Targeting Glycolysis: A Fragment Based Approach Towards Bifunctional Inhibitors of *h*LDH-5

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Electronic Supporting Information

1.1 General Information

Melting points (m.p.) were recorded on Stuart Scientific SMP1 and SMP3 melting point apparatus and are uncorrected. "250 dec." (e.g.) refers to decomposition observed at 250°C.

IR spectra were recorded using a Perkin Elmer SPECTRUM 1000 FT-IR spectrometer fitted with a golden gate solid phase sample mount, an Avatar 320 FT-IR with a golden gate solid phase sample mount, and a Bruker Tensor 27 FT-IR.

NMR spectra were recorded at 500 MHz, 400 MHz (^{1}H NMR) and 125 MHz, 100 MHz (^{13}C NMR) on Bruker 500 and 400 spectrometers respectively in $CDCl_3$, $(CD_3)_2CO$, or DMSO-d_6 using the residual solvent peaks as internal standards. Coupling constant *J* values are given in hertz (Hz) designated as s (singlet), d (doublet), t (triplet), q (quartet), apt t (apparent triplet), apt quin (apparent quintet), m (multiplet) and bs (broad singlet). Signal assignments were done using 2D NMR (COSY, HMQC, HMBC, NOESY and nOe experiments) and DEPT.

HRMS were conducted upon a Micromass Q-TTOF Ultima Global tandem mass spectrometer run under electrospray ionisation (ESI) or matrix assisted laser desorption/ionisation (MALDI) modes or a Bruker MicroTOF mass spectrometer run under ESI (+ve and –ve ion modes). CHN were conducted upon a Carlo Erba CHN1108 elemental analyser and an Exceter analytical CE-440 Elemental Analyser.

1.2 Bioassy

Plate Reader: A SUNRISE 96-well plate reader (supplied from Tecan) equipped with a 360nm filter and a UV/Vis detector was utilized for the collection of the data. Magellan V3.11 / 3,1,1,1 (provided by Tecan) was the software utilized to manipulate the data and calculate the rate of absorbance as a function of time (s).

Enzymes:

L-Lactate dehydrogenase solution, type II (*r*LDH-5): From rabbit muscle, crystalline suspension in 3.2M $(NH_4)_2SO_4$ solution pH 6.0. 0.38mL; 11.4 mg protein/mL (Biuret); 1150 units/mg protein. Provided by SIGMA.

L-Lactate dehydrogenase solution, type III (*b*LDH-1): From bovine heart, suspension in 2.1 M $(NH_4)_2SO_4$ solution pH 6.0 < 0.03% pyruvaye kinase activity 8.5 mg protein/mL (Biuret) 621 units/mg protein. Provided by SIGMA.

Lacatate dehydorgenase LHD-5 isoenzyme solution (*h*LDH-5): From human liver, $(NH_4)_2SO_4$ suspension of 75% in 50 mM tris-chloride, 1 mM DTE, 1 mM EDTA pH 8.3 : 450 units/mL. Purity 100% by electrophoresis. Provided by LEE BIOSOLUTIONS, INC.

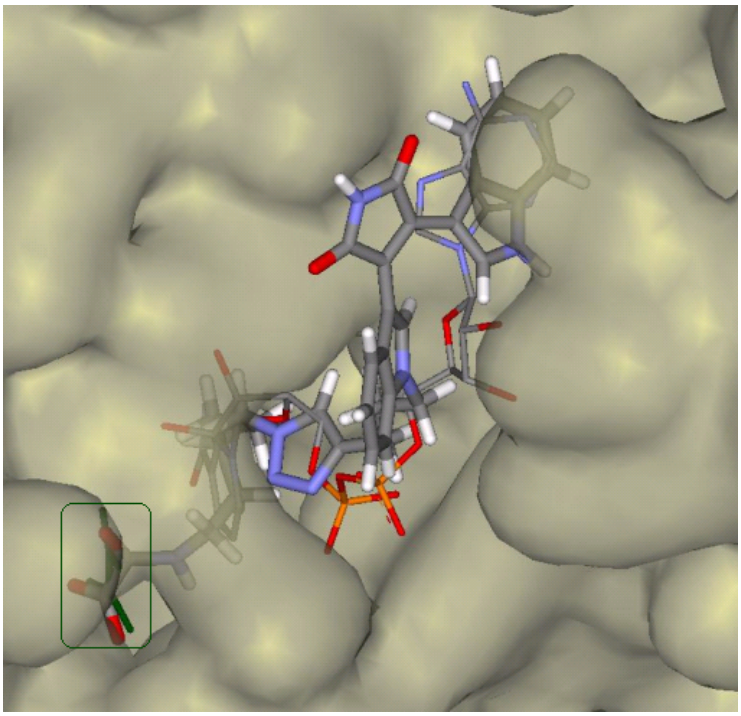
Briefly: LDH catalyses the conversion of pyruvate into lactate, in the presence of NADH as co-factor. In the process NADH, which absorb at 340 nm, is oxidised into NAD^+, which possess no UV-activity at this wavelength. The assay used was based on monitoring the rate of decrease in absorption of NADH as a function of time, in seconds, at 340 nm. Initially, all compounds were screened for inhibition at 50 and 100 μg/mL, using potassium orthophosphate buffer (50 mM), pH 7.01, as solvent medium. Each compound (2 mg) were dissolved in 0.5 mL of DMSO and diluted with buffer to a final concentration of 50 and 100 μg/mL.

Subsequently, each well (96-well plate) was filled up to a total volume of 0.2 mL with pyruvate (200 μM in 50 mM buffer), with a solution of the test compound and with a solution of enzyme. After a brief incubation period (204 s) at 30 ^{0}C, a solution of NADH (259 mM in 50 mM of buffer) was added to each well and the UV-absorption was monitored over 20 min at 30 ^{0}C. Meanwhile, two blanks were run alongside each compound; one having sodium oxamte and the other without any inhibitor. Compounds which were found to inhibit were re-investigate at 100, 50, 25, 20, 15, 12, 6, 3, 1.5 and 0 μg/mL and their IC_{50} was determined using a four-parameter logistic equation (software used GraphPad Prism for Windows V5.02).

1.3 Figures, Tables and Modeling

Preliminary modeling:

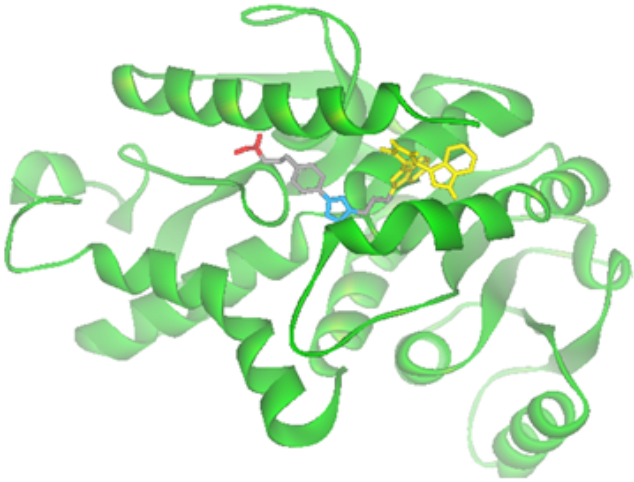
The protein data bank (PDB) file 1I10 of LDH in the ternary complex with NADH and oxamate was used as a target structure. One chain was selected and both ligands were deleted. A grid was prepared with the center defined by the position of native ligand. All three midpoint box diameters under "Advanced settings" were set to 14 Å and the "Dock ligands with length" was set to 10 Å. The docking was performed without scaling and default values were used for all other settings. Initially, the structure of NADH was docked into the binding site and comparison of the output pose from Glide and the experimentally observed pose of NADH was performed in Maestro by superimposition of all heavy atoms in common. Ligand **1** was then docked flexibly allowing generation of up to 5000 initial conformations and refinement of 400 poses with the best scoring pose retained. Output poses were exported as mol2 files and for comparison they imported into Accelrys DS visulaizer 1.7 to overlap with the position with native substrates (NADH and oxamate) in the LDH binding site.



F1: Docking of ligand **1** into the active site of *h*LDH-5. The thin green lines represent oxamate (within the green box) bound in the substrate site, the thin grey lines represent the cofactor (NADH), and the thick grey lines represent the ligand **1**.

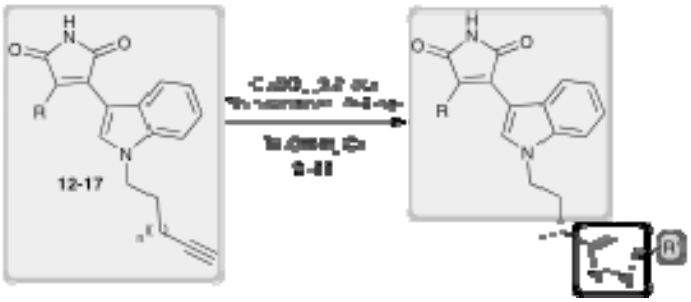
Modeling of 24, 29 and 31

Ligands **24**, **29** and **31** were subjected to a conformational search using Monte Carlo Multiple Minimum method and MMFFS force field implemented in Macromodel 9.5 (Schrodinger LLC). The resulting lowest energy conformation was used as a starting structure for the flexible docking into the binding site of the M-chain of LDH (PDB entry: 1i10). The protein and ligands were prepared using AutoDock Tools 1.54 and docking was carried out using AutoDock 4.2.



F2: The 3D representation of **24** docked into the binding site of M-chain of LDH. Proteins is represented as ribbon, BIM moiety in yellow, triazole linker in blue and carboxylic acid in red.

T1: Syntheses of bifunctional ligands **18-48** and initial high throughput screen.[a]



Alkyne / Azide	**12**	**13**	**14**	**15**	**16**	**17**
2	18 [52 %][a]	28 [60 %][a]	36 [58 %][a]	- -	- -	- -
3	19 [42 %][a]	29[b] [59 %][a]	37 [66 %][a]	- -	- -	- -
4	20 [56 %][a]	30 [59 %][a]	38 [64 %][a]	- -	- -	- -
5	21 [59 %][a]	- -	- -	43 [61 %][a]	- -	- -
6	22 [43 %][a]	31[b] [57 %][a]	- -	44 [60 %][a]	47 [61 %][a]	48 [59 %][a]
7	23 [57 %][a]	32 [49 %][a]	- -	45 [54 %][a]	- -	- -
8	24[b] [70 %][a]	33 [66 %][a]	39 [62 %][a]	46 [68 %][a]	- -	- -
9	25 [71 %][a]	34 [30 %][a]	40 [55 %][a]	- -	- -	- -
10	26 [76 %][a]	35 [32 %][a]	41 [55 %][a]	- -	- -	- -
11	27 [83 %][a]	- -	42 [79 %][a]	- -	- -	- -

[a] values in [square brackets] are isolated yields

[b] Displayed equivalent or superior activity against *h*LDH-5 in high throughput screen

T2: Compounds which showed LDH inhibition in the high concentration preliminary screen.

Compound	IC_{50} (μM)[a]		
	***h*LDH-5**	***r*LDH-5**	***b*LDH-1**
Sodium oxamate	130.6 ± 1.2	136.5 ± 1.1	123.6 ± 1.1
24	14.8 ± 1.2	10.0 ± 1.0	NA[b]
29	35.9 ± 1.2	NA[b]	NA[b]
31	173.8 ± 1.2	81.8 ± 1.1	NA[b]

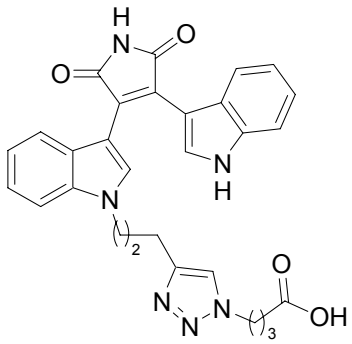
[a] The specific enzyme activity (concentration of active enzyme protein) for each enzyme was different and therefore, the IC_{50} of a particular enzyme cannot be directly compared.

