

Figure 1

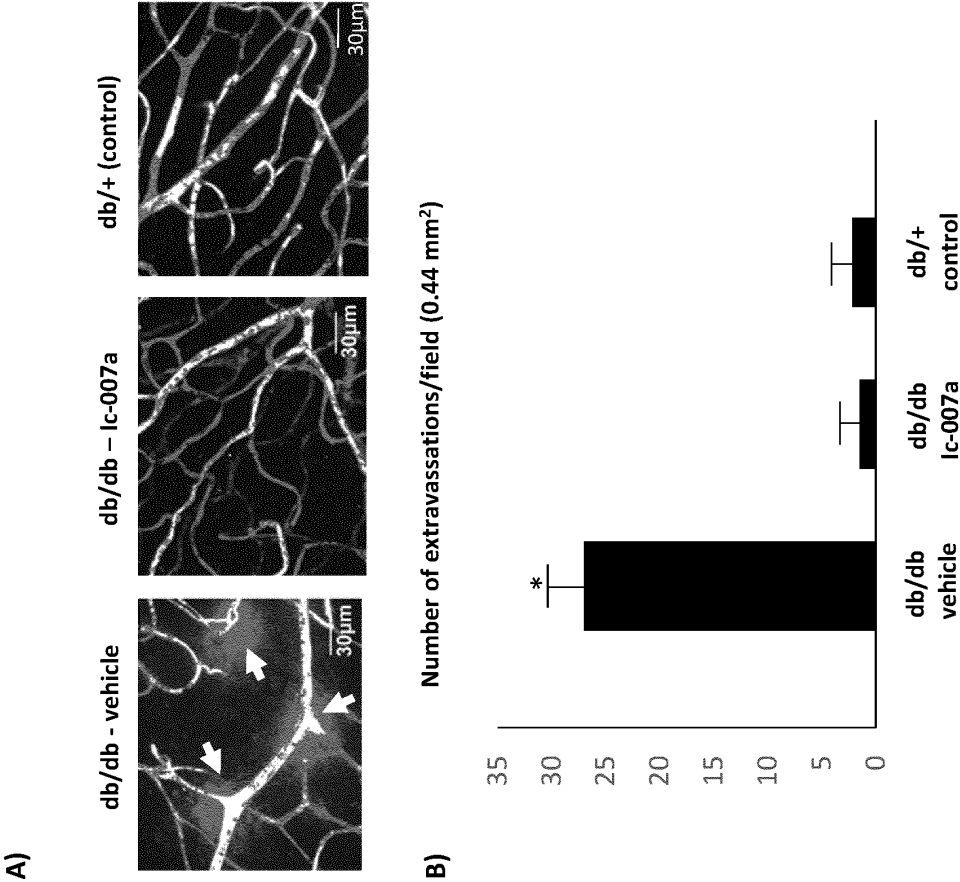


Figure 2

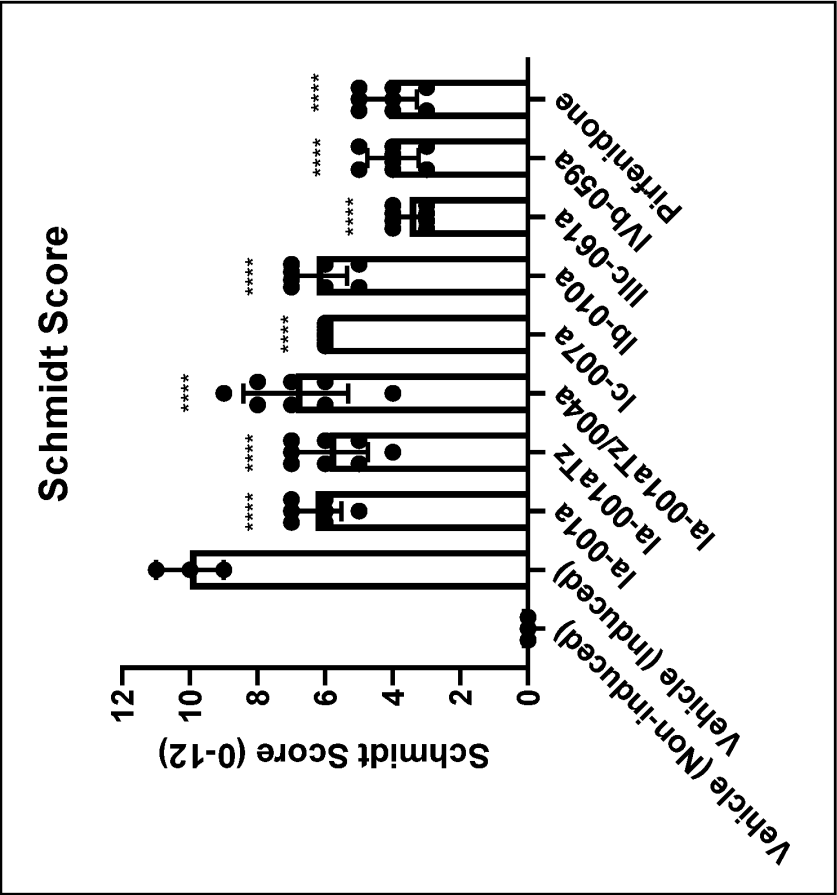


Figure 3 A

[illegible]

Cytokines		IL-1b	IL-2	IL-3	IL-4	IL-5	IL-6	IL-7	IL-8	IL-9	IL-10	IL-12p70	IL-13	IL-14	IL-15	IL-17A	IL-17F	IL-18	IL-21	IL-22	IL-23	IL-33	IFN γ	IFNb	TNF α	TGFbeta	TNFbeta	MCP-1	MMPs
		Diseases																											
Helminth infections										x																			
Inflammatory Bowel Disease		x						x			x	x		x	x	x	x			x									
JID juvenile idiopathic arthritis AID; autoimmune inflammatory disease including Still's disease		x					x																			x			
Lymphoma														x															
Multiple sclerosis		x						x							x			x						x					
Myocardial infection		x																											
Osteoarthritis		x							x																				x
Pancreatitis							x		x							x										x			
Parasites infections																						x							
Psoriasis		x					x		x			x			x	x		x			x				x				
Psoriatic arthritis																													
Rheumatoid arthritis		x					x	x	x	x	x				x	x		x	x	x				x	x	x			
Sjogren syndrome																													
Systematic Lupus Ery.							x			x	x		x	x	x				x					x					
Systemic Sclerosis																													
T cell mediated autoimmune diseases			x																										
Ulcerative colitis										x																			
Vascular diseases																					x								
Viral infections		x																							x				

