Donated Chemical Probe

Dual V1a/V2 Receptor Antagonist Pecavaptan

December 6th, 2023

Presenter:
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On behalf of the team

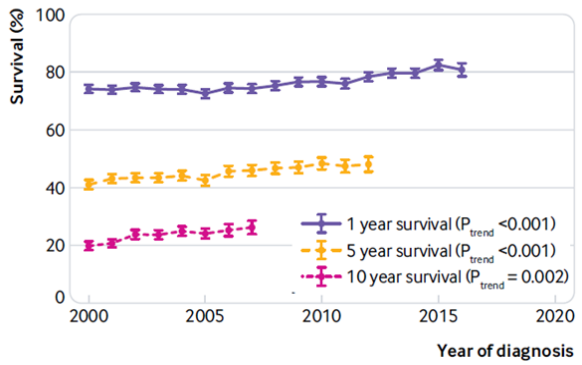
Rationale for the dual vasopressin V1a/V2 receptor antagonist Pecavaptan in congestive heart failure

Congestion: leading cause for HF hospitalization with global annual cost of HF ~ 108 billion US$

Mortality and readmission following HF hospitalization

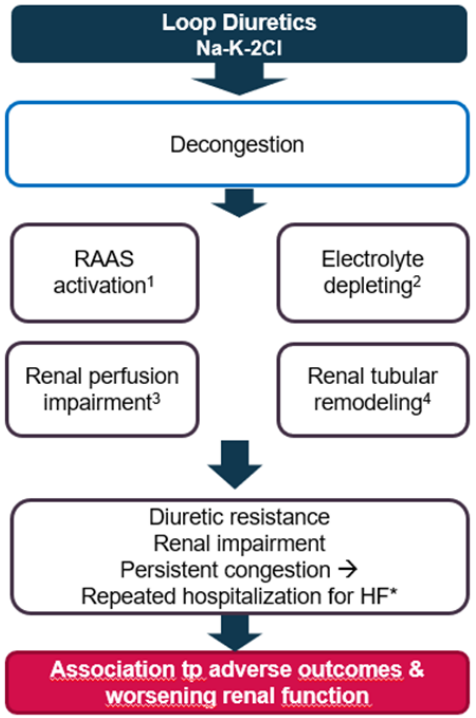
	30 days	1 year
Readmission	~ 20%	~ 55%
Mortality	~ 10%	~ 35%

HF Survival rates at one, five, and 10 years



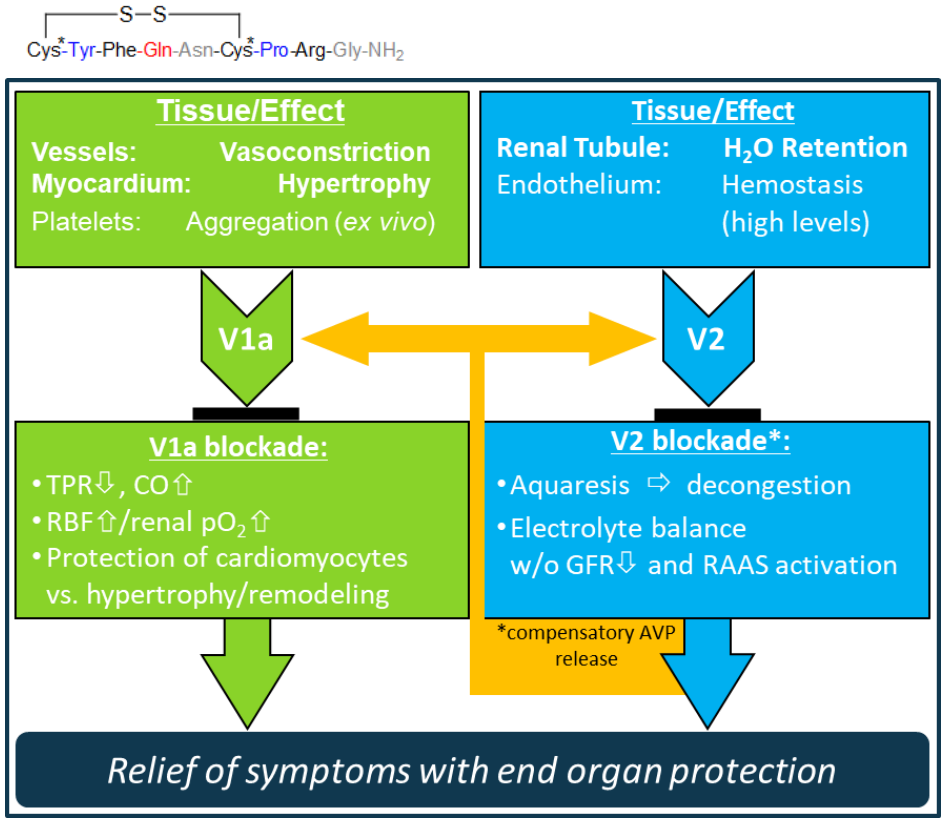
Gupta et al., JAMA cardiology 2018; DeVore, J Am Heart Assoc. 2014 ,Dharmarajan et al, Bueno et al, *JAMA* 2013, *JAMA* 2010 Taylor et al., BMJ 2019; *data from UK, population-based cohort

Limitations of standard of care: loop diuretics



[1]Damman at al., Eur J Heart Fail 2016; , Julo et al., ESC Heart Fail. 2016, [2]Cooper et al., Circulation 1999; [3]Costello-Boerrigter et al., Am J Physiol Renal Physiol 2006; [4]Ellison D et al. JCI 1989; [5]*Vaduganathan et al. EJHF, 2015 RAAS = Renin angiotensin aldosterone system, AVP = Arginin Vasopressin,* * Gheorghiade et al., Am J Med 2006;

Vasopressin is a nine amino acid, cyclic peptide hormone



TPR= total peripheral resistance
CO= cardiac output
RBF= renal blood flow

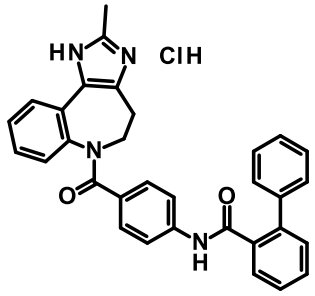
GFR= glomerular filtration rate
RAAS= renin-angiotensin-aldosterone system

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Reference compounds are structurally related to each other, featuring a tetrahydro-benzazepine motif

dual V1a/V2

Conivaptan[1)]



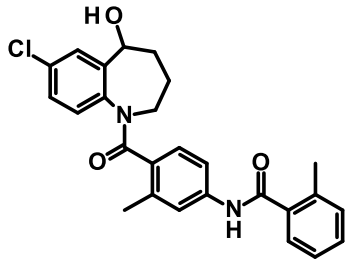
receptor binding [nM]

V1a	K_i = 0.48
V2	K_i = 3.04
V1b	K_i > 100µM
OTR	K_i = 44.4

- approved for hypovolemia, hyponatremia
- only intravenous administration for a limited duration (due to CYP3A4 inhibition)
- no approval for decompensated congestive heart failure

selective V2

Tolvaptan[2)]



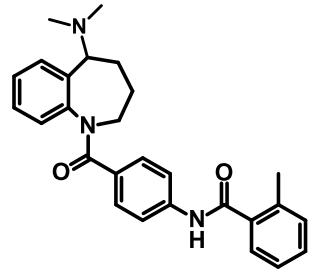
receptor binding [nM]

V1a	K_i = 12.3
V2	K_i = 0.43
V1b	K_i > 100µM
OTR	K_i = 413

- approved for hyponatremia and autosomal dominant polycystic kidney disease (ADPKD)
- failed in EVEREST outcome trial in worsening HF
- immediate increase in AVP counteracting effects, despite clear short-term efficacy

selective V2

Mozavaptan[3)]



receptor binding [nM]

V1a	K_i = 195
V2	K_i = 9.7
V1b	K_i n.a.
OTR	K_i = 660

- approved for hyponatremia caused by syndrome of inappropriate antidiuretic hormone (SIADH)

- Marketed reference compounds are active on both the V1a and V2 receptor and are adressing either one receptor more pronounced than the other. Therefore, they cannot be considered as balanced inhibitors
- Reference compounds show also activity on the oxytocin (OTC) receptor

OTR = oxytocin receptor

1) Ali, F et.al. (2007), Cardiovascular Drug Reviews, 25: 261-279. https://doi.org/10.1111/j.1527-3466.2007.00019.x

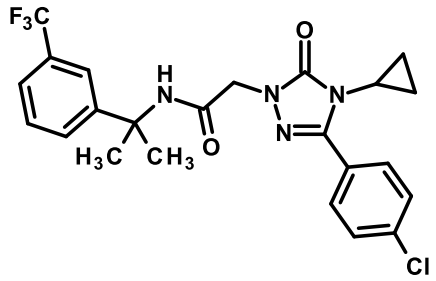
2) Miyazaki, T et.al. (2007), Cardiovascular Drug Reviews, 25: 1-13. https://doi.org/10.1111/j.1527-3466.2007.00001.x

3) Loison, S et. al., J. Med. Chem. 2012, 55, 20, 8588–8602

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Discovery and optimization trajectory

Initial Lead

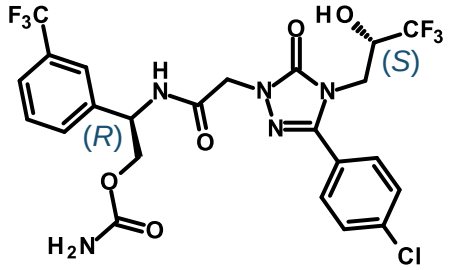


receptor binding [nM]
V1a K_i = 390
V2 K_i = 150
V1b K_i n.a.

OTR K_i n.a.

Ribuvaptan (BAY 868050)

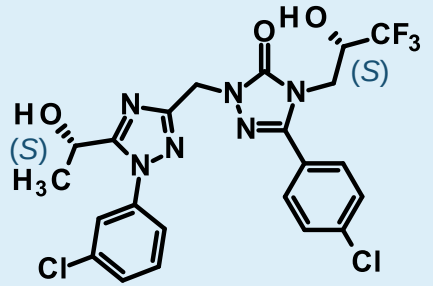
Donated by Bayer for Chemogenomic Library at EUbOPEN/SGC in 2023



receptor binding [nM]
V1a K_i = 4.4
V2 K_i = 29
V1b K_i n.a.

