REVIEW

Conus venom peptides that bind to ligand-gated ion channels and other molecular targets: Bioactivity, pharmacology, and therapeutic potential

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ABSTRACT

Conus venom peptides are classified under various pharmacological families. This review describes the diversity, physiological targets (subtypes and subunits), structure–activity relationships, peptide engineering, and potential therapeutic applications of selected conotoxins and their analogs. It covers conotoxins that bind to ligand-gated ion channels (nicotinic acetylcholine receptor and N-methyl-D-aspartate receptor); G protein-coupled receptors (neurotensin receptor, vasopressin receptor, adrenoceptor, and somatostatin receptor); norepinephrine transporter; insulin receptor; and includes a conotoxin that acts as a protease inhibitor. Conotoxins have drawn interest in drug design because they act on pharmacologically significant molecular targets with remarkable specificity and potency, making them valuable tools for examining neurological pathways. The review covers conotoxins characterized within the last two decades, including those that could be developed as therapeutic leads or pharmaceutical tools for neurological disorders, cancer, and other illnesses. A new generation of drugs with an enhanced benefit–risk ratio, improved mode of delivery, greater stability, and minimal adverse effects is needed. Natural resources such as *Conus* venom peptides and their analogs deserve further studies as sources of novel therapies.

INTRODUCTION

Cone snails (genus *Conus*; Figure 1) are predatory marine gastropods whose venoms contain relatively short peptides that interact with specific plasma membrane proteins with remarkable specificity and potency. The rapid divergence of *Conus* peptides (conotoxins or conopeptides) has produced a vast array of peptides in the venom of each of the ~1,000 *Conus* species. The venom contains a diverse set of pharmacologically active peptides that cone snails use to immobilize prey (fish, worms, or molluscs) and to defend themselves. Conotoxins are classified into gene superfamilies based on conserved signal-sequence regions, and into pharmacological families according to their molecular targets. The conotoxins target specific types of integral membrane proteins, including ion channels, receptors and transporters. To date, only a very small fraction of conotoxins has been pharmacologically characterized (Jin et al. 2019; Olivera et al. 2014, 2015).

Conus venom peptides have gained attention due to their potential as pharmacological agents. They are of great interest for novel drug development. The commercially available drug named ziconotide (Prialt), the synthetic form of omega-conotoxin MVIIA (ω-MVIIA) from *Conus magus*, serves as an analgesic that is stronger than morphine but does not cause opioid-like dependence (Rubiu et al. 2024).

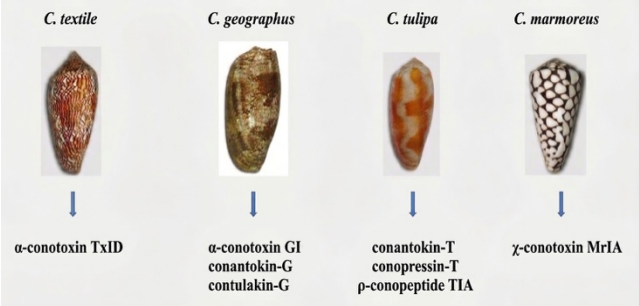

Figure 1: Shells of *Conus* species from which peptides described in this review were characterized.

This review focuses on conotoxin pharmacological families that bind to ion channels, receptors, and other molecular targets: the nicotinic acetylcholine (nACh), N-methyl-D-aspartate (NMDA),

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Email Address: **ecjimenez@up.edu.ph**
Date received: 11 April 2026
Dates revised: 25 July 2026; 27 August 2026
Date accepted: 12 October 2026
DOI: https://doi.org/10.54645/2026192GZS-88

KEYWORDS

nicotinic acetylcholine receptor, N-methyl-D-aspartate receptor, neurotensin receptor, vasopressin receptor, adrenoceptor, somatostatin receptor, norepinephrine transporter, insulin receptor

neurotensin, vasopressin, adrenergic and somatostatin receptors; the norepinephrine transporter; the insulin-receptor; and the target of a protease inhibitor. Conotoxins that target voltage-gated ion channels (calcium, sodium, and potassium channels) were covered in a recent review (Jimenez 2023). The review mainly discusses conotoxins documented within the last two decades, which continue to be investigated as potential therapeutic leads or pharmaceutical tools. For conotoxins identified earlier, the original discovery is credited but only recent updates are covered.

THE MOLECULAR TARGETS

Ligand-gated ion channels are an important class of plasma membrane proteins that mediate cell–cell communication and regulate cell excitability. They transduce neurotransmitter (ligand) signals in the nervous system and muscle. Nicotinic acetylcholine receptor (nAChR) is a pentamer of five transmembrane subunits. Neuronal nAChRs are either homopentamers of α subunits or heteropentamers of two α and three β subunits (Figure 2). Muscle nAChRs contain two α1, one β1, one δ, and either a γ subunit (fetal) or an ε subunit (adult) (Millar and Gotti 2009). The nAChRs have distinct pharmacological properties and are implicated in neuropathic and cardiovascular diseases and in cancer (Matta et al. 2021; Mucchietto et al. 2016).

N-methyl-D-aspartate receptor (NMDAR) is a tetramer. Conventional receptors contain two glycine-binding GluN1 subunits and two glutamate-binding GluN2 subunits (GluN2A–D), whereas unconventional receptors contain two GluN1 and two glycine-binding GluN3 subunits (GluN3A–B). A conventional GluN1/GluN2 receptor is therefore activated by both glycine and glutamate, whereas an unconventional GluN1/GluN3 receptor is activated only by glycine (Grand et al. 2018; Yamamoto et al. 2015). The NMDAR is involved in learning, memory, and synaptic plasticity. NMDAR antagonists are being investigated as potential medications for neuropathic pain, epilepsy, and ischemia, that are associated with receptor dysfunction (Balsara et al. 2015; Jimenez 2022).

G protein-coupled receptors (GPCRs) are the largest superfamily of membrane proteins. They transmit signals from a broad range of extracellular stimuli across the plasma membrane and activate intracellular effectors, chiefly G proteins. Neurotensin receptors (NTSR1 and NTSR2) are seven-transmembrane GPCRs that have been linked to various cancers (Ouyang et al. 2017).

Vasopressin receptors comprise V1a, V1b, and V2. V2 is expressed mainly in the kidney and controls water homeostasis; it is a pharmacological target in hyponatremia (low blood sodium level), diabetes insipidus, heart failure, and polycystic kidney disease (Gilles 2023).

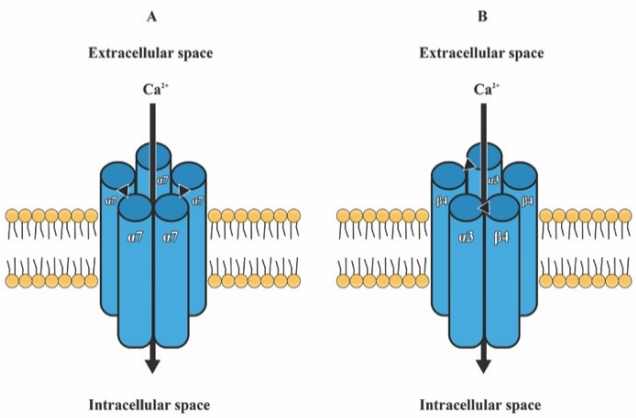

Figure 2: (A) Homopentameric $(α7)_5$ and (B) heteropentameric $(α3)_2(β4)_3$ neuronal nAChRs. The symbol (△) marks acetylcholine-binding sites. Binding of two acetylcholine molecules at subunit interfaces opens the pore; the homomeric α7 receptor has high Ca^{2+} permeability, whereas heteromeric receptors have lower Ca^{2+} permeability.

Adrenoceptor has seven transmembrane domains. The α-adrenoceptors comprise α1A, α1B, α1D, α2A, α2B, and α2C, and the β-adrenoceptors comprise β1, β2, and β3. Agonist binding causes a conformational change that activates G proteins and downstream signaling, including control of vasoconstriction and cardiac contractility. Adrenoceptor agonists and antagonists are widely used to manage cardiovascular and respiratory diseases (Xanthopoulos et al. 2021).

Somatostatin (SST) receptors comprise five subtypes, SST1–SST5, which share similar structures and signaling mechanisms but differ in their regulatory effects. They mediate the physiological actions of somatostatin, a potent inhibitor of hormone secretion and neuronal excitability. SST2 and SST5 are the main targets for treating pituitary adenomas and neuroendocrine tumors, and SST2 is the principal target for peptide-based radiopharmaceuticals used in diagnosis and therapy (Günther et al. 2018).

The norepinephrine (noradrenaline) transporter (NET) terminates noradrenergic signaling by rapidly taking up released norepinephrine into presynaptic neurons, driven by the sodium and chloride gradients. NET is a target of therapies for attention-deficit hyperactivity disorder, depression, and eating disorder (Bönisch and Brüss 2006). Structures of NET bound to noradrenaline showed that the binding mode, and the coordination of sodium and chloride ions, adjust as the transporter changes conformation. Bupropion (an antidepressant) and ziprasidone (an antipsychotic) stabilize NET in an inward-facing state through different binding pockets (Hu et al. 2024).