Figure 3 C

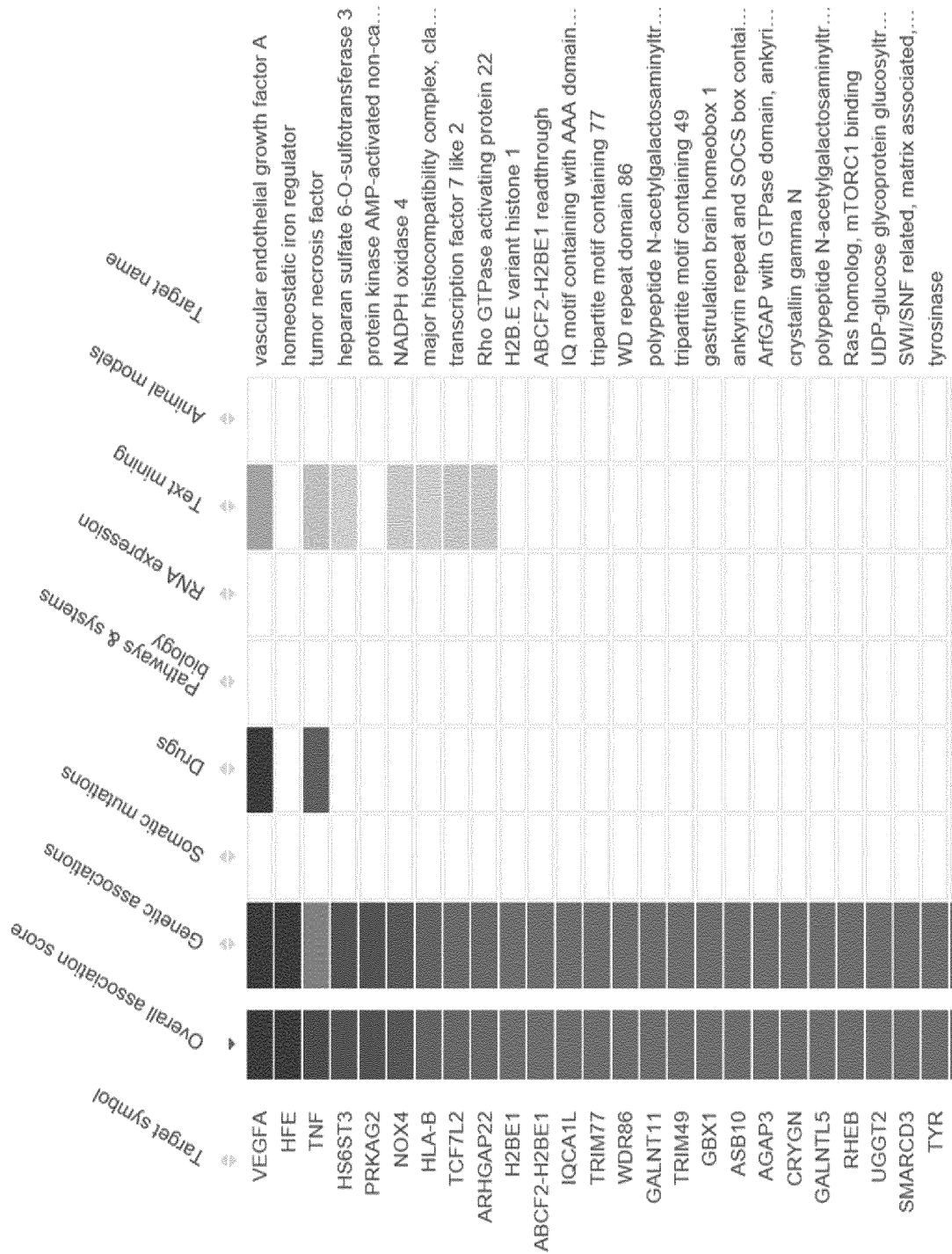


Figure 3 D

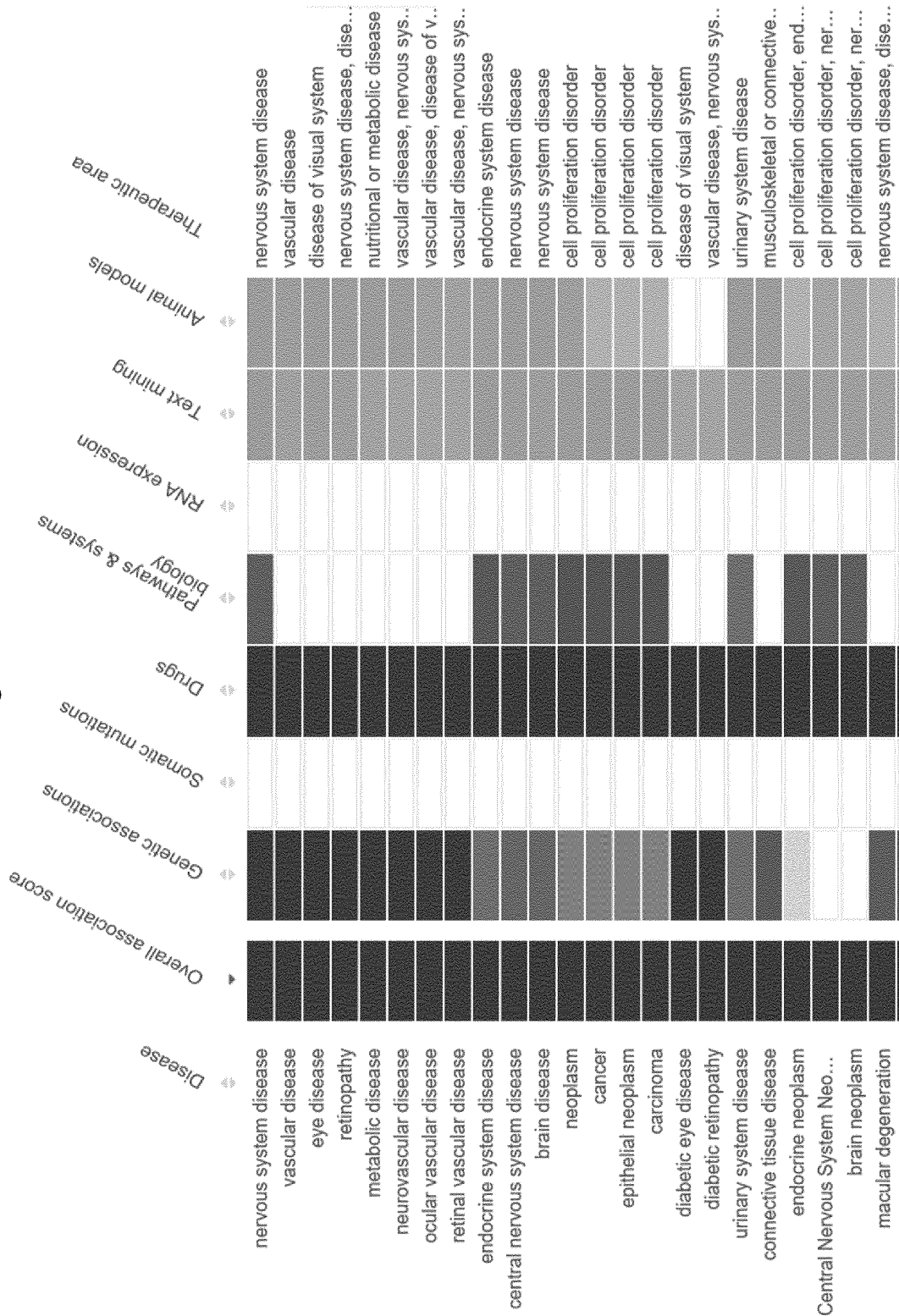


Figure 4A

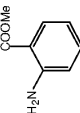
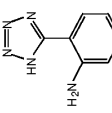
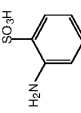
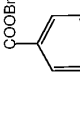
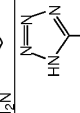
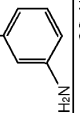
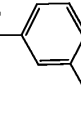
Products from KI-1 and KI-6		KI-1 and KI-6		R-NH ₂		Coupling conditions	Yield	Deprotection Conditions-A	Yield	Deprotection Conditions-B	Yield	Purification procedure	Final Product (amount, yield %)	Comments
ArCOOH														
KI-1 (12.95 g)						TCFH (1.2 eq) NMI (5 eq) MeCN	86%	LiOH (4 eq.) THF-H ₂ O Time = 36 h, T° = 23 °C	89%	H ₂ , Pd/C DCM/EtOH Time = 48 h, T° = 23 °C	84%	Trituration with MeCN	la-001a (13.4 g, 36%)	
KI-1 (53 g)						TCFH (1.2 eq) NMI (5 eq) MeCN	86%	LiOH (4 eq.) THF-H ₂ O Time = 26 h, T° = 23 °C	Quant.	H ₂ , Pd/C THF/EtOH Time = 18 h, T° = 23 °C	82%	Trituration with MeCN and Et ₂ O	la-001aTz (30 g, 40%)	
KI-1 (1 g)						1) SOCl ₂ (27 eq), DMF (drops) 2) DIPEA (2.2 eq), DMF	43%	LiOH (5 eq.) THF-H ₂ O Time = 18 h, T° = 23 °C	86%	H ₂ , Pd/C EtOAc Time = 18 h, T° = 23 °C	80%	Normal work up	la-001c (95 mg, 17%)	