[b] NA = not active

1.4 Experimental

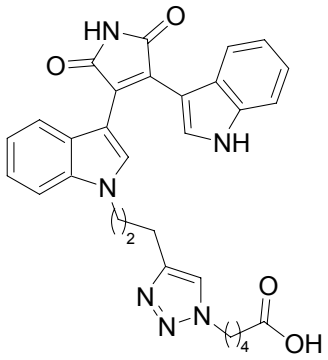
General procedureA: Azido acid (1.3 equiv.), the corresponding alkyne fragment (1 equiv.), $CuSO_4.5H_2O$ (0.2 equiv.), sodium ascorbate (0.5 equiv.), ^{t}BuOH (3.0 mL) and H_2O (1.0 mL) were added to a microwave vial. The microwave vial was then sealed and heated with microwave radiation for 20 min at 100 °C. The reaction mixture was then diluted with H_2O (20 mL) and cooled to 0 °C before the solid product was removed by filtration. The solid material was then passed through a short silica gel column (Et_2O to 50 % Acetone/Et_2O) to give the product.

Synthesis of 4-(4-(3-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3)triazol-1-yl)-butyric acid (18)



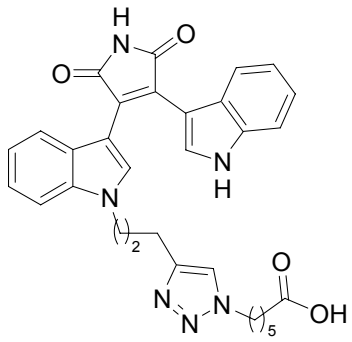
Following general **procedure A**: 4-Azidobutyric acid (85.0 mg, 0.659 mmol), and the corresponding alkyne fragment (200 mg, 0.509 mmol), gave the product as a bright red solid (140 mg, 0.268 mmol, 53 %); **m.p.** 229-231 °C; υ_{max} (solid)/cm^{-1} 1696 (CO);δ_H **(400 MHz, DMSO-d$_6$)** 1.96-2.12 (m, 4 H), 2.22 (t, *J* 7.0 Hz, 2 H), 2.56 (t, *J* 7.5 Hz, 2 H), 4.26-4.37 (m, 4 H), 6.57 (apt t, *J* 7.5 Hz, 1 H), 6.67 (apt t, *J* 7.5 Hz, 1 H), 6.75 (d, *J* 8.0 Hz, 1 H), 6.86 (d, *J* 8.0 Hz, 1 H), 6.92 (apt t, *J* 7.5 Hz, 1 H), 7.02 (apt t, *J* 7.6 Hz, 1 H), 7.34 (d, *J* 8.1 Hz, 1 H), 7.45 (apt t*J* 7.6 Hz, 1 H), 7.76 (s, 1 H), 7.78 (d, *J* 2.6 Hz, 1 H), 7.83 (s, 1 H), 10.89 (s, 1 H), 11.65 (s, 1 H), 12.16 (s, 1 H); δ_C **(100 MHz, DMSO-d$_6$)** 22.1, 25.2, 29.3, 30.4, 45.2, 48.5, 105.0, 105.5, 110.2, 111.7, 119.3, 119.5, 120.9, 121.2, 121.5, 121.7, 121.9, 125.2, 126.1, 127.0, 128.0, 129.2, 131.9, 135.7, 135.9, 146.0, 172.9 (2C), 173.6; **HRMS**: Found 521.1949 $C_{29}H_{25}N_6O_4[M-H]^-$ requires 521.1943.

Synthesis of 5-(4-(3-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3)triazol-1-yl)-pentanoic acid (19)



Following general **procedure A**: 5-azidopentanoic acid (95.0 mg, 0.664 mmol), and the corresponding alkyne fragment (200 mg, 0.509 mmol), gave the product as a bright red solid (115 mg, 0.214mmol, 42%); **m.p.** 224-228 °C; υ_{max} (solid)/cm^{-1} 1698 (CO); **δ_H (400 MHz, DMSO-d_6)** 1.44 (apt quin, *J* 7.4, 2 H), 1.78 (apt quin, *J* 7.4 Hz, 2 H), 2.05 (apt quin, *J* 7.3 Hz, 2 H), 2.24 (t, *J* 7.4 Hz, 2 H), 2.56 (t, *J* 7.6 Hz, 2 H), 4.30 (apt t, *J* 7.0 Hz, 4 H), 6.57 (apt t, 7.1 Hz, 1 H), 6.67 (apt t, *J* 7.2 Hz, 1 H), 6.74 (d, *J* 8.0 Hz, 1 H), 6.86 (d, *J* 8.0 Hz, 1 H), 6.92 (apt t, *J* 7.6 Hz, 1 H), 7.02 (apt t, *J* 7.6 Hz, 1 H), 7.34 (d, *J* 8.1 Hz, 1 H), 7.45 (d, *J* 8.3 Hz, 1 H), 7.76 (s, 1 H), 7.78 (d, *J* 2.8 Hz, 1 H), 7.82 (s, 1 H), 10.90 (s, 1 H), 11.66 (d, *J* 2.5 Hz, 1 H), 12.04 (s, 1 H); **δ_C (125 MHz, DMSO-d_6)** 21.5, 22.2, 29.2, 29.4, 32.9, 45.2, 48.9, 105.0, 105.5, 110.2, 111.8, 119.3, 119.5, 120.9, 121.2, 121.6, 121.7, 121.9, 125.3, 126.1, 127.0, 128.0, 129.3, 131.9, 135.7, 136.0, 145.9, 173.0 (2C), 174.3; **HRMS**: Found 535.2112 $C_{30}H_{27}N_6O_4$[M-H]$^-$requires 535.2099.

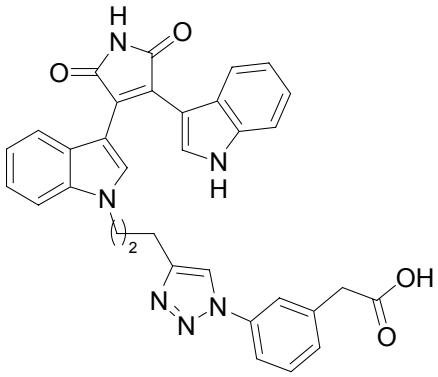
Synthesis of 6-(4-(3-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3)triazol-1-yl)-hexanoic acid (20)



Following general **procedure A**: 6-azidohexanoic acid (104 mg, 0.662 mmol), and the corresponding alkyne fragment (200 mg, 0.509 mmol), gave the product as a bright red solid (157 mg, 0.285 mmol, 56 %); m.p. 228-230 °C; υ_{max} (solid)/cm^{-1} 1697 (CO); **δ_H (400 MHz, DMSO-d_6)** 1.23 (apt quin, *J* 7.4 Hz, 2 H), 1.51 (apt quin, *J* 7.4 Hz, 2 H), 1.79 (apt quin, *J* 7.4 Hz, 2 H), 2.07 (apt quin, *J* 7.3 Hz, 2 H), 2.19 (t, *J* 7.4 Hz, 2 H), 2.56 (t, *J* 7.3 Hz, 2 H), 4.28 (t, *J* 7.4 Hz, 2 H), 4.30 (t, *J* 7.3 Hz, 2 H), 6.57 (apt t, *J* 7.6 Hz, 1 H), 6.67 (apt t, *J* 7.5 Hz, 1 H), 6.75 (d, *J* 8.0 Hz, 1 H), 6.86 (d, *J* 8.0 Hz, 1 H), 6.92 (apt t, *J* 7.6 Hz, 1 H), 7.02 (apt t, *J* 7.7 Hz, 1 H), 7.35 (d, *J* 8.1 Hz, 1 H), 7.45 (d, *J* 7.5 Hz, 1 H), 7.76 (s, 1 H), 7.79 (d, *J* 2.5 Hz, 1 H), 7.82 (s, 1 H), 10.91 (s, 1 H), 11.67 (d, *J* 2.5 Hz, 1 H), 11.99 (s, 1 H); **δ_C (125 MHz,DMSO-d_6)** 22.2, 23.9, 25.5, 29.4, 29.5, 33.5, 45.2, 49.1, 105.0, 105.5, 110.2, 111.8, 119.3, 119.6, 120.9, 121.2, 121.6, 121.7, 121.8, 125.3, 126.1, 127.0, 128.0, 129.3, 132.0, 135.7, 136.0, 145.9, 179.0, 173.0, 174.4; **HRMS**: Found 549.2253 $C_{31}H_{29}N_6O_4$[M-H]$^-$requires 549.2256.

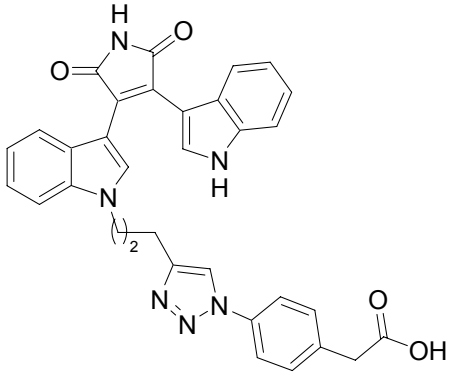
General procedure B: The aniline analogue (1.3 equiv.) was dissolved in CH_3CN (0.7 mL) and cooled to 0 °C in a microwave vial. To this solution was added ^{t}BuONO (1.3 equiv.) followed by $TMSN_3$ (1.3 equiv.) dropwise. The solution was then allowed to warm to r.t. and stirring was continued for 2 h. At this point, azide formation was complete as indicated by TLC analysis. Then the corresponding alkyne fragment (1 equiv.), $CuSO_4.5H_2O$ (0.2 equiv.), sodium ascorbate (0.5 equiv.), ^{t}BuOH (3.0 mL) and H_2O (1.0 mL) were added. The microwave vial was then sealed and heated with microwave radiation for 20 min at 100 °C. The reaction mixture was then diluted with H_2O (20 mL) and cooled to 0 °C before the solid product was removed by filtration. The solid material was then passed through a short silica gel column (Et_2O to 50 % Acetone/Et_2O) to give the pure product.

Synthesis of 3-(4-(3-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3) triazol-1-yl)-phenyl)-acetic acid (21)



Following the general **procedure B**: 3-Aminophenylaceic acid (100 mg, 0.662 mmol) and the corresponding alkyne fragment (200 mg, 0.509 mmol), give the pure product as a bright red powder (172 mg, 0.302 mmol, 59%);**m.p.** 245-248 °C; υ_{max} (solid)/cm^{-1} 1702 (CO); δ_H **(400 MHz, DMSO-d$_6$)** 2.16 (apt quin, *J* 7.1 Hz, 2 H), 2.67 (t, *J* 7.1 Hz, 2 H), 3.71 (s, 2 H), 4.36 (t, *J* 7.1 Hz, 2 H), 6.60 (apt t, *J* 7.6 Hz, 1 H), 6.68 (apt t, *J* 7.6 Hz, 1 H), 6.77 (d, *J* 8.1 Hz, 1 H), 6.87 (d, *J* 8.0 Hz, 1 H), 6.92 (apt t, *J* 7.6 Hz, 1 H), 7.04 (apt t, *J* 7.6 Hz, 1 H), 7.34 (d, *J* 7.6 Hz, 1 H), 7.36 (d, *J* 8.0 Hz, 1 H), 7.50 (d, *J* 7.9 Hz, 1 H), 7.52 (apt t, *J* 7.8 Hz, 1 H), 7.74 (d, *J* 8.1 Hz, 1 H), 7.75 (d, *J* 2.3 Hz, 1 H), 7.81 (s, 2 H), 8.53 (s, 1 H), 10.90 (s, 1 H), 11.65 (s, 1 H), 12.46 (s, 1 H); δ_C **(100 MHz, DMSO-d$_6$)**22.2, 29.1, 40.3, 45.2, 105.1, 105.5, 110.2, 111.8, 118.1, 119.3, 119.5, 120.3, 120.9 (2C), 121.2, 121.6, 121.7, 125.3, 126.1, 127.0, 128.0, 129.2, 129.5, 129.6, 132.0, 135.7, 136.0, 136.7, 137.1, 147.2, 172.3, 173.0 (2C); **HRMS**: Found 569.1957 $C_{33}H_{25}N_6O_4[M\text{-}H^+]^-$requires 569.1943.

