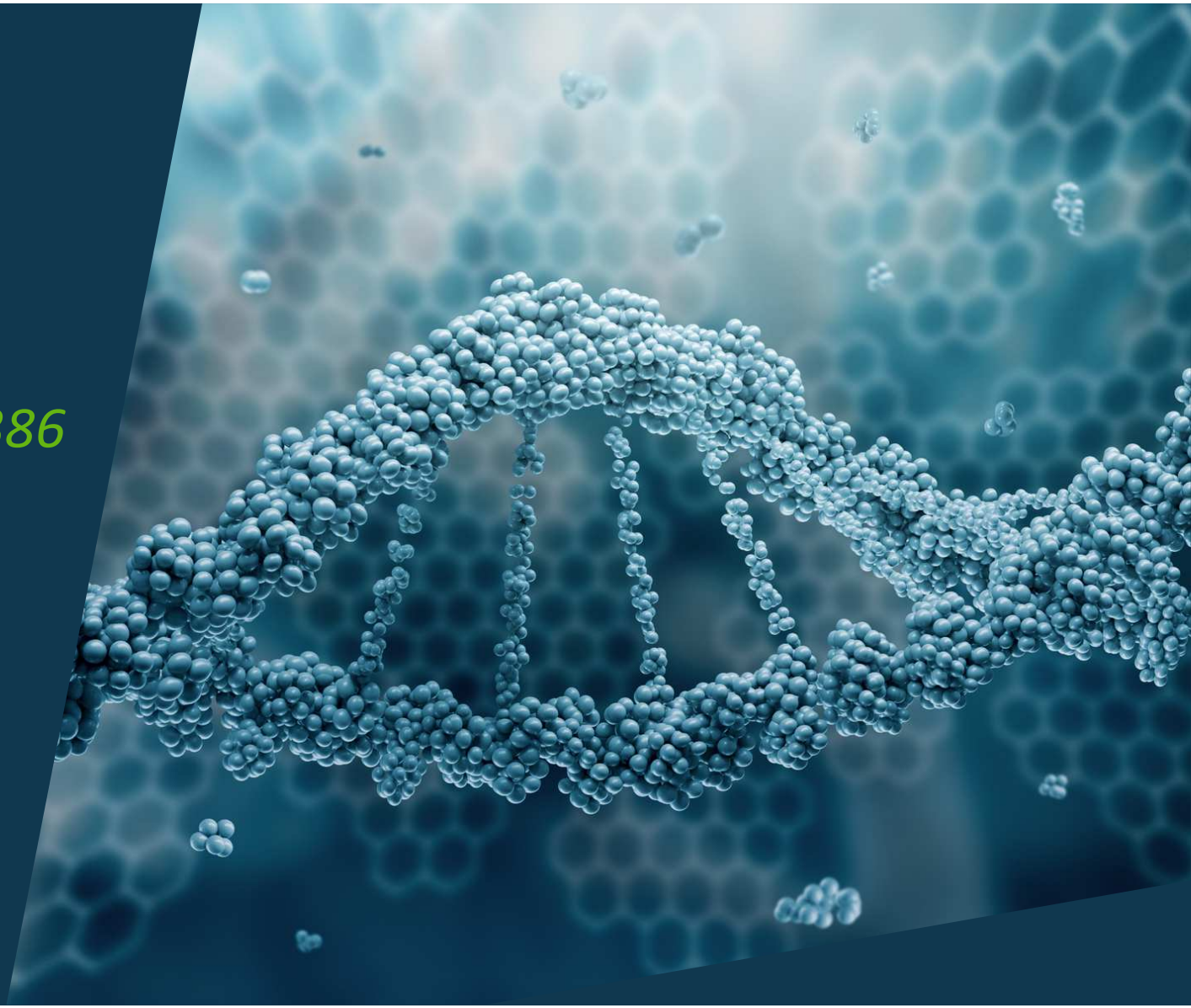
Donated Chemical Probe

Chemical Probe BAY-386
PAR-1 Antagonist



March, 2018

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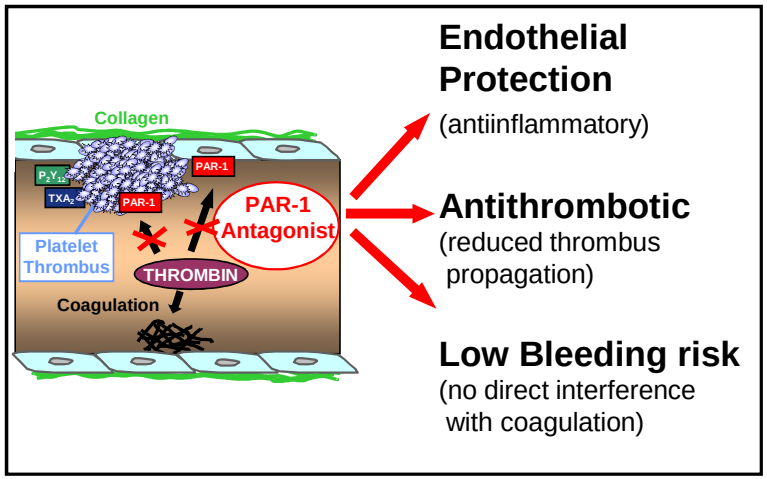
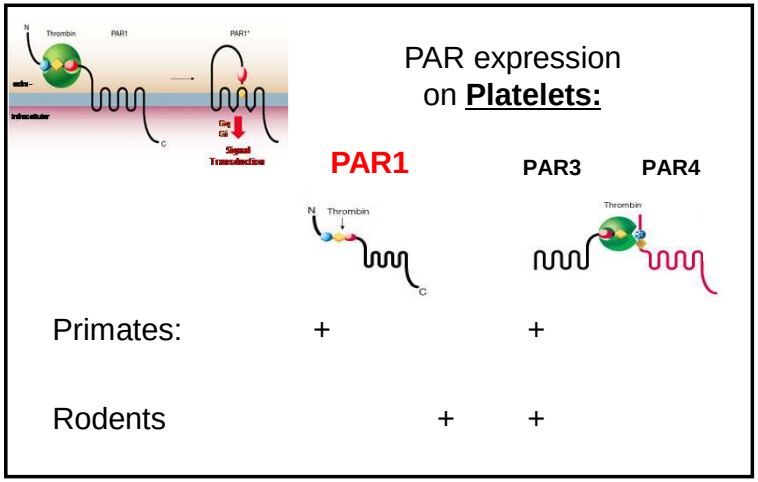
Kersten Matthias Gericke, Mario Jeske

PAR-1 Antagonist BAY-386:

Scientific rationale





// **Thrombin** = **most potent** physiologic **activator** of thrombocytes during aggregation

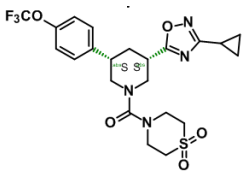
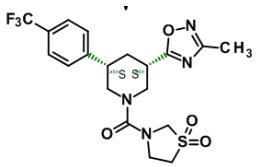
// Effects of thrombin on human platelets mediated **predominantly by PAR-1**

// Antagonists reduce ischemic events in atherosclerotic patients with previous MI or PAOD

PAR-1 Antagonists: new class potential for arterial thrombosis management

