

Supplementary data for the article:

Terzić, N.; Konstantinović, J.; Tot, M.; Burojević, J.; Djurković-Djaković, O.; Srbljanović, J.; Štajner, T.; Verbić, T.; Zlatović, M.; Machado, M.; et al. Reinvestigating Old Pharmacophores: Are 4-Aminoquinolines and Tetraoxanes Potential Two-Stage Antimalarials? *Journal of Medicinal Chemistry* **2016**, *59* (1), 264–281.
<https://doi.org/10.1021/acs.jmedchem.5b01374>

Supporting information-I

Reinvestigating Old Pharmacophores: Are 4-Aminoquinolines and Tetraoxanes Potential Two-Stage Antimalarials?

Natasa Terzić,[#] Jelena Konstantinović,[¶] Mikloš Tot,[¶] Jovana Burojević,[¶] Olgica Djurković-Djaković,[∇] Jelena Srbljanović,[∇] Tijana Štajner,[∇] Tatjana Verbić,[¶] Mario Zlatović,[¶] Marta Machado,[§] Inês S. Albuquerque,[§] Miguel Prudêncio,^{§,*} Rick Sciotti,[†] Stevan Pecic,[∇] Sarah D'Alessandro,[‡] Donatella Taramelli,[‡] Bogdan A. Šolaja^{¶,*}

[#]Institute of Chemistry, Technology, and Metallurgy, Belgrade, Serbia

[¶]Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 51, 11158, Belgrade, Serbia

[∇]Institute for Medical Research, University of Belgrade, Dr.Subotića 4, 11129 Belgrade, Serbia

[§]Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, 1649-028 Lisboa, Portugal

[†]Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Silver Spring, MD20910, USA

[∇]Division of Experimental Therapeutics Department of Medicine, Columbia University, New York, NY 10032, USA

[‡]Dipartimento di Scienze Farmacologiche e Biomolecolari, Università degli Studi di Milano, 20133 Milan, Italy

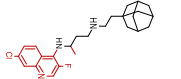
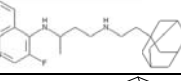
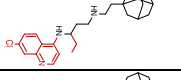
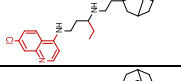
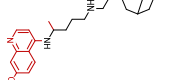
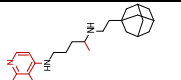
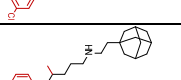
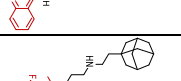
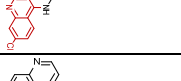
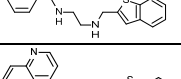
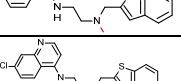
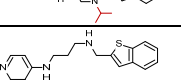
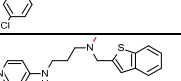
Table of contents

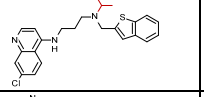
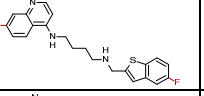
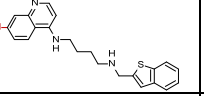
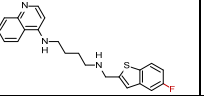
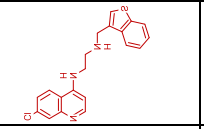
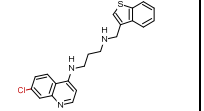
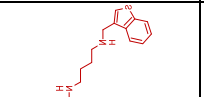
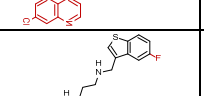
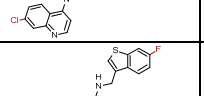
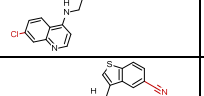
Table S1	S3
Figure S1	S9
Table S2	S10
BHIA plots	S11
Distribution diagrams	S14
Chemistry	S14

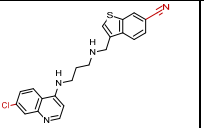
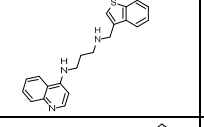
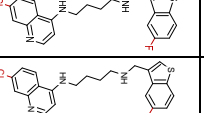
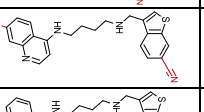
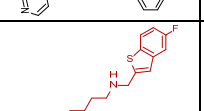
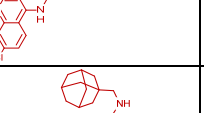
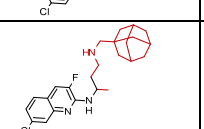
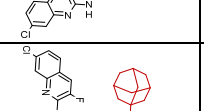
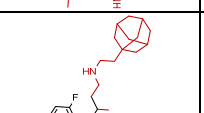
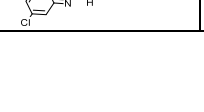

Table S1. Relevant data and activity of synthesized antiplasmodials.

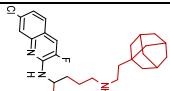
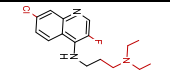
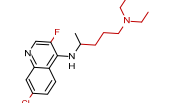
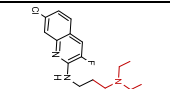
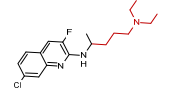
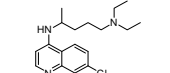
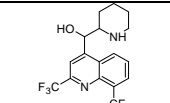
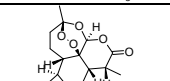
Structure	Compound	MW	logP _{ow} exp.	pK _{a1} ±S D	pK _{a2} ±S D	Dipole ^a	BHIA ^b	In vitro antimalarial activity ^{c, d} (<i>P. falciparum</i> , IC ₅₀ , nM)			HepG2 ^h (R AW 264.7) ⁱ IC ₅₀ ,nM	MLM ^j (min)	HLM ^k (min)	SI HepG2(RAW) /D6
								D6 ^e	C235 ^f	W2 ^g				
	1[#]	369.93	3.09					4	9	8	3437			859
	9	383.97	3.40	6.75± 0.03	8.18± 0.03			1	1	3	(2901)	10	11	(2901)
	10	383.97	3.17	6.51± 0.01	8.13± 0.01			2	9	10	(3771)	10	13	(1886)
	11	383.97	3.55					4	19	44	(1809)			(452)
	12	349.51	3.70					584	934	1713	4111			7
	20	401.96	3.02					585	948	1367	4252			7
	21	401.96	3.09					1261	3082	2269	6436	6	13	5
	22	398.00	3.93					4	15	22	(3161)	11	16	(790)
	23	398.00	3.85	6.96± 0.15	9.22± 0.14	6.04	1.84± 0.08	10	10	10	3045	60	60	305
	24	363.54	4.09	7.33± 0.09	9.21± 0.05	4.79	1.22± 0.09	17	135	185	2317	60	60	136

	25	415.99	3.25	4.92± 0.11	9.20± 0.20	3.10	0.61± 0.07	135	197	238	3967	21 (79 ^l)	13 (78 ^m)	29
	26	381.53	3.09	5.47± 0.05	8.16± 0.09	4.01	0.61± 0.05	60	259	157				0
	27	412.02	3.40					3	12	9	(5257)	13	34	(1752)
	28	412.02	3.78					7	19	25	2010	15	14	287
	29	412.02	4.16					21	23	22	24271	57	49	1156
	30	412.02	4.16					7	19	25	3090			441
	31	412.02	3.55					51	165	282	1612			32
	32	430.01	3.47					198	342	488	3549			18
	33	398.00	4.41	6.81± 0.04	8.63± 0.08	3.84		1	1	4	(2910)	60	57	(2910)
	34	398.00	3.78			3.47		6	7	7	25127	60	27	4188
	35	363.54	4.33					9	86	97	2345			261
	36	412.02	5.16			4.27		13	13	13	24271	60	60	1867
	37	377.57	4.85	7.13± 0.06	9.54± 0.03	3.39		7	102	126	1590			227

	38	430.01	4.33			2.87		143	171	203	3212			22
	39	395.56	4.13			2.96		154	546	394				0
	40	426.05	4.59					11	32	18	1767	22	16	161
	41	426.05	4.59					43	69	79	23472			546
	42	426.05	5.87			4.88		7	14	26	13273	60	60	1896
	43	426.05	4.85					9	47	81	2598			289
	44	391.59	5.37	7.24± 0.05	9.69± 0.09			12	286	393	1593			133
	45	444.04	4.67					288	590	547	2608			9
	46	367.90	1.97					55	48	97	33438			608
	47	381.90	2.69					120	257	296	5741	9	9	48
	48	410.00	3.12					34	56	68	7305	9	9	215
	49	381.90	2.38				0.85± 0.06	44	64	87	1906			43
	50	396.00	2.76					86	119	177	7336	9	6	85

	51	424.00	2.94					75	137	231	3054	8	5	41
	52	414.00	2.57					14	29	41	4435			317
	53	396.00	2.63					20	37	45	866			43
	54	379.50	2.94					32	177	240	3227			101
	55	367.90	2.44					30	19	22	6120	23	24	204
	56	381.90	2.82				0.66± 0.04	7	17	24	7780			1111
	57	396.00	3.06					8	68	31	2258			282
	58	399.90	2.63				0.41± 0.04	28	78	50	2463			88
	59	399.90	2.76				0.50± 0.05	33	20	28	5543			168
	60	406.90	2.11				0.99± 0.07	5	25	32	3971			794

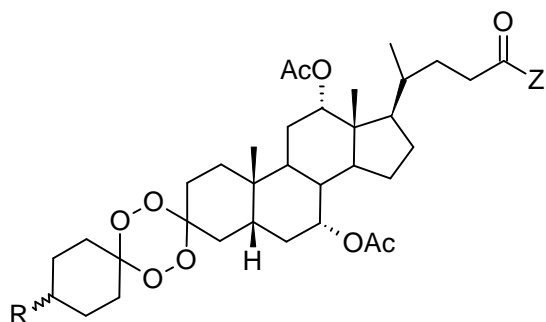
	61	406.90	2.24				0.78± 0.06	17	52	47	3880			228
	62	347.50	3.18				1.54± 0.10	89	280	283	5144			58
	63	414.00	2.82				0.38± 0.03	10	19	27	1649			165
	64	421.00	2.31					12	36	40	2929			244
	65	421.00	2.51				1.07± 0.08	10	24	40	3808			381
	66	361.50	3.30					65	299	275	4673			72
	67	442.00	2.88					20	32	36	3871			194
	68	401.96	3.40					3192	2918	1577	4048			1
	69	415.99	3.70					731	990	950	5481			7
	70	430.01	4.01					751	963	588	3639	60	60	5
	71	430.01	5.37					2821	2763	1884	8930	60	24	3

	72	444.04	5.26					2241	3432	1212	22992			10
	73	309.82	3.32	5.16± 0.09	9.25± 0.19		0.78± 0.08	1601	1354	1797	34983			22
	74	337.87	4.01	5.17± 0.12	9.46± 0.04		1.07± 0.09	405	412	565	18815			46
	75	309.82	4.01					800	626	423	30948			39
	76	337.87	4.16	3.77± 0.14	9.48± 0.18		2.42± 0.11	6772	3362	571	18712			3
	CQ	319.87		7.48± 0.02	9.58± 0.03		1.23± 0.10	12	139	456				
	MFQ	378.31						16	36	5				
	ART	282.33						9	13	7				

^a QikProp, version 3.5, Schrödinger, Inc., New York, NY, 2012. ^b aIC₅₀ values represent molar equivalents of compound, relative to hemin, that inhibit β-hematin formation by 50% (data expressed as means ± SD from an experiment done in triplicates, except for CQ which was tested 6 times). ^c Antiplasmodial IC₅₀ values (nM) (³H]hypoxanthine incorporation method) for isolates and clones of *P. falciparum*. ^d All in vitro experiments were done as technical triplicates with R2 within 0.96–1. ^e CQ susceptible *P. falciparum* African D6 clone. ^f *P. falciparum* multidrug resistant C235 strain (Thailand). ^g CQ resistant *P. falciparum* Indochina W2 clone. ^h Hepatocellular carcinoma. ⁱ Rat Macrophage Cell Line. ^j Mouse liver microsomes. ^k Human liver microsomes. ^l Mouse hepatocytes. ^m Human hepatocytes.

[#] Šolaja, B.; Opsenica, D.; Smith, K. S.; Milhous, W. K.; Terzić, N.; Opsenica, I.; Burnett, J. C.; Nuss, J.; Gussio, R.; Bavari, S. Novel 4-Aminoquinolines Active against Chloroquine-Resistant and Sensitive *P. falciparum* Strains that also Inhibit Botulinum Serotype A., *J. Med. Chem.* **2008**, *51*, 4388-4391.

Figure S1



77: R=H, Z=OCH₃⁵

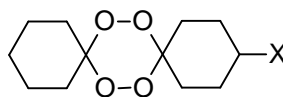
79: R=H, Z=NH₂^{5,8}

80: R=α-CH₃, Z=NH₂⁵

81: R=β-CH₃, Z=NH₂⁵

78: R=H, Z=NHPi^{5,8}

82: R=H, Z=NHCH₂CH₂N(CH₃)⁷



83: X=CONHPi³

84: X=CONHCH₂CH₂NH-4'-(7'-chloroquinoline)⁴

85: X=CH₂OH³

86: X=CH₂N₃³

87: X=CH₂NH₂³

88: X=CH₂NHCy³

89: X=CH₂NHCH₂CH₂NH-4'-(7'-chloroquinoline)⁴

Figure S1. Tetraoxanes tested for activity in the liver stage.

Table S2: Liver stage activity of tetraoxane antiplasmodials.

Compound	% LS infection (5 μ M) ^a	LS IC ₅₀ (μ M) ^b	LS in vivo, (mg/kg/day) ^c	IC ₅₀ (nM) ^d		RBC in vivo cure ^{d,e} (Thompson test, mg/kg/day)
				W2	D6	
77	31	<1		27.67	39.14	
78	0.55	0.33 \pm 0.05	40 (50); 9 (100)	4.74	11.83	50
79	13	1-5		0.58	1.17	50
80	16	1-5		14.10	20.04	50
81	6	1-5		6.80	14.76	200
82	11	3-4		14.49	28.16	40
83	21	1-5		7.54	9.40	37.5
84	~1	~1		2.00	2.33	80
85	100			6.54	15.18	
86	90			6.07	9.87	150
87	N.A.			7.79	12.84	37.5
88	28	1-5		6.17	11.18	37.5
89	~1	1-5		5.76	9.05	80
PQ	62 (10 μ M)					
CQ		ca. 9 ¹				
ART	>75 ²	ca. 121				
Artemisone		ca. 0.041				
ATQ		22 nM1				

^a 10 000 Huh7 cells/well seeded 24 h before infection. 10 000 PbA-LuciGFPcon spz/well. Confluency measured by a fluorimetric assay. Infection measured by a bioluminescence assay.

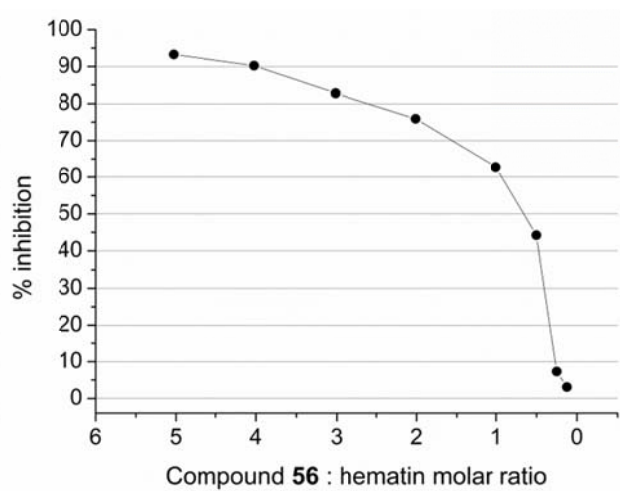
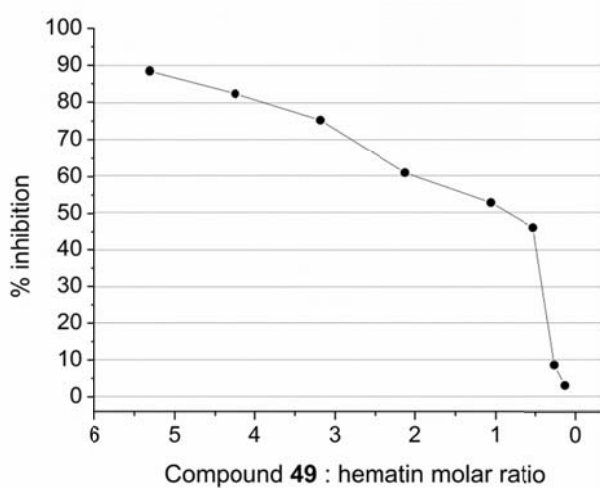
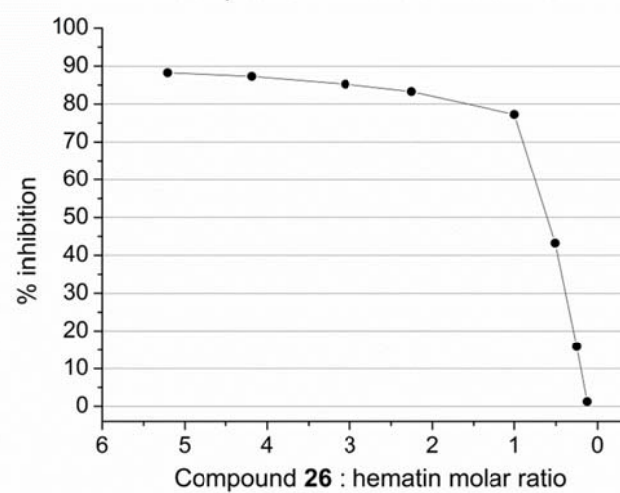
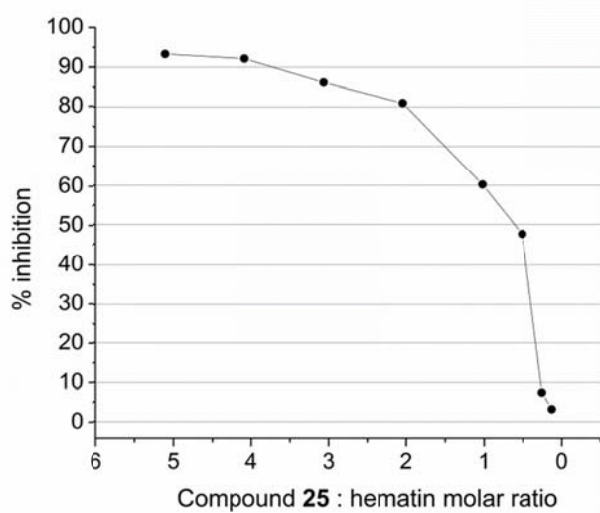
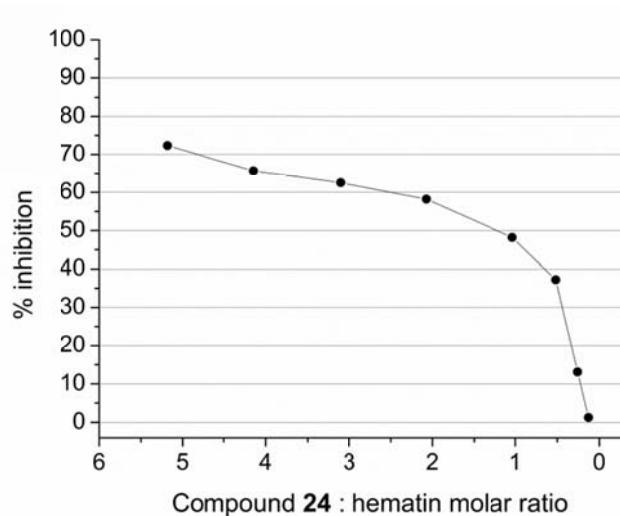
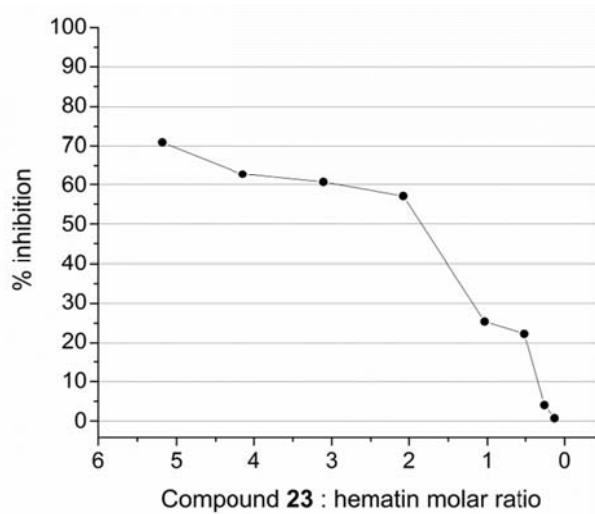
^b All dose-responses with at least 5 dosages.

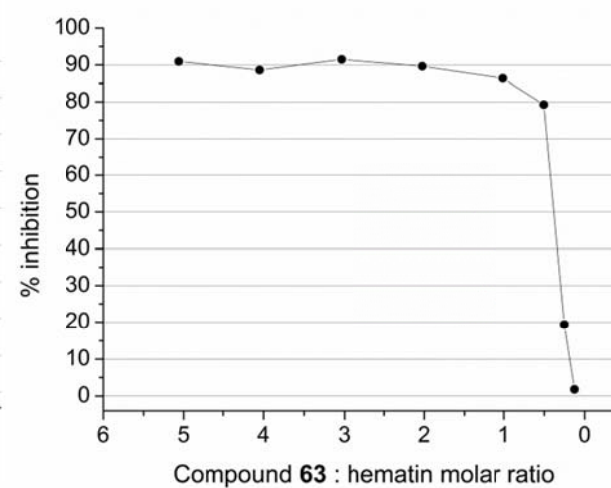
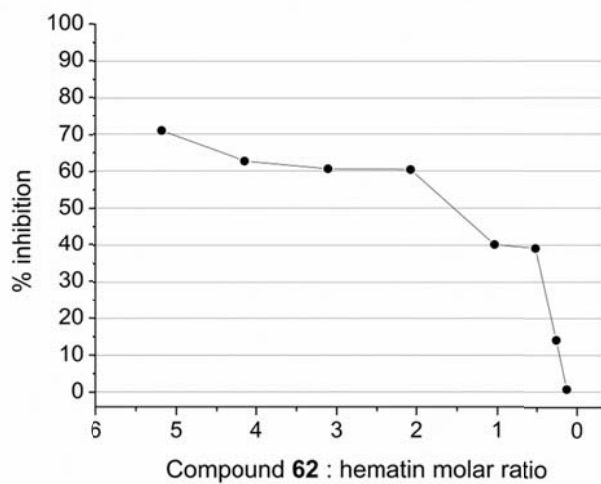
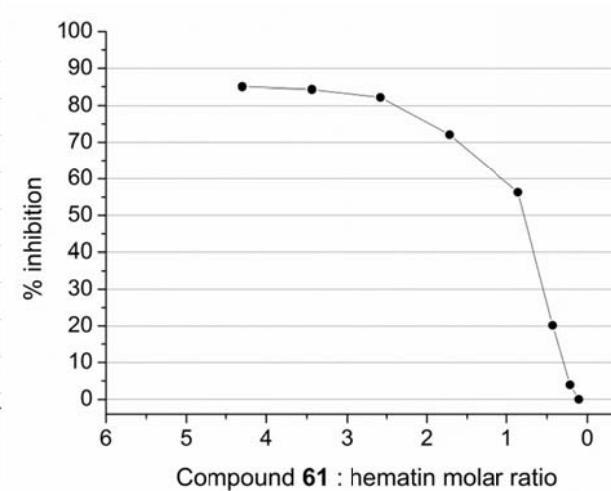
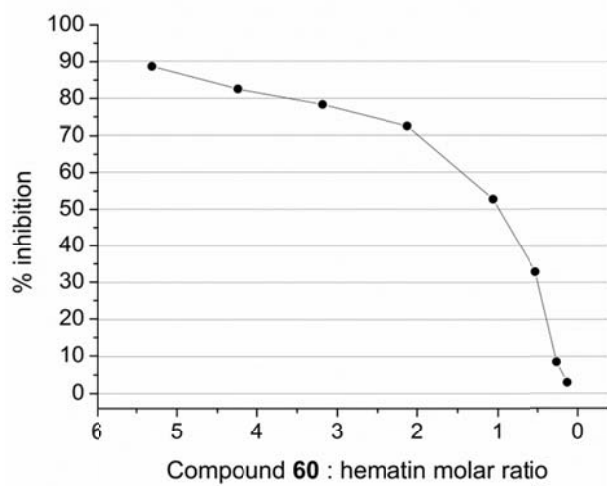
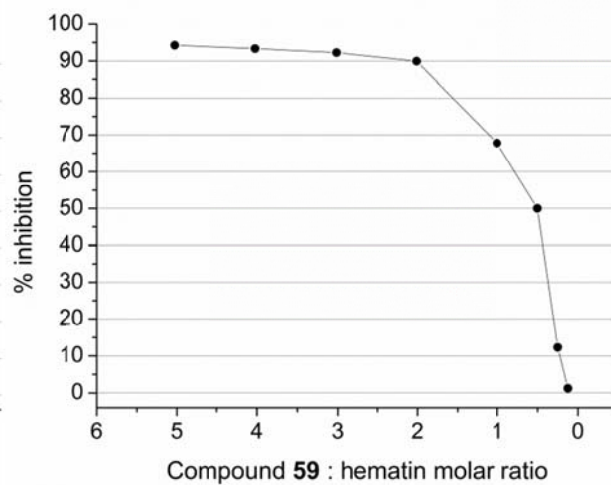
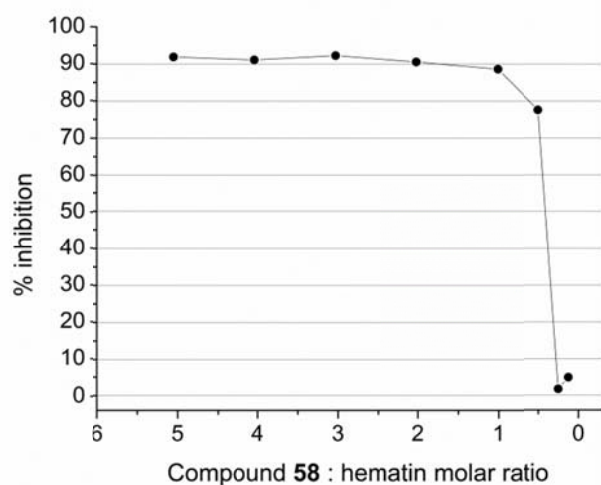
^c Measurement of liver load by qRT-PCR. Mean of 2 independent experiments. All mice were infected by i.v. injection of 10,000 *P. berghei* sporozoites. Control groups were treated by oral gavage with vehicle (equivalent % of DMSO, in sunflower oil). Experimental groups were treated by oral gavage administration of **78** at 50 and 100 mg/kg.

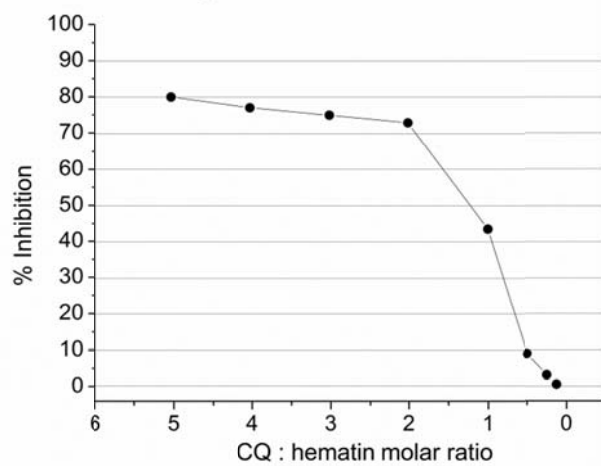
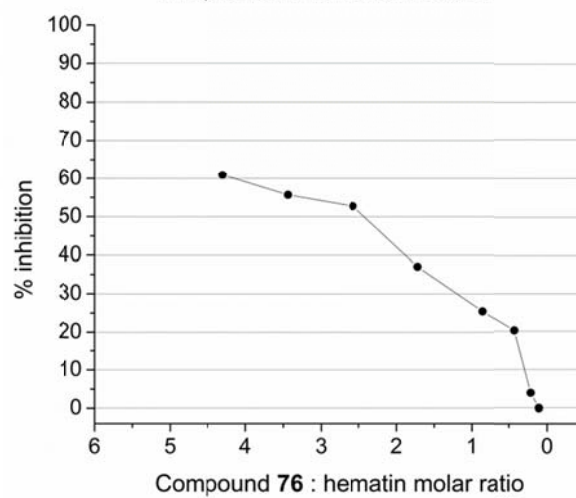
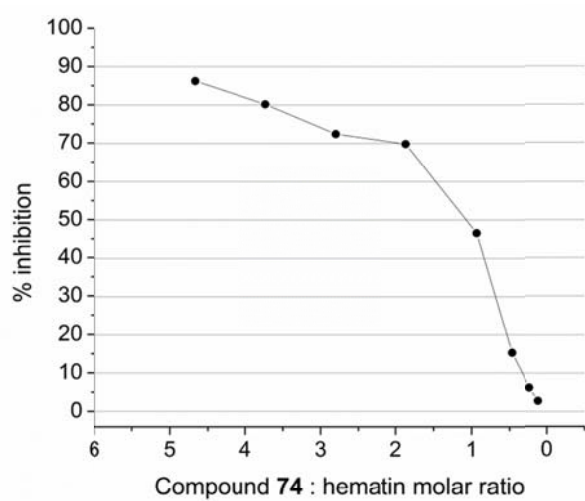
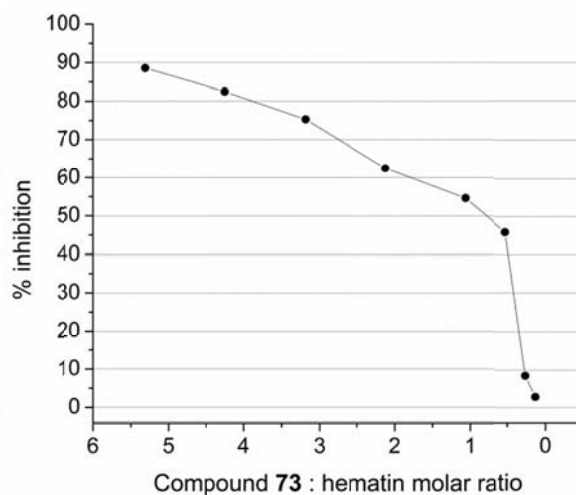
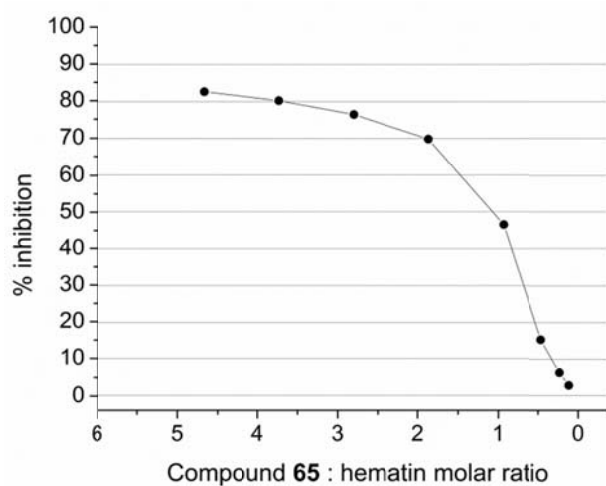
^d Taken from refs. 3, 4, 5, 6, 7, 8.

^e Lowest dose that cured mice in Thompson test (no parasitemia on D31).

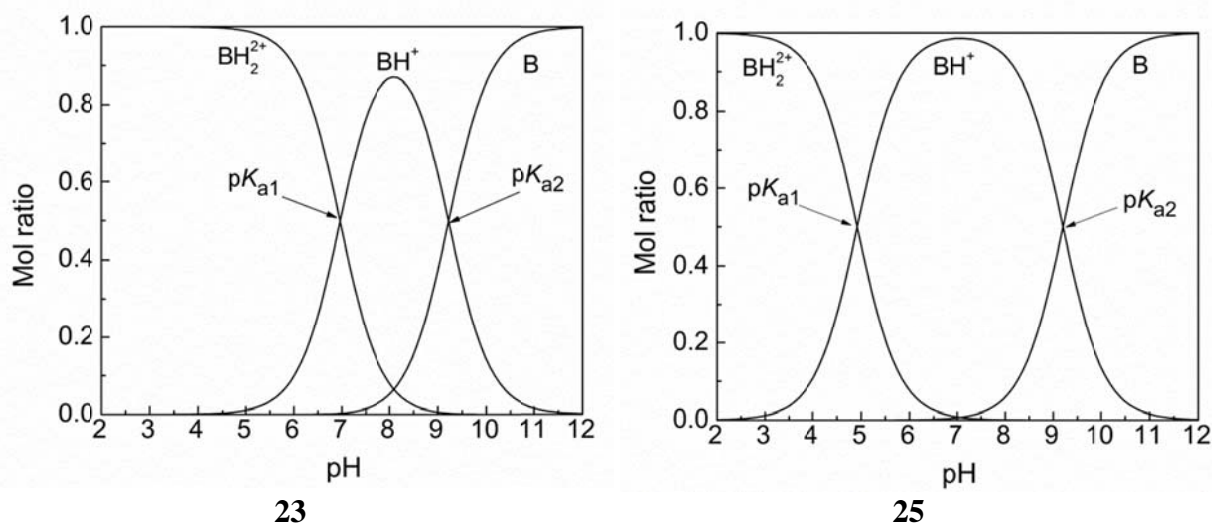
BHIA plots. Plots of the dose-dependent inhibition of β -hematin formation by studied compounds.







Distribution diagrams



Chemistry.

Melting points were determined on a Boetius PMHK apparatus and were not corrected. IR spectra were taken on a Thermo-Scientific Nicolet 6700 FT-IR diamond crystal. 1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 spectrometer (at 200 and 50 MHz, respectively), and a Bruker Ultrashield Advance III spectrometer (at 500 and 125 MHz, respectively) in the indicated solvent (*vide infra*) using TMS as the internal standard.

Chemical shifts are expressed in ppm (δ) values and coupling constants (J) in Hz. ESI-MS (HRMS) spectra of the synthesized compounds were acquired on a Agilent Technologies 1200 Series instrument equipped with Zorbax Eclipse Plus C18 (100 \times 2.1 mm i.d. 1.8 μ m) column and DAD detector (190-450 nm) in combination with a 6210 Time-of-Flight LC/MS instrument in positive and negative ion mode. The samples were dissolved in MeOH (HPLC grade). The selected values were as follows: capillary voltage 4 kV; gas temperature 350°C; drying gas 12 L min $^{-1}$; nebulizer pressure 45 psig; fragmentator voltage: 70 V. Mass spectral

analyses were done using electrospray ionization in positive ion mode on a Surveyor separations module coupled to a ThermoFinnigan TSQ AM triple quadrupole mass spectrometer. Compounds were analyzed for purity using: Agilent 1200 HPLC system equipped with Quat Pump (G1311B), Injector (G1329B) 1260 ALS, TCC 1260 (G1316A) and Detector 1260 DAD VL+ (G1315C), and Waters 1525 HPLC dual pump system equipped with an Alltech Select degasser system, and a dual k 2487 UV-Vis detector. All compounds were >95% pure. For each compound HPLC analysis was performed in two diverse systems:

Method A: Zorbax Eclipse Plus C18 4.6 × 150 mm, 1.8 μ, S.N. USWKY01594 was used as the stationary phase. Eluent was made from the following solvents: 0.2% formic acid in water (A) and methanol (B). Analyses were performed at the UV max of the compounds (at 330 nm for compounds **9, 10, 11, 12, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 46, 48, 49, 50, 51, 52, 53, 54, 55, 56, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 70, 73, 74, 75, 76** and at 254 nm for compounds **45, 47, 57, 68, 69, 71, 72** to maximize selectivity. Compounds were dissolved in methanol, final concentrations were ~1 mg/mL. Flow rate was 0.5 mL/min

Compounds **9, 10, 11, 20, 21, 22, 23, 25, 27, 28, 29, 30, 31, 32, 33, 34, 36, 40, 41, 42, 43, 66, 67, 68, 71, 72, 73, 74, 75** and **76** were eluted using gradient protocol: 0-1.5 min 95%A, 1-5 min 95%A → 5%A, 5-16 min 5%A, 16-18 min 5%A → 95%A, 18-20 min 5%A.

Compounds **26, 38** and **39** were eluted using gradient protocol: 0-1 min 95%A, 1-6 min 95%A → 5%A, 6-11 min 5%A, 11-14 min 5%A → 95%A, 14-15 min 5%A.

Compounds **24, 35** and **44** were eluted using gradient protocol: 0-3 min 25%A, 3-4 min 25%A → 5%A, 4-5 min 5%A, 5-7 min 5%A → 25%A, 7-8 min 25%A.

Compounds **12** and **37** were eluted using gradient protocol 0-3 min 30%A, 3-6 min 30%A → 5%A, 6-9 min 5%A, 9-10 min 5%A → 30%A, 10-11 min 30%A.

Compound **45** was eluted using gradient protocol 0-3 min 50%A → 30%A, 3-6 min 30%A → 0%A, 6-9 min 0%A → 50%A, 9-12 min 50%A.

Compounds **47, 48, 50, 51, 55, 56, 57** and **66** were eluted using gradient protocol: 0-1 min 95%A, 1-6 min 95%A → 5%A, 6-11 min 5%A, 11-14min 5%A → 95%A, 14-15 min 95%A.

Compounds **52, 53, 54, 61, 62** and (**65**) were eluted using gradient protocol: 0-1 min 95%A, 1-6 min 95%A → 5%A, 6-11 min 5%A, 11-14 min 5%A → 95%A. Compounds **46, 58, 59, 63, 64** and **67** were eluted using gradient protocol: 0-1 min 95%A, 1-6 min 95%A → 5%A, 6-11 min 5%A, 11-14 min 5%A → 95%A, 14-16 min 95%A.

Compounds **49** and **60** were eluted using gradient protocol: 0-1 min 95%A, 1-6 min 95%A → 5%A, 6-11 min 5%A, 11-14 min 5%A → 95%A, 14-18 min 95%A.

Method B: Zorbax Eclipse Plus C18 4.6 x 150 mm, 1.8 μ , S.N. USWKY01594 was used as the stationary phase. Eluent was made from the following solvents: 0.2% formic acid in water (A) and acetonitrile (B). Analyses were performed at the UV max of the compounds (at 330 nm for compounds **9, 10, 11, 12, 20, 21, 22, 23, 24, 25, 26, 27, 28**), **29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 46, 47, 48, 50, 51, 52, 53, 54, 55, 56, 57, 58, 61, 62, 64, 66, 67, 70, 73, 74, 75, 76** and at 254 nm for compounds **45, 59, 63, 65, 68, 69, 71, 72** to maximize selectivity. Compounds were dissolved in methanol, final concentrations were \sim 1 mg/mL.

Flow rate was 0.5 mL/min

Compounds **9, 10, 11, 12, 20, 21, 22, 23, 24, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 40, 41, 42, 43, 44, 67, 68, 71, 72, 74, 73, 75** and **76** were eluted using gradient protocol: 0-1.5 min 95%A, 1-5 min 95%A \rightarrow 5%A, 5-16 min 5%A, 16-18 min 5%A \rightarrow 95%A, 18-20 min 5%A.

Compounds **45, 25, 66, 38**) were eluted using gradient protocol: 0-1 min 95%A, 1-6 min 95%A \rightarrow 5%A, 6-11 min 5%A, 11-14 min 5%A \rightarrow 95%A, 14-15 min 5%A.

Compound **37** was eluted using gradient protocol 0-2 min 30%A, 2-6 min 30%A \rightarrow 5%A, 6-9 min 5%A, 9-10 min 5%A \rightarrow 30%A, 10-11 min 30%A.

Compounds **26** and **39** were eluted using gradient protocol 0-1 min 95%A, 1-5 min 95%A \rightarrow 5%A, 5-14 min 5%A, 14-15 min 5%A \rightarrow 95%A, 15-16 min 5%A.

Compounds **46, 52, 53, 54, 58, 61, 62, 64, 65** and **67** were eluted using gradient protocol: 0-1 min 95%A, 1-6 min 95%A \rightarrow 5%A, 6-11 min 5%A, 11-14 min 5%A \rightarrow 95%A.

Compounds **47, 48, 50, 51, 55, 56, 57, 59, 63** and **66** were eluted using gradient protocol: 0-1 min 95%A, 1-6 min 95%A \rightarrow 5%A, 6-11 min 5%A, 11-14 min 5%A \rightarrow 95%A, 14-15 min 95%A.

Method C: Poroshell 120 EC-C18, 4.6 x 50mm, 2.7 μ , S.N. USCFU07797 was used as the stationary phase. Eluent was made from the following solvents: 0.2% formic acid in water (A) and acetonitrile (B). Analyses were performed at the UV max of the compounds (at 254 nm for compounds **49, 60**) to maximize selectivity. Compounds were dissolved in methanol, final concentrations were \sim 1mg/mL. Flow rate was 0.5 mL/min

Compounds **49** and **60** were eluted using gradient protocol: 0-1 min 95%A, 1-6 min 95%A \rightarrow 5%A, 6-11 min 5%A, 11-14 min 5%A \rightarrow 95%A, 14-17 min 95%A.

N1-(7-Chloroquinolin-4-yl)ethane-1,2-diamine (**AQ2**), N1-(7-chloroquinolin-4-yl)propane-1,3-diamine (**AQ3**), N1-(7-chloroquinolin-4-yl)butane-1,4-diamine (**AQ4**), N1-(7-chloroquinolin-4-yl)-ethane-1,6-hexane (**AQ6**) and *N*-(quinolin-4-yl)propane-1,3-diamine (**AQ7**) and *N*-(quinolin-4-yl)butane-1,4-diamine(**AQ8**) were prepared according to known procedures.⁹

General procedures

Method A: General synthetic procedure for mono-protection of the asymmetrical diamines with Boc.¹⁰

Tert-butyl phenyl carbonate (2 equiv) was added to a stirred solution of unsymmetrical diamine (1 equiv) in absolute EtOH. The reaction mixture was refluxed overnight (18 h), followed by removal of the volatiles in vacuo. Water was added and 2M HCl was added until pH3, followed by extraction with CH₂Cl₂. The aqueous phase was then made strongly alkaline by addition of aqueous NaOH (2M) and extracted with CH₂Cl₂. The combined organic extracts were dried over anh. Na₂SO₄ and solvent was evaporated under reduced pressure to get the final product.

Method B: General procedure for the synthesis of *N*-Boc protected aminoquinolines¹¹

A mixture of 4,7-dichloroquinoline (1 equiv) and monoprotected diaminoalkane (2 equiv) was gradually warmed to 80 °C over 1 h with stirring and the stirring was continued for 6-8 h at 120-130 °C. The reaction mixture was cooled to r.t. and taken up in CH₂Cl₂. The organic layer was washed with NaHCO₃, water and brine. The organic layer was dried over anh. Na₂SO₄ and solvent was evaporated under reduced pressure to get final product.

Method C: Removal of the Boc-protecting groups with TFA.

A solution of *N*-Boc-protected amine in TFA/CH₂Cl₂ (v:v; 1:10), was stirred at r.t. for 6 h. Solvents were evaporated under reduced pressure and the remaining residue was treated with CH₂Cl₂/2.5M NaOH. The organic layer was dried over anh. MgSO₄, and the solvent was evaporated under reduced pressure.

Method D: General procedure for reductive amination.

To a solution of an amine in CH₂Cl₂ were added the appropriate aldehyde (1 equiv) and NaHB(OAc)₃ (2 equiv). After stirring the reaction mixture at r.t. for 24 h, aqueous NaOH was added. The organic layer was separated, and the aqueous layer was washed with CH₂Cl₂. The organic layer was dried over anh. Na₂SO₄, and the solvent was evaporated under reduced pressure.

Method E: General procedure for reductive amination.

Amine (1.25-1.5 equiv) and appropriate aldehyde (1 equiv) were dissolved in MeOH/CH₂Cl₂ mixture (v:v; 2:1), anh. AcOH (1.25-1.5 equiv) was added, and the mixture was stirred under Ar at r.t. for 3 h. Then, NaBH₄ (6 equiv) was added and stirring was continued for another 18 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH₂Cl₂. The organic layer was washed with 2M NH₄OH, water and brine, and dried over Na₂SO₄. Finally, the solvent was evaporated under reduced pressure.

Method F: General procedure for the synthesis aminoquinolines.

A mixture of diamine linker (1.2 equiv), 4,7-dichloroquinoline/4-chloroquinoline (1 equiv) and phenol (15 equiv) were heated at 120-130 °C, with stirring for 24 h or the reaction mixture was subjected to MW irradiation using a *Biotage Initiator 2.5 apparatus*. The reaction mixture was cooled to r.t. and taken up in CH₂Cl₂. The organic layer was successively washed several times with NaOH and finally with brine. The organic layer was dried over anh. Na₂SO₄ and solvent was removed under reduced pressure to get a final product.

Method G: General procedure for reductive amination.¹²

A mixture of appropriate aldehyde/ketone (1 equiv), amine (1.2 equiv) and Ti(OiPr)₄ (1.5 equiv) reaction mixture was stirred at r.t. overnight. Following, absolute EtOH and NaBH₄ (2 equiv) were added to the mixture and stirring was continued for 24 h. The reaction was quenched with 2M NaOH, and solvent was removed under reduced pressure. Aqueous layer was washed with CH₂Cl₂, and organic layer was dried over anh. Na₂SO₄. The solvent was evaporated, and the residue was purified by chromatography to yield the desired product.

Method H: General procedure for palladium catalyzed amination of quinolines.¹³

Vial was charged with mixture of Pd(OAc)₂ (4 mol%) and DPEphos (8 mol%)/SPhos (8 mol%) in dioxane and stirred for a few minutes under Ar at r.t. Subsequently, a haloquinoline (1.0 equiv), amine (1.2 equiv) and K₃PO₄ (2.5 equiv) were added to the reaction mixture. Resulting suspension was flushed with argon for several minutes. The vial was quickly capped, heated to 85 °C overnight and then cooled down to r.t. The mixture was adsorbed onto silica gel and purified.

Method I: General procedure for protection of amine with Cbz.¹⁴

Mono-Boc-protected diamine was dissolved in CH₂Cl₂ followed by addition of benzylchloroformate (1.95 equiv) and triethylamine (2.05 equiv). The reaction mixture was stirred at r.t. for 3 h and then quenched with aqueous NH₄OH. Aqueous layer was extracted several times with EtOAc. The organic layer was dried over anh. Na₂SO₄, and solvent was evaporated under reduced pressure to give crude product.

Method J: General procedure for removal of the Cbz-protecting group by hydrogenization. The Cbz-protected amine was hydrogenated using 10% Pd/C as catalyst under 2 atm of hydrogen MeOH. The mixture was stirred at r.t. for 8 h, the catalyst was removed by filtration and the solvent was evaporated under reduced pressure.

Method K: General procedure for N-methylation of aminoquinolines.¹⁵

To a stirred solution of aminoquinolines (1equiv) in MeOH containing 37% aqueous formaldehyde/acetone (2 equiv) was added mixture of ZnCl₂ (2 equiv) and NaHB₃CN (4 equiv) in MeOH. After the reaction mixture was stirred at r.t. for 4 h, the solution was taken up in 0.1M NaOH and most of methanol was evaporated under reduced pressure. Aqueous

solution was extracted with CH_2Cl_2 , the combined extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure.

Method L: Synthesis of methyl esters.¹⁶

Difluorobenzaldehyde or bromofluorobenzaldehyde (1 equiv) was dissolved in DMSO, followed by dropwise addition of methyl thioglycolate (1 equiv) and triethylamine (3 equiv). The resulting mixture was stirred under argon atmosphere at 80 °C for 2 h and then allowed to cool to room temperature. The reaction mixture was transferred to a separation funnel, water was added and extracted with EtOAc. Combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After filtration, the solvent was removed under reduced pressure. The product was purified using column chromatography.

Method M: Preparation of carboxylic acids.¹⁷

A mixture of the methyl ester (1 equiv), KOH (3 equiv), water and EtOH (1:8, v:v) was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure, acidified with conc. HCl at 0 °C and transferred to a separation funnel. Product was extracted with EtOAc/THF (4:1, v:v) and dried over anhydrous Na_2SO_4 . After filtration, the solvent was removed under reduced pressure. The product was purified using column chromatography.

Method N: Experimental procedure for decarboxylation by microwave heating.¹⁸

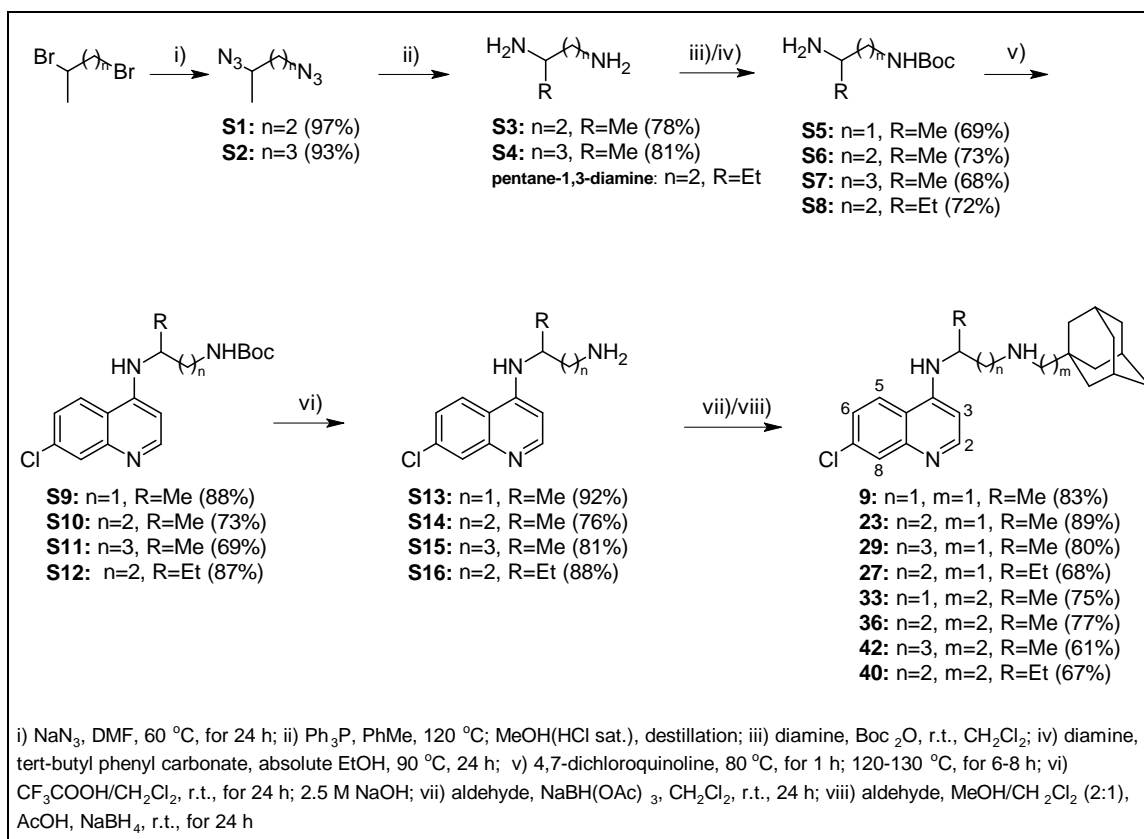
A mixture of the carboxylic acid (1 equiv) and DBU (2.5 equiv) in *N,N*-dimethylacetamide was heated in a sealed vessel in microwave reactor at 200 °C for 2 h. The product was purified using column chromatography.