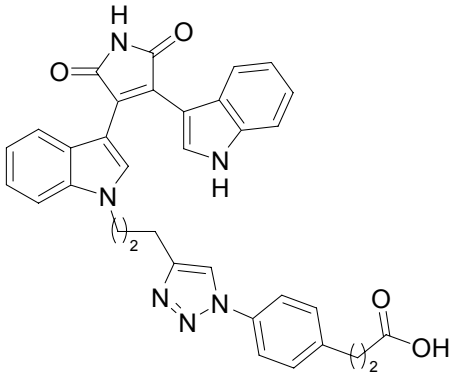
Synthesis of (4-(4-(3-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3) triazol-1-yl)-phenyl)-acetic acid (22)



Following general **procedure B**: 4-aminophenyl acetic acid (100 mg, 0.662 mmol) and the corresponding alkyne fragment (200 mg, 0.509 mmol), give the pure product as a bright red powder (126 mg, 0.221 mmol, 43%); **m.p.** 159-162 °C; υ_{max} (solid)/cm^{-1} 3340 (OH), 1706 (CO); δ_H **(400 MHz, DMSO-d$_6$)** 2.16 (apt quintet, *J* 7.0 Hz, 2 H), 2.67 (t, *J* 7.0 Hz, 2H), 3.67 (s, 2 H), 4.37 (t, *J* 7.0 Hz, 2 H), 6.60 (apt t, *J* 7.6 Hz, 1 H), 6.68 (apt t, *J* 7.5 Hz, 1 H), 6.77 (d, *J* 8.0 Hz, 1 H), 6.86 (d, *J* 8.0 Hz, 1 H), 6.92 (apt t, *J* 7.6 Hz, 1 H), 7.04 (apt t, *J* 7.6 Hz, 1 H), 7.34 (d, *J* 8.1 Hz, 1 H), 7.47 (d, *J* 8.3 Hz, 2 H), 7.50 (d, *J* 8.4 Hz, 1 H), 7.77 (d, *J* 2.5 Hz, 1 H), 7.79 (s, 1 H), 7.80 (d, *J* 8.3 Hz, 2 H), 8.51 (s, 1 H), 10.90 (s, 1 H), 11.65 (s, 1 H), 12.43 (s, 1 H); δ_C **(100 MHz, DMSO-d$_6$)**22.2, 29.1, 40.1, 45.2, 105.0, 105.5, 110.2, 111.7, 119.3, 119.3, 119.7 (2C), 120.3, 120.9, 121.2, 121.6, 121.7, 125.3, 126.1,

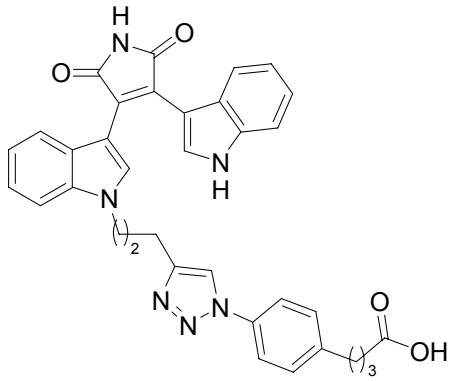
127.0, 128.0, 129.2, 130.8 (2C), 132.0, 135.4 (2C), 135.7, 136.0, 147.1, 172.4, 173.0 (2C); **HRMS**: Found 569.1961 $C_{33}H_{25}N_6O_4[M-H]^-$ requires 569.1943.

Synthesis of 3-(4-(4-(3-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2, 3)triazol-1-yl)-phenyl)-propionic acid (23)



Following general **procedure B**: 3-(4-aminophenyl) propionic acid (109 mg, 0.660 mmol) and the corresponding alkyne fragment (200 mg, 0.509 mmol) gave the product as a bright red solid (170 mg, 0.219 mmol, 57%); **m.p.** 244-246 °C; υ_{max} (solid)/cm^{-1} 1695 (CO);δ_H **(400 MHz, DMSO-d_6)** 2.15 (apt quin, *J* 7.1 Hz, 2 H), 2.59 (t, *J* 7.3 Hz, 2 H), 2.66 (t, *J* 7.1 Hz, 2 H), 2.89 (t, *J* 7.3 Hz, 2 H), 4.36 (t, *J* 7.1 Hz, 2 H), 6.59 (t, *J* 7.6 Hz, 1 H), 6.74 (t, *J* 7.6 Hz, 1 H), 6.76 (d, *J* 8.0 Hz, 1 H), 6.85 (d, *J* 8.0 Hz, 1 H), 6.91 (t, *J* 7.6 Hz, 1 H), 7.03 (t, *J* 7.6 Hz, 1 H), 7.34 (d, *J* 8.0 Hz, 1 H), 7.44 (d, *J* 8.2 Hz, 2 H), 7.50 (d, *J* 8.0 Hz, 1 H), 7.76 (d, *J* 8.2 Hz, 2 H), 7.77 (d, *J* 2.3 Hz, 1 H), 7.81 (s, 1 H), 8.50 (s, 1 H), 10.91 (s, 1 H), 11.67 (d, *J* 2.3 Hz, 1 H), 12.18 (s, 1 H); δ_C **(100 MHz, DMSO-d_6)**22.2, 29.1, 29.6, 35.0, 45.2, 105.0, 105.5, 110.2, 111.7, 119.3, 119.5, 119.8 (2C), 120.2, 120.9, 121.2, 121.5, 121.7, 125.2, 126.0, 127.0, 128.0, 129.2, 129.6 (2C), 132.0, 135.0, 135.67 135.9, 141.4, 147.0, 173.0 (2C), 173.6; **HRMS**: Found 583.2088 $C_{34}H_{27}N_6O_4[M-H]^-$requires 583.2099.

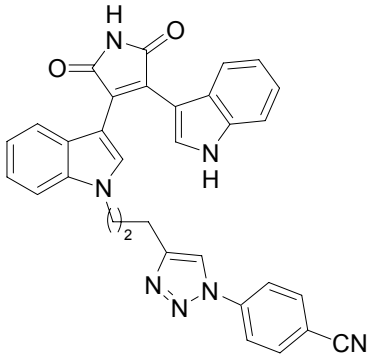
Synthesis of 4-(4-(4-(3-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2, 3)triazol-1-yl)-phenyl)-butyric acid (24)



Following general **procedure B**:4-(4-aminophenyl) butyric acid (118 mg, 0.659 mmol) and the corresponding alkyne fragment (200 mg, 0.509 mmol) gave the product as a bright red solid (214 mg, 0.358 mmol, 70%); **m.p.** 197-199 °C; υ_{max}(solid)/cm^{-1} 3307 (OH), 1695 (CO);δ_H **(500 MHz,$(CD_3)_2CO$)** 1.97 (apt quin, *J* 7.7 Hz, 2 H), 2.32 (apt quin, *J* 7.2 Hz, 2 H), 2.37 (t, *J* 7.3 Hz, 2 H), 2.77 (m, 4 H), 4.42 (t, *J* 6.8 Hz, 2 H), 6.65 (apt t, *J* 7.5 Hz, 1 H), 6.69 (apt t, *J* 7.5 Hz, 1 H), 6.91 (d, *J* 8.0 Hz, 1 H), 6.95 (apt t, *J* 7.6 Hz, 1 H), 7.01-7.06 (m, 2 H), 7.38 (d, *J* 8.1 Hz, 1 H), 7.44 (d, *J* 8.6 Hz, 2 H), 7.49 (d, *J* 8.2 Hz, 1 H), 7.77 (d, *J* 8.6 Hz, 2 H), 7.80 (s, 1 H), 7.89 (d, *J* 2.8 Hz, 1 H), 8.23 (s, 1 H), 9.64 (s, 1 H), 10.45 (s, 1 H), 10.79 (s, 1 H); δ_C **(125 MHz, $(CD_3)_2CO$)**23.2, 27.5, 30.0, 33.5, 35.2, 46.3, 106.7, 107.5, 110.9, 112.5, 120.5, 120.6, 120.7, 120.9 (2C), 122.4, 122.8 (3C), 126.7, 127.7, 128.8,

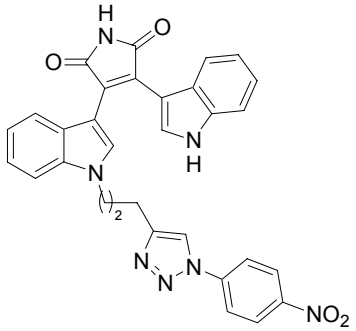
129.2, 130.1, 130.6 (2C), 133.0, 136.5, 137.2, 137.3, 143.3, 148.2, 172.0, 173.4 (2C); **HRMS**: Found 597.2262 $C_{35}H_{29}N_6O_4$[M-H]$^-$ requires 597.2256.

Synthesis of 4-(4-(3-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3)triazol-1-yl)-benzonitrile (25)



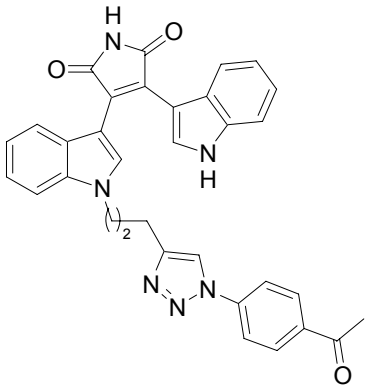
Following general **procedure B**: 4-aminobenzonitrile (78.0 mg, 0.661 mmol) and the corresponding alkyne fragment(200 mg, 0.509 mmol) gave the product as a bright red solid (194 mg, 0.361 mmol, 71 %); **m.p.** 245-247 °C; υ_{max} (solid)/cm^{-1} 1702 (CO);δ_H **(400 MHz, DMSO-d$_6$)** 2.16 (apt quin, *J* 7.1 Hz, 2 H), 2.68 (t, *J* 7.1 Hz, 2 H), 4.37 (t, *J* 7.1 Hz, 2 H), 6.59 (apt t, *J* 7.6 Hz, 1 H), 6.68 (apt t, *J* 7.7 Hz, 1 H), 6.76 (d, *J* 7.6 Hz, 1 H), 6.85 (d, *J* 7.7 Hz, 1 H), 6.91 (apt t, *J* 7.6 Hz, 1 H), 7.03 (t, *J* 7.7 Hz, 1 H), 7.33 (d, *J* 7.6 Hz, 1 H), 7.50 (d, *J* 7.7 Hz, 1 H), 7.77 (d, *J* 2.2 Hz, 1 H), 7.80 (s, 1 H), 8.10 (m, 4 H), 8.70 (s, 1 H), 10.91 (s, 1 H), 11.66 (d, *J* 2.2 Hz, 1 H); δ_C **(100 MHz, DMSO-d$_6$)** 22.1, 29.0, 45.1, 105.1, 105.5, 110.2, 110.7, 111.7, 118.1, 119.3, 119.5, 120.1 (2C), 120.5, 120.9, 121.2, 121.5, 121.7, 125.2, 126.1, 127.0, 128.0, 129.2, 131.9, 134.2 (2C), 135.7, 135.9, 139.6, 147.6, 172.9 (2C); **HRMS**: Found 538.1983 $C_{32}H_{24}N_7O_2$[M+H]$^+$ requires 538.1986.

Synthesis of 3-(1*H*-indol-3-yl)-4-(1-(3-(1-(4-nitro-phenyl)-1*H*-(1,2,3)triazol-4-yl)-propyl)-1*H*-indol-3-yl)-pyrrole-2,5-dione (26)



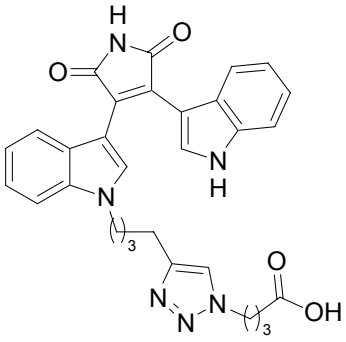
Following general **procedure B**: 4-nitroaniline (91.0 mg, 0.659 mmol) and the corresponding alkyne fragment (200 mg, 0.509 mmol) gave the product as a bright red solid (215 mg, 0.386 mmol, 76 %); m.p. 252-254 °C; υ_{max} (solid)/cm^{-1} 1693 (CO), 1530 (NO_2), 1338 (NO_2); δ_H **(400 MHz, DMSO-d$_6$)** 2.18 (apt quin, *J* 7.1 Hz, 2 H), 2.70 (t, *J* 7.1 Hz, 2 H), 4.37 (t, *J* 7.1 Hz, 2 H), 6.59 (apt t, *J* 7.5 Hz, 1 H), 6.68 (apt t, *J* 7.5 Hz, 1 H), 6.77 (d, *J* 8.0 Hz, 1 H), 6.86 (d, *J* 8.0 Hz, 1 H), 6.91 (apt t, *J* 7.6 Hz, 1 H), 7.04 (apt t, *J* 7.6 Hz, 1 H), 7.34 (d, *J* 8.1 Hz, 1 H), 7.50 (d, *J* 8.3 Hz, 1 H), 7.77 (d, *J* 2.6 Hz, 1 H), 7.80 (s, 1 H), 8.18 (d, *J* 9.0 Hz, 2 H), 8.45 (d, *J* 9.0 Hz, 2 H), 8.74 (s, 1 H), 10.89 (s, 1H), 11.65 (bs, 1 H);δ_C **(100 MHz, DMSO-d$_6$)** 22.1, 28.9, 45.2, 105.1, 105.5, 110.2, 111.7, 119.3, 119.5, 120.2 (2C), 120.8, 121.2, 121.6 (2C), 121.7, 125.2, 125.6 (2C), 126.1, 127.0, 128.0, 129.2, 132.0, 135.7, 136.0, 141.0, 146.5, 147.8, 173.0 (2C); **HRMS**: Found 558.1903 $C_{31}H_{24}N_7O_4$[M+H]$^+$ requires 558.1884.