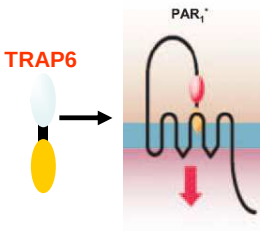
PAR-1 Antagonist BAY-386:

In vitro profile

		Probe BAY-386	Neg. Control BAY-448
	[µM]		
Human	PAR-1 (HEK cell) IC_{50}	**0.01**	**> 10**
	PAR-1 binding IC_{50}	**0.056**	
	$IPA_{plasma, hum, TRAP-6}$ $IC_{50/90}$	**0.43/0.68**	**> 10**
	$IPA_{plasma, hum,Thrombin}$ IC_{50}	**0.14**	
	PAR-4 (HEK cell) IC_{50}	**> 10**	**> 5**
	$IPA_{plasma, hum, ADP, Collagen}$ IC_{50}	**> 100**	
Cyno	$IPA_{plasma, cyno, TRAP-6}$ $IC_{50/90}$ in vitro	**0.15/0.61**	
	$IPA_{plasma, cyno, TRAP-6}$ IC_{90} ex vivo	**0.025**	

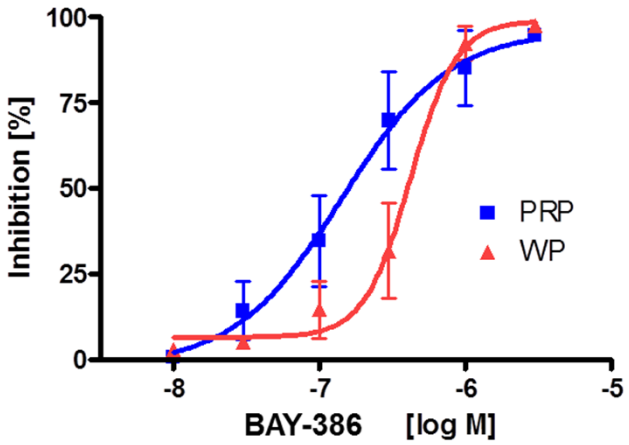
IPA = Inhibition of platelet aggregation

TRAP6 = thrombin receptor activating peptide



PAR-1 Antagonist BAY-386:

Reversibility - Human platelet wash-out experiment

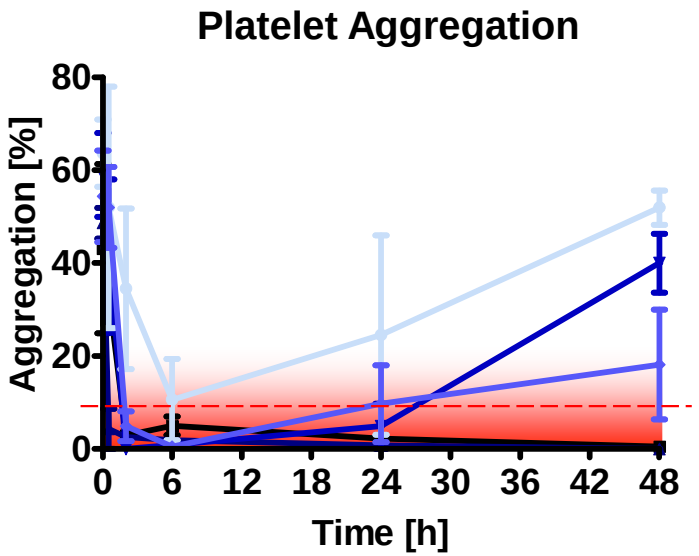


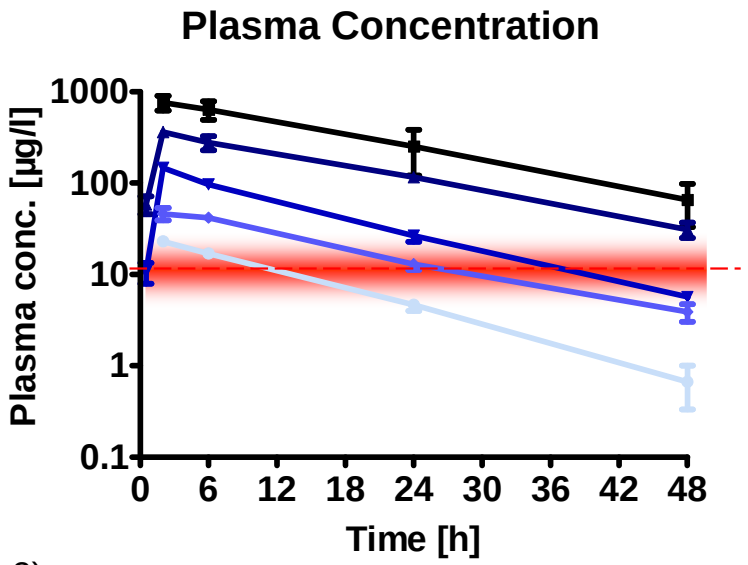
IPA apparent IC_{50} [µM, n=9]	**BAY-386**
Platelet rich plasma	0.143
Washed platelets	0.420

PAR-1 antagonist effect dissociates from platelets upon washing

PAR-1 Antagonist BAY-386:

Ex vivo anti-platelet effect - Cynomolgus monkey PD/PK (single dose p.o.)





TRAP6 100 µg/ml
Aggregation: Mean ± SEM
Plasma conc: geoMean
Lab. Gerdes / Gnoth

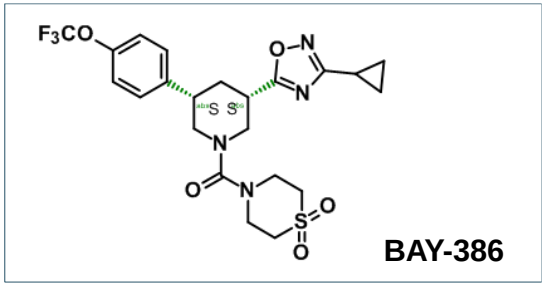
- 5.0 mg/kg (n=2)
- 1.5 mg/kg (n=4)
- 0.5 mg/kg (n=3)
- 0.15 mg/kg (n=9)
- 0.05 mg/kg (n=3)

Estimated effective concentration:
IC_{90} ex vivo ~ 13 µg/l, ~ 25 nM (total)

(> 90 % inhibition requirement)

PAR-1 Antagonist BAY-386 & neg. control BAY-448:

Molecular properties and PhysChem data



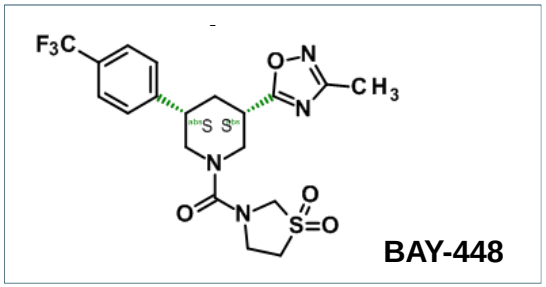
BAY-386

- **Molecular Properties**

MW [g/mol]	515
MWcorr [g/mol]	
TPSA [Å2]	
Rotatable bonds	

- **PhysChem**

Sw $^{pH\ 6.5}$ [mg/L]	30
log D (pH 7.5)	3.6



BAY-448

- **Molecular Properties**

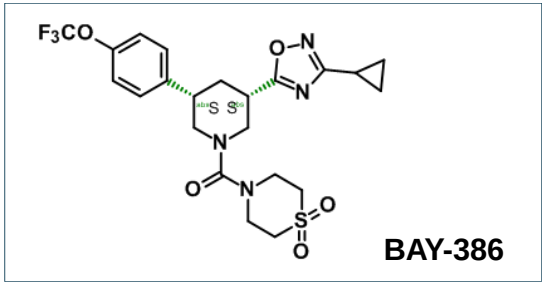
MW [g/mol]	458
MWcorr [g/mol]	
TPSA [Å2]	
Rotatable bonds	

- **PhysChem**

Sw $^{pH\ 6.5}$ [mg/L]	150
log D (pH 7.5)	3.3

PAR-1 Antagonist BAY-386 & neg. control BAY-448:

Broader selectivity assessment (GPCR Panel, Cereps)



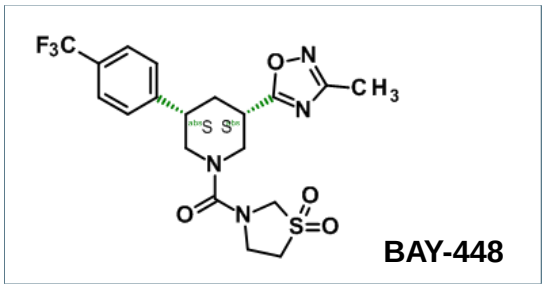
BAY-386

- **Selectivity in cellular functional assays (Cereps GPCR panel, total # of assay: 2x 25*)**

* antag. and agonistic set-up each

BAY-386 (10 µM)	**No significant results noted, except CB1 antag. (81%), and M1 antag. (57%)**

consistent with bdg. data (s. previous slides)



BAY-448

- **Selectivity in cellular functional assays (Cereps GPCR panel, total # of assay: 2x 25*)**

* antag. and agonistic set-up each

BAY-448 (10 µM)	**No significant results noted**

// Good selectivity confirmed for probe also in functional GPCR assays

// Neg. control is inactive against any GPCR tested

PAR-1 Antagonist BAY-386:

Summary of in vitro ADME Data

BAY-386		Rat	Dog	Cynomolgus	Human
CL Mic	[L/h/kg]	0.16	0.27	0.36	0.018
CL Hep	[L/h/kg]	0.46	0.20	n.d.	0.20
CL *in vivo*	[L/h/kg]	0.46	0.47	0.20 (pl)	n.d.

BAY-386		Rat	Dog	Cynomolgus	Baboon	Human
fu	[%]	5.9	5.3	6.9	3.4	3.6
Caco-2 P_{app}A-B	[nm/sec]					266
ER						0.9
P-gp ER						1.4

// BAY-386 shows *in vitro* a low CL in all species tested

// BAY-386 is highly permeable

// Free fraction shows slight species difference for BAY-386

// BAY-386 is no P-gp substrate

PAR-1 Antagonist BAY-386:

CYP Interaction Profile

	BAY-386
CYP-Inhibition (Microsomes)	
CYP 1A2, IC_{50} [µM],	> 20
CYP 2C8, IC_{50} [µM],	> 20
CYP 2C9, IC_{50} [µM],	> 20
CYP 2D6, IC_{50} [µM],	> 20
CYP 3A4, IC_{50} [µM],	> 20
CYP 3A4, IC_{50} [µM], preinc.	> 20
CYP-Induction	
induction of 1A2; NOEL [ng/ml]	>10000
CYP3A4: safety margin	≥ 600

// No Inhibition of CYP enzymes tested

// No relevant induction of CYP 3A4 and 1A2 observed for BAY-386

PAR-1 Antagonist BAY-386:

PK Parameters of BAY-386 in Animals

		BAY-386			
Species		Rat	Dog	Cynomolgus	Baboon
CL	[L/h/kg]	0.41	0.35	0.20	0.30
CL_{blood}	[L/h/kg]	0.46	0.47	n.d.	n.d.
V_{ss}	[L/kg]	3.3	4.9	2.8	2.1
$t_{1/2}$	[h]	5.6	11	10	5.0
p.o.					
AUC_{norm}	[kg·h/L]	2.1	1.8	3.8	n.d.
$C_{max,norm}$	[kg/L]	0.15	0.21	0.26	n.d.
t_{max} (Median)	[h]	5.0	1.0	1.0	n.d.
$t_{1/2}$	[h]	7.7	7.2	12	n.d.
F	[%]	88	62	78	n.d.

// BAY-386 shows a low CL and high Vss in all species tested and high bioavailability

// In rats BAY-386 shows no relevant renal CL (data not shown)

// Relative bioavailability from suspension (crystallin material) vs solution amounts to 81 % and 95% at doses of 0.24 and 2 mg/kg

PAR-1 Antagonist BAY-386:

Safety Pharmacology

Lead Profiling Screen (MDS/Ricerca) at 10 µM

significant inhibition of binding to CB1 receptor (88%) and Na^+ channel (55%)

⇒ >100-fold above PAR-1 activity (IC_{50} ~10 nmol/L) in mechanistic assay

hERG potassium channel (manual voltage clamp):

moderately potent inhibition with threshold (IC_{20}) ~1.1 µmol/L (IC_{50} ~3.8 µmol/L)

⇒ IC_{20} >100-fold above PAR-1 activity (IC_{50} ~10 nmol/L) in mechanistic assay

Ion channel cardiac profiler (Millipore, automated voltage clamp, IonWorks):

8 major cardiac channels at 0.4-33 µmol/L

hNav1.5, hKv1.5, hERG, hKv4.3/hKChIP2, hCav1.2, hKCNQ1/hminK, hKir2.1, HCN4

⇒ significant hERG inhibition (IC_{50} ~2.1 µmol/L)

all other channels: no effect at ≤11 µmol/L

⇒ **no relevant off-target activity**

moderately potent hERG K^+ channel inhibition

(>200-fold above predicted human $C_{max.u}$ ~2.6 µg/L)

