Joint Chemical Probe

USP21 Inhibitor BAY-805

September 21, 2022

Presenter:
Fabian Göricke
on behalf of the team

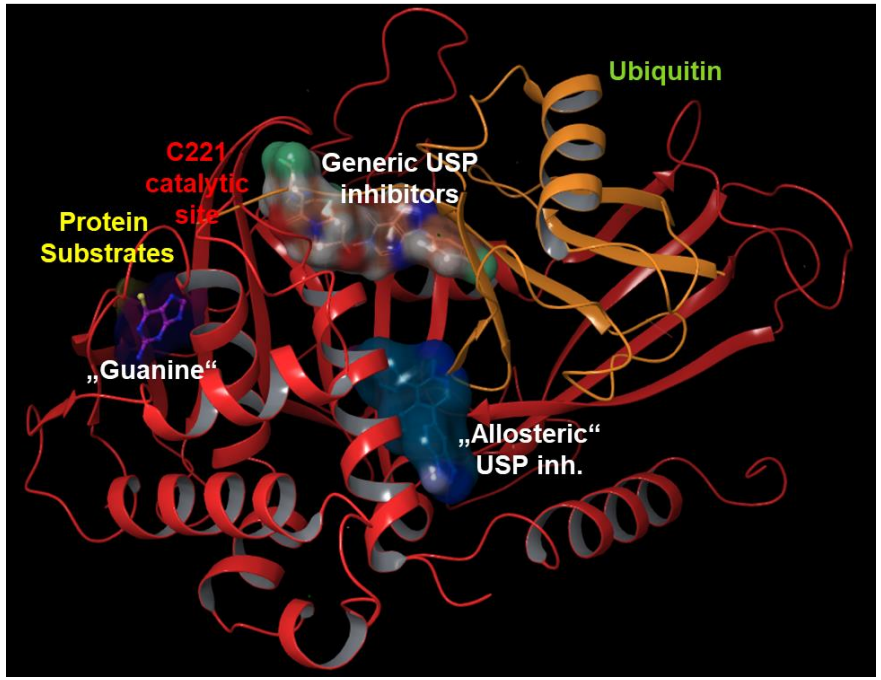
USP21 Probe BAY-805

Scientific Rationale

USP21 = ubiquitin-specific-processing protease 21

- 62 kDa, Gene ID: 27005
- ubiquitously expressed on mRNA level
- USP21 **cleaves K48-ubiquitin (degradation**), and **mono-Ubiquitin,**

  K11-, K63-, K29 and linear diUbiquitin
- **Cysteine 221 is essential for catalytic activity** and function
- **Several SMOL binding modes expected** (displacing either ubiquitin or protein substrates)



Model based on X-rays of USP21 + Ubi, USP7 and USP2: Ernst et al., Science 2013, 339, 590; Turnbull et al., Nature 2017, 550, 481; Kategaya et al., Nature 2017, 550, 534; Chuang et al. Sci. Rep. 2018, 8, 3102.

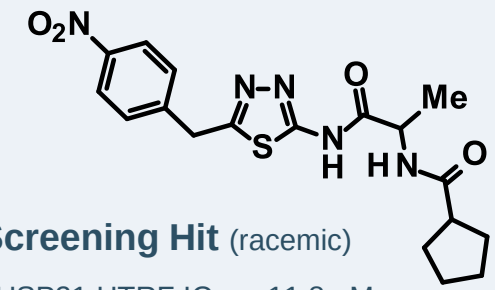
Mode of action:

- **Several substrates have been described, e.g. in the field of immune response and cancer cell growth**
- **USP21 deubiquitinates and inactivates STING** in an enzymatic activity-dependent matter
- USP21 inhibits tumor necrosis factor alpha-induced **NFκB activation** via binding to and deubiquitinating receptor-interacting protein 1 (**RIP1**)

Ye et al., EMBO Rep. 2011; Chen et al., J. Exp. Med. 2017; Xu et al., JBC 2010

USP21 Probe BAY-805

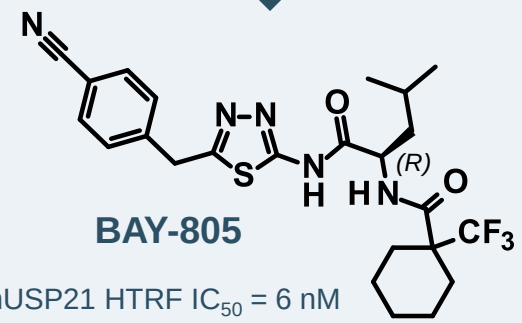
Discovery and Biochemical Activity



Screening Hit (racemic)

hUSP21 HTRF IC_{50} = 11.8 µM

hUSP21 Ub-Rhod IC_{50} > 22.5 µM

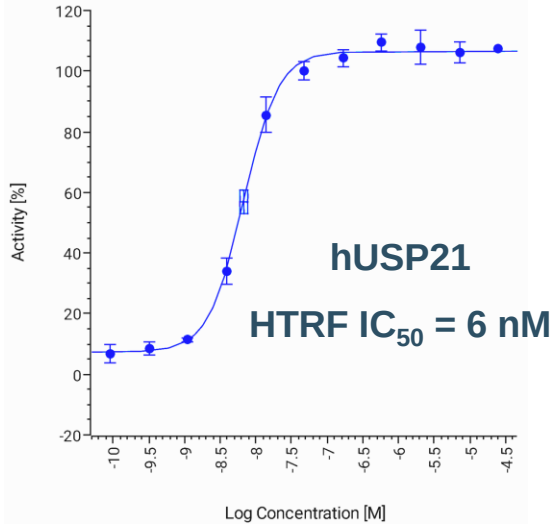


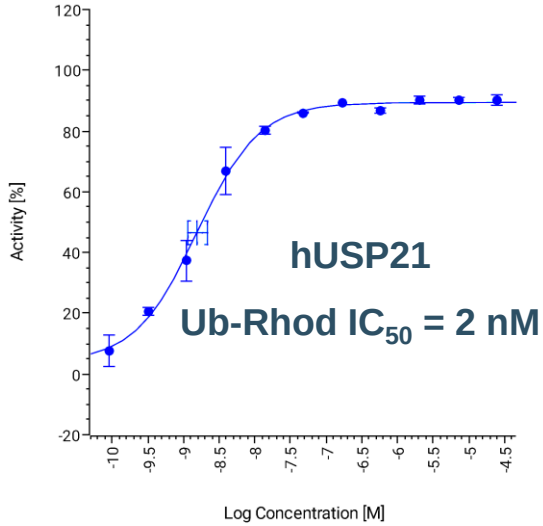
BAY-805

hUSP21 HTRF IC_{50} = 6 nM

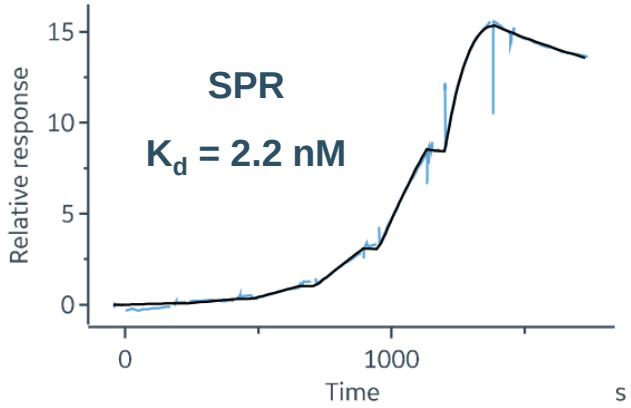
hUSP21 Ub-Rhod IC_{50} = 2 nM

Biochemical activity:





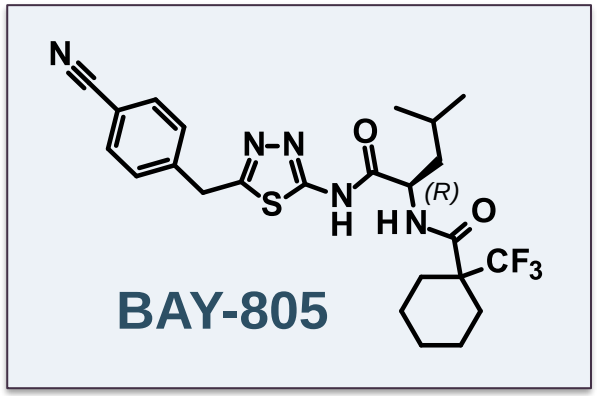
Biophysical proof of target engagement:

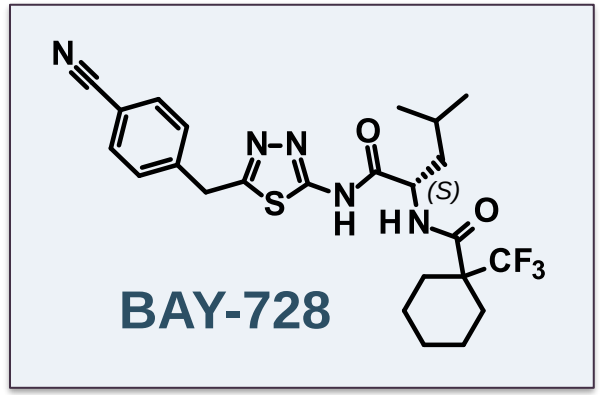


BAY-805 is highly potent in both biochemical assays and shows high binding affinity in SPR