Method O: General experimental procedure for Rieche formylation.¹⁹

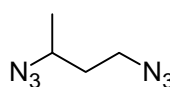
TiCl_4 (5 equiv) was dissolved in DCM at -10 °C, and then solution of dichloromethyl methyl ether (10 equiv) in DCM was added dropwise, followed by a solution of substituted benzothiophene (1 equiv) in DCM. After stirring for 1 h, the mixture was warmed to room temperature and then stirred for 24 h. The reaction mixture was poured onto ice-water, and conc. HCl was added. It was stirred for 30 min and then transferred to a separation funnel. Organic layer was washed well with saturated NaHCO_3 , brine and dried over anhydrous Na_2SO_4 . After filtration, the solvent was removed under reduced pressure. The product was purified using column chromatography.

Method P: Synthesis of cyano derivatives.²⁰

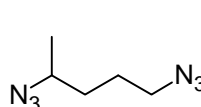
Bromobenzothiophene (1 equiv) and CuCN (2 equiv) were suspended in NMP and heated for 12 h at 190 °C. The mixture was cooled to 0 °C and 33% aq. ethylenediamine was added. After dilution with ether, the mixture was transferred to a separation funnel. Organic layer was washed with brine and dried over anhydrous Na_2SO_4 . After filtration, the solvent was removed under reduced pressure. The product was purified using column chromatography.



1,3-Diazidobutane (S1).

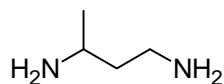

 Sodium azide (15.06 g, 231.58 mmol) was added to a solution of 1,3-dibromobutane (10 g, 46.31 mmol) in DMF (100 mL). Reaction mixture was stirred for 24 h at 60 °C cooled to r.t., and water was added to dissolve excess of NaN_3 and compound was extracted with EtOAc (3× 70 mL). The organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the desired product **S1** as colorless oil (6.30 g, 97%). IR(ATR): 3336w, 2975m, 2934m, 2877w, 2498w, 2099s, 1456m, 1380w, 1355w, 1323w, 1267m, 1134w, 1088w, 1020w, 904w, 869w, 780w, 634w cm^{-1} . $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ): 3.70-3.50 (m, 1H, $\text{N}_3\text{CH}(\text{CH}_3)-$), 3.50-3.35 (m, 2H, $-\text{CH}_2\text{N}_3$), 1.80-1.60 (m, 2H, $\text{N}_3\text{CH}(\text{CH}_3)\text{CH}_2-$), 1.32 (d, 3H, $J = 6.2$, CH_3). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ): 54.86; 48.05; 35.16; 19.23.

1,4-Diazidopentane (S2).


 Sodium azide (14.14 g, 217.44 mmol) was added to a solution of 1,4-dibromopentane (10 g, 43.68 mmol) in DMF (100 mL). The mixture was stirred for 24 h at 60 °C. After cooling to r.t., water was added to dissolve excess of NaN_3 and compound was extracted with EtOAc (3× 70 mL). The organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the desired product **S2** as colorless oil (6.2 g, 93%). IR(ATR): 3336w, 2973m, 2936m, 2874m, 2500w, 2097s, 1456m, 1381w, 1353w, 1258m, 1133w, 971w, 854w, 629w cm^{-1} . $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ):

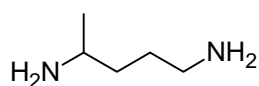
3.60-3.40 (m, 1H, $\text{N}_3\text{CH}(\text{CH}_3)-$), 3.40-3.20 (m, 2H, $-\text{CH}_2\text{N}_3$), 1.80-1.40 (m, 4H, $\text{N}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $\text{N}_3\text{CH}(\text{CH}_3)-$), 1.29 (d, 3H, $J = 6.8$, CH_3). ^{13}C -NMR (50 MHz, CDCl_3 , δ): 57.32; 50.96; 33.16; 25.38; 19.27.

Butane-1,3-diamine (S3).



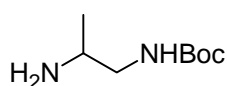
Mixture of 1,3-diazidobutane **S1** (13.50 g, 96.6 mmol) and Ph_3P (50.7 g, 193.2 mmol, 2 equiv) in toluene (150 mL) was stirred at 120 °C for 15 min, and cooled to r.t. Then H_2O (18 mL) was added, and the resulting mixture was stirred overnight at 120 °C. Reaction mixture was transferred into a separation funnel, lower layer was collected and transformed in salt using $\text{MeOH}(\text{HCl sat.})$. Solvent was evaporated and dried crystals of 1,3-butanediamine dihydrochloride (11.1 g, 68.9 mmol) were mixed with NaOH powder (18 g, 450 mmol). Distillation afforded colorless oil (4.8 g, 78%, b.p. 138.6 °C/760 Torr). IR(ATR): 3354s, 3281s, 3194m, 2956s, 2922s, 2869m, 2757w, 2664w, 1600s, 1456m, 1376m, 1348w, 1141w, 1091w, 1064w, 881m, 835m cm^{-1} . ^1H -NMR (500 MHz, CDCl_3 , δ): 3.05-2.95 (m, 1H, $\text{NH}_2\text{CH}(\text{CH}_3)-$), 2.85-2.75 (m, 2H, $-\text{CH}_2\text{NH}_2$), 1.60-1.40 (m, 2H, $-\text{CH}_2\text{CH}_2\text{NH}_2$), 1.08 (d, 3H, $J = 6.3$, CH_3). ^{13}C -NMR (125 MHz, D_2O , δ): 44.92; 43.48; 39.44; 24.35. Anal. ($\text{C}_4\text{H}_{14}\text{Cl}_2\text{N}_2$) Calcd: C, 29.83; H, 8.76; N, 17.39. Found: C, 29.86; H, 8.91; N, 17.48.

Pentane-1,4-diamine (S4).



Mixture of 1,4-diazidopentane **S2** (16.41 g, 106.3 mmol) and Ph_3P (55.7 g, 212.6 mmol, 2 equiv) in toluene (150 mL) was stirred at 120 °C 15 min, and cooled to r.t.. Then H_2O (23 mL) was added, the resulting mixture was stirred overnight at 120 °C. Reaction mixture was transferred into a separation funnel, lower layer was collected and transformed in salt using $\text{MeOH}(\text{HCl sat.})$. Solvent was evaporated and dried crystals of 1,4-pentanediamine dihydrochloride (15.6 g, 89.3 mmol) were mixed with NaOH powder (22 g, 550 mmol). Distillation afforded colorless oil (7.3 g, 81%, b.p. 162.4 °C/760 Torr). IR (ATR): 3427s, 3035s, 2440m, 1994w, 1604m, 1482s, 1469s, 1454s, 1392m, 1334w, 1290w, 1266m, 1201m, 1167m, 1103m, 1044m, 991w, 948m, 946m, 846, 759w, 508m, 437w, 421w cm^{-1} . ^1H -NMR (500 MHz, CDCl_3): 2.95-2.70 (m, 1H, $\text{NH}_2\text{CH}(\text{CH}_3)-$), 2.70-2.95 (m, 2H, $-\text{CH}_2\text{NH}_2$), 1.60-1.40 (m, 2H, $-\text{CH}_2\text{CH}_2\text{NH}_2$), 1.40-1.25 (m, 2H, $\text{NH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$), 1.07 (d, 3H, $J = 6.2$, $-\text{CH}_3$). ^{13}C -NMR (125 MHz, D_2O): 47.85; 42.85; 37.96; 30.86; 23.35.

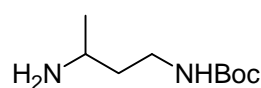
Tert-butyl (2-aminopropyl)carbamate (S5).



Compound **S5** was prepared from 1,2-propanediamine (2 mL, 23.48 mmol) and *tert*-butyl phenyl carbonate (8.7 mL, 46.95 mmol) by method A and was obtained after dry-flash chromatography: SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5$, as colorless solid (2.59 g, 69%); m.p. = 74-76 °C (Hex). IR (ATR): 3371m, 2979m,

2933m, 1686s, 1528s, 1458w, 1391w, 1367m, 1325w, 1274m, 1250m, 1172s, 1057w, 991w, 909w, 861w, 815w, 783w, 723w, 627m, cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 5.04 (bs, H-N), 3.20-3.10 (m, 1H, $-\text{CH}_2\text{NHBoc}$), 3.05-2.95 (m, 1H, $\text{NH}_2\text{CH}(\text{CH}_3)-$), 2.95-2.85 (m, 1H, $-\text{CH}_2\text{NHBoc}$), 1.44 (s, 9H, $-\text{NHCOO-C}(\text{CH}_3)_3$), 1.34 (bs, 2H-N), 1.07 (d, 3H, $J = 6.2$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 156.19; 79.06; 48.46; 46.81; 28.33; 21.44. HRMS: m/z 175.14451 corresponds to molecular formula $\text{C}_8\text{H}_{18}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: + 2.30). Anal. ($\text{C}_8\text{H}_{18}\text{N}_2\text{O}_2 \times 1/3 \text{CH}_2\text{Cl}_2$) Calcd: C, 49.41; H, 9.29; N, 13.83. Found: C, 49.27; H, 9.09; N, 13.83.

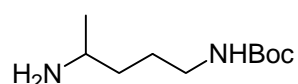
***Tert*-butyl (3-aminobutyl)carbamate (S6).**



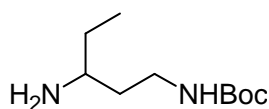
Compound **S6** was prepared by method A from 1,3-butandiamine (1.91 g, 21.55 mmol) and *tert*-butyl phenyl carbonate (8.0 mL, 43.11 mmol) and was obtained after dry-flash chromatography: SiO_2 , eluent:

$\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5$, as colorless viscous oil (2.96 g, 73%). IR (ATR): 3344w, 2973m, 2929w, 1686s, 1519m, 1452w, 1390w, 1364m, 1275m, 1249m, 1168s, 1041w, 1015w, 946w, 898w, 868w, 846w, 779w, 758w, 717w, 704w, 6814w, 659w, 644w, 596w, 578w, 566w, 539w, 530w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 5.04 (bs, 1H, $-\text{NH}$), 3.35-3.20 (m, 1H, $-\text{CH}_2\text{NHBoc}$), 3.20-3.05 (m, 1H, $-\text{CH}_2\text{NHBoc}$), 3.05-2.90 (m, 1H, $\text{NH}_2\text{CH}(\text{CH}_3)-$), 1.60-1.50 (m, 1H, $\text{NH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$), 1.50-1.35 (m, 10H, $\text{NH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{NHCOO-C}(\text{CH}_3)_3$), 1.31 (bs, 2H, $-\text{NH}_2$), 1.10 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 156.04; 78.82; 44.93; 39.33; 37.98; 28.29; 24.24. HRMS: m/z 189.15990 corresponds to molecular formula $\text{C}_8\text{H}_{20}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: + 0.79).

***Tert*-butyl (4-aminopentyl)carbamate (S7).**

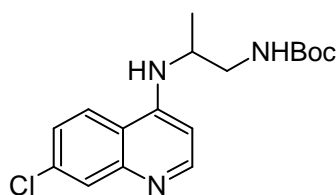


Compound **S7** was prepared by method A from 1,4-pentandiamine (3.00 g, 29.33 mmol) and *tert*-butyl phenyl carbonate (10.88 mL, 58.63 mmol) and was obtained after dry-flash chromatography: SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5$, as colorless viscous oil (4.03 g, 68%). IR (ATR): 3256w, 2897s, 2844m, 1610w, 1571s, 1535s, 1449m, 1376m, 1331m, 1277w, 1263w, 1201w, 1050w, 1119w, 1079w, 904w, 876w, 851w, 806w, 767w, 735m, 703w, 645w, 623w, 597w, 559w, 532w, 510w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 5.00 (bs, H-N), 3.20-3.00 (m, 2H, $-\text{CH}_2\text{NHBoc}$), 3.00-2.85 (m, 1H, $\text{NH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$), 2.04 (bs, H-N), 1.60-1.50 (m, 2H, $-\text{CH}_2\text{CH}_2\text{NHBoc}$), 1.50-1.40 (m, 9H, $-\text{NHCOO-C}(\text{CH}_3)_3$), 1.40-1.30 (m, 2H, $\text{NH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$), 1.08 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 155.88; 78.68; 46.45; 40.38; 36.69; 28.23; 26.71; 23.59. HRMS: m/z 203.17601 corresponds to molecular formula $\text{C}_{10}\text{H}_{22}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: + 2.97).

Tert-butyl (3-aminopentyl)carbamate (S8).

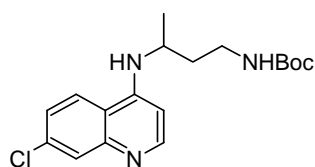
Compound **S8** was prepared by method A from 1,3-diaminopentane (4 mL, 33.47 mmol) and *tert*-butyl phenyl carbonate (12.5 mL, 66.94 mmol) and was obtained after dry-flash chromatography: SiO₂, eluent:

CH₂Cl₂/MeOH(NH₃ sat.) = 95/5 as colorless solid (4.87 g, 72%); m.p. = 77-79 °C (Hex). IR (ATR): 3363m, 2966m, 2931m, 2876w, 1683s, 1524m, 1457w, 1389w, 1364m, 1328w, 1272m, 1248m, 1169s, 1042w, 1022w, 953w, 921w, 870w, 816w, 780w, 741w, 509w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 5.21 (bs, H-N), 3.40-3.25 (m, 1H, -CH₂NHBoc), 3.25-3.15 (m, 1H, -CH₂NHBoc), 2.75-2.65 (m, 1H, H₂NCH(CH₂CH₃-), 5.34 (bs, 2H-N), 1.70-1.60 (m, 1H, -CH₂CH₂NHBoc), 1.50-1.40 (m, 10H, -CH₂CH₃, -NHCOO-C(CH₃)₃), 1.40-1.30 (m, 2H, -CH₂CH₃, -CH₂CH₂NHBoc), 0.92 (t, 3H, *J* = 7.4, -CH₂CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 156.04; 78.76; 51.07; 38.16; 36.70; 31.01; 28.33; 10.17. HRMS: *m/z* 203.17540 corresponds to molecular formula C₁₀H₂₂N₂O₂H⁺ (error in ppm: + 4.11). Anal.(C₁₀H₂₂N₂O₂ × 2/3 H₂O) Calcd: C, 56.05; H, 10.97; N, 13.07. Found: C, 56.12; H, 10.47; N, 12.67.

Tert-butyl {2-[(7-chloroquinolin-4-yl)amino]propyl}carbamate (S9).

Compound **S9** was prepared from 4,7-dichloroquinoline (3.18 g, 16.70 mmol) and mono-*N*-Boc-protected 1,2-diaminopropane **S5** (5.60 g, 32.14 mmol) by method B and was obtained after multiple chromatography: dry-flash SiO₂, eluent:

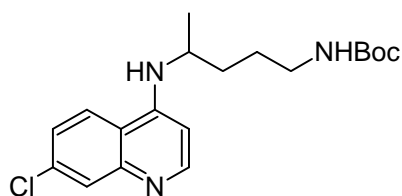
CH₂Cl₂/MeOH(NH₃ sat.) = 95/5 and flash chromatography (Biotage SP1 RP column, gradient: MeOH/H₂O = 6/4 → 7/3) as colorless solid (4.75 g, 88%); m.p. = 227-229 °C (Hex). IR (ATR): 3372s, 3187s, 2978s, 2933m, 1674s, 1612m, 1578s, 1537m, 1488w, 1452m, 1429w, 1380w, 1366w, 1335w, 1295m, 1252m, 1200w, 1172m, 1154m, 1082w, 1055w, 988w, 957w, 904w, 875w, 855w, 819w, 769w, 648w, 625w, 594w, 511w, 454w, 439w cm⁻¹. ¹H-NMR (500 MHz, CD₃OD, δ): 8.29 (d, *J* = 5.5, H-C(2)), 8.01 (d, *J* = 9.0, H-C(5)), 7.72 (d, *J* = 2.0, H-C(8)), 7.30 (dd, *J*₁ = 1.5, *J*₂ = 9.0, H-C(6)), 6.54 (d, *J* = 5.5, H-C(3)), 3.95-3.80 (m, 1H, ArNHCH(CH₃-), 3.35-3.25 (m, 1H, -CH₂NHBoc), 3.25-3.10 (m, 1H, -CH₂NHBoc), 1.36 (s, 9H, -NHCOO-C(CH₃)₃), 1.27 (d, 3H, *J* = 6.5, CH₃). ¹³C-NMR (125 MHz, CD₃OD, δ): 159.33; 152.41; 152.13; 149.75; 136.34; 127.65; 125.96; 124.42; 118.76; 100.02; 80.40; 46.25; 28.86; 17.78. HRMS: *m/z* 336.14733 corresponds to molecular formula C₁₇H₂₂ClN₃O₂H⁺ (error in ppm: - 0.41). Anal.(C₁₇H₂₂ClN₃O₂) Calcd: C, 60.80; H, 6.60; N, 12.51. Found: C, 60.57; H, 6.70; N, 12.71.

Tert-butyl {3-[(7-chloroquinolin-4-yl)amino]butyl}carbamate (S10).

Compound **S10** was prepared by method B from 4,7-dichloroquinoline (3.33 g, 16.81 mmol) and mono-*N*-Boc-

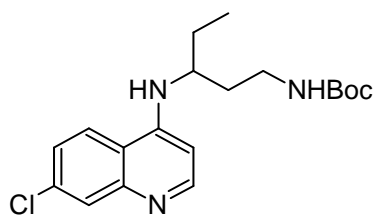
protected butane-1,3-diamine **S6** (3.82 g, 20.18 mmol) and was obtained after dry-flash chromatography SiO₂, gradient: CH₂Cl₂/MeOH(NH₃ sat.) = 95/5→8/2 as colorless solid (4.29 g, 73%); m.p. = 168-171 °C (Hex). IR (ATR): 3342m, 3192m, 2972m, 1677s, 1611m, 1579s, 1538m, 1488w, 1450w, 1434m, 1378w, 1366w, 1334w, 1284m, 1251w, 1228w, 1152m, 1131w, 1088w, 1066w, 1039w, 1017w, 985w, 956w, 930w, 885w, 855w, 808m, 764m, 737m, 645w, 624w, 600w, 576w, 551w, 515w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.50 (d, *J* = 5.4, H-C(2)), 7.94 (d, *J* = 2.1, H-C(8)), 7.78 (d, *J* = 7.6, H-C(5)), 7.35 (dd, *J*₁ = 2.2, *J*₂ = 9.0, H-C(6)), 6.39 (d, *J* = 5.4, H-C(3)), 5.36 (bs, H-N), 4.82 (bs, H-N), 3.85-3.75 (m, 1H, ArNHCH(CH₃)-), 3.35-3.27 (m, 1H, -CH₂NHBoc), 3.27-3.15 (m, 1H, -CH₂NHBoc), 2.00-1.80 (m, 2H, ArNHCH(CH₃)CH₂-), 1.45 (s, 9H, -NHCOO-C(CH₃)₃), 1.34 (d, 3H, *J* = 6.4, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 156.18; 151.91; 149.33; 148.93; 134.84; 128.74; 125.18; 121.29; 117.33; 99.10; 79.71; 46.46; 37.53; 36.83; 28.39; 20.20. HRMS: *m/z* 350.16298 corresponds to molecular formula C₁₈H₂₄ClN₃O₂H⁺ (error in ppm: + 0.87). Anal.(C₁₈H₂₄ClN₃O₂ × 3/2 H₂O) Calcd: C, 59.74; H, 7.06; N, 11.61. Found: C, 59.66; H, 7.00; N, 11.60.

***Tert*-butyl {4-[(7-chloroquinolin-4-yl)amino]pentyl}carbamate (S11).**



Compound **S11** was prepared by method B from 4,7-dichloroquinoline (881 mg, 4.45 mmol) and mono-*N*-Boc-protected pentane-1,4-diamine **S7** (1.80 g, 8.90 mmol) and was obtained after dry-flash chromatography SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5→8/2, as colorless solid (1.12 g, 69%); m.p. = 137-139 °C (Hex). IR (ATR): 3290w, 3183w, 2967w, 2925w, 2835w, 1677s, 1613w, 1570s, 1541m, 1492w, 1450w, 1438, 1432w, 1383w, 1364w, 1331w, 1294m, 1283m, 1254w, 1212w, 1165w, 1149m, 1105w, 1082w, 1068w, 1056w, 1026w, 978w, 912w, 900w, 878w, 863w, 852w, 819w, 805, 770w, 749w, 719w, 683w, 654w, 635w, 622w, 599w, 550w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.51 (d, *J* = 5.4, H-C(2)), 7.94 (d, *J* = 2.2, H-C(8)), 7.75 (d, *J* = 8.7, H-C(5)), 7.34 (dd, *J*₁ = 2.2, *J*₂ = 8.9, H-C(6)), 6.40 (d, *J* = 5.5, H-C(3)), 5.16 (bs, H-N), 4.66 (bs, H-N), 3.80-3.65 (m, 1H, ArNHCH(CH₃)-), 3.25-3.15 (m, 1H, -CH₂NHBoc), 3.15-3.05 (m, 1H, -CH₂NHBoc), 1.75-1.65 (m, 1H, ArNHCH(CH₃)CH₂-), 1.65-1.55 (m, 3H, ArNHCH(CH₃)CH₂-, -CH₂CH₂NHBoc), 1.45 (s, 9H, -NHCOO-C(CH₃)₃), 1.31 (d, 3H, *J* = 6.4, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 156.26; 151.97; 149.36; 148.92; 134.79; 128.79; 125.12; 121.17; 117.25; 79.41; 99.14; 48.43; 40.24; 33.22; 28.38; 27.28; 20.46. HRMS: *m/z* 364.17863 corresponds to molecular formula C₁₉H₂₆ClN₃O₂H⁺ (error in ppm: - 2.43). Anal.(C₁₉H₂₆ClN₃O₂ × 1/2 H₂O) Calcd: C, 61.20; H, 7.30; N, 11.27. Found: C, 60.76; H, 6.88; N, 11.46.

***Terc*-butyl 3-[(7-chloroquinolin-4-yl)amino]pentyl}carbamate (S12).**

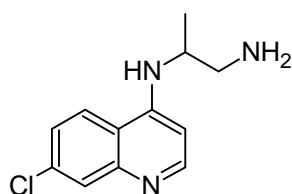


Compound **S12** was prepared by method B from 4,7-dichloroquinoline (4.08 g, 20.60 mmol) and mono-*N*-Boc-protected 1,3-diaminopentane **S8** (5.00 g, 24.72 mmol) and was obtained after dry-flash chromatography SiO₂, eluent:

CH₂Cl₂/MeOH(NH₃sat.) = 95/5 and flash chromatography

(Biotage SP1 RP column, eluent: MeOH/H₂O = 6/4) as colorless solid (7.82 g, 87%); m.p. = 58-60 °C (Hex). IR (ATR): 3325m, 2971m, 2932m, 2877w, 1687s, 1612w, 1574s, 1538m, 1453m, 1365m, 1332w, 1279m, 1248m, 1165m, 1147m, 1081w, 1042w, 903w, 853m, 805m, 766m, 643w, 599w, 496w cm⁻¹. ¹H-NMR (500 MHz, CD₃COOD, δ): 8.47 (d, *J* = 5.5, H-C(2)), 7.94 (d, *J* = 2.0, H-C(8)), 7.80 (d, *J* = 8.5, H-C(5)), 7.34 (dd, *J*₁ = 2.5, *J*₂ = 9.0, H-C(6)), 6.36 (d, *J* = 5.5, H-C(3)), 5.37 (bs, H-N), 4.95 (bs, H-N), 3.70-3.50 (m, 1H, ArNHCH(CH₂CH₃-)), 3.35-3.25 (m, 1H, -CH₂NHBoc), 3.25-3.10 (m, 1H, -CH₂NHBoc), 2.00-1.85 (m, 1H, -CH₂CH₂NHBoc), 1.85-1.70 (m, 1H, -CH₂CH₂NHBoc), 1.75-1.60 (m, 2H, -CH₂CH₃), 1.44 (s, 9H, -NHCOO-C(CH₃)₃), 0.98 (t, 3H, *J* = 7.5, -CH₂CH₃). ¹³C-NMR (125 MHz, CD₃COOD, δ): 156.18; 151.85; 149.42; 149.30; 134.82; 128.64; 125.13; 121.29; 117.27; 98.98; 79.59; 52.17; 37.54; 34.18; 28.37; 27.12; 10.22. HRMS: *m/z* 364.17865 corresponds to molecular formula C₁₉H₂₆ClN₃O₂H⁺ (error in ppm: + 0.06). Anal. (C₁₉H₂₆ClN₃O₂ × 1/2 H₂O) Calcd: C, 61.20; H, 7.30; N, 11.27. Found: C, 61.20; H, 7.22; N, 11.43.

N²-(7-Chloroquinolin-4-yl)propane-1,2-diamine (S13).

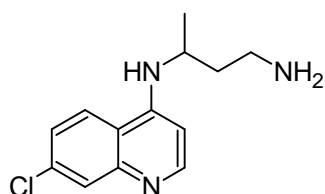


Compound **S13** was prepared by method C from **S9** (1.00 g, 2.98 mmol) and was obtained after dry-flash chromatography: SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) = 9/1 → 7/3 and flash

chromatography (Biotage SP1 RP column, eluent: MeOH/H₂O = 6/4),

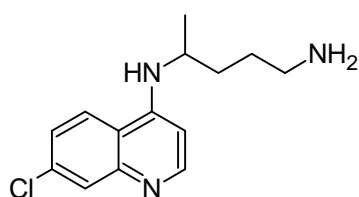
as yellow powder softens at 158-159 °C. Yield: 646 mg (92%). IR (ATR): 3312s, 2966s, 2906s, 2157w, 1611m, 1580s, 1541m, 1491w, 1450m, 1426w, 1368w, 1329w, 1283w, 1250w, 1205w, 1171w, 1152w, 1133w, 1050w, 1034w, 1014w, 906w, 872w, 861w, 798m, 762w, 739w, 669w, 645w, 622w, 603w, 567w, 531w, 516w, 491w, 428w cm⁻¹. ¹H-NMR (200 MHz, CDCl₃/CD₃OD, δ): 8.38 (d, *J* = 5.6, H-C(2)), 7.91 (d, *J* = 9.0, H-C(8)), 7.87 (d, *J* = 2.2, H-C(5)), 7.34 (dd, *J*₁ = 2.3, *J*₂ = 8.9, H-C(6)), 6.41 (d, *J* = 5.6, H-C(3)), 3.95-3.85 (m, H, ArNHCH(CH₃-)), 3.00-2.90 (m, 2H, -CH₂NH₂), 1.35-1.25 (d, 3H, *J* = 6.0, CH₃). ¹³C-NMR (50 MHz, CD₃OD, δ): 151.16; 149.81; 148.46; 134.99; 127.31; 125.03; 121.88; 117.28; 98.83; 45.72; 21.43; 17.17. HRMS: *m/z* 236.09395 corresponds to molecular formula C₁₂H₁₄ClN₃H⁺ (error in ppm: - 4.03). Anal. (C₁₂H₁₄ClN₃ × 1/3 CH₂Cl₂) Calcd: C, 56.11; H, 5.60; N, 15.92. Found: C, 55.75; H, 5.60; N, 15.58.

N³-(7-Chloroquinolin-4-yl)butane-1,3-diamine (S14).



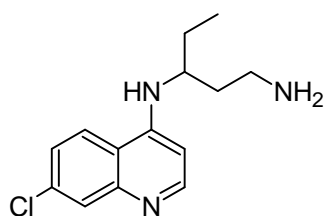
Compound **S14** was prepared by method C from **S10** (650 mg, 1.86 mmol) and was obtained after dry-flash chromatography: SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5→8/2, as colorless powder softens at 106-108 °C. Yield: 353 mg (76%). IR (ATR): 3243m, 2969m, 2927m, 2866w, 1609m, 1569s, 1537m, 1487w, 1448m, 1426m, 1365m, 1329m, 1279w, 1244w, 1198w, 1145m, 1078w, 873w, 854m, 806m, 766w, 731m, 701w, 643w, 622w, 596w, 571w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.48 (d, *J* = 5.4, H-C(2)), 7.91 (d, *J* = 2.1, H-C(8)), 7.72 (d, *J* = 9.0, H-C(5)), 7.30 (dd, *J* = 2.1, *J* = 9.0, H-C(6)), 7.22 (bs, H-N), 6.37 (d, *J* = 5.4, H-C(3)), 3.95-3.80 (m, 1H, ArNHCH(CH₃)-), 3.15-3.05 (m, 1H, -CH₂NH₂), 3.05-2.90 (m, 1H, -CH₂NH₂), 1.95-1.80 (m, 1H, -CH₂CH₂NH₂), 1.80-1.70 (m, 1H, -CH₂CH₂NH₂), 1.63 (bs, 2H-N), 1.32 (d, 3H, *J* = 6.4, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 151.94; 149.55; 149.33; 134.61; 128.52; 124.84; 121.94; 117.65; 98.58; 48.05; 38.64; 37.65; 19.27. HRMS: *m/z* 250.11106 corresponds to molecular formula C₁₃H₁₆ClN₃H⁺ (error in ppm: + 2.04). Anal. (C₁₃H₁₆ClN₃ × 1/3 CH₂Cl₂) Calcd: C, 61.05; H, 6.57; N, 16.43. Found: C, 61.35; H, 6.34; N, 16.18.

N⁴-(7-Chloroquinolin-4-yl)pentane-1,4-diamine (S15).



Compound **S15** was prepared by method C from **S11** (300 mg, 0.86 mmol) and was obtained after dry-flash chromatography: SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5→8/2, as colorless powder softens at 132-136 °C. Yield: 176 mg (81%). IR (ATR): 3238m, 3063w, 2968w, 2932m, 2851w, 1568w, 1570s, 1491w, 1452m, 1423m, 1384w, 1363w, 1329w, 1280w, 1251w, 1200w, 1156w, 1128w, 1084w, 941w, 903w, 869w, 842w, 818w, 796m, 771w, 700w, 682w, 643w, 621w, 598w, 561w, 534w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.51 (d, *J* = 5.4, H-C(2)), 7.94 (d, *J* = 2.2, H-C(8)), 7.70 (d, *J* = 9.0, H-C(5)), 7.33 (dd, *J*₁ = 2.2, *J*₂ = 8.9, H-C(6)), 6.45-6.35 (m, H-C(3)), 5.42 (d, *J* = 6.7, H-N), 3.75-3.65 (m, 1H, ArNHCH(CH₃)-), 2.80-2.70 (m, 2H, -CH₂NH₂), 1.85-1.65 (m, 2H, -ArNHCH(CH₃)CH₂-), 1.65-1.50 (m, 2H, -CH₂CH₂NH₂), 1.32 (d, 3H, *J* = 6.2, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 152.02; 149.41; 149.03; 134.72; 128.85; 125.01; 121.13; 117.34; 99.14; 48.28; 41.80; 33.83; 29.57; 20.21. HRMS: *m/z* 264.12589 corresponds to molecular formula C₁₄H₁₈ClN₃H⁺ (error in ppm: - 1.19). Anal. (C₁₄H₁₈ClN₃) Calcd: C, 63.75; H, 6.88; N, 15.93. Found: C, 63.59; H, 6.80; N, 15.96.

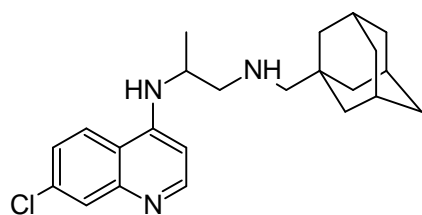
N³-(7-chloroquinolin-4-yl)pentane-1,3-diamine (S16).



Compound **S16** was prepared by method C from **S12** (540 mg, 1.37 mmol) and was obtained after dry-flash chromatography SiO₂,

gradient: CH₂Cl₂/MeOH(NH₃sat.) = 9/1→7/3 and flash chromatography (Biotage SP1 RP column, eluent: MeOH/H₂O = 65/35) as yellow powder softens at 142-144 °C. Yield: 318 mg (88%). IR (ATR): 3265m, 2898s, 2844s, 1610w, 1573s, 1536m, 1486w, 1448m, 1427w, 1366w, 1330w, 1282w, 1263w, 1247w, 1201w, 1136w, 1096w, 1078w, 903w, 876w, 853m, 804m, 763w, 736m, 702w, 644w, 622w, 600w, 539w, 499w, 456w, 429w, 407w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.48 (d, *J* = 5.4, H-C(2)), 7.92 (d, *J* = 2.2, H-C(8)), 7.72 (d, *J* = 8.9, H-C(5)), 7.32 (dd, *J*₁ = 2.2, *J*₂ = 8.9, H-C(6)), 6.92 (d, *J* = 5.4, H-N), 6.36 (d, *J* = 5.5, H-C(3)), 3.75-3.65 (m, 1H, ArNHCH-), 3.10-3.00 (m, 1H, -CH₂NH₂), 3.00-2.90 (m, 1H, -CH₂NH₂), 1.95-1.85 (m, 1H, -CH₂CH₂NH₂), 1.85-1.70 (m, 2H, -CH₂CH₂NH₂, -CH₂CH₃), 1.70-1.60 (m, 1H, -CH₂CH₃), 1.41 (s, 2H-N), 0.98 (t, 3H, *J* = 7.4, -CH₂CH₃). ¹³C-NMR (125 MHz, CD₃OD, δ): 152.03; 149.73; 149.47; 134.61; 128.68; 124.84; 121.75; 117.59; 98.58; 53.75; 38.64; 34.83; 26.16; 10.30. HRMS: *m/z* 264.12636 corresponds to molecular formula C₁₄H₁₈ClN₃H⁺ (error in ppm: + 0.59). Anal.(C₁₄H₁₈ClN₃) Calcd: C, 63.75; H, 6.88; N, 15.93. Found: C, 63.46; H, 6.98; N, 15.74.

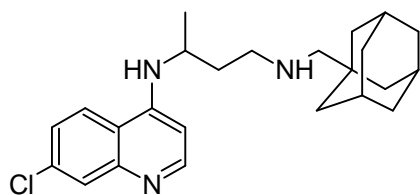
***N*¹-(1-Adamantylmethyl)-*N*²-(7-chloroquinolin-4-yl)propane-1,2-diamine (9).**



Compound **9** was prepared by method D from amine **S13** (254 mg, 1.08 mmol) and adamantane-1-carboxaldehyde (177 mg, 1.08 mmol) using NaBH(OAc)₃ (458 mg, 2.16 mmol) and was obtained after dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 100/2, as colorless

foam (343 mg, 83%) softens at 153-155 °C. IR (ATR): 3230m, 2897m, 9842w, 2804m, 1612w, 1586s, 1541m, 1488w, 1447m, 1370w, 1352w, 1332w, 1308w, 1282w, 1242w, 1198w, 1153m, 1138m, 1110w, 1097w, 1073w, 1029w, 1007w, 986m, 948w, 897w, 874w, 860w, 852w, 835m, 794m, 759m, 718w, 562w, 633w, 610m, 501m, 475w, 443w, 425w, 403w cm⁻¹. λ_{max}(ε) = 330 (10259), 254 (15366), 237 (13922) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 8.51 (d, *J* = 5.0, H-C(2)), 7.94 (d, *J* = 1.5, H-C(8)), 7.72 (d, *J* = 9.0, H-C(5)), 7.34 (dd, *J*₁ = 1.8, *J*₂ = 8.8, H-C(6)), 6.42 (d, *J* = 5.0, H-C(3)), 6.08 (d, *J* = 5.0, H-N), 3.75-3.65 (m, 1H, ArNHCH(CH₃)-), 2.90-2.80 (d, 2H, ArNHCH(CH₃)CH₂-), 2.32 (ABq, *H*_A, *J* = 11.5, -CH₂Ad), 2.24 (ABq, *H*_B, *J* = 11.5, -CH₂Ad), 1.95 (bs, 3H, -Ad), 1.75-1.55 (m, 6H, -Ad), 1.55-1.45 (m, 6H, -Ad), 1.29 (d, 3H, *J* = 6.5, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 151.94; 149.41; 149.26; 134.68; 128.64; 125.02; 121.28; 117.70; 99.45; 62.60; 55.14; 47.20; 40.83; 37.14; 33.61; 28.35; 18.07. HRMS: *m/z* 384.21930 corresponds to molecular formula C₂₃H₃₀ClN₃H⁺ (error in ppm: - 2.09). Anal. (C₂₃H₃₀ClN₃ × 1/2 H₂O) Calcd: C, 70.30; H, 7.95; N, 10.69. Found: C, 70.62; H, 7.90; N, 10.85. HPLC purity (λ = 330 nm): method A: RT 7.846 min, area 98.53%; method B: RT 9.628 min, area 98.46%.

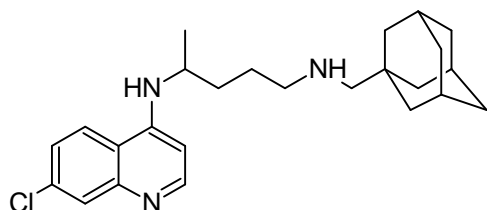
***N*¹-(1-Adamantylmethyl)-*N*³-(7-chloroquinolin-4-yl)butane-1,3-diamine (23).**



Compound **23** was prepared by method E from amine **S14** (430 mg, 1.72 mmol) and adamantane-1-carboxaldehyde (283 mg, 1.72 mmol) using AcOH (141 μ L, 2.15 mmol) and NaBH₄ (390 mg, 10.32 mmol) and was obtained after

dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, as colorless foam (610 mg, 89%)softens at 135-138 °C. IR(ATR): 3250m, 3061w, 2962w, 2897s, 2842m, 1611w, 1570s, 1542m, 1490w, 1450m, 1430m, 1365m, 1345w, 1330m, 1283w, 1253w, 1206w, 1184w, 1136w, 1079w, 928w, 901w, 870m, 850m, 821w, 801m, 770w, 756m, 637w, 612w, 602w, 502w cm⁻¹. $\lambda_{\max}(\epsilon)$ = 326 (10000), 254 (16260) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 8.49 (d, J = 5.4, H-C(2)), 7.92 (d, J = 2.0, H-C(8)), 7.80 (d, J = 8.9, H-C(5)), 7.35-7.20 (m, H-C(6)), 7.08 (d, J = 5.1, H-N), 6.40 (d, J = 5.4, H-C(3)), 3.90-3.80 (m, 1H, ArNHCH(CH₃)-), 2.95-2.85 (m, 1H, -CH₂NHCH₂Ad), 2.85-2.70 (m, 1H, -CH₂NHCH₂Ad), 2.30 (s, 2H, -CH₂Ad), 2.01 (s, 3H, -Ad), 1.95-1.85 (m, 1H, ArNHCH(CH₃)CH₂-), 1.85-1.65 (m, 7H, ArNHCH(CH₃)CH₂-, -Ad), 1.65-1.50 (m, 7H, -Ad, H-N-), 1.32 (d, 3H, J = 6.3, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 152.05; 149.61; 149.40; 134.59; 128.60; 124.54; 122.30; 117.67; 98.90; 63.68; 48.32; 47.81; 41.16; 37.17; 35.22; 33.36; 28.43; 19.36. HRMS: m/z 398.23673 corresponds to molecular formula C₂₄H₃₂ClN₃H⁺ (error in ppm: + 2.45). Anal. (C₂₄H₃₂ClN₃ × 1/2H₂O) Calcd: C, 70.83; H, 8.17; N, 10.32. Found: C, 70.71; H, 7.91; N, 10.53. HPLCpurity (λ = 330 nm): method A: RT 7.989 min, area 99.68%; method B: RT 9.636 min, area 99.31%.

N¹-(1-Adamantylmethyl)-N⁴-(7-chloroquinolin-4-yl)pentane-1,4-diamine (29).

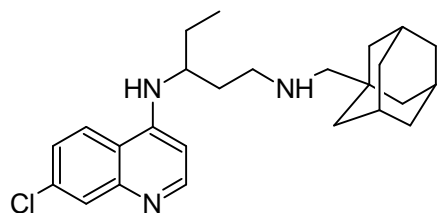


Compound **29** was prepared by method E from amine **S15** (75 mg, 0.28 mmol) and adamantane-1-carboxaldehyde (47 mg, 0.28 mmol) using AcOH (120 μ L, 0.35 mmol) and NaBH₄ (64 mg, 1.68 mmol) and was obtained after multiple chromatography: dry-flash

SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3) as colorless foam (94 mg, 80%)softens at 131-132 °C. IR (ATR): 3256w, 2897s, 2844m, 1610w, 1571s, 1535m, 1449m, 1377m, 1331m, 1277w, 1263w, 1201w, 1150m, 1119w, 1079w, 904w, 876w, 851w, 806m, 767w, 735m, 702w, 645w, 623w, 597w, 559w, 532w, 510w cm⁻¹. $\lambda_{\max}(\epsilon)$ = 329 (11176), 255 (16882) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 8.51 (d, J = 5.4, H-C(2)), 7.94 (d, J = 2.1, H-C(8)), 7.70 (d, J = 9.0, H-C(5)), 7.32 (dd, J_1 = 2.2, J_2 = 8.9, H-C(6)), 6.41 (d, J = 5.5, H-C(3)), 5.29 (d, J = 7.0, H-N), 3.80-3.65 (m, 1H, ArNHCH(CH₃)-), 2.70-2.55 (m, 2H, -CH₂NHCH₂Ad), 2.24 (s, 2H, -CH₂Ad), 1.97 (s, 3H, -Ad), 1.85-1.60 (m, 10H, ArNHCH(CH₃)CH₂-, -CH₂CH₂NHCH₂Ad, -Ad), 1.55-1.45 (m, 6H, -Ad), 1.32 (d, 3H, J = 6.4, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ):

152.02; 151.10; 148.96; 134.35; 128.87; 124.99; 121.13; 117.29; 99.22; 62.69; 50.14; 48.36; 41.00; 37.19; 33.77; 33.37; 28.44; 26.12; 20.25. HRMS: m/z 412.25177 corresponds to molecular formula $C_{25}H_{34}ClN_3H^+$ (error in ppm: + 0.89). Anal. ($C_{25}H_{34}ClN \times 1/2H_2O$) Calcd: C, 71.32; H, 8.38; N, 9.98. Found: C, 71.13; H, 8.11; N, 9.99. HPLC purity ($\lambda = 330$ nm): method A: RT 8.010 min, area 97.89%; method B: RT 9.514 min, area 95.43%.

N^1 -(1-Adamantylmethyl)- N^3 -(7-chloroquinolin-4-yl)pentane-1,3-diamine (27).



Compound **27** was prepared by method D from amine **S16**

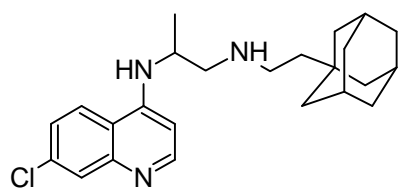
(51 mg, 0.19 mmol) and 1-adamantylacetaldehyde(32 mg, 0.19 mmol) using $NaBH(OAc)_3$ (80 mg, 0.38 mmol) and

was obtained after multiple chromatography: dry-flash

SiO_2 , eluent: $CH_2Cl_2/MeOH(NH_3sat.) = 100/4$, and flash

chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3) as yellow foam (54 mg, 68%),softens at 121-123 °C. IR (ATR): 3242m, 3063w, 2928m, 2869w, 1661w, 1610w, 1570s, 1541m, 1490w, 1452m, 1426m, 1366m, 1329m, 1283w, 1250m, 1200w, 1143m, 1127m, 1080m, 1005w, 978w, 903w, 874w, 852m, 804m, 869m, 641w, 622w, 599w, 528w, 497m, 447w, 426w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 8.48 (d, $J = 5.4$, H-C(2)), 7.92 (d, $J = 2.0$, H-C(8)), 7.80 (d, $J = 9.0$, H-C(5)), 7.26 (dd, $J_1 = 2.1$, $J_2 = 8.8$, H-C(6)), 6.82 (d, $J = 6.0$, H-N), 6.38 (d, $J = 5.8$, H-C(3)), 3.70-3.60 (m, 1H, ArNHCH(CH_2CH_3)-), 2.87-2.78 (m, 1H, - CH_2NHCH_2Ad), 2.78-2.70 (m, 1H, - CH_2NHCH_2Ad), 2.30 (ABq, H_A , $J = 11.6$, - CH_2Ad), 2.24 (ABq, H_B , $J = 11.6$, - CH_2Ad), 2.00 (m, 3H, -Ad), 1.95-1.85 (m, 1H, - $CH_2CH_2NHCH_2Ad$), 1.85-1.60 (m, 9H, -Ad, - CH_2CH_3 , - $CH_2CH_2NHCH_2Ad$), 1.60-1.50 (m, 6H, -Ad), 0.97 (t, 3H, $J = 7.5$, CH_3). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 152.02; 149.79; 149.42; 134.59; 128.61; 124.55; 122.12; 117.59; 98.84; 63.62; 54.00; 47.75; 41.11; 37.15; 33.33; 32.17; 28.41; 26.15; 10.31. HRMS: m/z 412.25140 corresponds to molecular formula $C_{25}H_{34}ClN_3H^+$ (error in ppm: - 0.31).Anal. ($C_{25}H_{34}ClN_3 \times 1/2H_2O$) Calcd: C, 71.32; H, 8.38; N, 9.98. Found: C, 71.52; H, 7.88; N, 10.15. HPLC purity ($\lambda = 330$ nm): method A: RT 8.009 min, area 98.18%; method B: RT 9.508 min, area 97.79%.

N^1 -[2-(1-Adamantyl)ethyl]- N^2 -(7-chloroquinolin-4-yl)propane-1,2-diamine (33).



Compound **33** was prepared by method D from amine **S13**

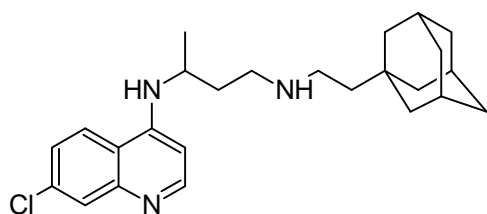
(180 mg, 0.76 mmol) and 1-adamantylacetaldehyde(136 mg, 0.76 mmol) using $NaBH(OAc)_3$ (58 mg, 1.52 mmol) and was

obtained after dry-flash chromatography: SiO_2 eluent:

$CH_2Cl_2/MeOH(NH_3sat.) = 95/5$, and flash chromatography (Biotage SP1 RP column, gradient: $MeOH/H_2O = 7/3 \rightarrow 9/1$) as colorless solid (227 mg, 75%),softens at 46-47 °C. IR (ATR): 3252m, 3063w, 2896s, 2843m, 1610w, 1573s, 1537m, 1447m, 1426w, 1376m, 1330m, 1279w, 1241w, 1205w, 1134m, 1078w, 966w, 901w, 870m, 843w, 805m, 763m,

645w, 623w, 600w, 540w, 513w, 490w, 421w cm^{-1} . $\lambda_{\text{max}}(\epsilon) = 327 (10189), 253 (16143) \text{ nm}$. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 8.48 (d, $J = 5.5$, H-C(2)), 7.92 (d, $J = 1.0$, H-C(8)), 7.74 (d, $J = 9.0$, H-C(5)), 7.32 (dd, $J_1 = 1.8, J_2 = 8.8$, H-C(6)), 6.40 (d, $J = 5.5$, H-C(3)), 5.90 (bs, H-N), 3.75-3.65 (m, 1H, $\text{ArNHCH}(\text{CH}_3)-$), 2.95-2.85 (m, 2H, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$), 2.70-2.60 (m, 2H, $-\text{CH}_2\text{CH}_2\text{Ad}$), 1.92 (bs, 3H, -Ad), 1.75-1.55 (m, 6H, -Ad), 1.48 (bs, 6H, -Ad), 1.35-1.20 (m, 6H, $-\text{CH}_2\text{Ad}, \text{CH}_3, \text{H-N}$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 151.82; 149.31; 149.13; 134.75; 128.46; 125.04; 121.44; 117.55; 99.31; 54.36, 47.41; 44.59; 44.44; 42.62; 37.03; 31.86; 28.58; 18.11. HRMS: m/z 398.23435 corresponds to molecular formula $\text{C}_{24}\text{H}_{32}\text{ClN}_3\text{H}^+$ (error in ppm: - 3.51). Anal. ($\text{C}_{24}\text{H}_{32}\text{ClN}_3 \times 1/2 \text{ H}_2\text{O}$) Calcd: C, 70.83; H, 8.17; N, 10.32. Found: C, 70.44; H, 7.91; N, 10.27. HPLC purity ($\lambda = 330 \text{ nm}$): method A: RT 7.891 min, area 97.79%; method B: RT 9.904 min, area 95.06%.

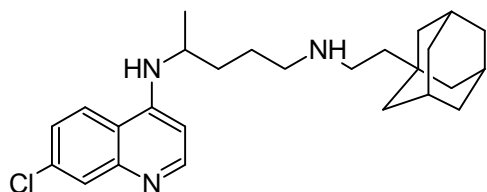
N^1 -[2-(1-Adamanty)ethyl]- N^3 -(7-chloroquinolin-4-yl)butane-1,3-diamine (36).



Compound **36** was prepared by method E from amine **S14** (90 mg, 0.36 mmol) and 1-adamantylacetaldehyde (64.3 mg, 0.36 mmol) using AcOH (26 μL , 0.45 mmol) and NaBH_4 (82 mg, 2.16 mmol) and was obtained after multiple chromatography: dry-flash:

SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5$, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 6/4) as colorless foam (596 mg, 77%), softens at 62-64 $^\circ\text{C}$. IR (ATR): 3219w, 2897s, 2843m, 1737m, 1610w, 1573s, 1538m, 1448m, 1427w, 1368m, 1330m, 1280w, 1242m, 1199w, 1149m, 1077w, 1046w, 976w, 849m, 804m, 764w, 716w, 644w, 604w, 518w, 505w cm^{-1} . $\lambda_{\text{max}}(\epsilon) = 328 (10358), 254 (16434) \text{ nm}$. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 8.47 (d, $J = 5.4$, H-C(2)), 7.91 (d, $J = 2.2$, H-C(8)), 7.87 (d, $J = 4.5$, H-N), 7.75 (d, $J = 9.0$, H-C(5)), 7.29 (dd, $J_1 = 2.2, J_2 = 9.0$, H-C(6)), 6.34 (d, $J = 5.6$, H-C(3)), 3.90-3.80 (m, 1H, $\text{ArNHCH}(\text{CH}_3)-$), 3.05-2.95 (m, 1H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Ad}$), 2.85-2.75 (m, 1H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Ad}$), 2.70-2.60 (m, 2H, $-\text{CH}_2\text{CH}_2\text{Ad}$), 2.00-1.90 (m, 4H, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$, -Ad), 2.00-1.90 (m, 7H, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$, -Ad), 1.55-1.45 (m, 6H, -Ad), 1.40-1.30 (m, 2H, $-\text{CH}_2\text{Ad}$), 1.32 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 152.01; 149.81; 149.40; 134.53; 128.52; 124.54; 122.41; 117.84; 98.51; 48.45; 46.40; 44.98; 44.50; 42.70; 37.09; 34.83; 31.87; 28.62; 19.05. HRMS: m/z 398.23435 corresponds to molecular formula $\text{C}_{25}\text{H}_{34}\text{ClN}_3\text{H}^+$ (error in ppm: - 1.75). Anal. ($\text{C}_{25}\text{H}_{34}\text{ClN}_3 \times 1/2 \text{ H}_2\text{O}$) Calcd: C, 71.32; H, 8.38; N, 9.98. Found: C, 71.11; H, 8.07; N, 10.08. HPLC purity ($\lambda = 330 \text{ nm}$): method A: RT 8.535 min, area 98.59%; method B: RT 9.910 min, area 95.42%.