OTR K_i = 100

Pecavaptan (BAY 1753011)



receptor binding [nM]
V1a K_i = 0.5
V2 K_i = 0.6
V1b K_i > 10000

OTR K_i = 5.1

- Pecavaptan is a potent, balanced V1a/V2 receptor antagonist, which also shows activity on the oxytocin receptor
- Structurally differentiated from known vasopressin inhibitors
- Suitable for *in vitro* & *in vivo* investigations; good safety profile in clinical studies

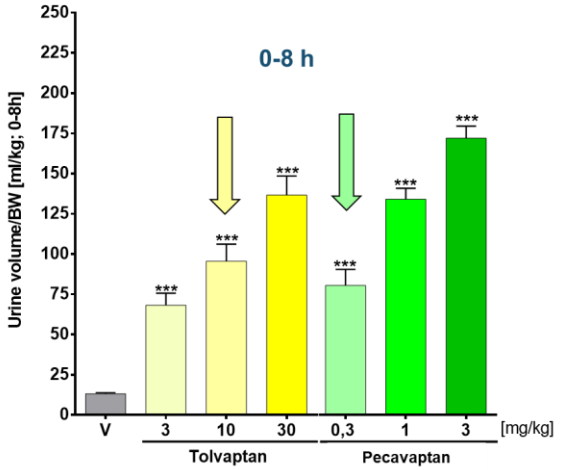
OTR = oxytocin receptor

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

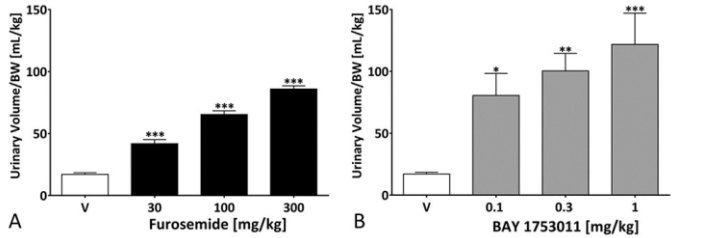
V2 receptor-mediated aquaretic effects in rats

Aquaretic effect with low dose 0.3 mg/kg pecavaptan comparable to 10 mg/kg tolvaptan

V2 assay	Species	Pecavaptan	Tolvaptan
cell based IC_{50} [nM]	human	1.7	1.1
	rat	0.7	0.6
binding IC_{50} [nM]	human	1.3	1.9
	rat	4.3	16

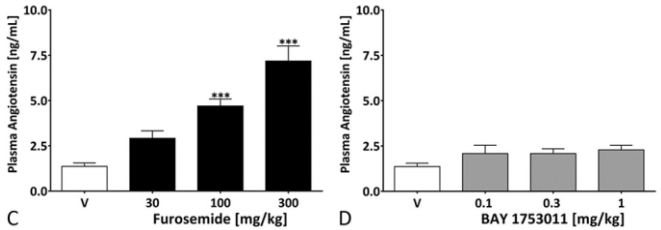


Furosemide (loop diuretic) **urinary volume** **Pecavaptan** (BAY 1753011)

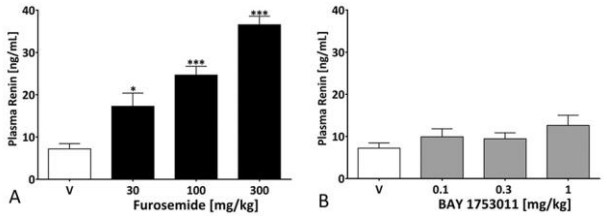


*P < 0.05, **P< 0.01, ***P < 0.005)

plasma renin



plasma angiotensin



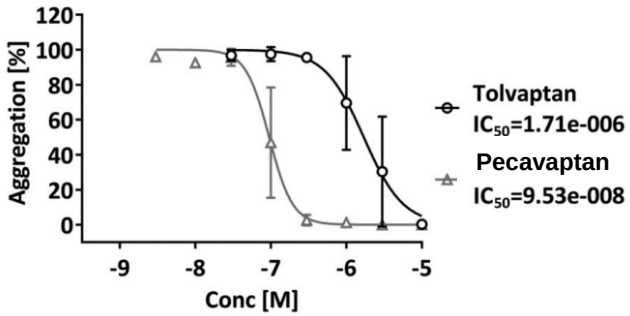
- Pecavaptan shows superior aquaretic effects in conscious rats, as compared to tolvaptan or furosemide
- No activation of RAAS by pecavaptan, in contrast to furosemide

Kolkhof *et al.*, *J. Cardiovasc. Pharmacol.* **2019**, *74*, 44–52

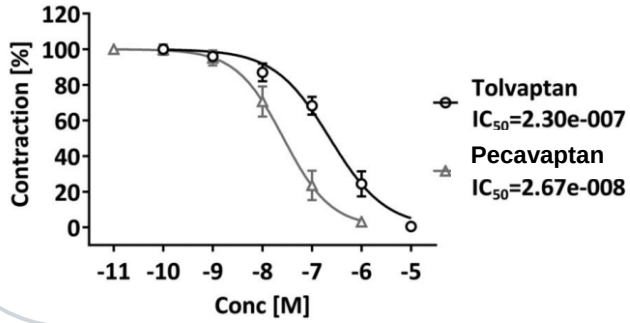
Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

V1a receptor-mediated functional effects

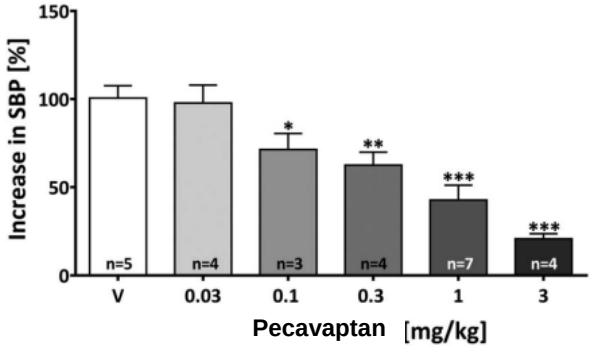
In vitro platelet (hum) aggregation



Inhibition of vasopressin-induced constriction of isolated rat aortic rings



Inhibition of vasopressin-induced rise in systolic blood pressure in anaesthetized rats



*P < 0.05, **P< 0.01, ***P < 0.005)

V1a assay	Species	Pecavaptan	Tolvaptan
cell based IC_{50} [nM]	human	3.6	21
	rat	53	310
binding IC_{50} [nM]	human	2.4	25
	rat*	160	1300

* unpublished

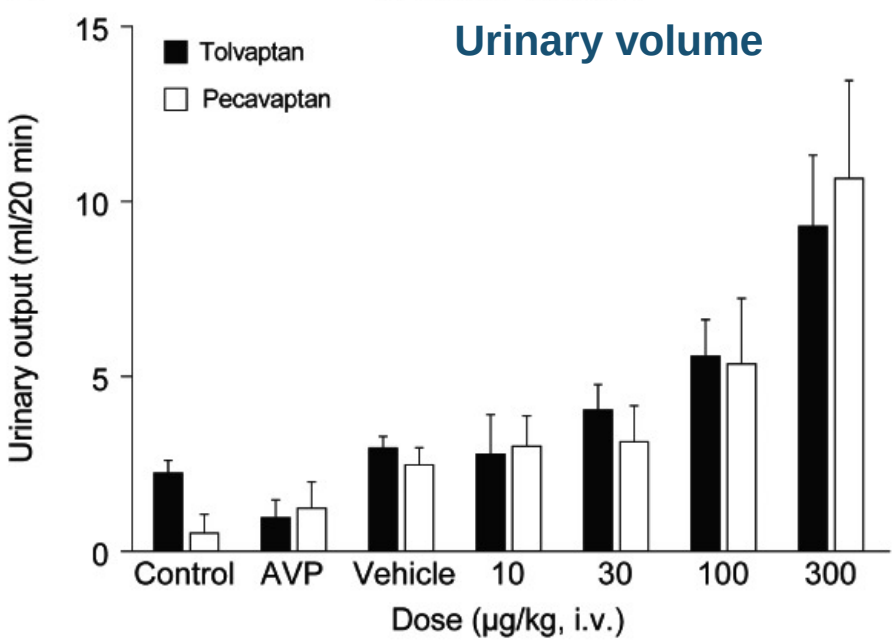
- Pecavaptan shows pronounced effects on human platelet aggregation and on vasopressin-induced vasoconstriction
- Dose-dependent reduction of vasopressin-induced blood pressure increase in rats

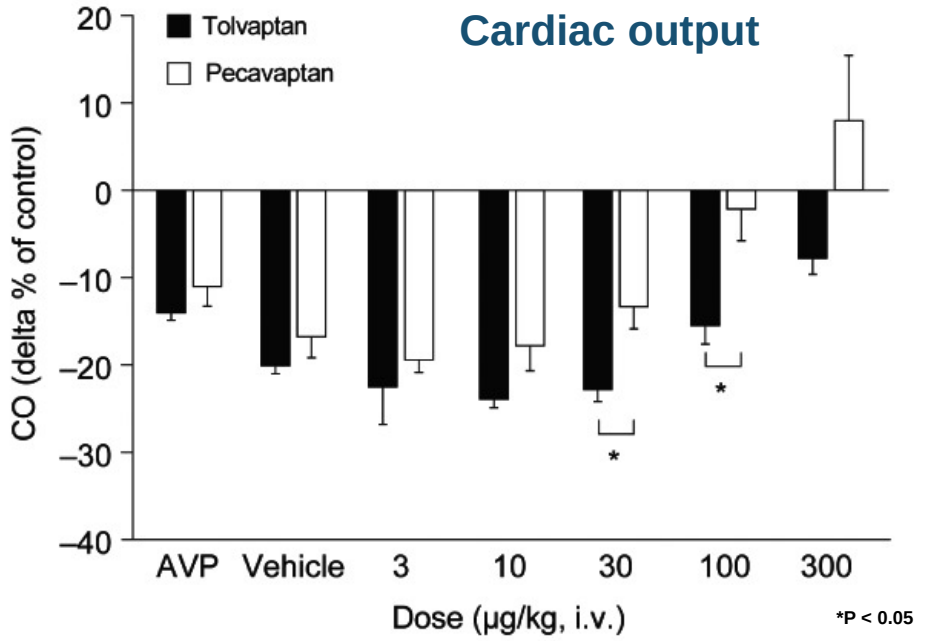
Kolkhof *et al.*, *J. Cardiovasc. Pharmacol.* **2019**, *74*, 44–52