Synthesis of 3-(1-(3-(1-(4-acetyl-phenyl)-1*H*-(1,2,3)triazol-4-yl)-propyl)-1*H*-indol-3-yl)-4-(1*H*-indol-3-yl)-pyrrole-2,5-dione (27)



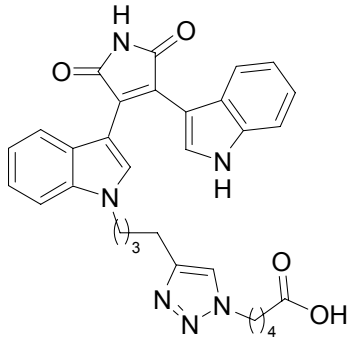
Following general **procedure B**: 4-aminoacetophenone (89.0 mg, 0.659 mmol) and the corresponding alkyne fragment(200 mg, 0.509 mmol) gave the product as a bright red solid (234 mg, 0.422 mmol, 83 %); **m.p.** 163-165 °C; υ_{max} (solid)/cm^{-1} 1686 (CO);δ_H **(400MHz, DMSO-d$_6$)** 2.18 (apt quin, *J* 7.0 Hz, 2 H), 2.64 (s, 3 H), 2.69 (t, *J* 7.0 Hz, 2 H), 4.37 (t, *J* 7.0 Hz, 2 H), 6.60 (apt t, *J* 7.5 Hz, 1 H), 6.68 (apt t, *J* 7.5 Hz, 1 H), 6.77 (d, *J* 8.0 Hz, 1 H), 6.86 (d, *J* 8.0 Hz, 1 H), 6.91 (apt t, *J* 7.5 Hz, 1 H), 7.03 (apt t, *J* 7.5 Hz, 1 H), 7.34 (d, *J* 8.1 Hz, 1 H), 7.50 (d, *J* 8.1 Hz, 1 H), 7.77 (s, 1 H), 7.81 (s, 1 H), 8.04 (d, *J* 8.4 Hz, 1 H), 8.16 (d, *J* 8.4 Hz, 1 H), 8.67 (s, 1 H), 10.89 (s, 1 H), 11.65 (s, 1 H); δ_C **(100MHz, DMSO-d$_6$)** 22.1, 26.7, 29.0, 45.1, 105.0, 105.4, 110.1, 111.7, 119.2, 119.3 (2C), 119.4, 120.3, 120.8, 121.1, 121.5, 121.6, 125.2, 126.0, 126.9, 127.9, 129.1, 130.0 (2C), 131.9, 135.6, 135.9, 136.0, 139.6, 147.4, 172.9 (2C), 196.8; **HRMS**: Found 555.2124 $C_{33}H_{27}N_6O_3[M+H]^+$ requires 555.2139.

Synthesis of 4-(4-(4-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)tr iazol-1-yl)-butyric acid (28)



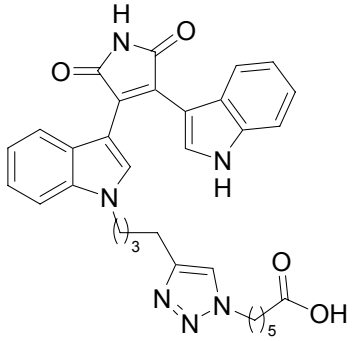
Following general **procedure A**: 4-azidobutyric acid (85.0 mg, 0.659 mmol), and the corresponding alkyne fragment (209 mg, 0.513 mmol), gave the product as a bright red solid (166 mg, 0.310 mmol, 60%); **m.p.** 142-144 °C; υ_{max} (solid)/cm^{-1} 1749 (CO), 1713 (CO); δ_H **(400 MHz, DMSO-d$_6$)** 1.54 (apt quin, *J* 7.3 Hz, 2 H), 1.76 (apt quin, *J* 7.6 Hz, 2 H), 1.98 (apt quin, *J* 7.2 Hz, 2 H), 2.19 (t, *J* 7.3 Hz, 2 H), 2.61 (t, *J* 7.4 Hz, 2 H), 4.25 (t, *J* 6.8 Hz, 2 H), 4.30 (t, *J* 7.0 Hz, 2 H), 6.53 (apt t, *J* 7.6 Hz, 1 H), 6.66 (apt t, *J* 8.0 Hz, 1 H), 6.71 (d, *J* 8.0 Hz, 1 H), 6.85 (d, *J* 8.0 Hz, 1 H), 6.94 (apt t, *J* 7.6 Hz, 1 H), 7.01 (apt t, *J* 7.6 Hz, 1 H), 7.35 (d, *J* 8.1 Hz, 1 H), 7.45 (d, *J* 8.3 Hz, 1 H), 7.74 (s, 1 H), 7.77 (d, *J* 2.5 Hz, 1 H), 7.78 (s, 1 H), 10.90 (s, 1 H), 11.66 (d, *J* 2.5, 1 H), 12.18 (s, 1 H); δ_C **(125 MHz, DMSO-d$_6$)** 24.6, 25.3, 26.1, 29.2, 30.4, 45.5, 48.4, 104.9, 105.5, 110.3, 111.8, 119.3, 119.5, 120.9, 121.2, 121.6, 121.7, 121.8, 125.2, 126.1, 127.1, 127.9, 129.2, 131.9, 135.8, 136.0, 146.6, 173.0 (2C), 173.7; **HRMS**: Found 535.2114 $C_{30}H_{27}N_6O_4[M-H]^-$requires 535.2099.

Synthesis of 5-(4-(4-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)tr iazol-1-yl)-pentanoic acid (29)



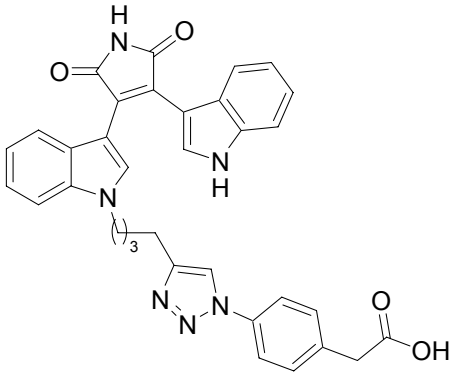
Following general **procedure A**: 5-azidopentanoic acid (95.0 mg, 0.664 mmol), and the corresponding alkyne fragment (209 mg, 0.513 mmol), gave the product as a bright red solid (167 mg, 0.304 mmol, 59 %); **m.p.** 95-99 °C; υ_{max} (solid)/cm^{-1} 1703 (CO);**δ_H (400 MHz, DMSO-d$_6$)** 1.42 (apt quin, *J* 7.6 Hz, 2 H), 1.54 (apt quin, *J* 7.4 Hz, 2 H), 1.73-1.81 (m, 4 H), 2.21 (t, *J* 7.4 Hz, 2 H), 2.61 (t, *J* 7.4 Hz, 2 H), 4.25 (t, *J* 7.2 Hz, 2 H), 4.27 (t, *J* 7.1 Hz, 2 H), 6.52 (apt t, *J* 7.1 Hz, 1 H), 6.66 (apt t, *J* 7.2 Hz, 1 H), 6.71 (d, *J* 8.1 Hz, 1 H), 6.85 (d, *J* 8.0 Hz, 1 H), 6.93 (apt t, *J* 7.6 Hz, 1 H), 7.01 (apt t, *J* 7.6 Hz, 1 H), 7.35 (d, *J* 8.1 Hz, 1 H), 7.45 (d, *J* 8.3 Hz, 1 H), 7.74 (s, 1 H), 7.76 (s, 1 H), 7.77 (d, *J* 2.7 Hz, 1 H), 10.89 (s, 1 H), 11.65 (d, *J* 2.7 Hz, 1 H), 12.04 (s, 1 H); **δ_C (125 MHz, DMSO-d$_6$)** 21.5, 24.6, 26.1, 29.2, 29.6, 32.9, 45.5, 48.9, 104.9, 105.5, 110.3, 111.8, 119.3, 119.5, 120.9, 121.2, 121.6, 121.7 (2C), 125.2, 126.0, 127.1, 127.9, 129.2, 131.9, 135.7, 136.0, 146.5, 173.0 (2C), 174.3; **HRMS**: Found 549.2253 $C_{31}H_{29}N_6O_4$[M-H]$^-$requires 549.2256.

Synthesis of 6-(4-(4-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)tr iazol-1-yl)-hexanoic acid (30)



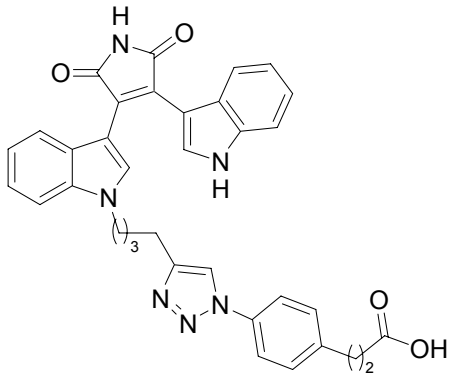
Following general **procedure A**: 6-azidohexanoic acid (104 mg, 0.662 mmol), and the corresponding alkyne fragment (209 mg, 0.513 mmol), gave the product as a bright red solid (166 mg, 0.302 mmol, 59 %); m.p. 244-246 °C; **υ_{max}** (solid)/cm^{-1} 1705 (CO); **δ_H (400 MHz, DMSO-d$_6$)** 1.17-1.24 (m, 2 H), 1.49 (apt quin, *J* 7.6 Hz, 2 H), 1.54 (apt quin, *J* 7.5 Hz, 2 H), 1.72-1.78 (m, 4 H), 2.17 (t, *J* 7.2 Hz, 2 H), 2.61 (t, *J* 7.4 Hz, 2 H), 4.25 (apt t, *J* 7.0 Hz, 4 H), 6.52 (apt t, *J* 7.2 Hz, 1 H), 6.66 (apt t, *J* 7.3 Hz, 1 H), 6.71 (d, *J* 8.0 Hz, 1 H), 6.85 (d, *J* 8.0 Hz, 1 H), 6.94 (apt t, *J* 7.6 Hz, 1 H), 7.01 (apt t, *J* 7.6 Hz, 1 H), 7.34 (d, *J* 8.1 Hz, 1 H), 7.45 (d, *J* 8.3 Hz, 1 H), 7.74 (s, 1 H), 7.75 (s, 1 H), 7.78 (d, *J* 2.6 Hz, 1 H), 10.88 (s, 1 H), 11.65 (d, *J* 2.6 Hz, 1 H), 11.97 (s, 1 H); **δ_C (125 MHz, DMSO-d$_6$)** 23.9, 24.6, 25.5, 26.1, 29.2, 29.5, 33.5, 45.5, 49.0, 104.9, 105.5, 110.3, 111.8, 119.3, 119.5, 120.9, 121.2, 121.6, 121.7 (2C), 125.3, 126.1, 127.1, 127.9, 129.2, 131.9, 135.7, 136.0, 146.5, 173.0 (2C), 174.4; **HRMS**: Found 563.2414 $C_{32}H_{31}N_6O_4$[M-H]$^-$requires 563.2412.