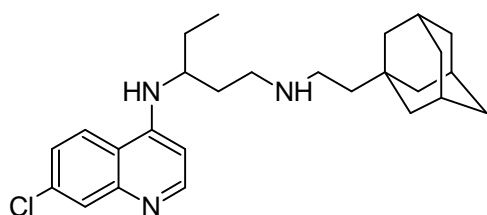
N^1 -[2-(1-Adamanty)ethyl]- N^4 -(7-chloroquinolin-4-yl)pentane-1,4-diamine (42).



Compound **42** was prepared by method E from amine **S15** (320 mg, 1.21 mmol) and 1-adamantylacetaldehyde (216 mg, 1.21 mmol) using AcOH (86 μ L, 1.51 mmol) and NaBH₄ (92 mg, 2.42 mmol) and was obtained after dry-flash

chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 9/1, as colorless foam (314 mg, 61%)softens at 49-51 °C. IR (ATR): 3422m, 2901s, 2845m, 1611w, 1578s, 1540w, 1450m, 1426w, 1379w, 1332w, 1280w, 1253w, 1201w, 1150w, 1081w, 905w, 877w, 854w, 806w, 768w, 646w, 601w, 401w cm⁻¹. $\lambda_{\max}(\epsilon)$ = 328 (11161), 255 (17040) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 8.50 (d, J = 5.4, H-C(2)), 7.93 (d, J = 2.1, H-C(8)), 7.73 (d, J = 9.0, H-C(5)), 7.33 (dd, J_1 = 2.2, J_2 = 8.9, H-C(6)), 6.39 (d, J = 5.5, H-C(3)), 5.52 (bs, H-N), 3.75-3.60 (m, 1H, ArNHCH(CH₃)-), 2.75-2.65 (m, 2H, -CH₂NHCH₂CH₂Ad), 2.65-2.55 (m, 2H, -CH₂CH₂Ad), 1.93 (bs, 3H, -Ad), 1.85-1.75 (m, 1H, ArNHCH(CH₃)CH₂-), 1.75-1.50 (m, 10H, ArNHCH(CH₃)CH₂-, -CH₂CH₂NHCH₂CH₂Ad, -Ad, H-N-), 1.45 (m, 6H, -Ad), 1.35-1.25 (m, 5H, CH₃, -CH₂Ad). ¹³C-NMR (125 MHz, CDCl₃, δ): 151.95; 149.32; 149.11; 134.72; 128.68; 124.96; 121.35; 117.35; 99.12; 49.57; 48.30; 44.48; 44.33; 42.60; 37.08; 34.05; 31.82; 28.61; 26.33; 20.16. HRMS: m/z 426.26752 corresponds to molecular formula C₂₆H₃₆ClN₃H⁺ (error in ppm: + 1.10). Anal.(C₂₆H₃₆ClN₃ × 3/2 H₂O) Calcd: C, 68.93; H, 8.68; N, 9.27. Found: C, 69.08; H, 9.04; N, 9.48. HPLCpurity (λ = 330 nm): method A: RT 8.000 min, area 95.37%; method B: RT 9.821 min, area 95.54%.

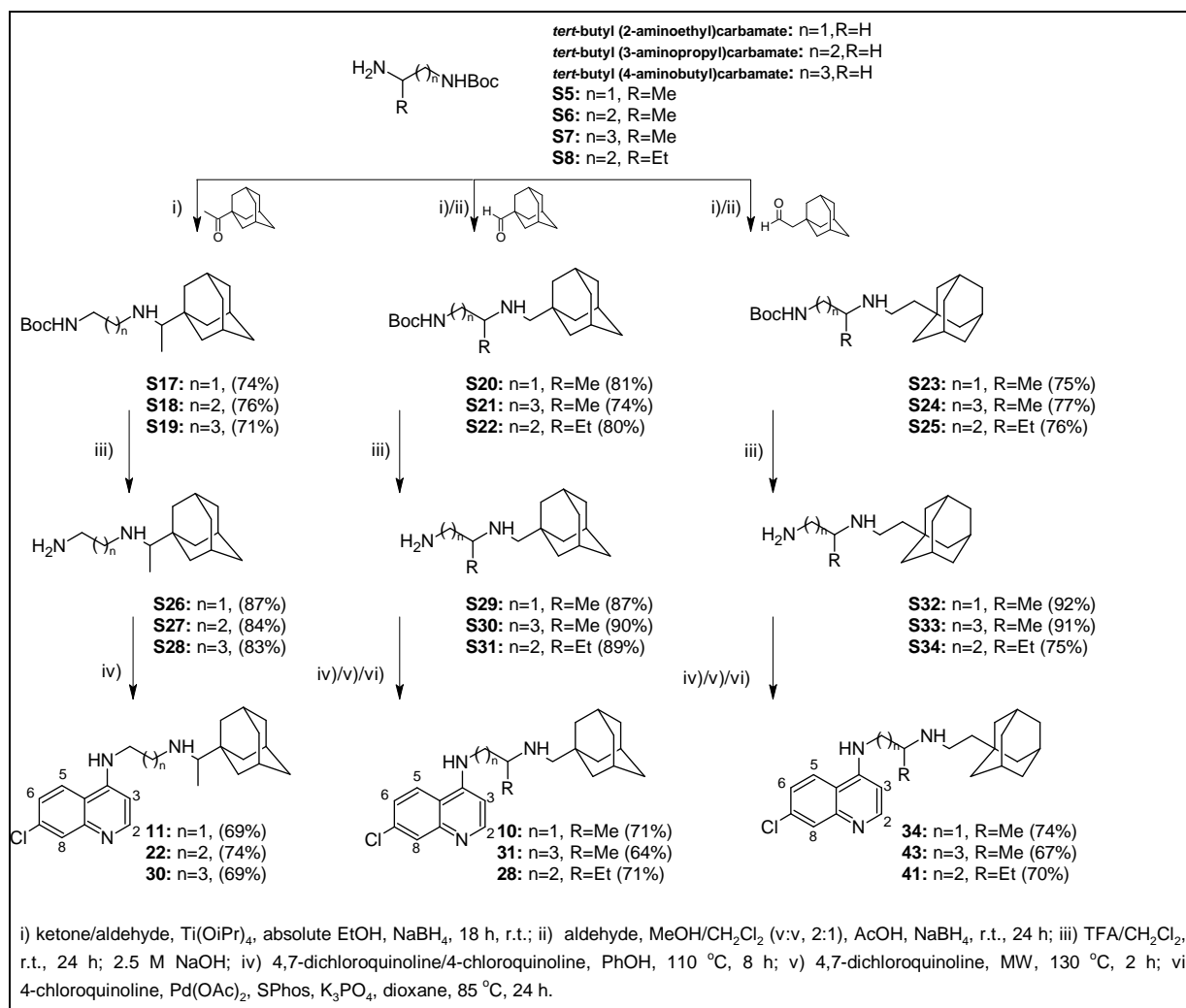
N¹-[2-(1-Adamantyl)ethyl]-N³-(7-chloroquinolin-4-yl)pentane-1,3-diamine (40).



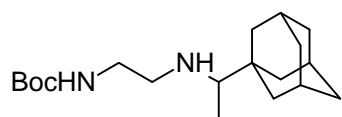
Compound **40** was prepared by method D from amine **S16** (157 mg, 0.60 mmol) and 1-adamantylacetaldehyde(106 mg, 0.60 mmol) using NaBH(OAc)₃ (254 mg, 1.20 mmol) and was obtained after multiple chromatography: dry-flash SiO₂, eluent:

CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 6/4) as colorless foam (171 mg, 67%),softens at 121-123 °C. IR (ATR): 3236m, 2897s, 2843m, 1610w, 1573s, 1538m, 1488w, 1448m, 1428m, 1366m, 1330m, 1281w, 1245w, 1198w, 1166w, 1141m, 1078w, 901w, 876w, 852m, 804m, 763w, 735m, 701w, 643w, 599w, 539w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.45 (d, J = 5.4, H-C(2)), 7.91 (d, J = 2.2, H-C(8)), 7.67 (d, J = 8.9, H-C(5)), 7.76 (d, J = 5.6, H-N), 7.29 (dd, J_1 = 2.2, J_2 = 8.9, H-C(6)), 6.32 (d, J = 5.8, H-C(3)), 3.61 (m, 1H, ArNHCH(CH₂CH₃)-), 3.00-2.90 (m, 1H, -CH₂NHCH₂CH₂Ad), 2.85-2.75 (m, 1H, -CH₂NHCH₂CH₂Ad), 2.65-2.55 (m, 2H, -CH₂CH₂Ad), 2.00-1.85 (m, 4H, -Ad, -CH₂CH₂NHCH₂CH₂Ad), 1.85-1.75 (m, 2H, -CH₂CH₃, -CH₂CH₂NHCH₂CH₂Ad), 1.75-1.55 (m, 7H, -Ad, -CH₂CH₃), 1.40-1.30 (m, 2H, -CH₂Ad), 0.97

(t, $J = 7.5$, CH_3). ^{13}C -NMR (125 MHz, CDCl_3 , δ): 151.91; 149.97; 149.36; 134.56; 128.43; 124.55; 122.30; 117.74; 98.46; 54.19; 46.53; 44.87; 44.49; 42.65; 37.06; 31.83; 31.62; 28.59; 25.79; 10.33. HRMS: m/z 426.26855 corresponds to molecular formula $\text{C}_{26}\text{H}_{36}\text{ClN}_3\text{H}^+$ (error in ppm: + 3.51). Anal. ($\text{C}_{26}\text{H}_{36}\text{ClN}_3 \times \text{H}_2\text{O}$) Calcd: C, 70.32; H, 8.63; N, 9.46. Found: C, 70.71; H, 8.48; N, 9.24. HPLC purity ($\lambda = 330$ nm): method A: RT 8.003 min, area 98.19%; method B: RT 9.862 min, area 96.49%.



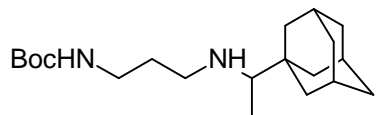
tert-Butyl (2-[[1-(1-adamantyl)ethyl]amino]ethyl)carbamate (**S17**).



Compound **S17** was prepared by method G from *tert*-butyl (2-aminoethyl)carbamate (330 mg, 2.06 mmol) and 1-(1-adamantyl)ethanone (306 mg, 1.72 mmol) using $\text{Ti}(\text{O}i\text{Pr})_4$ (610 μL , 2.06 mmol) and NaBH_4 (130 mg, 3.44 mmol) and was obtained after dry-flash chromatography: SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5$, as colorless oil (410 mg, 74%). IR (ATR): 3346m, 2973w, 2899s, 2846s, 1689s, 1518m, 1449m, 1390w, 1364m, 1345w, 1315w, 1271m, 1248m, 1153s, 1040w, 1015w, 991w, 926w, 863w, 812w, 777w, 758w, 736w, 700w, 667w, 637w, 627w, 618w, 600w, 562w, 555w, 541w, 522w, 509w, 503w

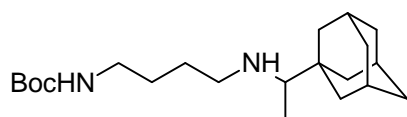
cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 4.96 (bs, H-N), 3.25-3.10 (m, 2H, -CH₂NHBoc), 2.90-2.80 (m, 1H, -CH₂CH₂NHBoc), 2.65-2.50 (m, 1H, -CH₂CH₂NHBoc), 2.05-2.00 (m, 1H, -CH(CH₃)Ad), 1.97 (bs, 3H, -Ad), 1.75-1.40 (m, 21H, -Ad, -NHCOO-C(CH₃)₃), 0.94 (d, *J* = 6.5, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 156.18; 79.02; 62.01; 47.84; 40.61; 38.67; 37.34; 36.14; 28.56; 28.43; 13.55. HRMS: *m/z* 323.26854 corresponds to molecular formula C₁₉H₃₄N₂O₂H⁺ (error in ppm: - 2.38).

tert-Butyl (3-[[1-(1-adamantyl)ethyl]amino]propyl)carbamate (S18).



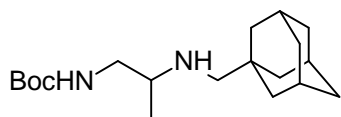
Compound **S18** was prepared by method G from tert-butyl (3-aminopropyl)carbamate (380 mg, 2.18 mmol) and 1-(1-adamantyl)ethanone (325 mg, 1.85 mmol), using Ti(OiPr)₄ (645 μL, 2.18 mmol) and NaBH₄ (140 mg, 3.70 mmol) and was obtained after dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, as colorless oil (475 mg, 76%). IR (ATR): 3313m, 2903s, 2847s, 2676w, 1574m, 1450m, 1362w, 1344w, 1316w, 1248w, 1103w, 1012w, 974w, 934w, 815w, 735w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 5.88 (bs, H-NBoc), 3.35-2.40 (m, 4H, -CH₂NHBoc, -CH₂NHCH(CH₃)Ad), 2.10-2.20 (m, 1H, -CH(CH₃)CHAd), 1.98 (m, 3H, -Ad), 1.75-1.40 (m, 23H, -Ad, -NHCOO-C(CH₃)₃), -CH₂CH₂CH₂NHBoc), 0.95 (d, *J* = 6.6, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 156.16, 78.64; 62.61; 47.47; 40.36; 38.69, 37.30; 36.09, 29.56; 28.56; 28.45; 13.19. HRMS: *m/z* 337.28334 corresponds to molecular formula C₂₀H₃₆N₂O₂H⁺ (error in ppm: - 4.79).

tert-Butyl (4-[[1-(1-adamantyl)ethyl]amino]butyl)carbamate (S19).



Compound **S19** was prepared by method G from tert-butyl (4-aminobutyl)carbamate (231 mg, 1.23 mmol) and 1-(1-adamantyl)ethanone (110 mg, 0.61 mmol) using Ti(OiPr)₄ (364 μL, 2.23 mmol) and NaBH₄ (45 mg, 1.22 mmol) and was obtained after dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, as colorless oil (152 mg, 71%). IR (ATR): 3330m, 2971w, 2900s, 2846m, 1692s, 1520m, 1449m, 1389w, 1364m, 1345w, 1315w, 1271w, 1248m, 1171s, 1118w, 1066w, 1039w, 993w, 870w, 781w, 735w, 702w, 670w, 654w, 647w, 640w, 595w, 589w, 561w, 548w, 511w, 503w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 4.99 (bs, H-N), 3.20-2.05 (m, 2H, -CH₂NHBoc), 2.80-2.65 (m, 1H, -CH₂NHCH(CH₃)Ad), 2.50-2.40 (m, 1H, -CH₂NHCH(CH₃)Ad), 2.10-2.00 (m, 2H, -CH(CH₃)Ad), 1.97 (m, 3H, -Ad), 1.75-1.40 (m, 25H, -Ad, -CH₂CH₂NHBoc, -CH₂CH₂CH₂NHBoc, -NHCOO-C(CH₃)₃), 0.94 (d, 3H, *J* = 6.5, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 155.98; 78.79; 62.49; 48.34; 40.48; 38.65; 37.30; 35.96; 28.52; 28.39; 27.83; 27.71; 13.40. HRMS: *m/z* 351.30112 corresponds to molecular formula C₂₁H₃₈N₂O₂H⁺ (error in ppm: + 1.48).

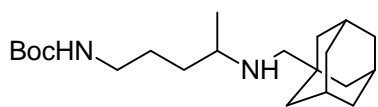
tert-Butyl {2-[(1-adamantylmethyl)amino]propyl}carbamate (S20).



Compound **S20** was prepared by method E from mono-*N*-Boc-protected amine **S5** (340 mg, 1.95 mmol) and adamantane-1-carboxaldehyde (320 mg, 1.95 mmol) using AcOH (139 μ L, 2.4

mmol) and NaBH₄ (443 mg, 11.7 mol) and was obtained after dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, as colorless oil (509 mg, 81%). IR (ATR): 3355m, 2972w, 2897s, 2845m, 1694s, 1500m, 1450m, 1390w, 1364m, 1345w, 1248m, 1165s, 1103w, 986m, 908w, 865w, 777w, 751w, 644w, 620w, 576w, 556w, 545w, 520w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 4.99 (bs, H-N), 3.20-3.10 (m, 1H, -CH₂NHBoc), 3.05-2.90 (m, 1H, -CH₂NHBoc), 2.75-2.60 (m, 1H, -CH(CH₃)NHCH₂Ad), 2.31 (ABq, H_A, *J* = 11.5, -CH₂Ad), 2.12 (ABq, H_B, *J* = 11.5, -CH₂Ad), 1.96 (s, 3H, -Ad), 1.75-1.60 (m, 6H, -Ad), 1.55-1.40 (m, 15H, -Ad, -NHCOO-C(CH₃)₃), 1.03 (d, 3H, *J* = 6.4, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 157.06; 77.57; 61.55; 59.68; 53.35; 40.81; 37.24; 33.37; 28.47; 28.469; 18.62. HRMS: *m/z* 323.26937 corresponds to molecular formula C₁₉H₃₄N₂O₂H⁺ (error in ppm: + 0.19).

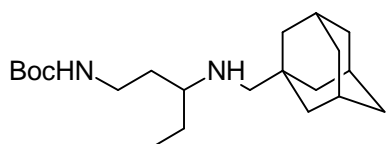
tert-Butyl {4-[(1-adamantylmethyl)amino]pentyl}carbamate (S21).



Compound **S21** was prepared by method E from mono-*N*-Boc-protected amine **S7** (396 mg, 1.96 mmol) and adamantane-1-carboxaldehyde (321 mg, 1.96 mmol) using AcOH (140 μ L,

2.4 mmol) and NaBH₄ (445 mg, 11.8 mol) and was obtained after dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, as colorless oil (508 mg, 74%). IR (ATR): 3196m, 3004w, 2962w, 2897s, 2846m, 2795w, 1710s, 1566m, 1465m, 1451m, 1383w, 1362m, 1343w, 1319w, 1302w, 1272m, 1245m, 1168m, 1138s, 1097w, 1076w, 1047w, 1036w, 1002w, 979m, 900w, 884w, 866w, 785w, 756m, 715w, 609w, 561w, 503w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 4.87 (bs, H-N), 3.20-3.00 (m, 1H, -CH₂NHBoc), 2.55-2.45 (m, 1H, -CH(CH₃)NHCH₂Ad), 2.74 (ABq, H_A, *J* = 11.3, -CH₂Ad), 2.15 (ABq, H_B, *J* = 11.3, -CH₂Ad), 1.96 (bs, 3H, -Ad), 1.75-1.60 (m, 6H, -Ad), 1.55-1.48 (8H, -Ad, -CH₂CH₂NHBoc), 1.48-1.40 (m, 11H, -CH₂CH₂CH₂NHBoc, -NHCOO-C(CH₃)₃), 1.40-1.25 (m, 1H, -CH₂CH₂CH₂NHBoc), 1.02 (d, 3H, *J* = 6.3, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 156.01; 78.89; 60.18; 53.59; 40.95; 40.82; 37.27; 34.32; 33.30; 28.50; 28.44; 26.43; 20.58. HRMS: *m/z* 351.29958 corresponds to molecular formula C₂₁H₃₈N₂O₂H⁺ (error in ppm: - 2.91).

tert-Butyl {3-[(1-adamantylmethyl)amino]pentyl}carbamate (S22).

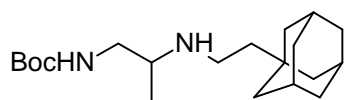


Compound **S22** was prepared by method E from mono-*N*-Boc-protected amine **S8** (370 mg, 1.96 mmol) and adamantane-1-carboxaldehyde (321 mg, 1.96 mmol) using AcOH (139 μ L,

2.4 mmol) and NaBH₄ (443 mg, 11.7 mol) and was obtained after dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, as colorless oil (549 mg, 80%). IR (ATR):

3331m, 2963w, 2898s, 2845m, 1692s, 1504m, 1451m, 1389w, 1363m, 1273w, 1247m, 1170s, 1087w, 1041w, 1022w, 932w, 871w, 808w, 778w, 751w, 623w, 648w, 608w, 588w, 551w, 530w, 521w, 509w, cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 6.64 (bs, H-N), 3.40-3.25 (m, 1H, $-\text{CH}_2\text{NHBoc}$), 3.25-3.05 (m, 1H, $-\text{CH}_2\text{NHBoc}$), 2.55-2.40 (m, 1H, $-\text{CH}(\text{CH}_2\text{CH}_3)\text{NHCH}_2\text{Ad}$), 2.29 (ABq, H_A , $J = 11.2$, $-\text{CH}_2\text{Ad}$), 2.21 (ABq, H_B , $J = 11.2$, $-\text{CH}_2\text{Ad}$), 1.97 (s, 3H, $-\text{Ad}$), 1.80-1.60 (m, 7H, $-\text{Ad}$, $-\text{CH}_2\text{CH}_2\text{NHBoc}$), 1.60-1.50 (m, 7H, $-\text{CH}_2\text{CH}_3$, $-\text{Ad}$), 1.50-1.30 (m, 11H, $-\text{CH}_2\text{CH}_2\text{NHBoc}$, $-\text{CH}_2\text{CH}_3$, $-\text{NHCOO-C}(\text{CH}_3)_3$), 0.86 (t, 3H, $J = 7.5$, $-\text{CH}_2\text{CH}_3$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 156.21; 78.30; 59.74; 59.48; 40.89; 39.27; 37.21; 33.29; 31.30; 28.48; 26.18; 9.87. HRMS: m/z 351.30038 corresponds to molecular formula $\text{C}_{21}\text{H}_{38}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: - 0.63).

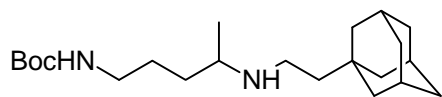
***tert*-Butyl (2-([2-(1-adamantyl)ethyl]amino)propyl)carbamate (S23).**



Compound **S23** was prepared by method G from mono-*N*-Boc-protected amine **S5** (275 mg, 1.58 mmol) and 1-adamantylacetaldehyde (280 mg, 1.58 mmol) using $\text{Ti}(\text{OiPr})_4$

(560 μL , 0.90 mmol) and NaBH_4 (120 mg, 3.16 mmol) and was obtained after dry-flash chromatography: SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5$, as colorless oil (398 mg, 75%). IR (ATR): 2972w, 2897s, 2844m, 1698s, 1499m, 1449m, 1390w, 1364m, 1345w, 1315w, 1268w, 1248m, 1166s, 1099w, 1050w, 1038w, 964w, 928w, 902w, 864w, 838w, 812w, 777w, 736m, 704w, 687w, 667w, 503w, 487w, 430w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 4.94 (bs, H-N), 3.20-3.05 (m, 1H, $-\text{CH}_2\text{NHBoc}$), 3.05-3.00 (m, 1H, $-\text{CH}_2\text{NHBoc}$), 2.85-2.75 (m, 1H, $-\text{CH}(\text{CH}_3)\text{NHCH}_2\text{CH}_2\text{Ad}$), 2.70-2.60 (m, 1H, $-\text{CH}_2\text{CH}_2\text{Ad}$), 2.55-2.45 (m, 1H, $-\text{CH}_2\text{CH}_2\text{Ad}$), 1.94 (bs, 3H, $-\text{Ad}$), 1.75-1.55 (m, 6H, $-\text{Ad}$), 1.53-1.47 (m, 6H, $-\text{Ad}$), 1.47-1.40 (m, 9H, $-\text{NHCOO-C}(\text{CH}_3)_3$), 1.30-1.15 (m, 2H, $-\text{CH}_2\text{Ad}$), 1.04 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 156.24, 79.02; 52.83; 45.54; 45.08; 42.68; 41.47, 37.14; 31.90; 28.67; 28.40; 18.52. HRMS: m/z 337.28422 corresponds to molecular formula $\text{C}_{20}\text{H}_{36}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: - 2.17).

***tert*-Butyl (4-([2-(1-adamantyl)ethyl]amino)pentyl)carbamate (S24).**

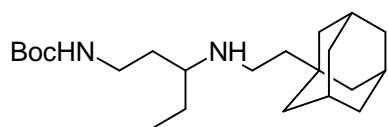


Compound **S24** was prepared by method G from mono-*N*-Boc-protected amine **S7** (360 mg, 1.78 mmol) and 1-adamantylacetaldehyde (317 mg, 1.78 mmol) using

$\text{Ti}(\text{OiPr})_4$ (632 μL , 2.13 mmol) and NaBH_4 (135 mg, 3.56 mmol) and was obtained after dry-flash chromatography: SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5$, as colorless oil (499 mg, 77%). IR (ATR): 3343w, 2967w, 2898s, 2844m, 1690s, 1520m, 1449m, 1389w, 1363m, 1345w, 1269m, 1248m, 1169s, 1041w, 1017w, 989w, 967w, 920w, 867w, 812w, 779w, 523w, 504w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 4.84 (bs, H-N), 3.20-3.05 (m, 2H, $-\text{CH}_2\text{NHBoc}$), 2.70-2.55 (m, 2H, $-\text{CH}(\text{CH}_3)\text{NHCH}_2\text{CH}_2\text{Ad}$, $-\text{CH}_2\text{CH}_2\text{Ad}$), 2.65-2.50 (m, 1H, $-\text{CH}_2\text{CH}_2\text{Ad}$), 1.94 (bs, 3H, $-\text{Ad}$), 1.75-1.55 (m, 6H, $-\text{Ad}$), 1.53-1.47 (m, 6H, $-\text{Ad}$), 1.47-1.40 (m, 9H, $-\text{NHCOO-C}(\text{CH}_3)_3$), 1.30-1.15 (m, 2H, $-\text{CH}_2\text{Ad}$), 1.04 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 156.24, 79.02; 52.83; 45.54; 45.08; 42.68; 41.47, 37.14; 31.90; 28.67; 28.40; 18.52. HRMS: m/z 353.30038 corresponds to molecular formula $\text{C}_{23}\text{H}_{40}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: - 2.17).

$\text{CH}_2\text{CH}_2\text{Ad}$), 1.94 (bs, 3H, -Ad), 1.75-1.60 (m, 6H, -Ad), 1.60-1.30 (m, 18H, -Ad, - $\text{CH}_2\text{CH}_2\text{NHBoc}$, - $\text{CH}_2\text{CH}_2\text{CH}_2\text{NHBoc}$, - $\text{NHCOO-C}(\text{CH}_3)_3$), 1.40-1.30 (m, 1H, - $\text{CH}_2\text{CH}_2\text{CH}_2\text{NHBoc}$), 1.30-1.20 (m, 2H, - CH_2Ad), 1.04 (d, 3H, $J = 6.2$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 156.00; 78.95; 53.12; 44.93; 42.66; 41.52; 40.78; 37.15; 34.31; 31.90; 28.68; 28.43; 26.51; 20.32. HRMS: m/z 365.31654 corresponds to molecular formula $\text{C}_{22}\text{H}_{40}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: + 0.78).

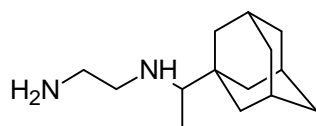
tert-Butyl (3-{[2-(1-adamantyl)ethyl]amino}pentyl)carbamate (S25).



Compound **S25** was prepared by method G from mono-*N*-

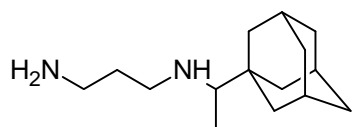
Boc-protected amine **S8** (350 mg, 1.73 mmol) and 1-adamantylacetaldehyde (308 mg, 1.73 mmol) using $\text{Ti}(\text{OiPr})_4$ (616 μL , 2.08 mmol) and NaBH_4 (131 mg, 3.46 mmol) and was obtained after dry-flash chromatography: SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5$, as colorless oil (479 mg, 76%). IR (ATR): 3330m, 2964m, 2899s, 2845m, 1692s, 1504m, 1449m, 1389w, 1363m, 1315w, 1271m, 1248m, 1170s, 1098w, 1041w, 1022w, 993w, 965w, 918w, 869w, 812w, 780w, 758w, 691w, 681w, 667w, 654w, 618w, 600w, 579w, 557w, 548w, 540w, 503w, 520w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 5.74 (bs, H-NBoc), 3.30-3.20 (m, 1H, - CH_2NHBoc), 3.20-3.10 (m, 1H, - CH_2NHBoc), 2.65-2.55 (m, 1H, - $\text{CH}_2\text{CH}_2\text{Ad}$), 2.55-2.45 (m, 2H, - $\text{CH}_2\text{CH}_2\text{Ad}$, - $\text{CH}(\text{CH}_2\text{CH}_3)\text{NHCH}_2\text{CH}_2\text{Ad}$), 1.94 (s, 3H, -Ad), 1.75-1.60 (m, 7H, -Ad, - $\text{CH}_2\text{CH}_2\text{NHBoc}$), 1.60-1.35 (m, 18H, -Ad, - $\text{CH}_2\text{CH}_2\text{NHBoc}$, - CH_2CH_3 , - $\text{NHCOO-C}(\text{CH}_3)_3$), 1.30-1.20 (m, 2H, - $\text{CH}_2\text{CH}_2\text{Ad}$), 0.88 (t, 3H, $J = 7.5$, - CH_2CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 156.16; 78.69; 58.14; 45.02; 42.68; 40.97; 38.39; 37.16; 32.36; 31.90; 28.68; 28.47; 26.30; 10.00. HRMS: m/z 365.31603 corresponds to molecular formula $\text{C}_{22}\text{H}_{40}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: - 0.61).

***N*-[1-(1-Adamantyl)ethyl]ethane-1,2-diamine (S26).**



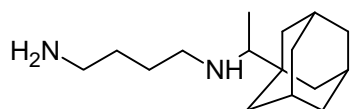
Compound **S26** was prepared using method C from **S17** (400 mg, 1.24 mmol) and was obtained after dry-flash chromatography: SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 9/1$ as a light yellow viscous oil

(239 mg, 87%). IR (ATR): 3238m, 3063w, 2968w, 2932m, 2851m, 1608w, 1570s, 1491w, 1452m, 1423m, 1384w, 1363m, 1329w, 1280w, 1251m, 1200w, 1156w, 1128w, 1084w, 941w, 903w, 869w, 842w, 818w, 796m, 770m, 700m, 682w, 643m, 621w, 598w, 561w, 534w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 2.85-2.75 (m, 2H, - CH_2NH_2 , - $\text{CH}_2\text{CH}_2\text{NH}_2$), 2.75-2.65 (m, 1H, - $\text{CH}_2\text{CH}_2\text{NH}_2$), 2.55-2.45 (m, 1H, - CH_2NH_2), 2.05-2.00 (m, 1H, - $\text{CH}(\text{CH}_3)\text{Ad}$), 1.97 (s, 3H, -Ad), 1.75-1.45 (m, 12H, -Ad), 1.31 (bs, 2H-N), 0.95 (d, 3H, $J = 6.5$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 62.31; 51.41; 42.07; 38.73; 37.37; 36.17; 28.59; 13.62. HRMS: m/z 223.21613 corresponds to molecular formula $\text{C}_{14}\text{H}_{26}\text{N}_2\text{H}^+$ (error in ppm: - 3.34).

***N*-[1-(1-Adamantyl)ethyl]propane-1,3-diamine (S27).**

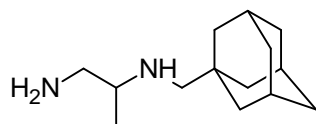
Compound **S27** was prepared using method C from **S18** (450 mg, 1.34 mmol) and was obtained after dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 9/1 as light yellow

viscous oil (266 mg, 84%). IR (ATR): 3322w, 2896s, 2844s, 2675w, 1636w, 1564m, 1444s, 1403w, 1372w, 1355m, 1345w, 1330w, 1298w, 1251w, 1149w, 1119w, 1100w, 1086w, 1064w, 1012w, 916w, 890w, 814w, 781w, 728w, 704w, 617w, 602m, 572w, 522w, 508w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 2.85-2.70 (m, 3H, -CH₂NH₂, -CH₂NHCH(CH₃)Ad), 2.55-2.40 (m, 1H, -CH₂NHCH(CH₃)Ad), 2.10-2.00 (m, 2H, -CH(CH₃)Ad), 1.97 (bs, 3H, -Ad), 1.75-1.40 (m, 14H, -CH₂CH₂NH₂, -Ad), 1.14 (bs, 2H-N and H-N), 0.94 (d, 3H, *J* = 6.5, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 62.64; 46.92; 40.76; 38.72; 37.37; 36.04; 34.18; 28.58; 13.50. HRMS: *m/z* 237.23171 corresponds to molecular formula C₁₅H₂₈N₂H⁺ (error in ppm: -3.44).

***N*-[1-(1-Adamantyl)ethyl]butane-1,4-diamine (S28).**

Compound **S28** was prepared using method C from **S19** (280 mg, 0.80 mmol) and was obtained after dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 9/1 as light yellow

viscous oil (166 mg, 83%). IR (ATR): 2897s, 2844s, 1572m, 1447s, 1374m, 1358w, 1344w, 1313m, 1248w, 1188w, 1146w, 1116m, 1104m, 1064w, 1045w, 1016w, 813w, 776w, 737w, 698w, 628w, 598w, 586w, 546w, 533w, 512w, 501w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 2.80-2.65 (m, 3H, -CH₂NH₂, -CH₂NHCH(CH₃)Ad), 2.50-2.35 (m, 1H, -CH₂NHCH(CH₃)Ad), 2.10-2.00 (m, 1H, -CH(CH₃)Ad), 1.97 (bs, 3H, -Ad), 1.75-1.45 (m, 16H, -Ad, -CH₂CH₂NH₂, -CH₂CH₂CH₂NH₂), 1.42 (bs, H-N and 2H-N), 0.94 (d, 3H, *J* = 6.5, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 62.41; 48.71; 42.03; 38.59; 37.24; 35.88; 31.51; 28.46; 27.59; 13.41. HRMS: *m/z* 251.24786 corresponds to molecular formula C₁₆H₃₀N₂H⁺ (error in ppm: -1.24).

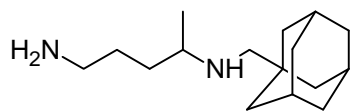
***N*²-(1-Adamantylmethyl)propane-1,2-diamine (S29).**

Compound **S29** was prepared using method C from **S20** (500 mg, 1.55 mmol) and was obtained after dry-flash chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 9/1 as light yellow viscous oil

(299 mg, 87%). IR (ATR): 2895s, 2844s, 1449m, 1370w, 1344w, 1315w, 1222w, 1152w, 1087w, 1052w, 998w, 987w, 951w, 932w, 853w, 813w, 778w, 734m, 625w, 600w, 586w, 542w, 521w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 2.75-2.65 (m, 1H, -CH₂NH₂), 2.55-2.45 (m, 2H, -CH₂NH₂, NH₂CH(CH₃)-), 2.34 (ABq, *H_A*, *J* = 11.4, -CH₂Ad), 2.12 (ABq, *H_B*, *J* = 11.4, -CH₂Ad), 1.96 (s, 3H, -Ad), 1.75-1.60 (m, 6H, -Ad), 1.55-1.45 (m, 6H, -Ad), 1.00 (d, 3H, *J* = 6.2, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 60.16; 56.12; 47.41; 40.94; 37.30; 33.45;

28.52; 18.50. HRMS: m/z 223.21628 corresponds to molecular formula $C_{14}H_{26}N_2H^+$ (error in ppm: - 2.65).

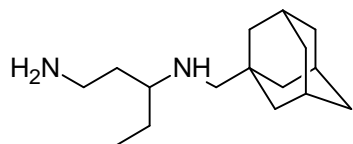
N^4 -(1-Adamantylmethyl)pentane-1,4-diamine (S30).



Compound **S30** was prepared by method C from **S21** (300 mg, 0.85 mmol) and was obtained after dry-flash chromatography: SiO_2 , eluent: $CH_2Cl_2/MeOH(NH_3sat.) = 9/1$ as light yellow

viscous oil (214 mg, 90%). IR (ATR): 3280w, 2895s, 2843s, 2675w, 2150w, 1577m, 1447m, 1369w, 1339w, 1311m, 1220w, 1150m, 1085m, 993w, 950w, 808m, 719m, 610w, 549w, 523w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 2.75-2.65 (m, 2H, $-CH_2NH_2$), 2.60-2.55 (m, 1H, $-CH(CH_3)NHCH_2Ad$), 2.28 (ABq, H_A , $J = 11.4$, $-CH_2Ad$), 2.17 (ABq, H_B , $J = 11.4$, $-CH_2Ad$), 1.96 (bs, 3H, $-Ad$), 1.75-1.60 (m, 6H, $-Ad$), 1.55-1.50 (m, 6H, $-Ad$), 1.50-1.40 (m, 3H, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$), 1.35-1.25 (m, 1H, $-CH_2CH_2CH_2NH_2$), 1.02 (d, 3H, $J = 6.4$, CH_3). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 60.29; 54.00; 42.53; 40.96; 37.27; 34.33; 33.29; 30.45; 28.50; 20.58. HRMS: m/z 251.24818 corresponds to molecular formula $C_{16}H_{30}N_2H^+$ (error in ppm: - 4.72).

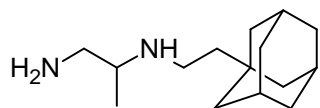
N^3 -(1-Adamantylmethyl)pentane-1,3-diamine (S31).



Compound **S31** was prepared from **S22** (350 mg, 1.00 mmol) by method Cand was obtained after dry-flash chromatography: SiO_2 , eluent: $CH_2Cl_2/MeOH(NH_3sat.) = 9/1$ as a yellow viscous oil (223 mg, 89%). IR (ATR): 3311m, 2903s, 2847s, 2678w, 2235w,

1644m, 1559m, 1448m, 1402w, 1367m, 1306w, 1223w, 1169w, 1134w, 1099w, 993w, 813w, 727w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 2.85-2.70 (m, 2H, $-CH_2NH_2$), 2.50-2.35 (m, 1H, $-CH(CH_2CH_3)NHCH_2Ad$), 2.25 (ABq, H_A , $J = 11.3$, $-CH_2Ad$), 2.15 (ABq, H_B , $J = 11.3$, $-CH_2Ad$), 1.95 (s, 3H, $-Ad$), 1.75-1.60 (m, 6H, $-Ad$), 1.60-1.45 (m, 8H, $-CH_2CH_2NH_2$, $-Ad$), 1.45-1.35 (m, 2H, $-CH_2CH_3$), 0.87 (t, 3H, $J = 7.5$, $-CH_2CH_3$). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 59.65; 58.25; 40.93; 39.77; 37.29; 33.44; 28.51; 26.66; 9.92. HRMS: m/z 251.24754 corresponds to molecular formula $C_{16}H_{30}N_2H^+$ (error in ppm: - 2.51).

N^2 -[2-(1-adamantyl)ethyl]propane-1,2-diamine (S32).

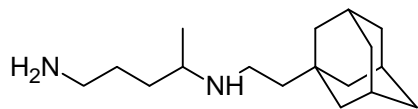


Compound **S32** was prepared from **S23** (350 mg, 1.04 mmol) by method C and was obtained after dry-flash chromatography: SiO_2 , eluent: $CH_2Cl_2/MeOH(NH_3sat.) = 9/1$ as a yellow viscous oil (226

mg, 92%). IR (ATR): 2897s, 2844s, 1495w, 1449m, 1370w, 1345w, 1316w, 1265w, 1183w, 1150w, 1099m, 812w, 728s, 695m, 631w, 617w, 600w, 590w, 530w, 522w, 506w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 2.75-2.67 (m, 2H, $-CH_2NH_2$, $-CH_2CH_2Ad$), 2.67-2.57 (m, 1H, $-CH(CH_3)NHCH_2CH_2Ad$), 2.57-2.45 (m, 2H, $-CH_2NH_2$, $-CH_2CH_2Ad$), 1.94 (bs, 3H, $-Ad$), 1.75-1.60 (m, 6H, $-Ad$), 1.55-1.45 (m, 6H, $-Ad$), 1.35-1.15 (m, 2H, $-CH_2Ad$), 1.03 (d, 3H, $J =$

6.2, CH_3). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 55.56; 47.61; 45.13; 42.70; 41.66; 37.17; 31.90; 28.70; 18.31. HRMS: m/z 237.23151 corresponds to molecular formula $C_{15}H_{28}N_2H^+$ (error in ppm: - 4.29).

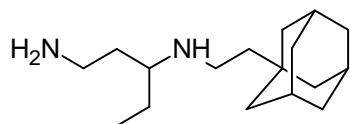
***N*⁴-[2-(1-Adamantyl)ethyl]pentane-1,4-diamine (S33).**



Compound **S33** was prepared from **S24** (300 mg, 0.82 mmol) by method C and was obtained after dry-flash chromatography: SiO_2 , eluent: $CH_2Cl_2/MeOH(NH_3sat.) = 9/1$ as a yellow viscous oil (198 mg, 91%). IR (ATR): 2896s, 2843s, 2656w, 1572m, 1448m,

1372w, 1314m, 1141w, 1098w, 988w, 967w, 922w, 879w, 812w, 703w, 619w, 591w, 572w, 533w, 512w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 2.75-2.65 (m, 2H, $-CH_2NH_2$), 2.65-2.60 (m, 2H, $-CH(CH_3)NHCH_2CH_2Ad$, $-CH_2CH_2Ad$), 2.60-2.50 (m, 1H, $-CH_2CH_2Ad$), 1.94 (bs, 3H, $-Ad$), 1.75-1.60 (m, 6H, $-Ad$), 1.55-1.40 (m, 9H, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-Ad$), 1.35-1.25 (m, 1H, $-CH_2CH_2CH_2NH_2$), 1.25-1.20 (m, 2H, $-CH_2Ad$), 1.05 (d, 3H, $J = 6.2$, CH_3). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 53.37; 45.07; 42.67; 42.50; 41.58; 37.16; 34.45; 31.89; 30.37; 28.68; 20.40. HRMS: m/z 256.26328 corresponds to molecular formula $C_{17}H_{32}N_2H^+$ (error in ppm: - 2.05).

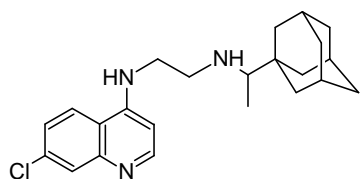
***N*³-[2-(1-Adamantyl)ethyl]pentane-1,3-diamine(S34).**



Compound **S34** was prepared from **S25** (250 mg, 0.74 mmol) by method C and was obtained after dry-flash chromatography (SiO_2 , eluent: $CH_2Cl_2/MeOH(NH_3sat.) = 9/1$) as a yellow viscous oil (147 mg, 75%). IR (ATR): 2957w, 2905s, 2844s, 1574m, 1448s, 1379w, 1344w, 1314m,

1099m, 812m, 775w, 722w, 700w, 680w, 620w, 608w, 599w, 590w, 582w, 501w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 2.85-2.70 (m, 2H, $-CH_2NH_2$), 2.70-2.50 (m, 3H, $-CH(CH_2CH_3)NHCH_2CH_2Ad$, $-CH_2CH_2Ad$), 1.94 (s, 3H, $-Ad$), 1.75-1.60 (m, 6H, $-Ad$), 1.60-1.50 (m, 8H, $-CH_2CH_2NH_2$, $-Ad$), 1.50-1.40 (m, 2H, $-CH_2CH_3$), 1.30-1.20 (m, 2H, $-CH_2Ad$), 0.87 (t, 3H, $J = 7.5$, $-CH_2CH_3$). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 57.63; 45.08; 42.68; 41.31; 39.52; 37.42; 37.17; 31.91; 28.69; 26.48; 9.87. HRMS: m/z 265.26347 corresponds to molecular formula $C_{17}H_{32}N_2H^+$ (error in ppm: - 1.33).

***N*-[1-(1-Adamantyl)ethyl]-*N'*-(7-chloroquinolin-4-yl)ethane-1,2-diamine (11).**

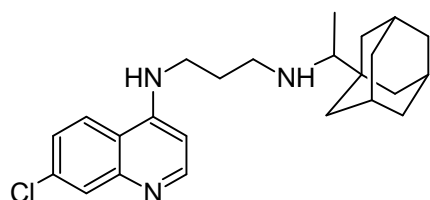


Amine **S26** (180 mg, 0.81 mmol) and 4,7-dichloroquinoline (481 mg, 2.43 mmol) were mixed in a MW cuvette under Ar. Reaction mixture was subjected to MW irradiation using a *Biotage Initiator 2.5 apparatus*, 4h, 130 °C. Compound **11** was obtained

after multiple chromatography dry-flash (SiO_2 , eluent: $CH_2Cl_2/MeOH(NH_3sat.) = 95/5$), and flash chromatography (*Biotage SP1 NH* column, eluent: Hex/EtOAc = 7/3) as colorless powder, softens at 96-98 °C. Yield: 214 mg (69%). IR (ATR): 3254w, 2898s, 2844m, 1610w,

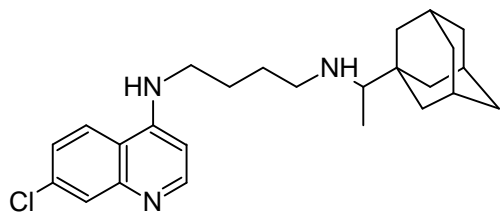
1577s, 1524m, 1446m, 1367m, 1327m, 1281w, 1240w, 1197w, 1159w, 1136m, 1101m, 1077m, 1014w, 968w, 921w, 876m, 846w, 804m, 761w, 736m, 702w, 643w, 623w, 600w, 542w, 527w, 506w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 8.53 (d, $J = 5.0$, H-C(2)), 7.95 (d, $J = 2.0$, H-C(8)), 7.72 (d, $J = 8.5$, H-C(5)), 7.35 (dd, $J_1 = 2.0$, $J_2 = 9.0$, H-C(6)), 6.38 (d, $J = 5.5$, H-C(3)), 6.17 (bs, H-N), 3.35-3.25 (m, 1H, ArNHCH_2-), 3.25-3.15 (m, 2H, ArNHCH_2- , $\text{ArNHCH}_2\text{CH}_2-$), 2.90-2.80 (m, 1H, $\text{ArNHCH}_2\text{CH}_2-$), 2.15-2.05 (m, 1H, $-\text{CH}(\text{CH}_3)\text{Ad}$), 1.98 (m, 3H, $-\text{Ad}$), 1.80-1.45 (m, 12H, $-\text{Ad}$), 1.03 (d, 3H, $J = 6.5$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 152.11; 150.00; 149.15; 134.73; 128.73; 125.13; 121.19; 117.46; 99.26; 61.64; 45.96; 42.14; 38.89; 37.31; 36.32; 28.52; 13.62. HRMS: m/z 384.22025 corresponds to molecular formula $\text{C}_{23}\text{H}_{30}\text{ClN}_3\text{H}^+$ (error in ppm: + 0.39). Anal. ($\text{C}_{23}\text{H}_{30}\text{ClN}_3$) Calcd: C, 71.95; H, 7.88; N, 10.94. Found: C, 71.76; H, 8.15; N, 10.88. HPLC purity ($\lambda = 330$ nm): method A: RT 7.986 min, area 99.01%; method B: RT 9.475 min, area 98.26%.

N-[1-(1-Adamantyl)ethyl]-N'-(7-chloroquinolin-4-yl)propane-1,3-diamine (22).



Amine **S27** (230 mg, 0.97 mmol) and 4,7-dichloroquinoline (385 mg, 1.95 mmol) were mixed in a MW cuvette under Ar. The reaction mixture was subjected to MW irradiation using a *Biotage Initiator 2.5 apparatus*, 4h, 130 °C. Compound **22** was obtained after multiple chromatography: dry-flash(SiO_2 , eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5$) and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 75/25) as colorless powder, softens at 90-92 °C. Yield: 174 mg (74%). IR(ATR): 3243m, 3067w, 2897s, 2844m, 1610w, 1583s, 1534m, 1447m, 1427m, 1365m, 1344m, 1328m, 1281w, 1241w, 1211w, 1158w, 1137m, 1097w, 1075m, 1042w, 1015w, 995w, 970w, 899m, 876m, 852m, 801m, 763m, 703w, 673w, 642w, 631w, 620w, 598w, 570w, 554w, 542w, 532w, 515w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 8.50 (d, $J = 5.4$, H-C(2)), 7.92 (d, $J = 2.2$, H-C(8)), 7.81 (d, $J = 8.9$, H-C(5)), 7.40 (bs, H-N), 7.26 (dd, $J_1 = 2.2$, $J_2 = 8.8$, H-C(6)), 6.32 (d, $J = 5.4$, H-C(3)), 3.50-3.40 (m, 1H, ArNHCH_2-), 3.35-3.25 (m, 1H, ArNHCH_2-), 2.95-2.85 (m, 1H, $\text{ArNHCH}_2\text{CH}_2\text{CH}_2-$), 2.85-2.80 (m, 1H, $\text{ArNHCH}_2\text{CH}_2\text{CH}_2-$), 2.10-2.05 (m, 1H, $-\text{CH}(\text{CH}_3)\text{Ad}$), 2.03 (m, 3H, $-\text{Ad}$), 2.00-1.85 (m, 2H, $\text{ArNHCH}_2\text{CH}_2-$), 1.80-1.55 (m, 12H, $-\text{Ad}$), 0.98 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 152.19; 150.42; 149.19; 134.57; 128.59; 124.52; 122.38; 117.49; 98.41; 63.84; 48.97; 44.22; 38.88; 37.23; 36.00; 28.51; 28.24; 13.74. HRMS: m/z 398.23424 corresponds to molecular formula $\text{C}_{24}\text{H}_{32}\text{ClN}_3\text{H}^+$ (error in ppm: - 3.80). Anal. ($\text{C}_{24}\text{H}_{32}\text{ClN}_3$) Calcd: C, 72.43; H, 8.10; N, 10.56. Found: C, 72.14; H, 8.27; N, 10.42. HPLC purity ($\lambda = 330$ nm): method A: RT 8.586 min, area 99.59%; method B: RT 9.697 min, area 98.93%.

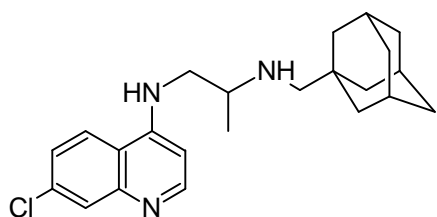
N-[1-(1-Adamantyl)ethyl]-N'-(7-chloroquinolin-4-yl)butane-1,4-diamine (30).