USP21 Probe BAY-805

Negative Control BAY-728

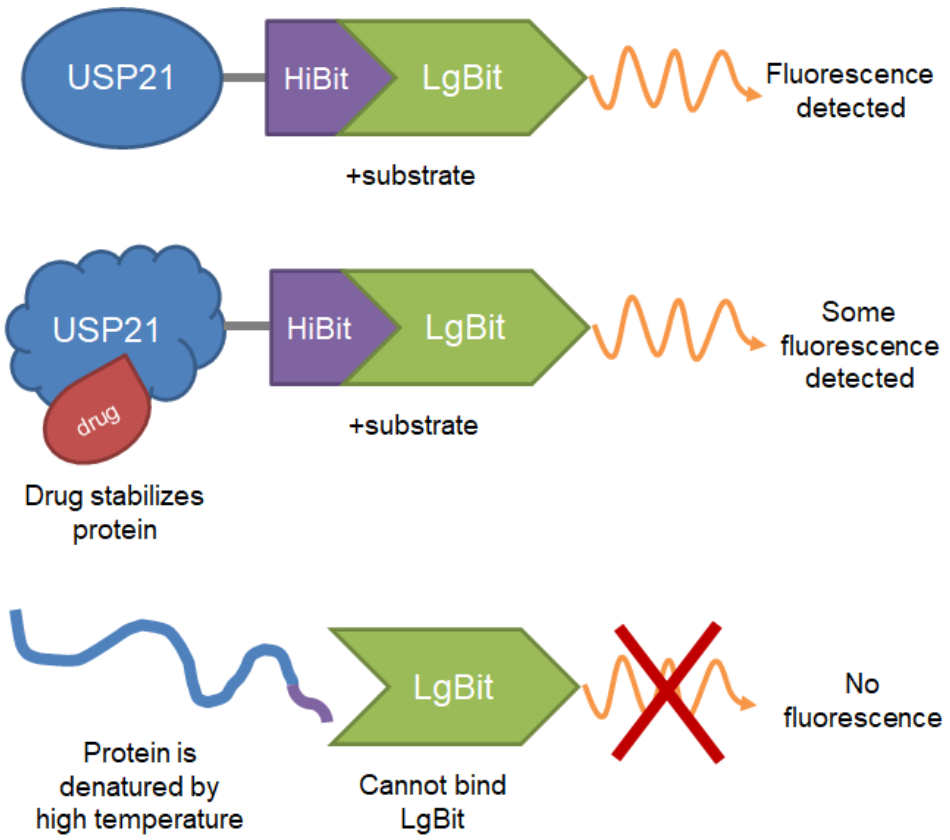


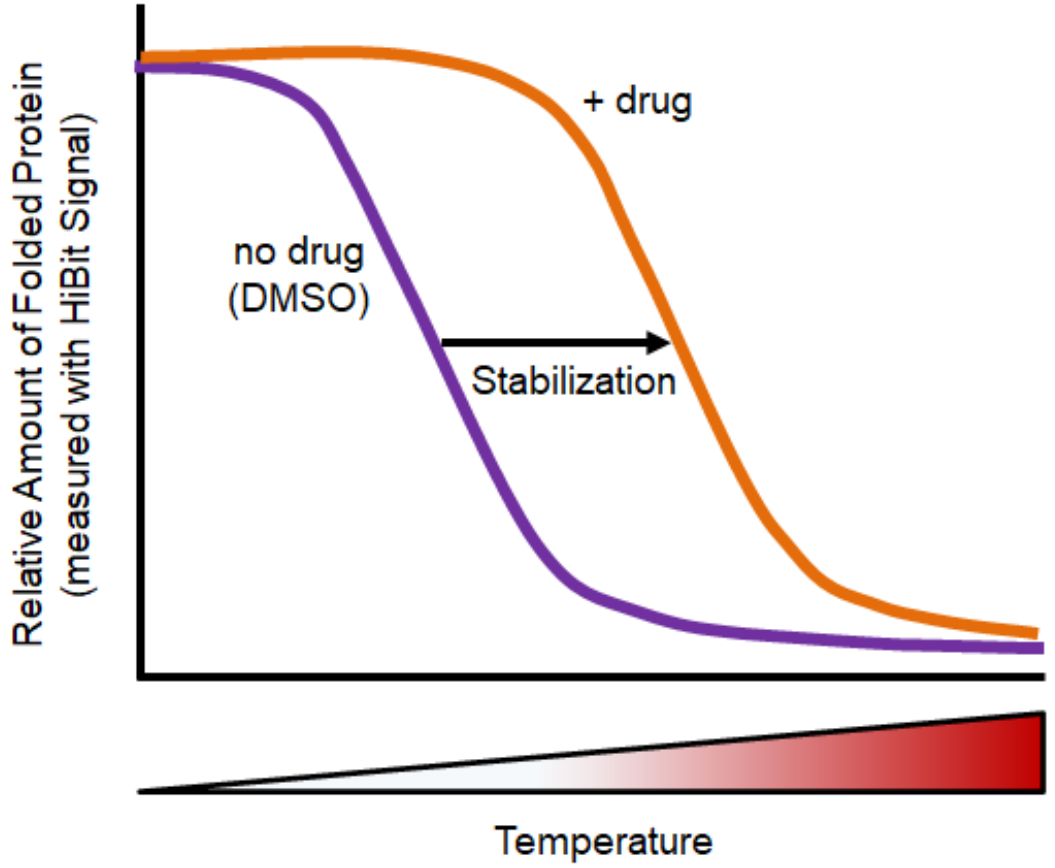


Probe Name	BAY-805 (Probe)	BAY-728 (Negative Control)
hUSP21 (HTRF) IC_{50} [nM]	6	12600
hUSP21 (Ub-Rhodamine) IC_{50} [nM]	2	16200
hUSP2 (Ub-Rhodamine) IC_{50} [nM]	>25000	>25000
SPR K_d [nM]	2.2	8686

USP21 Probe BAY-805

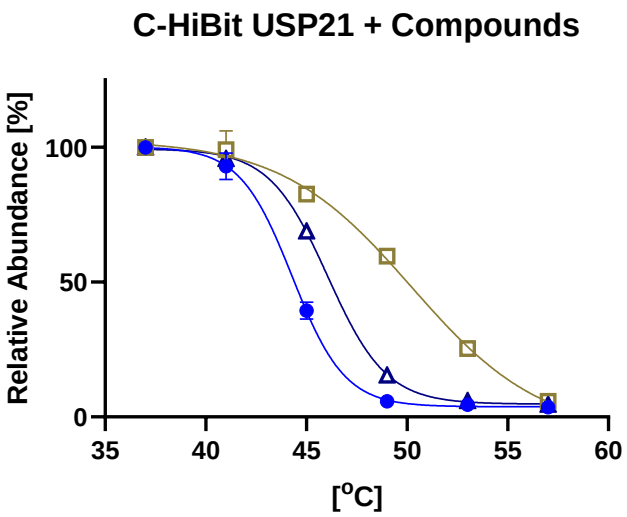
Cellular Target Engagement - USP21 HiBiT CETSA Design



