SUPPLEMENTAL INFORMATION

3-Thio-3,4,5-Trisubstituted-1,2,4-Triazoles: High Affinity Somatostatin Receptor-4 Agonist Synthesis and Structure-Activity Relationships

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Table S1. Corresponding residues in SST_4 structures under investigation.

Homology model	7XMS	Ballesteros-Weinstein
F60	F96	2.53
V67	V103	2.60
S70	S106	2.63
W76	W112	ECL1
L87	L123	3.29
D90	D126	3.32
G91	G127	3.33
M94	M130	3.36
F95	F131	3.37
T142	T178	4.57
I145	I181	4.60
C162	C198	ECL2
N163	N199	ECL2
L164	L200	ECL2
W166	W202	ECL2
S172	S208	5.35
F175	F211	5.38
V176	V212	5.39
T179	T215	5.42
W236	W272	6.48
F239	F275	6.51
Y240	Y276	6.52
Q243	Q279	6.55
N246	N282	6.58
A254	A290	7.32
N257	N293	7.35
H258	H294	7.36
L261	L297	7.39
Y265	Y301	7.43

Table S2a. Missing binding pocket residues in the cryo-EM SST_4 structure.

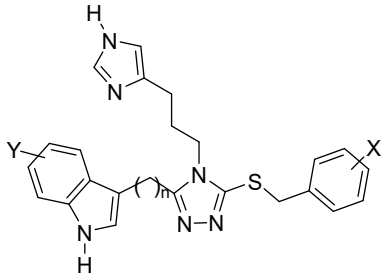
Res.	Position	Location
VAL	285	TM6
THR	286	ECL3
SER	287	ECL3
ALA	190	ECL2
ARG	191	ECL2
GLY	192	ECL2
GLY	193	ECL2
GLN	194	ECL2
ALA	195	ECL2
VAL	196	ECL2

Table S2b. Missing atoms in the binding site of the cryo-EM SST_4 structure.

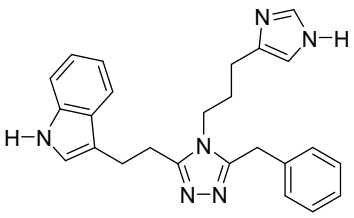
Res.	Position	Missing Atoms	Location
ASP	186	CG OD1 OD2	ECL2
ARG	120	CG CD NE CZ NH1 NH2	TM3
HIS	204	CG ND1 CD2 CE1 NE2	TM5
TRP	207	CG CD1 CD2 NE1 CE2 CE3 CZ2 CZ3 CH2	TM5
PHE	284	CG CD1 CD2 CE1 CE2 CZ	TM6
HIS	294	CG ND1 CD2 CE1 NE2	TM7
ILE	298	CG1 CG2 CD1	TM7

Supplemental Table S3a. 5-Indolyl-3-Thio-1,2,4-Triazoles with 95% confidence intervals (*MATCHED TO TABLE-1 of main manuscript*)

Compound #	Y	X	n	Binding Affinity Ki (nM) (95% confidence interval)					Activity EC_{50} (nM) SST_4 (95% confidence interval)
				SST_1	SST_{2A}	SST_3	SST_4	SST_5	
30	H	H	1	8591 (7048-10470)	>10000	>10000	20.9 (14.6-29.7)	>10000	21.9 (10.7-44.7)
31	H	3-CF_3	1	-	>10000	-	26.4 (18.9-36.8)	-	38.5 (19.5-75.9)
32	H	3-Br	1	1624 (1239-2130)	>10000	>10000	16.2 (11.8-22.2)	>10000	25.2 (15.2-41.7)
33	H	3,4-Cl_2	1	-	>10000	-	53.1 (38.3-73.6)	-	44.0 (21.4-90.8)
34	H	3-F	1	-	>10000	-	19.3 (13.0-28.8)	-	52.8 (27.0-103.3)
35	H	3-OCH_3	1	2250 (2058-3224)	>10000	>10000	16.5 (11.9-22.9)	>10000	13.9 (3.6-546)
36	H	3-CH_3	1	1644 (1182-2286)	>10000	>10000	13.8 (11.0-17.2)	>10000	8.4 (48-14.6)
37	H	4-Br	1	4645 (3783-5704)	7695 (5392-10980)	>10000	129.6 (88.3-190.4)	>10000	165.5 (69.0-396.9)
38	H	4-CO_2CH_3	1	>10000	>10000	>10000	152.2 (104.2-222.4)	>10000	612.8 (365.3-1028)
39	5-F	H	1	-	>10000	-	59.3 (42.1-83.6)	-	46.9 (20.6-107.2)
40	6-F	H	1	-	>10000	-	12.3 (8.2-18.4)	-	17.5 (9.4-32.6)
41	6-F	3-CH_3	1	2451 (2092-2871)	8094 (6451-10150)	5934 (4241-8304)	8.4 (5.8-12.1)	>10000	10.0 (5.5-18.1)
42	H	H	2	4076 (3435-4835)	>10000	2414 (1632-3569)	31.1 (21.9-44.1)	>10000	85.2 (67.9-106.9)
43	H	3-F	2	-	>10000	-	90.2 (63.1-129.0)	-	213.5 (92.8-491.4)
44	H	3-Cl	2	-	>10000	-	92.8 (68.1-126.6)	-	130.2 (73.1-232.0)
45	H	3,4-Cl_2	2	-	>10000	-	78.8 (66.1-93.9)	-	35.0 (17.3-70.9)
158*	-	-	-	>10000	>10000	>10000	12.0 (7.9 - 17.9)	>10000	16.5 (7.4 - 36.9)
180*	-	-	-	1518 (935.7 - 2461)	>10000	>10000	1.7 (1.2 - 2.5)	>10000	2.0 (1.0 - 4.1)



30-45



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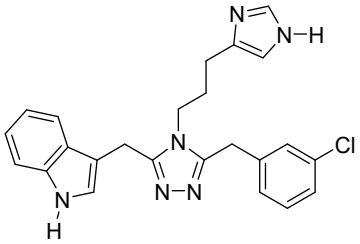
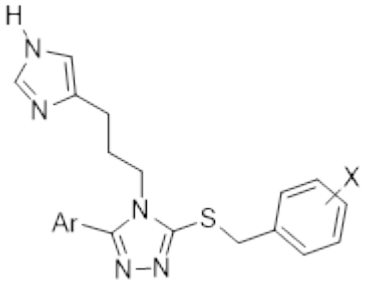


180*

Ki and EC50 values determined using non-linear regression. *Compounds 158 and 180 from ref[l]

Supplemental Table S3b. 5-Aryl and 5-Arylalkyl-3-*S*-Benzyl-1,2,4-Triazoles with 95%



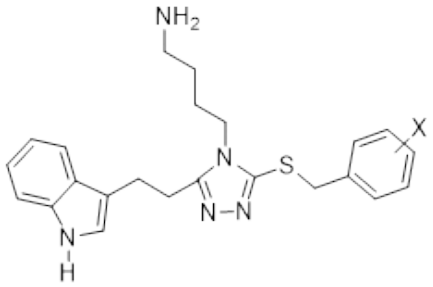
Confidence Intervals. (*MATCHED TO TABLE-2 of main manuscript*)

Compound #	**Ar**	**X**	**Binding Affinity Ki (nM)** (95% confidence interval)					**Activity EC_{50} (nM)** **SST_4** (95% confidence interval)
			SST_1	**SST_{2A}**	**SST_3**	**SST_4**	**SST_5**	
70	Ph	H	-	>10000	-	563.3 (422.8-750.6)	-	3778 (1554-9185)
71	$PhCH_2$	H	>10000	>10000	>10000	80.8 (62.2-104.8)	>10000	143.9 (82.6-250.7)

72	$PhCH_2$	3-OCH3	-	>10000	-	596.7 (400.3-889.3)	-	301.4 (191.7-473.9)
73	4-F-$PhCH_2$	H	-	>10000	-	53.3 (42.0-67.6)	-	153.1 (81.5-287.6)
74	$PhCH_2CH_2$	H	-	>10000	-	213.6 (165.2-276.1)	-	969.9 (391.5-2403)
75	$PhCH_2CH_2$	3-OCH_3	6633 (4353-10110)	>10000	>10000	151.8 (101.8-226.2)	>10000	289.6 (130.0-645.2)
76	4-F-$PhCH_2CH_2$	H	-	>10000	-	306.0 (214.2-47.2)	-	2708 (1453-5045)
77	1-Naphthyl	H	-	>10000	-	916.2 (623.1-1347)	-	-
78	2-Naphthyl	H	-	>10000	-	1347 (1027-1767)	-	-
79	2-Quinolinyl	H	-	>10000	-	959 (650.4-1415)	-	-
80	2-Indolyl	H	-	>10000	-	140.8 (118.3-167.7)	-	142.8 (66.0-309.3)
81	5-F-2-Indolyl	H	-	>10000	-	775.7 (551.6-1091)	-	1128 (441.2-2882)
82	3-Indolyl	H	>10000	>10000	>10000	76.1 (52.4-110.7)	>10000	104.6 (58.7-186.7)

Ki and EC50 values determined using non-linear regression.

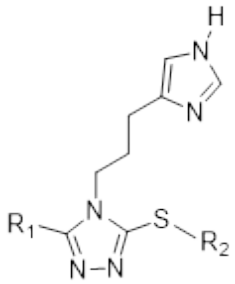
Supplemental Table S3c. 4-Aminobutyl-5-indolylethyl-3-*S*-Benzyl-1,2,4-Triazoles with 95% confidence intervals. (*MATCHED TO TABLE-3 of main manuscript*)



Compound #	X	Binding Affinity Ki (nM) (95% confidence interval)					Activity EC_{50} (nM) SST_4 (95% confidence interval)
		SST_1	SST_{2A}	SST_3	SST_4	SST_5	
85	H	-	>10000	-	3609 (1912-6810)	-	-
86[a]	3-F	-	>10000	-	1088 (709.4-1669)	-	-
87	3-Cl	-	>10000	-	2734 (1764-4236)	-	-
88[a]	3,4-Cl_2	-	>10000	-	1522 (1063-2177)	-	-

Ki and EC50 values determined using non-linear regression. [a]HCl salt.

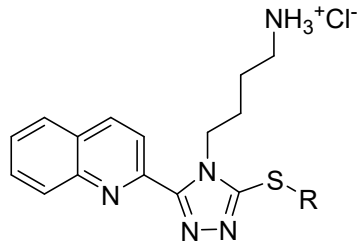
Supplemental Table S3d. 5-Arylalkyl-3-*S*-1,2,4-Triazoles with 95% confidence intervals. (*MATCHED TO TABLE-4 of main manuscript*)



Compound #	R_1	R_2	Binding Affinity Ki (nM) (95% confidence interval)					Activity EC_{50} (nM) SST_4 (95% confidence interval)
			SST_1	SST_{2A}	SST_3	SST_4	SST_5	
90	4-F-PhCH_2	4-F-Ph	-	>10000	-	2.6 (2.0-3.4)	-	25.8 (6.9-95.8)
91	4-F-PhCH_2	Cyclopentyl	-	>10000	-	66.6 (54.6-81.3)	-	146.1 (57.0-374.6)
92	1-Naphthyl-CH_2	SO_2Ph	139.3 (103.1-188.2)	5105	1917 (1619-2270)	0.4 (0.3-0.5)	>10000	0.4 (0.2-0.9)
93	3-Indolyl-CH_2	Ph	2770 (2140-3586)	>10000	>10000	0.85	>10000	0.6 (0.3-1.2)
94	3-Indolyl-CH_2	3,4-Cl_2-Ph	-	3352 (2851-3941)	-	5.7 (4.5-7.3)	-	1.1 (0.5-2.2)
95	3-Indolyl-CH_2	3-CH_3SO_2-Ph	-	>10000	-	0.7 (0.6-1.0)	-	2.3 (0.-6.7)
96	6-F-Indolyl-CH_2	3-CH_3SO_2-Ph	209.2 (155.9-280.8)	5003 (4261-5874)	3781 (3038-4706)	1.0 (0.7-1.4)	7954 (6142-10300)	-
97	6-F-Indolyl-CH_2	3-CH_3O-Ph	655.7 (512.4-839.0)	2876 (2467-3354)	2912 (2155-3935)	0.6 (0.5-0.8)	>10000	1.0 (0.6-1.6)
98	6-F-Indolyl-CH_2	3-CF_3-Ph	453.3 (313.8-654.9)	1066 (937.5-1213)	1265 (1083-1477)	1.3 (1.1-1.6)	9965 (8646-11490)	2.9 (1.4-5.7)
99	6-F-Indolyl-CH_2	4-F-Ph	314.6 (193.1-512.8)	2937 (2338-3689)	>10000	0.6 (0.5-0.8)	>10000	0.6 (0.4-1.1)
100	6-F-Indolyl-CH_2	3-CH_3-Ph	732.7 (549.2-977.4)	3918 (2824-5435)	5553 (4136-7456)	3.7 (2.6-5.4)	>10000	3.1 (1.8-5.3)
101	6-F-Indolyl-CH_2	3,4-Cl_2-Ph	-	2388 (2120-2690)	-	5.3 (4.1-7.0)	-	4.7 (0.9-25.2)
102	6-F-Indolyl-CH_2	2-Pyridyl	6066 (3201-11490)	>10000	>10000	32.1 (20.5-50.2)	>10000	27.0 (12.9-56.6)
103	6-F-Indolyl-CH_2	3-Pyridyl	2133 (1265-3598)	>10000	>10000	5.0 (3.3-7.5)	>10000	9.0 (3.8-21.4)

Ki and EC50 values determined using non-linear regression.

Supplemental Table S3e. 5-Quinolinyl-3-*S*-Substituted -1,2,4-Triazoles with 95% Confidence Intervals. (*MATCHED TO TABLE-5 of main manuscript*)



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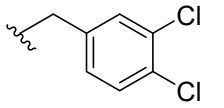

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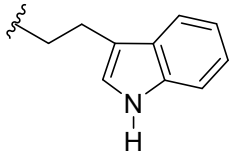

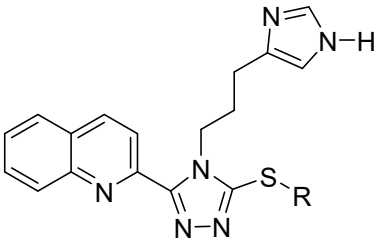

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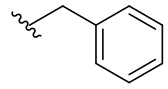

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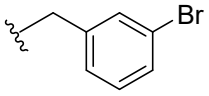

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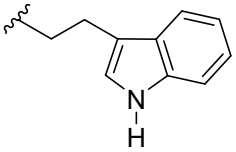
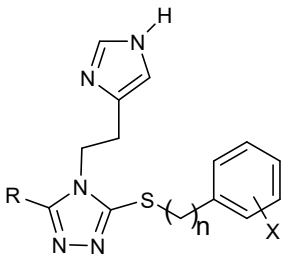


Compound #	**Binding Affinity Ki (nM)** (95% confidence interval)					**Activity EC_{50} (nM)** **SST_4** (95% confidence interval)
	SST_1	**SST_{2A}**	**SST_3**	**SST_4**	**SST_5**	
105	-	>10000	-	945.4 (712.8-1,254)	-	-
106	39.16 (26.3-58.4)	40.6 (36.0-45.8)	385.5 (292.7-507.7)	88.31 (64.9-120.2)	50.84 (46.1-56.1)	-
107	-	>10000	-	959.2 (650.4-1415)	-	-
108	-	>10000	-	236.8 (225.2-474.2)	-	1399 (505.7-3872)
109	2,134 (1722-2644)	>10000	>10000	27.32 (18.81-39.69)	>10000	89.27 (57.01-139.8)

Ki and EC50 values determined using non-linear regression.

Supplemental Table S3f. 4-(2-Imidazol-4-yl)ethyl-1,2,4-Triazoles with 95% Confidence Intervals. (MATCHED TO TABLE-6 of main manuscript)



122: R = 4-F-PhCH_2, X = H, n = 1
123: R = 3-F-PhCH_2, X = H, n = 1
124: R = Indolylmethyl, X = 3-Cl, n = 0
125: R = 6-F-Indolylmethyl, X = 3-F, n = 1
126: R = 6-F-Indolymethyl, X = 3-CH_3, n = 1

Compound	**Binding Affinity Ki (nM)** (95% confidence interval)					**Activity EC50 (nM)** **SST_4** (95% confidence interval)
	SST_1	**SST_{2A}**	**SST_3**	**SST_4**	**SST_5**	
122	>10000	>10000	>10000	242.9 (192.7-306.2)	>10000	-
123	>10000	>10000	>10000	266.9 (218.9-325.4)	>10000	420.5 (181.2-975.8)
124	-	2634 (1780-3896)	-	12.6 (8.1-19.6)	-	14.1 (9.9-20.1)
125	-	9157 (8422-9955)	-	178.4 (151.5-210.2)	-	302.4 (83.4-1097)
126	-	>10000	-	115.4 (103.0-129.3)	-	113.3 (49.7-58.1)

Ki and EC50 values determined using non-linear regression.

Supplemental Table S3g. $SST_{1\text{-}5}$ binding and SST_4 EC_{50} of other established ligands serving as comparators with 95% Confidence Intervals.

Compound	Binding Affinity Ki (nM) (95% confidence interval)					Activity EC_{50} (nM) SST_4 (95% confidence interval)
	SST_1	SST_{2A}	SST_3	SST_4	SST_5	
SRIF-28*	0.7 (0.6 - 0.7)	0.4 (0.4 - 0.5)	0.5 (0.4 -0.6)	2.2 (1.9 -2.4)	2.2 (1.9 - 2.4)	3.6 (2.0 - 6.8)
Octreotide*	-	4.5 (3.7 - 5.5)	-	-	-	-
L-803,087*	-	>10000	-	3.8 (2.7 - 5.4)	-	-
J-2156*	929.5 (753.0 - 1147)	6754 (5343 - 8538)	-	1.1 (0.6 - 1.4)	-	0.9 (0.4 - 2.0)

Ki and EC50 values determined using non-linear regression. SRIF-28 (Tocris, MN, USA) served as positive control for all SST subtypes and was evaluated with every new lot of Membrane Target Systems™ (Perkin-Elmer, Boston, MA, USA) and cAMP inhibition assay set to confirm assay viability. Only single set shown in table; however, SRIF-28 range shown was consistent across all evaluations. Additional controls included octreotide (Tocris) for SST_2, and L-803,087 (Tocris) and J-2156 (Tocris) for SST_4. *Data shown from Neumann et al., 2021[1]

EXPERIMENTAL METHODS

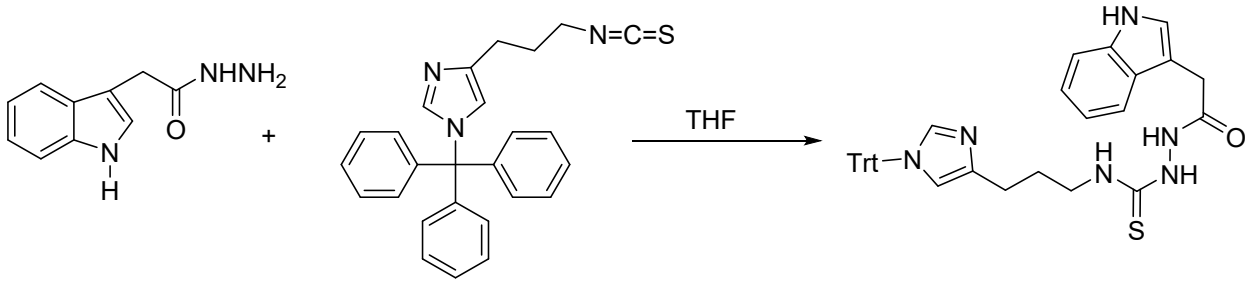
Chemistry

Synthetic Materials and Methods. Analytical thin layer chromatography (TLC) was performed on Analtech 0.15 mm silica get 60-GF254 plates. Visualization was accomplished with exposure to UV light, exposure to Iodine or by dipping in an ethanolic phosphomolybdic acid or $KMnO_4$ solution followed by mild heating. Solvents for extraction were HPLC or ACS grade. Flash chromatography was performed by the method of Still with Merck silica gel 60 (230-400 mesh) with the indicated solvent system. NMR spectra were collected on a JEOL ECS 400 spectrometer. ^{1}H NMR spectra were reported in ppm from tetramethylsilane on the δ scale. Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet, b = broadened, obs = obscured, app = apparent), coupling constants (Hz), and relative integration. ^{13}C NMR spectra were reported in ppm from the central deuterated solvent peak. Data are reported as follows: Chemical shift, and multiplicity (when determined). Grouped shifts are provided where an ambiguity has not been resolved. LCMS were run on a Waters Alliance – SQ 3100 system using a Thermo Scientific Hypersil GOLD (C18, 4.6 x 150 mm, 5-Micron) column and acetonitrile-water (0.05% TFA) gradients. High resolution MS were performed by the University of Notre Dame Mass Spectrometry and Proteomics Facility.

Starting materials and intermediates were obtained from Combi-Blocks, Aldrich, TCI-America, or Alfa and used without further purification.

General Procedure A: Condensation of Hydrazides with Isothiocyanate 9

The isothiocyanate **9** (1 eq.) was added to the desired hydrazide **5-8** (1 eq.) in anhydrous THF (minimum for solubilization) and the reaction was stirred at room temperature under N_2 for 18 to 24 h. The corresponding thiosemicarbazides were obtained after evaporation of the solvent and appropriate purification.



9

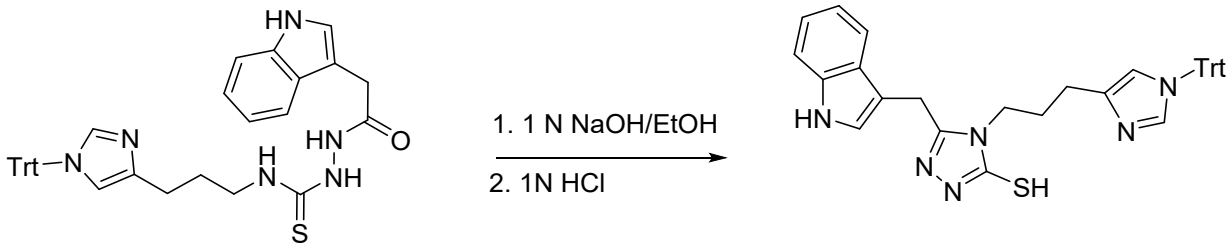
2-(2-(1H-Indol-3-yl)acetyl)-*N*-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazine-1-carbothioamide

Prepared according to **general procedure A** from 2-(1*H*-indol-3-yl)acetohydrazide **5** (424 mg, 2.24 mmol) and 3-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]propyl isothiocyanate (**9,** 1.009 g, 2.48 mmol) to afford 1.002 g (75% yield) 2-(2-1*H*-indol-3-yl)acetyl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propylhydrazine-1-carbothioamide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 9.87 (s, 1H), 9.18 (s, 1H), 7.95 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.42-7.21 (m, 12H), 7.11-7.02 (m, 7H), 6.96 (m, 1H), 6.65 (s, 1H), 3.56 (s, 2H), 3.44 (m, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 1.72 (m,2H).^{13}C NMR (100 MHz, DMSO-d_6).

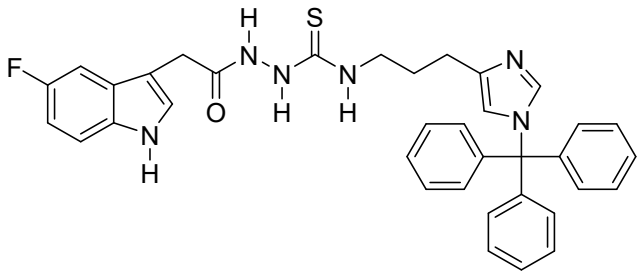
δ 142.40, 140.66, 137.69, 136.06, 129.26, 128.24, 127.99, 127.23, 123.97, 121.00, 118.78, 118.3 117.56, 111.31, 108.01, 74.42, 43.42, 30.66, 28.36, 25.22.

General Procedure B: Cyclization of Thiosemicarbazides to 3-Thio-1,2,4-Triazoles

Thesemicarbazide (1 eq.) was dissolved in EtOH (5mL/mmol), and NaOH 1 M (1.5 eq.) was added. The mixture was heated 85°C for 3h to 4h. At the end of the reaction, water was added. The aqueous layer was washed with DCM, acidified to pH 2 with 1M HCl, and extracted twice with DCM. After evaporation, the 3-thiol-1,2,4-triazoles **(10-13)** were purified by precipitation, recrystallization, flash chromatography, or used without further purification.

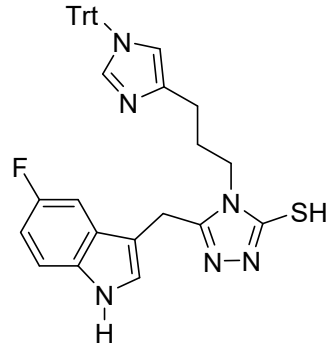


5-((1H-Indol-3-yl)methyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (10). Prepared according to **general procedure B from** 2-(1*H*-indol-3-acetyl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)hydrazine-1-carbothioamide (1.00 g, 1.67 mmol) to afford 829 mg (85%) of compound **10** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) d 11.07 (s, 1H), 8.47 (s, 1H), 7.47-7.39 (m, 10H), 7.31-7.28 (m, 2H), 7.14-7.09 (m, 7H), 7.03 (m, 1H), 6.93 (m, 1H), 4.19 (m, 2H), 3.86 (t, *J* = 7.3 Hz, 1H), 2.53 (m, 2H), 1.70 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) d 166.46, 151.36, 140.80, 136.62, 136.22, 134.76, 129.22, 128.56, 128.49, 127.78, 127.54, 126.65, 124.21, 121.29, 119.33, 118.66, 118.29, 111.62, 107.11, 76.68, 42.16, 26.44, 22.19, 21.92.



2-(2-(5-Fluoro-1*H*-indol-3-yl)acetyl)-*N*-(3-trityl-1*H*-imidazol-4-yl)propyl)hydrazinecarbothioamide

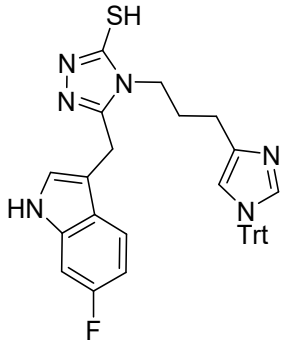
Prepared according to **general procedure A** from [1-(triphenylmethyl)-1*H*-imidazol-4-yl]propyl isothiocyanate (**9**,1.009 g, 2.44 mmol) and hydrazide **6** (506 mg, 2.44 mmol) to afford 1.38 g (92%) of the thiosemicarbazide as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.87 (s, 1H), 8.02 (s, 1H), 7.43-7.26 (m, 13H), 7.10-7.07 (m, 6H), 6.89 (m, 1H), 6.64 (s, 1H), 3.44 (m, 2H), 2.43 (m, 2H), 1.73 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.24, 157.86, 155.59, 142.40, 140.63, 137.67, 132.74, 129.25, 128.23, 127.98, 127.52, 126.14, 117.55, 112.28, 109.22 (d), 126.14, 117.55, 112.28, 109.22 (d), 108.34, 103.72 (d), 74.40, 67.05, 43.43, 30.59, 28.36, 25.17.



5-((5-Fluoro-1H-indol-3-yl)methyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4*H*-1,2,4-triazole-3-thiol (11)

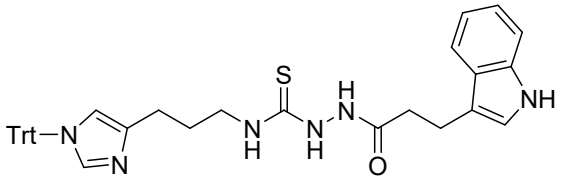
Prepared according to **General Procedure B** from the thiosemicarbazide (1.23 g, 2.00 mmol). Evaporation of the organic phase afforded the desired product **11** as a yellow foam (860 mg,

72%): ^{13}C NMR (400 MHz, DMSO-d_6) δ 11,19 (s, 1H), 7,48-7.39 (m, 10H), 7.32-7.21 (m, 3H), 7.17-7.14 (m, 6H), 6.90 (s, 1H, 4,17 (s, 2H), 3.86 (d, *J* = 7.4 Hz, 2H), 2.61 (d, 7.4, *J* = 7.4 Hz, 2H), 1.76 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.49, 157.82, 155.52, 151.24, 147.78, 140.47, 136,39, 133.66, 132.89, 129.23, 128.66, 127.79, 127.55, 127.00 (d), 126.674, 126.34, 119.77, 112.71 (d), 109.58 (d), 107.40 (d), 103.21 (d), 77.20, 42.02, 26.36, 21.74, 21.62.



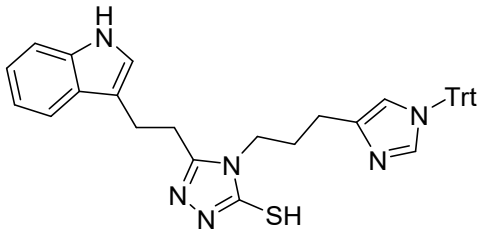
5-((6-Fluoro-1H-indol-3-yl)methyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (12). Prepared according to General Procedures A and B. To a solution of 4-(3-isothiocyanatopropyl)-1-trityl-1*H*-imidazole (**9,** 2.37 g, 5.78 mmol) and 2-(6-fluoro-1H-indol-3-yl)acetylhydrazide hydrochloride (1.41 g, 5.79 mmol) in DMF (70 mL) was added diisopropylethylamine (6.06 mL, 34.7 mmol) and the reaction was heated to 70 ºC for 3 h thereafter to effect formation of the acyl thiosemicarbazide intermediate. The mixture was concentrated and the residue was dissolved in EtOH (120 mL), treated with 2N NaOH (50 mL) and heated to 50 ºC for 3 h. The mixture was then cooled to 0-5 ºC (ice-bath) and treated with 4N HCl (20 mL) followed by 1N HCl (60 mL) to adjust the pH to ~4. Filtration and dessication of the precipitated solid afforded compound **12** as a light tan powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.39 – 7.31 (complex m, 10H), 7.27 – 7.14 (m, 3H). 7.06 – 7.01 (m, 6H). 6.75 (ddd, *J* = 9.8, 8.7, 2.4 Hz, 1H), 6.65 (s, 1H), 4.09 (s, 2H), 3.83 (dd, *J* = 9.2, 6.6 Hz, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 1.65 (quint., *J* = 7.6 Hz, 2H). LCMS (50-95% acetonitrile in

0.05% TFA over 10 minutes) retention time = 5.17 minutes, ESI m/z = 599, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 599.2386 (599.2388 calc'd for $C_{36}H_{32}FN_6S$), $[M + H]^+$.



2-(3-(1H-indol-3-yl)propanoyl)-N-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazinecarbothioamide

Prepared according to **general procedure A** from compound **9** (2.09 g, 5.1 mmol) and hydrazide **8** (942 mg, 4.6 mmol) to yield 2.41 g (77%) of the thiosemicarbazide as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 9.71 (s, 1H), 9.13 (s, 1H), 7.76 (m, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.40-7.31 (m, 11H), 7.25 (d, *J* = 1.4 Hz, 1H), 7.10-7.02 (m, 8H), 6.96 (t, *J* = 7.8 Hz, 1H), 3.33 (m, 2H, under H_2O peak), 2.94 (m, 2H), 2.46 (m, 2H under DMSO), 2.43 (m, 2H), 1.68 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.70, 142.38, 140.66, 137.65, 136.27, 129.24, 128.22, 127.96, 126.95, 122.23, 120.98, 118.31, 118.22, 117.53, 113.49, 111.38, 74.39, 43.32, 34.14, 28.40, 25.17, 20.39. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.28 min, ESI m/z = 613.36 $[M+H]^+$.

