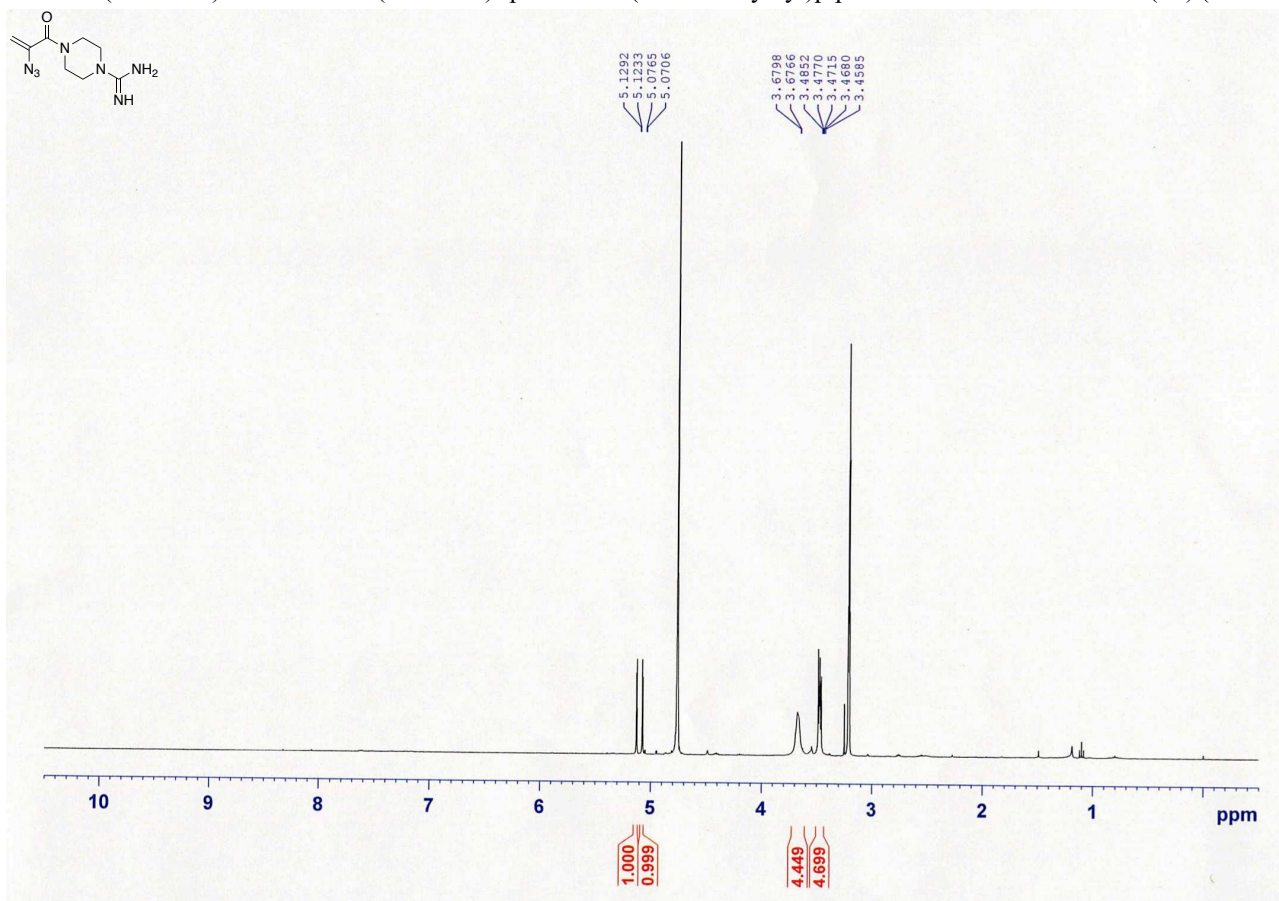
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of *tert*-butyl (*S*)-(1-(4-(2-azidoacryloyl)piperazin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate (**9b**) (CDCl₃)



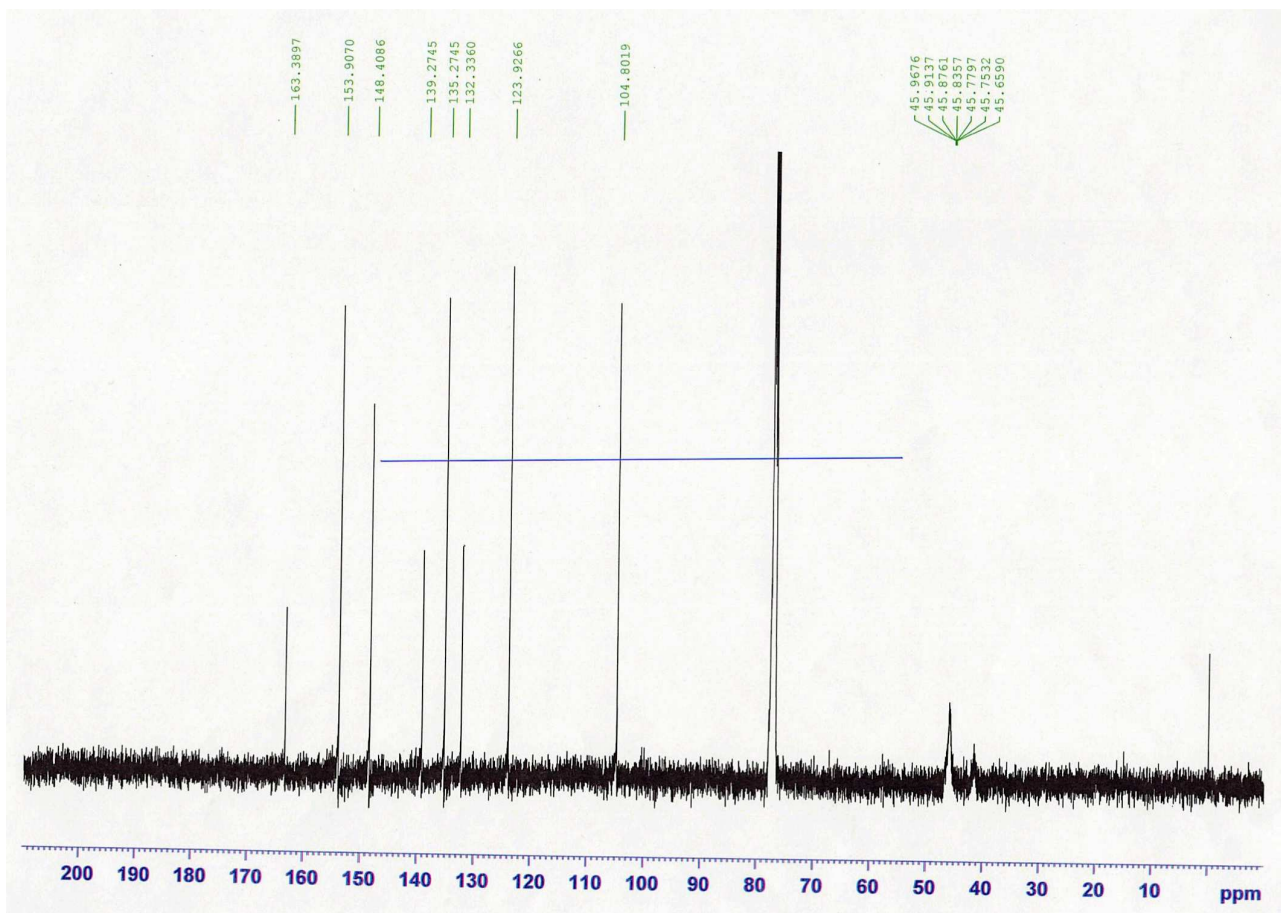
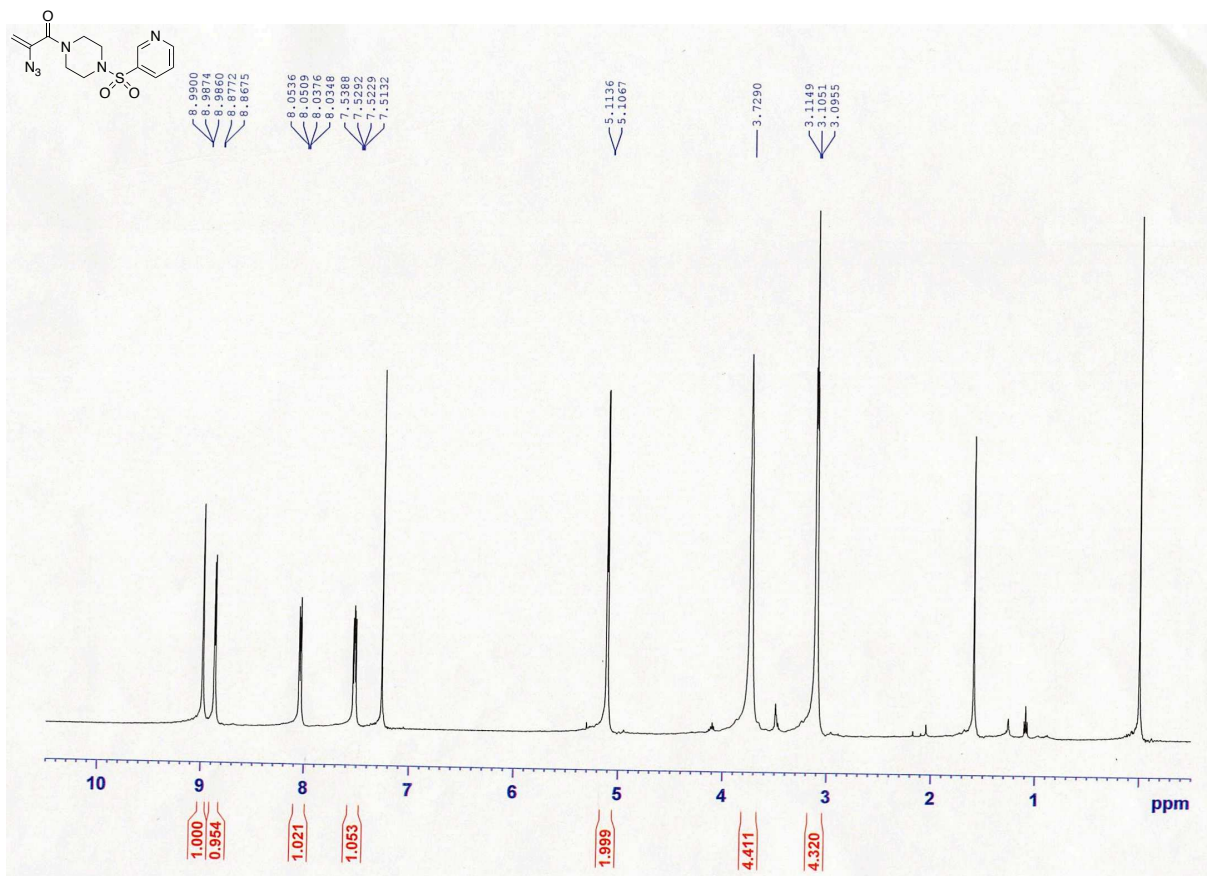
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 4-(2-azidoacryloyl)-*N*-isopropylpiperazine-1-carboxamide (**9c**) (CDCl₃)



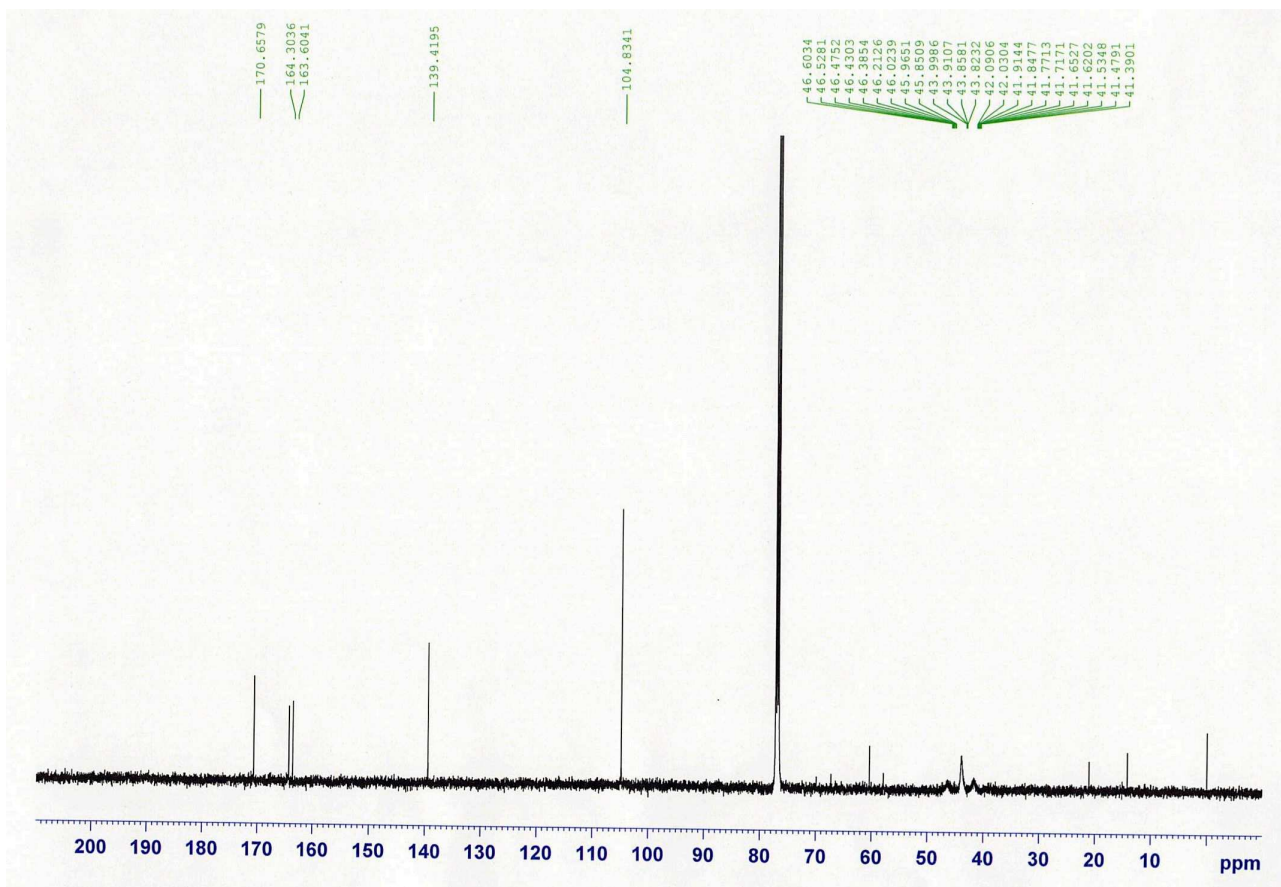
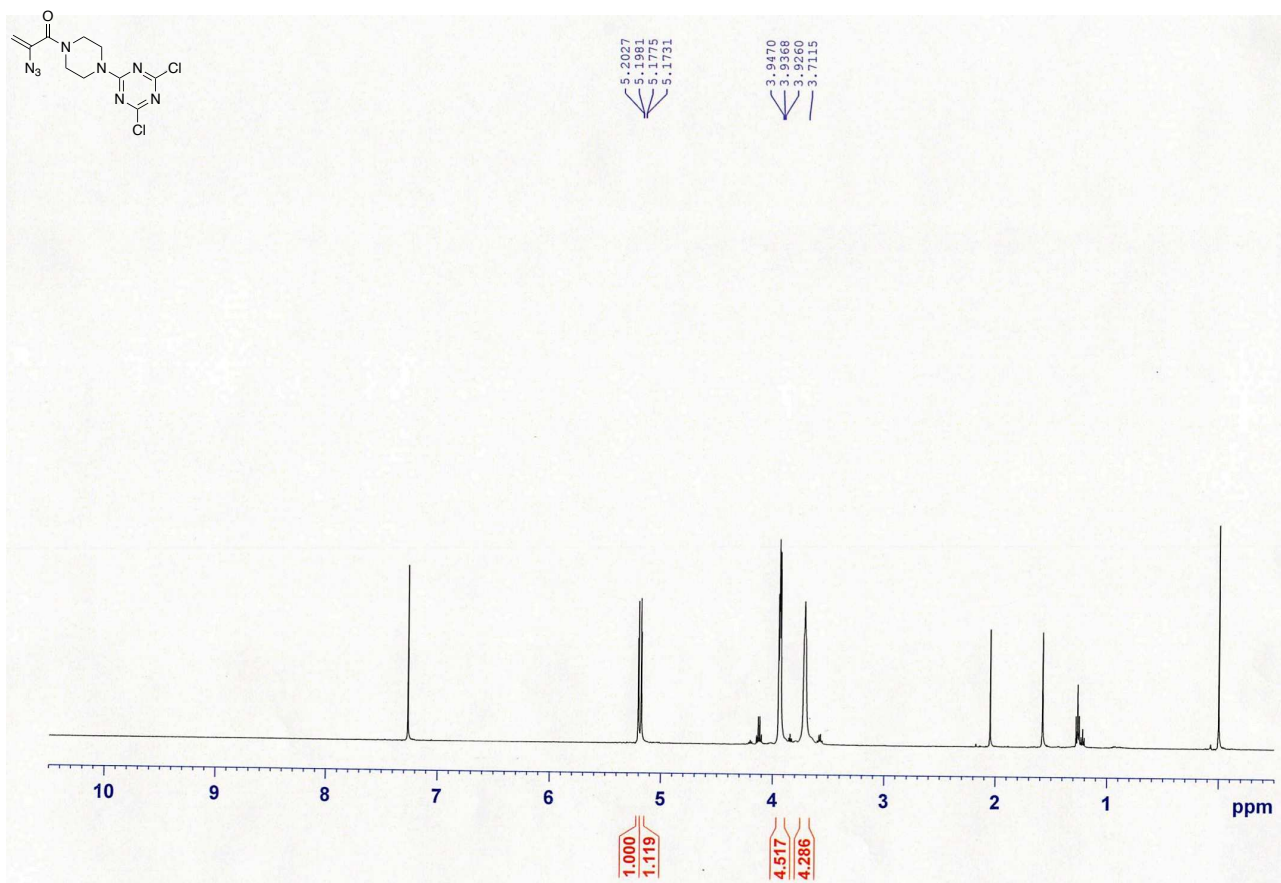
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 4-(2-azidoacryloyl)piperazine-1-carboximidamide (**9d**) (CDCl₃)