The insulin receptor (IR) is an enzyme-linked receptor of the receptor tyrosine kinase class. It is a disulfide-linked $α_2β_2$ heterotetramer (a dimer of αβ half-receptors): the two extracellular α subunits bind insulin, and the two transmembrane β subunits contain the tyrosine kinase domain. Insulin binding activates the receptor and triggers signaling cascades that regulate metabolism and growth. Impaired IR signaling is associated with diabetes and cancer (Choi and Bai 2023).

CONOTOXIN FAMILIES: STRUCTURE, MOLECULAR TARGETS, AND BIOACTIVITY

Conotoxins with nicotinic acetylcholine receptors as targets

Conotoxins from several families target nAChRs: the α-, αB-, αC-, αD-, αM-, αO-, and αS-conotoxins.

Alpha-conotoxins

α-Conotoxins contain two disulfide bonds with the Cys framework CC–C–C. Three disulfide isomers are possible: globular (C1–C3,

C2–C4), bead (C1–C2, C3–C4), and ribbon (C1–C4, C2–C3). The family includes α-GI, α-ImI, α-PnIA, α-AuIB, α-Vc1.1, α-RgIA, α-TxID, α-LsIA, α-AusIA, α-MilIA, α-VnIB, α-Bt1.8, α-Vt1.27, α-AtIA, α-NcIA, α-NcIA[E15U], α-NcIB, and α-NcIB[E13U] (Table 1).

Table 1: Sequences, molecular targets and potencies of α-conotoxins

Peptide	Sequence	nAChR subunits	IC50	References
α-GI	ECCNPACGRH YSC*	XO mα1β1δε	5.86 nM	Gray et al. 1981; Ning et al. 2018
α-ImI	GCCSDPRCAW RC*	hα7	440 nM	McIntosh et al. 1994, Wan et al. 2015
α-PnIA	GCCSLPPCAA NNPDYC*	XO rα7, XO rα3β2 XO hα7, XO hα3β2	No data	Fainzilber et al. 1994, Hopping et al. 2014
α-AuIB	GCCSYPPCFA TNPDC*	XO rα3β4	0.75 μM	Luo et al. 1998, Wu et al. 2018
α-Vc1.1	GCCSDPRCNY DHPEIC*	rα9α10, hα9α10	No data	Sandall et al. 2003, Yu et al. 2013
α-RgIA	GCCSDPRCRY RCR	rα9α10	No data	Ellison et al. 2006, Li et al. 2019
α-TxID	GCCSHPVCSA MSPIC*	rα3β4	12.5 nM	Luo et al. 2013a, Dong et al. 2023
α-LsIA	SGCCSNPACR VNNPNIC*	hα3β2, hα7	10 nM	Inserra et al. 2013, Abraham et al. 2017
α-AusIA	SCCARNPACR HNHPCV*	hα7, SH-SY5Y α7	47.0 ± 6.70 μM	Lebbe et al. 2014, Ho et al. 2021
α-MilIA	DMCCHPACMN HFNC*	XO $\alpha_1\beta_1\gamma\delta$	13130 ± 1125 nM	Peigneur et al. 2019
α-VnIB	GGCCSHPVCY TKNPNCG*	rα6β4, rα6/α3β4	12 nM, 18 nM	van Hout et al. 2019
α-Bt1.8	GCCSNPACIL NNPNQC*	rα6/α3β2β3, rα3β2	2.1 nM, 9.4 nM	Ning et al. 2021
α-Vt1.27	NCCMFHTCPI DYSRFNC*	HEK rα3β2	1160 nM	Wang et al. 2022a
α-AtIA	ZGCCSHPACS VNHPELCW	XO mα7	0.16 μM	Neves et al. 2024
α-NcIA	GGCCSNPPCI ANHPEIC*	No data	No data	Ramones et al. 2025
α-NcIA[E15U]	GGCCSNPPCI ANHPUIC*	No data	No data	Ramones et al. 2025
α-NcIB	CCSNOOCIAN HPEIC*	α7	102.7 nM	Ramones et al. 2025
α-NcIB[E13U]	CCSNOOCIAN HPUIC*	α7	64.4 nM	Ramones et al. 2025

nAChR, nicotinic acetylcholine receptor; Z, pyroglutamate; U, gamma-carboxyglutamate; O, *trans*-4-hydroxyproline; h, human; m, mouse; r, rat; XO, *Xenopus* oocyte expression system; HEK, Human Embryonic Kidney cell expression system; SH-SY5Y, Human neuroblastoma cell expression system; C*, C-terminal amide.

α-GI is a 13-mer peptide isolated from *C. geographus* venom (Gray et al. 1981); it binds the mouse α1β1δε nAChR. Alanine replacement showed that Pro5, Gly8, Arg9, and Tyr11 are crucial for inhibition of the α1β1δε nAChR, since each substitution caused a marked loss of potency. The α-GI[E1A] was 3-fold more potent at the mouse receptor. Molecular dynamics (MD) simulations indicated that loop 2 of α-GI contributes substantially to the interaction with the α1β1δε nAChR, with Tyr11 interacting with Leu93, Tyr95, and Leu103 of the δ subunit (Ning et al. 2018). In voltage-clamp recordings, both the globular and ribbon isomers of α-GI selectively inhibited human α1β1δε nAChRs expressed in *Xenopus* oocytes (Tae et al. 2021). Fatty-acid modification substantially improved the stability and albumin-binding ability of α-GI, in proportion to the length of the fatty acid, while the modified peptide retained its nAChR antagonist activity (Qi et al. 2023).

α-ImI that consists of 12 amino acid residues was purified from *C. imperialis* venom; it targets mammalian neuronal nAChRs (McIntosh et al. 1994). Surface plasmon resonance showed that α-ImI dendrimers (α-ImI units joined by polyethylene glycol spacers) bound *Aplysia californica* acetylcholine-binding protein (Ac-AChBP) with increased affinity. In electrophysiological assays the dendrimers were ~100-fold more potent at human α7 nAChRs (IC50 = 4 nM) than α-ImI (IC50 = 440 nM) (Wan et al. 2015).

α-PnIA, a 16-residue peptide isolated from *C. pennaceus* venom blocks neuronal nChRs of cultured *Aplysia* neurons (Fainzilber et al. 1994). The analog α-PnIA[A10L] potently and selectively inhibited rat and human α7 nAChRs expressed in *Xenopus* oocytes, with position 10 being identified as the key site. Electrophysiology and radioligand binding showed that Leu retained potency at both α7 and α3β2, whereas charged or polar residues decreased α7 binding. Substituting norleucine gave the largest increase in affinity for α7, yet the analog remained selective for α3β2. Docking showed that the hydrophobic interactions with α7 and α3β2 residues occur through a hydrophobic funnel (Hopping et al. 2014).

α-AuIB is a 15-mer peptide isolated from *C. aulicus* venom; it potently inhibits the α3β4 nAChR expressed in *Xenopus* oocytes (Luo et al. 1998). The ribbon isomer was 10-fold more potent than the globular isomer at rat nAChRs of parasympathetic neurons. Alanine scanning showed that Ser4 and Phe9 of the ribbon isomer are the major determinants of its interaction with the α3β4 nAChR. Computational modeling suggested that loop 1 of both ribbon and globular isomers bound to the "aromatic box" of the acetylcholine orthosteric binding site, but loop 2 and the termini of the ribbon isomer differed in orientation and interactions (Wu et al. 2018).

The 16-residue α-Vc1.1 identified from *C. victoriae* venom-duct mRNA inhibits vascular responses to sensory C-fiber activation in rats (Sandall et al. 2003). Vc1a, which has hydroxyproline-6 (Hyp6) and γ-carboxyglutamate-14 (Gla14), was deduced to be the native post-translationally modified form (Jakubowski et al. 2004). α-Vc1.1 is a potent antagonist of the α9α10 nAChR (Vincler et al. 2006). Its interactions with the α9α10 and α10α9 interfaces were consistent with computational models predicting preferential binding to the α10α9 interface. A hydrogen bond between α-Vc1.1

and position 59 of the α10α9 pocket conferred specificity for rat over human α9α10 nAChR (Yu et al. 2013). The hydroxyl group of Tyr10 formed a hydrogen bond with the carbonyl of α9 Asn107. Ser4 of α-Vc1.1 lies next to α9 Asp166 and Asp169, and substituting a positively charged residue enhanced binding affinity. The carboxyl group of Asp11 formed hydrogen bonds with α9 Asn154 and Arg81, and adding a second carboxyl group at this position markedly reduced potency (Chu et al. 2019). α-Vc1.1 selectively inhibited human α9α10 and α3β2 nAChRs. At the α9α10[N179A] mutant its potency decreased 20-fold relative to wild-type α9α10, due to loss of a hydrogen bond with the peptide. At α3β2[D86A] α-Vc1.1 was four-fold more potent than at wild-type α3β2, possibly because of the neighboring residue β2 Lys104. The potency of α-Vc1.1 doubled at α9α10[N213K], while it was unchanged at α9α10[N213R]. MD simulations indicated that altered interactions between the mutated α9 side chains (N179A, N213K, N213R) and Asp5 of α-Vc1.1 may partly explain the differences in potency (Tae et al. 2025). Cyclization of α-Vc1.1 improved serum stability and oral bioavailability. Polyethylene glycol (PEG) linkers preserved the stability of cyclic α-Vc1.1 in simulated intestinal fluid and its activity, and the peptide's helical structure was crucial for maintaining both (Zhang et al. 2025).

