SUPPLEMENTAL INFORMATION

Synthesis and Structure-Activity Relationships of 3,4,5-Trisubstituted-1,2,4-Triazoles: High Affinity and Selective Somatostatin Receptor-4 Agonists for Alzheimer's Disease Treatment

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Supplemental Table S1. Off-target actions of compounds 4, 208, 211, 212, and 214.

Receptor	Compound 4 Ki (nM)	Compound 208 Ki (nM)	Compound 211 Ki (nM)	Compound 212 Ki (nM)	Compound 214 Ki (nM)
5-HT1A	-	-	-	-	-
5-HT1B	-	-	-	-	-
5-HT1D	-	-	-	-	-
5-HT1E	-	-	-	-	-
5-HT2A	2086	-	-	2626	-
5-HT2B	-	-	-	1104	-
5-HT2C	-	-	-	1283	-
5-HT3	-	-	795.9	2965	-
5-HT5A	-	-	-	-	-
5-HT6	-	-	-	2472	-
5-HT7A	-	-	-	-	-
Alpha1A	-	-	-	1148	-
Alpha1B	>10000	-	-	3117	-
Alpha1D	-	-	-	-	-
Alpha2A	-	-	-	785.0	-
Alpha2B	-	-	-	-	-
Alpha2C	-	-	-	1263	-
Beta1	-	-	-	-	-
Beta2	-	-	-	6586	-
Beta3	-	-	-	-	-
BZP Rat Brain Site	-	-	-	-	-
D1	-	-	-	3471	-
D2	-	-	-	-	-
D3	-	-	-	-	-
D4	-	-	-	-	-
D5	-	-	-	-	-
DAT	-	-	-	-	-
DOR	>10000	-	-	-	-
GABA-A	-	-	-	-	-
H1	-	-	>10000	2016	-
H2	-	-	-	2167	-
H3	947.0	-	-	1734	487.8
H4	-	-	2034	1455	-
KOR	1735	-	-	918.1	-
M1	-	-	-	-	-
M2	-	-	-	-	-

M3	-	-	-	-	-
M4	-	-	3612	2446	-
M5	-	-	-	-	-
MOR	-	-	2786	2513	-
NET	-	-	-	9644	-
PBR	-	-	6386	>10000	-
SERT	-	-	-	5855	-
Sigma 1	-	-	-	-	-
Sigma 2	-	-	-	494.0	-
HERG	-	-	-	-	-

Off-target receptor binding profiles of compounds **4, 208, 211, 212,** and **214** were generously provided by the National Institute of Mental Health (NIMH) Psychoactive Drug Screening Program (PSPD).[1] Radioligand binding was first measured in the presences of 10 μM of the test compound. A Ki value was determined for receptors at which the test compound showed a > 50% inhibition *(grey box with dash indicates a >50% inhibition at 10 μM was not achieved and is thereby identified as not having any viable affinity for respective receptor*). For experimental details, refer to the PSPD website: https://pdsp.unc.edu/pdspweb/.

Supplemental Table S2. Predictive QSAR model to rank order designed synthetic targets.

Model Set				
Compound	**Observed Ki (nM)**	**Predicted Ki**	**Observed pKi**	**Predicted pKi**
219	653.4	1706.1	6.2	5.8
220	3224.0	2546.8	5.5	5.6
218	22640.0	2051.2	4.6	5.7
162	5.1	2.3	8.3	8.6
172	7.7	12.1	8.1	7.9
163	37.5	76.0	7.4	7.1
165	51.7	13.0	7.3	7.9
167	3.2	11.9	8.3	7.9
213	99.4	136.8	7.0	6.9
214	717.3	120.8	6.1	6.9
ID-34[a]	4471.0	1918.7	5.3	5.7
221[a]	2380.0	1059.3	5.6	6.0
4[a]	19.8	128.2	7.7	6.9
ID-137[a]	1426.0	3062.0	5.8	5.5
ID-139[a]	2032.0	2558.6	5.7	5.6
ID-137[a]	4803.0	3334.3	5.3	5.5
187	0.5	0.2	9.3	9.6
186	2.6	1.4	8.6	8.8
209	58.8	27.7	7.2	7.6
210	80.8	31.1	7.1	7.5
208	0.7	1.6	9.2	8.8
188	0.5	0.3	9.3	9.5
205	7.1	1.7	8.1	8.8
206	6.9	1.8	8.2	8.8
171	39.5	6.3	7.4	8.2
177	945.3	220.8	6.0	6.7
174	14.9	32.1	7.8	7.5
170	36.6	16.7	7.4	7.8
175	386.6	100.7	6.4	7.0
169	30.3	20.4	7.5	7.7
195	0.8	1.1	9.1	9.0
207	1.0	1.6	9.0	8.8
194	1.0	1.0	9.0	9.0
196	0.7	1.1	9.2	9.0
181	3.0	3.0	8.5	8.5
NNC[a]	148.0	44.6	6.8	7.4
190	0.8	9.5	9.1	8.0
198	0.7	1.3	9.1	8.9
200	0.5	1.4	9.3	8.8

201	0.6	1.3	9.2	8.9
193	1.7	1.7	8.8	8.8
192	1.2	1.2	8.9	8.9
183	1.7	11.3	8.8	7.9
189	1.4	6.6	8.8	8.2
202	2.2	7.6	8.7	8.1
180	1.7	3.1	8.8	8.5
182	3.1	4.2	8.5	8.4
185	2.8	13.2	8.6	7.9
204	3.3	13.8	8.5	7.9
197	1.8	2.1	8.5	8.7
203	5.1	8.4	8.3	8.1
211	57.1	11.0	7.2	8.0
212	0.7	8.0	9.2	8.1
158	12.0	40.7	7.9	7.4
173	267.2	73.3	6.6	7.1
159	12.4	15.2	7.9	7.8
166	5.5	11.8	8.3	7.9
160	16.2	24.8	7.8	7.6
164	40.4	85.3	7.4	7.1
168	11.0	10.6	8.0	8.0
179	827.6	957.2	6.1	6.0
176	7.0	17.9	8.2	7.7
Compound 1[b]	6.0	44.6	8.2	7.4
Compound 2[b]	14.0	11.2	7.9	8.0
Compound 3[b]	16.0	14.9	7.8	7.8
Compound 4[b]	23.0	97.9	7.6	7.0
Compound 5[b]	53.0	47.4	7.3	7.3
Compound 6[b]	62.0	24.6	7.2	7.6
Compound 7[b]	70.0	42.4	7.2	7.4
Compound 8[b]	104.0	179.5	7.0	6.7
Compound 9[b]	113.0	266.7	6.9	6.6
Compound 10[b]	0.7	1.5	9.2	8.8
Compound 11[b]	1.2	5.3	8.9	8.3
Compound 12[b]	1.5	2.2	8.8	8.7
Compound 13[b]	3.2	9.8	8.5	8.0
Compound 14[b]	3.6	3.8	8.4	8.4
Compound 15[b]	5.3	10.0	8.3	8.0
Compound 16[b]	6.5	4.1	8.2	8.4
Compound 17[b]	2.9	6.4	8.5	8.2
Compound 18[b]	3.3	5.1	8.5	8.3
Compound 20[b]	660.0	335.7	6.2	6.5
Compound 21[b]	1000.0	304.8	6.0	6.5
Compound 22[b]	1000.0	633.9	6.0	6.2

Compound 23[b]	1200.0	668.3	5.9	6.2
Compound 24[b]	1200.0	2483.1	5.9	5.6
Compound 25[b]	2080.0	6652.7	5.7	5.2
Compound 26[b]	2200.0	3250.9	5.7	5.5
Compound 27[b]	7000.0	3118.9	5.2	5.5
Compound 28[b]	8600.0	23120.6	5.1	4.6
Validation Set				
Compound	**Observed Ki (nM)**	**Predicted Ki**	**Observed pKi**	**Predicted pKi**
BN-VI-42[c]	16470.0	620.9	4.8	6.2
BN-VI-96[c]	11600.0	352.4	4.9	6.5
BN-VII-105[c]	32.1	10.2	7.5	8.0
BN-VII-126[c]	0.8	6.6	9.1	8.2
BN-VII-142[c]	131.8	153.8	6.9	6.8
BN-VII-170[c]	2.6	31.0	8.6	7.5
BN-VII-171[c]	66.6	35.0	7.2	7.5
BN-VII-86[c]	268.9	200.0	6.6	6.7
BN-VII-88[c]	83.1	136.1	7.1	6.9
KI-18A-9[c]	242.9	165.6	6.6	6.8
MM-I-74[c]	1448.0	1300.2	5.8	5.9
199	0.9	1.6	9.0	8.8
RF-I-55[c]	2.0	29.1	8.7	7.5
SK-I-130[c]	3.7	13.3	8.4	7.9
SK-I-132[c]	0.6	1.3	9.2	8.9
SK-I-134[c]	1.3	1.1	8.9	9.0
EP-18[d]	39.5	63.7	7.4	7.2
EP-19[d]	613.0	55.0	6.2	7.3
EP-26[d]	65.0	50.1	7.2	7.3
EP-33[d]	21.7	59.0	7.7	7.2
EP-39[d]	29.1	53.0	7.5	7.3
EP-42[d]	532.0	62.8	6.3	7.2
EP-47[d]	53.2	75.7	7.3	7.1
EP-6[d]	103.9	60.7	7.0	7.2
MCL-11[e]	106.5	50.2	7.0	7.3
MCL-22[e]	3.7	34.1	8.4	7.5
MCL-24[e]	2.9	29.7	8.5	7.5
MCL-25[e]	114.4	43.0	6.9	7.4
MCL-40[e]	37.1	57.9	7.4	7.2
MCL-47[e]	39.9	53.7	7.4	7.3
MCL-49[e]	4.5	47.6	8.3	7.3
MCL-56[e]	100.0	37.7	7.0	7.4
MCL-63[e]	68.9	44.2	7.2	7.4
MCL-78[e]	97.2	37.2	7.0	7.4
MCL-94[e]	15.9	47.2	7.8	7.3

MCL-101[e]	46.2	39.9	7.3	7.4
MCL-107[e]	3.4	43.8	8.5	7.4
MCL-138[e]	70.3	51.4	7.2	7.3
MCL-148 [e]	32.3	43.8	7.5	7.4

[a]From Daryaei et al., 2018 [2]
[b]From Liu, et al.2012 [3]
[c]From internal collection (undisclosed).
[d]From Patent WO2016075239 [4]
[e]From Patent WO2014184275 [5]

Supplemental Table S3. Physiochemical properties.

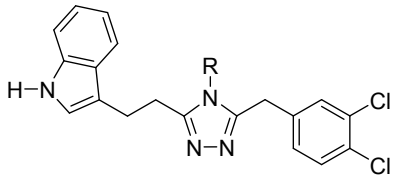
Compound #	MW	cLogP	PSA	HBD /HBA	Efflux Ratio
218	450.8	3.52	72.5	1 / 2	-
221 [a]	464.8	3.84	72.5	1 / 2	-
219	478.9	3.97	72.5	1 / 2	-
220	492.9	4.50	72.5	1 / 2	-
179	320.4	1.20	75.2	2 / 3	-
158	410.5	3.04	75.2	2 / 3	12.2
4 [a]	479.4	4.57	75.2	2 / 3	26.9
165	479.4	4.69	75.2	2 / 3	-
160	446.2	3.55	75.2	2 / 3	-
161	445.0	3.98	75.2	2 / 3	-
162	445.0	3.98	75.2	2 / 3	-
163	445.0	3.77	75.2	2 / 3	-
159	428.5	3.41	75.2	2 / 3	16.8
166	489.4	4.13	75.2	2 / 3	-
167	478.5	4.15	75.2	2 / 3	21.4
169	435.5	2.70	99.0	2 / 4	6.24
170	455.5	3.01	118.3	2 / 3	-
171	440.5	3.01	84.4	2 / 4	-
172	440.5	4.04	84.4	2 / 4	-
173	440.5	4.04	84.4	2 / 4	-
174	491.5	4.30	80.1	2 / 4	-
175	516.6	4.72	84.4	2 / 4	-
176	488.6	1.63	117.7	2 / 5	-
177	486.6	4.93	75.2	1 / 3	-
164	493.4	5.16	64.3	1 / 3	81.6
168	492.5	5.36	60.0	1 / 3	-

213	306.4	0.82	75.2	2 / 3	9.2
180	396.5	2.66	75.2	2 / 3	19.3
190	465.4	4.19	75.2	2 / 3	-
192	465.4	4.31	75.2	2 / 3	-
186	430.9	3.60	75.2	2/ 3	-
187	430.9	3.60	75.2	2 / 3	-
189	430.9	3.60	75.2	2 / 3	28.1
183	414.5	3.03	75.2	2 / 3	32.5
198	426.5	2.81	84.4	2 / 4	9.33
200	426.5	2.81	84.4	2 / 4	16.9
202	426.5	2.81	84.4	2 / 4	17.2
195	464.5	3.77	75.2	2 / 3	15.6
205	421.5	2.32	99.0	2 / 4	-
207	474.6	1.25	117.7	2 / 5	1.8
209	474.6	1.25	117.7	2 / 5	1.4
214	324.4	1.36	75.2	2/3	-
181	414.5	3.20	75.2	2 / 3	19.4
191	483.4	4.51	75.2	2/3	-
193	483.4	4.63	75.2	2/3	-
188	448.9	3.19	75.2	2/3	-
184	432.5	3.34	75.2	2/3	30.7
194	493.37	4.06	75.2	2 / 3	-
196	482.5	4.08	75.2	2 / 3	28.2
206	439.5	2.63	99.0	2/4	-
199	444.5	3.12	84.4	2/4	-
201	444.5	3.12	84.4	2/4	30.1
203	444.5	3.14	84.4	2/4	19.1
208	492.6	1.56	117.7	2/5	2.5
210	492.6	1.56	117.7	2/5	1.1

211	394.5	3.26	75.2	2/3	38.8
212	471.5	3.50	91.0	2/3	16.7
182	426.5	2.91	84.4	2 / 4	5.2
185	444.5	3.05	84.4	2 / 4	22.5
197	494.5	3.79	84.4	2 / 4	10.2
204	456.5	2.83	93.6	2 / 5	6.5

Molecular Weight (MW), cLogP, Polar Surface Area (PSA), Hydrogen binding donator (HBD) / Hydrogen binding acceptor (HBA), and Efflux Ratio for compounds from Tables 1-4 of main manuscript. The cLogP and MW were determined using ChemDraw Professional 17.1, Canvas [6] was employed for model construction and for physicochemical property calculations. Efflux ratio determined by P-glycoprotein efflux ratio determinations performed by Cyprotex US, LLC. (Watertown, MA), using Madin Darby canine kidney (MDCK) cells transfected with the *MDR1* gene, which encodes P-gp.[7] Efflux ratio determined as (B→A) permeability/(A→B) permeability. Efflux evaluations performed in duplicate. [a]Reference [2].

Supplemental Table S4a Evaluation of 4-Aminoalkyl-1,2,4-Triazoles, chain length assessment, with 95% Confidence Intervals. (*MATCHED TO TABLE-1 of main manuscript*)

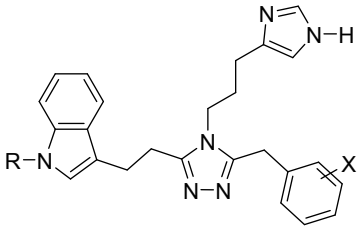


218-221

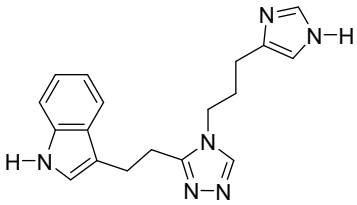
Compound #	R	Binding Affinity Ki (nM) (95% confidence interval)					Activity EC50 (nM) SST_4 (95% confidence interval)
		SST_1	SST_{2A}	SST_3	SST_4	SST_5	
218	$(CH_2)_2NH_2$	-	**>10000**	-	**>10000**	-	-
221 [a]	$(CH_2)_3NH_2$	-	**>10000**	-	**2380** (1463 - 3874)	-	-
219	$(CH_2)_4NH_2$	-	**>10000**	-	**653.4** (513.6 - 831.2)	-	**1065** (497.7 - 2268)
220	$(CH_2)_5NH_2$	-	**>10000**	-	**3224** (2133 - 4873)	-	-

Competitive radioligand binding experiments were performed for SRIF receptors using Membrane Target Systems™ (Perkin-Elmer, Boston, MA). Measurement of forskolin stimulated inhibition of cAMP was performed via time-resolved fluorescence resonance energy transfer (TR-FRET) LANCE assay (PerkinElmer). All evaluations performed in triplicate. Respective Ki and EC50 values determined for each compound was performed using non-linear regression.
[a]Reference [2].

Supplemental Table S4b. Modification of 5-position phenyl of 1,2,4-triazole ring, <u>with 95% Confidence Intervals</u>. (*MATCHED TO TABLE-2 of main manuscript*)



4, 158-177



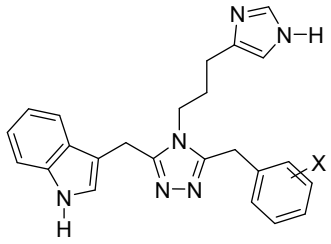
179

Compound #	X	R	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	
179	-	-	-	>10000	-	**827.6** (580.6 - 1179)	-	-
158	H	H	>10000	>10000	>10000	**12.0** (7.9 - 17.9)	>10000	**16.5** (7.4 - 36.9)
4 [a]	3,4-Cl_2	H	**4750** (3491 - 6464)	>10000	**6628** (4709 - 9329)	**19.8** (13.5 - 29.1)	>10000	**6.8** (5.4 - 8.5)
165	3,5-Cl_2	H	-	**6975** (6326 - 7691)	-	**51.7** (39.4 - 67.8)	-	**17.0** (8.5 - 33.9)
160	3,5-F_2	H	>10000	>10000	>10000	**16.2** (12.0 - 22.0)	>10000	**8.8** (3.0 - 25.8)
161	2-Cl	H	>10000	>10000	>10000	**21.5** (16.5 - 28.0)	>10000	**17.3** (8.2 - 36.5)
162	3-Cl	H	**6929** (5425 - 8849)	>10000	>10000	**5.1** (3.1 - 8.3)	>10000	**7.3** (3.9 - 13.6)
163	4-Cl	H	-	>10000	-	**37.5** (24.2 - 58.1)	-	**19.3** (8.7 - 42.8)
159	3-F	H	>10000	>10,000	>10000	**12.4** (7.1 - 21.7)	>10000	**21.0** (12.5 - 35.4)
166	3-Br	H	**4744** (3584 - 6279)	>10000	>10000	**5.5** (3.6 - 8.5)	>10000	**4.4** (1.9 - 10.0)
167	3-CF_3	H	**5309** (4404 - 6399)	>10000	>10000	**3.2** (2.2 - 4.8)	>10000	**6.1** (2.7 - 13.7)

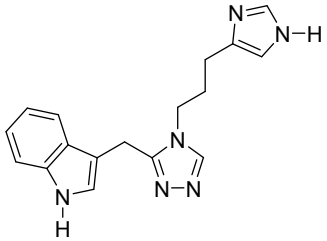
169	**3-CN**	**H**	**-**	**>10000**	**-**	**30.3** (20.2 - 45.5)	**-**	**75.8** (45.4 - 126.3)
170	**3-NO_2**	**H**	**-**	**>10000**	**-**	**36.6** (24.7 - 54.1)	**-**	**98.4** (47.2 - 205.3)
171	**2-OCH_3**	**H**	**>10000**	**>10000**	**>10000**	**39.5** (29.6 - 52.8)	**>10000**	**28.9** (12.6 - 66.3)
172	**3-OCH_3**	**H**	**>10000**	**>10000**	**>10000**	**7.7** (5.0 - 12.0)	**>10000**	**15.6** (8.5 - 28.6)
173	**4-OCH_3**	**H**	-	**>10000**	**-**	**267.2** (196.7 – 363.1)	**-**	-
174	**3-OCF_3**	**H**	**4076** (2684 - 6191)	**>10000**	-	**14.9** (9.6 - 23.2)	**-**	**55.0** (33.2 - 91.0)
175	**3-OBn**	**H**	-	**>10000**	**-**	**386.6** (290.1 -515.2)	**-**	**254.5** (108.7 - 596.0)
176	**3-SO_2CH_3**	**H**	**3653** (2458 - 5431)	**>10000**	**>10000**	**7.0** (4.4 - 11.1)	**>10000**	**22.7** (10.8 - 47.8)
177	**4-C_6H_5**	**H**	-	**>10000**	**-**	**945.3** (757.0 - 1180)	**-**	-
164	**3,4-Cl_2**	**CH_3**	**3172** (2695 - 3733)	**>10000**	**6989** (4317 - 11320)	**40.4** (27.9 - 58.5)	**>10000**	**21.3** (9.5 - 47.9)
168	**3-CF_3**	**CH_3**	**2236** (1738 - 2878)	**>10000**	**>10000**	**11.0** (7.9 - 15.4)	**>10000**	**10.7** (3.9 – 29.2)

Competitive radioligand binding experiments were performed for SRIF receptors using Membrane Target Systems™ (Perkin-Elmer, Boston, MA). Measurement of forskolin stimulated inhibition of cAMP was performed via time-resolved fluorescence resonance energy transfer (TR-FRET) LANCE assay (PerkinElmer). All evaluations performed in triplicate. Respective Ki and EC50 values determined for each compound was performed using non-linear regression.
[a]Reference [2].

Supplemental Table S4c. Impact of 1-C linker to the Indole, identifying SAR contributions with 95% Confidence Intervals. (*MATCHED TO TABLE-3 of main manuscript*)



180, 183, 186-187, 189, 190, 192 195, 200, 202, 205, 207, 209



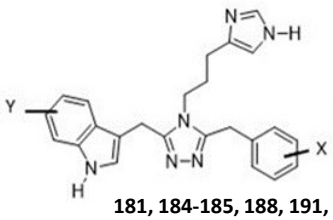
213

Compound #	X	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	
213	**-**	-	**>10000**	**-**	**99.4** (75.0 - 131.6)	**-**	**401.9** (245.9 - 653.7)
180	**H**	**1518** (935.7 - 2461)	**>10000**	**>10000**	**1.7** (1.2 - 2.5)	**>10000**	**2.0** (1.0 - 4.1)
190	**3,4-Cl_2**	-	**3697** (3119 - 4383)	**-**	**0.8** (0.6 - 1.1)	**-**	**0.3** (0.2 - 0.7)
192	**3,5-Cl_2**	-	**5111** (4525 - 5772)	**-**	**1.2** (1.0 - 1.4)	**-**	**1.3** (0.8 - 2.2)
186	**2-Cl**	-	**>10000**	**-**	**2.6** (1.9 - 3.6)	**-**	3.1 (1.7 - 5.7)
187	**3-Cl**	**1235** (1035 - 1474)	**4000** (3218 - 4971)	**4398** (2985 - 6479)	**0.5** (0.4 - 0.7)	**>10000**	**0.1** (0.06 - 2.2)
189	**4-Cl**	**624** (373.7 - 1043)	**7693** (6395 - 9254)	**4072** (2496 - 6643)	**1.4** (0.9 - 2.2)	**>10000**	**1.3** (0.8 - 2.1)
183	**4-F**	**1156** (761.7 - 1756)	**>10000**	**>10000**	**1.7** (1.4 - 2.2)	**>10000**	**1.8** (0.9 - 3.4)
198	**2-OCH_3**	-	**6303** (3627 - 10950)	-	**0.7** (0.6 - 0.9)	**-**	**1.9** (0.8 - 4.9)
200	**3-OCH_3**	-	**9185** (7226 - 11680)	-	**0.5** (0.4 - 0.6)	**-**	**0.5** (0.3 - 0.9)
202	**4-OCH_3**	**2576** (2058 - 3224)	**>10000**	**>10000**	**2.2** (1.4 - 3.5)	**>10000**	**7.3** (4.2 - 12.7)

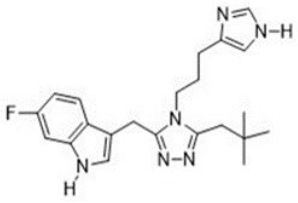
195	**3-CF_3**	**587.6** (491.4 - 702.6)	**>10000**	**2335** (1586 - 3439)	**0.8** (0.7 - 0.9)	**>10000**	**0.6** (0.4 - 0.9)
205	**3-CN**	-	**>10000**	**-**	**7.1** (5.6 - 9.1)	**-**	**10.7** (4.1 - 27.5)
207	**3-SO_2CH_3**	**660.7** (487.0 - 896.3)	**>10000**	**>10000**	**1.0** (0.8 - 1.3)	**>10000**	**3.3** (1.8 - 6.3)
209	**4-SO_2CH_3**	-	**>10000**	**-**	**58.8** (38.6 - 89.7)	**-**	**169.2** (67.7 - 423.2)

Competitive radioligand binding experiments were performed for SRIF receptors using Membrane Target Systems™ (Perkin-Elmer, Boston, MA). Measurement of forskolin stimulated inhibition of cAMP was performed via time-resolved fluorescence resonance energy transfer (TR-FRET) LANCE assay (PerkinElmer). All evaluations performed in triplicate. Respective Ki and EC50 values determined for each compound was performed using non-linear regression.

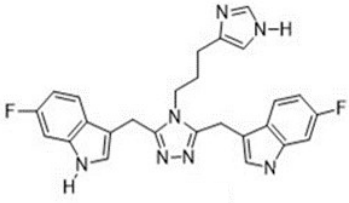
Supplemental Table S4d. Effect of Indole Ring Substitution and Variation of Electronic Substituent Effects, with 95% Confidence Intervals. (*MATCHED TO TABLE-4 of main manuscript*)



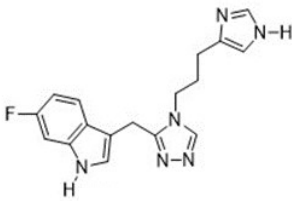
181, 184-185, 188, 191, 197-199, 201, 203-204, 206, 208, 210



211



212



214

Compound #	Y	X	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	
214	**-**	**-**	-	**>10000**	**-**	**717.3** (584.7 - 879.9)	**-**	**1036** (609.2 - 1763)
181	**6-F**	**H**	**1825** (1304 - 2553)	**>10000**	**>10000**	**3.0** (2.2 - 4.1)	**>10000**	**2.8** (1.6 - 4.9)
191	**6-F**	**3,4-Cl_2**	**872.6** (664.7 - 1145)	**1104** (808.0 - 1507)	**1557** (1317 - 1841)	**1.1** (0.8 - 1.4)	**>10000**	**1.0** (0.5 - 1.8)
193	**6-F**	**3,5-Cl_2**	-	**4862** (4031 - 5865)	-	**1.7** (1.3 - 2.2)	**-**	**2.2** (0.8 - 6.0)
188	**6-F**	**3-Cl**	-	**1734** (1540 - 1952)	**-**	**0.5** (0.4 - 0.6)	-	**0.8** (0.4 - 1.5)
184	**6-F**	**4-F**	**468.0** (324.8 - 674.4)	**3969** (3473 - 4536)	**>10000**	**0.9** (0.6 - 1.3)	**>10000**	**3.2** (1.5 - 6.9)
194	**6-F**	**3-Br**	**263.5** (186.2 - 373.0)	**2080** (1774 - 2437)	**2733** (1914 - 3904)	**1.0** (0.9 - 1.2)	**>10000**	**0.3** (0.1 - 0.6)
196	**6-F**	**3-CF_3**	**543.6** (312.2 -946.3)	**3278** (2664 - 4032)	**1613** (1119 - 2325)	**0.7** (0.5 - 1.0)	**6526** (4786-8900)	**0.2** (0.1 - 0.6)
206	**6-F**	**3-CN**	-	**5884** (4946 - 7002)	-	**6.9** (5.3 - 9.1)	-	**7.2** (3.2 - 16.1)
199	**6-F**	**2-OCH_3**	-	**5115** (4404 - 5941)	-	**0.89** (0.7 - 1.1)	-	**0.2** (0.1 - 0.8)
201	**6-F**	**3-OCH_3**	**971.1** (836.6 - 1127)	**5605** (4795 - 6553)	**5404** (4237 - 6892)	**0.6** (0.5 - 0.8)	**>10000**	**0.7** (0.3 - 1.7)
203	**6-F**	**4-OCH_3**	**1080** (843.1 - 1383)	**5304** (4426 - 6356)	**>10000**	**5.1** (3.8 - 6.9)	**>10000**	**6.7** (3.7 - 12.0)
208	**6-F**	**3-SO_2CH_3**	**443.2** (339.3 - 578.9)	**>10000**	**>10000**	**0.7** (0.6 - 0.8)	**>10000**	**2.5** (1.3 - 5.0)

210	**6-F**	**4-SO_2CH_3**	-	**>10000**	**-**	**80.8** (52.0 - 125.5)	-	**846.9** (381.7 - 1879)
211	**-**	**-**	**4336** (3045 - 6176)	**>10000**	**>10000**	**57.1** (45.0 - 72.4)	**>10000**	**77.7** (39.0 - 155.0)
212	**-**	**-**	**97.8** (76.1 - 125.7)	**639.7** (541.3 - 755.9)	**1736** (1351 - 2230)	**0.7** (0.6 - 0.9)	**9335** (8526 - 10220)	**0.7** (0.3 - 1.8)
182	**5-OCH_3**	**H**	**1716** (1258 - 2339)	**7103** (5618 - 8981)	**>10000**	**3.1** (1.9 - 5.1)	**>10000**	**6.0** (3.5 - 10.3)
185	**5-OCH_3**	**4-F**	**1032** (753.4 - 1413)	**5434** (4047 - 7297)	**>10000**	**2.8** (1.7 - 4.6)	**>10000**	**6.0** (2.5 - 14.6)
197	**5-OCH_3**	**3-CF_3**	**365.3** (253.9 - 525.5)	**1693** (1536 - 1866)	1129 (929.2 - 1373)	**1.8** (1.2 - 2.4)	**>10000**	**1.0** (0.4 - 2.7)
204	**5-OCH_3**	**4-OCH_3**	**1011** (661.6 - 1546)	**>10000**	**>10000**	**3.3** (2.0 - 5.4)	**>10000**	**5.6** (2.4 - 13.1)

Competitive radioligand binding experiments were performed for SRIF receptors using Membrane Target Systems™ (Perkin-Elmer, Boston, MA). Measurement of forskolin stimulated inhibition of cAMP was performed via time-resolved fluorescence resonance energy transfer (TR-FRET) LANCE assay (PerkinElmer). All evaluations performed in triplicate. Respective Ki and EC50 values determined for each compound was performed using non-linear regression.

Supplemental Table S4e. Controls with 95% Confidence Intervals.

Control	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	
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)

Competitive radioligand binding experiments were performed for SRIF receptors using Membrane Target Systems™ (Perkin-Elmer, Boston, MA). Measurement of forskolin stimulated inhibition of cAMP was performed via time-resolved fluorescence resonance energy transfer (TR-FRET) LANCE assay (PerkinElmer). All evaluations performed in triplicate. Respective Ki and EC50 values determined for each compound was performed 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.

EXPERIMENTAL METHODS

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. ^1H 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. The following compounds were purchased from Fisher, Combi-Blocks, Aldrich, TCI-America, or Alfa and used without further purification: Urocanic acid, 3-(1*H*-indol-3-yl)propanoic acid, 2-(2-chlorophenyl)acetic acid, 2-(3-chlorophenyl)acetic acid, 2-(4-chlorophenyl)acetic acid, 2-(2-methoxyphenyl)acetic acid, 2-(3-methoxyphenyl)acetic acid, 2-(4-methoxyphenyl)acetic acid, 2-(3,4-dichlorophenyl)acetic acid, 2-(3-fluorophenyl)acetic acid, 2-(3-bromophenyl)acetic acid, 2-(3-(trifluoromethyl)phenyl)acetic acid, 2-(3,5-dichlorophenyl)acetic acid, 2-(3,5-difluorophenyl)acetic acid, 2-([1,1'-biphenyl]-4-yl)acetic acid, 2-(naphthalen-1-yl)acetic acid, 2-(3-trifluoromethoxyphenyl)acetic acid, 2-(4-fluorophenyl)acetic

acid, 2-(3-cyanophenyl)acetic acid, 2-(1*H*-indol-3-yl)acetic acid, 2-(6-fluoro-1*H*-indol-3-yl)acetic acid, Methyl 2-(3-(methylsulfonyl)phenyl)acetate, 2-(3-(Methylsulfonyl)phenyl)acetic acid, 2-(4-(Methylsulfonyl)phenyl)acetic acid, 2-(5-Methoxy-1*H*-indol-3-yl)acetic acid, *tert*-butyl (2-aminoethyl)carbamate, *tert*-butyl (4-aminobutyl)carbamate, *tert*-butyl (5-aminopentyl)carbamate, 3,3-dimethylbutanoic acid.

General Method A. Synthesis of Amide Derivatives (EDC/HOBt Method) 16-26[8]

A mixture of carboxylic acid (1 mmol), EDC•HCl (1.5 mmol), and HOBt•H_2O (1.25 mmol), was dissolved in DMF (40 mL) and stirred at RT for 45 min. To the mixture was added the amine **12-15** (1 mmol) and TEA (2 mmol). The reaction was stirred at RT for 16 h. The product was isolated by either precipitation upon the addition of water, or by the aqueous peptide workup. For the aqueous workup, the reaction mixture was partitioned with EtOAc (200 mL) and H_2O (200 mL). The organic layer was washed with 1N $NaHSO_4$ (100mL), H_2O (100mL), sat. $NaHCO_3$ (100mL), and brine (100mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford the product. The product was dried by azeotropic co-evaporation with toluene (3 x ~30 mL), or by Dean-Stark distillation also with toluene.