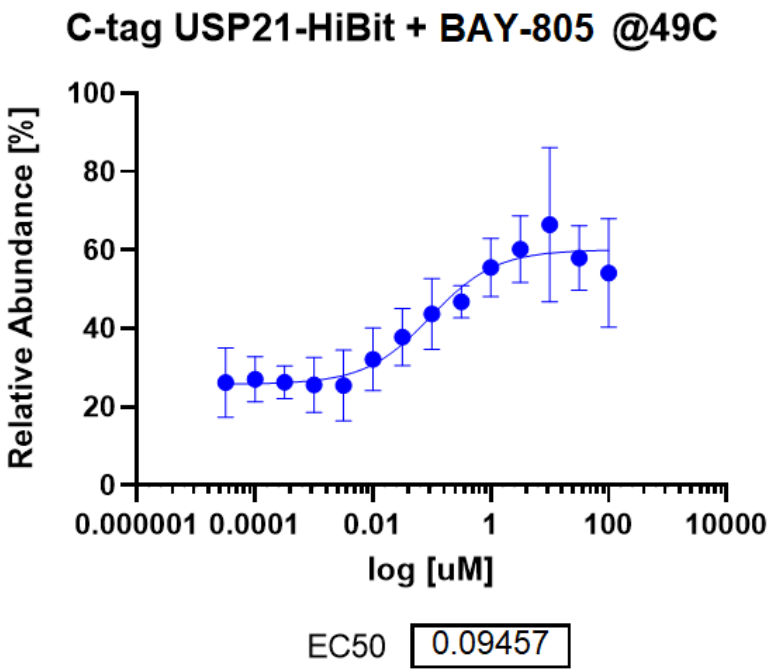


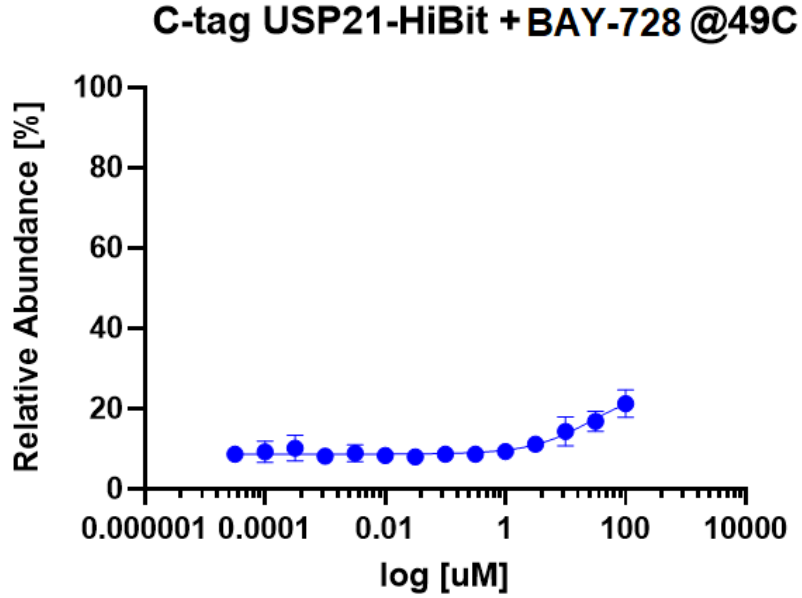
USP21 Probe BAY-805

Cellular Target Engagement - USP21 HiBiT CETSA



	BAY-805	BAY-728
T_m	50.22	46.06



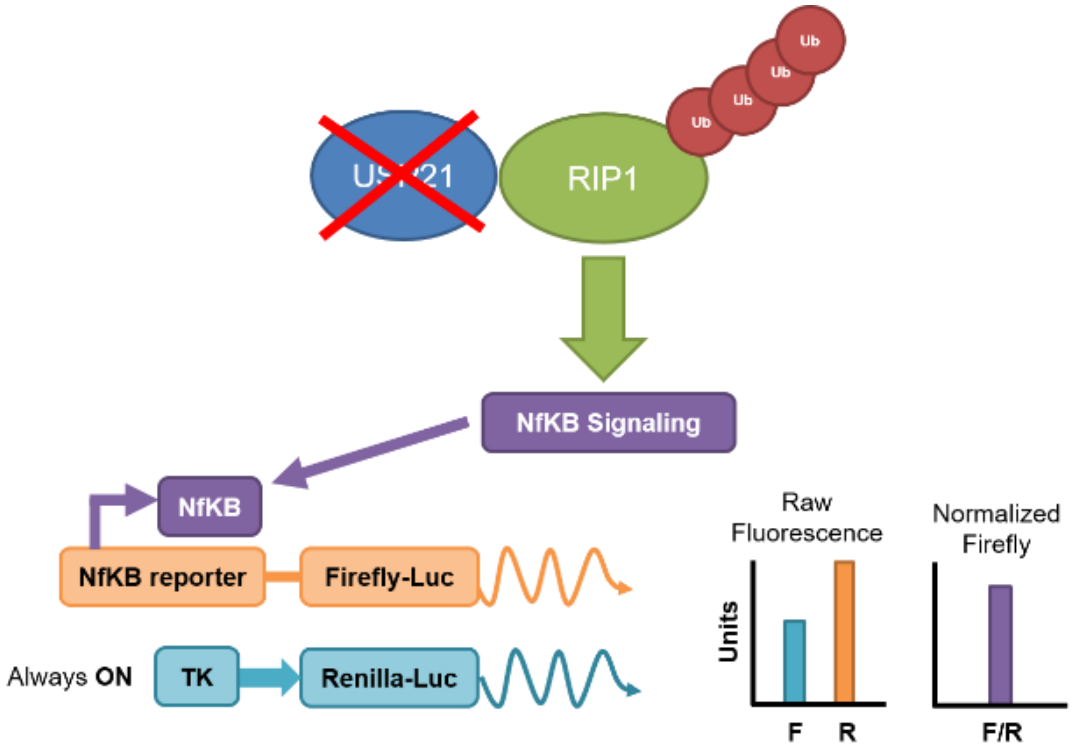


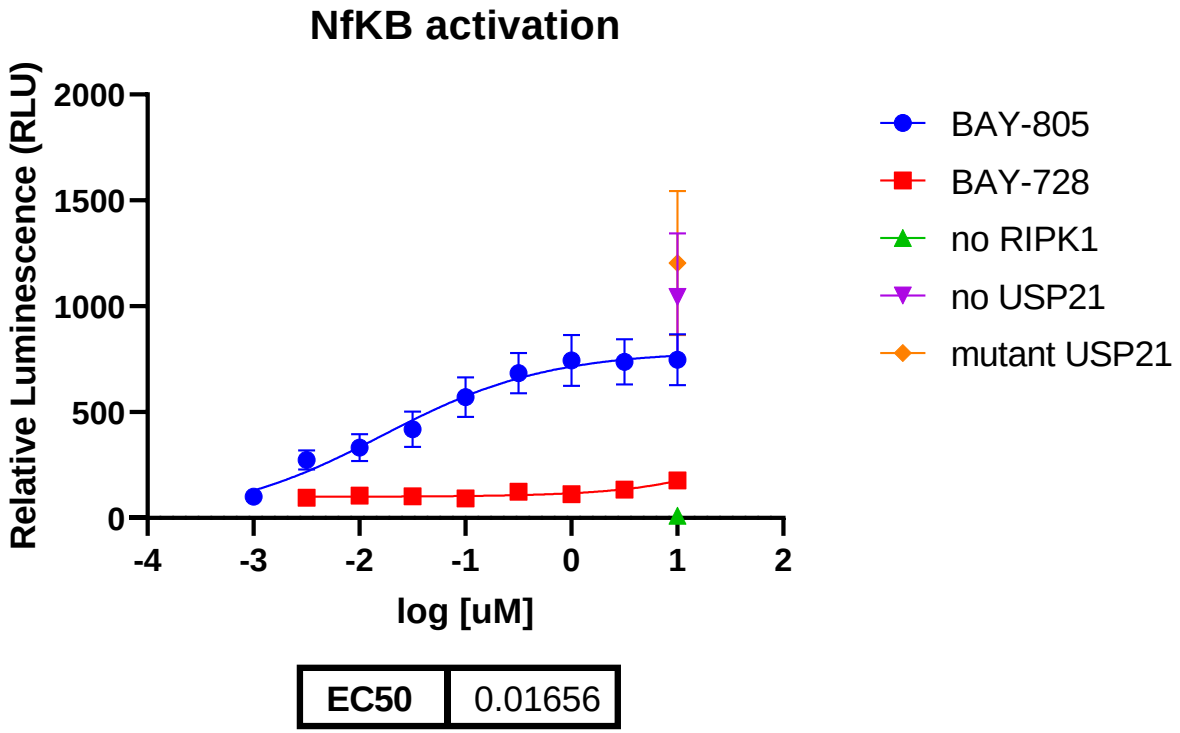
Experimental Setup: HEK293T cells transfected with HiBit constructs, the next day HEK293T cells were treated with compound for 1h @37C and heated for 3 min at indicated temperatures. LgBit solution followed by substrate were then added and luciferase signal measured. Technical quadruplicates.

Cellular USP21 target engagement for BAY-805 was shown by USP21 HiBiT CETSA (EC_{50} ~ 95 nM)