Synthesis of 4-(4-(4-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)triazol-1-yl)-phenyl)-acetic acid (31)



Following general **procedure B**: 4-aminophenyl acetic acid (100 mg, 0.662 mmol) and the corresponding alkyne fragment (207 mg, 0.513 mmol) gave the product as a bright red solid (161 mg, 0.293 mmol, 57 %); **m.p.** 250-252 °C; υ_{max} (solid)/cm^{-1} 1696 (CO);δ_H **(400 MHz, DMSO-d$_6$)** 1.62 (apt quin, *J* 7.1 Hz, 2 H), 1.82 (apt quin, *J* 7.1 Hz, 2 H), 2.72 (t, *J* 7.1 Hz, 2 H), 3.67 (s, 2 H), 4.29 (t, *J* 7.1 Hz, 2 H), 6.52 (t, *J* 7.6 Hz, 1 H), 6.66 (t, *J* 7.6 Hz, 1 H), 6.71 (d, *J* 8.0 Hz, 1 H), 6.86 (d, *J* 8.0 Hz, 1 H), 6.90 (t, *J* 7.6 Hz, 1 H), 7.00 (t, *J* 7.6 Hz, 1 H), 7.33 (d, *J* 8.0 Hz, 1 H), 7.45 (d, *J* 8.4 Hz, 2 H), 7.47 (d, *J* 7.6 Hz, 1 H), 7.76 (s, 2 H), 7.77 (s, 1 H), 7.78 (d, *J* 1.5 Hz, 1 H), 8.47 (s, 1 H), 10.90 (s, 1 H), 11.66 (d, *J* 1.5 Hz, 1 H), 12.44 (s, 1 H); δ_C **(100 MHz, DMSO-d$_6$)** 24.6, 25.9, 29.1, 40.0, 45.5, 105.0, 105.5, 110.2, 111.7, 119.2, 119.5, 119.7 (2C), 120.1, 120.9, 121.2, 121.5, 121.6, 125.2, 126.1, 127.1, 127.9, 129.2, 130.8 (2C), 131.9, 135.4 (2C), 135.7, 136.0, 147.7, 172.4, 173.0 (2C); **HRMS**: Found 583.2084 $C_{34}H_{27}N_6O_4[M\text{-}H]^-$ requires 583.2099.

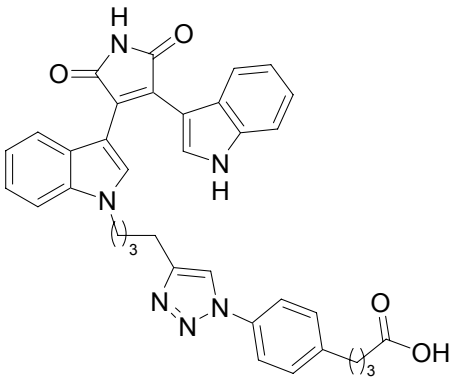
Synthesis of 3-(4-(4-(4-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)triazol-1-yl)-phenyl)-propionic acid (32)



Following general **procedure B**: 3-(4-aminophenyl) propionoic acid (109 mg, 0.660 mmol) and the corresponding alkyne fragment (209 mg, 0.513 mmol) gave the product as a bright red solid (150 mg, 0.251 mmol, 49%); **m.p.** 221-214 °C; υ_{max} (solid)/cm^{-1} 1706 (CO);δ_H **(500 MHz, (CD$_3$)$_2$CO)** 1.76 (apt quin, *J* 7.3 Hz, 2 H), 1.96 (apt quin, *J* 7.3 Hz, 2 H), 2.68 (t, *J* 7.6 Hz, 2 H), 2.80 (t, *J* 7.3 Hz, 2 H), 2.99 (t, *J* 7.6 Hz, 2 H), 4.37 (t, *J* 7.3 Hz, 2 H), 6.59 (apt t, *J* 7.1 Hz, 1 H), 6.67 (apt t, *J* 7.5 Hz, 1 H), 6.88 (d, *J* 8.0 Hz, 1 H), 6.93 (apt t, *J* 7.1 Hz, 1 H), 7.00-7.04 (m, 2 H), 7.37 (d, *J* 8.2 Hz, 1 H), 7.45-7.47 (m, 3 H), 7.71 (d, *J* 8.5 Hz, 2 H), 7.77 (s, 1 H), 7.87 (d, *J* 2.8 Hz, 1 H), 8.16 (s, 1 H), 9.70 (s, 1 H), 10.66 (s, 1 H), 10.82 (s, 1 H); δ_C **(125 MHz, (CD$_3$)$_2$CO)**25.8, 27.2, 30.3, 31.0, 35.7, 46.9, 106.6, 107.5, 110.9, 112.5, 120.3, 120.5 (2C), 120.9 (2C), 122.4, 122.7 (2C), 122.8,

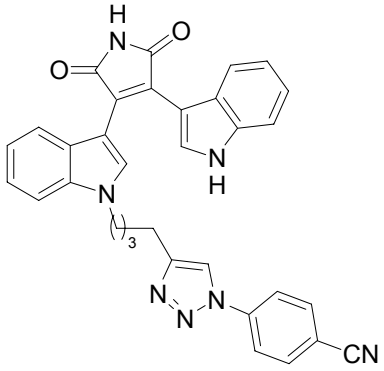
126.7, 127.7, 128.9, 129.1, 130.0, 130.6 (2C), 132.9, 136.6, 137.1, 137.3, 142.4, 148.9, 173.4 (2C), 173.8; **HRMS**: Found 597.2285 $C_{35}H_{29}N_6O_4$[M-H]$^-$ requires 597.2256.

Synthesis of 4-(4-(4-(4-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)triazol-1-yl)-phenyl)-butyric acid (33)



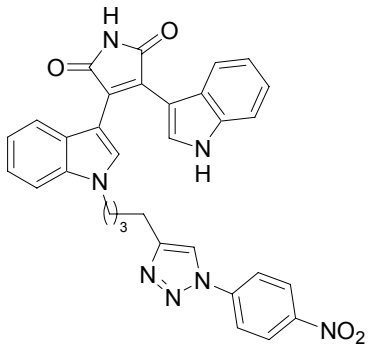
Following general **procedureB**: 4-(4-aminophenyl) butyric acid (118 mg, 0.659 mmol) and the corresponding alkyne fragment (209 mg, 0.513 mmol) gave the product as a bright red solid (206 mg, 0.336 mmol, 66 %); **m.p.** 220-222 °C; υ_{max}(solid)/cm^{-1} 3343 (OH), 1704 (CO);**δ_H (400 MHz, DMSO-d_6)** 1.62 (apt quin, *J* 7.5 Hz, 2 H), 1.81-1.86 (m, 4 H), 2.24 (t, *J* 7.5 Hz, 2 H), 2.66 (t, *J* 7.5 Hz, 2 H), 2.71 (t, *J* 7.2 Hz, 2 H), 4.29 (t, *J* 7.2 Hz, 2 H), 6.50 (apt t, *J* 7.6 Hz, 1 H), 6.65 (apt t, *J* 7.5 Hz, 1 H), 6.70 (d, *J* 8.1 Hz, 1 H), 6.85 (d, *J* 8.1 Hz, 1 H), 6.89 (apt t, *J* 7.5 Hz, 1 H), 7.00 (apt t, *J* 7.6 Hz, 1 H), 7.32 (d, *J* 8.1 Hz, 1 H), 7.38 (d, *J* 8.3 Hz, 2 H), 7.48 (d, *J* 8.3 Hz, 1 H), 7.73 (d, *J* 8.3 Hz, 2 H), 7.76 (s, 1 H), 7.77 (d, *J* 2.3 Hz, 1 H), 8.45 (s, 1 H), 10.91 (s, 1 H), 11.66 (d, *J* 2.3 Hz, 1 H), 12.03 (s, 1 H); **δ_C (100 MHz,DMSO-d_6)** 24.5, 25.8, 26.1, 29.0, 32.9, 33.8, 45.4, 104.9, 105.4, 110.1, 111.6, 119.1, 119.4, 119.7 (2C), 119.9, 120.8, 121.1, 121.4, 121.5, 125.1, 126.0, 127.0, 127.8, 129.1, 129.5 (2C), 131.8, 134.8, 135.6, 135.8, 141.9, 147.5, 172.9 (2C), 174.1; **HRMS**: Found 611.2431 $C_{36}H_{31}N_6O_4$[M-H]$^-$requires 611.2412.

Synthesis of 4-(4-(4-(3-(4-(1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)tr iazol-1-yl)-benzonitrile (34)



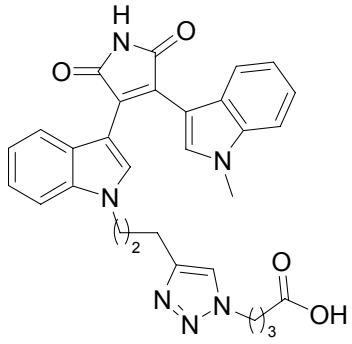
Following general **procedure B**: 4-aminobenzonitrile (78.0 mg, 0.661 mmol) and the corresponding alkyne (209 mg, 0.513 mmol) gave the product as a bright red solid (92.0 mg, 0.150 mmol, 30 %); **m.p.** 236-238 °C; **υ_{max}** (solid)/cm^{-1} 1707 (CO); **δ_H (400 MHz, DMSO-d_6)** 1.62 (apt quin, *J* 7.3 Hz, 2 H), 1.82 (apt quin, 7.3 Hz, 2 H), 2.74 (t, *J* 7.3 Hz, 2 H), 4.29 (t, *J* 7.3 Hz, 2 H), 6.51 (apt t, *J* 7.7 Hz, 1 H), 6.66 (apt t, *J* 7.8 Hz, 1 H), 6.70 (apt t, *J* 7.7 Hz, 1 H), 6.85 (d, *J* 7.8 Hz, 1 H), 6.89 (apt t, *J* 7.7 Hz, 1 H), 7.01 (apt t, *J* 7.8 Hz, 1 H), 7.32 (d, *J* 7.7 Hz, 1 H), 7.48 (d, *J* 7.8 Hz, 1 H), 7.75 (s, 1 H), 7.77 (d, *J* 2.4 Hz, 1 H), 8.08 (s, 1 H), 8.65 (s, 1 H), 10.90 (s, 1 H), 11.65 (d, *J* 2.4 Hz, 1 H); **δ_C (100 MHz, DMSO-d_6)** 24.5, 25.8, 29.0, 45.5, 104.9, 105.5, 110.2, 110.7, 111.7, 118.2, 119.2, 119.4, 120.1 (2C), 120.3, 120.9, 121.2, 121.5, 121.6, 125.2, 126.0, 127.0, 127.9, 129.2, 131.8, 134.2 (2C), 135.7, 135.9, 139.6, 148.3, 172.9 (2C); **HRMS**: Found 552.2131 $C_{33}H_{26}N_7O_2$[M+H]$^+$ requires 552.2142.