2-(1*H*-Indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)acetamide (16): Prepared according to the general method from 2-(1*H*-indol-3-yl)acetic acid (**5**, 953 mg, 5.44mmol), 3-(1-trityl-1*H*-imidazol-4-yl)propane-1-amine[9] (2.00 g, 5.44 mmol), EDC•HCl (1.56 g, 8.16 mmol), HOBt•H_2O (1.04 g, 6.80 mmol), and TEA (1.38 g, 1.90 mL, 13.6 mmol) to afford 2.57 g (90%) of compound **16** as a tan solid which was isolated by water precipitation and dried by co-evaporation with toluene. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.8 (s, 1H), 7.84 (t, *J* = 5.50 Hz, 1H), 7.47 (d, *J* = 7.80 Hz, 1H), 7.35 (m, 9H), 7.26 (d, *J* = 7.70 Hz, 1H), 7.19 (s, 1H), 7.11 (apparent d, *J* = 2.30 Hz, 1H), 7.03 (dd, *J* = 8.30, *J* = 1.40 Hz, 6H), 6.97 (dt, *J* = 6.80, *J* = 0.90 Hz, 1H), 6.84 (dt, *J* = 8.20, *J* =

0.90 Hz, 1H), 6.52 (s, 1H), 3.42 (s, 2H), 2.99 (apparent q, *J* = 6.40 Hz, 2H), 2.34 (t, *J* = 7.40 Hz, 2H), 1.59 (quint., *J* = 7.40 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.00, 142.90, 136.60, 129.71, 128.70, 128.45, 127.70, 124.23, 121.38, 119.15, 118.70, 111.79, 109.53, 74.84, 38.75, 33.31, 29.47, 25.80. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.23 minutes, ESI m/z = 525, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 525.2639 (525.2649 calc'd for $C_{35}H_{33}N_4O$, $[M + H]^+$.

2-(6-Fluoro-1*H*-indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)acetamide (17). Prepared according to the general method from 2-(6-fluoro-1*H*-indol-3-yl)acetic acid (**6**, 2.00 g, 10.4 mmol), amine 3-(1-trityl-1*H*-imidazol-4-yl)propane-1-amine[29] (3.80 g, 10.4 mmol), EDC•HCl (2.98 g, 15.5 mmol), HOBt•H_2O (1.98 g, 12.9 mmol), and TEA (2.10 g, 2.89 mL, 20.7 mmol) to afford 5.24 g (93%) of **17** as a tan solid which was isolated by both water precipitation and aqueous workup and dried by co-evaporation with toluene. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (bs, 1H), 7.89 (t, *J* = 5.48 Hz, 1H), 7.45 (dd, *J* = 8.69, 5.53 Hz, 1H), 7.37 – 7.23 (complex m, 9H), 7.19 (d, *J* = 1.20 Hz, 1H), 7.11 (d, *J* = 2.36 Hz, 1H), 7.06 – 7.01 (m, 7H), 6.73 (ddd, *J* = 11.04, 9.73, 2.33 Hz, 1H), 6.53 (bs, 1H), 3.40 (s, 2H), 2.98 (apparent q, *J* = 6.71 Hz, 2H), 2.35 (t, *J* = 7.44 Hz, 2H), 1.58 (quint., J = 7.19 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.84, 159.28 (d, J_{CF} = 234 Hz), 142.89, 141.15, 138.14, 136.41 (d, J_{CF} = 12.4 Hz), 129.71, 128.70, 128.45, 124.71, (d, J_{CF} = 22.0 Hz), 120.20 (d, J_{CF} = 10.5 Hz), 118.05, 109.84, 107.18 (d, J_{CF} = 23.9 Hz), 97.72 (d, J_{CF} = 25.9 Hz), 74.84, 38.75, 33.22, 29.41, 25.78. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.13 minutes, ESI m/z = 543, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 543.2542 (543.2555 calc'd for $C_{35}H_{33}FN_4O$, $[M + H]^+$.

2-(5-Methoxy-1*H*-indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)acetamide (18). Using general method A**,** 2-(5-methoxy-1*H*-indol-3-yl)acetic acid (**7**, 1.00 g, 4.87 mmol), 3-(1-trityl-1*H*-

imidazol-4-yl)propane-1-amine[9] (1.79 g, 4.87 mmol), EDC•HCl (1.40 g, 7.31 mmol), HOBt•H_2O (933 mg, 6.09 mmol), and TEA (986 mg, 1.36 mL, 9.74 mmol) gave 2.38 g (88%) of **18** as a tan solid which was isolated by water precipitation and dried by Dean-Stark distillation with toluene: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (bs, 1H), 9.94 (bt, *J* ~ 5.0 Hz, 1H), 7.38 – 7.30 (m, 9H), 7.15 (d, *J* = 9.10 Hz, 1H), 7.13 (d, *J* = 2.30 Hz, 1H), 7.07 – 7.03 (m, 8H), 6.64 (d, *J* = 2.30 Hz, 1H), 6.61 (bs, 1H), 3.91 (s, 2H), 3.63 (s, 3H), 3.44 (q, *J* = 6.80 Hz, 2H), 2.40 (t, *J* = 7.40 Hz, 2H), 1.76 (quint., *J* = 7.30 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.01, 153.46, 142.90, 141.7, 138.14, 131.75, 129.71, 128.70, 128.45, 128.00, 124.91, 118.02, 112.40, 111.59, 109.29, 100.96, 74.83, 55.75, 38.76, 33.42, 29.53, 25.83. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.87 minutes, ESI m/z = 555, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 555.2776 (555.2755 calc'd for $C_{36}H_{35}N_4O_2$, $[M + H]^+$).

3-(1*H*-Indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazo-4-yl)propyl)propanamide (19). Following general method A**,** 3-(1*H*-indol-3-yl)propanoic acid **(8**, 5.66 g, 29.9 mmol), 3-(1-trityl-1*H*-imidazol-4-yl)propane-1-amine[9] EDC·HCl (8.60 g, 44.9 mmol), HOBt·H_2O (5.70 g, 37.2 mmol), and Et_3N (6.00 mL, 43.0 mmol) in DMF (80 mL) gave after recrystallization from CH_3CN 11.8 g (73 %) of pure amide **19**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (bs, 1H), 7.78 (t, *J* = 5.50 Hz, 1H), 7.46 (d, *J* = 7.80 Hz, 1H), 7.31-7.38 (complex m, 9H), 7.25 (d, *J* = 7.80 Hz, 1H), 7.20-7.05 (m, 7H), 6.99 (t, *J* = 8.20 Hz, 1H), 6.56 (s, 1H), 2.99 (q, *J* = 5.9 Hz, 2H), 2.85 (t, *J* = 7.70, 2H), 2.34-2.38 (m, 4H), 1.58 (quint., *J* = 7.40 Hz, 2H). ^{13}C (100 MHz, DMSO-d_6) δ 172.20 (s), 141.17 (d), 138.14 (s), 136.71 (s), 129.72 (d), 128.71 (d), 128.47 (d), 127.54 (s), 122.57 (d), 121.36 (d), 118.87 (d), 118.60 (d), 118.11 (d), 114.3 (s), 111.78 (d), 74.85 (s), 38.58 (t), 36.89 (t), 29.37 (t), 25.79 (t), 21.61 (t). LCMS (50-95% CH_3CN in 0.05% TFA over 10 min) retention time = 4.87 min, ESI m/z = 539, $[M+H]^+$.

3-(1-Methyl-1*H*-indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)propanamide (20). Using general procedure A, 3-(1-methyl-1*H*-indol-3-yl)propanoic acid[10] (**9**, 503 mg, 2.47 mmol), 3-(1-trityl-1*H*-imidazol-4-yl)propane-1-amine[29](908 mg, 2.47 mmol), EDC•HCl (592 mg, 3.09 mmol), HOBt•H_2O (476 mg, 3.09 mmol), and TEA (700 □L, 5.00 mmol) gave 650 mg (48%) of **20** as a tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, *J* = 7.80 Hz, 1H), 7.30 – 7.34 (complex multiplets, 10H), 7.28 (d, *J* = 4.50 Hz, 1 H), 7.22 – 7.25 (m, 1H), 7.17 (dt, *J* = 6.80, 0.90 Hz, 1H), 7.08 – 7.11 (m, 5H), 7.02 (dt, *J* = 6.90, 0.90 Hz, 1H), 6.83 (s, 1H), 6.47 (s, 1H), 6.25 (bt, *J* = 4.60 Hz, 1H), 3.66 (t, 3H), 3.22 (apparent q, *J* ~ 6.00 Hz, 2H), 3.07 (t, *J* = 7.30 Hz, 2H), 2.51 (t, *J* = 7.80 Hz, 2H), 2.44 (t, *J* = 7.30 Hz, 2H), 1.72 (quint, *J* = 6.80 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.85, 142.40, 140.61, 138.17, 137.05 129.81, 128.15, 128.01, 126.57, 121.57, 118.93, 118.76, 118.25, 113.72, 109.24, 75.36, 39.11, 37.75, 32.63, 28.55, 25.46, 21.45. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.40 min, ESI m/z = 553, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 553.2961 (553.2962 calc'd for $C_{37}H_{37}N_4O$, $[M + H]^+$).

***(R)-tert*-Butyl (3-(1*H*-indol-3-yl)-1-oxo-1-((3-(1-trityl-1*H*-imidazol-4-yl)propyl)amino)-propan-2-yl)carbamate (21):** Following general method A, *N*-Boc-D-Trp (**10**, 597 mg, 1.96 mmol), EDC·HCl (470 mg, 2.45 mmol), HOBt·H_2O (375 mg, 2.45 mmol), 3-(1-trityl-1*H*-imidazol-4-yl)propane-1-amine[9] (720 mg, 1.96 mmol) and Et_3N (400 μL, 2.87 mmol) in DMF (30 mL) gave 1.02 g (80%) of **21** as a tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (bs, 1H), 7.84 (t, *J* = 6.00 Hz, 1H), 7.71 (d, *J* = 8.30 Hz, 1H), 7.32-7.39 (complex m, 10H), 7.27 (m, 2H), 7.20 (d, *J* = 0.90 Hz, 1H), 7.03-7.06 (m, 3H), 6.97 (t, *J* = 7.30 Hz, 1H), 6.89 (t, *J* = 6.80 Hz, 1H), 6.69 (d, *J* =8.20 Hz, 1H), 6.54 (s, 1H), 4.08 (dt, *J* = 8.70, 5.00 Hz, 1H*),* 2.95-3.02 (m, 3H), 2.80-2.86 (m, 1H), 2.33 (t, *J* = 7.30 Hz, 2H), 1.56 (quint, *J* = 7.30 Hz, 2H). LCMS (50-95% CH_3CN inn 0.05% TFA over 10 min) retention time = 5.88 min, ESI m/z = 654 $[M + H]^+$.

***tert*-Butyl (4-(2-(1*H*-indol-3-yl)acetamido)butyl)carbamate (22).** According to general procedure A, 2-(1H-indol-3-yl)acetic acid (**5**, 961 mg, 5.49 mmol), *tert*-butyl (4-aminobutyl)carbamate (**13**, 1.03 g, 5.49 mmol), EDC•HCl (1.58 g, 8.24 mmol), HOBt•H_2O (1.26 g, 8.24 mmol), and TEA (2.3 mL) afforded 1.87 g (99%) of **22** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (bs, 1H), 7.77 (t, *J* = 5.5 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.29 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.12 (s, 1H), 7.02 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.92 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.69 (bt, *J* = 5.4 Hz, 1H), 3.44 (s, 2H), 2.98 (apparent q, *J* = 6.0 Hz, 2H), 2.85 (apparent q, *J* = 5.7 Hz, 2H), 1.33 (s, 9H), 1.33 – 1.30 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.01, 156.12, 136.65, 127.79, 124.21, 121.41, 119.18, 118.77, 111.81, 109.54, 77.86, 38.96, 33.26, 28.82, 27.54, 27.10 (two Cs). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.20 min, ESI m/z = 346, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 346.2145 (346.2125 calc'd for $C_{19}H_{28}N_3O_3$), $[M + H]^+$.

***tert*-Butyl (2-(3-(1*H*-indol-3-yl)propanamido)ethyl)carbamate (23).** Prepared according to general procedure A from 3-(1*H*-indol-3-yl)propanoic acid (**8**, 3.00 g, 15.9 mmol), *tert*-butyl (2-aminoethyl)carbamate (**14**, 3.00 g, 20.8 mmol), EDC•HCl (4.56 g, 23.8 mmol), HOBt•H_2O (3.64 g, 23.8 mmol), and TEA (3.50 mL, 25.1 mmol) to afford 5.12 g (97%) of **23** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.84 (t, *J* = 5.6 Hz, 1H), 7.47 (dt, *J* = 7.8, 0.8 Hz, 1H), 7.28 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.07 – 6.98 (m, 2H), 6.92 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 6.75 (t, *J* = 5.5 Hz, 1H), 3.02 (apparent q, *J* = 6.3 Hz, 2H), 2.96 – 2.81 (m, 4H), 2.41 – 2.34 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.58, 156.15, 136.75, 122.59, 121.42, 118.85, 118.64, 114.38, 111.84, 78.18, 39.23, 36.90, 28.76, 21.55 (one carbon obscured by DMSO peak at ~40). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.87 min,

ESI m/z = 332, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 332.1978 (332.1969 calc'd for $C_{18}H_{26}N_3O_3$, $[M + H]^+$).

***tert*-Butyl (4-(3-(1*H*-indol-3-yl)propanamido)butyl)carbamate (24).** Following general procedure A, 3-(1*H*-indol-3-yl)propanoic acid (**8**, 1.00 g, 5.29 mmol), *tert*-butyl (4-aminobutyl)carbamate (**13**, 1.10 g, 5.82 mmol), EDC•HCl (1.52 g, 7.93 mmol), HOBt•H_2O (1.21 g, 7.93 mmol), and TEA (1.50 mL, 10.8 mmol) gave 1.90 g (100%) of **24** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (bs, 1H0, 7.59 (d, *J* = 7.80 Hz, 1H), 7.36 (d, *J* = 8.20 Hz, 1H), 7.17 (t, *J* = 7.30 Hz, 1H), 7.09 (t, *J* = 7.20 Hz, 1H), 6.99 (d, *J* = 1.40 Hz, 1H),5.47 (bs, 1H), 4.59 (bs, 1H), 3.09 – 3.13 (m, 4H), 2.97 – 3.02 (m, 2H), 2.54 (t, *J* = 6.90 Hz, 2H), 1.45 9s, 9H), 1.17 – 1.31 (complex multiplets, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.05, 156.39, 136.51, 127.09, 122.33, 121.98, 118.71, 114.53, 111.47, 79.51, 40.30, 39.12, 37.60, 28.57, 27.69, 26.79, 21.68. LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.83 min, ESI m/z = 360, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 360.2297 (360.2282 calc'd for $C_{20}H_{30}N_3O_3$), $[M + H]^+$.

***tert*-Butyl (5-(3-(1*H*-indol-3-yl)propanamido)pentyl)carbamate (25).** Prepared according to general procedure A from 3-(1*H*-indol-3-yl)propanoic acid (**8**, 1.00 g, 5.29 mmol), *tert*-butyl (5-aminopentyl)carbamate (**15**, 1.18 g, 5.82 mmol), EDC•HCl (1.52 g, 7.93 mmol), HOBt•H_2O (1.21 g, 7.93 mmol), and TEA (2.0 mL, 14.3 mmol) to yield 1.99 g (100% yield) of **25** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (bs, 1H), 7.58 (d, *J* = 7.80 Hz, 1H), 7.38 (d, *J* = 7.80 Hz, 1H), 7.17 (dt, *J* = 6.90, 1.00 Hz, 1H), 7.09 (dt, *J* = 7.80, 0.90 Hz, 1H), 7.00 (d, *J* = 2.30 Hz, 1H), 5.34 (bs, 1H), 4.62 (bs, 1H), 3.07 – 3.13 (m, 4H), 3.02 (apparent q, *J* ~ 6.75 Hz, 2H), 2.54 (t, *J* = 7.30 Hz, 2H), 1.46 (s, 9H), 1.33 (quint, *J* = 7.30 Hz, 2H), 1.20 – 1.26 (m, 2H), 0.93 – 1.01 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.05, 156.49, 136.67, 127.02, 122.42, 121.86, 119.17, 118.60,

114.21, 111.57, 79.57, 40.50, 39.16, 37.59, 30.05, 29.15, 28.55, 23.70, 21.72. LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.12 min, ESI m/z = 374, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 374.2448 (374.2438 calc'd for $C_{21}H_{32}N_3O_3$), $[M + H]^+$.

3,3-Dimethyl-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)butanamide (26). Following general method A, 3,3-dimethylbutanoic acid (**11**, 1.00 g, 8.61 mmol), 3-(1-trityl-1*H*-imidazol-4-yl)propane-1-amine[9] (3.0 g, 8.61 mmol), EDC•HCl (2.48 g, 12.9 mmol), HOBt•H_2O (1.65 g, 10.8 mmol), and TEA (1.74 g, 2.40 mL, 17.2 mmol). afforded 3.10 g (77%) of **26** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (t, *J* = 5.10 Hz, 1H), 7.35 (m, 9H), 7.20 (apparent d, *J* = 1.40 Hz, 1H), 7.04 (dd, *J* = 8.90, *J* = 2.60 Hz, 6H), 6.56 (apparent d, *J* = 1.40 Hz, 1H), 2.96 (q, *J* = 6.90 Hz, 2H), 2.37 (t, *J* = 7.40 Hz, 2H), 1.87 (s, 2H), 1.58 (quint., *J* = 7.30 Hz, 2H), 0.88 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.07, 142.90, 141.15, 138.17, 129.71, 128.70, 128.46, 118.09, 74.84, 49.38, 38.37, 30.88, 30.21, 29.45, 25.81. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.93 minutes, ESI m/z = 466, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 466.2855 (466.2853 calc'd for $C_{31}H_{36}N_3O$), $[M + H]^+$.

General Method B. Synthesis of Thioamides 27-37.

A mixture of amide (1 mmol, azeotropically dried by coevaporation with toluene) and Lawesson's Reagent (0.65 mmol) were dissolved in THF (35 mL), heated to reflux and stirred until the reaction complete as determined by TLC analysis (4-6h). The mixture was cooled and concentrated to afford crude product. The product was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH or $CHCl_3$/MeOH mixtures). **Synthesis of Thioamides. Non-Chromatographic Workup:** When the reaction was complete, the mixture was allowed to cool to RT, treated with hydrazine monohydrate (2 equiv.) and stirred at RT for 30 min. The mixture was partitioned with EtOAc and water. The layers were separated and the EtOAc layer was washed with water and

brine. The EtOAc layer was then stirred with decolorizing carbon (2g per 1 mmol) for 1 hour. Anhyd. Na_2SO_4 was added and the mixture was stirred for 10 min longer and filtered through celite. Evaporation of the EtOAc afforded thioamides that were pure enough to be used directly in the next step.

***tert*-Butyl (4-(2-(1*H*-indol-3-yl)ethanethioamido)butyl)carbamate (27).** Prepared according to general method B from amide (**22**, 1.87 g, 5.41 mmol) and Lawesson's reagent (1.31 g, 3.25 mmol). The non-chromatographic workup afforded 1.66 g (85%) of compound **27** as a colorless foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (bs, 1H), 9.89 (t, *J* = 4.28 Hz, 1H), 7.55 (d, *J* = 7.92 Hz, 1H), 7.29 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.01 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 6.92 (ddt, *J* = 7.8, 7.0, 0.9 Hz, 1H), 6.75 (t, *J* = 5.8 Hz, 1H), 3.96 (s, 2H), 3.42 (q, *J* = 6.6 Hz, 2H), 2.85 (q, *J* = 6.6 Hz, 2H), (quint., *J* = 7.5 Hz, 2H), 1.35-1.27 (obscured m, 2H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 202.10, 156.12, 136.61, 127.52, 124.50, 121.46, 119.33, 118.88, 111.88, 110.65, 77.91, 45.70, 42.79, 29.94, 28.81, 27.59, 25.16. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.17 min, ESI m/z = 362, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 362.1884 (362.1897 calc'd for $C_{19}H_{28}N_3O_2S$), $[M + H]^+$.

***tert*-Butyl (2-(3-(1*H*-indol-3-yl)propanethioamido)ethyl)carbamate (28).** Prepared according to general method B from amide (**23**, 4.74 g, 14.3 mmol) and Lawesson's reagent (3.18 g, 7.86 mmol). Purification by flash chromatography (SiO_2, 3:1 hexanes/EtOAc to 1:1) afforded 3.86 g (78%) of **28** as a yellow foam (this material was taken on to the triazole formation reaction without further purification): LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.45 min, ESI m/z = 348, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 348.1741 (348.1740 calc'd for $C_{18}H_{26}N_3O_2S$), $[M + H]^+$.

***tert*-Butyl (4-(3-(1*H*-indol-3-yl)propanethioamido)butyl)carbamate (29).** Prepared according general method B from amide (**24**, 654 mg, 1.82 mmol) and Lawesson's reagent (404 mg, 1.00 mmol). Purification by flash chromatography (SiO_2, 1:1 hexanes/EtOAc) afforded 471 mg (69%) of **29** as a yellow foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 7.61 (d, *J* = 7.80 Hz, 1H), 7.39 (d, *J* = 8.30 Hz, 1H), 7.32 (bs, 1H), 7.18 (dt, *J* = 7.10, 0.90 Hz, 1H), 7.10 (dt, *J* = 7.80, 0.90 Hz, 1H), 7.01 (s, 1H), 4.56 (bs, 1H), 3.46 (apparent q, *J* = 5.95 Hz, 2H), 3.25 (t, *J* = 6.90 Hz, 2H), 3.02 (t, *J* = 6.90 Hz, 2H), 2.95 (bt, *J* ~ 6.40 Hz, 1H), 1.46 (s, 9H), 1.27 – 1.34 (m, 2H), 1.10 – 1.18 (m, 2H). LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.78 min, ESI m/z = 376, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 372.2059 (376.2053 calc'd for $C_{20}H_{30}N_3O_2S$), $[M + H]^+$.

***tert*-Butyl (5-(3-(1*H*-indol-3-yl)propanethioamido)pentyl)carbamate (30).** Prepared from general method B from amide (**25**, 1.99 g, 5.33 mmol) and Lawesson's reagent (1.19 g, 2.93 mmol). Purification by flash chromatography (SiO_2, 40:1 to 20:1 CH_2Cl_2/MeOH) afforded 470 mg (78%) of **30** as a yellow foam (this material was taken on to the triazole formation reaction "as is"): LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.17 min, ESI m/z = 390, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 390.2205 (390.2210 calc'd for $C_{21}H_{32}N_3O_2S$), $[M + H]^+$.

2-(1*H*-Indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)ethanethioamide (31). Using general method B, (**16**, 2.08 g, 3.96 mmol) and Lawesson's reagent (1.04 g, 2.58 mmol), afforded ~3.4 g crude material as a brown foam. Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) afforded 1.52 g (71%) of compound **31** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (bs, 1H), 9.90 (t, *J* = 5.03 Hz, 1H), 7.53 (d, *J* = 7.80 Hz, 1H), 7.38 – 7.28 (m, 10H), 7.26 (d, *J* = 7.99 Hz, 1H), 7.16 (d, *J* = 2.31 Hz, 1H), 7.05 -7.02 (m, 6H), 6.97

(dt, *J* = 7.02, 0.58 Hz, 1H), 6.84 (dt, *J* = 7.89, 0.80 Hz, 1H), 6.57 (bs, 1H), 3.95 (s, 2H), 3.45 - 3.39 (m, 2H), 2.38 (t, *J* = 7.33 Hz, 2H), 1.75 (quint., *J* = 7.31, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 202.17, 142.56, 138.00, 136.61, 129.72, 128.78, 128.57, 127.47, 124.54, 121.43, 119.27, 118.82, 118.54, 111.86, 110.60, 75.36, 45.42, 42.86, 27.31, 25.23. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.53 minutes, ESI m/z = 541, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 541.2443 (541.2420 calc'd for $C_{35}H_{33}N_4S$), $[M + H]^+$

2-(6-Fluoro-1*H*-indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)ethanethioamide (32). Prepared according to the general method B from (**17**, 4.19 g, 7.72 mmol) and Lawesson's reagent (2.03 g, 5.02 mmol), which afforded ~8.5 g crude material as a brown foam. Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) afforded 2.76 g (64%) of **32** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (bs, 1H), 9.90 (t, *J* = 4.95 Hz, 1H), 7.52 (dd, *J* = 8.70, 5.53 Hz, 1H), 7.39 – 7.31 (complex m, 9H), 7.16 (d, *J* = 2.30 Hz, 1H), 7.08 – 7.03 (m, J = 7H), 6.73 73 (ddd, *J* = 11.05, 8.80, 2.32 Hz, 1H), 3.93 (s, 2H), 3.42 (apparent q, *J* = 6.65 Hz, 2H), 2.42 (t, *J* = 7.43 Hz, 2H), 1.76 (quint., *J* = 7.36 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 201.98, 159.30 (d, J_{CF} = 234.1 Hz), 142.56, 139.73, 137.99, 136.44 (d, J_{CF} = 12.7 Hz), 129.72, 128.78, 128.57, 125.11, 124.36, 120. 30 (d, J_{CF} = 10.3 Hz), 118.53, 110.95, 107.29 (d, J_{CF} = 24.3 Hz), 97.80 (d, J_{CF} = 25.7 Hz), 75.40, 45.44, 42.72, 27.26, 25.22. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.75 minutes, ESI m/z = 559, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 559.2329 (559.2326 calc'd for $C_{35}H_{32}FN_4S$), $[M + H]^+$.

2-(5-Methoxy-1*H*-indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)ethanethioamide (33). Following general method B, (**18**, 2.00 g, 3.61 mmol) and Lawesson's reagent (0.95 g, 2.34 mmol) afforded crude material as a brown oil after 3 h of reflux (reaction determined to be complete by LCMS). The crude was purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 30:1, to

20:1) which afforded 1.37 g of **33** as a tan foam (67%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (bs, 1H), 9.94 (bt, *J* ~ 5.0 Hz, 1H), 7.38 – 7.30 (m, 9H), 7.15 (d, *J* = 9.10 Hz, 1H), 7.13 (d, *J* = 2.30 Hz, 1H), 7.07 – 7.03 (m, 8H), 6.64 (d, *J* = 2.30 Hz, 1H), 6.61 (bs, 1H), 3.91 (s, 2H), 3.63 (s, 3H), 3.44 (q, *J* = 6.80 Hz, 2H), 2.40 (t, *J* = 7.40 Hz, 2H), 1.76 (quint., *J* = 7.30 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 202.13, 153.50, 142.65, 138.07, 131.71, 129.71, 128.76, 128.53, 127.76, 125.20, 118.39, 112.50, 111.57, 110.33, 101.15, 75.19, 55.78, 45.49, 42.94, 27.43. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.32 minutes, ESI m/z = 571, $[M+H]^+$.

3-(1*H*-Indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)propanethioamide (34). Prepared according to the general method B from (**19**, 6.46 g, 12.0 mmol) and Lawesson's reagent (3.15 g, 7.80 mmol). Purification by flash chromatography (SiO_2, 10:1 CH_2Cl_2/MeOH) afforded 3.34 g (50%) of thioamide **34** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) revealed that the sample contains a small amount of inseparable imidothioic phosphonate intermediate adduct of the starting amide with Lawesson's reagent *(*ESI m/z = 741, $[M+H]^+$); desired thioamide component: δ 10.73 (bs, 1H), 9.96 (t, *J* = 5.10 Hz, 1H), 7.50 (d, *J* = 7.80 Hz, 1H), 7.34 – 7.40 (complex multiplets, 10H), 7.26 (d, *J* = 7.80 Hz, 1H), 7.05 – 7.09 (m, 6H), 6.99 (t, *J* = 7.70 Hz, 1H), 6.90 (t, *J* = 7.70 Hz, 1H), 3.43 (apparent q, *J* = 6.00 Hz, 2H), 3.02 (apparent t, *J* = 7.80 Hz, 2H), 2.82 (apparent t, *J* = 7.75 Hz, 2H), 2.42 (t, *J* = 6.80 Hz, 2H), 1.76 (quint, *J* = 7.30 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 203.79 (s), 142.45 (s), 137.93 (s), 136.70 (d), 129.74 (d), 128.83 (d), 128.63 (d), 127.54 (s), 122.75 (d), 121.41 (d), 118.91 (d), 118.64 (d), 113.86 (s), 111.83 (s), 75.53 (s), 46.51 (t), 45.22 (t), 27.15 (t), 25.67 (t), 25.02 (t). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.85 min, ESI m/z = 555, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 555.2582 (555.2577 calc'd for $C_{36}H_{34}N_4S$, $[M + H]^+$.

3-(1-Methyl-1*H*-indol-3-yl)-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)propanethioamide (35). Prepared using general method B from (**20**, 620 mg, 1.12 mmol) and Lawesson's reagent (295 mg, 0.73 mmol). Purification by flash chromatography (SiO_2, 40:1 to 20:1 CH_2Cl_2/MeOH) gave 470 mg (78%) of compound **35** as a yellow foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (bt, J ~ 5.00 Hz, 1H), 7.51 (d, J = 8.20 Hz, 1H), 7.30 – 7.39 (complex multiplets, 10H), 7.27 (t, J = 8.20 Hz, 1H), 7.02 – 7.06 (m, 7H), 6.93 (t, J = 7.30 Hz, 1H), 6.60 (s, 1H), 3.62 (s, 3H), 3.42 (apparent q, J ~ 6.20 Hz, 2H), 3.01 (t, J = 7.40 Hz, 2H), 2.79 (t, J = 7.30 Hz, 2H), 2.36 (t, J = 7.30 Hz, 2H), 1.73 (quint, J = 7.30 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 203.59, 142.71, 140.29, 138.09, 137.08, 129.73, 128.77, 128.53, 127.85, 127.25, 121.53, 119.16, 118.73, 118.39, 113.15, 109.98, 75.13, 46.56, 45.33, 40.69, 32.70, 27.27, 25.45. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.40 min, ESI m/z = 569, $[M+H]^+$.

***(R)-tert*-Butyl (3-(1*H*-indol-3-yl)-thioxo-1-((3-(1-trityl-1*H*-imidazol-4-yl)propyl)amino)propan-2-yl)carbamate (36)**. Using the general method, **(21**, azeotropically dried by co-evaporation with toluene, 450 mg, 0.69 mmol) and Lawesson's reagent (240 mg, 0.59 mmol) in THF (40 mL) was heated at 65 °C for 4 h. The resulting mixture was allowed to cool to room temperature and concentrated. Purification by flash column chromatography (SiO_2, 1:1 hexanes/EtOAc) afforded 289 mg (58%) of **36** as an orange-brown foam: LCMS (50-95% CH_3CN in 0.05% TFA over 10 min) retention time = 6.81 min, ESI m/z = 670, $[M+H]^+$.

3,3-Dimethyl-*N*-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)butanethioamide (37). Prepared according general method B from (**26**, 2.95 g, 6.34 mmol) and Lawesson's reagent (1.67 g, 4.12 mmol), which afforded ~5.5 g crude material as a brown oil. Purification by flash chromatography (SiO_2, 80:1 CH_2Cl_2/MeOH to 40:1) afforded 1.32 g (43%) of **37** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (bs, 1H), 7.40-7.30 (complex m, 9H), 7.22 (apparent d, J = 1.3 Hz, 1H),

7.05-7.03 (complex m, 6H) 6.58 (apparent d, J = 1.4 Hz, 1H), 3.40 (q, J = 5.4 Hz, 2H), 2.45 (s, 2H), 2.43 (obs. d, J = 6.9 Hz, 2H), 1.76 (quint. J = 6.9 Hz, 2H), 0.91 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 201.12, 142.86, 140.73, 138.23, 129.72, 128.72, 128.47, 118.25, 74.88, 58.64, 45.37, 31.81, 30.19, 27.39, 25.84. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.13 minutes, ESI m/z = 482, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 482.2634 (482.2624 calc'd for $C_{31}H_{36}N_3S$), $[M + H]^+$.

General Method C. Synthesis of Boc-Protected Acyl Hydrazides 56-75.

A mixture of the carboxylic acid (1.00 mmol), EDC·HCl (1.25 mmol), HOBt·H_2O (1.25 mmol) in DMF (50 mL) was stirred at RT for 30 min. The resulting mixture was treated with *tert*-butyl hydrazinecarboxylate (1.25 mmol) and TEA (5 mL) and stirred for 16 h. The solvent was evaporated and the residue was partitioned between EtOAc (150 mL) and 1N $NaHSO_4$ (150 mL). The layers were separated and organic layer was washed with H_2O (150 mL), sat. $NaHCO_3$ (150 mL) and brine (150 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered, and concentrated.

***tert*-Butyl 2-(2-(3-fluorophenyl)acetyl)hydrazinecarboxylate (56).** Prepared according to general method C from 2-(3-fluorophenyl)acetic acid (**38**, 3.07 g, 19.9 mmol) and *tert*-butyl hydrazinecarboxylate (3.29 g, 24.9 mmol) to afford 5.14 g (96%) of compound **56** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (bs, 1H), 8.77 (bs, 1H), 7.31 (apparent q, J_{HF} ~ 6.90, J_{HH} ~ 6.90 Hz, 1H), 7.01 – 7.08 (m, 3H), 3.41 (s, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.68, 163.03 (d, J_{CF} = 247.3 Hz), 155.44, 136.01 (d, J_{CF} = 7.60 Hz), 130.58 (d, J_{CF} = 8.60 Hz), 125.16 (d, J_{CF} = 2.90 Hz), 116.51 (d, J_{CF} = 22.0 Hz), 114.64 (d, J_{CF} = 21.1 Hz), 82.2, 41.07, 28.19. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.98 min, ESI m/z

= 269, $[M+H]^+$, m/z = 537 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 269.1274 (269.1296 calc'd for $C_{13}H_{17}FN_2O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(4-Fluorophenyl)acetyl)hydrazinecarboxylate (57).** Using general C, 2-(4-fluorophenyl)acetic acid (**39**, 2.00 g, 13.0 mmol) and *tert*-butyl hydrazinecarboxylate (2.13 g, 16.1 mmol) gave 3.34 g (97% yield) of compound **57** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (bs, 1H), 8.71 (bs, 1H), 7.25 (apparent dd, J_{HF} = 8.65, 5.70 Hz, 2H), 7.08 (apparent t, J_{HF} = 8.96 Hz, 2H), 3.36 (s, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.08, 161.61 (d, J_{CF} = 241.9 Hz), 155.78, 132.33 (d, J_{CF} = 2.81 Hz), 131.36 (d, J_{CF} = 7.99 Hz), 115.43 (d, J_{CF} = 21.19 Hz), 79.62, 28.56. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.08 min, ESI m/z = 537, $[2M + H]^+$, 269 $[M + H]^+$.