Amine **S28** (263 mg, 1.05 mmol) and 4,7-dichloroquinoline (624 mg, 3.15 mmol) were mixed in a MW cuvette under Ar. The reaction mixture was subjected to MW irradiation using a *Biotage Initiator 2.5 apparatus*, 4h, 130 °C. Compound **30** was

obtained after multiple chromatography: dry-flash SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 55/45) as colorless powder, softens at 146-148 °C. Yield: 298 mg (69%). IR (ATR): 3254m, 2900m, 2844m, 2755w, 1609w, 1569s, 1536m, 1475w, 1448m, 1367m, 1344w, 1325m, 1285w, 1252w, 1228w, 1196w, 1161w, 1134m, 1116w, 1076m, 1019w, 978w, 902m, 875m, 850m, 825m, 804m, 763m, 741w, 645w, 621w, 598m, 553w, 516m cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.53 (d, *J* = 5.0, H-C(2)), 7.95 (d, *J* = 2.0, H-C(8)), 7.71 (d, *J* = 9.0, H-C(5)), 7.34 (dd, *J*₁ = 2.0, *J*₂ = 9.0, H-C(6)), 6.40 (d, *J* = 5.5, H-C(3)), 5.41 (bs, H-N), 3.40-3.25 (m, 2H, ArNHCH₂-), 2.85-2.75 (m, 1H, -CH₂NHCH(CH₃)Ad), 2.60-2.50 (m, 1H, -CH₂NHCH(CH₃)Ad), 2.15-2.05 (m, 1H, -CH₂NHCH(CH₃)Ad), 1.98 (m, 3H, -Ad), 1.90-1.80 (m, 2H, ArNHCH₂CH₂-), 1.75-1.45 (m, 14H, -Ad, ArNHCH₂CH₂CH₂-), 0.96 (d, 3H, *J* = 6.5, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 152.10; 149.75; 149.21; 134.73; 128.86; 125.05; 121.13; 117.19; 99.01; 62.28; 47.85; 43.20; 38.82; 37.33; 36.10; 28.56; 27.83; 26.34; 13.43. HRMS: *m/z* 412.24953 corresponds to molecular formula C₂₅H₃₄ClN₃H⁺ (error in ppm: -4.55). Anal.(C₂₅H₃₄ClN₃ × 1/2 H₂O) Calcd: C, 71.32; H, 8.38; N, 9.98. Found: C, 71.16; H, 7.88; N, 10.16. HPLC purity (λ = 330 nm): method A: RT 7.952 min, area 96.65%; method B: RT 9.593 min, area 97.85%.

N²-(1-Adamantylmethyl)-N¹-(7-chloroquinolin-4-yl)propane-1,2-diamine (10).

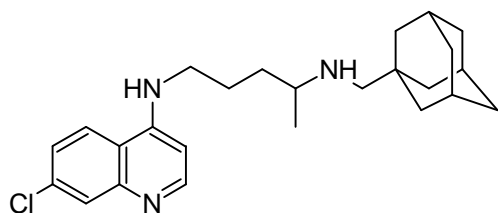


Compound **10** was prepared from amine **S29** (150 mg, 0.67 mmol) and 4,7-dichloroquinoline (111 mg, 0.56 mmol) in phenol (790 mg, 8.40 mmol) by method F and was obtained after multiple chromatography: dry-flash: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash

chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3) as colorless foam, softens at 148-150 °C. Yield: 149 mg (71%). IR (ATR): 3362w, 3335w, 3032w, 2958w, 2905s, 2842m, 1605w, 1578s, 1562s, 1520m, 1472m, 1444m, 1361w, 1345w, 1333w, 1295w, 1273w, 1246w, 1207w, 1183w, 1155m, 1136w, 1098w, 1083m, 1018w, 998w, 986w, 964w, 940w, 929w, 899m, 848m, 806m, 762m, 748m, 672w, 647w, 560m, 546w, 523m cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.52 (d, *J* = 5.0, H-C(2)), 7.95 (d, *J* = 2.0, H-C(8)), 7.72 (d, *J* = 9.0, H-C(5)), 7.35 (dd, *J*₁ = 2.0, *J*₂ = 9.0, H-C(6)), 6.34 (d, *J* = 5.5, H-C(3)), 6.25 (bs, H-NAr), 3.35-3.25 (m, 1H, ArNHCH₂-), 3.05-2.95 (m, 1H, ArNHCH₂CH(CH₃)-), 2.95-2.85 (m, 1H,

ArNHCH₂-), 2.43 (ABq, *H_A*, *J* = 11.5, -CH₂Ad), 2.14 (ABq, *H_B*, *J* = 11.5, -CH₂Ad), 1.99 (s, 3H, -Ad), 1.80-1.45 (m, 12H, -Ad), 1.22 (d, 3H, *J* = 6.5, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 152.14; 150.02; 149.18; 134.70; 128.74; 125.06; 121.24; 117.51; 99.20; 59.07; 52.16; 46.73; 40.94; 37.21; 33.47; 28.42; 19.54. HRMS: *m/z* 384.21824 corresponds to molecular formula C₂₃H₃₀ClN₃H⁺ (error in ppm: - 4.85). Anal.(C₂₃H₃₀ClN₃) Calcd: C, 71.95; H, 7.88; N, 10.94. Found: C, 71.76; H, 8.12; N, 11.12. HPLC purity (λ = 330 nm): method A: RT 8.000 min, area 99.64%; method B: RT 9.433 min, area 99.22%.

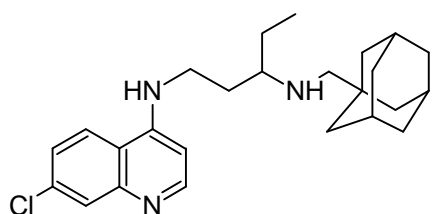
***N*⁴-(1-Adamantylmethyl)-*N*¹-(7-chloroquinolin-4-yl)pentane-1,4-diamine (31).**



Compound **31** was prepared from amine **S30** (239 mg, 0.95 mmol) and 4,7-dichloroquinoline (157 mg, 0.79 mmol) in phenol (1115 mg, 11.85 mmol) by method F and was obtained after multiple chromatography: dry-flash SiO₂, eluent:

CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 75/25) as colorless foam softens at 148-150 °C. Yield: 250 mg (64%). IR (ATR): 3200w, 3061w, 3007w, 2896s, 2841s, 2003w, 1609w, 1576s, 1548m, 1488w, 1449m, 1430m, 1366m, 1333w, 1302w, 1280w, 1250w, 1213m, 1150w, 1135m, 1098w, 1078w, 1018w, 979w, 951w, 897w, 882w, 868w, 848w, 816w, 800w, 764w, 748w, 724w, 714w, 667w, 643w, 620w, 599w, 573w, 557w, 505w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.52 (d, *J* = 5.5, H-C(2)), 7.93 (d, *J* = 2.0, H-C(8)), 7.72 (d, *J* = 8.5, H-C(5)), 7.34 (dd, *J*₁ = 2.5, *J*₂ = 9.0, H-C(6)), 6.39 (d, *J* = 5.5, H-C(3)), 5.66 (bs, H-NAr), 3.40-3.30 (m, 1H, ArNHCH₂-), 3.30-3.20 (m, 1H, ArNHCH₂-), 2.75-2.65 (m, 1H, -CH(CH₃)NHCH₂Ad), 2.29 (ABq, *H_A*, *J* = 11.3, -CH₂Ad), 2.20 (ABq, *H_B*, *J* = 11.3, -CH₂Ad), 1.97 (m, 3H, -Ad), 1.90-1.75 (m, 16H, ArNHCH₂CH₂-), 1.75-1.60 (m, 6H, -Ad), 1.60-1.45 (m, 8H, ArNHCH₂CH₂CH₂-, -Ad), 1.07 (d, 3H, *J* = 6.0, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 152.13; 149.83; 149.24; 134.70; 128.86; 125.01; 121.24; 117.28; 98.97; 59.40; 52.98; 43.50; 41.04; 37.23; 34.23; 33.34; 28.46; 24.90; 20.71. HRMS: *m/z*412.24972 corresponds to molecular formula C₂₅H₃₄ClN₃H⁺ (error in ppm: - 4.08). Anal. (C₂₅H₃₄ClN₃) Calcd: C, 72.88; H, 8.32; N, 10.20. Found: C, 72.68; H, 8.53; N, 9.95. HPLC purity (λ = 330 nm): method A: RT 8.054 min, area 97.97%; method B: RT 9.525 min, area 99.50%.

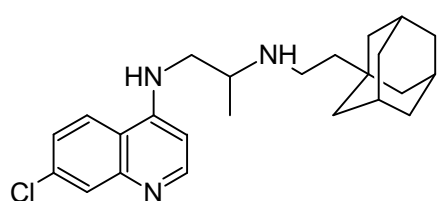
***N*³-(1-Adamantylmethyl)-*N*¹-(7-chloroquinolin-4-yl)pentane-1,3-diamine (28).**



Compound **28** was prepared from amine **S28** (350 mg, 1.40 mmol) and 4,7-dichloroquinoline (231 mg, 1.17 mmol) in phenol (165 mg, 17.55 mmol) by method F and was

obtained after multiple chromatography: dry-flash SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 65/35) as colorless foam, softens at 121-123 °C. Yield 409 mg (71%). IR(ATR): 3254m, 2897s, 2844m, 1610w, 1584s, 1537m, 1449m, 1428w, 1366m, 1329m, 1281w, 1243w, 1168w, 1140m, 1103w, 1077m, 902w, 876w, 849m, 805m, 765w, 737m, 701w, 644w, 623w, 606w, 687w, 673w, 643w, 514w, 506w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.50 (d, *J* = 5.2, H-C(2)), 7.93 (bs, H-C(8)), 7.91 (d, *J* = 8.9, H-C(5)), 7.54 (bs, H-NAr), 7.30-7.20 (m, H-C(6)), 6.33 (d, *J* = 5.4, H-C(3)), 3.45-3.38 (m, 1H, ArNHCH₂-), 3.38-3.30 (m, 1H, ArNHCH₂-), 2.70-2.60 (m, 1H, ArNHCH₂CH₂CH(CH₂CH₃)-), 2.41 (ABq, *H_A*, *J* = 11.4, -CH₂Ad), 2.39 (ABq, *H_B*, *J* = 11.4, -CH₂Ad), 2.05-1.95 (m, 8H, -Ad, ArNHCH₂CH₂-), 1.85-1.45 (m, 16H, -Ad, ArNHCH₂CH₂-, -CH₂CH₃), 0.94 (t, 3H, *J* = 7.4, -CH₂CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 152.17, 150.49, 149.17, 134.56, 128.54, 124.50, 122.42, 117.53, 98.48, 60.67; 60.32; 41.79; 41.22; 37.17; 33.38; 29.65; 28.43; 25.84; 10.38. HRMS: *m/z* 412.25061 corresponds to molecular formula C₂₅H₃₄ClN₃H⁺ (error in ppm: -1.92). Anal. (C₂₅H₃₄ClN₃) Calcd: C, 72.88; H, 8.32; N, 10.20. Found: C, 72.50; H, 7.97; N, 10.06. HPLC purity (λ = 330 nm): method A: RT 9.632 min, area 96.33%; method B: RT 9.550 min, area 95.41%;

N²-[2-(1-Adamantyl)ethyl]-N¹-(7-chloroquinolin-4-yl)propane-1,2-diamine (34).

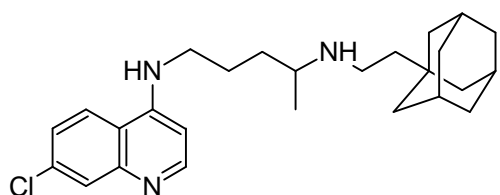


Compound **34** was prepared from amine **S32** (140 mg, 0.59 mmol) and 4,7-dichloroquinoline (97 mg, 0.49 mmol) in phenol (692 mg, 7.35 mmol) by method F and was

obtained after multiple chromatography: dry-flash SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 1/1) as colorless powder, softens at 134-136 °C. Yield: 174 mg (74%). IR (ATR): 3245w, 2895s, 2842m, 1737m, 1670w, 1566s, 1489w, 1449m, 1427m, 1367m, 1331w, 1304w, 1284w, 1238m, 1202w, 1156w, 1136m, 1076m, 1046m, 989w, 966w, 897w, 869w, 843m, 804m, 769m, 704w, 646w, 622w, 594w, 570w, 544w, 524w, 517w, 509w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.52 (d, *J* = 5.3, H-C(2)), 7.95 (d, *J* = 2.1, H-C(8)), 7.70 (d, *J* = 8.9, H-C(5)), 7.36 (dd, *J₁* = 2.2, *J₂* = 8.9, H-C(6)), 6.36 (d, *J* = 5.4, H-C(3)), 6.01 (bs, H-NAr), 3.35-3.25 (m, 1H, ArNHCH₂CH(CH₃)-), 3.15-3.05 (m, 1H, ArNHCH₂CH(CH₃)-), 3.05-2.95 (m, 1H, ArNHCH₂CH(CH₃)-), 2.80-2.70 (m, 1H, -NHCH₂CH₂Ad), 2.65-2.55 (m, 1H, -NHCH₂CH₂Ad), 1.94 (bs, 3H, -Ad), 1.75-1.55 (m, 6H, -Ad), 1.55-1.45 (m, 6H, -Ad), 1.35-1.25 (m, 3H, -NHCH₂CH₂Ad, H-N-), 1.22 (d, 3H, *J* = 6.0, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 152.12; 150.01; 149.19; 134.75; 128.76; 125.14; 121.25; 117.47; 99.20; 51.74; 47.22; 45.24; 42.77; 41.27; 37.10; 32.00; 28.64; 19.30. HRMS: *m/z* 398.23395 corresponds to molecular formula C₂₄H₃₂ClN₃H⁺ (error in ppm: -4.53). Anal. (C₂₄H₃₂ClN₃) Calcd: C, 72.43;

H, 8.10; N, 10.56. Found: C, 71.98; H, 8.49; N, 10.59. HPLC purity ($\lambda = 330$ nm): method A: RT 8.017 min, area 99.00%; method B: RT 9.696 min, area 98.87%.

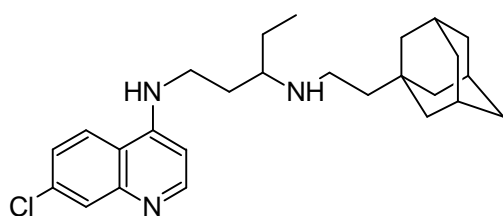
***N*⁴-[2-(1-Adamantyl)ethyl]-*N*¹-(7-chloroquinolin-4-yl)pentane-1,4-diamine (43).**



Compound **43** was prepared from amine **S33**(145 mg, 0.55 mmol) and 4,7-dichloroquinoline (91 mg, 0.46 mmol) in phenol (649 mg, 6.90 mmol) by method F was obtained after multiple chromatography: dry-

flash SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3) as colorless powder, softens at 140-143 °C. Yield: 157 mg, (67%). IR (ATR): 3252m, 3063w, 2898s, 2844s, 2017s, 1610w, 1587s, 1539m, 1449m, 1429w, 1367m, 1330m, 1279w, 1248w, 1204w, 1135m, 1098w, 1078w, 890w, 877w, 853w, 804w, 764w, 737w, 701w, 692w, 668w, 659w, 643w, 619w, 602w, 582w, 563w, 552w, 542w, 529w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃): 8.52 (d, *J* = 5.4, H-C(2)), 7.94 (d, *J* = 2.2, H-C(8)), 7.70 (d, *J* = 9.0, H-C(5)), 7.34 (dd, *J*₁ = 2.2, *J*₂ = 8.9, H-C(6)), 6.38 (d, *J* = 5.4, H-C(3)), 5.87 (bs, H-NAr), 3.40-3.20 (m, 2H, ArNHCH₂-), 2.80-2.70 (m, 1H, -CH(CH₃)NHCH₂CH₂Ad), 2.70-2.60 (m, 1H, -CH₂CH₂Ad), 2.60-2.50 (m, 1H, -CH₂CH₂Ad), 1.93 (m, 3H, -Ad), 1.90-1.75 (m, 2H, ArNHCH₂CH₂-), 1.75-1.52 (m, 8H, ArNHCH₂CH₂CH₂-, -Ad), 1.48 (m, 6H, -Ad), 1.35-1.20 (m, 2H, -CH₂Ad), 1.25 (d, 3H, *J* = 5.0, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 152.12; 149.93; 149.25; 134.69; 128.81; 125.01; 121.34; 117.33; 98.93; 52.84; 45.09; 43.56; 42.68; 41.35; 37.12; 34.70; 31.90; 28.65; 24.93; 20.50. HRMS: *m/z*426.26530 corresponds to molecular formula C₂₆H₃₆ClN₃H⁺ (error in ppm: - 4.11). Anal. (C₂₆H₃₆ClN₃ × 1/3 H₂O) Calcd: C, 72.28; H, 8.55; N, 9.73. Found: C, 72.02; H, 8.86; N, 9.40. HPLC purity ($\lambda = 330$ nm): method A: RT 8.089 min, area 99.50%; method B: RT 9.746 min, area 96.70%.

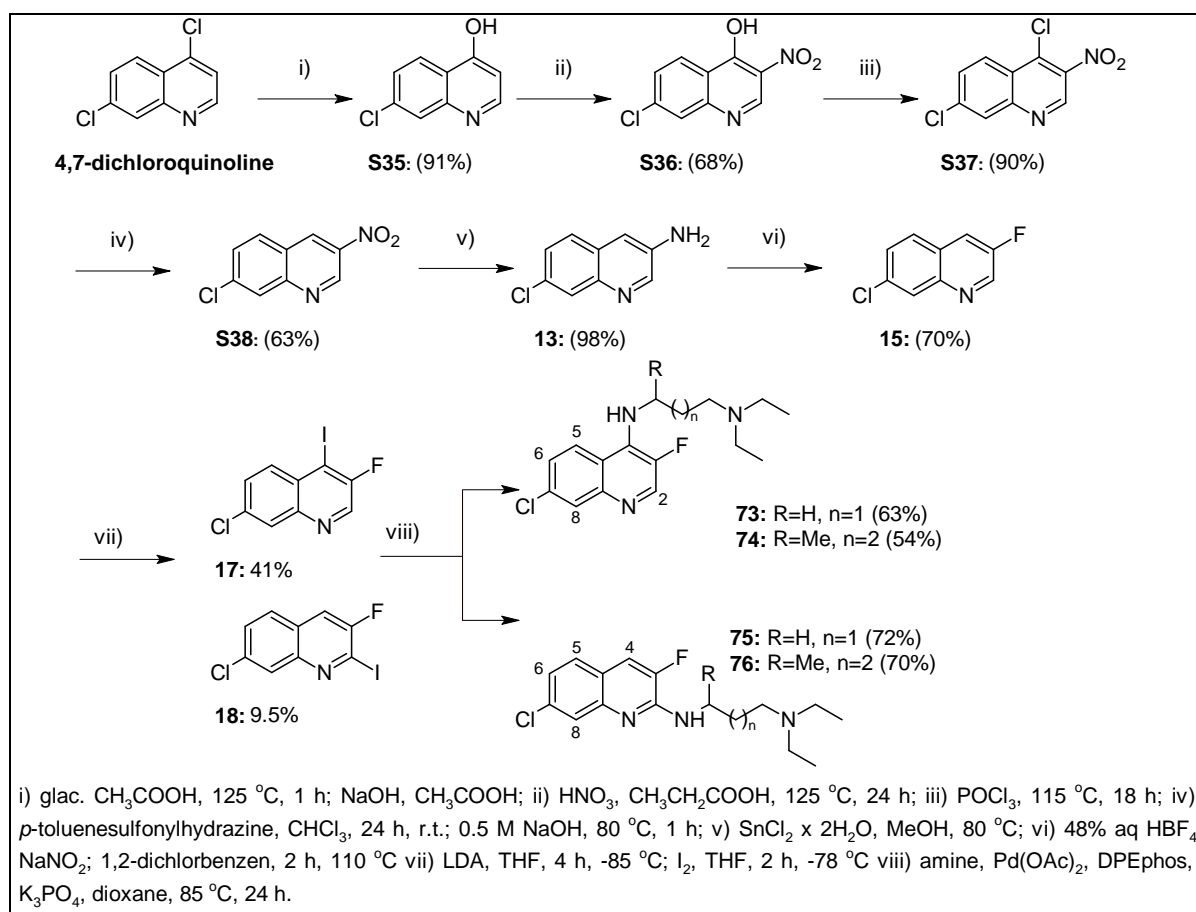
***N*³-[2-(1-Adamantyl)ethyl]-*N*¹-(7-chloroquinolin-4-yl)butane-1,3-diamine (41).**



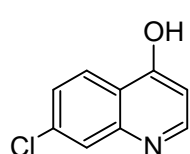
Compound **41** was prepared from amine linker **S34**(123 mg, 0.47 mmol) and 4,7-dichloroquinoline (77 mg, 0.39 mmol) in phenol (550 mg, 5.85 mmol) by method F and was obtained after multiple chromatography: dry-flash SiO₂, eluent:

CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 65/35) as colorless foam, softens at 131-134 °C. Yield: 139 mg (70%). IR (ATR): 3213w, 2897s, 2843m, 1738w, 1610w, 1578s, 1537m, 1448m, 1429w, 1365m, 1329m, 1282w, 1240w, 1218w, 1168w, 1140m, 1098w, 1077w, 1047w, 990w, 972w, 906w, 876w, 850w, 801m, 765w, 735w, 641w, 582w, 538w, 513w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.48 (d, *J* = 5.4, H-C(2)), 8.42 (bs, H-N), 7.95-7.90 (m, H-C(8)), 7.73 (d, *J* = 8.9,

H-C(5)), 7.28 (dd, $J_1 = 8.9$, $J_2 = 2.2$, H-C(6)), 6.27 (d, $J = 5.4$, H-C(3)), 3.50-3.35 (m, 1H, ArNHCH₂-), 3.35-3.25 (m, 1H, ArNHCH₂-), 2.80-2.70 (m, 2H, -(CH₂CH₃)CH-, -CH₂CH₂Ad), 2.70-2.60 (m, 1H, -CH₂CH₂Ad), 2.00-1.90 (m, 4H, -Ad, ArCH₂CH₂-), 1.75-1.55 (m, 8H, -Ad, -CH₂CH₃, ArCH₂CH₂-), 1.55-1.14 (m, 7H, -CH₂CH₃, -Ad), 1.45-1.35 (m, 1H, -CH₂Ad), 1.35-1.20 (m, 1H, -CH₂Ad), 0.94 (t, 3H, $J = 7.4$, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 151.99; 150.72; 148.96; 134.57; 128.26; 124.50; 122.55; 117.63; 98.03; 59.81; 45.37; 42.68; 42.08; 41.21; 37.04; 31.88; 29.29; 28.57; 25.96; 10.14. HRMS: m/z 426.26759 corresponds to molecular formula C₂₆H₃₆ClN₃H⁺ (error in ppm: - 1.26). Anal.(C₂₆H₃₆ClN₃ × 1/3 H₂O) Calcd: C, 72.28; H, 8.55; N, 9.73. Found: C, 72.76; H, 8.48; N, 9.70. HPLC purity ($\lambda = 330$ nm): method A: RT 7.869 min, area 95.47%; method B: RT 10.335 min, area 95.39%.



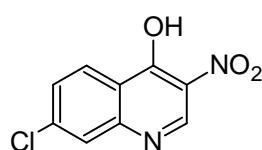
7-Chloroquinolin-4-ol (S35).²¹



A mixture of 4,7-dichloroquinoline (10 g, 50 mmol) and 6.5 equiv of glacial acetic acid (18.8 mL, 325 mmol) was refluxed at 125 °C for one hour. Dry ether was added to the cooled reaction mixture and the colorless solid was filtered off. Obtained crude product was dissolved in conc. NaOH, reaction mixture was filtered and acidified with acetic acid. Formed precipitate was collected by filtration, washed with water and dried. 7-Chloroquinolin-4-ol (S35) was obtained as colorless solid (9.07 g,

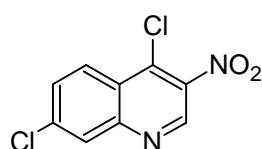
91%); m.p. = 276-279 °C (Et₂O). IR (ATR): 3228w, 3116w, 3057m, 2945m, 2877m, 2799m, 2635w, 1629m, 1599s, 1558s, 1507s, 1455s, 1414m, 1356m, 1300w, 1244w, 1206m, 1143w, 1080w, 1056w, 904w, 862m, 822m, 796s, 572m, 479m cm⁻¹. ¹H-NMR (200 MHz, DMSO, δ): 8.07 (d, *J* = 8.6, H-C(5)), 7.93 (d, *J* = 7.4, H-C(2)), 7.61 (d, *J* = 2.0, H-C(8)), 7.30 (dd, *J*₁ = 2.0, *J*₂ = 7.4, H-C(6)), 6.05 (d, *J* = 7.4, H-C(3)). ¹³C-NMR (125 MHz, CDCl₃, δ): 176.17; 141.19; 140.39; 136.04; 127.24; 124.44; 123.29; 117.73; 109.21. HRMS: *m/z*180.02100 corresponds to molecular formula C₉H₆ClNOH⁺ (error in ppm: - 0.40).

7-Chloro-3-nitroquinolin-4-ol (S36).²²



A mixture of 7-chloroquinolin-4-ol **S35** (2.00 g, 11.13 mmol) in propionic acid (20 mL) was heated to 125 °C with stirring. Nitric acid (65%, 964 μL, 13.92 mmol) was added dropwise to a stirred solution while maintaining the reaction mixture temperature at 125 °C. Upon completed addition the mixture was stirred for 18h and cooled to ambient temperature. The mixture was diluted with ethanol, and the solid was collected by filtration. 7-Chloro-3-nitroquinolin-4-ol was obtained after chromatography: SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 8/2 as light-yellow solid, softens at 199-202 °C (Hex). Yield: 1.95 g (79%). IR (ATR): 3442m, 3194w, 3156w, 3071w, 3039w, 2919m, 2852m, 1628s, 1557w, 1533m, 1499m, 1460w, 1404w, 1336s, 1267w, 1234w, 1198w, 1158w, 1113w, 1078w, 879w, 831w, 781m, 673w, 618m, 516w, 441w, 420w cm⁻¹. ¹H-NMR (500 MHz, MeOD, δ): 10.03 (s, H-C(2)), 9.03 (d, *J* = 8.4, H-C(5)), 8.55 (s, H-C(8)), 8.33 (d, *J* = 8.2, H-C(6)). ¹³C-NMR (125 MHz, CDCl₃, δ): 176.73; 152.97; 149.19; 147.29; 140.99; 137.80; 136.52; 135.63; 128.64. HRMS: *m/z*225.00527 corresponds to molecular formula C₉H₅ClN₂O₂H⁺ (error in ppm: - 3.89).

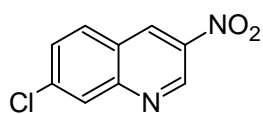
4,7-Dichloro-3-nitroquinoline (S37).



The mixture of 7-chloro-3-nitroquinolin-4-ol **S36** (1.00 g, 4.45 mmol) and POCl₃ (4 mL) was heated to 115 °C overnight. The resulting solution was cooled to ambient temperature and poured into an ice/water mixture (50 mL). A solid was collected by vacuum filtration, washed with water and dried. 4,7-Dichloro-3-nitroquinolin was obtained after dry-flash chromatography: SiO₂, eluent: Hex/EtOAc = 9/1 as light-yellow solid, softens at 153-155 °C (hexane). Yield: 974 mg, (90%). IR (ATR): 3064m, 1604m, 1581s, 1556s, 1531s, 1479m, 1438w, 1397w, 1373w, 1355s, 1333s, 1294m, 1253m, 1207m, 1168m, 1144w, 1080s, 1021m, 973w, 962w, 926m, 898m, 875m, 818s, 810s, 772m, 740w, 700m, 650w, 605m, 562w, 540m, 486w, 466w, 444m, 422m cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 9.27 (s, H-C(2)), 8.38 (d, *J* = 9.0, H-C(5)), 8.22 (d, *J* = 2.0, H-C(8)), 7.77 (dd, *J*₁ = 2.0, *J*₂ = 9.0, H-C(6)). ¹³C-NMR (125 MHz, CDCl₃, δ): 149.51; 145.68; 141.12; 139.80; 136.68; 130.76; 129.23; 127.27; 124.07. HRMS: *m/z*242.97178

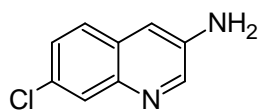
corresponds to molecular formula $C_9H_4Cl_2N_2O_2H^+$ (error in ppm: - 0.38). Anal. ($C_9H_4Cl_2N_2O_2$)
Calcd: C, 44.48; H, 1.66; N, 11.53. Found: C, 44.57; H, 1.36; N, 11.06.

7-Chloro-3-nitroquinoline (S38).²³



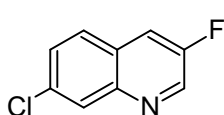
A solution of 4,7-dichloro-3-nitroquinoline **S37** (1.65 g, 6.79 mmol) and *p*-toluenesulfonylhydrazine (1.39 g, 7.47 mmol) in 60 mL of $CHCl_3$ was stirred at r.t. for 24 h and filtered to collect the cream-colored hydrazino intermediate. The precipitate was washed with cold $CHCl_3$ and air dried. The intermediate was dissolved in 0.5N NaOH (150 mL) and heated to 80 °C for 1h. The dark-red mixture was cooled to r.t., filtered, and the brown solid was washed thoroughly with water. Crude product was further purified by dry-flash chromatography: SiO_2 , eluent: Hex/EtOAc = 8/2 as light-yellow solid, softens at 136-138 °C (Hex). Yield: 892 mg (63%). IR (ATR): 3085m, 2960w, 2928w, 2857w, 2762w, 1606s, 1563m, 1539m, 1479m, 1437w, 1411w, 1380w, 1351s, 1320s, 1256w, 1219w, 1170m, 1142w, 1094w, 1064m, 975w, 933m, 914w, 875w, 831s, 787w, 770w, 740w, 677w, 633w, 544w, 521w, 470w, 446w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 9.65 (d, $J = 2.4$, H-C(2)), 9.02 (d, $J = 2.4$, H-C(4) or H-C(8)), 8.24 (d, $J = 1.2$, H-C(8) or H-C(4)), 8.00 (d, $J = 8.7$, H-C(5)), 7.70-7.60 (m, H-C(6)). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 150.34; 145.11; 140.96; 139.82; 132.02; 130.75; 130.04; 128.98; 124.38. HRMS: m/z 209.01116 corresponds to molecular formula $C_9H_5ClN_2O_2H^+$ (error in ppm: - 0.32).

7-Chloroquinolin-3-amine (13).



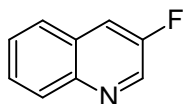
A solution of 7-chloro-3-nitroquinoline **S38** (200 mg, 0.96 mmol) and $SnCl_2$ (910 mg, 4.80 mmol) in MeOH was heated to reflux for 1 h under Ar atmosphere. Thereafter the excess MeOH was evaporated and the residue was dissolved in EtOAc and sat. $NaHCO_3$ solution was added. The resulting mixture was filtered through a celite followed by separation of organic layer via partitioning. Organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product which was purified by dry-flash chromatography: SiO_2 , eluent: Hex/EtOAc = 1/1 as yellow solid softens at 126-129 °C (Hex). Yield: 168 mg (98%). IR (ATR): 3315s, 3171s, 1637m, 1607s, 1566m, 1510w, 1489s, 1458m, 1364m, 1341m, 1282m, 1206s, 1135m, 1068m, 986m, 917m, 884m, 862m, 829m, 801m, 763m, 647m, 544w, 521w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 8.50 (d, $J = 2.8$, H-C(2)), 7.95 (d, $J = 2.0$, H-C(8)), 7.52 (d, $J = 8.9$, H-C(5)), 7.40-7.35 (m, H-C(6)), 7.20 (d, $J = 2.6$, H-C(4)), 3.96 (bs, 2H-N). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 143.94; 142.92; 139.90; 130.99; 128.08; 127.89; 127.55; 127.02; 114.64. HRMS: m/z 179.03700 corresponds to molecular formula $C_9H_7ClN_2H^+$ (error in ppm: - 0.26).

7-Chloro-3-fluoroquinoline (15).



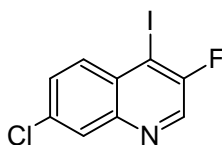
The mixture of amine **13** (500 mg, 2.80 mmol) and 48% tetrafluoroboric acid (730 μ L, 5.60 mmol) was stirred on ice bath. Solution of sodium nitrite (193 mg, 2.80 mmol) in water (1 mL) was added dropwise after 15 min. The reaction mixture was stirred as the temperature rose to r.t. The diazonium tetrafluoroborate precipitate was filtered off, washed with cold EtOH and Et₂O then dried under reduced pressure. Diazonium salt was suspended in 1,2-dichlorobenzene and the mixture was stirred for 2 h at 110 °C. 7-Chloro-3-fluoroquinoline **15** was obtained after dry-flash chromatography SiO₂, eluent: Hex/EtOAc = 9/1, as light-yellow solid, softens at 76-80 °C (Hex). Yield: 356 mg (70%). IR (ATR): 3076m, 3053m, 2957w, 2857w, 1615m, 1596s, 1565m, 1485m, 1443m, 1414w, 1359w, 1333s, 1263m, 1184s, 1149w, 1129w, 1094w, 1071m, 988m, 961w, 935w, 913m, 891s, 812m, 776m, 645m, 537m, 512m, 477m, 461m cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.81 (d, J = 2.8, H-C(2)), 8.11 (d, J = 1.8, H-C(8)), 7.80-7.70 (m, 2H, H-C(4) and H-C(5)), 7.55-7.50 (m, H-C(6)). ¹³C-NMR (125 MHz, CDCl₃, δ): 156.25 (d, J = 257.0, C(3)); 145.60 (C(8a)); 142.52 (d, J = 27.2, C(2)); 134.41 (C(7)); 128.73 (C(6)); 128.53 (C(5)); 129.20 (C(4a)); 128.35 (d, J = 5.1, C(8)); 118.31 (d, J = 17.3, C(4)). HRMS: m/z 182.01646 corresponds to molecular formula C₉H₅ClFNH⁺ (error in ppm: - 1.49).

3-Fluoro-quinoline (16).



A mixture of 3-aminoquinoline **14** (3.00 g, 20.96 mmol) and 48% tetrafluoroboric acid (30 mL, 41.93 mmol) was stirred on ice bath. Solution of sodium nitrite (1.44 g, 20.96 mmol) in water (6 mL) was added dropwise after 15 min. The reaction mixture was stirred as the temperature rose to r.t. Then diazonium tetrafluoroborate precipitate was filtered off, washed with cold EtOH and Et₂O then dried under reduced pressure. Diazonium salt was suspended in toluene and the mixture was warmed 1 h at the 110 °C. 3-Fluoroquinoline **16** was obtained after chromatography SiO₂, eluent: Hex/EtOAc = 9/1, as light-yellow solid (4.9 g, 97%). IR (ATR): 3414w, 3064m, 2927w, 1652w, 1612s, 1560w, 1498s, 1463s, 1426m, 1371w, 1339s, 1213s, 1155s, 984m, 957w, 894m, 859w, 782m, 735m, 710w, 611w, 472w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.82 (d, J = 2.8, H-C(2)), 8.13 (d, J = 8.5, H-C(8)), 7.85-7.75 (m, 2H, H-C(4) and H-C(5)), 7.75-7.65 (m, H-C(7)), 7.65-7.55 (m, H-C(6)). ¹³C-NMR (125 MHz, CDCl₃, δ): 156.25 (d, J = 255.0, C(3)); 145.40 (C(8a)); 141.54 (d, J = 27.6, C(2)); 129.49 (C(8)); 128.54 (C(7)); 128.42 (d, J = 5.7, C(4a)); 127.67 (C(6)); 127.27 (d, J = 4.6, C(5)); 118.32 (d, J = 17.2, C(4)). HRMS: m/z 148.05503 corresponds to molecular formula C₉H₆FNH⁺ (error in ppm: - 4.52).

7-Chloro-3-fluoro-4-iodoquinoline (17).



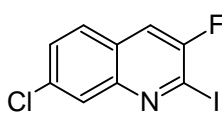
Diisopropylamine (1.8 mL, 12.89 mmol) was added to n-butyllithium/hexane (4.9 mL, 12.28 mmol) in THF (6.5 mL) at -78 °C.

After 30 min a solution 3-fluoro-7-chloroquinoline (2.23 g, 12.28 mmol) in 5.5 mL of THF was slowly added to solution of the formed LDA at -85 °C.

The resulting solution was stirred for 4h at -78 °C, and iodine (3.4 g, 13.51 mmol) in 6 mL THF was slowly added at -85 °C. Stirring was continued for 2h at -78 °C before the reaction was quenched by THF/H₂O = 9/1 (10 mL). Extraction with EtOAc, drying over anh. Na₂SO₄, filtration and solvent removal afforded crude product which was purified by multiple chromatography: dry-flash SiO₂, gradient: Hex/EtOAc = 95/5→9/1, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 9/1). Yield: 1.53 g (41%) of **17**. IR (ATR): 3080m, 3031w, 2959w, 2925w, 1837w, 1738w, 1602m, 1585s, 1551s, 1481s, 1441s, 1384w, 1357s, 1317s, 1307s, 1254m, 1210m, 1179m, 1139m, 1075m, 1018w, 949w, 925s, 895w, 870m, 851w, 814m, 755m, 642w, 576w, 536m, 509m, 429w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.60 (s, H-C(2)), 8.11 (d, *J* = 2.0, H-C(8)), 7.97 (d, *J* = 8.9, H-C(5)), 7.65-7.60 (m, H-C(6)). ¹³C-NMR (125 MHz, CDCl₃, δ): 157.11 (d, *J* = 255.3, C(3)); 145.36 (C(8a)); 140.80 (d, *J* = 30.0, C(2)); 135.37 (C(7)); 132.16 (C(5)); 129.93 (C(6)); 129.20 (C(4a)); 128.63 (C(8)); 94.90 (d, *J* = 23.0, C(4)). HRMS: *m/z*307.91326 corresponds to molecular formula C₉H₄ClFINH⁺ (error in ppm: - 0.36).

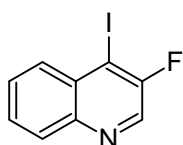
The compound **18** was also isolated as side product (359 mg, 9.5%).

7-Chloro-3-fluoro-2-iodoquinoline (**18**).



IR (ATR): 3171w, 3071w, 3037s, 2923s, 2853m, 1729w, 1689w, 1603m, 1481m, 1404m, 1373w, 1330s, 1297w, 1255w, 1191s, 1135w, 1071w, 1016m, 918m, 866w, 815w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.08 (d, *J* = 1.8, H-C(8)), 7.72 (d, *J* = 8.7, H-C(5)), 7.64 (d, *J* = 7.1, H-C(4)), 7.55 (dd, *J*₁ = 2.0, *J*₂ = 8.8, H-C(6)). ¹³C-NMR (125 MHz, CDCl₃, δ): 154.77 (d, *J* = 256.0, C(3)); 146.73 (C(8a)); 135.35 (C(7)); 129.27 (C(6)); 128.21 (d, *J* = 20.0, C(5)); 127.94 (C(8)); 126.36 (C(4a)); 117.50 (d, *J* = 85.2, C(4)); 111.95 (d, *J* = 120.1, C(2)). HRMS: *m/z*307.91325 corresponds to molecular formula C₉H₄ClFINH⁺ (error in ppm: - 0.40).

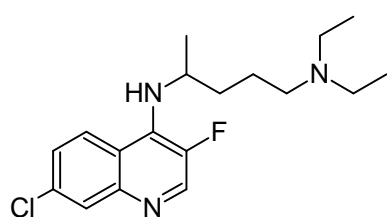
3-Fluoro-4-iodoquinoline (**19**).²⁴



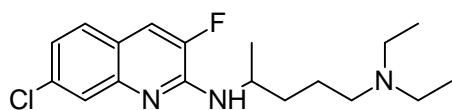
Diisopropylamine (1 mL, 7.14 mmol) was added to n-butyllithium/hexane (2.7 mL, 6.80 mmol) in THF (25 mL) at -78 °C. After 30 min a solution 3-fluoroquinoline (1.00 g, 6.80 mmol) in 5.5 mL of THF was slowly added to the solution of the formed LDA at -85 °C. The resulting solution was stirred for 4h at -78 °C, and iodine (1.90 g, 7.14 mmol) in 7 mL THF was slowly added at -85 °C. Stirring was continued for 2h at -78 °C before the reaction was quenched THF/H₂O = 9/1 (10 mL). Extraction with EtOAc, drying over anh. Na₂SO₄, filtration and solvent removal afforded

crude product which was purified by dry-flash chromatography SiO₂, gradient: Hex/EtOAc = 95/5 → 9/1. Yield: 1.30 g (70%) of **19**. IR (ATR): 3069m, 2924m, 2854w, 1586s, 1558s, 1491s, 1455s, 1414m, 1382w, 1339s, 1306s, 1262m, 1213s, 1141s, 1011w, 959w, 920m, 797w, 754s, 723m, 630w, 506w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.61 (s, H-C(2)), 8.09 (dd, *J*₁ = 0.6, *J*₂ = 8.1, H-C(8)), 8.02 (dd, *J*₁ = 1.5, *J*₂ = 8.4, H-C(5)), 7.75-7.70 (m, H-C(7)), 7.70-7.62 (m, H-C(6)). ¹³C-NMR (125 MHz, CDCl₃, δ): 157.02 (d, *J* = 252.7, C(3)); 145.33 (d, *J* = 1.8, C(8a)); 139.85 (d, *J* = 30.7, C(2)); 130.87 (d, *J* = 5.4, C(5)); 130.62 (C(4a)); 129.86 (C(8)); 129.15 (d, *J* = 2.7, C(7)); 129.07 (C(6)); 95.19 (d, *J* = 21.7, C(4)). HRMS: *m/z* 273.95195 corresponds to molecular formula C₉H₅FINH⁺ (error in ppm: - 1.46).

***N*⁴-(7-Chloro-3-fluoroquinolin-4-yl)-*N*¹,*N*¹-diethylpentane-1,4-diamine (**74**).**

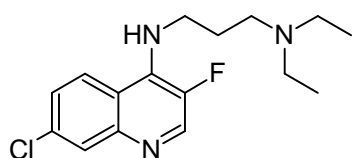


Compound **74** was prepared from 7-chloro-3-fluoro-4-iodoquinoline (300 mg, 0.98 mmol) and 2-amino-5-diethylaminopentane (378 μL, 1.95 mmol) using Pd(OAc)₂ (8.8 mg, 0.039 mmol), DPEphos (42 mg, 0.078 mmol) and K₃PO₄ (518 mg, 2.44 mmol) by method Hand and was obtained after multiple chromatography: dry-flash SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5 → 8/2 and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 8/2) as colorless foam (329 mg, 54%), softens at 48-50 °C. IR(ATR): 3304m, 3069w, 2970s, 2936m, 2871w, 2810w, 1595s, 1574s, 1536m, 1488w, 1452m, 1418m, 1380m, 1351m, 1294w, 1265m, 1221w, 1197w, 1140m, 1078m, 929w, 906w, 877w, 815m, 764w, 735w, 656w, 540w cm⁻¹. λ_{max}(ε) = 336 (11554), 252 (16869) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 8.52 (d, *J* = 5.5, H-C(2)), 7.96 (d, *J* = 2.2, H-C(8)), 7.75 (d, *J* = 9.1, H-C(5)), 7.42-7.36 (m, H-C(6)), 4.73 (d, *J* = 7.7, -NH), 4.20-4.05 (m, 1H, ArNHCH(CH₃-)), 2.54 (q, 4H, *J* = 7.2, -NH(CH₂CH₃)₂), 2.50-2.43 (m, 2H, -CH₂NH(CH₂CH₃)₂), 1.75-1.55 (m, 4H, ArNHCH(CH₃)CH₂-), ArNHCH(CH₃)CH₂CH₂-), 1.29 (dd, 3H, *J*₁ = 0.9, *J*₂ = 6.3, ArNHCH(CH₃-)), 1.01 (t, 6H, *J* = 7.0, -NH(CH₂CH₃)₂). ¹³C-NMR (125 MHz, CDCl₃, δ): 146.62 (C(8a)); 143.42 (d, *J* = 240.1, C(3)); 142.45 (d, *J* = 27.3, C(2)); 135.77 (d, *J* = 6.3, C(4)); 133.97 (C(7)); 128.96 (C(8)); 125.95 (C(6)); 121.89 (d, *J* = 5.4, C(5)); 119.45 (d, *J* = 4.5, C(4a)); 52.54; 51.34 (d, *J* = 8.1, ArNHCH(CH₃-)); 46.78; 36.12; 23.70; 22.30; 11.26. HRMS: *m/z* 338.18020 corresponds to molecular formula C₁₈H₂₅ClFN₃H⁺ (error in ppm: + 2.43. Anal. (C₁₈H₂₅ClFN₃ × 1/2 H₂O) Calcd: C, 62.33; H, 7.56; N, 12.11. Found: C, 62.00; H, 7.32; N, 11.85. HPLCpurity (λ = 330 nm) method A: RT 7.677min, area 98.24%; method B: RT 9.229 min, area 98.45%.

***N*⁴-(7-Chloro-3-fluoroquinolin-2-yl)-*N*¹,*N*¹-diethylpentane-1,4-diamine (76).**

Compound **76** was prepared from 7-chloro-3-fluoro-2-iodoquinoline (100 mg, 0.33 mmol) and 2-amino-5-diethylaminopentane (126 μ L, 0.65 mmol) using

$\text{Pd}(\text{OAc})_2$ (2.9 mg, 0.013 mmol), DPEphos (14 mg, 0.026 mmol) and K_3PO_4 (173 mg, 0.81 mmol) by method Hand and was obtained after multiple chromatography: dry-flash SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5 \rightarrow 8/2$, and flash chromatography (Biotage SP1 RP column, eluent: $\text{MeOH}/\text{H}_2\text{O} = 8/2$) as yellow viscous oil (76 mg, 70%). IR(ATR): 3440m, 3288m, 2968s, 2932m, 2871w, 2806w, 1637s, 1609m, 1568m, 1532s, 1492w, 1463m, 1416m, 1377w, 1345w, 1286w, 1261m, 1190m, 1145m, 1120m, 1098m, 1070m, 969w, 948w, 883m, 800w, 761w, 721w, 602w, 513w, 475w cm^{-1} . $\lambda_{\text{max}}(\epsilon) = 346$ (8397), 333 (8354), 243 (37616) nm. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.68 (d, $J = 2.0$, H-C(8)), 7.43 (d, $J = 8.4$, H-C(5)), 7.37 (d, $J = 11.3$, H-C(4)), 7.16 (dd, $J_1 = 1.6$, $J = 8.5$, H-C(6)), 5.21 (d, $J = 6.5$, H-N), 4.45-4.35 (m, 1H, $\text{ArNHCH}(\text{CH}_3)-$), 2.58 (q, 4H, $J = 7.2$, $-\text{NH}(\text{CH}_2\text{CH}_3)_2$), 2.55-2.50 (m, 2H, $-\text{CH}_2\text{NH}(\text{CH}_2\text{CH}_3)_2$), 1.75-1.55 (m, 4H, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$), 1.29 (d, $J = 1.3$, $\text{ArNHCH}(\text{CH}_3)-$), 1.04 (t, $J = 7.2$, $-\text{NH}(\text{CH}_2\text{CH}_3)_2$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 148.41 (d, $J = 13.6$, C(8a)); 147.15 (d, $J = 258.1$, C(3)); 143.86 (d, $J = 2.7$, C(2)); 133.87 (C(7)); 127.78 (d, $J = 5.0$, C(5)); 125.25 (C(8)); 123.08 (C(6)); 121.32 (d, $J = 4.1$, C(4a)); 115.90 (d, $J = 15.3$, C(4)); 52.63; 46.73 (d, $J = 5.4$, $\text{ArNHCH}(\text{CH}_3)-$); 45.84; 34.81; 23.15; 20.84; 11.06. HRMS: m/z 338.17891 corresponds to molecular formula $\text{C}_{18}\text{H}_{25}\text{ClFN}_3\text{H}^+$ (error in ppm: - 1.40). Anal. ($\text{C}_{18}\text{H}_{25}\text{ClFN}_3 \times 1/2 \text{H}_2\text{O}$) Calcd: C, 62.33; H, 7.56; N, 12.11. Found: C, 62.28; H, 7.69; N, 11.94. HPLCpurity ($\lambda = 330$ nm) method A: RT 8.042 min, area 96.24%; method B: RT 10.764 min, area 96.01%.

