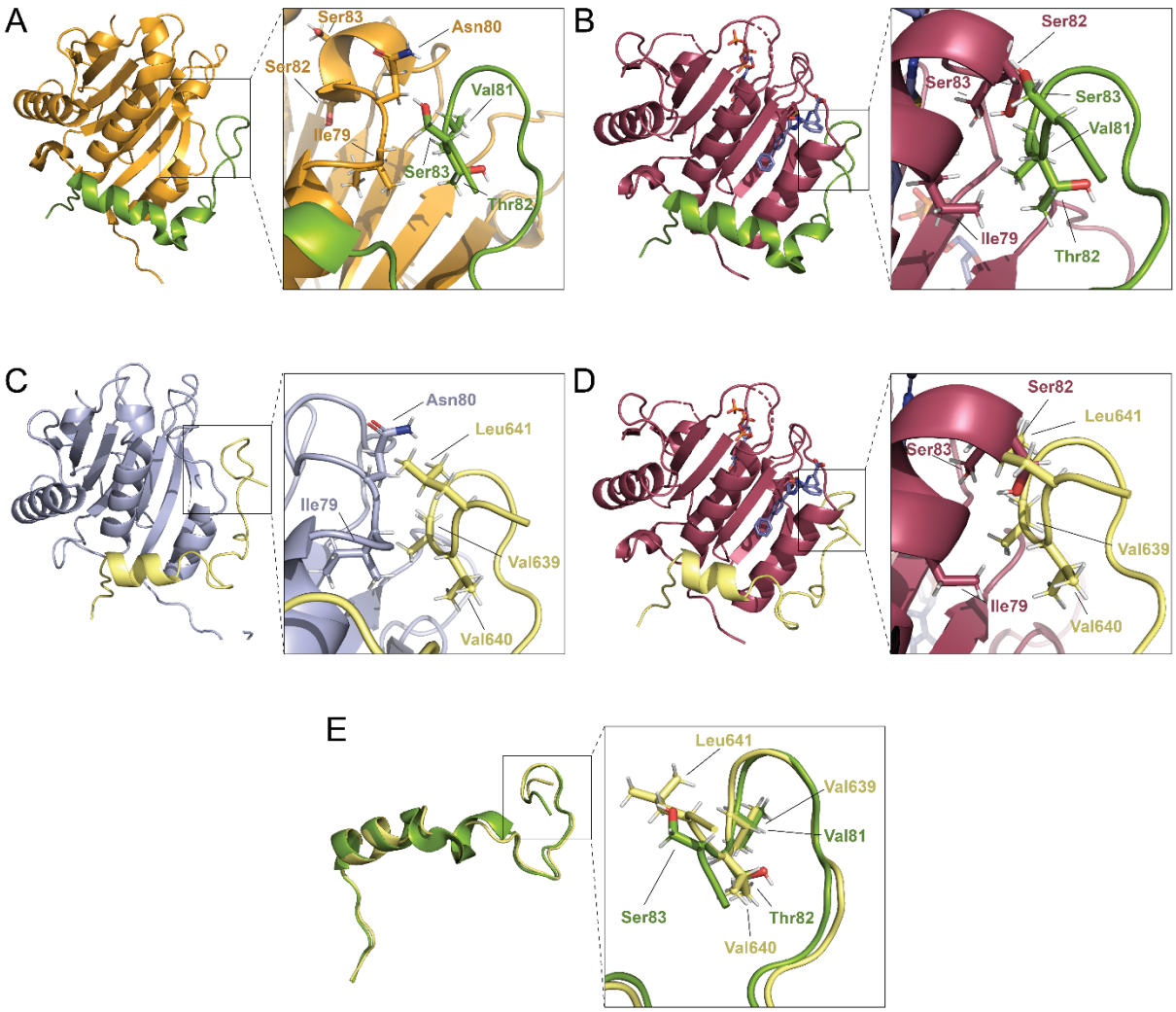
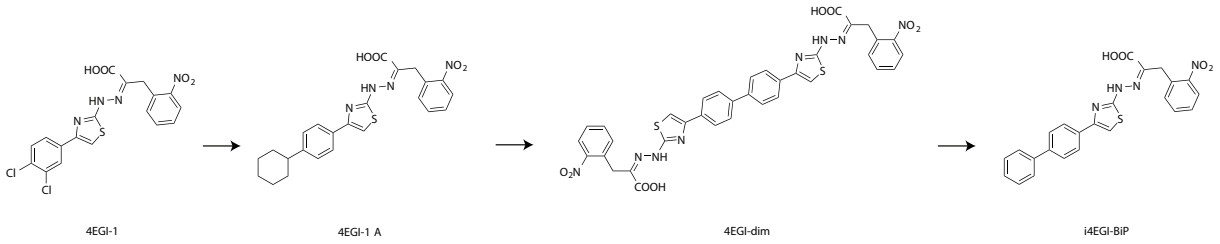
Supplementary Table 1 Data collection and refinement statistics

Source	APS Argonne National Laboratory
Wavelength	0.979180 Å
Resolution range	46.75 - 1.914 (1.983 - 1.914) Å
Space group	P 1 21 1
Unit cell	38.812 73.364 61.866 90 101.36 90
Total reflections	86728 (2621)
Unique reflections	25424 (1853)
Multiplicity	3.4 (1.4)
Completeness (%)	96.64 (70.35)
Mean I/sigma(I)	18.94 (2.91)
Wilson B-factor	17.85
R-merge	0.05771 (0.3349)
R-meas	0.06825 (0.4711)
R-pim	0.03603 (0.3309)
CC1/2	0.997 (0.788)
CC*	0.999 (0.939)
Reflections used in refinement	25416 (1853)
Reflections used for R-free	2000 (146)
R-work	0.1611 (0.2389)
R-free	0.2188 (0.3217)
CC(work)	0.962 (0.891)
CC(free)	0.927 (0.764)
Number of non-hydrogen atoms	3492
macromolecules	3117
ligands	99
solvent	276
Protein residues	370
RMS(bonds)	0.021
RMS(angles)	1.99
Ramachandran favored (%)	95.33
Ramachandran allowed (%)	3.85
Ramachandran outliers (%)	0.82
Rotamer outliers (%)	0.88
Clashscore	12.37
Average B-factor	25.39
macromolecules	24.77
ligands	29.47
solvent	31.00

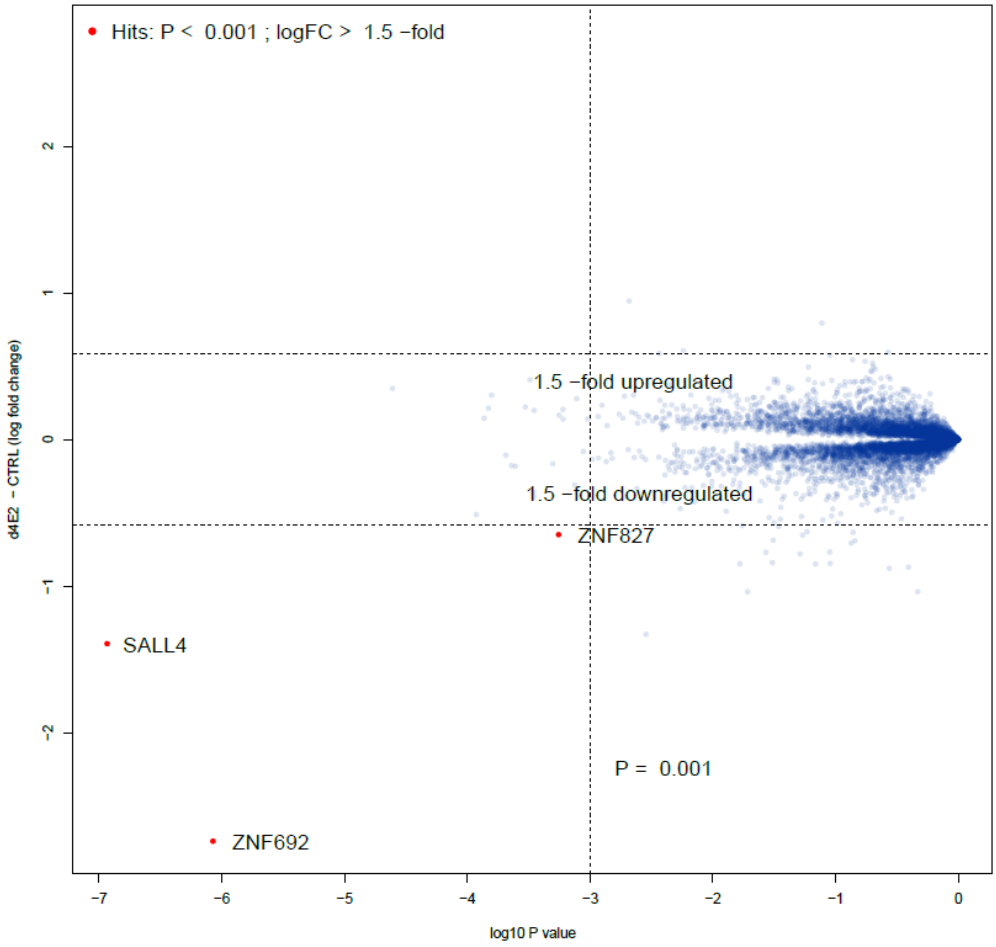
Supplementary Figure 1



Supplementary Figure 1 A. Structure of eIF4E bound to 4E-BP (pdb ID: 5BXV). eIF4E in orange and 4E-BP in green. **B.** Overlay of 4E-BP from 5BXV with the cocrystal structure of eIF4E bound to i4EG-BP (red). The extended helix with Ser82 and Ser83 of eIF4E is in proximity of the C-terminus of 4E-BP. **C.** Structure of eIF4E bound to eIF4G (pdb ID: 5T46). eIF4E in blue and eIF4G in yellow. **D.** Overlay of eIF4G from 5T46 with the cocrystal structure of eIF4E bound to i4EG-BP (red). Leu641 of eIF4G sterically clashes with the extended helix of eIF4E. **E.** Overlay of the binding modes of 4E-BP from 5BXV (green) and eIF4G from 5T46 (yellow). The structures superimpose almost perfectly identical, with the difference being the longer side chain of Leu641 from eIF4G compared to its counterpart Ser83 of 4E-BP.



Supplementary Figure 2: Evolution of the i4EG-BiP scaffold from 4EGI-1



Supplementary Figure 3: Scatterplot depicting the relative fold change in abundance of proteins following a 5-hour treatment of Kelly cells with 1 μM of d4E2 compared to DMSO vehicle control treatment. Significant changes were assessed using limma's moderated t-test (Ritchie et al., 2015), with log2 fold change displayed on the y-axis and negative log10 p-value on the x-axis (n=1 independent replicate for d4E2 and n=3 independent replicate for DMSO control).

Protein-related abbreviations and acronyms	
4E- BP	4E-binding protein (Inhibits translation by binding to eIF4E and preventing eIF4G from binding)
BET	Bromo- and Extra-Terminal domain
CRBN	Cereblon (Substrate recognition component of a DCX E3 protein ligase)
eIF4A	eukaryotic translation initiation factor 4A (helicase that unwinds secondary structure in the 5'UTR)
eIF4B	eukaryotic translation initiation factor 4B
eIF4E	eukaryotic translation initiation factor 4E (cap binding protein)
eIF4F	eukaryotic translation initiation factor 4F (complex of eIF4E, eIF4A and eIF4G)
eIF4G	eukaryotic translation initiation factor 4G (scaffold protein)
GFP	green fluorescent protein
mTORC	mammalian target of rapamycin complex
RFP	red fluorescent protein

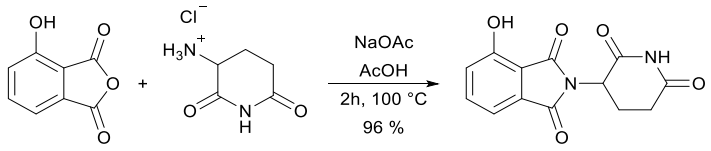
Chemistry related abbreviations	
Ac	Acetyl
Ac_2O	acetic anhydride
Bn	Benzyl
Boc	tert-butoxycarbonyl
CBz	benzyloxycarbonyl
EtOH	ethanol
HOAc	acetic acid
m^7GDP	7-methyl guanosine diphosphate
m^7GTP	7-methyl guanosine triphosphate
Me_2CO	acetone
NaOAc	sodium acetate
PEG	polyethylene glycol
PROTAC	proteolysis targeted chimera
*t*BuOAc	*tert*-butyl acetate

Other abbreviations	
5'-UTR	5'-untranslated region
CS-BLI	Compartment-Specific Bioluminescence Imaging
CSP	chemical shift perturbation
FP	fluorescence polarization
IRES	internal ribosomal entry site

Supplemental Table 2: List of acronyms and abbreviations used in the manuscript.

Chemistry

2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione



3-Hydroxyphthalic anhydride (1 g, 6.15 mmol, 1 Eq.) was dissolved in glacial acetic acid (3.5 mL). Sodium acetate (0.66 g, 7.99 mmol, 1.3 Eq.) was added, followed by 3-Aminopiperidine-2,6-dione (1.32 g, 7.99 mmol, 1.3 Eq.). The mixture was heated to 100 °C for 2 h. The color of the reaction mixture turned from yellow to purple. After cooling the reaction to room temperature, saturated sodium bicarbonate solution is added slowly until the mixture turns yellow. The resulting product is freeze dried and purified by chromatography (isco Combiflash, 12 g column, silica gel, ethylacetate).

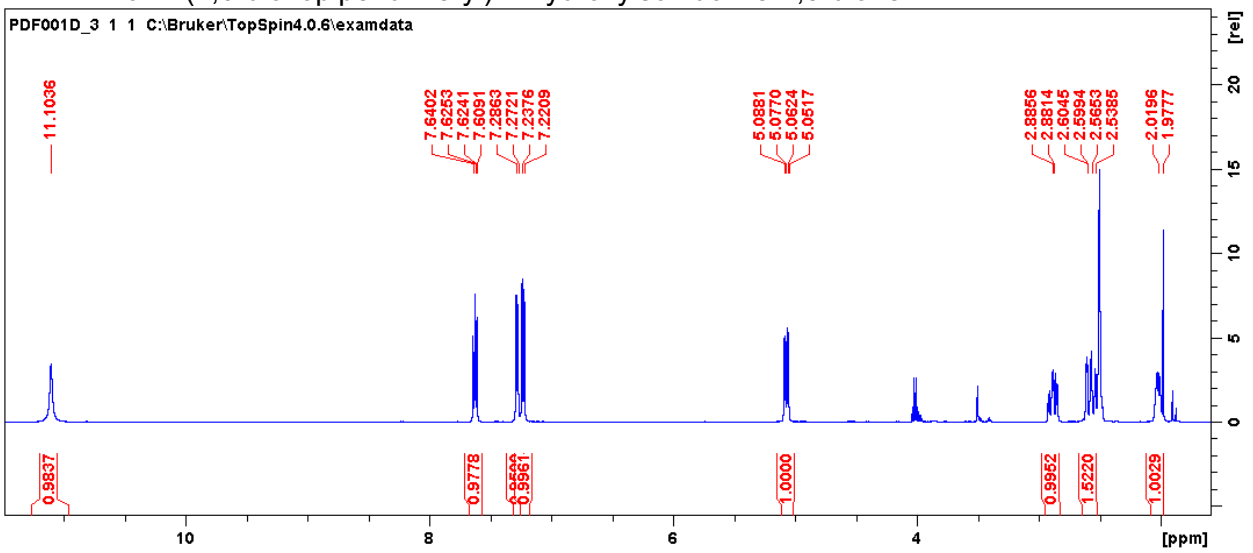
Yield: 1.62 g (5.90 mmol, 96 %) as a yellow solid.

^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 2.00 (m, 1H), 2.54 (m, 1H), 2.56 (m, 1H), 2.88 (m, 1H), 5.06 (dd, 1H, $^{3}J_{HH}$ = 12.09 Hz, 5.6 Hz), 7.21 (d, 1H, $^{3}J_{HH}$ = 8.4 Hz), 7.25 (d, 1H, $^{3}J_{HH}$ = 6.7 Hz), 7.61 (dd, 1H, $^{3}J_{HH}$ = 8.1 Hz, 7.3 Hz), 11.10 (s, 1H)

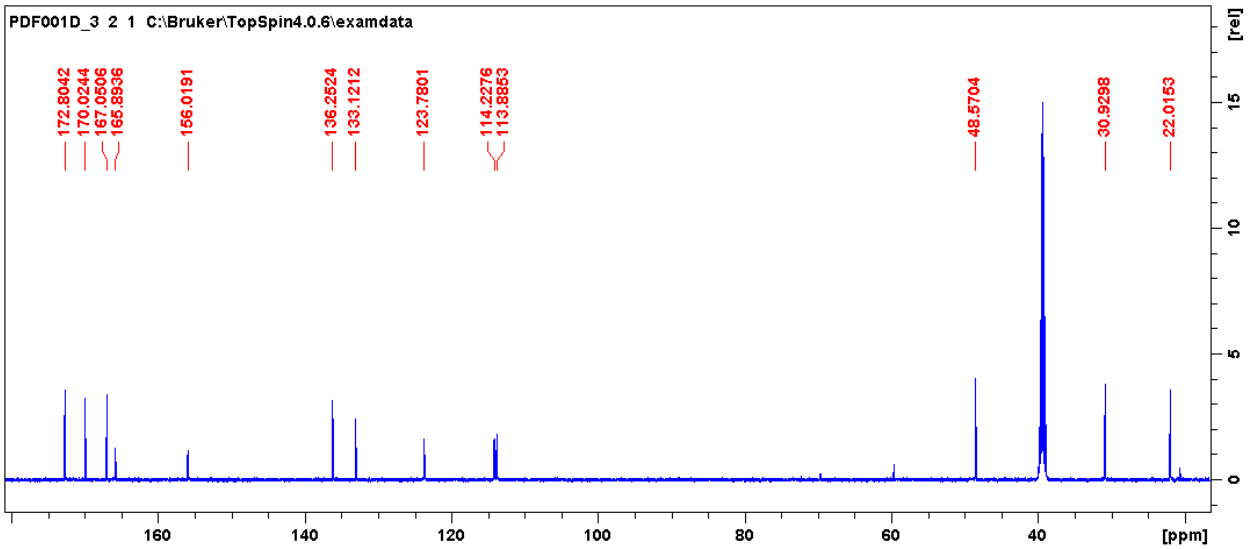
^{13}C NMR (126 MHz, DMSO-d6): δ [ppm] = 22.21, 31.00, 48.60, 113.53, 114.19, 124.15, 133.22, 136.21, 156.73, 166.06, 167.17, 170.10, 172.86

UPLC-MS: calc. [M + H]: 275.07, found [M + H]: 275.06

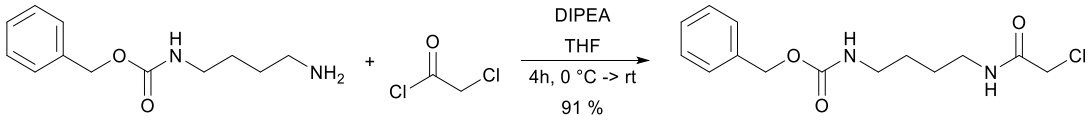
^{1}H NMR for 2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione



^{13}C NMR for 2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione



Benzyl-(4-(2-chloroacetamido)butyl)carbamate



Benzyl (4-aminobutyl)carbamate (58 mg, 0.26 mmol, 1 Eq.) was dissolved in THF (2 mL) and cooled to 0 °C. N,N-Diisopropylethylamine (DIPEA, 45.5 µL, 0.26 mmol, 1 Eq.) was added, followed by 2-chloroacetyl chloride (22.9 µL, 0.29 mmol, 1.1 Eq.) After 1.5 h, the ice bath is removed to allow heating to room temperature for another 1.5 h. The reaction mixture was extracted with ethylacetate to 10 mL and washed with water (3 x). The product was dried *in vacuo* and purified by chromatography (isco combiflash, 4 g column, silica gel, hexanes/ethylacetate 1-100% gradient).