***tert*-Butyl 2-(2-(3,5-difluorophenyl)acetyl)hydrazinecarboxylate (58).** Prepared according to general method C from 2-(3,5-difluorophenyl)acetic acid (**40**, 3.00 g, 17.4 mmol) and *tert*-butyl hydrazinecarboxylate (2.88 g, 21.8 mmol) to afford 3.05 g (61%) of **58** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (bs, 1H), 6.87 – 6.81 (m, 2H), 6.71 (tt, $^3J_{H,F}$ = 9.00 Hz, J = 2.40 Hz, 1H), 6.62 (bs, 1H), 3.35 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.11, 163.18 (dd, J_{CF} = 249.2 Hz, J_{CF} = 12.9 Hz), 155.59, 137.37 (t, J_{CF} = 9.6 Hz), 112.43 (dd, J_{CF} = 25.96 Hz, J_{CF} = 6.82 Hz), 103.13 (t, J_{CF} = 25.10 Hz), 82.36, 40.70, 28.18. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.45 min, ESI m/z = 287, $[M+H]^+$, m/z = 573 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 287.1173 (287.1202 calc'd for $C_{13}H_{17}F_2N_2O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(2-chlorophenyl)acetyl)hydrazinecarboxylate (59)**. Following general method C, 2-(2-chlorophenyl)acetic acid (**41**), 3.01 g, 17.6 mmol) and *tert*-butyl hydrazinecarboxylate (2.91 g, 22.1 mmol) gave 2.30 g (46% yield) of **59** as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.77 (s, 1H), 7.33-7.41 (m, 2H), 7.20-7.29 (m, 2H), 3.53 (s, 2H), 1.35 (s, 9H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 169.17, 155.74, 134.00, 132.32, 129.49, 129.06, 127.53, 79.61, 55.03, 38.03, 28.57. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.47 min, (ESI) m/z = 285, $[M+H]^+$, m/z = 569, $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 285.0977 (285.1000 calc'd for $C_{13}H_{18}ClN_2O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(3-chlorophenyl)acetyl)hydrazinecarboxylate (60).** Using general method C, 2-(3-chlorophenyl)acetic acid (**42**, 3.17 g, 18.6 mmol) and *tert*-butyl hydrazinecarboxylate (3.07 g, 23.3 mmol) gave 5.25 g (99%) of **60** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (bs, 1H), 7.24 (m, 2H), 7.17 – 7.19 (m, 1H), 6.64 (bs, 1H), 3.55 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.71 (s), 155.60 (s) 135.75 (s), 134.72 (s), 130.23 (d), 129.55 (d), 127.77 (d), 127.63 (d), 82.21 (s), 40.84 (t), 28.20 (q). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.73 min, (ESI) m/z = 285, $[M+H]^+$, m/z = 569 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 285.0984 (285.1000 calc'd for $C_{13}H_{18}ClN_2O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(4-chlorophenyl)acetyl)hydrazinecarboxylate (61).**[11] Prepared according to general method C from 2-(4-chlorophenyl)acetic acid (**43**, 3.00 g, 17.6 mmol) and *tert*-butyl hydrazinecarboxylate (2.91 g, 22.0 mmol) to yield 4.91 g (98%) of **61** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) □ 9.79 (bs, 1H), 8.75 (bs, 1H), 7.33 (d, J = 8.70 Hz, 2H), 7.25 (d, J = 8.70 Hz, 2H), 3.30 (s, 2H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.87, 155.45, 132.16, 130.79, 129.19, 82.18, 40.68, 28.18. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.65 min, ESI m/z = 285, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 285.0971 (285.1000 calc'd for $C_{13}H_{18}ClN_2O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(3,4-dichlorophenyl)acetyl)hydrazinecarboxylate (62).** Prepared according to general method C from 2-(3,4-dichlorophenyl)acetic acid (**44**, 2.43 g, 11.9 mmol) and *tert*-butyl hydrazinecarboxylate (1.97 g, 14.9 mmol) to afford 3.61g (95%) of **62** as a white solid: ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.95 (bs, 1H), 7.39 (d, *J* = 2.30 Hz, 1H), 7.38 (d, *J* = 8.30 Hz, 1H), 7.14 (dd, *J* = 8.30, 2.30 Hz, 1H), 6.67 (bs, 1H), 3.51 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.31, 155.51, 133.87, 132.93, 131.84, 131.36, 130.88, 128.81, 82.35, 40.17, 28.19. LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.10 min, ESI m/z = 319, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 319.0589 (319.0611 calc'd for $C_{13}H_{17}Cl_2N_2O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(3,5-dichlorophenyl)acetyl)hydrazinecarboxylate (63).** Following general method C, 2-(3,5-dichlorophenyl)acetic acid (**45**, 5.06 g, 24.7 mmol) and *tert*-butyl hydrazinecarboxylate (3.26 g, 24.7 mmol) gave 6.81 g (86%) of compound **63** as a white solid: ^1H NMR (400 MHz, $CDCl_3$) □ 7.96 (bs, 1H), 7.26 (t, *J* = 2.0 Hz, 1H), 7.19 (d, *J* = 2.0 Hz, 2H), 6.64 (bs, 1H), 3.51 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.04, 155.65, 137.00, 135.31, 127.90, 82.41, 40.29, 28.19. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.90 min, ESI m/z = 319, $[M + H]^+$; m/z = 639, $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 341.0441 (341.0430 calc'd for $C_{13}H_{16}Cl_2N_2NaO_3$, $[M + Na]^+$).

***tert*-Butyl 2-(2-(3-bromophenyl)acetyl)hydrazinecarboxylate (64).** Prepared according to general method C from 2-(3-bromophenyl)acetic acid (**46**, 5.00 g, 23.2 mmol) and *tert*-butyl hydrazinecarboxylate (3.84 g, 29.0 mmol) to give 7.14 g (97%) of compound **64** as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.45 (bs, 1H), 7.40 (d, *J* = 6.00 Hz, 1H), 7.17 – 7.23 (m, 2H), 6.60 (bs, 1H), 3.55 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.68, 155.56, 136.00, 132.43, 130.73, 130.54, 128.10, 122.95, 82.23, 40.83, 28.21. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.97 min, ESI m/z = 329, $[M+H]^+$, m/z = 657 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 329.0469 (329.0495 calc'd for $C_{13}H_{18}BrN_2O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(3-(trifluoromethy)phenyl)acetyl)hydrazinecarboxylate (65).** Using the **general method** 2-(3-(trifluoromethyl)phenyl)acetic acid **(47)** (3.00 g, 14.7 mmol) and *tert*-butyl

hydrazinecarboxylate (1.94 g, 14.7 mmol) gave 4.52 g (97%) of compound **65** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (bs, 1H), 7.49 – 7.54 (m, 3H), 7.41 – 7.45 (m, 1H), 3.61 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.64, 155.65, 134.81, 132.82, 131.18 (q, J_{CF} = 32.6 Hz), 129.39, 126.15 (q, J_{CF} = 3.80 Hz), 124.38 (q, J_{CF} = 3.90 Hz), 124.00 (q, J_{CF} = 272.2 Hz), 82.30, 40.78, 28.16. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.43 min, ESI m/z = 319, $[M+H]^+$, m/z = 637 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 319.1249 (319.1264 calc'd for $C_{14}H_{18}F_3N_2O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(3-cyanophenyl)acetyl)hydrazine-1-carboxylate (66).** Following general method C, 2-(3-cyanophenyl)acetic acid (**48**, 4.95 g, 30.7 mmol) and *tert*-butyl hydrazinecarboxylate (5.07 g, 38.4 mmol) gave 4.42 g (52%) of **66** as yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (bs, 1H), 8.77 (bs, 1H), 7.69 – 7.67 (m, 1H), 7.67 (s, 1H), 7.57 (d, *J* = 7.62 Hz, 1H), 7.49 (t, *J* = 7.94 Hz, 1H), 3.48 (bs, 2H), 1.35 (bs, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.53, 155.76, 137.80, 134.69, 133.11, 130.94, 130.03, 119.29, 111.68, 79.72, 28.55. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.70 min, ESI m/z = 276, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 276.1332 (276.1343 calc'd for $C_{14}H_{18}N_3O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(3-nitrophenyl)acetyl)hydrazinecarboxylate (67).** Using the general method C, 2-(3-nitrophenyl)acetic acid (**49**, 3.00 g, 16.6 mmol) and *tert*-butyl hydrazinecarboxylate (2.74 g, 20.7 mmol) gave 2.32 g (47%) of **67** as a yellow solid: ^{1}H NMR (400 MHz, CD_3OD) δ 8.18-8.23 (m,1H), 8.07-8.14 (m, 1H), 7.71 (d, *J* = 7.84 Hz, 1H), 7.54 (t, *J* = 7.93 Hz, 1H), 3.66 (bs, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.04, 156.39, 148.35, 137.09, 135.46, 129.30, 123.89, 121.61, 80.58, 39.34, 27.16. LCMS (50-95% CH_3CN in 0.05% TFA over 10 min) retention time = 3.00 min, ESI m/z = 196, $[M-Boc]^+$.

***tert*-Butyl 2-(2-(2-methoxyphenyl)acetyl)hydrazinecarboxylate (68).** Prepared according to the general method C from 2-(2-methoxyphenyl)acetic acid (**50**, 3.00 g, 18.0 mmol) and *tert*-butyl hydrazinecarboxylate (2.98 g, 22.5 mmol) to afford 4.62 g (91%) of compound **68** as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) *rotational isomers observed*, δ 7.52 (bd, $J \sim 2.80$ Hz, 1H), 7.24 – 7.29 (m, 2H), 6.93 (dt, $J = 7.70$, 1.30 Hz, 1H), 6.90 (d, $J = 8.20$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *rotational isomers observed*, δ 170.53, 157.09, 155.30, 131.35, 129.14, 122.50, 121.27, 110.86, 81.74, 55.69, 36.74, 28.16. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.07 min, ESI m/z = 281, $[M+H]^+$, m/z = 561 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 281.1529 (281.1496 calc'd for $C_{14}H_{21}N_2O_4$, $[M + H]^+$).

***tert*-Butyl 2-(2-(3-methoxyphenyl)acetyl)hydrazinecarboxylate (69).** Prepared according to general method C from 2-(3-methoxyphenyl)acetic acid (**51**, 2.43 g, 14.6 mmol) and *tert*-butyl hydrazinecarboxylate (2.41 g, 18.3 mmol) to give4.16 g (100%) of **69** as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (bs, 1H), 7.25 (t, $J = 8.3$ Hz, 1H), 6.81 – 6.87 (m, 3H), 6.51 (bs, 1H), 3.79 (s, 3H), 3.58 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.24 (s), 160.06 (s), 155.39 (s), 135.10 (s), 130.17 (d), 121.74 (d), 115.00 (d), 113.28 (d), 82.00 (s), 55.33 (q), 41.71 (t), 28.19 (q). LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.13 min, ESI m/z = 281, $[M+H]^+$, m/z = 561 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 281.1471 (281.1496 calc'd for $C_{14}H_{21}N_2O_4$, $[M + H]^+$).

***tert*-Butyl 2-(2-(4-methoxyphenyl)acetyl)hydrazinecarboxylate (70).** Prepared according to general method C from 2-(4-methoxyphenyl)acetic acid (**52**, 3.00 g, 18.0 mmol) and *tert*-butyl hydrazinecarboxylate (2.98 g, 22.5 mmol) to afford 4.97 g (98%) of **70** as white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (bs, 1H), 8.70 (bs, 1H), 7.14 (d, J = 8.70 Hz, 2H), 6.82 (d, J = 8.70 Hz, 2H), 3.68 (s, 3H), 3.29 (s, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.07,

158.89, 155.76, 130.51, 126.00, 114.34, 81.83, 55.03, 40.39, 28.21. LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.88 min, ESI m/z = 281, $[M+H]^+$, m/z = 561 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 281.1522 (281.1496 calc'd for $C_{14}H_{21}N_2O_4$, $[M + H]^+$).

***tert*-Butyl 2-(2-(3-(trifluoromethoxy)phenyl)acetyl)hydrazinecarboxylate (71).** Following general method C, 2-(3-trifluoromethoxyphenyl)acetic acid (**53**, 3.00 g, 13.6 mmol) and *tert*-butyl hydrazinecarboxylate (2.52 g, 19.1 mmol) afforded 3.80 g (83%) of **71** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (bs, 1H), 7.35 (t, J = 8.20 Hz, 1H), 7.24 (d, J = 7.70 Hz, 1H), 7.10 – 7.16 (m, 2H), 6.59 (bs, 1H), 3.59 (s, 2H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.52, 155.50, 149.56, 135.93, 130.33, 127.81, 122.00, 120.65 (q, J_{CF} = 256.9 Hz), 119.96, 82.26, 40.86, 28.16. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.77 min, ESI m/z = 235, $[M – Boc + H]^+$. HRMS (ESI Q-TOF) m/z = 357.1033 (357.1033 calc'd for $C_{14}H_{17}N_2NaO_4$, $[M + Na]^+$.

***tert*-Butyl 2-(2-(3-(benzyloxy)phenyl)acetyl)hydrazinecarboxylate (72).** Using general method C, 2-(3-benzyloxy)phenyl)acetic acid (**54**, 3.00 g, 12.4 mmol) and *tert*-butyl hydrazinecarboxylate (2.05 g, 15.5 mmol) yielded 4.06 g (92 %) of **72** as a yellow solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.44-7.36 (m, 2H), 7.35-7.25 (complex m, 3H), 7.18 (t, J = 7.93 Hz, 1H), 6.99 (bs, 1H), 6.90-6.80 (m, 2H), 5.04 (s, 2H),3.48 (bs, 2H), 1.44 (bs, 9H). ^{13}C (100 MHz, CD_3OD) δ 172.15, 159.05, 156.39, 137.40, 136.31, 129.17, 128.13, 127.50, 127.26, 121.46, 115.34, 113.22, 80.47, 69.56, 40.20, 27.19. LCMS (50-95% CH_3CN in 0.05% TFA over 10 min) retention time = 5.32 min, ESI m/z = 357, $[M+H]^+$.

***tert*-Butyl 2-(2-([1,1'-biphenyl]-4-yl)acetyl)hydrazinecarboxylate (73).** Prepared according to general method C from 2-([1,1'-biphenyl]-4-yl)acetic acid (**55**, 3.00 g, 14.1 mmol) and *tert*-butyl hydrazinecarboxylate (3.39 g, 25.7 mmol) to give3.96 g (86%) of **73** as a white solid: ^{1}H NMR

(400 MHz, DMSO-d_6) δ 9.80 (bs, 1H), 8.72 (bs, 1H), 7.55 – 7.62 (m, 4H), 7.41 (t, J = 7.30 Hz, 2H), 7.31 – 7.34 (m, 3H), 3.42 (s, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.16, 155.79, 140.49, 138.95, 135.44, 130.16, 129.44, 127.83, 127.08, 127.05, 79.62, 28.57. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.23 min, ESI m/z = 327, $[M + H]^+$, 653 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 327.1691 (327.1703 calc'd for $C_{19}H_{23}N_2O_3$, $[M + H]^+$.

***tert*-Butyl 2-(2-(1*H*-indol-3-yl)acetyl)hydrazine-1-carboxylate (74)**. Prepared according to general method C from 2-(1*H*-indol-3-yl)acetic acid (**5**, 500 mg, 2.59 mmol) and *tert*-butyl hydrazinecarboxylate (428 mg, 3.24 mmol) to afford 758 mg of **74** (95%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 9.69 (s, 1H), 8.70 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.02 (t, J = 8.1 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 3.46 (s, 2H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.81, 157.29, 136.54, 127.74, 124.30, 121.47, 119.30, 118.80, 111.77, 108.72, 79.52, 30.96, 28.60. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.90 minutes, ESI m/z = 290, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 290.1522 (290.1499 calc'd for $C_{15}H_{20}N_3O_3$, $[M + H]^+$).

***tert*-Butyl 2-(2-(6-fluoro-1*H*-indol-3-yl)acetyl)hydrazine-1-carboxylate (75)**. Following general method C, 2-(6-fluoro-1*H*-indol-3-yl)acetic acid (**6**, 500 mg, 2.59 mmol) and *tert*-butyl hydrazinecarboxylate (428 mg, 3.24 mmol) gave 758 mg of **75** (95%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.9 (s, 1H), 9.70 (s, 1H), 8.70 (s, 1H), 7.51 (dd, J_{HF} = 8.70, J_{HH} = 5.50 Hz, 1H), 7.17 (s, 1H), 7.06 (dd, J_{HF} = 10.0, J_{HH} = 2.30 Hz, 1H), 6.79 (td, J_{HF} = 10.1, J_{HH} = 2.30 Hz, 1H), 3.44 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.63, 162.84, 159.34 (d, J_{CF} = 234 Hz), 155.86, 136.35 (d, J_{CF} = 12.4 Hz), 124.73 (d, J_{CF} = 29.7 Hz), 120.35 (d, J_{CF} = 10.6 Hz),

109.01, 107.27 (d, J_{CF} = 24.9 Hz), 97.69 (d, J_{CF} = 25.9 Hz), 79.52, 36.30, 28.58. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.98 minutes, ESI m/z = 308, $[M+H]^+$.

General Method D. Synthesis of Hydrazides 76-95.

To the Boc-protected acyl hydrazide (1.00 mmol) in CH_2Cl_2 was added 4N HCl/Dioxane (10 mL) and the reaction was stirred at RT. After 1.5 h a white precipitate was formed. The precipitated HCl salt was filtered and washed with CH_2Cl_2 and dried under high vacuum. The salt (1.00 mmol) was suspended in CH_2Cl_2 (75 mL) or dissolved in methanol (or methanol/water) and treated with TEA (6 mL). The resulting mixture was stirred at RT for 30 min, transferred to a separatory funnel and partitioned with additional CH_2Cl_2 (75 mL) and water (150 mL). The layers were separated and the organic solution was dried (anhydrous Na_2SO_4), filtered, and concentrated.

2-(3-Fluorophenyl)acetic hydrazide (76).[12] Prepared according general method D from Boc-hydrazide (**56**, 5.06 g, 18.9 mmol) to yield 2.59 g (67% yield) of the intermediate HCl salt as a white solid. The HCl salt (2.47 g, 12.1 mmol) was then converted to 882 mg (43%) of freebase **76** (29% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (bs, 1H), 7.29 (dt, J = 6.90, 6.00 Hz, 1H), 6.99 – 7.05 (complex m, 3H), 4.20 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.55 (s), 162.52 (d, J_{CF} = 243 Hz), 139.55 (d, J_{CF} = 7.60 Hz), 130.57 (d, J_{CF} = 8.60 Hz), 125.64 (d, J_{CF} = 2.90 Hz), 116.19 (d, J_{CF} = 22.1 Hz), 113.72 (d, J_{CF} = 20.2 Hz), 40.55 (d, J_{CF} = 1.90 Hz). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.90 min, ESI m/z = 169, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 169.0787 (169.0772 calc'd for $C_8H_{10}FN_2O$, $[M + H]^+$).

2-(4-Fluorophenyl)acetic hydrazide (77).[12] Prepared according to general method D from Boc-hydrazide (**57**, 3.23 g, 12.0 mmol) to afford 2.18 g of the intermediate HCl salt (89%) as a white

solid. The HCl salt was then converted 1.57 g (90%) of the freebase **77** (78% over two steps), isolated as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 7.24 (dd, J_{HF} = 8.80, J_{HH} = 5.50 Hz, 2H), 7.07 (apparent t, J_{HF} = 8.70, J_{HH} =8.70 Hz, 2H), 4.17 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.95, 161.54 (d, J_{CF} = 243 Hz), 132.96, 131.25 (d, J_{CF} = 7.60 Hz), 115.39 (d, J_{CF} = 21.1 Hz), 40.73. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.85 minutes, ESI m/z = 169, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 169.0776 (169.0772 calc'd for $C_8H_{10}FN_2O$, $[M + H]^+$).

2-(3,5-Difluorophenyl)acetic hydrazide (78).[13] Following general method D, Boc-hydrazide (**58**, 3.05 g, 10.7 mmol) gave 2.02 g (85%) of the intermediate HCl salt as a white solid. The HCl salt (1.91 g, 8.58 mmol) was then converted to 740 mg (46%) of freebase **78** (39% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (bs, 1H), 7.05 (tt, J = 9.20, 2.30 Hz, 1 H), 6.91 – 6.96 (m, 2H), 4.21 (bs, 1H), 3.36 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.39 (s), 163.64 (dd, J_{CF} = 249, 13.4 Hz), 137.63 (t, J_{CF} = 8.60 Hz), 112.39 (dd, J_{CF} = 25.9, 7.70 Hz), 103.13 (t, J_{CF} = 24.9 Hz), 41.29 (t, CH_2). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.08 min, ESI m/z = 187. HRMS (ESI Q-TOF) m/z = 187.0688 (187.0677 calc'd for $C_8H_9F_2N_2O$, $[M + H]^+$).

2-(2-Chlorophenyl)acetic hydrazide (79).[14] Prepared according to the general method from Boc-hydrazide (**59**, 2.10 g, 7.37 mmol) to give 1.63 g (100%) of the intermediate HCl salt as a white solid. The HCl salt (1.23 g, 5.56 mmol) was then converted to 830 mg (81%) of freebase **79** (81% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (bs, 1H), 7.31 – 7.38 (complex m, 2H), 7.20 – 7.26 (complex m, 2 H), 4.20 (bs, 2H), 3.47 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.95, 134.54, 133.94, 132.32, 129.50, 128.90, 127.51, 38.34. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.08 min, ESI m/z = 185, [M+H

]$^+$; m/z = 369, [2M + H]$^+$; m/z = 391, [2M + Na]$^+$. HRMS (ESI Q-TOF) m/z = 185.0499 (185.0476 calc'd for $C_8H_9ClN_2O$, [M + H]$^+$).

2-(3-Chlorophenyl)acetic hydrazide (80).[14] According to general method D, *tert*-butyl 2-(2-(3-chlorophenyl)acetyl)hydrazinecarboxylate (**60**, 5.00 g, 17.6 mmol) afforded 3.02 g (78%) of the intermediate HCl salt as a white solid. The HCl salt was then converted to 1.73 g (69%) of freebase **80** (54% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (bs, 1H), 7.23 – 7.30 (complex m, 3H), 1.15 – 7.18 (complex m, 1H), 4.20 (bs, 2H), 3.32 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.00, 135.92, 134.83, 130.30, 129.52, 127.82, 127.60, 41.40. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.95 min, ESI m/z = 185, [M+H]$^+$; m/z = 369, [2M + H]$^+$; m/z = 391, [2M + Na]$^+$. HRMS (ESI Q-TOF) m/z = 185.0497 (185.0476 calc'd for $C_8H_9ClN_2O$, [M + H]$^+$).

2-(4-Chlorophenyl)acetic hydrazide (81).[15] Using general method D, Boc-hydrazide (**61**, 4.90 g, 17.2 mmol) gave 3.18 g (84%) of the intermediate HCl salt as a white solid. The HCl salt was then converted to 860 mg (32%) of freebase **81** (27% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) □ 9.19 (s, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 4.18 (s, 2H), 3.31 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.71, 135.82, 131.63, 131.34, 128.65, 40.17. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.08 min, ESI m/z = 185, [M+H]$^+$. HRMS (ESI Q-TOF) m/z = 185.0498 (185.0476 calc'd for $C_8H_9ClN_2O$, [M + H]$^+$).

2-(3,4-Dichlorophenyl)acetic hydrazide (96)[2, 16] Using general method D, Boc-hydrazide (**62**, 3.00 g, 9.40 mmol) gave 2.40 g (100%) of the intermediate HCl salt as a white solid. The HCl salt (549 mg, 2.15 mmol) was then converted to 473 mg (100 %) of freebase **96** (100% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.2 Hz, 1H), 7.37 (d, J = 2.1

Hz, 1H), 7.10 (dd, *J* = 8.2, 2.1, 1H), 6.86 (bs, 1H), 3.88 (bs, 2H), 3.47 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.64, 134.24, 132.97, 131.81, 131.29, 130.87, 128.75, 40.67. LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.38 min, ESI m/z = 219, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 219.0097 (219.0086 calc'd for $C_8H_9Cl_2N_2O$, $[M + H]^+$).

2-(3,5-Dichlorophenyl)acetic hydrazide (82). Prepared according to general method D from *tert*-butyl 2-(2-(3,5-dichlorophenyl)acetyl)hydrazinecarboxylate (**63**, 6.00 g, 18.8 mmol) to afford 4.34 g (90%) of the intermediate HCl salt as a white solid. The HCl salt (4.34 g, 17.0 mmol) was then converted to 2.65 g (71% of freebase **82** (64% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (bs, 1H), 7.42 (t, *J* = 1.90 Hz, 1H), 7.27 (d, *J* = 1.90 Hz, 2H), 4.20 (bs, 2H), 3.35 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.21, 137.21, 135.44, 127.86, 127.83, 40.93. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time.

2-(3-Bromophenyl)acetic hydrazide (83).[17] Prepared according to general method D from Boc-hydrazide (**64**, 7.41 g, 22.5 mmol) to yield 4.00 g (67%) of the intermediate HCl salt as a white solid. The HCl salt (4.00 g, 15.1 mmol) was then converted to 2.73 g (79%) of freebase **83** (53% for two steps), isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (bs, 1H), 7.43 – 7.44 (m, 1H), 7.37 – 7.40 (complex m, 1H), 7.20 – 7.23 (complex m, 2H), 4.26 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.01 (s), 136.28 (s), 132.40 (d), 130.71 (d), 130.55 (d), 128.07 (d), 122.99 (s), 41.32 (t). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.98 min, ESI m/z = 229, $[M+H]^+$;270, $[M + H + ACN]^+$;459 $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 228.9973 (228.8871 calc'd for $C_8H_{10}BrN_2O$, $[M + H]^+$).

2-(3-(Trifluoromethyl)phenyl)acetic hydrazide (84). Following general method D, Boc-hydrazide (**65**, 4.20 g, 13.2 mmol) gave 3.26 g (97%) of the intermediate HCl salt as a white solid. The HCl salt (3.26 g, 12.8 mmol) was then converted to 2.14 g (77%) of freebase **84** (75% for two

steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (bs, 1H), 7.45 – 7.54 (m, 3H), 3.53 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 170.92, 136.72, 132.61, 130.42 (q, J_{CF} = 32.6 Hz), 128.95, 125.42 (q, J_{CF} = 3.80 Hz), 124.30 (q, J_{CF} = 271 Hz), 123.37 (q, J_{CF} = 3.90 Hz), 39.93. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.00 min, ESI m/z = 219, $[M+H]^+$;437 $[2M+H]^+$. HRMS (ESI Q-TOF) m/z = 219.0756 (219.0741 calc'd for $C_9H_{10}F_3N_2O$, $[M + H]^+$).

2-(3-Cyanophenyl)acetic hydrazide (85). Using general method D, Boc-hydrazide (**66**, 4.32 g, 15.7 mmol) afforded 2.60 g (79%) of the intermediate HCl salt as a white solid. The HCl salt (2.60 g, 12.3 mmol) was then converted to 1.41 g (75%) of freebase **85** (59% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (bs, 1H), 7.68 – 7.65 (m, 2H), 7.57 – 7.54 (m, 1H), 7.47 (t, *J* = 7.79 Hz, 1H), 4.21 (bs, 2H), 3.39 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.29, 138.41, 134.59, 132.98, 130.82, 129.98, 119.32, 111.64, benzyl carbon obscured by DMSO-d_6 solvent peaks. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.07 minutes, ESI m/z = 176, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 176.0828 (176.0818 calc'd for $C_9H_{10}N_3O$, $[M + H]^+$).

2-(3-Nitrophenyl)acetic hydrazide (86). Following general method D, *tert*-butyl 2-(2-(3-nitrophenyl)acetyl)hydrazinecarboxylate (**67**, 2.27 g, 7.69 mmol) gave 1.66 g (93%) of the intermediate HCl salt as a white solid. The HCl salt (1.66 g, 7.17 mmol) was converted to 1.31 g (94%) of the freebase **86** (87% for two steps), isolated as a light yellow solid: ^{1}H NMR (400 MHz, CD_3OD) δ 8.19-8.17 (m, 1H), 8.12-8.10 (m, 1H), 7.68 (d, *J*= 7.10 Hz, 1H), 7.54 (t, *J* = 8.01 Hz, 1H), 3.59 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 170.57, 148.35, 137.60, 135/24. 129/33, 123/59, 121.56, 39.65. LCMS (50-95% CH_3CN) om 0.05% TFA over 10 min) retention time = 2.05 min, ESI m/z = 196, $[M+H]^+$; 237, $[M + H^+ + CH_3CN]^+$.

2-(2-Methoxyphenyl)acetic hydrazide (87):[18] Using general method D, Boc-hydrazide (**68**, 4.61 g, 16.4 mmol) afforded 3.08 g (86% yield) of the intermediate HCl salt as a white solid. The HCl salt (3.08 g, 14.2 mmol) was then converted to 1.88 g (73% yield) of freebase **87** (63% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (bs, 1H), 7.16 (dt, *J* = 7.80, 1.90 Hz, 1H), 7.11 (d, *J* = 7.30 Hz, 1H), 6.90 (d, *J* = 7.80 Hz, 1H), 6.82 (t, *J* = 7.30 Hz, 1H), 4.15 (bs, 1H), 3.70 (s, 3H),

2-(3-Methoxyphenyl)acetic hydrazide (88):[15] Prepared according to general method D, from Boc-hydrazide (**69**, 4.09 g, 14.6 mmol) to yield 3.10 g (98%) of the intermediate HCl salt as a white solid. The HCl salt (2.50 g, 11.5 mmol) was then converted to 1.10 g (53%) of freebase **88** (52% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (bs, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.79 (s, 1H), 6.74 – 6.77 (complex m, 2H), 4.17 (bs, 2H), 3.68 (s, 3H), 3.26 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.93, 159.63, 138.23, 129.69, 121.71, 115.20, 112.27, 55.45, 41.03. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.85 min, ESI m/z = 181, $[M+H]^+$; m/z = 361, $[2M + H]^+$. HRMS (ESI Q-TOF) m/z = 181.0993 (181.0972 calc'd for $C_8H_9ClN_2O$, $[M + H]^+$

2-(4-Methoxyphenyl)acetic hydrazide (89).[15] Using general method D, Boc-hydrazide (**70**, 4.67 g, 16.7 mmol) gave 2.78 g (77%) of the intermediate HCl salt as a white solid. The HCl salt (2.68 g, 12.4 mmol) was then converted to 1.18 g (53%) of freebase **89** (41% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (bs, 2H), 7.12 (d, *J* = 6.40 Hz, 2H), 6.81 (d, *J* = 6.90 Hz, 2H), 4.15 (bs, 2H), 3.67 (s, 3H), 3.22 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.44, 158.43, 130.44, 128.71, 114.13, 55.54, 40.08. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.18 min, ESI m/z = 181, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 181.1002 (181.0972 calc'd for $C_8H_9ClN_2O$, $[M + H]^+$).

2-(3-(Trifluoromethoxy)phenyl)acetic hydrazide (90). Using general method D, *tert*-butyl 2-(3-(trifluoromethoxy)phenyl)acetyl)hydrazinecarboxylate (**71**, 3.76 g, 11.2 mmol) yielded 2.54 g (83%) of the intermediate HCl as a white solid. The HCl salt (2.54 g, 9.37 mmol) was converted to 1.88 g (71 %) of freebase **90** (69% for two steps), isolated as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 5.86 Hz, 1H), 7.19 (bd, J = 7.73 Hz, 1H), 7.16-7.11 (m, 2H), 5.54 (s 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.86, 149.62, 136.22, 130.37, 127.77, 121.93, 120.47 (q, $J_{C,F}$ = 257.48 Hz), 119.96, 41.39. LCMS (15-95% CH_3CN in 0.05% TFA over 10 min) retention time = 6.17 min, ESI m/z = 235, $[M+H]^+$; $[M+H+CH_3CN]^+$.

2-(3-(Benzyloxy)phenyl)acetic hydrazide (91). Following general method D, Boc-hydrazide (**72**, 4.02 g, 11.3 mmol) afforded 2.65 g (81 %) of the intermediate HCl salt as a white solid. The HCl salt (2.65 g, 9.07 mmol) was converted to 2.00 g (86 %) of the free base **91** (70 % for two steps), isolated as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.42-7.25 (complex m, 5H), 7.18 (t, J = 8.00 Hz, 1H), 6.93 (apparent t, J = 1.90 Hz, 1H), 6.85 (dd, J = 8.10, 2.06 Hz, 2H), 5.04 (s, 2H), 3.40 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.69, 159.05, 137.37, 136.73, 129.21, 128.14, 127.51, 127.25, 121.27, 115.37, 113.00, 69.54, 40.45. LCMS (25-95% CH_3CN in 0.05% TFA over 10 min) retention time = 5.43 min (broad), ESI m/z = 257 $[M + H]^+$; 535 $[2M + Na]^+$.