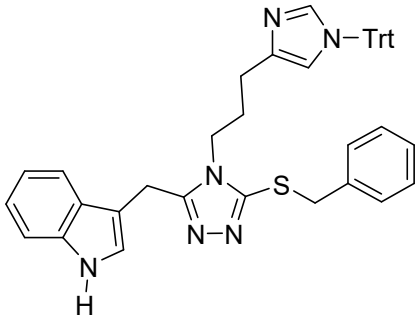


5-(2-(1H-Indol-3-yl)ethyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (13)

Prepared according to **general procedure B** from the thiosemicarbazide (2.41 g, 3.9 mmol)). Flash chromatography on silica gel (gradient DCM/MeOH 9:1) afforded the desired product **13** as a yellow foam (1.78 g, 76%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (s, 1H), 7.45 (d, *J*= 7.8 Hz, 1H), 7.37-7.26 (m, 11H), 7.17 (d, *J* = 1.4 Hz, 1H), 7.09 (s, 1H), 7.05-6.96 (m, 7H), 6.85 (t, *J* = 6.9 Hz, 1H), 3.83 (t, *J* = 8.2 Hz, 2H), 2.99 (m, 4H), 2.41 (t, *J* = 6.9 Hz, 2H), 1.82 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.65, 152.61, 142.86, 140.37, 138.23, 136.69, 129.71, 128.70, 128.43, 127.35, 123.15, 121.48, 118.79, 118.70, 118.18, 113.27, 111.90, 74.87, 43.04, 27.80, 26.20, 25.39, 22.03. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 7.08 min, ESI m/z = 595.41 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{37}H_{35}N_6S$ $(M+H)^+$ 595.2630, found 595.2638.

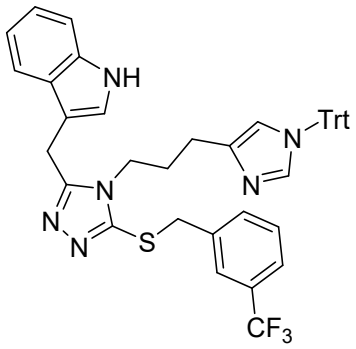
General Procedure C: Alkylation of the thiol

To a mixture of a benzyl bromide derivative (1 eq.) and the thiol (1 eq.) in DCM (8 mL/mmol) was added triethylamine (1 eq.). The reaction mixture was stirred 5 to 12h, and the solvent was evaporated and the residue was partitioned between EtOAc (150 mL) and brine (150 mL). The layers were separated, and the organic layer was dried (anhydrous $MgSO_4$), filtered, and concentrated. The reaction mixture was evaporated and purified by chromatography on silica column (gradient DCM to EtOAc or DCM to DCM/MeOH (9:1).



3-((5-(Benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (14)

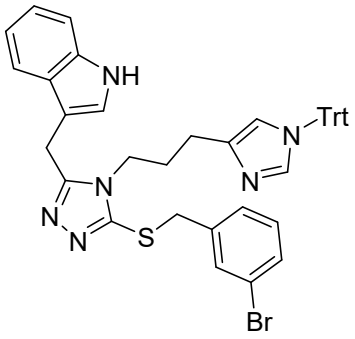
Prepared according to **general procedure C** from **10** (775 mg, 1.37 mmol) to afford 647 mg (72%) of compound **14** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.40-7.35 (m, 9H), 7.30-7.25 (m, 2H), 7.15-7.01 (m, 13H), 6.91 (s, 1H), 6.53 (s, 1H), 4.25 (s, 2H), 4.17 (s, 2H), 3.59 (t, *J* = 7.3 Hz, 2H), 2.24 (t, *J* = 7.3 Hz, 2H), 1.45 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.62, 148.38, 142.30, 139.45, 137.72, 137.23, 136.30, 129.21, 128.75, 128.36, 128.22, 128.00, 127.36, 126.74, 123.61, 121.24, 118.53, 117.62, 111.47, 108.44, 74.45, 42.68, 37.68, 28.69, 24.57, 21.69. This compound was used directly in the deprotection step without further purification.



3-((5-(3-(Trifluoromethyl)benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (15)

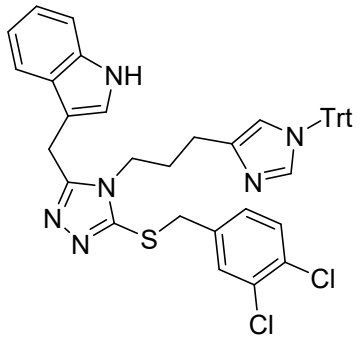
Prepared according to **general procedure C** from compound **10** (468 mg, 0.81 mmol) and 3-trifluoromethylbenzyl bromide (123 mL, 0.81 mmol) to give 474mg (80%) of compound **15** as a pale yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (d, *J* = 2.3 Hz, 1H), 7.60 (s, 1H), 7.39-6.97 (m, 24H), 6.46 (d, 1H), 4.34 (s, 2H), 4.12 (s, 2H), 3.61 (t, *J* = 7.4 Hz, 2H), 2.21 (t, *J* = 7.1 Hz, 2H), 1.40 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) d 154.83, 148.13, 142.37, 139.55, 139.15, 137.81, 136.31, 132.97, 129.42, 129.24, 129.01, 128.25, 128.03, 126.76, 125.49 (d),

124.07 (d), 123.66, 122.76, 121.29, 118.53 (d), 117.64, 111.53, 108.44, 74.45, 42.82, 36.46, 28.76, 24.61, 21.65. This compound was used directly in the deprotection step without further purification.



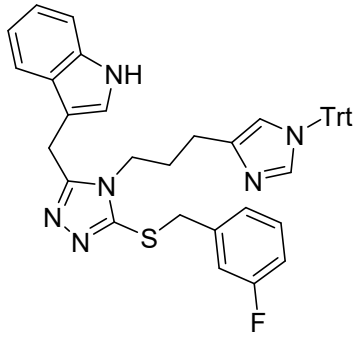
3-((5-(3-Bromobenzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (16)

Prepared according to **general procedure C** from **10** (510 mg, 0.88 mmol) and 3-bromobenzyl bromide (219 mg, 0.88 mmol) to yield 544 mg (83%) of **16** as a pale yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.48-7.00 (m, 24H), 6.92 (m, 1H), 6.53 (s, 1H), 4.28 (s, 2H), 4.17 (s, 2H), 3.68 (t, J = 7.8 Hz, 2H), 2.27 (t, J = 7.1 Hz, 2H), 1.47 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) d 154.71, 148.11, 142.32, 140.27, 139.52, 137.74 136.25, 131.54, 130.41, 130.16, 129.19, 128.17, 127.94, 127.84, 126.71, 123.60, 121.49, 121.19, 118.49, 117.56, 111.45, 108.42, 74.36, 42.77, 36.40, 28.74, 24.60, 21.61. This compound was used directly in the deprotection step without further purification.



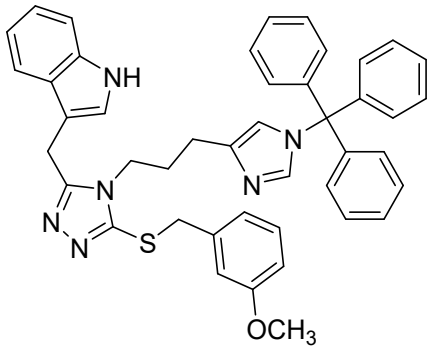
3-((5-(3,4-Dichlorobenzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (17)

Prepared according to **general procedure C** from **10** (519 mg, 0.89 mmol) and 3,4-dichlorobenzyl bromide (130 μL, 0.89 mmol) to afford 538 mg (81%) of compound **17** as a pale yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.45-7.00 (m, 23H), 6.90 (m, 1H), 6.54 (s, 1H), 4.29 (s, 2H), 4.18 (s, 2H), 3.68 (t, J = 7.6 Hz, 2H), 2.28 (t, J = 6.9 Hz, 2H), 1.50 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.78, 147.98, 142.32, 139.54, 138.80, 137.75 136.26, 130.83, 130.81, 130.38, 129.97, 129.19, 129.08, 128.16, 127.93, 126.71, 123.64, 121.18, 118.49, 117.58, 111.48, 108.36, 74.36, 42.77, 35.68, 28.78, 24.57, 21.64. This compound was used directly in the deprotection step without further purification.



3-((5-(3-fluorobenzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (18)

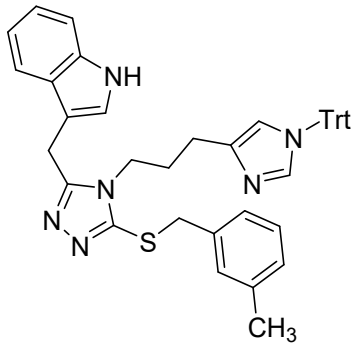
Prepared according to **general procedure C** from compound **10** (529 mg, 0.91 mmol) and 3-fluorobenzyl bromide (112 μL, 0.91 mmol) to afford 610 mg (97%) of **18** as a pale yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.40-7.34 (m, 10H), 7.29-7.23 (m, 2H), 7.14-6.98 (m, 12H), 6.90 (s, 1H), 6.53 (s, 1H), 4.30 (s, 2H), 4.18 (s, 2H), 3.66 (t, *J* = 7.8 Hz, 2H), 2.26 (t, *J* = 7.3 Hz, 2H), 1.48 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.11, 160.68, 154.68, 148.14, 142.32, 140.23 (d), 139.54, 137.72, 136.24, 130.26 (d), 129.17, 128.16, 127.92, 124.89, 123.57, 121.18, 118.47, 117.54, 115.69 (d), 114.29 (d), 111.43, 108.42, 74.35, 42.75, 36.56, 28.75, 24.58, 21.60. This compound was used directly in the deprotection step without further purification.



3-((5-(3-Methoxybenzylthio)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (19).

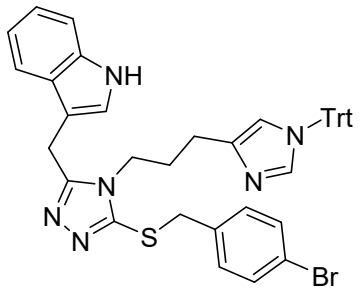
Prepared according to **General Procedure C** from **10** (500 mg, 0.86 mmol) and 3-methoxybenzyl bromide (121 μL, 0.86 mmol) to afford 441 mg (73%) of **19** as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.47 (d, *J* = 7.8 Hz, 1H), 7.39-7.34 (m, 9H), 7.29 (d, *J* =8.2 Hz, 1H), 7.23 (d, *J* = 1.4 Hz, 1H), 7.14 (d, *J* =2.3 Hz, 1H), 7.05-7.00 (m, 8H), 6.90 (m, 1H), 6.82 (m, 1H), 6.74-6.71 (m, 2H), 6.52 (s, 1H), 4.25 (s, 2H), 4.17 (s, 1H), 3.65 (m, 2H), 3.62 (s, 3H), 2.25 (m, 2H), 1.47 (m, 2H). ^{13}C NMR (100

MHz, DMSO-d_6) δ 159.16, 154.57, 148.37, 142. 31, 139.53, 138.66, 137.71, 136,24, 129.40, 129.17, 128.16, 127.92, 128.16, 127.92, 126.71, 123.57, 121.17, 120.93, 118.47, 117.55, 114.22, 113.04, 111.43, 108.46, 74.36, 54.92, 42.74, 37.35, 28.75, 24.60, 21.60. This compound was used directly in the deprotection step without further purification.



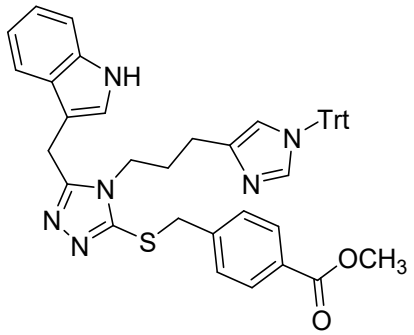
3-((5-((3-Methylbenzyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (20)

Prepared according to **General Procedure C** from **10** (513 mg, 0.88 mmol) and 3-methylbenzyl bromide (119 μL, 0.88 mmol) to afford 485 mg (80%) of **20** as a yellow foam: ^{1}H (400 MHz, DMSO-d_6) δ 10.93(s, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.40-7.36 (m, 9H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 1.4 Hz, 1 H), 7.14 (d, *J* = 2.3 Hz, 1H), 7.05-9.90 (m, 12H), 6.52 (s, 1H), 4.23 (s, 2H), 4.17 (s, 2H), 3.65 (t, *J* = 7.6 Hz, 2H), 2.13 (s, 3H), 1.45 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6 δ 154.54, 148.41, 142.31, 139.56, 137.70, 137.56, 137.00, 136.25, 129.17, 128.25, 128.16, 128.01, 127.92, 126.71, 125.84, 123.55, 121.17, 118.47, 117.53, 111.43, 108.46, 74.35, 42.71, 37.49, 28.72, 24.62, 20.79. This compound was used directly in the deprotection step without further purification.



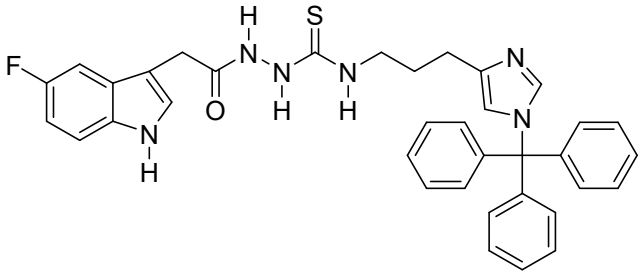
3-((5-((4-Bromobenzyl)thio)-4- (3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4 triazol-3-yl)methyl)-1H-indole (21).

Prepared from compound **10** (501 mg, 0.86 mmol), Et_3N (120 μL, 0.86 mmol), and 4-bromobenzyl bromide (0.215 g, 0.86 mmol) in CH_2Cl_2 (7 mL). Normal work-up gave 647 mg (87%) of **21** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.40 (m, 8H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.23 (m, 3H), 7.19 (s, 1H), 7.09 (m, 9H). 6.93 (t, 1H), 4.23 (s, 2H), 4.18 (s, 2H), 3.63 (t, *J* = 7.5 Hz, 2H), 2.27 (t, *J* = 7.8 Hz, 2H), 1.50 (m, 2H). ^{13}C (100 MHz, DMSO-d_6) δ 154.67, 148.10, 142.21, 139.53, 137.7, 136.84, 136.27, 131.18, 130.87, 129.18, 128.18, 128.17, 127.93, 126.71, 123.64, 121.16, 120.51, 118.51, 117.59, 111.49, 108.32, 74.35, 38.87, 36.65, 28.73, 24.57, 21.70. This compound was used directly in the deprotection step without further purification.



Methyl 4-(((5-((1H-indol-3-yl)methyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzoate (22)

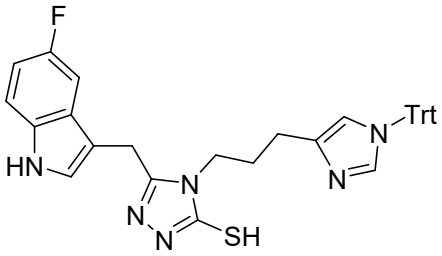
Using the **General Procedure C**, the following amounts were used: thiol **10** (493 mg, 0.85 mmol), Et_3N (118 µL), methyl-4-(bromomethyl)benzoate (194 mg. 0.85 mmol) in CH_2Cl_2 (7 mL) gave 390 mg (64%) of **22** as a tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.33 (m, 9H), 7.24 (m, 3H), 7.18 (s, 1H), 7.14 (s, 1H), 7.03 (m, 8H), 6.87 (t, *J*= 14.7 Hz, 1H), 6.49 (s, 1H), 4.28 (s, 2H), 3.78 (s, 3H), 3.60 (t , *J*=7.8 Hz, 2H), 2.22 (t, *J* = 6.8 Hz, 3H), 1.46 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.87, 154.71, 148.02, 142.95, 142.32, 139.53, 137.70, 136.25, 129.21, 129.17, 129.05, 128.16, 127.92, 118.46, 111.47, 108.30, 107.24, 74.34, 52.09, 39.50, 28.75, 24.54, 21.67. This compound was used directly in the deprotection step without further purification.



2-(2-(5-Fluoro-1H-indol-3-yl)acetyl-*N*-(3-(1-trity-1H-inidazol-4-yl)propyl)hydrazine-1-carbothioamide

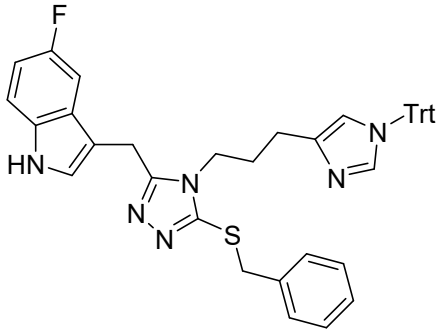
Prepared according to **General Procedure A** from compound **9** (1 g, 2.44 mmol) and hydrazide **6** (506 mg, 2.44 mmol) to afford 1.38 g (92%) of the thiosemicarbazide as a yellow foam: 1H NMR (400 MHz, DMSO-d6) 8 11.00 (s, 1H), 9.87 (s, 1H), 9.18 (s, 1H), 8.02 (s, 1H), 7.43-7.26 (m, 13H), 7.10-7.07 (m, 6H), 6.89 (m, 1H), 6.64 (s, 1H), 3.44 (m, 2H), 2.43 (m, 2H), 1.73 (m, 2H). 13C NMR (100 MHz, DMSO- *A6)* 8 170.24, 157.86, 155.59, 142.40,140.63,137.67,132.74, 129.25, 128.23, 127.98, 127.52 (d), 126.14, 117.55, 112.28, 109.22 (d), 108.34, 103.72 (d),

74.40, 67.05, 43.43, 30.59, 28.36, 25.17. The compound was used directly in the next step without further purification.



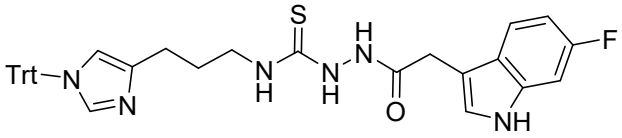
5-((5-Fluoro-lH-indol-3-yl)methyl)-4- (3-(l-trityl-lH-imidazol-4-yl)propyl)-4H-l,2,4-triazole- 3-thiol (11)

Prepared according to **General Procedure B** from the thiosemicarbazide (1.23 g, 2.00 mmol). Evaporation of the organic phase afforded the desired product **11** as a yellow foam (860 mg, 72%): ^{13}C NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 7.48-7.39 (m, 10H), 7.32-7.21 (m, 3H), 7.17-7.14 (m, 6H), 6.90 (s, 1H), 4.17 (s, 2H), 3.86 (d, J=7.4 Hz, 2H), 2.61 (d, J=7.3 Hz, 2H), 1.76 (m, 2H). ^{13}C NMR (100 MHz, DMSO- d6) 8 166.49, 157.82, 155.52, 151.24, 147.78, 140.47, 136.39, 133.66, 132.89, 129.23, 128.66, 127.79, 127.55, 127.00 (d), 126.67, 126.34, 119.77, 112.71 (d), 109.58 (d), 107.40 (d), 103.21 (d), 77.20, 42.02, 26.36, 21.74, 21.62. This compound was used directly in the deprotection step without further purification.



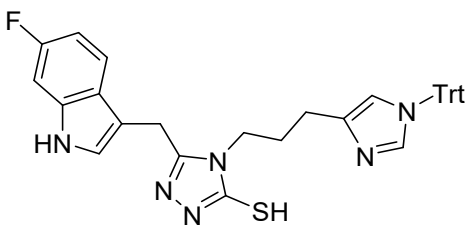
3-((5-Benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-5-fluoro-1H-indole (23)

Prepared according to General Procedure 2E from derivative **11**(400 mg, 0.58 mmol)) product as a yellow foam (57 mg, 21%): ^{1}H NMR (400 MHz, DMSO-d_6) 8 11.97 (s, 1H), 11.08 (s, 1H), 7.52 (s, 1H), 7.36-7.32 (m, 1H), 7.23-7.12 (m, 6H), 6.92 (m, 2H), 6.72 (s, 1H), 4.27 (s, 2H), 4.15 (s, 2H), 3.62 (m, 2H), 2.30 (m, 2H), 1.55 (m, 2H). The compound was used in the deprotection step without further purification.



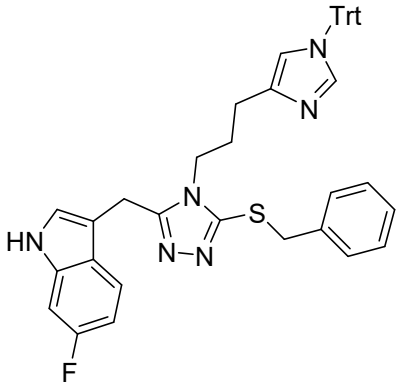
2-(6-Fluoro-1H-indol-3-yl)-N'-(5-(1-trityl-1H-imidazol-4-yl)pentanethioyl)acetohydrazide

Prepared according to **general procedure A** from compound **9** (1.12 g, 2.73 mmol) and hydrazide **7** (567 mg, 2.73 mmol) to afford 1.20 g (71%) of the thiosemicarbazide as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.85 (s, 1H), 9.14 (s, 1H), 7.97 (s, 1H), 7.50 (m, 1H), 7.41-7.33 (m, 9H), 7.25 (d, J = 1.4 Hz, 1H), 7.19 (d, J = 2.3 Hz, 1H), 7.10-7.04 (m, 6H), 6.82-6.76 (m, 1H), 6.63 (s, 1H), 3.51 (s, 2H), 2.41 (m, 2H), 1.75 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.26, 160.01, 157.68, 142.39, 140.64, 137.68 135.93 (d), 129.24, 128.22, 124.59 (d), 124.11, 119.93 (d), 117.55, 108.32, 106.90 (d), 97.36 (d), 74.40, 43.42, 30.58, 28.37, 25.21.



5-((6-Fluoro-1H-indol-3-yl)methyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol

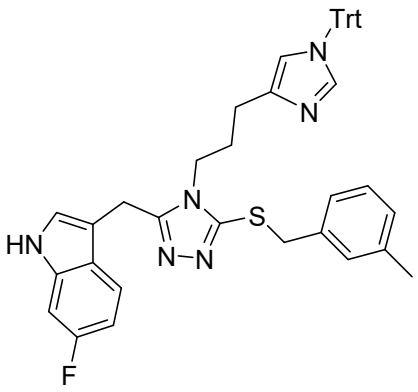
Prepared according to **general procedure B** from the thiosemicarbazide (1.50 g, 2.40 mmol), the evaporation of the organic phase afford the desired product as a yellow foam (1.46 g, quantitative yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.21 (s, 1H), 8.59 (s, 1H), 7.47-7.39 (m, 11H), 7.33 (s, 1H), 7.18-7.08 (m, 8H), 6.82 (s, 1H), 4.19 (s, 2H), 3.86 (m, 2H), 2.60 (m, 2H), 1.75 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.48, 160.05, 157.72, 151.21, 140.73, 136.58, 136.17 (d), 129.21, 128.58, 128.51, 124.86 (d), 123.55, 119.45 (d), 107.42, 107.34 (d), 97.70, 97.44, 76.80, 42.11, 26.41, 22.05, 21.81.



6-Fluoro-3-((5-(benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (24)

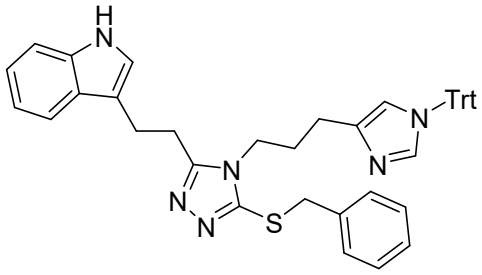
Prepared according to **general procedure C** from cyclized compound **12** (690 mg, 1.15 mmol) and benzyl bromide (138 μL, 1.15 mmol) to afford 500 mg (63%) of .the desired product **24** as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.47-7.43 (m, 1H), 7.40-7.35 (m, 9H), 7.24 (s, 1H), 7.16-7.04 (m, 13H), 6.79 (m, 1H), 6.54 (s, 1H), 4.26 (s, 2H), 4.17 (s, 2H), 3.61 (t, J = 7.8 Hz, 2H), 2.27 (t, J = 7.1 Hz, 2H), 1.48 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.05, 157.73, 154.40, 148.36, 142.31, 139.56, 137.72, 137.21, 136.19, 136.07, 129.17, 128.73,

128.31, 128.16, 127.93, 127.32, 124.18, 123.60, 119.62 (d), 117.53, 108.76 (d), 107.14 (d), 97.51 (d), 74.35, 42.66, 37.60, 28.66, 24.59, 21.56. This compound was used directly in the deprotection step without further purification.

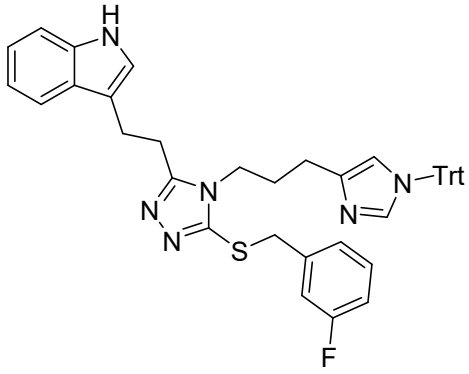


6-Fluoro-3-((5-(3-methylbenzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (25)

Prepared according to **general procedure C** from cyclized compound **12** (770 mg, 1.29 mmol) and 3-methylbenzyl bromide (174 μL, 1.29 mmol) to afford 545 mg (60%) of .the desired product **25** as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.47-7.43 (m, 1H), 7.39-7.36 (m, 10H), 7.24 (m, 1H), 7.15 (m, 1H), 7.07-6.93 (m, 11H), 6.78 (m, 1H), 6.54 (s, 1H), 4.23 (s, 2H), 4.16 (s, 2H), 3.64 (t, *J* = 7.8 Hz, 2H), 2.28 (t, *J* = 6.9 Hz, 2H), 2.13 (s, 3H), 1.47 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.07, 157.75, 154.40, 148.50, 142.31, 139.53, 137.73 (d), 137.02, 136.21 (d), 129.35, 129.18, 128.25, 128.18, 128.03, 127.95, 125.85, 124.17 (d), 123.61, 119.63 (d), 117.56, 108.81, 107.16 (d), 97.54 (d), 74.40, 42.72, 37.53, 28.69, 24.59, 21.54, 20.79. This compound was used directly in the deprotection step without further purification.

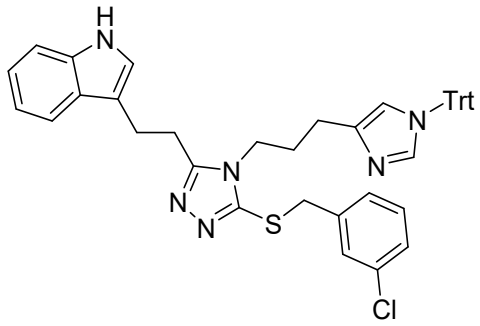


3-(2-(5-(Benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (26): Prepared according to **general procedure C** from thiol **13** (272 mg, 0.46 mmol) and benzyl bromide (55 μL, 0.46 mmol) to afford 218 mg (70%) of **26** as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (bs, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.36-7.32 (m, 9H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.23-7.19 (m, 6H), 7.10 (m, 1H), 7.04-7.01 (m, 7 H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.56 (s, 1H), 4.27 (s, 2H), 3.64 (t, *J* = 7.8 Hz, 2H), 3.06-2.95 (m, 4H), 2.33 (t, *J* = 6.8 Hz, 2H), 1.64 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.41, 147.03, 142.31, 139.50, 137.78, 137.22, 136.18, 129.18, 128.86, 128.42, 128.17, 127.94, 127.42, 126.89, 122.61, 120.93, 118.25, 118.15, 117.66, 113.15, 111.35, 74.36, 42.51, 37.40, 28.87, 25.53, 24.59, 22.64. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.28 min, ESI m/z = 685.44 [M+H] $^{+}$.



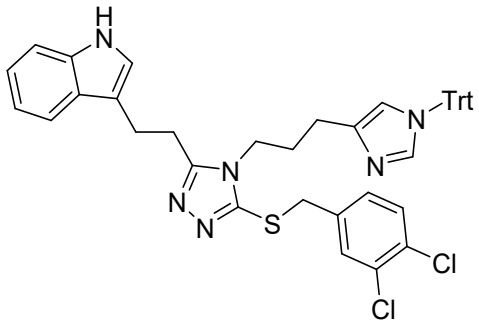
3-(2-(5-(3-Fluorobenzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (27): Prepared according to **general procedure C** from **13** (300 mg g, 0.51

mmol) and 3-fluorobenzyl bromide (62 μL, 0.51mmol) to afford 250 mg (73%) of compound **27** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.34-7.19 (m, 12H), 7.18 (d, *J* = 1.4 Hz, 1H), 7.10-7.04 (m, 2H), 7.01-6.96 (m, 8H), 6.85 (m, 1H), 6.54 (s, 1H), 4.27 (s, 2H), 3.64 (d, *J* = 7.8 Hz, 2H), 3.05-2.83 (m, 4H), 2.31 (t, *J* = 6.8 Hz, 2H), 1.64 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 207.10, 163.71, 161.24, 156.05, 148.36, 142.82, 140.76 (2), 140.00, 138.32, 136.69, 130.84 (2), 129.68, 128.68, 128.45, 127.39, 125.51, 123.11, 121.44, 118.76, 118.65, 118.18, 116.26, 116.04, 114.86, 114.65, 113.65, 111.88, 74.86, 43.06, 37.00, 31.23, 29.42, 26.05, 25.07, 23.15. LCMS (60-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.77 min, ESI m/z = 703.38 $[M+H]^+$.

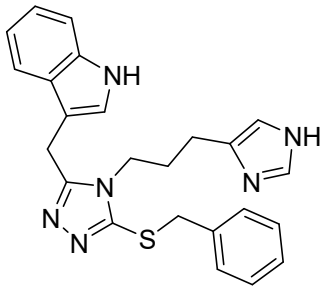


3-(2-(5-(3-Chlorobenzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (28): Prepared according to **general procedure C** from thiol **13** (323 mg 0.54 mmol) and 3-chlorobenzyl bromide (71 μL, 0.54 mmol) to afford 320 mg (82%) of **28** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (s, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.36-7.33 (m, 9H), 7.30-7.20 (m, 4H), 7.11 (d, *J* = 3.5 Hz, 1H), 7.04-7.01 (m, 8H), 6.87 (m, 1H), 6.58 (s, 1H), 4.29 (s, 2H), 3.64 (m, 2H), 3.06-2.96 (m, 4H), 2.32 (m, 2H), 1.66 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.57, 147.82, 142.32, 140.05, 139.49, 137.83, 136.19, 132.89, 130.26, 129.19, 128.71, 128.19, 127.96, 127.61, 127.35, 126.89, 122.62, 120.94, 118.27, 118.15, 117.67,

113.16, 111.38, 74.37, 42.56, 36.42, 28.89, 25.55, 24.58, 22.65. This compound was used directly in the deprotection step without further purification.

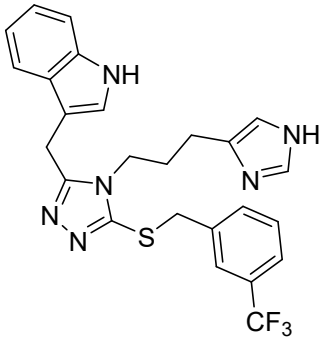


3-(2-(5-(3,4-Dichlorobenzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (29): Prepared according to **general procedure C** from **13** (526 mg, 0.88 mmol) and 3,4-dichlorobenzyl bromide (128 μL, 0.88 mmol) to afford 218 mg (70%) of compound **29** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.34-7.21 (m, 11H), 7.18 (d, *J* = 1.4 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 7.01-6.96 (m, 7H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.56 (s, 1H), 4.27 (s, 2H), 3.66 (t, *J* = 7.3 Hz, 2H), 3.05-2.92 (m, 4H), 2.32 (t, *J* = 6.8 Hz, 2H), 1.66 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 207.08, 156.14, 142.82, 139.99, 139.38*2, 138.34, 136.69, 131.34, 131.03, 130.51, 129.79, 129.72, 128.44, 128.16, 127.41*2, 123.15, 121.44, 118.78*2, 118.57, 118.19, 113.64, 74.87, 43.11, 36.10, 29.45, 26.02, 25.03, 23.10. LCMS (60-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.67 min, ESI m/z = 753.36 [M+H]$^{+}$.