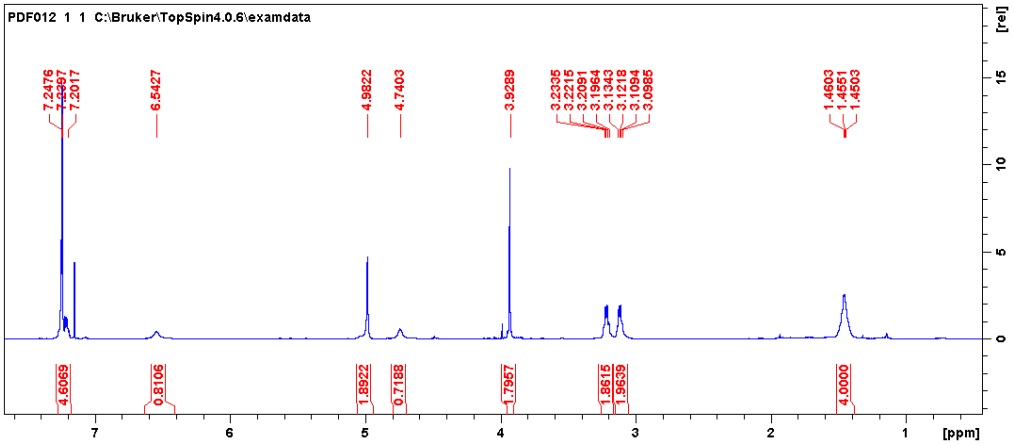
Yield: 71 mg (0.24 mmol, 91 %) of a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.46 (m, 4H), 3.12 (m, 2H), 3.22 (m, 2H), 3.93 (s, 2H), 4.74 (s, 1H), 4.98 (s, 2H), 6.54 (s, 1H), 7.20-7.25 (m, 5H)

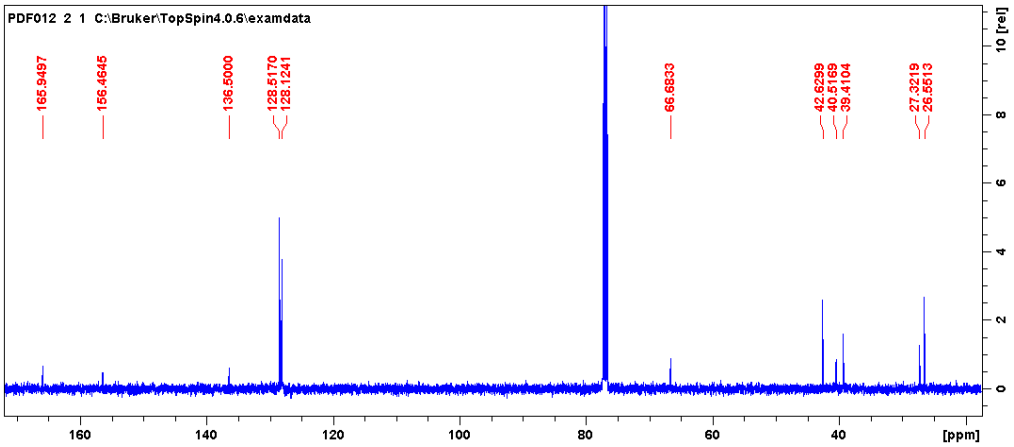
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 26.55, 27.32, 39.41, 40.52, 42.63, 66.68, 128.12, 128.52, 136.50, 156.46, 165.95

UPLC-MS: calc; [M +H]: 299.12, found [M + H]: 299.12

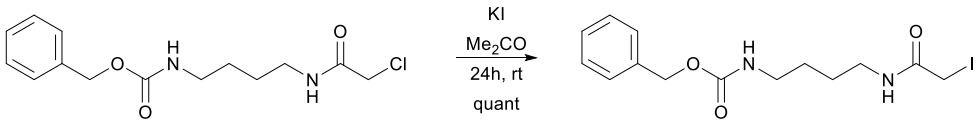
^{1}H NMR for Benzyl-(4-(2-chloroacetamido)butyl)carbamate



^{13}C NMR for Benzyl-(4-(2-chloroacetamido)butyl)carbamate

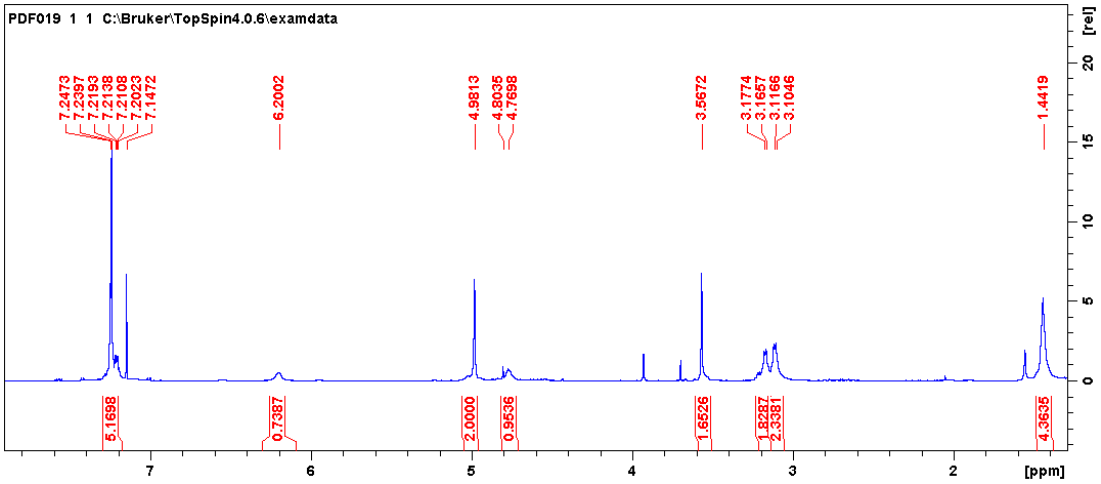


Benzyl (4-(2-iodoacetamido)butyl)carbamate

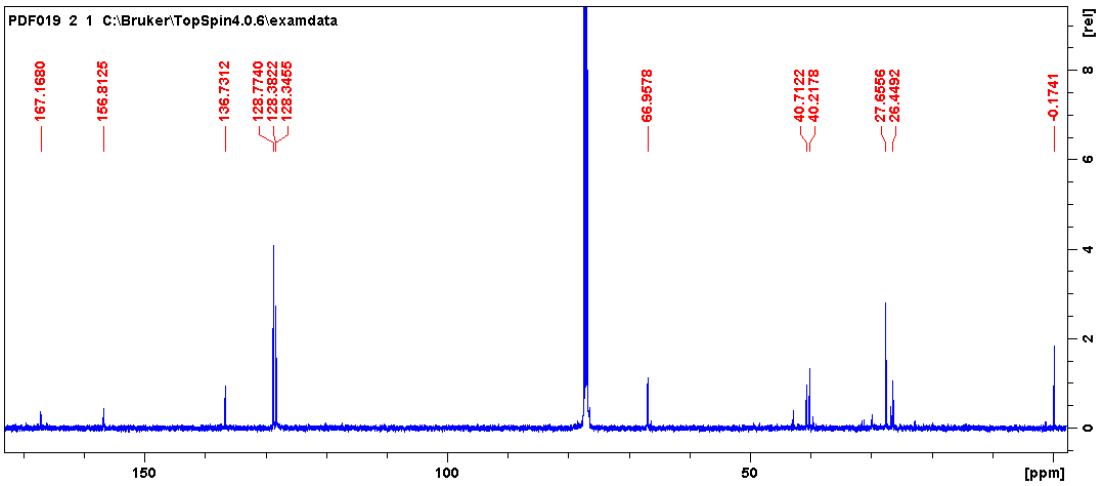


Benzyl-(4-(2-chloroacetamido)butyl)carbamate (50 mg, 0.17 mmol, 1 Eq.) was dissolved in acetone (2 mL). Potassium iodide (83.3 mg, 0.50 mmol, 3Eq.) was added and the reaction mixture was stirred at room temperature overnight (18 h). Then, the solvent was removed *in vacuo* and the remaining solid was resuspended in water (10 mL). The product was extracted with dichloromethane (3 x). No further purification was required.
Yield: 65.2 mg (0.17 mmol, 100 %) of a light yellow solid.
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.44 (m, 4H), 3.11 (m, 2H), 3.17 (m, 2H), 3.57 (s, 2H), 4.77 (s, 1H), 4.98 (s, 2H), 6.20 (s, 1H), 7.20-7.25 (m, 5H)
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = -0.17, 26.45, 27.66, 40.22, 40.71, 66.96, 128.35, 128.38, 128.77, 136.73, 156.81, 167.17
UPLC-MS: calc; [M +H]: 391.05, found [M + H]: 391.06

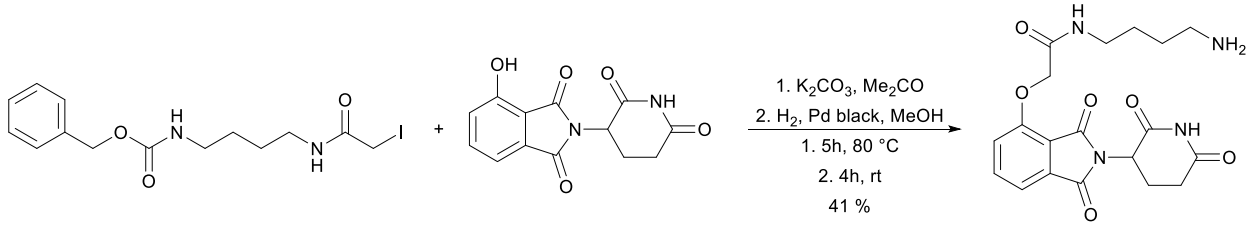
^{1}H NMR for Benzyl (4-(2-iodoacetamido)butyl)carbamate



^{13}C NMR for Benzyl (4-(2-iodoacetamido)butyl)carbamate

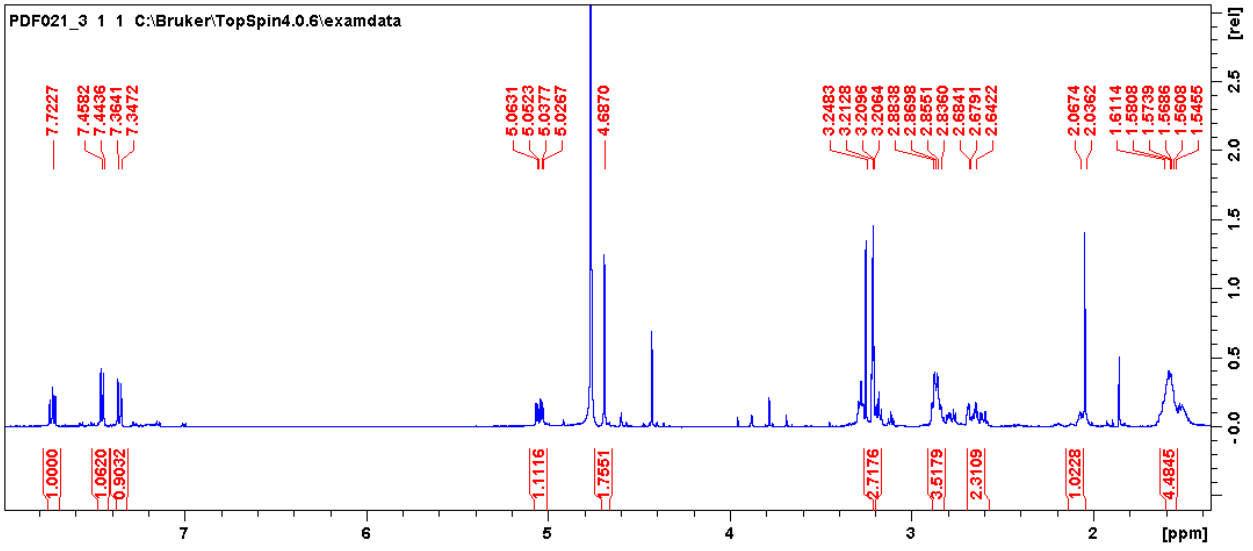


N-(4-aminobutyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide

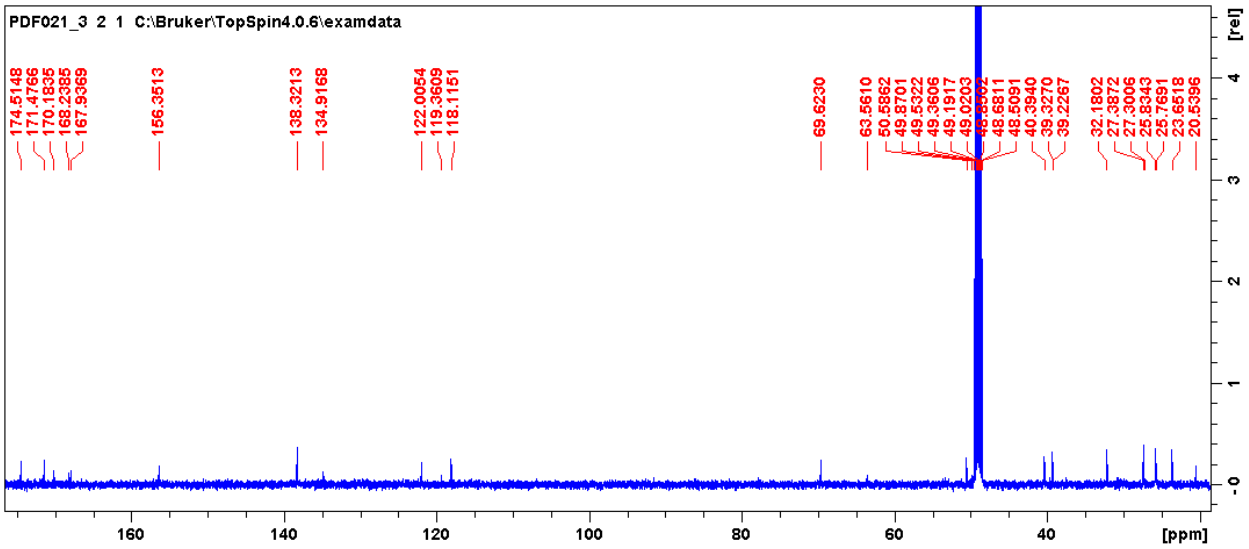


4-Hydroxythalidomide (45.8 mg, 0.17 mmol, 1 Eq.) and potassium carbonate (23.1 mg, 0.17 mmol, 2 Eq.) were dissolved in dimethylformamide (1 mL). Benzyl (4-(2-iodoacetamido)butyl)carbamate (65.2 mg, 0.17 mmol, 1 Eq.) was dissolved in dimethylformamide (2 mL) and added dropwise to the reaction mixture. The reaction was heated to 100 °C for 5 h. The product was extracted with dichloromethane and used without further purification after removal of the organic phase *in vacuo*. The crude product (30 mg, 55.9 µmol, 1 Eq.) was dissolved in dry methanol (1 mL). Palladium black (2 mg, 18.8 µmol, 0.3 Eq.) was added while stirring. A balloon filled with hydrogen gas was attached to the flask and the reaction mixture was stirred at room temperature for 1 day. The product was purified by removal of palladium black using a syringe filter and drying *in vacuo*. No further purification was required.
Yield: 22.5 mg (55.9 µmol, 41 %) of a white solid.
^{1}H-NMR (500 MHz, MeOD): δ [ppm] = 1.58 (m, 4H), 2.07 (m, 1H), 2.63 (m, 1H), 2.68 (m, 1H), 2.79 (m, 1H), 2.87 (m, 2H), 3.18-3.29 (m, 2H), 4.69 (s, 2H), 5.05 (dd, 1H, $^3J_{HH}$ = 12.7 Hz, 5.4 Hz), 7.36 (d, 1H, $^3J_{HH}$ = 8.2 Hz), 7.45 (d, 1H, $^3J_{HH}$ = 7.3 Hz), 7.72 (dd, 1H, $^3J_{HH}$ = 8.6 Hz, 7.6 Hz)
^{13}C-NMR (126 MHz, MeOD): δ [ppm] = 23.65, 25.83, 27.30, 32.18, 39.33, 40.39, 50.60, 69.62, 118.12, 119.36, 122.01, 134.92, 138.32, 156.35, 167.94, 170.18, 171.48, 174.51
UPLC-MS: calc; [M +H]: 403.16, found [M + H]: 403.15

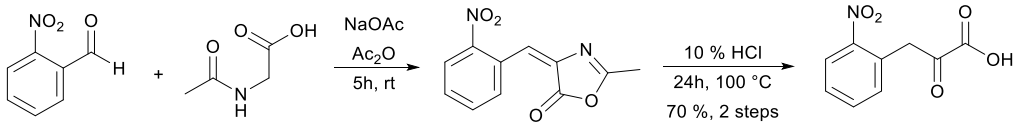
^{1}H NMR for N-(4-aminobutyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide



^{13}C NMR for N-(4-aminobutyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide



3-(2-nitrophenyl)-2-oxopropanoic acid



2-Nitrobenzaldehyde (500 mg, 3.3 mmol, 1 Eq.), N-acetylglycine (503 mg, 4.3 mmol, 1.3 Eq.) and sodium acetate (352 mg, 4.3 mmol, 1.3 Eq.) were dissolved in acetic anhydride (20 mL). The mixture was stirred for 3 h at 140 °C and extracted with dichloromethane and dried *in vacuo*. The crude product (2-methyl-5-(2-nitrobenzylidene)oxazol-4(5H)-one) was dissolved in 10 % hydrochloric acid in water (10 mL), heated to 100 °C and stirred overnight (24 h). The product was extracted with dichloromethane, dried *in vacuo* and purified by chromatography (isco Combiflash, 4 g column, silica gel, hexanes/ethylacetate 1-100% gradient).