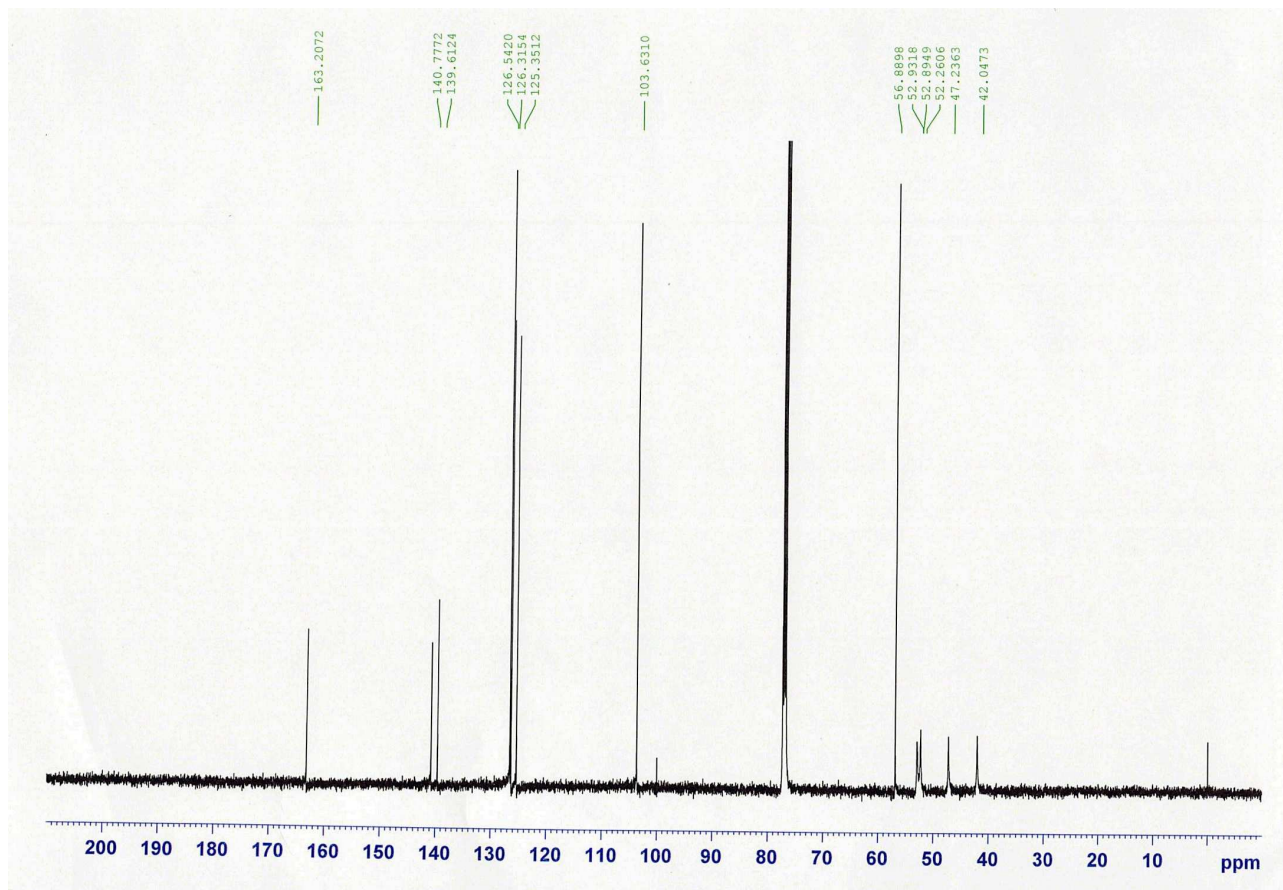
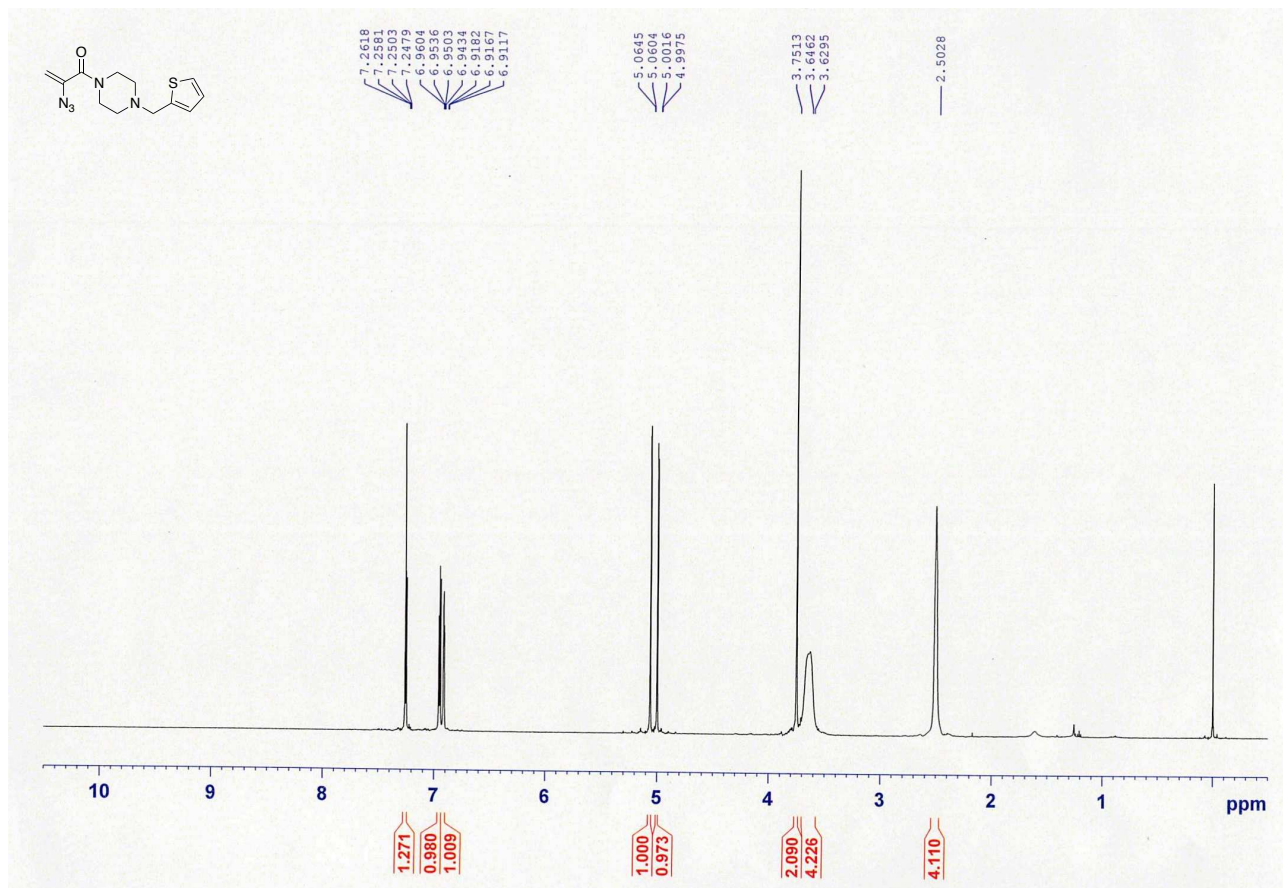
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of 2-azido-1-(4-(pyridin-3-ylsulfonyl)piperazin-1-yl)prop-2-en-1-one (**9e**) (CDCl_3)



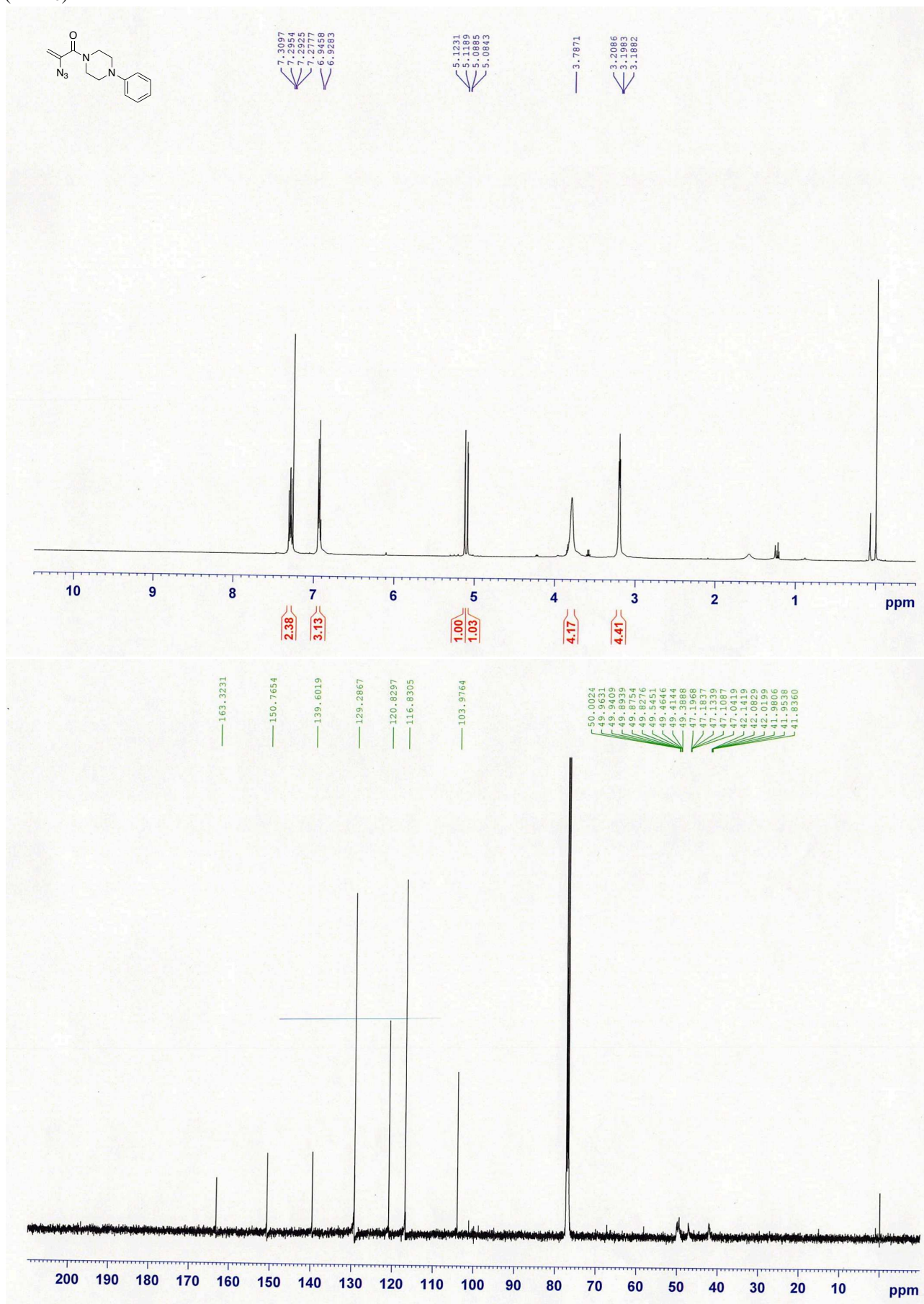
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 2-azido-1-(4-phenylpiperazin-1-yl)prop-2-en-1-one (**9f**) (CDCl₃)