The 13-residue α-RgIA identified by cDNA cloning from *C. regius* specifically blocks the α9α10 nAChR (Ellison et al. 2006). NMR was used to determine the solution structures of α-RgIA and the analogs [D5E], [P6V], and [Y10W], and resonance assignments were made for [R9A]. Asp5, Pro6, and Arg7 in loop 1 are crucial for blocking both α9α10 and α7 nAChRs. The loop-2 analog [Y10W] had a structure and activity like α-RgIA, with high potency at α9α10 and low potency at α7. Arg9 in loop 2 is vital for specific binding to α9α10 (Ellison et al. 2008). Globular α-RgIA bound Ac-AChBP more efficiently than the ribbon isomer (Kryukova et al. 2018). Docking and MD simulations indicated that α9 Asp168 and α10 Glu197 and Asp205 contributed to the interaction between α-RgIA and the rat α9α10 nAChR (Li et al. 2019). The Arg7 side chain length and charge were found to be important for α-RgIA activity at α9α10 nAChR (Huynh et al. 2020).

α-TxID, a 15-mer peptide identified in *C. textile* by cDNA cloning potently inhibits rat α3β4 nAChRs (Luo et al. 2013a). α-TxID[S9A] was 46-fold more potent at α3β4 than at α6/α3β4. Ser9 of α-TxID was involved in weak hydrogen bond with β4 Lys81 in the α6β4 binding site but not in the α3β4 binding site, and replacement by Ala caused disruption of the hydrogen bond (Wu et al. 2017a). The best selectivity for α3β4 was achieved with α-TxID [S9K], which inhibited α3β4 but had little effect on α6/α3β4 (Yu et al. 2018a). Native α-TxID blocked both rat α3β4 and α6/α3β4. Alanine-insertion mutants ([+9A], [+10A], [+14A]) and loop-2 truncation mutants showed reduced inhibition of both receptors (Dong et al. 2023).

The 17-residue α-LsIA isolated from *C. limpusi* venom potently inhibits α3β2 and α7 nAChRs. N-terminally truncated analogs were 9-fold less potent at α3β2 and α7 nAChRs. C-terminal carboxylation increased potency 3-fold at α3β2 but reduced it at α7 (Inserra et al. 2013). Interactions of α-LsIA[R10F] with β4 Lys57, and of the conserved –NN– motif with β4 Ile77 and Ile109, caused its activity at human α3β4 nAChRs (Abraham et al. 2017).

α-AusIA is a 16-mer peptide isolated from *C. australis* venom. Electrophysiology showed that the globular and ribbon isomers blocked the α7 nAChR, although the ribbon isomer is more stable (Lebbe et al. 2014). Loop 1 residues are essential determinants of potency. Deleting Ala4 or Arg5 made the globular isomer 11-fold and 86-fold more potent than the ribbon isomer, respectively. Truncating the C-terminal Val further increased the difference in potency between the isomers (Ho et al. 2021).

α-MilIA (14-residue peptide) was purified from *C. milneedwardsi* venom. It is a highly selective antagonist of muscle α1β1γδ nAChRs. The M9G and N10K substitutions produced strong discrimination between α1β1γδ and α1β1εδ receptors. α-MilIA[M9G, N10K] potently inhibited the acetylcholine-evoked current at α1β1γδ. The analog [Δ1, M2R, M9G, N10K, H11K] was significantly more potent than α-MilIA and preferred the α9α10 nAChR (Peigneur et al. 2019).

The 17-residue α-VnIB was characterized from *C. ventricosus* genomic DNA. It is selective for α6β4 nAChRs over α3β4 and α6β2β3 receptors. The α-VnIB potently inhibited acetylcholine-elicited currents at rat α6β4 and α6/α3β4 nAChRs. Greater selectivity was also shown for human α6/α3β4. The peptide exhibited greater selectivity for human α6/α3β4 and quick binding kinetics at rat α6/α3β4 (van Hout et al. 2019).

α-Bt1.8 (16-mer peptide) was identified by cDNA cloning from *C. betulinus*. It selectively blocked acetylcholine-induced currents in *Xenopus* oocytes expressing rat or human α6/α3β2β3 and α3β2 nAChRs. It had higher binding affinity with a slower dissociation rate for the rat α6/α3β2β3 compared with α3β2. The three-dimensional structure of α-Bt1.8 revealed a larger hydrophobic region that may account for its potent inhibition of α6/α3β2β3. Ala scan showed that Ile9, Leu10, Asn11, Asn12 and Asn14 were essential for the α6/α3β2β3 and α3β2 inhibition (Ning et al. 2021).

α-Vt1.27 with 17 amino acid residues was identified by cDNA cloning from *C. vitulinus*. It blocked rat α3β2 nAChRs in sensory neurons and high voltage-activated $Ca_V2.2$ channels expressed in HEK293T cells. Ala scan revealed that Phe5, Pro9, Ile10, and Ser13 significantly contributed to the activity. The α-Vt1.27 showed potent anti-allodynic effect after intramuscular injection in rat models of pain caused by sciatic nerve injury and chronic constriction injury (Wang et al. 2022a).

α-AtIA (18-mer peptide) was isolated from *C. ateralbus* venom. It substantially inhibited the acetylcholine-evoked calcium influx in the presence of PNU-120596 (an α7 positive allosteric modulator) based on constellation pharmacology assay on mouse dorsal root ganglion neurons. The two-electrode voltage clamp electrophysiology performed on *Xenopus* oocytes showed that α-AtIA potently inhibited mouse α7 nAChR (IC50=0.16 μM), but inhibited α6/α3β4 with low potency. Trp18 mainly contributed to the activity (Neves et al. 2024).

Four peptides isolated from *C. neocostatus* were found to have similar amino acid sequences. The identified peptides are α-NcIA, α-NcIA[E15U], α-NcIB and α-NcIB[E13U]. The α-NcIA and α-NcIA[E15U] consist of 17 residues, while α-NcIB and α-NcIB[E13U] have 15 residues. They were encoded by a single gene as revealed by transcriptomic analysis. Functional assays showed different selectivities for the nAChRs. While α-NcIA inhibited nicotine-evoked responses by more than 70%, α-NcIA[E15U] did not. α-NcIB[E13U] showed ~60% inhibitory effect, but not α-NcIB. α-NcIA[E15U], α-NcIB and α-NcIB[E13U] were almost fully inhibitory against choline-evoked responses, while NcIA was weakly inhibitory. The α-NcIB and α-NcIB[E13U] showed specificities for the α7 nAChR (Ramones et al. 2025).

AlphaB-conotoxin

αB-Conotoxins contain two disulfide bonds with the framework C–CC–C. The only identified member is αB-VxXXIVA (Table 2), a 40-residue peptide characterized by cDNA cloning from *C. vexillum*. It is an α9α10 nAChR antagonist (Luo et al. 2013b).

A hybridoma cell 5E4 secreting IgG2b against αB-VxXXIVA was screened by hybridoma technology, with MBP-αB-VxXXIVA tandem fusion protein as an immunogen. High specificity and affinity to αB-VxXXIVA was displayed by the 5E4 monoclonal antibody. Leu14 and Phe15 of epitope 1, the major binding region of αB-VxXXIVA (1-20), were crucial for the interaction with 5E4 monoclonal antibody. Thus, indirect competitive enzyme-linked

immunosorbent assay (ELISA) could be utilized with αB-VxXXIVA in drug analysis (Tang et al. 2022).

Table 2: Sequences, targets, and potencies of αB-, αC-, αD-, αM-, αO-, and αS-conotoxins

Peptide	Sequence	nAChR subunits	IC50	References
αB-VxXXIVA	VRCLEKSGAQ PNKLFRPPCC QKGPSFARHS RCVYYTQSRE	rα9α10	1.2 μM	Luo et al. 2013b; Tang et al. 2022
αC-PrXA	TYGIYDAKPO FSCAGLRGGC VLPONLROKF KE*	mα1β1εδ, mα1β1γδ	1.8 nM, 3.0 nM	Jimenez et al. 2007; Taiwe et al. 2019
αD-VxXXB	DDUSUCIINT RDSPWGRCCR TRMCGSMCCP RNGCTCVYHW RRGHGCSCPG	XO rα7	No data	Loughnan et al. 2006; Ho et al. 2022
αD-GeXXA	DVHRPCQSVR PGRVWGKCCL TRLCSTMCCA RADCTCVYHT WRGHGCSCVM	rα9α10 hα9α10	1.2 nM 28 nM	Xu et al. 2015; Yang et al. 2017
αD-PiXXA	AVKKTCIRST OGSNWGRCCL TKMCHTLCCA RSDCTCVYRS GKGHGCSCTS	XO hα7	6.2 μM	Hernández-Sámano et al. 2019
αD-FrXXA	EARITCQPRG RSKWGRCCLT QMCGNYCCYK HGCRCVYHSW RGHGCSC	hα7, hα3β2, mα1β1εδ, mα1β1γδ	125 nM, 282 nM, 351 nM, 447 nM	Rodriguez-Ruiz et al. 2022
αM-MIIIJ	ZKCCSGGSCP LYFRDRLICP CC	mαβδε, mαβδγ, hαβδε, hαβδγ	3.6 μM 44.4 μM 4.1 μM 19.6 μM	Rybin et al. 2020
αM-SIIID	CCGEGSSCPK YFKNNFICGC C	HEK hα7	880.71 ± 271.91 nM	Wang et al. 2022b
αO-lt14a	MCPPLCKPSC TNC*	rneuronal	No data	Peng et al. 2006; Ren et al. 2015b
αO-GeXIVA	TCRSSGRYCR SPYDRRRRYC RRITDACV*	rα9α10, hα9α10	4.6 nM	Luo et al. 2015; Wang et al. 2024b
αS-GVIIIB	SGSTCTCFTS TNCQGSCECL SPPGCYCSNN GIRQRGCSCT CPGT*	XO α9α10	9.8 nM	Christensen et al. 2015

nAChR, nicotinic acetylcholine receptor; O, *trans*-4-hydroxyproline; Z, pyroglutamate; h, human; m, mouse; r, rat; XO, *Xenopus* oocyte expression system; HEK, Human Embryonic Kidney cell expression system; C*, C-terminal amide.