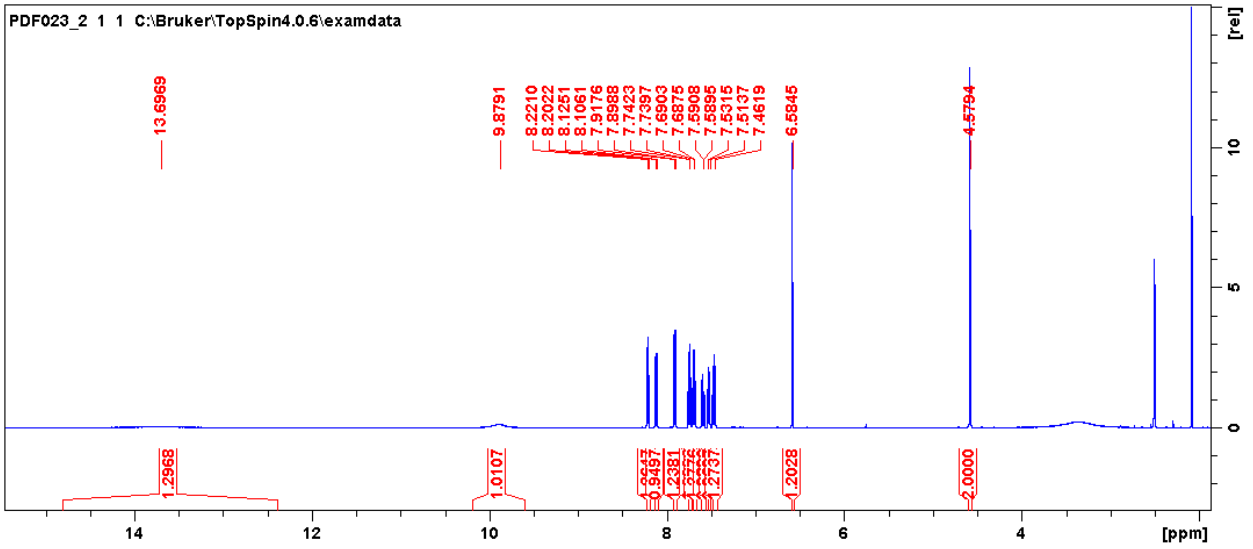
Yield: 483 mg (2.3 mmol, 70 %) of a yellow solid.

^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 4.58 (s, 2H), 6.58 (s, 1H), 7.46 (dd, 1H, $^{3}J_{HH}$ = 9.3 Hz, 7.3 Hz, $^{4}J_{HH}$ = 1.4 Hz), 7.52 (d, 1H, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.3 Hz), 7.59 (dd, 1H, $^{3}J_{HH}$ = 9.4 Hz, 8.1 Hz, $^{4}J_{HH}$ = 1.6 Hz), 7.69 (dd, 1H, $^{3}J_{HH}$ = 8.8 Hz, 7.65 Hz, $^{4}J_{HH}$ = 1.2 Hz), 7.74 (dd, 1H, $^{3}J_{HH}$ = 8.8 Hz, 7.6 Hz, $^{4}J_{HH}$ = 1.3 Hz), 7.91 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 1.3 Hz), 8.12 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 1.3 Hz), 8.21 (d, 1H, $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HH}$ = 1.3 Hz), 9.88 (s, 1H), 13.70 (s, 2H)

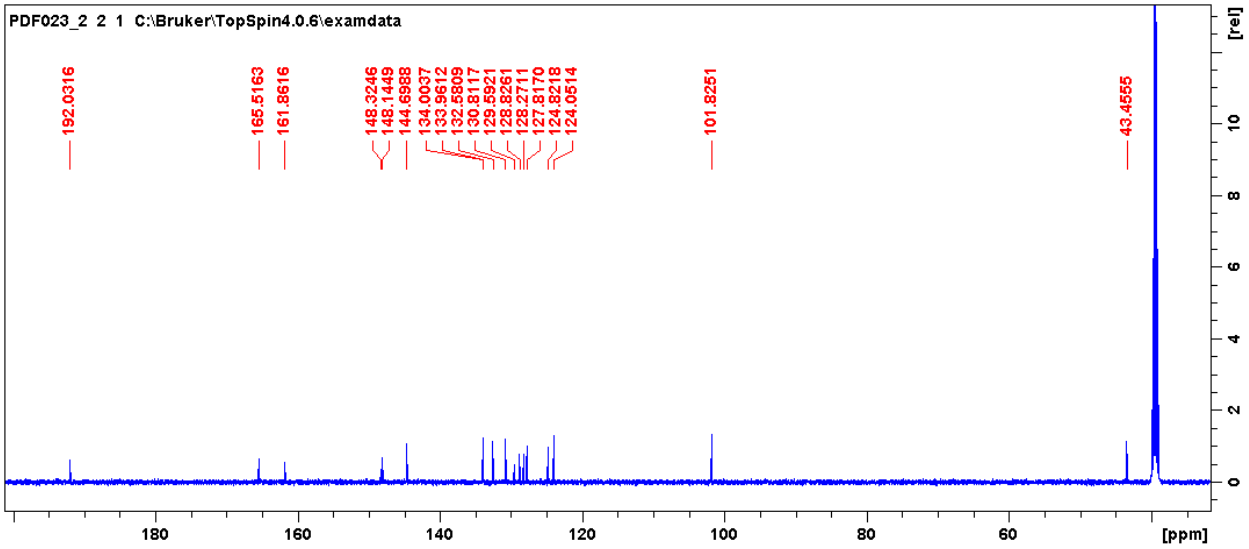
^{13}C-NMR (126 MHz, DMSO-d6): δ [ppm] = 43.46, 101.83, 124.05, 124.82, 127.82, 128.27, 128.83, 129.59, 130.81, 132.58, 133.96, 134.00, 144.70, 148.14, 148.32, 161.86, 165.52, 192.03

UPLC-MS: calc; [M +H]: 210.04, found [M + H]: 210.03

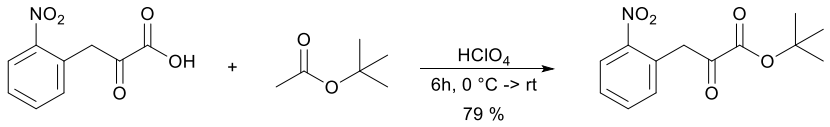
^{1}H NMR for 3-(2-nitrophenyl)-2-oxopropanoic acid



^{13}C NMR for 3-(2-nitrophenyl)-2-oxopropanoic acid

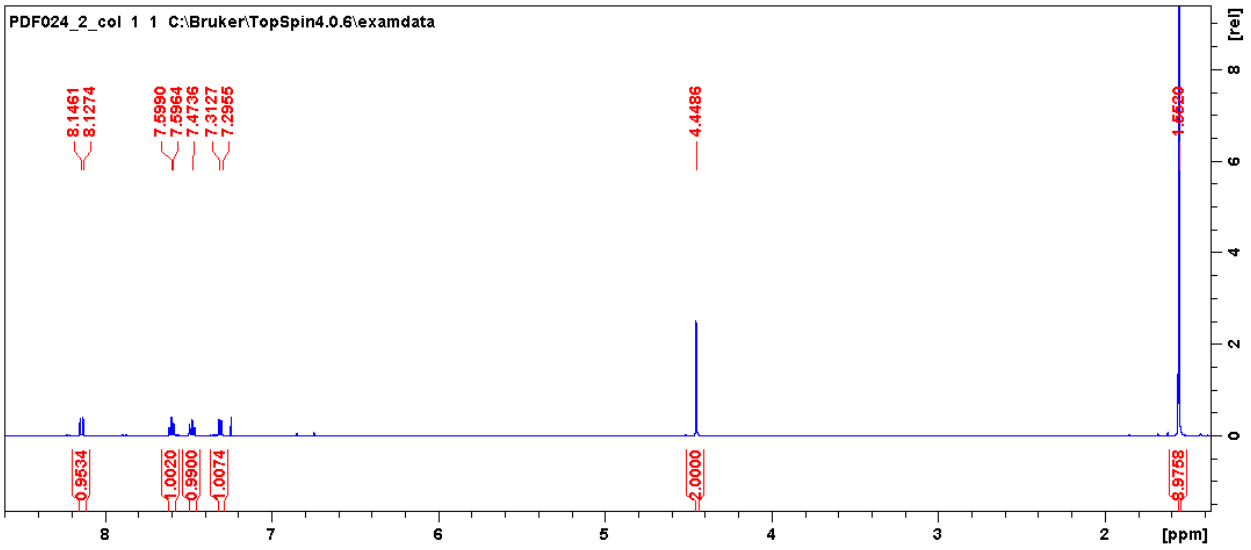


***tert*-butyl 3-(2-nitrophenyl)-2-oxopropanoate**

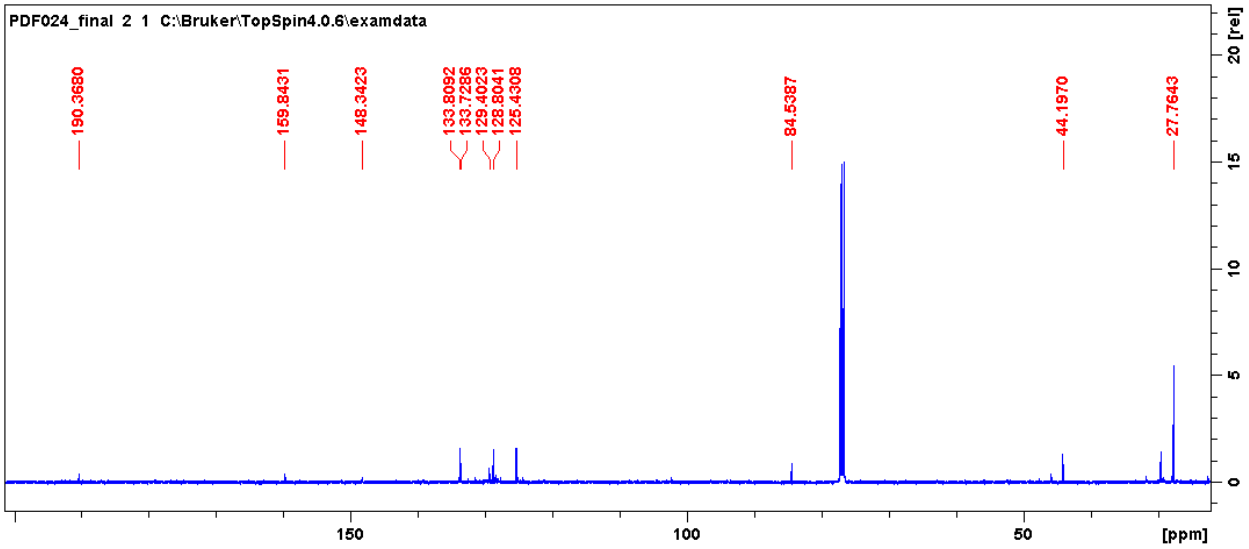


3-(2-nitrophenyl)-2-oxopropanoic acid (50 mg, 0.24 mmol, 1 Eq.) was dissolved in *tert*-butyl acetate (2 mL) and the mixture was cooled to 0 °C. Perchloric acid, 70 % in water, (29 µL, 0.39 mmol, 1.5 Eq.) were added and the ice bath was removed. The mixture was stirred at room temperature overnight (18 h). The solvent was removed *in vacuo* and the remaining solid was resuspended in water. The product was extracted with dichloromethane (3 x), dried *in vacuo* and purified by chromatography (isco Combiflash, 4 g column, silica gel, ethylacetate).
Yield: 50 mg (0.19 mmol, 79 %) of a yellow solid.
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.55 (s, 9H), 4.45 (s, 2H), 7.30 (d, 1H $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.3 Hz), 7.47 (dd, 1H, $^{3}J_{HH}$ = 9.5 Hz, 8.2), 7.60 (dd, 1H, $^{3}J_{HH}$ = 8.8 Hz, 7.6 Hz, $^{4}J_{HH}$ = 1.5 Hz), 8.14 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz)
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 27.76, 44.20, 84.54, 125.43, 128.80, 129.40, 133.73, 133.81, 148.34, 159.84, 190.37
UPLC-MS: calc; [M +H]: 266.10, found [M + H]: 266.10

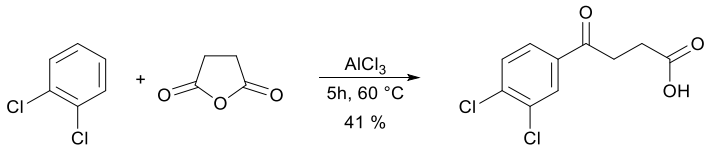
^{1}H NMR for *tert*-butyl 3-(2-nitrophenyl)-2-oxopropanoate



^{13}C NMR for *tert*-butyl 3-(2-nitrophenyl)-2-oxopropanoate

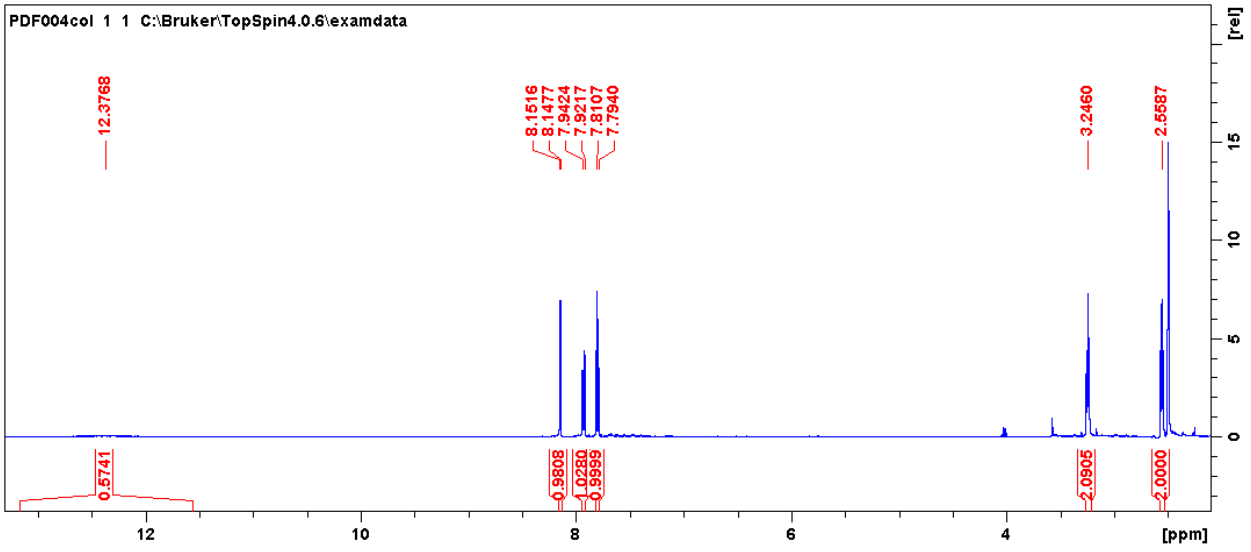


4-(3,4-dichlorophenyl)-4-oxobutanoic acid

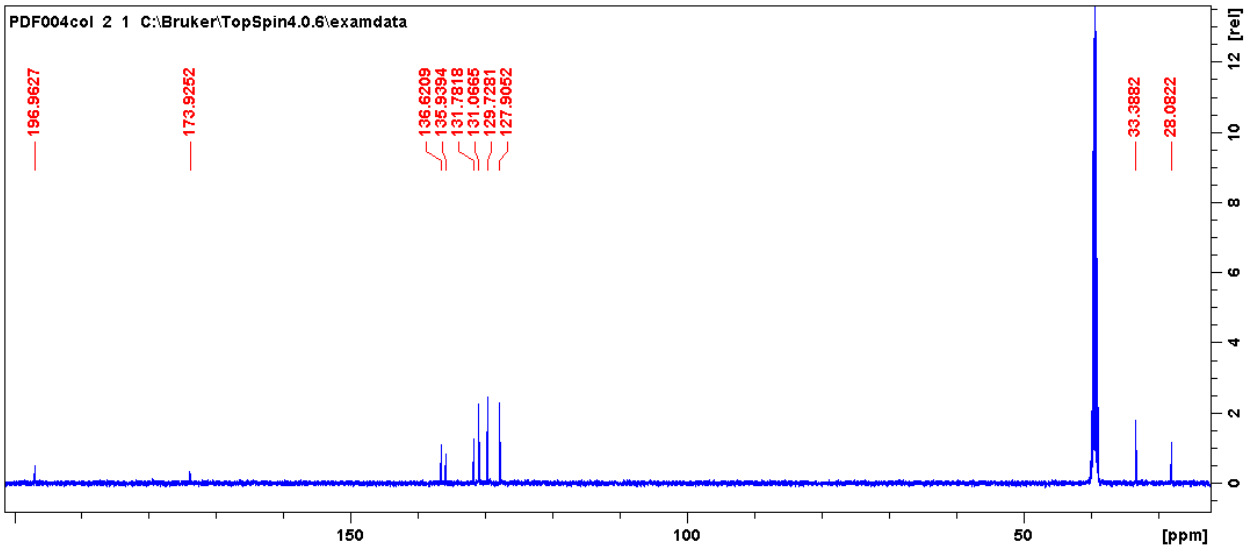


Succinic anhydride (5 g, 0.05 mol, 1 Eq.) was dissolved in 1,2-dichlorobenzene (44.1 g, 0.3 mol, 6 Eq.). Aluminum chloride (19.9 g, 0.15 mol, 3 Eq.) were added while stirring. The mixture was heated to 60 °C for 5 h. After cooling to 45 °C, the mixture was slowly poured into ice cold water (120 mL) and stirred for 0.5 h. Then, hexane (60 mL) was added and the mixture was stirred for 2 h. The resulting solid was filtered and dried *in vacuo*. No further purification was required.
Yield: 5.04 g (0.021 mol, 41 %) of a yellow solid.
^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 2.56 (t, 2H, $^{3}J_{HH}$ = 6.3 Hz), 3.25 (t, 2H, $^{3}J_{HH}$ = 6.3 Hz), 7.80 (d, 1H, $^{3}J_{HH}$ = 8.4 Hz), 7.93 (d, 1H, $^{3}J_{HH}$ = 8.4 Hz), 8.15 (s, 1H), 12.37 (s, 1H)
^{13}C-NMR (126 MHz, DMSO-d6): δ [ppm] = 28.08, 33.39, 127.91, 129.73, 131.01, 131.78, 135.94, 136.62, 173.93, 196.96
UPLC-MS: calc; [M +H]: 246.99, found [M + H]: 246.99