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Heart failure disease model in dogs

AVP application to dogs with HF leads to reduced cardiac output



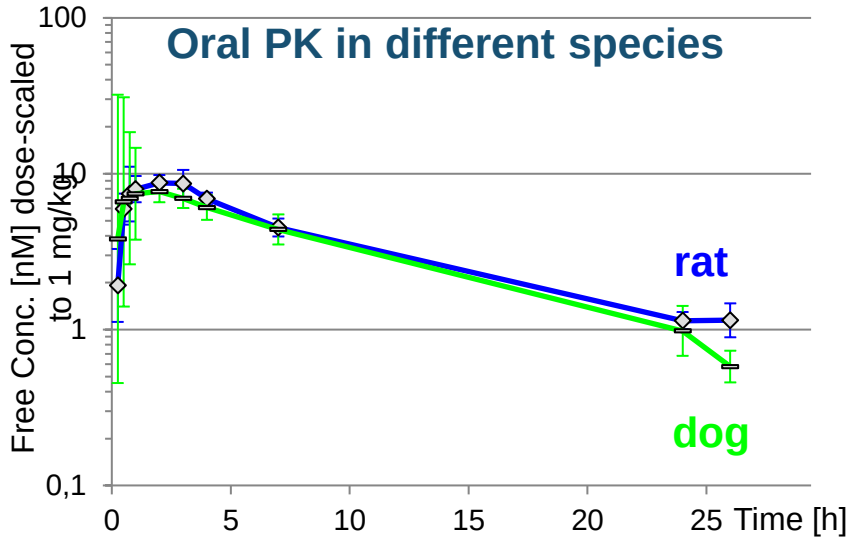


- Pecavaptan shows efficacious aquaresis in dogs with heart failure, with cardiac output maintained
- Differentiated cardiac output profile, as compared to Tolvaptan

Mondritzki *et al.*, *Eur. J. Heart Failure* **2021**, *23*, 743–750

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

In vivo Pharmacokinetics



Species		Rat	Dog
Strain		Wistar	Beagle
Sex		male	female
Dose equiv.	[mg/kg]	1.0	0.50
AUC_{norm}	[kg·h/L]	1.2	1.6
t_{max}	[h]	2.0	1.0
MRT	[h]	12	10
$t_{1/2}$	[h]	8.5	7.0
F	[%]	118	58
f_u	[%]	4.8	3.1

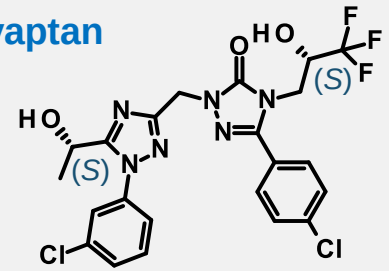
- Pecavaptan shows good oral PK in rats and dogs
- Well suited for *in vitro & in vivo* studies

Mondritzki *et al.*, *Eur. J. Heart Failure* **2021**, *23*, 743–750

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Technical in vitro profile

Pecavaptan



Structure confirmed by SMOL X-ray

Potency on hV1a und hV2 [nM]	
hV1a Receptor binding K_i [nM]	0.5
hV2 Receptor binding K_i [nM]	0.6
hV1a Cell-based IC_{50} [nM]	3.6
hV2 Cell-based IC_{50} [nM]	1.7

Physchem	
LogD @ pH 7.5	3.1
Sol @ pH 7.4 [g/L], cryst. material	108
MW / MW_{corr} / TPSA [g/mol / Å^2]	543.33 / 469.53 / 107.8
Stability (pH 1 / 7 / 10, 7 d, RT) [%]	100 / 100 / 100
Stability (r/h plasma 4 h, 37 °C) [%]	stable

in vitro DMPK Properties						
Caco2 permeability	P_{app}(A-B) [nm/s]		P_{app}(B-A) [nm/s]		efflux ratio	
	297		681		2.3	
Metabolic stability			CL [L/h/kg]		F_{max} [%]	
	rat hepatocytes		2.7		37	
	human hepatocytes		0.4		70	
CYP inhibition IC_{50} [µM]	1A2	2C8	2C9	2D6	3A4	3A4 preinc.
	> 20	19	> 20	> 20	> 20	> 20
CYP1A2 / 3A4 induction [µg/L]	No effect level (NOEL) > 370 / > 3333					

Selectivity / Safety / Tox	
hV1b receptor binding K_i [µM]	> 10
Oxytocin receptor binding K_i [nM]	5.1*
Kinase panel (378 kinases) IC_{50} [µM]	> 10 (NEK3: 61% Inh at 10 µM)
Panlabs safety screen of >120 targets @ 10 µM	Clean
Profiler of 6 ion channels IC_{50} [µM]	> 10
Ames	negative

* An oxytocin antagonist (Ki 4.6 nM, selectivity vs V1a and V2 ≥ 695 is available, see back-up for details

- Pecavaptan shows a benign overall profile

h = human, r = rat, d = dog

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Selectivity profile of Pecavaptan (Eurofins safety screen >120 assays & ion channel profiler) – **PART 1**

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.
Compound: CHH8-2014, PT #: 1178766						
200510	Adenosine A_1	348677	hum	2	10 µM	26
200610	Adenosine A_{2A}	348603	hum	2	10 µM	4
200720	Adenosine A_3	348657	hum	2	10 µM	16
203100	Adrenergic α_{1A}	348678	rat	2	10 µM	23
203200	Adrenergic α_{1B}	348532	rat	2	10 µM	3
203400	Adrenergic α_{1D}	348533	hum	2	10 µM	1
203630	Adrenergic α_{2A}	348604	hum	2	10 µM	3
204010	Adrenergic β_1	348596	hum	2	10 µM	5
204110	Adrenergic β_2	348513	hum	2	10 µM	9
206000	Androgen (Testosterone)	348531	hum	2	10 µM	12
212510	Bradykinin B_1	348487	hum	2	10 µM	0
212620	Bradykinin B_2	348488	hum	2	10 µM	1
214510	Calcium Channel L-Type, Benzothiazepine	348679	rat	2	10 µM	35
214600	Calcium Channel L-Type, Dihydropyridine	348481	rat	2	10 µM	37
216000	Calcium Channel N-Type	348536	rat	2	10 µM	-2
217030	Cannabinoid CB_1	348607	hum	2	10 µM	34
219500	Dopamine D_1	348608	hum	2	10 µM	1
219700	Dopamine D_{2S}	348691	hum	2	10 µM	14
219800	Dopamine D_3	348732	hum	2	10 µM	26
219900	Dopamine $D_{4.2}$	348473	hum	2	10 µM	3
224010	Endothelin ET_A	348665	hum	2	10 µM	18
224110	Endothelin ET_B	348666	hum	2	10 µM	5
225510	Epidermal Growth Factor (EGF)	348479	hum	2	10 µM	14
226010	Estrogen ERα	348537	hum	2	10 µM	8
226600	$GABA_A$, Flunitrazepam, Central	348609	rat	2	10 µM	-1
226500	$GABA_A$, Muscimol, Central	348482	rat	2	10 µM	-2
228610	$GABA_{B1A}$	348538	hum	2	10 µM	-4
232030	Glucocorticoid	348529	hum	2	10 µM	1
232700	Glutamate, Kainate	348688	rat	2	10 µM	-4
232810	Glutamate, NMDA, Agonism	348528	rat	2	10 µM	2
232910	Glutamate, NMDA, Glycine	348669	rat	2	10 µM	-10
233000	Glutamate, NMDA, Phencyclidine	348539	rat	2	10 µM	14
239610	Histamine H_1	348610	hum	2	10 µM	-1
239710	Histamine H_2	348507	hum	2	10 µM	-17

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.
239820	Histamine H_3	348664	hum	2	10 µM	-1
241000	Imidazoline I_2, Central	348483	rat	2	10 µM	21
243520	Interleukin IL-1	348709	mouse	2	10 µM	15
250460	Leukotriene, Cysteinyl $CysLT_1$	348526	hum	2	10 µM	5
251600	Melatonin MT_1	348667	hum	2	10 µM	-6
252610	Muscarinic M_1	348611	hum	2	10 µM	-5
252710	Muscarinic M_2	348611	hum	2	10 µM	7
252810	Muscarinic M_3	348612	hum	2	10 µM	8
257010	Neuropeptide Y Y_1	348692	hum	2	10 µM	11
257110	Neuropeptide Y Y_2	348511	hum	2	10 µM	6
258590	Nicotinic Acetylcholine	348598	hum	2	10 µM	-6
258700	Nicotinic Acetylcholine α1, Bungarotoxin	348693	hum	2	10 µM	-25
260130	Opiate δ_1 (OP1, DOP)	348694	hum	2	10 µM	4
260210	Opiate κ(OP2, KOP)	348600	hum	2	10 µM	19
260410	Opiate µ(OP3, MOP)	348613	hum	2	10 µM	24
264500	Phorbol Ester	348484	mouse	2	10 µM	3
265010	Platelet Activating Factor (PAF)	348544	hum	2	10 µM	17
265600	Potassium Channel [K_{ATP}]	348540	ham	2	10 µM	18
265900	Potassium Channel hERG	348492	hum	2	10 µM	-3
268420	Prostanoid EP_4	348521	hum	2	10 µM	16
268700	Purinergic P2X	348668	rabbit	2	10 µM	18
268810	Purinergic P2Y	348614	rat	2	10 µM	0
270000	Rolipram	348485	rat	2	10 µM	-2
271110	Serotonin (5-Hydroxytryptamine) 5-HT_{1A}	348695	hum	2	10 µM	-2
271700	Serotonin (5-Hydroxytryptamine) 5-HT_{2B}	348616	hum	2	10 µM	52
271910	Serotonin (5-Hydroxytryptamine) 5-HT_3	348696	hum	2	10 µM	-2
278110	Sigma σ_1	348486	hum	2	10 µM	15
279510	Sodium Channel, Site 2	348601	rat	2	10 µM	42
255520	Tachykinin NK_1	348599	hum	2	10 µM	20
285900	Thyroid Hormone	348541	rat	2	10 µM	6
220320	Transporter, Dopamine (DAT)	348595	hum	2	10 µM	4
226400	Transporter, GABA	348530	rat	2	10 µM	8
204410	Transporter, Norepinephrine (NET)	348594	hum	2	10 µM	62
274030	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	348697	hum	2	10 µM	6