3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-(benzylthio)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (30)

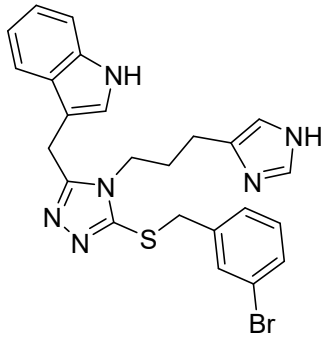
Prepared according to **general procedure E** from compound **14** (605 mg, 0.9 mmol) to yield 305 mg (79%) of **30** as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 10.94 (s, 1H), 7.50 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.16-7.04 (m, 7H), 6.94 (t, *J* = 7.8 Hz, 1H), 6.69 (s, 1H), 4.25 (s, 2H), 4.15 (s, 2H), 3.58 (m, 2H), 2.28 (m, 2H), 1.54 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.70, 148.56, 137.34, 136.41, 134.81, 128.83, 128.48, 127.45, 126.81, 123.68, 118.65, 111.59, 108.36, 42.78, 37.88, 29.01, 23.54, 21.82. HRMS (ESI+): m/z calculated for $C_{24}H_{25}N_6S$ $(M+H)^+$ 429.1886, found 429.1856.



3-((4-(3-(1H-imidazol-4-yl)propyl)-5-((3-(trifluoromethyl)benzyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (31)

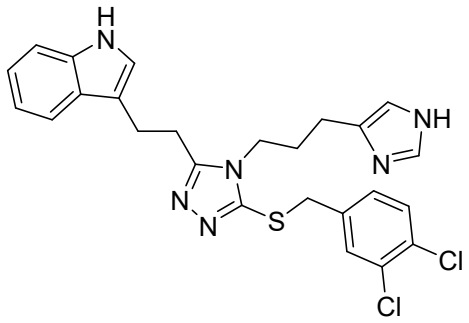
Prepared according to **general procedure E** from compound **15** (400 mg, 0.54 mmol) to yield 106 mg (44%) of **31** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 10.96 (s, 1H),

7.70 (s, 1H), 7.55-7.43 (m, 4H), 7.35-7.32 (m, 2H), 7.08-7.04 (m, 2H), 6.94 (m, 1H), 6.69 (s, 1H), 4.41 (s, 2H), 4.16 (s, 2H), 3.66 (m, 2H), 2.30 (m, 2H), 1.53 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.73, 148.08, 139.19, 136.30, 134.69, 132.93, 129.36, 126.71, 125.48, 124.02, 123.57, 121.23, 118.53, 111.49, 108.28, 42.77, 36.46, 28.93, 21.67. HRMS (ESI+): m/z calculated for $C_{25}H_{24}F_3N_6S$ $(M+H)^+$ 497.1764, found 497.1730.

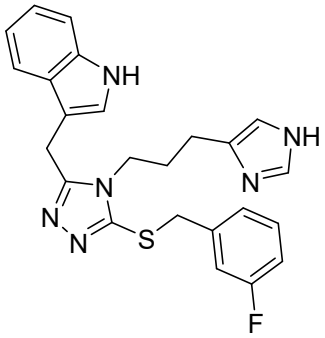


3-((4-(3-(1H-imidazol-4-yl)propyl)-5-(3-bromobenzylthio)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (32)

Prepared according to **general procedure E** from compound **16** (440 mg, 0.59 mmol) to yield 261 mg (88%) of **32** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) d 11.73 (s, 1H), 10.93 (s, 1H), 7.505-7.30 (m, 5H), 7.15 (m, 1H), 7.07-7.03 (m, 3H), 6.93 (m, 1H), 6.69 (s, 1H), 4.28 (s, 2H), 4.15 (s, 2H), 3.66 (m, 2H), 2.28 (m, 2H), 1.54 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) d 154.81, 148.30, 136.38, 134.78, 131.63, 130.54, 130.27, 127.93, 126.78, 123.64, 121.56 (d), 118.67 (d), 111.58, 108.37, 42.87, 36.56, 28.99, 21.75. HRMS (ESI+): m/z calculated for $C_{24}H_{24}BrN_6S$ $(M+H)^+$ 507.0956, found 507.0961.

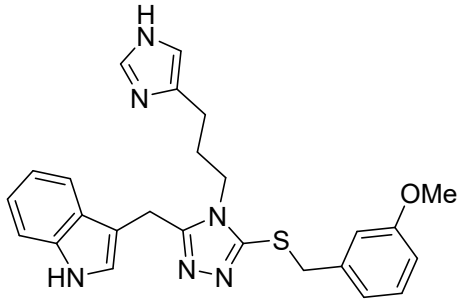


3-(2-(4-(3-(1H-imidazol-4-yl)propyl)-5-(3,4-dichlorobenzylthio)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (33): Prepared according to **general procedure E** from compound **17** (450 mg g, 0.60 mmol) to afford 223 mg (73%) of **33** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) d 10.82 (s, 1H), 7.57 (s, 1H), 7.53-7.43 (m, 3H), 7.34-7.24 (m, 2H), 7.13 (s, 1H), 7.05 (m, 1H), 6.95 (m, 1H), 6.71 (s, 1H), 4.31 (s, 2H), 3.69 (m, 2H), 3.05 (m, 2H), 2.98 (m, 2H), 2.37 (m, 2H), 1.72 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) d 155.67, 147.71, 139.00, 136.20, 134.71, 130.88, 130.81, 130.55, 129.98, 129.30, 127.78, 127.55, 126.91, 122.64, 120.97, 118.32, 118.15, 113.17, 111.40, 42.71, 35.68, 29.16, 25.56, 22.64. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.60 min, ESI m/z = 511.30 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{25}H_{25}Cl_2N_6S$ $(M+H)^+$ 511.1233, found 511.1246.



3-(2-(4-(3-(1H-imidazol-4-yl)propyl)-5-(3-fluorobenzylthio)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (34). Prepared according to **general procedure E** from **18** (250 mg, 0.36 mmol) to afford

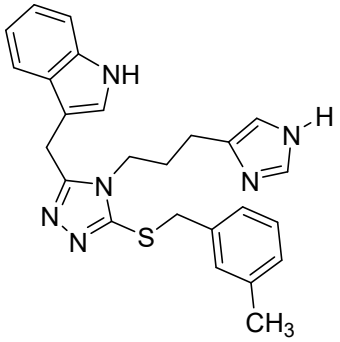
80 mg (49%) of **34** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) d 10.82 (s, 1H), 7.47 (s, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.33-7.28 (m, 2H), 7.16-7.03 (m, 5H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.70 (s, 1H), 4.32 (s, 2H), 3.67 (m, 2H), 3.07 (m, 2H), 2.98 (m, 2H), 2.37 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) d 156.10, 148.89, 140.89 (d), 136.71, 135.21, 130.92 (d), 127.42, 125.57, 125.54, 123.15, 121.47, 118.83 (d), 116.28 (d), 116.28 (d), 114.87 (d), 113.67, 111.90, 43.18, 37.04, 32.83, 29.64, 26.06, 23.18. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.27 min, ESI m/z = 461.39 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{25}H_{26}FN_6S$ $(M+H)^+$ 461.1918, found 461.1935.



3-((4-(3-(1H-imidazol-4-yl)propyl)-5-(3-methoxybenzylthio)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (35)

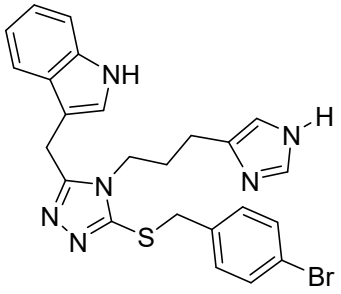
Prepared according to **general procedure E** from derivative **19** (441 mg, 0.63 mmol)) to yield **35** as a yellow foam (151 mg, 53%): ^{1}H NMR (400 MHz, DMSO-d_6) d 11.76 (s, 1H), 10.95 (s, 1H), 7.51-7.46 (m, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.08-7.02 (m, 3H), 6.97 (t, *J* = 7.8 Hz, 1H), 6.85 (s, 1H), 6.77-6.70 (m, 3H), 4.27 (s, 2H), 4.17 (s, 2H), 3.65 (m, 5H), 2.31 (m, 2H), 1.56 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) d 159.18, 154.57, 148.44, 138.74, 136.29, 134.64, 129.43, 126.72,

123.52, 121.22, 120.95, 118.53, 114.22, 113.06, 111.46, 108.37, 54.93, 42.78, 37.45, 28.96, 24.57, 21.66. HRMS (ESI+): m/z calculated for $C_{37}H_{35}N_6S$ $(M+H)^+$ 595.2630, found 595.2638.



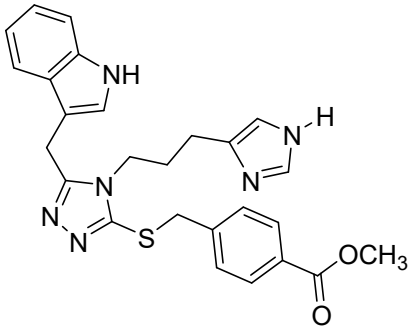
3-((4-(3(1H-imidazol-4-yl)propyl)-5-(3-methylbenzylthio)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (36)

Prepared according to **General Procedure E** from trityl derivative **20** to yield compound **36** as a yellow foam (139 mg, 51%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H)m 10.94 (s, 1H), 7.50-7.45 (m, 2H), 7.37-7.18 (m, 2H), 7.07-6.92 (m, 6H), 6.69 (s, 1H), 4.23 (s, 1H), 4.16 (s, 2H), 3.64 (m, 2H), 2.30 (m, 2H), 2.17 (s, 3H), 1.54 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 157.75, 155.46, 154.42, 148.46, 137.28, 134.68, 133.00, 128.77, 128.35, 127.36, 127.01 (d), 125.69, 112.55 (d), 109.52 (d), 109.52 (d), 108.63, 103.36, 42.68, 37.69, 21.56. HRMS (ESI+): m/z calculated for $C_{37}H_{35}N_6S$ $(M+H)^+$ 595.2630, found 595.2638.



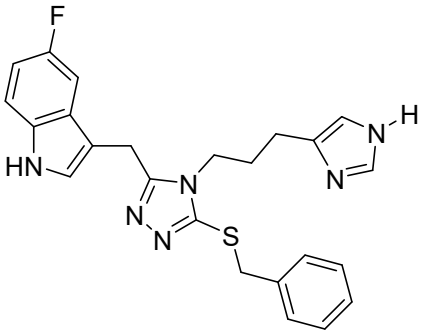
3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-(4-bromobenzylthio)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (37)

Following **General Procedure E** for the deprotection step, triazole **21** (0.49 g, 0.65 mmol) and 1N HCl (6.9 mL) in EtOH (17 mL) gave 160 mg (51%) of a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 10.94 (s, 1H), 7.50 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.29 (m, 3H), 7.09 (m, 4H), 6.95 (m, 1H), 6.68 (s, 1H), 4.21 (s, 2H), 4.16 (s, 2H), 3.59 (m, 2H), 2.28 (m, 2H), 1.53 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.68, 148.15, 136 33, 134.68, 131.21, 130.87, 127.77, 127.54, 126.72, 123.66, 121.22, 118.54, 111.55, 39.71, 39.50, 29.91, 25.78, 21.79. ESI-HRMS: Calculated for $C_{24}H_{24}BrN_6S$ [M+H] 507.0961 m/z, Found 507.0974.



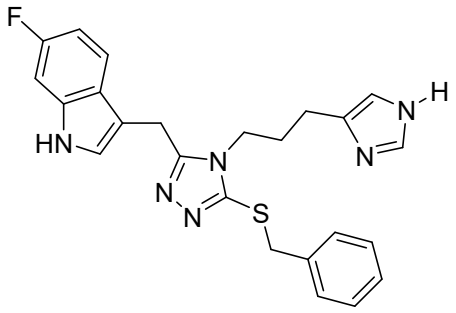
Methyl 4-(((4-(3-(1H-imidazol-4-yl)propyl)-5-((1H-indol-3-yl)methyl)-4H-1,2,4-triazol-3-yl)thio)methyl)benzoate (38)

Following **General Procedure E** deprotection of the trityl group, triazole **22** (390 mg, 54 mmol), 1N HCl (5.7 mmol), 1N (5.7 mL), and EtOH (14 mL) afforded 170 mg (60%) of a tan foam: ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.89, 154.72, 148.07, 143.08, 136.31, 134.63, 129.23, 129.04, 128.51, 126.70, 123.58, 121.22, 118.19, 52.11, 42.69, 37.17, 28.89, 23.50, 21.78. ESI-HRMS: calculated for $C_{26}H_{27}N_6O_2S$ $[M+H]^+$: 487.1911, m/z Found $[M+H]^+$: 487.1924.



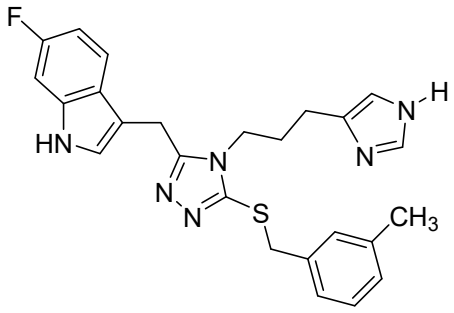
3-((4-(3-(l*H*-Imidazol-4-yl)propyl)-5- (benzylthio)-4H-l,2,4-triazol-3-yl)methyl)-5-fluoro-1*H*-indole (39)

Prepared according to **General Procedure E** from derivative **23** (400 mg, 0.58 mmol)) product **39** as a yellow foam (57 mg, 21%): ^{1}H NMR (400 MHz, DMSCEd6) 8 11.97 (s, 1H), 11.08 (s, 1H), 7.52 (s, 1H), 7.36-7.32 (m, 1H), 7.23-7.12 (m, 6H), 6.92 (m, 2H), 6.72 (s, 1H), 4.27 (s, 2H), 4.15 (s, 2H), 3.62 (m, 2H), 2.30 (m, 2H), 1.55 (m, 2H). ^{13}C NMR (100 MHz, DMSCEd6) 8 157.75, 155.46, 154.42,148.46, 137.28, 134.68, 133.00, 128.77, 128.35, 127.36, 127.01 (d), 125.69, 112.55 (d), 109.52 (d), 108.63, 103.36 (d), 42.68, 37.69, 21.56. HRMS (ESI+): m/z calculated for $C_{24}H_{24}FN_6S$ $(M+H)^+$ 447.1762, found 447.1787.



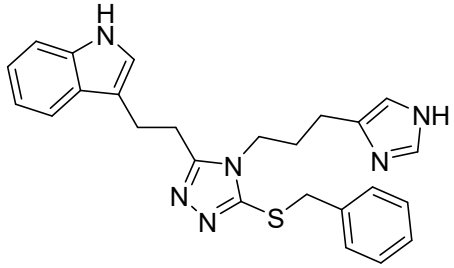
3-((4-(3-(lH-Imidazol-4-yl)propyl)-5- (benzylthio)-4H-l,2,4-triazol-3-yl)methyl)-6-fluoro-lH-indole (40)

Prepared according to General Procedure E from derivative **24** (405 mg, 0.59 mmol) to give product **40** as a yellow foam (112 mg, 43%): 1H NMR (400 MHz, DMSO- d6) 8 11.76 (s, 1H), 11.03 (s, 1H), 7.52 (s, 1H), 7.44 (m, 1H), 7.32-7.08 (m, 7H), 6.84 (m, 1H), 6.71 (s, 1H), 4.27 (s, 2H), 4.16 (s, 2H), 3.61 (m, 2H), 2.30 (m, 2H), 1.54 (m, 2H). 13C NMR (100 MHz, DMSO-d6) 8 160.11, 157.78, 154.46, 148.47, 147.79, 137.28, 136.26 (d), 134.72, 128.78, 128.37, 127.80, 127.56, 127.37, 126.67, 124.20 (d), 123.61, 119.66 (d), 108.64, 107.21 (d), 97.58 (d), 42.68, 37.72, 28.94, 21.64. HRMS (ESI+): m/z calculated for $C_{24}H_{24}FN_6S$ (M+H)+ 447.1762, found 447.1757.



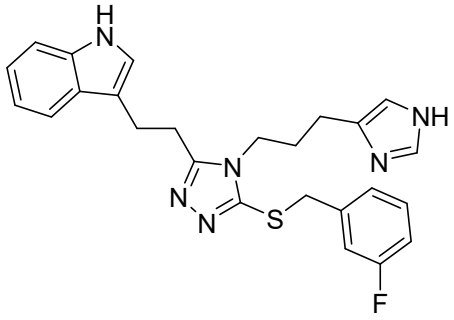
3-((4-(3-(lH-Imidazol-4-yl)propyl)-5- (3-methylbenzylthio)-4H-l,2,4-triazol-3-yl)methyl)-6-fluoro-lH-indole (41)

Prepared according to **General Procedure E** from derivative **25** (421 mg, 0.61 mmol)) to yield **41** as a yellow foam (139 mg, 51%): 1H NMR (400 MHz, DMSO- d6) 8 11.75 (s, 1H), 10.94 (s, 1H), 7.50-7.45 (m, 2H), 7.37-7.18 (m, 2H), 7.07-6.92 (m, 6H), 6.69 (s, 1H), 4.23 (s,2H), 4.16 (s, 2H), 3.64 (m, 2H), 2.30 (m, 2H), 2.17 (s, 3H), 1.54 (m, 2H). 13H NMR (100 MHz, DMSO-d6) 8 157.75, 155.46, 154.42, 148.46, 137.28, 134.68, 133.00, 128.77, 128.35, 127.36, 127.01 (d), 125.69, 112.55 (d), 109.52 (d), 108.63, 103.36 (d), 42.68, 37.69, 21.56. HRMS (ESI+): m/z calculated for $C_{37}H_{35}N_6S$ (M+H)+ 595.2630, found 595.2638.

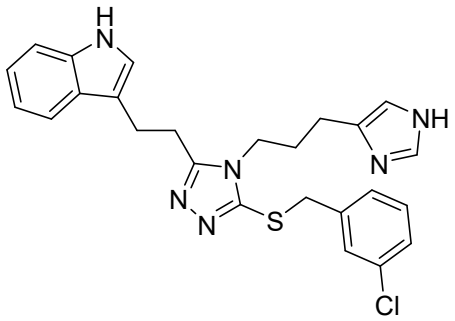


3-(2-(4-(3-(1H-imidazol-4-yl)propyl)-5-(benzylthio)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (42): Prepared according to **general procedure E** from trityl protected **26** (218 mg g, 0.32 mmol) to afford 69 mg (49%) of **42** as a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.79 (bs, 1H), 10.83 (bs, 1H), 7.48 (s, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.29-7.24 (m,

5H), 7.14 (d, *J* = 1.8 Hz, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.76 (s, 1H), 4.31 (s, 2H), 3.65 (m, 2H), 3.10-2.97 (m, 4H), 1.72 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.47, 148.09, 137.26, 136.19, 134.69, 128.91, 128.47, 127.45, 126.92, 122.65, 120.97, 118.32, 118.15, 113.16, 111.38, 42.68, 37.45, 29.25, 25.55, 22.68. LCMS (05-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.53 min, ESI m/z = 443.42 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{25}H_{27}N_6S$ $(M+H)^+$ 443.2012, found 443.2000.



3-(2-(4-(3-(1H-Imidazol-4-yl)propyl)-5-(3-fluorobenzylthio)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (43): Prepared according to **general procedure E** from **27** (250 mg, 0.36 mmol) to afford 80 mg (49%) of **43** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.47 (s, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.33-7.28 (m, 2H), 7.16-7.03 (m, 5H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.70 (s, 1H), 4.32 (s, 2H), 3.67 (m, 2H), 3.07 (m, 2H), 2.98 (m, 2H), 2.37 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.10, 148.89, 140.89 (d), 136.71, 135.21, 130.92 (d), 127.42, 125.57, 125.54, 123.15, 121.47, 118.83 (d), 116.28 (d), 116.28 (d), 114.87 (d), 113.67, 111.90, 43.18, 37.04, 32.83, 29.64, 26.06, 23.18. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.27 min, ESI m/z = 461.39 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{25}H_{26}FN_6S$ $(M+H)^+$ 461.1918, found 461.1935.



3-(2-(4-(3-(1H-Imidazol-4-yl)propyl)-5-(3-chlorobenzylthio)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (44): Prepared according to **general procedure E** from **28** (320 mg g, 0.44 mmol) to give 80 mg (38%) of **44** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 7.47-7.42 (m, 2H), 7.36-7.23 (m, 5H), 7.13 (d, J = 2.3 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 6.70 (s, 1H), 4.30 (s, 2H), 3.66 (m, 2H), 3.08-3.04 (m, 2H), 2.99-2.95 (m, 2H), 2.37 (m, 2H), 1.71 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.12, 148.37, 140.64, 136.70, 135.21, 133.39, 130.80, 129.23, 128.15, 127.87, 127.41, 123.15, 121.48, 118.84, 118.64, 113.68, 111.90, 43.17, 36.94, 29.64, 26.02, 23.17. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.83 min, ESI m/z = 477.34 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{25}H_{26}ClN_6S$ $(M+H)^+$ 477.1623, found 477.1633.

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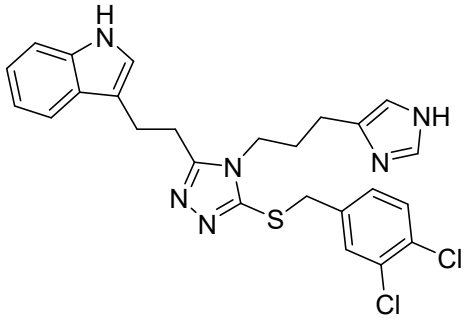
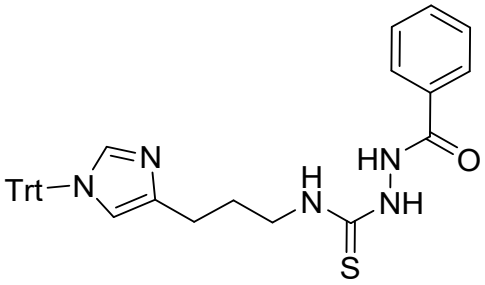
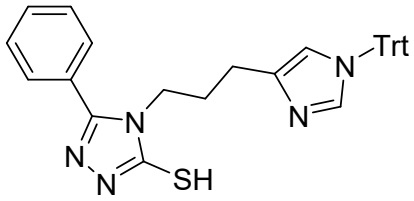


3-(2-(4-(3-(1H-imidazol-4-yl)propyl)-5-(3,4-dichlorobenzylthio)-4H-1,2,4-triazol-3-yl)ethyl)-1H-indole (45): Prepared according to **general procedure E** from compound **29** (450 mg g, 0.60 mmol) to afford 223 mg (73%) of **45** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.57 (s, 1H), 7.53-7.43 (m, 3H), 7.34-7.24 (m, 2H), 7.13 (s, 1H), 7.05 (m, 1H), 6.95 (m, 1H), 6.71 (s, 1H), 4.31 (s, 2H), 3.69 (m, 2H), 3.05 (m, 2H), 2.98 (m, 2H), 2.37 (m, 2H), 1.72 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.67, 147.71, 139.00, 136.20, 134.71, 130.88, 130.81, 130.55, 129.98, 129.30, 127.78, 127.55, 126.91, 122.64, 120.97, 118.32, 118.15, 113.17, 111.40, 42.71, 35.68, 29.16, 25.56, 22.64. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.60 min, ESI m/z = 511.30 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{25}H_{25}Cl_2N_6S$ $(M+H)^+$ 511.1233, found 511.1246.



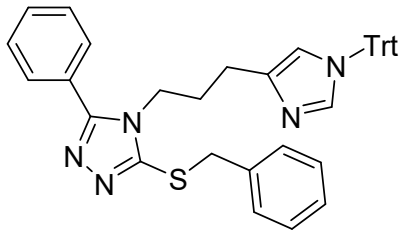
2-Benzoyl-N-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazinecarbothioamide Prepared according to **general procedure A** from phenylhydrazide (305 mg, 2.24 mmol) and **9** (1.009 g, 2.46 mmol) to yield 913 mg (75% yield) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.27 (s, 1H), 8.26 (s, 1H), 7.91 (d, *J* = 6.8 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.47-7.34 (m, 13H), 7.16 (s, 1H), 7.08-7.06 (m, 7H), 6.62 (s, 7H), 3.48-3.44 (m, 2H), 2.45 (d, *J* = 7.3 Hz, 2H), 1.74 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.90, 142.36, 140.67, 137.61, 132.48, 131.82, 129.22, 128.22, 127.96, 127.80, 117.45, 74.37, 43.54, 28.34, 25.24.



5-Phenyl-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (46)

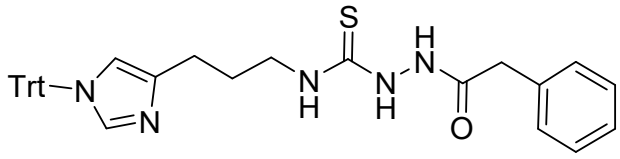
Prepared according to **general procedure B** from the thiosemicarbazide (890 mg, 1.63 mmol) to yield 851 mg (99%) of compound **46** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (m, 2H), 7.39-7.34 (m, 12H), 7.22 (s, 1H), 7.04-7.02 (m, 6H), 6.53 (s, 1H), 3.95 (t, *J* = 7.8 Hz,

2H), 2.37 (t, J = 7.3 Hz, 2H), 1.85 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.70, 150.66, 142.32, 140.02, 137.73, 129.25, 128.73, 128.64, 128.20, 127.99, 127.58, 117.83, 74.37, 43.16, 28.17, 25.05.



3-(Benzylthio)-5-phenyl-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (57)

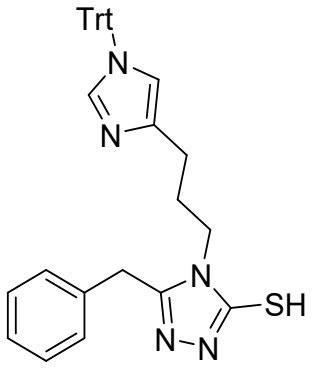
Prepared according to **general procedure C** from **46** (810 mg, 1.53 mmol) to yield 440 mg (46%) of **57** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (m, 2H), 7.47-7.42 (m, 3H) 7.37-7.19 (m 15H), 7.04-7.00 (m, 6H), 6.48 (s, 1H), 4.41 (s, 2H), 3.81 (t, J = 7.8 Hz, 2H), 2.30 (t, J = 6.8 Hz, 2H), 1.70 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.95, 149.99, 142.27, 139.13, 137.87, 137.14, 129.99, 129.22, 129.00, 128.93, 128.51, 128.36, 128.20, 128.02, 127.56, 127.27, 117.92, 74.39, 43.60, 37.34, 28.82, 24.48. This compound was used directly in the deprotection step without further purification.



2-(2-Phenylacetyl)-N-(3-(1-trityl-1H-pyrazol-3-yl)propyl)hydrazinecarbothioamide

Prepared according to **general procedure A** from compound **9** (1.10 g, 2.69 mmol) and phenylacetohydrazide (403 mg, 2.69 mmol) to afford 1.05 g (70%) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 9.05 (s, 1H), 7.94 (s, 1H), 7.35-7.28

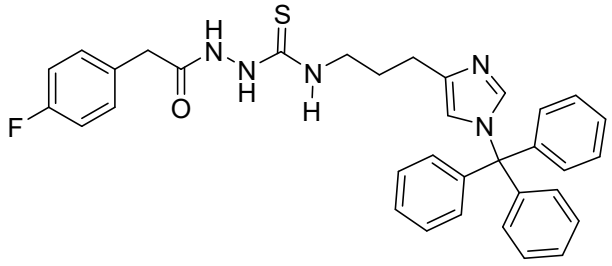
(m, 10H), 7.22 (m, 1H), 7.20-7.10 (m, 4H), 7.02-6.99 (m, 6H), 6.59 (s, 1H), 3.39 (s, 2H), 3.34 (m, 2H), 2.34 (m, 2H), 1.65 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.38, 140.65, 137.65, 165.49, 129.23, 128.20, 128.15, 127.95, 117.50, 74.37, 43.39, 33.37, 28.35, 25.19.



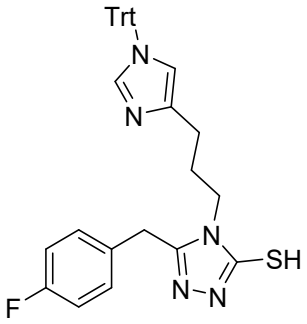
5-Benzyl-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (47)

Prepared according to **General Procedure B** from the thiosemicarbazide (879 mg, 1.55 mmol) to afford thiol **47** as a yellow foam (703 mg, 84%): 1H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.45-7.39 (m, 9H), 7.27-7.22 (m, 4H), 7.17-7.11 (m, 7H), 6.92 (s, 1H), 4.10 (s, 2H), 3.83 (m, 2H), 2.53 (m, 2H), 1.68 (m, 2H). 13C NMR (100 MHz, DMSO-$d_6$166.60, 151.15, 141.30, 136.98, 135.07, 129.21, 128.73, 128.63, 128.44, 128.32, 127.02, 118.7542.40, 30.72, 26.58, 23.08. This compound was used directly in the alkylation step without further purification.

2-(2-(4-Fluorophenyl)acetyl-N-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazinde-1-carbothioamide



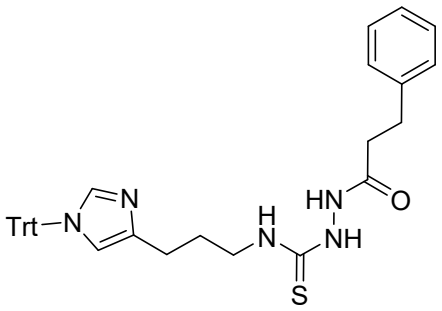
Prepared according to General **Procedure A** from 2-(4-fluorophenyl)acetohydrazide (2.5 g, 6.10 mmol) and isothiocyanate **9** (1.1 g, 6.10 mmol) to yield 2.3 g (65%) of a white solid: mp 180-185^{o} C.



5-(4-Fluorobenzyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (48)

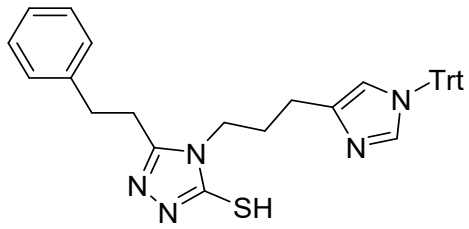
Prepared according to General Method B. To a solution of 4-(3-isothiocyanatopropyl)-1-trityl-1*H*-imidazole (**9,** 2.48 g, 6.06 mmol) and 2-(4-fluorophenyl)acetylhydrazide hydrochloride (1.24 g, 6.06 mmol) in DMF (75 mL) was added diisopropylethylamine (6.35 mL, 36.4 mmol) and the reaction was heated to 70 ºC for 3 h thereafter to effect formation of the acyl thiosemicarbazide intermediate. The mixture was concentrated and the residue was dissolved in EtOH (75 mL), treated with 2N NaOH (25 mL) and heated to 50 ºC for 2 h. The mixture was then cooled to 0-5 ºC (ice-bath) and treated with 4N HCl (13 mL) and enough 2N HCl (added dropwise) to adjust the pH to ~4. The mixture was then extracted with EtOAc (3 x 150 mL) and the combined extracts were dried (Na_2SO_4), filtered and concentrated to afford 3.25g (96% yield) of compound **48** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 7.81 (s, 1H), 7.37 – 7.30 (m, 10H), 7.21 – 7.13 (m, 2H), 7.11 – 6.97 (m, 6H), 6.64 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.53 (s, 1H), 3.39 (s, 2H), 3.27 (s, 2H), 3.00 (m, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.60 (quint., *J* = 7.1 Hz, 2H). LCMS

(30-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.20 minutes, ESI m/z = 560, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 560.2264 (560.2279 calc'd for $C_{34}H_{31}FN_5S$), $[M + H]^+$.



2-(3-Phenylpropanoyl)-N-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazinecarbothioamide

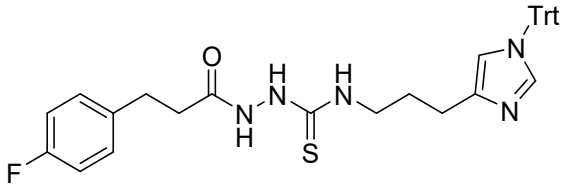
Prepared according to **general procedure A** from 3-phenylpropanehydrazide (417 mg, 2.5 mmol) and **9** (1.04 g, 2.5 mmol) to give 558 mg (38%) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.12 (s, 1H), 7.82 (m, 1H), 7.41-7.33 (m, 9H), 7.27-7.23 (m, 3H), 7.19-7.14 (m, 3H), 7.08 (m, 6H), 6.63 (s, 1H), 3.41 (m, 2H), 2.80 (m, 2H), 2.41 (m, 2H), 1.72 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.17, 142.38, 141.08, 140.65, 137.64, 129.23, 128.37, 128.22, 127.97, 125.99, 117.54, 74.39, 43.31, 34.90, 30.35, 28.40, 25.15.