Synthesis of 3-(1*H*-indol-3-yl)-4-(1-(4-(1-(4-nitro-phenyl)-1*H*-(1,2,3)triazol-4-yl)-butyl)-1*H*-indol-3-yl)-pyrrole-2,5-dione (35)



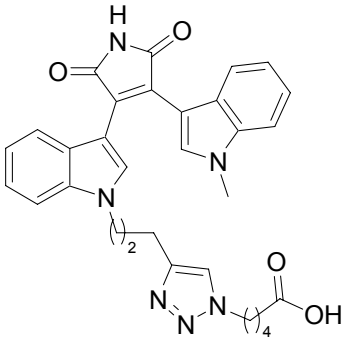
Following general **procedure B**: 4-nitroaniline (91.0 mg, 0.659 mmol) and the corresponding alkyne fragment (209 mg, 0.513 mmol) gave the product as a bright red solid (100 mg, 0.163 mmol, 32 %); **m.p.** 262-264 °C; υ_{max} (solid)/cm^{-1} 1708 (CO), 1527 (NO_2), 1341 (NO_2);δ_H **(400 MHz, DMSO-d$_6$)** 1.64 (apt quin, *J* 7.3 Hz, 2 H), 1.84 (apt quin, *J* 7.3 Hz, 2 H), 2.75 (t, *J* 7.3 Hz, 2 H), 4.29 (t, *J* 7.3 Hz, 2 H), 6.52 (apt t, *J* 7.5 Hz, 1 H), 6.66 (apt t, *J* 7.5 Hz, 1 H), 6.71 (d, *J* 8.0 Hz, 1 H), 6.85 (d, *J* 8.0 Hz, 1 H), 6.90 (apt t, *J* 7.6 Hz, 1 H), 7.01 (apt t, *J* 7.6 Hz, 1 H), 7.32 (d, *J* 8.1 Hz, 1 H), 8.27 (d, *J* 8.3 Hz, 1 H), 7.58 (s, 1 H), 7.77 (d, *J* 2.6 Hz, 1 H), 8.15 (d, *J* 9.0 Hz, 2 H), 8.44 (d, *J* 9.0 Hz, 2 H), 8.70 (s, 1 H), 10.89 (s, 1 H), 11.64 (bs, 1 H); δ_C **(100 MHz, DMSO-d$_6$)** 24.4, 25.7, 29.0, 45.4, 104.9, 105.5, 110.2, 111.7, 119.2, 119.4, 120.2 (2C), 120.5, 120.8, 121.2, 121.5, 121.6, 125.2, 125.6 (2C), 126.0, 127.0, 127.9, 129.2, 131.8, 135.7, 135.9, 141.0, 146.4, 148.5, 172.9 (2C); **HRMS**: Found 572.2022 $C_{32}H_{26}N_7O_4[M+H]^+$ requires 572.2041.

Synthesis of 4-(4-(3-(3-(4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3)triazol-1-yl)-butyric acid (36)



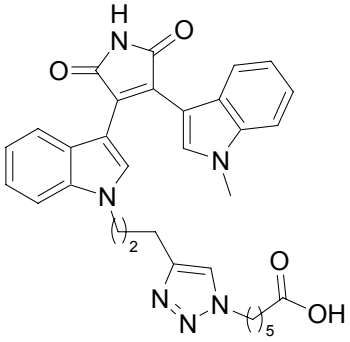
Following general **procedureA**: 4-azidobutyric acid (85.0 mg, 0.659 mmol), and the corresponding alkyne fragment (209 mg, 0.513 mmol), gave the product as a bright red solid (157 mg, 0.293 mmol, 58 %); **m.p.** 132-134 °C; υ_{max} (solid)/cm^{-1} 1697 (CO); δ_H **(400 MHz, DMSO-d$_6$)** 1.97-2.10 (m, 4 H), 2.21 (t, *J* 7.3 Hz, 2 H), 2.55 (t, *J* 7.4 Hz, 2 H), 3.86 (s, 3 H), 4.29 (t, *J* 7.3 Hz, 2 H), 4.33 (t, *J* 7.4 Hz, 2 H), 6.58 (apt t, *J* 7.5 Hz, 1 H), 6.66 (d, *J* 8.0 Hz, 1 H), 6.70 (apt t, *J* 7.6 Hz, 1 H), 6.92 (d, *J* 8.0 Hz, 1 H), 6.98 (apt t, *J* 7.6 Hz, 1 H), 7.03 (apt t, *J* 7.6 Hz, 1 H), 7.40 (d, *J* 8.2, 1 H), 7.46 (d, *J* 8.1 Hz, 1 H), 7.74 (s, 1 H), 7.84 (s, 1 H), 7.87 (s, 1 H), 10.92 (s, 1 H), 12.19 (s, 1 H); δ_C **(125 MHz, DMSO-d$_6$)** 22.2, 25.3, 29.4, 30.4, 32.9, 45.2, 48.5, 104.6, 105.1, 110.1, 110.3, 119.6 (2C), 121.1, 121.2, 121.7, 121.8, 121.9, 125.6, 126.3, 126.7, 127.7, 131.9, 133.2, 135.7, 136.5, 146.0, 173.0 (2C), 173.7; **HRMS**: Found 535.2094 $C_{30}H_{27}N_6O_4[M-H]^-$ requires 535.2099.

Synthesis of 5-(4-(3-(3-(4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl) -(1,2,3)triazol-1-yl)-pentanoic acid (37)



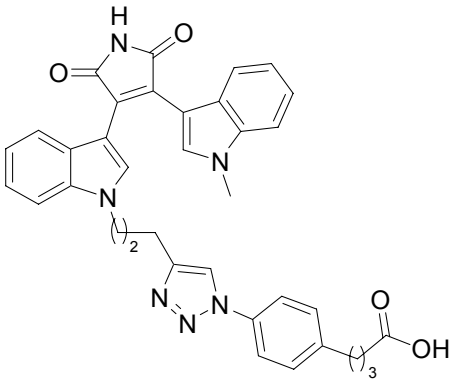
Following general **procedureA**: 5-azidopentanoic acid (95.0 mg, 0.664 mmol), and the corresponding alkyne fragment (209 mg, 0.513 mmol), gave the product as a bright red solid (186 mg, 0.338 mmol, 66 %); **m.p.** 110-114 °C; υ_{max} (solid)/cm^{-1} 1704 (CO); **δ_H (400 MHz, DMSO-d$_6$)** 1.44 (apt quin, *J* 7.6 Hz, 2 H), 1.81 (apt quin, *J* 7.6 Hz, 2 H), 2.05 (apt quin, *J* 7.5 Hz, 2 H), 2.24 (t, *J* 7.4 Hz, 2 H), 2.55 (t, *J* 7.6 Hz, 2 H), 3.86 (s, 3 H), 4.28 (t, *J* 6.3 Hz, 2 H), 4.31 (t, *J* 6.9 Hz, 2 H), 6.58 (apt t, *J* 7.2 Hz, 1 H), 6.66 (d, *J* 8.0 Hz, 1 H), 6.71 (apt t, *J* 7.3 Hz, 1 H), 6.92 (d, *J* 8.0 Hz, 1 H), 6.97 (apt t, *J* 7.6 Hz, 1 H), 7.03 (apt t, *J* 7.7 Hz, 1 H), 7.40 (d, *J* 8.2 Hz, 1 H), 7.46 (d, *J* 8.3 Hz, 1 H), 7.74 (s, 1 H), 7.82 (s, 1 H), 7.87 (s, 1 H), 10.92 (s, 1 H), 12.05 (s, 1 H); **δ_C (125 MHz, DMSO-d$_6$)**21.5, 22.2, 29.2, 29.6, 32.9 (2C), 45.2, 48.9, 104.6, 105.1, 110.1, 110.2, 119.6 (2C), 121.1, 121.2, 121.7, 121.8, 121.9, 125.6, 126.2, 126.7, 127.7, 131.9, 133.2, 135.7, 136.5, 145.9, 173.0 (2C), 174.3; **HRMS**: Found 549.2267 $C_{31}H_{29}N_6O_4$[M-H]$^-$ requires 549.2256.

Synthesis of 6-(4-(3-(3-(4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl) -(1,2,3)triazol-1-yl)-hexanoic acid (38)



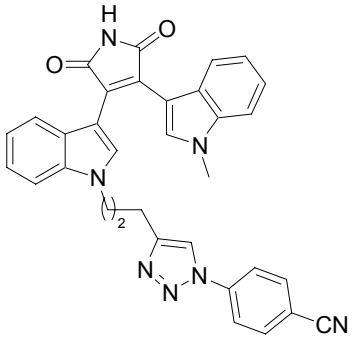
Following general **procedure A**: 6-azidohexanoic acid (104 mg, 0.662 mmol), and the corresponding alkyne fragment (209 mg, 0.513 mmol), gave the product as a bright red solid (184 mg, 0.326 mmol, 64 %); **m.p.** 96-101 °C; υ_{max} (solid)/cm^{-1} 1705 (CO);**δ_H (400 MHz, DMSO-d$_6$)** 1.23 (apt quin, *J* 7.6 Hz, 2 H), 1.51 (apt quin, *J* 7.6 Hz, 2 H), 1.79 (apt quin, *J* 7.5 Hz, 2 H), 2.06 (apt quin, *J* 7.5 Hz, 2 H), 2.18 (t, *J* 7.4 Hz, 2 H), 2.55 (t, *J* 7.6 Hz, 2 H), 3.86 (s, 3 H), 4.27-4.31 (m, 4 H), 6.58 (apt t, *J* 7.1 Hz, 1 H), 6.67 (d, *J* 8.0 Hz, 1 H), 6.70 (apt t, *J* 7.2 Hz, 1 H), 6.92 (d, *J* 8.0 Hz, 1 H), 6.98 (apt t, *J* 7.5 Hz, 1 H), 7.03 (apt t, *J* 7.6 Hz, 1 H), 7.40 (d, *J* 8.3 Hz, 1 H), 7.46 (d, *J* 8.3 Hz, 1 H), 7.74 (s, 1 H), 7.82 (s, 1 H), 7.87 (s, 1 H), 10.92 (s, 1 H), 11.99 (s, 1 H); **δ_C (125 MHz, DMSO-d$_6$)**22.9, 23.9, 25.5, 29.4, 29.5, 32.9, 33.5, 45.2, 49.1, 104.6, 105.1, 110.1, 110.2, 119.6 (2C), 121.1, 121.2, 121.7 (2C), 121.8, 125.6, 126.2, 126.7, 127.7, 131.9, 133.2, 135.7, 136.5, 145.9, 173.0 (2C), 174.4; **HRMS**: Found 563.2420 $C_{32}H_{31}N_6O_4$[M-H]$^-$ requires 563.2412.

Synthesis of 4-(4-(4-(3-(3-(4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3)triazol-1-yl)-phenyl)-butyric acid (39)



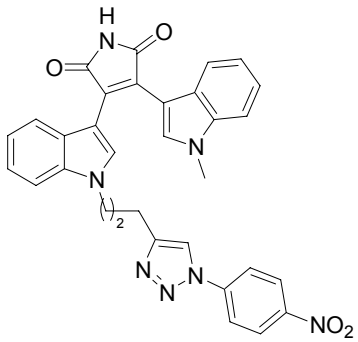
Following general **procedure B**: 4-(4-aminophenyl) butyric acid (118 mg, 0.659 mmol) and the corresponding alkyne fragment (209 mg, 0.513 mmol) gave the product as a bright red solid (192 mg, 0.314 mmol, 62%); **m.p.** 110-112 °C; υ_{max} (solid)/cm^{-1} 1707 (CO); δ_H **(400 MHz, DMSO-d$_6$)** 1.83 (apt quin, *J* 7.2 Hz, 2 H), 2.12 (apt quin, *J* 7.0 Hz, 2 H), 2.24 (t, *J* 7.2 Hz, 2 H), 2.65 (t, *J* 7.6 Hz, 2 H), 2.67 (t, *J* 7.6 Hz, 2 H), 3.85 (s, 3 H), 4.35 (t, *J* 7.6 Hz, 2 H), 6.60 (apt t, *J* 7.6 Hz, 1 H), 6.68 (d, *J* 7.6 Hz, 1 H), 6.70 (apt t, *J* 7.6 Hz, 1 H), 6.92 (d, *J* 7.6 Hz, 1 H), 6.97 (apt t, *J* 7.6 Hz, 1 H), 7.04 (apt t, *J* 7.6 Hz, 1 H), 7.39 (d, *J* 7.6 Hz, 1 H), 7.40 (d, *J* 8.5 Hz, 2 H), 7.50 (d, *J* 7.6 Hz, 1 H), 7.77 (d, *J* 8.5 Hz, 2 H), 7.79 (s, 1 H), 7.87 (s, 1 H), 8.49 (s, 1 H), 10.93 (s, 1 H), 12.11 (s, 1 H); δ_C **(100 MHz, DMSO-d$_6$)** 22.2, 26.1, 29.1, 32.1, 32.9, 33.0, 33.8, 45.2, 104.6, 105.1, 110.1, 110.2, 119.5 (2C), 119.9, 120.2, 121.1, 121.2, 121.6, 121.7, 125.6, 126.2, 127.7 (2C), 129.6 (2C), 131.9, 133.1, 134.9, 135.7, 136.5, 142.0, 147.0, 172.9 (2C), 174.2; **HRMS**: Found 611.2428 $C_{36}H_{31}N_6O_4[M\text{-}H]^-$requires 611.2412.