Cat #	Assay Name	Species	Conc.	% Inh.	IC_{50}*	K_i	n_H
260900	Oxytocin	hum	0.1 µM	84	15.5 nM	5.06 nM	0.89

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC_{50}*	K_i	n_H
Compound: BR-6819, PT #: 1177825									
260900	Oxytocin	346475	hum	2	1 µM	95	15.5 nM	5.06 nM	0.89
			hum	2	0.1 µM	84			
			hum	2	10 nM	41			
			hum	2	1 nM	6			
			hum	2	0.1 nM	3			

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Selectivity profile of Pecavaptan (Eurofins safety screen >120 assays & ion channel profiler) – **PART 2**

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.
Compound: CHH8-2014, PT #: 1178766						
107000	Aldose Reductase	357076	rat	2	10 µM	6
107710	ATPase, Na^+/K^+, Heart, Pig	356625	pig	2	10 µM	0
126000	Beta-Lactamase	357078	ba	2	10 µM	-17
112020	Carbonic Anhydrase II	356720	hum	2	10 µM	-4
104010	Cholinesterase, Acetyl, ACES	356403	hum	2	10 µM	2
116020	Cyclooxygenase COX-1	356383	hum	2	10 µM	-3
118010	Cyclooxygenase COX-2	356384	hum	2	10 µM	-12
124010	HMG-CoA Reductase	356579	hum	2	10 µM	9
132000	Leukotriene LTC_4 Synthase	357080	gp	2	10 µM	13
138000	Lipoxygenase 15-LO	356628	rabbit	2	10 µM	4
140010	Monoamine Oxidase MAO-A	356404	hum	2	10 µM	-3
144000	Nitric Oxide Synthase, Inducible (iNOS)	356304	mouse	2	10 µM	-1
142000	Nitric Oxide Synthase, Neuronal (nNOS)	356302	rat	2	10 µM	10
107300	Peptidase, Angiotensin Converting Enzyme	356624	rabbit	2	10 µM	2
163000	Peptidase, CASP1 (Caspase 1)	356292	hum	2	10 µM	0
112510	Peptidase, CTSG (Cathepsin G)	356279	hum	2	10 µM	0
166010	Peptidase, ELA2 (Neutrophil Elastase 2)	356312	hum	2	10 µM	1
114110	Peptidase, Matrix Metalloproteinase-1 (MMP-1)	356712	hum	2	10 µM	3
114910	Peptidase, Matrix Metalloproteinase-9 (MMP-9)	356287	hum	2	10 µM	-2
152000	Phosphodiesterase PDE3	356389	hum	2	10 µM	0
154000	Phosphodiesterase PDE4	356593	hum	2	10 µM	-4
156000	Phosphodiesterase PDE5	356594	hum	2	10 µM	-10
171120	Protein Serine/Threonine Kinase, MAPK1 (ERK2)	356407	hum	2	10 µM	-2
176610	Protein Serine/Threonine Kinase, MAPK14 (p38α)	356340	hum	2	10 µM	-1
171000	Protein Serine/Threonine Kinase, MAPK3 (ERK1)	356326	hum	2	10 µM	-7
180010	Protein Serine/Threonine Kinase, PRKCA (PKCα)	356345	hum	2	10 µM	-2
188020	Protein Serine/Threonine Phosphatase, PPP3CA (Calcineurin, PP2B)	356347	hum	2	10 µM	32
170020	Protein Tyrosine Kinase, EGF Receptor	356324	hum	2	10 µM	-6
174020	Protein Tyrosine Kinase, ERBB2 (HER2)	356335	hum	2	10 µM	15
172020	Protein Tyrosine Kinase, Fyn	356334	hum	2	10 µM	-6
176020	Protein Tyrosine Kinase, LCK	356621	hum	2	10 µM	-9

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.
190010	Protein Tyrosine Phosphatase, PTPRC (CD45)	356410	hum	2	10 µM	0
194020	Thromboxane Synthase	356575	hum	2	10 µM	-6
203710	Adrenergic α_{2B}	356488	hum	2	10 µM	8
203810	Adrenergic α_{2C}	356489	hum	2	10 µM	11
204200	Adrenergic β_3	356363	hum	2	10 µM	-10
210120	Angiotensin AT_2	356790	hum	2	10 µM	4
211000	Atrial Natriuretic Factor (ANF)	356497	gp	2	10 µM	1
213610	Calcitonin	356969	hum	2	10 µM	-7
215000	Calcium Channel L-Type, Phenylalkylamine	356366	rat	2	10 µM	22
217550	Chemokine CCR2B	356975	hum	2	10 µM	2
217660	Chemokine CCR4	356972	hum	2	10 µM	-2
217720	Chemokine CCR5	356973	hum	2	10 µM	-3
244500	Chemokine CXCR2 (IL-$8R_B$)	356514	hum	2	10 µM	-6
218020	Cholecystokinin CCK_1 (CCK_A)	356502	hum	2	10 µM	15
219600	Dopamine D_{2L}	356532	hum	2	10 µM	14
226810	$GABA_A$, Chloride Channel, TBOB	356510	rat	2	10 µM	30
232600	Glutamate, AMPA	356362	rat	2	10 µM	2
239000	Glycine, Strychnine-Sensitive	356693	rat	2	10 µM	12
243000	Insulin	356642	rat	2	10 µM	-1
251300	Melanocortin MC_3	356421	hum	2	10 µM	6
251350	Melanocortin MC_4	356420	hum	2	10 µM	4
251400	Melanocortin MC_5	356421	hum	2	10 µM	13
252910	Muscarinic M_4	356521	hum	2	10 µM	7
253010	Muscarinic M_5	356521	hum	2	10 µM	6
265200	Platelet-Derived Growth Factor (PDGF)	356638	mouse	2	10 µM	5
268020	Progesterone PR-B	356527	hum	2	10 µM	0
271200	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{1B}$	356445	rat	2	10 µM	-5
271800	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2C}$	356443	hum	2	10 µM	20
272000	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_4$	356827	gp	2	10 µM	19
272200	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_6$	356379	hum	2	10 µM	4
278200	Sigma σ_2	356745	rat	2	10 µM	5
255600	Tachykinin NK_2	356454	hum	2	10 µM	30
202000	Transporter, Adenosine	356483	gp	2	10 µM	21
286510	Tumor Necrosis Factor (TNF), Non-Selective	356948	hum	2	10 µM	-1
287010	Vasoactive Intestinal Peptide VIP_1	356425	hum	2	10 µM	10

Cat #	Assay Name	Species	Conc.	% Inh.	IC_{50}*	K_i	n_H
287530	Vasopressin V_{1A}	hum	10 nM	65	6.74 nM	1.33 nM	1.49

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC_{50}*
287560	Vasopressin V_{1B}	353830	hum	2	10 µM	43	>10.0 µM
			hum	2	1 µM	5	
			hum	2	0.1 µM	-5	
			hum	2	10 nM	-6	
			hum	2	1 nM	6	

Inhouse ion channel profiler: all IC_{50} > 10 µM

hKir2.1
hKvLQT1
hNav1.5
hCav1.2
hKv4.3
hERG

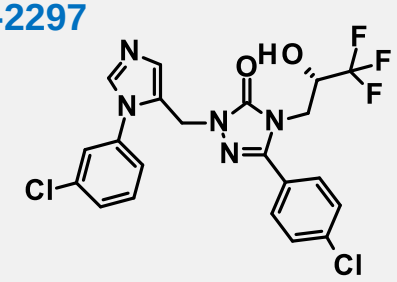
Pecavaptan shows clean off-target profile

- Safety screen (> 120 targets)
- Ion channel profiler of 6 ion channels
- Panel of 378 kinases (see backup)

Dual V1a/V2 Receptor Antagonist Probe

In vitro profile of negative control BAY-2297

BAY-2297



Potency on hV1a und hV2 [nM]	
hV1a Receptor binding IC_{50} [µM]	> 10
hV2 Receptor binding IC_{50} [µM]	> 10
hV1a Cell-based IC_{50} [µM]	> 10
hV2 Cell-based IC_{50} [µM]	> 10

Physchem	
LogD @ pH 7.5	2.7
Sol @ pH 7.4 [g/L], cryst. material	263
MW / MW_{corr} / TPSA [g/mol / Å^2]	481.83 / 410.43 / 73.96
Stability (pH 1 / 7 / 10, 24 h, 37 °C) [%]	100 / 100 / 99
Stability (r/h plasma 4 h, 37 °C) [%]	100 / 100

in vitro DMPK Properties						
Caco2 permeability	P_{app}(A-B) [nm/s]		P_{app}(B-A) [nm/s]		efflux ratio	
	197		169		0.86	
Metabolic stability			CL [L/h/kg]		F_{max} [%]	
	rat hepatocytes		3.8		8.9	
	human hepatocytes		n.d.		n.d.	
CYP inhibition IC_{50} [µM]	1A2	2C8	2C9	2D6	3A4	3A4 preinc.
	8.2	0.49	5.5	1.9	0.33	0.34
CYP1A2 & 3A4 induction [µM]	n.d.					