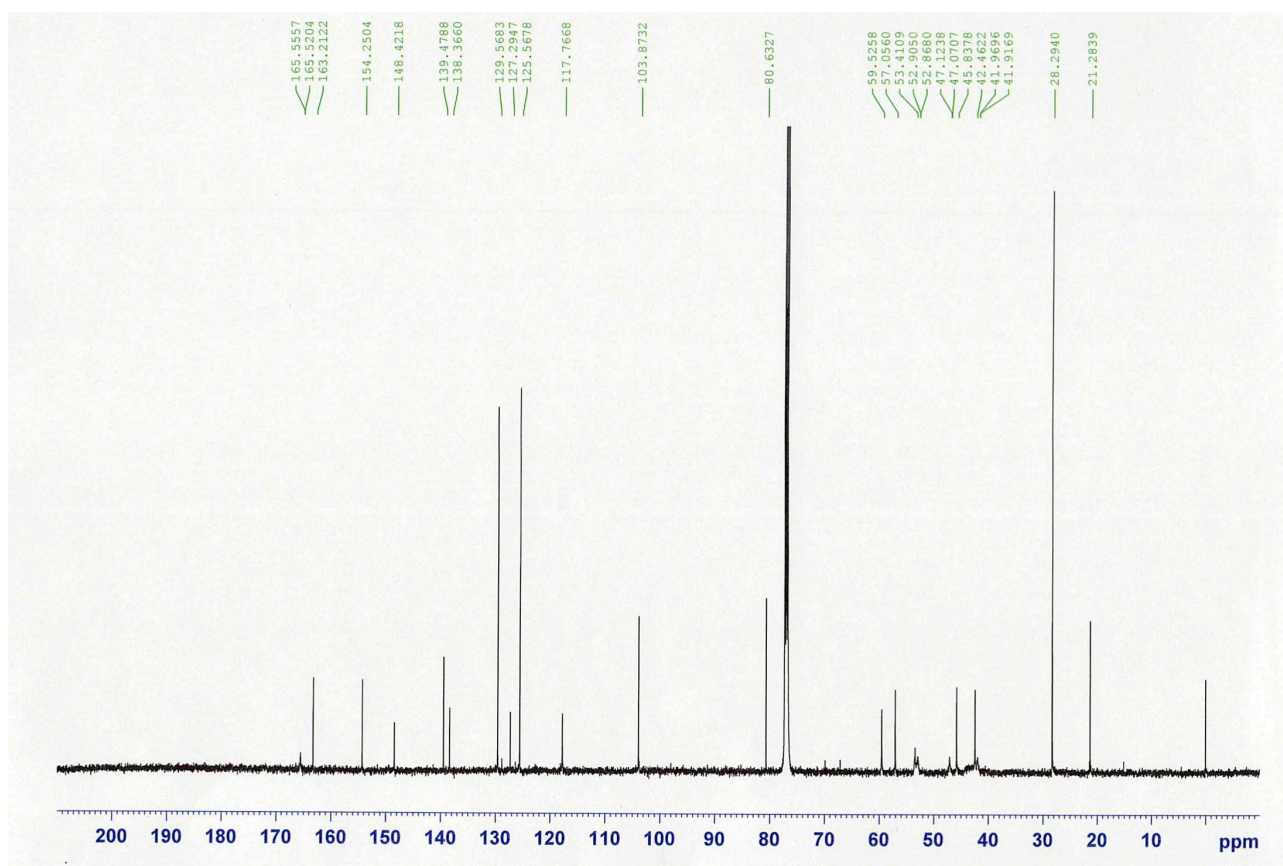
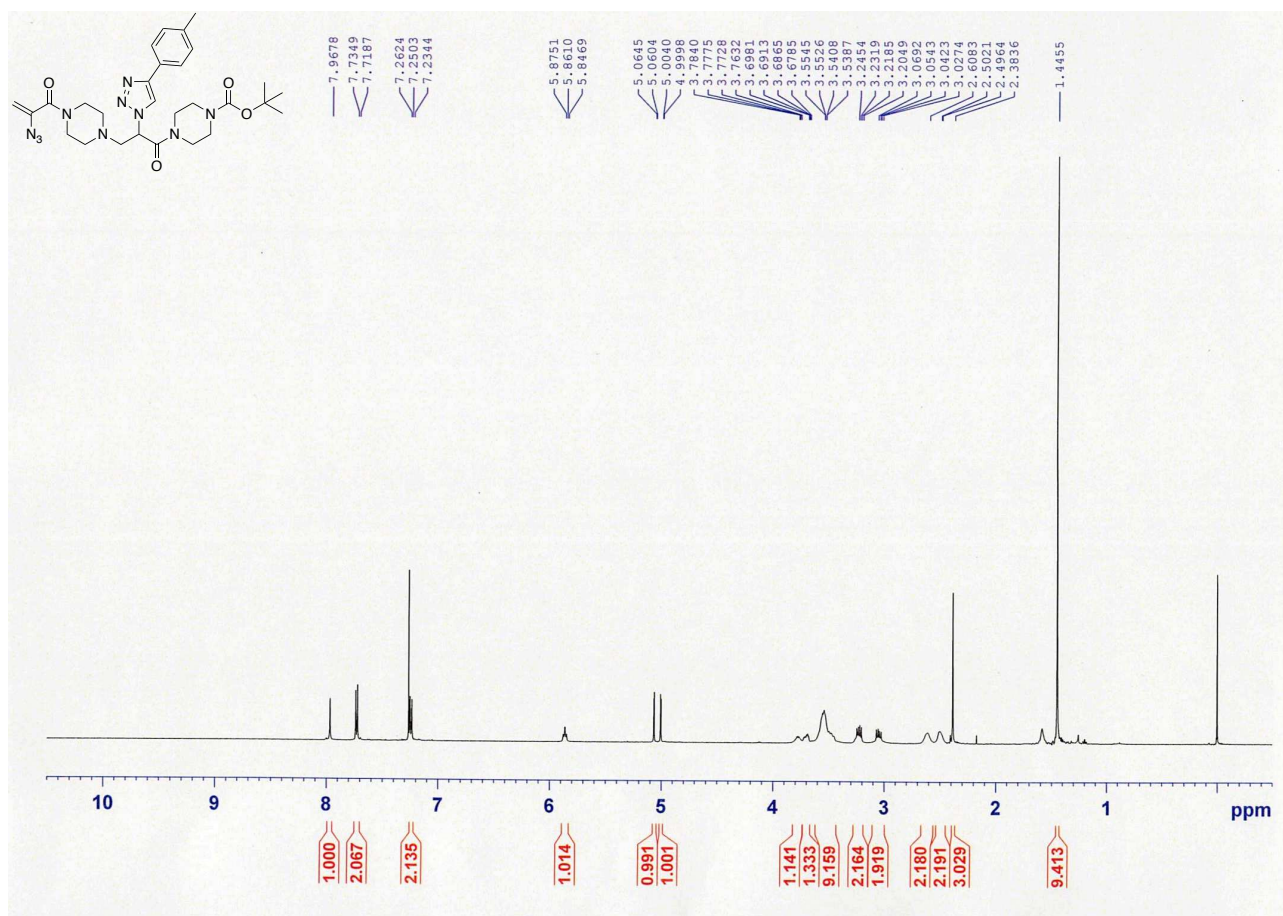
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 2-azido-1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)prop-2-en-1-one (**9g**) (CDCl₃)



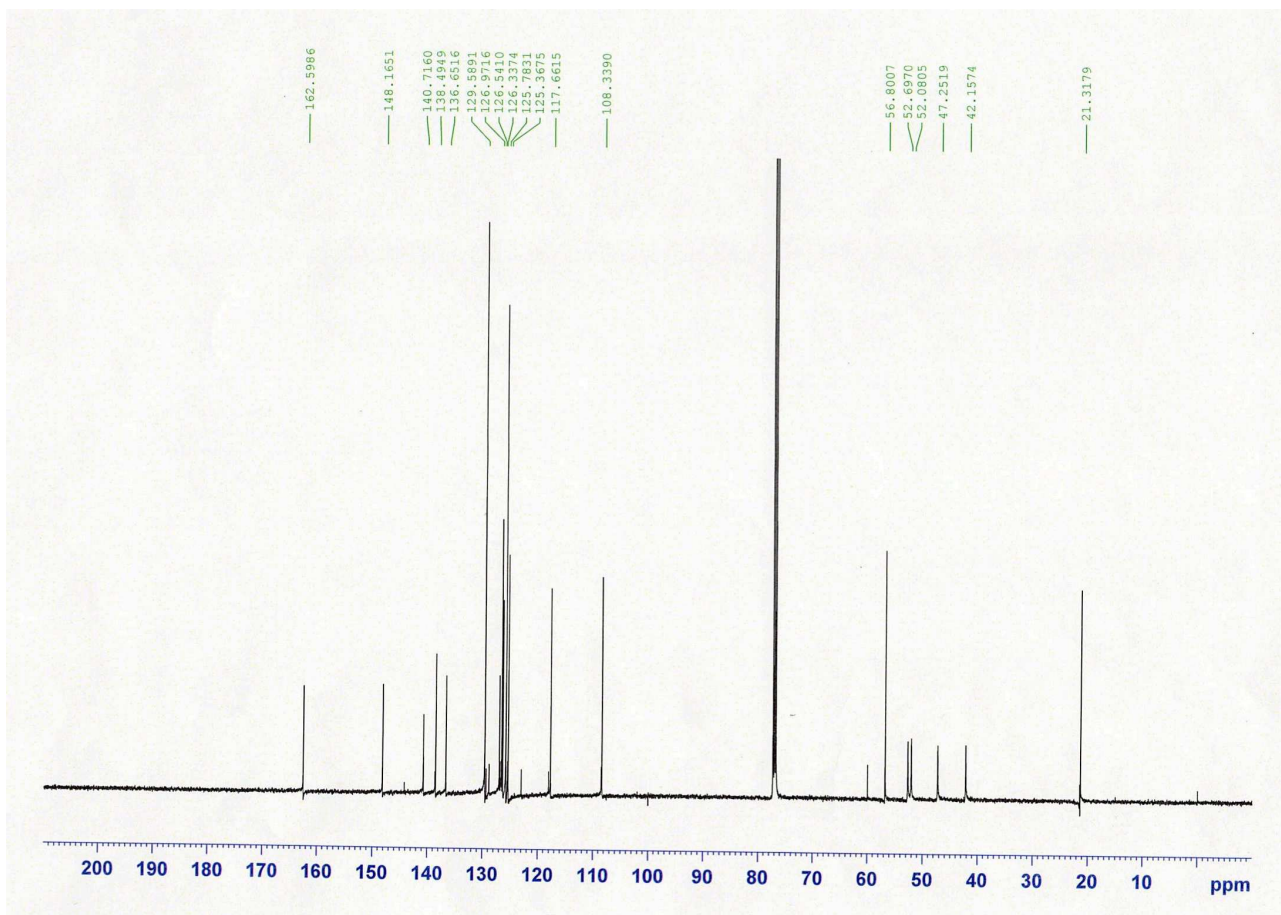
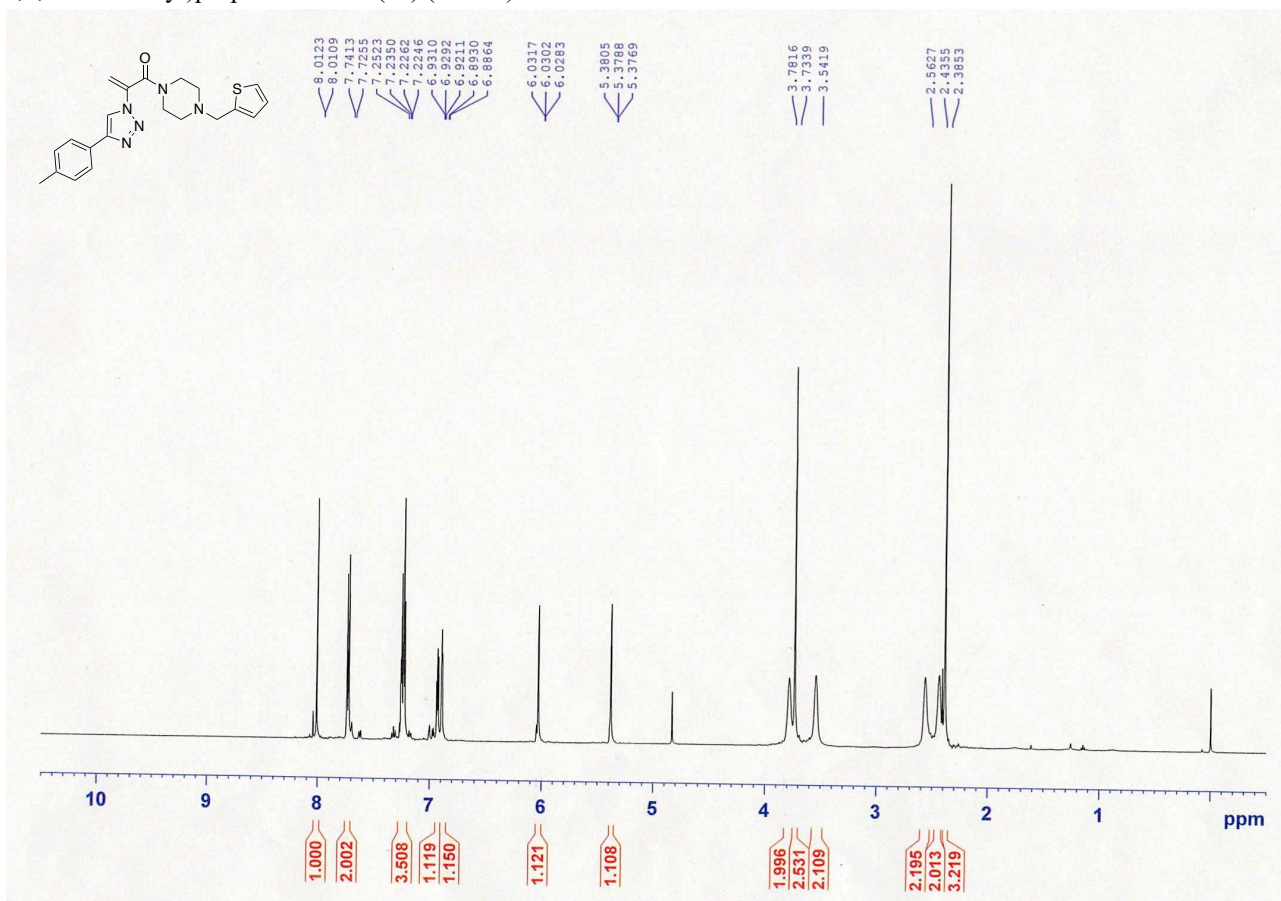
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 2-azido-1-(4-phenylpiperazin-1-yl)prop-2-en-1-one (**9h**) (CDCl₃)



