

Venom Toxins as Ion Channel Research Tools

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Venomous creatures deploy a wide array of proteins and peptides, active on a spectrum of targets, for prey immobilization. These toxins are small, rigid, highly potent and specific, and as such, serve as an important pharmacological tool for ion channel research. Some of these toxins are currently under evaluation as possible drugs for a number of pathological indications.

Venomous creatures deploy a wide arsenal of biologically active compounds to capture prey, acting on a vast array of targets.¹ Prey immobilization is achieved by either inhibiting or activating the electrical activity using very specific and potent compounds. The diverse array of venom components belong to a number of compound classes, including small molecular weight compounds, electrolytes, polyamines, neurotransmitters, amino acids, small peptides and high MW proteins. Recently it was reported that a single type of spider venom might contain up to 500 peptides and therefore, with an estimated 37,000 known species, it would represent a potential source of more than 18 million spider peptides.^{1,2} The great pharmacological wealth accumulated by nature over evolution has resulted in extremely complex mixtures of pharmacophores, a combinatorial

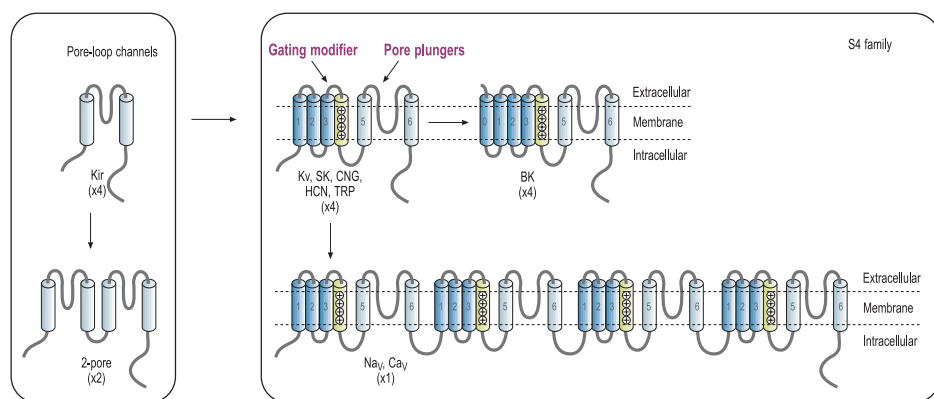
library of hundreds of thousands of potentially active and useful molecules.³ Venom components target different cellular mechanisms, and in many species, they specifically target ion channel families, which are the major components responsible for cellular membrane excitability.⁴ Due to their high potency and selectivity, venom proteins and peptides have emerged as invaluable tools for research, drug discovery and drug development.^{5,6} A number of venom toxins have been approved by the FDA as therapeutics, while others are currently in various stages of clinical trials as potential drugs for a number of indications, including pain, cardiovascular, and neurological pathologies.^{5,6} Due to the huge scope of this subject, this review we will highlight only a small fraction of examples for the use of venom toxins for the pharmacological characterization of ion channels.

Mode of Action of Toxins and the Structure of Ion Channels

Complex multicellular organisms require rapid and accurate transmission of information among cells and tissues and tight coordination of distant functions. Ion channels are integral membrane proteins that span lipid bilayers to form a central pore through which selected ions can pass at near diffusion-limited rates (approximately 10^7 ions⁻¹ s⁻¹).⁴ They are found in a wide range of organisms from viruses and bacteria to plants and animals.^{4,7,8} Most ion channels are gated, capable of making transitions between conducting and non-conducting conformations. Channel gating can be induced by extracellular ligands, intracellular second messengers and metabolites, protein-protein interactions, phosphorylation, and other factors.^{4,7} In addition, many ion channels are gated by the membrane potential itself.⁴ Voltage-gated ion channels respond to and modify the changes in membrane potential. For example, in vertebrates electrical signals and the resulting intracellular Ca²⁺ transients control contraction of muscle, secretion of hormones, perception of the environment, processing of information in the brain, and output from the brain to peripheral tissues.⁴ In nonexcitable cells, Ca²⁺ transients signal many key cellular events, including secretion, gene expression, and cell division.