KI-1 (203 mg)						1) SOCl ₂ (49 eq) DCM, 50 °C, 4h 2) DIPEA (1.1 eq) DCM	62%	H ₂ , Pd/C DCM/EtOH Time = 1.5h, T° = 23 °C	57%	NaOH aq (22 eq) 2h, then HCl 1N T° = 23 °C	60%	Filtration after addition of acid and trituration of solid in MeOH	la-002a (34 mg, 60%)	
KI-1 (1 g)						HATU (1.5 eq) DIPEA (5 eq) DMF	64%	LiOH (6 eq.) THF-H ₂ O Time = 18 h, T° = 23 °C	90%	H ₂ , Pd/C EtOAc/EtOH Time = 18 h, T° = 23 °C	91%	Trituration with MeCN and MTBE	la-002aTz (285 mg, 30%)	
KI-1 (190 mg) AX050 + LG043						1) SOCl ₂ (50 eq) DCM, 50 °C 2) NaOH aq. 0.5 M (1.1 eq), Na ₂ CO ₃ (0.6 eq), TBAB (0.1 eq), THF, rt, 5 d.	95% (Na ⁺ salt)	H ₂ , Pd/C H ₂ O/EtOH Time = 2.5h T° = 23 °C	88%	NaOH aq (18 eq) 2h15, then HCl 1N T° = 23 °C	50%	Filtration after addition of acid; lyophilisation of filtrate affords product	la-002c	
KI-1Bn (76 mg)						1) SOCl ₂ (50 eq) DCM, 50 °C, 3h 2) DIPEA (1.1 eq) DCM	82%	H ₂ , Pd(OH) ₂ DCM/EtOH Time = 4 h, T° = 23 °C	95%			Final product has low solubility in EtOH Purif. Chromatogr. AcOEt/AcOH 95:5	la-003a (11 mg, 95%)	Single deprotection step as both precursors are benzyl esters NMR ok