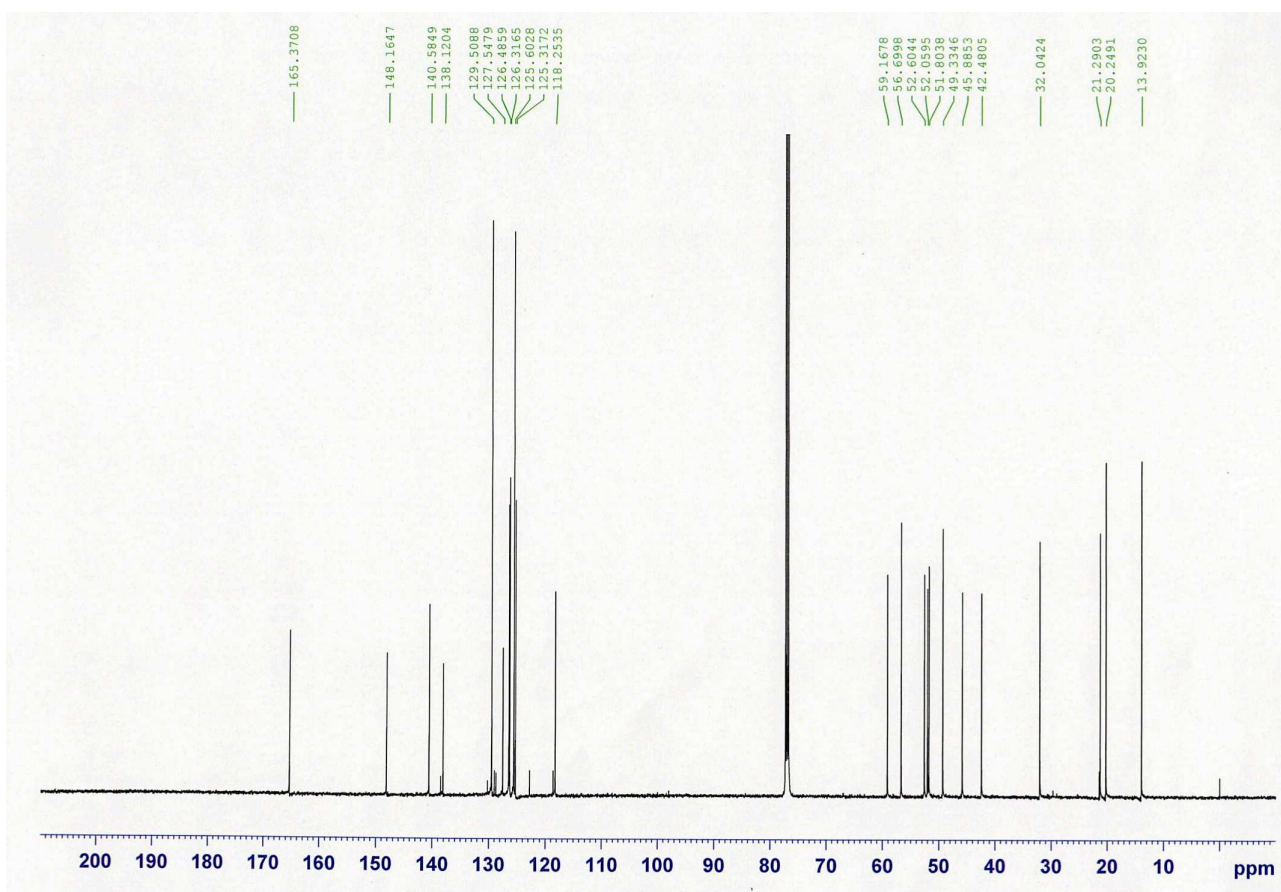
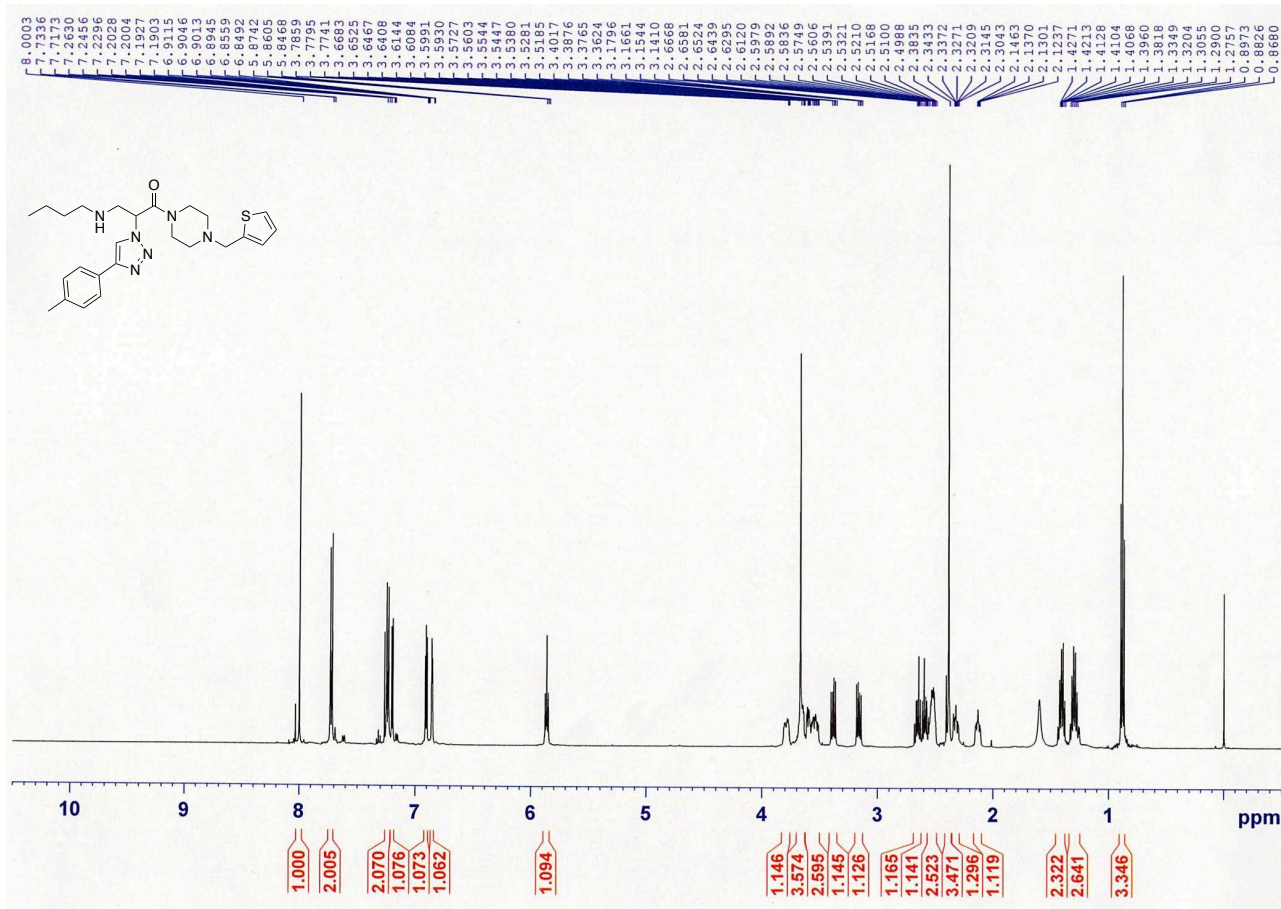
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of *tert*-butyl 4-(3-(4-(2-azidoacryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazine-1-carboxylate (**9i**) (CDCl_3)



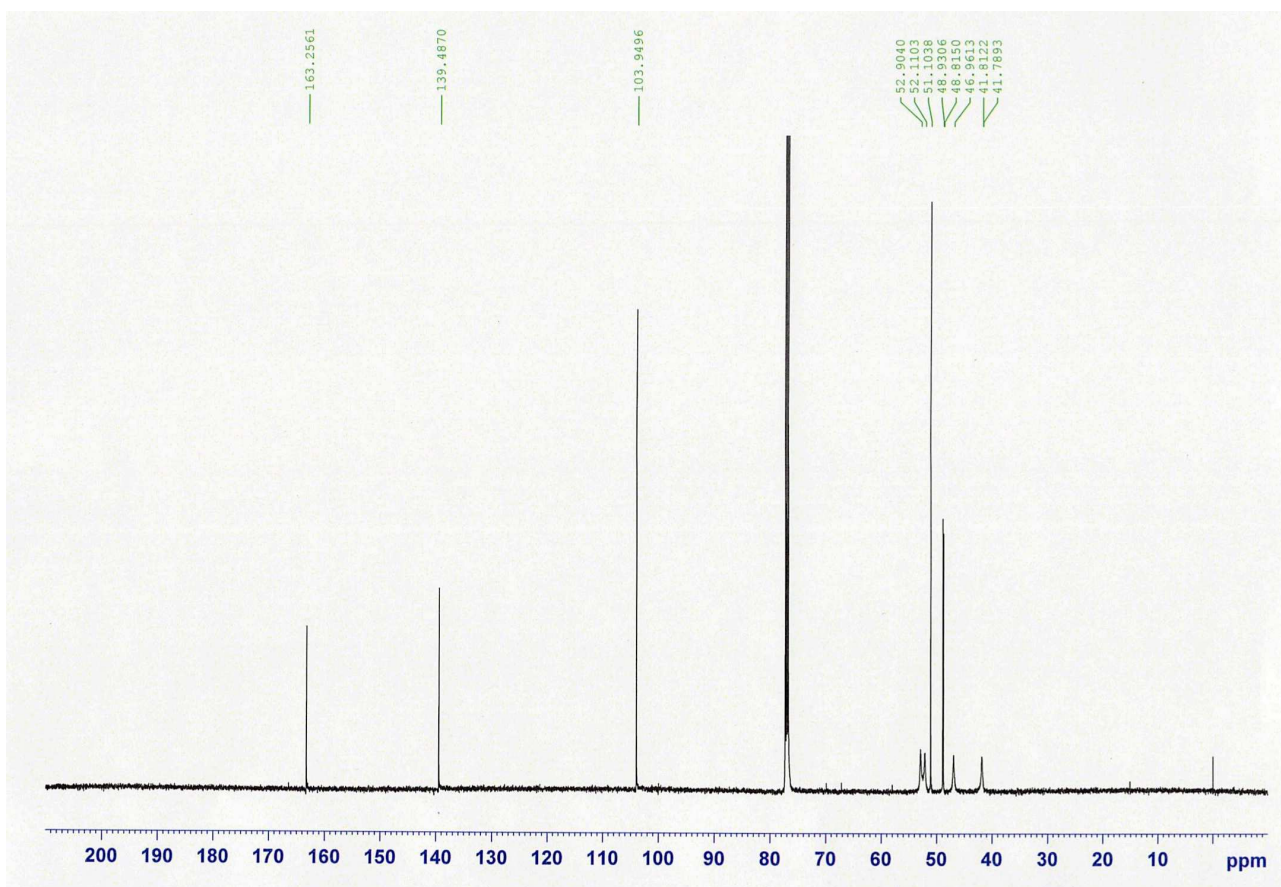
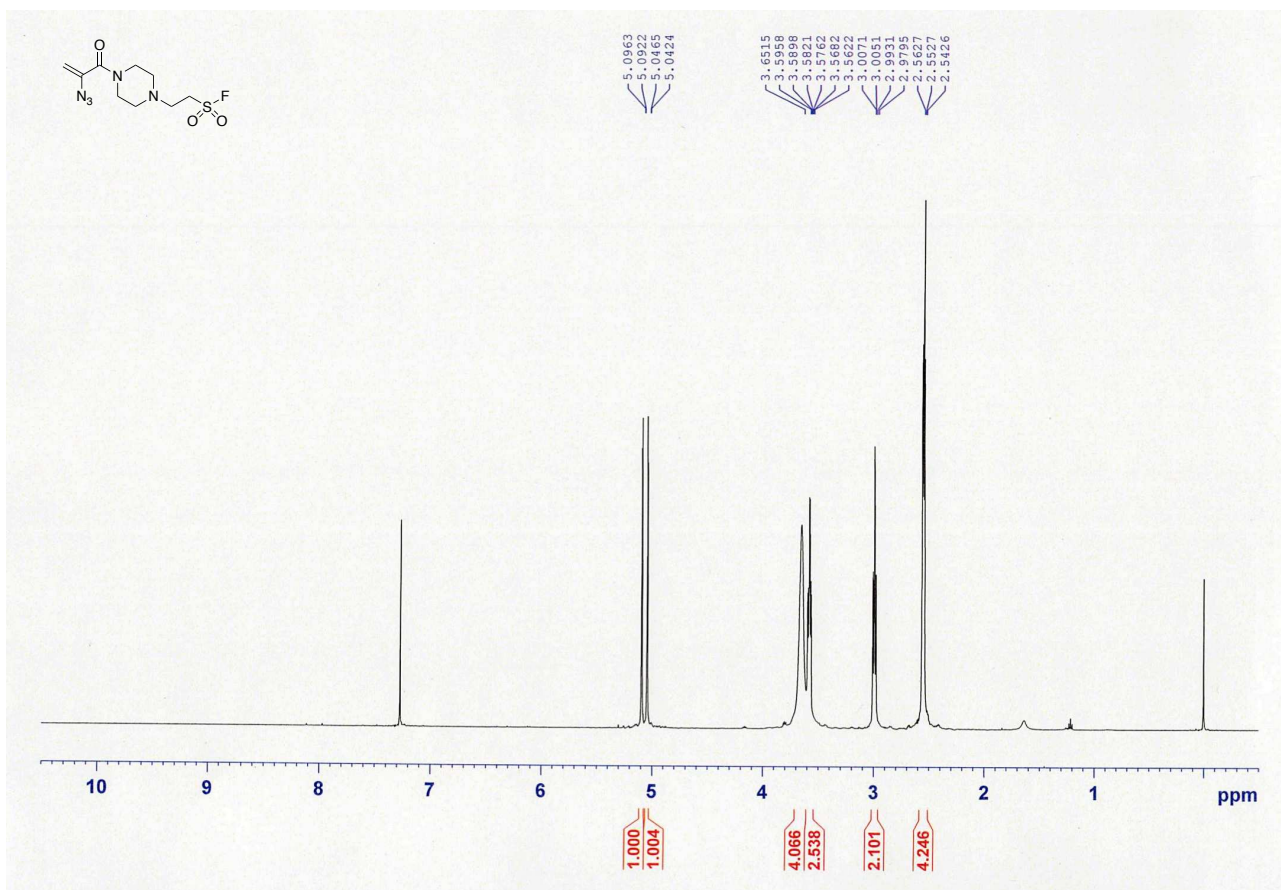
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)prop-2-en-1-one (**11**) (CDCl₃)