2-([1,1'-Biphenyl]-4-yl)acetic hydrazide (92).[19] Prepared according to general method D from Boc-hydrazide (**73**, 3.83 g, 11.7 mmol) to give 2.75 g (89%) of the intermediate HCl salt as a white solid. The HCl salt (2.75 g, 10.5 mmol) was then converted to 1.84 g (77 %) of freebase **92** (69% for two steps)**,** isolated as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (bs, 1H), 7.53 – 7.61 (m, 4H), 7.41 (t, J = 7.30 Hz, 2H), 7.29 – 7.32 (m, 3H), 4.19 (bs, 2H), 3.35 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.03, 140.53, 138.86, 136.07, 130.05, 129.44, 127.81, 127.08, 127.04, 40.68. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.25 min,

ESI m/z = 227, $[M+H]^+$; 453, [2M + H]. HRMS (ESI Q-TOF) m/z = 227.1185 (227.1179 calc'd for $C_{14}H_{15}N_2O$, $[M + H]^+$).

2-(3-(Methylsulfonyl)phenyl)acetylhydrazide (93).

Methyl 2-(3-(methylsulfonyl)phenyl)acetate (5.43 g, 23.8 mmol) was suspended in EtOH (150 mL) and treated with hydrazine hydrate (10 equiv., 238 mmol, 11.6 mL). The resulting mixture was heated at reflux for 16 h. The mixture was cooled and the precipitate was filtered, washed with EtOH and dried at high vacuum to afford 3.80 g (70%) of pure **93** as a white solid (an additional 1.21 g was recovered by concentration of the filtrate): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (bs, 1H), 7.79 – 7.75 (m, 2H), 7.59 – 7.53 (m, 2H), 4.22 (s, 2H), 3.45 (bs, 2H), 3.16 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.37, 141.29, 138.34, 134.78, 129.88, 127.62, 125.66, 40.50. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time 2.25 min, ESI m/z = 229, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 229.0616 (229.0641 calc'd for $C_9H_{13}N_2O_3S$, $[M + H]^+$).

2-(4-(Methylsulfonyl)phenyl)acetylhydrazide (94):[20] Methyl 2-(4-(methylsulfonyl)phenyl)-acetate (5.43 g, 23.8 mmol) was suspended in EtOH (150 mL) and treated with hydrazine hydrate (10 equiv., 238 mmol, 11.6 mL). The resulting mixture was heated at reflux for 16 h. The mixture was cooled and the precipitate was filtered, washed with EtOH and dried at high vacuum to afford 4.08 g (75%) of pure compound **94** as a white solid (an additional 1.36 g was recovered by concentration of the filtrate): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (bs, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 4.23 (bs, 2H), 3.44 (s, 2H), 3.15 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.19, 142.87, 130.44, 127.46, 44.13, 40.75. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time 2.12 min, ESI m/z = 229, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 229.0617 (229.0641 calc'd for $C_9H_{13}N_2O_3S$, $[M + H]^+$.

2-(6-Fluoro-1*H*-indol-3-yl)acetic hydrazide hydrochloride (95). Using general method D, the Boc-hydrazide (**75**, 758 mg, 2.47 mmol) afforded 464 mg of **95** (77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.27 (s, 1H), 11.05 (s, 1H), 7.53 (apparent q, J_{HF} = 8.7, J_{HH} = 6.0 Hz, 1H), 7.21 (s, 1H), 7.08 (apparent dd, J_{HF} = 10.1, J_{HH} = 2.3 Hz, 1H), 6.81 (apparent tt, J_{HF} = 9.3, J_{HH} = 1.9 Hz, 1H), 3.63 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.51, 159.37 (d, J_{CF} = 233.9 Hz), 136.40 (d, J_{CF} =12.5 Hz), 125.35, 124.38, 120.26 (d, J_{CF} = 10.5 Hz), 107.91, 107.47 (d, J_{CF} = 24.0 Hz), 97.86 (d, J_{CF} = 24.9 Hz), 30.51. LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.92 minutes, ESI m/z = 208, $[M+H-Cl^-]^+$. HRMS (ESI Q-TOF) m/z = 208.0895 (208.0881 calc'd for $C_{10}H_{11}FN_3O$, $[M + H]^+$).

General Method E. Synthesis of Trityl-Protected-1,2,4-Triazoles 97-151.

A mixture of thioamide (1 mmol) and hydrazide (1.2 mmol) was dissolved in CH_2Cl_2 (30 mL) and treated with silver benzoate (2 mmol) followed immediately with acetic acid (3 mmol). The brownish-black solution was stirred at room temperature overnight. The solution was concentrated and the residue was dissolved in 1:1 MeOH/CH_2Cl_2 and treated with 1N HCl (2 mmol). The mixture was stirred for 5 min, treated with diisopropylethylamine (~10 mmol) and concentrated. The residue was suspended in MeOH (50 mL), filtered through celite (1 inch pad) and concentrated. The final residue was purified by flash chromatography.

3-(2-(5-Benzyl-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (97). Prepared according to general method E from thioamide (**34**, 580 mg, 1.04 mmol) and 2-phenylacetic hydrazide (187 mg, 1.24 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 310 mg (46%) of **97** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (bs, 1H), 9.18 (bs, 1H), 7.90 (d, J = 6.90 Hz, 1H), 6.98 – 7.55 (complex multiplets, 24H), 6.84 (t, J = 6.80 Hz, 1H), 6.45 (s, 1H), 4.01 (s, 2H), 3.65 (apparent t, J = 8.30

Hz, 2H), 3.06 (apparent t, *J* = 8.20 Hz, 2H), 2.90 (apparent t, *J* = 7.80 Hz, 2H), 2.27 (t, J = 7.30 Hz, 2H), 1.47 (quint., J = 7.40 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.54 (s), 152.95 (s), 142.83 (s), 140.17, 138.26, 137.28, 136.81, 136.69, 133.35, 129.79, 129.68 (d), 129.47, 129.09, 128.98, 128.90, 128.70 (d), 128.48, 127.45, 127.08, 126.88, 123.10, 121.41, 118.74, 118.71, 118.16, 113.90, 111.86, 74.88, 42.51, 40.99, 30.77, 29.58, 25.9, 25.09, 23.22. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.97 min, ESI m/z = 653, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 653.3407 (653.3387 calc'd for $C_{44}H_{41}N_6$), $[M + H]^+$.

3-(2-(5-(3-Fluorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-5-yl)propyl)-4*H*-1,2,4-triazol-3-yl)-ethyl)-1*H*-indole (98). Prepared according to the general method E from (**34**, 514 mg, 0.93 mmol) and hydrazide (**76**, 188 mg, 1.11 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 300 mg (49%) of compound **98** as a white solid (*tautomeric N-trityl-imidazole isomers present – NMR data reflects major isomer*): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (bs, 1H), 9.20 (bs, 0.5 H), 7.90 (d, *J* = 6.40 Hz, 1H), 7.58 (t, *J* = 6.40 Hz, 0.5H), 6.90 – 7.46 (complex multiplets, 23H), 6.84 (t, *J* = 7.70 Hz, 1H), 6.48 (s, 1H), 4.05 (s, 2H), 3.69 (apparent t, *J* = 8.20 Hz, 2H), 3.06 (apparent t, *J* = 7.55 Hz, 2H), 2.91 (apparent, t, *J* = 7.55 Hz, 2H), 2.30 (apparent t, *J* = 6.90 Hz, 1H), 1.52 (quint., *J* = 7.30 Hz, 2H). LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.82 min, ESI m/z = 671, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 671.3309 (671.3293 calc'd for $C_{44}H_{40}FN_6$), $[M + H]^+$.

3-(2-(5-(3,5-Difluorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-5-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (99). Using general method E, thioamide (**34**, 500 mg, 0.90 mmol) and hydrazide (**78**, 206 mg, 1.10 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 300 mg (47%) of compound **99** as a white solid; *tautomeric N-trityl-imidazole isomers present – NMR data reflects major isomer*: ^{1}H NMR (400 MHz, DMSO-d_6) δ

10.74 (bs, 1H), 7.89 – 7.91 (m, 1H), 7.40 (d, *J* = 8.20 Hz, 1H), 7.29 – 7.33 (complex multiplets, 9H), 7.26 (d, *J* = 7.80 Hz, 1H), 7.19 (d, *J* = 1.30 Hz, 1H), 7.08 (d, *J* = 2.30 Hz, 1H), 6.07 – 7.01 (complex multiplets, 8H), 6.86 – 6.89 (m, 1H), 6.83 (t, *J* = 6.80 Hz, 1H), 6.51 (s, 1H), 4.07 (s, 2H), 3.72 (apparent t, *J* = 6.30 Hz, 2H), 3.06 (apparent t, *J* = 6.90 Hz, 2H), 2.92 (apparent t, *J* = 6.40 Hz, 2H), 2.33 (t, *J* = 6.90 Hz, 2H), 1.58 (quint, *J* = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.79 (dd, J_{CF} = 246, 13.4 Hz), 154.70 (s), 152.14 (s), 142.81 (s), 141.82 (t, J_{CF} = 9.50 Hz), 140.15, 138.30, 136.68, 129.77, 129.65 (d), 129.06, 128.69 (d), 128.45, 127.43, 123.08, 121.40, 118.71, 118.68, 118.13, 113.88, 112.35 (dd, J_{CF} = 18.2, 6.70 Hz), 111.85, 102.70 (t, J_{CF} = 24.9 Hz), 74.87, 42.51, 30.17, 29.67, 25.91, 24.99, 23.17. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.13 min, ESI m/z = 689, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 689.3205 (689.3199 calc'd for $C_{44}H_{39}F_2N_6$), $[M + H]^+$.

3-(2-(5-(2-Chlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (100). Prepared according to general method E from thioamide (**34**, 500 mg, 0.90 mmol) and hydrazide (**79**, 199 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 286 mg (46%) of compound **100** as a white solid; *tautomeric N-trityl-imidazole isomers present – NMR data reflects major isomer:* ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (bs, 1H), 7.43 – 7.17 (complex m, 18H), 7.08 – 7.03 (m, 2H), 7.01- 6.96 (complex m, 4H), 6.86 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.50 (s, 1H), 4.05 (s, 2H), 3.70 (t, *J* = 8.0 Hz, 2H), 3.07 (dd, *J* = 9.2, 6.1 Hz, 2H), 2.95 (dd, *J* = 9.2, 6.1 Hz, 2H), 2.33 (t, *J* = 7.0 Hz, 2H), 1.65 (quint., *J* = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.60, 151.83, 142.83, 138.343, 136.72, 134.94, 133.54, 132.32, 131.30, 129.67, 129.52, 129.11, 128.91, 128.68, 128.45, 127.81, 127.48, 123.15, 121.42, 118.75, 118.22, 113.86, 111.87, 74.89, 42.50, 29.67, 28.84, 25.93, 25.02, 23.32. LCMS

(50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.90 min, ESI m/z = 687, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 687.3009 (687.2997 calc'd for $C_{44}H_{40}ClN_6$), $[M + H]^+$.

3-(2-(5-(3-Chlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (101). Prepared following general method E from thioamide (**34**, 200 mg, 0.36 mmol) and hydrazide (**80**, 80.0 mg, 0.45 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 147 mg (60%) of compound **101** as a white solid: ^{1}H NMR (400 MHz, DMDO-d_6) δ 10.83 (bs, 1H), 8.73 (bs, 1H), 7.44 (d, *J* = 8.20 Hz, 1H), 7.37 – 7.42 (m, 10H), 7.21- 7.33 (complex multiplets, 4H), 7.05 – 7.15 (complex multiplets, 8H), 7.01 (t, *J* = 8.20 Hz, 1H), 6.90 (t, *J* = 8.20 Hz, 1H), 4.20 (s, 2H), 3.89 (distorted triplet, *J* = 7.30 Hz, 2H), 3.07 – 3.16 (m, 4H), 2.53 (distorted t, *J* = 7.30 Hz, 2H), 1.63 (quint, *J* = 7.40 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.22, 153.38, 140.86, 138.28, 137.13, 136.72, 133.73, 131.04, 129.69, 129.28, 129.22, 128.15, 127.60, 127.32, 123.43, 121.58, 119.98, 118.90, 118.65, 113.08, 112.00, 77.85, 43.04, 29.91, 28.15, 25.67, 22.40, 21.88. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.38 min, ESI m/z = 687, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 687.3009 (687.2997 calc'd for $C_{44}H_{40}ClN_6$), $[M + H]^+$.

3-(2-(5-(4-Chlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (102). Prepared following general method E from thioamide (**34**, 475 mg, 0.86 mmol) and hydrazide (**81**, 190 mg, 1.03 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 360 mg (61%) of compound **102** as a white solid; *tautomeric N-trityl-imidazole isomers present – NMR data reflects major isomer:* ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (bs, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.30 (complex m, 10H), 7.26 – 7.20 (m, 4H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.00 – 6.97 (m, 5H), 6.84 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.51 (bs, 1H), 4.01 (s, 2H), 3.64 (apparent t, *J* = 8.0 Hz, 2H), 3.05 (dd, *J* = 9.3, 6.1 Hz,

2H), 2.91 (dd, *J* = 9.3, 6.2 Hz, 2H), 2.30 (t, *J* = 7.0 Hz, 2H), 1.57 (quint., *J* = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.62, 152.62, 142.83, 140.13, 138.35, 136.70, 135.83, 131.79, 131.62, 130.82, 129.79, 129.74, 129.68, 128.92, 128.73, 128.71, 128.65, 128.47, 127.45, 123.12, 121.42, 118.75, 118.71, 118.21, 113.85, 111.86, 74.89, 42.46, 30.01, 29.61, 25.90, 24.99, 23.27. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.35 min, ESI m/z = 687, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 687.2984 (687.2997 calc'd for $C_{44}H_{40}ClN_6$), $[M + H]^+$.

3-(2-(5-(3,4-Dichlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-5-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1-methyl-1*H*-indole (103). Prepared according to general method E from thioamide (**35**, 0.440 g, 0.77 mmol) and 2-(3,4-dichlorophenyl)acetic hydrazide[2] (**96**, 0.203 g, 0.93 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) and recrystallization of the product from ACN afforded 0.390 g (67%) of **103** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 – 7.27 (complex m, 14H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.07 – 6.98 (m, 6H), 6.93 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.87 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 6.80 (s, 1H), 6.48 (s, 1H), 4.01 (s, 2H), 3.54 (s, 3H), 3.41 – 3.32 (m, 2H), 3.15 (t, *J* = 7.1 Hz, 2H), 2.98 (t, *J* = 7.2 Hz, 2H), 2.22 (t, *J* = 7.0 Hz, 2H), 1.38 (quint., *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, Methanol-d_4) δ 155.93, 152.48, 142.26, 139.00, 138.22, 137.14, 136.41, 132.28, 130.83, 130.63, 130.32, 129.47, 129.30, 128.08, 128.02, 127.97, 127.50, 126.59, 121.26, 118.55, 118.05, 112.49, 108.98, 75.46, 42.29, 31.36, 29.30, 28.67, 25.85, 24.11, 23.35. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.62 min, ESI m/z = 735, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 493.1629 (493.1669 calc'd for $C_{26}H_{27}Cl_2N_6$), $[M - Trt + H]^+$.

3-(2-(5-(3,5-Dichlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (104). Prepared according to general method E from thioamide (**34**, 500 mg,

0.90 mmol) and hydrazide (**82**, 237 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 378 mg (58%) of **104** as a white solid; *tautomeric N-trityl-imidazole isomers present – NMR data reflects major isomer:* ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (bs, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.29 (m, 10H), 7.28 – 7.23 (m, 4H), 7.20 (t, *J* = 1.1 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.03 – 6.95 (m, 6H), 6.84 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.52 (s, 1H), 4.05 (s, 2H), 3.81 – 3.68 (m, 2H), 3.06 (t, *J* = 7.7 Hz, 2H), 2.93 (dd, *J* = 9.3, 6.1 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.59 (quint., *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.72, 152.14, 142.86, 141.56, 140.20, 138.31, 136.74, 134.47, 129.68, 128.69, 128.10, 127.47, 126.87, 126.66, 123.09, 121.42, 118.74, 118.69, 118.09, 113.93, 111.87, 74.93, 42.55, 29.89, 29.75, 25.94, 25.04, 23.19. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.25 min, ESI m/z = 721, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 721.2603 (721.2608 calc'd for $C_{44}H_{39}Cl_2N_6$), $[M + H]^+$.

3-(2-(5-(3-Bromobenzyl)-4-(3-(1-trityl-1*H*-imidazol-5-yl)propyl)-4*H*-1,2,4-triazol-3yl)ethyl)-1*H*-indole (105). Prepared according to general method E from thioamide (**34**, 748 mg, 1.40 mmol) and hydrazide (**83**, 371 mg, 1.62 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 492 mg (48%) of compound **105** as a white solid; *tautomeric N-trityl-imidazole isomers present – NMR data reflects major isomer*: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (bs, 1H), 7.90 (d, *J* = 6.80 Hz, 1H), 6.98 – 7.47 (complex multiplets, 23H), 6.84 (t, *J* = 8.00 Hz, 1H), 6.49 (s, 1H), 4.03 (s, 2H), 3.70 (apparent t, *J* = 8.20 Hz, 2H), 3.05 – 3.07 (m, 2H), 2.89 – 2.933 (m, 2H), 2.28 – 2.32 (m, 2H), 1.51 (quint., *J* = 7.30 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.30 min, ESI m/z = 731, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 731.2450 (731.2492 calc'd for $C_{44}H_{40}N_6Br$), $[M + H]^+$.

3-(2-(5-(3-(Trifluoromethyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (106). Prepared according to general method E from (**34**, 500 mg, 0.90 mmol) and hydrazide (**84**, 236 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/methanol to 20:1) afforded 279 mg (36%) of **106** as a white solid (*this compound was taken on directly to the detritylation step*): LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.90 min, ESI m/z = 721, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 721.3265 (721.3261 calc'd for $C_{45}H_{40}F_3N_6$), $[M + H]^+$.

1-Methyl-3-(2-(5-(3-(trifluoromethyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (107). Prepared according to the general method from thioamide (**35**, 720 mg, 1.26 mmol) and hydrazide (**84**, 331 mg, 1.52 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/methanol to 20:1) afforded 463 mg (50%) of **107** as a white solid (*this compound was taken on directly to the detritylation step*): LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.47 min, ESI m/z = 735, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 735.3418 (735.3418 calc'd for $C_{46}H_{42}F_3N_6$), $[M + H]^+$.

3-((5-(2-(1*H*-indol-3-yl)ethyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)benzonitrile (108). Prepared according to the general method E from thioamide (**34**, 500 mg, 0.90 mmol) and hydrazide (**85**, 189 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/methanol to 20/1) afforded 330 mg (54%) of **108** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (bs, 1H), 7.90 (dd, *J* = 8.34, 1.46 Hz, 1H), 7.64 (s, 1H), 7.60 (dt, *J* = 7.23, 1.65 Hz, 1H), 7.48 – 7.45 (m, 1H), 7.43 (d, *J* = 7.50 Hz, 1H), 7.39 (d, *J* = 7.32 Hz, 1H), 7.35 – 7.29 (m, 9H), 7.26 (d, *J* = 8.15 Hz, 1H), 7.20 (d, *J* = 0.93 Hz, 1H), 7.08 (d, *J* = 2.19 Hz, 1H), 7.01- 6.95 (m, 6H), 6.83 (t, *J* = 7.26 Hz, 1H), 6.50 (s, 1H), 4.08 (s, 2H), 3.71 (apparent t, *J* = 7.89 Hz, 2H), 3.05 (apparent t, *J* = 7.09 Hz, 2H), 2.92 (dd, *J* = 8.63, 6.70 Hz, 2H),

2.32 (t, J = 7.02 Hz, 2H), 1.56 (quint., *J* = 7.52 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.70, 152.34, 142.81, 140.13, 138.96, 138.31, 136.68, 134.20, 133.39, 132.73, 130.99, 130.18, 129.78, 129.65, 129.10, 128.70, 128.46, 127.43, 123.10, 121.41, 119.20, 118.72, 118.67, 118.10, 113.85, 111.85, 74.85, 42.49, 30.10, 29.64, 25.90, 25.00, 23.20. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.58 minutes, ESI m/z = 678, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 678.3343 (678.3340 calc'd for $C_{45}H_{40}N_7$, $[M + H]^+$).

3-(2-(5-(3-Nitrobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,24-triazol-3-yl)ethyl)-1*H*-indole (109). Following the general method, thioamide (**34**, 500 mg, 0.90 mmol) and hydrazide (**86**, 211 mg, 1.08 mmol) gave 328 mg (52%) of **109** as a tan solid after purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 10:1: ^{1}H NMR (400 MHz, CD_3OD) δ 8.02-7.97 (m, 1H), 8.00 (s, 1H), 7.47-7.42 (m. 1H), 7.40-7.35 (m, 1H), 7.34-7.28 (m, 11H), 7.15 (d, *J* = 8.20 Hz, m 1H), 7.05-7.01 (m, 6H), 6.92 (t, *J* = 7.63 Hz, 1H), 6.89 (s, 1H), 6.83 (t, *J* = 7.70 Hz, 1H), 6.43 (s, 1H), 4.13 (s, 2H), 3.35-3.31 (m, 2H), 3.17 (t, *J* = 7.14 Hz, 2H), 3.02 (t, *J* = 6.92 Hz, 2H), 2.21 (t, *J* = 7.01 Hz, 2H), 1.38 (quint, *J* = 7.17 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 156.06, 152.36, 148.46, 142.23, 138.90, 138.20, 137.86, 136.65, 134.45, 132.34, 129.79, 129.44, 129.31, 128.00, 127.93, 126.99, 123.10, 122.20, 121.88, 121.10, 118.46, 117.68, 112.91, 111.07, 75.42, 42.23, 29.74, 28.61, 25.79, 24.08, 23.68. LCMS (50-95% CH_3CN in 0.05% TFA over 10 min) retention time = 3.87 min, ESI m/z = 698, $[M+H]^+$.

3-(2-(5-(2-Methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (110). Prepared according to general method E from (**34**, 500 mg, 0.90 mmol) and hydrazide (**87**, 195 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 30:1 to 20:1 CH_2Cl_2/methanol) afforded 203 mg (33%) of **110** as a white solid (*this compound was taken on directly to the detritylation step*): LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes)

retention time = 3.70 min, ESI m/z = 683, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 683.3488 (683.3493 calc'd for $C_{45}H_{43}N_6O$), $[M + H]^+$.

3-(2-(5-(3-Methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (111). Prepared according to the general method from thioamide (**34**, 500 mg, 0.90 mmol) and hydrazide (**88**, 195 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 20:1 to 10:1 CH_2Cl_2/methanol) afforded 190 mg (31%) of **111** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (bs, 1H), 7.49 (d, *J* = 7.80 Hz, 1H), 7.27 – 7.34 (complex multiplets, 10H), 7.21 (d, *J* = 8.30 Hz, 1H), 6.99 – 7.11 (complex multiplets, 9H), 6.86 (d, *J* = 2.30 Hz, 1H), 6.65 – 6.68 (m, 3H), 6.36 (s, 1H), 4.05 (s, 2H), 3.32 (apparent t, *J* = 7.80 Hz, 2H), 3.26 (t, J = 7.80 Hz, 2H), 2.97 (t, J = 7.80 Hz, 2H), 2.25 (t, J = 7.30 Hz, 2H), 1.51 (quint, J = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.91 (s), 155.16 (s), 152.17 (s), 142. 41 (s), 138.49, 137.61, 136.22 129.79, 129.77, 128.20, 128.17, 122.08, 122.00, 120.92, 119.50, 118.62, 118.14, 114.77, 114.16, 112.52, 111.24, 75.33 (s), 55.35 (q), 42.72 (t), 31.70 (t), 29.42 (t), 26.20 (t), 25.20 (t), 23.68 (t). LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.78 min, ESI m/z = 683, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 684.3473 (683.3493 calc'd for $C_{45}H_{43}N_6O$), $[M + H]^+$.

3-((5-(4-Methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (112). Prepared according to general method E from (**34**, 500 mg, 0.93 mmol) and hydrazide (**89**, 208 mg, 1.16 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 30:1, to 20:1) afforded 97 mg (16%) of **112** as a white foam (this material was taken on directly to the detritylation step): LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.63 minutes, ESI m/z = 669, $[M+H]^+$.

3-(2-(5-(3-(Trifluoromethoxy)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (113). Prepared according to the general method from thioamide (**34**, 325 mg, 0.59 mmol) and hydrazide (**90**, 165.8 mg, 0.71 mmol). Purification by flash chromatography (SiO_2, 30:1 CH_2Cl_2/methanol) afforded 203 mg (47%) of **113** as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (dd, *J* = 8.51, 1.45 Hz, 1H), 7.41 (t, *J* = 7.85 Hz, 1H), 7.33 – 7.30 (m, 9H), 7.28 (t, *J* = 7.85 Hz, 1H), 7.18 (d, *J* = 8.16 Hz, 1H), 7.05 – 7.02 (m, 8 H), 6.98 – 6.93 (m, 2H), 6.89 (s, 1H), 6.84 (t, *J* = 7.65 Hz, 1H), 6.44 (bs, 1H), 4.07 (s, 2H), 3.38 – 3.34 (m, 2H), 3.17 (t, *J* = 7.03 Hz, 2H), 3.00 (t, *J* = 7.06 Hz, 2H), 2.19 (t, *J* = 7.09 Hz, 1H), 1.36– 1.32 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD) δ 155.97, 152.63, 149.38, 142.24, 138.98, 138.28, 138.14, 136.67, 130.29, 129.44, 129.26, 127.99, 127.92, 126.97, 126.90, 122.13, 121.10, 120.88, 120.46 (q, J_{CF} = 255.77 Hz), 119.41, 118.45, 117.71, 112.95, 111.05, 75.42, 42.26, 29.85, 28.63, 25.79, 24.13, 23.57. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.25 minutes, ESI m/z = 737, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 737.3206 (737.3210 calc'd for $C_{45}H_{40}F_3N_6O$), $[M + H]^+$.

3-(2-(5-(3-(Benzyloxy)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (114). Prepared according to general method E from thioamide (**34**, 500 mg, 0.90 mmol) and hydrazide (**91**, 277 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 30:1 CH_2Cl_2/methanol to 20/1) afforded 335 mg (49%) of **114** as a white foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 – 7.26 (m, 11H), 7.25 – 7.23 (m, 4H), 7.18 (d, *J* = 8.12 Hz, 1H), 7.13 – 7.10 (m, 1H), 7.04 – 7.00 (m, 7H), 6.95 (t, *J* = 7.01 Hz, 1H), 6.89 (s, 1H), 6.88 (t, *J* = 7.31 Hz, 1H), 6.68 – 6.64 (m, 2H), 6.55 (d, J = 7.61 Hz, 1H), 6.36 (s, 1H), 5.65 (s, 2H), 4.90 (s, 2H), 3.98 (bs, 2H), 3.16 (t, *J* = 7.24, 2H), 2.97 (t, *J* = 7.15 Hz, 2H), 2.10 (t, *J* = 7.23 Hz, 2H), 1.15 (quint., *J* = 7.45 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.08, 155.83, 153.17, 142.24, 139.07, 138.05,

137.09, 137.01, 136.67, 129.70, 129.47, 128.18, 127.99, 127.94, 127.49, 127.18, 126.99, 122.12, 121.10, 120.43, 118.46, 118.41, 117.71, 114.52, 113.66, 112.98, 111.04, 75.41, 69.40, 42.33, 30.35, 28.45, 25.76, 24.29, 23.52. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.50 minutes, ESI m/z = 759, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 759.3818 (759.3806 calc'd for $C_{51}H_{47}N_6O$, $[M + H]^+$).

3-(2-(5-(3-(Methylsulfonyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (115). Prepared according to general method E from thioamide (**34**, 505 mg, 0.910 mmol) and hydrazide (**93**, 500 mg, 1.82 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) afforded 80 mg (12%) of **115** as a white solid (this material was taken on directly to the detritylation step): LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.98 min, ESI m/z = 731, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 731.3171 (731.3163 calc'd for $C_{45}H_{43}N_6O_2S$, $[M + H]^+$).

3-(2-(5-([1,1'-Biphenyl]-4-ylmethyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (116). Prepared according to general method E from (**34**, 500 mg, 0.90 mmol) and hydrazide (**92**, 244 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) and recrystallization of the product from ACN afforded 235 mg (36%) of **116** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (bs, 1H), 7.54 (d, J = 7.40 Hz, 2H), 7.48 (d, J = 8.20 Hz, 2H), 7.35 – 7.43 (m, 3H), 7.25 – 7.31 (complex m, 11H), 7.16 – 7.19 (complex m, 3H), 7.07 (d, J = 2.30 Hz, 1H), 6.96 – 6.98 (m, 7H), 6.85 (t, J = 7.30 Hz, 1H), 6.50 (s, 1H), 4.05 (s, 2H), 3.68 (apparent t, J = 8.20 Hz, 2H), 3.07 (apparent t, J ~ 7.55 Hz, 2H), 2.92 (apparent t, J = 7.80 Hz, 2H), 2.32 (t, J = 6.90 Hz, 2H), 1.61 (quint, J = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.54, 152.84, 142.81, 140.34, 140.18, 139.05, 138.31, 136.72, 136.47, 130.11, 129.65, 129.48, 129.39, 128.65, 128.42, 127.85, 127.47, 127.28, 127.06, 123.10, 121.39, 118.73,

118.69, 118.20, 113.90, 111.85, 74.90, 42.53, 30.40, 29.60, 25.95, 25.06, 23.28. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.40 min, ESI m/z = 729, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 729.3703 (729.3700 calc'd for $C_{50}H_{45}N_6$), $[M + H]^+$.

(*R*)-*tert*-Butyl(1-(5-(3-chlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethylcarbamate (117). Prepared according to general method E from thioamide (**36**, 289 mg, 0.43 mmol) and hydrazide (**80**, 95.6 mg, 0.52 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2./CH_3OH) gave 80 mg (23%) of **117** as a tan foam: LCMS (50-95% CH_3CN in 0.05% TFA over 10 min) retention time = 5.90 min, ESI m/z = 802, $[M+H]^+$.

3-(2-(4-(3-(1-Trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (118). Prepared according to general method E from thioamide (**34**, 500 mg, 0.90 mmol) and formic hydrazide (65 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 20:1 to 10:1 CH_2Cl_2/methanol) afforded 196 mg (25%) of **118** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.35 – 7.30 (m, 10H), 7.30 – 7.26 (m, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.10 – 7.04 (m, 6H), 6.95 (t, *J* = 8.2 Hz, 1H), 6.89 (s, 1H), 6.85 (t, 2H), 6.55 (s, 1H), 3.52 – 3.44 (m, 2H), 3.15 (t, *J* = 7.1 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.24 (t, *J* = 7.2 Hz, 2H), 1.69 (quint., *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.86, 143.35, 142.29, 139.17, 138.19, 136.72, 129.48, 128.00, 127.93, 127.00, 122.18, 121.13, 118.62, 118.50, 117.67, 112.89, 111.07, 75.44, 43.18, 28.92, 25.21, 24.09, 23.74. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.73 min, ESI m/z = 563, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 563.2931 (563.2918 calc'd for $C_{37}H_{35}N_6$), $[M + H]^+$.

3-((5-Benzyl-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (119) Prepared according to general method E from thioamide (**31**, 475 mg, 0.88 mmol)

and 2-phenylacetic hydrazide (165 mg, 1.10 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 30:1, to 20:1, to 10:1) afforded 237 mg (42%) of compound **119** as a tan foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (apparent dd, *J* = 8.7, 1.4 Hz, 1H), 7.42 (apparent t, *J* = 7.8 Hz, 1H), 7.37-7.28 (complex m, 11H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.11 (apparent d, *J* = 7.3 Hz, 1H), 7.06 (s, 1H), 7.04 (s, 1H), 7.01-6.98 (complex m, 7H), 6.97 (dt, *J* = 8.2, 0.9 Hz, 1H), 6.86 (broadened dt, *J* = 8.2, 0.9 Hz, 1H), 6.27 (s, 1H), 4.26 (s, 2H), 4.08 (s, 2H), 3.56 (apparent t, *J* = 8.2 Hz, 2H), 2.14 (t, *J* = 7.3 Hz, 2H), 1.23 (quint. *J* = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.67, 153.30, 142.81, 140.16, 138.21, 137.18, 136.73, 129.69, 128.92, 128.89, 128.70, 128.47, 127.27, 127.07, 123.99, 121.65, 119.08, 118.91, 118.14, 111.91, 109.34, 74.91, 42.74, 31.29, 29.40, 25.08, 21.90. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.23 minutes, ESI m/z = 639, [M+H]+. HRMS (ESI Q-TOF) m/z = 639.3228 (639.3231 calc'd for $C_{43}H_{39}N_6$), $[M + H]^+$.

3-((5-Benzyl-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (120). Prepared according to general method E from thioamide (**32**, 462 mg, 0.83 mmol) and 2-phenylacetic hydrazide (149 mg, 0.99 mmol). Purification by flash chromatography (SiO_2, 30:1 CH_2Cl_2/methanol to 20/1) afforded 202 mg (37%) of **120** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ10.90 (s, 1H), 7.36 – 7.30 (m, 10H), 7.26 - 7.25 (m, 3H), 7.22 (s, 1H), 7.16 – 7.10 (m, 3H), 7.09 – 7.05 (m, 2H), 7.02 – 6.97 (m, 6H), 6.71 (ddd, *J* = 9.7, 8.7, 2.3 Hz, 1H), 6.42 (s, 1H), 4.10 (s, 2H), 3.99 (s, 2H), 3.75 – 3.63 (m, 2H), 2.24 (t, *J* = 7.1 Hz, 2H), 1.38 (quint. , *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.42 (d, J_{CF} = 234.34 Hz), 153.58, 153.28, 142.83, 138.22, 137.19, 136.65 (d, J_{CF} = 13.4 Hz), 136.33, 133.38, 129.69, 129.53, 128.93, 128.90, 128.73, 128.70, 128.49, 127.09, 126.98, 120.15 (d, J_{CF} = 10.5 Hz), 118.14, 109.72, 107.46 (d, J_{CF} = 24.3 Hz), 97.87 (d, J_{CF} = 25.93 Hz), 74.97, 42.76, 30.77, 29.39, 21.57, 20.99. LCMS (50-95%

acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.78 minutes, ESI m/z = 657, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 657.3132 (657.3136 calc'd for $C_{43}H_{38}FN_6$), $[M + H]^+$.