Figure 4B

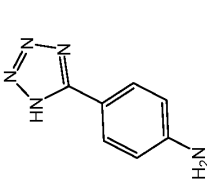
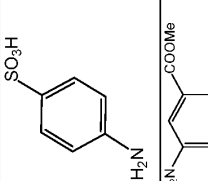
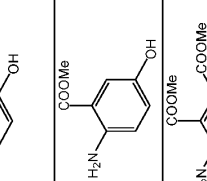
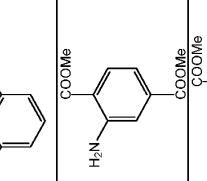
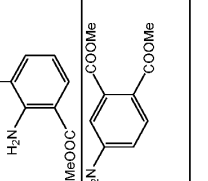
KI-1 (1 g)		HATU (1.5 eq) DIPEA (5 eq) DMF	96%	LiOH (6 eq.) THF-H ₂ O Time = 21 h, T° = 23 °C	37%	H ₂ , Pd/C EtOAc/EtOH Time = 18 h, T° = 23 °C	37%	Trituration with MeCN and MTBE	Ia-003aTz (0.022 g, 7%)
KI-1 (118 mg) (LG 038)		1) SOCl ₂ (58 eq) DCM, 50°C 2) NaOH aq. 0.5 M (1.1 eq), Na ₂ CO ₃ (0.5 eq), TBAB (0.12 eq), THF, rt.	69%	H ₂ , Pd/C H ₂ O/EtOH Time = 5.5h T° = 23 °C	88%	NaOH aq. 0.9 M, 2h, then HCl 37% (3.5 mL)	82%	Evaporation of solvents and elimination of salts by selective solubilisation in EtOH	Ia-003c (45 mg, 82%)
KI-1 (1 g)		1) SOCl ₂ (27 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM, DMF	24%	LiOH (6 eq.) THF/DMSO-H ₂ O Time = 5 days, T° = 75 °C	86%	H ₂ , Pd/C DMF/EtOH Time = 24 h, T° = 23 °C	76%	Trituration with MeCN and Et ₂ O	Ia-004a (0.145 g, 9%)
KI-1 (1 g)		1) SOCl ₂ (27 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM, DMF	33%	LiOH (6 eq.) THF-H ₂ O Time = 18 h, T° = 23 °C	94%	H ₂ , Pd/C EtOAc Time = 2 h, T° = 23 °C	84%	Normal work up	Ia-006a (0.155 g, 15%)
KI-1 (1 g)		1) SOCl ₂ (27 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM.	75%	LiOH (7 eq.) THF-H ₂ O Time = 18 h, T° = 23 °C	95%	H ₂ , Pd/C EtOAc/EtOH Time = 4 h, T° = 23 °C	66%	Normal work up	Ia-011a (0.46 g, 27%)
KI-1 (1 g)		1) SOCl ₂ (27 eq), DMF (drops) 2) DIPEA (1 eq), DCM	57%	LiOH (6 eq.) THF-H ₂ O Time = 20 h, T° = 23 °C	Quant	H ₂ , Pd/C DCM/EtOH Time = 1 h, T° = 23 °C	88%	Normal work up	Ia-012a (0.414 g, 28%)
KI-1 (1.125 g)		1) SOCl ₂ (27 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM	75%	LiOH (30 eq.) THF-H ₂ O Time = 36 h, T° = 23 °C	Quant	H ₂ , Pd/C DCM/EtOH Time = 18 h, T° = 23 °C	98%	Normal work up	Ia-013a (0.644 g, 42%)
KI-1 (2.11 g)		1) SOCl ₂ (27 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM	41%	LiOH (6 eq.) THF-H ₂ O Time = 18 h, T° = 23 °C	Quant	H ₂ , Pd/C DCM/EtOH Time = 18 h, T° = 23 °C	94%	Normal work up	Ia-014a (0.156 g, 22%)

Figure 4C

KI-1 (1.12 g)		1) SOCl ₂ (50 eq) DCM, 50°C, 4h 2) DIPEA (1.2 eq) DCM – 12h, rt col. chromatogr. PE/AcOEt		H ₂ , Pd/C DCM/EtOH Time = 18 h, T° = 23 °C	98%	NaOH aq (65 eq) 2h, rt, then HCl 37% at 0°C, Filtration, drying, wash with aq. HCl, EtOH	84%	Trituration in H ₂ O, drying	Ia-015a (380 mg, 84%)	Product partially soluble in EtOH, avoid EtOH for washings
KI-1 (0.5 g)		TCFH (1.2 eq) NMI (5 eq) MeCN	58%	LiOH (8 eq.) THF-H ₂ O Time = 42 h, T° = 23 °C	Quant	H ₂ , Pd/C THF/EtOH Time = 18 h, T° = 23 °C	41%	Trituration with MeCN	Ia-023a (0.054 g, 13%)	
KI-1Bn (84% + 16% diester)		1) SOCl ₂ (25 eq) DCM, 50°C, 4h 2) DIPEA (1.2 eq), DCM – 18h, rt col. chromatogr. PE/DCM 1:1 → DCM	86%	H ₂ , Pd/C DCM/EtOH Time = 2 h, T° = 23 °C	99%			Trituration with THF	Ia-032a (107 mg, 99%)	Single deprotection step as both precursors are benzyl esters
KI-1 (1 g)		1) SOCl ₂ (27 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM	73%	H ₂ , Pd/C EtOAc Time = 18 h, T° = 23 °C	97%	LiOH (8 eq.) THF-H ₂ O Time = 42 h, T° = 23 °C	83%	Normal work up	Ia-033a (0.147 g, 46%)	
KI-1 (1 g)		1) SOCl ₂ (27 eq), DMF (drops) 2) DIPEA (1.1 eq), DMF	39%	LiOH (6 eq.) THF-H ₂ O Time = 18 h, T° = 23 °C	85%	H ₂ , Pd/C DCM/EtOH Time = 20 h, T° = 23 °C	31%	Prep HPLC	Ia-034a (0.07 g, 6%)	
KI-1 (1 g)		HOBT (1.5 eq) EDC (1.5 eq) TEA (3.2 eq) DMF	57%	LiOH (6 eq.) THF-H ₂ O Time = 18 h, T° = 23 °C	96%	H ₂ , Pd/C DCM/EtOH Time = 2 h, T° = 23 °C	92%	Normal work up	Ia-035a (0.314 g, 22%)	Benzylation step before hydrolysis: BnBr (2 eq), K ₂ CO ₃ (2 eq), DMF. Time = 24 h T° = 23 °C, Y = 79%
KI-1 (1 g)		1) SOCl ₂ (26 eq) 2) DIPEA (2.2 eq) DCM	70%	--	--	CHCl ₃ (10 mL) AcOH (10 mL)	31%	Prep HPLC	Ia-035a-2 (0.081 g, 12%)	
KI-1 (1 g)		1) SOCl ₂ (28 eq) 2) DIPEA (2.2 eq) DCM	12%	LiOH (4 eq.) THF-H ₂ O Time = 18 h, T° = 23 °C	92%	H ₂ , Pd/C EtOH/EtOAc Time = 20 h, T° = 23 °C	34%	Prep HPLC	Ia-035a-3 (0.05 g, 1%)	Benzylation step before hydrolysis: BnBr (4 eq), K ₂ CO ₃ (4 eq), DMF. Time = 18 h T° = 23 °C, Y = 99%
KI-1 (0.5 g)		1) SOCl ₂ (25 eq) 2) DIPEA (2.2 eq) DMF	39%	LiOH (8 eq.) THF-H ₂ O Time = 18 h, T° = 23 °C	96%	H ₂ , Pd/C DCM/AcOH Time = 20 h, T° = 23 °C	24%	Prep HPLC	Ia-036a (0.036 g, 2%)	Benzylation step before hydrolysis: BnBr (5 eq), K ₂ CO ₃ (8 eq), DMF. Time = 18 h T° = 23 °C, Y = 51% Decomposed after prep purification (80% pure)