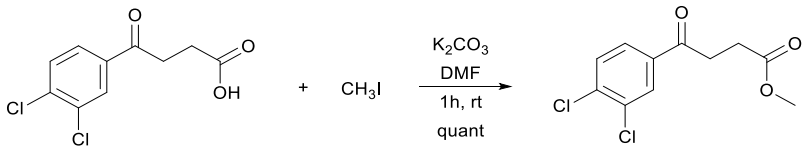
^{1}H NMR for 4-(3,4-dichlorophenyl)-4-oxobutanoic acid



^{13}C NMR for 4-(3,4-dichlorophenyl)-4-oxobutanoic acid

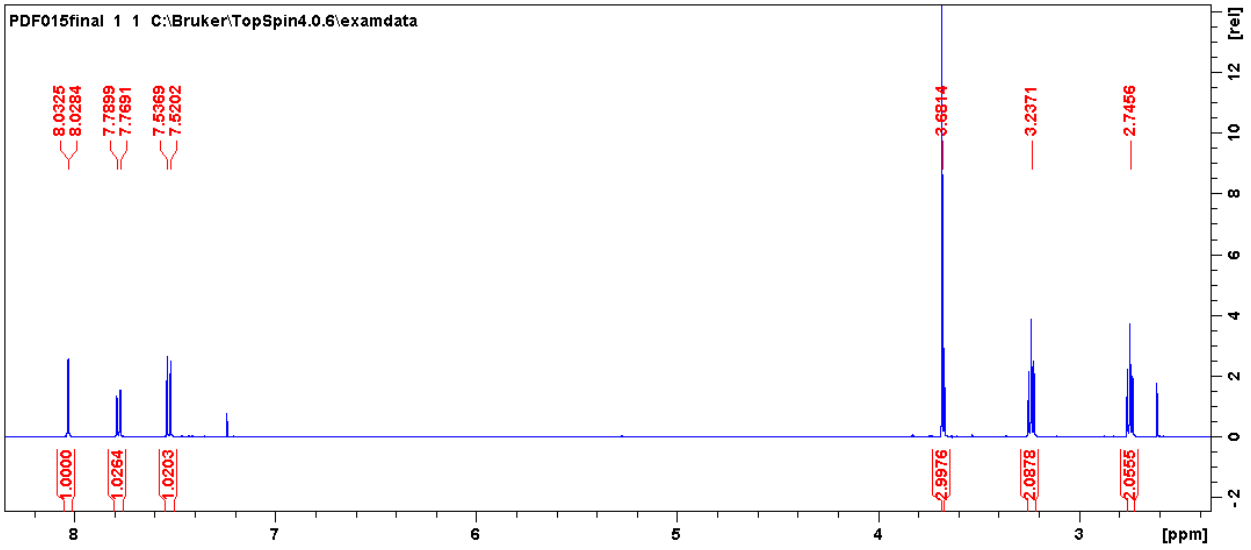


methyl 4-(3,4-dichlorophenyl)-4-oxobutanoate

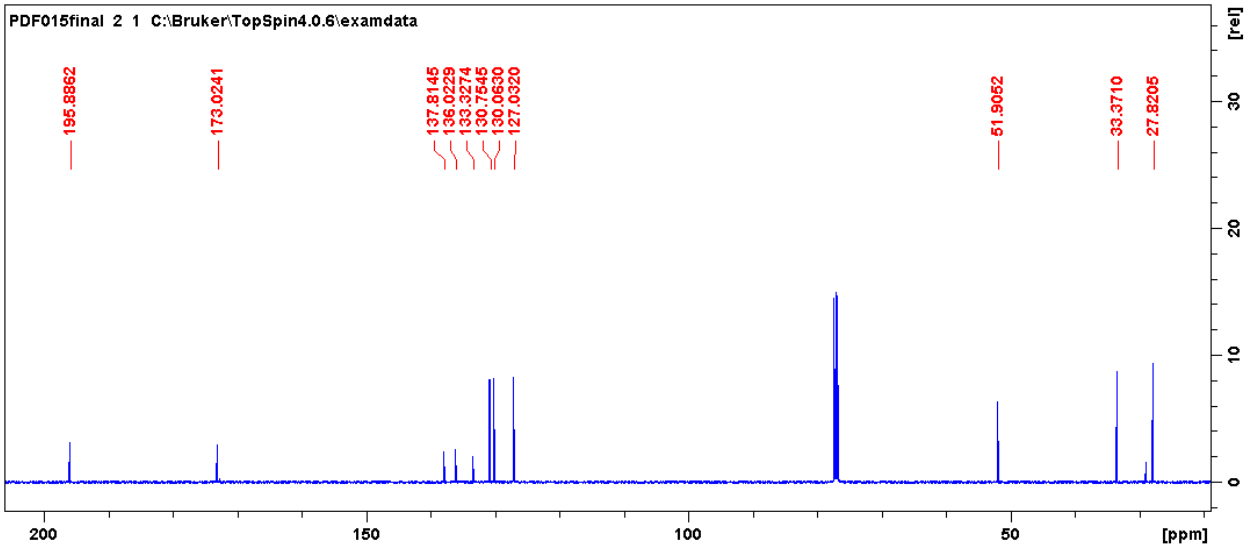


4-(3,4-dichlorophenyl)-4-oxobutanoic acid (3.19 g, 13 mmol, 1 Eq.) was dissolved in dimethyl formamide (10 mL). Potassium carbonate (2.34 g, 17 mmol, 1.3 Eq.) was added and the mixtures was stirred until it turns turbid. Then, iodomethane (1.37 mL, 22 mmol, 1.7 Eq.) was added and the mixture was stirred for 1 h at room temperature. The product was extracted with ethylacetate (100 mL) and washed with a mixture of saturated sodium carbonate solution and saturated sodium chloride solution (300 mL, 1:1). The organic solvent was removed in vacuo and the product was purified by chromatography (isco Combiflash, 24 g column, silica gel, dichloromethane/methanol 1-10 % gradient).
Yield: 3.39 g (13 mmol, 100 %) of an orange solid.
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 2.75 (t, 2H, $^{3}J_{HH}$ = 6.5 Hz), 3.24 (t, 2H, $^{3}J_{HH}$ = 6.4 Hz), 3.68 (s, 3H), 7.53 (d, 1H, $^{3}J_{HH}$ = 8.3 Hz), 7.78 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz, , $^{4}J_{HH}$ = 2.2 Hz), 8.03 (d, 1H, $^{4}J_{HH}$ = 2.1 Hz)
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 27.82, 33.37, 51.91, 127.03, 130.06, 130,73, 133.33, 136.03, 137.81, 173.02, 195.89
UPLC-MS: calc; [M +H]: 261.01, found [M + H]: 261.00

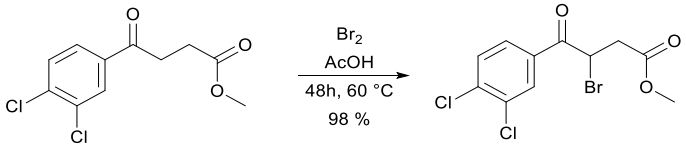
^{1}H NMR for methyl 4-(3,4-dichlorophenyl)-4-oxobutanoate



^{13}C NMR for methyl 4-(3,4-dichlorophenyl)-4-oxobutanoate



methyl 3-bromo-4-(3,4-dichlorophenyl)-4-oxobutanoate



Methyl 4-(3,4-dichlorophenyl)-4-oxobutanoate (2.08 g, 8 mmol, 1 Eq.) was dissolved in glacial acetic acid (20 mL). The mixture was stirred at room temperature until it became clear. Then, bromine (410 µL, 8 mmol, 1 Eq.) was added slowly and dropwise. The reaction mixture was heated to 60 °C and stirred for 48 h. The resulting product was diluted with water (20 mL) and extracted with dichloromethane until the organic phase is colorless (4 x 60 mL). The organic solvent was removed in vacuo. No further purification was required.

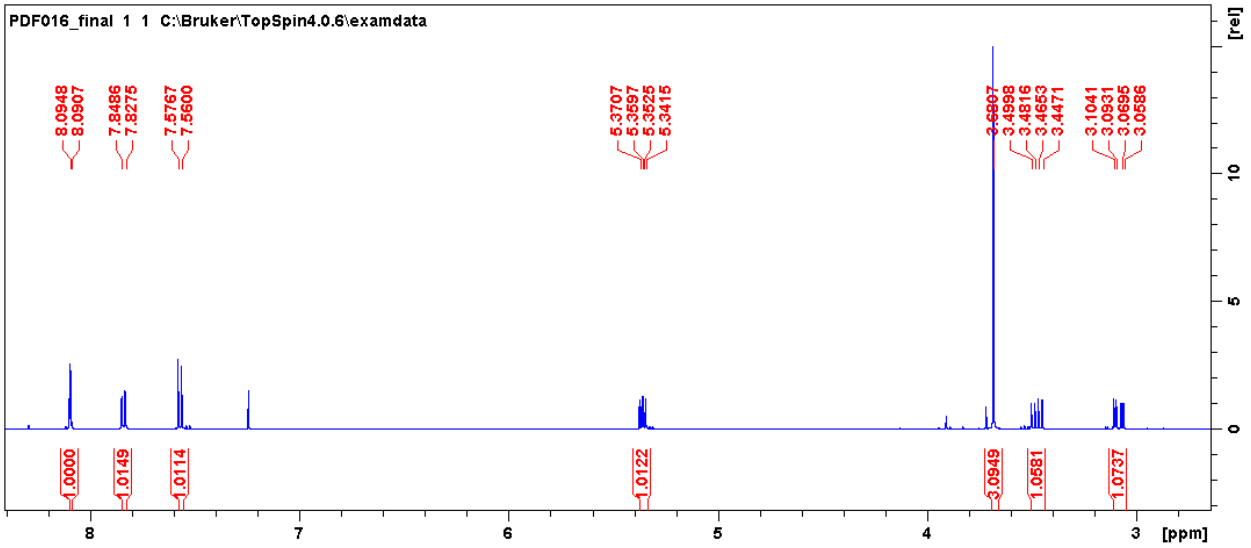
Yield: 2.58 g (7.64 mmol, 96 %) of an orange oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.08 (dd, 1H, $^{2}J_{HH}$ = 17.3 Hz, $^{3}J_{HH}$ = 5.5 Hz), 3.47 (dd, 1H, $^{2}J_{HH}$ = 17.3 Hz , $^{3}J_{HH}$ = 9.1 Hz), 3.68 (s, 3H), 5.36 (dd, 1H, $^{3}J_{HH}$ = 9.1 Hz, 5.5 Hz), 7.57 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz), 7.84 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz), 8.09 (d, 1H, $^{4}J_{HH}$ = 1.9 Hz)

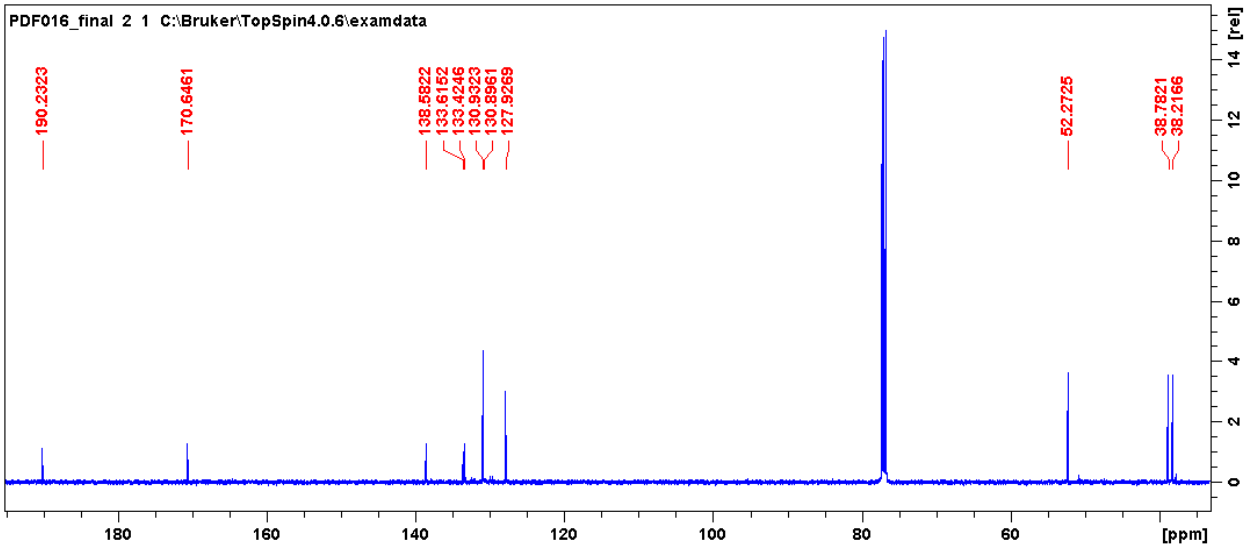
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 38.22, 38.78, 52.27, 127.93, 130.90, 130.93, 133.42, 133.62, 138.58, 170.65, 190.23

UPLC-MS: calc; [M +H]: 338.92, found [M + H]: 338.91

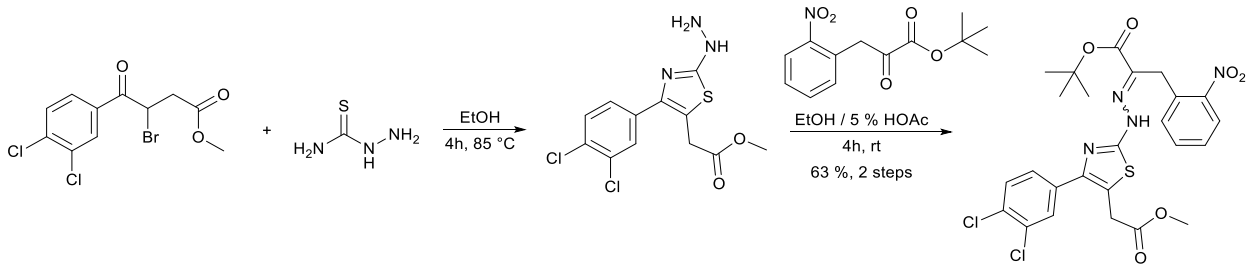
^{1}H NMR for methyl 3-bromo-4-(3,4-dichlorophenyl)-4-oxobutanoate



^{13}C NMR for methyl 3-bromo-4-(3,4-dichlorophenyl)-4-oxobutanoate



***tert*-butyl 2-(2-(4-(3,4-dichlorophenyl)-5-(2-methoxy-2-oxoethyl)thiazol-2-yl)hydrazineylidene)-3-(2-nitrophenyl)propanoate**



Methyl 3-bromo-4-(3,4-dichlorophenyl)-4-oxobutanoate (150 mg, 0.44 mmol, 1 Eq.) was dissolved in ethanol (10 mL). Thiosemicarbazide (40 mg, 0.44 mmol, 1 Eq.) was added and the mixture was heated to 85 °C for 4 h. The organic solvent was removed *in vacuo*. An aliquot of the crude product (16 mg, 60.4 µmol, 1 Eq.) and *tert*-butyl 3-(2-nitrophenyl)-2-oxopropanoate (20 mg, 60.4 µmol, 1 Eq.) were dissolved in acetic acid (2 mL, 5 % in ethanol). The mixture was stirred at room temperature for 4 h. The solvent was removed *in vacuo* and the product (a mixture of E/Z-isomers) was purified by chromatography (isco Combiflash, 4 g column, silica gel, methanol/dichloromethane gradient).