AlphaC-conotoxin

αC-Conotoxins have one disulfide bond with Cys pattern C–C. The characterized family member is αC-conotoxin PrXA (Table 2). αC-PrXA, a 32-residue peptide, was isolated from *C. parius* venom. It acted as a potent competitive antagonist of mouse α1β1γδ and α1β1εδ nAChRs (Jimenez et al. 2007).

AlphaD-conotoxins

αD-Conotoxins are homodimers; each monomer contains five disulfide bonds with the Cys framework C–CC–C–CC–C–C–C–C. The family includes αD-VxXXB (initially referred to as αD-VxXIIB), αD-GeXXA, αD-PiXXA and αD-FrXXA (Table 2).

αD-VxXXB, a dimer of a 50-residue peptide, was isolated from *C. vexillum* venom. It potently inhibited the α7 nAChR (Loughnan et al. 2006). The C-terminal domain blocked α7 and bound allosterically to *Lymnaea stagnalis* AChBP (Ls-AChBP), whereas the anti-parallel dimeric N-terminal domain inhibited α7 with reduced potency. The C-terminal domain and N-terminal–C-terminal domain variants acted as allosteric inhibitors. The similar potency of N-terminal–C-terminal domains and C-terminal domain(19–50) variant and the higher potency of αD-VxXXB suggested that the N-terminal domain had little contribution to the potency but may may affect the positioning of the two C-terminal domains for maximal potency (Ho et al. 2022).

αD-GeXXA, a homodimer of a 50-residue peptide, was characterized from *C. generalis* venom. The C-terminal domain of monomeric peptide retained the α9α10 nAChR inhibitory activity. The rat α10 nAChR His7 defined the species preference of αD-GeXXA and is possibly part of the binding site. The peptide cooperatively bound to two inter-subunit interfaces on the nAChR's top surface, causing allosteric disturbance of channel opening (Xu et al. 2015). The N-terminal domain, as an internal dimer, still inhibited nAChRs, indicating preferential binding to β subunits. A fully active single-chain cyclic N-terminal analog was obtained, in which four Arg residues interact with the receptor (Yang et al. 2017).

αD-PiXXA, a homodimer of 50-mer peptide, was isolated from the venom of *C. princeps*. It slowly and reversibly blocked the acetylcholine-evoked response of the human α7 nAChR expressed in *Xenopus* oocytes (Hernández-Sámano et al. 2019).

αD-FrXXA (a homodimer of a 47-residue peptide) was characterized from *C. fergusoni* by Edman degradation and transcriptomics. The conotoxin blocked the acetylcholine-induced response on human nAChRs α7, α3β2, and α4β2; mouse α1β1εδ and α1β1γδ nAChRs. In α7 and α3β2 nAChRs the inhibition was irreversible because the current amplitude did not increase in spite of time elapsed and washout of the peptide. In α1β1εδ and α1β1γδ nAChRs the inhibition was slightly reversible even though the current amplitude could not revert to its original values, implying that the peptide was not fully disconnected from the receptor. In α4β2 the blockade was almost entirely reversible within a few minutes, showing that the peptide had less affinity to the receptor (Rodriguez-Ruiz et al. 2022).

AlphaM-conotoxins
αM-Conotoxins contain three disulfide bonds with the framework CC–C–C–CC. The characterized family members are αM-MIIIJ and αM-SIIID (Table 2).

αM-MIIIJ with 22 amino acid residues was isolated from *C. magus* venom. Intracellular recordings from goldfish and frog showed that it blocked postsynaptic nAChRs. It inhibited the α1β1εδ and α1β1γδ receptors, possibly by interfering with acetylcholine binding. Its potency at mouse and human receptors was much lower than at fish nAChRs (Rybin et al. 2020).

αM-SIIID, a 21-mer peptide, was characterized from *C. striatus*. In HEK293 cells expressing nAChR subtypes, the isomer with (C1–C4, C2–C5, C3–C6) connectivity blocked human α7 currents evoked by acetylcholine in the presence of the positive allosteric modulator PNU-120596 much more strongly than the (C1–C5, C2–C4, C3–C6) and (C1–C6, C2–C4, C3–C5) isomers (Wang et al. 2022b).

AlphaO-conotoxins
αO-Conotoxins contain four Cys residues (framework C–C–C–C) that can form three disulfide connectivities: globular isomer (C1–C3, C2–C4), bead isomer (C1–C2, C3–C4), and ribbon isomer (C1–C4, C2–C3). The family includes αO-lt14a and αO-GeXIVA (Table 2).

αO-lt14a that is made up of 13 amino acid residues was characterized by cDNA cloning from *C. litteratus* venom ducts. It inhibited the neuronal nAChRs (Peng et al. 2006). In a rat pain model, it produced antinociception, and reduced c-fos mRNA expression in the spinal cord. Binding of the peptide to nAChRs at the surface of PC12 cells was reduced by pretreatment with tubocurarine chloride and hexamethonium bromide (both nAChR antagonists). αO-lt14a also suppressed morphine-withdrawal symptoms and did not cause drug dependence (Ren et al. 2015a). In mice, low doses (up to 10 mg/kg) prolonged pentobarbital-induced sleep without affecting locomotor activity; moderate doses (up to 200 mg/kg) did not raise the micronucleus rate; and high doses (up to 1,000 mg/kg) did not produce pathological changes in the heart or brain (Wu et al. 2021).

αO-GeXIVA (28-mer peptide) was identified by cDNA cloning from *C. generalis*. Its bead and ribbon isomers blocked the α9α10 nAChR with nearly equal potency (Luo et al. 2015). Both isomers were unstable when incubated at 37 °C in serum and digestive enzymes. The disulfide frameworks were readily scrambled in reduced glutathione and human serum albumin, and stability was strongly affected by alkaline pH, oxidation, and temperature (Yu et al. 2018b). Backbone cyclization with a two-residue linker increased the folding yield and serum stability of the ribbon isomer while maintaining activity at α9α10 (Wu et al. 2017b). Several disulfide-deficient analogs of the bead isomer retained potent inhibition of α9α10, and the most potent analog was less than 2-fold more potent than the parent bead isomer at rat and human receptors. Simulations indicated that the disulfide bonds and termini do not make stable contacts with the receptor (Xu et al. 2020). Alanine scanning showed that the [R17A] bead isomer had increased selectivity for α9α10, and the αO-GeXIVA[I23A] ribbon isomer was 10-fold more active at rat and human α9α10 receptors (Xu et al. 2023).

AlphaS-conotoxin
αS-Conotoxins have five disulfide bonds with framework C–C–C–C–C–C–C–C–C–C. The only characterized member is αS-GVIIIB (Table 2), a 44-residue peptide isolated from *C. geographus* venom and confirmed by cDNA cloning. Physiological studies revealed that αS-GVIIIB had great selectivity for the α9α10 nAChR. Inhibition by αS-GVIIIB was reversed much more slowly than inhibition by α-RgIA, which recovered completely within 1–2 min of washout. The acetylcholine response was fully blocked when both toxins were applied, and pre-application of α-RgIA prevented the slow reversible block by αS-GVIIIB (Christensen et al. 2015).

Conotoxins with N-methyl-D-aspartate receptors as targets
Conantokins contain either one disulfide bond (framework C–C) or none and generally contain several γ-carboxyglutamate (Gla) residues. The family includes conantokin-G, -T, -Pr3, -P, and -Bk-B (Table 3).