The architectural structure of the ion channel families consists of four variations built on a common pore-forming structural theme.^{7,8} Voltage-gated K⁺ channels exemplify the first basic theme in the ion channel superfamily.⁴ This basic structure consists of six regions that form membrane-spanning helices (termed segments S1 to S6) and a membrane-spanning loop between the S5 and S6 segments (Fig. 1). Other

Fig. 1: Ion Channel Classes



Predicted transmembrane topology of different types of channels. The numbers in parentheses refer to the number of subunits that make up the channel pore. The boxes indicate ligand-binding domains. The S4 domain is marked. K_v, voltage-gated K⁺ channel. Na_v, voltage-gated Na⁺ channel. Ca_v, voltage-gated Ca²⁺ channel. CNG; cyclic-nucleotide-gated channel. HCN, hyperpolarization-activated channel. TRP, transient receptor potential channel.

members of this superfamily are the voltage-gated Na⁺ and Ca²⁺ channels.⁷ Their principal subunits are composed of four homologous K_v domains (I to IV) that form the common structural motif for this family (Fig. 1).⁷⁻⁹ Experimental analysis of the ion channel structures shows that the four homologous domains surround a central pore and suggests laterally oriented entry ports in each domain for ion transit toward the central pore.⁴ Several other families of ion channels also have this tetrameric architecture. The inwardly rectifying K⁺ channels constitute the simplest structural motif in the ion channel protein superfamily. These channels are complexes of four subunits that each have only two transmembrane segments, termed M1 and M2, which are analogous in structure and function to the S5 and S6 segments of voltage-gated Na⁺, Ca²⁺, and K⁺ channels. Two of these pore motifs are linked together to generate the fourth structural theme, the two-pore K⁺ channels (Fig. 1). In the last few years, this field has advanced due to the solution of the three-dimensional structure of a number of K⁺-channels, including KcsA, KvAP and K_v1.2 by Roderick MacKinnon's group, for which Prof. MacKinnon was awarded the 2003 Nobel Prize in chemistry.¹⁰⁻¹²

Much of the knowledge on channel structure and function was elucidated using specific peptide ligands isolated from a number of venomous organisms. Toxins isolated from venomous animals are usually small peptides, ranging from 8-70 amino acids, with relatively small scaffold structures. They are highly compact and are mainly stabilized by disulfide bonds, although some are stabilized by hydrogen bonds made from post-translational-modified amino acids.⁶ Toxins have various pharmacological advantages including high specificity, high activity, no accumulation in organs, low toxicity and low immunogenicity. Furthermore, their small, disulfide cross-linked compact structures lead to enhanced chemical and thermal stability

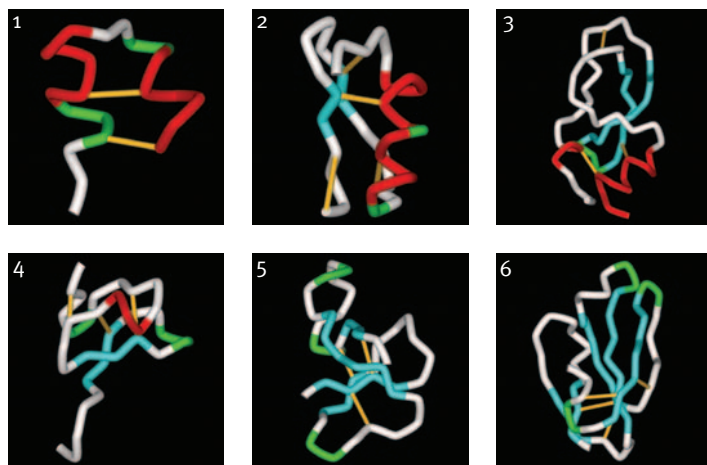
and relative insensitivity to proteases.¹³⁻¹⁵ The mode of action of these toxins can be roughly divided into two major groups: The “pore-plungers” and the “voltage-sensor modulators” or “gating-modifiers”. “Pore-plungers” bind to the pore region and physically block the ion transport through the pore. For example, the majority of K⁺ channel blockers are characterized by the presence of a dyad or triad, having a Lys in structural proximity to either one or two hydrophobic residues (Phe, Tyr, Trp).¹⁶ The Lys residue is “plunged” into the pore and interacts with the channel's Asp residues inside the pore, while the hydrophobic residues of the toxin interact with hydrophobic residues on the pore outer-surface.¹⁷ Toxin-channel selectivity is achieved by additional protein-protein interactions, thus discriminating between closely related channels. “Gating-modifier” toxins bind to the voltage sensor moiety (S4 helix), which is partially exposed to the extracellular space, modulates its movement, and thus modulates the mechanism of pore gating, although the exact mechanism remains controversial.^{12,18,19} Since these scaffolds are gaining interest as possible drugs for a vast array of indications, much research (including mutagenesis experiments, *in-silico* simulations, and structure determinations²⁰⁻²⁵) has been invested into elucidation of their structure/function relationship.