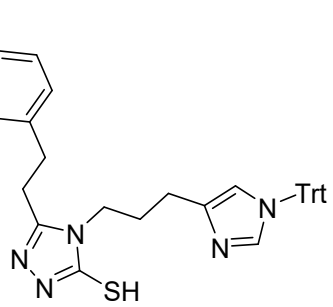
5-Phenethyl-4-(3-(1-trityl-1H-imidazol-4-yl) propyl)-4H-1,2,4-triazole-3-thiol (49)

Prepared according to **general procedure B** from the thiosemicarbazide (464 mg, 0.81 mmol) to afford 418 mg (93%) of compound **49** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.76 (s, 1H), 7.47-7.43 (m, 10H), 7.32-7.24 (m, 5H), 7.21-7.15 (m, 8H), 3.91 (t, J = 8.2 Hz, 2H), 3.01-2.93 (m, 4H), 2.68-2.64 (m, 2H), 1.95-1.88 (m, 2H). ^{13}C NMR (100 MHz, DMSO-

d_6) δ 166.33, 166.24, 151.75, 147.77, 140.68, 140.31, 136.62, 133.66, 132.55, 129.23, 128.61, 128.56, 128.46, 128.37, 128.33, 127.78, 127.55, 126.67, 126.25, 119.64, 115.56, 80.57, 41.94, 31.17, 26.49, 26.27, 21.24.

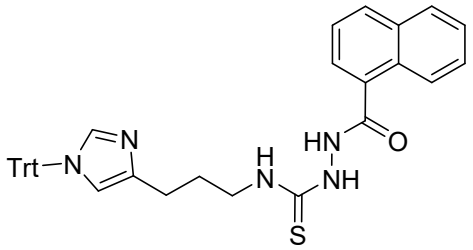


2-(3-(4-Fluorophenyl)propanoyl)-N-(3-(1-trityl-1H-imidazol-4 yl)propyl)hydrazinecarbothioamide Prepared according to **general procedure A** from 3-(4-fluorophenyl)propanehydrazide (356 mg, 1.95 mmol) and **9** (813 mg, 1.95 mmol) to afford 994 mg (85%) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 9.08 (s, 1H), 7.83 (s, 1H), 7.37-7.30 (m, 9H), 7.22-7.16 (m, 3H), 7.04 (m, 7H), 6.59 (s, 1H), 3.33 (m, 2H, under H_2O), 2.75 (m, 2H), 2.36 (m, 2H), 1.67 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.20, 161.96, 159.56, 142.41, 140.68, 137.71, 137.23, 130.10, 130.02, 129.30, 128.29, 128.05, 117.63, 115.18, 114.93, 74.46, 43.39, 35.02, 29.55, 25.19.

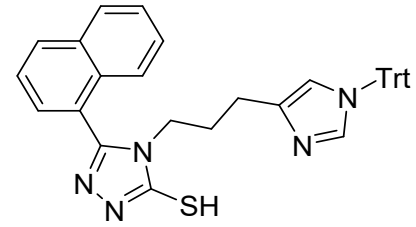


5-(4-Fluorophenethyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (50) Prepared according to **general procedure B** from the thiosemicarbazide (893 mg, 1.51 mmol) to afford 790 mg (91%) of **50** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 1H), 7.34-7.28 (m, 9H), 7.20-7.16 (m, 2H), 7.04-6.92 (m, 9H), 3.78 (m, 2H), 2.47 (m, 2H), 1.79 (m, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ166.24, 162.05, 159.64, 151.61, 147.80, 141.21, 136.94, 136.43, 133.61, 132.38, 130.35 (d), 129.24, 128.50 (d), 127.81, 127.57, 126.68, 119.09, 115.09 (d), 76.14, 42.07, 30.26, 26.78, 26.33, 22.85.

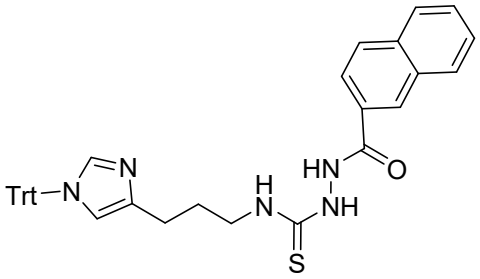


2-(1-Naphthoyl)-N-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazinecarbothioamide Prepared according to **general procedure A** from 1-naphthohydrazide (412 mg, 2.2 mmol) and **9** (997 mg, 2.43 mmol) to afford 1.27 g (96%) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 9.39 (s, 1H), 8.29 (m, 2H), 8.06 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 6.9 Hz, 1H), 7.57-7.50 (m, 3H), 7.43-7.35 (m, 11H), 7.09 (m, 6H), 6.71 (s, 1H), 3.52 (m, 2H), 3.45-3.43 (m, 2H), 1.79 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.19, 142.19, 140.07, 137.55, 133.15, 130.77, 130.05, 129.23, 128.27, 128.20, 128.04, 127.81, 127.58, 126.74, 126.45, 126.32, 125.73, 124.73, 117.75, 74.66, 43.43, 28.31, 24.85.

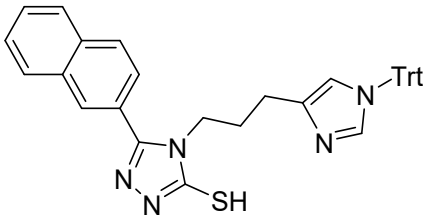


5-(naphthalen-1-yl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (51) Prepared according to **general procedure B** from the thiosemicarbazide (1.11 g, 1.86 mmol) to afford 733 mg (69%) of **51** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H) 7.80 (d, *J* = 7.1 Hz, 1H), 7.62-7.54 (m, 4H), 7.41-7.37 (m, 10H), 7.08 (s, 1H), 7.02 (m, 6H), 3.70 (m, 2H), 2.44 (m, 2H), 1.74 (m, 2H). ^{13}C NMR

(100 MHz, DMSO-d_6) δ 166.84, 149.71, 140.16, 136.32, 132.98, 132.69, 131.30, 131.23, 129.33, 129.18, 128.71, 127.93, 126.98, 125.44, 124.28, 122.92, 120.22, 77.43, 42.55, 26.47, 20.87.

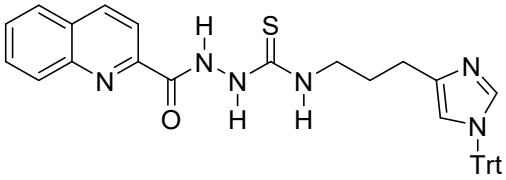


2-(2-Naphthoyl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)hydrazinecarbothioamide Prepared according to **general procedure A** from compound 2-naphthohydrazide (413 mg, 2.2 mmol) and **9** (1.00 g, 2.4 mmol) to yield 1.26 g (95%) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (bs, 1H), 9.32 (bs, 1H), 8.52 (s, 1H), 8.33 (bs, 1H), 8.00-7.95 (m, 5H), 7.60 (m, 2H), 7.35 (m, 10H), 7.04 (m, 7H), 6.61 (s, 1H), 3.46 (m, 2H), 2.45 (m, 2H), 1.74 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.97, 142.34, 140.67, 137.59, 134.33, 131.97, 129.92, 129.18, 128.92, 128.37, 128.19, 127.92, 127.77, 127.68, 126.84, 124.41, 117.45, 74.34, 43.51, 28.35, 25.23.



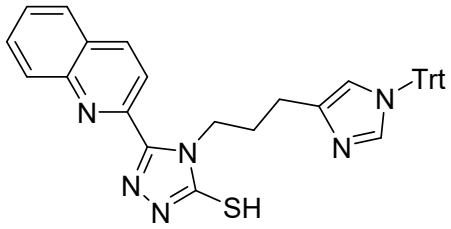
5-(Naphthalen-2-yl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazole-3-thiol (52) Prepared according to **general procedure B** from the thiosemicarbazide (1.25 g, 2.1 mmol) to afford 996 mg (82%) of thiol **52** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 0.9 Hz, 1Hδ, 1H), 7.55 (d, J = 7.3 Hz, 1H), 4.07 (m, 2H), 2.39 (m, 2H), 1.94 (m, 2H). ^{13}C NMR

(100 MHz, DMSO-d_6) δ 167.25, 151.29, 137.67, 133.40, 132.33, 129.14, 128.73, 128.60, 128.49, 128.11, 127.89, 127.75, 127.70, 126.97, 125.17, 123.40, 118.01, 74.28, 56.07, 43.75, 27.31, 24.73, 18.59.



2-(Quinoline-2-carbonyl)-N-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazinecarbothioamide

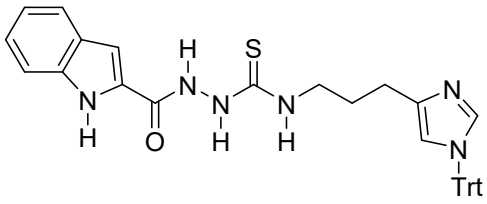
Prepared according to **general procedure A** from quinoline-2-carbohydrazide (415 mg, 2.2 mmol) and **9** (1.00 g, 2.4 mmol) to yield 873 mg (66%) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 9.38 (s, 1H), 8.55 (d, *J* = 8.7 Hz, 1H), 8.29 (s, 1H), 8.11-8.07 (m, 3H), 7.89 (t, *J* = 6.9 Hz, 1H), 7.75 (t, *J* = 6.9 Hz, 1H), 7.40-7.33 (m, 9H), 7.13 (s, 1H), 7.08-7.03 (m, 6H), 6.61 (s, 1H), 3.47 (m, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 1.75 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.25,149.54, 145.91, 142.33, 140.68, 137.62, 137.54, 130.56, 129.26, 129.16, 128.84, 128.25, 128.17, 127.91, 119.00, 117.39, 74.30, 43.58, 28.26, 25.24.



5-(Quinolin-2-yl)-4-(3-(1-trityl-1H-imidazol-4-yl) propyl)-4H-1,2,4-triazole-3-thiol (53)

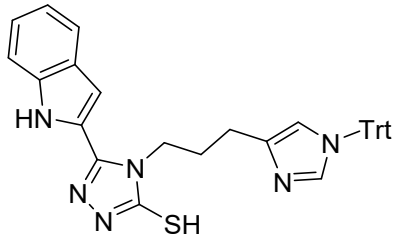
Prepared according to **general procedure B** from the thiosemicarbazide (873 mg, 1.46 mmol) to yield 800 mg (94%) of compound **53** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, *J* = 8.7 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 8.08-8.02 (m, 2H), 7.77-7.68 (m, 2H), 7.38-7.34 (m, 9H), 7.23 (s, 1H), 7.05-7.03 (m, 6H), 6.69 (s, 1H), 4.69 (t, *J* = 7.6 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, CH_2), 2.14-2.07 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.41, 148.57, 146.46, 145.85,

142.32, 140.13, 137.70, 130.55, 129.19, 128.13, 128.04, 127.90, 127.65, 119.76, 117.67, 74.36, 45.24,27.99, 25.40.



2-(1H-Indole-2-carbonyl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)hydrazinecarbothioamide

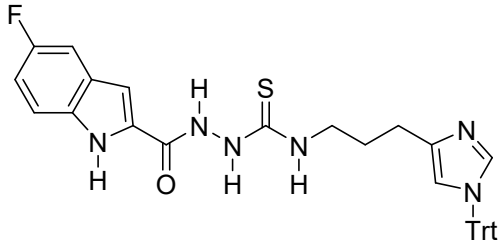
Prepared according to **general procedure A** from 1H-indole-2-carbohydrazide (349 mg, 1.99 mmol) and **9** (815 mg, 1.99 mmol) to afford 815 mg (70% yield) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 10.29 (s, 1H), 9.26 (s, 1H), 8.28 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.39-7.28 (m, 10H), 7.17-7.13 (m, 3H), 7.02-6.97 (m, 7H), 6.57 (s, 1H), 3.47 (m, 2H, under H_2O peak), 2.38 (m, 2H), 1.70 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 142.43, 140.74, 137.70, 136.65, 129.27, 128.31, 128.04, 126.99, 123.80, 121.76, 120.01, 117.50, 112.41, 103.90, 74.43, 43.64, 28.36, 25.33.



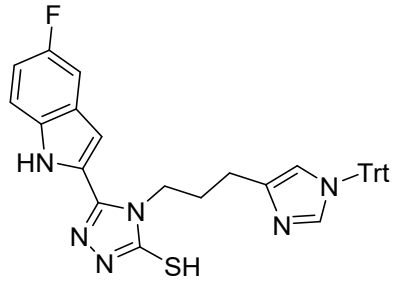
5-(1H-Indol-2-yl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (54)

Prepared according to **general procedure B** from the thiosemicarbazide (735 mg, 1.26 mmol) to afford 610 mg (86%) of compound **54** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.79 (s, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.45-7.35 (m, 12H), 7.22-7.10 (m, 7H), 7.06-6.99

(m, 2H), 4.23 (m, 2H), 2.75 (m, 2H), 2.04 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.28, 147.80, 145.17, 140.51, 136.80, 136.56, 133.63, 129.25, 128.65, 127.81, 127.58, 127.48, 126.69, 123.71, 122.43, 120.20, 120.04, 112.05, 103.31, 77.16, 43.13, 26.54, 25.17.



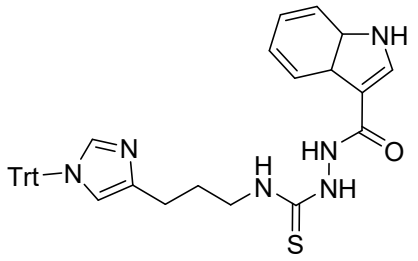
2-(5-Fluoro-1H-indole-2-carbonyl)-N-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazinecarbothioamide Prepared according to **general procedure A** from 5-fluoro-1H-2-carbohydrazide (434 mg, 2.25 mmol) and **9** (920 mg, 2.25 mmol) to yield 1.09 g (81%) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 10.38 (s, 1H), 9.32 (s, 1H), 8.35 (s, 1H), 7.41-7.32 (m, 11H), 7.15 (s, 1H), 7.05 (m, 7H), 6.60 (s, 1H), 3.44 (m, 2H), 2.42 (m, 2H), 1.73 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) d 160.77, 158.34, 156.02, 142.37, 140.66, 137.61, 133.30, 131.37, 129.19, 128.20, 127.93, 127.01, 126.90, 117.39, 113.59, (d), 112.59 (d), 103.72, 74.34, 56.06, 54.96, 54.96, 43.62, 28.26, 25.29, 18.59.



5-(5-Fluoro-1H-indol-2-yl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (55)

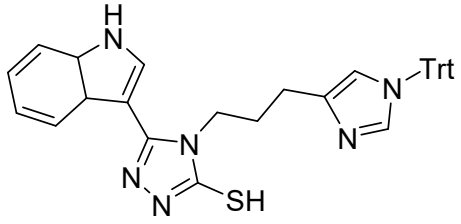
Prepared according to **general procedure B** from the thiosemicarbazide (1.09 g, 1.81 mmol) to yield 410 mg (39%) of **55** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H),

7.46-7.42 (m, 1H), 7.37-7.33 (m, 10H), 7.20-7.17 (m, 1H), 7.10-7.05 (m, 8H), 6.96 (s, 1H), 6.73 (s, 1H), 4.24 (m, 2H), 2.59 (m, 2H), 2.02 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.38, 158.33, 156.01, 144.86, 142.30, 139.55, 137.92, 133.43, 129.19, 128.13, 127.92, 124.24, 118.25, 113.14 (d), 112.33 (d), 105.43 (d), 103.11, 74.40, 43.78, 27.08, 24.79.



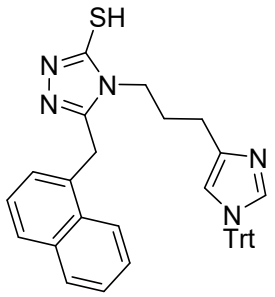
2-(1H-Indole-3-carbonyl)-N-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazinecarbothioamide

Prepared according to **general procedure A** from 1*H*-indole-3-carbohydrazide (396 mg, 2.3 mmol) and **9** (1.02 g, 2.5 mmol) to afford 1.11 g (85% yield) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 9.76 (s, 1H), 9.17 (s, 1H), 8.15-8.08 (m, 2H), 7.45 (d, J = 8.3 Hz, 1H), 7.40-7.33 (m, 9H), 7.18-7.06 (m, 10H), 6.62 (s, 1H), 3.47 (m, 2H), 2.42 (m, 2H), 1.75 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.36, 142.38, 140.73, 137.61, 135.94, 129.22, 128.91, 128.20, 127.94, 126.35, 122.12, 120.95, 120.72, 117.45, 111.92, 108.03, 74.36, 67.05, 43.43, 28.48, 25.29, 25.16.



5-(1H-indol-3-yl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (56)

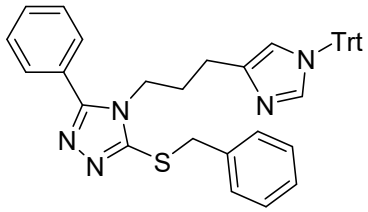
Prepared according to **general procedure B** from the thiosemicarbazide (1.09 g, 1.90 mmol) to afford 1.00 g (93%) of compound **56** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.02 (d, *J* = 2.8 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.41-7.37 (m, 9H), 7.25-7.21 (m, 1H), 7.17-7.09 (m, 7H), 6.97 (s, 1H), 4.18 (m, 2H), 2.61 (m, 2H), 2.00 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.11, 147.48, 141.54, 137.38, 135.91, 129.19, 128.36, 128.19, 127.77, 127.54, 126.38, 125.28, 122.64, 120.60, 120.48, 118.89, 112.03, 100.46, 75.57, 43.24, 26.60, 23.46.



5-(Naphthalen-1-ylmethyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (89)

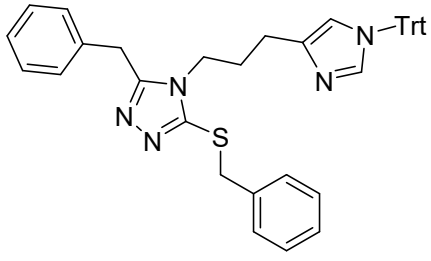
Prepared according to **General Method B**. To a solution of 4-(3-isothiocyanatopropyl)-1-trityl-1*H*-imidazole **(9**, 500 mg, 1.22 mmol) and 2-(naphthalen-1-yl)acetylhydrazide hydrochloride (244 mg, 1.03 mmol) in DMF (70 mL) was added diisopropylethylamine (1.29 mL, 7.32 mmol) and the reaction was heated to 70 ºC for 16 h thereafter to effect formation of the acyl thiosemicarbazide intermediate. The mixture was concentrated and the residue was dissolved in EtOH (50 mL), treated with 2N NaOH (15 mL) and heated to 50 ºC for 3 h. The mixture was then cooled to 0-5 ºC (ice-bath) and treated with 4N HCl (8 mL) to adjust the pH to ~1. The mixture was then extracted with EtOAc (3 x 50 mL) and the combined extracts were dried (Na_2SO_4), filtered and concentrated to afford compound **89** as a tan powder: ^{1}H NMR (400

MHz, DMSO-d_6) δ 13.52 (s, 1H), 8.01 (dt, *J* = 7.0, 3.6 Hz, 1H), 7.85 – 7.78 (m, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.44 (dt, *J* = 6.4, 3.4 Hz, 2H), 7.39 – 7.26 (m, 11H), 7.12 (d, *J* = 1.4 Hz, 1H), 7.02 – 6.95 (m, 6H), 6.51 (s, 1H), 4.48 (s, 2H), 3.95 – 3.82 (m, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 1.61 (quint., *J* = 7.9 Hz, 2H). LCMS (30-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.02 minutes, ESI m/z = 592, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 592.2517 (592.2529 calc'd for $C_{38}H_{34}FN_5S$), $[M + H]^+$.



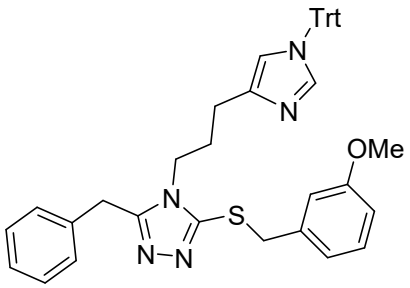
3-(Benzylthio)-5-phenyl-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (57)

Prepared according to **general procedure C** from **46** (810 mg, 1.53 mmol) to afford 440 mg (46%) of **57** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (m, 2H), 7.47-7.42 (m, 3H) 7.37-7.19 (m 15H), 7.04-7.00 (m, 6H), 6.48 (s, 1H), 4.41 (s, 2H), 3.81 (t, *J* = 7.8 Hz, 2H), 2.30 (t, *J* = 6.8 Hz, 2H), 1.70 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.95, 149.99, 142.27, 139.13, 137.87, 137.14, 129.99, 129.22, 129.00, 128.93, 128.51, 128.36, 128.20, 128.02, 127.56, 127.27, 117.92, 74.39, 43.60, 37.34, 28.82, 24.48. This compound was used directly in the deprotection step without further purification.



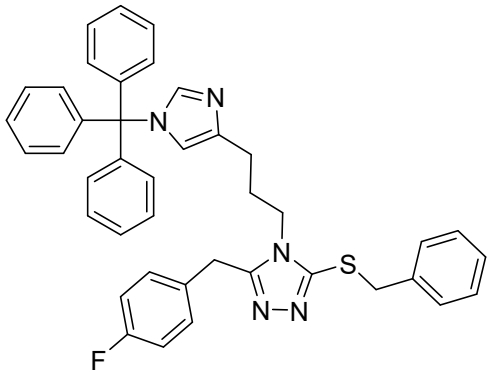
3-Benzyl-5-(benzylthio)-4-(3-(l-trityl- lH-imidazol-4-yl)propyl)-4H-l,2,4-triazole (58)

Prepared according to General Procedure C from thiol **47** (370 mg, 0.68 mmol) and benzyl bromide (82 pL, 0.68 mmol) to afford 252 mg (58%) of the desired product **58** as a white foam: 1H NMR (400 MHz, DMSO- d_6) δ 7.40-7.35 (m, 10H), 7.23-7.08 (m, 10H), 7.04-7.02 (m, 6H), 6.48 (s, 1H), 4.27 (s, 2H), 4.07 (s, 2H), 3.57 (t, J=7.6 Hz, 2H), 2.28 (t, J=7.2 Hz, 2H), 1.39 (m, 2H). 13C NMR (100 MHz, DMSO-d_6) δ 154.32, 148.65, 142.32, 139.50, 137.73, 137.21, 136.26, 129.20, 128.80, 128.53, 128.39, 128.20, 128.00, 127.39, 126.71, 117.57, 74.39, 42.76, 37.57, 30.40, 28.67, 24.64. This compound was used directly in the deprotection step without further purification.



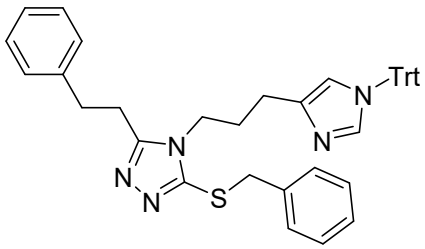
3-Benzyl-5-(3-methoxybenzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (59)

Prepared according to **general procedure C** from thiol **47** (333 mg, 0.61 mmol) and 3-methoxybenzyl bromide (86 μL, 0.61 mmol) to afford 266 mg (65%) of .the desired product **17n** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39-7.36 (m, 10H), 7.23-7.19 (m, 4H), 7.11-7.02 (m, 9H), 6.80-6.73 (m, 2H), 6.49 (s, 1H), 4.26 (s, 2H), 4.08 (s, 2H), 3.63 (s, 3H), 3.60 (m, 2H), 2.26 (m, 2H), 1.40 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.16, 154.31, 148.66, 142.32, 139.50, 138.67, 137.73, 136.27, 129.46, 129.18, 128.51, 128.37, 128.18, 127.97, 126.70, 120.97, 117.55, 114.26, 11305, 74.37, 42.80, 37.41, 30.39, 28.73, 24.64. This compound was used directly in the deprotection step without further purification.



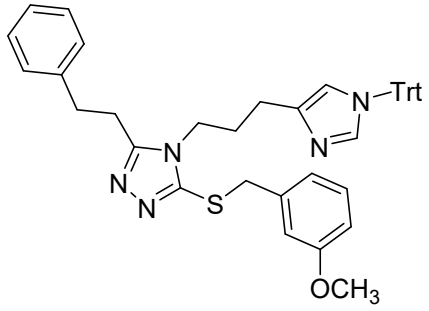
3-(Benzylthio)-5-(4-fluorobenzyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (60)

Thiol **48** (943 mg, 1.68 mmol), benzyl bromide (170 mg, 1.68 mmol), and Et_3N (170 mg, 1.68 mmol) in CH_2Cl_2 (10 mL) was reacted according to general method C to yield 1.10 g of product. Flash chromatography using CH_2Cl_2 as the solvent gave 670 mg (61%) of **60** as a white foam. This compound was used directly in the deprotection step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 5H), 7.03 (s, 11H), 6.86 (m, 3H), 6.46 (s, 1H), 4.32 (s, 2H), 4.05 (s, 2H), 3.45 (t, 2H), 2.36 (t, 2H), 1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.27 (d), 142.47, 139.53, 138.60, 136.84, 130.08, 130.00, 129.80, 129.05, 128.75, 128.67, 128.16, 127.73, 118.14, 115.98, 115.81, 115.60, 75.0, 43.37, 38.70, 30.96, 29.09, 25.23; HRMS (ESI-Q-TOF) m/z found 636.2597, calcd for $C_{40}H_{35}FN_5S$ $(M+H)^+$ 636.2597.



3-(benzylthio)-5-phenethyl-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (61)

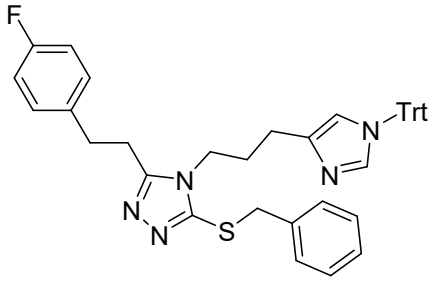
Prepared according to **general procedure C** from thiol **49** (388 mg, 0.70 mmol) to yield 335 mg (74%) of **61** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (m, 9H), 7.24-7.19 (m, 10H), 7.14 (m, 1H), 7.06-7.03 (m, 6H), 6.59 (s, 1H), 4.30 (s, 2H), 2.97-2.87 (m, 4H), 2.36 (m, 2H), 1.65 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.88, 148.11, 142.30, 140.62, 139.55, 137.76, 137.25, 129.18, 128.85, 128.40, 128.38, 128.23, 128.18, 127.96, 127.42, 126.10, 117.74, 74.38, 42.41, 37.34, 32.46, 28.76, 26.20, 24.51. This compound was used directly in the deprotection step without further purification.



3-(3-Methoxybenzylthio)-5-phenethyl-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (62)

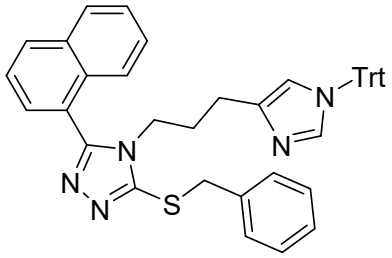
Following **General procedure B,** 5-phenethyl-4-(3-1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (**49**, 0.40 g, 0.72 mmol), DCM (7 mL), Et3N (100 μL), and 3-methoxybenzyl bromide (0.159 g, 0.79 mmol) gave 0.42 g (89%) of **62** as a clear solid: ^{1}H NMR (DMSO-d_6) δ 7.35 (m, 7H), 7.21 (d, J=1.37 Hz), 1H, 7.17 (m, 10H), 7.04 (m , 6H), 6.81 (m, 9H), 6.58 (s, 1H), 4.25 (s, 2H), 4.02 (q, J=6.87 Hz), 3.66 (m, 4H), 2.94 (m, 7H), 2.87 (m, 7H), 2.49 (s,1H), 2.36 (t, J=13.74 Hz), 1.97 (s,1H), 1.68 (t, J=29.31 Hz), 1.17 (t, J=14.20 Hz); 13C NMR (DMSO-d_6) δ 159.16, 154.89, 148.10, 142.31, 140.62, 139.54, 138.70, 137.76, 129.49, 129.18, 128.37, 128.23, 128.19, 127.96, 121.02, 114.32, 113.00, 74.36, 54.96,

40.12, 38.87, 32.47, 28.79, 26.20, 24.50. This compound was used directly in the deprotection step without further purification.



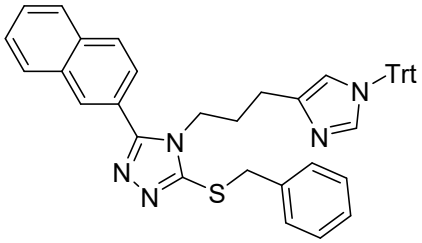
3-(Benzylthio)-5-(4-fluorophenethyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (63)

Prepared according to **general procedure C** from compound **50** (740 mg, 1.29 mmol) and benzyl bromide (154 μL, 1.29 mmol) to yield 636 mg (74%) of **63** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39-7.35 (m, 9H), 7.25-7.19 (m, 8H) 7.05-6.97 (m, 8H), 6.59 (s, 1H), 4.28 (s, 2H), 3.65 (m, 2H), 2.96-2.84 (m, 4H), 2.35 (m, 2H), 1.65 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.99, 159.59, 154.79, 148.18, 142.33, 139.57, 137.81, 137.28, 136.78, 130.29, 130.21, 129.21, 128.89, 128.44, 128.22, 128.01, 127.47, 117.79, 115.02 (d), 74.40, 42.42, 37.33, 31.49, 28.80, 26.25, 24.51. This compound was used directly in the deprotection step without further purification.



3-(Benzylthio)-5-(naphthalen-1-yl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (64)

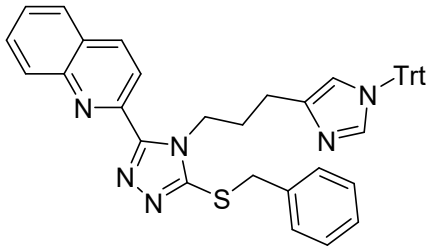
Prepared according to **general procedure C** from **51** (733 mg, 1.3 mmol) to afford 310 mg (37%) of compound **64** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98-7.92 (m, 2H), 7.53-7.45 (m, 4H), 7.33-7.19 (m, 15H), 7.00 (m, 1H), 6.92-6.88 (m, 6H), 6.21 (s, 1H), 4.37 (s, 2H), 3.46 (m, 2H), 2.02 (m, 2H), 1.39 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.65, 149.32, 142.23, 139.04, 137.62, 137.32, 133.00, 131.46, 130.50, 129.16, 129.01, 128.69, 128.55, 128.48, 128.17, 127.98, 127.56, 127.34, 126.63, 125.28, 124.62, 124.55, 117.56, 74.29, 59.83, 43.43, 28.91, 24.32. This compound was used directly in the deprotection step without further purification.



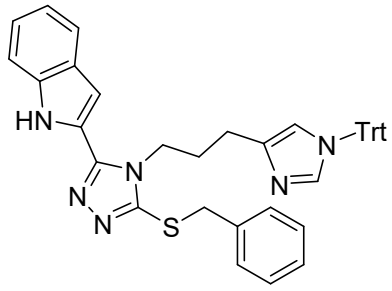
3-(Benzylthio)-5-(naphthalen-2-yl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (65)

Prepared according to **general procedure C** from compound **52** (417 mg, 0.72 mmol) to give 270 mg (56%) of trityl derivative **65** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.69 (dxd, J = 8.2, 1.4 Hz, 1H), 7.59 (t, J = 6.9 Hz, 1H), 7.51 (d, J = 6.9 Hz, 1H), 7.34-7.19 (m, 14H), 7.14 (d, J = 1.4 Hz, 1H), 7.14 (d, J =

1.4 Hz, 1H), 6.92-6.90 (m, 6H), 6.45 (s, 1H), 4.42 (s, 2H), 3.88 (t, *J* = 6.8 Hz, 2H), 2.31 (t, *J* = 6.4 Hz, 2H), 1.75 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.95, 150.19, 142.20, 139.16, 137.85, 137.15, 133.11, 132.45, 129.19, 128.99, 128.58, 128.50, 128.10, 127.90, 127.66, 127.53, 127.40, 126.83, 125.39, 124.57, 117.97, 74.28, 43.82, 28.81, 24.50. This compound was used directly in the deprotection step without further purification.