Figure 4D

KI-1 (1 g)		1) SOCl ₂ (27 eq) 2) DIPEA (2.2 eq) DCM	81%	—	—	LiOH (27 eq.) THF-H ₂ O DMSO Time = 120 h, T° = 25 °C	93%	H ₂ , Pd/C THF/EtOH Time = 18 h, T° = r.t.	44%	Prep HPLC	Ia-053a (106 mg, 20%)	
KI-1 (1 g)?		TCFH (1.2 eq) NMI (5 eq) Aniline (1.1 eq) MeCN	92%	LiOH (27 eq.) THF-H ₂ O DMSO Time = 120 h, T° = 25 °C	93%	H ₂ , Pd/C THF/EtOH Time = 18 h, T° = r.t.	80%	Trituration with MeCN and <i>n</i> - pentane			Ia-056a (322 mg, 39%)	
KI-1 (35.5 g, 2 eq)		HATU (3 eq) DIPEA (6 eq) DMF	87%	LiOH (6 eq.) THF-DMSO-H ₂ O Time = 48 h, T° = 23 °C	98%	H ₂ , Pd/C DCM/EtOH Time = 18 h, T° = 23 °C	98%	Trituration with MeCN			Ib-010a (19.3 g, 47%)	
KI-6 (500 mg)		TCFH (2.4 eq) NMI (6 eq) MeCN	74%	—	—	H ₂ , Pd/C DCM/EtOH Time = 18 h, T° = 23 °C	41%	Trituration with EtOH and Et ₂ O			Ic-001aTz2 (0.191 g, 17%)	
KI-6 (20.3 g)		1) SOCl ₂ (40 eq) 2) DIPEA (2.2 eq) DCM	85%	LiOH (6 eq.) DMSO-H ₂ O Time = 18 h, T° = 100 °C	71%	H ₂ , Pd/C DMF Time = 1 h, T° = 23 °C	quant	Trituration with MeCN			Ic-007a (25.7 g, 34%)	
KI-6 (1 g)		1) SOCl ₂ (23 eq) 2) DIPEA (2.2 eq) DCM/DMF	64%	NaOH (20 eq.) H ₂ O Time = 6 h, T° = 23 °C	88%	H ₂ , Pd/C DMF Time = 4 h, T° = 23 °C	24%	Trituration with acetone			Ic-009a (41 mg, 8%)	
KI-1 (70 g)		TCFH (1.2 eq) NMI (5 eq) MeCN	77%	LiOH (6 eq.) THF-H ₂ O Time = 96 h, T° = 23 °C	98%	H ₂ , Pd/C THF/EtOH Time = 36 h, T° = 23 °C	80%	Trituration with Et ₂ O			Ic-001aTz/004a (40.8 g, 34%)	The conditions for first coupling (R') and hydrolysis have been mentioned in Entry 2
KI-1 (0.5 g)		1) SOCl ₂ (28 eq) 2) DIPEA (2.2 eq) DMF	78%	LiOH (7 eq.) THF-H ₂ O Time = 72 h, T° = 23 °C	60%	H ₂ , Pd/C DCM/EtOH Time = 24 h, T° = 23 °C	15%	Prep HPLC			Id-030a (10 mg, 4%)	Cyclization step: MeSO ₃ H (3.3 eq), MeOH. Time = 17 h, T° = 70 °C

Figure 5A

Products from KI-2 and KI-7										
ArCOOH	R-NH ₂	Couplingconditions	Yield	Deprotection ConditionsA	Yield	Deprotection ConditionsB	Yield	Purification procedure	Final Product (amount, yield)	Comments
KI-2		1) SOCl ₂ (32 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM	72%	–	–	cHCl(10 mL) AcOH (10 mL) Time = 18 h, T° = 80 °C	64%	Trituration with DCM and MeOH	Ila-001a (142 mg, 46%)	
KI-2		TCFH (1.2 eq) NMI (5 eq) MeCN	71%	LiOH (6 eq.) THF-H ₂ O Time = 48 h, T° = r.t.	77%	H ₂ , Pd/C THF/EtOH Time = 18 h, T° = r.t.	53%	Trituration with MeCN, DCM and Et ₂ O	Ila-001aTz (125 mg, 29%)	
KI-2		1) SOCl ₂ (70 eq), DMF (drops) 2) DIPEA (2.2 eq), DMF	70%	LiOH (4 eq.) THF-H ₂ O Time = 72 h, T° = r.t.	15%	H ₂ , Pd/C EtOH Time = 18 h, T° = r.t.	54%	Trituration with MeCN	Ila-001c (20 mg, 4%)	
KI-2Aq 675 mg		1. SOCl ₂ , DCM, reflux, 5h, conc. 2. DCM, amine (1 eq), IprNEt (1.1 eq), 12h, rtExtract. column chromatogr	15%	EtOH, NaOH 1M, 0°C then 2h, rt. Acidification, conc.	55%	Not needed			Ila-002a	Compound made from the diacetate of 2,5-dihydroxyisø phthalic acid methyl ester
KI-2Aq 500 mg		1. SOCl ₂ , DCM, reflux, 5h, conc. 2. DCM, amine (1.1 eq), IprNEt (1.1 eq 12h rt; extraction, column chromat	16%	EtOH, NaOH 1M, 0°C then 2h, rt. Acidification, conc.	69%	Not needed			Ila-003a	Compound made from the diacetate of 2,5-dihydroxyisø phthalic acid methyl ester
KI-2Aq ₂		1) SOCl ₂ (30 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM	75%	–	–	cHCl (10 mL) AcOH (10 mL) Time = 18 h, T° = 80 °C	61%	Normal workup	Ila-004a (136 mg, 45%)	Compound from KI 2Aq ₂
KI-2		1) SOCl ₂ (26 eq), DMF (drops) 2) Pyridine (1.2 eq), DCM	72%	LiOH (6 eq.) THF-H ₂ O Time = 24 h, T° = r.t.	95%	H ₂ , Pd/C EtOH/EtOAc Time = 24 h, T° = r.t.	71%	Normal workup	Ila-006a (209 mg, 51%)	The starting aniline was protected with a tertButyldiphenyl silyl group