Scaffold Structures of Venom Peptides and Proteins

The majority of the experimental data acquired to date has been from toxins isolated from the venoms of snakes, scorpions, spiders, marine snails (*Conus* genus) and sea anemones.^{1,26-28} The use of toxin scaffolds as therapeutics has been the subject of a number of reviews.^{5,6,29-30}

Although a substantial number of toxin structures have been resolved to date, they represent a minute amount of all possible scaffold structures and activities of toxins in venoms. Classification into families and subfamilies is performed by structural and sequence data. Nevertheless, evolutionary diversity is found, with at least 14 scaffold representatives characterized.¹³ The scaffolds are composed of a combination of α -helices (α) and β -sheets (β), and can be roughly categorized as α 3₁₀, α , $\alpha\beta$, $\alpha\alpha$, 3₁₀ α , β , $\beta\beta$, $\beta\beta\beta$, $\beta_1\beta_1\beta_2\beta_2$, $\alpha\beta\beta$, $\beta\alpha\beta\beta$, α/β scaffolds (for clarification of the scaffolds, please refer to Mouhat, S. *et al.*¹³ A number of representative scaffolds are illustrated in (Fig. 2). At least eight distinct toxin scaffolds have been identified for K⁺ channel inhibition, eight scaffolds for Na⁺ channel modulation and four for Ca²⁺ channel blocking activity, where overlapping scaffolds are found between channel subtypes. As an example, the $\beta\beta\beta$ (Inhibitory Cysteine Knot) scaffold is found in κ -PVIIA (*Conus purpurascens*) which blocks K_v channel, ACTX-Hi:OB4219 (from the spider *Hadronyche infensa*) which slows the inactivation of Na_v channels, and ω -Conotoxin GVIA (marine cone snail *Conus geographus*) which blocks Ca_v channel activity.¹³ Furthermore, each of the scaffolds can be further divided into subgroups, for example, at least 18 sub-groups can be identified (based on Cys-pairing and activity) in the K⁺-channel blocker α/β α -KTX scorpion toxins family.³¹ It is fascinating to observe that the same channel can be blocked by a number of scaffolds that, in some cases, share a similar diad or triad, but in other cases, block the channel by a different mechanism, as exemplified by Tc32 (isolated from the venom of the Amazonian scorpion *Tityus cambridgei*).^{16,32} Alternatively, similar toxins sharing the same scaffold can have very distinct ion channel targets, for example the spider toxin **Stromatoxin-1** (*Stromatopelma calceata*) is active on the K⁺-channel K_v2.1 while **SNX-482** (*Hysteroocrates gigas*) is active on the R-type Ca²⁺ channel (Ca_v2.3).¹³ Additionally, APETx1

Fig. 2: Representative Toxin Scaffolds



1. κ -Hefutoxin-1: $\alpha\alpha$, (1HP9). Two consecutive α -helices within a peptide or protein structure.
2. rMaurotoxin (#RTM-340): $\alpha\beta$, (1TXM). Combination of α -helix (N-terminal) followed by a two-stranded β -sheet (C-terminal).
3. Dendrotoxin-I (#D-390): 3₁₀ $\beta\beta\alpha$ (1DEM). Kunitz/Bovine pancreatic trypsin inhibitor, arranged to form a twisted two-stranded antiparallel beta-sheet followed by an alpha helix.
4. rStromatoxin-1 (#RTS-350): 3₁₀ $\beta\beta$ (1CK) (based on the related structures of Hanatoxin-1 and ω -Grammotoxin SIA (#G-450), 1D1H.pdb and 1KOZ.pdb, respectively)¹ Belongs to the Knottin superfamily, having the Inhibitory Cysteine Knot structure, achieved when one disulfide bridge crosses the macrocycle formed by the two other disulfides and the interconnecting backbone.
5. ATX II (#A-700): $\beta\beta\beta\beta$ (1ATX), belongs to the Defensin/myotoxin-like superfamily. All beta structures are crosslinked by 3 cysteine bridges.
6. FS-2 (#F-700): $\beta_1\beta_1\beta_2\beta_2$ (1TFS). Three-finger motif, two consecutive (1 and 2) β -sheets (anti-parallel) within a peptide or protein structure (the first one being a two-stranded β -sheet and the second one a three-stranded β -sheet).

Images were generated using the ViewerLite freeware (Accelrys Inc.). The model structure of Stromatoxin was generated using Swiss Model.