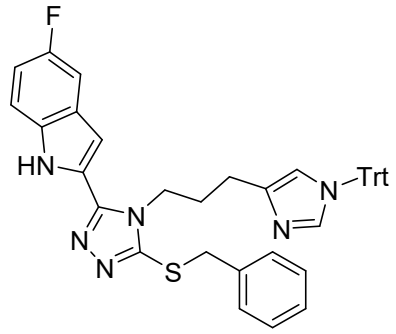


2-(5-(benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)quinoline (66) Prepared according to **general procedure C** from thiol **53** (550 mg, 0.95 mmol) to yield 460 mg (72%) of compound **66** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 8.7 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 8.05 (d, *J* = 6.9 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.75-7.55 (m, 5H), 7.37-7.19 (m, 13H), 7.05-7.01 (m, 5H), 6.62 (s, 1H), 4.49 (m, 2H), 4.48 (m, 2H), 2.54 (m, 2H), 1.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.42, 152.26, 147.16, 146.59, 142.30, 139.77, 137.77, 137.42, 137.06, 130.33, 129.17, 128.97, 128.47, 128.11, 127.99, 127.92, 127.60, 127.53, 127.37, 119.93, 117.72, 74.35, 45.50, 36.80, 29.26, 25.13. This compound was used directly in the deprotection step without further purification.



2-(5-(Benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)-1H-indole (67)

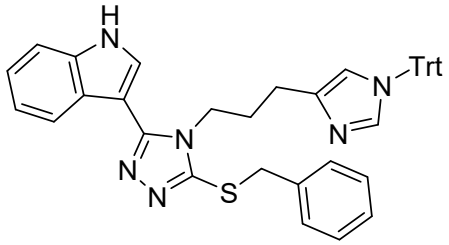
Prepared according to **general procedure C** from compound **54** (590 mg, 1.04 mmol) and benzyl bromide (125 mL, 1.04 mmol) to give 210 mg (31%) of **67** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 7.44-7.38 (m, 2H), 7.34-7.28 (m, 12H) 7.25-7.14 (m 4H), 7.04-6.96 (m, 7H), 6.76 (s, 1H), 6.62 (s, 1H), 4.40 (s, 2H), 4.00 (m, 2H), 2.46 (m, 2H), 1.82 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.22, 148.88, 142.28, 139.31, 137.97, 137.11, 136.57, 129.22, 128.96, 128.49, 128.17, 127.99, 127.55, 123.79, 123.08, 120.81, 119.70, 118.27, 74.44, 43.84, 37.52, 28.54, 24.61. This compound was used directly in the deprotection step without further purification.



2-(5-(Benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)-5-fluoro-1H-indole (68)

Prepared according to **general procedure C** from the thiol **55** (340 mg, 0.58 mmol) to yield 156 mg (39%) of compound **68** as a pale yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 7.40-7.37 (m, 1H), 7.30-7.25 (m, 12H) 7.21-7.10 (m 4H), 7.01-6.99 (m, 7H), 6.74 (s, 1H), 6.58 (s, 1H), 4.38 (s, 2H), 3.96 (m, 2H), 2.43 (m, 2H), 1.78 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.31, 155.99, 150.44, 148.67, 142.30, 139.27, 138.02, 137.09, 133.31, 129.21,

128.97, 128.51, 128.19, 128.01, 127.58, 125.55, 118.23, 113.05, 112.94, 111.74, 111.49, 105.27, 105.04, 101.53, 74.44, 43.89, 37.49, 28.54, 24.59. This compound was used directly in the deprotection step without further purification.



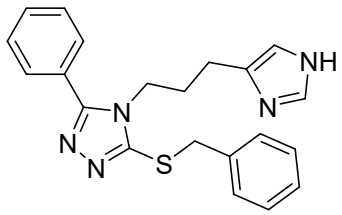
3-(5-(Benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)-1H-indole (69)

Prepared according to **general procedure C** from compound **56** (457 mg, 0.81 mmol) to afford 423 mg (80%) of **69** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 2.8 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.34-7.30 (m, 11H), 7.28 (s, 1H), 7.25-7.10 (m, 4H), 7.04-7.02 (m, 6H), 6.59 (s, 1H), 4.37 (s, 2H), 3.88 (t, *J* = 8.2 Hz, 1H), 2.42 (t, *J* = 6.8 Hz, 2H), 1.77 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.12, 148.23, 142.29, 139.15, 138.00, 137.32, 135.90, 129.17, 128.93, 128.44, 128.16, 127.92, 127.44, 125.71, 125.10, 122.34, 120.93, 120.20, 117.95, 111.78, 101.71, 74.41, 43.47, 37.57, 28.36. This compound was used directly in the deprotection step without further purification.

General Procedure D: Trityl deprotection

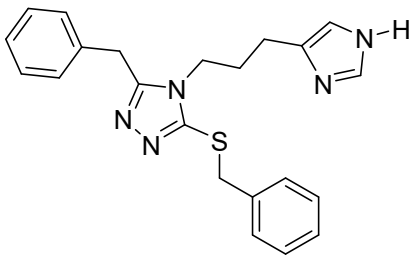
A mixture of the trityl-protected compound (1 mmol) in DCM (26.5 mL/mmol) was treated with 1N HCl (10.6 mL/mmol), and the mixture was refluxed overnight and evaporated under reduced pressure to haft of the volume. Water is added to the resulting mixture and extracted DCM. The

aqueous phase was then basified with NaOH 2N and extracted with DCM twice. This process was repeated a second time, if necessary, to remove the last trace of the protective group. After concentration of the organic phase, the desired deprotected compound was obtained with no further treatment.



4-(3-(1H-Imidazol-4-yl)propyl)-3-(benzylthio)-5-phenyl-4H-1,2,4-triazole (70)

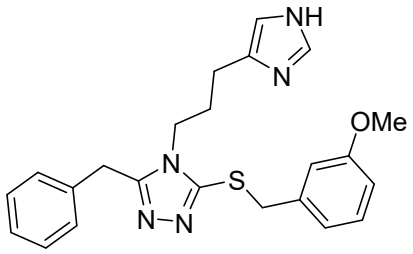
Prepared according to **general procedure D** from **57** (400 mg, 0.65 mmol) to afford 113 mg (47%) of compound **70** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51-7.44 (m, 6H), 7.32-7.14 (m, 8H), 4.38 (s, 2H), 3.79 (m, 2H), 2.25 (m, 2H), 1.70 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.05, 150.10, 147.85, 137.20, 134.86, 130.11, 129.09, 129.05, 128.61, 128.41, 127.86, 127.65, 127.27, 126.76, 48.71, 43.79, 37.42, 29.14. HRMS (ESI+): m/z calculated for $C_{21}H_{22}N_5S$ $(M+H)^+$ 376.1557, found 376.1590.



4-(3-1H-Imidazol-4-yl)propyl-3-benzyl-5-(benzylthio)-4H-1,2,4-triazole (71)

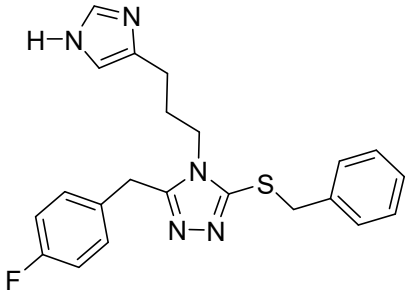
s**71** as a white solid (72 mg, 59%): 1H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H), 7.53 (s, 1H), 7.32-7.28 (m, 2H), 7.25-7.19 (m, 6H), 7.10 (m, 1H), 4.30 (s, 2H), 4.08 (s, 2H), 3.59 (m, 2H),

2.33 (m, 2H), 1.57 (m, 2H). 13C NMR (100 MHz, DMSO-d6) δ 154.35, 148.67, 137.24, 136.17, 134.69, 128.83, 128.61, 128.44, 128.40, 127.42, 126.78, 42.74,37.65, 30.44, 28.92. HRMS (ESI+): m/z calculated for $C_{22}H_{24}N_5S$ $(M+H)^+$ 390.1752, found 390.1747.



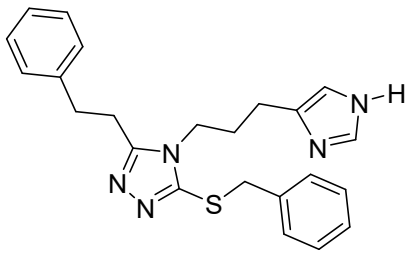
4-(3-(1H-Imidazol-4-yl)propyl)-3-benzyl-5-((3-methoxybenzyl)thio)-4H-1,2,4-triazole (72)

Prepared according to **general procedure D** from derivative **59** (200 mg, 0.30 mmol) to afford product **72** as a white solid (39 mg, 31%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.51 (s, 1H), 7.30-7.08 (m, 6H), 6.83-6.71 (m, 3H), 4.27 (s, 2H), 4.07 (s, 2H), 3.68 (s, 3H), 3.65 (m, 2H), 2.31 (m, 2H), 1.55 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.19, 154.34, 148.71, 138.73, 136.18, 134.69, 129.50, 128.60, 128.39, 126.77, 121.00, 114.27, 113.07, 54.98, 42.82, 37.51, 30.44, 28.93. HRMS (ESI+): m/z calculated for $C_{25}H_{26}FN_6S$ $(M+H)^+$ 461.1918, found 461.1926.



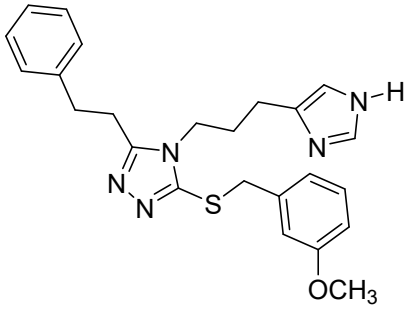
4-(3-(1H-Imidazol-4-yl)propyl)-3-(benzylthio)-5-(4-fluorobenzyl)-4H-1,2,4-triazole (73)

Prepared according to **general method D** from trityl derivative **60** (600 mg, 0.92 mmol) in a mixture of EtOH (30 mL) and 1N HCl (10 mL) to yield 161 mg (43%) of a white foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7,49 (br s, 1H), 7.28-7.17 (m, 4H), 7.08 (m, 4H), 6.69 (s,1H),4.25 (s, 2H), 4.03 (s, 2H), 3.58 (m, 2H), 2.35 (m, 2H), 1.52 (bs, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.61 (d, J_{CF} = 242 Hz), 154.81, 149.25, 140.0, 137.0, 135.22, 130.82, 129.36, 129.36, 128.95, 115.93, 115.72, 112.48, 43.0, 37.0, 30.10, 29.63, 25.00.



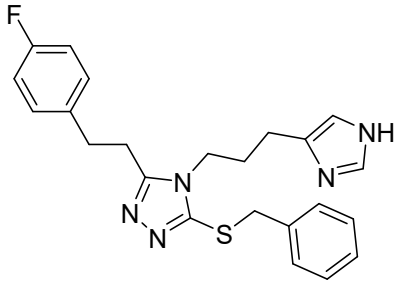
4-(3-(1H-imidazol-4-yl)propyl)-3-(benzylthio)-5-phenethyl-4H-1,2,4- triazole (74)

Prepared using **general procedure D** from **61** (300 mg, 0.46 mmol) to yield 83 mg (44%) of **74** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (s, 1H), 7.46 (s, 1H), 7.23-7.13 (m, 10H), 6.75 (s, 1H), 4.27 (s, 1H), 3.65 (m, 2H), 2.92-2.85 (m, 4H), 2.34 (m, 2H), 1.69 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.05, 148.30, 140.69, 137.32, 134.81, 128.95, 128.54, 128.49, 128.41, 127.55, 126.24, 42.62, 37.46, 32.60, 29.13, 26.29. HRMS (ESI+): m/z calculated for $C_{23}H_{26}N_5S$ $(M+H)^+$ 404.1910, found 404.1903.



4-(3-(1H-Imidazol-4-yl)propyl)-3-((3-methoxybenzyl)thio)-5-phenethyl-4H-1,2,4-Triazole (75)

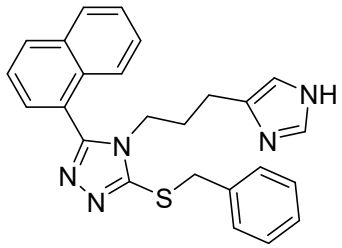
Following the **general procedure D** for deprotection of trityl group the following amounts of material were used: triazole **62** (0.39 g, 0.54 mmol), 1N HCl (5.7 mL), EtOH (14 mL) gave 0.162 g (55%) of **75** a tan foam: NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1*H*), 7.48 (s, 1*H*), 7.41 (s, 1H), 7.28 (s, 7H), 6.85 (m, 4H), 4.27 (s, 2H), 3.70 (s, 5H), 2.95 (m, 4H), 2.49 (m, 2H), 1.73 (m, 2H); 13C NMR (100 MHz, DMSO-d_6) δ 159.18, 154.57, 148.44, 138.74, 136.29, 134.64, 129.43, 126.82, 123.52, 121.22, 120.95, 118.53, 114.22, 113.06,111.46, 108.37, 54.93, 42.78, 37.45, 28.96, 24.57, 21.66. ESI-HRMS: Calculated for $C_{24}H_{27}N_5OS$ $[M+H]^+$ 434.2009 m/z, Found $[M + H]^+$ 434.2009.



4-(3-(1H-Imidazol-4-yl)propyl)-3-(benzylthio)-5-(4-fluorophenethyl)-4H-1,2,4-triazole (76)

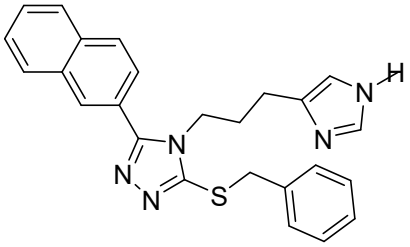
Prepared according to **general procedure D** from compound **63** (585 mg, 0.88 mmol) to afford 84 mg (23% yield) of **76** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (s, 1H), 7.27-7.22 (m, 8H) 7.08 (m, 2H), 4.31 (s, 2H), 3.68 (m, 1H), 2.95 (m, 2H), 2.88 (m, 2H), 2.38 (m, 2H),

1.71 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.03, 159.63, 154.82, 148.23, 137.29, 136.80, 134.75, 130.29 (d), 128.91, 128.47, 127.47, 115.07 (d), 42.55, 37.36, 31.50, 29.09, 26.28. HRMS (ESI+): m/z calculated for $C_{23}H_{25}FN_5S$ $(M+H)^+$ 422.1802, found 422.1809.



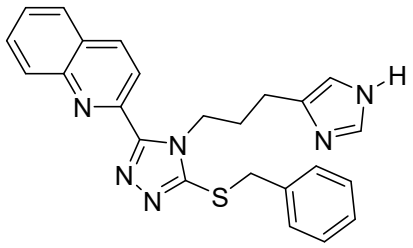
4-(3-(1H-Imidazol-4-yl)propyl)-3-(benzylthio)-5-(naphthalen-1-yl)-4H-1,2,4-triazole (77)

Prepared according to **general procedure D** from compound **64** (264 mg, 0.40 mmol) to afford 77 mg (46%) of **77** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.61-7.50 (m, 4H), 7.31-7.24 (m, 7H), 6.32 (s, 1H), 4.39 (s, 2H), 3.49 (m, 2H), 2.03 (m, 2H), 1.46 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.76, 149.41, 137.35, 134.62, 133.12, 131.44, 130.66, 129.08, 128.81, 128.63, 127.63, 127.46, 126.72, 125.42, 124.63, 124.55, 43.66, 38.12, 29.15. HRMS (ESI+): m/z calculated for $C_{25}H_{242}N_5S$ $(M+H)^+$ 426.1774, found 426.1747.



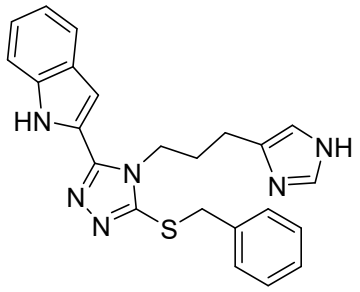
4-(3-(1H-Imidazol-4-yl)propyl)-3-(benzylthio)-5-(naphthalen-2-yl)-4H-1,2,4-triazole (78)

Prepared according to **general procedure D** from **65** (118 mg, 0.17 mmol) to give 24 mg (32% yield) of **78** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 8.01-7.95 (m, 3H), 7.67-7.65 (m, 1H), 7.59-7.57 (m, 2H), 7.39-7.16 (m, 6H), 6.63 (s, 1H), 6.41 (s, 1H), 4.41 (s, 2H), 3.93 (m, 2H), 2.27 (m, 2H), 1.75 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.94, 150.24, 137.18, 133.16, 132.54, 129.06, 128.64, 128.56, 127.89, 127.74, 127.60, 127.48, 126.96, 125.35, 124.62, 44.01, 37.34, 29.07. HRMS (ESI+): m/z calculated for $C_{25}H_{24}N_5S$ $(M+H)^+$ 426.1747, found 426.1747.



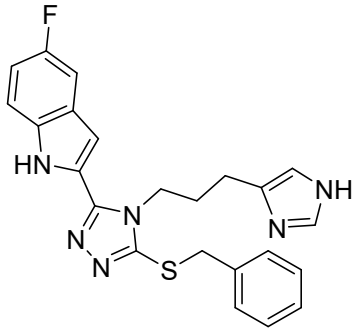
2-(4-(3-(1H-Imidazol-4-yl)propyl)-5-(2-(1H-indol-3-yl)ethylthio)-4H-1,2,4-triazol-3-yl)quinoline (79)

Prepared according to **general procedure D** from trityl derivative **66** (400 mg, 0.55 mmol) to yield 31.2 mg (12%) of **79** as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.53 (d, J = 8.7 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.85 (m, 2H), 7.71-7.64 (m, 2H), 7.50 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 7.08 (m, 1H), 7.00 (m, 1H), 4.65 (s, 2H), 3.59 (m, 2H), 3.18 (m, 4H), 2.11 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.17, 152.33, 147.33, 146.63, 137.42, 136.26, 134.70, 130.42, 129.14, 128.02, 127.60, 127.38, 126.95, 123.15, 121.07, 119.93, 118.42, 112.29, 111.48, 48.61, 45.64, 33.08, 29.64, 25.55. HRMS (ESI+): m/z calculated for $C_{27}H_{26}N_7S$ $(M+H)^+$ 480.1965, found 480.1983.



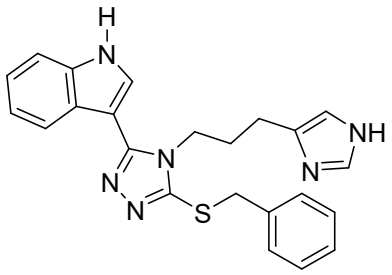
2-(4-(3-(1H-Imidazol-4-yl)propyl)-5-(benzylthio)-4H-1,2,4-triazol-3-yl)-1H-indole (80)

Prepared according to **general procedure D** from **67** (150 mg, 0.23 mmol) to yield 47.2 mg (50%) of compound **80** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 7.73 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.37-7.24 (m, 5H), 7.21-7.16 (m, 2H), 7.05 (m, 1H), 6.85 (s, 1H), 6.62 (d, *J* = 1.8 Hz, 1H), 4.44 (s, 2H), 4.08 (m, 2H), 2.55 (m, 2H), 1.87 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.83, 150.23, 148.84, 137.13, 136.54, 134.89, 130.32, 130.23, 129.02, 128.92, 128.54, 128.48, 127.77, 127.61, 127.49, 123.78, 123.11, 120.96, 123.11, 120.96, 119.72, 115.09, 114.88, 111.86, 101.35, 43.89, 37.54, 29.01, 23.64. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.10 min, ESI m/z = 415.40 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{23}H_{23}N_6S$ $(M+H)^+$ 415.1699, found 415.1709.



2-(4-(3-(1H-Imidazol-4-yl)propyl)-5-(benzylthio)-4H-1,2,4-triazol-3-yl)-5-fluoro-1H-indole (81)

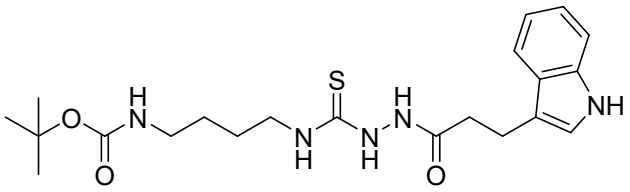
Prepared according to **general procedure D** from **68** (123 mg, 0.18 mmol) to give 26 mg (33%) of compound **81** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 9.04 (s, 1H), 7.47-7.25 (m, 8H), 7.07 (m, 1H), 6.81 (s, 1H), 4.46 (s, 2H), 4.09 (m, 2H), 2.68 (m, 2H), 1.93 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.35, 156.06, 150.52, 148.66, 137.06, 133.80, 133.38, 131.85, 129.01, 128.92, 128.72, 128.59, 128.40, 127.92, 127.82, 127.66, 127.60, 125.38, 115.90, 113.15 (d), 113.15 (d), 113.06, 111.92 (d), 105.41 (d), 101.66, 43.51, 37.68, 27.91, 20.96. HRMS (ESI+): m/z calculated for $C_{23}H_{22}FN_6S$ $(M+H)^+$ 433.1605, found 433.1622.



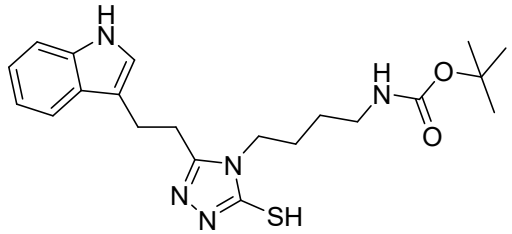
3-(4-(3-(1H-Imidazol-4-yl)propyl)-5-(benzylthio)-4H-1,2,4-triazol-3-yl)-1H-indole (82)

Prepared according to **general procedure D** from compound **69** (390 mg, 0.6 mmol) to yield 154 mg (63%) of **82** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.67 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H),7.71 (s, 1H), 7.51 (s, 1H), 7.48-7.46 (d, *J* = 7.8 Hz, 1H), 7.36-7.25 (m, 4H), 7.20 (t, *J* = 8.2 Hz, 1H), 7.12 (t, *J* = 8.3 Hz, 1H), 6.67 (s, 1H), 4.40 (s, 2H), 3.94 (m, 2H), 2.43 (m, 2H), 1.81 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.16, 148.37, 137.55, 135.93, 134.82, 129.01, 128.53, 127.52, 125.75, 125.02, 122.39, 120.91, 120.27, 111.85, 101.79, 43.63, 37.64, 28.89. HRMS (ESI+): m/z calculated for $C_{23}H_{23}N_6S$ $(M+H)^+$ 415.1699, found 415.1699.

Compounds in Scheme 5 (containing a primary amine at the 4-position of the triazole ring)

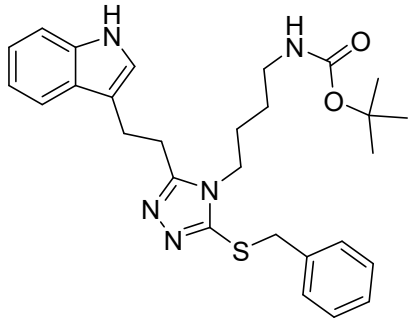


tert-Butyl 4-(2-(3-(1H-indol-3-yl)propanoyl)hydrazinecarbothioamido)butylcarbamate The thiosemicarbazide was obtained according to **general procedure A** from isothiocyanate **83** (crude mixture, 5.3 mmol) and hydrazide **8** (979 mg, 4.8 mmol). After evaporation of the solvent and purification by flash chromatography (DCM/EtOAc), the thiosemicarbazide was obtained as a yellow foam (1.53 g, 73%)): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.06 (s, 1H), 7.04-6.92 (m, 2H), 6.69 (m, 1H), 3.26 (m, 2H), 2.90-2.82 (m, 4H), 2.49 (m, 2H), 1.29 (s, 9H, under peak: m, 4H,). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.64, 156.30, 136.50, 127.27, 122.58, 121.64, 118.90 (2), 113.83, 111.87, 78.31, 43.66, 34.47, 28.71, 27.20, 26.57, 20.75.



tert-Butyl 4-(3-(2-(1H-indol-3-yl)ethyl)-5-mercapto-4H-1,2,4-triazol-4-yl)butylcarbamate (84): The thiosemicarbazide (2.32 g, 5.4 mmol) was treated following **general procedure B** to afford 2.20 g of the desired thiol **84** (2.20 g, 99%) as a foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 2.3 Hz,1H), 7.07 (td, *J* = 7.8, 0.9 Hz,1H), 6.98 (td, *J* = 6.8,0.9 Hz, 1H), 6.80 (t, *J* = 5.5 Hz, 1H), 3.95 (t, *J* = 7.8 Hz, 1H), 3.10-3.06 (m, 2H), 3.02-2.98 (m, 2H), 2.88 (m, 2H), 1.53 (m, 2H). ^{13}C NMR (100

MHz, DMSO-d_6) δ 166.69, 156.11, 136.72, 127.39, 123.21, 121.52, 118.87, 118.69, 113.30, 111.94, 77.94, 43.10, 28.76, 27.24, 26.23, 25.81, 22.05. HRMS (ESI+): m/z calculated for $C_{21}H_{30}N_5O_2S$ $(M+H)^+$ 416.2117, found 416.2115.



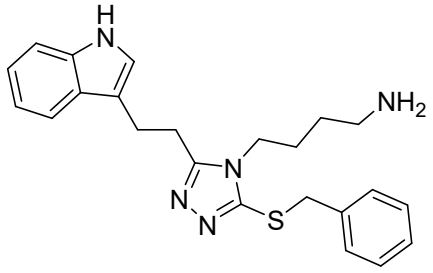
tert-Butyl-4-(3-(2-(1H-indol-3-yl)ethyl)-5-(benzylthio)-4H-1,2,4-triazol-4-yl)butylcarbamate

According to **general procedure C**, thiol **84** (246 mg, 0.60 mmol) and benzyl bromide (71 μL, 0.60 mmol) afforded 245 mg (82% yield) of the Boc-derivative as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.28-7.23 (m, 5H), 7.14 (s, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.75 (m, 1H), 4.30 (s, 2H), 3.59 (m, 2H), 3.11-2.97 (m, 4H), 2.80 (m, 2H), 1.33 (m, 2H), 1.31 (s, 9H), 1.18 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.29, 155.57, 155.37, 148.11, 137.27, 136.20, 128.90, 128.47, 127.47, 126.92, 122.67, 120.95, 118.32, 118.14, 113.17, 111.38, 77.42, 42.73, 37.52, 28.22, 26.79, 26.52, 25.57, 22.65. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.32 min, ESI m/z = 506.38 $[M+H]^+$.

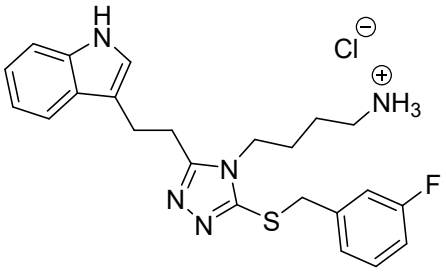
General Procedure E-Removal of the *tert*-butoxcarbonyl protecting group

The Boc-protected derivative (1.07 mmol) was stirred overnight in a mixture of CH_2Cl_2 (15 mL) and 5-6 N HCl in isopropanol (15 mL). The solvent was removed under reduced pressure, and the remaining residue was treated with absolute EtOH (15 mL) and re-evaporated. The residue was treated with 1N NaOH (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined

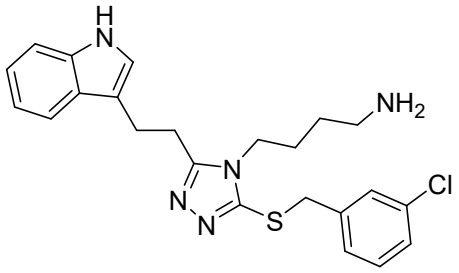
CH_2Cl_2 extract was washed with H_2O (1 x 25 mL), dried ($NaSO_4$), filtered, and evaporated. The resulting residue was dried under vacuum. In some cases, the free base was converted to the HCl salt and recrystallized from EtOH/Et_2O.



4-(3-(2-(1H-Indol-3-yl)ethyl)-5-(benzylthio)-4H-1,2,4-triazol-4-yl)butan-1-amine (85): Prepared according to **general procedure E** from the Boc-derivative (180 mg, 0.36 mmol) to afford 94 mg (65% yield) of compound **85 (free base)** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.29-7.25 (m, 5H), 7.17 (s, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 4.32 (s, 2H), 3.61 (m, 2H), 3.12 (m, 2H), 3.01 (m, 2H), 2.54 (m, 2H, under solvent), 1.37 (m, 2H), 1.27 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.44, 148.12, 137.31, 136.20, 128.92, 128.50, 127.49, 126.93, 122.78, 120.94, 118.32, 118.14, 113.15, 111.43, 42.68, 37.62, 26.64, 25.61, 22.62. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.13 min, ESI m/z = 406.46 [M+H] $^+$. HRMS (ESI+): m/z calculated for $C_{23}H_{28}N_5S$ (M+H) $^+$406.2060, found 406.2024.

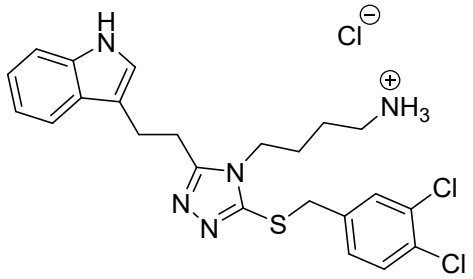


4-(3-(2-(1H-Indol-3-yl)ethyl)-5-(3-fluorobenzylthio)-4H-1,2,4-triazol-4-yl)butan-1-amine hydrochloride (86): Prepared according to **general procedure E** from Boc-derivative (230 mg, 0.44 mmol) to afford 200 mg (quantitative yield) of compound **86 (HCl salt)** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.97 (bs, 3H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.35-7.30 (m, 2H), 7.23-7.16 (m, 3H), 7.09 (m, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 4.4 (s, 2H), 3.80 (m, 2H), 3.18 (m, 4H), 2.63 (m, 2H), 1.43 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.21, 160.79, 155.86, 150.69, 139.36 (d), 136.19, 130.63 (d), 126.75, 125.23, 123.04, 121.12, 118.46 (d), 116.00 (d), 114.78 (d), 112.04, 111.51, 62.04, 43.91, 37.99, 36.20, 25.72, 25.51, 25.11, 23.94, 21.88. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.22 min, ESI m/z = 424.41 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{23}H_{27}FN_5S$ $(M+H)^+$424.1966, found 424.1930.



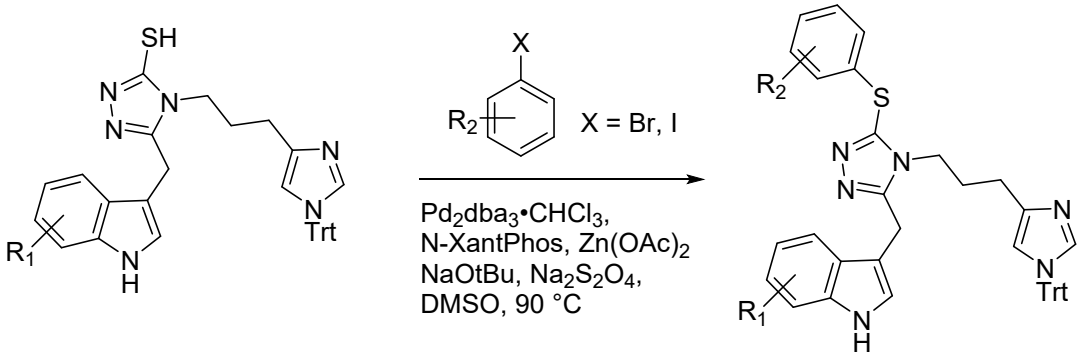
4-(3-(2-(1H-Indol-3-yl)ethyl)-5-(3-chlorobenzylthio)-4H-1,2,4-triazol-4-yl)butan-1-amine (87): Prepared according to **general procedure E** from the Boc-derivative (242 mg, 0.45 mmol) to yield 144 mg (73% yield) of compound **87 (free base)** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 7.34-7.23 (m, 3H), 7.14 (s, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.97 (t, *J* = 7.8 Hz, 1H), 4.32 (m, 2H), 3.59 (m, 2H), 3.16-2.98 (m, 4H), 2.39 (m, 2H), 1.34 (m, 2H), 1.13 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.62, 147.89, 140.23, 136.25, 132.94, 130.35, 128.74, 127.66, 127.41, 126.97, 122.81, 121.00, 118.36,

118.15, 113.18, 111.48, 42.97, 40.61, 36.62, 26.89, 26.66, 22.73. HRMS (ESI+): m/z calculated for $C_{23}H_{27}ClN_5S$ $(M+H)^+$ 440.1663, found 440.1670.