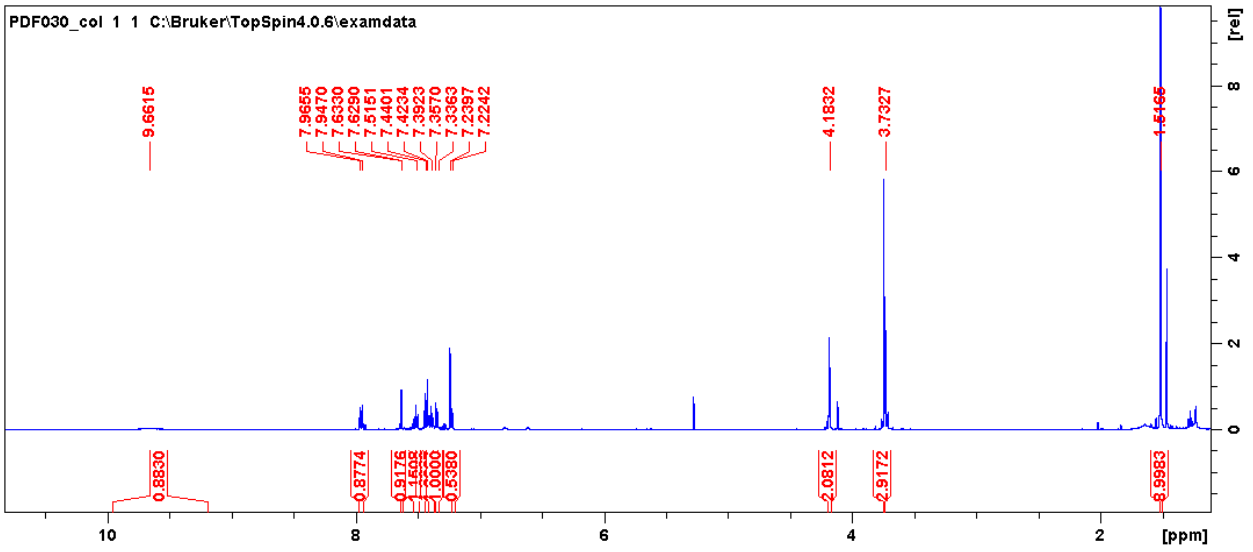
Yield: 22 mg (38.1 µmol, 63%) of a yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 1.52 (s, 9H), 3.73 (s, 2H), 3.74 (s, 3H), 4.28 (s, 2H), 7.23 (d, 1H, $^{3}J_{HH}$ = 7.9 Hz), 7.35 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz), 7.39 (dd, 1H, $^{3}J_{HH}$ = 8.6 Hz, 7.4 Hz), 7.43 (d, 1H, $^{3}J_{HH}$ = 8.5 Hz), 7.51 (dd, 1H, $^{3}J_{HH}$ = 8.6 Hz, 7.4 Hz), 7.63 (d, 1H, $^{4}J_{HH}$ = 1.9 Hz) 7.96 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz)

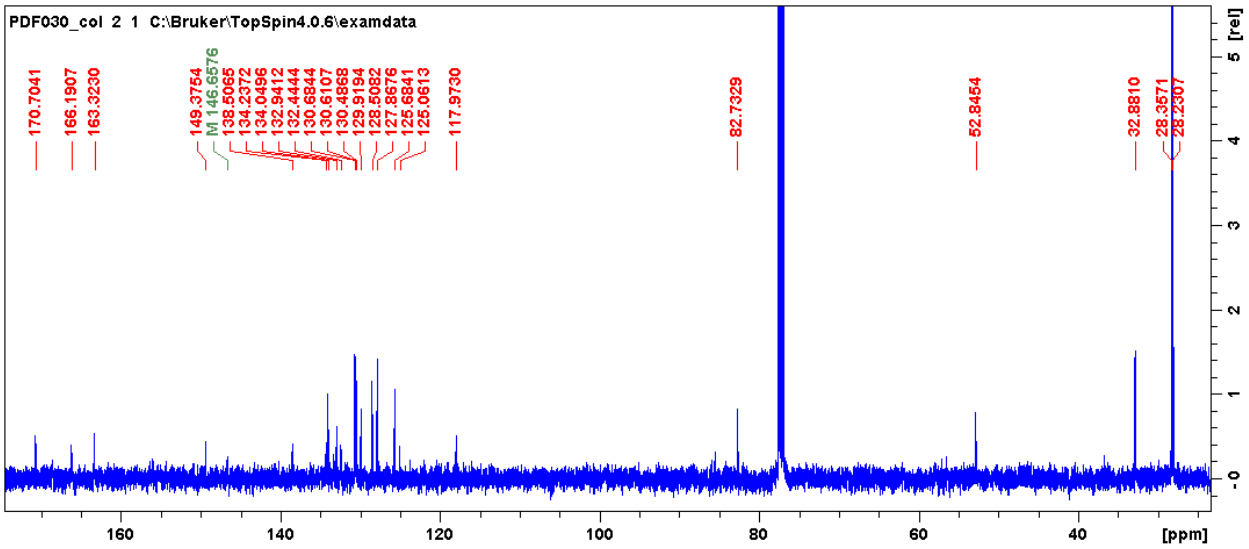
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 28.23, 28.36, 32.88, 52.85, 82.73, 117.97, 125.06, 125.68, 127.87, 128.51, 129.92, 130.49, 130.61, 130.68, 132.44, 132.94, 134.05. 134.24. 138.51, 146.66, 149.38, 163.32, 166.19, 170.70

UPLC-MS: calc; [M +H]: 579.09 found [M + H]: 579.08

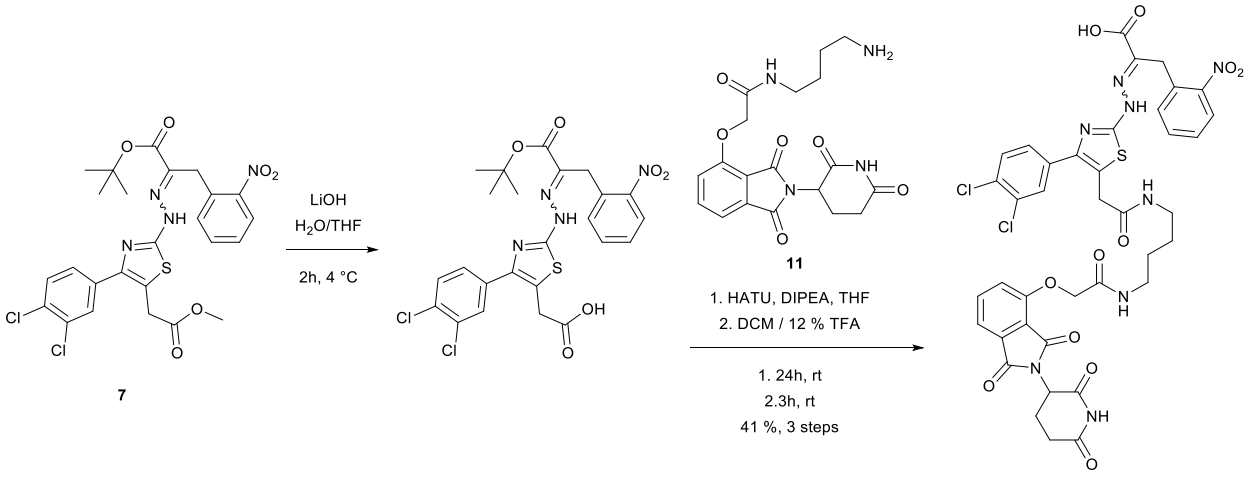
^{1}H NMR for tert-butyl 2-(2-(4-(3,4-dichlorophenyl)-5-(2-methoxy-2-oxoethyl)thiazol-2-yl)hydrazineylidene)-3-(2-nitrophenyl)propanoate



^{13}C NMR for tert-butyl 2-(2-(4-(3,4-dichlorophenyl)-5-(2-methoxy-2-oxoethyl)thiazol-2-yl)hydrazineylidene)-3-(2-nitrophenyl)propanoate

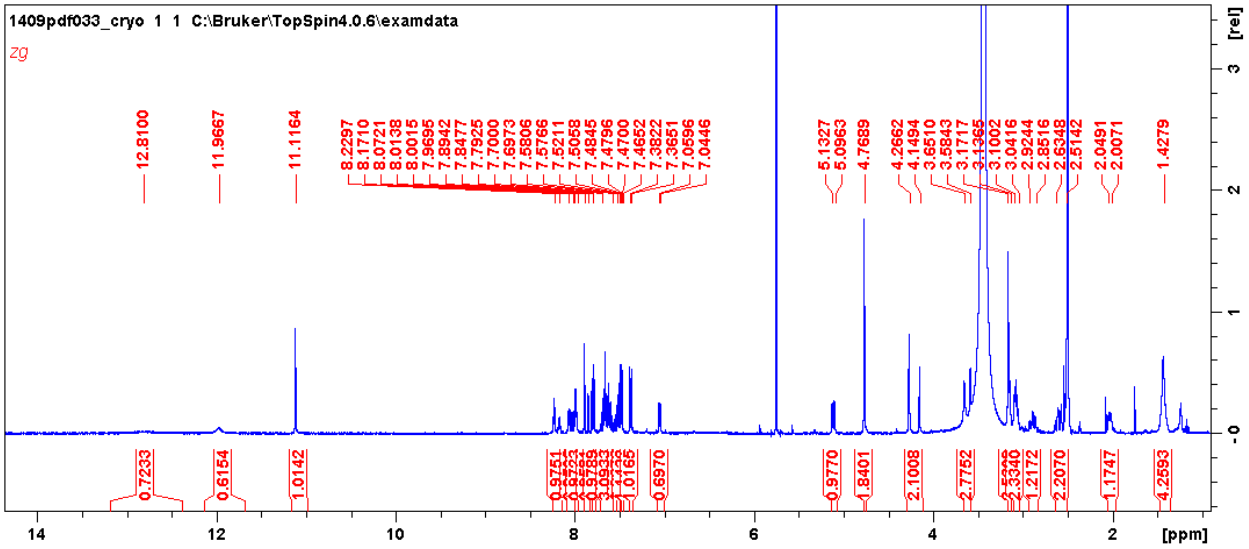


2-(2-(4-(3,4-dichlorophenyl)-5-(2-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)butyl)amino)-2-oxoethyl)thiazol-2-yl)hydrazineylidene)-3-(2-nitrophenyl)propanoic acid (d4E-1)

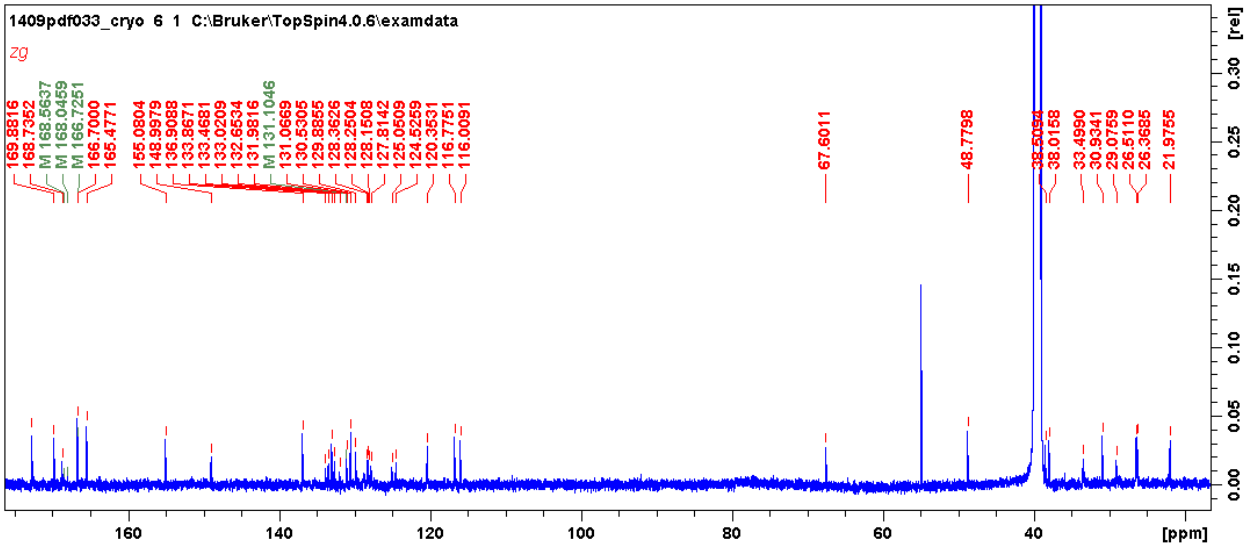


Tert-butyl 2-(2-(4-(3,4-dichlorophenyl)-5-(2-methoxy-2-oxoethyl)thiazol-2-yl)hydrazineylidene)-3-(2-nitrophenyl)propanoate (11 mg, 19 µmol, 1 Eq.) was dissolved in tetrahydrofurane (1 mL) at 4 °C. Lithium hydroxide (1.6 mg, 38 µmol, 2 Eq.) was dissolved in water (1 mL) and the resulting solution was added dropwise to the reaction mixture. After stirring for 2 h at 4 °C, the mixture was diluted with 1 M hydrochloric acid (2 mL) and extracted with dichloromethane. The organic solvent was removed *in vacuo*. An aliquot of the crude product (5 mg, 8.86 µmol, 1 Eq.), N-(4-aminobutyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide (3.6 mg, 8.86 µmol, 1 Eq.), and 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 3.4 mg, 8.86 µmol, 1 Eq.) were dissolved in tetrahydrofurane (2 mL). N,N-Diisopropylethylamine (DIPEA, 1.6 µL, 8.86 µmol, 1 Eq.) was added to the reaction mixture and stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the coupling product was used without further purification. Trifluoroacetic acetic (12 % in dichloromethane, 2 mL) was added and the mixture was stirred at room temperature for 3 h. The solvent was removed in vacuo and the product was purified using high performance liquid chromatography (HPLC, C18 reversed phase preparative column, water/acetonitrile 5/95).
Yield: 3.9 mg (4.34 µmol, 41 %) of a yellow solid.
^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 1.43 (m, 4H), 2.03 (m, 1H), 2.52 (m, 1H), 2.59 (m, 1H), 2.89 (m, 1H), 3.08 (m, 2H), 3.15 (m, 2H), 3.65 (s 2H), 4.15/4.27 (s, 2H), 4.77 (s, 2H), 5.11 (dd, 1H, $^{3}J_{HH}$ = 6.1 Hz), 7.05 (d, 1H, $^{3}J_{HH}$ = 7.6 Hz), 7.38 (d, 1H, $^{3}J_{HH}$ = 8.5 Hz), 7.48 (d, 1H, $^{3}J_{HH}$ = 7.2 Hz), 7.51 (d, 1H, $^{3}J_{HH}$ = 7.8 Hz), 7.60 (m, 1H), 7.64 (m, 1H), 7.66 (m, 1H), 7.79 (dd, 1H, $^{3}J_{HH}$ = 8.0 Hz), 7.87 (d, 1H, $^{4}J_{HH}$ = 2.0 Hz), 7.99 (t, 1H, $^{3}J_{HH}$ = 5.4 Hz), 8.02/8.07 (d, 1H, $^{3}J_{HH}$ = 8.4 Hz), 8.17/8.23 (t, 1H, $^{3}J_{HH}$ = 5.5 Hz), 11.12 (s, 1H), 11.97 (s, 1H), 12.80 (s, 1H)
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 21.98, 26.37, 26.52, 29.08, 30.94, 33.37/33.50, 35.90, 38.02, 38.52, 48.79, 67.61, 116.02, 116.78, 120.36, 124.53, 125.05, 127.82, 128.25, 128.80, 129.89, 130.54, 131.07, 131.10, 132.00, 132.66, 133.03, 133.47, 133.87, 135.29, 136.91, 149.00/149.06, 155.08, 164.13/165.48, 166.70, 168.54/168.74, 169.89, 172.78, 172.91, 174.32
UPLC-MS: calc; [M +H]: 893.15 found [M + H]: 893.15

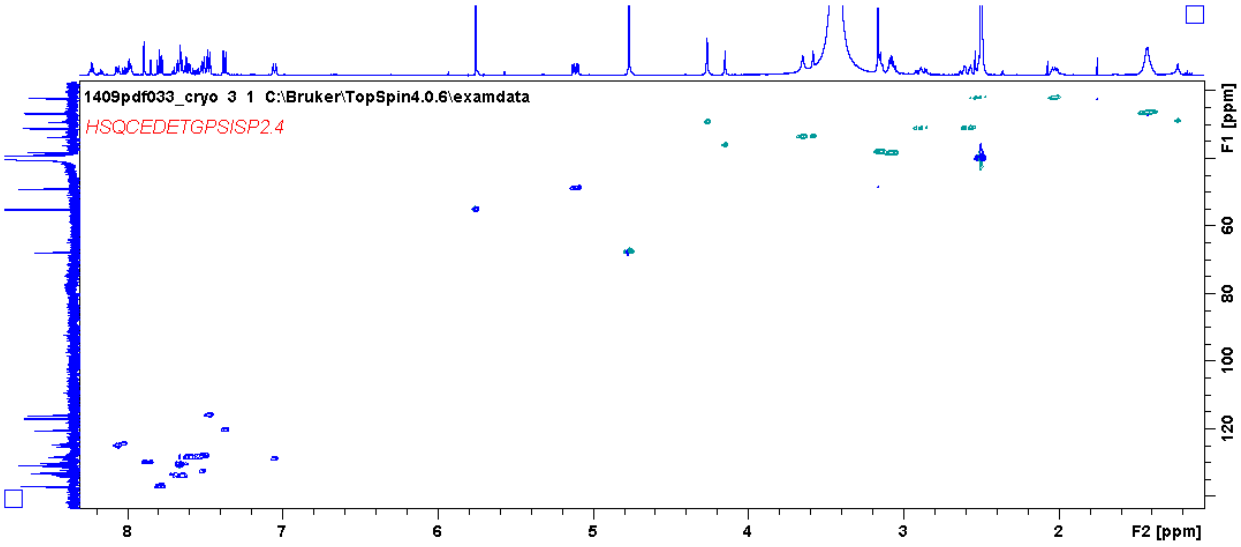
^{1}H NMR for d4E-1



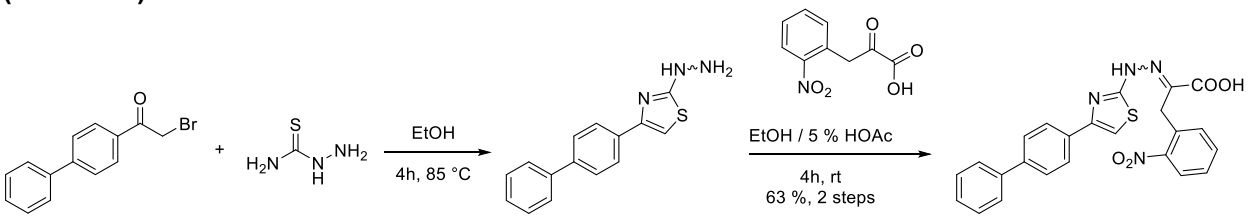
^{13}C NMR for d4E-1



^{1}H-^{13}C-HSQC for d4E-1

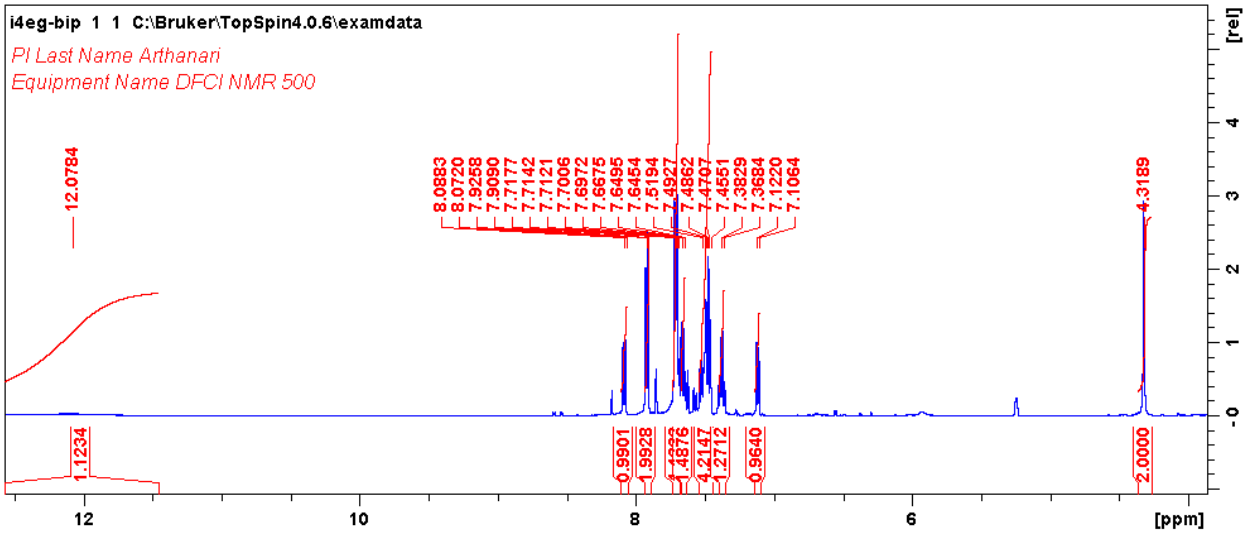


2-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazineylidene)-3-(2-nitrophenyl)propanoic acid (i4EG-BiP)