1. Peitsch, M.C. (1996) *Biochem. Soc. Trans.* **24**, 274.

Table 1: Potency of Venom-derived Peptide Toxins Acting on K⁺ Channels

Channel	Toxin Blockers (IC ₅₀)*
ShakerB	Aa1, K _d =4.5μM; Agitoxin-1, 0.16nM; Agitoxin-2, 0.64nM; Agitoxin-3, 0.64nM; Charybdotoxin, 227nM; Lq2, 7nM; Margatoxin, 150nM; Maurotoxin, 2.4nM.
K _v 1.1	Agitoxin-1, 136nM; Agitoxin-2, 44pM; α-Dendrotoxin, 0.4-4nM; β-Dendrotoxin, 100nM blocks 62%; γ-Dendrotoxin, Potent; δ-Dendrotoxin, 0.1-2nM; Dendrotoxin-I, 3.1nM; Dendrotoxin-K, 0.6nM; Hongotoxin-1, 31pM; Kaliotoxin, 1.5nM; MCD Peptide, 90-490nM; Maurotoxin, 45nM; Noxiustoxin, >25nM; Stichodactyla (ShK), 16pM.
K _v 1.2	α-Dendrotoxin, 1.1-12nM; β-Dendrotoxin, 100nM blocks 74%; Dendrotoxin-I, 130pM; Hongotoxin-1, 170pM; Kaliotoxin, 25nM; Margatoxin, 160-650pM; Maurotoxin, 0.1-0.8nM; MCD Peptide, 10-440nM; Noxiustoxin, 2nM; Tityustoxin Kα, 210pM.
K _v 1.3	Agitoxin-1, 1.7nM; Agitoxin-2, 0.0044nM; Hongotoxin-1, 86pM; Kaliotoxin, 100-650pM; Margatoxin, 30pM; Maurotoxin, 180nM; MCD Peptide, >2μM; Noxiustoxin, 1-6nM; Stichodactyla (ShK), 11-133pM; Tityustoxin Kα, 4-20nM.
K _v 1.4	Stichodactyla (ShK), 314pM; APETx1, ~100nM-30%.
K _v 1.5	MCD Peptide, >5μM; Noxiustoxin, >25nM.
K _v 1.6	Agitoxin-1, 149nM; Agitoxin-2, 0.036nM; α-Dendrotoxin, 9-25nM; δ-Dendrotoxin, 23nM; Hongotoxin-1, 6nM; Margatoxin, 5nM; Stichodactyla (ShK), 160pM.
K _v 1.7	Margatoxin, 116nM; Noxiustoxin, 18nM; Stichodactyla (ShK), 13nM.
K _v 1.8	α-Dendrotoxin, 100nM.
K _v 2.1	Stromatoxin-1 (ScTx-1), 12.7nM.
K _v 2.2	Stromatoxin-1 (ScTx-1), 21.4nM
K _v 3.1	MCD Peptide, >2μM.
K _v 3.2	Stichodactyla (ShK), 0.3nM (Kv3.2b).
K _v 3.4	BDS-I, 2.5μM; BDS-II, 2.8μM.
K _v 4.1	Heteropodatoxin-2, 100-500nM.
K _v 4.2	Heteropodatoxin-2, 100-500nM; Phrixotoxin-2, 34nM.
K _v 4.3	Heteropodatoxin-2, 100-500nM; Phrixotoxin-2, 71nM.
K _v 11.1	APETx1, 34nM; BeKm-1, 3.3nM; Ergtoxin-1, 16nM.
K _{ca} 1.1	Charybdotoxin, 2.9nM; Iberiotoxin, 1.7nM; Kaliotoxin, 4nM; Maurotoxin, 2.6nM; Noxiustoxin, 450nM; Slotoxin, 1.5nM.
K _{ca} 2.1	Apamin, 1nM; Maurotoxin, 1μM; Noxiustoxin, 310nM; Scyllatoxin, 80nM; Tamapin, 42nM.
K _{ca} 2.2	Apamin, ~1nM; Noxiustoxin, 310nM; Scyllatoxin, 287pM; Tamapin, 24pM.
K _{ca} 2.3	Apamin, ~1nM; Noxiustoxin, 310nM; Scyllatoxin, 20-30nM; Tamapin, 1.7nM.
K _{ca} 3.1	Charybdotoxin, 5nM; Maurotoxin, 1.4nM; Stichodactyla (ShK), 30nM.
K _v 1.1	δ-Dendrotoxin, 150nM; Lq2, 410nM; Tertiapin-Q, 2nM.
K _v 3.1	Tertiapin-Q, 8.6nM.
K _v 3.4	Tertiapin-Q, 8.6nM.