Figure 5B

KI-2Ac₂		1) SOCl ₂ (32 eq), DMF (drops) 2) DIPEA (2.2 eq), DCM	70%	–	–	NaOH aq (60 eq) 6.5h, then HCl 1N T° = r.t.	32%	Aqueous work-up then Prep HPLC	Ila-011a (130 mg, 22%)	Compound from KI- 2Ac ₂
KI-2Ac₂		1) SOCl ₂ (40 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM	33%	–	–	CHCl (10 mL) AcOH (10 mL) Time = 18 h, T° = 80 °C	29%	Prep HPLC	Ila-012a (58 mg, 9%)	Compound from KI- 2Ac ₂
KI-2Ac₂		1) SOCl ₂ (32 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM	34%	LiOH (12 eq.) THF-H ₂ O Time = 96 h, T° = r.t.	74%	H ₂ , Pd/C EtOH/EtOAc Time = 24 h, T° = r.t.	95%	Normal work-up	Ila-013a (58 mg, 23%)	The amide coupling was performed from the KI-2Ac ₂ , followed by quantitative methanolysis and subsequent re- protection with benzyl protecting groups.
KI-2		1) SOCl ₂ (61 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM	59%	LiOH (6 eq.) THF-H ₂ O Time = 48 h, T° = r.t.	93%	H ₂ , Pd/C EtOH/EtOAc Time = 18 h, T° = r.t.	77%	Trituration with MeCN	Ila-014a (170 mg, 42%)	
KI-2Ac₂ 675 mg		1. SOCl ₂ , (25 eq.), DCM, reflux, 5h, conc. 2. DCM, amine (1.0 eq), IprNEt ₂ (1.1 eq) 12h rt; extraction, column chromatogr	12%	EtOH, NaOH 1M, 0°C then 2h, rt. Acidification, conc.	77%	Not needed			Ila-015a	Compound made from the diacetate of 2,5-dihydroxyiso- phthalic acid methyl ester
KI-2Ac₂		1) SOCl ₂ (32 eq), DMF (drops) 2) DIPEA (1.1 eq), DCM	55%	–	–	CHCl (9 mL) AcOH (9 mL) Time = 24 h, T° = 100 °C	34%	Prep HPLC	Ila-033a (91 mg, 34%)	
KI-2		1) SOCl ₂ (25 eq), DMF (drops) 2) DIPEA (2.2 eq), DMF	35%	LiOH (8 eq.) THF-H ₂ O Time = 6 h, T° = r.t.	97%	H ₂ , Pd/C DCM/EtOAc Time = 24 h, T° = r.t.	26%	Trituration with MeCN	Ila-034a (37 mg, 8%)	

Figure 5C

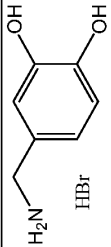
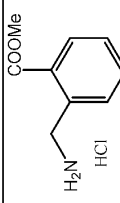
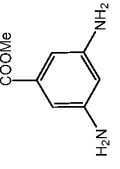
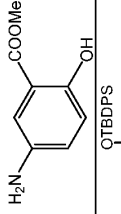
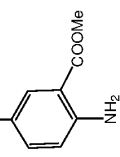
KI-2		1) SOCl ₂ (25 eq), DMF (drops) 2) DIPEA (2.2 eq), DMF 3) cHCl (5 mL)	97%	LiOH (4 eq.) THF-H ₂ O Time = 24 h, T° = r.t.	56%	H ₂ , Pd/C DCM/EtOH Time = 24 h, T° = r.t.	59%	Prep HPLC	Ila-035a (90 mg, 13%)	The amide coupling was performed from the KI-2Ac ₂ , followed by de-acetylation with cHCl in the work-up then subsequent protection with 4 benzyl protecting groups (43% yield) prior to LiOH hydrolysis.
KI-2Ac₂		1) SOCl ₂ (40 eq), DMF (drops) 2) DIPEA (2.2 eq), DMF	78%	–	–	cHCl (19 mL) AcOH (19 mL) Time = 17 h, T° = 80 °C	24%	Prep HPLC	Ila-035a (104 mg, 24%)	From KI-2Ac ₂
KI-2Ac₂		1) SOCl ₂ (40 eq), DMF (drops) 2) DIPEA (1.1 eq), Aniline (0.5 eq.), DCM	22%	LiOH (8 eq.) THF-H ₂ O Time = 24 h, T° = r.t.	34%	H ₂ , Pd/C THF/EtOH Time = 24 h, T° = r.t.	17%	Prep HPLC	Ilb-010a (8 mg, 5%)	The amide coupling was performed from the KI-2Ac ₂ , followed by methanolysis of the protecting acetyl (98% yield) and subsequent protection with 4 benzyl protecting groups (40% yield) prior to LiOH hydrolysis.
KI-7		TCFH (2.4 eq) NMI (10 eq) Aniline (2.4 eq) MeCN	Quant.	LiOH (6 eq.) THF-H ₂ O Time = 24 h, T° = 80 °C	70%	H ₂ , Pd/C THF Time = 24 h, T° = r.t.	88%	Trituration with MeCN and Et ₂ O	Ilc-007a (5.7 g, 61%)	
KI-7		1) SOCl ₂ (50 eq), DMF (drops) 2) Pyridine (2.2 eq), Aniline (2.2 eq.), DCM	76%	LiOH (6 eq.) THF-H ₂ O Time = 24 h, T° = r.t.	95%	H ₂ , Pd/C EtOAc/EtOH Time = 24 h, T° = r.t.	3%	Purified twice by Prep	Ilc-009a (11 mg, %)	The starting aniline was protected with a tert-Butyldiphenylsilyl (TBDPS) group.

Figure 6

Products from KI-8 and KI-9									
ArCOOH	R-NH ₂	Coupling conditions	Yield	Deprotection Conditions-A	Yield	Deprotection Conditions-B	Yield	Purification procedure	Final Product (amount, yield)
KI-8		1) (COCl) ₂ (6 eq), DMF (drops), DCM 2) DIPEA (1.1 eq), Aniline (1.1 eq), DCM	75%	LiOH (6 eq.) THF-H ₂ O Time = 24 h, T° = r.t.	80%	H ₂ , Pd/C DCM/EtOAc Time = 24 h, T° = r.t.	51%	Trituration with MeCN	IIIa-001a
KI-8		TCFH (1.2 eq) NMI (5 eq) Aniline (1.2 eq) MeCN	75%	LiOH (6 eq.) THF-H ₂ O Time = 18 h, T° = 70 °C	93%	H ₂ , Pd/C DCM/EtOH Time = 18 h, T° = r.t.	43%	Trituration with MeCN	IIIa-001aTz (27 mg, 29%)
KI-8		TCFH (1.2 eq) NMI (5 eq) Aniline (1.2 eq) MeCN	29%	LiOH (16 eq.) THF-H ₂ O Time = 48 h, T° = r.t.	Quant.	H ₂ , Pd/C DCM/EtOH Time = 18 h, T° = r.t.	Quant.	Trituration with Et ₂ O	IIIa-013a (50 mg, 29%)
KI-8		TCFH (1.2 eq) NMI (5 eq) Aniline (1.2 eq) MeCN	71%	LiOH (8 eq.) THF-H ₂ O Time = 18 h, T° = r.t.	90%	H ₂ , Pd/C DCM/EtOH Time = 18 h, T° = r.t.	26%	Prep HPLC	IIIa-015a (26 mg, 16%)
KI-8		TCFH (1.2 eq) NMI (3 eq) Aniline (0.5 eq) MeCN	75%	LiOH (6 eq.) THF-H ₂ O, DMSO Time = 72 h, T° = 55 °C	85%	H ₂ , Pd/C THF/EtOH Time = 18 h, T° = r.t.	57%	The residue was dissolved into water, filtered and the water was removed in a freeze-drier	IIIb-010a (755 mg, 57%)