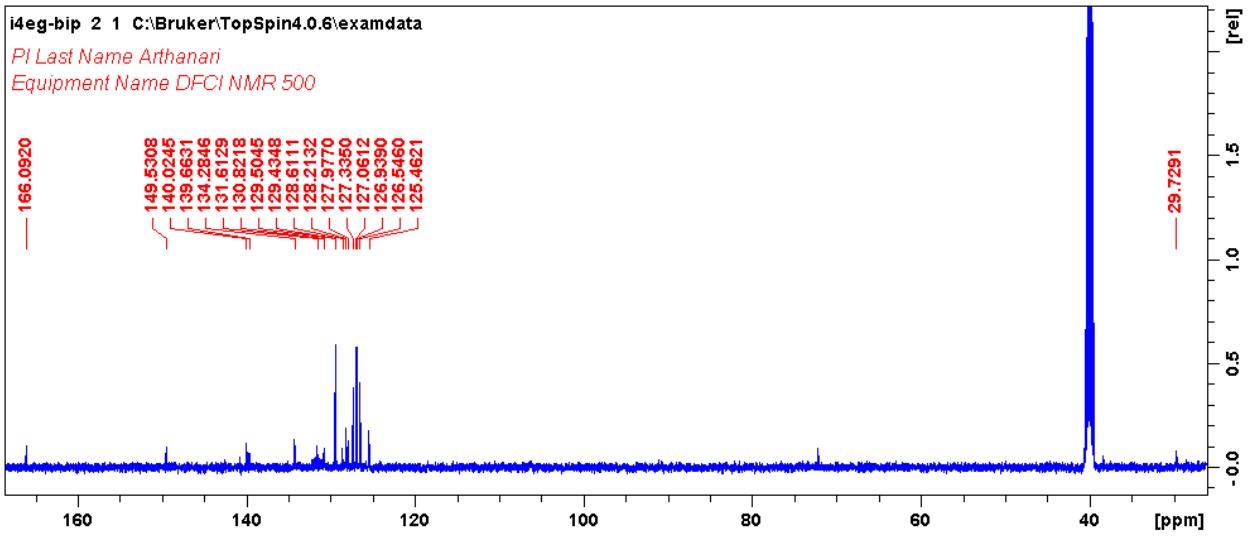


1-([1,1'-biphenyl]-4-yl)-2-bromoethan-1-one (500 mg, 1.82 mmol, 1 Eq.) was dissolved in ethanol (10 mL). Thiosemicarbazide (166 mg, 1.82 mmol, 1 Eq.) was added and the mixture was heated to 85 °C for 4 h. The organic solvent was removed *in vacuo*. An aliquot of the crude product (50 mg, 187 µmol, 1 Eq.) and 3-(2-nitrophenyl)-2-oxopropanoic acid (39 mg, 187 µmol, 1 Eq.) were dissolved in acetic acid (2 mL, 5 % in ethanol). The mixture was stirred at room temperature for 4 h. The solvent was removed *in vacuo* and the product (a mixture of E/Z-isomers) was purified by chromatography (isco Combiflash, 4 g column, silica gel, methanol/dichloromethane gradient).
Yield: 54 mg (117.8 µmol, 63%) of a yellow solid.
^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 4.32 (s, 2H), 7.12 (d, 1H, $^{3}J_{HH}$ = 7.8 Hz), 7.38 (dd, 1H, $^{3}J_{HH}$ = 13.1 Hz, 5.5 Hz), 7.46-7.52 (m, 4H), 7.65-7.72 (m, 6H), 7.92 (d, 2H, $^{3}J_{HH}$ = 8.4 Hz). 8.08 (d, 1H, $^{3}J_{HH}$ = 8.1 Hz), 12.08 (s, 1H)
^{13}C-NMR (126 MHz, DMSO-d6): δ [ppm] = 29.73, 125.46, 126.55, 126.94, 127.06, 127.34, 127.98, 128.21, 128.61, 129.43, 129.50, 130.82, 131.61, 134.28, 139.66, 140.02, 149.53, 166.09
UPLC-MS: calc; [M +H]: 459.11 found [M + H]: 459.11

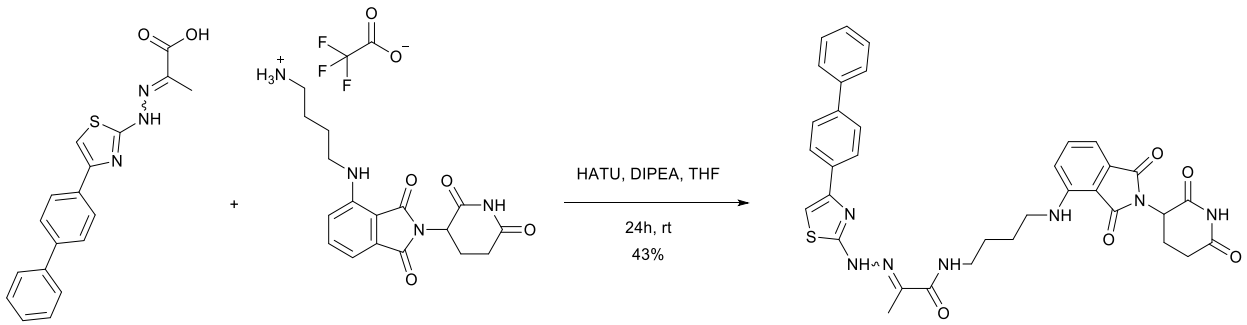
^{1}H NMR for i4EG-BiP



^{13}C NMR for i4EG-BiP

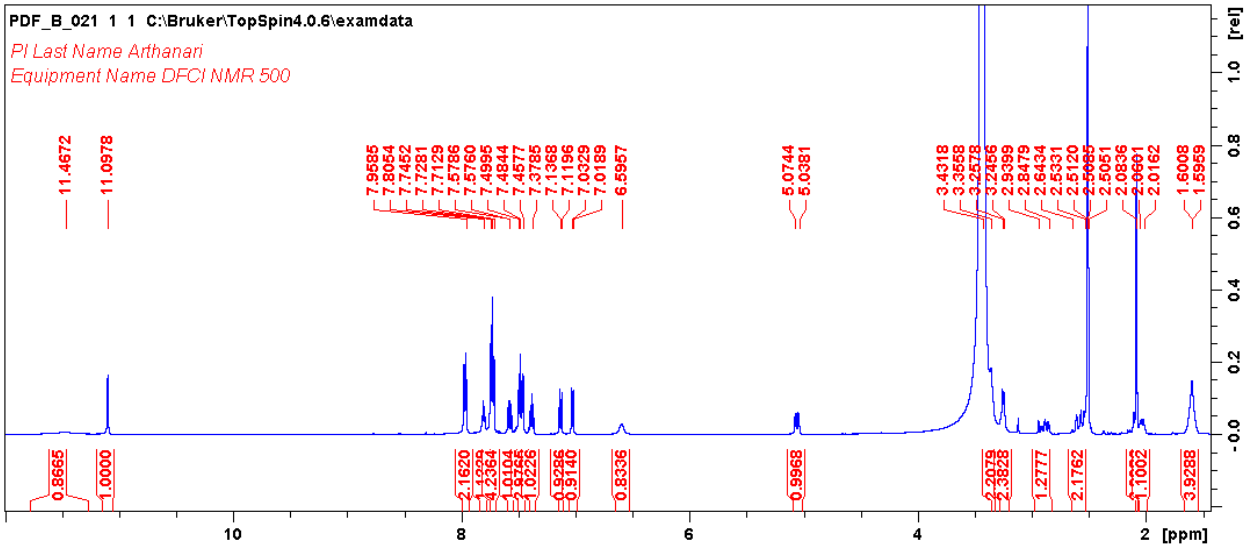


2-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazineylidene)-N-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)propenamide (d4E-2)

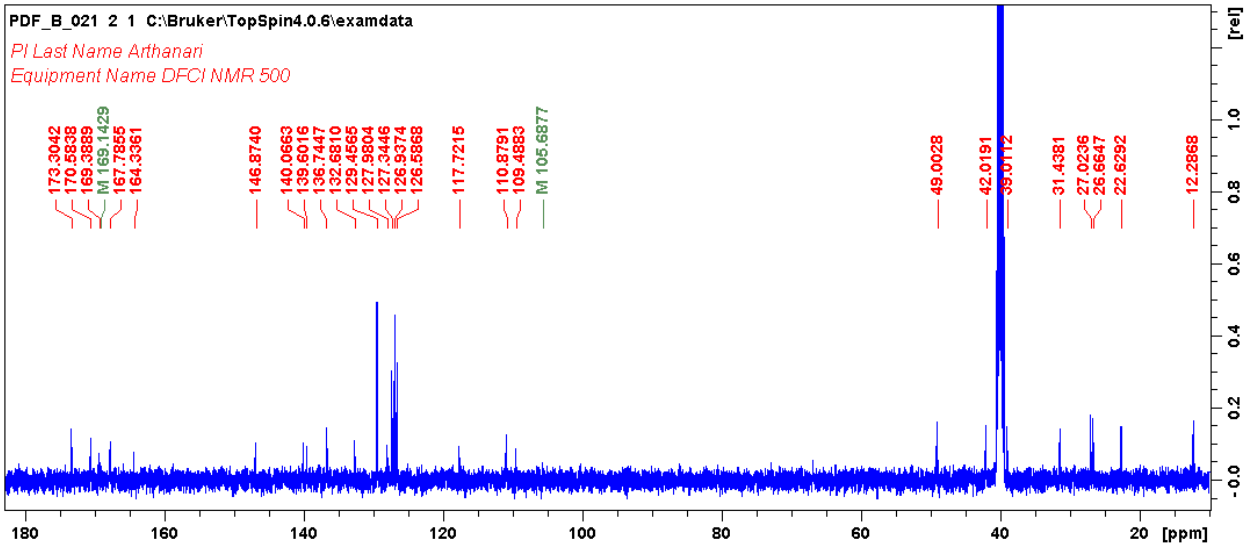


2-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazineylidene)propanoic acid (8.9 mg, 26.4 µmol, 1 Eq.), 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butan-1-aminium trifluoroacetate (12.1 mg, 26.4 µmol, 1 Eq.), and 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 10 mg, 26.4 µmol, 1 Eq.) were dissolved in tetrahydrofurane (2 mL). N,N-Diisopropylethylamine (DIPEA, 9.3 µL, 52.8 µmol, 2 Eq.) was added to the reaction mixture and stirred at room temperature for 24 h. The solvent was removed in vacuo and the product was purified using high performance liquid chromatography (HPLC, C18 reversed phase preparative column, water/acetonitrile 5/95).
Yield: 7.5 mg (11.4 µmol, 43 %) of a yellow solid.
^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 1.60 (m, 4H), 2.02-2.06 (m, 1H), 2.08 (s, 3H), 2.53-2.64 (m, 2H), 2.85-2.94 (m, 1H), 3.25 (m, 2H), 3.36 (m, 2H), 5.06 (dd, 1H, $^{3}J_{HH}$ = 13.1 Hz, 5.5 Hz), 6.60 (s, 1H), 7.03 (d, 1H, $^{3}J_{HH}$ = 7.0 Hz), 7.13 (d, 1H, $^{3}J_{HH}$ = 8.6 Hz), 7.38 (t, 1H, 7.3 Hz), 7.46-7.50 (m, 3H), 7.58 (dd, 1H, $^{3}J_{HH}$ = 8.6 Hz, 7.0 Hz), 7.73 (t, 4H, $^{3}J_{HH}$ = 8.1 Hz), 7.81 (t, 1H, $^{3}J_{HH}$ = 6.1 Hz), 7.97 (d, 1H, $^{3}J_{HH}$ = 8.5 Hz), 11.10 (s, 1H), 11.47 (s, 1H)
^{13}C-NMR (126 MHz, DMSO-d6): δ [ppm] = 12.29, 22.63, 26.66, 27.02, 31.44, 39.01, 42.02, 49.00, 105.69, 109.49, 110.88, 117.72, 126.59, 126.94, 127.34, 127.98, 129.46, 132.68, 136.74, 139.60, 140.07, 146.87, 164.34, 167.79, 169.14, 169.39, 170.58, 173.30
UPLC-MS: calc; [M +H]: 664.23 found [M + H]: 664.24

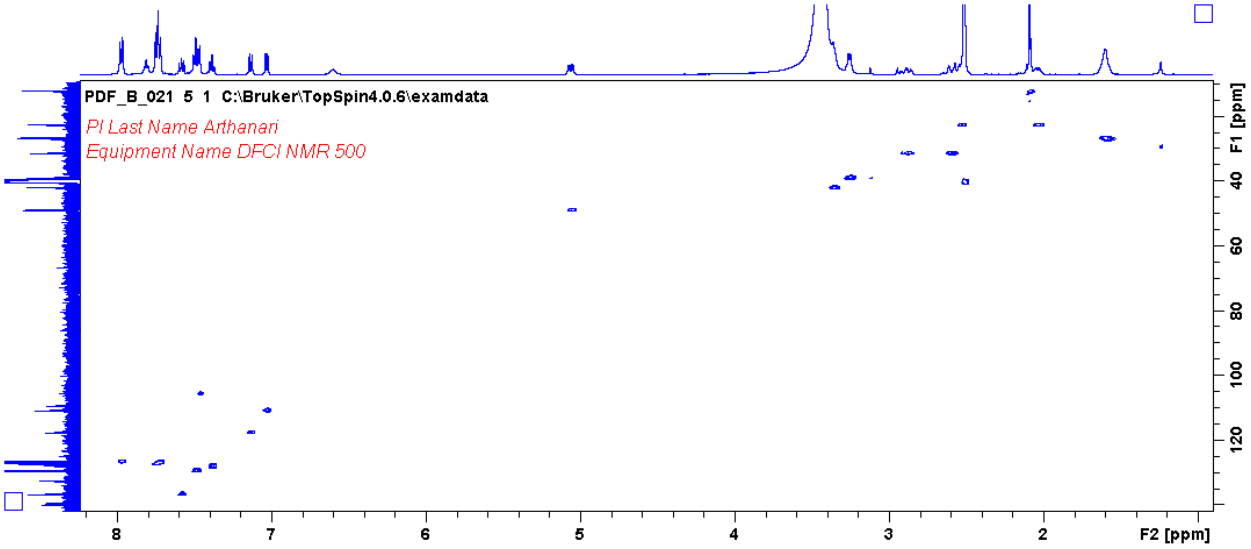
^{1}H NMR for d4E-2



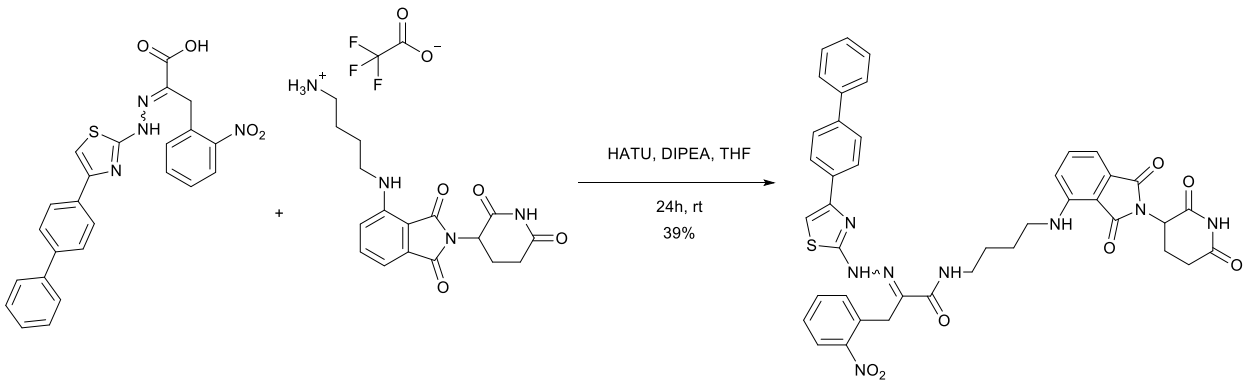
^{13}C NMR for d4E-2



^{1}H-^{13}C-HSQC for d4E-2



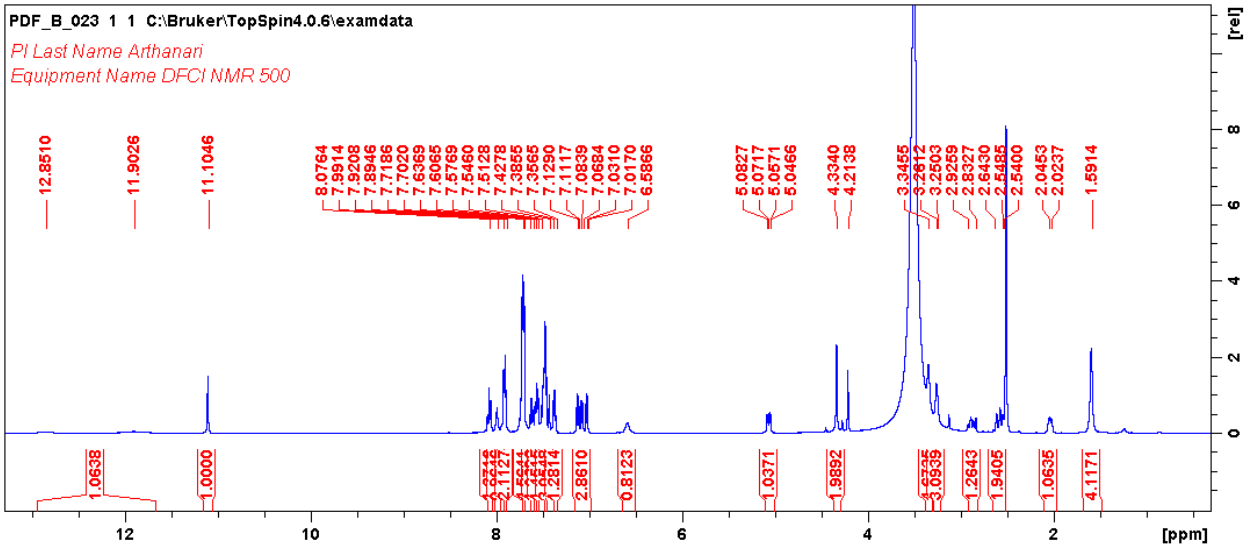
2-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazineylidene)-N-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)-3-(2-nitrophenyl)propenamide (d4E-3)