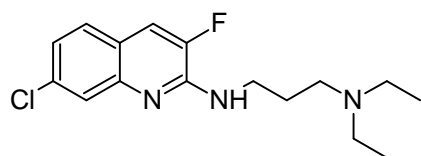
***N*¹-(7-Chloro-3-fluoroquinolin-4-yl)-*N,N*-diethylpropane-1,3-diamine (73).**

Compound **73** was prepared from 7-chloro-3-fluoro-4-iodoquinoline (100 mg, 0.32 mmol) and 3-diethylamino-1-propylamine (105 μ L, 0.65 mmol) using $\text{Pd}(\text{OAc})_2$ (2.9 mg, 0.013 mmol), SPhos (10.7 mg, 0.026 mmol) and K_3PO_4 (178 mg, 0.81

mmol) by method H and was obtained after multiple chromatography: dry-flash SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5 \rightarrow 8/2$, and flash chromatography (Biotage SP1 NH column, eluent: $\text{Hex}/\text{EtOAc} = 85/15$) as colorless foam (64 mg, 63%) softens at 47-48 $^\circ\text{C}$. IR(ATR): 3234m, 3065w, 2970s, 2934m, 2872w, 2822m, 1640w, 1597s, 1574s, 1540m, 1489w, 1470w, 1454w, 1429m, 1380m, 1360m, 1294w, 1268w, 1246w, 1195m, 1166w, 1138m, 1077m, 934m, 892m, 812m, 762m, 737w, 654w, 622w, 540w cm^{-1} . $\lambda_{\text{max}}(\epsilon) = 337$ (9690), 252 (15073) nm. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 8.45 (d, $J = 6.0$, H-C(2)), 7.91 (d, $J = 2.2$, H-C(8)), 7.75 (d, $J = 9.0$, H-C(5)), 7.32 (dd, $J_1 = 1.6$, $J_2 = 9.0$, H-C(6)), 3.90-3.80 (m,

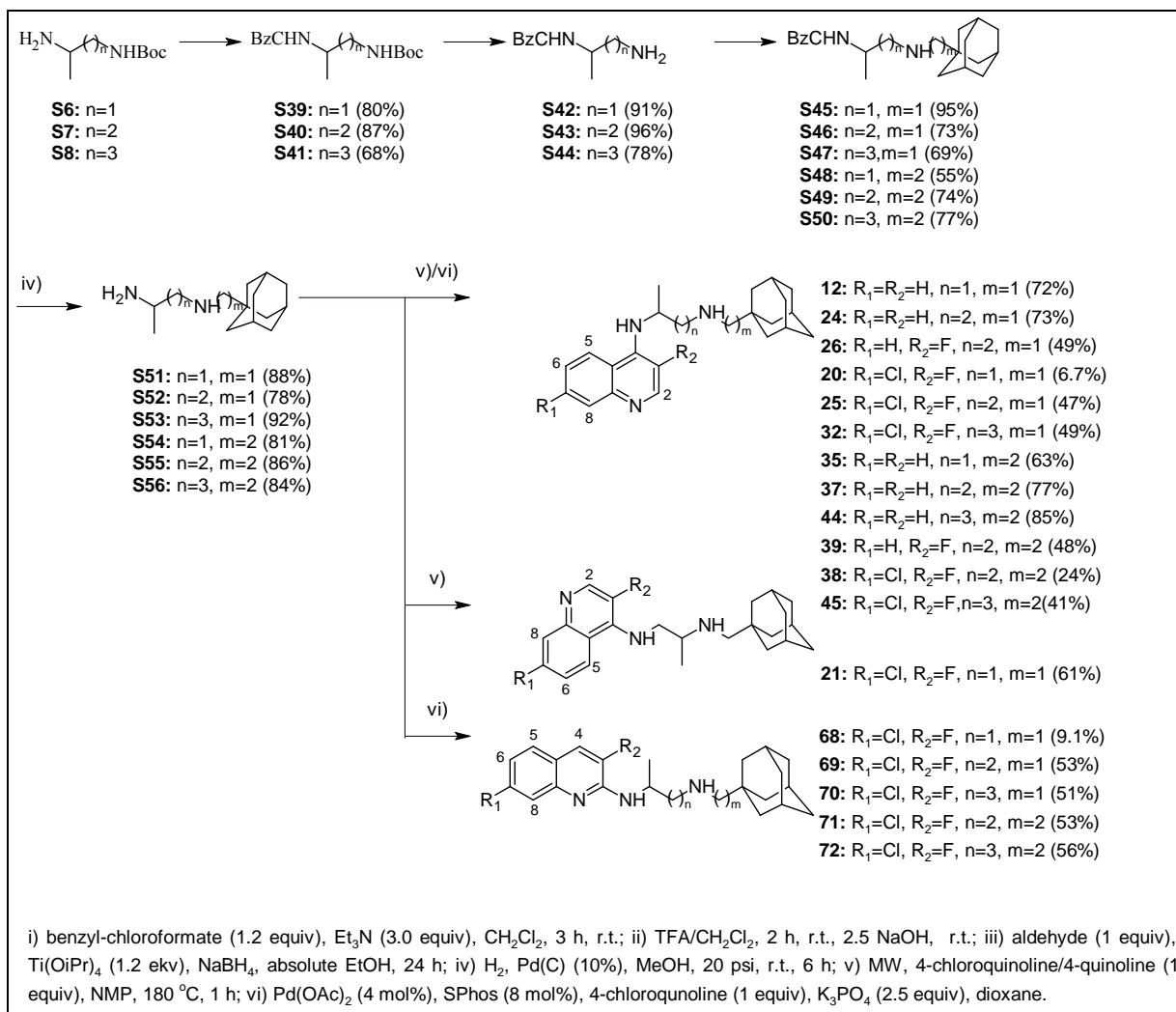
2H, ArNHCH₂-), 2.72-2.68 (m, 2H, -CH₂NH(CH₂CH₃)₂), 2.65 (q, 4H, *J* = 7.1, -NH(CH₂CH₃)₂), 2.04 (bs, H-N), 1.90-1.80 (m, 2H, ArNHCH₂CH₂-), 1.10 (t, 6H, *J* = 7.1, -NH(CH₂CH₃)₂). ¹³C-NMR (125 MHz, CDCl₃): 146.60 (C(8a)); 143.50 (d, *J* = 226.3, C(3)); 142.45 (d, *J* = 27.2, C(2)); 137.28 (d, *J* = 5.9, C(4)); 133.72 (d, *J* = 7.2, C(7)); 128.65 (C(8)); 125.23 (C(6)); 122.74 (d, *J* = 5.0, C(5)); 119.28 (d, *J* = 5.9, C(4a)); 53.50; 47.44 (d, *J* = 9.9, ArNHCH₂-); 47.03; 25.31; 11.28. HRMS: *m/z* 310.14830 corresponds to molecular formula C₁₆H₂₁ClFN₃H⁺ (error in ppm: + 0.71). (+)ESI-HRMS (*m/z* (%)): 310.14830 ([M+H]⁺, 100); calculated 310.14808 (error in ppm: 0.71). Anal. (C₁₆H₂₁ClFN₃ × 1/2 H₂O) Calcd: C, 60.28; H, 6.96; N, 13.18. Found: C, 60.65; H, 7.07; N, 12.79. HPLCpurity (λ = 330 nm) method A: RT 7.585min, area 99.71%; method B: RT 8.693 min, area 95.30%.

***N'*-(7-Chloro-3-fluoroquinolin-2-yl)-*N,N*-diethylpropane-1,3-diamine (75).**



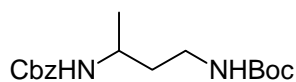
Compound **75** was prepared from 7-chloro-3-fluoro-2-iodoquinoline (100mg, 0.32 mmol) and 3-diethylamino-1-propilamine (74 μL, 0.46 mmol) using Pd(OAc)₂ (2.0 mg, 0.009 mmol), SPhos (7.5 mg, 0.018 mmol) and K₃PO₄ (124

mg, 0.57 mmol) by method H and was obtained after multiple chromatography: dry-flash SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5 → 8/2, and flash chromatography (Biotage SP1 RP column, eluent; MeOH/H₂O = 8/2) as yellow viscous oil (51 mg, 72%). IR(ATR): 3450w, 3241m, 2970m, 2931m, 2873w, 2815m, 1639m, 1610w, 1563w, 1537s, 1497w, 1459m, 1416m, 1378w, 1338m, 1292m, 1256m, 1193m, 1146m, 1124m, 1098w, 1070m, 1032w, 979w, 921w, 885m, 800w, 761w, 739w, 604w, 514w, 476w cm⁻¹. λ_{max}(ε) = 343 (8682), 332 (8760), 242 (35685) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 7.69 (d, *J* = 2.0, H-C(8)), 7.50-7.40 (bs, 1H, H-N-), 7.41 (d, *J* = 8.5, H-C(5)), 7.33 (d, *J* = 11.2, H-C(4)), 7.14 (dd, *J*₁ = 2.0, *J*₂ = 8.4, H-C(6)), 3.75-3.60 (m, 2H, ArNHCH₂-), 2.64 (t, 2H, *J* = 6.0, -CH₂NH(CH₂CH₃)₂), 2.57 (q, 4H, *J* = 7.1, -NH(CH₂CH₃)₂), 1.90-1.75 (m, 2H, ArNHCH₂CH₂-), 1.07 (t, 6H, *J* = 7.2, -NH(CH₂CH₃)₂). ¹³C-NMR (125 MHz, CDCl₃, δ): 149.16 (d, *J* = 14.0, C(8a)); 147.58 (d, *J* = 259.0, C(3)); 145.54 (d, *J* = 2.7, C(2)); 133.77 (d, *J* = 7.2, C(7)); 127.77 (d, *J* = 5.0, C(5)); 125.03 (C(8)); 122.80 (C(6)); 121.26 (d, *J* = 4.5, C(4a)); 115.56 (d, *J* = 15.4, C(4)); 53.00; 46.83; 41.57; 25.11; 11.53. HRMS: *m/z* 310.14742 corresponds to molecular formula C₁₆H₂₁ClFN₃H⁺ (error in ppm: - 2.14). Anal. (C₁₆H₂₁ClFN₃ × 1/4 H₂O) Calcd: C, 61.14; H, 6.89; N, 13.37. Found: C, 61.33; H, 6.96; N, 13.40. HPLCpurity (λ = 330 nm) method A: RT 7.559 min, area 99.45%; method B: RT 8.647 min, area 99.28%.

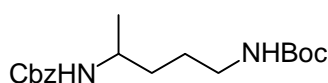


Benzyl *tert*-butyl propane-1,2-diylbiscarbamate (S39).

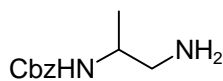
Compound **S39** was prepared from mono-Boc-protected 1,2-CbzHN(CH₂)_nNHBoc propanediamine (3.30 g, 18.94 mmol) using benzyl-chloroformate (3.2 mL, 22.72 mmol) and Et₃N (5.1 mL, 36.93 mmol) by method I and was obtained after dry-flash chromatography: SiO₂, gradient: Hex/EtOAc = 9/1 → 1/1, as colorless oil (4.67 g, 80%). IR(ATR): 3356s, 2981m, 2932w, 2880w, 1688s, 1537s, 1453w, 1389w, 1368w, 1318m, 1271m, 1230m, 1172m, 1065m, 998w, 915w, 865w, 779w, 730w, 695w, 666w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 7.40-7.28 (m, 5H, -Ph), 5.20-5.00 (m, 3H, -CH₂Ph, H-N), 4.95-4.70 (bs, H-N), 3.85-3.70 (m, 1H, CbzNHCH(CH₃)-), 3.25-3.10 (m, 2H, -CH₂NHBoc), 1.42 (s, 9 H, -NHCOO-C(CH₃)₃), 1.15 (d, 3H, J = 6.7, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 156.64; 156.20; 136.51; 128.48; 128.06; 79.54; 66.58; 48.14; 45.78; 28.31; 18.54. HRMS: *m/z*309.18088 corresponds to molecular formula C₁₆H₂₄N₂O₄H⁺ (error in ppm: -2.11).

Benzyl *tert*-butyl butane-1,3-diylbiscarbamate (S40).

Compound **S40** was prepared from mono-Boc-protected 1,3-butanediamine (488 mg, 2.6 mmol) using benzyl-chloroformate (513 μL , 5.70 mmol) and Et_3N (1.08 mL, 7.8 mmol) by method I and was obtained after dry-flash chromatography: SiO_2 , gradient: Hex/EtOAc = 9/1 \rightarrow 1/1, as colorless oil (728 mg, 87%). IR(ATR): 3354m, 3040w, 2976m, 2938w, 1745m, 1688s, 1597m, 1533s, 1475m, 1388w, 1368w, 1331w, 1257s, 1173m, 1113w, 1080w, 1006w, 947w, 875w, 814w, 783w, 756m, 697w, 647w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.40-7.30 (m, 5H, -Ph), 5.09 (s, 2H, - CH_2Ph), 4.66 (bs, H-N), 3.90-3.75 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)$ -), 3.40-3.25 (m, 1H, - $\text{CH}_2\text{NH-Boc}$) 3.05-2.90 (m, 1H, - $\text{CH}_2\text{NH-Boc}$), 1.75-1.60 (m, 1H), 1.55-1.35 (m, 10 H, - $\text{CH}_2\text{CH}_2\text{NH-Boc}$, - $\text{NHCOO-C}(\text{CH}_3)_3$), 1.18 (d, 3H, $J = 6.7$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 156.17; 156.01; 136.45; 128.52; 128.01; 79.04; 66.64; 44.61; 37.63; 37.15; 28.40; 21.40. HRMS: m/z 323.19590 corresponds to molecular formula $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_4\text{H}^+$ (error in ppm: - 1.95).

Benzyl *tert*-butyl pentane-1,4-diylbiscarbamate (S41).

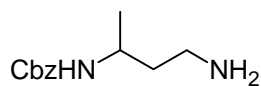
Compound **S41** was prepared from mono-Boc-protected 1,4-pentanediamine (2.02 g, 10 mmol) using benzyl-chloroformate (3.12 mL, 22 mmol) and Et_3N (4.16 mL, 30 mmol) by method I and was obtained by dry-flash chromatography: SiO_2 , gradient: Hex/EtOAc = 9/1 \rightarrow 1/1, as colorless oil (2.3 g, 68%). IR(ATR): 3320s, 2975m, 2942m, 2868w, 1684s, 1541s, 1454m, 1368w, 1341w, 1277s, 1257s, 1170m, 1108w, 1085w, 993w, 859w, 754w, 730w, 695w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.35-7.20 (m, 5H, -Ph), 5.01 (s, 1H, - CH_2Ph), 4.51 (bs, H-N), 3.70-3.55 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)$ -), 3.10-2.90 (m, 2H, - $\text{CH}_2\text{NH-Boc}$), 1.50-1.30 (m, 13H, $\text{CbzNHCH}(\text{CH}_3)\text{CH}_2$ -, $\text{CbzNHCH}(\text{CH}_3)\text{CH}_2\text{CH}_2$ -, - $\text{NHCOO-C}(\text{CH}_3)_3$), 1.07 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 155.98; 155.72; 136.59; 128.50; 128.07; 126.96; 66.52; 46.92; 40.37; 34.32; 28.39; 26.68; 21.24. HRMS: m/z 337.21241 corresponds to molecular formula $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_4\text{H}^+$ (error in ppm: + 0.68).

Benzyl (2-amino-1-methylethyl)carbamate (S42).

Compound **S42** was prepared from **S36** (1.80 g, 5.82 mmol) using method C and was obtained after dry-flash chromatography: SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5 \rightarrow 8/2$, as colorless oil (1.10 g, 91%). IR(ATR): 3312m, 3033w, 2968m, 1703s, 1534s, 1454m, 1377w, 1337w, 1253s, 1095m, 1049m, 914w, 747m, 699m cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.45-7.25 (m, 5H, -Ph), 5.20-5.05 (m, 2H, - CH_2Ph), 4.97 (bs, H-N), 3.80-3.65 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)$ -), 2.80-2.70 (m, 1H, - CH_2NH_2), 2.70-2.60 (m, 1H, - CH_2NH_2), 1.28 (s, 2H-N), 1.13 (d, 3H, $J = 6.9$, CH_3).

^{13}C -NMR (125 MHz, CDCl_3 , δ): 156.12; 136.56; 128.48; 128.04; 66.54; 49.13; 47.26; 18.40. HRMS: m/z 209.12811 corresponds to molecular formula $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: -1.63).

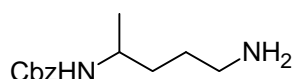
Benzyl (3-amino-1-methylpropyl)carbamate (S43).



Compound **S43** was prepared from **S40** (6.6 g, 20.6 mmol) using method C and was obtained after dry-flash chromatography: SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5 \rightarrow 8/2$, as colorless oil (4.40 g,

96%)softens at 88-90 °C. IR (ATR): 3329m, 3034w, 2967m, 2936m, 1537s, 1454m, 1338w, 1260s, 1098m, 1056m, 910w, 744w, 698w cm^{-1} . ^1H -NMR (500 MHz, CDCl_3 , δ): 7.40-7.25 (m, 5H, -Ph), 5.15-5.05 (m, 3H, $-\text{CH}_2\text{Ph}$, -NH), 3.95-3.80 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)-$), 2.85-2.70 (m, 2H, $-\text{CH}_2\text{NH}_2$), 1.65-1.55 (m, 1H, $-\text{CH}_2\text{CH}_2\text{NH}_2$), 1.55-1.45 (m, 1H, $-\text{CH}_2\text{CH}_2\text{NH}_2$), 1.26 (s, 2H-N), 1.17 (d, 3H, $J = 6.6$, CH_3). ^{13}C -NMR (125 MHz, CDCl_3 , δ): 155.95; 136.65; 128.46; 128.01; 66.44; 45.14; 40.39; 38.70; 21.33. HRMS: m/z 223.14348 corresponds to molecular formula $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: -2.82).

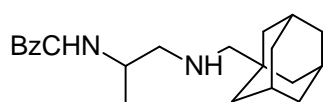
Benzyl (4-amino-1-methylbutyl)carbamate (S44).



Compound **S44** was prepared from **S41** (2.20 g, 6.5 mmol) using method C and was obtained after dry-flash chromatography: SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5 \rightarrow 8/2$, as colorless oil (1.21

g, 78%). IR (ATR): 3335s, 3058w, 3035w, 2986w, 2934m, 2164w, 1690s, 1566m, 1537s, 1463m, 1426w, 1386w, 1326m, 1261s, 1120w, 1076m, 1024w, 970w, 912w, 876w, 844w, 822w, 781w, 751w, 732w, 698w, 643w cm^{-1} . ^1H -NMR (500 MHz, CDCl_3 , δ): 7.45-7.20 (m, 5H, -Ph), 5.08 (s, 1H, $-\text{CH}_2\text{Ph}$), 4.72 (bs, H-N), 3.80-3.65 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)-$), 2.80-2.60 (m, 2H, $-\text{CH}_2\text{NH}_2$), 1.60-1.35 (m, 6H, $\text{CbzNHCH}(\text{CH}_3)\text{CH}_2-$, $\text{CbzNHCH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, 2H-N), 1.15 (d, 3H, $J = 6.7$, CH_3). ^{13}C -NMR (125 MHz, CDCl_3 , δ): 155.78; 136.65; 128.49; 128.05; 66.47; 46.97; 41.92; 34.42; 29.88; 21.18. HRMS: m/z 237.15860 corresponds to molecular formula $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: -4.87).

Benzyl {2-[(1-adamantylmethyl)amino]-1-methylethyl}carbamate (S45).

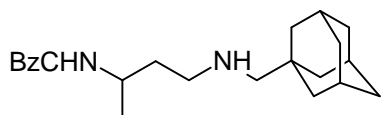


Compound **S45** was prepared from mono-*N*-Cbz-protected 1,2-propanediamine diamine **S42** (2.80 g, 13.4 mmol) and adamantane-1-carboxaldehyde (2.00 g, 12.18 mmol) using $\text{Ti}(\text{O}i\text{Pr})_4$ (5.4 mL,

18.12 mmol) and NaBH_4 (685 mg, 18.12 mmol) using method G and was obtained after dry-flash chromatography: SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 9/1 \rightarrow 7/3$, as colorless oil (4.1 g, 95%). IR (ATR): 3332m, 3089w, 3063w, 3033w, 2965w, 2901s, 2845s, 2676w, 1703s, 1532m, 1501m, 1452m, 1403w, 1372w, 1341w, 1311w, 1241m, 1156w, 1069m, 1026w, 774w, 737w, 698w, 646w, 604w cm^{-1} . ^1H -NMR (500 MHz, CDCl_3 , δ): 7.40-7.25 (m, 5H, -Ph), 5.15-5.05 (s, 2H, $-\text{CH}_2\text{Ph}$), 3.85-3.70 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)-$), 2.65-2.55 (m, 2H, -

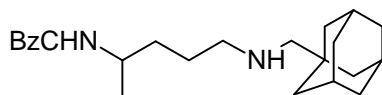
$\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.30-2.15 (m, 2H, $-\text{CH}_2\text{Ad}$), 1.95 (s, 3H, $-\text{Ad}$), 1.75-1.55 (m, 6H, $-\text{Ad}$), 1.54-1.40 (m, 6H, $-\text{Ad}$), 1.15 (d, 3H, $J = 6.6$, CH_3). ^{13}C -NMR (125 MHz, CDCl_3 , δ): 156.15; 136.76; 128.48; 128.00; 66.43; 62.68; 55.63; 46.52; 40.80; 37.22; 35.56; 28.45; 19.13. HRMS: m/z 357.25278 corresponds to molecular formula $\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: -2.44).

Benzyl {3-[(1-adamantylmethyl)amino]-1-methylpropyl}carbamate (**S46**).

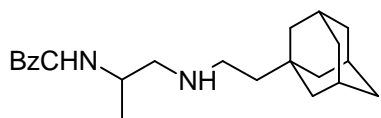


Compound **S46** was prepared by method G from mono-*N*-Cbz-protected 1,3-butanediamine **S43** (1.54 g, 6.9 mmol) and adamantane-1-carboxaldehyde (948 mg, 5.8 mmol) using $\text{Ti}(\text{OiPr})_4$ (2.6 mL, 8.66 mmol) and NaBH_4 (327 mg, 8.66 mmol) and was obtained after dry-flash chromatography: SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 9/1 \rightarrow 7/3$, as colorless oil (1.51 g, 73%). IR (ATR): 3319w, 3063w, 3032w, 2901s, 2845s, 2677w, 1707s, 1528m, 1451m, 1375w, 1343w, 1254m, 1154w, 1088m, 1030w, 979w, 775w, 736w, 697w cm^{-1} . ^1H -NMR (500 MHz, CDCl_3): 7.40-7.25 (m, 5H, $-\text{Ph}$), 6.44 (bs, 1H, $-\text{NH}$), 5.15-5.00 (m, 2H, $-\text{CH}_2\text{Ph}$), 3.90-3.75 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)-$), 2.80-2.70 (m, 1H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.70-2.60 (m, 1H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.23 (ABq, H_A , $J = 11.3$, $-\text{CH}_2\text{Ad}$), 2.20 (ABq, H_B , $J = 11.3$, $-\text{CH}_2\text{Ad}$), 1.92 (s, 3H, $-\text{Ad}$), 1.80-1.55 (m, 7H, $-\text{CH}_2\text{CH}_2\text{NHCH}_2\text{Ad}$, $-\text{Ad}$), 1.55-1.40 (m, 7H, $-\text{CH}_2\text{CH}_2\text{NHCH}_2\text{Ad}$, $-\text{Ad}$), 1.19 (d, 3H, $J = 6.4$, CH_3). ^{13}C -NMR (125 MHz, CDCl_3 , δ): 156.05; 136.89; 128.37; 127.81; 66.20; 62.90; 47.23; 46.56; 40.87; 37.16; 35.36; 33.25; 28.41; 20.82. HRMS: m/z 371.26950 corresponds to molecular formula $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: +0.52).

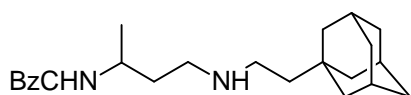
Benzyl {4-[(1-adamantylmethyl)amino]-1-methylbutyl}carbamate (**S47**).



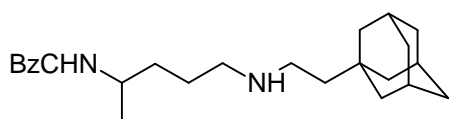
Compound **S47** was prepared by method G from mono-*N*-Cbz-protected 1,4-pentanediamine **S44** (1.28 g, 5.42 mmol) and adamantane-1-carboxaldehyde (780 mg, 4.75 mmol) using $\text{Ti}(\text{OiPr})_4$ (2.1 mL, 7.12 mmol) and NaBH_4 (269 mg, 7.12 mmol) and was obtained after dry-flash chromatography: SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 9/1 \rightarrow 7/3$ as colorless oil (1.26 g, 69%). IR (ATR): 3320w, 3033w, 2902s, 2846s, 1703s, 1533m, 1452m, 1342w, 1252m, 1090m, 911w, 733m, 697w cm^{-1} . ^1H -NMR (500 MHz, CDCl_3 , δ): 7.40-7.20 (m, 5H, $-\text{Ph}$), 5.08 (s, 1H, $-\text{CH}_2\text{Ph}$), 3.80-3.60 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)-$), 2.65-2.50 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.21 (s, 2H, $-\text{CH}_2\text{Ad}$), 1.94 (s, 3H, $-\text{Ad}$), 1.78-1.58 (m, 6H, $-\text{Ad}$), 1.58-1.40 (m, 10H, $\text{CbzNHCH}(\text{CH}_3)\text{CH}_2-$, $\text{CbzNHCH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-\text{Ad}$), 1.14 (d, 3H, $J = 6.4$, CH_3). ^{13}C -NMR (125 MHz, CDCl_3 , δ): 155.84; 136.72; 128.44; 128.06; 127.96; 66.38; 62.87; 50.58; 47.02; 40.89; 37.18; 34.54; 33.28; 28.43; 26.09; 21.12. HRMS: m/z 385.28474 corresponds to molecular formula $\text{C}_{24}\text{H}_{36}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: -0.56).

Benzyl (2-([2-(1-adamantyl)ethyl]amino)-1-methylethyl)carbamate (S48).

Compound **S48** was prepared by method G from mono-*N*-Cbz-protected 1,2-propanediamine **S42** (1.20 g, 5.76 mmol) and 1-adamantylacetaldehyde (890 mg, 5.00 mmol) using $\text{Ti}(\text{OiPr})_4$ (2.6 mL, 8.64 mmol) and NaBH_4 (327 mg, 8.64 mmol) and was obtained after dry-flash chromatography: SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 9/1 \rightarrow 7/3$, as colorless oil (1.38 g, 55%). IR (ATR): 3325m, 2903s, 2846s, 1716s, 1535m, 1453m, 1348w, 1254m, 1084w, 736w, 692w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.40-7.25 (m, 5H, -*Ph*), 5.22-5.05 (m, 3H, H-N, - CH_2Ph), 3.90-3.75 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)$ -), 2.70-2.64 (m, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Ad}$), 2.64-2.50 (m, 2H, - $\text{CH}_2\text{CH}_2\text{Ad}$), 1.93 (s, 3H, -Ad), 1.75-1.55 (m, 6H, -Ad), 1.53-1.42 (m, 6H, -Ad), 1.30-1.20 (m, 2H, - CH_2Ad), 1.16 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 156.08; 136.62; 128.46; 127.99; 66.49; 54.80; 46.55; 44.39; 44.20; 42.58; 37.09; 31.81; 28.62; 19.08. HRMS: m/z 371.26930 corresponds to molecular formula $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: - 0.91).

Benzyl (3-([2-(1-adamantyl)ethyl]amino)-1-methylpropyl)carbamate (S49).

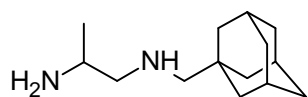
Compound **S49** was prepared by method G from mono-*N*-Cbz-protected 1,3-butanediamine **S43** (1.47 g, 6.63 mmol) and 1-adamantylacetaldehyde (1.07 mg, 6.05 mmol) using $\text{Ti}(\text{OiPr})_4$ (2.7 mL, 9.03 mmol) and NaBH_4 (343 mg, 9.03 mmol) and was obtained after dry-flash chromatography: SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 9/1 \rightarrow 7/3$, as colorless oil (1.71 g, 74%). IR (ATR): 3181w, 2964w, 2902s, 2846s, 1712s, 1559m, 1449m, 1370w, 1260m, 1095m, 1055w, 1024w, 839w, 768w, 737w, 695w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.45-7.25 (m, 5H, -*Ph*), 5.46 (bs, H-N) 5.15-5.05 (m, 2H, - CH_2Ph), 3.90-3.75 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)$ -), 2.76-2.67 (m, 1H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Ad}$), 2.67-2.60 (m, 1H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Ad}$), 2.60-2.50 (m, 2H, - $\text{CH}_2\text{CH}_2\text{Ad}$), 1.93 (s, 3H, -Ad), 1.75-1.57 (m, 6H, -Ad), 1.58-1.30 (m, 8H, $\text{CbzNHCH}(\text{CH}_3)\text{CH}_2$ -, -Ad), 1.30-1.20 (m, 2H, - CH_2Ad), 1.18 (d, 3H, $J = 6.6$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 155.94; 136.77; 128.43; 127.93; 66.32; 46.61; 45.96; 44.65; 44.28; 42.59; 37.11; 36.67; 31.80; 28.64; 21.20. HRMS: m/z 385.28474 corresponds to molecular formula $\text{C}_{24}\text{H}_{36}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: - 0.56).

Benzyl (4-([2-(1-adamantyl)ethyl]amino)-1-methylbutyl)carbamate (S50).

Compound **S50** was prepared by method G from mono-*N*-Cbz-protected 1,4-pentanediamine **S44** (1.58 g, 6.68 mmol) and 1-adamantylacetaldehyde (993 mg, 5.57 mmol) using $\text{Ti}(\text{OiPr})_4$ (2.5 mL, 8.35 mmol) and NaBH_4 (316 mg, 8.35 mmol) and was obtained after dry-flash chromatography: SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 9/1 \rightarrow 7/3$, as colorless oil (1.70 g, 77%). IR (ATR): 3312w, 3031w, 2898s, 2844s, 1696s, 1530s,

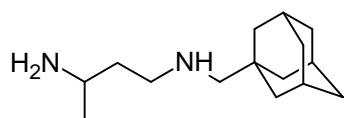
1449s, 1376w, 1344w, 1249s, 1182s, 1087m, 1063m, 1028w, 813w, 774w, 735m, 696s, 679w, 621w, 596w, 541w, 532w, 525w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.45-7.20 (m, 5H, -Ph), 5.20-5.05 (s, 1H, $-\text{CH}_2\text{Ph}$), 5.05-4.95 (bs, 1H, -NH), 3.80-3.65 (m, 1H, $\text{CbzNHCH}(\text{CH}_3)-$), 2.65-2.50 (m, 4H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Ad}$, $-\text{CH}_2\text{CH}_2\text{Ad}$), 2.00-1.85 (m, 3H, -Ad), 1.75-1.65 (m, 6H, -Ad), 1.55-1.40 (m, 10H, $\text{CbzNHCH}(\text{CH}_3)\text{CH}_2-$, $\text{CbzNHCH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, -Ad), 1.35-1.20 (m, 2H, $-\text{CH}_2\text{Ad}$), 1.14 (d, 3H, $J = 6.7$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 136.69; 128.46; 127.99; 66.40; 49.78; 46.92; 44.44; 44.22; 42.59; 37.12; 34.77; 31.81; 28.64; 26.19; 21.09. HRMS: m/z 399.29961 corresponds to molecular formula $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_2\text{H}^+$ (error in ppm: - 2.49).

N^1 -(1-Adamantylmethyl)propane-1,2-diamine (S51).

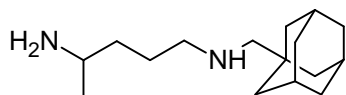


Compound **S51** was prepared by method J from **S45** (1.50 g, 4.2 mmol) using Pd/C 10% (150 mg) and was obtained by dry-flash chromatography: SiO_2 , gradient: $\text{EtOAc}/[\text{MeOH}/(\text{NH}_3 \text{ aq}) = 9/1] = 9/1 \rightarrow 8/2$, as colorless oil (823 mg, 88%). IR (ATR): 3346w, 2901s, 2845s, 2676w, 1583w, 1451m, 1368w, 1345w, 1312w, 1153w, 1100w, 1052w, 883w, 829w, 768w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 3.05-2.90 (m, 1H, $\text{NH}_2\text{CH}(\text{CH}_3)-$), 2.65-2.50 (m, 1H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.40-2.15 (m, 3H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$, $-\text{CH}_2\text{Ad}$), 1.96 (s, 3H, -Ad), 1.75-1.60 (m, 8H, 2H-N, -Ad), 1.55-1.45 (m, 6H, -Ad), 1.05 (d, 3H, $J = 6.2$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 62.79; 59.06; 46.25; 40.86; 37.22; 33.49; 28.44; 21.71. HRMS: m/z 223.21688 corresponds to molecular formula $\text{C}_{14}\text{H}_{26}\text{N}_2\text{H}^+$ (error in ppm: - 4.11).

N^1 -(1-Adamantylmethyl)butane-1,3-diamine (S52).

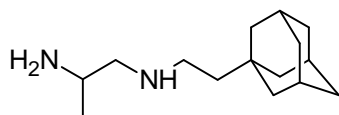


Compound **S52** was prepared by method J from **S46** (1.40 g, 3.9 mmol) using Pd/C 10% (140 mg) and was obtained by dry-flash chromatography: SiO_2 , gradient: $\text{EtOAc}/[\text{MeOH}/(\text{NH}_3 \text{ aq}) = 9/1] = 9/1 \rightarrow 8/2$, as colorless powder softness at 108-110 °C. Yield: 724 mg (78%). IR (ATR): 3284w, 2902s, 2845s, 2659w, 2574w, 1663w, 1633w, 1520m, 1470m, 1452w, 1425w, 1405m, 1366w, 1344w, 1311m, 1268w, 1152w, 1101w, 1033w, 948w, 878w, 810w, 764w, 641w, 593w cm^{-1} . $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 3.05-2.95 (m, 1H, $\text{NH}_2\text{CH}(\text{CH}_3)-$), 2.75-2.60 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.25 (ABq, H_A , $J = 11.4$, $-\text{CH}_2\text{Ad}$), 2.23 (ABq, H_B , $J = 11.4$, $-\text{CH}_2\text{Ad}$), 1.96 (s, 3H, -Ad), 1.75-1.60 (m, 6H, -Ad), 1.60-1.40 (m, 10H, $\text{NH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{NH}_2$, -Ad), 1.08 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 63.17; 48.77; 46.07; 40.95; 39.70; 37.23; 33.32; 28.47; 24.48. HRMS: m/z 237.23236 corresponds to molecular formula $\text{C}_{15}\text{H}_{28}\text{N}_2\text{H}^+$ (error in ppm: - 0.71).

***N*¹-(1-Adamantylmethyl)pentane-1,4-diamine (S53).**

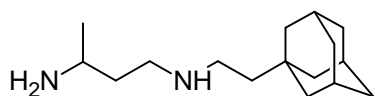
Compound **S53** was prepared by method J from **S47** (650 mg, 1.69 mmol) using 10%Pd/C (65 mg) and was obtained by dry-flash chromatography: SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) =

95/5 → 8/2, as colorless oil (389 mg, 92%). IR(ATR): 2902s, 2846s, 1582w, 1452m, 1367w, 1315w, 1154w, 1118w, 810w, 753m cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 2.95-2.80 (m, 1H, NH₂CH(CH₃)-), 2.65-2.50 (m, 2H, -CH₂NHCH₂Ad), 2.24 (s, 2H, -NHCH₂Ad), 1.96 (s, 3H, -Ad), 1.75-1.60 (m, 6H, -Ad), 1.60-1.40 (m, 8H, NH₂CH(CH₃)CH₂CH₂-, -Ad), 1.40-1.25 (m, 2H, NH₂CH(CH₃)CH₂-), 1.07 (d, 3H, *J* = 6.4, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 62.95; 51.11; 46.92; 40.95; 37.86; 37.21; 33.31; 28.46; 26.82; 24.00. HRMS: *m/z*251.24854 corresponds to molecular formula C₁₆H₃₀N₂H⁺ (error in ppm: + 1.45).

***N*¹-[2-(1-Adamantyl)ethyl]propane-1,2-diamine (S54).**

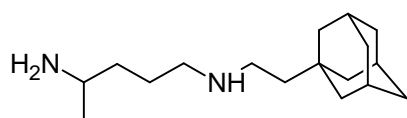
Compound **S54** was prepared by method J from **S48** (1.15 g, 3.1 mmol) using 10%Pd/C (115 mg) and was obtained by dry-flash chromatography: SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5

→ 8/2, as colorless oil (594 mg, 81%). IR (ATR): 3286w, 2902s, 2845s, 1575w, 1450m, 1374w, 1318w, 1105w, 814w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 3.00-2.90 (m, 1H, NH₂CH(CH₃)-), 2.70-2.50 (m, 3H, -CH₂NHCH₂CH₂Ad, -CH₂CH₂Ad), 2.45-2.30 (m, 1H, -CH₂NHCH₂CH₂Ad), 1.93 (s, 3H, -Ad), 1.80-1.60 (m, 6H, -Ad), 1.60-1.40 (m, 8H, 2H-N, -Ad), 1.35-1.20 (m, 2H, -CH₂Ad), 1.06 (d, 3H, *J* = 6.3, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 58.56; 46.56; 44.68; 44.38; 42.64; 37.14; 31.84; 28.66; 22.12. HRMS: *m/z*237.23155 corresponds to molecular formula C₁₅H₂₈N₂H⁺ (error in ppm: - 4.09).

***N*¹-[2-(1-Adamantyl)ethyl]butane-1,3-diamine (S55).**

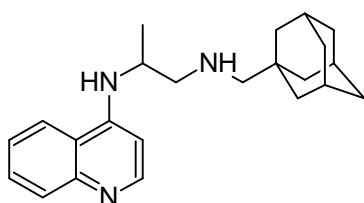
Compound **S55** was prepared by method J from **S49** (1.30 g, 3.4 mmol) using 10%Pd/C (130 mg) and was obtained by dry-flash chromatography: SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) =

95/5 → 8/2, as colorless oil (728 mg, 86%); m.p. = 55-57 °C. IR(ATR): 3334m, 3307m, 3275m, 3190m, 2966w, 2902s, 2845s, 2657w, 1609w, 1449m, 1385w, 1343w, 1316w, 1155w, 1119m, 1021w, 985w, 945w, 878w, 812w, 775w, 687w, 477w, 440w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 3.05-2.90 (m, 1H, NH₂CH(CH₃)-), 2.70-2.64 (m, 2H, NH₂CH(CH₃)CH₂CH₂-), 2.63-2.55 (m, 2H, -NHCH₂CH₂Ad), 1.93 (m, 3H, -Ad), 1.75-1.60 (m, 6H, -Ad), 1.60-1.40 (m, 8H, NH₂CH(CH₃)CH₂-, -Ad), 1.40-1.30 (m, 2H-N), 1.30-1.20 (m, 2H, -CH₂Ad), 1.08 (d, 3H, *J* = 6.2, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 47.73; 45.71; 44.76; 44.47; 42.63; 40.21; 37.14; 31.83; 28.65; 24.50. HRMS: *m/z*251.24756 corresponds to molecular formula C₁₆H₃₀N₂H⁺ (error in ppm: - 2.46).

***N*¹-[2-(1-Adamantyl)ethyl]pentane-1,4-diamine (S56).**

Compound **S56** was prepared by method J from **S50** (1.2 g, 3.0 mmol) using 10%Pd/C (120 mg) and was obtained by dry-flash chromatography: SiO₂, gradient:

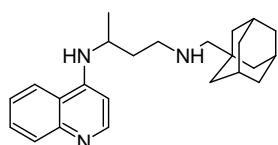
CH₂Cl₂/MeOH(NH₃sat.) = 95/5 → 8/2, as colorless powder softness at 80-81 °C. Yield: 669 mg (84%). IR(ATR): 3280w, 2902s, 2845s, 2675w, 1639w, 1572w, 1450m, 1374w, 1316w, 1295w, 1118w, 815w, 744 cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 2.95-2.85 (m, 1H, NH₂CH(CH₃)-), 2.70-2.60 (m, 4H, -CH₂NHCH₂CH₂Ad, -NHCH₂CH₂Ad), 1.93 (m, 3H, -Ad), 1.75-1.60 (m, 6H, -Ad), 1.60-1.30 (m, 10H, NH₂CH(CH₃)CH₂-, NH₂CH(CH₃)CH₂CH₂-, -Ad), 1.30-1.20 (m, 2H, -CH₂CH₂Ad), 1.15 (d, 3H, *J* = 6.7, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 50.31; 46.88; 44.73; 44.30; 42.64; 37.94; 37.15; 31.84; 28.67; 27.10; 24.01. HRMS: *m/z*265.26374 corresponds to molecular formula C₁₇H₃₂N₂H⁺ (error in ppm: - 0.33).

***N*¹-(1-Adamantylmethyl)-*N*²-quinolin-4-ylpropane-1,2-diamine (12).**

4-Chloroquinoline (405 mg, 1.82 mmol) and amine linker **S51** (298 mg, 1.82 mmol) were mixed in NMP (1.5 mL) in MW cuvette under Ar. The reaction mixture was subjected to MW irradiation using a *Biotage Initiator 2.5 apparatus*, 1h, 180 °C.

Compound **12** was obtained after multiple chromatography:

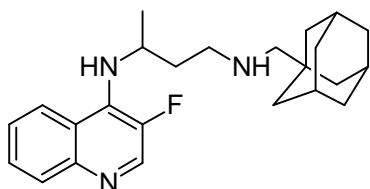
dry-flashSiO₂, eluent: EtOAc/MeOH/(NH₃ aq) 90/9/1 = 95/5, and flash chromatography (Biotage SP1-NH column, eluent: Hex/EtOAc = 6/4; RP column, eluent: MeOH/H₂O = 8/2), as colorless foam. Yield: 458 mg, (72%). IR(ATR): 3318m, 3069m, 2965m, 2901s, 2845s, 2676s, 1676m, 1617m, 1579s, 1532s, 1451s, 1394s, 1371s, 1340m, 1248w, 1223w, 1185m, 1152m, 1126w, 1048w, 885m, 810m, 762m, 737w, 702w, 651w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.53 (d, *J* = 5.3, H-C(2)), 7.97 (d, *J* = 8.3, H-C(8)), 7.79 (m, *J* = 8.2, H-C(5)), 7.70-7.55 (m, H-C(7)), 7.47-7.37 (m, H-C(6)), 6.45 (d, *J* = 5.5, H-C(3)), 6.01 (bs, H-N), 3.80-3.67 (m, 1H, ArNHCH(CH₃)-), 2.85 (d, 2H, *J* = 5.5, -CH₂NHCH₂Ad), 2.40-2.33 (m, 2H, -CH₂Ad), 2.05-1.90 (m, 3H, -Ad), 1.85-1.55 (m, 12H, -Ad), 1.30 (d, 3H, *J* = 6.4, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 150.79; 149.47; 148.36; 129.67; 128.96; 124.45; 119.64; 119.21 99.16; 62.69; 55.34; 47.30; 40.85; 37.17; 33.65; 28.39; 18.17. HRMS: *m/z*350.25887 corresponds to molecular formula C₂₃H₃₁N₃H⁺ (error in ppm: - 0.59). Anal. (C₂₃H₃₁N₃ × H₂O) Calcd: C, 75.16; H, 9.05; N, 11.43. Found: C, 75.64; H, 8.98; N, 11.23. HPLCpurity (λ = 330 nm) method A: RT 0.977 min, area 95.50%; method B: RT 9.286 min, area 95.16%.

***N*¹-(1-Adamantylmethyl)-*N*³-quinolin-4-ylbutane-1,3-diamine (24).**

Compound **24** was prepared by method H from amine linker **S52** (120 mg, 0.64 mmol) and 4-chloroquinoline (70 mg, 0.43 mmol) using

Pd(OAc)₂ (3.79 mg 0.017 mmol), SPhos (13.88 mg, 0.036 mmol) and K₃PO₄ (224mg, 1.08 mmol) and was obtained after dry-flash chromatography: SiO₂, gradient: EtOAc/[MeOH/(NH₃ aq) = 9/1] = 9/1 → 7/3, as a light yellow foam softens at 160-161 °C. Yield: 114 mg (73%). IR (ATR): 3270m, 3070m, 2965m, 2902s, 2846s, 1618s, 1580w, 1539s, 1451s, 1396m, 1395m, 1373w, 1340m, 1264m, 1151m, 1126m, 1103w, 809m, 763 m, 738m, 703w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.51 (d, *J* = 5.3, H-C(2)), 7.95 (dd, *J*₁ = 0.8, *J*₂ = 8.4, H-C(8)), 7.88 (dd, *J*₁ = 0.8, *J*₂ = 8.4, H-C(5)), 7.65-7.55 (m, H-C(7)), 7.40-7.30 (m, H-C(6)), 6.87 (bs, H-N), 6.42 (d, *J* = 5.6, H-C(3)), 3.95-3.80 (m, 1H, ArNHCH(CH₃)-), 2.95-2.85 (m, 1H, -CH₂NHCH₂Ad), 2.80-2.70 (m, 1H, -CH₂NHCH₂Ad), 2.29 (s, 2H, -NHCH₂Ad), 2.05-1.95 (m, 3H, -Ad), 1.95-1.85 (m, 1H, ArNHCH(CH₃)CH₂-), 1.84-1.60 (m, 8H, ArNHCH(CH₃)CH₂-, -Ad, H-N-), 1.58 (m, 6H, -Ad), 1.32 (d, 3H, *J* = 6.3, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 150.88; 149.60; 148.43; 129.56; 128.87; 124.00; 120.55; 119.14; 98.58; 63.65; 48.12; 47.83; 41.10; 37.17; 35.46; 33.44; 28.44; 19.15. HRMS: *m/z* 364.27556 corresponds to molecular formula C₂₄H₃₃N₃H⁺ (error in ppm: + 2.30). Anal. (C₂₄H₃₃N₃ × 1/2H₂O) Calcd: C, 77.37; H, 9.20; N, 11.28. Found: C, 77.37; H, 9.03; N, 11.18. HPLC purity (λ = 330 nm) method A: RT 0.953 min, area 99.05%; method B: RT 9.386 min, area 97.27%.

N¹-(1-Adamantylmethyl)-N³-(3-fluoroquinolin-4-yl)butane-1,3-diamine (26).

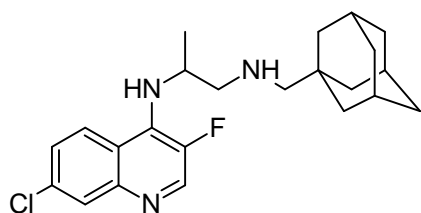


Compound **26** was prepared by method H from amine linker **S52** (880 mg, 3.72 mmol) and 3-fluoro-4-iodoquinoline **19** (1.00 g, 3.72 mmol) using Pd(OAc)₂ (33.4 mg, 0.15 mmol), DPEphos (160 mg, 0.30 mmol) and K₃PO₄ (1.97 g, 9.14 mmol) and was obtained after multiple chromatography: dry-

flash SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5 → 7/3 and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3 and RP column, gradient: MeOH/H₂O = 8/2 → 9/1, as colorless oil (572 mg, 49%). IR (ATR): 3265m, 2902s, 2845m, 1601s, 1574s, 1540s, 1496w, 1451m, 1398m, 1366w, 1345w, 1270w, 1202w, 1148w, 759m cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.51 (d, *J* = 5.7, H-C(2)), 8.00-7.88 (m, H-C(8) and H-C(5)), 7.60-7.54 (m, H-C(7)), 7.41-7.35 (m, H-C(6)), 6.31 (s, H-N), 4.37-4.27 (m, 1H, ArNHCH(CH₃)-), 2.95-2.85 (m, 1H, -CH₂NHCH₂Ad), 2.85-2.75 (m, 1H, -CH₂NHCH₂Ad), 2.30 (s, 2H, -CH₂Ad), 2.01-1.96 (m, 3H, -Ad), 1.80-1.60 (m, 9H, ArNHCH(CH₃)CH₂-, -Ad, H-N-), 1.60-1.50 (m, 6H, -Ad), 1.30 (dd, *J*₁ = 0.9, *J*₂ = 6.42, -CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 146.01 (C(8a)); 143.22 (d, *J* = 238.3, C(3)); 141.60 (d, *J* = 27.1, C(2)); 135.80 (d, *J* = 5.4, C(4)); 129.85 (C(8)); 127.90 (C(7)); 124.83 (C(6)); 124.68 (C(4a)); 121.27 (d, *J* = 5.4, C(5)); 63.70; 50.44 (d, *J* = 8.1, CH); 41.06; 37.15; 36.21; 33.33; 28.42; 21.71 (d, *J* = 2.7, CH₃). HRMS: *m/z* 382.26498 corresponds to molecular formula C₂₄H₃₂FN₃H⁺ (error in ppm: -

0.83).HPLCpurity ($\lambda = 330$ nm) method A: RT 7.545 min, area 99.28%; method B: RT 8.251 min, area 99.45%.

***N*¹-(1-Adamantylmethyl)-*N*²-(7-chloro-3-fluoroquinolin-4-yl)propane-1,2-diamine (20).**



Compound **20** was prepared from amine linker **S51** (120 mg, 0.51 mmol) and 7-chloro-3-fluoro-4-iodoquinoline **17** (148 mg, 0.48 mmol) in MW (*Biotage Initiator 2.5* apparatus, PrOH, 4h, 180 °C) and was obtained after dry-flash chromatography SiO₂ eluent: CH₂Cl₂/MeOH(NH₃sat.)

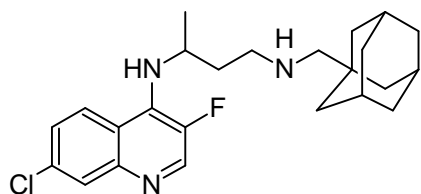
= 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3 and RP column, eluent: MeOH/H₂O = 85/15), as colorless viscous oil (13 mg, 6.7%). IR(ATR):

3331m, 3070w, 2903s, 2846s, 2675w, 1736w, 1598s, 1572s, 1521m, 1477w, 1449m, 1417m, 1380m, 1344m, 1315w, 1260m, 1192w, 1146w, 1078m, 1001w, 927m, 901w, 879w, 811m, 761m, 738w, 539w cm⁻¹. $\lambda_{\max}(\epsilon) = 334$ (7180) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 8.51 (d, *J* = 5.5, H-C(2)), 7.95 (d, *J* = 2.0, H-C(8)), 7.79 (d, *J* = 9.0, H-C(5)), 7.38 (dd, *J*₁ = 2.0, *J*₂ = 9.0, H-C(6)), 5.83 (d, *J* = 6.5, H-N), 4.25-4.05 (m, 1H, ArNHCH(CH₃)-), 2.90-2.75 (m, 1H, -CH₂NHCH₂Ad), 2.39 (ABq, *H*_A, *J* = 11.5, -CH₂Ad), 2.26 (ABq, *H*_B, *J* = 11.5, -CH₂Ad), 1.99 (s, 3H, -Ad), 1.80-1.60 (m, 6H, -Ad), 1.60-1.50 (m, 6H, -Ad), 1.28 (d, 3H, *J* = 6.5, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 146.62 (C(8a)); 143.46 (d, *J* = 239.1, C(3)); 142.40 (d, *J* = 27.1, C(2)); 135.93 (d, *J* = 5.9, C(4)); 133.92 (d, *J* = 2.3, C(7)); 128.88 (C(8)); 125.88 (C(6)); 121.95 (d, *J* = 5.4, C(5)); 119.71 (d, *J* = 5.4, C(4a)); 62.98; 55.68; 49.81 (d, ArNHCH(CH₃)-, *J* = 7.7); 40.94; 37.21; 33.72; 28.43; 20.15 (d, ArNHCH(CH₃)-, *J* = 3.6). HRMS:

*m/z*402.21082 corresponds to molecular formula C₂₃H₂₉ClFN₃H⁺ (error in ppm: + 0.35). Anal. (C₂₃H₂₉ClFN₃) Calcd: C, 68.73; H, 7.27; N, 10.45. Found: C, 68.39; H, 7.23; N, 10.44.

HPLCpurity ($\lambda = 330$ nm) method A: RT 8.000 min, area 97.70%; method B: RT 10.703 min, area 95.31%.

***N*¹-(1-Adamantylmethyl)-*N*³-(7-chloro-3-fluoroquinolin-4-yl)butane-1,3-diamine (25).**

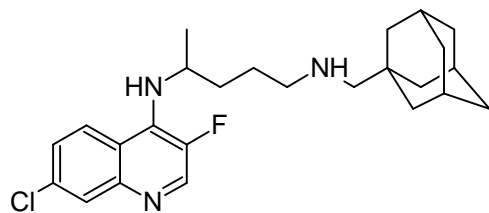


Compound **25** was prepared by method H from amine linker **S52** (135 mg, 0.57 mmol) and 7-chloro-3-fluoro-4-iodoquinoline **17** (159.6 mg, 0.52 mmol) using Pd(OAc)₂ (5.2 mg, 0.023 mmol), SPhos (18.88 mg, 0.046 mmol) and K₃PO₄ (303 mg, 1.43 mmol) and was obtained after

multiple chromatography: dry-flash SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5 → 8/2, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3 and RP column, eluent: MeOH/H₂O = 8/2) as colorless viscous oil (101.7 mg, 47%). IR (ATR): 3280m, 3070w, 2902s, 2846s, 2674w, 1596s, 1572s, 1540m, 1486w, 1450m, 1422m, 1380m, 1346m, 1295w, 1262m, 1191m, 1148m, 1115m, 1078m, 983w, 927m, 902w, 879m, 813m,

761w, 737m, 656w, 539w, 426w cm^{-1} . $\lambda_{\text{max}}(\epsilon) = 250 (15462), 337 (9685) \text{ nm}$. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 8.48 (d, $J = 5.8$, H-C(2)), 7.92 (d, $J = 1.6$, H-C(8)), 7.86 (d, $J = 9.0$, H-C(5)), 7.35-7.20 (m, H-C(6)), 6.63 (d, $J = 4.6$, H-N), 4.40-4.25 (m, 1H, $\text{ArNHCH}(\text{CH}_3)-$), 3.00-2.85 (m, 1H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.85-2.70 (m, 1H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.30 (s, 2H, $-\text{CH}_2\text{Ad}$), 2.05-1.90 (m, 4H, $-\text{Ad}$, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$), 1.90-1.60 (m, 8H, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$, $-\text{Ad}$, H-N-), 1.60-1.50 (m, 6H, $-\text{Ad}$), 1.30 (d, 3H, $J = 6.2$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 146.60 (C(8a)); 143.19 (d, $J = 239.1$, C(3)); 142.46 (d, $J = 27.5$, C(2)); 136.12 (d, $J = 5.4$, C(4)); 133.76 (d, $J = 7.2$, C(7)); 128.63 (C(8)); 125.37 (C(6)); 122.94 (d, $J = 5.0$, C(5)); 119.64 (d, $J = 5.4$, C(4a)); 50.58 (d, $J = 8.6$, $\text{ArNHCH}(\text{CH}_3)-$); 47.52; 41.05; 37.08; 35.75; 33.30; 28.36; 21.60. HRMS: m/z 416.22602 corresponds to molecular formula $\text{C}_{24}\text{H}_{31}\text{ClFN}_3\text{H}^+$ (error in ppm: - 0.75). Anal. ($\text{C}_{24}\text{H}_{31}\text{ClFN}_3 \times 2/3 \text{ H}_2\text{O}$) Calcd: C, 67.35; H, 7.61; N, 9.82. Found: C, 67.17; H, 7.47; N, 9.74. HPLCpurity ($\lambda = 330 \text{ nm}$) method A: RT 8.589min, area 97.89%; method B: RT 11.009 min, area 97.73%.