PAR-1 Antagonist BAY-386:

Ricerca Lead Profiling (in vitro)

Receptor specificity tested towards 70 targets by radioligand binding assay

⇒ Significant interactions observed @ 10 µM:

Sarcolemmal Na^+ channel site 2:	**55 % inhibition**
Cannabinoid CB1 receptor:	**88 % inhibition**

CB1 receptor functional test:

GTPγS binding:	**IC_{50} 10.6 µM**

⇒ **BAY-386: selective PAR-1 antagonist**

PAR-1 Antagonist BAY-386:

Summary / conclusion

Probe criteria	
Inhibitor/agonist potency: goal is < 100 nM (IC50, Kd)	Surpasses criteria; functional cellular assay (PAR-1, HEK cells) with IC_{50} 10 nM; binding assay (platelet membranes) IC_{50} 56 nM
Selectivity within target family: goal is >30-fold	Surpasses criteria; > 1,000fold selectivity vs PAR-4 (functional cellular assay: PAR-4 HEK cells, IC_{50} > 10 µM)
Selectivity outside target family: describe the off-targets (which may include both binding and functional data)	Surpasses criteria; No relevant activity in panel of > 70 off-targets; closest hits: hERG IC_{50} = 2-4 µM
On target cell activity for cell-based targets: goal is < 1 micromolar IC50/EC50	Surpasses criteria; functional cellular assay (HEK-cells, IC_{50} 10 nM);
On target cell activity for secreted targets: appropriate alternative such as mouse model or other mechanistic biological assay, e.g., explant culture	Surpasses criteria; mechanistic biological assay: Inhibition of thrombocyte aggregation in plasma ($IC_{50,\ Thromin-ind.}$ 140 nM, $IC_{50,\ TRAP6-ind.}$ 430 nM);
Neg ctrl: *in vitro* potency - > 100 times less; Cell activity - >100 times less potent than the probe	Surpasses criteria; functional cellular assays: > 1,000 times less active on target (PAR-1, HEK cells) with IC_{50} >10 µM; PAR-4 (>> 5 µM*) and panel of 25 other GPCRs (> 10 µM); ex vivo assay: > 100 times less active in inhibition of platelet aggregation (> 10 µM)

We ask for acceptance of PAR-1 antagonist BAY-386 as chemical probe, accompanied by BAY-448 as negative control

PAR-1 Antagonist BAY-386:

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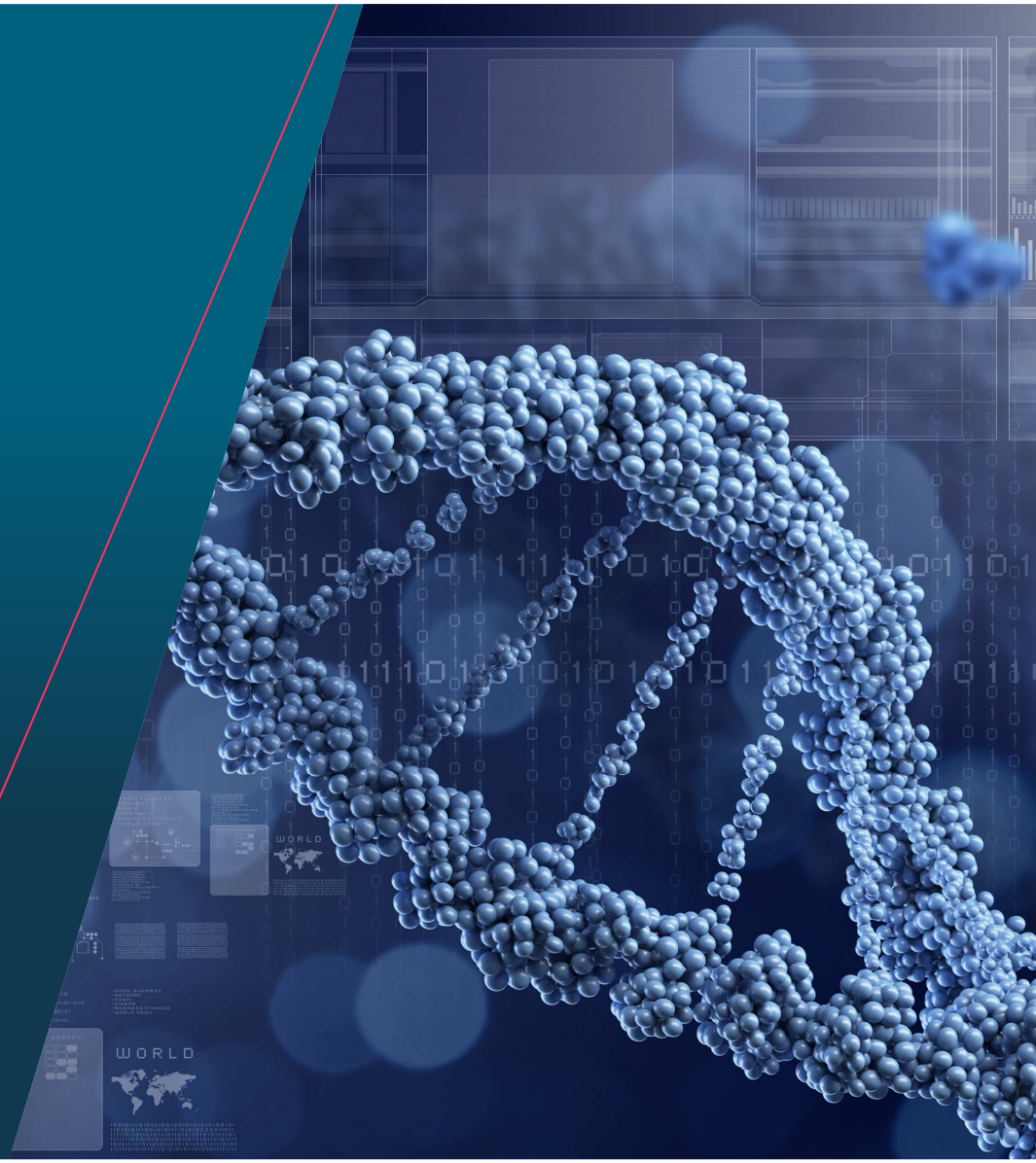
Thank You