Synthesis of 4-(4-(3-(3-(4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3)triazol-1-yl)-benzonitrile (40)



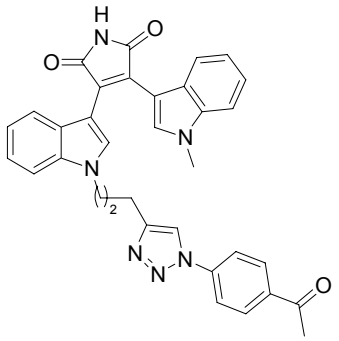
Following general **procedure B**: 4-aminobenzonitrile (78.0 mg, 0.661 mmol) and the corresponding alkyne(209 mg, 0.513 mmol) gave the product as a bright red solid (155 mg, 0.281 mmol, 55 %); **m.p.** 140-143 °C; υ_{max} (solid)/cm^{-1} 1701 (CO); δ_H **(400 MHz, DMSO-d$_6$)** 2.15 (apt quin, *J* 7.2 Hz, 2 H), 2.67 (t, *J* 7.5 Hz, 2 H), 3.85 (s, 3 H), 4.36 (t, *J* 6.6 Hz, 2 H), 6.60 (apt t, *J* 7.5 Hz, 1 H), 6.67 (d, *J* 7.5 Hz), 6.70 (apt t, *J* 7.5 Hz, 1 H), 6.91 (d, *J* 8.0 Hz, 1 H), 6.96 (apt t, *J* 7.5 Hz, 1 H), 7.04 (apt t, *J* 7.6 Hz, 1 H), 7.39 (d, *J* 8.2 Hz, 1 H), 7.51 (d, *J* 8.3 Hz, 1 H), 7.79 (s, 1 H), 7.87 (s, 1 H), 8.08-8.13 (m, 4 H), 8.72 (s, 1 H), 10.93 (s, 1 H); δ_C **(100 MHz, DMSO-d$_6$)** 22.1, 29.0, 32.9, 45.1, 104.6, 105.1, 110.1, 110.2, 110.7, 118.2, 119.5 (2C), 120.2 (2C), 120.5, 121.1, 121.2, 121.6, 121.7, 125.5, 126.2, 126.7, 127.7, 131.9, 133.1, 134.3 (2C), 135.7, 136.5, 139.7, 147.7, 172.9 (2C); **HRMS**: Found 552.2149 $C_{33}H_{26}N_7O_2[M+H]^+$ requires 552.2142.

Synthesis of 3-(1-methyl-1*H*-indol-3-yl)-4-(1-(3-(1-(4-nitro-phenyl)-1*H*-(1,2,3)triazol-4-yl)-propyl)-1*H*-indo l-3-yl)-pyrrole-2,5-dione (41)



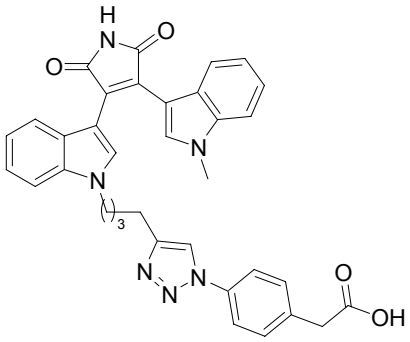
Following general **procedure B**: 4-nitroaniline (91.0 mg, 0.659 mmol) and the corresponding alkyne fragment (209 mg, 0.513 mmol) gave the product as a bright red solid (159 mg, 0.279 mmol, 55 %); **m.p.** 187-189 °C; υ_{max} (solid)/cm^{-1} 1697 (CO), 1532 (NO_2), 1338 (NO_2); **δ_H (400 MHz, DMSO-d$_6$)** 2.17 (apt quin, *J* 7.1 Hz, 2 H), 2.69 (t, *J* 7.1 Hz, 2 H), 3.85 (s, 3 H), 4.37 (t, *J* 7.1 Hz, 2 H), 6.61 (apt t, *J* 7.5 Hz, 1 H), 6.69 (d, *J* 9.1 Hz, 1 H), 6.70 (apt t, *J* 7.6 Hz, 1 H), 6.92 (d, *J* 8.0 Hz, 1 H), 6.97 (apt t, 7.5 Hz, 1 H), 7.05 (apt t, *J* 7.6 Hz, 1 H), 7.39 (d, *J* 8.2 Hz, 1 H), 7.51 (d, *J* 8.3 Hz, 1 H), 7.79 (s, 1 H), 7.86 (s, 1 H), 8.19 (d, *J* 9.0 Hz, 2 H), 8.45 (d, *J* 9.0 Hz, 2 H), 8.76 (s, 1 H), 10.91 (s, 1 H); **δ_C (100 MHz,DMSO-d$_6$)** 22.1, 29.0, 32.9, 45.2, 104.6, 105.1, 110.1, 110.2, 119.5 (2C), 120.2, 120.8 (2C), 121.1, 121.2, 121.6, 121.7, 125.6 (3C), 126.2, 126.7, 127.7, 131.9, 133.1, 135.7, 136.5, 141.0, 146.5, 147.8, 172.9 (2C); **HRMS**: Found 572.2031 $C_{32}H_{26}N_7O_4[M+H]^+$ requires 572.2041.

Synthesis of 3-(1-(3-(1-(4-acetyl-phenyl)-1*H*-(1,2,3)triazol-4-yl)-propyl)-1*H*-indol-3-yl)-4-(1-methyl-1*H*-ind ol-3-yl)-pyrrole-2,5-dione (42)



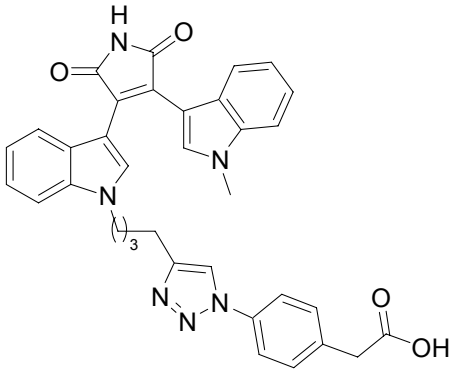
Following general **procedure B**: 4-aminoacetophenone (89.0 mg, 0.659 mmol) and the corresponding alkyne fragment (209 mg, 0.513 mmol) gave the product as a bright red solid (230 mg, 0.405 mmol, 79 %); **m.p.** 108-110 °C; υ_{max} (solid)/cm^{-1} 1707 (CO), 1693 (CO);**δ_H (400 MHz, DMSO-d$_6$)** 2.16 (apt quin, *J* 7.0 Hz, 2 H), 2.63 (s, 3 H), 2.68 (t, *J* 7.0 Hz, 2 H), 3.85 (s, 3 H), 4.37 (t, *J* 7.0 Hz, 2 H), 6.61 (apt t, *J* 7.4 Hz, 1 H), 6.69 (d, *J* 8.9 Hz, 1 H), 6.70 (t, *J* 8.4 Hz, 1 H), 6.92 (d, *J* 8.0 Hz, 1 H), 6.97 (apt t, *J* 7.5 Hz, 1 H), 7.05 (apt t, *J* 7.5 Hz, 1 H), 7.39 (d, *J* 8.1 Hz, 1 H), 7.51 (d, *J* 8.2 Hz, 1 H), 7.79 (s, 1 H), 7.86 (s, 1 H), 8.04 (d, *J* 8.4 Hz, 2 H), 8.16 (d, *J* 8.4 Hz, 2 H), 8.68 (s, 1 H), 10.91 (s, 1 H); **δ_C (100 MHz, DMSO-d$_6$)** 22.1, 26.8, 29.0, 32.9, 45.2, 104.6, 105.1, 110.1, 110.2, 119.4 (4C), 120.4, 121.1, 121.2, 121.6, 121.7, 125.6, 126.2, 126.7, 127.7, 130.0 (2C), 131.9, 133.1, 135.7, 136.1, 136.5, 139.7, 147.5, 172.9 (2C), 196.9; **HRMS**: Found 569.2295 $C_{34}H_{29}N_6O_3[M+H]^+$ requires 555.2296.

Synthesis of (3-(4-(4-(3-(4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl) -(1,2,3)triazol-1-yl)-phenyl)-acetic acid (43)



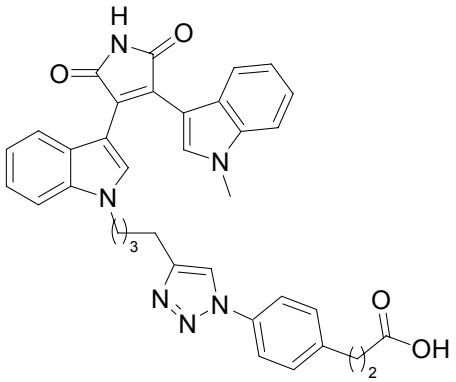
Following general **procedure B**: 3-aminophenyl acetic acid (71.0 mg, 0.470 mmol) and the corresponding alkyne fragment (200 mg, 0.475 mmol) gave the product as a bright red solid (172 mg, 0.288 mmol, 61%); **m.p.** 112-114 °C; υ_{max} (solid)/cm^{-1} 1705 (CO); **δ_H (400 MHz, DMSO-d$_6$)** 1.63 (apt quin, *J* 7.4 Hz, 2 H), 1.81 (apt quin, *J* 7.1 Hz, 2 H), 2.71 (t, *J* 7.4 Hz, 2 H), 3.71 (s, 2 H), 3.86 (s, 3 H), 4.27 (t, *J* 6.8 Hz, 2 H), 6.53 (apt t, *J* 7.1 Hz, 1 H), 6.63 (d, *J* 7.9 Hz, 1 H), 6.69 (apt t, *J* 7.3 Hz, 1 H), 6.93 (d, *J* 8.0 Hz, 1 H), 6.95 (apt t, *J* 7.3 Hz, 1 H), 7.02 (apt t, *J* 7.4 Hz, 1 H), 7.34-7.38 (m, 2 H), 7.47-7.53 (m, 2 H), 7.70 (dd, *J* 1.2 and 8.1 Hz, 1 H), 7.73 (s, 1 H), 7.77 (s, 1 H), 7.85 (s, 1 H), 8.46 (s, 1 H), 10.91 (s, 1 H), 12.47 (s, 1 H); **δ_C (125 MHz, DMSO-d$_6$)** 24.5, 25.8, 29.1, 32.8, 40.1, 14.5, 104.5, 105.0, 110.0, 110.2, 118.0, 119.4 (2C), 120.1, 120.8, 121.1, 121.2, 121.6, 121.6, 125.5, 126.2, 126.7, 127.6, 129.4, 129.6, 131.8, 133.1, 135.7, 136.5, 136.6, 137.0, 147.7, 172.2, 172.9 (2C); **HRMS**: Found 597.2260 $C_{35}H_{29}N_6O_4$[M-H]$^-$ requires 597.2256.

Synthesis of (4-(4-(4-(3-(4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl) -(1,2,3)triazol-1-yl)-phenyl)-acetic acid (44)



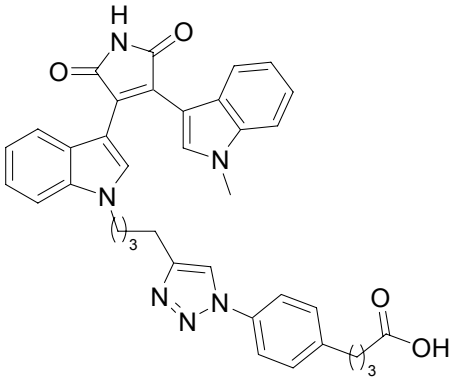
Following general **procedure B**: 4-aminophenyl acetic acid (71.0 mg, 0.470 mmol) and the corresponding alkyne fragment (200 mg, 0.475 mmol) gave the product as a bright red solid (171 mg, 0.286 mmol, 60%); **m.p.** 268-270 °C; υ_{max} (solid)/cm^{-1} 1697 (CO); **δ_H (400 MHz, DMSO-d$_6$)** 1.62 (apt quin, *J* 7.2 Hz, 2 H), 1.81 (apt quin, *J* 7.2 Hz, 2 H), 2.71 (t, *J* 7.2 Hz, 2 H), 3.68 (s, 2 H), 3.84 (s, 3 H), 4.27 (t, *J* 7.2 Hz, 2 H), 6.53 (apt t, *J* 7.6 Hz, 1 H), 6.64 (d, *J* 7.6 Hz, 1 H), 6.69 (apt t, *J* 7.6 Hz, 1 H), 6.93 (d, *J* 7.6 Hz, 1 H), 6.95 (apt t, *J* 7.6 Hz, 1 H), 7.02 (apt t, *J* 7.6 Hz, 1 H), 7.36 (d, *J* 7.6 Hz, 1 H), 7.46 (d, *J* 8.6 Hz, 2 H), 7.48 (d, *J* 7.6 Hz, 1 H), 7.73 (s, 1 H), 7.77 (d, *J* 8.6 Hz, 2 H), 7.86 (s, 1 H), 8.44 (s, 1 H), 10.92 (s, 1 H), 12.46 (s, 1 H); **δ_C (125 MHz, DMSO-d$_6$)**24.6, 26.0, 29.2, 32.9, 39.9, 45.5, 104.6, 105.0, 110.1, 110.3, 119.5, 119.5, 119.7 (2C), 120.1, 121.4, 121.2, 121.6, 121.7, 125.5, 126.2, 126.8, 127.6, 130.9 (2C), 131.9, 133.2, 135.5, 135.7, 135.7, 136.5, 147.8, 172.6, 173.0 (2C); **HRMS**: Found 597.2260 $C_{35}H_{29}N_6O_4$[M-H]$^-$ requires 597.2257.