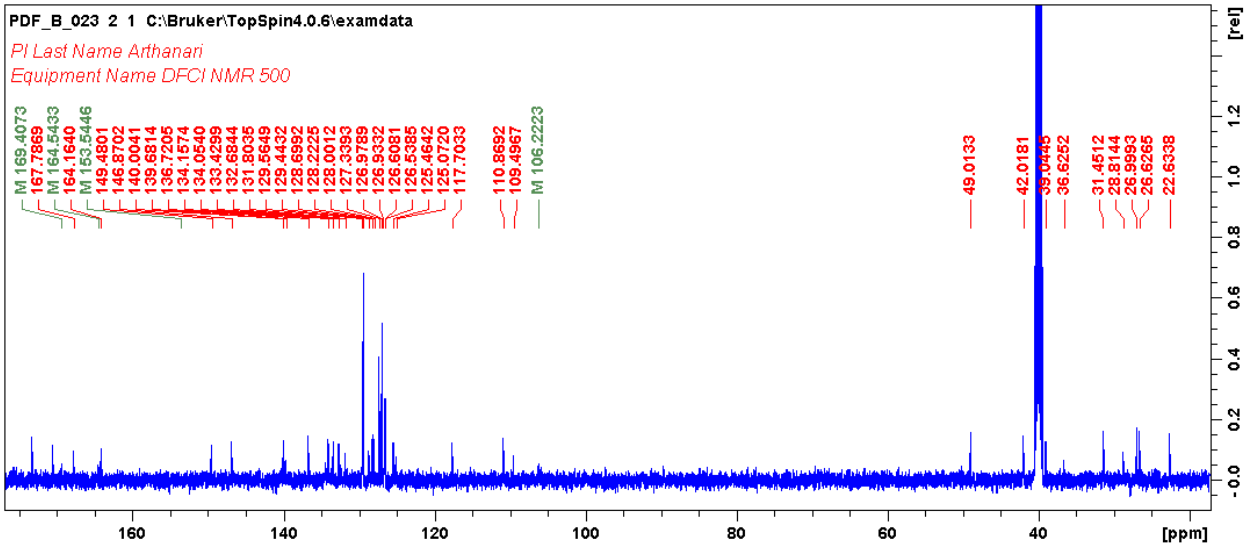
2-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazineylidene)-3-(2-nitrophenyl)propanoic acid (10.9 mg, 23.8 µmol, 1 Eq.), 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butan-1-aminium trifluoroacetate (10.9 mg, 23.8 µmol, 1 Eq.), and 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 9 mg, 23.8 µmol, 1 Eq.) were dissolved in tetrahydrofurane (2 mL). N,N-Diisopropylethylamine (DIPEA, 8.3 µL, 47.6 µmol, 2 Eq.) was added to the reaction mixture and stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the product was purified using high performance liquid chromatography (HPLC, C18 reversed phase preparative column, water/acetonitrile 5/95).
Yield: 7.3 mg (9.28 µmol, 39 %) of a yellow solid.
^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 1.59 (m, 4H), 2.02-2.05 (m, 1H), 2.54-2.64 (m, 2H), 2.83-2.93 (m, 1H), 3.25 (m, 2H), 3.35 (m, 2H), 4.21/4.33 (s, 2H), 5.06 (dd, 1H, $^{3}J_{HH}$ = 12.8 Hz, 5.5 Hz), 6.59 (s, 1H), 7.02 (d, 1H, $^{3}J_{HH}$ = 7.0 Hz), 7.08 (d, 1H, $^{3}J_{HH}$ = 7.7 Hz) 7.12 (d, 1H, $^{3}J_{HH}$ = 8.8 Hz), 7.37 (t, 1H, 7.3 Hz), 7.43-7.51 (m, 4H), 7.56 (dd, 1H, $^{3}J_{HH}$ = 8.6 Hz, 7.0 Hz), 7.62 (t, 1H, $^{3}J_{HH}$ = 7.6 Hz) 7.71 (t, 4H, $^{3}J_{HH}$ = 8.1 Hz), 7.89-7.92 (m, 1H), 7.99 (t, 1H, $^{3}J_{HH}$ = 6.1 Hz), 8.08 (t, 1H, $^{3}J_{HH}$ = 8.4 Hz) 11.10 (s, 1H), 11.90/12.85 (s, 1H)

^{13}C-NMR (126 MHz, DMSO-d6): δ [ppm] = 22.63, 26.63, 27.00, 28.81/36.63, 31.45, 39.04, 42.02, 49.01, 106.22, 109.49, 110.88, 117.72, 125.08, 125.47, 126.54, 126.61, 126.94, 126.98, 127.34, 128.01, 128.23, 128.70, 129.45/129.57, 131.81, 132.68, 133.43, 134.05, 134.15, 136.72, 139.68, 140.00, 146.87, 149.48, 149.60, 164.16, 164.53, 167.79, 169.14, 169.39, 170.58, 173.30
UPLC-MS: calc; [M +H]: 785.25 found [M + H]: 785.25

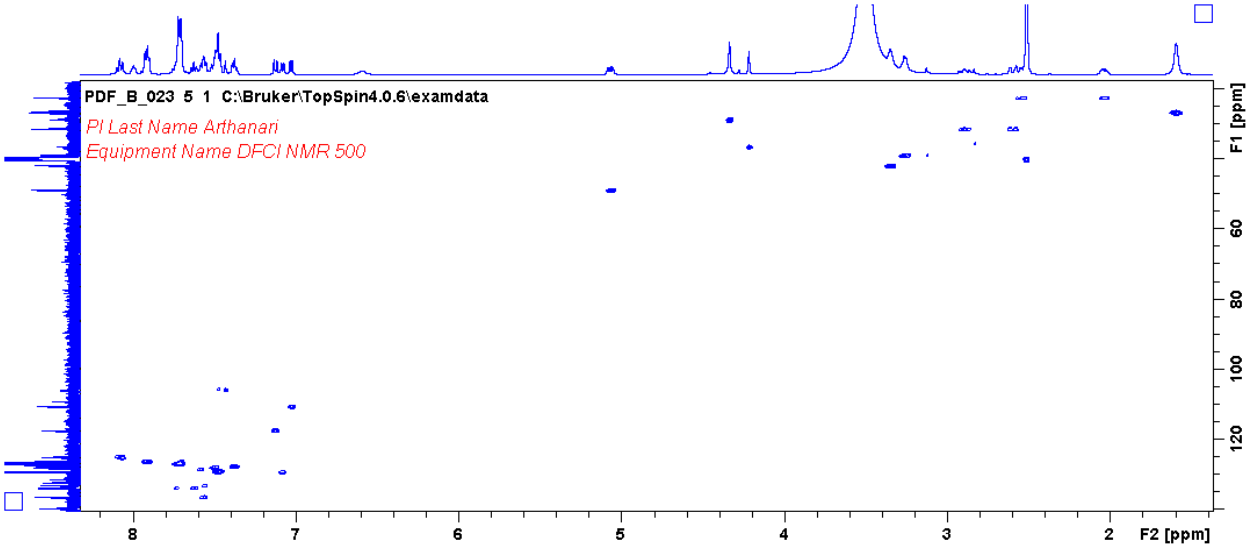
^{1}H NMR for d4E-3



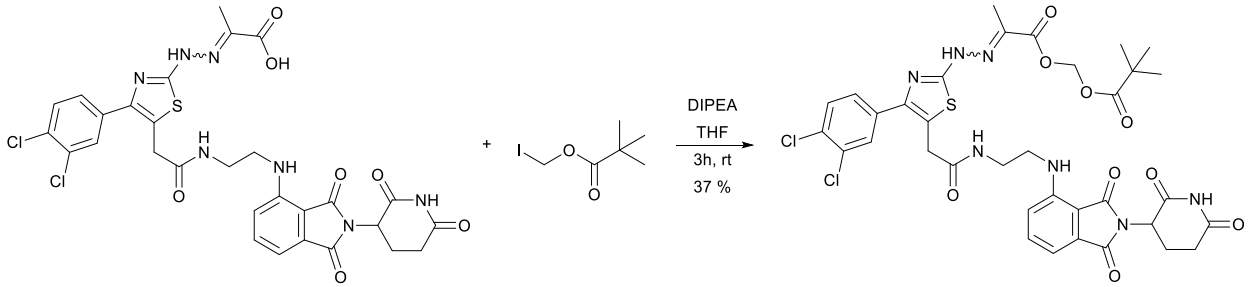
^{13}C NMR for d4E-3



^{1}H-^{13}C-HSQC for d4E-3



((2-(2-(4-(3,4-dichlorophenyl)-5-(2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)amino)-2-oxoethyl)thiazol-2-yl)hydrazineylidene)propanoyl)oxy)methyl pivalate (d4E-6)



2-(2-(4-(3,4-dichlorophenyl)-5-(2-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)amino)-2-oxoethyl)thiazol-2-yl)hydrazineylidene)propanoic acid (11 mg, 16 µmol, 1 Eq.) was dissolved in tetrahydrofurane (2 mL). Pivaloyloxymethyl iodide (4 µL, 16 µmol, 1 Eq.) and N,N-Diisopropylethylamine (DIPEA, 5.7 µL, 32 µmol, 2 Eq.) were added. The mixture was stirred at room temperature for 3 h. The solvent was removed *in vacuo* and the product was purified using high performance liquid chromatography (HPLC, C18 reversed phase preparative column, water/acetonitrile 5/95).

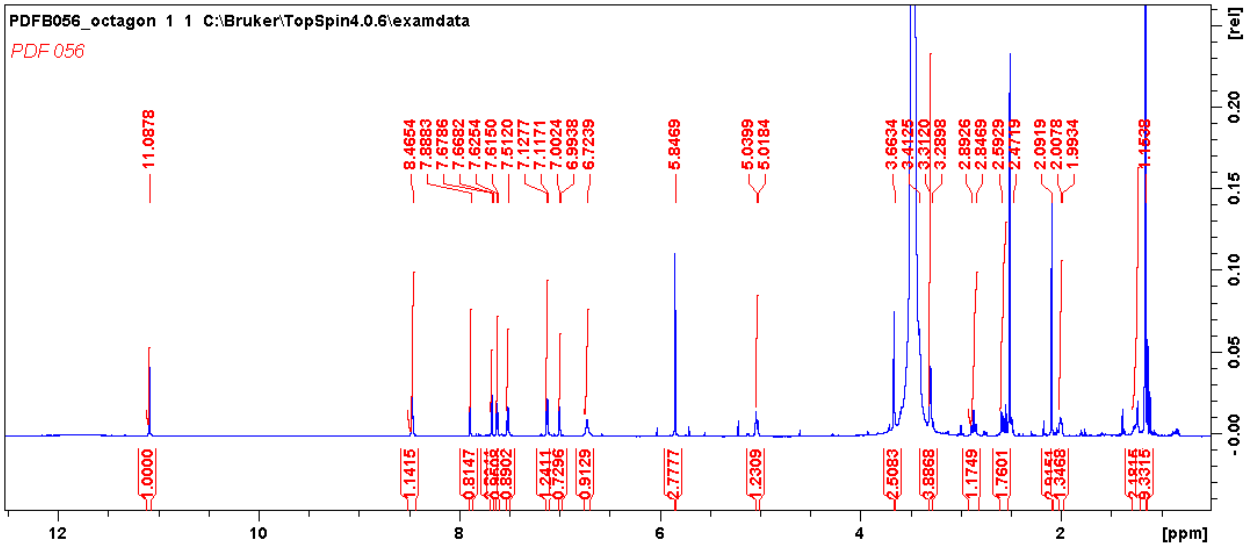
Yield: 4.7 mg (5.92 µmol, 37 %) of a yellow solid.

^{1}H-NMR (800 MHz, DMSO-d6): δ [ppm] = 1.15 (s, 9H), 1.99-2.01 (m, 1H), 2.09 (s, 3H), 2.47-2.59 (m, 2H), 2.85-2.89 (m, 1H), 3.29-3.31 (m, 2H), 3.41 (m, 2H), 3.66 (s, 2H), 5.02-5.04 (dd, 1H, $^{3}J_{HH}$ = 12.9 Hz, 5.3 Hz), 5.85 (s, 2H), 6.72 (s, 1H), 7.00 (d, 1H, $^{3}J_{HH}$ = 6.9 Hz), 7.12 (d, 1H, $^{3}J_{HH}$ = 7.9 Hz), 7.51 (t, 1H, $^{3}J_{HH}$ = 7.6 Hz), 7.62 (d, 1H, $^{3}J_{HH}$ = 8.4 Hz), 7.67 (d, 1H, $^{3}J_{HH}$ = 8.3 Hz), 7.89 (s, 1H), 8.47 (t, 1H, $^{3}J_{HH}$ = 5.3 Hz), 11.09 (s, 1H)

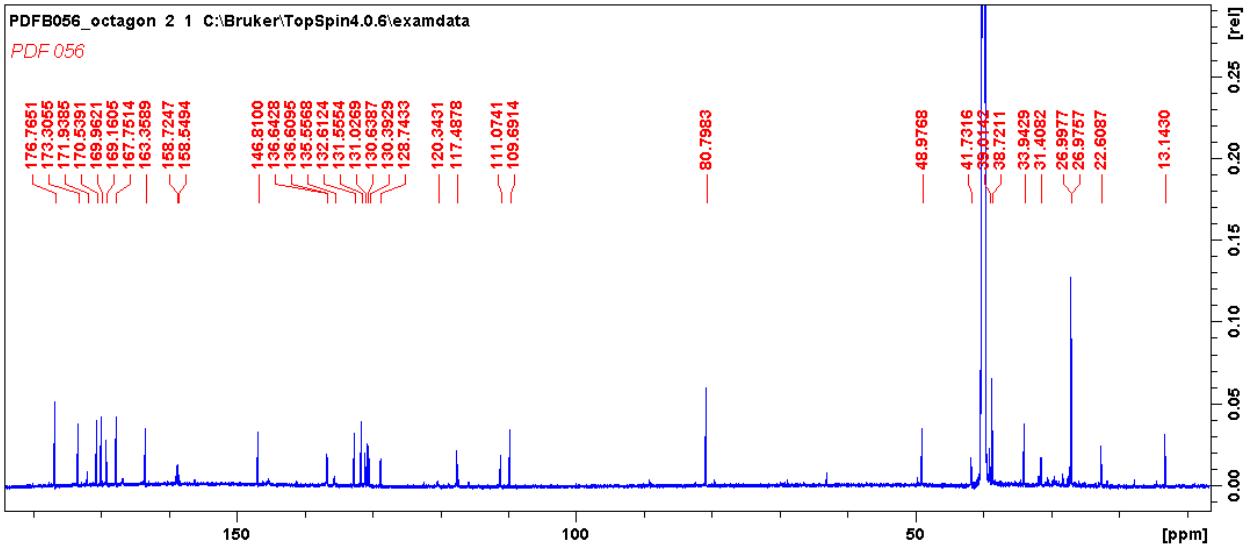
^{13}C-NMR (201 MHz, DMSO-d6): δ [ppm] = 12.86, 22.44, 31.29, 32.66, 33.87, 38.95, 48.91, 109.68, 111.08, 117.49, 120.04, 128.72, 128.76, 130.36, 130.42, 131.02, 131.53, 132.62, 135.86, 136.65, 136.71, 138.84, 146.83, 166.11, 167.75, 169.19, 170.03, 170.55, 173.23

UPLC-MS: calc; [M +H]: 800.17 found [M + H]: 800.15

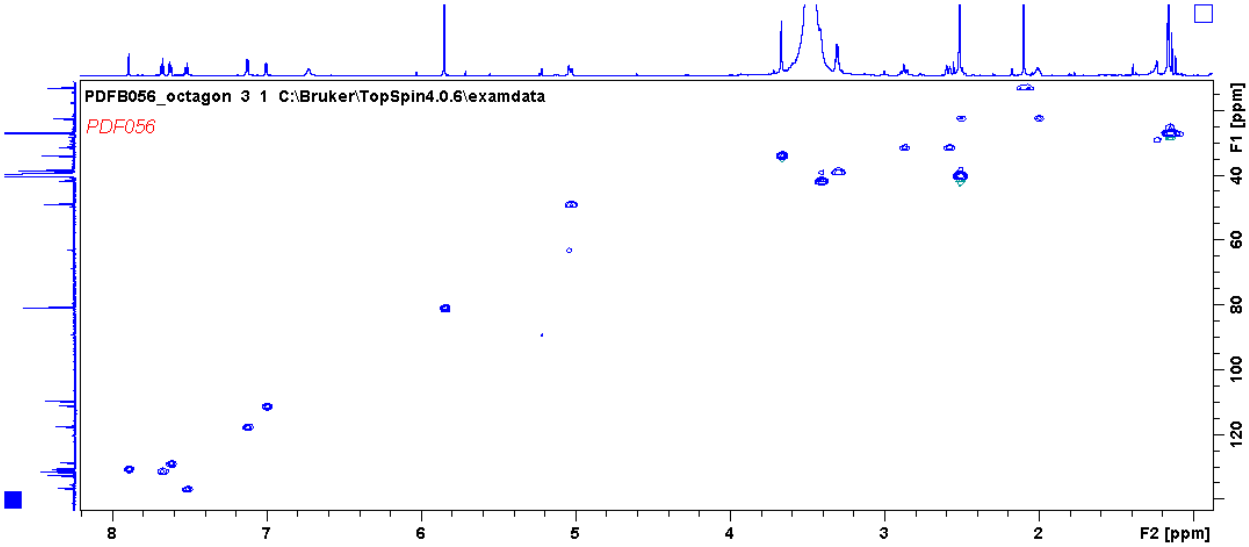
^{1}H NMR for d4E-6



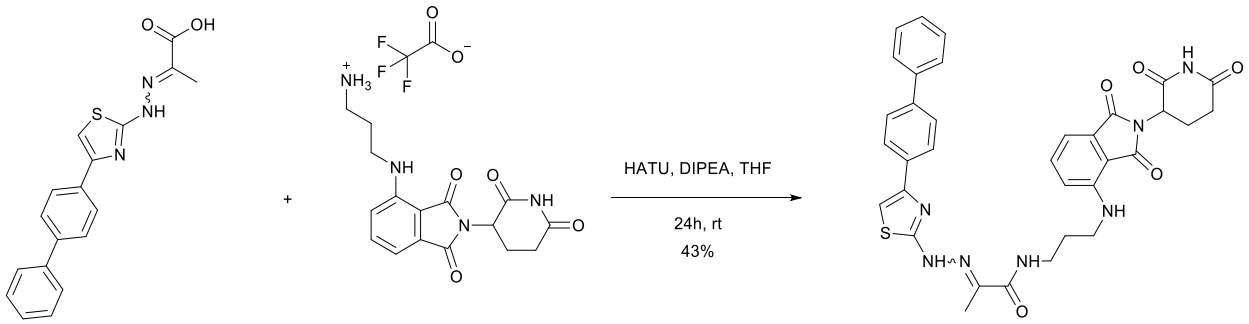
^{13}C NMR for d4E-6



^{1}H-^{13}C HSQC for d4E-6



2-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazineylidene)-N-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)propenamide (d4E-5)



2-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazineylidene)propanoic acid (7.5 mg, 22.3 µmol, 1 Eq.), 3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propan-1-aminium trifluoroacetate (9.9 mg, 22.3 µmol, 1 Eq.), and 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 8.5 mg, 22.3 µmol, 1 Eq.) were dissolved in tetrahydrofurane (2 mL). N,N-Diisopropylethylamine (DIPEA, 8 µL, 44.6 µmol, 2 Eq.) was added to the reaction mixture and stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the coupling product was used without further purification. Trifluoroacetic acetic (12 % in dichloromethane, 2 mL) was added and the mixture was stirred at room temperature for 3 h. The solvent was removed in vacuo and the product was purified using high performance liquid chromatography (HPLC, C18 reversed phase preparative column, water/acetonitrile 5/95).