* IC₅₀ values range due to different reports and different cell types.

and APETx2, isolated from the sea anemone *Anthopleura elegantissima*, share 65% sequence identity and 76% homology, but are active on very distinct targets namely, K_v11.1 and ASIC3, respectively.

For an extensive treatment of this topic see Refs. 13-15.

Use of Toxins as Pharmacological Tools

The understanding of the biophysical and pharmacological properties of channels has been greatly improved by the use of toxins, particularly in differentiation of specific channel activities (see Tables 1 and 2). The electrical currents generated by different channels can now be modulated by the use of toxins. As has been mentioned earlier, although numerous toxins have been discovered, they represent only a minute fraction of the toxin repertoire present in venoms.^{2,28} As more toxins are discovered, more channels and channel subtypes can be characterized. An example of differentiation of channel type by the use of toxins is given by the Ca²⁺ channels. Dihydropyridine-sensitive L-type Ca²⁺ channels (Ca_v1.x) can be selectively blocked by a number of toxins, including, **Calcicludine** (*Dendroaspis angusticeps*), **Calciseptine**, **FS-2** (*Dendroaspis p. polylepis*) and **TaiCatoxin** (*Oxyuranus s. scutellatus*), while high voltage-activated dihydropyridine-insensitive (Ca_v2.x) channels can be differentiated using the toxins ω-**Agatoxin IVA** (*Agelenopsis aperta*) for P/Q-type (Ca_v2.1), ω-**Conotoxin GVIA** for N-type (Ca_v2.2) and **SNX-482** for R-type (Ca_v2.3) Ca²⁺ channels. Low voltage-activated Ca²⁺-channels (Ca_v3.x) can be blocked by the relatively T-type selective blocker **Kurtoxin** (*Parabuthus transvaalicus*).³³⁻³⁵ Furthermore, it was recently published that even N-type channel variants, arising from splice isoforms or differential modulation by auxiliary subunits, can be distinguished using ω-**Conotoxin-CVID** (*Conus catus*), currently in clinical trials for pain indications (Table 2).³⁶⁻³⁷

Toxins have been shown to discriminate between members of the Ca²⁺-activated K⁺ channel family. Large-conductance Ca²⁺-activated K⁺ channel (BK, K_{ca}1.1) is blocked by **Iberiotoxin** (*Mesobuthus tamulus*), **Slotoxin** (*Centruroides noxius*), **Noxiustoxin** (*Centruroides noxius*), **Kaliotoxin** (*Androctonus m. mauritanicus*), and **Charybdotoxin** while the small-conductance Ca²⁺-activated K⁺ channel (K_{ca}2x) can be differentially blocked using **Apamin** (*Apis mellifera*), **Scyllatoxin** (*Leiurus quinquestriatus hebraeus*) and **Tamapin** (*Mesobuthus tamulus*). Intermediate-conductance Ca²⁺-activated K⁺ channel (IK, K_{ca}3.1) can be selectively modulated by **Maurotoxin** (*Scorpio maurus palmatus*) and **Charybdotoxin** (*Leiurus quinquestriatus hebraeus*) (Table 1).³⁸

Other examples of unique targets blocked by toxins can be illustrated by K_v11.1 (HERG) K⁺ channel block using **Ergtoxin-1** (*Centruroides noxius*),³⁹ **BeKm-1** (*Mesobuthus eupeus*)⁴⁰ and **APETx1** (*Anthopleura elegantissima*)⁴¹, ASIC1a channel using **Psalmotoxin**⁴², ASIC3 channel using **APETx2** (*Anthopleura elegantissima*)⁴³, K_v3.1 (GIRK) using **Tertiapin-Q** (*Apis mellifera*)⁴⁴, and K_v1.1 (ROMK) using **Lq2** (*Leiurus quinquestriatus hebraeus*).⁴⁵

Due to their small size, compact and rigid structure, high potency and selectivity, toxins have emerged as highly valuable tools for research and drug development for numerous indications. Tables 1 and 2 summarizes the published IC₅₀ for a number of toxins against their targets, which emphasizes the strength of these reagents as excellent pharmacological tools.