Table 3: Sequences, targets, and potencies of conantokins, contulakin, conopressins, ρ-conopeptide, consomatin, χ-conotoxins, con-Ins and conkazal

Peptide	Sequence	Molecular Targets	IC50/EC50	References
Conantokin-G	GEUULQUNQU LIRUKSN*	HEK GluN2B, mGluN2B	No data	McIntosh et al. 1984; Sheng et al. 2009; Balsara et al. 2015
Conantokin-T	GEUUYQKMLU NLRUAEVKKN A*	mGluN2B	No data	Haack et al 1990; Liu et al. 2021
Conantokin-Pr3	GEOUVAKWAU GLRUKAASN*	XO mGluN2B	IC50=0.5 μM	Teichert et al. 2007
Conantokin-P	GEUUHSKYQU CLRUIRVNKV QQUC*	XO rGluN2B	IC50=0.3 μM	Gowd et al. 2008
Conantokin Bk-B	GEUUYSUAI*	XO GluN2D	IC50=1.91 μM	Platt et al. 2014
Contulakin-G	ZSEEGGSNAT KKPYIL	HEK rNTSR1, HEK hNTSR1, HEK rNTSR2	EC50=524 nM EC50=960 nM EC50=730 nM	Craig et al. 1999; Lanoie et al. 2025
Conopressin-T	CYIQNCLRV*	hV1a	No data	Dutertre et al. 2008
Conopressin-M1	CFPGNCPDS*	hV1a, hV1b, hV2, zfV1a, zfV1b, zfV2	No data	Giribaldi et al. 2020
ρ-TIA	FNWRCCLIPA CRRNHKKFC*	zfARα1	No data	Sharpe et al. 2001; Lim et al. 2025
Consomatin Ro1	UGYKCVwKTC MOA	hSST1 hSST4	EC50=2.9 μM EC50=5.3 μM	Ramiro et al. 2022
χ-MrIA	NGVCCGYKLC HOC	rNET	No data	McIntosh et al. 2000; Hu et al. 2024
χ-AoIA	RCCGYKMCHO C	HEK hNET	IC50=1.06 ± 0.48 μM	Gupta et al. 2010; Belleza et al. 2026

Peptide	Sequence	Molecular Targets	IC50/EC50	References
χ-PnID	STCCGYRMCV PC*	rNET	IC50=10 μM	Espiritu et al. 2023
Con-Ins G1	A chain GVVUHCCHRP CSNAEFKKYC* B chain TFDTOKHRCG SUITNSYMDL CYR	hIR	EC50=16.3 nM	Menting et al. 2016; Ahorukomeye et al. 2019; Gorai & Vashisth 2022
Con-Ins T1A	A chain GVVUHCCHRP CSNAEFKKFC* B chain NSTDOKYRCG SUIPNSYIDL CF	hIR	EC50=12 nM	Ahorukomeye et al. 2019; Gorai & Vashisth 2022
Con-Ins K1	A chain GIVUDCCYND CTDEKLKEYC HTLQ* B chain SDSGTTLVRR RLCGSULVTY LGELCLGN	hIR	EC50=30.5 nM	Ahorukomeye et al. 2019; Gorai & Vashisth 2022
Conkazal-M1	QFFCPDSEND PLNCVETMAT TATCMQSNKD KSYSYACGYC GKKKESCFNG NKVPVRDYNC KSRNTVNPCG GAAL	Subtilisin A	No data	Hackney et al. 2026

U, gamma-carboxyglutamate; O, 4-*trans*-hydroxyproline; Z, pyroglutamate; w, 6-bromotryptophan; h, human; m, mouse; r, rat; zf, zebra fish; HEK, Human Embryonic Kidney cell expression system; XO, *Xenopus* oocyte expression system; NET, norepinephrine transporter; IR, insulin receptor; SST, somatostatin receptor; C*, C-terminal amide. For conopressin-M1, the given data are relative to vasotocin mean EC_{50} values.

Conantokin-G (17-residue peptide) was purified from *C. geographus* venom. It contains five Gla residues, which decarboxylated, causes the peptide to lose its sleep-inducing activity in mice (McIntosh et al. 1984). The selectivity of conantokin-G for GluN2B-containing receptors expressed in HEK293 cells depends on residues in the GluN2B S2 region. Substituting Met739 and Lys755 of GluN2B for Lys738 and Tyr754 of GluN2A, respectively, caused the inhibitory activity of conantokin-G into GluN2A-containing NMDAR (Sheng et al. 2009).

Conantokin-T (21-mer peptide) purified from *C. tulipa* venom inhibited NMDAR-facilitated calcium influx in central nervous system neurons (Haack et al. 1990). The analog conantokin-T[M8Q] selectively targeted the GluN2B subunit (Ren et al. 2015b).

Conantokin-Pr3 with 19 amino acid residues was characterized from the venom of *C. parius*. Electrophysiology showed greatest potency and selectivity for the GluN2B subunit (Teichert et al. 2007). Conantokin-Pr3 reduced the NMDA/Gly-evoked currents and intracellular calcium influx in rat hippocampal neurons. In cortical neurons from GluN2A knockout and GluN2B knockout mice, the conotoxin showed a better selectivity for GluN2B (Kunda et al. 2013).

The 24-residue conantokin-P was identified from genomic DNA of *C. purpurascens*. It has an unusually long disulfide loop (12 residues, including two Gla) between its two Cys residues. It inhibits GluN2B-containing receptors with submicromolar potency (Gowd et al. 2008).

Conantokin-Bk-B (9-mer peptide) was characterized by cDNA cloning from *C. bocki*. Electrophysiology in *Xenopus* oocytes coexpressing NMDAR subunits showed its greatest potency at GluN2D. Tyr5 is critical for potency, and removing the C-terminal amide (Bk-B[COOH]) eliminated activity (Platt et al. 2014).

Conotoxin with neurotensin receptor as target

Contulakins lack disulfide bonds. The only characterized member, contulakin-G (Table 3), is a 16-residue peptide isolated from *C. geographus* venom. The major form contains the disaccharide β-D-Galp-(1→3)-α-D-GalpNAc attached to Thr10. The glycosylated peptide was 10-fold more active than the non-glycosylated peptide. Contulakin-G is a potent agonist of rat NTSR1, with higher activity there than at human NTSR1 and rat NTSR2 (Craig et al. 1990).

Conotoxins with vasopressin receptors as targets

Conopressins contain one disulfide bond (framework C–C) and target vasopressin receptors. The family includes conopressin-T and conopressin-M1 (Table 3).

Conopressin-T (9 amino acid residues) was characterized from *C. tulipa* venom. Seven of its nine residues are identical to vasotocin, including the first six, which are also present in oxytocin. It has Arg8, which is important for vasopressin-like activity. Pro7 and Gly9, which are highly conserved in other vasopressin-like peptides including conopressin-G, are replaced by Leu7 and Val9 in conopressin-T. Conopressin-T acted as a selective antagonist of the human V1a receptor, binding only the oxytocin receptor and V1a; the L7P analog had enhanced affinity for V1a and weak binding to V2 (Dutertre et al. 2008).

The 9-mer conopressin-M1 was characterized from the venom gland transcriptome of *C. miliaris*. Conopressin-M1 was a weak partial agonist at human V1b and zebrafish V1a and a full, high-affinity agonist at zebrafish V2. There was a repulsion between Asp8 of conopressin-M1 and Asp297 of the human V2. In the zebrafish V2, Asp297 is substituted by Ser, substantially reducing the potential electrostatic repulsion with the Asp8 of conopressin-M1, resulting in the activity of conopressin-M1 on zebrafish V2 rather than on human V2 (Giribaldi et al. 2020). This suggests that replacing Asp8 with a neutral or positively charged residue could relieve electrostatic repulsion with human V2 Asp297.

Conotoxin with adrenoceptor as target

ρ-Conopeptides have two disulfide bonds (framework CC–C–C). ρ-TIA with 19 amino acid residues (Table 3) was isolated from *C. tulipa* venom; it inhibits the α1-adrenoceptor (Sharpe et al. 2001). It bound an allosteric site on the extracellular surface, formed by transmembrane helices 6 and 7 and extracellular loop 3 (Ragnarsson et al. 2013). ρ-TIA interacts with the α1B-adrenoceptor through (1) a salt bridge between Arg4 and Asp327 and a cation–π interaction between Arg4 and Phe330; (2) a T-stacking π interaction between Trp3 and Phe330; and (3) hydrogen bonds between Asn2 and Val197 and between Trp3 and Ser318, plus an interaction between the positively charged N-terminus and Glu186 (Ragnarsson et al. 2013). ρ-TIA markedly reduced the escape response of zebrafish larvae and blocked the zebrafish α1-

adrenoceptor, consistent with reversal of the stimulatory effects of norepinephrine (Dutt et al. 2019). NMB-1, an analog of ρ-TIA, and ρ-TIA inhibited mechanically activated currents in dorsal root ganglion neurons. In HEK cells expressing tentonin 3, NMB-1 strongly inhibited the channel whereas ρ-TIA weakly inhibited it (Lim et al. 2026).

Conotoxin with somatostatin receptor as target

Consomatins contain one disulfide bond (framework C–C). The only characterized member is consomatin Ro1 (Table 3), a 13-mer peptide purified from *C. rolani*. Consomatin Ro1 preferentially activated SST1 and SST4 and showed little or no activity at SST2, SST3, and SST5 (Ramiro et al. 2022).

Conotoxins with norepinephrine transporters as targets

χ-Conotoxins contain two disulfide bonds (framework CC–C–C) and can form three isomers: ribbon (C1–C4, C2–C3), globular (C1–C3, C2–C4), and bead (C1–C2, C3–C4). Native χ-conotoxins normally adopt ribbon configuration. The characterized family members are χ-MrIA, χ-AoIA and χ-PnID (Table 3).