USP21 Probe BAY-805

Cellular Activity in NFκB Reporter Assay



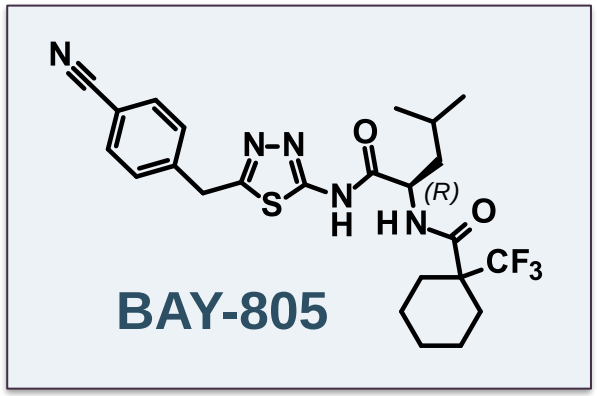


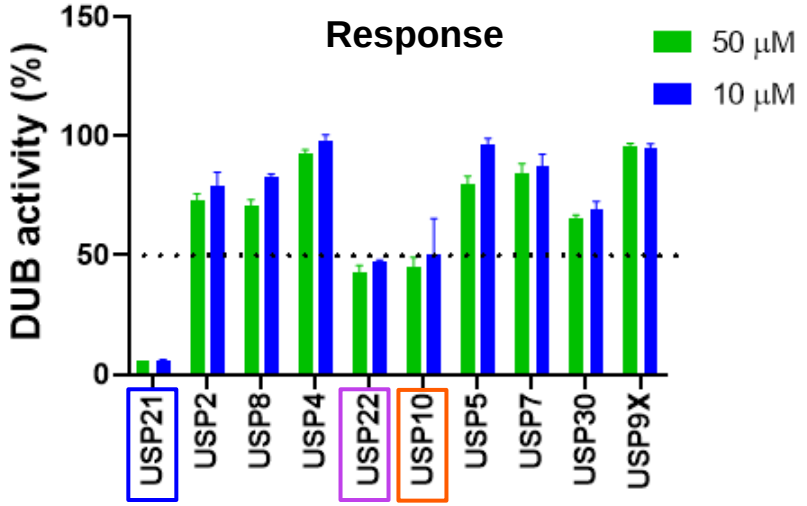
EC50	0.01656

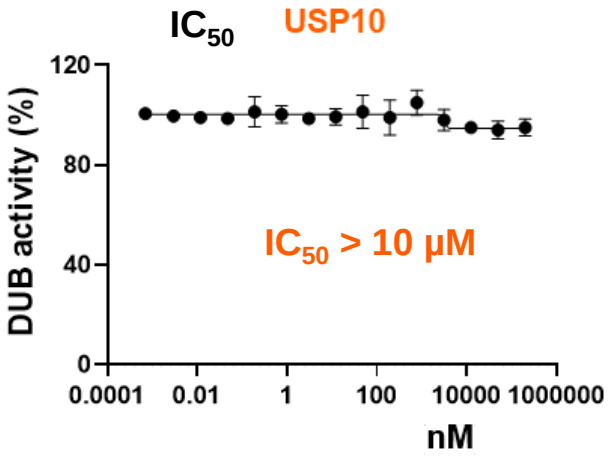
BAY-805 induces NFκB activation in a cell-based reporter assay (EC_{50} ~ 17 nM)

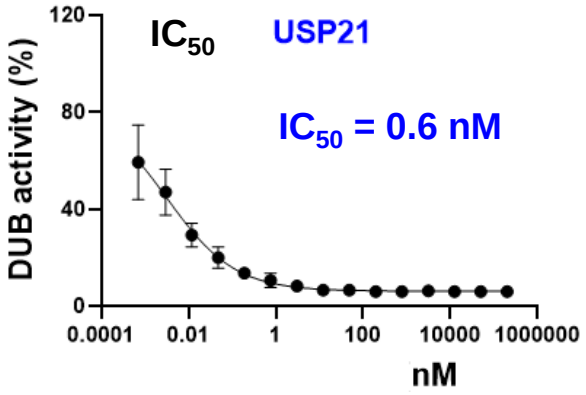
USP21 Probe BAY-805

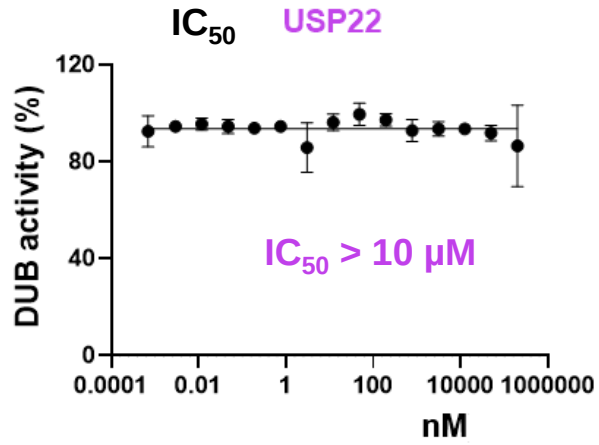
Selectivity Profile – USP Selectivity at SGC











BAY-805 displays very high selectivity against 9 USPs in the SGC DUB panel

USP21 Probe BAY-805

Selectivity Profile – DUB*profiler*™ (Ubiquigent)

DUB Target	Conc.	Activity (%)
USP1/UAF1	10 µM	111
USP2	10 µM	102
USP4	10 µM	103
USP5	10 µM	110
USP5 (+Ubiquitin @ Kd)	10 µM	110
USP5 (+Ubiquitin @ Bmax)	10 µM	101
USP6	10 µM	102
USP7	10 µM	100
USP8	10 µM	96
USP9x	10 µM	108
USP11	10 µM	115
USP12/UAF1/WDR20	10 µM	91
USP14 (Proteasome-VS @ Kd)	10 µM	98
USP15	10 µM	113
USP16	10 µM	98
USP17	10 µM	97
USP19	10 µM	101

DUB Target	Conc.	Activity (%)
USP20	10 µM	87
USP21	10 µM	9
USP25	10 µM	116
USP27x	10 µM	108
USP28	10 µM	102
USP30	10 µM	97
USP35	10 µM	105
USP36	10 µM	101
USP45	10 µM	96
USP46/UAF1/WDR20	10 µM	97
CYLD	10 µM	102
UCHL1	10 µM	114
UCHL3	10 µM	101
UCHL5	10 µM	98
BAP1	10 µM	106
OTU1	10 µM	104
OTUB2	10 µM	95

DUB Target	Conc.	Activity (%)
OTUD1	10 µM	99
OTUD3	10 µM	101
OTUD5 (p117S)	10 µM	90
OTUD6A	10 µM	99
OTUD6B	10 µM	92
Cezanne	10 µM	99
VCPIP	10 µM	114
AMSH-LP	10 µM	101
AMSH-LP (+Zinc)	10 µM	93
Ataxin3	10 µM	106
Ataxin3L	10 µM	111
JOSD1	10 µM	101
JOSD2	10 µM	113

USP21 Probe BAY-805

Selectivity Profile – Eurofins Safety Screen

Assay Name	Conc.	% Inh.
Aldose Reductase	10 µM	0
ATPase, Na^+/K^+, Heart, Pig	10 µM	-1
Carbonic Anhydrase II	10 µM	3
Cholinesterase, Acetyl, ACES	10 µM	72
Cyclooxygenase COX-1	10 µM	-2
Cyclooxygenase COX-2	10 µM	2
HMG-CoA Reductase	10 µM	16
Leukotriene LTC_4 Synthase	10 µM	35
Lipoxygenase 15-LO	10 µM	-3
Monoamine Oxidase MAO-A	10 µM	3
Monoamine Oxidase MAO-B	10 µM	7
Nitric Oxide Synthase, Neuronal (nNOS)	10 µM	-15
Nitric Oxide Synthetase, Inducible (iNOS)	10 µM	-1
Peptidase, Angiotensin Converting Enzyme	10 µM	-33
Phosphodiesterase PDE3A	10 µM	3
Phosphodiesterase PDE4D2	10 µM	1
Phosphodiesterase PDE5A	10 µM	13
Thromboxane Synthase	10 µM	-1
Adenosine A_1	10 µM	4
Adenosine A_{2A}	10 µM	2
Adenosine A_3	10 µM	12
Adrenergic α_{1A}	10 µM	1
Adrenergic α_{2A}	10 µM	13
Adrenergic α_{2B}	10 µM	4
Adrenergic α_{2C}	10 µM	6
Adrenergic β_1	10 µM	3
Adrenergic β_2	10 µM	3
Adrenergic β_3	10 µM	10
Androgen (Testosterone)	10 µM	4
Angiotensin AT_1	10 µM	14
Angiotensin AT_2	10 µM	-3
Bradykinin B_1	10 µM	6
Bradykinin B_2	10 µM	-7

Assay Name	Conc.	% Inh.
Cannabinoid CB_1	10 µM	8
Cannabinoid CB_2	10 µM	1
Dopamine D_1	10 µM	-3
Dopamine D_{2L}	10 µM	8
Dopamine D_{2S}	10 µM	24
Dopamine D_3	10 µM	9
Endothelin ET_A	10 µM	-7
Endothelin ET_B	10 µM	4
Estrogen ERα	10 µM	-6
$GABA_A$, Chloride Channel, TBOB	10 µM	9
$GABA_A$, Flunitrazepam, Central	10 µM	-7
$GABA_B$, Non-Selective	10 µM	-2
Glucocorticoid	10 µM	14
Glutamate, AMPA	10 µM	2
Glutamate, Kainate	10 µM	-7
Glutamate, NMDA, Agonism	10 µM	7
Glutamate, NMDA, Glycine	10 µM	6
Growth Hormone Secretagogue (GHS, Ghrelin)	10 µM	20
Histamine H_1	10 µM	-1
Histamine H_2	10 µM	-16
Histamine H_3	10 µM	-2
Insulin	10 µM	10
Motilin	10 µM	10
Muscarinic M_1	10 µM	18
Muscarinic M_2	10 µM	2
Muscarinic M_3	10 µM	7
Muscarinic M_4	10 µM	-4
Nicotinic Acetylcholine α3β4	10 µM	-3
Opiate δ_1 (OP1, DOP)	10 µM	-5
Opiate κ (OP2, KOP)	10 µM	6
Opiate µ (OP3, MOP)	10 µM	-1
Progesterone PR-B	10 µM	5
Purinergic P2X	10 µM	-4
Purinergic P2Y, Non-Selective	10 µM	5

Assay Name	Conc.	% Inh.
Serotonin (5-Hydroxytryptamine) 5-HT_{1A}	10 µM	2
Serotonin (5-Hydroxytryptamine) 5-HT_{2A}	10 µM	4
Serotonin (5-Hydroxytryptamine) 5-HT_{2B}	10 µM	3
Serotonin (5-Hydroxytryptamine) 5-HT_{2C}	10 µM	-5
Transporter, Adenosine	10 µM	62
Transporter, Dopamine (DAT)	10 µM	9
Transporter, GABA	10 µM	14
Transporter, Norepinephrine (NET)	10 µM	10
Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	10 µM	13
Vasopressin V_{1A}	10 µM	2