N^1 -(1-Adamantylmethyl)- N^4 -(7-chloro-3-fluoroquinolin-4-yl)pentane-1,4-diamine (32).

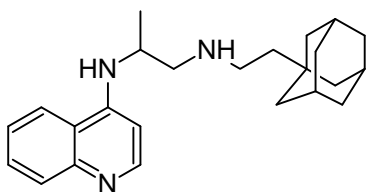


Compound **32** was prepared by method H from 7-chloro-3-fluoro-4-iodoquinoline **17** (105 mg, 0.34 mmol) and amine linker **S53** (94 mg, 0.38 mmol) using $\text{Pd}(\text{OAc})_2$ (3.0 mg, 0.014 mmol), DPEphos (14.65 mg, 0.027 mmol) and K_3PO_4 (180 mg, 0.85

mmol) and was obtained after multiple chromatography: dry-flash SiO_2 , gradient:

$\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5 \rightarrow 7/3$, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3 and RP column, gradient: $\text{MeOH}/\text{H}_2\text{O} = 8/2 \rightarrow 9/1$), as colorless foam (74 mg, 49%). IR(ATR): 3301m, 2902s, 2846s, 1596m, 1573s, 1536w, 1450m, 1418m, 1381m, 1351m, 1296w, 1264m, 1202w, 1147m, 928w, 878w, 814m, 761w, 738m, 657w, 541w cm^{-1} . $\lambda_{\text{max}}(\epsilon) = 252 (18402), 335 (11598) \text{ nm}$. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 8.50 (d, $J = 5.5$, H-C(2)), 7.95 (d, $J = 2.0$, H-C(8)), 7.74 (d, $J = 9.0$, H-C(5)), 7.36 (dd, $J_1 = 1.5, J_2 = 9.0$, H-C(6)), 4.59 (d, $J = 8.0$, H-N), 4.20-4.05 (m, 1H, $\text{ArNHCH}(\text{CH}_3)-$), 2.70-2.55 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.21 (s, 2H, $-\text{CH}_2\text{Ad}$), 1.96 (s, 3H, $-\text{Ad}$), 1.80-1.55 (m, 10H, $-\text{Ad}$, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$), 1.55-1.45 (m, 6H, $-\text{Ad}$), 1.30 (d, 3H, $J = 6.5$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 146.51 (C(8a)); 143.23 (d, $J = 242.8$, C(3)); 142.37 (d, $J = 27.5$, C(2)); 135.65 (d, $J = 5.4$, C(4)); 133.90 (d, $J = 2.3$, C(7)); 128.88 (C(8)); 125.87 (C(6)); 121.75 (d, $J = 4.9$, C(5)); 119.26 (d, $J = 5.0$, C(4a)); 62.72; 51.27 (d, $J = 9.0$, $\text{ArNHCH}(\text{CH}_3)-$); 50.35; 40.90; 37.13; 35.53; 33.27; 28.37; 26.19; 22.19. HRMS: m/z 430.24165 corresponds to molecular formula $\text{C}_{25}\text{H}_{33}\text{ClFN}_3\text{H}^+$ (error in ppm: - 0.76). HPLCpurity ($\lambda = 330 \text{ nm}$) method A: RT 8.579 min, area 98.70%; method B: RT 9.680 min, area 98.15%.

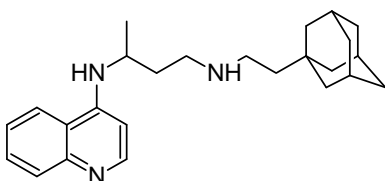
***N*¹-[2-(1-Adamantyl)ethyl]-*N*²-quinolin-4-ylpropane-1,2-diamine (35).**



Amine linker **S54** (260 mg, 1.10 mmol) and 4-chloroquinoline (180 mg, 1.10 mmol) and were mixed in NMP (1.5 mL) in MW cuvette under Ar. The reaction mixture was subjected to MW irradiation using a *Biotage Initiator 2.5 apparatus*, 1h, 180 °C. Compound **35** was obtained after multiple

chromatography: dry-flash SiO₂, eluent: [EtOAc/MeOH/(NH₃ aq) = 90/9/1] = 95/5 and flash chromatography (Biotage SP1-NH column, eluent: Hex/EtOAc = 6/4; RP column, eluent: MeOH/H₂O = 8/2), as light yellow foam softens at 112-113 °C. Yield: 253 mg (63%). IR (ATR): 3251m, 3059m, 2962m, 2902s, 2844s, 1708w, 1618w, 1578s, 1543s, 1451s, 1396s, 1374m, 1343m, 1280w, 1258w, 1159w, 1130w, 1108w, 909w, 807w, 763m, 733w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.53 (d, *J* = 5.3, H-C(2)), 7.97 (d, *J* = 8.0, H-C(8)), 7.81-7.76 (m, H-C(5)), 7.65-7.59 (m, H-C(7)), 7.46-7.37 (m, H-C(6)), 6.45 (d, *J* = 5.4, H-C(3)), 5.69 (bs, H-N), 3.87-3.73 (m, 1H, ArNHCH(CH₃)-), 2.91-2.81 (m, 2H, ArNHCH(CH₃)CH₂-), 2.70-2.61 (m, 2H, -CH₂CH₂Ad), 1.92 (s, 3H, -Ad), 1.73-1.57 (m, 7H, -NH-, -Ad), 1.55-1.44 (m, 6H, -Ad), 1.35-1.24 (m, 5H, CH₃, -CH₂Ad). ¹³C-NMR (125 MHz, CDCl₃, δ): 150.94; 149.21; 148.52; 129.81; 128.93; 124.45; 119.59; 119.12; 99.13; 54.69; 47.52; 44.79; 44.53; 42.69; 37.10; 31.91; 28.63; 18.30. HRMS: *m/z*364.27554 corresponds to molecular formula C₂₄H₃₃N₃H⁺ (error in ppm: - 1.37). Anal. (C₂₄H₃₃N₃ × H₂O) Calcd: C, 75.55; H, 9.25; N, 11.01. Found: C, 75.91; H, 8.82; N, 11.08. HPLC purity (λ = 330 nm) method A: RT 0.998 min, area 99.11%; method B: RT 9.586 min, area 95.01%.

***N*¹-[2-(1-Adamantyl)ethyl]-*N*³-quinolin-4-ylbutane-1,3-diamine (37).**

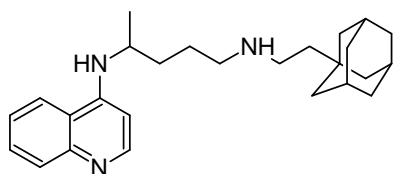


Compound **37** was prepared by method H from amine linker **S55** (150 mg, 0.60 mmol) and 4-chloroquinoline (82 mg, 0.50 mmol) using Pd(OAc)₂ (4.48 mg, 0.02 mmol), SPhos (16.38 mg, 0.04 mmol) and K₃PO₄ (265 mg, 1.25 mmol) and

was obtained after dry-flash chromatography: SiO₂, gradient: EtOAc/[MeOH/(NH₃ aq) = 9/1] = 9/1 → 7/3, as colorless foam softens at 64-66 °C. Yield: 146 mg (77%). IR (ATR): 3250m, 3069m, 2962m, 2902s, 2844s, 1654w, 1618w, 1543s, 1448m, 1397m, 1373m, 1340m, 1281w, 1263m, 1182w, 1148m, 1051w, 1025w, 960w, 810m, 764m, 737m, 702w, 651w, 633w cm⁻¹. ¹H-NMR (500 MHz, CDCl₃, δ): 8.49 (d, *J* = 5.4, H-C(2)), 7.94 (d, *J* = 8.3, H-C(8)), 7.84 (d, *J* = 8.2, H-C(5)), 7.70-7.50 (m, H-N and H-C(7)), 7.40-7.35 (m, H-C(6)), 6.37 (d, *J* = 5.5, H-C(3)), 3.95-3.80 (m, 1H, ArNHCH(CH₃)-), 3.15-2.90 (m, 1H, -CH₂NHCH₂CH₂Ad), 2.85-2.75 (m, 1H, -CH₂NHCH₂CH₂Ad), 2.70-2.60 (m, 2H, -CH₂CH₂Ad), 2.00-1.85 (m, 4H, -Ad, -ArNHCH(CH₃)CH₂-), 1.80-1.55 (m, 7H, ArNHCH(CH₃)CH₂-, -Ad), 1.55-1.45 (m, 6H, -Ad), 1.40-1.35 (m, 2H, -CH₂Ad), 1.32 (d, 3H, *J* = 6.3, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ):

150.76; 149.81; 148.35; 129.39; 128.83; 123.99; 120.69; 119.27; 98.21; 48.19; 46.60; 44.79; 44.45; 42.65; 37.07; 35.05; 31.83; 28.60; 19.21. HRMS: m/z 378.29070 corresponds to molecular formula $C_{25}H_{35}N_3H^+$ (error in ppm: + 0.85). HPLC purity ($\lambda = 330$ nm) method A: RT 0.999 min, area 97.38%; method B: RT 2.506 min, area 99.48%.

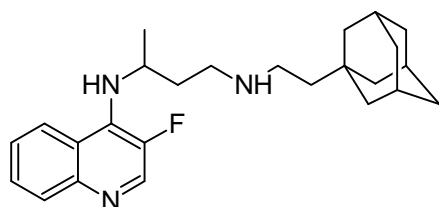
N^1 -[2-(1-Adamantyl)ethyl]- N^4 -quinolin-4-ylpentane-1,4-diamine (44).



Compound **44** was prepared by method H from amine linker **S56** (242 mg, 0.73 mmol) and 4-chloroquinoline (100 mg, 0.61 mmol) and using $Pd(OAc)_2$ (5.47 mg, 0.024 mmol), SPhos (20 mg, 0.049 mmol) and K_3PO_4 (324mg, 1.53 mmol)

and was obtained after dry-flash chromatography: SiO_2 , gradient: EtOAc/[MeOH/(NH_3 aq) = 9/1] = 9/1 \rightarrow 7/3, as yellow foam softens at 64-65 °C. Yield: 203 mg (85%). IR (ATR): 3651w, 3287m, 3067s, 2902s, 2845s, 1618w, 1580s, 1541s, 1450m, 1396m, 1342m, 1261w, 1225w, 1139w, 808w, 766m, 736w, 652w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 8.52 (d, $J = 5.4$, H-C(2)), 7.96 (d, $J = 8.5$, H-C(8)), 7.78 (d, $J = 8.4$, H-C(5)), 7.65-7.55 (m, H-C(7)), 7.45-7.35 (m, H-C(6)), 6.41 (d, $J = 5.3$, H-C(3)), 5.39 (d, $J = 6.1$, H-N), 3.80-3.65 (m, 1H, ArNHCH(CH_3)-), 2.70-2.63 (m, 2H, $-CH_2NHCH_2CH_2Ad$), 2.63-2.55 (m, 2H, $-CH_2CH_2Ad$), 1.97-1.87 (m, 3H, -Ad), 1.85-1.55 (m, 10H, ArNHCH(CH_3) CH_2 -, ArNHCH(CH_3) CH_2CH_2 -, -Ad), 1.50-1.40 (m, 6H, -Ad), 1.35-1.20 (m, 5H, CH_3 , $-CH_2Ad$). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 150.88; 148.99; 148.51; 129.78; 128.86; 124.30; 119.54; 118.84; 98.79; 49.67; 48.16; 44.51; 44.29; 42.57; 37.06; 34.12; 31.78; 28.59; 26.40; 20.20. HRMS: m/z 392.30696 corresponds to molecular formula $C_{26}H_{37}N_3H^+$ (error in ppm: + 2.38). Anal. ($C_{26}H_{37}N_3 \times H_2O$) Calcd: C, 76.24; H, 9.60; N, 10.26; Found: C, 76.28; H, 9.30; N, 10.19. HPLC purity ($\lambda = 330$ nm) method A: RT 1.000 min, area 98.19%; method B: RT 9.653 min, area 95.14%.

N^1 -[2-(1-Adamantyl)ethyl]- N^3 -(3-fluoroquinolin-4-yl)butane-1,3-diamine (39).

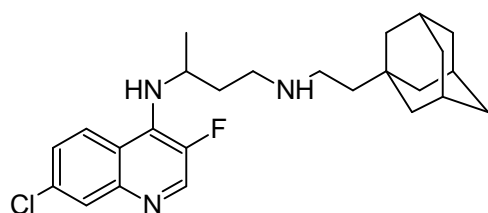


Compound **39** was prepared by method E from aminoquinoline **S56** (245 mg, 1.05 mmol) and 1-adamantylacetaldehyde (156 mg, 0.88 mmol) using AcOH (121 μ L, 1.32 mmol) and $NaBH_4$ (200 mg, 5.28 mmol) and was obtained after flash

chromatography SiO_2 , gradient: Hex/EtOAc = 7/3 \rightarrow 8/2, as colorless viscous oil (167 mg, 48%). IR (ATR): 3302m, 2904s, 2845s, 1680w, 1600m, 1577m, 1540m, 1449w, 1398m, 1364w, 1270w, 1200w, 1143w, 762w, 736w cm^{-1} . 1H -NMR (500 MHz, $CDCl_3$, δ): 8.50 (d, $J = 5.5$, H-C(2)), 8.05 (d, $J = 8.2$, H-C(8)), 7.95 (d, $J = 8.2$, H-C(5)), 7.63-7.56 (m, H-C(7)), 7.48-7.42 (m, H-C(6)), 6.21 (bs, H-N), 4.25 (s, 1H, ArNHCH(CH_3)-), 3.10-3.03 (m, 2H, ArNHCH(CH_3) CH_2 -), 2.85-2.73 (m, 2H, $-CH_2CH_2Ad$), 2.11-2.02 (m, 1H, ArNHCH(CH_3) CH_2CH_2 -), 2.02-1.94 (m, 1H, ArNHCH(CH_3) CH_2CH_2 -), 1.90 (s, 3H, -Ad),

1.75-1.53 (m, 6H, -Ad), 1.53-1.38 (m, 8H, -CH₂Ad, -Ad), 1.30 (d, 3H, *J* = 6.4, CH₃). ¹³C-NMR(125 MHz, CDCl₃, δ): 145.93 (C(8a)); 142.76 (d, *J* = 238.3, C(3)); 141.47 (d, *J* = 27.1, C(2)); 135.88 (d, *J* = 5.4, C(4)); 129.67 (C(8)); 127.72 (C(7)); 124.55 (C(6)); 121.35 (d, *J* = 5.4, C(4a)); 121.15 (d, *J* = 5.4, C(5)); 50.24 (d, *J* = 9.0, CH); 46.16; 44.69; 44.46; 42.55; 36.98; 35.44; 31.72; 28.52; 21.31 (d, *J* = 3.6, CH₃). HRMS: *m/z*396.28038 corresponds to molecular formula C₂₅H₃₄FN₃H⁺ (error in ppm: -1.45). HPLCpurity (λ = 330 nm) method A: RT 8.269 min, area 98.81%; method B: RT 8.721 min, area 99.15%.

***N*¹-[2-(1-Adamanty)ethyl]-*N*³-(7-chloro-3-fluoroquinolin-4-yl)butane-1,3-diamine (38).**

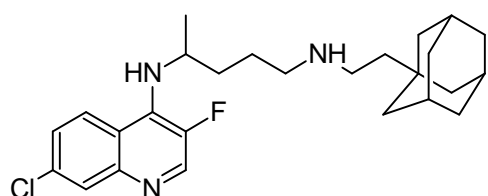


Compound **38** was prepared by method H from amine linker **S55** (123 mg, 0.49 mmol) and 7-chloro-3-fluoro-4-iodoquinoline **17** (137 mg, 0.45 mmol) using Pd(OAc)₂ (4.0 mg, 0.018 mmol), DPEphos (19.39 mg, 0.036 mmol) and K₃PO₄ (239 mg, 1.13 mmol) and

was obtained after multiple chromatography: dry-flash SiO₂, gradient:

CH₂Cl₂/MeOH(NH₃sat.) = 95/5 → 8/2, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3 and RP column, eluent: MeOH/H₂O = 8/2), as colorless viscous oil (46 mg, 24%). IR(ATR): 3283m, 2974w, 2906s, 2848s, 2779w, 2696w, 2448w, 1570s, 1493w, 1451w, 1416w, 1380m, 1346m, 1265w, 1194w, 1131m, 1075w, 1014w, 937m, 817m, 767m, 727m, 638w cm⁻¹. λ_{max}(ε) = 250 (13796), 331 (8004) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 8.46 (d, *J* = 6.0, H-C(2)), 7.91 (d, *J* = 2.0, H-C(8)), 7.84 (d, *J* = 9.5, H-C(5)), 7.48 (bs, H-N), 7.31 (dd, *J*₁ = 1.5, *J*₂ = 9.0, H-C(6)), 4.35 (bs, 1H, ArNHCH(CH₃)-), 3.05-2.95 (m, 1H, -CH₂NHCH₂CH₂Ad), 2.95-2.85 (m, 1H, -CH₂NHCH₂CH₂Ad), 2.75-2.60 (m, 2H, -CH₂CH₂Ad), 2.05-1.90 (m, 4H, -Ad, ArNHCH(CH₃)CH₂-), 1.75-1.60 (m, 7H, -Ad, ArNHCH(CH₃)CH₂-), 1.55-1.45 (m, 6H, -Ad), 1.45-1.30 (m, 2H, -CH₂Ad), 1.32 (d, 3H, *J* = 7.0, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 146.10 (C(8a)); 143.22 (d, *J* = 204.5, C(3)); 142.04 (d, *J* = 28.5, C(2)); 136.18 (d, *J* = 4.5, C(4)); 134.52 (d, *J* = 1.8, C(7)); 128.21 (C(8)); 126.50 (C(6)); 122.92 (d, *J* = 5.0, C(5)); 119.70 (d, *J* = 5.0, C(4a)); 50.06 (d, *J* = 10.5, ArNHCH(CH₃)-); 45.40; 43.08; 41.99; 39.72; 36.66; 33.32; 31.61; 28.25; 22.77. HRMS: *m/z*430.24104 corresponds to molecular formula C₂₅H₃₃ClFN₃H⁺ (error in ppm: -2.19). HPLCpurity (λ = 330 nm) method A: RT 5.879 min, area 96.49%; method B: RT 11.796 min, area 97.32%.

***N*¹-[2-(1-adamanty)ethyl]-*N*⁴-(7-chloro-3-fluoroquinolin-4-yl)pentane-1,4-diamine (45).**

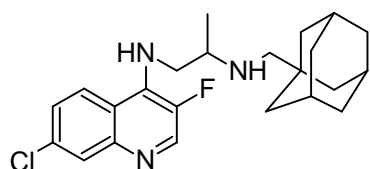


Compound **45** was prepared by method H from amine linker **56** (73 mg, 0.24 mmol) and 7-chloro-3-fluoro-4-iodoquinoline **17** (66 mg, 0.22 mmol) using Pd(OAc)₂

(2.1 mg, 0.009 mmol), DPEphos (4.7 mg, 0.019 mmol) and K_3PO_4 (117 mg, 0.6 mmol) and was obtained after multiple chromatography: dry-flash SiO_2 , gradient:

$CH_2Cl_2/MeOH(NH_3sat.) = 95/5 \rightarrow 7/3$, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3 and RP column, gradient: MeOH/ $H_2O = 8/2 \rightarrow 9/1$) as yellow foam (39 mg, 41%). IR(ATR): 3294m, 3069w, 2903s, 2846j, 2676w, 1734w, 1595m, 1574s, 1539m, 1487w, 1450m, 1419m, 1381m, 1350m, 1294w, 1265m, 1199w, 1142m, 1105m, 1078w, 928w, 877w, 815m, 763w, 738w, 656w, 540w cm^{-1} . $\lambda_{max}(\epsilon) = 237$ (10560), 251 (10259), 331 (6457), 338(6502) nm. 1H -NMR (500 MHz, $CDCl_3$, δ): 8.48 (d, $J = 5.6$, H-C(2)), 7.93 (d, $J = 2.0$, H-C(8)), 7.76 (d, $J = 9.0$, H-C(5)), 7.36 (dd, $J_1 = 2.0$, $J_2 = 9.0$, H-C(6)), 4.86 (d, $J = 7.8$, H-N), 4.20-4.05 (m, 1H, ArNHCH(CH_3)-), 2.70-2.60 (m, 2H, $-CH_2NHCH_2CH_2Ad$), 2.70-2.60 (m, 2H, $-CH_2CH_2Ad$), 1.91 (s, 3H, Ad), 1.75-1.55 (m, 10H, Ad, ArNHCH(CH_3) CH_2 -), ArNHCH(CH_3) CH_2CH_2 -), 1.50-1.40 (m, 6H, Ad), 1.27 (d, 3H, $J = 6.3$, CH_3), 1.30-1.20 (m, 2H, $-CH_2Ad$). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 146.56 (C(8a)); 143.24 (d, $J = 240.0$, C(3)); 142.43 (d, $J = 27.5$, C(2)); 135.76 (d, $J = 5.9$, C(4)); 133.95 (C(7)); 128.87 (C(8)); 125.93 (C(6)); 121.19 (d, $J = 5.0$, C(5)); 119.37 (d, $J = 5.0$, C(4a)); 51.25 (d, $J = 8.6$, ArNHCH(CH_3)-); 49.57; 44.30; 44.20; 42.56; 37.06; 35.64; 31.78; 28.59; 26.26; 22.27. HRMS: m/z 444.25601 corresponds to molecular formula $C_{26}H_{35}ClFN_3H^+$ (error in ppm: - 3.64). HPLCpurity ($\lambda = 254$ nm) method A: RT 4.409 min, area 95.01%; method B: RT 9.856 min, area 95.13%.

N^2 -(1-adamantylmethyl)- N^1 -(7-chloro-3-fluoroquinolin-4-yl)propane-1,2-diamine (21).

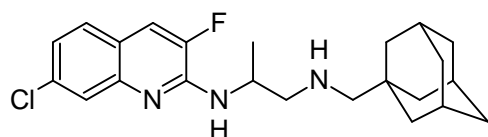


Compound **21** was prepared from amine linker **S20** (122 mg, 0.55 mmol) and 7-chloro-3-fluoro-4-iodoquinoline **17** (160 mg, 0.52 mmol) in MW (*Biotage Initiator 2.5 apparatus*, PrOH, 4h, 180 °C) and was obtained after multiple chromatography: dry-

flash SiO_2 , eluent: $CH_2Cl_2/MeOH(NH_3sat.) = 95/5$, and flash chromatography (Biotage SP1 RP column, eluent: MeOH/ $H_2O = 9/1$) as colorless viscous oil (127 mg, 61%). IR (ATR): 3322s, 2964w, 2910s, 2845s, 2659w, 1614m, 1598m, 1570m, 1519m, 1476m, 1454m, 1419w, 1377w, 1354w, 1310m, 1256m, 1211w, 1192w, 1159m, 1135w, 1097m, 1072w, 1054w, 953w, 922w, 897w, 875w, 809m, 759m, 656w, 577w, 538m, 495w cm^{-1} . $\lambda_{max}(\epsilon) = 237$ (14605), 250 (15056), 336 (9232) nm. 1H -NMR (500 MHz, $CDCl_3$, δ): 8.51 (d, $J = 5.5$, H-C(2)), 7.93 (d, $J = 2.0$, H-C(8)), 7.76 (d, $J = 9.0$, H-C(5)), 7.34 (dd, $J_1 = 2.0$, $J_2 = 9.0$, H-C(6)), 6.06 (s, H-N), 3.80-3.70 (m, 1H, ArNH CH_2 -), 3.35-3.25 (m, 1H, ArNH CH_2 -), 2.95-2.85 (m, 1H, $-CH(CH_3)NHCH_2Ad$), 2.43 (ABq, H_A , $J = 11.4$, $-CH_2Ad$), 2.13 (ABq, H_B , $J = 11.4$, $-CH_2Ad$), 1.99 (s, 3H, -Ad), 1.80-1.64 (m, 6H, -Ad), 1.64-1.45 (m, 6H, -Ad), 1.18 (d, 3H, $J = 6.4$, CH_3). ^{13}C -NMR (125 MHz, $CDCl_3$, δ): 146.49 (C(8a)); 143.51 (d, $J = 239.1$, C(3)); 142.22 (d, $J = 26.6$, C(2)); 136.88 (d, $J = 5.9$, C(4)); 133.80 (C(7)); 128.78 (C(8)); 125.62

(C(6)); 121.91 (d, $J = 5.4$, C(5)); 119.19 (d, $J = 5.0$, C(4a)); 59.14; 53.12; 49.15 (d, $J = 8.1$, ArNHCH(CH₃)-); 40.92; 37.16; 33.38; 29.64; 19.06. HRMS: m/z 402.21027 corresponds to molecular formula C₂₃H₂₉ClFN₃H⁺ (error in ppm: - 1.03). Anal. (C₂₃H₂₉ClFN₃) Calcd: C, 68.73; H, 7.27; N, 10.45. Found: C, 67.06; H, 6.98; N, 10.18. HPLC purity ($\lambda = 254$ nm) method A: RT 7.970 min, area 97.00%; method B: RT 9.932 min, area 99.14%.

***N*¹-(1-Adamantylmethyl)-*N*²-(7-chloro-3-fluoroquinolin-2-yl)propane-1,2-diamine (68).**

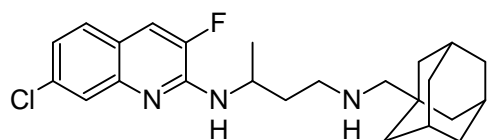


Compound **68** was prepared from amine linker **S51**

(166 mg, 0.75 mmol) and 7-chloro-3-fluoro-2-iodoquinoline **18** (153 mg, 0.50 mmol) in MW

(Biotage Initiator 2.5 apparatus, PrOH, 4h, 180 °C) and was obtained after multiple chromatography: dry-flash SiO₂, eluent: CH₂Cl₂/MeOH(NH₃sat.) = 95/5, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3 and RP column, eluent: MeOH/H₂O = 85/15), as colorless viscous oil (18.3 mg, 9.1%). IR(ATR): 3362m, 2902s, 2846s, 2675w, 1717w, 1637m, 1608m, 1566w, 1528s, 1492w, 1453m, 1451m, 1368w, 1344m, 1316w, 1260m, 1188m, 1148m, 1118m, 1073w, 976w, 929w, 880m, 801m, 760m, 602w, 513w cm⁻¹. $\lambda_{\text{max}}(\epsilon) = 241$ (32222), 331 (7158), 343 (6902) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 7.71 (d, $J = 1.8$, H-C(8)), 7.43 (d, $J = 8.5$, H-C(5)), 7.38 (d, $J = 11.2$, H-C(4)), 7.17 (dd, $J_1 = 1.8$, $J_2 = 8.4$, H-C(6)), 5.68 (d, $J = 5.4$, H-N), 4.45-4.35 (m, 1H, ArNHCH(CH₃)CH₂-), 2.85-2.75 (m, 1H, -CH₂NHCH₂Ad), 2.34 (ABq, H_A , $J = 11.7$, -CH₂Ad), 2.32 (ABq, H_B , $J = 11.7$, -CH₂Ad), 1.93 (s, 3H, -Ad), 1.80-1.55 (m, 6H, -Ad), 1.55-1.40 (m, 6H, -Ad), 1.33 (d, 3H, $J = 6.6$, CH₃). ¹³C-NMR (125 MHz, CDCl₃, δ): 148.87 (d, $J = 13.5$, C(8a)); 147.30 (d, $J = 258.6$, C(3)); 145.20 (d, $J = 2.7$, C(2)); 133.90 (d, $J = 2.3$, C(7)); 127.79 (C(5)); 125.26 (C(8)); 123.23 (C(6)); 121.48 (d, $J = 4.1$, C(4a)); 116.01 (d, $J = 15.4$, C(4)); 62.27; 55.65; 45.61; 40.66; 37.08; 33.48; 28.34; 18.93. HRMS: m/z 402.21021 corresponds to molecular formula C₂₃H₂₉ClFN₃H⁺ (error in ppm: - 1.16). Anal. (C₂₃H₂₉ClFN₃ × 1/3 H₂O) Calcd: C, 67.72; H, 7.33; N, 10.30. Found: C, 67.72; H, 6.99; N, 10.28. HPLCpurity ($\lambda = 254$ nm) method A: RT 8.772 min, area 95.58%; method B: RT 10.676 min, area 95.05%.

***N*¹-(1-Adamantylmethyl)-*N*³-(7-chloro-3-fluoroquinolin-2-yl)butane-1,3-diamine (69).**



Compound **69** was prepared by method H from amine

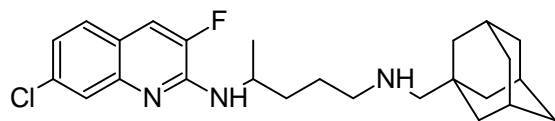
linker **S52** (78 mg, 0.33 mmol) and 7-chloro-3-fluoro-2-iodoquinoline **18** (93 mg, 0.30 mmol) using

Pd(OAc)₂ (2.7 mg, 0.012 mmol), SPhos (9.85 mg,

0.024 mmol) and K₃PO₄ (159 mg, 0.75 mmol) and was obtained after multiple chromatography: dry-flash SiO₂, gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5 → 8/2, and flash chromatography (Biotage SP1 NH column, eluent: Hex/EtOAc = 7/3 and RP column, eluent: MeOH/H₂O = 8/2), as colorless viscous oil (66 mg, 53%). IR(ATR): 3439w, 3262m, 3085w,

3040w, 2901s, 2845s, 2675w, 1637m, 1606w, 1568m, 1531s, 1492w, 1457m, 1416m, 1376w, 1345m, 1316w, 1289w, 1258m, 1189m, 1147m, 1119m, 1074w, 1005w, 970w, 930w, 882m, 799m, 760m, 739w, 601w, 512w cm^{-1} . $\lambda_{\text{max}}(\epsilon) = 242 (32836), 330 (8319), 341 (7836) \text{ nm}$. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.68 (d, $J = 1.7$, H-C(8)), 7.41 (d, $J = 8.5$, H-C(5)), 7.35 (d, $J = 11.3$, H-C(4)), 7.14 (dd, $J_1 = 1.7, J_2 = 8.4$, H-C(6)), 6.30 (d, $J = 6.4$, H-N), 4.55-4.45 (m, 1H, $\text{ArNHCH}(\text{CH}_3)-$), 2.85-2.75 (m, 1H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Ad}$), 2.75-2.65 (m, 1H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Ad}$), 2.27 (ABq, $H_A, J = 11.4$, $-\text{CH}_2\text{Ad}$), 2.19 (ABq, $H_B, J = 11.4$, $-\text{CH}_2\text{Ad}$), 2.00-1.90 (m, 3H, Ad), 1.90-1.80 (m, 1H, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$), 1.75-1.60 (m, 6H, Ad), 1.57-1.47 (m, 6H, Ad), 1.32 (d, 3H, $J = 6.4$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 148.59 (d, $J = 13.1$, C(8a)); 147.31 (d, $J = 259.0$, C(3)); 145.44 (d, $J = 2.7$, C(2)); 133.78 (d, $J = 2.7$, C(7)); 127.71 (d, $J = 5.0$, C(5)); 125.23 (C(8)); 122.88 (C(6)); 121.27 (d, $J = 4.0$, C(4a)); 115.76 (d, $J = 13.33$, C(4)); 63.19; 47.52; 45.26; 40.89; 37.20; 35.87; 33.26; 28.47; 20.55. HRMS: m/z 416.22589 corresponds to molecular formula $\text{C}_{24}\text{H}_{31}\text{ClFN}_3\text{H}^+$ (error in ppm: -1.07). HPLC purity ($\lambda = 254 \text{ nm}$) method A: RT 8.726min, area 95.12%; method B: RT 11.064 min, area 95.72%.

N^1 -(1-Adamantylmethyl)- N^4 -(7-chloro-3-fluoroquinolin-2-yl)pentane-1,4-diamine (70).

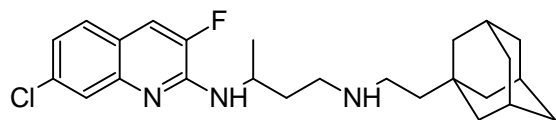


Compound **70** was prepared by method H from amine linker **S53** (67 mg, 0.27 mmol) and 7-chloro-3-fluoro-2-iodoquinoline **18** (75 mg, 0.24

mmol) using $\text{Pd}(\text{OAc})_2$ (2.2 mg, 0.009 mmol), DPEphos (10.34 mg, 0.019 mmol) and K_3PO_4 (127 mg, 0.6 mmol) and was obtained after multiple chromatography: dry-flash SiO_2 , gradient: $\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3\text{sat.}) = 95/5 \rightarrow 7/3$, and flash chromatography (Biotage SP1 NH column, eluent: $\text{Hex}/\text{EtOAc} = 7/3$ and RP column, eluent: $\text{MeOH}/\text{H}_2\text{O} = 8/2 \rightarrow 9/1$), as colorless viscous oil (55 mg, 51%). IR (ATR): 3442m, 3323w, 2902s, 2846m, 1637m, 1609w, 1568w, 1530s, 1492w, 1458m, 1415m, 1345w, 1262w, 1188w, 1146w, 1119w, 1069w, 883w, 799w, 760w, 733w, 602w, 514w cm^{-1} . $\lambda_{\text{max}}(\epsilon) = 242 (35870), 332 (7652), 345 (7674) \text{ nm}$. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.69 (d, $J = 1.5$, H-C(8)), 7.42 (d, $J = 9.0$, H-C(5)), 7.36 (d, $J = 11.5$, H-C(4)), 7.16 (dd, $J_1 = 2.0, J_2 = 8.5$, H-C(6)), 5.11 (d, $J = 6.5$, H-N), 4.50-4.30 (m, 1H, $\text{ArNHCH}(\text{CH}_3)-$), 2.70-2.55 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.22 (s, 2H, $-\text{CH}_2\text{Ad}$), 1.94 (s, 3H, Ad), 1.75-1.55 (m, 10H, Ad, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$), 1.55-1.45 (m, 6H, Ad), 1.29 (d, 3H, $J = 6.5$, CH_3). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 148.36 (d, $J = 13.5$, C(8a)); 147.14 (d, $J = 258.1$, C(3)); 145.37 (d, $J = 2.2$, C(2)); 133.86 (d, $J = 2.2$, C(7)); 127.74 (d, $J = 5.0$, C(5)); 125.32 (C(8)); 123.06 (C(6)); 121.29 (d, $J = 4.0$, C(5)); 115.84 (d, $J = 15.2$, C(4a)); 62.81; 50.62; 45.94; 40.90; 37.18; 34.36; 33.28; 28.44; 26.15; 20.79. HRMS: m/z 430.24169 corresponds to molecular formula $\text{C}_{25}\text{H}_{33}\text{ClFN}_3\text{H}^+$ (error in ppm: -

0.67).HPLCpurity ($\lambda = 330$ nm) method A: RT 9.631min, area 95.45%; method B: RT 10.444 min, area 98.16%.

***N*¹-[2-(1-Adamantyl)ethyl]-*N*³-(7-chloro-3-fluoroquinolin-2-yl)butane-1,3-diamine (71).**



Compound **71** was prepared by method H from

amine linker **S55**(89 mg, 0.36 mmol) and 7-

chloro-3-fluoro-2-iodoquinoline **18**(99 mg, 0.32

mmol) using Pd(OAc)₂ (2.9 mg, 0.013 mmol), DPEphos (13.79 mg, 0.026 mmol) and K₃PO₄

(169 mg, 0.8 mmol) and was obtained after multiple chromatography: dry-flash SiO₂,

gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5 → 7/3, and flash chromatography (Biotage SP1 NH

column, eluent: Hex/EtOAc = 7/3 and RP column, eluent: MeOH/H₂O = 8/2 → 9/1), as

colorless viscous oil (73 mg, 53%). IR(ATR): 3340m, 3233m, 2903s, 2845s, 2676w, 1637m,

1609w, 1567w, 1533s, 1492w, 1456m, 1415m, 1372w, 1344w, 1258w, 1189m, 1146m,

1119m, 1073w, 968w, 908w, 882m, 800w, 760w, 733m, 602w, 513w, 476w cm⁻¹. $\lambda_{\max}(\epsilon) =$

252 (28029), 347 (8156) nm. ¹H-NMR (500 MHz, CDCl₃, δ): 7.67 (d, *J* = 2.0, H-C(8)), 7.43

(d, *J* = 8.5, H-C(5)), 7.37 (d, *J* = 11.0, H-C(4)), 7.16 (dd, *J*₁ = 1.5, *J*₂ = 8.5, H-C(6)), 5.94 (d, *J*

= 6.5, H-N), 4.55-4.45 (m, 1H, ArNHCH(CH₃)-), 2.83-2.73 (m, 1H, -CH₂NHCH₂CH₂Ad),

2.73-2.65 (m, 1H, -CH₂NHCH₂CH₂Ad), 2.60-2.53 (m, 1H, -CH₂CH₂Ad), 2.53-2.45 (m, 1H, -

CH₂CH₂Ad), 1.95-1.80 (m, 4H, ArNHCH(CH₃)CH₂-, -Ad), 1.75-1.55 (m, 7H, -Ad,

ArNHCH(CH₃)CH₂-), 1.47-1.43 (m, 6H, -Ad), 1.33 (d, 3H, *J* = 6.5, CH₃), 1.20-1.30 (-

CH₂Ad). ¹³C-NMR (125 MHz, CDCl₃, δ): 148.64 (d, *J* = 13.5, C(8a)); 147.22 (d, *J* = 258.6,

C(3)); 145.32 (d, *J* = 2.8, C(2)); 133.91 (d, *J* = 2.2, C(7)); 127.81(d, *J* = 4.9, (C(5)); 125.19

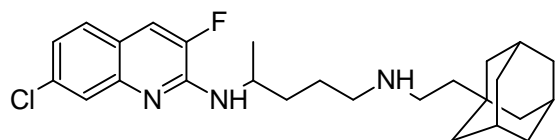
(C(8)); 123.06 (C(6)); 121.30 (d, *J* = 4.6, C(5)); 115.89 (d, *J* = 15.4, C(4a)); 46.69; 44.88;

44.76; 44.36; 42.57; 37.14; 36.81; 31.78; 28.67; 21.07. HRMS: *m/z*430.24162 corresponds to

molecular formula C₂₅H₃₃ClFN₃H⁺ (error in ppm: - 0.84).HPLCpurity ($\lambda = 254$ nm) method

A: RT 9.012min, area 95.42%; method B: RT 11.228 min, area 96.01%.

***N*¹-[2-(1-Adamantyl)ethyl]-*N*⁴-(7-chloro-3-fluoroquinolin-2-yl)pentane-1,4-diamine (72).**



Compound **72** was prepared by method H from

amine linker **S56** (89 mg, 0.34 mmol) and 7-

chloro-3-fluoro-2-iodoquinoline **18** (94 mg, 0.30

mmol) using Pd(OAc)₂ (2.7 mg, 0.012 mmol), DPEphos (12.9 mg, 0.024 mmol) and K₃PO₄

(159 mg, 0.75 mmol) and was obtained after multiple chromatography: dry-flash SiO₂,

gradient: CH₂Cl₂/MeOH(NH₃sat.) = 95/5 → 7/3, and flash chromatography (Biotage SP1 NH

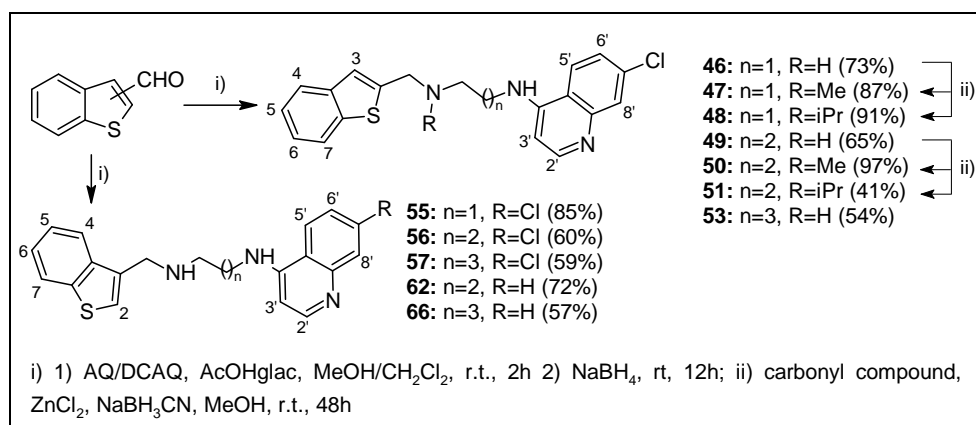
column, eluent: Hex/EtOAc = 7/3 and RP column, gradient: MeOH/H₂O = 8/2 → 9/1), as

colorless viscous oil (74 mg, 56%). IR(ATR): 2903s, 2846s, 2676w, 1628m, 1592w, 1514s,

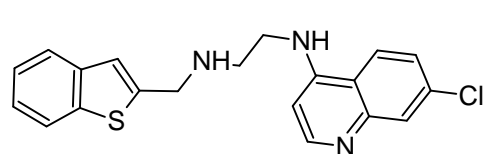
1463m, 1425m, 1379m, 1331w, 1252m, 1216w, 1196w, 1146m, 1119m, 1070m, 976w,

930m, 887m, 800m, 738m, 648w, 600w, 519w, 474w, 409w cm⁻¹. $\lambda_{\max}(\epsilon) = 253(26082), 349$

(7096) nm. $^1\text{H-NMR}$ (500 MHz, CDCl_3 , δ): 7.69 (d, $J = 2.0$, H-C(8)), 7.34 (d, $J = 8.5$, H-C(5)), 7.38 (d, $J = 11.0$, H-C(4)), 7.12 (dd, $J_1 = 2.0$, $J_2 = 8.5$, H-C(6)), 5.14 (d, $J = 6.5$, H-N), 4.50-4.30 (m, 1H, $\text{ArNHCH}(\text{CH}_3)-$), 2.70-2.60 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{Ad}$), 2.60-2.50 (m, 2H, $-\text{CH}_2\text{CH}_2\text{Ad}$), 1.92 (s, 3H, -Ad), 1.75-1.55 (m, 10H, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2-$, $\text{ArNHCH}(\text{CH}_3)\text{CH}_2\text{CH}_2$, -Ad), 1.55-1.45 (m, 6H, -Ad), 1.29 (d, 3H, $J = 6.5$, CH_3), 1.27-1.229 (d, 2H, $-\text{CH}_2\text{Ad}$). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3 , δ): 148.42 (d, $J = 13.0$, C(8a)); 147.17 (d, $J = 250.0$, C(3)); 145.39 (d, $J = 2.2$, C(2)); 133.65 (d, $J = 2.2$, C(7)); 127.80 (d, $J = 4.5$, C(5)); 125.30 (C(8)); 123.14 (C(6)); 121.35 (d, $J = 4.1$, C(5)); 115.92 (d, $J = 15.2$, C(4a)); 49.84; 45.83; 44.62; 44.24; 42.61; 37.15; 34.58; 31.83; 28.67; 26.36; 20.82. HRMS: m/z 444.25698 corresponds to molecular formula $\text{C}_{26}\text{H}_{35}\text{ClFN}_3\text{H}^+$ (error in ppm: - 1.46). HPLCpurity ($\lambda = 254$ nm) method A: RT 9.784 min, area 96.93%; method B: RT 12.131 min, area 96.48%.



N-(1-benzothiophen-2-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)ethane-1,2-diamine(**46**).

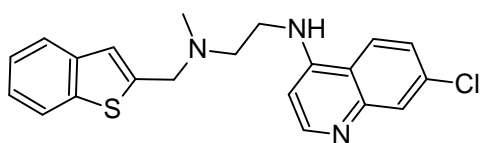


Compound **46** was prepared by method E from 1-benzothiophene-2-carbaldehyde (240 mg, 1.48 mmol), using amine **AQ2** (489 mg, 2.21 mmol). The product

was purified using column chromatography (dry-flash, SiO_2 , eluent EtOAc/Hex gradient 9/1 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow 6/4 and flash chromatography, Biotage SP1, RP column, eluent MeOH/ H_2O gradient 65/35 \rightarrow MeOH). Final product **46** was obtained as a pale yellow powder (396 mg, 73%). M.p. = 135 – 139 $^\circ\text{C}$. IR (ATR): 3226m, 3063m, 2946w, 2836w, 1578s, 1452m, 1374m, 1330w, 1285w, 1254w, 1210w, 1137m, 1080w, 1023w, 965w, 930w, 895w, 850w, 813w, 778m, 742w, 643w cm^{-1} . $^1\text{H NMR}$ (500 MHz, CDCl_3 , δ): 8.49 (d, $J = 5.3$, H-C(2')), 7.95 (d, $J = 2.1$, H-C(8')), 7.82-7.79 (m, H-C(7)), 7.76 (d, $J = 8.9$, H-C(5')), 7.70-7.67 (m, H-C(4)), 7.37 (dd, $J_1 = 8.9$, $J_2 = 2.3$, H-C(6')), 7.35-7.28 (m, H-C(5) and H-C(6)), 7.16-7.15 (m, H-C(3)), 6.34 (d, $J = 5.5$, H-C(3')), 5.87 (bs, H-N exchangeable with D_2O), 4.15-4.13 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}-$), 3.34-3.29 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}-$), 3.09-3.06 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}-$), 1.86 (s, H-N exchangeable with D_2O). $^{13}\text{C NMR}$

(125 MHz, CDCl₃, δ): 152.01, 149.78, 149.11, 144.98, 139.65, 139.45, 134.74, 128.65, 125.18, 124.32, 124.11, 123.16, 122.34, 121.56, 121.38, 117.34, 99.12, 48.56, 46.44, 42.09. HRMS: m/z 368.09836 corresponds to molecular formula C₂₀H₁₈ClN₃SH⁺ (error in ppm - 0.02). Anal. (C₂₀H₁₈ClN₃S \times 0.25H₂O) Calcd: C, 64.50; H, 5.01; N, 11.28; S, 8.61. Found: C, 64.67; H, 4.95; N, 11.31; S 8.53. HPLC purity (λ = 330 nm): method A: RT 8.938 min, area 98.51%; method B: RT 8.116 min, area 98.14%.

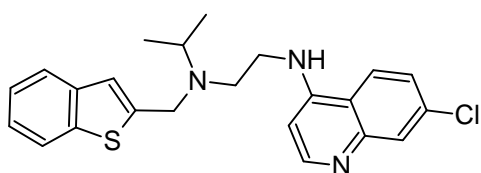
***N*-(1-benzothien-2-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)-*N*-methylethane-1,2-diamine(47).**



Compound **47** was prepared by method K from **46** (199 mg, 0.543 mmol). The product was purified using column chromatography (dry-flash, SiO₂, eluent

EtOAc/Hex gradient 1/1 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow 1/1). Final product **47** was obtained as yellow oil (180 mg, 87%). IR (ATR): 3395w, 3060w, 2950w, 2846w, 2801w, 1609m, 1581s, 1527m, 1452m, 1366m, 1330m, 1275w, 1241w, 1206w, 1130w, 1076w, 1032w, 879w, 809w, 747w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.49 (d, J = 5.3, H-C(2')), 7.95 (d, J = 2.1, H-C(5')), 7.86 (d, J = 8.9, H-C(8')), 7.82-7.79 (m, H-C(7')), 7.70-7.67 (m, H-C(4')), 7.41 (dd, J_1 = 8.9, J_2 = 2.2, H-C(6')), 7.35-7.28 (m, H-C(5) and H-C(6)), 7.16 (s, H-C(3)), 6.31 (d, J = 5.4, H-C(3')), 5.94 (bs, H-N exchangeable with D₂O), 3.89 (s, 2H, -CH₂N(CH₃)CH₂CH₂NH-), 3.29 (q, 2H, J = 4.6, -CH₂N(CH₃)CH₂CH₂NH-), 2.83 (t, 2H, J = 5.8, -CH₂N(CH₃)CH₂CH₂NH-), 2.40 (s, 3H, CH₃-N). ¹³C NMR (125 MHz, CDCl₃, δ): 151.94, 149.79, 149.00, 143.64, 139.66, 139.51, 134.78, 128.54, 125.14, 124.38, 124.28, 123.23, 122.47, 122.34, 121.62, 117.33, 99.08, 57.52, 53.92, 41.73, 39.63. HRMS: m/z 382.11463 corresponds to molecular formula C₂₁H₂₀ClN₃SH⁺ (error in ppm 1.86). Anal. (C₂₁H₂₀ClN₃S \times 0.5H₂O) Calcd: C, 64.52; H, 5.41; N, 10.75; S, 8.20. Found: C, 64.82; H, 5.05; N, 10.88; S, 8.56. HPLC purity (λ = 254 nm) method A: RT 8.685 min, area 95.12%; (λ = 330 nm) method B: RT 7.428 min, area 95.57%.

***N*-(1-benzothien-2-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)-*N*-isopropylethane-1,2-diamine(48).**

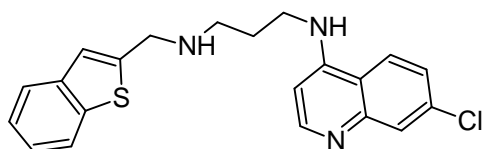


Compound **48** was prepared by method K from **46** (184 mg, 0.500 mmol). The product was purified using column chromatography (dry-flash, SiO₂, eluent EtOAc/hexane gradient 1/1 \rightarrow EtOAc, EtOAc/MeOH

gradient 9/1 \rightarrow 7/3). Final product **48** was obtained as pale yellow powder (187 mg, 91%). M.p. = 127 °C. IR (ATR): 3388s, 2960m, 2869w, 2829m, 1608m, 1583s, 1523m, 1477m, 1363w, 1328m, 1265w, 1237w, 1173w, 1122w, 1077w, 882w, 841w, 794w, 748m cm⁻¹. ¹H

NMR (500 MHz, CDCl₃, δ): 8.47 (d, $J = 5.3$, H-C(2')), 7.93 (d, $J = 2.2$, H-C(5')), 7.77-7.73 (m, H-C(8') and H-C(7)), 7.65-7.62 (m, H-C(4)), 7.34 (dd, $J_1 = 8.9$, $J_2 = 2.2$, H-C(6')), 7.32-7.25 (m, H-C(6) and H-C(5)), 7.15-7.13 (m, H-C(3)), 6.29 (d, $J = 5.4$, H-C(3')), 5.94 (bs, H-N exchangeable with D₂O), 3.88 (d, 2H, $J = 0.8$, -CH₂N(iPr)CH₂CH₂NH-), 3.25 (q, 2H, $J = 5.0$, -CH₂N(iPr)CH₂CH₂NH-), 3.13 (sept, 1H, $J = 6.6$, (CH₃)₂CH-N), 2.91 (t, 2H, $J = 5.8$, -CH₂N(iPr)CH₂CH₂NH-), 1.13 (d, 6H, $J = 6.6$, (CH₃)₂CH-N). ¹³C NMR (125 MHz, CDCl₃, δ): 151.97, 149.84, 149.09, 146.11, 139.75, 139.44, 134.71, 128.60, 125.12, 124.36, 124.14, 123.07, 122.34, 121.77, 121.59, 117.44, 99.15, 49.10, 48.89, 46.95, 39.87, 17.90. HRMS: m/z 410.14550 corresponds to molecular formula C₂₃H₂₄ClN₃SH⁺ (error in ppm 0.67). Anal. (C₂₃H₂₄ClN₃S) Calcd: C, 67.38; H, 5.90; N, 10.25; S, 7.82. Found: C, 67.09; H, 6.28; N, 10.16; S, 8.09. HPLC purity ($\lambda = 330$ nm): method A: RT 9.325 min, area 98.75%; method B: RT 7.604 min, area 97.41%.