3-((5-Benzyl-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-5-methoxy-1*H*-indole (121). Prepared according to general method E from thioamide (**33**, 300 mg, 0.53 mmol) and 2-phenylacetic hydrazide (99 mg, 0.66 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) gave 118 mg (33%) of compound **121**. ^1H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.90 (d, *J* = 7.40 Hz, 1H), 7.46 (t, *J* = 7.80 Hz, 1H), 7.33 (m, 9H), 7.20 (s, 1H), 7.13-7.03 (complex m, 5H), 6.99 (m, 6H), 6.90 (apparent d, *J* = 2.30 Hz, 1H), 6.62 (dd, *J* = 8.70, 2.30 Hz, 1H), 6.39 (s, 1H), 4.08 (s, 1H), 3.98 (s, 1H), 3.66 (t, *J* = 7.30 Hz, 2H), 2.22 (t, *J* = 6.90 Hz, 2H), 1.36 (quint., *J* = 9.20 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.79, 153.47, 153.24, 142.81, 140.17, 138.17, 137.19, 133.39, 131.85, 129.78, 129.67, 128.87, 128.70, 128.47, 127.63, 127.07, 124.62, 118.10, 112.57, 111.68, 109.02, 100.90, 74.88, 55.73, 42.73, 30.71, 29.40, 25.11, 21.89. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.43 minutes, ESI m/z = 669, $[M+H]^+$.

3-((5-(4-Fluorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (122). Prepared according to general method E from thioamide (**31**, 409 mg, 0.76 mmol) and hydrazide (**77**, 159 mg, 0.95 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) afforded 158 mg (32%) of **122** as a tan solid: ^1H NMR (400 MHz, CD_3OD) δ 7.34 – 7.28 (complex m, 12H), 7.17 (d, *J* = 8.1 Hz, 1H), 7.10 – 7.07 (m, 2H), 7.01 – 6.98 (m, 7H), 6.91 – 6.84 (m, 3H), 6.32 (s, 1H), 4.26 (s, 2H), 4.06 (s, 2H), 3.61 – 3.53 (m, 2H), 2.17 (t, *J* = 7.3 Hz, 2H), 1.30 (quint., *J* = 8.3 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.87 minutes, ESI m/z = 657, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 657.3147 (657.3136 calc'd for $C_{43}H_{38}FN_6$), $[M + H]^+$.

6-Fluoro-3-((5-(4-fluorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (123). Prepared according to general method E from thioamide (**32**, 547 mg, 0.98 mmol) and hydrazide (**77**, 206 mg, 1.22 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) afforded 327 mg (49%) of **123** (this material was carried on directly to the detritylation step): LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.42 minutes, ESI m/z = 675, $[M+H]^+$.

3-((5-(4-Fluorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-5-methoxy-1*H*-indole (124). Prepared according to general method E from thioamide (**33**, 300 mg, 0.53 mmol) and hydrazide (**77**, 111 mg, 0.66 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) afforded 159 mg (43%) of **124 (***tautomeric N-trityl-imidazole isomers present – NMR data reflects major isomer)*: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (bs, 1H), 7.90 (d, *J* = 8.20 Hz, 1H), 7.46 (t, *J* = 8.10 Hz, 1H), 7.36 – 7.29 (m, 9H), 7.21 (bs, 1H), 7.14 – 7.10 (m, 3H), 7.06 (d, *J* = 1.80 Hz, 1H), 7.00 - 6.98 (m, 6H), 6.91 (d, *J* = 2.30 Hz, 1H), 6.62 (dd, *J* = 8.30, 2.30 Hz, 1H), 6.45 (bs, 1H), 4.08 (s, 2H), 3.97 (s, 2H), 3.68 (apparent t, *J* = 7.80 Hz, 2H), 2.24 (t, *J* = 7.60 Hz, 2H), 1.41 (quint., *J* = 7.50 Hz, 2h). ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.47 (d, J_{CF} = 242 Hz), 160.26, 153.80, 153.47, 153.19, 142.82, 140.17, 138.25, 133.39, 133.31 (d, J_{CF} = 2.90 Hz), 131.85, 130.83 (J_{CF} = 8.70 Hz), 129.78, 139.66, 129.10, 128.69, 128.46, 127.63, 124.63 118.11, 115.64 (d, J_{CF} = 22.0 Hz), 112.57, 111.66, 109.02, 100.93, 74.87, 55.73, 42.70, 29.84, 29.44, 25.06, 21.87. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.77 minutes, ESI m/z = 687, $[M+H]^+$.

3-((5-(2-Chlorobenzyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (125). Prepared according to general method E from thioamide (**31**, 300 mg, 0.56 mmol) and hydrazide (**79**, 128 mg, 0.69 mmol). Purification by flash chromatography

(SiO_2, 20:1 CH_2Cl_2/methanol) afforded 209 mg (53%) of **125** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 – 7.26 (complex m, 12 H), 7.19 – 7.12 (m, 3H), 7.04 – 6.97 (m, 9H), 6.87 (dt, *J* = 8.80, 0.90 Hz, 1H), 6.32 (s, 1H), 4.29 (s, 2H), 4.13 (s, 2H), 3.67 – 3.62 (m, 2H), 2.21 (t, *J* = 7.30 Hz, 2H), 1.38 (quint., *J* = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 154.72, 153.27, 142.21, 139.01, 138.08, 136.77, 133.54, 133.40, 131.56, 130.25, 129.46, 128.72, 127.97, 127.89, 127.16, 126.67, 123.03, 121.56, 118.82, 118.55, 117.89, 111.23, 108.12, 75.42, 42.87, 28.59, 28.25, 24.24, 21.55. LCMS (75-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.12 min, ESI m/z = 673, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 673.2844 (673.2841 calc'd for $C_{43}H_{38}ClN_6$), $[M + H]^+$.

3-((5-(3-Chlorobenzyl)-4-(3-(1-trityl-1H-imidazol-4-yl)propyl)-4H-1,2,4-triazol-3-yl)methyl)-1H-indole (126). Prepared according to the general method E from thioamide (**31**, 500 mg, 0.93 mmol) and hydrazide (**80**, 205 mg, 1.11 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 320 mg (51%) of **126** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (bs, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.39 – 7.28 (complex m, 10H), 7.26 – 7.24 (m, 2H), 7.19 – 7.09 (m, 2H), 7.08 – 7.04 (m, 7H), 7.02 – 6.98 (m, 2H), 6.92 (s, 1H), 6.29 (s, 1H), 4.25 (s, 2H), 4.05 (s, 2H), 3.51 (t, *J* = 8.3 Hz, 2H), 2.21 (t, *J* = 7.3 Hz, 2H), 1.40 (quint., *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.18, 152.94, 142.31, 139.27, 138.40, 137.93, 136.24, 134.64, 130.08, 129.81, 128.59, 128.38, 128.28, 128.23, 127.26, 126.84, 126.75, 122.90, 122.44, 119.89, 118.88, 118.27, 111.32, 109.80, 75.42, 43.34, 31.17, 29.51, 25.06, 22.31. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.12 min, ESI m/z = 673, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 673.2853 (673.2841 calc'd for $C_{43}H_{38}ClN_6$), $[M + H]^+$.

3-((5-(3-Chlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (127). Prepared according to general method E from thioamide (**32**, 502 mg, 0.90 mmol) and hydrazide (**80**, 199 mg, 1.07 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 255 mg (41%) of **127** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 – 7.25 (m, 11H), 7.15 – 7.07 (m, 3H), 7.03 – 6.98 (m, 8H), 6.90 (dd, *J* = 9.9, 2.3 Hz, 1H), 6.67 (ddd, *J* = 9.7, 8.7, 2.3 Hz, 1H), 6.37 (d, *J* = 1.4 Hz, 1H), 4.24 (s, 2H), 4.09 (s, 2H), 3.61 (t, *J* = 8.3 Hz, 2H), 2.23 (t, *J* = 7.3 Hz, 2H), 1.31 (quint., *J* = 7.3 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.53 min, ESI m/z = 691, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 691.2742 (691.2747 calc'd for $C_{43}H_{37}ClFN_6$), $[M + H]^+$.

3-((5-(4-Chlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (128). Prepared according general method E from thioamide (**31**, 500 mg, 0.93 mmol) and hydrazide (**81**, 213 mg, 1.16 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 30:1, to 20:1) afforded 220 mg (35%) of **128** as a tan foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 – 7.23 (complex m, 13 H), 7.18 – 7.14 (m, 3H), 7.04 (d, *J* = 8.70 Hz, 2H), 7.00 – 6.94 (m, 6H), 6.88 – 6.84 (m, 1H), 6.32 (s, 1H), 4.26 (s, 2H), 4.06 (s, 2H), 3.57 – 3.53 (m, 2H), 2.17 (t, *J* = 7.10 Hz, 2H), 1.32 (quint., J = 7.30 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 154.91, 153.75, 142.20, 138.93, 138.08, 136.73, 134.34, 143.76, 132.46, 130.33, 129.47, 127.99, 127.90, 126.65, 123.03, 121.56, 118.82, 118.66, 117.83, 111.23, 108.05, 75.42, 42.82, 29.60, , 28.43, 24.19, 21.49. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.25 minutes, ESI m/z = 673, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 673.2848 (673.2841 calc'd for $C_{43}H_{38}ClN_6$, $[M + H]^+$).

3-((5-(3,4-Dichlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (129). Prepared according to general method E from thioamide (**31**, 500 mg, 0.925 mmol) and 2-(3,4-dichlorophenyl)acetic hydrazide[2] (**96**, 246 mg, 1.11 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 149 mg (23%) of compound **129** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (bs, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.29 (complex m, 10H), 7.23 – 7.17 (m, 3H), 7.08 – 7.05 (m, 7H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.33 (s, 1H), 4.26 (s, 2H), 4.02 (s, 2H), 3.53 (t, 7.3 Hz, 2H), 2.23 (t, *J* = 7.3 Hz, 2H), 1.49 (quint., *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.25, 152.64, 142.31, 139.21, 138.49, 136.21, 136.09, 132.83, 131.27, 130.69, 129.80, 128.40, 128.29, 128.24, 127.97, 126.82, 122.84, 122.50, 119.94, 118.83, 118.35, 111.34, 109.85, 75.42, 43.29, 30.51, 29.52, 24.95, 22.28. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.67 min, ESI m/z = 707, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 707.2457 (707.2451 calc'd for $C_{43}H_{37}Cl_2N_6$), $[M + H]^+$.

3-((5-(3,4-Dichlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (130). Prepared according to general method E from thioamide (**32**, 400 mg, 0.716 mmol) and hydrazide (**96**, 188 mg, 0.859 mmol).[2] Purification by flash chromatography (SiO_2, 40:1 to 20:1 $CHCl_3$/methanol) afforded 195 mg (37% yield) of **130** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (bs, 1H), 7.42 – 7.36 (m, 2H), 7.34 – 7.27 (m, 9H), 7.24 – 7.20 (m, 2H), 7.08 – 7.04 (m, 6H), 6.96 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.88 (dd, *J* = 9.6, 2.2 Hz, 2H), 6.76 (ddd, *J* = 9.6, 8.7, 2.3 Hz, 1H), 6.39 (d, *J* = 1.4 Hz, 1H), 4.21 (s, 2H), 4.03 (s, 2H), 3.60 – 3.52 (m, 2H), 2.29 (t, *J* = 7.1 Hz, 2H), 1.54 (quint., *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.16 (d, J_{CF} = 237.8 Hz), 153.96, 152.63, 142.38, 139.35, 138.62, 136.30 (d, J_{CF} = 12.5 Hz), 136.09, 132.86, 131.33, 130.70, 130.40, 129.78, 128.26, 128.22, 127.93, 123.49,

123.01 (d, J = 3.8 Hz), 119.76 (d, J_{CF} = 10.1 Hz), 118.29, 110.02, 108.72 (d, J_{CF} = 24.5 Hz), 97.63 (d, J_{CF} = 26.1 Hz), 75.38, 43.26, 30.57, 29.47, 25.06, 22.35. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.33 min, ESI m/z = 725, $[M+H]^+$.

3-((5-(3,5-Dichlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (131). Prepared according to general method E from thioamide (**31**, 500 mg, 0.925 mmol) and hydrazide (**82**, 230 mg, 1.05 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 284mg (43%) of **131** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (bs, 1H), 7.49 (d, J = 8.40 Hz, 1H), 7.37 (s, 1H), 7.35 – 7.27 (complex m, 9H), 7.21 (d, J = 8.30 Hz, 1H), 7.11 – 6.99 (complex m, 10H), 6.92 (s, 1H), 6.34 (s, 1H), 4.25 (s, 2H), 4.02 (s, 2H), 3.57 – 3.53 (2H), 2.23 (t, J = 7.30 Hz, 2H), 1.39 (quint., J = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.25, 152.28, 142.41, 139.39, 139.30, 138.54, 136.25, 135.29, 129.78, 128.18, 127.43, 127.04, 122.78, 122.48, 119.96, 118.81, 118.22, 111.30, 109.85, 75.33, 43.32, 30.81, 29.56, 25.04, 22.31. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.03 min, ESI m/z = 707, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 707.2459 (707.2451 calc'd for $C_{43}H_{37}Cl_2N_6$, $[M + H]^+$).

3-((5-(3,5-Dichlorobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (132). Prepared according to general method E from thioamide (**32**, 500 mg, 0.895 mmol) and hydrazide (**82**, 235 mg, 1.07 mmol). Purification by flash chromatography (SiO_2, 40:1 to 20:1 CH_2Cl_2/methanol) afforded 227 mg (39%) of compound **132** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (bs, 1H), 7.40 – 7.28 (complex m, 10H), 7.10 – 7.02 (complex m, 9H), 6.90 – 6.88 (m, 2H), 6.79 – 6.65 (m, 1H), 6.39 (s, 1H), 4.22 (s, 2H), 4.03 (s, 2H), 3.56 (t, J = 7.80 Hz, 2H), 2.28 (t, J = 6.90 Hz, 2H), 1.53 – 1.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.155, (d, J_{CF} = 239 Hz), 153.99, 152.32, 142.36, 139.26 (d, J_{CF} = 6.70 Hz),

138.56, 136.28 (d, J_{CF} = 12.4 Hz), 135.32, 129.76, 128.23, 128.20, 127.01, 123.45, 123.00, 119.75 (d, J_{CF} = 9.60 Hz), 118.23, 109.95, 108.79 (d, J_{CF} = 24.9 Hz), 97.61 (d, J_{CF} = 25.9 Hz), 75.37, 30.82, 29.53, 25.03, 22.38. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.00 min, ESI m/z = 725, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 725.2346 (725.2357 calc'd for $C_{43}H_{36}Cl_2FN_6$, $[M + H]^+$).

3-((5-(3-Bromobenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (133). Prepared according to general method E from thioamide (**32**, 350 mg, 0.63 mmol) and hydrazide (**83**, 172 mg, 0.75 mmol). Purification by flash chromatography (SiO_2, 30:1 CH_2Cl_2/methanol to 20/1) afforded 224 mg (49%) of **133** as a white foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, *J* = 8.63, 1H), 7.55 – 7.38 (complex overlapping m, 2H), 7.36 – 7.26 (complex m, 9H), 7.23 – 7.18 (m, 2H), 7.05 – 7.00 (complex overlapping m, 8H), 6.90 (dd, *J* = 9.88, 2.24 Hz, 1H), 6.67 (dt, *J* = 9.59, 2.26 Hz, 1H), 6.38 (s, 1H), 4.24 (s, 2H), 4.08 (s, 2H), 3.63 – 3.59 (m, 2H), 2.23 (t, *J* = 7.31 Hz, 2H), 1.30 (quint., *J* = 7.43 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.78 minutes, ESI m/z = 735, 737, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 737.2250 (737.2242 calc'd for $C_{43}H_{37}N_6BrF$).

3-((5-(3-(Trifluoromethyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (134). Prepared according to general method E from thioamide (**31**, 300 mg, 0.55 mmol) and hydrazide (**84**, 144 mg, 0.67 mmol). Purification by flash chromatography (SiO_2, 30:1 CH_2Cl_2/methanol to 20/1) afforded 268 mg (69%) of **134** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (bs, 1H), 7.898 (dd, *J* = 8.39, 1.38 Hz, 1H), 7.389 – 7.37 (complex m, 5H), 7.35 – 7.30 (m, 9H), 7.22 (d, *J* = 8.11 Hz, 1H), 7.20 (d, *J* = 1.06 Hz, 1H), 7.12 (d, *J* = 2.15 Hz, 1H), 7.00 – 6.98 (m, 6H), 6.96 (t, *J* = 7.92 Hz, 1H), 6.82 (t, *J* = 7.33 Hz, 1H), 6.42 (s, 1H), 4.12 (s, 2H), 4.10 (s, 2H), 3.75 (apparent t, *J* = 7.80 Hz, 2H), 2.25 (t, *J* = 7.08 Hz, 2H), 1.41 (quint.,

J = 7.89 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.22 minutes (broad), ESI m/z = 707, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 707.3096 (707.3105 calc'd for $C_{44}H_{38}F_3N_6$), $[M + H]^+$. HRMS (ESI Q-TOF) m/z = 465.2007 (465.2009 calc'd for $C_{25}H_{24}F_3N_6$, $[M – Trt + H]^+$).

6-Fluoro-3-((5-(3-(trifluoromethyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (135). Prepared according to general method E from thioamide (**32**, 322 mg, 0.58 mmol) and hydrazide (**84**, 151 mg, 0.89 mmol). Purification by flash chromatography (SiO_2, 30:1 CH_2Cl_2/methanol to 20/1) afforded 169 mg (40%) of **135** as a white foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 – 7.96 (m, 1H), 7.64 – 7.48 (overlapping complex m, 2H), 7.46 (s, 1H), 7.43 – 7.39 (m, 1H), 7.37 – 7.27 (m, 11H), 7.02 – 6.99 (m, 6H), 6.88 (dd, *J* = 9.86, 2.22 Hz, 1H), 6.65 (dt, *J* = 9.55, 2.32 Hz, 1H), 6.36 (s, 1H), 4.24 (s, 2H), 4.18 (s, 2H), 3.69 – 3.64 (m, 2H), 2.23 (t, *J* = 7.31 Hz, 2H), 1.32 (quint., *J* = 7.49 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 161.16 (d, J_{CF} = 236.03 Hz), 154.67, 153.65 142.21, 139.02, 138.08, 137.07, 136.75 (d, J_{CF} = 12.43 Hz), 132.10, 130.90, 130.57, 129.44, 127.98, 127.90, 125.41, 124.88 (q, $J_{,F}$ = 3.64 Hz), 124.07 (q, J_{CF} = 271.71 Hz), 123.73 (q, J_{CF} = 3.64 Hz), 3.93(q, J_{CF} = 3.64 Hz), 123.46, 123.49, 123.38, 118.85, 118.75, 108.38, 107.37 (d, J_{CF} = 24.80 Hz), 97.14 (d, J_{CF} = 25.76 Hz), 75.39, 42.84, 29.89, 28.49, 24.22, 21.45. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.20 minutes, ESI m/z = 725, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 725.3013 (725.3010 calc'd for $C_{44}H_{37}F_4N_6$), $[M + H]^+$.

5-Methoxy-3-((5-(3-(trifluoromethyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (136). Prepared according to general procedure E from thioamide (**33**, 360 mg, 0.63 mmol), hydrazide (**84**, 172 mg, 0.79 mmol), silver benzoate (286 mg, 1.26 mmol), and acetic acid (113 mg, 108 μL, 1.89 mmol), which afforded 932 mg of crude

material. The crude was purified by flash chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH to 10:1) to afford 209 mg (45%) of **136**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.90 (d, *J* = 8.20 Hz, 1H), 7.60-7.38 (complex m, 3H), 7.32 (m, 9H), 7.19 (s, 1H), 7.11 (d, *J* = 8.70 Hz, 1H), 7.06 (s, 1H), 6.99 (m, 6H), 6.91 (apparent d, *J* = 1.80 Hz, 1H), 6.62 (dd, *J* = 8.70, *J* = 2.30 Hz, 1H) 6.43 (s, 1H), 4.10 (s, 2H), 4.09 (s, 2H), 3.75 (t, *J* = 7.30 Hz, 2H), 3.59 (s, 3H), 2.25 (t, *J* = 6.90 Hz, 2H), 1.42 (*J* = 7.70 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 7.98 minutes, ESI m/z = 737, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 737.3203 (737.3210 calc'd for $C_{45}H_{40}F_3N_6O$), $[M + H]^+$.

3-((5-(2-Methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (137). Prepared according to general method E from thioamide (**31**, 408 mg, 0.754 mmol) and hydrazide (**87**, 163 mg, 0.904 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 212 mg (42%) of triazole **137** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.27 (m, 9H), 7.17 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.10 – 7.02 (m, 9H), 7.02 – 6.95 (m, 2H), 6.89 (d, *J* = 2.4 Hz, 1H), 6.76 (td, *J* = 7.5, 1.1 Hz, 1H), 6.71 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.24 (d, *J* = 1.4 Hz, 1H), 4.23 (d, *J* = 1.0 Hz, 2H), 4.06 (s, 2H), 3.68 (s, 2H), 3.59 – 3.51 (m, 2H), 2.21 (t, *J* = 7.7 Hz, 2H), 1.42 (quint., *J* = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.64, 154.02, 153.65, 142.45, 139.85, 138.36, 136.28, 130.12, 129.83, 128.28, 128.21, 128.17, 126.92, 124.40, 122.83, 122.32, 120.89, 119.77, 119.00, 118.03, 111.24, 110.36, 110.11, 75.28, 55.39, 43.21, 29.58, 25.48, 24.79, 22.37. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.20 min, ESI m/z = 669, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 669.3346 (669.3336 calc'd for $C_{44}H_{41}N_6O$), $[M + H]^+$.

6-Fluoro-3-((5-(2-methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (138). Prepared according to general method E from thioamide (**32**, 500

mg, 0.89 mmol) and hydrazide (**87**, 194 mg, 1.07 mmol). Purification by flash chromatography (SiO_2, 40:1 to 20:1 CH_2Cl_2/methanol) afforded 179 mg (29%) of triazole **138** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (complex m, 12H). 7.06 – 6.98 (complex m, 9H), 6.87 – 6.85 (m, 1H), 6.77 – 6.70 (m, 2H), 6.27 (s, 1H), 4.19 (s, 2H), 4.06 (s, 2H), 3.67 (s, 3H), 3.58 – 3.54 (m, 2H), 2.25 (t, J = 7.80 Hz, 2H), 1.40 (quint., J = 7.70 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.05 (d, J_{CF} = 248 Hz), 156.61, 154.07, 153.39, 142.32, 139.58, 138.29, 136.32 (d, J_{CF} = 12.5 Hz), 129.77, 128.25, 128.19, 124.28, 123.54, 123.14 (d, J_{CF} = 3.90 Hz), 120.90, 119.89 (d, J_{CF} = 9.80 Hz), 118.07, 110.37, 110.04, 108.47 (d, J_{CF} = 23.9 Hz), 97.54 (d, J_{CF} = 26.9 Hz), 75.08, 55.38, 43.18, 29.45, 25.33, 24.78, 22.44. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.85 min, ESI m/z = 687, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 687.3244 (687.3242 calc'd for $C_{44}H_{40}FN_6O$, $[M + H]^+$).

3-((5-(3-Methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (139). Prepared according to the general method from thioamide (**31**, 390 mg, 0.721 mmol) and hydrazide (**88**, 156 mg, 0.866 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 291 mg (60%) of triazole **139** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.80 Hz, 1H), 7.44 – 7.30 (complex m, 11H), 7.16 (d, J = 8.30 Hz, 1H), 7.09 – 6.97 (complex m, 8H), 6.92 (s, 1H), 6.84 – 6.78 (m, 2H), 6.68 – 6.58 (m, 1H), 6.26 (s, 1H), 4.25 (s, 2H), 4.07 (s, 2H), 3.59 (s, 3H), 3.52 – 3.48 (m, 2H), 2.20 (t, J = 7.30 Hz, 2H), 1.37 (quint., J = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.93, 153.99, 153.45, 142.28, 139.31, 138.28, 137.42, 136.19, 129.80, 128.27, 128.22, 122.82, 122.41, 121.74, 120.76, 119.85, 118.99, 118.23, 113.63, 113.09, 112.94, 111.22, 109.98, 75.42, 55.22, 42.11, 31.72, 29.41, 25.13, 22.34. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.01

min, ESI m/z = 669, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 669.3342 (669.3336 calc'd for $C_{44}H_{41}N_6O$, $[M + H]^+$).

6-Fluoro-3-((5-(3-methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (140). Prepared following general method E from thioamide (**32**, 400 mg, 0.72 mmol) and hydrazide (**88**, 155 mg, 0.86 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) afforded 150 mg (30%) of triazole **140** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.46 – 7.28 (m, 10H), 7.10 – 6.97 (m, 6H), 6.90 – 6.80 (m, 3H), 6.74 (dt, *J* = 9.3, 2.1 Hz, 1H), 6.69 – 6.56 (m, 3H), 6.31 (s, 1H), 4.20 (s, 2H), 4.07 (s, 2H), 3.60 (s, 3H), 3.55 – 3.49 (m, 2H), 2.24 (t, *J* = 7.4 Hz, 2H), 1.39 (quint., *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.65 (d, J_{CF} = 238.26 Hz), 159.99, 153.74, 153.48, 142.34, 139.39, 138.39, 137.41, 136.28 (d, J_{CF} = 12.5 Hz),129.79, 128.28, 128.22, 123.52, 123.05 (d, J_{CF} = 3.3 Hz), 121.66, 120.75, 119.94 (d, J_{CF} = 10.1 Hz), 118.21, 114.94, 113.77, 112.88, 110.13, 108.63 (d, J_{CF} = 24.6 Hz), 75.42, 55.21, 41.61, 31.74, 29.36, 25.21. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.87 minutes, ESI m/z = 687, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 687.3251 (687.3242 calc'd for $C_{44}H_{40}FN_6O$, $[M + H]^+$).

3-(2-(5-(4-Methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-5-yl)propyl)-4*H*-1,2,4-triazol-3-yl)-ethyl)-1*H*-indole (141). Prepared according to general method E from thioamide (**31**, 540 mg, 0.97 mmol) and hydrazide (**89**, 209 mg, 1.16 mmol). Purification by flash chromatography (SiO_2, 30:1 to 20:1 CH_2Cl_2/methanol) afforded 250 mg (38%) of triazole **141** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (bs, 1H), 6.73 – 7.91 (complex multiplets, 25H), 6.51 (s), 3.93 (s, 2H), 3.63 (apparent t, *J* = 7.40 Hz, 2H), 3.61 (s, 3H), 3.05 (apparent t, *J* = 7.40 Hz, 2H), 2.89 (apparent t, J = 6.90 Hz, 2H), 2.29 (t, J = 6.90 Hz, 2H), 1.54 (quint, J = 7.30 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.44, 154.46, 153.21, 142.82, 140.16, 138.30, 136.67, 130.51, 129.90,

129.66, 128.95, 128.69, 128.46, 127.43, 123.08, 121.40, 118.72, 118.19, 114.38, 114.14, 113.87, 111.84, 74.88, 55.49, 42.43, 29.92, 29.55, 25.88, 25.05, 23.22. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.75 min, ESI m/z = 683, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 683.3513 (683.3493 calc'd for $C_{45}H_{43}N_6O$), $[M + H]^+$.

6-Fluoro-3-((5-(4-methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (142). Prepared according to general method E from thioamide (**32**, 300 mg, 0.54 mmol) and hydrazide (**89**, 121 mg, 0.67 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) afforded 234 mg (63%) of triazole **142**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (bs, 1H), 7.91 – 7.89 (m, 2H), 7.45 (t, *J* = 7.80 Hz, 2H), 7.39 – 7.30 (complex overlapping m, 8H), 7.22 (d, *J* = 1.40 Hz, 1H), 7.11 (d, *J* = 2.30 Hz, 1H), 7.01 – 6.97 (m, 6H), 6.73 – 6.68 (m, 3H), 6.47 (bs, 1H), 4.08 (s, 2H), 3.90 (s, 2H), 3.59 (s, 3H), 3.67 – 3.63 (m, 2H), 2.25 (t, *J* = 7.30 Hz, 2H), 1.41 (apparent quint., *J* ~ 7.30 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.43 minutes, ESI m/z = 687, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 687.3251 (687.3242 calc'd for $C_{44}H_{40}FN_6O$, $[M + H]^+$).

5-Methoxy-3-((5-(4-methoxybenzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (143). Prepared according to the general method from thioamide (**33**, 311 mg, 0.54 mmol) and hydrazide (**89**, 123 mg, 0.68 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) afforded 132 mg (39%) of triazole **143**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.7 (s, 1H), 7.90 (d, *J* = 6.80 Hz, 1H), 7.45 (t, *J* = 7.80 Hz, 1H), 7.33 (m, 9H), 7.21 (s, 1H), 7.11 (d, *J* = 8.70 Hz, 1H), 7.04 (apparent d, *J* = 1.80 Hz, 1H), 6.99 (m, 6H), 6.90 (apparent d, *J* = 2.30 Hz, 1H), 6.70 (d, *J* = 8.70 Hz, 2H), 6.62 (dd, *J* = 8.70, *J* = 2.30 Hz, 1H) 6.46 (s, 1H), 4.06 (s, 2H), 3.90 (s, 2H), 3.64 (partially obs. t, *J* = 7.30 Hz, 2H), 3.59 (s, 3H),

3.59 (s, 3H), 2.23 (t, J = 6.80 Hz, 2H), 1.41 (quint., J = 6.80 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.38 minutes, ESI m/z = 699, $[M+H]^+$.

3-((5-((1*H*-Indol-3-yl)methyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)benzonitrile (144). Prepared according to general method E from (**31**, 506 mg, 0.94 mmol) and hydrazide (**85**, 197 mg, 1.12 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/methanol to 20:1) afforded 347 mg (56%) of triazole **144** as a white foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 – 7.38 (m, 3H), 7.37 – 7.27 (m, 12H), 7.16 (dt, J = 8.2, 0.9 Hz, 1H), 7.04 – 6.99 (m, 7H), 6.95 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 6.87 (ddt, J = 8.0, 7.0, 0.9 Hz, 1H), 6.32 (d, J = 1.4 Hz, 1H), 4.28 (s, 2H), 4.14 (s, 2H), 3.66 – 3.59 (m, 2H), 2.19 (t, J = 7.4 Hz, 2H), 1.30 (quint., J = 7.3, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.22 minutes, ESI m/z = 664, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 664.3174 (664.3183 calc'd for $C_{44}H_{38}N_7$, $[M + H]^+$).

3-((5-((6-Fluoro-1*H*-indol-3-yl)methyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)benzonitrile (145). Prepared according to general method E from thioamide (**32**, 507 mg, 0.91 mmol) and hydrazide (**85**, 191 mg, 1.09 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/methanol to 20:1) afforded 271 mg (44%) of triazole **145** as a white foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 – 7.39 (m, 3H), 7.38 – 7.25 (m, 12H), 7.05 – 6.98 (m, 7H), 6.89 (dd, J = 9.8, 2.3 Hz, 1H), 6.73 – 6.61 (m, 1H), 6.39 (s, 1H), 4.25 (s, 2H), 4.14 (s, 2H), 3.70 – 3.62 (m, 2H), 2.26 (t, J = 7.2 Hz, 2H), 1.37 (quint., J = 7.3 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.90 (d, J_{CF} = 235.9 Hz), 154.73, 153.41, 142.24, 139.03, 138.17, 137.47, 136.78 (d, J_{CF} = 12.5 Hz), 133.08, 131.86, 130.75, 129.65, 129.46, 128.01, 127.95, 123.58 (d, J_{CF} = 3.4 Hz), 123.42, 118.82 (d, J_{CF} = 10.3 Hz), 118.45, 118.02, 112.56, 108.39, 107.42 (d, J_{CF} = 24.9 Hz), 97.17 (d, J_{CF} = 25.9 Hz), 75.45, 42.86, 29.72, 28.53, 24.22, 21.49. LCMS (50-95%

acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.55 minutes, ESI m/z = 682, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 682.3087 (682.3089 calc'd for $C_{44}H_{37}FN_7$), $[M + H]^+$.

3-(2-(5-(3-(Methylsulfonyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (146). Prepared according to general method E from thioamide (**31**, 505 mg, 0.910 mmol) and hydrazide (**93**, 500 mg, 1.82 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/MeOH) afforded 80 mg (12%) of triazole **146** as a white solid (this material was taken on directly to the detritylation step): LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.98 min, ESI m/z = 731, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 731.3171 (731.3163 calc'd for $C_{45}H_{43}N_6O_2S$, $[M + H]^+$).

6-Fluoro-3-((5-(3-(methylsulfonyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (147). Prepared according to general method E from thioamide (**32**, 501 mg, 0.90 mmol) and hydrazide (**93**, 246 mg, 1.08 mmol). Purification by flash chromatography (SiO_2, 40:1 CH_2Cl_2/methanol to 10:1) afforded 406 mg (61%) of triazole **147** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (d, *J* = 2.4 Hz, 1H), 7.79 (t, *J* = 1.9 Hz, 1H), 7.70 (dt, *J* = 6.9, 1.9 Hz, 1H), 7.48 (dd, *J* = 2.2, 1.2 Hz, 1H), 7.41 – 7.29 (m, 11H), 7.22 (d, *J* = 1.4 Hz, 1H), 7.13 (d, *J* = 2.3 Hz, 1H), 7.02 – 6.96 (m, 7H), 6.71 (ddd, *J* = 9.8, 8.7, 2.4 Hz, 1H), 6.47 (d, *J* = 1.4 Hz, 1H), 4.13 (s, 2H), 4.11 (s, 2H), 3.83 – 3.72 (m, 2H), 3.08 (s, 3H), 2.27 (t, *J* = 7.1 Hz, 2H), 1.41 (quint., *J* = 7.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.38 (d, J_{CF} = 234.3 Hz), 153.70, 152.84, 142.84, 141.45, 138.84, 138.29, 136.61 (d, J_{CF} = 12.8 Hz), 134.49, 129.68, 128.72, 127.51, 125.83, 124.63, 124.17, 120.14 (d, J_{CF} = 10.5 Hz), 118.07, 109.65, 107.50 (d, J_{CF} = 24.4 Hz), 97.88 (d, J_{CF} = 25.0 Hz), 74.88, 44.00, 30.33, 29.46, 25.02, 21.81. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.08 minutes, ESI m/z = 735, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 735.2910 (735.2912 calc'd for $C_{44}H_{40}FN_6O_2S$, $[M + H]^+$).