Inhibition >50% at 10 µM compound concentration for the following targets:

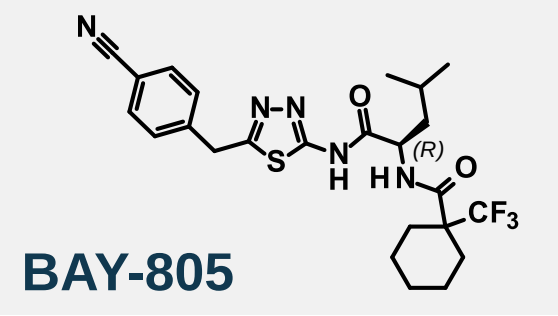
Assay Name	Species	Conc.	% Inh.
Cholinesterase, Acetyl, ACES	hum	10 µM	72
Transporter, Adenosine	hum	10 µM	62

Cholinesterase, Acetyl, ACES: IC_{50} = 7.61 µM

BAY-805 shows good off-target selectivity

USP21 Probe BAY-805

Technical *in vitro* Profile



BAY-805

Potency	
hUSP21 (HTRF) IC_{50} [nM]	6
hUSP21 (Ub-Rhod) IC_{50} [nM]	2
SPR K_d [nM]	2.2
USP21 HiBiT CETSA IC_{50} @ 49°C [nM]	95
Cell-based NFκB activation EC_{50} [nM]	17

Properties & Physchem	
LogD @ pH 7.5 / LLE	3.6 / 5.1
MW / MW corr / TPSA [Å²]	508 / 466 / 108
Solubility @ pH 6.5 [µmol/L]	3.37
Stability (pH 1/7/10, 24h, 37°C) [%]	100 / 100 / 100
Stability (r /h plasma, 4h, 37°C) [%]	99 / 99

***in vitro* DMPK Properties**

Caco2 Permeability	P_{app}(A-B) [nm/s]		P_{app}(B-A) [nm/s]		efflux ratio	
	42		27		0.6	
metabolic stability			CL [L/h/kg]		F_{max} [%]	
	liver mics (m / r / d / h)		n.d.		n.d.	
	rat hepatocytes		3.8		10	
	human hepatocytes		n.d.		n.d.	
CYP inhibition IC_{50} [µM]	1A2	2C8	2C9	2D6	3A4	3A4 preinc.
	>5	4.7	>5	4.6	0.4	0.41
PXR	n.d.					

Selectivity

USP panel at SGC*	>50% remaining activity @ 10 µM (9 USPs)
Cysteine protease panel	IC_{50} >20 µM (6 proteases)
In-house kinase panel	IC_{50} >20 µM (21 kinases)

Antiproliferative Activity (human tumor cell lines)

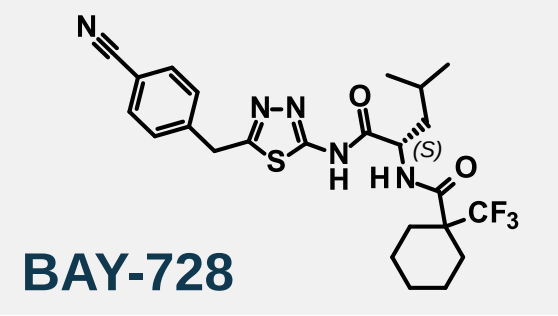
Jurkat, Molm13, A549	all IC_{50} > 30 µM
MDA-MB-231, U2OS	

- BAY-805 has high *in vitro* potency and good selectivity
- BAY-805 induces NFκB activation in a cell-based reporter assay

*BAY-805 was additionally profiled in the DUB*profiler*™ (Ubiquigent) against 44 DUB targets showing very good selectivity for USP21.

USP21 Probe BAY-805

In vitro profile of Negative Control BAY-728



BAY-728

Potency	
hUSP21 (HTRF) IC_{50} [nM]	12600
hUSP21 (Ub-Rhod) IC_{50} [nM]	16200
SPR K_d [nM]	8686
USP21 HiBiT CETSA IC_{50} @ 49°C [nM]	-
Cell-based NfKB activation IC_{50} [nM]	>10000

Properties & Physchem	
LogD @ pH 7.5	3.64
MW / MW corr / TPSA [Å²]	508 / 466 / 108
Solubility @ pH 6.5 [µmol/L]	2.88
Stability (pH 1/7/10, 24h, 37°C) [%]	100 / 99 / 100
Stability (r /h plasma, 4h, 37°C) [%]	100 / 100

***in vitro* DMPK Properties**

Caco2 Permeability	P_{app}(A-B) [nm/s]		P_{app}(B-A) [nm/s]		efflux ratio	
	107		76		0.7	
metabolic stability			CL [L/h/kg]		F_{max} [%]	
	liver mics (m / r / d / h)		n.d.		n.d.	
	rat hepatocytes		3.0		28	
	human hepatocytes		n.d.		n.d.	
CYP inhibition IC_{50} [µM]	1A2	2C8	2C9	2D6	3A4	3A4 preinc.
	>5	>5	>5	>5	0.46	0.53
PXR	n.d.					

Selectivity

USP panel at SGC*	>40% remaining activity @ 10 µM (10 USPs)
Cysteine protease panel	IC_{50} >20 µM (6 proteases)
In-house kinase panel	IC_{50} >20 µM (21 kinases)

Antiproliferative Activity (human tumor cell lines)

Jurkat, Molm13, A549	all IC_{50} > 30 µM
MDA-MB-231, U2OS	

BAY-728 is 2100-fold (HTRF) and 8100-fold (Ub-Rhod) less potent compared to BAY-805;
BAY-728 does not induce NFκB activation in a cell-based reporter assay at 10 µM

*BAY-728 was additionally profiled in the DUB*profiler*™ (Ubiquigent) against 44 DUB targets. See back-up.