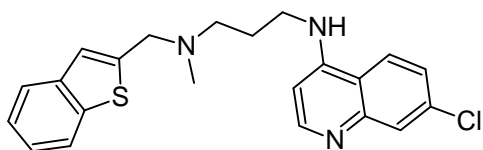
***N*-(1-benzothiophen-2-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)propane-1,3-diamine (49).**



Compound **49** was prepared by method E from 1-benzothiophene-2-carbaldehyde (314 mg, 1.93 mmol), using amine **AQ3** (682 mg, 2.89 mmol). The

product was purified using column chromatography (dry-flash, SiO₂, eluent EtOAc/Hex gradient 9/1 → EtOAc, EtOAc/MeOH gradient 95/5 → 6/4 and flash chromatography, Biotage SP1, RP column, eluent MeOH/H₂O gradient 75/25 → MeOH). Final product **49** was obtained as a pale yellow powder (480 mg, 65%). M.p. = 120 – 122 °C. IR (ATR): 3648w, 3266m, 3058w, 2924w, 2843w, 1609w, 1581s, 1537w, 1453w, 1366w, 1331w, 1281w, 1241w, 1204w, 1138w, 1077w, 878w, 853w, 808w, 748w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.48 (d, $J = 5.3$, H-C(2')), 7.91-7.89 (m, H-C(8')), 7.79 (d, $J = 7.8$, H-C(7)), 7.70 (d, $J = 7.3$, H-C(4)), 7.57 (d, $J = 10.2$, H-C(5')), 7.39-7.30 (m, H-C(5) and H-C(6)), 7.16 (bs, H-C(3)), 7.13-7.08 (m, H-N exchangeable with D₂O), 7.05-7.01 (m, H-C(6')), 6.31 (d, $J = 5.3$, H-C(3')), 4.12 (s, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.43-3.38 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 2.98-2.94 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 1.96-1.80 (m, 2H, -CH₂NHCH₂CH₂CH₂NH- and H-N exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃, δ): 152.02, 150.25, 149.09, 144.04, 139.62, 139.54, 134.58, 128.41, 124.87, 124.44, 124.24, 123.25, 122.40, 122.02, 121.98, 117.43, 98.38, 49.34, 48.51, 43.36, 27.54. HRMS: m/z 382.11399 corresponds to molecular formula C₂₁H₂₀ClN₃SH⁺ (error in ppm 0.29). Anal. (C₂₁H₂₀ClN₃S×0.25H₂O) Calcd: C, 65.27; H, 5.35; N, 10.87; S, 8.30. Found: C, 65.31; H, 5.30; N, 10.93; S, 8.18. HPLC purity ($\lambda = 330$ nm) method A: RT 7.941 min, area 98.67%; ($\lambda = 254$ nm) method C: RT 5.254 min, area 98.63%.

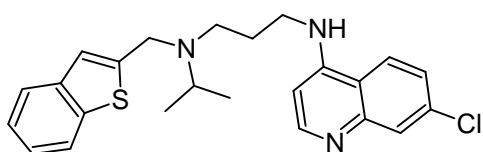
***N*-(1-benzothien-2-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)-*N*-methylpropane-1,3-diamine (50).**



Compound **50** was prepared by method K from **49** (201 mg, 0.524 mmol). The product was purified using column chromatography (dry-flash, SiO₂, eluent EtOAc/Hex gradient 1/1 → EtOAc, EtOAc/MeOH

gradient 95/5 → 1/1). Final product **50** was obtained as yellow oil (202 mg, 97%). IR (ATR): 3270m, 3060w, 2949m, 2845w, 2804w, 1610m, 1582s, 1539w, 1456w, 1368w, 1333w, 1138w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.50 (d, *J* = 5.4, H-C(2')), 7.91 (d, *J* = 2.2, H-C(5')), 7.75-7.72 (m, H-C(7)), 7.69-7.66 (m, H-C(4)), 7.40 (d, *J* = 8.9, H-C(8')), 7.37-7.29 (m, H-C(5) and H-C(6)), 7.16-7.14 (m, H-C(3)), 7.03 (dd, *J*₁ = 8.9, *J*₂ = 2.2, H-C(6')), 6.72 (bs, H-N exchangeable with D₂O), 6.35 (d, *J* = 5.4, H-C(3')), 3.85 (d, 2H, *J* = 0.6, -CH₂N(CH₃)CH₂CH₂CH₂NH-), 3.45-3.41 (m, 2H, -CH₂N(CH₃)CH₂CH₂CH₂NH-), 2.65 (t, 2H, *J* = 5.7, -CH₂N(CH₃)CH₂CH₂CH₂NH-), 2.43 (s, 3H, CH₃-N), 1.92 (quin, 2H, *J* = 5.8, -CH₂N(CH₃)CH₂CH₂CH₂NH-). ¹³C NMR (125 MHz, CDCl₃, δ): 152.00, 150.21, 149.15, 143.00, 139.84, 139.51, 134.59, 128.47, 124.94, 124.39, 124.29, 123.27, 122.95, 122.39, 121.65, 117.45, 98.57, 58.17, 55.84, 42.74, 42.26, 24.83. HRMS: *m/z* 396.13031 corresponds to molecular formula C₂₂H₂₂ClN₃SH⁺ (error in ppm 1.87). Anal. (C₂₂H₂₂ClN₃S×0.5H₂O) Calcd: C, 65.25; H, 5.72; N, 10.38; S, 7.92. Found: C, 65.73; H, 5.91; N, 10.66; S, 7.75. HPLC purity (λ = 330 nm): method A: RT 8.443 min, area 95.02%; method B: RT 7.444 min, area 96.11%.

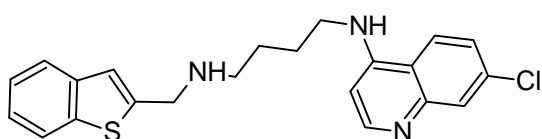
***N*-(1-benzothien-2-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)-*N*-isopropylpropane-1,3-diamine (51).**



Compound **51** was prepared by method K from **49** (249 mg, 0.652 mmol). The product was purified using column chromatography (dry-flash, SiO₂, eluent EtOAc/Hex gradient 1/9 → EtOAc, EtOAc/MeOH

gradient 95/5 → MeOH, EtOAc/MeOH/NH₃ gradient 18/1/1 → 9/1/1). Final product **51** was obtained as pale yellow powder (115 mg, 41%). M.p. = 86 – 88 °C. IR (ATR): 3240w, 3060w, 2964m, 1610m, 1580s, 1534m, 1455m, 1366m, 1330w, 1280w, 1221w, 1169w, 1135w, 1079w, 1022w, 879w, 853w, 810w, 744m cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.45 (d, *J* = 5.4, H-C(2')), 7.86 (d, *J* = 2.2, H-C(5')), 7.77-7.74 (m, H-C(7)), 7.69-7.65 (m, H-C(4)), 7.39-7.30 (m, H-C(5) and H-C(6)), 7.17-7.14 (d, *J* = 9.0, H-C(8') and H-C(3)), 6.87 (dd, *J*₁ = 8.9, *J*₂ = 2.2, H-C(6')), 6.32 (d, *J* = 5.4, H-C(3')), 5.96 (bs, H-N exchangeable with D₂O), 3.85 (s, 2H, -CH₂N(iPr)CH₂CH₂CH₂NH-), 3.42 (q, 2H, *J* = 5.7, -CH₂N(iPr)CH₂CH₂CH₂NH-), 3.21-3.12 (m, 1H, (CH₃)₂CH-N), 2.67 (t, 2H, *J* = 5.8, -CH₂N(iPr)CH₂CH₂CH₂NH-), 2.01 (bs, H-N

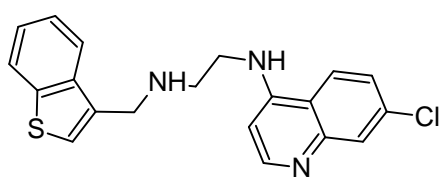
exchangeable with D₂O), 1.89-1.82 (m, 2H, -CH₂N(iPr)CH₂CH₂CH₂NH-), 1.08 (d, 6H, *J* = 6.6, (CH₃)₂CH-N). ¹³C NMR (125 MHz, CDCl₃, δ): 151.89, 149.82, 149.07, 146.12, 139.79, 139.59, 134.53, 128.42, 124.77, 124.40, 124.18, 123.14, 122.41, 122.10, 121.39, 117.19, 98.64, 49.40, 49.15, 47.51, 41.74, 25.45, 17.57. HRMS: *m/z* 424.16183 corresponds to molecular formula C₂₄H₂₆ClN₃SH⁺ (error in ppm 2.25). Anal. (C₂₄H₂₆ClN₃S×0.5H₂O) Calcd: C, 66.57; H, 6.28; N, 9.70; S, 7.41. Found: C, 66.94; H, 6.44; N, 9.54; S, 6.95. HPLC purity (λ = 330 nm): method A: RT 8.478 min, area 95.72%; method B: RT 7.472 min, area 95.45%. ***N*-(1-benzothiophen-2-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)butane-1,4-diamine (53).**



Compound **53** was prepared by method E from 1-benzothiophene-2-carbaldehyde (162 mg, 0.999 mmol), using amine **AQ4** (375 mg, 1.52 mmol).

The product was purified using column chromatography (dry-flash, SiO₂, eluent EtOAc/Hex gradient 9/1 → EtOAc, EtOAc/MeOH gradient 95/5 → 6/4 and flashchromatography, Biotage SP1, RP column, eluent MeOH/H₂O gradient 85/15 → MeOH). Final product **53** was obtained as pale yellow powder (320 mg, 54%). M.p. = 101 – 104 °C. IR (ATR): 3436w, 3283m, 3137w, 3105w, 3062w, 2935m, 2858w, 2180w, 1610w, 1580s, 1537w, 1453m, 1366w, 1332w, 1136w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.50 (d, *J* = 5.5, H-C(2')), 7.94-7.92 (m, H-C(8')), 7.78 (d, *J* = 8.0, H-C(5')), 7.70-7.64 (m, 2H-Ar), 7.35-7.21 (m, 3H-Ar), 7.14 (s, H-C(3)), 6.36 (d, *J* = 5.3, H-C(3')), 5.72-5.66 (m, H-N exchangeable with D₂O), 4.09 (s, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 3.32-3.27 (m, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 2.78 (t, 2H, *J* = 6.6, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.86 (quin, 2H, *J* = 6.8, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.73-1.45 (m, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH- and H-N exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃, δ): 152.06, 149.82, 149.16, 144.90, 139.70, 139.53, 134.68, 128.73, 125.05, 124.25, 123.98, 123.11, 122.34, 121.38, 121.18, 117.22, 98.91, 49.11, 48.35, 43.17, 27.64, 26.25. HRMS: *m/z* 396.12788 corresponds to molecular formula C₂₂H₂₂ClN₃SH⁺ (error in ppm 0.73). Anal. (C₂₂H₂₂ClN₃S×0.25H₂O) Calcd: C, 65.74; H, 5.68; N, 10.45; S, 7.98. Found: C, 65.60; H, 5.61; N, 10.36; S, 7.83. HPLC purity (λ = 330 nm): method A: RT 11.020 min, area 98.99%; method B: RT 8.229 min, area 97.99%.

***N*-(1-benzothiophen-3-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)ethane-1,2-diamine(55).**

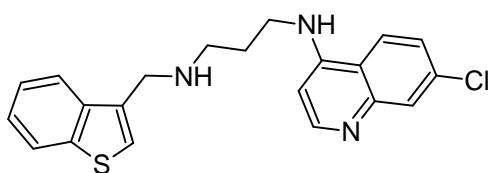


Compound **55** was prepared by method E from 1-benzothiophene-3-carbaldehyde (70.0 mg, 0.432 mmol), using amine **AQ2** (144 mg, 0.648 mmol). The product was purified using column chromatography (dry-flash,

SiO₂, eluent EtOAc/Hex gradient 1/9 → EtOAc, EtOAc/MeOH gradient 95/5 → 7/3 and flashchromatography, Biotage SP1, RP column, eluent MeOH/H₂O gradient 8/2 → MeOH).

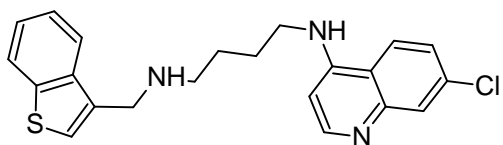
Final product **55** was obtained as pale yellow powder (135 mg, 85%). M.p. = 104 – 108 °C. IR (ATR): 3324w, 3219m, 3036m, 2967m, 1583s, 1490w, 1454m, 1427m, 1372m, 1334w, 1281m, 1242w, 1211w, 1167w, 1136m, 1078w, 898w, 850m, 797w, 761m, 731m, 641w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ): 8.48 (d, $J = 5.3$, H-C(2')), 7.92 (d, $J = 2.2$, H-C(8')), 7.91-7.85 (m, 2H-Ar), 7.40-7.34 (m, 3H-Ar), 7.30 (s, H-C(2)), 7.24 (dd, $J_1 = 2.3$, $J_2 = 9.1$, H-C(6')), 6.30 (d, $J = 5.4$, H-C(3')), 5.76 (bs, H-N exchangeable with D_2O), 4.10 (s, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}$ -), 3.30-3.26 (m, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}$ -), 3.10-3.06 (m, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}$ -), 1.74 (bs, H-N exchangeable with D_2O). ^{13}C NMR (125 MHz, CDCl_3 , δ): 151.99, 149.71, 149.03, 140.86, 138.21, 134.69, 134.60, 128.58, 125.10, 124.51, 124.09, 123.68, 123.07, 121.89, 121.23, 117.24, 99.11, 47.16, 46.79, 41.95. HRMS: m/z 368.09643 corresponds to molecular formula $\text{C}_{20}\text{H}_{18}\text{ClN}_3\text{SH}^+$ (error in ppm -5.00). HPLC purity ($\lambda = 330$ nm): method A: RT 8.402 min, area 98.48%; method B: RT 7.404 min, area 98.45%.

***N*-(1-benzothiophen-3-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)propane-1,3-diamine (**56**).**



Compound **56** was prepared by method E from 1-benzothiophene-3-carbaldehyde (90.0 mg, 0.555 mmol), using amine **AQ3** (196 mg, 0.832 mmol).

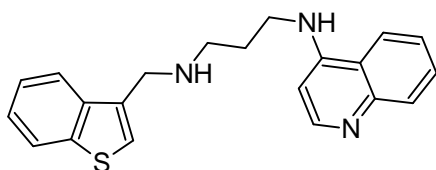
The product was purified using column chromatography (dry-flash, SiO_2 , eluent EtOAc/Hex gradient 1/9 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow 8/2, flashchromatography, Biotage SP1, NH column, eluent EtOAc/Hex gradient 7/3 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow MeOH, Biotage SP1, SiO_2 column, eluent EtOAc/MeOH+ NH_3 (9/1) gradient 95/5 \rightarrow 7/3). Final product **56** was obtained as pale yellow powder (127 mg, 60%). M.p. = 122 – 123 °C. IR (ATR): 3298w, 3214m, 3059w, 2952m, 2888w, 2827w, 1611w, 1581s, 1539m, 1456m, 1426m, 1358w, 1327m, 1277w, 1224w, 1168w, 1139w, 1112w, 1082w, 893w, 848w, 811w, 764m, 731m, 636w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ): 8.46 (d, $J = 5.4$, H-C(2')), 7.91 (d, $J = 8.0$, H-C(4)), 7.87 (d, $J = 2.0$, H-C(8')), 7.79 (d, $J = 8.1$, H-C(5')), 7.44-7.27 (m, 4H-Ar and H-N exchangeable with D_2O), 6.91 (dd, $J_1 = 2.0$, $J_2 = 8.8$, H-C(6')), 6.27 (d, $J = 5.4$, H-C(3')), 4.09 (s, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 3.43-3.38 (m, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 3.04 (t, 2H, $J = 5.5$, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 2.05-1.93 (m, 2H, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{NH}$ - and H-N exchangeable with D_2O). ^{13}C NMR (125 MHz, CDCl_3 , δ): 151.85, 150.37, 148.84, 140.67, 138.12, 134.56, 134.45, 128.17, 124.79, 124.62, 124.27, 123.49, 123.04, 121.88, 121.42, 117.33, 98.23, 49.41, 47.59, 43.81, 27.38. HRMS: m/z 382.11218 corresponds to molecular formula $\text{C}_{21}\text{H}_{20}\text{ClN}_3\text{SH}^+$ (error in ppm -4.57). Anal. ($\text{C}_{21}\text{H}_{20}\text{ClN}_3\text{S}$) Calcd: C, 66.04; H, 5.28; N, 11.00; S, 8.40. Found: C, 65.69; H, 5.54; N, 10.84; S, 8.00. HPLC purity ($\lambda = 330$ nm): method A: RT 8.487 min, area 99.20%; method B: RT 7.438 min, area 99.18%.

***N*-(1-benzothiophen-3-ylmethyl)-*N'*-(7-chloroquinolin-4-yl)butane-1,4-diamine (57).**

Compound **57** was prepared by method E from 1-benzothiophene-3-carbaldehyde (80.0 mg, 0.493 mmol), using amine **AQ4** (185 mg, 0.740 mmol).

The product was purified using column

chromatography (flash, Biotage SP1, SiO₂ column, eluent EtOAc/MeOH+NH₃(9/1) gradient 95/5 → 7/3). Final product **57** was obtained as pale yellow powder (115 mg, 59%). M.p. = 82 – 85 °C. IR (ATR): 3304w, 3220m, 3056w, 2927m, 2851w, 2817w, 1582s, 1540m, 1459m, 1427m, 1365w, 1327m, 1276w, 1255w, 1228w, 1164w, 1136m, 1079w, 898w, 864w, 835w, 749w, 724w, 638w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.49 (d, *J* = 5.4, H-C(2')), 7.92 (d, *J* = 2.0, H-C(8')), 7.89-7.85 (m, H-C(4)), 7.81-7.78 (m, H-C(7)), 7.58 (d, *J* = 8.9, H-C(5')), 7.40-7.33 (m, 2H-Ar), 7.30 (s, H-C(2)), 7.12 (dd, *J*₁ = 2.0, *J*₂ = 8.9, H-C(6')), 6.34 (d, *J* = 5.4, H-C(3')), 5.83 (bs, H-N exchangeable with D₂O), 4.06 (s, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 3.32-3.26 (m, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 2.81 (t, 2H, *J* = 6.6, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.88 (quin, 2H, *J* = 6.8, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.80 (bs, H-N exchangeable with D₂O), 1.72 (quin, 2H, *J* = 6.8, -CH₂NHCH₂CH₂CH₂CH₂NH-). ¹³C NMR (125 MHz, CDCl₃, δ): 151.98, 149.96, 149.02, 140.73, 138.22, 134.86, 134.74, 128.58, 125.01, 124.50, 124.11, 123.04, 122.99, 121.57, 121.23, 117.22, 98.87, 48.91, 47.62, 43.16, 27.70, 26.34. HRMS: *m/z* 396.12784 corresponds to molecular formula C₂₂H₂₂ClN₃SH⁺ (error in ppm -4.38). HPLC purity (λ = 254 nm) method A: RT 8.153 min, area 97.42%; (λ = 330 nm) method B: RT 7.519 min, area 97.71%.

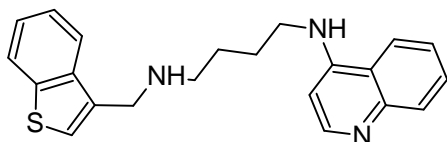
***N*-(1-benzothiophen-3-ylmethyl)-*N'*-(quinolin-4-yl)propane-1,3-diamine(62).**

Compound **62** was prepared by method E from 1-benzothiophene-3-carbaldehyde (115 mg, 0.709 mmol), using amine **AQ7** (214 mg, 1.06 mmol). The product was purified using column chromatography (dry-flash,

SiO₂, eluent EtOAc/Hex gradient 1/1 → EtOAc, EtOAc/MeOH gradient 95/5 → 7/3). Final product **62** was obtained as pale yellow oil (177 mg, 72%). IR (film): 3750w, 3673w, 3648w, 3447s, 2917w, 2845w, 1650w, 1576w, 1557w, 1541w, 1458w, 1433w, 1397w, 1370w, 1338w, 1132w, 763w, 732w, 617w cm⁻¹. ¹H NMR (500 MHz, CDCl₃-exchange with D₂O, δ): 8.50 (d, *J* = 5.5, H-C(2')), 7.94-7.89 (m, 2H-Ar), 7.83-7.80 (m, H-C(8')), 7.56-7.49 (m, 2H-Ar), 7.38-7.31 (m, 3H-Ar), 7.14-7.09 (m, H-C(6)), 6.33 (d, *J* = 5.2, H-C(3')), 4.10 (s, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.42 (t, 2H, *J* = 6.0, -CH₂NHCH₂CH₂CH₂NH-), 3.02 (t, 2H, *J* = 5.6, -CH₂NHCH₂CH₂CH₂NH-), 2.00-1.94 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-). ¹³C NMR (125 MHz, CDCl₃, δ): 150.66, 150.26, 147.46, 140.68, 138.17, 134.49, 129.07, 128.85, 124.56, 124.41, 124.24, 123.47, 123.02, 121.47, 120.28, 118.77, 97.92, 49.20, 47.64, 43.65, 27.57.

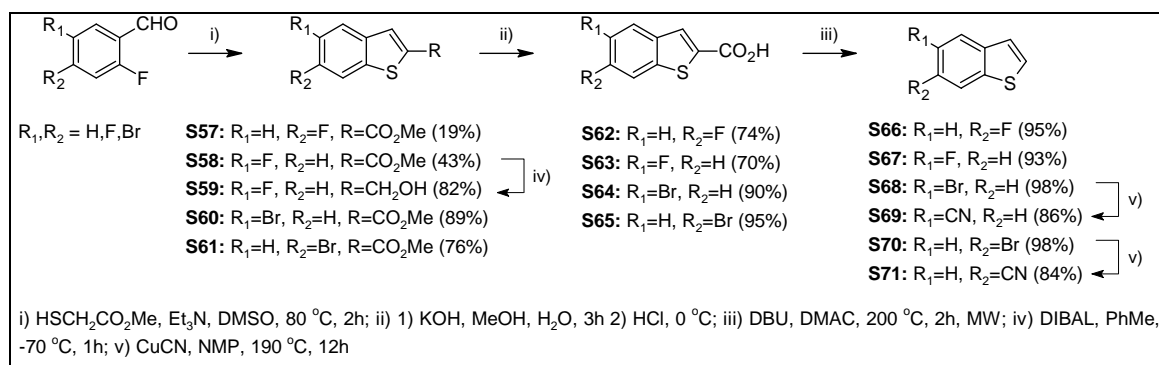
HRMS: m/z 348.15179 corresponds to molecular formula $C_{21}H_{21}N_3SH^+$ (error in ppm -3.18). HPLC purity ($\lambda = 330$ nm): method A: RT 8.708 min, area 97.43%; method B: RT 7.815 min, area 97.16%.

N-(1-benzothiophen-3-ylmethyl)-*N'*-(quinolin-4-yl)butane-1,4-diamine (**66**).

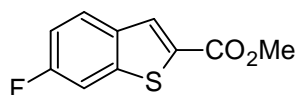


Compound **66** was prepared by method E from 1-benzothiophene-3-carbaldehyde (80.0 mg, 0.493 mmol), using amine **AQ8** (159 mg, 0.739 mmol). The product was purified using column chromatography

(dry-flash, SiO_2 , eluent EtOAc/Hex gradient 2/8 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow 1/9, and flash, Biotage SP1, NH column, eluent EtOAc/Hex gradient 7/3 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow MeOH). Final product **66** was obtained as pale yellow oil (101 mg, 57%). IR (ATR): 3307m, 3077m, 2935m, 2859m, 2818m, 1585s, 1547m, 1500s, 1442m, 1401w, 1376w, 1343w, 1283w, 1257w, 1226w, 1130w, 1035m, 809w, 766m, 733w, 652w cm^{-1} . 1H NMR (500 MHz, CD_3OD , δ): 8.31 (d, $J = 5.4$, H-C(2')), 8.08-8.04 (m, H-C(8')), 7.86-7.83 (m, H-C(4)), 7.82-7.76 (m, 2H-Ar), 7.62-7.58 (m, H-C(7')), 7.42 (bs, H-C(2)), 7.41-7.30 (m, 3H-Ar), 6.46 (d, $J = 5.7$, H-C(3')), 4.00 (s, 2H, $-CH_2NHCH_2CH_2CH_2CH_2NH-$), 3.36 (t, 2H, $J = 6.9$, $-CH_2NHCH_2CH_2CH_2CH_2NH-$), 2.73 (t, 2H, $J = 7.2$, $-CH_2NHCH_2CH_2CH_2CH_2NH-$), 1.81-1.74 (m, 2H, $-CH_2NHCH_2CH_2CH_2CH_2NH-$), 1.73-1.65 (m, 2H, $-CH_2NHCH_2CH_2CH_2CH_2NH-$). ^{13}C NMR (125 MHz, CD_3OD , δ): 152.69, 151.12, 148.80, 141.93, 139.68, 135.53, 130.46, 128.69, 125.55, 125.46, 125.13, 124.54, 123.76, 122.57, 122.20, 120.26, 99.14, 49.96, 47.56, 43.76, 28.02, 27.21. HRMS: m/z 362.16853 corresponds to molecular formula $C_{22}H_{23}N_3SH^+$ (error in ppm -0.08). HPLC purity ($\lambda = 330$ nm): method A: RT 8.366 min, area 97.01%; method B: RT 7.416 min, area 96.78%.



Methyl 6-fluoro-1-benzothiophene-2-carboxylate (**S57**).

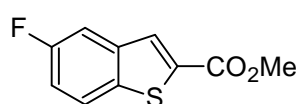


Compound **S57** was prepared from 2,4-difluorobenzaldehyde (7.91 g, 55.6 mmol) by method L. The product was purified using column chromatography (dry-flash, SiO_2 , eluent Hex \rightarrow Hex/EtOAc = 95/5).

Final product **S57** was obtained as colorless crystals (2.22 g, 19%). M.p. = 86 – 89 $^\circ C$ (Hex/EtOAc=95/5); lit.²⁵ m.p. 85.5-86 $^\circ C$ (MeOH). IR (ATR): 3413w, 3106w, 3065w,

2960w, 2847w, 1726s, 1609w, 1567w, 1527m, 1465w, 1434w, 1338w, 1308w, 1250s, 1193m, 1068w, 1045w, 960w, 908w, 884w, 849w, 803w, 777w, 751w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.02 (s, H-C(3)), 7.85-7.80 (m, H-C(4)), 7.55-7.51 (m, H-C(7)), 7.16 (td, $J_1 = 2.3$, $J_2 = 9.0$, H-C(5)), 3.94 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃, δ): 162.95 (d, $J = 16.2$), 161.03, 143.36 (d, $J = 10.8$), 135.23, 133.18 (d, $J = 3.6$), 130.08, 126.89 (d, $J = 9.0$), 114.48 (d, $J = 25.4$), 108.69 (d, $J = 25.3$), 52.52. HRMS: m/z 211.02230 corresponds to molecular formula C₁₀H₇FO₂SH⁺ (error in ppm -0.27).

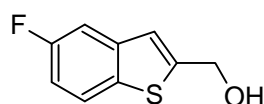
Methyl 5-fluoro-1-benzothiophene-2-carboxylate (S58).



Compound **S58** was prepared from 2,5-difluorobenzaldehyde (5.00 g, 35.2 mmol) by method L. The product was purified using column chromatography (dry-flash, SiO₂, eluent Hex → Hex/EtOAc = 95/5).

Final product **S58** was obtained as colorless crystals (3.18 g, 43%). M.p. = 68 – 71 °C (Hex/EtOAc=95/5); lit.²⁶ m.p. 75-76 °C. IR (ATR): 3409w, 3240w, 3087w, 2961w, 2846w, 2772w, 1717s, 1607w, 1574w, 1527s, 1497w, 1430m, 1327w, 1295w, 1253s, 1204s, 1144w, 1078w, 1057w, 944w, 876w, 809w, 770w, 750w, 708w, 651w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.00 (s, H-C(3)), 7.80 (dd, $J_1 = 4.7$, $J_2 = 8.8$, H-C(7)), 7.53 (dd, $J_1 = 2.5$, $J_2 = 9.0$, H-C(4)), 7.23 (td, $J_1 = 2.5$, $J_2 = 8.9$, H-C(6)), 3.95 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃, δ): 162.38 (d, $J = 128.2$), 159.93, 139.54 (d, $J = 9.9$), 137.65, 135.73, 129.98 (d, $J = 4.5$), 124.08 (d, $J = 9.0$), 116.19 (d, $J = 25.3$), 110.56 (d, $J = 22.6$), 52.6. GC/MS (m/z , %): 210.0 ([M⁺], 64), 179.0 (100), 151.0 (20), 107.0 (45).

(5-fluoro-1-benzothiophen-2-yl)methanol(S59).

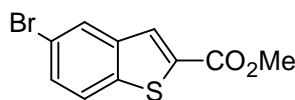


Compound **S58** (590mg, 2.8 mmol) was dissolved with stirring in dry PhMe (15 mL) under Ar at -70 °C, followed by slow addition of 0.6 M DIBAL (19 mL, 11 mmol). Reaction was quenched after 1 h with

MeOH/H₂O (4/1) and the solvent was removed under reduced pressure. The crude mixture was dissolved in DCM (40 mL), transferred to a separation funnel, washed with water (2 × 30 mL) and brine (30 mL), and dried over anh. Na₂SO₄. After filtration, the solvent was removed under reduced pressure. The product was purified using column chromatography (dry-flash, SiO₂, eluent Hex → Hex/EtOAc = 7/3). Final product **S59** was obtained as a white powder (420mg, 82%). M.p. = 89 – 90 °C (lit.²⁷ m.p. 94 °C (*i*Pr₂O-hexane). IR (ATR): 3249s, 2932m, 2352w, 1750w, 1601m, 1576w, 1538m, 1442s, 1362w, 1297w, 1251w, 1192w, 1143s, 1014s, 947w, 876s, 839w, 812s, 779w, 721w, 693w, 664, 641w, 588w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 7.72 (dd, $J_1 = 4.8$, $J_2 = 8.7$, H-C(7)), 7.38 (dd, $J_1 = 2.5$, $J_2 = 9.4$, H-C(4)), 7.16 (s, H-C(3)), 7.07 (td, $J_1 = 2.5$, $J_2 = 8.9$, H-C(6)), 4.92 (d, 2H, $J = 5.2$, -CH₂OH), 2.02 (t, $J = 5.8$, H-O). ¹³C NMR (125 MHz, CDCl₃, δ): 160.85 (d, $J = 239.2$), 147.48, 140.51 (d, $J = 9.9$),

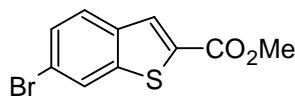
135.21, 123.54 (d, $J = 9.0$), 121.51 (d, $J = 4.5$), 113.08 (d, $J = 25.3$), 108.98 (d, $J = 23.5$), 60.82. GC/MS ($m/z, \%$): 182.0 ($[M^+]$, 95), 165.0 (90), 153.0 (100), 109.0 (53).

Methyl 5-bromo-1-benzothiophene-2-carboxylate(S60).



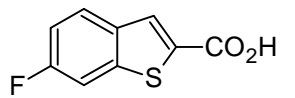
Compound **S60** was prepared from 5-bromo-2-fluorobenzaldehyde (1.00 g, 4.92 mmol) by method L. The product was purified using column chromatography (dry-flash, SiO₂, eluent Hex → Hex/EtOAc = 95/5). Final product **S60** was obtained as pale yellow powder (1.19 g, 89%). M.p. = 110 °C. IR (ATR): 3083w, 2999w, 2956w, 1720s, 1554m, 1517s, 1435m, 1310w, 1285m, 1251s, 1196m, 1168m, 1062m, 949w, 882m, 796m, 750m, 711w, 542w, 479w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.02-8.00 (m, H-C(4)), 7.97-7.96 (m, H-C(3)), 7.74-7.71 (m, H-C(7)), 7.54 (dd, $J_1 = 1.9, J_2 = 8.6$, H-C(6)), 3.95 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃, δ): 162.76, 140.64, 140.17, 135.12, 130.02, 129.43, 127.96, 124.10, 118.91, 52.64. HRMS: m/z 270.9422 corresponds to molecular formula C₁₀H₇BrO₂SH⁺ (error in ppm -0.32).

Methyl 6-bromo-1-benzothiophene-2-carboxylate(S61).



Compound **S61** was prepared from 4-bromo-2-fluorobenzaldehyde (5.00 g, 24.6 mmol) by method L. The product was purified using column chromatography (dry-flash, SiO₂, eluent Hex → Hex/EtOAc = 9/1). Final product **S61** was obtained as pale yellow powder (5.10 g, 76%). M.p. = 114 °C (lit.²⁸ m.p. 113-115 °C). IR (ATR): 3405w, 3068w, 2956w, 2842w, 1805w, 1710s, 1580m, 1503m, 1429m, 1380m, 1329w, 1307m, 1283s, 1192m, 1169s, 1136m, 1086s, 1062s, 956w, 917m, 865s, 809s, 751s, 719m, 700w, 641w, 565m, 490w, 456w, 429m, 403w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.02-7.99 (m, H-C(7) and H-C(2)), 7.72 (d, $J = 8.4$, H-C(4)), 7.51 (dd, $J_1 = 1.7, J_2 = 8.6$, H-C(5)), 3.94 (s, 3H, CH₃). ¹³C NMR (125 MHz, CDCl₃, δ): 162.84, 143.47, 137.34, 133.90, 130.09, 128.58, 126.54, 125.28, 121.26, 52.60. GC/MS ($m/z, \%$): 271.9 ($[M^+]$, 87), 269.9 (89), 240.9 (100), 210.9 (22), 168.9 (20), 131.9 (41).

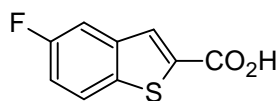
6-fluoro-1-benzothiophene-2-carboxylic acid (S62).²⁹



Compound **S62** was prepared from methyl ester **S57** (247 mg, 1.18 mmol) by method M. The product was purified using column chromatography (dry-flash, SiO₂, eluent DCM → DCM/MeOH = 9/1). Final product **S62** was obtained as white powder (171 mg, 74%). M.p. = 182 – 186 °C. IR (ATR): 2811w, 2575w, 1665s, 1604m, 1566w, 1523s, 1468w, 1438m, 1341w, 1319m, 1279w, 1255m, 1196m, 1177m, 1062w, 921m, 870w, 845w, 806w, 759w cm⁻¹. ¹H NMR (500 MHz, CD₃OD, δ): 8.04 (s, H-C(3)), 7.94 (dd, $J_1 = 5.2, J_2 = 8.7$, H-C(4)), 7.68 (dd, $J_1 = 2.4, J_2 = 9.0$, H-C(7)), 7.22 (td, $J_1 = 2.4, J_2 = 9.0$, H-C(5)). ¹³C NMR (125 MHz, CD₃OD, δ): 165.38, 163.45 (d, $J = 244.6$), 144.88 (d, $J = 10.8$), 137.06, 135.81 (d, $J = 3.6$), 131.13, 128.29 (d, $J =$

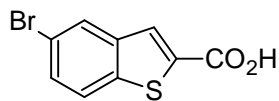
9.9), 115.29 (d, $J = 24.4$), 109.55 (d, $J = 25.3$). HRMS: m/z 194.99178 corresponds to molecular formula $[C_9H_5SFO_2-H]^-$ (error in ppm -1.91).

5-fluoro-1-benzothiophene-2-carboxylic acid(S63).



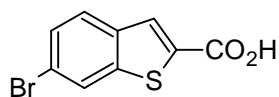
Compound **S63** was prepared from methyl ester **S58** (1.30 g, 6.2 mmol) by method M. The product was purified using column chromatography (dry-flash, SiO_2 , eluent DCM \rightarrow DCM/MeOH = 7/3). Final product **S63** was obtained as white powder (850mg, 70%). M.p. = 220-224 °C. IR (ATR): 2966m, 2848m, 2803m, 2633m, 2565m, 2524m, 1677s, 1603w, 1571w, 1525s, 1446w, 1409m, 1332w, 1305s, 1271s, 1242w, 1209s, 1147w, 1130w, 1079w, 1055w, 954w, 930w, 882w, 809w, 760w, 711w, 655w, 598w, 509w cm^{-1} . 1H NMR (500 MHz, CD_3OD , δ): 8.00 (s, H-C(3)), 7.91 (dd, $J_1 = 4.8$, $J_2 = 8.9$, H-C(7)), 7.64 (dd, $J_1 = 2.5$, $J_2 = 9.2$, H-C(4)), 7.27 (td, $J_1 = 2.8$, $J_2 = 8.9$, H-C(6)). ^{13}C NMR (125 MHz, CD_3OD , δ): 166.55, 162.33 (d, $J = 240.1$), 141.31 (d, $J = 9.9$), 139.21, 131.34, 131.06 (d, $J = 12.6$), 125.39 (d, $J = 9.0$), 116.94 (d, $J = 25.3$), 111.42 (d, $J = 22.6$). HRMS: m/z 194.99273 corresponds to molecular formula $[C_9H_5SFO_2-H]^-$ (error in ppm 2.98).

5-bromo-1-benzothiophene-2-carboxylic acid(S64).



Compound **S64** was prepared from methyl ester **S60** (1.19 g, 4.39 mmol) by method M. The product was purified using column chromatography (dry-flash, SiO_2 , eluent DCM \rightarrow DCM/MeOH = 9/1). Final product **S64** was obtained as white powder (1.01 g, 90%). M.p. = 234 – 236 °C (lit.³⁰ m.p. 235 °C ($H_2O/EtOH$)). IR (ATR): 2977m, 2828m, 2662m, 2557m, 1667s, 1551s, 1517s, 1439m, 1401w, 1302s, 1265m, 1178s, 1072w, 1042w, 936w, 886m, 799m, 759m, 711w, 600w, 507w, 473w, 424w cm^{-1} . 1H NMR (500 MHz, CD_3OD , δ): 8.11-8.09 (m, H-C(4)), 8.00-7.97 (m, H-C(3)), 7.84-7.81 (m, H-C(7)), 7.22 (dd, $J_1 = 1.8$, $J_2 = 8.7$, H-C(6)). ^{13}C NMR (125 MHz, CD_3OD , δ): 165.24, 142.17, 141.96, 137.87, 130.95, 130.54, 129.05, 125.41, 119.80. HRMS: m/z 254.91145 corresponds to molecular formula $[C_9H_5BrO_2S-H]^-$ (error in ppm 4.69).

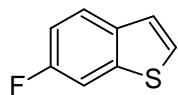
6-bromo-1-benzothiophene-2-carboxylic acid(S65).



Compound **S65** was prepared from methyl ester **S61** (2.00 g, 7.38 mmol) by method M. The product was purified using column chromatography (dry-flash, SiO_2 , eluent Hex \rightarrow Hex/EtOAc = 1/1). Final product **S65** was obtained as white powder (1.80 g, 95%). M.p. = 260 – 265 °C. IR (ATR): 3082m, 2982m, 2839m, 2690m, 2579m, 1664s, 1586m, 1552w, 1513m, 1425m, 1383w, 1333w, 1316m, 1276w, 1244w, 1181w, 1139w, 1090w, 1051w, 918w, 871w, 803w, 754w, 564w, 514w cm^{-1} . 1H NMR (500 MHz, $CD_3OD+CDCl_3$, δ): 8.08-8.05 (m, H-C(7)), 7.98 (bs, H-C(3)), 7.78 (d, $J = 8.5$, H-C(4)), 7.51 (dd, $J_1 = 1.7$, $J_2 = 8.6$, H-C(5)). ^{13}C NMR

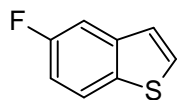
(125 MHz, CD₃OD+CDCl₃, δ): 165.42, 144.71, 138.91, 130.78, 129.35, 127.61, 126.12, 121.83. HRMS: m/z 254.91154 corresponds to molecular formula [C₉H₅BrO₂S-H]⁻ (error in ppm -2.13).

6-fluoro-1-benzothiophene(S66).



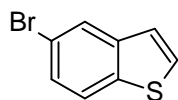
Compound **S66** was prepared from carboxylic acid **S62** (163 mg, 0.831 mmol) by method N. The product was purified using column chromatography (dry-flash, SiO₂, eluent Hex). Final product **S66** was obtained as colorless liquid (121 mg, 95%). IR (film): 3106w, 3073w, 2927w, 1879w, 1754w, 1697w, 1625w, 1606m, 1565m, 1530w, 1496w, 1467s, 1392w, 1342w, 1310w, 1251s, 1218s, 1184w, 1118w, 1081w, 1040w, 912s, 884w, 844m, 811s, 783w, 745w, 689m, 649w cm⁻¹. ¹H NMR (200 MHz, CDCl₃, δ): 7.75 (dd, $J_1 = 5.3$, $J_2 = 8.7$, H-C(4)), 7.55 (dd, $J_1 = 2.2$, $J_2 = 9.0$, H-C(7)), 7.38, 7.30 (ABq, $J_{AB} = 14.1$, H-C(2) and H-C(3)), 7.12 (td, $J_1 = 2.4$, $J_2 = 8.8$, H-C(5)). ¹³C NMR (50 MHz, CDCl₃, δ): 172.86, 162.94, 125.98 (d, $J = 3.6$), 124.48 (d, $J = 9.1$), 123.35, 113.49, 113.25 (d, $J = 23.7$), 108.43 (d, $J = 24.6$). GC/MS ($m/z, \%$): 152.0 ([M⁺], 100).

5-fluoro-1-benzothiophene(S67).



Compound **S67** was prepared from carboxylic acid **S63** (1.40 g, 7.1 mmol) by method N. The product was purified using column chromatography (dry-flash, SiO₂, eluent Hex). Final product **S67** was obtained as colorless liquid (1.00 g, 93%). IR (film): 3907w, 3084w, 3012w, 2927w, 2372w, 2175w, 1879w, 1781w, 1725w, 1618w, 1582w, 1563m, 1525w, 1501w, 1455w, 1421m, 1319w, 1422m, 1319w, 1267w, 1248m, 1232w, 1139m, 1092w, 1051w, 942w, 891m, 862s, 833m, 808s, 750s, 694s, 632w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 7.79 (dd, $J_1 = 4.9$, $J_2 = 8.8$, H-C(7)), 7.52 (d, $J = 5.2$, H-C(3)), 7.47 (dd, $J_1 = 2.5$, $J_2 = 9.4$, H-C(4)), 7.29 (d, $J = 5.2$, H-C(2)), 7.13-7.07 (m, H-C(6)). ¹³C NMR (125 MHz, CDCl₃, δ): 160.8 (d, $J = 240.0$), 140.58 (d, $J = 8.8$), 135.12, 128.78, 123.56 (d, $J = 5.0$), 123.46, 113.12 (d, $J = 23.8$), 108.98 (d, $J = 22.5$). GC/MS ($m/z, \%$): 152.0 ([M⁺], 100).

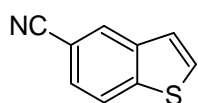
5-bromo-1-benzothiophene(S68).



Compound **S68** was prepared from carboxylic acid **S64** (1.00 g, 3.89 mmol) by method N. The product was purified using column chromatography (dry-flash, SiO₂, eluent Hex). Final product **S68** was obtained as white powder (814 mg, 98%). M.p. = 43 – 44 °C (lit.³¹ m.p. 47 °C). IR (ATR): 3102m, 2924m, 2850w, 2176w, 2004w, 1874w, 1775w, 1730w, 1579s, 1545m, 1491m, 1431s, 1404s, 1310m, 1272w, 1250m, 1223m, 1191s, 1151m, 1090m, 1061s, 940w, 887m, 866m, 811s, 798s, 751s, 727s, 691s, 546w, 475m, 412w, 402w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 7.97-7.95 (m, H-C(4)), 7.75-7.71 (m, H-C(7)), 7.48-7.46 (m, H-C(2)), 7.45-7.41 (m, H-C(6)), 7.28-7.26 (m, H-C(3)).

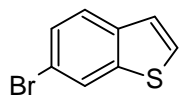
^{13}C NMR (125 MHz, CDCl_3 , δ): 141.22, 138.34, 128.14, 127.26, 126.23, 123.76, 123.10, 118.22. GC/MS (m/z , %): 213.9 ($[\text{M}^+]$, 100), 133.0 (55), 89.0 (45).

1-benzothiophene-5-carbonitrile(S69).



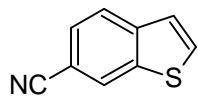
Compound **S69** was prepared from compound **S68** (735 mg, 3.45 mmol) by method P. The product was purified using column chromatography (dry-flash, SiO_2 , eluent Hex \rightarrow Hex/EtOAc = 9/1). Final product **S69** was obtained as colorless crystals (472 mg, 86%). M.p. = 67 – 69 °C (Hex/EtOAc=9/1); lit.³² m.p. 63 °C. IR (ATR): 3107s, 3087m, 2223s, 1777w, 1594w, 1540w, 1429m, 1320m, 1257m, 1225w, 1134w, 1090m, 1050w, 907m, 823s, 758m, 704s, 623w, 598w, 574w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ): 8.15 (s, H-C(4)), 7.97 (d, $J = 8.4$, H-C(7)), 7.61 (d, $J = 5.5$, H-C(2)), 7.57-7.54 (m, H-C(6)), 7.41 (d, $J = 5.5$, H-C(3)). ^{13}C NMR (125 MHz, CDCl_3 , δ): 143.80, 139.31, 129.05, 128.16, 126.14, 123.68, 123.44, 119.36, 107.96. GC/MS (m/z , %): 159.0 ($[\text{M}^+]$, 100).

6-bromo-1-benzothiophene(S70).

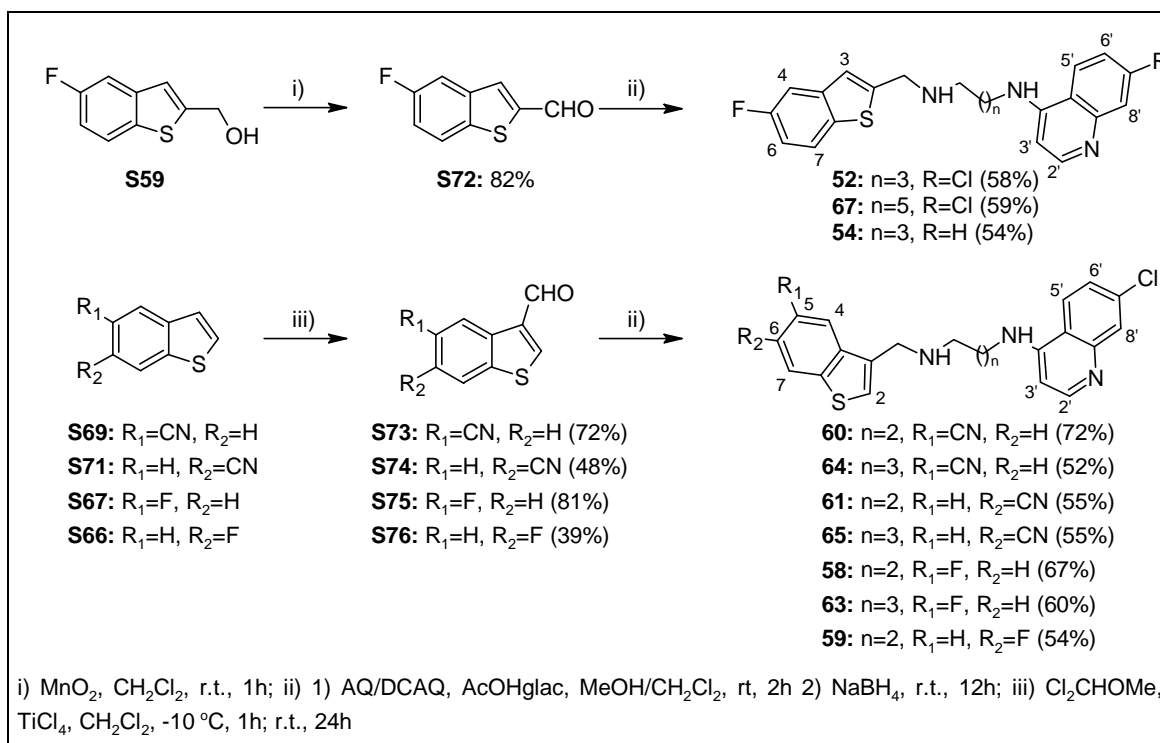


Compound **S70** was prepared from carboxylic acid **S65** (1.00 g, 3.89 mmol) by method N. The product was purified using column chromatography (dry-flash, SiO_2 , eluent Hex). Final product **S70** was obtained as white powder (811 mg, 98%). M.p. = 53 – 54 °C (lit.³⁰ m.p. 56°C). IR (ATR): 3105w, 3076w, 1576m, 1541w, 1482w, 1439m, 1377m, 1336m, 1300w, 1246w, 1200w, 1061m, 950w, 866m, 816s, 744m, 689m, 566m, 427w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ): 8.01 (s, H-C(7)), 7.66 (d, $J = 8.5$, H-C(4)), 7.48-7.44 (m, H-C(5)), 7.41, 7.29 (AMq, $J_{AM} = 5.5$, H-C(2) and H-C(3)). ^{13}C NMR (125 MHz, CDCl_3 , δ): 141.26, 138.32, 127.62, 126.90, 124.96, 124.65, 123.54, 118.14. GC/MS (m/z , %): 213.9 ($[\text{M}^+]$, 100), 211.9 (99), 133.0 (48), 89.0 (38).

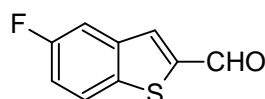
1-benzothiophene-6-carbonitrile(S71).