χ-MrIA (originally called mr10a; 13 amino acid residues) was isolated from *C. marmoreus* venom. It potently increased withdrawal latency in the hot-plate assay, indicating analgesia (McIntosh et al. 2000). Linking the N- and C-termini (backbone cyclization) can markedly reduce proteolytic susceptibility without loss of activity (Clark et al. 2012). A stable backbone-cyclized χ-MrIA was engineered by grafting an integrin-binding Arg-Gly-Asp motif between the N- and C-termini. The construct had improved plasma stability and retained bioactivity, with no adverse effects in rats (Clark et al. 2012; Dekan et al. 2012).

χ-AoIA with 11 amino acid residues was isolated from *C. araneosus* venom (Gupta et al. 2010). A cryo-electron microscopy (cryo-EM) structure of the human NET–χ-AoIA complex showed that the peptide occupied the outer vestibule of NET and part of the central substrate-binding site (S1) (Belleza et al. 2026). The chemical properties of Tyr5 and Lys6 of χ-AoIA complement the S1 microenvironment, accounting for its high affinity. χ-AoIA was more potent than its globular isomer. χ-AoIA caused potent antinociception in mice with inflammatory pain, without sedation or motor dysfunction after subcutaneous injection (Belleza et al. 2026).

The 12-mer χ-PnID was purified from *C. pennaceus* venom. It selectively blocked norepinephrine uptake at the rat NET. The globular χ-PnID exhibited >10 times less activity, whereas the bead isomer did not show any measurable activity (Espiritu et al. 2023).

Conotoxins with insulin receptors as targets

Con-Ins peptides consist of an A chain (four Cys; framework CC–C–C) and a B chain (two Cys; framework C–C), linked into three disulfide bonds: one within the A chain and two between the A and B chains. The con-Ins that were characterized are con-Ins G1, con-Ins T1A and con-Ins K1 (Table 3).

Con-Ins G1 from *C. geographus*, the smallest known natural insulin, has 20 and 23 amino acid residues in the A chain and in the B chain, respectively. It lacks the C-terminal segment of the human insulin B chain. Con-Ins G1 potently bound the human insulin receptor and activated receptor signaling. The crystal structure of Con-Ins G1 showed a tertiary structure very analogous to that of human insulin, but the peptide lacks the key receptor-engaging residue PheB24 in human insulin (Menting et al. 2016, Ahorukomeye et al. 2019).

Con-Ins T1A (A chain and B chain: 20 and 22 amino acid residues) was characterized from *C. tulipa*; con-Ins K1 (24 and 28 amino acid residues) from *C. kinoshitai*. These peptides bound to and activated the human insulin receptor. MD simulations suggest binding modes distinct from those of natural insulins. In a streptozotocin-induced diabetes model they significantly reduced blood glucose (Ahorukomeye et al. 2019; Gorai and Vashisth 2022).

Conotoxin acting as a protease inhibitor

Conkazals contain four disulfide bonds (framework C–C–C–C–C–C–C–C). Conkazal-M1, from *C. magus*, was the first characterized member of the MKAVA superfamily (Table 3). Conkazal-M1 was shown to assume a fold typical of the Kazal-type protease inhibitor family, with a Glu residue positioned at the inhibitory P1. Conkazal-M1 inhibited the protease subtilisin A and moderately inhibited calcium transients in mouse sensory neurons, suggesting a possible role in regulating ion-channel activity. This dual function resembles that of toxins with a Kunitz-type fold. It did not inhibit chymotrypsin or GluC (Hackney et al. 2026).

CONOTOXINS AS THERAPEUTIC LEADS OR PHARMACEUTICAL TOOLS

Among the conotoxins covered here, those with the most advanced studies or significant findings, and therefore the strong candidates as therapeutic leads or pharmaceutical tools, are conantokin-G (CGX-1007), contulakin-G (CGX-1160), α-Vc1.1 (ACV1), Xen2174 (a χ-MrIA analog), α-RgIA, α-TxID, α-ImI, α-PnIA, α-AuIB, α-LsIA, αC-PrXA, αO-GeXIVA, conantokin-T, conantokin-Pr3, conantokin-P and con-Ins GI.

CGX-1007, CGX-1160, ACV1, and Xen2174 showed analgesic efficacy in animal models, and in some cases in humans, and have reached clinical trials (Safavi-Hemami et al. 2018). Despite difficulties in their development, studies continue to advance them as therapeutics.

In a rat model of ischemic stroke, conantokin-G (CGX-1007) binding to GluN2B reduced the damaging effects of ischemia. It did so by restoring the normal localization of GluN1 and GluN2B in the peri-infarct area, thereby reducing stroke-induced NMDAR excitotoxicity (Balsara et al. 2015). CGX-1007 is a potent analgesic that reached a Phase I clinical trial for pain and epilepsy (Safavi-Hemami et al. 2018).

Intrathecal administration of CGX-1160 was validated to be safe and could relieve neuropathic pain caused by spinal cord injury (Sang et al. 2016). CGX-1160 reached Phase Ib clinical trial for the management of chronic intractable pain (Safavi-Hemami et al. 2018). Since neurotensin receptor agonists have been implicated in stimulating cell proliferation in certain cancers (Ouyang et al. 2017), the long-term safety of contulakin-G needs to be considered. Spinal contulakin-G probably produces antinociception by activating presynaptic NTSR2. Intrathecal administration dose-dependently inhibited thermal and mechanical hypersensitivity in rodent models of inflammatory and neuropathic pain (Martin et al. 2022). In a mouse model of cancer-induced bone pain, intrathecal CGX-1160 reduced spontaneous pain behavior and *reversed* mechanical hypersensitivity. The antinociception depended on NTSR2 expression and CaV2.3, and contulakin-G had no effect on motor behavior in rodents (Martin et al. 2025). Analogs with a non-glycosylated Thr10, and with non-glycosylated Thr10 plus a Gln-cycloheptyl substitution, retained antinociceptive efficacy and reversed mechanical allodynia in a neuropathic pain model, comparable to contulakin-G (Lanoie et al. 2025). N-terminal truncations resulted in reduced plasma half-life and loss of antinociceptive efficacy, highlighting the significance of the N-terminal region. Molecular modeling further showed that full-length analogs engage a broader NTSR2 binding interface than truncated derivatives (Lanoie et al. 2025).

ACV1 advanced to preclinical and clinical studies because of its potent activity in neuropathic pain models, including sciatica and shingles. In a Phase IIa trial, it failed because of very low potency

at the human α9α10 nAChR compared with the rat receptor (Safavi-Hemami et al. 2018). Further studies undertaken to develop α-Vc1.1 as a therapeutic lead confirmed that the peptide inhibited the α9-containing nAChRs. The inhibition is significant because these receptors are involved in neuroinflammation, suggesting a possible strategy for relieving inflammatory and neuropathic pain (Tae et al. 2025).

Xen2174, developed from the χ-MrIA pharmacophore by a single amino-acid replacement, proved to be a more stable NET inhibitor and a potent analgesic in the chronic constriction injury model of neuropathic pain. The χ-MrIA re-engineering by converting its N-terminal Asn to pyroglutamate resulted in the analog, Xen2174, which was subjected to clinical trials for neuropathic pain (Brust et al. 2009, Carstens et al. 2011). Xen2174 had improved stability and a longer analgesic duration without loss of efficacy. It was reported to relieve severe chronic pain rapidly in cancer patients and underwent a Phase IIb trial for post-bunionectomy pain (Lewis 2012). In contrast, a study in healthy volunteers found no statistically significant effect on experimentally induced pain, and earlier clinical studies had not shown adequate efficacy in humans (Okkerse et al. 2017). Homogeneous tetrameric and octameric χ-MrIA dendrimers retained the χ-MrIA tertiary structure and showed slightly enhanced potency in a NET reuptake assay. When administered intrathecally to rats with neuropathic pain, they had no anti-allodynic effect, possibly because the larger dendrimers cannot diffuse through spinal cord tissue (Wan et al. 2016). Several χ-MrIA analogs had human NET-inhibitory activity comparable to χ-MrIA, but none considerably increased potency; analogs with a disrupted pharmacophore had much lower activity (Ziegman et al. 2019). More studies involving peptide engineering are necessary for the development of χ-MrIA or its analogs.

α-RgIA is less potent at human than at rat nAChRs. The analog RgIA4 is highly potent at both human and rat α9α10 receptors and more selective for α9α10 than for GABAB and opioid receptors (Romero et al. 2017). RgIA4 inhibited chemotherapy-induced neuropathic pain in rats and blocked cold allodynia induced by oxaliplatin (a chemotherapeutic for colorectal cancer) in wild-type mice. Its efficacy is attributed to inhibition of α9-containing nAChRs (Romero et al. 2017). Hot-plate, cold-allodynia, grip-strength, and von Frey tests showed that α-RgIA alleviated long-term oxaliplatin-induced peripheral neuropathy in mice. Histology of dorsal root ganglion neurons showed improved nuclear morphology (Dyachenko et al. 2022).

α-TxID was tested on human cervical cancer cell lines. The α3 and β4 nAChR subunits were overexpressed in SiHa cells compared with normal ectocervical Ect1/E6E7 cells. α-TxID markedly inhibited SiHa cell proliferation, providing a basis for potential cervical cancer therapy (Liu et al. 2019). α3 and β4 subunits were upregulated in the lung cancer cell lines A549 and NCI-H1299, and co-treatment with α-TxID enhanced the inhibitory effect of adriamycin (doxorubicin) on cell growth (Qian et al. 2019).