Selectivity / Safety	
hV1b receptor binding IC_{50} [µM]	> 10
Oxytocin receptor binding IC_{50} [µM]	> 10
Kinase panel (378 kinases) IC_{50} [µM]	> 10
Panlabs safety screen of 80 targets @ 10 µM	clean
Profiler of 5 ion channels IC_{50} [µM]	> 10

n.d. = not determined
h = human, r = rat, d = dog

- Negative control BAY-2297 is inactive on target family members and shows a clean off-target profile

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Summary / Conclusion

Probe criteria	
Inhibitor potency: goal is < 100 nM (IC_{50})	**Meets criteria** Receptor binding hV1a K_i 0.5 nM, hV2 K_i 0.6 nM; Balanced profile Cell-based hV1a IC_{50}: 3.6 nM, hV2 IC_{50}: 1.7 nM
Selectivity within target family: goal is > 30-fold	**Comparable profile to closest reference conivaptan** Selectivity factors versus vasopressin receptor V1b > 1000-fold Selectivity factor versus oxytocin receptor: 10-fold, an oxytocin antagonist (Ki 4.6 nM, selectivity vs V1a and V2 > 695 is available, see back-up for details
Selectivity outside target family: describe the off-targets (which may include both binding and functional data)	**Meets criteria** Clean selectivity profile in a panel of > 120 targets, plus 378 kinases
On target cell activity for cell-based targets: goal is < 1 µM IC_{50}/EC_{50}	**Meets criteria** Cell-based hV1a IC_{50}: 3.6 nM; hV2 IC_{50}: 1.7 nM
On target cell activity for secreted targets: appropriate alternative such as mouse model or other mechanistic biological assay, e.g., explant culture	**Meets criteria** Functional readouts mediated by V1a receptor (platelet aggregation, vasoconstriction, blood pressure) and V2 receptor (diuresis) Well suited for *in vitro* & *in vivo* studies
Neg ctrl: *in vitro* potency – > 100 times less; Cell activity – >100 times less potent than the probe	**Meets criteria** Negative control BAY-2297 is > 1000-fold less active than probe pecavaptan

We ask for acceptance of dual V1a/V2 receptor antagonist pecavaptan (BAY 1753011) as chemical probe, accompanied by BAY-2297 as negative control

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Project team / Acknowledgement

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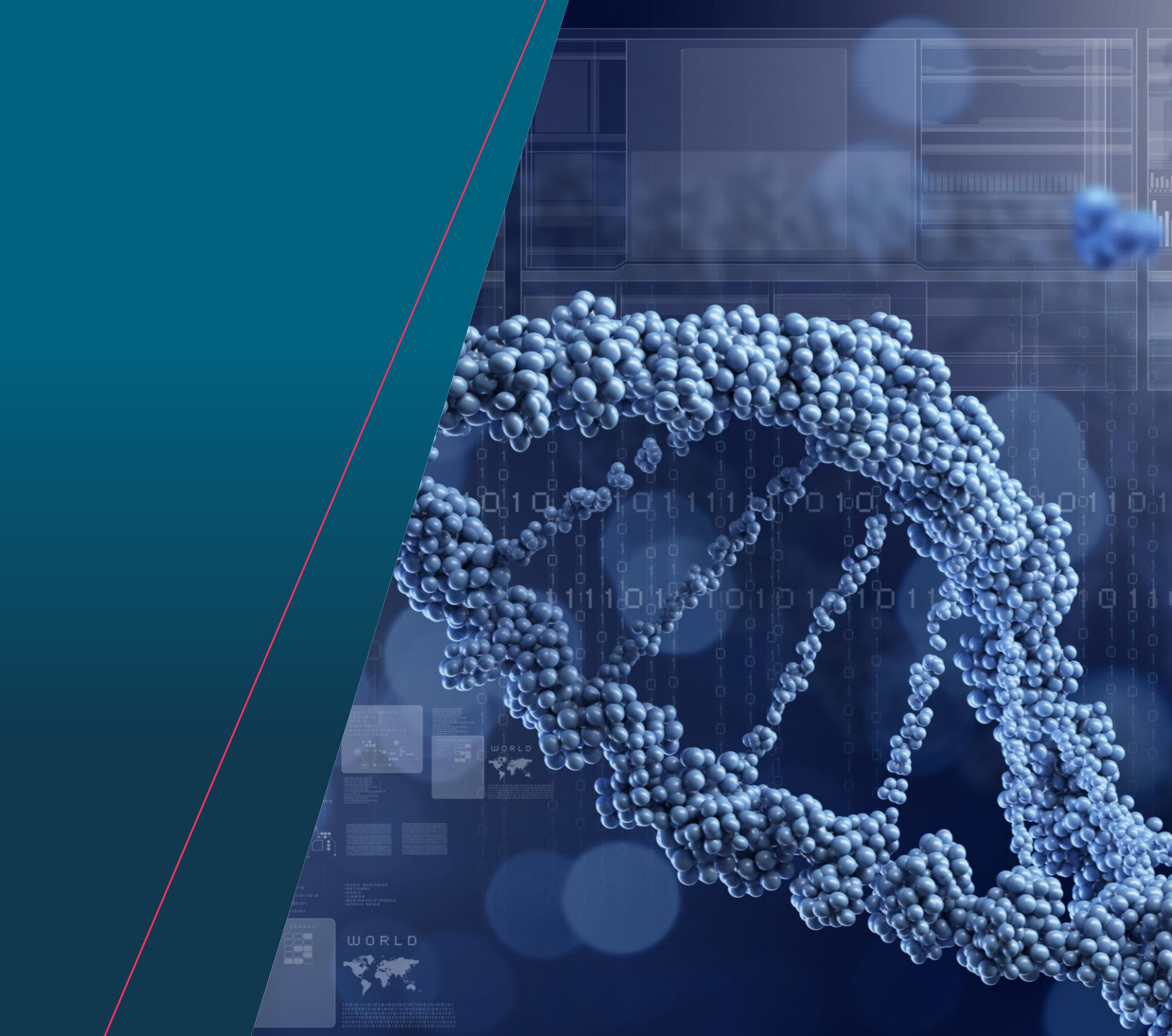
and ***Peter Kolkhof***

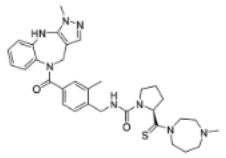
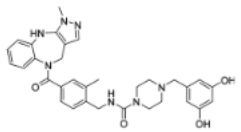
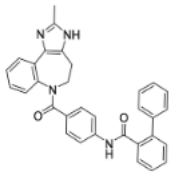
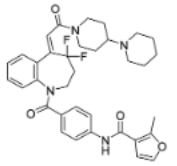
…and to all colleagues involved in research and development

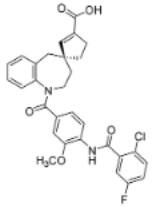
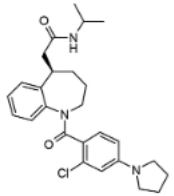
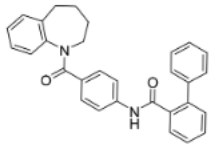
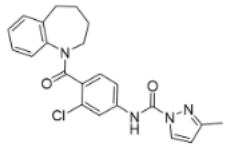
Thank You



Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Overview on other Vasopressin Receptor Antagonists

Name[ref]	Structure	Affinity (K_i or IC_{50}, nM) and/or function (agonist: EC_{50}, nM; antagonist: IC_{50}, nM)			
		V_{1a}-R	V_{1b}-R	V_2-R	OT-R
Ferring[48]		$K_i = 330$[49]		$EC_{50} = 850$[48,a] $K_i > 1000$[49]	$EC_{50} = 33$[48,a] $K_i = 147$[49]
WAY-267464[40,51]		$K_i > 1000$[40] $K_i = 113$[51]	$K_i > 1000$[40]	$K_i > 1000$[40]	$K_i = 58.4$[40] $EC_{50} = 61.3$[40,b] $K_i = 978$[51]
YM087 or Conivaptan[54]		$K_i = 0.48$[54]	>10000[54]	$K_i = 3.04$[54]	$K_i = 44.4$[54]
YM218[55]		$K_i = 0.30$[55]	$K_i = 25500$[55]	$K_i = 381$[55]	$K_i = 71$[55]

Name[ref]	Structure	Affinity (K_i or IC_{50}, nM) and/or function (agonist: EC_{50}, nM; antagonist: IC_{50}, nM)			
		V_{1a}-R	V_{1b}-R	V_2-R	OT-R
JNJ17158063[56]		$IC_{50} = 5$[56]		$IC_{50} = 34$[56]	
OPC-51803[57]		$K_i = 819$[57]	$IC_{50} > 100$ μM[57]	$K_i = 91.9$[57] $EC_{50} = 189$ nM[57]	nd[c]
Yamanouchi[58]		$IC_{50} = 2.74$	nd[c]	$IC_{50} = 0.57$	$IC_{50} = 109$
Otsuka[59]		$IC_{50} = 19$	>1000	$IC_{50} = 13$ Agonist $EC_{50} = 4.0$	$IC_{50} = 37.0$

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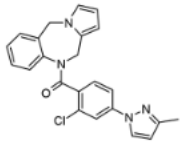
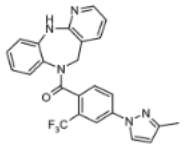
Journal of Medicinal Chemistry **2018** *61* (19), 8670-8692
DOI: 10.1021/acs.jmedchem.8b00697

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Overview on other Vasopressin Receptor Antagonists

Name[ref]	Structure	Affinity (K_i or IC_{50}, nM) and/or function (agonist: EC_{50}, nM; antagonist: IC_{50}, nM)			
		V_{1a}-R	V_{1b}-R	V_2-R	OT-R
WAY-VNA-932[60]		K_i = 465 antagonist IC_{50} = 1660[d]	K_i >1 µM	K_i = 39.9 agonist EC_{50} = 0.7[d]	K_i = 125 antagonist IC_{50} = 55[e]
WAY-141608[61]		IC_{50} = 5954 antagonist IC_{50} > 30 µM[e]	No activity	IC_{50} = 493 agonist EC_{50} = 1.7[d]	nd antagonist IC_{50} =1259[e]

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Journal of Medicinal Chemistry **2018** *61* (19), 8670-8692
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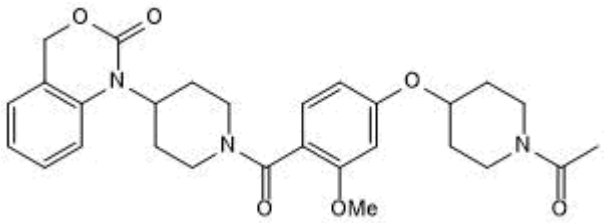
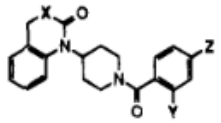
Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