Compound **S71** was prepared from compound **S70** (600mg, 2.8 mmol) by method P. The product was purified using column chromatography (dry-flash, SiO_2 , eluent Hex \rightarrow Hex/EtOAc = 9/1). Final product **S71** was obtained as pale yellow powder (380mg, 84%). M.p. = 41 – 42 °C (lit.³³ m.p. 41.5-42 °C (acetone/ligroin)). IR (ATR): 3818w, 3541w, 3415w, 3102m, 2971w, 2782w, 2621w, 2275w, 2225s, 2173w, 1907w, 1774w, 1647w, 1594m, 1550w, 1484w, 1454m, 1391m, 1344m, 1311m, 1259m, 1192m, 1137w, 1084m, 1049w, 959w, 893m, 825s, 777m, 760m, 702m, 633w, 604m, 510w, 485w, 455, 406w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ): 8.22-8.20 (m, H-C(7)), 7.90 (d, $J = 7.9$, H-C(4)), 7.72 (d, $J = 5.5$, H-C(3)), 7.59 (dd, $J_1 = 1.2$, $J_2 = 8.2$, H-C(5)), 7.43-7.41 (m, H-C(2)). ^{13}C NMR (125 MHz, CDCl_3 , δ): 142.40, 139.58, 131.20, 127.27, 126.81, 124.30, 123.94, 119.27, 107.56. GC/MS (m/z , %): 159.0 ($[\text{M}^+]$, 100).

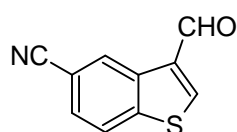


5-fluoro-1-benzothiophene-2-carbaldehyde(S72).



Alcohol **S59** (300 mg, 1.6 mmol) was dissolved in DCM (30 mL) and MnO₂ (1.40 g, 16 mmol) was added. Resulting mixture was stirred at room temperature for 1 h. The mixture was filtrated through Celite, solvent was removed under reduced pressure and product **S72** was used in the next step without further purification. **S72** was obtained as white powder (240mg, 82%). M.p. = 117 – 119 °C (lit.²⁷ m.p. 122 °C (EtOH)). IR (ATR): 3449s, 3101w, 3065w, 2921w, 2850w, 2793w, 1886w, 1671s, 1566w, 1518w, 1440w, 1383w, 1330w, 1282w, 1247w, 1167m, 1115w, 952w, 868w, 808w, 718w, 657w, 597w, 489w, 418w, 403w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 10.11 (s, 1H, CHO), 7.99 (s, H-C(3)), 7.85 (dd, *J*₁ = 4.8, *J*₂ = 9.0, H-C(7)), 7.60 (dd, *J*₁ = 2.5, *J*₂ = 8.9, H-C(4)), 7.28 (td, *J*₁ = 2.5, *J*₂ = 8.7, H-C(6)). ¹³C NMR (125 MHz, CDCl₃, δ): 184.46, 161.01 (d, *J* = 242.5), 145.52, 139.41, 138.16, 133.47 (d, *J* = 5.0), 124.68 (d, *J* = 8.8), 117.40 (d, *J* = 25.0), 111.20 (d, *J* = 22.5). GC/MS (*m/z*, %): 180.0 ([M⁺], 100), 179 (91), 151 (20), 107 (48).

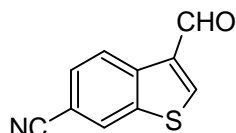
3-formyl-1-benzothiophene-5-carbonitrile(S73).



Compound **S73** was prepared from compound **S69** (393 mg, 2.47 mmol) by method O. The product was purified using column chromatography (dry-flash, SiO₂, eluent Hex → Hex/EtOAc = 3/7). Final product **S73** was obtained as white powder (331 mg, 72%). M.p. = 107–108 °C. IR (ATR): 3824w, 3317w, 3084s, 2931w, 2838m, 2744w, 2358w, 2228s, 1907w, 1810w, 1676s, 1597w, 1545w, 1507m, 1437s, 1387w, 1352w, 1305w, 1259w, 1168m, 1099m, 1041m, 906w, 885w, 861w, 812m, 736w, 715w, 695w, 637w, 512w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 10.16 (s, 1H, CHO),

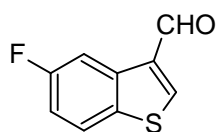
9.05 (s, H-C(2)), 8.47 (s, H-C(4)), 8.00 (d, $J = 8.5$, H-C(7)), 7.70-7.67 (m, H-C(6)). ^{13}C NMR (125 MHz, CDCl_3 , δ): 184.86, 144.65, 144.14, 135.91, 135.11, 129.62, 128.27, 123.43, 118.74, 110.18. GC/MS ($m/z, \%$): 187.0 ($[\text{M}^+$], 76), 186.0 (100), 158.0 (20), 114.0 (40).

3-formyl-1-benzothiophene-6-carbonitrile(S74).



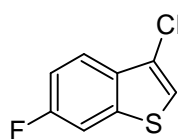
Compound **S74** was prepared from compound **S71** (120mg, 0.75 mmol) by method O. The product was purified using column chromatography (dry-flash, SiO_2 , eluent Hex \rightarrow Hex/EtOAc = 3/7). Final product **S74** was obtained as a white powder (68 mg, 48%). M.p. = 129 – 132 °C. IR (ATR): 3821w, 3417w, 3325w, 3096m, 3066m, 2838w, 2750w, 2222m, 1932w, 1797w, 1666s, 1595w, 1494m, 1458w, 1396m, 1263w, 1191w, 1142m, 1098m, 1044w, 1007w, 902w, 839m, 719w, 650w, 614w cm^{-1} . ^1H NMR (500 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$, δ): 10.00 (s, 1H, CHO), 8.63 (d, $J = 8.4$, H-C(4)), 7.56 (s, H-C(2)), 8.14-8.13 (m, H-C(7)), 7.61 (dd, $J_1 = 1.4$, $J_2 = 8.4$, H-C(5)). ^{13}C NMR (125 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$, δ): 185.36, 147.02, 140.15, 137.98, 135.66, 128.50, 126.99, 125.31, 118.30, 109.13. GC/MS ($m/z, \%$): 187.0 ($[\text{M}^+$], 76), 186.0 (100), 158.0 (20), 114.0 (40).

5-fluoro-1-benzothiophene-3-carbaldehyde(S75).



Compound **S75** was prepared from compound **S67** (300mg, 2.0 mmol) by method O. The product was purified using column chromatography (dry-flash, SiO_2 , eluent Hex \rightarrow Hex/EtOAc = 9/1). Final product **S75** was obtained as white powder (290 mg, 81%). M.p. = 111 – 112 °C (lit.³⁴ m.p. 111-113 °C (50 % EtOH)). IR (ATR): 3324w, 3168w, 3089m, 2954w, 2888w, 2832w, 2806w, 2740w, 1670s, 1628w, 1600m, 1568m, 1502m, 1449m, 1433m, 1385m, 1348w, 1312w, 1286w, 1250m, 1196m, 1144m, 1090w, 1040w, 912m, 866m, 798m, 737w, 716w, 641w, 626w, 535w, 472w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ): 10.11 (s, 1 h, CHO), 8.41-8.36 (m, H-C(2) and H-C(4)), 7.82 (dd, $J_1 = 4.8$, $J_2 = 9.0$, H-C(7)), 7.23 (td, $J_1 = 2.3$, $J_2 = 8.5$, H-C(6)). ^{13}C NMR (125 MHz, CDCl_3 , δ): 185.06, 161.60 (d, $J = 242.5$), 144.89, 136.38 (d, $J = 10.0$), 136.14 (d, $J = 5.0$), 135.72, 123.48 (d, $J = 123.48$), 115.14 (d, $J = 26.2$), 110.80 (d, $J = 23.8$). GC/MS ($m/z, \%$): 180.0 ($[\text{M}^+$], 96), 180.0 (100), 151.0 (21), 107.0 (49).

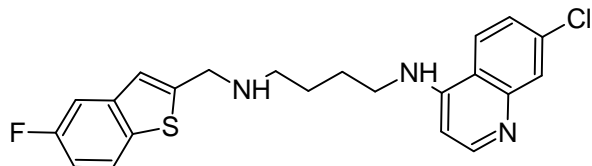
6-fluoro-1-benzothiophene-3-carbaldehyde (S76).Compound **S76** was prepared from



compound **S66** (350mg, 2.3 mmol) by method O. The product was purified using column chromatography (dry-flash, SiO_2 , eluent Hex \rightarrow Hex/EtOAc = 95/5. Final product **S76** was obtained as white powder (160mg, 39%). M.p. = 92 – 96 °C. IR (ATR): 3319w, 3110m, 3073w, 2991w, 2843w, 2745w, 1667s, 1622m, 1601m, 1570m, 1498m, 1470m, 1388m, 1323w, 1242m, 1207m, 1152w, 1129m, 1085w, 1039w, 896m, 858m, 827m, 715m, 676w, 445w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ): 10.11 (s, 1H, CHO), 8.68-8.63 (m, H-C(4)), 8.28 (s, H-C(2)), 7.58-7.55 (m, H-C(7)), 7.27 (td, $J_1 =$

2.5, $J_2 = 8.9$, H-C(5)). ^{13}C NMR (125 MHz, CDCl_3 , δ): 185.15, 161.24 (d, $J = 245.0$), 142.73, 141.37 (d, $J = 10.0$), 135.95, 131.64, 126.08 (d, $J = 8.8$), 115.11 (d, $J = 22.5$), 108.57 (d, $J = 25.0$). GC/MS (m/z , %): 180.0 ($[\text{M}^+$], 96), 180.0 (100), 151.0 (24), 107.0 (48).

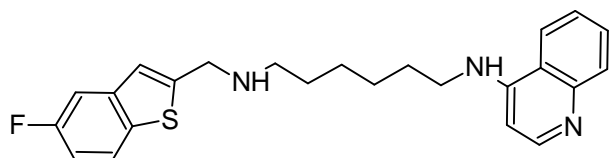
***N*-(7-chloroquinolin-4-yl)-*N'*-[(5-fluoro-1-benzothiophen-2-yl)methyl]butane-1,4-diamine(52).**



Compound **52** was prepared from aldehyde **S72** (97.4 mg, 0.540 mmol) by method E, using amine **AQ4** (202 mg, 0.811 mmol). The product was purified using column

chromatography (dry-flash, SiO_2 , eluent Hex/EtOAc gradient 1/1 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow 8/2). Final product **52** was obtained as pale yellow powder (128 mg, 58%). M.p. = 105 – 106 °C. IR (ATR): 3232m, 3062m, 2934m, 2862m, 1582s, 1545m, 1448m, 1366m, 1332w, 1279w, 1250w, 1204w, 1137w, 1083w, 952w, 900w, 864m, 802m, 765w, 675w, 639w cm^{-1} . ^1H NMR (500 MHz, CD_3OD , δ): 8.30 (d, $J = 5.7$, H-C(2')), 8.07 (d, $J = 9.2$, H-C(5')), 7.77-7.72 (m, 2H-Ar), 7.40-7.34 (m, 2H-Ar), 7.18 (s, H-C(3)), 7.05 (td, $J_1 = 2.5$, $J_2 = 8.9$, H-C(6)), 6.48 (d, $J = 5.7$, H-C(3')), 4.05-4.03 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$), 3.38-3.34 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$), 2.71 (t, 2H, $J = 7.2$, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$), 1.79 (quin, 2H, $J = 7.3$, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$), 1.72-1.65 (m, 2H, $-\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$). ^{13}C NMR (125 MHz, CD_3OD , δ): 152.50 (d, $J = 91.2$), 152.14, 149.39, 148.07, 142.35, 136.52 (d, $J = 25.3$), 136.42, 127.35, 125.99, 124.58 (d, $J = 10.0$), 124.35, 123.10 (d, $J = 3.8$), 118.72, 113.54 (d, $J = 26.2$), 109.51 (d, $J = 23.8$), 99.63, 43.81, 27.96, 27.07. HRMS: m/z 414.12065 corresponds to molecular formula $\text{C}_{22}\text{H}_{21}\text{ClN}_3\text{SFH}^+$ (error in ppm 1.20). HPLC purity ($\lambda = 330$ nm): method A: RT 7.750 min, area 96.09%; method B: RT 7.897 min, area 96.80%.

***N*-(7-chloroquinolin-4-yl)-*N'*-[(5-fluoro-1-benzothiophen-2-yl)methyl]hexane-1,6-diamine(67).**

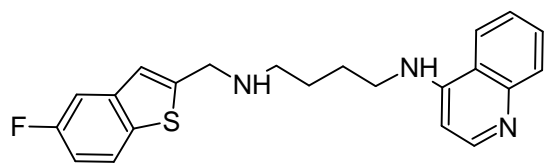


Compound **67** was prepared from aldehyde **S72** (73.5 mg, 0.408 mmol) by method E, using amine **AQ6** (169 mg, 0.608 mmol).

The product was purified using column chromatography (dry-flash, SiO_2 , eluent Hex/EtOAc gradient 1/1 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow 8/2 and flash, Biotage SP1, NH column, eluent EtOAc/Hex gradient 8/2 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow MeOH). Final product **67** was obtained as white powder (106 mg, 59%). M.p. = 71–74 °C. IR (ATR): 3226m, 3108m, 3066m, 3011m, 2929m, 2888m, 2855m, 2832m, 2774w, 1733w, 1700w, 1652w, 1581s, 1546m, 1492w, 1472m, 1443s, 1370m, 1331w, 1298w, 1255w, 1208m, 1166w, 1130m, 1085w, 1028w, 974w, 952w,

906w, 884w, 863m, 808m, 777w, 757w, 736w, 680w, 647w, 600w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ): 8.54-8.51 (m, H-C(2')), 7.97-7.95 (m, H-C(8')), 7.71-7.66 (m, H-C(7)), 7.65-7.62 (m, H-C(5')), 7.36-7.31 (m, H-C(4) and H-C(6')), 7.09 (s, H-C(3)), 7.03 (td, $J_1 = 2.4$, $J_2 = 8.8$, H-C(6)), 6.40 (d, $J = 5.5$, H-C(3')), 4.98 (bs, H-N exchangeable with D_2O), 4.06 (s, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 3.33-3.26 (m, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 2.70 (t, 2H, $J = 7.0$, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 1.80-1.65 (m, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ - and H-N exchangeable with D_2O), 1.60-1.52 (m, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 1.50-1.40 (m, 4H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ -). ^{13}C NMR (125 MHz, CDCl_3 , δ): 160.78 (d, $J = 239.2$), 152.02, 149.66, 149.07, 148.46, 140.74 (d, $J = 9.0$), 134.87, 134.84, 128.81, 125.26, 123.36 (d, $J = 9.9$), 120.72 (d, $J = 9.0$), 117.06, 112.50 (d, $J = 25.3$), 108.54 (d, $J = 23.5$), 99.05, 49.20, 49.02, 43.17, 29.91, 28.81, 26.96. HRMS: m/z 442.15060 corresponds to molecular formula $\text{C}_{24}\text{H}_{25}\text{ClN}_3\text{SFH}^+$ (error in ppm -1.93). HPLC purity ($\lambda = 330$ nm): method A: RT 9.345 min, area 99.36%; method B: RT 8.823 min, area 99.17%.

***N*-[(5-fluoro-1-benzothiophen-2-yl)methyl]-*N'*-(quinolin-4-yl)butane-1,4-diamine (**54**).**

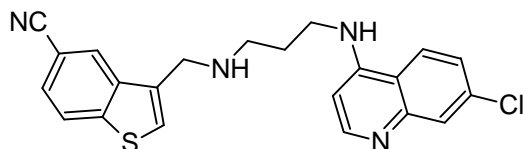


Compound **54** was prepared from aldehyde **S72** (90.0 mg, 0.499 mmol) by method E, using amine **AQ8** (161 mg, 0.749 mmol). The product was purified using column chromatography (dry-

flash, SiO_2 , eluent EtOAc/Hex gradient 1/9 \rightarrow EtOAc, EtOAc/MeOH gradient 95/5 \rightarrow 8/2 and flash, Biotage SP1, SiO_2 column, eluent EtOAc/MeOH+ NH_3 (9/1) gradient 95/5 \rightarrow 3/7). Final product **54** was obtained as pale yellow oil (101 mg, 54%). IR (ATR): 3435w, 3266m, 3117w, 3063m, 3012w, 2933m, 2858m, 1580s, 1541m, 1495w, 1443m, 1396w, 1374w, 1341m, 1282w, 1255w, 1223w, 1206w, 1152w, 1128m, 952w, 864w, 803w, 764w, 737w, 689w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ): 8.54 (d, $J = 5.5$, H-C(2')), 7.97 (d, $J = 8.5$, H-C(8')), 7.74 (d, $J = 8.5$, H-C(5')), 7.69 (dd, $J_1 = 4.8$, $J_2 = 8.8$, H-C(7)), 7.63-7.57 (m, H-C(7')), 7.37-7.33 (m, H-C(4) and H-C(6')), 7.10 (s, H-C(3)), 7.04 (td, $J_1 = 2.5$, $J_2 = 8.8$, H-C(6)), 6.40 (d, $J = 5.5$, H-C(3')), 5.48 (bs, H-N exchangeable with D_2O), 4.09 (s, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 3.36-3.31 (m, 2H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 2.78 (t, 2H, $J = 6.8$, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ -), 1.91-1.67 (m, 4H, - $\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}$ - and H-N exchangeable with D_2O). ^{13}C NMR (125 MHz, CDCl_3 , δ): 160.82 (d, $J = 239.2$), 151.03, 149.74, 148.38, 147.99, 140.71 (d, $J = 9.9$), 134.87, 129.89, 128.92, 124.46, 123.41 (d, $J = 9.0$), 120.91 (d, $J = 4.5$), 119.38, 118.75, 112.62 (d, $J = 25.3$), 108.61 (d, $J = 22.6$), 98.67, 49.16, 48.51, 43.15, 27.66, 26.38. HRMS: m/z 380.15894 corresponds to molecular formula

$C_{22}H_{22}N_3SFH^+$ (error in ppm -0.48). HPLC purity ($\lambda = 330$ nm): method A: RT 8.950 min, area 97.85%; method B: RT 7.746 min, area 97.41%.

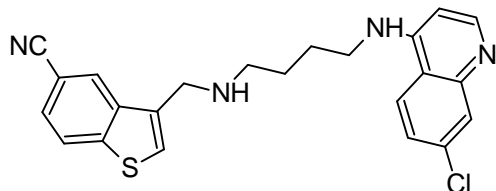
3-[(3-[(7-chloroquinolin-4-yl)amino]propyl)amino)methyl]-1-benzothiophene-5-carbonitrile(60).



Compound **60** was prepared from aldehyde **S73** (79.6 mg, 0.425 mmol) by method E, using amine **AQ3** (151 mg, 0.630 mmol). The product was purified using column chromatography (dry-flash,

SiO₂, eluent Hex/EtOAc gradient 1/1 → EtOAc, EtOAc/MeOH gradient 95/5 → 8/2). Final product **59** was obtained as white powder (124 mg, 72%). M.p. = 129 – 130 °C. IR (ATR): 3215m, 3061m, 3013m, 2965m, 2838m, 2225m, 1581s, 1439m, 1367m, 1282w, 1261w, 1235w, 1137m, 1079w, 897w, 851w, 801w, 768w, 735w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.49 (d, $J = 5.2$, H-C(2')), 8.14-8.12 (m, H-C(4)), 7.95 (d, $J = 8.2$, H-C(7)), 7.88 (d, $J = 2.2$, H-C(8')), 7.53 (dd, $J_1 = 1.6$, $J_2 = 8.2$, H-C(6)), 7.49 (s, H-C(2)), 7.35 (d, $J = 8.8$, H-C(5')), 7.00 (dd, $J_1 = 2.2$, $J_2 = 8.8$, H-C(6')), 6.82 (s, H-N exchangeable with D₂O), 6.32 (d, $J = 5.2$, H-C(3')), 4.10 (s, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.45-3.39 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.05-3.01 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 2.02-1.95 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 1.82 (bs, H-N exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃, δ): 152.07, 150.04, 149.03, 144.77, 138.13, 134.84, 134.50, 128.56, 126.43, 126.36, 125.80, 124.74, 123.90, 121.38, 119.19, 117.28, 107.95, 98.55, 49.06, 47.41, 43.26, 27.79. HRMS: m/z 407.10826 corresponds to molecular formula C₂₂H₁₉ClN₄SH⁺ (error in ppm - 2.23). HPLC purity ($\lambda = 330$ nm) method A: RT 8.036 min, area 98.36%; ($\lambda = 254$ nm) method C: RT 5.223 min, area 97.09%.

3-[(4-[(7-chloroquinolin-4-yl)amino]butyl)amino)methyl]-1-benzothiophene-5-carbonitrile(64).

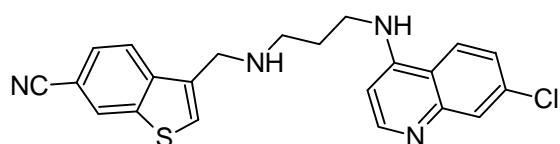


Compound **64** was prepared from aldehyde **S73** (118 mg, 0.630 mmol) by method E, using amine **AQ4** (236 mg, 0.945 mmol). The product was purified using column chromatography (dry-flash, SiO₂,

eluent Hex/EtOAc gradient 1/1 → EtOAc, EtOAc/MeOH gradient 95/5 → 8/2 and flash, Biotage SP1, NH column, eluent EtOAc/Hex gradient 8/2 → EtOAc, EtOAc/MeOH gradient 95/5 → MeOH). Final product **64** was obtained as white powder (137 mg, 52%). M.p. = 112 – 113 °C. IR (ATR): 3309m, 3270w, 3106w, 3054w, 3005m, 2972w, 2944m, 2875m, 2840w, 2227m, 1613w, 1579s, 1545m, 1455w, 1432w, 1367w, 1332w, 1308w, 1277w, 1240w, 1203w, 1140w, 1108w, 1085w, 1047w, 925w, 895w, 865w, 846w, 803m, 761w, 743w, 677w, 627w, 602w, 567w, 542w cm⁻¹. ¹H NMR (500 MHz, CDCl₃ + CD₃OD, δ): 8.54-8.50 (m, H-

C(2''), 8.22 (s, H-C(8')), 7.95-7.91 (m, H-C(7) and H-C(5')), 7.62-7.58 (m, H-C(4)), 7.56-7.52 (m, H-C(6')), 7.45 (bs, H-C(2)), 7.25-7.20 (m, H-C(5)), 6.38 (d, $J = 5.4$, H-C(3')), 5.44 (bs, H-N exchangeable with D₂O), 4.07 (s, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 3.35-3.30 (m, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 2.82 (t, 2H, $J = 6.8$, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.89 (quin, 2H, $J = 6.8$, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.74 (quin, 2H, $J = 6.9$, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.60 (bs, H-N exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃ + CD₃OD, δ): 151.14, 150.49, 148.18, 144.82, 138.05, 135.08, 134.46, 127.20, 126.38, 126.20, 125.83, 125.06, 123.78, 121.68, 119.28, 117.05, 107.41, 98.48, 46.91, 42.72, 27.18, 26.01. HRMS: m/z 421.12435 corresponds to molecular formula C₂₃H₂₁ClN₄SH⁺ (error in ppm -1.11). HPLC purity ($\lambda = 330$ nm): method A: RT 8.920 min, area 99.20%; method B: RT 8.539 min, area 96.73%.

3-[(3-[(7-chloroquinolin-4-yl)amino]propyl)amino)methyl]-1-benzothiophene-6-carbonitrile(61).

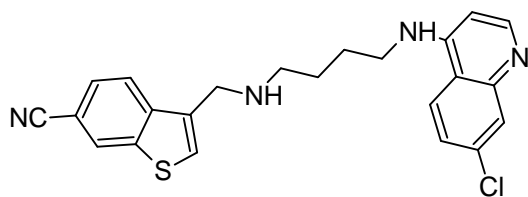


Compound **61** was prepared from aldehyde **S74** (58.5 mg, 0.312 mmol) by method E, using amine **AQ3** (111 mg, 0.469 mmol). The product was purified using column chromatography (dry-

flash, SiO₂, eluent Hex/EtOAc gradient 1/1 → EtOAc, EtOAc/MeOH gradient 95/5 → 75/25, flash, Biotage SP1, NH column, eluent EtOAc/Hex gradient 8/2 → EtOAc, EtOAc/MeOH gradient 95/5 → MeOH and flash, Biotage SP1, SiO₂ column, eluent

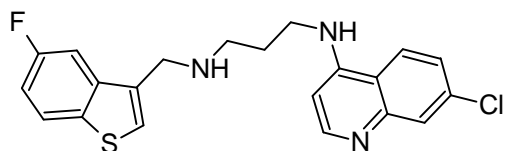
EtOAc/MeOH+NH₃(9/1) gradient 95/5 → 1/1). Final product **61** was obtained as white powder (70.3 mg, 55%). M.p. = 48 – 50 °C. IR (film): 3256m, 3058m, 2945m, 2849m, 2226s, 1916w, 1610s, 1581s, 1537s, 1454s, 1367, 1331m, 1281m, 1264m, 1242m, 1199m, 1169w, 1139m, 1078w, 1052w, 899m, 878m, 851m, 818s, 766m, 736s, 702m, 646w, 606w, 503w, 458w, 432w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.51-8.48 (m, H-C(2'')), 8.22-8.19 (m, H-C(8')), 7.92-7.89 (m, H-C(7)), 7.86 (d, $J = 8.4$, H-C(5')), 7.61 (s, H-C(2)), 7.51-7.47 (m, H-C(6')), 7.36-7.32 (m, H-C(4)), 7.00-6.90 (m, H-C(5) and H-N exchangeable with D₂O), 6.32 (d, $J = 5.5$, H-C(3')), 4.12 (s, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.45-3.40 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.05-3.02 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 2.02-1.96 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 1.77 (bs, H-N exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃, δ): 152.04, 141.01, 140.55, 134.97, 128.07, 127.62, 126.84, 124.79, 122.37, 121.46, 118.98, 117.26, 107.98, 98.48, 49.22, 47.42, 43.50, 27.70. HRMS: m/z 407.10922 corresponds to molecular formula C₂₂H₁₉ClN₄SH⁺ (error in ppm 0.13). HPLC purity ($\lambda = 330$ nm): method A: RT 8.763 min, area 96.57%; method B: RT 7.719 min, area 97.71%.

3-[(4-[(7-chloroquinolin-4-yl)amino]butyl)amino)methyl]-1-benzothiophene-6-carbonitrile(65).



Compound **65** was prepared from aldehyde **S74** (62.7 mg, 0.335 mmol) by method E, using amine **AQ4** (125 mg, 0.502 mmol). The product was purified using column chromatography (dry-flash, SiO₂, eluent Hex/EtOAc gradient 1/1 → EtOAc, EtOAc/MeOH gradient 95/5 → 8/2). Final product **65** was obtained as white powder (88.2 mg, 65%). M.p. = 62 – 65 °C. IR (ATR): 3296m, 3125m, 3052m, 2938s, 2863m, 2821m, 2222m, 1611m, 1580s, 1538m, 1455m, 1371m, 1326m, 1282w, 1256w, 1199w, 1139w, 1080w, 1022m, 907w, 874w, 855w, 823m, 800m, 606w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.53-8.50 (m, H-C(2')), 8.19-8.17 (m, H-C(7)), 7.95-7.89 (m, H-C(7) and H-C(5')), 7.61-7.56 (m, H-C(2) and H-C(6') and H-C(4)), 7.22-7.19 (m, H-C(5)), 6.38 (d, *J* = 5.5, H-C(3')), 5.48 (bs, H-N exchangeable with D₂O), 4.09-4.06 (m, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 3.35-3.30 (m, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 2.81 (t, 2H, *J* = 6.8, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.88 (quin, 2H, *J* = 6.8, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.73 (quin, 2H, *J* = 6.9, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.64 (bs, H-N exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃, δ): 152.03, 141.16, 140.60, 135.44, 134.81, 128.79, 127.72, 127.57, 126.71, 125.12, 122.63, 120.89, 119.18, 117.13, 107.79, 98.97, 49.14, 47.53, 43.14, 27.70, 26.45. HRMS: *m/z* 421.12558 corresponds to molecular formula C₂₃H₂₁ClN₄SH⁺ (error in ppm 1.81). HPLC purity (λ = 330 nm) method A: RT 10.621 min, area 98.74%; (λ = 254 nm) method B: RT 7.777 min, area 95.86%.

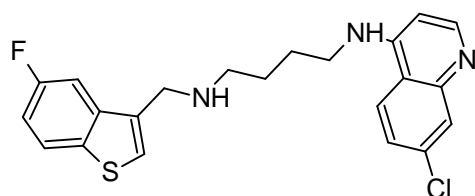
***N*-(7-chloroquinolin-4-yl)-*N'*-[(5-fluoro-1-benzothiophen-3-yl)methyl]propane-1,3-diamine(58).**



Compound **58** was prepared from aldehyde **S75** (181 mg, 1.00 mmol) by method E, using amine **AQ3** (353 mg, 1.50 mmol). The product was purified using column chromatography (dry-flash, SiO₂, eluent EtOAc/Hex gradient 1/9 → EtOAc, EtOAc/MeOH gradient 95/5 → 4/6, flash, Biotage SP1, NH column, eluent EtOAc/Hex gradient 8/2 → EtOAc, EtOAc/MeOH gradient 95/5 → MeOH and flash, Biotage SP1, SiO₂ column, eluent EtOAc/MeOH+NH₃(9/1) gradient 95/5 → 7/3). Final product **58** was obtained as a white powder (269 mg, 67%). M.p. = 133 – 134 °C. IR (ATR): 3240m, 3060w, 2953w, 2852w, 1607m, 1579s, 1535m, 1435m, 1360w, 1329m, 1279w, 1251w, 1230w, 1205w, 1137w, 1104w, 1082w, 913w, 850w, 800w, 761w, 718w, 665w, 642w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.50-8.47 (m, H-C(2')), 7.90-7.88 (m, H-C(8')), 7.83 (dd, *J*₁ = 4.8, *J*₂ = 8.9, H-C(7)), 7.46 (dd, *J*₁ = 2.4, *J*₂ = 9.5, H-C(4)), 7.43

(s, H-C(2)), 7.35 (d, $J = 9.0$, H-C(5')), 7.17-7.09 (m, H-C(6) and H-N exchangeable with D₂O), 7.01-6.97 (m, H-C(6')), 6.32 (d, $J = 5.5$, H-C(3')), 4.06 (s, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.45-3.40 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.06-3.02 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 2.01-1.94 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 1.69 (bs, H-N exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃, δ): 160.88 (d, $J = 240.1$), 152.04, 150.24, 149.05, 139.37 (d, $J = 9.0$), 135.98, 134.48 (d, $J = 22.5$), 128.48, 125.89, 124.81, 124.17 (d, $J = 9.9$), 121.61, 117.36, 113.51 (d, $J = 25.3$), 107.28 (d, $J = 22.5$), 98.39, 49.36, 47.64, 43.68, 27.60. HRMS: m/z 400.10388 corresponds to molecular formula C₂₁H₁₉ClFN₃SH⁺ (error in ppm -1.56). Anal. (C₂₁H₁₉ClFN₃S) Calcd: C, 63.07; H, 4.79; N, 10.51; S, 8.02. Found: C, 63.09; H, 4.77; N, 10.30; S, 7.72. HPLC purity ($\lambda = 330$ nm): method A: RT 8.998 min, area 98.73%; method B: RT 8.544 min, area 99.17%.

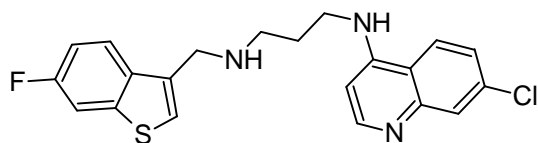
***N*-(7-chloroquinolin-4-yl)-*N'*-[(5-fluoro-1-benzothiophen-3-yl)methyl]butane-1,4-diamine(63).**



Compound **63** was prepared from aldehyde **S75** (181 mg, 1.00 mmol) by method E, using amine **AQ4** (376 mg, 1.51 mmol). The product was purified using column chromatography (dry-flash, SiO₂, eluent

EtOAc/Hex gradient 1/9 → EtOAc, EtOAc/MeOH gradient 95/5 → 1/1, flash, Biotage SP1, NH column, eluent EtOAc/Hex gradient 8/2 → EtOAc, EtOAc/MeOH gradient 95/5 → MeOH and flash, Biotage SP1, SiO₂ column, eluent EtOAc/MeOH+NH₃(9/1) gradient 95/5 → 1/1). Final product **63** was obtained as a white powder (251 mg, 60%). M.p. = 110 – 113 °C. IR (ATR): 3228m, 3063w, 2945w, 2855w, 2810w, 1579s, 1543m, 1490w, 1433m, 1366w, 1330w, 1279w, 1245w, 1225w, 1196w, 1161w, 1134w, 1078w, 954w, 898w, 854w, 806w, 782w, 640w, 619w, 543w, 483w, 452w, 423w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.50 (d, $J = 5.2$, H-C(2')), 7.94-7.91 (m, H-C(8')), 7.77 (dd, $J_1 = 4.8$, $J_2 = 8.7$, H-C(7)), 7.59 (d, $J = 8.9$, H-C(5')), 7.51-7.46 (m, H-C(4)), 7.38 (s, H-C(2)), 7.18-7.14 (m, H-C(6')), 7.10 (td, $J_1 = 2.4$, $J_2 = 8.8$, H-C(6)), 6.36 (d, $J = 5.3$, H-C(3')), 5.65 (bs, H-N exchangeable with D₂O), 4.00 (s, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 3.32-3.27 (m, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 2.80 (t, $J = 6.6$, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.88 (quin, 2H, $J = 6.8$, -CH₂NHCH₂CH₂CH₂CH₂NH-), 1.75-1.55 (m, 2H, -CH₂NHCH₂CH₂CH₂CH₂NH- and H-N exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃, δ): 160.74 (d, $J = 240.1$), 152.01, 149.82, 149.08, 139.46 (d, $J = 9.0$), 135.97, 134.81, 134.74 (d, $J = 9.0$), 128.68, 125.43, 125.02, 123.98 (d, $J = 9.0$), 121.05, 117.18, 113.29 (d, $J = 24.4$), 107.47 (d, $J = 22.6$), 98.91, 48.99, 47.67, 43.14, 27.69, 26.40. HRMS: m/z 414.11939 corresponds to molecular formula C₂₂H₂₁ClFN₃SH⁺ (error in ppm -1.85). HPLC purity ($\lambda = 330$ nm) method A: RT 9.136 min, area 99.72%; ($\lambda = 254$ nm) method B: RT 7.522 min, area 95.22%.

***N*-(7-chloroquinolin-4-yl)-*N'*-[(6-fluoro-1-benzothiophen-3-yl)methyl]propane-1,3-diamine(**59**).**



Compound **59** was prepared from aldehyde **S76** (161 mg, 0.888 mmol) by method E, using amine **AQ3** (314 mg, 1.33 mmol). The product was purified using column chromatography (dry-flash,

SiO₂, eluent EtOAc/Hex gradient 1/9 → EtOAc, EtOAc/MeOH gradient 95/5 → 4/6, flash, Biotage SP1, NH column, eluent EtOAc/Hex gradient 8/2 → EtOAc, EtOAc/MeOH gradient 95/5 → MeOH and flash, Biotage SP1, SiO₂ column, eluent EtOAc/MeOH+NH₃(9/1) gradient 95/5 → 3/7). Final product **59** was obtained as a white powder (194 mg, 54%). M.p. = 149 – 150 °C. IR (ATR): 3433w, 3294m, 3210m, 3067m, 3015m, 2927m, 2853m, 1606m, 1581s, 1539m, 1466m, 1430w, 1369w, 1330w, 1282w, 1251w, 1208w, 1168w, 1139w, 1109w, 1080w, 896w, 854w, 807w, 761w, 737w, 683w, 646w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ): 8.50-8.47 (m, H-C(2')), 7.90 (bs, H-C(8')), 7.74-7.70 (m, H-C(4)), 7.60-7.56 (m, H-C(7)), 7.37-7.33 (m, H-C(5')), 7.30 (s, H-C(2)), 7.22 (bs, H-N exchangeable with D₂O), 7.07-7.01 (m, H-C(5)), 7.00-6.96 (m, H-C(6')), 6.31 (d, *J* = 5.2, H-C(3')), 4.08 (s, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.45-3.40 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 3.06-3.03 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 2.01-1.95 (m, 2H, -CH₂NHCH₂CH₂CH₂NH-), 1.76 (bs, H-N exchangeable with D₂O). ¹³C NMR (125 MHz, CDCl₃, δ): 160.70 (d, *J* = 243.7), 151.97, 150.31, 141.61 (d, *J* = 9.9), 134.71, 134.12, 128.39, 124.83, 122.98, 122.46 (d, *J* = 10.0), 121.70, 117.33, 113.28 (d, *J* = 23.5), 109.07 (d, *J* = 25.3), 98.36, 49.37, 47.69, 43.75, 27.52. HRMS: *m/z* 400.10427 corresponds to molecular formula C₂₁H₁₉ClFN₃SH⁺ (error in ppm - 0.56). HPLC purity (λ = 330 nm) method A: RT 9.049 min, area 95.99%; (λ = 254 nm) method B: RT 7.455 min, area 97.07%.

***N*-(quinolin-4-yl)propane-1,3-diamine (**AQ7**).**

¹H NMR (500 MHz, CD₃OD, δ): 8.35 (d, *J* = 5.7, H-C(2)), 8.09-8.06 (m, H-C(8)), 7.77 (d, *J* = 8.0, H-C(5)), 7.64-7.60 (m, H-C(6)), 7.45-7.40 (m, H-C(5)), 6.52 (d, *J* = 5.5, H-C(3)), 3.43 (t, 2H, *J* = 7.1, ArNHCH₂-), 2.80 (t, 2H, *J* = 6.9, ArNHCH₂CH₂CH₂-), 1.90 (quin, 2H, *J* = 7.1, ArNHCH₂CH₂-). ¹³C NMR (125 MHz, CD₃OD, δ): 152.77, 151.41, 149.07, 130.57, 128.98, 125.72, 122.28, 120.46, 99.32, 41.81, 40.48, 32.40. HRMS: *m/z* 202.13373 corresponds to molecular formula C₁₂H₁₅N₃H⁺ (error in ppm -0.73).

***N*-(quinolin-4-yl)butane-1,4-diamine (**AQ8**).**

¹H NMR (200 MHz, CD₃OD, δ): 8.31 (d, *J* = 14.0, H-C(2)), 8.11-8.04 (m, H-C(8)), 7.82-7.75 (m, H-C(5)), 7.63-7.53 (m, H-C(6)), 7.44-7.34 (m, H-C(5)), 6.42 (d, *J* = 14.0, H-C(3)), 3.30 (t, 2H, *J* = 18.5, ArNHCH₂-), 2.65 (t, 2H, *J* = 16.8, ArNHCH₂CH₂CH₂CH₂-), 1.80-1.47 (m, 4H, ArNHCH₂CH₂CH₂-). ¹³C NMR (50 MHz, CD₃OD, δ): 152.65, 151.30, 148.97, 130.46,

128.87, 125.56, 122.26, 120.33, 99.16, 43.81, 42.32, 31.39, 26.88. HRMS: m/z 216.14910 corresponds to molecular formula $C_{13}H_{17}N_3H^+$ (error in ppm -1.94).

References

- (1) Delves, M.; Plouffe, D.; Scheurer, C.; Meister, S.; Wittlin, S.; Winzeler, E. A.; Sinden, R. E.; Leroy, D. The activities of current antimalarial drugs on the life cycle stages of plasmodium: A comparative study with human and rodent parasites. *PLoS Med.* **2012**, *9*, e1001169.
- (2) Oliveira, R.; Guedes, R.; Meireles, P.; Albuquerque, I.; Gonçalves, L.; Pires, E.; Bronze, M.; Gut, J.; Rosenthal, P.; Prudêncio, M.; Moreira, R.; O'Neill, P.; Lopes, F. Tetraoxane–Pyrimidine Nitrile Hybrids as Dual Stage Antimalarials. *J. Med. Chem.* **2014**, *57*, 4916–4923.
- (3) Opsenica, I.; Opsenica, D.; Smith, K. S.; Milhous, W. K.; Šolaja, B. A. Chemical Stability of the Peroxide Bond Enables Diversified Synthesis of Potent Tetraoxane Antimalarials. *J. Med. Chem.* **2008**, *51*, 2261–2266.
- (4) Opsenica, I.; Opsenica, D.; Lanteri, C.A.; Anova, L.; Milhous, W.K.; Smith, K.S.; Šolaja, B.A. New Chimeric Antimalarials with 4-Aminoquinoline Moiety Linked to a Tetraoxane Skeleton. *J. Med. Chem.* **2008**, *51*, 6216–6219.
- (5) Šolaja, B. A.; Terzić, N.; Pocsfalvi, G.; Gerena, L.; Tinant, B.; Opsenica, D.; Milhous, W. K. Mixed Steroidal 1,2,4,5-Tetraoxanes: Antimalarial and Antimycobacterial Activity. *J. Med. Chem.* **2002**, *45*, 3331–3336.
- (6) Opsenica, I.; Terzić, N.; Opsenica, D.; Milhous, W. K.; Šolaja, B. A. 7,8,15,16-Tetraoxa-dispiro[5.2.5.2]hexadecane-3-carboxylic acid derivatives and their antimalarial activity. *J. Serb. Chem. Soc.* **2004**, *69*, 919–922.
- (7) Terzić, N.; Opsenica, D.; Milić, D.; Tinant, B.; Smith, K. S.; Milhous, W. K.; Šolaja, B. A. Deoxycholic Acid-Derived Tetraoxane Antimalarials and Antiproliferatives. *J. Med. Chem.* **2007**, *50*, 5118–5127.
- (8) Opsenica, I.; Terzić, N.; Opsenica, D.; Angelovski, D.; Lehnig, M.; Eilbracht, P.; Tinant, B.; Juranić, Z.; Smith, K. S.; Yang, Y. S.; Diaz, D. S.; Smith, P. L.; Milhous, W. K.; Doković, D.; Šolaja, B. A. Tetraoxane Antimalarials and Their Reaction with Fe(II). *J. Med. Chem.* **2006**, *49*, 3790–3799.
- (9) a) Musonda, C. C.; Gut, J.; Rosenthal, P. J.; Yardley, V.; Carvalho de Souza, R. C.; Chibale, K. Application of Multicomponent Reactions to Antimalarial Drug Discovery. Part 2: New Antiplasmodial and Antitrypanosomal 4 Aminoquinoline Gamma- and Delta-Lactams via a “Catch and Release” Protocol. *Bioorg. Med. Chem.* **2006**, *14*, 5605–5615. b) Peck, R. M.; Preston, R. K.; Creech, H. J. Nitrogen Mustard Analogs of Antimalarial Drugs. *J. Am. Chem. Soc.* **1958**, *81*, 3984–3989. c) Price, C. C.; Leonard, N. J.; Peel, E. W.; Reitsem, R. H. Some 4-Amino-7-chloroquinoline Derivatives. *J. Am. Chem. Soc.* **1946**, *68*, 1807–1808. d) Singh, C.; Malik, H.; Puri, S. K. Synthesis and Antimalarial Activity of a New Series of Trioxaquinones. *Bioorg. Med. Chem.* **2004**, *12*, 1177–1182.
- (10) (a) Pittelkow, M.; Lewinsky, R.; Christensen, J. B. Selective Synthesis of Carbamate Protected Polyamines Using Alkyl Phenyl Carbonates. *Synthesis*, **2002**, *15*, 2195–2202; (b) Pittelkow, M.; Lewinsky, R.; Christensen, J. B. Mono carbamate protection of aliphatic diamines using alkyl phenyl carbonates [(2-aminoethyl)carbamic acid *tert*-butyl ester]. *Org. Synth.* **2007**, *84*, 209–214.

- (11) Solaja, B. A.; Opsenica, D.; Smith, K. S.; Milhous, W. K.; Terzic, N.; Opsenica, I.; Burnett, J. C.; Nuss, J.; Gussio, R.; Bavari, S., Novel 4-Aminoquinolines Active against Chloroquine-Resistant and Sensitive *P.falciparum* Strains that also Inhibit Botulinum Serotype A. *J. Med. Chem.* **2008**, *51*, 5623–5625.
- (12) Bhattacharyya, S. Titanium(IV) mediated reductive amination of 1-adamantyl methyl ketone: facile preparation of potential antiviral agents rimantadine and its analogues. *J. Chem. Soc. Perkin Trans I* **1995**, 1845-1847.
- (13) Margolis, B. J.; Long, K. A.; Laird, D. L. T.; Ruble, J. C.; Pulley, S. R. Assembly of 4-Aminoquinolines via Palladium Catalysis: A Mild and Convenient Alternative to S_NAr Methodology. *J. Org. Chem.* **2007**, *72*, 2232–2235.
- (14) Raynham, T. M.; Hammonds, T. R.; Gilliatt, J. H.; Charles, M. D.; Pave, G. A.; Foxton, C. H.; Carr, J. L.; Mistry, N. S. Aminoethylamino-aryl (AEAA) compounds as PKD inhibitors and their preparation, pharmaceutical compositions and use in the treatment of PKD-mediated diseases. PCT Int. Appl. (2007), **WO 2007125331 A2**.
- (15) Kim, S.; Oh, C. H.; Oh, Ko, J. S.; Ahn, K. H.; Kim, Y. J. Zinc-modified cyanoborohydride as a selective reducing agent. *J. Org. Chem.* **1985**, *50*, 1927–1932.
- (16) Fedi, V.; Altamura, M.; Catalioto, R. M.; Giannotti, D.; Giolitti, A.; Giuliani, S.; Guidi, A.; Harmat, N. J. S.; Lecci, A.; Meini, S.; Nannicini, R.; Pasqui, F.; Tramontana, M.; Triolo, A.; Maggi, C. A. Discovery of a New Series of Potent and Selective Linear Tachykinin NK2 Receptor Antagonists. *J. Med. Chem.* **2007**, *50*, 4793-4807.
- (17) Pessoa-Mahana, H.; Kosche, C. J.; Ron, H., N.; Recabarren-Gajardo, G.; Saitz, B., C.; Araya-Maturana, R.; Pessoa-Mahana, C. D. Solvent-Free Microwave Synthesis of 3-(4-Benzo[b]thiophene-2-carbonyl)-1-piperazinyl-1-benzo[b]thiophen-2-yl-1-propanones. New Hetero Bis-Ligands with Potential 5-HT_{1A} Serotonergic Activity. *Heterocycles* **2008**, *75*, 1913-1929.
- (18) Tilstam, U. A Continuous Protodecarboxylation of Heteroaromatic Carboxylic Acids in Sulfolane. *Org. Process Res. Dev.* **2012**, *16*, 1449-1454.
- (19) Shi, J. P.; Wu, D. L.; Ding, Y.; Wu, D. H.; Hu, H. W.; Lu, G. Y. Synthesis of novel H-shaped chromophores. *Tetrahedron* **2012**, *68*, 2770-2777.
- (20) (a) Noland, W. E.; Baude, F. J. The Cycloaddition Reaction of 3-Alkylindoles with p-Benzoquinone. *J. Org. Chem.* **1966**, *31*, 3321-3337. (b) Allen, J. G.; Briner, K.; Cohen, M. P.; Galka, C. S.; Hellman, S. L.; Martinez-Grau, M. A.; Reinhard, M. R.; Rodriguez, M. J.; Rothhaar, R. R.; Tidwell, M. W.; Vistor, F.; Williams, A. C.; Zhang, D.; Boyd, S. A.; Conway, R. G.; Deo, A. S.; Lee, W. M.; Siedem, C. S.; Singh, A. 6-Substituted 2,3,4,5-Tetrahydro-1H-benzo[d]azepines as 5-HT_{2C} Receptor Agonists, PCT Int. Appl. **2005**, WO 2005082859.
- (21) Cutler, R. A.; Surrey, A. R. Reaction of 4,7-dichloroquinoline with acetic acid. *J. Am. Chem. Soc.* **1950**, *72*, 3394-3395.
- (22) Gerster, J. F.; Lindstrom, K. J.; Miller, R. L.; Tomai, M. A.; Birmachu, W.; Bomersine, S. N.; Gibson, S. J.; Imbertson, L. M.; Jacobson, J. R.; Knafla, R. T.; Maye, P. V.; Nikolaides, N.; Oneyemi, F. Y.; Parkhurst, G. J.; Pecore, S. E.; Reiter, M. J.; Scribner, L. S.; Testerman, T. L.; Thompson, N. J.; Wagner, T. L.; Weeks, C. E.; Andre, J. D.; Lagain, D.; Bastard, Y.; Lupu, M. Synthesis and structure-activity-relationships of 1H-imidazo[4,5-c]quinolines that induce interferon production. *J. Med. Chem.* **2005**, *48*, 3481-91.
- (23) Heindel, N. D.; Fine, S. A., 3-Nitro-7-Chloroquinoline. *Organic Preparations and Procedures* **1969**, *1*, 279-281.

-
- (24) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. First Total Synthesis of Cryptomisine. *Tetrahedron* **1999**, *55*, 12149-12156.
- (25) Mezlova, M.; Petrickova, H.; Malon, P.; Kozmik, V.; Svoboda, J. Axially Chiral 3,3'-bi(1-benzothiophene)-2,2'-dicarboxylic Acid and Its Derivatives. *Collect. Czech. Chem. C.* **2003**, *68*, 1020-1038.
- (26) Zeng, F.; Alper, H. Palladium-Catalyzed Domino C-S Coupling/Carbonylation Reactions: An Efficient Synthesis of 2-Carbonylbenzo[b]thiophene Derivatives. *Org. Lett.* **2011**, *13*, 2868-2871.
- (27) Matsunaga, N.; Kaku, T.; Itoh, F.; Tanaka, T.; Hara, T.; Miki, H.; Iwasaki, M.; Aono, T.; Yamaoka, M.; Kusaka, M.; Tasaka, A. C_{17,20}-Lyase inhibitors I. Structure-based de novo design and SAR study of C_{17,20}-lyase inhibitors. *Bioorg. Med. Chem.* **2004**, *12*, 2251-2273.
- (28) Zuckerman, N. B.; Kang, X.; Chen, S.; Konopelski, J. P. Synthesis of a ferrocene-functionalized unsymmetrical benzo[b]thienyl-thienylethene photoswitch with a cyclopentene core. *Tetrahedron Lett.* **2013**, *54*, 1482-1485.
- (29) Cheng, K.; Wang, X.; Yin, H. Small-Molecule Inhibitors of the TLR3/dsRNA Complex. *J. Am. Chem. Soc.* **2011**, *133*, 3764-3767.
- (30) Badger, G. M.; Clark, D. J.; Davies, W.; Farrer, K. T. H.; Kefford, N. P. Thionaphthencarboxylic acids. *J. Chem. Soc.* **1957**, 2624-30.
- (31) Banfield, J. E.; Davies, W.; Ennis, B. C.; Middleton, S.; Porter, Q. N. The synthesis of thionaphthen derivatives. Part I. The cyclisation of arylthioacetaldehyde diethyl acetals. *J. Chem. Soc.* **1956**, 2603-2608.
- (32) D'Alo, F.; Masserini, A.; Bonacina, F. N-Alkylalkanolamines of the benzo[b]thiophene series. *Bull. Chim. Farm.* **1964**, *103*, 709-26.
- (33) Hansch, C.; Schmidhalter, B. Synthesis of 6-Substituted Thianaphthenes. *J. Org. Chem.* **1955**, *20*, 1056-61.
- (34) Brabander, H. J. The synthesis of benzo[b]thiophene-3-carboxaldehydes and 3-carboxylic acids by light catalyzed NBS bromination of 3-methylbenzo[b]thiophenes. *J. Het. Chem.* **1973**, *10*, 127-129.