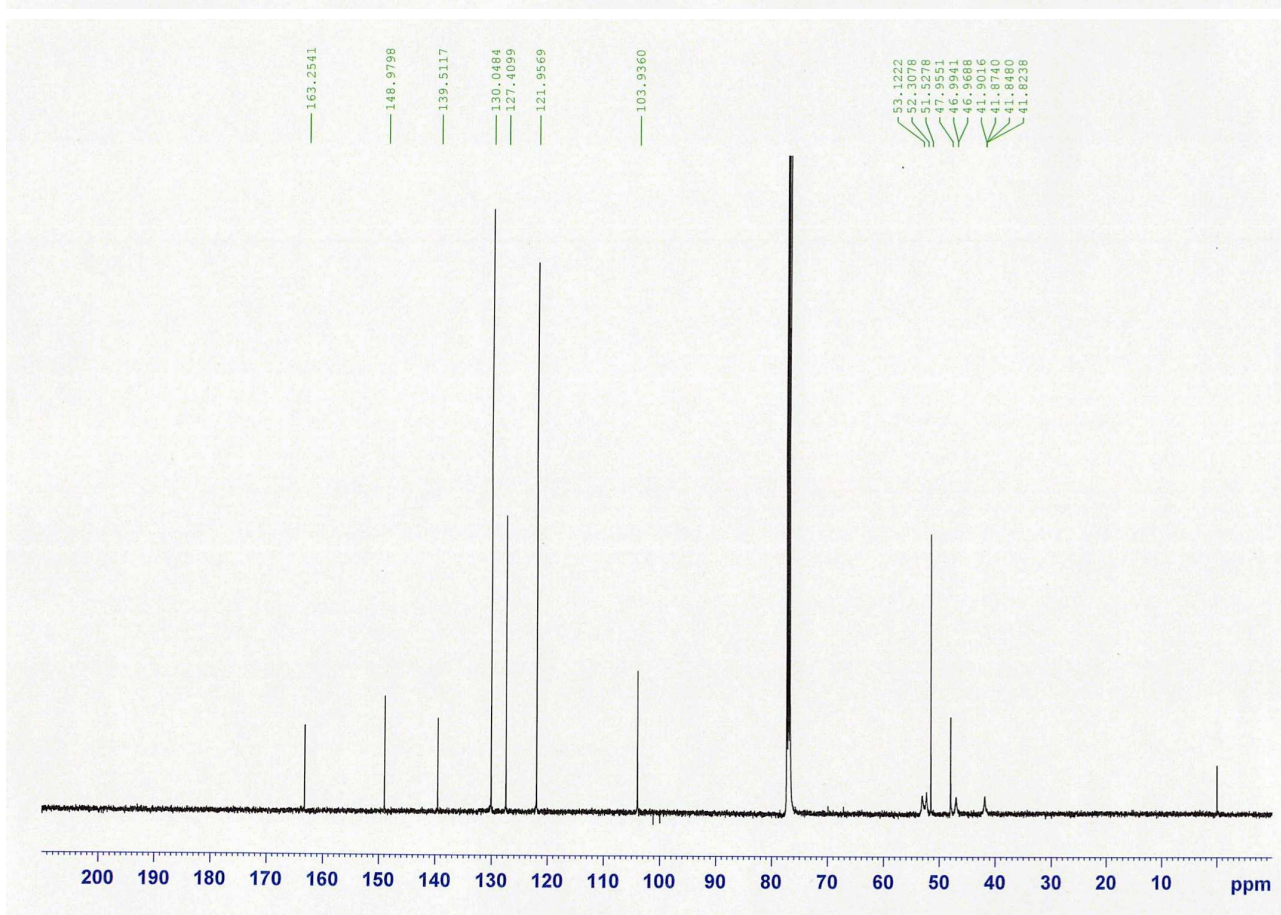
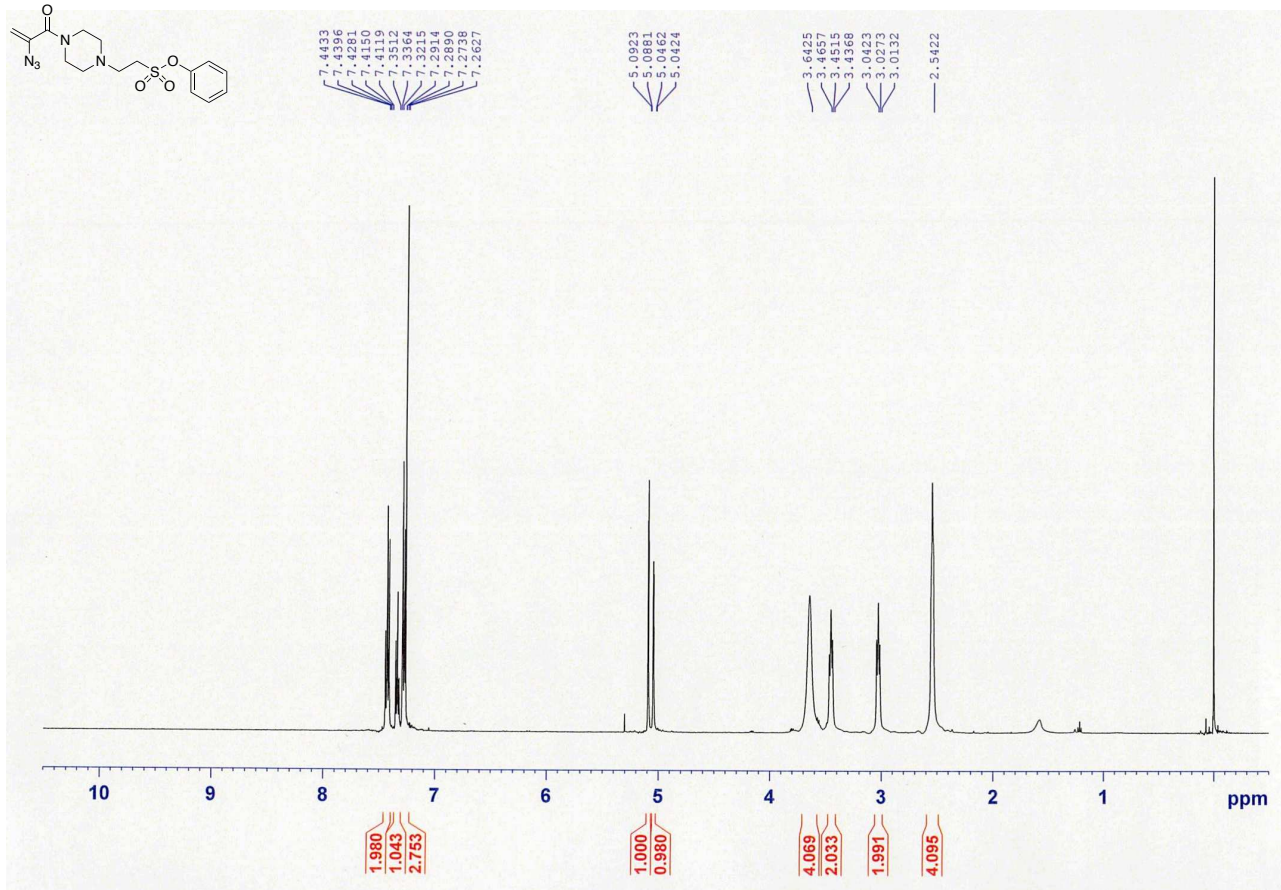
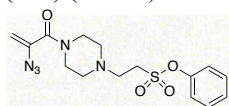
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 1-(4-(thiophen-2-ylmethyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)prop-2-en-1-one (13) (CDCl₃)



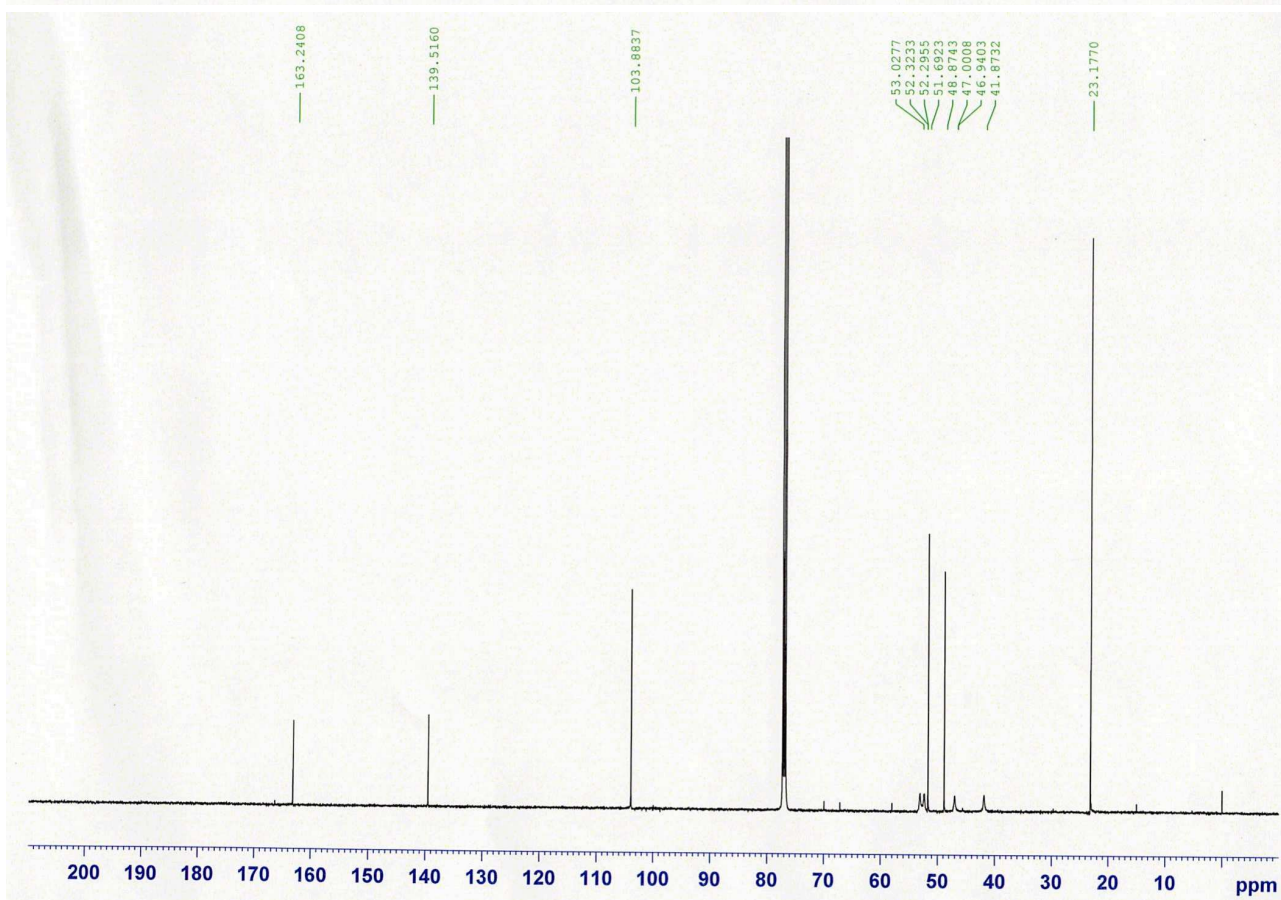
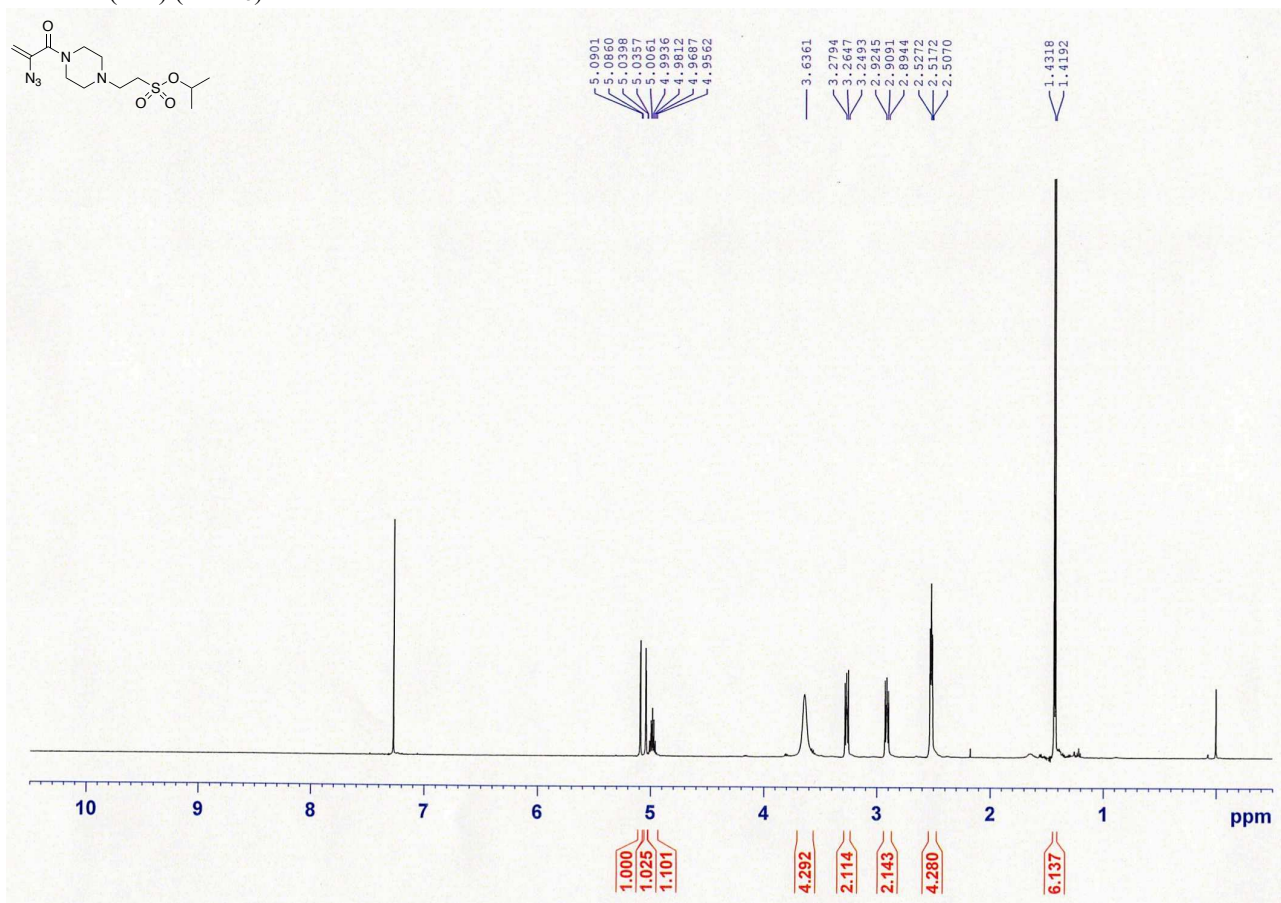
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**5a**) (CDCl₃)