USP21 Probe BAY-805

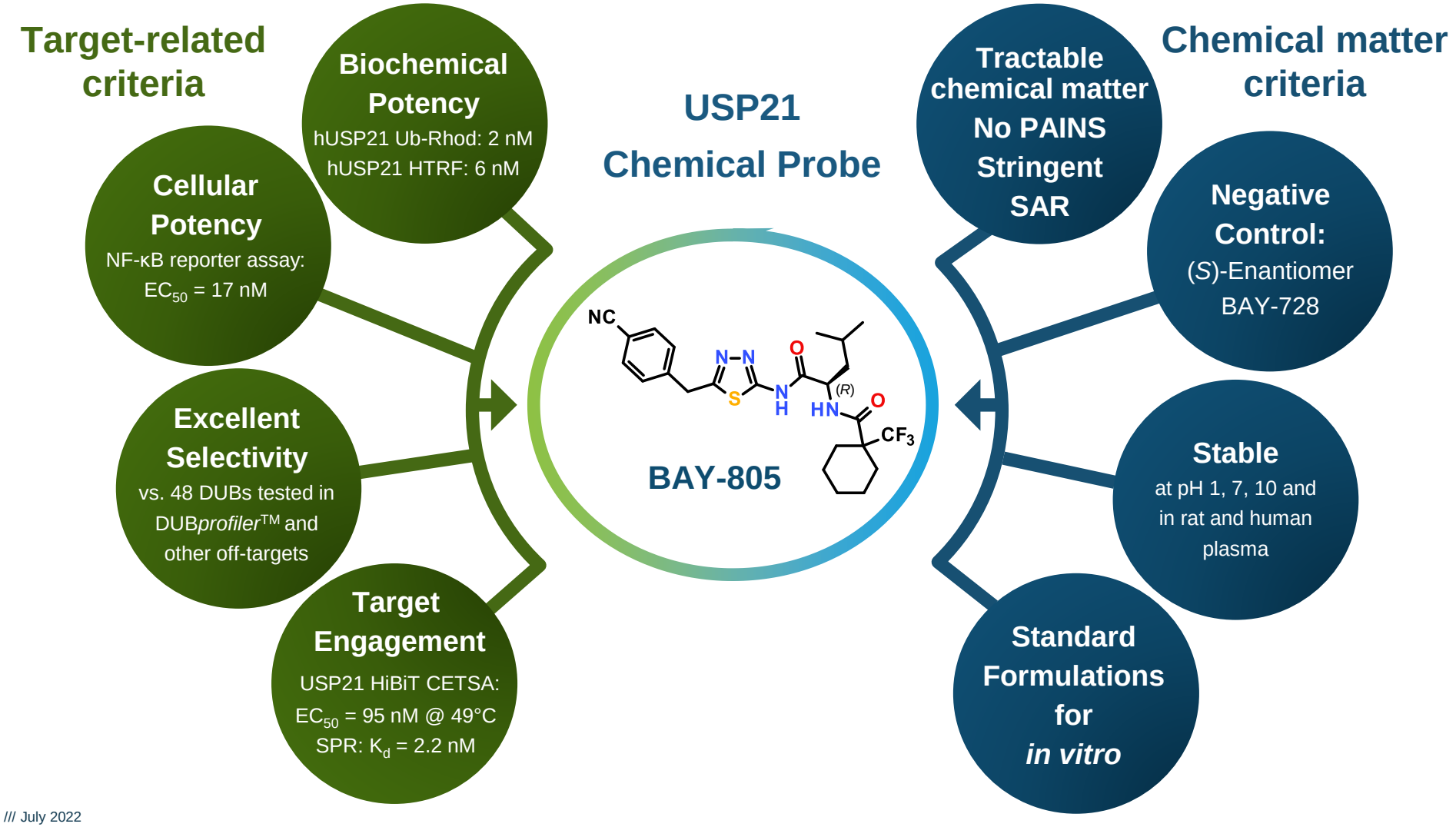
Summary / Conclusion

Probe criteria	
Inhibitor/agonist potency: goal is < 100 nM (IC_{50}, Kd)	**Surpasses criteria**; biochemical assays: hUSP21 (HTRF) IC_{50} = 6 nM, hUSP21 (Ub-Rhod) IC_{50} = 2 nM, SPR K_d = 2.2 nM
Selectivity within target family: goal is > 30-fold	**Surpasses criteria**; good selectivity within DUB family, >50% remaining DUB activity at 10 µM for 9 other USPs
Selectivity outside target family: describe the off-targets (which may include both binding and functional data)	**Surpasses criteria**; IC_{50} >20 µM for 21 tested inhouse kinases and 6 tested cysteine proteases, good selectivity in Eurofins Safety Screen
On target cell activity for cell-based targets: goal is < 1 µM IC_{50}/EC_{50}	**Surpasses criteria**; cellular activity in NFκB reporter assay with EC_{50} at 17 nM, cellular target engagement shown with USP21 HiBiT CETSA
Recommended cell assay concentration	use at concentration of 1 µM for BAY-805, use with control for best interpretation of data
Neg ctrl: *in vitro* potency – > 100 times less; Cell activity – >100 times less potent than the probe	**Surpasses criteria**; BAY-728 is 2100- fold (HTRF) and 8100-fold (Ub-Rhod) less potent compared to BAY-805, BAY-728 does not induce NFκB activation at 10 µM

We ask for acceptance of USP21 inhibitor BAY-805 as chemical probe, accompanied by less active enantiomer BAY-728 as negative control.

USP21 Probe BAY-805

Summary / Conclusion



USP21 Probe BAY-805

Project Team / Acknowledgement

Bayer

Kirstin Petersen

Fabian Göricke

Gerd Wohlfahrt

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Dennis Kirchhoff

Stefan Gradl

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Niels Lindner

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Nuvisan ICB

Norbert Schmees

Jan Naujoks

Tamara Kanashova

Raphael Böhm

Namik Akkilic

Martina Schäfer

Ulrike Scheib

Ulf Bömer

Jörg Weiske

Barbara Nicke

Strutural Genomics Consortium Toronto

Victoria Vu

Masoud Vedadi

Santha Santhakumar

Cheryl Arrowsmith

Dalia Barsyte-Lovejoy

Leanna Smith

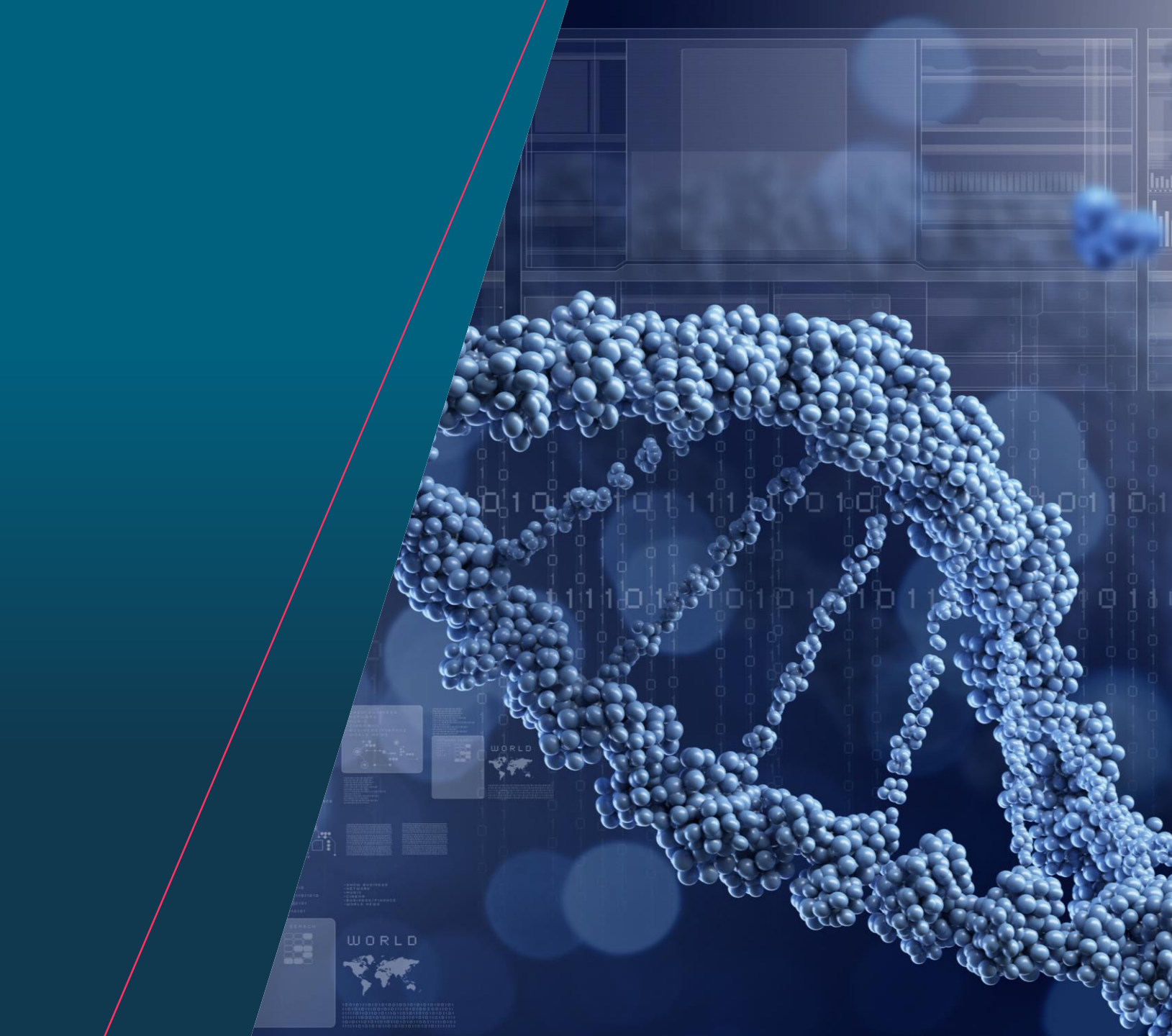
Suzanne Ackloo

Levon Halabelian

Peter Brown

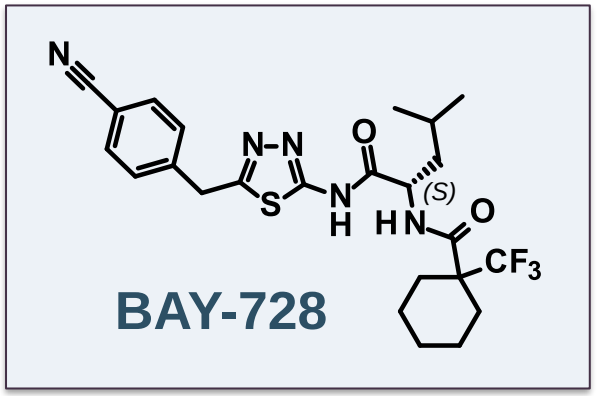
Thank you to the whole team!