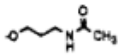
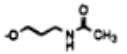
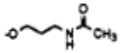
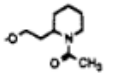
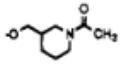
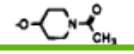
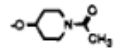
Oxytocin receptor antagonist with selectivity towards V1a and V2



Commercially available from TOCRIS

Table 1. Rat and Human OT/AVP Receptor Affinities



cmpd	X	Y	Z	K_i (nM)[a] OT: rat uterus / human uterus	AVP-V_{1a}: rat liver / human platelet	AVP-V_2: rat kidney / human kidney
1 (OPC 21268)	CH_2	H		230 ± 35 170 ± 49	32 ± 5.2 52,000 (14,000; 11,000)[b]	≥30,000 >81,000
2	NH	H		2,400 2,100	>1,000 62,000	>3,000 [c]
3	O	H		200 ± 12 130	31 ± 5.4 36,000	35,000 [c]
4[d]	O	H		130 150	15 22,000	11,000 [c]
5[d]	O	H		340 200	24 38,000	11,000 [c]
6	O	H		69 ± 22 24	5.6 12,000	35,000 [c]
7 (L-371,257)	O	OCH_3		19 ± 2.1 4.6 ± 0.25	3.7 ± 0.79 3,200 ± 82	≥30,000 37,000 ± 5,500

[a] Radioligand binding assays were performed as described in refs 15 and 17. K_i values are reported as group means ±SEM for compounds for which there were at least three separate determinations. OT column: displacement of [^{3}H]OT from specific binding sites in uterine tissue obtained from diethylstilbestrol propionate-pretreated rats or pregnant non-labor women undergoing cesarean section at 38−39 weeks gestation. AVP-V_{1a} column: displacement of [^{3}H]AVP from specific binding sites in rat liver or human platelets. AVP-V_2 column: displacement of [^{3}H]AVP from specific binding sites in kidney medulla obtained from rats or early postmortem human donors. [b] K_i values for inhibition of [^{3}H]AVP binding to AVP-V_{1a} sites in human liver and human uterus, respectively (ref 17). [c] Not determined. [d] Compound is racemic.

Williams PD, Clineschmidt BV, Erb JM, Freidinger RM, Guidotti MT, Lis EV, Pawluczyk JM, Pettibone DJ, Reiss DR, Veber DF, et al. 1-(1-[4-[(N-acetyl-4-piperidinyl)oxy]-2-methoxybenzoyl]piperidin-4- yl)-4H-3,1-benzoxazin-2(1H)-one (L-371,257): a new, orally bioavailable, non-peptide oxytocin antagonist. J Med Chem. 1995 Nov 10;38(23):4634-6. doi: 10.1021/jm00023a002. PMID: 7473590.

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Cell-based assay description in more detail

Cellular *in vitro* assay for determining vasopressin receptor activity

The identification of agonists and antagonists of the V1a and V2 vasopressin receptors from humans, rats and dogs as well as the quantification of the activity of the compounds of the invention is carried out using recombinant cell lines. These cell lines originally derive from a hamster's ovary epithelial cell (Chinese Hamster Ovary, CHO K1, ATCC: American Type Culture Collection, Manassas, VA 20108, USA). The test cell lines constitutively express the human, rat or dog V1a or V2 receptors. In case of the $G_{\alpha q}$-coupled V1a receptors, cells are also stably transfected with a modified form of the calcium-sensitive photoproteins aequorin (human and rat V1a) or obelin (dog V1a), which, after reconstitution with the cofactor coelenterazine, emit light when there are increases in free calcium concentrations [Rizzuto R, Simpson AW, Brini M, Pozzan T, *Nature* 358, 325-327 (1992); Illarionov BA, Bondar VS, Illarionova VA, Vysotski ES, *Gene* 153 (2), 273-274 (1995)]. The resulting vasopressin receptor cells react to stimulation of the recombinantly expressed V1a receptors by intracellular release of calcium ions, which can be quantified by the resulting photoprotein luminescence. The G_s-coupled V2 receptors are stably transfected into cell lines expressing the gene for firefly luciferase under control of a CRE-responsible promoter. Activation of V2 receptors induces the activation of the CRE-responsive promoter *via* cAMP increase, thereby inducing the expression of firefly luciferase. The light emitted by photoproteins of V1a cell lines as well as the light emitted by firefly luciferase of V2 cell lines corresponds to the activation or inhibition of the respective vasopressin receptor. The bioluminescence of the cell lines is detected using a suitable luminometer [Milligan G, Marshall F, Rees S, *Trends in Pharmacological Sciences* 17, 235-237 (1996)].

Test procedure:

Vasopressin V1a receptor cell lines:

On the day before the assay, the cells are plated out in culture medium (DMEM/F12, 2% FCS, 2 mM glutamine, 10 mM HEPES, 5 µg/ml coelenterazine) in 384-well microtiter plates and kept in a cell incubator (96% humidity, 5% v/v CO_2, 37°C). On the day of the assay, test compounds in various concentrations are placed for 10 minutes in the wells of the microtiter plate before the agonist [Arg^8]-vasopressin at EC_{50} concentration is added. The resulting light signal is measured immediately in the luminometer.

Vasopressin V2 receptor cell lines:

On the day before the assay, the cells are plated out in culture medium (DMEM/F12, 2% FCS, 2 mM glutamine, 10 mM HEPES) in 384-well microtiter plates and kept in a cell incubator (96% humidity, 5% v/v CO_2, 37°C). On the day of the assay, test compounds in various concentrations and the agonist [Arg^8]-vasopressin at EC_{50} concentration are added together to the wells, and plates are incubated for 3 hours in a cell incubator. Upon addition of the cell lysis reagent Triton™ and the substrate luciferin, luminescence of firefly luciferase is measured in a luminometer.

Dual V1a/V2 Receptor Antagonist Probe

Eurofins kinase panel (378 kinases), inhibition >10% for pecavaptan & negative control BAY-2297

Compound	Kinase	ATP Conc. [mol/L]	Concentration [mol/L]	Inhibition [%]
Pecavaptan	NEK3(h)	1.0E-05	1.0E-05	60.98
Pecavaptan	PKCepsilon(h)	1.0E-05	1.0E-05	19.08
Pecavaptan	PKCzeta(h)	1.0E-05	1.0E-05	18.7
Pecavaptan	ROCK-II(h)	1.0E-05	1.0E-05	18.07
Pecavaptan	NEK11(h)	1.0E-05	1.0E-05	16.19
Pecavaptan	DYRK1B(h)	1.0E-05	1.0E-05	15.81
Pecavaptan	PI3 Kinase (p120g)(h)	1.0E-05	1.0E-05	14.13
Pecavaptan	GCN2(h)	1.0E-05	1.0E-05	13.11
Pecavaptan	NEK4(h)	1.0E-05	1.0E-05	13.07
Pecavaptan	DMPK(h)	1.0E-05	1.0E-05	12.73
Pecavaptan	VRK1(h)	1.0E-05	1.0E-05	12.27
Pecavaptan	PI3KC2a(h)	1.0E-05	1.0E-05	11.58
Pecavaptan	PRAK(h)	1.0E-05	1.0E-05	11.45
Pecavaptan	MLK3(h)	1.0E-05	1.0E-05	11.35
Pecavaptan	Aurora-A(h)	1.0E-05	1.0E-05	11.17
Pecavaptan	BMPR2(h)	1.0E-05	1.0E-05	11.12
Pecavaptan	MAPK2(h)	1.0E-05	1.0E-05	11.11
Pecavaptan	ULK3(h)	1.0E-05	1.0E-05	10.92
Pecavaptan	MELK(h)	1.0E-05	1.0E-05	10.8
Pecavaptan	WNK4(h)	1.0E-05	1.0E-05	10.52
Pecavaptan	GAK(h)	1.0E-05	1.0E-05	10.44
Pecavaptan	CaMKIV(h)	1.0E-05	1.0E-05	10.35

Compound	Kinase	ATP Conc. [mol/L]	Concentration [mol/L]	Inhibition [%]
BAY-2297	PI3KC2a(h)	1.0E-05	1.0E-05	27.49
BAY-2297	PRK2(h)	1.0E-05	1.0E-05	27.4
BAY-2297	IRE1(h)	1.0E-05	1.0E-05	19.25
BAY-2297	NEK11(h)	1.0E-05	1.0E-05	15.84
BAY-2297	VRK1(h)	1.0E-05	1.0E-05	15.71
BAY-2297	DYRK1B(h)	1.0E-05	1.0E-05	15.38
BAY-2297	MLK3(h)	1.0E-05	1.0E-05	14.87
BAY-2297	PKCtheta(h)	1.0E-05	1.0E-05	14.54
BAY-2297	BMPR2(h)	1.0E-05	1.0E-05	14.38
BAY-2297	JNK3(h)	1.0E-05	1.0E-05	13.23
BAY-2297	Aurora-A(h)	1.0E-05	1.0E-05	12.7
BAY-2297	GCN2(h)	1.0E-05	1.0E-05	12.42
BAY-2297	DAPK2(h)	1.0E-05	1.0E-05	11.7
BAY-2297	Flt4(h)	1.0E-05	1.0E-05	11.34
BAY-2297	MAPK2(h)	1.0E-05	1.0E-05	11.3
BAY-2297	PKCepsilon(h)	1.0E-05	1.0E-05	10.98
BAY-2297	PKCeta(h)	1.0E-05	1.0E-05	10.79
BAY-2297	Plk4(h)	1.0E-05	1.0E-05	10.64
BAY-2297	VRK2(h)	1.0E-05	1.0E-05	10.42
BAY-2297	LOK(h)	1.0E-05	1.0E-05	10.39
BAY-2297	LRRK2(h)	1.0E-05	1.0E-05	10.35
BAY-2297	ATR/ATRIP(h)	1.0E-05	1.0E-05	10.2