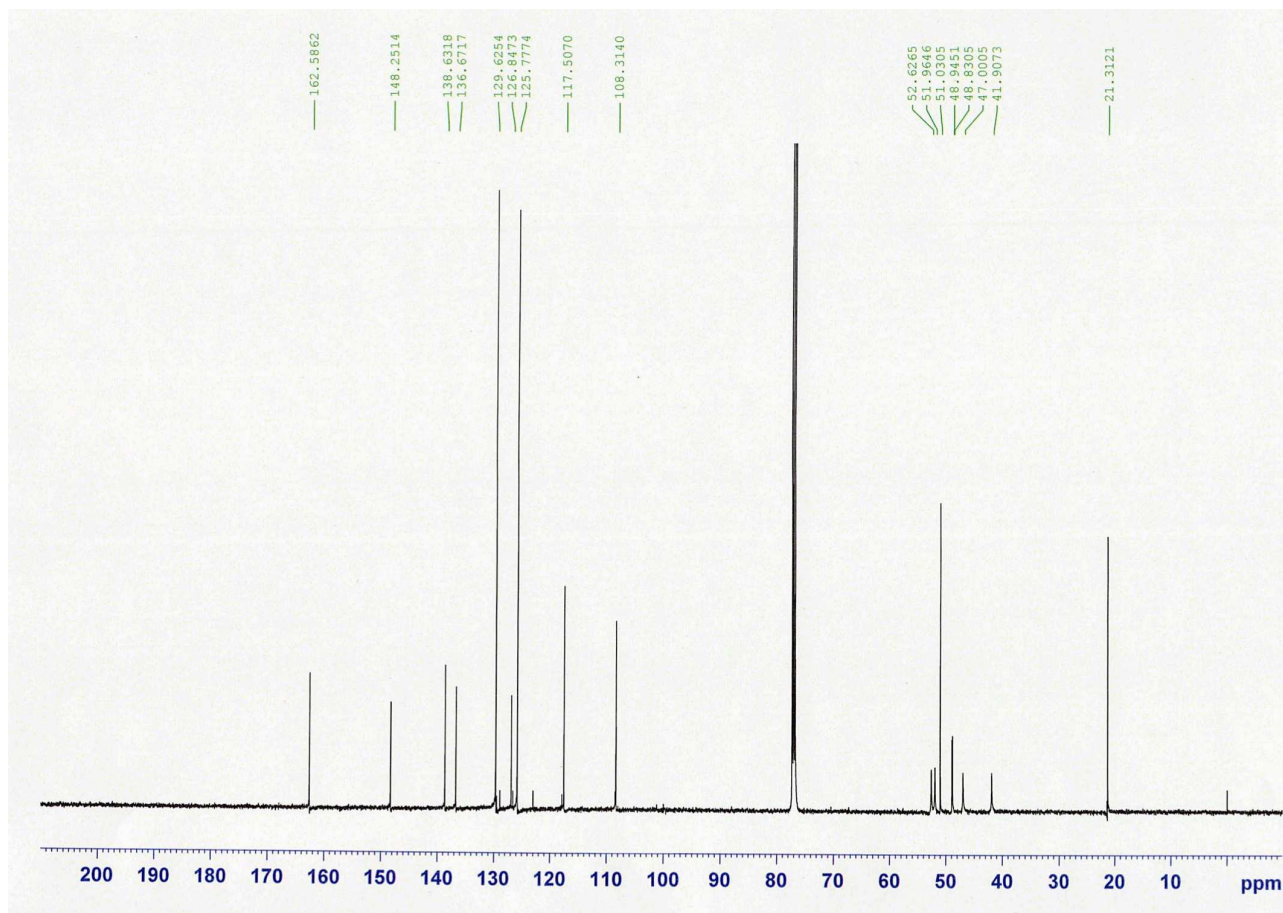
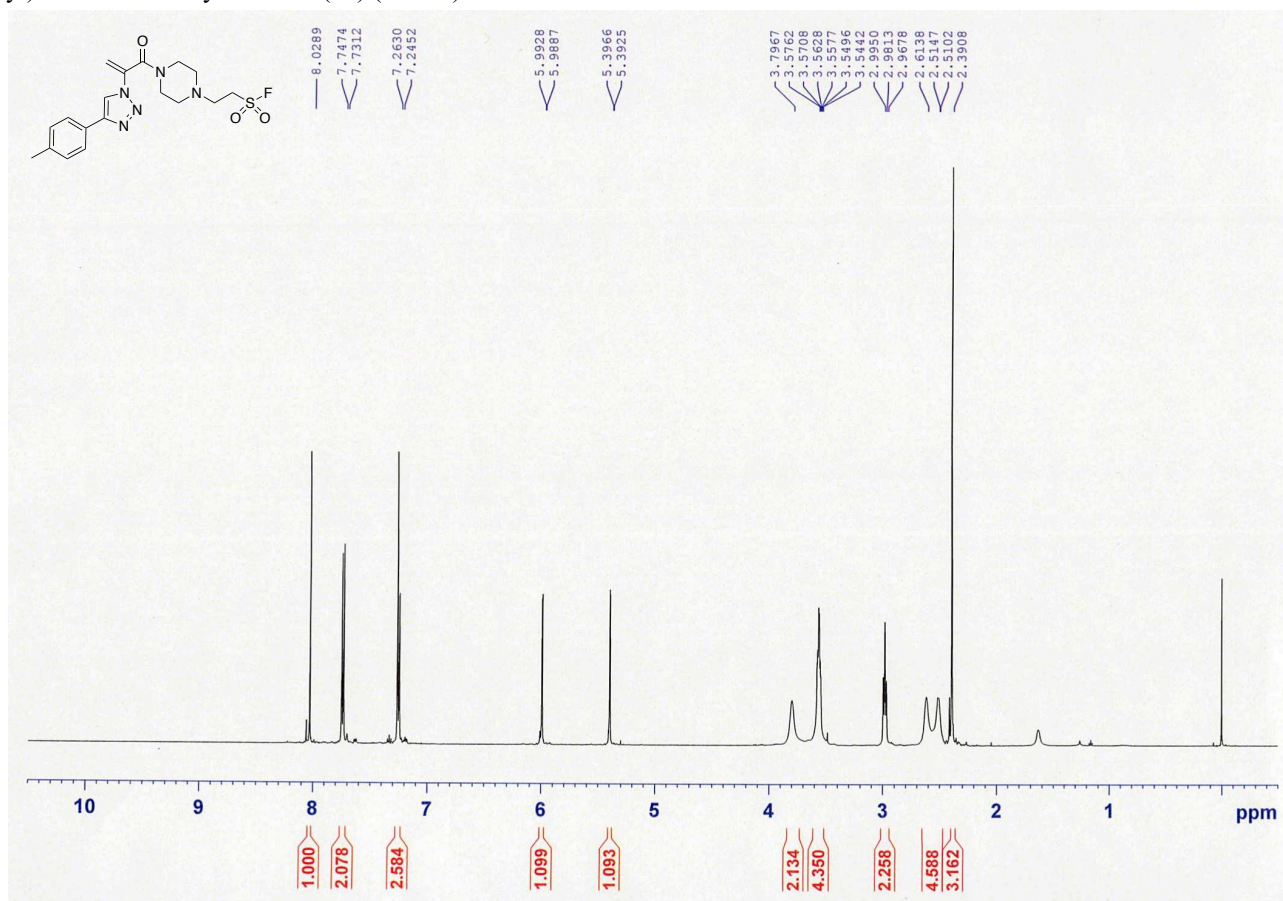
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of phenyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (**15a**) (CDCl₃)



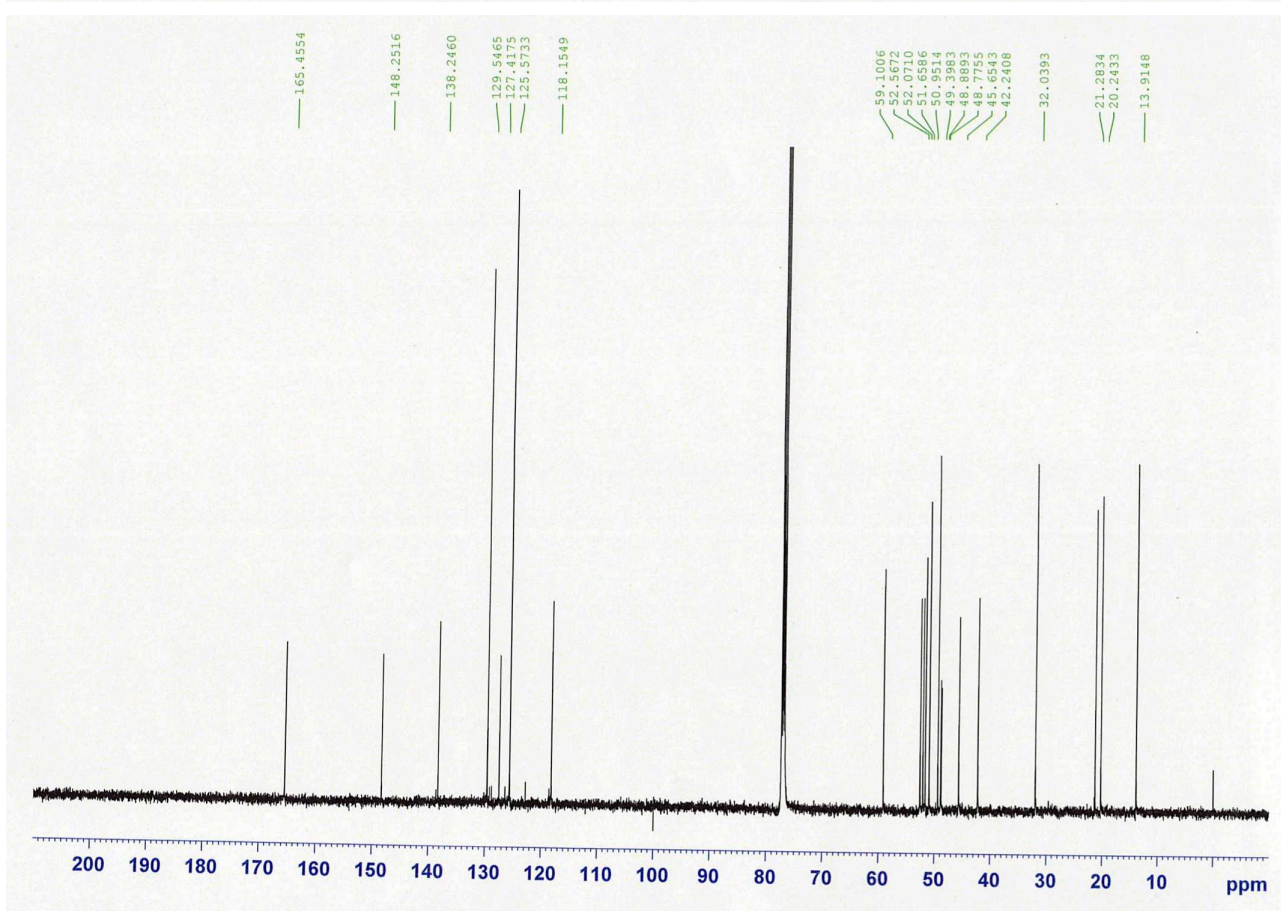
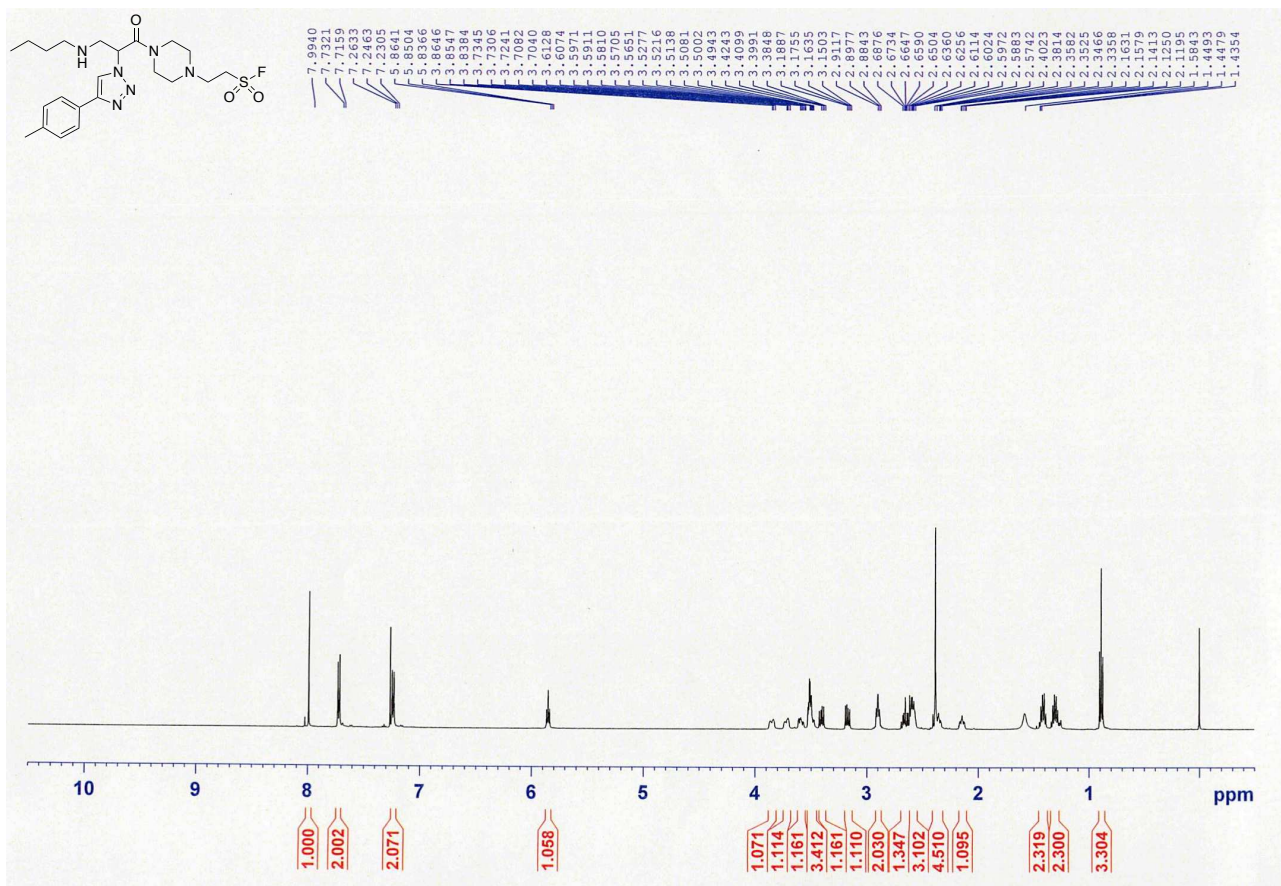
^1H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra of isopropyl 2-(4-(2-azidoacryloyl)piperazin-1-yl)ethane-1-sulfonate (**15b**) (CDCl_3)