PAR-1 Antagonist BAY-386:

LeadprofilingScreen (Eurofins, Panlabs) data

Cat. #	TARGET	BATCH®	SPP.	n=	CONC.	%
118050	CYP450, 1A2	260499	hum	2	10 µM	2
118070	CYP450, 2C19	260501	hum	2	10 µM	43
118060	CYP450, 2C9	260500	hum	2	10 µM	30
♦ 118080	CYP450, 2D6	260502	hum	2	10 µM	-60
118090	CYP450, 3A4	260503	hum	2	10 µM	-27
200510	Adenosine A_1	260145	hum	2	10 µM	-6
200610	Adenosine A_{2A}	260146	hum	2	10 µM	0
200720	Adenosine A_3	260148	hum	2	10 µM	12
203100	Adrenergic α_{1A}	260166	rat	2	10 µM	1
203200	Adrenergic α_{1B}	260167	rat	2	10 µM	9
203400	Adrenergic α_{1D}	260168	hum	2	10 µM	-4
203620	Adrenergic α_{2A}	260169	hum	2	10 µM	8
204010	Adrenergic β_1	260170	hum	2	10 µM	-13
204110	Adrenergic β_2	260171	hum	2	10 µM	0
285010	Androgen (Testosterone) AR	260285	rat	2	10 µM	11
212510	Bradykinin B_1	260150	hum	2	10 µM	6
212610	Bradykinin B_2	260284	hum	2	10 µM	11
214510	Calcium Channel L-Type, Benzothiazepine	260343	rat	2	10 µM	16
214600	Calcium Channel L-Type, Dihydropyridine	260174	rat	2	10 µM	14
216000	Calcium Channel N-Type	260470	rat	2	10 µM	3
♦ 217030	Cannabinoid CB_1	260144	hum	2	10 µM	88
219500	Dopamine D_1	260152	hum	2	10 µM	4
219700	Dopamine D_{2S}	260153	hum	2	10 µM	1
219800	Dopamine D_3	260154	hum	2	10 µM	-1
219900	Dopamine $D_{4.2}$	260155	hum	2	10 µM	-9
224010	Endothelin ET_A	260471	hum	2	10 µM	2
224110	Endothelin ET_B	260472	hum	2	10 µM	-4
225510	Epidermal Growth Factor (EGF)	260473	hum	2	10 µM	-7
226010	Estrogen ERα	260474	hum	2	10 µM	-1
226600	$GABA_A$, Flunitrazepam, Central	260158	rat	2	10 µM	-3
226500	$GABA_A$, Muscimol, Central	260157	rat	2	10 µM	10

Cat. #	TARGET	BATCH®	SPP.	n=	CONC.	%
228610	$GABA_{BIA}$	260476	hum	2	10 µM	10
232020	Glucocorticoid	260347	hum	2	10 µM	9
232700	Glutamate, Kainate	260478	rat	2	10 µM	15
232810	Glutamate, NMDA, Agonism	260479	rat	2	10 µM	-2
232910	Glutamate, NMDA, Glycine	260342	rat	2	10 µM	12
233000	Glutamate, NMDA, Phencyclidine	260159	rat	2	10 µM	0
239610	Histamine H_1	260175	hum	2	10 µM	0
239710	Histamine H_2	260369	hum	2	10 µM	-3
239810	Histamine H_3	260336	hum	2	10 µM	-3
241000	Imidazoline I_2, Central	260176	rat	2	10 µM	0
243520	Interleukin IL-1	260273	mouse	2	10 µM	16
250460	Leukotriene, Cysteinyl $CysLT_1$	260340	hum	2	10 µM	1
251600	Melatonin MT_1	260337	hum	2	10 µM	14
252610	Muscarinic M_1	260177	hum	2	10 µM	-3
252710	Muscarinic M_2	260178	hum	2	10 µM	-3
252810	Muscarinic M_3	260179	hum	2	10 µM	-2
257010	Neuropeptide Y Y_1	260483	hum	2	10 µM	1
257110	Neuropeptide Y Y_2	260484	hum	2	10 µM	2
258590	Nicotinic Acetylcholine	260163	hum	2	10 µM	-4
258700	Nicotinic Acetylcholine α1, Bungarotoxin	260165	hum	2	10 µM	-2
260110	Opiate δ (OP1, DOP)	260272	hum	2	10 µM	-17
260210	Opiate κ (OP2, KOP)	260486	hum	2	10 µM	-3
260410	Opiate µ (OP3, MOP)	260151	hum	2	10 µM	6
264500	Phorbol Ester	260182	mouse	2	10 µM	5
265010	Platelet Activating Factor (PAF)	260615	hum	2	10 µM	0
265600	Potassium Channel [K_{ATP}]	260183	ham	2	10 µM	4
265900	Potassium Channel hERG	260160	hum	2	10 µM	22
268420	Prostanoid EP_4	260184	hum	2	10 µM	1
268700	Purinergic P_{2X}	260487	rabbit	2	10 µM	9
268810	Purinergic P_{2Y}	260488	rat	2	10 µM	12
270000	Rolipram	260185	rat	2	10 µM	3