Figure 7

Products from KI-8 and KI-9		SUBSTRATE		Deprotection ConditionsA	Yield	Deprotection ConditionsB	Yield	Purification procedure	Final Product (amount, yield)	Comments
Deprotection Procedures										
				LiOH (6 eq.) THF-H ₂ O Time = 72 h, T° = 70 °C	Quant.	H ₂ , Pd/C DCM/EtOH Time = 18 h, T° = r.t.	50%	Trituration with MeCN	IIIc-056a (44 mg, 50%)	The product may possibly be the HCl salt (HCl/Dioxane test didn't revealed protons shifts)
				LiOH (15 eq.) THF-H ₂ O Time = 96 h, T° = 40 °C	Quant.	H ₂ , Pd/C DCM/EtOH Time = 48 h, T° = r.t.	67%	Trituration with Et ₂ O	IIIc-057a	
				Same conditions		Same conditions			IIIc-058a	
				Same conditions		Same conditions			IIIc-059a	
				LiOH (6 eq.) THF-H ₂ O Time = 24 h, T° = 70 °C	Quant.	H ₂ , Pd/C DCM Time = 18 h, T° = r.t.	55%	Prep HPLC	IIIc-060a (39 mg, 55%)	
				LiOH (18 eq.) THF-H ₂ O Time = 96 h, T° = 80 °C	87%	H ₂ , Pd/C THF/EtOH Time = 18 h, T° = r.t.	73%	Trituration with water/acetone	IIIc-061a (9.1 g,	Large scale synthesis

Figure 8

ArCOOH	R-NH ₂	Coupling conditions	Yield	Deprotection Conditions-A	Yield	Deprotection Conditions-B	Yield	Purification procedure	Final Product (amount, yield)
		TCFH (4.2 eq) NMI (9 eq) MeCN	58%	LiOH (8 eq.) DMSO-H ₂ O Time = 18 h, T° = 100 °C	42%	H ₂ , Pd/C THF/EtOH Time = 18 h, T° = 23 °C	88%	Trituration with MeCN and Et ₂ O	V-001a (110 mg, 21%)
		TCFH (2.2 eq) NMI (6 eq) MeCN	76%	LiOH (10 eq.) THF-H ₂ O Time = 48 h, T° = r.t.	77%	H ₂ , Pd/C THF/EtOH Time = 48 h, T° = r.t.	90%	Trituration with Et ₂ O	V-002a (513 mg, 52%)
Deprotection Procedures									
				LiOH (20 eq.) THF-H ₂ O Time = 168 h, T° = from r.t to 80 °C	76%	H ₂ , Pd/C THF/EtOH Time = 72 h, T° = r.t.	67%	Trituration with Et ₂ O	V-003a (48 mg, 50%)