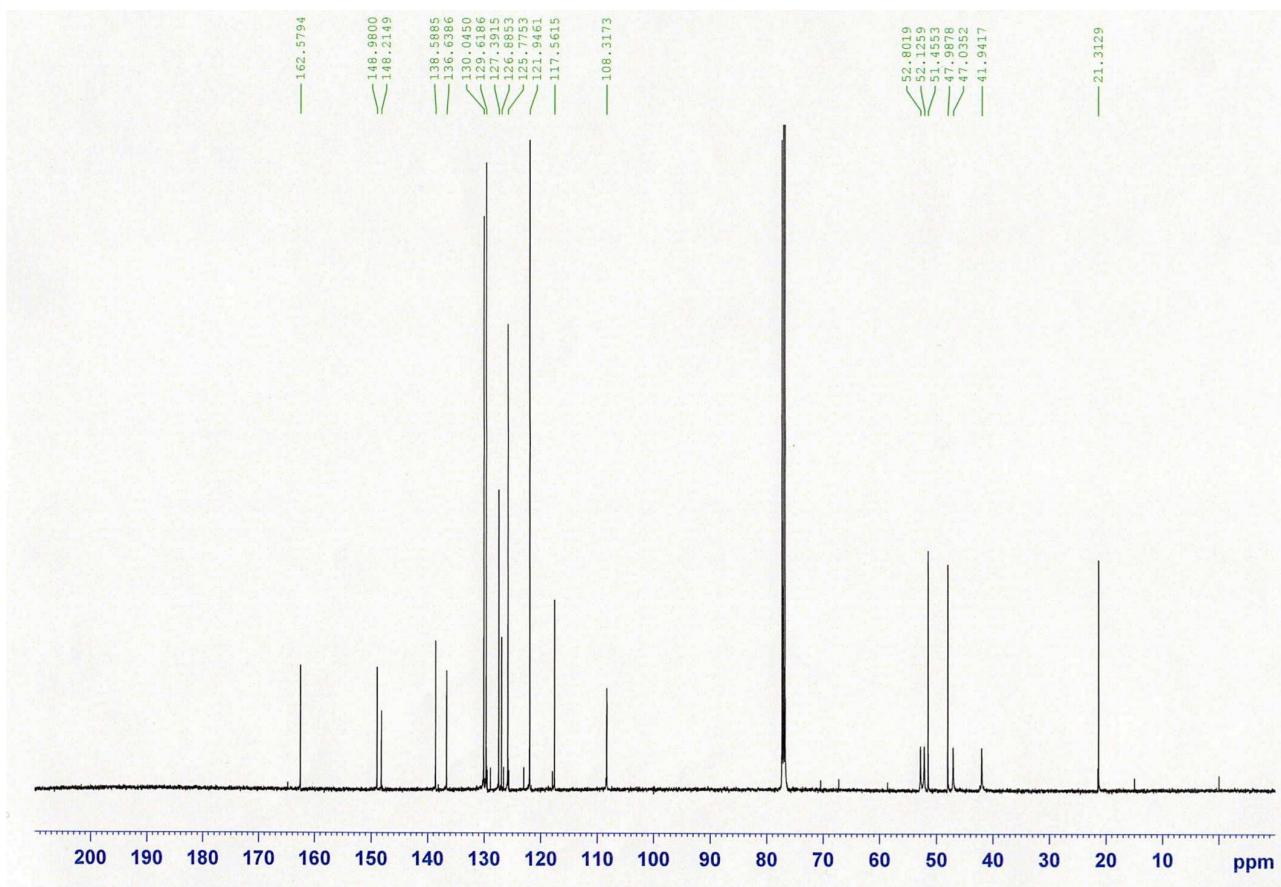
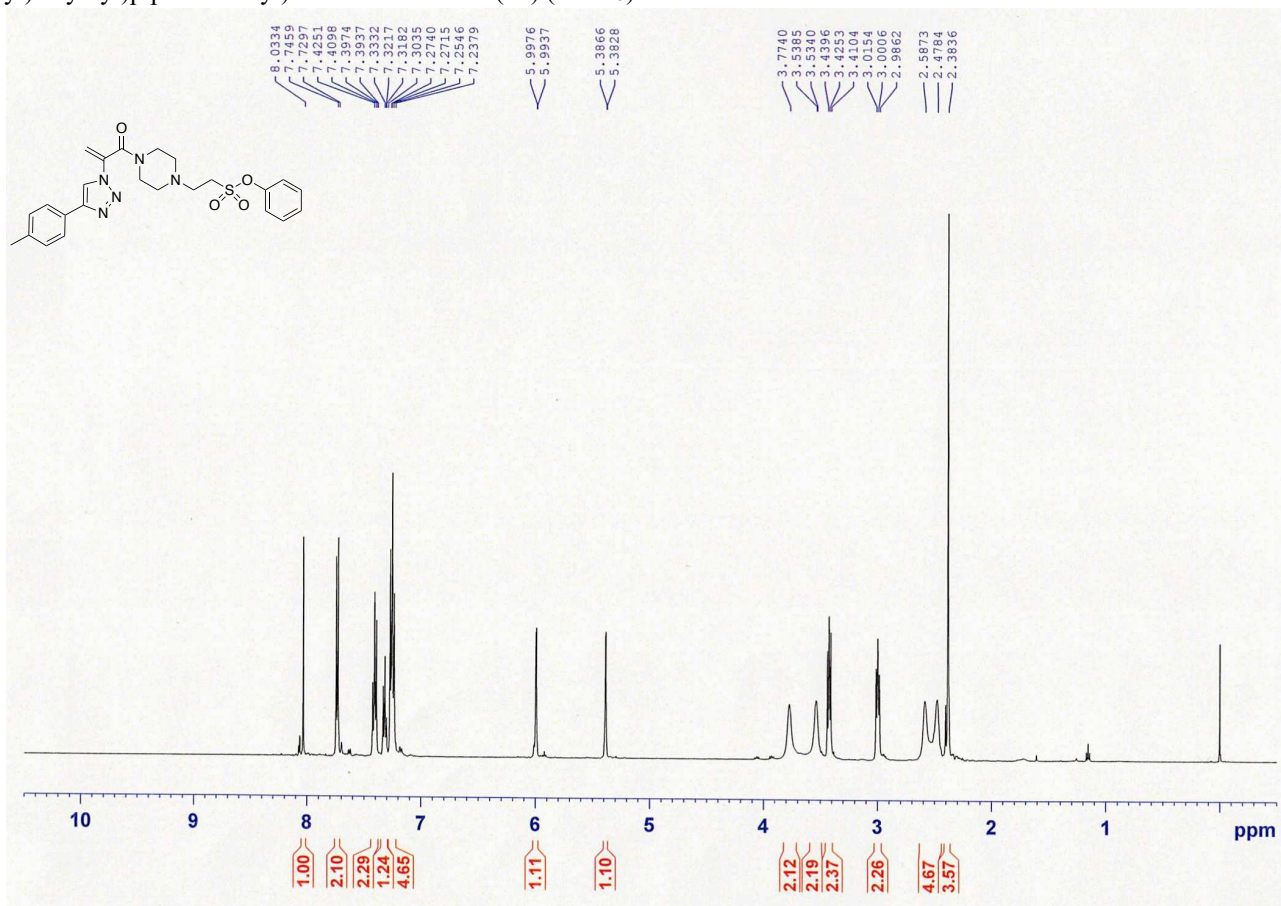
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 2-(4-(2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**17**) (CDCl₃)



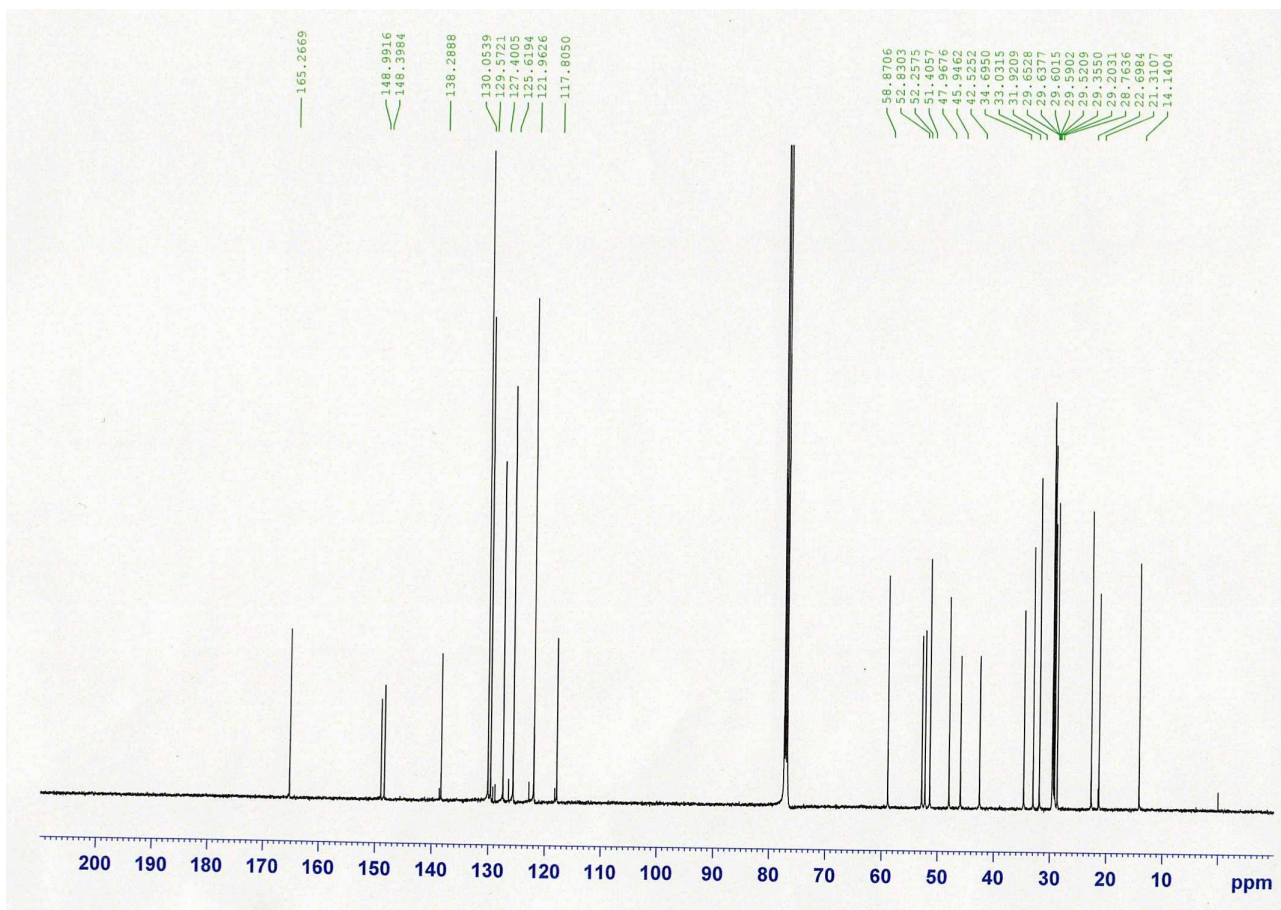
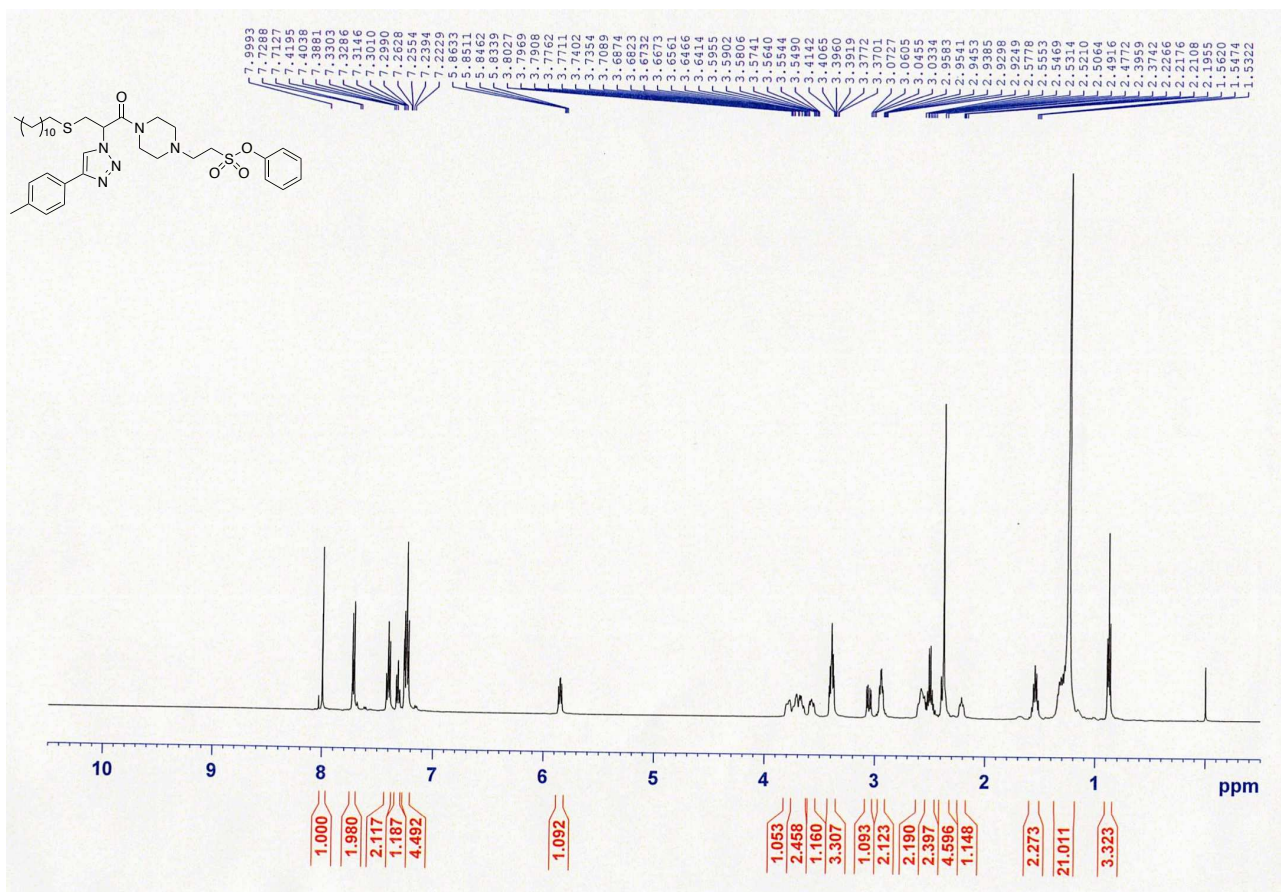
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of 2-(4-(3-(butylamino)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonyl fluoride (**18**) (CDCl₃)