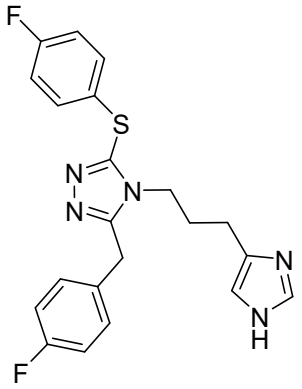


4-(3-(2-(1H-Indol-3-yl)ethyl)-5-(3,4-dichlorobenzylthio)-4H-1,2,4-triazol-4-yl)butan-1-amine hydrochloride (88): Prepared according to **general procedure E** from Boc-derivative (200 mg, 0.35 mmol) to give 150 mg (91% yield) of compound **88 (HCl salt)** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.90 (bs, 3H), 7.62 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H),7.32-7.29 (m, 2H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 4.37 (s, 2H), 3.12 (m, 6H), 2.62 (m, 2H), 1.41 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.85, 149.26, 138.51, 136.22, 131.05, 130.91, 130.69, 129.46, 126.86, 122.95, 121.06, 118.42, 112.58, 111.51, 48.63, 43.35, 38.13, 35.63, 26.13, 25.38, 24.04, 22.19. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.55 min, ESI m/z = 474.37 $[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{23}H_{26}Cl_2N_5S$ $(M+H)^+$ 474.1286, found 474.1259.

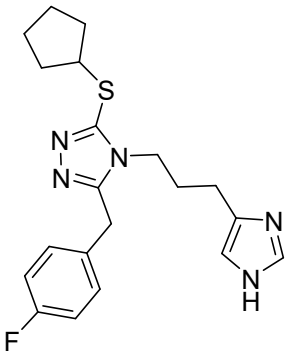
General Method F: Synthesis of 3-Thiotriazole Arylsulfides via Cross Coupling with Aryl Halides



A mixture of 3-thiotriazole (1 mmol), $Zn(OAc)_2$ (1.5-2 mmol), sodium dithionite (2 mmol), sodium *tert*-butoxide (2.5 mmol), *N*-XantPhos (0.1 mmol) and $Pd_2dba_3•CHCl_3$ (0.05 mmol) was subjected to 3 vacuum/argon purge cycles. In a separate flask, a solution of the aryl halide (3-5 mmol) in DMSO (15 mL) was sparged with dry Argon for 15 min and transferred to the main reaction flask with a pressurized cannula. The reaction was heated at 90 ºC for 16 h thereafter. The mixture was cooled and partitioned with EtOAc (150 mL) and water (100 mL). The layers were separated and the EtOAc solution was washed with water (2 x 50 mL) and brine (50 mL). The EtOAc layer was dried (Na_2SO_4), filtered and concentrated to afford the desired aryl sulfide product which was further purified by flash chromatography.

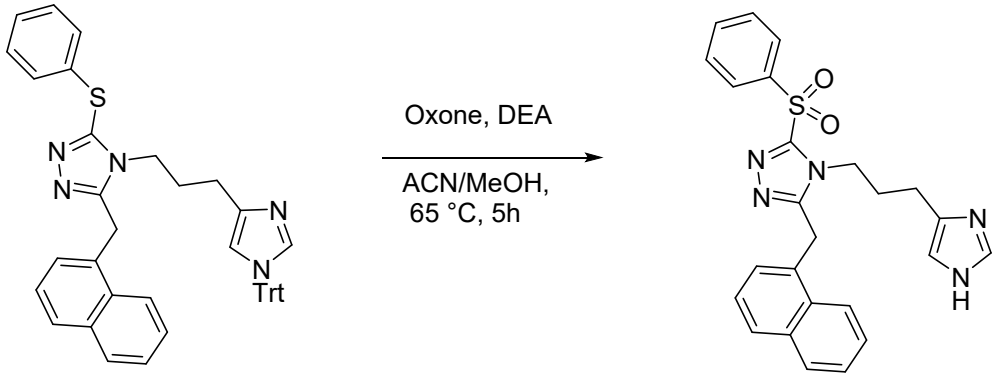


4-(3-(1H-Imidazol-4-yl)propyl)-3-(4-fluorobenzyl)-5-((4-fluorophenyl)thio)-4H-1,2,4-triazole (90): Prepared according to **General Method F** from 3-(4-fluorobenzyl)-5-((4-fluorophenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (273 mg, 0.42 mmol) and afforded 160 mg (93% yield) of compound **90** as a clear glass: ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (s, 1H), 7.38 – 7.32 (m, 2H), 7.15 – 7.05 (m, 4H), 7.04 – 6.98 (m, 2H), 6.71 (s, 1H), 4.13 (s, 2H), 3.92 – 3.81 (m, 2H), 2.47 (t, J = 7.0 Hz, 2H), 1.61 (quint., J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 163.00 (d, J_{CF} = 248 Hz), 162.15 (d, J_{CF} = 245 Hz), 156.13, 149.11, 134.90, 132.87 (d, J = 8.6 Hz), 130.97 (d, J = 3.5 Hz), 130.11 (d, J = 8.1 Hz), 129.57 (d, J = 4.3 Hz), 126.22 (d, J = 3.4 Hz), 116.56 (d, J = 22.6 Hz), 115.39 (d, J = 22.0 Hz), 43.70, 30.06, 29.12, 23.33. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.28 min, ESI m/z = 412 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 412.1402 (412.1402 calc'd for $C_{21}H_{20}F_2N_5S$), $[M + H]^+$.



4-(3-(1H-Imidazol-4-yl)propyl)-3-(cyclopentylthio)-5-(4-fluorobenzyl)-4H-1,2,4-triazole (91): Prepared according to **General Method F** from 3-(cyclopentylthio)-5-(4-fluorobenzyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole (135 mg, 0.22 mmol) and afforded 83 mg (98% yield) of compound **91** as a clear glass: ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (bs, 1H), 7.15

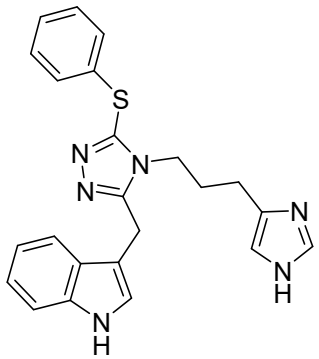
– 7.08 (m, 2H), 7.05 – 6.97 (m, 2H), 6.76 (bs, 1H), 4.11 (s, 2H), 3.83 (apparent t, J = 6.7 Hz, 2H), 2.51 (t, J = 7.1 Hz, 2H), 2.15 – 1.97 (m, 2H), 1.81 – 1.69 (m, 4H), 1.69 – 1.52 (m, 4H). ^{1}C NMR (100 MHz, CD_3OD) δ 162.12 (d, J_{CF} = 244.9 Hz), 154.74, 151.53, 134.88, 131.25 (d, J_{CF} = 3.3 Hz), 130.01 (d, J_{CF} = 8.1 Hz), 115.38 (d, J_{CF} = 22.0 Hz), 43.33, 33.29, 29.87, 29.06, 24.08, 23.42 (broad). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.15 min, ESI m/z = 386 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 386.1811 (386.1809 calc'd for $C_{20}H_{25}FN_5S$), $[M + H]^+$.



4-(3-(1H-Imidazol-4-yl)propyl)-3-(naphthalen-1-ylmethyl)-5-(phenylsulfonyl)-4H-1,2,4-triazole (92)

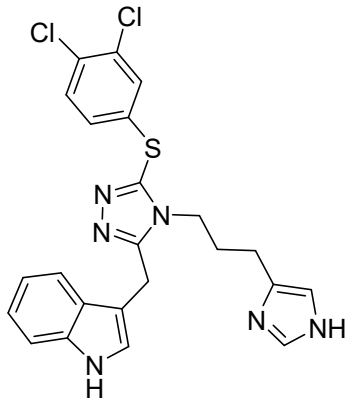
To a solution of 3-(naphthalen-1-ylmethyl)-5-(phenylthio)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazole (250 mg, 0.37 mmol) in ACN (6 mL) and methanol (20 mL) was added diethylamine (8 μL, 0.08 mmol). To this mixture was added a solution of oxone (500 mg, 0.81 mmol) in H_2O (12 mL). The resulting reaction mixture was heated to 65 ºC for 5h. The reaction was cooled and partitioned with EtOAc (200 mL) and sat. $NaHCO_3$ (200 mL). The layers were separated and the aqueous layer was extracted (5 x 50 mL) with EtOAc. The combined extracts were dried (Na_2SO_4), filtered and concentrated. Purification by flash chromatography (10:1 $CHCl_3$/MeOH) afforded 37 mg (22% yield) of compound **92** as a

colorless glass: ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 – 7.98 (m, 1H), 7.96 (dt, *J* = 8.1, 1.1 Hz, 2H), 7.90 – 7.83 (m, 1H), 7.82 – 7.70 (m, 2H), 7.66 – 7.59 (m, 2H), 7.54 – 7.44 (m, 3H), 7.35 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.11 (dd, *J* = 7.0, 1.1 Hz, 1H), 6.65 (s, 1H), 4.21 – 4.09 (m, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 1.70 (quint., *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 157.08, 153.13, 138.58, 135.01, 134.15, 131.71, 130.35, 129.57, 128.61, 128.25, 126.73, 125.88, 125.18, 123.12, 44.92, 29.47, 28.34, 23.24. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.00 min, ESI m/z = 458 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 458.1638 (458.1645 calc'd for $C_{25}H_{24}N_5O_2S$, $[M + H]^+$)

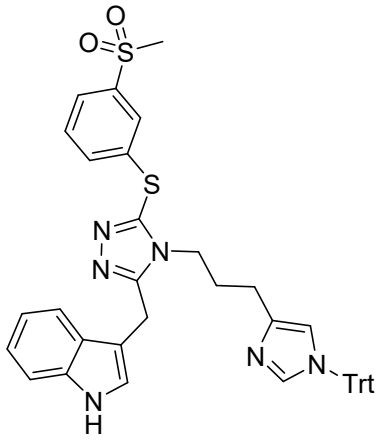


3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-(phenylthio)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (93): Prepared according to **General Method F** from 3-((5-(phenylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (163 mg, 0.29 mmol) and afforded 83 mg (69% yield) of compound **93** as a tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (bs, 1H), 10.87 (bs, 1H), 7.45 (s, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.17 (m, 4H), 7.17 – 7.08 (m, 3H), 7.03 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.91 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 6.57 (s, 1H), 4.23 (s, 2H), 3.81 (t, *J* = 7.9 Hz, 2H), 2.30 (t, *J* = 7.2 Hz, 2H), 1.56 (quint., *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.40, 146.49, 136.87, 135.10, 133.12, 130.07 (2 carbons),

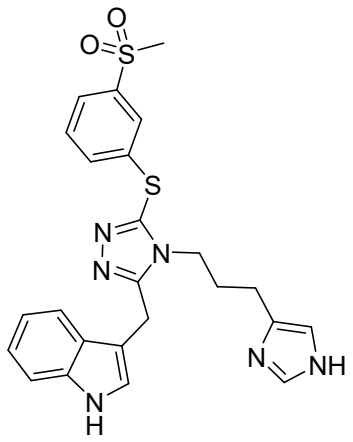
129.01 (2 carbons), 127.94, 127.24, 124.21, 121.76, 119.11, 118.94, 112.04, 108.67, 43.94, 30.39, 29.77, 22.54. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.30 minutes, ESI m/z = 415, $[M+H]^+$.



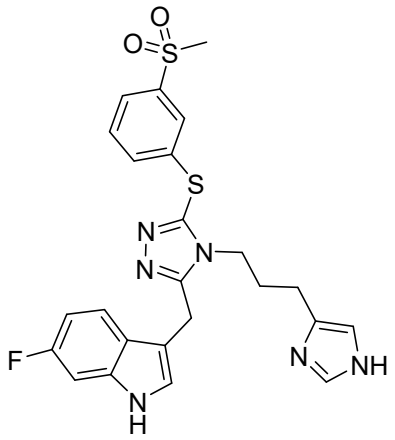
3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-((3,4-dichlorophenyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (94): Prepared according to **General Method F** from 3-((5-((3,4-dichlorophenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1H-indole (261 mg, 0.36 mmol) and afforded 103 mg (59% yield) of compound **94** as a tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.35 – 7.29 (m, 3H), 7.08 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.05 – 7.00 (m, 2H), 6.95 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.55 (s, 1H), 4.35 (s, 2H), 3.85 – 3.76 (m, 2H), 2.31 (t, *J* = 7.1 Hz, 2H), 1.48 (quint., *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.24, 147.22, 136.89, 133.13, 132.49, 131.82, 131.21, 130.26, 128.47, 126.62, 123.21, 121.60, 119.01, 117.73, 111.29, 107.44, 43.89, 28.98, 23.30 (broad), 22.18. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.33 minutes, ESI m/z = 483, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 483.0922 (483.0920 calc'd for $C_{23}H_{21}Cl_2N_6S$, $[M + H]^+$).



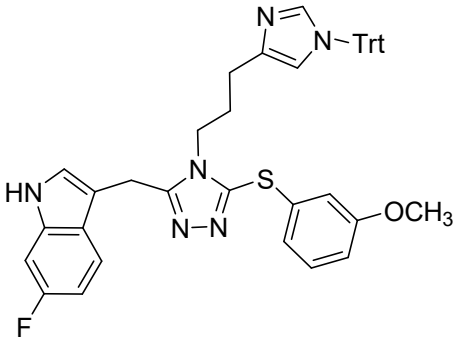
3-((5-((3-(Methylsulfonyl)phenyl)thio)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole: Prepared according to **General Method F** from 4-(3-(1*H*-imidazol-4-yl)propyl)-5-((1*H*-indol-3-yl)methyl)-4*H*-1,2,4-triazole-3-thiol **(10)** (500 mg, 0.86mmol) and 1-bromo-3-(methylsulfonyl)benzene (607 mg, 2.58 mmol) using $Zn(OAc)_2$ (237 mg, 1.29 mmol), sodium dithionite (300 mg, 1.72 mmol), potassium *tert*-butoxide (207 mg, 2.15 mmol), *N*-XantPhos (47 mg, 0.085 mmol) and Pd_2dba_3•$CHCl_3$ (45 mg, 0.044 mmol). Reaction and purification by flash chromatography (40:1 $CHCl_3$/MeOH), afforded 291 mg (97 % yield) of phenyl sulfide as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (dt, *J* = 7.0, 1.9 Hz, 1H), 7.69 (td, *J* = 1.8, 0.7 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.38 – 7.26 (m, 11H), 7.18 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.07 – 7.00 (m, 8H), 6.97 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.89 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.37 (d, *J* = 1.4 Hz, 1H), 4.36 (s, 2H), 3.86 – 3.75 (m, 2H), 2.95 (s, 3H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.40 (quint., *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.72, 145.54, 142.85, 142.47, 139.99, 138.29, 135.43, 133.40, 131.17, 129.70, 128.72, 128.47, 127.20, 126.61, 126.33, 124.27, 121.75, 119.10, 118.90, 118.07, 112.02, 74.87, 44.03, 43.82, 29.60, 25.10, 22.45. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.62 min, ESI m/z = 735 $[M+H]^+$.



3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-((3-(methylsulfonyl)phenyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (95): Prepared according to **General Method F** from 3-((5-((3-(methylsulfonyl)phenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (266 mg, 0.36 mmol) and afforded 150 mg (84% yield) of compound **95** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 10.94 (s, 1H), 7.84 – 7.66 (m, 2H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.46 (s, 1H), 7.44 – 7.38 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.03 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.56 (bs, 1H), 4.25 (s, 2H), 3.86 (t, *J* = 7.9 Hz, 2H), 3.14 (s, 3H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.53 (quint., *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.73, 145.57, 142.50, 136.81, 135.41, 135.18, 133.38, 131.24, 127.19, 126.59, 126.35, 124.24, 121.80, 119.18, 118.94, 112.05, 108.57, 44.03, 43.81, 29.82, 24.40 (broad), 22.50. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.97 min, ESI m/z = 493 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 493.1478 (493.1475 calc'd for $C_{24}H_{25}N_6O_2S_2$, $[M + H]^+$).

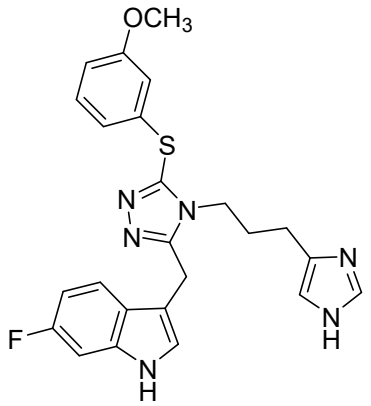


3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-((3-(methylsulfonyl)phenyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (96): Prepared according to **General Method F** from 6-fluoro-3-((5-((3-(methylsulfonyl)phenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (244 mg, 0.34 mmol) and afforded 82 mg (56% yield) of compound **96** as a colorless glass: ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (ddd, J = 7.7, 1.8, 1.1 Hz, 1H), 7.71 (td, J = 1.9, 0.5 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.46 (ddd, J = 7.9, 1.9, 1.2 Hz, 1H), 7.32 (ddd, J = 8.8, 5.3, 0.5 Hz, 1H), 7.04 – 6.98 (m, 2H), 6.77 (ddd, J = 9.7, 8.7, 2.4 Hz, 1H), 6.57 (d, J = 1.1 Hz, 1H), 4.33 (d, J = 1.0 Hz, 2H), 3.92 – 3.77 (m, 2H), 3.00 (s, 3H), 2.38 – 2.28 (m, 2H), 1.52 (quint., J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.98 (d, J_{CF} = 236.2 Hz), 157.06, 147.11, 142.32, 136.84 (d, J_{CF} = 12.7 Hz), 134.76, 134.54, 133.42, 130.57, 126.86, 126.36, 123.75 (d, J_{CF} = 3.5 Hz), 123.37, 118.80 (d, J_{CF} = 10.4 Hz), 107.84, 107.55 (d, J_{CF} = 24.9 Hz), 97.16 (d, J_{CF} = 26.2 Hz), 43.92, 42.76, 29.09, 23.29, 22.04. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.13 min, ESI m/z = 511 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 511.1395 (511.1381 calc'd for $C_{24}H_{24}FN_6O_2S_2$), $[M + H]^+$.

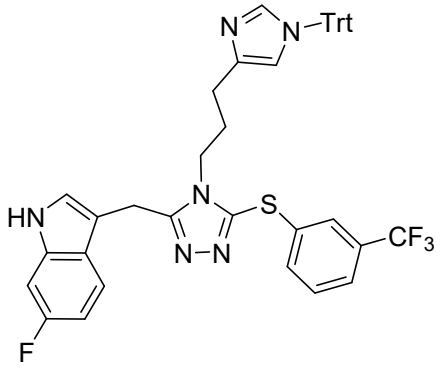


6-Fluoro-3-((5-((3-methoxyphenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole

Prepared according to **General Procedure F** from 5-((6-fluoro-1H-indol-3-yl)methyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol **(12)** (300 mg, 0.50mmol) and 3-bromoanisole (317 μL, 468 mg, 2.50 mmol) using $Zn(OAc)_2$ (138 mg, 0.75 mmol), sodium dithionite (174 mg, 1.00 mmol), sodium t-butoxide (120 mg, 1.25 mmol), N-XantPhos (28 mg, 0.05 mmol) and Pd_2dba_3•$CHCl_3$ (26 mg, 0.025 mmol). Purification by flash chromatography (SiO_2, 40:1 CH2Cl2/MeOH to 20:1) afforded 264 mg (75% yield) of compound sulfide as a tan solid: ^{1}H NMR (400 MHz, DMSO-d_6, t = 25 ºC, peaks are broadened due to slow rotational interconversion) δ 10.96 (bs, 1H), 7.38 – 7.28 (complex overlapping m, 10H), 7.17 (bs, 2H), 7.07 (t, J = 8.30 Hz, 1H), 7.03 – 6.97 (m, 7H), 6.74 – 6.67 (m, 2H), 6.58 (m, 2H), 6.43 (s, 1H), 4.21 (s, 2H), 3.84 – 3.81 (m, 2H), 3.52 (s, 3H), 2.27 – 2.24 (m, 2H), 1.51 – 1.43 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.21, 159.39 (d, $^1J_{CF}$ = 234 Hz), 156.35, 146. 13, 142.82, 140.08, 138.20, 136.62 (d, J_{CF} = 4.40 Hz), 134.55, 130.93, 129.67, 128.69, 128.46, 124.87 (d, J_{CF} = 2.90 Hz), 124.05, 120.09, 119.99 (d, J_{CF} = 9.50 Hz), 117.98, 113.71, 113.50, 109.00, 107.59 (d, J_{CF} = 23.9 Hz), 97.95 (J_{CF} = 24.9 Hz), 74.85, 55.59, 43.93, 29.51, 25.19, 22.38. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.67 min, ESI m/z = 705 $[M+H]^+$.

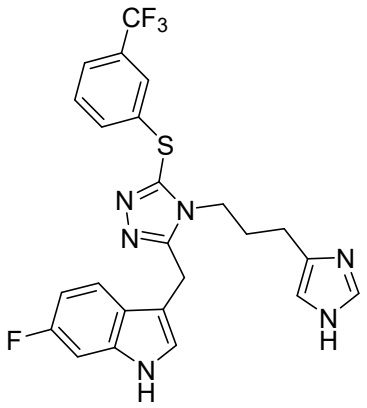


3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-((3-methoxyphenyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (97): Prepared according to **General Method F** from 6-fluoro-3-((5-((3-methoxyphenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (82 mg, 0.12 mmol) and afforded 49 mg (91% yield) of compound **97** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, J = 1.40 Hz, 1H), 7.29 (dd, J = 8.70, 5.50 Hz, 1H), 7.14 (t, J = 7.80 Hz, 1H), 7.00 (dd, J = 10.0, 2.30 Hz, 1H) 6.98 (s, 1H), 6.75 (dd, J = 8.70, 2.30 Hz, 2H), 6.71 – 6.67 (m, 1H), 6.64 (t, J = 1.80 Hz, 1H), 6.55 (s, 1H), 4.30 (s, 2H), 3.82 – 3.78 (m, 2H), 3.61 (s, 3H), 2.34 (t, J = 7.40 Hz, 2H), 1.53 (quint., J = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 160.58, 159.99 (d, J_{CF} = 235 Hz), 156.74, 148.15, 136.87 (d, J_{CF} = 12.4 Hz), 134.64, 132.64, 130.25, 123.67 (d, J_{CF} = 2.90 Hz), 123.35, 120.83, 118.80 (d, J_{CF} = 9.50 Hz), 114.03, 113.45, 107.90, 107.45 (d, J_{CF} = 24.9 Hz), 97.12 (d, J_{CF} = 25.9 Hz), 54.44, 43.82, 28.86, 23.50 (broad), 22.08. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.67 min, ESI m/z = 463 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 464.1792 (464.1774 calc'd for $C_{24}H_{23}DFN_6OS$, deuterated from storage CD_3OD, $[M + H]^+$).



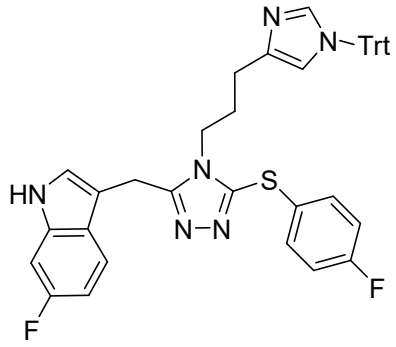
6-Fluoro-3((5-((3-Trifluoromethyl)phenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole

Prepared according to **General Procedure F** from 5-((6-fluoro-1H-indol-3-yl)methyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol **(12)** (300 mg, 0.50mmol) and 1-iodo-3-(trifluoromethyl)benzene (360 μL, 680 mg, 2.50 mmol) using $Zn(OAc)_2$ (138 mg, 0.75 mmol), sodium dithionite (174 mg, 1.00 mmol), sodium t-butoxide (120 mg, 1.25 mmol), N-XantPhos (28 mg, 0.05 mmol) and Pd_2dba_3•$CHCl_3$ (26 mg, 0.025 mmol). Reaction afforded 377 mg (100 % yield) of the trityl intermediate as a tan solid which was carried on "as is": ^{1}H NMR (400 MHz, CD_3OD). δ 7.97 (m, 1H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.45 (s, 2H), 7.40-7.26 (complex overlapping m, 9H), 7.05-7.01 (complex overlapping m, 7H), 6.90 (dd, *J* = 9.6, 2.3 Hz, 1H), 6.67 (td, *J* = 9.6, 2.2 Hz, 1H), 6.42 (s, 1H), 4.33 (s, 2H), 3.84 (apparent t, *J* = 8.2 Hz, 2H), 2.29 (t, *J* = 7.3 Hz, 2H), 1.44 (quint. *J* = 7.8 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.18 min, ESI m/z = 743 $[M+H]^+$.

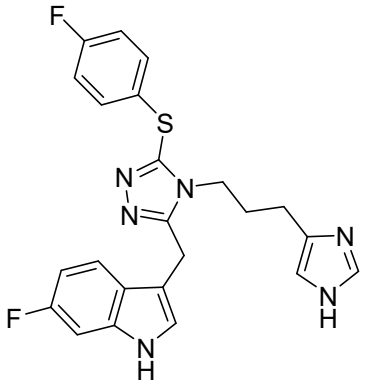


3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-((3-(trifluoromethyl)phenyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (98): Prepared according to **General Method D** from 6-fluoro-3-((5-((3-(trifluoromethyl)phenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (270 mg, 0.39 mmol) and afforded 77 mg (44% yield) of compound **98** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6, t = 30 ºC, peaks are broadened due to slow rotational interconversion and/or tautomeric equilibration) δ 11.73 (bs, 1H), 11.00 (bs, 1H), 7.48 (bs, 1H), 7.36 (apparent t, J ~ 6.90 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.16 – 7.12 (m, 3H), 7.06 (bd, J ~ 10.0 Hz, 1H), 6.78 (bt, J = 8.70 Hz, 1H), 6.64 (bs, 0.6H), 6.46 (bs, 0.4H), 4.19 (s, 2H), 3.867 – 3.75 (bm, 2H), 2.38 – 2.25 (bm, 2H), 1.54 – 1.46 (bm, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 160.01 (d, J_{CF} = 235.9 Hz), 156.96, 147.35, 136.95, 136.82, 134.71, 133.90, 132.30, 131.79, 131.47, 130.27, 127.96, 127.28, 126.64, 125.15 (d, J_{CF} = 4.2 Hz), 124.34 (d, J_{CF} = 3.8 Hz), 123.68 (d, J_{CF} = 3.5 Hz), 123.60 (q, J_{CF} = 271.88 Hz), 123.36, 118.74 (d, J_{CF} = 10.1 Hz), 107.84, 107.48 (d, J_{CF} = 24.9 Hz), 97.15 (d, J_{CF} = 26.2 Hz), 43.89, 31.03, 29.02, 22.07. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.73 min, ESI m/z = 501 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 501.1484 (501.1479 calc'd for $C_{24}H_{21}F_4N_6S$, $[M + H]^+$).

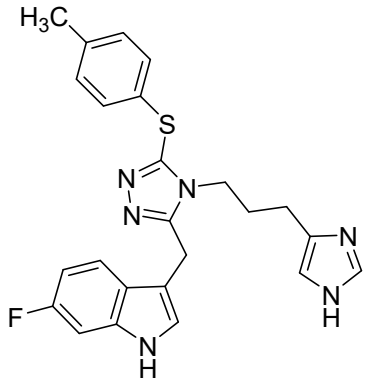
6-Fluoro-3-((5-((4-fluorophenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole



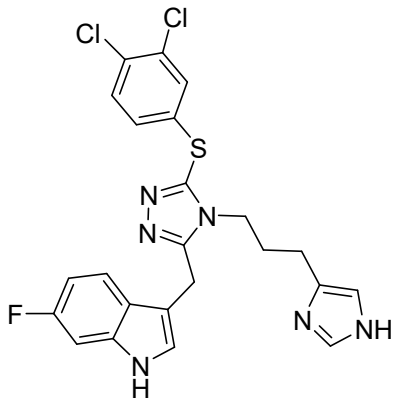
Prepared according to **General Procedure F** from 5-((6-fluoro-1H-indol-3-yl)methyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazole-3-thiol (**12,** 216 mg, 0.36 mmol) and 1-fluoro-4-iodobenzene (208 μL, 400 mg, 1.80 mmol) using $Zn(OAc)_2$ (99 mg, 0.54 mmol), sodium dithionite (125 mg, 0.72 mmol), sodium t-butoxide (86 mg, 0.90 mmol), N-XantPhos (20 mg, 0.036 mmol) and Pd_2dba_3•$CHCl_3$ (10 mg, 0.018 mmol) to afford 307 mg of the trityl-phenyl sulfide as an orange oil (this material was used in the next step without further purification): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (bs, 1H), 7.71 (dd, *J* = 8.70, 5.10 Hz, 1H), 7.37 – 7.29 (complex overlapping m, 10H), 7.23 – 7.20 (m, 2H), 7.16 (d, *J* = 1.80 Hz, 1H), 7.07 (t, *J* = 8.70 Hz, 1H), 7.03 – 6.97 (m, 6H), 6.73 (dt, *J* = 8.70, 2.30 Hz, 1H), 6.48 (bs, 1H), 4.19 (s, 2H), 3.84 (apparent t, *J* ~ 7.00 Hz, 2H), 2.29 (t, *J* = 6.90 Hz, 2H), 1.49 (quint., *J* = 7.00 Hz, 2H). LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 8.60 min, ESI m/z = 693 $[M+H]^+$.



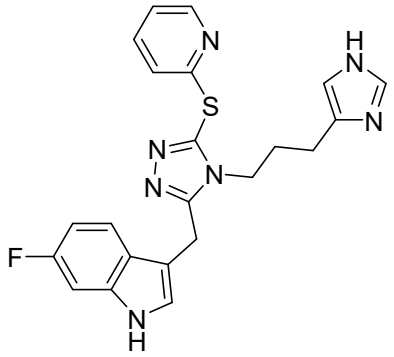
3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-((4-fluorophenyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (99): Prepared according to **General Method D** from 6-fluoro-3-((5-((4-fluorophenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (270 mg, 0.39 mmol) and afforded 77 mg (44% yield) of compound **99** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6, t = 30 ºC, peaks are broadened due to slow rotational interconversion and/or tautomeric equilibration) δ 11.73 (bs, 1H), 11.00 (bs, 1H), 7.48 (bs, 1H), 7.36 (apparent t, J ~ 6.90 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.16 – 7.12 (m, 3H), 7.06 (bd, J ~ 10.0 Hz, 1H), 6.78 (bt, J = 8.70 Hz, 1H), 6.64 (bs, 0.6H), 6.46 (bs, 0.4H), 4.19 (s, 2H), 3.867 – 3.75 (bm, 2H), 2.38 – 2.25 (bm, 2H), 1.54 – 1.46 (bm, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.03 (d, J_{CF} = 247.8 Hz), 159.20 (d, J_{CF} = 235.9 Hz), 155.76, 148.01, 136.06 (d, J_{CF} = 12.5 Hz), 133.90, 131.62 (d, J_{CF} = 8.6 Hz), 127.15, 126.47, 125.69 (d, J_{CF} = 3.3 Hz), 122.88 (d, J_{CF} = 3.4 Hz), 122.57, 117.99 (d, J_{CF} = 10.1 Hz), 115.64 (d, J_{CF} = 23.0 Hz), 107.13, 106.61 (d, J_{CF} = 24.9 Hz), 96.33 (d, J_{CF} = 25.9 Hz), 42.95, 28.12, 22.51, 21.17. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.05 min, ESI m/z = 451 $[M+H]^+$.