Figure 9

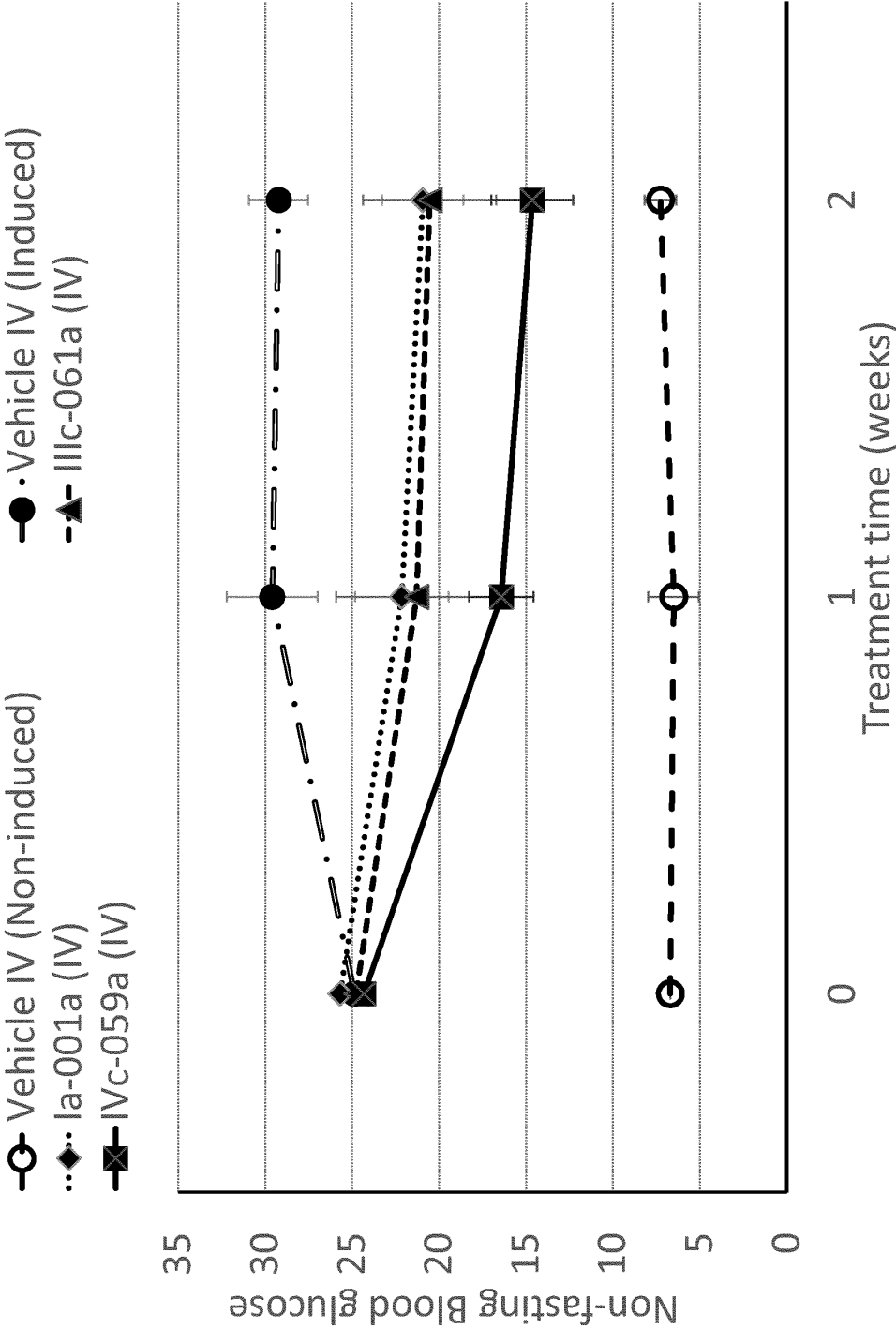


Figure 10

Day 7 of treatment

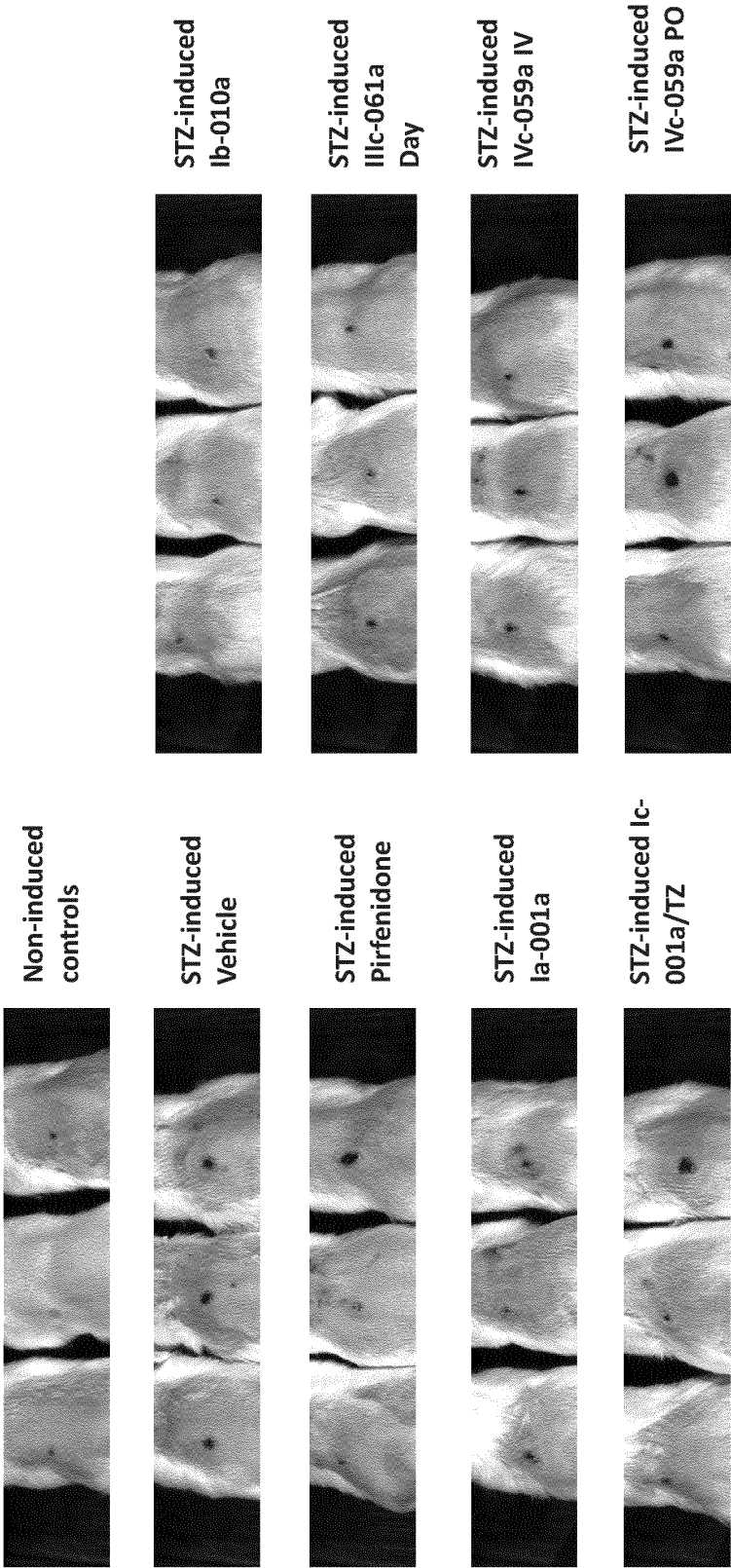
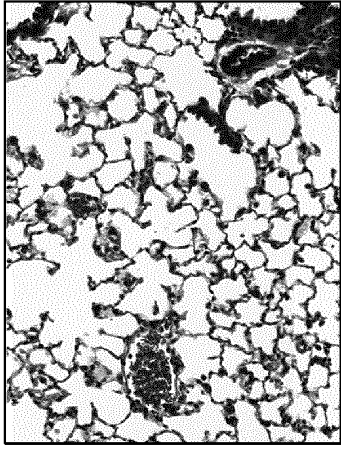
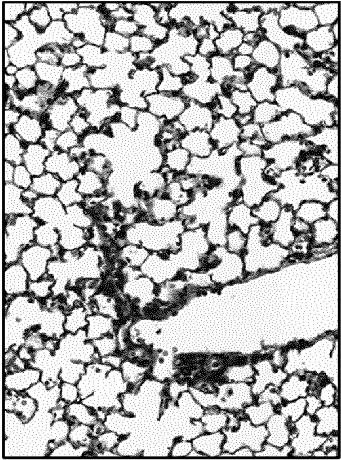
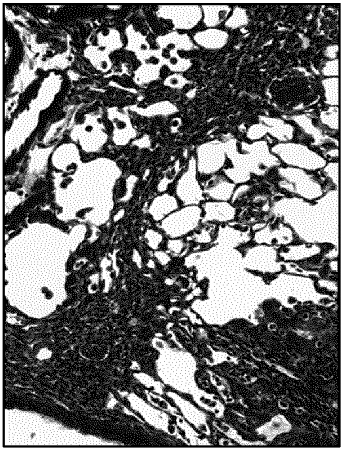
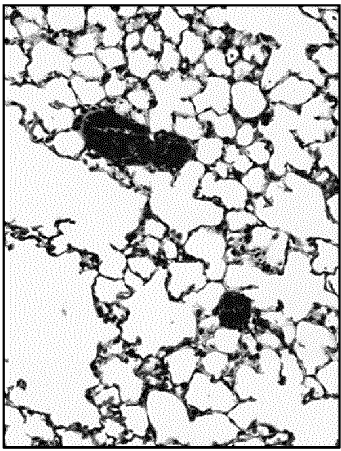


Figure 11

Day 21 of treatment

A



B