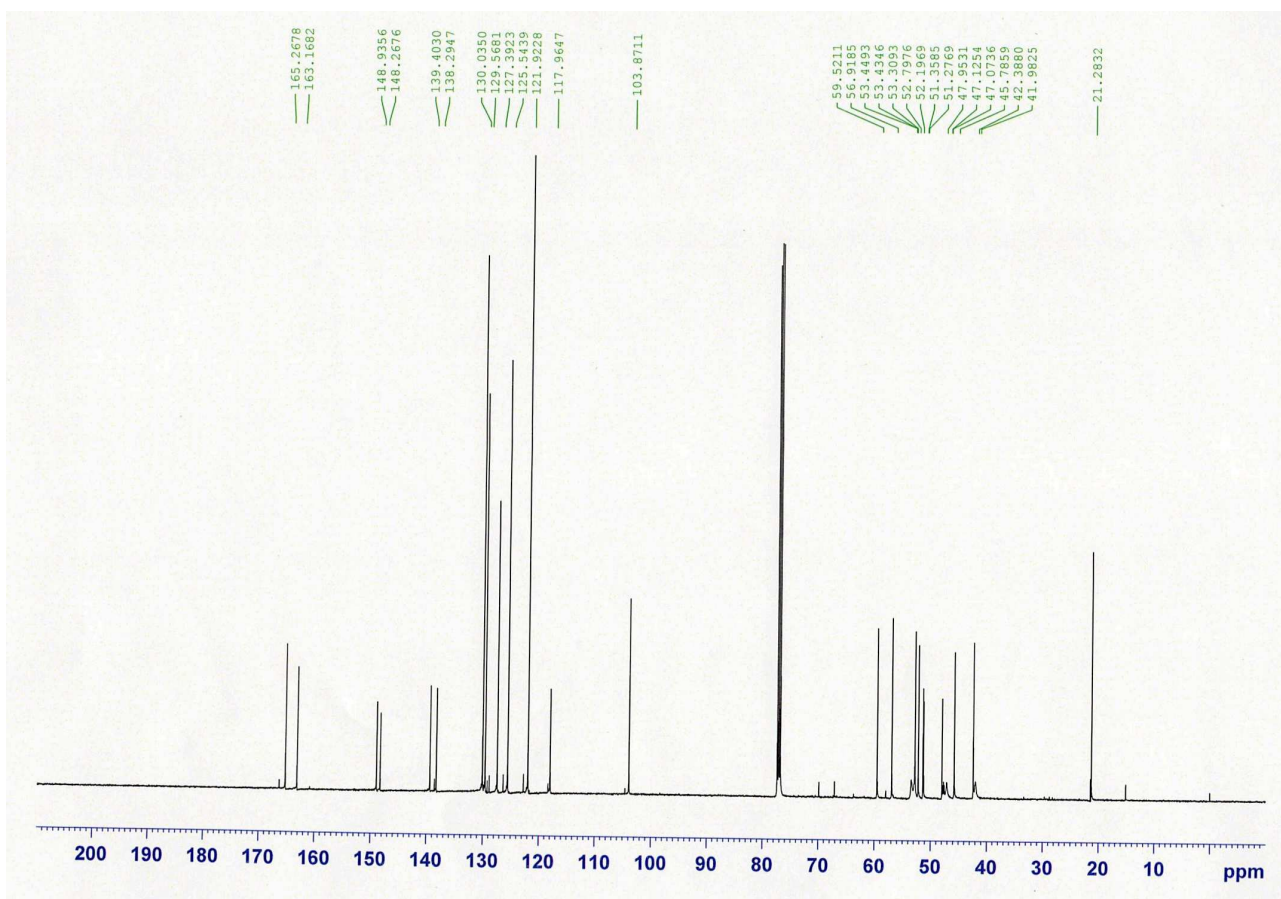
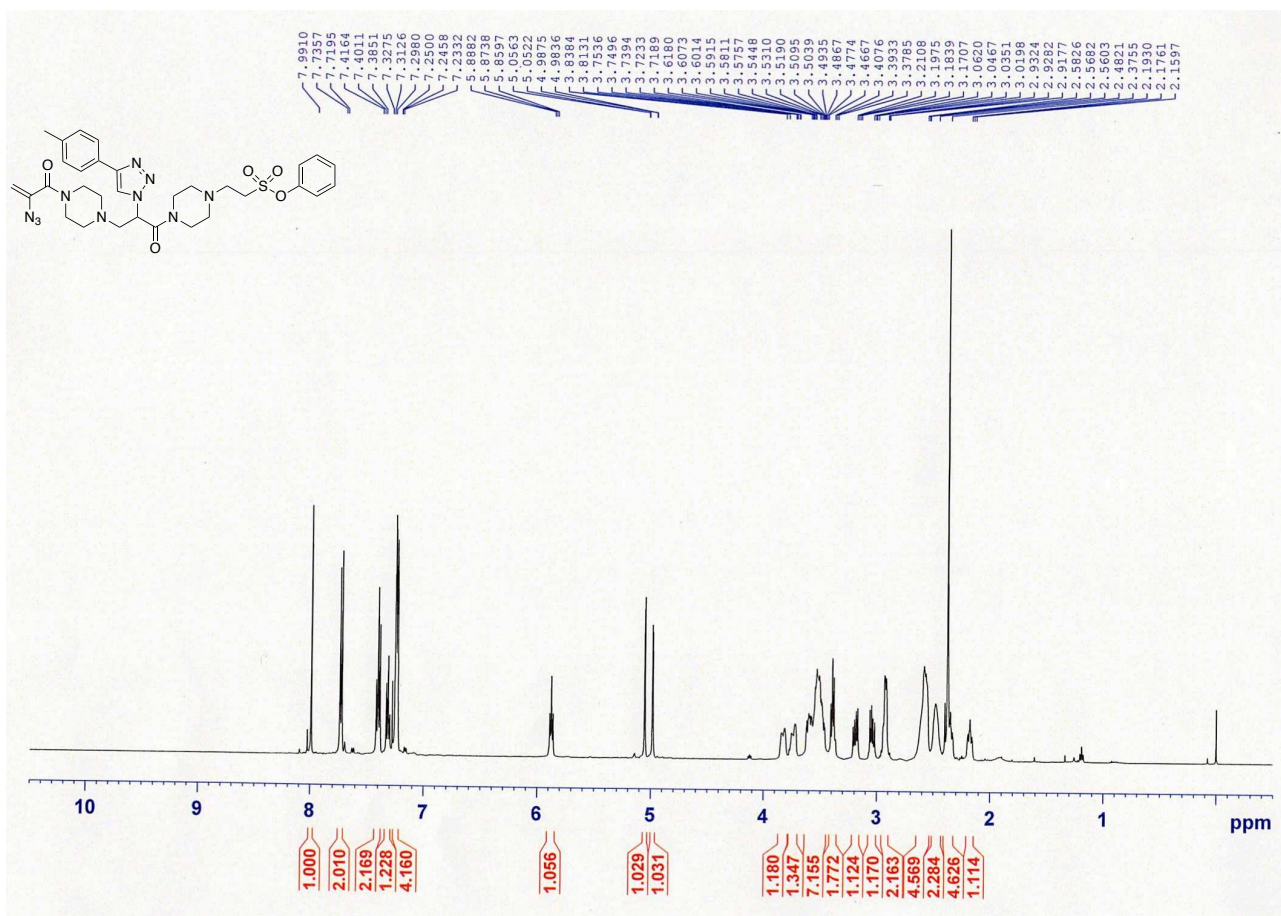
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of phenyl 2-(4-(2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)ethane-1-sulfonate (**19**) (CDCl₃)



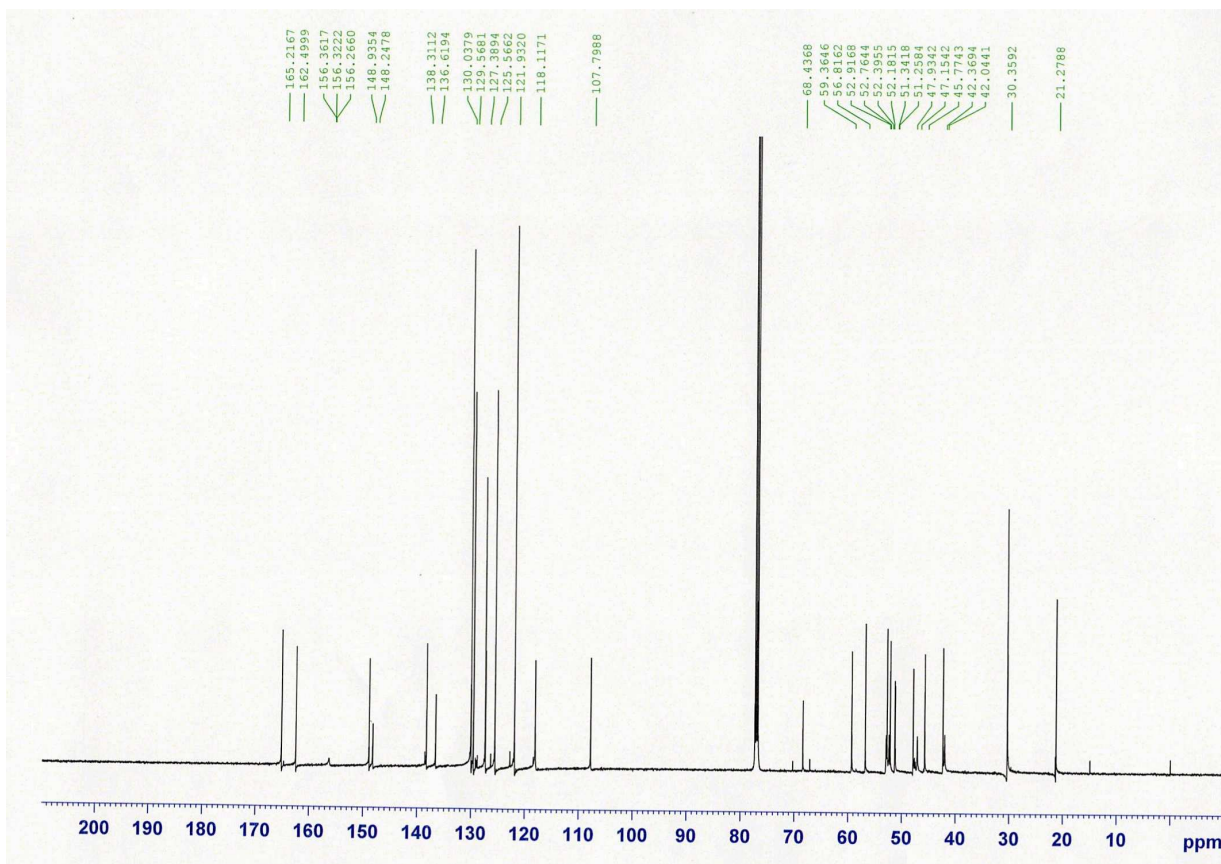
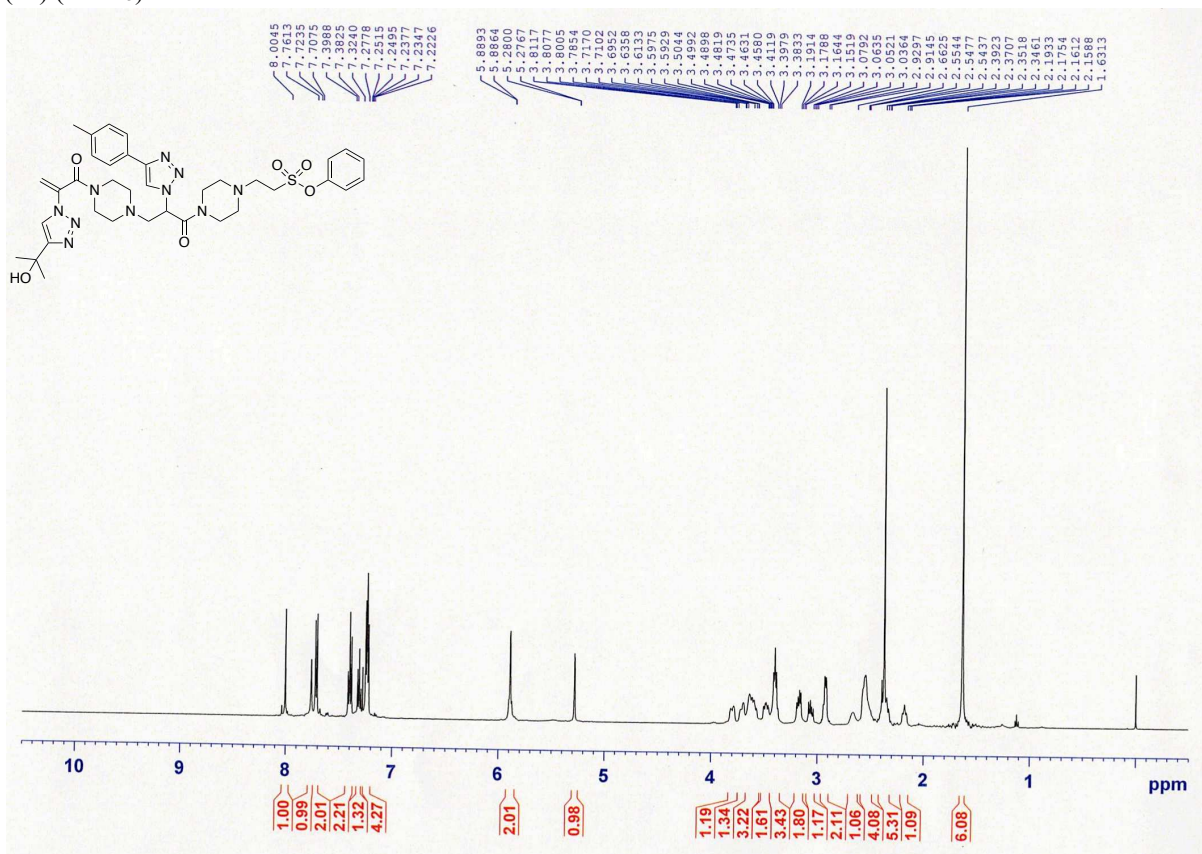
¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of phenyl 2-(4-(3-(dodecylthio)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**21**) (CDCl₃)



¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of phenyl 2-(4-(3-(4-(2-azidoacryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1*H*-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**22**) (CDCl₃)



¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of phenyl 2-(4-(3-(4-(2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)acryloyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**23**) (CDCl₃)



¹H NMR (500 MHz) and ¹³C NMR (126 MHz) spectra of phenyl 2-(4-(3-(4-(3-(butylamino)-2-(4-(2-hydroxypropan-2-yl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)-2-(4-(4-tolyl)-1H-1,2,3-triazol-1-yl)propanoyl)piperazin-1-yl)ethane-1-sulfonate (**24**) (CDCl₃)