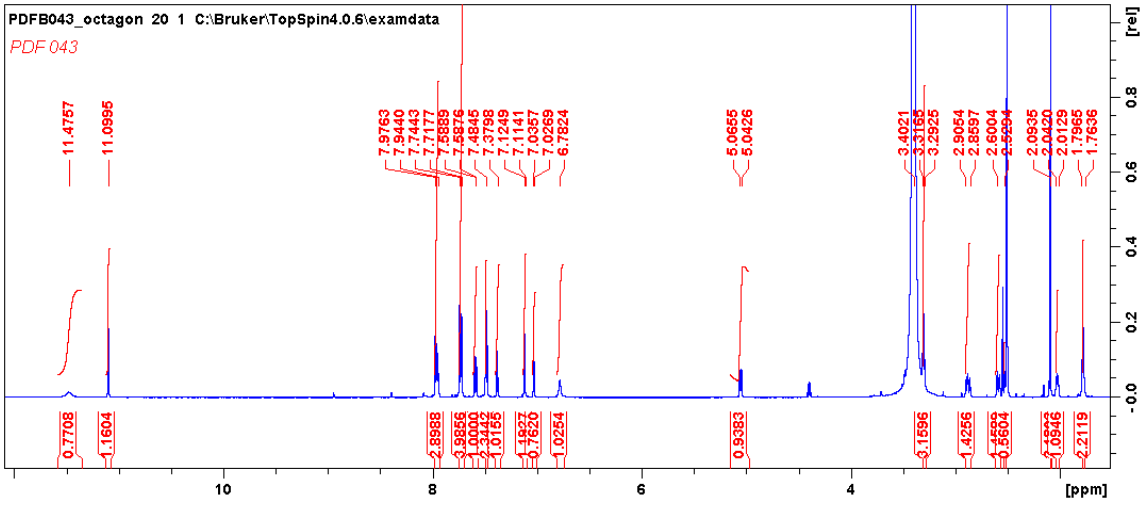
Yield: 6.2 mg (9.6 µmol, 43 %) of a yellow solid.

^{1}H-NMR (800 MHz, DMSO-d6): δ [ppm] = 1.76-1.80 (dt, 2H, $^{3}J_{HH}$ = 6.4 Hz, 6.8 Hz), 2.01-2.04 (m, 1H), 2.09 (s, 3H), 2.53-2.60 (m, 2H), 2.86-2.91 (m, 1H), 3.29-3.32 (m, 4H), 5.04-5.07 (dd, 1H, $^{3}J_{HH}$ = 12.6 Hz, 4.9 Hz), 6.78 (s, 1H), 7.03 (d, 1H, $^{3}J_{HH}$ = 7.0 Hz), 7.12 (d, 1H, $^{3}J_{HH}$ = 8.6 Hz), 7.38 (t, 1H, $^{3}J_{HH}$ = 7.3 Hz), 7.48 (t, 2H, $^{3}J_{HH}$ = 7.6 Hz), 7.59 (dd, 1H, $^{3}J_{HH}$ = 8.4 Hz, 7.3 Hz), 7.72-7.74 (m, 4H), 7.94-7.98 (m, 3H), 11.10 (s, 1H), 11.47 (s, 1H)

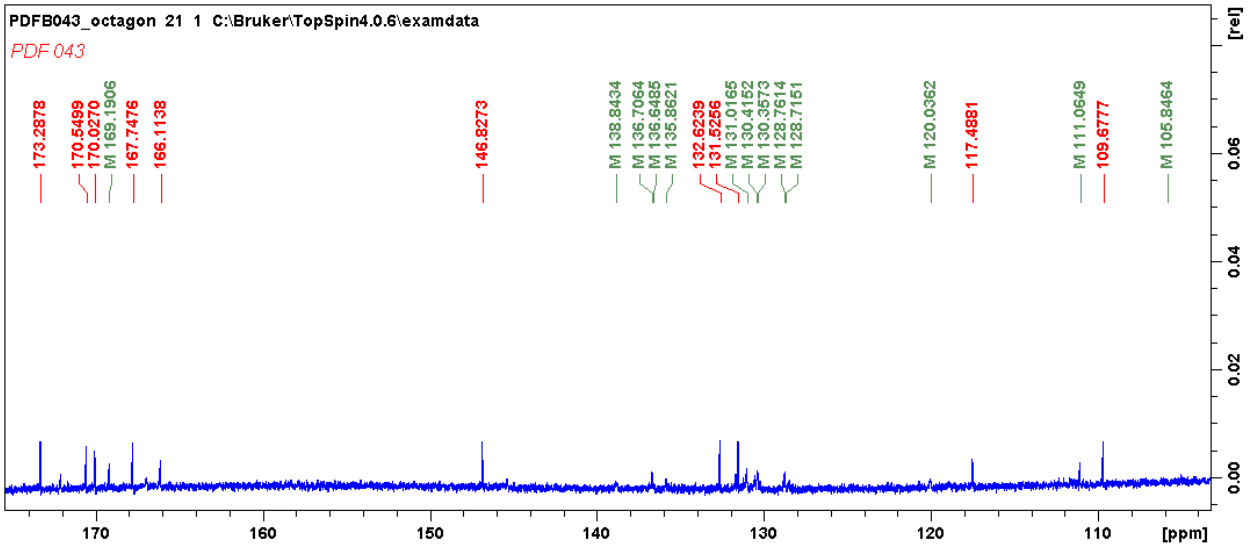
^{13}C-NMR (201 MHz, DMSO-d6): δ [ppm] = 13.14, 22.61, 26.98, 27.00, 31.41, 33.94, 38.72, 39.01, 41.73, 80.80, 105.85, 109.69, 111.07, 117.49, 120.34, 128.74, 130.39, 130.64, 131.03, 131.56, 132.61, 135.56, 136.61, 136.64, 146.81, 158.55, 158.72, 163.36. 167.75, 169.16, 170.54, 171.94, 173.31, 176.77

UPLC-MS: calc; [M +H]: 650.22 found [M + H]: 650.21

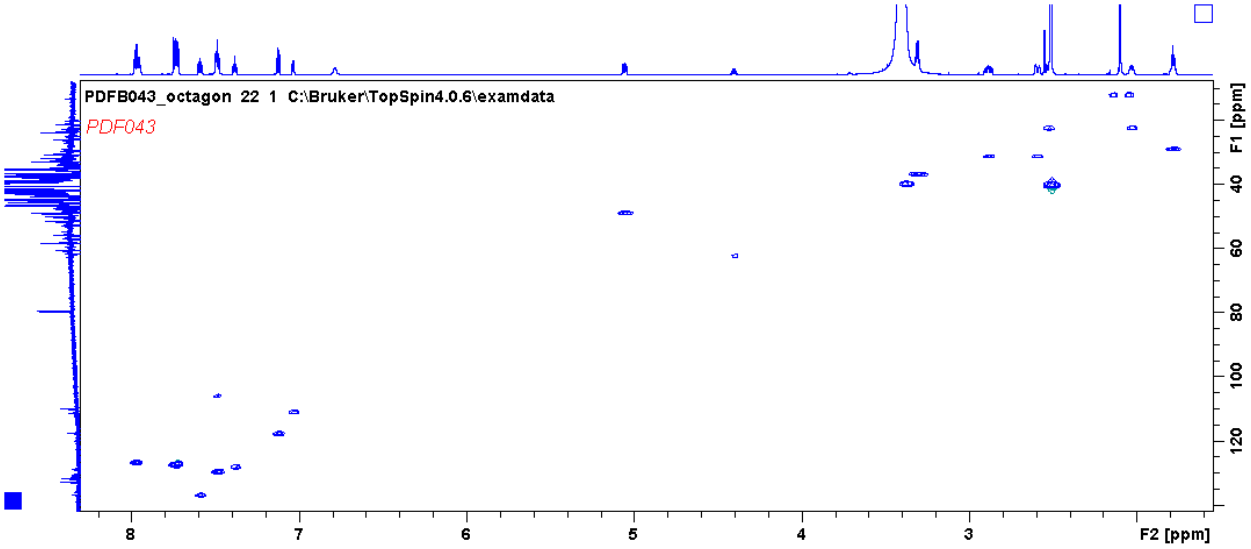
^{1}H NMR for d4E-5



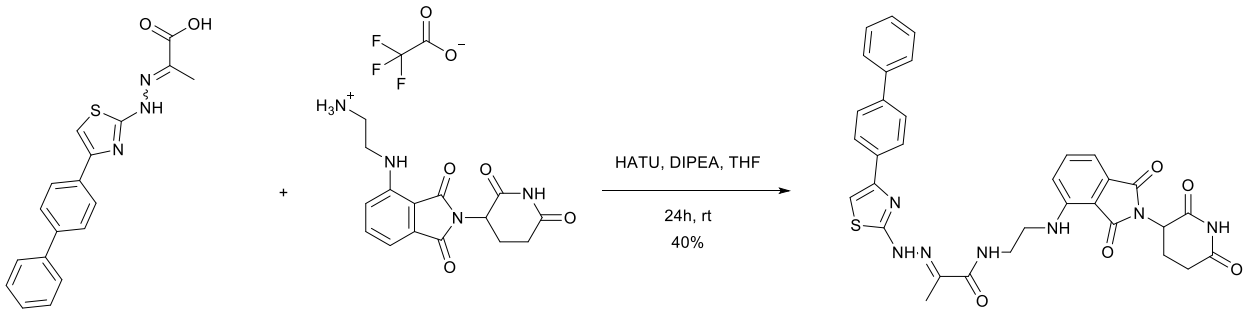
^{13}C NMR for d4E-5 (aromatics and carbonyl, aliphatic carbon peaks were assigned from HSQC)



^{1}H-^{13}C HSQC for d4E-5

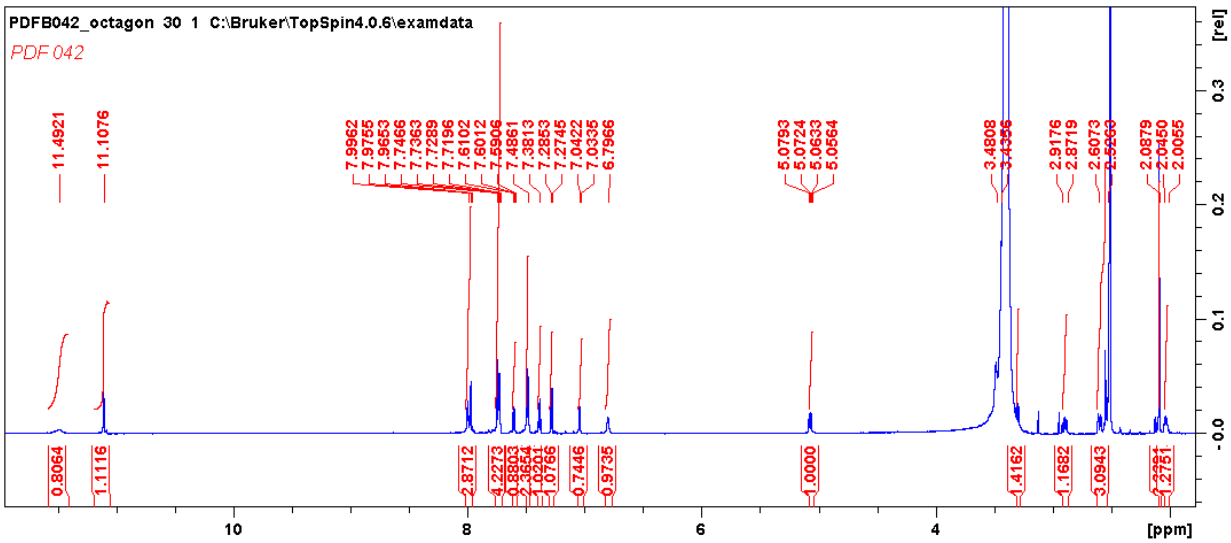


2-(2-(4-([1,1'-biphenyl]-4-yl)thiazol-2-yl)hydrazineylidene)-N-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)propenamide (d4E-4)

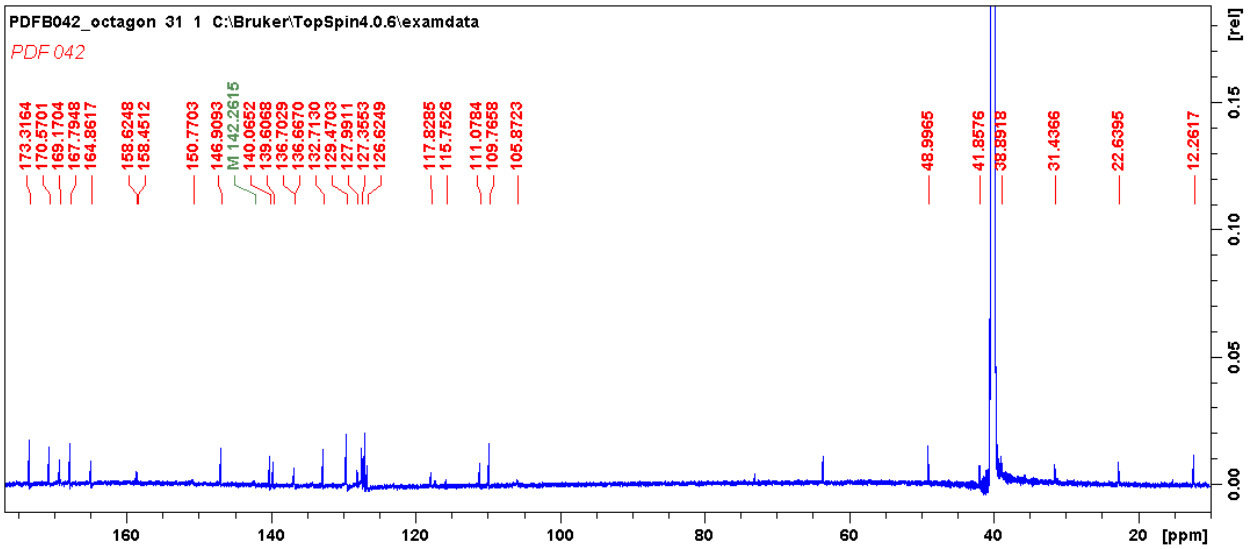


^{1}H-NMR (800 MHz, DMSO-d6): δ [ppm] = 2.01-2.05 (m, 1H), 2.09 (s, 3H), 2.53-2.61 (m, 2H), 2.87-2.92 (m, 1H), 3.43 (m, 2H), 3.48 (m, 2H), 5.06-5.05 (dd, 1H, $^{3}J_{HH}$ = 13.2 Hz, 5.9 Hz), 6.80 (s, 1H), 7.04 (d, 1H, $^{3}J_{HH}$ = 7.0 Hz), 7.28 (d, 1H, $^{3}J_{HH}$ = 8.7 Hz), 7.38 (t, 1H, $^{3}J_{HH}$ = 7.3 Hz), 7.48-7.50 (t, 2H, $^{3}J_{HH}$ = 7.9 Hz), 7.59-7.61 (dd, 1H, , $^{3}J_{HH}$ = 7.4 Hz, 6.7 Hz), 7.72-7.75 (m, 4H), 7.97 (d, 2H, $^{3}J_{HH}$ = 8.2 Hz), 8.00 (t, 1H, $^{3}J_{HH}$ = 5.9 Hz), 11.11 (s, 1H), 11.49 (s, 1H)
^{13}C-NMR (201 MHz, DMSO-d6): δ [ppm] = 12.26, 22.64, 31.44, 38.89, 41.86, 49.00, 105.87, 109.76, 111.08, 115.75, 117.83, 126.62, 127.36, 127.99, 129.47, 132.71, 136.67, 136.70, 139.61, 140.07, 142.26, 146.91, 150.77, 158.45, 158.62, 164.86, 167.96, 169.17, 170.57, 173.32
UPLC-MS: calc; [M +H]: 650.22 found [M + H]: 650.21

^{1}H NMR for d4E-4



^{13}C NMR for d4E-4



^{1}H-^{13}C HSQC for d4E-4