3-((5-(4-(Methylsulfonyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (148). Prepared according to general method E from thioamide (**31**, 480 mg, 0.89 mmol) and hydrazide (**94**, 243 mg, 1.07 mmol). Purification by flash chromatography (SiO_2, 30:1 CH_2Cl_2/methanol to 10/1) afforded 271 mg (43%) of **148** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.28 (m, 10H), 7.23 (d, *J* = 1.7 Hz, 12H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.02 – 6.98 (m, 6H), 6.96 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 6.83 (t, *J* = 8.2,1H), 6.51 (d, *J* = 1.4 Hz, 1H), 4.12 (s, 2H), 4.11 (s, 2H), 3.74 (t, *J* = 8.1 Hz, 2H), 3.46 (s, 3H), 2.28 (t, *J* = 6.9 Hz, 2H), 1.50 (quint., *J* = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.84, 152.64, 142.85, 139.68, 138.31, 136.74, 130.52, 130.16, 129.69, 128.73, 128.48, 127.64, 127.47, 127.46, 124.06, 121.67, 119.09, 118.95, 118.24, 111.94, 109.31, 74.91, 44.08, 42.73, 30.49, 29.54, 24.96, 21.88. LCMS (30-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 7.40 minutes (broad), ESI m/z = 717, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 717.3015 (717.3006 calc'd for $C_{44}H_{41}N_6O_2S$), $[M + H]^+$.

6-Fluoro-3-((5-(4-(methylsulfonyl)benzyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (149). Prepared according to general method E from thioamide (**32**, 739 mg, 1.32 mmol) and hydrazide (**94**, 363 mg, 1.59 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 174 mg (18% yield) of triazole **149** as a white foam (this material was taken on directly to the detritylation step): LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.15 minutes, ESI m/z = 735, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 735.2925 (735.2912 calc'd for $C_{44}H_{40}FN_6O_2S$, $[M + H]^+$).

6-Fluoro-3-((5-neopentyl-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (150). To a solution of thioamide (**37**, 300 mg, 0.62 mmol) and 6-fluoro-2-(1H-indol-3-yl)acetic hydrazide hydrochloride (**95**, 189 mg, 0.78 mmol) in CH_2Cl_2 (40 mL) was

added silver benzoate (284 mg, 1.24 mmol) followed immediately with acetic acid (112 mg, 106 µL, 1.86 mmol). To the black solution (Ag_2S formation) was added TEA (78 mg, 108 µL, 0.78 mmol) and the resulting mixture was stirred at RT for 18 hr. Additional silver benzoate (284 mg, 1.24 mmol) and acetic acid (112 mg, 106 µL, 1.86 mmol) were added to the reaction and stirring was continued for an additional 72 hr. The solution was concentrated and the residue was dissolved in 1:1 MeOH/CH_2Cl_2 and treated with 1N HCl (1.24 mmol, 1.24 mL). The mixture was stirred for 5 min, treated with diisopropylethylamine (~10 mmol, ~5 mL) and concentrated. The residue was suspended in MeOH (120 mL), filtered through celite (1 inch pad) and concentrated to afford 1.11 g of crude material. The crude residue was purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1) afforded 200 mg (51%) of compound **150**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (td, *J* = 7.7, 3.9 Hz, 1H), 7.36 – 7.22 (m, 10H), 7.06 – 7.02 (m, 6H), 6.98 (s, 1H), 6.91 (dd, *J* = 9.9, 2.3 Hz, 1H), 6.69 – 6.61 (m, 1H), 6.54 (s, 1H), 4.26 (s, 2H), 3.78 – 3.68 (m, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.60 (quint., *J* = 8.2 Hz, 2H), 0.90 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.91 (d, *J* = 236.2 Hz), 153.74, 153.61, 142.23, 139.13, 138.25, 136.80 (d, *J* = 12.6 Hz), 129.46, 128.01, 127.92, 127.33, 123.41, 123.38, 118.86 (d, *J* = 10.4 Hz), 108.67, 107.33 (d, *J* = 24.9 Hz), 97.16 (d, *J* = 25.9 Hz), 75.51, 42.80, 31.88, 30.61, 28.96, 28.59, 24.14, 21.63. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.62 minutes, ESI m/z = 637, $[M+H]^+$.

3,3'-((4-(3-(1-Trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3,5-diyl)bis(methylene))bis(6-fluoro-1*H*-indole) (151). To a solution of thioamide (**32**, 300 mg, 0.54 mmol) and hydrazide hydrochoride (**95**, 164 mg, 0.68 mmol), in CH_2Cl_2 (40 mL) was added silver benzoate (247 mg, 1.08 mmol) followed immediately with acetic acid (97 mg, 93 µL, 1.62 mmol). To the black solution (Ag_2S formation) was added TEA (68 mg, 94 µL, 0.68 mmol) and the

mixture was stirred at RT for 18 hrs. LCMS showed modest reaction progress. Additional silver benzoate (247 mg, 1.08 mmol) and acetic acid (97 mg, 93 μL, 1.62 mmol) were added and the reaction was allow to stir at RT for an additional 72 hrs. The solution was concentrated and the residue was dissolved in 1:1 MeOH/CH_2Cl_2 and treated with 1N HCl (1.08 mmol, 1.08 mL). The mixture was stirred for 5 min, treated with diisopropylethylamine (~10 mmol, ~5 mL) and concentrated. The residue was suspended in MeOH (120 mL), filtered through celite (1 inch pad) and concentrated to afford 1.18 g of crude material. The crude residue was purified by flash chromatography (SiO_2, 40:1 CH_2Cl_2/MeOH to 20:1, to 10:1) afforded 68 mg (18%) of triazole **151** as a colorless glass: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 – 10.76 (m, 2H), 7.94 – 7.88 (m, 1H), 7.49 – 7.42 (m, 1H), 7.38 – 7.29 (m, 10H), 7.22 (s, 1H), 7.07 (d, J = 2.3 Hz, 2H), 7.01 – 6.95 (m, 7H), 6.66 (ddd, J = 9.8, 8.7, 2.4 Hz, 2H), 6.46 (s, 1H), 4.06 (s, 4H), 3.69 (t, J = 8.0 Hz, 2H), 2.24 (t, J = 7.1 Hz, 2H), 1.46 (quint., J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ159.37 (d, J_{CF} = 234.3 Hz), 153.38, 142.81, 138.22, 136.61 (d, J_{CF} = 12.5 Hz), 133.40, 131.29, 129.80, 129.11, 128.70, 128.45, 124.54 (d, J_{CF} = 3.3 Hz), 124.16, 120.13 (d, J_{CF} = 10.2 Hz), 118.15, 109.74, 107.41 (d, J_{CF} = 24.4 Hz), 97.85 (d, J_{CF} = 25.3 Hz), 42.71, 29.40, 25.00, 21.82. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.32 minutes, ESI m/z = 714, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 714.3148 (714.3151 calc'd for $C_{45}H_{38}F_2N_7$), $[M + H]^+$.

Synthesis of 3-Thiol-3,4-Disubstituted-1,2,4-Triazoles 154-155.

5-((1*H*-indol-3-yl)methyl-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazole-3-thiol (154). To a solution of 4-(3-isothiocyanatopropyl)-1-trityl-1*H*-imidazole[21] (**152**, 2.00 g, 5.06 mmol) and 2-(1*H*-indol-3-yl)acetylhydrazide hydrochloride (**153**, 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 **154** 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 $C_{35}H_{31}N_6S$), $[M + H]^+$.

5-((6-Fluoro-1*H*-indol-3-yl)methyl)-4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazole-3-thiol (155). To a solution of 4-(3-isothiocyanatopropyl)-1-trityl-1*H*-imidazole[21] (**152**, 2.37 g, 5.78 mmol) and 2-(6-fluoro-1H-indol-3-yl)acetylhydrazide hydrochloride (**95**, 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 **155** 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 $C_{36}H_{32}FN_6S$), $[M + H]^+$.

3-((4-(3-(1-Trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (156). A solution of thiol (**154**, 300 mg, 0.52 mmol) in CH_2Cl_2 (4.5 mL) at 0-5 ºC (ice-bath) was treated with a mixture of 30% hydrogen peroxide (120 µL, 1.17 mmol) and acetic acid (450 µL, 7.87 mmol) dropwise. The resulting mixture was stirred at 0-5 ºC for 30 min and allowed to warm to RT. After 1.5 h the reaction was made basic with 4N NaOH (3 mL), diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with brine (50 mL) and dried (Na_2SO_4). Filtration and concentration afforded the crude product. Purification by flash chromatography (SiO_2, 10:1 $CHCl_3$/methanol) afforded 81 mg (28%) of **156** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.98 (s, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.27 (m, 10H), 7.27 – 7.21 (m, 1H), 7.15 – 7.05 (m, 7H), 7.02 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.42 (s, 1H), 4.28 (s, 2H), 3.75 (t, *J* = 7.4 Hz, 2H), 2.35 (t, *J* = 7.2 Hz, 2H), 1.83 (quint., *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.06, 143.94, 142.44, 139.53, 138.70, 136.32, 129.79, 128.22,128.18, 126.85, 122.74, 122.45, 119.87, 118.89, 118.33, 111.34, 109.92, 75.30, 43.85, 29.83, 24.86, 21.78. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.78 min, ESI m/z = 549, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 549.2759 (549.2761 calc'd for $C_{36}H_{33}N_6$), $[M + H]^+$.

6-Fluoro-3-((4-(3-(1-trityl-1*H*-imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (157). A solution of thiol (**155**, 345 mg, 0.58 mmol) in CH_2Cl_2 (6 mL) at 0-5 ºC (ice-bath) was treated with a mixture of 30% hydrogen peroxide (133 µL, 1.31 mmol) and acetic acid (502 µL, 8.78 mmol) dropwise. The resulting mixture was stirred at 0-5 ºC for 30 min and allowed to warm to RT. After 1.5 h the reaction was made basic with 4N NaOH (3.3 mL), diluted with water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with brine (50 mL) and dried (Na_2SO_4). Filtration and concentration afforded the crude product. Purification

by flash chromatography (SiO_2, 20:1 to 10:1 $CHCl_3$/methanol) afforded 126 mg (38%) of **157** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 7.95 (s, indole NH partially exchanged), 7.37 – 7.25 (m, 11H), 7.10 – 7.03 (m, 6H), 6.99 (d, *J* = 1.0 Hz, 1H), 6.91 (dd, *J* = 9.8, 2.3 Hz, 1H), 6.66 (ddd, *J* = 9.7, 8.7, 2.3 Hz, 1H), 6.50 (d, *J* = 1.4 Hz, 1H), 4.26 (s, 2H), 3.88 – 3.78 (m, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.76 (quint., *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.90 (d, J_{CF} = 236.1 Hz), 153.58, 144.38, 142.28, 139.27, 138.13, 136.77 (d, J_{CF} = 12.5 Hz), 129.47, 127.98, 127.92, 123.49 (d, J_{CF} = 3.3 Hz), 123.43, 118.84 (d, J_{CF} = 10.1 Hz), 118.52, 108.49, 107.34 (d, J_{CF} = 24.9 Hz), 97.11 (d, J_{CF} = 26.1 Hz), 75.44, 43.75, 29.22, 24.24, 20.85. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.55 min, ESI m/z = 567, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 567.2661 (567.2667 calc'd for $C_{36}H_{32}FN_6$), $[M + H]^+$.

General Method F. Trityl Deprotection and Synthesis 1,2,4-Triazoles 158-214. To a mixture of the trityl-protected analogue (1 mmol) in ethanol (30 mL) was added 2N HCl (10 mL) and the mixture was heated to 70 °C for 2-4 hr. The reaction was cooled, transferred to a separatory funnel, and diluted with water (100 mL). The solution was extracted with CH_2Cl_2 (3 x 100 mL) and the CH_2Cl_2 layers were discarded. The resulting aqueous solution was made basic with 2N NaOH (checked with pH paper) and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated. The residue was purified by recrystallization, flash chromatography, or used as is.

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (158). Prepared according to general method F from (**97**, 250 mg, 0.38 mmol). Recrystallization from ACN afforded 46 mg (30%) of **158** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) *imidazole tautomers observed – data reflects major tautomer:* δ 11.74 and 9.18 (2 bs, 1H overall), 10.77 (bs, 1H), 7.47 (s, 1H), 7.42 (d, *J* = 8.20 Hz, 1H), 7.15 – 7.30 (complex m, 5H), 7.06 – 7.10 (m,

3H), 7.02 (t, J = 7.30 Hz, 1H), 6.91 (t, J = 7.40 Hz, 1H), 6.67 and 6.53 (2 bs, 1H overall), 4.01 (s, 2H), 3.62 – 3.69 (bm, 2H), 3.06 (apparent t, J ~ 7.55 Hz, 2H), 2.92 (apparent t, J ~ 7.80 Hz, 2H), 2.30 – 2.35 (bm, 2H), 1.53 – 1.64 (bm, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) *imidazole tautomers observed:* δ 154.58, 152.95, 137.18, 136.68, 135.19, 129.46, 129.05, 128.91, 128.69, 127.45, 127.13, 126.87, 123.11, 121.43, 118.80, 118.71, 113.90, 111.87, 42.45, 30.81, 29.78 (broadened), 25.90, 24.86 (broadened), 23.22. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.88 min, ESI m/z = 411, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 411.2295 (411.2292 calc'd for $C_{25}H_{27}N_6$), $[M + H]^+$.

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-fluorobenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (159): Prepared according to general method F from (**98**, 112 mg, 0.16 mmol) to give 67 mg (92%) of **159** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6), *imidazole* tautomers observed, δ 11.75 and 9.21 (two bs, 1H overall), 10.78 (bs, 1H), 7.47 (s, 1H), 7.42 (d, J = 7.70 Hz, 1H), 7.29 (apparent q, J = 7.80 Hz, 2H), 7.10 (bs, 1H), 6.97 – 7.05 (m, 3H), 6.89 – 6.95 (m, 2H), 6.65 (bs, 1H), 4.05 (s, 2H), 3.70 (apparent t, J = 7.80 Hz, 2H), 3.07 (apparent t, J = 7.55 Hz, 2H), 2.93 (apparent t, J = 7.55 Hz, 2H), 2.35 (t, J = 6.90 Hz, 2H), 1.61 (quint, J = 7.30 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.68 (d, J_{CF} = 243 Hz), 162.68 (d, J_{CF} = 243 Hz), (s), 154.68 (s), 152.56 (s), 140.07 (d, J_{CF} = 7.60 Hz), 139.54 (d, J_{CF} = 7.60 Hz), 136.60, 135.21, 130.99 (d, J_{CF} = 8.70 Hz), 130.55 (d, J_{CF} = 8.70 Hz), 127.45, 125.63, 125.09, 123.11, 121.44, 118.79, 118.70, 116.18 (d, J_{CF} = 22.1Hz), 115.82 (d, J_{CF} = 21.1Hz), 114.12, 113.91, 113.71 (d, J_{CF} = 21.1Hz), 111.87, 42.27 (t), 31.22 (t), 30.35 (t), 29.81 (t), 25.92 (t), 23.2 (t). LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.88 min, ESI m/z = 429, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 429.2161 (429.2197 calc'd for $C_{25}H_{26}FN_6$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3,5-difluorobenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (160). Using general method F (**99**, 250 mg, 0.36 mmol) afforded 130 mg (80%) of **160** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) imidazole tautomers observed: δ 11.74 (bs, 1H), 10.77 (bs, 1H), 7.48 (bs, 1H), 7.41 (d, *J* = 7.70 Hz, 1H), 7.28 (d, *J* = 8.30 Hz, 1H), 7.05 – 7.11 (m, 2H), 7.01 (t, *J* = 7.40 Hz, 1H), 6.86 – 6.92 (m, 3H), 6.72 and 6.51 (two bs, 1H overall), 4.07 (s, 2H), 3.66 – 3.76 (m, 2H), 3.05 – 3.08 (m, 2H), 2.92 – 2.95 (m, 2H), 2.33 – 2.37 (m, 2H), 1.59 – 1.68 (m, 2H). LCMS (5-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.40 min, ESI m/z = 447, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 447.2104 (447.2103 calc'd for $C_{25}H_{25}F_2N_6$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(2-chlorobenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (161). Prepared using general method F from (**100**, 234 mg, 0.34 mmol). Recrystallization from ACN afforded 76 mg (50%) of **161** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) *imidazole tautomers observed – data reflects major tautomer*: δ 11.77 and 11.70 (two overlapping bs, 1H overall), 10.78 (bs, 1H), 7.41 – 7.44 (m, 3H), 7.29 (d, *J* = 8.20 Hz, 1H), 7.22 – 7.27 (m, 2H), 7.06 – 7.10 (complex m, 2H), 7.02 (t, *J* = 7.30 Hz, 1H), 6.92 (t, J = 7.30 Hz, 1H), 6.71 and 6.51 (two broadened s, 1H overall), 4.08 (s, 2H), 3.68 – 3.78 (m, 2H), 3.05 – 3.08 (m, 2H), 2.94 – 2.98 (m, 2H), 2.36 (t, *J* = 6.90 Hz, 2H), 1.71 (quint., *J* = 7.30 Hz, 2H). LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.98 minutes, ESI m/z = 445, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 445.1903 (445.1902 calc'd for $C_{25}H_{26}ClN_6$), $[M + H]^+$.

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-chlorobenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (162). Prepared according to general method F from (**101**, 48.0 mg, 0.07 mmol) to yield 27.0 mg (87%) of **162** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (s, 1H), 7.28 (dd, *J* = 13.2, 8.1 Hz, 2H), 7.22 – 7.20 (m, 2H), 7.08 (s, 1H), 7.03 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.95 –

6.83 (m, 3H), 6.60 (s, 1H), 3.99 (s, 2H), 3.17 (t, *J* = 7.0 Hz, 2H), 3.02 (t, *J* = 7.0 Hz, 2H), 2.27 (t, *J* = 7.1 Hz, 2H), 1.41 (quint., *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 156.09, 152.69, 137.77, 136.69, 134.77, 134.33, 130.15, 128.19, 127.05, 126.99, 126.45, 122.17, 121.13, 118.51, 117.64, 112.91, 111.02, 42.08, 29.87, 28.70, 25.78, 23.69, 22.96. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.38 min, ESI m/z = 445, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 445.1892 (445.1902 calc'd for $C_{25}H_{26}ClN_6$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-chlorobenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (163). Prepared according to general method F from (**102**, 257 mg, 0.37 mmol) to afford 114 mg (69%) of compound **163** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (s, 1H), 7.32 – 7.19 (m, 6H), 7.04 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.95 – 6.86 (m, 4H), 6.57 (s, 1H), 3.96 (s, 2H), 3.27 – 3.22 (m, 2H), 3.17 (t, *J* = 7.0 Hz, 2H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.26 (t, *J* = 7.0 Hz, 2H), 1.40 (quint., *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, Methanol-d_4) δ 156.07, 152.78, 136.67, 134.82, 134.19, 132.70, 130.35, 129.57, 128.65, 128.23, 127.00, 122.21, 121.11, 118.52, 117.67, 112.88, 111.02, 42.10, 29.97, 29.66, 28.80, 25.78, 23.70. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.43 min, ESI m/z = 445, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 445.1903 (445.1902 calc'd for $C_{25}H_{26}ClN_6$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1-methyl-1*H*-indole (164). Prepared according to general method F from (**103**, 320 mg, 0.44 mmol) to afford 120 mg (56 %) of **164** as a white foam: ^{1}H NMR (400 MHz, DMSO-d_6) *imidazole tautomers observed* δ 11.75 and 9.20 (2 bs, 1H overall), 7.52 (d, *J* = 8.20 Hz, 1H), 7.47 – 7.49 (bm, 1H), 7.45 (d, *J* = 1.80 Hz, 1H), 7.41 (d, *J* = 7.80 Hz, 1H), 7.32 (d, *J* = 8.20 Hz, 1H), 7.05 – 7.12 (complex m, 3H), 6.94 (t, *J* = 7.40 Hz, 1H), 6.66 (bs, 1H), 4.05 (s, 2H), 3.65 – 3.72 (m, 2H),

3.66 (s, 3H), 3.05 (apparent t, *J* ~ 7.55 Hz, 2H), 2.91 (apparent t, *J* ~ 7.55 Hz, 2H), 2.36 (t, *J* = 7.30 Hz, 2H), 1.61 (quint, *J* = 7.30 Hz, 2H). LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.45 min, ESI m/z = 493, $[M+H]^+$.

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3,5-dichlorobenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (165) Using general method F, (**104**, 328 mg, 0.45 mmol) gave 179 mg (83 %) of **165** as a tan solid: ^{1}H NMR (400 MHz, DMSO-d_6) *imidazole tautomers observed, NMR data reflects major isomer,* δ 11.73 and 9.19 (2 bs, 1H overall), 10.74 (bs, 1H), 7.40 – 7.47 (m, 3H), 7.25 – 7.30 (m, 3H), 7.10 (s, 1H), 7.02 (t, *J* = 6.90 Hz, 1H), 6.91 (t, *J* = 6.90 Hz, 1H), 6.72 and 6.58 (2 bs, 1H overall), 4.07 (s, 2H), 3.73 – 3.79 (bm, 2H), 3.08 (apparent t, *J* = 7.40 Hz, 2H), 2.94 (apparent *t*, J = 7.40 Hz, 2H), 2.35 – 2.42 (bm, 2H), 1.67 (quint., *J* = 6.80 Hz, 2H). ^{13}H NMR (100 MHz, DMSO-d_6) δ 154.86, 152.26, 141.40, 136.69, 135.25, 134.53, 134.23, 128.32, 128.08, 127.43, 126.98, 123.11, 121.48, 118.83, 118.68, 113.86, 111.89, 42.50, 29.83, 29.82, 25.88, 23.16. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.82 min, ESI m/z = 479, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 479.1507 (479.1512 calc'd for $C_{25}H_{25}Cl_2N_6$), $[M + H]^+$.

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-bromobenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (166). Prepared according to general method F from (**105**, 0.270 g, 0.370 mmol) to afford 0.100 g (55%) of **166** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6)*, imidazole tautomers observed, NMR data reflects major tautomer,* δ 11.75 (bs, 1H), 10.77 (bs, 1H), 7.48 (s, 1H), 7.42 (d, *J* = 8.30 Hz, 1H), 7.38 – 7.40 (m, 2H), 7.15 – 7.34 (complex multiplets, 5H), 7.08 – 7.11 (m, 2H), 7.02 (t, *J* = 6.90 Hz, 1H), 6.91 (t, *J* = 7.30 Hz, 1H), 6.66 (bs), 4.04 (s, 2H), 3.71 (apparent t, *J* = 7.70 Hz, 2H), 3.07 (apparent t, *J* = 7.55 Hz, 2H), 2.93 (apparent t, *J* = 7.55 Hz, 2H), 2.36 (t, *J* = 7.30 Hz, 2H), 1.62 (quint, *J* = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) major tautomer δ

154.67, 152.57, 140.02, 136.69, 135.20, 131.81, 131.16, 130.08, 128.40, 128.29, 128.17, 128.06, 127.45, 123.11, 122.24, 121.44, 118.80, 118.70, 113.90, 111.87, 42.48, 31.24, 30.18, 29.94, 25.91, 23.20. LCMS (5-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.47 min, ESI m/z = 489, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 489.1368 (489.1356 calc'd for $C_{25}H_{26}BrN_6$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(trifluoromethyl)benzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (167). Following general method F, (**106**, 268 mg, 0.37 mmol) afforded 121 mg (68%) of **167** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C), *imidazole tautomers observed*, δ 11.54 and 9.06 (2 bs, 1H overall), 10.56 (bs, 1H), 7.58 (s, 1H), 7.48 – 7.55 (m, 3H), 7.41 – 7.44 (m, 2H), 7.30 (d, *J* = 8.20 Hz, 1H), 7.07 (s, 1H), 7.02 (t, *J* = 6.80 Hz, 1H), 6.92 (t, *J* = 7.80 Hz, 1H), 6.66 (bs, 1H),4.14 (s, 2H), 3.71 – 3.79 (m, 2H), 3.10 (apparent t, *J* = 6.80 Hz, 2H), 2.96 (apparent t, *J* = 7.30 Hz, 2H), 2.36 – 2.41 (m, 2H), 1.69 (b quint, *J* ~ 6.50 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, 80 °C) δ 156.06, 152.63, 136.92, 136.67, 134.83, 131.88, 130.72 (q, J_{CF} = 32.6 Hz), 129.46, 126.97, 124.91 (q, J_{CF} = 3.80 Hz), 124.14 (q, J_{CF} = 271 Hz), 123.68 (q, J_{CF} = 3.80 Hz), 122.13, 121.10, 118.46, 117.62, 112.91, 111, 42.08, 29.93, 28.79, 25.81, 23.66, 23.16. LCMS (5-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.58 minutes, ESI m/z = 479, $[M+H]^+$.

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(trifluoromethyl)benzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1-methyl-1*H*-indole (168). Prepared according to general method F from (**107**, 620 mg, 0.84 mmol) to afford 220 mg (77%) of **168** as a yellow solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 – 7.51 (m, 2H), 7.46 – 7.42 (m, 2H), 7.28 (d, *J* = 8.00 Hz, 1H), 7.24 -7.22 (m, 2H), 7.10 (dt, *J* = 7.00, 0.84 Hz, 1H), 6.93 (dt, *J* = 7.23, 0.78 Hz, 1H), 6.77 (s, 1H), 6.55 (bs, 1H), 4.09 (s, 2H), 3.60 (s, 3H), 3.35 – 3.31 (m, 2H), 3.15 (t, *J* = 7.15 Hz, 2H), 3.00 (t, *J* = 6.79 Hz, 2H), 2.26 (t, *J* = 7.07

Hz, 2H), 1.41 (quint., J = 7.18 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 155.98, 152.66, 137.13, 136.96, 134.85, 131.97, 130.74 (q, J_{CF} = 32.2 Hz), 129.48, 127.48, 126.56, 124.92 (q, J_{CF} = 3.76 Hz), 124.14 (q, $J_{C,F}$ = 271.3 Hz), 123.71 (q, J_{CF} = 3.73 Hz), 121.24, 118.53, 117.96, 112.42, 108.93, 42.13, 31.25, 29.94, 28.75, 25.87, 23.47, 23.15. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.98 minutes, ESI m/z = 493, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 493.2322 (493.2322 calc'd for $C_{27}H_{28}F_3N_6$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(2-(1*H*-indol-3-yl)ethyl)-4*H*-1,2,4-triazol-3-yl)methyl)benzonitrile (169). Prepared according to general method F from (**108**, 292 mg, 0.43 mmol) to afford 135 mg (72%) of **169** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (bs, 1H), 10.77 (s, 1H), 7.68 (dt, J = 6.91, 1.58 Hz, 1H), 7.64 (s, 1H), 7.50 – 7.44 (m, 3H), 7.40 (d, J = 7.85 Hz, 1H), 7.28 (d, J = 8.11 Hz, 1H), 7.11 (d, J = 2.17 Hz, 1H), 7.01 (dt, J = 7.01, 0.76 Hz, 1H), 6.91 (t, J = 7.26 Hz, 1H), 6.70 (bs, 1H), 4.10 (bs, 2H), 3.72 (bt, J = 6.70 Hz, 2H), 3.07 (dd, J = 8.50, 5.42 Hz, 2H), 2.93 (dd, J = 8.66, 5.49 Hz, 2H), 2.36 (bt, J = 6.23 Hz, 2H), 1.63 (quint., J = 7.29 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.74, 152.36, 138.92, 136.68, 135.22, 134.20, 132.71, 131.08, 130.25, 127.45, 123.13, 121.44, 119.25, 118.80, 118.69, 113.88, 111.88, 42.49, 30.18, 29.87 (2 broadened carbons), 25.92, 23.22. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.70 min, ESI m/z = 436, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 436.2251 (436.2244 calc'd for $C_{26}H_{26}N_7$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl-5-(3-nitrobenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl-1*H*-indole (170). Using general method F, (**109**, 148 mg, 0.212 mmol) gave 85 mg (88%) of **170** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) imidazole tautomers observed: δ 8.05-8.12 (m, 1H), 7.97 (bs, 1H), 7.44-7.55 (m, 2H), 7.21-7.37 (m, 4H), 6.98-7.05 (m, 1H), 6.85-6.95 (m, 2H), 6.57 (bs, 1H), 4.10 (s, 2H), 3.31 (obs s, 1H), 3.17 (apparent t, J = 6.9 Hz, 2H), 3.03 (apparent t, J = 8.08 Hz, 2H),

2.28 (apparent t, J = 7.1, 2H), 1.46 (quint., J = 7.71, 2H). ^{13}C NMR (100 MHz, CD_3OD) imidazole tautomers observed: δ 156.14, 152.36, 148.50, 137.75, 136.66, 134.88, 134.42, 129.80, 126.98, 123.04, 122.19, 121.80, 121.09, 118.47, 117.59, 112.89, 111.00, 42.07, 32.42, 29.75, 28.80, 25.84, 23.74. LCMS (50-95% CH_3CN in 0.05% TFA over 10 min) retention time = 3.87 min, ESI m/z 699, [M+H].