Synthesis of 3-(4-(4-(4-(3-(4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)triazol-1-yl)-phenyl)-propionic acid (45)



Following general **procedure B**: 3-(4-aminophenyl) propionic acid (102 mg, 0.618 mmol) and the corresponding alkyne fragment (200 mg, 0.475 mmol) gave the product as a bright red solid (156 mg, 0.255 mmol, 54 %); **m.p.** 110-112 °C; υ_{max} (solid)/cm^{-1} 1705 (CO);**δ_H (400 MHz, d^6-DMSO)** 1.61 (apt quin, *J* 7.2 Hz, 2 H), 1.79 (apt quin, *J* 7.2 Hz, 2 H), 2.59 (t, *J* 7.5 Hz, 2 H), 2.71 (t, *J* 7.2 Hz, 2 H), 2.89 (t, *J* 7.5 Hz, 2 H), 3.84 (s, 3 H), 4.27 (t, *J* 7.2 Hz, 2 H), 6.53 (apt t, *J* 7.6 Hz, 1 H), 6.64 (d, *J* 7.6 Hz, 1 H), 6.69 (apt t, *J* 7.6 Hz, 1 H), 6.92 (d, *J* 7.6 Hz, 1 H), 6.95 (apt t, *J* 7.6 Hz, 1 H), 7.02 (apt t, *J* 7.6 Hz, 1 H), 7.37 (d, *J* 7.6 Hz, 1 H), 7.42 (d, *J* 8.4 Hz, 2 H), 7.48 (d, *J* 7.6 Hz, 1 H), 7.72 (d, *J* 8.4 Hz, 2 H), 7.73 (s, 1 H), 7.85 (s, 1 H), 8.42 (s, 1 H), 10.90 (s, 1 H), 12.15 (s, 1 H); δ_C (125 MHz, d^6-DMSO) 24.6, 26.0, 29.2, 29.8, 32.9, 35.0, 45.5, 104.6, 105.0, 110.1, 110.3, 119.5 (2C), 119.8 (2C), 120.1, 121.1, 121.2, 121.6, 121.7, 125.5, 126.2, 126.7, 127.6, 129.6 (2C), 131.9, 133.2, 135.0, 135.7, 136.5, 141.3, 147.7, 173.0 (2C), 173.7; **HRMS**: Found 611.2398 $C_{36}H_{31}N_6O_4[M\text{-}H]^-$ requires 611.2412.

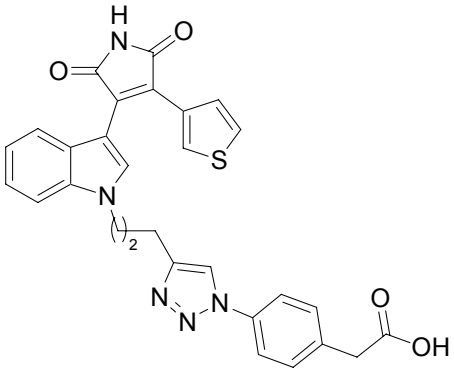
Synthesis of 4-(4-(4-(4-(3-(4-(1-methyl-1H-indol-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)triazol-1-yl)-phenyl)-butyric acid (46)



Following general **procedure B**: 4-(4-aminophenyl) butanoic acid (111 mg, 0.620 mmol) and the corresponding alkyne fragment (200 mg, 0.475 mmol) gave the product as a bright red solid (202 mg, 0.323 mmol, 68 %); **m.p.** 110-112 °C; υ_{max} (solid)/cm^{-1} 1707 (CO); **δ_H (400 MHz,DMSO-d$_6$)** 1.61 (apt quin, *J* 7.4 Hz, 2 H), 1.77-1.87 (m, 4 H), 2.24 (t, *J* 7.3 Hz, 2 H), 2.66 (t, *J* 7.7 Hz, 2 H), 2.71 (t, *J* 7.4 Hz, 2 H), 3.84 (s, 3 H), 4.27 (t, *J* 7.4 Hz, 2 H), 6.53 (apt t, *J* 7.5 Hz, 1 H), 6.63 (d, *J* 8.0 Hz, 1 H), 6.68 (apt t, *J* 7.5 Hz, 1 H), 6.92 (d, *J* 7.5 Hz, 1 H), 6.94 (apt t, *J* 7.4 Hz, 1 H), 7.02 (apt t, *J* 7.6 Hz, 1 H), 7.36 (d, *J* 6.9 Hz, 1 H), 7.38 (d, *J* 8.1 Hz, 1 H), 7.48 (d, *J* 8.3 Hz, 1 H), 7.72-7.74 (m, 3 H), 7.85 (s, 1 H), 8.42 (s, 1 H), 10.90 (s, 1 H), 12.06 (s, 1 H); **δ_C (125 MHz, DMSO-d$_6$)** 24.5, 25.9, 26.1, 29.1, 32.8, 33.0, 33.8, 45.5, 104.5, 105.0, 110.0, 110.2, 119.4, 119.4, 119.8 (2C), 120.0, 121.1, 121.2,

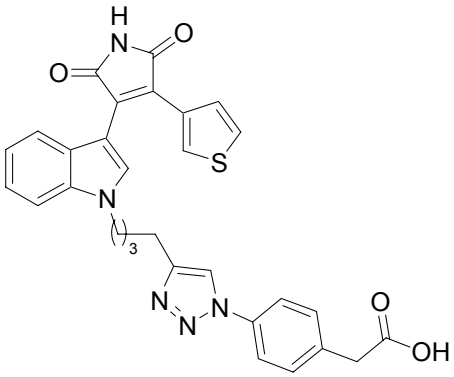
121.5, 121.6, 125.5, 126.2, 126.7, 127.5, 129.6 (2C), 131.8, 133.1, 134.8, 135.7, 136.5, 141.9, 147.6, 172.9 (2C), 174.2; **HRMS**: Found 625.2599 $C_{37}H_{33}N_6O_4$[M-H]$^-$ requires 625.2569.

Synthesis of 4-(4-(3-(3-(2,5-dioxo-4-thiophen-3-yl-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-propyl)-(1,2,3)tria zol-1-yl)-phenyl)-acetic acid (47)



Following general **procedure B**: 4-aminophenyl acetic acid (71.0 mg, 0.470 mmol) and the corresponding alkyne fragment (171 mg, 0.475 mmol) gave the product as a bright red solid (155 mg, 0.289 mmol, 61 %); **m.p.** 262-264 °C; υ_{max} (solid)/cm^{-1} 1706 (CO); δ_H **(400 MHz, DMSO-d$_6$)** 2.24 (apt quin, *J* 7.2 Hz, 2 H), 2.76 (t, *J* 7.2,2 H), 3.66 (s, 2 H), 4.45 (t, *J* 7.2 Hz, 2 H), 6.78 (d, *J* 7.7 Hz, 1 H), 6.96 (apt t, *J* 7.7 Hz, 1 H), 7.03 (apt t, *J* 4.4 Hz, 1 H), 7.21 (apt t, *J* 7.7 Hz, 1 H), 7.24 (d, *J* 4.4 Hz, 1 H), 7.45 (d, *J* 8.4 Hz, 2 H), 7.64 (d, *J* 7.7 Hz, 1 H), 7.72 (d, *J* 4.4 Hz, 1 H), 7.79 (d, *J* 8.4 Hz, 2 H), 8.00 (s, 1 H), 8.58 (s, 1 H), 11.15 (s, 1 H), 12.41 (s, 1 H); δ_C **(125 MHz, DMSO-d$_6$)**22.4, 29.2, 39.9, 45.6, 103.1, 111.0, 119.7 (2C), 120.1, 120.4, 121.8, 122.2, 124.4, 125.0, 127.1, 128.5, 130.5, 130.6 (2C), 130.9 (2C), 133.4, 135.5 (2C), 136.4, 147.1, 172.0, 172.1, 172.5; **HRMS**: Found 536.1410 $C_{29}H_{22}N_5O_4S$ [M-H]$^-$ requires 536.1398.

Synthesis of 4-(4-(4-(3-(2,5-dioxo-4-thiophen-3-yl-2,5-dihydro-1*H*-pyrrol-3-yl)-indol-1-yl)-butyl)-(1,2,3)triaz ol-1-yl)-phenyl)-acetic acid (48)



Following general **procedure B**: 4-aminophenyl acetic acid (71.0 mg, 0.470 mmol) and the corresponding alkyne fragment (178 mg, 0.476 mmol) gave the product as a bright red solid (155 mg, 0.281 mmol, 59 %); m.p. 258-260 °C; υ_{max} (solid)/cm^{-1} 1698 (CO); δ_H **(400 MHz, DMSO-d$_6$)** 1.71 (apt quin, *J* 7.3 Hz, 2 H), 1.93 (apt quin, *J* 7.3 Hz, 2 H), 2.76 (t, *J* 7.3 Hz, 2 H), 3.68 (s, 2 H), 4.37 (t, *J* 7.3 Hz, 2 H), 6.78 (d, *J* 7.6 Hz, 1 H), 6.95 (apt t, *J* 7.6 Hz, 1 H), 7.02 (apt t, *J* 4.2 Hz, 1 H), 7.19 (apt t, *J* 7.6 Hz, 1 H), 7.25 (d, *J* 4.2 Hz, 1 H), 7.45 (d, *J* 8.4 Hz, 2 H), 7.61 (d, *J* 7.6 Hz, 1 H), 7.69 (d, *J* 4.2 Hz, 1 H), 7.77 (d, *J* 8.4 Hz, 2 H), 7.96 (s, 1 H), 8.47 (s, 1 H), 11.14 (s, 1H), 12.42 (s, 1 H); δ_C **(125 MHz, DMSO-d$_6$)**24.5, 26.0, 29.1, 40.0, 45.7, 103.0, 110.8, 119.6 (2C), 120.0, 120.1, 121.6, 122.0, 124.5, 125.1, 127.0, 128.6, 130.4, 130.5 (2C), 131.0 (2C), 133.1, 135.4 (2C), 136.3, 147.7, 171.9, 172.0, 172.3; **HRMS**: Found 550.1543 $C_{30}H_{24}N_5O_4S$ [M-H]$^-$ requires 550.1554.

1.5 HPLC purities

Method: Column: Analytical: C-18 YMC-Pack R & D ODS-A. 100 x 46 mmI.D; Solvents: 10 % (MeOH (0.1% TFA)), 90 % (H_2O (0.1% TFA))-isocratic. Flow rate: 0.5 mL/min.

Table 1. HPLC purities for final compounds

Compound	Purity (%)	Compound	Purity (%)
18	98	**34**	-
19	99	**35**	-
20	>99	**36**	>99
21	98	**37**	>99
22	98	**38**	>99
23	>99	**39**	>99
24	>99	**40**	-
25	-	**41**	-
26	-	**42**	-
27	-	**43**	98
28	>99	**44**	99
29	>99	**45**	>99
30	>99	**46**	>99
31	99	**47**	98
32	89	**48**	>99
33	>99		