Dual V1a/V2 Receptor Antagonist Probe

Selectivity profile of negative control BAY-2297 (Eurofins safety screen, 80 assays & ion channel profiler)

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.
Compound: CHH043-2023, PT #: 1278374						
107010	Aldose Reductase	507622	hum	2	10 µM	15
107710	ATPase, Na^+/K^+, Heart, Pig	507595	pig	2	10 µM	-1
112020	Carbonic Anhydrase II	507596	hum	2	10 µM	-1
104010	Cholinesterase, Acetyl, ACES	507630	hum	2	10 µM	2
116030	Cyclooxygenase COX-1	507689	hum	2	10 µM	11
118030	Cyclooxygenase COX-2	507690	hum	2	10 µM	0
124010	HMG-CoA Reductase	507691	hum	2	10 µM	-18
132000	Leukotriene LTC_4 Synthase	507629	gp	2	10 µM	6
199020	Lipoxygenase 15-LOX-2	507598	hum	2	10 µM	-3
140010	Monoamine Oxidase MAO-A	507624	hum	2	10 µM	2
140120	Monoamine Oxidase MAO-B	507625	hum	2	10 µM	28
142000	Nitric Oxide Synthase, Neuronal (nNOS)	507694	rat	2	10 µM	-6
199010	Nitric Oxide Synthetase, Inducible (iNOS)	507631	mouse	2	10 µM	5
107310	Peptidase, Angiotensin Converting Enzyme	507682	hum	2	10 µM	-16
152300	Phosphodiesterase PDE3A	507586	hum	2	10 µM	-6
154420	Phosphodiesterase PDE4D2	507587	hum	2	10 µM	4
156020	Phosphodiesterase PDE5A	507588	hum	2	10 µM	31
194020	Thromboxane Synthase	507748	hum	2	10 µM	12
200510	Adenosine A_1	507634	hum	2	10 µM	8
200610	Adenosine A_{2A}	507634	hum	2	10 µM	1
200720	Adenosine A_3	507700	hum	2	10 µM	7
203110	Adrenergic α_{1A}	507604	hum	2	10 µM	3
203630	Adrenergic α_{2A}	507615	hum	2	10 µM	5
203710	Adrenergic α_{2B}	507678	hum	2	10 µM	2
203810	Adrenergic α_{2C}	507617	hum	2	10 µM	-3
204010	Adrenergic β_1	507672	hum	2	10 µM	5
204110	Adrenergic β_2	507617	hum	2	10 µM	0
204200	Adrenergic β_3	507608	hum	2	10 µM	6
206000	Androgen (Testosterone)	507676	hum	2	10 µM	9
210030	Angiotensin AT_1	507712	hum	2	10 µM	-6
210120	Angiotensin AT_2	507712	hum	2	10 µM	-3
212520	Bradykinin B_1	507713	hum	2	10 µM	-3
212620	Bradykinin B_2	507605	hum	2	10 µM	-10

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.
217050	Cannabinoid CB_1	507599	hum	2	10 µM	19
217100	Cannabinoid CB_2	507600	hum	2	10 µM	14
219500	Dopamine D_1	507674	hum	2	10 µM	-6
219600	Dopamine D_{2L}	507715	hum	2	10 µM	16
219700	Dopamine D_{2S}	507715	hum	2	10 µM	-3
219800	Dopamine D_3	507736	hum	2	10 µM	-8
224010	Endothelin ET_A	507620	hum	2	10 µM	-3
224110	Endothelin ET_B	507606	hum	2	10 µM	1
226010	Estrogen ERα	507717	hum	2	10 µM	4
226810	$GABA_A$, Chloride Channel, TBOB	507619	rat	2	10 µM	12
226600	$GABA_A$, Flunitrazepam, Central	507615	rat	2	10 µM	-1
228510	$GABA_B$, Non-Selective	507718	rat	2	10 µM	8
232030	Glucocorticoid	507714	hum	2	10 µM	32
232600	Glutamate, AMPA	507681	rat	2	10 µM	3
232710	Glutamate, Kainate	507647	rat	2	10 µM	-11
232810	Glutamate, NMDA, Agonism	507649	rat	2	10 µM	-8
232910	Glutamate, NMDA, Glycine	507649	rat	2	10 µM	-4
239300	Growth Hormone Secretagogue (GHS, Ghrelin)	507700	hum	2	10 µM	25
239610	Histamine H_1	507719	hum	2	10 µM	9
239710	Histamine H_2	507672	hum	2	10 µM	-13
239820	Histamine H_3	507716	hum	2	10 µM	-12
243000	Insulin	507720	rat	2	10 µM	1
252200	Motilin	507637	hum	2	10 µM	12
252610	Muscarinic M_1	507723	hum	2	10 µM	1
252710	Muscarinic M_2	507723	hum	2	10 µM	17
252810	Muscarinic M_3	507724	hum	2	10 µM	4
252910	Muscarinic M_4	507724	hum	2	10 µM	0
258730	Nicotinic Acetylcholine α3β4	507728	hum	2	10 µM	-5
260130	Opiate δ_1 (OP1, DOP)	507613	hum	2	10 µM	2
260210	Opiate κ (OP2, KOP)	507927	hum	2	10 µM	10
260410	Opiate μ (OP3, MOP)	507611	hum	2	10 µM	-6
260900	Oxytocin	507725	hum	2	10 µM	12
299005	Progesterone PR-B	507721	hum	2	10 µM	25
299036	Purinergic P2X	507730	rat	2	10 µM	-5

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.
268820	Purinergic P2Y, Non-Selective	507729	rat	2	10 µM	4
271110	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{1A}$	507657	hum	2	10 µM	-1
271650	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2A}$	507844	hum	2	10 µM	-2
271700	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2B}$	507650	hum	2	10 µM	12
271800	Serotonin (5-Hydroxytryptamine) $5\text{-}HT_{2C}$	507785	hum	2	10 µM	-1
202020	Transporter, Adenosine	507677	hum	2	10 µM	10
220320	Transporter, Dopamine (DAT)	507711	hum	2	10 µM	19
226400	Transporter, GABA	507646	rat	2	10 µM	9
204410	Transporter, Norepinephrine (NET)	507710	hum	2	10 µM	8
274030	Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	507713	hum	2	10 µM	1
287530	Vasopressin V_{1A}	507680	hum	2	10 µM	28
287560	Vasopressin V_{1B}	507640	hum	2	10 µM	7
287610	Vasopressin V_2	507904	hum	2	10 µM	29

Inhouse ion channel profiler: all IC_{50} > 10 µM

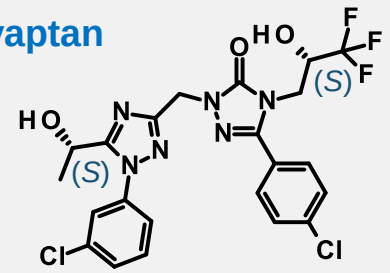
hKir2.1
hKvLQT1
hNav1.5
hCav1.2
hKv4.3

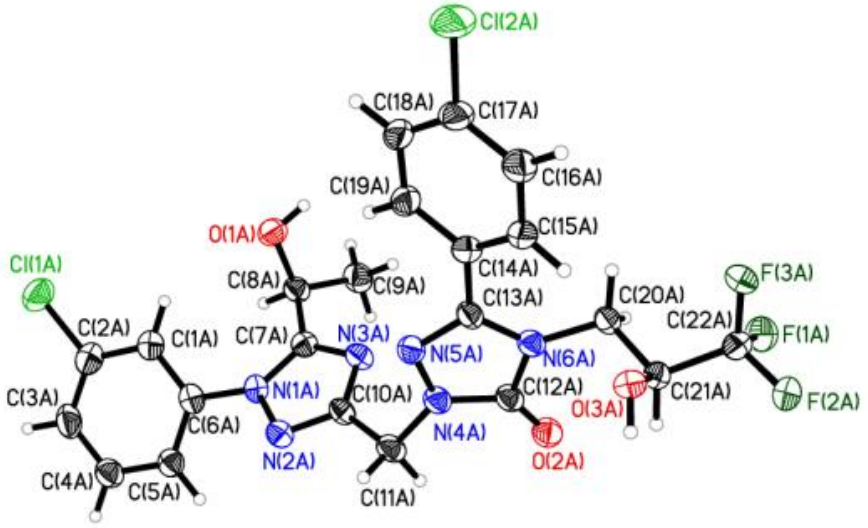
BAY-2297 shows clean off-target profile: No significant results at safety screen and at ion channel profiler