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Related Products

Compound	Product #
Voltage-Gated Ca²⁺ Channel Blockers	
ω-Agatoxin IVA	A-500
ω-Agatoxin TK	A-530
Calcicludine	C-650
Calciseptine	C-500
ω-Conotoxin GVIA	C-300
ω-Conotoxin MVIIA	C-670
ω-Conotoxin MVIIC	C-150
ω-Conotoxin SVIB	C-570
FS-2	F-700
ω-Grammotoxin SIA	G-450
PLTX-II	P-510
SNX-482	S-500
TaiCatoxin	T-800

K⁺ Channel Blockers

rAa1	RTA-400
rAgitoxin-1	RTA-150
rAgitoxin-2	RTA-420
rAgitoxin-2-Cys	RTA-420-C
rAgitoxin-2-Cys-TAMRA	RTA-420-T
rAgitoxin-3	RTA-390
Apamin	A-200
BDS-I	B-400
BDS-II	B-450
rBeKm-1	RTB-470
rCharybdotoxin	RTC-325
α-Dendrotoxin	D-350
β-Dendrotoxin	D-360
γ-Dendrotoxin	D-370
δ-Dendrotoxin	D-380
Dendrotoxin-I	D-390
Dendrotoxin-K	D-400
rErgtoxin-1	RTE-450
rHeteropodatoxin-2	RTH-340
rHongotoxin-1	RTH-400
rIberitoxin	RTI-400
rKalitoxin-1	RTK-370
rLq2	RTL-550
rMargatoxin	RTM-325
rMaurotoxin	RTM-340
MCD Peptide	M-250
rNoxiustoxin	RTN-340
Phrixotoxin-2	P-700
rScyllatoxin	RTS-370
Stichodactyla Toxin (ShK)	S-400
rStromatoxin-1 (rScTx-1)	RTS-350
rTamapin	RTT-400
Tertiapin	T-250
rTertiapin-Q	RTT-170
rTityustoxin Kα	RTT-360

Voltage-Gated Na⁺ Channel Activators

Anthopleurin-C (APE2-1)	A-400
APE 1-2	A-470
ATX II	A-700
α-Pompilidotoxin (α-PMTX)	P-170
β-Pompilidotoxin (β-PMTX)	P-180

Voltage-Gated Na⁺ Channel Blocker

μ-Conotoxin GIIIB	C-270
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Table 2: Potency of Venom-derived Toxins Acting on Na_v and Ca_v Channels

Channel	Toxin Blocker (IC ₅₀)*	Toxin Activator (IC ₅₀)*
Ca _v 1.X L-Type	Calcicludine, 88nM; Calciseptine, 15-500nM; DW13.3, 26.8nM; FS-2, 23nM-2μM; Kurtoxin, 250-500 nM; TaiCatoxin, 50-500nM.	
Ca _v 2.1 P/Q-Type	ω-Agatoxin IVA, 2-1000nM; ω-Agatoxin TK, 10-1000nM; ω-Conotoxin MVIIC, 0.05-1μM; ω-Conotoxin SVIB, 0.1-2μM; DW13.3, 4.3nM; Kurtoxin, 250-500 nM.	
Ca _v 2.2 N-Type	ω-Conotoxin GVIA, 20-1000nM; ω-Conotoxin MVIIA, 0.2-2μM; ω-Conotoxin MVIIC, 0.05-1μM; ω-Conotoxin SVIB, 0.1-2μM; DW13.3, 14.4nM; ω-Grammotoxin SIA, ~50nM; Kurtoxin, 250-500 nM; SNX-482, 300-500nM.	
Ca _v 2.3 R-Type	DW13.3, 96.4nM; ω-Grammotoxin SIA, ~50-500nM; Kurtoxin, 250-500 nM; SNX-482, 20nM.	
Ca _v 3.1 T-Type	Kurtoxin, 15-50nM.	
Ca _v 3.2 T-Type	Kurtoxin, 15-50nM.	
Na _v 1.1 1.2, 1.3, 1.4, 1.6, 1.7 TTX-Sensitive	μ-Conotoxin GIIIB, 5-25μM (Na _v 1.4).	Kurtoxin, 500nM (Na _v 1.2); Anthopleurin-C (APE 2-1), 1-5nM; APE 1-2, 1μM; ATX II, 10-100nM; α-Pompilidotoxin, 10nM; β-Pompilidotoxin, 1-5nM.
Na _v 1.5 1.8, 1.9 TTX-Resistant	μ-Conotoxin SIIIA, 0.1-1μM.	

* IC₅₀ values range due to different reports, different cell types and different preparations using auxiliary subunits.