Cat. #	TARGET	BATCH®	SPP.	n=	CONC.	%
271110	Serotonin (5-Hydroxytryptamine) 5-HT_{1A}	260251	hum	2	10 µM	-9
271700	Serotonin (5-Hydroxytryptamine) 5-HT_{2B}	260186	hum	2	10 µM	-18
271910	Serotonin (5-Hydroxytryptamine) 5-HT_3	260491	hum	2	10 µM	16
278110	Sigma σ_1	260161	hum	2	10 µM	12
♦ 279510	Sodium Channel, Site 2	260162	rat	2	10 µM	55
255510	Tachykinin NK_1	260482	hum	2	10 µM	-2
285900	Thyroid Hormone	260493	rat	2	10 µM	11
220320	Transporter, Dopamine (DAT)	260362	hum	2	10 µM	10
226400	Transporter, GABA	260475	rat	2	10 µM	14
204410	Transporter, Norepinephrine (NET)	260173	hum	2	10 µM	17
274030	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	260344	hum	2	10 µM	3

PAR-1 Antagonist BAY-386 & negative control BAY-448:

GPCR Screen (Eurofins, Cereps) antagonistic effect data

Compound I.D.	Client Compound I.D.	Test Concentration	% Inhibition of Control Agonist Response 1st	2nd	Mean
A_{2B} *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	12.9	-13.6	-0.3
100041490-2	ESD0007806	1.0E-05 M	-0.6	-16.4	-8.5
A_3 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-9.9	-16.4	-13.1
100041490-2	ESD0007806	1.0E-05 M	8.9	15.4	12.2
α_{1L} *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	12.1	25.5	18.8
100041490-2	ESD0007806	1.0E-05 M	1.6	7.1	4.3
α_{2A} *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-13.5	10.0	-1.7
100041490-2	ESD0007806	1.0E-05 M	-13.5	-13.5	-13.5
β_1 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	8.7	-9.2	-0.2
100041490-2	ESD0007806	1.0E-05 M	6.8	6.7	6.8
β_2 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-20.3	6.5	-6.9
100041490-2	ESD0007806	1.0E-05 M	13.0	7.3	10.2
CB_1 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	87.9	73.6	80.7
100041490-2	ESD0007806	1.0E-05 M	2.4	-3.7	-0.6
D_1 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-32.6	-30.6	-31.6
100041490-2	ESD0007806	1.0E-05 M	11.0	16.8	13.9
D_{2S} *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	5.6	7.6	6.6
100041490-2	ESD0007806	1.0E-05 M	7.6	9.6	8.6
H_1 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	7.2	6.6	6.9
100041490-2	ESD0007806	1.0E-05 M	-18.6	-10.5	-14.6
H_2 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	12.1	7.1	9.6
100041490-2	ESD0007806	1.0E-05 M	9.1	-14.7	-2.8
H_3 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-5.1	-2.2	-3.7
100041490-2	ESD0007806	1.0E-05 M	-6.1	-2.2	-4.2