α-ImI-modified PEG-DSPE micelles (α-ImI-PMs) improved delivery of paclitaxel to MCF-7 human breast cancer cells that overexpress α7 nAChRs, through binding of α-ImI to the receptor. Paclitaxel delivered with α-ImI-PMs was more cytotoxic, induced more apoptosis, and was more effective in mice bearing MCF-7 tumors (Mei et al. 2015). In macrophage-like cells derived from THP-1 pre-monocytic leukemic cells, α-ImI upregulated the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) while the anti-inflammatory cytokine TGF-β was almost unaffected. α-ImI may therefore serve as a molecular probe of α7 nAChR function in these cells (Padilla et al. 2017). Docetaxel loaded in α-ImI-PMs had a stronger antiproliferative effect on non-small cell lung cancer cells (Mei et al. 2018). Simulations of the 2×α-ImI dendrimer with the α7 nAChR indicated greater potency than the α-ImI monomer, due to a stable hydrogen-bond network formed by the linker (Xu et al. 2019). α-ImI was fused to alpha-fetoprotein domain 3 (AFP3), a prototype anticancer agent. The fusion protein α-ImI-AFP3 had enhanced anticancer activity, acted synergistically with gefitinib, and inhibited the growth and migration of A549 and NCI-H1299 lung cancer cells, suggesting therapeutic potential, particularly for hepatoid adenocarcinoma of the lung (Chen et al. 2024).

Combining α-PnIA (an α3β2 nAChR inhibitor) with baicalein (a 12-lipoxygenase inhibitor that is cytotoxic to Ehrlich carcinoma cells *in vitro*) inhibited Ehrlich carcinoma growth and increased mouse survival. Activation of nAChRs and the arachidonic acid cascade both promote tumor survival, so inhibiting both pathways together produced a distinct antitumor effect (Osipov et al. 2020).

α-AuIB reduced the viability of small cell lung carcinoma cells, whereas nicotine promoted it. Variants in the nAChR genes *CHRNA3*, *CHRNA5*, and *CHRNB4* have been linked to both susceptibility to lung cancer and nicotine dependence, and these genes are important for small cell lung carcinoma viability (Improgo et al. 2013). In medial habenula neurons, α-AuIB abolished nicotine-evoked currents. *Chrna3* hypomorphic mice, which express low levels of the α3 subunit, consumed more nicotine than wild-type mice, and knocking down the gene transcript in rats markedly increased nicotine consumption. α3β4 nAChRs thus control the stimulatory effect of nicotine on the medial habenula–interpeduncular nucleus circuit and nicotine-avoidance behavior (Elayouby et al. 2021).

An α-LsIA analog stapled at cysteines 2 and 4 was produced using five linkers. An alkynylbenzyl bromide linker carrying coumarin 120 or camptothecin (a DNA topoisomerase I inhibitor) was stapled across Cys2 and Cys4, and the conjugates retained inhibitory activity at human α7 and rat α3β2 nAChRs. The stapled peptide-drug conjugates also retained cytotoxic activity against human A549 cancer cells (Sun et al. 2024).

α-Conotoxin αC-PrXA was used to select peptide-binding DNA aptamers, which effectively neutralized the toxin-induced displacement of radiolabeled α-bungarotoxin from nAChRs, the inhibition of muscle contraction, and lethality in mice. These fast-acting aptamers are promising antidote candidates and a potential alternative to donor sera in the treatment of envenomation (El-Aziz et al. 2017). Patch-clamp recordings in TE671 cells expressing muscle-type nAChRs were used to examine the effect of αC-PrXA on acetylcholine-evoked responses. Two DNA aptamers reduced the affinity of αC-PrXA for the receptor, probably by interfering with its pharmacophore. When co-administered, the aptamers also reduced αC-PrXA-induced spasmodic muscle contraction and lethality in mice, consistent with formation of a stable toxin–aptamer complex (Taiwe et al. 2019).

αO-GeXIVA reduced hyperalgesia in the rat chronic-constriction-injury (CCI) model of neuropathic pain without affecting motor activity (Luo et al. 2015). Both bead and ribbon isomers significantly decreased mechanical allodynia in CCI rats, and the bead isomer's effect lasted up to two weeks after intramuscular treatment (Li et al. 2016). In the rat CCI model of neuropathic pain, αO-GeXIVA bead isomer decreased mechanical hyperalgesia without effect on motor activity. The isomers differed ~5-fold in potency at human versus rat α9α10 receptors but had the same affinity at the rat receptor (Zhangsun et al. 2017). The lyophilized bead isomer, formulated with trehalose as the stabilizer and mannitol as the bulking agent, gave stable analgesia in paclitaxel-induced neuropathic pain in von Frey and tail-flick tests (Li et al. 2021). In oxaliplatin-treated rats, the bead isomer produced analgesia without tolerance and promoted recovery from neuropathic pain after repeated oxaliplatin treatment. Its effect on mechanical allodynia lasted 10 days after the end of a 16-day treatment, without affecting hind-limb grip strength or body weight (Wang et al. 2019). Repeated injections of the bead isomer for several weeks in mice with oxaliplatin-induced neuropathy had no effect on locomotor activity or anxiety-like behavior (Wang et al.

2024). αO-GeXIVA also blocked proliferation and induced apoptosis in MDA-MB-157 breast cancer cells, apparently by downregulating α9 nAChR expression, and suppressed their migration. The growth of an α9 nAChR-knockout MDA-MB-157 line was not further inhibited, consistent with action through this receptor (Sun et al. 2020).

The GluN2B antagonist con-T[M8Q] blocked naloxone-induced jumping and conditioned place preference in morphine-dependent mice with a potency about 100-fold higher than ifenprodil, another GluN2B antagonist. It inhibited morphine dependence with few adverse effects and did not substantially affect locomotor activity or spatial memory in mice (Liu et al. 2021).

Conantokin-Pr3 partially blocked NMDAR-induced phosphorylation of CREB (cAMP-response element-binding protein) at Ser133, implying that it controls calcium entry and thereby CREB activation. Because it effectively inhibits NMDAR-evoked current and calcium influx, receptor-linked CREB signaling may be sustained, which could enhance neuronal plasticity and survival in neurological conditions (Kunda et al. 2013).

A variant of conantokin-P lacking post-translational modification (naked con-P, in which Gla residues are replaced by Glu) blocked GluN2B but also potentiated GluN2A-containing NMDARs. Naked con-P enhanced NMDAR-mediated synaptic events in primary hippocampal neurons and reduced neuronal damage caused by staurosporine, a protein kinase inhibitor and potent inducer of apoptosis (Carmi et al. 2025).

Mini-Ins, a structurally minimized but fully potent human des-octapeptide insulin analog, was developed based on con-Ins G1. It is monomeric, lacks the canonical B-chain C-terminal octapeptide, and binds the insulin receptor with an affinity comparable to human insulin. Four mutations appeared to compensate for the contacts normally made by the missing octapeptide, and its full bioactivity showed that the PheB24–PheB25–TyrB26 aromatic triplet is not essential (Xiong et al. 2020).

GENERAL PERSPECTIVES

Conus species produce a great variety of peptides that deserve renewed attention for therapeutic development. Structural and biological studies of several conotoxin families indicate that these peptides are potential agents for treating neurological disorders, cancer, and other illnesses, and many selectively regulate their targets, making them important ligands for investigating the roles of those targets in health and disease.

Abnormal ion-channel and receptor activity has been associated with neuropathic conditions, including pain. Neuropathic pain may arise when nerves are damaged by diseases, such as cancer and AIDS. Because of their high potency and remarkable selectivity for ion channels, receptors, and transporters, conotoxins have attracted much interest as pharmacological agents.

Conotoxins that target the nAChRs are valuable neuropharmacological tools with potential therapeutic applications. Although several nAChR subtypes have been characterized as promising drug targets for neuropathic pain, there are still no FDA-approved therapies that target nAChRs. Nevertheless, preclinical and clinical evidence indicate that selective ligands for specific subtypes have potential for treating chronic pain with fewer adverse effects (Hone and McIntosh 2023; Tae and Adams 2023; Tao et al. 2025). α-Vc1.1, α-RgIA, α-Vt1.27, αO-lt14a, and αO-GeXIVA have shown analgesic effects through their specific actions on neuronal nAChRs and could be advanced for the management of neuropathic pain (Tae et al. 2025; Romero et al. 2017; Dyachenko et al. 2022; Wang et al. 2022a; Ren et al. 2015a; Wang et al. 2024).

Conotoxin engineering can benefit from rapid computational techniques. Novel α-conotoxin analogs designed with these methods showed enhanced properties and pointed out the way to subtype-specific nAChR ligands (Wu et al. 2024). Dendrimerization and stapling improve pharmaceutical properties, as shown for α-ImI and α-LsIA (Mei et al. 2018; Sun et al. 2024), and may find application in targeted drug delivery. The binding of α-ImI dendrimers to α7 nAChR (Xu et al. 2019) opens an opportunity to design more selective conotoxin dendrimers as drug carriers. Further studies on conotoxins as vehicles for targeting cancer cells that overexpress specific nAChR subunits are warranted.