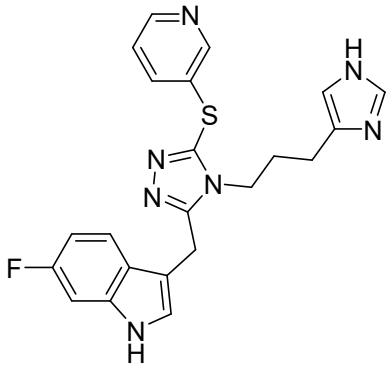
3-((4-(3-(1H-imidazol-4-yl)propyl)-5-(p-tolylthio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (100): Prepared according to **General Method D** from 6-fluoro-3-((5-(p-tolylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (162 mg, 0.24 mmol) and afforded 94 mg (88% yield) of compound **100** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6, t = 100 ºC, peaks are broadened due to slow rotational interconversion and/or tautomeric equilibration) δ 11.43 (bs, 1H), 10.73 (bs, 1H), 7.41 (bs, 1H), 7.37 (dd, J = 8.70, 5.50 Hz, 1H), 7.12 – 7.06 (complex overlapping m, 5H), 7.04 (d, J = 2.30 Hz, 1H), 6.75 (dt, J = 8.70, 2.30 Hz, 1H), 6.61 (bs, 0.6H), 6.47 (bs, 0.4H), 4.19 (s, 2H), 3.89 – 3.81 (bm, 2H), 2.38 – 2.31 (bm, 2H), 2.22 (s, 3H), 1.69 – 1.60 (bm, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.46 (d, J_{CF} = 234.3 Hz), 156.09, 147.05, 139.79, 137.90, 136.68 (d, J_{CF} = 12.6 Hz), 135.13, 130.71, 129.76, 129.14, 124.84, 124.10, 120.03 (d, J_{CF} = 10.4 Hz), 112.38, 109.06, 107.63 (d, J_{CF} = 24.4 Hz), 97.96 (d, J_{CF} = 25.4 Hz), 43.96, 31.96, 29.87, 25.14, 22.34. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.15 min, ESI m/z = 447 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 447.1772 (447.1762 calc'd for $C_{24}H_{24}FN_6S$, $[M + H]^+$).



3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-((3,4-dichlorophenyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (101): Prepared according to **General Method D** from 3-((5-((3,4-dichlorophenyl)thio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (459 mg, 0.62 mmol) and afforded 62 mg (20% yield) of compound **101** as a colorless glass: ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (d, J = 1.2 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.06 (dd, J = 8.5, 2.3 Hz, 1H), 7.04 – 6.98 (m, 2H), 6.75 (ddd, J = 9.7, 8.7, 2.3 Hz, 1H), 6.59 (s, 1H), 4.32 (s, 2H), 3.88 – 3.78 (m, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.52 (quint., J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 160.00 (d, J = 235.9 Hz), 157.00, 147.30, 136.87 (d, J = 12.5 Hz), 134.74, 133.15, 132.43, 131.89, 131.22, 130.32, 128.57, 123.74 (d, J = 3.4 Hz), 123.36, 118.75 (d, J = 10.2 Hz), 107.80, 107.51 (d, J = 24.9 Hz), 97.17 (d, J = 26.3 Hz), 43.87, 29.03, 23.54 (broad), 22.07. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.62 minutes, ESI m/z = 501, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 501.0834 (501.0826 calc'd for $C_{23}H_{20}Cl_2FN_6S$, $[M + H]^+$).

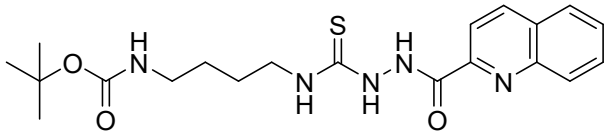


3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-(pyridin-2-ylthio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (102): Prepared according to **General Method D** from 6-fluoro-3-((5-(pyridin-2-ylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (162 mg, 0.24 mmol) and afforded 15 mg (14% yield) of compound **102** as a white glass: ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (ddd, J = 5.0, 2.0, 0.9 Hz, 1H), 7.61 (td, J = 7.8, 1.9 Hz, 1H), 7.47 (d, J = 1.2 Hz, 1H), 7.34 (dd, J = 8.7, 5.3 Hz, 1H), 7.30 – 7.18 (m, 1H), 7.14 (ddd, J = 7.6, 4.9, 1.0 Hz, 1H), 7.07 – 6.98 (m, 3H), 6.77 (ddd, J = 9.7, 8.7, 2.3 Hz, 1H), 6.54 (s, 1H), 4.35 (d, J = 1.0 Hz, 2H), 3.91 – 3.80 (m, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.63 (quint., J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 160.00 (d, J_{CF} = 235.9 Hz), 157.02, 155.74, 149.79, 146.08, 137.81, 136.89 (d, J_{CF} = 12.5 Hz), 134.65, 128.42, 127.96, 127.38, 127.30, 126.64, 123.74 (d, J_{CF} = 3.4 Hz), 123.41, 121.62, 121.61, 118.94 (d, J_{CF} = 10.1 Hz), 107.98, 107.40 (d, J_{CF} = 24.9 Hz), 97.13 (d, J_{CF} = 25.9 Hz), 44.01, 29.02, 23.41 (broad), 22.17. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.02 min, ESI m/z = 434 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 434.1544 (434.1558 calc'd for $C_{22}H_{21}FCl_2N_7S$), $[M + H]^+$.



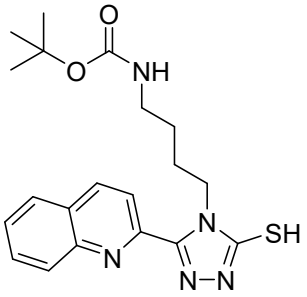
3-((4-(3-(1H-Imidazol-4-yl)propyl)-5-(pyridin-3-ylthio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (103): Prepared according to **General Method D** from 6-fluoro-3-((5-(pyridin-3-ylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1H-indole (350 mg, 0.50 mmol) and afforded 97 mg (45% yield) of compound **103** as a white glass: ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 – 8.42 (m, 2H), 7.68 (ddd, J = 8.3, 2.30, 1.40 Hz, 1H), 7.54 (d, J = 0.90 Hz, 1H), 7.33 (ddd, J = 8.30, 3.20, 0.90 Hz, 1H), 7.29 (dd, J = 8.70, 5.50 Hz, 1H), 7.02 – 6.99 (m, 2H), 6.77 - 6.72 (m, 1H), 6.60 (s, 1H), 4.31 (s, 2H), 3.90 – 3.86 (m, 2H), 2.38 (t, J = 7.30 Hz, 2H), 1.55 (quint., J = 7.30 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.97 (d, J_{CF} = 235.8 Hz), 156.76, 149.34, 148.34, 147.41, 138.23, 136.83 (d, J_{CF} = 12.4 Hz), 134.75, 129.86, 124.71, 123.74 (d, J_{CF} = 2.90 Hz), 123.36, 118.76 (d, J_{CF} = 9.60 Hz), 107.81, 107.46 (d, J_{CF} = 24.9 Hz), 97.14 (d, J_{CF} = 25.8 Hz), 43.84, 29.09, 23.58, 21.98. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.82 min, ESI m/z = 434 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 434.1559 (434.1558 calc'd for $C_{25}H_{26}FN_6$, $[M + H]^+$).

Synthesis of Compounds Shown in Scheme 7



tert-Butyl 4-(2-(quinoline-2-carbonyl)hydrazinecarbothioamido)butylcarbamate

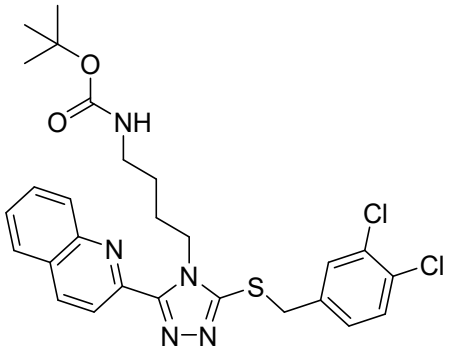
The thiosemicarbazide was obtained according to **general procedure A** using isothiocyanate **9** (crude mixture, 8.2 mmol) and quinoline-2-carbohydrazide (1.54 g, 8.2 mmol). At the end of the reaction, DCM was added to the residue resulting in a white precipitate. After filtration, 1.83 g of the thiosemicarbazide was obtained (54%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (bs, 1H, NH), 9.35 (bs, 1H, NH), 8.58 (d, *J* = 8.7 Hz, 1H), 8.16-8.09 (m, 4H, NH, 3H$_{arom}$), 7.90 (t, *J* = 6.9 Hz, 1H, H$_{arom}$), 7.75 (t, *J* = 7.3 Hz, 1H, H$_{arom}$), 6.78 (t, *J* = 5.5 Hz, 1H, NH), 3.41-3.37 (under water, m, 2H, CH_2-NHBoc), 3.16 (d, *J* = 5.0 Hz, 2H), 2.91 (q, *J* = 6.4 Hz, 2H), 1.47-1.42 (m, 2H), 1.34 (s+m, 9H+2H, tBu+CH_2). ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.31, 155.58, 149.51, 145.94, 137.68, 130.60, 129.31, 128.91, 128.31, 128.13, 119.06, 77.35, 43.55, 28.29, 26.92, 26.22. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.98 min, ESI m/z = 418.40 $[M+H]^+$.



tert-butyl 4-(3-Mercapto-5-(quinolin-2-yl)-4H-1,2,4-triazol-4-yl)butylcarbamate (104)

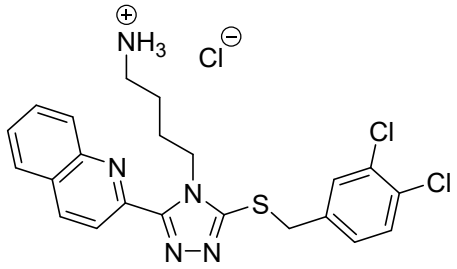
The thiosemicarbazide (1.72 g, 4.1 mmol) was treated following **general method B**. Evaporation of the organic phase afforded the desired product **104** as a solid (1.65 g, quantitative yield): ^{1}H

NMR (400 MHz, DMSO-d_6) δ 8.57 (d, *J* = 8.3 Hz, 1H), 8.15-8.07 (m, 3H, H_{arom}), 7.89 (t, *J* = 8.3 Hz, 1H, H_{arom}), 7.75 (t, *J* = 7.8 Hz, 1H, H_{arom}), 6.84 (t, *J* = 5.5 Hz, 1H, NH), 4.68 (t, *J* = 7.6 Hz, 2H), 2.98 (q, *J* = 6.4 Hz, 2H), 1.81 (m, 2H), 1.50 (m, 2H), 1.31 (s, 9H, tBu). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.46, 155.57, 148.41, 146.47, 145.88, 137.71, 130.64, 129.21, 128.06 (2), 127.67, 119.72, 77.33, 45.10, 28.20 (2), 26.99, 25.96. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.88 min, ESI m/z = 400.39 $[M+H]^+$.

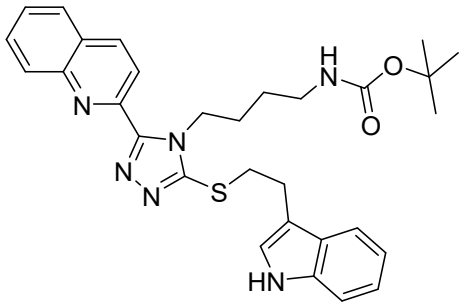


tert-butyl 4-(3-(3,4-dichlorobenzylthio)-5-(quinolin-2-yl)-4H-1,2,4-triazol-4yl)butylcarbamate. Prepared according to **general procedure C** from thiol **104** (439 mg, 1.1 mmol) and 3,4-dichlorobenzyl bromide (160 μL, 1.1 mmol) to give 456 mg (74% yield) of the Boc-intermediate as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, *J* = 8.2 Hz, 1H, H_{arom}), 8.29 (d, *J* = 8.7 Hz, 1H, H_{arom}), 8.05 (d, *J* = 7.8 Hz, 2H, H_{arom}), 7.84 (t, *J* = 8.2 Hz, 1H, H_{arom}), 7.70-7.66 (m, 2H, H_{arom}), 7.58 (d, *J* = 7.8 Hz, 1H, H_{arom}), 7.43 (d, *J* = 8.2 Hz, 1H, H_{arom}), 6.80 (t, *J* = 5.7 Hz, 1H, NH), 4.52 (s+m, 4H, CH_2-S, CH_2), 2.92 (q, *J* = 6.4 Hz, 2H), 1.69 (m, 2H), 1.42 (m, 2H), 1.28 (s, 9H, tBu). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.58, 152.47, 151.95, 147.16, 146.61, 138.83, 137.48, 131.02, 130.88, 130.61, 130.45, 130.12, 129.41, 129.13, 128.05,

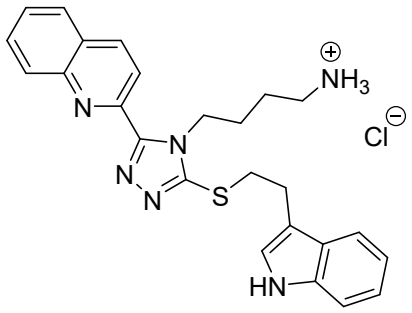
127.67, 127.44, 119.94, 77.37, 45.55, 35.10, 28.18 (2), 27.25, 26.80. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 8.07 min, ESI m/z = 558.39 $[M+H]^+$.



4-(3-(3,4-Dichlorobenzylthio)-5-(quinolin-2-yl)-4H-1,2,4-triazol-4-yl)butan-1-amine hydrochloride (105): Prepared according to **general procedure E** from the Boc-derivative (370 mg, 0.66 mmol) to afford 327 mg (quantitative yield) of compound **105** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, *J* = 8.7 Hz, 1H, H_{arom}), 8.34 (d, *J* = 8.7 Hz, 1H, H_{arom}), 8.14 (d, *J* = 8.7 Hz, 1H, H_{arom}), 8.09 (d, *J* = 8.2 Hz, 1H, H_{arom}), 8.01 (bs, 3H, NH_3^+), 7.88 (t, *J* = 7.3 Hz, 1H, H_{arom}), 7.74-7.69 (m, 2H, H_{arom}), 7.62 (d, *J* = 8.2 Hz, 1H,H_{arom}), 7.47 (dxd, *J* = 8.2, 1.4 Hz, 1H, H_{arom}), 4.59 (m, 2H), 4.55 (s, 2H, CH_2-S), 2.79 (m, 2H), 1.80 (m, 2H), 1.65 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.37 (d), 146.95 (d), 138.76, 137.60, 131.08, 130.89, 130.68, 130.59, 130.15, 129.51, 129.35, 128.07, 127.80, 127.50, 119.98, 45.41, 38.44, 35.31, 26.91, 24.24. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.92 min, ESI m/z = 458.33$[M+H]^+$. HRMS (ESI+): m/z calculated for $C_{22}H_{22}Cl_2N_5S$ $(M+H)^+$ 458.0967, found 458.0966.

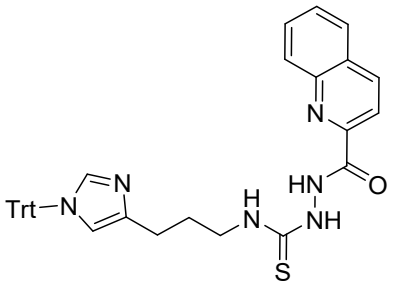


tert-Butyl 4-(3-(2-(1H-indol-3-yl)ethylthio)-5-(quinolin-2-yl)-4H-1,2,4-triazol-4-yl)butylcarbamate. The Boc-protected thiol (331 mg, 0.83 mmol) was dissolved in DMF (6.6 mL) followed by the addition of K_2CO_3 (115 mg, 0.83 mmol) and 3-(2-bromoethyl)-1H-indole (186 mg, 0.83 mmol). The reaction was stirred at 40°C overnight and the precipitate was filtered and washed with cold diethyl ether to afford 280 mg (62%) of the *S*-substituted derivative as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.56 (d, *J* = 9.2 Hz, 1H), 8.34 (d, *J* = 8.7 Hz, 1H), 8.08 (m, 2H), 7.84 (m, 1H), 7.70 (m, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.08 (m, 1H), 7.00 (m, 1H), 6.83 (t, *J* = 5.7, 1H), 4.57 (t, *J* = 7.4 Hz, 2H), 3.60 (t, *J* = 7.4 Hz, 2H), 3.19 (t, *J* = 7.4 Hz, 2H), 2.95 (m, 2H), 1.80 (m, 2H), 1.47 (m, 2H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.61, 153.12, 152.31, 147.36, 146.65, 137.45, 136.27, 130.44, 129.15, 128.08, 127.62, 127.44, 126.96, 123.14, 121.09, 119.99, 118.43, 112.29, 111.48, 77.38, 45.54, 33.09, 28.20, 28.04, 27.31, 26.90, 25.56. This derivative was carried on without further purification in the deprotection step.



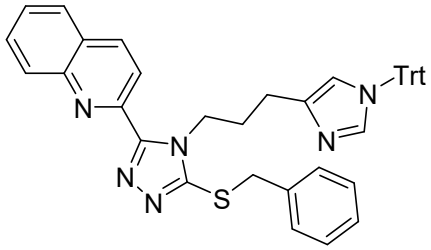
4-(3-(2-(1H-Indol-3-yl)ethylthio)-5-(quinolin-2-yl)-4H-1,2,4-triazol-4-yl)butan-1-amine hydrochloride (106): Prepared according to **general procedure E** from the Boc-derivative (200 mg, 0.37 mmol) to afford 20 mg (11%) of **106** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.57 (d, *J* = 8.7 Hz, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 8.01 (bs, 3H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* =

7.8 Hz, 1H), 7.26 (d, *J* = 1.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 4.64 (t, *J* = 7.3 Hz, 2H), 3.64 (t, *J* = 7.4 Hz, 2H), 3.22 (t, *J* = 7.3 Hz, 2H), 2.80 (m, 2H), 1.87 (m, 2H), 1.67 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.30, 152.13, 147.00, 146.62, 137.59, 136.28, 130.59, 129.36, 128.10, 127.79, 127.51, 126.94, 123.25, 121.08, 120.04, 118.43, 112.12, 111.51, 45.42, 38.49, 33.42, 26.87, 25.47, 24.28. HRMS (ESI+): m/z calculated for $C_{25}H_{26}ClN_6S$ $(M+H)^+$ 477.1623, found 477.1645.



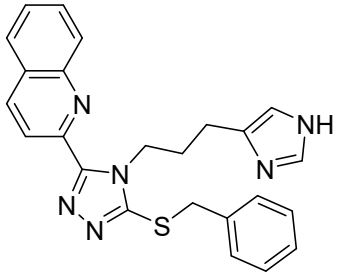
2-(Quinoline-2-carbonyl)-N-(3-(1-trityl-1H-imidazol-4-yl)propyl)hydrazinecarbothioamide

Prepared according to **general procedure A** from quinoline-2-carbohydrazide (**53**, 415 mg, 2.2 mmol) and **9** (1.00 g, 2.4 mmol) to yield 873 mg (66%) of the thiosemicarbazide as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 9.38 (s, 1H), 8.55 (d, *J* = 8.7 Hz, 1H), 8.29 (s, 1H), 8.11-8.07 (m, 3H), 7.89 (t, *J* = 6.9 Hz, 1H), 7.75 (t, *J* = 6.9 Hz, 1H), 7.40-7.33 (m, 9H), 7.13 (s, 1H), 7.08-7.03 (m, 6H), 6.61 (s, 1H), 3.47 (m, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 1.75 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.25,149.54, 145.91, 142.33, 140.68, 137.62, 137.54, 130.56, 129.26, 129.16, 128.84, 128.25, 128.17, 127.91, 119.00, 117.39, 74.30, 43.58, 28.26, 25.24.



2-(5-(Benzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)quinoline

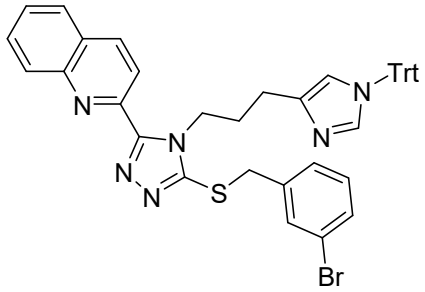
Prepared according to **general procedure C** from thiol **53** (550 mg, 0.95 mmol) to yield 460 mg (72%) of the trityl derivative as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 8.7 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 8.05 (d, *J* = 6.9 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.75-7.55 (m, 5H), 7.37-7.19 (m, 13H), 7.05-7.01 (m, 5H), 6.62 (s, 1H), 4.49 (m, 2H), 4.48 (m, 2H), 2.54 (m, 2H), 1.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.42, 152.26, 147.16, 146.59, 142.30, 139.77, 137.77, 137.42, 137.06, 130.33, 129.17, 128.97, 128.47, 128.11, 127.99, 127.92, 127.60, 127.53, 127.37, 119.93, 117.72, 74.35, 45.50, 36.80, 29.26, 25.13. This compound was used directly in the deprotection step without further purification.



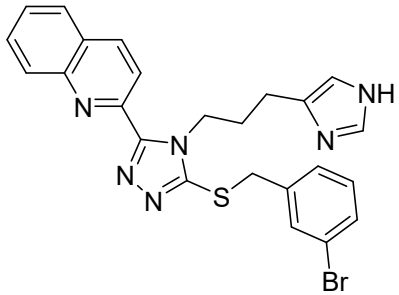
2-(4-(3-(1H-Imidazol-4-yl)propyl)-5-(benzylthio)-4H-1,2,4-triazol-3-yl)quinoline (107)

Prepared following **general procedure D** from the trityl derivative (310 mg, 0.46 mmol) to give 49 mg (25%) of **107** as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, *J* = 8.2 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.84-7.80 (m, 1H), 7.69-7.65 (m, 1H), 7.46-7.39 (m, 2H), 7.33-7.18 (m, 5H), 6.72 (s, 1H), 4.56 (m, 2H), 4.51 (s, 2H), 2.57 (m, 2H), 1.99 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.37, 147.79, 147.20,

146.61, 137.46, 137.12, 134.67, 130.45, 129.14, 129.05, 128.54, 128.02, 127.79, 127.66, 127.58, 127.56, 127.39, 126.67, 119.91, 45.62, 36.76, 29.61, 24.61. HRMS (ESI+): m/z calculated for $C_{24}H_{23}N_6S$ $(M+H)^+$ 427.1693, found 427.1699.

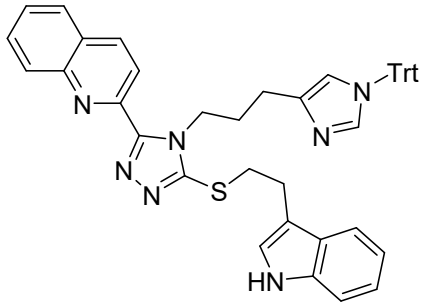


2-(5-(3-Bromobenzylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)quinoline Prepared according to **general procedure C** from thiol **53** (480 mg, 0.83 mmol) and 3-bromobenzyl bromide (207 mg, 0.83 mmol) to afford 325 mg (52%) of trityl derivative as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 8.2 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.75-7.64 (m, 2H), 7.60 (m, 1H), 7.41-7.32 (m, 11H), 7.25-7.20 (m, 2H), 7.05-7.01 (m, 6H), 6.64 (s, 1H), 4.49 (m, 4H), 2.55 (m, 2H), 1.99 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.51, 151.98, 147.11, 146.57, 142.29, 140.13,139.73, 137.79, 137.40, 131.65, 130.54, 130.30, 129.16, 128.09, 127.96, 127.90, 127.58, 127.35, 121.52, 119.91, 117.70, 74.33, 45.53, 35.80, 29.26, 25.12. This compound was used directly in the deprotection step without further purification.



2-(4-(3-(1H-Imidazol-4-yl)propyl)-5-(3-bromobenzylthio)-4H-1,2,4-triazol-3-yl)quinoline (108)

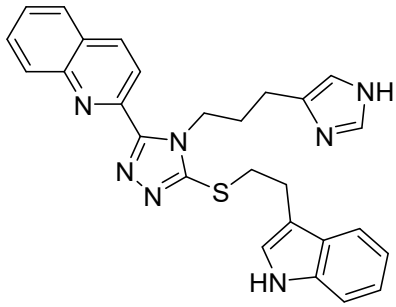
Prepared according to **general procedure E** from the trityl derivative (265 mg, 0.35 mmol) to give product **108** as a white solid (74 mg, 41%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s,1H), 11.73 (s, 1H), 8.54 (d, *J* = 8.7 Hz, 1H), 8.31 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.93 (m, 1H), 7.85 (t, d, *J* = 8.3 Hz, 1H), 7.70 (t, *J* = 8.2 Hz, 1H), 7.64 (s, 1H), 7.48-7.42 (m, 3H), 7.28 (m, 1H), 6.81 (s, 1H), 4.58 (m, 2H), 4.52 (m, 2H), 2.52 (m, 2H), 2.01 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.43, 152.09, 147.15, 146.58, 140.24, 137.43, 134.66, 131.71, 130.63, 130.42, 130.35, 129.13, 128.12, 127.99, 127.64, 127.38, 121.53, 119.90, 45.63, 35.79, 29.58.



2-(5-(2-(1H-Indol-3-yl)ethylthio)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)quinoline

The thiol **53** (515 mg, 0.89 mmol) was dissolved in DMF (7.1 mL) followed by the addition of K_2CO_3 (123 mg, 0.89 mmol) and 3-(2-bromoethyl)-1H-indole (199 mg, 0.89 mmol). The reaction was stirred at 40°C overnight and the precipitate was filtered and washed with cold diethyl ether to afford 496 mg (77%) of as a brown solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.53 (d, *J* = 8.7 Hz, 1H), 8.29 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 6.9 Hz, 1H), 7.99

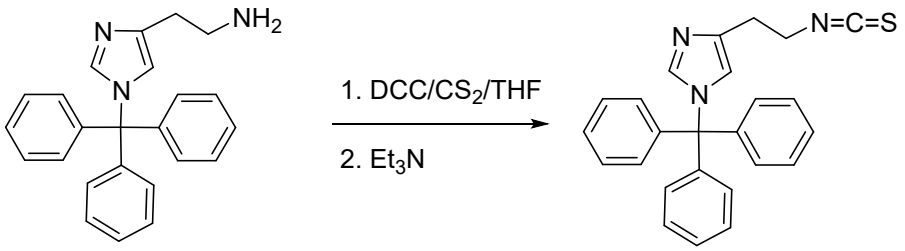
(d, J = 8.7 Hz, 1H), 7.74-7.60 (m, 3H) 7.35-7.32 (m, 10H), 7.25-7.23 (m, 2H), 7.08-6.95 (m, 8H), 6.66 (s, 1H), 4.57 (m, 2H), 3.55 (m, 2H), 3.16 (m, 2H), 2.59 (m, 2H), 2.10 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.66, 150.01, 147.78, 146.40, 143.79, 143.65, 138.67, 133.63, 133.53, 132.13, 131.38, 129.50, 129.22, 128.27, 127.91, 127.79, 127.55, 127.00, 126.66, 124.40, 120.63, 120.32, 119.58, 115.80, 112.00, 105.17, 80.57, 48.00, 30.43, 27.94, 27.81, 21.12. This compound was used directly in the deprotection step without further purification.



2-(4-(3-(1H-Imidazol-4-yl)propyl)-5-(2-(1H-indol-3-yl)ethylthio)-4H-1,2,4-triazol-3-yl)quinoline (109)

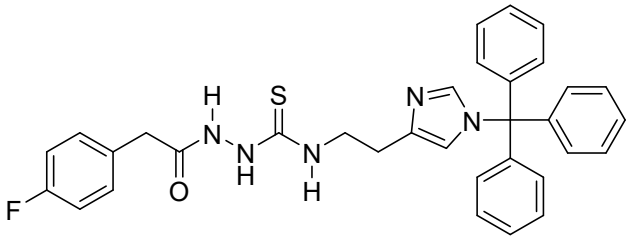
Prepared according to **general procedure D** from the trityl derivative (400 mg, 0.55 mmol) to yield 31.2 mg (12%) of **109** as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (s, 1H), 8.53 (d, J = 8.7 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.85 (m, 2H), 7.71-7.64 (m, 2H), 7.50 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 2.3 Hz, 1H), 7.08 (m, 1H), 7.00 (m, 1H), 4.65 (s, 2H), 3.59 (m, 2H), 3.18 (m, 4H), 2.11 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.17, 152.33, 147.33, 146.63, 137.42, 136.26, 134.70, 130.42, 129.14, 128.02, 127.60, 127.38, 126.95, 123.15, 121.07, 119.93, 118.42, 112.29, 111.48, 48.61, 45.64, 33.08, 29.64, 25.55. HRMS (ESI+): m/z calculated for $C_{27}H_{26}N_7S$ $(M+H)^+$ 480.1965, found 480.1983.

Synthesis of compounds shown in Scheme 8



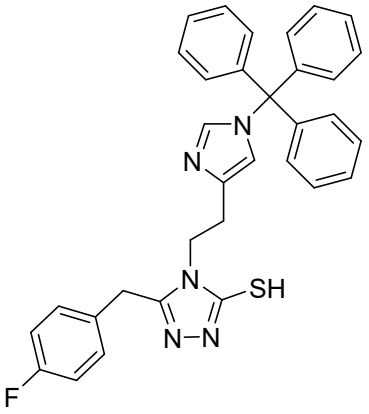
4-(2-Isothiocynatoethyl)-1-trityl-1*H*-imidazole (110)

A mixture of dicyclohexylcarbodiimide (DCC, 2.91 g, 14.1 mmol) and carbon disulfide (10.7 g, 14.1 mmol) was dissolved in THF (30 mL) and cooled to 0-5 ^{o}C and stirred under nitrogen. The tritylamine (5.0 g, 14.1 mmol) was added dropwise in THF (30 mL) and allowed to warm to RT and stir overnight. The mixture was then treated with Et_3N (11.9 mL, 84.8 mmol) and stir under nitrogen for 18 h. The solvent was evaporated under reduced pressure, and the resulting residue was dissolved in a mixture of CH_2Cl_2 (100 mL)-hexanes (10 mL) and placed in the freezer to stand overnight. Dicyclohexylthiourea was filtered, and the filtrate was evaporated to yield a light tan solid. Recrystallization from CH_3CN gave 2.12 g (63%) of pure isothiocyanate: mp 163-166 ^{o}C. ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.39 (d, 1H), 7.33 (m, 9H), 7.14 (m, 5H), 6.70 (s,1H), 3.79 (t, J = 8 Hz, 2H), 2.88 (t, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.43, 139.09, 136.54, 129.88, 128.19, 128.13, 119.96, 74.5, 44.94, 29.55. HRMS (ESI Q-TOF) m/z calculated for $C_{25}H_{22}NS$ $(M + H)^+$ 396.1534, found 396.1529.



2-(2-(4-Fluorophenyl)acetyl)-N-(2-(1-trityl-1H-imidazol-4-yl)ethyl)hydrazine-1-carbothioamide (111)

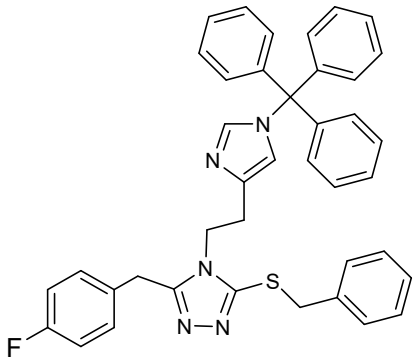
Using **General Method A,** 2-(4-fluorophenyl)acetohydrazide (2.0 g, 11.5 mmol) and 4-(2-isothiocyanatoethyl)-1trityl-1H-imidazole (**110**, 4.56 g, 11.5 mmol) was stirred for 10 min and then refluxed for 7 h under nitrogen. The reaction mixture was evaporated under reduced pressure to yield a brown foam. Trituration with CH_3CN (30 mL) gave a tan solid, which was filtered and dried to yield 5.71 g (84 %) of the thiosemicarbazide **111**. HRMS (ESI Q-TOF) m/z calculated for $C_{33}H_{31}FN_5OS$ $(M + H)^+$ 564.2233, found 564.2228.