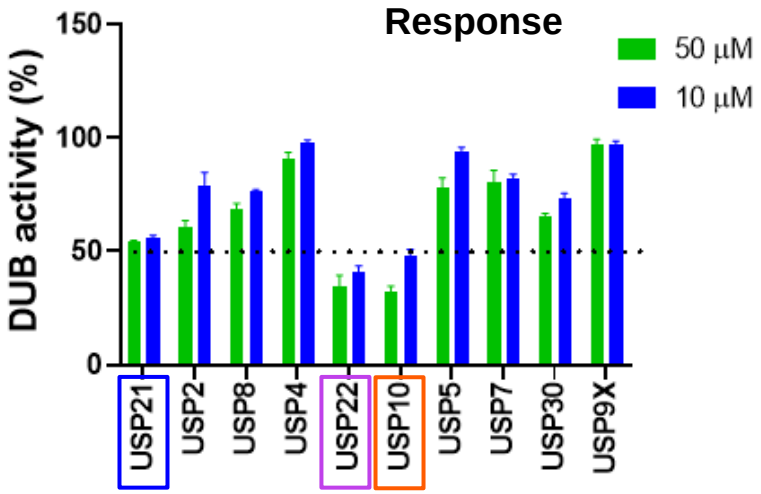
Thank You

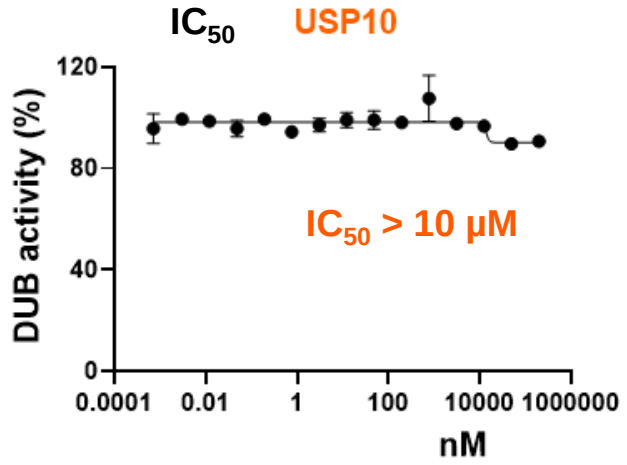


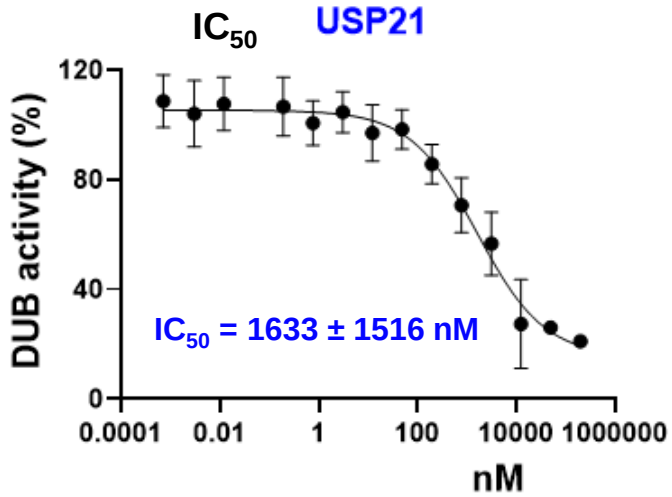
USP21 Probe BAY-805

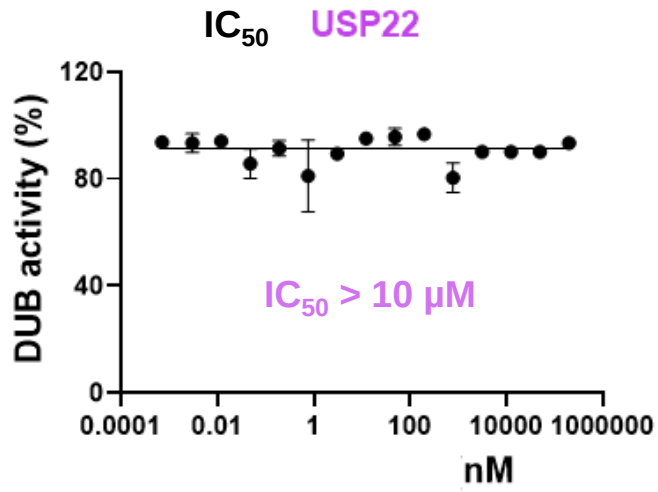
Negative Control BAY-728 – USP Selectivity at SGC











USP21 Probe BAY-805

Negative Control BAY-728 – DUB*profiler*™ (Ubiquigent)

DUB Target	Conc.	Activity (%)
USP1/UAF1	10 µM	97
USP2	10 µM	82
USP4	10 µM	94
USP5	10 µM	105
USP5 (+Ubiquitin @ Kd)	10 µM	90
USP5 (+Ubiquitin @ Bmax)	10 µM	101
USP6	10 µM	105
USP7	10 µM	87
USP8	10 µM	109
USP9x	10 µM	99
USP11	10 µM	102
USP12/UAF1/WDR20	10 µM	106
USP14 (Proteasome-VS @ Kd)	10 µM	112
USP15	10 µM	105
USP16	10 µM	107
USP17	10 µM	88
USP19	10 µM	96

DUB Target	Conc.	Activity (%)
USP20	10 µM	113
USP21	10 µM	40
USP25	10 µM	105
USP27x	10 µM	96
USP28	10 µM	106
USP30	10 µM	103
USP35	10 µM	110
USP36	10 µM	95
USP45	10 µM	98
USP46/UAF1/WDR20	10 µM	100
CYLD	10 µM	100
UCHL1	10 µM	103
UCHL3	10 µM	106
UCHL5	10 µM	147
BAP1	10 µM	92.4
OTU1	10 µM	113
OTUB2	10 µM	101

DUB Target	Conc.	Activity (%)
OTUD1	10 µM	104
OTUD3	10 µM	100
OTUD5 (p117S)	10 µM	121
OTUD6A	10 µM	105
OTUD6B	10 µM	100
Cezanne	10 µM	93
VCPIP	10 µM	115
AMSH-LP	10 µM	88
AMSH-LP (+Zinc)	10 µM	107
Ataxin3	10 µM	90
Ataxin3L	10 µM	106
JOSD1	10 µM	99
JOSD2	10 µM	110

USP21 Probe BAY-805

Selectivity Profile for Negative Control BAY-728 – Eurofins Safety Screen

Assay Name	Conc.	% Inh.
Aldose Reductase	10 µM	2
ATPase, Na^+/K^+, Heart, Pig	10 µM	-3
Carbonic Anhydrase II	10 µM	1
Cholinesterase, Acetyl, ACES	10 µM	75
Cyclooxygenase COX-1	10 µM	3
Cyclooxygenase COX-2	10 µM	5
HMG-CoA Reductase	10 µM	1
Leukotriene LTC_4 Synthase	10 µM	5
Lipoxygenase 15-LO	10 µM	-3
Monoamine Oxidase MAO-A	10 µM	5
Monoamine Oxidase MAO-B	10 µM	5
Nitric Oxide Synthase, Neuronal (nNOS)	10 µM	-5
Nitric Oxide Synthetase, Inducible (iNOS)	10 µM	0
Peptidase, Angiotensin Converting Enzyme	10 µM	-28
Phosphodiesterase PDE3A	10 µM	4
Phosphodiesterase PDE4D2	10 µM	1
Phosphodiesterase PDE5A	10 µM	27
Thromboxane Synthase	10 µM	15
Adenosine A_1	10 µM	-2
Adenosine A_{2A}	10 µM	3
Adenosine A_3	10 µM	24
Adrenergic α_{1A}	10 µM	13
Adrenergic α_{2A}	10 µM	13
Adrenergic α_{2B}	10 µM	1
Adrenergic α_{2C}	10 µM	12
Adrenergic β_1	10 µM	4
Adrenergic β_2	10 µM	6
Adrenergic β_3	10 µM	8
Androgen (Testosterone)	10 µM	7
Angiotensin AT_1	10 µM	27
Angiotensin AT_2	10 µM	-2
Bradykinin B_1	10 µM	23
Bradykinin B_2	10 µM	-7

Assay Name	Conc.	% Inh.
Cannabinoid CB_1	10 µM	3
Cannabinoid CB_2	10 µM	4
Dopamine D_1	10 µM	2
Dopamine D_{2L}	10 µM	17
Dopamine D_{2S}	10 µM	25
Dopamine D_3	10 µM	2
Endothelin ET_A	10 µM	7
Endothelin ET_B	10 µM	29
Estrogen ERα	10 µM	-15
$GABA_A$, Chloride Channel, TBOB	10 µM	14
$GABA_A$, Flunitrazepam, Central	10 µM	-10
$GABA_B$, Non-Selective	10 µM	-1
Glucocorticoid	10 µM	43
Glutamate, AMPA	10 µM	-21
Glutamate, Kainate	10 µM	-5
Glutamate, NMDA, Agonism	10 µM	5
Glutamate, NMDA, Glycine	10 µM	19
Growth Hormone Secretagogue (GHS, Ghrelin)	10 µM	8
Histamine H_1	10 µM	5
Histamine H_2	10 µM	0
Histamine H_3	10 µM	2
Insulin	10 µM	-5
Motilin	10 µM	4
Muscarinic M_1	10 µM	36
Muscarinic M_2	10 µM	24
Muscarinic M_3	10 µM	4
Muscarinic M_4	10 µM	-8
Nicotinic Acetylcholine α3β4	10 µM	-1
Opiate δ_1 (OP1, DOP)	10 µM	5
Opiate κ (OP2, KOP)	10 µM	12
Opiate µ (OP3, MOP)	10 µM	-3
Progesterone PR-B	10 µM	16
Purinergic P2X	10 µM	3
Purinergic P2Y, Non-Selective	10 µM	22

Assay Name	Conc.	% Inh.
Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{1A}$	10 µM	5
Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2A}$	10 µM	2
Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2B}$	10 µM	2
Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2C}$	10 µM	14
Transporter, Adenosine	10 µM	43
Transporter, Dopamine (DAT)	10 µM	41
Transporter, GABA	10 µM	23
Transporter, Norepinephrine (NET)	10 µM	37
Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	10 µM	11
Vasopressin V_{1A}	10 µM	5

Inhibition >50% at 10 µM compound concentration for the following targets:

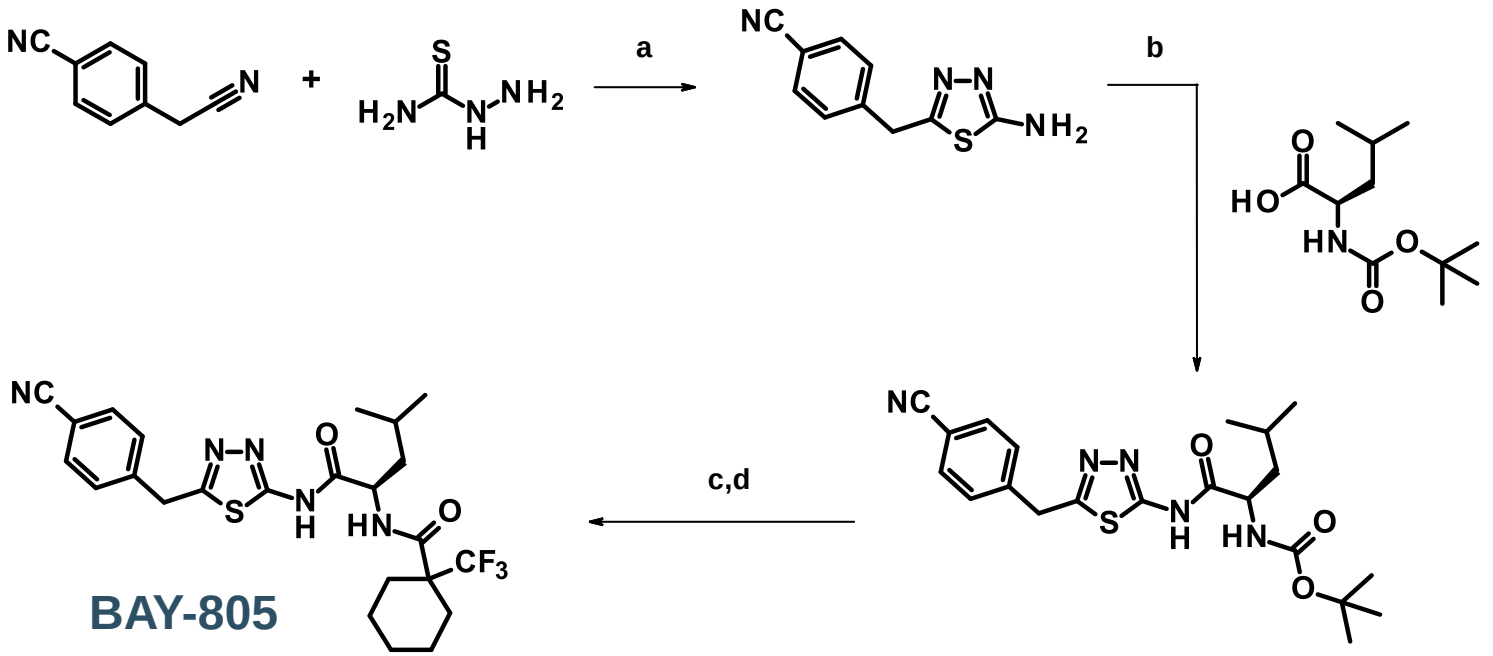
Assay Name	Species	Conc.	% Inh.
Cholinesterase, Acetyl, ACES	hum	10 µM	75

Cholinesterasem Acetyl, ACES: IC_{50} = 6.87 µM

BAY-728 shows good off-target selectivity

USP21 Probe BAY-805

Chemical Synthesis of BAY-805



Reagents and conditions:

(a) TFA, rt; (b) HATU, DIPEA, DMF, rt;

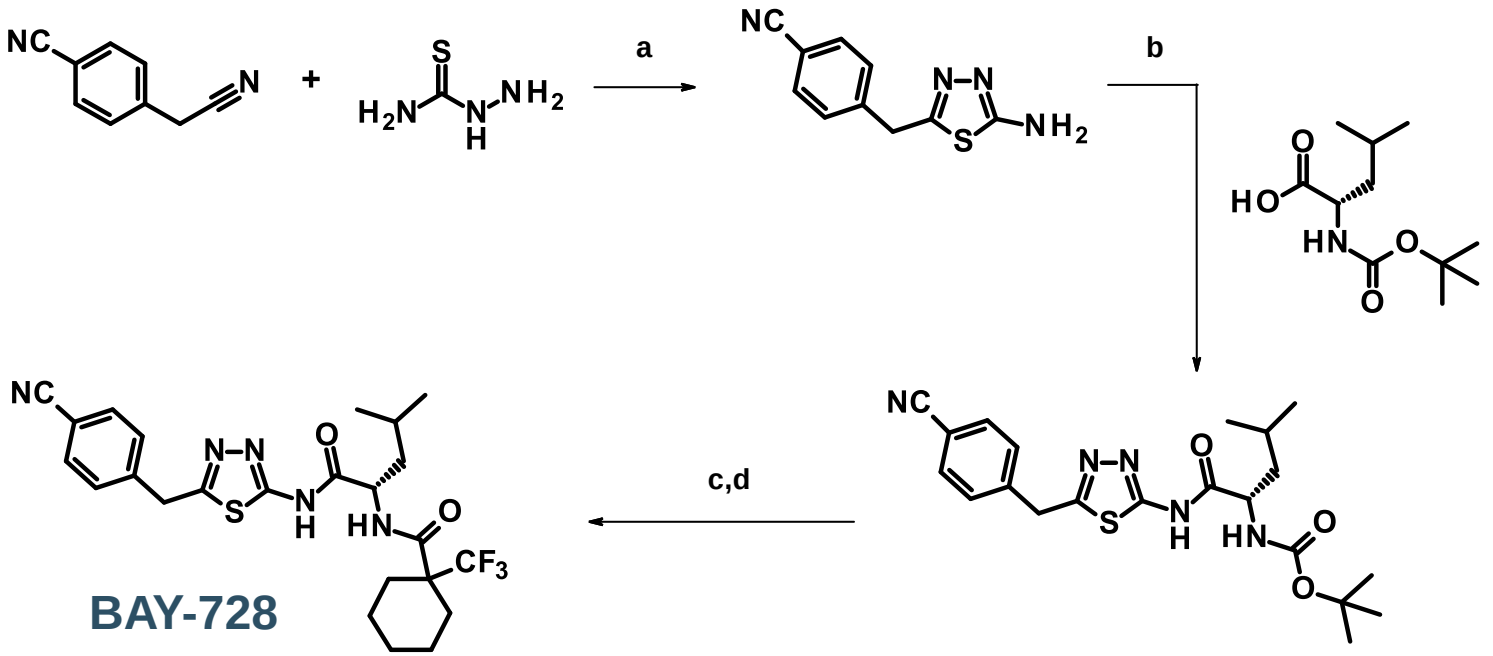
(c) 4N HCl in dioxane, rt;

(d) 1-(trifluoromethyl)cyclohexane-1-carboxylic acid, EDC·HCl, HOBt H_2O, DIPEA, DMF, rt.

BAY-805 was synthesized in a linear sequence of 4 steps

USP21 Probe BAY-805

Chemical Synthesis of Negative Control BAY-728



Reagents and conditions:

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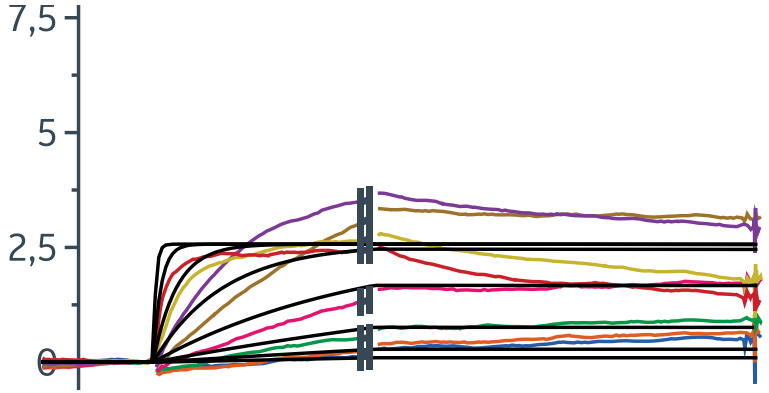
BAY-728 was synthesized in a linear sequence of 4 steps

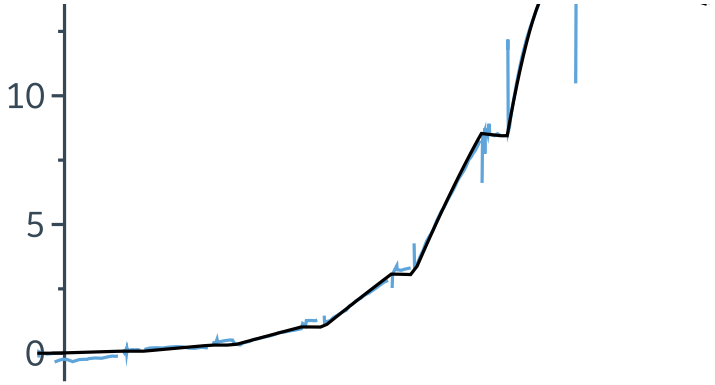
USP21 Probe BAY-805

SPR

Multicycle Mode



Single Cycle Mode



BAY-805 has a very slow

off-rate in multicycle mode

K_d [nM]	ka (1/Ms)	kd (1/s)
2,2 ± 0,9	2,19E5 ± 6,63E4	4,46E-4 ± 2,82E-5