Fatty-acid modification, which improved the stability and albumin-binding of α-GI while preserving its nAChR antagonism (Qi et al. 2023), deserves further investigation. Peptide engineering by insertion, deletion, truncation, and cyclization, as with α-TxID, α-AusIA, and αO-GeXIVA (Dong et al. 2023; Ho et al. 2021; Wu et al. 2017b), has provided insights into toxin–target interactions and ways to reduce proteolytic susceptibility while maintaining activity.

Several of the conotoxins presented, including α-ImI, α-PnIA[A10L], α-AusIA, α-AtIA, αD-VxXXB, αD-PiXXA, αD-FrXXA, and αM-SIIID, act on the neuronal α7 nAChR (Wan et al. 2015; Hopping et al. 2014; Lebbe et al. 2014; Neves et al. 2024; Loughnan et al. 2006; Hernández-Sámano et al. 2019; Rodriguez-Ruiz et al. 2022; Wang et al. 2022b). The role of α7 nAChR in pain, with potential pharmacological applications, has been documented (Tao et al. 2025). Chimeric peptides that combine residues interacting with specific nAChR subtypes could be explored. Comparing the contributions of individual residues might allow peptides to be engineered with high specificity, potency, and stability.

Studies on muscle nAChR-targeted conotoxins, such α-MilIA, αC-PrXA, αD-FrXXA and αM-MIIIJ (Peigneur et al. 2019, Taiwe et al. 2019, Rodriguez-Ruiz et al. 2022, Rybin et al. 2020) could be undertaken alongside α-GI, with a view to developing them as pharmacological agents.

As an archetype of ligand-gated ion channels, nAChRs have been investigated mainly in neurons, but evidence also indicates roles in cancer, nicotine addiction, and envenomation. nAChR expression is increased in certain cancers and has been linked to cell proliferation and evasion of programmed cell death. nAChR-mediated signaling in cancer offers opportunities for novel nAChR-targeted anticancer therapies, such as α-TxID and αO-GeXIVA (Liu et al. 2019; Sun et al. 2020). The use of α-AuIB to probe nicotine addiction, and possibly to develop treatments for it, is worth pursuing. The use of αC-PrXA to identify peptide-binding DNA aptamers El-Aziz et al. 2017), which may serve as alternatives to horse serum antivenoms for lethal venoms, such as snake toxins deserves further study.

The GluN2B-targeted con-T[M8Q], with high efficacy and few adverse effects, is a potentially useful lead for managing opioid dependence (Liu et al. 2021). Continuing studies on the activity of GluN2B-targeted conantokin-Pr3 in relation to the receptor-linked CREB signaling, with possible effects in neuronal survival (Kunda et al. 2013) are worth pursuing. Conantokin-Bk-B, a short peptide that targets GluN2D (Platt et al. 2014) rather than GluN2B, the usual target of conantokins-G, -T, -Pr3, and -P, is worth further investigation A thorough characterization of the bioactivity and pharmacology of GluN2B-selective and GluN2D-selective antagonists would be valuable for designing NMDAR-selective medications. Studies have shown that NMDAR-subtype specificity can be engineered into conantokins for managing neurological

conditions, and the molecular determinants of GluN2B/GluN2D selectivity may help clarify GluN2-mediated neurological processes.

Contulakin-G is an effective analgesic in rodent models of neuropathic pain (Martin et al. 2022), but the studies so far present challenges for the development of neurotensin-targeted leads, including limited penetration of the blood–brain barrier. Whether analogs with improved penetration are feasible and safe should be investigated. Given its evaluated efficacy and side-effect profile, the use of contulakin-G as an analgesic warrants further study.

Conotoxins could be explored as leads for treating disorders linked to the vasopressin V2 receptor. V2, expressed in the kidney, mediates vasopressin-controlled functions such as water homeostasis, and disruption of these functions has serious consequences. Despite many efforts to develop V2-targeted drugs, only one agonist (for diabetes insipidus and enuresis) and one antagonist (for hyponatremia) are in clinical use (Gilles 2023). More research on vasopressin-receptor-targeted conotoxins as therapeutic leads for such disorders is worthwhile.

Selective inhibition of tentonin 3 by NMB-1, a ρ-TIA analog, provides a basis for developing pharmacological tools that target tentonin-3-linked channelopathies (Lim et al. 2026). Channelopathies are disorders caused by malfunction of ion channels, such as those that control the flow of calcium, sodium, and potassium ions across the cell membrane; they disrupt electrical signaling in the brain or heart.

Con-Ins peptides (Menting et al. 2016; Ahorukomeye et al. 2019; Gorai and Vashisth 2022) have unique properties relevant to the design of insulin therapies and offer insights into new treatments for diabetes. Because they reveal how insulin receptors can be activated by a minimized ligand, work on mini-Ins (Xiong et al. 2020) provides a direction for the advancement of novel, minimized therapeutic insulin.

Conantokin-G (CGX-1007), contulakin-G (CGX-1160), α-Vc1.1 (ACV1), and Xen2174 reached human clinical trials. CGX-1007 (for pain and epilepsy) and CGX-1160 (for pain) were licensed to Cognetix, Inc., but clinical development was halted when the company encountered funding problems. ACV1, for sciatica, was developed by Metabolic Pharmaceuticals Ltd but failed because of very low efficacy in humans, and its clinical development was terminated (Safavi-Hemami et al. 2018). Xen2174, for pain management, was licensed to Xenome Ltd (Lewis 2012), but clinical studies showed no conclusive analgesic effect in humans (Okkerse et al. 2017).

Generally, the conotoxins represent key molecular probes for elucidating the physiological roles of specific types of ligand-gated ion channels, G protein-coupled receptors, norepinephrine transporter and insulin receptor towards potential pharmacological applications. An exhaustive characterization of the structures, molecular targets, structure-activity correlations and pharmacology of selective inhibitors would be helpful in the design of effective therapeutics. The studies so far have determined the possibility of designing antagonist specificities into conotoxins. The agonists with distinct abilities to modulate those ion channels/ receptors/ transporters underscores the prospects for conotoxins as novel therapeutic leads and pharmaceutical tools. In this view, further studies on conotoxins are important.

Although some conotoxins show analgesic efficacy in animal models of neuropathic pain and, in some cases, in human trials (Safavi-Hemami et al. 2018; Lewis 2012), improved peptide delivery and stability and reduced adverse effects are still needed. A case in point is ziconotide, the synthetic form of ω-MVIIA, which produces strong analgesia by inhibiting N-type calcium channels and is the only conotoxin approved by the U.S. FDA, for severe chronic pain. Despite favorable features such as the absence of respiratory depression, tolerance, and withdrawal symptoms, ziconotide's use is limited by its intrathecal route of administration and narrow therapeutic window (Lin et al. 2024) and by neuropsychiatric adverse effects (Peraire et al. 2024; Rubiu et al. 2024). A study showing the plausibility of delivering ziconotide to the cerebrospinal fluid intranasally (Manda et al. 2016) could be extended to other conotoxins as novel therapies.

Studies on ω-MVIIA were initially carried out on venom purified from *Conus magus* collected from the Philippine seawaters. The biochemical characterization was initially undertaken at the University of Utah in collaboration with the University of the Philippines (Olivera et al. 1987). This review is expected to motivate continuing studies, encourage funding agencies to support conotoxin research, and stimulate pharmaceutical interest in collaboration, possibly replicating the initial success of ω-MVIIA. It is hoped that peptide engineering and modern techniques will eventually resolve ziconotide's intrathecal administration, narrow therapeutic window, and neuropsychiatric side effects.

Conotoxins are a vast resource for drug discovery, and because they are highly specific, they are being developed as therapeutic leads and pharmaceutical tools. Yet there are biosecurity concerns linked to *Conus* venoms. Because some conotoxins are highly toxic to humans, regulatory measures have been recommended to prevent their misuse as biological weapons, while continued conotoxin discovery is encouraged. With high-throughput DNA and RNA sequencing and current bioinformatics, conotoxins are potential drug candidates for conditions such as neuropathic pain, epilepsy, and diabetes (Bjørn-Yoshimoto et al. 2020).

CONCLUSION

Conus venom peptides are invaluable tools for investigating the structure and function of their molecular targets and for understanding neurological pathways. Members of the conotoxin families are vital for mapping binding sites on specific targets, and their known specificities have helped distinguish among ion-channel, receptor, and transporter subtypes. Many conotoxins selectively regulate their targets, making them important ligands for determining the roles of these targets in various illnesses.

Classification of the target structures provides a benchmark for developing highly specific receptor antagonists for therapeutic use. Conotoxins have been documented to bind to ligand-gated ion channels, G protein-coupled receptors, the norepinephrine transporter, and the insulin receptor, all of which are drug targets for neurological conditions, cancer, diabetes, and other illnesses. Conotoxins can serve as therapeutic leads and pharmaceutical tools, if concerns regarding drug delivery, stability, and severe adverse effects can be resolved

ACKNOWLEDGMENT

The author greatly appreciates the administrative support from the University of the Philippines Baguio, the technical assistance of Lean Paolo J. Sastrillo, and the reviewers' contribution to the improvement of the paper.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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