	Sarafotoxins	Exendin-4	Conopressin-T
Source	*Atractaspis engaddensis* (Takasaki et al., 1988; Kloog et al., 1988; Ducancel, 2005)	*Heloderma suspectum* (Eng et al., 1990)	*Conus tulipa* (Dutertre et al., 2008)
Endogenous ligand	Endothelins (Ducancel, 2005)	GLP-1 (Eng et al., 1990)	Oxytocin, vasopressin (Dutertre et al., 2008)
Target and pharmacological profile *in vitro*	SRTX-6a: agonist ETB subnM SRTX-6b: agonist ETB and ETA subnM SRTX-6c: agonist ETB subnM (Barton & Yanagisawa, 2019; Ducancel, 2005)	Agonist GLP-1R (IC_{50} = 8.9 nM) (Mann et al., 2010)	Cono-T: antagonist V1aR (Ki = 319 nM), partial agonist OTR and V1bR, no activity on V2R (Dutertre et al., 2008; Dutt et al., 2019)
Size and sequence	21 AA: SRTX-6a: CSCKDMTDKECLNFCHQDVIW SRTX-6b: CSCKDMTDKECLYFCHQDVIW SRTX-6c: CTCNDMTDEECLNFCHQDVIW (Takasaki et al., 1988; Kloog et al., 1988)	39 AA: HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS (Eng et al., 1990)	9 AA: CYIQNCLRV (Dutertre et al., 2008)
SAR	Critical residues for activity: Trp21, Asp8, Glu10, Phe14 Cys1, Cys3, Cys11, Cys15 (Nakajima et al., 1989; Tam et al., 1994)	Interaction L-R: (Adelhorst et al., 1994; Suzuki et al., 1989) C-ter of Ex-4 interacts with the N-ter extracellular domain of GLP-1R Positions 7, 10, 12, 13, 15 Critical residues for activity: (Runge et al., 2008) His7: stimulating insulin release C-ter PSSGAPPPS = "Trp cage" of Ex-4, absent in GLP-1, not implied in the binding of Ex-4 to GLP-1R but decreases stabilization of GLP-1R Critical residues for agonism/antagonism switch: (Chen et al., 2006; Eng et al., 1992) Gly2-Glu3 → Ser2-Asp3 All peptide → Truncated N-ter (1→9) ↑ antagonism with Glu16, Val19 and Arg20 Critical residues for enhanced half-life: (Doyle et al., 2003) Ala8 → Gly8 Additional C-ter extension (9 AA)	Critical residues for agonism/antagonism property: Val9 → antagonist V1aR Critical residues for activity: Arg8: pressor activity Aromatic residue 3: increases selectivity for V1aR and V1bR Basic residue 4 → reduces potency V2R Cono-G *and* Cono-S: additional positive charge in position 4 (Dutertre et al., 2008; Giribaldi et al., 2020; Postina et al., 1996)
Scaffold/PDB structure	4 disulfide bridges SRTX-6b (5glh) (Shihoya et al., 2018; Shihoya et al., 2016; Izume et al., 2020)	No disulfide bridge, **α**-helix Ex-4(9-39) (3c5t) (Runge et al., 2008)	1 disulfide bridge, cyclic conotoxin (Dutertre et al., 2008)
***In vivo* effects**	On human: oedema, erythema, numbness, general weakness, sweating, pallor, vomiting and watery non-bloody diarrhea (Ducancel, 2005)	On isolated rat islets, inhibits glucagon secretion, stimulates insulin synthesis, protects against ß-cell apoptosis (Silvestre et al., 2003) On patients (T2D) Ex-4 decreases glycaemia and raises the ß-cell sensitivity to glucose (Egan et al., 2003)	Supposed renal homeostasis (Dutertre et al., 2008)
Therapeutical interest	IRL-1620 (Sovateltide®): peptidomimetic SRTX, agonist ETB, for acute cerebral ischemic stroke, phase III (Pharmazz, Inc. 2021; Gulati et al., 2021)	Exenatide (Byetta®): antidiabetic (T2D) Exenatide LAR: weekly injection Liraglutide: C-16 free-fatty acid derivative (Drucker et al., 2010)	

Table S1: Main characteristics of the agonist-mimicking toxins

	Contulakin-G	Conorphin-T	MIT1
Source	*Conus geographus* (Craig et al., 1999)	*Conus textile* (Luo et al., 2006)	*Dendroaspis polylepis* (Schweitz et al., 1990)
Endogenous ligand	Neurotensin (Craig et al., 1999)	Dynorphin-A (Brust et al., 2016)	Prokineticins (Li et al., 2001)
Target and pharmacological profile *in vitro*	Agonist NTSR1 (IC_{50} = 0.96 µM), NTSR2 (IC_{50} = 0.73 µM), NTSR3 (IC_{50} = 0.25 µM) (Craig et al., 1999)	Agonist KOR (Ki = 80 nM) (Brust et al., 2016)	Agonist PKR1 (Ki = 4.1 nM) and PKR2 (Ki = 0.67 nM) (Masuda et al., 2002)
Size and sequence	16 AA: pyroE-SEEGGSNA-[***β***-D-Galp-(1→3)-***α***-D-GalpNAc-(1→)-TKKPYIL (Thr10 O-glycosylated) (Craig et al., 1999)	9 AA: NCCRRQICC (Luo et al., 2006)	81 AA; AVITGACERDLQCGKGTCCAVSLWIKSVRVCTPVGTSGEDCHPASHKIPFSGQRMHHTCPCA PNLACVQTSPKKFKCLSKS (Schweitz et al., 1990)
SAR	<u>Critical residues:</u> C-ter tail PYIL: interaction with NTRS1 Uncharged residue 7: decreases desensitization of NTSR1 Lys9 → Glu9: decreases activity Thr10 deglycosylated: increases affinity and activity *in vitro* (Lee et al., 2015; Craig et al., 1999)	<u>Critical residues for affinity:</u> Asp6 → aromatic: increases affinity Ile7 <u>Critical residues for activity:</u> Tyr1 → Asn1: decreases activity Substitution of RRQICC: decreases activity (Brust et al., 2016)	<u>Critical residues for activity:</u> AVITGA conserved sequence N-ter tail Cys18 substitution: decreases activity <u>Critical residues for agonism/antagonism property:</u> Ala1 → Met1 Addition Met on N-ter (Boisbouvier et al., 1998; Bullock et al., 2004)
Scaffold/PDB structure	Linear Neurotensin (Craig et al., 1999)	2 disulfide bridges (Brust et al., 2016)	10 cysteines (Schweitz et al., 1990)
***In vivo* effects**	On rat: central anti-nociceptive effects, peripheral effects (gastrointestinal motility, vasodilatation) (Craig et al., 1999)	On rat: antinociceptive (Deuis et al., 2015)	On guinea pig: contraction ileum and distal colon (Schweitz et al., 1999)
Therapeutical interest	CGX-1160 (synthesized form): orphan drug status for the treatment of chronic intractable pain following intrathecal administration in patients with spinal cord injury by FDA (Sang et al., 2016)	Conorphin-1 (synthetic peptidomimicking): analgesic effects on rat (Deuis et al., 2015)	