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(2-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (171). Prepared according to general method F from (**110**, 102 mg, 0.15 mmol) to afford 21 mg (74% yield) of **171** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) *imidazole tautomers observed, NMR data is a summary of both isomers*: δ 11.75 and 11.69 (two overlapping bs, 1H overall), 10.77 (bs, 1H), 7.41 – 7.44 (m, 2H), 7.29 (d, J = 8.30 Hz, 1H), 7.18 (broadened dt, J = 6.40, 1.80 Hz, 1H), 7.09 (d, J = 1.80 Hz, 1H), 7.02 (dt, J = 6.90, 0.9 Hz, 1H), 6.90 – 6.95 (m, 2H), 6.80 – 6.88 (m, 3H), 6.69 and 6.50 (two bs, 1H overall), 3.92 and 3.91 (two overlapping s, 2H overall), 3.73 and 3.72 (two overlapping s, 3H overall), 3.64 – 3.73 (m, 2H), 3.04 – 3.09 (m, 2H), 2.91 -2.95 (m, 2H), 2.38 and 2.33 (two t, J = 7.80 and 6.90 Hz, respectively, 2H overall), 1.61 – 1.70 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) *imidazole tautomers observed, NMR data reflects the major isomer*: δ 157.08, 154.35, 152.87, 139.82, 136.71, 135.19, 130.09, 128.61, 127.47, 125.15, 123.13, 121.45, 120.90, 118.81, 118.73, 113.91, 112.41, 111.88, 111.30, 55.91, 42.62, 30.00, 25.95, 25.16, 24.89, 23.34. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.95 min, ESI m/z = 441, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 441.2400 (441.2397 calc'd for $C_{26}H_{29}N_6O$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (172). Using general method F**,** (**111**, 177 mg, 0.26 mmol) gave 96 mg (84%) of **172** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (bs, 1H), 10.78 (bs, 1H), 7.49 (s, 1H), 7.43

(d, *J* = 7.80 Hz, 1H), 7.29 (d, *J* = 7.80 Hz, 1H), 7.15 (t, *J* = 7.80 Hz, 1H), 7.10 (d, *J* = 1.80 Hz, 1H), 7.02 (t, *J* = 7.40 Hz, 1H), 6.92 (t, *J* = 7.40 Hz, 1H), 6.72 – 6.76 (m, 2H), 6.62 – 6.68 (m, 2H), 3.99 (s, 2H), 3.69 (apparent t, *J* = 7.40 Hz, 2H), 3.07 (apparent t, *J* = 6.90 Hz, 2H), 2.92 (apparent t, *J* = 6.90 Hz, 2H), 2.34 (t, *J* = 6.80 Hz, 2H), 1.59 (quint, *J* = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.88 (s), 154.57 (s), 152.91 (s), 138.74, 136.71, 135.19, 130.13, 127.47, 123.10, 121.45, 121.11, 118.81, 118.73, 114.69, 113.94, 112.55, 111.88, 55.50 (q), 42.50 (t), 30.79 (t), 29.74 (t), 25.91 (t), 23.19 (t). LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 4.02 min, ESI m/z = 441, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 441.2404 (441.2397 calc'd for $C_{26}H_{29}N_6O$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (173). Prepared according to general method F from (**112**, 210 mg, 0.30 mmol) to give 110 mg (83%) of **173** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) *imidazole tautomers observed:* δ 11.73 (bs, 1H), 10.77 (bs, 1H), 7.49 and 7.45 (2 bs, 1H overall), 7.42 (d, *J* = 7.40 Hz, 1H), 7.11 – 7.34 (complex multiplets, 5H), 7.09 (d, *J* = 2.30 Hz, 1H), 7.02 (dt, *J* = 6.60, 0.90 Hz, 1H), 6.97 (d, *J* = 8.30 Hz, 2H), 6.92 (t, *J* = 6.90 Hz, 1H), 6.78 – 6.81 (m, 2H), 6.69 and 6.50 (2 bs, 1H overall), 3.93 (s, 2H), 3.66 (s, 3H), 3.60 – 3.66 (m, 2H), 3.06 (apparent t, *J* = 8.20 Hz, 2H), 2.91 (apparent t, *J* = 6.90 Hz, 2H), 2.29 – 2.38 (m, 2H), 1.53 – 1.62 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) *imidazole tautomers observed:* δ 158.48 (s), 154.53 (s), 153.24 (s), 148.29, 144.63, 139.80, 136.68, 135.20, 130.43, 129.91, 128.93, 128.65, 128.41, 128.29, 128.06, 127.45, 127.17, 123.11, 121.43, 118.80, 118.71, 114.45, 114.2, 113.90, 112.55, 111.86, 55.54, 42.49, 42.34, 29.99, 29.90, 29.52, 25.88, 25.00, 23.26, 23.18. LCMS (5-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.30 min, ESI m/z = 441, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 441.2396 (441.2397 calc'd for $C_{26}H_{29}N_6O$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(trifluoromethoxy)benzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (174). Using general method F, (**113**, 172 mg, 0.23 mmol) afforded 82 mg (71 %) of **174** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (s, 1H), 7.34 (t, *J* = 7.97 Hz, 1H), 7.27 (t, *J* = 7.74 Hz, 2H), 7.10 (bd, *J* = 8.24 Hz, 1H), 7.03 (t, *J* = 7.85 Hz, 1H), 7.02 (bd, *J* = 1.54 Hz, 1H), 6,92 (d, *J* = 7.65 Hz, 2H), 6.89 – 6.87 (m, 1H), 6.57 (s, 1H), 4.04 (s, 2H), 3.34 – 3.30 (m, obscured by NMR solvent, 2H), 3.16 (t, *J* = 7.13 Hz, 2H), 3.01 (t, *J* = 7.14 Hz, 2H), 2.26 (t, *J* = 7.03 Hz, 2H), 1.43 (quint., *J* = 7.12 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 156.07, 152.61, 149.39, 138.16, 136.67, 134.81, 130.30, 126.97, 126.86, 122.13, 121.10, 120.83, 120.51 (q, J_{CF} = 255.66 Hz), 119.36, 118.47, 117.62, 112.91, 111.00, 42.10, 29.85, 28.77, 25.81, 23.65, 23.12. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.15 minutes, ESI m/z = 495, $[M+H]^+$, 989 $[2M+H]^+$. HRMS (ESI Q-TOF) m/z = 495.2117 (495.2115 calc'd for $C_{26}H_{26}F_3N_6O$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(benzyloxy)benzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (175). Following general method F, (**114**, 148 mg, 0.21 mmol) gave 85 mg (88%) of **175** as a white solid: ^{1}H NMR (400 MHz, CD_3OD), δ 7.52 (bs, 1H), 7.34 – 7.22 (m, 5H), 7.14 (t, *J* = 7.90 Hz, 1H), 7.03 (t, *J* = 7.28 Hz, 1H), 6.92 (t, *J* = 7.45 Hz, 1H), 6.87 (s, 1H), 6.82 (dd, *J* = 8.13, 1.31 Hz, 1H), 6.67 (s, 1H), 6.54 (d, *J* = 7.41 Hz, 1H), 4.99 (s, 2H), 3.96 (s, 2H), 3.29 – 3.25 (m, obscured by NMR solvent, 2H), 3.16 (bt, *J* = 6.87 Hz, 2H), 2.98 (bt, *J* = 6.67 Hz, 2H), 2.22 – 2.15 (bm, 2H), 1.34 – 1.25 (bm, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.15, 137.19, 136.88, 136.67, 129.71, 128.18, 127.52, 127.22, 126.98, 122.11, 121.10, 120.47, 118.48, 117.64, 114.58, 113.52, 112.93, 111.00, 69.45, 42.23, 30.37, 28.63, 25.80, 23.57, 23.25 (broad). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.20 min, ESI m/z = 517, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 517.2703 (517.2710 calc'd for $C_{32}H_{33}N_6O$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(methylsulfonyl)benzyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (176). Prepared according to general method F from (**115**, 80 mg, 0.11 mmol) to yield 39 mg (73%) of compound **176** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, *J* = 7.80 Hz, 1H), 7.70 (s, 1H), 7.54 – 7.50 (m, 2H), 7.30 – 7.25 (m, 4H), 7.04 (t, *J* = 7.31 Hz, 1H), 6.92 (t, *J* = 7.69 Hz, 1H), 6.88 (s, 1H), 6.57 (s, 1H), 4.10 (s, 2H), 3.31 – 3.26 (obscured m, 2H), 3.17 (t, *J* = 7.00 Hz, 2H), 3.08 – 3.01 (m, 1H), 3.05 (s, 3H), 2.26 (t, *J* = 7.04 Hz, 2H), 1.44 (quint., *J* = 7.26 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 156.13, 152.45, 141.30, 137.47, 136.64, 134.90, 133.53, 129.80, 126.98, 126.91, 125.88, 122.20, 121.13, 118.51, 117.62, 112.85, 111.02, 42.90, 42.80, 29.94, 28.81, 25.77, 23.72, 23.15. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.73 minutes, ESI m/z = 489, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 489.2059 (489.2067 calc'd for $C_{26}H_{29}N_6O_2S$, $[M + H]^+$).

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-([1,1'-biphenyl]-4-ylmethyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (177): Using general method F, (**116**, 204 mg, 0.28 mmol) afforded 36 mg (26 %)of **177** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 – 7.54 (complex m, 3H), 7.47 (d, *J* = 7.30 Hz, 2H), 7.39 (t, *J* = 7.40 Hz, 2H), 7.28 – 7.32 (m, 2H), 7.26 (d, *J* = 7.80 Hz, 1H), 7.01 – 7.06 (m, 1H), 7.00 (d, *J* = 8.30 Hz, 2H), 6.92 (dt, *J* = 7.80 Hz, 1H), 6.89 (s, 1H), 6.53 (bs, 1H), 4.03 (s, 2H), 3.31 (apparent t, *J* = 7.30 Hz, 2H), 3.81 (apparent t, *J* = 6.90 Hz, 2H), 3.01 (apparent t, *J* = 6.90 Hz, 2H), 2.25 (t, *J* = 7.30 Hz, 2H), 1.38 (apparent quint., *J* ~ 7.80 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 156.03, 153.15, 140.44, 140.06, 136.67, 135.99 (broadened), 134.73, 134.38, 129.21, 128.53, 128.46, 127.13, 127.09, 126.55, 122.19, 121.10, 118.50, 117.68, 115.68, 112.90, 111.00, 42.19, 30.05, 28.68, 25.77, 23.68, 23.13. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.30 minutes, ESI m/z = 487, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 487.2601 (487.2605 calc'd for $C_{31}H_{31}N_6$, $[M + H]^+$).

(*R*)-1-(4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-chlorobenzyl)-4*H*-1,2,4-triazol-3-yl)-2-(1*H*-indol-3-yl)ethanamine (178). Prepared according to general method F from (**117**, 80.0 mg, 0.10 mmol) to yield 32 mg (72 %) of **178** as a tan foam: LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.00 min, ESI m/z = 460, $[M+H]^+$.

3-(2-(4-(3-(1*H*-Imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)ethyl)-1*H*-indole (179). Following general method F, (**118**, 180 mg, 0.32 mmol) to afford 40 mg (39%) of **179** as a white foam: ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 7.52 (s, 1H), 7.41 – 7.17 (m, 3H), 7.04 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.94 (dt, *J* = 7.4, 6.9, 1.1 Hz, 1H), 6.90 (s, 1H), 6.66 (s, 1H), 3.50 (dd, *J* = 8.5, 6.7 Hz, 2H), 3.17 (t, *J* = 7.0 Hz, 2H), 3.06 (dd, *J* = 8.3, 6.6 Hz, 2H), 2.30 (dt, *J* = 7.2, 3.8 Hz, 3H), 1.72 (quint., *J* = 7.4 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.83 minutes, ESI m/z = 321, $[M+H]^+$. HRMS, sample deuterated by storage in the NMR solvent CD_3OD, (ESI Q-TOF) m/z = 323.1947 (323.1948 calc'd for $C_{18}H_{19}D_2N_6$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (180). Prepared according to general method F from (**119**, 237 mg, 0.37 mmol) to afford 113 mg (77%) of **180** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (s, 1H), 7.35 (d, *J* = 7.92 Hz, 1H), 7.30 (d, *J* = 8.21 Hz, 1H), 7.23 – 7.14 (complex m, 3H), 7.06 (dt, *J* = 7.11, 0.66 Hz, 1H), 7.02 (d, *J* = 6.89, 2H), 6.94 (apparent t, *J* = 6.83 Hz, 2H), 6.51 (s, 1H), 4.25 (s, 2H), 4.06 (s, 2H), 3.59 (apparent t, *J* = 8.33 Hz, 2H), 2.24 (t, *J* = 7.07 Hz, 2H), 1.35 (quint., *J* = 7.21 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 154.82, 154.21, 136.84, 135.41, 134.66, 128.59, 128.01, 126.89, 126.66, 122.96, 121.51, 118.83, 117.88, 111.16, 107.93, 42.75, 30.37, 28.88, 23.18, 21.55. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.75 minutes, ESI m/z = 397, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 397.2147 (397.2135 calc'd for $C_{24}H_{25}N_6$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (181). Using general method F, (**120**, 180 mg, 0.27 mmol) gave 89 mg (78%) of **181** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (bs, 1H), 7.30 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.26 (m, 1H), 6.97 – 7.05 (m,2H) 6.96 (s, 1H), 6.73 (dt, *J* = 9.60, 2.30 Hz, 1H), 6.55 (bs, 1H), 4.23 (s, 2H), 4.07 (s, 2H), 3.57- 3.65 (m, 2H), 2.28 (t, *J* = 6.85 Hz, 2H), 1.38 (quint., *J* = 7.75 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.95 (d, J_{CF} = 235.8), 154.60, 154.27, 136.82 (d, J_{CF} = 12.4 Hz), 135.39, 134.72, 128.68, 128.60, 128.20, 128.02, 126.92, 126.58, 123.49 (d, J_{CF} = 3.42 Hz), 123.39, 118.92, 118.82, 108.26, 107.30 (d, J_{CF} = 25 Hz), 97.05 (d, J_{CF} = 25.8 Hz), 42.73, 40.43, 30.38, 28.70, 21.48. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.78 minutes, ESI m/z = 415, $[M+H]^+$. HRMS (sample deuterated by storage in NMR solvent CD_3OD) (ESI Q-TOF) m/z = 416.2097 (416.2104 calc'd for $C_{24}H_{23}DFN_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-benzyl-4*H*-1,2,4-triazol-3-yl)methyl)-5-methoxy-1*H*-indole (182). Prepared according to general method F from (**121**, 118 mg, 0.18 mmol) to afford 64 mg (85%) of **182** as a tan solid. ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.54 (s, 1H), 7.23 – 7.14 (complex m, 4H), 7.02 (d, *J* = 6.80 Hz, 2H), 6.92 (s, 1H), 6.84 (d, *J* = 2.20 Hz, 1H), 6.72 (dd, *J* = 8.70 Hz, 2.70 Hz, 1H), 6.52 (s, 1H), 4.23 (s, 2H), 4.06 (s, 2H), 3.70 (s, 3H), 3.61 – 3.57 (m, 2H), 2.25 (t, *J* = 6.80 Hz, 2H), 1.35 (quint., *J* = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, MeOH-d_4) δ 154.82, 154.27, 153.92, 135.43, 134.67, 131.98, 128.58, 127.99, 126.89, 123.58, 111.91, 107.54, 99.51, 54.77, 42.77, 30.04, 28.61, 23.24 (broad), 21.73. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.80 minutes, ESI m/z = 427, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 427.2254 (427.2241 calc'd for $C_{13}H_{18}ClN_2O_3$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-fluorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (183). Following general method F, (**122**, 150 mg, 0.23 mmol) afforded 86 mg (91%) of

183 as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (s, 1H), 7.34 (d, J = 8.02 Hz, 1H), 7.30 (d, J = 8.23 Hz, 1H), 7.28 – 7.25 (m, 1H), 4.26 (s, 2H), 4.04 (s, 2H), 3.63 – 3.59 (m, 2H), 2.27 (t, J = 7.07 Hz, 2H), 1.39 (t, J = 7.10 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 161.20 (d, J_{CF} = 244.4 Hz), 154.06, 153.29, 136.04, 133.91, 130.54 (d, J_{CF} = 3.8 Hz), 129.66, 129.05 (d, J_{CF} = 7.6 Hz), 125.84, 122.17, 120.70, 118.02, 117.05, 114.43 (d, J_{CF} = 21.1 Hz), 114.08, 110.36, 107.09, 41.92, 38.65, 28.71, 27.94, 20.74. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.78 minutes, ESI m/z = 415, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 415.2034 (415.2041 calc'd for $C_{24}H_{24}FN_6$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-fluorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (184). Using general method F, (**123**, 136 mg, 0.20 mmol) to yield 51 mg (59%) of **184** as a tan foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (bs, 1H), 10.95 (s, 1H), 7.51 (s, 1H), 7.38 (dd, J = 8.70, 5.5 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.14 – 7.02 (complex overlapping m, 7H), 6.77 (dt, J = 8.70, 2.30 Hz, 1H), 6.67 (bs, 1H), 4.09 (s, 2H), 3.97 (s, 2H), 3.71 – 3.65 (m, 2H), 2.32 – 2.26 (m, 2H), 1.49 – 1.40 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 162.04 (d, J_{CF} = 244.5 Hz), 159.98 (d, J_{CF} = 236 Hz), 154.66, 154.18, 136.84 (d, J_{CF} = 12.5 Hz), 136.28, 134.77, 131.36 (d, J_{CF} = 3.3 Hz), 130.49 (d, J_{CF} = 8.1 Hz), 123.54 (d, J_{CF} = 3.4 Hz), 123.41, 118.88 (d, J_{CF} = 10.1 Hz), 115.38, 115.16, 114.80 (d, J_{CF} = 21.9 Hz), 108.27, 107.34 (d, J_{CF} = 24.9 Hz), 97.08 (d, J_{CF} = 26.2 Hz), 42.73, 29.56, 28.77, 23.23, 21.48. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.83 minutes, ESI m/z = 433, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 434.2026 (434.2010 calc'd for $C_{24}H_{22}DF_2N_6$, deuteration of imidazole due to storage in CD_3OD, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-fluorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-5-methoxy-1*H*-indole (185). Prepared according to general method F from (**124**, 144 mg, 0.21

mmol) and afforded 66 mg (71%) of compound **185** as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (s, 1H), 7.19 (d, *J* = 8.70 Hz, 1H), 7.05 – 7.02 (m, 2H), 6.96 – 6.92 (m, 3H), 6.83 (d, *J* = 2.30 Hz, 1H), 6.72 (dd, *J* = 8.70, 2.30 Hz, 1H), 6.55 (s, 1H), 4.24 (s, 2H), 4.04 (s, 2H), 3.70(s, 3H), 3.63 – 3.59 (m, 2H), 2.28 (t, *J* = 7.40 Hz, 2H), 1.38 (quint., *J* = 6.90 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 162.0 (d, J_{CF} = 244.4 Hz), 154.87, 154.16, 153.92, 134.71, 131.99, 131.36, 129.84 (d, J_{CF} = 8.60 Hz), 126.97, 123.61, 115.22 (d, J_{CF} = 22.1 Hz), 111.89, 107.52, 99.54, 54.78, 42.75, 29.51, 28.69, 23.33, 21.72. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.92 minutes, ESI m/z = 445, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 445.2140 (445.2147 calc'd for $C_{25}H_{26}FN_6$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(2-chlorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (186). Following general method F, **(125**, 184 mg, 273 mmol) gave 94 mg (80%) of **186** as a white foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (s, 1H), 7.39 – 7.33 (m, 2H), 7.33 – 7.28 (m, 1H), 7.27 – 7.13 (m, 4H), 7.10 – 7.01 (m, 2H), 6.98 – 6.91 (m, 2H), 6.53 (s, 1H), 4.28 (s, 2H), 4.16 (s, 2H), 3.74 – 3.64 (m, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.46 (quint., *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) *imidazole tautomers observed – data reflects major tautomer*: δ 154.74, 153.38, 136.89, 134.70, 133.60, 133.30, 130.26, 129.44, 128.72, 127.96, 127.30, 127.16, 126.68, 123.01, 121.54, 118.85, 117.94, 111.19, 107.95, 42.89, 38.01, 28.88, 28.22, 21.64. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.60 minutes, ESI m/z = 431, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 431.1778 (431.1745 calc'd for $C_{24}H_{24}ClN_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-chlorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (187). Prepared according to general method F from (**126**, 294 mg, 0.44 mmol) to yield 123 mg (65 %) of **187** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (bs, 1H), 10.87 (s, 1H), 7.50 (d, *J* = 1.1 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.33 – 7.14 (m, 5H), 7.08 – 7.05 (m,

2H), 7.01 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 6.89 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 4.12 (s, 2H), 4.01 (s, 2H), 3.69 (t, J = 8.7 Hz, 2H), 2.31 (t, J = 7.1 Hz, 2H), 1.49 (quint., J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.83, 152.88, 139.68, 136.80, 135.18, 133.58, 130.81, 128.92, 128.31, 128.06, 127.83, 127.29, 127.18, 123.99, 121.70, 119.08, 119.01, 111.96, 109.23, 42.68, 30.23, 30.19, 29.69, 21.99. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.30 min, ESI m/z = 431, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 431.1727 (431.1745 calc'd for $C_{24}H_{24}ClN_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-chlorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (188). Using general method F, (**127**, 221 mg, 0.32 mmol) gave 90 mg (63 %) of **188** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, J = 1.2 Hz, 1H), 7.29 (dd, J = 8.7, 5.3 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.09 (dt, J = 2.4, 1.1 Hz, 1H), 7.02 – 6.93 (m, 3H), 6.73 (ddd, J = 9.7, 8.7, 2.3 Hz, 1H), 6.60 (d, J = 1.2 Hz, 1H), 4.24 (d, J = 1.0 Hz, 2H), 4.07 (s, 2H), 3.69 – 3.58 (m, 2H), 2.31 (t, J = 7.1 Hz, 2H), 1.42 (quint., J = 7.2 Hz, 2H). ^{13}H NMR (100 MHz, DMSO-d_6) δ 159.42 (d, J_{CF} = 234.3 Hz), 153.70, 152.94, 139.75 (d, J_{CF} = 14.3 Hz), 139.26, 136.64 (d, J_{CF} = 12.7 Hz), 135.22, 133.58, 133.27, 130.84, 130.58, 129.28, 128.90, 128.26, 127.84, 127.20, 126.92, 124.63 (d, J_{CF} = 3.4 Hz), 124.16, 120.13 (d, J_{CF} = 10.3 Hz), 112.55, 109.58, 107.56 (d, J_{CF} = 24.5 Hz), 97.91 (d, J_{CF} = 25.6 Hz), 42.71, 30.20, 29.77, 24.90, 21.86. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.22 minutes, ESI m/z = 449, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 449.1656 (449.1651 calc'd for $C_{24}H_{23}ClFN_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-chlorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (189). Following general method F, (**128**, 220 mg, 0.33 mmol) afforded 115 mg (83%) of **189** as a tan foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (s, 1H), 7.34 (d, J = 7.91 Hz, 1H), 7.30

(d, *J* = 8.07 Hz, 1H), 7.26 – 7.20 (m, 4H), 7.07 (dt, J = 8.01, 0.97 Hz, 1H), 7.01 (d, J = 8.43 Hz, 2H), 6.96 - 6.92 (m, 2H), 4.26 (s, 2H), 4.04 (s, 2H), 3.63 – 3.59 (m, 2H), 2.26 (t, *J* = 7.10 Hz, 2H), 1.38 (t, *J* = 7.02 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 154.91, 153.85, 136.85, 134.71, 134.24, 129.68, 128.62, 126.65, 122.99, 121.51, 118.84, 117.85, 111.18, 107.90, 42.75, 29.67, 28.78, 21.56. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.82 minutes, ESI m/z = 431, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 431.1724 (431.1745 calc'd for $C_{24}H_{24}ClN_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (190). Prepared according to general method F from (**129**, 248 mg, 0.35 mmol) to give 108 mg (66 %) of **190** as a white foam: ^{1}H NMR (400 MHz, CD_3OD*) imidazole tautomers observed, NMR data reflects major isomer,* δ 7.55 (d, *J* = 1.2 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.32 (ddt, *J* = 13.9, 8.2, 0.9 Hz, 2H), 7.25 (d, *J* = 2.2 Hz, 1H), 7.07 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.00 – 6.92 (m, 3H), 6.56 (s, 1H), 4.28 (s, 2H), 4.05 (s, 2H), 3.70 – 3.60 (m, 2H), 2.29 (t, *J* = 7.1 Hz, 2H), 1.40 (quint., *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 155.00, 153.43, 136.86, 136.31, 134.78, 132.32, 130.88, 130.59, 130.23, 128.74, 128.08, 127.30, 126.67, 123.03, 121.54, 118.90, 117.84, 111.20, 107.86, 42.77, 39.22, 29.31, 28.84, 21.59. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.18 min, ESI m/z = 465, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 465.1339 (465.1356 calc'd for $C_{24}H_{23}Cl_2N_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (191). Using general method F, (**130**, 165 mg, 0.23 mmol) yielded 73 mg (66 %) of **191** as a white foam: ^{1}H NMR (400 MHz, CD_3OD*) imidazole tautomers observed, NMR data reflects major isomer,* δ 7.62 – 7.57 (bs, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.30 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.03 – 6.95 (m, 3H), 6.73 (ddd, *J* = 9.6, 8.7, 2.3 Hz, 1H), 6.61

(s, 1H), 4.25 (s, 2H), 4.06 (s, 2H), 3.75 – 3.62 (m, 2H), 2.33 (t, *J* = 7.1 Hz, 2H), 1.44 (quint., *J* = 7.2 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.73 min, ESI m/z = 483, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 483.1265 (483.1262 calc'd for $C_{24}H_{22}Cl_2FN_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3,5-dichlorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (192). Prepared according to general method F from (**131**, 284 mg, 0.40 mmol) to afford 113 mg (61 %) of **192** as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (d, *J* = 1.1 Hz, 1H), 7.33 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.30 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.28 (t, *J* = 1.9 Hz, 1H), 7.09 – 7.03 (m, 3H), 6.99 – 6.91 (m, 2H), 6.58 (d, *J* = 1.3 Hz, 1H), 4.28 (s, 2H), 4.06 (s, 2H), 3.72 – 3.60 (m, 2H), 2.30 (t, *J* = 7.1 Hz, 2H), 1.50 – 1.35 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 155.04, 153.18, 139.48, 136.86, 135.14, 134.81, 127.00, 126.91, 126.68, 123.02, 121.54, 118.94, 117.81, 111.20, 107.86, 42.79, 29.50, 28.83, 23.31, 21.60. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.38 min, ESI m/z = 465, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 465.1350 (465.1356 calc'd for $C_{24}H_{23}Cl_2N_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3,5-dichlorobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (193). Following general method F, (**132**, 227 mg, 0.31 mmol) gave 63 mg (42 %) of **193** as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (s, 1H), 7.31 – 7.25 (m, 2H), 7.05 (d, *J* = 1.9 Hz, 2H), 7.00 (dd, *J* = 9.9, 2.3 Hz, 1H), 6.97 (s, 1H), 6.73 (ddd, *J* = 9.5, 8.7, 2.3 Hz, 1H), 6.62 (s, 1H), 4.26 (s, 2H), 4.07 (s, 2H), 3.74 – 3.63 (m, 2H), 2.34 (t, *J* = 7.1 Hz, 2H), 1.46 (quint., *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 161.15 (d, J_{CF} = 236.0 Hz), 154.82, 153.24, 139.47, 136.85 (d, J_{CF} = 12.5 Hz), 135.15, 134.85, 127.01, 126.90, 123.57 (d, J_{CF} = 3.5 Hz), 123.40, 118.80 (d, J_{CF} = 10.4 Hz), 108.19, 107.45 (d, J_{CF} = 24.9 Hz), 97.09 (d, J_{CF} = 25.9 Hz), 42.77, 29.51, 28.86, 23.28 (broad), 21.55. LCMS (50-95% acetonitrile in 0.05% TFA over

10 minutes) retention time = 2.25 min, ESI m/z = 483, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 483.1257 (483.1262 calc'd for $C_{24}H_{22}Cl_2FN_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-bromobenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (194). Prepared according to general method F from (**133**, 180 mg, 0.24 mmol) to afford 94 mg (78%) of **194** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (bs, 1H), 7.35 (d, J = 8.85 Hz, 1H), 7.29 (dd, J = 8.72, 5.27 Hz, 1H), 7.25 (m, 1H), 7.15 (t, J = 7.84 Hz, 1H), 7.03 – 6.09 (m, 2H), 6.95 (s, 1H), 6.74 (dt, J = 9.59, 2.30 Hz, 1H), 6.59 (bs, 1H), 4.24 (s, 2H), 4.06 (s, 2H), 3.66 – 3.62 (m, 2H), 2.31 (t, J = 7.04 Hz, 2H), 1.38 (quint., J = 7.13 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.95 (d, J_{CF} = 235.84 Hz), 154.70, 153.71, 138.04, 136.82 (d, J_{CF} = 12.54 Hz), 134.80, 131.71, 131.07, 130.34, 130.08, 126.97, 123.53 (d, J_{CF} = 2.91Hz), 123.38, 122.44, 118.87, 118.77, 108.20, 107.39 (d, J_{CF} = 24.81Hz), 97.06 (d, J_{CF} = 25.93Hz), 42.75, 29.80, 28.79, 23.37, 21.52. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.18 minutes, ESI m/z = 493 $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 493.1150 (493.1146 calc'd for $C_{24}H_{23}FBrN_6$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(trifluoromethyl)benzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (195). Using general method F, (**134**, 242 mg, 0.34 mmol) afforded 120 mg (75%) of **195** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 – 7.49 (m, 2H), 7.45 – 7.41 (m, 2H), 7.32 (m, 3H), 7.06 (dt, J = 8.05, 0.79 Hz, 1H), 6.95 (s, 1H), 6.93 (t, J = 7.30 Hz, 1H), 6.53 (bs, 1H), 4.27 (s, 2H), 4.16 (s, 2H), 3.68 – 3.64 (m, 2H), 2.27 (t, J = 7.10 Hz, 2H), 1.40 (quint., J = 7.20 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 154.93, 153.61, 136.97, 136.85, 134.73, 132.60, 131.99, 130.78 (q, J_{CF} = 31.9 Hz), 129.40, 128.95, 126.65, 124.80 (q, J_{CF} = 3.58 Hz), 124.1 (q, J_{CF} = 271.3 Hz), 123.71 (q, J_{CF} = 3.69 Hz), 122.96, 121.51, 118.86, 117.82, 111.17, 107.88, 42.78,