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

X-ray pecavaptan

Pecavaptan

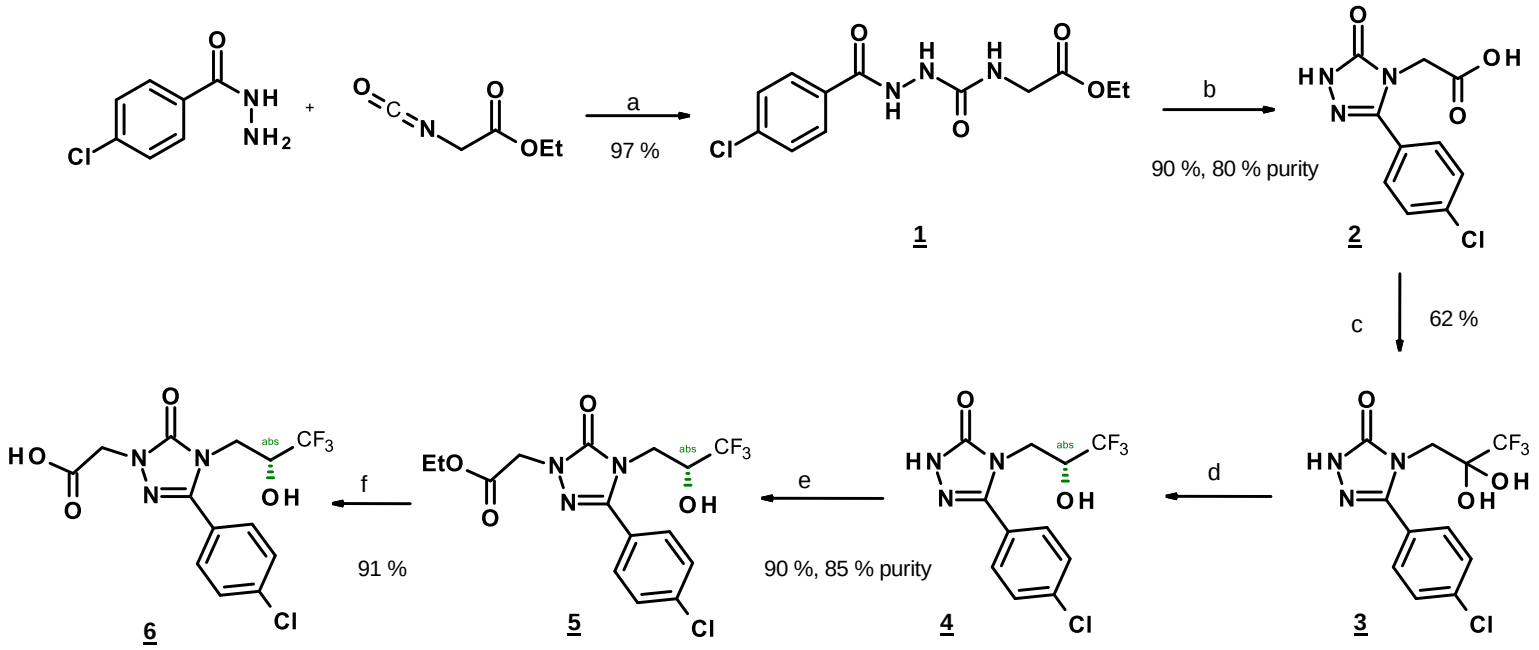




Absolute configuration confirmed by SMOL X-ray

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

Building block synthesis

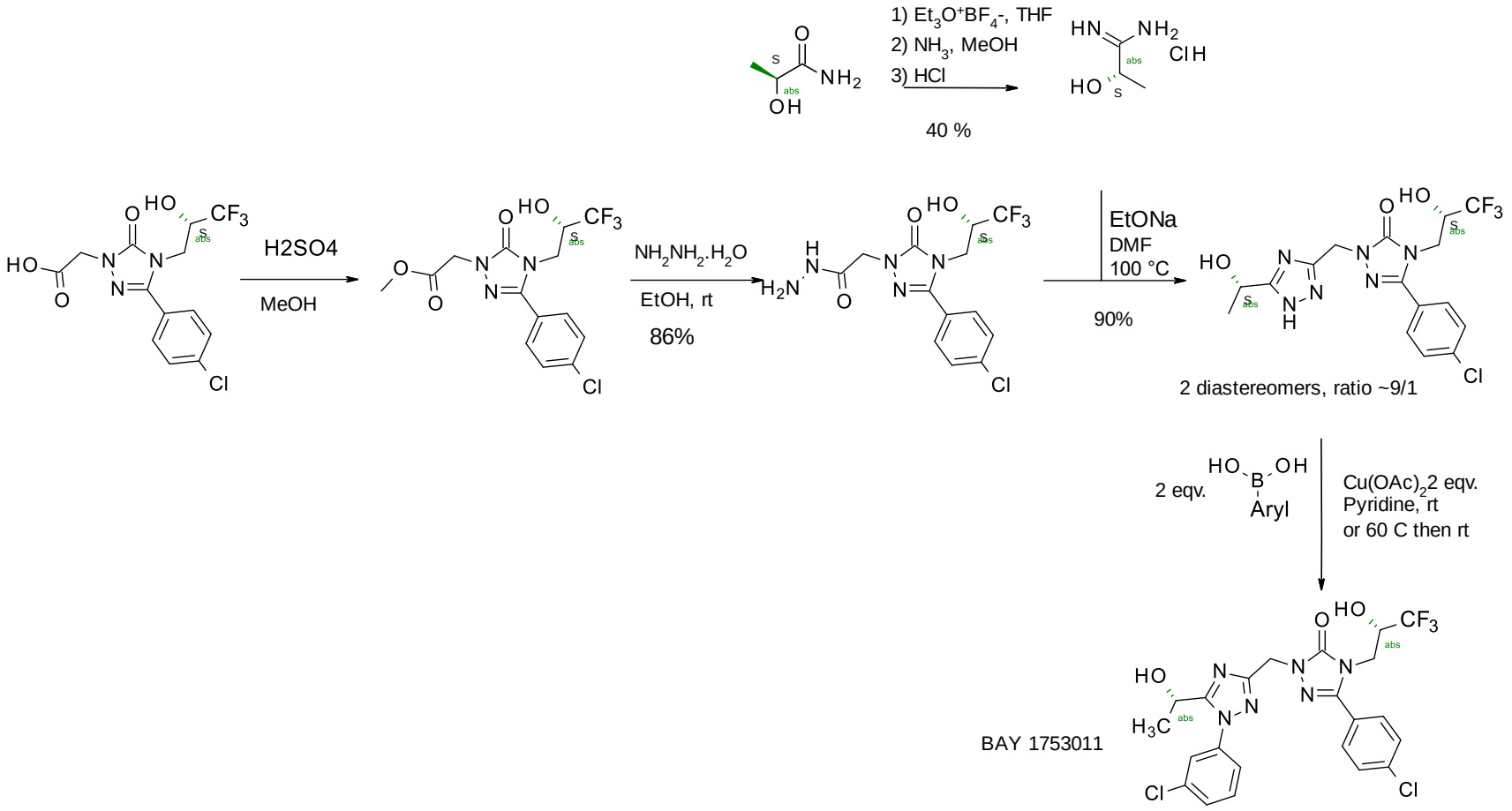


a) THF, 50°C. b) 3N NaOH, reflux (125°C). c) Trifluoroaceticacid anhydride 5 eq, Pyridine 35°C. d) $NaBH_4$, then chiral chromatography, or asymmetric hydrogenation with Ru-Komplex. e) $ClCH_2COOEt$ 1.05 eq, K_2CO_3 2eq, CH_3CN reflux. f) LiOH, MeOH, RT.

A triazolone building block was synthesized in a sequence of 6 steps

Dual V1a/V2 Receptor Antagonist Probe Pecavaptan

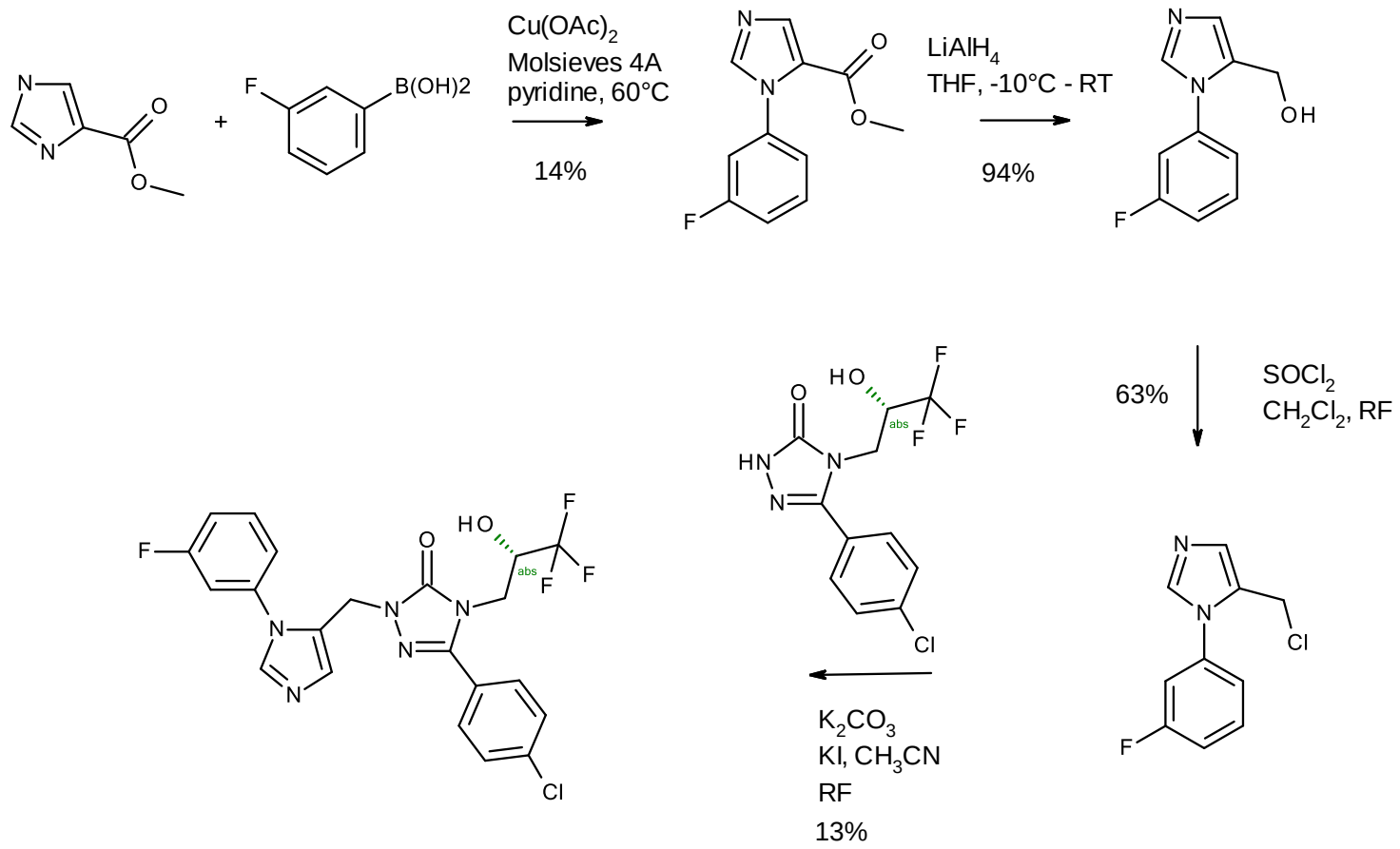
Synthesis of Pecavaptan



Pacavaptan was synthesized in overall 5 steps using the triazolone building block

Dual V1a/V2 Receptor Antagonist Probe

Synthesis of negative control BAY-2297



BAY-2297 was synthesized in 4 steps using a triazolone building block