Compound I.D.	Client Compound I.D.	Test Concentration	% Inhibition of Control Agonist Response 1st	2nd	Mean
MC_4 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	0.2	-16.5	-8.1
100041490-2	ESD0007806	1.0E-05 M	16.0	12.6	14.3
motilin *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	30.2	28.1	29.2
100041490-2	ESD0007806	1.0E-05 M	-0.3	2.1	0.9
M_1 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	56.4	57.6	57.0
100041490-2	ESD0007806	1.0E-05 M	2.4	18.0	10.2
M_4 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	4.9	6.7	5.8
100041490-2	ESD0007806	1.0E-05 M	2.7	1.1	1.9
NK_1 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	22.7	24.0	23.3
100041490-2	ESD0007806	1.0E-05 M	1.3	2.8	2.1
κ (KOP) (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	3.4	5.5	4.5
100041490-2	ESD0007806	1.0E-05 M	4.2	-1.6	1.3
μ (MOP) *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	6.6	0.7	3.7
100041490-2	ESD0007806	1.0E-05 M	-5.1	-4.6	-4.8
EP_3 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-11.2	-4.9	-8.0
100041490-2	ESD0007806	1.0E-05 M	-0.2	1.4	0.6
$P2Y_2$ *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	51.2	32.5	41.9
100041490-2	ESD0007806	1.0E-05 M	24.0	34.1	29.1
5-HT1A *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	32.5	18.7	25.6
100041490-2	ESD0007806	1.0E-05 M	-25.4	-20.7	-23.0
$5\text{-}HT_{2B}$ *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	10.2	3.9	7.0
100041490-2	ESD0007806	1.0E-05 M	-0.6	-5.4	-3.0
$5\text{-}HT_C$ *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	16.2	26.0	21.1
100041490-2	ESD0007806	1.0E-05 M	3.4	0.7	2.1
sst_4 *(h)* (antagonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-4.9	-1.7	-3.3
100041490-2	ESD0007806	1.0E-05 M	4.1	-1.6	1.2

ESD0007805 = BAY-386
ESD0007806 = BAY-448

PAR-1 Antagonist BAY-386 & negative control BAY-448:

GPCR Screen (Eurofins, Cereps) agonistic effect data

Compound I.D.	Client Compound I.D.	Test Concentration	% of Control Agonist Response 1st	2nd	Mean
A_{2B} *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	3.6	3.3	3.5
100041490-2	ESD0007806	1.0E-05 M	2.0	1.0	1.5
A_3 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	1.8	3.2	2.5
100041490-2	ESD0007806	1.0E-05 M	21.7	16.7	19.2
α_{1A} *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	13.0	10.0	11.5
100041490-2	ESD0007806	1.0E-05 M	-0.2	-0.6	-0.4
α_{2A} *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	2.5	10.0	6.3
100041490-2	ESD0007806	1.0E-05 M	0.7	4.4	2.5
β_1 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	3.6	3.2	3.4
100041490-2	ESD0007806	1.0E-05 M	-2.1	2.7	0.3
β_2 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-3.5	0.0	-1.7
100041490-2	ESD0007806	1.0E-05 M	2.2	2.3	2.3
CB_1 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-315.0	-218.4	-266.7
100041490-2	ESD0007806	1.0E-05 M	-26.4	-8.9	-17.6
D_1 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	0.4	-3.2	-1.4
100041490-2	ESD0007806	1.0E-05 M	-3.5	1.1	-1.2
D_{2S} *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	3.1	4.9	4.0
100041490-2	ESD0007806	1.0E-05 M	3.1	3.1	3.1
H_1 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	2.6	5.7	4.1
100041490-2	ESD0007806	1.0E-05 M	-1.3	1.8	0.3
H_2 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-2.5	1.1	-0.7
100041490-2	ESD0007806	1.0E-05 M	0.9	4.4	2.6
H_3 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	8.1	4.2	6.2
100041490-2	ESD0007806	1.0E-05 M	32.4	-4.5	13.9

Compound I.D.	Client Compound I.D.	Test Concentration	% of Control Agonist Response 1st	2nd	Mean
MC_4 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	0.1	-2.5	-1.2
100041490-2	ESD0007806	1.0E-05 M	-1.5	-2.1	-1.8
motilin *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	16.6	16.8	16.7
100041490-2	ESD0007806	1.0E-05 M	7.9	6.0	6.9
M_1 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	12.7	12.9	12.8
100041490-2	ESD0007806	1.0E-05 M	1.5	1.0	1.2
M_4 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-4.7	-25.4	-15.0
100041490-2	ESD0007806	1.0E-05 M	24.9	25.2	25.1
NK_1 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	1.7	1.8	1.8
100041490-2	ESD0007806	1.0E-05 M	0.9	-0.3	0.3
κ (KOP) (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	16.5	24.7	20.6
100041490-2	ESD0007806	1.0E-05 M	10.9	7.0	9.0
μ (MOP) *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	20.2	-18.2	1.0
100041490-2	ESD0007806	1.0E-05 M	34.4	37.5	36.0
EP_3 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	6.2	2.8	4.5
100041490-2	ESD0007806	1.0E-05 M	-1.2	-0.1	-0.6
$P2Y_2$ *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-0.8	2.3	0.7
100041490-2	ESD0007806	1.0E-05 M	-3.7	-4.7	-4.2
5-HT1A *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	0.9	-1.4	-0.2
100041490-2	ESD0007806	1.0E-05 M	2.5	-0.4	1.1
$5\text{-}HT_{2B}$ *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	0.3	2.9	1.6
100041490-2	ESD0007806	1.0E-05 M	0.2	0.6	0.4
$5\text{-}HT_6$ *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	8.2	-2.6	2.8
100041490-2	ESD0007806	1.0E-05 M	0.5	2.3	1.4
sst_4 *(h)* (agonist effect)					
100041490-1	ESD0007805	1.0E-05 M	-20.8	-5.1	-13.0
100041490-2	ESD0007806	1.0E-05 M	-3.7	-0.3	-2.0

ESD0007805 = BAY-386
ESD0007806 = BAY-448