29.93, 28.76, 23.22, 21.58. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.05 minutes, ESI m/z = 465, $[M+H^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(trifluoromethyl)benzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (196). Prepared according to general method F from (**135**, 125 mg, 0.17 mmol) to yield 60 mg (72%) of **196** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (s, 1H), 7.51 (d, J = 7.79 Hz, 1H), 7.44 (t, J = 7.61 Hz, 1H), 7.42 (s, 1H), 7.34 – 7.28 (m, 2H), 6.99 (dd, J = 9.98, 2.22 Hz, 1H), 6.95 (s, 1H), 6.72 (dt, J = 9.63, 2.32 Hz, 1H), 6.57 (bs, 1H), 4.25 (s, 2H), 4.17 (s, 2H), 3.70 – 3.66 (m, 2H), 2.31 (t, J = 7.08 Hz, 2H), 1.42 (quint., J = 7.12 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.97 (d, J_{CF} = 235.96 Hz), 154.71, 153.67, 136.95, 136.80 (d, J_{CF} = 12.54 Hz), 134.77, 132.60, 132.02, 130.78 (q, J_{CF} = 32.24 Hz), 129.42, 128.95, 124.80 (q, J_{CF} = 3.70 Hz), 124.10 (q, J_{CF} = 271.45 Hz), 123.71(q, J_{CF} = 3.68 Hz), 123.50 (d, J_{CF} = 2.84 Hz), 123.37, 122.74, 118.86, 118.76, 108.20, 107.34 (d J_{CF} = 24.93 Hz), 97.06 (d, J_{CF} = 26.00 Hz), 42.75, 29.92, 29.42, 28.78, 21.51. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.07 minutes, ESI m/z = 483, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 484.1982 (484.1978 calc'd for $C_{25}H_{22}DF_4N_6$, deuterated from storage in CD_3OD, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(trifluoromethyl)benzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-5-methoxy-1*H*-indole (197). Following general method F, (**136**, 209 mg, 0.28 mmol) to afford 105 mg (76%) of **197** as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 – 7.41 (complex overlapping m, 5H), 7.31 (d, J = 7.80 Hz, 1H), 7.18 (d, J = 8.70 Hz, 1H), 6.93 (s, 1H), 6.85 (d, J = 2.30 Hz, 1H), 6.72 (dd, J = 8.70, 2.30 Hz, 1H), 6.54 (bs, 1H), 4.25 (s, 2H), 4.16 (s, 2H), 3.70 (s, 3H), 3.69 – 3.66 (m, 2H), 2.28 (t, J = 7.30 Hz, 2H), 1.39 (quint., J = 7.50 Hz, 2H). LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.85 minutes, ESI m/z = 495, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 495.2110 (495.2115 calc'd for $C_{26}H_{26}F_3N_6O$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(2-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (198). Prepared according to general method F from (**137**, 197 mg, 0.29 mmol) to afford 71 mg (56%) of **198** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (s, 1H), 7.38 – 7.28 (m, 2H), 7.23 – 7.14 (m, 1H), 7.10 – 7.04 (m, 1H), 6.96 – 6.85 (m, 4H), 6.80 (dd, *J* = 8.0, 6.9 Hz, 1H), 6.51 (s, 1H), 4.26 (s, 2H), 4.01 (s, 2H), 3.70 – 3.66 (m, 2H), 3.67 (s, 3H), 2.28 (t, *J* = 7.2 Hz, 2H), 1.44 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 157.03, 154.58, 154.33, 136.88, 134.63, 130.58, 129.45, 128.45, 128.28, 126.69, 123.62, 122.95, 121.50, 120.42, 118.82, 117.96, 111.15, 110.39, 108.04, 54.47, 42.77, 35.17, 28.81, 24.69, 21.63. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.30 min, ESI m/z = 427, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 427.2274 (427.2241 calc'd for $C_{25}H_{27}N_6O$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(2-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (199). Following general method F, (**138**, 125 mg, 0.78 mmol) afforded 36 mg (45%) of **199** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (s, 1H), 7.29 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.22 – 7.16 (m, 1H), 6.99 (dd, *J* = 9.9, 2.3 Hz, 1H), 6.96 – 6.87 (m, 3H), 6.81 (td, *J* = 7.5, 1.1 Hz, 1H), 6.72 (ddd, *J* = 9.7, 8.7, 2.4 Hz, 1H), 6.56 (s, 1H), 4.22 (s, 2H), 4.02 (s, 2H), 3.70 (7, *J* = 8.3 Hz, 1H), 2.32 (t, *J* = 7.2 Hz, 2H), 1.47 (quint., *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.96 (d, J_{CF} = 236.1 Hz), 157.06, 154.62, 154.08, 136.85 (d, J_{CF} = 12.5 Hz), 134.70, 129.47, 128.48, 128.28, 123.61, 123.49 (d, J_{CF} = 3.4 Hz), 123.42, 118.95 (d, J_{CF} = 10.4 Hz), 110.43, 108.40, 107.30 (d, J_{CF} = 24.8 Hz), 97.05 (d, J_{CF} = 26.2 Hz), 54.49, 42.76, 28.81, 24.70, 23.42 (broad), 21.56. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.95 min, ESI m/z = 445, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 445.2141 (445.2147 calc'd for $C_{25}H_{26}FN_6O$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (200). Prepared according to general method F from (**139**, 460 mg, 0.67 mmol) to give 126 mg (43%) of **200** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) *imidazole tautomers observed, NMR data reflects the major isomer*: δ 7.53 (d, *J* = 1.2 Hz, 1H), 7.35 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.30 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.15 – 7.03 (m, 2H), 6.96 – 6.90 (m, 2H), 6.85 – 6.69 (m, 2H), 6.58 (bs, 1H), 6.52 (s, 1H), 4.26 (s, 2H), 4.04 (s, 2H), 3.65 (s, 3H), 3.65 – 3.57 (m, 2H), 2.25 (t, *J* = 7.1 Hz, 2H), 1.36 (quint., *J* = 7.1 Hz, 2H). ^{13}C NMR (400 MHz, CD_3OD) δ 160.23, 154.84, 154.17, 136.87, 134.68, 129.63, 129.18, 126.67, 122.97, 121.51, 120.19, 118.85, 117.89, 114.32, 113.46, 112.40, 112.08, 111.17, 107.91, 54.24, 42.79, 30.34, 28.68, 28.66, 21.59. LCMS (30-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 3.60 min, ESI m/z = 427, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 427.2268 (427.2241 calc'd for $C_{25}H_{27}N_6O$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (201). Prepared according to general method F from (**140**, 138 mg, 0.20 mmol) to afford 66 mg (74% yield) of **200** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) *imidazole tautomers observed, NMR data reflects the major isomer*: δ 7.54 (s, 1H), 7.29 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.16 – 7.11 (m, 1H), 6.99 (dd, *J* = 9.9, 2.3 Hz, 1H), 6.94 (s, 1H), 6.72 (ddd, *J* = 10.7, 8.6, 2.4 Hz, 2H), 6.61 - 6.59 (m, 2H), 6.56 (s, 1H), 4.23 (s, 2H), 4.05 (s, 2H), 3.64 (s, 3H), 3.64 – 3.60 (m, 2H), 2.29 (t, *J* = 7.1 Hz, 2H), 1.40 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 161.14, 159.97 (d, J_{CF} = 235.8), 154.63, 154.23, 136.87, 134.73, 129.64, 129.17, 127.90, 123.51 (d, *J* = 3.4 Hz), 123.40, 120.21, 118.89 (d, J_{CF} = 10.2 Hz), 114.34, 113.57, 112.35, 112.09, 108.27, 107.35 (d, J_{CF} = 24.9 Hz), 97.06 (d, J_{CF} = 26.3 Hz), 54.24, 42.78, 30.35, 28.68, 23.30, 21.52. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.13 min, ESI m/z = 445, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 445.2138 (445.2147 calc'd for $C_{25}H_{26}FN_6O$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (202). Following general method F, (**141**, 97 mg, 0.15 mmol) afforded 48 mg (77%) of **202** as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.19 – 7.14 (m, 1H), 7.07 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 6.98 – 6.90 (m, 4H), 6.85 – 6.80 (m, 1H), 6.79 – 6.73 (m, 2H), 6.52 (s, 1H), 4.25 (s, 2H), 3.99 (s, 2H), 3.69 (s, 3H), 3.63 – 3.53 (m, 2H), 2.24 (t, *J* = 7.1 Hz, 2H), 1.33 (quint., *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 158.99, 154.80, 154.55, 136.85, 134.66, 129.71, 129.08, 127.11, 126.68, 122.97, 121.51, 118.84, 117.90, 113.96, 113.59, 111.17, 107.96, 54.31, 42.76, 32.11, 29.61, 28.66, 21.54. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.72 minutes, ESI m/z = 427, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 427.2245 (427.2241 calc'd for $C_{25}H_{27}N_6O$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (203). Following general method F, (**142**, 224 mg, 0.33 mmol) yielded 111 mg (76%) of **203** as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (bs, 1H), 10.95 (bs, 1H), 7.51 (s, 1H), 7.38 (dd, *J* = 8.20, 5.90 Hz, 1H), 7.06 – 7.03 (m, 2H), 6.97 (d, *J* = 8.20 Hz, 2H), 6.79 – 6.74 (m, 3H), 6.66 (s, 1H), 4.08 (s, 2H), 3.90 (s, 2H), 3.64 (s, 3H), 3.62 – 3.56 (bm, 2H), 2.32 – 2.24 (bm, 2H), 1.48 – 1.38 (bm, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.40 (d, J_{CF} = 234 Hz), 158.47, 153.63, 153.53, 136.61 (d, J_{CF} = 13.4 Hz), 135.18, 130.42, 129.93, 128.79, 124.57 (d, J_{CF} = 2.80 Hz), 124.16, 120.15 (d, J_{CF} = 9.60 Hz), 114.41, 114.11, 109.59, 107.52 (d, J_{CF} = 24.9 Hz), 98.88 (d, J_{CF} = 25.8 Hz), 55.51, 42.61, 29.96, 29.59, 24.94 (broad), 21.84. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.78 minutes, ESI m/z = 445, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 445.2144 (445.2147 calc'd for $C_{25}H_{26}FN_6O$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-methoxybenzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-5-methoxy-1*H*-indole (204). Prepared according to general method F from (**143**, 112 mg, 0.16 mmol) to afford 67 mg (92%) of compound **204** as a tan foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (s, 1H), 7.18 (d, *J* = 8.70 Hz, 1H), 6.94 – 6.90 (m, 3H), 6.83 (d, *J* = 2.70 Hz, 1H), 6.77 – 6.74 (m, 2H), 6.72 (dd, *J* = 8.70, 2.70 Hz, 1H), 6.53 (bs, 1H), 4.23 (s, 2H), 3.99 (s, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.61 – 3.56 (m, 2H), 2.25 (t, *J* = 7.40 Hz, 2H), 1.33 (quint., *J* = 7.70 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 158.97, 154.78, 154.59, 153.92, 134.64, 131.99, 129.03, 127.12, 126.97, 123.58, 113.93, 111.89, 107.57, 99.54, 54.78, 54.31, 42.77, 29.56, 28.58, 23.59 (broad), 21.71. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.75 minutes, ESI m/z = 457, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 457.2335 (457.2347 calc'd for $C_{26}H_{29}N_6O_2$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-((1*H*-indol-3-yl)methyl)-4*H*-1,2,4-triazol-3-yl)methyl)benzonitrile (205). Using general method F, (**144**, 301 mg, 0.45 mmol) gave 125 mg (65%) of compound **205** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6)δ 11.77 (s, 1H), 10.89 (s, 1H), 7.66 (dt, *J* = 6.6, 2.0 Hz, 1H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.52 – 7.42 (m, 3H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.28 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 7.01 (ddt, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.89 (ddt, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.62 (s, 1H), 4.13 (s, 2H), 4.07 (s, 2H), 3.73 (t, *J* = 8.0 Hz, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 1.50 (quint., *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.85, 138.85, 136.79, 135.19, 134.30, 132.74, 131.09, 130.21, 127.28, 124.03, 121.71, 119.22, 119.09, 119.01, 111.97, 111.87, 109.19, 42.69, 30.11, 29.68, 23.97 (broad), 21.98. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.92 minutes, ESI m/z = 422, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 422.2072 (422.2088 calc'd for $C_{25}H_{24}N_7$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-((6-fluoro-1*H*-indol-3-yl)methyl)-4*H*-1,2,4-triazol-3-yl)methyl)benzonitrile (206). Prepared according to general method F from (**145**, 271 mg, 0.40 mmol) to afford 92 mg (52%) of **206** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6)δ 10.97 (bs, 1H), 7.66 (dt, *J* = 6.4, 2.1 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 1.1 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.37 (dd, *J* = 8.7, 5.5 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 7.05 (dd, *J* = 10.2, 2.4 Hz, 1H), 6.76 (ddd, *J* = 9.6, 8.7, 2.4 Hz, 1H), 6.63 (s, 1H), 4.11 (s, 2H), 4.07 (s, 2H), 3.77 – 3.69 (m, 2H), 2.33 (t, *J* = 7.2 Hz, 2H), 1.50 (quint., *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.44 (d, J_{CF} = 234.3 Hz), 153.76, 152.77, 138.83, 136.73, 135.20, 134.29, 132.72, 131.09, 130.21, 124.65 (d, J_{CF} = 3.4 Hz), 124.17, 120.13 (d, J_{CF} = 10.3 Hz), 119.21, 111.89, 109.53, 107.55 (d, J_{CF} = 24.4 Hz), 97.91 (d, J_{CF} = 25.4 Hz), 42.71, 31.31, 29.68, 23.91, 21.88. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.40 minutes, ESI m/z = 440, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 440.1994 (440.1993 calc'd for $C_{25}H_{23}FN_7$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(methylsulfonyl)benzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (207). According to general method F, (**146**, 65 mg, 0.09 mmol) afforded 37 mg (86%) of **207** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (d, *J* = 7.79 Hz, 1H), 7.71 (s, 1H), 7.54 (bs, 1H), 7.51 (t, *J* = 7.75 Hz, 1H), 7.42 (d, *J* = 7.73 Hz, 1H), 7.36 (d, *J* = 7.91 Hz, 1H), 7.30 (d, *J* = 8.23 Hz, 1H), 7.06 (dt, *J* = 8.08, 0.84 Hz, 1H), 6.97 (s, 1H), 6.95 (dt, *J* = 8.03, 0.77 Hz, 1H), 6.55 (bs, 1H), 4.28 (s, 2H), 4.19 (s, 2H), 3.69 – 3.65 (m, 2H), 2.98 (s, 3H), 2.29 (t, *J* = 7.07 Hz, 2H), 1.41 (t, *J* = 6.95 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 154.97, 153.51, 141.35, 137.51, 136.85, 134.81, 133.64, 129.75, 126.91, 126.67, 125.92, 123.02, 121.52, 118.91, 117.85, 111.19, 107.89, 42.89, 42.81, 29.93, 28.84, 23.34, 21.59. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.72 minutes, ESI m/z = 475, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 475.1905 (475.1911 calc'd for $C_{25}H_{27}N_6O_2S$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(3-(methylsulfonyl)benzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (208). Prepared according to general method F from (**147**, 380 mg, 0.52 mmol) to yield 120 mg (47%) of **208** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (ddd, *J* = 7.7, 1.9, 1.0 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.55 (d, *J* = 1.1 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.32 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.00 (dd, *J* = 9.9, 2.3 Hz, 1H), 6.97 (d, *J* = 0.9 Hz, 1H), 6.79 – 6.70 (m, 1H), 6.59 (s, 1H), 4.25 (d, 2H), 4.20 (s, 2H), 3.75 – 3.65 (m, 2H), 3.00 (s, 3H), 2.33 (t, *J* = 7.1 Hz, 2H), 1.45 (quint., *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.96 (d, J_{CF} = 236.0 Hz), 154.76, 153.56, 141.39, 137.52, 136.84 (d, J_{CF} = 12.7 Hz), 134.87, 133.68, 129.77, 127.96, 127.30, 126.92, 125.96, 125.61, 123.57 (d, J_{CF} = 3.4 Hz), 123.42, 118.87 (d, J_{CF} = 10.4 Hz), 108.26, 107.42 (d, J_{CF} = 24.9 Hz), 97.08 (d, J_{CF} = 25.9 Hz), 42.89, 42.79, 29.93, 28.88, 23.25 (broad), 21.52. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.95 minutes, ESI m/z = 493, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 493.1810 (493.1816 calc'd for $C_{25}H_{26}FN_6O_2S$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-(methylsulfonyl)benzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (209). According to general method F, (**148**, 207 mg, 0.28 mmol) afforded 73 mg (55%) of **209** as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 – 7.78 (m, 2H), 7.54 (d, *J* = 1.2 Hz, 1H), 7.38 – 7.28 (m, 4H), 7.07 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 6.99 (s, 1H), 6.94 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.55 (s, 1H), 4.28 (s, 2H), 4.18 (s, 2H), 3.69 – 3.60 (m, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.39 (quint., *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 155.01, 153.37, 142.04, 139.67, 136.87, 134.78, 129.88, 129.28, 127.63, 127.27, 126.68, 123.07, 121.55, 118.88, 117.88, 111.21, 107.88, 42.95, 42.82, 30.16, 29.78, 28.85, 21.60. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.57 minutes, ESI m/z = 475, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 475.1925 (475.1911 calc'd for $C_{25}H_{27}N_6O_2S$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-(4-(methylsulfonyl)benzyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (210). Using general method F, (**149**, 157 mg, 0.21 mmol) gave 71 mg (68% yield) of **210** as a white foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.90 – 7.80 (m, 2H), 7.57 – 7.51 (m, 2H), 7.37 – 7.28 (m, 3H), 7.03 – 6.96 (m, 2H), 6.74 (ddd, J = 9.4, 8.8, 2.3 Hz, 1H), 6.59 (s, 1H), 4.25 (s, 2H), 4.19 (s, 2H), 3.73 – 3.64 (m, 2H), 3.03 (s, 3H), 2.32 (t, J = 7.1 Hz, 2H), 1.43 (quint., J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.98 (d, J_{CF}= 236.2 Hz), 154.78, 153.41, 142.02, 139.70, 136.85 (d, J_{CF} = 12.9 Hz), 134.83, 129.88, 129.31, 127.65, 127.27, 123.60 (d, J_{CF} = 3.3 Hz), 123.42, 118.89 (d, J_{CF} = 10.2 Hz), 108.24, 107.36 (d, J_{CF} = 24.9 Hz), 97.09 (d, J_{CF} = 26.0 Hz), 42.95, 42.80, 30.18, 28.88, 23.33 (broad), 21.50. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.83 minutes, ESI m/z = 493, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 493.1820 (493.1817 calc'd for $C_{25}H_{26}FN_6O_2S$, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-5-neopentyl-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (211). Prepared according to general method F from (**150**, 134 mg, 0.21 mmol) to yield 69 mg (83%) of **211** as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (s, 1H), 7.27 (dd, J = 8.7, 5.3 Hz, 1H), 7.01 (dd, J = 9.9, 2.3 Hz, 1H), 6.97 (s, 1H), 6.75 – 6.66 (m, 2H), 4.26 (s, 2H), 3.82 – 3.70 (m, 2H), 2.42 (t, J = 7.0 Hz, 2H), 1.62 (quint., J = 7.1 Hz, 2H), 0.88 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.98 (d, J_{CF} = 236.0 Hz), 153.80, 153.65, 136.88 (d, J_{CF} = 12.5 Hz), 134.88, 131.37, 128.27, 126.83, 123.45 (d, J_{CF} = 3.4 Hz), 123.42, 118.89 (d, J_{CF} = 10.1 Hz), 108.48, 107.29 (d, J_{CF} = 24.9 Hz), 97.08 (d, J_{CF} = 26.0 Hz), 42.59, 36.70, 31.80, 29.20, 28.50, 23.22, 21.69. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.80 minutes, ESI m/z = 395, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 395.2361 (395.2354 calc'd for $C_{22}H_{28}FN_6$, $[M + H]^+$).

3,3'-((4-(3-(1*H*-Imidazol-4-yl)propyl)-4*H*-1,2,4-triazole-3,5-diyl)bis(methylene))bis(6-fluoro-1*H*-indole) (212). Prepared according to general method F from (**151**, 68 mg, 0.095 mmol) to

yield 33 mg (73%) of **212** as a tan solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (s, 1H), 7.27 (dd, *J* = 8.7, 5.3 Hz, 2H), 6.97 (dd, *J* = 9.9, 2.3 Hz, 2H), 6.88 (s, 2H), 6.69 (ddd, *J* = 9.8, 8.7, 2.4 Hz, 2H), 6.48 (s, 1H), 4.19 (s, 4H), 3.69 – 3.59 (m, 2H), 2.22 (t, *J* = 7.1 Hz, 2H), 1.36 (quint., *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.95 (d, *J* = 235.8 Hz), 154.52, 136.83 (d, *J* = 12.6 Hz), 134.64, 123.44, 124.41, 123.40, 118.88 (d, *J* = 10.2 Hz), 108.36, 107.29 (d, *J* = 24.9 Hz), 97.02 (d, *J* = 26.0 Hz), 42.79, 28.66, 23.47, 21.48. (LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.97 minutes, ESI m/z = 472, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 473.2133 (473.2134 calc'd for $C_{26}H_{23}DFN_7$, deuterated from storage in CD_3OD, $[M + H]^+$).

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-1*H*-indole (213). Prepared according to general method F from (**156**, 62 mg, 0.11 mmol) to afford 10 mg (30%) of **213** as a white foam: ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (s, 1H), 7.50 (s, 1H), 7.34 (ddt, *J* = 23.6, 8.2, 1.0 Hz, 2H), 7.07 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.01 – 6.85 (m, 2H), 6.57 (s, 1H), 4.29 (s, 2H), 3.85 (dd, *J* = 8.4, 6.8 Hz, 2H), 2.36 (t, *J* = 7.4 Hz, 2H), 1.85 – 1.67 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 153.80, 144.38, 136.87, 135.66, 134.07, 126.71, 122.98, 121.51, 121.52, 118.85, 117.85, 111.17, 108.04, 43.74, 29.34, 23.23 (b), 20.96. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 2.07 minutes, ESI m/z = 307, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 307.1671 (307.1666 calc'd for $C_{17}H_{19}N_6$), $[M + H]^+$.

3-((4-(3-(1*H*-Imidazol-4-yl)propyl)-4*H*-1,2,4-triazol-3-yl)methyl)-6-fluoro-1*H*-indole (214). Prepared according to the general method from (**157**, 109 mg, 0.19 mmol) to afford 20 mg (32% yield) of **214** as a tan foam: ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (s, 1H), 7.52 (d, *J* = 1.2 Hz, 1H), 7.32 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.05 – 6.95 (m, 2H), 6.73 (ddd, *J* = 9.8, 8.7, 2.3 Hz, 1H), 6.66 – 6.52 (m, 1H), 4.27 (s, 2H), 3.94 – 3.78 (m, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.79 (quint., *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 159.99 (d, *J* = 236.1 Hz), 153.62, 144.41, 136.84 (d, *J* =

12.5 Hz), 134.76 (broad, 2Cs), 123.51 (d, *J* = 3.5 Hz), 123.44, 108.37, 107.34 (d, *J* = 24.8 Hz), 97.06 (d, *J* = 26.2 Hz), 43.73, 29.36, 23.24, 20.88. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.98 minutes, ESI m/z = 325, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 325.1555 (325.1571 calc'd for $C_{17}H_{18}FN_6$), $[M + H]^+$.

Synthesis of Boc-protected-1,2,4-Triazoles 215-217.

***tert*-Butyl (2-(3-(2-(1*H*-indol-3-yl)ethyl)-5-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-4-yl)ethyl)-carbamate (215).** Prepared according to general method E from thioamide (**28**, 670 mg, 1.93 mmol) and 2-(3,4-dichlorophenyl)acetic hydrazide[2] (**96**, 507 mg, 2.31 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) and recrystallization of the product from ACN afforded 701 mg (71% yield) of **215** as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (bs, 1H), 7.54 (d, *J* = 8.20 Hz, 1H), 7.51 (d, *J* = 2.20 Hz, 1H), 7.44 (d, *J* = 7.80 Hz, 1H), 7.29 (d, *J* = 7.70 Hz, 1H), 7.16 (dd, *J* = 8.20, 1.80 Hz, 1H), 7.13 (d, *J* = 2.20 Hz, 1H), 6.98 – 7.04 (m, 2H), 6.90 (dt, *J* = 6.90, 0.90 Hz, 1H), 4.05 (s, 2H), 3.73 (apparent t, *J* = 6.00 Hz, 2H), 3.07 – 3.11 (m, 2H), 2.99 – 3.04 (m, 2H), 2.93 – 2.97 (m, 2H), 1.24 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.16, 154.96, 152.58, 138.25, 136.72, 131.50, 131.37, 131.11, 129.89, 129.71, 127.47, 123.08, 121.46, 118.79, 114.00, 111.86, 78.67, 42.70, 40.43, 29.75, 28.58, 35.98, 23.05. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.22 min, ESI m/z = 514, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 514.1786 (514.1771 calc'd for $C_{26}H_{30}Cl_2N_5O_2$), $[M + H]^+$.

***tert*-Butyl (4-(3-(2-(1*H*-indol-3-yl)ethyl)-5-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-4-yl)butyl)-carbamate (216).** Prepared according to general method E from thioamide (**29**, 461 mg, 1.23 mmol) and 2-(3,4-dichlorophenyl)acetic hydrazide[2] (**95**, 323 mg, 1.47 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol, then reflashed with EtOAc to EtOAc/Ethanol

10:1) afforded 340 mg (51% yield) of compound **216** as a yellowish foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.77 (bs, 1H), 7.54 (d, *J* = 8.20 Hz, 1H), 7.52 (d, *J* = 0.90 Hz, 1H), 7.43 (d, *J* = 7.80Hz, 1H), 7.29 (d, *J* = 8.70 Hz, 1H), 7.16 (dd, *J* = 8.20, 1.40 Hz, 1H), 7.12 (d, *J* = 1.80 Hz, 1H), 7.01 (t, *J* = 7.80 Hz, 1H), 6.91 (dt, *J* = 7.80, 1.00 Hz, 1H), 6.73 (bt, *J* = 6.00 Hz, 1H), 4.08 (s, 2H), 3.67 (apparent t, *J* = 6.50 Hz, 2H), 3.08 (apparent t, *J* ~ 7.55 Hz, 2H), 2.95 (apparent t, *J* ~ 7.45 Hz, 2H), 2.77 (apparent q, *J* = 6.00 Hz, 2H), 1.29 (s, 9H), 1.18 – 1.30 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.15, 154.72, 152.37, 138.46, 136.71, 131.48, 131.27, 131.12, 129.87, 129.63, 127.46, 123.16, 121.45, 118.82, 118.68, 113.87, 111.89, 78.00, 42.70, 39.64, 29.63, 28.73, 27.54, 27.02, 25.95, 23.23. LCMS (50-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.38 min, ESI m/z = 542, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 542.2094 (542.2084 calc'd for $C_{28}H_{34}Cl_2N_5O_2$), $[M + H]^+$.

***tert*-Butyl (5-(3-(2-(1*H*-indol-3-yl)ethyl)-5-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-4-yl)pentyl)-carbamate (217).** Prepared according to general method E from thioamide (**30**, 836 mg, 2.15 mmol) and 2-(3,4-dichlorophenyl)acetic hydrazide[2] (**96**, 564 mg, 2.57 mmol). Purification by flash chromatography (SiO_2, 20:1 CH_2Cl_2/methanol) afforded 348 mg (29%) of **217** as a yellowish foam: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (bs, 1H), 7.53 (d, *J* = 8.20 Hz, 1H), 7.51 (d, *J* = 1.30 Hz, 1H), 7.42 (d, *J* = 7.70 Hz, 1H), 1.29 (d, *J* = 8.70 Hz, 1H), 7.15 (dd, *J* = 8.30, 1.40 Hz, 1H), 7.11 (d, *J* = 1.90 Hz, 1H), 7.01 (t, *J* = 7.70 Hz, 1H), 6.91 (t, *J* = 7.80 Hz, 1H), 6.70 (bt, *J* = 5.90 Hz, 1H), 4.08 (s, 2H), 3.62 (apparent t, *J* = 7.30 Hz, 2H), 3.09 (apparent t, *J* ~ 7.55 Hz, 2H), 2.95 (apparent t, *J* ~ 7.75 Hz, 2H), 2.76 (apparent q, *J* = 6.40 Hz, 2H), 1.30 (s, 9H), 1.13 – 1.20 (m, 4H), 0.98 – 1.08 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.12, 154.77, 152.32, 138.49, 136.71, 131.50, 131.25, 131.13, 129.88, 129.61, 127.45, 123.16, 121.45, 118.81, 118.66, 113.85, 111.89, 77.90, 42.95, 39.90, 29.78, 29.69, 29.56, 28.77, 25.94, 23.70, 23.31. LCMS (50-95%

acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.62 min, ESI m/z = 556, $[M+H]^+$. HRMS (ESI Q-TOF) m/z = 556.2238 (556.2241 calc'd for $C_{29}H_{36}Cl_2N_5O_2$, $[M + H]^+$).

Synthesis of 4-Aminoalkyl-1,2,4-Triazoles 218-220.

4-(3-(2-(1*H*-Indol-3-yl)ethyl)-5-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-4-yl)butan-1-amine hydrochloride (219). To a solution of (**216**, 168 mg, 0.31 mmol) in CH_2Cl_2 (20 mL) was added 4N HCl/dioxane (2.0 mL). The reaction was stirred at RT for 1h and concentrated. The residue was dissolved in methanol (1.5 mL), treated with ether (2 mL) and filtered. Concentration of the filtrate afforded 74 mg (50% yield) of **219** as a colorless glass. Due to obscured peaks in the proton NMR when the hydrochloride was run in DMSO-d_6, a small sample of free base was prepared for ^{1}H NMR analysis by treatment with triethylamine and aqueous workup: ^{1}H NMR (400 MHz, CD_3OD), *free base,* δ 7.43 (d, *J* = 8.20 Hz, 1H), 7.37 (d, *J* = 1.80 Hz, 1H), 7.33 (d, *J* = 7.80 Hz, 1H), 7.28 (d, *J* = 8.30 Hz, 1H), 7.04 (dt, *J* = 8.20, 1.40 Hz, 1H), 6.90 – 6.98 (m, 3H), 4.05 (s, 2H), 3.36 (apparent t, *J* ~ 7.80 Hz, 2H), 3.23 (apparent t, *J* ~ 7.55 Hz, 2H), 3.07 (apparent t, *J* = 6.90 Hz, 2H), 2.20 – 2.37 (broadened m, 2H), 1.03 – 1.12 (m, 2H), 0.89 – 0.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6), *HCl salt,* δ 155.63, 153.94, 136.69, 135.60, 131.88, 131.74, 131.39, 130.75, 130.25, 127.21, 123.64, 121.68, 119.02, 118.62, 112.32, 112.05, 44.03, 38.53, 29.11, 26.18, 25.32, 24.35, 22.14. LCMS (40-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 1.93 min, ESI m/z = 442, $[M-Cl+H]^+$. HRMS (ESI Q-TOF) m/z = 442.1553 (442.1560 calc'd for $C_{23}H_{26}Cl_2N_5$, $[M + H]^+$).

2-(3-(2-(1*H*-Indol-3-yl)ethyl)-5-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-4-yl)ethan-1-amine hydrochloride (218). Prepared in a similar manner as described for **219** from (**215**, 651 mg, 1.27 mmol) to afford 532 mg (93%) of **218** as a tan foam: ^{1}H NMR (400 MHz, CD_3OD*)* δ 7.56 (d, *J* = 1.80 Hz, 1H), 7.52 (d, *J* = 7.70 Hz, 1H), 7.34 (dt, *J* = 8.30, 0.90 Hz, 2H), 7.16 – 7.19 (m, 2H) 7.08

(dt, *J* = 7.40, 1.40 Hz, 1H), 6.95 (dt, *J* = 6.90, 1.0 Hz, 1H), 4.33 (s, 2H), 4.24 (t, *J* = 7.30 Hz, 2H), 3.45 (apparent t, *J* = 7.20 Hz, 2H), 3.34 (apparent t, *J* ~ 6.20 Hz, 2H), 3.11 (t, *J* = 7.80 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 156.60, 154.38, 136.69, 133.13, 132.58, 131.86, 131.29, 130.89, 128.96, 126.59, 121.46, 118.85, 117.19, 111.33, 111.21, 41.10, 37.01, 29.00, 25.67, 21.89. LCMS (15-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 6.27 min, ESI m/z = 414, $[M\text{-}Cl+H]^+$. HRMS (ESI Q-TOF) m/z = 414.1248 (414.1247 calc'd for $C_{21}H_{22}Cl_2N_5$, $[M + H]^+$).

5-(3-(2-(1*H*-Indol-3-yl)ethyl)-5-(3,4-dichlorobenzyl)-4*H*-1,2,4-triazol-4-yl)pentan-1-amine (220). To a solution of (**217**, 280 mg, 0.50 mmol) in CH_2Cl_2 (20 mL) was added TFA (5 mL). The reaction was stirred for 30 min at RT and concentrated. The residue was dissolved in methanol (3.0 mL) and filtered through a 0.45 mm frit. The filtrate was treated with 1N HCl in ether (2 mL) and concentrated to afford 201 mg (81% yield) of **220** as a tan foam: ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 -7.52 (m, 2H), 7.37 (d, *J* = 7.80 Hz, 1H), 7.34 (d, *J* = 8.30 Hz, 1H), 7.07 – 7.14 (m, 3H), 6.98 (t, *J* = 7.30 Hz, 1H), 4.28 (s, 2H), 3.80 (apparent t, *J* ~ 7.30 Hz, 2H), 3.30 – 3.39 (m, 4H), 2.76 (t, *J* = 7.30 Hz, 2H), 1.40 – 1.48 (m, 2H), 1.12 – 1.20 (broadened m, 4H). ^{13}C NMR (400 MHz, CD_3OD) δ 156.32 (b), 153.92 (b), 136.76, 133.86, 132.53, 131.68, 131.35, 131.07, 130.89, 129.30, 128.81, 126.67, 122.77, 121.48, 118.89, 117.29, 111.40, 111.39, 44.40, 38.93, 28.95, 28.08, 26.56, 25.52, 22.86, 22.30. LCMS (25-95% acetonitrile in 0.05% TFA over 10 minutes) retention time = 5.78 min, ESI m/z = 456, $[M\text{-}Cl+H]^+$. HRMS (ESI Q-TOF) m/z = 456.1702 (456.1716 calc'd for $C_{24}H_{28}Cl_2N_5$, $[M + H]^+$).

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 S4e)**. 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 S4a-e)**.

Off-target receptor profiling of select compounds was performed by the National Institute of Mental Health (NIMH) Psychoactive Drug Screening Program (PSPD).[1] Radioligand binding was first measured in the presences of 10 µM of the test compound. A Ki value was determined for receptors at which the test compound showed a > 50% inhibition. For experimental details, refer to the PSPD website: https://pdsp.unc.edu/pdspweb/.

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 somatostatin-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.

P-glycoprotein Efflux. P-glycoprotein (P-gp) efflux determinations performed by Cyprotex US, LLC. (Watertown, MA), a contract research organization. Per Cyprotex protocol, assay measured bi-directional permeability of compounds using Madin Darby canine kidney (MDCK) cells transfected with the *MDR1* gene, which encodes P-gp.[7] Cells were grown in tissue culture flasks, trypsinized, suspended in medium, and the suspensions applied to wells of a Millipore 96 well plate. The cells were grown and differentiated for five days, feeding at 2-day intervals. For apical to basolateral (A→B) permeability, compound (10 μM) was added to the A side and amount of permeation was determined on the B side; for basolateral to apical (B→A) permeability, compound (10 μM) was added to the B side and the amount of permeation was

determined on the A side. The buffer solution contained 100 μM lucifer yellow dye, in transport buffer (1.98 g/L glucose in 10 mM HEPES, 1x Hank's Balanced Salt Solution) pH 7.4. Cells were incubated with respective compounds for 2 hr, and at the end of the assay, donor and receiver side solution samples will be collected, quenched by 100 % methanol containing an internal standard and centrifuged at 5000 rpm for 10 min at 4 ºC. Each sample was performed in duplicate, and Talinolol served the P-gp control. Following centrifugation, the supernatant for donor and receiver side samples are analyzed by LC-MS/MS. Efflux ratio determined as (B→A) permeability/(A→B) permeability.

Animals, Dosing, and Testing. Twelve-month old male SAMP8 mice were used for all behavioral and post-treatment (*ex vivo*) assessments. Mice were housed in rooms with a 12 hr light/dark cycle (20–22°C) with water and food available *ad libitum*. *All experiments were conducted in accordance with the institutional approval of the animal use subcommittee, which subscribes to the NIH Guide for Care and Use of Laboratory Animals.* SAMP8 mice were obtained from the breeding colony at the Veterans Affairs Medical Center - VA hospital (St. Louis, MO). The colony is derived from siblings generously provided by Dr. Takeda (Kyoto University, Japan).

Measurement of the effects of compound **208** on acquisition learning and retention were performed following chronic i.p. and oral administration in 12-month-old male SAMP8 mice. Dosing for i.p. administration (0.001-1.0 mg/kg/day) was evaluated against vehicle (20% ethanol/saline) control. Oral administration evaluations (0.001-10.0 mg/kg/day) were evaluated against vehicle (20% ethanol/buffer, pH=3). Respective doses were given once a day over a period of 28 days. Learning and memory assessment was assessed by the T-maze model. Individual performing test was blind to respective dosing. Learning evaluations were conducted after three

weeks of treatment on day 21, while memory retention of the learned task was assessed after one additional week of treatment on day 28. Body weights were evaluated weekly, with no animals in the study exhibiting weight loss or abnormal behaviors.

The T-maze avoidance apparatus training and testing procedures have been previously described, and shown as an effective means to assess learning and memory in SAMP8 mice against drug treatments.[23-25] The T-maze consisted of a black plastic alley with a start box at one end and two goal boxes at the other. The start box was separated from the alley by a plastic guillotine door, which prevented movement down the alley until training began. An electrifiable stainless steel rod floor ran throughout the maze to deliver scrambled foot-shock. Mice were trained and tested between 07:00 and 15:00 h. Mice were not permitted to explore the maze prior to training. A training trial began when a mouse was placed into the start box. The guillotine door was raised and the buzzer sounded simultaneously. After 5 s, footshock was applied. The goal box the mouse first entered on the first trial was designated as 'incorrect'. Footshock was continued until the mouse entered the other goal box, which on all subsequent trials was designated 'correct' for that particular mouse. At the end of each trial, the mouse was removed from the goal box and returned to its home cage. A new trial began by placing the mouse in the start box, sounding the buzzer, and raising the guillotine door. Footshock was applied 5 s later if the mouse did not leave the start box or failed to enter the correct goal box. The mean trials to first avoidance represents acquisition learning, the retention of the learned task (1 week later, day-28) was reported as the mean trails to criterion. One-way ANOVA, with Dunnett's post-hoc. Data are expressed as means ± SEM. Significance set at $p < 0.05$.

Protein Preparation - Computational

Protein Preparation Wizard, a function within Maestro 10.3, was employed to prepare the model built SST_4 receptor for subsequent docking experiments. Bond orders were assigned, and disulfide bonds were created. Hydrogens were assigned at physiological pH, followed by optimization and restrained minimization for heavy atom convergence to RMSD 0.3 Å.

Ligand Preparation and Ligand Docking - Computational

Compounds were built in Discovery Studio 4.5, and minimized with the CHARMM force field, 200 steps steepest descent, followed by 1000 steps conjugate gradient. The minimized structures were imported into Maestro 10.3. Docking was performed using Glide 6.8.[26] A receptor grid was generated with an inner box (indicating where the ligand center can be) of 14 Å, and an outer box of 34 Å (ligand length). Residues Asp90 and His258 defined the binding pocket. A scaling factor of 0.8 was set with a partial charge cutoff at 0.15. Non-planar amide torsions were penalized, while Epik state penalties[27, 28] were added. Six thousand poses per ligand were kept after the initial docking phase, while the best 500 poses for each ligand were kept for energy minimization, with default settings otherwise and 15 resultant poses. Final pose selection was based on visual inspection and the Emodel scoring function.[26] Emodel includes contributions from GlideScore, internal energy, and the Coulomb van der Waals energy.

QSAR Modeling - Computational

Canvas [29] was employed for model construction and for physicochemical property calculations. Dendritic fingerprints [30] were generated for all compounds, with 32-bit precision, atom/bond typing set to 'daylight invariant', and no scaling. Direct kernel-based PLS (DKPLS) regression [31] was used to generate the model, with p*K*i being the dependent variable. Kernel non-linearity was 0.05, maximum number of KPLS factors were selected to be three, uncertainty on test set predictions was checked with the default value of 10 bootstrapping cycles. Original seed

was 12345 and random assignment 70:30% for training:test sets, with the final model having a distribution of 73:27%, respectively. To further validate the model, an additional 40 compounds were screened using a maximum of three KPLS factors with Kernel nonlinearity at default 0.05, and 10 bootstrapping cycles for uncertainties. In the end, a predictive model with three KPLS factors was chosen based on the following statistics: (1) Training set: R^2= 0.8842 and Standard Deviation (SD)=0.4494; (2) Test set: Q^2=0.8204 and Root Mean Square Error (RMSE)=0.4690, and (3) Validation set: Q^2=0.5993 and RMSE=0.6397. Selection was based on criteria that the test and validation set Q^2 needs to be >0.5, R^2 for the training set should be between 0.8 and 0.9, and the test set root mean square error < 1.5 x SD.

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