5-(4-Fluorobenzyl)-4-(2-(1-trityl-1H-imidazol-4-yl)ethyl)-4H-1,2,4-triazole-3-thiol (114)

According to **General Method** B, thiosemicarbazide **111** (5.0 g, 8.87 mmol) and 2N NaOH (20 mL) was refluxed for 6 h under nitrogen and then stirred overnight at RT. The reaction mixture

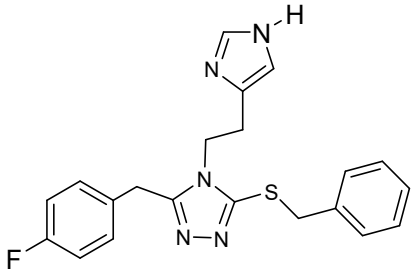
was treated with 1N HCl (35 mL) to yield **114** as a yellow solid. The solid was washed with EtOH and dried under vacuum to yield 3.93 g (81 %). A small sample was recrystallized from EtOH to yield a white powder: mp 220-228 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (m, 10H), 7.13 (t, 2H), 7.01 (m, 8H), 6.46 (s,1H), 3.98 (t, J = 8 Hz, 2H), 3.31 (s, 2H), 2.69 (t, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.48, 151.31, 142.20, 138.09, 136.72, 130 97, 130.81, 130.74, 129.16, 128.25, 128.01, 118.97, 115.47, 115.25, 74.50, 29.82, 25.68. HRMS (ESI Q-TOF) m/z calculated for $C_{33}H_{29}FN_5S$ $(M + H)^+$ 546.2128, found 546.2122.



3-(Benzylthio)-5-(4-fluorobenzyl)-4-(2-(1-trityl-1H-imidazol-4-yl)ethyl)-4H-1,2,4-triazole (118)

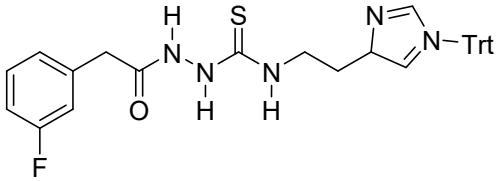
Following **General Procedure C,** thiol **114** (3.66 g, 6.71 mmol) in DMF (30 mL) was treated with K_2CO_3 (927 mg, 6.71 mmol) followed by the dropwise addition of benzyl bromide (1.14 g, 6.71 mmol) in DMF (5 mL). The reaction mixture was warmed to 40 ^{o}C and stirred overnight. The reaction mixture was evaporated under reduced pressure, and the residue was taken up into in EtOAc (100 mL) and filtered. The EtOAc layer was washed with 1N NaOH (3 x 50 mL), and water (1 x 50 mL). The EtOAc was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield a brown foam. Flash chromatography on SiO_2 using CH_2Cl_2 98 : MeOH 2 followed by elution of the product with CH_2Cl_2 95: MeOH 5 gave compound **114** as a white solid. Recrystallization from CH_3CN afforded 2.36 g (55%). ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.34

(m, 8H), 7.17 (m, 2H), 7.03 (m, 11H), 6.88 (t, 2H), 4.32 (s, 2H), 3.74 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.43, 149.83, 142.14, 138.87, 136.93, 135.75, 130.13, 130.05, 129.63, 128.14, 127.53, 120.00, 115.63, 115.41, 75.38, 43.33, 38.59, 30.39, 28.43. HRMS (ESI Q-TOF) m/z calculated for $C_{40}H_{35}FN_5S$ $(M+H)^+$ 636.2597, found 636.2592.



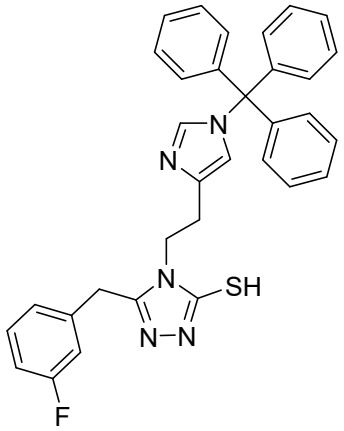
4-(2-(1*H*-Imidazol-4-yl)ethyl)-3-(benzylthio)-5-(4-fluorobenzyl)-4*H*-1,2,4-triazole (122)

Using **General Method D,** the trityl-1,2,4-triazole **118** (2.0 g, 3.14 mmol) was refluxed overnight under nitrogen in a mixture of EtOH (100 mL) and 1N HCl (30 mL). The EtOH was evaporated, and the aqueous acid was extracted with CH_2Cl_2 (3 x 50 mL). The CH_2Cl_2 was washed with H_2O (1 x 50mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield 500 mg (40%) of **122** as a white solid, mp: 50-55 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.20 (m, 4H), 7.05 (m, 2H), 6.94 (m, 2H), 6.28 (s, 1H), 4.31 (s, 2H), 3.71 (t, 2H), 3.61 (s, 2H), 2.68 (t, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.70, 130.93 (d), 130.13, 130.04, 128.92, 128.61, 127.71, 115,73, 115.52, 43.62, 38.79, 30.11, 28.11. (ESI Q-TOF) m/z calculated for $C_{21}H_{21}FN_5S$ $(M+H)^+$ 394.1502, found 394.1496.



2-(2-(3-Fluorophenyl)acetyl)-N-(2-(1-trityl-1*H*-imidazol-4-yl)ethyl)hydrazine-1-carbothioamide (112)

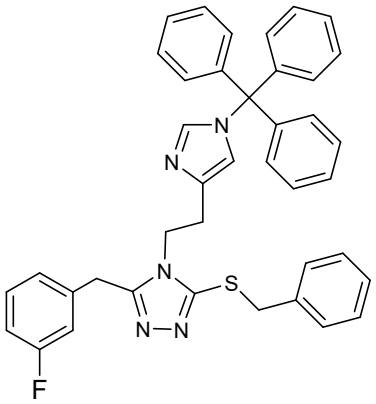
Using **General Method** A, 2-(3-fluorophenyl)acetohydrazide (2.72 g, 6.88 mmol) and 4-(2-isocyanatoethyl)-1-trityl-1*H*-imidazole (**110**, 2.72 g, 6.88 mmol) in THF (100 mL) was refluxed overnight under nitrogen. The reaction mixture was cooled, and the solvent was evaporated to yield a brown foam. The crude thiosemicarbazide was dissolved in CH_2Cl_2 (100 mL) and washed with 1N HCl (2 x 50 mL) followed by H_2O (1 x 50 mL). The CH_2Cl_2 was dried (Na_2SO_4), filtered, and evaporated to yield 1.8 g (46%) of the thiosemicarbazide, which was carried forward without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (m, 10H), 7.00 (m, 9H), 6.48 (s, 1H), 4.00 (t, J = 8 Hz, 2H), 3.83 (s, 2H), 2.70 (t, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.49, 150.95, 142.20, 138,10, 136.71, 129.16, 128,01, 125.02, 118.99, 115.87, 75.41, 43.0, 29.50, 25.50.



5-(3-Fluorobenzyl)-4-(2-(1-trityl-1H-imidazol-4-yl)ethyl)-4H-1,2,4-triazole-3-thiol (115)

Following **General Method** B, the thiosemicarbazide **112 (**1.5 g, 2.66 mmol) in a mixture of EtOH (100 mL) and 2N NaOH (10 mL) was refluxed overnight under nitrogen. The EtOH was removed under reduced pressure, and the aqueous phase was acidified with 1N HCl to yield a white solid. After filtering and drying 0.67 g (46%) of the thiol **115** was obtained. ^{1}H NMR (100 MHz, DMSO-d_6) δ 7.37 (m, 11H), 7.01 (m, 11H), 6.53 (s, 1H), 4.01 (t, J = 8 Hz, 2H), 3.85 (s, 2H), 2.72 (t, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.88 (d, J_{CF} = 246 Hz),

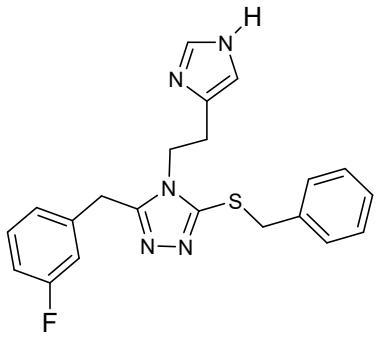
154.01, 149.84, 142.15, 138.91, 138.10, 138.02, 136.92, 135.75, 130.1, 130.0, 128.89, 128.50, 128.12, 128.09, 127.56, 124.20, 119.97, 115.64, 115.64, 114.10, 113.89, 74.75, 42.4, 30.23, 25.49. HRMS (ESI Q-TOF) m/z calculated for $C_{33}H_{29}FNS$ $(M+H)^+$ 546.2128, found 546.2122.



4-(2-(1-Trityl-1H-imidazol-4-yl)ethyl)-3-(benzylthio)-5-(3-fluorobenzyl)-4H-1,2,4-trizole (119)

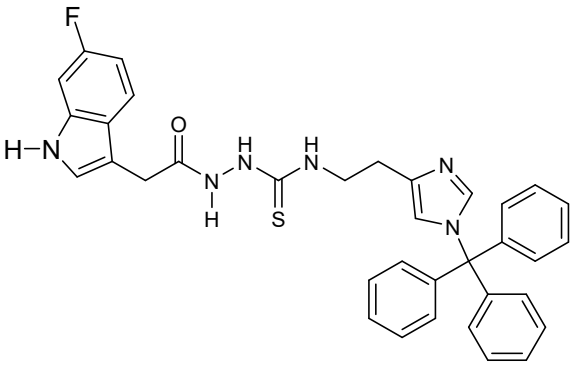
Using **General Method C**, thiol **115** (1.1 g, 2.0 mmol) and K_2CO_3 (0.28 g, 2.0 mmol) in DMF (25 mL) was treated dropwise with benzyl bromide (0.2 mL, 2.0 mmol) via a syringe. The reaction mixture was stirred overnight at 40 ^oC under nitrogen. The solvent was removed under reduced pressure, and the residue was taken up into EtOAc (100 mL). The EtOAc was washed with 1N NaOH (1 x 25 mL) and H_2O (3 x 25 mL), dried (Na_2SO_4), filtered, and evaporated to yield a light yellow solid. The solid was filtered, washed with a small amount of Et_2O, and dried to afford 337 mg (26%) of compound **119**, mp: 139-141.5. ^1H NMR (100 MHz, DMSO-d_6) δ 7.34 (m, 10H), 7.17 (m, 4H), 7.03 (m, 10H), 6.12 (s, 1H), 4.33 (s, 2H), 3.81 (2, 2H), 3.73 (t, J = 8 Hz, 2H), 2.56 (t, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.88 (d, J_{CF} = 246 Hz, 1H), 154.01, 149.84, 142.15, 138.91, 135.76, 129.62, 128.89, 128.50, 128.12, 128.09, 127.56,

119.97, 74.50, 43.33, 38.67, 30.85, 28.85. HRMS (ESI Q-TOF) m/z calculated for $C_{40}H_{35}FN_2S$ $(M+H)^+$ 636.2597, found 636.2592.



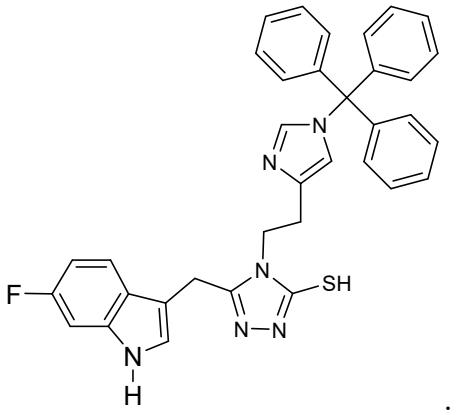
4-(2-(1H-Imidazol-4-yl)ethyl)-5-(3-fluorobenzyl)-3-(benzylthiol)-4H-1,2,4-triazole (123)

According to **General Method C,** the trityl derivative **119** (347 mg, 0.54 mmol) was refluxed in a mixture of EtOH (25 mL) and 1N HCl (15 mL) for 17 h under nitrogen. EtOH was removed under reduced pressure, and the aqueous phase was basified with 1N NaOH and extracted with CH_2Cl_2 (3 x 50 mL). The CH_2Cl_2 was washed with H_2O (2 x 50 mL) and filtered. The CH_2Cl_2 layer was again washed with H_2O (1 x 25 mL), separated, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield 102 mg (48 %) of **125** as a white foam. ^1H NMR (100 MHz, DMSO-d_6) δ HRMS (ESI Q-TOF) m/z calculated for $C_{21}H_{21}FN_5S$ $(M+H)^+$ 394.1502, found 394.1502.



2-(2-(6-Fluoro-1H-indol-3-yl)acetyl)-N-(2-(1-trityl-1H-imidazol-4-yl)ethyl)hydrazine-1-carbothioamide (113)

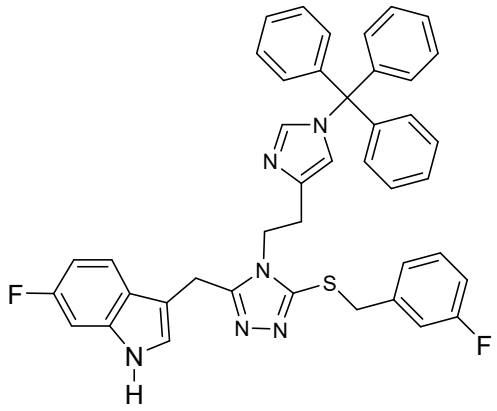
Using **General Method** A, 2-(6-fluoroindole)acetohydrazide (1.51 g, 7.58 mmol) and 4-(2-isocyanatoethyl)-1-trityl-1*H*-imidazole (**110**, 3.0 g, 7.58 mmol) in THF (100 mL) was refluxed overnight under nitrogen. The reaction mixture was evaporated under reduced pressure to yield 4.57 (100 %) of the thiosemicarbazide **115**, which was used directly in the next step without further purification. HRMS (ESI-Q-TOF) m/z calculated for $C_{35}H_{32}FN_6OS$ $(M+H)^+$ 603.2342, found 603.2337.



5-((6-Fluoro-1H-indol-3-yl)methyl)-4-(2-(1-trityl-1H-imidazol-4-yl)ethyl)-4H-1,2,4-triazole-3-thiol (117)

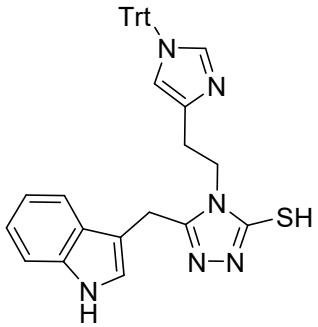
Following **General Method** B, the thiosemicarbazide **113** (4.57 g, 7.58 mmol) was heated at reflux overnight in a mixture of EtOH (100 mL) and 1N NaOH (100 mL) under nitrogen. The reaction mixture was filtered, and the filtrate was acidified with 1N HCl (125 mL) to yield a pink solid. The solid was filtered and resuspended in CH_2Cl_2 (50 mL) and stirred for 30 min under nitrogen. The solid was filtered and dried to yield 3.64 g (82%) of **117** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 7.56 (br s, 1H), 7.37-7.01 (m, 20 H), 6.43 (s, 1H) 4.05 (t , *J* = 8 Hz, 2H), 3.88 (s, 2H), 2.68 (t, *J* = 8 Hz, 2H). ^{13}C NMR (100 HMz, DMSO-d_6) δ 164.49,

157.72, 151.46, 151.26, 148.5, 141.96, 129.12, 128.32, 128.07, 127.78, 127.55, 124.64, 123.49, 119.16, 107.40, 107.30, 97.71, 97.45, 74.89, 42.00, 25.37, 21.54. HRMS (ESI-Q-TOF) m/z calculated for $C_{35}H_{30}FN_6S$ $(M+H)^+$ 585.2237, found 585.2237.

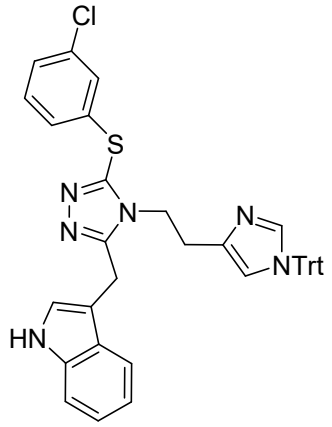


3-((4-(2-(1-Trityl-1H-imidazol-4-yl)ethyl)-5-((3-fluorobenzyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (120)

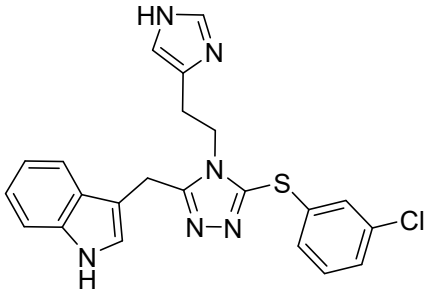
Using **General Method C,** a mixture of thiol **117** (2.60 g, 4.44 mmol) and K_2CO_3 (0.61 g, 4.44 mmol) in DMF (40 mL) was treated dropwise with a mixture of *m*-fluorobenzyl bromide (0.54 mL, 4.44 mmol) in DMF (5 mL). The reaction mixture was heated to 40°C overnight under nitrogen, and the solvent was removed under reduced pressure to yield an oil. The residue as dissolved in EtOAc (50 mL) and washed with H_2O (2 x 50 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure to yield a light tan solid. Recrystallization from EtOH gave 1.06 g (34%) of **120 as** a brown powder, mp: 167-172 °C. ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.50, 160.66, 156.0, 154.53, 148.72, 137.96, 129.08, 127.90, 124.83, 123.54, 123.54, 119.11, 115.54, 119.11, 115.47, 108.66, 107.50, 97.28, 74.39, 44.0, 36.50, 27.74, 21.48. HRMS (ESI Q-TOF) m/z calculated for $C_{42}H_{35}F_2N_6S$ $(M+H)^+$ 693.2612, found 694.2606.



5-((1*H*-Indol-3-yl)methyl)-4-(2-(1-trityl-1*H*-imidazol-4-yl)ethyl)-4*H*-1,2,4-triazole-3-thiol (116) This compound was prepared using **general procedures A and B.** To a solution of 4-(2-isothiocyanatoethyl)-1-trityl-1H-imidazole (**110**, 2.00 g, 5.06 mmol) and 2-(1*H*-indol-3-yl)acetylhydrazide hydrochloride (**5**, 1.14 g, 5.05 mmol) in DMF (75 mL) was added diisopropylethylamine (3.00 mL, 17.2 mmol) and the reaction was heated to 70 ºC for 2 h thereafter to effect formation of the acyl thiosemicarbazide intermediate. The mixture was concentrated and the residue was dissolved in EtOH (80 mL), treated with 2N NaOH (25 mL) and heated to 50 ºC for 2 h. The mixture was then cooled to 0-5 ºC (ice-bath) and treated with 4N HCl (13 mL) and enough 2N HCl (added dropwise) to adjust the pH to ~4. The mixture was then extracted with EtOAc (3 x 150 mL) and the combined extracts were dried (Na_2SO_4), filtered and concentrated to afford 1.54 g (54% yield) of compound **116** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.39 – 7.32 (m, 8H), 7.30 – 7.22 (m, 2H), 7.18 – 7.14 (m, 2H), 7.02 (m, 6H), 6.85 – 6.79 (m, 1H), 6.42 (s, 1H), 4.01 (t, *J* = 6.8 Hz, 2H), 3.87 (s, 2H), 2.67 (t, *J* = 6.7 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.75 minutes, ESI m/z = 567, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 567.2318 (567.2325 calc'd for $C_{35}H_{31}N_6S$).

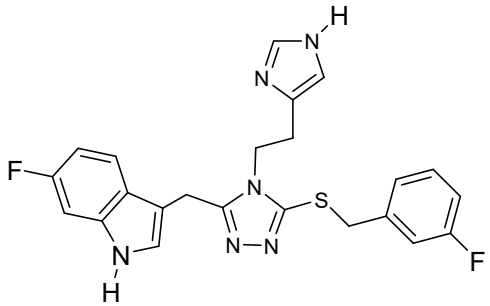


3-((5-((3-Chlorophenyl)thio)-4-(2-(1-trityl-1*H*-imidazol-4-yl)ethyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole: Prepared according to **General Method F** from 5-((1*H*-indol-3-yl)methyl)-4-(2-(1-trityl-1*H*-imidazol-4-yl)ethyl)-4*H*-1,2,4-triazole-3-thiol (612 mg, 1.08 mmol) and 1-chloro-3-iodobenzene (401 µL, 3.24 mmol) using $Zn(OAc)_2$ (297 mg, 1.62 mmol), sodium dithionite (376 mg, 2.16 mmol), sodium *tert*-butoxide (259 mg, 2.70 mmol), *N*-XantPhos (60 mg, 0.11 mmol) and Pd_2dba_3•$CHCl_3$ (56 mg, 0.055 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) afforded 205 mg (28% yield) of the trityl derivative as a off white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.37 – 7.31 (m, 10H), 7.29 – 7.25 (m, 2H), 7.22 – 7.11 (m, 4H), 7.06 (dq, *J* = 7.8, 1.4 Hz, 1H), 6.98 – 6.94 (m, 7H), 6.79 (td, *J* = 8.1, 7.6, 1.2 Hz, 1H), 6.11 (s, 1H), 4.07 (s, 2H), 4.03 (t, *J* = 6.8 Hz, 2H), 2.49 – 2.48 (m, peak partially obscured by DMSO solvent peak, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.57 min, ESI m/z = 677 $[M+H]^+$.



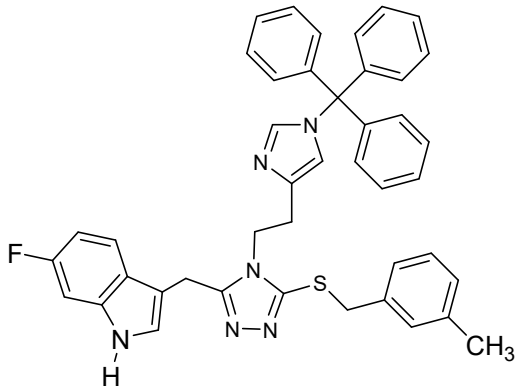
3-((4-(2-(1*H*-Imidazol-4-yl)ethyl)-5-((3-chlorophenyl)thio)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (124)

Prepared according to **General Method D** from 3-((5-((3-chlorophenyl)thio)-4-(2-(1-trityl-1*H*-imidazol-4-yl)ethyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (195 mg, 0.29 mmol) and afforded 45 mg (36% yield) of compound **124** as a clear glass: ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (s, *J* = 1H), 7.36 – 7.30 (m, 2H), 7.25 – 7.20 (m, 3H), 7.14 (s, 1H), 7.12 – 7.05 (m, 2H), 6.95 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.30 (s, 1H), 4.16 (s, 2H), 4.07 (t, *J* = 7.0 Hz, 2H), 2.50 (t, *J* = 7.0 Hz, 2H). ^{1}C NMR (100 MHz, CD_3OD) δ 157.25, 147.72, 136.95, 135.38, 134.39, 130.67, 128.17, 127.66, 126.91, 126.66, 121.60, 118.98, 117.86, 111.27, 107.50, 44.37, 39.08, 21.96. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.18 min, ESI m/z = 435 $[M+H]^+$.



3-((4-(2-(1H-Imidazol-4-yl)ethyl)-5-((3-fluorobenzyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (125)

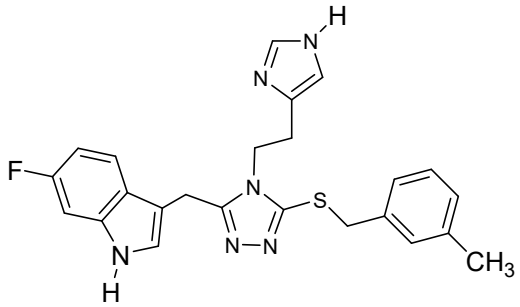
Following **General Method** C, the trityl-protected triazole **120** (1.0 g, 1,44 mmol) was dissolved in a mixture of EtOH (25 mL) and 1N HCl (15 mL) and refluxed or 20 h under nitrogen. The reaction mixture was cooled, and the EtOH evaporated under reduced pressure. The remaining aqueous phase was extracted with EtOAc (3 x 50 mL), basified with 1N NaOH, and extracted with EtOAc (3 x 50 mL). The combined EtOAc extracts were washed with H_2O (1 x 50 mL), dried (Na_2SO_4), filtered, and evaporated to give 340 mg (60%) of a pink solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (s, 1H), 7.37 (dd, 1), 7.12 (m, 5H), 6.99 (m, 3H), 6,78 (m,1H), 6.51 (s, 1H) 4.26 (s, 2H), 3.94 (s, 2H), 3.80 (t, *J* = 8 Hz, 2H), 2.39 (t, *J* = 8 Hz, 2H). HRMS (ESI Q-TOF) m/z calculated for $C_{23}H_{20}F_2N_6S$ (M + H) 451.1516, found 451.1517.



6-Fluoro-3-((5-((3-methylbenzyl)thio)-4-(2-(1-trityl-1H-imidazol-4-yl)ethyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (121)

According to **General Method** C, a mixture of the thiol **117** (2.59 g, 4.43 mmol) and K_2CO_3 (0.62 g, 4.43 mmol) in DMF (50 mL) was treated dropwise with 3-methylbenzyl bromide (0.6 mL, 4.43) in DMF (5 mL). The DMF was removed under reduced pressure, and the residue was treated with EtOAc (100 mL) and filtered. The EtOAc was washed with 1N NaOH (1 x 50 mL), and H_2O (50 mL), dried (Na_2SO_4), filtered and evaporate. The resulting solid was suspended in H_2O (50 mL), stirred for 1 h, filtered, and dried under vacuum. Recrystallization from EtOH

afforded 0.94 g (31%) of **123:** ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.85 (d, J^{CF} 233 Hz), 154.38, 148.90, 142.20, 137.94, 137.22, 136.14, 136.05, 129.38, 129.09, 128.20, 128.13, 127.90, 125.79, 124.12, 123.55, 119.63, 119.52, 119.11, 74.38, 42.50, 39.29, 27.76, 21.45, 20.76. (HRMS (ESI Q-TOF) m/z calculated for $C_{43}H_{38}FN_6S$ $(M+H)^+$ 689.2863, found 689.2857.



3-((4-(2-(1H-Imidazol-4-yl)ethyl)-5-((3-methylbenzyl)thio)-4H-1,2,4-triazol-3-yl)methyl)-6-fluoro-1H-indole (126)

Using **General Method** D, the trityl-protected 1,2,4-triazole **121 (**700 mg, 1.02 mmol) was dissolved in a mixture of EtOH (30 mL) and 1N HCl (20 mL) and refluxed overnight under nitrogen. The reaction mixture was cooled, filtered, and the EtOH evaporated under reduced pressure. The resulting aqueous phase was basified with 1N NaOH and extracted with CH_2Cl_2 (3 x 50 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organic extracts were washed with H_2O (2 x 100 mL), dried (Na_2SO_4), filtered, and evaporated to yield 186 mg (41%) of **126** as light tan flakes. ^1H NMR (400 MHz, DMSO-d_6) δ 11.79 (s, 1H), 11.20 (s, 1H), 7.52 (s, 1H), 7.13-6.92 (m, 1H), 6.82-6.77 (s, 1H), 6,52 (s, 1H), 4.20 (s, 2H), 3.94 (s, 2H), 3.78 (t, 2H), 2.36 (t, 2H), 2.14 (s, 3H). HRMS (ESI Q-TOF) m/z calculated for $C_{24}H_{24}FN_6S$ $(M+H)^+$ 447.1767, found 447.1762.

Receptor Binding. All chemicals unless otherwise noted were purchased from Sigma-Aldrich (St. Louis, MO.). Competitive radioligand binding experiments were performed for SRIF receptors using Membrane Target Systems™ (Perkin-Elmer, Boston, MA), performed in triplicate. Assessment of human somatostatin SST_{2A} (ES-521-M400UA) and SST_4 (ES-524-M400UA) receptors was performed for all compounds, representing both SRIF receptor families. SST_{2A} is the human splice variant. Subsequent evaluations of SST_1 (ES-520-M400UA), SST_3 (ES-523-M400UA), and SST_5 (ES522M400UA) were conducted for key compounds meeting advancement requirements. SRIF-28 (Tocris, MN, USA. cat#1165) positive control confirmation used with each lot, along with additional control checks that included octreotide (Tocris, cat#1818) for SST_2, and L-803,087 (Tocris, cat#1979) and J-2156 (Tocris, cat#6201) for SST_4 **(Table S3g)** [1]. The respective membrane receptor preparations were suspended in assay buffer (25mM HEPES, 10 mM MgCl2, 1mM CaCl2, 0.5% BSA, pH=7.4) at a 1:150 dilution. Binding assays were performed using ^{125}I-Tyr-SRIF 14 (Perkin-Elmer) dissolved in 1mM HCl. Binding assays were performed in triplicate for each concentration of ligand in a total volume of 200µl (25µl ligand, 25µl radioligand, 150µl receptors) and incubated at room temperature for 90 min using a shaking table. Binding was terminated by filtration through GF/B glass fiber filters that were presoaked in 0.5% polyethyleneimine for a minimum of 4 h. Filters were washed 9 x with 1000 µl ice cold wash buffer (50 mM Tris-HCl, pH=7.4, 0.2% BSA). Filters were scored, transferred into plastic test tubes and counted in a gamma counter (Wizard2, Perkin-Elmer). Determination of the Ki for each compound was performed using non-linear regression with GraphPad Prism 5 software. The 95% confidence intervals for all ligand binding and activity evaluations shown in Supplemental Information matched to the tables within the formal manuscript **(Tables S3a-g)**.

Functional Activity. Measurement of forskolin stimulated inhibition of cAMP was performed via time-resolved fluorescence resonance energy transfer (TR-FRET) LANCE assay (AD0262, PerkinElmer Life Science, Inc., Boston MA), performed in triplicate. Recombinant Chinese hamster ovary (CHO-K1) cells expressing human somatostatin SST_4 cells (ES-524-CF, PerkinElmer Life Science, Inc., Boston MA) were thawed (37°C), resuspended in 10 mL Hanks' balanced salt solution- no phenol red (HBSS, Invitrogen, Carlsbad CA), and then centrifuged (150 x g, 5 min). Cellular pellets were resuspended in stimulation buffer containing HBSS 1x, HEPES 5 mM, Protease free BSA 0.1% (PerkinElmer), and 3-Isobutyl-1-methylxanthine 0.5 mM (pH 7.4) and seeded in 96-well plates at 4000 cells/well. The LANCE cAMP assay was performed per manufacturer instruction (Sigma-Aldrich Co., St. Louis, MO), for respective compounds, against 5 μM forskolin, performed in triplicate. A SRIF-28 control was performed (EC_{50} = 0.21 nM). Fluorescence signal was measured at 2.5 and 20 hr (ex. 340 nm and em. 665 nm, 400-μs delay) via TR-FRET (FLUOstar Omega-F, BMG Labtech, Inc., Cary, NC). Data was calculated using non-linear regression via GraphPad Prism-5 software.

Molecular Modeling. Structure preparation and molecular docking were carried out in Maestro v13.6 using Schrodinger 2023-2 software. Macromolecules were prepared using Protein Preparation Wizard. Hydrogens were added, Epik was used to assign residue pKa's at physiological pH, and loops were refined with Prime. Ligands were prepared using LigPrep, with the OPLS4 forcefield and ionization states at pH 7 +/- 2 using Epik 7. A receptor grid was generated for the experimental structure that consisted of a 10Å3 inner box and a 24Å3 outer box centered around Asp1263.32 and Gln2796.55. Glide standard precision was used to dock the ligands to both macromolecules with and without canonicalization. Ligands were allowed flexibility and nitrogen inversions were sampled, but only trans amide conformations were

allowed. Epik state penalties were added to docking scores. A total of 6,000 poses per ligand were kept from initial Glide screens, and 500 poses per ligand were energy minimized. Post-docking minimization was performed on 30 poses per ligand and the remaining settings were kept as defaults. Final poses were refined using MM-GBSA post-processing. Upon visual inspection, the rotamers of $N199^{ECL2}$ and $Q279^{6.55}$ were changed if more favorable interactions were deemed plausible.

References (*Specific to Supplementary Materials*)

1. W. L. Neumann, K. E. Sandoval, S. Mobayen, M. Minaeian, S. G. Kukielski, K. N. Srabony, R. Frare, O. Slater, S. A. Farr, M. L. Niehoff, A. Hospital, M. Kontoyianni, A. M. Crider and K. A. Witt, *RSC medicinal chemistry*, 2021, **12**, 1352-1365.